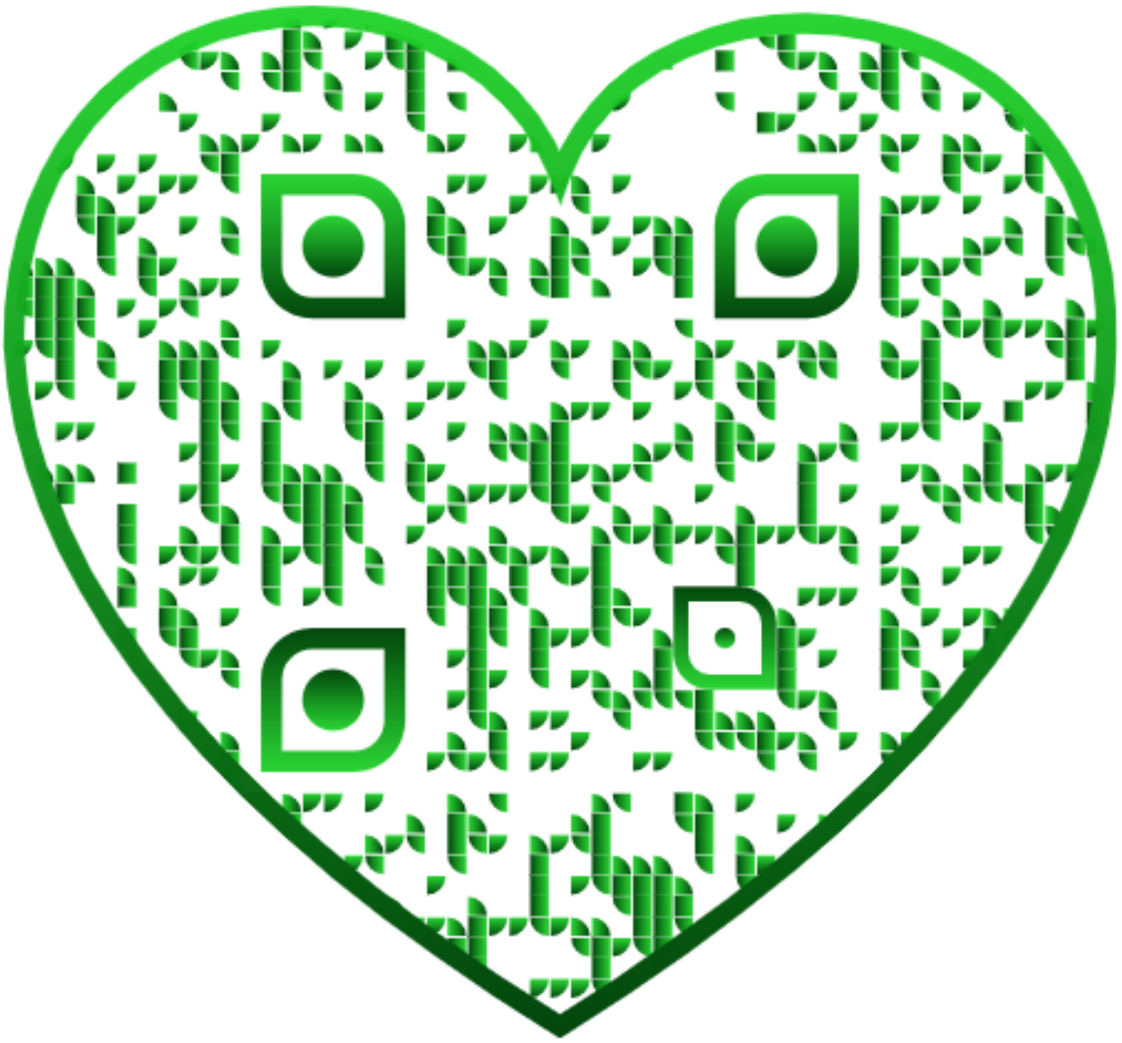
Applied Therapeutics

TWELFTH EDITION

The Clinical Use of Drugs

Caroline S. Zeind
Michael G. Carvalho
Judy W. M. Cheng
Kathy Zaiken
Trisha LaPointe

Wolters Kluwer



VOLUME ONE

APPLIED THERAPEUTICS

The Clinical Use of Drugs

TWELFTH Edition

A L G r a w a n y

VOLUME ONE

APPLIED THERAPEUTICS

The Clinical Use of Drugs

TWELFTH Edition

CAROLINE S. ZEIND, PHARMD

Vice President for Academic Affairs/Provost
Professor of Pharmacy Practice
Academic Affairs
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

MICHAEL G. CARVALHO, BS, PHARMD, BCPP

Professor Emeritus of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

JUDY W. CHENG, PHARMD, MPH, BCPS, FCCP

Professor and Chair
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences

Boston, Massachusetts

KATHY ZAIKEN, PHARMD

Professor of Pharmacy Practice
Director, International Pharmacy Residency Program
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

TRISHA LAPOINTE, PHARMD, BCPS, FASHP

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Wolters Kluwer

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

ALGrawany

Acquisitions Editor: Matt Hauber
Development Editors: Kelly Horvath/Deborah Bordeaux
Editorial Coordinator: Venugopal Loganathan
Editorial Assistant: Parisa Saranj
Marketing Manager: Phyllis Hitner
Production Project Manager: Catherine Ott
Manager of Graphic Arts and Design: Steve Druding
Art Director: Jennifer Clements
Manufacturing Coordinator: Margie Orzech
Prepress Vendor: S4Carlisle Publishing Services

Twelfth Edition

Copyright © 2024 Wolters Kluwer.

Copyright © 2018, 2013, 2009, 2005 by Lippincott Williams & Wilkins, a Wolters Kluwer business. All rights reserved. This book is protected by copyright. No part of this book may be reproduced or transmitted in any form or by any means, including as photocopies or scanned-in or other electronic copies, or utilized by any information storage and retrieval system without written permission from the copyright owner, except for brief quotations embodied in critical articles and reviews. Materials appearing in this book prepared by individuals as part of their official duties as U.S. government employees are not covered by the above-mentioned copyright. To request permission, please contact Wolters Kluwer at Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103, via email at permissions@lww.com, or via our website at shop.lww.com (products and services).

9 8 7 6 5 4 3 2 1

Printed in Mexico

Library of Congress Cataloging-in-Publication Data

ISBN-13: 978-1-975167-09-7

Cataloging in Publication data available on request from publisher.

This work is provided “as is,” and the publisher disclaims any and all warranties, express or implied, including any warranties as to accuracy, comprehensiveness, or currency of the content of this work.

This work is no substitute for individual patient assessment based upon healthcare professionals’ examination of each patient and consideration of, among other things, age, weight, gender, current or prior medical conditions, medication history,

laboratory data and other factors unique to the patient. The publisher does not provide medical advice or guidance and this work is merely a reference tool. Healthcare professionals, and not the publisher, are solely responsible for the use of this work including all medical judgments and for any resulting diagnosis and treatments.

Given continuous, rapid advances in medical science and health information, independent professional verification of medical diagnoses, indications, appropriate pharmaceutical selections and dosages, and treatment options should be made and healthcare professionals should consult a variety of sources. When prescribing medication, healthcare professionals are advised to consult the product information sheet (the manufacturer's package insert) accompanying each drug to verify, among other things, conditions of use, warnings and side effects and identify any changes in dosage schedule or contraindications, particularly if the medication to be administered is new, infrequently used or has a narrow therapeutic range. To the maximum extent permitted under applicable law, no responsibility is assumed by the publisher for any injury and/or damage to persons or property, as a matter of products liability, negligence law or otherwise, or from any reference to or use by any person of this work.

shop.lww.com

A L G r a w a n y

Dedication

As we near the 50th anniversary of Applied Therapeutics, *the editors wish to honor Dr. Mary Anne Koda-Kimble and Dr. Lloyd Young who created* Applied Therapeutics, *the gold standard textbook used in the teaching of patient-centered drug therapeutics. Their vision and legendary contributions have advanced health professions education for generations of healthcare students who are making a difference in the lives of their patients and the communities in which they serve.*

After embarking on the twelfth edition of Applied Therapeutics, *the COVID-19 pandemic brought forward unexpected challenges to a dedicated team of over 200 contributors for this edition. Many of our contributors served in dual roles as health professions educators and as healthcare providers on the front lines managing the pandemic. We dedicate this twelfth edition to them, as well as the health professions students who demonstrated resilience to advance their education and training during the pandemic. Finally, we wish to thank our*

families for their patience and unwavering support as we navigated through the winding roads of this journey and completed this twelfth edition of the textbook.

Preface

Health professions education was significantly affected by the COVID-19 pandemic, as there was a significant need to adapt the delivery of clinical education. Many health professions programs redesigned curriculum to incorporate virtual educational tools with enhancements to online education. The pandemic has shown us more than ever the importance of educating students who are able to think critically and to utilize problem-solving skills to address healthcare challenges. Approximately five decades later, the founding principle for this textbook—a patient-centric, case-based approach to learning—remains the cornerstone of health professions education. Our authors present approximately 900 patient cases that stimulate the reader to integrate and apply therapeutic principles in the context of specific clinical situations. Health professions students and practitioners gain a glimpse into the minds of expert clinicians as they work to assess and solve therapeutic problems and develop their own critical thinking and problem-solving skills.

Readers familiar with past editions of the book will notice that the overall design of the book is consistent with the eleventh edition, which incorporates a Core Principles section at the beginning of each chapter, providing the most important “take home” information from the chapter. Each Core Principle is mapped to specific cases within the chapter where the principle is discussed in detail. Key references and websites are listed at the end of each chapter, whereas the full reference lists for each chapter have been moved online.

Building upon the excellent foundation of case-based learning provided in previous editions, the twelfth edition has incorporated changes to meet the evolving educational needs of health professions educators and students across the globe. The editors and contributors have utilized the five Institute of Medicine (IOM) core competencies as a broad framework for proposing case studies and questions within the textbook: patient-centered care, interprofessional teams, evidence-based practice, quality improvement, and informatics. In addition, the Accreditation Council for Pharmacy Education (ACPE) Accreditation Standards 2016, the Center for the Advancement of Pharmacy Education (CAPE) Educational Outcomes, and the North American Pharmacist Licensure Examination (NAPLEX) revised competency statements have served as road maps for the editorial team and contributors in designing the twelfth edition.

Featuring contributions from more than 200 experienced health professions educators, every chapter has been revised and updated to reflect our ever-changing knowledge of drugs and the application of this knowledge to the individualized therapy of patients. Given the importance of incorporating Interprofessional Practice and Education (IPE) within health professions curricula, we have dedicated a chapter on IPE, as well as an array of IPE case studies prepared by contributors that are representative of various sections of the textbook. These IPE cases, along with answer guides, will be available for instructors on the textbook's website (see the "Additional Resources" section).

We welcome your feedback as we undertake planning for the next edition. The authors have drawn on information from the literature, current standards, and their own clinical experiences to share the process involved in making sound and thoughtful therapeutic decisions. *However, it remains the responsibility of every practitioner to evaluate the appropriateness of a particular opinion in the context of the actual clinical situation, bearing in mind any recent developments in the field. We strongly urge students and practitioners to consult several appropriate information sources when working with new and unfamiliar drugs*.

A L G r a w a n y

Acknowledgments

We are deeply indebted to the many dedicated people who have given of themselves to complete the twelfth edition of *Applied Therapeutics: The Clinical Use of Drugs*. We are grateful to our contributing authors who have worked tirelessly and with resolve to provide the highest quality of work, while providing vital services to patients during the pandemic, along with numerous responsibilities as educators, clinicians, and researchers. We are grateful for the exceptional work of our 28 section editors, who provided critical feedback necessary both in the organizational structure of the textbook and in the individual editing of chapters; without their dedication and support, this edition would not have been possible. We sincerely thank the past editorial team of *Applied Therapeutics*, with special thanks to Dr. B. Joseph Guglielmo for his guidance and support and contributions to this textbook.

The team from Wolters Kluwer, Matt Hauber, Deborah Bordeaux, Kelly Horvath, Venugopal Loganathan, Sean Hanrahan, and Susan Thomas, deserves special recognition for their efforts. Their exceptional patience, attention to detail, and guidance have been critical to the success of this project. We sincerely thank Catherine Ott (project management) and Subhash Nataraj (production) for their assistance in completing this edition. Most importantly, we wish to acknowledge the love, understanding, and unwavering support of our spouses and families. They selflessly gave to us early mornings, late nights, weekends, and vacation time that we spent writing and editing.

Consistent with past editions, we continue to dedicate our work to our students who inspire us and to the many patients we have been privileged to care for and who have taught us invaluable lessons. We also dedicate the twelfth edition to those health professions educators and clinicians who have served as pioneering leaders and role models in the delivery of patient-centered care using team-based approaches.

A L G r a w a n y

Additional Resources

The twelfth edition of *Applied Therapeutics: The Clinical Use of Drugs* includes additional resources for both instructors and students, available on the book's companion website at **http://thepoint.lww.com/AT12e**.

STUDENT RESOURCES

Students who have purchased *Applied Therapeutics: The Clinical Use of Drugs*, Twelfth Edition, have access to the following additional resources for each chapter:

- A full online reference list for that chapter

INSTRUCTOR RESOURCES

Approved adopting instructors will be given access to the following additional resources:

- Interprofessional Education (IPE) Case Studies and Answer Guides
- Each chapter will map which NAPLEX competency statements are addressed within it, which will be a helpful resource for instructors.

Section Editors

Mary G. Amato, PharmD, MPH, FCCP, BCPS
Professor Emerita of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Michael C. Angelini, PharmD, MA, BCPP
Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Judith L. Beizer, PharmD, CGP, FASCP
Clinical Professor
Department of Clinical Pharmacy Practice
College of Pharmacy & Allied Health Professions
St. John's University
Jamaica, New York

Snehal H. Bhatt, PharmD, BCPS
Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences

Clinical Pharmacist
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Michael G. Carvalho, BS, PharmD, BCPP

Professor Emeritus of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Judy W. Cheng, PharmD, MPH, BCPS, FCCP

Professor and Chair
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

R. Rebecca Couris, PhD, RPh

Professor of Nutrition Science and Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Elizabeth Anne Farrington, PharmD, FCCP, FCCM, FPPA, BCPS, BCNSP, BCPPS

Clinical Pharmacist–Pediatrics
Department of Pharmacy
Novant Health New Hanover Regional Medical Center
Wilmington, North Carolina

Steven Gabardi, PharmD, BCPS, FAST, FCCP

Abdominal Organ Transplant Clinical Specialist
Brigham and Women's Hospital
Assistant Professor of Medicine
Harvard Medical School
Mass General Brigham
Boston, Massachusetts

Jennifer D. Goldman, PharmD, CDCES, BC-ADM, FCCP

Professor of Pharmacy Practice
Clinical Pharmacist, Well Life
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Christy S. Harris, PharmD, BCOP, FHOPA

Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Timothy R. Hudd, BS, PharmD, AE-C

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Susan Jacobson, MS, EdD, RPh

Associate Professor of Pharmacy Practice
School of Pharmacy—Boston

Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Katie Kiser, PharmD, BCACP

Associate Professor of Pharmacy Practice
Director, Interprofessional Education
Ambulatory Care Clinical Specialist–NHC Farragut
South College School of Pharmacy
Knoxville, Tennessee

Maria Kostka-Rokosz, PharmD, RPh

Assistant Dean of Academic Affairs
Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Susan A. Krikorian, MS, PharmD

Professor Emerita of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Trisha LaPointe, PharmD, BCPS, FASHP

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Michele Matthews, PharmD, BCACP, CPE, FASHP

Professor and Vice Chair
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Susan L. Mayhew, PharmD

Dean and Professor
Pharmacy Practice
Appalachian College of Pharmacy
Oakwood, Virginia

Oussayma Moukhachen, PharmD, BCPS, BCCCP

Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Kamala M. Nola, PharmD, MS, FAPhA

Associate Dean of Academic Affairs and Professor
Department of Pharmacy Practice
Lipscomb University College of Pharmacy
Nashville, Tennessee

Dorothea Rudorf, PharmD, MS (Germany), RPh

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

David Schnee, PharmD, BCACP

A L G r a w a n y

Professor and Vice Chair
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Carrie A. Sincak, PharmD, BCPS, FASHP

Associate Dean for Clinical Affairs
Professor of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Adrian Wong, PharmD, MPH, FCCM, BCCCP

Adjunct Associate Professor
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

G. Christopher Wood, PharmD, FCCP, FCCM, BCCCP

Professor
Department of Clinical Pharmacy and Translational Science
College of Pharmacy
University of Tennessee Health Science Center
Memphis, Tennessee

Kathy Zaiken, PharmD

Professor of Pharmacy Practice
Director, International Pharmacy Residency Program
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences

Boston, Massachusetts

Caroline S. Zeind, PharmD

Vice President for Academic Affairs/Provost
Professor of Pharmacy Practice
Academic Affairs
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

A L G r a w a n y

Contributors

Jessica L. Adams, PharmD

Scientific Director
Infectious Diseases
Clinical Care Options
Reston, Virginia

Sulaiman Almohaish, PharmD, BCPS

Post-doc/Fellow
Pharmacotherapy and Outcomes Sciences
Virginia Commonwealth University
Richmond, Virginia
Lecturer Pharmacy Practice
King Faisal University
Al-Ahsa Eastern Region, Saudi Arabia

Michael C. Angelini, PharmD, MA, BCPP

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Kevin E. Anger, PharmD, BCPS

Clinical Pharmacy Manager
Department of Pharmacy
Brigham and Women's Hospital
Boston, Massachusetts

Michael Armahizer, PharmD, BCCCP
Clinical Pharmacy Specialist, Neurocritical Care
Department of Pharmacy
University of Maryland Medical Center
Baltimore, Maryland

Timothy J. Atkinson, PharmD, BCPS, CPE
Clinical Pharmacy Specialist, Pain Management
Director, PGY2 Pain Management Residency Pharmacy
VA Tennessee Valley Healthcare System
Murfreesboro, Tennessee

Albert Bach, PharmD, APh
Assistant Professor of Pharmacy Practice
Department of Pharmacy Practice
Chapman University School of Pharmacy
Irvine, California

David T. Bearden, PharmD
Clinical Professor
Department of Pharmacy Practice
Oregon State University College of Pharmacy
Portland, Oregon

Carolyn M. Bell, PharmD
Clinical Pharmacy Specialist—Medical Surgical
ICU Pharmacy
Medical University of South Carolina Hospital Authority
Charleston, South Carolina

Sandra Benavides, PharmD
Associate Director, Outcomes and Assessment
CME Outfitters
Radnor, Pennsylvania

Paul M. Beringer, PharmD

Professor and Chair
Titus Family Department of Clinical Pharmacy
University of Southern California
Los Angeles, California

M. Brooke Bernhardt, PharmD, MS, BCOP, BCPPS

Assistant Professor of Pediatrics
Section of Pediatric Hematology/Oncology
Baylor College of Medicine
Houston, Texas

Christie M. Bertram, PharmD

Assistant Professor of Pharmacy Practice
Department of Pharmacy Practice
Rosalind Franklin University of Medicine and Science College of Pharmacy
North Chicago, Illinois

Kylie Marie Besz, BA, MBS, MPH

Clinical Coordinator
Department of Allergy and Immunology
Brigham and Women's Hospital
Boston, Massachusetts

Swati Betharia, PhD

Associate Professor of Pharmaceutical Sciences
Department of Pharmaceutical Sciences
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Snehal H. Bhatt, PharmD, BCPS

Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences

Clinical Pharmacist
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Marlo Blazer, PharmD, BCOP

Director of Pharmacy
Columbus Oncology Associates
Columbus, Ohio

Suzanne Bollmeier, PharmD, FCCP, BCPS, AE-C

Professor
Pharmacy Practice
University of Health Sciences and Pharmacy in St. Louis
St. Louis, Missouri

Laura M. Borgelt, PharmD, MBA

Doctor of Pharmacy and Masters in Business Administration
Associate Vice Chancellor of Strategic Initiatives and Professor
Clinical Pharmacy and Family Medicine
University of Colorado—Anschutz Medical Campus: University of Colorado Denver—Anschutz Medical Campus
Aurora, Colorado

Nicole J. Brandt, PharmD, MBA, BCPP, BCGP, FASCP

Executive Director, The Peter Lamy Center on Drug Therapy and Aging
Professor, Pharmacy Practice and Science
School of Pharmacy
University of Maryland School of Pharmacy
Baltimore, Maryland

Gildon Brooke, PharmD

Professor
Department of Pharmacy Practice
Southwestern Oklahoma State University—College of Pharmacy

Weatherford, Oklahoma

Gretchen M. Brophy, PharmD, BCPS, FCCP, FCCM, FNCS, MCCM

Professor
Pharmacotherapy & Outcomes Science and Neurosurgery
Virginia Commonwealth University
Richmond, Virginia

Kamaria K. Brown, PharmD

Clinical Manager
Division of Pharmacy
Atrium Health
Charlotte, North Carolina

Deanna J. Buehrle, PharmD

Clinical Pharmacist
Medicine
VA Pittsburgh Healthcare System
Pittsburgh, Pennsylvania

Tamara Bystrak, PharmD, BCPS, BCPP

Clinical Pharmacy Specialist
Behavioral Health Coatesville
VA Medical Center
Coatesville, Pennsylvania

Charles F. Caley, PharmD, BCPP

Chair and Professor of Pharmacy Practice
Department of Pharmacy Practice
Western New England University
Springfield, Massachusetts

Katherine Carey, PharmD

Associate Professor of Pharmacy Practice

ALGrawany

School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

J. Todd Carter, PharmD

Assistant Professor of Pharmacy Practice
Appalachian College of Pharmacy
Oakwood, Virginia

Michael G. Carvalho, BS, PharmD, BCPP

Professor Emeritus of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Mariana C. Castells, MD, PhD

Director of Drug Hypersensitivity and Desensitization
Director of Mastocytosis
Department of Allergy and Immunology
Brigham and Women's Hospital
Boston, Massachusetts

Jamie J. Cavanaugh, PharmD

Clinical Associate Professor
Department of Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Michelle Ceresia, PharmD, FACVP

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Laura Chadwick, PharmD

Mendon, Massachusetts

Lin H. Chen, MD, FACP, FASTMH, FISTM

Director, Mount Auburn Travel Medicine Center
Department of Medicine Mount
Auburn Hospital and Harvard Medical School
Cambridge, Massachusetts

Judy W. Cheng, PharmD, MPH, BCPS, FCCP

Professor and Chair
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Janet S. Cho, PharmD

Clinical Pharmacist, Autoimmune Conditions Specialty
Department of Pharmacy Services
University of Southern California, School of Pharmacy
Los Angeles, California

Jennifer W. Chow, PharmD

Experiential Program Coordinator and Assistant Professor, Office of Experiential Learning
Department of Clinical Pharmacy and Translational Science
The University of Tennessee Health Science Center
Memphis, Tennessee

Cary R. Chrisman, PharmD

Assistant Professor
Clinical Pharmacy and Translational Science
The University of Tennessee Health Science Center College of Pharmacy/Methodist Medical Centre
Oak Ridge, Tennessee

Edith Claros, PhD, PMHNP-BC

Psychiatric Mental Health Nurse Practitioner Program Track Coordinator
Professor, School of Nursing
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

John Cleary, PharmD

Emeritus Professor
Pharmacy Practice
University of Mississippi
Jackson, Mississippi

Michelle Condren, PharmD, BCPPS, AE-C, CDE, FPPA

Professor and Vice Chair for Research
Department of Pediatrics
The University of Oklahoma School of Community Medicine
Tulsa, Oklahoma

Christopher K. Cooper, MPAS

Associate Professor of Physician Assistant Studies
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Maryann R. Cooper, PharmD, BCOP

Professor of Pharmacy Practice
School of Pharmacy—Manchester
Massachusetts College of Pharmacy and Health Sciences
Manchester, New Hampshire

Amanda H. Corbett, PharmD

Assistant Dean
Pharmacotherapy and Experimental Therapeutics
University of North Carolina Eshelman School of Pharmacy
Chapel Hill, North Carolina

Mackenzie L. Cottrell, PharmD, MS

Assistant Professor
Division of Pharmacotherapy and Experimental Therapeutics
University of North Carolina at Chapel Hill Eshelman School of Pharmacy
Chapel Hill, North Carolina

R. Rebecca Couris, PhD, RPh

Professor of Nutrition Science and Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Steven J. Crosby, MA, BSP, RPh, FASCP

Assistant Dean of Student Engagement & Success
Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Jason Cross, PharmD

Associate Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Ryan G. D'Angelo, PharmD, BCPS

Clinical Pharmacy Specialist
Department of Cardiology
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Aimee Dawson, PharmD

Associate Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences

Worcester, Massachusetts

Jeremy R. DeGrado, PharmD, BCCCP, BCPS
Clinical Pharmacy Manager
Department of Pharmacy
Brigham and Women's Hospital
Boston, Massachusetts

Sandeep Devabhakthuni, PharmD, BCCP
Associate Professor of Cardiology
Director of Postgraduate Training
Department of Pharmacy
University of Maryland School of Pharmacy
Baltimore, Maryland

Aaron S. Devanathan, PharmD
Postdoctoral Fellow
Division of Pharmacotherapy and Experimental Therapeutics
University of North Carolina at Chapel Hill Eshelman School of Pharmacy
Chapel Hill, North Carolina

Lisa M. DiGrazia, PharmD
Clinical Oncology Pharmacist
Department of Pharmacy
Rush University Medical Center
Chicago, Illinois

Suzanne Dinsmore, PharmD, BSP, BCGP, FASCP
Associate Professor of Pharmacy Practice
Associate Director of the Post BS PharmD Pathway
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Rachid Douglas-Louis, PharmD

Clinical Translational Research Fellow
Clinical Pharmacy
University of Southern California School of Pharmacy
Los Angeles, California

Richard H. Drew, PharmD, MS, FCCP, FIDP

Professor and Vice Chair of Research and Scholarship
Department of Pharmacy Practice
Campbell University College of Pharmacy and Health Sciences
Buies Creek, North Carolina
Professor of Infectious Diseases
Duke University School of Medicine
Durham, North Carolina

Robert L. Dufresne, PhD, PhD, BCPS, BCPP

Professor of Pharmacy
Department of Pharmacy Practice
University of Rhode Island College of Pharmacy
Kingston, Rhode Island

Kaelen C. Dunican, PharmD

Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Brianne Dunn, PharmD

Associate Dean for Assessment and Clinical Associate Professor
College of Pharmacy
University of South Carolina
Columbia, South Carolina

Robert E. Dupuis, PharmD

Professor
Eshelman School of Pharmacy
University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

Cheryl R. Durand, PharmD
Professor of Pharmacy Practice
School of Pharmacy—Manchester
Massachusetts College of Pharmacy and Health Sciences
Manchester, New Hampshire

Megan J. Ehret, PharmD, MS, BCPP
Professor
Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy
Baltimore, Maryland

Shareen El-Ibiary, PharmD, FCCP, BCPS
Professor and Chair
Department of Pharmacy Practice
Midwestern University College of Pharmacy—Glendale
Glendale, Arizona

Katie D. Ellis, PharmD, BCPPS, AE-C
Assistant Professor
Department of Pharmacy Practice
Presbyterian College School of Pharmacy
Clinton, South Carolina

Justin C. Ellison, PharmD, BCPP
Clinical Pharmacist Practitioner in Mental Health
Department of Pharmacy
Providence VA Medical Center
Hyannis, Massachusetts

Amanda Eloma, PharmD, BCPP, CDTM
Pharmacist
Psychiatry Behavioral Health

Medical Clinic Kings County Hospital Center
Brooklyn, New York

Rachel Elsey, PharmD

Cancer Genomics Pharmacy Coordinator
Cancer Genomics
Avera McKennan Hospital and University Health Center
Sioux Falls, South Dakota

Gregory A. Eschenauer, PharmD

Clinical Associate Professor
Clinical Pharmacy
University of Michigan College of Pharmacy
Ann Arbor, Michigan

John Fanikos, RPh, MBA

Executive Director of Pharmacy Services
Department of Pharmacy
Brigham and Women's Hospital
Boston, Massachusetts

Elizabeth Anne Farrington, PharmD, FCCP, FCCM, FPPA, BCPS, BCNSP, BCPPS

Clinical Pharmacist–Pediatrics
Department of Pharmacy
Novant Health New Hanover Regional Medical Center
Wilmington, North Carolina

Lisa M. Feagin, PharmD, BCPPS

Neonatal Intensive Care Clinical Pharmacy Specialist
Clinical Instructor, Pharmacy and Pediatrics
Children's Hospital of The King's Daughters and Eastern Virginia Medical School
Norfolk, Virginia

Erika Felix-Getzik, PharmD

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Jonathan D. Ference, PharmD

Associate Provost for Student Success
Provost's Office, Wilkes University
Wilkes-Barre, Pennsylvania

Victoria F. Ferraresi, PharmD

Volunteer Associate Clinical Professor
Department of Clinical Pharmacy
University of California San Francisco School of Pharmacy
San Francisco, California

Joseph W. Ferullo, PharmD

Director, Pharmacy Practice Laboratories
Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Christopher K. Finch, PharmD, FCCM, FCCP

Chair and Professor
Clinical Pharmacy and Translational Science
The University of Tennessee Health Science Center
Memphis, Tennessee

Douglas N. Fish, PharmD

Professor and Chair
Department of Clinical Pharmacy
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado—Anschutz Medical Campus
Aurora, Colorado

Alexander H. Flannery, PharmD, FCCM, BCCCP, BCPS
Assistant Professor of Pharmacy Practice and Science
University of Kentucky College of Pharmacy
Lexington, Kentucky

Andrea S. Franks, PharmD
Professor and Vice Chair
Clinical Pharmacy and Translational Science
The University of Tennessee Health Science Center—College of Pharmacy
Knoxville, Tennessee

Michael Frei, PharmD
Clinical Pharmacy Specialist
The University of Texas MD Anderson Cancer Center
Houston, Texas

Lynn Z. Fuller, PhD, RPh
Assistant Professor
Department of Pharmaceutical Sciences
Sullivan University College of Pharmacy and Health Sciences
Louisville, Kentucky

Leigh Furman, PharmD
Clinical Pharmacist
Department of Pharmacy
University of Minnesota Children's Hospital
Minneapolis, Minnesota

Adinoyi Garba, PharmD
Clinical Associate Professor and Vice Chair
Department of Pharmacy Practice
D'Youville School of Pharmacy
Buffalo, New York

Joshua A. Garcia, PharmD

Assistant Professor
Department of Pharmacy Practice
Marshall B. Ketchum University—College of Pharmacy
Fullerton, California

Virginia Ghafoor, PharmD, MBA

Clinical Pharmacy Specialist
Pain Management
Pharmacy University of Minnesota Medical Center
Minneapolis, Minnesota

Jennifer D. Goldman, PharmD, CDCES, BC-ADM, FCCP

Professor of Pharmacy Practice
Clinical Pharmacist, Well Life
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Joel Goldstein, MD

Psychiatrist Mental Health
Massachusetts Department of Mental Health
Lexington, Massachusetts

Larry Goodyer, PhD

Professor of Pharmacy Practice
School of Pharmacy
De Montfort University
Leicester, United Kingdom

Mary-Kathleen Grams, BSP, PharmD

Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences

Boston, Massachusetts

Philip Grgurich, PharmD, MBA, BCPS, BCCCP
Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

B. Joseph Guglielmo, PharmD
Professor and Dean Emeritus
University of California San Francisco School of Pharmacy
San Francisco, California

Karen M. Gunning, PharmD
Professor, Associate Dean, Clinical Pharmacist Pharmacotherapy
College of Pharmacy
University of Utah
Salt Lake City, Utah

Kathleen M. Gura, BS, PharmD, BCNSP, FASHP, FPPAG
Manager, Pharmacy Clinical Research Program
Department of Pharmacy
Boston Children's Hospital
Boston, Massachusetts

Mary A. Gutierrez, PharmD, BCPP
Professor
Department of Pharmacy Practice
Chapman University School of Pharmacy
Irvine, California

Jason S. Haney, PharmD
Associate Professor
Department of Clinical Pharmacy & Outcomes Sciences

Medical University of South Carolina—College of Pharmacy
Charleston, South Carolina

Christy S. Harris, PharmD, BCOP, FHOPA

Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Sarah M. Hayes, PharmD

Hematology/Oncology Clinical Pharmacy Specialist
Department of Pharmacy
North Memorial Health Hospital
Robbinsdale, Minnesota

Mary F. Hebert, PharmD

Professor
Department of Pharmacy
University of Washington School of Pharmacy
Seattle, Washington

Emily L. Heil, PharmD, MS

Associate Professor
Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy
Baltimore, Maryland

Erika L. Hellenbart, PharmD, BCPS

Clinical Assistant Professor
Department of Pharmacy Practice
University of Illinois at Chicago College of Pharmacy
Clinical Pharmacist
Ambulatory Care/Cardiology
UI Health
Chicago, Illinois

Bridget C. Hendricks, OD, MS, FAAO

Associate Professor, Chief of Glaucoma Service
The Eye & Vision Center School of Optometry
Massachusetts College of Pharmacy and Health Sciences—Worcester Campus
Worcester, Massachusetts

Christopher M. Herndon, PharmD, BCACP

Professor
School of Pharmacy—Worcester
Southern Illinois University Edwardsville
Edwardsville, Illinois

Janelle I. Herren, PharmD, MSE

Assistant Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Karl M. Hess, PharmD, APh, CTH, FCPhA, FAPhA, AFTM RCPS (Glasg)

Associate Professor of Pharmacy Practice
Director, Community Pharmacy Practice Innovations
CPESN Executive Pharmacy Residency Program Director
Department of Pharmacy Practice
Chapman University School of Pharmacy
Irvine, California

Evan Horton, PharmD

Associate Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Priscilla P. How, PharmD, BCPS

Associate Professor

Pharmacy Lead, National Collaborative Prescribing Program
Principal Clinical Pharmacist
Department of Pharmacy
Faculty of Science
National University of Singapore
Singapore, Singapore

Molly E. Howard, PharmD, BCPS, BCACP

Clinical Pharmacy Specialist—Primary Care
VA VISN 7 Clinical Resource Hub
PGY1 Residency Program Director
Central Alabama Veterans Health Care System
Montgomery VA Clinic
Montgomery, Alabama

Timothy R. Hudd, BS, PharmD, AE-C

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Rupali Jain, PharmD

Clinical Associate Professor
Department of Pharmacy
University of Washington
Seattle, Washington

Steven W. Johnson, PharmD, CPP, AAHIVP

Associate Professor
Department of Pharmacy Practice
Campbell University College of Pharmacy and Health Sciences
Winston-Salem, North Carolina

Donyika Joseph, PharmD

Clinical Pharmacy Specialist
Department of Pharmacy

The University of Texas MD Anderson Cancer Center
Houston, Texas

Nicole A. Kaiser, BS Pharmacy

Clinical Pharmacy Specialist
Department of Pharmacy
Children's Hospital Colorado
Aurora, Colorado

James S. Kalus, PharmD

Director of Pharmacy
Department of Pharmacy Services
Henry Ford Health
Detroit, Michigan

Amy Kang, PharmD

Assistant Professor
Department of Pharmacy Practice
Chapman University School of Pharmacy
Harry and Diane Rinker Health Science Campus
Irvine, California
Infectious Diseases Pharmacist
Department of Pharmacy
Harbor-UCLA Medical Centre
Torrance, California

Neha Kashalikar, PharmD

Clinical Pharmacist
Office of Clinical Affairs, Commonwealth Medicine
University of Massachusetts Chan Medical School
Quincy, Massachusetts

Marina D. Kaymakcalan, PharmD, BCOP

Genitourinary Clinical Pharmacy Specialist & Oral Anticancer Education Manager
Department of Pharmacy
Dana-Farber Cancer Institute

Boston, Massachusetts

Michael B. Kays, PharmD, FCCP, BCIDP
Associate Professor
Department of Pharmacy Practice
Purdue University College of Pharmacy
Indianapolis, Indiana

Jacob K. Kettle, PharmD
Director—Ellis Fischel Cancer Center
University of Missouri Health Care
Columbia, Missouri

Steven S. Kheloussi, PharmD, MBA
Assistant Professor of Pharmacy Practice
Department of Pharmacy Practice
Nesbitt School of Pharmacy
Wilkes University
Wilkes-Barre, Pennsylvania

Hyun Kim, PharmD
Clinical Pharmacist
Clinical Pharmacogenomics Service
Department of Pharmacy
Boston Children's Hospital
Boston, Massachusetts

Abigail Klutts, PharmD
Clinical Pharmacy Specialist, Ambulatory Care Pharmacy
The Johns Hopkins Hospital
Baltimore, Maryland

Mary P. Kovacevic, PharmD, BCCCP, BCPS
Clinical Pharmacy Specialist
Department of Pharmacy

Brigham and Women's Hospital
Boston, Massachusetts

Lee A. Kral, PharmD, CPE

Clinical Assistant Professor
Anesthesia Department
University of Iowa Carver College of Medicine
Iowa City, Iowa

Susan A. Krikorian, MS, PharmD

Professor Emerita of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Jerika T. Lam, PharmD, AAHIVP, FCSHP

Associate Professor of Pharmacy Practice
Chapman University School of Pharmacy
Irvine, California

Trisha LaPointe, PharmD, BCPS, FASHP

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Alan H. Lau, PharmD

Professor of Pharmacy Practice
University of Illinois at Chicago
Chicago, Illinois

Elaine J. Law, PharmD, BCPS, FCSHP

Associate Clinical Professor
Department of Pharmacy Practice
University of the Pacific Thomas J. Long School of Pharmacy

Stockton, California

Kimberly Lenz, PharmD, MBA
Senior Pharmacy Director
Office of Clinical Affairs, Commonwealth Medicine
University of Massachusetts Chan Medical School
Quincy, Massachusetts

Russell E. Lewis, PharmD
Associate Professor of Medicine, Infectious Diseases
Department of Medical and Surgical Sciences
University of Bologna
Bologna, Italy

Troy Lynn Lewis, PharmD
Assistant Professor of Pharmacy Practice
Nesbitt School of Pharmacy
Wilkes University
Wilkes-Barre, Pennsylvania

Rachel C. Long, PharmD, BCPS, CPP, CDCES
Ambulatory Care Pharmacist Pharmacy
Atrium Health
Charlotte, North Carolina

Ann M. Lynch, PharmD, RPh, AE-C
Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Matthew R. Machado, PharmD
Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences

Boston, Massachusetts

Daniel R. Malcom, PharmD, BCPS, BCCCP
Associate Professor and Chair
Department of Pharmacy Practice
Sullivan University College of Pharmacy and Health Sciences
Louisville, Kentucky

Shannon F. Manzi, PharmD
Director, Safety & Quality
Assistant Professor of Pediatrics
Department of Pharmacy
Boston Children's Hospital, Harvard Medical School
Boston, Massachusetts

Kathleen Marquis, PharmD, PhD
Clinical Pharmacist
Department of Pharmacy
Brigham and Women's Hospital
Boston, Massachusetts

Joel C. Marrs, PharmD, MPH
Clinical Associate Professor
Pediatrics and Child Health Associate/Physician Assistant Program
University of Colorado School of Medicine
Aurora, Colorado
Ambulatory Pharmacy Clinical Coordinator
Department of Pharmacy
Billings Clinic
Billings, Montana

John Marshall, PharmD, BCPS, BCCCP, FCCM
Vice President, Clinical Pharmacy Services
Department of Pharmacy
Beth Israel Lahey Health
Westwood, Massachusetts

Shedrick Martin, PharmD, BCPP

Clinical Pharmacist Specialist
Department of Pharmacy
Santa Rosa Memorial Hospital
Santa Rosa, California

Susan L. Mayhew, PharmD

Dean and Professor
Pharmacy Practice
Appalachian College of Pharmacy
Oakwood, Virginia

Sarah E. McBane, PharmD, BCPS, FCCP, FCPhA, FSCHP, APh

Founding Associate Dean of Pharmacy Education
Department of Clinical Pharmacy Practice
UCI School of Pharmacy and Pharmaceutical Sciences
Irvine, California

Chephra McKee, PharmD

Clinical Pharmacy Specialist, NICU
UT Southwestern Medical Center
Dallas, Texas

Mary Mihalyo, BS, PharmD, BCPS

Assistant Professor
Department of Clinical Pharmacy Practice
Duquesne University Mylan School of Pharmacy
Pittsburgh, Pennsylvania

Emi Minejima, PharmD

Associate Professor
Department of Clinical Pharmacy
University of Southern California School of Pharmacy
Los Angeles, California

Molly G. Minze, PharmD, FCCP, BCACP

Associate Professor of Pharmacy Practice
Associate Dean of Student Affairs & Admissions
Department of Pharmacy Practice
Jerry H. Hodge School of Pharmacy
Texas Tech University Health Sciences Centre
Abilene, Texas

Amee Mistry, PharmD

Professor of Pharmacy Practice
Director, Biopharmaceutical Industry Fellowship Program
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Anna K. Morin, PharmD

Associate Provost Worcester/Manchester and Professor of Pharmacy Practice
Academic Affairs
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Pamela Morris, MD

Professor of Medicine
Medical University of South Carolina
Charleston, South Carolina

Oussayma Moukhachen, PharmD, BCPS, BCCCP

Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Kelly A. Mullican, PharmD, BCACP

Clinical Pharmacy Coordinator
Department of Pharmacy

Kaiser Permanente Mid-Atlantic States
Washington, District of Columbia

Margaret K. Murphy, PharmD

Clinical Pharmacist, GI/Nutrition
Department of Pharmacy
Boston Children's Hospital
Boston, Massachusetts

Yulia A. Murray, PharmD

Associate Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Victoria Nachar, PharmD, BCOP

Clinical Pharmacist Specialist, Ambulatory Hematology
Department of Pharmacy
University of Michigan Rogel Cancer Center
Ann Arbor, Michigan

Milap C. Nahata, MS, PharmD, FCCP, FASHP, FAPhA, FPPA

Director, Institute of Therapeutic Innovations and Outcomes
Professor Emeritus of Pharmacy, Pediatrics and Internal Medicine
Colleges of Pharmacy and Medicine
The Ohio State University
Columbus, Ohio

Matthew Newman, PharmD, MEHP, BCOP

Clinical Pharmacist Practitioner, Hematologic Malignancies
Department of Pharmacy
The Johns Hopkins Hospital
Baltimore, Maryland

Kimmy Nguyen, PharmD
Assistant Professor
Department of Pharmacy Practice
Wilkes University
Wilkes-Barre, Pennsylvania

Richard S. Nicholas, PharmD, ND
Chair, Department of Pharmacy Practice
Appalachian College of Pharmacy
Oakwood, Virginia

Samar E. Nicolas, PharmD
Assistant Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Stefanie C. Nigro, PharmD
Associate Clinical Professor
Department of Pharmacy Practice
University of Connecticut
Storrs, Connecticut

Cindy L. O'Bryant, PharmD, BCOP, FCCP, FHOPA
Professor
Associate Dean of Academic and Faculty Affairs
Department of Clinical Pharmacy
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado—Anschutz Medical Campus
Aurora, Colorado

Kirsten H. Ohler, PharmD, FCCP, BCPS, BCPPS
Clinical Associate Professor of Pharmacy Practice
College of Pharmacy
University of Illinois at Chicago

Clinical Pharmacy Specialist
Neonatal ICU
University of Illinois Chicago Hospital & Health Sciences System
Chicago, Illinois

Julie L. Olenak, PharmD

Associate Dean/Professor
Nesbitt School of Pharmacy
Wilkes University
Wilkes-Barre, Pennsylvania

Jacqueline L. Olin, MS, PharmD

Scientific Director
Clinical Education Alliance
Reston, Virginia

Neeta Bahal O'Mara, PharmD, BCPS

Clinical Pharmacist
Dialysis Clinic, Inc.
North Brunswick, New Jersey

Nicole E. Omecene, PharmD, BCPPS

Assistant Professor
Pharmacotherapy and Outcomes Science
Virginia Commonwealth University
Richmond, Virginia

Stephanie M. Ozalas, PharmD, BCPS, BCGP

Clinical Assistant Professor and Geriatrics
Clinical Pharmacy Specialist
University of Maryland School of Pharmacy and VA Maryland Health Care System
University of Maryland, Baltimore
Baltimore, Maryland

Robert Lee Page II, PharmD, MSPH

Professor of Clinical Pharmacy, Medicine, and Physical Medicine
University of Colorado Schools of Pharmacy and Medicine
Aurora, Colorado

Louise Parent-Stevens, PharmD, BCPS

Forest Park, Illinois

Jaini Patel, PharmD, BCACP

Associate Professor
Clinical Pharmacist, Advocate Medical Group Chronic Disease Management
Department of Pharmacy Practice
Midwestern University College of Pharmacy, Downers Grove Campus (CPDG)
Downers Grove, Illinois

Jennifer T. Pham, PharmD, BCPS, BCPPS

Clinical Associate Professor, Clinical Pharmacist—Neonatal/Pediatrics
Department of Pharmacy Practice
University of Illinois at Chicago, College of Pharmacy
Chicago, Illinois

Jonathan Picker, MBChB, PhD

Clinical Geneticist, Director of Pharmacogenomic Service
Assistant Professor in Genetics
Department of Genetics
Boston Children’s Hospital, Harvard Medical School
Boston, Massachusetts

Nicole A. Pilch, PharmD, MSCR, CPHQ, BCPS, FAST

Professor
Department of Pharmacy and Clinical Sciences
Medical University of South Carolina
Charleston, South Carolina

David J. Quan, PharmD, BCPS

Pharmacist Specialist—Solid Organ Transplant
Department of Pharmaceutical Services
UCSF Medical Centre
Health Sciences Clinical Professor of Pharmacy
Department of Clinical Pharmacy
University of California San Francisco
San Francisco, California

Erin C. Raney, PharmD, FCCP, BCPS, BC-ADM

Professor
Department of Pharmacy Practice
Midwestern University College of Pharmacy—Glendale
Glendale, Arizona

Joshua Reardon, PharmD, BCOP

Oncology Specialty Pharmacist
Columbus Oncology Associates
Columbus, Ohio

Valerie Relias, PharmD, BCOP

Clinical Pharmacy Specialist
Assistant Professor of Medicine
Division of Hematology/Oncology
Tufts University School of Medicine
Boston, Massachusetts

Michelle M. Richardson, PharmD

Special and Scientific Staff
William B. Schwartz Division of Nephrology
Tufts Medical Center
Boston, Massachusetts

Charmaine Rochester-Eyeguokan, PharmD

Professor
Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy

Baltimore, Maryland

Carol J. Rollins, MS, RD, PharmD
Clinical Professor
Pharmacy Practice and Science
The University of Arizona College of Pharmacy
Tucson, Arizona

Melody Ryan, PharmD, MPH
Professor
Department of Pharmacy Practice and Science
University of Kentucky College of Pharmacy
Lexington, Kentucky

Melissa Sandler, PharmD, BCCCP
Post-doc/Fellow
Department of Pharmacotherapy and Outcomes Science
Virginia Commonwealth University
Richmond, Virginia

Nikhil A. Sangave, PharmD, BCACP
Adjunct Assistant Professor of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

David Schnee, PharmD, BCACP
Professor and Vice Chair
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Eric F. Schneider, BS Pharmacy, PharmD
Vice Provost for Institutional Effectiveness
Office of the Provost
Wingate University

Wingate, North Carolina

Sheila M. Seed, PharmD, MPH, CTH, AFTM RCPS (Glasg), RPh

Professor and Chair of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Nancy L. Shapiro, PharmD, FCCP, BCACP, CACP

Clinical Professor and Assistant Head for Education
Department of Pharmacy Practice
University of Illinois at Chicago College of Pharmacy
Clinical Pharmacist and Coordinator
Antithrombosis Clinic
UI Health
Chicago, Illinois

Iris Sheinhait, PharmD

Certified Poison Information Specialist
Pharmacology/Toxicology
Boston Children's Hospital
Boston, Massachusetts

Devon A. Sherwood, PharmD, BCPP

Associate Professor
Department of Pharmacy Practice
University of New England School of Pharmacy
Westbrook College of Health Professions
Portland, Maine

Richard J. Silvia, PharmD, BCPP

Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences

Boston, Massachusetts

Divita Singh, PharmD
Clinical Assistant Professor
Department of Pharmacy Practice
Temple University School of Pharmacy
Philadelphia, Pennsylvania

Harleen Singh, PharmD
Clinical Professor
School of Pharmacy
University of Texas at El Paso
El Paso, Texas

Linda M. Spooner, PharmD
Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Karyn M. Sullivan, PharmD, MPH
Assistant Dean of IPE and Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Allison E. Symonds, PharmD
Postdoctoral Pharmacokinetics & Pharmacodynamics Fellow
Division of Pharmacotherapy and Experimental Therapeutics
University of North Carolina at Chapel Hill Eshelman School of Pharmacy
Chapel Hill, North Carolina

Kristen Szempruch, PharmD
Clinical Pharmacy Specialist—Inpatient Abdominal Transplant
Assistant Professor of Clinical Education—UNC Eshelman School of Pharmacy

Department of Pharmacy
University of North Carolina Medical Center
Chapel Hill, North Carolina

David J. Taber, PharmD, MS

Professor
Division of Transplant Surgery, Department of Surgery
Medical University of South Carolina
Charleston, South Carolina

Kimberly Tallian, PharmD, APh, BCPP, FASHP, FCCP

Advanced Practice Pharmacist—Neuropsychiatry Pharmacy
Scripps Mercy Hospital, San Diego
San Diego, California

Yasar O. Tasnif, PharmD, BCPS, FAST

Associate Professor of Practice
School of Pharmacy
University of Texas at El Paso
El Paso, Texas

Kate Deen Taucher, PharmD, MHA, FASHP, BCOP

System Manager
Oncology & Infusion Pharmacy Services
UC Health
Aurora, Colorado

Daniel J. G. Thirion, PharmD, FCSHP

Full Clinical Professor
Pharmacist and Researcher
Faculty of Pharmacy
Department of Pharmacy
Universite de Montreal
McGill University Health Center

Montreal, Quebec, Canada

Angela M. Thompson, PharmD, BCPS
Senior Clinical Instructor
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado—Anschutz Medical Campus
Aurora, Colorado

Lisa A. Thompson, PharmD, BCOP
Specialist in Oncology
Department of Clinical Pharmacy
Kaiser Permanente Colorado
Lafayette, Colorado

Ricky B. Thumar, PharmD, RPh
Assistant Professor of Pharmacy Practice
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Dominick P. Trombetta, PharmD, BCPS, BCGP, FASCP
Associate Professor
Department of Pharmacy Practice Geriatrics/Internal Medicine
Wilkes University
Wilkes-Barre, Pennsylvania

Toby C. Trujillo, PharmD, FCCP, FAHA, BCPS
Associate Professor
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado—Anschutz Medical Campus
Clinical Specialist
Cochair, Anticoagulation Subcommittee UC Health
Anticoagulation/Cardiology
University of Colorado Hospital

Aurora, Colorado

Anne Walsh, PA-C, MMSc, DFAAPA

Clinical Associate Professor
PA Studies Program
Physician Assistant Studies
Crean College of Health and Behavioral Sciences
Chapman University
Irvine, California

Kaiwen Wang, PharmD

Clinical Pharmacy Specialist
Department of Pharmacy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sheila K. Wang, PharmD

Associate Professor of Pharmacy Practice
Department of Pharmacy Practice
Midwestern University College of Pharmacy
Downers Grove, Illinois

Ying Wang, PharmD

Assistant Professor of Clinical Pharmacy
Director, Professional Experience Programs
Supervisor, USC Safety-Net Clinical Pharmacy
Titus Family Department of Clinical Pharmacy
University of Southern California School of Pharmacy
Los Angeles, California

Kellie Jones Weddle, PharmD

Clinical Professor of Pharmacy Practice
Purdue University College of Pharmacy
Indianapolis, Indiana

C. Michael White, PharmD

Distinguished Professor
Department of Pharmacy Practice
University of Connecticut School of Pharmacy
Storrs, Connecticut

Barbara S. Wiggins, PharmD

Clinical Pharmacy Specialist—Cardiology Medicine
Department of Pharmacy Services
Medical University of South Carolina
Charleston, South Carolina

Kristine C. Willett, PharmD

Professor of Pharmacy Practice
School of Pharmacy—Manchester
Massachusetts College of Pharmacy and Health Sciences
Manchester, New Hampshire

Casey B. Williams, PharmD

Chief Scientific Officer and Executive Director of Cancer Research
Avera McKennan Hospital and University Health Center
Sioux Falls, South Dakota

Dennis M. Williams, PharmD

Associate Professor
Division of Pharmacotherapy and Experimental Therapeutics
UNC Eshelman School of Pharmacy
Chapel Hill, North Carolina

Adrian Wong, PharmD, MPH, FCCM, BCCCP

Adjunct Associate Professor
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Chelsea Wong, PharmD
Clinical Pharmacy Specialist
The University of Texas MD Anderson Cancer Center
Houston, Texas

Annie Wong-Beringer, PharmD
Professor of Pharmacy
Associate Dean for Research
Department of Clinical Pharmacy
University of Southern California School of Pharmacy
Los Angeles, California

Dinesh Yogaratnam, PharmD
Associate Professor of Pharmacy Practice
School of Pharmacy—Worcester
Massachusetts College of Pharmacy and Health Sciences
Worcester, Massachusetts

Kathy Zaiken, PharmD
Professor of Pharmacy Practice
Director, International Pharmacy Residency Program
School of Pharmacy—Boston
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Caroline S. Zeind, PharmD
Vice President for Academic Affairs/Provost
Professor of Pharmacy Practice
Academic Affairs
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Kristin M. Zimmerman, PharmD
Associate Professor
Department of Pharmacotherapy & Outcomes Sciences

ALGrawany

Virginia Commonwealth University
Richmond, Virginia

Brief Table of Contents

Preface
Acknowledgments
Additional Resources
Section Editors
Contributors
Detailed Table of Contents

VOLUME ONE

SECTION 1: GENERAL PRINCIPLES

Section Editors: Mary G. Amato and Maria Kostka-Rokosz

1 Medication Therapy Management and Assessment of Therapy
Matthew R. Machado, Joseph W. Ferullo, and Amee Mistry

2 Interpretation of Clinical Laboratory Tests

Erika Felix-Getzik, Yulia A. Murray, and Stefanie C. Nigro

3 Drug Interactions
Michelle Ceresia, Caroline S. Zeind, John Fanikos, and Michael G. Carvalho

4 Pharmacogenomics and Personalized Medicine
Hyun Kim, Shannon F. Manzi, Laura Chadwick, and Jonathan Picker

5 Managing Drug Overdoses and Poisonings
Iris Sheinhait

6 End-of-Life Care
Victoria F. Ferraresi and Mary Mihalyo

7 Interprofessional Practice and Education
Michael G. Carvalho, Edith Claros, Christopher K. Cooper, and Kaelen C. Dunican

SECTION 2: CARDIAC AND VASCULAR DISORDERS

Section Editors: Judy W. Cheng and Snehal H. Bhatt

8 Dyslipidemias, Atherosclerosis, and Coronary Heart Disease

Barbara S. Wiggins and Pamela Morris

9 Essential Hypertension
Judy W. Cheng

10 Peripheral Vascular Disorders
Snehal H. Bhatt

11 Thrombosis
Nancy L. Shapiro and Erika L. Hellenbart

12 Chronic Stable Angina
Angela M. Thompson and Toby C. Trujillo

13 Acute Coronary Syndrome
Brianne Dunn and Robert Lee Page II

14 Heart Failure
Harleen Singh and Joel C. Marrs

15 Cardiac Arrhythmias
C. Michael White and James S. Kalus

16 Hypertensive Crises
Sandeep Devabhakthuni, Ryan G. D'Angelo, and Michael Armahizer

17 Shock

Jason S. Haney and Carolyn M. Bell

SECTION 3: PULMONARY DISORDERS

Section Editors: Timothy R. Hudd and Kathy Zaiken

18 Asthma
Cary R. Chrisman and Christopher K. Finch

19 Chronic Obstructive Pulmonary Disease
Timothy R. Hudd and Kathy Zaiken

20 Acute and Chronic Rhinitis
Suzanne Bollmeier and Dennis M. Williams

21 Cystic Fibrosis
Paul M. Beringer and Michelle Condren

SECTION 4: GASTROINTESTINAL DISORDERS

Section Editor: Carrie A. Sincak

22 Nausea and Vomiting
Lisa M. DiGrazia and J. Todd Carter

23 Upper Gastrointestinal Disorders
Elaine J. Law and Ricky B. Thumar

24 Lower Gastrointestinal Disorders

Charmaine Rochester-Eyeguokan, Divita Singh, and Abigail Klutts

25 Complications of End-Stage Liver Disease
Yasar O. Tasnif and Mary F. Hebert

SECTION 5: RENAL DISORDERS

Section Editors: Susan A. Krikorian and Oussayma Moukhachen

26 Acid–Base Disturbances
Mary P. Kovacevic, Jeremy R. DeGrado, and Kevin E. Anger

27 Fluid and Electrolyte Disorders
Priscilla P. How and Alan H. Lau

28 Chronic Kidney Disease
Adinoyi Garba

29 Acute Kidney Injury
Susan A. Krikorian, Oussayma Moukhachen, and Alexander H. Flannery

30 Dialysis Treatment for Chronic Kidney Failure
Michelle M. Richardson

31 Dosing of Drugs in Kidney Failure

David J. Quan

SECTION 6: IMMUNOLOGIC DISORDERS

Section Editor: Steven Gabardi

32 Drug Hypersensitivity Reactions
Mariana C. Castells, Kathleen Marquis, and Kylie Marie Besz

33 Systemic Lupus Erythematosus
Jerika T. Lam, Ann M. Lynch, and Mary A. Gutierrez

34 Kidney and Liver Transplantation
David J. Taber, Robert E. Dupuis, Nicole A. Pilch, and Kristen Szempruch

SECTION 7: NUTRITION ISSUES

Section Editors: R. Rebecca Couris and Susan L. Mayhew

35 Basics of Nutrition and Patient Assessment
Margaret K. Murphy, Leigh Furman, and Kathleen M. Gura

36 Obesity
Kaelen C. Dunican and Aimee Dawson

37 Adult Enteral Nutrition
Carol J. Rollins

38 Adult Parenteral Nutrition
Susan L. Mayhew and Richard S. Nicholas

SECTION 8: DERMATOLOGIC DISORDERS

Section Editor: Katie Kiser

39 Dermatotherapy and Drug-Induced Skin Disorders
Daniel R. Malcom and Lynn Z. Fuller

40 Acne
Jamie J. Cavanaugh and Kelly A. Mullican

41 Psoriasis
Rachel C. Long and Kelly A. Mullican

42 Photosensitivity, Photoaging, and Burn Injuries
Molly E. Howard

SECTION 9: RHEUMATIC AND MUSCULOSKELETAL DISEASES

Section Editor: Kamala M. Nola

43 Osteoarthritis

Dominick P. Trombetta and Christopher M. Herndon

44 Rheumatoid Arthritis
Janet S. Cho and Ying Wang

45 Gout and Hyperuricemia
Troy Lynn Lewis and Kimmy Nguyen

46 Connective Tissue Disorders
Steven S. Kheloussi, Julie L. Olenak, and Jonathan D. Ference

SECTION 10: WOMEN'S HEALTH

Section Editor: Trisha LaPointe

47 Contraception
Shareen El-Ibiary

48 Infertility
Erin C. Raney

49 Obstetric Drug Therapy
Trisha LaPointe

50 Disorders Related to the Menstrual Cycle
Laura M. Borgelt and Karen M. Gunning

51 The Transition Through Menopause
Louise Parent-Stevens and Trisha LaPointe

SECTION 11: ENDOCRINE DISORDERS

Section Editors: Jennifer D. Goldman and David Schnee

52 Thyroid Disorders
Eric F. Schneider and Kamaria K. Brown

53 Diabetes Mellitus
Jennifer D. Goldman, Nikhil A. Sangave, and David Schnee

VOLUME TWO

SECTION 12: EYE DISORDERS

Section Editor: Susan Jacobson

54 Eye Disorders
Katherine Carey and Bridget C. Hendricks

SECTION 13: NEUROLOGIC DISORDERS

ALGrawany

Section Editors: Michele Matthews and Adrian Wong

55 Pain and Its Management
Virginia Ghafoor, Lee A. Kral, and Timothy J. Atkinson

56 Care of the Critically Ill Adult
Philip Grgurich, Adrian Wong, and John Marshall

57 Multiple Sclerosis
Melody Ryan

58 Headache
Steven J. Crosby

59 Parkinson Disease and Other Movement Disorders
Shedrick Martin and Kimberly Tallian

60 Seizure Disorders
Sulaiman Almohaish, Melissa Sandler, Nicole E. Omecene, and Gretchen M. Brophy

61 Acute Ischemic and Hemorrhagic Stroke
Oussayma Moukhachen and Philip Grgurich

SECTION 14: INFECTIOUS DISEASES

Section Editors: Dorothea Rudorf, G. Christopher Wood, and Caroline S. Zeind

62 Principles of Infectious Diseases
Joshua A. Garcia and B. Joseph Guglielmo

63 Antimicrobial Prophylaxis for Surgical Procedures
Daniel J. G. Thirion

64 Vaccinations
Molly G. Minze and Katie D. Ellis

65 Central Nervous System Infections
Deanna J. Buehrle and Gregory A. Eschenauer

66 Endocarditis
Annie Wong-Beringer, Rachid Douglas-Louis, and Emi Minejima

67 Respiratory Tract Infections
Jason Cross, Evan Horton, and Dinesh Yogaratnam

68 Tuberculosis
Michael B. Kays

69 Infectious Diarrhea
Rupali Jain and David T. Bearden

70 Intra-Abdominal Infections
Christie M. Bertram and Sheila K. Wang

71 Urinary Tract Infections
Douglas N. Fish

72 Sexually Transmitted Diseases
Albert Bach, Anne Walsh, and Karl M. Hess

73 Osteomyelitis and Septic Arthritis
Jacqueline L. Olin, Linda M. Spooner, and Karyn M. Sullivan

74 Skin and Soft Tissue Infections
Cheryl R. Durand and Kristine C. Willett

75 Prevention and Treatment of Infections in Neutropenic Cancer Patients
Richard H. Drew and Steven W. Johnson

76 Pharmacotherapy of Human Immunodeficiency Virus Infection
Aaron S. Devanathan, Allison E. Symonds, Jessica L. Adams, and Mackenzie L. Cottrell

77 Opportunistic Infections in Patients Living With HIV
Emily L. Heil and Amanda H. Corbett

78 Fungal Infections
John Cleary and Russell E. Lewis

79 Viral Infections
Sandra Benavides, Neeta Bahal O'Mara, and Milap C. Nahata

80 Viral Hepatitis
Jerika T. Lam and Amy Kang

81 Parasitic Infections
Sheila M. Seed, Janelle I. Herren, Samar E. Nicolas, Larry Goodyer, and Caroline S. Zeind

82 Tick-Borne Diseases
Caroline S. Zeind, Michelle Ceresia, and Lin H. Chen

SECTION 15: PSYCHIATRIC DISORDERS AND SUBSTANCE ABUSE

Section Editors: Michael C. Angelini and Michael G. Carvalho

83 Anxiety Disorders
Tamara Bystrak and Amanda Eloma

84 Sleep Disorders
Devon A. Sherwood and Anna K. Morin

85 Schizophrenia
Richard J. Silvia, Robert L. Dufresne, and Justin C. Ellison

86 Depressive Disorders
Michael C. Angelini

87 Bipolar Disorders
Megan J. Ehret and Charles F. Caley

88 Developmental Disorders
Kimberly Lenz and Neha Kashalikar

89 Attention-Deficit Hyperactivity Disorder in Children, Adolescents, and Adults
Michael C. Angelini and Joel Goldstein

90 Substance Use Disorders
Swati Betharia and Michael C. Angelini

91 Tobacco Use and Dependence
Andrea S. Franks and Sarah E. McBane

SECTION 16: HEMATOLOGY AND ONCOLOGY

Section Editor: Christy S. Harris

92 Anemias
Cindy L. O'Bryant, Kate Deen Taucher, and Lisa A. Thompson

93 Neoplastic Disorders and Their Treatment: General Principles
Michael Frei, Donyika Joseph, Kaiwen Wang, and Chelsea Wong

94 Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents
Victoria Nachar and Matthew Newman

95 Pediatric Malignancies
M. Brooke Bernhardt and Nicole A. Kaiser

96 Adult Hematologic Malignancies
Casey B. Williams, Rachel Elsey, Sarah M. Hayes, and Jacob K. Kettle

97 Breast Cancer
Kellie Jones Weddle

98 Lung Cancer

Maryann R. Cooper

99 Colorectal Cancer
Marlo Blazer and Joshua Reardon

100 Prostate Cancer
Marina D. Kaymakcalan and Christy S. Harris

101 Hematopoietic Stem Cell Transplantation
Valerie Relias

SECTION 17: PEDIATRICS

Section Editor: Elizabeth Anne Farrington

102 Pediatric Pharmacotherapy
Elizabeth Anne Farrington

103 Pediatric Fluid, Electrolytes, and Nutrition
Jennifer W. Chow and Lisa M. Feagin

104 Common Pediatric Illnesses
Chephra McKee and Gildon Brooke

105 Neonatal Therapy
Jennifer T. Pham and Kirsten H. Ohler

106 Care of the Critically Ill Child

Elizabeth Anne Farrington

SECTION 18: GERIATRIC THERAPY

Section Editor: Judith L. Beizer

107 Geriatric Drug Use
Suzanne Dinsmore, Mary-Kathleen Grams, and Kristin M. Zimmerman

108 Geriatric Neurocognitive Disorders
Nicole J. Brandt and Stephanie M. Ozalas

109 Geriatric Urologic Disorders
Jaini Patel

110 Osteoporosis
Mary-Kathleen Grams, R. Rebecca Couris, and Suzanne Dinsmore

Drug Index
Subject Index

Detailed Table of Contents

Preface
Acknowledgments
Additional Resources
Section Editors
Contributors
Brief Table of Contents

VOLUME ONE

SECTION 1: GENERAL PRINCIPLES

Section Editors: *Mary G. Amato* and Maria Kostka-Rokosz

1 Medication Therapy Management and Assessment of Therapy
Matthew R. Machado, Joseph W. Ferullo, and Amee Mistry

Introduction
Sources of Patient Information

Effective Communication and the Patient Interview
Obtaining a Patient History
Approach to and Assessment of Patient Therapy
Medication Therapy Management Services in the Community Pharmacy or Ambulatory Setting
Medication Therapy Management in the Acute Care Setting
Medication Therapy Management and Pharmacogenomics
Conclusion
Acknowledgments
Key References and Websites

2 Interpretation of Clinical Laboratory Tests
Erika Felix-Getzik, Yulia A. Murray, and Stefanie C. Nigro

Introduction
General Principles
Fluids and Electrolytes
Multichemistry Panels
Proteins
Cardiac Markers
Liver Function Tests
Miscellaneous Tests
Hematology
Urinalysis
Therapeutic Drug Monitoring
Patient-Directed Monitoring and Testing
Key References and Websites

3 Drug Interactions

ALGrawany

Michelle Ceresia, Caroline S. Zeind, John Fanikos, and Michael G. Carvalho

Introduction
Definition
Risk Factors for Drug Interactions
Mechanisms of Drug Interactions
Management of Drug Interactions
Resources and Evidence for Clinical Decision Support
Conclusion
Key References and Websites

4 Pharmacogenomics and Personalized Medicine
Hyun Kim, Shannon F. Manzi, Laura Chadwick, and Jonathan Picker

Introduction
Pharmacokinetic Implications
Pharmacodynamic Implications
Implications in Acute Toxicity
Drug Target Implications
Nonmetabolic Implications
CYP2D6 Peculiarities
Impact of Pediatric Enzyme Development on Pharmacogenomics
Familial Implications of Pharmacogenetics
Making the Case for Pharmacogenomics
Conclusion
Key References and Websites

5 Managing Drug Overdoses and Poisonings
Iris Sheinhait

Introduction
General Management
Assessment of Salicylate Ingestion
Assessment of Iron Ingestion
Assessment of Central Nervous System Depressant Versus Antidepressant Ingestion
Assessment of Acetaminophen Ingestion
Conclusion
Key References and Websites

6 End-of-Life Care
Victoria F. Ferraresi and Mary Mihalyo

Introduction
Symptom Management
Key References and Websites

7 Interprofessional Practice and Education
Michael G. Carvalho, Edith Claros, Christopher K. Cooper, and Kaelen C. Dunican

Introduction
Core Interprofessional Education Competencies
Interprofessional Education Terminology
Interprofessional Education Models
Incorporating Interprofessional Education Into the Curriculum

Interprofessional Education Guidance Document
Interprofessional Education: Future Directions and Resources
Key References and Websites

SECTION 2: CARDIAC AND VASCULAR DISORDERS

Section Editors: Judy W. Cheng and Snehal H. Bhatt

8 Dyslipidemias, Atherosclerosis, and Coronary Heart Disease
Barbara S. Wiggins and Pamela Morris

Introduction
Lipid Metabolism
Abnormalities in Lipid Metabolism
Lipoproteins and Atherosclerotic Cardiovascular Disease Risk
Clinical Evaluation and Management of Atherosclerotic Cardiovascular Disease Risk
Pharmacologic Therapy
Key References

9 Essential Hypertension
Judy W. Cheng

Introduction
Clinical Evaluation

Principles of Treatment
Hypertension Management
Clinical Scenarios
Key References and Websites

10 Peripheral Vascular Disorders
Snehal H. Bhatt

Introduction
Raynaud Phenomenon
Key References and Websites

11 Thrombosis
Nancy L. Shapiro and Erika L. Hellenbart

Introduction
Deep Vein Thrombosis
Pulmonary Embolism
Prevention of Cardiogenic Thromboembolism
Bridge Therapy
Drug Interactions
Key References

12 Chronic Stable Angina
Angela M. Thompson and Toby C. Trujillo

Introduction
Overview of Drug and Nondrug Therapy
Clinical Presentation of Chronic Stable Angina
Revascularization

Variant Angina (Coronary Artery Spasm)
Microvascular Angina
Key References and Websites

13 Acute Coronary Syndrome
Brianne Dunn and Robert Lee Page II

Introduction
Overview of Drug and Nondrug Therapy
Clinical Presentation of Acute Coronary Syndrome
Treatment for ST-Segment Elevation Myocardial Infarction
Treatment for Unstable Angina or Non–ST-Segment Elevation Myocardial Infarction
Long-Term Therapy
Lifestyle Modifications
Summary
Key References and Websites

14 Heart Failure
Harleen Singh and Joel C. Marrs

Introduction
Patient Evaluation
Treatment
Heart Failure With Preserved Ejection Fraction
Key References

15 Cardiac Arrhythmias
C. Michael White and James S. Kalus

Introduction

Electrophysiology
Supraventricular Arrhythmias
Conduction Blocks
Ventricular Arrhythmias
Cardiopulmonary Arrest
Key References and Websites

16 Hypertensive Crises
Sandeep Devabhakthuni, Ryan G. D'Angelo, and Michael Armahizer

Introduction
Clinical Presentation of Hypertensive Urgency
Clinical Presentation of Hypertensive Emergency
Overview of Treatment
Hypertensive Urgencies
Hypertensive Emergencies
Key References and Websites

17 Shock
Jason S. Haney and Carolyn M. Bell

Introduction
Causes
Pathophysiology
Clinical Presentation and Diagnosis
Treatment Overview
Hemodynamic Monitoring
Etiologic Classification of Shock and Common Mechanisms

Hypovolemic Shock
Cardiogenic Shock
Distributive Shock
Key References and Websites

SECTION 3: PULMONARY DISORDERS

Section Editors: Timothy R. Hudd and Kathy Zaiken

18 Asthma
Cary R. Chrisman and Christopher K. Finch

Introduction
Chronic Asthma
Exercise-Induced Bronchoconstriction
Drug-Induced Asthma
Nocturnal Asthma
Patient Education
Outcomes
Nondrug Options
Acknowledgment
Key References and Websites

19 Chronic Obstructive Pulmonary Disease
Timothy R. Hudd and Kathy Zaiken

Introduction
Diagnosis and Patient Assessment
General Management Considerations
Pharmacotherapy

Initial Pharmacologic Therapy by Disease Severity
Chronic Obstructive Pulmonary Disease Exacerbation
Chronic Obstructive Pulmonary Disease Group A (Low Risk, Less Symptoms)
Chronic Obstructive Pulmonary Disease With Disease Progression
Chronic Obstructive Pulmonary Disease With Disease Progression
Key References and Websites

20 Acute and Chronic Rhinitis
Suzanne Bollmeier and Dennis M. Williams

Introduction
Causes and Classifications
Epidemiology and Impact
Anatomy and Physiology
Etiology of Allergic Rhinitis
Pathophysiology
Clinical Presentation and Assessment of Rhinitis
Overview of Treatment
Specific Therapeutic Options
Drug-Induced Nasal Congestion: Rhinitis Medicamentosa
Idiopathic Rhinitis
Mixed Allergic–Nonallergic Rhinitis
Summary
Key References

21 Cystic Fibrosis
Paul M. Beringer and Michelle Condren

Introduction
Genetic Basis
Clinical Manifestations
Diagnosis
Early Interventions and Therapy
Lung Transplantation
Key References and Websites

SECTION 4: GASTROINTESTINAL DISORDERS

Section Editor: Carrie A. Sincak

22 Nausea and Vomiting
Lisa M. DiGrazia and J. Todd Carter

Introduction
Epidemiology and Clinical Presentation
Pathophysiology
Diagnosis
Motion Sickness
Chemotherapy-Induced Nausea and Vomiting
Radiation-Induced Nausea and Vomiting
Postoperative Nausea and Vomiting
Key References

23 Upper Gastrointestinal Disorders
Elaine J. Law and Ricky B. Thumar

Introduction
Physiology of the Upper Gastrointestinal Tract

Pharmacotherapy of Drugs Used to Treat Acid-Related Disorders
Dyspepsia
Peptic Ulcer Disease
***Helicobacter Pylori*–Related Peptic Ulcer**
Nonsteroidal Anti-Inflammatory Drug–Induced Peptic Ulcer
Zollinger–Ellison Syndrome
Gastroesophageal Reflux Disease
Upper Gastrointestinal Bleeding
Key References

24 Lower Gastrointestinal Disorders
Charmaine Rochester-Eyeguokan, Divita Singh, and Abigail Klutts

Introduction
Ulcerative Colitis
Irritable Bowel Syndrome
Key References

25 Complications of End-Stage Liver Disease
Yasar O. Tasnif and Mary F. Hebert

Introduction
Pathogenesis of Cirrhosis
Complications of Cirrhosis
Ascites
Esophageal Varices
Hepatic Encephalopathy
Hepatorenal Syndrome

ALGrawany

Key References

SECTION 5: RENAL DISORDERS

Section Editors: Susan A. Krikorian and Oussayma Moukhachen

26 Acid–Base Disturbances
Mary P. Kovacevic, Jeremy R. DeGrado, and Kevin E. Anger

Introduction
Normal Acid–Base Physiology
Stepwise Approach to the Evaluation of Simple Acid–Base Disturbances
Metabolic Acidosis
Metabolic Alkalosis
Respiratory Disturbances
Key References

27 Fluid and Electrolyte Disorders
Priscilla P. How and Alan H. Lau

Introduction
Disorders in Volume Regulation
Sodium Disorders
Potassium
Calcium
Phosphorus
Magnesium

Key References

28 Chronic Kidney Disease
Adinoyi Garba

Introduction
Clinical Assessment of Kidney Function
Complications of Chronic Kidney Disease
Prevention of Chronic Kidney Disease and Its Progression
Diabetic Kidney Disease
Fluid and Electrolyte Complications
Anemia of Chronic Kidney Disease
Cardiovascular Complications
Mineral and Bone Disorders
Other Complications of Chronic Kidney Disease
Glomerular Diseases
Drug-Induced Causes of Chronic Kidney Disease
Key References and Websites

29 Acute Kidney Injury
Susan A. Krikorian, Oussayma Moukhachen, and Alexander H. Flannery

Introduction
Epidemiology
Prognosis
Pathogenesis
Clinical Evaluation
Prerenal and Functional Acute Kidney Injury
Intrinsic Acute Kidney Injury

Supportive Management of Acute Kidney Injury
Key References and Websites

30 Dialysis Treatment for Chronic Kidney Failure
Michelle M. Richardson

Introduction
General Principles of Dialysis
Hemodialysis
Peritoneal Dialysis
Key References and Websites

31 Dosing of Drugs in Kidney Failure
David J. Quan

Introduction
Pharmacokinetics and Pharmacodynamics of Specific Drugs in Kidney Failure
Effect of Kidney Failure on Metabolized Drugs
Assessing Kidney Function in the Elderly
Summary
Key References and Websites

SECTION 6: IMMUNOLOGIC DISORDERS

Section Editor: Steven Gabardi

32 Drug Hypersensitivity Reactions
Mariana C. Castells, Kathleen Marquis, and Kylie Marie Besz

Introduction
Definition
Pathogenesis
Predisposing Factors
Diagnosis
Generalized Reactions
Organ-Specific Reactions
Non-IgE Reactions
Prevention and Management of Allergic Reactions
Key References

33 Systemic Lupus Erythematosus
Jerika T. Lam, Ann M. Lynch, and Mary A. Gutierrez

Introduction
Epidemiology
Pathophysiology
Classification Criteria
Clinical Presentation
Diagnosis
Pharmacologic and Nonpharmacologic Treatments
Drug-Induced Lupus Erythematosus
Investigational Agents
Treatment Approaches
Role of Pharmacists
Key References and Websites

34 Kidney and Liver Transplantation

David J. Taber, Robert E. Dupuis, Nicole A. Pilch, and Kristen Szempruch

Introduction
Transplantation Immunology
Immunosuppressive Agents and Mechanism of Action
Kidney Transplantation
Liver Transplantation
Key References and Websites

SECTION 7: NUTRITION ISSUES

Section Editors: R. Rebecca Couris and Susan L. Mayhew

35 Basics of Nutrition and Patient Assessment
Margaret K. Murphy, Leigh Furman, and Kathleen M. Gura

Introduction
Nutrition Basics
Malnutrition
Nutrition Screening and Assessment
Patient Assessment: Male With Ulcerative Colitis
Acknowledgements
Key References and Websites

36 Obesity
Kaelen C. Dunican and Aimee Dawson

Introduction
Definitions
Epidemiology
Etiology and Pathophysiology
Clinical Features
Assessment and Treatment
Key References and Websites

37 Adult Enteral Nutrition
Carol J. Rollins

Introduction
Patient Selection and Route of Feeding
Feeding Tube Placement and Site of Formula Delivery
Formula Selection
Initiation of Feedings
Transition From Continuous to Intermittent/Bolus Feeding
Fluid Provision
Nutrition in Critical Illness
Immune-Modulating Formulas
Pulmonary Disease
Renal Failure
Monitoring Enteral Nutrition Support
Medications and Nutrition by Enteral Access Device
Key References and Websites

38 Adult Parenteral Nutrition
Susan L. Mayhew and Richard S. Nicholas

Introduction

Vascular Access
Components of Parenteral Nutrient Formulations
Parenteral Nutrition
Key References and Websites

SECTION 8: DERMATOLOGIC DISORDERS

Section Editor: Katie Kiser

39 Dermatotherapy and Drug-Induced Skin Disorders
Daniel R. Malcom and Lynn Z. Fuller

Introduction
Dermatologic Drug Delivery Systems
Patient Assessment
Topical Corticosteroids
Allergic Contact Dermatitis: Poison Ivy, Poison Oak, or Poison Sumac
Drug Eruptions
Key References and Websites

40 Acne
Jamie J. Cavanaugh and Kelly A. Mullican

Introduction
Pathophysiology
Clinical Presentation
Diagnosis
Overview of Therapy

Comedonal Acne
Maculopapular Acne
Nodular Acne
Key References and Websites

41 Psoriasis
Rachel C. Long and Kelly A. Mullican

Introduction
Treatment of Mild-to-Moderate Psoriasis
Treatment of Moderate-to-Severe Psoriasis
Key References and Websites

42 Photosensitivity, Photoaging, and Burn Injuries
Molly E. Howard

Introduction
Photoaging
Burn Injuries
Key References and Websites

SECTION 9: RHEUMATIC AND MUSCULOSKELETAL DISEASES

Section Editor: Kamala M. Nola

43 Osteoarthritis
Dominick P. Trombetta and Christopher M. Herndon

Introduction
Etiology
Pathogenesis
Overview of Drug Therapy
Clinical Manifestations
Treatment of Osteoarthritis
Key References and Websites

44 Rheumatoid Arthritis
Janet S. Cho and Ying Wang

Introduction
Etiology
Pathophysiology
Extra-Articular Manifestations and Complications
Juvenile Idiopathic Arthritis
Key References and Websites

45 Gout and Hyperuricemia
Troy Lynn Lewis and Kimmy Nguyen

Introduction
Acute Gout
Hyperuricemia
Pharmacist's Role
Key References

46 Connective Tissue Disorders
Steven S. Kheloussi, Julie L. Olenak, and Jonathan D. Ference

Introduction
Key References and Websites

SECTION 10: WOMEN'S HEALTH

Section Editor: Trisha LaPointe

47 Contraception
Shareen El-Ibiary

Introduction
Hormonal Contraception Background and Pharmacology
Combination Hormonal Contraceptives
Contraceptive Patch and Ring
Progestin-Only Contraceptives
Intrauterine Device and Intrauterine System
Other Nonhormonal Contraception
Emergency Contraception
Medical Abortion
Key References and Websites

48 Infertility
Erin C. Raney

Introduction
Pathophysiology and Diagnosis
Treatment Approaches
Key References and Websites

49 Obstetric Drug Therapy

ALGrawany

Trisha LaPointe

Introduction
Teratogenicity
Management of Conditions in Pregnancy
Urinary Tract Infections
Diabetes Mellitus
Hypertension and Preeclampsia
Drug Therapy Management in Labor and Delivery
Postpartum Hemorrhage
Prevention of Rh D Alloimmunization
Lactation
Drug Excretion in Human Milk
Acknowledgment
Key References and Websites
Medication Use in Pregnancy and Lactation
General Information

50 Disorders Related to the Menstrual Cycle
Laura M. Borgelt and Karen M. Gunning

Introduction
Polycystic Ovary Syndrome
Dysmenorrhea
Endometriosis
Premenstrual Syndrome and Premenstrual Dysphoric Disorder
Key References and Websites

51 The Transition Through Menopause

Louise Parent-Stevens and Trisha LaPointe

Introduction
Pathophysiology
Clinical Presentation
Key References and Websites

SECTION 11: ENDOCRINE DISORDERS

Section Editors: Jennifer D. Goldman and David Schnee

52 Thyroid Disorders
Eric F. Schneider and Kamaria K. Brown

Introduction
Thyroid Tests
Hypothyroidism
Hyperthyroidism
Drug-Induced Thyroid Disease
Key References and Websites

53 Diabetes Mellitus
Jennifer D. Goldman, Nikhil A. Sangave, and David Schnee

Introduction
Definition, Classification, and Epidemiology
Carbohydrate Metabolism
Type 1 Diabetes

Type 2 Diabetes
Gestational Diabetes Mellitus
Long-Term Complications
Relationship of Glycemic Control to Microvascular and Macrovascular Disease
Prevention of Type 1 and Type 2 Diabetes Mellitus
Treatment
Insulin
Treatment of Type 1 Diabetes: Clinical Use of Insulin
Diabetic Ketoacidosis
Treatment of Type 2 Diabetes: Antidiabetic Agents
Treatment of Patients With Type 2 Diabetes
Drug-Induced Alterations in Glucose Homeostasis
Acknowledgment
Key References and Websites

VOLUME TWO

SECTION 12: EYE DISORDERS

Section Editor: Susan Jacobson

54 Eye Disorders
Katherine Carey and Bridget C. Hendricks

Introduction
Ocular Anatomy and Physiology
Glaucoma
Primary Open-Angle Glaucoma

Angle-Closure Glaucoma
Ocular Side Effects of Drugs
Ocular Emergencies
Common Ocular Disorders
Ophthalmic Corticosteroids
Systemic Side Effects From Ophthalmic Medication
Ocular Nonsteroidal Anti-Inflammatory Drugs
Ocular Herpes Simplex Virus Infections
Age-Related Macular Degeneration
Acknowledgments
Key References and Websites

SECTION 13: NEUROLOGIC DISORDERS

Section Editors: Michele Matthews and Adrian Wong

55 Pain and Its Management
Virginia Ghafoor, Lee A. Kral, and Timothy J. Atkinson

Introduction
Low Back Pain
Neuropathic Pain
Functional Pain Syndromes
Key References and Websites

56 Care of the Critically Ill Adult
Philip Grgurich, Adrian Wong, and John Marshall

Introduction
Home Medications in the Intensive Care Unit
Pharmacokinetic Alterations in the Intensive Care Unit and Management Strategies
Interprofessional Care
Key References

57 Multiple Sclerosis
Melody Ryan

Introduction
Pathophysiology
Clinical Presentation
Diagnosis
Overview of Treatment
Key References and Websites

58 Headache
Steven J. Crosby

Introduction
Migraine Headache
Cluster Headache
Tension-Type Headache
Key References and Websites

59 Parkinson Disease and Other Movement Disorders
Shedrick Martin and Kimberly Tallian

Introduction
Restless Legs Syndrome and Periodic Limb Movements of Sleep
Essential Tremor
Key References

60 Seizure Disorders
Sulaiman Almohaish, Melissa Sandler, Nicole E. Omecene, and Gretchen M. Brophy

Introduction
Terminology, Classification, and Diagnosis of Epilepsies
Diagnosis
Treatment
Clinical Assessment and Treatment of Epilepsy
Absence Seizures
Generalized Tonic–Clonic Seizures Accompanying Absence Seizures
Acute Repetitive (Cluster) Seizures
Febrile Seizures
Skin Rash: Hypersensitivity Reactions to Antiseizure Drugs
Other Therapeutic Considerations
Status Epilepticus
Key References and Websites

61 Acute Ischemic and Hemorrhagic Stroke
Oussayma Moukhachen and Philip Grgurich

Introduction
Epidemiology

Pathophysiology
Clinical Presentation
General Treatment Principles
Acute Ischemic Stroke and Transient Ischemic Attack
Spontaneous Intracerebral Hemorrhage
Rehabilitation
Key References and Websites

SECTION 14: INFECTIOUS DISEASES

Section Editors: Dorothea Rudorf, G. Christopher Wood, and Caroline S. Zeind

62 Principles of Infectious Diseases
Joshua A. Garcia and B. Joseph Guglielmo

Introduction
Establishing the Presence of an Infection
Establishing the Severity of an Infection
Problems in the Diagnosis of an Infection
Establishing the Site of the Infection
Determining Likely Pathogens
Microbiologic Tests and Susceptibility of Organisms
Determination of Isolate Pathogenicity
Antimicrobial Toxicities
Antimicrobial Costs of Therapy
Route of Administration
Antimicrobial Dosing
Pharmacokinetics and Pharmacodynamics
Antimicrobial Failure

Key References

63 Antimicrobial Prophylaxis for Surgical Procedures
Daniel J. G. Thirion

Introduction
Determining Risk Factors for Infection
Classification of Surgical Site Infections
Optimizing Surgical Antimicrobial Prophylaxis
Key References and Websites

64 Vaccinations
Molly G. Minze and Katie D. Ellis

Introduction
Vaccine Principles
Guidelines
Inactivated Vaccines
Live Attenuated Vaccines
Administration Techniques
Legal Requirements
Key References and Websites

65 Central Nervous System Infections
Deanna J. Buehrle and Gregory A. Eschenauer

Introduction
Review of Central Nervous System
Meningitis

Brain Abscess
Treatment
Key References

66 Endocarditis
Annie Wong-Beringer, Rachid Douglas-Louis, and Emi Minejima

Introduction
Viridans Group *Streptococcus* Endocarditis
***Staphylococcus Epidermidis:* Prosthetic Valve Endocarditis**
***Staphylococcus Aureus* Endocarditis**
Enterococcal Endocarditis
Fungal Endocarditis Caused by *Candida Albicans*
Gram-Negative Bacillary Endocarditis Caused by *Pseudomonas Aeruginosa*
Culture-Negative Endocarditis
Prophylactic Therapy
Key References

67 Respiratory Tract Infections
Jason Cross, Evan Horton, and Dinesh Yogaratnam

Acute Bronchitis
Acute Exacerbation of Chronic Obstructive Pulmonary Disease
Prevention of Common Respiratory Infections by Vaccination
Community-Acquired Pneumonia

Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia
Key References and Websites

68 Tuberculosis
Michael B. Kays

Introduction
Treatment of Active Disease
Treatment of Latent Tuberculosis Infection
Adverse Drug Events
Special Treatment Considerations
Therapeutic Drug Monitoring
Key References and Websites

69 Infectious Diarrhea
Rupali Jain and David T. Bearden

Introduction
Definitions
Pathogenesis
Management Overview
Evaluation and Treatment of Patients With Infectious Diarrhea
Clinical Presentation
Viral Gastroenteritis
Vibrio Species
Staphylococcus Aureus, Bacillus Cereus,* and *Clostridium Perfringens
Cryptosporidium Parvum
Salmonella

Asymptomatic Stool Carriage
***Shigella* Species**
Campylobacter Jejuni
Travelers' Diarrhea
Postinfectious Complications of Traveler's Diarrhea
***Escherichia Coli* O157:H7**
***Clostridioides (Clostridium) Difficile* Infection**
Key References and Websites

70 Intra-Abdominal Infections
Christie M. Bertram and Sheila K. Wang

Introduction
Infections of the Biliary Tract
Primary Peritonitis
Secondary Peritonitis
Infections After Abdominal Trauma and Postoperative Complications
Duration of Antimicrobial Therapy
Key References

71 Urinary Tract Infections
Douglas N. Fish

Introduction
Lower Urinary Tract Infection
Treatment of Lower Tract Infection in Renal Failure
Recurrent Urinary Tract Infections
Asymptomatic Bacteriuria
Hospital-Acquired Acute Urinary Tract Infection
Prostatitis

Key References

72 Sexually Transmitted Diseases
Albert Bach, Anne Walsh, and Karl M. Hess

Introduction
Gonorrhea
Pelvic Inflammatory Disease
Complicated Gonorrhea
Chlamydia Trachomatis
Syphilis
Chancroid
Vaginitis
Genital Herpes
Genital Warts
Key References and Websites

73 Osteomyelitis and Septic Arthritis
Jacqueline L. Olin, Linda M. Spooner, and Karyn M. Sullivan

Introduction
Septic Arthritis
Key References and Websites

74 Skin and Soft Tissue Infections
Cheryl R. Durand and Kristine C. Willett

Introduction
Skin and Soft Tissue Infections

Erysipelas
Skin and Soft Tissue Infections in Diabetes
Animal Bite Wounds
Human Bite Wounds
Key References

75 Prevention and Treatment of Infections in Neutropenic Cancer Patients
Richard H. Drew and Steven W. Johnson

Introduction
Risk Factors for Infection
Most Common Pathogens
Stratification for Risk of Infection
Prophylaxis Against Infection
Infections in Neutropenic Cancer Patients
Empiric Antibiotic Therapy
Antibiotic Dosing, Administration, and Monitoring Considerations
Host Factors Influencing Response to Therapy
Modifying Initial Empiric Antibiotic Therapy
Antimicrobial Adjuvants
Key References and Websites

76 Pharmacotherapy of Human Immunodeficiency Virus Infection
Aaron S. Devanathan, Allison E. Symonds, Jessica L. Adams, and Mackenzie L. Cottrell

Introduction

Epidemiology
Pathophysiology
Pharmacotherapy
Diagnosis
Surrogate Marker Data
Antiretroviral Therapy
Resistance, Viral Genotyping, Phenotyping, and Viral Fitness
Special Circumstances
Keeping Current
Conclusion
Key References and Websites

77 Opportunistic Infections in Patients Living With HIV
Emily L. Heil and Amanda H. Corbett

Introduction
***Pneumocystis Jirovecii* Pneumonia**
***Toxoplasma Gondii* Encephalitis**
Cytomegalovirus Disease
Cryptococcosis
Mycobacterium Tuberculosis
***Mycobacterium Avium* Complex Disease**
Mucocutaneous Candidiasis
Acknowledgments
Key References and Websites

78 Fungal Infections
John Cleary and Russell E. Lewis

Introduction
Mycology
Antimycotics
Superficial and Cutaneous Mycoses
Subcutaneous Mycoses
Systemic Mycoses
Key References

79 Viral Infections
Sandra Benavides, Neeta Bahal O'Mara, and Milap C. Nahata

Introduction
Herpes Simplex Virus Infections
Varicella Zoster Infections
Influenza
Respiratory Syncytial Virus Infections
Hantavirus
West Nile Virus
Severe Acute Respiratory Syndrome
Middle East Respiratory Syndrome
Common Cold
Key References and Websites

80 Viral Hepatitis
Jerika T. Lam and Amy Kang

Introduction
Causative Agents and Characteristics
Hepatitis A Virus

Hepatitis B Virus
Hepatitis C Virus
Hepatitis D Virus
Hepatitis E Virus
Immunizations for Persons With Viral Hepatitis
Summary
Key References and Websites

81 Parasitic Infections
Sheila M. Seed, Janelle I. Herren, Samar E. Nicolas, Larry Goodyer, and Caroline S. Zeind

Introduction
Malaria
Amebiasis
Giardiasis
Enterobiasis
Cestodiasis
Pediculosis
Scabies
Acknowledgment
Key References and Websites

82 Tick-Borne Diseases
Caroline S. Zeind, Michelle Ceresia, and Lin H. Chen

Introduction
Lyme Disease
Erythema Migrans

Lyme Disease Treatment
Relapsing Fever
Other Bacterial Diseases: Tularemia
Rickettsia: Rocky Mountain Spotted Fever, *Rickettsia Parkeri* Infection, Ehrlichiosis, and Anaplasmosis
Protozoa: Babesiosis
Viruses: Colorado Tick Fever, Tick-Borne Encephalitis, and Other Virally Mediated Tick-Borne Diseases
Toxins: Tick Paralysis
Mixed Infections
Summary
Key References and Websites

SECTION 15: PSYCHIATRIC DISORDERS AND SUBSTANCE ABUSE

Section Editors: Michael C. Angelini and Michael G. Carvalho

83 Anxiety Disorders
Tamara Bystrak and Amanda Eloma

Introduction
Generalized Anxiety Disorder
Panic Disorder
Social Anxiety Disorder and Specific Phobias
Posttraumatic Stress Disorder and Acute Stress Disorder
Obsessive–Compulsive Disorder
Key References

84 Sleep Disorders
Devon A. Sherwood and Anna K. Morin

Introduction
Circadian Rhythm and Sleep Cycles
Neurochemistry of the Sleep–Wake Cycle
Insomnia
Insomnia in an Ill Patient
Insomnia and Psychiatric Disorders
Insomnia in the Elderly
Pediatric Insomnia
Pregnancy and Lactation
Sleep Apnea
Narcolepsy
Key References and Websites

85 Schizophrenia
Richard J. Silvia, Robert L. Dufresne, and Justin C. Ellison

Introduction
Epidemiology
Economic Burden
Etiology
Clinical Presentation
Treatment
Considerations in Specific Populations
Key References and Websites

86 Depressive Disorders

Michael C. Angelini

Introduction
Major Depressive Disorder
Drug Management
Key References and Websites

87 Bipolar Disorders
Megan J. Ehret and Charles F. Caley

Introduction
Clinical Assessment
Treatment of Acute Mania
Treatment of Acute Bipolar Depression
Maintenance Therapy of Bipolar Disorder
Key References and Websites

88 Developmental Disorders
Kimberly Lenz and Neha Kashalikar

Introduction
Epidemiology, Natural Course of the Disease, and Prognosis
Pathophysiology: Disease Etiology, Anatomy, and Physiology
Clinical Presentation
Diagnosis
Overview of Treatment
Repetitive Behaviors
Self-Injurious Behavior
Anxiety/Depression

Sleep
Key References

89 Attention-Deficit Hyperactivity Disorder in Children, Adolescents, and Adults
Michael C. Angelini and Joel Goldstein

Introduction
Epidemiology
Pathophysiology
Diagnosis, Signs, and Symptoms
Comorbidity and Prognosis
Treatment
Adults With Attention-Deficit Hyperactivity Disorder
Key References and Websites

90 Substance Use Disorders
Swati Betharia and Michael C. Angelini

Introduction
Opioids
Sedative-Hypnotics (Non-Ethanol Alcohol)
Central Nervous System Stimulants
Dissociative Drugs: Phencyclidine, Ketamine, and Dextromethorphan
Hallucinogens
Cannabinoids
Inhalants
Alcohol Use Disorders
Alcohol Toxicity

ALGrawany

Alcohol Withdrawal
Adjunctive Treatments
Pharmacotherapy of Alcohol Dependence
Disulfiram
Acamprosate
Naltrexone
Combination Pharmacotherapy
Key References and Websites

91 Tobacco Use and Dependence
Andrea S. Franks and Sarah E. McBane

Introduction
Epidemiology of Tobacco Use and Dependence
Pharmacotherapy for Treating Tobacco Use and Dependence
Key References and Websites

SECTION 16: HEMATOLOGY AND ONCOLOGY

Section Editor: Christy S. Harris

92 Anemias
Cindy L. O'Bryant, Kate Deen Taucher, and Lisa A. Thompson

Introduction
Iron Deficiency Anemia
Megaloblastic Anemias
Sickle Cell Anemia

Anemia of Inflammation
Key References

93 Neoplastic Disorders and Their Treatment: General Principles
Michael Frei, Donyika Joseph, Kaiwen Wang, and Chelsea Wong

Introduction
Treatment
Handling of Cytotoxic Drugs
Key References and Websites

94 Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents
Victoria Nachar and Matthew Newman

Introduction
Common and Acute Toxicities
Long-Term Complications of Anticancer Therapy
Key References and Websites

95 Pediatric Malignancies
M. Brooke Bernhardt and Nicole A. Kaiser

Introduction
Pediatric Solid Tumors
Acute Lymphoblastic Leukemia of Childhood
Pediatric Non-Hodgkin Lymphoma
Key References and Websites

96 Adult Hematologic Malignancies
Casey B. Williams, Rachel Elsey, Sarah M. Hayes, and Jacob K. Kettle

Introduction
Chronic Myelogenous Leukemia
Lymphoma
Key References

97 Breast Cancer
Kellie Jones Weddle

Introduction
Metastatic Breast Cancer
Key References

98 Lung Cancer
Maryann R. Cooper

Introduction
Acknowledgment
Key References and Websites

99 Colorectal Cancer
Marlo Blazer and Joshua Reardon

Introduction
Chemotherapy and Radiation for Early-Stage Rectal Cancer
Acknowledgment

Key References and Websites

100 Prostate Cancer
Marina D. Kaymakcalan and Christy S. Harris

Introduction
Pathophysiology
Clinical Presentation and Diagnosis
Overview of Treatment
Risk Factors
Screening
Prognostic Factors and Risk Stratification
Localized Disease
Recurrence and Progression
Metastatic Disease
Treatment Options for Advanced Disease
Adverse Effects of Prostate Cancer Therapy
Prevention
Survivorship
Key References and Websites

101 Hematopoietic Stem Cell Transplantation
Valerie Relias

Introduction
Autologous Hematopoietic Stem Cell Transplantation
Allogeneic Hematopoietic Stem Cell Transplantation
Complications Associated With Hematopoietic Stem Cell Transplantation
Graft-Versus-Host Disease
Infectious Complications

Issues of Survivorship After Hematopoietic Stem Cell Transplantation
Key References and Websites

SECTION 17: PEDIATRICS

Section Editor: Elizabeth Anne Farrington

102 Pediatric Pharmacotherapy
Elizabeth Anne Farrington

Introduction
Growth and Development During Childhood
Pediatric Pharmacokinetic Differences
Pediatric Pharmacodynamic Differences
Medication Dosing in Children
Preventing Medication Errors in Children
Increasing Availability of Pediatric Medication Information
Key References and Websites

103 Pediatric Fluid, Electrolytes, and Nutrition
Jennifer W. Chow and Lisa M. Feagin

Introduction
Fluid and Electrolyte Maintenance
Infant Enteral Nutrition
Key References and Websites

104 Common Pediatric Illnesses
Chephra McKee and Gildon Brooke

Introduction
Administering Medication to Children
Pediatric Care
Viral Gastroenteritis
Gastroesophageal Reflux
Common Pediatric Infections
Key References and Websites

105 Neonatal Therapy
Jennifer T. Pham and Kirsten H. Ohler

Introduction
Respiratory Distress Syndrome
Bronchopulmonary Dysplasia
Patent Ductus Arteriosus
Necrotizing Enterocolitis
Neonatal Sepsis and Meningitis
Congenital Infections
Apnea of Prematurity
Neonatal Seizures
Key References and Websites

106 Care of the Critically Ill Child
Elizabeth Anne Farrington

Introduction
Pediatric Cardiopulmonary Resuscitation
Respiratory Distress
Medications for Intubation and Mechanical Ventilation
Pediatric Shock

Sepsis and Septic Shock in Infants and Children
Initial Management of Pediatric Septic Shock
Cardiovascular Drug Therapy
Corticosteroid Administration in Pediatric Septic Shock
Adjunctive Therapies
Congenital Heart Disease
Pediatric Traumatic Brain Injury
Key References and Websites

SECTION 18: GERIATRIC THERAPY

Section Editor: Judith L. Beizer

107 Geriatric Drug Use
Suzanne Dinsmore, Mary-Kathleen Grams, and Kristin M. Zimmerman

Introduction
Age-Related Physiologic, Pharmacokinetic, and Pharmacodynamic Changes
Pharmacodynamic Changes
Problems Associated With Drug Use in Older Adults
Disease-Specific Geriatric Drug Therapy
Long-Term Care Facilities
Key References and Websites

108 Geriatric Neurocognitive Disorders
Nicole J. Brandt and Stephanie M. Ozalas

Introduction

Geriatric Dementias
Alzheimer Disease
Lewy Body Dementias
Vascular Dementia
Behavioral Disturbances in Dementia
Key References and Websites

109 Geriatric Urologic Disorders
Jaini Patel

Introduction
Benign Prostatic Hyperplasia
Sexual Dysfunction
Key References and Websites

110 Osteoporosis
Mary-Kathleen Grams, R. Rebecca Couris, and Suzanne Dinsmore

Introduction
Key References and Websites

Drug Index
Subject Index

SECTION 1

General Principles

Section Editors: Mary G. Amato and Maria Kostka-Rokosz

1

Medication Therapy Management and Assessment of Therapy

Matthew R. Machado, Joseph W. Ferullo, and Amee Mistry

CORE PRINCIPLES		CHAPTER CASES
1	Medication therapy management services (MTMS) are a service or group of services that optimize therapeutic outcomes for individual patients.	**Case 1-4 (Questions 1–4)**
2	A successful MTMS encounter includes medication reconciliation and a comprehensive medication history.	**Case 1-1 (Questions 1–3)**
3	Sources of patient information for MTMS include the patient, the electronic health record, the paper chart, and the pharmacy information system.	**Case 1-4 (Questions 1, 5), Table 1-1**
4	A careful and complete patient interview should include medical, medication, and	**Case 1-1 (Questions 1–3), Table 1-2, Online Content**

	social histories, and must be provided in a culturally sensitive manner.	
5	A successful MTMS encounter must be well documented following the problem-oriented medical record (POMR). Documentation involves collecting subjective and objective data to identify the primary problem.	**Case 1-2 (Question 1)** **Case 1-3 (Question 1)** **Case 1-4 (Question 1), Table 1-4**
6	The clinician must assess the drug therapy or disease-specific problem and create a treatment plan.	**Case 1-4 (Questions 1, 2)**
7	The final step in documenting the MTMS encounter is developing the medication action plan and processing any billing requirements.	**Case 1-4 (Questions 1, 2, 4)**
8	Accurate and complete communication of the MTMS encounter to the patient's health care team is vital.	**Case 1-4 (Question 3)**

INTRODUCTION

This chapter discusses medication therapy management services (MTMS) with a focus on the assessment of drug therapy. The illustrations in this chapter primarily focus on the pharmacist; however, the principles used to assess patient response to drug therapy are of value to all health care providers.

As defined by the American Pharmacists Association (APhA), *medication therapy management (MTM)* is a term used to describe a broad range of health care services provided by pharmacists, the medication experts on the health care team. A consensus definition created by 11 national pharmacy associations, adopted by the

pharmacy profession in 2004, defines MTM as a service or group of services that optimize therapeutic outcomes for individual patients.[1] Pharmacists provide MTM to help patients get the best benefits from their medications by actively managing drug therapy and identifying, preventing, and resolving medication-related problems.

When practiced in the outpatient setting, MTMS can be used to assess patient adherence to medications, identify potential drug duplications, and provide an overall counseling service for medication therapy. MTM allows pharmacists to decrease medication-related errors while also educating patients on their medication regimens. A pharmacist plays a vital role in a patient's therapy management and can help relay information to a physician. During MTMS services, a pharmacist has the opportunity to confirm the potential use and appropriateness of medication in relation to a specific disease state. The Pharmacists Patient Care Process (PPCP) may be utilized in such instances. The process's five steps include collect, assess, plan, implement, and follow-up: monitor and evaluate. By utilizing the PPCP tool, a pharmacist can provide well-rounded care to each individual based on their specific conditions and needs.[2]

MTMS provide a significant opportunity to optimize drug regimens and create patient-centered care. The utilization of such services is crucial to a pharmacist's role in the health care system. In addition to the therapeutic outcome benefits, there is the potential for a considerable financial benefit from conducting MTMS because these services are primarily focused on patients with multiple chronic conditions, which can pose a significant burden on our health care system. According to a study evaluating MTMS, it was observed that a 31% reduction in total health care expenditures occurred, resulting in a 12:1 savings to cost ratio.[2] Therefore, MTMS are a valuable tool that all pharmacists should utilize when necessary because they can provide a great therapeutic benefit and a potential reduction in health care costs.

MTM has a direct relationship to pharmaceutical care. Pharmaceutical care has been described as *the responsible provision of drug therapy to achieve definite outcomes that are*

intended to improve a patient's quality of life.[3,4] In fact, MTM has been described as a service provided in the practice of pharmaceutical care.[5] However, unlike pharmaceutical care, MTM is recognized by payers, has current procedural terminology (CPT) codes specifically for pharmacists, and has several clearly defined interventions. Therefore, MTMS will be the term used to describe the activity of MTM in various patient populations.

With the passage of the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act of 2010, pharmacists have tremendous opportunities in the implementation of health care reform.[6,7] One of the hallmarks of this law is delivery system reform. As health care delivery systems change, pharmacists have an opportunity to improve overall quality of care, to become involved in coordinated health care approaches such as medical home teams and accountable care organizations, and to collaborate to improve care for high-risk patients and those with chronic conditions in primary care settings. Chronic diseases are prevalent and costly in the United States. Approximately 133 million (or 45%) of all Americans suffer from at least one chronic condition, and the number is increasing. According to the Centers for Disease Control and Prevention (CDC), in the United States, chronic diseases account for 75% of health care spending, or $5300 per person annually.[8] These chronic conditions are often not singular in nature, with one in four adults having two or more chronic conditions, making treatment efforts even more challenging, and with that number expected to continue to rise over the next several years through the end of 2029.[9]

Pharmacists have additional opportunities because hospitals have financial incentives to improve quality, reduce costs, and decrease hospital-acquired conditions.[6,7] Both patient self-care and medication reconciliation are critical aspects of any MTMS encounter regardless of the setting (ie, inpatient, community, ambulatory, or institutional). Patient self-care requires the patient to take responsibility for the illness; however, the help of a professional to structure healthy self-care is important. For example, patients with diabetes who monitor their blood glucose levels regularly and adjust their diet according to

the guidelines published by the American Diabetes Association (ADA) would be practicing self-care. Self-care is often the work that the patient performs between visits with the provider. The patient should be involved in their own care to ensure the best outcomes.

Medication reconciliation is the comprehensive evaluation of a patient's medication regimen any time there is a change in therapy in an effort to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions, as well as to observe compliance and adherence patterns. This process should include a comparison of the existing and previous medication regimens and should occur at every transition of care in which new medications are ordered, existing orders are rewritten or adjusted, or when the patient has added nonprescription medications to their self-care.[10] Although not a new concept to the profession of pharmacy, there has been heightened awareness and intensified effort in this area of practice as a result of the Joint Commission. In 2005, the Joint Commission announced its National Patient Safety Goal (NPSG) 8A and 8B to *accurately and completely reconcile medications across the continuum of care*. This goal requires institutions to develop and test processes for medication reconciliation in ambulatory and acute care settings.[11] In 2015, the Joint Commission's NPSG 3 continued its focus on improving the safe use of medications, in particular by *maintaining and communicating accurate patient medical information.*[12] In 2020, the Joint Commission's NPSG 3 refined its focus even further, emphasizing recording and passing along correct information about a patient's medications, comparing past and present medication lists, providing written information about the patient's medications, and bringing up-to-date medication lists to all physician appointments.[13]

The Centers for Medicare & Medicaid Services (CMS), the largest purchaser of health insurance in the United States, is directly connecting reimbursement for Medicare services to patient outcomes. CMS developed star ratings as a means to move away from the pay-for-service model of health care and move toward a new quality-based model. CMS annually rates Medicare health plans on a scale of 1 to 5 stars, with 5 stars representing the highest

quality. The star ratings include measures across five broad categories: outcomes, intermediate outcomes, patient experience, access, and process.[14] For specific details and updates, visit https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/Downloads/2020-Star-Ratings-Fact-Sheet-.pdf.

It is important for pharmacists to realize that MTMS are integral to improving health outcomes and are continuing to gain acceptance from payers, in both the private and public sectors. The opportunity for pharmacists to continue to expand their role, while offering high-level care, along with the potential for improvement in pharmacy compensation is in line with the CMS star ratings.

The general approach to an MTMS patient encounter in various clinical settings is discussed in the next sections. **Figure 1-1** provides a visual representation of a systematic process for a comprehensive and effective approach for delivering MTMS.

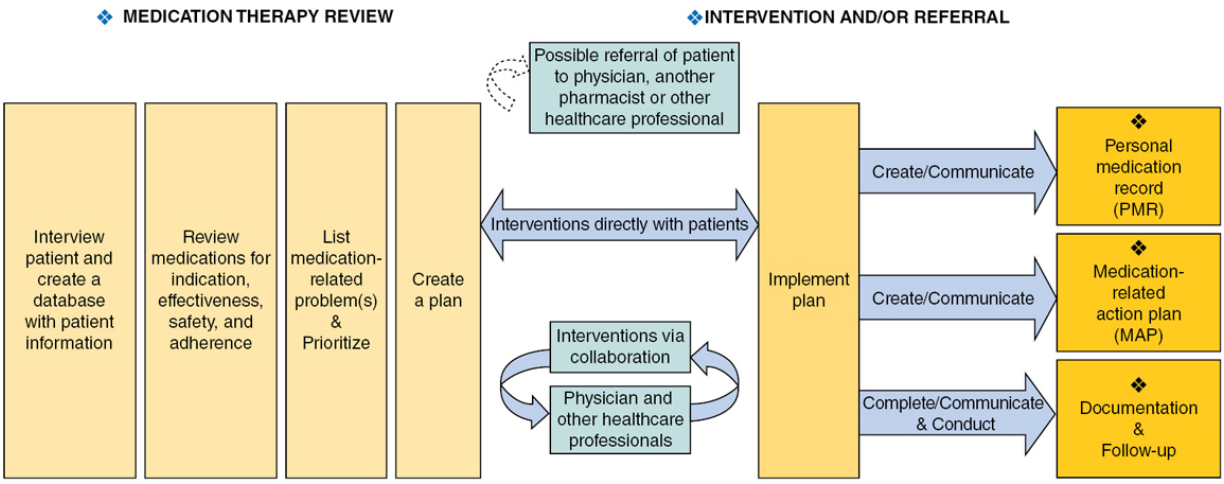


Figure 1-1 General approach to a medication therapy management services (MTMS) patient encounter. (Reprinted from American Pharmacists Association; National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core elements of an MTM service model (version 2.0). *J Am Pharm Assoc (2003)*. 2008;48(3):341–353. © 2008 American Pharmacists Association, with permission.)

SOURCES OF PATIENT INFORMATION

Successful patient assessment and monitoring requires gathering and organizing relevant information.[4,15] The patient, family member, or caregiver is always the primary source of information. The provider asks the patient a series of questions to obtain subjective information that is helpful in making a diagnosis or evaluating ongoing therapy. Likewise, providers without direct access to patient data must also obtain subjective data or measure objective physical data to guide recommendations for therapy and to monitor previously prescribed therapy.

Data-Rich and Data-Poor Environments

In a "data-rich environment," such as a hospital, long-term facility, or outpatient medical clinic, a wealth of information is available to practitioners from the medical record, pharmacy profile, and medication administration record (MAR). In these settings, physicians, nurses, other health care providers, and patients are readily available. This facilitates timely, effective communication among providers involved in the drug therapy decision-making process. Objective data (eg, diagnosis, physical examination, laboratory and other test results, vital signs, weight, medications, medication allergies, intravenous flow rates, and fluid balance) are readily available. The patient record provides information that is needed to identify and assess medical problems, which is necessary to design patient-specific care plans and document MTMS. In some settings, patient insurance information is important to help understand the formulary choices and access to medications.

In a "data-poor environment," such as a community pharmacy, clinicians are often required to make assessments with limited information. Although the information may be limited to (a) the medication profile, (b) patient demographic data, (c) medication allergy history, and (d) the patient's insurance coverage, it is still valuable.

The information in **Table 1-1** is an illustrative summary of sources of patient information.

Table 1-1
Sources of Patient Information

Data-Rich Environment	Data-Poor Environment

Paper Charts
▪ Decreasing use across the practice continuum
▪ Limitations
  ▪ Not consistent from site to site
  ▪ Difficult to access if more than one user
  ▪ Delays in data entry
Electronic Health Record (EHR)
▪ Electronic version of a paper chart
▪ Differs across practice settings
▪ One of the most complete sources of reliable information
▪ Can interface with other software systems in the pharmacy, laboratories, etc
▪ Data shared between systems in real time
	Pharmacy Information Systems (PIS)—Outpatient and Inpatient
	▪ Mainly focus on pharmacy billing, inventory management, production of medication labels
	▪ Limited documentation of clinical pharmacy

Pharmacy information systems (PIS) are generally considered data poor. Early PIS were established for pharmacy billing and inventory management. These initial systems provided medication fill lists, generated patient profiles, and produced medication labels that were valuable to institutional pharmacies as the profession moved toward a unit-dose medication distribution system. More modern functionalities allow for some limited documentation of clinical pharmacy activities, but the PIS are still considered to be data poor.

An initiative by the U.S. Department of Health and Human Services, called the *EHR Incentive Program*, exemplifies the importance of the integration of PIS with other computerized systems.[16] This initiative, the "Meaningful Use of an EHR," allows

Medicare and Medicaid to provide incentive payments to providers and hospitals for the “meaningful use” of certified health information technology products. Eligibility for these incentive payments involves transitioning PIS to a more data-rich clinical information system (CIS), which includes direct computerized physician order entry, clinical decision support, an electronic health record (EHR), an electronic medication administration record (eMAR), and integration of various information systems such as pharmacy and laboratory services. Additional functionality incorporates the use of barcode technology, which allows the ability to track and promote quality assurance during the medication administration process. Information generated by the CIS is electronically transmitted to the pharmacy in real time, eliminating lost, illegible, or incomplete medication orders.

In a data-poor environment, the clinician must be a proactive interviewer and may become an investigator. The investigative approach is direct and requires strong problem-solving abilities and active listening skills. Questions should be formulated to obtain information such as the medication history, actual medication use, patient perception of care, use of over-the-counter (OTC) and natural or herbal products, and health beliefs (cultural or otherwise). This approach can help verify and ensure the accuracy of other data sources. Clinicians should be mindful that not all patients are reliable historians, and some are poor sources of information. Even when the patient is a poor historian, the interview provides critical information (eg, indicator of poor adherence and need for a caregiver or interpreter) that cannot be obtained from other sources.

EFFECTIVE COMMUNICATION AND THE PATIENT INTERVIEW

The ability to use effective communication principles and history-taking skills is crucial to a successful patient interaction.[4,15] The importance of interviewing the patient, how to set the stage for the

interview, general interview rules, and the essential information to be obtained from the interview are outlined in **Table 1-2**. Information obtained from the patient is critical for assessment and planning in MTM.

Table 1-2
Interviewing the Patient

Importance of Interviewing the Patient
Establishes professional relationship with the patient to do the following: ▪ Obtain subjective data on medical problems. ▪ Obtain patient-specific information on drug efficacy and toxicity. ▪ Assess the patient's knowledge about, attitudes toward, and pattern of medication use. ▪ Formulate a problem list. ▪ Formulate plans for medication teaching and pharmaceutical care.
How to Set the Stage for the Interview ▪ Have the patient complete a written health and medication questionnaire, if available. ▪ Make the setting as private as possible. ▪ Maintain eye contact. ▪ Encourage the patient to be descriptive. ▪ Clarify by restatement or patient demonstration (eg, of a technique).
General Interview Rules ▪ Read the chart or patient profile first. ▪ Ask for the patient's permission to conduct an interview or make an appointment to do so. ▪ Begin with open-ended questions. ▪ Move to close-ended questions. ▪ Document interaction.
Information to Be Obtained ▪ History of allergies ▪ History of adverse drug reactions ▪ Weight and height ▪ Drugs: dose, route, frequency, and reason for use ▪ Perceived efficacy of each drug ▪ Perceived side effects

- Adherence to prescribed drug regimen
- Nonprescription medication use (including complementary and alternative medications)
- Possibility of pregnancy in females of childbearing age
- Family or other support systems

Source: Teresa O'Sullivan, PharmD, University of Washington.

Motivational interviewing (MI) is another useful method created by Miller and Rollnick that can be utilized during patient counseling to improve patient adherence to therapy. It is an empathetic and collaborative style of counseling based on five key principles: expressing empathy, developing discrepancy, adapting to resistance, avoiding arguments, and supporting self-efficacy, as seen in **Table 1-3**. The basis of MI is aimed at improving a patient's ambivalence to drug therapy through behavioral changes. It should be noted that MI does not require a long-standing pharmacist–patient relationship to be effective, because individual sessions have been shown to be helpful.[17,18]

Table 1-3
Principles of Motivational Interviewing

Expressing empathy	Convey to your patient that you understand their condition. This will allow the patient to be more open minded.
Develop discrepancy	Point out to the patient that there is a difference between current behavior and being able to reach their goals.
Adapt to resistance	Use different approaches to encourage the patient to channel their resistance into positive change.
Avoid arguments	Do not argue with your patient or force them to view things as you do.
Support self-efficacy	Assist the patient with believing that their own decisions will make a difference to behavioral change. Instead of telling the patient what to do, empower them to figure out what will be effective.

Sources: Adapted from Miller WR, Rollnick S. *Motivational Interviewing: Preparing People to Change Addictive Behavior.* Guilford Press; 1991. Center for Substance Abuse Treatment. Motivational interviewing as a counseling style. In: *Enhancing Motivation for Change in Substance Abuse Treatment*. Substance Abuse and

Mental Health Services Administration (US); 1999:chap 3. Treatment Improvement Protocol (TIP) Series, No. 35. http://www.ncbi.nlm.nih.gov/books/NBK64964/.

OBTAINING A PATIENT HISTORY

Those who provide MTMS should develop standardized forms to record patient information obtained from the patient interview. Standardization facilitates quick retrieval of information, minimizes the inadvertent omission of data, and enhances the ability of other practitioners to use shared records.[4,15]

The patient interview and record can be divided into sections with subjective and objective data as well as an assessment and plan (including expected outcomes). Components of subjective and objective data are the medical history, medication history, and social history. In some situations, histories can be supplemented by the generation of flowchart diagrams to monitor changes in specific variables with time. These charts and documentation systems may be incorporated into the EHR, PIS, or a similar electronic platform.

Medical History

A medical history is essential to the provision of MTMS. It can be as extensive as the medical records that are maintained in an institution or a physician's office, or it can be a simple patient profile that is maintained in a community pharmacy. The purpose of the medical history is to identify significant past medical conditions or procedures; identify, characterize, and assess current acute and chronic medical conditions and symptoms; and gather all relevant health information that could influence drug selection or dosing (eg, function of major organs such as the gastrointestinal tract, liver, and kidney; height and weight, including recent changes in either; age and sex; pregnancy and lactation status; and special nutritional needs). Not all interviews require the interviewer to ask for this much general information; however, in a data-poor environment, more

information is required directly from the patient. A more focused interview may be appropriate in settings in which the information required is available electronically or is specific to a single disease state.

CASE 1-1

QUESTION 1: P.J., a 45-year-old female of normal height and weight, states that she has diabetes.

What questions might the practitioner ask P.J. to determine whether type 1 or type 2 diabetes should be documented in her medical history?

Patients usually can enumerate their medical problems in a general way, but the practitioner often will have to probe more specifically to refine the diagnosis and assess the severity of the condition. Diabetes mellitus is used to illustrate the types of questions that can be used to gather important health information and assess drug therapy. The following questions should generate information that will help determine whether P.J. has type 1 or type 2 diabetes.

- How old were you when you were told you had diabetes?
- Do any of your relatives have diabetes? What do you know of their diabetes?
- Do you remember your symptoms? Please describe them to me.
- What medications have you used to treat your diabetes?

When questions such as these are combined with knowledge of the pathophysiology of diabetes, appreciation of the typical presenting signs and symptoms of the disease, and understanding of the drugs generally used to treat both forms of diabetes, meaningful MTM can be provided.

Medication History

In the community pharmacy setting, patients generally present themselves in one of four ways: (a) with a self-diagnosed condition

for which nonprescription drug therapy is sought, (b) with a newly diagnosed condition for which a drug has been prescribed, (c) with a chronic condition that requires a refill of a previously prescribed drug or the initiation of a new drug, or (d) upon referral from their health plan or provider, or self-referral for focused medication therapy review (MTR).

In the first and second situations, the practitioner must confirm the diagnosis using disease-specific questions, as illustrated in Case 1-1, Question 1. In the third situation, the practitioner uses the same type of questioning as in the first two situations; however, this time the practitioner needs to evaluate whether the desired therapeutic outcomes have been achieved. The practitioner must evaluate the information gleaned during follow-up visits in the context of the history and incorporate it into their assessment and medication action plan (MAP). In the fourth situation, in which patients require a focused MTR, the medication and medical history information are equally important. Without the medical history, it is not possible to evaluate whether the drug therapy is appropriate, and without an accurate medication history, it is not possible to determine whether the patient has reached the desired goals of therapy for her condition.

The goal of the medication history is to obtain and assess the following information: the specific prescription and nonprescription drugs that the patient is taking (such as OTC medications, botanicals, dietary supplements, recreational drugs, alcohol, tobacco, and home remedies); the intended purpose or indications for each of these medications; how it is taken (eg, route, ingestion in relation to meals), how much, and how often these medications are used; how long these agents have been taken or used (start and stop dates); whether the patient believes that any of these agents are providing therapeutic benefit; whether the patient is experiencing or has experienced any adverse effects that could be caused by each of these agents (idiosyncratic reactions, toxic effects, adverse effects); whether the patient has stopped taking any of the medications for any reason; and allergic reactions or history of hypersensitivity or other severe reactions to drugs. This information

should be as specific as possible, including a description of the reaction, the treatment, and the date of its occurrence.

A successful medication reconciliation process consists of a standardized systematic approach, with the initial step in this process involving the collection of the best medication history possible from every patient that enters any point in the health care system. Although pharmacists are uniquely qualified and have demonstrated increased accuracy in acquiring the medication history,[19] medication reconciliation requires a multidisciplinary effort in which all available resources are integrated into each step of the process when appropriate.[20] Shared accountability using key members of the health care team such as nurses, pharmacy technicians, pharmacists, and prescribers is essential in this process. Once an accurate medication history is obtained, this information is used to ensure that as the patient moves through the health care system, any deviation from the prescribed regimen is deliberate and based on acute changes in the patient's condition. If an observed discrepancy is the result of an intended therapeutic decision by the prescribing clinician, appropriate documentation with either the reason for or intention to change, hold, or discontinue the medication should be completed in a manner that is clear to all members of the health care team. Unintentional variances in the medication lists should be considered as potential medication errors pending clarification from the prescribing clinician.

Medication errors most commonly occur during transitions of care. It is essential to conduct medication reconciliation when a patient is admitted to or discharged from a health care facility.[21,22] A crucial final step in the reconciliation process, and a vital piece of MTMS, occurs at discharge to avoid therapeutic duplication, drug interactions, and omissions of medications that may have been discontinued or placed on hold during hospitalization. On departure from a health care facility, a complete list of the patient's medications must be communicated to the patient and the next provider of service regardless of the setting. This process allows for informed prescribing decisions and creates a safer environment for patients by

improving the accuracy of medication administration throughout the continuum of care.

Perhaps the most important aspect of the medication history is to ensure that no assumptions related to medication use go unverified with the patient. The provider should ask questions related to how the current medication therapy is actually taken by the patient. The interviewer should then compare the use of medications as defined by the patient to the prescription information on the prescription bottle or in the PIS/EHR. This information may identify discrepancies or misunderstandings between the prescriber and the patient. The patient may not have adequate health literacy, and the interpretation of the medication instructions printed on the bottle or described by a health professional may not be understandable to a patient. The review of the medication history is an ideal time to identify and clarify such misunderstandings.

CASE 1-1, QUESTION 2: P.J. has indicated that she is injecting insulin to treat her diabetes. What questions might be asked to evaluate P.J.'s use of and response to insulin?

The following types of questions, when asked of P.J., should provide the practitioner with information on P.J.'s understanding about the use of and response to insulin.

DRUG IDENTIFICATION AND USE

- What type of insulin do you use?
- How many units of insulin do you use?
- When do you inject your insulin?
- Where do you inject your insulin?
- Please show me how you usually prepare your insulin for injection. (This allows the patient to demonstrate a skill.)
- What, if anything, keeps you from taking your insulin as prescribed?

ASSESSMENT OF THERAPEUTIC RESPONSE

- How do you know your insulin is working?
- What blood glucose levels are you aiming for?
- What foods or meals do you find affect your blood sugar most?
- How often and when do you test your blood glucose level?
- Do you have any blood glucose readings that you could share with me?
- Please show me how you test your blood glucose.
- What is your understanding of the hemoglobin A_{1c} blood test?
- When was the last time you had this test done?
- What were the results of the last hemoglobin A_{1c} test?

ASSESSMENT OF ADVERSE EFFECTS

- Do you ever experience reactions from low blood glucose?
- What symptoms warn you of such a reaction?
- When do these typically occur during the day?
- How often do they occur?
- What circumstances seem to make them occur more frequently?
- What do you do when you have low blood glucose?

The patient's responses to these questions on drug use, therapeutic response, and adverse effects will allow a quick assessment of the patient's knowledge of insulin and whether she is using it in a way that is likely to result in blood glucose concentrations that are neither too high nor too low. The responses to these questions should also provide the practitioner with insight about the extent to which the patient has been involved in establishing and monitoring therapeutic outcomes. Based on this information, the practitioner can begin to formulate the patient's therapeutic plan.

Social History

The social history is used to determine the patient's occupation and lifestyle; important family relationships or other support systems; any particular circumstances (eg, a disability) or stresses in her life that could influence the MAP; and attitudes, values, and feelings about health, illness, and treatments.

CASE 1-1, QUESTION 3: A patient's occupation, lifestyle, insurance status, ability to pay, and attitudes often can determine the success or failure of drug therapy. Therefore, P.J.'s prescription drug coverage, nutritional history, her level of activity or exercise in a typical day or week, the family dynamics, and any particular stresses that may affect glucose control need to be documented and assessed. What questions might be asked of P.J. to gain this information?

WORK

- Describe your typical workday and a typical weekend day.

INSURANCE/COST

- What type of prescription drug coverage do you have? How much do you pay for your insulin and diabetic supplies? How often do you go without your insulin or supplies because of cost?

EXERCISE

- Describe your exercise habits. How often, how long, and when during the day do you exercise? Describe how you change your meals or insulin when you exercise.

DIET

- How many times per day do you usually eat? Describe your usual mealtimes.
- What do you usually eat for each of your main meals and snacks?
- Are you able to eat at the same time each day?
- What do you do if a meal is delayed or missed?
- Who cooks the meals at home? Does this person understand foods to prepare for someone with diabetes?

- How often do you eat meals in a restaurant?
- How do you order meals in a restaurant to maintain a proper diet for your diabetes? (*Note:* This is asked of patients who frequently dine in restaurants.)

SUPPORT SYSTEMS

- Who else lives with you? What do they know about diabetes? How do they respond to the fact that you have diabetes? How do they help you with your diabetes management? Does it ever strain your relationship? What are the issues that seem to be most troublesome? (*Note:* These questions apply equally to the workplace or school setting. Often, the biggest barrier to multiple daily injections is refusal of the patient to inject insulin while at work or school.)

ATTITUDE

- How do you feel about having diabetes?
- What worries or bothers you most about having diabetes? (*Note:* Participate in the patient's care. This approach is likely to enhance the patient–provider relationship, which should translate into improved care.)

APPROACH TO AND ASSESSMENT OF PATIENT THERAPY

The provider–patient encounter will vary based on the location and type of services provided and access to necessary information. However, the general approach to the patient encounter should follow the problem-oriented medical record (POMR). Organizing information according to medical problems (eg, diseases) helps break down a complex situation (eg, a patient with multiple medical problems requiring multiple drugs) into its individual parts.[1,3] The medical community has long used a *POMR* or *SOAP note* to record

information in the medical record or chart using a standardized format (**Table 1-4**). Each medical problem is identified, listed sequentially, and assigned a number. *Subjective* and *objective* data in support of each problem are delineated, an *assessment* is made, and a *plan* of action identified. The first letter of the four key words (*s*ubjective, *o*bjective, *a*ssessment, and *p*lan) serves as the basis for the SOAP acronym.

Table 1-4

Elements of the Problem-Oriented Medical Record

Problem name: Each "problem" is listed separately and given an identifying number. Problems may be a patient report of a symptom (eg, headache), a laboratory abnormality (eg, hypokalemia), or a specific disease name if prior diagnosis is known. When monitoring previously described drug therapy, more than one drug-related problem may be considered (eg, lack of adherence, an adverse drug reaction or drug interaction, or inappropriate dose). Under each problem name, the following information is identified:	
Subjective	Information that explains the reason for the encounter. Information that the patient reports concerning symptoms, previous treatments, medications used, and adverse effects encountered. These are considered nonreproducible data because the information is based on the patient's interpretation and recall of past events.
Objective	Information from physical examination, laboratory test results, diagnostic tests, pill counts, and pharmacy patient profile information. Objective data are measurable and reproducible.
Assessment	A brief but complete description of the problem, including a conclusion or diagnosis that is supported logically by the abovementioned subjective and objective data. The assessment should not include a problem or diagnosis that is not defined earlier.
Plan	A detailed description of recommended or intended further workup (laboratory tests, radiology, consultation), treatment (eg, continued observation, physiotherapy, diet, medications, surgery), patient education (self-care, goals of therapy, medication use, and monitoring), monitoring, and follow-up relative to the abovementioned assessment.

Sometimes referred to as the *SOAP* (*s*ubjective, *o*bjective, *a*ssessment, *p*lan) note.

The POMR is a general approach and helps focus on the encounter, which provides a structure for the documentation of the services provided. The following section describes the POMR and SOAP note in more detail.

Problem List

Problems are listed in order of importance and are supported by the subjective and objective evidence gathered during the patient encounter. Each problem in the list can then be given an identifying number. All subsequent references to a specific problem can be identified or referenced by that number (eg, “problem 1” or simply “1”). These are generally thought of in terms of a diagnosed disease, but they also may be a symptom complex that is being evaluated, a preventive measure (eg, immunization, contraception), or a cognitive problem (eg, lack of adherence). Any condition that requires a unique management plan should be identified as a problem to serve as a reminder to the practitioner that treatment is needed for that problem. Different settings and activities or clinical services will determine the priority of the problems identified.

Medical problems can be *drug related*, including prescribing errors, dosing errors, adverse drug effects, adherence issues, and the need for medication counseling. Drug-related problems may be definite (ie, there is no question that the problem exists) or possible (ie, further investigation is required to determine whether the problem really exists). The most commonly encountered types of drug-related problems are listed in **Table 1-5**.[4,15]

Table 1-5
Drug-Related Problems

Drug Needed
Drug indicated but not prescribed; a medical problem has been diagnosed, but there is no indication that treatment has been initiated (maybe it is not needed).
Correct drug prescribed but not taken (lack of adherence)
Wrong or Inappropriate Drug

ALGrawany

No apparent medical problem justifying the use of the drug
Drug not indicated for the medical problem for which it has been prescribed
Medical problem no longer exists.
Duplication of other therapy
Less expensive alternative available
Drug not covered by formulary
Failure to account for pregnancy status, age of patient, or other contraindications
Incorrect nonprescription medication self-prescribed by the patient
Recreational drug use
Wrong Dose
Prescribed dose too high (includes adjustments for renal and hepatic function, age, body size)
Correct prescribed dose but overuse by patient (overadherence)
Prescribed dose too low (includes adjustments for age, body size)
Correct prescribed dose but underuse by patient (underadherence)
Incorrect, inconvenient, or less-than-optimal dosing interval (consider use of sustained-release dosage forms)
Adverse Drug Reaction
Hypersensitivity reaction
Idiosyncratic reaction
Drug-induced disease
Drug-induced laboratory change
Drug Interaction
Drug–drug interaction
Drug–food interaction
Drug–laboratory test interaction
Drug–disease interaction

The distinction between medical problems and drug-related problems sometimes is unclear, and overlap can exist. For example, a medical problem (ie, a disease, syndrome, symptom, or health condition) can be prevented, cured, alleviated, or exacerbated by

medications. When assessing drug therapy, several situations could exist: treatment is appropriate and therapeutic outcomes have been achieved; drugs that have been selected are ineffective or therapeutic outcomes are partially achieved; dosages are subtherapeutic or medication is taken improperly; an inappropriate drug for the medical condition being treated has been prescribed or is being used; or the condition is not being treated.

Likewise, a drug-related problem can cause or aggravate a medical problem. Such drug-related problems could include hypersensitivity reactions; idiosyncratic reactions; toxic reactions secondary to excessive doses; adverse reactions (eg, insulin-induced hypoglycemia or weight gain); drug–drug, drug–disease, drug–laboratory test, and drug–lifestyle interactions; or polypharmacy, which may increase the risk of adverse drug events.[23]

Subjective and Objective Data

Subjective and objective data in support of a problem are important because assessment of patients and therapies requires the gathering of specific information to verify that a problem continues to exist or that therapeutic objectives are being achieved. Subjective data refer to information provided by the patient or another person that cannot be confirmed independently. This is the data most commonly obtained during a patient interview. Objective data refer to information observed or measured by the practitioner (eg, laboratory tests or blood pressure [BP] measurements). Objective data are most commonly obtained from the electronic medical record (EMR) or paper chart (data-rich environment). However, some objective data can be obtained in data-poor environments. In the absence of a medical record, weight, height, pulse, BP, blood glucose readings, and other objective information can be gathered during the provider–patient encounter.

CASE 1-2

QUESTION 1: P.N., a 28-year-old male, has a BP of 140/100 mm Hg.

What is the primary problem? What subjective and objective data support the problem, and what additional subjective and objective data are not provided, but usually are needed, to define this particular problem?

The primary problem is hypertension. No subjective data are given. The objective data are the patient's age, sex, and BP of 140/100 mm Hg. Each of these is important in designing a patient-specific therapy plan. Because hypertension often is an asymptomatic disease (see Chapter 9, Essential Hypertension), subjective reports such as headache, tiredness or anxiety, shortness of breath (SOB), chest pain, and visual changes usually are absent. If long-term complications such as rupturing of blood vessels in the eye, glomerular damage, or encephalopathy were present, subjective symptoms might be blurring or loss of vision, fatigue, or confusion. Objective data would include a report by the physician on the findings of the chest examination (abnormal heart or lung sounds if secondary heart failure [HF] has developed), an ocular examination (eg, presence of retinal hemorrhages), and laboratory data on renal function (blood urea nitrogen, creatinine, or creatinine clearance). To place these complications in better perspective, the rate of change should be stated. For example, the serum creatinine has increased from a level of 1 mg/dL 6 months ago to a value of 3 mg/dL today. Vague descriptions such as "eye changes" or "kidney damage" are of little value because progressive damage to these end organs results from uncontrolled high BP and disease progression needs to be monitored more precisely.

CASE 1-3

QUESTION 1: C.S., a 58-year-old female, reports fatigue, ankle swelling, and SOB, especially when lying down, for the past week. Physical examination shows distended neck veins, bilateral rales, an S_3 gallop rhythm, and lower extremity edema. A chest radiograph shows an enlarged heart. She is diagnosed with HF and is being treated with furosemide and digoxin.

What is/are the primary problem(s)? What subjective and objective data support the problem(s)? What additional subjective and objective data are not provided but usually are needed to define this (these) particular problem(s)?

The primary problem is systolic HF. Subjectively, C.S. claims to be experiencing fatigue, ankle swelling, and SOB, especially when lying down. She claims to have been taking furosemide and digoxin. An expanded description of these symptoms and her medication use would be helpful. The findings on physical examination and the enlarged heart on chest radiograph are objective data in support of the primary problem of HF. In addition, other objective findings that would help in her assessment would be the pulse rate, BP, serum creatinine, serum potassium concentration, digoxin blood level, a more thorough description of the rales on lung examination, extent of neck vein distension, and degree of leg edema. Pharmacy records could be screened to determine current dosages and refill patterns of the medications.

In this case, a second primary problem may be present. Current recommendations for the management of HF include use of an angiotensin-converting enzyme (ACE) inhibitor before or concurrent with digoxin therapy. Thus, a possible drug-related problem is the inappropriate choice of drug therapy (“wrong drug”). The patient or prescriber should be consulted to ascertain whether an ACE inhibitor has been used previously, any contraindications exist, or possible adverse effects were encountered.

Assessment

After the subjective and objective data have been gathered in support of specific listed problems, the practitioner should assess the acuity, severity, and importance of these problems. They should then identify all factors that could be causing or contributing to the problem. The assessment of the severity and acuity is important because the patient expects relief from the symptoms that are of particular concern at this time. During the initial encounter with a patient, it might be discovered that the medical problem is only a symptom complex and that a diagnosis is needed to more accurately identify the problem and further define its severity.

The assessment is usually performed during or immediately after the data gathering, while the provider keeps in mind evidence-based practices. For example, if diabetes is assessed and pertinent subjective data (medication history, social history, diet, exercise, etc) and objective data exist (laboratory test results such as hemoglobin A_{1c}, low-density lipoprotein cholesterol [LDL-C], BP, etc), then the assessment of diabetes may be to determine whether the patient is meeting the goals for the disease as defined by the ADA. If the patient is not at goal, then the explanation of the reasons why would be described in the assessment, and the plan would then be centered on helping that patient get to goal. Sometimes, the distinction between subjective information provided by the patient and assessments made by the practitioner are confused in the POMR. What the patient reveals belongs in the subjective data, and how the provider interprets it belongs in the assessment. For example, a patient stating that she is having difficulty affording her medications belongs in the subjective information. However, a patient appearing to have cost-related lack of adherence belongs in the assessment, because it is the provider's interpretation of what the patient has stated.

DRUG THERAPY ASSESSMENT

A responsibility of the practitioner is to monitor the response of patients to prescribed therapeutic regimens. The purpose of drug therapy monitoring is to identify and solve drug-related problems and to ensure that all therapeutic objectives are being achieved. Unless proved otherwise, the medical diagnosis should be assumed to be correct. On occasion, the diagnosis may not be readily apparent, or a drug-induced problem may have been diagnosed incorrectly as being a disease entity.

Health care practitioners share the responsibility of assessing and monitoring patient drug therapy. For the pharmacist, medication reconciliation and the drug therapy assessment may occur in many practice settings, including the community pharmacy while dispensing or refilling prescriptions or counseling patients, during an

MTMS encounter in the home or in the clinic, while assessing therapy for the hospitalized patient, or as part of routine monthly evaluations of patients residing in long-term care facilities. Many states have enacted legislation allowing pharmacists to develop collaborative drug therapy agreements with physicians for disease-state management of common disorders such as asthma, diabetes, dyslipidemia, and hypertension. Additional services commonly provided by pharmacists through collaborative drug therapy agreements include anticoagulation monitoring, emergency contraception, and immunizations.[6] These services often involve more detailed drug therapy evaluation and assessment and may occur within or outside the traditional pharmacy setting. Regardless, the patient's need, time constraints, working environment, and practitioner's skill level govern the extent of monitoring. Similarly, the exact steps used to monitor therapy and the order in which they are executed need to be adapted to a practitioner's personal style. Thus, the examples given in this chapter should be used by the reader as a guide rather than as a recipe in a cookbook.

Plan

The next step in the problem-oriented (ie, SOAP) approach is to create a plan, which at the minimum should consist of a diagnostic plan and a MAP that includes patient education. The plan is the action that was justified in the assessment. The plan is clear and direct and does not require explanation (this should be explained in the assessment). For example, if a patient is experiencing constipation while taking an opioid pain reliever, the plan would be to recommend a stool softener or stimulant laxative such as docusate sodium. The plan should also include any follow-up that would be necessary as a result of the action taken.

Patient Education

Educating patients to better understand their medical problem(s) and treatment is an implied goal of all treatment plans. This process is categorized as the development of a patient education plan. The level of teaching has to be tailored to the patient's needs, health literacy, willingness to learn, and general state of health and mind. The patient should be taught the knowledge and skills needed to achieve and evaluate their therapeutic outcome. An important component of the patient education plan emphasizes the need for patients to follow prescribed treatment regimens.

The POMR will allow the provider to focus on the interview and the encounter independent of the site or service offered. The POMR facilitates documentation of the provision of MTMS across multiple sites and services (across the continuum of care).

The next few sections discuss how to approach MTMS in various clinical settings.

MEDICATION THERAPY MANAGEMENT SERVICES IN THE COMMUNITY PHARMACY OR AMBULATORY SETTING

The core elements of MTMS have been described by the APhA and the National Association of Chain Drug Stores (NACDS).[20] According to these organizations, the core elements of MTMS should include the following components:

1. Medication therapy review (MTR)
2. Personal medication record (PMR)
3. Medication action plan (MAP)
4. Intervention or referral
5. Documentation and follow-up

Medication Therapy Review

The MTR may be a comprehensive review, including medication reconciliation, in which the provider reviews all of the medications the patient is currently taking, or it may be a focused review of one medication-related issue such as an adverse event. Examples of services provided during the MTR are described in **Table 1-6**. MTR is dependent on the information that is available from the patient or other data sources.

Table 1-6
Examples of Services Provided During a Medication Therapy Review

- Assess the patient's health status.
- Assess cultural issues, health literacy, language barriers, financial status, and insurance coverage or other patient characteristics that may affect the patient's ability to take medications appropriately.
- Interview the patient or caregiver to assess, identify, and resolve actual or potential adverse medication events, therapeutic duplications, untreated conditions or diseases, medication adherence issues, and medication cost considerations.
- Monitor medication therapy, including response to therapy, safety, and effectiveness.
- Monitor, interpret, and assess patient laboratory values, especially because they relate to medication use/misuse.
- Provide education and training on the appropriate use of medications.
- Communicate appropriate information to other health professionals, including the use and selection of medication therapy.

Personalized Medication Record

Regardless of the setting, a necessary tool to help with the gathering of the medication information is the PMR. This medication record should be updated after any change in medication therapy and should be shared with other health care providers. The goal of this record is to promote self-care and ownership of the medication regimen.[24] The PMR should be used at all levels of care, thereby facilitating the medication reconciliation process required across the continuum of care. An example of a PMR is shown in **Figure 1-2**.

My Medication Record

Name: MC ———————— Birth Date: May 28, 1939 ————————

Include all of your medications on this record: prescription medications, nonprescription medications, herbal products, and other dietary supplements. Always carry your medication record with you and show it to all your doctors, pharmacists, and other health care providers.

Drug	Take for…	When do I tak e it?	Start	Stop	Doctor	Special Instructions
Lisinopril	40 mg	High blood pressure	Once daily	1/2/15	Sara Smith, MD	
Metoprolol	50 mg	High blood pressure	Twice daily	1/2/15	Sara Smith, MD	9 A.M. and 9 P.M.
Glipizide	5 mg	Diabetes	Once daily	1/2/15	Sara Smith, MD	9 A.M.
Indomethacin	50 mg	Back Pain	Up to 3 times daily if needed	1/2/15	Sara Smith, MD	Take with food. Do not take this medicine with other anti-inflammatory medicines (e.g., ibuprofen, naproxen). Do not take this medication unless you have pain.
Crestor (rosuvastatin)	40 mg	Cholesterol	Once daily	4/2/15	Ted Hart, MD	

This sample Personal Medication Record (PMR) is provided only for general informational purposes and does not constitute professional health care advice or treatment. The patient (or other user) should not, under any circumstances, solely rely on, or act on the basis of, the PMR or the information therein. If he or she does so, then he or she does so at his or her own risk. While intended to serve as a communication aid between patient (or other user) and health care provider, the PMR is not a substitute for obtaining professional health care advice or treatment. This PMR may not be appropriate for all patients (or other users). The National Association of Chain Drug Stores Foundation and the American Pharmacists Association assume no responsibility for the accuracy, currentness, or completeness of any information provided or recorded herein.

This form is based on forms developed by the American Pharmacists Association and the National Association of Chain Drug Stores Foundation. Reproduced with permission from APhA and the NACDS Foundation.

Figure 1-2 Example of a personal medication record (PMR).

Once the patient interview has occurred and the PMR has been updated, the provider may still require information to make an assessment. In such cases, the provider must do their best with the available information, or they may obtain missing information such as the medical history or objective data from other providers. In some encounters, obtaining the necessary information and medication reconciliation may take the entire visit, necessitating a follow-up encounter.

Medication Action Plan

If adequate information is available to assess the current problem, a MAP should be developed. Because the MAP is patient centered and is prioritized according to the urgency of need, the provider and the patient should develop the plan together. An example of a MAP can be seen in **Figure 1-3**.

My Medication-Related Action Plan	
Patient:	MC
Doctor (Phone):	Sara Smith, MD
Pharmacy/Pharmacist (Phone):	Rite Mart/Mary John, PharmD
Date Prepared:	May 10, 2015
The list below has important Action Steps to help you get the most from your medications. Follow the checklist to help you work with your pharmacist and doctor to manage your medications AND make notes of your actions next to each item on your list.	
Action steps → What I need to do…	**Notes → What I did and when I did it….**
☐ **For your muscle weakness and soreness** Stop Crestor (rosuvastatin) 40mg. We asked Dr. Hart to change to a lower dose or different agent such as simvastatin. Obtain blood test from Dr. Hart's office. Follow-up with Dr. Hart in 2 days.	
☐ **Medicine Cost** We have asked Dr. Hart to stop Crestor (rosuvastatin) as it is too expensive. A generic medicine such as simvastatin will cost you less and was recommended to Dr. Hart as an alternative. Continue to ask your pharmacist and doctor whether the medications you are taking are covered by your Medicare Part D plan and whether there are any alternatives that may be less expensive.	
☐ **For Pain** Take to Dr. Sara Smith about other pain medications, because the indomethacin may not be the best choice for you due to its side effects/ Some choices might include other medications such as Vicodin (hydrocodone and acetaminophen), over-the-counter acetaminophen, or naproxen or ibuprofen.	
My next appointment with my pharmacist is on: _____ (date) at _____ ☐ AM ☐ PM	
This sample Medication-Related Action Plan (MAP) is provided only for general informational purposes and does not constitute professional health care advice or treatment. The patient (or other user) should not, under any circumstances, solely rely on, or act on the basis of, the MAP or the information therein. If he or she does so, then he or she does so at his or her own risk. While intended to serve as a communication aid between patient (or other user) and health care provider, the MAP is not a substitute for obtaining professional health care advice or treatment. This MAP may not be appropriate for all patients (or other users). The National Association of Chain Drug Stores Foundation and the American Pharmacists Association assume no responsibility for the accuracy, currentness, or completeness of any information provided or recorded herein.	

This form is based on forms developed by the American Pharmacists Association and the National Association of Chain Drug Stores Foundation. Reproduced with permission from APhA and the NACDS Foundation.

Figure 1-3 Example of a medication action plan (MAP).

Intervention and Referral

The MAP often describes the intervention performed in an MTM encounter and may serve as documentation that can be shared with the patient and other health care providers (similar to the PMR). The primary purpose of the MAP is to make the action plan patient centered and to provide the patient with documentation of what they need to do next in the action plan. It also provides space for the patient to document what they did related to this action and when it was done. In some instances, the MAP may involve referral to another provider (a physician or pharmacist with additional

qualifications) if the issue is beyond the scope of the intervening pharmacist.

Coordination of care is a key element of MTMS and MTR.[1] This may include improving the communication between the patient and other health care providers, enhancing the patient's understanding of their health issues or concerns, maximizing health insurance coverage, advocating on behalf of the patient to get the needed medications using available resources and programs, and various other functions that will improve the patient's understanding of their health care environment and promote self-care. Coordination of care may be the primary action taken on behalf of the patient and may be included in the MAP.

Documentation and Follow-up

The development of a documentation process is a necessary component of MTMS.[24] Documentation should be standardized and based on the POMR format. All appropriate records, including the PMR and MAP, should be shared with other providers to promote communication and continuity of care. If the encounter requires follow-up, the documentation should reflect the timing of the follow-up care, and any expectations of the patient and providers should be included. Thorough documentation of the encounter allows all providers to quickly assess the progress of the patient and determine that the desired outcome has been achieved.

An important aspect of documenting the encounter is to submit billing for the encounter when appropriate. Those who provide MTMS should understand the reimbursement process to obtain compensation for providing these valuable cognitive services. Sources of reimbursement can be categorized into two, Medicare Part D and non-Medicare D payers (eg, employer-based health plans, state-sponsored MTM programs in some states, Accountable Care Organizations, and directly to patients if they agree to receive MTMS).

The implementation of Medicare Part D in 2006 allowed pharmacists in pharmacies contracted with prescription drug plans to provide MTMS to plan-identified Medicare recipients. Pharmacists bill these plans through the contracted pharmacy using a national provider identifier (NPI) and CPT codes. The NPI number designates the provider to be paid, and the CPT determines the amount of payment based on the services rendered. There have been substantial changes to the Part D MTM program requirements since 2006 regarding eligibility criteria, types of MTMS provided, and reporting requirements, creating more opportunities for pharmacists to provide MTMS to Medicare recipients.[25]

Visit the 2019 Medicare Part D MTM Fact Sheet for the latest details on eligibility criteria and the MTMS that are required: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/CY2019-MTM-Fact-Sheet.pdf.

The CPT codes specific to pharmacists providing MTMS include the following:

CPT 99605: Initial face-to-face assessment or intervention by a pharmacist with the patient for 1 to 15 minutes

CPT 99606: Subsequent face-to-face assessment or intervention by a pharmacist with the patient for 1 to 15 minutes

CPT 99607: Each additional 15 minutes spent face-to-face by a pharmacist with the patient; used in addition to 99605 or 99606

For more information about the MTM CPT Codes, visit the Pharmacist Services Technical Advisory Coalition (PSTAC) website at www.pstac.org/services/mtms.codes.html.

Pharmacists should know that all Medicare D payers may not use CPT codes and that non-Medicare D payers may have their own billing procedures. It is essential to become familiar with specific billing methods and any pertinent codes. Furthermore, it is important to realize that reimbursement for MTMS varies by plan and negotiated contract. Pharmacists have also developed patient self-pay reimbursement strategies and contracts with self-insured employers and state-run Medicaid programs to provide services.[26,27]

The APhA provides additional options to bill payers outside of Medicare Part D if one cannot determine the means to bill the payer (https://www.pharmacist.com/sites/default/files/files/mtm_billing_tips.pdf).

The Patient Protection and Affordable Care Act of 2010 and the Health Care and Education Reconciliation Act of 2010 describe the need for payment reform that promotes improved quality of care. Other providers also see these laws providing new opportunities for pharmacists to participate in care teams such as the patient-centered medical home and pay-for-performance programs to improve medication-related care coordination, quality scores, and patient outcomes.[28,29] The enhanced payment for improving quality in medication-related areas could be used to fund the pharmacist in this activity.

With increasing recognition of MTMS' value both with Medicare and non-Medicare payers and the growing opportunities for pharmacists to provide these services, pharmacists who will be providing MTMS may want to consider certification. For a comparison of the credentialing programs available for pharmacists, requirements, and benefits, visit the National Board of Medication Therapy Management at https://www.nbmtm.org/mtm-certification-truly-authentic/.

CASE 1-4

QUESTION 1: M.C. is a 76-year-old female who comes for a focused MTR appointment at the community pharmacy with her daughter. She has a Medicare Part D prescription drug plan and is asking for help with her medication costs. She indicates that she has type 2 diabetes, hypertension, back pain, and hyperlipidemia. Her medications include lisinopril 40 mg once daily, metoprolol 50 mg twice daily, glipizide 5 mg once daily, indomethacin 50 mg up to three times daily as needed for pain, and rosuvastatin 40 mg once daily. M.C. tells you that she has trouble paying for her rosuvastatin (tier 3, $60 copayment) and would rather have a different generic that costs less (tier 1, $5 copayment). Further, she reports muscle soreness and weakness during the past 3 weeks.

What is the primary problem? What objective information can be obtained in a community pharmacy setting? What additional information is necessary to

determine the cause of her problem? How would a clinician assess and document her problem(s) in a SOAP format?

Although the patient presented for an MTR, the primary problem is the patient's self-reported muscle weakness and soreness during the past 3 weeks. Assuming that M.C. is a patient of this pharmacy, the practitioner could gather the necessary medication history from the PIS. Because the patient is present, this is a good opportunity to develop a PMR with M.C. This process will help quickly identify any medication discrepancies between the pharmacy computer system and the patient's understanding of medication administration. If discrepancies are noted, the practitioner can clarify them with M.C. right away as part of the intervention. The PMR should also include a section to list medication allergies. The type of reaction should also be included on the PMR so that other providers will know the severity of the medication allergy (ie, intolerance vs anaphylactic reaction). Based on the data gathered from the pharmacy computer and M.C., a PMR (depicted in Fig. 1-3) could be developed.

Reviewing the medications alone often does not provide enough information to determine whether M.C. is experiencing a medication-related event. Further questioning related to the onset of her symptoms of muscle soreness and weakness may help determine whether this is a medication-related problem.

The practitioner can develop an assessment from this questioning and the PMR of the current problem that she is experiencing. As indicated on the PMR, M.C. started rosuvastatin most recently. The initiation of this medication corresponds to the onset of her recent soreness and weakness. β-Hydroxy-b-methylglutaryl-CoA (HMG-CoA) reductase inhibitors such as rosuvastatin are known to cause myositis, or muscle breakdown, which may lead to weakness and muscle soreness. Furthermore, the prescribed dose is high for a female of M.C.'s age. Based on this information, an assessment of the problem can be pursued. If rosuvastatin is the suspected agent, the plan would include actions necessary to solve the problem or to determine whether rosuvastatin is the cause of her muscle soreness and weakness. Unfortunately, not all of the necessary information is

available (eg, her baseline cholesterol, serum creatinine, liver function tests, or creatine kinase levels) to develop a formal plan of action to resolve the adverse medication event. However, part of the plan may be to obtain the laboratory test results necessary to identify or act on the adverse medication event. An example of the documentation of the SOAP note follows:

PRIMARY PROBLEM

Muscle soreness and weakness (possible adverse medication event)

SUBJECTIVE

M.C. reports weakness and soreness, predominantly in her legs during the past 3 weeks. She has difficulty rising from her chair after sitting for long periods and describes the pain as aching. The patient reports taking her medications as prescribed and rarely misses a dose.

OBJECTIVE

Total cholesterol: 137 mg/dL; LDL-C: 56 mg/dL; high-density lipoprotein (HDL): 54 mg/dL; Triglycerides: 136 mg/dL
Temperature: 98.5 °F (36.94 °C)
Blood pressure: 144/68 mm Hg

ASSESSMENT

M.C. has muscle weakness and soreness in her large muscle groups. According to the American College of Cardiology and the American Heart Association, M.C. is considered to be at risk for heart disease because of her age and concurrent disease states.[30] Her current lipid therapy is rosuvastatin 40 mg once daily, which was started by her cardiologist 6 weeks ago. The initiation of rosuvastatin 40 mg correlates to the timing of her muscle soreness and weakness. HMG-CoA reductase inhibitors (ie, rosuvastatin) are known to cause myositis or myalgias, and this patient is at particular risk given her age, sex, and starting dose. It is possible that the rosuvastatin could be causing her muscle soreness and weakness.

Other lipid-lowering agents could be tried or the dose of rosuvastatin could be reduced, which might eliminate or reduce this adverse event. A creatine kinase level should be obtained to determine the severity of myositis. Serum creatinine should also be measured because myositis can lead to renal damage and rhabdomyolysis in severe cases; however, this is usually accompanied by fever and other symptoms that the patient is not currently experiencing.

PLAN

Drug-Related Adverse Event

- Discussed the possibility of an adverse medication event with the patient, which included the signs and symptoms of myalgias and myositis.
- Contacted Dr. Hart (M.C.'s cardiologist) to discuss the current problem with rosuvastatin.
- Per discussion with Dr. Hart, will obtain a creatine kinase level and serum creatinine.
- Discontinue rosuvastatin per the pharmacist's recommendation. Dr. Hart agreed that M.C. should temporarily stop her rosuvastatin until her laboratory values are reviewed.
- Alternative dosing of rosuvastatin 5 mg or another equivalent agent (atorvastatin 10 mg or simvastatin 20 mg) was discussed with Dr. Hart.
- M.C. is to see Dr. Hart in the cardiology clinic in 2 days to discuss the laboratory values and alternative therapies.
- Discussed the entire plan with M.C., and she verbalized understanding of steps that she is to take with respect to her current medication-induced problem.

CASE 1-4, QUESTION 2: From M.C.'s medication profile, what other problems can be identified with her medication therapy? What can be done to address these issues?

There are two remaining issues that may need to be addressed. The first issue relates to the pain medicine (indomethacin) that M.C. is taking. It is suggested that indomethacin may have a higher rate of central nervous system side effects in the elderly compared with other agents in the same class.[31] Furthermore, the American Geriatric Society guidelines on the management of mild-to-moderate persistent pain caution the use of nonsteroidal anti-inflammatory agents in older adults, preferring acetaminophen as a first-line agent.[32] Other prescription medications or nonprescription medication such as acetaminophen alone could be used to help treat M.C.'s pain (see Chapter 55, Pain and Its Management, and Chapter 107, Geriatric Drug Use).

Second, it is not clear from the current information whether the various providers are communicating. It is the responsibility of the pharmacist to help coordinate care among multiple prescribers, as described by the APhA MTMS consensus document.[1] Therefore, it is important to be sure that both providers (Drs. Smith and Hart) receive a copy of the documentation of the issues addressed during the visit (SOAP note).

CASE 1-4, QUESTION 3: What additional information can be provided to M.C. at this time?

Finally, M.C. came into the pharmacy asking for help with her medication costs. To assess this problem, it is important to ask whether there are specific cost issues with a particular drug or whether it is her overall medication regimen that causes her concern. Another question to ask is whether she has stopped taking any medications or changed the way she takes them because of cost. Many patients will discuss cost and adherence issues with their pharmacist because the point of sale for medications occurs at the pharmacy. However, they may not discuss this problem with the prescriber. Cost and lack of adherence because of cost are medication-related problems that the pharmacist must communicate to the prescriber on behalf of the patient. In assessing drug cost,

several steps can be taken. First, determine the patient's ability to pay for medications; implement low-cost, medically appropriate interventions targeted at patient needs; facilitate enrollment into relevant benefit programs; and confirm medication changes with the patient and prescribers.

For M.C., the rosuvastatin is her biggest concern because it costs $60 per month and her Medicare Part D plan lists it as a nonpreferred (tier 3) agent on the formulary. With the possible discontinuation of her rosuvastatin, it is important for the pharmacist to anticipate an alternative lipid-lowering agent and determine a cost-effective alternative that may be appropriate. This information can then be relayed to the prescriber. Furthermore, the alternative lipid-lowering formulary choice can be integrated into the plan developed for the primary issue of muscle soreness and weakness (see Case 1-4, Question 1). The integration of multiple problems is a complicated but an important aspect of the MAP.

As discussed previously, an important part of MTMS involves the MAP. The MAP is a document that may empower the patient and promote self-care. The information on the MAP is important for both the patient and the provider, and it facilitates communication among multiple providers. When a patient presents the PMR and MAP to all providers, complex medication information can be shared across the continuum of care. An example of M.C.'s MAP is included in Figure 1-3.

Because extensive information was communicated to the patient and other providers, follow-up (phone or face-to-face) would be appropriate and necessary to determine the resolution of the medication-related issues identified. Follow-up should occur in a timely manner, likely after M.C. has obtained the necessary laboratory test results and has been evaluated by her cardiologist as outlined in the plan. The follow-up should include questions related to the changes that were (or were not) made based on the practitioner recommendations and any new issues that have surfaced. Follow-up should be considered after any encounter in which an action plan is developed to determine whether the medication-related problem has been resolved. In addition, problems

may be identified and prioritized during the initial visit but, because of time constraints, may not be addressed. A follow-up visit allows for assessment of these problems.

Case 1-4, Question 4: Assuming that the pharmacy provider had an NPI number and a contract with M.C.'s Medicare Part D prescription drug plan, how could the 30 minutes spent with M.C. be billed to her insurance?

Provided that M.C. was identified by her Medicare prescription drug plan as eligible for MTMS, the practitioner could bill for the 30-minute encounter. Using the practitioner's NPI number and the appropriate CPT codes, the practitioner could bill for one CPT 99605 (for the first 15 minutes of initial face-to-face MTM encounter) and one CPT 99607 (for an additional 15 minutes spent with the patient in a face-to-face MTM encounter). M.C.'s Medicare Part D plan may require the practitioner to bill the prescription drug plan initially, and then the plan would pay the community pharmacy directly instead of reimbursing the individual pharmacist. Documentation of the visit would need to be stored at the site of the encounter in case any information was requested from M.C.'s prescription drug plan.

Case 1-4, Question 5: M.C. has just been hospitalized in a large medical center for renal failure and urosepsis. The pharmacist has access to the medical chart, nursing record, MAR, and a computer that directly links to the clinical laboratory. The pharmacists at this facility assess the patient's drug therapy and routinely provide clinical pharmacokinetic monitoring. How would the pharmacist approach M.C. differently in this inpatient setting compared with the pharmacist in Case 1-4, Question 1 who worked in a community pharmacy?

MEDICATION THERAPY MANAGEMENT IN THE ACUTE CARE SETTING

Similar to the outpatient setting, the SOAP format is often used when documenting the encounter of the hospitalized patient; however,

obtaining the information needed poses unique challenges. In this setting, subjective information may be more difficult to obtain at the time of assessment in those patients presenting with cognitive impairment resulting from their acute condition, such as the seriously ill or injured patient. Objective data, on the other hand, are more readily available and retrievable with access to pharmacy, laboratory, and other medical record information. On admission to the health care facility, the medication reconciliation process should be initiated to identify any variances in the admission orders when compared with the patient's home medication list. With acute medical problems superimposed on chronic conditions, it is not unusual to have new medications added and home medications held, changed, or discontinued.

Assessing the appropriateness of drug therapy requires a basic understanding of both pharmacokinetic (eg, absorption, distribution, metabolism, and elimination) and pharmacodynamic (eg, relief of pain with an analgesic or reduction of BP with an antihypertensive agent) principles. This detailed assessment and monitoring is dependent on the availability of robust patient and laboratory data. The inpatient setting is a relatively data-rich environment in which access to needed information is readily available. Knowledge of the patient's height, body weight, and hepatic and renal function are essential for proper dosage considerations. The type of hospitalized patient will vary from the short-stay elective surgery patient to the critically ill hemodynamically compromised patient. The pharmacist must be aware of how pharmacokinetics and pharmacodynamics can be altered throughout the hospitalization or disease-state process in each patient evaluated. This heightened awareness will allow for timely interventions and minimize medication errors resulting from improper or delayed dosage adjustments because the clinical status of the patient changes. Drug level monitoring may be suitable for certain medications and is of great clinical value; nevertheless, it is important to take into consideration clinical response to drug therapy along with the assessment of a specific laboratory value. Accurate interpretation of any drug level requires review of the nursing MAR (or eMAR), evaluating time of drug

administration to serum sample acquisition. When serum drug levels are obtained, they must be reviewed for validity before alterations in medication regimens are made. If a serum drug concentration seems unusually high or low, the clinician must consider all of the various factors that might influence the serum concentration of the drug in that particular patient. When the reason for an unexpected abnormal serum drug concentration is not apparent, the test should be repeated before considering a dose change that may cause supratherapeutic or subtherapeutic concentrations resulting from erroneous data (see Chapter 2, Interpretation of Clinical Laboratory Tests).

When M.C. was seen in the community pharmacy, the pharmacist assessed her chronic conditions, her cost issues, and her drug therapy. Monitoring in the community pharmacy–based MTM program occurs at regular time intervals and is less sensitive to the day-to-day changes of the patient. However, in the inpatient setting, M.C. has acute conditions (renal failure and urosepsis) in addition to her chronic conditions. Monitoring of medication therapy will occur frequently, resulting in a dynamic treatment plan for her acute and chronic conditions.

Although the inpatient setting is relatively data rich, the information gathered and the assessment and plan formulated in the facility must be communicated to other providers once the patient is discharged. At discharge, it is critical to ensure that the patient has follow-up with their primary care physician or coordinated care team in a timely manner. At this point, it is again critical for the pharmacist to perform medication reconciliation to determine exactly what did happen once the patient returned home. This closes the loop at a critical time when the patient is prone to medication errors and readmission.

MEDICATION THERAPY MANAGEMENT AND PHARMACOGENOMICS

The use of genetic information to predict an individual's response to a drug, known as *pharmacogenomics*, is currently factoring into drug design and development. Using genetic information to tailor drug therapy for an individual will reduce the risk of adverse events, potentially improve patient outcomes, and create a more efficient drug development process. By transforming drug therapy into a patient-specific approach, the health care community is one step closer to achieving the new medical paradigm of personalized health care.[33]

MTM can be the vehicle to allow pharmacists to serve an integral role in applying pharmacogenomics into clinical practice to improve the quality and safety of health care. Incorporating pharmacogenomics into MTMS allows pharmacists to lend their expertise to the treatment planning process to optimize treatment outcomes. Pharmacists, working collaboratively with prescribers and laboratory facilities, could review medications prescribed for a patient and the patient's genomic data to then offer an assessment on whether a prospective drug would provide the best fit for the condition and patient. Through MTMS and pharmacogenomics, pharmacists can optimize drug choice and maximize therapy outcomes (see Chapter 4, Pharmacogenomics and Personalized Medicine).

To successfully integrate a pharmacogenomic component within the clinical decision-making process, key pharmacogenomic data must be identified. The challenge is complex, and research has begun to bring the application of pharmacogenomics to patients as part of the health care delivery system. The pharmacy profession must define a process for the application of pharmacogenomic data into pharmacy clinical practice that is aligned with MTMS delivery. A viable business model that encourages and promotes the use of the clinical expertise of pharmacists working in collaboration with other health care providers and laboratories should be developed for these practices. The development of technology solutions that support the pharmacist's role in this emerging field should also be encouraged and directed.[33]

CONCLUSION

MTMS are intended to be applicable to patients in all care settings where the patients or their caregivers can be actively involved with managing their medication therapy. The goals of all pharmacists providing MTMS are to confirm that the patient's medication therapy is ideal and that the best possible outcomes from treatment are achieved. The MTM process needs to be properly documented and accurately shared with all providers who are part of the patient's health care team. As drug therapy and technology options continue to evolve, pharmacists are encouraged to provide and optimize MTMS to improve patient outcomes and medication use.

ACKNOWLEDGMENTS

The authors acknowledge Mary Anne Koda-Kimble, Wayne Kradjan, Robin Corelli, Lloyd Young, B. Joseph Guglielmo, Brian Alldredge, Marilyn Stebbins, Timothy Cutler, and Patricia Parker for their contributions to the version of this chapter found in previous editions.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American Pharmacists Association, National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core

elements of an MTM service model (version 2.0). *J Am Pharm Assoc (2003).* 2008;48(*3*):341–353. (24)

Bluml BM. Definition of medication therapy management: development of professionwide consensus. *J Am Pharm Assoc (2003).* 2005;45(*5*):566–572. (1)

Cipolle RJ, Strand L, Morley P, Cipolle R, eds. *Pharmaceutical Care Practice: The Clinician's Guide*. 2nd ed. McGraw-Hill; 2004. (15)

Health Care and Education Reconciliation Act of 2010. Pub L No. 111–152, 124 Stat 1029. (7)

Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm.* 1990;47(*3*):533–543. (3)

Office of the National Coordinator for Health Information Technology (ONC), Department of Health and Human Services. Health information technology: initial set of standards, implementation specifications, and certification criteria for electronic health record technology. *Fed Regist*. 2010;75(*144*):44589–44654. (16)

Patient Protection and Affordable Care Act (PPACA). Pub L No. 111–148, 124 Stat 119. (6)

Rovers JP, Currie JD, eds. *A Practical Guide to Pharmaceutical Care: A Clinical Skills Primer*. 3rd ed. American Pharmacists Association; 2007. (4)

Key Website

Ambulatory Health Care: 2022 National Patient Safety Goals. Joint Commission on Accreditation of Healthcare Organizations. https://www.jointcommission.org/standards/national-patient-safety-goals/ambulatory-health-care-national-patient-safety-goals/

COMPLETE REFERENCES CHAPTER 1 MEDICATION THERAPY MANAGEMENT AND ASSESSMENT OF THERAPY

1. Bluml BM. Definition of medication therapy management: development of profession wide consensus. *J Am Pharm Assoc (2003)*. 2005;45(5):566–572.
2. Wolters Kluwer. A decade of Medicare Part D: driving MTM services. Accessed November 6, 2020. https://www.wolterskluwer.com/en/expert-insights/a-decade-of-medicare-part-d-driving-mtm-services
3. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm*. 1990;47(3):533–543.

4. Rovers JP, Currie JD, eds. *A Practical Guide to Pharmaceutical Care: A Clinical Skills Primer*. 3rd ed. American Pharmacists Association; 2007.
5. Isetts BJ, Buffington DE; Pharmacist Services Technical Advisory Coalition. CPT code-change proposal: national data on pharmacists' medication therapy management services. *J Am Pharm Assoc (2003)*. 2007;47(4):491–495.
6. Patient Protection and Affordable Care Act (PPACA). Pub L No. 111–148, 124 Stat 119, to be codified as amended at scattered sections of 42 USC. Enacted March 23, 2010.
7. Health Care and Education Reconciliation Act of 2010. Pub L No. 111–152, 124 Stat 1029. Enacted March 30, 2010.
8. Raghupathi W. An empirical study of chronic diseases in the United States: a visual analytics approach to public health. *Int J Environ Res Public Health*. 2018;15(3):431. doi:10.3390/ijerph15030431
9. Tinker A. How to improve patient outcomes for chronic diseases and comorbidities. Accessed December 30, 2020. http://www.healthcatalyst.com/wp-content/uploads/2014/04/How-to-Improve-Patient-Outcomes.pdf
10. ASHP-APhA Medication Reconciliation Initiative Workgroup Meeting, February 12, 2007. Accessed July 4, 2017. https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/quality-improvement/care-coordination-medication-reconciliation-initiative-workgroup-meeting.pdf
11. National Patient Safety Goals. Joint Commission on Accreditation of Healthcare Organizations. Accessed July 4, 2017. https://www.jointcommission.org/standards/national-patient-safety-goals/
12. National Patient Safety Goals. Joint Commission on Accreditation of Healthcare Organizations. Accessed June 17, 2015. http://www.jointcommission.org/standards_information/npsgs.aspx
13. 2020 National Patient Safety Goals. Joint Commission on Accreditation of Healthcare Organizations. Accessed December 1, 2020. https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2020/simplified_2020-ome-npsgs-eff-july-final.pdf
14. Centers for Medicare and Medicaid Services. 2017 Start Ratings. Accessed December 1, 2020. https://www.cms.gov/newsroom/fact-sheets/2017-star-ratings
15. Cipolle RJ, Strand L, Morley P, Cipolle R, eds. *Pharmaceutical Care Practice: The Clinician's Guide*. 2nd ed. McGraw-Hill; 2004.
16. Office of the National Coordinator for Health Information Technology (ONC), Department of Health and Human Services. Health information technology: initial set of standards, implementation specifications, and certification criteria for electronic health record technology. *Fed Regist*. 2010;75(144):44589–44654.

17. Miller WR, Rollnick S. *Motivational Interviewing: Preparing People to Change Addictive Behavior*. Guilford Press; 1991.
18. Center for Substance Abuse Treatment. Motivational interviewing as a counseling style. In: *Enhancing Motivation for Change in Substance Abuse Treatment*. Substance Abuse and Mental Health Services Administration (US); 1999:chap 3. Treatment Improvement Protocol (TIP) Series, No. 35. http://www.ncbi.nlm.nih.gov/books/NBK64964/
19. Nester TM, Hale LS. Effectiveness of a pharmacist-acquired medication history in promoting patient safety. *Am J Health Syst Pharm*. 2002;59(22):2221–2225.
20. Varkey P, Cunningham J, O'Meara J, Bonacci R, Desai N, Sheeler R. Multidisciplinary approach to inpatient medication reconciliation in an academic setting. *Am J Health Syst Pharm*. 2007;64(8):850–854.
21. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Ann Intern Med*. 2003;138(3):161–167.
22. Unroe KT, Pfeiffenberger T, Riegelhaupt S, Jastrzembski J, Lokhnygina Y, Colón-Emeric C. Inpatient medication reconciliation at admission and discharge: a retrospective cohort study of age and other risk factors for medication discrepancies. *Am J Geriatr Pharamcother*. 2010;8(2):115–126.
23. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiol Drug Saf*. 2010;19(9):901–910.
24. American Pharmacists Association, National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core elements of an MTM service model (version 2.0). *J Am Pharm Assoc (2003)*. 2008;48(3):341–353.
25. Gray C, Cooke CE, Brandt N. Evolution of the Medicare Part D Medication Therapy Management Program from inception in 2006 to the present. *Am Health Drug Benefits*. 2019;12(5):243–251.
26. Cranor CW, Bunting BA, Christensen DB. The Asheville Project: long-term clinical and economic outcomes of community pharmacy diabetes care program. *J Am Pharm Assoc (Wash)*. 2003;43(2):173–184.
27. Chrischilles EA, Carter BL, Lund BC, et al. Evaluation of the Iowa Medicaid pharmaceutical case management program. *J Am Pharm Assoc (2003)*. 2004;44(3):337–349.
28. Bodenheimer T, Chen E, Bennett HD. Confronting the growing burden of chronic disease: can the U.S. health care workforce do the job? *Health Aff (Millwood)*. 2009;28(1):64–74.
29. Smith M, Bates DW, Bodenheimer T, Cleary PD. Why pharmacists belong in the medical home. *Health Aff (Millwood)*. 2010;29(5):906–913.
30. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American

College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596–e646. https://doi.org/10.1161/CIR.0000000000000678

31. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults. *Arch Intern Med*. 2003;163(22):2716–2724.
32. American Geriatrics Society. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331–1346.
33. Reiss SM; American Pharmacists Association. Integrating pharmacogenomics into pharmacy practice via medication therapy management. *J Am Pharm Assoc*. 2011;51:e64–e74.

2

Interpretation of Clinical Laboratory Tests

Erika Felix-Getzik, Yulia A. Murray, and Stefanie C. Nigro

CORE PRINCIPLES		CHAPTER CASES
1	Laboratory findings should be used to complement other subjective and objective findings and must not be evaluated in isolation. The values must be assessed in context of the clinical situation and incorporate understanding of human physiology.	**Case 2-3 (Question 1)** **Case 2-4 (Question 1), Table 2-2** **Case 2-5 (Questions 1, 2), Table 2-3** **Case 2-6 (Questions 1, 2)**
2	Lack of availability, expense, or inconvenience may limit the usefulness of some clinical laboratory tests. Estimations by means of equations or nomograms may be used in clinical practice to overcome these barriers.	**Case 2-1 (Question 1), Table 2-2**
3	Test reliability is impacted by various	**Case 2-1 (Question 1)** **Case 2-2 (Question 1)**

	factors including statistical and preanalytical variations, accuracy, and precision.	**Case 2-4 (Question 1), Table 2-1, Table 2-2**
4	Laboratory findings can be helpful in assessing clinical disorders, establishing a diagnosis, assessing drug therapy, or evaluating disease progression.	**Case 2-1 (Question 1), Table 2-2** **Case 2-2 (Question 1), Table 2-3** **Case 2-3 (Question 1)** **Case 2-4 (Question 1)** **Case 2-5 (Questions 1, 2)** **Case 2-6 (Questions 1, 2)**

INTRODUCTION

This chapter provides the reader with an overview of laboratory tests commonly used in clinical practice. Specialized laboratory tests, which are used to monitor specific disease states or specific drug therapies, are integrated into the case histories, questions, and answers in the disease-specific chapters of this textbook. Over-the-counter or patient-directed laboratory tests are briefly discussed at the end of this chapter because of their increased availability and use. All stated laboratory ranges were obtained from the key references listed at the end of this chapter.[1–3]

GENERAL PRINCIPLES

Generally, laboratory tests should be ordered only if the results of the test will guide decisions about the care of the patient. Serum, urine, and other bodily fluids can be analyzed routinely; however, the economic cost and impact on the quality of life related to obtaining

these data must always be balanced by benefit to patient-specific outcomes.

Reference Ranges

The term *reference range* is typically preferred in clinical practice rather than *normal range* because there are several factors that contribute to the "normal" value for each individual. Laboratory findings, within and outside the reference range, can be helpful in assessing clinical disorders, establishing a diagnosis, assessing drug therapy, or evaluating disease progression. In addition, baseline laboratory tests are often necessary to evaluate disease progression and response to therapy or to monitor the development of toxicities associated with therapy.

When assessing laboratory findings, it is important to be mindful that values outside the reference range may not require clinical intervention. Values must be assessed in context of the clinical situation and incorporate understanding of human physiology. Likewise, values that fall within the reference range may need further assessment secondary to limitations of the test or impact of biologic or physiologic considerations. Laboratory findings should also be used to complement other subjective and objective findings, and must not be evaluated in isolation.

Laboratory test results are specific to the clinical laboratory conducting the test and can vary based on the type of equipment and testing methods used. Consequently, clinicians should rely on reference ranges listed by their own clinical laboratory when assessing laboratory tests.

Evaluating Laboratory Results

The reference ranges provided in this chapter are for general illustrative purposes. When applying this information to the clinical setting, appropriate clinical assessment and judgment should be applied. Patient-specific attributes such as the individual's age,

biologic sex, race, clinical presentation, medication history, and lifestyle are factors that may influence reported laboratory results and, therefore, must be taken into consideration. Statistical and preanalytical variations are common, and must also be evaluated in the context of the result obtained. Refer to **Table 2-1** for examples of common preanalytical variables.

Table 2-1

Preanalytical Variation: Factors Affecting the Test Result from the Time the Test Is Ordered Until It Arrives at the Laboratory

Variable	Example(s)
Incorrect test ordered	Albumin ordered to assess the impact of recent dietary change (prealbumin better marker for acute changes)
Sample incorrectly labeled	Sample obtained from one patient and labeled with another name
Improper preparation for test	Fasting indicated, but not followed: fasting glucose, complete lipid panel Pretest medications not administered in the appropriate manner Pretest diet restrictions not met: rare meat ingested before guaiac test
Medication	Medication interfered with testing procedure or by pharmacologic effect: β-agonist can reduce serum potassium concentrations, thiazides can increase serum uric acid levels.
Improper timing of test	Vancomycin trough taken after first dose (rather than before the fourth dose) aPTT measured 2 hours after initial dose (rather than 6 hours after start)
	Fasting glucose test completed shortly after a meal, TSH measured 2 weeks after dose change (rather than 4–6 weeks after change)
Collection incomplete or improper	Abnormal 24-hour urine collection secondary to patient forgetting to void in provided container, blood specimen obtained from extremity with IV infusion site resulting in dilutional effect of glucose, BUN, and electrolytes, specimen collected in incorrect container
Improper handling or	Hyperkalemia because of hydrolysis of blood specimen

storage	
Poor accuracy or precision	Faulty or outdated laboratory reagents in use
Technical	Result incorrectly read, computer keying error
Biologic sex	Many laboratory findings are sex dependent.
Age	Neonatal, pediatric, adult, and geriatric populations have unique reference ranges for numerous laboratory tests.
Pregnancy	Gestational status impacts numerous laboratory findings: alkaline phosphatase, cholesterol, iron, etc.
Posture	Being in upright position during laboratory sampling can increase albumin, calcium, iron, etc.
Exercise	Strenuous exercise before testing can impact lactate, creatine kinase, ALT, AST, uric acid, etc.
Normal physiologic fluctuations	Circadian rhythm can impact cortisol, serum iron, serum creatinine, WBC count, etc.
Medical procedures	Blood transfusion with red blood cells before hemoglobin A_{1c} measured results in normal A_{1c} for poorly controlled individual with diabetes, creatine kinase elevated secondary to recent cardioversion

A_{1c}, hemoglobin A_{1c} (also glycated hemoglobin); ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; IV, intravenous; TSH, thyroid-stimulating hormone; WBC, white blood cell.

Test Reliability

As a result of probability, if the same test is completed multiple times on the same sample, typically 1 of 20 results or 5% will be reported outside of the provided reference range. Indicators of test reliability include accuracy, precision, sensitivity, and specificity. Precision refers to the repeatability of a laboratory test (ie, test results fall within a similar value when repeated), whereas accuracy is the ability of a test to provide a result that is reflective of the “true” value

(ie, the test result matches the actual value). Quality control and assurance practices at each laboratory are monitored regularly to ensure reliability of results. Typically, if a result that is significantly outside the reference range is obtained, the laboratory will repeat the test to confirm or refute the finding.

Research studies generally establish the sensitivity and specificity of laboratory tests. Clinically, these are essential to distinguish the presence or absence of a disease or condition. Sensitivity is the ability of the test to correctly identify the disease or condition. If a test is 95% sensitive, then 95% of the individuals will be correctly identified as having the disease or condition, but 5% will have a negative test result even though they have the disease or condition (false negative). Specificity is the ability of the test to rule out individuals who do not have the disease or condition. If a test is 95% specific, then 95% of the individuals without disease will have a correct negative result, but 5% will be identified as having the disease or condition even though they are negative (false positive).

Units of Measure

The International System of Units (SI) reports clinical laboratory values using the metric system. The basic unit of mass for the SI system is the *mole*, which is not influenced by the added weight of salt or ester formulations. Therefore, the mole is technically and pharmacologically more meaningful than is the gram because each physiologic reaction occurs on a molecular level. Efforts to implement the SI system internationally for laboratory test reports have been resisted in the United States. Despite adopting SI transition policies in the late 1980s, major American medical journals have since reverted to the traditional units for laboratory test reporting.[4,5] In this chapter, reference ranges for common laboratory tests are presented in both conventional and SI units, along with "conversion factors" to interchange traditional and SI units (**Tables 2-2** and **2-3**).

Table 2-2
Blood Chemistry Reference Values

Laboratory Test	Normal Reference Values		Conversion Factor	Comments
	Conventional Units	SI Units		
Electrolytes				
Sodium	135–147 mEq/L or mmol/L	135–147 mmol/L	1	Low sodium is usually caused by excess water (eg, ↑ serum antidiuretic hormone) and is treated with water restriction. ↑ in severe dehydration, diabetes insipidus, significant renal and GI losses
Potassium	3.5–5 mEq/L	3.5–5 mmol/L	1	↑ with renal dysfunction, acidosis, K-sparing diuretics, hemolysis, burns, crush injuries. ↓ by diuretics, alkalosis, severe vomiting and diarrhea, heavy NG suctioning
CO_2 content	21–32 mEq/L	21–32 mmol/L	1	Sum of HCO_3^- and dissolved CO_2. Reflects acid–base balance and compensatory pulmonary (CO_2) and renal (HCO_3^-) mechanisms. Primarily reflects HCO_3^-
Chloride	95–110 mEq/L	95–110 mmol/L	1	Important for acid–base balance. ↓ by GI loss of chloride-rich fluid (vomiting, diarrhea, GI suction, intestinal fistulas, overdiuresis)
BUN	8–20 mg/dL	2.8–7.1 mmol/L	0.357	End product of protein metabolism, produced by liver, transported in blood, excreted renally. ↑ in renal dysfunction, high protein intake, upper GI bleeding, volume contraction
Creatinine	≤1.5 mg/dL	≤133 μmol/L	88.4	Major constituent of muscle; rate of formation constant; affected by muscle mass (lower with aging and gender); excreted renally. ↑ in renal dysfunction. Used as a primary marker for renal function (GFR)
CrCl	90–130 mL/minute	1.5–2.16 mL/s	0.01667	Reflects GFR; ↓ in renal dysfunction. Used to adjust dosage of renally eliminated drugs
Estimated GFR	90–120 mL/minute/1.73 m^2	n/a	n/a	Possibly a more accurate reflection of renal function than is CrCl. Still influenced by muscle mass

Homocysteine	4–12 µmol/L	4–12 µmol/L	1	Damages vessel endothelial, which may increase the risk for cardiac disease. Associated with deficiencies in folate, vitamin B_6, and vitamin B_{12}
LDH	100–250 IU/L	1.67–4.17 µkat/L	0.01667	High in heart, kidney, liver, and skeletal muscle. Five isoenzymes: LD1 and LD2 mostly in heart, LD5 mostly in liver and skeletal muscle, LD3 and LD4 are nonspecific. ↑ in malignancy, extensive burns, PE, renal disease
BNP	<100 pg/mL	<100 ng/L	1	BNP >500 ng/L indicates congestive heart failure. Released from ventricles with ↑ workload placed on heart
NT-proBNP	<400 pg/mL	<400 ng/L	1	NT-proBNP >2000 ng/L indicates congestive heart failure.
CRP	0–1.6 mg/dL	0–16 mg/L	10	Nonspecific indicator of acute inflammation. Similar to ESR, but more rapid onset and greater elevation. CRP >3 mg/dL increases risk of cardiovascular disease.
hs-CRP	0–1.0 mg/dL	0–10 mg/L	10	More sensitive measure of CRP
Liver Function				
AST	0–35 IU/L	0–0.58 µkat/L	0.01667	Large amounts in heart and liver; moderate amounts in muscle, kidney, and pancreas. ↑ with MI and liver injury. Less liver specific than is ALT
ALT	0–35 IU/L	0–0.58 µkat/L	0.01667	From heart, liver, muscle, kidney, pancreas. ↑ negligible unless parenchymal liver disease. More liver specific than is AST
ALP	20–130 IU/L	0.33–2.17 µkat/L	0.01667	Large amounts in bile ducts, placenta, bone. ↑ in bile duct obstruction, obstructive liver disease, rapid bone growth (eg, Paget disease), pregnancy
GGT				Sensitive test reflecting hepatocellular injury; not helpful in differentiating liver disorders. Usually high in chronic alcoholics
Male	9–50 IU/L			
Female	8–40 IU/L			
Bilirubin—total	0.1–1 mg/dL	2–18 µmol/L	17.1	Breakdown product of hemoglobin, bound to albumin, conjugated in liver. Total bilirubin includes direct (conjugated) and indirect bilirubin. ↑ with hemolysis, cholestasis, liver injury
Bilirubin—direct	0–0.2 mg/dL	0–4 µmol/L	17.1	
Miscellaneous				
Amylase	35–118 IU/L	0.58–1.97 µkat/L	0.01667	Pancreatic enzyme; ↑ in pancreatitis or duct obstruction
Lipase	10–160 IU/L	0–2.67 µkat/L	0.01667	Pancreatic enzyme, ↑ acute pancreatitis, elevated for a longer period than is amylase
PSA	0–4 ng/mL	0–4 µg/L	1	↑ in BPH and also in prostate cancer. PSA levels of 4–10 ng/mL should be worked up. Risk of prostate cancer increased if free PSA/total PSA <0.25
TSH	0.5–4.7 µIU/mL	0.5–4.7 mIU/L	1	↑ TSH in primary hypothyroidism requires exogenous thyroid supplementation; ↓ TSH in hyperthyroidism
Procalcitonin	<0.5 ng/mL	<0.5 µg/L	1	↑ Bacterial infections—low risk of sepsis if <0.5 ng/mL; high risk of severe sepsis if >2.0 ng/mL

Total cholesterol	<200 mg/dL	<5.2 mmol/L	0.02586	Consult current guidelines.
LDL	<100 mg/dL	<2.58 mmol/L	0.02586	Current guidelines recommend starting moderate- to high-intensity statin therapy based on risk stratification; consult current guidelines.
HDL	Female: >50 mg/dL Male: >40 mg/dL	Female: >1.29 mmol/L Male: >1.03 mmol/L	0.02586	Consult current guidelines.
Triglycerides (fasting)	<150 mg/dL	<1.70 mmol/L	0.0113	↑ by alcohol, saturated fats, drugs. Obtain fasting level. Consult current guidelines.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BPH, benign prostatic hypertrophy; BUN, blood urea nitrogen; CHF, congestive heart failure; CK, creatine kinase (formerly known as creatine phosphokinase); CrCl, creatinine clearance; CRP, C-reactive protein; cTnI, cardiac troponin I; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; GGT, γ-glutamyl transferase; GI, gastrointestinal; HDL, high-density lipoprotein; IM, intramuscularly; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MI, myocardial infarction; NG, nasogastric; PE, pulmonary embolism; PSA, prostate-specific antigen; SI, International System of Units; TPN, total parenteral nutrition; TSH, thyroid-stimulating hormone.

Table 2-3
Hematologic Laboratory Values

Laboratory Test	Normal Reference Values		Comments
	Conventional Units	SI Units	
RBC Count			
■ Male	4.3–5.9 × 10^6/μL	4.3–5.9 × 10^{12}/L	
■ Female	3.5–5.0 × 10^6/μL	3.5–5.0 × 10^{12}/L	
Hct			↓ with anemias, bleeding, hemolysis. ↑ with polycythemia, chronic hypoxia
■ Male	40.7%–50.3%	0.4–0.503	
■ Female	36%–44.6%	0.36–0.446	
Hgb			Similar to Hct
■ Male	13.8–17.5 g/dL	138–175 g/L	
■ Female	12.1–15.3 g/dL	121–153 g/L	
MCV	80–97.6 μm^3	80–97.6 fL[a]	Describes average RBC size; ↑ MCV—macrocytic, ↓ MCV—microcytic
MCH	27–33 pg/cell	1.66–2.09 fmol/cell	Measures average weight of Hgb in RBC
MCHC	33–36 g/dL	20.3–22 mmol/L	More reliable index of RBC hemoglobin than is MCH. Measures average concentration of Hgb in RBC. Concentration will not change with weight or size of RBC.
Reticulocyte count (adults)	0.5%–1.5%	0.005–0.015	Indicator of RBC production; ↑ suggests ↑ number of immature erythrocytes released in response to stimulus (eg, iron in iron deficiency anemia)
ESR	0–30 mm/hour	0–30 mm/hour	Nonspecific; ↑ with inflammation, infection, neoplasms, connective tissue disorders, pregnancy, nephritis. Useful monitor of temporal arteritis and polymyalgia rheumatica
WBC count	3.8–9.8 × 10^3/μL	3.8–9.8 × 10^9/L	Consists of neutrophils, lymphocytes, monocytes, eosinophils, and basophils; ↑ in infection and stress
ANC	2000 cells/mμL		ANC − WBC × (% neutrophils + % bands)/100; if <500 ↑ risk infection, if >1000 ↓ risk infection
Neutrophils	40%–70%	0.4–0.7	↑ in neutrophils, suggests bacterial or fungal infection. ↑ in bands, suggests bacterial infection
Bands	0%–10%	0–0.1	
Lymphocytes	22%–44%	0.22–0.44	
Monocytes	4%–11%	0.04–0.11	

Eosinophils	0%–8%	0–0.08	Eosinophils ↑ with allergies, parasitic infections, and certain neoplasms
Basophils	0%–3%	0–0.03	
Platelets	150–450 × 10^3/μL	150–450 × 10^9/L	<100 × 10^3/μL: thrombocytopenia <20 × 10^3/μL: ↑ risk of severe bleeding
Iron			
■ Male	45–160 μg/dL	8.1–31.3 μmol/L	Body stores two-thirds in Hgb; one-third in bone marrow, spleen, liver; only small amount present in plasma. Blood loss major cause of deficiency
■ Female	30–160 μg/dL	5.4–31.3 μmol/L	↑ needs in pregnancy and lactation
■ TIBC	220–420 μg/dL	39.4–75.2 μmol/L	↑ capacity to bind iron with iron deficiency

ANC, absolute neutrophil count; ESR, erythrocyte sedimentation rate; Hct, hematocrit; Hgb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; RBC, red blood cell; SI, International System of Units; TIBC, total iron-binding capacity; WBC, white blood cell.

[a]fL, femtoliter; femto, 10^{-15}; pico, 10^{-12}; nano, 10^{-9}; micro, 10^{-6}; milli, 10^{-3}.

FLUIDS AND ELECTROLYTES

Refer to Chapter 27, Fluid and Electrolyte Disorders, for more detailed information.

Sodium

Reference Range: 135–147 mEq/L or mmol/L

Sodium is the predominant cation of the extracellular fluid (ECF), and human cells reside in salt water. Along with chloride, potassium, and water, sodium is important in establishing serum osmolarity and osmotic pressure relationships between intracellular fluid (ICF) and ECF. Osmoregulatory system regulates the plasma sodium concentrations to remain in a normal range by controlling water intake and excretion.[6] An increase in the serum sodium concentration could suggest either impaired sodium excretion or volume contraction. On the contrary, a decrease in the serum sodium concentration to less-than-normal values could reflect hypervolemia, abnormal sodium losses, or sodium starvation. Although healthy individuals are able to maintain sodium

homeostasis without difficulty, patients with kidney failure, heart failure (HF), or lung disease often encounter sodium and water imbalances. In adults, changes in serum sodium concentrations most often represent water rather than sodium imbalance. Therefore, serum sodium concentrations are more reflective of a patient's fluid status rather than of sodium balance. Clinical manifestations of hyponatremia or hypernatremia are mostly neurologic, and rapid changes in serum sodium concentrations can lead to severe and sometimes fatal brain injury.[6]

HYPONATREMIA

Hyponatremia can result from dilution of the sodium concentration in serum or from a total body depletion of sodium. The finding of hyponatremia implies that sodium has been diluted throughout all body fluids because water moves freely across cell membranes in response to oncotic pressures. Hyponatremia can denote low, high, or normal tonicity. Dilutional hyponatremia is the most common form and results from water retention.[7] Some clinical conditions such as cirrhosis, congestive heart failure (CHF), the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and renal impairment, as well as the administration of osmotically active solutes (eg, albumin and mannitol) are commonly associated with dilutional hyponatremia. Drugs that can induce SIADH, thereby causing a reversible hyponatremia (especially in the elderly), include cyclophosphamide, carbamazepine, desmopressin, oxcarbazepine, oxytocin, serotonin selective reuptake inhibitors, and vincristine.[7–9] Hyponatremia that results from sodium depletion presents as a low serum sodium concentration in the absence of edema. Sodium-depletion hyponatremia can be caused by mineralocorticoid deficiencies, sodium-wasting renal disease, or replacement of sodium-containing fluid losses with nonsaline solutions.[7] Therapy with thiazide diuretics may also lead to the development of severe hyponatremia. Hyponatremia is frequently seen in hospitalized patients; however, morbidity varies significantly in severity, and

serious complications can be due to the disorder itself or due to the inappropriate management and rapid correction of the sodium levels.

HYPERNATREMIA

Hypernatremia represents a state of relative water deficiency in relation to the body's sodium stores. Because sodium contributes to the cell's tonicity, hypernatremia denotes hypertonicity and at least transient cellular dehydration.[10] Some of the causes of hypernatremia are loss of free water, loss of hypotonic fluid, or excessive sodium intake. Free water loss is uncommon, except in the presence of diabetes insipidus. Diarrhea is the most common cause of hypotonic fluid loss in infants and the elderly. Increased retention of sodium in patients with hyperaldosteronism can also increase serum sodium concentrations. Excessive salt intoxication is usually accidental or iatrogenic, and most commonly results from inappropriate intravenous (IV) administration of hypertonic salt solutions. Some β-lactam antibiotics (eg, ticarcillin) contain a modest sodium load and can cause fluid overload when high dosages are administered.

The primary defense against hypertonicity is thirst and subsequent fluid intake. Hypernatremic syndromes, therefore, usually occur in patients who are unable to drink sufficient fluids. For example, demented elderly patients are at increased risk because they depend on others for their water requirements. Similarly, patients who are vomiting, comatose, or not allowed oral fluids are at risk for hypernatremia.

Potassium

Reference Range: 3.5–5.0 mEq/L or mmol/L

Potassium is the most abundant intracellular cation in the body responsible for regulating enzymatic function and neuromuscular tissue excitability. Approximately 90% of the total body potassium is found in the ICF, with the majority in skeletal muscle, and only about 10% available in the ECF. The intracellular and extracellular

potassium concentrations are regulated by the sodium–potassium adenosine triphosphatase (Na^+-K^+-ATPase) pump. The potassium ion in the ECF is filtered freely at the glomerulus of the kidney, reabsorbed in the proximal tubule, and secreted into the distal segments of the nephron. Because the majority of potassium is sequestered within cells, a serum potassium concentration is not a good measure of total body potassium. Intracellular potassium, however, cannot be measured easily. Fortunately, the clinical manifestations of potassium deficiency (eg, fatigue, drowsiness, dizziness, confusion, electrocardiographic changes, muscle weakness, and muscle pain) correlate well with serum concentrations. The serum potassium concentration is buffered and can be within normal limits despite abnormalities in total body potassium. During potassium depletion, potassium moves from the ICF into the ECF to maintain the serum concentration. When the serum concentration decreases by a mere 0.3 mEq/L, the total body potassium deficit is ~100 mEq. Serum potassium concentrations, therefore, can be misleading when interpreted in isolation from other considerations, and assumptions should not be made as to the status of total body potassium concentration based solely on a serum concentration measurement. Disorders of potassium are commonly the result of (a) alterations in intake, (b) alterations with excretion, and/or (c) unbalanced transcellular shifting of potassium (eg, metabolic acidosis/alkalosis).

HYPOKALEMIA

The kidneys are responsible for about 90% of daily potassium loss (~40–90 mEq/day), and the remaining 10% of potassium is excreted in the stool and a negligible amount in sweat. The kidneys, however, have only a limited ability to conserve potassium. Even when potassium intake has ceased, the urine will contain at least 5 to 20 mEq of potassium per 24 hours. Therefore, prolonged IV therapy with potassium-free solutions in a patient unable to obtain potassium in foods (eg, nothing by mouth) can result in hypokalemia. Hypokalemia can also be induced by osmotic diuresis (eg, mannitol

and glucosuria), use of thiazide or loop diuretics (eg, hydrochlorothiazide, furosemide, respectively), excessive mineralocorticoid activity, or protracted vomiting. Although the fluid secreted along most of the upper gastrointestinal (GI) tract contains only a modest amount of potassium (ie, 5–20 mEq/L), vomiting can induce hypokalemia because of the combined effect from decreased food intake, loss of acid, alkalosis, and loss of sodium. The loss of large amounts of colonic fluid through severe diarrhea and/or laxative abuse can cause potassium depletion because fluid in the colon is high in potassium content (ie, 30–40 mEq/L). Insulin and stimulation of β_2-adrenergic receptors can also induce hypokalemia because both increase the movement of potassium into cells from the ECF. The magnitude of a potassium deficiency is difficult to establish because of the limited presence of potassium in the ECF. Equation 2-1 can be used to estimate the potassium deficit with hypokalemia:

$$\text{Kdeficit (mmol)} = (K_{\text{normal lower limit}} - K_{\text{measured}}) \times \text{kg of body weight} \times 0.4$$

(Eq. 2-1)

It is also important to note that hypomagnesemia often accompanies hypokalemia, because magnesium is necessary for the shifting of sodium, potassium, and calcium in and out of cells. As a result, individuals with hypokalemia not responding to potassium therapy may be refractory to treatment until hypomagnesemia is corrected. Some laboratories omit magnesium from the general electrolyte panel, so this test may need to be specially ordered.

HYPERKALEMIA

Hyperkalemia most commonly results from decreased renal excretion of potassium (eg, renal failure, renal hypoperfusion, and hypoaldosteronism), excessive exogenous potassium administration, or excessive cellular breakdown (eg, hemolysis, burns, crush injuries, surgery, and infections). Drug-induced causes include angiotensin-converting enzyme (ACE) inhibitors, angiotensin-

receptor blockers (ARBs), aldosterone antagonists, and nonsteroidal anti-inflammatory drugs, to name a few. Metabolic acidosis can also induce hyperkalemia because hydrogen ions move into cells in exchange for potassium and sodium. Abnormal potassium concentrations in the serum primarily affect excitability of nerve and muscle tissue (eg, myocardial tissue). As a result, arrhythmias can be induced by hyperkalemia or hypokalemia. Potassium also affects some enzyme systems and acid–base balance, as well as carbohydrate and protein metabolism.

Carbon Dioxide Content

Reference Range: 21–32 mEq/L or mmol/L

The carbon dioxide (CO_2) content in the serum represents the sum of bicarbonate (HCO_3^-) and dissolved CO_2 concentrations. The dissolved CO_2 represents a relatively small component of total CO_2 content, making CO_2 essentially a measure of the serum bicarbonate. Chloride and bicarbonate are the primary negatively charged anions that offset the positively charged cations (ie, sodium and potassium). CO_2 is a waste product that is produced after we burn food for energy. Healthy individuals are able to maintain CO_2 in an appropriate range. A CO_2 level below the reference range is associated with such conditions as diabetic ketoacidosis, Addison disease, and metabolic acidosis. A CO_2 level above the reference range is associated with dehydration, Cushing syndrome, and metabolic alkalosis.

Although several buffer systems (eg, hemoglobin [Hgb], phosphate, and protein) participate in regulating pH within physiologic limits, the carbonic acid–bicarbonate system is the most important. From a clinical standpoint, most disturbances of acid–base balance result from imbalances of the carbonic acid–bicarbonate system. The importance of bicarbonate in maintaining physiologic pH is presented in Chapter 26, Acid–Base Disturbances.

Chloride

Reference Range: 95–110 mEq/L or mmol/L

Chloride (Cl^-) is the principal inorganic anion of the ECF; changes in chloride concentration are usually related to sodium concentration in an effort to maintain a neutral charge. Serum chloride has no real diagnostic significance. The relationship between serum concentrations of sodium, bicarbonate, and chloride is described by Eq. 2-2, where *R* represents the anion gap (AG):

$$Cl^- + HCO_3^- + R = Na^+ \quad \textbf{(Eq. 2-2)}$$

As with bicarbonate, chloride contributes to maintaining acid–base balance. A decreased serum chloride often accompanies metabolic alkalosis, whereas an increased serum chloride may indicate a hyperchloremic metabolic acidosis. The serum chloride, however, can also be slightly decreased in acidosis if organic acids or other acids are the primary cause of the acidosis. *Hyperchloremia*, absence of metabolic acidosis, is seldom encountered because chloride retention is usually accompanied by sodium and water retention. *Hypochloremia* can result from excessive GI loss of chloride-rich fluid (eg, vomiting, diarrhea, gastric suctioning, and intestinal fistulas). Because chloride ions are excreted with cations by the kidneys, hypochloremia may also result from significant diuresis.

Anion Gap

Reference Range: 7–16 mEq/L or mmol/L

The R factor, or AG, represents the contribution of unmeasured acids, such as lactate, phosphates, sulfates, and proteins. As displayed in Eq. 2-2, a patient's AG is determined by subtracting the primary anions (Cl^- and HCO_3^-) from the primary cation (Na^+). Some clinicians include potassium in this determination and subtract the anions from both major cations (Na^+ and K^+). If potassium is not incorporated in the calculation, a normal AG is typically 5 to 12

mEq/mL. If potassium is considered, a normal AG would be <16 mEq/mL.

An elevated AG may be indicative of metabolic acidosis caused by an increase in lactic acids, ketoacids, salicylic acids, methanol, or ethylene glycol. A low AG may be the result of reduced concentrations of unmeasured anions (eg, hypoalbuminemia) or from systematic underestimation of serum sodium (eg, hyperviscosity of myeloma). See Chapter 26, Acid–Base Disturbances, for a more detailed discussion of the clinical use of the AG.

Blood Urea Nitrogen

Reference Range: 8–20 mg/dL or 2.8–7.1 mmol/L

Urea nitrogen is a waste product that comes from protein breakdown. It is produced solely by the liver, transported in the blood, and excreted by the kidneys. The serum concentration of urea nitrogen (ie, blood urea nitrogen [BUN]) is reflective of renal function because the urea nitrogen in the blood is filtered completely at the glomerulus of the kidney and then reabsorbed and tubularly secreted within nephrons. Acute or chronic renal failure is the most common cause of an elevated BUN. Although the BUN is an excellent screening test for renal dysfunction, it does not sufficiently quantify the extent of renal disease. In addition, several nonrenal factors such as unusually high protein intake, disease states that increase protein catabolism (or upper GI bleeding), and glucocorticoid therapy can increase the BUN concentration. Liver disease and a low protein diet can lead to a lower BUN concentration. A patient's hydration status will also influence BUN; a water deficit tends to concentrate the urea nitrogen, and a water excess dilutes the urea nitrogen. The ratio of BUN to serum creatinine (SCr) can also be of clinical use. A normal ratio is roughly 15:1. Ratios >20:1 are observed in patients with decreased blood flow to the kidney (eg, prerenal disease such as dehydration or conditions involving reduced cardiac output) or conditions involving increased protein in the blood (eg, dietary intake

or an upper GI bleed). Situations in which the BUN:SCr ratio is <15:1 are seen in patients with renal failure, significant malnourishment (decreased intake of protein), or severe liver disease in which the liver is no longer able to form urea. It is important to note that BUN can change independent of the renal function, and, therefore, SCr is more useful in estimating renal function.

Creatinine

Reference Range: ≤1.5 mg/dL or ≤133 µmol/L

Creatinine is derived from the creatine and phosphocreatine metabolism in the skeletal muscle. Its rate of formation for a given individual is remarkably constant and is determined primarily by an individual's muscle mass or lean body weight. Therefore, the SCr concentration is slightly higher in muscular subjects, but, unlike the BUN, it is less directly affected by exogenous factors or liver impairment. Once creatinine is released from muscle into plasma, it is excreted renally almost exclusively by glomerular filtration and is not reabsorbed or metabolized by the kidney. A decrease in the glomerular filtration rate (GFR) results in an increase in the SCr concentration. Thus, careful interpretation of the SCr concentration is used widely in the clinical evaluation of patients with suspected renal disease. However, SCr concentration on its own should not be utilized to assess the level of kidney function in an individual.

A doubling of the SCr level roughly corresponds to a 50% reduction in the GFR. This general rule of thumb only holds true for steady-state creatinine levels.[11]

Of importance, as patients become older, there is a reduction in muscle mass and creatinine production is progressively decreased. Furthermore, the SCr concentration in female patients is generally 0.2 to 0.4 mg/dL (85%–90%) less than that for males because females have less muscle mass.

Creatinine Clearance

Reference Range: 90–130 mL/minute

Because creatinine is cleared almost exclusively through the glomerulus in the kidney, creatinine clearance (CrCl) can be used as a clinically useful measure of a patient's GFR. CrCl serves as a valuable clinical parameter because many renally eliminated drugs are dose adjusted based on the patient's renal function. To determine actual CrCl, the patient's urine is collected for a 24-hour period, and the concentration of urine creatinine (mg/dL), total volume of urine collected during the 24-hour period (mL/minute), and SCr (mg/dL) are determined. The patient-specific measured CrCl is determined using Eq. 2-3:

$$\mathrm{CrCl} = \mathrm{U}_{\mathrm{creatinine}} \times \mathrm{U}_{\mathrm{volume}} / \mathrm{SCr} \times \mathrm{Time\ (minutes)} \quad \textbf{(Eq. 2-3)}$$

Unfortunately, urine collections are time-consuming and expensive, and incomplete collections can substantially underestimate renal function. In lieu of measuring actual CrCl, simplistic equations are commonly used to estimate a patient's CrCl. The following Cockcroft–Gault formula incorporates age, body weight, and SCr.[12] This formula can be utilized to estimate renal function when SCr is stable. Typically, clinicians use ideal body weight (IBW) in the calculation of estimated CrCl; however, actual body weight (ABW) may be used when ABW is less than IBW. For obese patients who are >20% to 30% of their IBW, an adjusted body weight (0.4 [ABW − IBW] + IBW) should be used.[13] Equation 2-4 has the highest correlation and the greatest accuracy in patients with SCr concentrations <1.5 mg/dL[14]:

$$\text{Estimated CrCl for males (mL/minute)} = (140 - \text{Age})\ (\text{body weight in kg}) / (72)(\mathrm{SCr}_{(\mathrm{mg/dL})}) \quad \textbf{(Eq. 2-4)}$$

The Cockcroft–Gault formula must be multiplied by 85% to calculate CrCl for females to account for the fact that females have less muscle mass.

Another commonly used approach to estimating CrCl is the Jelliffe method,[14] shown in Eq. 2-5:

$$\text{Estimated CrCl for males (mL/minute/1.73 m}^2) = 98 - [(0.8)(\text{Age} - 20)]/ (\text{SCr}_{(\text{mg/dL})}) \quad \text{(Eq. 2-5)}$$

This Jelliffe formula must be multiplied by 90% to calculate the CrCl for females. The use of this method substantially underestimates CrCl for patients with SCr values <1.5 mg/dL,[15] whereas Cockcroft–Gault appears to have the highest correlation and greatest accuracy in patients with SCr values <1.5 mg/dL.[14] For patients with liver dysfunction, all methods of calculating CrCl from an SCr value are associated with significant overpredictions of CrCl.[16] Thus, methods for predicting CrCl should be used cautiously when attempting to adjust drug dosages in patients with liver disease. These equations should not be utilized in patients with rapidly changing GFR (eg, acute kidney injury) because they will not provide accurate estimates of the GFR.

CASE 2-1

QUESTION 1: A 24-hour CrCl determination was ordered for D.B., a 72-year-old, 136.69-pound (62-kg) White male. The following data were returned from the clinical laboratory (total collection time was 24 hours):

Total urine volume: 1000 mL
Urine creatinine concentration: 42 mg/dL
SCr: 2.0 mg/dL

What are the measured and the estimated CrCl for D.B. based on the given data?

Using Eq. 2-3, D.B. has a 24-hour measured CrCl of ~15 mL/minute. His estimated CrCl is 29.2 mL/minute using the Cockcroft–Gault method (Eq. 2-4). Based on both methods, D.B.'s ability to clear renally eliminated drugs is impaired, and adjustments to the dose/frequency will need to be made. An incomplete collection of urine during the 24-hour period or possible mishandling of the specimen can be explanations for the lower value seen with the measured CrCl. Because D.B. had an elevated SCr of 2.0 mg/dL, the accuracy of the Cockcroft–Gault estimation might also be

compromised. D.B.'s baseline SCr will need to be established, and if it is determined that SCr of 2.0 mg/dL is corresponding with his baseline, then the Cockcroft–Gault estimation will hold true; if SCr of 2.0 mg/dL represents an acute change, then the Cockcroft–Gault equation should not be used to estimate renal function in D.B.

Estimated Glomerular Filtration Rate

An alternative approach to the Cockcroft–Gault method of estimating an adult patient's clearance was developed as part of the Modification of Diet in Renal Disease (MDRD) study and has been referred to as the MDRD equation.[17] The originally described equation has been modified into an abbreviated format (Eq. 2-6), as follows:

$$\text{Estimated GFR}_{(\text{mL/minute/1.73 m}^2)} = 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}) \quad \textbf{(Eq. 2-6)}$$

where SCr is the serum creatinine in mg/dL, age is in years, and the appropriate additional components are included for female or African American patients. Equation 2-6 is applicable to laboratories reporting SCr values that have not been standardized. Starting in 2005, laboratories began standardizing their SCr values using an isotope dilution mass spectrometry to minimize the variation observed in SCr results from different clinical laboratories. In settings in which the SCr results have been standardized, the initial parameter in the MDRD equation is adjusted downward. The following is used to estimate GFR:

$$\text{Estimated GFR}_{(\text{mL/minute/1.73 m}^2)} = 175 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}) \quad \textbf{(Eq. 2-7)}$$

When compared with the Cockcroft–Gault approach, MDRD estimations of GFR were more consistent with actual measurements of GFR. However, because both approaches rely on SCr, the influence of muscle mass and dietary intake still must be taken into consideration. In certain patient populations (eg, obese and elderly patients), use of the MDRD can be less accurate, because the MDRD study equation was primarily derived from White subjects with a mean age of 51 years who had nondiabetic renal disease. It is important to note that recent evidence supports removing the race multiplier in the MDRD equation because it may overestimate renal function in patients designated as African American.[18] Although this may increase the prevalence and severity staging of chronic kidney disease (CKD), removal of the race multiplier can increase access to specialists, kidney transplant services, and medical nutrition therapy. It may also promote the early use of pharmacotherapies known to delay kidney progression (eg, ACE inhibitors, ARBs) and prompt dose reductions and/or discontinuation of drugs unknown to be nephrotoxic.[19] A more detailed description of the MDRD equation to estimate GFR is addressed in Chapter 28, Chronic Kidney Disease.

Cystatin C

Reference Range: ≤1.0 mg/L or ≤0.749 mmol/L

Although SCr has long been the gold standard for assessing renal function, cystatin C is a newer biomarker that has been shown to be subject to less biologic variability and more sensitive to early declines in kidney function.[20] Reference ranges for cystatin C are similar to that of SCr (≤1.0 mg/L). But unlike SCr, which is produced from muscle cells, cystatin C is produced by the blood cells and is not appreciably influenced by factors such as muscle mass, diet, age, biologic sex, and race; however, higher levels of cystatin C have been observed in males and patients with higher height and weight, and higher lean body mass. It has also been observed that cystatin C levels are increased with age.[21] Cystatin C is cleared predominantly through the kidneys and is not reabsorbed. Elevated

levels are observed in patients with declining renal function. Elevations in serum cystatin C levels tend to occur earlier than do increases in SCr, which do not tend to rise until ~50% of kidney function is lost, and make it possible to detect renal insufficiency in patients at an earlier stage.[22] This is particularly desirable in patients with diabetes, hypertension, or cardiovascular disease who may be at higher risk for the development of renal disease.

Glucose

Reference Range: 65–115 mg/dL or 3.6–6.3 mmol/L (fasting)

The glucose concentration in the ECF is tightly regulated by homeostatic mechanisms to provide tissues and cells with a reliable source of energy. Two endocrine hormones, insulin and glucagon, work synergistically to maintain normal glucose concentrations. Insulin is released from pancreatic β cells to lower blood glucose concentrations, whereas glucagon (released from the pancreatic α cells), along with the counterregulatory hormones, epinephrine, cortisol, and growth hormone, raises glucose levels. Because plasma glucose concentrations fluctuate in response to ingestion of meals, most glucose concentrations are measured in either the fasting or the postprandial state, depending on the type of information desired. Generally, normal glucose values refer to the plasma glucose concentration in the fasting state. The specific laboratory assay of blood sugar determinations must also be considered because different assay methods vary in their specificity and sensitivity to glucose. Glucose testing using whole blood from capillary finger sticks (eg, self-monitoring of blood glucose) is used in conjunction with blood glucose monitoring devices for patients with diabetes. Because glucometer results rely on enzymatic reactions, results can potentially be altered by oxygen saturation, temperature, and interfering substances (eg, acetaminophen, ascorbic acid).[23] Whole blood measurements using these devices are typically 10% to 15% lower than are corresponding plasma glucose levels. Newer technologies such as continuous glucose monitors (CGMs) measure

interstitial glucose rather than capillary blood samples to estimate plasma glucose levels.The accuracy of these monitors is believed to lead to a clinically and statistically significant decline in both A_{1c} and hypoglycemia.[24]

GLYCATED HEMOGLOBIN

Reference Range: 3.8%–6.4%

Hgb is the oxygen-carrying component of the red blood cell (RBC). During the functional life span of RBCs (~4 months), glucose molecules irreversibly bind to Hgb, which results in glycated HgbA_{1c} (A_{1c}). The concentration of A_{1c} reflects a patient's average blood glucose concentration for the life span of circulating RBCs. As a result, measurement of A_{1c} concentrations is useful to diagnose diabetes, monitor disease progression, and/or assess the efficacy of drug therapy. In a patient without diabetes, about 5% of Hgb is glycated. To diagnose diabetes, two confirmatory A_{1c} ≥6.5% are needed.[25] Of note, point-of-care (POC) A_{1c} testing is generally not recommended for diagnostic purposes because of concerns about standardization and accuracy. Use of POC testing is limited to assessment of glycemic control in the clinic setting.[22] In situations when the A_{1c} is deemed unreliable because of changes in cell turnover (eg, sickle cell anemia, hemodialysis, and pregnancy), plasma glucose testing should be used for diagnosis.[22] Both fasting plasma glucose (FPG) and postprandial glucose contribute variably to the A_{1c} measurement. One study suggests that the higher the A_{1c} (>8.5%), the greater the contribution of FPG to the A_{1c}.[26] As such, the contribution of FPG decreases as the A_{1c} decreases. The American Diabetes Association suggests that an A_{1c} of 7% correlates to an estimated average glucose (eAG) of 154 mg/dL. eAG can be calculated using the following equation: eAG (mg/dL) − (28.7 − A_{1c}) − 46.7.[25] It has been estimated that for every 1% reduction in A_{1c}, the risk of microvascular complications is reduced by 37% and the risk of acute myocardial infarction (MI) by 14%.[27]

HYPERGLYCEMIA AND HYPOGLYCEMIA

Hyperglycemia and hypoglycemia are nonspecific signs of abnormal glucose metabolism. Diabetes mellitus is the most common cause of hyperglycemia along with suboptimal use of insulin and/or other antidiabetic agents, high carbohydrate dietary intake, physical inactivity, recent illness or infection, and increased emotional stress. Hyperglycemia may be caused or worsened by certain medications such as corticosteroids, niacin (doses >2 g/day), thiazide and loop diuretics, protease inhibitors, atypical antipsychotics, and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). Insufficient carbohydrate intake because of a missed meal is the most common cause of hypoglycemia in a patient receiving insulin or another hypoglycemic medication. In addition to insulin, drug-induced hypoglycemia includes insulin secretagogues, fluoroquinolone antibiotics, and select herbal products (eg, ginseng, bitter melon, and cinnamon).

CASE 2-2

QUESTION 1: T.C., a 68-year-old male, visits his primary care provider to assess control of his type 2 diabetes. His average blood sugar over the past 90 days recorded by his blood glucose monitor is 195 mg/dL. However, T.C.'s A_{1c} is 9%, which correlates with an eAG of 240 mg/dL. T.C. is confused that these values are different because he routinely ensures his blood glucose machine is calibrated and coded properly.

Why is the laboratory average different?

T.C. should not be alarmed by the difference in these values. His blood glucose monitor is likely working properly and adequately measuring his plasma glucose concentrations. However, the monitor may be reflecting a lower average glucose concentration because of the timing of his daily testing for glucose. For example, measuring blood glucose in a fasting state more frequently than after mealtime could contribute to lower average concentrations because fasting values are typically lower than are postprandial concentrations. The A_{1c} is more indicative of his average blood sugar control during the

past 90 days than the 90-day average recorded by his blood glucose monitor.

Refer to Chapter 53, Diabetes Mellitus, for more detailed information regarding glucose and $HgbA_{1c}$.

Osmolality

Reference Range: 280–300 mOsm/kg or mmol/kg

The osmolality of a solution is a measure of the number of osmotically active ions (ie, particles present) per unit of solution. It is the total number of particles in the solution, not the weight of the particle or the nature of the particle that determines osmolality. Because 1 mole of a substance contains 6×10^{23} molecules, equimolar concentrations of all substances in the undissociated state exert the same osmotic pressure. A mole of an ionized compound such as Na^+Cl^- contributes twice as many particles in solution as 1 mole of an undissociated compound such as glucose. In most situations, the primary determinants of serum osmolality in the ECF are sodium (and its accompanying anions), glucose, and BUN. If one corrects for the concentrations of glucose and BUN, the serum concentration of sodium closely mirrors the serum osmolality. A useful formula (Eq. 2-8) is as follows:

$$\text{Osmolality} = (2 \times \text{Na}^+) + (\text{Glucose}/18) + (\text{BUN}/2.8) \quad \textbf{(Eq. 2-8)}$$

Serum osmolality is helpful when evaluating fluid and electrolyte disorders, particularly sodium imbalances. The difference between the measured serum osmolality and the calculated serum osmolality is commonly referred to as the *osmol gap*. Note that, in practice, osmolality and osmolarity are often used interchangeably. The reader is referred to Chapter 27, Fluid and Electrolyte Disorders, for a more detailed discussion of osmolality.

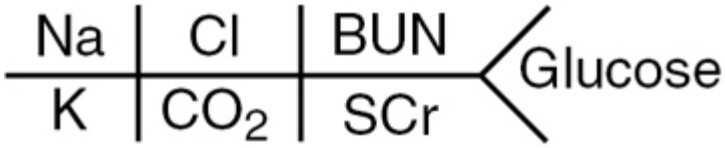
MULTICHEMISTRY PANELS

Frequently, multiple laboratory tests are needed for a given patient. Common clinical laboratory panels include a basic metabolic panel (BMP), comprehensive metabolic panel, electrolyte, hepatic function, and renal function panels (**Table 2-4**). Clinicians will often use the following abbreviated method to report a BMP in written medical records:

Table 2-4
Common Multichemistry Panels

Laboratory Panels	Electrolyte	BMP	CMP	Hepatic	Renal
Sodium	✓	✓	✓		✓
Potassium	✓	✓	✓		✓
Chloride	✓	✓	✓		✓
CO_2	✓	✓	✓		✓
Glucose		✓	✓		✓
Creatinine		✓	✓		✓
BUN		✓	✓		✓
Calcium		✓	✓		✓
Phosphorous					✓
Albumin, total			✓	✓	✓
Total protein			✓	✓	
Alkaline phosphatase (ALP)			✓	✓	
Alanine aminotransferase (ALT, SGPT)			✓	✓	
Aspartate aminotransferase (AST, SGOT)			✓	✓	
Bilirubin, total			✓	✓	
Bilirubin, direct				✓	

BMP, basic metabolic panel; BUN, blood urea nitrogen; CMP, comprehensive metabolic panel; SGOT, serum glutamic:oxaloacetic transaminase; SGPT, serum glutamic:pyruvic transaminase.



Multichemistry tests have become routinely used because they quickly provide basic information concerning organ function at a relatively low cost. In addition, laboratory automation frequently makes it more cost effective to order a battery of tests within a panel versus a single test. A potential disadvantage of obtaining a battery

of tests, however, is that clinicians may be inclined to pursue further laboratory testing when “abnormalities” are not clinically relevant. It is important to note that the individual laboratory tests included in a particular multichemistry panel may vary among clinical laboratories.

Calcium

Reference Range: 8.6–10.3 mg/dL or 2.2–2.74 mmol/L

Calcium has two key physiologic functions within our body; it is an essential intracellular messenger in cells and tissues and a key component of hydroxyapatite, which provides strength, rigidity, and elasticity to the skeleton. All calcium in the body resides primarily in the skeleton, with only about 1% freely exchangeable with that in the ECF. This reservoir of calcium in bones maintains the concentration of calcium in the plasma constant despite pronounced changes in the external balance of calcium. If the homeostatic factors (ie, parathyroid hormone, vitamin D, and calcitonin) that regulate the calcium content of body fluid are intact, a patient can lose 25% to 30% of total body calcium without a change in the concentration of calcium ions in the plasma. Alterations in serum calcium concentrations may have a significant impact on a patient’s renal, GI, and neurologic function. Hypercalcemia is associated with a malignancy, use of thiazide diuretics, hyperthyroidism, and renal failure. Hypocalcemia may indicate a presence of vitamin D deficiency, hypothyroidism, rhabdomyolysis, and CKD.[28] About 40% of the calcium in the ECF is bound to plasma proteins (especially albumin); 5% to 15% is complexed with phosphate and citrate; and about 45% to 55% is in the unbound, ionized form. Most laboratories measure the total calcium concentration; however, it is the free, ionized calcium concentration that is important and closely regulated physiologically. Most laboratories are also able to measure the ionized form of calcium, which has a reference range of 4.5 to 5.6 mg/dL (1.13–1.4 mmol/L). Ionized calcium measures free calcium; however, it is not routinely ordered.[28] It is important to obtain an

albumin level in patients to calculate a corrected calcium level that would account for hypoalbuminemia.

CASE 2-3

QUESTION 1: P.M. is a 61-year-old male admitted status post (s/p) fall because of alcohol intoxication. He has no known drug allergies. P.M.'s past medical history is significant for alcohol-induced seizures, alcohol abuse × 20 years, and hypertension. P.M.'s laboratory tests revealed the following:

Albumin: 2.0 g/dL
Ca: 6.8 mg/dL
Total bilirubin: 10.8 mg/dL
Serum aspartate aminotransferase (AST): 280 IU/L
Alkaline phosphatase: 240 IU/L

Would P.M. be considered hypocalcemic, and how should he be managed?

This case presentation provides insufficient patient data to make a conclusion concerning treatment. However, it does illustrate the importance of treating the patient as a whole, not as a specific laboratory value. Because calcium in the serum is partially bound to plasma proteins (mostly albumin), the serum calcium concentration is affected by the concentration of these plasma proteins. If the albumin concentration is low, the reported serum calcium will generally be less than the lower limit of normal. A useful method to estimate a corrected value for serum calcium in the presence of low serum albumin is to use the following guideline: the total serum calcium will decrease by 0.8 mg/dL for each decrease of 1.0 g/dL in serum albumin concentration. Thus, evaluating P.M.'s corrected calcium is indicated: $(4 - \text{albumin}_{\text{patient}} \times 0.8) + \text{calcium} - \text{corrected calcium}$. For P.M., his "corrected" serum calcium is 8.4 mg/dL, which is just below the reference range, and probably does not warrant treatment with calcium supplementation unless his serum calcium continues to decline. Direct measurement of ionized calcium is independent of albumin concentration, making it unnecessary to correct calcium concentrations in the presence of hypoalbuminemia.

Unfortunately, some clinical laboratories do not have the capability of measuring ionized calcium.

Magnesium

Reference Range: 1.3–2.2 mEq/L or 0.65–1.1 mmol/L

Magnesium is primarily an intracellular electrolyte principally stored in bone and, together with potassium and calcium, helps maintain a neutral charge within the cell. Magnesium also serves an important metabolic role in the phosphorylation of adenosine triphosphate (ATP). Magnesium is necessary for the formation of bone and teeth and for normal nerve and muscle function.

A primary cause of hypomagnesemia is malnourishment. Some other factors associated with hypomagnesemia are the use of proton-pump inhibitors, chronic diarrhea, alcoholism, and diuretic use. Toxemia in pregnancy is associated with hypomagnesemia. Hypomagnesemia needs to be corrected before attempting to correct hypokalemia or hypocalcemia. Attempts to replace potassium or calcium in patients with hypomagnesemia will be ineffective until the low magnesium concentrations are adequately addressed. Excessive ingestion of magnesium-containing antacids can lead to hypermagnesemia. Increased concentrations of magnesium are also observed in patients with reduced renal function. Hypermagnesemia can slow conduction in the heart, prolong PT intervals, and widen the QRS complex.

Phosphate

Reference Range: 2.5–5 mg/dL or 0.80–1.6 mmol/L

The extracellular concentration of phosphate as inorganic phosphorus is the prime determinant of the intracellular concentration, which in turn is the source of phosphate for ATP and phospholipid synthesis. Intracellular phosphate is also important in the regulation of nucleotide degradation.

The ECF concentration of phosphate is influenced by parathyroid hormone, intestinal phosphate absorption, renal function, bone metabolism, and nutrition. Moderate hypophosphatemia is encountered by malnourished patients (especially when anabolism is induced), patients who excessively use antacids (aluminum-containing antacids bind phosphorus in the GI tract), chronic alcoholics, and patients with sepsis. Clinical consequences of severe hypophosphatemia involve nervous system dysfunction, muscle weakness, rhabdomyolysis, cardiac irregularities, and dysfunction of leukocytes and erythrocytes. Hyperphosphatemia is most commonly caused by renal insufficiency, although increased vitamin D, hypoparathyroidism, and advanced malignancies are also significant causes.

Uric Acid

Reference Range: 3–8 mg/dL or 179–476 µmol/L

Uric acid is an end product of the metabolic breakdown of purines. It is commonly referred to as a *metabolically inert compound* offering little biologic utility. The renal system is responsible for 60% to 70% of total body uric acid excretion. Most uric acid is freely filtered, with ~90% reabsorbed via the nephron.

Increased serum uric acid concentrations can result from either a decrease in urate excretion (eg, renal dysfunction, competition with drugs using the same transporters for elimination [thiazide diuretics, niacin]) or excessive urate production (eg, increased purine metabolism resulting from cytotoxic therapy of neoplastic or myeloproliferative disorders). Gout, a common arthritic condition characterized by hyperuricemia, is usually associated with increased serum concentrations of uric acid along with deposits of monosodium urate crystals in joints. Low serum uric acid concentrations are inconsequential, and are usually reflective of drugs that have hypouricemic activity (eg, high dosages of salicylates).

PROTEINS

Prealbumin

Reference Range: 19.5–35.8 mg/dL or 195–358 mg/L

Prealbumin is an important serum protein, but in comparison with other proteins, it accounts for a relatively small percentage of all circulating proteins. It is also referred to as thyroxine-binding prealbumin owing to its role as a transport mechanism for triiodothyronine (T_3) and thyroxine (T_4). However, it is most frequently used to monitor patients at risk for poor nutrition (eg, patients with eating disorders, patients with human immunodeficiency virus, or patients receiving total parenteral nutrition). Compared with the long half-life of albumin (about 3 weeks), the half-life of prealbumin is only 1 to 2 days. This shorter half-life provides a more accurate reflection of acute changes in protein synthesis, catabolism, and, ultimately, immediate nutrition status. Hepatic disease and malnutrition are associated with decreases in prealbumin (and albumin). Hodgkin lymphoma, pregnancy, CKD, and corticosteroid use can increase prealbumin serum concentrations.

Albumin

Reference Range: 3.6–5 g/dL or 36–50 g/L

Albumin, produced by the liver, contributes ~80% to serum colloid osmotic pressure. As a result, hypoalbuminemic states are commonly associated with edema and third spacing of ECF. A lack of essential amino acids from malnutrition or malabsorption, or impaired albumin synthesis by the liver, can result in decreased serum albumin concentrations. Most forms of hepatic insufficiency are associated with decreased synthesis of albumin. It can be lost directly from the blood because of hemorrhage, burns, or exudates or it may be lost directly into the urine because of nephrosis. Serum albumin concentrations seldom increase, but increases may be

noted in volume depletion, in shock, or immediately after the administration of large amounts of IV albumin. In addition to its diagnostic value, albumin concentration is an important consideration in the therapeutic monitoring of drugs and electrolytes that are highly protein bound (eg, phenytoin, digoxin, and calcium). In cases of severe hypoalbuminemia, determination of the “free” or unbound concentration of these entities might be necessary for an accurate assessment of drug therapy.

Globulin

Reference Range: 2.3–3.5 g/dL or 23–35 g/L

In addition to albumin, globulin is another primary plasma protein. Albumin principally functions to maintain serum oncotic pressure, whereas globulins play an active role in immunologic processes. The globulins can be separated into several subgroups such as α, β, and γ. The γ-globulins can be separated further into various immunoglobulins (Igs; eg, IgA, IgM, and IgG). Chronic infection or rheumatoid arthritis can increase Ig levels, and fractionation of Igs can provide useful information in the evaluation of immune disorders. Because globulin is not manufactured solely by the liver, the ratio of albumin to globulin (the A/G ratio) is changed in patients with liver disease. Changes in this ratio result from decreased albumin concentration and a compensatory increase in globulin concentration.

CARDIAC MARKERS

Cardiac biomarkers are useful for the evaluation, diagnosis, and monitoring of patients with suspected heart damage. These markers, which include some enzymes, are often released into the blood when the myocardium becomes damaged or dies. Enzyme activity is typically expressed in terms of international units (IUs), where 1 IU is the enzyme amount needed to catalyze the conversion of 1 μmol of

substrate per minute. The analogous expression in SI terms involves the term katal (kat). One katal is the amount of enzyme to catalyze 1 mole of substrate per second, making 1.0 µkat the amount for 1.0 µmol/second. Based on this information, the conversion between µkat and IU is 1 µkat—60 IU.

Creatine Kinase

Reference Range: Female, 20–170 IU/L or 0.33–2.83 µkat/L; Male, 30–220 IU/L or 0.5–3.67 µkat/L

Creatine kinase (CK) catalyzes the transfer of high-energy phosphate groups in tissues that consume large amounts of energy (eg, skeletal muscle, myocardium, and brain). The serum concentration of CK can be increased by strenuous exercise, intramuscular injections of tissue-irritating drugs (eg, diazepam and phenytoin), crush injuries, myocardial damage, rhabdomyolysis, or high doses of certain HMG-CoA reductase inhibitors.

CK is composed of M and B subunits and is divided into three isoenzymes: MM, BB, and MB. The CK-MM isoenzyme is found predominantly in skeletal muscle, the CK-BB is predominantly in the brain, and the CK-MB is predominantly in the myocardium. Myocardial CK activity consists of 80% to 85% CK-MM and 15% to 20% CK-MB. Noncardiac tissues that contain large amounts of CK have either CK-MM or CK-BB. The MB fraction is rare in tissues other than in the myocardium, making it a more specific cardiac marker.

CK-MB typically begins to increase 3 to 6 hours after an acute MI, peaks at 12 to 24 hours, and accounts for about 5% or more of the total CK.[29] Myocardial damage appears to correlate with the amount of CK-MB released into the serum (ie, the higher the amount of CK-MB, the more extensive the myocardial injury). Although CK-MB levels >25 IU/L are usually associated with an MI, the absolute amount can vary, depending on the assay method.[30] Generally, if the amount of CK-MB exceeds 6% of the total CK, myocardial injury has

presumably occurred. Analysis of CK-MB provides a rapid, sensitive, specific, cost effective, and definitive means of detecting MI.[31]

Troponin

Reference Range: Cardiac Troponin T (cTnT) 0–0.1 ng/mL or µg/L; Cardiac Troponin I (cTnI) 0–0.3 ng/mL or µg/L; High-Sensitivity Cardiac Troponin T (hs-cTnT) 0–14 ng/L; High-Sensitivity Cardiac Troponin I (hs-cTnI) 0–6 ng/L

Troponins are proteins that regulate the calcium-mediated interaction of actin and myosin within muscles. There are two cardiac-specific troponins, cardiac troponin I (cTnI) and cardiac troponin T (cTnT). cTnT is present in cardiac and skeletal muscle cells, whereas cTnI is present only in cardiac muscle.[32,33] Although compared with the detection of CK-MB, the presence of cTn is a more sensitive and specific indicator of myocardial necrosis,[34] it should be noted that other conditions can cause an elevation in cTn (cardiac, renal, pulmonary, etc). The concentration of cTn increases within 2 to 5 hours of an acute MI. On average, troponin remains elevated for about 10 days compared with the 2- to 3-day elevation typically observed with CK-MB. cTnI levels >0.3 ng/mL and cTnT levels >0.1 ng/mL are suggestive of acute myocardial tissue necrosis, but these values may vary slightly by assay (because of lack of standardization) and by institution. High-sensitivity cardiac troponin (hs-cTn) can be employed for rapid MI rule-out or rule-in.[35] Hs-cTn can measure cTn at much lower concentrations than do older conventional assays. There are several methods for MI rule-out using these assays. One such method is the 0/2 method; an hs-cTn should be drawn on arrival (0h) and again 2 hours later (2h).[35,36] These lab values are used in conjunction with all relevant clinical data (eg, electrocardiogram [ECG], validated risk scores, and past and current comorbid conditions) to help rule out MI. To be considered a rule-out using the hs-cTnT, the levels at 0h and 2h should be <14 ng/L and change from baseline at 2h should be <4 ng/L.[35,36] Using the hs-cTnI, the 0h and 2h levels should be <6 ng/L,

and the change from baseline should be <2 ng/L.[35] Patients who present and do not completely fit the abovementioned criteria may require a third hs-cTn lab test to confirm rule out. For rapid MI rule-in, the patient would need to present with an hs-cTnT ≥53 ng/mL or hs-cTnI ≥64 ng/L or have a change in hs-cTnT ≥10 ng/L or hs-cTnI ≥15 ng/L at 2h.[35] Owing to differences in heart mass, estrogen levels, and so on, females have lower baseline levels of circulating hs-cTn. This has led to a proposal of using a lower cutoff for female patients, but it remains controversial.[35–37] The reader is referred to Chapter 13, Acute Coronary Syndrome, for a more detailed discussion of the use of cardiac markers.

CASE 2-4

QUESTION 1: J.R., a 57-year-old male with a history of stable angina, presents to a hospital emergency department. He has sudden-onset chest pressure and tightness, diaphoresis, and nausea that has been waxing and waning for the past few hours. J.R. describes his discomfort as severe at times and not relieved by position change, antacids, or sublingual nitroglycerin. An ECG reveals ST depressions consistent with myocardial ischemia. His cardiac biomarkers reveal CK 220 IU/L, CK-MB 5%, hs-cTnT at 0h is 12 ng/L and at 2h is 16 ng/L. Based on his presentation, ECG, and cardiac biomarkers, J.R. is diagnosed with an MI (non–ST segment-elevation MI) and is admitted for a cardiac catheterization.

Why are the total CK and CK-MB serum concentrations within the reference range despite clear evidence, including elevated hs-cTnT, supporting an acute MI?

Although CK and CK-MB are very helpful laboratory values for identifying and assessing myocardial damage/necrosis, the utility of these values alone can be quite limited. Troponin levels are very sensitive and specific to myocardial cell death, can become positive sooner than do CK and CK-MB, and will remain elevated for a much longer period (up to 10 days). Even if the CK and CK-MB are not elevated, the hs-cTnT can pick up even the smallest amount of myocardial cell death. Based on the clinical picture and the elevated troponin, the patient would be classified as having a non–ST segment-elevation MI.

Myoglobin

Reference Range: Female 12–76 µg/L; Male 19–92 µg/L

Myoglobin, a protein in heart and skeletal muscle cells, provides oxygen to working muscles. Damaged muscle releases myoglobin into the bloodstream. As a cardiac biomarker, myoglobin concentrations in serum rise within 3 hours of insult to the myocardial tissue, peak in about 8 to 12 hours, and return to normal in about a day. Because myoglobin serum concentrations rise more quickly than does CK-MB after myocardial injury, this parameter can be of value in helping rule out MI in the emergency department. Myoglobin serum concentrations, however, tend to be less specific for myocardial tissue compared with CK-MB and troponin; trauma or ischemic injury to noncardiac tissue can also increase serum myoglobin.

Homocysteine

Reference Range: 4–12 µmol/L

Patients with deficiencies in folate, vitamin B_6, or vitamin B_{12} tend to have elevated serum levels of homocysteine. Homocysteine is believed to have a destructive effect on vascular epithelium. With time, patients with elevated homocysteine levels (>12 µmol/L) are believed to be at increased risk for cardiac disease.[38] Screening individuals with a positive family history for elevated homocysteine or those with premature atherosclerosis without typical risk factors has been advocated. Understanding the association between increased homocysteine levels and specific vitamin deficiencies, supplementation of folate, vitamin B_6, and vitamin B_{12} has been used clinically. Although hyperhomocysteinemia may be an independent risk factor for atherosclerosis, to date no studies have shown that lowering homocysteine levels improves cardiovascular outcomes in patients with preexisting atherosclerosis or cardiovascular disease (CVD).[39]

Lactate Dehydrogenase

Reference Range: 100–250 IU/L (adult) or 1.67–4.17 µkat/L

The enzyme lactate dehydrogenase (LDH) is present in the heart, kidney, liver, and skeletal muscle. It is also abundantly present in erythrocytes and lung tissue. Because increased serum concentrations of LDH can be associated with diseases in many different organs and tissues, the diagnostic usefulness of an LDH determination is somewhat limited. There are, however, five isoenzymes of LDH. Although most tissues contain all five isoenzymes, some tissues have a predominance of one of the isoenzymes. LDH_1 and, to a lesser extent, LDH_2 predominate in the heart. Skeletal muscle and the liver have a predominance of LDH_5. LDH_3 and LDH_4 are found in a variety of tissues, including the lungs, RBCs, kidneys, brain, and pancreas. Consequently, identifying specific isoenzymes can increase the diagnostic usefulness of serum LDH determinations.

Brain Natriuretic Peptide

Reference Range: Brain Natriuretic Peptide (BNP) <100 pg/mL or <100 ng/L: >500 pg/mL or >500 ng/L is considered elevated; N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) <400 pg/mL or <400 ng/L: >2000 pg/mL or >2000 ng/L is considered elevated.

BNP is released from the ventricles because of increased myocardial demand. Elevations in BNP are indicative of patients with CHF and volume overload. To reduce the workload on the heart, BNP counteracts the renin–angiotensin–aldosterone system and causes vasodilatory effects, along with natriuresis (increased excretion of sodium), all geared at reducing blood volume. Patients with some degree of CHF typically have BNP levels >100 ng/L. BNP levels >500 ng/L represent definite CHF, but further evaluation is warranted to more fully characterize the extent of impaired cardiac function.[40] It should be noted that BNP is a substrate of neprilysin and that use of

an angiotensin receptor–neprilysin inhibitor (ARNI) can increase BNP levels.[41] This is not the case for NT-proBNP.[42] NT-proBNP is a by-product from the cleaving of pro-BNP to form BNP; it is also being used in the clinical setting to assess HF. Similar to BNP, there are three generally accepted ranges for NT-proBNP. Patients presenting with an NT-proBNP level <400 ng/L are unlikely to have HF. A level >2000 ng/L is indicative of an HF diagnosis, whereas values 400 to 2000 ng/L are considered uncertain. In both acute and ambulatory HF, there is extensive evidence supporting the use of BNP and NT-proBNP to aid in HF diagnosis; this is especially true in patients presenting with shortness of breath of unknown etiology.[43–57] The reader is referred to Chapter 14, Heart Failure, for a more detailed discussion of the use of BNP and NT-proBNP.

C-Reactive Protein

R***eference Range: 0–1.6 mg/dL or 0–16 mg/L***

C-reactive protein (CRP) is a nonspecific, acute-phase reactant helpful in the diagnosis and monitoring of inflammatory processes (eg, rheumatoid arthritis and bacterial infections). CRP is produced by the liver in response to inflammation. Although an elevation in CRP indicates the presence of an acute inflammatory event, the nonspecific nature of the test does little to identify the cause or location of the inflammation. CRP is similar to an older test, the erythrocyte sedimentation rate (ESR), but it tends to be more sensitive than is ESR and is also associated with a more rapid and greater response to acute inflammation. A potential use of CRP is as a novel risk factor for CVD.[58] CRP has also been used to assess chronic inflammatory diseases such as rheumatoid arthritis and Crohn disease. In addition, because viral infections do not typically increase CRP serum concentrations, the use of CRP as a diagnostic tool to differentiate viral from bacterial infections might be clinically helpful. High-sensitivity CRP is a more sensitive test that has been thought to be a better predictor of CVD risk and statin response, but

its use remains controversial. Routine testing is not part of current guidelines, and stratification and targets have not been validated.[59,60]

LIVER FUNCTION TESTS

Aspartate Aminotransferase

Reference Range: 0–35 IU/L or 0–0.58 µkat/L

The AST enzyme is abundant in heart and liver tissue and moderately present in skeletal muscle, kidney, and pancreas. In cases of acute cellular injury to the heart or liver, the enzyme is released into the blood from the damaged cells. In practice, AST determinations have been used to evaluate myocardial injury and to diagnose and assess the prognosis of liver disease resulting from hepatocellular injury. The serum AST level is increased in >95% of patients after an MI. However, the increase in AST does not occur until 4 to 6 hours after the onset of myocardial injury. Peak AST concentrations are seen in the serum after 24 to 36 hours, returning to the normal range in about 4 to 5 days.

Serum AST values are elevated significantly in patients with acute hepatic necrosis, whether caused by viral hepatitis or a hepatotoxin (eg, carbon tetrachloride). In these situations, the serum concentrations of both AST and alanine aminotransferase (ALT) will be increased, even before the appearance of clinical symptoms (eg, jaundice). The AST and ALT serum concentrations can be increased by as much as 100 times the usual upper limits of normal in the presence of parenchymal liver disease. Patients with intrahepatic cholestasis, posthepatic jaundice, or cirrhosis usually experience more moderate elevations of AST, depending on the extent of cell necrosis. The AST serum concentration is usually higher than that of ALT in patients with cirrhosis, and the AST increase is usually about four to five times greater than is the upper limit of normal.

Alanine Aminotransferase

Reference Range: 0–35 IU/L or 0–0.58 µkat/L

The ALT enzyme is found in essentially the same tissues that have high concentrations of AST, but ALT is generally considered to be more specific to the liver, because ALT concentrations in nonhepatic tissues are low.[61] Elevations in serum ALT are more specific for liver-related injuries or diseases. Although ALT is relatively more abundant in hepatic tissue versus cardiac tissue than is AST, the liver still contains 3.5 times more AST than ALT. Serum concentrations of both AST and ALT increase when disease processes affect liver cell structure. Evaluating the ratio of ALT to AST can be potentially useful, particularly in the diagnosis of viral hepatitis. The ALT/AST ratio frequently exceeds 1.0 with alcoholic cirrhosis, chronic liver disease, or hepatic cancer. However, ratios <1.0 tend to be observed with viral hepatitis or acute hepatitis, which can be useful when diagnosing liver disease.[62]

Alkaline Phosphatase

Reference Range: 20–130 IU/L or 0.33–2.17 µkat/L

The alkaline phosphatases (ALPs) constitute a large group of isoenzymes that play important roles in the transport of sugar and phosphate. These isoenzymes of ALP have different physiochemical properties and originate from different tissues (eg, liver, bone, placenta, and intestine). In normal adults, ALP is derived primarily from liver and bone and found in smaller quantities in the intestines, kidneys, and white blood cells (WBCs).[61] Although only small amounts of ALP are present in the liver, this enzyme is secreted into the bile, and substantially elevated ALP serum concentrations can be seen with mild intrahepatic or extrahepatic biliary obstruction. Thus, the presence of early bile duct abnormalities can result in elevated ALP before increases in the serum bilirubin are observed. Drug-induced cholestatic jaundice (eg, chlorpromazine or sulfonamides) can increase serum ALP concentrations. In mild cases of acute liver cell damage, ALP levels are seldom elevated.

Even in cirrhosis, ALP concentrations are variable and depend on the degree of hepatic decompensation and obstruction.

The osteoblasts in bone produce large amounts of ALP, and marked serum elevations can be seen in Paget disease of the bone, hyperparathyroidism, osteogenic sarcoma, osteoblastic cancer metastatic to bone, and other conditions of pronounced osteoblastic activity. The serum ALP is increased during periods of rapid bone growth (eg, infancy, early childhood, and healing bone fractures) and during pregnancy because of the contributions of the placenta and fetal bones.

Gamma-Glutamyl Transferase

Reference Range: Male, 9–50 IU/L; Female, 8–40 IU/L

Although the enzyme γ-glutamyl transferase (GGT) is found in the kidney, liver, intestine, prostate, and pancreas, its major clinical value is in the evaluation of hepatobiliary disease. An increase in the serum concentration of GGT parallels the increase of ALP in obstructive jaundice and infiltrative disease of the liver. However, increased ALP in the presence of a normal GGT is more suggestive of muscular or bone-related issues, because GGT is not found in bone. GGT is one of the more sensitive liver enzymes for identifying biliary obstruction and cholecystitis. GGT can also be elevated in patients with obesity.[61] Because GGT is a hepatic microsomal enzyme, tissue concentrations increase in response to microsomal enzyme induction by alcohol and other drugs (eg, carbamazepine, phenobarbital, and phenytoin). As a result, GGT is a sensitive indicator of recent or chronic alcohol exposure.

Bilirubin

Total Bilirubin—Reference Range: 0.1–1.0 mg/dL or 2–18 µmol/L
Direct (Conjugated) Bilirubin—Reference Range: 0–0.2 mg/dL or 0–4 µmol/L

Bilirubin is primarily a breakdown product of Hgb and is formed in the reticuloendothelial system (**Fig. 2-1**, step 1). It is then transferred into the blood (step 2), where it is almost completely bound to serum albumin (step 3). When bilirubin arrives at the sinusoidal surface of the liver cells, the free fraction is rapidly taken up into the cell (step 4) and converted primarily to bilirubin diglucuronide (step 5). A monoglucuronide that is metabolized predominantly to the diglucuronide is also formed. The conjugated bilirubin diglucuronide is then excreted into the bile (step 6) and appears in the intestine, where bacteria convert most of it to urobilinogen (step 7). The majority of urobilinogen is destroyed or excreted in the feces (step 13), but a small portion is reabsorbed into the blood (step 8) and either reabsorbed into the liver (step 9) and subsequently excreted into the bile (step 12) or excreted into the urine (step 10). Urobilinogen is responsible for the straw color of the urine and the yellowish-brown color of the feces. The mechanism by which conjugated bilirubin in the liver cell is transferred to the blood (step 14) is not well understood. However, in many types of liver disease, conjugated (direct) bilirubin is present in increased concentrations in the blood. When this concentration exceeds 0.2 to 0.4 mg/dL, bilirubin will begin to appear in the urine (step 11). Unconjugated (indirect) bilirubin is water insoluble and is highly bound to serum albumin; both factors account for its lack of excretion in the urine.[63]

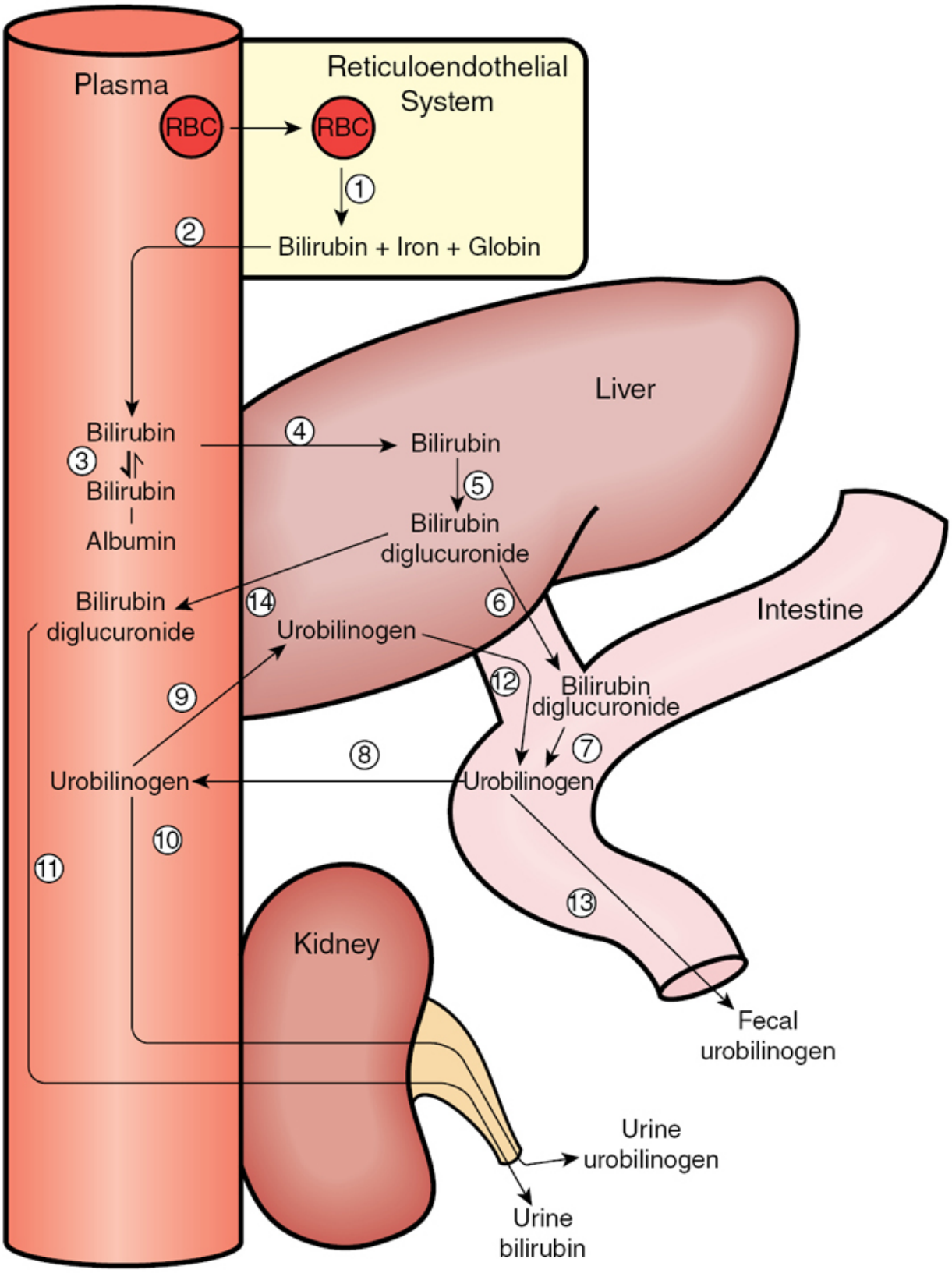


Figure 2-1 Bilirubin metabolism.

When bilirubin is reported by the lab, it is usually reported as total bilirubin, which consists of both conjugated and unconjugated fractions. If there is an elevation in any of the fractions, it will lead to an elevation of total bilirubin concentrations. It is important to note that with the exception of neonates, the majority of bilirubin should consist of the conjugated fraction.[61]

MISCELLANEOUS TESTS

Amylase and Lipase

Amylase (reference range: 35–118 IU/L or 0.58–1.97 μkat/L) and lipase (reference range: 10–160 IU/L or 0–2.67 μkat/L) are enzymes produced by the pancreas and secreted into the duodenum to assist in the digestive process. Small amounts of both enzymes are also found in the saliva and stomach. Significantly elevated levels of either enzyme are suggestive of pancreatic damage.

Amylase is responsible for breaking down complex carbohydrates into simple sugars. Significant elevations in serum amylase are observed in patients with acute pancreatitis or pancreatic duct obstruction. Amylase levels tend to rise 6 to 48 hours after onset of the disease and usually return to normal 3 days after the acute event. In chronic pancreatitis or obstruction, amylase levels may remain elevated for longer periods. Other nonpancreatic conditions (eg, bowel perforation, biliary disease, perforated peptic ulcer, ectopic pregnancy, and mumps) can be associated with elevated serum amylase levels.

Lipase is responsible for breaking down triglycerides (TGs) into fatty acids. Elevated serum lipase levels are also suggestive of pancreatic disease and tend to be more specific for pancreatic disease than for amylase. Nonpancreatic conditions such as gallbladder disease or biliary cirrhosis can also lead to elevated lipase levels. The onset of lipase elevation is similar to that of amylase; however, lipase typically remains elevated for 5 to 7 days,

and can be useful in diagnosing patients in later stages of pancreatic disease. Narcotics (eg, morphine) can constrict the sphincter of Oddi and increase serum concentrations of both amylase and lipase.

Prostate-Specific Antigen

Reference Range: 0–4 ng/mL or 0–4 µg/L

Prostate-specific antigen (PSA) is a protease glycoprotein produced almost exclusively by prostate epithelial cells. Large quantities of PSA are carried in semen; only low levels are found in the blood. Serum concentrations of PSA are increased when the normal prostate glandular structure is disrupted by benign or malignant tumor or inflammation (prostatitis). More than half of males with benign prostatic hyperplasia (BPH) have elevated serum PSA concentrations. PSA is also a valuable parameter for staging and monitoring the progression and response to therapy of prostate cancer.[64]

The prostate gland increases in size with age; therefore, it is expected that older males will have higher PSA levels compared with younger males. PSA serum concentrations can also increase after prostatic manipulation such as digital rectal examination (DRE), catheter placement, transrectal ultrasound, cystoscopy, or biopsy of the prostate. In addition, serum PSA will increase 24 to 48 hours after ejaculation. Although elevated serum concentrations of PSA can occur in males with BPH, concentrations tend to be higher and encountered more often in males with cancer. Males with PSA levels between 4 and 10 ng/mL should be evaluated further for potential prostate cancer.

The serum half-life of PSA is 2 to 3 days, but serum PSA concentrations can remain high for several weeks after manipulation of the prostate. Circulating serum PSA is bound to plasma proteins, and the capability exists to measure both total and free (unbound) PSA concentrations. Increased risk of prostate cancer has been observed in males with a free PSA to total PSA ratio of <0.25.[65] An

aggressive approach to localize prostate cancer for males with life expectancies >10 years is now favored.[64,66]

Thyroid-Stimulating Hormone

Reference Range: 0.5–4.7 µIU/mL or mIU/L

Thyroid-stimulating hormone (TSH, also known as thyrotropin) is secreted by the pituitary gland to stimulate the thyroid gland to produce the thyroid hormones T_4 and T_3. TSH is measured, often in conjunction with the thyroid hormones, to diagnose thyroid disorders and to monitor exogenous thyroid supplementation therapy. The reader is referred to Chapter 52, Thyroid Disorders, because it provides a more detailed discussion of the clinical implications of altered thyroid laboratory findings.

Procalcitonin

Procalcitonin is a precursor of calcitonin and is typically undetectable in healthy individuals. Elevations in procalcitonin occur in patients with inflammation secondary to bacterial infections; however, a similar increase is not observed in patients with inflammation secondary to viral infections or noninfectious conditions. Once there is a systemic inflammation due to bacterial infection, synthesis of procalcitonin will be induced in almost all tissues and then released into the blood.[67] Interestingly, increases in calcitonin are not seen in patients with elevated procalcitonin. In patients with sepsis or sepsis syndrome, procalcitonin levels <0.5 ng/mL have been associated with a low risk of progression to severe sepsis, and levels >2.0 ng/mL represent a high risk for severe sepsis. Trials involving lower respiratory tract infections have suggested that antibiotic therapy should be discouraged in patients with procalcitonin levels <0.25 ng/mL but encouraged for those with levels ≥0.5 ng/mL. These criteria have also been used as a guide for discontinuing therapy as infections resolve; however, there are differences in how procalcitonin levels are managed among different institutions.

Additional further trials will help accurately define the role of procalcitonin testing.

Cholesterol and Triglycerides

A detailed discussion of hypercholesterolemia and lipid disorders is provided in Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease. For convenience, the current range of desired values for total cholesterol (TC), low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and fasting TGs has been incorporated in **Table 2-2**.

HEMATOLOGY

There are several different hematologic cell types that originate from the hematopoietic stem cell. Each cell line has a defined role and unique contribution to the overall homeostatic process and may be found in the bone marrow, lymph system, or blood. Typically, routine clinical laboratory testing involves measuring concentrations of mature myeloid cells found in the blood. **Figure 2-2** illustrates the various lineages derived from the hematopoietic stem cell.[68] The cells derived from the myeloid linage are the focus of the following discussion. Readers are encouraged to refer to Section 16, Hematology and Oncology, to gain further understanding of the clinical relevance of lymphoid and myeloid cells (Fig. 2-2).

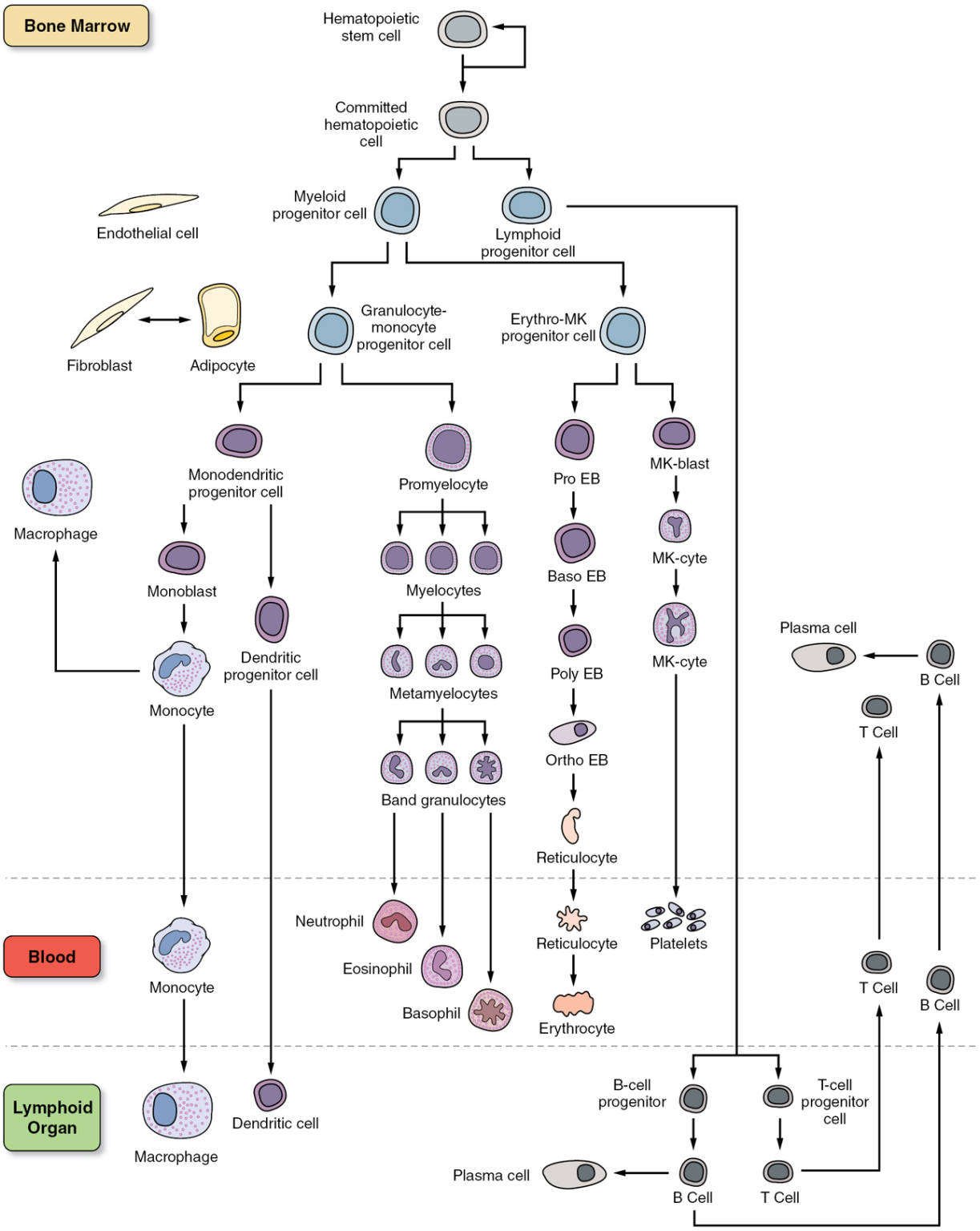
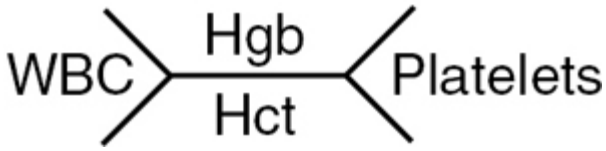


Figure 2-2 Hematopoietic stem cell lineage. MK, megakaryocyte; EB, erythroblast. (Adapted with permission from Greer JP, Foerster

J, Rodgers GM, et al, eds. *Wintrobe's Clinical Hematology*. 12th ed. Lippincott Williams & Wilkins; 2009:80.)

Complete Blood Count

The complete blood count (CBC) is one of the most commonly ordered clinical laboratory tests. A CBC measures the RBCs, Hgb, hematocrit (Hct), platelets, mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), mean platelet volume (MPV), and total WBCs. CBC with differential will measure all the values mentioned earlier; in addition, it will also measure the number of each type of WBCs. An abbreviated method of noting hematologic parameters in clinical practice is noted in the following figure.



Red Blood Cells (Erythrocytes)

Reference Range: Males, 4.3–5.9 × 10^6/μL or 4.3–5.9 × 10^{12}/L
Reference Range: Females, 3.5–5 × 10^6/μL or 3.5–5 × 10^{12}/L
Erythrocytes or RBCs are produced in the bone marrow, released into the peripheral blood, circulated for ~120 days, and cleared by the reticuloendothelial system. The primary function of RBCs is to transport oxygen linked to Hgb from the lungs to tissues. The concentration of RBCs in the blood can be measured to detect anemia, calculate RBC indices, or calculate the Hct. Hct and Hgb concentrations are generally used to monitor quantitative changes in RBCs.

Hematocrit

Reference Range: Males, 40.7%–50.3% or 0.4–0.503
Reference Range: Females, 36%–44.6% or 0.36–0.446

Hct (packed cell volume) is the percentage of RBCs to the total blood volume and is determined by centrifuging a capillary tube of whole blood and comparing the height of the settled RBCs to the height of the column of whole blood. A decrease in Hct may result from bleeding, the bone marrow suppressant effects of drugs, chronic diseases, genetic alterations in RBC morphology, or hemolysis. An increase in Hct may result from hemoconcentration, polycythemia vera, or polycythemia secondary to chronic hypoxia.

Hemoglobin

Reference Range: Males, 13.8–17.5 g/dL or 138–175 g/L
Reference Range: Females, 12.1–15.3 g/dL or 121–153 g/L
Hgb is the major oxygen-carrying compound contained in RBCs. Therefore, total Hgb concentration primarily depends on the number of RBCs in the blood sample. As mentioned with Hct, medical conditions that impact the number of RBCs will also affect Hgb concentration. As discussed previously, glycated Hgb (A_{1c}) is a related test used to monitor diabetes mellitus.

Red Blood Cell Indices

RBC indices (also known as Wintrobe indices) are useful in the classification of anemias. These indices include the MCV, the mean cell hemoglobin (MCH), and the MCHC. These indices are calculated in Eqs. 2-9 to 2-11:

$$\text{MCV} = \text{HCT}\,(\%) \times 10/\text{RBC}\,(\text{in millions}/\mu\text{L}) = 80 - 97.6\,(\text{in } \mu\text{m}^3 \text{ or Fl}) \quad \textbf{(Eq. 2-9)}$$

$$\text{MCH} = \text{Hgb}\,(\text{in g/dL}) \times 10/\text{RBC}\,(\text{in millions}/\mu\text{L}) = 27 - 33\,(\text{in pg}) \quad \textbf{(Eq. 2-10)}$$

$$\text{MCHC} = \text{Hgb (in g/dL)} \times 100/\text{Hct (\%)} = \quad \textbf{(Eq. 2-11)}$$
$$33 - 36 \text{ (in g/dL)}$$

MEAN CELL VOLUME

The MCV detects changes in cell size. A decreased MCV indicates a microcytic cell, which can result from iron deficiency anemia or anemia of chronic inflammation. A large MCV indicates a macrocytic cell, which can be caused by a vitamin B_{12} or folic acid deficiency. Underlying disease states (eg, habitual alcohol ingestion, chronic liver disease, anorexia nervosa, hypothyroidism, reticulocytosis, and hematologic disorders) may also present with an elevated MCV secondary to deficiencies in these vitamins.[69] The MCV can be normal in a patient with a "mixed" (microcytic and macrocytic) anemia. Note that a direct assessment of a blood smear by a microscopic examination is the gold standard for confirming RBC size.

MEAN CELL HEMOGLOBIN

The MCHC is a more reliable index of RBC Hgb than is MCH. MCH measures the weight of Hgb in the RBCs in a sample, and MCHC measures the concentration of the RBCs contained within a sample. In normochromic anemias, changes in the size of RBCs (MCV) are associated with corresponding changes in the weight of Hgb (MCH), but the concentration of Hgb (MCHC) remains normal. Changes in the Hgb content of RBCs alter the color of these cells. Thus, hypochromic refers to a decrease in RBC Hgb, reflected by reduced MCHC, and may indicate iron deficiency anemia. Conversely, hyperchromic RBCs have an elevated MCHC because of the presence of greater amounts of Hgb. Hyperchromic cells are not commonly encountered.

Reticulocytes

Reference Range: Adults, 0.5%–1.5% of RBCs or 0.005–0.015

Reticulocytes are young, immature erythrocytes, and typically comprise about 1% of the RBCs. The reticulocyte count measures the percentage of these new cells in the circulating blood. An increase in the number of reticulocytes implies that an increased number of erythrocytes are being released into the blood in response to a stimulus. Reticulocyte count is a good indicator of bone marrow activity because it represents a recent production. Because erythrocytes regenerate rapidly, reticulocytosis can be noted within 3 to 5 days of hemolysis or after a hemorrhagic episode. Appropriate treatment of anemias caused by iron, vitamin B_{12}, or folic acid deficiencies should result in an increased reticulocyte count. Caution must be exercised in the interpretation of reticulocyte counts. Changes in the number of RBCs will result in proportional changes in the reticulocyte count because the latter is reported as a percentage of the number of RBCs.

Erythrocyte Sedimentation Rate

Reference Range: 0–30 mm/hour

The ESR is the rate (expressed in mm/hour) at which erythrocytes settle to the bottom of a test tube through the forces of gravity and in response to fibrinogen levels in the blood. The ESR is a nonspecific value and may be increased abnormally in acute and chronic inflammatory processes, acute and chronic infections, neoplasms, infarction, tissue necrosis, rheumatoid-collagen disease, dysproteinemias, nephritis, and pregnancy. However, ESR can also be affected by changes not related to the inflammation (eg, change in erythrocyte size, shape, or number). Laboratory technique can also affect the sedimentation rate substantially. Because many factors can enhance the settling rate of RBCs, moderate to marked elevation of the ESR merely indicates an inflammatory component to a disease state. An increased ESR in the setting of a normal physical examination is usually transient and is rarely the harbinger of serious occult disease.[70]

White Blood Cells

Reference Range: 3.8–9.8 × 10^3/μL or 3.8–9.8 × 10^9/L

Leukocytes or WBCs comprise five different types of cells. Neutrophils are the most abundant of the circulating WBCs, followed in order of frequency by lymphocytes, monocytes, eosinophils, and basophils. The neutrophils, eosinophils, basophils, and monocytes are formed from stem cells in the bone marrow. Lymphocytes are formed primarily in the lymph nodes, thymus, spleen, and, to a lesser extent, in the bone marrow (Fig. 2-2). Each WBC type has a unique function, and it is best to consider them independently rather than collectively as "leukocytes."[71] Ultimately, all WBCs contribute to host defense mechanisms.

NEUTROPHILS

Reference Range: 40%–70% of WBCs

The terms *polys, segs, polymorphonuclear neutrophils,* and *granulocytes* are synonymous with the term *neutrophil* in clinical practice. The number of neutrophils is commonly increased during bacterial or fungal infections because these cells are essential in killing invading microorganisms. Although the bone marrow increases the production of new leukocytes, there is also an increase in the number of circulating immature neutrophils (eg, bands); this phenomenon is commonly referred to as a *left shift*, which suggests acute bacterial infection.

However, neutrophils are also important in the pathogenesis of tissue damage in some noninfectious diseases, such as rheumatoid arthritis, inflammatory bowel disease, asthma, MI, or gout.[72] Increased neutrophils or neutrophilia can also be encountered during metabolic toxic states (eg, diabetic ketoacidosis, uremia, and eclampsia) and during physiologic response to stress (eg, physical exercise and childbirth). Drugs (eg, epinephrine and corticosteroids) can also cause significant neutrophilia, primarily caused by demargination from blood vessel walls.

Agranulocytosis and absolute neutrophil count

The condition involving decreased neutrophils, or *neutropenia*, is defined as a neutrophil count of <2000 cells/μL; *agranulocytosis* refers to severe neutropenia. The most common causes of neutropenia are metastatic carcinoma, lymphoma, and chemotherapeutic agents. The degree of neutropenia is often expressed by the absolute neutrophil count (ANC). The ANC is defined as the total number of granulocytes (polymorphonuclear leukocytes and band forms) present in the circulating pool of WBCs and can be calculated as WBC × (% neutrophils + % bands)/100. Generally, the risk of infection is low when the ANC exceeds 1000/μL; however, the risk of infection increases significantly when the ANC is <500/μL. The risk of developing bacteremia is increased further as the ANC decreases to <100/μL, a condition commonly referred to as *profound neutropenia*. The most common causes of neutropenia are metastatic carcinoma, lymphoma, and chemotherapeutic agents. The reader is referred to Chapter 75, Prevention and Treatment of Infections in Neutropenic Cancer Patients, for a more detailed explanation.

LYMPHOCYTES

Reference Range: 22%–44% of WBCs

Lymphocytes constitute the second most common WBC in circulating blood. These leukocytes respond to foreign antigens by initiating the immune defense system. The vast majority of lymphocytes are located in the spleen, lymph nodes, and other organized lymphatic tissue. The lymphocytes circulating in blood represent <5% of the total amount in the body.

There are two major types of lymphocytes. T lymphocytes (thymic dependent) participate in cell-mediated immune responses, and B lymphocytes (bone marrow derived) are responsible for humoral antibody responses. Therefore, diseases affecting lymphocytes primarily manifest themselves as immune deficiency disorders that render the patient unable to defend against normal pathogens (see Chapter 76, Pharmacotherapy of Human Immunodeficiency Virus

Infection) or as autoimmune diseases in which immune responses are directed against the body's own cells.[71]

Increased numbers of lymphocytes on a white count differential sometimes accompany lymphoma (see Chapter 96, Adult Hematologic Malignancies) and viral infections. A relative lymphocytosis is sometimes encountered when the total lymphocytes have remained constant despite a decline in the total neutrophils.

MONOCYTES

Reference Range: 4%–11% of WBCs

Monocytes are formed in the bone marrow and are the precursors to macrophages and antigen-presenting cells (dendritic cells), which are found in the body's tissues.[73] Macrophages and dendritic cells are phagocytic cells that engulf foreign antigens or dead or dying cells. Dendritic cells also present fragments of antigens to T and B lymphocytes. Monocytosis may be observed in mononucleosis, subacute bacterial endocarditis, malaria, and tuberculosis, as well as during the recovery phase of some infections.

EOSINOPHILS

Reference Range: 0%–8% of WBCs

Because eosinophils have surface receptors that bind IgG and IgE, they can modify reactions associated with IgG- and IgE-mediated degranulation of mast cells. Primary lysosomal granules, small dense granules, and specific or secondary granules are the three types of granules found within eosinophils. The latter granules account for most of the biologic activity of eosinophils and are toxic to parasites, tumor cells, and some epithelial cells.[74]

Eosinophils have phagocytic activity, catalyze the oxidation of many substances, facilitate killing of microorganisms, initiate mast cell secretion, protect against various parasites, and play some role in host defense. Eosinophilia is probably most commonly associated with allergic reactions to drugs, allergic disorders (eg, hay fever, asthma, and eczema), invasive parasitic infections (eg, hookworm,

schistosomiasis, and trichinosis), collagen vascular diseases (eg, rheumatoid arthritis, eosinophilic fasciitis, and eosinophilia–myalgia syndrome), and malignancies (eg, Hodgkin lymphoma).[74–77]

BASOPHILS

Reference Range: 0%–3% of WBCs

During infection or inflammation, basophils leave the blood and mobilize as mast cells to the affected site and release granules. These granules contain histamine, serotonin, prostaglandins, and leukotrienes. Degranulation results in an increased blood flow to the site and may compound inflammatory processes. An increase in basophils commonly accompanies allergic and anaphylactic responses, chronic myeloid leukemia, myelofibrosis, and polycythemia vera. A decrease in the number of basophils is generally not readily apparent because of the small number of these cells in the blood.[71]

CASE 2-5

QUESTION 1: K.T., a 50-year-old female, is hospitalized with a sustained high fever of 102.56 °F (39.2 °C) and severe back pain. The results of the CBC and leukocyte differential are as follows:

Total WBC count: 21,000/μL
Neutrophils: 74%
Bands: 6%
Lymphocytes: 14.6%
Monocytes: 8%
Eosinophils: 1%
Basophils: 0%

Imaging and other blood work were ordered. K.T. is diagnosed with an abscess in her lower back and *Staphylococcus aureus* bacteremia.

How is K.T.'s laboratory report consistent with a systemic bacterial infection?

WBCs are the host's chief defense system, and the neutrophil is the main component of that system. During bacterial infections, the leukocyte count and the neutrophils are generally increased, and a left shift (increase in bands) may be noticeable. The percentage of

other types of WBCs is decreased proportionately because the number of neutrophils is increased.

As the infection progresses, the percentage of band cells may decrease as a result of an increase in the number of neutrophils that have a longer half-life. This decrease in bands does not necessarily indicate improvement. A decrease in the percentage of neutrophils with a decrease in the total WBC count is characteristic of effective antibiotic therapy.

CASE 2-5, QUESTION 2: The *S. aureus* causing K.T.'s bacteremia is found to be methicillin sensitive, and she is started on oxacillin 2 million units IV every 4 hours for treatment. After about a week of therapy, K.T. develops a fine red rash all over her body, mild lymphadenopathy, low-grade fever, and generalized swelling. The CBC shows a total WBC count of 8600/μL with 11% eosinophils. What is the significance of this eosinophil count?

In the clinical setting, absolute leukocyte counts may be used in conjunction with normal reference values. Absolute counts are calculated by multiplying the percentage of each individual cell by the total leukocyte count. Eosinophils are usually increased in allergic reactions; therefore, a drug-induced hypersensitivity reaction is a strong probability in K.T., with an absolute count of 946 eosinophils/μL (ie, 11% of 8600 leukocytes). The clinician should be suspicious of an allergic drug reaction when absolute eosinophil counts exceed 300 cells/μL. Eosinophils may increase before, after, or concurrent with other evidence of allergy (eg, rash). Eosinophilia without evidence of allergy is not sufficient cause to discontinue a suspected medication unless the eosinophilia is significant (ie, >2000 cells/μL). In addition, the absence of eosinophilia certainly does not rule out an allergic diagnosis in a patient exhibiting clear clinical manifestations of an apparent allergic reaction.

Thrombocytes

Reference Range: 150–450 × 10^3/μL or 150–450 × 10^9/L

Thrombocytes, commonly referred to as platelets, are tiny fragments of cells that assist with normal blood clotting. Platelet testing is included as part of a CBC and is often ordered along with other coagulation studies to evaluate bleeding and/or clotting disorders. Decreased platelet counts or thrombocytopenia may lead to petechiae, ecchymosis, and spontaneous hemorrhage.

Causes include decreased platelet production, accelerated destruction, loss from excessive bleeding or trauma, dilution of blood samples secondary to blood transfusion, sequestration secondary to hypersplenism, disseminated intravascular coagulation, infection, or systemic lupus erythematosus. Malignancy, rheumatoid arthritis, iron deficiency anemia, polycythemia vera, and post splenectomy syndromes are the most common causes of elevated platelet counts or thrombocytosis.

Coagulation Studies

The control of bleeding depends on the formation of a platelet plug and the formation of a stable fibrin clot. The formation of this clot depends on the complex interactions of plasma proteins and clotting factors. The prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) are used to diagnose coagulation abnormalities or to monitor the effectiveness of patients receiving anticoagulation therapy. When used to assess drug therapy, achieving a value outside the reference range is in fact a therapeutically desirable outcome.

ACTIVATED PARTIAL THROMBOPLASTIN TIME

Reference Range: 22–37 seconds

aPTT measures the time it takes the body to form a clot. aPTT depends on the activity of factors VIII, IX, XI, and XII (intrinsic pathway) and the factors involved in the final common pathway of the clotting cascade (II, X, and V). aPTT is commonly measured to detect bleeding disorders and coagulation deficiencies and monitor unfractionated heparin therapy. The reader is referred to Chapter 11,

Thrombosis, for more detailed information regarding the use of coagulation parameters in treating and monitoring thrombotic disorders.

PROTHROMBIN TIME

Reference Range: 10–13 seconds

Prothrombin is synthesized in the liver, and is converted to thrombin during the blood clotting process. Thrombin formation is the critical event in the hemostatic process because thrombin creates fibrin monomers that ultimately assemble into a clot and stimulates platelet activation. The PT test evaluates the integrity of the extrinsic and common pathways and directly measures the activity of clotting factors V, VII, and X, prothrombin (factor II), and fibrinogen (factor I). Automated laboratory instruments measure PT by recording the time required for the blood to clot after a reagent (ie, tissue thromboplastin) has been added to the patient's blood sample. It is recorded in seconds and is compared to a normal range that reflects PT values in healthy individuals. An abnormal PT is often caused by liver injury and/or by treatment with systemic blood thinners.

INTERNATIONAL NORMALIZED RATIO

Because different labs use different reagents, the PT results obtained from one reagent cannot be reliably compared with another reagent. Therefore, the INR is used as a standard unit to report the result of a PT test. The INR is the recommended method to monitor both the initiation and maintenance of anticoagulant therapy, most notably warfarin. Individuals who have normal blood clotting and are not on anticoagulation therapy should have an INR of 1. For patients on anticoagulation therapy, the target INR (ie, therapeutic range) is usually between 2.0 and 4.0 depending on the clinical indication and other patient-specific factors. Outside of the therapeutic range, the higher the INR, the higher the likelihood of bleeding because the blood is taking longer to clot. Conversely, if the INR is lower, there is an increased risk of developing a clot. Many factors including medications (eg, metronidazole, trimethoprim–sulfamethoxazole,

amiodarone, and azole antifungals), vitamin K intake, alcohol use, and certain medical conditions (eg, HF, cancer, and thyroid disorders) can influence the INR.

The INR is calculated using Eq. 2-12, where the prothrombin ratio (PTR) is the ratio between the patient's PT and the laboratory's control PT, and the ISI is the international sensitivity index. Commercial manufacturers quantify the ISI for the specific thromboplastin reagent used in each lot and report this information in the product package insert:

$$\mathrm{INR} = \{\mathrm{PT\ (patient)} / \mathrm{PT(control)}\}^{\mathrm{ISI}} = \mathrm{PTR}^{\mathrm{ISI}} \qquad \textbf{(Eq. 2-12)}$$

URINALYSIS

A standard urinalysis includes physical, chemical, and microscopic evaluations to assist with diagnosis of various urologic conditions. It begins with a simple observation of the color and the gross general appearance of the urine specimen. The urine pH and specific gravity are then recorded. Formed elements in the urine are examined microscopically, and the urine is searched routinely for pathologically significant substances that are normally not present (eg, glucose, blood, ketones, and bile pigments). Urine specimens should be evaluated quickly after collection to minimize unreliable results. The reader is referred to Chapter 71, Urinary Tract Infections, for a more detailed description of the use of urinalysis in the detection and monitoring of urinary tract infections (UTIs).

Gross Appearance of the Specimen

The concentrated, first-morning urine specimen is usually analyzed to eliminate effects of undue dilution as a result of water intake. The color should be slightly yellow, depending on the degree of dilution, and the appearance should be clear. The appearance of the urine may reveal clouds of crystals, bilirubin, blood, porphyrins, proteins,

food or drug colorings, or melanin. Discolored urine is abnormal. A red coloration of the urine may be imparted by blood, porphyria, or ingestion of phenolphthalein. A brown urine color may be caused by the acid hematin of blood or from melanin pigments. Medications such as nitrofurantoin and/or metronidazole can also contribute to this color change. Excessive excretion of urobilinogen or the effects of drugs such as rifampin or phenazopyridine may cause a dark orange urine color. A blue to blue-green color of the urine may result from the systemic administration of methylene blue.

Specimen pH

When freshly produced, urinary pH can range from 4.5 to 8 but is mostly acidic because of metabolic activity. Alkaline urine may indicate an aged specimen, systemic alkalosis, failure of renal acidifying mechanisms, or infection in the urinary tract.

Specific Gravity

Urinary specific gravity provides information regarding a patient's hydration status. A normal morning urine specimen should have a specific gravity of 1.003 to 1.030. The upper end of this range is close to the maximal concentrating ability of the kidney. A value of ≤1.010 supports relative hydration, whereas a value >1.020 indicates relative dehydration.

Protein

Proteinuria is a classic sign of renal injury. If proteinuria is found during the evaluation of a patient with a nonrenal illness, it suggests that the disease may also involve the kidneys (ie, hypertension and diabetes).[78] A healthy adult generally excretes 30 to 130 mg/day of protein into the urine.

Protein in a urine sample is generally tested qualitatively on a random urine sample by a dipstick method and is usually reported on

a scale of 0 (<30 mg/dL), 1+ (30–100 mg/dL), 2+ (100–300 mg/dL), 3+ (300–1000 mg/dL), and 4+ (>1000 mg/dL). A positive qualitative test result for urine protein should be repeated after a few days because transient proteinuria can accompany various physiologic and pathologic states, even when kidney function is normal. Therefore, patients with HF, seizures, or febrile illnesses and normal renal function need not undergo invasive renal function tests if the proteinuria is modest and likely to be transient. Another qualitative evaluation of proteinuria can be performed in about 2 weeks to confirm the diagnosis of transient proteinuria.[79] If subsequent qualitative test results are positive, a 24-hour urine sample should be collected to quantitatively test for protein and creatinine (see the section on Creatinine Clearance). In patients with a normal 24-hour urinary protein concentration, previous positive qualitative test results probably represent either false-positive results or a transient phenomenon.[78] A laboratory parameter being used with increased frequency to assess proteinuria is the urine albumin to urine creatinine ratio (UACR). This measurement tends to be less influenced by fluctuations in urine concentration and may offer a more reliable indication of proteinuria. The reference range for UACR is <30 mg/g.

MICROSCOPIC EXAMINATION

The urine sediment is examined for RBCs, WBCs, casts, yeast, crystals, and epithelial cells.

RBCs should be absent in normal urine, although <4 to 6 RBCs per high-power field (HPF) would still be considered in the normal range. Bleeding or clotting disorders, some collagen diseases, and various bladder, urethral, and prostatic conditions may cause microscopic hematuria. In females, vaginal blood occasionally contaminates the urine specimen, but the presence of numerous squamous epithelial cells should be sufficient to alert clinicians to this artifact.

WBCs should be virtually absent in normal urine, although up to 5 WBCs/HPF would still be within the reference range. Similarly,

leukocyte esterase, an enzyme found in most WBCs, is absent in normal urine. The presence of elevated WBCs in the urine (pyuria) and/or leukocyte esterase suggests an acute infection in the urinary tract. Some noninfectious inflammatory diseases of the kidney, ureter, or bladder may also contribute WBCs to the urine sediment.

Normal urine also contains chemicals called nitrates. When certain bacteria like *Escherichia coli* enter the urinary tract, nitrates are enzymatically converted to nitrites, suggesting that a UTI is present. A urine sample finding that is positive for leukocyte esterase, but negative for nitrites, may still indicate an infection.

Casts may be used to identify the location of disease in the genitourinary tract. Casts are composed of proteinaceous or fatty material that outlines the shape of the renal tubules where they are deposited. The presence of casts must be interpreted in light of other factors related to the kidney and its function; however, fatty casts, RBC casts, and WBC casts are always significant. RBC casts usually suggest glomerular injury, and WBC casts suggest tubular or interstitial injury. Lipid casts with proteinuria are characteristic findings in patients with nephrotic syndrome or hypothyroidism.[78] The finding of hyaline casts alone in the presence of proteinuria suggests a renal origin for the protein. Hyaline or granular casts alone, however, only suggest some defects in factors that affect cast formation and are therefore difficult to interpret.

Crystals may originally appear as a cloud in the urine. Their formation is pH dependent, and they often appear only as the urine cools to room temperature or in concentrated urine. In acidic urine, crystals may be uric acid or calcium oxalate; in alkaline urine, they may be phosphates. Crystals per se are not highly significant, although they may reflect a tendency toward the formation of renal calculi.

CASE 2-6

QUESTION 1: S.T. is a 33-year-old female with type 1 diabetes who presents to the urgent care clinic with a 3-day history of fever, malaise, dysuria, and flank pain. Upon interview, you learn that over the past few days, S.T. has been

unable to keep down any food because of feelings of nausea. Because of this, she has not taken her insulin for 48 hours. Today, her finger-stick blood glucose is 415 mg/dL, and a STAT midstream urinalysis and Gram stain indicate the following:

pH: 5.2
Appearance: cloudy
Specific gravity: 1.033
Urine protein: 3+
Urine glucose: 4+
Urine ketones: positive
Urine bacteria: 4+
Urine WBC: too numerous to count (TNTC)
Squamous epithelial: few per HPF
Urine nitrite: positive
Gram stain: numerous gram-negative rods

What objective data from the urinalysis indicate a UTI?

The cloudy appearance of S.T.'s urine indicates the presence of bacteria, protein, and WBCs, which is supported by the urinalysis results. The lack of a significant amount of squamous epithelial cells, the presence of a significant number of nitrite-producing bacteria, and the Gram stain indicate a clean-catch urine specimen and a UTI involving gram-negative organisms (most likely *E. coli* that causes a majority of UTIs).

Case 2-6, Question 2: What objective data from the urinalysis indicate uncontrolled diabetes?

Glucose is normally filtered in the glomerulus and a majority is reabsorbed in the proximal tubule of the kidney. S.T.'s glycosuria (4+ glucose) and finger stick of 415 mg/dL indicate the filtered amount of glucose exceeds the capacity for reabsorption (~180 mg/dL). In addition, the presence of positive ketones indicates the body is utilizing fat, not glucose, for energy. High levels of ketones can predispose S.T. to dehydration, resulting in diabetic ketoacidosis.

THERAPEUTIC DRUG MONITORING

Many drugs have a wide dosing range that can achieve efficacy with a low risk of toxicity. Drugs that have a narrow dosing range with a high risk of toxicity (narrow therapeutic index) often have their blood levels monitored. Results from therapeutic drug monitoring assist clinicians with appropriate dosing adjustments to prevent toxicity and achieve appropriate clinical outcomes. Pharmacokinetic parameters and drug interactions may significantly impact the laboratory results and must be integrated into the clinical assessment of the data. Similarly, for certain drugs and drug classes, there are recommended laboratory tests that should be performed to monitor their potential adverse effects on organ systems. Ideally, blood level monitoring should occur after the drug has reached steady state and at a consistent time within the dosing interval.

PATIENT-DIRECTED MONITORING AND TESTING

Often patient-directed self-monitoring is an essential component to successful management of certain disease states such as blood pressure monitoring for hypertension and blood glucose monitoring for diabetes mellitus. When used appropriately, data obtained from these monitoring devices can be used by health care providers and consumers to initiate or modify therapies accordingly.

Additional laboratory, self-monitoring tests or devices are also available for consumers to purchase for independent testing or screening purposes at home. Tests that are designed specifically to be used by the consumer without the involvement of a provider are called direct-to-consumer (DTC) tests. Some products provide an immediate result, whereas others require submitting a completed kit to a laboratory for analysis. Samples may be obtained from various sources, including urine, blood, saliva, stool, or hair samples. The

incidence of consumers using these products has significantly increased and likely will continue to climb because of increased access via the Internet as well as additional tests becoming available.

In the United States, some, but not all, DTC tests have been approved by the U.S. Food and Drug Administration (FDA). A current listing of approved products is available through the FDA's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) and can be accessed online at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm. Consumers should be cautioned about the accuracy of tests that have not been approved and the validity of all test results, especially for diagnostic purposes, because many factors can impact or interfere with the sensitivity (probability of obtaining a positive result when a sample is truly positive) and specificity (probability of obtaining a negative result when the sample is truly negative). Follow-up assessment with a health care provider should be encouraged to confirm or refute patient-directed test results.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Facts & Comparison® eAnswers. Reference values for blood, plasma, or serum laboratory tests. 2015 Clinical Drug Information, LLC. Updated March 24, 2015. (2)

Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. *N Engl J Med*. 2004;351:1548–1563. (1)

Lee M. *Basic Skills in Interpreting Laboratory Data*. 6th ed. American Society of Health-System Pharmacists; 2017. (3)

Key Websites

Mayo Medical Laboratories Mobile App. https://www.mayocliniclabs.com/

Merck Manual. http://www.merckmanuals.com/professional/appendixes/normal-laboratory-values/normal-laboratory-values

COMPLETE REFERENCES CHAPTER 2 INTERPRETATION OF CLINICAL LABORATORY TESTS

1. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. *N Engl J Med*. 2004;351:1548–1563.
2. Facts & Comparison® eAnswers. Reference values for blood, plasma, or serum laboratory tests. 2015 Clinical Drug Information, LLC. Updated March 24, 2015. https://www.wolterskluwer.com/en/solutions/lexicomp/facts-and-comparisons
3. Lee M. *Basic Skills in Interpreting Laboratory Data*. 6th ed. American Society of Health-System Pharmacists; 2017.
4. Evans PC, Cleary JD. SI units—are we leaders or followers? *Ann Pharmacother*. 1993;27(1):96.
5. Vaughan LM. SI units: is it pass the mass but hold the mole? *Ann Pharmacother*. 1993;29(1):99–100.
6. Sterns RH. Disorders of plasma sodium-causes, consequences, and correction. *N Engl J Med*. 2015:372(1):55–65.
7. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342(21):1581–1589.
8. Liamis G, Milionis H, Elisaf M. et al. A review of drug-induced hyponatremia. *Am J Kid Dis*. 2008;52(1):144–153.
9. Shepshelovich D, Schechter A, Calvarysky B, Diker-Cohen T, Rozen-Zvi B, Gafter-Gvili A. Medication-induced SIADH: distribution and characterization according to medication class. *Br J Clin Pharmacol*. 2017;83(8):1801–1807. doi:10.1111/bcp.13256
10. Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med*. 2000;342(20):1493–1499.

11. Winter ME. *Basic Clinical Pharmacokinetics*. 4th ed. Lippincott Williams & Wilkins; 2004.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
13. Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. *Pharmacotherapy*. 2012;32(7):604–612.
14. Rhodes PJ, Rhodes RS, McClelland GH, Culbertson VL, Jahnigen DW, Bloedow DC. Evaluation of eight methods for estimating creatinine clearance in men. *Clin Pharm*. 1987;6(5):399–406.
15. Jelliffe RW. Letter: creatinine clearance: bedside estimate. *Ann Intern Med*. 1973;79(4):604–605.
16. Hull JH, Hak LJ, Koch GG, Wargin WA, Chi SL, Mattocks AM. Influence of range of renal function and liver disease on predictability of creatinine clearance. *Clin Pharmacol Ther*. 1981;29(4):516–521.
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461–470.
18. Ahmed S, Nutt CT, Eneanya ND, et al. Examining the potential impact of race multiplier utilization in estimated glomerular filtration rate calculation on African-American care outcomes. *J Gen Intern Med*. 2021;36(2):464–471. doi:10.1007/s11606-020-06280-5
19. Diao JA, Wu GJ, Taylor HA, et al. Clinical implications of removing race from estimates of kidney function. *JAMA*. 2021;325(2):184–186. doi:10.1001/jama.2020.22124
20. Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. *Curr Opin Nephrol Hypertens*. 2015;24(3):295–300.
21. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin levels other than renal function and the impact on renal function measurement. *Kidney Int*. 2004;65(4):1416–1421.
22. Kar S, Paglialunga S, Islam R. Cystatin C is a more reliable biomarker for determining eGFR to support drug development studies. *J Clin Pharmacol*. 2018;58(10):1239–1247.
23. Klonoff DC, Parkes JL, Kovatchev BP, et al. Investigation of the accuracy of 18 marketed blood glucose monitors. *Diabetes Care*. 2018;41(8):1681–1688.
24. JDRF CGM Study Group. JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods. *Diabetes Technol Ther*. 2008;10(4):310–321.
25. American Diabetes Association. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*.

2020;43(suppl 1):S14–S31.
26. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. *Diabetes Care*. 2003;26:881–885.
27. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405–412.
28. Bushinsky DA, Monk RD. Electrolyte quintet: calcium. *Lancet*. 1998;352:306–311.
29. Lee TH, Goldman L. Serum enzyme assays on the diagnosis of acute myocardial infarction. Recommendations based on a quantitative analysis. *Ann Intern Med*. 1986;105(2):221–233.
30. White RD, Grande P, Califf L, Palmeri ST, Califf RM, Wagner GS. Diagnostic and prognostic significance of minimally elevated creatinine kinase-MB in suspected acute myocardial infarction. *Am J Cardiol*. 1985;55(13 pt 1):1478–1484.
31. Roberts R. Where, oh where has the MB gone? *N Engl J Med*. 1985;313(17):1081–1083.
32. Hamm CW. New serum markers for acute myocardial infarction. *N Engl J Med*. 1994;331(9):607–608.
33. Chapelle JP. Cardiac troponin I and troponin T: recent players in the field of myocardial markers. *Clin Chem Lab Med*. 1999;37(1):11–20.
34. Malasky BR, Alpert JS. Diagnosis of myocardial injury by biochemical markers: problems and promises. *Cardiol Rev*. 2002;10(5):306–317.
35. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol*. 2017;70(8):996–1012.
36. Sandoval Y, Jaffe AS. Using high-sensitivity cardiac troponin T for acute cardiac care. *Am J Med.* 2017;130:1358–1365.
37. Romiti GF, Cangemi R, Toriello F, et al. Sex-specific cut-offs for high-sensitivity cardiac troponin: is less more? *Cardiovasc Ther*. 2019;2019:9546931.
38. Rasouli ML, Nasir K, Blumenthal RS, Park R, Aziz DC, Budoff MJ. Plasma homocysteine predicts progression of atherosclerosis. *Atherosclerosis*. 2005;181(1):159–165.
39. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. *Nutr J*. 2015;14:6.
40. Cardarelli R, Lumicao TG Jr. B-type natriuretic peptide: a review of its diagnostic, prognostic, and therapeutic monitoring value in heart failure for primary care physicians. *J Am Board Fam Pract*. 2003;16(4):327–333.
41. Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in

surviving patients with heart failure. *Circulation*. 2015;131:54–61.
42. Zile MR, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*. 2016;68:2425–2436.
43. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2017;70(6):776–803.
44. Richards AM, Doughty R, Nicholls MG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Australia-New Zealand Heart Failure Group. *J Am Coll Cardiol*. 2001;37:1781–1787.
45. Tang WH, Girod JP, Lee MJ, et al. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation*. 2003;108:2964–2966.
46. Zaphiriou A, Robb S, Murray-Thomas T, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail*. 2005;7:537–541.
47. Son CS, Kim YN, Kim HS, et al. Decision-making model for early diagnosis of congestive heart failure using rough set and decision tree approaches. *J Biomed Inform*. 2011;45:999–1008.
48. Kelder JC, Cramer MJ, Van WJ, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation*. 2011;124:2865–2873.
49. Booth RA, Hill SA, Don-Wauchope A, et al. Performance of BNP and NT-proBNP for diagnosis of heart failure in primary care patients: a systematic review. *Heart Fail Rev*. 2014;19:439–451.
50. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol*. 2001;37:379–385.
51. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161–167.
52. Moe GW, Howlett J, Januzzi JL, et al. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation*. 2007;115:3103–3110.
53. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004;350:647–654.
54. van Kimmenade RR, Pinto YM, Bayes-Genis A, et al. Usefulness of intermediate amino-terminal pro-brain natriuretic peptide concentrations for

diagnosis and prognosis of acute heart failure. *Am J Cardiol*. 2006;98:386–390.
55. Januzzi JL Jr, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. *Am J Cardiol*. 2008;101:29–38.
56. Santaguida PL, Don-Wauchope AC, Ali U, et al. Incremental value of natriuretic peptide measurement in acute decompensated heart failure (ADHF): a systematic review. *Heart Fail Rev*. 2014;19:507–519.
57. Hill SA, Booth RA, Santaguida PL, et al. Use of BNP and NT-proBNP for the diagnosis of heart failure in the emergency department: a systematic review of the evidence. *Heart Fail Rev*. 2014;19:421–438.
58. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA*. 2001;285(19):2481–2485.
59. Yousuf O, Mohanty B, Martin SS, et al. High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? *J Am Coll Cardiol*. 2013;62:397–408.
60. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation*. 2003;108:2292–2297.
61. Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. *Gut*. 2018;67:6–19.
62. Botros M, Sikaris KA. The de ritis ratio: the test of time. *Clin Biochem Rev*. 2013;34(3):117–130.
63. Schmid R. Bilirubin metabolism in man. *N Engl J Med*. 1972;287(14):703–709.
64. Barry MJ. Clinical practice. Prostate-specific-antigen testing for early diagnosis of prostate cancer. *N Engl J Med*. 2001;344(18):1373–1377.
65. Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *JAMA*. 1998;279(19):1542–1547.
66. Lange PH. New information about prostate-specific antigen and the paradoxes of prostate cancer. *JAMA*. 1995;273(4):336–337.
67. Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab*. 1994;79(6):1605–1608.
68. Greer JP, Foerster J, Rodgers GM, et al, eds. *Wintrobe's Clinical Hematology*. 12th ed. Lippincott Williams & Wilkins; 2009.
69. Keenan WF Jr. Macrocytosis as an indicator of human disease. *J Am Board Fam Pract*. 1989;2(4):252–256.

70. Sox HC Jr, Liang MH. The erythrocyte sedimentation rate. Guidelines for rational use. *Ann Intern Med*. 1986;104(4):515–523.
71. Winkelstein A, Sacher RA, Kalpan S, Roberts G. *White Cell Manual*. 5th ed. FA Davis; 1998.
72. Malech HL, Gallin JI. Current concepts: immunology. Neutrophils in human diseases. *N Engl J Med*. 1987;317(11):687–694.
73. Cline MG, Lehrer RI, Territo MC, Golde DW. UCLA Conference. Monocytes and macrophages: functions and diseases. *Ann Intern Med*. 1978;88(1):78–88.
74. Beeson PB. Cancer and eosinophilia. *N Engl J Med*. 1983;309(13):792–793.
75. Butterworth AE, David JR. Eosinophil function. *N Engl J Med*. 1981;304(3):154–156.
76. Clauw DJ, Nashel DJ, Umhau A, Katz P. Tryptophan-associated eosinophilic connective-tissue disease. *JAMA*. 1990;263(11):1502–1506.
77. Dombrowicz D, Capron M. Eosinophils, allergy and parasites. *Curr Opin Immunol*. 2001;13(6):716–720.
78. Abuelo JG. Proteinuria: diagnostic principles and procedures. *Ann Intern Med*. 1983;98(2):186–191.
79. Reuben DB, Wachtel TJ, Brown PC, Driscoll JL. Transient proteinuria in emergency medical admissions. *N Engl J Med*. 1982;306(17):1031–1033.

3

Drug Interactions

Michelle Ceresia, Caroline S. Zeind, John Fanikos, and Michael G. Carvalho

CORE PRINCIPLES		CHAPTER CASES
1	A drug interaction is either the result of pharmacokinetic changes of a drug or its metabolites owing to alteration in absorption, distribution, metabolism, or excretion or is the result of pharmacodynamic changes, impacting the effect or mechanism of action. There are several types of drug interactions. Although the classic interaction involves two drugs (drug–drug interaction or DDI), a drug interaction can involve the interaction of a drug with a nutrient, chemical, food, herbal, disease, or laboratory test.	**Case 3-1 (Questions 2–6)** **Case 3-2 (Questions 2, 3)** **Case 3-3 (Question 1), Tables 3-1, 3-3, and 3-4**
2	Some patient populations are more vulnerable to drug interactions because	**Case 3-1 (Question 1)** **Case 3-2 (Question 1)**

	of age, gender, race, and comorbidities, such as renal and hepatic insufficiency. Drugs that have a higher potential for an interaction are those with a narrow therapeutic index (NTI).	**Case 3-3 (Question 1), Table 3-2**
	PHARMACOKINETIC CHANGES	
1	Administration/absorption: Drug interactions resulting from alterations in absorption are caused by (a) changes in gastric pH, (b) formation of complexes in the gastrointestinal (GI) tract, (c) changes in GI motility, and (d) modulation of P-glycoprotein (P-gp) intestinal absorption of drugs.	**Case 3-1 (Question 1)** **Case 3-2 (Question 3), Table 3-3**
2	Distribution: Drug interactions resulting from displacement of drug bound to protein sites (eg, albumin), particularly with drugs with a high degree of plasma protein binding that are more likely to be displaced by a drug with greater affinity for the same binding site.	**Case 3-1 (Question 2), Figure 3-1, Table 3-3**
3	Metabolism: A common cause of clinically significant drug interactions during multiple drug therapy involves drug metabolism in which cytochrome P450 (CYP) isoenzymes play a significant role. Many drug interactions occur as a result of inhibition or induction of CYP enzymes.	**Case 3-1 (Questions 3, 5, 6)** **Case 3-2 (Question 2)** **Case 3-3 (Question 1), Figure 3-2, Table 3-3**
4	Excretion/elimination: Drugs are eliminated mainly through renal tubular excretion and biliary excretion. Drug	**Case 3-2 (Question 2), Table 3-3**

	interactions may occur during the elimination of drugs and their metabolites by the kidney as a result of competition at the level of active tubular secretion, interference with tubular transport, or during tubular reabsorption.	

PHARMACODYNAMICS CHANGES

1	Pharmacodynamic interactions occur when the presence of one drug changes the effect of another drug without pharmacokinetic alterations. It may be owing to competition at the drug receptor level by indirect systems, involving interference with physiologic mechanisms, resulting in additive or synergistic interactions or antagonistic interactions.	**Case 3-1 (Question 4)** **Case 3-2 (Questions 2, 3), Table 3-4**

RESOURCES AND EVIDENCE FOR CLINICAL DECISION SUPPORT

1	Patient safety initiatives have expanded in efforts to improve the health care delivery system with medication error prevention as a high-priority area. Health care providers have become increasingly challenged on devising optimal approaches to managing drug interactions. A key challenge is that computerized drug interaction screening systems detect a large number of DDIs of questionable clinical significance. Expert groups have provided recommendations to improve the	**Case 3-1 (Question 6)**

usability of clinical decision support (CDS) alerts for managing drug interactions.

INTRODUCTION

Because health care professionals are committed to ensuring patient safety and preventing drug-related harm, it is important to understand drug interaction principles and how to apply drug interaction decision support tools to provide evidence-based clinical decisions. This chapter introduces the reader to general principles and concepts of drug interactions. Case studies are incorporated to illustrate the application of key concepts and to highlight the importance of understanding the mechanisms by which drugs interact and how it impacts the clinical assessment and management of drug therapy. Disease-specific chapters within this textbook will also apply drug interaction concepts and incorporate case studies relevant to disease management.

DEFINITION

Drug interactions can be broadly categorized as either pharmacokinetic or pharmacodynamic in nature.[1,2] Pharmacokinetic drug interactions involve absorption, distribution, metabolism, and excretion, whereas pharmacodynamic interactions can be characterized into three subgroups: (a) direct effect at receptor function, (b) interference with a biologic or physiologic control process, and (c) additive or attenuated pharmacologic effect.[3] Another key area of consideration is the biologic variance in a given individual: genetics, age, disease, and the internal environmental factors (ie, the patient's medications, dietary intake, and social habits such as smoking and alcohol consumption).[4]

A *drug–drug interaction* (DDI) is defined "as a clinically meaningful alteration in the exposure and/or response to a drug (object drug) that has occurred as a result of the coadministration of another drug (precipitant drug)."[1–2,5,6] Drug interactions may have beneficial effects because some drug interactions are used to enhance therapeutic outcomes, whereas other interactions may have deleterious effects that result in serious toxicity or may inhibit the effects of a drug, leading to suboptimal therapeutic outcomes. Although the classic interaction involves two drugs (DDI), a drug interaction can involve the interaction of a drug with a nutrient, chemical, food, herbal, disease, or laboratory test.[7,8] A *potential drug interaction* is defined "as the occurrence in which two drugs that are known to interact are concurrently prescribed, regardless of whether adverse events occurred."[8]

In 2015, consensus recommendations for evaluating DDIs were published by an expert group that included definitions of relevant terminology for evaluation of DDI evidence.[5] **Table 3-1** highlights their recommendations for key terms of relevant terminology for evaluation of DDI evidence. (The reader is referred to the complete list of definitions agreed upon by this expert group that are provided in their supplementary publication.)[5] They emphasize the importance of consistent use of relevant terminology for evaluation of DDI evidence. For example, a clinically relevant DDI is defined as one that is associated with either toxicity or loss of efficacy that warrants the attention of health care professionals.[2]

Table 3-1
Terminology Related to DDI

Terminology	
DDI	Clinically meaningful alteration in the exposure and/or response to a drug (object drug) that has occurred as a result of the coadministration of another drug (precipitant drug)
Potential DDI	Coprescription of two drugs known to interact; therefore, a DDI could occur in the exposed patient.
Clinically relevant	Drug–drug interaction associated with either toxicity or loss of efficacy that warrants the attention of health care professionals

DDI	
NTI drugs	Drugs for which even a small change in drug exposure may lead to toxicity or loss of efficacy

DDI, drug–drug interaction; NTI, narrow therapeutic index.

Source: Adapted by permission from Springer. Scheife RT, Hines LE, Boyce RD, et al. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. *Drug Saf*. 2015;38(2):197–206.

The Food and Drug Administration (FDA) has now provided guidance to evaluate DDIs as part of a company's assessment of the drug's benefits and risks during the drug development process.[9] Clinically relevant DDIs should be recognized at the time of drug approval, monitored after approval, and communicated in the package labeling. Studies will be completed to determine whether cytochrome P450 (CYP) enzyme- and transporter-mediated DDIs alter the pharmacokinetics of new drug or the pharmacokinetics of other drugs. Studies will also determine the clinical significance of the observed or expected DDIs and any appropriate management or prevention strategies. Because known agents will be used to determine whether a new medication is a victim or perpetrator of DDIs, clinicians can expect to see a list of common offending medications reported in the package labeling.

RISK FACTORS FOR DRUG INTERACTIONS

Some patient populations are more vulnerable to drug interactions because of age, gender, and comorbidities, such as renal and hepatic insufficiency. Polypharmacy, defined as the concomitant use of multiple drugs or the administration of more medications that are indicated clinically, is a leading cause of DDIs, resulting in higher rates of adverse events, higher drug costs, and medication nonadherence.[10–12] Elderly patients are at an increased risk of drug interactions given the rates of polypharmacy (estimated at 20%–50%) in the older population, along with multiple comorbidities.[13–15]

Adverse drug reactions (ADRs) have been observed two to three times more frequently in older persons and account for 5% to 17% of all hospital admissions.[16] Age alone is a key risk factor in the elderly population as altered pharmacokinetics and pharmacodynamics may result in a slower intestinal transit time, diminished absorption capacity, decreased liver metabolism and renal excretion, and alterations in volemia and body fat distribution.[17,18] Within the older population, the frail elderly represents a subgroup in which comorbidities primarily account for the observed changes in pharmacokinetic and pharmacodynamic properties.[13] When considering the impact of aging, it is important to differentiate the subgroup of fit elderly from that of the frail elderly, because those who are frail are at increased risk of death, institutionalization, and worsening disability.[13,19,20] A number of studies have shown that females are at higher risk for drug interactions.[21–24] Further research is needed in this area to better understand gender differences with drug interactions.[21–24] The distribution of many drugs may be significantly altered because of marked increases in total body weight (TBW).[25] Drugs that are lipophilic will have an increased volume of distribution. Patients who are obese and those who are malnourished will have altered levels of metabolizing enzymes, increasing their susceptibility to drug interactions.[16,26] Critically ill patients, those with poor nutritional status, and patients who are immunocompromised are at higher risk of drug interactions. Cigarette smoking can affect drug therapy by both pharmacokinetic and pharmacodynamic mechanisms. It can affect drug therapy by enzyme induction of CYP; enzymes induced by tobacco smoking may also increase the risk of cancer by enhancing metabolic activation of carcinogens.[27] Drugs that have a higher potential for an interaction are ones with a narrow therapeutic index (NTI) because there are small differences between therapeutic and toxic doses. For example, lithium, a monovalent cation, is a drug with an NTI that is influenced by changes of serum sodium. Patients taking lithium and who are also receiving chronic treatment with thiazides are at risk of lithium toxicity because thiazides can cause a high excretion of sodium that may increase lithium reabsorption.[3]

An individual's genetic makeup determines their complement of metabolizing enzymes, and based on their genotype, patients may be classified as having a phenotype for ultrarapid metabolizer, extensive metabolizer, intermediate metabolizer, or poor metabolizer (refer to Chapter 4, Pharmacogenomics and Personalized Medicine).[28] Individuals who use multiple providers and/or multiple pharmacies are more likely to have incomplete information available for both the providers and themselves; this impacts clinical decision-making and increases the likelihood that a drug interaction may go undetected. Individuals who self-prescribe and take over-the-counter (OTC) products (including dietary supplements, vitamins, minerals, and herbal agents) may not understand the potential risk for drug interactions. In addition, if they do not maintain a complete listing of OTC products for themselves and their providers, there is a greater likelihood for ADRs and drug interactions. Although disease-specific chapters in this textbook will provide a wide array of risk factors for drug interactions, **Table 3-2** outlines examples of risk factors for drug interactions.

Table 3-2
Risk Factors for Drug Interactions[1,13–34]

Category	Risk Factor	Potential Effect
Patient characteristics Demographics	Age (<5 years and ≥65 years)	Alterations in drug distribution; ↓ clearance that may result in drug accumulation
	Female gender	↓ Ability to metabolize compared to males
Social factors	Nutrition	Affects cytochrome p450 (CYP) activity (eg, grapefruit juice inhibits CYP3A4 activity)
	Smoking	Affects CYP activity (ie, induces CYP1A2)
	Alcohol	Affects CYP activity, specifically CYP2E1
Organ dysfunction	↓ Renal function	↓ Clearance, which may result in ↑ serum concentrations of drug

		and accumulation
	↓ Hepatic function	↓ Metabolism, which may result in ↑ serum concentrations and accumulation of the parent drug and/or metabolite
	Heart failure (HF)	↑ Risk owing to the number of medications prescribed with comorbidities
	Chronic obstructive pulmonary disease (COPD)	↑ Risk owing to the number of medications prescribed with comorbidities
Metabolic and endocrine	Obesity	↑ Distribution of lipophilic drugs
	Fatty liver	Altered metabolism
	Hypoproteinemia	↑ Serum drug concentration
Genetic[a]	Genetic polymorphisms (ultrarapid, extensive, intermediate, or poor metabolizers)	Altered metabolism
Acute medical conditions	Dehydration	↑ Serum drug concentrations
	Hypotension	↓ Clearance
	Hypothermia	↓ Clearance
	Infection	↑ Catabolism
Drug characteristics	Narrow therapeutic index (NTI)	↑ Risk of dose-related adverse drug events
	Highly protein bound	↑ Free fraction (active drug) from protein displacement
	Small volume of distribution	Drug confined to the plasma
	CYP substrate	↓↑ Serum drug concentration with coadministration of inducer or inhibitor precipitant drug
	P-glycoprotein substrate	↓↑ Serum drug concentration with coadministration of inducer or inhibitor precipitant drug
Other factors	Polypharmacy	Risk of adverse drug interactions ↑ with increase in number of medicines

	Number of prescribers	Number of prescribed drugs ↑ with multiple prescribers
	Number of pharmacies utilized	Number of prescribed drugs ↑ with multiple pharmacies Pharmacist may not have knowledge of all drugs prescribed to patient.
	Self-prescribing	OTC medicines interacting with prescribed medicines
	Duration of hospital stay	Susceptible to hospital-acquired conditions and subsequent drug therapy

OTC, over-the-counter.

[a]Refer to Chapter 4, Pharmacogenomics and Personalized Medicine for further information.

CASE 3-1

QUESTION 1: F.D. is a 79-year-old female patient who underwent a total hip replacement at a large teaching hospital. The medical team plans to start F.D. on warfarin therapy for venous thromboembolism prophylaxis with an international normalized ratio (INR) target range of 1.8 to 2.3 for a total duration of 3 weeks. The first dose will be administered in the evening on the day of surgery.

Her medical history includes newly diagnosed osteoporosis, recently started on alendronate; epilepsy that developed several years ago, controlled with phenytoin; and hypercholesterolemia for the past 9 years, for which she takes fluvastatin. She does not drink alcohol and has never smoked. She takes an OTC medicine, but does not recall the name of the product. She has some renal dysfunction (creatinine clearance 70 mL/minute). Her hepatic function is within normal range. F.D. requests that the medical team electronically transmit her new prescriptions postdischarge to a pharmacy located in close proximity to her friend's home because she will be recuperating there.

What are F.D.'s risk factors for drug interactions with the addition of warfarin postsurgery?

F.D. has multiple factors including patient- and drug-specific ones that increase her risk for drug interactions. Her patient risk factors include age, gender, and renal dysfunction.

Patient Risk Factors

- Older age: 79 years old—altered pharmacokinetics and pharmacodynamics
- Female gender: decreased ability to metabolize compared to males
- Renal dysfunction: decreased clearance of renally eliminated medications, which may result in increased serum concentrations of drug and accumulation

With regard to drug-specific factors, F.D. has been taking phenytoin, a drug with an NTI, for the past several years. She will be receiving warfarin, another agent with NTI. Both medications are metabolized via the CYP system. In addition, F.D. is at increased risk of additional drug interactions owing to polypharmacy because she has chronic disease comorbidities (ie, seizure disorder, hypercholesterolemia, and osteoporosis).

Drug Risk Factors

- Warfarin—NTI, highly protein bound to albumin, small volume of distribution, metabolized by the CYP system
- Phenytoin—NTI, highly protein bound to albumin, metabolized by CYP2C9 and CYP2C19 isoforms, and susceptible to drugs that inhibit hepatic microsomal enzymes
- Fluvastatin and other agents in this class (eg, atorvastatin, rosuvastatin, and simvastatin)—suspected or known to alter the INR in patients who receive warfarin, whereas pravastatin does not appear to interact with warfarin[35–37]
- Unknown OTC product

Other Risk Factors

- Polypharmacy—before admission, she is already taking three prescription drugs and also takes OTC products. She is a poor historian.

- Number of pharmacies used—pharmacist may not have knowledge of all drugs prescribed to patient.

MECHANISMS OF DRUG INTERACTIONS

Pharmacokinetics

ADMINISTRATION/ABSORPTION

Following oral administration, most drug absorption occurs in the proximal small intestine.[38] However, drug interactions that alter absorption may occur throughout the gastrointestinal (GI) tract by a variety of mechanisms, including complexation (adsorption or chelation), changes in pH, changes in GI motility, altered drug transport, and enzymatic metabolism. The net effect of one or more of these mechanisms is a change in the rate of absorption, the extent of absorption, or a combination of both. Although interactions that result in a reduced rate of absorption are generally not clinically significant for drugs given over the long term in multiple doses, for acutely administered drugs, such as analgesics or hypnotics, this can lead to an unaccepted delay or therapeutic failure.[1,39]

With regard to changes in gastric pH, the majority of drugs that are orally administered must be dissolved and absorbed in a gastric pH between 2.5 and 3. Drugs, such as antacids, proton-pump inhibitors (PPIs), or H_2-antagonists, can alter the kinetics of coadministered drugs.[3] Antifungal agents, such as ketoconazole or itraconazole, require an acidic environment to be properly dissolved. Coadministration with drugs that increase gastric pH may cause a reduction in the dissolution and absorption of antifungal drugs. It is recommended that these antifungal agents be administered at least 2 hours after the administration of antacids.

Coadministration of medications around the same time can result in drug interactions that may be clinically significant. Some antibiotics, such as tetracyclines, will combine with metal ions (eg, calcium, magnesium, aluminum, iron) to form complexes that are

poorly absorbed. Antacids also reduce the absorption of fluoroquinolones (eg, ciprofloxacin) because the metal ions form complexes with the drug. Therefore, the antacids and fluoroquinolones should be administered at least 2 hours apart. These types of interactions can decrease clinical effectiveness of the antibiotic and can lead to the emergence of resistant organisms.[34] Drugs that are able to increase the gastric transit, such as metoclopramide owing to its prokinetic properties, may accelerate gastric emptying, resulting in decreased absorption of drugs, such as digoxin or theophylline.

Altered drug transport

Transport proteins, which are present in the intestinal mucosa, are important considerations in clinically relevant DDIs.[38] Some proteins are involved in the transport of compounds from the lumen of the intestine into the portal bloodstream, whereas others are involved in the efflux of compounds from the intestinal mucosa back into the gut lumen. The efflux transporters, particularly a specific glycoprotein, which resides in the cell membrane, P-glycoprotein (P-gp), are the most well known. P-gp is an adenosine triphosphate (ATP)-dependent transporter that is genetically encoded and located on the apical surface of mucosal cells in the intestine, generally in increasing concentration from the stomach to the colon. In addition, P-gp is also present on a number of lymphocyte subsets and within the brain capillary endothelial cells. The primary role of P-gp is to limit systematic drug exposure, pumping compounds from the inside of the cell back into the gut lumen, into renal tubules in the kidney, and into bile in the liver. Given its presence in various anatomic locations, drug-induced modulation of P-gp activity may affect the absorption and/or distribution of a coadministered substrate medication. There are several drugs that are known to block the action of P-gp and are known as P-gp inhibitors, and there are drugs that have been shown to cause induction of P-gp. Coadministration of a P-gp substrate with an inhibitor increases the amount of substrate available for absorption and may result in an elevated

serum drug concentration. For drugs such as rifampin that increase expression of P-gp (ie, P-gp inducer), the coadministration of a substrate results in an enhanced efflux of the substrate into the gut lumen and lowers serum concentration of the substrate.

DISTRIBUTION

CASE 3-1, QUESTION 2: What is the interaction of warfarin and phenytoin based on protein binding?

Following administration and absorption, drugs are distributed throughout the body.[38,39] Drugs such as warfarin and phenytoin are highly bound to protein (primarily to albumin) with the same affinity binding sites (**Fig. 3-1**). Drugs that are highly protein bound (>90%), those with an NTI, and those with a small volume of distribution are more likely to result in significant drug interactions.

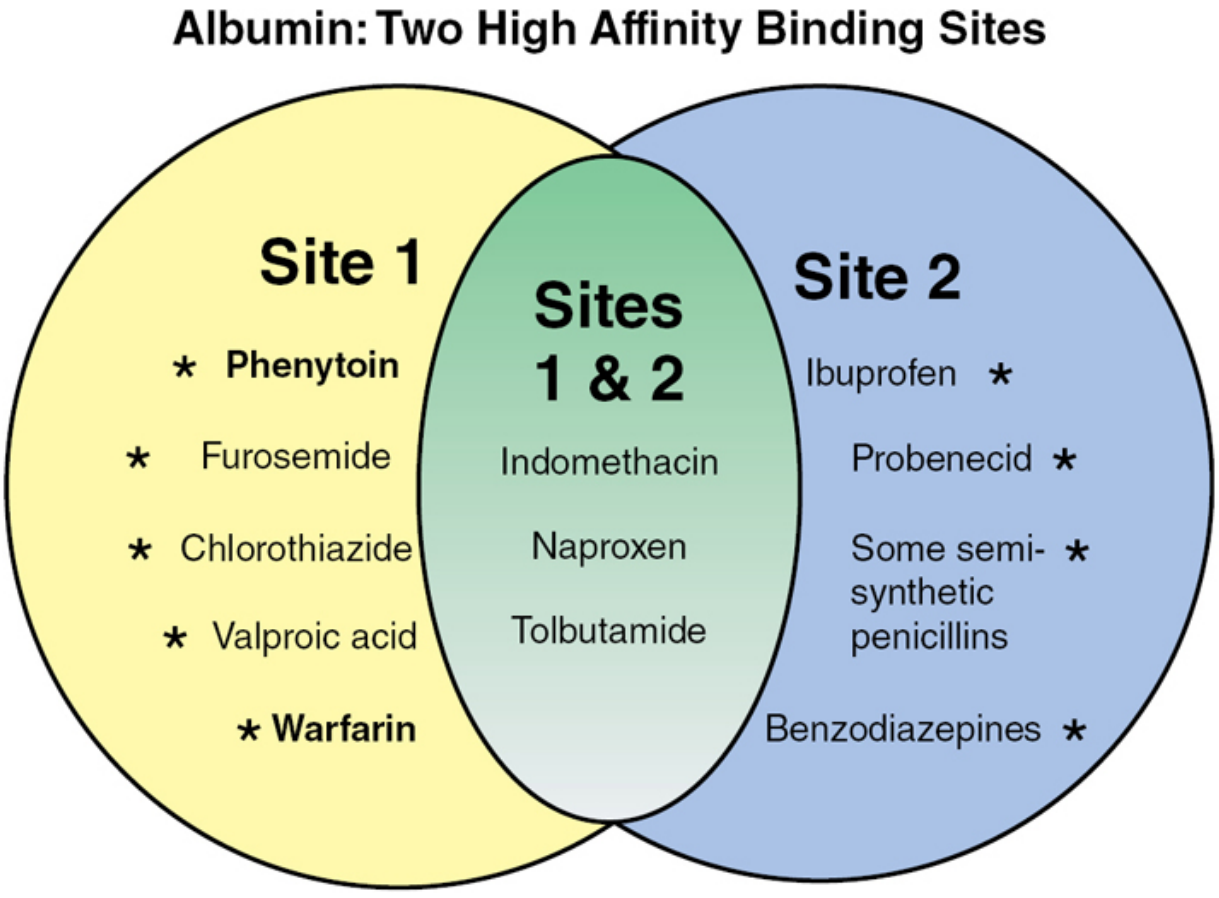


Figure 3-1 Examples of drugs that bind to and compete for one of two sites, designation I and II, on albumin. (Adapted with permission from Drug interactions. In: Derendorf H, Schmidt S, eds. *Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. 5th ed. Wolters Kluwer; 2020.)

Warfarin can be displaced from protein-binding sites by drugs such as phenytoin. Although this displacement occurs quickly with rapid changes in serum warfarin levels, typically, this interaction is not clinically significant. Warfarin that is displaced from protein-binding sites is readily available for elimination by hepatic metabolism, resulting in increased clearance without a significant change in the free drug concentration. Because warfarin's anticoagulant action takes several days because of the long half-lives of some of the vitamin K–dependent clotting factors, warfarin equilibrium is reestablished before a new steady state can be reached for these clotting factors.[33]

METABOLISM

Pharmacokinetic interactions that involve changes in metabolism are a common cause of clinically significant drug interactions. Drug metabolism is divided into two general categories: phase I and phase II reactions.[38,39] Phase I reactions involve intramolecular changes including oxidation, reduction, and hydrolysis, which increases the polar nature of the drug, generally making it less toxic. Phase II reactions generally involve combining a phase I product with an endogenous substance, resulting in glucuronidation, sulfation, acetylation, and methylation, and primarily results in termination of biologic activity of the drug.[40,41] The main enzymes that are responsible for drug-metabolizing systems in phase I reactions are the CYP enzymes, which play a key role in many therapeutically important drug interactions.[1,2] Drugs that are metabolized by the same CYP enzyme family, when administered concurrently, may interact with each other as a result of induction or inhibition.[40,41] Of the human CYP enzyme family, the six isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5

contribute to the metabolism of a vast majority of drugs compared with other enzymes (**Fig. 3-2**).[6,42–44] Examples of drug that induce enzymes are rifampin, phenytoin, carbamazepine, St. John's wort, and nevirapine. Enzyme inducers cause an increase in the synthesis of the enzyme(s) responsible for metabolism of the substrate drug. The mechanisms of induction are complex involving presystemic metabolism via induction of hepatic and/or intestinal drug–metabolizing enzymes, subsequently reducing serum concentrations with a loss of pharmacologic activity of the drug. In some cases, induction will increase the formation of metabolites that are pharmacologically or toxicologically active.[1,44,45] There are many drugs that are inhibitors of CYP including some drugs within these classes: statins, macrolide antibiotics, antifungal azoles, fluoroquinolones, and HIV protease inhibitors. Inhibition of drug metabolism slows down the rate of drug metabolism, resulting in an increase in the amount of drug in the body and potential toxicity. Grapefruit juice is an inhibitor of CYP3A4 and has been known to increase the bioavailability and reduce the clearance of many drugs, including HMG-CoA reductase inhibitors (statins), calcium antagonists, HIV protease inhibitors, and immunosuppressant agents.[46–49] Inhibition can be described as reversible or irreversible, with the reversible ones being a more common process. There are three mechanisms of reversible inhibition: competitive inhibition (competition between the inhibitor and the substrate for the enzyme's active site), noncompetitive inhibition (binding of the inhibitor to a separate site on the enzyme, rendering the enzyme complex nonfunctional), and uncompetitive inhibition (binding of the inhibitor only to the substrate–enzyme complex, rendering it ineffective).[1,49,50] Irreversible inhibition occurs when the perpetrator drug forms a reactive intermediate with the enzyme that leads to a permanent inhibition of the enzyme. Irreversible drug interactions tend to be more profound than those caused by reversible mechanisms. Examples of drugs that are known to cause irreversible inhibition include macrolide antibiotics, erythromycin, clarithromycin, paroxetine, and diltiazem.[16,51,52]

CASE 3-1, QUESTION 3: The medical team starts warfarin therapy for F.D. for postoperative thromboembolism prophylaxis. What are the mechanisms of drug interactions to consider with the use of warfarin and phenytoin because F.D. has been taking phenytoin for several years and her seizure disorder has been controlled on it?

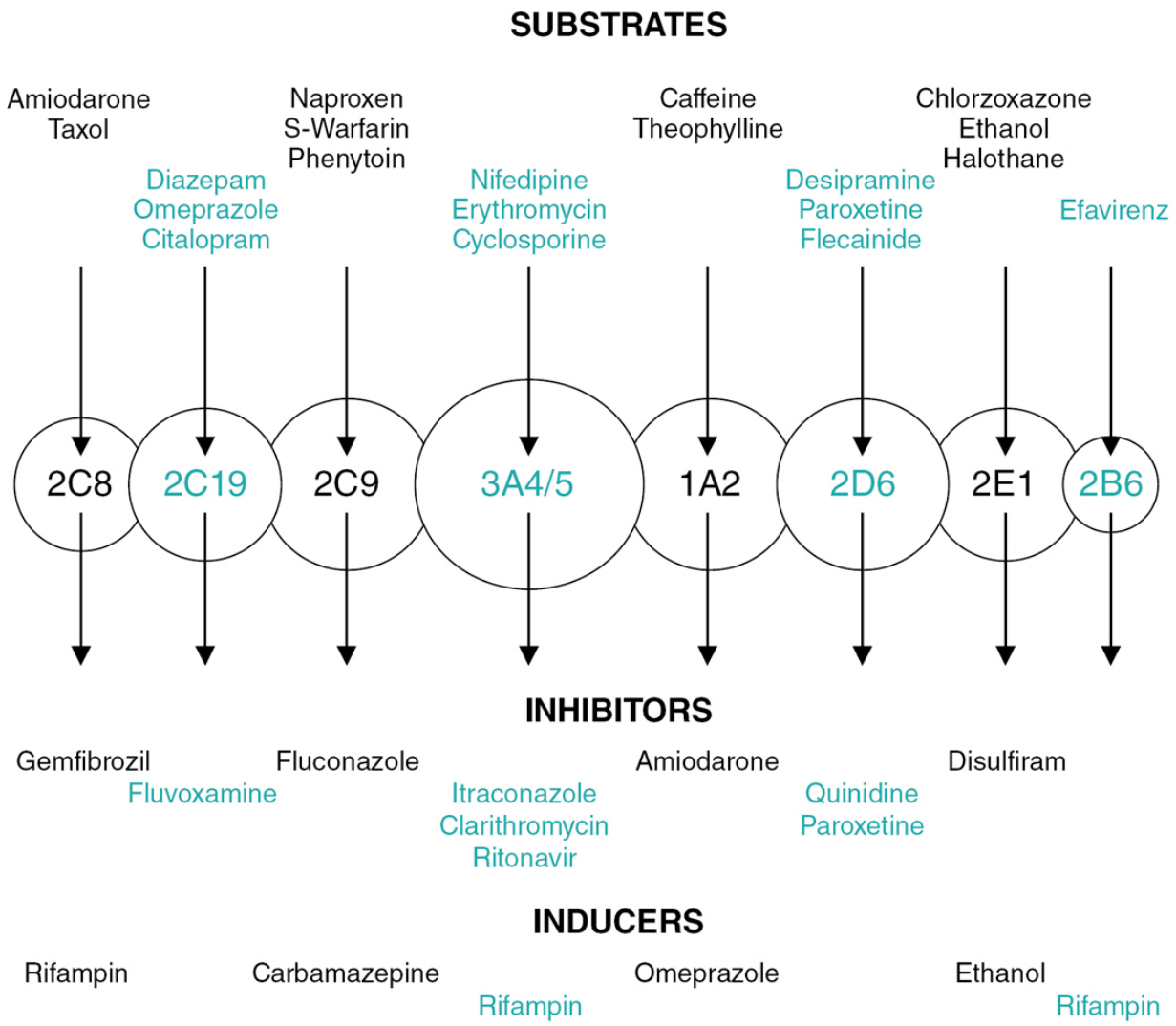


Figure 3-2 Graphic representation of the different forms of cytochrome P450 (circles) in humans with different but some overlapping substrate specificities. The arrows indicate single metabolic pathways. Representative substrates are listed for each enzyme. Also listed are relatively selective inhibitors and inducers of the enzymes. (Reprinted with permission from Drug interactions. In: Derendorf H, Schmidt S, eds. *Rowland and Tozer's Clinical*

Pharmacokinetics and Pharmacodynamics: Concepts and Applications. 5th ed. Wolters Kluwer; 2020.)

There are two potential mechanisms for a warfarin (drug)–phenytoin (drug) interaction. In early therapy, there could be a displacement of warfarin from protein-binding sites by phenytoin (as described in the previous case question) and a possible enhancement of the anticoagulant effect and risk for bleeding. This is primarily a concern in patients with hepatic impairment. With prolonged therapy, there could be a phenytoin-induced CYP enzyme induction, thereby enhancing warfarin metabolism, resulting in a decreased warfarin effect. INR monitoring on postoperative days 1 through 5 will provide information on the impact of the DDI, and incorporation of a warfarin initiation guideline or algorithm will help adjust dosing until a stable regimen is established. After the initial period, weekly INR monitoring will provide information on enzyme induction and further adjustment of warfarin doses.

Warfarin is rapidly and completely absorbed after oral administration, with the proximal duodenum appearing to be the most likely location of absorption. Case reports of warfarin malabsorption, whether acquired, related to surgery, or inflammatory conditions, are rare.[53]

The rate and extent of phenytoin absorption varies considerably among oral dosage forms.[54] Phenytoin suspension is poorly absorbed when administered via feeding tube with continuous enteral feedings.[55] The time to reach maximum plasma levels increases with increasing dose.[56] This is a reflection of low phenytoin solubility and capacity-limited metabolism. Therefore, a small change in the dosage form or bioavailability, coupled with limited metabolism, can produce a large change in plasma drug concentration.[57] GI surgery and GI inflammatory conditions (Crohn disease, ulcerative colitis, scleroderma, etc.) can change the anatomy of the GI tract. Alterations to surface area, gastric emptying time, gastric pH, and inflammation of the intestinal lining may lead to abnormal plasma concentrations.[58]

F.D.'s GI function is still preserved after orthopedic surgery. Warfarin administration and absorption is unlikely to be impacted. She should continue on the same phenytoin dose and formulation that she has been taking at home with appropriate monitoring.

Pharmacokinetic interactions influencing the metabolism of warfarin and clinically significant interactions are likely with warfarin use when its metabolism is induced or inhibited.[49] Warfarin is a racemic mixture of *R*- and *S*-enantiomers. Interactions involving agents known to influence the hepatic microsomal enzyme systems responsible for the metabolism of the more potent *S*-enantiomer (CYP2C9) are more significant than those that influence the enzymes that metabolize *R*-enantiomer (CYP1A2, CYP3A4). Phenytoin is also predominately metabolized via the CYP2C9 enzyme and has been reported to interact with warfarin in a biphasic manner.[50–52]

Genetic polymorphism also is a significant factor affecting warfarin dosing and response. Nucleotide polymorphisms have been identified that influence warfarin metabolism and sensitivity, including variants of CYP2C9 and variants in vitamin K epoxide reductase complex (*VKORC1*).[59]

EXCRETION/ELIMINATION

Drugs are excreted and eliminated mainly via the kidneys (glomerular filtration, tubular reabsorption, and active tubular secretion); other important, though less common, routes are via biliary secretion, plasma esterases, and other minor pathways. Drug interactions may occur during the elimination of drugs and their metabolites by the kidney as a result of competition at the level of active tubular secretion, interference with tubular transport, or during tubular reabsorption.

Urinary alkalinization and acidification by some drugs can affect the excretion of other drugs changing their elimination rate. For example, the use of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, increases the serum

concentration of penicillins, which can be used for therapeutic purposes.

Pharmacodynamics

Pharmacodynamic interactions occur when the response of one drug is modified by the presence of another one without alterations in pharmacokinetics. These types of interactions may be predicted if the pharmacologic effects of a drug are known, and the patient response may be additive or antagonistic.[2,8] For example, there may be an interaction in which one drug, an angiotensin-converting enzyme (ACE) inhibitor, and another drug, a thiazide diuretic, each act by a different mechanism of action to lower blood pressure (BP), producing an exaggerated hypotensive effect.

Case 3-1, Question 4: What pharmacodynamic interactions are clinically relevant to warfarin?

Pharmacodynamic interactions with warfarin are those that alter the physiology of hemostasis, particularly interactions that influence the synthesis or degradation of clotting factors or that increase the risk of bleeding through inhibition of platelet aggregation. In patients receiving warfarin, the addition of any drugs that increase or decrease clotting factor synthesis, enhance or reduce clotting factor catabolism, or that impair vitamin K production by normal flora will increase the risk of drug interactions.

Tables 3-3 and **3-4** provide examples of common mechanisms of pharmacokinetic and pharmacodynamic drug interactions, respectively.

Table 3-3
Common Mechanisms of Pharmacokinetic Drug Interactions[1,3,6,17,32–34,38,60–65]

	Mechanism	Example

	Mechanism	Example
Pharmacokinetics: administration/absorption	Drugs that alter the pH of the stomach can affect absorption of other drugs	Itraconazole requires an acidic gastric pH to become soluble; absorption may be decreased if a patient is taking a drug that increases gastric pH such as a PPI or H_2-blocker.
	Induction or inhibition of CYP enzymes in the GI tract	Grapefruit juice inhibits intestinal CYP3A4, potentially increasing the bioavailability of CYP3A4 substrates such as nifedipine and verapamil.
	Induction or inhibition of P-gp (an efflux pump that expels drugs) in GI tract	Dabigatran, a substrate for P-gp, peak concentrations may be increased by P-gp inhibitors (eg, ketoconazole, clarithromycin, amiodarone), leading to a significantly increased risk of bleeding.
	Increase or delay gastric emptying/motility	Erythromycin, a potent prokinetic agent, is a motilin receptor agonist that increases gastric motility; absorption of coadministered drugs may be affected.
	Killing enteric bacteria	Antibiotics can kill bacteria that produce deconjugating enzymes; drugs that undergo enterohepatic circulation such as birth control pills may have decreased blood concentrations and half-life because of increased excretion in the feces.
	Chelation	Cations such as aluminum or magnesium antacids decrease the GI absorption of tetracycline antibiotics by forming drug–metal complexes.

	Mechanism	Example
	Physiochemical inactivation	Mixing a furosemide solution with an acidic solution (ie, with midazolam) decreases the pH sufficiently to cause furosemide precipitation and reduced availability when administered intravenously.
Pharmacokinetics: distribution	Interaction between two highly protein-bound drugs (eg, a precipitant drug has stronger affinity for the same protein-binding site)	Sulfamethoxazole displaces warfarin from protein-binding sites, increasing the free fraction. Sulfamethoxazole also inhibits the metabolism of warfarin. As a result, the body cannot compensate to increase the elimination of the high free (active) fraction of warfarin. The end result is likely an increase in the INR and potential risk for bleeding. See Chapter 11 for detailed warfarin–sulfamethoxazole drug interaction.
	Inhibition of carrier proteins such as P-gp located in blood–brain barrier and OATPs located in the liver	Cyclosporine may inhibit the transporter OATP1B1, decreasing the hepatic uptake of most statins; efficacy of the statin may be lost because the site of action is located in the liver.
Pharmacokinetics: metabolism	Induction or inhibition of CYP enzymes in the liver	*Example 1:* Fluoroquinolones inhibit metabolism of theophylline via CYP1A2 enzyme; the extent of the interaction varies between the different fluoroquinolones. *Example 2:* Rifampin has a half-life of 4 hours; however, time to steady-state induction with propranolol does not occur until 10–14 days.

	Mechanism	Example
Pharmacokinetics: excretion/elimination	Administration of two drugs that use the same transport system and undergo active tubular secretion by the kidneys	Methotrexate clearance may be reduced in the presence of salicylates. Salicylates decrease renal perfusion via PGE_2, having the potential to cause renal impairment and competitively inhibit the tubular secretion of methotrexate.
	Increased or decreased renal tubular absorption	*Example 1:* Alkalization of the urine with sodium bicarbonate will decrease the reabsorption of acidic compounds such as salicylates, a treatment in overdose. *Example 2:* Thiazide diuretics initially cause sodium excretion, followed by compensatory sodium reabsorption. Administered with lithium, a cation can cause increased lithium reabsorption and possible toxic concentrations.

GI, gastrointestinal; INR, international normalized ratio; OATP, organic anion transporting peptide; P-gp, P-glycoprotein; PPI, proton-pump inhibitor.

Table 3-4
Common Mechanisms of Pharmacodynamic Drug Interactions[66]

	Mechanism	Example
Pharmacodynamics	Additive—two or more medications with comparable pharmacodynamic effects result in an exaggerated and/or toxic response	An adverse effect of each of the drugs, clarithromycin and saquinavir, is QTc prolongation. Administration of them together increases the risk for QTc prolongation and an increase in plasma concentrations.

	Mechanism	Example
	Antagonistic—the effects of one drug oppose the actions of another drug	*Example 1:* Antagonism at the same receptor site: reversal of benzodiazepines with flumazenil *Example 2:* Opposing pharmacodynamics actions: glucocorticoids cause hyperglycemia opposing the effects of hypoglycemic medications.

Source: Reprinted from Pleuvry BJ. Pharmacodynamic and pharmacokinetic drug interactions. *Anaesth Intensive Care Med*. 2005;6(4):129–133. Copyright © 2005 Elsevier. With permission.

MANAGEMENT OF DRUG INTERACTIONS

CASE 3-1, QUESTION 5: The medical intern on the team also plans to prescribe a combination analgesic (oxycodone/acetaminophen) in place of intravenous (IV) morphine for the pain management.

In addition, F.D. remembers St. John's wort is the name of the OTC product that she takes. She said it helps with her seasonal depression.

As the pharmacist on the multidisciplinary team, your role is to assess therapy and make recommendations as needed. What recommendations regarding F.D.'s therapy do you make, including the use of St. John's wort?

Although acetaminophen is a commonly used nonprescription analgesic and antipyretic medication for mild-to-moderate pain and fever, its presence is often unrecognized in combination products containing opioids prescribed for moderate-to-severe pain. Several studies have identified acetaminophen as a culprit drug in potentiating the effects of warfarin.[67,68] Patients who take four 325-mg acetaminophen tablets per day for longer than a week were more likely to have an INR >6.0 than those who did not take acetaminophen.

There is no evidence for a pharmacokinetic interaction between acetaminophen and warfarin.[69] However, acetaminophen is

metabolized by CYP2E1, producing the metabolite *N*-acetyl-*p*-benzoquinone-imine (NAPQ1). NAPQ1 oxidizes vitamin K-hydroquinone (KH2), the "active" form of vitamin K, and directly inhibits vitamin K–dependent carboxylation.[70] There may be other oxidative changes, producing enzymatic disruption, that impact vitamin K synthesis and activity. The end result is an exaggerated response to warfarin and an increased INR.

Therefore, if F.D. is to be placed on oxycodone/acetaminophen therapy, her INR should be monitored more frequently and her dose adjusted accordingly. This is important particularly if she requires higher sustained doses of warfarin.

Dietary supplements, including herbal medicinals, amino acids, and other nonprescription products, are not tested before marketing for interactions with other medications, including warfarin. Little is known about their interactive properties, other than published case reports of varying quality. In addition, dietary supplements are not required to meet U.S. Pharmacopeia standards for tablet content uniformity.

St. John's wort, an herb whose yellow flowers and leaves are used to make herbal supplements, has been used for the treatment of depression. It has also been shown to lower patient INR values and potentially decrease warfarin's effectiveness.[71,72] Although this interaction is probably because of the induction of CYP2C9, the degree of induction is unpredictable owing to variable quality and quantity of the herbal constituent in the preparations. Similarly, St. John's wort has been suspected of reducing phenytoin plasma concentrations through induction of CYP3A4.

The addition of St. John's wort to F.D.'s current drug regimen would not be advisable because it would increase her risk for drug interactions. The implications for initiating St. John's wort in F.D. would require measurement of phenytoin and more frequent INR testing to ensure a new steady state for each agent has been reached. At this point, it is important to assess F.D.'s depression and to evaluate therapeutic options that would provide the least risk of drug interactions, as well as psychosocial treatment.

Case 3-1, Question 6: The medical team would like to resume F.D.'s medications that she was taking before admission. However, when the medical resident enters the order into the computer, they receive an electronic health record drug interaction alert regarding the statin and warfarin. How should this be managed?

Fluvastatin is metabolized extensively by the CYP system, primarily by CYP2C9 and to a lesser extent by CYP3A4 and CYP2C8. Fluvastatin is also a substrate for the transport protein OATP1B3. OATP transports statins from the blood to the liver for metabolism or excretion into the bile and feces. The combination of fluvastatin and warfarin has resulted in an increase in the INR, hence increasing the risk of bleeding.[3,35,36] In addition to this, fluvastatin when coadministered with phenytoin has been reported to increase phenytoin serum concentrations.[73] Each of the statin agents is metabolized by different CYP isoenzymes and to different degrees (**Table 3-5**). The goal of lipid management is to prescribe an agent with the least side effects and at the lowest effective dose. If a patient, such as F.D., requires a drug that interacts with statin metabolism (CYP), switching to a statin that has a more favorable elimination profile may be the best option. For example, pravastatin is a good alternative because its elimination is not dependent on CYP metabolism and is eliminated 20% by the renal route.[74] F.D. has minor renal dysfunction with a creatinine clearance of 70 mL/minute; pravastatin would not require dose adjustment unless F.D.'s glomerular filtration rate (GFR) drops <30 mL/minute.[75] However, if fluvastatin is continued with warfarin therapy more frequent, monitoring of the INR is recommended until a stable INR has been reached. It is vital to monitor the patient's INR during initiation and discontinuance of fluvastatin therapy.[73] Table 3-5 provides a summary of the metabolism of HMG-CoA reductase inhibitors.[36,74,76,77] Refer to Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease, for more information on the use of statins, including drug interactions.

Table 3-5
Transport, Metabolism, and Excretion of HMG-CoA Reductase Inhibitors (Statins)

Statins	Transport Protein[a]	Isoenzyme	Renal Excretion (%)
Atorvastatin	P-gp, OATP1B1	CYP3A4	<2
Fluvastatin	OATP1B3	CYP2C9, CYP3A4/2C8 (minor)	5
Lovastatin	P-gp	Significant CYP3A4	10
Pitavastatin	P-gp, OATP1B1	Primarily glucuronide conjugation CYP2C9, CYP2C8 (minor)	15
Pravastatin	OATP1B1, OATP1B3	No appreciable CYP—CYP3A4 extremely minor pathway	20
Rosuvastatin	OATP1B1, OATP1B3	CYP2C9 (10%)	10
Simvastatin	P-gp, OATP1B1	Significant CYP3A4	13

CYP, cytochrome P450 isoenzyme; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein.

[a]Efflux transporter, P-gp prevents oral absorption of statins and OATP facilitates hepatic uptake of statins from the blood → drugs that inhibit these transporters may ↑ statin plasma concentrations.

Sources: Adapted from Wiggins BS, Saseen JJ, Page RL 2nd, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease a scientific statement from the American Heart Association. *Circulation*. 2016;134:e468–e495. PL detail-document. Clinically significant statin drug interactions. Pharmacist's Letter/Prescriber's Letter. April 2012. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet*. 2001;40(4):263–281. Hatanaka T. Clinical pharmacokinetics of pravastatin. *Clin Pharmacokinet*. 2000;39(6):397–412.

CASE 3-2

QUESTION 1: J.A. is a 69-year-old previously healthy male admitted to the medical intensive care unit (ICU) with lower left lobe pneumonia, and he has developed septic shock. His hospital course for the first 18 days of admission consisted of a worsening bilateral pneumonia characterized by profound hypoxia and acute respiratory distress syndrome (ARDS). J.A. is currently deeply sedated and receiving neuromuscular blockade to manage his ARDS, high peak inspiratory pressures (PIPs), and low oxygen saturation (Sao_2).

Medications:

- Propofol IV infusion and fentanyl IV infusion for sedation and analgesia
- Cisatracurium IV infusion for neuromuscular blockade—goal is to improve oxygenation (Pao_2/FIO_2 ratio)
- Pantoprazole IV for stress ulcer prophylaxis

- Heparin subcutaneous (SC) and pneumatic compression boots for deep venous thrombosis (DVT) prophylaxis
- Hydrocortisone IV for corticosteroid insufficiency in critical illness
- Amikacin IV and imipenem/cilastatin IV for day 5 treatment of a multidrug-resistant organism
- Norepinephrine and vasopressin IV infusions for septic shock secondary to pneumonia
- Ophthalmic ointment to lubricate eye while on prolonged neuromuscular blockade
- Lactated Ringer IV infusion for hypotension secondary to septic shock

Vitals: T 101 °F (38.33 °C), heart rate (HR) 105, respiratory rate (RR) 20, BP 95/60

Laboratory values: arterial blood gas (ABG): pH 7.30/P_{CO_2} 42/P_{O_2} 80/CO_2 19/Sao_2 90% on mechanical ventilation: Assist control RR 20, tidal volume 400 mL, positive end-expiratory pressure (PEEP) 10, F_{IO_2} 50%.

Na^+	138 mEq/L	White blood cell count (WBC)	14,600 × 10^3 µL
K^+	4.8 mEq/L	Poly	80%
Cl^-	98 mEq/L	Bands	12%
HCO_3^-	19 mEq/L	Hemoglobin (Hgb)	9.0 g/dL
Blood urea nitrogen (BUN)	45 mg/dL	Hematocrit (Hct)	28%
Serum creatinine (SCr)	1.8 mg/dL (baseline SCr 1.0 mg/dL)	Platelets	202 × 10^3 µL
Glucose	142 mg/dL	Aspartate transaminase (AST)	105 U/mL
Serum phosphate	0.9 mg/dL	Alanine transaminase (ALT)	85 U/mL

J.A.'s train-of-four (TOF) is 0/4. A peripheral nerve stimulator, the TOF, is a clinical tool used to monitor neuromuscular blockade. The TOF Scale includes the following: 0/4 indicates that no twitch elicited, neuromuscular blocker agent occupies 100% of postsynaptic nicotinic receptors, and a 100% blockade, whereas 4/4 indicates that <75% of the postsynaptic nicotinic receptors are blocked. The goal of neuromuscular therapy is to achieve an adequate neuromuscular blockade, a TOF of 1/4 or 2/4 (80%–90% of receptors blocked) or the desired clinical effect (eg, accepting ventilation and not over breathing the ventilator), with the lowest dose of neuromuscular agent necessary.[78,79]

What are J.A.'s risk factors for drug interactions?

There are several risk factors for drug interactions in critically ill patients. Critically ill patients are susceptible to drug interactions as a result of a debilitated condition and/or disease state (eg, changes in physiologic pH and body temperature, electrolyte imbalances, organ failure), as well as the multitude of medications prescribed as treatment. Patients in ICU also have altered pharmacokinetics, placing them at an increased risk for an interaction. These changes include the following:

- Decreased GI absorption of enterally administered medications owing to the following: hypoperfusion from shock, increased stomach pH from PPI and histamine blocker therapy, decreased GI motility, or drug effect on carrier proteins, for example, P-gp
- Decreased SC absorption owing to the following: edema, vasopressor therapy, or disease-induced peripheral vasoconstriction
- Increased volume of distribution (V_d) for hydrophilic medications owing to increased total body water from fluid resuscitation and third spacing
- Altered free drug fraction owing to increased α-acid glycoprotein from systemic inflammation and decreased albumin plasma concentrations
- Half-life ($t_{½}$) and clearance (CL) may be affected from decreased hepatic blood flow, renal or hepatic insufficiency, and induction or inhibition of hepatic enzymes by drugs. Patients without renal insufficiency may exhibit augmented clearance.[80,81]

The mode of mechanical ventilation that is used most commonly today is positive pressure ventilation, whereby air is forced into the lungs to improve gas exchange. The use of mechanical ventilation may also affect drug pharmacokinetics by decreasing cardiac output secondary to reduced preload, which, in turn, may compromise perfusion to the liver and kidneys as well as GFR and urine output.[82] This effect is most pronounced in patients who are hypovolemic.

These hemodynamic changes can result in a decrease of the clearance of several drugs.

J.A. has several risk factors for drug interactions. Many of his risk factors are patient specific, including J.A.'s age, organ dysfunction, and acute medical conditions. Additional risk factors are the extended hospital stay in the ICU and multiple medications. J.A.'s specific risk factors are outlined as follows.

Patient Risk Factors

- Age: 69 years old—altered pharmacokinetics and pharmaco-dynamics
- Renal dysfunction: baseline SCr 1.0 mg/dL and current SCr 1.8 mg/dL—decreased renal clearance
- Mild hepatic dysfunction: AST 105 U/mL and ALT 85 U/mL—decreased metabolism
- Pneumonia: T 101 °F (38.33 °C), WBC 14.6 × 10^3 µL, poly 80%, bands 12%—increased catabolism
- Hypotension (result of shock): BP 95/60 on norepinephrine, vasopressin, and lactated Ringer solution—decreased clearance
- Hyperthermia: T 101 °F (38.33 °C)—increased clearance
- Hypophosphatemia: phosphate 0.9 mg/dL—increased neuromuscular blockade (see discussion Case 3-2, Question 2)
- Norepinephrine and vasopressin infusions: potential for decreased blood delivery to the liver and kidneys
- Mechanical ventilation: decreased cardiac output

Other Risk Factors

- Polypharmacy: risk of adverse drug interaction increases with multiple medications
- Duration of hospital stay: 18 days—susceptible to hospital-acquired conditions and subsequent drug therapy

Case 3-2, Question 2: The medical team is concerned that J.A.'s condition may have worsened; he may have had a neurologic event (eg, stroke) overnight. J.A. is clinically unstable to bring to computed tomography (CT). The team needs J.A. to be alert for purposes of conducting a neurologic examination. To undergo the examination, J.A. must have his neuromuscular blockade discontinued and sedation lightened. One and one-half hours after discontinuation of cisatracurium, J.A. is still not moving (TOF 0/4). The medical team feels cisatracurium's paralytic effect should have worn off by now and is concerned about his prognosis. Why has J.A.'s neuromuscular blockade not worn off?

After reviewing the case, the clinician identifies potential drug–condition/disease and drug–drug pharmacodynamic interactions that may contribute to the prolonged neuromuscular blockade. These interactions are discussed as follows.

Background: The incidence of ICU-acquired weakness (polyneuropathy and myopathy) in patients with ARDS is 34% to 60%. This condition can last for months to years and can severely affect a patient's quality of life.[83] There are several risk factors for ICU-acquired weakness that includes prolonged mechanical ventilation, number of days with dysfunction in two or more organs before wakening, corticosteroids, female sex,[84] toxins (eg, botulism), neuromuscular disease states (eg, Guillain–Barré syndrome), severe electrolyte imbalances, prolonged recovery from neuromuscular blockers, deconditioning, length of vasopressor support, and hyperglycemia, just to name a few.[83,85,86] Neuromuscular blockade alone has been associated with ICU-acquired weakness. However, in a multicenter, double-blind trial, investigators found no statistical difference in ICU-acquired paresis between cisatracurium and placebo groups at day 28 or ICU discharge.[85,87] Prolonged recovery from neuromuscular blockade may occur in patients with organ failure and/or conditions that affect the overall clearance of the neuromuscular blocking agent (eg, decreased metabolism of a parent drug, decreased elimination of the parent drug, and/or the active metabolite). In addition to these, certain disease states, conditions, or drugs that may potentiate a blockade may also lead to an increased recovery time.[85,86]

Drug–Condition/Disease Interactions

PHARMACOKINETICS—DRUG METABOLISM/ELIMINATION

The nondepolarizing agent, cisatracurium, is a benzylisoquinolinium compound. It is one of the 10 isomers of the intermediate-acting neuromuscular blocker, atracurium. It is primarily eliminated by Hofmann degradation; optimal breakdown occurs at physiologic temperature (37 °C or 98.60 °F) and pH (7.40).[79] This process results in therapeutically inactive metabolites, monoquaternary alcohol, monoquaternary acrylate, and laudanosine.[88] Cisatracurium's organ-independent elimination is a benefit for J.A. because he has renal and hepatic insufficiency. However, because cisatracurium is degraded by the Hofmann process, alterations in pH and temperature will affect the elimination of the drug. For example, the neuromuscular blockade effect is prolonged with acidosis, whereas elimination is enhanced with an increase in pH. In addition, hypothermia decreases the elimination of cisatracurium, whereas hyperthermia accelerates it. In patients with ICU, the recovery rate from neuromuscular blockade is reported to range from 45 to 75 minutes after discontinuation of a prolonged cisatracurium infusion.[89–91] Because J.A. has both a fever (101 °F [38.33 °C]) and metabolic acidosis (pH 7.30 and HCO_3^- 19), it is difficult to predict the clearance of the neuromuscular blocker.

PHARMACODYNAMIC INTERACTION

A second condition that may add to J.A.'s prolonged blockade is his low phosphate (phosphate 0.9 mg/dL). Phosphate is a building block of ATP. ATP produces energy via an enzymatic reaction by releasing a phosphate group. This reaction is necessary for physiologic and metabolic functions, including muscle contraction. Therefore, a patient with hypophosphatemia is at risk for a myopathy.[92]

Drug–Drug Interaction

PHARMACODYNAMIC—ADDITIVE EFFECTS OF MEDICATIONS

J.A.'s medications may also have additive effects with cisatracurium. A rare adverse effect of amikacin is neuromuscular blockade. The mechanism of blockade involves inhibiting acetylcholine release by competing with Ca^{2+} at the preganglionic nerve terminal and, to a smaller degree, noncompetitive blocking of the receptor.[93] Corticosteroids (eg, hydrocortisone) may also enhance blockade and increase recovery time. Proposed mechanisms for steroidal ICU-acquired weakness include increased muscle sensitivity to corticosteroids because of the lack of movement and skeletal muscle atrophy from the steroid's catabolic actions. In addition, corticosteroids may cause myopathy by denervation; corticosteroids have been shown to inhibit the nicotinic receptor; when combined with the neuromuscular blocking agent, vecuronium, this inhibition is potentiated.[83,94] It is thought that this interaction is more likely to occur with neuromuscular blockers that have a steroid structural ring, such as the aminosteroids (eg, pancuronium, pipecuronium, vecuronium, and rocuronium). However, there have been case reports of prolonged paralysis with the benzylisoquinoliniums (eg, atracurium, cisatracurium, doxacurium, mivacurium, and d-tubocurarine).[85,86,95]

J.A. may need a longer period than 1½ hours to recover from his paralysis because of the following factors: decreased elimination of cisatracurium as a result of acidosis, hypophosphatemia, and medications (amikacin and hydrocortisone). J.A. should also have his phosphate slowly repleted.

Case 3-2, Question 3: How do you explain the drug interactions affecting the antibiotic efficacy of J.A.'s regimen to the medical team?

After reviewing the case, the clinician identifies potential drug–drug physiochemical interaction, as well as drug–condition and drug–drug pharmacodynamic interactions. The mechanism of action of these interactions is discussed in the subsequent section.

Drug–Drug Interaction

PHYSIOCHEMICAL INACTIVATION

It has been well documented that the coadministration of β-lactam antibiotics with aminoglycoside antibiotics can lead to inactivation of the aminoglycoside. The mechanism involves the amino group of the aminoglycoside antibiotic forming an inactive amide with the β-lactam ring of penicillin antibiotics.[96,97] Because penicillins have wide therapeutic index, this interaction primarily affects the efficacy of the aminoglycoside antibiotic.

This interaction has been shown to occur with the extended-spectrum penicillins (eg, azlocillin, carbenicillin, mezlocillin, ticarcillin, and piperacillin). J.A. is currently on amikacin and imipenem–cilastatin antibiotics for the treatment of a multiresistant organism. According to the literature, amikacin is the aminoglycoside that is least susceptible to this interaction.[97] In addition, no inactivation of amikacin was observed when incubated in cilastatin 120 µg/mL human serum for 48 hours at 98.6 °F (37 °C).[98]

This inactivation increases with contact time and is directly proportional to the concentration of penicillin.[99] The rate of elimination of aminoglycoside and imipenem–cilastatin may be decreased because of J.A.'s renal dysfunction. This would increase the contact time of the medications.

Recommendations for J.A.'s antibiotic therapy include administration of medications separately; serum concentrations of aminoglycosides should be assayed immediately after drawn, or if analysis is delayed, either add penicillinase to the blood sample or freeze at −158 °F (−70 °C); and because of his renal dysfunction, close monitoring of aminoglycoside serum concentrations is indicated.[99,100]

Drug–Condition/Disease Interaction

PHARMACODYNAMIC INTERACTION

The pharmacodynamic actions of amikacin may be decreased because J.A. is acidotic.

Amikacin enters the bacterial cell and reaches its site of action in three stages: ionic binding, energy-dependent phase I (EDP-I), and energy-dependent phase II (EDP-II) transport or uptake.

Ionic Binding to the Outer Membrane: At physiologic pH, amikacin (pK_a 8.1) is a highly ionized basic cation. It binds to anionic lipopolysaccharides (LPSs), polar heads of phospholipids, and proteins on the outer cell membrane of gram-negative bacteria and phospholipids and teichoic acids of Gram-positive bacteria.[101] This leads to displacement of cell wall Mg^{2+} and Ca^{2+} bridges that link LPS, resulting in the formation of pores in the cell wall where amikacin can enter into the periplasmic space.[102]

EDP-I: Amikacin is transported across the cytoplasmic membrane. EDP-I is dependent on pH and oxygen. Amikacin activity will decline in low pH and anaerobic conditions (eg, abscesses).[102]

EDP-II: Amikacin is transported to the site of action, binding to the ribosomes.[102]

Drug–Drug Interaction

PHARMACODYNAMIC—ADDITIVE/SYNERGISTIC EFFECT OF MEDICATIONS

Penicillins form a covalent bond with the enzymes, the penicillin-binding proteins (PBPs) (specifically transpeptidase, endopeptidase, and carboxypeptidase), inhibiting their action. These enzymes are needed for the final step of bacterial cell wall synthesis, the cross-linking between peptide side chains on the polysaccharide backbones of the peptidoglycan.[103] Cell wall inhibitors such as penicillins and vancomycin may expedite aminoglycoside entry into the bacterial cell, resulting in synergistic effects when treating some organisms.[102]

J.A. is critically ill with renal failure, ARDS, pneumonia caused by a multiresistant organism, septic shock, and a metabolic acidosis. It is important to closely monitor his aminoglycoside therapy for efficacy (peaks) and toxicity (troughs).

This case illustrates the difficulties surrounding drug interaction identification, assessment, and follow-up intervention. Clinicians must recognize that literature to support the presence of a drug interaction is often scant and not always definitive and that the optimal intervention may rely on clinical judgment. Refer to Chapter 56, Care of the Critically Ill Adult.

CASE 3-3

Question 1: D.T. is a 67-year-old male who began taking imatinib about 10 years ago to treat a rare sarcoma: partially resected gastrointestinal stromal tumor (GIST). D.T. currently takes 600-mg imatinib daily, as well as rabeprazole and furosemide. He states that he is currently not taking any nonprescription medications. He continues to go to the cancer treatment center for continued monitoring. He contacts the cancer clinic to let them know that in 4 weeks he will be traveling to Africa to go on a safari. He mentioned that the friends whom he will be traveling with told him that he will need malaria prophylaxis.

Are there are any potential drug interactions, and which antimalarial agent would be an appropriate selection?

Imatinib mesylate belongs to a class of drugs known as selective tyrosine kinase inhibitors (TKIs).[104] It inhibits the BCR-ABL tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid proteins.[97] It also inhibits the tyrosine kinase for platelet-derived growth factor (PDGF) and c-kit. TKIs, such as imatinib, are extensively metabolized via CYP enzymes (with a large degree of interindividual variability).[105] Imatinib is metabolized primarily by CYP3A4, whereas CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A5 are reported to have a minor role in its metabolism.[106] In addition, imatinib is a substrate of human organic cation transporter type 1 (hOCT1), P-gp, and BCRP, though it is unclear whether imatinib is a substrate or an inhibitor of Breast Cancer Resistance Protein (BCRP).[107–110] Imatinib also competitively inhibits the metabolism of drugs that are CYP2C9, CYP2C19, CYP2D6, and CYP3A4 substrates.[111] It is also highly protein bound, with ~95% bound to human plasma proteins.[106,112–114]

Drug–Drug Interaction

PHARMACOKINETICS—DRUG METABOLISM/ELIMINATION

There are several considerations of potential drug interactions with imatinib. Drug interactions should be considered when imatinib is administrated with other agents in the CYP3A family.[104] In particular, interactions are likely with inhibitors of CYP3A4, such as voriconazole or amiodarone, resulting in increases in the plasma concentration of imatinib. Concomitant use of rifampicin or other strong CYP3A4 inducers with imatinib should be avoided. In addition, concomitant administration of imatinib with agents that are both inhibitors of CYP3A4 and P-gp increases plasma and intracellular imatinib concentrations. Examples of dual CYP3A4 and P-gp inhibitors include verapamil, erythromycin, clarithromycin, ketoconazole, fluconazole, and itraconazole.[107,115,116] TKIs, such as imatinib, also can inhibit drug transporters and enzymes, resulting in changes in the exposure of coadministered drugs. St. John's wort significantly altered the pharmacokinetic profile of imatinib, with reductions of 30% in the medium area under the concentration–time curve (AUC). Patients should be cautioned regarding the concomitant use of products, such as St. John's wort, as well as other inducers, that may necessitate an increase in imatinib dosing to maintain therapeutic efficacy.[117,118] Drug interactions involving protein binding of imatinib and other highly protein-bound drugs are not well understood.[104]

A study published in 2016 examined DDIs observed in patients treated with imatinib.[119] The investigators performed two observational studies to identify the medications that were most frequently dispensed simultaneously with imatinib through the French health insurance reimbursement database SNIIRAM (Systeme National d'Information Inter-Regimes Assurance Maladie) as well as the ADRs related to DDIs involving imatinib using the French Pharmacovigilance Database. A sample of 544 patients from SNIIRAM with at least one reimbursement for imatinib were identified between January 2012 and August 2015. Of this cohort of 544 patients, 89.3% (486) of patients had at least one prescription

medication that could potentially interact with imatinib based on mechanism of action (eg, metabolism pathways). The results of the study also found that the most frequent DDI was with paracetamol (acetaminophen; 77.4%), which resulted in an increased risk of paracetamol toxicity. Other study findings with >10% of patients with potential DDIs were with PPIs (33.3% for omeprazole) or dexamethasone (23.7%) that could reduce imatinib's effectiveness and with levothyroxine (18.5%) that could decrease levothyroxine's effectiveness. The suspected mechanisms of this drug interaction with levothyroxine are an induction by imatinib of nondeiodination clearance or induction by imatinib of uridine diphosphate glucuronyl transferases.[120,121] Study results also found that the most frequently used drugs that could increase imatinib toxicity were ketoconazole and clarithromycin (5.1% and 4.7%, respectively).[119] The overall findings of this study suggest that at least 40% of patients who are receiving imatinib are at risk of DDIs and may reach an even higher rate according to the results of the study performed in SNIIRAM. The highest rate of potential DDIs in this study with imatinib was with the following agents: paracetamol, PPIs, dexamethasone, or levothyroxine. Based on the study findings, the investigators provided recommendations regarding the use of imatinib with specific agents. It is recommended that the reader refers to the package insert of imatinib for drug interactions and dosing guidelines. Further study regarding DDIs with imatinib, as well as other TKIs, is warranted.

With regard to selection of an antimalarial agent for D.T., chloroquine, mefloquine, and atovaquone-proguanil (Malarone®) may have potential interactions with imatinib. The proguanil component is metabolized via the CYP2C19 pathway. Given the options that can be used for malaria prophylaxis in D.T., doxycycline would be an appropriate antimalarial agent used for malaria prophylaxis that does not interact with imatinib or D.T.'s other medications (refer to Chapter 81, Parasitic Infections, for malaria prophylaxis options). The most commonly reported adverse effects with doxycycline are GI effects, including nausea, vomiting, abdominal pain, and diarrhea. Esophageal ulceration associated with doxycycline is a rare but well-

described adverse event. D.T. should be counseled to take doxycycline with food and plentiful fluids, in an upright position in order to minimize GI adverse effects. Because doxycycline can cause photosensitivity and D.T. will be on a safari, the risk of photosensitivity can be reduced by the use of an appropriate sunscreen and wearing protective clothing, including a hat. D.T. should also be counseled regarding the use of paracetamol (acetaminophen) and also to check in advance with his pharmacist before taking any natural products that may be metabolized via CYP.

RESOURCES AND EVIDENCE FOR CLINICAL DECISION SUPPORT

Health care providers have become increasingly challenged on devising optimal approaches to managing drug interactions. Patient safety initiatives have expanded in efforts to improve the health care delivery system with medication error prevention as a high-priority area. The consensus recommendations published by the expert group in 2015 have provided a road map for addressing the key concerns to improve the approach to evaluating DDI evidence for clinical decision-making.[5] As part of this process, it was important to review existing methods for evaluating DDIs. The Drug Interaction Probability Scale (DIPS), a 10-item scale, was developed to evaluate individual case reports for DDIs by assessing an adverse event for causality by a DDI.[122] This tool was developed to address limitations of previous assessment instruments, such as the Naranjo scale. The reader is referred to Appendix C of the consensus recommendations for further information regarding DIPS and other available instruments.[5] The expert group also discussed the current systematic approaches using clinical decision support (CDS) systems, their limitations, and the need for a new assessment instrument to objectively evaluate a body of evidence to establish the existence of a DDI. One of the key challenges of CDS systems is to

determine what evidence is required for a DDI to be applicable to an entire drug class. Pharmacokinetic interactions are rarely generalizable to all agents within a drug class, and if there is class effect, the magnitude of the effect can often vary, which typically necessitates that each drug is reviewed individually. In some cases, pharmacokinetic interaction data may be extrapolated from one agent to other agents in the small class if the purported mechanism of interaction involves common pharmacologic effects.

To advance this important initiative, recently, another group of experts convened to address the following: (a) to outline the process to use for developing and maintain a standard set of DDIs, (b) to determine the information that should be included in a knowledge base of standard DDIs, (c) to determine whether a list of contraindicated drug pairs can or should be established, and (d) to determine how to more intelligently filter DDI alerts.[123] Their recommendations for selecting DDIs for CDS were released in 2016. The reader is referred to both the 2015 and the 2016 recommendations.[5,123]

Because various avenues are examined to reduce the risk of drug interactions within society, it is essential as health care providers that we improve patient education regarding medication information. This strategy includes our communications with patients both verbal instructions and patient instruction leaflets given with the prescription. It is important to consider translation of information into different languages and to also promote culturally competent communication within every health care setting. The use of auxiliary warning labels placed on the medication package, books, and referring patients to quality health information on the Internet. Pharmacists are uniquely positioned to provide important information regarding OTC medications, including herbal products when patients receive prescription information, and when they are seeking recommendations for OTC products.[124]

CONCLUSION

Given the complexities of data on drug interactions and the complexities within the health care systems, health care providers have become increasingly challenged on devising optimal approaches to managing drug interactions.[3] Patient safety initiatives have expanded in efforts to improve the health care delivery system with medication error prevention as a high-priority area. Medication errors may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.[2,4] Because exposure to DDIs is a significant source of preventable drug-related harm, appropriate medication use, including drug interaction management, will avoid medication errors.[5]

Although the majority of drug interactions are clinically insignificant, in certain circumstances, drug interactions are considered to be highly significant and can cause harm. Patients should be informed of the importance of maintaining a complete medication profile, including OTC medications, herbs, and dietary supplements. The incorporation of pharmacogenetic information into risk assessment of patients will improve our ability to prevent DDIs and to better evaluate interactions with biologic drugs.

More well-controlled studies are needed after drug approvals. Population-based studies are useful to determine the severity of, incidence of, and clinical importance of drug interactions. Pharmacogenetic research can further improve the precision of DDI evidence and CDS by identifying patient-specific predisposing factors. Future directives will identify the most appropriate process to rate the quality of DDI evidence and provided graded recommendations to reduce the risk of adverse consequences.[5]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Caterina P, Di Paolo A, Giofrè C, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. *J Res Med Sci.* 2013;18: 601–610. (3)

Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med.* 2005;165:1095–1106. (68)

Scheife RT, Hines LE, Boyce RD, et al. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. *Drug Saf*. 2015;38:197–206. (5)

Tilson H, Hines LE, McEvoy G, et al. Recommendations for selecting drug-drug interactions for clinical decision support. *Am J Health Syst Pharm*. 2016;73(*8*):576–585. (123)

Key Websites

IBM Micromedex® Drug Interaction Checking (electronic version). IBM Watson Health. Accessed July 4, 2021. https://www-micromedexsolutions-com.ezproxymcp.flo.org/ (73)

Interactions. Lexicomp. Wolters Kluwer Health, Inc. Accessed July 4, 2021. http://online.lexi.com (61)

COMPLETE REFERENCES CHAPTER 3 DRUG INTERACTIONS

1. Robertson S, Penzak S. Drug interactions. In: Atkinson AJ Jr, Abernethy DR, Daniels CE, Dedrick RL, Markey SP, eds. *Principles of Clinical Pharmacology*. 3rd ed. Elsevier Academic Press; 2012:239–257.
2. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse reactions caused by drug-drug interactions. *Expert Opin Drug Saf*. 2012;11(1):83–94.
3. Caterina P, Di Paolo A, Giofrè C, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. *J Res Med Sci*. 2013;18:601–610.

4. Derendorf H, et al. Variability. In: Derendorf H, Schmidt S, eds. *Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. 5th ed. Wolters Kluwer Lippincott Williams & Wilkins; 2020:361–392.
5. Scheife RT, Hines LE, Boyce RD, et al. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. *Drug Saf*. 2015;38:197–206.
6. Derendorf H, et al. Drug Interactions. In: Derendorf H, Schmidt S, eds. *Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. 5th ed. Wolters Kluwer Lippincott Williams & Wilkins; 2020:531–576.
7. Oates JA. The science of drug therapy. In: Brunton LL, ed. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill, Medical Publishing Division; 2006.
8. Hines LE, Murphy JE. Potentially harmful drug-drug interactions in the elderly: a review. *Am J Geriatr Pharmacother*. 2011;9(6):364–377.
9. Food and Drug Administration, U.S. Department of Health and Human Services, Center for Drug Evaluation and Research. Clinical drug interaction studies—cytochrome P450 enzyme- and transporter-mediated drug interactions guidance for industry. January 2020. Accessed July 1, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions
10. Sharifi H, Hasanloei MAV, Mahmoudi J. Polypharmacy-induced drug-drug interactions; threat to patient safety. *Drug Res*. 2014;64:633–637.
11. Wallace J, Paauw DS. Appropriate prescribing and important drug interactions in older adults. *Med Clin North Am*. 2015;99:295–310.
12. Gnjidic D, Johnell K. Clinical implications from drug-drug and drug-disease interactions in older people. *Clin Exp Pharmacol Physiol*. 2013;40:320–325.
13. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab*. 2011;12:601–610.
14. Maeda K. Systematic review of the effects of improvement of prescription to reduce the number of medications in the elderly with polypharmacy. *Yakugaku Zasshi*. 2009;129(5):631–645.
15. Pizzuti R, Caffari B, Binkin N; Gruppo ARGENTO. Prescription drugs and the elderly: results of the Agrento study. *Ig Sanita Pubbl*. 2006;62(1):11–26.
16. Kalula SZ. Drugs and the older person. *CME*. 2007;25(9):422–425.
17. Shapiro LE, Shear NH. Drug interactions: proteins, pumps, and P-450s. *J Am Acad Dermatol*. 2002;47:467–484.
18. Sitar DS. Aging issues in drug disposition and efficacy. *Proc West Pharmacol Soc*. 2007;50:16–20.
19. Polidoro A, Dornbusch T, Vestri A, Di Bona S, Alessandri C. Frailty and disability in the elderly: a diagnostic dilemma. *Arch Gerontol Geriatr*.

2011;52(2):e75–e78.
20. Hubbard RE, Woodhouse KW. Frailty, inflammation and the elderly. *Biogerontology*. 2010;11(5):635–641.
21. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol*. 2003;38:843–853.
22. Costa AJ. Potential drug interactions in an ambulatory geriatric population. *Fam Pract*. 1991;8:234–236.
23. Gorski JC, Jones DR, Haehner-Daniels BD, Hamman MA, O'Mara EM Jr, Hall SD. The contribution of intestinal and hepatic CYHP3A4 to the interaction between midazolam and clarithromycin. *Clin Pharmacol Ther*. 1998;64:133–143.
24. Bhardwaj S, Selvarajah S, Schneider EB. Muscular effects of statins in the elderly female; a review. *Clin Interv Aging*. 2013;8:47–59.
25. Blouin RA, Ensom MHH. Special pharmacokinetic considerations in the obese. In: Burton ME, Shaw LM, Schentag JJ, Evans WE, eds. *Applied Pharmacokinetics & Pharmacodynamics: Principles of Therapeutic Drug Monitoring*. 4th ed. Lippincott Williams & Wilkins; 2006:231–241.
26. McCabe BJ. Prevention of food-drug interactions with a special emphasis on older adults. *Curr Opin Clin Nutr Metab Care*. 2004;7:21–26.
27. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet*. 1999;36(6):425–438.
28. Samer CF, Ing Lorenzini K, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical settings. *Mol Diagn Ther*. 2013;17:165–184.
29. Grattagliano I, Portincasa P, D'Ambrosio G, Palmieri VO, Palasciano G. Avoiding drug interactions: here's help. *J Fam Pract*. 2010;59(6):322–329.
30. Corsonello A, Abbatecola AM, Fusco S, et al. The impact of drug interactions and polypharmacy on antimicrobial therapy in the elderly. *Clin Microbiol Infect*. 2015;21(1):20–26.
31. Zhou J, Poloyac SM. The effect of therapeutic hypothermia on drug metabolism and drug response: cellular mechanisms to organ function. *Expert Opin Drug Metab Toxicol*. 2011;7(7):803–816.
32. Thelen K, Dressman JB. Cytochrome P450-mediated metabolism in the human gut. *J Pharm Pharmacol*. 2009;61:541–558.
33. Finch A, Pillans P. P-glycoprotein and its role in drug-drug interactions. *Aust Prescr*. 2014;37:137–139.
34. Doligalski CT, Tong Logan A, Silverman A. Drug interactions: a primer for the gastroenterologist. *Gastroenterol Hepatol*. 2012;8(6):376–383.
35. Andrus MR. Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature. *Pharmacotherapy*. 2004;24:285–290.
36. Wiggins BS, Saseen JJ, Page RL 2nd, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific

statement from the American Heart Association. *Circulation*. 2016;134:e468–e495.
37. Horn JR, Hansten PD. Statins and OATP interactions. *Pharm Times*. 2014:42. http://www.hanstenandhorn.com/hh-article-June-2014.pdf
38. Manzi SF, Shannon M. Drug interactions—a review. *Clin Ped Emerg Med*. 2005;6:93–102.
39. Middleton RK. Drug interactions. In: Quan H, Helms RA, Quan DJ, Hernfindal ET, Gourley DR, eds. *Textbook of Therapeutics Drug and Disease Management*. 8th ed. Lippincott Williams and Wilkins; 2006.
40. Benet LZ, Hoener B. Changes in plasma protein binding have little clinical relevance. *Clin Pharmcol Ther*. 2002;71:115–121.
41. Boobis A, Watelet JB, Whomsley R, Benedetti MS, Demoly P, Tipton K. Drug interactions. *Drug Metab Rev*. 2009;41(3):486–527.
42. Zhou SF, Xue CC, Yu X-Q, Li C, Wang G. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. *Ther Drug Monit*. 2007;29(6):687–710.
43. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *Am Fam Physician*. 2007;76(3):391–396.
44. Ladda MA, Goralski KB. The effects of CKD on cytochrome P450-mediated drug metabolism. *Adv Chronic Kidney Dis*. 2016;23(2):67–75.
45. Anaisi N. Drug interactions involving immunosuppressive agents. *Graft*. 2001;4(4):232–247.
46. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. *Br J Clin Pharmacol*. 1998;46(2):101–110.
47. Evans AM. Influence of dietary components on the gastrointestinal metabolism and transport of drugs. *Ther Drug Monit*. 2000;22(1):131–136.
48. Thummel KE, Kunze KL, Shen DD, et al. Metabolically-based drug-drug interactions. Principles and mechanisms. In: Levy RH, Thummel KE, Trayer WF, Hansten PD, Eichelbaum M, eds. *Metabolic Drug Interactions*. Lippincott Williams & Wilkins; 2000:3–47.
49. Bachmann KA, Ring BJ, Wrighton SA. Drug-drug interactions and the cytochromes P450. In: Lee JS, Obach RS, Fisher MB, eds. *Drug Metabolizing Enzymes: Cytochrome P450 and Other Enzymes in Drug Discovery and Development*. Marcel Dekker, Inc; 2003:311–336.
50. Obach RS. Drug-drug interactions: an important negative attribute in drugs. *Drugs Today*. 2003;39:301–338.
51. Weaver RJ. Assessment of drug-drug interactions: concepts and approaches. *Xeobiotica*. 2001;31:499–538.
52. Cheng JW, Frishman WH, Aronow WS. Updates of cytochrome P450-mediated cardiovascular drug interactions. *Am J Ther*. 2009;16:155–163.

53. Sabol BJ, Basa RR, Wilkins CE. Malabsorption-associated warfarin resistance. *Am J Health Syst Pharm*. 2009;66:1548–1553.
54. Gugler R, Manion CV, Azarnoff DL. Phenytoin: pharmacokinetics and bioavailability. *Clin Pharm Ther*. 1976;19:135–142.
55. Maynard GA, Jones KM, Guidry JR. Phenytoin absorption from tube feedings. *Arch Intern Med*. 1987;147:1821.
56. Jung D, Powell JR, Walson P, Perrier D. Effect of dose on phenytoin absorption. *Clin Pharmacol Ther*. 1980;28:479–485.
57. Martin E, Tozer TN, Sheiner LB, Riegelman S. The clinical pharmacokinetics of phenytoin. *J Pharmacokinet Biopharm*. 1977;5:579–596.
58. Gubbins PO, Bertch KE. Drug absorption in gastrointestinal disease and surgery. Clinical pharmacokinetic and therapeutic implications. *Clin Pharmacokinet*. 1991;21:431–447.
59. Gulseth MP, Grice GR, Dager WE. Pharmacogenomics of warfarin: uncovering a piece of the warfarin mystery. *Am J Health Syst Pharm*. 2009;66:123–133.
60. Gorbach SL. Microbiology of the gastrointestinal tract. In: Baron S, ed. *Medical Microbiology*. 4th ed. University of Texas Medical Branch at Galveston; 1996. Accessed July 12, 2021. http://www.ncbi.nlm.nih.gov/books/NBK7670/
61. Interactions. *Lexicomp*. Wolters Kluwer Health, Inc. Accessed July 4, 2021. http://online.lexi.com
62. Preston CL, ed. *Stockley's Drug Interactions*. 12th ed. Pharmaceutical Press; 2019.
63. Foinard A, Décaudin B, Barthélémy C, Debaene B, Odou P. Impact of physical incompatibility on drug mass flow rates: example of furosemide-midazolam incompatibility. *Ann Intensive Care*. 2012;2:28.
64. Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *CPJ/RPC*. 2011;144(1):21–25.e9.
65. Horn JR, Hansten PD. Time course for enzyme induction and deinduction. *Pharm Times*. 2011;77(4):46
66. Pleuvry BJ. Pharmacodynamic and pharmacokinetic drug interactions. *Anaesth Intensive Care Med*. 2005;6(4):129–133.
67. Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA*. 1998;276:657–662.
68. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165:1095–1106.
69. Lopes RD, Horowitz JD, Garcia DA, Crowther MA, Hylek EM. Warfarin and acetaminophen interaction: a summary of the evidence and biologic plausibility. *Blood*. 2011;118:6269–6273.

70. Leong D, Wu PE. Warfarin and acetaminophen interaction in a 47-year-old woman. *CMAJ*. 2020;192(19):E506–E508. doi:10.1503/cmaj.191532
71. Yue Q, Bergquist C, Gerdén B. Safety of St John's wort (*Hypericum perforatum*). *Lancet*. 2000;355:576–577.
72. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol*. 2002;54:349–356.
73. IBM Micromedex® Drug Interaction Checking (electronic version). IBM Watson Health. Accessed July 4, 2021. https://www-micromedexsolutions-com.ezproxymcp.flo.org/
74. Hatanaka T. Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. *Clin Pharmacokinet*. 2000;39(6):397–412.
75. Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. *Am Fam Physician*. 2007;75:1487–1496.
76. PL detail-document. Clinically significant statin drug interactions. Pharmacist's Letter/Prescriber's Letter. April 2012. https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2016/Mar/Clinically-Significant-Statin-Drug-Interactions-9486
77. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. *Clin Pharmacokinet*. 2001;40(4):263–281.
78. McGrath CD, Hunter JM. Monitoring of neuromuscular block. *Contin Educ Anaesth Crit Care Pain*. 2006;6(1):7–12.
79. Warr J, Thiboutot Z, Rose L, Mehta S, Burry LD. Current therapeutic uses, pharmacology, and clinical considerations of neuromuscular blocking agents for critically ill adults. *Ann Pharmacother*. 2011;45:1116–1126.
80. Roberts DJ, Hall RI. Drug absorption, distribution, metabolism and excretion considerations in critically ill adults. *Expert Opin Drug Metab Toxicol*. 2013;9(9):1067–1084.
81. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest*. 2012;141(5):1327–1336.
82. Cawley MJ. Mechanical ventilation: a tutorial for pharmacists. *Pharmacotherapy*. 2007;27(2):250–266.
83. Hraiech S, Forel J-M, Papazian L. The role of neuromuscular blockers in ARDS: benefits and risks. *Curr Opin Crit Care*. 2012;18:495–502.
84. DeJonghe B. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288:2859–2867.
85. Murray MJ, DeBlock H, Erstad B, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med*. 2016;44(11):2079–2103.
86. American College of Critical Care Medicine of the Society of Critical Care Medicine, American Society of Health-System Pharmacists, American College of Chest Physicians. Clinical practice guidelines for sustained

neuromuscular blockade in the adult critically ill patient. *Am J Health Sys Pharm*. 2002;59:179–195.

87. Papazian L, Forel J-M, Gacouin A, et al; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107–1116.
88. Sunjic KM, Webb AC, Šunjic´ I, Creus MP, Folse SL. Pharmacokinetic and other considerations for drug therapy during targeted temperature management. *Crit Care Med*. 2015;43:2228–2238.
89. Kisor DF, Schmith VD. Clinical pharmacokinetics of cisatracurium besilate. *Clin Pharmacokinet*. 1999;36(1):27–40.
90. Lagneau F, D'honneur G, Plaud B, et al. A comparison of two depths of prolonged neuromuscular blockade induced by cisatracurium in mechanically ventilated critically ill patients. *Intensive Care Med*. 2002;28:1735–1741.
91. Sessler CN. Train-of-four to monitor neuromuscular blockade? *Chest*. 2004;126(4):1018–1022.
92. Latcha S. Electrolyte disorders in critically ill patients. In: Oropello JM, Pastores SM, Kvetan V, eds. *Critical Care*. McGraw Hill. Accessed July 12, 2021. https://accessmedicine-mhmedical-com.ezproxymcp.flo.org/content.aspx?bookid=1944&sectionid=143517373
93. Hibbs RE, Zambon AC. Nicotine and agents acting at the neuromuscular junction and autonomic ganglia. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 13th ed. McGraw Hill. Accessed July 12, 2021. https://accesspharmacy-mhmedical-com.ezproxymcp.flo.org/content.aspx?bookid=2189&sectionid=167889972
94. Kindler CH, Verotta D, Gray AT, Gropper MA, Yost CS. Additive inhibition of nicotinic acetylcholine receptors by corticosteroids and the neuromuscular blocking drug vecuronium. *Anesthesiology*. 2000;92:821–832.
95. Price D, Kenyon NJ, Stollenwerk N. A fresh look at paralytics in the critically ill: real promise and real concern. *Ann Intensive Care*. 2012;2:43.
96. Waitz A, Drube CG, Moss EL Jr, Oden EM, Bailey JV. Biological aspects of the interaction between gentamicin and carbenicillin. *J Antibiot*. 1974;25:219–225.
97. Shwed JA. Lack of effect of clavulanic acid on aminoglycoside inactivation by ticarcillin. *J Infect Dis Pharmacother*. 1995;1(2):35–43.
98. Walterspiel JN, Feldman S, Van R, Ravis WR. Comparative inactivation of isepamicin, amikacin, and gentamicin by nine β-lactam and two β-lactamase inhibitors, cilastatin and heparin. *Antimicrob Agents Chemother*. 1991;35(9):1875–1878.
99. Pickering LK, Rutherford I. Effect of concentration and time upon inactivation of tobramycin, gentamicin, netilmicin and amikacin by azlocillin, carbenicillin, mecillinam, mezlocillin and piperacillin. *J Pharmacol Exp Ther*. 1981;217:345–349.

100. American Society of Health-System Pharmacists. *AHFS Drug Information®—2021st ed*. American Society of Health-System Pharmacists®. 2021. STAT!Ref Online Electronic Medical Library. Accessed July 11, 2021. https://online.statref.com/document/zrgja2xRITkSeOsK3G0o7N
101. Taber HW, Mueller JP, Miller PF, Arrow AS. Bacterial uptake of aminoglycoside antibiotics. *Microbiol Rev*. 1987;51(4):439–457.
102. Leggett JE. Aminoglycosides. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Health Sciences; 2020. Accessed July 12, 2021. https://www-r2library-com.ezproxymcp.flo.org/Resource/Title/0323482554/ch0025s0003
103. Davis BD. Bactericidal synergism between β-lactams and aminoglycosides: mechanism and possible therapeutic implications. *Rev Infect Dis*. 1982;4(2):237–245.
104. Haouala A, Widmer N, Duchosal MA, Montemurro M, Buclin T, Decosterd LA. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. *Blood*. 2011;117(8):e75–e87.
105. Rochat B, Fayet A, Widmer N, et al. Imatinib metabolite profiling in parallel to imatinib quantification in plasma of treated patients using liquid chromatography-mass spectrometry. *J Mass Spectrom*. 2008;43(6):736–752.
106. Peng B, Lloyd P, Schran H, et al. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet*. 2005;44(9):879–894.
107. Kompendium ch [homepage]. Compendium Suisse des medicaments 2010 [updated 2010]. Accessed March 10, 2017. http://www.kompendium.ch/
108. Brendel C, Scharenberg C, Dohse M. Imatinib mesylate and nilotinib (AMN 107) exhibit high-affinity interaction with ABCG2 on primitive hematopoietic stem cells. *Leukemia*. 2007;21(6):1267–1275.
109. Ozvegy-Laczka C, Hegedus T, Várady G, et al. High-affinity interaction of tyrosine kinase inhibitors with the ABCG2 multidrug transporter. *Mol Pharmacol*. 2004;65(6):1485–1495.
110. White DL, Saunders VA, Dang P, et al. OCT-1-mediated influx is a key determinant of the intracellular uptake of imatinib but not nilotinib (AMN 107): reduced OCT-1 activity is the cause of low in vitro sensitivity to imatinib. *Blood*. 2006;108(2):687–704.
111. Van Erp NP, Gelderblom H, Guchelaar H-J. Clinical pharmacokinetics of tyrosine kinase inhibitors. *Cancer Treat Rev*. 2009;35(8):692–706.
112. Petain A, Kattygnarath D, Azard J, et al. Population pharmacokinetics and pharmacogenetics of imatinib in children and adults. *Clin Cancer Res*. 2008;14(21):7102–7109.
113. Widmer N, Decosterd LA, Csajka C, et al. Population pharmacokinetics ofimatinib and the role of alpha-acid glycoprotein. *Br J Clin Pharmacol*. 2006;62(1):97–112.

114. Widmer N, Decosterd LA, Leyvraz S, et al. Relationship of imatinib-free plasma levels and target genotype with efficacy and tolerability. *Br J Cancer*. 2008;98(10):1633–1640.
115. Azuma M, Nishioka Y, Aono Y, et al. Role of alpha 1-acid glycoprotein in therapeutic antifibrotic effects of imatinib with macrolides in mice. *Am J Respir Crit Care Med*. 2007;176(12):1243–1250.
116. Dutreix C, Peng B, Mehring G, et al. Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. *Cancer Chemother Pharmacol*. 2004;54(4):290–294.
117. Frye RF, Fitzgerald SM, Lagattuta TF, Hruska MW, Egorin MJ. Effect of St John's wort on imatinib mesylate pharmacokinetics. *Clin Pharmacol Ther*. 2004;76(4):323–329.
118. Smith P, Bullock JM, Booker BM, Haas CE, Berenson CS, Jusko WJ. The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy*. 2004;24(11):1508–1514.
119. Recoche I, Rousseau V, Bourrel R, et al. Drug-drug interactions with imatinib: an observational study. *Medicine*. 2016;95(40):e5076.
120. Cholongitas E, Pipili C, Katsogridakis K, Relos K, Dasenaki M. Dermatitis after suspected imatinib-levothyroxine interaction in a patient with gastrointestinal stromal tumor. *Cancer Chemother Pharmacol*. 2008;61:1083–1084.
121. De Grrot JWB, Zonnenberg BA, Plukker JTM, van Der Graaf WTA, Links TP. Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin Pharmacol Ther*. 2005;78:433–438.
122. Horn JR, Hansten PD, Chan L-N. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother*. 2007;41(4):674–680.
123. Tilson H, Hines LE, McEvoy G, et al. Recommendations for selecting drug-drug interactions for clinical decision support. *Am J Health Syst Pharm*. 2016;73(8):576–585.
124. Hansten PD. Drug interaction management. *Pharm World Sci*. 2003;25(3):94–97.

4

Pharmacogenomics and Personalized Medicine

Hyun Kim, Shannon F. Manzi, Laura Chadwick, and Jonathan Picker

CORE PRINCIPLES		CHAPTER CASES
1	Pharmacogenomics is an important component of the broader concept of personalized medicine, which incorporates a variety of factors, both genetic and nongenetic, to guide targeted and individualized therapeutic decisions.	**Case 4-1 (Question 1), Figure 4-1, Tables 4-1, 4-2**
2	Pharmacogenomic effects can be both pharmacokinetic and pharmacodynamic in nature. Pharmacokinetic effects are observed when variants affect the absorption, distribution, metabolism, or excretion of a drug. Pharmacodynamic polymorphisms may result in variable amounts of drug target enzymes or	**Case 4-2 (Questions 1, 2)**

	receptors, as well as possible changes in the drug target shape. These variations may render therapy ineffective or necessitate dose changes in certain affected populations.	
3	DNA polymorphisms affecting drug metabolizing enzymes can result in gain of function, loss of function, or have no effect on function of the enzyme produced. In some cases, significant toxicity can result.	**Case 4-3 (Question 1), Figure 4-2, Table 4-3** **Case 4-4 (Question 1), Table 4-4**
4	Drug transport proteins and binding targets can also be affected by pharmacogenomic variants.	**Case 4-5 (Questions 1, 2), Table 4-5**
5	Human leukocyte antigen (*HLA*) genes are unique in that the presence of a variant does not impact the metabolism of a drug, but instead may indicate the likelihood of the development of a life-threatening reaction.	**Case 4-6 (Questions 1–3), Table 4-6**
6	Test interpretation is crucial to the practical application of pharmacogenomic data. In particular, cytochrome P450 (CYP) 2D6 is a well-described CYP enzyme responsible for ~25% of all drug metabolism. However, *CYP2D6* is a complicated gene locus subject to multiple variants, pseudogene interference, and copy number variation, making interpretation difficult.	**Case 4-7 (Questions 1, 2), Table 4-7** **Case 4-8 (Question 1)**
7	Age-based development adds a level of complexity when assessing	**Case 4-9 (Question 1), Figure 4-3**

	pharmacogenomic markers in pediatric patients. Many of the pharmacogenomic dosing guidelines have not been validated in infants and children.	
8	Implementation of pharmacogenomics into practice is increasing but continues to face many challenges, including the appropriate determination of when and whom to test; storage, analysis, and security of genetic data; and considerations for using pharmacogenomic data and recommendations in practice.	**Case 4-10 (Question 1)** **Case 4-11 (Questions 1, 2)**

INTRODUCTION

Pharmacogenomics is the study and application of gene expression on drug pharmacokinetics and pharmacodynamics. This term is often used interchangeably with "pharmacogenetics." By strict definition, pharmacogenetics is used in the context of a single gene's influence on a drug, whereas pharmacogenomics refers to the broader study of the full genomic impact on drug behavior.[1] Because genetic variants are specific to the individual, the use of pharmacogenomics in clinical practice has become a core component of the personalized medicine and precision medicine movements.[2,3]

The study of pharmacogenomics is not new because there are cases in the literature from the 1950s and 1960s describing the influence of a person's genetics on drug toxicity.[4,5] The first recognition of individual differences in response to consumption of a product was favism, a form of hemolytic anemia described by the ancient Greek physicians before the third century BC.[6] They

recognized that in some people the consumption of fava beans had potentially severe consequences. Whether this was the source for Pythagoras' famous abhorrence of the beans, however, remains uncertain. More recently, with the advent of newer, cheaper, faster DNA sequencing techniques, the study of pharmacogenomics has exploded. We are now able to begin transitioning pharmacogenomic knowledge from the research realm to the clinic, although not without challenges.

A brief review of the basics of human genetics in the context of pharmacogenomics is discussed here. Students are encouraged to utilize the selected references at the end of the chapter for further review. Although somatic tumor genetics and the study of mutations found in cancer cells are becoming increasingly important when selecting antineoplastic drugs, this chapter primarily focuses on germline mutations in human DNA that affect drug absorption, distribution, metabolism, and excretion.

Genes code for proteins, such as enzymes, structural components of cells, hormones, antibodies, and transport molecules. In pharmacogenomics, the gene and the enzyme often share the same name. For example, the gene that codes for cytochrome P450 CYP3A4 is known as *CYP3A4* and the gene that codes for thiopurine methyltransferase (TPMT) is known as *TPMT*.

The human genome is made up of 3 billion nucleotide base pairs arranged on 23 pairs of chromosomes. Nucleotides include adenine (A), guanine (G), cytosine (C), and thymine (T), with variants in nucleotide sequences contributing to each individual's unique physiologic characteristics, traits, and features, such as hair color, eye color, height, risk of disease, and ability to process medication.

In most, but not all, cases, two copies of each gene are present: one inherited from your mother and one from your father. Each copy of a gene is referred to as an *allele*. If both the maternal and paternal alleles are the same, then the individual is considered homozygous for that gene. If the parental copies differ, then the patient is considered to be heterozygous for that gene. Nucleotide changes that differ from the most commonly observed sequence are referred to as *variants*. Although the formal variant definition states that the

observed change occurs in at least 1% of the population, the term is often used in practice regardless of population frequency.

A change in a single base pair is termed a *single-nucleotide polymorphism*, or SNP (pronounced “snip”) (**Fig. 4-1**). SNP locations are mapped and named using a reference SNP cluster ID, or rsID, discussed in more detail in Case 4-5. An SNP that adversely changes the function of the protein encoded for by a gene is called a *pathogenic variant* or, historically and colloquially, a *mutation*. Many of the pharmacogenetic variants discussed in this chapter are SNPs. SNPs are responsible for 90% of pharmacogenetic variability and can result in gain of function with greater production of the associated enzyme and higher than normal enzymatic activity, or loss of function with reduced or no enzyme production and decreased enzymatic activity. Other variant types include nucleotide insertions or deletions, commonly referred to as *indels*. In many cases, indels terminate protein production as a result of frameshift changes that alter the translation of amino acids.

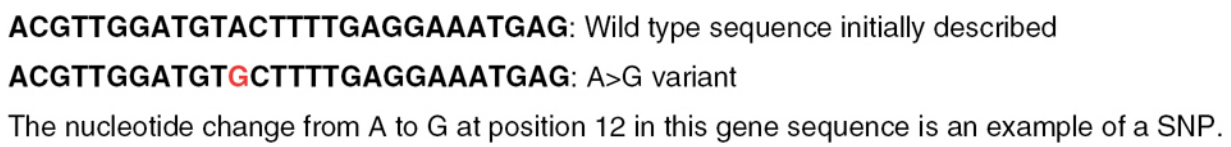


Figure 4-1 Example of a single-nucleotide polymorphism (SNP).

In classical Mendelian genetics, most inheritance of disorders occurs in either a dominant or recessive manner. For dominant disorders, a change in a single allele is sufficient to elicit an undesired physiologic effect. These changes can be passed down from one generation to the next or occur as new, or de novo, mutations within an individual for the first time. With recessive disorders, a person must inherit two defective copies of a gene for there to be a functional consequence. Parents who are heterozygous for a gene associated with a recessive disorder are usually unaffected by the disorder and are termed *carriers*. When both parents are carriers, one in four of their offspring is at risk for inheriting the disorder even with no family history of the disease.

Unlike the discrete pattern of dominant and recessive disorder inheritance, pharmacogenes, or genes associated with drug action and kinetics, tend to operate on more of a continuum. Variants within pharmacogenes often result in a spectrum of effects, ranging from mild to more pronounced, depending on the number of functional alleles present. Pharmacogenetic variants are also typically "silent" in the absence of relevant drug exposure, making family history a somewhat less reliable tool.

The nucleotides, including any variants if present, make up alleles that determine a person's genotype for a given gene. The term *phenotype* refers to the expression, or physical manifestation, of a genotype. In some cases, a phenotype is visibly obvious, such as skin color, eye color, or hair color. In other cases, it is measurable, such as is the case for a person's blood type or the amount of a CYP450 metabolizing enzyme they generate. In the context of pharmacogenomics and metabolizing enzymes, patients are often classified as having a phenotype of ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, or poor metabolizers based on their genotype.[7] There are several other relevant phenotypes relating to pharmacogenomics that are discussed in this chapter, particularly those that deal with drug targets or pharmacodynamic responses.

The complexity of most drug metabolism pathways can make applying phenotypes to clinical drug dosing decisions complex. It is rare for a pathway to involve a single enzyme resulting in one inactive metabolite that is immediately excreted by the body. Instead, most drugs utilize multiple metabolizing enzyme pathways, rely on several drug transporters, and have many metabolites of varying activity. Each of these pathways may be subject to variable gene expression, coupled with indirect genetic and environmental effects on other characteristics such as disease, weight, nutrition, and age. With the spectrum of factors to consider, using pharmacogenomic interpretations in a clinical setting can be extremely complicated.

For common pharmacogenes, the representation of a person's genotype is often noted by a "*," known as a *star allele*. For example, a normal or "wild-type" allele status is often denoted as **1/*1*.[8] As

other alleles are discovered, they are numbered sequentially as *2, *3, and so on. Because discoveries are inevitably sometimes reported simultaneously from different sources, there is occasionally an overlap of star alleles and the variants represented. There are several worldwide databases for reporting new pharmacogenomic variants, including the Human Cytochrome P450 (CYP) Allele Nomenclature Database, http://www.cypalleles.ki.se/, and the Database of Genomic Variants, http://dgv.tcag.ca/dgv/app/home.

During drug development and postmarketing analyses, it often becomes clear that some patients either have severe adverse drug reactions (ADRs) or do not respond to the population-derived standard dose. Adverse drug reactions (ADRs) are defined as *unintended outcomes occurring in the absence of medication error or lack of proper adherence to the drug*, and are costly.[9,10] The 2000 Institute of Medicine (IOM) "To Err Is Human" report cited over 2 million reported ADRs in the United States per year resulting in ~100,000 deaths and at a cost of $29 billion annually.[11] It is estimated that 87.7% of outer quadrant adults are taking at least one prescription drug, 35.8% are taking more than five prescription drugs, 37.9% use over-the-counter medications, and 63.7% use dietary supplements.[12] It is well known that ADRs often go unnoticed and even more frequently unreported, making the actual numbers likely far higher.

The clinical application of pharmacogenomics has allowed us to not only explain some of these historical reactions but also helps clinicians predict who may be at higher risk for developing an adverse reaction if exposed to a drug or drug class.[13] With this understanding, clinical decisions can be made to lower a person's risk of adverse reactions. Given that >90% of individuals carry at least one potential clinically significant pharmacogene genotype, overall risk in the pharmacogenetic space is not insignificant.[14] Avoidance of ADRs has a measurable impact on a patient's quality of life, decreases overall health care costs, and lessens the time burden on health care providers managing the adverse reactions. However, acceptance of clinical pharmacogenomic testing is not

universal and there remains the challenge of conclusively validating the genetic variant association with the adverse reaction.[15]

Guidelines for drug dosing and selection have been developed by the Clinical Pharmacogenomics Implementation Consortium (CPIC, pronounced “See-Pick”) and the Pharmacogenetics Working Groups of the Royal Dutch Pharmacists Association (DPWG). Each guideline is rated on the level of evidence available to support the recommendation.[16] Currently, there are 26 CPIC Level I Evidence published guidelines available on www.pharmgkb.org, a website supported by the National Institutes of Health (NIH) and hosted by Stanford University.[17] The site houses a wealth of information, including pathway diagrams, annotated bibliographies, and look-up tables. Importantly, the guidelines do not address who should be tested but instead focus on what to do with the data if available.

PHARMACOKINETIC IMPLICATIONS

CASE 4-1

QUESTION 1: A.S. is a 2-year-old female diagnosed with active multidrug resistant tuberculosis (MDR TB). The Centers for Disease Control and Prevention (CDC) treatment protocol recommends isoniazid, rifampin, ethambutol, and pyrazinamide for initial therapy. Her mother is concerned because several family members in their home country of China had developed serious “liver problems” when they took isoniazid, and she insists on the “gene test” for A.S.

What genetic testing is A.S.’s mother referring to and what are the risks of toxicity in relation to isoniazid therapy?

Isoniazid is part of the four-drug regimen used to treat both active and latent tuberculosis (TB) infection because it is bactericidal against *Mycobacterium tuberculosis* organisms.[18] One of the most commonly reported side effects, sometimes leading to premature discontinuation of the drug, is drug-induced liver injury (DILI).

The metabolism of isoniazid is complex, with the *N*-acetyltransferase-2 (NAT2) enzyme playing a key role in the pathway.[19] In the metabolism of isoniazid, NAT2 acetylates both the parent drug and a hydrazine metabolite, converting the hydrazine metabolite to acetyl hydrazine (AcHz).[20] The AcHz metabolite is believed to be the main cause of the liver injury observed with isoniazid therapy.

The NAT2 enzyme is generated from a gene of the same name, with several known polymorphisms leading to alleles associated with either slow or rapid acetylation rates. Individuals homozygous for slow alleles are considered "slow acetylators," those homozygous for rapid alleles "rapid acetylators," and heterozygotes deemed "intermediate acetylators" (**Table 4-1**). When NAT2 acetylation rates are reduced, it allows for a buildup of AcHz; therefore, DILI has been found to be highest in patients who are slow acetylators.[21] In addition to isoniazid, NAT2 is also a known acetylator of drugs and/or metabolites in other drug pathways, although the clinical effects of *NAT2* genotype on these drugs are less studied: sulfonamides (sulfamethoxazole, metabolites of sulfasalazine); and aromatic and aliphatic amines (procainamide, dapsone, metabolite of clonazepam, mescaline).[22]

Table 4-1
***NAT2* Genotypes and Phenotypes**

***NAT2* Allele Activity**		
Slow	**5–7, *10, *12D, *14, *17, *19*	
Rapid	**4* (wild type), **11, *12A–C, *13, *18*	
NAT2 Phenotype Summary		
Genotype	**Acetylator Rate**	**Clinical Manifestation With Isoniazid Therapy**
Homozygous slow	Slow	Increased risk of adverse drug events
Heterozygous	Intermediate	No increased risk of adverse drug events or treatment failure related to genotype
Homozygous	Fast/rapid	Possible increased risk of treatment failure

rapid		

The “gene test” mentioned by A.S.’s mother is a test for the *NAT2* gene. A variety of pharmacogenomic tests are available to examine SNPs in the *NAT2* gene and assign a patient’s genotype, either from a targeted assay or as part of a more extensive gene panel. Preemptive *NAT2* testing before isoniazid therapy is not currently the standard of care; however, evidence suggests that this practice may be beneficial in some populations with a high prevalence of DILI in slow acetylators.[23–28] Asian cohorts have been found to have the highest rates of DILI in the setting of a slow acetylator status (see summary of studies in **Table 4-2**). Although there are no formal dosing guidelines set for isoniazid therapy in the context of genotype or acetylator status, a study completed by Azuma et al with 155 Japanese patients with TB proposed a modified, genotype-based dosing regimen with successful outcomes that were both clinically and statistically significant (results summarized in **Table 4-3**).[29]

Table 4-2
Summary of *NAT2* Genotypes and Hepatotoxicity Risk With Isoniazid Studies

Study	Study Type	Population	Metric	Result
Sun et al[24]	Meta-analysis *N* = 5 case–control studies 133 cases (hepatotoxicity) 492 controls	Chinese Japanese East Indian Caucasian	Prevalence of SA status in hepatotoxicity cases vs control	*Overall*: no significant finding *Asian subgroup analysis*: ↑ risk hepatotoxicity for SAs OR 2.52 (CI: 1.5–4.3)
Wang et al[25]	Meta-analysis *N* = 14 case–control studies 11 Asian, 3 non-Asian 474 cases (hepatotoxicity) 1446 controls	Japan China Taiwan India Korea Turkey Switzerland USA (8%)	SA hepatotoxicity risk vs RA	↑ risk hepatotoxicity for SAs OR_Asian: 4.9 (CI: 3.3–7.1) OR_non-Asian: 3.7 (CI 1.3–10.5) ↑ risk hepatotoxicity in combination regimen
Ben Mahmoud et al[26]	Observational case–control *N* = 65	Tunisian	SA hepatotoxicity risk vs RA and IAs	↑ risk hepatotoxicity for SAs OR 4.3; CI: 1.5–18
Du et al[27]	Meta-analysis *N* = 26 studies 1198 cases 2921 controls	Asian Caucasian Middle Eastern Brazilian	Prevalence of SA status in hepatotoxicity cases vs control	*Overall*: ↑ risk hepatotoxicity for SAs OR 3.1 (CI: 2.5–3.9) *Caucasian*: no significant finding
Huang et al[28]	Observational case–control *N* = 224	Taiwan	SA hepatotoxicity risk vs RA	↑ risk hepatotoxicity for SAs OR 2.8 (CI: 1.3–6.2)
Pasipanodya et al[23]	Meta-analysis *N* = 3471	United Kingdom Asia East Africa United States Prague	RA treatment failure risk vs SA	↑ risk of treatment failure for RAs RR 2 (CI: 1.5–2.7)

CI, confidence interval; IA, intermediate acetylator; OR, odds ratio; RA, rapid acetylator; RR, risk ratio; SA, slow acetylator.

Sources: Pasipanodya JG, Srivastava S, Gumbo T. Meta-analysis of clinical studies supports the pharmacokinetic variability hypothesis for acquired drug resistance and failure of antituberculosis therapy. *Clin Infect Dis*. 2012;55(2):169–177. doi:10.1093/cid/cis353; Sun F, Chen Y, Xiang Y, Zhan S. Drug-metabolising enzyme polymorphisms and predisposition to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int J Tuberc Lung Dis*. 2008;12(9):994–1002; Wang PY, Xie SY, Hao Q, Zhang C, Jiang BF. NAT2 polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int J Tuberc Lung Dis*. 2012;16(5):589–595. doi:10.5588/ijtld.11.0377; Ben Mahmoud L, Ghozzi H, Kamoun A, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatotoxicity in Tunisian patients with tuberculosis. *Pathol Biol (Paris)*. 2012;60(5):324–330. doi:10.1016/j.patbio.2011.07.001; Du H, Chen X, Fang Y, et al. Slow N-acetyltransferase 2 genotype contributes to anti-tuberculosis drug-induced hepatotoxicity: a meta-analysis. *Mol Biol Rep*. 2013;40(5):3591–3596. doi:10.1007/s11033-012-2433-y; Huang YS, Chern HD, Su WJ, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatol Baltim Md*. 2002;35(4):883–889. doi:10.1053/jhep.2002.32102.

Table 4-3
NAT2 Genotype–Based Dosing Recommendations for Isoniazid

Summary of Results From Azuma et al[29]					
	Genotype-Based Dosing Recommendation	*AE*	*Standard 5 mg/kg*	*Genotype-Based Dosing*	*P*
Slow	50% dose decrease (~2.5 mg/kg)	DILI	77.8%	0%	.003
		TF	22.2%	0%	NR
Intermediate	Standard (5 mg/kg)	DILI	4.7%		NR
		TF	26.8%		NR
Rapid	50% dose increase (~7.5 mg/kg)	DILI	4.2%	4.5%	NS
		TF	39.5%	15%	.013

AE, adverse effects; DILI, drug-induced liver injury; NR, no result; NS, nonsignificant; TF, treatment failure.

Source: Azuma J, Ohno M, Kubota R, et al. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy. *Eur J Clin Pharmacol*. 2013;69(5):1091–1101. doi:10.1007/s00228-012-1429-9.

Several questions remain as to how to most safely and appropriately incorporate *NAT2* genotype results into a widespread clinical application. For example, pediatric patients such as A.S. offer a unique set of challenges because recommended isoniazid starting doses are within a higher range (10–15 vs 5 mg/kg for adults), and dose modifications based on genotype have not been studied in this population. Genotype concordance with predicted phenotype has also been found to be lower in pediatric patients.[30] In addition, ethnic variation among study results also suggests that testing may be more beneficial in certain groups, namely, those with Asian ancestry. As is the case when using ethnicity to determine whether to complete any genetic test, self-reported ancestry is not always a reliable means of predicting someone's actual genetic lineage. With a foundation of promising preliminary studies, a continued focus on the *NAT2* genotype effects on isoniazid safety has the potential to result in institutions and organizations adopting policies to proactively test *NAT2* in the context of isoniazid treatment to both prevent adverse drug events and increase treatment success.

PHARMACODYNAMIC IMPLICATIONS

CASE 4-2

QUESTION 1: E.F. is a 51-year-old male status post ST-elevation myocardial infarction (STEMI) and atrial fibrillation with a residual left ventricular thrombus. Despite aggressive dose escalations of warfarin, his international normalized ratio (INR) will not budge above 1.7. His current dose of warfarin is 10 mg daily and he reports no dietary changes or excessive vitamin K intake. There are no drug–drug interactions identified in his regimen. The cardiology team asks about pharmacogenomic testing.

What is known about the genes involved in warfarin response that would impact E.F.'s INR?

Warfarin works by inhibiting vitamin K epoxide reductase complex subunit 1 (VKORC1), a key enzymatic component in the vitamin K clotting pathway.[31] By inhibiting VKORC1, synthesis of vitamin K–dependent clotting factors II, VII, IX, and X is reduced, and anticoagulation is achieved under conditions where thrombosis is a concern, such as atrial fibrillation. The amount of VKORC1 present in a person is linked to the *VKORC1* gene, a key pharmacodynamic consideration. Patients with the GG genotype at *VKORC1* rs9923231 are considered warfarin insensitive, meaning they are likely to require larger doses of warfarin to effectively inhibit the VKORC1 pathway. The AA genotype has been associated with lesser amounts of VKORC1, and therefore these patients are warfarin sensitive and require lower doses of warfarin for inhibition and anticoagulation.[32]

Another significant factor affecting warfarin dosing and response is the effect of genetic variants on warfarin metabolism. Warfarin is taken orally as a racemic mixture of R- and S-enantiomers, and its subsequent metabolism is complex, involving multiple genes and pathways. The primary pathway of the S-enantiomer, the more active form of the drug, is via the CYP2C9 enzyme.[32] CYP2C9 is the predominant enzyme pathway responsible for >25% of the variation in warfarin metabolism. *CYP2C9* is highly polymorphic, with several known variants within the population linked to reduced metabolic rates, including the *CYP2C9 *2* and *3* alleles. Reduced warfarin metabolism leads to increased concentrations of the active form of

the drug. These patients may require lower warfarin doses, and thus may be at increased risk for bleeding using standard dosing algorithms.[32]

A more recent gene of focus with limited evidence relating to warfarin sensitivity is *CYP4F2*.[33] *CYP4F2* affects the metabolism and, therefore, the physiologic levels of vitamin K. Patients with the TT genotype for *CYP4F2* rs2108622 are thought to maintain higher concentrations of vitamin K, and therefore require ~1 mg more warfarin per day than do patients with the CC genotype. Although current dosing models focus strictly on *CYP2C9* and *VKORC1* genotypes for warfarin initiation, *CYP4F2* has shown early promise as a potential factor for strengthening the effectiveness of dose prediction algorithms in some ethnicities.[34]

It is important to remember that many nongenetic factors such as age, weight, diet, smoking status, medication interactions, and others contribute to great variability in warfarin dosing within patient populations. Drug–drug interactions in which the CYP2C9 enzyme may be induced or inhibited can affect both the rate of warfarin metabolism and the pharmacogenomic phenotype, a phenomenon termed *phenoconversion*. In addition, a diet high in vitamin K will make warfarin less effective because this facilitates increased synthesis of vitamin K–dependent clotting factors. Algorithms for determining appropriate starting doses for patients older than age 18 years based on both nongenetic and genetic factors are available at www.warfarindosing.org. Close monitoring of INR is also recommended to ensure proper anticoagulation and reduced risk of bleeding.

CASE 4-2, QUESTION 2: What other drugs are significantly affected by the CYP2C9 pathway?

CYP2C9 is estimated to play a role in the metabolism of up to 20% of commonly used medications.[35] From these medications, several associations have been found linking variants in the CYP2C9 pathway to both increased rates of adverse drug events and variable

medication response. Examples of such drugs include phenytoin, certain nonsteroidal anti-inflammatory drugs (NSAIDs, such as celecoxib and diclofenac), sulfonylureas, losartan, and certain statins (such as fluvastatin and simvastatin). Patients with *2 or *3 alleles may be at increased risk for toxicities at standard doses of drugs that are processed through the CYP2C9 pathway because of decreased metabolism and increased parent drug concentrations and may require reduced dosing or increased monitoring.

IMPLICATIONS IN ACUTE TOXICITY

Many known variants within the genes that code for enzyme proteins exist, possibly affecting the rate at which the enzyme is able to metabolize drugs through its pathway. These variants may result in either reduced enzyme function, leading to increased concentration of the parent drug, or increased enzyme activity with decreased concentrations of a parent drug. The clinical effects of variants depend on whether the parent drug is pharmacologically active or a prodrug.

CASE 4-3

QUESTION 1: T.B. is a 10-year-old male admitted for status epilepticus, treated with intravenous (IV) lorazepam and IV fosphenytoin on presentation, aborting the seizures. His past medical history is significant for congenital hydrocephalus, a ventriculoperitoneal (VP) shunt, and refractory epilepsy secondary to an in utero right middle cerebral artery (MCA) stroke. On day 5 of his hospitalization, he is still extremely lethargic, and his free phenytoin level is high, peaking at 3 µg/mL on day 2 and 1.4 µg/mL on day 5. Looking at his records, he received the initial loading dose of IV fosphenytoin 500 mg phenytoin sodium equivalents (PE) (18 mg PE/kg) followed by a single maintenance dose of IV fosphenytoin 140 mg PE (5 mg PE/kg) 5 hours later on day 1 of the hospitalization (**Fig. 4-2**). He has no clinically relevant drug–drug interactions, and his albumin is normal.

What is a possible reason for the toxicity T.B. is experiencing?

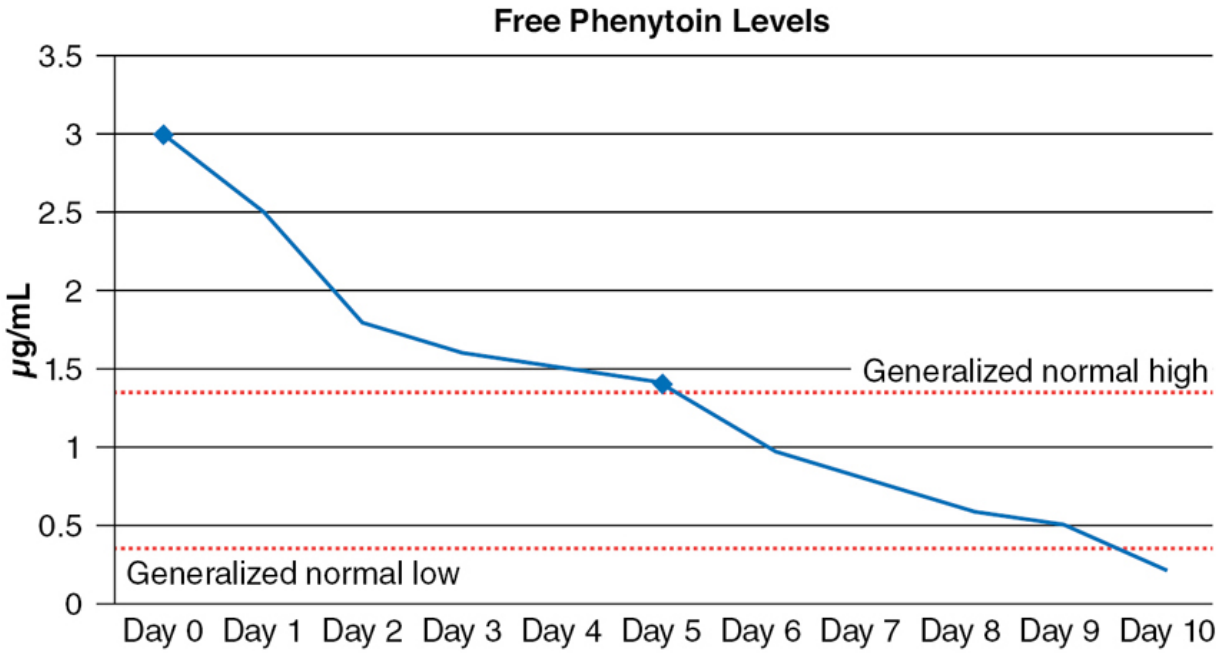


Figure 4-2 Free phenytoin levels (Case 4-3).

Phenytoin/fosphenytoin serum concentrations can be difficult to control and are complicated by multiple factors including Michaelis–Menten kinetics or capacity-limited metabolism. Drugs that follow Michaelis–Menten kinetics go from first to zero order, meaning that metabolism increases with increasing concentration until enzyme saturation takes place.[36] Once saturation is reached, drug plasma concentrations can increase to toxic levels in a fast and unpredictable manner. In addition, many factors affect an individual's safe and effective phenytoin dose, including albumin levels, other medications in the patient's regimen, and pharmacogenetics.

Phenytoin has many chronic effects associated with long-term use including hepatotoxicity, osteoporosis, megaloblastic anemia, gingival hyperplasia, hirsutism, and peripheral neuropathy.[37] In the acute setting of toxic plasma concentrations or an overdose, phenytoin toxicity can manifest with a variety of signs and symptoms, including central nervous system (CNS) effects (dizziness, confusion, drowsiness, and ataxia) as well as gastrointestinal (GI) upset and nausea. Phenytoin is also associated with severe cutaneous reactions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrosis (TEN), discussed in Case 4-6.

Fosphenytoin is a prodrug that is converted by plasma esterases to the active drug phenytoin. Phenytoin is further metabolized by CYP2C9 to phenytoin arene oxide, which is then broken down to multiple metabolites that are eventually excreted.[38,39] The contribution of these various metabolites to toxicity and efficacy of phenytoin is not well understood.

T.B. is found to carry a loss-of-function variant for *CYP2C9* with the genotype **1/*2*. With loss of CYP2C9 enzyme function comes decreased breakdown of the active drug phenytoin at standard doses. Given the narrow therapeutic index of phenytoin and the drug's propensity to cause side effects, T.B. ultimately experienced drug toxicity and accompanying symptoms. The evidence relating genotypes such as T.B.'s to the development of adverse drug events is strong, and CPIC has published dosing guidelines based on the *CYP2C9* genotype, summarized in **Table 4-4**.[40] Note that only the maintenance, not the loading dose, has adjustment recommendations so that acute seizure activity can be immediately terminated.

Table 4-4
***CYP2C9* Genotype–Based Dosing Recommendations for Phenytoin/Fosphenytoin**

***CYP2C9* Metabolizer Status**	**Sample Genotype(s)**	**Recommendation**
Extensive metabolizer	**1/*1*	Initiate therapy with recommended maintenance dose.
Intermediate metabolizer	**1/*2, *1/*3*	Consider *25% reduction* of recommended starting maintenance dose and adjust according to therapeutic drug monitoring and response.
Poor metabolizer	**2/*2, *3/*3, *2/*3*	Consider *50% reduction* of recommended starting maintenance dose and adjust according to therapeutic drug monitoring and response.

CASE 4-4

Question 1: J.P. is a 110.23-pound (50-kg), 17-year-old female status post kidney transplant. She is currently receiving azathioprine 100 mg by mouth (PO) daily to prevent rejection. She is brought to the emergency department 5 days after starting the medication with lethargy, fever, and malaise. A white blood cell (WBC) count comes back with a critically low value of 0.9×10^9 cells/L (normal range, $4.5–11.0 \times 10^9$ cells/L), with an absolute neutrophil count (ANC) of 760 cells/μL (normal range, 2500–6000).

What factors might explain such severe neutropenia, and what pharmacogenomic test should be ordered for J.P.?

Azathioprine is an immunosuppressive agent in the thiopurine class, acting as a prodrug of 6-mercaptopurine. These drugs are purine analogs and antagonize purine synthesis, inhibiting synthesis of DNA, RNA, and proteins.[41] Thiopurines are used in a variety of conditions including renal transplant, rheumatoid arthritis, certain cancers, and inflammatory bowel disease.

Azathioprine is further metabolized to 6-mercaptopurine (an active drug) via glutathione S-transferase (GST) reduction. 6-Mercaptopurine is then converted into the active 6-methylmercaptourine ribonucleotide (6-MMPR) and several inactive metabolites such as 6-methylmercaptopurine (6-MMP) through multiple pathways.[42] The two primary enzymes contributing to 6-mercaptopurine breakdown are TPMT and hypoxanthine guanine phosphoribosyltransferase (HPRT). TPMT metabolism results in the generation of the inactive metabolite 6-MMP, whereas HPRT contributes to a pathway that leads to the generation of active 6-MMPR and 6-thioguanine nucleotide (6-TGN) metabolites.[43] Furthermore, active 6-TGN metabolites are then inactivated by TPMT. The accumulation of active 6-TGN metabolites via HPRT is associated with myelosuppression with thiopurine therapy. In summary, TPMT acts as the detoxifying enzyme for drugs in the thiopurine class, and its activity is directly linked to risk of drug toxicities.

The severe neutropenia J.P. experienced 5 days after beginning azathioprine is very likely the result of starting a full dose (2 mg/kg/day) in the setting of a homozygous variant *TPMT* genotype,

such as **3B/*3C*. Owing to the near-absent enzyme level produced by homozygous variants, the TGN metabolites build up, resulting in severe, and sometimes, life-threatening neutropenia.

It is important to note that the genotype **3B/*3C* is nearly impossible to distinguish from the less clinically impactful heterozygous genotype of **1/*3A* on most commercially available *TPMT* assays. In cases of suspected homozygous variant status, parental studies may be necessary for absolute determination. Alternative therapy or a 90% reduction in the azathioprine dose is advised for J.P.'s *TPMT* genotype. In the case of a heterozygous genotype such as **1/*3C*, the dose would be decreased by 30% to 70%.[44]

DRUG TARGET IMPLICATIONS

CASE 4-5

Question 1: L.K. is a 45-year-old female referred for interpretation of pharmacogenomic results provided by a certified clinical lab as part of a research study. The report states that her genotype for *SLCO1B1* is CC. L.K. asks if she is at risk for severe muscle pain, or myopathy, with statin therapy that she heard about on a recent TV malpractice commercial.

What information do you need to answer her question?

"Statins" or β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor drugs are associated with muscle toxicity ranging from mild aches to the development of severe debilitating myopathy and rhabdomyolosis in a segment of the population.[45] Regardless of severity, this adverse drug event is a common cause for drug discontinuation.[46] Recent published literature links the risk of developing these muscle-related side effects to certain variants in the *SLCO1B1* gene.

Keeping in mind that a raw result from DNA analysis is essentially a string of As, Cs, Ts, and Gs within each individual gene, the CC genotype for *SLCO1B1* information provided by L.K. is insufficient.

To accurately review the available evidence and make recommendations, it is essential to know the actual variant location that the CC call was based on. Although there are multiple polymorphisms that have been identified in the *SLCO1B1* gene, only a few are linked to clinical effect.[46]

An rs number, or rsID, is used to point to a specific nucleotide location within a gene. Known SNPs within a gene are defined by rsID for the purpose of clinical guidelines and research reporting. This ensures standardization and proper assessment of variants. For *SLCO1B1*, the rsID most commonly associated with development of myopathy with HMG-CoA reductase inhibitors is rs4149056.[46] This rsID should be provided with results to make the proper assessments, and most clinical labs will include the associated rsID numbers for any SNP results to help clinicians make appropriate decisions about drug selection and dose alteration.

Case 4-5, Question 2: The clinical lab confirms the *SLCO1B1* genotype CC call was based on rs4149056. What is your answer to L.K.'s question regarding her risk of developing severe myopathy with statin use?

The C allele at *SLCO1B1* rs4149056 has been associated with decreased statin intracellular transport and clearance.[46] SLCO1B1 is a transporter protein with a primary function of drug uptake into the liver. Variants affecting the hepatic uptake of drugs via SLCO1B1 ultimately increase overall area under the curve (AUC) and drug exposure, resulting in higher risks of adverse drug events such as myopathy. Patients with a homozygous variant status such as L.K. are at significantly increased risk for developing muscle toxicity with statin use. Although all statins may have adverse event profiles linked to this variant, the evidence is strongest for simvastatin. Published CPIC guidelines for simvastatin with SLCO1B1 rs4149056 variant status are summarized in **Table 4-5**.

Table 4-5
***SLCO1B1* Genotype–Based Dosing Recommendations for HMG-**

CoA Reductase Inhibitors

SLCO1B1 rs4149056 Genotype	Myopathy Risk With Simvastatin Use	Simvastatin Dosing Recommendation
TT	Normal	Prescribe standard starting dose and modify based on tolerance and disease response.
TC	Intermediate	Prescribe a lower dose or consider alternative statin (such as pravastatin or rosuvastatin). Routine monitoring of CK may be considered.
CC	High	Prescribe a lower dose or consider alternative statin (such as pravastatin or rosuvastatin). Routine monitoring of CK may be considered.

CK, creatine kinase; HMG-CoA, β-hydroxy-β-methylglutaryl-coenzyme A.

Source: Adapted from Ramsey LB, Johnson SG, Caudle KE, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. *Clin Pharmacol Ther*. 2014;96(4):423–428. © 2014 American Society for Clinical Pharmacology and Therapeutics. Reprinted by permission of John Wiley & Sons, Inc.

NONMETABOLIC IMPLICATIONS

CASE 4-6

QUESTION 1: J.C. is an 18-year-old female with a past medical history of epilepsy. Following a failed course of levetiracetam, her physician has decided to start her on carbamazepine therapy for seizure control. Approximately 2 months after starting the drug, J.C. has been seizure free but started feeling flu-like symptoms with a headache and fever. She also noticed that her skin was becoming red and itchy in several locations. The rash quickly progressed to the point where she notes swelling and the formation of blisters on her nostrils, eyes, and lips. J.C. then realized that she might be experiencing something more than a common rash and called the pharmacy in a panic to ask if it was possible that she is reacting to her medication, even though she had been on it for some time.

Given the known side effects of carbamazepine, is it possible that J.C. is experiencing a drug reaction?

ADRs are often thought to happen soon after initial doses of medication. However, delayed hypersensitivity is also possible. In the case of carbamazepine, these reactions are linked to DNA changes within the human leukocyte antigen (*HLA*) genes. There is a strong association between positive *HLA-B*1502* gene variant carrier status and increased risk of severe cutaneous adverse reactions.[47] A less-established link has also been seen with carriers of the *HLA-A*31:01* variant, more common in Japanese and Europeans.[48]

The *HLA* genes code for proteins that form an immunologic complex found on all nucleated cells. This complex is responsible for presenting both self and foreign peptides to immune cells, such as T cells.[49] When a foreign peptide is presented and then recognized by a T cell, there is an immunologic response. Examples of peptides that may be recognized as foreign include viruses, bacteria, tumor antigens, and drugs. Although this complex may play a role in drug-induced reactions seen with *HLA* variants, there is still significant uncertainty as to whether or not there are other mechanisms at play.[50] Evidence has suggested that drug concentrations are also higher in patients who experience cutaneous reactions, hinting that CYP loss-of-function alleles and *HLA* variants may work synergistically to increase a patient's risk of SJS and TEN.[50] This possibility is supported by the fact that not all patients who carry an *HLA* allele will experience a cutaneous reaction.[47]

HLA class I genes are highly polymorphic.[51] Variants within these genes are thought to result in structural changes in the HLA complex that increase the recognition and subsequent response of the immune system to certain drugs, resulting in hypersensitivity. Reactions related to these variants tend to be dermatologic in nature with or without systemic involvement, ranging from a mild maculopapular rash or progressing to more severe cases of SJS and TEN.

Case 4-6, Question 2: What is the appropriate advice for the pharmacist to provide to J.C. given her presentation?

J.C. should be advised to seek care immediately at the closest and most accessible hospital emergency department. SJS and TEN have significant associated complications and typically require inpatient treatment with fluids, corticosteroids, analgesics, nutritional supplementation, and antibiotics. Mortality rates with TEN are estimated to be >30%.[48] In all cases, the suspected offending agent should be discontinued with no rechallenge.

Case 4-6, Question 3: In questioning J.C., the pharmacist learns that she has no prior history of adverse drug or food reactions. She is of Chinese descent and has never had genetic testing. What would have been an appropriate course of action for a patient with J.C.'s history before starting carbamazepine therapy?

Differing from CYP enzyme genotypes, HLA phenotypes do not lie on a spectrum, and patients are reported as positive if at least one variant is present or negative if no variant is present. Carriers of certain *HLA* variants are at increased risk for cutaneous ADRs; however, recommendations and guidelines for preemptive testing are either nonspecific or lacking. Other *HLA* variants have been linked to liver injury, leading to the theory that the amount and location of HLA expression may be a determining factor relating to which organ systems are affected.[51] Determining when and whom to test before therapy is typically left to the discretion of the provider or institution-specific protocols. The exception to this is for the HIV drug abacavir, for which CPIC and the U.S. Food and Drug Administration (FDA) recommendations state that all patients should have *HLA-B*57:01* testing before initiating regimens with either of these therapies.[52]

Variants of the *HLA* genes are seen more commonly within certain ethnicities. In some cases, owing to the high prevalence of allele carrier status in these populations, patients with particular ethnic backgrounds may be recommended for testing. Certain Asian populations are known to have higher rates of certain variants, warranting caution when using certain therapies (**Table 4-6**). In the case of carbamazepine and J.C., her physician may have justifiably

ordered pharmacogenomic testing to determine her *HLA-B*15:02* carrier status based on the fact that she identifies as Chinese. Relying on self-reported ethnicity can be problematic, however, because many people are not fully knowledgeable of their complete lineage.

Table 4-6
***HLA* Variants, Affected Drugs, and Population Incidence**

***HLA* Variant**	**Drugs With Associated Adverse Cutaneous Reactions**	**Highest Variant Frequencies by Ethnicity[48,54–57]**
*HLA-B*57:01*	Abacavir	Caucasian: 5%–8%
*HLA-B*58:01*	Allopurinol	Han Chinese: 6%–8% Korean: 12%
*HLA-B*15:02*	Phenytoin, carbamazepine	Han Chinese: ~10% Populations from Hong Kong, Thailand, Malaysia, Vietnam, Philippines, India, and Indonesia: >5%
*HLA-A*31:01*	Carbamazepine	Northern European: 2%–5% Japanese: up to 17.5%

HLA, human leukocyte antigen.

Sources: Karnes JH, Rettie AE, Somogyi AA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and HLA-B genotypes and phenytoin dosing: 2020 update. *Clin Pharmacol Ther*. 2021;109(2):302–309. doi:10.1002/cpt.2008; Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. *Clin Pharmacol Ther*. 2018;103(4):574–581. doi:10.1002/cpt.1004; Martin MA, Hoffman JM, Freimuth RR, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing: 2014 update. *Clin Pharmacol Ther*. 2014;95(5):499–500. doi:10.1038/clpt.2014.38; Saito Y, Stamp LK, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. *Clin Pharmacol Ther*. 2016;99(1):36–37. doi:10.1002/cpt.161.

Testing recommendations vary, but if a patient is a known carrier of an *HLA* variant, it is recommended that they avoid the use of

drugs for which there is an *HLA*-variant–associated risk of adverse reaction.[40,47,52,53]

CYP2D6 PECULIARITIES

CASE 4-7

Question 1: P.F. is a 37-year-old-female with a history of depression and anxiety who presents to the local pharmacy with a printed report from a for-profit pharmacogenomic testing company. The report states that P.F. is an extensive metabolizer for CYP2D6, and she is concerned that her paroxetine is still not providing any relief of her depressive symptoms despite having taken the drug correctly for the past 3 months.

What information would you want to know about the testing modality the company used before answering her question regarding the interpreted genotype?

There are several pharmacogenomic testing platforms, with the majority of commercially available panels being SNP based. The advantages of SNP-based platforms include lower cost, faster turnaround time, vendor-provided interpretation software, and reliable calling for known variants. The main disadvantage of SNP-based platforms is that they are only capable of delivering results for the genes and specific variants on the panel. If a person carries any unique or rare variants, the SNP-based panel will not detect them. This scenario increases the risk of there being a discrepancy between a patient's reported genotype and phenotype, or how they actually process and/or respond to drugs affected by the variant. *CYP2D6* is also a very polymorphic gene, and it is not uncommon for individuals to carry more than two allele copies. Differences in the *CYP2D6* copy number is referred to as *copy number variation (CNV)*, and knowing the CNV is extremely important in interpreting a person's *CYP2D6* genotype.[58] Once CNV is determined, all of the allele copies identified should be genotyped, which is not always possible on commercially available assays because the process

requires extra primers. Another issue is that *CYP2D7* is a pseudogene (a gene with no function) that can accidentally be included in the *CYP2D6* analysis if the assay is not designed correctly.[59]

In addition to targeted SNP-based assays, pharmacogenetic data can come from other types of genetic tests. The coding region of DNA is the exome, and whole-exome sequencing or assays targeting specific regions of interest within the exome can provide significant pharmacogenomic data. With exome sequencing, uncommon or previously unidentified variants could be reported, often deemed variants of unknown significance (VUS) because their clinical effects are not yet known. Because there remains a lot of variability in how exomes are analyzed and reported, both sensitivity and specificity of results are mutable. As a result, it can be a challenge to manage and meaningfully interpret exome findings, particularly when a distinct phenotype cannot be readily correlated. In addition, exome- and whole-genome sequencing can yield incidental or secondary findings of disease-state markers. The hybrid test, a sequence-based targeted panel of pharmacogenes, has become a hot area of development, attempting to incorporate the best features of both sequencing and limited gene interrogation.

P.F.'s report shows a genotype of *CYP2D6 *1/*2* but does not indicate the copy number of the *CYP2D6* gene. This is a red flag for interpretation and should prompt the pharmacist to call the company to obtain a detailed explanation of the assay used and understand how P.F.'s extensive metabolizer phenotype was determined.

Case 4-7, Question 2: Per the company, P.F.'s copy number was equal to 3. Does this information change the interpretation of P.F.'s phenotype?

A *CYP2D6* copy number of 3 with **1/*2* alleles is associated with the ultrarapid metabolizer phenotype.[58] Unique to *CYP2D6*, an activity score is calculated based on the number of copies of the gene present because all influence drug metabolism. The activity score was introduced by Gaedigk in 2013 to better categorize the

metabolism status of persons with extra copies of the gene.[60] An example of how CNV can change a phenotype is represented in **Table 4-7**.

Table 4-7
***CYP2D6* Genotypes, Phenotypes and Activity Scores**[58-60]

Number of Copies	Genotype	Activity Score	Phenotype
1	*1/*5	1	Intermediate metabolizer
2	*1/*2	2.0	Normal metabolizer
>2	*1/*2	>2.0	Ultrarapid metabolizer

Gaedigk A. Complexities of CYP2D6 gene analysis and interpretation. *Int Rev Psychiatry*. 2013;25(5):534–553. doi:10.3109/09540261.2013.825581; Riffel AK, Dehghani M, Hartshorne T, et al. CYP2D7 sequence variation interferes with TaqMan CYP2D6 (*) 15 and (*) 35 genotyping. *Front Pharmacol*. 2015;6:312. doi:10.3389/fphar.2015.00312; Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing CYP2D6 genotype to phenotype translation: consensus recommendations from the clinical pharmacogenetics implementation consortium and Dutch Pharmacogenetics Working Group. *Clin Transl Sci*. 2020;13(1):116–124. doi:10.1111/cts.12692.

As an ultrarapid metabolizer, P.F.'s lack of response to a standard paroxetine dose aligns with her phenotype. Per the associated CPIC guideline, her provider should choose another drug not primarily metabolized via the CYP2D6 pathway.[61] Because P.F. spent 3 months taking a medication with no response, this case serves as a prime example of the important role pharmacogenomic data can play in guiding treatment choices before initiating therapy.

CASE 4-8

QUESTION 1: You have started to work at a pediatric hospital and notice that codeine is not orderable in the electronic medical record. When you ask a coworker, he informs you that the black box warning placed on all codeine products by the FDA in 2012 has resulted in the majority of pediatric institutions removing the drug from formularies.

What specific genotype is correlated with the risk of life-threatening apnea with codeine use?

Codeine is metabolized by CYP2D6 to the active metabolite morphine, which provides analgesic properties. CYP2D6 ultrarapid metabolizers can generate morphine at higher rates, exceeding the body's ability to convert it to less toxic metabolites and resulting in life-threatening apnea.[62] Approximately 4% of the population are thought to be CYP2D6 ultrarapid metabolizers.[63]

In contrast, there are several loss-of-function variants across ethnicities that confer little to no CYP2D6 enzyme function, resulting in a lack of morphine formation. The loss-of-function **4* allele, for example, is found in 6% of African Americans, 5% of Asians, and in up to 18% of European Americans/Europeans.[63] Patients carrying loss-of-function *CYP2D6* alleles are likely to show decreased response to codeine.[64]

IMPACT OF PEDIATRIC ENZYME DEVELOPMENT ON PHARMACOGENOMICS

CASE 4-9

QUESTION 1: As part of a voluntary research study in the neonatal intensive care unit (NICU), pharmacogenomic results are returned to the provider for an ex-30 week, 36.5-week corrected gestational age female. The provider notes that her genotype for CYP2C19 is *17/*17, which would typically indicate that she is an ultrarapid metabolizer for this enzyme. The provider states he would like to start her on voriconazole for a presumed fungal infection and asks what the dosing should be given her genotype.

What other information would be necessary to recommend a voriconazole dose for this infant?

Voriconazole is metabolized via multiple enzyme pathways including CYP3A4, CYP2C9, and CYP2C19, with the most significant contribution coming from CYP2C19.[65] The Royal Dutch

Pharmacists Association has guidelines in place recommending monitoring of voriconazole serum concentrations for CYP2C19-poor and CYP2C19-intermediate metabolizers because these patients have been found to have higher concentrations of active drug and increased risk of toxicity. The consideration for a person with the *CYP2C19 *17/*17* is the potential for increased breakdown of active drug and treatment failure.[66]

Given this patient's young age, multiple complex factors need to be considered for dosing, both genetic and nongenetic. Because voriconazole is dosed by body weight, the actual body weight of the child is necessary for an appropriate dose calculation. Drug–drug interactions should also be considered if the patient is taking medications that induce or inhibit enzymes in the drug's pathway. Other variables contributing to complicated infant dosing and clearance unpredictability include developing GI and renal function and fluctuations in body fat and water composition affecting density of drug distribution.[67] In addition, although the patient's genotype suggests she will have increased breakdown of the active drug, it is known that, regardless of genotype, humans are not born with fully functional CYP enzymes.[67,68]

CYP enzyme development occurs at variable rates over time, making it difficult to determine the contribution of pharmacogenomic variants on optimal dosing (**Fig. 4-3**).[69-71] An excellent summary review of enzyme maturation by Kearns and colleagues was published in the *New England Journal of Medicine* in 2003.[67] CYP1A2, for example, is virtually undetectable at birth, with initial development of low-level enzyme concentrations being seen over the first month of life. Although general trends are observed, it is also understood that development rates vary among individuals throughout childhood, particularly in the first year of life.[67] Given this consideration, pharmacogenomics in the neonatal and infant population may be a less influential factor than it is in older children and adults, and its overall contribution remains unpredictable because few studies are dedicated to the effects of pharmacogenomic variants in the youngest patients. Therefore, it is particularly important to monitor drug concentrations, response, and

toxicities in the younger pediatric population and to dose adjust accordingly. Voriconazole is of particular concern with this group because evidence suggests that current pediatric dosing recommendations could lead to subtherapeutic concentrations and a general increased risk of treatment failure.[72]

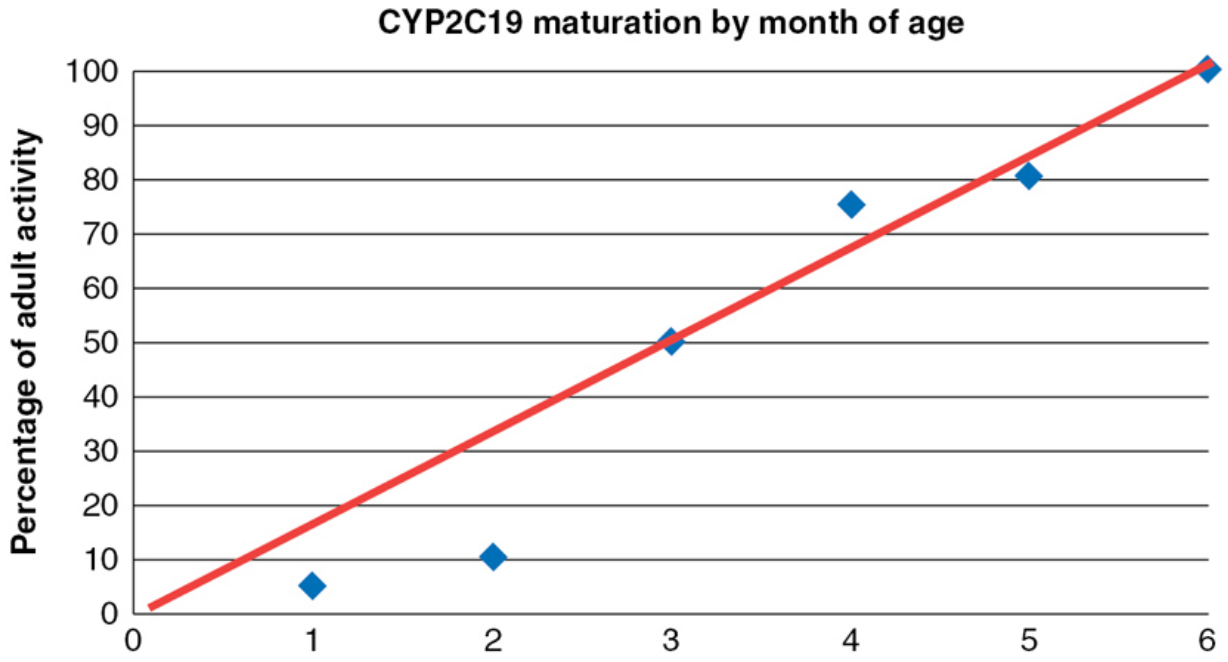


Figure 4-3 CYP2C19 enzyme activity by age. (Adapted from Ward RM, Kearns GL. Proton pump inhibitors in pediatrics: mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. *Paediatr Drugs*. 2013;15(*2*):119–131. doi:10.1007/s40272-013-0012-x; Koukouritaki SB, Manro JR, Marsh SA, et al. Developmental expression of human hepatic CYP2C9 and CYP2C19. *J Pharmacol Exp Ther*. 2004;308(*3*):965–974. doi:10.1124/jpet.103.060137.)

FAMILIAL IMPLICATIONS OF PHARMACOGENETICS

CASE 4-10

QUESTION 1: H.T. is a 12-year-old female who had an operation resulting in the development of malignant hyperthermia (MH). Following recovery, she is found to have a pathogenic SNP variant (mutation) at the 7300 nucleotide (referred to as c.7300G>A) in the *RYR1* gene, a common variant associated with predisposition to MH. H.T.'s providers discuss the influence of this finding on her future medical and drug management.

What additional clinical considerations should her providers address following H.T.'s genetic findings and presentation?

Genes are inherited, so any discussion relating to clinically significant genetic variants should also include raising awareness of the variant's implications beyond the patient who was tested. In the case of H.T., the mutation associated with MH is dominant, the clinical consequence can be life-threatening, and the likelihood of inheritance is high. Counseling and testing of parents and extended family members could therefore be recommended. When an individual is being counseled on pharmacogenomic testing results before any related incident, it is important to raise the possibility that the results could have implications for the greater family.[73]

MAKING THE CASE FOR PHARMACOGENOMICS

In general, several studies have shown that patients are more adherent with their medication regimes after receiving personalized genotyping results, even if the findings show "normal" enzyme function.[74] Because medication adherence is an ongoing challenge in optimizing patient care, pharmacogenomic testing could offer a potential incentive.

An increased understanding of pharmacogenomics has also allowed pharmaceutical companies to design and develop drugs that specifically target protein changes associated with certain mutations, making regimens more personalized and effective. To determine whether a patient will benefit from these targeted therapies,

companion tests (pharmacogenetic assays that target the variants of interest) are usually required. A pharmacist must understand which medications require companion testing and know how to interpret and apply the associated results. Possible hurdles for companion testing requirements by drug manufacturers may include the potential wait time in getting insurance approval for the companion test that could delay care.

CASE 4-11

QUESTION 1: K.D. is a 22-year-old female with cystic fibrosis. Her pulmonologist is interested in prescribing the drug ivacaftor. K.D. comes to the pharmacy and mentions the need for a special test before starting this new treatment, but she cannot remember why the test is necessary.

What test is K.D. likely getting to determine whether she is eligible to receive ivacaftor?

Ivacaftor (Kalydeco®) is a drug used to treat cystic fibrosis, and it acts at the cystic fibrosis transmembrane conductance regulator (CFTR) channel. CFTR protein is found on a variety of tissue surfaces, including the lungs. When functioning properly, the CFTR protein is a key component in maintaining intracellular salt balance.[75] Cystic fibrosis results from a variety of possible genetic mutations, causing dysfunctional CFTR protein and leading to fluid imbalances, the buildup of secretions, and several related complications.

Kalydeco® is an oral agent approved for patients with cystic fibrosis carrying 10 specific variants in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *R117H*, *S1251N*, *S1255P*, *S549N*, and *S549R*. For this subset of patients, the drug acts as a CFTR potentiator, increasing CFTR activity, restoring electrolyte balance, reducing the buildup of secretions, and improving health outcomes, such as pulmonary function and weight gain for affected patients.[76] For patients with cystic fibrosis affected by other mutations, the drug will be ineffective. K.D.'s doctor likely ordered a genetic test to determine which mutation was the cause of her cystic fibrosis diagnosis.

Ivacaftor was approved in 2012 for patients with the *G551D* mutation, offering promise for continued future development of therapies targeting the underlying causes of genetic diseases. This promise remains encouraging because the use of ivacaftor has since been approved in the treatment of several additional gene mutations. In addition, new similar targeted therapies such as lumacaftor (Orkambi™), a CFTR corrector, and combination products such as elexacaftor/tezacaftor/ivacaftor (Trikafta™) continue to enter the market.[77]

Another potential use of pharmacogenomics involves salvaging drugs with high toxicity profiles. Historically, many drugs have been taken off the market after an unacceptable number of patients either suffered significant morbidity or mortality secondary to the use of the drug. In some cases, pharmacogenomic studies may be able to determine which patients could continue to benefit from the drug and which patients should avoid use.

Despite the many advances in testing and clinical application, preemptive pharmacogenomic testing before the development of an adverse effect or lack of response is not currently widely used, for several reasons. A major barrier comes from the fact that health care professionals, including pharmacists, lack the knowledge necessary to apply pharmacogenomic data. One recent study found that only 29% of the physicians surveyed received any formal education around pharmacogenomics, and only 10.3% felt knowledgeable enough to prescribe or discuss the results of pharmacogenomic testing.[78] Another large impediment to implementation is the lack of consistent reimbursement policies by insurance providers. To achieve widespread and consistent pharmacogenomic testing coverage by insurance companies, there is a need for concerted regulatory efforts and continued proof that pharmacogenomic testing improves outcome and decreases cost.[2,15,79]

At this time, the majority of preemptive pharmacogenomic testing is happening in places where there is institutional support of targeted program development, such as academic medical and cancer centers, or where programs can directly bill patients for services not

covered by insurance, as is seen with for-profit pharmacogenomic testing companies.

Case 4-11, Question 2: What references could be used to assist pharmacists and providers in interpreting pharmacogenomic results and applying any variant findings to subsequent drug dosing decisions?

The FDA and European Medicines Agency (EMA) currently list pharmacogenomic markers in 326 and 78 drug labels, respectively.[80,81] To be included in the FDA labeling, a pharmacogenomic marker must have known clinical consequence, such as an increase in adverse effects or reduction in efficacy, or actionable recommendations for alternative treatment or dose modification. In addition, as referenced earlier, PharmGKB, CPIC, and DPWG provide a valuable and accessible resource for pharmacists.

Incorporating pharmacogenomic data into electronic medical record systems is challenging. Result reports from laboratories capable of running these tests are rarely in a machine-readable format and are generally delivered as PDF documents to be scanned into a patient's chart.[82] This scenario presents a major systemic challenge in being able to provide relevant pharmacogenomic data at the time they are most needed, during the drug prescribing and dispensing processes. Pharmacogenomic results remain relevant throughout a person's lifetime and require significant bioinformatics expertise to house, retrieve, interpret, and present to the end user at the right time.[83] To ensure that the most recent variant knowledge is being applied, it is also important to track the evolution of testing options over time. It is possible that updated analyses could be needed, such as sequencing a new sample or reprocessing a previous sample with new algorithms. A payment model for reinterpretation without retesting is extremely uncommon in the field of laboratory medicine today.

Other extremely important considerations around housing, storing, and using pharmacogenomic data include security and privacy. Data

security refers to protection of information from breaches and inadvertent dissemination, whereas data privacy relates to respecting patient preferences for data sharing, both with the patient directly as well as with the larger health care community. The recent European Union (EU) implementation of the General Data Protection Regulation (GDPR) is of particular interest in this realm given its focus on digital data (https://gdpr-info.eu/ [accessed February 15, 2022]). The GDPR was designed to ensure that personal data are gathered legally and under strict conditions. In addition, those who collect and manage personal data are obliged to protect it from misuse and exploitation, as well as to respect the rights of data owners with reach beyond the EU.

Ultimately, how is the decision made to offer and incorporate pharmacogenomic testing into practice? In a nonideal scenario, health care providers have no choice when patients hand them a printed report from direct-to-consumer pharmacogenetic testing services. These patients look to their health care team to consider the results when prescribing and dispensing decisions are made, making pharmacogenomic knowledge critical. Academic medical programs have begun to incorporate pharmacogenomic science into core curricula, but it is often in the form of a single 1- to 2-hour lecture. This level of training will be inadequate in preparing providers to deal with the era of personalized medicine and the eventual day when everyone will have access to their own genomic data.

When assessing the value of incorporating pharmacogenomic testing into practice, several factors impact the return on investment and influence on clinical outcomes. These factors include, but are not limited to, the number of patients needed to be tested to find one patient with an actionable variant, ethnic variation given that populations are now blended and clear ancestry knowledge is often lacking, the cost of testing, the likelihood of insurance reimbursement, and the cost savings offset by averting serious adverse reactions or nonresponse.[79]

Genetic testing can also introduce challenging ethical questions, particularly when dealing with broader tests covering large sections

of DNA such as whole-exome or whole-genome sequencing. Although most people want to know whether they should take a medication, many do not wish to know their risk of developing Alzheimer disease or breast cancer. The American College of Medical Genetics (ACMG) updated a position statement relating to this topic in 2021, listing a total of 73 genes with pathogenic variants causing specific defined diseases when tested, irrespective of the age of the patient.[84] However, consent should be obtained to fully inform the patient and/or their parent(s)/legal guardian(s) of the implications, including with respect to the risks to them and their relatives of developing the disorders and the potential for insurance discrimination based on pathogenic findings.[85,86] Although the 2008 Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance coverage to be denied because of genetic findings, there is no protection for life or long-term care insurance coverage.[87]

CONCLUSION

Pharmacogenomics is simultaneously an exciting and a challenging component of personalized medicine and the practice of pharmacy. One of the most important points to remember when working with pharmacogenomic data is that they serve as an additional clinical marker but are rarely the only answer. A patient's organ function, disease state, diet, smoking status, other environmental factors, and drug–drug interactions play a very large role in the disposition of drugs. Age-based maturation of enzyme function must also be accounted for when determining the impact of the genotype on drug metabolism in younger pediatric patients.

Pharmacists are uniquely qualified to interpret and apply pharmacogenetic findings to medication selection and dosing decisions. To adequately fulfill this role in a clinical setting, pharmacists need focused education on the topic of pharmacogenomics, understanding of how to apply validated algorithms, access to continually updated literature, and a

partnership with genetic experts, including geneticists and genetic counselors.[88] This chapter has only briefly touched upon examples of actionable pharmacogenes. The following key references and websites provide extensive information for further study.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Gaedigk A. Complexities of CYP2D6 gene analysis and interpretation. *Int Rev Psychiatry.* 2013;25(5):534–553. doi:10.3109/09540261.2013.825581 (58)

Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157–1167. doi:10.1056/NEJMra035092 (67)

Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther*. 2013;17:165–184. doi:10.1007/s40291-013-0028-5 (7)

Key Websites

FDA gene list, https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

The *All of Us* Research Program (formerly named the Precision Medicine Initiative Cohort Program), https://allofus.nih.gov/

PharmGKB.org, http://www.pharmgkb.org

Warfarin dosing, http://www.warfarindosing.org/Source/Home.aspx

COMPLETE REFERENCES CHAPTER 4 Pharmacogenomics and Personalized Medicine

1. Hansen NT, Brunak S, Altman RB. Generating genome-scale candidate gene lists for pharmacogenomics. *Clin Pharmacol Ther*. 2009;86(2):183–189. doi:10.1038/clpt.2009.42
2. Shabaruddin FH, Fleeman ND, Payne K. Economic evaluations of personalized medicine: existing challenges and current developments. *Pharmacogenomics Pers Med*. 2015;8:115–126. doi:10.2147/PGPM.S35063
3. Scott SA. Personalizing medicine with clinical pharmacogenetics. *Genet Med*. 2011;13(12):987–995. doi:10.1097/GIM.0b013e318238b38c
4. Motulsky AG. Drug reactions enzymes, and biochemical genetics. *J Am Med Assoc*. 1957;165(7):835–837. doi:10.1001/jama.1957.72980250010016
5. Wessler S, Avioli LV. Pharmacogenetics. Glucose-6-phosphate dehydrogenase deficiency. *JAMA*. 1968;205(10):679–683. doi:10.1001/jama.205.10.679
6. Zhmud L. *Pythagoras and the Early Pythagoreans*. OUP Oxford; 2012.
7. Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther*. 2013;17(3):165–184. doi:10.1007/s40291-013-0028-5
8. Sim SC, Ingelman-Sundberg M. The Human Cytochrome P450 (CYP) Allele Nomenclature website: a peer-reviewed database of CYP variants and their associated effects. *Hum Genomics*. 2010;4(4):278–281. doi:10.1186/1479-7364-4-4-278
9. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279(15):1200–1205. doi:10.1001/jama.279.15.1200
10. Watanabe JH, McInnis T, Hirsch JD. Cost of prescription drug-related morbidity and mortality. *Ann Pharmacother*. 2018;52(9):829–837. doi:10.1177/1060028018765159
11. Institute of Medicine (US) Committee on Quality of Health Care in America. *To Err Is Human: Building a Safer Health System* (Kohn LT, Corrigan JM, Donaldson MS, eds.). National Academies Press (US); 2000. Accessed January 28, 2022. http://www.ncbi.nlm.nih.gov/books/NBK225182/
12. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Intern Med*. 2016;176(4):473–482. doi:10.1001/jamainternmed.2015.8581
13. Sikka R, Magauran B, Ulrich A, Shannon M. Bench to bedside: pharmacogenomics, adverse drug interactions, and the cytochrome P450

system. *Acad Emerg Med*. 2005;12(12):1227–1235. doi:10.1197/j.aem.2005.06.027

14. Luo S, Jiang R, Grzymski JJ, Lee W, Lu JT, Washington NL. Comprehensive allele genotyping in critical pharmacogenes reduces residual clinical risk in diverse populations. *Clin Pharmacol Ther*. 2021;110(3):759–767. doi:10.1002/cpt.2279
15. Beitelshees AL, Veenstra DL. Evolving research and stakeholder perspectives on pharmacogenomics. *JAMA*. 2011;306(11):1252–1253. doi:10.1001/jama.2011.1343
16. Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab*. 2014;15(2):209–217. doi:10.2174/1389200215666140130124910
17. Caudle KE, Gammal RS, Whirl-Carrillo M, Hoffman JM, Relling MV, Klein TE. Evidence and resources to implement pharmacogenetic knowledge for precision medicine. *Am J Health Syst Pharm*. 2016;73(23):1977–1985. doi:10.2146/ajhp150977
18. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med*. 2003;167(4):603–662. doi:10.1164/rccm.167.4.603
19. Khan S, Mandal RK, Elasbali AM, et al. Pharmacogenetic association between NAT2 gene polymorphisms and isoniazid induced hepatotoxicity: trial sequence meta-analysis as evidence. *Biosci Rep*. 2019;39(1):BSR20180845. doi:10.1042/BSR20180845
20. Wang P, Pradhan K, Zhong XB, Ma X. Isoniazid metabolism and hepatotoxicity. *Acta Pharm Sin B*. 2016;6(5):384–392. doi:10.1016/j.apsb.2016.07.014
21. Daly AK. Drug-induced liver injury: past, present and future. *Pharmacogenomics*. 2010;11(5):607–611. doi:10.2217/pgs.10.24
22. Sim E, Abuhammad A, Ryan A. Arylamine N-acetyltransferases: from drug metabolism and pharmacogenetics to drug discovery. *Br J Pharmacol*. 2014;171(11):2705–2725. doi:10.1111/bph.12598
23. Pasipanodya JG, Srivastava S, Gumbo T. Meta-analysis of clinical studies supports the pharmacokinetic variability hypothesis for acquired drug resistance and failure of antituberculosis therapy. *Clin Infect Dis*. 2012;55(2):169–177. doi:10.1093/cid/cis353
24. Sun F, Chen Y, Xiang Y, Zhan S. Drug-metabolising enzyme polymorphisms and predisposition to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int J Tuberc Lung Dis*. 2008;12(9):994–1002.
25. Wang PY, Xie SY, Hao Q, Zhang C, Jiang BF. NAT2 polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int J Tuberc Lung Dis*. 2012;16(5):589–595. doi:10.5588/ijtld.11.0377

26. Ben Mahmoud L, Ghozzi H, Kamoun A, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatotoxicity in Tunisian patients with tuberculosis. *Pathol Biol (Paris)*. 2012;60(5):324–330. doi:10.1016/j.patbio.2011.07.001
27. Du H, Chen X, Fang Y, et al. Slow N-acetyltransferase 2 genotype contributes to anti-tuberculosis drug-induced hepatotoxicity: a meta-analysis. *Mol Biol Rep*. 2013;40(5):3591–3596. doi:10.1007/s11033-012-2433-y
28. Huang YS, Chern HD, Su WJ, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatol Baltim Md*. 2002;35(4):883–889. doi:10.1053/jhep.2002.32102
29. Azuma J, Ohno M, Kubota R, et al. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy. *Eur J Clin Pharmacol*. 2013;69(5):1091–1101. doi:10.1007/s00228-012-1429-9
30. Keller GA, Fabian L, Gomez M, Gonzalez CD, Diez RA, Di Girolamo G. Age-distribution and genotype-phenotype correlation for N-acetyltransferase in Argentine children under isoniazid treatment. *Int J Clin Pharmacol Ther*. 2014;52(4):292–302. doi:10.5414/CP201957
31. Rost S, Fregin A, Ivaskevicius V, et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature*. 2004;427(6974):537–541. doi:10.1038/nature02214
32. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. *Clin Pharmacol Ther*. 2017;102(3):397–404. doi:10.1002/cpt.668
33. Caldwell MD, Awad T, Johnson JA, et al. CYP4F2 genetic variant alters required warfarin dose. *Blood*. 2008;111(8):4106–4112. doi:10.1182/blood-2007-11-122010
34. Limdi NA, Brown TM, Yan Q, et al. Race influences warfarin dose changes associated with genetic factors. *Blood*. 2015;126(4):539–545. doi:10.1182/blood-2015-02-627042
35. Van Booven D, Marsh S, McLeod H, et al. Cytochrome P450 2C9-CYP2C9. *Pharmacogenet Genomics*. 2010;20(4):277–281. doi:10.1097/FPC.0b013e3283349e84
36. Millares-Sipin CA, Alafris A, Cohen H. Phenytoin and fosphenytoin. In: Cohen H, eds. *Casebook in Clinical Pharmacokinetics and Drug Dosing*. McGraw Hill; 2015. Accessed March 31, 2022. https://accesspharmacy.mhmedical.com/content.aspx?bookid=1514&sectionid=88805062
37. Patocka J, Wu Q, Nepovimova E, Kuca K. Phenytoin—an anti-seizure drug: overview of its chemistry, pharmacology and toxicology. *Food Chem Toxicol*. 2020;142:111393. doi:10.1016/j.fct.2020.111393

38. Claesen M, Moustafa MA, Adline J, Vandervorst D, Poupaert JH. Evidence for an arene oxide-NIH shift pathway in the metabolic conversion of phenytoin to 5-(4-hydroxyphenyl)-5-phenylhydantoin in the rat and in man. *Drug Metab Dispos*. 1982;10(6):667–671.
39. Komatsu T, Yamazaki H, Asahi S, et al. Formation of a dihydroxy metabolite of phenytoin in human liver microsomes/cytosol: roles of cytochromes P450 2C9, 2C19, and 3A4. *Drug Metab Dispos*. 2000;28(11):1361–1368.
40. Karnes JH, Rettie AE, Somogyi AA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and HLA-B genotypes and phenytoin dosing: 2020 update. *Clin Pharmacol Ther*. 2021;109(2):302–309. doi:10.1002/cpt.2008
41. Sandborn WJ. A review of immune modifier therapy for inflammatory bowel disease: azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate. *Am J Gastroenterol*. 1996;91(3):423–433.
42. Eklund BI, Moberg M, Bergquist J, Mannervik B. Divergent activities of human glutathione transferases in the bioactivation of azathioprine. *Mol Pharmacol*. 2006;70(2):747–754. doi:10.1124/mol.106.025288
43. Rufo PA, Bousvaros A. Current therapy of inflammatory bowel disease in children. *Paediatr Drugs*. 2006;8(5):279–302. doi:10.2165/00148581-200608050-00002
44. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther*. 2019;105(5):1095–1105. doi:10.1002/cpt.1304
45. Zuckner J. Drug-related myopathies. *Rheum Dis Clin North Am*. 1994;20(4):1017–1032.
46. Ramsey LB, Johnson SG, Caudle KE, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. *Clin Pharmacol Ther*. 2014;96(4):423–428. doi:10.1038/clpt.2014.125
47. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. *Clin Pharmacol Ther*. 2018;103(4):574–581. doi:10.1002/cpt.1004
48. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med*. 2011;364(12):1134–1143. doi:10.1056/NEJMoa1013297
49. Shiina T, Inoko H, Kulski JK. An update of the HLA genomic region, locus information and disease associations: 2004. *Tissue Antigens*. 2004;64(6):631–649. doi:10.1111/j.1399-0039.2004.00327.x
50. Wilson JT, Höjer B, Tomson G, Rane A, Sjöqvist F. High incidence of a concentration-dependent skin reaction in children treated with phenytoin. *Br Med J*. 1978;1(6127):1583–1586. doi:10.1136/bmj.1.6127.1583

51. Pirmohamed M, Ostrov DA, Park BK. New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity. *J Allergy Clin Immunol*. 2015;136(2):236–244. doi:10.1016/j.jaci.2015.06.022
52. Martin MA, Hoffman JM, Freimuth RR, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and abacavir dosing: 2014 update. *Clin Pharmacol Ther*. 2014;95(5):499–500. doi:10.1038/clpt.2014.38
53. Saito Y, Stamp LK, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. *Clin Pharmacol Ther*. 2016;99(1):36–37. doi:10.1002/cpt.161
54. Ma JD, Lee KC, Kuo GM. HLA-B*5701 testing to predict abacavir hypersensitivity. *PLoS Curr*. 2010;2:RRN1203. doi:10.1371/currents.RRN1203
55. Dean L, Kane M. Allopurinol therapy and HLA-B*58:01 genotype. In: Pratt VM, Scott SA, Pirmohamed M, et al, eds. *Medical Genetics Summaries*. National Center for Biotechnology Information (US); 2012. Accessed January 28, 2022. http://www.ncbi.nlm.nih.gov/books/NBK127547/
56. Ferrell PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics*. 2008;9(10):1543–1546. doi:10.2217/14622416.9.10.1543
57. Mushiroda T, Takahashi Y, Onuma T, et al. Association of HLA-A*31:01 screening with the incidence of carbamazepine-induced cutaneous adverse reactions in a Japanese population. *JAMA Neurol*. 2018;75(7):842–849. doi:10.1001/jamaneurol.2018.0278
58. Gaedigk A. Complexities of CYP2D6 gene analysis and interpretation. *Int Rev Psychiatry*. 2013;25(5):534–553. doi:10.3109/09540261.2013.825581
59. Riffel AK, Dehghani M, Hartshorne T, et al. CYP2D7 sequence variation interferes with TaqMan CYP2D6 (*) 15 and (*) 35 genotyping. *Front Pharmacol*. 2015;6:312. doi:10.3389/fphar.2015.00312
60. Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing CYP2D6 genotype to phenotype translation: consensus recommendations from the clinical pharmacogenetics implementation consortium and Dutch Pharmacogenetics Working Group. *Clin Transl Sci*. 2020;13(1):116–124. doi:10.1111/cts.12692
61. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther*. 2015;98(2):127–134. doi:10.1002/cpt.147
62. Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med*. 2004;351(27):2827–2831. doi:10.1056/NEJMoa041888

63. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. *Clin Pharmacol Ther*. 2021;110(4):888–896. doi:10.1002/cpt.2149
64. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metab Rev*. 2009;41(2):89–295. doi:10.1080/03602530902843483
65. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet*. 2006;45(7):649–663. doi:10.2165/00003088-200645070-00002
66. Abidi MZ, D'Souza A, Kuppalli K, Ledeboer N, Hari P. CYP2C19*17 genetic polymorphism—an uncommon cause of voriconazole treatment failure. *Diagn Microbiol Infect Dis*. 2015;83(1):46–48. doi:10.1016/j.diagmicrobio.2015.05.002
67. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157–1167. doi:10.1056/NEJMra035092
68. Lu H, Rosenbaum S. Developmental pharmacokinetics in pediatric populations. *J Pediatr Pharmacol Ther*. 2014;19(4):262–276. doi:10.5863/1551-6776-19.4.262
69. Sadler NC, Nandhikonda P, Webb-Robertson BJ, et al. Hepatic cytochrome P450 activity, abundance, and expression throughout human development. *Drug Metab Dispos*. 2016;44(7):984–991. doi:10.1124/dmd.115.068593
70. Ward RM, Kearns GL. Proton pump inhibitors in pediatrics: mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. *Paediatr Drugs*. 2013;15(2):119–131. doi:10.1007/s40272-013-0012-x
71. Koukouritaki SB, Manro JR, Marsh SA, et al. Developmental expression of human hepatic CYP2C9 and CYP2C19. *J Pharmacol Exp Ther*. 2004;308(3):965–974. doi:10.1124/jpet.103.060137
72. Brüggemann RJM, van der Linden JWM, Verweij PE, Burger DM, Warris A. Impact of therapeutic drug monitoring of voriconazole in a pediatric population. *Pediatr Infect Dis J*. 2011;30(6):533–534. doi:10.1097/INF.0b013e318204d227
73. Netzer C, Biller-Andorno N. Pharmacogenetic testing, informed consent and the problem of secondary information. *Bioethics*. 2004;18(4):344–360. doi:10.1111/j.1467-8519.2004.00401.x
74. Haga SB, LaPointe NMA. The potential impact of pharmacogenetic testing on medication adherence. *Pharmacogenomics J*. 2013;13(6):481–483. doi:10.1038/tpj.2013.33
75. Guggino WB, Banks-Schlegel SP. Macromolecular interactions and ion transport in cystic fibrosis. *Am J Respir Crit Care Med*. 2004;170(7):815–820. doi:10.1164/rccm.200403-381WS

76. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med*. 2013;187(11):1219–1225. doi:10.1164/rccm.201301-0153OC
77. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet Lond Engl*. 2019;394(10212):1940–1948. doi:10.1016/S0140-6736(19)32597-8
78. Stanek EJ, Sanders CL, Taber KAJ, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. *Clin Pharmacol Ther*. 2012;91(3):450–458. doi:10.1038/clpt.2011.306
79. Wu AC, Fuhlbrigge AL. Economic evaluation of pharmacogenetic tests. *Clin Pharmacol Ther*. 2008;84(2):272–274. doi:10.1038/clpt.2008.127
80. *Table of Pharmacogenomic Biomarkers in Drug Labeling. FDA*. Published online August 18, 2021. Accessed January 28, 2022. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
81. Ehmann F, Caneva L, Prasad K, et al. Pharmacogenomic information in drug labels: European Medicines Agency perspective. *Pharmacogenomics J*. 2015;15(3):201–210. doi:10.1038/tpj.2014.86
82. Bell GC, Crews KR, Wilkinson MR, et al. Development and use of active clinical decision support for preemptive pharmacogenomics. *J Am Med Inform Assoc*. 2014;21(e1):e93–e99. doi:10.1136/amiajnl-2013-001993
83. Rasmussen-Torvik LJ, Stallings SC, Gordon AS, et al. Design and anticipated outcomes of the eMERGE-PGx project: a multicenter pilot for preemptive pharmacogenomics in electronic health record systems. *Clin Pharmacol Ther*. 2014;96(4):482–489. doi:10.1038/clpt.2014.137
84. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1381–1390. doi:10.1038/s41436-021-01172-3
85. COMMITTEE ON BIOETHICS, COMMITTEE ON GENETICS, AND, AMERICAN COLLEGE OF MEDICAL GENETICS AND, GENOMICS SOCIAL, ETHICAL, LEGAL ISSUES COMMITTEE. Ethical and policy issues in genetic testing and screening of children. *Pediatrics*. 2013;131(3):620–622. doi:10.1542/peds.2012-3680
86. American College of Medical Genetics and Genomics. Incidental findings in clinical genomics: a clarification. *Genet Med*. 2013;15(8):664–666. doi:10.1038/gim.2013.82
87. Prince AER, Roche MI. Genetic information, non-discrimination, and privacy protections in genetic counseling practice. *J Genet Couns*. 2014;23(6):891–902. doi:10.1007/s10897-014-9743-2

88. Mills R, Haga SB. Clinical delivery of pharmacogenetic testing services: a proposed partnership between genetic counselors and pharmacists. *Pharmacogenomics*. 2013;14(8):957–968. doi:10.2217/pgs.13.76

5

Managing Drug Overdoses and Poisonings

Iris Sheinhait

CORE PRINCIPLES

GENERAL MANAGEMENT

CHAPTER CASES

1 The most important aspect of patient management is to support airway, breathing, and circulation (the “ABCs”). There is no “cookbook” method to treat all poisoned patients, so it is important to treat the patient, not the poison or the laboratory values. The assessment and treatment of the potentially poisoned patient can be separated into seven functions: (a) gather history of exposure, (b) evaluate clinical presentation (ie, “toxidromes”), (c) evaluate clinical laboratory patient data, (d) remove the toxic source (eg, irrigate eyes,

Case 5-4 (Questions 1, 3, 5, 6)

decontaminate exposed skin), (e) consider antidotes and specific treatment, (f) enhance systemic clearance, and (g) monitor patient outcome.

GASTROINTESTINAL DECONTAMINATION

1

The most appropriate method for gastrointestinal (GI) tract decontamination is unclear because sound comparative data for different methods of GI decontamination are not available. Lavage, emesis, and cathartics are rarely performed because there is no evidence that they improve patient outcome. Activated charcoal is generally safe to use, but it should not be administered if the benefit is not greater than the risk. Whole-bowel irrigation using a polyethylene glycol–balanced electrolyte solution can successfully remove substances (iron, lithium, sustained-release dosage forms) from the entire GI tract in a period of several hours.

Case 5-3 (Questions 6, 7)
Case 5-4 (Questions 11, 12, 16)
Case 5-5 (Question 3)

ANTIDOTES

1

An antidote is a drug that reverses the toxicity of another substance. Some antidotes displace drugs from receptor sites (eg, naloxone for opioids, flumazenil for benzodiazepines), and some can inhibit the formation of toxic metabolites (eg, *N*-acetylcysteine [NAC]

Case 5-4 (Questions 2, 4)

for acetaminophen, fomepizole for ethylene glycol and methanol).

TOXICOLOGY LABORATORY SCREENING

1

Urine drug screens can be useful in a patient with coma of unknown etiology, when the presented history is inconsistent with clinical findings, or when more than one drug might have been ingested. Qualitative screening is intended to identify unknown substances involved in the toxic exposure. A benzodiazepine screen can detect oxazepam, a common benzodiazepine metabolite, but it will not detect alprazolam and lorazepam because they are not metabolized to oxazepam. Opioid screens may not detect synthetic opioids such as fentanyl and methadone. Quantitative testing determines how much of a known drug is present and can help determine the severity of toxicity and the need for aggressive interventions (eg, hemodialysis in ethylene glycol, methanol, and salicylate).

Case 5-4 (Questions 1, 7, 8)

TOXIDROMES

1

A toxidrome is a consistent constellation of signs and symptoms associated with some specific classes of drugs. The most common toxidromes are those associated with anticholinergic activity, increased sympathetic activity, and

Case 5-4 (Questions 1, 2, 5)

central nervous system (CNS) stimulation or depression. Anticholinergic drugs increase heart rate and body temperature, decrease GI motility, dilate pupils, and produce drowsiness or delirium. Sympathomimetic drugs increase CNS activity, heart rate, body temperature, and blood pressure. Opioids, sedatives, hypnotics, and antidepressants depress the CNS, but the specific class of CNS depressants often cannot be easily identified.

SALICYLATES

1 Acute ingestion of 150 to 300 mg/kg aspirin causes mild-to-moderate intoxication, >300 mg/kg indicates severe poisoning, and >500 mg/kg is potentially lethal. Symptoms of intoxication include vomiting, tinnitus, delirium, tachypnea, metabolic acidosis, respiratory alkalosis, hypokalemia, irritability, hallucinations, stupor, coma, hyperthermia, coagulopathy, and seizures. Salicylate intoxication mimics other medical conditions and can be easily missed. Patients with a chronic salicylate exposure, acidosis, or CNS symptoms, and those who are elderly are at high risk and should be considered for early dialysis.

Case 5-1 (Questions 1–3)
Case 5-2 (Questions 1–6)

IRON

1	Acute elemental iron ingestions of <20 mg/kg are usually nontoxic; doses of 20 to 60 mg/kg result in mild-to-moderate toxicity, and doses of >60 mg/kg are potentially fatal. Symptoms of toxicity include nausea, vomiting, diarrhea, abdominal pain, hematemesis, bloody stools, CNS depression, hypotension, and shock. Patients with severe iron poisoning do not exhibit the second stage of the so-called recovery but continue to deteriorate.	**Case 5-3 (Questions 1–14)**

TRICYCLIC ANTIDEPRESSANTS

1	Severe toxicity has been associated with doses of 15 to 25 mg/kg. Symptoms include tachycardia with prolongation of the PR, QTc, and QRS intervals; ST and T-wave changes; acidosis; seizures; coma; hypotension; and acute respiratory distress syndrome. A QRS segment >100 milliseconds is commonly seen in severe tricyclic antidepressant overdoses.	**Case 5-4 (Questions 9–17)**

ACETAMINOPHEN

1	Toxicity is associated with acute ingestions >150 mg/kg or >7.5 g total in adults. Symptoms in patients with toxicity include vomiting, anorexia, abdominal pain, malaise, and progression to characteristic centrilobular hepatic necrosis.	**Case 5-5 (Questions 1–15)**

Acetaminophen-induced hepatotoxicity is universal by 36 hours after ingestion, but patients who receive NAC within 8 to 10 hours of ingestion rarely exhibit hepatotoxicity. There is no consensus as to the best route of NAC administration, the optimal dosage regimen, or the optimal duration of therapy.

INTRODUCTION

This chapter reviews common strategies for the evaluation and management of drug overdoses and poisonings. Information regarding the management of specific drug overdoses is best obtained from a poison control center (reached by calling 1-800-222-1222 anywhere in the United States).

Epidemiologic Data

AMERICAN ASSOCIATION OF POISON CONTROL CENTERS AND DRUG ABUSE WARNING NETWORK

Toxicity secondary to drug and chemical exposure commonly occurs in children. The incidence of exposure to specific agents and the severity of outcomes vary based on the population studied.[1–3] The number of reported toxic exposures in the United States in 2018 was ~2.1 million, according to the American Association of Poison Control Centers (AAPCC).[3] Approximately 70% of the reported cases were treated at home, saving millions of dollars in medical costs.

According to the Drug Abuse Warning Network, almost 5.1 million U.S. emergency department (ED) visits involved drug misuse or abuse in 2011. Illicit drugs include cocaine, heroin, marijuana,

ecstasy, γ-hydroxybutyric acid, flunitrazepam (Rohypnol®), ketamine, lysergic acid, phencyclidine, and hallucinogens. Of those cases, illicit drug use was mentioned >2.7 million times because many of the visits involved multiple drugs of abuse.[4]

AGE-SPECIFIC DATA

Stratifying patients by age can be useful in assessing the likelihood of severe toxicity from an exposure. Most unintentional ingestions by children ages 1 to 6 years occur because children are curious, becoming more mobile, and beginning to explore their surroundings, and they often put objects or substances into their mouths.[5] Severe toxicity in young children is relatively uncommon because exposures usually involve the ingestion of relatively small amounts of a single substance.[5,6] AAPCC epidemiologic data also report medication errors, which in the pediatric population commonly result from confusing units of measurement (eg, teaspoons vs milliliters or tablespoons vs teaspoons), incorrect formulation or concentration administered, dispensing cup errors, and incorrect formulation or concentration dispensed from the pharmacy.[3]

In children older than age 6 years, the reasons for toxic exposure to medications are less clear.[7] Adolescent children generally have poor knowledge of the toxicity of medications and can overdose themselves unintentionally.[5,8] The potential for suicide attempts or intentional substance abuse should not be ignored in older children. These intentional overdoses commonly involve mixed exposures to illicit drugs, prescribed medications, or ethanol and are associated with more severe toxicity and death than with unintentional toxic exposures.

In geriatric patients, overdoses tend to have a greater potential for severe adverse effects compared with overdoses in other age groups.[9] Although the elderly constitute 13% of the population, they account for 33% of the drug use and 16% of the suicides.[10] Patients ages 65 years and older take an average of 5.7 prescription medications along with two to four nonprescription drugs daily.[9,10] The elderly are more likely to have underlying illnesses and often

have access to a variety of potentially dangerous medications. This results in higher rates of completed suicides than that in other age groups.[10,11]

Information Resources

COMPUTERIZED DATABASES

A vast number of substances can be involved in a poisoning or overdose. Reliable data about the contents of products, toxicities of substances, and treatment approaches need to be readily accessible. POISINDEX, a computerized database,[11] provides information on thousands of drugs by brand name, generic name, and street name, as well as foreign drugs, chemicals, pesticides, household products, personal care items, cleaning products, poisonous insects, poisonous snakes, and poisonous plants. Annual subscriptions to POISINDEX are expensive and are generally available only in large medical centers.[12]

PRINTED AND ELECTRONIC PUBLICATIONS

Textbooks and manuals also provide useful clinical information about the presentation, assessment, and treatment of toxicities. *Goldfrank's Toxicologic Emergencies*[13] and *Poisoning and Drug Overdose*[14] are valuable, less-expensive alternatives to computerized database programs, and are available in print and electronically. Books, however, are less useful than are computerized databases because information must be condensed and cannot be updated as frequently. Some drug package inserts also refer to treatment of acute toxicities; however, the information can be inadequate or inappropriate.[15,16]

POISON CONTROL CENTERS

Poison control centers provide the most cost-effective and accurate information to health care providers and to the general public.[17,18] Poison centers are staffed by trained poison information specialists who have a pharmacy, nursing, or medical background. Physician

backup is provided 24 hours a day by board-certified medical toxicologists. The nonphysician clinical toxicologists, pharmacists, and nurses who staff poison control centers are certified as specialists in poison information by the AAPCC or as clinical toxicologists by the American Board of Applied Toxicology.[19]

The poison information specialist must accurately and efficiently assess event-specific toxicity by telephone, without the benefit of direct observation of the patient. The specialist must communicate this assessment along with treatment information quickly, accurately, and professionally in a reassuring manner. Subsequent to telephone consultations, poison control center staff should initiate follow-up calls to determine the effectiveness of the recommended treatment and the need for additional evaluation or treatment.[20,21]

EFFECTIVE COMMUNICATION

Effective communication is essential to the assessment of potential poisonings. In most situations, the person seeking guidance on the management of a potentially toxic exposure is the parent of a small child who may have ingested a substance. The caller is usually anxious about the child and may feel guilty about the exposure. To calm the caller, the health care provider should quickly reassure the individual that telephoning for help was appropriate and that the best assistance possible will be provided.[21] If English is not the first language of the caller, or if there are other communication barriers (eg, panic), solutions must be found to enhance outcomes. Most poison centers subscribe to translation services or have bilingual staff to communicate with non–English-speaking callers. Poison centers also have special equipment to serve the hearing- and speech-impaired populations.

Once calm, effective communication is established, the health care provider should first determine whether the patient is conscious and breathing and has a pulse. If life-threatening symptoms have occurred, the caller should call 911 for emergency services. If the health care provider does not have the knowledge or resources to provide poison information, he or she should refer the caller to the

closest poison control center. Information on the location and phone number of the nearest poison control center can be found at http://www.aapcc.org or by calling 1-800-222-1222 in the United States.

GENERAL MANAGEMENT

Supportive Care and "ABCs"

Management of poisoned or overdosed patients is primarily based on symptomatic and supportive care. Specific antidotes exist only for a small percentage of the thousands of potential drugs and chemicals that can cause a poisoning.

The first aspect of patient management should always be basic support of airway, breathing, and circulation (the "ABCs"). The assessment and treatment of the potentially poisoned patient can be separated into seven primary functions: (a) gathering history of exposure, (b) evaluating clinical presentation (ie, "toxidromes"), (c) evaluating clinical laboratory patient data, (d) removing the toxic source (eg, irrigating eyes, decontaminating exposed skin), (e) considering antidotes and specific treatment, (f) enhancing systemic clearance, and (g) monitoring outcome.[22–24]

GATHERING EXPOSURE HISTORY

Comprehensive information about the history of the toxic exposure should be gathered from as many different sources as possible (eg, patient, family, friends, prehospital health care providers). This information should be compared for consistency and evaluated relative to clinical findings and laboratory results. The patient's history of the exposure is often inaccurate and should be confirmed with objective findings.[22,23,25] For example, a patient who presents to an ED with a supposed hydrocodone and carisoprodol overdose is expected to be lethargic or comatose. If the patient arrives wide

awake with tachycardia and agitation, the clinician should suspect exposure to other substances.

Specific information should be sought concerning the patient's state of consciousness, symptoms, probable intoxicant(s), and maximal amount and dosage form(s) of substance ingested, as well as when the exposure occurred. Medications, allergies, and prior medical problems also should be ascertained to facilitate development of treatment plans (eg, a history of renal failure may indicate the need for hemodialysis to compensate for decreased renal drug clearance).[22,23]

EVALUATING CLINICAL PRESENTATION AND TOXIDROMES

A thorough physical examination is needed to characterize the signs and symptoms of overdose, and it should be conducted serially to determine the evolution or resolution of the patient's intoxication. An evaluation of the presenting signs and symptoms can provide clues to the drug class causing the toxicity, confirm the data on the history surrounding the toxic exposure, and suggest initial treatment.[22,26–28] The patient may be asymptomatic on presentation, even though a potentially severe exposure has occurred, if absorption of the drug or toxic substance is incomplete or if the substance has not yet been metabolized to a toxic substance.[29–31]

Characteristic toxidromes (ie, a constellation of signs and symptoms consistent with a syndrome) can be associated with some specific classes of drugs.[23,27,28] The most common toxidromes are those associated with anticholinergic activity, increased sympathetic activity, and central nervous system (CNS) stimulation or depression. Anticholinergic drugs can increase heart rate and body temperature, decrease gastrointestinal (GI) motility, dilate pupils, and produce drowsiness or delirium. Sympathomimetic drugs can increase CNS activity, heart rate, body temperature, and blood pressure (BP). Opioids, sedatives, hypnotics, and antidepressants can depress the CNS, but the specific class of CNS depressant often cannot be easily identified.

Classic findings may not be present for all drugs within a therapeutic class. For example, opioids generally induce miosis, but meperidine can produce mydriasis. Furthermore, the association of symptoms with a particular class of toxic substances is difficult when more than one substance has been ingested. Practitioners should not focus only on the specific clinical findings associated with a toxidrome. Rather, they should consider all subjective and objective data gathered from the history of the exposure, the patient's medical history, physical examination, and laboratory findings.[27]

INTERPRETATION OF LABORATORY DATA

Drug screens

A urine drug screen can be useful in identifying the presence of drugs and their metabolites in selected patients but is not indicated in all cases of drug overdose. Urine drug screens can be useful in a patient with coma of unknown etiology, when the presented history is inconsistent with clinical findings, or when more than one drug might have been ingested.[32,33]

Pharmacokinetic considerations

The absorption, distribution, metabolism, and elimination of drugs in the overdosed patient can be quite different from when the drug is taken in usual therapeutic doses.[29–31] The expected pharmacodynamic and pharmacokinetic features of drugs can be substantially altered by large drug overdoses, especially with drugs that exhibit dose-dependent pharmacokinetics. The rate of drug absorption is generally slowed by large overdoses, and the time to reach peak serum drug concentrations can be delayed.[32,34] For example, peak serum concentrations of phenytoin can be delayed for 2 to 7 days after an orally ingested overdose.[35,36] The volume of distribution of an overdosed drug can be increased, and when usual metabolic pathways become saturated, secondary clearance pathways can be important. For example, large overdoses of acetaminophen saturate glutathione mechanisms of metabolism, resulting in hepatotoxicity.[37]

When the pharmacokinetic parameters of an overdosed drug are altered, serial plasma concentration measurements can better define the absorption, distribution, and clearance phases of the ingested substance. Pharmacokinetic parameters that have been derived from therapeutic doses should not be used to predict whether absorption is complete or to predict the expected duration of intoxication caused by large overdoses.[31,38,39]

DECONTAMINATION

After the airway and the cardiopulmonary system are supported, efforts should be directed toward removing the toxic substance from the patient (ie, decontamination).[22,40] Decontamination presumes that both the dose and the duration of toxin exposure are important in determining the extent of toxicity and that prevention of continued exposure will decrease toxicity.[29–31,40] This intuitive concept is clearly relevant to ocular, dermal, and respiratory exposures when local tissue damage is the primary problem. Respiratory decontamination involves removing the patient from the toxic environment and providing fresh air or oxygen to the patient. Decontamination of skin and eyes involves flushing the affected area with large volumes of water or saline to physically remove the toxic substance from the surface.[22,23]

Gastrointestinal decontamination

Because most poisonings and overdoses result from oral ingestions, measures to decrease or prevent continued GI absorption have commonly been used to limit the extent of exposure.[22,23,37] GI decontamination should be considered if the ingestion is large enough to produce potentially significant toxicity, or if the potential severity of the ingestion is unknown and the time since ingestion is <1 hour. The following methods have historically been used: (a) evacuation of gastric contents by emesis or gastric lavage, (b) administration of activated charcoal as an adsorbent to bind the toxic substance remaining in the GI tract, (c) use of cathartics or whole-

bowel irrigation (WBI) to increase the rectal elimination of unabsorbed drug, or (d) a combination of any of these methods.[41–46]

The efficacy of GI decontamination varies, depending on when the process is initiated relative to the time of ingestion, dose ingested, and other factors. Furthermore, ipecac-induced emesis, gastric lavage, cathartics, and activated charcoal are not directly associated with improved patient outcomes.[41–46]

The most appropriate method for GI tract decontamination remains unclear because sound comparative data for different methods of GI decontamination are not available. Clinical research in healthy subjects, by necessity, must use nontoxic doses of drugs. Studies using nontoxic doses are not applicable to the overdose situation because alterations in GI absorption can occur with large doses. In addition, low-dose studies generally rely on pharmacokinetic end points such as peak plasma concentrations, area under the plasma concentration–time curve, or quantity of drug recovered from the urine.[41,42,44–46] In contrast, clinical studies of GI decontamination methods in patients who have ingested toxic doses of a substance use clinical outcomes or a directional change in serum drug concentrations.[41,42,45,46] These latter trials are not standardized with respect to the dose ingested or to the time interval between drug ingestion and GI decontamination.[41–46]

Ipecac-Induced Emesis and Gastric Lavage

Ipecac-induced emesis and gastric lavage primarily remove substances from the stomach. Their efficacy is affected significantly by the time the ingested substance remains in the stomach. Gastric lavage and ipecac-induced emesis are most effective when implemented before the substance moves past the stomach into the intestine (usually within 1 hour).[41,42]

The commonly used adult gastric lavage tube (36F) has an internal diameter too small to allow the recovery of large tablet or capsule fragments. An even smaller diameter lavage tube is used for children.[42] Gastric lavage may be useful only if large amounts of a liquid substance were ingested and the patient arrived within 1 hour

of the ingestion.[45] However, patients usually arrive in the ED more than an hour after ingestion, when absorption of the toxin has most likely already occurred. As a result, the efficacy of these procedures in overdose situations is minimal, and no studies have confirmed that use of gastric lavage or ipecac-induced emesis improves the outcome of the patient.[41,42,47] For these reasons, ipecac is no longer used, and gastric lavage is used only in rare, specific situations.

Activated Charcoal

In 1963, a review article concluded that activated charcoal was the most valuable agent available for the treatment of poisoning.[48] This conclusion was based only on studies in fasting patients who had nontoxic exposures. Nevertheless, data from those studies were extrapolated to poisoned patients. Since then, activated charcoal has become the preferred method of GI decontamination for the treatment of toxic ingestions.[22,40,48]

The goal of the therapy is to decrease the absorption of the substance and reduce or prevent systemic toxicity.[43] Unfortunately, there are no satisfactorily designed clinical studies assessing the benefit from the use of activated charcoal to guide the use of this therapy. There is also no evidence that the administration of activated charcoal improves clinical outcomes.[43]

The use of activated charcoal at a dose of 1 g/kg should be considered when the patient has ingested a toxic substance that is known to be absorbed by activated charcoal within 1 hour of the ingestion. The potential for benefit is unknown if the activated charcoal is given >1 hour after ingestion.[43] It should be noted that iron and lithium are not absorbed by activated charcoal. Other forms of GI decontamination must be used to remove those substances from the GI tract.[43]

Generally, the use of activated charcoal is safe. Although there are relatively few reports of adverse effects from the use of activated charcoal, there are numerous reports of complications, usually involving aspiration. It is essential that the patient has an intact or a protected airway (intubation) before activated charcoal is

administered, especially in drowsy patients or in patients who may rapidly become obtunded.[43]

Vomiting with aspiration of activated charcoal occurs in about 5% of patients who receive activated charcoal.[43,49–51] The resulting pulmonary problems can be caused by aspiration of acidic stomach contents or the charcoal. Decreased oxygenation can occur immediately, or pulmonary effects can occur later.[51–55] Acute respiratory distress syndrome has resulted after the unintentional instillation of charcoal into the lung.[51] Aspiration of charcoal can result in chronic lung disease or fatalities, whereas the toxic exposure, for which the charcoal was administered, is often not lethal or even serious.[52,56]

Cathartics

Historically, sorbitol (a cathartic) was often administered with activated charcoal to enhance passage of the charcoal–substance complex through the GI tract. However, decreased transit time through the bowel has not been proved to decrease absorption because drug absorption does not take place in the large bowel.[44] Sorbitol is also associated with vomiting and aspiration.[44] Hypernatremia can also develop subsequent to the administration of repeat doses of activated charcoal with sorbitol.[57,58] Currently, most EDs use aqueous activated charcoal mixtures rather than charcoal–sorbitol combinations. Because cathartics are not effective in reducing drug absorption or increasing patient outcome, their use is no longer advised.[44]

Whole-Bowel Irrigation

WBI with a polyethylene glycol–balanced electrolyte solution (eg, Colyte®, GoLYTELY®) can successfully remove substances from the entire GI tract in a period of several hours. WBI is effective with ingestions of sustained-release dosage forms, as well as with substances that form bezoars (concretions of tablets or capsules), such as ferrous sulfate or phenytoin.[23,45,59] WBI is also indicated when the toxic agent is not adsorbed by activated charcoal (eg, body

packer packets, lithium, iron, potassium).[22,23,45,59] This method of GI decontamination takes much longer to complete and is associated with poor patient compliance because large volumes of fluid (2 L/hour for adults until the effluent is clear) need to be ingested to be effective.[59] A nasogastric (NG) tube can be inserted, and the WBI fluid can be administered via the NG tube so that lack of patient compliance is no longer a factor.[45]

ANTIDOTES AND SPECIFIC TREATMENTS

An antidote is a drug that reverses the toxicity of another substance. Some antidotes can displace a drug from receptor sites (eg, naloxone for opioids, flumazenil for benzodiazepines), and some can inhibit the formation of toxic metabolites (eg, *N*-acetylcysteine [NAC] for acetaminophen, fomepizole for methanol).[23,60,61] Some treatments are highly effective for the management of individual drug overdoses but do not meet the definition of an antidote. For example, sodium bicarbonate is used to treat the cardiotoxicity arising from tricyclic antidepressant (TCA) overdoses, and benzodiazepines are used to treat CNS toxicity associated with cocaine and amphetamine overdoses.[62–64] However, for antidotes to be effective, they must be readily available at the health care facility in adequate doses to treat the patient in a timely manner.[65]

ENHANCING SYSTEMIC CLEARANCE

Hemodialysis and manipulation of urine pH can enhance the clearance of substances. Hemodialysis can successfully treat some specific intoxications (eg, methanol, ethylene glycol, aspirin, theophylline, lithium). Hemodialysis can also be used in patients with severe acid–base disturbances or renal dysfunction.[47] Alkalinization of the urine can enhance the elimination of drugs such as aspirin and phenobarbital.[66–68]

MONITORING OUTCOME

Selecting the appropriate parameters and length of time to monitor a patient who has been exposed to a toxic agent requires knowledge

of toxic effects and the time course of the intoxication.[33,34] Most patients who are at risk for moderate or severe toxicity should be monitored in an intensive care unit (ICU) with assessments of cardiac, pulmonary, and CNS function.[69,70]

ASSESSMENT OF SALICYLATE INGESTION

Gathering a History

CASE 5-1

QUESTION 1: A.J., the mother of a 3-year-old child, states that her son, R.J., has ingested some aspirin tablets.

What additional information should be obtained from or given to A.J. at this time?

Obtaining an initial assessment of the patient's status is essential. The caller's telephone number should be obtained in the event that the call is disconnected, initial recommendations need to be modified, or subsequent follow-up is needed. The health care provider should ask for patient-specific information with questions that are nonthreatening and nonjudgmental. The caller should be reassured that calling for help was the right thing to do.

Evaluating Clinical Presentation

CASE 5-1, QUESTION 2: On further questioning, A.J. states that R.J. is crying and has a stomachache. Otherwise, the child is acting normally. R.J. was found sitting on the bedroom floor with an aspirin bottle in his hand and some partially chewed tablets on the floor next to him. A.J. states that the child had the same look on his face that he has when he eats things that he does not like. A.J. reports that she can see white tablet material on the child's teeth. The mother was gone no more than 5 minutes and had asked her 6-year-old son to watch his brother. What additional information is needed to correctly assess the potential for toxicity in R.J.?

To determine the potential toxicity of an unintentional ingestion, it is important to assess the presence of symptoms and to identify the substance ingested. Inquiries should begin with open-ended questions to determine the facts that the caller is certain of versus what may have been assumed. The answers usually point to more specific information that is needed to accurately assess the exposure.[20]

R.J.'s symptoms presently are not life-threatening. His behavior is consistent with being scared in response to the mother's anxiety. Once it has been established that the child does not need immediate life-saving treatment, the caller is generally able to answer additional questions.

A.J. has already provided information about the child's symptoms. More information is needed to determine the identity of the ingested substance, the time of ingestion, the brand of aspirin (to ensure that the product is not an aspirin-combination or even an aspirin-free formulation), the dosage form, the number of dosage units in a full container, and the number of remaining dosage units in the container. The parent should be advised to look for tablets under beds, rugs, or other locations out of sight (eg, wastepaper baskets, toilets, pet food dishes, pockets). The dosage forms in the container should be identical in appearance, and the contents should be what are stated on the label. Information concerning the child's weight and health status, as well as whether the child is taking other medications, is also important. The child's weight is useful in determining the maximum milligram per kilogram dose of aspirin that was ingested.

When more than one child is present during an ingestion, the caller should be questioned as to whether other children also could have participated in the ingestion. In this situation, the children could have shared equally in the missing medication, all of the drug could have been fed to one child, or all of the drug could have been ingested by the oldest or most aggressive child. When it is unclear how much is missing among a group of children, each child should be evaluated and managed as if he or she may have ingested the total missing quantity.

Triage of Call

Case 5-1, Question 3: A.J. has now determined that a total of seven tablets, each containing 81 mg per tablet of aspirin, are missing from the bottle. Because A.J. recalls having taken two aspirin tablets from this bottle, it is not likely that her son took more than seven tablets. A.J. states that R.J. weighs 41.88 pounds (19 kg). What treatment is needed for this child?

The maximal dose of aspirin ingested by this child is likely to be much less than the minimal dose required to cause significant symptoms based on his weight for his age (ie, ~41.88 pounds [19 kg]). A dose of 150 mg/kg of aspirin is the smallest dose at which treatment or assessment at a health care facility is necessary.[68,71] A.J. is likely to have ingested a maximum of 567 mg of aspirin (ie, seven 81-mg tablets), which is about 29.8 mg/kg (567 mg divided by 41.88 pounds [19 kg]). If this child is healthy, takes no medications, and is not allergic to aspirin, the child does not require any treatment. With this history of ingestion, the only adverse effect that might occur is some mild nausea. Providing information to the mother that her child had not ingested a toxic or dangerous amount will be reassuring.

For many years, aspirin was the most common cause of unintentional poisoning and poisoning deaths among children.[71–73] However, safety closure packaging and reduction of the total aspirin content in a full bottle of children's aspirin to ~3 g has steadily reduced the frequency of pediatric aspirin poisoning and deaths.[72–74] Although acute aspirin poisoning remains a problem, the largest percentage of life-threatening intoxications now results from therapeutic overdose.[68] Therapeutic overdoses occur when a dose is given too frequently, when both parents unknowingly dose the child with the drug, or when too large a dose is given. Therapeutic overdoses are especially problematic when excessive doses are given for a prolonged period and the drug is able to accumulate.[68]

Patient Outcome

Follow-up telephone consultation on toxic ingestions is important to identify children who unexpectedly develop symptoms that might need to be treated. A telephone call to A.J. 6 to 24 hours after her initial call would be appropriate to follow up on the child. On a call back to A.J., she stated that she gave R.J. lunch at the appropriate usual time. R.J. then watched cartoons, took his usual nap, and remained asymptomatic.

Acute and Chronic Salicylism

SIGNS AND SYMPTOMS

CASE 5-2

QUESTION 1: A.S., a 71-year-old, 130.07-pound (59-kg) female with a history of chronic headaches, has taken 10 to 12 aspirin tablets daily for several months. On the evening of admission, she became lethargic, disoriented, and combative. Additional history revealed that she ingested up to 95 aspirin tablets on the morning of admission (about 11 hours earlier) in a suicide attempt. She reported ringing in her ears, nausea, and two episodes of vomiting. She is disoriented and lethargic. Vital signs were BP 148/95 mm Hg, pulse 114 beats/minute, respirations 38 breaths/minute, and temperature 101.2 °F (38.44 °C). A.S.'s laboratory data obtained on admission were as follows:

Serum sodium (Na), 144 mEq/L
Potassium (K^+), 2.5 mEq/L
Chloride (Cl^-), 103 mEq/L
Bicarbonate, 9 mEq/L
Glucose, 58 mg/dL
Blood urea nitrogen (BUN), 38 mg/dL
Creatinine, 2.5 mg/dL

Arterial blood gas (ABG) values (room air) were as follows: pH, 7.14; P_{CO_2}, 18 mm Hg; and P_{O_2}, 96 mm Hg. A serum salicylate concentration measured ~12 hours after the acute ingestion was 90 mg/dL. Her hemoglobin was 9.6 g/dL, with a hematocrit of 28.9% and a prothrombin time (PT) of 16.4 seconds.

Is A.S. at high risk because of her ingestion?

The symptoms and severity of salicylate intoxication depend on the dose consumed; the patient's age; and whether the ingestion

was acute, chronic, or a combination of the two.[73,75,76] This case illustrates an acute ingestion in someone who has also chronically ingested aspirin. Acute ingestion of 150 to 300 mg/kg of aspirin is likely to produce mild-to-moderate intoxication, >300 mg/kg indicates severe poisoning, and >500 mg/kg is potentially lethal.[68,71] A.S., who ingested ~523 mg/kg, has taken a potentially lethal dose. Chronic salicylate intoxication is usually associated with ingestion of >100 mg/kg/day for >2 days.[68,71] A.S. has been taking 66 mg/kg/day for her headaches in addition to her acute ingestion. A.S. demonstrates many of the findings typical of severe acute salicylism (see sections on Pathophysiology of Salicylate Intoxication and Assessment of Toxicity). A.S.'s prognosis is potentially poor because she is elderly and has taken a potentially lethal overdose of aspirin.

Pathophysiology of Salicylate Intoxication

Case 5-2, Question 2: What are the pathophysiological and clinical features of acute and chronic salicylism?

Toxicity from salicylate exposure results in direct irritation of the GI tract, direct stimulation of the CNS respiratory center, stimulation of the metabolic rate, lipid and carbohydrate metabolism disturbances, and interference with hemostasis.[68,71,73,75,76] Toxic doses of salicylate directly stimulate the medullary respiratory center, leading to nausea, vomiting, tinnitus, delirium, tachypnea, seizures, and coma and influence several key metabolic pathways.[68,73–77] Direct stimulation of the respiratory drive increases the rate and depth of ventilation, which can result in primary respiratory alkalosis. The respiratory alkalosis causes increased renal excretion of bicarbonate, resulting in decreased buffering capacity. The patient usually presents with a partially compensated respiratory alkalosis.[68,74,75,77] Hypokalemia can result from increased GI and renal losses of potassium, as well as from systemic alkalosis.[68,75,76] Although marked metabolic and neurologic abnormalities are most commonly observed in young children with advanced salicylate intoxication, adolescents or adults

acutely poisoned with a large dose of salicylates can exhibit these symptoms as well.[68,74,75] Acute salicylism in a young child often takes a more severe course than that typically seen in adults. After acute ingestion, children quickly pass through the phase of pure respiratory alkalosis. Renal bicarbonate loss secondary to respiratory alkalosis reduces the buffering capacity more profoundly in a child and facilitates the development of metabolic acidosis.[68,73,75,77]

Salicylates have toxic effects on several biochemical pathways that contribute to metabolic acidosis and other symptoms.[68,75,77] Mitochondrial oxidative phosphorylation is uncoupled and results in an impaired ability to generate high-energy phosphates, increased oxygen use and carbon dioxide production, increased heat production and hyperpyrexia, increased tissue glycolysis, and increased peripheral demand for glucose. Salicylates also inhibit key dehydrogenase enzymes within the Krebs cycle, resulting in increased levels of pyruvate and lactate. The increased demand for peripheral glucose causes increased glycogenolysis, gluconeogenesis, lipolysis, and free fatty acid metabolism. The latter results in enhanced formation of keto acids and ketoacidosis.[73,77]

The patient may become severely volume depleted through several mechanisms.[68,75,77] Hyperthermia and hyperventilation produce increased insensible water loss, vomiting may promote GI fluid losses, and the solute load caused by altered glucose metabolism results in osmotic diuresis. Depending on the patient's acid–base balance and net fluid and electrolyte intake and output, serum sodium and potassium concentrations may be normal, elevated, or decreased. Hypernatremia and hypokalemia are most common.[73,75]

Blood glucose concentration is usually normal or slightly elevated, although hypoglycemia may accompany chronic salicylism (eg, as illustrated by A.S.) or occur late in acute intoxication. CNS glucose levels can be markedly reduced in the presence of normal blood glucose concentrations because increased CNS glucose utilization to generate high-energy phosphate exceeds the rate at which glucose can be supplied.[68,73,75,77]

ASSESSMENT OF TOXICITY

CASE 5-2, QUESTION 3: What signs, symptoms, and laboratory values in A.S. are consistent with salicylate intoxication?

A.S. demonstrates many of the findings typical of severe acute salicylism. Hyperventilation has resulted from the direct respiratory stimulant effects of salicylate and as compensation for her metabolic acidosis (P_{CO_2}, 18 mm Hg; pH, 7.14; serum bicarbonate, 9 mEq/L; respiratory rate, 38 breaths/minute). Hypokalemia (2.8 mEq/L) in the presence of metabolic acidosis represents severe potassium depletion because of increased renal and, possibly, GI losses. Hyperpyrexia caused by salicylate is present in A.S., although an infectious cause must also be considered. Her neurologic symptoms of lethargy, disorientation, and combativeness, as well as tinnitus, nausea, and vomiting, are commonly seen in severe salicylate intoxication. In addition, being elderly and taking a lethal amount of aspirin bodes ill for this patient's outcome.

LABORATORY EVALUATION

CASE 5-2, QUESTION 4: What objective evaluations should be assessed in a patient with presumed salicylate intoxication?

A.S.'s workup illustrates a thorough initial patient evaluation. Laboratory evaluation should include ABG values, serum electrolytes, BUN, serum creatinine, blood glucose, and a complete blood cell count.[73,74] Urine should be tested for specific gravity and pH.[73] In symptomatic patients, a PT or an international normalized ratio (INR) and partial thromboplastin time are useful to assess the presence of salicylate-induced coagulopathy. Vitals signs should be monitored for an increased respiratory rate and hyperpyrexia.[74,75] Physical examination should include an evaluation of chest radiograph, cardiopulmonary and neurologic function, and measurement of urine output.[75]

A salicylate blood concentration should be obtained immediately and every 2 hours in patients.[24,64,73,75] Serum salicylate concentrations should be reassessed every 2 hours to verify that the original concentration represented a peak level and that the salicylate level is decreasing rather than increasing.[24,68,73,76,78] Obtaining the units of measurement on salicylate serum concentrations is essential because different laboratories report concentrations in different units (eg, mg/dL, µg/mL, mmol/L). An incorrect interpretation of the salicylate unit of measurement can result in overestimates or underestimates of the severity.[24]

Manifestations of severe acute salicylism include a variety of neurologic signs and symptoms: disorientation, irritability, hallucinations, lethargy, stupor, coma, and seizures.[69,73] Hyperthermia may be marked and can result in the inappropriate administration of aspirin as an antipyretic. Coagulopathy can occur because of impaired platelet function, hypoprothrombinemia, reduced factor VII production, and increased capillary fragility, especially when aspirin is taken chronically.[75–77] Pulmonary edema and acute renal failure also can occur, but the former occurs more commonly after chronic intoxication.[75,77,78]

Chronic salicylism symptoms are similar to that of acute intoxications. However, patients with chronic exposures may have fewer GI symptoms, but they generally appear more ill and have more CNS symptoms.[71,79] In both adults and children, the principal signs of chronic salicylism are a partially compensated metabolic acidosis, increased anion gap, ketosis, dehydration, electrolyte loss, hyperventilation, tremors, agitation, confusion, stupor, memory deficits, renal failure, and seizures.[73,75,76,80] The severity of CNS manifestations is related to the cerebrospinal fluid (CSF) salicylate concentration.[74,75] CSF concentrations may increase in the presence of systemic acidosis because a greater fraction of salicylate is not ionized and can cross the blood–brain barrier. Therefore, metabolic acidosis is especially dangerous in a salicylate-intoxicated patient.[73,75]

Unless the history of salicylate intake is specifically sought, the problem may not be immediately apparent, especially in the elderly

in whom such findings are likely to be attributed to other causes (eg, encephalitis, meningitis, diabetic ketoacidosis, myocardial infarction).[24,75,79] Delay in diagnosis has been associated with increased mortality.[24,68,75,79] Unfortunately, plasma salicylate concentrations do not correlate well with the degree of poisoning in chronically intoxicated patients. It is more important to treat the patient according to the clinical status rather than according to his or her salicylate concentration.[71] Death in patients with salicylism, whether acute or chronic, results from CNS or cardiac dysfunction, or pulmonary edema.[73,75,79]

MANAGEMENT

Case 5-2, Question 5: What would be a reasonable management plan for A.S.?

Management of salicylate intoxication depends on the degree of acid–base and electrolyte disturbances.[68,73,75] Activated charcoal is not indicated for A.S. because the ingestion occurred ~10 hours ago and she has a somewhat altered mental status.[46] The risk of aspiration is greater than the value of possibly adsorbing any remaining aspirin from the GI tract. In addition, A.S. already has symptoms of salicylate poisoning, indicating that the aspirin has been absorbed. Others might argue that if she ingested 95 tablets, some of the drug may still be present in the GI tract and giving activated charcoal late may bind some of the drug still present. The benefit versus risk of giving activated charcoal must be assessed. A.S.'s hypokalemia, acidosis, and hypoglycemia must be corrected, and it is probably best accomplished through the administration of intravenous (IV) hypotonic saline–dextrose solutions combined with potassium supplementation. This solution is administered at a rate that replaces the patient's deficits and keeps pace with continued losses.[68,73,75–77] Care should be taken to avoid overzealous fluid therapy, which can predispose the patient to cerebral or pulmonary

edema.[73,77] Administration of an IV dextrose bolus is also indicated because A.S. is hypoglycemic (60 mg/dL).[73,75–77]

Sodium bicarbonate

It is important to correct A.S.'s acidosis because acidosis will increase CSF salicylate concentrations.[74,75] Correction of acidosis can be accomplished by adding sodium bicarbonate to her IV fluids.[68,73–76] A.S.'s serum sodium and potassium concentrations should be monitored closely because adding potassium to IV fluids will mostly likely be required.[81] Providing adequate ventilation to prevent respiratory alkalosis is essential. With a respiratory rate of 36 breaths/minute, placing the patient on a ventilator to assist with breathing might be considered. However, forced mechanical ventilation can interfere with the patient's need to compensate to maintain the serum pH. Patients on ventilators can become severely acidotic, which can result in death because of an inability to compensate adequately.[73,82]

Seizures

Seizures are not evident in A.S. but can be encountered in cases of severe salicylate poisoning. Seizures generally carry a poor prognosis and are indicative of severe salicylate intoxication that requires hemodialysis.[73] Other treatable causes of seizures (eg, marked alkalosis, hypoglycemia, hyponatremia) can be present in individuals such as A.S. and should be ruled out. If seizures occur, benzodiazepines are the drugs of choice for treatment.[73]

Coagulopathy and hyperthermia

Coagulopathy generally responds to vitamin K_1, which should be given if the PT or INR is prolonged.[73] GI bleeding or other hemorrhage can occur, but it is not common.[73,75,76] Mild hyperthermia usually does not require therapy, but cooling fans and mist may be required for extremely elevated temperatures.[73,77]

Pulmonary edema

Noncardiogenic pulmonary edema commonly occurs in salicylate intoxications, especially when the overdose is attributable to chronic ingestions.[73,75,78] Pulmonary edema is associated with a high incidence of neurologic symptoms in patients and can occur even without fluid overload.[75,78] Increased alveolar capillary membrane permeability, prostaglandin effects, and a metabolic interaction with platelets that release membrane permeability substances are the primary mechanisms for the cause of pulmonary edema associated with salicylate overdose. Treatment is aimed at reducing salicylate levels via alkalinization or hemodialysis.[78]

Alkalinization

Case 5-2, Question 6: What measures will enhance salicylate elimination? Which of these may be indicated in A.S.?

Alkalinization of the urine and hemodialysis can enhance the excretion of salicylate in overdose situations.[68,74] Hemodialysis is preferred because it can also correct fluid and electrolyte imbalances.[75,78,79] Sodium bicarbonate is recommended for alkalinization to increase the arterial pH with the goal of minimizing salicylate transport into the CNS.[74,75,77]

Although large doses of sodium bicarbonate can enhance the renal elimination of the weak acid and shorten its half-life, this treatment does not favorably influence the morbidity or mortality of patients with salicylism. Alkalinization with forced fluid diuresis can also place the patient at risk for sodium and fluid retention, as well as pulmonary edema if too much fluid is given too quickly.[76,78–83] Whether the urine can be adequately alkalinized (pH > 7) in severely intoxicated pediatric patients has been questioned because of the large acid load that is excreted.[68,73,74] Nevertheless, urine alkalinization with sodium bicarbonate should be attempted in severely salicylate-intoxicated adult patients such as A.S.

Potassium replacement in patients receiving alkalinization is essential.[73,75,77] These patients may require large amounts of potassium supplementation as a result of renal wasting of potassium. The risk of pulmonary edema can be minimized if this is done without forcing fluids.[73,75–77]

Hemodialysis should be considered in patients who show progression of severe salicylate intoxication and seizure activity, renal failure, or plasma salicylate concentrations in the potentially fatal range.[68,75,76,78,80] Patients with a chronic exposure, acidosis, or CNS symptoms and those who are elderly or ill are at high risk and should be considered for early dialysis.[75,80] Because A.S. has many of the risk factors, she is a candidate for emergent hemodialysis.

CLINICAL OUTCOME

A repeat salicylate level 6 hours later (18 hours after ingestion) had increased to 95 mg/dL. Her chemistry panel revealed serum sodium, 143 mEq/L; potassium, 2.2 mEq/L; chloride, 99 mEq/L; bicarbonate, 8 mEq/L; glucose, 77 mg/dL; creatinine, 4.9 mg/dL; and BUN, 43 mg/dL. Her hemoglobin was 8.4 g/dL, with a hematocrit of 23% and a PT of 16.6 seconds. A.S.'s pH on blood gases remained in the 7.2 to 7.3 range. Urinary alkalinization was attempted with a high-dose IV sodium bicarbonate infusion in an attempt to reach a urine pH of 7.5. However, her urine pH never increased above pH 5.7. A.S. became fluid overloaded and exhibited dyspnea. She was placed on a ventilator with worsening of her symptoms. A chest radiograph showed pulmonary edema. A.S. became confused and agitated, pulling at her IV lines and trying to get out of bed. Nephrology was consulted to provide emergent hemodialysis to correct the acidosis, electrolyte abnormalities, and fluid overload. As the catheter was being placed, the patient had a tonic-clonic seizure. Lorazepam 2 mg IV was administered, and the seizure stopped. At this time, the patient was unresponsive. She had another tonic-clonic seizure, went into respiratory arrest, and was coded, but could not be resuscitated.

ASSESSMENT OF IRON INGESTION

Gathering History and Communications

CASE 5-3

QUESTION 1: The babysitter of K.M., a 21-month-old female, calls the ED because the child is vomiting and appears to have been playing with an open, unlabeled bottle of green tablets. The child was left alone in her room for about 20 minutes to take a nap.

Why might the consultation with this babysitter be expected to be more difficult than was the consultation in Case 5-1, Question 1?

In cases of unintentional pediatric ingestions, phone calls to a health care provider, a health care facility, or a poison control center made by individuals other than the parent are usually more difficult to manage because the caller is often unable to provide all patient-specific information needed (eg, patient weight, chronic medications) to accurately assess the drug ingestion. Additional information is often needed from a parent. Nonparent callers also tend to be more upset about an unintentional ingestion and may have more difficulty than a parent in taking decisive action.

Triage of Call

CASE 5-3, QUESTION 2: Despite additional questioning, K.M.'s babysitter cannot identify the tablets. K.M. is still vomiting; and the vomitus is green, similar to the color of the tablets. According to the babysitter, K.M. is the child of a single mother who is not known to have flu or any GI illness at this time. The child's mother is currently at work and is not answering her cell phone. What recommendations could be provided to K.M.'s babysitter at this time?

With this history, the practitioner should consider whether the information presented by K.M.'s babysitter is consistent with a drug ingestion and whether this incident is likely to be associated with a

significant adverse outcome. Most 2-year-old children experience limited toxicity with unintentional drug ingestions because the amount of substance actually ingested is usually small.[5,6] Nevertheless, some substances (eg, methanol, ethylene glycol, nicotine, caustic substances, camphor, chloroquine, clonidine, diphenoxylate-atropine, theophylline, oral hypoglycemic agents, calcium channel blockers, TCAs, opioids) can produce significant toxicity even when small amounts are ingested.[6,84,85]

Although the history of drug ingestion in K.M. is somewhat vague, the description of green tablets and green-colored vomitus suggests possible ingestion of iron tablets. Because this is a possible exposure with a realistic potential for severe toxicity, K.M. should be brought to the ED for evaluation. Depending on the distance to the hospital and the anxiety level of the babysitter, the practitioner might want to instruct the babysitter to call for an ambulance. She should be instructed to bring the green tablets to the ED along with the child so that the tablets can be identified. Other medications in the house should also be brought to the ED, and the mother should be contacted.

Substance Identification

Case 5-3, Question 3: K.M.'s mother was reached and confirmed that the only green tablets in the house are her iron supplements. The babysitter was instructed to bring K.M. to the nearest ED, and the mother will meet them there. On arrival, K.M. is still vomiting but is fully awake and alert, with a heart rate of 122 beats/minute, a respiratory rate of 26 breaths/minute, a rectal temperature of 98.9 °F (37.17 °C), and pulse oximetry of 100%. How can the maximal potential severity of this ingestion be estimated at this time?

K.M.'s vital signs, when corrected for age, are normal. Attention should now focus on identifying the ingested substance and the maximal potential severity of the ingestion. Although this case involves an unknown ingestion, with a possibility of being a severe case of iron intoxication, the identity of the tablets still has not been

verified. Therefore, K.M. must be carefully assessed, and the ingestion history reaffirmed.

All solid dosage prescription drugs are required by the U.S. Food and Drug Administration (FDA) to have identification markings. Online Resources (eg, *Facts and Comparisons*,[86] *Prescriber's Digital Reference*[87]), computerized databases (eg, Micromedex),[88] and the product manufacturers can assist in identifying solid dosage forms. Websites such as http://www.rxlist.com[89] and http://www.drugs.com[90] can also be useful in obtaining drug identification information.

The imprint code markings on the green tablet brought to the ED with K.M. and the mother's assistance should be sufficient to correctly identify the medication. Once the tablet has been identified, the maximal number of tablets ingested should be estimated.

In K.M.'s case, the bottle containing the green tablets was unlabeled. In most cases, the label on the medication container can provide information on the identity and number of tablets dispensed. The date the prescription was obtained, the number of estimated doses taken, and the number currently remaining in the medication container can be used to approximate the maximal number of tablets ingested.

K.M.'s vital signs and symptoms should be monitored closely to evaluate whether her clinical status is consistent with expectations based on the suspected ingestion. Nausea, vomiting, diarrhea, and abdominal pain are common early signs of iron intoxication.[91–96] The absence of symptoms, especially within a short time of the presumed ingestion, should not be interpreted as an indication that a poisoning has not occurred.[91,93–96]

Evaluating Severity of Toxicity

Case 5-3, Question 4: K.M. weighs 24.25 pounds (11 kg), appears to be in no distress, and has stopped vomiting. About 25 mL of dark-colored vomitus was recovered, but no tablets are found. The vomitus tested negative for blood. A maximum of seven tablets was ingested based on the mother's recall. What degree of toxicity should be expected in K.M.?

The potential severity of toxicity can be estimated for commonly ingested drugs such as acetaminophen,[97] salicylates,[71] iron,[91] and TCAs[98] because of well-established dose–toxicity relationships. Acute elemental iron ingestions of <20 mg/kg are usually nontoxic, doses of 20 to 60 mg/kg result in mild-to-moderate toxicity, and doses >60 mg/kg are potentially fatal.[92,94,96]

The independent verification of the tablet by K.M.'s mother and the tablet imprint indicate that each tablet contained 325 mg of ferrous fumarate in an enteric-coated formulation. Because the dose–toxicity relationship of iron is based on the amount of elemental iron ingested, knowledge of the specific iron salt is important in calculating the ingested dose. Ferrous fumarate contains 33% elemental iron, whereas ferrous gluconate contains 12%, and ferrous sulfate contains 20%.[91,92,94,95] Therefore, each 325-mg ferrous sulfate tablet contains 108 mg of elemental iron. K.M. ingested a maximum of seven enteric-coated ferrous fumarate 325-mg tablets, and she weighs 24.25 pounds (11 kg). Her ingestion of ~69 mg/kg (108 mg per tablet × 7 tablets = 756 mg total ÷ 24.25-pound [11-kg] patient weight) of iron places her at risk for severe toxicity. Although K.M.'s only symptom is vomiting at this time, absorption could be delayed because she ingested an enteric-coated formulation.

Abdominal Radiographs

Case 5-3, Question 5: K.M. is expected to experience potentially severe toxicity from her iron ingestion. Why would an abdominal radiograph be useful to verify the number of iron tablets ingested?

In theory, radiopaque substances (eg, iron, enteric-coated tablets, chloral hydrate, phenothiazines, heavy metals) can be visualized in the GI tract by an abdominal radiograph.[99] The ability of a radiograph to detect the presence of a radiodense substance depends on the dosage form, concentration, and molecular weight of the substance. The intact dosage form can often be detected if the tablet has not already disintegrated or dissolved.[99]

Less than one-third of pediatric abdominal radiographs show positive evidence of tablets or granules after iron poisoning.[100] Children are more likely than are adults to chew tablets rather than swallow them whole, and false-negative results can occur when whole tablets have not started to disintegrate. If the tablets were chewed, an abdominal radiograph is not likely to be useful for verifying the number of iron tablets ingested. However, an abdominal radiograph after the completion of GI decontamination can help assess whether additional decontamination is needed.[99]

Gastrointestinal Decontamination

Case 5-3, Question 6: Would gastric lavage or activated charcoal not be indicated for the management of K.M.'s iron ingestion? Why or why not?

When selecting a method of GI decontamination, consider the substance ingested, maximal potential toxicity expected from the drug dosage form, potential time course of toxicity, time elapsed between ingestion and the initiation of treatment, symptoms, and physical examination findings. Decontamination with activated charcoal is not indicated in K.M. because iron tablets are not adsorbed by activated charcoal.[49,91,99] Gastric lavage would also be ineffective because the removal of large undissolved iron tablets from the stomach is limited by the small internal diameter of the gastric lavage tube, especially in pediatric patients.[99,100]

Whole-Bowel Irrigation

Case 5-3, Question 7: What other method of GI decontamination should be considered for K.M.?

WBI with a polyethylene glycol electrolyte solution can be considered in this case. WBI fluid can be administered orally or by an NG tube at a rate of 1.5 to 2 L/hour for adults and at a rate of 500

mL/hour for children.[59,101] Although the ingestion of a large volume of fluid over several hours and the likelihood of nausea and vomiting often result in poor patient compliance, K.M. is hospitalized and the fluid can be infused by an NG tube. WBI should be continued until the rectal effluent is clear, which can take many hours.[59,101,102]

MONITORING EFFECTIVENESS OF TREATMENT

Case 5-3, Question 8: How should the effectiveness of GI decontamination be assessed in the ED?

To assess the effectiveness of GI decontamination, the return fluid from the WBI is visually inspected for tablets or tablet fragments. Increasing serum iron concentrations, deteriorating clinical status, or evidence of radiodense tablets in the GI tract on abdominal radiograph are all indications for more aggressive treatment.[92,94,102]

Serum Iron Concentrations

Case 5-3, Question 9: At this time, K.M. does not appear to be experiencing any CNS or cardiovascular symptoms associated with toxic iron ingestions. She did have one episode of diarrhea that tested negative for blood. A serum iron concentration, obtained about 4 hours after the ingestion, was 480 µg/dL (normal, 60–160 µg/dL). What conclusions as to severity or likely clinical outcome can be derived from this serum iron concentration?

The serum iron concentration provides an indication as to whether more aggressive therapy is needed.[96,100,103] The higher than normal serum iron concentration confirms the suspicion that K.M. has ingested iron tablets despite both her current lack of serious symptoms and the absence of tablet evidence in the rectal effluent or by abdominal radiograph.

The time course of absorption is probably the most difficult pharmacokinetic parameter to evaluate with toxic ingestions. Drug concentrations can continue to rise after an overdose despite GI

decontamination.[93,95,96,103] This prolongation of absorption time is further complicated when sustained-release or enteric-coated dosage formulations have been ingested because the onset of symptoms is unpredictable.[94]

K.M.'s serum iron concentration of 480 µg/dL suggests a serious ingestion because peak serum iron concentrations >500 µg/dL are usually predictive of significant toxicity.[93–96,100,103] This single serum iron concentration does not provide information as to whether the serum concentration is rising or declining or when the serum iron concentration will peak as a result of her iron ingestion.[104] Iron tablets may also clump together and form a bezoar, which can result in prolonged absorption and delay the onset of toxicity.[93,96] Samples for peak serum iron concentration should be obtained 4 to 6 hours after ingestion.[94–96,103] Although K.M.'s serum iron concentration was measured ~3 hours after ingestion, another serum iron level is needed in 2 to 4 hours because she ingested an enteric-coated formulation.

Blood Glucose, White Blood Cell Count, and Total Iron–Binding Capacity

Case 5-3, Question 10: K.M. was administered WBI through the NG tube for several hours until the rectal effluent was clear. At this time, K.M. had three more episodes of vomiting and became drowsy and fussy. A repeat serum iron concentration was ordered at 6 hours after ingestion. What other laboratory tests could be helpful in assessing the potential toxicity of iron in K.M.?

Blood glucose concentrations and white blood cell (WBC) counts usually are increased when serum iron concentrations are >300 µg/dL. A WBC count >15,000/mL and a blood glucose concentration >150 mg/dL within 6 hours of ingestion generally suggest a higher likelihood of severe toxicity.[93] These tests provide supplemental confirmation of iron intoxication and may be useful in medical facilities in which serum iron concentrations cannot be obtained. These laboratory tests are not routinely monitored in iron poisoning

because of the poor sensitivity (about 50%).[94] Treatment should not be based on a WBC and glucose concentration alone.[93–95,100] If a patient with severe iron toxicity presents to a health care facility that cannot perform timely serum iron levels, either the blood iron sample must be sent to a laboratory that can do the testing quickly or the patient must be transferred to a health care facility that can do serum iron testing for patient monitoring.

It was once believed that if the serum iron concentration exceeded the total iron–binding capacity concentration, it would indicate substantial iron toxicity. However, this theory has not held up, and the total iron–binding capacity test is no longer used to monitor iron toxicity.[99]

Stages of Iron Toxicity

Case 5-3, Question 11: It is now 6 hours since K.M. ingested the iron tablets. Her second serum iron concentration is not yet available. She continues to be drowsy and fussy, and she has missed her usual nap. She is still vomiting. Why is K.M.'s relatively mild course at this time not particularly reassuring?

The time between the ingestion of an overdose of drugs and the development of severe toxicity can be delayed. It is unclear why there may be an asymptomatic period, but it may be secondary to delayed absorption of the ingested drug, the time required for the drug distribution, or the time needed to form a toxic metabolite. Consequently, K.M. may still exhibit further symptoms of severe toxicity. Four distinct stages of symptoms can be encountered with iron toxicity.[91–96]

STAGE I

Stage I symptoms usually take place within 6 hours of ingestion, during which nausea, vomiting, diarrhea, and abdominal pain occur, probably secondary to the erosive effects of iron on the GI mucosa. The caustic effects of free iron can cause bleeding, as evidenced by

blood in the vomitus and stool. In more severe intoxications, CNS and cardiovascular toxicity can be present during stage I.[93–96]

STAGE II

The second stage of iron toxicity has been suggested as a period of reduced symptoms and an apparent clinical improvement. This stage can last for up to 12 to 24 hours after the ingestion and could be misinterpreted as resolving toxicity. This stage may represent the time needed for the absorbed iron to distribute throughout the body before systemic symptoms develop.[91] In most severe cases, stage II does not occur and the patient's condition continues to deteriorate.[93–96]

STAGE III

Stage III generally occurs 12 to 48 hours after iron ingestion and is characterized by CNS toxicity (eg, lethargy, coma, seizures) and cardiovascular toxicity (eg, hypotension, shock, pulmonary edema). Metabolic acidosis, hypoglycemia, hepatic necrosis, renal damage, and coagulopathy can also happen during this stage.[93–96]

STAGE IV

The final stage is apparent 4 to 6 weeks after acute iron ingestion and consists of delayed-onset GI tract sequelae secondary to the initial local toxicity. In this stage, prior tissue damage can progress to gastric scarring and strictures at the pylorus, resulting in permanent abnormalities of GI function.[93–96]

Patients can present to the health care facility in any stage of iron toxicity and can have a fatal outcome in any stage. Determination of a stage of toxicity should be based on clinical symptoms rather than time of ingestion.[95]

Deferoxamine Chelation

CASE 5-3, QUESTION 12: The second serum iron concentration that was obtained 6 hours after ingestion has increased from 480 to 560 µg/dL. The child has continued to vomit and appears pale. What criteria are most important in determining whether K.M. is a candidate for the antidote deferoxamine?

Deferoxamine (Desferal®) chelates iron by binding ferric ions in plasma to form the iron complex ferrioxamine.[94] Deferoxamine prevents iron toxicity at a cellular level by removing iron from mitochondria.[92] Unfortunately, deferoxamine is not a very effective antidote because a relatively small amount of iron is bound (~9 mg of iron to 100 mg of deferoxamine).[104,105] The iron–deferoxamine complex is primarily excreted renally as ferrioxamine.[92,94,95] Renal elimination of the ferrioxamine usually results in pinkish orange urine, often described as "vin rosé."[92,94,95] Deferoxamine therapy should be initiated when serum iron concentrations exceed 500 µg/dL and when symptoms of iron toxicity (eg, GI symptoms, hemorrhage, coma, shock, seizures) are present.[92–95] K.M. is experiencing symptoms, she presumably ingested up to 69 mg/kg of elemental iron, and iron absorption appears to be ongoing based on the increase in her serum iron concentration. Therefore, K.M. should be treated with deferoxamine.

DEFEROXAMINE DOSE

CASE 5-3, QUESTION 13: What dose of deferoxamine should be prescribed for K.M., and how should it be administered?

Deferoxamine is most effective when administered as a continuous IV infusion because of its short half-life (76 ± 10 minutes).[95,104] Clinically, a slow IV infusion is preferred over intramuscular (IM) administration because the IV dose is better controlled, less painful, and better absorbed than is an IM dose.[95,96] Deferoxamine is usually administered in a continuous IV infusion at a dose of 15 mg/kg/hour. However, doses up to 45 mg/kg/hour have been used in patients with severe iron poisoning.[93–96,104]

Administering IV boluses of deferoxamine too rapidly can result in hypotension.[94,96,104,105] According to the manufacturer, the total deferoxamine dose should not exceed 6 g every 24 hours in children or adults, but adverse effects have not been seen in patients who received >6 g every 24 hours.[105]

Deferoxamine therapy should be initiated in K.M. at a lower rate of about 8 mg/kg/hour, and her clinical status should be monitored closely. If the dose is tolerated, the rate can be increased every 5 minutes until the desired rate of 15 mg/kg/hour is reached.[90]

MONITORING AND DISCONTINUATION

Case 5-3, Question 14: K.M. is admitted to the pediatric ICU shortly after the initiation of a deferoxamine infusion at 8 mg/kg/hour. How should deferoxamine therapy be monitored, and when should it be discontinued?

The rate of deferoxamine infusion should be increased with symptoms of severe iron toxicity and decreased if patients experience adverse effects.[93,94,96,105] Treatment should continue until the serum iron concentration is <100 µg/dL and symptoms of iron toxicity resolve.[105] Patients usually require chelation therapy for about 1 to 2 days, depending on the severity of symptoms.[93–95] Unnecessarily prolonged chelation therapy should be avoided because deferoxamine infusion for >24 hours has been associated with the development of acute respiratory distress syndrome.[93–98]

The urine color change to vin rosé indicates ferrioxamine in the urine.[92,96] The lack of a color change is not a reliable indication of adequate deferoxamine therapy because not all patients experience vin rosé urine.[92,96] There is also no correlation between the amount of iron ingested, serum iron concentration, and the urine color change.[92]

Deferoxamine can interfere with some laboratory methods used to measure serum iron concentrations and cause falsely low values.[92,93,103,106] Atomic absorptive spectroscopy is a recommended method for monitoring serum iron concentrations once deferoxamine

treatment has been started.[105] When initiating deferoxamine therapy, the clinical laboratory should be contacted to clarify whether deferoxamine will interfere with their serum iron analysis.

Patient Outcome

K.M. was admitted to the pediatric ICU overnight and treated with a constant infusion of deferoxamine at 15 mg/kg/hour for 13 hours. Her GI symptoms resolved, she became more alert, and her vital signs were stable. Her serum iron level was 70 µg/dL the next morning, and she was discharged home that afternoon.

ASSESSMENT OF CENTRAL NERVOUS SYSTEM DEPRESSANT VERSUS ANTIDEPRESSANT INGESTION

Validation of Ingestion

CASE 5-4

Question 1: A.G., a 40-year-old male, was found unconscious in a pool of vomitus with a suicide note. The note stated that he had ingested 30 of his pills. A.G.'s 75-year-old mother called paramedics. When the paramedics arrived, A.G.'s heart rate was 150 beats/minute, BP was 115/70 mm Hg, and respirations were 14 breaths/minute and shallow. A.G. responded only to painful stimuli. The paramedics immediately started an IV line after completing their assessment of his ABCs.

Why should the drug overdose information from this suicidal patient be validated?

Assessing the accuracy of the ingestion history information in adult drug exposures is difficult, and many health care professionals question the validity of information, especially from suicidal patients.[22–25,27] The ingestion history could be inaccurate because

the patient's altered mental status might prevent accurate recollection of what occurred. He may also try to intentionally mislead health care providers to avoid appropriate care. Studies have demonstrated a poor correlation between reported drug ingestions and urine drug test results.[23–25,27,32,33,107] There are also numerous false-positive results that can be misleading because of drug interference.[108,109]

Urine drug screens generally detect all recent drug and substance use, rather than just an overdosed drug. Urine drug screen results, therefore, are not reliable indicators of acute exposures. Every effort should be made to validate the history with information from other sources. In suicidal patients, one should consider all drugs that may have been available to the patient, as well as the patient's presenting symptoms, laboratory tests, and information obtained from family members, police, paramedics, and other individuals who know the patient.[22–25,27]

Interventions by Protocol

Case 5-4, Question 2: In addition to managing the ABCs, what pharmacologic interventions should be authorized for the paramedics to administer to A.G. in addition to the initiation of an IV solution?

GLUCOSE AND THIAMINE

Emergency medical service personnel often have protocols directing them to treat patients who are unconscious from an unknown cause. These protocols generally include administration of glucose, thiamine, and naloxone.[23,27,60,110] If paramedics cannot measure a blood glucose concentration immediately, A.G. should be given 50 mL of 50% dextrose to treat possible hypoglycemia. The risks of hyperglycemia from this dose of glucose are negligible relative to the significant benefits if the patient is hypoglycemic. Thiamine should be administered concurrently with glucose because glucose can precipitate Wernicke–Korsakoff complex in thiamine-deficient patients[111] (see Chapter 90, Substance Use Disorders). Wernicke

encephalopathy is a reversible neurologic disturbance consisting of generalized confusion, ataxia, and ophthalmoplegia. Korsakoff psychosis is believed to be irreversible and is associated with a more prolonged deficiency of thiamine.[111,112] The unconscious patient should also be evaluated for blood loss, sepsis, hypoxia, and evidence of head trauma.[25]

NALOXONE

The pure opioid antagonist, naloxone, is indicated for the treatment of respiratory depression induced by opioids,[110,113] but many emergency medical service protocols authorize paramedics to routinely administer naloxone to all patients with any decreased mental status.[114] Naloxone reportedly has reversed coma and acute respiratory depression in intoxicated patients who have no evidence of opioid use.[60,112] The response of these patients to naloxone might have been secondary to opioids that were not detected by the urine toxicology screens (eg, oxycodone, methadone, fentanyl). Reports of naloxone success in patients without opioid use could also have been the result of responses to other stimuli rather than a response to naloxone.

Administering naloxone to a patient with opioid use disorder can precipitate withdrawal symptoms (eg, agitation, combativeness, vomiting, diarrhea, lacrimation, rhinorrhea) that can further complicate the intoxication picture.[60] Small doses of naloxone should be administered initially to determine the patient's response to this medication. Violent and aggressive behavior can result when sudden increased consciousness is induced by naloxone.[27] This can complicate emergency care in an emergency transport vehicle and put caregivers and patients at risk for trauma.[60]

Initial Treatment

Case 5-4, Question 3: The paramedics arrive at the ED with A.G. 30 minutes after his mother called. A.G.'s heart rate in the ED is 155 beats/minute, BP is 89/50 mm Hg, and respirations have decreased from 14 to 9 breaths/minute,

with assisted ventilation. A.G. remains unresponsive. The paramedics were unable to find any prescriptions or other medications in the house. The mother thinks her son was taking medication for depression. The medical team will try to obtain more details from A.G.'s pharmacy. What initial treatment should be provided for A.G. in the ED?

A.G. should be intubated and mechanically ventilated with 100% oxygen because of his shallow, slow respirations and the likelihood that vomitus could have been aspirated into his lungs. A bolus of IV fluid should be administered to A.G. to determine whether an increase in intravascular fluid volume will increase his BP and improve his mental status.[22,40]

Antidotes

Case 5-4, Question 4: A.G. fills his prescriptions at several pharmacies, and it is taking a while to obtain his medication list. What antidotes can be administered in the ED for diagnostic purposes? Should flumazenil (Romazicon®) be administered?

Theoretically, antidotes such as naloxone, flumazenil, deferoxamine, and digoxin-specific antibody (FAB) fragments could be administered in a hospitalized setting to identify an unknown toxin.[22,26,27,113,115,116] However, the cost and time required for administration, and increased risks from these antidotes, preclude their use for diagnostic purposes without some plausible suspicion of a specific drug ingestion.[113,115]

Organ System Evaluations

Case 5-4, Question 5: How can the initial physical assessment, using an organ systems approach, help in identifying the drugs ingested by A.G.?

The patient's ABCs and CNS and cardiopulmonary functions should be assessed, with special attention to clinical manifestations

that suggest ingestion of a specific class of drugs.[27,40] A.G.'s history of depression suggests that antidepressants, antipsychotics, lithium, or benzodiazepines are candidates for ingestion. An organ system evaluation will help determine whether these (or other) drugs might have been ingested. Commonly used nonprescription medications such as aspirin, acetaminophen, decongestants, and antihistamines, should also be considered because adult drug ingestions usually involve more than one drug.

CENTRAL NERVOUS SYSTEM FUNCTION

Changes in CNS function are probably the single most common finding associated with drug intoxication.[27] CNS depression or stimulation, seizures, delirium, hallucinations, coma, or any combination of these can be seen in intoxicated patients. CNS changes can be the direct result of an ingested drug or may be attributed to other underlying CNS processes or medical conditions.[116] Clinical manifestations of drug overdoses may differ depending on where the patient is in the time course of the intoxication, and the amount of drug(s) ingested.[27,64]

Drugs with anticholinergic properties can produce disorientation, confusion, delirium, and visual hallucinations early in the course of the intoxication; coma can become apparent as toxicity progresses. Generally, overdoses with anticholinergic drugs do not produce true hallucinations, but rather pseudohallucinations. When a patient with an intact baseline mental status presents with psychosis, paranoia, or visual hallucinations, CNS stimulants such as cocaine or amphetamines should be considered.[30,65]

Drug intoxication–induced alterations in CNS function are initially difficult to distinguish from those caused by underlying psychiatric disorders, trauma, hypoxia, or metabolic disorders, such as hepatic encephalopathy or hypoglycemia. However, as time passes, decreased CNS function secondary to drug toxicity is more likely to wax and wane in severity in contrast to the persistent CNS depression that occurs with significant trauma or metabolic disorders. Drug toxicity also rarely produces focal neurologic

findings. Changes in pupil size, reflexes, and vital signs can provide insights into the pharmacologic class of drug involved in the intoxication.[23,27,28]

CNS depression, seizures, disorientation, and other CNS changes that are commonly associated with psychiatric drugs should be evaluated carefully in A.G. For example, A.G.'s pupil size would most likely be dilated if he had ingested a TCA because of the anticholinergic effects of these drugs. TCA intoxications can also cause myoclonic spasms,[27] which are often difficult to differentiate from seizure activity caused by TCA overdoses, although the spasms are often asymmetric and more persistent.[117]

CARDIOVASCULAR FUNCTION

Assessment of heart rate, rhythm, conduction, and measurements of hemodynamic function can also be used to help identify the type of drug ingested. Overdoses of sympathomimetic drugs usually increase heart rate, whereas overdoses of cardiac glycosides or β-blockers can slow the heart rate. Although drugs can increase or decrease heart rate directly, indirect cardiac effects (eg, reflex tachycardia in response to hypotension) also need to be considered. Abnormal heart rates produced by drug overdoses are usually not treated unless accompanied by hypotension or severe dysrhythmias.[27,40]

PULMONARY FUNCTION

Evaluating the rate and depth of respiration and the effectiveness of gas exchange in an intoxicated patient can also help identify drugs ingested. A decrease in respiratory rate is commonly associated with the ingestion of CNS depressants. An increased respiratory rate and depth is generally associated with CNS stimulant toxicity and can also be secondary to respiratory compensation for drug-induced metabolic acidosis.[27] Aspiration of gastric contents after vomiting is common in drug ingestions. Aspiration pneumonitis is the most common pulmonary abnormality associated with significant intoxications.[43] Noncardiogenic acute pulmonary edema has been

associated with salicylate overdoses[80] (especially with chronic intoxications) and drugs of abuse (eg, cocaine and heroin).[114,118–124]

TEMPERATURE REGULATION

Body temperature is an important and sometimes overlooked parameter when assessing potential intoxications.[27,40] Decreased mental status is often associated with a loss of thermoregulation, resulting in a body temperature that falls or increases toward the ambient temperature. Increased body temperature (hyperthermia) caused by overdoses of CNS stimulants (eg, cocaine, amphetamines, ecstasy), salicylates, hallucinogens (eg, phencyclidine), serotonergic agents, or anticholinergic drugs or plants (eg, jimsonweed) can have serious consequences.[27,29,40] Body temperature should be measured rectally to obtain an accurate representation of core body temperature.[125]

Hyperthermia caused by drug overdoses is commonly seen in hot, humid environments or when the intoxication is associated with physical exertion, increased muscle tone, or seizures. In these patients, it is important to obtain renal function tests (eg, BUN, serum creatinine) and a serum creatine kinase measurement to determine whether rhabdomyolysis has occurred secondary to breakdown of muscle tissue.[27,40,125]

GASTROINTESTINAL FUNCTION

The GI tract should be assessed for decreased motility because drug absorption can be delayed or prolonged.[27,126,127] When this is the case, decontamination may be beneficial after an oral ingestion even if a long time has elapsed since the ingestion. The presence of blood in either emesis or stool may suggest ingestion of a GI irritant or caustic substance.[128]

SKIN AND EXTREMITIES

The physical examination should include a thorough examination of the body surface for causes of trauma that may also explain the patient's condition. Examination of the skin and extremities can

provide evidence of drug intoxication, especially with IV or subcutaneous drug injection needle marks.[27] Drugs can be hidden in the rectum or vagina.[27] Drug patches (eg, fentanyl) may be found in hidden areas of the body such as the back of the neck or scrotum. Fluid-filled bullae at gravity-dependent sites that have been in contact with hard surfaces for a long time suggest prolonged coma.[27] Muscle tone should also be assessed.[30] Increased tone or myoclonic spasms can be caused by some drug overdoses (eg, TCAs) and can produce rhabdomyolysis or hyperthermia.[27,125] Dry, hot, red skin may also be an indication of anticholinergic toxicity.[27,40]

In summary, an organ system assessment of A.G. can provide useful insights into the identity of drugs that might have been ingested, the viability of organ function that might have been adversely affected, and the treatment needed.

Laboratory Tests

Case 5-4, Question 6: What laboratory tests should be ordered for A.G.?

The laboratory assessment of an intoxicated patient should be guided by the history of the events surrounding the ingestion, clinical presentation, and past medical history.[22,129] The status of oxygenation, acid–base balance, and blood glucose concentration must be determined, especially in patients with altered mental status such as A.G.[40] Oxygenation can be assessed initially by pulse oximetry, and acid–base status by ABGs and serum electrolyte concentrations.[129,130] A.G. was given oxygen and a bolus of IV fluid on arrival at the ED, and paramedics administered glucose during transportation.

A medical history of organ dysfunction or medical disorders (eg, diabetes, hypertension) that can damage organs of elimination (eg, kidney, liver) will also guide the need for laboratory tests. A serum creatinine concentration and liver function tests (eg, aspartate aminotransferase [AST], alanine aminotransferase [ALT]) should be

ordered. Other more specific tests reflective of his past medical history can be ordered subsequent to a dialogue with his psychiatrist. A complete blood cell count, complete chemistry panel, serum osmolality, and other baseline laboratory tests should be obtained.[27] Pregnancy tests should be considered in female patients of childbearing age because unwanted pregnancies are common causes of overdose.[131,132]

A baseline electrocardiogram (ECG) should be obtained when exposure to a cardiotoxic drug is suspected or whenever the cardiovascular or hemodynamic status is altered.[23,26,40,130] A 12-lead ECG should be ordered because A.G. is likely to have ingested a psychotropic agent. Continuous cardiac monitoring should be instituted because of the significant cardiotoxicity associated with overdoses of these agents. Patients with severe TCA overdoses frequently present with symptoms of coma, tachycardia with a widened QRS interval, seizures, hypotension, and respiratory depression.[133–136]

A chest radiograph is useful when the potential exists for either direct pulmonary toxicity or aspiration.[23,26] A chest radiograph is indicated because A.G. had vomitus in his mouth, and TCAs are associated with the development of acute respiratory distress syndrome and pulmonary edema.[133,137,138]

Qualitative Screening

Case 5-4, Question 7: Should A.G.'s urine and blood be screened to assist in identifying the ingested substance? What is your rationale?

Toxicology laboratory testing can be used to identify the substances involved in a toxic exposure, to exclude substances, or to measure the concentration of substances in serum or other biologic fluids.[24,129,130] The identification and quantification of compounds should be considered as two distinct types of toxicologic testing.[24,139] *Qualitative* screening is used to identify which substance

or class of substances is involved in the toxic exposure. *Quantitative* testing determines how much of a known substance is present.[24]

Screening of various biologic fluids can identify unknown substances. Urine is screened much more commonly than is blood, whereas gastric fluid is rarely evaluated. A urine drug screen is preferred to a blood drug screen because urine generally contains a higher concentration of a drug and its metabolites than do other body fluids.[140]

When reviewing the results of urine screening panels for drugs and other substances, one must remember that the presence of a substance in urine is not necessarily related to a concurrent toxicity. A positive result on a urine screening panel merely indicates that the patient has ingested or has been exposed to the substance, but it does not differentiate between toxic and nontoxic doses. If a drug and its metabolites are eliminated slowly into the urine for a prolonged time, and if the testing methodology detects small concentrations of the substance, urine drug screening could identify the presence of a substance days, weeks, or even months after the exposure (eg, marijuana).[24,130]

It is important to know which drugs or substances are tested at a given laboratory. Many laboratories restrict the number of drugs for which they test because 15 drugs account for >90% of all drug overdoses.[32] Some urine toxicology screens only detect common drugs of abuse (eg, amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, opioids).[130] Some drugs of abuse are not detected on routine drug screening (eg, γ-hydroxybutyrate, ketamine, flunitrazepam).[24] Some analyses detect only antibodies to drug metabolites. For example, a benzodiazepine screen detects oxazepam, a common benzodiazepine metabolite. However, alprazolam and lorazepam are not metabolized to oxazepam and will not be detected in a urine screen. Likewise, an opioid screen may not detect synthetic opioids such as fentanyl and methadone.[130]

Results of qualitative toxicology screening tests are difficult to interpret. False negatives, false positives, cross-reactivity with related drugs, chronicity of exposure, and length of time since last exposure all complicate results.[108,109,130] Urine toxicology screen

results rarely change clinical management of the patient. Monitoring mental, cardiovascular, and respiratory status and other laboratory parameters provide better clues than do the results of a urine toxicology screen.[23,24,129,130,139]

Toxicology screening can be appropriate when the history of a suspected toxic exposure is unavailable, inaccurate, or inconsistent with the clinical findings.[24] However, it is important to know which drugs are detected on a given toxicology screen.[130] A comprehensive qualitative urine drug screen can be considered for A.G. because information about the substance(s) he ingested is not yet known.

Quantitative Testing

Case 5-4, Question 8: Should a quantitative toxicology laboratory test be ordered for A.G. as well? What is your rationale?

After a qualitative urine analysis for drugs, a quantitative analysis of drug concentration in blood can help determine the severity of toxicity and the need for aggressive interventions (eg, hemodialysis).[24,33,130,139] Quantitative tests are especially useful when assessing the potential toxicity of drugs with delayed clinical toxicity or when the toxicity primarily is caused by metabolites (eg, ethylene glycol, methanol). The concentration of a drug in serum is sometimes much more predictive of end-organ damage than are clinical findings (eg, acetaminophen effect on the liver).

Quantifying the amount of drug in serum is useful when (a) the concentration of the substance correlates with toxic effects, (b) the turnaround time for results is rapid, and (c) treatment can be guided by the serum concentration.[32,132,142] To aid in the care of poisoned patients, stat quantitative serum concentrations of acetaminophen, carbamazepine, carboxyhemoglobin, digoxin, ethanol, ethylene glycol, iron, lithium, methanol, methemoglobin, phenobarbital, salicylates, and theophylline should be available at laboratories of large health care facilities.[23,24,33,129,139]

When blood samples are collected to quantitate potentially intoxicating substances, as much information as possible should be obtained about the time course of events to determine whether absorption and distribution of the substance is complete. Serial samples may be needed to determine whether significant absorption is still occurring.[29,30] In contrast to the interpretation of therapeutic serum concentrations of chronically administered drugs, the serum concentration of a substance ingested in an overdose is not likely to be at a steady state.

Quantitative toxicologic testing will likely not benefit A.G. at this point in time because the identity of the ingested substance is unknown. Nevertheless, a serum ethanol concentration could be obtained because alcohol is often ingested concurrently in overdose situations.[132] Most poison centers also recommend obtaining a quantitative acetaminophen level on all intentional ingestions because serious hepatotoxicity can occur if acetaminophen ingestion is missed.[24,129,130]

Assessment

Case 5-4, Question 9: A.G.'s clinical status has not changed in the past 10 minutes. A urine toxicology screen, blood acetaminophen, blood alcohol, and ABGs have been ordered. The 12-lead ECG shows a prolonged QRS interval of 0.13 seconds (normal, <0.1 seconds). No antidotes have been administered. A.G.'s physical examination did not detect any evidence of trauma to his head. His pupils were dilated and slowly responsive to light, and his bowel sounds were hypoactive. What conclusions can be made at this time with regard to the likely substance ingested by A.G.?

Although the ingested substance still has not been specifically identified, the available data provide some clues as to the likely pharmacologic class of drug that was ingested. The presence of CNS depression (A.G. is unresponsive), slowed ventricular conduction (widened QRS on ECG), tachycardia (heart rate, 155 beats/minute), hypotension (BP, 89/50 mm Hg), and decreased GI motility (hypoactive bowel sounds), and the history of a possible

depressive illness (history from mother) are all consistent with a TCA drug overdose. The antidepressant could have been ingested alone or with other agents.

Antidepressant Toxicities

Case 5-4, Question 10: How would the different toxicities of the many available antidepressants affect the treatment of A.G.?

The major pharmacologic effects and toxicities of the antidepressants are similar for all drugs within the same class. When a specific drug within a therapeutic class has not yet been identified, the overdose should be managed as if the ingested drug can produce the most severe toxicity of any drug in the class. Therefore, A.G.'s presumed antidepressant drug overdose should be evaluated and managed initially as TCA (eg, amitriptyline) ingestion.[135,141] Antidepressants with different structures and actions (eg, trazodone [Desyrel®], fluoxetine [Prozac®], sertraline [Zoloft®]) generally do not produce toxicity as severe as that of the TCAs.[135,141,142]

Gastrointestinal Decontamination

Case 5-4, Question 11: If a TCA ingestion is presumed, why might GI decontamination be appropriate at this time?

The longer GI decontamination is delayed relative to the time of ingestion, the less effective it is likely to be because drug absorption will already have occurred. Because the time of ingestion is unknown and A.G. is unresponsive, he probably already has absorbed significant amounts of the drug, making him more vulnerable to aspiration. In addition, A.G. might already have aspirated because he was found in a pool of vomitus. TCA overdoses can also cause seizures, which would be a relative contraindication to GI

decontamination. In consideration of these concerns, many would not support GI decontamination for A.G.[41–44,51–54]

Others might support GI decontamination because TCAs have strong central and peripheral anticholinergic properties that slow GI emptying, which could result in erratic absorption and delayed toxicity, but A.G. would first need to be intubated to protect his airway. Furthermore, TCAs have a large volume of distribution (10–50 L/kg), and both the parent drug and its metabolite undergo enterohepatic recirculation. The half-life of TCAs in overdose situations is 37 to 60 hours. For those reasons, activated charcoal could be reasonably administered in an effort to adsorb any drug that may not yet be absorbed from the GI tract.[49]

Repeated doses of activated charcoal have been used to increase the elimination of TCAs because of the long half-life of TCAs and the enterohepatic recirculation. In clinical studies, multiple-dose activated charcoal has increased the elimination of amitriptyline, but the data are insufficient to support or exclude its use.[47]

MONITORING EFFICACY

Case 5-4, Question 12: How should the effectiveness of GI decontamination be monitored in A.G.?

If activated charcoal is administered, A.G. must first be intubated to protect his airway, and the charcoal must be administered via an NG tube because he is unconscious. The insertion of the NG tube could stimulate the gag reflex, causing vomiting and possible aspiration. A.G.'s lung sounds should be monitored closely to determine whether aspiration pneumonitis is developing, particularly because A.G. was found unconscious and had already vomited.

Activated charcoal, especially in multiple doses, can produce ileus, GI obstruction, or intestinal perforation, particularly when administered to patients who have ingested drugs that slow GI motility.[47,49,101] Bowel sounds must be monitored frequently to ensure that an ileus is not developing. Once the patient passes a charcoal-

laden stool, the activated charcoal can be considered to have successfully passed through the GI tract.

Sodium Bicarbonate and Hyperventilation

Case 5-4, Question 13: According to A.G.'s psychiatrist, he prescribed amitriptyline 100 mg at bedtime for his severe depression. How does this new information alter A.G.'s treatment plan?

This information confirms the assumptions that a TCA was ingested. It also specifically identifies the drug ingested. In TCA ingestions, severe toxicity has been associated with doses of 15 to 25 mg/kg.[98] A.G. ingested a total of 3000 mg based on his suicide note that said he took 30 tablets. If he weighs about 154.32 pounds (70 kg) and was truthful about the amount taken, he ingested a significantly toxic dose (about 43 mg/kg).

On the ECG, TCA toxicity will manifest as tachycardia with prolongation of the PR, QTc, and QRS intervals, ST- and T-wave changes, and abnormalities of the terminal 40-millisecond vector.[98,117,133,136,142–146] TCAs have anticholinergic, adrenergic, and quinidine-like membrane effects on the heart.[117,133,135,141,144] It is believed that the anticholinergic effect causes the tachycardia and the quinidine-like effect causes the ECG changes.

In addition, TCAs are sodium channel blockers.[147] Sodium channel blockade slows the maximum uptake stroke of phase 0 of the action potential and decreases automaticity. Blockade decreases conduction velocity in the Purkinje fibers, which increases the QRS interval.[144] Myocardial depression, ventricular tachycardia, and ventricular fibrillation are the most common causes of death from TCAs.[136] Therefore, admission to the ICU with continuous cardiac monitoring is essential for A.G.[143]

The primary therapy for reversing ventricular arrhythmias and conduction delays is alkalinization of the serum and sodium loading with IV hypertonic sodium bicarbonate.[117,133,135,136,144,145,148] Indications for sodium bicarbonate include hypotension, widened QRS interval

(>100 milliseconds), right bundle branch block, and wide complex tachycardia.[135,145] Alkalinization increases serum protein binding of the TCAs and reduces the amount of free active drug (likely a minor consideration).[116,133,136,145] Correction of the serum pH is beneficial because underlying acidosis worsens TCA-induced cardiotoxicity.[145] Furthermore, sodium bicarbonate has been found useful even in patients with a normal pH because sodium bicarbonate purportedly overcomes the sodium channel blockade and reduces cardiotoxicity.[145,147]

On the basis of A.G.'s tachycardia and a widened QRS segment on ECG, he should be treated with IV sodium bicarbonate with the goal of achieving an arterial pH of 7.45 to 7.55.[136,145] Sodium bicarbonate could have been administered earlier because the suspicion of an antidepressant overdose was strong initially, his ECG demonstrated QRS widening and worsening myocardial conduction, and his BP continued to decline from the time he was first seen by the paramedics. If not monitored closely, the use of IV sodium bicarbonate could introduce the risk of sodium overload and subsequent pulmonary edema.[98,146]

An alternative is to hyperventilate the patient to a pH of 7.5 by adjusting his ventilator setting, thereby reducing the cardiotoxicity of the TCA.[133,136,146] The combination of IV bicarbonate and mechanical ventilation is more likely to produce severe alkalemia. Careful and frequent monitoring of the serum pH of patients on dual therapy is essential.[133,147]

MONITORING EFFICACY

Case 5-4, Question 14: How should the sodium bicarbonate therapy in A.G. be monitored?

Patients intoxicated with TCAs often present with severe acidosis. Large doses of sodium bicarbonate may be required to normalize the arterial pH. The efficacy of sodium bicarbonate administration can be

evaluated by monitoring acid–base status using ABGs, especially if the patient is also being ventilated mechanically.[133,147,148]

Sodium bicarbonate should be administered IV as a bolus of 1 to 2 mEq/kg for a 1- to 2-minute period. Continuous ECG monitoring is needed to monitor results of the bolus on cardiac abnormalities. Repeat bolus doses are administered as needed until the QRS interval narrows and tachycardia slows. Blood pH should be tested after several boluses to determine whether a target pH of 7.5 to 7.55 has been obtained.[145] At a minimum, ABGs should be determined within an hour of starting sodium bicarbonate therapy to determine pH response.[148] Bicarbonate boluses can be followed by a constant sodium bicarbonate infusion of 150 mEq/L to maintain an alkaline pH.[145] ABGs must be monitored frequently to ensure a response.[133,147,148] Serial ECGs to measure the QRS interval are useful for evaluating the efficacy of sodium bicarbonate therapy. A widened QRS interval will generally normalize after the systemic pH has been increased to about 7.5.[148]

Seizures

Case 5-4, Question 15: A.G. gradually developed more severely altered mental status and became comatose, not responding even to painful stimuli. He suddenly experienced a tonic-clonic seizure, which lasted about 1 minute and terminated spontaneously. Should anticonvulsant therapy be initiated for A.G. at this time?

CNS toxicity is common in TCA overdoses. Symptoms include agitation, hallucinations, coma, myoclonus, and seizures.[117,133–136] Seizures can cause significant increases in acidosis and increase cardiotoxicity. Seizures are often seen immediately before cardiopulmonary arrest. Because of the severe consequences of prolonged seizures, aggressive drug treatment with rapid onset of action is indicated, and benzodiazepines are the drugs of choice.[133,136]

Drug overdose–induced grand mal seizures are most commonly single seizures that terminate before drug therapy can be administered.[135] Seizure activity is not expected to persist, so instituting long-term anticonvulsant therapy is not indicated. However, if A.G.'s seizure did not stop within 1 to 2 minutes, a benzodiazepine would have been indicated.[117,133,136] The onset of action of phenobarbital is too slow for acute seizures, and phenytoin is usually ineffective in treating drug toxicity–related seizures.[117] After a seizure, the patient may become more acidotic and hypotensive.[136] Blood gases, creatine kinase, and ECG changes should be monitored immediately after a seizure.

Interpretation of Urine Screens

Case 5-4, Question 16: A.G.'s BP fell to 80/42 mm Hg, and dopamine was started. His pH on repeat ABGs was 7.20. A.G.'s ECG normalized after the administration of 150 mL of sodium bicarbonate by IV bolus. After dopamine, his BP increased to 100/56 mm Hg, and seizure activity ceased. The urine drug screen results were positive for amitriptyline and nortriptyline. Acetaminophen, salicylates, and ethanol were not detected in his blood. Does the presence of nortriptyline indicate that A.G. has ingested other drugs in addition to his amitriptyline?

Nortriptyline is a metabolite of amitriptyline and, therefore, was identified on the urine drug screen. Metabolites, as well as the parent compound, are often identified on comprehensive urine drug screens.[132]

Duration of Hospitalization

Case 5-4, Question 17: How long should A.G. be monitored?

A.G. should be admitted to the ICU and monitored until all evidence of CNS and cardiovascular toxicity has been reversed.[117] There is some controversy over how long symptomatic patients

should be observed. Some believe symptomatic patients need cardiac monitoring for 24 hours after ingestion.[135] Others believe that patients with TCA overdose need to be monitored until they are symptom-free for 24 hours because of a few reports of late development of symptoms.[139] However, 98% of signs of cardiotoxicity and arrhythmias are seen within the first 24 hours of TCA ingestion.[117,134] Because the incidence of late-occurring symptoms is rare, most patients are discharged after they are fully awake.[133] After the toxicity has completely resolved, A.G. should be evaluated by a psychiatrist to determine whether he should be admitted for inpatient treatment of his suicidal ideation.[133–135]

Patient Outcome

A.G. had no further seizure activity. He remained on a dopamine infusion for 8 hours and required several more boluses of IV sodium bicarbonate. The next afternoon, he started to awaken and expressed regret that his suicide attempt was not successful. Arrangements were made to transfer him to an inpatient psychiatric hospital once he was medically cleared.

ASSESSMENT OF ACETAMINOPHEN INGESTION

Mechanism of Hepatotoxicity

CASE 5-5

QUESTION 1: B.W., an 18-year-old female who is about 30 weeks pregnant, presents to the ED 8 hours after ingesting 40 acetaminophen 500-mg tablets. She is depressed and hoped to end her pregnancy by ingesting acetaminophen. Her pregnancy was unplanned, and she has received no prenatal care. B.W. has vomited spontaneously six times since the ingestion and is reporting abdominal pain; her heart rate is 95 beats/minute, BP is 110/74

mm Hg, and temperature is 98.5 °F (36.94 °C). B.W. does not have any chronic diseases, and the remainder of her medical history is unremarkable.

How does an overdose of acetaminophen cause toxicity?

Acetaminophen is metabolized in the liver by glucuronidation and sulfation. The mixed-function oxidase system cytochrome P-450 (CYP) 2E1 metabolizes a portion of the acetaminophen to the highly reactive metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI). In therapeutic doses, this metabolite is detoxified in the liver by glutathione. At toxic serum acetaminophen concentrations, the glucuronidation and sulfation metabolic pathways become saturated. Usually, NAPQI is detoxified by conjugation with glutathione, but increased amounts of the toxic metabolite deplete hepatic glutathione stores. When glutathione stores are decreased to about 30% of normal, the toxic metabolite binds to liver cells, resulting in the characteristic centrilobular hepatic necrosis seen in acetaminophen overdoses.[149–152]

Complication of Pregnancy

Case 5-5, Question 2: How does B.W.'s pregnancy change the management of her acetaminophen ingestion?

Pregnancy does not alter the initial approach to the assessment or treatment of potentially toxic ingestions, and assessment should focus initially on the pregnant patient.[153,154] Overdoses during pregnancy are often associated with attempted abortions, depression, prior loss of a child or children, potential loss of a lover, or economic reasons.[131,132,153,154] Intentional ingestions of analgesics, prenatal vitamins, iron, psychotropic agents, and antibiotics account for 74% of the overdoses during pregnancy.

The fetus is at risk when the pregnant patient overdoses on acetaminophen because acetaminophen crosses the placenta. The fetal liver can oxidize acetaminophen to its hepatotoxic metabolite by 14 weeks of gestation.[151] However, the fetal liver has only about 10%

of the capability of the adult liver to metabolize acetaminophen. The fetal liver can conjugate acetaminophen with both glutathione and sulfate, but detoxification by glutathione conjugation appears to be decreased.[155,156]

In studies of maternal acetaminophen toxicity, most of the pregnant females survived without damage to themselves or their babies. However, there were also maternal and fetal deaths as a result of overdose.[155,157] Acetaminophen overdoses during pregnancy did not appear to increase the risk of birth defects or adverse pregnancy outcomes unless the mother suffered severe toxicity, emphasizing the need to treat the mother promptly.[149,155]

Gastrointestinal Decontamination

Case 5-5, Question 3: Should GI decontamination be initiated for B.W.? What is your rationale?

B.W.'s acetaminophen ingestion occurred 8 hours ago; therefore, the drug is likely to be totally absorbed, and no GI decontamination should be initiated.

Estimating Potential Toxicity

Case 5-5, Question 4: How should the potential toxicity of the acetaminophen ingestion be assessed in B.W.?

Acetaminophen toxicity results from ingestions >150 mg/kg or >7.5 g total in adults. However, serum acetaminophen concentrations better predict acetaminophen-induced hepatotoxicity than does the dose of acetaminophen acutely ingested.[158,159] The Rumack–Matthew nomogram is used in the United States to assess the potential for hepatotoxicity from acute overdoses of acetaminophen.[160,161] The treatment line is defined by a serum acetaminophen concentration of 200 µg/mL at 4 hours after

acetaminophen ingestion and 30 µg/mL at 15 hours after ingestion on a semilogarithmic graph.[152] Many prefer to be more conservative and use the bottom line of 150 µg/mL at 4 hours to begin treatment as histories of ingestion are often inaccurate. The serum acetaminophen concentration is plotted on a graph against the time of ingestion.[159] The nomogram predicts the probability that the AST or ALT will be >1000 IU/L and can be used to guide therapy by indicating whether a specific acetaminophen concentration is in the toxic range.[162] The nomogram is useful only for acute ingestions because it underestimates the potential for toxicity in chronic acetaminophen ingestions. It should be noted that although the nomogram is used to plot acetaminophen concentrations for all patients, it has been validated only in healthy nonalcoholic adults.[152]

Acetaminophen Treatment Nomogram

Case 5-5, Question 5: When is the preferred time to measure a serum acetaminophen concentration?

Acetaminophen absorption generally is complete within 1.5 to 2.5 hours of ingestion of solid or liquid dosage forms.[159] The Rumack–Matthew nomogram is not applicable before 4 hours after ingestion because it is based on complete drug absorption.[159] Most clinical laboratories can complete their assays and report acetaminophen serum concentration results within 2 hours.

Stages of Acetaminophen Toxicity

Case 5-5, Question 6: What are the clinical signs and symptoms of acetaminophen toxicity?

Early detection of an acetaminophen overdose is difficult because there are no characteristic early diagnostic findings. Toxicity appears in stages that may overlap and are not clear-cut. About 30 minutes

to 24 hours after ingestion, the patient may exhibit anorexia, nausea, vomiting, malaise, and diaphoresis that can easily be attributed to other causes. The second stage of acetaminophen toxicity occurs about 24 to 48 hours after ingestion and is the stage in which hepatotoxicity develops. Hepatotoxicity is universal by 36 hours after ingestion. An AST measurement is the most sensitive measure of hepatotoxicity because AST abnormalities always precede evidence of actual liver impairment.[152,160,163]

In the third stage, 72 to 96 hours after ingestion, maximal liver dysfunction is evident with the return of anorexia, nausea, vomiting, and malaise. Symptoms can range from mild to fulminant liver failure with hepatic encephalopathy, coma, and hemorrhage. AST and ALT serum concentrations can be >10,000 IU/L. There are also increases in bilirubin and INR measurements, as well as abnormalities in glucose and pH readings. Death, if it occurs, is usually a result of multiorgan failure or hemorrhage caused by hepatic failure. Most deaths occur 3 to 5 days after exposure. Patients who survive this stage go into recovery.[152,160,163]

Antidotes

Case 5-5, Question 7: What antidote for acetaminophen ingestion should be considered in B.W.? How does the antidote work, and when is it most effective?

Toxicity is determined by the results of a serum acetaminophen concentration measured at least 4 hours after ingestion.[159] NAC is the antidote for acetaminophen toxicity. It is a sulfhydryl donor that converts to cysteine, which is subsequently converted to glutathione.[149,160,162,163] NAC acts as a glutathione substitute and directly combines with the toxic acetaminophen metabolite, NAPQI, reducing it to a nontoxic cysteine conjugate.[163] NAC can also substitute for sulfation, which increases the nontoxic metabolism through that route as well. NAC increases intrahepatic microcirculation and is believed to possess hepatoprotective

properties, showing some value even after liver damage has already occurred.[149,160]

Instituting therapy early with NAC is essential. When NAC is started within 8 to 10 hours of the ingestion, hepatotoxicity resulted in only 1.6% of cases. In patients who were started on NAC >10 hours after ingestion, 53% developed liver damage.[152,160]

Safety of *N*-Acetylcysteine in Pregnancy

Case 5-5, Question 8: Is NAC safe to use during pregnancy?

Acetaminophen overdose in pregnant patients should be managed in the same manner as in nonpregnant patients.[155–157] If the life of the pregnant patient is not saved, the fetus will not survive (unless the child is near term and is emergently delivered). NAC therapy is not contraindicated in pregnant patients and might be helpful because it crosses the placenta and can protect the fetus from hepatotoxicity.[155,157]

NAC therapy appears to be protective for both the pregnant patient and fetus.[152,155,158–160,162,163] When used as an antidote for acetaminophen overdose in pregnancy, NAC did not appear to cause toxic effects to the fetus.[149,152,155,157] The probability of fetal death was increased with the delay in NAC treatment after acetaminophen overdose.[152,156,160]

Route of Administration of *N*-Acetylcysteine

Case 5-5, Question 9: The 9-hour acetaminophen concentration in B.W. was 170 µg/mL. By what route should NAC be administered?

This concentration of acetaminophen at 6 hours is above the treatment line on the Rumack–Matthew nomogram.[161] Because there was some delay from the time of ingestion to presentation at the ED

and B.W. was already vomiting, it will be more difficult for B.W. to tolerate oral NAC. For this reason, IV NAC is recommended.

An FDA-approved sterile, pyrogen-free formulation of NAC is available as Acetadote®.[164–166] The use of IV NAC is not completely risk-free because of a possible anaphylactoid reaction during the first dose of the IV NAC. The incidence of adverse reactions ranges from 14.3% to 23%. Patients with asthma and patients with ectopy should receive the drug slowly and carefully, while being watched for symptoms of a reaction.[166]

A majority of the adverse reactions include nausea, vomiting, urticaria, flushing, and pruritus. Bronchospasm, angioedema, hypotension, and death have rarely occurred and must be carefully monitored when the IV route is being used.[167,168] Most reactions occur during or just after the first 15 minutes of the initial antidote infusion and appear to be dose related.[168] Because of the timing issue, the first dose of IV NAC is usually administered for 60 minutes instead of 15 minutes, even though a study comparing adverse reactions in the two infusion rates did not show clinically significant differences.[166,169]

Intravenous *N*-Acetylcysteine

Case 5-5, Question 10: How should IV NAC be administered to B.W.?

The FDA-approved IV NAC protocol is the same 20-hour dosing regimen used in Europe, known as the Prescott protocol.[164,165,166] A 150 mg/kg loading dose of NAC in 5% dextrose is infused IV slowly for 60 minutes while watching for symptoms of a possible anaphylactoid reaction. This is followed by a maintenance dose of 50 mg/kg infused for 4 hours and then followed with a 100 mg/kg dose infused for 16 hours. This regimen provides a total of 300 mg/kg NAC during the 20 hours after the loading dose.[166]

Oral *N*-Acetylcysteine

Case 5-5, Question 11: Once she is able to tolerate oral NAC treatment, what dosing regimen would be appropriate for B.W.?

The standard oral NAC protocol is based on the original clinical studies.[163] The loading dose of NAC is 140 mg/kg orally using either the 10% or 20% mucolytic solutions that were formulated for inhalation therapy. Seventeen additional maintenance doses of 70 mg/kg of NAC are administered at 4-hour intervals after the initial dose, for a total of 72 hours of therapy. This provides a total of 1330 mg/kg NAC during 72 hours.[170] Because oral NAC contains a sulfhydryl group, the substance has a very disagreeable taste and smell (similar to that of rotten eggs) that commonly results in nausea and vomiting in the patient. To mask the unpleasant taste and odor, NAC is diluted to a concentration of 5% using a carbonated beverage or fruit juice.[163] Because the entire dose of oral NAC passes through the liver, high concentrations are produced, which is seen as an advantage of oral therapy.[164]

Shorter oral NAC regimens are currently being used based on the efficacy of IV therapy.[171,172] Short-course oral NAC follows the same 20-hour time course as IV NAC. Patients receive the usual 140 mg/kg oral loading dose of NAC, followed by 70 mg/kg every 4 hours for five additional doses (20 hours of therapy). Serum acetaminophen, liver function tests, and INR are repeated at 20 hours after the loading dose, which is after the fifth maintenance dose. If 20-hour liver function tests and coagulation studies are normal and the acetaminophen level is less than the lower limits of detection, NAC can be stopped. A repeat set of liver function tests is recommended at 36 hours after ingestion. In other versions of the 20-hour NAC therapy, the dosage regimen is the same, but the laboratory studies are measured initially, and then at 16, 36, and 48 hours after ingestion.[172]

Efficacy of *N*-Acetylcysteine

Case 5-5, Question 12: Which route of NAC administration is more effective?

There is no proven evidence that one route of NAC administration is superior to the other.[161,164,173–175] Patient outcome after an acetaminophen overdose depends more on the time after the ingestion that treatment begins rather than on the route of administration of NAC. Patients who are started on NAC within 8 to 10 hours of ingestion, regardless of the route, rarely develop hepatotoxicity. Patients who present late or have a delay in the time of NAC treatment have higher rates of hepatotoxicity.[150,161,164,170,174–176]

In one comparative study of IV NAC to oral NAC therapy, both were effective in reducing hepatotoxicity when therapy was initiated within 10 hours of ingestion. Vomiting delayed oral administration of the drug, but IV administration resulted in significantly longer delays in instituting therapy.[174] IV NAC avoids the problems of the vomiting patient, but oral NAC is safer. Oral NAC is associated with nausea and vomiting, whereas IV NAC is associated with bronchospasm, urticaria, and angioedema during administration.[149,160] In addition, oral therapy is much less expensive.[176]

Although the time of initiation of therapy is one of the key factors in reducing hepatotoxicity from acetaminophen ingestions, length of therapy has become another factor.[175,177] Because the duration of therapy with the IV formulation is 21 hours, patients with severe toxicity may be undertreated. It is essential that the patient be reevaluated at the end of the 21 hours to make sure that acetaminophen levels are not detectable and that liver enzymes are trending downward significantly. If there is still measurable acetaminophen and liver enzymes are still elevated, therapy with NAC must be continued.

Starting oral NAC may take less time to prepare than does IV NAC therapy and is less expensive. If the patient presents early after an acetaminophen ingestion and does not have nausea and vomiting, oral therapy would be indicated. If the patient presents late (>10 hours after ingestion) with signs and symptoms of hepatotoxicity

along with intractable nausea and vomiting, IV NAC should be instituted at once.[164,170]

Monitoring Efficacy of *N*-Acetylcysteine

Case 5-5, Question 13: How should the efficacy of NAC therapy be monitored in B.W.?

The effectiveness of NAC intervention in B.W. should be monitored by daily assessment of her acetaminophen concentration (as long as it is still measurable), AST, ALT, total bilirubin, glucose, and INR. The AST and ALT serum concentrations typically increase within 36 hours (range, 24–72 hours) of ingestion.[160,174] As the hepatic damage continues, the liver enzymes may peak at several tens of thousands units, even with NAC therapy. In most patients, AST and ALT begin to decline after 3 days and then return to baseline values.[160]

In a small number of patients, usually those who presented late after the ingestion, fulminant hepatic failure may develop. Symptoms of severe or persistent acidosis, coagulopathy, a significantly increased serum creatinine, and grade III to IV encephalopathy are consistent with fatal outcomes in patients with fulminant hepatic failure. Liver transplantation might be a consideration for these patients.[152,178–181]

Duration of *N*-Acetylcysteine Therapy

Case 5-5, Question 14: How long should NAC administration be continued?

The original NAC dosing protocol was based on an assumption that the half-life of acetaminophen was 4 hours. After five half-lives (20 hours), the acetaminophen should be metabolized, and NAC could be discontinued. An NAC dose of 6 mg/kg/hour was determined to be necessary based on the rate of glutathione

turnover relative to NAPQI production. To ensure that patients received an adequate NAC dose, the FDA recommended that this dose be changed to 18 mg/kg/hour for 72 hours.[182] This recommendation serves as the basis for the traditional 72-hour oral course of NAC therapy.

When using the traditional 72-hour oral course of NAC, therapy can be discontinued if the liver function tests are trending toward normal, other laboratory tests (ie, coagulation studies, glucose, pH, bilirubin) are within normal ranges, and acetaminophen is no longer present in the serum. As long as acetaminophen is present, it can be metabolized to NAPQI and cause further toxicity.[162,171,182] Continued NAC will not be harmful to the patient and can be beneficial.

When using the shorter 20-hour course of oral NAC, if liver function tests and coagulation studies are normal and the 20-hour acetaminophen concentration can no longer be measured in the serum, NAC therapy can be stopped.[172] However, if 20-hour liver function test or coagulation study results are abnormal, or if the 20-hour acetaminophen concentration measurement reveals acetaminophen still present in the serum, NAC therapy should be continued for at least another 24 hours.[173,174] Laboratory tests should be repeated every 24 hours, and the patient's progress must be monitored closely. If the patient is not improving, NAC should be continued until the patient recovers, receives a liver transplant, or dies.[152]

At this time, there is no consensus as to the best route of NAC administration, optimal dosage regimen, or optimal length of therapy.[160,164,182] There is consensus, however, that for optimal results, NAC therapy must be instituted within 10 hours of ingestion.[149,160,164,170,173,176] For patients who do not exhibit any signs of hepatotoxicity, shorter course NAC therapy reduces the amount of NAC administered to the patient, decreases the quantity of laboratory tests, shortens hospital stay, and is less costly.[164,171,182]

N-Acetylcysteine Toxicity

Case 5-5, Question 15: How should the toxicity of NAC therapy be monitored in B.W.?

With the exception of vomiting, oral NAC is remarkably safe and has not been associated with toxicity.[149,161,164] Oral NAC must be retained for a minimum of 1 hour after ingestion to be successfully absorbed. If B.W. vomits within an hour of her oral NAC dose, the dose should be repeated. If she experiences protracted vomiting, administration of antiemetic drugs (eg, ondansetron, metoclopramide) or placement of a duodenal feeding tube can improve GI tolerance.[164,183,184] If the patient cannot tolerate oral liquids, NAC therapy should continue via IV administration.

IV NAC therapy has been associated with anaphylactoid reactions in up to 14% of the patients. Although most reactions are not severe, bronchospasm, angioedema, and respiratory arrest have been reported.[149,160,164,182] Patients should be monitored for allergic and anaphylactoid reactions when NAC is administered via IV infusion. Most reactions can be avoided by infusing the NAC loading dose slowly for 60 minutes.[149,160,164]

Patient Outcome

B.W. continued to have nausea and vomiting and had difficulty tolerating liquids. IV NAC was continued. An obstetrics consultation was requested to evaluate B.W.'s pregnancy. Fetal monitoring was instituted during her hospital admission. A sonogram was taken of the fetus. Once B.W. saw the child's image from the sonogram, her depressed mood seemed to lift. Approximately 36 hours after ingestion, her acetaminophen level was no longer detectable, and her liver function tests showed a mild elevation of her AST at 274 units/L and an ALT of 188 units/L. Her INR and total bilirubin values were normal at 0.7 seconds and 0.8 mg/dL, respectively.

B.W. was seen by a psychiatrist. She was scheduled for counseling and prenatal classes. B.W. seemed eager to attend the classes, and she talked enthusiastically about the pregnancy when

family members came to visit. Because of B.W.'s pregnancy, the decision was made to continue NAC for a full 72-hour course, with the goal of protecting the fetal liver as much as possible. Six weeks later, she had a normal delivery of a healthy 6.06-pound (2.75 kg) newborn female.

CONCLUSION

Unfortunately, there is no set formula to treat all poisoned patients. Each exposure is unique and patient-specific factors must be considered. Treatment of the poisoned patient often involves controversy because solid, evidence-based science to support a given decision is frequently lacking. When challenged with a poisoning exposure, consult with a poison control center by calling 1-800-222-1222, where consultation is available 24 hours a day in the United States.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. *Clin Toxicol (Phila)*. 2013;51:*140–146*. (42)

Boyle JS, Bechtel LK, Holstege CP. Management of the critically poisoned patient. *Scand J Trauma Resusc Emerg Med.* 2009;17:29. (26)

Chyka PA, Erdman AR, Christianson G, et al. Salicylate poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol*

(Phila). 2007;45:*95–131.* (71)

Chyka PA, Seger D, Krenzelok EP, Vale JA; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *Clin Toxicol (Phila)*. 2005;43:61–87. (43)

Committee on Poison Prevention and Control, Board on Health Promotion and Disease Prevention, Institute of Medicine of the National Academies. Poison control center activities, personnel, and quality assurance. In: *Forging a Poison Prevention and Control System*. The National Academies Press; 2004: chap 5. (19)

Forsberg S, Höjer J, Enander C, Ludwigs U. Coma and impaired consciousness in the emergency room: characteristics of poisoning versus other causes. *Emerg Med J.* 2009;26:100–102. (116)

Gummin DD, Mowry JB, Spyker DA, et al. 2018 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. *Clin Toxicol (Phila)*. 2019;57(*12*):1220–1413. (3)

Höjer J, Troutman WG, Hoppu K, et al. Position paper update: ipecac syrup for gastrointestinal decontamination. *Clin Toxicol (Phila).* 2013;51:134–139. (41)

Kociancic T, Reed MD. Acetaminophen intoxication and length of treatment: how long is long enough. *Pharmacotherapy.* 2003;23:1052–1059. (182)

Manoguerra AS, Erdman AR, Booze LL, et al. Iron ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*. 2005;43:553–570. (91)

[No authors listed]. Position paper: cathartics [published correction appears in *J Toxicol Clin Toxicol.* 2004;42:1000]. *J Toxicol Clin Toxicol.* 2004;42:243–253. (44)

Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. *J Toxicol Clin Toxicol.* 2004;42:1–26. (66)

Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose: 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med.* 1981;141*(3, Spec No*):380–385. (162)

Shannon M, Liebelt EL. Targeted management strategies for cardiovascular toxicity from tricyclic antidepressant overdose: the pivotal role for alkalinization and sodium loading. *Pediatr Emerg Care.* 1998;14:*293–298*. (145)

Thanacoody R. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. *Clin Toxicol (Phila)*. 2015;53:5–12. (45)

United States Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Drug abuse warning network (DAWN), 2011. Inter-university Consortium for Political and Social Research [distributor]; 2015. https://doi.org/10.3886/ICPSR34565.v3 (4)

Key Websites

American Association of Poison Control Centers. www.aapcc.org

Centers for Diseases Control and Prevention, Injury Prevention and Control: Data and Statistics (WISQARS). www.cdc.gov/injury/wisqars/index.html

United States Department of Health and Human Services. Substance Abuse and Mental Health Services Administration Center for Behavorial Health Statistics and Quality Drug Abuse Warning Network (DAWN). https://doi.org/10/3886/ICPSR34565.v3

COMPLETE REFERENCES CHAPTER 5 MANAGING DRUG OVERDOSES AND POISONINGS

1. Woolf AD, Lovejoy FR Jr. Epidemiology of drug overdose in children. *Drug Saf*. 1993;9:291–308.
2. Madden MA. Pediatric poisonings: recognition, assessment, and management. *Crit Care Nurs Clin North Am*. 2005;17:395–404.
3. Gummin DD, Mowry JB, Spyker DA, et al. 2018 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. *Clin Toxicol (Phila)*. 2019;57(12):1220–1413.
4. United States Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Drug abuse warning network (DAWN), 2011. Inter-university Consortium for Political and Social Research [distributor]; 2015. https://doi.org/10.3886/ICPSR34565.v3
5. Schille SF, Shehab N, Thomas KE, Budnitz DS. Medication overdoses leading to emergency department visits among children. *Am J Prev Med*. 2009;37:181–187.
6. Fung LS. Pediatric accidental ingestions—monitoring and treatment options. *US Pharmacist*. March 2010:51.
7. Dean B, Krenzelok EP. Adolescent poisoning: a comparison of accidental and intentional exposures. *Vet Hum Toxicol*. 1998;30:579–681.
8. Huott MA, Storrow AB. A survey of adolescents' knowledge regarding toxicity of over-the-counter medications. *Acad Emerg Med*. 1997;4:214–218.
9. Chan P. Pharmacokinetic and pharmacodynamic considerations in geriatrics. *Calif J Health Syst Pharmacy*. 2010;22:5.

10. Johnston CB. *Drugs and Elderly: Practical Considerations*. University of California San Francisco, Division of Geriatrics; 2001. *Primary Care Lecture Series*.
11. IBM Micromedex® POISINDEX® [electronic version]. IBM Watson Health. Accessed October 9, 2020. www.micromedexsolutions.com
12. Caravati EM, McElwee NE. Use of clinical toxicology resources by emergency physicians and its impact on poison control centers. *Ann Emerg Med*. 1991;20:147–150.
13. Nelson LS, Howland MN, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS, eds. *Goldfrank's Toxicologic Emergencies*. 11th ed. McGraw-Hill; 2019.
14. Olson KR, Anderson IB, Benowitz NL, et al, eds. *Poisoning and Drug Overdose*. 7th ed. McGraw-Hill; 2018.
15. Mullen WH, Anderson IB, Kim SY, Blanc PD, Olson KR. Incorrect overdose management advice in the Physicians' Desk Reference. *Ann Emerg Med*. 1997;29:255–261.
16. Cohen JS. Dose discrepancies between the Physicians' Desk Reference and the medical literature, and their possible role in the high incidence of dose-related adverse drug events. *Arch Intern Med*. 2001;161:957–964.
17. Harrison DL, Draugalis JR, Slack MK, Langley PC. Cost-effectiveness of regional poison control centers. *Arch Intern Med*. 1996;156:2601–2608.
18. Miller TR, Lestina DC. Costs of poisoning in the United States and savings from poison control centers: a benefit-cost analysis. *Ann Emerg Med*. 1997;29:239–245.
19. Committee on Poison Prevention and Control, Board on Health Promotion and Disease Prevention, Institute of Medicine of the National Academies. Poison control center activities, personnel, and quality assurance. In: *Forging a Poison Prevention and Control System.* The National Academies Press; 2004: chap 5.
20. Ford PS. A telephone history taking and poisoning care process. *Vet Hum Toxicol*. 1981;23:428–432.
21. Veltri JC. Regional poison control services. *Hosp Formul*. 1982;17:1469–1472.
22. [No authors listed]. Clinical policy for the initial approach to patients presenting with acute toxic ingestion or dermal or inhalation exposure. American College of Emergency Physicians. *Ann Emerg Med*. 1995;25:570–585.
23. Kulig K. Initial management of ingestions of toxic substances. *N Engl J Med*. 1992;326:1677–1681.
24. Eldridge DL, Holstege CP. Utilizing the laboratory in the poisoned patient. *Clin Lab Med*. 2006;26:13–30.
25. Wright N. An assessment of the unreliability of the history given by self-poisoned patients. *Clin Toxicol*. 1980;16:381–384.

26. Boyle JS, Bechtel LK, Holstege CP. Management of the critically poisoned patient. *Scand J Trauma Resusc Emerg Med*. 2009;17:29.
27. Olson KR, Pentel PR, Kelley MT. Physical assessment and differential diagnosis of the poisoned patient. *Med Toxicol*. 1987;2:52–81.
28. Nice A, Leikin JB, Maturen A, Madsen-Konczyk LJ, Zell M, Hryhorczuk DO. Toxidrome recognition to improve efficiency of emergency urine drug screens. *Ann Emerg Med*. 1988;17:676–680.
29. Spyker DA, Minocha A. Toxicodynamic approach to management of the poisoned patient. *J Emerg Med*. 1988;6:117–120.
30. Roberts DM, Buckley N. Pharmacokinetic considerations in clinical-toxicology. *Clin Pharmacokinet*. 2007;46:897–939.
31. Sue YJ, Shannon M. Pharmacokinetics of drugs in overdose. *Clin Pharmacokinet*. 1992;23:93–105.
32. Mahoney JD, Gross PL, Stern TA, et al. Quantitative serum toxic screening in the management of suspected drug overdose. *Am J Emerg Med*. 1990;8:16–22.
33. Hepler BR, Sutheimer CA, Sunshine I. Role of the toxicology laboratory in the treatment of acute poisoning. *Med Toxicol*. 1986;1:61–75.
34. Buckley NA, Dawson AH, Reith DA. Controlled release drugs in overdose: clinical considerations. *Drug Saf*. 1995;12:73–84.
35. Mellick LB, Morgan JA, Mellick GA. Presentations of acute phenytoin overdose. *Am J Emerg Med*. 1989;7:61–67.
36. Chaikin P, Adir J. Unusual absorption profile of phenytoin in a massive overdose case. *J Clin Pharmacol*. 1987;27:70–73.
37. Mitchell JR, Thorgeirsson SS, Potter WZ, Jollow DJ, Keiser H. Acetaminophen-induced hepatic injury: protective role of glutathione in man and rationale for therapy. *Clin Pharmacol Ther*. 1974;16:676–684.
38. Rosenberg J, Benowitz NL, Pond S. Pharmacokinetics of drug overdose. *Clin Pharmacokinet*. 1981;6:161–192.
39. Baud FJ. Pharmacokinetic-pharmacodynamic relationships: how are they useful in human toxicology? *Toxicol Lett*. 1998;102–103:643–648.
40. Greene SL, Dargan PI, Jones AL. Acute poisoning: understanding 90% of cases in a nutshell. *Postgrad Med J*. 2005;81:204.
41. Hojer J, Troutman WG, Hoppu K, et al. Position paper update: ipecac syrup for gastrointestinal decontamination. *Clin Toxicol*. 2013;51:134–139.
42. Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. *Clin Toxicol*. 2013;51:140–146.
43. Chyka PA, Seger D, Krenzelok EP, Vale JA; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *Clin Toxicol (Phila)*. 2005;43:61–87.
44. [No authors listed]. Position paper: cathartics [published correction appears in *J Toxicol Clin Toxicol*. 2004;42:1000]. *J Toxicol Clin Toxicol*. 2004;42:243–

253.
45. Thanacoody R. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. *Clin Toxicol (Phila)*. 2015;53:5–12.
46. [No authors listed]. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol*. 1999;37:731–751.
47. Vale JA. Clinical toxicology. *Postgrad Med J*. 1993;69:19–32.
48. Holz LE Jr, Holz PH. The black bottle. A consideration of the role of charcoal in the treatment of poisoning in children. *J Pediatr*. 1963;63:306–314.
49. Neuvonen PJ, Olkkola KT. Oral activated charcoal in the treatment of intoxications: role of single and repeated doses. *Med Toxicol Adverse Drug Exp*. 1988;3:33–58.
50. Bond GR. The role of activated charcoal and gastric emptying in gastrointestinal decontamination: a state-of-the-art review. *Ann Emerg Med*. 2002;39:273–286.
51. Harris CR, Filandrinos D. Accidental administration of activated charcoal into the lung: aspiration by proxy. *Ann Emerg Med*. 1993;22:1470–1473.
52. Graff GR, Stark J, Berkenbosch JW, Holcomb GW 3rd, Garola RE. Chronic lung disease after activated charcoal aspiration. *Pediatrics*. 2002;109:959–961.
53. Elliot CG, Colby TV, Kelly TM, Hicks HG. Charcoal lung: bronchiolitis obliterans after aspiration of activated charcoal. *Chest*. 1989;96:672–674.
54. Givens T, Holloway M, Wason S. Pulmonary aspiration of activated charcoal: a complication of its misuse in overdose management. *Pediatr Emerg Care*. 1992;8:137–140.
55. Golej J, Boigner H, Burda G, Hermon M, Trittenwein G. Severe respiratory failure following charcoal application in a toddler. *Resuscitation*. 2001;49:315–318.
56. Tomaszewski C. Activated charcoal—treatment or toxin? *J Toxicol Clin Toxicol*. 1999;37:17–18.
57. Gazda-Smith E, Synhavsky A. Hypernatremia following treatment of theophylline toxicity with activated charcoal and sorbitol. *Arch Intern Med*. 1990;150:689–692.
58. Allerton JP, Strom JA. Hypernatremia due to repeated doses of charcoal-sorbitol. *Am J Kidney Dis*. 1991;17:581–584.
59. Tenebein M. Whole bowel irrigation as a gastrointestinal decontamination procedure after acute poisoning. *Med Toxicol Adverse Drug Exp*. 1988;3:77–84.
60. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness: controversies in the use of the “coma cocktail.” *JAMA*. 1995;274:562–569.

61. Trujillo MH, Guerrero J, Fragachan C, Fernandez MA. Pharmacologic antidotes in critical care medicine: a practical guide for drug administration. *Crit Care Med*. 1988;26:377–391.
62. Goldfrank LR, Hoffman RS. The cardiovascular effects of cocaine. *Ann Emerg Med*. 1991;20:165–175.
63. Wrenn K, Smith BA, Slovis CM. Profound alkalemia during treatment of tricyclic antidepressant overdose: a potential hazard of combined hyperventilation and intravenous bicarbonate. *Am J Emerg Med*. 1992;10:553–555.
64. Olson KR, Kearney TE, Dyer JE, Benowitz NL, Blanc PD. Seizures associated with poisoning and drug overdose. *Am J Emerg Med*. 1994;12:392–395.
65. Dart RC, Borron SW, Caravati EM, et al. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. *Ann Emerg Med*. 2009;54:386–394.
66. Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. *J Toxicol Clin Toxicol*. 2004;42:1–26.
67. Garrettson LK, Geller RJ. Acid and alkaline diuresis: when are they of value in the treatment of poisoning? *Drug Saf*. 1990;5:220–232.
68. Temple AR. Acute and chronic effects of aspirin toxicity and their treatment. *Arch Intern Med*. 1981;141(3 Spec No):364–369.
69. Kulling P, Persson H. Role of the intensive care unit in the management of the poisoned patient. *Med Toxicol*. 1986;1:375–386.
70. Alapat PM, Zimmerman JL. Toxicology in the critical care unit. *Chest*. 2008;133:1006–1013.
71. Chyka PA, Erdman AR, Christianson G, et al. Salicylate poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*. 2007;45:95–131.
72. Clarke A, Walton WW. Effect of safety packaging on aspirin ingestion by children. *Pediatrics*. 1979;63:687–693.
73. Done AK, Temple AR. Treatment of salicylate poisoning. *Mod Treat*. 1971;8:528–551.
74. Done AK. Aspirin overdosage: incidence, diagnosis, and management. *Pediatrics*. 1978;62(5, pt 2 Suppl):890–897.
75. Yip L, Dart RC, Gabow PA. Concepts and controversies in salicylate toxicity. *Emerg Med Clin North Am*. 1994;12:351–364.
76. Notarianni L. A reassessment of the treatment of salicylate poisoning. *Drug Saf*. 1992;7:292–303.
77. Temple AR. Pathophysiology of aspirin overdosage toxicity, with implications for management. *Pediatrics*. 1978;62(5, pt 2 Suppl):873–876.
78. Heffner JE, Sahn SA. Salicylate-induced pulmonary edema: clinical features and prognosis. *Ann Intern Med*. 1981;95:405–409.

79. Anderson RJ, Potts DE, Gabow PA, Rumack BH, Schrier RW. Unrecognized adult salicylate intoxication. *Ann Intern Med*. 1976;85:745–748.
80. Bailey RB, Jones SR. Chronic salicylate intoxication: a common cause of morbidity in the elderly. *J Am Geriatr Soc*. 1989;37:556–561.
81. Done AK. Salicylate intoxication: significance of measurements of salicylate in blood in cases of acute ingestion. *Pediatrics*. 1960;26:800–807.
82. Greenberg MI, Hendrickson RG, Hofman M. Deleterious effects of endotracheal intubation in salicylate poisoning. *Ann Emerg Med*. 2003;41:583–584.
83. Dargan PI, Wallace CI, Jones AL. An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. *Emerg Med J*. 2002;19:206–209.
84. Koren G. Medications which can kill a toddler with one tablet or teaspoonful. *J Toxicol Clin Toxicol*. 1993;31:407–413.
85. Litovitz T, Manoguerra A. Comparison of pediatric poisoning hazards: an analysis of 3.8 million exposure incidents: a report from the American Association of Poison Control Centers. *Pediatrics*. 1992;89(6, pt 1):999–1006.
86. Drug Facts and Comparisons [electronic version]. Wolters Kluwer Health, Inc. Accessed October 9, 2020. https://www.wolterskluwer.com/en/solutions/lexicomp/facts-and-comparisons
87. Prescribers Digital Reference: PDR® Network, LLC [electronic version]. IBM Watson Health. Accessed October 9, 2020. www.micromedexsolutions.com or www.pdr.net
88. IBM Micromedex® Drug Identification® [electronic version]. IBM Watson Health Accessed October 9, 2020. www.micromedexsolutions.com
89. Rxlist.com. Pill identification tool. Accessed October 9, 2020. http://www.rxlist.com/
90. Drugs.com. Drug information online. Accessed October 9, 2020. http://www.drugs.com/
91. Manoguerra AS, Erdman AR, Booze LL, et al. Iron ingestion: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*. 2005;43:553–570.
92. Klein-Schwartz W, Oderda GM, Gorman RL, Favin F, Rose SR. Assessment of management guidelines: acute iron ingestion. *Clin Pediatr (Phila)*. 1990;29:316–321.
93. Fine JS. Iron poisoning. *Curr Probl Pediatr*. 2000;30:71–90.
94. McGuigan MA. Acute iron poisoning. *Pediatr Ann*. 1996;25:33–38.
95. Mills KC, Curry SC. Acute iron poisoning. *Emerg Med Clin North Am*. 1994;12:397–413.
96. Banner W Jr, Tong TG. Iron poisoning. *Pediatr Clin North Am*. 1986;33:393–409.

97. Caravati EM. Safety of childhood acetaminophen overdose [letter]. *Ann Emerg Med*. 2001;37:115–116.
98. Woolf AD, Erdman AR, Nelson LS, et al. Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*. 2007;45:203–233.
99. Jaeger RW, Decastro FJ, Barry RC, Gerren LJ, Brodeur AE. Radiopacity of drugs and plants in vivo limited usefulness. *Vet Hum Toxicol*. 1981;23(Suppl 1):2–5.
100. James JA. Acute iron poisoning: assessment of severity and prognosis. *J Pediatr*. 1970;77:117–119.
101. Perrone J, Hoffman RS, Goldfrank LR, et al. Special considerations in gastrointestinal decontamination. *Emerg Med Clin North Am*. 1994;12:285–299.
102. Tenebein M. Whole bowel irrigation in iron poisoning. *J Pediatr*. 1987;111:142–145.
103. Chyka PA, Butler AY, Holley JE. Serum iron concentrations and symptoms of acute iron poisoning in children. *Pharmacotherapy*. 1996;16:1053–1058.
104. Lovejoy FH Jr. Chelation therapy in iron poisoning. *J Toxicol Clin Toxicol*. 1982;19:871–874.
105. Engle JP, Polin KS, Stile IL. Acute iron intoxication: treatment controversies. *Drug Intell Clin Pharm*. 1987;21:153–159.
106. Helfer RE, Rodgerson DO. The effect of deferoxamine on the determination of serum iron and iron-binding capacity. *J Pediatr*. 1966;68:804–806.
107. Ingelfinger JA, Isakson G, Shine D, Costello CE, Goldman P. Reliability of the toxic screen in drug overdose. *Clin Pharmacol Ther*. 1981;29:570–575.
108. Rogers SC, Pruitt CW, Crouch DJ, Caravati EM. Rapid urine drug screens: diphenhydramine and methadone cross-reactivity. *Pediatr Emerg Care*. 2010;26:665–666.
109. Brahm NC, Yeager LL, Fox MD, Farmer KC, Palmer TA. Commonly prescribed medications and potential false-positive urine drug screens. *Am J Health Syst Pharm*. 2010;67:1344–1350.
110. Yealy DM, Paris PM, Kaplan RM, Heller MB, Marini SE. The safety of prehospital naloxone administration by paramedics. *Ann Emerg Med*. 1990;19:902–905.
111. Watson AJ, Walker JF, Tomkin GH, Finn MM, Keogh JA. Acute Wernickes encephalopathy precipitated by glucose loading. *Ir J Med Sci*. 1981;150:301–303.
112. Zubaran C, Fernandes JG, Rodnight R. Wernicke-Korsakoff syndrome. *Postgrad Med J*. 1997;73:27–31.
113. Handal KA, Schauben JL, Salamone FR. Naloxone. *Ann Emerg Med*. 1983;12:438–445.
114. Lora-Tamayo C, Tena T, Rodriguez A. Cocaine-related deaths. *J Chromatogr A*. 1994;674:217–224.

115. Weinbroum A, Rudick V, Sorkine P, et al. Use of flumazenil in the treatment of drug overdose: a double-blind and open clinical study in 110 patients. *Crit Care Med*. 1996;24:199–206.
116. Forsberg S, Höjer J, Enander C, Ludwigs U. Coma and impaired consciousness in the emergency room: characteristics of poisoning versus other causes. *Emerg Med J*. 2009;26:100–102.
117. Callaham M. Tricyclic antidepressant overdose. *JACEP*. 1979;8:413–425.
118. Ettinger NA, Albin RJ. A review of the respiratory effects of smoking cocaine. *Am J Med*. 1989;87:664–668.
119. Finkle BS, McCloskey KL. The forensic toxicology of cocaine (1971–1976). *J Forensic Sci*. 1978;23:173–189.
120. Kline JN, Hirasuna JD. Pulmonary edema after freebase 3 cocaine smoking —not due to an adulterant. *Chest*. 1990;97:1009–1010.
121. Cucco RA, Yoo OH, Cregler L, Chang JC. Nonfatal pulmonary edema after “freebase” cocaine smoking. *Am Rev Respir Dis*. 1987;136:179–181.
122. Duberstein JL, Kaufman DM. A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. *Am J Med*. 1971;51:704–714.
123. Warner-Smith M, Darke S, Day C. Morbidity associated with non-fatal heroin overdose. *Addiction*. 2002;97:963–967.
124. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema. *Chest*. 2001;120:1628–1632.
125. Chan TC, Evans SD, Clark RF. Drug-induced hyperthermia. *Crit Care Clin*. 1997;13:785–808.
126. Albertson TE, Fisher CJ Jr, Shragg TA, Baselt RC. A prolonged severe intoxication after ingestion of phenytoin and phenobarbital. *West J Med*. 1981;135:418–422.
127. Adams BK, Mann MD, Aboo A, Isaacs S, Evans A. Prolonged gastric emptying half-time an gastric hypomotility after drug overdose. *Am J Emerg Med*. 2004;22:548–554.
128. Knopp R. Caustic ingestions. *JACEP*. 1979;8:329–336.
129. Dawson AH, Whyte IM. Therapeutic drug monitoring in drug overdose. *Br J Clin Pharmacol*. 1999;48:278–283.
130. Hoffman RJ, Nelson L. Rational use of toxicology testing in children. *Curr Opin Pediatr*. 2001;13:183–188.
131. Rayburn W, Aronow R, DeLancey B, Hogan MJ. Drug overdose during pregnancy: an overview from a metropolitan poison control center. *Obstet Gynecol*. 1984;64:611–614.
132. Perrone J, Hoffman RS. Toxic ingestions in pregnancy: abortifacient use in a case series of pregnant overdose patients. *Acad Emerg Med*. 1997;4:206–209.
133. Crome P. Poisoning due to tricyclic antidepressant overdosage: clinical presentation and treatment. *Med Toxicol*. 1986;1:261–285.

134. Callaham M, Kassel D. Epidemiology of fatal tricyclic antidepressant ingestion: implications of management. *Ann Emerg Med*. 1985;14:1–9.
135. Dziukas L, Cameron P. Management of antidepressants in overdose. *CNS Drugs*. 1994;2:367–380.
136. Frommer DA, Kulig KW, Marx JA, Rumack B. Tricyclic antidepressant overdose: a review. *JAMA*. 1987;257:521–526.
137. Guharoy SR. Adult respiratory distress syndrome associated with amitriptyline overdose. *Vet Hum Toxicol*. 1994;36:316–317.
138. Shannon M, Lovejoy FH Jr. Pulmonary consequences of severe tricyclic antidepressant ingestion. *J Toxicol Clin Toxicol*. 1987;25:443–461.
139. Sohn D, Byers J 3rd. Cost effective drug screening in the laboratory. *Clin Toxicol*. 1981;18:459–469.
140. Garriott JC. Interpretive toxicology. *Clin Lab Med*. 1983;3:367–384.
141. Henry JA. Epidemiology and relative toxicity of antidepressant drugs in overdose. *Drug Saf*. 1997;16:374–390.
142. Phillips S, Brent J, Kulig K, Heiligenstein J, Birkett M. Fluoxetine versus tricyclic antidepressants: a prospective multicenter study of antidepressant drug overdoses. The Antidepressant Study Group. *J Emerg Med*. 1997;15:439–445.
143. Singh N, Singh HK, Khan IA. Serial electrocardiographic changes as a predictor of cardiovascular toxicity in acute tricyclic antidepressant overdose. *Am J Ther*. 2002;9:75–79.
144. Pentel P, Benowitz N. Efficacy and mechanism of action of sodium bicarbonate in the treatment of desipramine toxicity in rats. *J Pharmacol Exp Ther*. 1984;230:12–19.
145. Shannon M, Liebelt EL. Targeted management strategies for cardiovascular toxicity from tricyclic antidepressant overdose: the pivotal role for alkalinization and sodium loading. *Pediatr Emerg Care*. 1998;14:293–298.
146. Kingston ME. Hyperventilation in tricyclic antidepressant poisoning. *Crit Care Med*. 1979;7:550–551.
147. Wrenn K, Smith BA, Slovis CM. Profound alkalemia during treatment of tricyclic antidepressant overdose: a potential hazard of combined hyperventilation and intravenous bicarbonate. *Am J Emerg Med*. 1992;10:553–555.
148. Seger DL, Hantsch C, Zavoral T, Wrenn K. Variability of recommendations for serum alkalinization in tricyclic antidepressant overdose: a survey of U.S. poison center medical directors. *J Toxicol Clin Toxicol*. 2003;41:331–338.
149. Kozer E, Koren G. Management of paracetamol overdose: current controversies. *Drug Saf*. 2001;24:503–512.
150. Davis M, Simmons CJ, Harrison NG, Williams R. Paracetamol overdose in man: relationship between pattern of urinary metabolites and severity of liver damage. *Q J Med*. 1976;45:181–191.

151. Corcoran GB, Mitchell JR, Vaishnav YN, Horning EC. Evidence that acetaminophen and N-hydroxyacetaminophen form a common arylating intermediate, N-acetyl-p-benzoquinoneimine. *Mol Pharmacol*. 1980;18:536–542.
152. Zed PJ, Krenzelok EP. Treatment of acetaminophen overdose. *Am J Health Syst Pharm*. 1999;56:1081–1091.
153. Lester D, Beck AT. Attempted suicide and pregnancy. *Am J Obstet Gynecol*. 1988;158:1084–1085.
154. Czeizel A, Lendvay A. Attempted suicide and pregnancy [letter]. *Am J Obstet Gynecol*. 1989;161:497.
155. Riggs BS, Bronstein AC, Kulig K, Archer PG, Rumack BH. Acute acetaminophen overdose during pregnancy. *Obstet Gynecol*. 1989;74:247–253.
156. Rollins DE, von Bahr C, Glaumann H, Moldéus P, Rane A. Acetaminophen: potentially toxic metabolite formed by human fetal and adult liver microsomes and isolated fetal liver cells. *Science*. 1979;205:1414–1416.
157. McElhatton PR, Sullivan FM, Volans GN, Fitzpatrick R. Paracetamol poisoning in pregnancy: an analysis of the outcomes of cases referred to the Teratology Information Service of the National Poisons Information Service. *Hum Exp Toxicol*. 1990;9:147–153.
158. Prescott LF, Roscoe P, Wright N, Brown SS. Plasma-paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. *Lancet*. 1971;1:519–522.
159. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics*. 1975;55:871–876.
160. Anker AL, Smilkstein MJ. Acetaminophen: concepts and controversies. *Emerg Med Clinic North Am*. 1994;12:335–349.
161. Acetaminophen (N-Acetyl-P-Aminophenol, APAP). *Drug Facts and Comparisons. Facts and Comparisons* [database online]. Wolters Kluwer Health; September 2020. Accessed October 9, 2020. https://www.wolterskluwer.com/en/solutions/lexicomp/facts-and-comparisons
162. Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose: 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med*. 1981;141(3, Spec No):380–385.
163. Linden CH, Rumack BH. Acetaminophen overdose. *Emerg Med Clinic North Am*. 1984;2:103–119.
164. Prescott L. Oral or intravenous N-acetylcysteine for acetaminophen poisoning? *Ann Emerg Med*. 2005;45:409–413.
165. Prescott LF. Treatment of severe acetaminophen poisoning with intravenous acetylcysteine. *Arch Intern Med*. 1981;141(3, Spec No):386–389.
166. Acetadote (acetylcysteine) injection labeling. Product information. Cumberland Pharmaceuticals; 2006.

167. Smilkstein MJ, Bronstein AC, Linden C, Augenstein WL, Kulig KW, Rumack BH. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med*. 1991;20:1058–1063.
168. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med*. 1998;31:710–715.
169. Kerr F, Dawson A, Whyte IM, et al. The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med*. 2005;45:402–408.
170. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol*. 1999;37:759–767.
171. Woo OF, Mueller PD, Olson KR, Anderson IB, Kim SY. Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. *Ann Emerg Med*. 2000;35:363–368.
172. Yip L, Dart RC. A 20-hour treatment for acute acetaminophen overdose. *N Engl J Med*. 2003;348:2471–2472.
173. Clarke S, Herren K. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. Oral or intravenous antidote for paracetamol overdose. *Emerg Med J*. 2002;19:247–248.
174. Perry HE, Shannon MW. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label clinical trial. *J Pediatr*. 1998;132:149–152.
175. Yarema MC, Johnson DW, Berlin RJ, et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. *Ann Emerg Med*. 2009;54:606–614.
176. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose: analysis of the national multicenter study (1976–1985). *N Engl J Med*. 1988;319:1557–1562.
177. Doyon S, Klein-Schwartz W. Hepatotoxicity despite early administration of intravenous N-acetylcysteine for acute acetaminophen overdose. *Acad Emerg Med*. 2009;16:34–39.
178. Bernal W, Wendon J, Rela M, Heaton N, Williams R. Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. *Hepatology*. 1998;27:1050–1055.
179. Mitchell I, Bihari D, Chang R, Wendon J, Williams R. Earlier identification of patients at risk from acetaminophen-induced acute liver failure. *Crit Care Med*. 1998;26:279–284.
180. Gow PJ, Smallwood RA, Angus PW. Paracetamol overdose in a liver transplantation centre: an 8-year experience. *J Gastroenterol Hepatol*. 1999;14:817–821.
181. Harrison PM, O'Grady JG, Keays RT, Alexander GJ, Williams R. Serial prothrombin time as prognostic indicator in paracetamol induced fulminant hepatic failure. *BMJ*. 1990;301:964–966.

182. Kociancic T, Reed MD. Acetaminophen intoxication and length of treatment: how long is long enough. *Pharmacotherapy*. 2003;23:1052–1059.
183. Wright RO, Anderson AC, Lesko SL, Woolf AD, Linakis JG, Lewander WJ. Effect of metoclopramide dose on preventing emesis after oral administration of N-acetylcysteine for acetaminophen overdose. *J Toxicol Clin Toxicol*. 1999;37:35–42.
184. Reed MD, Marx CM. Ondansetron for treating nausea and vomiting in the poisoned patient. *Ann Pharmacother*. 1994;28:331–333.

6

End-of-Life Care

Victoria F. Ferraresi and Mary Mihalyo

CORE PRINCIPLES		CHAPTER CASES
1	End-of-life care consists of palliative and hospice care. It is ideally introduced early in the disease progression to provide support to patients of all ages with a serious chronic or life-threatening illness. Medicare patients who enter a hospice program agree to relinquish their regular Medicare benefits because they relate to the terminal illness and accept the palliative rather than the curative approach that will be provided by hospice. Hospice provides all care related to the hospice diagnosis under a managed-care model at a fixed reimbursement.	**Case 6-1 (Question 1)**
2	In 2008, the Hospice Conditions of Participation were updated to include a	**Case 6-1 (Question 2)**

	review of the medication profile as part of the initial assessment of new patients. The medication regimens of hospice patients should be continually reviewed and updated, with unnecessary, ineffective, or duplicative medications discontinued.	
3	Patients near end of life can experience a number of distressing symptoms. These should be anticipated and treated in a timely manner that is acceptable to the patients and their families.	**Case 6-1 (Question 3), Table 6-3**
4	Well-trained pharmacists can improve medication management for hospice patients, while helping the hospice manage their drug costs.	**Case 6-1 (Question 2)**
5	Many barriers exist regarding pain management and the use of opioids.	**Case 6-1 (Question 4)**
6	Effective pain management uses a variety of approaches.	**Case 6-2 (Question 1)**
7	Pain and symptom management may at times require an aggressive approach.	**Case 6-3 (Questions 1–3)**

INTRODUCTION

Hospice and Palliative Care

End-of-life care is care provided in the period leading up to an inevitable death and can be provided under hospice or palliative care or outside of a formal program.[1] *Hospice care* and *palliative care* are

similar, but distinct terms sharing the common belief that the relief of suffering is a long-standing, central, and fully legitimate aim of medicine. The basic principle of end-of-life care is to optimize the quality of life for the patient and family in the last weeks and months of life as well as to provide support for the family beyond the end of life into bereavement.

Palliative care, which includes hospice care, is ideally introduced early in the disease progression to provide support to patients of all ages with a serious chronic or life-threatening illness. It can be provided concurrently with other treatments to cure or reduce disease or it can be provided independently. The word *palliation*, derived from the Latin word *pallium* (a cloak), has been defined as "treatment to reduce the violence of a disease."[2,3] The World Health Organization and the National Consensus Project for Quality Palliative Care define palliative care as a patient- and family-centered approach that improves the quality of life of patients and their families who are facing a life-threatening illness, by preventing and relieving suffering through early identification, assessment, and management of pain and other physical, psychosocial, and spiritual problems while affirming life and regarding death as a normal process.[4,5] Palliative care can be provided wherever patients receive care: in the hospital, physician practice sites, ambulatory clinics, community pharmacies, and long-term care facilities.

Hospice and palliative medicine became a recognized subspecialty of internal medicine in 2006, awarded by the American Board of Medical Specialties and is currently a subspecialty certification for nine other specialty areas, including anesthesiology, emergency medicine, and pediatrics.[6] The Joint Commission offers an Advanced Certification Program for Palliative Care to recognize hospitals that provide high-quality palliative care services.[7] There is currently no specialty certification available for pharmacists in hospice or palliative care, although there are 26 American Society of Health-System Pharmacists (ASHP)-accredited PGY2 (post-graduate year 2) residencies in palliative care and pain management.[8,9] A small number of advanced degree programs are

available, offering additional training for pharmacists in palliative care, and ASHP offers a certificate program in pain management.

Hospice, originally a place or way station for people making a pilgrimage, is considered both a philosophy of care and a place to deliver care. *Hospice care* focuses on the palliation of pain and other symptoms when active treatment to cure a terminal illness ends. Hospice care can be delivered in a building designated as a hospice, in the patient's home, or in a facility where the patient resides. As a programmatic model for delivering palliative care, hospice care provides an interdisciplinary team approach to individualized symptom management (eg, pain), as well as psychosocial, emotional, spiritual, and bereavement support for the patient and his or her family and caregivers during the last months of life while no longer pursuing active or curative treatment.[10]

Hospice Care in the United States

Most hospice care in the United States is provided under the Medicare Hospice Benefit by hospice programs certified by the Centers for Medicare and Medicaid Services (CMS). According to estimates of the National Hospice and Palliative Care Organization (NHPCO), there were approximately 4639 Medicare-certified hospice programs in the United States in 2018.[10] Of all deaths of Medicare recipients in the United States, 50.7% occurred under hospice care, with 1.55 million beneficiaries enrolled in a hospice program for 1 day or more during 2018. During the Medicare demonstration project (1980–1982, just before the creation of the Medicare Hospice Benefit as part of the Social Security Act), 93% of home hospice patients had cancers of various types.[11] In 2018, hospices provided care for patients with a wider variety of terminal illnesses (eg, cancer [29.6% of all admissions], circulatory or heart disease [17.4%], dementia [15.6%], respiratory disease [11%], stroke [9.5%], chronic kidney disease [2.2%], and other [14.7%]).[10] This care was provided primarily in the patient's home (55.6%), in an inpatient facility (0.8%), or in another unspecified location (6.6%).[10]

Adults age younger than 65 years account for <5.1% of the hospice population under the Medicare benefit.[10] Pediatric patients, who may range in age from prenatal to young adults, represent a unique challenge for hospice care. Regulatory, financial, cultural, and educational barriers play a role in diminished access to hospice care for pediatric patients because treatment is often pursued late in the progression of disease.[12–14] Referrals for pediatric oncology patients to palliative care often occurs late in the course of illness.[15] Although states are required to offer hospice care to pediatric patients under Medicaid and other state programs as part of the Affordable Care Act expanding benefits to improve coordination of care,[16] community-based pediatric palliative care may be a better initial alternative for these patients and can serve as a bridge to subsequent hospice admission.[14]

Medicare Hospice Benefit

The regulatory framework for the provision of hospice care under Medicare is defined in 42 CFR (Code of Federal Regulations) Part 418, Medicare and Medicaid Programs: Hospice Conditions of Participation and is funded from Part A (the hospital portion) of Medicare.[17,18] Patients are eligible for this benefit if, in the opinion of two physicians (ie, patient's primary care physician and hospice medical director), the natural course of their disease will result in death within 6 months. The hospice medical director determines and documents the terminal diagnosis and any other conditions contributing to the terminal prognosis. Eligibility for hospice can continue beyond the initial certification if the hospice medical director recertifies eligibility at defined intervals, called certification periods. Other insurance payers generally follow this criterion. In electing this benefit when signing the hospice election form, patients accept the palliative rather than the curative approach provided by hospice. All care related to these diagnoses is coordinated, provided, and paid for by the Medicare-certified hospice program. CMS has clarified that virtually all diagnoses are related to the terminal diagnosis and

prognosis; if a program disagrees, the hospice medical director must specifically document why a diagnosis is not related.[19,20]

Hospice care is provided (and reimbursed) under Medicare at four levels, all of which can be modified at any time based on a patient's condition or caregiving needs:

1. Routine home care (day-to-day care in the home, skilled nursing or assisted living facility)
2. Continuous home care (when more skilled care in the home is required owing to symptom management or a caregiving crisis) where a nurse or home health aide provides care for at least 8 hours in a day (ending at midnight); 50% of this care must be provided by a nurse.
3. General inpatient care (reimbursement for an inpatient stay in a hospital or skilled nursing facility related to symptoms that cannot be managed in the home)
4. Inpatient respite care (up to 5 days in a skilled nursing facility) to give the caregiver a break or respite

Most care, consisting of pain and symptom management and assistance with activities of daily living, as well as psychosocial support, is provided to hospice patients at the routine level of care.

Unlike home health care under Medicare, patients in hospices do not have to be homebound. They may freely visit their primary care provider (ie, physician or nurse practitioner) for any reason, including reasons that are documented as unrelated to their terminal illness. The primary care provider will be paid directly by Medicare. Patients may use their regular Medicare benefits for the documented unrelated illnesses; visits to providers for care or treatments unrelated to the primary hospice diagnosis are not limited or restricted. Patients may revoke (terminate) their election of the Medicare Hospice Benefit at any time (eg, end hospice care to pursue curative treatment or seek treatment outside the hospice plan of care [POC] or if they move outside of the hospice service area). Patients may, at a later date, choose to return to hospice care or

change to a different hospice program, without restrictions or loss of benefits.[18]

It is common for patients to be referred to hospice when death is imminent. Median lengths of stay have declined, from 37.1 days during the Medicare demonstration project (1980–1982) to 26 days in 2005 and to 18 days in 2018.[10,11] Approximately 27.9% of patients admitted to a hospice program in 2018 died or were discharged within 7 days; 40% received services for ≤14 days.[10]

Hospice programs have historically received a fixed daily payment to provide all care related to the terminal diagnosis (eg, medications, supplies, durable medical equipment, procedures, home health aides, provider visits, spiritual care, bereavement services). The reimbursement rates for the four levels of hospice care under the Medicare Hospice Benefit are established each summer for the following fiscal year, effective October 1. A baseline reimbursement rate is set, along with an adjustment for wage differentials (the wage index) based on the local cost of living. There are additional adjustments made for rural hospices and for the submission of quality data. Effective in fiscal year 2014, hospices that do not submit quality data receive a 2% reduction in reimbursement for all levels of care.[21]

Programs generally have high costs at the start of care due to personnel costs involved in the admission, assessment, and development of the initial POC, as well as obtaining medications, medical equipment, and medical supplies. High costs are also encountered nearer to the end of a patient's life, when new problems can appear and symptoms often intensify. In recognition of this, CMS implemented a tiered hospice payment system in January 2016. This system consists of higher payments at the start of care (for days 1–60) and for the 5 days before death near the end of life via a service intensity add-on (SIA) to account for greater care needs during these periods.[22]

Hospice reimbursement rates have not kept pace with rising costs. The total unadjusted hospice daily payment rate for routine level of care increased from $146.63 to $161.89 per day from 2011 to the first quarter of 2016 (just before when rates moved to the two-tier

model), an increase of 2.1% annually.[22,23] For fiscal year 2021, the rate for days 1 to 60 has been increased to $199.25 per day for hospices that submit quality data from $194.50 in 2020, a 2.44% increase.[24,25] In 2018, drug prices for the 267 top products used by older adults in the United States increased on average by 5.8%. In the period from 2010 to 2018, these drug price increases peaked at a 15.8% rise with a 1.6% general inflation rate in 2014.[26] In addition, prices have increased for generic drugs because of fewer generic drug manufacturers (less competition), drug shortages, and the U.S. Food and Drug Administration (FDA) Unapproved Drug Initiative, which converted some generic drugs back to branded products.[27–31] Prices for drugs for pain and inflammation increased by 15.7% in 2014. This resulted in some generic drugs traditionally used extensively for palliation (eg, atropine, chlorpromazine, promethazine, prochlorperazine) no longer being used as first-choice agents by many hospice programs.

In reviewing hospice beneficiary use of Medicare Part D, CMS has reminded Medicare Part D Plans, pharmacies, and hospices that hospices are required to pay for virtually all care (including all related medications) for patients in hospices (via Part A). An initiative to block Part D access to such patients was subsequently reversed by CMS with the clear expectation that hospices provide analgesics, antiemetics, laxatives, and anxiolytics and to coordinate drug coverage with the Part D plans.[32–34] Hospices are allowed to establish formularies, but if the hospice does not provide a related medication for any reason, the beneficiary may not use their Part D plan to obtain it. The result has been hospices paying for many more medications than they did in the past (ie, covering medications used to treat rather than just palliate related conditions). Effective October 1, 2020, an addendum must be submitted as part of the hospice election at admission and subsequently if requested by the patient (or their representative) that specifically identifies noncovered items, services, and drugs.[25] This must be submitted at the start of care (within 5 days) and thereafter within 72 hours of the request.

These variables (ie, referrals to hospice later in the course of terminal illness, higher costs at the start of care, shortened lengths of

stay, higher drug costs, providing more medications) have placed intense pressure on hospice programs to manage expenses. Because it is difficult to influence the time when patients are referred to hospice, the duration of time in hospice care, or the inherently higher costs when patients are first enrolled into hospice, the management of drug costs has taken a high priority in providing cost-effective hospice care.

Improving Patient Care and Managing Drug Costs

In 2008, the Hospice Conditions of Participation were updated to be more patient centered and outcome oriented.[18] Coverage of medications is mandated as described in 42 CFR §418.106 Drugs and biologicals, medical supplies, and durable medical equipment: ". . .drugs and biologicals related to the palliation and management of the terminal illness and related conditions, as identified in the hospice POC, must be provided by the hospice while the patient is under hospice care." CMS has stated that it will be the rare exception that a hospice patient is taking a medication that is not paid for by the hospice.

The regulations state that the comprehensive assessment must "take into consideration" the drug profile (42 CFR §418.54). This is defined as "[a] review of all of the patient's prescription and over-the-counter drugs, herbal remedies and other alternative treatments that could affect drug therapy" and is to include the following:

- Effectiveness of drug therapy
- Drug side effects
- Actual or potential drug interactions
- Duplicate drug therapy
- Drug therapy currently associated with laboratory monitoring

Although the regulations specify that the hospice registered nurse complete the initial and comprehensive assessments, pharmacists are uniquely qualified, as part of the hospice interdisciplinary team, to perform or provide input on the medication assessment.

Well-trained pharmacists can improve patient care and positively affect the fiscal margins of hospice programs by discouraging inappropriate use of medications, establishing evidence-based formularies, promulgating prior authorization policies for specific targeted drugs, establishing policies for adhering to the use of generic drugs, and managing the quantities of medications to be dispensed. In addition to managing drug expenditures, pharmacists provide drug information both to patients and providers and work integrally with other members of the hospice health care team to improve the safe and effective use of medications and collaborate in providing pain and symptom management.[35–52] In 2016, ASHP published a comprehensive guideline detailing the role and contribution of the palliative and hospice care pharmacist (PHP).[53]

Referral to Hospice

ELIGIBILITY

CASE 6-1

Question 1: M.P. is an 89-year-old female referred to hospice for end-stage Alzheimer dementia. She lives in a residential care home for the elderly with a hired caregiver. Her husband has been unable to care for her at home for some time because she requires full assistance with all activities of daily living. She was recently hospitalized with aspiration pneumonia and a urinary tract infection (UTI) and completed a course of intravenous (IV) vancomycin and piperacillin/tazobactam. Her medical history includes osteoporosis, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), hypercholesterolemia, and hypothyroidism. She is not oriented to person, place, or date. Her speech is unintelligible or nonsensical. She cannot feed herself, but will eat the thick pureed food that is fed to her. She is bedbound and incontinent of urine and stool. She is restless and irritable at times, especially at night. Her Palliative Performance Scale Version 2 (PPS) is 30%. Weight is 112 pounds (50.80 kg), decreased from 135 pounds (61.23 kg) a year ago, and a recent serum albumin is 2.2 g/dL.

What criteria does M.P. meet for eligibility for hospice services under the Medicare Hospice Benefit?

Patients with chronic diseases (eg, Alzheimer disease, Parkinson disease, stroke, heart failure, lung disease) can be sufficiently ill and debilitated to need custodial care, but might not be sufficiently ill to meet the definition of a terminal illness. This differentiation between terminally ill versus chronically ill requiring custodial care is important because to qualify for hospice services under the Medicare Hospice Benefit, patients must be at a stage where death is expected within the next 6 months. For cancer diagnoses, the presence of widespread metastatic disease may make this prognosis more easily evident. However, for other chronic diseases, this is not as clear. Further, a cancer diagnosis will have a different disease trajectory than do chronic debilitating diseases. There are three primary models for decline in the face of serious illness that must be considered in determining hospice eligibility as well as in creating a treatment plan. In cancer, patients typically show steady disease progression followed by a sudden steep decline leading to death. Patients with respiratory and cardiac disease may show a long decline with acute exacerbations and deterioration followed by sudden death. Chronic debilitating diseases such as Parkinson disease, amyotrophic lateral sclerosis (ALS), and dementia generally show a prolonged gradual decline, with death often attributed to an intervening comorbidity such as pneumonia, sepsis, or malnutrition.[54]

The Medicare Administrative Contractors (MACs) have issued criteria to assist in the determination of eligibility for hospice care, as well as criteria to meet a 6-month terminal prognosis for a number of diseases. These criteria, or local coverage determinations (LCDs), provide guidelines for meeting an overall decline in clinical status, for meeting non–disease-specific data to establish a baseline, for establishing the effect of comorbidities (eg, renal failure, liver disease), and for the submission of documentation for having met criteria. Criteria have been established for patients with cancer and noncancer diagnoses, and these criteria are used in the determination of eligibility for service and reimbursement.[55] Criteria for the noncancer diagnoses have been developed for ALS, dementia as a result of Alzheimer disease and related disorders, heart disease, human immunodeficiency virus disease, liver disease,

pulmonary disease, renal disease, stroke, and coma. Patients with cancer are eligible if they present with metastatic disease or progression from an earlier stage to metastatic disease with either a continued decline in spite of therapy or if they decline further disease-directed therapy.

The determination of whether M.P. meets eligibility requirements for Medicare Hospice Benefits must be based on the established LCDs for dementia as a result of Alzheimer disease. These criteria include the following, from the Functional Assessment Staging Tool (FAST) Scale[56–58]:

- Stage 7 or beyond, according to the FAST Scale
- Stage 7A: Can speak six or fewer intelligible words in a day or during an interview
- Stage 7B: Speech ability limited to the use of a single intelligible word in a day or during an interview
- Stage 7C: Cannot ambulate without assistance
- Stage 7D: Cannot sit up without assistance
- Stage 7E: Loss of ability to smile
- Stage 7F: Loss of ability to hold head up independently
- Unable to ambulate without assistance
- Unable to dress without assistance
- Unable to bathe without assistance
- Urinary and fecal incontinence, intermittent or constant
- No consistently meaningful verbal communication; stereotypical phrases only or the ability to speak is limited to six or fewer intelligible words
- One of the following within the past 12 months: aspiration pneumonia, pyelonephritis, septicemia, decubitus ulcers (multiple, stages 3 and 4), fever (recurrent after antibiotic treatment)
- Inability to maintain sufficient fluid and caloric intake with 10% weight loss during the previous 6 months or serum albumin <2.5 g/dL

The Palliative Performance Score Version 2 (PPS) (**Table 6-1**) gradates the extent of disability and can be used to assist in the determination of hospice eligibility.[59] M.P. meets the previous criteria and is eligible for hospice because of her Alzheimer disease. She clearly is debilitated. She is unable to speak intelligently, cannot feed herself, is not oriented to time or place, is incontinent of urine and stool, has lost about 20% of her weight during the past year, has a serum albumin of 2.2 g/dL, and has a PPS rating of 30% (ie, totally bedbound, unable to do any activity, confused). In addition, she has a number of comorbidities, experienced a recent episode of aspiration pneumonia, and finished a course of antibiotic therapy.

Table 6-1
Palliative Performance Score (PPS) Version 2

PPS Level (%)	Ambulation	Activity and Evidence of Disease	Self-care	Intake	Conscious Level
100	Full	Normal activity and work No evidence of disease	Full	Normal	Full
90	Full	Normal activity and work Some evidence of disease	Full	Normal	Full
80	Full	Normal activity with effort Some evidence of disease	Full	Normal or reduced	Full
70	Reduced	Unable to do normal job/work Significant disease	Full	Normal or reduced	Full
60	Reduced	Unable to do hobby/housework Significant disease	Occasional assistance necessary	Normal or reduced	Full or confusion
50	Mainly sit/lie	Unable to do any work Extensive disease	Considerable assistance required	Normal or reduced	Full or confusion
40	Mainly in bed	Unable to do most activity Extensive disease	Mainly assistance	Normal or reduced	Full or drowsy with or without confusion
30	Totally bedbound	Unable to do any activity Extensive disease	Total care	Normal or reduced	Full or drowsy with or without confusion
20	Totally bedbound	Unable to do any activity Extensive disease	Total care	Minimal to sips	Full or drowsy with or without confusion
10	Totally bedbound	Unable to do any activity Extensive disease	Total care	Mouth care only	Drowsy or coma with or without confusion
0	Death				

Instructions: PPS level is determined by reading left to right to find a "best horizontal fit." Begin at left column reading downward until current ambulation is determined; then, read across to next and downward until each column is determined. Thus, "leftward" columns take precedence over "rightward" columns.

Source: Reprinted with permission from Victoria Hospice Society. *Palliative Performance Scale (PPSv2), Version 2. Medical Care of the Dying*. 4th ed. Victoria, British Columbia, Canada: Victoria Hospice Society; 2006:120. http://www.victoriahospice.org/health-professionals/clinical-tools. Accessed April 13, 2016. Copyright © 2001 Victoria Hospice Society. The Palliative Performance

Scale version 2 (PPSv2) tool is copyright to Victoria Hospice Society and replaces the first PPS published in 1996 [*J Palliat Care.* 9(4):26–32]. Victoria Hospice Society, 1952 Bay Street, Victoria, BC, V8R 1J8, Canada, www.victoriahospice.org.

MEDICATION MANAGEMENT

Case 6-1, Question 2: M.P. has no known allergies. Her current medications are memantine 10 mg twice daily, aspirin 81 mg once daily, alendronate 70 mg weekly, esomeprazole 20 mg daily, lovastatin 20 mg with dinner, megestrol 40 mg/mL 5 mL (200 mg) twice daily, levothyroxine 0.1 mg daily, multivitamin daily, beclomethasone metered-dose inhaler one puff daily, albuterol 2.5 mg/ipratropium 0.5 mg via nebulizer every 4 hours as needed for wheezing or shortness of breath, acetaminophen 325 to 650 mg every 6 hours as needed for mild pain or fever, olanzapine 5 mg at bedtime as needed for restlessness and aggressive behavior, milk of magnesia 30 mL daily for constipation, and a bisacodyl suppository 10 mg every 3 days as needed if there is no bowel movement. The hospice medical director has determined that the aspiration pneumonia, UTI, and COPD are related to M.P.'s terminal prognosis. What is your assessment of M.P.'s medication regimen? Which medications is the hospice required to provide, and which might be discontinued?

Hospices are required to provide (pay for) all medications related to the terminal diagnosis and secondary diagnoses that contribute to the terminal prognosis within the hospice POC. The POC is the individualized plan of treatment developed for each patient formulated at the start of care and updated regularly by the interdisciplinary group or team (IDG/IDT). The Conditions of Participation mandate that the IDG be composed of a physician, registered nurse, social worker, and a pastoral or other counselor.[18] A registered nurse coordinates the implementation of the POC. Some hospice program IDGs have incorporated a pharmacist into the group to review medication issues.

The large array of medications being taken by M.P. is similar to the medication lists of many hospice patients. These patients are often elderly and have a long history of several chronic medical conditions for which they have been taking multiple medications. In most cases, the medication lists of patients who are admitted into a hospice program have seldom been reviewed, updated, or modified in light of

the present medical situation. Admission to a hospice program represents a change in the level of care and is the most appropriate time for a review and reconciliation of all medications to ascertain the necessity of each, with the goal of optimizing efficacy and minimizing the potential for adverse effects, medication errors, and inappropriate costs.

In reviewing medications for the elderly, *The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* is frequently used to identify medications that may cause adverse events and subsequent harm. In the 2019 version, under “Intent of Criteria,” it states that the criteria are not intended for use in the hospice and palliative care setting.[60] While alerting clinicians to the potential for problems with included medications, this does acknowledge that in end-of-life care, medications are often used specifically for their adverse effects, such as anticholinergics to reduce sialorrhea (drooling) in patients with ALS, doxepin for sedation or itching, and mirtazapine for sedation or appetite stimulation and should not necessarily be avoided in these patients.

Because M.P. is to be enrolled into a hospice program, her care should not be focused on curative treatments, but rather on the management of discomforting symptoms and on improving her quality of life in the time remaining. M.P.’s medications should be analyzed with the goal of simplification. Unnecessary medications should be discontinued and alternatives added to manage two or more symptoms concurrently. The hospice medical director has determined that CAD, COPD, UTI, aspiration pneumonia, and multiple wounds are related to M.P.’s terminal prognosis and thus are identified as secondary diagnoses for hospice care. The following changes should be considered:

Acetaminophen. This analgesic is often helpful in relieving mild pain, particularly in immobile elderly patients.[61] A trial of around-the-clock acetaminophen could be helpful, and the hospice would pay for it.

Albuterol/ipratropium combination. The hospice program is required to pay for medications related to M.P.’s aspiration

pneumonia and COPD. This combination inhalation formulation (or the components as separate products) should be continued if she is able to participate in her nebulizer treatments and it improves her breathing (see Chapter 19, Chronic Obstructive Pulmonary Disease and Chapter 107, Geriatric Drug Use).

Alendronate. This bisphosphonate drug can be discontinued because the treatment of osteoporosis is not an important consideration at this terminal stage of her life nor is it related to her terminal prognosis. Thus, the hospice would not cover it. Furthermore, M.P. is bedbound; alendronate should be ingested in the upright position, and patients should remain upright after taking the medication to decrease the risk of alendronate-induced esophageal irritation (see Chapter 110, Osteoporosis). Pain that she may experience from osteoporosis can be treated with analgesics.

Aspirin. The low-dose aspirin is intended to decrease the risk of cardiovascular clotting. The aspirin will not increase M.P.'s comfort or quality of life. It would be covered by her Medicare Hospice Benefit, and can be continued unless her primary care provider prefers its discontinuation or she experiences adverse effects.

Beclomethasone. This patient is not functioning well cognitively (ie, not oriented to time, person, or place) and would be unable to effectively time the inhalation of a breath to the actuation of her metered-dose inhaler and it should be discontinued. If needed, a systemic corticosteroid (eg, prednisone) might improve her COPD symptoms and also improve her appetite and sense of well-being. The potential for adverse effects is modest with short-term corticosteroid use.

Bisacodyl, milk of magnesia. Constipation in patients with terminal illnesses is common, occurring in as many as 87% to 90% because of decreased gastrointestinal (GI) motility with advanced age, metabolic disturbances, decreased physical activity, lack of adequate fiber and fluid intake, and use of constipating medications (eg, opioids, anticholinergics, psychotropic agents).[62–65] The milk of magnesia, with an occasional bisacodyl suppository,

has been an adequate laxative regimen for this patient; however, the milk of magnesia should be discontinued if her renal function deteriorates. If an opioid is later prescribed for M.P., a mild stimulant laxative (eg, senna) can be added, from two tablets at bedtime up to eight tablets daily.[66] Osmotic agents such as polyethylene glycol (PEG), oral sorbitol, or lactulose can be prescribed if needed. Mineral oil 30 mL daily is an option if the stool is hard; however, mineral oil should not be considered for M.P. because of her risk of aspiration. Bulk-forming laxatives should also be avoided in this population because they may not ingest adequate water to prevent a fecal impaction. In cases of refractory constipation, the use of methylnaltrexone bromide, an opioid antagonist available as a subcutaneous injection and an oral tablet, can reverse opioid-induced constipation by antagonizing opioid effects within the GI tract without affecting systemic analgesia.[67–70] This quaternary derivative of naltrexone does not cross the blood–brain barrier. Dosing is weight based and should be adjusted if a patient's creatinine clearance (CrCl) is <60 mL/min and the patient is in severe hepatic impairment. The most common adverse events in adults with advanced illness are abdominal pain, flatulence, nausea, dizziness, and diarrhea.[67] Other FDA-approved alternatives for opioid-induced constipation are naloxegol, naldemedine, and lubiprostone (see Chapter 24, Lower Gastrointestinal Disorders).

Esomeprazole. This proton-pump inhibitor may be unnecessary because alendronate-induced esophageal or GI irritation would not be an issue subsequent to its discontinuation. However, if a proton-pump inhibitor is needed, nonprescription generic omeprazole or lansoprazole is preferred because they are more cost-effective.[71] If a patient such as M.P. cannot swallow intact tablets, a capsule formulation can be opened with the contents mixed with soft food and swallowed intact.

Levothyroxine. This thyroid medication should be continued until M.P. is no longer able to swallow. This medication, however, would not be covered under her Medicare Hospice Benefit, which is

based on her Alzheimer disease, and was deemed not related to the terminal prognosis.

Lovastatin. Cholesterol-lowering agents are not necessary during the last 6 months of life and can be discontinued without resulting in harm to M.P.[72] Lovastatin would not improve the quality of her life at this stage of her terminal illness and would not be covered by her Medicare Hospice Benefit.

Megestrol. The progesterone derivative, megestrol, in doses of 400 to 800 mg daily, can substantially stimulate appetite and induce weight gain.[73,74] If an undernourished hospice patient desires to eat more, the patient or their family may desire an appetite stimulant. It is unclear whether stimulation of appetite in a cognitively impaired patient will result in weight gain or improved nutritional status. Because the benefits in this situation are unclear, the potential of adverse effects (eg, venous thrombosis) of megestrol needs to be considered, especially in M.P., who is not ambulatory and had been taking low-dose aspirin for prevention of cardiovascular clotting.[75] If M.P. is given an oral corticosteroid, as discussed previously, she may experience improved appetite as an added benefit, thus negating the need to utilize megestrol acetate.

Memantine. Because the *N*-methyl-D-aspartate (NMDA) antagonist, memantine, has been modestly effective in improving performance in patients with moderate-to-severe Alzheimer disease, but with decreasing effectiveness over time, it is probably of limited utility for M.P.[76] (see Chapter 108, Geriatric Neurocognitive Disorders). It would be reasonable to taper and discontinue M.P.'s memantine subsequent to discussion with appropriate hospice team members and M.P.'s family.[77,78] It can be restarted if her behavior deteriorates. If she continues with it, the hospice would provide it.

Multivitamins. Multivitamins and other nutritional supplements are unlikely to improve M.P.'s comfort or quality of life. The discontinuation of these drugs would simplify medication administration, decrease the potential for medication errors, and decrease costs.

Olanzapine. An antipsychotic (eg, olanzapine, haloperidol, quetiapine) is often prescribed off-label to manage the agitation and confusion encountered by patients with dementia. Behavioral modifications can be tried (see Chapter 108, Geriatric Neurocognitive Disorders), but paranoid or delusional behavior may require drug therapy. Small doses of antipsychotics, such as haloperidol or olanzapine, may offer a dual effect and be very useful in treating opioid-induced nausea and vomiting, although randomized clinical trials demonstrating efficacy are lacking.[79,80] They would be covered by M.P.'s Medicare Hospice Benefit. Quetiapine is the agent of choice when more sedation is required and has replaced the use of chlorpromazine because of cost considerations.[71]

SYMPTOM MANAGEMENT

The National Consensus Project for Quality Palliative Care has developed Clinical Practice Guidelines for Quality Palliative Care.[5] The purpose of this document "is to promote access to quality palliative care, foster consistent standards and criteria, and encourage continuity of palliative care across settings." In *Domain 2: Physical Aspects of Care*, guidelines and criteria are provided for interdisciplinary collaboration using available scales and other tools, for the assessment, documentation, and treatment of pain and other symptoms that are acceptable to both the patients and their families as a preferred practice.[5] The Center to Advance Palliative Care (CAPC) provides tools, education, communication, and training for practitioners to provide optimal palliative care.[81]

CASE 6-1, QUESTION 3: As soon as the hospice admission and assessment is completed, the nurse, in consultation with the IDG, develops a plan for symptom management and orders a comfort kit for M.P. What are the components of this kit, and why is it useful?

Some hospices use an order set or a general comfort kit to provide medications to treat anticipated symptoms for a specific patient.[82,83] These medications are placed in the home or facility where the patient resides. This facilitates the availability of medications to patients who encounter anticipated symptoms and is convenient when caregivers are instructed by the patient's primary care provider or the hospice physician to provide the medication to the patient. Patients at end of life experience a large number of symptoms including pain, anorexia, cachexia, weakness and fatigue, dyspnea, cough, nausea and vomiting, dysphagia, constipation, diarrhea, dry mouth, oral sores, wounds and pressure sores, edema, ascites, incontinence, confusion, delirium, anxiety, and depression.[84]

In general, the prevalence of each symptom is difficult to measure or predict and demonstrates a high degree of variability. The occurrence of symptoms, however, can vary significantly, even within the last week of life, and the need for frequent assessment of patients cannot be overemphasized. Some combination of morphine, lorazepam, haloperidol (or olanzapine), ondansetron, and an anticholinergic agent generally provided as a concentrated oral liquid, an orally disintegrating tablet (ODT), or a rectal suppository are commonly ordered for hospice patients. Drugs that can palliate more than one symptom, such as morphine for pain or dyspnea, or haloperidol or olanzapine for agitation or nausea, are particularly suited to inclusion in a comfort kit.

Morphine. Every hospice patient should have a short-acting opioid available for the palliation of unrelieved dyspnea and pain. Although morphine can cause respiratory depression, small doses are very effective in controlling dyspnea by multiple mechanisms: vasodilation, reduced peripheral vascular resistance, inhibition of baroreceptor responses, reduction of brainstem responsiveness to carbon dioxide (the primary mechanism of opioid-induced respiratory depression), and lessened reflex vasoconstriction caused by increased blood P_{CO_2} levels. Opioids can reduce the anxiety associated with dyspnea and might also act directly on opioid receptors present in the airways.[85–90] They can be given in low doses

orally, sublingually, parenterally, or via inhalation for this purpose without causing respiratory depression. A Cochrane Review, however, showed that due to the small number of randomized, blinded, controlled studies, the evidence for the use of opioids to palliate dyspnea was of low quality.[91] In addition, no evidence to support the use of nebulized opioids was found, although this route may be useful if patients are experiencing intolerable side effects from systemic agents.[92] **Table 6-2** provides an overview of both the nonpharmacologic and pharmacologic treatment of dyspnea.

Table 6-2
Treatment of Dyspnea at End of Life

Nonpharmacologic Methods
Pursed-lip breathing Upright position Relaxation Meditation Use of a fan or open window to circulate air over the face
Pharmacologic Therapy
Systemic opioids (short-acting agents) in small doses given orally, sublingually, or via injection can be given every 1–2 hours as needed.
Long-acting agents can be added to supplement the routine use of short-acting opioids.
Inhaled opioids deliver medication via nebulization directly into the airway, avoiding first-pass metabolism, allowing use of smaller doses, theoretically minimizing side effects such as drowsiness. May cause local histamine release, leading to bronchospasm. Use nonpreserved sterile injectable products. More cumbersome and expensive owing to use of nebulizer and nonpreserved parenteral products; evidence does not show that nebulized opioids provide greater benefit than does nebulized saline.
Agents: morphine 2.5–10 mg in 2 mL of 0.9% saline; hydromorphone 0.25–1 mg in 2 mL of 0.9% saline; fentanyl 25 µg in 2 mL of 0.9% saline
Generally given every 2–4 hours as needed for breathlessness
Benzodiazepines are useful for the anxiety associated with breathlessness.

Sources: Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, et al, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2006:547; Parshall MB, Schwartzstein RM, Adams L, et al.

An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185(4):435–452; Mularski RA, Reinke LF, Carrieri-Kohlman V, et al. An official American Thoracic Society workshop report: assessment and palliative management of dyspnea crisis. *Ann Am Thorac Soc*. 2013;10(5):S98–S106; Mercadante S. Episodic breathlessness in patients with advanced cancer: characteristics and management. *Drugs*. 2018;78:543–547; Hallenbeck J. Pathophysiologies of dyspnea explained: why might opioids relieve dyspnea and not hasten death? *J Palliat Med*. 2012;15(8):848–853; Lok CW. Management of breathlessness in patients with advanced cancer: a narrative review. *Am J Hosp Palliat Care*. 2016;33(3):286–290; Afolabi TM, Nahata MC, Pai V. Nebulized opioids for the palliation of dyspnea in terminally ill patients. *Am J Health Syst Pharm*. 2017;74(14):1053–1061; Simon ST, Higginson IJ, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev*. 2016;10(10):CD007354.

Hospice patients generally do not have IV access (ie, an IV catheter) into which medications can be easily administered. As a result, medications are primarily administered orally and, occasionally, by sublingual, buccal, transdermal, rectal, or subcutaneous (if an infusion is warranted) routes of administration. When patients lose the ability to swallow near the end of life (or have a condition that precludes swallowing), the sublingual or buccal routes of administration are the most useful, especially if drugs are lipophilic. The use of ODTs may also be useful at this time. Morphine is hydrophilic, and although some of it might be absorbed across the mucous membranes, the primary clinical effect probably results from GI absorption after the drug has trickled down the back of the throat.

Oral morphine sulfate, in a concentration of 100 mg/5 mL (20 mg/mL), is commonly dispensed in a 30-mL bottle at the beginning of hospice care. This bottle of morphine can provide 60 doses of 10 mg, and, at this concentration, only 0.5 mL of morphine needs to be administered. Patients should be provided with appropriate oral dosing syringes or use the dropper provided by the manufacturer to prevent dosing errors. Oxycodone or hydromorphone, in comparable adjusted doses, can be substituted for morphine when needed. There is no evidence demonstrating the superiority of any of these over the others in severe cancer pain.[93]

Lorazepam. A short-acting benzodiazepine (eg, lorazepam 0.5 mg every 4 hours as needed) is useful for the treatment of anxiety (see Chapter 83, Anxiety Disorders). Patients, especially those with respiratory symptoms, can experience episodes of extreme anxiety near the end of life, and low doses of a benzodiazepine can provide effective palliation.[94] Caution should be used to not overuse these drugs in the elderly because they can increase the risk of falling or cause paradoxic reactions and worsen delirium or restlessness. The combined use of benzodiazepines with opioids increases the risk of respiratory depression and potentially fatal overdose and should be used with extreme caution in the lowest possible doses.[95,96]

Haloperidol. Small doses of haloperidol (eg, 0.5–1 mg) are useful for the treatment of restlessness, delirium, or nausea and vomiting.[97,98]

Olanzapine. Low-dose olanzapine (2.5–5 mg) can be used to manage restlessness, delirium, or nausea and vomiting, and can be used as an alternative to haloperidol.[97] It is available in multiple dosage forms including an ODT.

Anticholinergic agent. As death approaches, patients can have difficulty in clearing pharyngeal secretions and, as a result, generate a sound commonly known as a death rattle.[99,100] Although patients are often unconscious at this point, this sound can be very distressing to those nearby.[101,102] A long-standing practice is to use an anticholinergic agent (eg, glycopyrrolate, hyoscyamine, scopolamine, atropine) in an attempt to prevent these pharyngeal secretions from forming. Systematic reviews found these agents to be no more effective than placebo.[103,104] Nonetheless, anticholinergic medications continue to be widely prescribed in end-of-life care. Patient positioning and gentle suctioning can remove secretions already present. If used, this treatment modality is usually initiated after the patient has become obtunded; if begun too early, patients might develop problems with thickened bronchial or pulmonary secretions, tachycardia, delirium, dry mouth, urinary retention, or other adverse anticholinergic effects.[105] Glycopyrrolate, available as a tablet, injectable formulation, and oral solution, is a good choice for an anticholinergic agent because it minimally crosses the blood–

brain barrier. The 1-mg tablets could be crushed and placed under the tongue every 8 hours. Hyoscyamine is available as oral tablets, ODT, oral sustained-release tablets, sublingual tablets, oral liquid, oral solution, and injection. The ODT, sublingual tablets, or oral solution of hyoscyamine can be given in a 0.125- to 0.25-mg dose sublingually every 4 hours as needed. Scopolamine transdermal patches have a slow onset of action (blood levels are detected 4 hours after application)[106] and are of limited utility in this situation. The oral or sublingual administration of atropine ophthalmic solution 1% is convenient to administer. Recent shortages and price increases have made it less cost-effective.[71] Families and caregivers must be instructed not to use this in the eye.

Case 6-1, Question 4: The hospice nurse for M.P. has difficulty finding oral morphine sulfate available from a pharmacy and difficulty in finding a pharmacy willing to accept a faxed or an electronic prescription. Why is morphine so difficult to obtain, and how should the nurse manage this problem?

Providing relief for pain or other symptoms with opioids is often difficult owing to numerous barriers. Patients and caregivers are often fearful of opioids, or mistakenly believe these medications will cause addiction or hasten death.[107,108] Pharmacists can create barriers by not having opioids in the pharmacy, sometimes because of the fear of robbery, fear of investigation by drug regulatory agencies, or insufficient appreciation of the usefulness of opioids in pain management and palliative care.[109,110] In response to the opioid crisis, recent legislative and regulatory changes in some states have restricted quantities of controlled substances that can be dispensed and mandated the use of prescription drug monitoring programs (PDMPs). Patients with cancer and those who are terminally ill may be exempt from these requirements.[111–113] Pharmacists who are inexperienced in providing service to hospice patients might not be knowledgeable about federal regulations governing the provision of controlled substances to hospice patients. Federal statutes, as well as most state statutes, permit prescriptions for Schedule II controlled

substances for hospice patients to be faxed. According to the CFR (21 CFR 1306.11) paragraph (g):

A prescription prepared in accordance with 1306.05 written for a Schedule II narcotic substance for a patient enrolled in a hospice care program certified and/or paid for by Medicare under Title XVIII or a hospice program which is licensed by the state may be transmitted by the practitioner or the practitioner's agent to the dispensing pharmacy by facsimile. The practitioner or the practitioner's agent will note on the prescription that the patient is a hospice patient. The facsimile serves as the original written prescription for purposes of this paragraph (g) and it shall be maintained in accordance with 1304.04(h).[114]

Electronic prescribing of controlled substances (EPCS), including Schedule II medications, is now legal per federal DEA regulations in all 50 states.[115,116] Some states mandate the electronic prescribing of all controlled substances. The SUPPORT (*S*ubstance *U*se-Disorder *P*revention That *P*romotes *O*pioid *R*ecovery and *T*reatment) for Patients and Communities Act requires the use of EPCS for all controlled substances under Medicare Part D by January 1, 2021, although it has not been fully implemented.[117]

The process of ordering controlled substances for use by hospice patients at home can take many hours, and sometimes as much as an entire day. Hospice providers should anticipate possible difficulties when placing orders for Schedule II controlled substance medications. M.P.'s nurse should take the time to address any concerns that M.P.'s caregivers and family may have about these medications (ie, how they may affect her, any worries about addiction, side effects) and allow ample time to order them so that symptoms can be managed as they develop.

CASE 6-2

QUESTION 1: G.G., a 40-year-old female, is admitted to hospice with stage IV ovarian cancer, metastatic to her pelvis, liver, and lungs. She was diagnosed after many months of nonspecific gastric distress and bloating. On laparotomy, she was evaluated as stage III and underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy and tumor debulking at that time. She has

undergone subsequent chemotherapy and repeated tumor debulkings. In the past 6 months, her weight has decreased from 175 pounds (79.37 kg) to 153 pounds (69.38 kg; she is 62 inches [157.48 cm] tall). Her primary problems are constant nausea, constipation, and gripping abdominal pain, which she characterizes as burning and twisting. She quantifies the pain as 8 of 10 (on a 0- to 10-point scale) and describes the pain as one that moves into her groin and leg. Her family is unhappy about the drowsiness she experiences from her medications; they believe she is overmedicated. She is starting to have difficulty swallowing. She has no known allergies. Her current medications include fentanyl transdermal system 75 µg/hour every 72 hours, extended-release morphine sulfate capsules 50 mg three times daily (usually intended for once-daily administration), docusate sodium 250 mg daily, lansoprazole 30 mg daily, and lorazepam 0.5 mg every 4 hours as needed for nausea and anxiety.

What is the most accurate assessment of her pain management regimen?

G.G. is currently using two long-acting opioids (ie, fentanyl transdermal and sustained-release morphine that is being dosed too frequently), but is still unable to achieve relief of her pain, which is probably neuropathic pain (described as burning and twisting). It is estimated that up to 39% of patients with cancer pain have neuropathic pain.[118–120] This may be caused by tumor growth around nerves, postoperative nerve damage, chemotherapy-induced neuropathy, or following radiation therapy. Opioids alone may be of limited value or may require higher than usual dosing.[118] The addition of adjuvant analgesics such as antidepressants, anticonvulsants, and local anesthetics play an important role in treating neuropathic pain[121] (see Chapter 55, Pain and Its Management).

The use of two long-acting agents is duplicative and should be replaced with one opioid. Methadone may be a better long-acting agent for G.G. because it has activity against neuropathic pain (see Chapter 55, Pain and Its Management) and can reduce the amount of medication she uses. Methadone is a µ-opioid receptor agonist, blocks the NMDA receptor and monoaminergic reuptake transporter for serotonin.[122–124] Clinicians find it very effective for intractable neuropathic pain, but studies do not show methadone to be superior to other opioids.[125,126] Advantages of using methadone for G.G. include long half-life, high bioavailability, excellent absorption across mucous membranes, lack of active metabolites, and lower cost. All

dosage forms of methadone, including the oral solution are long-acting ones. Use of the oral solution may be useful when patients lose the ability to swallow as death approaches. Disadvantages in using methadone are its long and variable elimination half-life, drug–drug interactions, prolongation of the QTc interval, and the variability of dosing equivalence with other opioids. Dosing methadone is complex and should be undertaken by experienced clinicians.[124–127]

When converting fentanyl and morphine to methadone, the following should be considered: (a) patient adherence and ability to follow prescription directions, (b) use of an appropriate conversion formula, (c) converting a transdermal formulation of fentanyl to an oral opioid formulation, and (d) a supplemental opioid for breakthrough pain.

Because of its long and variable elimination half-life, the dose of methadone should generally be adjusted only once every 5 to 7 days, and patients must be able and willing to precisely follow directions for its use. The methadone prescribing information can be used for the conversion, with a general rule of thumb being that the initial methadone dose should not exceed 30 mg/day.[128] An alternative, conservative dosing conversion scheme developed by a panel of experts in hospice and palliative care for patients who are opioid tolerant is presented in **Table 6-3**.

Table 6-3

Dosing Conversion to Methadone in Patients Who Are Opioid Tolerant

Oral Morphine or OME/Day	Oral Methadone Dose (No >30 mg Initially)
<60 mg oral morphine or OME	Give 2.5–7.5 mg methadone/day
60–199 mg oral morphine or OME AND patient age <65 years	10:1 conversion 10 mg OME:1 mg oral methadone
≥200 mg oral morphine or OME AND/OR age >65 years	20:1 conversion 20 mg OME:1 mg oral methadone

OME, oral morphine equivalent.

Source: Adapted from McPherson ML, Walker KA, Davis MP, et al. Safe and appropriate use of methadone in hospice and palliative care: expert consensus

white paper. *J Pain Symptom Manage*. 2019;57(3):635–645.e4. © 2018 American Academy of Hospice and Palliative Medicine. With permission.

Safety guidelines recommend electrocardiographic monitoring before and during methadone use[129,130]; the need for this in terminally ill patients should be balanced by life expectancy and goals of care. Caution should be used in patients with electrolyte abnormalities (hypokalemia or hypomagnesemia), impaired liver function, heart disease, prolonged QT syndrome, or the use of other QTc-prolonging drugs (eg, amiodarone, azithromycin, citalopram, fluconazole, haloperidol, ondansetron).[127,129,130]

Once the conversion is made, the calculated dose is adjusted and the dosing interval is set at every 12, 8, or, rarely, every 6 hours, based on patient age, previous use of opioids, and current clinical status. Clinical judgment is vital in individualizing a regimen for each patient based on his or her needs.

Before calculating the conversion to methadone for G.G., an important consideration in patients using transdermal fentanyl is an assessment of its absorption. Fentanyl from the transdermal system is absorbed through several layers of the skin and deposited in the subcutaneous fat, from which it is absorbed into the systemic circulation.[131] It is generally observed that transdermal fentanyl is not effective in very thin, cachectic patients. In those cases, the conversion would be made without including the fentanyl. The patch would be removed at initiation of the first methadone dose and supplemented with medication for breakthrough pain if needed. In patients using multiple patches, one patch can be removed every 3 days. Despite weight loss, G.G. (62 inches [157.48 cm] and 153 pounds [69.38 kg]) is not cachectic, and the fentanyl should be included when calculating the conversion of her current opioid dose to a comparable methadone dose. In this patient, her sustained-release morphine formulation (50 mg three times daily) is equivalent to 150 mg/day of oral morphine. Her fentanyl transdermal system 75 μg/hour is equivalent to about 150 mg/day of oral morphine.[132] (This is based on a conversion ratio of parenteral to oral morphine of 1:3 in patients who are opioid tolerant, rather than the 1:6 ratio that is used

in the dosing table in the Duragesic® prescribing information.) G.G.'s total oral morphine equivalents (OMEs) per day are 150 plus 150 mg, or 300 mg. Her caregiver reports that she generally takes 150 mg of oral morphine solution daily for breakthrough pain, and yesterday she used 180 mg. This brings the total daily OME to 480 mg, and we would use the 20:1 conversion from **Table 6-3** for conversion of OMEs to methadone. The calculated dose of oral methadone is 24 mg/day. This is a conservative amount; in certain situations, an experienced clinician may choose to start with a higher daily dose. For example, the methadone prescribing information uses a conversion for 480 OMEs of 8% to 12%, which would result in a methadone dose of 48 mg/day.[128]

G.G. can be started on methadone 7.5 mg every 8 hours or 10 mg every 12 hours. Because she is relatively young, has been using opioids for some time, and has severe pain (quantified at 8 of 10), a methadone dose of 7.5 mg every 8 hours (ie, 22.5 mg/day) would be appropriate. The dose can be increased, if needed, based on her clinical response after 5 to 7 days. This smaller initial dose would accommodate for some incomplete cross-tolerance from the morphine and fentanyl and for any fentanyl that remains in her system for the next several days. Patients who have been on much higher doses of opioids, alternatively, can be converted during a period of several days (eg, converting one-third of the previous daily dose of opioid every 3 days). This is an especially useful method for converting opioid doses for thin, cachectic patients who have been on multiple transdermal patches. A clinician should be in touch with G.G. frequently during the first several days after her conversion to methadone. A telephone call should be made 2 to 4 hours after the first dose to assess for efficacy and toxicity (primarily somnolence, confusion, or nausea) and then daily for 5 days. If pain relief with the first dose does not last for the entire dosing interval, it can be adjusted, or G.G. can be instructed to take a one-time extra dose of methadone.

An added benefit in changing to methadone for G.G. is a financial one for the hospice. Outpatient prescription prices for long-acting opioids are very steep and significantly add to hospice costs. The

prudent use of methadone can improve overall pain management and keep costs in check. When methadone is not appropriate, generic extended-release morphine is a good second choice. Transdermal fentanyl should be reserved for patients who cannot take oral medication or for when there are significant compliance issues. Extended-release oxycodone is an option when patients cannot tolerate morphine, have significant renal impairment, or have other contraindications to its use. By converting to methadone, G.G.'s daily cost for the opioid alone will decrease substantially, while still providing appropriate and effective pain management.

G.G. will also need a supplemental analgesic for breakthrough pain. Some practitioners use small doses of methadone, 2.5 or 5 mg, as often as every 3 hours. This is a good choice in a well-supervised (ie, inpatient) setting with nurses familiar with the use of methadone. However, if caregivers treat methadone as if it were morphine, which is much more commonly used for breakthrough pain, the risk of overmedicating the patient is very real. This can have disastrous consequences, especially in frail, elderly patients. Because G.G. is not in an inpatient setting and has tolerated morphine well in the past, 30 mg or 1.5 mL of morphine 100 mg/5 mL (20 mg/mL) can be prescribed to be taken every 2 hours as needed for breakthrough pain.

G.G. should also start a bowel regimen; the use of a stool softener alone is inadequate.[62–65] The nurse should perform a rectal examination to determine if stool is present in the rectal vault. An enema or suppository can be given if needed and then senna or PEG can be taken on a routine basis.

Because the fentanyl transdermal patches and the extended-release morphine have been discontinued, they should be properly discarded. The safe disposal of controlled substances is important in preventing drug diversion. Hospices are required to educate patients and their caregivers at the time of admission about proper drug disposal and must have policies and procedures for the management and disposal of controlled substances.[18] Options for disposal of controlled substances include take-back events, mail-return programs, and DEA-registered collection receptacles.[133] With

the enactment of the SUPPORT for Patients and Communities Act of 2018, hospice personnel are allowed to dispose of controlled substances for their patients by following criteria specified in the law (Section 3222, Disposal of Controlled Substances of a Hospice Patient by Employees of a Qualified Hospice Program).[117]

Aggressive Symptom Management and Palliative Sedation

CASE 6-3

Question 1: D.V., a 35-year-old male with gastric cancer metastasized to the esophagus with periaortic involvement, is hospitalized. He was diagnosed 10 months ago, and his disease has progressed despite multiple courses of chemotherapy. A double-lumen, peripherally inserted central catheter line has been inserted. He has lost 65 pounds (29.48 kg) since diagnosis, weighs 150 pounds (68.04 kg) at 72 inches (182.88 cm) tall, and presents with abdominal pain, severe nausea, vomiting, obstipation (intractable constipation), and general malaise. D.V. describes his pain as a 7 of 10 in intensity and as "burning like a knife through my stomach." He uses 50- to 75 patient-controlled analgesia (PCA) bolus doses every 24 hours. He has no other medical problems. D.V. is referred to hospice care because he and his wife have agreed to stop chemotherapy and do not want to go back to the hospital. He states a history of allergic reactions to morphine, ondansetron, and diphenhydramine, although these reactions are not noted. He is presently receiving hydromorphone 2 mg/hour in an IV infusion with 1-mg PCA bolus dose every 5 minutes, hydromorphone 4 mg orally every 4 hours as needed for pain, fentanyl transdermal 275 µg/hour every 3 days, ketamine 20 mg orally every 3 hours, senna two tablets twice daily, docusate sodium 250 mg twice, PEG 3350 17 g daily, lactulose 15 mL as needed for constipation, lorazepam 2 mg orally every 4 hours as needed for nausea or vomiting, metoclopramide 10 mg orally every 6 hours as needed for nausea or vomiting, ondansetron 4 mg IV every 8 hours as needed for nausea or vomiting, baclofen 10 mg orally every 8 hours as needed for hiccups, and pantoprazole 40 mg orally once daily.

What is your assessment of D.V.'s medication regimen?

D.V.'s drug regimen is unnecessarily complicated for a patient at home. It may be possible to simplify it by looking at each problem anew. His pain is poorly managed as evidenced by his pain intensity

at 7 of 10 (on a scale of 0–10), the use of multiple opioids, and the use of excessive PCA boluses. Once an infusion with PCA dosing is started, there is no need to continue other long-acting opioids (ie, transdermal fentanyl) or oral agents for breakthrough pain. The PCA doses serve as the rescue doses for breakthrough pain, and pain relief should be titrated using this method alone. Once pain is well controlled, an oral long-acting agent can be considered if the patient is able to swallow. To do otherwise creates a chaotic approach. Patients reporting allergic reactions to opioids should be carefully asked to describe the precise nature of the purported allergic reaction. True allergies to opioids are rare; patients often refer to an adverse reaction as an allergy or have experienced an effect from the histamine release that is associated with opioids. Hydromorphone, especially injectable hydromorphone, is much more expensive and no more effective than is morphine and is best reserved for use in patients who cannot tolerate morphine because of adverse effects. Patients who are truly allergic to morphine should be treated with fentanyl or methadone because of the low incidence of cross-reactivity with these agents.

Although D.V. had been prescribed ketamine every 3 hours in the hospital, it is unrealistic to expect that this can be continued in the home setting. D.V. and his wife would probably be glad to discontinue it and replace it with an alternative because of his need to be dosed so often. Discontinuation may result in an exacerbation of pain, and he should be monitored.

D.V.’s constipation is currently treated with multiple medications within the same therapeutic class. It would be more prudent to maximize the use of a single agent within a category, rather than using two products at less than the maximally recommended doses. D.V. can use a higher dose of senna (up to four tablets twice daily), and then, if necessary, continue to use the PEG 3350.[62–65]

D.V. also takes multiple medications for his nausea and vomiting. The serotonin antagonist ondansetron provided as an ODT can be a good option, as an alternative to IV ondansetron. Another good alternative is olanzapine ODT because it provides anticholinergic, anti-dopamine and anti-serotonin activity.[80] He had also been

directed to take lorazepam for his nausea and vomiting; however, benzodiazepines are not effective antiemetics. They are given to manage the anxiety associated with nausea and vomiting and are particularly useful in managing the anticipatory nausea and vomiting that is commonly encountered during chemotherapy administration. Metoclopramide can be useful for D.V.'s nausea and vomiting if his physical examination reveals hypoactive bowel sounds. It is also useful for treating hiccups, and the need for baclofen can be reassessed.

Case 6-3, Question 2: A few days after arriving home, D.V. asks his hospice nurse, "Can't you just give me something to end it all?" He has not been sleeping well, is tired of taking so many medications, and wants to alleviate the burden he feels he is imposing on his wife. How should the hospice nurse respond?

In patients who are terminally ill, suffering may continue despite maximal palliative efforts. As a result, practitioners continually encounter patients' requests for the ending of their lives because of overwhelming suffering. Medical aid-in-dying is legally available in several states, and although substantial numbers of clinicians can imagine situations in which aid-in-dying would be requested, willingness to actively participate in the ending of a patient's life is low.[134–150] A recent literature review did not find any studies examining pharmacists' direct experiences with aid-in-dying.[151] Nonetheless, pharmacists should be aware of and understand issues around the practice. The NHPCO has developed comprehensive resources, the LAD (Legally Accelerated Death) Series, for clinicians.[152] The State Information document contains links to state statutes and statistics, organizational policy statements (including ASHP's), and provides a bibliography.[153] In a small number of patients, it may be desirable to reduce suffering by the thoughtful use of medications to induce light to moderate sedation.[154–157] Unlike aid-in-dying, the intent of palliative sedation is to relieve suffering, not to hasten death. Death may, however, result as an unintended consequence of escalated drug dosing, as a

double effect. Data is lacking on the effect of palliative sedation on quality of life and survival following this intervention, and patients may continue to experience pain, dysphoria, or other adverse events.[158,159] Palliative sedation should only be initiated as a last resort in severe cases not responsive to other palliative measures, and only after thorough discussion of the important clinical and ethical issues with the patient, family, and other clinical team members.[160–162]

Medications used successfully to induce sedation for these patients include benzodiazepines, barbiturates, and propofol, generally given in combination.[163] The goal is to attain light to moderate sedation to preserve the airway. Opioids are continued to manage pain and prevent withdrawal. A best practice is to develop organizational policies, standardized orders, and quality assurance monitoring.[164] A trial of palliative sedation with IV midazolam could be initiated and managed by the hospice nurse at a rate of 1 mg/hour and gradually increased if needed to the desired effect.[163] For use in the home, crushed phenobarbital tablets administered via a rectal catheter could be added if the desired effect is not attained with midazolam alone.[165] Use of other agents such as propofol and dexmedetomidine are best reserved for use in inpatient settings.

Before considering palliative sedation, patients should be thoroughly assessed for insomnia, depression, pain, and other symptoms. Underlying reasons for insomnia should be explored and treated. Poor pain management is often the cause for considering palliative sedation. As many as 10% to 20% of patients with cancer may have pain that does not respond to standard systemic analgesics.[166] Interventional techniques, including the administration of spinal opioids and/or local anesthetics may be useful, but may not be practical to initiate for the actively dying patient at home.[167–169]

Case 6-3, Question 3: Repeated increases in the hydromorphone infusion basal rate (he is now at 25 mg/hour) had little effect on managing D.V.'s pain, and his consistent use of up to 120 PCA attempts in 24 hours reflects his continued pain. He describes the intensity of his pain as 8 of 10. Before

considering palliative sedation, what other therapeutic interventions can be implemented for D.V.?

In D.V., lidocaine 0.5 to 1 mg/kg/hour administered IV or subcutaneously might be useful to assist in the management of his severe neuropathic pain.[170–173] Lidocaine purportedly interrupts pain transmission by blocking sodium channels (see Chapter 55, Pain and Its Management). D.V. was started on lidocaine 1 mg/kg/hour IV. A bolus dose was not given because of the short half-life of lidocaine. Overnight, his use of hydromorphone boluses dropped to one. He now reports his pain as 1 of 10 and that he slept through the night for the first time in months. During the next 2 days, the hydromorphone basal rate was tapered to 5 mg/hour. He did not experience any lidocaine toxicity, such as perioral numbness, metallic taste, or somnolence. D.V. continued on lidocaine, using no hydromorphone boluses for the next 2 weeks, until he died at home surrounded by his family.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Electronic Code of Federal Regulations. Title 42, Chapter IV, Subchapter B, Part 418. Hospice care. Updated February 8, 2021. Accessed February 9, 2021. https://www.ecfr.gov/current/title-42/part-418 (18)

Herndon CM, Nee D, Atayee RS, et al. ASHP guidelines on the pharmacist's role in palliative and hospice care. *Am J Health Syst Pharm*. 2016;73: 1351–1361. (53)

Hughes MT. The pharmacist and medical aid in dying. *Am J Health Syst Pharm*. 2017;74(16):1253–1260. (149)

Institute of Medicine. *Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life.* The National Academies Press; 2015. (84)

McPherson ML, Walker KA, Davis MP, et al. Safe and appropriate use of methadone in hospice and palliative care: expert consensus white paper. *J Pain Symptom Manage*. 2019;57(3):635–645. (127)

National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care*. 4th ed. National Coalition for Hospice and Palliative Care; 2018. Accessed September 28, 2020. https://www.nationalcoalitionhpc.org/ncp (5)

The American Society of Health-System Pharmacy. Policy position on medical aid-in-dying. Accessed January 9, 2021. https://www.ashp.org/-/media/assets/policy-guidelines/docs/policy-positions/policy-positions-ethics.ashx (150)

Key Websites

American Academy of Hospice and Palliative Medicine (AAHPM). http://www.aahpm.org/

Center to Advance Palliative Care (CAPC). http://www.capc.org/

Centers for Medicare & Medicaid Services (CMS). https://www.cms.gov/Center/Provider-Type/Hospice-Center.html

End of Life Online Curriculum. http://endoflife.stanford.edu/M00overview/introlrnoverv.html

Hospice Foundation of America (HFA). http://www.hospicefoundation.org/

International Association for Hospice & Palliative Care (IAHPC). http://www.hospicecare.com/

MedlinePlus. Hospice care. http://www.nlm.nih.gov/medlineplus/hospicecare.html

National Hospice and Palliative Care Organization (NHPCO). http://www.nhpco.org/

National Hospice and Palliative Care Organization (NHPCO). Pediatric palliative care and hospice. http://www.nhpco.org/pediatric

Palliative Care Network of Wisconsin Fast Facts and Concepts. https://www.mypcnow.org/fast-facts/

Pallimed: A Palliative Medicine Blog. http://www.pallimed.org/

Society of Palliative Care Pharmacists. http://www.palliativepharmacist.org

The National Consensus Project for Quality Palliative Care. http://www.nationalconsensusproject.org

COMPLETE REFERENCES CHAPTER 6 END-OF-LIFE CARE

1. Razmaria AA. JAMA Patient Page. End-of-life care. *JAMA*. 2016;316:115.
2. Merriam-Webster.com. Pallium. Accessed September 28, 2020. https://www.merriam-webster.com/dictionary/pallium
3. Merriam-Webster.com. Palliate. Accessed September 28, 2020. https://www.merriam-webster.com/dictionary/palliate
4. World Health Organization. WHO definition of palliative care. Accessed September 28, 2020. http://www.who.int/cancer/palliative/definition/en
5. National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care*. 4th ed. National Coalition for Hospice and Palliative Care; 2018. Accessed September 28, 2020. https://www.nationalcoalitionhpc.org/ncp
6. American Board of Medical Specialties. Specialty and subspecialty certificates. Accessed September 28, 2020. http://www.abms.org/member-boards/specialty-subspecialty-certificates/
7. The Joint Commission. Advanced certification for palliative care programs. Accessed September 28, 2020. http://www.jointcommission.org/certification/palliative_care.aspx
8. Board of Pharmacy Specialties. Candidates guide. Accessed November 13, 2020. https://www.bpsweb.org/specialty-exams/candidates-guide/
9. American Society of Health-System Pharmacist. Palliative care/pain management PGY2 accredited residencies. Accessed November 19, 2020. https://accreditation.ashp.org/directory/#/program/residency
10. National Hospice and Palliative Care Organization. NHPCO facts and figures: 2020 edition. Accessed September 28, 2020. https://www.nhpco.org/wp-content/uploads/NHPCO-Facts-Figures-2020-edition.pdf
11. Brinbaum HG, Kidder D. What does hospice cost? *Am J Pub Health*. 1984;74:689–697.
12. Friebert S, Williams C. *NHPCO Facts and Figures: Pediatric Palliative and Hospice Care in America*. National Hospice and Palliative Care Organization; 2015. Accessed September 28, 2020. https://www.nhpco.org/wp-content/uploads/2019/04/Pediatric_Facts-Figures-1.pdf
13. Carroll JM, Torkildson C, Winsness JS, et al. Issues related to providing quality pediatric care in the community. *Pediatr Clin North Am*. 2007;54:813–827.
14. Kaye EC, Rubenstein J, Levine D, Baker JN, Dabbs D, Friebert SE. Pediatric palliative care in the community. *CA Cancer J Clin*. 2015;65:316–333.

15. Cheng BT, Rost M, De Clercq E, Arnold L, Elger BS, Wangmo T. Palliative care initiation in pediatric oncology patients: a systematic review. *Cancer Med*. 2019;8:3–12.
16. National Hospice and Palliative Care Organization. Pediatric concurrent care. 2016. Accessed October 7, 2020. https://www.nhpco.org/palliative-care-overview/pediatric-palliative-and-hospice-care/pediatric-concurrent-care/
17. The Social Security Act. Section 1861dd. Accessed October 7, 2020. https://www.ssa.gov/OP_Home/ssact/title18/1861.htm
18. Electronic Code of Federal Regulations. Title 42, Chapter IV, Subchapter B, Part 418. Hospice care. Updated February 8, 2021. Accessed February 9, 2021. https://www.ecfr.gov/current/title-42/part-418
19. US Department of Health and Human Services. Office of Inspector General. Medicare Part D is still paying millions for drugs already paid for under the Part A hospice benefit. 2019. Accessed October 7, 2020. https://oig.hhs.gov/oas/reports/region6/61708004.asp
20. National Hospice and Palliative Care Organization. OIG report on Part D and hospice. 2019. Accessed October 7, 2020. https://www.nhpco.org/wp-content/uploads/2019/08/OIG_Part_D_Reg-Alert_August2019.pdf
21. Centers for Medicare & Medicaid Services. Medicare program; hospice quality reporting. Accessed November 19, 2020. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Hospice-Quality-Reporting
22. Centers for Medicare and Medicaid Services, Department of Health and Human Services. Medicare program; FY 2016 hospice wage index and payment rate update and hospice quality reporting requirements; Final rule (Codified at 42 CFR §418). Accessed October 7, 2020. https://www.govinfo.gov/content/pkg/FR-2015-08-06/pdf/2015-19033.pdf
23. Centers for Medicare and Medicaid Services, Department of Health and Human Services. Update to hospice payment rates, hospice cap, hospice wage index, and the hospice pricer for FY 2011 (Transmittal 2004, Change Request 7077). 2010. Accessed October 7, 2020. https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R2004CP.pdf
24. Centers for Medicare & Medicaid Services. Medicare program; FY 2020 hospice wage index and payment rate update and hospice quality reporting requirements. Accessed October 7, 2020. https://www.federalregister.gov/documents/2019/08/06/2019-16583/medicare-program-fy-2020-hospice-wage-index-and-payment-rate-update-and-hospice-quality-reporting
25. Centers for Medicare & Medicaid Services. Medicare program; FY 2021 hospice wage index and payment rate update. Accessed October 7, 2020. https://www.govinfo.gov/content/pkg/FR-2020-08-04/pdf/2020-16991.pdf
26. Purvis L, Schondelmeyer SW. *Rx Price Watch Report: Trends in Retail Prices of Specialty Prescription Drugs Widely Used by Older Americans,*

2006 to 2020. AARP Public Policy Institute; 2019. Accessed November 13, 2020. https://www.aarp.org/ppi/info-2019/trends-in-retail-prices-of-drugs.html
27. Hernandez I, Good CB, Gellad WF, Parekh N, He M, Shrank WH. Number of manufacturers and generic drug pricing from 2005 to 2017. *Am J Manag Care*. 2019;25:348–352.
28. Dave CV, Hartzema A, Kesselheim AS. Prices of generic drugs associated with numbers of manufacturers. *N Engl J Med*. 2017;377:2597–2598.
29. Dave CV, Kesselheim AS, Fox ER, Qiu P, Hartzema A. High generic drug prices and market competition: a retrospective cohort study. *Ann Intern Med*. 2017;167:145–151.
30. Hernandez I, Sampathkumar S, Good CB, Kesselheim AS, Shrank WH. Changes in drug pricing after drug shortages in the United States. *Ann Intern Med*. 2019;170:74–76.
31. Hakim A, Gupta R, Ross JS. High costs of FDA approval for formerly unapproved marketed drugs. *JAMA*. 2017;318:2181–2182.
32. Centers for Medicare and Medicaid Services, Department of Health and Human Services. Announcement of Calendar Year (CY) 2014 Medicare advantage capitation rates and Medicare advantage and Part D payment policies and final call letter. 2013:134–137. Accessed November 11, 2020. www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Downloads/Announcement2014.pdf
33. Centers for Medicare and Medicaid Services, Department of Health and Human Services. Part D payment for drugs for beneficiaries enrolled in hospice—final 2014 guidance. 2014. Accessed November 11, 2020. https://www.cms.gov/medicare/medicare-fee-for-service-payment/hospice/downloads/part-d-payment-hospice-final-2014-guidance.pdf
34. Centers for Medicare and Medicaid Services, Department of Health and Human Services. Part D payment for drugs for beneficiaries enrolled in Medicare hospice. 2014. Accessed November 11, 2020. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/Hospice/Downloads/2014-PartD-Hospice-Guidance-Revised-Memo.pdf
35. Lucas C, Glare PA, Sykes JV. Contribution of a liaison clinical pharmacist to an inpatient palliative care unit. *Palliat Med*. 1997;11:209–216.
36. Snapp J, Kelley D, Gutgsell TL. Creating a hospice pharmacy and therapeutics committee. *Am J Hosp Palliat Care*. 2002;19:129–134.
37. Lycan J, Grauer P, Mihalyo M, Houchen B. Improving efficacy, efficiency and economics of hospice individualized drug therapy. *Am J Hosp Palliat Care*. 2002;19:135–138.
38. Varga J. A prescription for drug cost savings. *Am J Hosp Palliat Care*. 2002;19:153.

39. Lee J, McPherson MF. Outcomes of recommendations by hospice pharmacists. *Am J Health Syst Pharm*. 2006;63:2235–2239.
40. Hill RR. Clinical pharmacy services in a home-based palliative care program. *Am J Health Syst Pharm*. 2007;64:806, 808, 810.
41. Atayee RS, Best BM, Daniels CE. Development of an ambulatory palliative care pharmacist practice. *J Palliat Med*. 2008;11:1077–1082.
42. Suhrie EM, Hanlon JT, Jaffe EJ, Sevick MA, Ruby CM, Aspinall SL. Impact of a geriatric nursing home palliative care service on unnecessary medication prescribing. *Am J Geriatr Pharmacother*. 2009;7:20–25.
43. Kemp LO, Narula P, McPherson ML, Zuckerman I. Medication reconciliation in hospice: a pilot study. *Am J Hosp Palliat Care*. 2009;26:193–199.
44. Martin CM. Exploring new opportunities in hospice pharmacy. *Consult Pharm*. 2009;24:114–119.
45. Walker KA, Scarpaci L, McPherson ML. Fifty reasons to love your palliative care pharmacist. *Am J Hosp Palliat Care*. 2010;27:511–513.
46. Herndon CM, Lynch JC. A mock “on-call” experience for pharmacy students in a pain and palliative care elective. *J Pain Palliat Care Pharmacother*. 2010;24:387–392.
47. Wilson S, Wahler R, Brown J, Doloresco F, Monte SV. Impact of pharmacist intervention on clinical outcomes in the palliative care setting. *Am J Hosp Palliat Care*. 2011;28(5):316–320.
48. O’Connor M, Pugh J, Jiwa M, Hughes J, Fisher C. The palliative care interdisciplinary team: where is the community pharmacist? *J Palliat Med*. 2011;14:7–11.
49. Atayee RS, Sam AM, Edmonds KP. Patterns of palliative care pharmacist interventions and outcomes as part of inpatient palliative care consult service. *J Palliat Med*. 2018;21:1761–1767.
50. Ma JD, Tran V, Chan C, Mitchell WM, Atayee RS. Retrospective analysis of pharmacist interventions in an ambulatory palliative care practice. *J Oncol Pharm Pract*. 2016; 22:757–765.
51. Pruskowski J, Arnold R, Skledar SJ. Development of a health-system palliative care clinical pharmacist. *Am J Health Syst Pharm*. 2017;74:e6–e8.
52. Naidu D, Jones K, Kanyer D, Hausdorff J. Palliative care pharmacist interventions in a community hospital. *Am J Health Syst Pharm*. 2018;75:933–936.
53. Herndon CM, Nee D, Atayee RS, et al. ASHP guidelines on the pharmacist’s role in palliative and hospice care. *Am J Health Syst Pharm*. 2016;73:1351–1361.
54. Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. *Br Med J*. 2005;330:1007–1011.
55. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): hospice-determining terminal status (L25678). Accessed October 30,

2020. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=34538
56. Reisberg B. Functional assessment staging (FAST). *Psychopharmacol Bull*. 1988;24(4):653–659.
57. Auer S, Reisberg B. The GDS/FAST staging system. *Int Psychogeriatr*. 1997;9(Suppl 1):167–171.
58. Hanrahan P, Raymond M, McGowan E, Luchins DJ. Criteria for enrolling dementia patients in hospice: a replication. *Am J Hosp Palliat Med*. 1999;16(1):395–400.
59. Victoria Hospice Society. *Palliative Performance Scale (PPSv2), Version 2. Medical Care of the Dying*. 4th ed. Victoria Hospice Society; 2006:120. Accessed April 13, 2016. http://www.victoriahospice.org/health-professionals/clinical-tools
60. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67:674–694.
61. Kress HG, Untersteiner G. Clinical update on benefit versus risks of oral paracetamol alone or with codeine: still a good option? *Curr Med Res Opin*. 2017;33:289–304.
62. Davies A, Leach C, Caponero R, et al. MASCC recommendations on the management of constipation in patients with advanced cancer. *Support Care Cancer*. 2020;28(1):23–33.
63. Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P. Laxatives for the management of constipation in people receiving palliative care. *Cochrane Database Syst Rev*. 2015;2015(5):CD003448.
64. Muldrew DHL, Hasson F, Carduff E, et al. Assessment and management of constipation for patients receiving palliative care in specialist palliative care settings: a systematic review of the literature. *Palliat Med*. 2018;32:930–938.
65. Sera L, McPherson ML. Management of opioid-induced constipation in hospice patients. *Am J Hosp Palliat Care*. 2018;35(2):330–335.
66. Lexi-Drugs. Lexicomp. Wolters Kluwer Health. Senna. Updated November 20, 2020. Accessed November 21, 2020. https://www.pdr.net/drug-summary/Senokot-sennosides-3182
67. Relistor (methylnaltrexone bromide). Prescribing information. Salix Pharmaceuticals. Accessed November 20, 2020. https://shared.salix.com/shared/pi/relistor-pi.pdf?id=8251081
68. Argoff CE, Brennan MJ, Camilleri M, et al. Consensus recommendations on initiating prescription therapies for opioid-induced constipation. *Pain Med*. 2015;16:2324–2337.
69. Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people

receiving palliative care. *Cochrane Database Syst Rev*. 2018;6(6):CD006332.
70. Barnett V, Twycross R, Mihalyo M, Wilcock A. Opioid antagonists. *J Pain Symptom Manage*. 2014;47:341–352.
71. RedBook Online [database online]. IBM Micromedex. Updated periodically. Accessed November 20, 2020. https://www.ibm.com/products/micromedex-red-book
72. Kutner JS, Blatchford PJ, Taylor DH Jr. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med*. 2015;175(5):691–700.
73. Taylor JK, Pendleton N. Progesterone therapy for the treatment of non-cancer cachexia: a systematic review. *BMJ Support Palliat Care*. 2016;6:276–286.
74. Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, Gonzalvez Perales JL, Bort-Marti S. Megestrol acetate for treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev*. 2013;2013(3):CD004310.
75. Megesterol acetate oral. Facts and Comparisons®. Updated November 3, 2020. Accessed November 20, 2020. https://fco.factsandcomparisons.com/lco/action/home
76. Buckley JS, Salpeter SR. A risk-benefit assessment of dementia medications: systematic review of the evidence. *Drugs Aging*. 2015;32:453–467.
77. Zueger PM, Holmes HM, Calip GS, Qato DM, Pickard AS, Lee TA. Older Medicare beneficiaries frequently continue medications with limited benefit following hospice admission. *J Gen Intern Med*. 2019;34(10):2029–2037.
78. Tjia J, Briesacher BA, Peterson D, Liu Q, Andrade SE, Mitchell SL. Use of medications of questionable benefit in advanced dementia. *JAMA Intern Med*. 2014;174(11):1763–1771.
79. Murray-Brown F, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. *Cochrane Database Syst Rev*. 2015;2015(11):CD006271.
80. Saudemont G, Prod'Homme C, Da Silva A, et al. The use of olanzapine as an antiemetic in palliative medicine: a systematic review of the literature. *BMC Palliat Care*. 2020;19(1):56.
81. The Center to Advance Palliative Care. Icahn School of Medicine at Mount Sinai. Accessed November 22, 2020. https://www.capc.org/
82. Bishop MF, Stephens L, Goodrich M, Byock I. Medication kits for managing symptomatic emergencies in the home: a survey of common hospice practice. *J Palliat Med*. 2009;12(1):37–44.
83. Leigh AE, Burgio KL, Williams BR, Kvale E, Bailey FA. Hospice emergency kit for veterans: a pilot study. *J Palliat Med*. 2013;16(4):356–361.
84. Institute of Medicine. *Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life*. The National Academies Press;

2015.
85. Gutstein HB, Akil H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, et al, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2006:547.
86. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185(4):435–452.
87. Mularski RA, Reinke LF, Carrieri-Kohlman V, et al. An official American Thoracic Society workshop report: assessment and palliative management of dyspnea crisis. *Ann Am Thorac Soc*. 2013;10(5):S98–S106.
88. Mercadante S. Episodic breathlessness in patients with advanced cancer: characteristics and management. *Drugs*. 2018;78:543–547.
89. Hallenbeck J. Pathophysiologies of dyspnea explained: why might opioids relieve dyspnea and not hasten death? *J Palliat Med*. 2012;15(8):848–853.
90. Lok CW. Management of breathlessness in patients with advanced cancer: a narrative review. *Am J Hosp Palliat Care*. 2016;33(3):286–290.
91. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev*. 2016;3(3):CD011008.
92. Afolabi TM, Nahata MC, Pai V. Nebulized opioids for the palliation of dyspnea in terminally ill patients. *Am J Health Syst Pharm*. 2017;74(14):1053–1061.
93. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13(2):e58–e68.
94. Simon ST, Higginson IJ, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev*. 2016;10(10):CD007354.
95. Horsfall JT, Sprague JE. The pharmacology and toxicology of the 'Holy Trinity'. *Basic Clin Pharmacol Toxicol*. 2017;120(2):115–119.
96. Sun EC, Dixit A, Humphreys K, et al. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *BMJ*. 2017;356:j760.
97. Henson LA, Maddocks M, Evans C, Davidson M, Hicks S, Higginson IJ. Palliative care and the management of common distressing symptoms in advanced cancer: pain, breathlessness, nausea and vomiting, and fatigue. *J Clin Oncol*. 2020;38(9):905–914.
98. Albert RH. End-of-life care: managing common symptoms. *Am Fam Physician*. 2017;95(6):356–361.
99. Lokker ME, van Zuylen L, van der Rijt CC, van der Heide A. Prevalence, impact, and treatment of death rattle: a systematic review. *J Pain Symptom Manage*. 2014;47(1):105–122.

100. Mercadante S. Death rattle: critical review and research agenda. *Support Care Cancer*. 2014;22:571–575.
101. van Esch HJ, Lokker ME, Rietjens J, van Zuylen L, van der Rijt CCD, van der Heide A. Understanding relatives' experience of death rattle. *BMC Psychol*. 2020;8(1):62–71.
102. Campbell ML. Assuaging listener distress from patient death rattle. *Ann Palliat Med*. 2019;8(suppl 1):S58–S60.
103. Jansen K, Haugen DF, Pont L, Ruths S. Safety and effectiveness of palliative drug treatment in the last days of life—a systematic literature review. *J Pain Symptom Manage*. 2018;55(2):508–521.
104. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev*. 2008;(1):CD005177.
105. Mercadante S, Marinangeli F, Masedu F, et al. Hyoscine butylbromide for the management of death rattle: sooner rather than later. *J Pain Symptom Manage*. 2018;56(6):902–907.
106. Transderm Scop (scopolamine). Prescribing information. Perrigo New York Inc. Accessed November 30, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cb93bfad-3e37-4a27-92f6-f21703ae7bdf
107. Edwards H, Bennett M. Access to opioids for patients with advanced disease. *Curr Pharm Des*. 2019;25(30):3203–3208.
108. Paice JA. Cancer pain management and the opioid crisis in America: how to preserve hard-earned gains in improving the quality of cancer pain management. *Cancer*. 2018;124(12):2491–2497.
109. Brown JH, Torres HP, Maddi RD, et al. Cancer patients' perceived difficulties filling opioid prescriptions after receiving outpatient supportive care. *J Pain Symptom Manage*. 2020;60(5):915–922.
110. Jefferson K, Quest T, Yeager KA. Factors associated with black cancer patients' ability to obtain their opioid prescriptions at the pharmacy. *J Palliat Med*. 2019;22(9):1143–1148
111. Twillman RK, Gilson AM, Duensing KN. State policies regulating the practice of pain management: statutes, rules, and guidelines that shape pain care. *Anesthesiol Clin*. 2016;34(2):409–424.
112. Bonnie RJ, Schumacher MA, Clark JD, Kesselheim AS. Pain management and opioid regulation: continuing public health challenges. *Am J Public Health*. 2019;109(1):31–34.
113. National Academies of Sciences, Engineering, and Medicine. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*. The National Academies Press; 2017.
114. U.S. Food and Drug Administration. Code of Federal Regulations. Title 21. 21 CFR 1306. Accessed November 30, 2020. https://www.ecfr.gov/cgi-bin/text-idx?

SID=40855a45033124df0ceeb2446776b800&mc=true&node=pt21.9.1306&rgn=div5
115. Electronic Prescriptions for Controlled Substances. Drug enforcement administration. Accessed October 30, 2020. https://www.deadiversion.usdoj.gov/ecomm/e_rx/
116. American Pharmacists Association. Controlled substance e-prescribing now legal in all 50 states. Accessed October 30, 2020. https://www.pharmacist.com/article/controlled-substance-e-prescribing-now-legal-all-50-states#:~:text=Electronic%20prescribing%20of%20controlled%20substances,but%20does%20not%20require%20it
117. CONGRESS.GOV. H.R. 6—SUPPORT for Patients and Communities Act. Accessed October 30, 2020. https://www.congress.gov/bill/115th-congress/house-bill/6
118. Vadalouca A, Raptis E, Moka E, Zis P, Sykioti P, Siafaka I. Pharmacological treatment of neuropathic cancer pain: a comprehensive review of the current literature. *Pain Pract*. 2012;12:219–251.
119. Piano V, Verhagen S, Schalkwijk A, et al. Treatment for neuropathic pain in patients with cancer: comparative analysis of recommendations in national clinical practice guidelines from European countries. *Pain Pract*. 2014;1:1–7.
120. Mennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain*. 2012;153:359–365.
121. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nat Rev Dis Primers*. 2017;3:17002–17047.
122. Schumacher MA, Basbaum AI, Naidu RK. Opioid agonists & antagonists. In: Katzung BG, ed. *Basic & Clinical Pharmacology*. 14th ed. McGraw-Hill; Accessed December 2, 2020. https://accessmedicine-mhmedical-com.ucsf.idm.oclc.org/content.aspx?bookid=2249&sectionid=175220393
123. Aggarwal S, Mortensen OV. Overview of monoamine transporters. *Curr Protoc Pharmacol*. 2017;79:12.16.1–12.16.17.
124. Hanna V, Senderovich H. Methadone in pain management: a systematic review. *J Pain*. 2021;22(3):233–245.
125. McNicol ED, Ferguson MC, Schumann R. Methadone for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;5(5):CD012499.
126. Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. *Cochrane Database Syst Rev*. 2017;2(2):CD003971.
127. McPherson ML, Walker KA, Davis MP, et al. Safe and appropriate use of methadone in hospice and palliative care: expert consensus white paper. *J Pain Symptom Manage*. 2019;57(3):635–645.
128. Methadone hydrochloride (methadone hydrochloride tablets). Prescribing information. Glenmark Pharmaceuticals. Revised November 2019. Accessed

December 1, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4f732f01-0529-4aa6-b6a9-67fb7817a138

129. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain*. 2014;15:321–337.
130. Tisdale JE, Chung MK, Campbell KB, et al. Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association. *Circulation*. 2020;142(15):e214-e233.
131. Duragesic (fentanyl transdermal system). Highlights of prescribing information. Janssen Pharmaceuticals, Inc. Updated September 2018. Accessed December 3, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019813s075s076lbl.pdf
132. McPherson ML. Transdermal and parenteral fentanyl. In: *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*. 2nd ed. American Society of Health-System Pharmacists. 2018:83–106.
133. U.S. Department of Justice, Drug Enforcement Administration. Diversion control division. Accessed November 21, 2020. https://www.deadiversion.usdoj.gov/drug_disposal/index.html
134. Emanuel EJ, Onwuteaka-Philipsen BD, Urwin JW, Cohen J. Attitudes and practices of euthanasia and physician-assisted suicide in the United States, Canada, and Europe. *JAMA*. 2016;316(1):79–90.
135. Quill TE, Back AL, Block SD. Responding to patients requesting physician-assisted death: physician involvement at the very end of life. *JAMA*. 2016;315(3):245–246.
136. Yang YT, Curlin FA. Why physicians should oppose assisted suicide. *JAMA*. 2016;315(3):247–248.
137. Goslin LO, Roberts AE. Physician-assisted dying: a turning point? *JAMA*. 2016;315(3):249–260.
138. Nyugen HQ, Gelman EJ, Bush TA, Lee JS, Kanter MH. Characterizing Kaiser Permanente Southern California's experience with the California End of Life Option Act in the first year of implementation. Research letter. *JAMA Intern Med*. 2018;178(3):417–421.
139. Hetzler PT 3rd, Nie J, Zhou A, Dugdale LS. A report of physicians' beliefs about physician-assisted suicide: a national study. *Yale J Biol Med*. 2019;92(4):575–585.
140. Campbell CS. Mortal responsibilities: bioethics and medical-assisted dying. *Yale J Biol Med*. 2019;92(4):733–739.
141. Dugdale LS, Lerner BH, Callahan D. Pros and cons of physician aid in dying. *Yale J Biol Med*. 2019;92(4):747–750.
142. Sulmasy LS, Mueller PS. Ethics and the legalization of physician-assisted suicide: an American College of Physicians position paper. *Ann Intern Med*.

2017;167:576–578.
143. Oakman BN, Campbell HE, Runk LM. Death with dignity; the developing debate among health care professionals. *Consult Pharm*. 2015;30:352–355.
144. Fass J, Fass A. Physician-assisted suicide: ongoing challenges for pharmacists. *Am J Health Syst Pharm*. 2011;68:846–849.
145. Quill TE, Arnold RM, Youngner SJ. Physician-assisted suicide: finding a path forward in a changing legal environment. *Ann Intern Med*. 2017;167(8):597–598.
146. Kussmaul WG 3rd. The slippery slope of legalization of physician-assisted suicide. *Ann Intern Med*. 2017;167(8):595–596.
147. Fujioka JK, Mirza RM, McDonald PL, Klinger CA. Implementation of medical assistance in dying: a scoping review of health care providers' perspectives. *J Pain Symptom Manage*. 2018;55(6):1564–1576.
148. Cobaugh DJ. Medical aid in dying. *Am J Health Syst Pharm*. 2017;74(16):1214–1215.
149. Hughes MT. The pharmacist and medical aid in dying. *Am J Health Syst Pharm*. 2017;74(16):1253–1260.
150. The American Society of Health-System Pharmacy. Policy position on medical aid-in-dying. Accessed January 9, 2021. https://www.ashp.org/-/media/assets/policy-guidelines/docs/policy-positions/policy-positions-ethics.ashx
151. Woods P, Schindel TJ, King MA, Mey A. Pharmacy practice in the domain of assisted dying: a mapping review of the literature. *Res Social Adm Pharm*. 2020;16(3):267–276.
152. National Hospice and Palliative Care Organization. Resource list: NHPCO LAD resource series. Accessed January 8, 2021. https://www.nhpco.org/wp-content/uploads/LAD_resource_List.pdf
153. National Hospice and Palliative Care Organization. State information and links: NHPCO LAD resource series. Accessed January 8, 2021. https://www.nhpco.org/wp-content/uploads/LAD_state_information.pdf
154. The American Academy of Hospice and Palliative Medicine. Statement on palliative sedation. Accessed January 10, 2021. http://aahpm.org/positions/palliative-sedation#:~:text=Palliative%20sedation%20(PS)%2C%20as,with%20severe%20and%20refractory%20symptoms
155. Kirk TW, Mahon MM, Palliative Sedation Task Force of the National Hospice and Palliative Care Organization Ethics Committee. National Hospice and Palliative Care Organization (NHPCO) position statement and commentary on the use of palliative sedation in imminently dying terminally ill patients. *J Pain Symptom Manage*. 2010;39:914–923.
156. Gurschick L, Mayer DK, Hanson LC. Palliative sedation: an analysis of international guidelines and position statements. *Am J Hosp Palliat Care*. 2015;32(6):660–671.

157. Ciancio AL, Mirza RM, Ciancio AA, Klinger CA. The use of palliative sedation to treat existential suffering: a scoping review on practices, ethical considerations, and guidelines. *J Palliat Care*. 2020;35(1):13–20.
158. Beller EM, van Driel ML, McGregor L, Truong S, Mitchell G. Palliative pharmacological sedation for terminally ill adults. *Cochrane Database Syst Rev*. 2015;1(1):CD010206.
159. Kon AA. Palliative sedation: it's not a panacea. *Am J Bioeth*. 2011;11(6):41–42.
160. Meilaender G. Comforting when we cannot heal: the ethics of palliative sedation. *Theor Med Bioeth*. 2018;39(3):211–220.
161. Curlin FA. Palliative sedation: clinical context and ethical questions. *Theor Med Bioeth*. 2018;39(3):197–209.
162. Raus K, Sterckx S, Mortier F. Is continuous sedation at the end of life an ethically preferable alternative to physician-assisted suicide? *Am J Bioeth*. 2011;11(6):32–40.
163. Bodnar J. A review of agents for palliative sedation/continuous deep sedation: pharmacology and practical applications. *J Pain Palliat Care Pharmacother*. 2017;31(1):16–37.
164. Ghafoor VL, Silus LS. Developing policy, standard orders, and quality-assurance monitoring for palliative sedation therapy. *Am J Health Syst Pharm*. 2011;68:523–527.
165. Lam YWF, Lam A, Macy B. Pharmacokinetics of phenobarbital in microenema via Macy Catheter versus suppository. *J Pain Symptom Manage*. 2016;51(6):994–1001.
166. Afsharimani B, Kindl K, Good P, Hardy J. Pharmacological options for the management of refractory cancer pain—what is the evidence? *Support Care Cancer*. 2015;23:1473–1481.
167. Mercadante S. Managing difficult pain conditions in the cancer patient. *Curr Pain Headache Rep*. 2014;18:395–401.
168. Vissers KC, Besse K, Wagemans M, et al. Pain in patients with cancer. *Pain Pract*. 2011;11:453–475.
169. Brant JM, Keller L, McLeod K, Yeh C, Eaton LH. Chronic and refractory pain: a systematic review of pharmacologic management in oncology. *Clin J Oncol Nurs*. 2017;21(suppl 3):31–53.
170. Lee JT, Sanderson CR, Xuan W, Agar M. Lidocaine for cancer pain in adults: a systematic review and meta-analysis. *J Palliat Med*. 2019;22(3):326–334.
171. Seah DSE, Herschtal A, Tran H, et al. Subcutaneous lidocaine infusion for pain in patients with cancer. *J Palliat Med.* 2017;20:667–671.
172. Peixoto RD, Hawley P. Intravenous lidocaine for cancer pain without electrocardiographic monitoring: a retrospective review. *J Palliat Med.* 2015;18:373–377.
173. Kintzel PE, Knol JD, Roe G. Intravenous lidocaine administered as twice daily bolus and continuous infusion for intractable cancer pain and wound

care pain. *J Palliat Med*. 2019;22(3):343–347.

7

Interprofessional Practice and Education

Michael G. Carvalho, Edith Claros, Christopher K. Cooper, and Kaelen C. Dunican

CORE PRINCIPLES		CHAPTER CASES
1	The Interprofessional Practice and Education Collaborative (IPEC) produced an original report with a 2016 update developed by an expert panel that established four core competencies of interprofessional practice and education (IPE): (a) values and ethics for interprofessional practice; (b) roles and responsibilities; (c) interprofessional communication; and (d) teams and teamwork.	**Case 7-1 (Question 1)** **Case 7-3 (Questions 1–5)**
2	The IPEC report considers communication a key competency. Unfortunately, this can be negatively	**Case 7-2 (Question 1)**

	impacted by demographic and professional differences that may exist between health care professionals. To address this issue, the IPEC report encourages all team members to be willing to speak up in a respectful way if they have a patient-related concern.	
3	Although one should understand what IPE is, it is also important to clarify what does not constitute IPE. Experiences on Advanced Pharmacy Practice Experience (APPE) rotations that are directed by someone from another profession that do not include sharing of responsibility for patient care are not considered IPE.	**Case 7-4 (Question 1)**
4	One element of an IPE model is understanding that different professions may vary in how they approach patient care. Team-based care means a shared responsibility for patient care on the part of all team members and should not be dominated by any one profession. IPE models can take place in a variety of settings, such as a classroom, laboratory, and a patient care setting. Regardless of the environment, IPE-related activities should represent a “real-world” experience.	**Case 7-5 (Question 1)**
5	Incorporating IPE in the pharmacy curriculum should involve early exposure to enhance students’ confidence in their professional value,	**Case 7-6 (Question 1)** **Case 7-7 (Questions 1, 2)**

	support their respecting the contributions of other professions, and better prepare them for providing team-based patient care. These early IPE experiences also increase the appeal of collaborating with other professions, reduce any negative stereotypical attitudes toward these other professions, and strengthen communication skills.	
6	The Health Professions Accreditors Collaborative (HPAC), in association with the National Center for Interprofessional Practice and Education (National Center), provided a guidance document on developing quality interprofessional education for the health professions. They stated that IPE plans should include four characteristics: (a) a rationale; (b) outcome-based goals; (c) a deliberate design; and (d) assessment and evaluation.	**Case 7-7 (Questions 3, 4)**

INTRODUCTION

Interprofessional practice and education (IPE) is a concerted effort to prepare medical, pharmacy, nursing, physician assistant (PA), and other health profession students to collaborate and deliver patient care as part of a team.[1] In the early 1970s, the Institute of Medicine (IOM) report “Educating for the Health Team” addressed pharmacy as a component of the team as well as medicine, nursing, and

dentistry.[2] However, there remains a concern that many practitioners, including pharmacists, are commonly trained in programs that are removed from other health care professionals. This educational separation could potentially have a detrimental effect on the beliefs and values that these practitioners may have on the contribution of other providers to patient care.[3,4] In 2003, the IOM addressed this matter in its report "Health Professions Education: A Bridge to Quality."[5] The report stressed incorporating interprofessional experiences into health care education and establishing core competencies for IPE. The 2003 IOM report states "all health professionals should be educated to deliver patient-centered care as members of an interprofessional team, emphasizing evidence-based practice, quality improvement approaches, and informatics."[5] These IOM recommendations generated the momentum for health professions to advance the need for IPE.[1,4] It is evident that with the increasing prevalence of chronic diseases and the complexities of delivering health care today, an interprofessional approach toward patient care is important.[3] In addition, new approaches to health care have stimulated a movement toward team-centered health care, such as the patient-centered medical home (PCMH) concept that encourages interprofessional teamwork in providing primary care.[6] With the PCMH model, physicians share responsibility with nurses, pharmacists, social workers, and others to manage complex patient care cases. The PCMH model puts the patient at the center of his/her health care and expands access and improves mechanisms for patient–provider communication, including the use of technology for patients to interact with their health care provider and have access to other health care resources.[6]

The evolution of an IPE model that incorporates collaborative practice along with fundamental and continuing interprofessional education is referred to as the *new IPE*.[7] This is a way to create a shared space between interprofessional education, interprofessional practice, and collaborative practice to improve health care outcomes while reducing cost.[7] Thus, IPE is crucial in establishing integrated interprofessional teams that provide patient- and family-centered care to achieve what the Institute for Healthcare Improvement has

termed the *Triple Aim*.[8] In this model, the three dimensions of care are to (a) improve the patient experience of care, (b) improve the health of populations, and (c) reduce the per capita cost of health care. More recently there has been an expansion to a fourth goal: (d) of improving the work life of health care providers including clinicians and staff.[9] This "Quadruple Aim" recognizes "provider burnout" as an impediment to effective health care that needs to be addressed. Interprofessional patient care could potentially reduce individual caregiver burden and enhance each team members' sense of contributing to shared outcomes.

CORE INTERPROFESSIONAL EDUCATION COMPETENCIES

CASE 7-1

QUESTION 1: You are enrolled in an IPE seminar with pharmacy, nursing, PA, and medical students. Each week you will be assigned cases to work on in groups.

Your initial impression is that these exercises are primarily designed to help foster teamwork, but are there any other areas that IPE helps develop as well?

The Interprofessional Practice and Education Collaborative (IPEC) was formed in 2009 from six national associations of schools of health professions (dentistry, medicine, nursing, osteopathic medicine, pharmacy, and public health), to promote joint efforts to advance interprofessional learning experiences with the goal of helping prepare students to participate in team-based patient care. An expert panel from its members produced a report in 2011 that established Core Competencies for Interprofessional Collaborative Practice.[10] In 2016, IPEC published an update that organized and broadened the competencies within the domain of interprofessional collaboration to better achieve the Triple Aim with an emphasis on

population health.[11] A subsequent update is currently being developed and is due to be released in early 2023.[12]

The far-reaching impact of IPEC on health education since its inception has been demonstrated by the addition of associations of other health professions to its original core group including nutrition and dietetics, PA, podiatry, respiratory care, physical therapy, occupational therapy, psychology, speech-language and hearing, chiropractic medicine, optometry, veterinary medicine, and health library science.[13]

The four IPEC competencies are (a) values and ethics for interprofessional practice, (b) roles and responsibilities, (c) interprofessional communication, and (d) teams and teamwork.[10,11] These competencies were identified to create a coordinated effort across the different health care professions to incorporate key content into their respective curricula and to guide curricular development. The competencies also provide a foundation for lifelong learning, as well as offer information to the different professions' educational program accrediting bodies that can be used to set common accreditation standards.[10,11,14]

In the first competency, IPEC considers interprofessional values and ethics as important elements in establishing a professional and interprofessional identity. These values and ethics are patient centered and grounded in a shared purpose to provide compassionate patient care. Working in teams adds value to patient/family and community outcomes that promote overall health and disease prevention beyond just the more traditional treatment of disease. In addition to being patient centered, competency in this area helps develop trusting relationships with patients, families, and other members of the health care team. There is also an expectation that one maintains competency in one's own profession relative to his/her area of practice.[10,11]

The second competency addresses the importance that IPEC places on one's understanding of how professional roles and responsibilities complement each other in providing patient care to advance the health care needs of patients and populations. It is this diversity of expertise that is the foundation of an effective health care

team. Coordination of care occurs more effectively when each profession knows what the other can contribute to patient care.[11] Pharmacists should be able to effectively articulate to other team members what they can contribute in executing a treatment plan, especially when it comes to preventing and identifying any drug-related problems. Sharing roles has also been shown to enhance patient outcomes and reduce costs.[3] For example, a nurse, social worker, and pharmacist can collaborate to develop a discharge plan that reduces the potential for hospital readmission by addressing such issues as community resources that may be available for assistance, medication adherence, patient education, and health care provider follow-up.[3] The IPEC documents note that one should also understand the limitations of one's abilities, knowledge, and skills and engage in continuous interprofessional development to improve team performance.[10,11]

IPEC places communication as the third key competency. The expert panel states that one should communicate with patients, families, and both health care and non–health care professionals in a responsive and responsible manner. Characteristics such as being available, being well-informed, showing interest, and being receptive are key aspects of this communication area as well. Listening and encouraging the input of other members are also important attributes for this competency. Presenting information in a manner that patients, families, and other team members can understand helps enhance the safety and effectiveness of interprofessional care.[10,11]

CASE 7-2

Question 1: You are a pharmacy student on your Advanced Pharmacy Practice Experience (APPE) rotation in internal medicine participating in medical rounds with a medical team that includes a very intimidating attending physician. Your team is evaluating a patient presenting with an upper respiratory tract infection. You note from the medical record that the patient is on warfarin. The attending physician directs the medical resident to order an antibiotic that you know may interact with warfarin and possibly increase the risk of bleeding.

How should you communicate your concerns to the attending?

Communication can be negatively impacted by demographic and professional differences that may exist between health care professionals (eg, older attending physician and younger pharmacist). To address this issue, the IPEC report encourages all team members to be willing to speak up in a respectful way if they have a patient-related concern. You should politely and very clearly explain to the attending what your concern is and provide evidence-based literature to support the nature and severity of the interaction. Despite the attending's intimidating demeanor, failure to communicate the problem could result in harm to the patient. Being able to provide and receive feedback with confidence helps promote team-based care.[10,11]

The fourth competency of IPEC, teams and teamwork, means working together for common patient care goals. Working in teams not only relates to shared problem-solving but also being able to constructively manage any disagreements that arise with other health care professionals as well as patients and family. Conflicts may occur when power is confused with expertise based on professional background. Staying focused on patient outcome and addressing any potential conflict openly through shared problem-solving and utilizing effective communication skills can help establish a more effective team. Besides, the report indicates that working in teams also means giving up some professional autonomy. Health care teams function best when the knowledge and expertise of the different professions on the team are integrated to make better patient care decisions.[10,11]

As a consequence of this shift toward teamwork, most health care profession–accrediting organizations, including pharmacy, nursing, and medicine, now incorporate interprofessional collaboration and teamwork as part of their standards.[14] In fact, the Health Professions Accreditors Collaborative (HPAC), consisting of many of the accrediting bodies of professions that are part of IPEC, was founded in 2014 in part to help facilitate the incorporation of intentional IPE throughout the curricula of its member bodies.[15] The basic principle of IPE is that if students from different health care professions learn

together, they will be better positioned to work together in teams to provide optimal patient care.[11]

CASE 7-3

Question 1: A.Z. is a 66-year-old female, mother of six, widowed, non–English-speaking Muslim refugee with limited medical literacy, who comes to urgent care with a 3-day history of cough and fever. You are an ambulatory care pharmacist working with the medical team responsible for the care of A.Z. that includes a bilingual (English to Arabic) translator, nurse practitioner, nurse, physician, PA, and social worker. Her medical history includes type 2 diabetes mellitus, hypertension, hyperlipidemia, posttraumatic stress disorder (PTSD), and anxiety. She takes metformin 1000 mg twice a day, simvastatin 20 mg daily, lisinopril/hydrochlorothiazide (HCTZ) 10 mg/12.5 mg daily, and clonazepam 0.5 mg three times a day as needed. A.Z. is accompanied by her eldest son who translates for her and guides the medical decision-making process. A.Z. and her children practice traditional folk remedies such as black seed oil for respiratory problems and honey for diabetes. A review of A.Z.'s vital signs and laboratory work indicates that her blood pressure is 166/88 mm Hg, preprandial blood glucose is 210 mg/dL, and total cholesterol is 220 mg/dL.

How can we address each of the IPEC core competencies regarding this case?

Values and Ethics

Case 7-3, Question 2: To respect A.Z. and her family's cultural beliefs while delivering high-quality and effective health care, what aspect of the care plan can be customized to ensure this patient receives care that reflects the patient's values?

Patients of different cultures and religions may experience conflicts regarding their values or morals when interacting with members of the health care team. Health care providers' awareness of and sensitivity to such issues can benefit patients and increase the quality of care they receive. It is important to understand the religious implications, culture, family perspectives, health practices, and beliefs of people of the Islamic faith. It is also important to validate the patient's use of home remedies and work together to

incorporate as many cultural practices as possible. Creating and maintaining clinical relationships based on trust and good communication is essential. Protecting the patient's freedom of belief, and maintenance of life and intellect while preserving honor and integrity is paramount in the Islamic faith.[16]

The team should be cohesive in its approach to maintain a climate of mutual respect and shared values between team members as well as with patients and their families.

Roles and Responsibilities

Case 7-3, Question 3: You use your knowledge of your own role and those of other professions to appropriately assess and address A.Z.'s health care needs and the needs of her family to promote health and well-being. How does the pharmacist's approach differ from that of the other team members?

The pharmacist can explain to the family the medication regimen prescribed for the patient and discuss the rationale for treatment while being mindful of her cultural background. Prescription records can be reviewed for evidence of validating adherence. The pharmacist could research and provide information to the rest of the team on the herbal remedies that A.Z. is using. These home remedies can be explored for potential interaction with the prescribed medication (eg, how is the cultural use of "honey for diabetes" potentially affecting her treatment and could its judicious use be incorporated into her treatment regimen). The pharmacist's knowledge of dietary supplements could also be helpful in suggesting alternative treatments that may be culturally acceptable to the patient and family.

The nurse practitioner or PA could initiate, manage, and coordinate A.Z.'s health care needs with the interdisciplinary team. Tasks will include, but not be limited to, prescribing medication, assessing efficacy of current medication and treatment plan, educating the patient and family about current treatment modalities, health promotion, and harm reduction. The primary care provider

(physician, PA, or nurse practitioner) can consider a referral to a mental health professional for counseling and mental health treatment as indicated. Other team health care members such as the social worker could assess how the patient's PTSD and the role of the family dynamics could be affecting her health and treatment. A nutritionist could be helpful in assessing and addressing her dietary requirements in the context of her cultural orientation.

Communication

Case 7-3, Question 4: A.Z.'s son tells you in confidence that his mother does not take any of her medications because the family uses home remedies. Should you communicate this information to the rest of the team and, if so, how would you do it?

It would be important to discuss with the son the need to share any vital information that could affect his mother's health and well-being with the team. Explain to the son that his mother is an integral part of the team and is, in fact, its *center*. As such, she will not be ostracized by the team; rather, her actions and beliefs will be taken into consideration and become a part of the team plan. Communicating with the patient and her son about the role of medications is a necessary part of the teaching process. Being open to patient/family questions or concerns is crucial. Complete and open communication with the rest of the interprofessional team is essential for quality and consistency of care.[17]

Teams and Teamwork

Case 7-3, Question 5: The pharmacist, translator, mental health care nurse practitioner, nurse, physician, PA, and social worker meet with A.Z. and her children as part of care planning, delivery of care, and discharge. What teamwork skills are necessary to deliver patient-centered care that is safe, timely, efficient, effective, and equitable?

Teamwork skills include communication, problem-solving, listening, self-awareness, and collaboration. These are essential for providing quality health care. Effective team skills can improve patient outcomes, prevent errors, improve efficiency, and increase patient satisfaction. It is important to establish at the onset of care how patients and families want to be involved in their care. Engaging them in designing their plan of care increases their understanding of tests, procedures, and anticipated care outcomes, ensuring a successful discharge. Each member of the team contributes, within the confines of their own specialty, the needed skills to optimize the patient's health and clinical care.[18]

This unified approach achieved through the blending of multiple disciplines, with the patient and family at its center, is the key to a successful interprofessional team.

The end game of IPE is to establish and support fully functioning interprofessional teams that collaborate to promote the Quadruple Aim[9] to optimize effective, compassionate, and cost-effective patient/community care while validating caregiver knowledge, skills, and teamwork. The IPEC core competencies can be seen not only as goals of preprofessional training but also as a grounding in the learning continuum of team members throughout the practice trajectory (**Fig. 7-1**).[11]

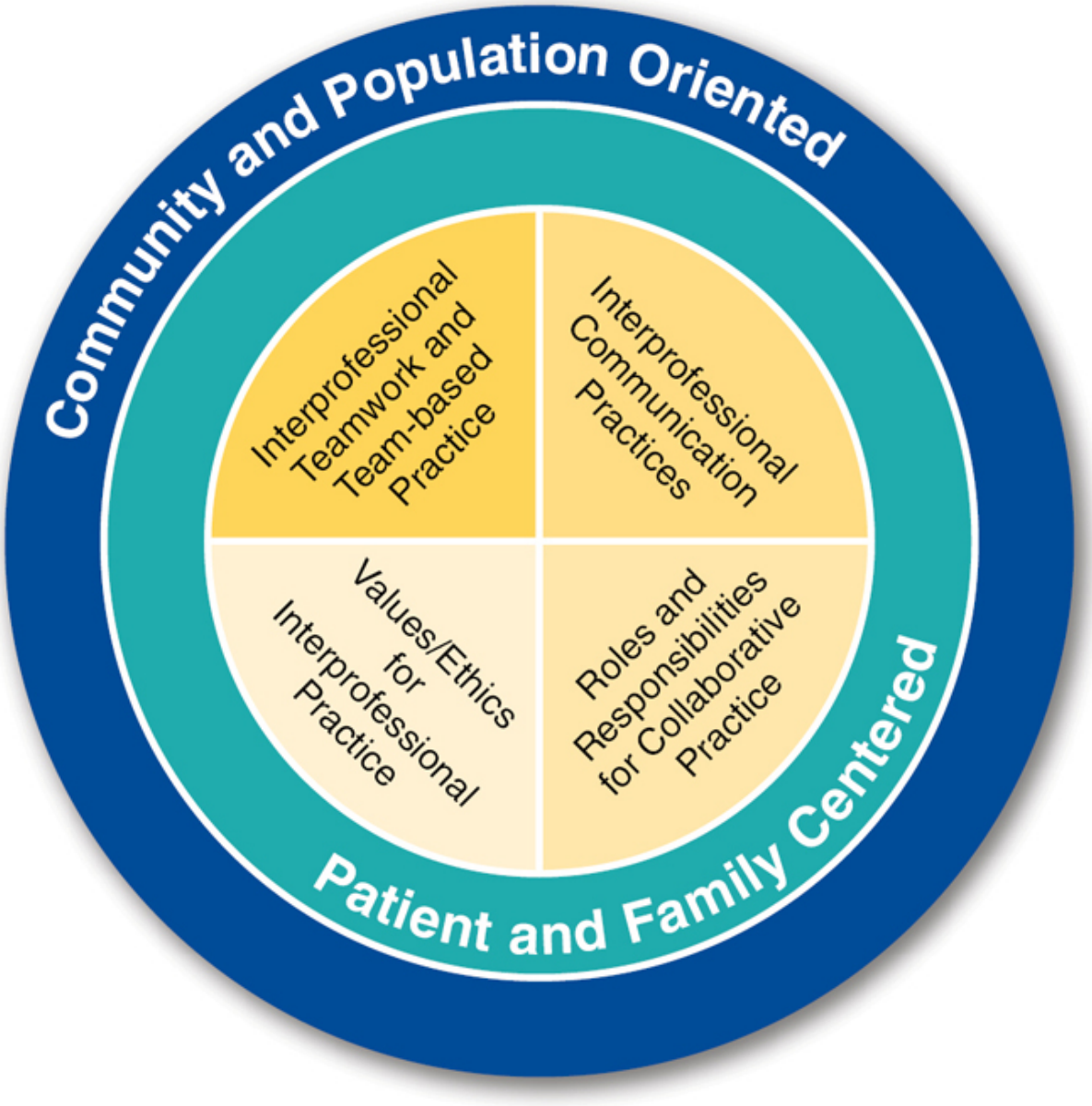


Figure 7-1 Interprofessional collaboration competency domain. (Source: Interprofessional Education Collaborative. Core competencies for interprofessional collaborative practice: 2016 update. Interprofessional Education Collaborative. 2016. Accessed April 5, 2022. https://ipec.memberclicks.net/assets/2016-Update.pdf. Reprinted with permission from Association of American Medical Colleges.)

INTERPROFESSIONAL EDUCATION TERMINOLOGY

The terminology related to IPE can be confusing because meanings of "multidisciplinary," "interdisciplinary," and "interprofessional" may differ in the literature.[4] The former terms describe a simple and additive approach to patient care, with several health care providers providing independent services and each responsible for their own specialty. As described earlier, IPE is a more coordinated approach in which there is an integration and collaboration to include the viewpoints of many different professions to optimize patient care.[4]

To help clarify and standardize interprofessional terminology, HPAC has compiled a consensus table (**Table 7-1**).[14]

Table 7-1
Consensus Terminology in the Published Literature

Term	Definition	Organization
Interprofessional education	"When students from two or more professions learn about, from and with each other to enable effective collaboration and improve health outcomes."	WHO[a]
Interprofessional collaborative practice	"When multiple health workers from different professional backgrounds work together with patients, families, carers[b], and communities to deliver the highest quality of care."	WHO[a]
Interprofessional teamwork	"The levels of cooperation, coordination and collaboration characterizing the relationships between professions in delivering patient-centered care."	IPEC[c]
Interprofessional team-based care	"Care delivered by intentionally created, usually relatively small work groups in health care who are recognized by others as well as by themselves as having a collective identity and shared responsibility for a patient or group of patients (e.g., rapid response team, palliative care team,	IPEC[c]

	primary care team, and operating room team)."	

[a]World Health Organization. *Framework for Action on Interprofessional Education & Collaborative Practice.* 2010. http://whqlibdoc.who.int/hq/2010/WHO_HRH_HPN_10.3_eng.pdf.

[b]The term *caregivers* is more commonly used in the United States.

[c]Interprofessional Education Collaborative. *Core Competencies for Interprofessional Collaborative Practice: 2016 Update.* 2016. https://ipec.memberclicks.net/assets/2016-Update.pdf

Source: Health Professions Accreditors Collaborative. *Guidance on Developing Quality Interprofessional Education for the Health Professions*. Health Professions Accreditors Collaborative. 2019. https://healthprofessionsaccreditors.org/wp-content/uploads/2019/02/HPACGuidance02-01-19.pdf.

CASE 7-4

QUESTION 1: You are on an internal medicine APPE rotation and on rounds with a patient care team that includes a medical student, nursing student, and dietetics student. The medical resident presents a case of an elderly patient recently admitted with worsening heart failure and determines what the treatment plan would be without involving anyone else on the team.

Is your experience considered an example of IPE?

Although one should understand what IPE is, it is also important to clarify what does not constitute IPE. For example, students from different health professions learning the same topic in a classroom setting (eg, pharmacology) without interacting and discussing the material as it pertains to their respective discipline are not considered IPE.[4] Nor is it IPE when a faculty member from another profession lectures pharmacy students unless that person incorporates some component on how the professions would interact in providing patient care.[4] Also, experiences on APPE rotations that are directed by someone from another profession that do not include sharing of responsibility for patient care are not considered IPE.[3] Consequently, the experience described in Case 7-4, Question 1, is not considered IPE. Clearly, the underlying theme of any IPE activity is that it should be a collaborative effort of students representing different professions.

INTERPROFESSIONAL EDUCATION MODELS

The creation of an effective model for IPE should start with the understanding that this is just the initial step in providing patient-directed care.[3] An interprofessional environment helps students from one profession learning from individuals representing another discipline to better develop skills that will help improve their own profession-specific skills and to more effectively work in a team-based setting.[3] There also needs to be a commitment that IPE be incorporated within the curricula of all programs within an institution to help sustain its future viability.[3] In addition to other health profession students, pharmacy students should be considered essential to any IPE model. As the practice of pharmacy has evolved into more of a patient-focused, clinically oriented dynamic, pharmacy students must be able to step into frontline roles with other health professional students who have had a tradition of “hands-on” patient care.

Outreach to other institutions that educate important health care students critical to the IPE team, such as medicine, dentistry, and social work, will become necessary. This requires communication, shared planning and training, and, ultimately, formal agreements among institutions to participate in IPE.

The stage of socialization within the specific profession must be considered when creating interprofessional teams as well.[3] Socialization of health care students has been defined as “the acquisition of knowledge, skills, values, roles and attitudes associated with the practice of that particular profession,” and can be exhibited by the language, behavior, and demeanor that are representative of that specific discipline.[3] It is important that students maintain their professional identity when participating in an IPE model. When creating student teams, one should try to balance them regarding where they are in their professional education and socialization.[3] Medical students who are in the fourth year of their program paired with less experienced health care students may

negatively impact the learning of other students if the medical student assumes a more dominant role.[3]

CASE 7-5

Question 1: M.M. is a 65-year-old retired male who presented to his provider 3 days ago with reporting increased shortness of breath (dyspnea) upon exertion. He reports noting swelling in his ankles for months that has started to get worse over the past 2 weeks. This is making it difficult to go up the stairs to his apartment and to wear his shoes toward the end of the day. In the past week, he has had a decreased appetite, nausea and vomiting, and tenderness in the right upper quadrant of the abdomen. He reports that he has not taken his medications in the past month because he did not think they were helping him. The patient lives alone with his dog in a small two-bedroom apartment on the second floor of a multifamily home. He has a daughter who lives in another state and who visits him during the holidays. The patient was hospitalized and treated for a diagnosis of exacerbation of congestive heart failure (CHF) and is now being discharged home. A physician, PA, nurse, social worker, and pharmacist are part of a discharge planning team working with M.M.

How does the approach of the pharmacist to M.M.'s care differ from that of the other team members?

One element of an IPE model is understanding that different professions may vary in how they approach patient care. Medicine and pharmacy tend to focus on eliminating or "ruling out" causes of a patient's patient's reported symptoms, whether it is medical or drug related.[3] Although the physician or PA may focus primarily on the medical evaluation of M.M., the pharmacist would determine whether any of his medications were causing effects that may have contributed to his belief that they were not helping him. The pharmacist would also work with M.M. to develop a plan that would enhance adherence to his discharge medications. Some other members of the team, such as the nurse and social worker, may take a more holistic approach and address the patient from a broader perspective.[3] This would include considering any family or environment issues that may affect M.M.'s progress such as ability for self-care when living alone and not having a relative living close by. They could plan to make sure that M.M. has the proper support at home. The nurse can also educate the patient about the

importance of adherence to proper diet and to recognize early signs and symptoms of exacerbation. Some professions such as social work or psychology tend to be more involved with the patient or family for a more prolonged period of time, particularly if a change in behavior is warranted.[3] Another consideration with how different professions approach patient care is that medical students are typically trained to be decision-makers regarding clinical problem-solving, which has been a long-standing part of the culture of medicine.[19] As noted previously, team-based care means a shared responsibility for patient care on the part of all team members and should not be dominated by any one profession.

INCORPORATING INTERPROFESSIONAL EDUCATION INTO THE CURRICULUM

CASE 7-6

QUESTION 1: In your first professional year in pharmacy school, you are in an introductory health care seminar course with other health profession students. A fellow classmate shares that she would prefer to be with only other pharmacy students until later in the curriculum.

What are the possible benefits of having other health care students in an introductory-level course?

The goal of IPE is to develop knowledge, skills, and attitudes that result in interprofessional team competence.[10] This includes not only clinical skills but also communication, conflict resolution, and team building skills, in addition to respecting the roles and responsibilities of other health professions.[3] IPE is best when it is incorporated throughout the entire curriculum in a vertically and horizontally integrated manner, in which collaboration, teamwork, and patient-centered care are introduced to students before their entering the professional phase of the curriculum.[10] It has been reported that early exposure to the IPE approach enhances students' confidence

in their professional value, supports their respecting the contributions of other professions, and better prepares them for providing patient care.[20] It has additionally been noted that early educational experiences within an IPE program increase the appeal of collaborating with other professions, reduce any potential negative stereotypical attitudes one may have toward these other professions, and enhance communication skills regardless of any specialized knowledge one may have.[21]

The American Council for Pharmacy Education (ACPE), the pharmacy education accrediting body, included IPE in Standard 11 of their 2016 Standards and Guidelines for Accreditation.[22] To meet this standard, the PharmD curriculum "should prepare all students to provide entry level, patient-centered care in a variety of practice settings as a contributing member of an interprofessional team. In the aggregate, team exposure includes prescribers as well as other healthcare professionals."[22] Pharmacy schools must develop an interprofessional education plan throughout the didactic and experiential portions of the curriculum applying to all students in a variety of practice settings.

The key elements of this standard include interprofessional team dynamics, interprofessional team education, and interprofessional team practice that incorporate all the IPEC core competencies. The interprofessional dynamics section of the standard addresses values and ethics, interprofessional communication, conflict resolution, and honoring interprofessional roles and responsibilities. The standard indicates that "these skills should be introduced, reinforced, and practiced in the didactic and Introductory Pharmacy Practice Experience (IPPE) components of the curriculum, and competency is demonstrated in the Advanced Pharmacy Practice Experience (APPE) settings."[22]

The interprofessional team education component includes "opportunities for students to learn about, from, and with other members of the interprofessional health care team. Through interprofessional education activities, students gain an understanding of the abilities, competencies, and scope of practice of team members."[22]

The team practice section mandates that "all students competently participate as a healthcare team member in providing direct patient care and engaging in shared therapeutic decision-making." They all should "participate in experiential educational activities with prescribers/student prescribers and other student/professional healthcare team members, including face-to-face interactions that are designed to advance interprofessional team effectiveness."[22]

In January 2018, the ACPE Board added the additional guidance that the expectation for IPE experiences in both the didactic and experiential components of the curriculum would include prescribers/student prescribers with the "mix of prescribers to include (but is not limited to) physicians and their students in both the didactic and experiential components of the curriculum."[23]

INTERPROFESSIONAL EDUCATION GUIDANCE DOCUMENT

As more health professions accrediting bodies have mandated IPE activities in their respective training programs, there has been a movement to provide more guidance to ensure the quality and viability of these programs. Quality IPE training also helps develop collaborative practice teams that will proliferate and become a model of patient care to help promote better population health. The National Center for Interprofessional Practice and Education (National Center) is a public/private partnership housed at the University of Minnesota that was founded in 2012 to "provide the leadership, evidence and resources needed to guide the nation on the use of interprofessional education and collaborative practice to enhance the experience of health care, improve population health and reduce the overall cost of care."[7]

The National Center collaborated with the HPAC to release its Guidance on Developing Quality Interprofessional Education for the Health Professions in 2019.[14] The goals were to "facilitate the

preparation of health professional students for interprofessional collaborative practice through accreditor collaboration and to provide consensus guidance to enable institutions to develop, implement, and evaluate systematic IPE approaches and IPE plans."[13]

The document recommends that quality IPE plans include the following characteristics: (a) a rationale; (b) outcome-based goals; (c) a deliberate design; and (d) assessment and evaluation. The rationale should articulate a vision, framework, and justification for the IPE plan. Outcome-based goals should be achievable by students to demonstrate interprofessional competencies for collaborative practice. A deliberate design of the IPE plan should incorporate a variety of intentional interprofessional activities that are integrated longitudinally into the entire length of the curriculum and demonstrate achievement of the outcome-based goals appropriate for the level of the learner. The assessment and evaluation process should quantify the students' proficiency in interprofessional competencies throughout the curriculum and serve as an evaluation of the institutional IPE plan for quality improvement.[14]

CASE 7-7

QUESTION 1: Your school of pharmacy would like to incorporate a foundational IPE activity into the didactic curriculum.

How should planning be initiated for an activity involving students from multiple health care professions?

As mentioned previously, IPE must be incorporated into the pharmacy curriculum for all students throughout the length of the curriculum to meet ACPE accreditation standards.[22]

The HPAC/National Center guidance document[14] will function as a blueprint in the development of the rationale, outcome-based goals, deliberate design, and the assessment/evaluation of the proposed activity.

The overall IPE curricular plan must be considered when designing the first activity because subsequent programming will continue to build upon this foundation. An interprofessional team is

vital for successful development of any IPE activity in academia. Faculty and staff are most often the activity developers. Each student profession targeted to participate in the activity should be represented on the faculty/staff development team and this team must agree on an activity that will benefit all participants. As mentioned earlier, participating students should be at similar levels within their professional education. Faculty and staff who value IPE and interprofessional collaboration are best suited for the development team as opposed to assigned participation by a department chair/supervisor. Having student members on the development team is extremely beneficial. Students can provide a reality check for what is being expected of the participants during the activity and the level of knowledge/skills of the activity participants.

The focus of the activity must be linked to one or more of the IPEC core competencies,[11] and specific, measurable objectives must be developed. Each objective should then correspond with an assessment method that will allow evaluation of students' achievement. An interactive component is essential for any IPE activity because students should be learning about, with, and from each other. The quality of an IPE activity is dependent on the quality of the student interaction. Careful consideration needs to be given to the type of interaction that can reasonably fit within the timeframe of the activity. Examples of interactions include patient case discussions, group assignments, role-play, and simulation.

Case 7-7, Question 2: The interprofessional development team will develop an IPE activity that will involve pharmacy students and several other health care profession students that are local to the School of Pharmacy. What are additional considerations for the team?

Scheduling is often the rate-limiting step for any IPE activity. The challenge of making sure that the activity is part of the curriculum requires that there is synchronization within all professional curricula to allow for interprofessional education. There should be buy-in from upper administration as well as close cooperation between the administrative faculty and curriculum committees of each

representative health profession. It is vital that the members of the IPE development team communicate with their respective faculty so that there is an opportunity for the recruitment of ideas and preceptors to assist in the activity.

The ACPE requirement for involvement with "physicians and their students" in IPE activities would require agreements with area medical schools and coordination with their respective IPE leaders to participate in IPE programs. It may be easier to engage medical programs that are housed in the same university setting as the pharmacy schools, but more difficult if there is a logistical or cultural divide between the two professional schools. Medical schools are under the same accreditation pressure to include IPE into their curriculum, so it is imperative that pharmacy IPE leaders become proactive in promoting the need for pharmacy students/faculty in the mix for joint IPE activities.

Virtual, online platforms such as Zoom may allow more flexibility with scheduling and would eliminate any constraints due to physical space for large group gatherings.

Another consideration is what students already know about IPE before the activity. Has IPE been introduced within each profession's curriculum and has consistent terminology been used? If not, introductory information on IPE will need to be discussed at the start of the activity. The IPE planning team must also decide on the deliverables of the activity. Will the students be required to submit prework of any kind? Will there be a group assignment, and would it include a graded component? Weighting of graded assignments should be balanced for all participating students to encourage a consistent level of effort. A discussion of the value of IPE and a joint show of support from the interprofessional planning team should also precede the program.

Case 7-7, Question 3: The interprofessional development team would like to design an introductory IPE activity that will focus on two IPEC competencies: interprofessional communication and roles/responsibilities. How might this IPE activity be implemented?

An example of an introductory roles and responsibilities IPE activity that has been implemented in various schools of pharmacy centers on a simple checklist of health professionals' routine tasks. This 60- to 90-minute activity begins with students independently completing a checklist of professional activities performed by various health care practitioners. Examples of items on the checklist include "Administer immunizations" and "Prescribe scheduled medication." The checklist instructions ask students to indicate which items fall within the scope of practice for an entry-level practitioner from each of the participating health care programs. Students then work together in interprofessional teams to complete the checklist a second time with the goal of identifying activities that are similar (applying to all the health care practitioners) and activities that are unique to each profession. Interprofessional teams of 8 to 10 students are preassigned to ensure that students are engaged with all other programs. Facilitators include faculty (health care professionals) from each of the programs involved. This IPE activity exposes pharmacy students to the roles and responsibilities of their own profession as well as those of the other professions. It is also the first opportunity for pharmacy students to interact and communicate with students from other programs within a required course. This activity can be presented in both live (in person) or via a virtual (Zoom) format.

This IPE activity includes three outcome-based objectives: (a) communicate one's roles and responsibilities to an interprofessional group; (b) identify unique and similar responsibilities among health care professionals; and (c) explain how the interprofessional team works together to provide patient care. This initial IPE activity is ideal for first-year students because it sets a foundation for the overall IPE plan. The framework for the IPE curriculum should be deliberately designed to build in breadth and depth with more case-based, clinical activities as the didactic/clinical curriculum progresses.

CASE 7-7, QUESTION 4: How is the activity assessed?

The activity concludes with an evaluation based on the session objectives and overall rating of the activity. There are also a variety of IPE assessment scales that have been published that can be utilized to assess student attitudes and achievements of competencies in IPE.

The Readiness for Interprofessional Learning Scale (RIPLS)[24] and the extended RIPLS[25] are two well-established tools for assessing interprofessional attitudes, but these were developed before the establishment of the IPEC core competencies. The more recent Interprofessional Attitudes Scale (IPAS)[26] is a validated 27-item scale that links IPE assessment to the IPEC core competencies. This scale can be completed by participants in 10 minutes and has been given pre- and postactivity to measure changes in IPE attitudes. The Student Perceptions of Physician-Pharmacist Interprofessional Clinical Education (SPICE) instrument was developed to specifically measure changes in the perceptions of medical and pharmacy students after IPE activities.[27] Elimination of profession-specific language in SPICE-Revised allowed this instrument to be used across all health professions.[28] Further refinement and validation of this tool resulted in the appearance of the most recent SPICE-R 2.[29]

The IPEC Competency Self-Assessment Tool[30,31] was designed to allow students to self-assess their progress on items linked to the 42 subcompetencies of the IPEC core competencies. This validated tool can be administered periodically throughout the curriculum (eg, at each year's baseline and at end of each year) to help monitor the progression of developing IPE competencies.

These and other IPE assessment tools can be accessed on The National Center for Interprofessional Practice and Education website, which maintains an updated Measurement Instrument Collection at https://nexusipe.org/advancing/assessment-evaluation.

INTERPROFESSIONAL EDUCATION: FUTURE DIRECTIONS AND RESOURCES

To sustain the IPE momentum that has developed over the past several years requires the necessary resources to support it, both at the academic and professional levels.[32] Further opportunities for collaboration between professions need to be identified, and health care education needs to advance to the point where interprofessional team–based learning becomes the norm.[33] Quality academic and clinical research needs to demonstrate that interprofessional collaboration results in the advancement of the Quadruple Aim.[34] Functional interprofessional teams need to be developed, fostered, and supported by the health care industry, recognized by insurers, and valued by consumers as the best practice.

Codification of IPE into the health professional education accreditation standards is a first step,[14] but continuing education revolving around the IPEC core competencies is needed for all practicing professionals. As a move in this direction, the Joint Accreditation for Interprofessional Education™ has offered Interprofessional Continuing Education (IPCE) credits for learning and change that can be used by jointly accredited providers to identify activities that have been planned by and for the health care team.[35] Jointly accredited providers may choose to award single profession or IPCE credits to athletic trainers, dentists, dietitians, nurses, optometrists, PAs, pharmacists, physicians, psychologists, and social workers without needing to obtain separate accreditations.[36]

The landscape of interprofessional practice and education and the concept of collaborative care has moved from an experimental process into the mainstream. The appearance of multiple resources over the past decade that encourage, support, and guide this collaboration as well as promote the research to validate its importance is encouraging. The reader is advised to peruse the section Key Websites to access a wealth of further information.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American College of Clinical Pharmacy. Interprofessional education: principles and application. An update. *J Am Coll Clin Pharm*. 2018;1(*1*):17e–28e. (3)

Interprofessional Education Collaborative. Core competencies for interprofessional collaborative practice. 2016 Update. https://ipec.memberclicks.net/assets/2016-Update.pdf (11)

World Health Organization. Framework for action on interprofessional education & collaborative practice. 2010. http://apps.who.int/iris/bitstream/handle/10665/70185/WHO_HRH_HPN_10.3_eng.pdf;jsessionid=0152FB99C9DF9D95B944A7ED0FD56682?sequence=1 (1)

Key Websites

Health Professions Accreditors Collaborative. https://healthprofessionsaccreditors.org

Interprofessional Education Collaborative. https://www.ipecollaborative.org

National Center for Interprofessional Practice and Education. https://nexusipe.org

COMPLETE REFERENCES CHAPTER 7 INTERPROFESSIONAL PRACTICE AND EDUCATION

1. World Health Organization. Framework for action on interprofessional education & collaborative practice. 2010. Accessed April 12, 2022. http://apps.who.int/iris/bitstream/handle/10665/70185/WHO_HRH_HPN_10.3_eng.pdf;jsessionid=0152FB99C9DF9D95B944A7ED0FD56682?sequence=1
2. Institute of Medicine. *Educating for the Health Team*. National Academy of Sciences; 1972.

3. American College of Clinical Pharmacy. Interprofessional education: principles and application. An update. *J Am Coll Clin Pharm*. 2018;1(1):17e–28e.
4. Buring SM, Bhushan A, Broeseker A, et al. Interprofessional education: definitions, student competencies, and guidelines for implementation. *Am J Pharm Educ*. 2009;73:59.
5. Greiner A, ed. *Institute of Medicine Report. Health Professions Education: A Bridge to Quality*. National Academies Press; 2003.
6. Rittenhouse DR, Shortell SM. The patient-centered medical home. Will it stand the test of health reform? *JAMA*. 2009;301:2038–2040.
7. National Center for Interprofessional Practice and Education. About IPE. Accessed April 12, 2022. https://nexusipe.org/informing/about-ipe
8. Institute for Healthcare Improvement. Triple aim for populations. Accessed April 12, 2022. http://www.ihi.org/Topics/TripleAim/Pages/default.aspx
9. Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. *Ann Fam Med*. 2014;12:573–576.
10. Interprofessional Education Collaborative. Core competencies for interprofessional collaborative practice. Report of an expert panel. 2011. Accessed April 12, 2022. https://ipec.memberclicks.net/assets/2011-Original.pdf
11. Interprofessional Education Collaborative. Core competencies for interprofessional collaborative practice. 2016 Update. Accessed April 12, 2022. https://ipec.memberclicks.net/assets/2016-Update.pdf
12. Interprofessional Education Collaborative. IPEC Core Competencies Revision, 2021-2023. Accessed April 12, 2022. https://www.ipecollaborative.org/2021-2023-core-competencies-revision
13. Interprofessional Education Collaborative. Membership. Accessed April 12, 2022. https://www.ipecollaborative.org/membership
14. Health Professions Accreditors Collaborative. IPE guidance. Accessed April 12, 2022. https://healthprofessionsaccreditors.org/ipe-guidance/
15. Health Professions Accreditors Collaborative. History. Accessed April 12, 2022. https://healthprofessionsaccreditors.org/history/
16. Attum B, Hafiz S, Malik A, Shamoon Z. Cultural competence in the care of Muslim patients and their families. *StatPearls*. 2021. Accessed April 12, 2022. https://www.ncbi.nlm.nih.gov/books/NBK499933/
17. Gatrad AR, Sheikh A. Medical ethics and Islam: principles and practice. *Arch Dis Child.* 2001;84:72–75.
18. Carney PA, Thayer EK, Palmer R, et al. The benefits of interprofessional learning and teamwork in primary care ambulatory training settings. *J Interprof Educ Pract*. 2019;15:119–126.
19. Leape LL, Berwick DM. Five years after to err is human: what have we learned? *JAMA*. 2005;293:2384–2390.

20. Cooper H, Spencer-Dawe E, McLean E. Beginning the process of teamwork: design, implementation, and evaluation of an inter-professional education intervention for first year undergraduate students. *J Interprof Care*. 2005;19:492–508.
21. Tunstall-Pedoe S, Rink E, Hilton S. Students' attitudes to understanding interprofessional education. *J Interprof Care*. 2003;17:161–172.
22. Accreditation Council for Pharmacy Education. Accreditation standards and key elements for the professional program in pharmacy leading to the Doctor of Pharmacy degree. ("Standards 2016"). 2016. Accessed April 12, 2022. https://www.acpe-accredit.org/pdf/Standards2016FINAL.pdf
23. ACPE Standard 11 guidance document. 2018. Accessed April 12, 2022. file:///C:/Users/Owner/Documents/ACPE%20IPE%20Feb2018.pdf
24. Parsell G, Bligh J. The development of a questionnaire to assess the readiness of health care students for interprofessional learning (RIPLS*). Med Educ*. 1999;33:95–100.
25. McFadyen AK, Webster V, Strachan K, et al. The readiness for interprofessional learning scale: a possible more stable sub-scale model for the original version of RIPLS. *J Interprof Care*. 2005;19:595–603.
26. Norris J, Carpenter JG, Eaton J, et al. Development and construct validation of the interprofessional attitudes scale. *Acad Med*. 2015;90:1394–1400.
27. Zorek JA, MacLaughlin EJ, Fike DS, MacLaughlin AA, Samiuddin M, Young RB. Measuring changes in perception using the Student Perceptions of Physician-Pharmacist Interprofessional Clinical Education (SPICE) instrument. *BMC Med Educ*. 2014;14:101. Accessed April 12, 2022. https://bmcmededuc.biomedcentral.com/articles/10.1186/1472-6920-14-101
28. Dominguez DG, Fike DS, MacLaughlin EJ, Zorek JA. A comparison of the validity of two instruments assessing health professional student perceptions of interprofessional education and practice. *J Interprof Care*. 2015;29:144–149.
29. Zorek JA, Fike DS, Eickhoff JC, et al. Refinement and validation of the student perceptions of physician-pharmacist interprofessional clinical education instrument. *Am J Pharm Educ*. 2016;80:47.
30. Dow A, DiazGranados D, Mazmanian PE, Retchin SM. An exploratory study of an assessment tool derived from the competencies of the Interprofessional Education Collaborative. *J Interprof Care*. 2014;28:299–304.
31. Lockeman KS, Dow AW, DiazGranados D, et al. Refinement of the IPEC Competency Self-Assessment Survey: results from a multi-institutional study. *J Interprof Care*. 2016;30:726–731.
32. Cox M, Cuff P, Brandt B, Reeves S, Zierler B. Measuring the impact of interprofessional education on collaborative practice and patient outcomes. *J Interprof Care*. 2016;30:1–3.
33. Schot E, Tummers L, Noordegraaf M. Working on working together. A systematic review on how healthcare professionals contribute to

interprofessional collaboration. *J Interprof Care*. 2020;34:332–342.
34. Fraher E, Brandt B. Toward a system where workforce planning and interprofessional practice and education are designed around patients and populations not professions. *J Interprof Care*. 2019;33:389–397.
35. Joint Accreditation for Interprofessional Continuing Education. New credit recognizes interprofessional continuing education for healthcare teams. 2017. Accessed April 12, 2022. https://www.jointaccreditation.org/new-credit-recognizes-interprofessional-continuing-education-healthcare-teams
36. Joint Accreditation for Interprofessional Continuing Education. Accredited providers. Accessed April 12, 2022. https://www.jointaccreditation.org/accredited-providers

SECTION 2

Cardiac and Vascular Disorders

Section Editors: Judy W. Cheng and Snehal H. Bhatt

8

Dyslipidemias, Atherosclerosis, and Coronary Heart Disease

Barbara S. Wiggins and Pamela Morris

CORE PRINCIPLES	CHAPTER CASES
1 The risk of atherosclerosis is directly related to increasing levels of serum cholesterol. Cholesterol, specifically lipoproteins, plays a central role in the pathogenesis of atherosclerosis. Thus, low-density lipoprotein cholesterol (LDL-C) is the primary target for intervention. The American College of Cardiology/American Heart Association (AHA/ACC) Multisociety guidelines recommend management for patients at high risk. This includes patients with atherosclerotic cardiovascular disease (ASCVD) as well as those with familial hypercholesterolemia (FH).	**Case 8-1 (Question 1)**

2	Every patient with dyslipidemia should be evaluated for secondary causes of elevated LDL-C, non–high-density lipoprotein cholesterol (non–HDL-C), or triglycerides (TGs). These causes may be related to concomitant medications or due to a clinical condition.	**Case 8-1 (Questions 2, 3), Table 8-5**
3	LDL-C and the thresholds for instituting therapeutic lifestyle changes (TLC) and pharmacotherapy are guided by the presence of clinical atherosclerosis or based on CV risk.	**Case 8-2 (Questions 1, 2)** **Case 8-3 (Question 1)** **Case 8-4 (Questions 1, 2)**
4	An adequate trial of TLC should be used in all patients, but pharmacotherapy should be instituted concurrently in high-risk patients and the patients should be monitored for adverse effects.	**Case 8-2 (Question 2)** **Case 8-5 (Question 1)**
5	Statins are considered first-line therapy to treat high LDL-C due to their ability to substantially lower LDL-C, ability to reduce morbidity and mortality from atherosclerotic disease, convenient once-daily dosing, and low risk of side effects. Management of these adverse effects is necessary in order to optimize benefit.	**Case 8-2 (Question 2)** **Case 8-3 (Questions 2, 3)**
6	Statins are the agents of choice to reduce LDL-C with low risk of adverse effects. However, drug interaction knowledge is needed in order to optimize efficacy without compromising safety.	**Case 8-4 (Question 3)**

7	Patients with high TGs are at increased risk of acute pancreatitis. The primary goal in these individuals is to lower their TG levels with diet, exercise, weight reduction, and TG-lowering drugs such as fibrates or ω-3 fatty acids.	**Case 8-5 (Question 2)** **Case 8-6 (Question 1)**
8	Combination drug therapy is often needed in patients with severe lipid abnormalities, higher risk individuals with lower LDL-C goals, or patients with multiple lipid abnormalities such as those with the metabolic syndrome who have a secondary target of non–HDL-C.	**Case 8-6 (Question 2)**

INTRODUCTION

Dyslipidemias (one or more abnormalities of blood lipids) play an important etiologic role in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD), including coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease (PAD).[1] Successful lifestyle changes and pharmacologic management of dyslipidemias have been shown to reduce the risk of ASCVD events, such as heart attack and stroke.[2–4] For cardiovascular disease (CVD) prevention, the clinician estimates the individual patient's ASCVD risk with available risk assessment tools, determines the intensity of lipid-modulating therapy to match the patient's level of risk, and implements appropriate treatments to meet and maintain treatment goals.[5]

LIPID METABOLISM

Knowledge of lipid and lipoprotein metabolism is essential to understanding therapeutic targets for pharmacologic agents. Lipids are small molecules that function in the body's storage of energy, in cellular signaling, and as components of cell membranes. Cholesterol, an essential lipid, is the precursor molecule for the formation of bile acids (which are required for absorption of nutrients), the synthesis of steroid hormones (which provide important modulating effects in the body), and the formation and integrity of cellular membranes. However, excess cholesterol plays a central role in atherogenesis and subsequent atherothrombotic complications.

Cells derive cholesterol in two ways: by intracellular synthesis or by uptake from the systemic circulation. Within each cell, cholesterol is synthesized through a series of biochemical steps, many of which are catalyzed by enzymes (**Fig. 8-1**). The irreversible and rate-limiting step in cholesterol production is the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonic acid, which is catalyzed by HMG-CoA reductase. One of the most effective lipid-lowering therapies developed to date for managing dyslipidemias, HMG-CoA reductase inhibitors or statins, competitively interferes with the binding of substrate to this critical enzyme, thereby reducing the cellular synthesis of cholesterol. The biosynthesis of cholesterol in humans follows a circadian rhythm with maximum cholesterol synthesis occurring near midnight and minimum synthesis at midday.[5,6]

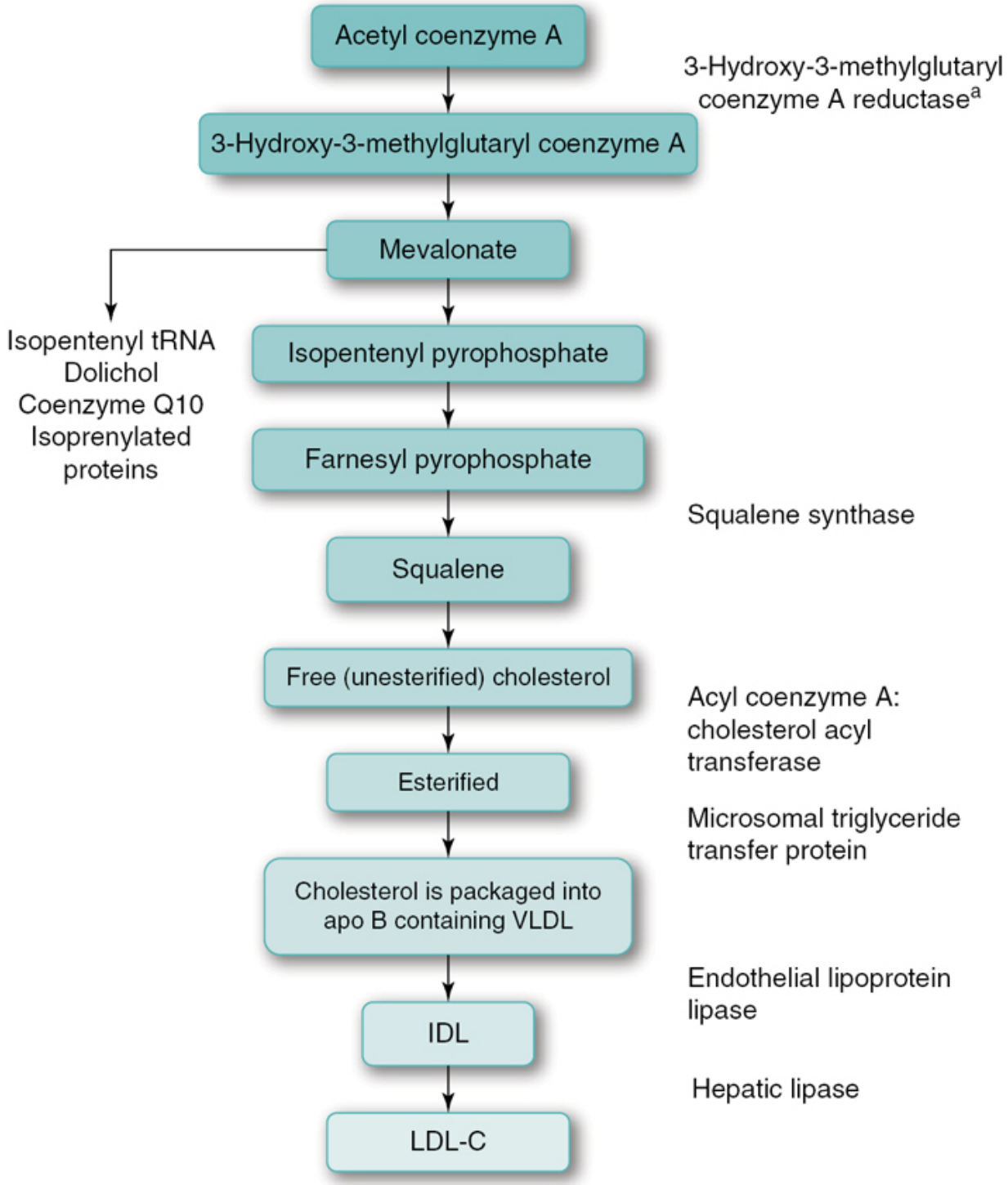


Figure 8-1 Biosynthetic pathway of cholesterol. apo B, apolipoprotein B; IDL, intermediate-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein.[a]The rate-limiting step in cholesterol biosynthesis.

Free cholesterol is esterified to cholesteryl esters (CEs) for intracellular storage by the action of the enzyme acetyl-CoA acetyl transferase (ACAT). Two forms of ACAT have been identified. ACAT1 is present in many tissues, including inflammatory cells, whereas ACAT2 is present in intestinal mucosa cells and hepatocytes. ACAT2 is required for the esterification and absorption of dietary cholesterol from the gut. In theory, inhibition of this enzyme could reduce the absorption of dietary cholesterol, the secretion of cholesterol by the liver, and even the uptake and storage of circulating cholesterol in inflammatory cells in the arterial wall. Several inhibitors of ACAT have been developed; however, in clinical trials, they did not appear to reduce atherosclerosis and were possibly proatherogenic.[7] It is unlikely that there will be any further development of this class of drugs for CV prevention.

Triglycerides (TGs) are lipids that serve as an important source of stored energy in adipose tissue. TGs are synthesized from three molecules of fatty acids esterified to a glycerol backbone. Phospholipids (PLs) are a class of lipids formed from fatty acids, a negatively charged phosphate group, nitrogen-containing alcohol, and a glycerol backbone. PLs are essential for cellular function and the absorption, storage, and transport of lipids in the circulation. They form the monolayer on the surface of lipoproteins, which function to transport neutral lipids throughout the body. PLs are amphipathic with a hydrophilic head and hydrophobic tail and form a membrane bilayer of lipoproteins to deliver hydrophobic cargo (cholesterol and energy in the form of fat) to other organs. PLs are also secreted into bile to aid in the digestion and absorption of dietary fat and lipid-soluble nutrients from the diet. They stabilize proteins within the membrane, function as cofactors in enzymatic reactions, and participate in the oxidation of lipoproteins in the arterial wall (**Fig. 8-2**).

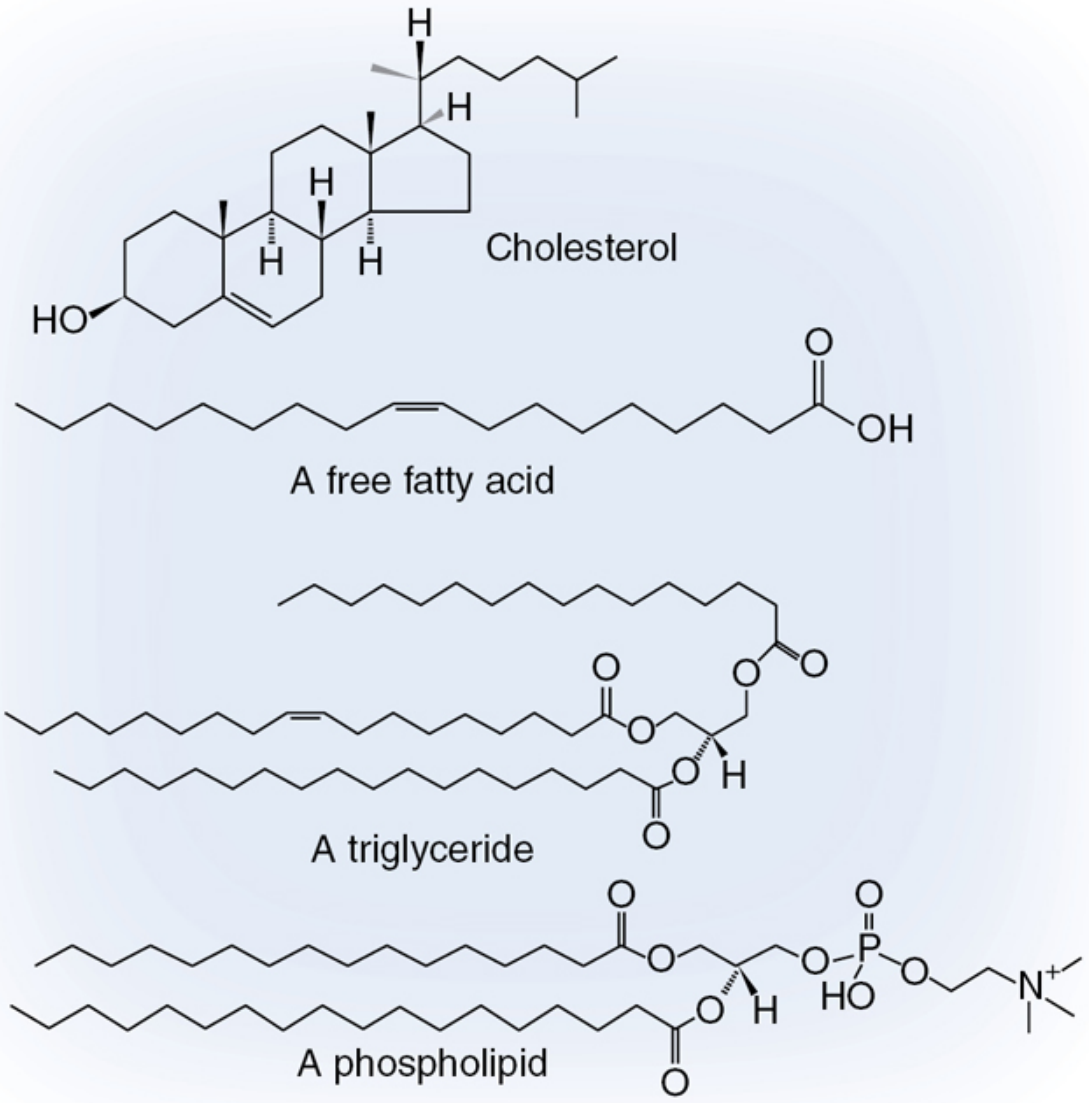


Figure 8-2 Chemical structure of lipids. At the top is cholesterol, followed by oleic acid. In the middle is a triglyceride composed of an oleoyl, stearoyl, and palmitoyl chain attached to a glycerin backbone. At the bottom is a phospholipid.

Lipoproteins

Cells also obtain cholesterol by extracting it from the systemic circulation. The source of this cholesterol is the liver, where it is synthesized and secreted into the systemic circulation. As discussed

earlier, cholesterol and other fatty substances are insoluble in water. Therefore, cholesterol, TGs, and PLs are packaged into water-soluble complexes called lipoproteins in the hepatocyte and enterocytes before being secreted into the aqueous medium of the blood. These lipoproteins contain an oily inner lipid core made up of CEs and TGs and an outer hydrophilic coat made up of PLs and unesterified cholesterol (**Fig. 8-3**). The outer coat also contains at least one of a number of proteins known as "apoproteins," which provide the ligand for interaction with receptors on cell surfaces, act as cofactors for various enzymes, and add structural integrity.

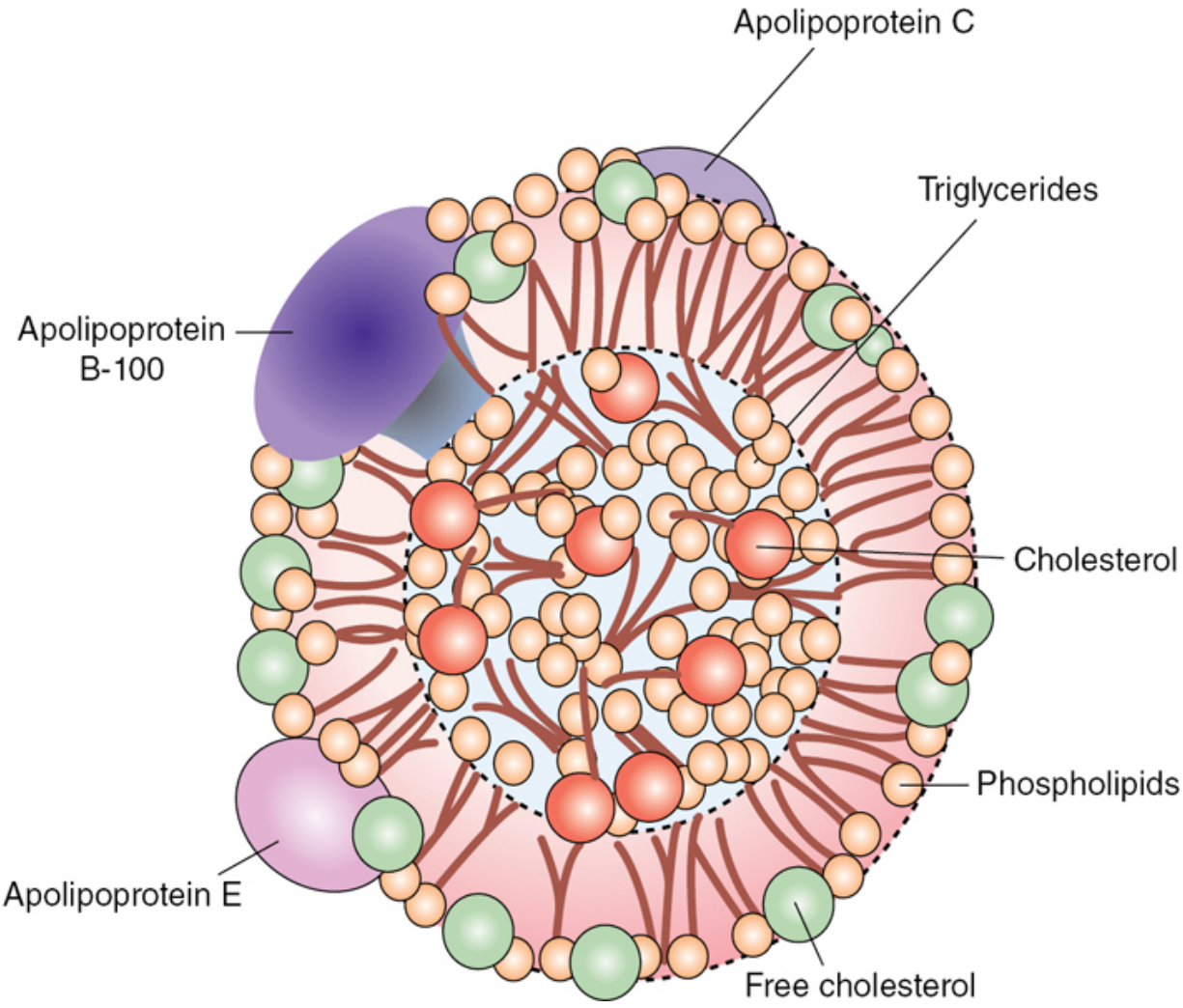


Figure 8-3 Basic structure of lipoproteins. Lipoproteins vary in the amount of cholesterol esters and triglyceride content. In addition, they have varying numbers and types of surface apolipoproteins.

The three major lipoproteins found in the blood of fasting (10–12 hours) patients are very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL).[8] These particles vary in size, cholesterol and TG composition, and accompanying proteins (**Table 8-1** and **Fig. 8-4**).[9,10]

Table 8-1
Classification and Properties of Plasma Lipoproteins

Lipoprotein	Origin	Density Range (g/mL)	Size (nm)	Cholesterol Concentration in Plasma (mmol/L)[a]	Triglyceride Concentration in Plasma (mmol/L)[b]	Major Apolipoprotein	Other Apolipoprotein
Chylomicrons	Intestine	<0.95	100–1000	0.0	0	B-48	A-I, C
VLDL	Liver	<1.006	40–50	0.1–0.4	0.2–1.2	B-100	A-I, C
IDL	VLDL	1.006–1.019	25–30	0.1–0.3	0.1–0.3	B-100	
LDL	IDL	1.019–1.063	20–25	1.5–3.5	0.2–0.4	B-100	
HDL	Tissues	1.063–1.21	6–10	0.9–1.6	0.1–0.2	A-I	A-II, A-IV
Lp(a)	Liver	1.051–1.082	30–50			B-1, (a)	

HDL, high-density lipoprotein; IDL, immediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein A; VLDL, very low-density lipoprotein.

[a]For mg/dL, multiply by 38.67.

[b]For mg/dL, multiply by 88.5.

From Genest J. Lipoprotein disorders and cardiovascular risk. *J Inherit Metab Dis*. 2002;26(2–3):267–287. © 2003 SSIEM. Reprinted by permission of John Wiley & Sons, Inc.

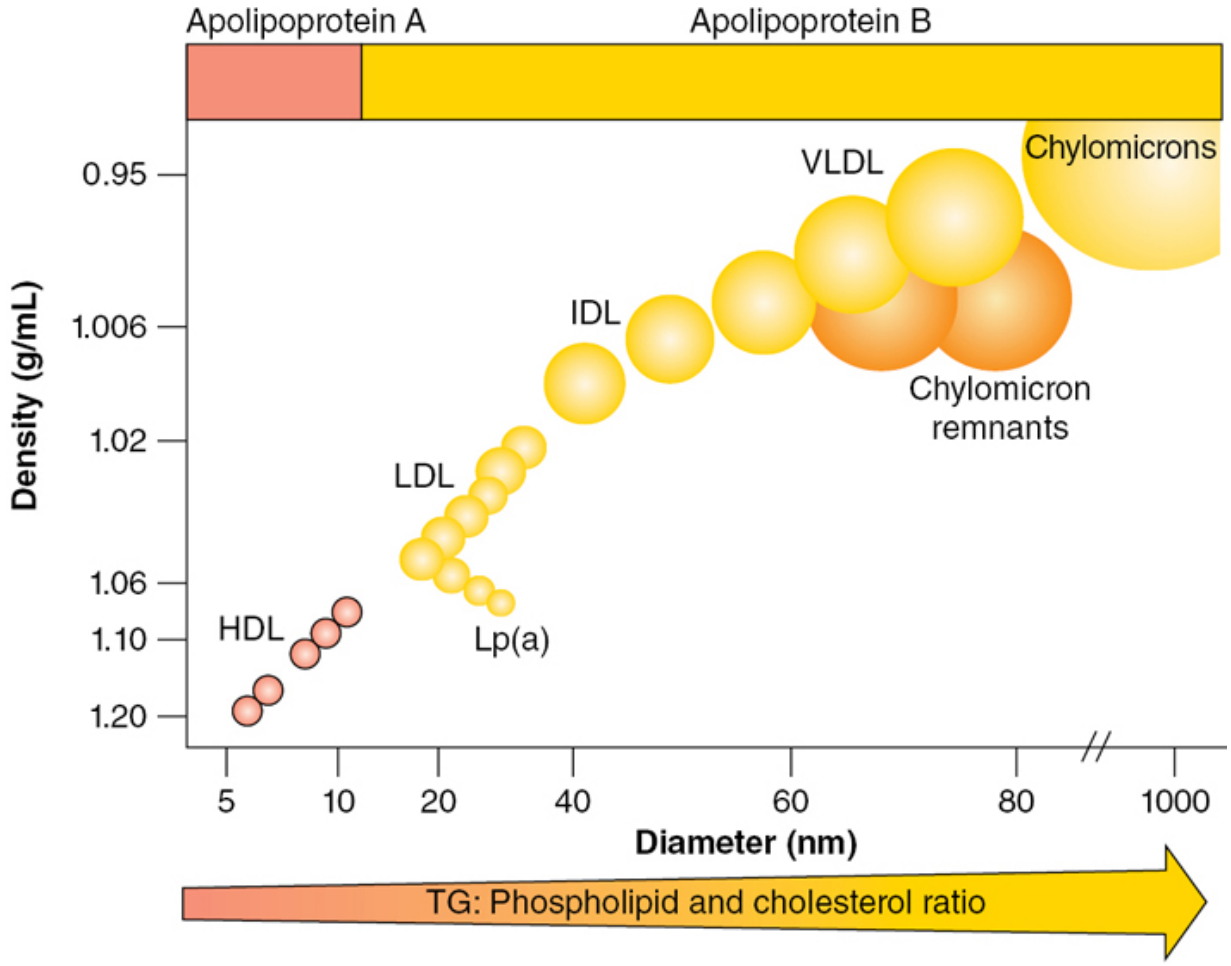


Figure 8-4 Relative lipoprotein sizes and densities. Relative lipoprotein particle densities: In general, a subclass distribution of increased small LDL, decreased large HDL, and increased large VLDL particle size is most associated with increased CHD risk. CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein. (From Bays H, Stein EA. Pharmacotherapy for dyslipidaemia—current therapies and future agents. *Expert Opin Pharmacother*. 2003;4(11):1901–1938. Reprinted by permission of Taylor & Francis Ltd, http://www.tandfonline.com)

VERY LOW-DENSITY LIPOPROTEINS

VLDL particles are formed in the liver. Free fatty acids are taken up by the hepatocyte where the enzyme diglycerol acyltransferase (DGAT) catalyzes TG formation from diacylglycerol and the

coenzyme acyl-CoA. The enzyme microsomal triglyceride transfer protein (MTP) lipidates apoprotein B by transfer of CEs and TG to form VLDL, which is then secreted by the liver into the circulation. Inhibitors of MTP reduce production of VLDL and downstream intermediate-density lipoprotein (IDL) and LDL. One of these agents, lomitapide, is currently approved for the treatment of the homozygous form of familial hypercholesterolemia (FH).[11] DGAT inhibitors that reduce TG synthesis are currently under investigation for the management of obesity and hypertriglyceridemia.[12]

VLDL particles normally contain 15% to 20% of the total blood cholesterol concentration and most of the total blood TG concentration. The concentration of cholesterol in these particles is approximately one-fifth of the total TG concentration; thus, if the total TG concentration is known, the VLDL cholesterol (VLDL-C) level can be estimated by dividing total TGs by 5. Newly secreted VLDL particles are too large to migrate into the arterial wall and appear to play only a small role in the pathogenesis of atherosclerosis.

VERY LOW-DENSITY LIPOPROTEIN REMNANTS

In the circulation, the enzyme lipoprotein lipase (LPL) hydrolyzes TGs in VLDL particles. The removed TGs are converted to fatty acids and stored as an energy source in adipose tissue. As TGs are removed, the VLDL particle becomes progressively smaller and relatively more cholesterol rich. The particles formed through this process include small VLDL particles (called remnant VLDL), IDL, and LDL (**Fig. 8-5**). Approximately 50% of the remnant VLDL and IDL particles are removed from the systemic circulation by LDL or apolipoprotein (apo) B-100/apo E receptors on the surface of the liver; the other 50% are converted into LDL particles by further hydrolytic action of hepatic lipase. VLDL remnant particles are found in the arterial wall, though in smaller numbers than LDL. Drugs that enhance the activity of LPL, such as the fibrates, increase hydrolysis of TG in VLDL particles and lower blood TG levels.

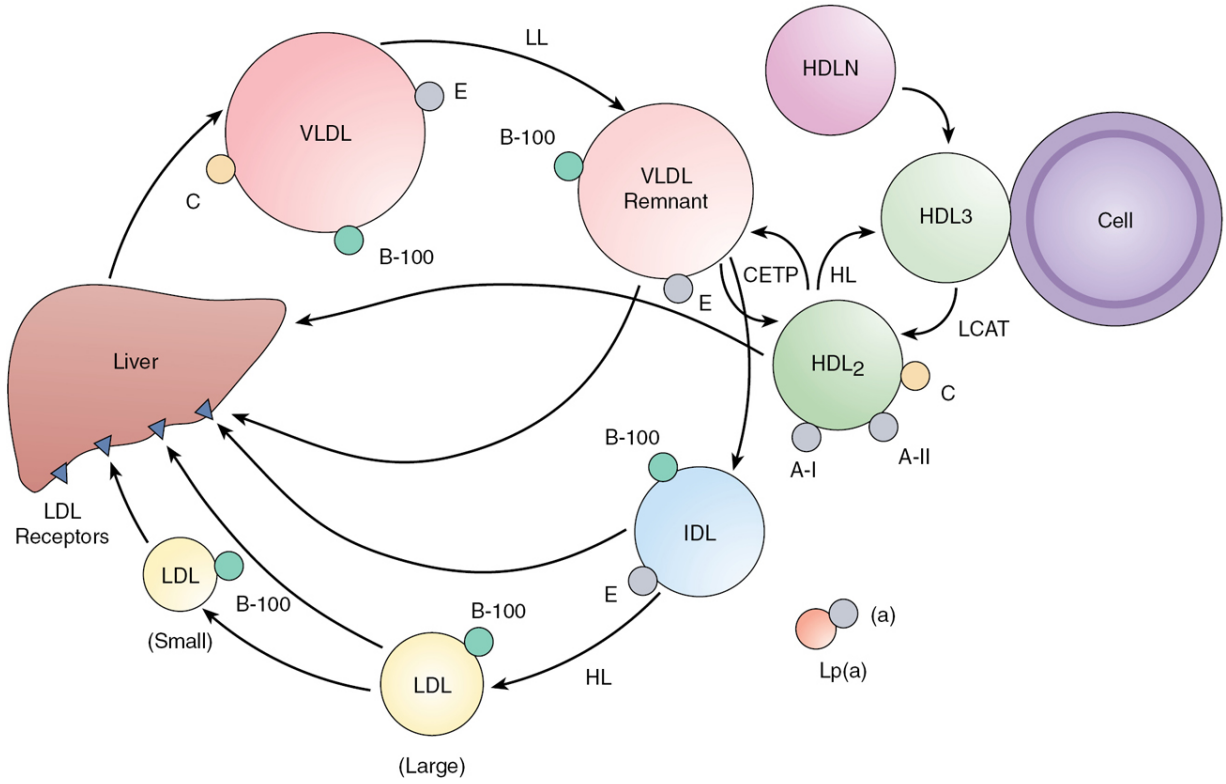


Figure 8-5 The lipoproteins, apolipoproteins, and enzymes involved in the transport of cholesterol and triglycerides. A-I, apolipoprotein A-I; A-II, apolipoprotein A-II; B-100, apolipoprotein B-100; C, apolipoprotein C; CETP, cholesteryl ester transfer protein; E, apolipoprotein E; HDL, high-density lipoprotein; HDLN, nascent high-density lipoprotein; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; LL, lipoprotein lipase; Lp(a), lipoprotein (a); VLDL, very low-density lipoprotein.

LOW-DENSITY LIPOPROTEINS

LDL particles are cholesterol enriched and carry 60% to 70% of the total blood cholesterol. LDL plays a central role in the pathogenesis of atherosclerosis and is the primary target of lipid-lowering therapy. Approximately half of the LDL particles are removed from the systemic circulation by the liver; the other half may be taken up by peripheral cells or deposited in the intimal space of coronary, carotid, and other peripheral arteries, where atherosclerosis can develop. The probability that atherosclerosis will develop is directly related to

the concentration of LDL-C in the systemic circulation and the duration of exposure to elevated LDL-C levels; thus, the cumulative risk of ASCVD in males and females with hypercholesterolemia increases with age.

HIGH-DENSITY LIPOPROTEINS

HDL particles transport cholesterol from peripheral, lipid-rich inflammatory cells in the arterial wall back to the liver, a process called *reverse cholesterol transport.*[13] In epidemiologic studies, HDL cholesterol (HDL-C) concentrations are inversely associated with the risk of ASCVD, presumably because cholesterol is being removed from vascular tissue and is not available to contribute to atherogenesis. In peripheral cells, the adenosine triphosphate binding cassette transporter A-1 (ABCA-1) and adenosine triphosphate binding cassette transporter G-1 facilitate the efflux of both cholesterol and PLs to apo A1 to form nascent HDL particles. Cholesterol acquired from peripheral cells by HDL particles is converted into an esterified form through the action of the enzyme lecithin cholesterol acyltransferase (LCAT). HDL particles may either transport cholesterol directly to the liver through interaction with the scavenger receptor, SR-B1, on the surface of hepatocytes or transfer it to circulating remnant VLDL and LDL particles by the action of cholesteryl ester transfer protein (CETP). CETP transfers cholesterol from HDL particles to VLDL and LDL in exchange for TGs, making the HDL particle less cholesterol rich. If the latter occurs, cholesterol may be returned to the liver for clearance from the circulation or delivered back to peripheral cells. Patients have been identified who have a deficiency of CETP and high plasma concentration of HDL-C, which appears to be associated with a low incidence of CHD. Drugs that inhibit CETP can raise HDL-C levels and are being studied in long-term CV outcomes trial.[14]

NON–HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

Though elevated LDL-C is most commonly associated with ASCVD risk, in some patients, the assessment of LDL-C alone may

underestimate the risk of events. Non–HDL-C, calculated by subtracting HDL-C from total cholesterol (TC), provides a measure of cholesterol carried by all potentially atherogenic particles, including VLDL, VLDL remnants, IDL, and LDL particles. Also, in the presence of postprandial hypertriglyceridemia, the calculation of LDL-C may be inaccurate, whereas non–HDL-C is reliable when measured in the nonfasting state.

CHYLOMICRONS

Unlike the lipoproteins that transport cholesterol from the liver to peripheral cells and back (endogenous lipid transport), chylomicrons transport TGs and cholesterol derived from the diet or synthesized in the enterocytes from the gut to the liver (exogenous lipid transport) (see **Fig. 8-5** and Table 8-1). Chylomicrons are large, TG-rich lipoproteins. As they pass through capillary beds on the way to the liver, some of the TG content is removed through the action of LPL in a manner similar to that described for hydrolysis of TGs from VLDL particles. In the rare individual who has LPL deficiency, chylomicrons are inefficiently metabolized and TG levels in the blood may become severely elevated (eg, 1000–5000 mg/dL).

After a fatty meal, the number of TG-rich chylomicron particles is elevated and TG levels rise. Following a 10- to 12-hour period of fasting, chylomicrons will be removed from the blood by LPL-mediated hydrolysis of TGs and removal of chylomicron remnants in the liver. TG concentrations measured in the fasting state reflect primarily TGs that are produced by the liver as well as TGs carried in VLDL and other remnant particles. For this reason, most patients are asked to fast before a lipoprotein profile is obtained. A blood sample that is rich in chylomicrons (and to a lesser extent VLDL particles) appears turbid; the higher the TG level, the more turbid the sample. If the sample from a patient with hyperchylomicronemia is refrigerated, chylomicrons will float to the top and form a frothy white layer, whereas smaller VLDL particles stay suspended below.

Apolipoproteins

Each lipoprotein particle contains proteins on the outer surface called *apolipoproteins* (see **Fig. 8-5** and Table 8-1). These proteins serve four main functions: (a) they serve as major structural components of lipoproteins, (b) they serve as cofactors for activation of enzyme systems, (c) they act as ligands for binding to receptors on cell surfaces, and (d) they are required for assembly and secretion of lipoproteins.[12] Abnormal metabolism of apolipoproteins can result in faulty enzyme activity or cholesterol transport and an increased risk of atherosclerosis. Clinicians may consider assessment of blood levels of apolipoproteins to evaluate dyslipidemic patients, especially those who have a family history of premature CHD. The five most clinically relevant apolipoproteins are B-100, C, E, A-I, and A-II.

VLDL particles contain apo B-100, apo E, and apo C (see **Fig. 8-5**). The B and E proteins are ligands for LDL receptors (also called *B-E receptors*) on the surface of hepatocytes and peripheral cells. Linkage allows the transfer of cholesterol from the circulating lipoprotein into the cell through absorptive endocytosis and cellular uptake of the particle. Defects in these proteins reduce the ability of lipoproteins to bind with receptor proteins and may result in defective clearance of lipoproteins from the systemic circulation and increased levels of circulating cholesterol.

Apo C-II is a cofactor or activator of LPL. By activating LPL, apo C-II stimulates the hydrolysis of TGs from lipoprotein particles in the capillary beds. Deficiency of apo C-II may result in faulty TG metabolism and subsequent hypertriglyceridemia. Apo C-III downregulates LPL activity and interferes with the hepatic uptake of VLDL remnant particles. This leads to increased concentrations of small VLDL remnant particles, which are small enough to penetrate into the arterial wall and contribute to atherogenesis. Apo C-III is a marker of atherogenic dyslipidemia (elevated TGs, reduced HDL-C, near-normal levels of LDL-C, and elevated LDL particle concentration), which is associated with an increased risk of ASCVD events. In addition, prolonged residence of VLDL and LDL particles in the systemic circulation results in the formation of small, highly

atherogenic LDL particles and the atherogenic dyslipidemia (see later).[15]

Each VLDL, IDL, and LDL particle contains one molecule of apo B-100. Thus, the blood concentration of apo B-100 is an indication of the total number of VLDL, VLDL remnant, IDL, and LDL particles in the circulation. An increased number of lipoprotein particles and an increased apo B-100 concentration are strong predictors of ASCVD risk.[16] Remnant VLDL particles retain both apo B-100 and apo E during the delipidization process; LDL particles contain only apo B-100 (see **Fig. 8-5**). Some patients have high levels of apo B-100, suggesting an increased number of atherogenic particles in the circulation, even though the LDL-C level is in the desirable range. These patients have an increased risk of atherosclerosis. Apo B-100 and the measurement of LDL particle concentrations by nuclear magnetic resonance spectroscopy are considered recommended treatment targets by some guidelines for the management of dyslipidemia.[17,18]

HDL particles contain apo A-I, apo A-II, and apo C. Apo A-I is an activator of LCAT, which catalyzes the esterification of free cholesterol in HDL particles. Levels of apo A-I have a stronger inverse correlation with CHD risk than apo A-II levels. HDL particles that contain only A-I apolipoproteins are associated with a lower CHD risk than are HDL particles containing both A-I and A-II.[19]

Low-Density Lipoprotein Receptor

Cholesterol is taken up by peripheral and hepatic cells via binding of the ligands, apo B-100, and apo E, on circulating lipoproteins to cell-surface LDL receptors. The concentration of LDL receptors is mediated by intracellular cholesterol concentration. Synthesis of LDL receptors is stimulated by a low intracellular cholesterol concentration. Conversely, the concentration of cell-surface LDL receptors may be downregulated by the action of proprotein convertase subtilisin/kexin type 9 (PCSK9), which targets the LDL receptor for degradation within intracellular lysozymes.[20] Within the

cell, the receptor protein is synthesized in the mitochondria and migrates to clathrin-coated pits on the cell surface. The LDL receptor may then bind to lipoproteins that contain apo E or apo B-100, including VLDL, remnant VLDL, IDL, and LDL. Because remnant VLDL and IDL particles contain both B-100 and E proteins, they may have a higher affinity for LDL receptors than do LDL particles, which contain only the B protein. Drugs that upregulate the synthesis of LDL receptors (eg, statins), therefore, may increase the clearance of both VLDL remnant particles and LDL particles from the circulation. Thus, statins may reduce serum TG levels as well as cholesterol levels. Following binding of lipoproteins to the LDL receptor, the lipoproteins undergo endocytosis and are taken up by lysosomes, where they are metabolized into elemental substances for use by the cell. The cholesterol is transferred into the intracellular cholesterol pool. The LDL receptor may be returned to the cell surface, where it can bind with another circulating apo E– or apo B–containing lipoprotein.

ABNORMALITIES IN LIPID METABOLISM

Lipid synthesis and transport is complex with hundreds of possible steps that can malfunction resulting in a lipid disorder. However, there are only a few relatively common and important lipid disorders seen in clinical practice. The first two described subsequently, polygenic hypercholesterolemia and atherogenic dyslipidemia, are largely the result of an interaction between genes and lifestyle choices. Several prominent, but rarer, familial lipid disorders are subsequently described. **Table 8-2** summarizes the characteristics of the most common lipid disorders.

Table 8-2
Characteristics of Common Lipid Disorders

Disorder	Metabolic Defect	Lipid Effect	Main Lipid Parameter	Diagnostic Features
Polygenic hypercholesterolemia	↓LDL clearance	↑LDL-C	LDL-C: 130–250 mg/dL	None distinctive
Atherogenic dyslipidemia	↑VLDL secretion ↑Apo C-III synthesis ↓LPL activity ↓VLDL removal	↑TG ↑Remnant VLDL ↓HDL ↑Small, dense LDL	TG: 150–500 mg/dL HDL-C: <40 mg/dL	Frequently accompanied by central obesity or diabetes
Familial hypercholesterolemia heterozygous	Reduction in functional LDL receptor, defective apo B, gain-of-function mutations PCSK9	↑LDL-C	LDL-C: 250–450 mg/dL	Family history of premature CHD, tendon xanthomas, corneal arcus
Familial hypercholesterolemia homozygous	Absent LDL receptors, defective apo B, gain-of-function mutations PCSK9	↑LDL-C	LDL-C: >450 mg/dL	Family history of premature CHD, tendon xanthomas, corneal arcus; affected individuals exhibit CHD by the second decade of life
Familial defective apo B-100	Defective apo B on LDL and VLDL	↑LDL-C	LDL-C: 250–450 mg/dL	Family history of CHD, tendon xanthomas
Dysbetalipoproteinemia (type III hyperlipidemia)	Apo E2:E2 phenotype, ↓VLDL remnant clearance	↑Remnant VLDL, ↑IDL	LDL-C: 300–600 mg/dL TGs: 400–800 mg/dL	Palmar xanthomas, tuberoeruptive xanthomas
Familial combined hyperlipidemia	↑Apo B and VLDL production	↑CH, TG, or both	LDL-C: 250–350 mg/dL TGs: 200–800 mg/dL	Family history, CHD Family history, hyperlipidemia
Familial hyperapobetalipoproteinemia	↑Apo B production	↑Apo B	Apo B: >125 mg/dL	None distinctive
Hypoalphalipoproteinemia	↑HDL catabolism	↓HDL-C	HDL-C: <40 mg/dL	None distinctive

Apo B, apolipoprotein B; apo C-III, apolipoprotein C-III; apo E, apolipoprotein E; CH, cholesterol; CHD, coronary heart disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides; VLDL, very low-density lipoprotein.

Polygenic Hypercholesterolemia

Polygenic hypercholesterolemia is the most prevalent primary disorder causing an increase in cholesterol. It is caused by a combination of environmental (eg, poor nutrition, sedentary lifestyle) and multiple genetic factors. In patients with this disorder, a diet high in saturated fatty acids can reduce LDL receptor activity, thus reducing the clearance of LDL particles from the systemic circulation. Patients with polygenic hypercholesterolemia have mild-to-moderate LDL-C elevations (usually in the range of 130–250 mg/dL), but no unique physical findings are usually present. A family history of premature CHD is present in ~20% of cases. These patients may often be effectively managed with dietary restriction of saturated fats and cholesterol and by drugs that lower LDL-C levels (statins, bile acid sequestrants [BASs], and ezetimibe).

Atherogenic Dyslipidemia

Atherogenic dyslipidemia is characterized by moderate elevations of TG (150–500 mg/dL, indicative of the elevated VLDL remnant particles), low HDL-C levels (<40 mg/dL), and mild-to-moderate elevations of LDL-C level.[21] These patients have increased concentrations of small, dense, cholesterol-poor LDL particles, non–HDL-C, and apo B-100. Most commonly, patients have increased visceral adiposity and are hypertensive and insulin resistant.

In the presence of increased visceral adiposity, there is impaired glucose metabolism and/or diabetes with increased mobilization of fatty acids from adipose cells to the systemic circulation. The excess of free fatty acids leads to increased TG synthesis and secretion of TG-rich VLDL particles by the liver. These TG-rich particles contain apo C-III, which inhibits the action of LPL, thus retarding lipolysis of TGs from VLDL particles. This results in an excess of TG-rich VLDL remnant particles.[22] CETP mediates the exchange of TGs from these particles with CEs from HDL, resulting in VLDL remnant particles that are enriched with cholesterol (**Fig. 8-6**). TGs are also exchanged from VLDL remnant particles with CEs from LDL particles. Thus, VLDL remnants become even more cholesterol enriched and LDL particles become TG enriched. The cholesterol-enriched, small VLDL remnant particle is atherogenic. TG-rich LDL undergoes lipolysis catalyzed by hepatic lipase to remove TGs, resulting in small, cholesterol-poor LDL particles (called *small dense LDL*) that are highly atherogenic. Lipolysis of TG-rich HDL results in low HDL because of excretion of lipid-poor apo A-I by the kidneys.

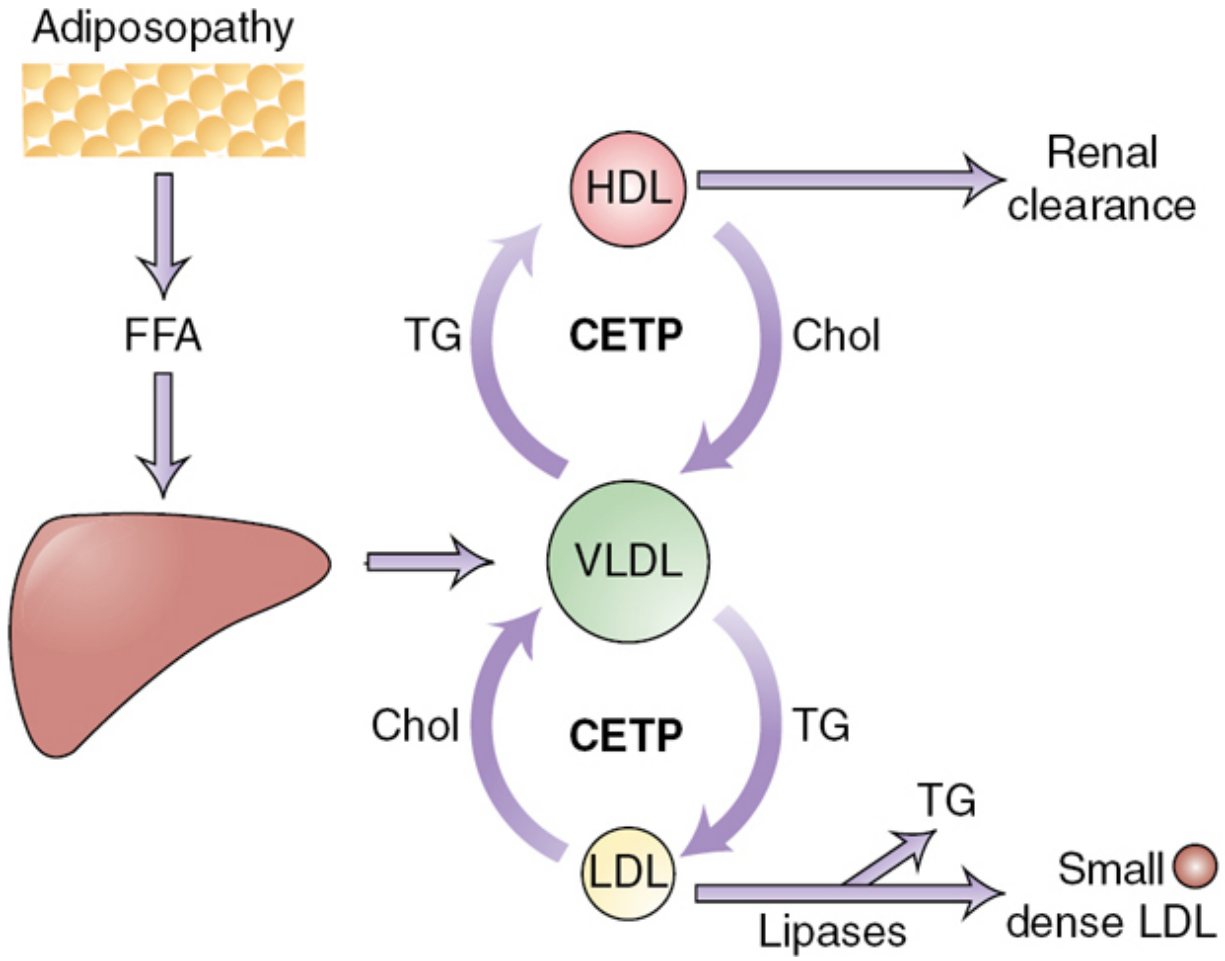


Figure 8-6 The role of CETP in creation of atherogenic dyslipidemia. Role of CETP in the creation of an atherogenic lipid of someone with hypertriglyceridemia. Cholesterol-rich VLDL, low HDL-C, as well as small dense LDL-C is a pattern often observed in patients with metabolic syndrome as well as those with type 2 diabetes. CETP, cholesteryl ester transfer protein; FFA, fenofibric acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein. (From Bays H, Stein EA. Pharmacotherapy for dyslipidaemia—current therapies and future agents. *Expert Opin Pharmacother*. 2003;4(11):1901–1938. Reprinted by permission of Taylor & Francis Ltd, http://www.tandfonline.com)

Patients with atherogenic dyslipidemia may be effectively managed with weight reduction and increased physical activity. Pharmacologic agents that enhance the removal of remnant VLDL

and small dense LDL particles (ie, statins) and that lower TG levels (ie, ω-3 fatty acids or fibrates) may be effective in the management of these patients.

Familial Hypercholesterolemia

FH is a disorder of defective LDL-C clearance. This autosomal dominant disorder is strongly associated with premature CHD.[23,24] Most recent estimates indicate that the prevalence of heterozygous FH (HeFH) ranges from 1 of 250 to 1 of 500 people in the United States.[25] Homozygous FH (HoFH) may occur in 1 of 1 million to 1 of 250,000 people in the United States. The most common cause of this disorder is a genetic mutation, resulting in a defective or absent LDL receptor. Consequently, heterozygotes possess approximately half the number of functioning LDL receptors and double the LDL-C level of unaffected patients (LDL-C levels ranging between 250 and 450 mg/dL). Clinically, patients with FH may exhibit excess cholesterol deposition in the iris, clinically manifested as arcus senilis. Cholesterol may also deposit in tendons, particularly the Achilles' tendon and extensor tendons of the hands, resulting in tendon xanthomas. The clinical diagnosis of FH is established by documenting a very high LDL-C level, a strong family history of hypercholesterolemia and premature CHD events, and the presence of tendon xanthomas. Untreated HeFH patients have approximately a 5% chance of a myocardial infarction (MI) by age 30 years, a 50% chance by age 50 years, and an 85% chance by age 60 years. The mean age of death in untreated male heterozygotes is in the mid-50s; for untreated female heterozygotes, it is in the mid-60s.[24]

Homozygotes generally have LDL-C levels >500 mg/dL. This rare disorder results in CHD by ages 10 to 20 years. Because these individuals have lost the ability to clear cholesterol-carrying lipoproteins from the circulation, combination pharmacotherapy and/or LDL apheresis may be required to help remove atherogenic particles.

Familial Defective Apo B-100

Familial defective apo B-100 (FDB) is a genetic disorder clinically indistinguishable from HeFH. These patients have normally functioning LDL receptors, but defective apo B-100, resulting in reduced binding of LDL particles to the LDL receptor and reduced clearance of LDL particles from the systemic circulation.[26–28] As with FH, LDL-C levels are usually 250 to 450 mg/dL. Presumably, the apo E and half of the apo B in heterozygous FDB patients function normally, providing mechanisms for removal of some lipoproteins from the systemic circulation. Clinical diagnosis of FDB is based on a very high LDL-C level, a family history of premature CHD, and tendon xanthomas. The definitive diagnosis requires molecular screening techniques.

Proprotein Convertase Subtilisin/Kexin Type 9 Gain-of-Function Gene Mutation

FH may also be caused by “gain-of-function” mutations in the gene encoding for PCSK9, an enzyme that plays an important role in cholesterol homeostasis.[29] The frequency of these mutations in patients with FH is uncertain. When PCSK9 is secreted into the plasma, it binds to the epidermal growth factor–like repeat A (EGF-A) domain of the cell-surface LDL receptors. PCSK9 binding leads to endocytosis of the LDL–LDL receptor–PCSK9 complex into intracellular lysozymes for degradation, resulting in a reduced number of LDL receptors and increased LDL-C (~300 mg/dL). Drugs that inhibit PCSK9 have demonstrated significant reductions in LDL-C in patients with HeFH, HoFH, and polygenic hypercholesterolemia.[30]

Familial Combined Hyperlipidemia

Familial combined hyperlipidemia (FCHL) is caused by increased production of apo B–containing particles, VLDL, and LDL.[31] Patients

with FCHL have an elevated apo B-100 level, hypercholesterolemia with LDL-C usually in the range of 250 to 350 mg/dL, elevated TGs (usually between 200 and 800 mg/dL), and reduced levels of HDL-C. First-degree relatives of these individuals frequently have a lipid disorder, and there is often a family history of ASCVD. Patients with FCHL commonly are overweight, are hypertensive, and may have metabolic disturbances, such as insulin resistance, diabetes, or hyperuricemia. The diagnosis of FCHL is presumed in patients who have increased cholesterol or TG levels, a strong family history of premature CHD, and a family history of dyslipidemia.

Familial Dysbetalipoproteinemia

Familial dysbetalipoproteinemia, also called type III hyperlipidemia or remnant disease, is caused by poor clearance of VLDL and chylomicron particles from the systemic circulation as a result of a defect in apo E.[32,33] Apo E is necessary for the normal clearance of chylomicrons and VLDL. It is inherited as an E2, E3, or E4 isoform from each parent. The E2 isoform has a low binding affinity for the LDL receptor. Thus, individuals with an apo E2/E2 phenotype have delayed clearance of VLDL remnant (and possibly chylomicron) particles from the circulation and a reduced conversion of IDL to LDL particles. However, a clinically significant lipid disorder usually does not result unless triggered by other metabolic problems, such as diabetes, hypothyroidism, or obesity. Patients with this disorder have high cholesterol due to enrichment of cholesterol esters in VLDL remnant particles, high TGs in the range of 400 to 800 mg/dL, and a VLDL-C to TG ratio >0.3. Patients may have palmar xanthomas (yellow-orange discoloration in the creases of the palms and fingers) and tuberoeruptive xanthomas (small, raised lesions in areas of pressure, particularly the elbows and knees). A personal and family history of premature atherosclerotic vascular disease is often present. As noted earlier, these patients often have diabetes mellitus, hypertension, obesity, and hyperuricemia.

Familial Disorders of Triglyceride Metabolism

Familial hypertriglyceridemia (FHTG) is associated with an increase in both TG-rich VLDL particles and chylomicrons. LDL-C is generally not significantly elevated (<130 mg/dL), and HDL-C is decreased (<40 mg/dL). FHTG is usually relatively mild and asymptomatic unless secondary causes of hypertriglyceridemia are present (poorly controlled diabetes, obesity, medications, etc.). TG levels are in the range of 200 to 500 mg/dL, but may be >1000 mg/dL. Patients with more marked TG elevations (>500 mg/dL) may present with eruptive xanthomas and/or acute pancreatitis.

Rare mutations in the *LPL* or cofactor *apo CII* genes may also be associated with severe hypertriglyceridemia.[34] Familial LPL deficiency usually presents in childhood with TG levels from 2000 to 25,000 mg/dL and lipemic plasma, pancreatitis, eruptive xanthomas, and lipemia retinalis (creamy white appearance of retinal blood vessels). The clinical presentation of familial deficiency in apo CII is similar to familial LPL deficiency in homozygotes, but heterozygous individuals may have normal plasma lipid concentrations. Patients with familial hepatic lipase deficiency may also present with severe hypertriglyceridemia (>500–1000 mg/dL) associated with modest elevations in LDL-C and normal to increased HDL-C. This disorder is most common in individuals of Indian ancestry.

Hypoalphalipoproteinemia

Isolated low HDL-C (<40 mg/dL) without an increase in TG level is fairly uncommon, but is associated with increased ASCVD risk. The precise molecular defects causing this problem are uncertain, although genetic influences are likely involved.[35] Tangier disease, which is characterized by low HDL-C, orange tonsils, and hepatosplenomegaly, has been linked to a defect in the ABCA-1 transporter responsible for the efflux of cholesterol from peripheral cells (ie, inflammatory cells in the arterial wall). The inherited tendency to have low HDL-C is accentuated by lifestyle factors, such as obesity, smoking, and lack of exercise. Despite strong

epidemiologic evidence showing an inverse relationship between HDL-C and CHD, clinical trials demonstrating a benefit of raising isolated low HDL-C with drugs are lacking. Therapy in patients with low HDL-C is, therefore, directed at lowering LDL-C to reduce ASCVD risk. Therapies to raise HDL-C by novel mechanisms are under investigation to determine whether HDL-directed strategies can reduce CHD risk.[36]

LIPOPROTEINS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

Epidemiologic studies have conclusively established a direct relationship between blood cholesterol concentrations in a population and the incidence of ASCVD events.[37–39] For every 1% increase in blood cholesterol levels, there is a 1% to 2% increase in the risk of CHD. In addition, using gene variants that exclusively affect a biomarker of interest (ie, that do not have pleiotropic effects on other factors), investigators have confirmed LDL-C as a causal risk factor for coronary artery disease (CAD). HDL-C is inversely associated with CHD risk. For every 1% *decrease* in HDL-C levels, there is a 1% to 2% *increase* in the risk of CHD events.[40] However, gene variants that affect HDL-C have cast doubt on whether HDL-C directly influences risk for CAD.

The role of TGs in the pathogenesis of ASCVD continues to be a subject of important investigation.[22] Most epidemiologic studies have found that a high TG level is an independent risk factor for CHD when evaluated with univariate analysis. When other lipid abnormalities such as increased LDL-C or low HDL-C are included in a multivariate analysis, TGs may lose independent predictive power. This is, in part, because it is difficult to establish a causal relationship in observational epidemiology, especially given the correlations among TGs, LDL-C, and HDL-C. Patients with hypertriglyceridemia usually have low HDL-C (due to the action of CETP and increased

renal clearance of apo AI), which is an important predictor of ASCVD risk. In addition, elevated TG levels are associated with increased levels of TG-rich lipoprotein remnants (remnant VLDL and chylomicron particles and IDL), increased LDL particle concentration, and small, dense LDL particles. These particles are all potentially atherogenic and mediate a higher CHD risk than that associated with an elevated LDL-C alone.[41–44] Recent meta-analyses of epidemiologic studies found that TGs independently predicted CHD risk, even after adjustment for other lipid risk factors.[22] High TG levels are also found in certain familial disorders, including dysbetalipoproteinemia and FCHL, which carry increased CHD risk.[32,33] In addition, hypertriglyceridemia is associated with a procoagulant state, which promotes coronary thrombosis.[44]

A recent analysis of 185 common genetic variants mapped for plasma lipids examined the role of TGs in risk for CAD. In a model accounting for effects on LDL-C and/or HDL-C levels, the strength of a polymorphism's effect on TG levels was correlated with the magnitude of its effect on CAD risk.[45] These results suggest that TG-rich lipoproteins causally influence risk for CAD.

Paradoxically, very high TG levels (>500 mg/dL) are not commonly associated with an increased CHD risk but do cause an increased risk of pancreatitis, especially when levels exceed 1000 mg/dL. Often, a genetic defect in LPL is present in these cases that impair the removal of TGs from TG-rich particles (VLDL and chylomicrons). These particles do not become enriched with cholesterol and, therefore, are not often atherogenic.[46] If the blood sample is stored in the refrigerator overnight, a thick creamy layer often appears on the surface, indicating the presence of chylomicrons. Although most patients with very high TGs remain free of CHD throughout their lives, some do experience ASCVD events.

Pathogenesis of Atherosclerosis

Circulating cholesterol plays a central etiologic role in the pathogenesis of atherosclerosis.[1] Atherosclerotic vascular lesions

begin in the first decade of life and may progress in the presence of elevated levels of cholesterol and other uncontrolled ASCVD risk factors.[47] Atherosclerosis is considered to be a chronic inflammatory process in response to injury of the vascular endothelium by factors such as glycoxidation products in diabetes, shear stress, excess free fatty acids released by adipocytes, bacterial products, and neurohormonal abnormalities, among other factors. The damaged endothelium becomes prothrombotic, has reduced release of nitric oxide and impaired vasodilatory capacity, and releases chemoattractants for inflammatory cells and platelets. Regulation of blood cholesterol levels and management of other risk factors can restore endothelial function, nitric oxide release, and the vasodilatory response.

In patients with excess apo B–containing lipoproteins (VLDL remnants, IDL, LDL, and Lp[a]), atherogenic particles migrate through the endothelial junction into the subendothelial space or intima. The subsequent accumulation and retention of lipoproteins in the subendothelium (**Fig. 8-7**)[47] is the result of binding to subendothelial matrix molecules, such as chondroitin sulfate proteoglycans.

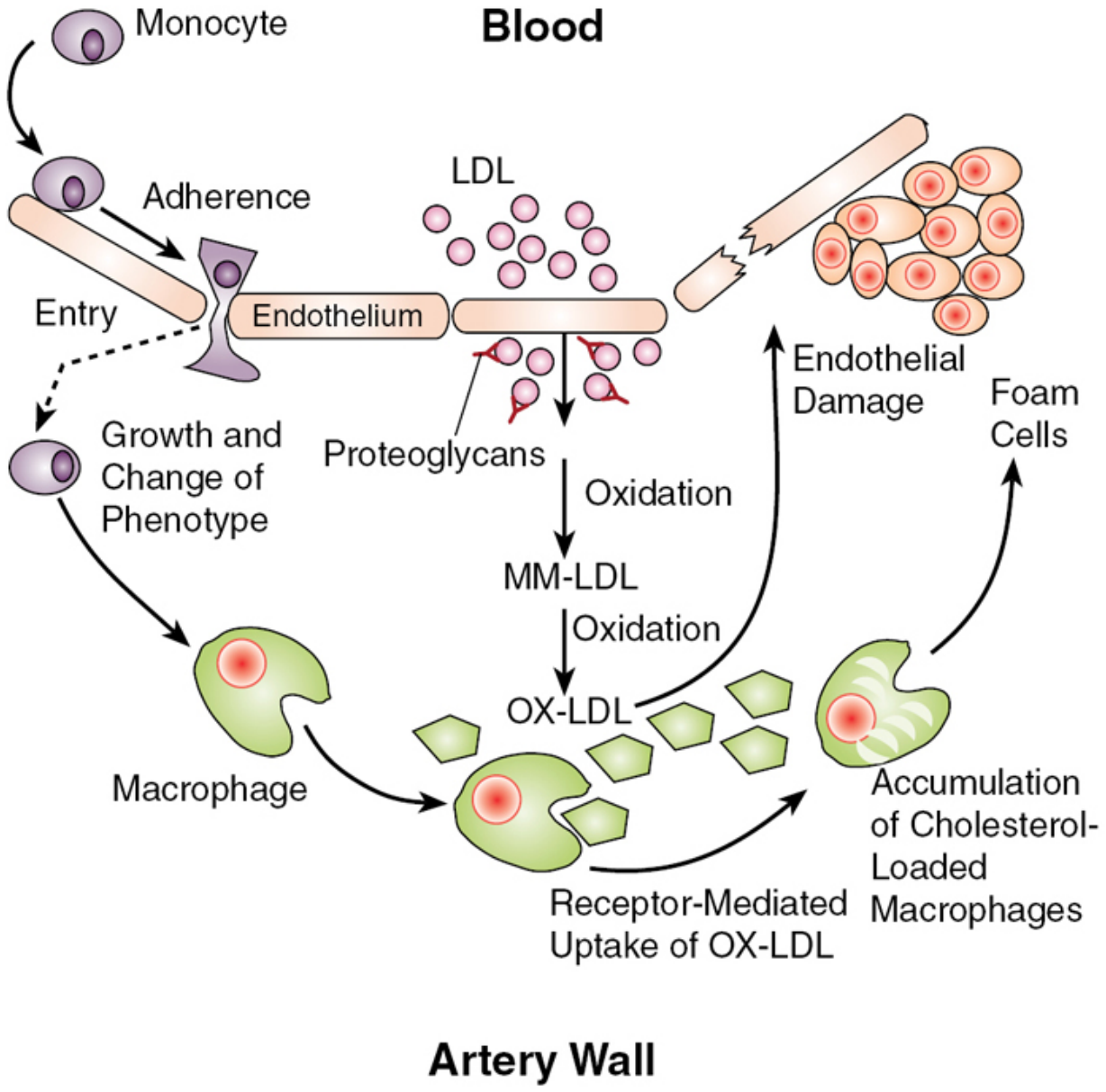


Figure 8-7 Pathogenesis of atherosclerosis and the role of oxidized LDL. LDL, low-density lipoprotein; MM-LDL, minimally oxidized low-density lipoprotein; OX-LDL, oxidized low-density lipoprotein.

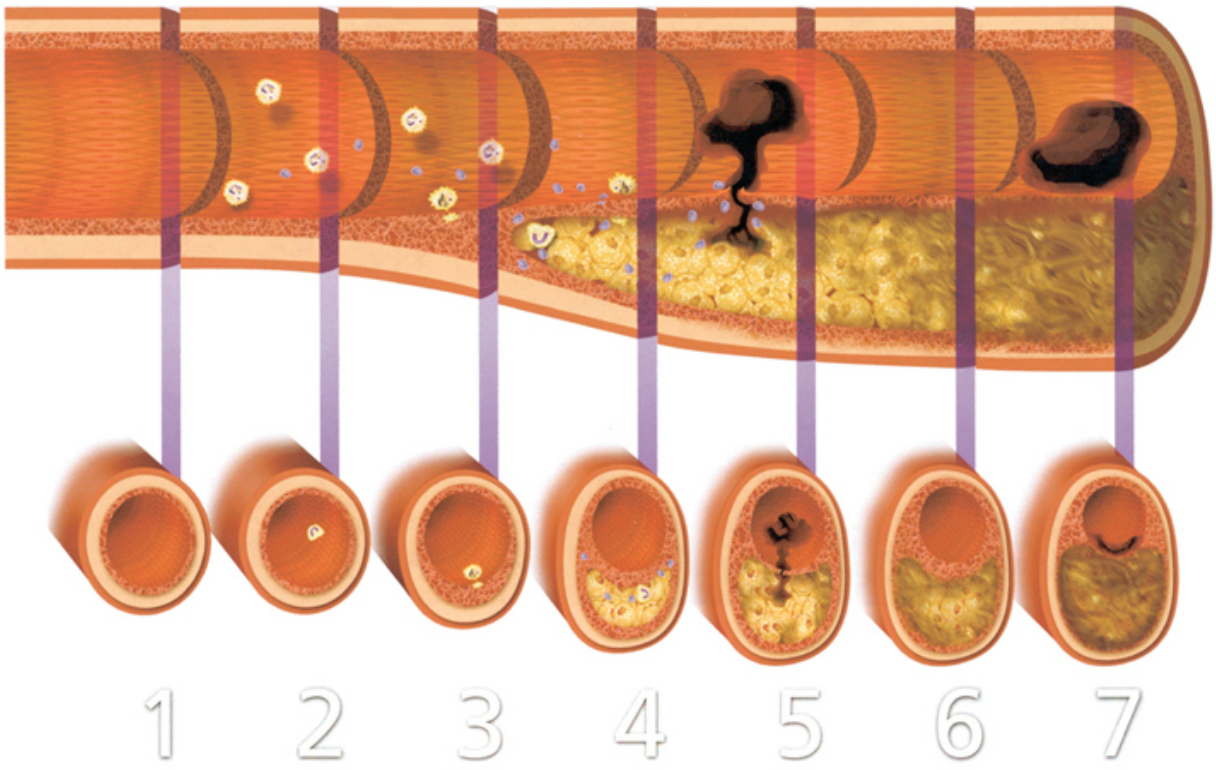


Figure 8-8 Initiation, progression, and complication of human coronary atherosclerotic plaque (numbers indicate order of progression).

Soon after taking up residence in the subendothelial space, lipoproteins are structurally modified primarily by oxidation. Modified lipoproteins stimulate dysfunctional endothelial cells to release cell adhesion molecules (intracellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin) and chemoattractants (monocyte chemotactic factor 1 and macrophage colony–stimulating factor), which promote adhesion and stimulate transmigration of monocytes and lymphocytes into the intimal space.[48–50] Thus, atherosclerosis is an inflammatory process in response to retained and modified lipoproteins. Once recruited, monocytes are converted to macrophages, which ingest oxidized lipoprotein particles via special scavenger or acetyl LDL receptors on the surface of macrophage cells.[51] Further engorgement with oxidized lipoproteins inhibits mobility of resident macrophages, and the cells become cytotoxic, causing further damage to the vascular endothelium. As

the uptake of modified lipoproteins into macrophage cells continues, the cells become laden with lipid and eventually become *foam cells* (**Fig. 8-8**). Monocytes and foam cells continue to secrete growth factors and cytokines, establishing a chronic inflammatory process and progression to a more complex atherosclerotic plaque.

During plaque growth, smooth muscle cells from the media migrate upward and proliferate near the luminal surface.[52] Collagen synthesis is also increased. This leads to conversion of early atherosclerotic lesions that are lipid rich with a thin fibrous cap to a potentially more stable lesion that has a small inner lipid core and more collagen and matrix proteins. At any given time, atherosclerotic lesions at various stages of development can be found all along the vascular arterial tree in high-risk patients (see **Fig. 8-7**).

As atherosclerotic lesions grow, the coronary artery remodels to accommodate the lipid-rich core. Lesions initially enlarge away from the lumen toward the media/adventitia, thus preserving the vascular lumen and ensuring normal blood flow (positive remodeling). Late in the growth of the lesion, however, the luminal space is invaded and becomes progressively narrowed as the atherosclerotic lesion progresses (negative remodeling). Inflammatory cells secrete matrix metalloproteinases that degrade collagen and fibrin produced by arterial smooth muscle cells, causing a weakened fibrous cap and a lesion more vulnerable to plaque rupture.[53] Apoptosis (cell death) of smooth muscle cells in the shoulders of the atherosclerotic cap further weakens the lesion.[54] These processes increase the chance that the atherosclerotic lesion may rupture or erode, especially at the shoulders of the lesion, and expose the underlying tissue to circulating blood elements.[55] Collagen in the exposed plaque can trigger platelet activation, and tissue factor produced by macrophages and smooth muscle cells activates the coagulation cascade. Platelets may adhere, and microthrombi may form. The resultant clot can occlude blood flow entirely, causing MI. More commonly, only partial occlusion of blood flow occurs, causing transient ischemic symptoms or unstable angina (UA). The clot creates a barrier between the underlying tissue and the circulating blood and allows healing of the plaque rupture. This process of

fissuring and rehealing appears to lead to the more complicated lesions of atherosclerosis.

Atherosclerotic lesions exist along a continuum from vulnerable lipid-rich lesions that are prone to rupture and cause a thrombosis to more stable lipid-poor, fibrin- and collagen-rich lesions. Younger atherosclerotic lesions occupy only the intimal space, whereas the older lesions may protrude into the luminal space. In fact, the culprit lesion that results in acute MI is usually not at the site of the greatest stenosis, but distal to it.[54]

CLINICAL EVALUATION AND MANAGEMENT OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

Assessment of the Standard Lipid Panel and the Role of Advanced Lipid Testing

The routine lipid panel includes standardized measurements of TC, HDL-C, and TGs. Although it is possible to measure LDL-C directly, it is common for most laboratories to calculate LDL-C. TC, HDL-C, and TGs are measured directly and then the Friedewald equation is applied to calculate LDL-C:

$$\text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{VLDL-C}) \qquad \textbf{(Eq. 8-1)}$$

Because the ratio of cholesterol to TGs in VLDL is 1:5, VLDL-C is estimated by dividing the total TG level by 5. Thus, the formula is rewritten as:

$$\text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{TG}/5) \qquad \textbf{(Eq. 8-2)}$$

When TGs are >400 mg/dL, the formula for estimating VLDL-C by utilizing the Friedewald equation is not accurate and, therefore, LDL-C cannot be calculated. An accurate LDL-C calculation by the

Friedewald equation also requires that the patient fast for 10 to 12 hours, which provides sufficient time for exogenous TGs, carried by chylomicrons, to be cleared from the systemic circulation. Most laboratories can measure LDL-C directly, but this is only necessary when the TG level is >400 mg/dL or the patient has not fasted. Of note, the Friedewald equation also lacks accuracy in the setting of low LDL-C. A new equation has now been developed, known as the Martin/Hopkins equation, with the primary intent to provide a more accurate estimation of LDL-C in patients with either moderately elevated TGs (140–400 mg/dL) or low LDL-C (<70 mg/dL).[56] Unlike the Friedewald equation, fasting is not required. However, the Martin/Hopkins equation does require the use of tables or an application for use. Some commercial laboratories now use this calculation rather than the Friedewald equation. The application is titled “LDL-Calculator” and is available for download from the app store. The application requires the user to input TC, HDL-C, and TGs as well as choose your preferred unit of measure. The calculator then takes over and provides an LDL-C estimate. The AHA/ACC Multisociety guideline currently recommends that LDL-C either be directly measured or the Martin/Hopkins equation be utilized in patients with an LDL-C <70 mg/dL.[5] In patients with TG levels >400 mg/dL, direct LDL-C measurement is still recommended.

In addition, in the presence of cardiometabolic disturbances including the metabolic syndrome, insulin resistance, impaired glucose tolerance, diabetes, hypertriglyceridemia, and chronic kidney disease (CKD), the calculated or direct measurement of LDL-C may not provide a complete assessment of the lipid-related CV risk. Cardiometabolic disorders are often associated with the atherogenic dyslipidemia described earlier, in which there are near-normal to modest elevations of LDL-C, reduced HDL-C levels, elevations of TGs, and an excess of atherogenic small, dense LDL particles. When LDL-C levels are near-normal to modestly elevated and the LDL particle concentration (LDL-P) is elevated, the measures are considered to be “discordant.”

There are a number of advanced lipid/lipoprotein tests to determine the concentration and/or the relative size distribution of

both LDL and HDL particles, including gradient gel electrophoresis, vertical automated profile, nuclear magnetic resonance spectroscopy, and ion mobility analysis. Data from both the Framingham Offspring Study and the Multi-Ethnic Study of Atherosclerosis demonstrated that patients with discordantly high LDL-P compared to LDL-C had higher CVD event rates, whereas patients with discordantly low LDL-P compared to LDL-C had lower CVD event rates.[57,58] CVD risk, therefore, tracked most closely with levels of LDL-P. Apo B is another measure of concentrations of atherogenic lipoproteins, including remnant VLDL particles and LDL particles, and is strongly related to CVD risk.[59]

Non–HDL-C provides a simple and easily calculated estimate of the excess CVD risk associated with the atherogenic dyslipidemia.[17] It is a single measurement of cholesterol carried by all potentially atherogenic particles, including VLDL, VLDL remnants, IDL, and LDL particles, and can give the clinician information regarding the patient's CVD risk when LDL-C cannot reliably be calculated or in the presence of excess VLDL-C and excess LDL particle concentration. Non–HDL-C is calculated by the following formula:

$$\text{Non–HDL-C} = \text{TC} - \text{HDL-C} \qquad \textbf{(Eq. 8-3)}$$

As mentioned previously, non–HDL-C can be calculated in both the fasting and the nonfasting state because VLDL-C does not need to be estimated.

Guidelines for the Management of Dyslipidemia to Reduce Atherosclerotic Cardiovascular Disease Risk

In 2018, the AHA/ACC published updated multisociety endorsed guidelines for the management of blood cholesterol to reduce ASCVD risk.[5] These guidelines have emphasized the implementation of lifestyle modifications, utilization of high-intensity statin to achieve an LDL-C reduction of least 50% in patients with ASCVD, and the consideration of nonstatin therapy for further LDL-C

reduction in very high-risk individuals with ASCVD and LDL-C >70 mg/dL. In addition, four patient groups were identified in which there is the most extensive evidence of net clinical benefit of statin therapy for the prevention of ASCVD. These patient groups include (a) individuals with clinical ASCVD, (b) individuals with primary elevations of LDL-C ≥190 mg/dL, (c) individuals ages 40 to 75 years with diabetes and LDL-C 70 to 189 mg/dL, and (d) individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%.

For each patient group, the guidelines recommend an intensity of statin therapy, either moderate or high intensity (**Table 8-3** and **Fig. 8-9**). Low-intensity statins are recommended only in patients who have experienced or are at risk for adverse effects of treatment. Measurement of the lipid panel is recommended at 4 to 12 weeks after initiation of statin therapy to assess adherence to lifestyle recommendations and medication, as well as response to therapy. Regular monitoring of the lipid panel is then recommended every 3 to 12 months as clinically indicated.

Table 8-3
Intensity of the Various Statins

High intensity (when taken as prescribed will reduce LDL-C by ≥50%)	Atorvastatin (40 mg)[a]—80 mg Rosuvastatin 20 (40) mg
Moderate intensity (when taken as prescribed will reduce LDL-C by 30%, but <50%)	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg*

	Fluvastatin 40 mg bid **Pitavastatin 2–4 mg**
Low intensity (when taken as prescribed will reduce LDL-C by <30% on average)	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

The doses listed in parenthesis were not evaluated in randomized controlled trials. Bold indicates doses of statins that were evaluated in randomized controlled trials.

LDL-C, low-density lipoprotein cholesterol.

[a]Evidence is from one randomized controlled trial.

Source: Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168–3209.

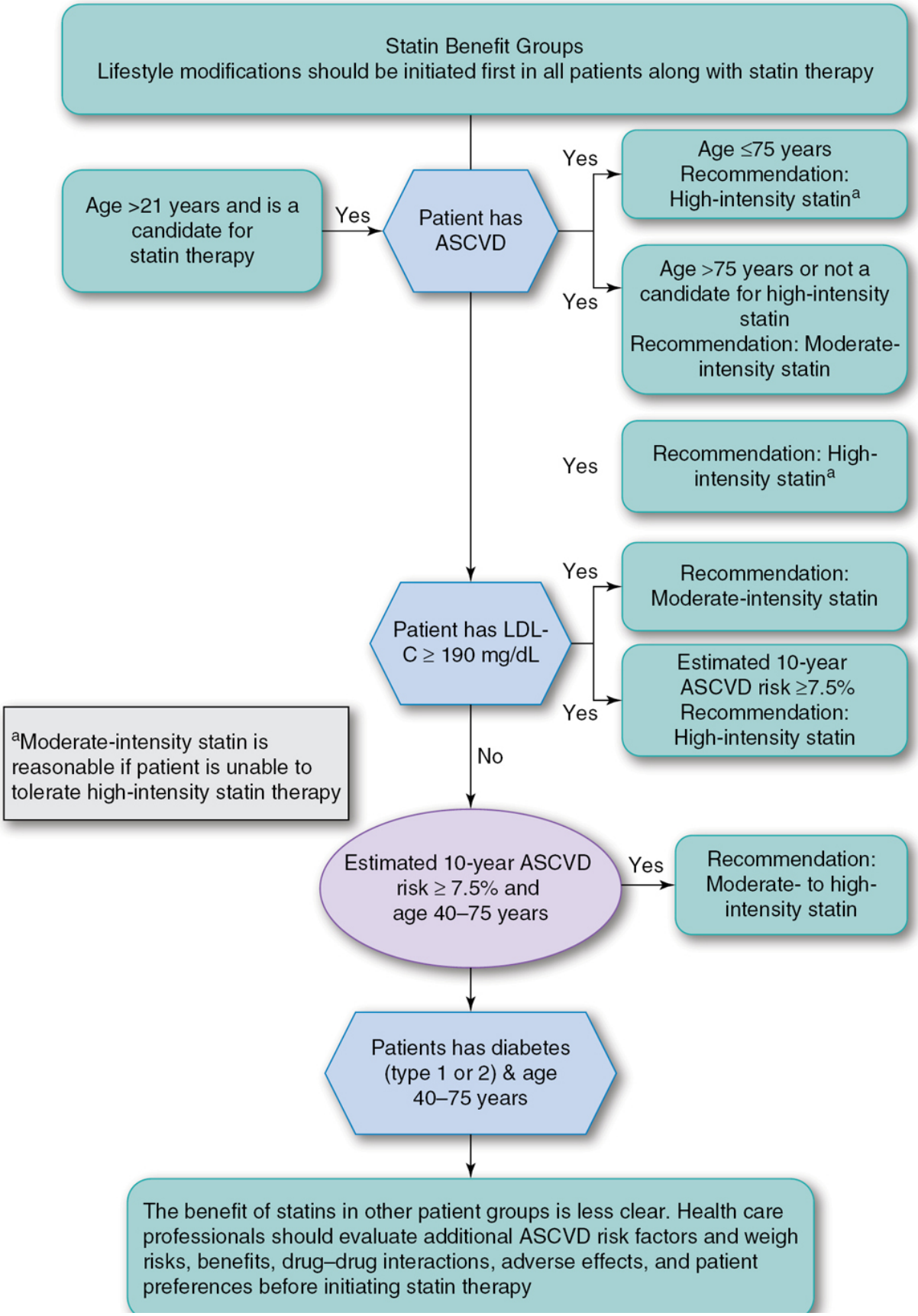

Statin Benefit Groups
Lifestyle modifications should be initiated first in all patients along with statin therapy
Age >21 years and is a candidate for statin therapy
Yes
Patient has ASCVD
Yes
Age ≤75 years
Recommendation: High-intensity statin[a]
Yes
Age >75 years or not a candidate for high-intensity statin
Recommendation: Moderate-intensity statin
Yes
Recommendation: High-intensity statin[a]
Patient has LDL-C ≥ 190 mg/dL
Yes
Recommendation: Moderate-intensity statin
Yes
Estimated 10-year ASCVD risk ≥7.5%
Recommendation: High-intensity statin
[a]Moderate-intensity statin is reasonable if patient is unable to tolerate high-intensity statin therapy
No
Estimated 10-year ASCVD risk ≥ 7.5% and age 40–75 years
Yes
Recommendation: Moderate- to high-intensity statin
Patients has diabetes (type 1 or 2) & age 40–75 years
The benefit of statins in other patient groups is less clear. Health care professionals should evaluate additional ASCVD risk factors and weigh risks, benefits, drug–drug interactions, adverse effects, and patient preferences before initiating statin therapy

Figure 8-9 Recommendations for the intensity of statin therapy based on statin benefit group diagram. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. (Adapted from Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889–2934. © 2014 Elsevier. With permission.)

For primary prevention of ASCVD, the recommended risk assessment tool is the new CV Risk Calculator based on the Pooled Cohort Equations as described in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.[5,6] The equations are derived from large, diverse, community-based cohorts that are generally representative of the U.S. population of Whites and African Americans. The calculator provides race- and sex-specific estimates of the 10-year risk of first-hard ASCVD event (nonfatal MI, CHD death, fatal or nonfatal stroke) and should be used in non-Hispanic African American and non-Hispanic Whites ages 40 to 79 years. Lifetime or 30-year risk is also provided for individuals ages 20 to 59 years who are not at high short-term risk. Variables considered in the risk calculation include age, sex, race, TC, HDL-C, systolic blood pressure (BP), treatment for hypertension, tobacco use, and diabetes. To further refine risk assessment, optional factors that may be considered include family history of premature ASCVD, high-sensitivity C-reactive protein (hs-CRP), LDL-C ≥160 mg/dL, coronary artery calcium scoring, and ankle brachial index. The National Lipid Association Patient-Centered Recommendations: Part 2 provides recommendations for risk assessment in non-Hispanic Whites and other racial and ethnic groups, which were not a part of populations used to derive the ACC/AHA Pooled Cohort Equations.[60]

Patients with a 10-year risk of ≥7.5% should be engaged in a patient–clinician discussion of the ASCVD risk reduction benefits of

statin therapy, potential adverse drug effects, potential drug–drug interactions, and consideration of patient preferences to determine whether statin therapy is appropriate (**Fig. 8-10**).

CASE 8-1

QUESTION 1: B.C. is a 46-year-old perimenopausal White female who has recently relocated to the area and is establishing care with a gynecologist. As part of her annual evaluation, a routine lipid panel is obtained. She takes no prescription medications but does take a number of dietary supplements and vitamins, including krill oil, multivitamin, B-complex, and vitamin D. She has no history of tobacco use, hypertension, or diabetes. She states she was told a number of years ago that her LDL "bad" cholesterol was elevated, but her HDL "good" cholesterol was high and no treatment was indicated. She has enjoyed jogging and spin classes, but says that as she gets older she is more fatigued and sore with exercise. She follows a Mediterranean style diet and has a glass of red wine daily.

Her father is alive at age 72 years and takes statin therapy for hyperlipidemia, though she is uncertain of the severity of his lipid disorder. He has no history of CVD. Her mother is a 71-year-old with diabetes who underwent coronary stent placement last year following the onset of angina and an abnormal stress test. She was started on statin therapy at the time of her procedure. Her brother is overweight, has hypertension and borderline diabetes, and is also on statin therapy and fenofibrate.

On physical examination, the patient has the following: normotensive (128/76 mm Hg); carotid pulses with normal amplitude and no bruits; 2/6 crescendo/decrescendo noted at the left sternal border; no abdominal bruit; peripheral pulses 2+; no tendon xanthomas, corneal arcus, or xanthelasmas.

Following a 12-hour fast, the patient's lipid panel shows the following results:

TC, 290 mg/dL
HDL-C, 56 mg/dL
LDL-C calculated, 218 mg/dL
TG, 132 mg/dL

What is your assessment of B.C.'s lipid panel results?

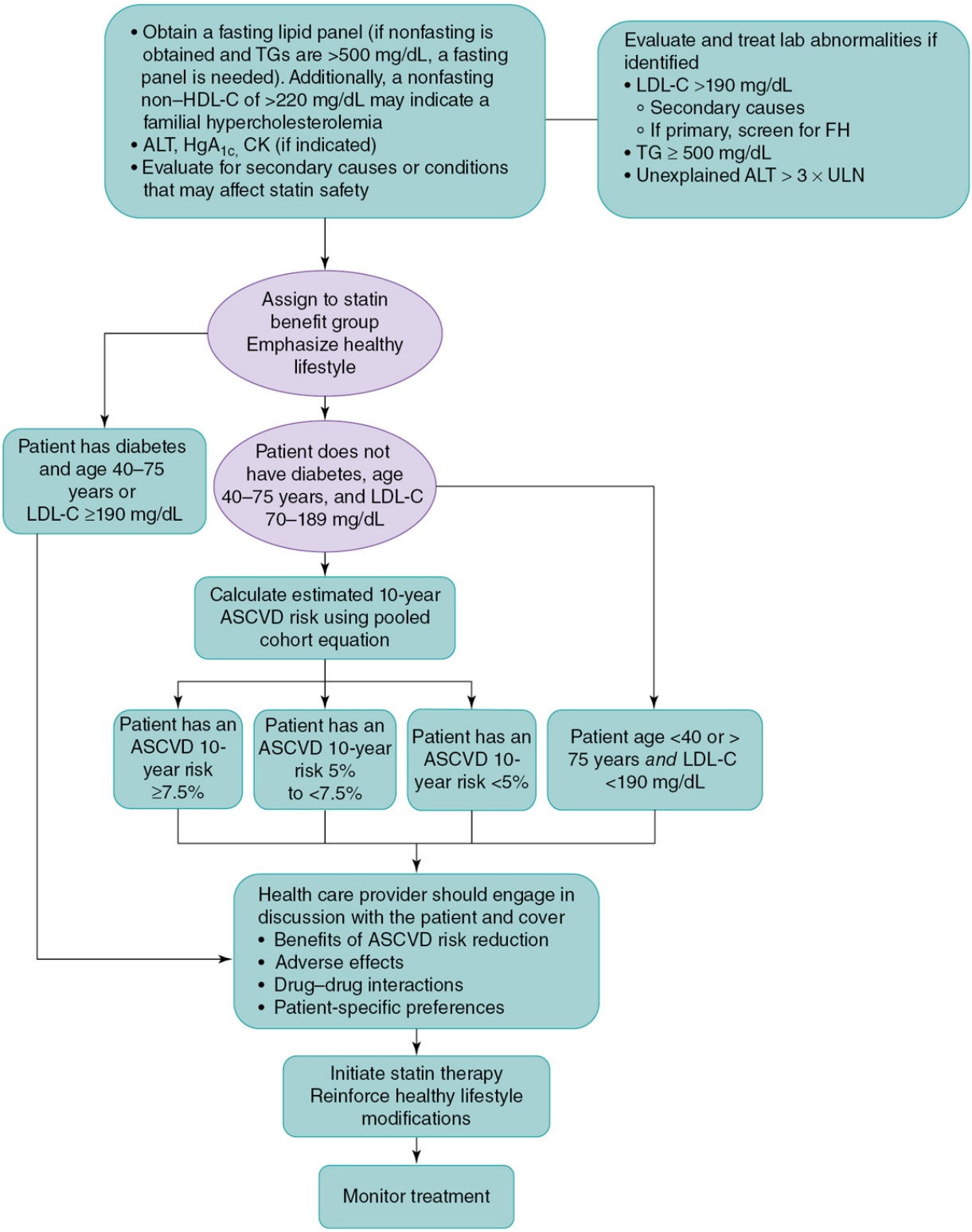


Figure 8-10 Recommendations for initiating statin therapy in patients *without* clinical ASCVD. ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol;

LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. (Adapted from Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889–2934. © 2014 Elsevier. With permission.)

The patient's LDL-C is very high, and she would qualify for statin therapy as defined by the 2018 AHA/ACC Multisociety guideline recommendations for the management of hypercholesterolemia. Her HDL-C is near the average range for a female, and her TG level is considered normal (<150 mg/dL). There has been a misconception among some providers and patients that a normal or high HDL-C level is "protective" in the presence of hypercholesterolemia, based on a TC/HDL-C ratio of <3.5, and that statin therapy is not indicated. However, in the presence of very high elevations of LDL-C levels, all current and previous guidelines recommend statin therapy, regardless of baseline HDL-C.

In the presence of very high LDL-C levels, it is important to consider a number of issues before initiation of therapy. The patient's lifestyle, including diet and exercise, may play an important role in B.C.'s new diagnosis of dyslipidemia. However, she is actually quite concern with lifestyle recommendations for optimal CV health, and this is unlikely to be a factor in her lipid levels. Careful review of family history of hypercholesterolemia and ASCVD by construction of a detailed pedigree can identify patients with possible HeFH or HoFH. B.C.'s father has dyslipidemia of uncertain severity and is on statin therapy, but he has no history of premature ASCVD. Her mother developed ASCVD after age 65 years and a long history of diabetes. Statin therapy was not prescribed until her stent placement and FH is unlikely. Her brother has a mixed dyslipidemia, most likely exacerbated by overweight and poorly controlled diabetes. Thus, based on this brief pedigree, the diagnosis of FH is unlikely. Classic physical examination findings of tendon xanthomas, corneal arcus before age 45 years, and xanthelasmas are often, but not always

present in FH. B.C. does not have these findings. The patient does have a systolic murmur on cardiac examination, which may be indicative of aortic valvular disease, a very common problem in patients with HoFH.

Mean TC is typically lower in premenopausal females than in age-matched males. Premenopausal females have a less proatherogenic lipid profile with higher HDL-C levels (average 10 mg/dL) and lower LDL-C and non–HDL-C levels than age-matched males. Owing to the hormonal alterations during the perimenopausal period, LDL-C levels rise and are often higher than in age-matched males. Postmenopausal females also have a higher incidence of high TG and low HDL-C levels, with an increase in small, dense LDL particles. It is not uncommon for females without a prior history of dyslipidemia to be newly diagnosed in the perimenopausal period and B.C. may be just such a patient.

CASE 8-1, QUESTION 2: Is there any evidence for other potential causes of B.C.'s dyslipidemia?

As a routine, every patient with dyslipidemia should be evaluated for secondary causes of elevated LDL-C, non–HDL-C, or TG. Conditions that may be associated with lipid abnormalities include diabetes, CKD and nephrotic syndrome, obstructive liver disease, hypothyroidism, anorexia nervosa, polycystic ovarian syndrome, and pregnancy, among others (**Table 8-4**).[5] Average values of TC, LDL-C, HDL-C, and TG steadily rise throughout pregnancy and levels peak near full term. In uncomplicated or "normal" pregnancies, neither TC nor TG exceeds 250 mg/dL at any time during pregnancy. A number of drugs are associated with dyslipidemia or worsening of baseline lipid abnormalities, including exogenous estrogen and progesterone therapy, and a careful review of the patient's medication regimen is necessary before initiation of lipid-lowering therapy. B.C. is currently perimenopausal and does not take any medications associated with exacerbation of dyslipidemia nor any

form of exogenous hormone replacement therapy or oral contraception.

Table 8-4
Classification of Secondary Causes of Dyslipidemia

Cause	Increased LDL-C	Increased TG
Drugs/medications	Glucocorticoids, amiodarone, diuretics, cyclosporine	Hormone therapy, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, tamoxifen, sirolimus, atypical antipsychotics (predominately olanzapine and clozapine), raloxifene, β-blockers, thiazide diuretics
Dietary influences	Anorexia, trans fats or saturated fats, weight gain	Very low-fat diets, weight gain, high carbohydrate intake (refined), and excessive alcohol use
Disease states	Nephrotic syndrome, biliary obstruction	Nephrotic syndrome, chronic renal failure, lipodystrophies
Disorders of metabolism	Obesity, pregnancy, hypothyroidism	Hypothyroidism, poorly controlled diabetes, pregnancy, and obesity

LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Source: Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168–3209.

Case 8-1, Question 3: Further review of B.C.'s laboratory studies showed the following:

Glucose, 92 mg/dL
Alanine aminotransferase (ALT), 24 mg/dL
Aspartate aminotransferase (AST), 18 mg/dL
Creatinine, 0.9 mg/dL
Thyroid-stimulating hormone (TSH), 57 IU/mL

Laboratory evaluation has revealed that B.C.'s fatigue and muscle soreness are likely due to hypothyroidism, which has also exacerbated her previous dyslipidemia. She is placed on thyroid replacement therapy, and with normalization of her thyroid function, her follow-up laboratory results show the following:

TSH, 1.254 IU/mL
TC, 215 mg/dL
HDL-C, 59 mg/dL
LDL-C calculated, 132 mg/dL
TG, 118 mg/dL

What is the next step in the evaluation of B.C.'s ASCVD risk?

B.C. has no other ASCVD risk factors or risk equivalents other than mild dyslipidemia. Using the ACC/AHA Pooled Cohort Equations or CV Risk Calculator, her 10-year risk of ASCVD event is 0.9%. According to current guidelines, there is currently no indication for initiation of statin therapy.

The 2015 Standards of Diabetes Care of the American Diabetes Association (ADA) were revised to recommend initiation and intensification of statin therapy (high vs moderate) in patients with diabetes based on the individual patient's risk profile.[61] However, the ADA notes that the presence of diabetes confers significant risk of ASCVD and that the ACC/AHA CV Risk Estimator is of limited use in diabetics. Recommendations are made for patients younger than 40, 40 to 75, and older than 75 years of age for moderate- or high-intensity statin therapy in the presence of ASCVD risk factors or overt ASCVD (**Table 8-5**).

Table 8-5
ADA Recommendations for Statin Treatment in People with Diabetes

Age	<40 Years	40–75 Years	>75 Years
Risk factors	Zero risk factor(s) for CHD[a] Overt CHD[b]	Zero risk factor(s) for CHD Overt CHD	Zero risk factor(s) for CHD Overt CHD
Recommended dose of statin	No statin if zero risk factors Moderate or high intensity in the presence of CHD risk factor(s) High if overt CHD	Moderate if no risk factors High intensity in the presence of CHD risk factor(s) High if overt CHD	Moderate if no risk factors Moderate or high intensity in the presence of CHD risk factor(s) High if overt CHD
Recommended monitoring of lipid panel	Annually or as needed	As needed to assess for adherence	As needed to assess for adherence

Statin therapy should be initiated as an adjunct to lifestyle modifications.

CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

[a]CHD risk factors include hypertension, smoking, LDL-C ≥100 mg/dL, being overweight, and obesity.

[b]Overt CHD includes those who have had a previous cardiovascular event or an acute coronary syndrome.

Adapted from Cromwell WC, Otvos JD, Keyes MJ, et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—implications for LDL management. *J Clin Lipidol*. 2007;1(6):583–592. © 2007 National Lipid Association. With permission.

The 2013 Clinical Practice Guideline for Lipid Management in CKD, published by the Kidney Disease: Improving Global Outcomes (KDIGO) Panel, notes that in non–dialysis-dependent CKD patients, the relationship between LDL-C and ASCVD events is weaker than in the general population.[62] This is likely related to lipoprotein metabolic abnormalities characterized by lower levels of LDL-C, elevated LDL-P, an increase in small dense LDL, reduced HDL-C, and elevated TG. Therefore, according to KDIGO guidelines, the measured LDL-C may be less useful as a marker of coronary risk among people with advanced non–dialysis-dependent CKD and does not serve as an indication for pharmacologic treatment. Instead, therapy is guided by the absolute risk of coronary events based on patient age and stage of CKD or estimated glomerular filtration rate (eGFR). Specific doses of individual statins are recommended for each stage of CKD or eGFR, and dose titration is not indicated. Statin therapy or combination therapy with statin and ezetimibe is not recommended in adults with dialysis-dependent CKD owing to the lack of evidence of ASCVD risk reduction in patients with stage 5 CKD. However, therapy may be continued in patients already receiving therapy at the time of initiation of dialysis (**Table 8-6**).

Table 8-6
KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

Chronic Kidney Disease Severity	Treatment Recommendations
Age ≥50 years of age with eGFR <60 mL/min/1.73 m^2 not on HD or have a history of kidney transplant	Statin or statin/ezetimibe combination
Age ≥50 years with CKD and eGFR >60 mL/min/1.73 m^2	Statin
Age 18–49 years with CKD not on HD or history of kidney transplant with one or more of the following ▪ Diabetes mellitus ▪ Prior stroke ▪ Known CAD ▪ Estimated 10-year risk of CAD death or nonfatal MI >10%	Statin
Dialysis-dependent CKD	No initiation of therapy

CHD, coronary heart disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, hemodialysis.

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl*. 2013;3(3):259–305. © 2013 International Society of Nephrology. With permission.

CASE 8-2

Question 1: S.W. is a 51-year-old African American male with CKD due to polycystic kidney disease. He has no history of tobacco use or diabetes, but is treated for hypertension. He is very active and works in landscape maintenance, but does not have a program of consistent aerobic exercise. He follows a heart-healthy diet consistent with the DASH (Dietary Approaches to Stop Hypertension) recommendations and has maintained a normal body mass index (BMI). He is referred for nephrology consultation and the following results are obtained:

eGFR, 42 mL/min
TC, 187 mg/dL
HDL, 39 mg/dL
LDL-C calculated, 102 mg/dL
TG, 230 mg/dL
$HgbA_{1c}$, 6.8%
BP, 126/68 mm Hg

What is your assessment of S.W.'s ASCVD risk and his lipid panel results?

S.W. has stage 3b CKD defined as an eGFR between 30 and 44 mL/min/1.73 m^2. The ACC/AHA Multisociety guidelines identify CKD as a risk-enhancing factor and recommend initiation of moderate-intensity statin or moderate-intensity statin combined with ezetimibe in those ages 40 to 75 years with an LDL-C 70 to 189 mg/dL who have a 10-year ASCVD risk of 7.5% or higher.[5]

CASE 8-2, QUESTION 2: Would this patient require treatment at this time?

The 2013 KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease provides guidance on lipid management and treatment for all patients with CKD (non–dialysis dependent, dialysis dependent, kidney transplant recipients, and children). According to KDIGO experts, in patients with CKD who are non–dialysis dependent, the relationship between LDL-C and ASCVD events is weaker than in the general population likely related to the atherogenic dyslipidemia characteristic in CKD. Thus, the measured LDL-C does not serve as an indication for treatment. KDIGO guidelines recommend that lipid therapy be guided by the absolute risk of coronary events based on patient age and stage of CKD or eGFR, regardless of baseline lipids. Statin or statin/ezetimibe therapy is recommended in non–dialysis-dependent adults age 50 years or older with eGFR <60 mL/min/1.73 m^2. In adults age 50 years or older with CKD and eGFR ≥60 mL/min/1.73 m^2, only statin therapy is recommended. In adults ages 18 to 49 years with CKD but not treated with chronic dialysis or kidney transplantation, statin treatment is suggested if one of the following is present: known CHD (MI or coronary revascularization), diabetes mellitus, prior ischemic stroke, or estimated 10-year incidence of coronary death or nonfatal MI >10% by the Framingham Risk Score. Statin therapy is also recommended in adult kidney transplant recipients. Therefore, according to KDIGO guidelines as well as

other treatment guidelines, S.W. may be treated with statin or statin/ezetimibe therapy.

PHARMACOLOGIC THERAPY

3-Hydroxy-3-Methylglutaryl Coenzyme A Inhibitors (Statins)

MECHANISM OF ACTION

Statins competitively inhibit HMG-CoA reductase, the enzyme responsible for converting HMG-CoA to mevalonate in an early, rate-limiting step in the biosynthetic pathway of cholesterol (**Fig. 8-11**; also see **Fig. 8-1**). This causes decreased production of mevalonate and its subsequent conversion to cholesterol and a subsequent compensatory increase in the synthesis of LDL receptors. The increased LDL receptor density results in an increase in hepatic update of LDL-C, and to a lesser extent VLDL particles, and significantly lower levels of plasma LDL-C. In addition to the reduction in LDL-C, statins also reduce apo B, TG, and TC concentrations.[63–67]

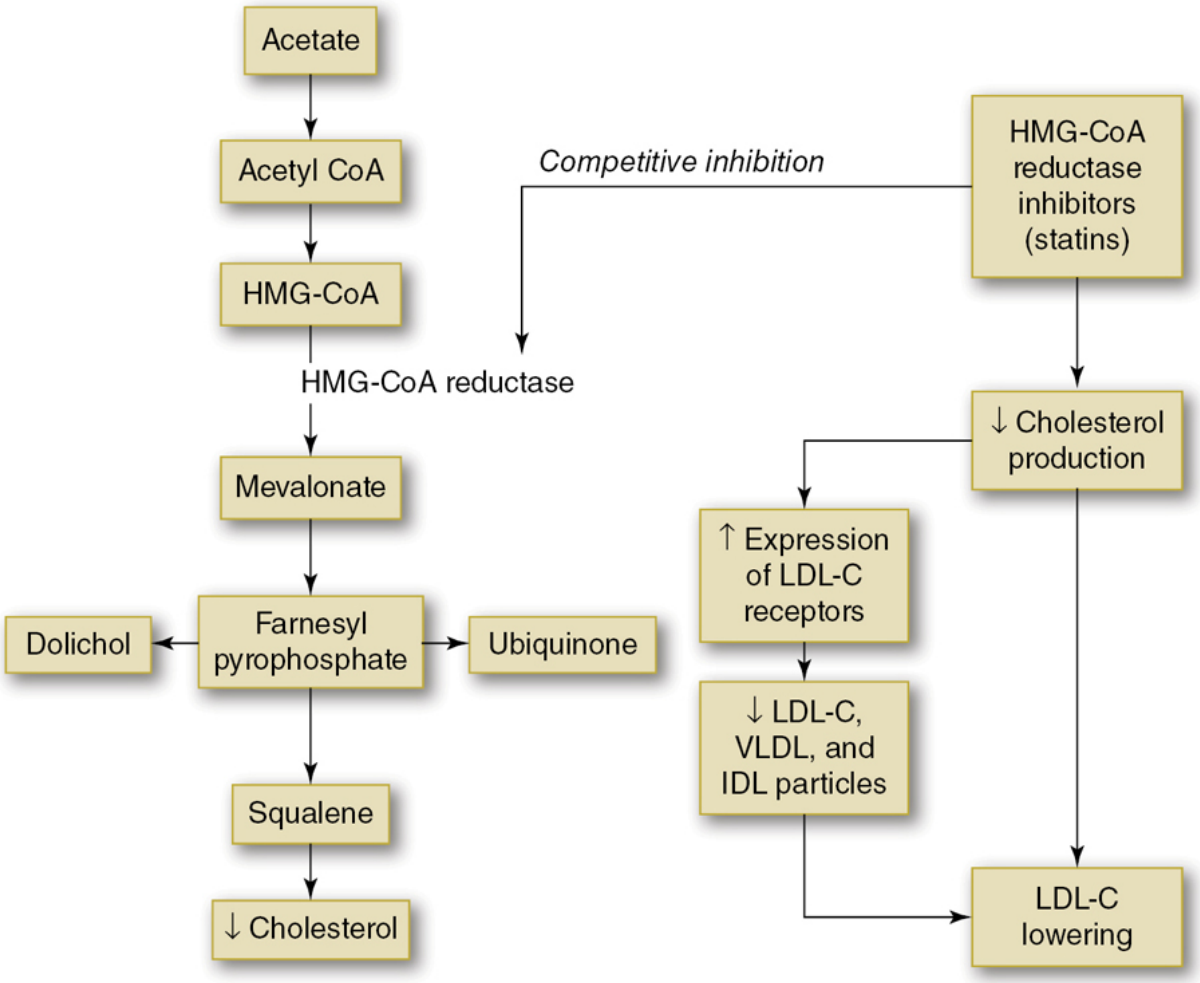


Figure 8-11 Reaction catalyzed by HMG-CoA reductase. Acetyl-CoA, acetyl coenzyme A; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IDL, intermediate-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein.

EFFICACY

Lipid-lowering therapy for patients with ASCVD is now accepted as standard of care.[5] Beginning in the mid-1990s, the results of clinical trials with more potent statins were reported. Five of these (Scandinavian Simvastatin Survival Study [4S], Cardiovascular and Recurrent Events [CARE], the Long-Term Intervention with Pravastatin in Ischemic Disease Study [LIPID], Treating to New Targets [TNT], and Incremental Decrease in End Points through Aggressive Lipid Lowering [IDEAL]) were secondary prevention trials

conducted in patients with known CHD.[68–72] In 4S, CARE, and LIPID, CHD death and nonfatal MI occurred in 13% to 22% of placebo-treated patients in the 5-year follow-up period, compared with event rates of 10% to 14% with patients on statin therapy.[68–70] Total mortality was reduced significantly in two of these trials, 4S and LIPID, that were powered to assess total mortality. In addition, fewer revascularization procedures were required in patients receiving statin therapy and 31% fewer strokes occurred.[73] The TNT and IDEAL trials demonstrated additional CV benefit for high-intensity versus moderate-intensity statin therapy in patients with stable CHD. These trials randomly assigned patients to receive either high-dose atorvastatin 80 mg versus atorvastatin 10 mg or simvastatin 20 mg with an approximate follow-up period of 5 years. In both trials, more intensive lowering of LDL-C to significantly <100 mg/dL was associated with a reduction in CHD.[71,72] The further reductions in the incidence of heart attacks, revascularizations, and ischemic strokes with more intensive lowering of LDL-C with statins compared with less intensive statin regimens were verified in a recent meta-analysis of randomized trials. An additional 38.6-mg/dL reduction of LDL-C in patients on high-intensity therapy was associated with a 38% relative reduction in major vascular events ($P < .0001$).[73]

The Heart Protection Study (HPS)[74] extended the results of earlier secondary prevention statin trials (4S),[68] CARE,[69] and LIPID.[70] The HPS included 20,536 patients with a history of CHD or cerebrovascular disease (stroke or transient ischemic attacks), peripheral vascular disease, or diabetes not considered by their general practitioner to have a clear indication for statin therapy because of relatively low baseline cholesterol levels (mean LDL-C 131 mg/dL).[74] A reduction in CHD events was achieved in both males and females; in all age groups, including those ages 75 to 85 years; and regardless of the baseline LDL-C, including those with initial levels <100 mg/dL.

Trials in patients with acute coronary syndrome (ACS) have also demonstrated CHD risk reduction. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study randomly assigned patients presenting to the hospital with UA or

non–Q-wave MI to statin therapy or placebo for 4 months. This resulted in a 24% reduction in symptomatic ischemia requiring emergency hospitalization and a 60% reduction in nonfatal strokes in those receiving the statin.[75,76] More recently, the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction (PROVE-IT) is considered a landmark trial that demonstrated superior CV event lowering when high-intensity statin therapy (atorvastatin 80 mg) was implemented within 10 days of ACS versus moderate-intensity (pravastatin 40 mg) statin therapy.[77] After 2 years of treatment, mean LDL-C levels in patients randomly assigned to receive atorvastatin 80 mg and pravastatin 40 mg were 62 and 95 mg/dL, respectively. The composite CV end point (death from any cause, MI, documented UA requiring rehospitalization, revascularization, and stroke) was significantly reduced by 16% with high-intensity atorvastatin compared with moderate-intensity pravastatin.[77] Data from the National Registry of Myocardial Infarction 4 demonstrated that early initiation of statins in the acute setting (with the first 24 hours of an acute MI) was associated with a significantly lower rate of early complications and in-hospital mortality.[78] In addition, discontinuation of statin in patients who present with an ACS is associated with increased event rates above those who are statin naive.[79,80]

PHARMACOKINETICS/PHARMACODYNAMICS

The currently available statins are atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. These agents possess different pharmacokinetic properties that may play a role in their efficacy and safety.

Three statins are derived from fungi (simvastatin, pravastatin, and lovastatin),[81–83] whereas the others (atorvastatin, rosuvastatin, pitavastatin, and fluvastatin) are synthetic.[84–87] Lovastatin and simvastatin are prodrugs and must be converted to their active form to exert a pharmacologic effect. Rosuvastatin and atorvastatin have the longest half-lives of 19 and 14 hours, respectively, which enables longer inhibition of the HMG-CoA enzyme and greater LDL-C

reductions compared to other agents.[84,86] Both of these agents lower LDL-C by a mean of ~60% at maximum doses (rosuvastatin 40 mg daily and atorvastatin 80 mg daily). The long half-life also allows for administration at any time of day rather than at bedtime for maximum effect, which is recommended for simvastatin, lovastatin, pravastatin, and fluvastatin.[81–83,85] Although pitavastatin has a shorter half-life (12 hours) than rosuvastatin and atorvastatin, it may also be taken at any time of day.[84,86] The administration of the shorter acting agents at bedtime is important because cholesterol biosynthesis occurs at its highest rate in the evening hours, thus allowing these agents to have the greatest effect on HMG-CoA reductase inhibition and on lowering of LDL-C. However, with extended-release (ER) formulations of lovastatin and fluvastatin, bedtime administration is less important.[81–88]

The amount of statin that reaches the systemic circulation is relatively small. Bioavailability ranges from <5% with lovastatin and simvastatin to 51% with pitavastatin (oral solution). Pravastatin, fluvastatin, and rosuvastatin are hydrophilic agents and may have less tissue distribution and result in less muscle toxicity. However, this aspect is more theoretical than it is clinically valid. All statins are eliminated primarily by the liver, with substantial biliary excretion. However, several statins require dose adjustments in patients with significant renal insufficiency (**Table 8-7**).[81–88]

Table 8-7

Dosing of Statins in Patients with Renal Insufficiency

Statin	Creatinine Clearance 30–50 mL/min	Creatinine Clearance 15–29 mL/min	Creatinine Clearance <15 mL/min or on Hemodialysis
Atorvastatin	Doses up to 80 mg may be used	Doses up to 80 mg may be used	Doses up to 80 mg may be used
Fluvastatin	Doses up to 80 mg may be used	Doses up to 40 mg may be used	Doses up to 40 mg may be used
Lovastatin	Doses up to 80 mg may be used	Doses up to 40 mg may be used	Doses up to 40 mg may be used
Pitavastatin	Doses up to 2 mg may be used	Doses up to 2 mg may be used	Doses up to 2 mg may be used
Pravastatin	Doses up to 40 mg may be used	Doses up to 40 mg may be used	Doses up to 40 mg may be used
Simvastatin	Doses up to 80 mg may be used	Doses up to 20 mg may be used	Doses up to 20 mg may be used
Rosuvastatin	Doses up to 40 mg may be used	Doses up to 10 mg may be used	No data

Sources: Simvastatin (Zocor). Prescribing information. Merck & Co., Inc; October 2012; Pravastatin (Pravachol). Prescribing information. Bristol-Myers Squibb; October 2012; Lovastatin (Mevacor). Prescribing information. Merck & Co., Inc; October 2012; Atorvastatin (Lipitor). Prescribing information. Pfizer; October 2012;

Fluvastatin sodium (Lescol, Lescol XL). Prescribing information. Novartis Pharmaceuticals Corporation; February 2012; Rosuvastatin (Crestor). Prescribing information. AstraZeneca Pharmaceuticals; October 2012; Pitavastatin (Livalo). Prescribing information. Kowa Pharmaceuticals; October 2012; Lovastatin extended-release tablets (Altoprev). Prescribing information. Watson Laboratories; 2012.

ADVERSE EFFECTS

Statins are generally well tolerated. The most common adverse effects reported include muscle pain and weakness (myalgias); headache; gastrointestinal (GI) symptoms, including dyspepsia, flatus, constipation, and abdominal pain; and skin rashes.[81–91] These symptoms are usually mild and often dissipate with continued therapy. Less common adverse effects include myopathy, elevated hepatic transaminases, and diabetes. Cognitive dysfunction may be potentially associated with statin therapy, but this has not yet been demonstrated to be causally related to statin treatment.

Muscle-related adverse effects associated with statins are divided into three different types based on symptoms and the presence or absence of creatine kinase (CK) elevations. These include myalgias, myopathy, and rhabdomyolysis. Myalgias are the most commonly reported muscle symptoms with an incidence of around 32%.[92] Myalgias are defined as muscle aches or weakness without CK elevations. This adverse effect is the most common reason for patients to discontinue statin therapy.[92]

Myopathy is defined as the presence of myalgias, including aches, soreness, or weakness, and an increase in serum CK >10 times the upper lipid of normal (ULN). Myopathy occurs in ~0.1% to 1% of patients and is a dose-dependent effect. If myopathy is present, a careful history is necessary to rule out usual causes (ie, trauma, increased physical activity). Rhabdomyolysis is defined as a CK of at least 10 times the ULN with an elevated serum creatinine and symptoms requiring treatment.[93] Rhabdomyolysis is the least common of the muscle-related adverse effects, but can be life-threatening with acute renal failure, cardiac arrest, or arrhythmias due to severe electrolyte abnormalities. Most cases of rhabdomyolysis have occurred with high doses of statins, in patients

with impaired renal or hepatic function, in older individuals, or when statins are used in combination with interacting drugs. The most common areas affected are in the belly of larger muscles. It is important to distinguish between this and joint pain that may be associated with arthritis.

Simvastatin at a dose of 80 mg daily is associated with the highest incidence of rhabdomyolysis among the statins agents. However, this dose is no longer recommended by the U.S. Food and Drug Administration (FDA) or the 2018 AHA/ACC Multisociety cholesterol guideline.[5,81]

Management of statin-associated muscle adverse effects can be challenging. Routine monitoring of CK levels in asymptomatic patients is unnecessary. However, unexplained symptoms of muscle aches, weakness, or soreness should prompt evaluation of CK and other potential underlying etiologies. Myopathy is more likely to occur with high systemic concentrations of statin and when there are underlying risk factors (eg, age older than 80 years, severe CKD, hypothyroidism, trauma, interacting medications, or flulike syndromes). If a patient develops signs and symptoms consistent with myopathy, statin therapy should be withdrawn until CK levels return to normal. If rhabdomyolysis is diagnosed, statin therapy should be discontinued immediately and etiology determined. Rechallenge of a statin may be considered if the cause was secondary to an interacting medication or other underlying cause that can be identified and corrected. Occasionally, symptoms of myalgia are bothersome or intolerable to the patient, even when the CK level is normal or elevated <10 times the ULN. In these cases, the statin should be discontinued. Once symptoms subside, statin therapy can be restarted at the same or reduced dose, or with a different statin. Alternate-day and even once-weekly dosing of statins have been used in patients who have statin intolerance caused by myopathy.[94] However, these alternative regimens have not been evaluated in CV outcome trials.

Statins may also cause an elevation in transaminase enzyme levels of more than three times the ULN in 1% to 1.5% of patients in a dose-dependent manner. The transaminase level will often return

to normal spontaneously in 70% of cases, even with continued statin therapy.[93] Elevations in transaminases will also return to normal if the statin is discontinued. A rechallenge with the same or a different statin after enzymes have returned to normal limits is acceptable. If the medication is tolerated on rechallenge, it can be continued; recurrence of transaminase elevation warrants further evaluation of other potential causes. It is recommended that before initiating statin therapy, patients should have baseline liver function tests (LFTs) performed. The report of the NLA Statin Safety Task Force recommends that if ALT or AST is one to three times the ULN during statin therapy, there is no need to discontinue the statin.[93] If ALT or AST exceeds three times the ULN during statin therapy, monitor the patient and repeat the transaminase measures. There is no need to discontinue the statin. If a patient's transaminase levels continue to rise or if there is further objective evidence (ie, hepatomegaly, jaundice, elevated direct bilirubin, related symptoms) of liver injury, the statin should be discontinued. The estimated incidence of statin-associated liver failure is 1 per million person-years of use.[95] There is evidence that patients with chronic liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis may safely receive statin therapy.[96]

In 2012, the FDA required an update to the statin prescribing labeling to include information regarding a potential increased risk of reversible cognitive impairment, to include memory loss. Some case reports have suggested that the statins may cause cognitive impairment or memory loss.[97] However, data from randomized controlled trials have failed to show an association, and some data even suggest a beneficial effect on the progression of Alzheimer disease.[74,98,99] Therefore, if a patient presents with cognitive deficits, he should first undergo an evaluation to identify other potential causes. If the statin is suspected, it is reasonable to consider discontinuing therapy for up to 3 months and monitor for improvement.[93] If improvement is noted, then a speculation may be made that the statin was the cause. However, one must carefully balance the decision to discontinue the statin due to the proven benefit of these agents. Consideration should be given to perhaps

reintroduce a different statin or a different statin dose and monitor for recurrence of deficits. In addition, because improvement in cognitive function is subjective, an objective test such as a Mini Mental State Examination (MMSE) should be considered before discontinuation and repeated after discontinuation to assess for any changes.

CASE 8-3

QUESTION 1: M.T. is a 56-year-old White female who presents for new patient evaluation with a 10-year history of type 2 diabetes and hypertension. Current medications include metformin, lisinopril, and chlorthalidone. She currently smokes about 1/2 pack of cigarettes/day, but is considering a quit date. She reports that she struggles with weight management (BMI 33.8 kg/m^2) and has difficulty with exercise due to previous knee injury and a torn rotator cuff. She has a strong family history of premature ASCVD, diabetes, hyperlipidemia, and obesity. Her father underwent coronary artery bypass grafting at age 51 years. Her mother suffered a mild stroke at age 62, but has no residual deficits. She has four siblings of which two have known CHD. On physical examination, her BP is 148/88; bilateral carotid bruits; cardiac examination unremarkable; abdominal bruit; peripheral pulses 1+ bilaterally; no tendon xanthomas, corneal arcus, or xanthelasmas. Her initial laboratory results demonstrate the following:

TC, 273 mg/dL
HDL-C, 43 mg/dL
LDL-C, 158 mg/dL
TGs, 360 mg/dL
$HgbA_{1c}$, 8.2%

What are your initial recommendations for lipid management for M.T.?

All available guidelines for the management of dyslipidemia and diabetes recommend lifestyle counseling as the foundation of therapy. M.T.'s BMI is consistent with obesity, and she has inadequately controlled diabetes and hypertension. Nutrition counseling and weight management will be critical to improve control of these important ASCVD risk factors. Tobacco cessation counseling, referral to a cessation program, and possible pharmacotherapy and/or nicotine replacement therapy are important in this very high-risk patient with a strong family history of premature ASCVD. Given the patient's ongoing knee and shoulder pain, her

ability to engage in significant aerobic activity may be limited until successful weight loss is achieved.

According to the 2018 AHA/ACC Multisociety and ADA guideline recommendations for the management of dyslipidemia, M.T. qualifies for statin therapy in a high-risk diabetic. Her 10-year ASCVD risk by the ACC/AHA CV Risk Calculator is 27.2% and high-intensity statin is, therefore, indicated. Patients with diabetes and two or more other major ASCVD risk factors are considered to be at very high risk and lipid-lowering therapy is recommended. The ADA recommends statin therapy in all patients between the ages of 40 and 75 with type 1 or type 2 diabetes. The 2018 AHA/ACC Multisociety guidelines recommend a reduction in LDL-C by ≥50%.[5] The intensity of statin therapy is based upon the patient's 10-year ASCVD risk by the ACC/AHA CV Risk Calculator. High-intensity statin is considered reasonable in patients with 10-year risk ≥7.5%. Thus, the recommendation for high-intensity statin therapy for M.T. is consistent across all U.S. guidelines.

Case 8-3, Question 2: M.T. is started on atorvastatin 40 mg but, within the next 3 months, returns to clinic with joint and muscle symptoms, noting that her knees and shoulder are more painful. How would you approach the evaluation of possible statin-related muscle symptoms?

Statin-related muscle symptoms present a significant challenge to clinicians, though the prevalence of true statin intolerance is likely quite low. A systematic approach to possible statin intolerance is required to confirm the diagnosis, particularly in a very high-risk patient like M.T. The AHA/ACC Multisociety guideline and NLA provide similar strategies for patient evaluation and management, and these recommendations have been incorporated into the ACC Statin Intolerance App for all mobile devices as well as a web-based version.

It is important for clinicians to take a careful musculoskeletal history and review of systems and document patient ailments before initiation of statin therapy. As reported by M.T., patients may report baseline muscle and joint symptoms that have varied in severity and

frequency before lipid management. Following initiation of statin therapy, patient's muscle symptoms should be compared to those at baseline evaluation to determine whether symptoms are new or merely coincidental exacerbations of prior existing ones. True statin-related myalgias are typically symmetric and are described as aching, soreness, stiffness, tenderness, weakness, or cramping of large proximal muscle groups. Tingling, numbness, sharp or stabbing pain, twitching, nocturnal cramps, arthralgias/arthritis, or unilateral symptoms are less likely to be statin related. Clinicians should consider factors that may increase the risk for statin-related muscle symptoms, such as heavy exercise or exertion, dehydration, substance abuse, frailty, low BMI, female gender, multiple or serious comorbidities, renal insufficiency, hepatic dysfunction, or drug interactions. Other potential primary causes of muscle symptoms should be evaluated, such as hypothyroidism, vitamin D deficiency, trauma, previous or new primary muscle diseases, rheumatologic disorders, metabolic disorders (adrenal insufficiency, hypoparathyroidism, Cushing syndrome), or PAD.

CASE 8-3, QUESTION 3: What recommendations would you give the patient regarding continuation of statin therapy?

Both the AHA/ACC Multisociety guidelines and NLA guidelines recommend temporary discontinuation of statin when a patient reports muscle symptoms that they believe are related to treatment. Statin-related symptoms usually resolve within a few days to 2 weeks, though there have been rare case reports of persistent myopathy following discontinuation of statin therapy. When symptoms have resolved and the patient is asymptomatic, treatment with the same statin at original or lower dose is reinitiated to determine whether the symptoms are definitively related to statin. If muscle symptoms recur, it is assumed that symptoms may be related to drug therapy and that statin should be discontinued. Most algorithms for evaluation and management of possible statin intolerance recommend a trial of at least two to three statins, with

discontinuation and rechallenge if the patient again reports muscle-related symptoms.

The seven currently available statins differ in metabolism, half-life, and lipophilicity, and some providers recommend that the second (or third) statin prescribed in a patient with possible statin intolerance be chosen based on characteristics that differ from the initial agent. There is no trial evidence that this strategy is effective. There have been a number of smaller trials evaluating the potential benefits of ubiquinone or coenzyme Q10 in patients with possible statin-related muscle symptoms, but the results have been inconsistent.

If a patient has failed a systematic challenge/rechallenge approach with two to three statins, guidelines suggest consideration of nonstatin therapies, such as ezetimibe, BASs, or PCKS9 inhibitors.[100]

DIABETES

Statins have been associated with an increased risk of type 2 diabetes. A review of 13 trials involving 19,140 patients showed a 9% relative increased risk for the incidence of diabetes in those taking statins compared to placebo. This equates to approximately one new case of diabetes for every 255 patients treated over a 4-year period.[101] A meta-analysis of five trials comparing high-dose versus low-dose statins showed a 12% increased relative risk for incident diabetes over a 2- to 5-year follow-up in those patients who received higher doses of statins.[102] Based on the data, there appears to be an increased risk of developing diabetes, albeit small. However, owing to the demonstrated clinical benefit of statin therapy, the benefit clearly outweighs the risk of developing diabetes, and statin therapy should not be avoided because of the concern for this adverse effect.

Overall, the incidence of adverse effects with statins varies, with myalgia being the most common. When choosing a statin as well as a statin dose, one must consider the various pharmacokinetic characteristics of that statin, the patients' comorbid conditions, and concomitant medications to minimize risk.

PLACE IN THERAPY

Statins are considered a first-line pharmacologic therapy for the prevention of ASCVD events. They have demonstrated significant reductions in morbidity and mortality across many patient populations.[68–72,103,104] Statin therapy should be initiated before or simultaneously with therapeutic lifestyle modifications.[5]

The initial dose of statin is determined by certain criteria that then place them into any of the four statin benefit groups. The criteria are based on age, the presence or absence of ASCVD, the presence or absence of diabetes, LDL-C level, and their estimated risk based on the Pooled Cohort Equation.[5] High-intensity statin therapy is recommended in the following patient populations: patients younger than 75 years who have clinical ASCVD, patients older than 21 years and an LDL-C of >190 mg/dL, and patients with diabetes (type 1 or type 2) ages 40 to 75 years with an estimated 10-year ASCVD risk of >7.5%. Moderate-intensity therapy is recommended in patients older than 75 years if not a candidate for high intensity, LDL-C >190 mg/dL (if not a candidate for high intensity), type 1 or type 2 diabetes and ages 40 to 75 years, and a 10-year ASCVD risk of >7.5% and ages 40 to 75 years. The later population may be initiated on high-intensity therapy if clinically indicated. The intensity of doses of the various statins is outlined in Table 8-3.[5] Of note, in patients with LDL-C >190 mg/dL, combination therapy with a nonstatin agent may be needed to achieve additional LDL-C lowering if desired.

There are two patient populations for which there are limited data on the benefit of statin therapy: patients with ASCVD and heart failure (HF) (New York Heart Association Class II–IV) and patients on chronic hemodialysis. There are currently no recommendations to initiate statin therapy in these patient populations.[5]

In addition to their ability to lower LDL-C, statin also have many “pleiotropic” effects that play a role in patients with ASCVD, independent of their ability to lower LDL-C. These effects include improvement in endothelial function, plaque stabilization, antithrombotic effects, anti-inflammatory, antioxidant effects,

increased nitric oxide bioavailability, and reduced plaque progression.[105]

Although well demonstrated as beneficial in patients with established CHD, this benefit in primary prevention is less well defined. In patients without CHD, statins have not been shown to reduce mortality. They have demonstrated a lowering of future vascular events over a time frame of 5 to 10 years, albeit small. As a result, prescribing statins in patients without ASCVD but ages 40 to 75 years with an estimated ASCVD risk of ≥7.5% remains controversial.

DRUG INTERACTIONS

Drug interactions with statins that result in higher blood levels of the statin or an active metabolite can increase the risk of myositis. Statins that depend on the cytochrome P-450 (CYP) 3A4 enzyme system to be metabolized are most vulnerable to this interaction (ie, lovastatin, simvastatin, and, to a lesser extent, atorvastatin). Fluvastatin is primarily a substrate of the 2C9 isoenzyme and, to a lesser extent, 2C8 and 3A4 and, therefore, is more vulnerable to interactions with drugs that directly inhibit CYP2C9 or act as competitive inhibitors (substrates) for this alternative system. Pravastatin, pitavastatin, and rosuvastatin are not extensively metabolized by the CYP enzyme system.[85–87] Rosuvastatin is metabolized minimally (about 10%), with CYP2C9 and CYP2C19 being the primary isoenzymes involved. Pitavastatin is marginally metabolized by CYP2C9 and, to a lesser extent, by CYP2C8. The major metabolite in human plasma is lactone, which is formed via glucuronidation by uridine 5′-diphospho-glucuronosyltransferases UGTA3 and UGT2B7. Pravastatin undergoes isomerization in the gut to a relatively inactive metabolite. Variability of gastric metabolism has been shown to be associated with the LDL-C-lowering effects of pravastatin.[106] Therefore, rosuvastatin and pravastatin have the lowest potential for interaction with medications that inhibit the CYP metabolic pathways. Some of the most commonly encountered medications that interact with statins by inhibiting the CYP3A4

enzyme system are azole antifungals (itraconazole, ketoconazole, and miconazole), certain calcium channel blockers (diltiazem and verapamil), macrolide antibiotics (clarithromycin and erythromycin), protease inhibitors (eg, ritonavir), grapefruit juice (>1 quart), cyclosporine, and antidepressants (nefazodone). Drugs that are substrates for the CYP3A4 system include certain benzodiazepines (alprazolam, midazolam, triazolam), calcium channel blockers (especially diltiazem), carbamazepine, cyclosporine, estradiol, felodipine, loratadine, and quinidine. When these substrate drugs are used together with simvastatin or lovastatin (and to a lesser extent atorvastatin), systemic blood levels of the statin may be increased because of competitive inhibition of the CYP3A4 enzymes, and this may increase the risk for myositis.

Added caution should also be exercised when adding gemfibrozil with a statin to treat patients who also have elevated TG levels. Gemfibrozil interferes with the glucuronidation of statins, thereby interfering with their renal clearance. This impact may be minimal or up to a threefold to fourfold increase in statin levels depending upon the specific agent.[107–116] Owing to the significance of this interaction, fenofibrate is the preferred fibric acid derivative to use in combination with statins. However, gemfibrozil may be used in combination with certain statins if clinically indicated.[86,109–114,117,118] A list of select statin drug interactions is presented in **Table 8-8**.

Table 8-8
Select Drug Interactions With Statins

	Contraindicated Medications	Medications With Dose Limits	Maximum Dose of Statin When Used in Combination
Atorvastatin	Tipranavir plus ritonavir Telaprevir	Boceprevir Clarithromycin Itraconazole Nelfinavir Cyclosporine/tacrolimus/ everolimus/sirolimus	Do not exceed 40 mg daily Do not exceed 20 mg daily Do not exceed 20 mg daily Do not exceed 40 mg daily Do not exceed 10 mg daily
Fluvastatin		Fluconazole Itraconazole Cyclosporine	Do not exceed 20 mg daily Do not exceed 20 mg daily Do not exceed 40 mg daily
Lovastatin	Boceprevir Clarithromycin Cyclosporine Erythromycin Gemfibrozil Ketoconazole Nefazodone HIV protease inhibitors Itraconazole Posaconazole Telaprevir Telithromycin Voriconazole	Amiodarone Danazol Diltiazem Verapamil Dronedarone Lomitapide	Do not exceed 40 mg daily Do not exceed 20 mg daily Do not exceed 20 mg daily Do not exceed 20 mg daily Do not exceed 10 mg daily Do not exceed 20 mg daily
Pitavastatin		Rifampin	Do not exceed 2 mg daily
Pravastatin		Clarithromycin Cyclosporine/tacrolimus/ everolimus/sirolimus	Do not exceed 40 mg daily Do not exceed 20 mg daily
Rosuvastatin		Cyclosporine/tacrolimus/ everolimus/sirolimus Gemfibrozil Lopinavir/ritonavir Atazanavir/ritonavir	Do not exceed 5 mg daily Do not exceed 10 mg daily Do not exceed 10 mg daily Do not exceed 10 mg daily
Simvastatin	Boceprevir Clarithromycin Cyclosporine Erythromycin Gemfibrozil Itraconazole Ketoconazole HIV protease inhibitors Itraconazole Posaconazole Telaprevir Telithromycin Voriconazole	Amiodarone Amlodipine Diltiazem Verapamil Dronedarone Lomitapide Ranolazine	Do not exceed 20 mg daily Do not exceed 20 mg daily Do not exceed 10 mg daily Do not exceed 10 mg daily Do not exceed 10 mg daily Do not exceed 20 mg daily Do not exceed 20 mg daily

Sources: Simvastatin (Zocor). Prescribing information. Merck & Co., Inc; October 2012; Pravastatin (Pravachol). Prescribing information. Bristol-Myers Squibb; October 2012; Lovastatin (Mevacor). Prescribing information. Merck & Co., Inc; October 2012; Atorvastatin (Lipitor). Prescribing information. Pfizer; October 2012;

Fluvastatin sodium (Lescol, Lescol XL). Prescribing information. Novartis Pharmaceuticals Corporation; February 2012; Rosuvastatin (Crestor). Prescribing information. AstraZeneca Pharmaceuticals; October 2012; Pitavastatin (Livalo). Prescribing information. Kowa Pharmaceuticals; October 2012. Lovastatin extended-release tablets (Altoprev). Prescribing information. Watson Laboratories; 2012; Wiggins BS, Saseen JJ, Page RL 2nd. Recommendations for management of clinically significant drug–drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2016;134(21):e468–e495.

CASE 8-4

QUESTION 1: J.G. is a 63-year-old White female who implemented lifestyle modifications for her dyslipidemia 7 months ago and is in clinic for follow-up. She has a history of gout, chronic nonischemic HF (left ventricular ejection fraction [LVEF] 26%), and diabetes (diet controlled) as well as a 20 pack-year smoking history (quit 5 years ago). Her medications include lisinopril, furosemide, and metoprolol succinate 25 mg once daily. Her vital signs include BP 124/80 mm Hg and heart rate 75 beats/min. Her laboratory results are as follows: HDL-C 64 mg/dL, LDL-C 101 mg/dL, TG 98 mg/dL, and TC 185 mg/dL.

What is her 10-year ASCVD risk based on the calculator?

CASE 8-4, QUESTION 2: Based on her risk, what is the most appropriate next step for J.G.?

CASE 8-4, QUESTION 3: Four months later, J.G. is admitted to the hospital with atrial fibrillation and is started on amiodarone and apixaban 5 mg twice daily (bid). What medication modifications should be done to J.G.'s medication regimen at this time?

The addition of amiodarone to her medication regimen necessitates a reduction in her dose of simvastatin to 20 mg daily. This dose is still within moderate-intensity range and is acceptable. The other option would be to switch her to different statin that is either not metabolized by CYP3A4 or metabolized to a lesser extent than simvastatin. Reasonable choices of statins would be pravastatin 40 to 80 mg daily, fluvastatin 40 mg bid or XL 80 mg daily, atorvastatin 10 to 80 mg daily, pitavastatin 2 to 4 mg daily, lovastatin 40 mg daily, and rosuvastatin 5 to 40 mg daily.

CLINICAL PEARLS

Approximately 50% of patients discontinue statin therapy within 6 months of initiation, and only one-third are still adherent after a year. Therefore, it is important to minimize adverse effects and be able to identify if the statin may be the cause. The incidence of statin intolerance is estimated to be 5% to 10% among statin-treated patients. However, in light of the new cholesterol guidelines, 13 million more individuals have become eligible for statin therapy, and the overall prevalence of statin intolerance in the United States is likely to increase. Diagnosing statin intolerance is challenging as no universal definition exists. The NLA has several definitions of statin intolerance, but the one most clinically useful is the inability to tolerate at least two statins. The two statins should be one that was prescribed and taken at the lowest starting dose and another one that was taken at any dose. In addition to the two statins challenge, patients need to have either objectionable symptoms or abnormal laboratory values, which are temporally related to statin therapy and reverse upon statin discontinuation and recur upon reinitiation. The ACC has also developed an application called “ACC Statin Intolerance App” designed to assist providers in making the diagnosis of true statin intolerance. The application provides the clinician with a systematic strategy for evaluation of symptoms, management recommendations, as well as information regarding statin characteristics and drug interactions. This application is available on the web at http://tools.acc.org/StatinIntolerance, via Itunes at https://itunes.apple.com/us/app/statin-intolerance/id985805274?mt=8 or via Google Play at https://play.google.com/store/apps/details?id=org.acc.StatinIntolerance&hl=en.

Routine monitoring of LFTs is no longer recommended during statin treatment. However, patients should be made aware of symptoms that may indicate potential hepatic disease, such as flulike symptoms, fatigue, sluggishness, anorexia, weight loss, right upper quadrant pain, yellowing of eyes, or jaundice.

All patients should have a fasting lipid panel before statin initiation. The 2018 AHA/ACC Multisociety guidelines for monitoring of statin therapy recommend a follow-up lipid panel in 4 to 12 weeks following statin initiation to assess patient adherence and response to therapy and then every 3 to 12 months as clinically indicated.[5]

Coenzyme Q10 is an isoprenoid that plays a unique role in cellular electron transport and energy synthesis. It is essential for the normal functioning of muscles. Statins have been shown to reduce blood levels of coenzyme Q10, but muscle tissue concentrations are unaffected. Evidence of the value of supplementing coenzyme Q10 in patients experiencing statin-induced myopathy has been mainly anecdotal. However, the risk of taking CQ10 is relatively small and may be considered in patients with muscle aches in the absence of symptoms that are concerning for more serious muscle-related disease.

Cholesterol Absorption Inhibitor (Ezetimibe)

MECHANISM OF ACTION

Cholesterol that is ingested in the diet and circulated through the bile from the liver is actively reabsorbed in the intestines. Once transported across the intestinal lumen into the enterocyte, it is combined with TG and apo B-48 to form chylomicron particles that transport the lipids through the lymphatic system to the hepatocyte. The TG and cholesterol can then be packaged into VLDL particles and secreted into the systemic circulation (**Fig. 8-12**).

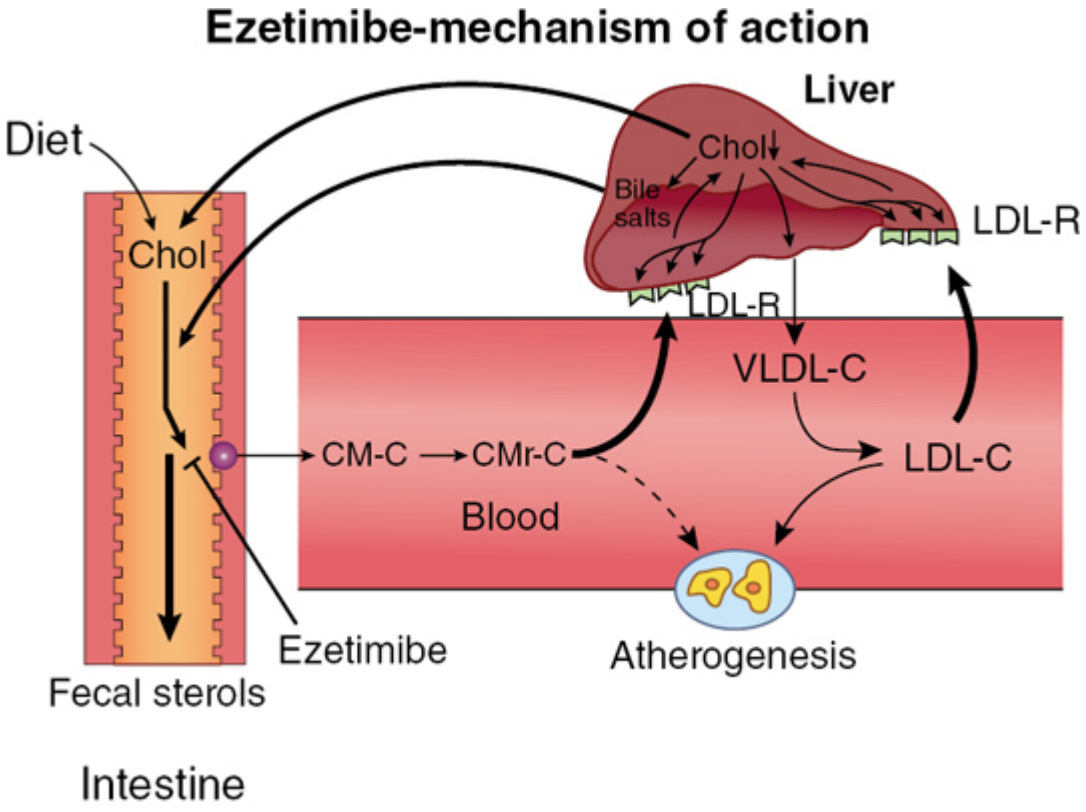


Figure 8-12 Mechanism of action of cholesterol absorption inhibitors. Chol, cholesterol; CM-C, chylomicron cholesterol; CMr-C, chylomicron remnant cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein real; VLDL-C, very low-density lipoprotein cholesterol.

In the small intestine, the Niemann–Pick C1L1 (NPC1L1) transporter is responsible for the uptake of dietary and biliary cholesterol into the small intestine. Ezetimibe interferes with the active absorption of cholesterol and plant sterols from the intestinal lumen into the enterocyte by binding to and inhibiting this transporter. By interfering with the absorption of cholesterol, about 50% less cholesterol is transported from the intestines to the liver by the chylomicrons. This causes an upregulation of hepatic LDL receptors and increased clearance of circulating VLDL and LDL particles. There is also an upregulation in hepatic cholesterol synthesis, which is diverted to the intestines via the bile to replenish the cholesterol available for intestinal absorption processes. The net effect of the inhibition of the NPC1L1 transporter is ~70% increase in GI sterol

excretion, a 50% reduction in hepatic cholesterol concentration, a 90% increase in hepatic cholesterol synthesis, and ~20% increase in LDL-C clearance from the systemic circulation via upregulated LDL receptors.[119,120]

Ezetimibe also inhibits the absorption of sitosterol and other plant sterols from the gut, resulting in about a 40% reduction in blood sitosterol levels. The occurrence of sitosterolemia is rare, but is associated with a high CHD risk. Ezetimibe provides one of the first effective treatments for this rare disorder.

EFFICACY

The ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial was a randomized, double-blind, placebo-controlled trial comparing simvastatin 80 mg combined with ezetimibe 10 mg versus simvastatin 80 mg alone administered once daily in 720 patients with HeFH.[121] The primary outcome was the change in mean carotid intima–media thickness (CIMT) after 24 months of treatment. This trial was not statistically powered to determine differences in vascular disease event rates between treatments because of the short study duration and the small number of patients. Mean baseline LDL-C (319 vs 318 mg/dL) and CIMT (0.69 vs 0.70 mm) were similar between the treatment groups. The percent change in LDL-C was significantly ($P < .01$) greater in the simvastatin–ezetimibe group (−55.6%) compared with the simvastatin–placebo group (−39.1%). However, there was no regression in CIMT in either treatment group, and the mean changes in the CIMT were similar between the treatment groups ($P = .29$) after 24 months of treatment. Why was there not a greater change in CIMT in patients randomly assigned to the simvastatin–ezetimibe group compared with the simvastatin–placebo group, given that these patients had a greater reduction in LDL-C? Before randomization, ~80% of the patients in both treatment groups were receiving statin therapy. Moreover, these patients had thinner or near-normal CIMT at baseline when compared with patients with HeFH studied in previously published statin trials[122,123] that did

demonstrate reduced CIMT with high-dose statin therapy. Collectively, this suggests that the patients studied in the ENHANCE trial were aggressively managed for their cholesterol for many years, resulting in the depletion of vascular wall lipids. Therefore, additional aggressive treatment would unlikely result in further regression of an already lipid-depleted carotid vascular wall. In contrast, Avellone et al[124] recently demonstrated that ezetimibe combined with simvastatin caused a significant reduction in CIMT in FH patients with and without a history of MI. These patients had similar mean baseline LDL-C (301 mg/dL) to patients studied in the ENHANCE trial; however, baseline CIMTs in this trial were much larger (1.82 mm without a history of MI and 1.98 mm with a history of MI) than those observed in the ENHANCE trial and were consistent with CIMTs in patients with FH who have not been aggressively treated.

When ezetimibe was combined with simvastatin versus placebo in 1873 patients with mild-to-moderate, asymptomatic aortic stenosis and no previous history of vascular disease, diabetes mellitus, or any other indications for cholesterol-lowering therapy, significantly fewer patients treated with simvastatin–ezetimibe (15.7%) had ischemic CV events compared with the placebo group (20.1%), mainly related to a reduction in coronary artery bypass grafting (P = .02).[125]

The incremental benefits of adding ezetimibe to statin therapy were evaluated in the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT).[126] This was a multicenter, randomized, double-blinded trial involving 18,144 patients that sought to determine the clinical benefit and safety of combination therapy with ezetimibe and simvastatin compared to simvastatin monotherapy in high-risk patients presenting with ACS. This was the first large trial to evaluate the clinical efficacy of adding a nonstatin (ezetimibe 10 mg/day + simvastatin 40 mg/day) to statin (simvastatin 40 mg/day) monotherapy. The primary end point was CV death, nonfatal MI, rehospitalization for UA, coronary revascularization ≥30 days following randomization, or stroke. Over a median follow-up of 57 months, the addition of ezetimibe to simvastatin 40 mg reduced the primary end point by 6.4% when compared with patients who received simvastatin alone (P = .016). The absolute reduction in risk

over 7 years was 2.0%. The reduction in the primary end point was largely driven by a statistically significant reduction in the risk of MI and ischemic stroke. Overall, there was a significant 10% reduction in the risk of CV death, nonfatal MI, or nonfatal stroke. However, there was no difference in all-cause mortality between the two treatment groups. The average LDL-C during the study was 53.7 mg/dL in the simvastatin–ezetimibe group, compared to 69.5 mg/dL in the simvastatin monotherapy group ($P < .001$). The results of this study support the "lower-is-better" premise for LDL-C.[126]

PHARMACOKINETICS/PHARMACODYNAMICS

Ezetimibe is a prodrug that is rapidly conjugated to an active phenolic glucuronide (ezetimibe-glucuronide).[120] The drug is primarily metabolized in the small intestine via glucuronide conjugation with subsequent renal and biliary excretion. The elimination half-life is ~22 hours. Absorption is not affected by food, and ezetimibe may be administered at any time of day without regard to meals. There are no dose adjustments necessary for patients with renal impairment or with mild hepatic insufficiency.

ADVERSE EFFECTS

Ezetimibe is generally well tolerated with minimal adverse effects. The adverse effects that are the most reported include diarrhea, arthralgias, cough, fatigue, abdominal pain, and back pain. However, the incidence is no more frequent with ezetimibe than with placebo. Elevations in serum transaminases have also been reported. When used as monotherapy, the incidence of consecutive elevations (three times or lower the ULN) in serum transaminases is similar between ezetimibe (0.5%) and placebo (0.3%); however, when combined with a statin, the incidence of consecutive elevations in serum transaminases is 1.3% and only 0.4% in patients taking a statin alone. These elevations are usually transient and return to baseline after discontinuation. Although very rare, cases of myopathy and rhabdomyolysis have been reported with ezetimibe monotherapy.

PLACE IN THERAPY

Ezetimibe may be used either alone or in combination with a statin or fenofibrate along with diet for the management of dyslipidemia, specifically to lower LDL-C. Ezetimibe reduces LDL-C by 18% to 22%, but has little effect on TG or HDL-C.[127] In combination with a statin, it demonstrates an additive effect, enhancing LDL-C lowering by an additional 10% to 20%. In fact, when added to a low dose of a statin, the net LDL-C reduction can be similar to the lowering achieved with the maximal dose of the statin.[128] When added to the maximal dose of a statin, it causes further LDL-C reduction, an effect important in patients with very high LDL-C levels requiring substantial reduction to achieve treatment goals.

DRUG INTERACTIONS

Ezetimibe has been evaluated in combination with several other medications. When combined with statins or fenofibrate, there is minimal impact on either drug in terms of an alteration in metabolism and increased bioavailability that requires any additional intervention.[120] Postmarketing data have shown that there are some elevations in the international normalized ratio (INR) when ezetimibe is added to warfarin. The exact mechanism of this interaction is not fully understood, and no specific dose adjustments are necessary for either medication. However, when ezetimibe is initiated in a patient on warfarin, closer monitoring of the INR may be warranted. Cyclosporine in combination with ezetimibe results in increased exposure of both medications. When used in combination, serum concentrations of cyclosporine should be closely monitored and adjusted as clinically indicated. In addition, the recommended initial dose of ezetimibe when used in combination with cyclosporine is 5 mg daily.

When cholestyramine or colestipol is in combination with ezetimibe, there is an 80% reduction in the area under the curve (AUC) of ezetimibe. Therefore, when these combinations are used, ezetimibe should be administered at least 2 hours prior or 4 ounces following the administration of cholestyramine or colestipol.[120] The

absorption of ezetimibe is not affected by colesevelam, and this combination may be preferred.

CLINICAL PEARLS

Adding ezetimibe to a statin results in greater LDL-C reduction than increasing the dose of the statin. Doubling the dose of any statin provides only an additional 6% reduction in LDL-C. The addition of ezetimibe to statin therapy results in ~18% additional reduction in LDL-C. However, maximally tolerated statin therapy is always recommended before consideration of the addition of nonstatin therapy.

Owing to a risk of increased hepatic serum transaminases, these laboratory values should be measured before the addition of ezetimibe to statin therapy and again following 6 weeks of combination therapy.

Ezetimibe monotherapy or combination therapy with statin should be avoided in patients with active liver disease or persistent elevations in serum transaminases that are otherwise unexplained.

Niacin

On the basis of currently available evidence of nonefficacy and potential harms, there are no clear indications for the routine use of niacin preparations, and niacin is, therefore, not considered in this discussion.

CASE 8-5

QUESTION 1: R.P. is a 62-year-old male, with history of CHD (bypass 2 years ago), diabetes, and end-stage renal disease (ESRD) who is on hemodialysis Monday, Wednesday, and Friday. He is on lisinopril 10 mg daily, atorvastatin 40 mg daily, aspirin 81, metoprolol succinate 50 mg daily, insulin, and calcium acetate 667 mg three times daily. His BP is 136/82 mm Hg; HgA_{1c} 11.6%; weight 291.01 pounds (132 kg); height 70 inches (177.80 cm); fasting lipid panel TC = 250 mg/dL, HDL-C = 30 mg/dL, TG = 450 mg/dL.

What would be the most appropriate treatment for R.P. and his dyslipidemia?

While R.P. does have elevated TGs, per the Endocrinology and AHA guidelines, pharmacologic therapy is not indicated at this time. The most important intervention for R.P. is lifestyle modifications. Controlling his diabetes and losing weight can successfully lower his TGs as much if not more than pharmacologic therapy.

Case 8-5, Question 2: If pharmacologic therapy were initiated on R.P. for his hypertriglyceridemia, which agent(s) would be the most appropriate?

All fibric acid derivatives undergo renal elimination, and none of these agents are approved for patients on hemodialysis and are, therefore, not a good option in R.P. ω-3 Fatty acids would be the best option to use in combination with atorvastatin that he is already taking.

Fibric Acid Derivatives

MECHANISM OF ACTION

Fibrates activate peroxisome proliferator-activated receptors α (PPARα), causing most of the beneficial effects on blood lipids.[129] PPARα are located in the nucleus of cells and are ligand-dependent transcription factors that regulate target gene expression. Stimulation of PPARα suppresses the gene responsible for the synthesis of apo C-III and stimulates the gene responsible for LDL receptor synthesis.[129,130] As a result, lipolysis of TGs from VLDL particles and the removal of these particles via hepatic LDL receptors are enhanced. Stimulation of PPARα also increases fatty acid oxidation, reducing the synthesis of TGs in the liver, reducing the TG content of secreted VLDL particles.[130] Stimulation of PPARα may increase the synthesis of apo A-I, the critical building block of nascent HDL, thereby enhancing reverse cholesterol transport. Research also suggests that fibrates stimulate the expression of ABCA-1 transporters in macrophage cells, which are responsible for bringing cholesterol from within the cell to the cell surface, where it can be

taken up by nascent HDL particles and removed from the cell[129] (**Fig. 8-13**).

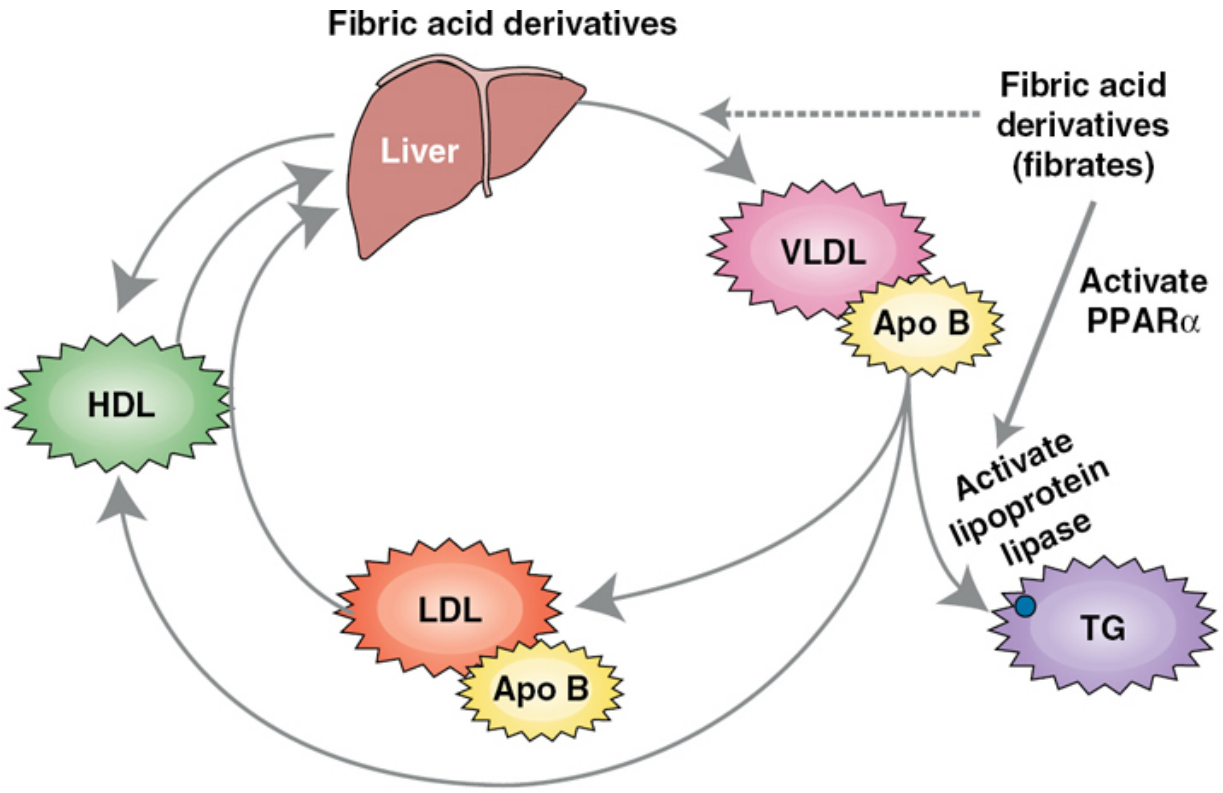


Figure 8-13 Mechanism of action of fibric acid derivatives. apo B, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPARα, peroxisome proliferator-activated receptor α; TG, triglycerides.

EFFICACY

The results of three major primary prevention trials have raised questions about the safety of fibrates. In the World Health Organization trial, clofibrate reduced nonfatal MI by 25%, but caused an increase in total mortality.[131,132] As a result, its use has declined markedly in the United States. Some of these deaths may have been related to gallstone disease.[131] In the Helsinki Heart Study (HHS), gemfibrozil reduced fatal and nonfatal MI by 37%, but was associated with a slight increase in non-CHD mortality such that there was no net reduction in total mortality.[133] Follow-up evaluations of therapies without gemfibrozil were associated with continued

event reduction. In the Veterans Affairs High-Density Lipoprotein Intervention (VA-HIT) trial, there was a significant 22% relative risk reduction in death from CHD with gemfibrozil ($P < .006$). There was also a 24% reduction in the combined end point of death from coronary revascularization, hospitalization due to angina, nonfatal MI, and stroke ($P < .001$). However, there was no significant effect on mortality.[134] In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate did not significantly reduce CHD deaths and nonfatal MI compared with placebo. In addition, more patients receiving fenofibrate had pancreatitis or a pulmonary embolism compared with those given placebo.[135] Fenofibrate was also evaluated versus placebo in 418 patients with diabetes and at least one visible lesion on angiographic evaluation in the Diabetes Atherosclerosis Intervention Study (DAIS) trial.[136] The trial was not powered to examine clinical end points, but fewer events, including deaths, occurred in the fenofibrate group. In summary, the clinical trial evidence for CV benefit of the fibric acid derivatives is not as robust as for the statins. The data supporting the use of gemfibrozil in the primary and secondary prevention setting have been established. In contrast, clear improvements in CHD-related outcomes are still lacking for fenofibrate. Thus, these data support the use of fibric acid derivatives as second-line agents, with the exception of use in patients with severe hypertriglyceridemia. More recently, the incremental benefits of adding fenofibrate to background simvastatin therapy on CHD events in patients with diabetes were reported. Only patients with the highest tertile (≥204 mg/dL) of TGs and the lowest tertile (≤34 mg/dL) of HDL-C showed a benefit when fenofibrate was added to statin therapy. Overall, there was an insignificant 8% reduction in the composite CV end point, and fenofibrate appeared to be harmful in females compared with males.[137]

PHARMACOKINETICS/PHARMACODYNAMICS

Fenofibrate and fenofibric acids are well absorbed from the GI tract.[138–145] Fenofibrate is primarily metabolized by conjugation with

peak plasma concentrations within 6 to 8 hours after administration. It is highly bound to plasma proteins, with an elimination half-life of 20 hours. The primary route of excretion is via the urine in the form of metabolites.

On the other hand, gemfibrozil is completely absorbed following administration and reaches peak plasma concentrations within 1 to 2 hours.[146] The rate and extent of absorption is optimal when taken 30 minutes before meals as food can result in a 14% to 44% reduction in the AUC. It is highly bound to plasma proteins, with an elimination half-life of 1.5 hours. It undergoes extensive hepatic metabolism via oxidation of the ring methyl group to form carboxyl and hydroxymethyl metabolites. Gemfibrozil relies significantly on renal excretion, with ~70% being eliminated by the kidneys as a glucuronide conjugate.[146]

Dosing of fibric acid derivatives in patients with renal insufficiency is outlined in **Table 8-9**.

Table 8-9
Dosing of Fibric Acid and Fenofibric Acid Derivatives in Renal Insufficiency

Medication	Usual Dose	Creatinine Clearance 30–59 mL/min	Creatinine Clearance 31–80 mL/min	Creatinine Clearance 30 mL/min or Hemodialysis
Gemfibrozil	600 mg twice daily		No specific recommendations	Not recommended
Fenofibrate (Fenoglide®)	40–120 mg daily		Start at lowest dose of 40 mg daily	Contraindicated
Fenofibrate (Tricor®)	48–145 mg daily	Start at lowest dose of 48 mg		Contraindicated
Fenofibrate (Fibricor®)	35–105 mg daily		Start at lowest dose of 35 mg	Contraindicated
Fenofibrate (Liofen®)[a]	50–150 mg daily		Start at lowest dose of 50 mg daily	Contraindicated
Fenofibrate (Antara®)	43–130 mg daily		Start at lowest dose of 43 mg daily	Contraindicated
Fenofibrate (Lofibra® tablets)	54–160 mg daily		Start at lowest dose of 54 mg	Contraindicated
Fenofibrate (Lofibra® micronized)	67–200 mg daily		Start at lowest dose of 67 mg	Contraindicated
Fenofibrate (Triglide®)	160 mg daily		Avoid use	Contraindicated
Fenofibrate (Trilipix®)	45–135 mg daily	Start at lowest dose of 45 mg		Contraindicated

[a]CrCl is 30–89 mL/min.

ADVERSE EFFECTS

Gemfibrozil, fenofibric acid, and fenofibrate are usually well tolerated. The most common adverse effects associated with fibric acid derivatives include nausea, vomiting, dyspepsia, diarrhea, abdominal pain, flatulence, and constipation. Gemfibrozil causes mild GI symptoms (nausea, dyspepsia, abdominal pain) in about one-third of patients. Fenofibrate causes a rash in 2% to 4% of patients. Fibrate therapy can also cause muscle side effects, including myositis and rhabdomyolysis.[138–143] Most cases of muscle toxicity have been reported with gemfibrozil, especially when it is used in combination with a statin. Recent studies reveal that the area under the blood concentration curve of most statins is increased twofold to fourfold when given concurrently with gemfibrozil. These effects have not been observed with fenofibrate. The mechanism causing this interaction appears to be related to inhibition of glucuronidation by gemfibrozil, which is a metabolic pathway for statins, thereby reducing clearance of statins from the systemic circulation.[147]

Fibric acid derivatives have also been associated with abnormalities in LFTs, including bilirubin and alkaline phosphatase.[138–146] However, these elevations are often not worrisome and usually return to baseline levels upon discontinuation. Fenofibrate has been shown to cause a reversible increase in serum creatinine.[138–145] Although also observed with gemfibrozil, the incidence is lower. Despite this increase, there does not appear to be a resultant decrease in GFR and the mechanism for this effect has not been clearly defined. Gemfibrozil also increases biliary secretion of cholesterol, which increases the lithogenicity of bile and results in the development of cholesterol gallstones. Presumably, the same effect occurs with all fibrates.

PLACE IN THERAPY

Gemfibrozil, fenofibric acid, and fenofibrate are all indicated for the reduction of TG levels in patients with hypertriglyceridemia.[138–146] The 2018 AHA/ACC Multisociety guidelines define severe hypertriglyceridemia at a TG level ≥500 mg/dL.[5] The guidelines state

that to prevent acute pancreatitis, it is reasonable to reduce TGs whenever levels exceed 500 mg/dL by addressing and eliminating the secondary causes, implementing a very low-fat diet, and adding fibrates or ω-3 fatty acids. If a fibrate is necessary in a patient being treated with a statin, it is safer to use fenofibrate than gemfibrozil because of the lower risk of severe myopathy. Similarly, in patients with familial dysbetalipoproteinemia, fibric acid derivatives are highly effective and are considered the drugs of choice. Fibrates also have a place in the management of combined or mixed hyperlipidemia. Support for this comes primarily from the results of the HHS and the VA-HIT trials, in which gemfibrozil combined with diet therapy was associated with a reduction in CHD deaths and nonfatal MI.[133,134] These positive outcomes are attributed to significant reductions in serum TGs (and, therefore, a reduction in TG-rich VLDL remnants and in small, dense LDL) and an increase in HDL-C. Persons most likely to benefit are those with diabetes or the lipid triad found in patients with the metabolic syndrome.

DRUG INTERACTIONS

Drug interactions associated with fibric acid derivatives are fairly well known, and several of these drug interactions can be managed by careful monitoring. The most clinically significant interactions occur with statins, warfarin, repaglinide, cholestyramine, and colestipol. The combination of statins and gemfibrozil increases systemic concentrations of the statin and raises the risk for the development of myopathy and rhabdomyolysis. As previously mentioned, data suggest that there is less risk of a significant drug interaction with fenofibrate and subsequently a lower risk of myopathy and rhabdomyolysis. The combination of gemfibrozil should be avoided with lovastatin, pravastatin, and simvastatin. The maximum dose of rosuvastatin should be 10 mg daily when combined with gemfibrozil. Although gemfibrozil does interact with atorvastatin and pitavastatin, the increase in statin concentrations is minor, and the combination may be utilized if clinically indicated. However, there are no data demonstrating that adding a fibrate to a statin will reduce CHD risk.

The coadministration of gemfibrozil with ezetimibe may cause increased cholesterol excretion into the bile, increasing the risk of cholelithiasis.[120,146] This does not appear to be a concern with fenofibrate and ezetimibe combination.

CASE 8-6

QUESTION 1: J.S. is a 46-year-old male with a history of hypertension and diabetes. He presented to his primary care physician with abdominal pain that began 2 days ago and radiated to his mid-back. He also has some vomiting. All of his vital signs were within normal limits. On physical examination, he has tenderness over his abdominal area that is more severe in the epigastric region.

Pertinent laboratory values include an HgA_{1c} of 13.6% and the following cholesterol panel: TC 467 mg/dL, HDL-C 30 mg/dL, TG 1872 mg/dL, LDL-C was unable to be calculated, amylase 325 U/L, and lipase 3265 U/L.

Following acute management of his pancreatitis, what would be the most appropriate treatment for J.S.?

This is an individual who is at high risk for pancreatitis as well as ASCVD. His risk score using the new risk calculator based on recent guidelines reveals a 10-year risk of about 18.6% and a statin is indicated. In addition, the endocrinology guidelines define a TG level of ≥1000 mg/dL as severe and the AHA/ACC Multisociety guidelines define a level ≥500 mg/dL as very high and that pharmacologic therapy should be initiated. J.S. should be initiated on a statin and a fibric acid derivative, or two different agents to lower TGs first such as ω-3 fatty acids plus fibric acid derivative to get TGs down and then consider the addition of a statin.

CASE 8-6, QUESTION 2: What are some considerations when using fibric acid derivatives in combination with statins?

The risk of adverse effects of statin–fibrate combination therapy is dependent on pharmacokinetic interactions that alter statin metabolism and clearance. One of the most significant drug interactions with statins and a fibric acid derivative is the combination of a statin with gemfibrozil. Gemfibrozil inhibits glucuronidation,

which is an elimination pathway of all statins, with the exception of fluvastatin. This interaction can lead to increased concentrations of these statins, increasing the risk of toxicity. In contrast, fenofibrate appears to have a minimal effect and is considered a safer alternative. The use of gemfibrozil with simvastatin, pravastatin, or lovastatin should be avoided. The combination of gemfibrozil with atorvastatin, pitavastatin, and rosuvastatin may be considered if fenofibrate is not an option.[118] However, lower doses of statins should be used to minimize adverse effects. Labeling for rosuvastatin suggests limiting the daily dose of rosuvastatin to 10 mg daily when used with gemfibrozil.

CLINICAL PEARLS

Many different formulations of fenofibrate are available, with the dose ranging from 130 to 200 mg. All products are dosed once daily. For the treatment of hypertriglyceridemia, the initial dose may be at the lower end of the dosing range. If the initial dose chosen is lower than the maximum dose, it should be titrated upward at 4- to 8-week intervals based on patient response up to the maximum dose.

Obtain a baseline serum creatinine before the initiation of therapy.

Gemfibrozil is preferred in renal insufficiency.

Consider discontinuation of fibric acid derivative or a dose reduction in the setting of otherwise unexplained increases in serum creatinine.

Fenofibrate is the preferred agent to use when combination with a statin is warranted.

Obtain a baseline CK before adding a fibrate to statin therapy and in those patients at high risk.

Patients who receive any fibric acid derivative therapy either alone or in combination with a statin should be monitored for symptoms of muscle soreness and pain. If these symptoms emerge, a CK level should be obtained. CK level ≥10 times the ULN in combination with muscle symptoms supports a diagnosis of myositis. If other possible causes are not apparent, such as increased physical exercise or a

recent trauma or fall, the presence of myositis is an indication to withdraw fibrate therapy.

v-3 Fatty Acids

MECHANISM OF ACTION

The exact mechanism by which the ω-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), lower TGs is not fully understood. There are currently three prescription fish oil formulations available: combined EPA and DHA in ethyl ester form, EPA ethyl ester only, and EPA and DHA in carboxylic acid form.[148–150] The ethyl ester formulation may possibly work through inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal B oxidation. However, DHA and EPA inhibit the esterification of other fatty acids, and TG lowering may be due to a reduction in hepatic TG synthesis.[148] The active metabolite of icosapent ethyl ester reduces hepatic VLDL-TG synthesis and/or secretion and increases TG clearance from circulating VLDL particles.[149] The potential mechanisms of action for the carboxylic acid formulation include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal oxidation in the liver, decreased lipogenesis in the liver, and increased plasma LPL activity. This agent may reduce the synthesis of TGs in the liver.[149]

EFFICACY

Consumption of foods rich in ω-3 fatty acids (eg, fish) several times a week has been associated with a reduced risk of heart disease and is recommended as part of a low-fat diet. Supplements of fish oils demonstrated a reduction in CHD in patients with a recent MI[151] as well as patients taking statins.[152] Recently, however, other trials have failed to demonstrate the benefits of ω-3 fatty acids in addition to standard CV drugs, such as statins, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and antiplatelet agents.[153] Commercial sources of fish oils vary in their content. The ω-3 fatty

acids used in the GISSI study, which demonstrated a CHD risk reduction, contained 850 mg of combined EPA and DHA. Recently, two trials, the Reduction of Cardiovascular Events with EPA-Intervention trial (REDUCE-IT) and Outcome Study to Assess Statin Residual Risk Reduction with Epanova in Hypertriglyceridemia (STRENGTH), evaluated CV outcomes in patients with CHD or at high risk for CHD (REDUCE-IT) or high risk for CHD (STRENGTH) already taking statin therapy.[154,155]

The STRENGTH trial was an international, randomized, double-blind, placebo-controlled trial evaluating the effects of ω-3 carboxylic acid preparation on reducing the rate of CV events in high-risk patients with hypertriglyceridemia and low HDL-C levels. Inclusion criteria were a TG level ≥180 to 500 mg/dL and HDL-C <42 mg/dL. Patients were also required to be on background statin therapy for at least 4 weeks and have an LDL-C of <100 mg/dL. However, an LDL-C of >100 mg/dL was allowed if on maximum tolerated statin therapy. Patients either received 4 g daily of ω-3 carboxylic acid or placebo. The primary outcome was time to first event of CV death, MI, stroke, coronary revascularization, or hospitalization for UA. The study was stopped early based on recommendation from an independent data monitoring board because of the low likelihood of the study demonstrating a benefit.[154]

However, results from The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) evaluating EPA demonstrated CV benefits.[155] This was a multicenter, randomized, double-blind, placebo-controlled trial comparing icosapent ethyl 2 g bid to placebo in 8179 patients for secondary prevention of CV events. This study included patients established CVD or with diabetes and other risk factors, who had been receiving statin therapy a fasting TG level between 150 and 499 mg/dL and LDL-C 41 to 100 mg/dL. The median follow-up period was 4.9 years. All patients were on background statin therapy. The primary end point was a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or UA. The results revealed a significant reduction in the occurrence of the primary end point of 17.2% in the icosapent ethyl group compared to 22% in the placebo (hazard ratio [HR] 0.75;

95% confidence interval [CI] 0.68–0.83; *P* < .001). A significant reduction in the rate of additional ischemic events, including CV death, was also observed with icosapent ethyl (4.3%) compared to placebo (5.2%; *P* = .03). However, there was a significantly higher risk of atrial fibrillation or flutter in the icosapent ethyl group compared to placebo (3.1% vs 2.1%; *P* = .004).

PHARMACOKINETICS/PHARMACODYNAMICS

There is limited pharmacokinetic or pharmacodynamic data available for these agents. The combined EPA and DHA ethyl ester formulation (Lovaza®, Omtryg®) is well absorbed following oral administration. The EPA and DHA carboxylic acid preparation (Epanova®) is directly absorbed in the small intestines subsequently entering the systemic circulation mainly via the thoracic duct lymphatic system.[150] Steady-state concentrations of EPA and DHA in plasma are achieved within 2 weeks following repeat daily dosing. The ω-3 fatty acids in carboxylic acid form may be administered without regard to meals. They are mainly oxidized in the liver and do not undergo renal elimination.

Following oral administration, the EPA ethyl ester preparation (Vascepa®) is de-esterified during process, and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system.[149] Peak plasma concentrations of EPA are reached in ~5 hours. No studies on the effect of food on this product have been conducted. However, the recommendation is for it to be taken with or following a meal. The EPA ethyl ester is mainly metabolized by the liver via β-oxidation. This β-oxidation splits the long carbon chain of EPA into acetyl coenzyme A, which is then converted into energy via the Krebs cycle. EPA ethyl ester does not undergo renal elimination.

ADVERSE EFFECTS

The most common adverse effects associated with Lovaza® are eructation, dyspepsia, and taste perversion. In addition to eructation, Epanova® has also been reported to cause diarrhea, nausea, and

abdominal pain. The most common adverse effect reported with Vascepa® is arthralgia.

PLACE IN THERAPY

Fish oils predominantly contain long-chain polyunsaturated (ω-3) fatty acids, EPA and DHA, which lower TG levels significantly (30%–60%) but have variable effects on cholesterol levels. They do not provide clinically significant LDL-C reduction. All of the available prescription products may be used as an adjunct to diet to treat hypertriglyceridemia (≥500 mg/dL). However, based on the results of the REDUCE-IT trial, icosapent ethyl is also indicated as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and UA requiring hospitalization in adults with elevated TG levels (≥150 mg/dL), AND established CVD, or diabetes mellitus and two or more additional risk factors for CVD. The National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated TGs and high or very high ASCVD risk recommends icosapent ethyl for ASCVD risk reduction in high- and very high-risk patients who are either 45 years and older with clinical ASCVD or 50 years and older with type 2 diabetes, fasting TGs 135 to 499 mg/dL and at least one additional risk factor.[156] For patients with type 2 diabetes, icosapent ethyl is recommended only if patients are on maximum tolerated doses of a statin, with or without ezetimibe (NLA). The ADA guideline recommendations are very similar in that icosapent ethyl should be reserved for patients whose TG levels persist between 135 and 499 mg/dL despite statin therapy.[157]

The recommended dose of Lovaza® is 4 g/day in either a single or divided dose. The dose for Vascepa® is 2 g bid with food and for Epanova® is 2 to 4 g daily.

DRUG INTERACTIONS

No significant drug interactions have been reported with any of the prescription products. However, some studies suggest that the use of ω-3 fatty acids may prolong bleeding time. However, there have

been no thorough clinical trials conducted to determine the magnitude of this interaction. Therefore, patients taking these along with other anticoagulants should be evaluated more closely for any signs of increased bleeding.

CLINICAL PEARLS

ω-3 Fatty acid capsules should be swallowed whole. Do not break open, crush, dissolve, or chew.

Administering fish oil before meals may decrease the fishy taste.

EPA has negligible effect on LDL-C. Both EPA and DHA lower TGs, but DHA as well as the combination of EPA/DHA are more effective than EPA-only preparations. DHA-containing preparations may increase LDL-C, mechanism likely due to increase in apo C-III production.

Bile Acid Resins

MECHANISM OF ACTION

Bile acids are secreted into the intestines and are responsible for emulsifying fat and lipid particles in food. Most of the bile acids that are secreted are reabsorbed and returned to the liver by enterohepatic circulation. The BASs are anion exchange resins that bind bile acids in the intestinal lumen and cause them to be eliminated in the stool.[158–161] By disrupting the normal enterohepatic recirculation of bile acids from the intestinal lumen to the liver, the liver is stimulated to convert hepatocellular cholesterol into bile acids. This results in a reduction in the concentration of cholesterol in the hepatocyte, prompting upregulation of LDL receptor synthesis. Finally, circulating LDL-C levels are lowered by binding to the newly formed LDL receptors on the liver surface (**Fig. 8-14**).

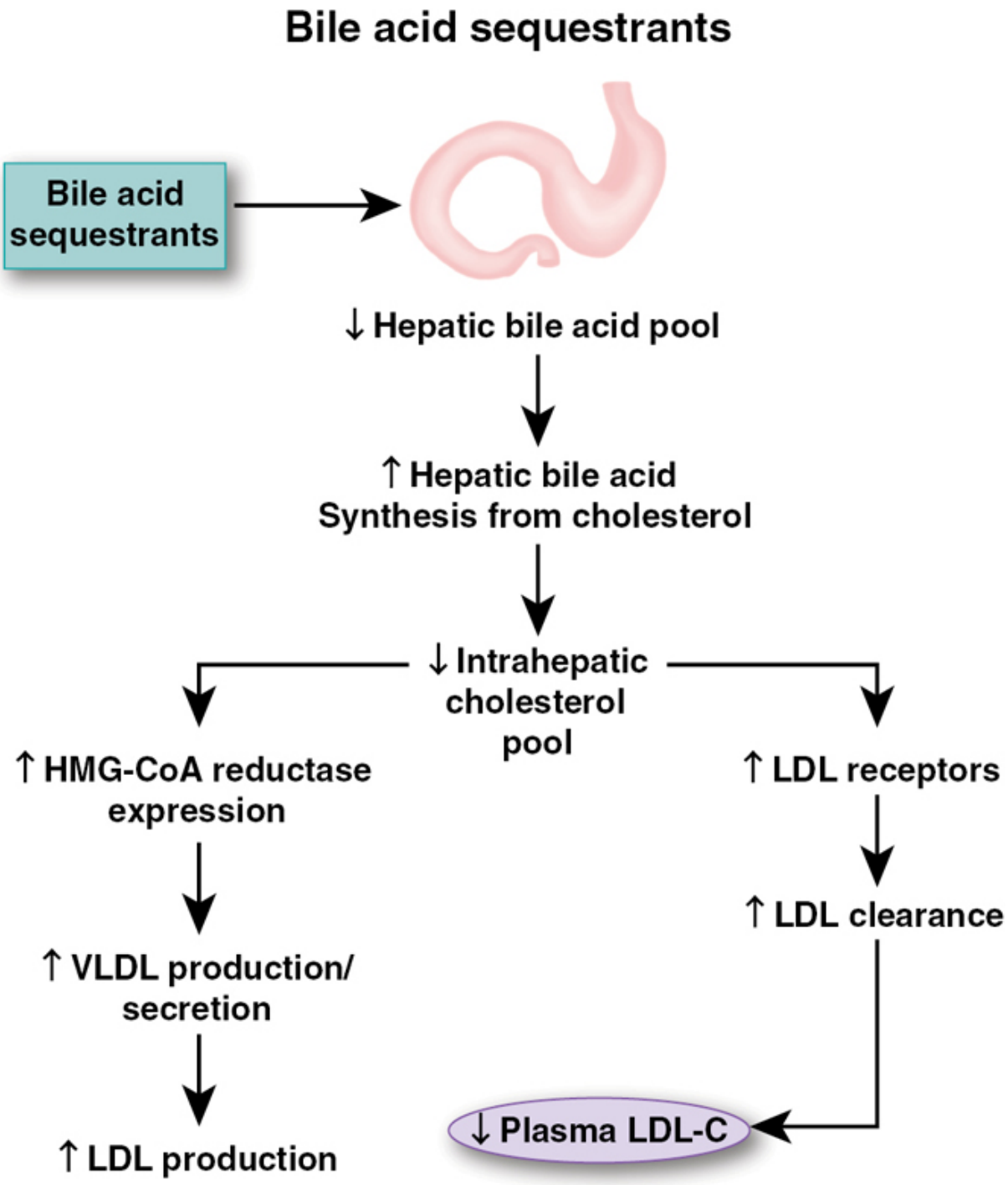


Figure 8-14 Mechanism of action of bile acid sequestrants. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein.

EFFICACY

The BAS agents have demonstrated the ability to reduce CHD events in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CCPT).[162] This was a randomized, multicenter trial evaluating the efficacy of cholesterol lowering in reducing CAD risk in 3806 males with primary hypercholesterolemia. In conjunction with diet, patients were randomized to cholestyramine 24 g/day or placebo. The mean follow-up was 7.4 years. The primary end point of combined CAD death and nonfatal MI was reduced by 19% in the patients treated with cholestyramine compared to placebo-treated patients ($P < .05$). This study also supports the "lower-is-better" hypothesis of LDL-C.[162,163] These agents reduce LDL-C between 12% and 27% and TC by 8% and 27%. HDL-C is increased minimally by around 3% to 10%. All of the BAS also may raise TG levels by 3% to 10% or more, especially in patients with high TG levels.

PHARMACOKINETICS/PHARMACODYNAMICS

Colesevelam is a nonabsorbable polymeric compound that binds to bile acids more strongly and more specifically than the other available BAS.[161] Colestipol and cholestyramine are nonabsorbable hydrophilic basic anion exchange resins. All of these agents are insoluble in water.[159,160]

ADVERSE EFFECTS

The most common adverse effect associated with these agents is constipation. Additional adverse effects include abdominal bloating, epigastric fullness, nausea, vomiting, steatorrhea, and flatulence.[159–162] The incidence of these GI symptoms is less with colesevelam.

PLACE IN THERAPY

BAS are indicated as an adjunct to diet and exercise to lower LDL-C. These agents may be used either alone or in combination with statins. The BAS have appealed in the management of hypercholesterolemia because they have a strong safety record and they effectively lower LDL-C. They are not absorbed from the GI

tract and thus lack systemic toxicity. Older BAS (cholestyramine, colestipol) are not well tolerated because of numerous GI side effects and the unpleasant granular texture of the powder. Therefore, colesevelam is currently the preferred agent. Colesevelam is indicated as either monotherapy or in combination with a statin to reduce LDL-C levels in boys and postmenarchal girls, ages 10 to 17 years, with HeFH. Therapy may be initiated following adequate trial of diet if LDL-C remains ≥190 mg/dL or LDL-C remains ≥160 mg/dL and there is a positive family history of premature ASCVD or two or more other CVD risk factors. Colesevelam is also approved by the FDA for use in type 2 diabetes to improve glycemic control.[161]

DRUG INTERACTIONS

Reduction in the absorption of fat-soluble vitamins and folic acid has been reported with high dosages of BAS, but this is rarely a problem in otherwise healthy patients consuming a nutritionally balanced diet. Cholestyramine and colestipol may reduce or delay the absorption of medications when coadministered.[159–161] This can be minimized by administering other medications 1 hour before or 4 hours after the resin dose. The resins may also reduce the absorption of warfarin, levothyroxine, thiazide diuretics, β-blockers, and, presumably, other anionic drugs. Colesevelam has been shown to reduce the levels of glimepiride, glipizide, glyburide, levothyroxine, cyclosporine, olmesartan, and oral contraceptives containing ethinylestradiol and norethindrone. To avoid these interactions, these agents should be administered 4 hours before colesevelam. Colesevelam has also been shown to increase metformin levels, and patients should be monitored for clinical response. Postmarketing reports have also shown an interaction with phenytoin. As with the other drug interactions, phenytoin should be administered 4 hours before colesevelam.

CLINICAL PEARLS

The use of BAS should be avoided in patients with complete biliary obstruction.

BAS agents are contraindicated if TGs are >500 mg/dL and in patients with a history of hypertriglyceridemia-induced pancreatitis.

Colesevelam for oral suspension should be mixed with 4 to 8 ounces of water, fruit juice, or diet soft drinks.

These agents should be initiated only when TG levels are <300 mg/dL.

Microsomal Triglyceride Protein Inhibitors (Lomitapide)

MECHANISM OF ACTION

Lomitapide is the first in a new class of antihyperlipidemic agents to improve lipoprotein profiles in patients with HoFH. MTP resides in the lumen of the endoplasmic reticulum. Inhibiting MTP production prevents the assembly of apo B–containing lipoproteins in enterocytes and hepatocytes. This subsequently inhibits the production and subsequent secretion of chylomicrons and VLDL, and subsequent production of LDL-C.[164]

EFFICACY

There is one pivotal phase 3 study that ultimately led to the approval of lomitapide. This was a multinational, single-arm, open-label, 78-week trial in 29 patients with HoFH.[165] Following a 6-week run in phase, patients were initiated on lomitapide 5 mg daily and titrated to doses of 10, 20, 40 mg, up to 60 mg, based on tolerability and liver enzymes levels.[165] Patients were also instructed to follow a low-fat diet (<20% of calories from fat) as well as to take dietary supplements to replace fat-soluble nutrients.

Initial efficacy was assessed after 26 weeks and then patients were continued on the study medication for an additional 52 weeks to assess for long-term safety. The primary end point was change in LDL-C from baseline at 26 weeks. The results showed that lomitapide, when added to the existing lipid-lowering therapy, significantly reduced LDL-C by an average of 40% from baseline at week 26.[165]

PHARMACOKINETICS/PHARMACODYNAMICS

Lomitapide undergoes extensive hepatic metabolism. Metabolic pathways include oxidative-*N*-dealkylation, glucuronide conjugation, oxidation, and piperidine ring opening. The CYP3A4 isoenzyme metabolizes lomitapide to its major metabolites. Lomitapide is highly bound to plasma proteins (99.8%) and has a mean terminal elimination half-life of 39.7 hours. Approximately 59.5% and 33.4% of the dose are excreted in the urine and feces, respectively.[164]

PLACE IN THERAPY

Lomitapide is approved as an adjunct to a low-fat diet and other lipid-lowering therapies, including LDL apheresis, to reduce LDL-C, TC, apo B, and non–HDL-C in patients with HoFH. Owing to the concern for liver injury, the drug is only available through a Risk Evaluation and Mitigation Strategies (REMS) program. Given the risk of adverse effects, unknown effects on CV morbidity and mortality and the absence of data in the non-HoFH population, lomitapide treatment should be restricted to patients with HoFH.

ADVERSE EFFECTS

The primary adverse effects associated with lomitapide include GI symptoms, elevated transaminases, and hepatic steatosis. The most common GI symptom report was diarrhea, which occurred in 79% of patients, followed by nausea (65%), dyspepsia (38%), and vomiting (34%). Additional GI symptoms that have been reported include abdominal pain and discomfort, constipation, and flatulence. To minimize the risk of these adverse effects, patients should adhere to a diet that is low in fat (<20% of daily energy). Elevations in hepatic transaminases occurred in 34% of patients. The degree of elevation ranged from an ALT or AST of three times or above the ULN to five times the ULN. However, no patients in the clinical trial had to discontinue therapy because of elevated transaminases.

DRUG INTERACTIONS

The use of lomitapide in combination with strong inhibitors of CYP3A4 (boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, voriconazole, telithromycin), moderate inhibitors of CYP3A4 (amprenavir, aprepitant, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil, crizotinib, atazanavir, diltiazem, darunavir/ritonavir) as well as grapefruit juice is contraindicated. Strong CYP3A4 inhibitors in combination with lomitapide can result in ~27-fold increase in exposure of lomitapide. Moderate CYP3A4 inhibitors in combination with lomitapide have not been fully evaluated but are expected to increase lomitapide levels. Even weak CYP3A4 inhibitors can increase lomitapide exposure by approximately twofold. When lomitapide is used in combination with warfarin, the INR may increase by as much as 22%. Lomitapide in combination with simvastatin leads to doubling of simvastatin exposure. When used in combination with statin therapy, the dose of statin should be reduced by 50% and the dose of simvastatin should be limited to 20 mg daily. A dose of simvastatin of 40 mg daily may be used if patients have previously tolerated simvastatin for at least a year at a dose of 80 mg daily. Although specific drug interactions between lomitapide and lovastatin have not been studied, given that the metabolizing enzymes and transporters responsible for the disposition of these two agents are similar, a reduced dose of lovastatin should be considered. Lomitapide is also an inhibitor of P-glycoprotein (P-gp). The use of lomitapide in combination with P-gp substrates (aliskiren, fexofenadine, topotecan, sitagliptin, saxagliptin, imatinib, maraviroc, digoxin, dabigatran, ambrisentan, colchicine, everolimus, lapatinib, nilotinib, posaconazole, sirolimus, talinolol, tolvaptan) may lead to increased absorption of these agents, and dose reduction should be considered. Although not tested, it is recommended that BAS be administered at least 4 hours apart from lomitapide. This is to avoid potential interference with absorption of lomitapide.[162]

CLINICAL PEARLS

The initial dose of lomitapide is 5 mg once daily with a full glass of water, and at least 2 hours following the evening meal.

Patients should adhere to a low-fat diet consisting of <20% of their dietary intake when prescribed lomitapide.

Patients should also consume supplements (provided by pharmacy with lomitapide prescription) that contain vitamin E (400 IU), linoleic acid (200 mg), α-linolenic acid (210 mg), EPA (110 mg), and DHA (80 mg).

The dose of lomitapide can be increased after 2 weeks to 10 mg once daily and then titrated upward as follows: at 6 weeks, increase the dose to 20 mg once daily; at 10 weeks, increase to 40 mg once daily; and after 14 weeks, the dose may be increased to the maximum dose of 60 mg.

The maximum dose in patients with ESRD on hemodialysis or mild hepatic impairment is 40 mg once daily.

The use of lomitapide is contraindicated in patients with active liver disease (unexplained persistent elevations of serum transaminases), moderate-to-severe hepatic impairment, pregnancy, as well in combination with moderate or strong CYP3A4 inhibitors, as outlined earlier.

Patients on warfarin along with lomitapide should have their INR closely monitored and warfarin dosage adjusted as needed.

Obtain ALT, AST, and total bilirubin before initiation of therapy, before each dose increase, or monthly, whichever comes first.

After the first year of therapy, ALT, AST, and total bilirubin should be monitored at least every 3 months and before any dose increase. If the LFTs are greater than three times the ULN and less than five times the ULN, repeat labs in 1 week to confirm the elevation. If the elevation is confirmed, reduce the dose and obtain additional liver-related tests. Repeat labs weekly and discontinue therapy if LFTs increase to greater than five times the ULN and do not decrease to less than three times the ULN within ~4 weeks.

Apo B Antisense Oligonucleotides

MECHANISM OF ACTION

Mipomersen is an antisense oligonucleotide targeted to human messenger ribonucleic acid (mRNA) for apo B-100. Mipomersen is complementary to the coding region of the mRNA for apo B-100 and binds by Watson and Crick (guanine–cytosine and adenine–thymine) base pairing. The hybridization of this agent to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA, thereby inhibiting translation of the apo B-100 protein. This action leads to reduced apo B synthesis, the structural core for all atherogenic lipids, including LDL-C.[165–168]

EFFICACY

Mipomersen has been evaluated in two phase 3 studies. The first was a randomized, double-blind, placebo-controlled multicenter trial in 58 patients with FH. Patients were included if their LDL-C was ≥140 mg/dL or LDL-C ≥92 mg/dL plus CAD, on maximally tolerated lipid-lowering therapy. Patients were administered subcutaneous (SQ) dose of 200 mg of mipomersen weekly for 26 weeks or placebo.[169] The results showed a 36% reduction in LDL-C versus a 13% increase with placebo ($P < .001$). In addition, apo B and lipoprotein(a) were also significantly reduced ($P < .001$). ALT and AST were increased in 21% and 13% of patients, respectively. Hepatic steatosis was observed, with an incidence of 13%. The second phase III study was also a randomized, double-blind, multicenter study evaluating 158 patients with baseline LDL-C ≥100 mg/dL with or at high risk for CAD and on maximum tolerated lipid-lowering therapy.[170] As with the previous study, mipomersen 200 mg was administered SQ once a week for 26 weeks. The results revealed a 36.9% reduction in LDL-C compared to a 4.5% reduction with placebo ($P < .001$). Apo B was significantly reduced by 38% as was lipoprotein(a) by 24% ($P < .001$). In addition, half of the patients achieved LDL-C levels of <70 mg/dL in the mipomersen group. Elevations in ALTs observed were similar to other studies, and ALT greater than three times the ULN occurred in 10% of patients.

PHARMACOKINETICS/PHARMACODYNAMICS

Mipomersen is administered via SQ injection. The drug has a bioavailability ranging from 54% to 78%. Peak plasma concentrations are generally obtained within 3 to 4 hours. With weekly administration, steady state is reached within ~6 months. It is highly bound to human plasma (≥90%) and has an elimination half-life of 1 to 2 months following SQ administration. Mipomersen is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. Mipomersen is not a substrate for the CYP450 enzyme system. Elimination occurs via metabolism in the tissues and urinary excretion.[166]

ADVERSE EFFECTS

The most common adverse effects associated with mipomersen with an incidence of ≥10% include injection site reactions, flulike symptoms, nausea, headache, and elevated hepatic transaminases, specifically ALT. Injection site reactions occur in 84% of patients and consist of pain, tenderness, erythema, pruritus, and local swelling. Flulike symptoms occur in 30% of patients and are usually noticed within 2 days after the injection, including pyrexia, myalgia, chills, arthralgia, fatigue, and malaise. Elevations in hepatic transaminases occurred in ~12% of patients, with 9% having an ALT three times or above the ULN. Hepatic steatosis has also been reported.

PLACE IN THERAPY

Mipomersen is indicated as an adjunct therapy to a low-fat diet and other lipid-lowering agents to reduce LDL-C, apo B, TC, and non-HDL in patients with HoFH.[166] Owing to the concern for hepatotoxicity, mipomersen is also available only through an REMS program. Although mipomersen has only been studied in combination with simvastatin and ezetimibe therapies, its use with other nonstatin lipid-lowering agents as well as in patients undergoing LDL-C apheresis is not recommended. The effect of mipomersen on CV morbidity and mortality is unknown. In addition,

the safety and efficacy of mipomersen has not been established in patients with hypercholesterolemia not secondary to HoFH. Maximum LDL-C reduction is usually seen after ~6 months of therapy.

DRUG INTERACTIONS

Secondary to the unique metabolism of mipomersen, there are no known clinically significant drug interactions. However, caution should be exercised when used with other medications known to have potential for hepatotoxicity (eg, isotretinoin, amiodarone, acetaminophen [>4 g/day for ≥3 days/week]), methotrexate, tetracyclines, and tamoxifen. If used in combination, more frequent monitoring of liver-related tests may be necessary.

CLINICAL PEARLS

Alcohol consumption should be limited to no more than 1 drink/day because it may increase hepatic fat and induce or exacerbate the risk of liver injury.

The recommended dose of mipomersen is 200 mg by SQ injections once a week.

If a dose is missed, the injection should be given at least 3 days from when the next weekly dose is due.

Mipomersen should be stored in the refrigerator but removed from the refrigerator and allowed to reach room temperature for at least 30 minutes before administration.

Injection sites include the abdomen, thigh area, or the outer area of upper arm.

Mipomersen should not be injected into any site that has injury to the skin, such as sunburn, rash, skin infections, inflammation, or active areas of psoriasis, or in areas with tattoos or scars.

A full liver panel to include ALT, AST, total bilirubin, and alkaline phosphatase should be obtained before therapy initiation.

Mipomersen is contraindicated in patients with moderate or severe hepatic impairment or active liver disease.

For the first year, liver-related tests at least an ALT and AST should be checked monthly.

After the first year of therapy, liver tests should be checked at least every 3 months.

Discontinue therapy if persistent or clinically significant elevations occur.

If transaminase elevations are accompanied by clinical symptoms of liver injury, increases in bilirubin by two times or above the ULN, or active liver disease, therapy should be discontinued.

Lipid levels should be monitored at least every 3 months for the first year.

Proprotein Convertase Subtilisin/Kexin Type 9 monoclonal Antibodies (PCSK9 mAb)

MECHANISM OF ACTION

PCSK9 is a member of the proprotein convertase family, which consists of nine members. PCSK9 is thought to play a critical role in modulating the number of LDL receptors on the surface of the hepatocyte and consequently the amount of LDL-C in the plasma. PCKS9 binds irreversibly to LDL receptors on the hepatocyte and is internalized into the liver cells. This prevents the LDL receptor from being recycled back to the cell surface and the LDL-R/PCSK9 complex is degraded along with the LDL-C. Monoclonal antibodies to PCKS9, or PCSK9 inhibitors, neutralize PCSK9 and prevent PCSK9-mediated LDL receptor degradation, allowing more LDL receptors to return back to the cell surface. An increase in the number of LDL receptors leads to enhanced clearance of LDL-C and thus lowers LDL-C levels (**Fig. 8-15**).[171,172]

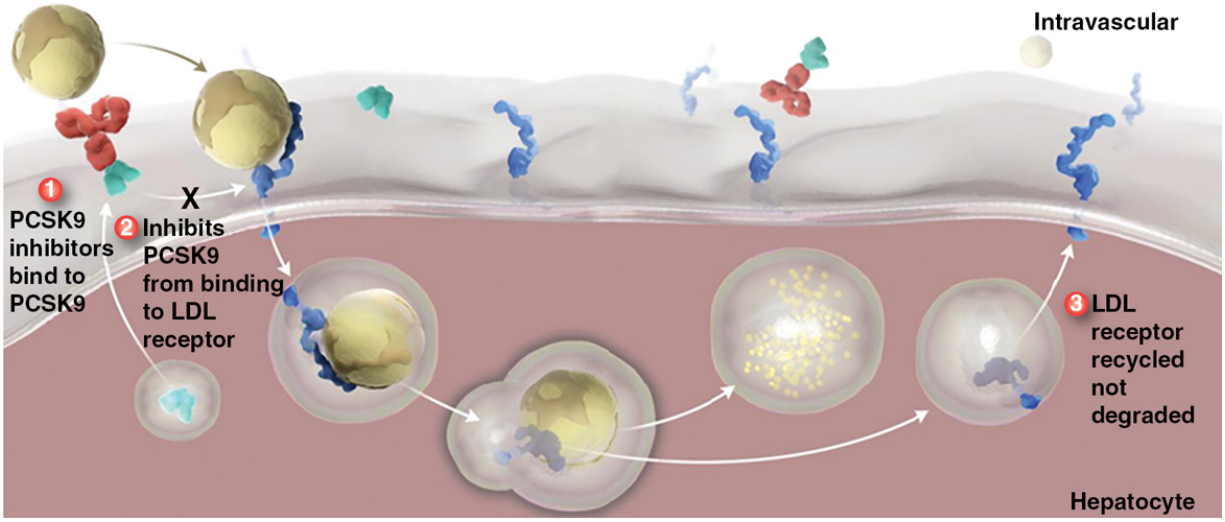


Figure 8-15 Mechanism of action of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. 1. PCSK9 inhibitors bind to PCSK9 made in the hepatocyte. 2. By binding to the PCSK9 receptor, PCKS9 inhibitors prevent PCSK9-mediated low-density lipoprotein (LDL) receptor degradation. 3. Secondary to reduce degradation, more LDL receptors are recycled back to the cell surface that subsequently leads to lower LDL-C levels. Used with permission of Amgen.

EFFICACY

These agents have been evaluated in patients with HeFH and HoFH and in patients with ASCVD who have been on maximally tolerated statin doses and require further LDL-C reduction.

The LAPLACE-2 (LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy) trial was a 12-week trial to evaluate the safety and efficacy of evolocumab in 2067 patients with primary hypercholesterolemia and mixed dyslipidemia.[173] The study included 296 patients with clinical ASCVD. Patients were randomized to a specific, open-label regimen of three different statin doses (atorvastatin 80 mg daily, rosuvastatin 40 mg daily, or simvastatin 40 mg daily) and either fixed-dose evolocumab 140 mg every 2 weeks, evolocumab 240 mg once a month, or placebo. The primary end point was change in baseline LDL-C at 12 weeks, with a secondary end point of percent of

patients achieving LDL-C <70 mg/day. The results showed that in patients already on either moderate- or high-intensity statin therapy and clinical ASCVD, evolocumab demonstrated an additional mean reduction in LDL-C of 71% for the twice-weekly dose and 63% for the once-monthly dose compared to placebo ($P < .0001$). In addition, 90% of evolocumab-treated patients achieved LDL-C <70 mg/dL. The Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES) was a randomized, double-blind, placebo-controlled 52-week trial comparing evolocumab versus placebo in 901 patients on background lipid-lowering therapy.[174] Background therapy included atorvastatin 80 mg with or without ezetimibe 10 mg daily. Of the entire study population, 139 patients had ASCVD. Evolocumab was administered 420 mg SQ once monthly. The results showed that in patients with ASCVD who received evolocumab, the mean percent LDL-C reduction was 54% ($P < .0001$). Alirocumab was evaluated in the COMBO study.[175] This was a multicenter, double-blind, placebo-controlled trial that randomly assigned patients to alirocumab or placebo in addition to maximally tolerated doses of statins with or without additional lipid-lowering therapy who required additional LDL-C lowering. The dose of alirocumab was 75 mg every 2 weeks. If additional LDL-C lowering was still needed at 12 weeks, the dose of alirocumab was increased to 150 mg every 2 weeks and continued for another 12 weeks. At 24 weeks, the mean reduction in LDL-C with alirocumab was 44% compared to 2% with placebo ($P < .0001$). A significant portion (84%) of the study population had ASCVD. After 12 weeks, the mean reduction in LDL-C from baseline was 45% versus 1% with placebo. Alirocumab has been evaluated in the Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial in 2341 patients at high risk for CHD.[176] Patients were randomly assigned alirocumab 150 mg twice weekly to placebo in addition to maximum tolerated statin therapy with or without additional lipid-lowering therapy. Patients with ASCVD composed 69% of the trial. At 24 weeks, the percent change in LDL-C reductions with alirocumab

compared to placebo was 58% ($P < .0001$). This reduction in LDL-C was sustained over a 78-week treatment period.

The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) was the first trial published to demonstrate reduction in CV outcomes with the addition of a PCSK9 inhibitor.[177] This was a randomized, double-blind, placebo-controlled trial that included 27,564 patients age 40 to 85 years with clinical ASCVD. Patients were included if they had ASCVD defined as either MI, nonhemorrhagic stroke, or symptomatic PAD. Study subjects were also required to have at least one major ASCVD risk factor or two minor risk factors. The minor risk factors were defined as a history of non–MI-related coronary revascularization, residual CAD with ≥40% stenosis in two or more large vessels, HDL-C <40 mg/dL for males and <50 mg/dL for females, hs-CRP >2 mg/L, LDL-C ≥130 mg/dL or non-HDL-C ≥160 mg/dL, or metabolic syndrome. Patients also had to have a fasting LDL-C level >70 mg/dL or a non–HDL-C levels ≥100 mg/dL after ≥4 weeks of stable dose of atorvastatin 20, 40, or 80 mg daily, with or without ezetimibe, and fasting TG ≤400 mg/dL. The median LDL-C at baseline was 92 mg/dL. Patients were randomized to receive evolocumab administered SQ at a dose of 140 mg every 2 weeks (or 420 mg monthly) or matching placebo. The median duration of therapy was 2.2 years. The results demonstrated that treatment with evolocumab significantly reduced the risk of the primary end point (composite of CV death, MI, stroke, hospitalization for UA, or coronary revascularization) (HR, 0.85; 95% CI, 0.79–0.92, $P < .001$) and the key secondary end point (CV death, MI, or stroke) (HR, 0.80; 95% CI, 0.73–0.88; $P < .001$). The degree of risk reduction in CV death, MI, or stroke increased over time, from 16% in the first year of follow-up to 25% after 1 year. In terms of LDL-C reduction, at 48 weeks, the mean LDL-C was reduced by 59% (mean 56 mg/dL). Approximately 87% of patients achieved an LDL-C of <70 mg/dL. In addition, 67% of patients had LDL-C levels <40 mg/dL, and 42% reached levels of <25 mg/dL. There was a slightly higher rate of injection site reactions in the patients receiving evolocumab compared with placebo (2.1% vs 1.6%).

The ODYSSEY Outcomes trial was a multicenter, double-blind, placebo-controlled trial that evaluated the effect of alirocumab on CV outcomes in 18,924 patients with a recent ACS (MI or UA within the past 1–12 months).[178] Additional inclusion criteria included an LDL-C ≥70 mg/dL, non–HDL-C ≥100 mg/dL, and apo B of ≥80 mg/dL. Mean baseline LDL-C was 92 mg/dL, and all patients were on background statin therapy. Patients were randomized in a 1:1 manner to receive alirocumab 75 mg SQ or placebo every 2 weeks. The median duration of follow-up was 2.8 years. The primary end point was a composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or UA requiring hospitalization. The primary end point occurred in 9.5% in the alirocumab group and in 11.1% in the placebo group (HR, 0.85; 95%, CI, 0.78–0.93; $P < .001$). The mean LDL-C achieved with alirocumab at 48 months was 53 mg/dL, equating to an average reduction of 54.7%. The results of this trial demonstrate that the benefit is likely a class effect and that obtaining dramatically low levels of LDL-C does not appear to result in adverse effects. However, longer term data will be needed to confirm these results.

Both alirocumab and evolocumab have been evaluated in patients with HeFH.[179–181] All patients in these studies were on maximally tolerated doses of statins. In the combined studies evaluating alirocumab, patients had an average baseline LDL-C of 141 mg/dL. Patients were treated for 12 weeks with alirocumab 75 mg every 2 weeks or placebo. At the end of the treatment period, the mean LDL-C reduction observed with alirocumab was 48%. As with other studies with alirocumab, if additional LDL-C lowering was needed, patients were given an additional 12 weeks of therapy with an increased dose of 150 mg every 2 weeks. Following an additional 12 weeks of treatment, the mean LDL-C reduction from baseline was 54% ($P < .0001$). Almost half (42%) of the study population received the higher dose. Evolocumab was evaluated in the patient population in the RUTHERFORD-2 trial.[181] Patients were randomized to receive 140 mg every 2 weeks of evolocumab, or 420 mg once monthly or placebo. The mean baseline LDL-C was 156 mg/dL, with 76% on high-intensity statin therapy. Following 12 weeks of therapy,

evolocumab reduced baseline LDL-C by 61% with twice-weekly dosing and 62% with monthly dosing ($P < .0001$).

Evolocumab has been studied in patients with HoFH in the Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities (TESLA Part B).[182] This was a multicenter, double-blind, randomized, placebo-controlled 12-week trial in 49 patients. Patients received 420 mg monthly of evolocumab or placebo. The mean LDL-C at baseline was 349 mg/dL. All patients were on either atorvastatin or rosuvastatin, with 92% also being on ezetimibe. Following 12 weeks of treatment with evolocumab, the mean decrease in LDL-C from baseline was 31% ($P < .0001$).

PHARMACOKINETICS/PHARMACODYNAMICS

Alirocumab and evolocumab are both human monoclonal immunoglobulin g2 (IGg2) antibodies and, therefore, must be administered via SQ injection to exert an effect. Maximum suppression of PCSK9 occurs in ~4 hours with evolocumab and 4 to 8 hours with alirocumab. Maximum serum concentrations reached in 3 to 4 days with evolocumab and 3 to 7 days with alirocumab. The volume of distribution for both agents is small; therefore, these agents are expected to stay in the extracellular space. Alirocumab is eliminated through degradation to small peptides and amino acids, whereas evolocumab is cleared based on its concentration. At low concentrations, it is cleared primarily through saturable binding to PCSK9, and at higher concentrations, it is eliminated via a nonsaturable proteolytic pathway. The half-life of alirocumab is 17 to 20 days and 11 to 17 days for evolocumab.

ADVERSE EFFECTS

The most common adverse effects reported in the 52 weeks study with evolocumab were nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. However, the difference in the incidence compared to placebo is relatively small. The most common injection site reactions were erythema, pain, and bruising. The most common adverse effect leading to

discontinuation was myalgia that occurred in 0.3% of evolocumab patients and 0% in those receiving placebo. In pooled studies, the types of adverse effects reported were relatively similar. Allergic reactions occurred in 5.1% of evolocumab-treated patients and 4.6% in those treated with placebo. Neurocognitive events were reported in less than 0.2% of patients. Hypersensitivity reactions such as rash and urticaria were also reported in 1% and 0.4%, respectively, with cases resulting in discontinuation of therapy. The adverse reactions reported with alirocumab were nasopharyngitis, injection site reactions, influenza, and urinary tract infection. The main adverse effects associated with discontinuation were allergic reactions (0.6% vs 0.2% for placebo) and elevated liver enzymes (0.3% vs <0.1% for placebo). Injection site reactions were similar to those reported with evolocumab. Neurocognitive events were reported in 0.8% of patients treated with alirocumab compared to 0.7% for placebo. Hypersensitivity reactions also occurred with alirocumab. However, hypersensitivity vasculitis as well as hypersensitivity reactions requiring hospitalizations were reported with alirocumab, but not with evolocumab. Neutralizing antibodies were detected in 1.2% of patients treated with alirocumab, and no cases were reported in patients taking evolocumab. However, the long-term consequences from developing neutralizing antibodies are currently unknown.

PLACE IN THERAPY

Both alirocumab and evolocumab are indicated as an adjunct to diet and maximally tolerated statin therapy in patients with HeFH or clinical ASCVD, who require additional reductions in LDL-C. These agents should be considered as add-on therapy to either patients already on statin therapy who need additional LDL-C lowering or in patients who are deemed statin intolerant.[100] Evolocumab is also indicated for use in combination with other lipid-lowering therapies including LDL apheresis in patients with HoFH who require additional lowering in LDL-C. Alirocumab is administered as a dose of 75 mg every 2 weeks and may be increased in 4 to 8 weeks to 150 mg every 2 weeks if additional LDL-C lowering is required. Evolocumab

is dosed at 140 mg every 2 weeks or 420 mg once monthly for HeFH and those with primary hypercholesterolemia with clinical ASCVD. In patients with HoFH, the dose is 420 mg once monthly. Alirocumab has only been studied in patients age older than 18 years, whereas evolocumab may be used in the adolescent population with HoFH ages 13 to 17 years. Neither agent requires a dose adjustment in patients with mild-to-moderate renal insufficiency. No data are available for patients with creatinine clearance (CrCl) <30 mL/min. Because these proteins do not rely upon the kidneys as a method of excretion, they can likely be used in patients with low CrCl, including those undergoing hemodialysis. However, the PCSK9 inhibitors have not been studied in this patient population. In addition, because they are large molecules, it is unlikely they would be removed by hemodialysis. No dose adjustment is necessary in patients with hepatic impairment.

Current guidelines recommend consideration for the addition of a PCSK9 in the following situations: (a) patients with established ASCVD who are judged to be at very high risk for recurrent events and LDL-C above the threshold of 70 mg/dL despite high-intensity or maximally tolerated statin therapy, (b) patients with severe primary hypercholesterolemia (LDL-C ≥190 mg/dL) with LDL-C above the threshold of 100 mg/dL on treatment with a statin plus ezetimibe, and (c) patients ages 40 to 75 years with a baseline LDL-C ≥220 mg/dL with LDL-C above the threshold of 130 mg/dL on statin and ezetimibe therapy.[5]

CLINICAL PEARLS

- Allow evolocumab injections to warm at room temperature for at least 30 minutes before use and alirocumab 30 to 40 minutes before use.
- Do not warm evolocumab by any other means than setting at room temperature (eg, rolling between hands).
- If you miss a dose of evolocumab and the time to next dose is >7 days, administer the dose. If <7 days, hold the dose and get back on usual schedule.

- Evolocumab and alirocumab may be injected into the thigh, abdomen, or the upper arm.
- Evolocumab can remain at room temperature but expires in 30 days.
- Alirocumab should not be left unrefrigerated for >24 hours.

Bempedoic Acid

MECHANISM OF ACTION

Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor. ACL is an enzyme that works upstream of 3-hydroxy-3-methyl-glutaryl-coenzyme reductase in the cholesterol biosynthesis pathway. Inhibition of ACL results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of LDL receptors.

EFFICACY

Several phase 3 trials, known as the CLEAR trials (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen), have evaluated the effects of bempedoic acid in patients at high CV risk as well as those with a history of intolerance to statin therapy.[183–185] CLEAR Serenity trial was a double-blind, placebo-controlled trial that evaluated the efficacy of bempedoic acid in patients with hypercholesterolemia and a history of intolerance to at least two statins.[183]A total of 345 patients were randomized to either bempedoic acid 180 mg or placebo once daily for 24 weeks. The primary end point was mean percent change in LDL-C from baseline to week 12. The mean baseline lipoproteins were a mean LDL-C of 157.6 mg/dL, non–HDL-C 192.6 mg/dL, TC 244.2 mg/dL, and apo B of 141.3 mg/dL. The results demonstrated a significant reduction in LDL-C with bempedoic acid compared to placebo (−23.6% vs −1.3%, $P < .001$). Significant reductions with bempedoic acid versus placebo were also observed for non–HDL-C (−17.9%), TC (−14.8%), and apo B (−15.0%) ($P < .001$). Overall, bempedoic acid was well

tolerated. Bempedoic acid offers a safe and effective oral therapeutic option for lipid lowering in patients who cannot tolerate statins.

The CLEAR Wisdom trial evaluated bempedoic acid versus placebo in 779 patients with ASCVD or HeFH, or both.[184] This was a double-blind, placebo-controlled trial in which patients were randomized to bempedoic acid 180 mg or placebo in addition to maximally tolerated statin therapy. The primary end point was percent change in LDL-C from baseline at 12 weeks, with a secondary end point of changes from baseline of other lipid parameters and biomarkers. The median lipoprotein parameters at baseline were an LDL-C of 120.4 mg/dL, non–HDL-C of 152 mg/dL, apo B of 117 mg/dL, TC 203 mg/dL, and hs-CRP of ~1.75 mg/L. Treatment with bempedoic acid for 12 weeks resulted in a significant reduction in LDL-C (15.1%) compared to placebo (2.4%; $P < .001$). Significant reduction in other lipid parameters were also observed with bempedoic acid: TC (−9.9% vs 1.3 %; $P < .001$), apo B (−9.3% vs 3.7%, $P < .001$), and non–HDL-C (−10.8% vs −2.3%, $P < .001$). Bempedoic acid demonstrated a positive benefit in lowering LDL-C in patients already taking statin therapy.

The CLEAR Harmony trial was the largest of these trials.[185] A total of 2230 patients with ASCVD and/or HeFH and an LDL-C ≥70 mg/dL were randomized to bempedoic acid 180 mg or placebo. The primary end point was overall safety, whereas the secondary endpoint was efficacy that was assessed by percent change in LDL-C from baseline to 12 weeks. The mean baseline LDL-C was 103 mg/dL. The results at week 12 demonstrated a mean reduction in LDL-C by 16.5% from baseline, 18.1 percentage points more than with placebo ($P < .001$). At weeks 24 and 52, bempedoic acid was associated with greater percent LDL-C lowering compared to placebo of 16.1% and −13.6%, respectively ($P < .001$). Although CV events were reported and the adjudicated major CV events occurred at a lower rate in the bempedoic acid group compared to placebo (4.6% and 5.7%, respectively), the trial was too short and underpowered to look at outcomes. However, CV outcomes trials are ongoing. In terms of safety, bempedoic acid was associated with more adverse events

leading to discontinuation (10.9% vs 7.1%, *P* = .005) as well as a higher incidence of gout (1.2% vs 0.3%, *P* = .03).

Bempedoic acid has also been evaluated in combination with ezetimibe in patients with clinical ASCVD or HeFH and baseline LDL-C ≥100 mg/dL, or those with multiple CV risk factors and an LDL-C ≥130 mg/dL. All were receiving maximum tolerated doses of statins, which could have included no statin treatment. The primary end point was a change in LDL-C at 12 weeks, with a mean LDL-C at baseline ranging from 145 to 154 mg/dL. The results demonstrated a significant reduction in LDL-C with the bempedoic acid/ezetimibe combination (−36.2%), compared to bempedoic acid alone (−17.2%) or ezetimibe monotherapy (−23.2%), *P* < .001 for all comparisons). As in other trials, significant reductions in other lipid parameters were also observed with the combination or either as monotherapy.

PHARMACOKINETICS/PHARMACODYNAMICS

Bempedoic acid is metabolized through acyl glucuronide and is converted to an active metabolite. Following oral administration, the drug reaches peak levels in ~3 hours and reaches steady state after 7 days. The mean half-life is 21 +/11 hours at steady state. When evaluated in patients with mild, moderate, or severe renal impairment, the AUC of bempedoic acid increased by 1.5-, 2.3-, and 2.4-fold, respectively. It is important to note that clinical trials did not include patients with severe renal impairment (eGFR <30 mL/min) or patients on hemodialysis. In patients with moderate hepatic impairment, a lower AUC was observed in those taking bempedoic acid; however, this is not considered to be clinically significant. There are no data in patients with severe hepatic impairment.

ADVERSE EFFECTS

Increased uric acid levels were more common in patients taking bempedoic acid. The proposed mechanism is due to inhibition of tubular OAT2 by this agent, resulting in increased uric acid levels. The increase usually occurs within the first 4 weeks of treatment.

This increase in uric acid may increase the risk of gout, with a higher incidence reported in those with a prior history. Patients should be monitoring for gout symptoms upon initiation of therapy.

There is also a risk of tendon rupture that has been reported. In clinical trials, the incidence was 0.5% for bempedoic acid compared to placebo (0%). Patients who appear to be at higher risk are those over the age of 60, taking corticosteroids, fluoroquinolone antimicrobials, renal failure, and those with a prior history of tendon disorders.

PLACE IN THERAPY

Bempedoic acid is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional LDL-C lowering. Current guidelines have not yet been updated to provide clinicians with where this agent fits into therapy. However, until results of CV outcomes are available, its role is likely limited to patients who are deemed high risk and not able to achieve their target LDL-C despite treatment with other agents.

CLINICAL PEARLS

- Limit the dose of simvastatin to 20 mg when combined with bempedoic acid.
- Limit the dose of pravastatin to 40 mg when combined with bempedoic acid.
- May be administered with or without food
- Currently available as a combination tablet containing ezetimibe
- Avoid use in patients with a history of tendon rupture.

Inclisiran

MECHANISM OF ACTION

Inclisiran is a first in class small interfering RNA (siRNA) agent designed to lower LDL-C. Following uptake into the hepatocytes,

inclisiran binds to liver-expressed asialoglycoprotein receptors. Inclisiran also contains a guide strand, and therefore once in the hepatocyte, it is loaded into the RNA-induced silencing complex (RISC) and inhibits translation of the PCSK9 protein. The end result is a reduction in LDL-C secondary to an increase in LDL receptor density and increase in LDL-C uptake and clearance.

EFFICACY

Inclisiran has been evaluated in a number of trials, including ORION I.[186] This was a placebo-controlled, double-blind, randomized phase 2, multiple-ascending-dose trial that evaluated the efficacy of inclisiran in 501 patients at high risk for ASCVD. All patients were on maximum tolerated doses of statins and subsequently randomized to either a single dose or double dose of inclisiran or placebo. The primary end point was the change from baseline in LDL-C. At the end of the study period of 180 days, inclisiran demonstrated a dose-dependent reduction in LDL-C with mean reductions of 41.9% following a single dose of inclisiran compared to a 2.1% increase with placebo and a 52.5% reduction after the two-dose regimen for inclisiran compared to a 1.8% increase for placebo ($P < .001$). ORION 10 and ORION 11 and two phase 3 trials evaluated the efficacy of inclisiran in patients with ASCVD or an ASCVD risk equivalent with elevated LDL-C (≥70 mg/dL in ORION 10 and ≥100 mg/dL in ORION 11).[187] Patients were also required to be on maximum tolerated statin therapy for at least 30 days. A total of 3178 patients were randomized 1:1 to receive either 284 mg of inclisiran administered by SQ injection or placebo. Doses were administered on days 1, 90, and then every 6 months for up to 540 days. The co-primary end points in each trial were the placebo-corrected percentage change in LDL-C from baseline to day 510 as well as time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540. The results demonstrated a mean reduction in LDL-C at day of 52.3% for inclisiran in the ORION 10 trial and 49.9% in the ORION 11 trial ($P < .001$). These data suggest that administering inclisiran once every 6 months will provide a sustained

reduction in LDL-C. To date, all trials evaluating inclisiran have demonstrated significant reductions in LDL-C across a variety of patient populations, all of whom were on maximum tolerated doses of statin therapy.

PHARMACOKINETICS/PHARMACODYNAMICS

Inclisiran is administered via subcutaneous injection at a dose of 284 mg initially, then repeated at 3 months, followed by every 6 months thereafter. After a single subcutaneous dose, the volume of distribution is approximately 5 L, with a half-life of 9 hours.[188] Inclisiran is not a substrate for CYP450 or transporters and is primarily metabolized by nucleases to shorter nucleotides. Although no formal drug-drug interaction studies have been conducted, due to the nature of its metabolism, no clinical significant drug interactions are anticipated. Approximately 16% undergoes renal elimination and no dose adjustments are needed in patients with mild-to-severe renal function. No data is available regarding use in patients with end stage renal disease. No dose adjustment are needed in patients with mild-to-moderate hepatic dysfunction, however, inclisiran has not been studied in patients with severe hepatic impairment.

ADVERSE EFFECTS

The adverse effects attributed to inclisiran in clinical trials were relatively minor with injection site reactions being the most common. Other adverse effects that occurred with $\geq$3% incidence included arthralgia, diarrhea, dyspnea, urinary tract infection, pain in extremity, and bronchitis.[186,187]

PLACE IN THERAPY

Inclisiran recently received FDA approval as an adjunct to diet in patients with ASCVD and heterozygous FH with elevated LDL-C despite maximally tolerated statin doses. Based on the trial results, this agent shows potential promise as an additional agent in our armamentarium to lower LDL-C. However, its overall role in clinical practice will be further defined based on the CV outcomes trial

ORION-4 that is currently underway. This trial will evaluate the CV outcomes with inclisiran at 180 sites in 15,000 patients with ASCVD.[189]

CLINICAL PEARLS

- The medication should be given initially then an additional dose given 3 months later, followed by every 6 months
- Inclisiran should be discontinued once pregnancy is recognized
- No data in the pediatric population currently available

Evinacumab

MECHANISM OF ACTION

Evinacumab is a recombinant human IgG4 monoclonal antibody that binds to and inhibits angiopoietin life protein 3 (ANGPTL3). By blocking ANGTPL3, the catalytic activity of LPL and endothelial lipase is disinhibited, resulting in a reduction in TGs, LDL-C, and non–HDL-C.[190] The reductions in LDL-C occur independently of the presence of LDL receptor. This is likely due to the promotion of VLDL processing and upstream clearance of LDL formation, secondary to the inhibition of endothelial lipase activity.[191]

EFFICACY

The Evinacumab Lipid Studies in Patients with Homozygous Familial Hypercholesterolemia (ELIPSE HoFH) trial was a placebo-controlled study to evaluate evinacumab in patients with HoFH.[192] A total of 65 patients were randomized to receive either evinacumab administered via intravenous (IV) infusion at a dose of 15 mg/kg every 4 weeks or placebo. Of note, 53 of the patients enrolled had a genetically confirmed diagnosis of HoFH. The mean baseline LDL-C was 255.2 mg/dL. All patients were receiving background lipid-lowering therapy. Of these, 94% receiving statin therapy, of which 77% were high intensity, 77% were receiving a PCSK9 inhibitor, 75% ezetimibe, 25% lomitapide, and 34% were undergoing apheresis. The primary outcome was the percent change in LDL-C from baseline to week 24

of treatment.[192] The results demonstrated a significant 47.1% reduction in LDL-C in those treated with evinacumab compared to a 1.9% increase in the placebo group ($P < .001$), a mean difference of 49%. With regard to the LDL-C reduction, in patients treated with evinacumab, 47% achieved an LDL-C of <100 mg/dL, with the majority (56%) achieving at least a 50% reduction from baseline. Reductions in other lipoprotein parameters including apo B (41.4%), non–HDL-C (49.7%), and TC (47.4%) ($P < .001$) were also observed.[192]

There are additional trials that are ongoing to further evaluate the efficacy of evinacumab in various patient populations, including patients with HeFH or non-HeFH with a history of ASCVD; those with persistent hypercholesterolemia (LDL-C ≥70 mg/dL) with clinical ASCVD, or ≥100 mg/dL without clinical ASCVD, HoFH, or hypertriglyceridemia; and in the pediatric patient population (ages 5−11 years with HoFH).

PHARMACOKINETICS/PHARMACODYNAMICS

Evinacumab is administered by IV injection at a dose of 15 mg/kg every 4 weeks and reaches steady-state concentration after 4 doses. The volume of distribution is ~4.8 L, and the half-life is dependent upon serum concentration and is, therefore, variable.[190] Based on pharmacokinetic analysis, the time for serum concentrations of evinacumab to fall below the lower limit of quantification is ~19 weeks following the last steady-state dose.[190] The exact metabolic pathway of metabolism for evinacumab has not been fully elucidated, however; but most likely, it is degraded into small peptides and amino acids via catabolic pathways.[190,193] Evinacumab does not undergo renal excretion with no impact on concentrations in patients with mild-to-moderate renal insufficiency. There are no data on the use of evinacumab in patients with severe renal impairment or in patients with hepatic impairment.

ADVERSE EFFECTS

Adverse effects observed in clinical trials with evinacumab were minimal and rarely led to discontinuation of therapy. The most common adverse effects reported (occurring in >3% of patients) and with greater frequency than placebo included nasopharyngitis, flulike illness, dizziness, nausea, asthenia, pain in extremity, and rhinorrhea.

PLACE IN THERAPY

Evinacumab has been approved by the FDA for use in the treatment of HoFH for adults and pediatric patients age 12 years or older. However, these indications will likely expand based on the results of ongoing clinical trials. Currently, in the absence of CV outcomes data, the use of evinacumab in clinical practice should be reserved as an adjunctive treatment option in patients who require additional LDL-C lowering despite being optimized on cholesterol-lowering therapies that have demonstrated benefit.

CLINICAL PEARLS

- The medication should be given at 4-week intervals.
- A negative pregnancy test should be confirmed before therapy initiation.
- Birth control should be utilized for at least 5 months following last dose of evinacumab.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American Diabetes Association. 2015 standards of diabetes care. *Diabetes Care*. 2015;38(suppl 1):S49–S57. doi:10.2337/dc15-S011 (61)

Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51:1512–1524. doi:10.1016/j.jacc.2008.02.034 (21)

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24): 3168–3209. (5)

Hopkins PN, Toth PP, Ballantyne CM, et al. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5:S9–S17. (25)

Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. *J Clin Lipidol*. 2015;9:129–169. (17)

Jacobson TA, Maki KC, Orringer CE, et al. National lipid association patient-centered recommendations for management of dyslipidemia: part 2. *J Clin Lipidol*. 2015;9(Suppl 6):S1–S122. doi:10.1016/j.jacl.2015.09. 002 (60)

Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int*. 2013;3:259–305. (62)

McKenney JM, Davidson MH, Jacobson TA, Guyton JR, National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association statin safety assessment task force. *Am J Cardiol*. 2006;97:S89–S94. (93)

COMPLETE REFERENCES CHAPTER 8 DYSLIPIDEMIAS, ATHEROSCLEROSIS, AND CORONARY HEART DISEASE

1. Berliner JA, Navab M, Fogelman AM, et al. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation*. 1995;91:2488–2496.
2. Cholesterol Treatment Trialists' Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease:

meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–590.

3. Buchwald H, Varco RL, Boen JR, et al. Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. *Arch Intern Med*. 1998;158:1253–1261.
4. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk. *Circulation*. 2014;129:S76–S99. doi:10.1161/01.cir.0000437740.48606.d1
5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168–3209.
6. Jurevics H, Hostettler J, Barrett C, Morell P, Toews AD. Diurnal and dietary-induced changes in cholesterol synthesis correlate with levels of mRNA for HMG-CoA reductase. *J Lipid Res*. 2000;41:1048–1054.
7. Nissen SE, Tuzcu EM, Brewer HB, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis [published correction appears in *N Engl J Med*. 2006;355:638]. *N Engl J Med*. 2006;354:1253–1263.
8. Schaefer EJ, Eisenberg S, Levy RI. Lipoprotein apoprotein metabolism. *J Lipid Res*. 1978;19:667.
9. Genest J. Lipoprotein disorders and cardiovascular risk. *J Inherit Metab Dis*. 2003;26(2):267–287.
10. Bays H, Stein EA. Pharmacotherapy for dyslipidemia—current therapies and future agents. *Expert Opin Pharmacother*. 2003;4(11):1901–1938.
11. Das G, Rees A. Microsomal triglyceride transfer protein inhibition: a novel treatment for lowering plasma cholesterol. *Curr Opin Lipidol*. 2014;25:471–473.
12. Naik R, Obiang-Obounou BW, Kim M, Choi Y, Lee HS, Lee K. Therapeutic strategies for metabolic diseases: small-molecule diacylglycerol acyltransferase (DGAT) inhibitors. *ChemMedChem*. 2014;9:2410–2424. doi:10.1002/cmdc.201402069
13. Kwiterovich PO Jr. The metabolic pathways of high-density lipoprotein, low-density lipoprotein, and triglycerides: a current review. *Am J Cardiol*. 2000;86(12A):5L–10L.
14. Kingwell BA, Chapman MJ, Kontush A, Miller NE. HDL-targeted therapies: progress, failures and future. *Nat Rev Drug Discov*. 2014;13:445–464. doi:10.1038/nrd4279
15. Hodis HN, Mack WJ. Triglyceride-rich lipoproteins and the progression of coronary artery disease. *Curr Opin Lipidol*. 1995;6:209–214.

16. Davidson MH, Ballantyne CM, Jacobson TA, et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists. *J Clin Lipidol*. 2011;5:338–367.
17. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. *J Clin Lipidol*. 2015;9:129–169.
18. Morris PB, Ballantyne CM, Birtcher KK, et al. Review of clinical practice guidelines for the management of LDL-related risk. *J Am Coll Cardiol*. 2014;64:196–206.
19. Schmitz G, Brüning T, Williamson E, Nowicka G, et al. The role of HDL in reverse cholesterol transport and its disturbances in Tangier disease and HDL deficiency with xanthomas. *Eur Heart J*. 1990;11(suppl E):197–211.
20. McKenney JM. Understanding PCSK9 and anti-PCSK9 therapies. *J Clin Lipidol*. 2014;9:170–186.
21. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51:1512–1524. doi:10.1016/j.jacc.2008.02.034
22. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease risk. *Lancet*. 2014;384:626–635.
23. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science*. 1986;232:34–47.
24. Mabuchi H, Koizumi J, Shimizu M, Takeda R. Development of coronary heart disease in familial hypercholesterolemia. *Circulation*. 1989;79:225–232.
25. Hopkins PN, Toth PP, Ballantyne CM, et al. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5:S9–S17.
26. Soria LF, Ludwig EH, Clarke HR, Vega GL, Grundy SM, McCarthy BJ. Association between a specific apolipoprotein B mutation and familial defective apolipoprotein B-100. *Proc Natl Acad Sci U S A*. 1989;86:587–591.
27. Vega GL, Grundy SM. In vivo evidence for reduced binding of low-density lipoproteins to receptors as a cause of primary moderate hypercholesterolemia. *J Clin Invest*. 1986;78:1410–1414.
28. Whitfield AJ, Barrett PHR, van Bockxmeer FM, Burnett JR. Lipid disorders and mutations in the APOB gene. *Clin Chem*. 2004;50:1725–1732.
29. Lambert G. Unravelling the functional significance of PCSK9. *Curr Opin Lipidol*. 2007;18:304–309.
30. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *J Am Coll Cardiol*. 2015;65:2638–2651. doi:10.1016/j.jacc.2015.05.001

31. van Greevenbroek MM, Stalenhoef AF, de Graaf J, Brouwers MC. Familial combined hyperlipidemia: from molecular insights to tailored therapy. *Curr Opin Lipidol*. 2014;25:176–182.
32. Hopkins PN, Brinton EA, Nanjee MN. Hyperlipoproteinemia type 3: the forgotten phenotype. *Curr Atheroscler Rep*. 2014;16:440. doi:10.1007/s11883-014-0440-2
33. Brewer HB Jr, Zech LA, Gregg RE, Schwartz D, Schaefer EJ. NIH conference. Type III hyperlipoproteinemia: diagnosis, molecular defects, pathology, and treatment. *Ann Intern Med*. 1983;98:623–640.
34. Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2014;2:655–666.
35. Rader DJ, deGoma EM. Approach to the patient with extremely low HDL-cholesterol. *J Clin Endocrinol Metab*. 2012;97:3399–3407. doi:10.1210/jc.2012-2185
36. Rader DJ, Hovingh GK. HDL and cardiovascular disease. *Lancet*. 2014;384:618–625.
37. Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:1490–1500.
38. Jacobs D, Blackburn H, Higgins M, et al. Report of the conference on low blood cholesterol: mortality associations. *Circulation*. 1992;86:1046–1060.
39. Castelli WP. Epidemiology of coronary heart disease: the Framingham study. *Am J Med*. 1984;76:4–12.
40. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation*. 1989;79:8–15.
41. Reardon MF, Nestel PJ, Craig IH, Harper RW. Lipoprotein predictors of the severity of coronary artery disease in men and women. *Circulation*. 1985;71:881–888.
42. Steiner G, Schwartz L, Shumak S, Poapst M. The association of increased levels of intermediate-density lipoproteins with smoking and with coronary heart disease. *Circulation*. 1987;75:124–130.
43. Grundy SM. Small LDL, atherogenic dyslipidemia, and the metabolic syndrome. *Circulation*. 1997;95:1–4.
44. Grundy SM. Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. *Am J Cardiol*. 1998;81(4A):18B–25B.
45. Do R, Willer CJ, Schmidt EM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet*. 2013;45:1345–1352. doi:10.1038/ng.2795
46. Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. *J Clin Gastroenterol*. 2014;48:195–203.

47. Tabas I, Williams KJ, Borén J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation*. 2007;116:1832–1844.
48. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modifications of low-density lipoprotein that increases its atherogenicity. *N Engl J Med*. 1989;320:915–924.
49. Davies MJ, Krikler DM, Katz D. Atherosclerosis: inhibition or regression as therapeutic possibilities. *Br Heart J*. 1991;65:302–310.
50. Faggiotto A, Ross R, Harker L. Studies of hypercholesterolemia in the nonhuman primate. I. Changes that lead to fatty streak formation. *Arteriosclerosis*. 1984;4:323–340.
51. Witztum JL, Steinberg D. Role of oxidized low-density lipoprotein in atherogenesis. *J Clin Invest*. 1991;88:1785–1792.
52. Ross R, Agius L. The process of atherogenesis: cellular and molecular interaction: from experimental animal models to humans. *Diabetologia.* 1992;35(Suppl 2):S34.
53. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med*. 1999;340:115–126.
54. Libby P. Molecular bases of the acute coronary syndromes. *Circulation*. 1995;91:2844–2850.
55. Fuster V, Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and acute coronary syndromes. *N Engl J Med*. 1992;326:242–250.
56. Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density-lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310(19):2061–2068.
57. Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011;5:105–113.
58. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—implications for LDL management. *J Clin Lipidol*. 2007;1:583–592.
59. de Nijs T, Sniderman A, de Graaf J. ApoB versus non-HDL-cholesterol: diagnosis and cardiovascular risk management. *Crit Rev Clin Lab Sci*. 2013;50:163–171. doi:10.3109/10408363.2013.847897
60. Jacobson TA, Maki KC, Orringer CE, et al. National lipid association patient-centered recommendations for management of dyslipidemia: part 2. *J Clin Lipidol*. 2015;9(suppl 6):S1–S122. doi:10.1016/j.jacl.2015.09.002
61. American Diabetes Association. 2015 standards of diabetes care. *Diabetes Care*. 2015;38(suppl 1):S49–S57. doi:10.2337/dc15-S011
62. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int*. 2013;3:259–305.

63. Chong PH. An overview of lipid management with HMG-CoA reductase inhibitors. *Consult Pharm*. 1998;4:399–420.
64. Grundy SM, Vega GL. Influence of mevinolin on metabolism of low density lipoproteins in primary moderate hypercholesterolemia. *J Lipid Res*. 1985;26:1464–1475.
65. Aguilar-Salinas CA, Barrett H, Schonfeld G. Metabolic modes of action of the statins in the hyperlipoproteinemias. *Atherosclerosis*. 1998;141:203–207.
66. Colosimo RJ, Nunn-Thompson C. HMG-CoA reductase inhibitors. *P&T*. 1993;65:21–31.
67. McEvoy GK, ed. HMG-CoA reductase inhibitors: general statement. In: *AHFS Drug Information*. American Society of Health-System Pharmacists; 2001:1705–1717.
68. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383–1389.
69. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335(14):1001–1009.
70. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339(19):1349–1357.
71. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352(14):1425–1435.
72. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294(19):2437–2445.
73. Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
74. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
75. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711–1718.
76. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin

versus Revascularization Treatment Investigators. *N Engl J Med*. 1999;341:70–76.
77. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350(15):1495–1504.
78. Bavry AA, Kumbhani DJ, Rassi AN, et al. Benefit of early statin therapy during acute coronary syndromes: a meta-analysis. Presented at Society for Cardiovascular Angiography and Interventions (SCAI) 29th Annual Scientific Sessions; May 10–13, 2006; Chicago, IL.
79. Heeschen C, Hamm CW, Laufs U, et al. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation*. 2002;105:1446–1452.
80. Spencer FA, Fonarow GC, Frederick PD, et al. Early withdrawal of statin therapy in patients with non-ST-segment elevation myocardial infarction: national registry of myocardial infarction. *Arch Intern Med*. 2004;164:2162–2168.
81. Simvastatin (Zocor). Prescribing information. Merck & Co., Inc; October 2012.
82. Pravastatin (Pravachol). Prescribing information. Bristol-Myers Squibb; October 2012.
83. Lovastatin (Mevacor). Prescribing information. Merck & Co., Inc; October 2012.
84. Atorvastatin (Lipitor). Prescribing information. Pfizer; October 2012.
85. Fluvastatin sodium (Lescol, Lescol XL). Prescribing information. Novartis Pharmaceuticals Corporation; February 2012.
86. Rosuvastatin (Crestor). Prescribing information. AstraZeneca Pharmaceuticals; October 2012.
87. Pitavastatin (Livalo). Prescribing information. Kowa Pharmaceuticals; October 2012.
88. Lovastatin extended-release tablets (Altoprev). Prescribing information. Watson Laboratories; 2002.
89. Hunninghake DB, Mellies MJ, Goldberg AC, et al. Efficacy and safety of pravastatin in patients with primary hypercholesterolemia. II: once-daily versus twice-daily dosing. *Atherosclerosis*. 1990;85(2–3):219–227.
90. Hunninghake DB, Knopp RH, Schonfeld G, et al. Efficacy and safety of pravastatin in patients with primary hypercholesterolemia. I: a dose-response study. *Atherosclerosis*. 1990;85:81–89.
91. Dujovne CA, Chremos AN, Pool JL, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. IV: additional perspectives on the tolerability of lovastatin. *Am J Med*. 1991;91(1B):25S–30S.
92. Cohen JD, Brinton EA, Ito MK, et al. Understanding statin use in America and Gaps in Patient Education (USAGE): An internet-based survey of 10,138

current and former statin users. Journal of Clinical Lipidology. 2012;6(3):208-215.

93. McKenney JM, Davidson MH, Jacobson TA, Guyton JR, National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association statin safety assessment task force. *Am J Cardiol*. 2006;97:S89–S94.
94. Backes JM, Moriarty PM, Ruisinger JF, Gibson CA. Effects of once weekly rosuvastatin among patients with a prior statin intolerance. *Am J Cardiol*. 2007;100:554–555.
95. Law MR, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol*. 2006;97(8A):52C–60C.
96. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet*. 2010;376:1916–1922.
97. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports review of the literature. *Pharmacotherapy*. 2003;23:871–880.
98. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet*. 2002;360:1623–1630.
99. Brass LM, Alberts MJ, Sparks L, et al. An assessment of statin safety by neurologists. *Am J Cardiol*. 2006;97(8A):86C–88C.
100. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC Expert Consensus Decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. A report of the American College of Cardiology Task Force on expert consensus decision pathways. *J Am Coll Cardiol*. 2017;70(14):1785–1822.
101. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–742.
102. Preiss D, Seshasai SRK, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305:2556–2564.
103. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333(20):1301–1307.
104. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279(20):1615–1622.

105. Davignon J. The cardioprotective effects of statins. *Curr Atheroscler Rep*. 2004;6:27–35.
106. Ito MK. Effects of extensive and poor gastrointestinal metabolism on the pharmacodynamics of pravastatin. *J Clin Pharmacol*. 1998;38:331–336.
107. Backman JT, Kyrklund C, Kivistö KT, Wang JS, Neuvonen PJ. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther*. 2000;68:122–129.
108. Kyrklund C, Backman JT, Kivistö KT, Neuvonen M, Laitila J, Neuvonen PJ. Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther*. 2001;69:340–345.
109. Whitfield LR, Porcari AR, Alvey C, Abel R, Bullen W, Hartman D. Effect of gemfibrozil and fenofibrate on the pharmacokinetics of atorvastatin. *J Clin Pharmacol*. 2011;51:378–388.
110. Backman JT, Luurila H, Neuvonen M, Neuvonen PJ. Rifampin markedly decreased and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther*. 2005;78:154–167.
111. Kyrklund C, Backman JT, Neuvonen M, Neuvonen PJ. Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther*. 2003;73:538–544.
112. Schneck DW, Birmingham BK, Zalikowski JA, et al. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther*. 2004;75:455–463.
113. Bergman E, Matsson EM, Hedeland M, Bondesson U, Knutson L, Lennernäs H. Effect of a single gemfibrozil dose on the pharmacokinetics of rosuvastatin in bile and plasma in healthy volunteers. *J Clin Pharmacol*. 2010;50:1039–1049.
114. Mathew P, Cuddy T, Tracewell WG, Salazar D. An open-label study on the pharmacokinetics (PK) of pitavastatin (NK-104) when administered concomitantly with fenofibrate or gemfibrozil in healthy volunteers. *Clin Pharmacol Ther*. 2004;75:P33.
115. Noe J, Portmann R, Brun ME, Funk C. Substrate-dependent drug-drug interactions between gemfibrozil, fluvastatin and other organic anion-transporting peptide (OATP) substrates on OATP1B1, OATP2B1, and OATP1B3. *Drug Metab Dispos*. 2007;35:1308–1314.
116. Spence JD, Munoz CE, Hendricks L, Latchinian L, Khouri HE. Pharmacokinetics of the combination of fluvastatin and gemfibrozil. *Am J Cardiol*. 1995;76:80A–83A.
117. Wiggins BS, Saseen JJ, Morris PB. Gemfibrozil in combination with statins—is it really contraindicated? *Curr Atheroscler Rep*. 2016;18(4):18.
118. Wiggins BS, Saseen JJ, Page RL 2nd. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2016;134(21):e468–e495.

119. Sudhop T, Lütjohann D, Kodal A, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation*. 2002;106:1943–1948.
120. Ezetimibe (Zetia). Prescribing information. Merck & Co. Inc.; June 2012.
121. Kastelein JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358:1431–1443.
122. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet*. 2001;357:577–581.
123. de Sauvage Nolting PR, de Groot E, Zwinderman AH, Buirma RJ, Trip MD, Kastelein JJ. Regression of carotid and femoral artery intima-media thickness in familial hyper-cholesterolemia. *Arch Intern Med*. 2003;163:1837–1841.
124. Avellone G, Di Garbo V, Guarnotta V, et al. Efficacy and safety of long-term ezetimibe/simvastatin treatment in patients with familial hyper-cholesterolemia. *Int Angiol*. 2010;29:514–524.
125. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–1356.
126. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
127. Bays HE, Moore PB, Drehobl MA, et al. Ezetimibe Study Group. Effectiveness and tolerability of ezetimibe in patients with primary hyper-cholesterolemia: pooled analysis of two phase II studies. *Clin Ther*. 2001;23:1209–1230.
128. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol*. 2002;40:2125–2134.
129. Berger J, Moller DE. The mechanisms of action of PPARs. *Annu Rev Med*. 2002;53:409–435.
130. Grundy SM, Vega GL. Fibric acids: effects on lipids and lipoprotein metabolism. *Am J Med*. 1987;83(5B):9–20.
131. W.H.O. cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. Report of the Committee of Principal Investigators. *Lancet*. 1980;2:379–385.
132. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. *Br Heart J*. 1978;40:1069–1118.
133. Frick MH, Haapa K, Heinonen OP, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety

of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237–1245.

134. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341:410–418.
135. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial [published corrections appear in *Lancet.* 2006;368:1415]. *Lancet*. 2005;366:1849–1861.
136. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet*. 2001;357:905–910.
137. The ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus [published correction appears in *N Engl J Med.* 2010;362:1748]. *N Engl J Med*. 2010;362:1563–1574.
138. Fenofibrate (TriCor). Prescribing information. Abbott Laboratories; September 2011.
139. Fenofibrate (Lipofen). Prescribing information. Kowa Pharmaceuticals; October 2011.
140. Fenofibrate (Antara). Prescribing information. Lupin Pharma; August 2012.
141. Fenofibrate (Fenoglide). Prescribing information. Shore Therapeutics, Inc.; October 2010.
142. Fenofibrate (Lofibra). Prescribing information. Gate Pharmaceuticals; January 2010.
143. Fenofibrate (Triglide). Prescribing information. Shionogi Pharma, Inc.; January 2012.
144. Fenofibric Acid (Trilipix). Prescribing information. AbbVie Inc.; 2015.
145. Fenofibric acid (Fibricor). Prescribing information. AR Scientific, Inc.; 2014.
146. Gemfibrozil (Lopid). Prescribing information. Parke-Davis; September 2012.
147. Prueksaritanont T, Zhao JJ, Ma B, et al. Mechanistic studies on metabolic interactions between gemfibrozil and statins. *J Pharmacol Exp Ther*. 2002;301:1042–1051.
148. Omega-3-acid ethyl esters 90 (Lovaza). Prescribing information. GlaxoSmithKline; August 2012.
149. Icosapent ethyl (Vascepa). Prescribing information. Catalent Pharma Solutions, LLC; September 2012.
150. Omega-3-carboxylic acids (Epanova). Prescribing information. AstraZeneca Pharmaceuticals; 2014.
151. Dietary supplementation with omega-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico

[published corrections appear in *Lancet.* 2007;369:106]. *Lancet*. 1999;354:447–455.

152. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis [published correction appears in *Lancet*. 2007;370:220]. *Lancet*. 2007;369:1090–1098.
153. Rauch B, Schiele R, Schneider S, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation*. 2010;122:2152–2159.
154. Clinicaltrials.gov. Outcomes study to assess STatin Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs with Hypertriglyceridemia (STRENGTH). Accessed October 2020. http://clinicaltrials.gov/ct2/show/NCT02104817?term=epanova&rank=5
155. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22.
156. Orringer CE, Jacobson TA, Maki KC. National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. *J Clin Lipid*. 2019;13(6):860–872.
157. American Diabetes Association. 10. Cardiovascular disease and risk management: *standards of medical care in diabetes*—2019. http://care.diabetesjournals.org/content/42/Supplement_1/S103. https://www.diabetes.org/newsroom/press-releases/2019/ada-issues-critical-updates-to-2019-standards-of-care
158. Einarsson K, Ericsson S, Ewerth S, et al. Bile acid sequestrants: mechanisms of action on bile acid and cholesterol metabolism. *Eur J Clin Pharmacol*. 1991;40(suppl 1):S53–S58.
159. Cholestyramine (Questran). Prescribing information. Bristol-Myers Squibb; 1997.
160. Colestipol (Colestid). Prescribing information. Pharmacia & Upjohn; June 2006.
161. Colesevelam hydrochloride (Welchol). Prescribing information. Daiichi Sankyo; June 2012.
162. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;25(3):351–364.
163. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251:365–374.
164. Lomitapide (Juxtapid). Prescribing information. Aegerion Pharmaceuticals; December 2012.

165. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013;381(9860):40–46.
166. Mipomersen (Kynamro). Prescribing information. Genzyme Corporation; 2013.
167. Crooke ST. *Antisense Drug Technology. Principles, Strategies, and Applications*. 2nd ed. CRC Press; 2008.
168. Dias N, Stein CA. Antisense oligonucleotides: basic concepts and mechanisms. *Mol Cancer Ther*. 2002;1:347–355.
169. McGowan MP, Tardif J-C, Ceska R, et al. Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. *PloS One*. 2012;7(11):e49006.
170. Thomas GS, Cromwell WC, Ali S, Chin W, Flaim JD, Davidson M. Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2013;62(23):2178–2184.
171. Evolocumab (Repatha). Prescribing information. Amgen Pharmaceuticals; August 2015.
172. Alirocumab (Praluent). Prescribing information. Regeneron Pharmaceuticals; July 2015.
173. Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of Evolocumab or Ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia. The LAPLACE-2 Randomized Clinical Trial. *JAMA*. 2014;311(18):1870–1882.
174. Blom DJ, Hala T, Bolognese M, et al. A 52-weeks placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med*. 2014;370(19):1809–1819.
175. Colhoun HM, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. *BMC Cardiovasc Disord*. 2014;14:121–131.
176. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
177. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713–1722.
178. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107.

179. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy. The ODYSSEY COMBO 1 study. *Am Heart J*. 2015;169(6):906–915.
180. Kastelein JP, Ginsberg HN, Langslet G, et al. ODYSSEY FH1 and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2015;36(43):2996–3003.
181. Raal FJ, Stein EA, Dufour R, et al. PCKS9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;385:331–340.
182. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomized double-blind, placebo-controlled trial. *Lancet*. 2015;385:341–350.
183. Laufs U, Banach M, Mancini GB, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. *JAMA*. 2019;9(7):e011662. doi:10.1161/JAHA.118.011662
184. Goldberg AC, Leiter LA, Stroes ES, et al. Effect of bempedoic acid versus placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease. The CLEART wisdom randomized clinical trial. *JAMA*. 2019;322(18):1780–1788.
185. Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med*. 2019;380:1022–1032.
186. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med*. 2017;376(15):1430–1440. doi:10.1056/NEJMoa1615758
187. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382(16):1507–1519. doi:10.1056/NEJMoa1912387
188. Inclisiran (LEQVIO). Prescribing information. Novartis Pharmaceuticals Corporation. Assessed January 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214012lbl.pdf
189. A randomized trial assessing the effects of inclisiran on clinical outcomes among people with cardiovascular disease (ORION-4). Accessed October 2020. https://clinicaltrials.gov/ct2/show/NCT03705234
190. Evinacumab-dgnb (Evkeeza). Prescribing information. Regeneron Pharmaceuticals; 2021.
191. Adam RC, Mintah IJ, Alexa-Braun CA, et al. Angiopoietin-like protein 3 governs LDL-cholesterol levels thru endothelial lipase-dependent VLDL clearance. *J Lipid Res*. 2020;61:1271–1286.
192. Raal FJ, Rosenson RS, Reeskamp LF. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383:711–720.

193. Temrikar ZH, Suryawanshi S, Meibohm B. Pharmacokinetics and clinical pharmacology of monoclonal antibodies in pediatric patients. *Paediatr Drugs*. 2020;22(2):199–216.

9

Essential Hypertension

Judy W. Cheng

CORE PRINCIPLES		CHAPTER CASES
1	A diagnosis of hypertension is based on the mean of two or more properly measured seated blood pressure (BP) measurements taken on two or more occasions.	**Case 9-1 (Questions 3-5), Tables 9-1, 9-4, Figure 9-1**
2	Patients with hypertension have a recommended BP 140/90 mm Hg threshold for initiation of pharmacologic therapy if their atherosclerotic cardiovascular disease (ASCVD) risk is ≤10%. Patients with atherosclerotic heart disease (coronary artery disease, stroke, peripheral arterial disease) or whose ASCVD is ≥10% have a BP threshold for pharmacologic treatment of >130/80 mm Hg.	**Case 9-1 (Questions 6–8)**
		Case 9-1 (Questions

		11–13), Table 9-5
3	Lifestyle modifications are the foundation for preventing hypertension, and they are an important component of first-line therapy in all patients treated with antihypertensive drug therapy.	
4	Evidence supports the use of an angiotensin-converting enzyme inhibitor (ACEI), angiotensin-receptor blocker (ARB), calcium channel blocker (CCB), or thiazide diuretic as first-line therapy to prevent cardiovascular (CV) events for most patients.	**Case 9-1 (Questions 9, 14, 15)** **Case 9-3 (Question 2)** **Case 9-4 (Questions 1–9)** **Case 9-6 (Questions 1, 2, 6–10), Tables 9-8, 9-9, 9-11, 9-12, 9-13**
5	In the Black population, including those with diabetes, evidence supports the use of thiazide diuretics and CCBs as first-line treatment.	**Case 9-1 (Questions 16, 17)** **Case 9-5 (Question 1-3, 6-10)**
6	Pharmacotherapy recommendations for patients with hypertension and other comorbidities are specifically based on evidence demonstrating reduced risk of CV events.	**Case 9-1 (Question 10)** **Case 9-3 (Questions 2, 4)** **Case 9-6 (Question 2), Table 9-7**
7	Elderly patients with hypertension and no other comorbidity should be managed using the same general treatment principles and have a BP goal similar to that of other patients with hypertension. However, clinicians should implement careful titration of antihypertensive therapy and monitoring plan in those with high comorbidity burden, because they may be more	**Case 9-2 (Questions 1, 2)**

	sensitive to the BP-lowering effects of antihypertensive agents.	
8	In the population age 18 years or older with chronic kidney disease (CKD) and those age older than 70 years, evidence supports initial (or add-on) antihypertensive treatment to include an ACEI or ARB to improve renal outcomes. This applies to all patients with CKD with hypertension regardless of race or diabetes status.	**Case 9-3 (Questions 1, 3)** **Case 9-5 (Question 5)**
9	If goal BP is not attained within a month of treatment, increase the dose of the initial drug, or add a second drug (ACEI, ARB, CCB, or thiazide diuretic). If goal BP cannot be reached with two drugs, add and titrate a third drug. If goal BP cannot be reached using only the drugs recommended as first line, because of a contraindication or the need to use more than three drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated.	**Case 9-4 (Question 10)** **Case 9-6 (Question 1)** **Case 9-7 (Questions 1–3)** **Case 9-8 (Questions 1–4)** **Case 9-9 (Questions 1–3)** **Case 9-10 (Questions 1–3)** **Case 9-11 (Questions 1–4), Tables 9-2, 9-3, 9-10, 9-14, 9-15**

INTRODUCTION

In 2016, approximately 46% of the U.S. population (149 million people) had hypertension, also called high blood pressure (BP).[1] About 53% of those used antihypertensive medication, but only 25% of those were controlled (defined as both systolic blood pressure

[SBP] <140 mm Hg and diastolic blood pressure [DBP] <90 mm Hg). Hypertension is also one of the most significant risk factors for cardiovascular (CV) morbidity and mortality resulting from target-organ damage to blood vessels in the heart, brain, kidney, and eyes. These complications can manifest as either atherosclerotic vascular disease or other forms of CV disease. The exact etiology of essential hypertension is unknown; however, lifelong management with lifestyle modifications and pharmacotherapy are usually needed.

Blood Pressure

During systole, the left ventricle contracts, ejecting blood systemically into the arteries and causing a sharp rise in arterial BP. This is SBP. The left ventricle then relaxes during diastole, and arterial BP decreases to a trough value as blood returns to the heart from the venous system. This is DBP. When recording BP (eg, 120/76 mm Hg), the numerator is the SBP, and the denominator is the DBP. BP has a predictable diurnal rhythm, with fluctuations throughout the day. Values are lowest during the nighttime, sharply rise starting in the early morning, and peak in the late morning to early afternoon.

Mean arterial pressure (MAP) is sometimes used to represent BP, especially in patients with a hypertensive emergency. MAP collectively reflects both SBP and DBP, with one-third of the pressure from SBP and two-thirds from DBP. It is calculated using the following equation (Eq. 9-1):

$$\mathrm{MAP} = (\mathrm{SBP} \times 1/3) + (\mathrm{DBP} \times 2/3) \qquad \textbf{(Eq. 9-1)}$$

Hypertension is defined as an elevated SBP, DBP, or both. A clinical diagnosis of hypertension is based on the mean of two or more properly measured seated BP measurements taken on two or more occasions. Since 1976, the National Heart Lung and Blood Institute (NHLBI) has collaborated with researchers and practitioners to develop clinical practice guidelines focused on the management of hypertension (the Joint National Commission [JNC]). In late 2013,

the eighth edition of the JNC guidelines was released.[2] Unlike previous editions of the JNC guidelines, definitions and staging of BP were not addressed, but thresholds for pharmacologic treatment were defined. Furthermore, in 2017, the American College of Cardiology (ACC) and American Heart Association (AHA) collaborated with the NHLBI and stakeholder and professional organizations to publish hypertension treatment guidelines. These guidelines further define BP definition and treatment goals in patients with different CV risk factors and diseases.[3]

PATHOPHYSIOLOGY OF BLOOD PRESSURE REGULATION

Various neural and humoral factors are known to influence and regulate BP.[4] These include the adrenergic nervous system (controls α- and β-adrenergic receptors), the renin–angiotensin–aldosterone system (RAAS) (regulates systemic and renal blood flow), renal function and renal blood flow (influences fluid and electrolyte balance), several hormonal factors (adrenal cortical hormones, vasopressin, thyroid hormone, and insulin), and the vascular endothelium (regulates release of nitric oxide [NO], bradykinin, prostacyclin, and endothelin). BP is normally regulated by compensatory mechanisms that respond to changes in cardiac demand. An increase in cardiac output (CO) normally results in a compensatory decrease in total peripheral resistance (TPR); likewise, an increase in TPR results in a decrease in CO. These events regulate MAP, as is represented in the following equation (Eq. 9-2):

$$\mathrm{MAP} = \mathrm{CO} \times \mathrm{TPR} \qquad \textbf{(Eq. 9-2)}$$

Adverse changes in BP can occur when these compensatory mechanisms do not function properly. It has been suggested that in hypertension an initial increase in fluid volume increases CO and arterial pressure. Eventually, with long-standing hypertension, it is believed that TPR increases so that CO returns to normal.

The kidney plays an important role in the regulation of arterial pressure, especially through the RAAS. Decreases in BP and renal

blood flow, volume depletion or decreased sodium concentration, and an activation of the sympathetic nervous system can all trigger an increased secretion of the enzyme renin from the cells of the juxtaglomerular apparatus in the kidney. Renin acts on angiotensinogen to catalyze the formation of angiotensin I. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II (see Figs. 14-2 and 14-6 in Chapter 14, Heart Failure). Angiotensin II is a potent vasoconstrictor that acts directly on arteriolar smooth muscle and also stimulates the production of aldosterone by the adrenal glands. Aldosterone causes sodium and water retention and the excretion of potassium. Several factors influence renin release, especially those that alter renal perfusion. The resultant increase in BP results in suppression of renin release through negative feedback.

Arterial BP is also regulated by the adrenergic nervous system, which causes contraction and relaxation of vascular smooth muscle. Stimulation of α-adrenergic receptors in the central nervous system (CNS) results in a reflex decrease in sympathetic outflow, causing a decrease in BP. Stimulation of postsynaptic α_1-receptors in the periphery causes vasoconstriction. The α-receptors are regulated by a negative feedback system; because norepinephrine is released into the synaptic cleft and it stimulates presynaptic α_2-receptors, further norepinephrine release is inhibited. This negative feedback results in a balance between vasoconstriction and vasodilatation. Stimulation of postsynaptic β_1-receptors located in the myocardium causes an increase in heart rate and contractility, whereas stimulation of postsynaptic β_2-receptors in blood vessels results in vasodilation.

A direct association exists between sodium and BP. Although there is a considerably high degree of patient variability in BP sensitivity to sodium (likely affected by heredity and interactions with other environmental exposures), patients with a high dietary sodium intake generally have a greater prevalence of hypertension than those with a low sodium intake. The mechanism by which excess sodium intake contributes to hypertension is uncertain, but it is

believed to involve an undetermined natriuretic hormone (not the A- and B-type natriuretic peptides associated with heart failure) that may be induced as a consequence of impaired renal sodium excretion. This natriuretic hormone might also cause an increase in intracellular sodium and calcium, resulting in increased vascular tone and hypertension. Epidemiologic evidence and clinical trials have demonstrated an inverse relationship between calcium and BP. One proposed mechanism for this relationship involves an alteration in the balance between intracellular and extracellular calcium. Increased intracellular calcium concentrations can increase peripheral vascular resistance (PVR), resulting in increased BP.

A decrease in dietary potassium has been associated with an increase in PVR. In theory, diuretic-induced hypokalemia could counteract some of the antihypertensive effects of diuretic therapy, but this has not been seen in clinical trials. It is important, however, that potassium concentrations be maintained within the normal range because hypokalemia increases the risk of CV events, such as sudden death.

Insulin resistance and hyperinsulinemia also have been associated with hypertension. Kaplan[4] suggests that insulin resistance is responsible for the frequent coexistence of hyperglycemia, dyslipidemia, hypertension, and abdominal obesity (called *metabolic syndrome*).[5] The exact role of insulin resistance in the development of hypertension is still evolving.

The vascular epithelium is a dynamic system in which vascular tone is regulated by numerous substances. As noted previously, angiotensin II promotes vasoconstriction of the vascular epithelium. However, several other substances regulate vascular tone. NO is produced in the endothelium and is a potent vasodilatory chemical that relaxes the vascular smooth muscle. Hypothetically, some patients with hypertension have an intrinsic deficiency in NO release and inadequate vasodilation, which could contribute to hypertension and its vascular complications.

Factors that regulate BP are well understood and continue to evolve, but the cause of essential hypertension is still unknown. It is impossible to target therapy to specific abnormalities. Therefore,

antihypertensive therapy should be selected based on evidence from clinical trials that have demonstrated reductions in hypertension-associated complications, as is discussed later in this chapter.

CARDIOVASCULAR RISK AND BLOOD PRESSURE

Direct correlations between BP values and risk of CV disease have been established based primarily on epidemiologic data. Beginning at a benchmark BP of 115/75 mm Hg, the risk of CV disease doubles with every increment of 20/10 mm Hg.[5] Clinically, it is important to note that incremental elevations in SBP are more predictive of CV disease than are elevations in DBP, especially for patients older than 50 years of age. Therefore, SBP is the target of evaluation and intervention for most patients with hypertension. In younger patients with hypertension, elevated DBP may be the only BP abnormality present.

MEASURING BLOOD PRESSURE

Auscultatory method

The measurement of BP should be standardized to minimize variability in readings. The AHA technique for auscultatory BP measurement (**Table 9-1**)[6] should be used in most patients.[7]

Table 9-1

Auscultatory Method for Blood Pressure Measurement in Adults as Recommended by the American Heart Association

Patient: Patient should be seated for 5 minutes with arm bared, unrestricted by clothing, and supported at heart level. Smoking or food ingestion should not have occurred in the 30 minutes before the measurement.

Cuff: An appropriately sized cuff should be used. The internal inflatable bladder width should be at least 40% of the bladder length and cover at least 80% of the upper arm circumference. The cuff should be wrapped snugly around the arm, with the center of the bladder over the brachial artery.

Monitor: Measurements should be taken with a correctly calibrated mercury sphygmomanometer, an aneroid manometer, or a validated electronic device.

Palpatory method: SBP should be estimated using the palpatory method. The cuff is rapidly inflated in 10 mm Hg increments, while simultaneously palpating the radial pulse on the patient's wrist on the cuffed arm and observing the

manometer. The pressure when the radial pulse is no longer palpable is the estimated SBP. The cuff is then deflated rapidly.

Korotkoff sounds: The head of the stethoscope, ideally using the bell, should be placed over the brachial artery, with each earpiece in the clinician's ear. The cuff should then be rapidly inflated to 20–30 mm Hg above the estimated SBP from the palpatory method. The cuff is slowly deflated at a rate of 2 mm Hg/second while the clinician simultaneously listens for phase 1 (the first appearance of sounds) and phase 5 (the disappearance of sounds) Korotkoff sounds while also observing the manometer. When the pressure is 10–20 mm Hg below phase 5, the cuff can be rapidly deflated.

Documentation: BP values should always be recorded. The BP values (SBP/DBP) should be recorded using even numbers (rounded up from an odd number)[a] along with the patient's position (seated, standing, or supine), arm used, cuff size, time, and date.

Repeat: A second measurement should be taken after at least 1 minute in the same arm. If the readings differ by >5 mm Hg, additional measurements should be obtained. The mean of these values should be used to make clinical decisions. BP should be taken in both arms at the initial visit, with the BP measured in the arm with the higher reading at subsequent visits.

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]Terminal digit preference (ie, tendency to report readings that end in 0 or 5) should be avoided.

Reprinted with permission from Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112(17):2735–2752.

Correct BP measurements require that the clinician listen through a stethoscope that is placed over the brachial artery for the appearance of the five phases of the Korotkoff sounds. Each sound has distinct features, which are depicted in **Figure 9-1**.[7]

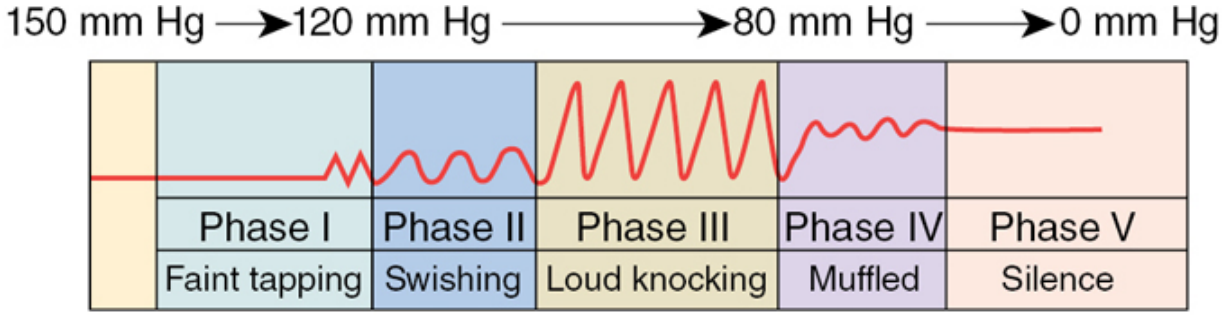


Figure 9-1 Phases of the Korotkoff sounds heard when indirectly measuring blood pressure. (Reprinted with permission from Timby BK. *Fundamental Nursing Skills and Concepts*. 11th ed. Wolters Kluwer; 2017.)

Out-of-office blood pressure monitoring

Home BP measurements can provide information on response to therapy and may help improve adherence to therapy and goal BP achievement in some patients.[8,9] Devices for home measurement should be validated for accuracy according to established protocols from either the British Hypertension Society or the Association for Advancement of Medical Instrumentation. When placed in service, they should be routinely checked against office-based readings for accuracy, especially when readings between office and home are widely discrepant. Patients with average home BP values >135/85 mm Hg are considered hypertensive.[8] Wrist or finger devices that measure BP are generally not accurate and should not be routinely used.

Ambulatory blood pressure monitoring (ABPM) typically measures BP every 15 to 30 minutes throughout the day and nighttime using a portable, noninvasive oscillometric device typically worn for 24 hours.[6] This form of specialized monitoring is indicated for patients with suspected white-coat hypertension and may also be helpful in patients with apparent drug resistance, hypotensive symptoms while receiving antihypertensive therapy, episodic hypertension, and autonomic dysfunction.[6] Similar to self-BP measurements, ABPM values are typically lower than office-based measurements. As a comparison, the normal upper limit for BP in most patients is 140/90 mm Hg for office-based measurement, 130/80 mm Hg for ABPM (135/85 mm Hg while awake and 120/75 mm Hg while asleep), and 135/85 mm Hg for self-BP measurements.[6] Therefore, the threshold for normal versus abnormal is lower than that obtained during office-based measurements.

Evidence indicates that ABPM recordings can predict clinical outcomes more strongly than do office-based BP measurements,

most likely because the device factors in BP throughout nighttime hours, which provides a more accurate reflection of the overall average pressure load.[10] However, in clinical practice, ABPM is not recommended for routine evaluation of responses to treatment for a number of reasons, including lack of widespread availability, cost, and intrusiveness of performing multiple ABPM sessions in the same patient.[6]

BP values measured outside the office should be considered in the overall treatment of patients with hypertension. However, it is important to acknowledge that office-based BP measurements have been the source used in the major clinical trials establishing that treatment of hypertension reduces morbidity and mortality rates. Therefore, they are still considered the standard values that should guide evaluation of response to antihypertensive drug therapy in most patients.

The reliability and accuracy of automated BP monitors, whether they are used in the office or out of the office, can vary significantly. For a summary of commercially available automatic monitors and whether they have passed validation protocols, refer to the dabl® Educational Trust website (http://www.dableducational.org). The use of BP measurements from automated machines commonly found in grocery stores and pharmacies may have questionable reliability. Measurements using these publicly available machines should not be relied on to make clinical decisions, but should be used to direct patients for follow-up with their medical provider as a screening tool.

Types of Hypertension

ESSENTIAL HYPERTENSION

Most patients with hypertension have essential hypertension (also known as primary hypertension), in which there is no identifiable cause for their chronically elevated BP.

SECONDARY HYPERTENSION

Patients with secondary hypertension have a specific identified cause for elevated BP (**Table 9-2**). Although only 5% to 10% of those among the hypertensive population have causes that are purely secondary, further diagnostic evaluation should occur if physical or laboratory findings suggest the possibility of a secondary cause (**Table 9-3**).[4,11,12] Some secondary causes are potentially reversible and may normalize BP (eg, coarctation of the aorta), whereas others are more often superimposed on and worsen an already elevated BP (eg, obstructive sleep apnea). The distinction is important because treatment of an underlying cause may not always be expected to completely normalize BP and allow discontinuation of antihypertensive therapies. In patients who have resistant hypertension (requiring three or more drugs for BP control) or who have a sudden and significant increase in BP, further diagnostic workup for secondary causes should be considered.

Table 9-2
Secondary Causes of Hypertension

Alcoholism
Chronic kidney disease
Chronic steroid therapy and Cushing syndrome
Coarctation of the aorta
Drug induced or drug related: • Amphetamines (amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, phendimetrazine, and phentermine) • Antidepressants (bupropion, desvenlafaxine, and venlafaxine) • Antihypertensive agents that are abruptly stopped (only β-blockers and central α_2-agonists) • Anabolic steroids (eg, testosterone) • Calcineurin inhibitors (cyclosporine and tacrolimus) • Cocaine and other illicit drugs • Corticosteroids (cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone) • Ephedra alkaloids • Erythropoiesis-stimulating agents (darbepoetin-α and erythropoietin) • Ergot alkaloids (ergonovine and methysergide)

• Estrogen-containing oral contraceptives (ethinyl estradiol) • Licorice (including some chewing tobacco) • Monoamine oxidase inhibitors (isocarboxazid, phenelzine, tranylcypromine sulfate) when given with tyramine-containing foods or with an interacting drug • Nonsteroidal anti-inflammatory drugs (all types) • Oral decongestants (eg, pseudoephedrine) • Phenylephrine (ocular administration) • Vascular endothelial growth factor inhibitor (bevacizumab) • Vascular endothelial growth factor receptor tyrosine kinase inhibitor (sorafenib and sunitinib)
Pheochromocytoma
Primary aldosteronism
Renovascular disease
Sleep apnea
Thyroid or parathyroid disease

Reprinted with permission from Verdecchia P, Reboldi GP, Anjeli F, et al. Short- and long-term incidence of stroke in white-coat hypertension. *Hypertension*. 2005;45(2):203–208.

Table 9-3
Clinical Findings Suggestive of Secondary Hypertension

Causes	Historical Findings	Physical Examination Findings	Laboratory Findings
Sleep apnea	Daytime fatigue and somnolence	Large neck circumference; overweight or obese	Abnormal sleep studies with frequent awakenings and anoxic episodes
Renovascular disease	Moderate or severe high BP before age 30 or after 55; rapidly progressive hypertension	Abdominal bruits; funduscopic hemorrhages	Suppressed or stimulated plasma renin activity; IVP (rapid sequence); digital subtraction angiography
Renoparenchymal disease	Dysuria, polyuria, nocturia; urinary tract infections; kidney stones; family history of polycystic or other types of kidney disease	Edema	Proteinuria; hematuria; bacteriuria
Coarctation of the aorta	Intermittent claudication	Diminished or absent femoral pulses compared with carotids; lower SBP in leg compared with arm	—
Pheochromocytoma	Paroxysmal headaches, palpitations, sweating, dizziness, and pallor	Nervousness, tremor, tachycardia, orthostatic hypotension	Clonidine suppression tests[a]; high urinary metanephrine or vanillylmandelic acid
Primary aldosteronism	Weakness, polyuria, polydipsia, intermittent paralysis	Orthostatic hypotension	Hypokalemia
Cushing syndrome	Menstrual irregularity	Moon face; truncal obesity; buffalo hump; hirsutism; violet striae	↑ serum glucose; ↑ plasma cortisol after suppression with dexamethasone

BP, blood pressure; IVP, intravenous pyelogram; SBP, systolic blood pressure.

[a]Failure of plasma catecholamines to ↓ by 50% within 3 hours of administration of 0.3 mg clonidine highly suggests pheochromocytoma.

WHITE-COAT HYPERTENSION

White-coat hypertension describes patients who have consistently elevated BP values measured in a clinical environment in the presence of a health care professional (eg, physician's office), yet when measured elsewhere or with 24-hour ambulatory monitoring, BP is not elevated.[6,7] Home BP monitoring or 24-hour ABPM is warranted in patients suspected of having white-coat hypertension to differentiate this from true hypertension.[6] The commonly used definition is a persistently elevated average office BP of >140/90 mm Hg and an average awake ambulatory reading of <135/85 mm Hg.[9] The label *white-coat hypertension* applies only to patients without target-organ disease who are not on antihypertensive therapy.

Significant controversies surround white-coat hypertension. Although this does not represent a clinical diagnosis, patients with white-coat hypertension are at risk for eventually developing essential hypertension. Moreover, patients with white-coat hypertension are at a higher risk for CV disease than are normotensive patients.[13] The decision to treat or not treat white-coat hypertension is controversial. Many patients enrolled in the landmark clinical trials that demonstrated reductions in CV morbidity and mortality with antihypertensive therapy likely had white-coat hypertension because only office BP measurements were used for inclusion. At minimum, patients with white-coat hypertension should be treated with lifestyle modifications and need to be closely monitored with a device that can measure BP outside the clinic environment if they are not treated with antihypertensive drug therapy.

HYPERTENSIVE CRISES

Hypertensive crises are situations in which measured BP values are markedly elevated (>180/110 mm Hg). They are classified as either a hypertensive emergency (with acute or progressive target-organ damage) or urgency (without acute or progressive target-organ

damage). Hypertensive emergencies require hospitalization for immediate BP lowering. Hypertensive urgencies do not require immediate BP lowering; instead, BP should be slowly reduced within 24 hours (but not generally to goal BP so quickly) (see Chapter 16, Hypertensive Crises).

Hypertension Management

Hypertension is treated with both lifestyle modifications and pharmacotherapy. As of today, the 2017 ACC/AHA Hypertension Treatment Guidelines are considered the "gold standard" consensus guidelines for the management of hypertension in the United States.[3] The overall principle is to implement lifestyle modifications in addition to pharmacotherapy to control BP in patients with general hypertension. In addition, the 2017 ACC/AHA Guidelines also focus on the presence of specific comorbidities in patients with hypertension and selection of specific pharmacotherapy for these patients. These issues are discussed later in this chapter.

GOALS

The overarching goal of treating patients with hypertension is to reduce associated morbidity and mortality. These manifest as hypertension-associated complications (**Table 9-4**), which include atherosclerotic vascular disease and other forms of CV disease.

Table 9-4
Hypertension-Associated Complications and Major Cardiovascular Risk Factors

Hypertension-Associated Complications
• Atherosclerotic vascular disease • Coronary artery disease (sometimes called coronary heart disease) • Myocardial infarction • Acute coronary syndromes • Chronic stable angina • Carotid artery disease

- Ischemic stroke
- Transient ischemic attack
- Peripheral arterial disease
- Abdominal aortic aneurysm
- Other forms of CV disease
- Left ventricular dysfunction (systolic heart failure)
- Chronic kidney disease
- Retinopathy

Major CV Risk Factors

- Advanced age (older than 55 years for males, older than 65 years for females)
- Cigarette smoking
- Diabetes mellitus
- Dyslipidemia
- Family history of premature atherosclerotic vascular disease (males younger than 55 years or females younger than 65 years) in primary relatives
- Hypertension
- Kidney disease (microalbuminuria or estimated GFR <60 mL/min/1.73 m^2)
- Obesity (BMI ≥ 30 kg/m^2)
- Physical inactivity

BMI, body mass index; CV, cardiovascular; GFR, glomerular filtration rate.

Goal blood pressure values

Achieving goal BP is an important step in the overall treatment of patients with hypertension. According to the 2017 ACC/AHA Hypertension Treatment Guidelines, patients older than 18 years with hypertension and atherosclerotic cardiovascular disease (ASCVD) risk ≤10% should have a BP threshold of 140/90 mm Hg to initiate pharmacologic therapy.[3] For those with CV risk factors and comorbidities and ASCVD risk >10%, the BP threshold for initiation of pharmacologic therapy is 130/80 mm Hg.

The issue of whether more aggressive BP goals (ie, <130/80 or <120/80 mm Hg) result in better reductions in risk of CV events than does the standard goal of <140/90 mm Hg for patients with ASCVD risk ≥10% over the year has been through some controversies, especially in some patient populations such as the elderly and patients with diabetes or CKD.

In elderly patients, moderate-quality earlier evidence from three trials (Systolic Hypertension in the Elderly Program [SHEP], Syst-Eur, and the UK Prospective Diabetes Study Group [UKPDS]) has shown that treatment of hypertension to an SBP goal of <150 mm Hg improves CV and cerebrovascular health outcomes and lowers mortality in adults with diabetes and hypertension.[14–16] However, within this population, the only clear prospective data supporting the benefits of antihypertensive therapy is from the Hypertension in the Very Elderly Trial (HYVET), which used a BP goal of <150/80 mm Hg.[17] It is important to note that BP goals among the elderly have always been based primarily on expert consensus. The BP treatment goal for individual elderly patients, to a certain extent, should be determined by their frailty and their ability to tolerate side effects of antihypertensive agents (such as orthostatic hypotension).

In patients with diabetes, an earlier recommendation for an SBP goal was <140 mm Hg. This was supported by the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD BP) trial, which demonstrated[18] no difference in the primary end point of major CV events when patients with type 2 diabetes were treated to an SBP goal of <120 mm Hg compared with an SBP goal of <120 mm Hg after a mean of 4.7 years.

Similarly, in patients with CKD, earlier evidence of moderate quality demonstrating no benefit in slowing the progression of kidney disease from treatment with antihypertensive drug therapy to a lower BP goal (eg, <130/80 mm Hg) compared with a goal of <140/90 mm Hg.[19–21]

However, in 2015, the publication of the results of the Systolic Blood Pressure Intervention Trial (SPRINT) changed some of these perspectives. SPRINT is a randomized, multicenter clinical trial that compares intensive hypertension treatment (SBP goal <120 mm Hg) with standard treatment (SBP goal <140 mm Hg) in 9361 patients with hypertension and at least one other CV risk factor (patients with a history of diabetes or stroke are excluded). At 1 year, the mean SBP was 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a

significantly lower rate of the primary composite outcome (myocardial infarction [MI], acute coronary syndrome [ACS] not resulting in MI, stroke, acute decompensated heart failure, or death from CV causes) in the intensive treatment group than in the standard treatment group (1.65% vs 2.19% per year; $P < .001$).[22] Based on the result of the SPRINT trial, in 2017, the ACC and AHA collaborated with the NHLBI and stakeholder and professional organizations to publish a new hypertension treatment guideline, addressing treatment goals for patients with hypertension and at least one other CV risk factor or other CV comorbidity (including the elderly and CKD).[3] Some of these CV risk factors and comorbidities are discussed in more detail later in this chapter. In this guideline, it is recommended that except patients who have 10 years' ASCVD risk <10%, all other patients should have a BP treatment goal of <130/80 mm Hg. Patients with ASCVD risk <10% can have a pharmacologic treatment threshold of >140/90 mm Hg (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/). When their BP is between 130/80 and 140/90 mm Hg, they can be managed with nonpharmacologic management alone.

LIFESTYLE MODIFICATIONS

Lifestyle modifications are the cornerstone of management for preventing and treating hypertension. AHA guidelines for lifestyle modifications recommend both diet and exercise.[23,24] These recommendations are summarized in **Table 9-5**. Engaging in these modifications is encouraged for all persons to prevent the development of hypertension; however, they are recommended as a component of first-line therapy in all patients with prehypertension and in all patients with a diagnosis of hypertension regardless of whether their BP values are at goal or not.[2,3] Independent of BP lowering, CV risk may also be reduced.

Table 9-5
Lifestyle Modifications to Prevent and Treat Hypertension

Lifestyle Modification	Recommendations
Weight management	Approximately 1 mm Hg for every 1 kg reduction in body weight
DASH diet	Consume diet rich in fruits, vegetable, whole grains, low-fat dairy, with reduced saturated or total fat
Sodium restriction	<1500 mg/day
Potassium intake	3500–5000 mg/day
Physical exercise	Aerobic exercise 90–150 minutes/week
Alcohol consumption	Males ≤2 drinks daily; Females ≤1 drink daily[a]

DASH, dietary approaches to stop hypertension.

[a]One drink contains ~14 g of pure alcohol [12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol)].

Weight reduction

Weight loss as small as 5% to 10% of body weight in overweight individuals may significantly lower CV risk. For most patients, an average weight loss of 22.04 pounds (10 kg) can reduce SBP by 5 to 20 mm Hg, a reduction comparable to that achieved from the addition of an antihypertensive drug used as monotherapy.[2,3]

DASH eating plan

The DASH (Dietary Approaches to Stop Hypertension) diet is rich in fruits, vegetables, and low-fat dairy foods, coupled with reduced saturated and total fat.[25] The patient education publication entitled "Your Guide to Lowering Your Blood Pressure With DASH" can be found at https://www.nhlbi.nih.gov/files/docs/public/heart/new_dash.pdf. The DASH diet can substantially reduce BP (8–14 mm Hg in SBP for most patients) and yield results similar to that of single-drug therapy. The low-fat component of this diet is important because weight loss

is more readily achieved by a reduced-calorie diet (fats contribute more calories per gram than do either carbohydrates or protein) and lowered fat intake also reduces the risk of CV disease by lowering cholesterol.

Dietary sodium restriction

The average intake of sodium in the United States is >6 g/day. Restricting sodium should be encouraged in patients with prehypertension or hypertension, and the current recommendation to restrict daily sodium intake to ≤1.5 g is lower than what has traditionally been suggested. Some clinicians may argue that the efficacy of implementing sodium restriction in patients with hypertension may vary. Evidence from clinical trials has shown, however, that sodium restriction provides mean reductions in BP of 5/2.7 mm Hg in patients with hypertension.[25] Restricting sodium to <1.5 g daily has been shown to decrease SBP by >20 mm Hg in patients with resistant hypertension.[26] Some populations (patients with diabetes and Black and elderly patients) respond better to sodium restriction than do the general population, but all patients with hypertension should be instructed to reduce their sodium intake. They should be counseled not to add salt to foods and to avoid or minimize ingestion of processed or packaged foods, foods with high sodium content, and nonprescription drugs containing sodium.

Increased potassium intake

Increasing dietary potassium intake is recommended, although it is not commonly identified by most patients as a dietary modification that will lower BP. Adhering to a DASH eating plan will usually assure an intake of the recommended 4.7 g daily. Dietary supplementation should be the primary strategy to increase potassium. Implementing potassium supplementation outside of dietary sources for the sole purpose of lowering BP should be avoided because of the potential harm from hyperkalemia. Moreover, potassium supplementation in patients with hypertension who are treated with a potassium-sparing diuretic, aldosterone antagonist,

angiotensin-converting enzyme inhibitor (ACEI), or an angiotensin-receptor blocker (ARB) may cause hyperkalemia. This can also occur in patients with hypertension and CKD who are treated with potassium supplementation.

Moderate alcohol consumption

Explaining the need to limit alcohol consumption is complicated. Although data suggest that small daily doses of alcohol (eg, one glass of red wine with dinner) are associated with lower CV risk, excessive alcohol intake can elevate BP, decrease the effectiveness of antihypertensive medications, and increase the risk of stroke. Patients who consume three to four drinks per day experience a 3 to 4 mm Hg increase in SBP and a 1 to 2 mm Hg increase in DBP compared with those who do not drink. These increases are even higher in patients who consume more alcohol. Moderate alcohol consumption of two or fewer drinks daily in males and one or fewer drinks daily in females or lighter weight individuals can decrease SBP approximately 2 to 4 mm Hg. Patients should be instructed that one drink is equal to 1.5 oz of 80-proof whiskey, 5 oz of wine, or 12 oz of beer.

Physical activity

Regular physical activity can reduce SBP by 4 to 9 mm Hg in most patients.[2,3] Benefits include reducing the incidence of hypertension, assisting weight loss and weight loss maintenance, and improving overall CV fitness. Most patients with hypertension can safely increase their regular aerobic activity. Those with more severe forms of target-organ damage (eg, angina and previous MI) may, however, need a medical evaluation before increasing their activity level. Physical activity should ideally occur for at least 30 minutes, at least 5 days of the week, but preferably daily. Walking, running, cycling, swimming, and cross-country skiing are examples of aerobic exercise that are recommended for physical activity.

PHARMACOTHERAPY

Numerous clinical trials have demonstrated that antihypertensive pharmacotherapy reduces the risk of hypertension-associated complications (eg, CV morbidity and mortality). The ACC/AHA Hypertension Guidelines recommend that in the general non-Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), ACEI, or ARB. In the general Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. In the population older than 18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all patients with CKD having hypertension regardless of race or diabetes status. Evidence obtained since the 2003 JNC-7 guidelines demonstrates that, for first-line treatment in primary prevention patients, β-blocker therapy is not as effective in reducing CV events compared with ACEI, ARB, CCB, or thiazide diuretic therapy.[27] Therefore, unlike previous versions of the JNC Hypertension Treatment Guidelines, β-blocker is no longer recommended as one of the first-line treatment options, unless comorbidities such as MI and heart failure require them to receive β-blocker therapy. Moreover, newer evidence also suggests that the reductions in CV events with ACEI, ARB, CCB, or thiazide diuretic are comparable, so that one agent is not automatically preferred over another.[26]

First-line agents

Angiotensin-Converting Enzyme Inhibitors

The ACEIs directly inhibit ACE, blocking the conversion of angiotensin I to angiotensin II. This action reduces angiotensin II–mediated vasoconstriction and aldosterone secretion and ultimately lowers BP. Because additional pathways exist for the formation of angiotensin II, ACEIs do not completely block the production of angiotensin II. Aldosterone release is indirectly suppressed by ACEIs; thus, hyperkalemia is possible and potassium concentrations should be monitored. Patients with CKD or volume depletion may be

more susceptible to hyperkalemia or to further kidney dysfunction owing to a higher dependence on the vasoconstriction provided by angiotensin II to support glomerular filtration rate (GFR) among these patients.

Inhibiting ACE also prevents the breakdown and inactivation of bradykinin, which may lead to additive vasodilation by enhancing NO. However, bradykinin accumulation can also cause a nonproductive cough in some patients, which is the most frequent, yet harmless, side effect of ACEI therapy. ACEI therapy has been associated with angioedema, which is a rare, but serious, hypersensitivity reaction. Angioedema typically presents as swelling of the tongue, lips, and mouth, but it can also involve the eyes and upper airway.

The development of angioedema requires discontinuation of the ACEI. These agents are metabolically neutral and may have a positive effect on insulin resistance and risk of progression to type 2 diabetes.[28]

Angiotensin-Receptor Blockers

The ARBs modulate the RAAS by directly blocking the angiotensin II type 1 receptor site, preventing angiotensin II–mediated vasoconstriction and aldosterone release. Overall, ARBs are the best tolerated of the first-line agents.[29] They do not affect bradykinin and are therefore associated with less incidence of cough. Because aldosterone is indirectly suppressed, monitoring of potassium is important to avoid hyperkalemia. Similar to the ACEIs, patients with CKD or volume depletion may be more susceptible to hyperkalemia or to further kidney dysfunction. These agents are metabolically neutral and may have a positive effect on insulin resistance and risk of progression to type 2 diabetes.[28]

Calcium Channel Blockers

The CCBs are pharmacologically complex. They reduce calcium entry into smooth muscles, which causes coronary and peripheral vasodilation and lowers BP. All decrease cardiac contractility (except

amlodipine and felodipine). Dihydropyridine CCBs are primarily vasodilators that can cause a reflex tachycardia. This is in contrast to the nondihydropyridine CCBs (verapamil and diltiazem) that directly block the atrioventricular (AV) node, decrease heart rate, and decrease cardiac contraction, yet have vasodilatory effects. Side effects depend on the type of CCB, but can include flushing, peripheral edema, tachycardia, bradycardia or heart block, and constipation.

Thiazide Diuretics

Diuretics, particularly thiazide and thiazide-like (eg, chlorthalidone) diuretics, have been extensively studied in large landmark clinical trials for hypertension. When initially started, they induce a natriuresis that causes diuresis and decreases plasma volume and CO. With chronic use, diuresis usually dissipates, and CO gradually returns to near-normal levels. The long-term BP-lowering effect in the face of these changes suggests a sustained decrease in PVR as the primary mechanism responsible.

Dose-related electrolyte and metabolic alterations (eg, hypokalemia, hyperuricemia, hyperglycemia, and hypercholesterolemia) can occur with thiazide diuretics. These effects were particularly problematic when high doses were used many years ago (eg, hydrochlorothiazide [HCTZ] 100–200 mg/day), but are drastically minimized using lower doses that are now considered the standard of care (eg, HCTZ 12.5–25 mg/day).[30] Thiazide diuretics can be used in combination with a potassium-sparing diuretic (ie, triamterene and amiloride) to minimize potential potassium depletion. Other biochemical changes in glucose and cholesterol are minimal and mostly transient with low-dose therapy.

Second-line agents

β-Blockers

β-Blockers have several direct effects on the CV system. They can decrease cardiac contractility and CO, lower heart rate, blunt sympathetic reflex with exercise, reduce central release of

adrenergic substances, inhibit norepinephrine release peripherally, and decrease renin release from the kidney. All these contribute to their antihypertensive effects. Adverse metabolic effects include altered lipids and increased glucose concentrations. Similar to thiazide diuretics, these changes are generally temporary and have minimal to no clinical significance. These agents were considered first line for the treatment of most patients with hypertension in previous hypertension treatment guidelines. However, more recent treatment has further defined their role.[27] Unless patients have other indication for β-blockers (eg, coronary artery disease [CAD] or left ventricular dysfunction), they should not be used as a first-line agent for primary prevention of CV events in patients with hypertension.

Aldosterone Antagonists

Spironolactone and eplerenone are aldosterone antagonists. Potent blockade of the aldosterone receptor inhibits sodium and water retention and inhibits vasoconstriction. These agents are also considered potassium-sparing diuretics. Hyperkalemia is a known dose-dependent effect with aldosterone antagonists and is more prominent in patients with CKD or in patients taking a concurrent RAAS blocking agent (ACEI, ARB, or direct renin inhibitor). Gynecomastia is a side effect of spironolactone, usually more common with higher doses, that does not occur with eplerenone.

Other agents

There are other antihypertensive drug classes, many of which are older agents, which should primarily be used to provide additional BP lowering only after first-line and second-line agents have been implemented.

Loop diuretics (eg, furosemide and torsemide) can be used in some patients for hypertension.[30] When dosed appropriately; they can provide BP reductions similar to those seen with a thiazide diuretic. Because they are short acting and subject to a significant postdose antinatriuretic effect, they should generally be reserved for patients with heart failure or severe CKD in whom their diuretic

action remains prolonged. Significant edema usually accompanies these conditions, such that they generally require a loop diuretic instead of a thiazide diuretic for adequate diuresis and volume removal. Because they are more potent at inducing diuresis compared with thiazide diuretics, they can cause more electrolyte disturbances (eg, hypokalemia).

Aliskiren is the only direct renin inhibitor. Similar to an ACEI or ARB, this agent is a RAAS blocker. It is approved for treatment of hypertension and has been studied in combination with an ACEI, ARB, or a thiazide diuretic. It is the newest antihypertensive drug class; therefore, its exact role will continue to evolve as additional clinical data are generated.

α-Blockers (eg, doxazosin, prazosin, and terazosin) attach to peripheral α_1-receptors, inhibiting the uptake of catecholamines in smooth muscle, and cause vasodilation. Although effective in lowering BP, they have more side effects than first-line or second-line agents. The most prominent side effect is hypotension, which is most evident after the first dose and with postural changes (arising from a lying position to a standing position).

Direct vasodilators (eg, hydralazine and minoxidil) work on the arterial vasculature. They should be reserved for patients with specific conditions (eg, severe CKD) or those with very difficult to control BP. Concomitant drug therapy with both a diuretic and an agent that lowers heart rate (a β-blocker, diltiazem, or verapamil) is usually needed to mitigate the associated fluid retention and reflex tachycardia that frequently occur.

Central α_2-agonists (eg, clonidine and methyldopa) work in the vasomotor centers of the brain where they stimulate inhibitory neurons and decrease sympathetic outflow from the CNS. The resultant decrease in PVR and CO lowers BP. These agents commonly cause anticholinergic side effects (eg, sedation, dizziness, dry mouth, and fatigue) and possibly sexual dysfunction. Although α_2-agonists lower BP, they often cause fluid retention and should be used in combination with a diuretic.

CLINICAL EVALUATION

Patient Presentation

CASE 9-1

QUESTION 1: D.C. is a 44-year-old Black male who presents to his primary care provider concerned about high BP. At an employee health screening last month, he was told he had hypertension. His medical history is significant for allergic rhinitis. His BP was 144/84 and 146/86 mm Hg last year during an employee health screening at work. D.C.'s father had hypertension and died of an MI at age 54. His mother had diabetes and hypertension and died of a stroke at age 68. D.C. smokes one pack per day of cigarettes and thinks his BP is high because of job-related stress. He does not believe that he really has hypertension. D.C. does not engage in any regular exercise and does not restrict his diet in any way, although he knows he should lose weight.

Physical examination shows he is 68.89 inches (175 cm) tall, weighs 238.09 pounds (108 kg) (body mass index [BMI] 35.2 kg/m^2), BP is 148/88 mm Hg (left arm) and 156/86 mm Hg (right arm) while sitting, and heart rate is 80 beats/min. Six months ago, his BP values were 152/88 and 160/84 mm Hg when he was seen by his primary care provider for allergic rhinitis. Funduscopic examination reveals mild arterial narrowing and arteriovenous nicking, with no exudates or hemorrhages. The other physical examination findings are essentially normal.

D.C.'s fasting laboratory serum values are as follows:
Blood urea nitrogen (BUN), 24 mg/dL
Creatinine, 1.0 mg/dL
Glucose, 105 mg/dL
Potassium, 4.4 mEq/L
Uric acid, 6.5 mg/dL
Total cholesterol, 196 mg/dL
Low-density lipoprotein cholesterol (LDL-C), 141 mg/dL
High-density lipoprotein cholesterol (HDL-C), 32 mg/dL
Triglycerides, 170 mg/dL

An electrocardiogram (ECG) is normal except for left ventricular hypertrophy (LVH).

Why does D.C. have hypertension?

D.C. has hypertension. He has had elevated BP values, measured in clinical environments, and meets the diagnostic criteria for

hypertension because two or more of his BP measurements are elevated on separate days.

Case 9-1, Question 2: What is the proper assessment of D.C.'s BP?

D.C. has essential hypertension; therefore, the exact cause is not known. He has several characteristics (eg, family history of hypertension and obesity) that may have increased his chance of developing hypertension. Race and sex also influence the prevalence of hypertension. Across all age groups, Blacks have a higher prevalence of hypertension than do Whites and Hispanics.[1] Similar to other forms of CV disease, hypertension is more severe, more likely to include hypertension-associated complications, and occurs at an earlier age in Black patients.

Patient Evaluation and Risk Assessment

The presence or absence of hypertension-associated complications as well as other major CV risk factors (Table 9-4) must be assessed in D.C. Also, secondary causes of hypertension (Table 9-2), if suggested by history and clinical examination findings, should be identified and managed accordingly. The presence of concomitant medical conditions (eg, diabetes) should be assessed, and lifestyle habits should be evaluated so that they can be used to guide therapy.

HYPERTENSION-ASSOCIATED COMPLICATIONS

Case 9-1, Question 3: Which hypertension-associated complications are present in D.C.?

A complete physical examination to evaluate hypertension-associated complications includes examination of the optic fundi; auscultation for carotid, abdominal, and femoral bruits; palpation of the thyroid gland; heart and lung examination; abdominal

examination for enlarged kidney, masses, and abnormal aortic pulsation; lower extremity palpation for edema and pulses; and neurologic assessment. Routine laboratory assessment after diagnosis should include the following: ECG; urinalysis; fasting glucose; hematocrit; serum potassium, creatinine, and calcium; and a fasting lipid panel. Optional testing may include measurement of urinary albumin excretion or albumin-to-creatinine ratio, or additional tests specific for secondary causes if suspected.

D.C. does not yet have hypertension-associated complications. He is exhibiting early signs, however, based on his physical examination that, if left untreated, will likely develop into such complications. These early signs have likely evolved from his long-standing, poorly controlled hypertension. D.C.'s ECG revealed LVH, indicating early cardiac damage. Although the gold standard for confirming LVH is echocardiography, this confirmatory procedure is not necessary unless symptoms are present indicating that LVH has progressed to left ventricular dysfunction (eg, peripheral edema and shortness of breath). His funduscopic examination reveals mild arterial narrowing and arteriovenous nicking, which are early signs of retinopathy and atherosclerosis. D.C.'s serum creatinine is normal, ruling out overt CKD. Additional testing for microalbuminuria is needed, however, to confirm that he does not have early-stage kidney disease.

CASE 9-1, QUESTION 4: What other forms of hypertension-associated complications is D.C. at risk for?

Hypertension adversely affects many organ systems, including the heart, brain, kidneys, peripheral circulation, and eyes. These are summarized in Table 9-4. Damage to these systems resulting from hypertension is termed *hypertension-associated complications*, *target-organ damage*, or *CV disease.* There are often misconceptions about the terms CV disease and CAD. CV disease encompasses the broad scope of all forms of hypertension-associated complications. CAD is simply a subset of CV disease and refers specifically to disease related to the coronary vasculature,

including ischemic heart disease and MI. Hypertension-associated complications and major risk factors for developing such complications should be assessed by a thorough patient history, a complete physical examination, and laboratory evaluation.

Hypertension can affect the heart either indirectly, by promoting atherosclerotic changes, or directly, via pressure-related effects. Hypertension can promote CV disease and increase the risk of *ischemic events*, such as angina and MI. Antihypertensive therapy has been shown to reduce the risk of these coronary events. Hypertension also promotes the development of LVH, which is a myocardial (cellular) change, not an arterial change. However, these two conditions often coexist. It is commonly believed that LVH is a compensatory mechanism of the heart in response to the increased resistance caused by elevated BP. LVH is a strong and independent risk factor for CAD, left ventricular dysfunction, and arrhythmia. LVH does not indicate the presence of left ventricular dysfunction, but it is a risk for progression to left ventricular dysfunction, which is considered a hypertension-associated complication. This may be caused by ischemia, excessive LVH, or pressure overload. Ultimately, left ventricular dysfunction results in a decreased ability to contract (systolic dysfunction).

Hypertension is one of the most frequent causes of cerebrovascular disease. Cerebrovascular signs can manifest as transient ischemic attacks, ischemic strokes, multiple cerebral infarcts, and hemorrhages. Residual functional deficits caused by stroke are among the most devastating forms of hypertension-associated complications. Clinical trials have demonstrated that antihypertensive therapy can significantly reduce the risk of both initial and recurrent stroke. A sudden, prolonged increase in BP can also cause hypertensive encephalopathy, which is classified as a hypertensive emergency.

The GFR is used to estimate kidney function, which declines with aging. This rate of decline is greatly accelerated by hypertension. Hypertension is associated with nephrosclerosis, which is caused by increased intraglomerular pressure. CKD, whether mild or severe, can progress to kidney failure (stage 5 CKD) and the need for

dialysis. Studies have demonstrated that controlling hypertension is the most important strategy to slow the rate of kidney function decline,[31] but it may not be entirely effective in slowing the progression of renal impairment in all patients.

CKD is staged based on estimated glomerular filtration rate (eGFR) values.[32] Stage 3 CKD (moderate) is defined as an eGFR 30 to 59 mL/min/1.73 m^2, stage 4 CKD (severe) is 15 to 29 mL/min/1.73 m^2, and stage 5 (kidney failure) is <15 mL/min/1.73 m^2 or the requirement of dialysis. In hypertension, stage 3 CKD or worse is considered a hypertension-associated complication. An eGFR of <60 mL/min/1.73 m^2 corresponds approximately to a serum creatinine concentration of >1.5 mg/dL in an average male and >1.3 mg/dL in an average female. The presence of persistent albuminuria (>300 mg albumin in a 24-hour urine collection or 200 mg albumin/g creatinine on a spot urine measurement) also indicates significant CKD. (Note: These definitions of the stages of kidney disease and albuminuria will be used throughout the remaining cases in this chapter.) Assessment of kidney function is discussed in Chapter 2, Interpretation of Clinical Laboratory Tests, and Chapter 28, Chronic Kidney Disease.

Peripheral arterial disease, a noncoronary form of atherosclerotic vascular disease, is considered a hypertension-associated complication. It is equivalent in CV risk for CHD.[4] Risk factor reduction, BP control, and antiplatelet agent(s) are needed to decrease progression. Complications of peripheral arterial disease can include infection and necrosis, which in some cases require revascularization procedures or extremity amputation.

Hypertension causes retinopathies that can progress to blindness. Retinopathy is evaluated according to the Keith, Wagener, and Barker funduscopic classification system. Grade 1 is characterized by narrowing of the arterial diameter, indicating vasoconstriction. Arteriovenous nicking is the hallmark of grade 2, indicating atherosclerosis. Long-standing, untreated hypertension can cause cotton wool exudates and flame hemorrhages (grade 3). In severe cases (eg, hypertensive emergency), papilledema occurs, and this is classified as grade 4.

MAJOR RISK FACTORS

CASE 9-1, QUESTION 5: Which major CV risk factors are present in D.C.?

Hypertension is one of nine major CV risk factors (Table 9-4). These are not risk factors for developing hypertension; rather, they increase the risk of hypertension-associated complications. D.C. has multiple CV risk factors: smoking, dyslipidemia, family history of premature coronary heart disease (CHD) in a first-degree relative (father), hypertension, obesity, and physical inactivity.

D.C. is a primary prevention patient because he does not yet have any hypertension-associated complications. He has multiple major CV risk factors, so controlling his BP is of paramount importance to reduce the risk of developing hypertension-associated complications.

Many of D.C.'s risk factors are modifiable. He is a smoker, and this significantly increases his CV risk and may reduce the efficacy of antihypertensive therapy. Smoking cessation may not independently lower D.C.'s BP, but it will decrease his overall risk of CV disease (see Chapter 91, Tobacco Use and Dependence). D.C. is obese, based on his BMI. His lack of physical activity and dietary patterns have likely contributed to his obesity. A more focused patient interview on diet and exercise would be helpful to reinforce the assumption that he has a sedentary lifestyle. D.C.'s dyslipidemia increases his CV risk, and lipid-lowering therapy should be considered to further decrease the risk of CV disease (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease).[33]

Advanced age is considered a major CV risk factor. Although CHD in the elderly is not considered premature, increasing age increases the risk of hypertension-associated complications. Premenopausal females are at low risk for CV disease. However, CV risk in females increases significantly after menopause, similar to the increased risk in males. Therefore, cutoff values for age as a risk factor in males and females are separated by 10 years (>55 years for males, >65 years for females). At age 50, D.C. does not yet have this risk factor.

Case 9-1, Question 6: What is D.C.'s BP goal?

The overarching goal of treating hypertension is to lower hypertension-associated complications. Control of BP is the most feasible clinical end point to guide therapy and should be viewed as a surrogate for attaining this goal. D.C.'s goal BP is <130/80 mm Hg, according to the 2017 ACC/AHA Hypertension Guidelines. His calculated ASCVD goal is ~11%. The presence of LVH reflects subclinical CV disease, according to the SPRINT study.[22]

PRINCIPLES OF TREATMENT

Goals of Therapy

Case 9-1, Question 7: What are the goals of treating D.C.?

Pharmacotherapy principles to achieve these goals include selecting a treatment regimen with antihypertensive agent(s) that reduces risk of CV events, complemented by appropriate lifestyle modifications (Table 9-5).

Health Beliefs and Patient Education

Case 9-1, Question 8: What patient education should be provided to D.C. regarding his hypertension?

Patient education is needed to ensure that D.C. understands his disease and its complications (**Table 9-6**). This should comprehensively include information on disease, treatment, adherence, and complications. Several approaches can be effective, but all methods should include direct communication between the clinician and the patient. Multidisciplinary approaches to disease-

state management in hypertension can effectively use a team of different clinicians (eg, physicians, nurse practitioners, physician assistants, and pharmacists). Providing face-to-face education is most common, but the key components in patient education can be delivered via indirect interactions (eg, telephone).

Table 9-6

Patient–Provider Interactions for Hypertension

Patient Education

- Assess patient's understanding and acceptance of the diagnosis of hypertension.
- Discuss patient's concerns and clarify misunderstandings.
- When measuring BP, inform the patient of the reading both verbally and in writing.
- Assure patient understands his or her goal BP value.
- Ask patient to rate (1–10) his or her chance of staying on treatment.
- Inform patient about recommended treatment, including lifestyle modification. Provide specific written information using standard brochures when available.
- Elicit concerns and questions and provide opportunities for patient to state specific behaviors to carry out treatment recommendations.
- Emphasize
  - the need to continue treatment.
  - that control does not mean cure.
  - that elevated BP is usually not accompanied by symptoms.

Individualize Treatment Regimens

- Include the patient in decision-making.
- Simplify the regimen to once-daily dosing, whenever possible.
- Incorporate treatment into patient's daily lifestyle.
- Set realistic short-term objectives for specific components of the medication and lifestyle modification plan.
- Encourage discussion of diet and physical activity, adverse drug effects, and concerns.
- Encourage self-monitoring with validated BP devices.
- Minimize the cost of therapy, when possible.
- Discuss adherence at each clinical encounter.
- Encourage gradual sustained weight loss.

BP, blood pressure.

Education should be tailored to the patient's specific needs. For example, some patients are able to comprehend the importance of achieving controlled BP by reading written materials, whereas others understand this only after implementing self-BP monitoring. The patient education process must be continuous throughout the duration of therapy. Not all aspects need to be discussed during each clinical interaction. Careful selection of both written and verbal information should be considered so that patients are not overwhelmed or intimidated. The NHLBI patient education materials are available at http://www.nhlbi.nih.gov/health/public/heart/index.htm#hbp. It is important that clinicians review all materials provided to patients to identify the source of information, assess ease of reading, and identify omitted information and sources of confusion or anxiety (eg, drug side effects).

Patients such as D.C. often incorrectly explain BP elevation as stress related. Although certain patients (eg, those with white-coat hypertension) may have BP that is more highly reactive, most patients with essential hypertension will have an elevated BP regardless of their stress level. D.C. should be informed about the cause of his disease and the lack of correlation between stress or symptoms and high BP. Importantly, D.C. needs to realize that elevated BP is almost always asymptomatic and that it can cause serious long-term complications. It is essential that he understands the chronic nature of hypertension and the need for long-term therapy. Otherwise, he may adhere to his treatment only when he "feels his BP is high" or during stressful events.

Some patients believe they can control their BP by stress management rather than with antihypertensive drug therapy and lifestyle modifications. Controlled trials have not consistently proved that stress management is beneficial in treating hypertension.[34] It is important to determine the patient's health beliefs and attitudes and to provide education about the etiology and management of hypertension to promote BP control.

Another common myth patients believe is that treating hypertension commonly leads to fatigue, lethargy, and sexual

dysfunction. This misconception can compromise adherence and be a limiting factor in appropriate management. Clinical trials have repeatedly reported that quality of life is better with active medication than with placebo.[35–38] Data have indicated that as many as 27% of males with hypertension have erectile dysfunction.[7] Although many patients believe this to be a medication-related side effect and that incidence rates vary among antihypertensive agents and classes, erectile dysfunction is likely caused by penile arterial changes (probably atherosclerosis), which is related to uncontrolled or untreated hypertension.[39]

Benefits of Treatment

Case 9-1, Question 9: How can antihypertensive drug therapy reduce D.C.'s risk of hypertension-associated complications?

Without a doubt, antihypertensive therapy reduces the risk of CV disease and CV events in patients with hypertension. Numerous landmark placebo-controlled studies have clearly demonstrated these benefits. The first large-scale trial, published in 1967, was the Veterans Administration (VA) study in males with DBP between 115 and 129 mm Hg.[40] This study was prematurely stopped because benefits of treatment were so dramatic. Antihypertensive therapy significantly reduced cerebral hemorrhage, MI, left ventricular dysfunction, retinopathy, and kidney disease. Other landmark placebo-controlled studies have evaluated antihypertensive therapy in patients with less severe hypertension and have shown a reduced risk of CV events (stroke, ischemic heart disease, and left ventricular dysfunction) and even CV death.[31,32,41,42] Placebo-controlled studies evaluating morbidity and mortality in hypertension are now not only unnecessary but also considered unethical because of the well-established benefits of treatment. Even small reductions in BP have been associated with significant CV benefits. Based on prospective observational studies, a persistent 5 mm Hg reduction in DBP is

associated with a 21% reduction in CHD and a 34% reduction in stroke.[43,44]

Most antihypertensive drugs reduce LVH through varying mechanisms. It is logical that regression of LVH is desirable, but this remains unproved.

Case 9-1, Question 10: Will D.C.'s early signs of hypertension-associated complications improve or reverse with appropriate BP control?

Reductions in BP can reverse many of the changes associated with D.C.'s retinopathy. Studies have demonstrated that the risk of retinopathy in diabetes increases significantly when BP is elevated and that BP lowering can slow this progression. Although D.C. has an elevated fasting glucose, he does not have diabetes. Regardless, lowering BP is desirable for anticipated beneficial effects on his retinopathy.

HYPERTENSION MANAGEMENT

Lifestyle Modifications

Case 9-1, Question 11: Should D.C. start antihypertensive drug therapy, or are lifestyle modifications alone sufficient?

It is reasonable to assume that lifestyle modifications can partially help D.C. achieve his BP goal. D.C. has multiple major CV risk factors and has early evidence of hypertension-associated complications. Lifestyle modifications are germane to the appropriate treatment of hypertension, but prospective clinical trials have not proved that this treatment approach prevents CV disease in patients with hypertension similar to what is proven antihypertensive drug therapy. Hence, initiation of drug therapy should not be delayed unnecessarily, especially for patients with CV risk factors.

MODALITIES THAT LOWER BLOOD PRESSURE

CASE 9-1, QUESTION 12: Which lifestyle modifications can D.C. implement to lower his BP?

Weight reduction through dietary modifications and physical activity and sodium restriction are the most apparent lifestyle modifications for D.C. to lower his BP. A thorough patient interview (diet history to quantify total calories, sodium, fat, and cholesterol, and social history to determine alcohol consumption and confirm cigarette use) should be obtained. Based on this interview, customized recommendations can be made.

The DASH diet should be strongly encouraged in D.C. based on proven benefits.[23]

D.C.'s BMI of 30 kg/m^2 classifies him as obese. As little as a 5% to 10% loss in weight 11.02 to 24.25 pounds (5–11 kg) will provide global health benefits. Strategies that increase his aerobic activity, in addition to diet, can augment weight loss.

OTHER CARDIOVASCULAR RISK REDUCTION STRATEGIES

Smoking cessation

CASE 9-1, QUESTION 13: Aside from treating hypertension, which other CV risk reduction strategies should be recommended in D.C.?

Smoking is an important modifiable major CV risk factor. Cigarette smoking has been shown to independently increase CV and overall mortality, and cessation can decrease the incidence of CV disease.[45] Although smoking does not chronically lower BP, smoking cessation is strongly recommended to improve overall health. Hypertensive smokers should be continually educated about the risks associated with cigarette smoking and directed to behavior-modification programs that can assist smoking cessation efforts (see Chapter 91, Tobacco Use and Dependence).

Low-dose aspirin

The United States Preventive Services Taskforce (USPSTF) recommends initiating low-dose aspirin (81 mg daily) use for the primary prevention of CV disease and in adults ages 50 to 59 years who have a ≥10% 10-year ASCVD risk, are not at increased risk for bleeding, have a life expectancy of ≥10 years, and are willing to take low-dose aspirin daily for ≥10 years.[46] D.C. is not yet a candidate for low-dose aspirin based on his age.

Controlling other comorbid diseases

In addition to treating hypertension and lowering BP to goal, controlling other comorbidities, which are themselves associated with increased CV risk, should be performed. When present, dyslipidemia, diabetes mellitus, obesity, and any other forms of CV disease should be diligently treated and controlled. D.C. has dyslipidemia and requires statin treatment (individuals without clinical ASCVD or diabetes, who are age 40–75 years with LDL-C 70–189 mg/dL, and have an estimated 10-year ASCVD risk of ≥7.5%—D.C.'s calculated risk is 9.6%), and his CV risk would be reduced with better control of this condition (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease).

Pharmacotherapy for Primary Prevention Patients

EVIDENCE-BASED RECOMMENDATIONS

Case 9-1, Question 14: Which treatment principles need to be considered when choosing an initial antihypertensive agent for D.C.?

Selecting an antihypertensive drug is complex. There are numerous choices, and all agents can effectively lower BP. Depending on the dose used, BP reductions are similar.[47] BP reduction, however, is only a surrogate end point of therapy and

does not necessarily reflect overall effectiveness. Reducing hypertension-associated complications is the ultimate goal of treatment.

Case 9-1, Question 15: Which antihypertensive agents are appropriate first-line treatments for D.C.?

Because D.C. is Black and does not have CKD, the 2017 ACC/AHA Hypertension Guidelines recommend thiazide-like diuretics or CCBs as first-choice antihypertensive therapy. This recommendation is based on the propensity of data showing reduced morbidity and mortality with these drug classes.[48]

Traditional landmark placebo-controlled hypertension studies (eg, the SHEP,[41] Swedish Trial in Old Patients with Hypertension,[33] and the Medical Research Council[31]) established that treating hypertension produces significant reductions in CV events (eg, stroke and MI) and mortality. These traditional landmark trials used thiazide diuretic–based therapy, and thus thiazide diuretics have been the quintessential antihypertensive agent for most patients. Subsequently, several clinical trials evaluating newer agents (ACEI, ARB, and CCB) have provided additional evidence on CV event reduction.[14,20,42,49–68] Most of these trials do not include a placebo group (because it is unethical to use placebo in long-term studies); rather, they use an active antihypertensive agent as the comparator (often a thiazide diuretic or β-blocker or both). In those studies in which newer antihypertensive agents were compared with thiazide diuretics, very similar effects were seen. One of these studies was the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[50] In the ALLHAT, 33,357 patients with hypertension were randomly assigned in a double-blind manner to thiazide diuretic (chlorthalidone), CCB (amlodipine), or ACEI (lisinopril)-based therapy. After a mean follow-up to 4.9 years, the incidence of the primary end point of fatal CHD or nonfatal MI was similar among all three treatment arms.

Case 9-1, Question 16: Should monotherapy or two-drug therapy be started in D.C. as his initial regimen?

A monotherapy approach is an option for D.C. Monotherapy with a CCB, or thiazide diuretic as recommended, will likely reduce his BP to <130/80 mm Hg. If D.C. were not Black, an ACEI and an ARB would also be optimal alternatives.

SPECIAL POPULATIONS

Black patients

Case 9-1, Question 17: How should D.C.'s race influence the selection of an antihypertensive regimen?

As monotherapy, it is well documented that a thiazide diuretic or a CCB is highly effective in lowering BP in Black patients. This is likely because of the profile of low renin coupled with high plasma volume pattern of hypertension that is commonly seen in Black patients with hypertension. Conversely, ACEI, ARB, or β-blocker monotherapy is less effective in lowering BP in Black compared with White patients. However, when these agents are used in combination, especially with a thiazide diuretic, these race-based differences seen in BP lowering with monotherapy are abolished. This information may aid in selecting one drug option over another in a primary prevention patient, but does not apply to Black patients with other comorbidities, in whom choice of therapy follows an evidence-based approach to selection based on the comorbidities.

D.C. does not have any other comorbidities for specific antihypertensive drug therapy. His first-line treatment option is CCB or thiazide diuretic. Monotherapy with either a thiazide diuretic or a CCB would be very effective in BP lowering; either of these two drugs is an acceptable treatment option for him.

Elderly patients

CASE 9-2

QUESTION 1: B.D. is an 83-year-old female with a medical history of hypertension, osteoporosis, and hypothyroidism. Her present medications are levothyroxine 100 µg daily, alendronate 70 mg weekly, vitamin D 800 IU daily, and calcium carbonate 600 mg twice daily. She has been diagnosed with hypertension for 2 years, and it has been treated with lifestyle modifications (sodium restriction and exercise three times weekly). B.D. is 64 inches (162.56 cm) tall and weighs 121.25 pounds (55 kg). Her current BP is 160/78 mm Hg (160/80 mm Hg when repeated). All serum laboratory tests are normal. Her provider has been reluctant to start antihypertensive drug therapy because of B.D.'s age.

How is treatment of B.D.'s hypertension different from that of a younger patient?

Older patients with hypertension (age older than 65 years) have the lowest rates of BP control, and this rate decreases in even older populations.[1] Very elderly patients such as B.D., similar to Black patients, respond best to thiazides and CCBs and less to ACEIs, ARBs, and β-blockers when these are used as monotherapy. However, it is unclear whether these small differences in BP lowering among classes are clinically significant; thus, they are all recommended as first choice per treatment guidelines.

Isolated Systolic Hypertension

B.D. has isolated systolic hypertension (ISH), which is defined as an elevated SBP with a normal DBP.[2] This pattern of hypertension is most common in older patients and incurs a significant risk of CV disease. It was once thought that patients with ISH required high SBP to ensure normal perfusion of the heart and brain and that treating ISH would further lower DBP and worsen organ perfusion. Evidence clearly demonstrates, however, that treating ISH with antihypertensive drug therapy reduces the risk of CV events.[33,41,56] B.D.'s hypertension should be managed with drug therapy in addition to lifestyle modifications.

CASE 9-2, QUESTION 2: What data support antihypertensive drug therapy in patients who are very elderly, similar to B.D.?

The care of patients with ISH, including the very elderly, should follow the same general hypertension care principles that apply to all patients, except using a gentler dose initiation approach to reduce the risk of orthostatic hypotension. The 2017 ACC/AHA Guidelines support the same BP goal in the elderly with ASCVD risk ≥10% compared to younger patients (<130/80 mm Hg).[3] In SPRINT, prespecified subgroup analysis of the elderly cohort including those considered frail did sustain benefit from the lower BP target.[22] However, it recognized that lower doses should be used when first starting therapy in elderly patients because of the higher risk of developing orthostatic hypotension. Orthostatic hypotension occurs when standing upright results in an SBP decrease of >20 mm Hg (or a DBP decrease of >10 mm Hg) after 3 minutes of standing and is often accompanied by dizziness or fainting. This is a risk of rapid BP lowering. Orthostatic hypotension is more frequent in elderly patients (especially those with ISH), diabetes, autonomic dysfunction, volume depletion, and in patients taking certain drugs (ie, diuretics, nitrates, α-blockers, psychotropic agents, and phosphodiesterase inhibitors). Antihypertensive dose increases should be gradual to minimize the risk of hypotension. Moreover, initial therapy with two drugs should probably be avoided in the elderly (age 80 years or older) owing to the increased risk of orthostatic hypotension.

The very elderly (ie, patients 80 years or older) have traditionally been underrepresented in landmark placebo-controlled clinical trials. However, the HYVET was a placebo-controlled, randomized trial evaluating the effect of antihypertensive pharmacotherapy (ACEI with or without a thiazide-like diuretic) in patients with hypertension age 80 years or older.[22] This trial was stopped prematurely, after 1.8 median years, owing to a significant reduction in overall mortality in the treatment arm. The HYVET provides compelling evidence that treatment of hypertension in the very elderly provides significant benefits. B.D. should be started on a low-dose thiazide diuretic or CCB for the treatment of her hypertension. For elderly patients with existing incontinence, diuretic therapy will be problematic. Under this

circumstance, a CCB would be a more reasonable first-line option. Considering her advanced age, starting with monotherapy is appropriate to reduce her risk of orthostatic hypotension.

ADDITIONAL CONSIDERATIONS

CASE 9-3

QUESTION 1: You are developing a collaborative drug therapy management (CDTM) protocol for treatment of hypertension that will be used by clinical pharmacists. In your CDTM protocol, you include multiple pharmacotherapy options (ACEIs, ARBs, CCBs, and thiazide diuretics) as equally recommended in primary prevention patients. However, you wish to include additional guidance on how to select an individual drug class to treat hypertension.

What additional factors should be considered in your protocol when selecting a first-line agent for a specific primary prevention patient?

It cannot be emphasized enough that selecting pharmacotherapy should follow an evidence-based philosophy. In patients with other comorbidities, certain antihypertensive drug classes are recommended in place of other options. In patients without other comorbidities, factors such as concomitant diseases, medication costs, serum electrolytes, and prior medication intolerances should be considered (**Table 9-7**). These are helpful when selecting initial therapy for a patient requiring primary prevention and has more than one acceptable drug class as a first-line option or when selecting add-on therapy to further lower BP. These are discussed later in this chapter.

Table 9-7
Additional Considerations in Antihypertensive Drug Choice[a]

Antihypertensive Agent	Situations With Potentially Favorable Effects	Situations With Potentially Unfavorable Effects[b]	Avoid Use
ACEI	Low-normal potassium, elevated fasting glucose, microalbuminuria (with or without diabetes)	High-normal potassium or hyperkalemia	Pregnancy, bilateral renal artery stenosis, history of angioedema
ARB	Low-normal potassium, elevated fasting glucose, microalbuminuria (with or without diabetes)	High-normal potassium or hyperkalemia	Pregnancy, bilateral renal artery stenosis
CCB: dihydropyridine	Raynaud phenomenon, elderly patients with isolated systolic hypertension, cyclosporine-induced hypertension	Peripheral edema, left ventricular dysfunction (all except amlodipine and felodipine), high-normal heart rate or tachycardia	
CCB: nondihydropyridine	Raynaud phenomenon, migraine headache, supraventricular arrhythmias, high-normal heart rate or tachycardia	Peripheral edema, low-normal heart rate	Second- or third-degree heart block, left ventricular dysfunction
Thiazide diuretic	Osteoporosis or at increased risk for osteoporosis, high-normal potassium	Gout, hyponatremia, elevated fasting glucose (as monotherapy), low-normal potassium or sodium	

High-normal refers to patients in the high end of the normal range, but not above the range.

Low-normal refers to patients in the low end of the normal range, but not below the range.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

[a]These considerations should never replace drug recommendations for a compelling indication.

[b]May use but requires diligent monitoring.

The costs of treating hypertension and related complications are substantial to patients and health systems.[69] With expanding availability of generic agents, costs attributed to drug acquisition are small in comparison with expenses for laboratory evaluations, office visits, and medical care for hypertension-associated complications. Whenever possible, affordable regimens that do not compromise efficacy should be designed. Generic antihypertensive products are equally effective and less expensive than are brand-name products, and all first- and second-line antihypertensive classes have generic alternatives. The frequency of administration can influence treatment. Once-daily administration assists adherence; all major drug classes contain agents that are either naturally long-acting or formulated in long-acting preparations.

Pharmacotherapy for Patients With Other Comorbidities

Case 9-3, Question 2: In your CDTM protocol, when should an ACEI or ARB be identified as first-line therapy ahead of other antihypertensive agents?

There are other coexisting diseases or hypertension-associated complications in patients that may warrant the use of certain classes of antihypertensive because these agents show significant benefits in reducing CV morbidity or mortality in patients with those specific comorbidities.

DIABETES

Kidney disease and CV disease are both long-term hypertension-associated complications that are at high risk for occurring in patients with diabetes. The 2017 ACC/AHA Hypertension Management Guidelines recommend the same four classes of antihypertensive agents as first choice in non-Black patients with diabetes for primary prevention of CV events (ACEI, ARB, CCB, and thiazide diuretics) and thiazide diuretics and CCB in Black patients.[3] When compared head to head, ACEIs are superior to dihydropyridine CCBs in reducing CV events.[59,60] Subgroup analyses of larger clinical trials further support CV event reduction with ACEIs and ARBs. Therefore, ACEI and ARB may be the preferred initial antihypertensive therapy for a patient with diabetes if there is no other contraindication.

Case 9-3, Question 3: In your CDTM protocol, how should significant CKD be defined so that patients with CKD can be identified and treated appropriately?

CHRONIC KIDNEY DISEASE

It is common that CKD presents initially with microalbuminuria (30–299 mg albumin in a 24-hour urine collection) that can progress over the course of several years to overt kidney failure.[32] Progression is

accelerated in the presence of both hypertension and diabetes. The 2017 ACC/AHA Hypertension Treatment Guidelines recommend ACEI (if intolerance is due to cough, ARB therapy) to be used as first-line therapy in patients with CKD if albuminuria (≥300 mg/day or ≥300 mg/g creatinine by first morning void) is present.[3] Both ACEI and ARB have also been shown to reduce the progression of CKD in type 1 diabetes,[68] in type 2 diabetes,[61,62] and in those without diabetes.[66-71] Recently, ARB therapy has also been shown to decrease risk of developing microalbuminuria in patients with diabetes.[72]

Although many of the long-term benefits of ACEI or ARB therapy may be from BP lowering, their evidence base is robust enough to support their first-line use in CKD.[73,74] After ACEI or ARB therapy has been implemented, data support a CCB as the second drug because this has been shown to reduce progression of CKD better than does a thiazide diuretic as the second drug added based on the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial.[73]

Patients with stage 3 to 4 CKD (eGFR of 20 to <60 mL/min/1.73 m^2) comprised 28% of the SPRINT study population, and, in this group, intensive BP management seemed to provide the same benefits for reduction in the CV disease composite primary outcome and all-cause mortality as were seen in the full study cohort. Given that most patients with CKD die from CV complications, based on evidence from SPRINT, the 2017 guidelines support patients with CKD with ASCVD risk >10% to have a lower BP target of <130/80 mm Hg.[22]

CHRONIC AND ACUTE CORONARY ARTERY DISEASE

CASE 9-3, QUESTION 4: In your CDTM protocol, although β-blocker is no longer considered as a first choice for primary prevention, are there any cases when β-blocker therapy would be identified as an appropriate first-line antihypertensive drug therapy?

The ACC and AHA have guidelines for chronic CAD that recommend treatment with a β-blocker, followed shortly thereafter by the addition of an ACEI.[75] β-Blockers (those without intrinsic sympathomimetic activity [ISA]) decrease the risk of a subsequent MI or sudden cardiac death by decreasing the adrenergic burden on the heart, and progression of coronary atherosclerosis. ACEI therapy promotes cardiac remodeling, improves cardiac function, and reduces the risk of CV events. An ARB is an alternative in patients who do not tolerate an ACEI, because fewer data that assess the long-term impact of an ARB on CV events compared with an ACEI in chronic CAD exist.[76,77] A thiazide diuretic can be added to the core regimen of a β-blocker with an ACEI (or ARB) if additional BP reduction is needed. However, if an additional agent is needed to treat ischemic symptoms for patients with chronic stable angina, a dihydropyridine CCB can be added to this core regimen. If a β-blocker cannot be used because of intolerance or contraindication, a nondihydropyridine CCB can be used as an alternative to a β-blocker. Acute CAD, also called acute coronary syndrome, includes unstable angina, non–ST-segment elevation MI, and ST-segment elevation MI. The ACC/AHA Guidelines for these conditions indicate a β-blocker as first-line pharmacotherapy.[78] The 2017 ACC/AHA Hypertension Treatment Guideline recommends that these patients have a BP goal of <130/80 mm Hg.[3]

LEFT VENTRICULAR DYSFUNCTION

Pharmacotherapy for left ventricular dysfunction should include a three-drug combination of an ACEI, a β-blocker, and an aldosterone antagonist, plus loop diuretics depending on the need for diuresis.[79] ACEIs, β-blockers, and aldosterone antagonists, all have numerous landmark clinical trials showing reduced morbidity and mortality rates, whereas diuretics provide primarily symptomatic relief of edema.[79]

According to evidence-based medicine principles, only metoprolol, carvedilol, and bisoprolol are indicated for left ventricular dysfunction. Other β-blockers (eg, atenolol) should not be used in

patients with left ventricular dysfunction because they do not have supporting data demonstrating that they reduce CV event rates in these patients. Patients should be clinically euvolemic and hemodynamically stable before adding a β-blocker. As discussed in Chapter 14, Heart Failure, it is important to start with very low doses of a β-blocker, then slowly titrate upward over the course of several weeks to the recommended dosing range for left ventricular dysfunction. An ARB can be used as an alternative to an ACEI.[79]

Potassium serum concentrations must be carefully monitored in the situation when an ACEI (or ARB) and an aldosterone antagonist are used together. Alternatively, the combination of hydralazine with isosorbide dinitrate can be added in Black patients.[80] This combination has been demonstrated to improve CV outcome in this patient population. The 2017 ACC/AHA Hypertension Treatment Guideline recommends that these patients have a BP goal of <130/80 mm Hg.[3]

Monitoring Therapy

Four aspects of treatment must always be considered: (a) BP response to attain goal, (b) adherence to lifestyle modifications and pharmacotherapy, (c) progression to hypertension-associated complications, and (d) drug-related toxicity.

Reduction in BP should be evaluated 1 to 4 weeks after starting or modifying therapy for most patients. BP usually begins to decrease within 1 to 2 weeks of starting an agent, but steady-state antihypertensive effects can take up to 4 weeks. If patients are in hypertensive crisis, evaluation should occur sooner, within hours to days (see Chapter 16, Hypertensive Crises).

Two BP values separated by at least 1 minute should be measured during each clinical evaluation, with the average used to make a proper assessment. If dehydration or orthostatic hypotension is suspected, BP should be measured in both the seated and standing positions to detect orthostatic changes. For routine monitoring, measuring BP in the seated position is sufficient. Self-BP

monitoring values should be considered if available. Normally, however, they are slightly lower (5 mm Hg) than are clinical values even in patients without white-coat hypertension. For example, patients with a goal BP value of <140/90 mm Hg should have home measurements that are <135/85 mm Hg.[9]

All patients should be questioned in a nonthreatening manner regarding adherence to lifestyle modifications and drug therapy. This is especially important for complex regimens, when drug intolerance is likely, or when financial constraints hinder acquisition of medications. Evaluating hypertension-associated complications and drug side effects are essential. New hypertension-associated complications may necessitate changes to treat a compelling indication or attain a new BP goal. Drug-related side effects may similarly require therapy modifications.

CASE 9-4

QUESTION 1: B.A. is a 58-year-old White female who is postmenopausal, does not smoke, and never drinks alcohol. Since being diagnosed with hypertension, she has modified her diet, begun routine aerobic exercise, and has lost 22.04 pounds (10 kg) in the past 18 months. She now weighs 158.73 pounds (72 kg) and is 64.96 inches (165 cm) tall. Her BP is now 150/94 mm Hg (150/92 mm Hg when repeated) and has consistently remained near this value for the past year. Her BP when first diagnosed was 156/96 mm Hg. Physical examination shows no LVH and no retinopathy. Urinalysis is negative for protein. Other laboratory tests are normal, except for dyslipidemia (total cholesterol 200 mg/dL, HDL 38 mg/dL, LDL120 mg/dL). B.A. has no health insurance and is concerned about the cost of therapy. She takes over-the-counter calcium with vitamin D, and her provider wants to start HCTZ 25 mg/day.

Is HCTZ an appropriate agent for B.A.?

CLINICAL SCENARIOS

Diuretics

B.A. is a primary prevention patient with uncontrolled hypertension. Her 10 years' calculated ASCVD risk is 4.7%. According to 2017 ACC/AHA Guidelines, her BP goal is <140/90 mm Hg.[2,3] Initial monotherapy is reasonable. Appropriate first-line treatment options include an ACEI, ARB, a CCB, or thiazide diuretic. All these drug classes have generic options and should be easily affordable for B.A. A thiazide diuretic may also benefit her osteoporosis (Table 9-7) and is an appropriate choice. Several types of diuretics are used to manage hypertension (**Table 9-8**).[30] All lower BP, with differences being duration of action, potency of diuresis, and electrolyte abnormalities.

Table 9-8
Diuretics in Hypertension

Category	Selected Products	Usual Dosage Range (mg/day)	Dosing Frequency
Thiazide and thiazide-like	Chlorthalidone	12.5–25	Daily
	Hydrochlorothiazide	12.5–25	Daily
	Indapamide	1.25–5	Daily
	Metolazone	2.5–10	Daily
	Metolazone	0.5–1.0	Daily
Loop	Bumetanide	0.5–4	bid
	Furosemide	20–80	bid
	Torsemide	2.5–10	Daily
Potassium sparing	Amiloride	5–10	Daily to bid
	Triamterene	50–100	Daily to bid
Potassium-sparing combination	Triamterene/HCTZ	37.5/25–75/50	Daily
	Spironolactone/HCTZ	25/25–50/50	Daily
	Amiloride/HCTZ	5–10/50–100	Daily
Aldosterone antagonist	Eplerenone	50–100	Daily to bid
	Spironolactone	12.5–50	Daily to bid

bid, two times daily; HCTZ, hydrochlorothiazide.

THIAZIDES

Thiazides are diuretics of choice for most patients with hypertension. Similar to loop diuretics, an initial diuresis is experienced. After approximately 4 to 6 weeks of thiazide diuretic therapy, the diuresis dissipates. In exchange, it has a consistent PVR reduction effect, which is responsible for sustaining antihypertensive effects.

Case 9-4, Question 2: How should a thiazide diuretic be started in B.A.?

Hydrochlorothiazide versus chlorthalidone

HCTZ and chlorthalidone have been used in several major outcome trials, although only chlorthalidone-based regimens have proved to be of benefit in the low doses commonly used in practice today.[31,33,41,50,56,81,82] Both agents are inexpensive and dosed once daily, but HCTZ is most frequently used in the United States and is more widely available in fixed-dose combination products. The usual starting dose of HCTZ or chlorthalidone is 12.5 mg once daily. A maintenance dose of 25 mg once daily can effectively lower BP and has a low incidence of side effects (eg, hypokalemia and hyperuricemia) that can be managed with routine monitoring.[35,47,48]

Significant controversy surrounds the comparative efficacy of HCTZ and chlorthalidone. Most clinicians assume a class effect for these two drugs.[10] However, class effects can be legitimized only after assurance of equipotent dosing; for antihypertensives, when they are not directly compared in a CV event trial, it assumes that if two agents achieve similar BP lowering, then both achieve similar reduction in CV events. With regard to HCTZ and chlorthalidone, this assumption is unproven. Chlorthalidone is more potent on a milligram-per-milligram basis and has a longer half-life than does HCTZ (50–60 vs 9–10 hours).[83] Based on a comparative study using 24-hour ABPM, it appears that the equipotent dose of chlorthalidone 25 mg daily is HCTZ 50 mg daily, but this dose of HCTZ is unpopular because of increased side effects. Consequently, it is believed by some that the antihypertensive efficacy of chlorthalidone is greater than that of HCTZ when contemporary doses are used; the 12.5- to 25-mg doses of chlorthalidone do not appear to significantly increase the risk of hypokalemia more so than does HCTZ.[84] Complicating this issue is evidence demonstrating that office BP tends to overestimate the response to HCTZ, and the 24-hour BP lowering with HCTZ is only comparable to other common agents (ACEI, ARB, CCB, and even β-blockers) when 50 mg daily is used.[85] Data from

the Multiple Risk Factor Intervention Trial indicate that chlorthalidone reduces CV events more than does HCTZ.[85] Although chlorthalidone is the most optimal and evidence-based thiazide diuretic for B.A., HCTZ remains currently accepted in the clinical environment as a reasonable thiazide diuretic for hypertension assuming her BP goal can be readily achieved with its use.

LOOP DIURETICS

Loop diuretics produce a more potent diuresis, but a smaller decrease in PVR, and less vasodilation than do thiazide diuretics. They are subject to a significant postdose antinatriuretic period, which offsets their antihypertensive effect. Therefore, a thiazide is more effective at lowering BP than are loop diuretics in most patients. Loop diuretics are usually considered only for patients with severe CKD (eGFR <30 mL/min/1.73 m^2), left ventricular dysfunction, or severe edema. In these patients, potent diuresis is often needed. Furosemide has a short duration of effect and should be given twice daily when used in hypertension, whereas torsemide has a longer duration of action and can be given once daily.

POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics (triamterene and amiloride) should be reserved for patients who experience hypokalemia while on a thiazide diuretic. With low-dose thiazide diuretics, <25% of patients develop hypokalemia, and most cases are not severe. Triamterene and amiloride usually do not provide significant additional BP lowering when added to a thiazide diuretic. Several fixed-dose products that include HCTZ with triamterene or amiloride are available. Empirically starting all patients with hypertension treated with a thiazide diuretic on triamterene or amiloride to avoid hypokalemia is not rational or necessary unless baseline serum potassium is in the low-normal range.

A thiazide diuretic is an optimal first-line option in primary prevention in patients such as B.A., and she has no contraindications (**Table 9-9**). Although B.A. has dyslipidemia,

thiazide diuretics are unlikely to have a clinically significant effect on cholesterol when used in low doses.[86,87] An appropriate starting dose of HCTZ is 12.5 or 25 mg daily. B.A. has no additional risks for orthostatic hypotension, so starting at the higher 25-mg daily dose is safe and will have a better chance of lowering her BP to goal than the lower 12.5-mg dose because most antihypertensive agents provide a 10-mm Hg reduction in SBP and 5-mm Hg reduction in DBP with a standard starting dose.[88]

Table 9-9
Side Effects and Contraindications of Antihypertensive Agents

	Side Effects			Contraindications
	Innocuous but Sometimes Annoying	**Potentially Harmful**	**Usually Requires Cessation of Therapy, at Least Temporarily**	
Thiazide diuretics	Increased urination (at onset of therapy), muscle cramps, hyperuricemia (without gout)	Hypokalemia,[a] hyponatremia, hyperglycemia, hypovolemia, pancreatitis, photosensitivity, hypercholesterolemia, hypertriglyceridemia, hyperuricemia with gout, orthostatic hypotension (more frequent in elderly)	Hypercalcemia, azotemia, skin rash (cross-reacts with only certain sulfonamide allergies), purpura, bone marrow depression, lithium toxicity in patients on lithium therapy, hyponatremia	Anuria, kidney failure
Loop diuretics	Increased urination, muscle cramps, hyperuricemia (less than with thiazides)	Hypokalemia,[a] hyperglycemia, hypovolemia, pancreatitis, hypercholesterolemia, hypertriglyceridemia, hearing loss with large IV doses, orthostatic hypotension (more pronounced in the elderly)	Hyponatremia, hypocalcemia, azotemia, skin rash (cross-reacts with only certain sulfonamide allergies), photosensitivity, lithium toxicity in patients on lithium therapy	Anuria
ACEI	Dizziness, dry cough	Orthostatic hypotension (more pronounced in the elderly treated with a diuretic), increased serum creatinine, increased potassium	Angioedema, severe hyperkalemia, increase in serum creatinine >35%	Bilateral renal artery stenosis, volume depletion, hyponatremia, pregnancy, history of angioedema
ARB	Dizziness	Orthostatic hypotension (more pronounced in the elderly treated with a diuretic), increased serum creatinine, increased potassium	Severe hyperkalemia, increase in serum creatinine >35%	Bilateral renal artery stenosis, volume depletion, hyponatremia, pregnancy
CCB: dihydropyridines	Dizziness, headache, flushing	Peripheral edema, tachycardia	Significant peripheral edema	Left ventricular dysfunction (not with amlodipine or felodipine)
CCB: nondihydropyridines	Dizziness, headache, constipation	Bradycardia	Heart block, left ventricular dysfunction, interactions with certain drugs	Left ventricular dysfunction, second- or third-degree heart block, sick sinus syndrome
β-Blocker	Bradycardia, weakness, exercise intolerance	Masking the symptoms of hypoglycemia in diabetes, hyperglycemia, aggravation of peripheral arterial disease, erectile dysfunction, increased triglycerides, decreased HDL-C	Left ventricular dysfunction (not with carvedilol, metoprolol, bisoprolol), bronchospasm in patients with asthma or COPD (more pronounced with nonselective agents)	Severe asthma, second- or third-degree heart block, acute left ventricular dysfunction exacerbation, coronary artery disease for agents with intrinsic sympathomimetic activity
Aldosterone antagonist	Menstrual irregularities (spironolactone only) or gynecomastia (spironolactone only)	Increased potassium	Hyperkalemia, hyponatremia	Kidney failure. kidney impairment (for eplerenone: CrCl <50 mL/min, or type 2 diabetes with proteinuria, and creatinine >1.8 in females, >2.0 in males), hyperkalemia, hyponatremia

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HDL-C, high-density lipoprotein cholesterol; IV, intravenous.

[a]Routine addition of potassium supplementation or empiric concurrent potassium-sparing diuretics should be discouraged unless hypokalemia is demonstrated, the patient is taking digoxin, or potassium is in the low-normal range.

PATIENT EDUCATION

CASE 9-4, QUESTION 3: B.A. is prescribed HCTZ 25 mg daily. How should she be counseled regarding this therapy?

Several counseling points are summarized in Table 9-6. Some patients disregard lifestyle modifications when they start antihypertensive therapy, so B.A. must be encouraged to continue lifestyle modification to maximize her response to drug therapy. B.A. should be informed that diuretics lower both BP and risk of CV events, and that taking her dose at about the same time each morning to minimize nocturia and provide consistent effects is recommended. B.A. should expect to experience increased urination when starting HCTZ, but she should be informed that this diminishes with time. Inform B.A. that missed doses should be taken as soon as possible within the same day, but doubling doses the next day is not recommended. The potential for hypokalemia, which is easily identified and managed, and the need for routine monitoring of serum potassium should be reviewed. She should be counseled on the signs and symptoms of electrolyte abnormalities (eg, leg cramps and muscle weakness) and encouraged to report these to her health care provider if they occur. Increasing dietary intake of potassium-rich foods to minimize electrolyte depletion is an option to minimize potassium loss. This should be encouraged only with thiazide and loop diuretics, but not with potassium-sparing agents.

Despite improvements with lifestyle modifications and reported adherence to HCTZ, B.A.'s goal BP of <140/90 mm Hg has not been met (her BP average is 141/83 mm Hg). No new signs of hypertension-associated complications are seen. She should be encouraged to continue with her current efforts, but other interventions are warranted.

CASE 9-4, QUESTION 4: After 4 weeks of HCTZ 25 mg daily, B.A. has no problems and has not missed a dose. She is exercising and is following the DASH diet. Her BP values are 142/86 mm Hg (140/84 mm Hg when repeated). Her fasting laboratory values are as follows:

Serum potassium, 3.8 mEq/L
Uric acid, 7.3 mg/dL
Glucose, 99 mg/dL

All other values are unchanged. Last month, potassium was 4.0 mEq/L, uric acid was 6.8 mg/dL, and fasting glucose was 95 mg/dL. What is your assessment regarding the efficacy and toxicity of B.A.'s antihypertensive therapy?

POTASSIUM LOSS

Adverse reactions with low-dose thiazide diuretics (eg, HCTZ 12.5–25 mg daily) are minimal compared with higher dose therapy (HCTZ >25 mg daily). Moreover, side effects and tolerability with low-dose thiazide diuretic therapy are similar to other first-line drug therapy options and not much higher than what is seen with placebo.[35,37,38] Regardless, signs and symptoms of electrolyte and metabolic changes, such as hypokalemia, hyponatremia, hyperglycemia, or hyperuricemia, should be evaluated in all patients treated with thiazide diuretics. B.A. has experienced small changes in serum potassium and uric acid, which are typical thiazide-induced abnormalities. B.A. should be questioned about muscle cramps or weakness, which can be caused by decreased potassium.

CASE 9-4, QUESTION 5: Is B.A.'s potassium decrease concerning? If so, how should this be managed?

Most total body potassium is intracellular (~98%). Thiazide diuretics can cause potassium loss and can result in potassium serum concentrations in the low end of the normal range. However, with low-dose therapy, overt hypokalemia is not common. HCTZ in doses of 12.5, 25, and 50 mg daily can decrease serum potassium by an average of 0.21, 0.34, and 0.5 mEq/L, respectively.[35,87,89] This is usually considered mild, with serum potassium concentrations reaching a nadir within the first month of therapy and remaining stable thereafter. Restriction of dietary sodium in patients receiving diuretic therapy has been shown to reduce the loss of potassium and should be encouraged in B.A.[90]

Hypokalemia

Case 9-4, Question 6: When is potassium correction needed to manage diuretic-induced hypokalemia?

B.A.'s potassium is within the normal range. Potassium replacement is not indicated. Diuretic-associated hypokalemia should be treated when serum concentrations are below normal regardless of whether symptoms (eg, muscle cramps) are present. Serum potassium should be measured at baseline and 2 to 4 weeks after initiating therapy or increasing the diuretic dose.

Potassium-rich foods (eg, dried fruit, bananas, potatoes, and avocados) may help prevent small decreases in potassium, but they cannot be used as sole therapy to correct hypokalemia. For instance, one medium-size banana has only 11.5 mEq of potassium. The usual replacement dose of prescribed potassium chloride is 20 to 40 mEq/day but can range from 10 to >100 mEq/day. Potassium chloride, bicarbonate, gluconate, acetate, and citrate salts are available for potassium replacement therapy. Rather than supplement potassium, which does not effectively correct the underlying mechanisms responsible for hypokalemia, a more appropriate and effective strategy to manage diuretic-induced hypokalemia is to add a potassium-sparing diuretic. Hypomagnesemia often accompanies diuretic-induced hypokalemia and must be normalized before hypokalemia can be effectively reversed.

Other metabolic abnormalities

Case 9-4, Question 7: How should the increase in B.A.'s uric acid be managed?

Thiazide diuretics can increase serum uric acid concentrations in a dose-dependent manner. Uric acid increases also occur with loop diuretics, but to a lesser extent. Increased proximal tubular renal

reabsorption, decreased tubular secretion, or increased postsecretory reabsorption of uric acid contributes to diuretic-induced hyperuricemia. Thiazide-induced hyperuricemia is usually small (≤0.5 mg/dL) and is not clinically significant in patients without a history of gout.[88] For patients with a history of gout, diuretics are not contraindicated, but an increase in serum uric acid may require a decrease in dose or possibly discontinuation of the diuretic, especially for those not on preventive antihyperuricemic therapy (eg, allopurinol and febuxostat). Acute gouty arthritis precipitated by diuretic therapy should be treated, and the diuretic should be dose reduced or discontinued, at least temporarily. Future use of the diuretic will depend on whether long-term antihyperuricemic therapy is to be added and the risk versus benefit for continuing the diuretic. B.A.'s serum uric acid concentration is elevated, but switching to a different agent or lowering the dose of HCTZ is unnecessary because she has no symptoms of gout.

It should be noted that changes in parameters such as uric acid can be informative regarding dosing. When a given dose of a diuretic fails to lower BP, it is often unclear as to whether the failure is a result of mechanisms other than volume driving the hypertension or a result of the diuretic dose being insufficient to achieve the desired physiologic effect. For example, the absence of an increase in uric acid suggests that the administered dose was insufficient, and that a higher dose merits consideration. In B.A.'s case, the increase in uric acid confirms that the given dose was sufficient to have had a physiologic effect, so adding an antihypertensive agent from a different drug class would be preferable to increasing the diuretic dose if further BP lowering is necessary.

Case 9-4, Question 8: How much will HCTZ alter B.A.'s cholesterol values?

Small increases in LDL-C and triglycerides are potential side effects of diuretic therapy. Dietary fat restrictions help minimize, but do not necessarily prevent, these effects. Contrary to other biochemical disturbances, diuretic-induced changes in the lipid

profile are not dose related, and overall changes are small. Many clinical trials lasting >1 year have shown that these alterations with diuretic therapy are not sustained with prolonged use.[86,87] Even if these changes are persistent, they are very small and are not clinically significant. The presence of dyslipidemia should never be a reason to avoid diuretic therapy.

Case 9-4, Question 9: What other potential electrolyte abnormalities should be evaluated in B.A. because of her thiazide diuretic therapy?

Hyponatremia is a serious, yet infrequent, adverse effect of diuretics. Changes in sodium concentrations are usually small, and most patients are usually asymptomatic. Frail, elderly females appear more susceptible to experiencing severe hyponatremia (<120 mEq/L) from diuretics, which rarely occurs, but requires discontinuation of therapy. Attention should be paid to the presence of other medications that can contribute to hyponatremia (eg, selective serotonin reuptake inhibitors and psychotropic drugs), and patients should be counseled to avoid excessive free water intake.

Hypomagnesemia is an often-overlooked metabolic complication of diuretic therapy. Both thiazide and loop diuretics increase urinary excretion of magnesium in a dose-dependent manner. Symptoms of significant hypomagnesemia include muscle weakness, muscle tremor or twitching, mental status changes, and cardiac arrhythmias. The presence of these symptoms would necessitate magnesium supplementation or use of a potassium-sparing agent as noted earlier if hypokalemia is also present.

Thiazide diuretics decrease urinary calcium excretion and can be used to prevent calcium-related kidney stones. The retention of calcium does not significantly increase serum calcium concentrations and does not place patients at risk for hypercalcemia. This effect, however, may be beneficial in females at risk for osteoporosis (eg, postmenopausal) such as B.A. or in patients with osteoporosis. Conversely, loop diuretics increase renal clearance of calcium.

Reasons for Inadequate BP Control

Case 9-4, Question 10: What are the common reasons for inadequate patient response to antihypertensive pharmacotherapy?

B.A. has been on her current dose of HCTZ for 4 weeks. The full antihypertensive effect of HCTZ should have been achieved, but she still has uncontrolled hypertension. She has had a response, but it remains inadequate. Potential reasons for an inadequate response, or lack of attaining BP goal values, with an antihypertensive should be considered before modifying her drug therapy regimen (**Table 9-10**). A comprehensive medication history and medical evaluation is needed to rule out identifiable causes, in particular nonadherence to the prescribed regimen. Her BP reduction with HCTZ is typical. Her kidney function is good, and no evidence exists of edema, so volume overload is unlikely. There are no apparent secondary causes of elevated BP. It is reasonable to conclude that B.A. needs additional therapy to achieve her goal BP. It is very common that most patients require two or more agents to attain BP goal values.

Table 9-10
Reasons for Not Attaining Goal Blood Pressure Despite Antihypertensive Pharmacotherapy

Drug Related	Health Condition or Lifestyle Related	Other
Nonadherence	Volume overload	Improper blood pressure measurement
Inadequate antihypertensive dose	Excess sodium intake	Resistant hypertension
Inappropriate antihypertensive combination therapy	Volume retention from chronic kidney disease	White-coat hypertension
Inadequate diuretic therapy	Secondary disease causes (Table 9-2)	Pseudohypertension

Secondary drug-induced causes (Table 9-2)	Obesity	
Clinician's failure to intensify or augment therapy (ie, clinical inertia)	Excessive alcohol intake	

Modifying Therapy

When a patient cannot achieve optimal BP control with initial antihypertensive, it is recommended that the dose of the first drug may be increased (if the patient has not yet achieved maximum dose of the agent), or a low dose of a second agent may be added. Second agents of choice would be ACEI, ARB, CCB, or thiazide diuretics, whichever one the patient is not already taking.[2] B.A.'s present dose of HCTZ is appropriate and should not be increased to the maximal recommended dose of 50 mg daily (considered high-dose therapy) because it may increase risk of electrolyte and metabolic side effects. B.A.'s potassium dropped to 3.8 mEq/L with HCTZ, and further dosage increases may produce hypokalemia (<3.5 mEq/L) requiring correction. Her hyperuricemia may also be worsened. The slightly increased antihypertensive response expected from increasing to 50 mg/day is therefore not justified.[85] Discontinuing HCTZ and starting a different agent is an option, but it is not prudent to abandon the HCTZ; she tolerated the treatment and experienced a reasonable BP response, and the HCTZ will augment the efficacy of nearly any other agent that may be added and may benefit her osteoporosis.

TWO-DRUG REGIMENS

The role of two-drug regimens in the treatment of hypertension is very clear. Most patients require multiple agents for BP control.

Adding a second agent to B.A.'s regimen is needed to reduce BP to her goal. She is a primary prevention patient, so three potential add-on antihypertensive agents that are considered first line include an ACEI, ARB, or a CCB. Ideally, a combination of two drugs with

different mechanisms of action should be selected to produce a complementary effect to lower BP.

Adding an ACEI or ARB to B.A.'s HCTZ will result in additive antihypertensive effects that are independent of reversing fluid retention. Diuretics reduce BP initially by decreasing fluid volume but maintain their antihypertensive effects by lowering PVR. BP lowering, however, can stimulate renin release from the kidney and activate the RAAS. This compensatory mechanism is an in vivo attempt to neutralize BP changes and regulate fluid loss. An ACEI or ARB blocks the RAAS, explaining why combinations of these agents with diuretics are additive. Data from the ACCOMPLISH trial support combination therapy for hypertension. In this randomized, double-blind trial, 11,506 patients with hypertension were randomly assigned to the combination of an ACEI with thiazide diuretic or an ACEI with a CCB.[91] After a mean follow-up of 3 years, the risk of CV events was significantly lower with the ACEI with CCB combination. Switching B.A.'s HCTZ to an ACEI with a CCB may be more effective in lowering CV events than adding an ACEI to her current HCTZ. This would be an acceptable modification. However, considering her response to HCTZ, simply adding an ACEI is also reasonable.

Fixed-dose combination products

Several fixed-dose combination products including two or three drugs are available.

Although individual dose titration is not simple with fixed-dose combination products, their use can reduce the number of tablets or capsules taken by patients. This has been demonstrated to improve adherence compared with using two separate single-drug products.[92] Improved adherence may increase the likelihood of achieving goal BP values.

Most fixed-dose combinations include a thiazide diuretic, and many are available generically. Other fixed-dose combination products combine a CCB with either an ACEI or ARB. These combinations, similar to a thiazide with an ACE or ARB, are highly

effective in lowering BP. An economic advantage may even exist to using a fixed-dose combination if it allows the patient to receive two drugs for one medication copayment. The Simplified Treatment Intervention to Control Hypertension Study demonstrated that initiating therapy with a fixed-dose combination product according to a treatment algorithm was superior in attaining goal BP values when compared with usual management according to national guidelines.[93] These data further support using a fixed-dose combination product for initial therapy.

B.A. is a candidate for a fixed-dose combination product. If the combination of an ACEI with HCTZ is selected for her, many options exist. All of the products with an ACEI also include HCTZ at the dose she is currently on. If the combination of an ACEI with a CCB is selected, fewer options exist, but there are products that contain an ACEI with a dihydropyridine CCB or a nondihydropyridine CCB. Cost should be considered because this is a concern for B.A. Multiple ACEI with thiazide diuretic combinations are available generically, but there is only one generic ACEI with CCB combination. Many ARBs are gradually becoming generic, so those may be potential options as well; therefore, a combination of ARB plus thiazide diuretic may also be an option eventually.

Angiotensin-Converting Enzyme Inhibitor

CASE 9-5

Question 1: A.R. is a 49-year-old Black female with type 2 diabetes. She started lisinopril 10 mg daily 2 weeks ago when her BP values were around 155/90 mm Hg. Since then, she has had weekly BP measurements, and her values have averaged 145/85 mm Hg despite strict adherence to her lifestyle modifications. Her BP today is 144/84 mm Hg (142/88 mm Hg when repeated), and her heart rate is 78 beats/min. She is not a smoker, and her BMI is 29 kg/m^2. All her laboratory test results, including kidney function, are within normal limits, except that her spot urine albumin-to-creatinine ratio is 80 mg/g (2 weeks ago it was 90 mg/g).

Is 2 weeks of lisinopril therapy long enough to assess her antihypertensive response?

Several ACEIs are available (**Table 9-11**). Most ACEIs are dosed once daily in hypertension (Table 9-11). In general, most ACEIs, if used in equivalent doses, are considered interchangeable.

Table 9-11
Angiotensin-Converting Enzyme Inhibitors in Hypertension

Drug	Usual Starting Dose (mg/day)[a]	Usual Dosage Range (mg/day)	Dosing Frequency
Benazepril	10	20–40	Daily to bid
Captopril	25	50–100	bid to tid
Enalapril	5	10–40	Daily to bid
Fosinopril	10	20–40	Daily
Lisinopril	10	20–40	Daily
Moexipril	7.5	7.5–30	Daily to bid
Perindopril	4	4–16	Daily
Quinapril	10	20–80	Daily to bid
Ramipril	2.5	2.5–20	Daily to bid
Trandolapril	1	2–4	Daily

bid, two times daily; tid, three times daily.

[a]Starting dose may be decreased 50% if patient is volume depleted, has acute heart failure exacerbation, or is very elderly (75 years or older).

The time to reach steady-state BP conditions is similar to what is seen with other antihypertensive agents. It may take several weeks before the full antihypertensive effects of ACEIs are seen. Therefore, evaluating BP response 2 to 4 weeks after starting or changing the dose of an ACEI is appropriate. A.R. has been taking lisinopril for 2 weeks, and her present BP should be used to determine whether she has attained goal BP. Both her BP range during the past few

weeks and today's average BP are above her goal of <140/90 mm Hg.

Case 9-5, Question 2: Why should A.R. have serum potassium and serum creatinine monitored while on lisinopril therapy?

Serum potassium can increase with ACEI therapy as a result of aldosterone reduction. Potassium increases with ACEI monotherapy are small (typically 0.1–0.2 mEq/L) and usually do not cause hyperkalemia. This risk is increased when ACEIs are used in patients with significant CKD (GFR <60 mL/min/1.73 m^2) or when they are used in combination with other drugs that can also raise potassium.

ACEI therapy can also cause a small increase in serum creatinine owing to decreased vasoconstriction of the efferent arteriole in the kidney. This results in a minor decrease in GFR that may be evidenced by a small increase in serum creatinine. A common mistake is to discontinue an ACEI in response to this rise in serum creatinine. Increases in serum creatinine of up to 30% from the baseline creatinine value are safe and anticipated. In these patients, the ACEI should be continued because a strong association exists between acute increases in serum creatinine of up to 30% that stabilize within the first 2 months of ACEI therapy and long-term preservation of renal function.[94] Patients with an increase in serum creatinine of >30% should have their ACEI therapy temporarily discontinued, because this may indicate other medical problems. Some of these problems can be underlying renal disease (such as bilateral renal artery stenosis) or other situations that may be compromising renal blood flow (eg, volume depletion, concomitant nonsteroidal anti-inflammatory drug therapy, and heart failure). Serum potassium and serum creatinine, in addition to BP, should be monitored in A.R. within 2 to 4 weeks of starting ACEI therapy or increasing the dose.

Case 9-5, Question 3: A.R.'s lisinopril dose is increased to 20 mg daily. Will this doubling of her dose place her at risk for significant hypotension?

The very elderly patients with volume depletion and patients with heart failure exacerbation may experience a significant first-dose response to an ACEI. This can manifest as orthostatic hypotension, dizziness, or syncope. The increased pretreatment activity of the RAAS, coupled with blockade of this system, explains this effect. In these patients, ACEI therapy should be initiated at half the normal dose (Table 9-11), followed by slow titration to standard doses.

Concurrent diuretic therapy may predispose some patients to first-dose hypotension. When ACEIs were first approved, dosing guidelines recommended starting at half the standard dose of the ACEI, decreasing the dose of the diuretic, or stopping the diuretic before initiating the ACEI. This was owing to fear that BP would sharply and acutely drop. These dosing recommendations are not necessary unless the patient is hemodynamically unstable (volume depleted, hyponatremic, or has poorly compensated heart failure) or very elderly. A.R. does not have any of these characteristics and can safely increase her dose of lisinopril.

Case 9-5, Question 4: Is an ACEI an effective therapy in a Black patient such as A.R.?

ACEI monotherapy is generally more effective at lowering BP in White patients than in Black or elderly patients. In fact, the 2017 ACC/AHA Hypertension Treatment Guideline does not recommend the use of ACEI or ARB as first-choice antihypertensive in Black patients for primary prevention, including those with diabetes (unless they have CKD or other comorbidities such as coronary artery disease or heart failure with reduced ejection fraction that may benefit from ACEI or ARB to improve CV outcomes).[2,3] Elderly and Black patients are more likely to have low renin hypertension, which may partially explain some of the differences in response. Nevertheless, many of these patients still respond to ACEIs as

monotherapy just to a less extent. Combination therapy, especially with a thiazide diuretic, usually mitigates this race- and age-related difference in BP response.

When an antihypertensive agent is being selected as initial monotherapy in a Black patient, an ACEI should generally not be chosen unless the patient has CKD. A thiazide diuretic or CCB is otherwise preferred. In this case, considering switching to a different agent (thiazide and CCB) may be a good alternative to improve A.R.'s BP control. Of note, Black patients have a two- to fourfold increased risk of angioedema and cough with ACEIs compared with White patients.[95] This does not preclude ACEI use in Black patients unless there is a prior history of angioedema.

Case 9-5, Question 5: A.R. has microalbuminuria, and lisinopril may help preserve kidney function. Is there a risk that lisinopril can cause acute renal dysfunction?

The ACEIs are effective in patients with hypertension-associated renal disease. They are contraindicated, however, in several situations, including bilateral renal artery stenosis, pregnancy, and volume depletion (Table 9-9). In the case of bilateral renal artery stenosis or volume depletion, high angiotensin concentrations maintain renal blood flow, and acute renal dysfunction can occur when an ACEI is started. Because it is often not known whether a patient has bilateral renal artery stenosis, problems with ACEI can be minimized by starting with recommended doses and careful monitoring of serum creatinine within 2 to 4 weeks of starting therapy. Modest elevations in serum creatinine that are <30% (for baseline creatinine values <3.0 mg/dL) do not warrant adjustment in therapy.[94] If greater increases occur, ACEI therapy should be stopped, and further medical evaluation should occur. Patients with elevated serum creatinine at baseline (up to 3.0 mg/dL) may particularly benefit from the vasodilatory effects of ACEIs in the kidney, but they require careful drug initiation and close monitoring. A.R.'s serum creatinine was normal after 4 weeks of lisinopril

therapy. She is not experiencing any kidney-related adverse effects from lisinopril.

Case 9-5, Question 6: What are the risks of using ACEIs in females of childbearing age?

Because ACEIs are teratogenic in the second and third trimester,[96] their use in pregnancy is contraindicated. Moreover, their use in females of childbearing potential is discouraged. If used in this population, patient education should be explicitly clear regarding risks to the fetus, which include potentially fatal hypotension, anuria, renal failure, and developmental deformities. A highly effective form of contraception should be strongly recommended.

Angiotensin-Receptor Blockers

Case 9-5, Question 7: A.R.'s lisinopril is increased to 20 mg daily, then to 40 mg daily during a period of 8 weeks. Her current BP is 136/78 mm Hg (134/76 mm Hg when repeated) at an office visit today. Her serum potassium and creatinine are unchanged from previous values. However, she reports a persistent dry cough for the past few months. She has no additional signs suggesting upper respiratory infection or left ventricular dysfunction. How should A.R.'s therapy be modified?

A well-known side effect of ACEIs is a nonproductive, dry cough, which can occur in up to 15% of patients, with some estimates of cough prevalence being higher.[97] Patients may describe this as a tickling sensation in the back of the throat that commonly occurs late in the evening. This is distinctly different from the cough associated with left ventricular dysfunction, which might be associated with crackles and rales (on auscultation) indicating possible pulmonary edema. ACEI-related cough resolves with discontinuation. Many agents have been used to treat an ACEI cough with poor results. The best treatment option for a patient with an intolerable ACEI cough is to switch agents.

CASE 9-5, QUESTION 8: How is an ARB different from an ACEI?

For A.R., switching to an ARB would likely eliminate the cough.[98] Although her first-choice antihypertensive should be CCB or thiazide diuretics, A.R. will also require the addition of a second agent, either a CCB or thiazide diuretic, because she has not achieved her goal BP of <130/80 mm Hg. ARBs are first line. There are eight ARBs (**Table 9-12**), and many are available as two-drug fixed-dose combination products.

Table 9-12
Angiotensin-Receptor Blockers in Hypertension

Drug	Starting Dose (mg/day)[a]	Usual Dosage Range (mg/day)	Dosing Frequency
Azilsartan medoxomil	80	80	Daily
Candesartan cilexetil	16	8–32	Daily to bid
Eprosartan mesylate	600	600–800	Daily to bid
Irbesartan	150	75–300	Daily
Losartan potassium	50	25–100	Daily to bid
Olmesartan medoxomil	20	20–40	Daily
Telmisartan	40	20–80	Daily
Valsartan	80–160	80–320	Daily

bid, two times daily.

[a]Starting dose may be decreased 50% if patient is volume depleted, very elderly, or taking a diuretic.

PHARMACOLOGIC DIFFERENCES BETWEEN AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR AND AN ANGIOTENSIN-RECEPTOR BLOCKER

Unlike ACEIs, ARBs specifically bind to angiotensin II receptors in vascular smooth muscle, adrenal glands, and other tissues. Access of angiotensin II to its receptors is blocked, and angiotensin I–mediated vasoconstriction and aldosterone release is prevented, resulting in BP reduction. ARBs do not affect bradykinin; therefore, dry cough does not occur.

Considerable investigation has focused on describing the pharmacologic differences between the angiotensin II type 1 and type 2 receptors. Stimulation of the type 1 receptor causes vasoconstriction, salt and water retention, and vascular remodeling. Other deleterious effects from type 1 receptor stimulation include myocyte and smooth muscle hypertrophy, fibroblast hyperplasia, cytotoxic effects in the myocardium, altered gene expression, and possible increased concentrations of plasminogen activator inhibitor. Stimulation of the type 2 receptor results in antiproliferative actions, cell differentiation, and tissue repair.

Case 9-5, Question 9: Under what circumstances would an ARB be a more appropriate initial antihypertensive agent than an ACEI?

Theoretically, an ideal antihypertensive agent would block only type 1 and not type 2 receptors as is the case with ARBs. Therefore, it is possible that an ARB would be superior to an ACEI in reducing hypertension-associated complications because ACEIs ultimately decrease stimulation of both type 1 and type 2 receptors by decreasing production of angiotensin II. This argument is purely speculative and is not supported by clinical trial data. *ON*going *T*elmisartan *A*lone and in Combination With *R*amipril *G*lobal *E*ndpoint *T*rial (ONTARGET) was a prospective, double-blind,

randomized controlled trial that directly compared ARB-based therapy, ACEI-based therapy, and the combination of an ACEI with an ARB.[99] After a median of 56 months, the incidence of CV events was no different among all three treatment groups. Therefore, ARB therapy is as effective as, but no more superior than, ACEI therapy in the overall management of hypertension.

Case 9-5, Question 10: If A.R. experienced angioedema from lisinopril, would treatment with an ARB be appropriate?

A history of ACEI-induced angioedema does not preclude the use of ARB therapy. The cross-reactivity between angioedema with an ACEI and ARB is not exactly known. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Alternative Study prospectively included patients with a history of ACEI intolerance who were randomly assigned, in a double-blind manner, to placebo or candesartan. Of the 2028 patients enrolled, 39 had a history of ACEI angioedema, and only 1 of these patients experienced repeat angioedema that required discontinuation of the ARB.[99] In the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease trial, 5926 patients with a history of ACEI intolerance were randomly assigned in this double-blind trial to an ARB or a placebo for a median duration of 56 months.[100] A total of 75 patients had a history of ACEI angioedema, and none of those patients who were randomly assigned to the ARB treatment arm experienced repeat angioedema. Therefore, cross-reactivity in angioedema between ACEIs and ARBs appears possible, but unlikely and very small. ARBs are an alternative for patients who experience ACEI angioedema but should be reserved for patients with a compelling indication for an ACEI. Of note, the ACC/AHA Guidelines recommend an ARB in patients who have experienced angioedema from an ACEI.[79]

Calcium Channel Blockers

CCBs effectively lower BP. Elderly and Black patients generally have greater BP reduction with a CCB than with other agents (β-blockers, ACEIs, and ARBs). The addition of a diuretic to a CCB provides additive antihypertensive effects. CCBs do not alter serum lipids, glucose, uric acid, or electrolytes.

All CCBs inhibit the movement of extracellular calcium, but there are two primary subtypes: dihydropyridines and nondihydropyridines (ie, diltiazem and verapamil). Each has distinctly different pharmacologic effects.

DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS

Dihydropyridines are potent vasodilators of peripheral and coronary arteries. They do not block AV nodal conduction and do not treat arrhythmias. Moreover, the potent vasodilation associated with most dihydropyridines can induce a reflex tachycardia. With the exception of amlodipine and felodipine, dihydropyridines decrease cardiac contractility and should be avoided in patients with left ventricular dysfunction. Side effects of dihydropyridines are related to their potent vasodilatory effects (eg, tachycardia, headache, and peripheral edema).

Peripheral edema with CCB therapy, especially a dihydropyridine CCB, is a dose-dependent side effect. It is a direct result of the potent peripheral arterial vasodilation. When there is not equal vasodilation in the venous vasculature, a risk exists for leaking through the capillaries in the legs and, thus, an increased risk of peripheral edema. The best way to manage this side effect is to reduce the dose of the dihydropyridine or to add an agent that blocks the RAAS to decrease the effects of angiotensin II, which will result in a more balanced pressure gradient across her peripheral vasculature by providing vasodilation of both the arteries and veins. Adding either an ACEI or ARB can be used to accomplish this, with the added benefit of further lowering BP. Clinicians should note that using diuretics for the primary purpose of treating peripheral edema that is secondary to CCB use is not recommended and is not effective.

NONDIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS

The two nondihydropyridine CCBs, diltiazem and verapamil, are similar to each other. Relative to dihydropyridines, they are only moderately potent vasodilators, but they directly decrease AV nodal conduction and have greater decreases in cardiac contractility. The blockade of AV nodal conduction can slow heart rate and is the basis for their use in controlling supraventricular tachycardias associated with certain arrhythmias (eg, atrial fibrillation). Most patients only have a modest decrease in heart rate. However, heart block (first, second, or third degree) is a potential adverse effect, especially with large doses. Both diltiazem and verapamil should be avoided in patients with an underlying second- or third-degree heart block. Under these circumstances, a dihydropyridine can be used if a CCB is needed. Verapamil and diltiazem should be avoided in patients with left ventricular dysfunction because they can significantly reduce cardiac contractility. When patients with left ventricular dysfunction require a CCB to treat another condition (ie, angina or hypertension), amlodipine or felodipine may be used. They are the only CCBs that have been safely used in clinical trials of patients with left ventricular dysfunction. Unlike many other antihypertensive agents, they do not, however, protect against left ventricular dysfunction–related mortality. Diltiazem may have a lower incidence of constipation than does verapamil. Verapamil is also an effective agent in migraine prophylaxis and can be used if patients also have migraine. Patients with Raynaud phenomenon can obtain symptomatic relief from the peripheral vasodilation associated with a dihydropyridine CCB. Lastly, CCBs are effective in treating cyclosporine-induced hypertension, but should be used cautiously because verapamil and diltiazem increase cyclosporine concentration.

OTHER CONSIDERATIONS

Formulations

Several CCBs are available for the treatment of hypertension. They are listed in **Table 9-13**. Immediate-release formulations should be avoided (see Chapter 16, Hypertensive Crises).

Table 9-13
Calcium Channel Blockers in Hypertension[a]

Drug	Usual Dosage Range (mg/day)	Dosing Frequency
Nondihydropyridines[b]		
Diltiazem, sustained release	120–480	Daily
Diltiazem, extended release[c]	120–540	Daily
Verapamil, sustained release	180–480	Daily to bid
Verapamil, controlled-onset extended release[c]	180–480	qhs
Verapamil, chronotherapeutic oral drug absorption system[c]	100–400	qhs
Dihydropyridines		
Amlodipine	2.5–10	Daily
Felodipine, extended-release tablet	2.5–10	Daily
Isradipine, controlled-release tablet	5–20	Daily
Nicardipine, sustained-release capsule	60–120	bid
Nifedipine, sustained-release tablet[d]	30–90	Daily
Nisoldipine, extended-release tablet	17–34	Daily

bid, two times daily; qhs, every night.

[a]Immediate-release (IR) diltiazem, nifedipine, and verapamil should be avoided in hypertension.

[b]Many different long-acting products exist. Because their individual release characteristics vary, they are not exactly interchangeable using a milligram-per-milligram conversion.

[c]Chronotherapeutic agents are dosed primarily at bedtime and have a delayed drug release for a period of hours, followed by slow delivery of the drug that starts just before morning, with no delivery during the early evening; because they use different delivery systems, they are not interchangeable products.

[d]Only sustained-release nifedipine is approved for hypertension. Immediate-release nifedipine should be avoided for the management of hypertension.

Sustained-release formulations

CASE 9-6

QUESTION 1: C.F. is a 60-year-old male with hypertension, asthma, and type 2 diabetes. His hypertension is treated with HCTZ 25 mg daily and ramipril 20 mg daily for many years. Today, his BP is 148/74 mm Hg (144/72 mm Hg when repeated), and his heart rate is 90 beats/min. C.F.'s physician would like to add a CCB to his regimen to improve BP control.

What are the differences between controlled-onset, extended- release verapamil, and sustained-release verapamil? Are they interchangeable?

All CCBs have short half-lives, except amlodipine. Immediate-release forms require multiple daily doses to provide 24-hour effects. Sustained-released formulations are preferred when a CCB is used to treat hypertension. Various sustained-release delivery devices are available. Serum drug concentrations differ among sustained-release CCBs, but overall BP lowering is usually similar. Nonetheless, most of these products that include the same drug are not rated by the U.S. Food and Drug Administration as equivalent and identical. Insurance formularies often encourage therapeutic substitution between these agents. Therapeutic interchange between modified-release drug delivery formulations that allow for once- or twice-daily dosing (eg, sustained-release, extended-release, and chronotherapeutic products), however, are not equivalent using a milligram-per-milligram conversion. Therapeutic substitution among these products may result in variable BP-lowering effects if not adjusted appropriately. BP and heart rate monitoring should occur within 2 weeks of interchanging sustained-release CCBs.

CASE 9-6, QUESTION 2: Is there any clinical evidence on the use of CCB in diabetic outcomes?

CALCIUM CHANNEL BLOCKER AND DIABETES

CCBs have been shown to reduce risk of CV events in patients with diabetes,[99] although the evidence is not as convincing as that seen with an ACEI. The results of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial and Appropriate Blood

Pressure Control in Diabetes Trial suggest that ACEIs have more CV protection than do CCBs.[58,59]

Nondihydropyridine CCBs (particularly diltiazem) may slow the progression of CKD, although evidence is not as extensive or definitive as it is with an ACEI or ARB. The proposed mechanism is dilation of both the afferent and efferent arterioles, which would decrease intraglomerular pressure. Dihydropyridines have unclear effects on progression of kidney disease. The prevailing opinion is that the renal protective effects of an ACEI and ARB are superior to that of a CCB.

Resistant Hypertension

CASE 9-7

QUESTION 1: R.R. is a 52-year-old male with hypertension for 10 years. He has not yet experienced any hypertension-associated complications or target-organ damage. He does not have a history of diabetes and does not smoke. He has been treated with HCTZ 25 mg daily, amlodipine 10 mg daily, valsartan 320 mg daily, and carvedilol 12.5 mg twice daily for 1 year. He reports rarely missing a dose of his medications, measures his BP at home every day, and follows recommended lifestyle modifications as diligently as possible. He has tried other medications that resulted in intolerances (doxazosin, dizziness; clonidine, dry mouth). His BP has never been <140/90 mm Hg, which is his goal. His BP today is 150/90 mm Hg (152/92 mm Hg when repeated), his heart rate is 60 beats/min, serum potassium is 4.2 mEq/L, and serum creatinine is 1.0 mg/dL. He is 72.04 inches (183 cm) tall and weighs 187.39 pounds (85 kg).

Does R.R. have resistant hypertension? What are his treatment options?

R.R. has resistant hypertension. If goal BP is not reached within a month of treatment of initial drug treatment, increase the dose of the initial drug or add a second drug from one of the first-choice classes of antihypertensives (thiazide diuretic, CCB, ACEI, or ARB). If goal BP cannot be reached with maximal tolerable doses of two drugs, add and titrate a third drug from the preferred drugs provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in the preferred list, because

of a contraindication or the need to use more than three drugs to reach goal BP, then antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the abovementioned strategy or for the management of patients with complications for whom additional clinical consultation is needed to rule out secondary causes of hypertension. R.R.'s treatment options are limited. Amlodipine and valsartan are both at the maximal doses. Carvedilol could be increased to 25 mg twice daily, but this should not be done because his heart rate is 60 beats/min and increasing this dose would place him at risk for bradycardia. It is possible to increase HCTZ to 50 mg daily because this higher dose provides larger BP reductions than does 12.5 or 25 mg daily based on 24-hour ABPM.[85] The limitation of this approach is an increased risk of electrolyte abnormalities and metabolic side effects.

Case 9-7, Question 2: How safe is it to add lisinopril 5 mg daily or spironolactone 25 mg daily in R.R.?

For resistant hypertension, three global treatment philosophies should be considered: (a) assuring appropriate diuretic therapy, (b) appropriate use of effective drug combination, and (c) use of alternative antihypertensive agents as appropriate.[15] Adding an ACEI to an already maximum dose of valsartan would not be recommended. The combination of an ACEI and ARB overall is not very beneficial. This combination should not be used specifically for the purpose of BP lowering, especially in primary prevention patients. When this combination was evaluated in the ONTARGET, the ACEI with ARB combination treatment arm provided only minimal additional reduction in BP compared with either agent alone and, most importantly, did not additionally lower risk of CV events. Moreover, there was a higher risk of adverse events (eg, kidney dysfunction and hypotension) with the combination arm.

The combination of an ACEI with ARB has been used in patients with left ventricular dysfunction based on promising data of a

reduced risk of heart failure hospitalizations.[101,102] However, the overall clinical benefits of an ACEI with an ARB versus an ACEI without an ARB are very small; addition of an aldosterone antagonist is the preferred next step in patients with left ventricular dysfunction who are already treated with the standard regimen of a diuretic, ACEI, and a β-blocker.[79] One potential niche for the use of an ACEI with an ARB is in the setting of CKD with significant proteinuria (300 mg albumin/day or 500 mg protein/day or per gram of urinary creatinine), in which the combination of an ACEI with an ARB seems to reduce progression of proteinuria better than either drug alone.[74]

Many patients with resistant hypertension have a significant component of volume expansion. Detecting this may not be easily observed using routine clinical examinations. However, identifying occult volume expansion using serial hemodynamic measurements from noninvasive bioimpedance testing, followed by enhancing diuretic therapy, has been shown to reduce BP better than did treatment selected by an experienced hypertension specialist.[103] Options to assure appropriate diuretic therapy include switching diuretic agents, switching diuretic classes, increasing the dose, or adding a different class of diuretic. Instead of increasing HCTZ to 50 mg daily, switching HCTZ to the more long-acting chlorthalidone is another possible option to enhance BP lowering. This is an option in R.R.'s case. Another option is switching HCTZ to a loop diuretic (eg, furosemide or torsemide). This should be considered for patients with stage 4 or 5 CKD (GFR <30 mL/min/1.73 m^2) or for those who need diuresis because of edema. This is not a reasonable treatment option for R.R. because he does not have CKD. Another option is to add an aldosterone antagonist, which is considered an alternative antihypertensive agent.[104] Patients with resistant hypertension often require the use of an agent(s) (**Table 9-14**) that is not widely used as either a first- or a second-line therapy. These therapies should not be used as monotherapy or a cornerstone of a multidrug regimen because there is less evidence to support their role in reducing CV events. It should be acknowledged, however, that some of these agents (eg, hydralazine) served as add-on agents to diuretics and β-blockers in early placebo-controlled, stepped-care approach trials in

hypertension. R.R. has already failed to fully respond to, or tolerate, several drug classes that typically are associated with reductions in hypertension-associated complications. To attain his BP goal of <140/90 mm Hg, an alternative agent, other than clonidine, should be selected because he did not tolerate it in the past.

Table 9-14

Alternative Antihypertensive Agents

Drugs/Mechanism of Action	Usual Dosage Range (mg/day)	Dosing Frequency
Aldosterone Antagonists (See Table 14-9)		
α_1-Blockers		
Doxazosin	1–8	Daily
Prazosin	2–20	bid to tid
Terazosin	1–20	Daily to bid
Direct Renin Inhibitor		
Aliskiren	150–300	Daily
α_2-Agonists (Central)		
Clonidine	0.1–0.8	bid
Clonidine	0.17–0.52	Daily
Clonidine transdermal	0.1–0.3	Once weekly
Methyldopa	250–1000	bid
Arterial Vasodilators		
Hydralazine	25–100	bid to tid
Minoxidil	2.5–80	Daily to bid

bid, two times daily; tid, three times daily.

ALTERNATIVE ANTIHYPERTENSIVE AGENTS

Aldosterone antagonists

Spironolactone and eplerenone are aldosterone antagonists that are especially useful as an add-on therapy in patients with resistant hypertension and would be a reasonable addition to R.R.'s

regimen.[10,104] Many patients with resistant hypertension have increased activation of the RAAS, which can result in increased aldosterone. Moreover, up to 20% of patients with resistant hypertension have primary aldosteronism.[10] These characteristics of patients with resistant hypertension make the addition of an aldosterone antagonist very effective in lowering BP in resistant hypertension.

R.R.'s potassium is in the normal range but could increase after adding spironolactone. Therefore, it should be monitored 2 to 4 weeks after therapy is started to assure that R.R. does not experience hyperkalemia. Eplerenone is more specific than is spironolactone in aldosterone blockade, although some data suggest that spironolactone is more effective in primary aldosteronism.[105] Compared with spironolactone, gynecomastia is less frequent with eplerenone. However, the incidence of hyperkalemia may be greater with eplerenone. When used for hypertension, eplerenone is contraindicated in populations at high risk for hyperkalemia including patients with an estimated creatinine clearance of <50 mL/min or elevated serum creatinine (>1.8 mg/dL in females and >2.0 mg/dL in males).

Case 9-7, Question 3: How beneficial would more intensive lifestyle modifications be in R.R.?

In addition to nonadherence to drug therapy, lifestyle factors (obesity, sodium ingestion, and heavy alcohol intake) are a significant contributor to resistant hypertension.[10] Lifestyle modifications should continually be reinforced in patients, especially those with resistant hypertension. As previously discussed, these modifications should include dietary changes and physical activity. R.R. should be instructed to restrict his daily sodium to <1.5 g because this has been shown to decrease SBP by >20 mm Hg in resistant hypertension.[25]

α-Blockers

CASE 9-8

QUESTION 1: J.L. is a 64-year-old male with hypertension. His BP is 158/84 mm Hg (156/86 mm Hg when repeated). His current antihypertensive regimen is HCTZ 25 mg daily, irbesartan 300 mg daily, and nifedipine extended release 60 mg daily. J.L. is not completely adherent to lifestyle modifications, but insists he is doing the best he can. He has been experiencing frequent nocturia, difficulty in starting urination, and a decrease in his urinary flow for the past several months and is diagnosed with benign prostatic hyperplasia (BPH).

J.L.'s physician is considering changing one of his antihypertensive agents to an α-blocker.

How do α-blockers compare with other agents in reducing CV events?

α-Blockers are not first-line agents in the management of hypertension. The ALLHAT study originally included an α-blocker (doxazosin) treatment arm.[50] Interim results after a mean follow-up of 3.3 years revealed that doxazosin had a statistically higher risk of combined CV disease and heart failure when compared with chlorthalidone.[106] Therefore, the ALLHAT data show that chlorthalidone was more effective in lowering some hypertension-associated complications than was doxazosin. This study did not include a placebo group; therefore, to conclude that doxazosin is harmful is inaccurate. For J.L., discontinuing HCTZ, irbesartan, or nifedipine to start an α-blocker is not prudent. It may be appropriate, however, to add an α-blocker to his regimen; an α-blocker will also have a benefit on his BPH (Table 9-7).

CASE 9-8, QUESTION 2: How can an α-blocker improve J.L.'s BPH?

The smooth muscle surrounding the prostate is innervated by α_1-receptors. By blocking these receptors, an α-blocker can improve the symptoms of BPH by reducing urethral tone and alleviating bladder outlet obstruction. Terazosin and doxazosin are both approved for the treatment of BPH. Prazosin should not be used because of the need for frequent dosing. Improvements in BPH symptoms with α-blockers are dose related. A high dose is often needed, and this increases the risk of side effects, such as orthostatic hypotension. In

J.L., an α-blocker will lower his BP and improve his urinary symptoms.

CASE 9-8, QUESTION 3: J.L. prefers to try doxazosin rather than undergo surgery to relieve his symptoms of BPH. How should this agent be started?

For J.L., it would be best to add a low dose of doxazosin to his present regimen. Based on his BP response and tolerance, the dose can be titrated up. One of his other antihypertensive agents can be decreased if he becomes hypotensive. The initial dose of doxazosin should not exceed 1 mg daily, and it should be given at bedtime. This can minimize orthostatic hypotension, which is the most frequent side effect of α-blockers. This complication is most pronounced with the first dose, but it can persist in some patients. Moreover, if an α-blocker is selected as add-on therapy in patients such as J.L. with resistant hypertension, nighttime administration of an α-blocker has been shown to be effective in further lowering BP.[107]

CASE 9-8, QUESTION 4: How should J.L. be counseled regarding side effects of doxazosin?

α-Blockers are well tolerated if dosed appropriately. J.L. could experience side effects, such as drowsiness, headache, weakness, palpitations from reflex tachycardia, and nausea, but these do not occur in all patients. Patients starting an α-blocker should be instructed to take the initial dose at bedtime and to anticipate the first-dose effect of orthostatic hypotension. Specifically, patients should be counseled to rise more slowly from a seated or supine position.

Miscellaneous Agents

ALISKIREN

CASE 9-9

QUESTION 1: R.P. is a 68-year-old male with hypertension and a history of ischemic stroke (1 year ago). Two months ago, his BP value was 164/94 mm Hg (162/98 mm Hg when repeated), with a heart rate of 62 beats/min while on sustained-release diltiazem 240 mg daily. He was started on benazepril/HCTZ 10/12.5 mg daily 2 months ago. His BP today is 142/82 mm Hg (144/82 mm Hg when repeated). All his laboratory values are normal except his serum creatinine, which is 1.9 mg/dL. J.L. has implemented lifestyle modification to the best of his ability.

His physician is wondering, should aliskiren be added to his drug regimen considering he is also on ACEI?

What kind of antihypertensive is Aliskerin?

DIRECT RENIN INHIBITORS

Aliskiren is a direct renin inhibitor. It inhibits the first step of the RAAS, which results in reduced plasma renin activity (PRA) and BP lowering.

CASE 9-9, QUESTION 2: How is aliskiren different from an ACEI or ARB?

This is different from the decreased production of angiotensin II with ACEIs and the blocked angiotensin II receptor effects with ARBs; however, BP-lowering effects are similar to those with ACEIs and ARBs. Aliskiren has a 24-hour half-life and, similar to most ACEIs and ARBs, is dosed once daily.

Some similarities and differences exist among the side effects associated with aliskiren when compared with ACEIs and ARBs. Aliskiren should not be used in pregnancy because of the known teratogenic effects from blocking the RAAS system. Increases in serum creatinine and serum potassium have been associated with aliskiren. These are similar to ACEI and ARB therapy and are mediated by the inhibition of angiotensin II vasoconstrictive effects on the efferent arterioles of the kidney and blocking of aldosterone. Monitoring of serum creatinine and serum potassium should be done in patients treated with aliskiren, particularly in those treated with the combination of aliskiren and an ACEI, ARB, potassium-sparing

diuretic, or aldosterone antagonist. Angioedema has also been reported in patients treated with aliskiren.

CASE 9-9, QUESTION 3: What is the role of aliskiren in treating R.P.'s hypertension?

The exact role of aliskiren in the treatment of hypertension is unclear. It is approved as monotherapy or in combination therapy. The BP reductions with aliskiren as monotherapy are similar to those seen with an ACEI, ARB, or CCB (specifically amlodipine). Aliskiren provides additive BP lowering when used in combination with HCTZ, ACEI, ARB, and CCB. However, its efficacy in combination with maximal doses of ACEI is unknown. Aliskiren is an alternative antihypertensive agent at this time because of the unknown long-term effects on CV events.

MIXED α-BLOCKERS AND NEBIVOLOL

Labetalol and carvedilol (**Table 9-15**) are nonselective β-blockers that also have an α_1-receptor blocking activity. Their antihypertensive effects are only somewhat similar to a combination of a nonselective β-blocker with an α_1-antagonist.

Table 9-15
Common β-Blockers in Hypertension

Drug	Usual Dosage Range (mg/day)	Dosing Frequency	Half-Life (hours)	β1-Selectivity	Lipid Solubility
Atenolol	25–100	Daily to bid	6–7	++	Low
Bisoprolol	5–20	Daily	9–12	+++	High
Carvedilol	12.5–50	bid	6–10	0	High
Carvedilol	10–80	Daily	6–10	0	High
Labetalol	200–800	bid	6–8	0	Moderate
Metoprolol tartrate	100–400	bid	3–7	+	Moderate to high
Metoprolol succinate	25–400	Daily	3–7	+	Moderate to high
Nebivolol	5–10	Daily	12–19	+++	High
Propranolol	40–180	Daily (LA and XL) or bid	3–5	0	High

bid, two times daily; LA, long acting; XL, extended release.

These agents produce vasodilation because of the α-blocker effects. The only other β-blocker that provides vasodilation is nebivolol. However, nebivolol produces vasodilation without blockade of α-receptors. The same precautions and contraindications relevant to nonselective β-blockers apply to both carvedilol and labetalol because they block both β_1- and β_2-receptors (Table 9-9).

Carvedilol is approved for both hypertension and left ventricular dysfunction. Carvedilol has been shown to reduce morbidity and mortality in a wide range of patients with left ventricular dysfunction.[108,109] Labetalol and carvedilol have no clear advantage over other β-blockers in most patients with hypertension, with the exception that they offer a dual mechanism of action within a single-drug formulation. In patients with type 2 diabetes, carvedilol has been shown to have no significant effect on glucose in comparison with metoprolol, which may slightly increase glucose.[110]

CENTRAL α_2-AGONISTS

The antihypertensive effects of α_2-agonists (Table 9-14) are attributed to their central α_2-agonist activity. Stimulation of α_2-receptors in the CNS inhibits sympathetic outflow (via negative feedback) to the heart, kidneys, and peripheral vasculature, resulting in peripheral vasodilation. Although the α_2-agonists effectively lower BP, they have many potential side effects and have not been evaluated in trials focused on CV events.

CASE 9-10

QUESTION 1: T.M. is a 43-year-old male. He is a truck driver with a 5-year history of hypertension. He does not have hypertension-associated complications. Secondary causes have been ruled out. His regimen is losartan/HCTZ 100/25 mg daily and sustained-release diltiazem 240 mg daily. Other antihypertensive drugs have failed because of various side effects (captopril and lisinopril, dry cough; atenolol and carvedilol, fatigue; nifedipine and amlodipine, edema; terazosin, orthostasis). T.M. has been adherent to his present medications and lifestyle modification, but has been unable to quit

smoking. His clinic values have been similar and averaged 150/95 mm Hg for the past 3 months. Clonidine 0.1 mg twice daily is added to his regimen.

What problems might occur if T.M. is not adherent to clonidine therapy?

Clonidine

α_2-Agonists are most effective when used with a diuretic because they all can cause fluid retention. Ideally, they should be used with agents that have different mechanisms of action and with agents that do not affect other central adrenergic receptors. Clonidine can cause rebound hypertension when abruptly stopped. T.M.'s occupation may place him at risk for this complication if he misses doses because of unusual work hours or prolonged travel.

Case 9-10, Question 2: How should T.M.'s clonidine dose be titrated?

Clonidine should be started at a low dosage and gradually increased to achieve optimal BP lowering with minimal side effects. The immediate-release tablet is started as 0.1 mg twice daily, with 0.1- or 0.2-mg/day increases every 2 to 4 weeks until his BP goal is achieved, or side effects appear. Clonidine is also available as an extended-release tablet and as a transdermal patch. The patch formulation releases the drug at a controlled rate for 7 days and may have fewer side effects than does the oral dosage form. The onset of initial BP effect may be delayed for 2 to 3 days after application; thus, rebound hypertension might occur when oral clonidine is switched to transdermal. To prevent this, an oral dose should be taken on the first day that the transdermal patch is used. Anticholinergic side effects, such as sedation and dry mouth, are the most frequent and bothersome side effects of clonidine. These are especially problematic in elderly patients.

Case 9-10, Question 3: After several months, T.M.'s BP is 148/84 mm Hg with clonidine 0.2 mg twice daily. However, he is now experiencing daytime somnolence and dry mouth. What other α_2-agonists are available?

Methyldopa

Methyldopa has been extensively evaluated and is considered safe in pregnancy. Therefore, it is recommended as a first-line agent when hypertension is first diagnosed during pregnancy.[111] Beyond that, little role exists for methyldopa in the management of hypertension. The usual initial dose is 250 mg administered twice daily up to 2000 mg/day. Methyldopa causes side effects similar to those associated with clonidine, including sedation, lethargy, postural hypotension, dizziness, dry mouth, headache, and rebound hypertension. These may decrease with continued use. Other significant side effects include hemolytic anemia and hepatitis. Although these are both rare, they necessitate discontinuing the medication.

Others

Guanfacine and guanabenz have a high incidence of side effects. These agents can cause dry mouth, sedation, dizziness, orthostatic hypotension, insomnia, constipation, and impotence, and are no longer commonly used. The adverse effects of other α_2-agonists (methyldopa, guanfacine, and guanabenz) are nearly identical to those of clonidine. In general, patients who do not tolerate one α_2-agonist will not tolerate the others. An antihypertensive agent from a different class (aldosterone antagonist, aliskiren, or an arterial vasodilator) should be chosen for T.M.

CASE 9-11

Question 1: C.M. is a 56-year-old female with a history of hypertension and severe CKD (eGFR of 14 mL/min/1.73 m^2). Her antihypertensive regimen consists of torsemide 40 mg daily, amlodipine/olmesartan 10/40 mg daily, and metoprolol succinate 200 mg daily. She started hydralazine 25 mg three times daily 4 weeks ago when her BP readings were 148/92 and 146/90 mm Hg. She has been very compliant, and her BP is now 146/88 mm Hg with a heart rate of 82 beats/min. Her lung fields are clear, with 1+ bilateral pitting edema. Serum electrolytes are within normal limits.

Why was hydralazine used in C.M.?

ARTERIAL VASODILATORS

Hydralazine

Hydralazine causes direct relaxation of arteriolar smooth muscle. Arterial vasodilators are infrequently used, except for patients with severe CKD. In this population, hypertension is difficult to control and often requires four or five agents. Severe CKD results in increased renin release and increased fluid retention. Potent vasodilation, in combination with diuresis, is often effective in lowering BP under these conditions. This vasodilation, however, stimulates the sympathetic nervous system and results in a reflex tachycardia, increased PRA, and fluid retention. Thus, the hypotensive effects of direct arterial vasodilators can quickly diminish with time when used as monotherapy. To prevent this, arterial vasodilators need to be used in combination with an agent that can slow down the heart rate (eg, β-blocker or nondihydropyridine CCB) to counteract reflex tachycardia, as well as a diuretic (often a loop diuretic if used in severe CKD) to minimize fluid retention.

CASE 9-11, QUESTION 2: After 18 months, C.M.'s hydralazine dose is 50 mg three times daily, and her BP is at goal. She now has joint pain in both hands, which extends to the wrists, and generalized weakness with frequent fevers. Laboratory findings for C.M. showed a positive antinuclear antibodies test (diffuse) result, a white blood cell count of 3500/μL, and an erythrocyte sedimentation rate of 45 mm/hour, and she is diagnosed with drug-induced lupus (DIL). How should this be managed?

C.M.'s symptoms are consistent with DIL. Hydralazine is one of the most common agents reported to cause DIL. Musculoskeletal pains are the most frequent symptoms, but systemic symptoms and rash may also occur. Hydralazine doses as low as 100 mg/day can cause DIL, and the risk significantly increases when >200 mg/day is used.

Hydralazine should be discontinued. Symptoms should subside within days or weeks, and complete resolution can be expected.

Case 9-11, Question 3: What alternatives to hydralazine are available for C.M.?

Minoxidil

C.M.'s BP responded to hydralazine, so she would likely benefit from another arterial vasodilator. Minoxidil, a potent arterial vasodilator, is similar to hydralazine with regard to reflex tachycardia, increased CO, increased PRA, and fluid retention. Therefore, concomitant β-blocker and diuretic therapy is still needed. Minoxidil should be reserved for patients such as C.M. who have severe CKD or possibly for resistant hypertension.

Case 9-11, Question 4: How should C.M. be counseled if minoxidil is started?

Hypertrichosis is a common adverse effect of oral minoxidil, occurring in 80% to 100% of patients. The hair growth is not associated with an endocrine abnormality and begins within the first few weeks. It commonly occurs on the temples, between the eyebrows, on the cheeks, and on the pinna of the ear. Hair growth can extend to the back of the legs, arms, and scalp with continued use. Some patients, especially females, find the hypertrichosis so intolerable that they stop treatment. Topical minoxidil is an approved therapy for male-pattern baldness, but topical administration does not provide BP-lowering effects.

Fluid retention with minoxidil is common, presenting as edema and weight gain. If adequate diuresis is not maintained during minoxidil therapy, left ventricular dysfunction may be precipitated or worsened. This also occurs with hydralazine. The compensatory reflex tachycardia with minoxidil may also precipitate angina in patients who have, or are at risk for, CAD.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585. (*18*)

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to ACE inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [published corrections appear in *JAMA*. 2004;291:2196; *JAMA*. 2003;289:178]. *JAMA*. 2002;288:2981–2997. (*51*)

Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887–1898. (*17*)

Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117:e510–e526. (*9*)

Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002; 359:995–1003. (*50*)

Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005; 366:895–906. (*66*)

Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in Blacks: an update of the International Society on Hypertension in Blacks consensus statement. *Hypertension*. 2010;56:780–800. (*95*)

James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guidelines for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507–520. (*2*)

ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559. (*99*)

The SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med*. 2015;373:2103–2116. (*22*)

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guidelines

for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018; 71(6):e13–e115. (*3*)

Key Websites

National Heart, Lung, and Blood Institute. Management of blood pressure in adults: systematic evidence review from the Blood Pressure Expert Panel. Published November 2013. http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/blood-pressure-in-adults

National Kidney Foundation. Calculators for health care professionals. http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm

COMPLETE REFERENCES CHAPTER 9 ESSENTIAL HYPERTENSION

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report from American Heart Association. *Circulation.* 2020;141(9):e139–e596.
2. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guidelines for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507–520.
3. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71(6):e13–e115.
4. Kaplan NM. *Kaplan's Clinical Hypertension*. 11th ed. Wolters Kluwer; 2014.
5. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [published corrections appear in *Circulation*. 2005;112:e297; *Circulation*. 2005;112:e298]. *Circulation*. 2005;112(17):2735–2752.
6. Agarwal R, Bills JE, Hecht TJW, Light RP. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. *Hypertension*. 2011;57:29–38.

7. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA*. 1999;282:539–546.
8. Saseen JJ. Hypertension. In: Tisdale JE, Miller DA, eds. *Drug-Induced Diseases: Prevention, Detection, and Management.* 2nd ed. American Society of Health-Systems Pharmacists; 2010:516.
9. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117:e510–e526.
10. Verdecchia P, Reboldi GP, Angeli F, et al. Short- and long-term incidence of stroke in white-coat hypertension. *Hypertension*. 2005;45:203–208.
11. Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention [published correction appears in *Circulation*. 2007;116:e121]. *Circulation*. 2007;115:2761–2788.
12. Mancia G, Backer GD, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) [published correction appears in *J Hypertens*. 2007;25:1749]. *J Hypertens*. 2007;25:1105–1187.
13. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755–1762.
14. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA*. 1996;276(23):1886–1892.
15. Tuomilehto J, Rastenyte D, Birkenhäger WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med*. 1999;340(9):677–684.
16. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317(7160):703–713.
17. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887–1898.
18. ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585.

19. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*. 2005;365(9463):939–946.
20. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288(19):2421–2431.
21. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994;330(13):877–884.
22. The SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med.* 2015;373:2103–2116.
23. Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee [published corrections appear in *Circulation*. 2006;114:e27; *Circulation*. 2006;114:e629]. *Circulation*. 2006;114:82–96.
24. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2006;47:296–308.
25. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336:1117–1124.
26. Pimenta E, Gaddam KK, Oparil S, et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension*. 2009;54:475–481.
27. Wright JM, Musini VM, Gill R, et al. First-line drugs for hypertension. *Cochrane Database Syst Rev*. 2009;(3):CD001841.
28. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201–207.
29. Kronish IM, Woodward M, Sergie Z, et al. Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation*. 2011;123:1611–1621.
30. Ernst ME, Moser M. Use of diuretics in patients with hypertension [published correction appears in *N Engl J Med*. 2010;363:1877]. *N Engl J Med*. 2009;361:2153–2164.
31. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ*. 1992;304:405–412.
32. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;43(5 suppl 1):S1–S290.
33. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension

(STOP-Hypertension). *Lancet*. 1991;338:1281–1285.
34. Whelton PK, Appel L, Charleston J, et al. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I [published correction appears in *JAMA.* 1992;267:2330]. *JAMA*. 1992;267:1213–1220.
35. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents [published correction appears in *N Engl J Med.* 1994;330:1689]. *N Engl J Med*. 1993;328:914–921.
36. Grimm RH Jr, Grandits GA, Prineas RJ, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS). *Hypertension*. 1997;29(1 Pt 1):8–14.
37. Grimm RH Jr, Grandits GA, Cutler JA, et al. Relationships of quality-of-life measures to long-term lifestyle and drug treatment in the Treatment of Mild Hypertension Study. *Arch Intern Med*. 1997;157:638–648.
38. Grimm RH Jr, Flack JM, Grandits GA, et al. Long-term effects on plasma lipids of diet and drugs to treat hypertension. Treatment of Mild Hypertension Study (TOMHS) Research Group. *JAMA*. 1996;275:1549–1556.
39. Jensen J, Lendorf A, Stimpel H, Frost J, Ibsen H, Rosenkilde P. The prevalence and etiology of impotence in 101 male hypertensive outpatients. *Am J Hypertens*. 1999;12:271–275.
40. [No authors listed]. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA*. 1967;202:1028–1034.
41. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991;265:3255–3264.
42. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet*. 1997;350:757–764.
43. Collins R, Peto R, MacMohan S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990;335:827–838.
44. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765–774.

45. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. A clinical practice guideline for treating tobacco use and dependence: a US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. *JAMA*. 2000;283:3244–3254.
46. Bibbins-Domingo K, on behalf of the U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164(12):836–845. doi:10.7326/M16-0577
47. Neaton JD, Grimm RH Jr, Prineas RJ, et al. Treatment of mild hypertension study. Final results. Treatment of Mild Hypertension Study Research Group. *JAMA*. 1993;270:713–724.
48. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA*. 2003;289:2534–2544.
49. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*. 2003;289:2073–2082.
50. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
51. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [published corrections appear in *JAMA.* 2004;291:2196; *JAMA*. 2003;289:178]. *JAMA*. 2002;288:2981–2997.
52. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack [published corrections appear in *Lancet.* 2001;358:1556; *Lancet*. 2002;359:2120]. *Lancet*. 2001;358:1033–1041.
53. Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet*. 2000;356:359–365.
54. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity—the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999;354:1751–1756.
55. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999;353:611–616.

56. Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. *Arch Intern Med*. 2000;160:211–220.
57. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348:583–592.
58. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators [published correction appears in *Lancet.* 2000;356:860]. *Lancet*. 2000;355:253–259.
59. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med*. 1998;338:645–652.
60. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care*. 1998;21:597–603.
61. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ*. 1998;317:713–720.
62. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
63. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
64. Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870–878.
65. Dickstein K, Kjekshus J, OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet*. 2002;360:752–760.
66. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.
67. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or

amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031.
68. Schrader J, Lüders S, Kulschewski A, et al. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke*. 2005;36:1218–1226.
69. Cutler DM, Long G, Berndt ER, et al. The value of antihypertensive drugs: a perspective on medical innovation. *Health Aff (Millwood)*. 2007;26:97–110.
70. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group [published correction appears in *N Engl J Med*. 1993;330:152]. *N Engl J Med*. 1993;329:1456–1462.
71. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet*. 1997;349:1857–1863.
72. Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med*. 2011;364:907–917.
73. Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet*. 2005;366:2026–2033.
74. Kunz R, Friedrich C, Wolbers M, Mann JFE. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med*. 2008;148:30–48.
75. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. *Circulation*. 2014;130:1749–1767.
76. Baker WL, Coleman CI, Kluger J, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. *Ann Intern Med*. 2009;151:861–871.
77. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guidelines for the management of patients with non-ST elevation acute coronary syndromes: executive summary. *Circulation*. 2014;130:2354–2394.
78. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary. *Circulation*. 2013;127:529–555.
79. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary. *Circulation*. 2013;128:1810–1852.
80. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure [published correction appears in *N Engl J Med.* 2005;352:1276]. *N Engl J Med*. 2004;351:2049–2057.

81. Materson BJ, Reda DJ, Preston RA, et al. Response to a second single antihypertensive agent used as monotherapy for hypertension after failure of the initial drug. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Arch Intern Med*. 1995;155:1757–1762.
82. Psaty BM, Lumley T, Furberg CD. Meta-analysis of health outcomes of chlorthalidone-based vs nonchlorthalidone-based low-dose diuretic therapies. *JAMA*. 2004;292:43–44.
83. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension*. 2006;47:352–358.
84. Ernst ME, Carter BL, Zheng S, Grimm RH Jr. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am J Hypertens*. 2010;23:440–446.
85. Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. *J Am Coll Cardiol*. 2011;57:590–600.
86. Lakshman MR, Reda DJ, Materson BJ, Cushman WC, Freis ED. Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Arch Intern Med*. 1999;159:551–558.
87. Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. *Arch Intern Med*. 1998;158:741–751.
88. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*. 2003;326:1427.
89. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension*. 2011;57:689–694.
90. Ram CV, Garrett BN, Kaplan NM, et al. Moderate sodium restriction and various diuretics in the treatment of hypertension. *Arch Intern Med*. 1981;141:1015–1019.
91. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet*. 2010;375:1173–1181.
92. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis.

Hypertension. 2010;55:399–407.

93. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. *Lancet*. 2011;377:312–320.
94. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med*. 2000;160:685–693.
95. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in Blacks: an update of the International Society on Hypertension in Blacks consensus statement. *Hypertension*. 2010;56:780–800.
96. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med*. 2006;354:2443–2451.
97. Luque CA, Vazquez Ortiz M. Treatment of ACE inhibitor-induced cough. *Pharmacotherapy*. 1999;19:804–810.
98. Bakris GL, Sowers JR, on behalf of the American Society of Hypertension Writing Group. ASH position paper: treatment of hypertension in patients with diabetes—an update. *J Clin Hypertens (Greenwich)*. 2008;10:707–713.
99. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
100. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators; Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial [published correction appears in *Lancet*. 2008;372:1384]. *Lancet*. 2008;372:1174–1183.
101. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362:767–771.
102. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both [published correction appears in *N Engl J Med.* 2004;350:203]. *N Engl J Med*. 2003;349:1893–1906.
103. Taler SJ, Textor SC, Augustine JE, et al. Resistant hypertension: comparing hemodynamic management to specialist care. *Hypertension*. 2002;39:982–988.
104. Calhoun DA, White WB. Effectiveness of the selective aldosterone blocker, eplerenone, in patients with resistant hypertension. *J Am Soc Hypertens*. 2008;2:462–468.
105. Parthasarathy HK, Ménard J, White WB, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and

spironolactone in patients with hypertension and evidence of primary aldosteronism. *J Hypertens*. 2011;29:980–990.

106. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. [published correction appears in *JAMA.* 2002;288:2976]. *JAMA*. 2000;283:1967–1975.
107. Hermida RC, Ayala DE, Fernández JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. *Hypertension*. 2008;51:69–76.
108. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357:1385–1390.
109. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651–1658.
110. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs. metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004;292:2227–2236.
111. National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. *Am J Obstet Gynecol*. 2000;183:S1–S22.

10

Peripheral Vascular Disorders

Snehal H. Bhatt

CORE PRINCIPLES		CHAPTER CASES
1	Peripheral arterial disease (PAD) is stenosis or occlusion in the peripheral arteries of the legs, usually caused by atherosclerosis. A sometimes-painful complication called intermittent claudication (IC) can be associated with PAD and is described as aching, cramping, tightness, or weakness of the legs, which usually occurs during exertion.	**Case 10-1 (Question 1)**
2	Treatment for PAD should include therapeutic lifestyle changes and pharmacologic intervention based on risk factors present. Specific interventions may include smoking cessation; exercise; management of dyslipidemia, hypertension, and	**Case 10-1 (Questions 2–11)**

	diabetes; antiplatelet therapy; and verapamil.	
RAYNAUD PHENOMENON		
1	Raynaud phenomenon (RP) is an exaggerated vasospastic response to cold or emotion, likely mediated through sympathetic response to the precipitating stimuli. RP is classified as primary or secondary, in which secondary causes include connective tissue diseases and occupational-related neural damage.	**Case 10-2 (Question 1)**
2	Treatment for RP should include therapeutic lifestyle changes and pharmacologic intervention based on clinical presentation and underlying etiology. First-line interventions may include avoidance of cold stimuli and medications associated with vasoconstriction and treatment with calcium channel blockers. Several other therapies may be emerging as possible therapeutic options, including renin–angiotensin–aldosterone inhibitors, topical nitroglycerin, statins, peripheral α-adrenergic blockers, intravenous prostanoids, endothelin antagonists, and oral phosphodiesterase inhibitors.	**Case 10-2 (Questions 2–4)**

INTRODUCTION

Peripheral arterial disease (PAD) is a common and sometimes-painful complication from stenosis or occlusion in the peripheral arteries of the legs, usually caused by atherosclerosis. Similar to coronary artery disease (CAD) resulting in chest pain, PAD pain can be classified as “angina” of the legs. When closely comparing the risk factors and pathology of both the diseases, the association with CAD and intermittent claudication (IC) becomes clear.

IC is described as aching, cramping, tightness, or weakness of the legs, which usually occurs in the calves during walking and is relieved at rest. Tissue ischemia, resulting in numbness or continuous pain in the toes or foot, may be present and can lead to ulceration. IC is a painful condition that can severely limit mobility and lead to tissue necrosis or amputation of the affected limb. Many patients with PAD, however, are asymptomatic or have atypical lower limb symptoms, such as leg fatigue, difficulty walking, or similar nonspecific symptoms. Patients may not seek medical attention until the condition is advanced because of the gradual onset of symptoms associated with IC.

Epidemiology

PAD is a relatively common condition that affects males and females equally, with a prevalence of 12%,[1] although males have a twofold increased prevalence of symptomatic IC.[2] The annual incidence of IC increases dramatically with age (**Table 10-1**). Most patients with PAD are asymptomatic. In one study in which the prevalence of IC symptoms was 2%, only 11.7% of patients had detectable large-vessel atherosclerosis of the lower extremities.[3] This disparity between IC symptoms and the presence of PAD contributes to the observation that 50% to 90% of patients with IC do not mention PAD symptoms to their physician. Patients attribute the symptoms of IC to normal walking difficulties associated with aging, not a medical condition requiring treatment.[4] Public knowledge of the definition of PAD, risk factors for the development of the disease, associated symptoms and disease states, and amputation risk were evaluated

in adults older than age 50 years in a cross-sectional, population-based telephone survey. Unfortunately, only 25% of the population reported awareness of PAD.[5]

Table 10-1
Annual Incidence of Intermittent Claudication by Age

Age Group (years)	Annual Incidence (%)
40–49	2.0
50–59	4.2
60–69	6.8
70	9.2

Source: Caspary L. Epidemiology of vascular disease. *Dis Manage Health Outcomes.* 1997;2(suppl 1):9–17.

Risk factors for developing occlusive PAD are similar to those for CAD. Long-standing diabetes is the most significant risk factor, with 30% of patients with diabetes affected by PAD.[6] Each 1% increase in glycated hemoglobin is associated with a 28% risk of incident PAD.[7] Other atherosclerotic risk factors associated with PAD include cigarette smoking, hypertension, and dyslipidemia.[8] Hypertriglyceridemia is a more significant risk factor for PAD than for CAD, and this may partially explain the increased prevalence of PAD in patients with diabetes.[9]

Cigarette smoking is the strongest risk factor for PAD and the development of IC pain than any other risk factors, and the risk increases dramatically with the duration of smoking history and number of cigarettes smoked per day.[10] In patients with hypertension or diabetes, smoking further increases the rate of claudication development. Smoking confers a sevenfold increase in risk for PAD compared with not smoking.[11]

Epidemiologic studies following PAD patients over 4 to 9 years show that IC is nonprogressive in 75% of patients, whereas 25% of patients with IC will have worsening painful ischemic episodes. Ischemic tissue changes, ulceration, and gangrene can accompany advanced PAD. Amputation of the affected limb is rare, but can occur

in up to 5% of patients with claudication.[12] The presence of two independent risk factors, such as diabetes and cigarette smoking, has an additive effect on the risk for the development of progressive IC and serious limb complications (**Table 10-2**). Finally, disease location in patients with severe disease may be associated with prognosis. Proximal disease may be associated with poor outcomes when compared with distal lesions, although further studies are needed to confirm these findings.[13]

Table 10-2
Long-Term Incidence of Outcomes in Patients With Intermittent Claudication

Patient Population	Abrupt Limb Ischemia (%)	Amputation (%)
All patients	23	7
Diabetes	31	11
Smokers	35	21

Sources: McDaniel CD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg.* 1989;3:273–277; Hertzer NR. The natural history of peripheral vascular disease: implications for its management. *Circulation.* 1991;83(2 suppl):I12–I19.

During a relatively short 2-year follow-up of patients with IC, 3.6% of patients died, whereas 22% experienced a nonfatal cardiovascular event (defined as any cardiac, cerebral, or peripheral vascular event). Walking capacity declined in 26% during the same time frame; thus, it is paramount to recognize that severe, short-term morbidity is highly likely in this patient population.[14,15]

Pathophysiology

IC is the predominant complication of occlusive PAD because of the resulting pain and subsequent decreased mobility. The major cause of occlusive PAD is arteriosclerosis obliterans, defined as the development of atherosclerotic plaques in the peripheral vasculature. These plaques develop as a result of endothelial activation in

association with conditions such as dyslipidemia, diabetes mellitus, hypertension, and smoking. Plaques also result from the proliferation of vascular smooth muscle, with subsequent damage to the vascular structure. This damaged endothelium has impaired vasodilatory capabilities because secretion of nitric oxide is decreased and secretion of vasoconstrictive substances, such as endothelin, is increased, impeding blood flow to the extremities. Further growth of atherosclerotic lesions can physically limit blood flow. Exercise may induce IC symptoms in patients who have lesions with >50% stenosis, whereas patients with lesions of >80% stenosis can have pain at rest. The lesions themselves can become unstable and rupture, or adjacent smaller vessels experiencing high hemodynamic pressure caused by nearby plaques may rupture as well. Either situation can lead to acute vascular occlusion, analogous to unstable angina or acute myocardial infarction (MI) in coronary arteries.[16]

Figure 10-1 illustrates the common sites of atherosclerosis. Plaques that develop in central vessels (eg, in the aorta and iliac artery) are primarily associated with buttock pain and erectile dysfunction. Those confined to the more distal femoral and popliteal arteries characteristically cause thigh and calf pain. Occlusion of the tibial arteries will produce claudication pain in the foot. When more than one arterial bed is affected by severe atherosclerosis, symptoms of IC will be diffused. Symptoms of IC indicate an inadequate supply of arterial blood to peripheral muscles. Exercise, including walking, increases the metabolic demands of the muscles and can lead to claudication pain.

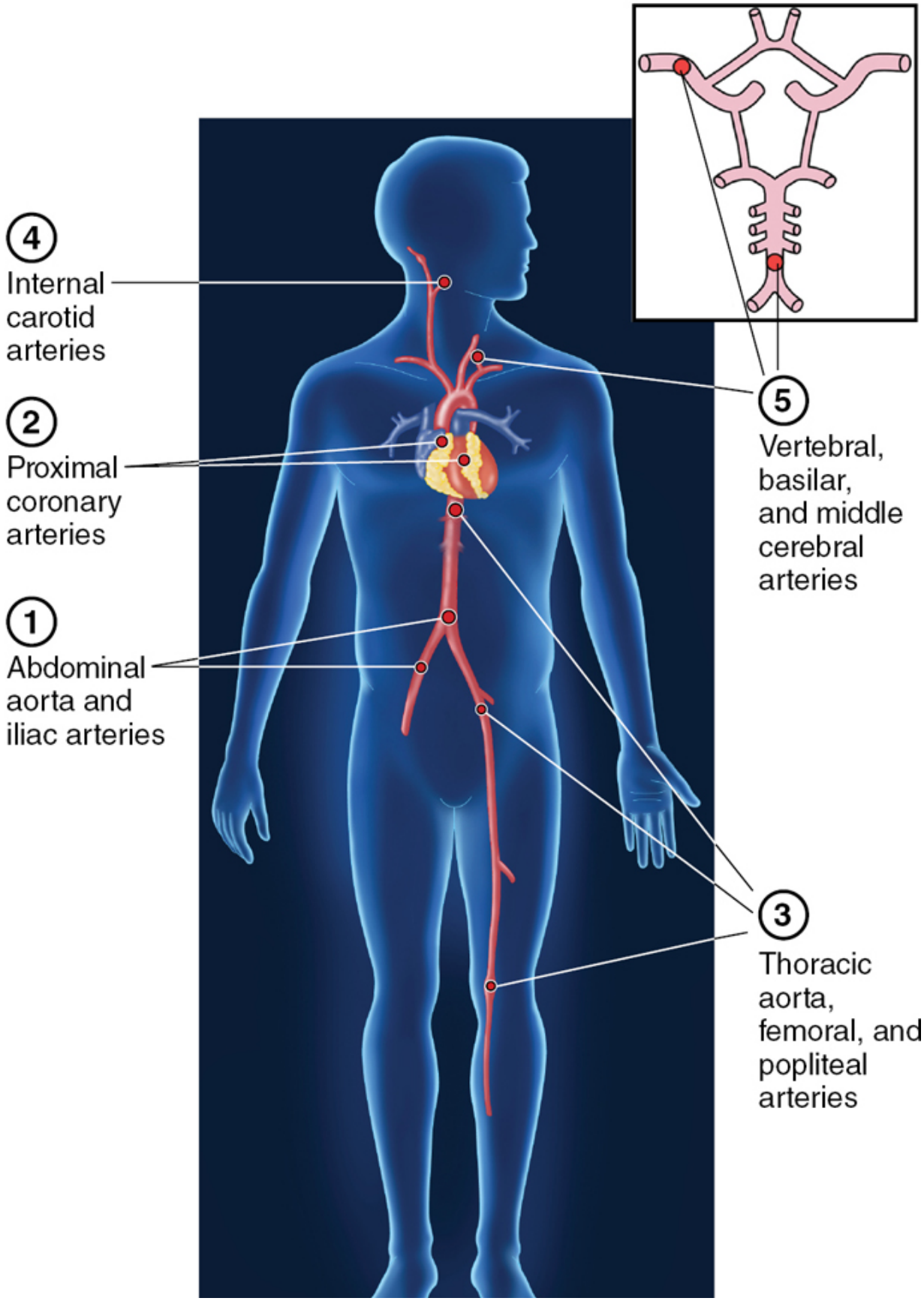

4
Internal carotid arteries
2
Proximal coronary arteries
1
Abdominal aorta and iliac arteries
5
Vertebral, basilar, and middle cerebral arteries
3
Thoracic aorta, femoral, and popliteal arteries

Figure 10-1 Sites of severe atherosclerosis in order of frequency. (Reprinted with permission from Strayer DS, Saffitz JE, *Rubin E. Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 8th ed. Wolters Kluwer; 2019.)

Erythrocyte deformability is an important factor for in vitro capillary perfusion.[17,18] In areas without compromised blood flow, normal red blood cells (RBCs) have the ability to deform when passing through a small capillary. By aligning themselves in a planar manner, RBCs reduce viscosity of the blood suspension, enabling them to pass smoothly through capillaries. In many patients with IC, RBCs have a marked decreased ability to deform, resulting in increased blood viscosity. This defect is promoted by chronic tissue ischemia and hypoxia caused by increased intracapillary leukocyte adherence, platelet aggregation, and activation of complement and clotting factors.[16] The vascular responses to hypoxia are detrimental because this sequence of events further inhibits blood flow and oxygen delivery to the tissues (**Fig. 10-2**).

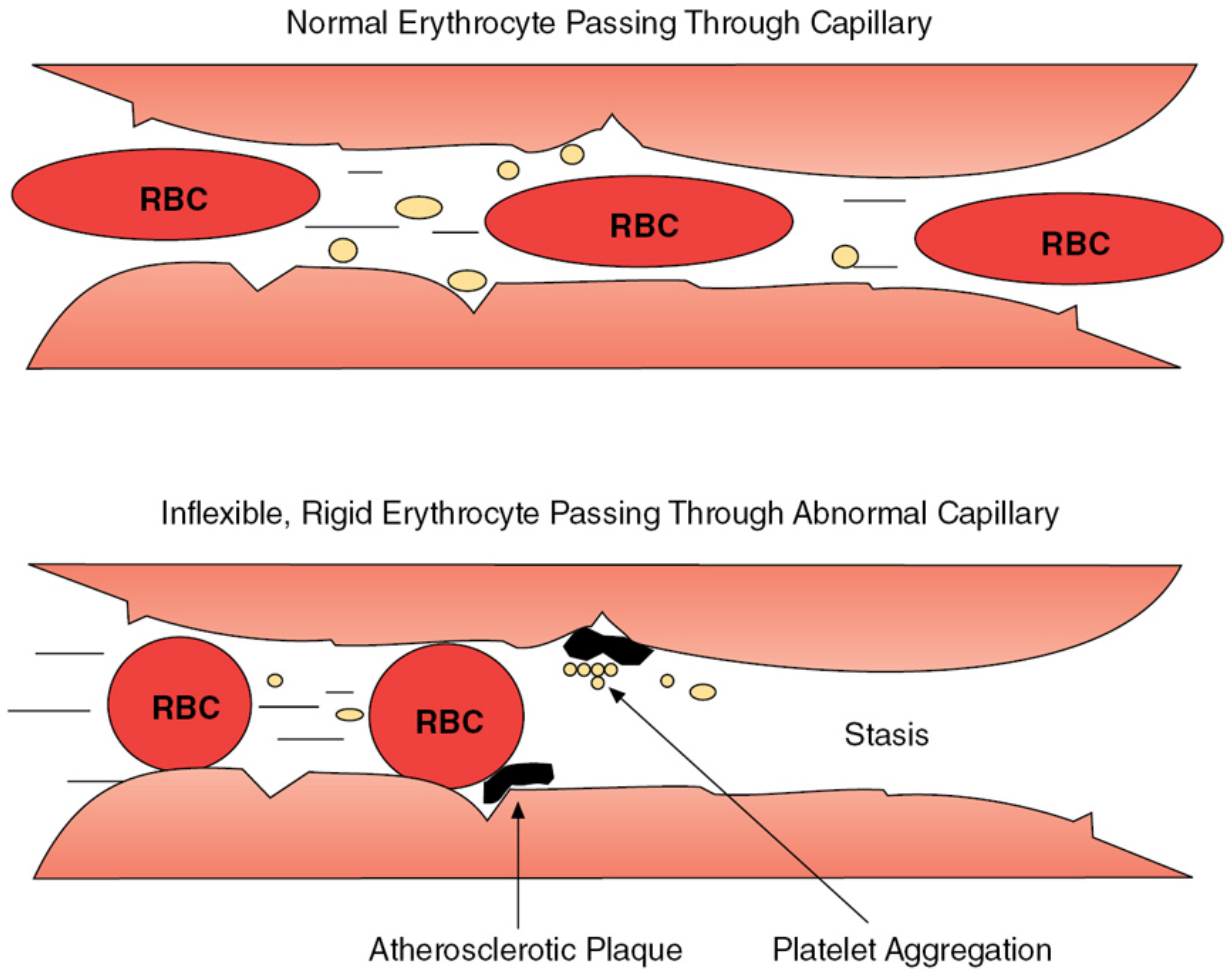


Figure 10-2 Erythrocyte inflexibility in intermittent claudication.

Clinical Presentation

CASE 10-1

Question 1: R.L. is a 60-year-old, 242.51-pound (110-kg) male with a history of type 2 diabetes mellitus, chronic stable angina, dyslipidemia, and smoking. He comes in today with right upper thigh pain while walking around the block. The pain has gradually increased during the past 12 months, but only recently has become intolerable. The pain is relieved within minutes after he stops walking. R.L. smokes two packs of cigarettes a day.

His most recent laboratory results are significant for the following results:

Total cholesterol, 290 mg/dL (SI units, 7.49 mmol/L)
Fasting triglycerides, 350 mg/dL (SI units, 3.95 mmol/L)
Low-density lipoproteins (LDLs), 188 mg/dL (SI units, 4.86 mmol/L)

High-density lipoproteins (HDLs), 32 mg/dL (SI units, 0.83 mmol/L)
Serum creatinine (SCr), 0.8 mg/dL (SI units, 61 mmol/L)
Blood urea nitrogen (BUN), 18 mg/dL (SI units, 6.4 mmol/L)
Hemoglobin (Hgb) A_{1c}, 8.2% (SI units, 10.5 mmol/L)
Fasting glucose, 175 mg/dL (SI units, 9.64 mmol/L)
Blood pressure (BP), 170/95 mm Hg
Heart rate (HR), 89 beats/minute
His posterior tibial artery pulse is not palpable. A Doppler ultrasound study is performed, and his ankle–brachial index (ABI) is 0.7 (normal, >0.90). R.L.'s medication list includes isosorbide mononitrate 60 mg daily, aspirin 81 mg daily, and ramipril 5 mg daily. His metformin doses have progressively increased to 1000 mg twice daily.

What risk factors and elements of R.L.'s presentation are consistent with a diagnosis of IC?

R.L.'s medical history illustrates classic risk factors for vascular occlusion and IC, including dyslipidemia, diabetes, hypertension, and smoking. His diabetes is not adequately controlled based on elevated A_{1c} and fasting glucose levels, and he is obese. This constellation of disorders is known as *metabolic syndrome.* These factors, along with smoking, are commonly seen together and have been linked with insulin resistance and accelerated atherosclerosis (**Fig. 10-3**).[19,20] The presence of angina indicates CAD, so it is not surprising that he has peripheral vascular occlusion as well.

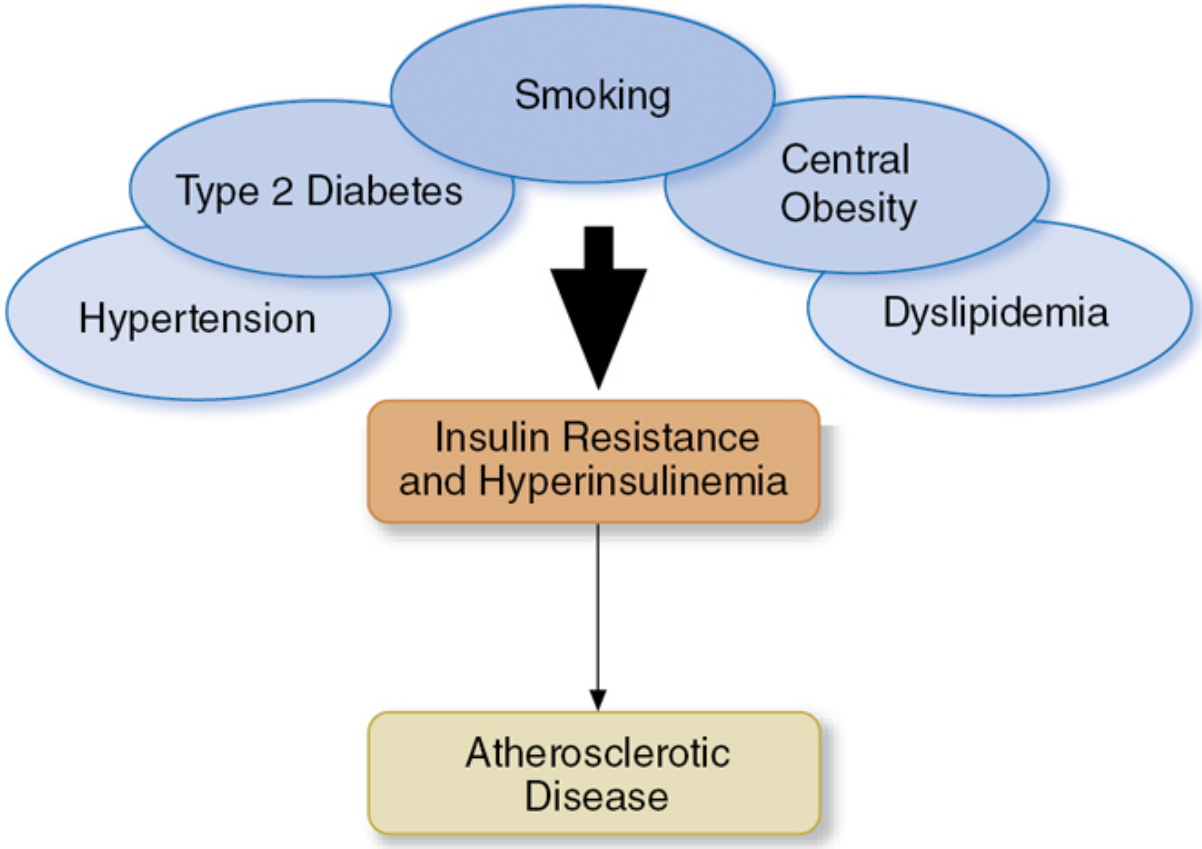


Figure 10-3 The metabolic syndrome in atherosclerosis.

The classic pain of IC described by R.L. is associated with exercise of the affected muscle group(s) and subsides with a few minutes of rest. Other common symptoms of extensive atherosclerosis include cold feet and persistent aching of the feet during rest or sleep. Restricted blood flow to the feet along with pooling of blood secondary to inadequate pressure needed to propel blood back up the leg can lead to rubor (red or purple color of the foot). Other indicators of peripheral atherosclerosis are the loss of hair from the top of the feet, thickening of the toenails, and absence of sweating of the lower legs and feet, all caused by poor circulation.[16]

The results of objective studies performed on R.L. are consistent with IC. Doppler ultrasound of the spine is helpful in excluding pseudoclaudication caused by spinal stenosis and other neurogenic or musculoskeletal causes of leg pain. Ultrasound is also useful to

measure BP of the lower extremities. An ABI of 0.7 means that the ankle systolic BP reading is only 70% of the systolic pressure in the brachial artery supplying blood to the arm. In patients with IC, this is caused by atherosclerotic obstruction of blood flow in the lower limbs and subsequent decreased perfusion pressures in the ankle compared with the arm (**Table 10-3**). As the ABI decreases, blood flow to the extremities is reduced and the severity of symptoms is greater. An ABI <0.9 is diagnostic for PAD. Loss of the posterior tibial pulse, as seen in R.L., is common in those with peripheral vascular occlusion.

Table 10-3
Severity of Arterial Obstruction as Assessed by Ankle–Brachial Index

Severity	Ankle–Brachial Index[a]
Normal	>0.90
Mild	0.70–0.89
Moderate	0.50–0.69
Severe	>0.50

[a]Ankle–brachial index is the systolic blood pressure in the ankle divided by the systolic blood pressure in the arm.

Source: Gray BH, Sullivan TM. Vascular claudication: how to individualize treatment. *Cleve Clin J Med.* 1997;64:429–436.

Treatment

THERAPEUTIC OBJECTIVES AND NONPHARMACOLOGIC INTERVENTIONS

CASE 10-1, QUESTION 2: What are the therapeutic goals in treating R.L.? What interventions should be initiated to prevent claudication pain and arrest progression of his disease?

Specific treatment goals include preventing further claudication pain, lessening his current pain, arresting the progression of

underlying disease, and decreasing his risk of cardiovascular events. Achieving these goals will provide R.L. with the best chance of avoiding further mobility impairment, amputation, and cardiovascular events. An important concept that should be stressed when explaining these treatment goals to R.L. is that all his diseases are closely interrelated and that a beneficial intervention for one disease is beneficial for all. Interventions that can be initiated include diet modification; exercise and weight loss; and attainment of goal BP, lipids, Hgb A_{1c}, and fasting and postprandial blood glucose levels. The American College of Cardiology and American Heart Association (ACC/AHA) have published guidelines that thoroughly evaluate the interventions and medications that have been used to treat IC and PAD.[8] **Table 10-4** summarizes these recommendations. The two most important things that R.L. can do for his IC are summed up in five words: "Stop smoking and keep walking."[21]

Table 10-4

Medical Treatment of Peripheral Arterial Disease and Expected Outcomes

Intervention	Improve Leg Symptoms?	Prevent Systemic Complications?
Smoking cessation	Yes	Yes
Exercise	Yes	No
Cilostazol	Yes	No
Statin drugs	Yes	Yes
Angiotensin converting enzyme inhibitors	Yes	Yes
Blood pressure control	No	Yes
Antiplatelet therapy[a]	No	Yes

[a]Aspirin or clopidogrel.

Sources: Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2017; 69:e71–e126; Kuunti J, Wijns W, Saraste A, et al. 2019

ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020;41:407–477.

Smoking cessation

The importance of smoking cessation cannot be overemphasized to patients with IC. It is the most important modifiable factor in preventing the development of rest pain, prolonged limb ischemia, need for amputation, and reducing the risk for cardiovascular events. Several studies document improved survival and decreased amputation rates in patients with IC who stopped smoking compared with patients who continue to smoke.[22,23] Other benefits, such as improved treadmill walking distance, decreased disease progression, and decreased complications after vascular reconstructive surgery, have been shown in patients who quit smoking compared with patients who continue.[8,22,24–27] It is the one intervention that will decrease R.L.'s claudication pain most rapidly. He will also decrease his risk of MI and mortality by threefold and fivefold, respectively. **Table 10-5** summarizes the risk of cigarette smoking and the value of smoking cessation on cardiovascular complications.

Table 10-5
Patient Outcomes Based on Smoking Status After Intermittent Claudication Diagnosis

Outcome	Length of Follow-Up (years)	Patient Population	
		Current Smokers (%)	Past Smokers (%)[a]
Rest pain	7	16	0
Myocardial infarction	10	53	11
Amputation	5	11	0
Mortality	10	54	18

[a]Quit after intermittent claudication diagnosis.

Sources: McDaniel CD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg.* 1989;3:273–277; Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complications, myocardial infarction, and mortality. *Acta Med Scand.* 1987;221:253–260.

Many pharmacologic products and strategies are available to aid R.L. to stop smoking (see Chapter 91, Tobacco Use and Dependence). However, nicotine itself has harmful effects on the vasculature via catecholamine release and vasoconstriction, and it may play a role in endothelial damage and atherosclerosis progression.[28]

Exercise

An individualized and supervised exercise program is endorsed for patients with PAD and will benefit most of R.L.'s other risk factors as well.[8,24] IC pain results in decreased mobility, and because of deconditioning from lack of exercise, patients with IC may slowly become dependent on others for activities of daily living. An exercise program is the most effective way to both preserve and increase mobility. It is more effective than the best pharmacologic therapy currently available.[29] The ideal exercise program consists of walking for a minimum of 30 to 45 minutes at least three times a week, for a minimum of 12 weeks.[8] R.L. should walk as fast and far as he can until the pain becomes severe; he should then wait until the pain subsides, and then resume walking.[30] At first, R.L. may experience several painful episodes during each exercise session, but these should gradually decrease as the beneficial effects of exercise therapy begin to emerge. Studies have documented that this type of exercise program can more than double the pain-free distance a patient with IC is able to walk.[31] Lower extremity resistance training can provide improved functional performance measured by the following: quality of life, treadmill walking time, and ability to climb stairs.[32] An appropriate exercise program results in superior outcomes compared with angioplasty and stenting, and equal in

terms of walking distance compared with surgery, but without any of the significant complications and mortality associated with surgery.[31]

Rheologic abnormalities of increased blood viscosity, impaired RBC filterability, hyperaggregation, and polycythemia (elevated hematocrit) have been shown to return to normal in many patients with IC who participate in a regular exercise program.[33] Exercise may offset the need for pharmacologic intervention. The potential mechanisms by which exercise benefits patients with IC are listed in **Table 10-6**.

Table 10-6
Primary Mechanisms of Symptom Improvement With Exercise Therapy in Intermittent Claudication

Decrease of blood viscosity
Metabolic changes in the muscle
Improved muscle metabolism
Improved oxygen extraction
Improved endothelial function and microcirculation
Decreased occurrence of ischemia and inflammation
Atherosclerosis risk factors improved via
Weight loss
Glycemic control
Blood pressure control
Increased high-density lipoprotein (HDL)
Decreased triglycerides
Decreased thrombotic tendency

Source: Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med.* 2002;347:1941–1951.

Dyslipidemia management

Case 10-1, Question 3: Is lipid-lowering therapy indicated for R.L.?

Because IC is a consequence of atherosclerosis, arresting the progression of R.L.'s atherosclerotic disease is important (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease). Initiation of the nutritional and exercise recommendations

should be recommended as outlined in the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease[34] and endorsed by the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol.[35] Therapeutic lifestyle changes and cholesterol-lowering agents are the cornerstones for attaining this goal. Considerable data suggest that aggressive dietary and pharmacologic management of dyslipidemia, particularly lowering low-density lipoprotein cholesterol (LDL-C), leads to regression of atherosclerotic lesions in the coronary and carotid vasculature.[36–38] In contrast, relatively few prospective data exist about the effect of successful lipid-lowering therapy on the regression or stabilization of peripheral lesions, or on clinical events in patients with PAD. A post hoc analysis of a large lipid-lowering study in subjects with known CAD treated with simvastatin demonstrated a significant decrease in new or worsening IC, suggesting that in high-risk patients, lipid lowering can prevent development of clinically symptomatic PAD.[39] The Heart Protection Study randomly assigned patients with known arterial disease of various types to simvastatin 40 mg daily or placebo. After 5 years, a 15% decrease was found in noncardiac revascularizations, including amputations, among the patients receiving simvastatin.[40] Short-term outcomes (eg, 6 months–1 year), such as improved walking distance and walking time, have also been documented with simvastatin 40 mg/day.[41,42]

A meta-analysis of 10,049 subjects from several randomized trials using a variety of lipid-lowering therapies in patients with PAD demonstrated reduced claudication severity and decreased disease progression as measured by angiography. A decrease in mortality did not reach statistical significance.[43] Limited data suggest that high apolipoprotein [Lp(a)] concentrations may be particularly important in the development of PAD.[44]

Patients with PAD fall into one of the four major statin benefit groups, specifically falling into the group with known atherosclerotic cardiovascular disease (ASCVD). Because R.L. is <75 years old, he warrants high-intensity statin therapy, which is defined as statin

therapy at doses that are expected to provide at least a 50% reduction in LDL cholesterol (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease). There is a paucity of outcome data with other agents for dyslipidemia, as trials of ω-3 fatty acid, niacin, or fibric acid derivative have failed to demonstrate a reduction in cardiovascular events in patients with increased risk for cardiovascular events like R.L.[8,24,34,35,45–48]

Case 10-1, Question 4: R.L.'s BP is elevated to 170/95 mm Hg despite ramipril therapy. Because he has angina, and his HR is 89, a β-adrenergic blocker is considered. Are there alternative antihypertensive therapies that might be preferable for R.L.?

Management of hypertension

R.L.'s hypertension has likely contributed to the development of his atherosclerosis and PAD. Hypertension (see Chapter 9, Essential Hypertension) has been associated with deficiencies in the synthesis of vasodilating substances, such as prostacyclin, bradykinin, and nitric oxide, by the endothelial cells lining the vasculature, along with increases in vasoconstricting substances like angiotensin II. Increased vascular tone can alter local hemodynamics, especially in the presence of a stenotic lesion. Although it has not been determined whether normalization of BP has a positive effect on IC, it is well established that uncontrolled BP results in vascular complications such as MI and stroke. In light of R.L.'s numerous risk factors for these complications, improvement in his BP is warranted.

β-Blockers are frequently cited as contraindicated in IC patients owing to the potential for unopposed α-adrenergic-mediated vasoconstriction during peripheral β-blockade. However, evidence to document worsening IC by β-blockade is lacking. Overall, controlled studies have been inconclusive, and a meta-analysis of placebo-controlled trials and studies with control groups concludes that β-blockers do not worsen claudication.[49,50]

Angiotensin converting enzyme (ACE) inhibitors are first-line agents in patients with PAD.[8,24] Compared with other

antihypertensive agents, the data available support their beneficial effects in this population. Compared with placebo, walking distance is increased with both perindopril and ramipril in patients with PAD.[51,52] The Heart Outcomes Prevention Evaluation (HOPE) study compared ramipril versus placebo in over 9000 patients who had evidence of vascular disease or diabetes. Impressively, they enrolled more than 4000 patients with PAD, and similar to the overall trial population, patients with PAD derived a benefit in the composite end point of decreased mortality, MI, and stroke.[53] The ONTARGET trial compared telmisartan, ramipril, and the combination of the two in patients with vascular disease or high-risk diabetes without heart failure for a composite end point of cardiovascular death, MI, stroke, or hospitalization for heart failure. The results suggested equivalency of telmisartan to ramipril for the primary end point with similar BP reduction in both groups; however, the combination therapy group experienced more adverse events without any benefit.[54] Based on these data, ARBs may be a suitable substitute for ACE inhibitors, but combination therapy is not recommended.

R.L.'s. BP goal is <130/80 mm Hg.[55–57] His dose of ramipril could be increased, or a low-dose diuretic, such as hydrochlorothiazide or chlorthalidone,[55,56] could be added. Given his history of chronic stable angina, the addition of a calcium channel blocker (CCB) or a β-blocker would be an option as well. The ACCOMPLISH trial compared the combination of benazepril–amlodipine with benazepril– hydrochlorothiazide in patients with hypertension who were at high risk for cardiovascular events. Amlodipine therapy reduced cardiovascular events compared with hydrochlorothiazide, even though BP control was not significantly different.[58] Although β-blockers are typically used in patients with CAD, the outcome data supporting their use are less clear.[59]

Management of diabetes

Case 10-1, Question 5: Will improving R.L.'s diabetes control or slow the progression of his PAD? What changes in his diabetes management do you

recommend?

Patients with type 2 diabetes mellitus (see Chapter 53, Diabetes Mellitus) are able to minimize macrovascular and microvascular complications of their disease with aggressive glucose control.[7,60,61] Historically, insulin, sulfonylurea, or metformin therapies have a beneficial effect on slowing the development of the microvascular complications of diabetes, such as retinopathy and nephropathy. Metformin has specifically been shown to further reduce the occurrence of macrovascular complications such as stroke or MI compared with insulin or sulfonylureas in obese patients with type 2 diabetes,[60] whereas recent data with sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide 1(GLP-1) agonists have demonstrated significant reduction in ASCVD risk and have been given priority status for reducing ASCVD risk in patients with type 2 diabetes.[62]

R.L.'s diabetes is a significant risk factor for progression to further ischemic events (**Table 10-7**). He has a twofold greater risk of death and a sevenfold greater risk of amputation compared with a patient without diabetes. Although a specific benefit for IC has not been demonstrated, it seems prudent to initiate or continue aggressive diabetes management in patients with type 2 diabetes mellitus and IC. In addition to metformin, addition of either an SGLT-2 inhibitor or GLP-1 agonist to R.L.'s therapy would improve his blood glucose control and decrease his risk of ASCVD. It is hoped that R.L. can reach his Hgb A_{1c} goal of <7% and a fasting blood glucose of 80 to 130 mg/dL and 2-hour postprandial glucose of <180 mg/dL with diet and exercise, while adding metformin to his current therapy.[62,63]

Table 10-7
Effect of Diabetes Mellitus on Intermittent Claudication Outcomes After 5 Years

	Patients With Diabetes (%)	Patients Without Diabetes (%)
Mortality	49	23
Major amputation	21	3

Deterioration	35	19

Source: Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J.* 1999;20:344–353.

R.L. also must take proper care of his feet to prevent ulcerative complications of IC. He should be encouraged to keep his feet warm, dry, and moisturized and to wear properly fitted shoes and perform daily foot inspections.[8] He should seek medical attention immediately for minor trauma to his feet or legs.[4] These measures can reduce the incidence of amputation in patients with diabetes.

PHARMACOLOGIC THERAPIES

Antiplatelet therapies

Case 10-1, Question 6: Is R.L.'s aspirin therapy beneficial for preventing further complications of IC? Would alternative antiplatelet therapies offer advantages over aspirin?

Aspirin is one of several antiplatelet agents that may be considered for indefinite use in patients with PAD. There is limited data on the effects of aspirin on IC symptoms. Whether aspirin has any beneficial effects on walking distance or claudication pain has not been studied. Available data address the impact of aspirin on overall cardiovascular morbidity and mortality. Although aspirin has no direct effect on plaque regression, it does prevent and retard the role platelets play in the thrombogenic events that occur in the vicinity of atherosclerotic plaques.[64] Aspirin is an effective antithrombotic agent at dosages ranging from 50 to 1500 mg daily. The lowest dosages proven to decrease cardiovascular events are 75 to 100 mg daily,[65] with the higher dosage showing benefit in active processes, such as acute ischemic stroke[66] and acute MI.[67] A dosage of 75 mg daily has demonstrated benefit in patients with hypertension[68] and stable angina.[69] No evidence indicates that these

“low doses” are any more or any less effective than dosages of 900 to 1500 mg daily.[70]

Aspirin is recommended in patients with vascular disease of any origin (stroke, MI, PAD). At dosages of 75 to 162 mg/day, aspirin decreases vascular death by ~15% and all serious vascular events (MI, stroke, or vascular death) by ~20% in high-risk patients, including those with PAD.[62,65,69] In patients with PAD, aspirin can delay the progression of established lesions as assessed by angiography. When used for primary prevention of cardiovascular disease in males, aspirin decreased the need for arterial reconstructive surgery, which was needed because of PAD.[71] In a meta-analysis of 5269 subjects with PAD, aspirin was associated with a significant reduction in nonfatal stroke with a statistically insignificant decrease of cardiovascular events.[72] However, in a recent large randomized, controlled trial in 3350 patients ages 50 to 75 years without clinically evident cardiovascular disease but with a screening ABI of 0.95 or less, aspirin 100 mg/day was found to be no more effective than placebo in reducing the primary end point of fatal and nonfatal coronary events, stroke, or revascularization (13.7 events per 1000 person-years in the aspirin group vs 13.3 in the placebo group; hazard ratio, 1.03; 95% confidence interval, 0.84–1.27).[73]

Because all dosages of aspirin are similarly efficacious in decreasing vascular events in this patient population, side effects influence the dose chosen. Although few studies have directly compared varying doses, side effects appear to be dose related. Aspirin 30 mg daily results in less minor bleeding compared with ~300 mg daily,[74] and 300 mg daily results in fewer gastrointestinal (GI) side effects compared with 1200 mg daily.[75] Therefore, R.L. should take the lowest effective dose of aspirin: 75 to 100 mg daily. Of note, R.L.’s hypertension should be controlled before initiating aspirin therapy to decrease the small increased incidence of cerebral hemorrhage associated with its use.[76]

Ticlopidine is the first thienopyridine derivative that blocks adenosine 5′-diphosphate (ADP) receptors on platelets and decreases platelet–fibrinogen binding.[77] Several studies document

its efficacy in patients with PAD on end points such as walking distance, cardiovascular death, and the need for revascularization surgery.[78,79] However, hematologic toxicities (neutropenia and, rarely, thrombotic thrombocytopenic purpura) limit its use.[80,81]

Clopidogrel initially replaced ticlopidine largely because of its improved safety profile. The effects of clopidogrel on specific PAD outcomes are unknown, but it has been compared with aspirin in patients with known atherosclerotic disease. Dosages of 75 mg daily significantly reduced cardiovascular end points by ~25% compared with aspirin in this patient population.[82] The treatment effect was most pronounced in the PAD subgroup, leading to the suggestion that clopidogrel may be preferable in the patient population with PAD. No measure was taken of clopidogrel's effect on walking distance or claudication pain, however, and these results have not been confirmed by further studies.

The combination of aspirin and clopidogrel was compared with aspirin alone in more than 15,000 patients at high risk of vascular events, of whom >20% had a history of PAD and ~10% had IC.[83,84] In this large study that assessed cardiovascular end points, no benefit was found for dual antiplatelet therapy with aspirin plus clopidogrel.[80] Thus, although clopidogrel has the same guideline recommendation as aspirin, clinically it is often used as an appropriate alternative to aspirin in patients unable to take aspirin therapy,[65] perhaps owing to a serious allergy.[8] It should not be used in addition to aspirin, however, because the risk of bleeding and increased cost outweigh any measurable vascular benefit.[84,85]

Ticagrelor was compared with clopidogrel in 13,885 patients with known symptomatic PAD but without documented CAD.[86] There was no difference between the two groups with regard to the primary composite end point of death, MI, and stroke. Ticagrelor was discontinued more frequently than clopidogrel because of the occurrence of side effects (dyspnea and minor bleeding). Based on these data, ticagrelor cannot be recommended to reduce the risk of cardiovascular events in PAD patients at this time. These data also question whether there are differences in cardiovascular risk in patients with both CAD and PAD versus those with PAD alone.

Case 10-1, Question 7: Are there any medications that can be used to increase the walking abilities of patients with IC?

Cilostazol

Cilostazol is one of the few agents approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of IC. Several studies have confirmed that cilostazol 100 mg twice daily increases walking distance by ~50%[87–90] and that discontinuation of cilostazol results in a decline in function.[91] Cilostazol possesses antiplatelet and vasodilatory effects mediated by the inhibition of phosphodiesterase III.[92] In vitro observations suggest that these pharmacologic effects of cilostazol are particularly pronounced at the blood–vessel interface,[92] which may explain its particular efficacy in the patients with PAD. Studies that included quality-of-life measurements have found that cilostazol improved overall quality of life.[87,93] Small improvements in ABI with chronic cilostazol therapy have also been observed.[94] Two small studies indicate cilostazol is associated with a reduction in restenosis after endovascular therapy in femoropopliteal lesions.[95,96]

Despite these positive findings with cilostazol, several drawbacks exist. It is contraindicated in patients with heart failure based on data with other phosphodiesterase inhibitors demonstrating excess mortality, presumably because of increased arrhythmias.[97] Other common side effects include headache, occurring in up to one-third of patients, and loose stools or diarrhea.[88,98] Cilostazol is a cytochrome P-450 3A4 substrate; therefore, any inhibitor of this enzyme system may substantially increase cilostazol concentrations.

Cilostazol is an important advancement in the treatment of IC. It is the first pharmacologic agent to demonstrate a consistent effect on a significant source of IC disability: walking and mobility measures. Although limited data address its impact on other important end points, such as amputation and revascularization procedures or cardiovascular events,[99] it should be added to R.L.'s existing medication regimen at a dosage of 100 mg twice daily to attenuate his symptoms of IC.

Rheologic agents

Case 10-1, Question 8: Has pentoxifylline been shown to be efficacious in patients such as R.L.? How does this drug benefit patients with IC?

Pentoxifylline, a methylxanthine derivative, is another agent approved by the FDA for the treatment of IC. Pentoxifylline appears to decrease blood viscosity by decreasing fibrinogen, improving the deformability of both red and white blood cells, and eliciting antiplatelet effects, although the exact mechanism of action is unclear.[100] Although the theoretic and in vitro data are unique and positive, data demonstrating its clinical usefulness are controversial. Improvements in walking distances from study to study are unpredictable, and the clinical importance of the sometimes minimal increases in walking distances is not clear (eg, pain-free walking of ~30 m greater than with placebo).[101] Some experts assert that these potential benefits of questionable clinical significance are not worth the expense of drug therapy or the GI side effects.[102]

Pentoxifylline's role in IC therapy is limited. It may have a role in patients who are unable to engage in exercise therapy, or in patients with markedly reduced walking distances, or in whom any small increase in walking distance would greatly improve a patient's activity level.[103] It also may be tried in patients who have not gained the desired benefit from smoking cessation and exercise therapy and in patients with contraindications, intolerance, or failure of cilostazol. A 2-month trial of pentoxifylline is adequate to determine whether the patient will benefit from therapy.[30] R.L. is not severely debilitated, and the benefits of smoking cessation, exercise therapy, and cilostazol have not been fully realized. Therefore, pentoxifylline should not be added until his response to these well-proven therapies has been determined and the need for further improvement in walking distance is established.

Vasodilators

Case 10-1, Question 9: R.L. is already taking isosorbide mononitrate for angina. Because IC is made worse by vasoconstriction, should another vasodilating agent be added to treat both his hypertension and IC?

The use of vasodilators for R.L. would at first appear to be a logical pharmacologic intervention to prevent claudication pain. Vasodilators, including isosorbide, directly or indirectly relax blood vessel walls and increase both skin and muscle blood flow as long as cardiac output is maintained. With obstructive arterial disease, however, vessels are sclerotic and unable to further dilate. As a result, healthy vessels dilate to a greater extent than diseased vessels, and blood flow is redistributed (shunted) away from areas that have the greatest need. BP and perfusion paradoxically drop even further in tissues affected by atherosclerosis, resulting in increased pain. If this process produces ischemia, it is known as the *steal phenomenon.* Thus, although nitrates are not contraindicated in patients like R.L, they may not be as helpful as their mechanism of action may suggest.

Numerous vasodilators (ie, prostaglandin E_1, prostacyclin, isoxsuprine, papaverine, ethaverine, cyclandelate, niacin derivatives, reserpine, guanethidine, methyldopa, tolazoline, nifedipine) have been used to treat IC. None, however, has convincingly or consistently improved exercise performance, despite earlier beliefs that they were effective.[104,105] Limited data suggest L-carnitine 1 g twice daily may have benefit in walking distance and initial claudication distance.[106] ACE inhibitors are the exception to this rule, as their beneficial effects are likely independent of their vasodilator properties. One small, controlled study demonstrated improvement in walking distance with verapamil, a CCB, compared with placebo in patients with IC.[107] Further studies with verapamil are needed before its use can be recommended.

Smoking cessation, an exercise program, and cilostazol are the interventions that should reduce R.L.'s symptoms of IC to the greatest degree. Verapamil is a moderate cytochrome P-450 3A4 inhibitor and would be expected to increase concentrations of

cilostazol. The magnitude of this interaction has not been characterized, nor has its impact on efficacy and bleeding events been assessed. Based on the necessity of cilostazol therapy in R.L., along with the poorly characterized benefits of verapamil in IC and the plethora of other antihypertensive and antianginal agents, avoidance of verapamil is prudent at this time. If additional BP or antianginal effects are needed, β-blockade or amlodipine can be initiated.

OTHER ANTITHROMBOTIC ALTERNATIVES

Case 10-1, Question 10: If R.L. experienced a cardiovascular event while on aspirin, what changes to his antithrombotic regiment should be made?

Although there are limited data regarding antithrombotic therapy in patients with PAD, vorapaxar has been approved with potential to provide a benefit in reducing cardiovascular events. Vorapaxar is a platelet protease-activated receptor (PAR)-1 antagonist, which inhibits thrombin-mediated platelet and recently received FDA approval for reducing thrombotic cardiovascular events in patients with PAD. The indication approval was based on a recent study, which enrolled 26,449 patients with stable atherosclerotic vascular disease who were already receiving dual antiplatelet therapy, of which 14% had PAD.[108] The results showed that treatment with vorapaxar reduced the composite primary end point of cardiovascular death, MI stroke, although only the incidence of MI was reduced significantly. Importantly, major bleeding was increased significantly in the vorapaxar group; thus, the true benefit of the addition of vorapaxar in these patients is unclear at this time.

Dual pathway inhibition with low-dose oral factor Xa inhibitor rivaroxaban plus low-dose aspirin was recently evaluated in two studies that demonstrate its benefit in patients with PAD. The first study evaluated 27,295 patients with stable ASCVD, of which 27% had PAD. Patients were randomized to one of three groups: rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban

5 mg twice daily, or aspirin 100 mg daily.[109] The trial was stopped early because of the significant outcome benefit in the patients who received the combination of rivaroxaban 2.5 mg twice daily plus aspirin. This combination reduced the primary composite end point of cardiovascular death, MI, and stroke, along with death from any cause, and the results were consistent across all ASCVD groups. Guidelines have now included this combination as an option to reduce ASCVD risk.[24]

CASE 10-1, QUESTION 11: Three years have passed, and R.L. stopped smoking 6 months ago. His current medications include isosorbide mononitrate 60 mg daily, aspirin 81 mg daily, and ramipril 10 mg daily; carvedilol 6.25 mg twice a day; NPH insulin 55 units in the morning and 40 units in the evening; and atorvastatin 80 mg daily. His symptoms of IC have remained fairly stable until the recent development of a nonhealing ulcer on his toe. What options are there for R.L. if nonpharmacologic and pharmacologic interventions are not sufficient?

Surgical intervention eventually may be necessary for persistent and complicated disease. Because success rates for preventing amputation and postsurgical complications vary from institution to institution, surgery should be considered only for severely ischemic limbs and should be performed in a hospital with a good record of success.[110] Arterial bypass grafting and percutaneous transluminal angioplasty of the femoral or iliac arteries, similar to cardiac revascularization, are two procedures that can be performed. Angioplasty is beneficial in patients with localized disease, especially in the iliac or superficial femoral arteries, and should be considered in patients who truly are incapacitated by their activity limitations.[111] Angioplasty with or without stent deployment, atherectomy, and the use of drug-eluting stents in the peripheral arteries are all options.[8] The more invasive reconstructive arterial (bypass) surgery can be used if diffuse lesions preclude the use of localized angioplasty. The true benefits and pitfalls of these skilled interventions remain unclear.[112]

Emergency surgical intervention may be required if acute, persistent ischemia develops. This is frequently because of

thrombosis associated with advanced atherosclerosis, although other causes, such as cardiac emboli, cannot be excluded.[103] Both surgical thrombectomy and localized thrombolytic administration[113] with tissue-plasminogen activator or urokinase have equal success in alleviating acute limb-threatening ischemia.[114,115] After surgical intervention, patients are advised to resume and remain on antiplatelet therapy indefinitely to reduce the risk of future events.

Dual pathway inhibition with low-dose rivaroxaban plus aspirin is a promising option for patients who require intervention. The Voyager study evaluated 6564 patients with PAD who had undergone lower extremity revascularization and were at high risk for major limb and cardiovascular events.[116] Compared to patients receiving aspirin alone, the combination of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily significantly reduced the primary composite end point of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes.

RAYNAUD PHENOMENON

Raynaud phenomenon (RP) is a clinical syndrome caused by episodic vasospasm and ischemia of the extremities in response to cold, emotional, or physical stimuli.[117–122] Episodes include changes in color of the extremities from white, because of vasoconstriction, to blue, signaling tissue hypoxia, and then red when reperfusion occurs.[118] It is usually limited to the skin of the fingers, and less often the toes, but can also occur on the nose, cheeks, and ears.[119] Between attacks, the digits may appear cool and moist or normal. In most cases, the ischemia produced by the phenomenon does not have important consequences; however, in severe cases, atrophy of the skin, irregular nail growth, and wasting or ulceration of the tissue pads can occur.[119] Although both IC and RP are disorders of the peripheral arterial circulation, they differ significantly in that IC results primarily from atherosclerotic obstruction, whereas Raynaud disease is caused by vasospasm.

Diagnosis

This disorder can be separated into primary RP, indicating an idiopathic origin, and secondary RP, which consists of signs and symptoms of RP in the presence of an associated disease or condition, most commonly a connective tissue disorder, such as systemic sclerosis (formerly known as scleroderma), mixed connective tissue disease, rheumatoid arthritis, or systemic lupus erythematosus. Primary RP is more common (89% of patients) and is more likely to occur in younger patients (<30 years), generally presents with less severe symptoms, normal erythrocyte sedimentation rate, negative antinuclear antibodies, and no associated signs of underlying disease. Patients with secondary RP are more likely to have severe disease with painful symptoms, which can progress to ulceration or gangrene in extremities if untreated.[119] The diagnosis is generally a subjective one, consisting of clinical signs and symptoms, cold hands, feet, or both without normal recovery after a cold stimulus, emotional stress, or physical stress (such as vibrations) to the extremities.[121,122] In unaffected individuals, a cold provocation should result in some mottling and cyanotic changes in the hands, with recovery once the stimuli are removed. In patients with RP, however, the same cold provocation causes closure of the digital arteries, which produces a sharply demarcated pallor and cyanosis of the digits that persists despite removal of the stimulus.[121]

Epidemiology

In general, the prevalence of RP is about 3% to 5% across several ethnic groups[120]; however, it is higher in some geographically defined populations.[120] It is more common in females than males, is more frequent in non-Hispanic Whites, and has a higher prevalence in patients with family members who also experience RP. An onset in the teenage years suggests primary RP, whereas an onset after age 30 years suggests a secondary cause.[120] Secondary RP is usually associated with a connective tissue disorder, but several other

conditions may predispose individuals to its development. These include occupational-related exposures to vibratory machinery (eg, drills, chain saws) that cause neural damage,[120] vinyl chloride, or hand trauma.[122–124] Approximately 15% of patients diagnosed with primary RP will go on to develop a connective tissue disorder within 10 years.[125]

RP can also be associated with medications, including β-adrenergic blocking agents, ergots, cytotoxic drugs, chemotherapy, amphetamines and other sympathomimetics, and interferon, all of which can induce vasoconstriction.[126–128] Although avoidance of β-adrenergic blocking agents in patients with RP appears prudent, no discernible effect, as measured by skin temperature and blood flow, was found with the administration of both selective and nonselective β-blockers to patients with RP.[129] RP not associated with a connective tissue disorder is often transient and does not interfere with daily activities.[129] The effect of smoking on RP has yielded conflicting results. Overall, there appears to be a negligible effect of smoking on the prevalence of RP and the incidence of attacks, although there is some evidence that the severity of attacks may be decreased with smoking cessation.[130,131]

Pathophysiology

The pathophysiology involved in the exaggerated, abnormally long-lasting vasoconstriction in response to stimuli seen in RP is complex and still not completely understood. Control of blood vessel reactivity involves a balance of mediators released from circulating cells, the vascular endothelium, hormones, and neurotransmitters.[118,122] Cold-induced vasospastic attacks in patients with primary RP involve a heightened vasoconstriction of digital arteries that is mediated by a subset of peripheral α_2-adrenergic receptors.[118,122,132]

Vascular abnormalities noted in RP can include a deficiency of the vasodilator nitric oxide (NO), an increase in endothelial production of the potent vasoconstrictor endothelin-1, and increased activity of the renin–angiotensin system resulting in vasoconstriction induced by

angiotensin II.[122] In secondary RP, structural changes resulting from connective tissue disease may cause arterial damage that results in the α_2-adrenoreceptor aberrancy and endothelial injury that stimulates vasoconstriction, platelet activation, and impaired fibrinolysis.[118,122] It is also possible that serotonin receptors play a role in RP. Serotonin agonists have caused decreased finger blood flow, and, conversely, antagonists have increased digital blood flow.[133,134]

CASE 10-2

Question 1: L.G., a 39-year-old male, presents today with a 4-day history of left hand pain. He notes that the third digit of his left hand is "cold and somewhat blue," especially in the distal area. The other areas of his hand have recovered, but the distal portion of the digit remains cyanotic and numb. He has used acetaminophen and warm- water soaks without success. He is a construction worker who uses his hands "quite a bit" in his work. He has a history of gastroesophageal reflux and has no medication allergies. His social history is significant for smoking 1.5 packs of cigarettes a day for 19 years. On physical examination, his extremities reveal appropriate sensation of the forearm and hand. Some blue areas are noted on the distal portion on the third phalanx, with no other signs and symptoms. When L.G.'s opposite hand was placed in cold water, several white splotches appeared, and he experienced tingling in this hand as a result of the cold-water exposure. He is diagnosed as having RP.

Does L.G. present with primary or secondary RP?

Clinical Presentation

L.G. presents with what is most likely secondary RP owing to one of several potential underlying causes. His clinical presentation is classic for RP, with vasospasm, pallor, and a cyanotic overtone. The diagnosis is confirmed by the cold-water test, which indicates that the vasospastic attack is precipitated by cold exposure. He has a work history that may easily include hand trauma and the use of vibrating machinery, and his age also suggests secondary RP. Because of its association with connective tissue disorders, other

laboratory tests such as an antinuclear antibody and erythrocyte sedimentation rate should be checked.

Treatment

NONPHARMACOLOGIC MANAGEMENT

Case 10-2, Question 2: What conservative measures can be taken with L.G. to prevent or decrease the painful vasospasm of RP?

Most patients with either primary or secondary RP will respond to conservative management to reduce exposure to triggers such as cold and emotional stress.[119] L.G. should be instructed to protect his hands and fingers from exposure by using mittens and insulated wrappers when handling cold drinks and to protect other parts of his body from cold exposure. He should also try to minimize emotional stress and occupational exposure to vibrating machinery and avoid medications that can induce vasoconstriction, particularly sympathomimetics, clonidine, serotonin receptor agonists, and ergot preparations.[119,120] He should be encouraged to stop smoking, which may not affect occurrence of attacks but may decrease their severity and provide an overall positive health benefit.[130]

L.G. has new-onset and relatively mild RP. For others who have more severe symptoms and manifestations, especially patients with underlying connective tissue disorders, it is important to immediately and aggressively manage any ulcers that develop on the digits and to be extremely vigilant in detecting infected digits. Rarely, patients who have severe symptoms including ulceration or thrombosis may require surgical intervention such as peripheral sympathectomy, embolectomy, or ulcer debridement.[119,134,135]

CALCIUM CHANNEL BLOCKERS

Case 10-2, Question 3: Nifedipine extended-release 30 mg every day is ordered for L.G. What is the rationale for using a CCB in this case?

Medications can be used to treat primary and secondary RP if symptoms interfere with the patient's ability to work or perform daily activities or if digital lesions develop. Most proposed treatments for RP are variably effective, and they introduce the risk for significant side effects.[136,137] Drug therapy should always be in addition to nonpharmacologic measures.

Dihydropyridine CCBs decrease calcium ion influx and prevent vascular smooth muscle contraction, especially vascular responses evoked by cold exposure. Nifedipine, a potent peripheral vasodilator, has been studied the most and has become the drug of choice in patients with RP not controlled by conservative measures. In primary RP, 10 or more episodes per week are common. A meta-analysis showed a decrease of 2.8 to 5 attacks per week and a decrease in severity by 33%.[137] Patients with secondary RP experience a similar decrease in attack severity and also achieve a decrease in number of attacks with nifedipine therapy. Because their baseline number of attacks per week often exceeds 20, the relative benefit is not as great as with primary RP, averaging ~25% decrease in weekly episodes.[138] Although doses of 10 to 30 mg three times daily of immediate-release nifedipine are beneficial in studies,[137,138] most clinicians administer nifedipine as an extended-release formulation to increase convenience and decrease side effects such as dizziness, headache, facial flushing, and peripheral edema, which can occur in up to 50% of patients,[119,122,137] and this practice is supported by clinical studies.[139,140]

Although less thoroughly studied than nifedipine, other vasoselective CCBs, such as amlodipine, felodipine, isradipine, and nisoldipine, decrease the frequency and severity of ischemic attacks.[141–144] Patients who do not benefit from nifedipine likely will not benefit by switching to another CCB. Patients who cannot tolerate the side effects of nifedipine (eg, peripheral edema, headache) might benefit by switching to another CCB.

L.G. should be warned of the potential side effects with nifedipine therapy, especially dizziness associated with hypotension, and should return in 2 weeks for assessment. A 30-mg daily dose of extended-release nifedipine is a reasonable starting dose. He should

keep a diary documenting the number of attacks he experiences and the details surrounding each attack, such as time course and precipitating factors. In addition to the usual side effects mentioned above, L.G. should be aware that his symptoms of gastroesophageal reflux could worsen with nifedipine therapy, which can cause a decreased lower esophageal sphincter pressure. This side effect should be specifically assessed at his follow-up appointment.

OTHER THERAPEUTIC AGENTS

CASE 10-2, QUESTION 4: What other drugs may be tried if L.G. cannot tolerate the CCB?

Other than CCBs, no proven therapy for RP exists. Many agents, however, have been used based on limited data. The α_1-adrenergic antagonist prazosin, 1 mg three times a day, yielded moderate benefit in two-thirds of patients in two small studies.[145,146] Side effects of prazosin are significant at maximal doses and include dizziness, edema, fatigue, and orthostasis. The longer acting α_1-adrenergic antagonist terazosin was evaluated in one small study, and it improved symptomatology as well as objective measures of blood flow.[147] Insufficient data with this class of drugs exist to routinely recommend their initial use in patients with RP. Topical nitrates have been used clinically for several years and newer formulations have recently been studied, but data showing efficacy are limited.[119]

Several therapeutic approaches are being vigorously investigated and show promise as future therapies for RP. These include the intravenous prostaglandin analogs iloprost and alprostadil, which enhance nitric oxide–mediated vasodilation[148]; endothelin antagonists, such as bosentan[149]; and oral phosphodiesterase inhibitors[150–152] which also promote vasodilation. A meta-analysis of phosphodiesterase inhibitors for the treatment of secondary RP showed a modest decrease in frequency and duration of attacks, although further larger trials are needed.[152] Botulinum toxin-A has also been studied.[153] Because of side effects, cost, and

administration difficulties, these agents are primarily being studied in the most severe cases of secondary RP with digital ulcers or other systemic complications associated with connective tissue diseases. If benefit is proved, however, it will shed light on the pathogenesis of the disorder, and perhaps lead to therapies appropriate for the larger population with RP.

Statins may have promise in severe cases resulting in digital ulcers secondary to systemic sclerosis (SSc). Pleiotropic effects of atorvastatin 40 mg/day on endothelial function compared with placebo were investigated in 84 SSc patients who fulfilled the American College of Rheumatology criteria for classification of SSc with secondary RP despite ongoing vasodilator therapy. The study found a significant decrease in both new and the total number of digital ulcers in the atorvastatin group compared with placebo.[154]

The renin–angiotensin system mediators act as vasodilators and have been investigated in several small studies. ACE inhibitors and angiotensin receptor blockers, however, have yielded conflicting results with respect to beneficial effects in patients with RP.[155–158] Small beneficial effects have been realized, specifically with captopril 25 mg three times a day and losartan 12.5 to 25 mg/day; however, no benefit has been found with enalapril 20 mg once daily.[155] Fluoxetine, a selective serotonin reuptake inhibitor, was shown in one study to reduce the symptoms of RP.[159] It is hypothesized to exert its effect by depleting platelet serotonin, rendering the platelet unable to release a significant amount of the vasoconstrictive serotonin during activation and aggregation.

Alternative therapies, such as Ginkgo biloba and L-arginine, have also been studied in small trials with positive results; however, larger trials are needed to confirm the findings before these therapies can be recommended.[160–162]

All patients with RP should be counseled regarding cold avoidance and other protective measures. A CCB, extended-release nifedipine if tolerated, should be initiated if conservative measures are ineffective and titrated to the highest tolerated dose and symptom resolution. Combination therapies have not been investigated, but

another agent, such as an α_1-adrenergic antagonist, may be considered in addition to the CCB if symptom resolution is not satisfactory and side effects permit.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: antithrombotic therapy and prevention of thrombosis, 9th ed: american College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141:e669S–e690S. (65)

Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev*. 2007;(4):CD000123. (43)

Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2017;69:e71–e126. (8)

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2019;73(*24*):e285–e350. (35)

Kuunti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020;41:407–477. (24)

Lane DA, Lip GY. Treatment of hypertension in peripheral arterial disease. *Cochrane Database Syst Rev*. 2009;(4):CD003075. (51)

Robless P, Mikhailidis DP, Stansby GP. Cilostazol for peripheral arterial disease. *Cochrane Database Syst Rev*. 2008;(1):CD003748. (90)

Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2008;(4):CD000990. (31)

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension.* 2018;71(*6*):e13–e115. (55)

Key Websites

National Heart, Lung, and Blood Institute. Peripheral Artery Disease. https://www.nhlbi.nih.gov/health/peripheral-artery-disease

Peripheral Artery Disease (PAD). https://cardiovascularcoalition.com/cardiovascular-care/peripheral-artery-disease-pad/

AC Forum Medical Management of PAD Virtual Learning Series. https://acforum.org/eLearning-PAD/#/lessons/jdP9033diHGhAMjp4O7YgFacHsxIFX6M

Vascular Disease Foundation. http://www.vdf.org

COMPLETE REFERENCES CHAPTER 10 PERIPHERAL VASCULAR DISORDERS

1. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 1985;71:510–515.
2. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. *J Am Geriatr Soc*. 1985;33:13–18.
3. Caspary L. Epidemiology of vascular disease. *Dis Manage Health Outcomes*. 1997;2(suppl 1):9–17.
4. Boccalon H. Intermittent claudication in older patients. Practical treatment guidelines. *Drugs Aging*. 1999;14:247–259.
5. Hirsch A, Murphy TP, Lovell MB, et al. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. *Circulation*. 2007;116:2086–2094.
6. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham Study. *JAMA*. 1979;241:2035–2038.

7. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837–853.
8. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2017;69:e71–e126.
9. MacGregor AS, Price JF, Hau CM, Lee AJ, Carson MN, Fowkes FG. Role of systolic blood pressure and plasma triglycerides in diabetic peripheral arterial disease. The Edinburgh Artery Study. *Diabetes Care*. 1999;22:453–458.
10. Willigendael EM, Teijink JA, Bartelink ML, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg*. 2004;40:1158–1165.
11. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J*. 1999;20:344–353.
12. McDaniel CD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg*. 1989;3:273–277.
13. Aboyans V, Desormais I, Lacroix P, Salazar J, Criqui MH, Laskar M. The general prognosis of patients with peripheral arterial disease differs according to the disease localization. *J Am Coll Cardiol*. 2010;55:898–903.
14. Hertzer NR. The natural history of peripheral vascular disease: implications for its management. *Circulation*. 1991;83(2 suppl):I12–I19.
15. Brevetti G, Martone VD, Perna S, et al. Intermittent claudication and risk of cardiovascular events. *Angiology*. 1998;49:843–848.
16. Rockson SG, Cooke JP. Peripheral arterial insufficiency: mechanisms, natural history, and therapeutic options. *Adv Intern Med*. 1998;43:253–277.
17. Weed RI. The importance of erythrocyte deformability. *Am J Med*. 1970;49:147–150.
18. Braasch D. Red cell deformability and capillary blood flow. *Physiol Rev*. 1971;51:679–701.
19. Kaplan NM. The deadly quartet. Upper body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med*. 1989;149:1514–1520.
20. Sowers JR. Insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and accelerated atherosclerosis. *J Clin Pharmacol*. 1992;32:529–535.
21. Housley E. Treating claudication with five words. *Br Med J (Clin Res Ed)*. 1988;296:1483–1484.
22. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complications,

myocardial infarction, and mortality. *Acta Med Scand*. 1987;221:253–260.
23. Faulkner KW, House AK, Castleden WM. The effect of cessation of smoking on the accumulative survival rates of patients with symptomatic peripheral vascular disease. *Med J Aust*. 1983;1:217–219.
24. Kuunti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.
25. Wiseman S, Kenchington G, Dain R, et al. Influence of smoking and plasma factors on patency of femoropopliteal vein grafts. *BMJ*. 1989;299:643–646.
26. Quick CR, Cotton LT. Measured effect of stopping smoking on intermittent claudication. *Br J Surg*. 1982;69(suppl):S24–S26.
27. Hughson WG, Mann JI, Tibbs DJ, Woods HF, Walton I. Intermittent claudication: factors determining outcome. *Br Med J*. 1978;1:1377–1379.
28. Powell JT. Vascular damage from smoking: disease mechanisms at the arterial wall. *Vasc Med*. 1998;3:21–28.
29. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med*. 2002;347:1941–1951. (29)
30. Gray BH, Sullivan TM. Vascular claudication: how to individualize treatment. *Cleve Clin J Med*. 1997;64:429–436.
31. Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2008;(4):CD000990.
32. McDermott MM, Ades P, Guralnik JM, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA*. 2009;301:165–174.
33. Ernst EE, Matrai A. Intermittent claudication, exercise, and blood rheology. *Circulation*. 1987;76:1110–1114.
34. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;74(10):e177–e232.
35. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73(24):e285–e350.
36. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323:1289–1298.
37. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts [published correction appears in *JAMA*. 1988;259:2698]. *JAMA*. 1987;257:3233–3240.

38. Blankenhorn DH, Azen SP, Kramsch DM, et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med*. 1993;119:969–976.
39. Pedersen TR, Kjekshus J, Pyörälä K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian simvastatin survival study (4S). *Am J Cardiol*. 1998;81:333–335.
40. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
41. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. *Am J Med*. 2003;114:359–364.
42. Aronow WS, Nayak D, Woodworth S, Ahn C. Effect of simvastatin versus placebo on treadmill exercise time until the onset of intermittent claudication in older patients with peripheral arterial disease at six months and at one year after treatment. *Am J Cardiol*. 2003;92:711–712.
43. Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev*. 2007;(4):CD000123.
44. Hiatt W. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001;334:1608–1621.
45. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563–1574.
46. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
47. The HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371:203–212.
48. The ORIGIN Trial Investigators. N-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367:309–318.
49. Radack K, Deck C. β-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Arch Intern Med*. 1991;151:1769–1776.
50. Paravastu SC, Mendonca D, Da Silva A. β blockers for peripheral arterial disease. *Cochrane Database Syst Rev*. 2008;(4):CD0005508.
51. Lane DA, Lip GY. Treatment of hypertension in peripheral arterial disease. *Cochrane Database Syst Rev*. 2009;(4):CD003075.
52. Ahimastos AA, Lawler A, Reid CM, Blombery PA, Kingwell BA. Brief communication: ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. *Ann Intern Med*. 2006;144:660–664.

53. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators [published corrections appear in *N Engl J Med*. 2000;342:1376; *N Engl J Med*. 2000;342:748]. *N Engl J Med*. 2000;342:145–153.
54. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
55. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. 2018;71(6):e13–e115.
56. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens*. 2014;32:3–15.
57. American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45(suppl 1):S144–S174.
58. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.
59. Banglore S, Steg G, Deedwania P, et al. β-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA*. 2012;308:1340–1349.
60. UK Prospective Diabetes Study Group. Effect of intensive blood—glucose control with met form in on complications in overweight patients with type 2 diabetes (UKPDS 34). [published correction appears in *Lancet*. 1998;352:1558]. *Lancet*. 1998;352:854–865.
61. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383–393.
62. American Diabetes Association. Standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45(suppl 1):S1–S259.
63. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45(suppl 1):S125–S143.
64. Patrono C, Coller B, Dalen JE, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. *Chest*. 1998;114(5 suppl):470S–488S.

65. Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e669S–e690S.
66. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349:1641–1649.
67. ISIS-2 (Second International Study of Infant Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;2:349–360.
68. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755–1762.
69. Juul-Moller S, Edvardsson N, Jahnmatz B, Rosén A, Sørensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet*. 1992;340:1421–1425.
70. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published correction appears in *BMJ*. 2002;324:141]. *BMJ*. 2002;324:71–86.
71. Goldhaber SZ, Manson JE, Stampfer MJ, et al. Low-dose aspirin and subsequent peripheral arterial surgery in the Physicians' Health Study. *Lancet*. 1992;340:143–145.
72. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA*. 2009;301:1909–1919.
73. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA*. 2010;303:841–848.
74. The Dutch TIA Trial Study Group; van Gijn J, Algra A, Kappelle J, Koudstaal PJ, van Latum A. A comparison of two doses of aspirin (30 mg versus 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med*. 1991;325:1261–1266.
75. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54:1044–1054.
76. Meade TW, Brennan PJ. Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised controlled trial. *BMJ*. 2000;321:13–17.

77. Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med*. 1998;129:394–405.
78. Arcan JC, Panak E. Ticlopidine in the treatment of peripheral occlusive arterial disease. *Semin Thromb Hemost*. 1989;15:167–170.
79. Balsano F, Coccheri S, Libretti A, et al. Ticlopidine in the treatment of intermittent claudication: a 21 month double-blind trial. *J Lab Clin Med*. 1989;114:84–91.
80. Love BB, Biller J, Gent M. Adverse haematological effects of ticlopidine. Prevention, recognition and management. *Drug Saf*. 1998;19:89–98.
81. Chen DK, Kim JS, Sutton DM. Thrombotic thrombocytopenic purpura associated with ticlopidine use: a report of 3 cases and review of the literature. *Arch Intern Med*. 1999;159:311–314.
82. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
83. Bhatt DL, Fox KA, Hacke W, et al. A global view of atherothrombosis: baseline characteristics in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial [published correction appears in *Am Heart J*. 2006;151:247]. *Am Heart J*. 2005;150:401.
84. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717.
85. Squizzato A, Keller T, Romualdi E, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. *Cochrane Database Syst Rev*. 2011;(1):CD005158.
86. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376:32–40.
87. Beebe HG, Dawson DL, Cutler BS, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. *Arch Intern Med*. 1999;159:2041–2050.
88. Money SR, Herd JA, Isaacsohn JL, et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg*. 1998;27:267–274.
89. Dawson DL, Cutler BS, Meissner MH, Strandness DE Jr. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. *Circulation*. 1998;98:678–686.
90. Robless P, Mikhailidis DP, Stansby GP. Cilostazol for peripheral arterial disease. *Cochrane Database Syst Rev*. 2008;(1):CD003748.
91. Dawson DL, DeMaioribus CA, Hagino RT, et al. The effect of withdrawal of drugs treating intermittent claudication. *Am J Surg*. 1999;178:141–146.

92. Jacoby D, Mohler ER 3rd. Drug treatment of intermittent claudication. *Drugs*. 2004;64:1657–1670.
93. Regensteiner JG, Ware JE Jr, McCarthy WJ, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. *J Am Geriatr Soc*. 2002;50:1939–1946.
94. Mohler ER 3rd, Beebe HG, Salles-Cuhna S, et al. Effects of cilostazol on resting ankle pressures and exercise-induced ischemia in patients with intermittent claudication. *Vasc Med*. 2001;6:151–156.
95. Soga Y, Yokoi H, Kawasaki T, et al. Efficacy of cilostazol after endovascular therapy for femoropopliteal artery disease in patients with intermittent claudication. *J Am Coll Cardiol*. 2009;53:48–53.
96. Iida O, Nanto S, Uematsu M, Morozumi T, Kitakaze M, Nagata S. Cilostazol reduces restenosis after endovascular therapy in patients with femoropopliteal lesions. *J Vasc Surg*. 2008;48:144–149.
97. Cruickshank JM. Phosphodiesterase III inhibitors: long-term risks and short-term benefits. *Cardiovasc Drugs Ther*. 1993;7:655–660.
98. Thompson PD, Zimet R, Forbes WP, Zhang P. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. *Am J Cardiol*. 2002;90:1314–1319.
99. Hiatt WR, Money SR, Brass EP. Long-term safety of cilostazol in patients with peripheral arterial disease: the CASTLE study (Cilostazol: A Study in Long-term Effects). *J Vasc Surg*. 2008;47:330–336.
100. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol*. 1994;30:603–621.
101. Frampton JE, Brogden RN. Pentoxifylline (oxpentifylline). A review of its therapeutic efficacy in the management of peripheral vascular and cerebrovascular disorders. *Drugs Aging*. 1995;7:480–503.
102. Ward A, Clissold SP. Pentoxifylline: a review of its pharmacokinetic and pharmacodynamic properties, and its therapeutic efficacy. *Drugs*. 1987;34:50–97.
103. Jackson MR, Clagett GP. Antithrombotic therapy in peripheral arterial occlusive disease. *Chest*. 1998;114(5 suppl):666S.
104. Cameron HA, Waller PC, Ramsay LE. Drug treatment of intermittent claudication: a critical analysis of the methods and findings of published clinical trials, 1965–1985. *Br J Clin Pharmacol*. 1988;26:569–576.
105. Reiter M, Bucek RA, Stümpflen A, Minar E. Prostanoids for intermittent claudication. *Cochrane Database Syst Rev*. 2004;(1):CD000986.
106. Abramowicz M. L-carnitine. *Med Lett Drugs Ther*. 2004;46:95–96.
107. Bagger JP, Helligsoe P, Randsbaek F, Kimose HH, Jensen BS. Effect of verapamil in intermittent claudication. A randomized, double-blind, placebo

controlled, cross-over study after individual dose-response assessment. *Circulation*. 1997;95:411–414.
108. Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med*. 2012;366:1404–1413.
109. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017;377:1319–1330.
110. Coffman JD. Intermittent claudication—be conservative. *N Engl J Med*. 1991;325:577–578.
111. Pentecost MJ, Criqui MH, Dorros G, et al. Guidelines for peripheral percutaneous transluminal angioplasty of the abdominal aorta and lower extremity vessels. A statement for health professionals from a special writing group of the Councils on Cardiovascular Radiology, Arteriosclerosis, Cardio-Thoracic and Vascular Surgery, Clinical Cardiology, and Epidemiology and Prevention, the American Heart Association. *Circulation*. 1994;89:511–531.
112. Tunis SR, Bass EB, Steinberg EP. The use of angioplasty, bypass surgery and amputation in the management of peripheral vascular disease. *N Engl J Med*. 1991;325:556–562.
113. Working Party on Thrombolysis in the Management of Limb Ischemia. Thrombolysis in the management of lower limb peripheral arterial occlusion —a consensus document. *Am J Cardiol*. 1998;81:207–218.
114. Nilsson L, Albrechtsson U, Jonung T, et al. Surgical treatment versus thrombolysis in acute arterial occlusion: a randomised controlled study. *Eur J Vasc Surg*. 1992;6:189–193.
115. Ouriel K, Shortell CK, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg*. 1994;19:1021–1030.
116. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med.* 2020;382:1994–2004.
117. Raynaud M. *On Local Asphyxia and Symmetrical Gangrene of the Extremities*. In: Barlow T, trans. Selected Monographs, 121. The Sydenham Society; 1888:1.
118. Herrick AL. Pathogenesis of Raynaud's phenomenon. *Rheumatology (Oxford)*. 2005;44:587–596.
119. Goundry B, Bell L, Langtree M, Moorthy A. Diagnosis and management of Raynaud's phenomenon. *BMJ*. 2012;344:e289.
120. Prete M, Fatone MC, Favoino E, Perosa F. Raynaud's phenomenon: from molecular pathogenesis to therapy. *Autoimmun Rev*. 2014;13:655–667.
121. Gasser P, Müller P, Mauli D, Stäubli C. Evaluation of reflex cold provocation by laser Doppler flowmetry in clinically healthy subjects with a history of cold hands. *Angiology*. 1992;43:389–394.
122. Stoyneva Z, Lyapina M, Tzvetkov D, Vodenicharov E. Current pathophysiological views on vibration-induced Raynaud's phenomenon.

Cardiovasc Res. 2003;57:615–624.
123. Belch J. Raynaud's phenomenon. *Cardiovasc Res*. 1997;33:25–30.
124. Wigley FM. Clinical practice. Raynaud's phenomenon. *N Engl J Med*. 2002;347:1001–1008.
125. Ziegler S, Brunner M, Eigenbauer E, Minar E. Long-term outcome of primary Raynaud's phenomenon and its conversion to connective tissue disease: a 12-year retrospective patient analysis. *Scand J Rheumatol*. 2003;32:343–347.
126. Schapira D, Nahir AM, Hadad N. Interferon-induced Raynaud's syndrome. *Semin Arthritis Rheum*. 2002;32:157–162.
127. Franssen C, Wollersheim H, de Haan A, Thien T. The influence of different β-blocking drugs on the peripheral circulation in Raynaud's phenomenon and in hypertension. *J Clin Pharmacol*. 1992;32:652–659.
128. Bakst R, Merola JF, Franks AG Jr, Sanchez M. Raynaud's phenomenon: pathogenesis and management. *J Am Acad Dermatol*. 2008;59:633–653.
129. Suter LG, Murabito JM, Felson DT, Fraenkel L. The incidence and natural history of Raynaud's phenomenon in the community. *Arthritis Rheum*. 2005;52:1259–1263.
130. Suter LG, Murabito JM, Felson DT, Fraenkel L. Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. *Am J Med*. 2007;120:264–271.
131. Palesch YY, Valter I, Carpentier PH, Maricq HR. Association between cigarette and alcohol consumption and Raynaud's phenomenon. *J Clin Epidemiol*. 1999;52:321–328.
132. Freedman RR, Baer RP, Mayes MD. Blockade of vasospastic attacks by α2-adrenergic but not α1-adrenergic antagonists in idiopathic Raynaud's disease. *Circulation*. 1995;92:1448–1451.
133. Coffman JD, Cohen RA. Serotonergic vasoconstriction in human fingers during reflex sympathetic response to cooling. *Am J Physiol*. 1988;254:H889–H893.
134. Landry GJ. Current medical and surgical management of Raynaud's syndrome. *J Vasc Surg*. 2013;57:1710–1716.
135. Huisstede BM, Hoogvliet P, Paulis WD, et al. Effectiveness of interventions for secondary Raynaud's phenomenon: a systematic review. *Arch Phys Med Rehabil*. 2011;92:1166–1180.
136. Stewart M, Morling JR. Oral vasodilators for primary Raynaud's phenomenon. *Cochrane Database Syst Rev*. 2012;(7):CD006687.
137. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)*. 2005;44:145–150.
138. Thompson AE, Shea B, Welch V, Fenlon D, Pope JE. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum*. 2001;44:1841–1847.

139. Finch MB, Copeland S, Passmore AP, Johnston GD. A double-blind cross-over study of nifedipine retard in patients with Raynaud's phenomenon. *Clin Rheumatol*. 1988;7:359–365.
140. Raynaud's Treatment Study Investigators. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon. Results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med*. 2000;160:1101–1108.
141. Leppert J, Jonasson T, Nilsson H, Ringqvist I. The effect of isradipine, a new calcium-channel antagonist, in patients with primary Raynaud's phenomenon: a single-blind dose-response study. *Cardiovasc Drugs Ther*. 1989;3:397–401.
142. La Civita L, Pitaro N, Rossi M, et al. Amlodipine in the treatment of Raynaud's phenomenon. *Br J Rheumatol*. 1993;32:524–525.
143. Schmidt JF, Valentin N, Nielsen SL. The clinical effect of felodipine and nifedipine in Raynaud's phenomenon. *Eur J Clin Pharmacol*. 1989;37:191–192.
144. Kallenberg CG, Wouda AA, Meems L, Wesseling H. Once daily felodipine in patients with primary Raynaud's phenomenon. *Eur J Clin Pharmacol*. 1991;40:313–315.
145. Wollersheim H, Thien T, Fennis J, van Elteren P, van't Laar A. Double-blind, placebo controlled study of prazosin in Raynaud's phenomenon. *Clin Pharmacol Ther*. 1986;40:219–225.
146. Wollersheim H, Thien T. Dose-response study of prazosin in Raynaud's phenomenon: clinical effectiveness versus side effects. *J Clin Pharmacol*. 1988;28:1089–1093.
147. Paterna S, Pinto A, Arrostuto A, et al. Raynaud's phenomenon: effects of terazosin. *Minerva Cardioangiol*. 1997;45:215–221.
148. Marasini B, Massarotti M, Bottasso B, et al. Comparison between iloprost and alprostadil in the treatment of Raynaud's phenomenon. *Scand J Rheumatol*. 2004;33:253–256.
149. Humbert M, Cabane J. Successful treatment of systemic sclerosis digital ulcers and pulmonary arterial hypertension with endothelin receptor antagonist bosentan. *Rheumatology (Oxford)*. 2003;42:191–193.
150. Fries RF, Shariat K, von Wilmowsky H, Böhm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilator therapy. *Circulation*. 2005;112:2980–2985.
151. Caglayan E, Huntgeburth M, Karasch T, et al. Phosphodiesterase type 5 inhibition is a novel therapeutic option in Raynaud disease. *Arch Intern Med*. 2006;166:231–233.
152. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomized trials. *Ann Rheum Dis*. 2013;72:1696–1699.

153. Smith L, Polsky D, Franks AG Jr. Botulinum toxin-A for the treatment of Raynaud's Syndrome. *Arch Dermatol*. 2012;148:426–428.
154. Abou-Raya A, Abou-Raya S, Helmii M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. *J Rheumatol*. 2008;35:1801–1808.
155. Challenor VF. Angiotensin converting enzyme inhibitors in Raynaud's phenomenon. *Drugs*. 1994;48:864–867.
156. Dziadzio M, Denton CP, Smith R, et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel group, controlled trial. *Arthritis Rheum*. 1999;42:2646–2655.
157. Wood HM, Ernst ME. Renin-angiotensin system mediators and Raynaud's phenomenon. *Ann Pharmacother*. 2006;40:1998–2002.
158. Gliddon AE, Doré CJ, Black CM, et al. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. *Arthritis Rheum*. 2007;56:3837–3846.
159. Coleiro B, Marshall SE, Denton CP, et al. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford)*. 2001;40:1038–1043.
160. Rembold CM, Ayers CR. Oral L-arginine can reverse digital necrosis in Raynaud's phenomenon. *Mol Cell Biochem*. 2003;244:139–141.
161. Muir AH, Robb R, McLaren M, Daly F, Belch JJ. The use of ginkgo biloba in Raynaud's disease: a double-blind placebo-controlled trial. *Vasc Med*. 2002;7:265–267.
162. Malenfant D, Catton M, Pope JE. The efficacy of complementary and alternative medicine in the treatment of Raynaud's phenomenon: a literature review and meta-analysis. *Rheumatology (Oxford)*. 2009;48:791–795.

11

Thrombosis

Nancy L. Shapiro and Erika L. Hellenbart

CORE PRINCIPLES		CHAPTER CASES
1	Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is caused by numerous additive risk factors, with diagnosis based on clinical findings and objective criteria.	**Case 11-1 (Questions 1–3)** **Case 11-5 (Question 1)**
2	VTE treatment includes parenteral anticoagulants (low-molecular-weight heparins or fondaparinux) bridging to a therapeutic international normalized ratio (INR) with warfarin, parenteral anticoagulants given before transitioning to dabigatran or edoxaban, or as monotherapy with rivaroxaban or apixaban.	**Case 11-1 (Questions 4–6, 9)** **Case 11-5 (Questions 2, 3)**
3	Unfractionated heparin is monitored with	**Case 11-1 (Questions 7, 8, 10–12)**

	the activated partial thromboplastin time (aPTT) test; dosing adjustments are used to maintain the aPTT in therapeutic range, as well as monitoring for adverse effects, including thrombocytopenia and bleeding.	**Case 11-2 (Question 1)**
4	Outpatient treatment of VTE is preferred over hospitalization for patients with DVT and low-risk PE and home circumstances that are adequate.	**Case 11-3 (Questions 1, 2)**
5	Anticoagulation prophylaxis should be used in hospitalized patients at risk for VTE.	**Case 11-4 (Question 1)**
6	Warfarin therapy is dosed and monitored according to therapeutic response as measured by the INR. Monitoring for adverse effects including hemorrhage is also essential for all anticoagulants.	**Case 11-5 (Questions 4–6)** **Case 11-6 (Questions 5, 6)** **Case 11-7 (Question 1)**
7	Warfarin therapy is influenced by multiple factors, and patients on warfarin require extensive and ongoing education to maintain safe and effective anticoagulation.	**Case 11-6 (Questions 1–4)** **Case 11-8 (Question 1)** **Case 11-13 (Question 1)** **Case 11-14 (Questions 1, 2)**
8	Warfarin and the direct oral anticoagulants (DOACs) are used for stroke prevention in nonvalvular atrial fibrillation. Warfarin is the only long-term oral option for stroke prevention or	**Case 11-9 (Questions 1–3)** **Case 11-10 (Question 1)** **Case 11-11 (Question 1)**

	thrombosis prevention in patients with mechanical heart valve replacement.	
9	Pharmacists can play an important role in the management of anticoagulant therapy for invasive procedures.	**Cases 11-12 (Question 1)**
10	Although the DOACs do not need monitoring to measure their efficacy, monitoring of baseline renal function and complete blood cell counts are necessary to ensure appropriateness of dosing and to minimize risk of anticoagulation-related bleeding complications.	**Case 11-3 (Question 1)** **Case 11-5 (Questions 2, 6)**

INTRODUCTION

Thrombosis is the process involved in the formation of a fibrin blood clot. Platelets and a series of coagulant proteins (clotting factors) contribute to clot formation. An embolus is a small part of a clot that breaks off and is carried by blood flow to another part of the vascular system. Damage is caused when the embolus becomes trapped in a small vessel, causing occlusion and leading to ischemia or infarction of the surrounding tissue. Normal clot formation maintains the integrity of the vasculature in response to injury, but pathologic clotting can occur in many clinical settings. Abnormal thrombotic events include venous thromboembolism (VTE; deep vein thrombosis [DVT] and its primary complication, pulmonary embolism [PE]), as well as stroke and other systemic manifestations of embolization of clots that form within the heart. Anticoagulant drug therapy is aimed at preventing pathologic clot formation in patients at risk and at preventing clot extension and/or embolization in patients who have experienced thrombosis. This chapter emphasizes arterial

and venous thromboembolic disease and the use of the parenteral anticoagulants (unfractionated heparin [UFH], low-molecular-weight heparins [LMWHs], indirect factor Xa inhibitors, and injectable direct thrombin inhibitors) and oral agents (vitamin K antagonists [VKAs], direct oral anticoagulants [DOACs], which include the oral direct thrombin inhibitors, and the oral direct factor Xa inhibitors). Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease; Chapter 13, Acute Coronary Syndrome; and Chapter 61, Acute Ischemic and Hemorrhagic Stroke, provide more in-depth discussions of thrombolytic agents and antiplatelet therapy.

Etiology of Thromboembolism

Three primary factors influence the formation of pathologic clots and are described in a model referred to as the *Virchow triad* (**Fig. 11-1**).[1] Abnormalities of blood flow that cause venous stasis can result in DVT, which can progress to PE if embolization occurs. Intracardiac stasis of blood can also result in clot formation within the heart chambers, and embolization of intracardiac thrombi may lead to stroke or other systemic manifestations. Abnormalities of blood vessel walls, such as those that occur in injury or trauma to the vasculature, are a second source of thrombus formation. The presence of foreign material within the vasculature, including artificial heart valves and central venous catheters, is also thrombogenic and, as with vascular injury, represents the presence of an abnormal surface in contact with blood. Finally, hypercoagulability resulting from alterations in the availability or the integrity of blood clotting components or naturally occurring anticoagulants also represents a significant risk factor for thromboembolic disease.[2]

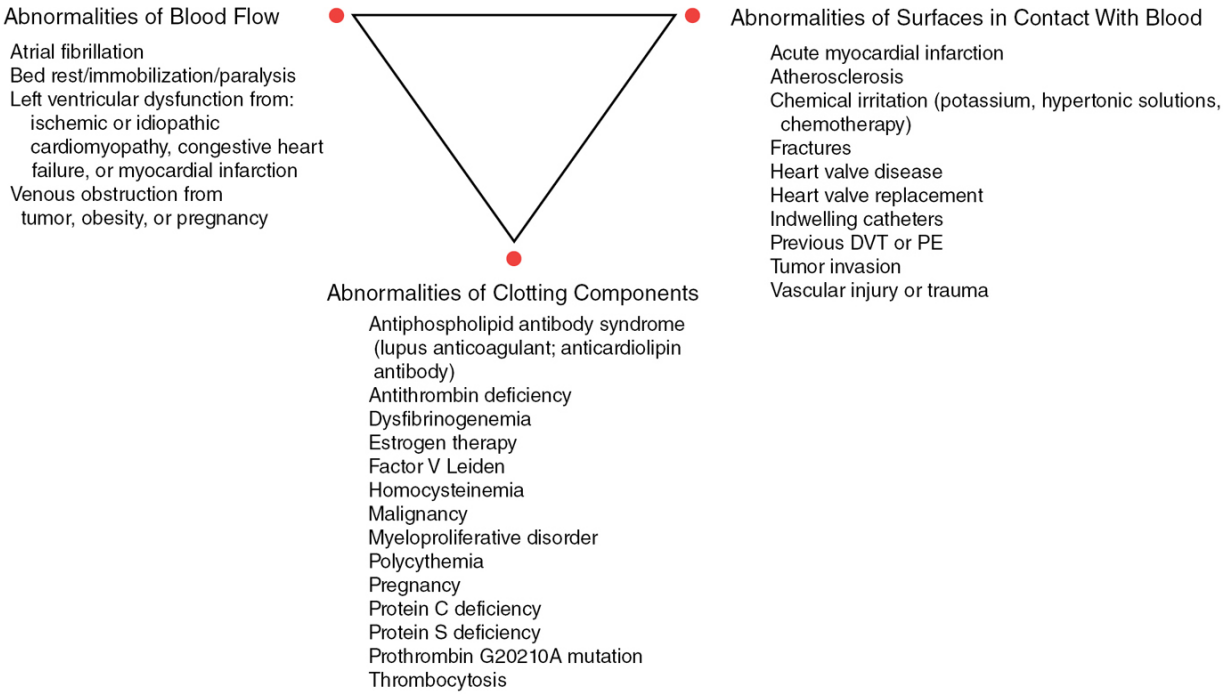


Figure 11-1 Risk factors for thromboembolism. DVT, deep vein thrombosis; PE, pulmonary embolism.

Clot Formation

The intact endothelial lining of blood vessels normally repels platelets and inhibits clot formation through secretion of numerous inhibitory substances. Damage to the endothelium leads to exposure of circulating blood to subendothelial substances, and this results in the formation of a fibrin clot.[2]

PLATELET ADHESION, ACTIVATION, AND AGGREGATION

Endothelial damage leads to exposure of blood to subendothelial collagen and phospholipids, resulting in platelet adhesion to the surface. Von Willebrand factor serves as the binding ligand for platelet adhesion, via the glycoprotein (GP) I receptor on the platelet surface. Adhered platelets become activated and release numerous compounds, including adenosine diphosphate and thromboxane A2, which stimulate platelet aggregation. Fibrinogen serves as the

binding ligand for platelet aggregation, via the GPIIb/IIIa receptor on the platelet surface.[2]

CLOTTING CASCADE

Transformation of the relatively unstable platelet plug (ie, the aggregated platelets) to a stable fibrin clot occurs as a result of an imbalance between other procoagulant and anticoagulant factors. In addition to stimulating the platelet response, endothelial damage results in activation of the extrinsic pathway of the clotting cascade by the release of thromboplastin (tissue factor) (**Fig. 11-2**). Tissue factor converts factor VII to factor VIIa, which mediates the activation of factor X. The intrinsic pathway of the clotting cascade is activated by exposure of factor XII to subendothelial components exposed during vessel injury. The intrinsic pathway mediates factor X activation via a chain of events initiated by factor XI. The distinction between these pathways is primarily an in vitro phenomenon; in vivo, the two pathways are activated simultaneously.

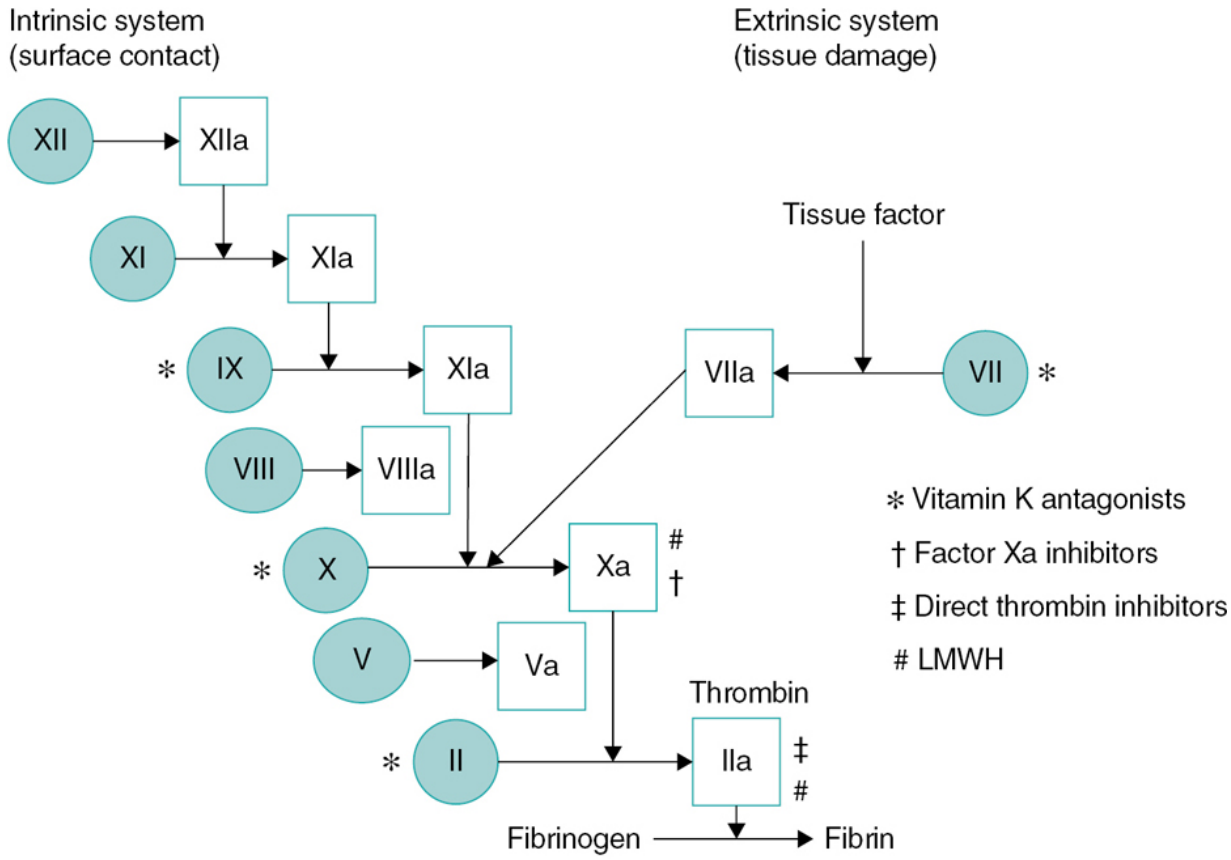


Figure 11-2 Simplified clotting cascade and respective anticoagulant targets. LMWH, low-molecular-weight heparin.

Once stimulated, both the extrinsic and intrinsic pathways activate the common pathway of the clotting cascade via factor X. Activated forms of factors V and VIII serve independently to accelerate this process. The final steps include conversion of factor II (prothrombin) to factor IIa (thrombin), with eventual formation of a stable fibrin clot.

Naturally occurring inhibitors of clotting factors play a role in localizing fibrin formation to the sites of injury and in maintaining the fluidity of circulating blood. **Table 11-1** outlines these clotting inhibitors and their primary actions. In addition, the fibrinolytic system is involved in degradation of fibrin clots. The actions of both clotting inhibitors and the fibrinolytic system prevent excessive coagulation. Thus, the process of clot formation is dynamic and involves various factors that can stimulate, inhibit, and dissolve a fibrin clot.

Table 11-1
Inhibitors of Clotting Mechanisms

Inhibitor	Target
Antithrombin	Inhibits factors IIa, IXa, and Xa
Protein S	Cofactor for activation of protein C
Protein C	Inactivates factors Va and VIIIa
Tissue factor pathway inhibitor	Inhibits activity of factor VIIa
Plasminogen	Converted to plasmin via tissue plasminogen activator
Plasmin	Lyses fibrin into fibrin degradation products

PATHOLOGIC THROMBI

Pathologic thrombi are sometimes classified according to location and composition. Arterial thrombi are composed primarily of platelets, although they also contain fibrin and occasional leukocytes. Arterial thrombi generally occur in areas of rapid blood flow (ie, arteries) and are typically initiated by spontaneous or

mechanical rupture of atherosclerotic plaques followed by aggregation of platelets (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease; and Chapter 13, Acute Coronary Syndrome). Venous thrombi are found primarily in the venous circulation and are composed almost entirely of fibrin and erythrocytes. Venous thrombi have a small platelet head and generally form in response to either venous stasis or vascular injury after surgery or trauma. The areas of stasis prevent dilution of activated coagulation factors by normal blood flow.

The selection of an antithrombotic agent is influenced by the type of thrombus to be treated. The anticoagulant heparin, LMWHs, indirect and direct factor Xa inhibitors, direct thrombin inhibitors, and warfarin are used in the treatment and prevention of both arterial and venous thrombi. Drugs that alter platelet function (eg, aspirin, clopidogrel), alone and/or in combination with anticoagulants, are primarily used in the prevention of arterial thrombi. Fibrinolytic agents are used for rapid dissolution of thromboemboli, most notably during myocardial infarction (MI).

Pharmacology of Antithrombotic Agents

HEPARIN

Heparin is a rapid-acting anticoagulant that is administered parenterally. Standard heparin (UFH) is a heterogeneous mixture of glycosaminoglycans of varying molecular weights obtained from bovine lung or porcine intestinal mucosa (**Table 11-2**). The action of heparin is facilitated by its binding to the naturally circulating anticoagulant antithrombin (AT), a serine protease also referred to as heparin cofactor. Binding of heparin to AT accelerates the anticoagulant effect of AT. The heparin–AT complex attaches to and irreversibly inactivates factor IIa (thrombin) and factor Xa as well as activated factors IX, XI, and XII.[3] Approximately one-third of the molecules present in UFH bind to AT and provide the anticoagulant properties of heparin. The remaining two-thirds of the heparin molecules bind to plasma proteins and to endothelial cells. In

addition to its anticoagulant effects, heparin inhibits platelet function and increases vascular permeability; these properties contribute to the hemorrhagic effects of heparin.

Table 11-2

Comparison of Unfractionated Heparin, Low-Molecular-Weight Heparins, and Fondaparinux

Property	UFH	LMWH	Fondaparinux
Molecular weight range[a]	3000–30,000	1000–10,000	1728
Average molecular weight[a]	12,000–15,000	4000–5000	1728
Anti-Xa: anti-IIa activity	1:1	2:1–4:1	>100:1
aPTT monitoring required	Yes	No	No
Inactivation by platelet factor 4	Yes	No	No
Capable of inactivation of platelet-bound factor Xa	No	Yes	Yes
Inhibition of platelet function	++++	++	No
Increases vascular permeability	Yes	No	No
Protein binding	++++	+	No
Endothelial cell binding	+++	+	No
Dose-dependent clearance	Yes	No	No
Primary route of elimination	Saturable binding processes Renal	Renal	Renal
Elimination half-life	30–150 minutes	2–6 hours	17 hours

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin +, low; ++, moderate; +++, high; ++++, very high.

[a]Measured in Daltons.

Source: Reprinted from Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e24S–e43S. © 2012 The American College of Chest Physicians. With permission.

In cases of acute DVT or PE, the clotting cascade has been activated, generating abnormal quantities of thrombin and fibrin. In these situations, thrombin must be inactivated directly, a process that may require relatively large doses of heparin. However, when the clotting cascade is in a normal balance, it is possible to indirectly inactivate thrombin with smaller heparin doses by complexing factor Xa. Because of the amplification effect of the clotting cascade, inactivation of relatively small amounts of factor Xa indirectly prevents the production of large quantities of thrombin. This

phenomenon is the basis for low-dose heparin prophylaxis after surgery or in cases of prolonged bed rest or immobilization.

Heparin may be administered intravenously (IV) by continuous infusion, or subcutaneously (SC), although its bioavailability is significantly reduced by SC administration. Intramuscular administration of heparin (as well as intramuscular administration of other drugs in patients who are anticoagulated) should be avoided because of the potential for hematoma formation.

After IV administration, the anticoagulant effect of heparin is noted immediately. During active thromboembolism, the high concentration of clotting factors necessitates a higher concentration of heparin to neutralize them. This increased dosing requirement may also be related to continuing thrombin formation on the surface of the thrombus. Once endothelialization (localization and incorporation of the clot into the vascular endothelium) of the clot begins and the concentration of clotting factors decreases, dosing requirements typically decrease. Considerable variability in dosing requirements among patients necessitates routine therapeutic monitoring to maintain an appropriate intensity of anticoagulation with heparin. The primary laboratory test for monitoring therapeutic heparinization is the activated partial thromboplastin time (aPTT; see section on Tests Used to Monitor Antithrombotic Therapy).

The plasma half-life of heparin varies from 30 to 150 minutes, but the half-life increases with increasing doses. Heparin is cleared by extensive binding to plasma proteins and endothelial cells, saturable processes that explain both its nonlinear kinetics and the variability in dosing requirements among patients. Additional clearance occurs by transfer to the reticuloendothelial system, with ultimate elimination controlled by the kidneys.

LOW-MOLECULAR-WEIGHT HEPARINS

Using chemical or enzymatic depolymerization techniques, UFH can be separated into fragments based on molecular weight.[3] Several LMWH molecules have been isolated and commercially marketed as anticoagulants. The LMWH products available in the United States

are dalteparin and enoxaparin, and tinzaparin is available in the non-U.S. market (**Table 11-3**). These products have replaced the use of UFH in many clinical situations. These compounds differ substantially from UFH with respect to molecular weight, antithrombotic and pharmacokinetic properties, adverse effect profiles, and monitoring requirements (see Table 11-2).

Table 11-3
Low-Molecular-Weight Heparin Products

Generic Name	Brand Name	Average Molecular Weight (Range)[a]	Anti-Xa: Anti-IIa Activity
Dalteparin	Fragmin®	5000 (2000–9000)	2.0:1
Enoxaparin	Lovenox®	4500 (3000–8000)	2.7:1
Tinzaparin[b]	Innohep®	4500 (3000–6000)	1.9:1

[a]Measured in Daltons.

[b]Not available in the United States.

To inactivate factor Xa, only the AT component of the heparin–AT complex is required to bind to factor Xa. Both the longer, high-molecular-weight fragments of UFH and the shorter, low-molecular-weight fragments of LMWHs are capable of inactivating factor Xa. However, to inactivate factor IIa (thrombin), both the heparin component and the AT component of the heparin–AT complex are required to bind to factor IIa. This binding requires heparin molecules of at least 18 saccharide units in length, which are less prevalent in LMWHs. Therefore, the anti-Xa properties of LMWHs are more significant than are their anti-IIa properties. The resultant antithrombotic effect does not prolong the aPTT, meaning that these compounds do not require laboratory monitoring in most clinical circumstances to ensure a therapeutic effect.

Additional advantages of LMWHs over UFH are explained by their reduced binding affinity for plasma proteins and endothelial cells. These compounds display improved bioavailability after SC injection, a predictable dose response, and a longer pharmacodynamic effect compared with UFH. In general, these compounds are administered SC every 12 to 24 hours at fixed doses. The LMWH products have been studied in the prevention and treatment of thromboembolic disease. They differ significantly in their molecular weight

distributions, methods of preparation, and the ratio of anti-Xa: anti-IIa activities, as well as in their pharmacokinetic and pharmacodynamic characteristics (see Table 11-2).

FACTOR XA INHIBITORS

Fondaparinux is a selective indirect factor Xa inhibitor that is indicated for the prevention of venous thrombosis associated with orthopedic and abdominal surgeries, and for the treatment of DVT and PE.[3,4] It is a synthetic derivative of the five-residue saccharide sequence found in both UFH and LMWH that binds to AT to inactivate factor Xa with no direct impact on factor IIa. This agent has a long elimination half-life, allowing for once-daily SC administration at a fixed dose without the need for routine coagulation monitoring (see Table 11-2).

Direct factor Xa inhibitors include the oral agents apixaban, edoxaban, rivaroxaban, and betrixaban. The first three are approved by the U.S. Food and Drug Administration (FDA) for stroke prevention in nonvalvular atrial fibrillation, and prevention and treatment of VTE, with other indications described (**Table 11-4**). Betrixaban is indicated for prophylaxis of VTE in adult patients hospitalized for an acute medical illness but is no longer marketed in the United States. These agents have a short onset of action and elimination half-life, are given at fixed doses, and do not require routine monitoring or dose adjustments, which offer significant benefits to warfarin therapy as chronic therapy (**Table 11-5**). Each has varying dependence on renal function for elimination, but all require dose adjustments in patients with renal dysfunction. However, low body weight or advanced age necessitates a dose reduction for apixaban (Table 11-4). All are substrates of P-glycoprotein (P-gp); thus, concomitant use of inducers and inhibitors of P-gp can, respectively, decrease and increase its serum concentration. In addition, rivaroxaban and apixaban are both substrates of cytochrome P450 enzyme 3A4 (CYP3A4) and require dose adjustments when used concomitantly with certain CYP3A4 inhibitors or inducers (**Tables 11-4** and **11-6**).

Table 11-4
Indications and Doses for DOACs

DOAC	Indication	Dose
Dabigatran	Stroke prevention in NVAF	CrCl >30 mL/minute: 150 mg bid CrCl 30–50 mL/minute: decrease to 75 mg bid or avoid if on P-gp inhibitor CrCl 15–30 mL/minute: 75 mg bid or avoid if on P-gp inhibitor CrCl <15 mL/minute or on dialysis: contraindicated
	Treatment of DVT and PE	CrCl >30 mL/minute: LMWH or UFH × 5–10 days, then dabigatran 150 mg bid CrCl <50 mL/minute and on P-gp inhibitor: avoid coadministration CrCl ≤30 mL/minute or on dialysis: dosing recommendations cannot be provided.
	Prevention of recurrent DVT and PE	(CrCL >30 mL/minute): 150 mg bid
	Prevention of VTE after total hip replacement	(CrCl >30 mL/minute): 110 mg × 1 day, then 220 mg daily
Rivaroxaban	Stroke prevention in NVAF	Dosed with evening meal: CrCl >50 mL/minute: 20 mg daily CrCl 15–50 mL/minute: 15 mg daily CrCl <15 mL/minute: avoid
	Treatment of DVT and PE	CrCl ≥30 mL/minute: 15 mg bid × 21 days, then 20 mg daily CrCl <30 mL/minute: avoid
	Prevention of recurrent DVT and PE	10 mg daily
	Prevention of VTE after TKR and THR	10 mg daily for 12 days (TKR) or 35 days (THR)
	Prevention of VTE in hospitalized acutely ill medical patients	10 mg daily in hospital and after hospital discharge for total duration of 31–39 days

DOAC	Indication	Dose
	Prevention of MACE in patients with chronic CAD or PAD	2.5 mg bid in combination with aspirin (75–100 mg) daily
Apixaban	Stroke prevention in NVAF	Most patients: 5 mg bid Any two of the following: 2.5 mg bid: SCr ≥1.5 mg/dL Age ≥80 years Weight ≤132.28 pounds (60 kg)
	Treatment of DVT and PE	10 mg bid × 7 days, then 5 mg bid No dose adjustment is recommended for renal function.[a] Strong dual inhibitors of CYP3A4 and P-gp: reduce dose by 50% or avoid coadministration. Dual P-gp inducers and strong CYP3A4 inducers: Avoid concomitant use.
	Prevention of recurrent DVT and PE	2.5 mg bid
	Prevention of VTE after TKR and THR	2.5 mg bid for 12 days (TKR) or 35 days (THR)
Edoxaban	Stroke prevention in NVAF	CrCl >95 mL/minute: Do not use. CrCl >50–95 mL/minute: 60 mg daily CrCl 15–50 mL/minute: 30 mg daily CrCl <15 mL/minute: Use is not recommended.
	Treatment of DVT and PE	CrCl >50 mL/minute: LMWH or UFH × 5–10 days, then edoxaban 60 mg daily CrCl 15–50 mL/minute: 30 mg daily CrCl <15 mL/minute: Use is not recommended. Patients ≤60 kg or on P-gp inhibitors: 30 mg daily
Betrixaban	Prevention of DVT and PE in adults hospitalized for acute medical illness	CrCl >30 mL/minute: 160 mg × 1 dose, then 80 mg daily for 35–42 days CrCl 15–30 mL/minute: 80 mg × 1 dose, then 40 mg daily × 35–42 days

bid, twice daily; CAD, coronary artery disease; CrCl, creatinine clearance; CYP, cytochrome P450; DVT, deep vein thrombosis; MACE, major cardiovascular events; NVAF, nonvalvular atrial fibrillation; PAD, peripheral artery disease; PE, pulmonary embolism; P-gp, P-glycoprotein; SCr, serum creatinine; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

[a]Patients with creatinine clearance (CrCl) <25 mL/minute excluded from clinical trials for apixaban.

Sources: Pradaxa (dabigatran). Package insert. Boehringer Ingelheim Pharmaceuticals, Inc.; 2020; Xarelto (rivaroxaban). Package insert. Janssen Pharmaceuticals, Inc; 2020; Eliquis (apixaban). Package insert. Bristol-Myers Squibb Company; 2020; Savaysa (edoxaban). Package insert. Daiichi Sankyo; 2020; Bevyxxa (betrixaban). Package insert. Portola Pharmaceuticals, Inc.; 2019.

Table 11-5
Comparative Pharmacokinetic and Pharmacodynamics Properties of the DOACs

Agent	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Mechanism	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Bioavailability (%)	6	60–80	66	62	34
T_{max} (hours)	2–3	2–4	1–3	1–2	3–4
Renal excretion of unchanged drug (%)	80	33	25	50	11
Half-life (hours)	14–17	5–9 11–13 (elderly)	8–15	10–15	19–27
Dialyzable	Yes	No	No	No	Unknown
CYP enzyme substrate	No	CYP 3A4 CYP 2J2	CYP 3A4	Minimal	Minimal
P-gp substrate	Yes	Yes	Yes	Yes	Yes
Hepatic impairment	Recommendations not available	Avoid in moderate or severe impairment or with any hepatic disease associated with coagulopathy.	Not recommended in severe impairment	Not recommended in moderate or severe impairment	Not recommended

CYP, cytochrome P450; DOACs, direct oral anticoagulants; P-gp, P-glycoprotein.

Table 11-6
Examples of Major DOAC Drug–Drug Interactions

DOAC	Drug Interaction	Recommendations
Dabigatran	P-gp inhibitors	Reduce dose or avoid depending on renal function.
	P-gp inducers	Avoid use.

Apixaban	Strong CYP3A4 inhibitor + P-gp inhibitor	Reduce dose or avoid use.
	Moderate CYP3A4 inhibitor + P-gp inhibitor	No dose adjustment required; use with caution. Avoid use in severe renal insufficiency.
	Strong CYP3A4 inducer + P-gp inducer	Avoid use.
Rivaroxaban	Strong CYP3A4 inhibitor + P-gp inhibitor	Avoid use.
	Moderate CYP3A4 inhibitor + P-gp inhibitor	No dose adjustment required; avoid use in severe renal insufficiency.
	Strong CYP3A4 inducer or P-gp inducer	Avoid use.
Edoxaban	P-gp inhibitors	AF: Do not reduce dose. VTE treatment: reduce dose.
	P-gp inducers	Avoid use with rifampin.

Refer to current product package inserts for further information as well as the U.S. Food and Drug Administration (FDA) website at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Example drug interactions:

Strong CYP3A4 inhibitor + P-gp inhibitor: itraconazole, ketoconazole, ritonavir

Moderate CYP3A4 inhibitor + P-gp inhibitor: clarithromycin, diltiazem

Strong CYP3A4 inducer + P-gp inducer: carbamazepine, phenytoin, rifampin, St. John wort

Strong CYP3A4 inducers: carbamazepine, phenytoin, rifampin, St. John's wort

P-gp inhibitors: amiodarone, clarithromycin, cyclosporine, dronedarone, erythromycin, ketoconazole, nifedipine, ticagrelor, tacrolimus, verapamil

P-gp inducers: carbamazepine, phenytoin, rifampin, St. John's wort

AF, atrial fibrillation; CYP, cytochrome P450; DOAC, direct oral anticoagulant; P-gp, P-glycoprotein; VTE, venous thromboembolism.

DIRECT THROMBIN INHIBITORS

Argatroban and bivalirudin are injectable direct thrombin inhibitors that are used as alternative anticoagulants in patients with heparin-

induced thrombocytopenia (HIT; **Table 11-7**).[5] Direct thrombin inhibitors bind to specific sites on the thrombin molecule to inhibit its activity, without acting through a cofactor such as AT. These agents are administered by continuous infusion and require aPTT monitoring for appropriate dosing adjustments. Bivalirudin is also used in patients with acute coronary syndrome, including those undergoing percutaneous coronary intervention (see Chapter 13, Acute Coronary Syndrome).

Table 11-7
Pharmacologic and Clinical Properties of Injectable Direct Thrombin Inhibitors

	Bivalirudin	**Argatroban**
Route of administration	IV	IV
FDA-approved indication	Patients with UA undergoing PTCA; PCI with provisional use of GPI; patients with or at risk for HIT/HITTS undergoing PCI	Treatment of thrombosis in patients with HIT; patients at risk for HIT undergoing PCI
Binding to thrombin	Partially reversible at catalytic site and exosite-1	Reversible at catalytic site
Half-life in healthy subjects	25 minutes	40–50 minutes
Monitoring	aPTT/ACT SCr/CrCl	aPTT/ACT Liver function
Clearance	Enzymatic (80%) Renal (20%)	Hepatic
Antibody development	May cross-react with antihirudin antibodies	No
Effect on INR	Slight increase	Increase
Initial dose for HIT	No bolus Infusion: 0.15 mg/kg/hour	No bolus Infusion: 2 µg/kg/minute[a] In critically ill patients: Consider lower infusion rate of 0.2–1 µg/kg/minute

Initial dose for PCI	Bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/hour	Bolus: 350 μg/kg Infusion: 25 μg/kg/minute

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; GPI, glycoprotein IIb-IIIa inhibitor; HIT, heparin-induced thrombocytopenia; HITTS, heparin-induced thrombocytopenia and thrombosis syndrome; IV, intravenous; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SCr, serum creatinine; UA, unstable angina.

[a]In some cases, an initial infusion rate of <1.5 μg/kg/minute may be more appropriate.

Dabigatran is an oral direct thrombin inhibitor, approved for stroke prevention in patients with nonvalvular atrial fibrillation, the treatment of VTE, and the extended treatment of VTE.[6] Similar to the direct factor Xa inhibitors, dabigatran is given at a fixed dose without the need for routine coagulation monitoring or dosing adjustments.[6] It has a short onset of action and elimination half-life in patients with normal renal function, which reduces the need for bridging therapy with LMWH as is necessary during warfarin initiation or interruption (see Table 11-4). Owing to its low bioavailability, dabigatran is administered as a prodrug, dabigatran etexilate, in a capsule form that contains small micropellets that coat dabigatran with tartaric acid, creating an acidic microenvironment. It is then rapidly converted to the active compound by hydrolysis and then eliminated renally. When it is not supplied or stored in the original packaging, capsule exposure to humidity leads to degradation of dabigatran etexilate via hydrolysis. The shelf life of dabigatran is 4 months if stored and sealed in the original bottle and desiccant-containing cap. Blister packs are available for unit-dose administration. Elimination of dabigatran is highly dependent on renal function, so dosing adjustments are required in these patients (see Table 11-5). Dabigatran is a substrate of P-gp; thus, concomitant use of inducers and inhibitors of P-gp can, respectively, decrease and increase its serum concentrations. However, because dabigatran is not metabolized by cytochrome P450 (CYP) enzymes, it is not susceptible to CYP-mediated drug interactions (see Table 11-6). Collectively, the oral direct thrombin inhibitors and the oral direct

factor Xa inhibitors are referred to as *direct oral anticoagulants (DOACs)*. The DOACs are the preferred anticoagulant agents for most patient care scenarios and provide opportunities for pharmacist involvement in drug selection, patient education, and long-term therapeutic management.

WARFARIN

Warfarin is an oral anticoagulant with a delayed onset of effect that acts as a VKA. Vitamin K is essential for the conversion (carboxylation) of precursors to clotting factors II, VII, IX, and X into inactive clotting factors and for the synthesis of the naturally occurring anticoagulants, protein C and protein S. During factor conversion, vitamin K is oxidized to inactive vitamin K epoxide (**Fig. 11-3**). In the nonanticoagulated patient, vitamin K epoxide is in reversible equilibrium with vitamin K, but this equilibrium is disrupted in patients taking oral VKAs. Warfarin interferes with the hepatic recycling of vitamin K by inhibiting vitamin K epoxide reductase (VKOR), the enzyme that converts vitamin K epoxide to vitamin K.[6] The accumulation of vitamin K epoxide reduces the effective concentration of vitamin K and reduces the synthesis of coagulation factors. Concentrations of clotting factors II, VII, IX, and X are diminished gradually at rates commensurate with their elimination half-lives (**Table 11-8**). Thus, the onset of the anticoagulant effect of warfarin is delayed. It takes ~5 to 7 days to reach a steady state of anticoagulation after warfarin therapy is initiated or after dosing changes. Protein C and its cofactor protein S are also vitamin K dependent, and these proteins are depleted by warfarin at rates dependent on their elimination half-lives.

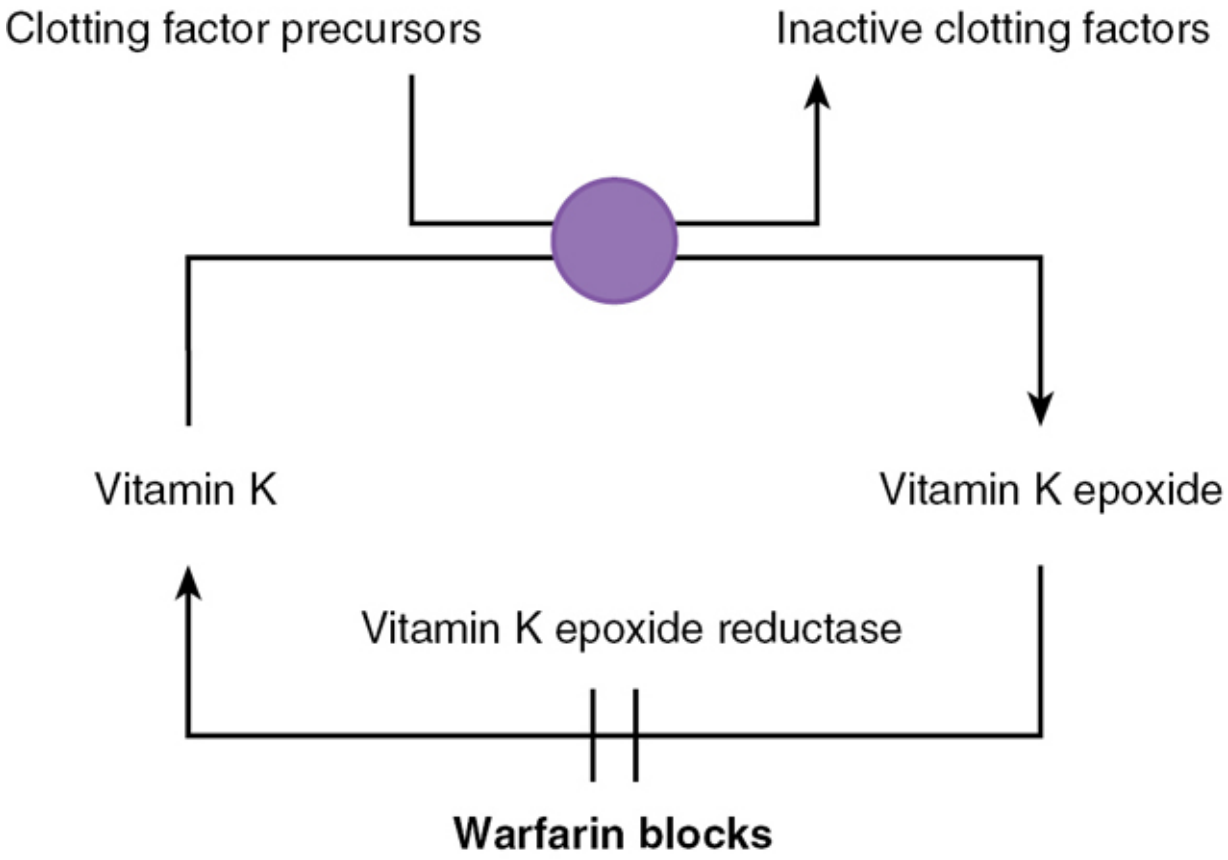


Figure 11-3 Mechanism of action of warfarin.

Table 11-8
Elimination Half-Lives of Vitamin K–Dependent Clotting Factors

Clotting Factor	Half-Life (hours)
II	42–72
VII	4–6
IX	21–30
X	27–48
Protein C	9
Protein S	60

Warfarin is rapidly and completely absorbed in the upper gastrointestinal (GI) tract by passive diffusion, with nearly 100% bioavailability. Peak absorption of warfarin occurs in 60 to 120 minutes. It is ~99% bound to serum albumin. The volume of

distribution for warfarin is 12.5% of body weight. This small volume of distribution is consistent with the extensive binding of warfarin to albumin. The primary laboratory test for monitoring warfarin therapy is the prothrombin time (PT). No correlation appears to exist between PT and the dose of warfarin, the total warfarin concentration, or the free warfarin concentration for any population of treated patients, although in individual patients, an increasing dose of warfarin will increase the serum concentration (free and total) and the PT.

Warfarin is administered orally as a racemic mixture containing equal parts of the enantiomers R(+)-warfarin and S(−)-warfarin. The S(−)-isomer is 2.7 to 3.8 times more potent as an anticoagulant than the R(+)-isomer, has a longer elimination half-life, and is primarily metabolized by CYP2C9. Comparatively, R(+)-warfarin is metabolized primarily by CYP1A2 and CYP3A4. Many drugs interact with warfarin by stereoselectively inhibiting the metabolism of the R(+)-isomer or the S(−)-isomer (see section on Drug Interactions).

Genetic expression of CYP2C9 influences the rate of metabolism of warfarin and thus impacts dosing requirements to meet a particular therapeutic end point.[7] Variability in genetic expression of VKORC1 (the complex 1 subunit on the gene that codes for vitamin K epoxide reductase) also influences dosing requirements in patients taking warfarin. Genetic testing for CYP2C9 genotype and VKORC1 haplotype can be incorporated with clinical and demographic information to predict warfarin dose requirements in individual patients, using dosing algorithms that have been developed and investigated. A practical example is available online at www.warfarindosing.org. Routine pharmacogenomic testing of warfarin is not currently endorsed at this time.

Tests Used to Monitor Antithrombotic Therapy

Before the initiation of any antithrombotic therapy, an assessment of baseline hemostatic status is necessary. The clinician should obtain a baseline platelet count and hemoglobin (Hgb) and/or hematocrit

(Hct), as well as evaluate the baseline integrity of the extrinsic and intrinsic coagulation pathways with PT and aPTT, the tests used to monitor warfarin and heparin, respectively. The DOACs do not require routine monitoring of laboratory tests to monitor their efficacy; however, baseline creatinine clearance (CrCl) and liver function tests (LFTs) are also needed with these agents.

PROTHROMBIN TIME/INTERNATIONAL NORMALIZED RATIO

The PT is prolonged by deficiencies of clotting factors II, V, VII, and X, as well as by low levels of fibrinogen and very high levels of heparin. It reflects alterations in the extrinsic and common pathways of the clotting cascade, but not in the intrinsic system.[8] The PT is measured by adding calcium and tissue thromboplastin to a sample of plasma from which platelets have been removed by centrifugation. The time to clot formation is detected by automated instruments using light scattering techniques that measure optical density. The mean normal PT, obtained by averaging a number of PT results from nonanticoagulated subjects, is ~12 seconds for most reagents.

The thromboplastins used in PT monitoring are extracted from various tissue sources by a number of techniques and prepared for commercial use as reagents. Unfortunately, thromboplastins are not standardized among manufacturers or among batches of reagent produced by the same manufacturer, leading to significant variability in PT results for anticoagulated patients. To standardize PT results, the World Health Organization developed a system by which all commercially available thromboplastins are compared with an international reference thromboplastin and then assigned an international sensitivity index (ISI). This value is used to mathematically convert PT to the international normalized ratio (INR) by exponentially multiplying the PT ratio to the power of the ISI of the thromboplastin being used in the laboratory to measure the test:

$$\mathrm{INR} = (\mathrm{PT\ patient} / \mathrm{PT\ mean\ normal})^{\mathrm{ISI}} \qquad \textbf{(Eq. 11-1)}$$

The ISI of the international reference thromboplastin is 1.0.

The INR is the internationally recognized standard for monitoring warfarin therapy.[6] Current recommendations for intensity of oral anticoagulation therapy for accepted clinical indications are summarized in **Table 11-9**. Regular intensity therapy is defined as dosing warfarin to reach a goal INR of 2.5 (range, 2.0–3.0) and is appropriate for most settings that require the prevention and/or treatment of thromboembolic disease. High-intensity therapy is used in mechanical valve replacement and certain situations of thromboembolic recurrence, despite adequate anticoagulation, and is defined as dosing warfarin to reach a goal INR of 3.0 (range, 2.5–3.5).

Table 11-9
Optimal Therapeutic Range and Duration of Anticoagulation

Indication	INR Goal	Minimum Duration
Prophylaxis of VTE (DVT, PE)	2–3	~1–4 weeks depending on patient status and risk factors
Treatment of first VTE with transient risk factors	2–3	3–6 months
First episode of unprovoked VTE	2–3	3–6 months Consider extended treatment if first episode of VTE is PE or proximal DVT with no bleeding risk factors.
Second episode of unprovoked VTE	2–3	Indefinitely
VTE and cancer	2–3	Indefinitely or until cancer resolved[a]
VTE prophylaxis after hip or knee arthroplasty, hip fracture surgery	2–3	Up to 35 days after surgery
AF (persistent or paroxysmal)/atrial flutter	2–3	Long term
Following placement of left atrial appendage occlusion device	2–3	45 days from procedure or until adequate seal of left atrial appendage is confirmed

Any mechanical valve in mitral position	2.5–3.5	Long term
Bileaflet mechanical valve or tilting disk valve in aortic position in sinus rhythm	2–3	Long term
Caged ball valve in aortic position	2.5–3.5	Long term
Mechanical On-X® valve in aortic position	2–3 1.5–2	3 months After initial 3 months of therapy
Mechanical aortic heart valves with additional risk factors (AF, previous VTE, LV dysfunction, hypercoagulable conditions)[b]	2.5–3.5	Long term
Bioprosthetic valve in aortic or mitral position[c]	2–3	3 to 6 months
Bioprosthetic valves with additional risk factors (AF, previous VTE, LV dysfunction, hypercoagulable conditions)[d]	2–3	Long term

AF, atrial fibrillation; DVT, deep vein thrombosis; INR, international normalized ratio; LV, left ventricle; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]Low-molecular-weight heparin preferred for patients with venous thromboembolism (VTE) and cancer.

[b]Higher goal international normalized ratio (INR) recommended by the American Heart Association/American College of Cardiology (AHA/ACC). INR 2 to 3 recommended by the American College of Chest Physicians (ACCP).

[c]Long-term aspirin (75–100 mg) also recommended. Can be used alone in the absence of other indications for oral anticoagulation.

[d]Direct oral anticoagulant (DOAC) use may be considered after third postoperative month in patients with atrial fibrillation.

Sources: Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693–4738; January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guidelines for the management of patients with atrial fibrillation. *Circulation.* 2019;140:e125–e151; Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2021;77(4):e25–e197. doi: 10.1016/j.jacc.2020.11.018.

ACTIVATED PARTIAL THROMBOPLASTIN TIME

The aPTT reflects alterations in the intrinsic pathway of the clotting cascade and is used to monitor heparin and injectable direct thrombin inhibitors.[8,9] The test is performed by adding a surface-activating agent (kaolin or micronized silica), a partial thromboplastin reagent (phospholipid; platelet substitute), and calcium to the plasma sample. Mean normal values vary among reagents but typically fall between 24 and 36 seconds.

Similar to PT, the aPTT is a highly variable test based on differences among commercially available partial thromboplastin reagents. However, a system equivalent to the INR has not been developed for standardization of aPTT results. Heparinization to prolong the aPTT to 1.5 to 2.5 times the mean normal value historically was considered adequate to prevent propagation or extension of thrombus, but is no longer recommended because it is not appropriate for all reagents and testing systems. Instead, the aPTT should be calibrated for each reagent lot and coagulometer, and a reagent-specific therapeutic range in seconds that corresponds to therapeutic heparin levels of 0.3 to 0.7 IU/mL by factor Xa inhibition (anti-Xa activity) should be determined.[3,9,10] For direct thrombin inhibitors, the same aPTT goal range is used.

Hospital-based and independent clinical laboratories that offer aPTT monitoring will report the reagent-specific therapeutic range in seconds and adjust it as new reagents are purchased and used clinically.

ANTI-FACTOR XA ACTIVITY

Owing to the limitations of aPTT monitoring, researchers developed direct heparin concentration monitoring using heparin anti-Xa levels. Compared to the aPTT, the anti-Xa method is less impacted by biologic variables, although preanalytic and analytic variability remains.[11] The anti-Xa test costs more than the aPTT, but has some potential advantages, including fewer monitoring tests, fewer dose changes, and a shorter time to obtain therapeutic anticoagulation.[12] National guidelines for heparin monitoring recognize that there are

limitations to both approaches and do not recommend a preferred method.[10,13]

Although LMWHs do not require coagulation monitoring to ensure an appropriate antithrombotic effect or to adjust dosing, certain clinical situations may warrant assessment of the anti-factor Xa activity of LMWHs.[3] Because these agents are eliminated renally, patients with severe renal dysfunction may accumulate LMWHs, leading to an increased risk of hemorrhagic complications. Evaluation of trough anti-factor Xa activity at the end of the dosing interval can assess this accumulation effect and may be considered for patients with severe renal dysfunction.[10] LMWHs are dosed according to total body weight, but clinical trials have included only limited numbers of obese patients. Routine monitoring of anti-factor Xa activity in patients is not suggested for obese and nonobese patients.[10] Anti-factor Xa activity may also be evaluated in patients who experience unexpected bleeding complications secondary to anticoagulation with LMWHs, and in pregnant patients in whom LMWHs are used for treatment or prevention of thrombosis.

Anti-factor Xa activity is measured using a chromogenic assay. If peak activity levels are used to assess dosing in obese and pregnant patients, they should be obtained once the patient has reached steady state, typically after three or four doses of LMWH. The anti-factor Xa level should be drawn ~4 hours after an SC dose of LMWH, with empiric dosing adjustments to maintain a level of roughly 0.5 to 1.0 IU/mL for therapeutic anticoagulation given every 12 hours, and slightly higher peaks up to 1.5 for therapeutic doses given every 24 hours.[3,9] However, there is little correlation between peak anti-factor Xa activity and therapeutic effect, and thus monitoring is not routinely recommended.[10] Trough anti-factor Xa levels are expected to be <0.4 IU/mL at the end of the dosing interval. As with other measures of hemostasis, results vary considerably, requiring both instrument-specific and method-specific determination of therapeutic ranges.

DEEP VEIN THROMBOSIS

Clinical Presentation

SIGNS AND SYMPTOMS

CASE 11-1

Question 1: J.T., a 60-year-old, overweight (202.83 pounds [92 kg], 72-inch [182.88 cm] tall) male, was admitted to the hospital 3 days ago for management of acute cellulitis of his left ankle that occurred after cutting himself with a lawn tool a week ago. He was started on IV antibiotics and had limited mobility in the hospital owing to the pain at the wound site and is being evaluated by orthopedics for possible osteomyelitis and surgical intervention. On the third day of hospitalization, while the wound was improving, he noted progressive swelling and soreness of the left calf and around his left knee. He denied shortness of breath (SOB), cough, or chest pain. His medical history includes coronary artery disease, diabetes, and hypercholesterolemia. His medications are lisinopril 10 mg/day orally (PO), isosorbide mononitrate 120 mg/day PO, atenolol 50 mg/day PO, aspirin 81 mg/day PO, metformin 1000 mg PO twice daily, and atorvastatin 80 mg PO every evening. Initial laboratory values include:

Hct, 36.5%
PT, 10.8 seconds (INR, 1.0)
aPTT, 23.6 seconds
Platelet count, 255,000/μL

What signs and symptoms demonstrated by J.T. are consistent with DVT?

Patients with DVT typically present with unilateral leg swelling that often is accompanied by warmth and local tenderness or pain.[10] A tender, cordlike entity caused by venous obstruction can sometimes be palpated in the affected area. J.T. presented with the sudden onset of swelling along with soreness, but without evidence of a cord. Discoloration of the affected limb, including pallor from arterial spasm, cyanosis from venous obstruction, or a reddish color from perivascular inflammation, may also occur. The presence or absence of a positive Homan sign (pain behind the knee or calf on dorsiflexion of the foot) is rarely helpful in making the diagnosis because it is present in only about 30% of patients with DVT. Many

patients (>50%) can present with asymptomatic disease, but even asymptomatic patients can have long-term complications such as recurrent DVT or postthrombotic syndrome. Because symptoms of DVT are nonspecific, the diagnosis must be confirmed by objective testing.[14,15]

RISK FACTORS

Case 11-1, Question 2: What risk factors associated with DVT does J.T. exhibit?

The diagnosis of DVT depends not only on the presenting signs and symptoms but also on the presence of risk factors (see Fig. 11-1). J.T. has presented with obesity and immobilization (ie, prolonged bed rest), two important risk factors for thromboembolism, as well as an acute medical illness. It is common for more than one risk factor to be present in patients who exhibit DVT, and these factors are cumulative in their effect.[16]

DIAGNOSIS

Case 11-1, Question 3: How should the final diagnosis of DVT be made in J.T.?

After evaluation of the signs and symptoms of DVT and consideration of risk factors for the development of thrombus, a definitive diagnosis should be made. Diagnostic strategies should include an assessment of pretest clinical probability (clinical suspicion), D-dimer assay (an evaluation of the presence of fibrin degradation products, indicative of clot formation; see Chapter 2, Interpretation of Clinical Laboratory Tests), and noninvasive imaging tests.[14,15]

Despite its limitations as a single diagnostic tool, clinical assessment can improve the diagnostic accuracy of noninvasive testing. A clinical prediction rule, such as the Wells criteria, takes into

account signs, symptoms, and risk factors to categorize patients as being at low, intermediate, or high probability of having DVT (https://www.mdcalc.com/wells-criteria-dvt).[17] The D-dimer test can be used in conjunction with clinical evaluation or a clinical prediction rule to help "rule out" DVT in patients with a low clinical suspicion and thus decrease the need for imaging tests in these patients.[15] If the clinical suspicion of DVT is high, diagnostic imaging is indicated, and if the imaging is negative, the D-dimer is helpful to rule out the diagnosis.[14]

The most common noninvasive test is duplex scanning, which combines B-mode imaging or color flow imaging with Doppler ultrasonography to visualize veins and thrombi while investigating flow patterns. Other noninvasive testing options include iodine 125 (^{125}I)-fibrinogen leg scanning (injection of radiolabeled fibrinogen followed by scanning to detect areas of accumulation corresponding to thrombosis), impedance plethysmography (use of pneumatic cuffs to detect leg blood volume changes associated with thrombosis), and Doppler ultrasonography alone (use of a transducer to audibly detect venous flow changes indicative of thrombosis). Each option differs with respect to sensitivity, specificity, and cost. Venography (radiographic visualization of the involved vessels with injection of radiocontrast material), an invasive diagnostic test, was previously considered the most sensitive and specific method for diagnosis of DVT but is no longer routinely recommended because it exposes patients to the risks associated with contrast material, and is not readily available in many hospitals.[15]

Treatment

BASELINE INFORMATION

Case 11-1, Question 4: What additional baseline data should be obtained before administering anticoagulants to J.T.?

In addition to assessing the integrity of the clotting process with platelet count, Hgb/Hct, PT, and aPTT, the patient's baseline renal function should be evaluated and documented because some anticoagulants are renally eliminated. Baseline values are used for comparison with the parameters that will be used in monitoring both therapeutic and adverse effects of anticoagulant therapy.

INITIATION OF THERAPY

Case 11-1, Question 5: Duplex scanning reveals clot formation in J.T.'s left calf extending to the left thigh. He does not exhibit signs of PE. What is the appropriate therapy for J.T., and how should it be initiated?

Prompt and optimal anticoagulant therapy is indicated to minimize thrombus extension and its vascular complications, as well as to prevent PE. Acute anticoagulation treatment options include injectable IV UFH initiated with a loading dose followed by a continuous infusion, adjusted-dose SC UFH, SC LMWH, or SC fondaparinux.[18] Alternatively, initial treatment with oral rivaroxaban or apixaban can be selected, without any initial parenteral anticoagulation. LMWH or UFH may be continued as monotherapy or transitioned to treatment with a VKA, dabigatran, or edoxaban. Because J.T. is currently hospitalized and may need further surgical procedures, IV UFH is selected for initial treatment of his DVT.

HEPARIN

Loading dose

Case 11-1, Question 6: J.T.'s medical resident ordered a heparin bolus dose of 5000 IU IV, to be followed by a continuous infusion of 1000 units/hour. Is this heparin dosing regimen appropriate?

A loading dose of heparin is required for several reasons. Based on pharmacokinetic principles, a therapeutic serum level will be achieved more quickly; thus, pharmacodynamic and therapeutic

responses to help prevent progression of the clot will occur rapidly. Second, a relative resistance to anticoagulation exists during the active clotting process. Therefore, a larger initial dose generally is necessary to achieve a therapeutic effect.

Although standardized doses of heparin for initiation of therapy (ie, 5000 units loading dose; 1000 units/hour maintenance dose) were used historically, this approach can result in significant delays in reaching a therapeutic intensity of anticoagulation. Body weight represents the most reliable predictor of heparin dosing requirement. For patients who do not have extremes of body weight (ie, <363.763 pounds [165 kg]), the use of the actual body weight (ABW) has been recommended to calculate the initial UFH dose.[10] For patients >363.76 pounds (165 kg), the use of the ABW is controversial, and the use of an adjusted-dosing weight is recommended by some experts.[10] Options include two different "dosing weight" calculations:

$$\text{Ideal Body Weight (IBW)} + 0.3 \times (\text{ABW} - \text{IBW}) \quad \textbf{(Eq. 11-2)}$$

or

$$\text{IBW} + 0.4 \times (\text{ABW} - \text{IBW}) \quad \textbf{(Eq. 11-3)}$$

Compared with standardized dosing, weight-based dosing (80 units/kg loading dose; 18 units/kg/hour initial infusion rate) increases the frequency of therapeutic aPTT at 6 and 24 hours, and decreases the risk of recurrent VTE.[19–21]

Initial heparin loading doses of 60 to 100 units/kg followed by an infusion rate of 13 to 25 units/kg/hour are commonly recommended.[22] Selection of the lower or upper dosage range is guided by the severity of the patient's symptoms and his or her potential sensitivity to adverse effects. For this 202.83-pound (92-kg) patient, a midrange loading dose of 7400 units (202.83 pounds [92 kg] × 80 units/kg), followed by a continuous infusion of 1700 units/hour (202.83 pound [92 kg] × 18 units/kg/hour), is recommended. Loading doses are typically rounded to the nearest

500 units and maintenance infusion rates to the nearest 100 units for convenience of administration.

Dose adjustments

Case 11-1, Question 7: The orders for J.T. were rewritten by his attending physician. Based on data shown subsequently, what are potential explanations for the variability in laboratory results? (At this institution, aPTT values of 60–100 seconds correspond with heparin plasma concentrations of 0.3–0.7 units/mL determined by anti-factor Xa assay.)

Time	aPTT (seconds)	Heparin Dosage Order
0800	31	(baseline) 7400 units bolus followed by 1700 units/hour infusion
0900	130	Hold infusion for 30 minutes, then to 1500 units/hour
1500	40	Rebolus with 2400 units, then to 1700 units/hour
2100	85	Continue at 1700 units/hour; recheck aPTT every morning

Although the aPTT drawn 1 hour after the initiation of the maintenance infusion (9:00 AM) demonstrates excessive prolongation of the aPTT (130 seconds), this value is most likely explained by inappropriate timing of the test. When aPTT values are drawn too soon after a heparin bolus dose (ie, before the maintenance infusion has achieved a steady-state concentration in serum), they are predictably very high, but are not associated with a bleeding risk and do not accurately reflect the anticipated level of anticoagulation in the patient. To ensure accuracy, the clinician should obtain aPTT values no sooner than 6 hours after a bolus dose or any change in the infusion rate. Even results obtained at 6 hours may be excessively prolonged in some patients because of the dose-dependent pharmacokinetic characteristics of heparin.

J.T.'s heparin dose was decreased at 9:00 AM based on this prolonged, yet inappropriately timed, value. A repeat aPTT at 3:00

PM was only 40 seconds. The decrease in the dosage to 1500 units/hour and the repeat aPTT of 40 seconds reflect near-steady-state conditions because 6 hours have elapsed since the dosage change. Because the aPTT was subtherapeutic at 3:00 PM (40 seconds), administration of a smaller repeat bolus dose (2000 units) and an increase in the maintenance infusion to 1700 units/hour was the correct course of action. Subsequent aPTT values reflected therapeutic anticoagulation.

Dosing nomograms or protocols have been recommended for adjustment of heparin dosing based on aPTT results.[3,10] Nomogram-based dosing reduces the time to reach therapeutic range compared with empiric dosing.[23] Attaining a therapeutic aPTT in <24 hours has been shown to lower in-hospital and 30-day mortality rates.[24] After initiation based on patient weight, dosing adjustments may also be weight based or may simply be made in international units per hour. A sample heparin dosing nomogram specific for a reagent with a therapeutic aPTT range of 60 to 100 seconds (and used in the adjustment of heparin doses for J.T.) is illustrated in **Table 11-10**.

Table 11-10
Sample Heparin Dosing Nomogram

1. Suggested loading dose
   - Treatment of DVT/PE: 80 units/kg (rounded to nearest 500 units)
   - Prevention, including cardiovascular indications: 70 units/kg (rounded to nearest 500 units)
2. Suggested initial infusion
   - Treatment of DVT/PE: 18 units/kg/hour (rounded to nearest 100 units)
   - Prevention, including cardiovascular indications: 15 units/kg/hour (rounded to nearest 100 units)
3. First aPTT check: 6 hours after initiating therapy
4. Dosing adjustments: per this chart (rounded to nearest 100 units)

aPTT[a] (seconds)	Heparin Bolus	Infusion Hold Time	Infusion Rate Adjustment	Next aPTT
<50	4000 units	0	Increase by 200 units/hour	In 6 hours
50–59	2000 units	0	Increase by 100 units/hour	In 6 hours
60–100	0	0	None	Every AM
101–110	0	0	Decrease by 100 units/hour	In 6 hours
111–120	0	0	Decrease by 200 units/hour	In 6 hours
121–150	0	30 minutes	Decrease by 200 units/hour	In 6 hours
151–199	0	60 minutes	Decrease by 200 units/hour	In 6 hours
>200	0	PRN	Hold until aPTT < 100	Every hour until <100

aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; PE, pulmonary embolism; PRN, as necessary.

[a]Based on activated partial thromboplastin time (aPTT) reagent-specific therapeutic range of 60 to 100 seconds corresponding to a plasma heparin

concentration of 0.3 to 0.7 units/mL determined by anti-factor Xa activity.

Responses to changes in infusion rates of heparin are not always linear, and, to some extent, heparin doses are adjusted by trial and error. As the patient's condition improves after several days and endothelialization of the clot occurs, heparin dosing requirements may decrease.

Therapeutic monitoring

Case 11-1, Question 8: How should J.T.'s heparin therapy be monitored?

Once baseline clotting parameters have been established and a loading dose of heparin has been administered, the aPTT should be measured routinely to guide subsequent dosing adjustments. The aPTT should be evaluated no sooner than 6 hours after the loading dose or after any changes in infusion rate, as noted previously. If dosing is stable, the aPTT should be evaluated once daily (Table 11-10).

Additional monitoring parameters for heparin therapy include evaluation for potential adverse reactions and possible therapeutic failure. The Hgb and/or Hct and a platelet count should be checked every 1 to 2 days. J.T. should be examined for signs of bleeding as well as for signs and symptoms associated with thrombus extension and PE. Finally, if unusual or unexpected aPTT results are reported, the clinician should consider the possible influence of solution preparation errors (see Chapter 2, Interpretation of Clinical Laboratory Tests), infusion pump failure, infusion interruption, and administration or charting errors in the assessment of J.T.'s heparin therapy.[25]

Duration of therapy

Case 11-1, Question 9: How long should heparin therapy be continued in J.T. if the patient starts warfarin?

Adherence of a thrombus to the vessel wall and subsequent endothelialization usually take 7 to 10 days. However, anticoagulation therapy must generally continue for 3 months to prevent recurrent thrombosis.[18] For many years, warfarin was preferred for this long-term anticoagulation because it can be administered orally, and it is generally initiated on the same day as heparin. The long elimination half-life of warfarin and the long elimination half-lives of clotting factors II and X necessitate a prolonged period of overlap between warfarin and heparin. Therefore, if warfarin is initiated, heparin is continued for a minimum of 5 days and until the INR is >2.0 for 24 hours. If the INR exceeds the therapeutic range (ie, INR >3.0) prematurely, it is acceptable to stop parenteral therapy before the patient has received 5 days of treatment.[18]

Case 11-1, Question 10: On day 2 of heparin therapy, J.T.'s complete blood count (CBC) reveals a platelet count of 180,000/μL, decreased from 255,000/μL at baseline. What is a reasonable explanation for this thrombocytopenia and how should it be managed?

Adverse effects

Thrombocytopenia

Thrombocytopenia induced by heparin has two distinct presentations.[5] Heparin-associated thrombocytopenia (HAT) occurs as a direct effect of heparin on platelet function, causing transient platelet sequestration and clumping with reductions in platelet count, but usually remaining >100,000/μL. This reversible form of thrombocytopenia occurs within the first several days of heparin therapy. Patients remain asymptomatic, and platelet counts return to normal even when heparin therapy is continued. J.T.'s reduction in platelet count is somewhat modest and likely represents HAT. His platelet count should be monitored daily, and heparin therapy should be continued.

Reductions in platelet count >50% from baseline suggest the development of HIT, a more severe immune-mediated reaction with

a typical delay in onset of 5 to 10 days after the initiation of heparin therapy. In contrast, “rapid-onset” HIT can occur rapidly (within 24 hours of UFH initiation) and is strongly associated with recent heparin exposure. And “delayed-onset” HIT is associated with an onset of thrombocytopenia that begins several days after heparin has been stopped.[5]

Heparin use leads to the formation of immunoglobulin G (IgG) antibodies that recognize multimolecular complexes of a platelet protein called platelet factor 4 (PF4) and heparin that forms on the surface of platelets.[5] Antibodies against PF4–heparin complexes are responsible for the prothrombotic nature of HIT owing to their capability to induce platelet activation by cross-linking platelet Fcc receptor IIa (CD32a),[26] and release procoagulant, platelet-derived microparticles, resulting in a large generation of thrombin and the formation of venous and arterial thromboses. The diagnosis of immune-mediated HIT is made based on clinical findings supplemented by laboratory tests confirming the presence of platelet-activating anti-PF4/heparin antibodies.[5,27,28] The 4T score is the most common pretest probability test and is recommended to estimate the likelihood of HIT based on extent and timing of platelet count reduction, the presence of thrombus, and the possibility of other causes of thrombocytopenia (**Table 11-11**).[5,27,29]

Table 11-11
The 4T Score: Pretest Probability of Heparin-Induced Thrombocytopenia

Category	2 Points	1 Point	0 Points
1. Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20 × 10^9 L^{-1}	Platelet count fall 30%–50% or platelet nadir 10–19 × 10^9 L^{-1}	Platelet count fall <30% or platelet nadir <10 × 10^9 L^{-1}
2. Timing of platelet count fall	Clear onset between days 5 and 10 or platelet fall ≤1 day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (eg, missing platelet counts) or onset after day 10 or fall ≤1 day (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent heparin exposure
3. Thrombosis or other sequelae	New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis or nonnecrotizing (erythematous) skin lesions or suspected thrombosis (not proven)	None
4. Other causes for thrombocytopenia	None apparent	Possible	Definite

Total score <3, low probability of HIT; 4–5, intermediate probability of HIT; >6, high probability of HIT.

Source: From Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. 2006;4(4):759–765. © 2006 International Society on Thrombosis and Haemostasis. Reprinted by permission of John Wiley & Sons, Inc.

The overall incidence of HIT is <3% after 5 days of UFH use, but the cumulative incidence can be as high as 6% after 14 days of continuous heparin use. Despite its low incidence, HIT is a life-threatening condition with a reported mortality rate of 5% to 10%. The condition in which patients have acute heparin-induced thrombocytopenia complicated by thrombosis is called *HITT*, whereas acute HIT without thrombosis is referred to as *isolated HIT*. Venous thrombosis is the most common complication secondary to HIT, with rates reported at 2.4 to 1 more common than arterial thrombosis (limb artery thrombosis, thrombotic stroke, and MI).[30] Limb gangrene has been reported at 5% to 10%, with a resulting risk of amputation.[31]

In patients who have acute HITT or isolated HIT, heparin therapy should be stopped immediately, and treatment with an alternative non-heparin anticoagulant should be initiated.[5,29] Although associated with a lower risk of HIT (<1%) than UFH, LMWH products are contraindicated in patients with HIT because of a high incidence of immunologic cross-reactivity with heparin.[5,29] The future use of heparin in patients with HIT, especially in the first 3 months after the diagnosis, should be avoided. Treatment options for patients with critical illness, increased bleeding risk, or increased potential need for urgent procedures include the direct thrombin inhibitors argatroban and bivalirudin, although only argatroban is approved for this indication by the FDA. The dose of argatroban is administered as an IV infusion because of its short half-life and should be titrated based on aPTT testing. Bivalirudin is a suitable alternative for the treatment of HIT owing to its short-half life, low immunogenicity, minimal effect on INR, and enzymatic metabolism. Various patient-related factors (such as the presence of renal or hepatic dysfunction;

drug availability, cost, and institutional preference) should be used to select the most appropriate agent[5,29] (Table 11-7). Although off-label and with limited data, the 2018 American Society of Hematology (ASH) Guidelines conditionally support the use of DOACs and fondaparinux in isolated HIT and acute HITT in stable patients at average risk for bleeding.[29]

CASE 11-1, QUESTION 11: On day 3 of heparin therapy, J.T.'s Hct has dropped from a baseline of 37.5% to 28%, and the patient noted blood in his commode after urination. What is an effective approach to evaluate and interpret this event?

Hemorrhage

Bleeding is the most common adverse effect associated with heparin. A summary of eight studies reporting heparin-associated bleeding found the absolute frequency of fatal, major, and all (major or minor) bleeding to be 0.4%, 6%, and 16%, respectively.[32] The corresponding average daily frequencies were 0.05% for fatal bleeding, 0.8% for major bleeding, and 2% for major or minor bleeding; cumulative risk increased with the duration of therapy. The most common sites for heparin-associated bleeding are soft tissues, the GI and urinary tracts, the nose, and the oral pharynx. The use of different criteria to define major versus minor bleeding accounts for much of the variability in reported frequency of bleeding among studies.

In addition to length of therapy, many factors influence the risk of bleeding during heparinization, including advanced age, serious comorbid illnesses (heart disease, renal insufficiency, hepatic dysfunction, cerebrovascular disease, malignancy, and severe anemia), and concomitant antithrombotic therapy.[32] The incidence of UFH-associated bleeding complications is minimal with SC prophylactic doses, but higher (2%–4%) with therapeutic doses given via IV infusion. Soft tissue bleeding commonly occurs at sites of recent surgery or trauma. Previously undiagnosed abnormalities, including malignancy and infection, may be identified in some

patients with GI or urinary tract bleeding associated with heparin therapy.

The influence of the intensity of heparinization on bleeding risk is controversial. Although an elevated aPTT has historically been considered a risk factor for bleeding complications, several investigators have been unable to substantiate a relationship between supratherapeutic aPTT values and hemorrhagic effects.[3] In addition, bleeding episodes can occur when coagulation test results are within the therapeutic range. These conflicting results may be explained in part by the influence of additional risk factors for bleeding and by the effect of heparin on platelet function and vascular permeability.

J.T. has developed hematuria despite an acceptable intensity of anticoagulation. He should be questioned and examined for the presence of nose bleeding (epistaxis), increased tendency to bruise (ecchymosis), bright red blood in the stool (hematochezia), black or tarry stool (melena), or coughing up of blood (hemoptysis). Blood pressure and pulse, both sitting and standing, should be obtained to determine whether orthostasis representing blood loss is present. A thorough evaluation of the urinary tract may reveal a previously unknown abnormality that will explain the bleeding episode. Although his concurrent low-dose aspirin therapy may increase the risk of minor bleeding complications, aspirin therapy would not be discontinued because of his history of coronary artery disease.

CASE 11-1, QUESTION 12: What other side effects of heparin should be considered in J.T.?

Osteoporosis

The development of osteoporosis has been associated with the administration of >20,000 IU/day of heparin for 6 months or longer.[33] Various mechanisms have been suggested, but the underlying pathophysiology of this rare adverse effect remains unclear. Affected patients may present with bone pain and/or radiographic findings suggestive of fractures. The possibility of osteoporosis should be

considered in patients receiving long-term, high-dose heparin therapy such as pregnant patients, postmenopausal females, and elderly patients.

Hypersensitivity Reactions

Other rarely occurring adverse effects associated with heparin include generalized skin reactions that can progress to necrosis, alopecia, and hypersensitivity reactions, resulting in hypotension, nausea, and SOB. In 2007, an increase in hypersensitivity reactions to heparin was attributed to oversulfated chondroitin sulfate in the heparin manufacturing process.[34]

Reversal of effect

CASE 11-2

QUESTION 1: K.G. is a 72-year-old female with a DVT that occurred during her hospital stay. On day 4 of heparin therapy, she received a full bag of 25,000 units of heparin during a 1-hour period as a result of an infusion pump malfunction. The infusion was stopped and within 30 minutes, she became diaphoretic and hypotensive. Bright red blood was evident on rectal examination, and a large retroperitoneal mass was noted.

How should the excessive heparin effect be reversed?

K.G. has definite signs of hemorrhage from the GI tract, a site of bleeding associated with considerable mortality. Heparin should be discontinued immediately, and treatment should include maintenance of fluid volume and replacement of clotting factors with whole blood, fresh frozen plasma, or clotting factor concentrates. If hemorrhage had not been present and the only manifestation of overdose had been a prolonged aPTT, administration of heparin simply could have been discontinued, permitting the effects to clear within a few hours.

Protamine can be used to neutralize heparin by forming an inactive protamine–heparin complex.[3] Protamine has a rapid onset of action, with effects lasting about 2 hours. Protamine sulfate is

infused slowly over 3 to 5 minutes, as a 1% solution at a dose of 1 mg for each 100 IU of heparin administered in the past 2 to 3 hours. The maximum single recommended dose of protamine is 50 mg, but doses may be repeated if bleeding persists. Response to protamine therapy can be assessed by a return of the aPTT to baseline. Adverse effects associated with protamine include systemic hypotension secondary to rapid administration; anaphylaxis characterized by edema, bronchospasm, and cardiovascular collapse; and catastrophic pulmonary vasoconstriction[35] (see Chapter 32, Drug Hypersensitivity Reactions).

CASE 11-3

Question 1: N.C. is a 32-year-old female who presents to the emergency department (ED) with right leg pain behind the right knee of 2-day duration. She denies recent injury, but her medication history reveals that she recently started combination oral contraceptive tablets. She has no significant medical history and has no family history of clotting disorders. A duplex ultrasound finding is positive for DVT and immediate anticoagulation is indicated.

What therapeutic alternatives to hospitalization for IV UFH are available for this patient?

Outpatient treatment of deep vein thrombosis

In the past, hospitalization with UFH was the initial treatment of choice for acute DVT; however, the ease of SC dosing and self-administration of LMWHs and fondaparinux made them practical treatment alternatives to UFH, and allowed for outpatient management while transitioning to therapeutic warfarin.[18] In addition, meta-analysis data suggest that LMWH therapy for acute VTE results in fewer deaths, major hemorrhages, and recurrent VTE when compared to UFH.[36] Based on these advantages, outpatient use of LMWH became a common approach to treatment of uncomplicated DVT in patients who transition to warfarin. Home treatment is safe and effective and is preferred for uncomplicated DVT treatment.[37] Fondaparinux can also be considered as an alternative treatment because it has been shown to be as effective

and safe as LMWH in the treatment of DVT.[38] In addition, weight-based SC UFH (initial dose of 333 IU/kg followed by 250 IU/kg every 12 hours) without routine aPTT monitoring while patients become therapeutic on warfarin is an alternative for the treatment of acute VTE.[39] Vials of UFH at a concentration of 20,000 IU/mL are used by the pharmacy or the patient to draw up the weight-based dose. Although routine aPTT monitoring is not necessary, platelet count monitoring during the first 2 weeks is required to evaluate the possible development of HIT.

For N.C. to be treated at home with LMWH, she or a family member must be willing and able to administer SC injections, and she must be able to return for frequent follow-up visits, particularly during the first few weeks while warfarin therapy is initiated. In addition, her health care insurance should cover the cost of the drug, or she must be able to pay out of pocket. Contraindications to outpatient treatment of VTE include a preexisting condition that requires hospitalization, clinical symptoms of PE with hemodynamic instability, and recent or active bleeding.

N.C. meets the eligibility requirements for home treatment of her DVT. However, DOACs are preferred over warfarin as the first-line agents for the initial treatment of DVT.[18,37] She is a suitable candidate for a DOAC and prefers to not have to perform self-injections of medication. Currently, there are two DOACs, rivaroxaban and apixaban, approved in the United States for monotherapy, and they do not require an initial period of parenteral anticoagulant. Advantages to the use of a DOAC compared to warfarin include the lack of routine monitoring for assessing drug efficacy, fewer drug and food interactions, and a lower rate of major bleeding compared to warfarin. Currently, dabigatran has an FDA-approved agent for reversal, idarucizumab, and rivaroxaban and apixaban can be reversed with andexanet-α.[40] When selecting a DOAC, it is important to know the patient's renal function because these agents have varying doses based on current renal function. A baseline CBC should also be checked, because all anticoagulants have the potential for bleeding, and it is important to know the baseline Hgb level in case bleeding occurs on treatment. Baseline LFTs are also

recommended because there are precautions with some of the DOACs in hepatic dysfunction (see Table 11-5). In this case, N.C. received an injection of LMWH while in the ED, and rivaroxaban is selected for monotherapy, at 15 mg twice daily with food for 21 days, followed by 20 mg daily with food for the remainder of her 3-month duration of treatment. N.C. should be advised to follow up with her primary care provider regarding her new diagnosis, and it should be stressed to the patient the importance of proper transitioning of the dose from the twice-a-day to the once-a-day schedule. Anticoagulation clinics may also be involved in N.C.'s care to follow up and make sure she was able to obtain the medication without insurance barriers, that the DOAC dose was appropriate, that her DVT symptoms are improving, that she is tolerating the medication, and that she transitions to the correct dose appropriately.[41,42] Higher risk patients, such as those with lower health literacy and multiple medical problems, may benefit from face-to-face clinical visits if this information cannot be obtained by telephone. Centralized anticoagulation management services are expanding beyond traditional monitoring to include patients on DOACs by prospectively following them up to ensure optimal therapeutic outcomes. There are some cases where it may be necessary to test whether the DOAC is present, such as in a patient with acute stroke, need for urgent surgery, or in the case of major bleeding.[43] Tests that are suitable for quantitation of DOACs are not often readily available. Of those that are readily available, a dilute thrombin time may be used to detect dabigatran presence, and the anti-factor Xa calibrated for the factor Xa inhibitors.[43] Tests that provide a suitable qualitative assessment of DOAC presence include thrombin time for dabigatran; and for the factor Xa inhibitors, a PT or an anti-factor Xa that is used for UFH or LMWH may be used.[43]

CASE 11-3, QUESTION 2: During a follow-up call to N.C. from the anticoagulation clinic the next morning, it is discovered that N.C. was not able to get the rivaroxaban filled at her pharmacy last night because her insurance does not cover any DOAC therapy without first documenting a treatment failure to warfarin. What alternative treatment is available for N.C.?

Before the DOACs, treatment with self-injected LMWH bridging to warfarin at home was the standard of care. Possible treatment options and doses for N.C. are listed in **Table 11-12**. In this case, enoxaparin is the LMWH preferred by her insurance because it is available generically. The usual dosing of enoxaparin for treatment of DVT is 1 mg/kg total body weight SC every 12 hours, rounded to the nearest 10-mg increment. Once-daily dosing at 1.5 mg/kg SC every 24 hours is also an option, but this strategy is inferior to twice-daily dosing in patients with malignancy or obesity.[44] N.C.'s medical history is suitable for the once-daily dose of enoxaparin, which is more convenient for administration. At 143.30 pounds (65 kg), a dose of 1.5 mg/kg would be 97.5 mg, which will be rounded to the nearest 10-mg increment. N.C. will therefore receive 100 mg SC every 24 hours. Warfarin therapy is initiated concurrently to expedite the conversion to oral treatment.

Table 11-12

Dosing of Low-Molecular-Weight Heparin and Fondaparinux for the Treatment of Venous Thromboembolism

Dalteparin	Enoxaparin	Tinzaparin	Fondaparinux
100 IU/kg SC every 12 hours *or* 200 IU/kg SC every 24 hours	1 mg/kg SC every 12 hours *or* 1.5 mg/kg SC every 24 hours	175 IU/kg SC every 24 hours	5 mg SC every 24 hours if weight <50 kg 7.5 mg SC every 24 hours if weight 50–100 kg 10 mg SC every 24 hours if weight >100 kg

SC, subcutaneously.

Because LMWHs are eliminated renally, patients with significant renal impairment require dose reductions to prevent drug accumulation and to minimize the risk of bleeding complications.[45] The degree of drug accumulation can vary between the various LMWH preparations, and thus specific guidelines for dose adjustments are agent specific (**Table 11-13**).[46] Routine monitoring of trough anti-Xa activity in patients with severe renal impairment that are treated with LMWH for an extended period of time (ie, >1 week) is not recommended.[10] Fondaparinux is also renally excreted and is contraindicated in patients with creatinine clearance <30 mL/minute.

Table 11-13

Dosing of Low-Molecular-Weight Heparins in Patients With Renal Impairment (CrCl <30 mL/minute)[a]

LMWH	Dalteparin	Enoxaparin	Tinzaparin
Product information recommendations	Use with caution.	Prophylaxis: 30 mg SC daily Treatment: 1 mg/kg SC daily	Use with caution.
Dosing suggestions based on agent-specific pharmacokinetic observations	CrCl <30 mL/minute[a]: No dose adjustment needed up to 1 week with prophylactic doses. For use >1 week, consider monitoring of trough anti-Xa activity and adjust dose if accumulation is noted. CrCl 30–50 mL/minute: No dose adjustment needed.	CrCl <30 mL/minute[a]: Consider a 40%–50% dose decrease and subsequent monitoring of trough anti-Xa activity. CrCl 30–50 mL/minute: Consider a 15%–20% dose decrease with prolonged use (>10–14 days) and subsequent monitoring of anti-Xa activity.	CrCl <30 mL/minute[a]: Consider a dose decrease of 20% and subsequent monitoring of trough anti-Xa activity. CrCl 30–50 mL/minute: no dose adjustment needed

[a]In patients with a creatinine clearance (CrCl) <30 mL/minute, data are very limited, and use of unfractionated heparin is suggested.

CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; SC, subcutaneously.

N.C. should be educated regarding the potential adverse effects of LMWH therapy (bleeding, thrombocytopenia, pain, and bruising at the injection site), required laboratory monitoring, and the expected duration of anticoagulation. At baseline, Hgb and/or Hct, INR, serum creatinine (SCr), and platelet count should be determined. Platelets will continue to be monitored at least every 2 to 3 days while the patient is receiving LMWH therapy, to a maximum of 10 to 14 days. N.C. can expect to continue enoxaparin therapy for a minimum of 5 days. If by day 5 her INR is therapeutic and stable, enoxaparin can be discontinued. Oral anticoagulation with warfarin should be continued for 3 to 6 months.[18,37] N.C. should also be advised against further use of estrogen-containing contraceptives.[47]

To ensure the safety and efficacy of home treatment, N.C. should be provided with the names and telephone numbers of the health care providers who will assume responsibility for her care, including her primary physician and her anticoagulation management team. No patient should be sent home with LMWH without an adequate follow-up plan.

Prevention of Venous Thromboembolism

CASE 11-4

QUESTION 1: M.G., a 63-year-old obese male, is to undergo elective abdominal surgery for treatment of an umbilical hernia. He has a medical history significant for hypertension, currently controlled by enalapril 10 mg daily (blood pressure, 130/80 mm Hg), and gout, controlled with allopurinol 300 mg daily.

What therapeutic interventions might decrease the risk of DVT or PE in M.G.?

Surgical procedures represent a significant risk factor for DVT formation. However, all hospitalized patients, including both surgical and nonsurgical/medical patients, should be stratified for risk of VTE based on the presence of various factors.[16,48,49] There are several risk stratification scoring tools available for clinicians to evaluate a patient's individual risk for VTE, such as Caprini, international medical prevention registry on venous thromboembolism (IMPROVE), international medical prevention registry on venous thromboembolism with D-dimer (IMPROVEDD), and Padua scores.[50–53] These help clinicians select the most appropriate interventions to prevent DVT and reduce the risk of fatal PE, and include both mechanical and pharmacologic strategies.[54,55]

NONPHARMACOLOGIC MEASURES

Mechanical interventions aimed at preventing venous stasis and increasing venous return include the use of graduated compression stockings, as well as leg elevation, leg exercises, and early postoperative ambulation. Intermittent pneumatic compression (IPC) of the leg muscles, using inflatable cuffs applied to the calf and thigh, represents another alternative for the prevention of DVT.[16] In patients undergoing major surgery, IPCs have a conditional recommendation over graduated compression stockings.[55] Because it is generally less effective than is pharmacologic prophylaxis, mechanical prophylaxis is most commonly used in patients at high risk for bleeding, or as an adjunct to pharmacologic prophylaxis in patients at very high risk for VTE.

PHARMACOLOGIC MEASURES

Fixed, low-dose unfractionated heparin (LDUFH), administered as 5000 units SC every 8 to 12 hours depending on the indication, is an inexpensive and effective pharmacologic approach to DVT prevention in the setting of venous stasis in patients with acute medical illness, or after certain surgical procedures. Because LDUFH inactivates factor Xa without a direct effect on factor IIa, the aPTT is not prolonged, and therefore aPTT monitoring is unnecessary. Bleeding complications are minimized using this dosing regimen.

Fixed-dose SC LMWH and fondaparinux are alternative approaches for preventing DVT. Enoxaparin 30 mg SC every 12 hours or 40 mg SC once daily, dalteparin 2500 to 5000 IU SC once daily, and fondaparinux 2.5 mg SC once daily are effective strategies, although enoxaparin has been studied for a larger number of indications. The DOACs rivaroxaban, apixaban, and dabigatran have been FDA approved for DVT prophylaxis in patients undergoing orthopedic surgery. Betrixaban 160 mg as a single dose followed by 80 mg daily is approved for VTE prophylaxis in adult patients hospitalized for an acute medical illness, but it is no longer currently available in the United States. Current recommendations for prevention of VTE based on risk stratification are presented in **Table 11-14**.[54,55]

Table 11-14
Prevention of Venous Thromboembolism

Clinical Scenario	Recommendations
Major Surgery	Suggests the following: ▪ Pharm or mechanical prophy ▪ If do not receive pharm prophy, use mechanical prophy over no mechanical prophy ▪ Use IPC over GCS. ▪ Use combined prophy with mechanical and pharm prophy over pharm prophy alone. ▪ Depending on VTE and bleeding risk based on patient and surgery: Use combined prophy or mechanical prophy alone.

Clinical Scenario	Recommendations
	Suggests against IVC filters
	Suggests extended prophy (>3 weeks) over short-term prophy (<2 weeks) Suggests using early or delayed prophy (12-hour cutoff point between early and delayed)
Orthopedic surgery	THR or TKR: suggests ASA or anticoagulants. When anticoagulants used, suggests DOACs over LMWH. If DOAC not used, suggests LMWH over warfarin, and recommends LMWH over UFH
	Hip fracture surgery: suggests pharm over no pharm prophy Suggests LMWH or UFH
Major general surgery	Suggests pharm prophy over no pharm prophy Suggests LMWH or UFH
Laparoscopic cholecystectomy	Suggests against pharm prophy
Major neurosurgical procedures	Suggests against pharm prophy If pharm prophy used, suggests LMWH over UFH
Urologic procedures	TURP: suggests against pharm prophy If pharm prophy used, suggests LMWH or UFH
	Radical prostatectomy: suggests against pharm prophy If pharm prophy used, suggests LMWH or UFH
Cardiac or major vascular surgery	Suggests pharm prophy over no pharm prophy Suggests LMWH or UFH
Major trauma	Low to moderate risk of bleeding: suggests pharm prophy over no pharm prophy High risk for bleeding: suggests against pharm prophy If pharm prophy used, suggests LMWH or UFH
Major gynecologic surgery	Suggests pharm prophy over no pharm prophy Suggests LMWH or UFH

Clinical Scenario	Recommendations
Acutely ill medical patients	Suggests UFH, LMWH, or fondaparinux over no parenteral AC Suggests LMWH or fondaparinux over UFH Recommends LMWH over DOACs Recommends inpatient VTE prophy with LMWH only, over inpatient and extended-duration VTE prophy with DOACs Recommends inpatient over inpatient plus extended-duration VTE prophy
Critically ill medical patients	Recommends UFH or LMWH over no UFH or LMWH Suggests LMWH over UFH Recommends inpatient over inpatient plus extended-duration outpatient VTE prophy
Acute or critically ill medical patients	Suggests pharm prophy over mechanical prophy If not receiving pharm prophy, suggests mechanical prophy Suggests pharm or mechanical prophy alone over mechanical combined with pharm prophy Suggests IPC or GCS
Chronically ill medical or nursing home patients	Suggests not using VTE prophy over any VTE prophy
Medical outpatient with minor provoking risk factors	Suggests not using VTE prophy
Long-distance travelers	Without VTE risk factors: suggests not using GCS, LMWH, or ASA for VTE prophy Substantially increased VTE risk: suggests GCS or prophy LMWH Substantially increased VTE risk and LMWH or GCS not feasible: suggests ASA over no VTE prophy

AC, anticoagulation; ASA, aspirin; DOAC, direct oral anticoagulant (refer to Table 11-4 for DOAC dosing); GCS, graduated compression stockings; IPC, intermittent pneumatic compression; IVC, inferior vena cava; LMWH, low-molecular-weight heparin (enoxaparin 40 mg SC daily or 30 mg SC every 12 hours; dalteparin 2500–5000 IU SC; fondaparinux [2.5 mg SC daily]); pharm, pharmacologic; prophy, prophylaxis; TURP, transurethral resection of the prostate; UFH, unfractionated heparin (5000 international units [IU] subcutaneously [SC] every 8–12 hours); VTE, venous thromboembolism.

Sources: Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2(22):3198–3225. doi:10.1182/bloodadvances.2018022954; Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv*. 2019;3(23):3898–3944. doi:10.1182/bloodadvances.2019000975.

M.G. is at high risk for DVT and PE, not only because of general surgery but also because of his age (older than 40 years) and the presence of other risk factors for VTE (obesity and probable postoperative immobilization). Options for DVT prevention include SC heparin at 5000 IU every 8 hours or an LMWH (enoxaparin 40 mg SC daily, or dalteparin 2500 IU initial dose followed by 5000 IU SC daily). The first dose is generally given 12 or more hours postoperatively until he is fully ambulatory. If bleeding risk is of concern, IPC could be used as an alternative. VTE prophylaxis is typically continued until hospital discharge but may be continued for up to 30 days in certain high-risk populations, including patients with cancer, orthopedic surgery, bariatric surgery, or with a prior history of VTE.

CASE 11-5

Question 1: A.W. is a 52-year-old, 154.32-pound (70-kg) female. She recently returned from a 12-hour car ride during which she only stopped to stretch twice. Yesterday she noticed a swollen right calf that is painful and warm. This swelling gradually increased, affecting the entire right leg to the groin, and prompted her to seek medical attention. In the ED, she also notes the recent onset of right-sided pleuritic chest pain without SOB or hemoptysis. Her medical history includes a gastric ulcer 4 years ago, treated with proton-pump inhibitor therapy that has not recurred. Physical examination reveals an enlarged right leg and moderate tenderness in the entire leg. Chest examination reveals labored respirations, equal breath sounds, and no wheezing or crackles. Vital signs include blood pressure, 160/90 mm Hg; heart rate, 100 beats/minute; and respiratory rate, 28 breaths/minute and regular. Laboratory data include the following:

Hct, 26.7%
SCr 1.1 mg/dL

Arterial blood gases (on room air)
P_{O_2}, 72 mm Hg (normal, 75–100)
P_{CO_2}, 30 mm Hg (normal, 35–45)
pH 7.48 (normal, 7.35–7.45)

Chest CT shows a PE in the distal right main pulmonary artery extending into the right lower lobe. The electrocardiogram (ECG) shows sinus tachycardia. The lower extremity duplex ultrasound finding is positive for acute occluding thrombus from the right femoral vein all the way down to the soleal vein. Coagulation test results include the following:

PT, 11.2 seconds (INR, 1.0)
aPTT, 28 seconds
Platelet count, 248,000/μL

What subjective and objective evidence in A.W. is consistent with PE?

PULMONARY EMBOLISM

Clinical Presentation

SIGNS AND SYMPTOMS

The clinical diagnosis of PE is often difficult to make because of the nonspecificity of symptoms.[56] The most common symptoms of PE include tachypnea, cough, substernal and pleuritic chest pain, dyspnea, hemoptysis, fever, and unilateral leg pain. Signs and symptoms such as hypotension, tachycardia, presence of B-type natriuretic peptides (BNP) or NT-pro-BNP (N-terminal pro-brain natriuretic peptide), troponins (I or T), serum lactate, hypoxia, and ECG changes suggestive of right ventricular strain are important to recognize because these may indicate more severe thromboembolism and increased risk for 30-day mortality.[56] DVT precedes PE in ≥80% of patients. A combination of these signs and symptoms provides further evidence for acute PE.

DEFINITIONS

There are varying ways to define the severity of a PE. Some define PE based on a patient's in-hospital or 30-day risk for mortality, whereas other literature will cite terms such as massive and submassive PE.[56,57] Low-risk PE is classified as the presence of thromboembolism without changes in hemodynamics, right ventricular function, or cardiac biomarkers. These types of severity in patients can also be classified as small-to-moderate PE. High-risk PE is defined by the presence of shock (manifesting as tissue hypoperfusion, and hypoxia, cool clammy extremities, alterations in consciousness) or hypotension, specifically defined as a systolic blood pressure <90 mm Hg or a ≥40 mm Hg drop in systolic blood pressure for >15 minutes that is not attributed to new-onset arrhythmia, hypovolemia, or sepsis. These patients can also be classified as having massive PE.[57] Patients with right ventricular dysfunction characterized by echocardiographic evidence or by positive cardiac biomarkers (BNP >90 pg/mL or NT-pro BNP >500 pg/mL, troponin I >0.4 ng/mL, troponin T >0.1 ng/mL) are classified as having submassive PE if they are hemodynamically stable.[57]

DIAGNOSIS

Because the clinical signs and symptoms of PE are difficult to distinguish from many other medical conditions, further evaluation is necessary.[15,56] Chest radiograph, ECG, and arterial blood gas (alveolar–arterial oxygen gradient) abnormalities are often present in patients with PE, but as with clinical signs and symptoms, they are somewhat nonspecific. Pulmonary imaging is necessary to diagnose or definitely rule out PE. Although many methods are clinically available for chest imaging, the computed tomographic (CT) pulmonary angiography and ventilation–perfusion lung scanning ($\dot{V}/\dot{Q}$ scan) are the most common tests used for the diagnosis of PE, with the multidetector computed tomography (MDCT) being the imaging test of choice because of its ability to visualize the pulmonary arteries in the greatest detail. Lung scans that incorporate an assessment of perfusion, or regional distribution of pulmonary blood flow, and ventilation are referred to as $\dot{V}/\dot{Q}$ scans; they involve

both the injection and the inhalation of radiolabeled compounds. Test results are expressed as a high, intermediate, or low probability of PE. When ventilation (air movement) is normal over an area that shows abnormal perfusion (blood flow), a $\dot{V}/\dot{Q}$ mismatch exists, and PE is highly probable. If a matched defect is noted (abnormal ventilation over an area of abnormal perfusion), another disease state, such as chronic obstructive airway disease, is more likely.

As in the case of DVT, clinical assessment of PE can improve the diagnostic accuracy of noninvasive tests such as CT, MRI, or $\dot{V}/\dot{Q}$ scanning. Validated assessment tools can be used to stratify a patient's probability of a PE[58–61] (**Table 11-15**). In patients with a low clinical probability of PE, measuring a high-sensitivity D-dimer is recommended, and, if negative, PE can be ruled out, eliminating the need for further imaging studies.[15] In patients with a moderate-to-high clinical probability of PE, diagnostic imaging studies should be performed.

Table 11-15
Original and Simplified Pulmonary Embolism Severity Index (PESI) Scoring Systems

Parameter	Original Scoring Version (Points)	Simplified Scoring Version (Points)
Age	Points: age (years)	1 (if age >80 years)
Male sex	10	–
Cancer	30	1
Chronic heart failure	10	1[a]
Chronic pulmonary disease	10	1[a]
Heart rate >110 bpm	20	1
Systolic blood pressure <100 mm Hg	30	1
Respiratory rate >30 breaths/minute	20	–
Temperature <96.8 °F (36	20	–

°C)		
Altered mental status	60	–
Arterial oxygen saturation <90%	20	1
30-Day Mortality Risk (%)		
Very low: 0–1.6	Class I: <65	0 points: 1%
Low: 1.7–3.5	Class II: 66–85	
Moderate: 3.2–7.1	Class III: 86–105	
High: 4–11.4	Class IV: 106–125	≥1 point: 10.9%
Very high: 10–24.5	Class V: >125	

bpm, beats per minute; mm Hg, millimeters of mercury.

[a]Only 1 point can be obtained for chronic heart failure and/or chronic pulmonary disease. Patients with both of these comorbidities can obtain only 1 point.

Sources: Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005;172:1041–1046; Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med*. 2010;170:1383–1389.

Treatment

Case 11-5, Question 2: What anticoagulant strategy should be initiated for A.W.?

When the diagnosis of PE is suspected, anticoagulation should be initiated immediately while awaiting results of more definitive diagnostic procedures. There are several agents that can be used for the acute treatment of PE. IV UFH therapy initiated with a loading dose followed by a continuous infusion was the mainstay of therapy for many years. Now IV UFH is generally reserved for high-risk patients with PE in whom reperfusion therapy is being considered, patients with severe renal insufficiency, and in patients with severe obesity. For high- and intermediate-probability PE, weight-based LMWH or fondaparinux are preferred over IV UFH. LMWHs are

noninferior to UFH in the management of PE and are recommended over UFH in stable patients with PE because of their ease of use, less major bleeding, and ability for outpatient management or early discharge.[62,63] Fondaparinux demonstrated noninferiority when compared with IV UFH for rate of recurrent PE, with similar rates of major bleeding.[64] In addition, the DOACs have been evaluated for both the initial and long-term management of VTE, with dabigatran, rivaroxaban, apixaban, and edoxaban all FDA approved for the initial management of PE, and preferred over warfarin.[18,56] All of the DOACs were compared to LMWH/VKA and found to be noninferior for the rate of recurrent VTE.[65–69] Rivaroxaban and apixaban were studied as monotherapy, whereas patients on dabigatran and edoxaban were initially treated with at least 5 days of parenteral therapy before receiving a DOAC. If A.W. is being kept in the hospital for observation because of the severity of her symptoms, UFH therapy could be started at a loading dose of 5600 units (80 IU/kg × 154.32 pounds [70 kg]), followed by continuous infusion of 1300 units/hour (18 units/kg/hour × 154.32 pounds [70 kg]). Monitoring of the aPTT would be used to adjust dosing to maintain treatment within the therapeutic range (see Table 11-10).

Alternatively, SC LMWH 70 mg every 12 hours (1 mg/kg every 12 hours × 154.32 pounds [70 kg]) or SC fondaparinux 7.5 mg daily may be given while transitioning the patient to warfarin (see Table 11-12). A.W. could receive fixed-dose enoxaparin 70 mg SC every 12 hours (1 mg/kg every 12 hours × 154.32 pounds [70 kg]) or dalteparin 15,000 IU SC every 24 hours (200 IU/kg, rounded to nearest syringe size). Use of initial therapies such as LMWH, fondaparinux, and DOACs allows for outpatient therapy and early discharge in hospitalized patients with acute PE. For patients with low-risk PE and home circumstances that are adequate, early discharge is suggested over standard discharge.[15]

Reperfusion therapy, which includes systemic thrombolytic therapy, percutaneous catheter-directed treatment, and surgical embolectomy reverses right ventricular dysfunction and restores pulmonary perfusion more rapidly than does anticoagulant therapy alone.[56] Systemic thrombolytic therapy is generally reserved for

patients with a high risk of mortality and a low risk of bleeding.[56] Percutaneous catheter-directed treatment provides localized delivery of fibrinolytics to the pulmonary thrombi and is an alternative invasive method for removal of pulmonary emboli. It is a less invasive approach compared to surgical embolectomy in patients who are not candidates for systemic thrombolytic therapy. For patients with moderate- to high-risk PE, surgical embolectomy or percutaneous catheter-directed treatment should be considered in case of hemodynamic deterioration on anticoagulation treatment as an alternative to systemic thrombolytic therapy.[56]

WARFARIN

Transition from injectable anticoagulant therapy

Case 11-5, Question 3: If A.W. is to start on warfarin, rather than on a DOAC, when should it be administered, and how should the transition from injectable anticoagulant therapy be accomplished?

As in the treatment of DVT, if warfarin is to be started, the use of heparin, LMWH, or fondaparinux therapy for PE treatment should be continued for at least 5 days and until warfarin therapy is therapeutic for at least 24 hours. Warfarin should be started on the first day of treatment and continued for 3 months, or longer if indicated. However, a delay in the initiation of warfarin may be acceptable in the setting of an anticipated extended hospitalization, recent or anticipated surgery or other invasive procedures, or a medical condition with the potential for uncontrolled bleeding.[37]

There are several reasons to overlap heparin/LMWH/fondaparinux and warfarin therapy.[6] The onset of warfarin activity depends not only on its inherent pharmacokinetic characteristics (half-life >36 hours) but also on the rate of elimination of circulating clotting factors. Although warfarin inhibits production of the vitamin K–dependent clotting factors, previously synthesized clotting factors must be eliminated at rates that correspond with their elimination half-lives (see Table 11-8). Approximately four half-lives are required

for these factors to reach a new steady state after their production is inhibited, so the effect of warfarin can be delayed for several days. Initial increases in the INR reflect only reductions in factor VII activity, but full anticoagulation with warfarin requires adequate suppression of factors II and X, which have significantly longer elimination half-lives. By overlapping a quick-onset injectable anticoagulant such as heparin/LMWH/fondaparinux with warfarin therapy, adequate anticoagulation can be continued until warfarin therapy reaches a therapeutic intensity.

In addition to suppressing the synthesis of the vitamin K–dependent clotting factors, warfarin also inhibits the formation of the naturally occurring anticoagulant protein C and its cofactor, protein S. In patients with congenital protein C or protein S deficiency, initial warfarin therapy can suppress these proteins to concentrations that may result in hypercoagulability with possible thrombus extension, unless concurrent heparin therapy provides adequate anticoagulation. To prevent these complications, heparin/LMWH/fondaparinux and warfarin therapy should overlap.

Heparin therapy has been observed to prolong the INR,[70] and warfarin can prolong the aPTT by several seconds.[71] Thus, interference with laboratory tests should be considered in the evaluation of the intensity of anticoagulation during the overlap of heparin and warfarin therapy.

Initiation of warfarin therapy

Case 11-5, Question 4: In an effort to discharge A.W. from the hospital as soon as possible, an initial dose of warfarin 10 mg PO every evening for 3 days has been ordered. Is such a “loading dose” reasonable? What are more effective approaches to initiating therapy?

Initiation of warfarin dosing is complex because dosing requirements vary significantly among individuals. Daily doses as low as 0.5 mg and as high as 20 mg or more may be required in individual patients to reach a therapeutic INR.[72] Two primary

methods for initiation of warfarin therapy are used.[73] The average daily dosing method relies on an understanding that although dosing requirements for warfarin vary significantly among patients, an average dosing requirement of 4 to 5 mg/day of warfarin is necessary to maintain an INR of 2.0 to 3.0 in most patients. When average daily dosing is used for initiation of warfarin therapy, patients are typically started at 4 to 5 mg daily, with dosing adjustments as necessary until the therapeutic goal is reached. However, patients who may be more sensitive to the effects of warfarin (**Table 11-16**) are expected to require lower dosages of warfarin. In these patients, therapy should be initiated at 1 to 3 mg daily, with subsequent dosing adjustments as necessary. Several dosing algorithms, using a 4- to 5-mg initiation dose, have been developed to aid with dosing decisions after the first few doses of warfarin have been administered.[74–76] Another popular dosing algorithm recommended by the American College of Chest Physicians (ACCP) for outpatients uses a 10-mg initiation dose for the first 2 days, with the INR on day 3 measured to guide dosing on days 3 and 4, and the INR on day 5 used to guide the next three doses[22,77] (**Fig. 11-4**). Although using this dosing algorithm helps achieve a therapeutic INR more quickly than using a 5-mg initial dose, these findings may not be generalizable to all patient populations because the patients evaluated were relatively healthy, young outpatients.[78] The 10-mg initiation dose may lead to overanticoagulation and heightened bleeding risk in elderly and ill patients with multiple medical problems.[79] Average daily dosing is often used to initiate therapy in ambulatory patients; in this case, the first INR should be evaluated within 3 to 5 days of initiation of warfarin therapy (**Table 11-17**). In hospitalized patients, it is more common to evaluate the INR daily during initiation of therapy.

Table 11-16

Factors That Increase Sensitivity to Warfarin

Age older than 75 years
Weight <45 kg

Clinical congestive heart failure
Clinical hyperthyroidism
Decreased oral intake
Diarrhea
Drug–drug interactions
Elevated baseline INR (>1.4)
End-stage renal disease
Fever
Hepatic disease
Hypoalbuminemia
Known CYP2C9 or VKORC1 variant
Malignancy
Malnutrition
Postoperative status

CYP, cytochrome P450; INR, international normalized ratio; VKORC1, vitamin K epoxide reductase complex 1.

	Days/dose (mg)	
Day-3 INR	3	4
<1.3	15	15
1.3–1.4	10	10
1.5–1.6	10	5
1.7–1.9	5	5
2.0–2.2	2.5	2.5
2.3–3.0	0	2.5
>3.0	0	0

	Days/dose (mg)		
Day-5 INR	5	6	7
<2.0	15	15	15
2.0–3.0	7.5	5	7.5
3.1–3.5	0	5	5
>3.5	0	0	2.5
<2.0	7.5	7.5	7.5
2.0–3.0	5	5	5
3.1–3.5	2.5	2.5	2.5
>3.5	0	2.5	2.5
<2.0	15	5	5
2.0–3.0	2.5	5	2.5
3.1–3.5	0	2.5	0
>3.5	0	0	2.5
<2.0	2.5	2.5	2.5
2.0–3.0	2.5	0	2.5
3.1–4.0	0	2.5	0
>4.0	0	0	2.5

Figure 11-4 Warfarin initiation dosing algorithm based on starting with 10-mg doses on days 1 and 2. INR, international normalized ratio. (Source: Reprinted with permission from Kovacs MJ, Anderson DA, Wells PS, et al. Prospective assessment of a nomogram for the initiation of oral anticoagulant therapy for outpatient treatment of venous thromboembolism. *Pathophysiol Haemost Thromb*. 2002;32(3): 131–133. © 2002 Karger Publishers, Basel, Switzerland.)

Table 11-17
Warfarin Initiation for Outpatients Using the Average Daily

Dosing Method

	Nonsensitive Patients	Sensitive Patients[a]
Initial dose	5 mg daily	2.5 mg daily
First INR	3 days	3 days
<1.5	7.5–10 mg daily	5–7.5 mg daily
1.5–1.9	5 mg daily	2.5 mg daily
2.0–3.0	2.5 mg daily	1.25 mg daily
3.1–4.0	1.25 mg daily	0.5 mg daily
>4.0	Hold	Hold
Next INR	2–3 days	2–3 days
Subsequent dosing and monitoring	Continue dose escalation and frequent monitoring until lower limit of therapeutic range is reached.	

INR, international normalized ratio.

[a]See Table 11-16 on factors that increase sensitivity to warfarin.

Source: Warfarin Use in Adults: Clinical Care Guideline, University of Illinois Hospital and Health Sciences System.

Flexible initiation of warfarin is an alternative approach for starting therapy that is based on evaluating the rate of increase in the INR and making daily dosing adjustments based on daily INR evaluation, with a goal of determining the eventual maintenance dosing requirement. A popular flexible initiation nomogram is readily cited.[79,80,81] Using this nomogram, warfarin can be initiated with either a 10-mg or a 5-mg starting dose, with daily dosing adjustments based on the rate of increase in the INR. Flexible initiation does not necessarily shorten the time to reach the goal INR, and initiating therapy with a 10-mg dose as described in some protocols may be associated with an increased risk of early overanticoagulation in

certain patients. Nonetheless, these methods offer a more individualized approach to initiation of therapy.

The baseline INR for A.W. was 1.0. Using a flexible initiation protocol, the first dose of warfarin should be 10 mg administered in the evening on the first day of hospitalization. Subsequent INR values obtained daily will guide dosing requirements until a therapeutic INR is reached. The order for warfarin 10 mg orally every evening for three doses should be discontinued and replaced with daily orders for warfarin and INR monitoring.

Intensity and duration of therapy

Case 11-5, Question 5: What is the goal INR for A.W., and how long should anticoagulation be continued?

In patients with DVT or PE, warfarin doses that prolong the PT to an INR of 2.0 to 3.0 are defined as regular intensity therapy. This therapeutic range is recommended to maximize the antithrombotic effect of warfarin while minimizing potential bleeding complications associated with excessive anticoagulation.[6] Once formed, venous clots adhere to the blood vessel wall. Thus, the first step in the resolution of a thrombus involves covering the clot with a layer of endothelial cells to prevent additional platelet aggregation at the site of vessel injury. This endothelialization process generally takes 7 to 10 days to be completed. Initial anticoagulant treatment is used to prevent clot extension while allowing adequate endothelialization to occur. Continued anticoagulation prevents further clotting.

The appropriate duration of warfarin therapy is based on the likelihood of a recurrent venous thromboembolic event and the risk of bleeding in each patient (see Table 11-9). Patients with unprovoked (idiopathic) DVT or PE should be treated for at least 3 to 6 months, but considered for indefinite therapy as their likelihood of having a recurrent event can be as high as 30% over 5 years.[18,37] Patients with DVT or PE associated with transient or reversible risk factors (provoked VTE) are usually treated for 3 to 6 months, as in

the case of A.W., whose VTE-provoking risk factor was a prolonged car ride, because the risk of recurrence is lower (~10% over 5 years). In cancer-associated thrombosis, first-line treatment consists of DOACs (in patients without gastric or gastroesophageal lesions), or LMWH (in patients with gastric or gastroesophageal lesions), with fondaparinux, UFH, and warfarin also being options. Considerations include individual patient bleeding risk, patient preferences, tolerability, and drug costs.[82–84]

Adverse effects

Case 11-5, Question 6: What possible adverse effects from oral anticoagulation therapy should be considered in A.W. and how should they be monitored?

Hemorrhage

Bleeding is the most common adverse effect associated with anticoagulation. A summary of experimental and observational inception cohort studies determined that the average annual frequency of fatal, major, and all (major or minor) bleeding in patients treated with warfarin was 0.6%, 3%, and 9.6%, respectively.[32] However, wide variation in bleeding frequencies has been reported, likely due to differences in patient characteristics, treatment protocols, and the definition and assessment of bleeding among trials.

The most common sites for anticoagulation-related bleeding are the nose, oral pharynx, and soft tissues, followed by the GI and urinary tracts. Hemarthrosis (bleeding into joint spaces) and retroperitoneal and intraocular bleeding represent less common hemorrhagic complications of anticoagulation therapy.[6] GI and urinary tract bleeding in anticoagulated patients is often caused by previously undiagnosed lesions. Menstrual blood flow may also be increased and prolonged in females taking anticoagulants. This problem may be clinically significant if there is an underlying

pathologic condition (ovarian cysts, uterine fibroids, or polyps) resulting in abnormal vaginal bleeding.

For VTE treatment, the DOACs rivaroxaban and apixaban both showed significantly lower rates for major bleeding in clinical trials compared to warfarin, whereas edoxaban and dabigatran showed comparable rates. A meta-analysis demonstrated no statistically significant differences for efficacy and safety associated with most treatment strategies used to treat acute VTE compared with the LMWH/VKA combination.[85] However, it showed that the UFH/VKA combination is associated with a higher rate of recurrent VTE and that rivaroxaban and apixaban demonstrated a lower risk of major bleeding.

Although it is uncommon, intracranial bleeding resulting in hemorrhagic stroke represents the most common cause of fatal bleeding associated with warfarin therapy. Rates of intracranial hemorrhage associated with anticoagulants have been estimated to range from 0.3% to 2%, and up to 60% are fatal.[6] The DOACs have been shown to be as effective as warfarin for stroke prevention in patients with atrial fibrillation and are associated with lower rates of intracranial hemorrhage and reduced all-cause mortality. However, all of the DOACs, except for apixaban, are associated with a 25% increased risk of GI bleeding.[86]

Many factors influence the risk of hemorrhagic complications associated with warfarin. The frequency of bleeding is higher in the first 3 months of therapy than during the subsequent months.[87] Unlike heparin, the intensity of anticoagulation with warfarin directly influences the risk of bleeding, including intracranial hemorrhage.[88] Other patient-specific variables that influence the risk of warfarin-associated bleeding include a history of GI bleeding, serious comorbid disease (including malignancy), and concomitant therapy with aspirin, clopidogrel, or nonsteroidal anti-inflammatory drugs (NSAIDs).[6]

Several bleeding risk scores are available, including HAS-BLED (*H*ypertension, *A*bnormal renal or liver function, *S*troke, *B*leeding, *L*abile INR, *E*lderly, *D*rugs and alcohol) and ATRIA (anticoagulation and risk factors in atrial fibrillation), which may identify patients at

higher risk for bleeding.[89,90] A meta-analysis showed that the HAS-BLED has the best evidence for predicting bleeding risk in atrial fibrillation.[91] None of these bleeding risk scores have been very effective at predicting risk of major or fatal bleeding in the first 3 months of anticoagulation for VTE, and none have performed well in the elderly in predicting major bleeding in the first 90 days of anticoagulation for VTE.[92–96]

Bleeding complications in A.W. can be minimized by careful attention to the signs and symptoms of bleeding by the patient and her caregivers, maintenance of the INR within the therapeutic range, avoidance of therapy with concomitant drugs known to increase the risk of bleeding or to increase the INR, and routine outpatient follow-up for INR monitoring and clinical assessment.

Skin Necrosis

Warfarin-induced skin necrosis is a rare but serious adverse effect of oral anticoagulation, occurring in ~0.01% to 0.1% of patients treated with warfarin.[97] Patients present within 3 to 6 days of the initiation of warfarin therapy with painful discoloration of the breast, buttocks, thigh, or penis. The lesions progress to frank necrosis with blackening and eschar. Skin necrosis appears to be the result of extensive microvascular thrombosis within SC fat and has been associated with hypercoagulable conditions, including protein C or protein S deficiency. In these patients, rapid depletion of protein C before depletion of vitamin K–dependent clotting factors during early warfarin therapy can result in an imbalance between procoagulant and anticoagulant activity, leading to initial hypercoagulability and thrombosis. Adequate use of injectable UFH, LMWH, or fondaparinux during initiation of warfarin can prevent the development of early hypercoagulability.

Warfarin therapy should be discontinued in patients who develop skin necrosis. However, subsequent warfarin therapy is not necessarily contraindicated if it is required for treatment or prevention of thromboembolic disease. In patients with protein C or protein S deficiency and a history of skin necrosis, warfarin therapy

can be restarted at low dosages if given with UFH/LMWH/fondaparinux. Therapy is maintained until the INR has been within the therapeutic range for 72 hours. Supplementation of protein C through administration of fresh frozen plasma also may be indicated.

Purple Toe Syndrome

Purple toe syndrome is a rarely reported adverse effect that typically occurs 3 to 8 weeks after the initiation of warfarin therapy and is unrelated to intensity of anticoagulation.[98] Patients initially present with painful discoloration of the toes that blanches with pressure and fades with elevation. The pathophysiology of this syndrome has been related to cholesterol microembolization from atherosclerotic plaques, leading to arterial obstruction. Because cholesterol microembolization has been associated with renal failure and death, warfarin therapy should be discontinued in patients who develop purple toe syndrome.

Patient education

CASE 11-6

QUESTION 1: E.N. is a 42-year-old male newly diagnosed with unprovoked DVT. He will be treated as an outpatient with enoxaparin 1.5 mg/kg SC daily and started on warfarin 5 mg PO daily using average daily dosing initiation. His primary care physician would like him to receive follow-up care in the medical center's pharmacist-managed anticoagulation clinic.

What are the benefits of formal anticoagulation management services?

One of the keys to successful oral anticoagulant therapy is appropriate outpatient management. In comparison with routine medical care, management of warfarin therapy by anticoagulation clinics is associated with significant reductions in bleeding and thromboembolic complications, with reductions in the rates of warfarin-related hospital admissions and ED visits, and with outcome-based cost savings for health care organizations.[99]

Specialized anticoagulation management services, often led by pharmacists, offer many benefits for the management of anticoagulation therapy, including improved dosing regulation, continuous patient education, early identification of risk factors for adverse events, and timely intervention to avoid or minimize complications, and have been widely recommended.[41,100] E.N.'s referral to a pharmacist-managed anticoagulation clinic is likely to improve his overall satisfaction with care and his clinical outcomes.

The availability of portable INR self-testing devices also allows the option of anticoagulation monitoring in the home setting. Patient self-testing and patient self-management of INRs have been suggested for suitable patients who have been well educated and have demonstrated competency to perform the tests.[41] For patients who may prefer this monitoring method, a structured education and follow-up program should be designed and integrated with the patient's provider or the anticoagulation management service.

Case 11-6, Question 2: At his initial visit to the anticoagulation clinic, E.N. will receive extensive education about his warfarin therapy. What information should be conveyed to him by his anticoagulation provider to ensure the safety and efficacy of warfarin therapy?

Successful warfarin therapy depends on the active participation of knowledgeable patients.[6] The anticoagulant effect of warfarin is influenced by various factors, and fluctuations in the intensity of the anticoagulant effect of warfarin can increase the risk of both hemorrhagic complications and recurrent thromboembolism. Pharmacists and other providers can improve adherence to the medication schedule, as well as ensure the safety and efficacy of warfarin therapy, by providing appropriate education to patients treated with this agent.

Key elements that form the basis of a thorough patient education program for anticoagulation therapy are listed in **Table 11-18**. This information may be conveyed through written teaching materials, recorded instruction, individual or group discussion, or a combination of these approaches. Many useful educational tools are available

from the manufacturers of the oral anticoagulants and from other noncommercial sources.

Table 11-18
Key Elements of Patient Education Regarding Oral Anticoagulation

Identification of generic and brand names
Purpose of therapy
Expected duration of therapy
Dosing and administration
Visual recognition of drug and tablet strength
What to do if a dose is missed
Recognition of signs and symptoms of bleeding
Recognition of signs and symptoms of thromboembolism
What to do if bleeding or thromboembolism occurs
Potential for interactions with prescription and over-the-counter medications and natural/herbal products
Limiting use of alcohol
Avoidance of pregnancy
Significance of informing other health care providers that patient is taking anticoagulation, and when to notify anticoagulation provider when invasive procedures are being scheduled
When, where, and with whom follow-up will be provided
Dabigatran only: Swallow whole, keep in original container, caution about potential for GI upset
Rivaroxaban only: Take with food (evening meal).
Warfarin only: importance of INR monitoring and expected frequency, consistency of vitamin K

GI, gastrointestinal; INR, international normalized ratio.

E.N. should receive extensive education about warfarin therapy in an individual teaching session or an organized education program. A wallet card, medical bracelet, or an alternative method of identifying him as a patient treated with warfarin should be provided. The health

care provider who assumes responsibility for his outpatient warfarin therapy will need to provide continuing reinforcement of the essential elements of medication information at each follow-up visit.

Case 11-6, Question 3: After receiving 6 days of enoxaparin therapy and six doses of warfarin 5 mg/day PO, E.N.'s INR is 2.4. Enoxaparin is discontinued and E.N. is instructed to continue his current dosage of warfarin. He is scheduled to return to the anticoagulation clinic in 1 week for reevaluation. At that time, his INR is 1.7. What factors might account for this change in the intensity of anticoagulation?

Factors that influence warfarin dosing

Patients should always be questioned about their understanding of the prescribed dose and their adherence to the prescribed regimen. Questions might include, "What dose of the medication have you been taking?" "What time of the day do you take your medication?" and "How many times in the past week did you miss a dose of your medication?" If there is no evidence of misunderstanding of the correct dose or of noncompliance, numerous other factors that are known to influence warfarin dosing requirements in individual patients during both initiation and maintenance phases of therapy should be considered. Changes in dietary vitamin K intake, underlying disease states and clinical condition, alcohol ingestion, genetic factors, and concurrent medications can significantly change the intensity of therapy, resulting in the need for dosing adjustments to maintain the INR within the therapeutic range. In a dosing cohort of 1015 patients on warfarin therapy, body surface area, age, target INR, amiodarone use, smoker status, race, current thrombosis, VKORC1 polymorphism 1639/3673 G.A, CYP2C9(*)3, and CYP2C9(*)2 were all independent predictors of warfarin therapeutic dose.[101]

Dietary Vitamin K Intake

The two primary sources of vitamin K in humans are the biosynthesis of vitamin K_2 (menaquinone) by intestinal bacteria and dietary intake

of vitamin K_1 (phytonadione). The U.S.-recommended daily allowance for vitamin K is 70 to 140 µg/day, and the typical Western diet provides ~300 to 500 µg/day.[102] Vitamin K is found in high concentrations in certain foods, including green leafy vegetables (asparagus, broccoli, Brussels sprouts, cabbage, cauliflower, collard greens, endive, kale, lettuce, parsley, spinach, and turnip greens), soy milk, certain oils, certain nutritional supplements, and multiple vitamin products.

Variations in vitamin K intake have been linked to INR fluctuations in patients taking warfarin.[103,104] In addition, diets high in vitamin K content have been associated with acquired warfarin resistance, defined as excessive warfarin dosing requirements to reach a therapeutic INR range.[105] Numerous cases have also been reported in which patients previously stabilized with warfarin experienced elevations in INR with or without hemorrhagic complications when dietary sources of vitamin K were eliminated. Conversely, reductions in INR with or without thromboembolic complications have been reported in patients in whom dietary sources of vitamin K have been added.

This data illustrates the potential clinical significance of dietary changes in patients taking warfarin. To minimize these potential effects, E.N. should be counseled to maintain a consistent intake of dietary vitamin K.[106] His final warfarin maintenance dose will be partially influenced by his typical diet. However, restriction of dietary vitamin K intake is unnecessary, except in cases of significant resistance to the anticoagulant effect of warfarin. E.N. should be aware of the types of foods and supplements that contain large quantities of vitamin K, and should be counseled to maintain a consistent diet, to avoid bingeing on foods high in vitamin K content, and to report significant dietary changes to his health care provider. Appropriate assessment and follow-up are essential to prevent hemorrhagic or thromboembolic complications that may arise from changes in INR resulting from dietary alterations.

Underlying Disease States and Clinical Conditions

The presence or exacerbation of various medical conditions can also influence anticoagulation status[73] (**Table 11-19**). Diarrhea-associated alterations in intestinal flora can reduce vitamin K absorption, resulting in elevations in INR. Fever enhances the catabolism of clotting factors and can increase INR. Heart failure, hepatic congestion, and liver disease can also cause significant elevations in INR because of a reduction in warfarin metabolism. End-stage renal disease is associated with decreased CYP2C9 activity, resulting in lower warfarin dose requirements.

Table 11-19
Warfarin Interactions With Disease States and Clinical Conditions

Clinical Condition	Effect on Warfarin Therapy
Advanced age	Increased sensitivity to warfarin because of reduced vitamin K stores and/or lower plasma concentrations of vitamin K–dependent clotting factors
Pregnancy	Teratogenic; avoid exposure during pregnancy.
Lactation	Not excreted in breast milk; can be used postpartum by nursing mothers
Alcohol use	▪ Acute ingestion: inhibits warfarin metabolism, with acute elevation in INR ▪ Chronic ingestion: induces warfarin metabolism, with higher dose requirements
Liver disease	▪ May induce coagulopathy by decreased production of clotting factors, with baseline elevation in INR ▪ May reduce clearance of warfarin
Kidney disease	Reduced activity of CYP2C9, with lower warfarin dose requirements
Heart failure	Reduced warfarin metabolism because of hepatic congestion
Nutritional status	Changes in dietary vitamin K alter response to warfarin.
Tube feedings	Decreased sensitivity to warfarin, possibly caused by changes in absorption or vitamin K content of nutritional supplements

Smoking and tobacco use	▪ Smoking: may induce CYP1A2, increasing warfarin dosing requirements ▪ Chewing tobacco: may contain vitamin K, increasing warfarin dosing requirements
Fever	Increased catabolism of clotting factors, causing acute increase in INR
Diarrhea	Reduction in secretion of vitamin K by gut flora, causing acute increase in INR
Acute infection/inflammation	Increased sensitivity to warfarin

CYP, cytochrome P450; INR, international normalized ratio.

The impact of changes in thyroid function on warfarin dose requirements is controversial.[107] It had been suggested that levothyroxine initiation accelerates clotting factor catabolism, enhancing warfarin's anticoagulation effect; however, a retrospective review did not show a difference in the mean warfarin dose/INR ratios before and after levothyroxine initiation, suggesting that no clinical interaction exists, and additional monitoring may not be necessary.[107,108]

Acute physical or psychological stress has been reported to increase INR. Increased physical activity has also been reported to increase the warfarin dosing requirement. Smoking can induce CYP1A2, which may increase warfarin metabolism in certain patients, resulting in increased dose requirements.[109] Owing to its high vitamin K content, chewing smokeless tobacco can suppress the INR response.[110]

Thorough education of patients taking warfarin should include detailed attention to recognizing the signs and symptoms of changes in underlying disease states and clinical conditions that can influence warfarin dosing requirements. They should be instructed to contact their anticoagulation management program whenever changes that might influence INR and warfarin dose requirement occur.

Alcohol Ingestion

Chronic alcohol ingestion has been associated with the induction of the hepatic enzyme systems that metabolize warfarin. Therefore, warfarin dosing requirements are sometimes higher in patients who are alcoholic. Conversely, acute ingestion of large amounts of alcohol can slow warfarin metabolism through competitive inhibition of metabolizing enzymes, leading to elevations in INR and an increased risk of bleeding complications.[6,106] It is believed that moderate intake of alcoholic beverages is not associated with alterations in the metabolism or the therapeutic effect of warfarin as measured by INR. Patients taking warfarin should be educated to limit their alcohol consumption to less than one to two alcoholic beverages per day. Chronic drinkers should be counseled to limit their drinking and maintain a regular pattern to avoid fluctuations in INR.[106] E.N. does not need to abstain from drinking alcoholic beverages in moderation, but he should be counseled to avoid the sporadic ingestion of large amounts of alcohol.

Conversely, alcoholic liver disease (ie, cirrhosis) can alter multiple hemostatic mechanisms and reduce the production of hepatic clotting factors. Decreased production and clearance of vitamin K–dependent clotting factors accounts for the prolonged PT and INR often seen in these patients. Therefore, an increased response to warfarin would be expected in patients with liver impairment. Worsening liver function is also a predictor of bleeding complications and patients with end-stage liver disease are at increased risk for bleeding. Before instituting warfarin therapy in these patients, the risks of bleeding associated with both the underlying liver disease and warfarin therapy must be weighed against the benefit of preventing thromboembolic events. If warfarin is indicated, the best approach would be to use a cautious initiation and dose titration approach by starting with lower doses and titrating up slowly to goal. Small increases in dosage should be made, if indicated, recognizing that the full effect of any dose adjustment may be delayed in patients with severe liver dysfunction. Monitoring for bleeding complications is essential, even at goal INR ranges, when warfarin is used in patients with liver dysfunction.

Genetic Factors

The CYP2C9 and VKORC1 genotypes have been associated with warfarin dose requirements, and dosing algorithms incorporating genetic and clinical information have been shown to be predictive of stable warfarin dose.[111] However, dosing algorithms that incorporate CYP2C9 genotype and VKORC1 haplotype along with other patient characteristics to predict warfarin maintenance doses showed mixed results in randomized, prospective clinical trials.[112–115] Based on current data failing to show a clear benefit, ACCP recommends against the routine use of pharmacogenetic testing for guiding doses of VKA (grade 1B).[22]

Case 11-6, Question 4: How should E.N. be assessed and evaluated at this clinic appointment?

At each clinic visit, E.N. should be assessed for signs and symptoms of bleeding, and for signs and symptoms of clot progression and/or recurrence. The accuracy and reliability of the INR test should be also considered. In addition, E.N. should be asked about missed or extra doses of warfarin, dietary changes (increases or decreases in vitamin K, alcohol use), medication changes, recent illnesses (such as nausea/vomiting/fever/chills/diarrhea), any recent falls, and any known upcoming procedures. Regardless of the INR result, all factors that may influence E.N.'s anticoagulation status should be evaluated carefully.

Dosing adjustments

Case 11-6, Question 5: After a thorough assessment, it is determined that E.N. has adhered to his prescribed warfarin dosage schedule and that there is no apparent explanation to account for his reduction in INR. How should his warfarin dosage be adjusted?

When over- or underanticoagulation is verified, an adjustment in warfarin dosing may be necessary. **Table 11-20** describes approaches to warfarin dosing adjustments for maintenance therapy. Typically, dosing adjustments of 5% to 20% of the total daily dose (or the total weekly dose) are appropriate to reach the therapeutic range.[116] Because warfarin does not follow linear kinetics, small adjustments in dose can lead to large INR changes, and thus large dose adjustments (ie, >20% increase or decrease of the total weekly dose) are not recommended. These maintenance dosing guidelines should only be applied to patients who have reached a steady-state dose and not in the initiation phase of therapy.

Table 11-20
Warfarin Dose Adjustment Nomogram for Maintenance Therapy

INR (Goal 2–3)	Suggested Change in Total "Weekly" Dose
<1.5	Give extra one-time daily dose and increase weekly dose by 10%–20%.
1.5–1.9	Increase weekly dose by 5%–15% (may give extra one-time daily dose).[a]
2.0–3.0	Maintain current dose.
3.1–4.0[b]	Hold up to one daily dose and decrease weekly dose by 5%–20%.[a]
4.1–5.0[b]	Hold up to two daily doses and decrease weekly dose by 10%–20%.[a]

[a]If transient cause identified, may need not increase/decrease weekly dose.

[b]Assumes no active bleeding.

Source: Warfarin Use in Adults: Clinical Care Guideline, University of Illinois Hospital and Health Sciences System.

Because E.N. is currently taking 5 mg daily, an adjustment of 15% would increase his dosage to ~5.5 mg/day. This dosing adjustment can be made by having him take one 5-mg tablet and half of a 1-mg tablet each day (same daily dosing) or by having him take 7.5 mg 2 days per week and 5 mg all other days of the week (alternate-day

dosing). Patient preference about breaking tablets in half, the likelihood of confusion about different tablet sizes, and potential confusion on taking different doses on different days of the week should be the primary considerations when selecting a dosing method.[117]

Frequency of follow-up

Case 11-6, Question 6: E.N. agrees to increase his warfarin dosage to 5.5 mg/day. A new prescription for 1-mg tablets is written for him, and he is instructed about the use of these tablets. When should his INR be reassessed and his anticoagulation status, including physical assessment, be reevaluated?

It will take several days for his INR to reach a new steady state because of the long elimination half-lives of both warfarin and the vitamin K–dependent clotting factors. His INR should be rechecked ~1 week after a dosing adjustment has been made. Once a stable dose has been reached, patient assessment and INR monitoring typically occurs every 4 to 6 weeks. However, if E.N. displays any signs of medical instability or nonadherence, a follow-up schedule of every 1 to 2 weeks is indicated (**Table 11-21**). For carefully selected patients with well-controlled INRs, recall frequencies up to 12 weeks can be recommended.[22,41] For patients taking warfarin with previously stable therapeutic INRs who present with a single out-of-range INR of ≤0.5 below or above therapeutic, continuing the current dose and testing the INR within 1 to 2 weeks is suggested, rather than changing the overall daily dose.[22]

Table 11-21
Frequency of International Normalized Ratio Monitoring and Patient Assessment During Warfarin Therapy

Initiation Therapy	
Inpatient initiation	Daily
Outpatient flexible initiation method	Daily through day 4, then within 3–5 days

Outpatient average daily dosing method	Within 3–5 days, then within 1 week
After hospital discharge	Within 3–5 days
First month of therapy	Every 1–4 days until therapeutic, then weekly
Maintenance Therapy	
Medically stable inpatients	Every 1–3 days
Medically unstable inpatients	Daily
After hospital discharge	If stable, within 3–5 days; if unstable, within 1–3 days
Routine follow-up in medically stable and reliable patients	Every 4–12 weeks
Routine follow-up in medically unstable or unreliable patients	Every 1–2 weeks
Dose held today for significant overanticoagulation	In 1–2 days
Dosage change today	Within 1–2 weeks
Dosage change <2 weeks ago	Within 2–4 weeks

Management of overanticoagulation

CASE 11-7

QUESTION 1: V.G., who has been taking warfarin for 3 years with good INR control, noted bright red blood after a bowel movement (hematochezia) that resolved and has not returned. In the ED, an INR of 5.6 was reported. Her Hct and Hgb were both within normal limits, as were her vital signs. A stool guaiac test result was positive, and multiple external hemorrhoids were detected.

How should this adverse effect of warfarin be treated in V.G.?

Management of overanticoagulation depends on the clinical presentation of the patient. In the case of an elevated INR without bleeding complications, interruption of warfarin therapy by holding one or two doses until the INR returns to the therapeutic range is usually sufficient.[22] Minor bleeding complications accompanied by an elevated INR can also be managed by withholding warfarin therapy

for a short period until bleeding resolves. In either case, the patient should be questioned to determine a possible cause for the overanticoagulation, including intake of extra doses of warfarin, changes in diet or alcohol intake, changes in underlying medical conditions, or the use of other medications. In some cases, no apparent explanation is identified. Depending on the cause, a reduction in the maintenance dosing of warfarin may be necessary.

The time required for INR to return to the therapeutic range after warfarin is withheld depends on several patient characteristics. Advanced age, lower warfarin maintenance dose requirements, and higher INR are associated with increased time for INR correction.[118] Other factors that can prolong the time for INR to return to the therapeutic range include decompensated heart failure, active malignancy, and recent use of medications known to potentiate warfarin.

Although previously recommended and commonly used, low-dose vitamin K in patients with elevated INR 4.5 to 10 and are not bleeding is not associated with a reduction in major bleeding, and is no longer routinely recommended.[22] However, patients with INRs >10 and are not bleeding may benefit from small doses of oral vitamin K 1 to 2.5 mg. The decision on whether to give vitamin K to patients who are not bleeding needs to be based on the patient's individual risk for bleeding and thrombosis.[22] An oral dose of 1 to 2.5 mg can correct overanticoagulation in 24 to 48 hours without causing prolonged resistance to warfarin therapy, a problem commonly seen with larger (10 mg) doses of vitamin K. Intramuscular administration is contraindicated owing to the risk of hematoma formation, and SC administration of vitamin K is not recommended because of variable absorption.[119]

IV doses of 0.5 to 1 mg of vitamin K can correct overanticoagulation within 24 hours.[6] This approach is also useful for reversal of therapeutic anticoagulation before invasive procedures and can be used to correct overanticoagulation in high-risk cases. IV vitamin K should be diluted in a minimum of 50 mL IV fluid and administered with an infusion pump over a minimum of 20 minutes to prevent flushing, hypotension, and cardiovascular collapse.[6]

Although these symptoms resemble anaphylaxis, the mechanism of this adverse response is unclear. It is not known whether it is caused by phytonadione or by the vehicle in which phytonadione is formulated. If this adverse reaction occurs, administration of epinephrine may be indicated as well as other standard measures to support blood pressure and maintain the airway.

Rapid reversal of warfarin therapy is indicated in the setting of major, life-threatening bleeding (ie, severe GI bleeding, intracranial hemorrhage). Fresh frozen plasma or factor concentrates to replace clotting factors will decrease the INR for 4 to 6 hours and should be administered as needed with careful monitoring of volume status.[22] Supplementation with high-dose IV vitamin K (10 mg) may also be indicated. Administration of IV vitamin K will reverse the effects of warfarin within 6 to 12 hours. However, if continued warfarin therapy is indicated when bleeding resolves, anticoagulation with heparin may be necessary for as long as 7 to 14 days until the effect of high-dose vitamin K is diminished and warfarin responsiveness returns.

Hematochezia may be an early sign of more serious bleeding, but in many cases, this condition is associated with minor bleeding episodes and identifiable causes such as hemorrhoids. In a reliable patient, holding the warfarin until the INR returns to a therapeutic level usually suffices, along with the addition of a bowel regimen to prevent straining with bowel movements, topical cream to minimize swelling and irritation, increased fluids, and/or increased fiber intake. Because V.G. appears to have only minor bleeding from the stool, is hemodynamically stable, and has a stable Hgb, withholding warfarin is appropriate. If the patient has never had a colonoscopy, then evaluation for the appropriateness of this test may be warranted.

Use in pregnancy

CASE 11-8

Question 1: M.P., a 25-year-old female, takes warfarin for chronic therapy for recurrent DVTs. She tells you today that she missed her menses and thinks she may be pregnant. A pregnancy test ordered today returned a positive result.

What effects might warfarin have on the fetus? Are UFH or LMWHs safer alternatives in this situation?

Warfarin and other coumarin anticoagulants cross the placental barrier and may place the fetus at risk for hemorrhage and teratogenic effects.[120,121] Up to 30% of pregnancies that involve exposure to coumarin result in abnormal liveborn infants, and up to 30% in spontaneous abortion or stillbirth. Congenital abnormalities such as stippled calcifications and nasal cartilage hypoplasia primarily occurred in infants born to mothers receiving warfarin during the first trimester of pregnancy, with the highest risk during weeks 6 to 12. Other abnormalities, involving the central nervous system and eyes, are more likely to occur when the mother is taking warfarin later in the pregnancy. In addition, because warfarin crosses the placenta, fatal bleeding complications may occur.

Females of childbearing age who require anticoagulation should be counseled about options for contraception. Patients who become pregnant while receiving warfarin should be informed of the risks of continued anticoagulation to the fetus, as well as the risk to themselves of discontinuing anticoagulation.

Other options for pregnant females who require anticoagulation include UFH and LMWHs.[120,121] Because these agents do not cross the placenta, they are preferred over warfarin for use in pregnancy. Many clinical trials have validated the safety and efficacy of UFH and LMWHs in the prevention and treatment of DVT and PE during pregnancy, with LMWH generally preferred to UFH for long-term management throughout pregnancy.[120–123] When used at full doses for the treatment of VTE during pregnancy, dosing must be adjusted throughout the pregnancy to account for the expected increase in the body weight of the mother and the reported increase in clearance of LMWH during pregnancy.[123] Selected current recommendations for use of anticoagulants in pregnancy are outlined in **Table 11-22**.

Table 11-22
Selected Recommendations for Anticoagulation During

Pregnancy

Clinical Situation	Antepartum Options	Postpartum
1. Prophylaxis: Prior VTE		
Low risk of recurrent VTE (single episode of VTE associated with transient RF not related to pregnancy or use of estrogen)	Clinical vigilance	Prophylactic or intermediate-dose LMWH or VKA (INR 2–3) for 6 weeks over no prophylaxis
Moderate/high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term AC)	Prophylactic or intermediate-dose LMWH over clinical vigilance or routine care	Prophylactic or intermediate-dose LMWH or VKA (INR 2–3) for 6 weeks over no prophylaxis
On long-term VKA	Adjusted-dose LMWH or 75% of a therapeutic dose of LMWH throughout pregnancy, over prophylactic dose LMWH	Resumption of long-term AC
2. Prophylaxis: No Prior VTE		
Homo-FVL or prothrombin mutation and positive FH for VTE	Prophylactic or intermediate-dose LMWH	Prophylactic or intermediate-dose LMWH or VKA (INR 2–3) for 6 weeks over no prophylaxis
All other patients with thrombophilias who have positive FH for VTE	Clinical vigilance	Prophylactic or intermediate-dose LMWH or, in females who are not protein C or -S deficient, VKA (INR 2–3) over routine care
Homo-FVL or prothrombin mutation and no positive FH for VTE	Clinical vigilance	Prophylactic or intermediate-dose LMWH or VKA (INR 2–3) for 6 weeks over routine care

All other thrombophilias with no positive FH for VTE	Clinical vigilance	Clinical vigilance
Long-term oral anticoagulants for mechanical valve replacement	▪ Adjusted-dose SC UFH ▪ Adjusted-dose bid LMWH (adjusted to achieve manufacturer-recommended 4-hour postdose peak anti-factor Xa concentration) ▪ UFH or LMWH (as given earlier) until the 13th week, with substitution by VKA until close to delivery when UFH or LMWH is resumed	Long-term warfarin to prior INR goal with UFH/LMWH overlap until INR above the lower limit of therapeutic range

Adjusted-dose unfractionated heparin (UFH): UFH subcutaneous (SC) q12h in doses adjusted to target a mid-interval activated partial thromboplastin time (aPTT) into the therapeutic range.

Prophylactic LMWH: dalteparin 5000 units SC q24h, tinzaparin 4500 units SC q24h, or enoxaparin 40 mg SC q24h (at extremes of body weight modification of dose may be required).

Intermediate-dose LMWH: dalteparin 5000 units SC q12h, enoxaparin 40 mg SC q12h.

Adjusted-dose LMWH: weight-adjusted, full treatment doses of LMWH, given once or twice daily: dalteparin 200 units/kg daily, tinzaparin 175 units/kg daily, dalteparin 100 units/kg q12h, or enoxaparin 1 mg/kg q12h.

AC: anticoagulation; bid, two times daily; FH, family history; FVL, factor V Leiden mutation; INR, international normalized ratio; LMWH, low-molecular-weight heparin; RF: risk factor; SC, subcutaneous; UFH, unfractionated heparin; VKA: vitamin K antagonist; VTE, venous thromboembolism.

Source: Reprinted from Bates SM. Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e691S–e736S. © 2012 The American College of Chest Physicians. With permission.

After being informed of the risks associated with warfarin, M.P. decided to continue her pregnancy and to begin anticoagulation with LMWH. Because pregnant females were excluded from clinical trials with the DOACs owing to their increased risk for maternal and fetal bleeding, their use in pregnancy is not recommended at this time. Warfarin therapy should be discontinued immediately and LMWH initiated using SC treatment doses as previously described. Dosing adjustments may be required throughout pregnancy based on changes in body weight and clearance, and the routine use of anti-factor Xa monitoring is not recommended. Potential adverse effects of LMWH use, including hemorrhage, thrombocytopenia, and osteoporosis, should be monitored appropriately.

For females desiring spinal anesthesia during delivery, treatment doses of LMWH should be discontinued a minimum of 24 hours before induction of labor, cesarean section, or placement of an epidural catheter, and restarted no sooner than 24 hours postoperatively, and with adequate hemostasis in place.[124] Neuraxial anesthesia should not be used in females on anticoagulation therapy (ie, within 24 hours of the last treatment dose of LMWH, or for patients receiving IV UFHs that have prolonged aPTTs). In patients not receiving epidural catheters, postpartum anticoagulation may be started 12 to 24 hours after delivery as long as there are no bleeding concerns.[124] Consider IV UFH in females at high risk for bleeding, with LMWH reasonable for most females. Restart warfarin when hemostasis has occurred, bridging with UFH or LMWH until the INR is therapeutic. Warfarin, LMWH, and UFH do not accumulate in breast milk and do not induce an anticoagulant effect in the infant and may be used in females who breast-feed[120]; therefore, M.P. can safely breastfeed. The DOACs are not currently recommended during breast-feeding.[121,123]

PREVENTION OF CARDIOGENIC THROMBOEMBOLISM

Atrial Fibrillation

ANTICOAGULATION BEFORE CARDIOVERSION

CASE 11-9

QUESTION 1: T.S., a 66-year-old female with hypertension and no other significant past medical history, presents to the cardiology clinic reporting of several days of fatigue and a "racing heart." On physical examination, her pulse is irregularly irregular, and her heart rate is 120 beats/minute. Using ECG, a diagnosis of atrial fibrillation is made and cardioversion planned.

Should T.S. be anticoagulated before cardioversion?

In atrial fibrillation, atrial activity and atrial enlargement cause stasis of blood within the atria and the left atrial appendage (LAA), which can result in atrial thrombus formation. Atrial thrombus formation increases the risk of systemic embolization; clinical manifestations include arterial embolization of the extremities or embolization of the splenic, renal, or abdominal arteries. However, the most prevalent site of embolization is the cerebral arterial system, resulting in transient ischemic attack (TIA) or stroke with potentially devastating neurologic and functional impairment. Atrial fibrillation carries a fivefold risk of ischemic stroke without thromboprophylaxis.[125]

Both direct current cardioversion and pharmacologic cardioversion using antiarrhythmic drugs expose patients to an initial short-term increase in stroke risk from embolization secondary to resumption of normal atrial mechanical activity (see Chapter 15, Cardiac Arrhythmias). Data from a prospective cohort study of 437 patients noted a stroke incidence of 5.3% in patients with atrial fibrillation who were cardioverted without prior anticoagulation, but a significant reduction in stroke incidence to 0.8% was noted if patients who had received cardioversion were anticoagulated.[126] In addition to preventing the development of new atrial thrombi, anticoagulation allows any thrombus that may be present to endothelialize and adhere to the atrial wall so that the thromboembolic risk is minimized. Based on the assumed time course of thrombus

development, as well as the presumed time course of clot endothelialization, patients who have been in atrial fibrillation for >48 hours or of unknown duration should receive 3 weeks of therapeutic anticoagulation with either warfarin to a target INR of 2.5 (range, 2.0–3.0) or a DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban).[125,127] Despite a lower risk of stroke than that associated with atrial fibrillation, patients with atrial flutter should be treated similarly.

Whether T.S. has been in atrial fibrillation for 48 hours is not known; therefore, she requires a 3-week course of oral anticoagulation before cardioversion is attempted. If T.S. cannot tolerate her heart symptoms despite control of the ventricular response rate, her medical team might consider immediate cardioversion without anticoagulation if transesophageal echocardiography (TEE) is used to rule out left atrial thrombi. TEE is much more sensitive than is transthoracic echocardiography (TTE) to visualize the left atrium and the LAA.

In a clinical trial, 1222 patients with atrial fibrillation for a duration of ≥2 days were randomly assigned to either cardioversion guided by TEE or to conventional anticoagulation before cardioversion.[128] Patients assigned to conventional treatment and patients in the TEE group in whom thrombus was detected received a 3-week course of warfarin before cardioversion. Patients without detectable thrombus by TEE were cardioverted without prior anticoagulation. All patients received 4 weeks of postcardioversion anticoagulation. Thromboembolic rates were identical between patients who received conventional treatment and those whose treatment was guided by TEE.[128]

ANTICOAGULATION AFTER CARDIOVERSION

Case 11-9, Question 2: After 3 weeks of regular intensity warfarin therapy, T.S. is successfully cardioverted to normal sinus rhythm. Should anticoagulation be discontinued?

Despite normalization of atrial electrical activity, restoration of effective atrial mechanical activity after cardioversion of atrial fibrillation can be delayed for up to 3 weeks. In addition, many patients who are cardioverted successfully will revert to atrial fibrillation during the first month. These factors contribute to the recognized delay in stroke presentation after cardioversion in patients with atrial fibrillation. Therefore, anticoagulation should be continued after cardioversion for a minimum of 4 weeks. Longer duration of anticoagulation therapy should be based on the individual patient's thromboembolic risk profile.[125,127]

CASE 11-9, QUESTION 3: Two weeks after successful cardioversion, T.S. presents to the ED with chest palpitations and light-headedness. An ECG is performed and indicates atrial fibrillation again. What decisions regarding anticoagulation need to be made?

ANTICOAGULATION FOR PAROXYSMAL, PERMANENT, OR PERSISTENT ATRIAL FIBRILLATION

Anticoagulation in valvular atrial fibrillation

Atrial fibrillation secondary to valvular heart disease has historically been recognized as a significant risk factor for stroke. Patients with atrial fibrillation who have a history of rheumatic mitral valve disease have a 17-fold higher incidence of stroke than that in matched controls. Patients with valvular atrial fibrillation require long-term, regular intensity anticoagulation with warfarin to a target INR of 2.5 (range, 2.0–3.0) to prevent thromboembolism and stroke. The landmark DOAC trials excluded patients with significant (moderate or severe) mitral stenosis and mechanical heart valves, which have been termed *valvular atrial fibrillation*. To date, DOACs have not been studied in this patient population and should be avoided at this time.[125,127]

Anticoagulation in nonvalvular atrial fibrillation

Nonvalvular heart disease is the most common cause of atrial fibrillation and, similar to valvular heart disease, represents a

significant risk of stroke in patients with atrial fibrillation. Five clinical trials have substantiated the role of warfarin in the primary prevention of systemic embolization and stroke in chronic, nonvalvular atrial fibrillation.[125,127,129] All five trials compared warfarin with a placebo and were terminated before completion because of the substantial benefit of warfarin. In comparison with a placebo, warfarin significantly reduced the risk of stroke from ~5% per year to ~2% per year, with an average relative risk reduction of 67%. Based on the results of these trials, long-term anticoagulation with warfarin to a goal INR of 2.5 (range, 2.0–3.0) is recommended in patients such as T.S., who have atrial fibrillation secondary to nonvalvular heart disease.[125,127,129]

Several clinical trials have attempted to define the comparative efficacy of warfarin versus aspirin in the prevention of stroke associated with atrial fibrillation.[125,127,130] Compared with a placebo or control, aspirin decreases the risk of stroke in patients with atrial fibrillation. However, that reduction is not as substantial as the reduction seen with warfarin. In clinical trials comparing warfarin and aspirin, the risk reduction associated with warfarin is significantly larger than that with aspirin. Subsequent trials have confirmed the superiority of warfarin over the combination of aspirin plus clopidogrel for stroke prevention in atrial fibrillation, and the increased risk of intracranial hemorrhage when aspirin and clopidogrel are combined.[131,132] As such, antiplatelet therapy (aspirin monotherapy or aspirin in combination with clopidogrel) is no longer recommended for stroke prevention in patients with atrial fibrillation. The CHA_2DS_2-VASc score is an individualized risk assessment tool endorsed by ACCP, the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS), and the European Society of Cardiology (ESC), which recommends full anticoagulation in males with a score of >1 and females ≥2[125,127,133] (see Chapter 15, Cardiac Arrhythmias).

Although oral anticoagulation is preferred for stroke prevention in patients with atrial fibrillation, percutaneous LAA occlusion has been approved as an alternative for patients deemed to be poor

candidates for long-term anticoagulation (eg, intracranial bleeding without a reversible cause). LAA occlusion with the Watchman device was noninferior to VKAs for stroke prevention in patients with atrial fibrillation and with lower bleeding rates. Following LAA occlusion with a Watchman device, aspirin 75 to 325 mg daily is initiated indefinitely, whereas warfarin (INR range; 2–3) is used for 45 days postoperatively or until adequate LAA sealing is confirmed by TEE. When warfarin is discontinued, clopidogrel is started for 6 months. The ESC Guidelines also list the use of a DOAC as a possible alternative to warfarin.[127,133] A small retrospective review has shown DOACs to be noninferior to warfarin when used post the Watchman procedure and may result in fewer adverse outcomes.[134] Patients tend to be referred for LAA occlusion when they have a high-bleeding risk. However, many patients previously thought to be poor candidates for warfarin may do well on a DOAC. Recently, a study in the Czech Republic, which included high stroke risk (mean CHA_2DS_2-VASc score of 4.7) and patients with atrial fibrillation at risk for bleeding, showed LAA occlusion was noninferior to DOACs in preventing major atrial fibrillation–related cardiovascular, neurologic, and bleeding events.[135] Similarly, a retrospective analysis of Danish registry data in patients undergoing LAA occlusion with an Amplatzer Amulet Left Atrial Appendage Occluder® device (Amplatzer Amulet Left Atrial Appendage Occluder® by Abbott Medical), was shown to have similar stroke prevention efficacy and lower bleeding when compared to those receiving stroke prevention with a DOAC.[136] Therefore, the decision to undergo LAA occlusion and specific postoperative anticoagulation must be individualized.

Direct Oral Anticoagulants

The direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have all been compared to warfarin for stroke prevention in patients with nonvalvular atrial fibrillation.[137–140]

DOACs are currently recommended over warfarin as first-line therapy for stroke prevention in patients with atrial fibrillation by

ACCP and AHA/ACC/HRS and as an equivalent option to warfarin by the ESC.[125,127,133] Patient-specific characteristics such as age, renal function, weight, concomitant medications, bleeding risk, and past medical history should be considered when selecting the most appropriate anticoagulant for initial therapy. Cost, insurance coverage, and patient preference with regard to number of daily doses, frequency of monitoring, and so on must also be taken into consideration[141] (see Chapter 15, Cardiac Arrhythmias).

The decision to continue long-term anticoagulation with warfarin in T.S. should be based on an evaluation of the likelihood that her atrial fibrillation will become chronic with a paroxysmal, persistent, or permanent presentation, as well as an assessment of her risk of stroke compared with her risk of anticoagulant-associated bleeding complications. Because of her age, history of hypertension, and that she is female (CHA_2DS_2-VASc score of 3), the appropriate strategy should be long-term anticoagulation, either with full-dose DOAC therapy or warfarin at a goal INR of 2.5 (range, 2.0–3.0).

Cardiac Valve Replacement

MECHANICAL PROSTHETIC VALVES

CASE 11-10

QUESTION 1: P.B., a 59-year-old female with a history of rheumatic mitral valve disease, has undergone mitral valve replacement (MVR). A St. Jude™ (Abbott) (bileaflet mechanical) valve has been implanted, and heparin therapy is initiated postoperatively.

Does P.B. require continued anticoagulation with warfarin?

Mechanical prosthetic valves confer a significant thromboembolic risk by providing a foreign surface in contact with blood components on which platelet aggregation and thrombus formation can occur. Valvular thrombosis can impair the integrity of valve function and can lead to embolization with systemic manifestations, including stroke.[142,143] The incidence of thromboembolic complications

depends on the type of artificial valve (caged ball [Starr-Edwards, Edwards Lifesciences] > tilting disk [Medtronic-Hall, Medtronic; Björk-Shiley, Pfizer] > bileaflet [St. Jude™]), as well as the anatomic position of the replacement (dual valve replacement > mitral > aortic).[144]

Long-term anticoagulation is required in patients with mechanical valve replacement because it significantly reduces the risk of stroke and other manifestations of systemic embolization (see Table 11-9). Trials comparing different intensities of oral anticoagulation with warfarin in mechanical valve replacement helped identify the intensity of anticoagulation that protects against thromboembolic risk while reducing the incidence of hemorrhagic complications.[145] Patients with a mechanical aortic valve replacement (AVR) (St. Jude™ bileaflet or single tilting disk) in the aortic position should receive long-term anticoagulant therapy with warfarin to a target INR of 2.5 (range, 2.0–3.0).[142,143] For patients without risk factors who receive a mechanical On-X® (On-X Life Technologies) aortic heart valve, warfarin targeted to an INR of 2.5 (range, 2.0–3.0) in addition to low-dose aspirin is recommended. After the initial 3 months of therapy, the INR goal can be lowered to a range of 1.5–2.0.[143] For all other mechanical valve types in the aortic position (caged ball) or in those with additional risk factors (atrial fibrillation, previous VTE, left ventricular dysfunction, hypercoagulable state), and for any mechanical MVR, chronic warfarin therapy with a target INR of 3.0 (range, 2.5–3.5) is recommended (see Table 11-9). The concurrent use of low-dose aspirin (81 mg daily) is recommended for patients with mechanical mitral or aortic valve at low-bleeding risk.

In 2012, the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial was halted early after demonstrating a significant increase in thromboembolic events such as valve thrombosis, MI, TIA, and stroke as well as a significant increase in bleeding when taking dabigatran versus warfarin in patients with mechanical prosthetic valves.[146] Based on these results as well as on case reports reporting valve thrombosis following transition from warfarin to dabigatran, the FDA issued a MedWatch

safety alert recommendation that dabigatran should not be used in any patient with a mechanical heart valve. Subsequently, dabigatran's product information was also updated to include this contraindication. Based on the results of this trial, no other DOAC has been tested in the population; thus, no DOAC should be used in patients with mechanical prosthetic valves. Therefore, P.B. would be required to continue warfarin indefinitely with a target INR of 3.0 (range, 2.5–3.5) to reduce the risk of stroke and other systemic embolism.

BIOPROSTHETIC VALVES

CASE 11-11

Question 1: E.F., an 82-year-old female with a history of symptomatic aortic stenosis, has received a bioprosthetic (mammalian) AVR.

Is anticoagulant therapy required in E.F.?

Bioprosthetic heart valves extracted from mammalian sources (porcine or bovine xenografts, homografts) are significantly less thrombogenic than are mechanical prosthetic valves. The period of greatest thromboembolic risk appears to be during the first 3 months after implantation. Therefore, anticoagulation with warfarin to an INR goal of 2.5 (range, 2.0–3.0) is recommended for 3 to 6 months following implantation of a bioprosthetic aortic or mitral valve in patients at low risk for bleeding (see Table 11-9). Alternatively, in the absence of other indications for oral anticoagulation, treatment with only aspirin 75 to 100 mg daily is also reasonable in patients with a bioprosthetic aortic or mitral valve. Regardless of whether anticoagulation is initiated, long-term aspirin therapy (75–100 mg) is recommended.[142,143] More about E.F.'s bleeding risk would need to be determined; however, because of her age, long-term aspirin therapy only may be reasonable.[143] The RIVER (*R*ivaroxaban for valvular heart disease and atrial fibrillation) trial was designed to assess the efficacy and safety of rivaroxaban compared with warfarin in those patients with atrial fibrillation receiving a

bioprosthetic mitral valve. The majority of patients were randomized >3 months after receiving the mitral valve implantation. Rivaroxaban was shown to be noninferior to warfarin with respect to mean time until the occurrence of major clinical events (death, major cardiovascular events, or major bleeding at 12 months).[147] The 2017 ESC Guidelines recommend VKA therapy when long-term anticoagulation therapy is needed in patients with a bioprosthetic valve. However, they also suggest that a DOAC may be used in patients with atrial fibrillation associated with a bioprosthesis after the third postoperative month.[148] The 2020 ACC/AHA Guidelines state that the decision to choose warfarin or a DOAC for patients with atrial fibrillation and a bioprosthetic valve should be made in a shared decision-making process based on the CHA_2DS_2-VASc score.[143]

Transcatheter aortic valve implantation (TAVI) is a new technique that avoids the open chest approach. The 2020 AHA/ACC Guidelines recommend lifelong aspirin (75–100 mg daily) with either clopidogrel 75 mg daily for the first 3 to 6 months or warfarin with a goal INR of 2.5 (range, 2.0–3.0) for the first 3 months following surgery in low-bleed risk patients.[143] The GALILEO (*G*lobal study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to *O*ptimize clinical outcomes) trial compared low-dose rivaroxaban (10 mg daily) plus low-dose aspirin (75–100 mg daily) to low-dose aspirin plus clopidogrel (75 mg daily). This trial was terminated prematurely because the rivaroxaban strategy was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than with those in the antiplatelet-based strategy.[149] Therefore, in the absence of other indications for oral anticoagulation, this regimen is contraindicated following TAVI.[143] The POPular TAVI trial randomized patients already receiving anticoagulation with a VKA or DOAC to receive either clopidogrel or no clopidogrel for 3 months following TAVI. Patients receiving anticoagulation alone had a lower incidence of

serious bleeding over 1 year than those receiving anticoagulation plus clopidogrel.[150]

BRIDGE THERAPY

Management of Anticoagulation Around Invasive Procedures

CASE 11-12

QUESTION 1: L.P. is a 48-year-old female with a history of valvular heart disease and a St. Jude™ MVR. She is adequately anticoagulated with warfarin 7.5 mg once daily to a goal INR range of 2.5 to 3.5. Recently, she has reported episodic rectal bleeding and is scheduled for a colonoscopy in several weeks. Her gastroenterologist calls the anticoagulation clinic to determine the most appropriate plan for reversal of her warfarin before the procedure.

What are the periprocedural options?

When an invasive procedure is planned, it is often necessary to reverse the effects of warfarin to minimize the risk of bleeding complications associated with the procedure, which can be worsened by the presence of an anticoagulant. It can take several days for the anticoagulant effect of warfarin to be reversed after discontinuation of the drug, but in that period of time, a patient may be at risk for thromboembolic complications associated with underanticoagulation. *Bridge therapy* is the term that refers to the use of a relatively short-acting injectable anticoagulant (UFH, LMWH) as a substitute for warfarin before and immediately after an invasive procedure to shorten the period of time a patient is without any anticoagulation.[143,151] Because UFH and LMWH have shorter elimination half-lives than does warfarin, they can be stopped just before the invasive procedure without increasing the risk of bleeding associated with the procedure. The last dose of LMWH and SC UFH should be given at least 24 hours before the scheduled procedure,

whereas IV UFH infusions are discontinued 6 hours before the procedure. The timing of the last dose of LMWH may need to be extended based on a patient's renal function because it is renally eliminated. Because of their faster onsets of effect, these agents are resumed after invasive procedures once hemostasis is achieved to establish an immediate degree of anticoagulation. Resumption of therapeutic injectable anticoagulants after a high-bleeding risk surgery should be delayed until at least 48 to 72 hours postoperatively, whereas patients undergoing lower bleeding risk procedures can be restarted 24 hours later. Warfarin is resumed simultaneously, and the bridging anticoagulant is continued until the INR reaches the therapeutic range.[143,151]

Current bridging recommendations are based on clinical trials as well as on results from case series, observational studies, and nonrandomized trials involving patients with various indications for anticoagulation, including valve replacement. The decision to use bridging depends on the risk of bleeding associated with continued anticoagulation for the surgery or procedure to be performed and on the risk of thromboembolism associated with underanticoagulation in the patient in question. A large registry called the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) included patients with atrial fibrillation who underwent temporary interruption of oral anticoagulation therapy and showed that bridging was associated with higher risk of bleeding and adverse events.[152] Shortly after, the results of the BRIDGE (Bridging anticoagulation in patients who require temporary interruption of warfarin therapy for an elective invasive procedure or surgery) trial that randomized patients with atrial fibrillation to receive bridging therapy with LMWH or placebo showed findings similar to that of the ORBIT-AF registry. The study showed no difference in the rate of arterial thromboembolism between the bridging and nonbridging group; however, the bridging group showed significantly higher rates of major bleeding. The mean $CHADS_2$ score was 2.3 and patients with mechanical heart valve or stroke, systemic embolism, and TIA within the previous 12 weeks were excluded from the trial. Major surgical

procedures associated with high rates of arterial thromboembolism and bleeding were also underrepresented. Therefore, the results from the BRIDGE trial should not be applied to patients who were underrepresented.[153] Individualized risk assessment and bridge therapy planning are necessary for each patient who may require temporary discontinuation of warfarin. Recommendations for risk stratification are outlined in **Table 11-23**. In 2017, the ACC published a consensus decision pathway regarding the periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. High-risk patients with a CHA_2DS_2VASc score of 7 to 9 or ischemic stroke, TIA, or systemic embolism within the previous 3 months should likely receive parenteral anticoagulation bridging if warfarin requires interruption. Those at low risk for thromboembolism with a CHA_2DS_2VASc score of <4 or without previous ischemic stroke, TIA, or systemic embolism do not require parenteral bridging if warfarin interruption is required. Patients at moderate risk with a CHA_2DS_2VASc score of 5 or 6 or those with a previous ischemic stroke, TIA, or systemic embolism >3 months prior require further evaluation of patient's individualized bleeding risk. If patients have a high-bleeding risk, bridging therapy is not recommended. However, if patients have a low-bleeding risk, bridging should be considered in those with a history of ischemic stroke, TIA, or systemic embolism.[154] The ACC/AHA also include recommendations regarding bridge therapy in patients with valvular disease in the latest 2020 guidelines. Here, parenteral anticoagulation bridge therapy is recommended in those with mechanical MVR, mechanical AVR with any thromboembolic risk factor, or an older generation AVR unless the bleeding risk outweighs the thromboembolic risk.[143] The bleeding risk of a performed procedure or surgery must also be weighed. Efforts should be made to continue oral anticoagulation in a patient with high thromboembolic risk undergoing a procedure with low-bleeding risk, such as a dental extraction or cataract surgery. **Table 11-24** includes examples of high- versus low-bleeding risk surgeries.

Table 11-23
Risk Stratification for Determining the Need for Bridge Therapy

	Indication for VKA Therapy		
Risk Stratum	**Mechanical Heart Valve**	**Atrial Fibrillation**	**Venous Thromboembolism**
High	■ Any mitral valve prosthesis ■ Older (caged ball) aortic valve prosthesis ■ Recent (within 6 months) stroke or transient ischemic attack	■ $CHADS_2$-VASc score of >7, recent (within 3 months) stroke or transient ischemic attack ■ Rheumatic valvular heart disease	■ Recent (within 3 months) VTE ■ Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin, antiphospholipid antibodies, or multiple abnormalities)
Moderate	■ Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 years	■ $CHADS_2$-VASc score of 5–6 or prior stroke or transient ischemic attack > 3 months previously	■ VTE within the past 3–12 months (consider VTE prophylaxis rather than full intensity bridge therapy) ■ Nonsevere thrombophilic conditions (eg, heterozygous factor V Leiden mutation, heterozygous factor II mutation) ■ Recurrent VTE ■ Active cancer (treated within 6 months or palliative)
Low	■ Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	■ $CHADS_2$-VASc score of 1–4 (no prior stroke or transient ischemic attack)	■ Single VTE occurred >12 months ago and no other risk factors

CHADS2-VASc score, congestive heart failure: 1 pt; hypertension: 1 pt; age: ≥75 years 2 pts; diabetes mellitus: 1 pt; prior stroke or TIA or thromboembolism: 2 pts; vascular disease: 1 pt; age: 65 – 74 years 1 pt; sex category: 1 pt female; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Source: Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e326S–e350S. © 2012 The American College of Chest Physicians. With permission.

Table 11-24
Bleed Risk of Selected Procedures

Minimal Bleeding Risk	**Low-Bleeding Risk (2-day risk of major bleed <2%)**	**High-Bleeding Risk (2-day risk of major bleed >2%)**
Minor dermatologic procedures (eg, excision of basal and squamous skin cancers, actinic keratosis, and premalignant or cancerous skin nevi)	Minor dental procedures (eg, simple dental extractions, restorations, prosthetics, endodontics)	Cancer surgery
Cataract procedures	Cutaneous/lymph node biopsies	Major orthopedic surgery

Dental cleanings, fillings	Shoulder/foot/hand surgery	Reconstructive plastic surgery
	Coronary angiography	Transurethral prostate resection, bladder resection, or tumor ablation
	Gastrointestinal endoscopy +/− biopsy	Nephrectomy, kidney biopsy
	Colonoscopy +/− biopsy	Colonic polyp resection
	Abdominal hysterectomy	Bowel resection
	Hemorrhoidal surgery	PEG placement, ERCP
	Bronchoscopy +/− biopsy	Cardiac, intracranial, or spinal surgery
	Epidural injections with INR <1.2	Surgery in high vascular organs (kidneys, liver, spleen)
	Pacemaker battery change	Any major operation (procedure duration >45 minutes)
	Arthroscopy	Pacemaker or cardioverter-defibrillator device implantation

For other surgeries and bleed risk, see http://jaccjacc.acc.org/Clinical_Document/PMAC_Online_Appendix.pdf

ERCP, endoscopic retrograde cholangiopancreatography; INR, international normalized ratio; PEG, percutaneous endoscopic gastrostomy.

Source: Warfarin Use in Adults: Clinical Care Guideline, University of Illinois Hospital and Health Sciences System.

Clinical outcomes in patients bridged with LMWH or UFH are similar and overall costs are lower for LMWH because of the avoidance of hospital admission for IV UFH administration; therefore, the use of LMWH is recommended whenever possible.[151] UFH may be preferred in patients with significant renal impairment (CrCl <30 mL/minute), or if LMWHs are used, reduced doses are suggested.[10] Monitoring anti-Xa levels for accumulation may be prudent if patients require a prolonged course of therapy (over 7 days). A sample plan for bridge therapy based on the risk of thromboembolism and on renal function is presented in **Table 11-25**.

Table 11-25
Sample LMWH Bridging Plan

	Action		
Day	**Warfarin**	**LMWH**	**Laboratories**
−6	Last warfarin dose	N/A	INR; skip dose if supratherapeutic.
−5	No warfarin	N/A	
−4	No warfarin	Start LMWH	
−3	No warfarin	LMWH	
−2 to −1	No warfarin	LMWH; last dose 24–36 hours before procedure	
0–day of procedure	Resume warfarin at usual dose if hemostasis is achieved.[a]	No LMWH	Ensure INR is appropriate for surgery.[b] CBC
1	Resume warfarin if not started the day prior.	LMWH; resume following minor surgery No LMWH following major surgery	
2–3	Warfarin	LMWH; resume following major surgery if bleeding controlled	
4	Warfarin	LMWH	
5–7	Warfarin	LMWH	INR; discontinue when therapeutic Consider CBC, CrCl, anti-Xa level with continued need for LMWH.

CBC, complete blood count; CrCl, creatinine clearance; INR, international normalized ratio; LMWH, low-molecular-weight heparin.

[a]Consider giving 1.5 times the usual warfarin dose for first 2 days when warfarin is reinitiated.

[b]INR <1.5 required for most surgical procedures.

Because L.P. has a mechanical MVR, her risk of thromboembolism associated with underanticoagulation is

considered high. Therefore, she should receive bridge therapy with an injectable anticoagulant while warfarin is held. Her renal function is normal, and her health care insurance covers injectable drugs. Therefore, her plan will include early discontinuation of warfarin 5 days before the procedure and substitution with enoxaparin 1 mg/kg every 12 hours when the INR falls below the lower limit of the therapeutic range. The last dose of enoxaparin should be given 24 hours before the procedure to minimize the risk of bleeding at the time of the procedure. After the procedure, warfarin should be restarted at her usual dose, and enoxaparin should be continued until the INR is >2.5, the lower limit of L.P.'s therapeutic range. For indications other than mechanical valves, enoxaparin 1.5 mg/kg every 24 hours may be used as an alternative to avoid twice-daily injections.

The relatively short half-lives of DOACs allow for a reduced duration of underanticoagulation when therapeutic interruption is required. Patients receiving DOAC therapy do not require bridge therapy with parenteral anticoagulants because the half-lives are similar. Preoperative discontinuation of a DOAC is based on a patient's individual renal function, so this must be assessed before providing perioperative recommendations. Similar to LMWH, DOACs can be restarted on the day following the procedure assuming hemostasis has been achieved. Following high-bleed risk procedures, it is reasonable to wait 48 to 72 hours before resuming the DOAC.[154] This was confirmed with the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) trial. This cohort study evaluated rates of major bleeding and arterial thromboembolism in patients taking dabigatran, rivaroxaban, or apixaban for atrial fibrillation who were scheduled for an elective procedure. DOAC regimens were stopped 1 to 2 days before a low- or high-bleed risk procedure, respectively, and resumed 1 day after a low-bleed risk procedure and 2 to 3 days following a high-bleed risk procedure. Edoxaban was not evaluated because it was not yet approved at the time of enrollment. After 30 postoperative days, patients with atrial fibrillation who had DOAC therapy interrupted for elective surgery or procedure without heparin bridging or

measurement of coagulation function was associated with low rates of major bleeding and arterial thromboembolism.[155] **Table 11-26** summarizes recommendations for perioperative DOAC interruption.

Table 11-26

Perioperative Recommendations for Interruption of Direct Oral Anticoagulants

Drug	Renal Function CrCl (mL/minute)	Low-Bleed Risk Surgery	High-Bleed Risk Surgery	Resumption of Therapy: Low-Bleed Risk Surgery[a]	Resumption of Therapy: High-Bleed Risk Surgery[a]
Dabigatran	CrCl >50	1–2 days before	3 days before	1 day after[b]	2–3 days after[b]
	CrCl 30–50	3 days before	3–4 days before		
	CrCl <30	3 days before	5–6 days before		
Rivaroxaban	CrCl >50	1–2 days before	1–3 days before	1 day after[b]	2–3 days after[b]
	CrCl 30–50	2 days before	2–3 days before		
	CrCl 15–29.9	3 days before	2–3 days before		
Apixaban	CrCl >50	1–2 days before	2–3 days before	1 day after[b]	2–3 days after[b]
	CrCl 30–50	2–3 days before	2–3 days before		
Edoxaban	CrCl >15	1–2 days before	2–3 days before	1 day after[b]	2–3 days after[b]
	Discontinue edoxaban at least 24 hours before invasive or surgical procedures				

CrCl, creatinine clearance; DOAC, direct oral anticoagulant.

[a]Ensure adequate hemostasis is achieved before resuming anticoagulation.

[b]When initiating a direct oral anticoagulant (DOAC) after an orthopedic procedure for venous thromboembolism (VTE) prophylaxis, anticoagulant should be taken 12 to 24 hours after surgery once hemostasis has been established.

Source: Direct Oral Anticoagulant Use in Adults: Clinical Care Guideline, University of Illinois Hospital and Health Sciences System.

DRUG INTERACTIONS

Interactions With Prescription Drugs

CASE 11-13

QUESTION 1: P.T., a 48-year-old female, received a mechanical mitral valve prosthesis 5 years ago and has been anticoagulated with warfarin 6 mg/day

with good control. She asks to see you today in your anticoagulation clinic. After returning from an urgent appointment with her primary care physician for treatment of a skin infection that yielded a positive test result for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) and was given a prescription for trimethoprim–sulfamethoxazole (TMP-SMX) twice a day for 10 days today. She is allergic to penicillin and has gastric intolerance to tetracycline.

How will the combination of warfarin and TMP-SMX affect P.T.'s anticoagulation control? Should her warfarin dosage be adjusted or another drug substituted for TMP-SMX?

Drug interactions with warfarin occur by a number of different mechanisms and can have a significant impact on the anticoagulant effect of warfarin.[156,157] Elevations or reductions in INR have been observed when interacting drugs are added to or discontinued from the medication regimens of patients taking warfarin or when used intermittently. Clinically significant hemorrhagic or thromboembolic complications can result. Careful selection of both prescription and nonprescription medications, appropriate INR monitoring, and detailed patient education regarding drug interactions are important interventions for pharmacists caring for patients taking warfarin. A selection of the hundreds of drugs that have been reported to interact with warfarin, including mechanisms of interaction and effect on INR, is provided in **Table 11-27**. Further information regarding the management of drug interactions can be found in Chapter 3, Drug Interactions.

Table 11-27
Warfarin Drug Interactions

Target	Effect	Response		Examples (Not Inclusive)		
Clotting factors	Increased synthesis	Decreased INR	Vitamin K			
	Decreased synthesis	Increased INR	Broad-spectrum antibiotics			
	Increased catabolism	Increased INR	Thyroid hormones			
	Decreased catabolism	Decreased INR		Methimazole		Propylthiouracil
Warfarin metabolism	Inhibition	Increased INR	Acetaminophen	Allopurinol	Amiodarone	Azole antifungals
			Cimetidine	Fluoroquinolones	Macrolides	Metronidazole
			Propafenone	SSRIs	Statins	Sulfa antibiotics
	Induction	Decreased INR	Barbiturates	Carbamazepine	Doxycycline	Griseofulvin
Nafcillin		Phenytoin	Primidone	Rifampin		
Hemostasis	Additive antithrombotic effects	Increased bleeding risk	Aspirin	NSAIDs	Salicylates	GPIIb/IIIa inhibitors
	Additive antico-agulant response	Increased bleeding risk	Heparin	LMWH	Direct thrombin inhibitors	Thrombolytics
		Decreased INR	Cholestyramine	Colestipol	Sucralfate	
Absorption	Reduced	Decreased INR	Ascorbic acid	Azathioprine	Corticosteroids	Cyclosporine
Unknown		Increased INR	Androgens	Fenofibrate	Cyclophosphamide	Gemfibrozil

GP, glycoprotein; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Although warfarin is highly bound to protein (primarily to albumin), and can be displaced from protein-binding sites by a number of weakly acidic drugs, these interactions typically do not result in clinically significant elevations in PT/INR.[158] Warfarin displaced from protein-binding sites is readily available for elimination by hepatic metabolism, resulting in increased clearance without a significant change in the free-drug concentration.

Other types of interactions with warfarin are much more significant. Pharmacodynamic interactions are those that alter the physiology of hemostasis, particularly interactions that influence the synthesis or degradation of clotting factors or that increase the risk of bleeding through inhibition of platelet aggregation. Pharmacokinetic interactions influence the absorption and metabolism of warfarin, and many clinically significant interactions with warfarin occur when warfarin metabolism is induced or inhibited. Interactions involving agents known to influence the hepatic microsomal enzyme systems responsible for the metabolism of the more potent S(−)-warfarin

(CYP2C9) are more significant than are those that influence the enzymes that metabolize R(+)-warfarin (CYP1A2, CYP3A4).

Sulfamethoxazole can increase the effect of warfarin significantly by stereoselectively inhibiting the metabolism of the more potent S(−)-enantiomer of warfarin. Potentiation of warfarin activity after inhibition of metabolism usually takes several days, and the effect may be slow to resolve once the offending agent is discontinued. In addition, fever associated with the infection for which TMP-SMX has been prescribed may enhance the catabolism of vitamin K–dependent clotting factors, resulting in an accentuated hypoprothrombinemic response. This effect will dissipate as the fever abates with antibiotic therapy.

For P.T., the ideal choice would be to discontinue TMP-SMX and use a noninteracting alternative. The decision of which agent to use must consider both the treatment(s) of choice for the clinical indication along with patient factors such as reported allergies or intolerances. In P.T.'s case, she has a penicillin allergy and intolerance to tetracyclines, both of which would prevent their use. If a noninteracting alternative is not clinically appropriate, the concomitant use of an interacting agent is not absolutely contraindicated in patients taking warfarin. Use of TMP-SMX in P.T. would be acceptable if she is monitored frequently and carefully, with adjustment of warfarin dosages as necessary to maintain her INR within the therapeutic INR range of 2.5 to 3.5 and with attention to potential hemorrhagic complications. No initial change in the dosage of warfarin should be made because it may take several days for the interaction to become apparent. The INR should be repeated within 3 days, with warfarin dosing adjustments and subsequent monitoring guided by initial INR results.

CASE 11-14

QUESTION 1: G.H. is a 54-year-old male on long-term anticoagulation for multiple, bilateral DVTs, most recently 1 year ago, for which he takes warfarin 7.5 mg daily. He had a knee replacement surgery 6 months ago and had a complication of infected hardware, for which he needs to start IV rifampin in a skilled nursing facility for several weeks. His orthopedic physician is asking

about whether G.H. can be switched to an alternate anticoagulant because he knows that there is a drug interaction with warfarin and rifampin.

What options are available to him?

Although the DOACs are less prone to drug interactions than is warfarin, all of them are P-gp substrates and can have their concentrations reduced by rifampin, which is a strong P-gp inducer.[159] At this time, dabigatran, rivaroxaban, apixaban, and edoxaban are all contraindicated with rifampin per package labeling and are not suitable options for G.H. Drug interactions for DOACs are summarized in Table 11-6.

The interaction with warfarin and rifampin can be significant, with a potentially large dose increase (sometimes up to three times the original dose) of warfarin necessary to maintain G.H. in the therapeutic range. If G.H. is in a facility where his INRs can be measured frequently, such as every few days, it may be appropriate to maintain him on warfarin while continuing the rifampin, until the degree of the interaction can be detected, and a new stable dose can be determined. Alternatively, if G.H. is receiving the antibiotics at home, it may be appropriate for him to acquire a home INR meter and perform warfarin self-testing of his INRs. It has been shown that individuals performing patient self-testing (almost all testing weekly) had better time in therapeutic range (TTR) than did those who underwent in-clinic testing every 4 weeks using high-reduced anticoagulation management.[160] A substudy of this trial also showed that individuals on chronic anticoagulation who perform self-testing more often (ie, weekly or twice weekly) had a modestly higher TTR compared to monthly testing.[161] The costs of the self-testing meter and supplies are often covered by the patient's insurance; however, sometimes the poor reimbursement for managing anticoagulation services this way can limit providers' willingness to offer patient-self testing. If reimbursement is not a concern (such as in a closed insurance system), then patient self-testing can be a way to empower patients to take more control of their warfarin management and reduce the burden of INR monitoring.

LMWH, UFH, and fondaparinux are also reasonable options for G.H. to use, especially if his INRs cannot be stabilized while receiving the rifampin. However, again, there could be barriers to self-injection and insurance limitations that may make it difficult to continue these agents for a prolonged length of time.

Case 11-14, Question 2: Can G.H. return to using his ibuprofen for pain control?

This question illustrates one of the most difficult therapeutic dilemmas for a patient taking warfarin. All NSAIDs have the potential to cause gastric irritation by inhibiting cytoprotective prostaglandins, thereby providing a focus for GI bleeding. In addition, most NSAIDs inhibit platelet aggregation, which compromises effective clotting and can lead to bleeding complications.[162]

These effects can increase the risk of hemorrhagic complications significantly in patients taking warfarin who are prescribed concurrent NSAID therapy. In a retrospective cohort study of patients ages 65 years and older, the risk of hospitalization for bleeding peptic ulcer disease was approximately three times higher for patients taking concurrent warfarin and an NSAID versus those taking either drug alone, and almost 13 times higher than in patients taking neither warfarin nor an NSAID.[163] Warfarin therapy is considered a relative contraindication to NSAID use.

In patients such as G.H., routine use of NSAIDs with long-term anticoagulation should be avoided. Any patients requiring combined warfarin and NSAID therapy for limited periods of time should be followed up closely and observed routinely for signs and symptoms of bleeding, with frequent stool testing for GI bleeding. Patients should be counseled to avoid additional NSAID use whenever possible, including use of aspirin, and to seek assistance from a pharmacist to prevent inadvertent NSAID use when selecting over-the-counter (OTC) medications, because some OTC cold preparations contain NSAIDs, aspirin, or aspirin-related compounds.

The analgesic and antipyretic of choice in patients taking warfarin is acetaminophen, which has not been consistently shown to increase the risk of bleeding. At doses >2 g/day, acetaminophen can enhance the anticoagulant effect of warfarin.[164] It has been suspected of directly inhibiting CYP2C9 and CYP1A2, and toxic metabolites of acetaminophen have been suspected of inhibiting hepatic enzymes as well. Nevertheless, it can be used safely when used occasionally, and even when used routinely. INR monitoring is sufficient to detect any potential interaction. Other pain-relieving options to be considered that do not increase the bleeding risk include tramadol, gabapentin, pregabalin, topical lidocaine patches, and opiates.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e44S–e88S. (6)

Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22): 3317–3359. doi:10.1182/bloodadvances.2018024802 (123)

Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791. (148)

Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv*. 2018;2(22):3360–3392. doi:10.1182/bloodadvances.2018024489 (29)

Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert Consensus Decision Pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2017;69(7):871–898. (154)

Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e24S–e43S. (3)

Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy. *Chest*. 2012;141:e152S–e184S. (22)

January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation*. 2019;140:e125–e151. (127)

Kearon C, Akl EA, Ornelas J, Blaivas A, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest.* 2016;149(2): 315–352. doi:10.1016/j.chest.2015.11.026 (18)

Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv.* 2018;2(22):3226–3256. doi:10.1182/bloodadvances.2018024828 (15)

Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693–4738. doi:10.1182/bloodadvances.2020001830 (37)

Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2021;77(4):e25–e197. doi:10.1016/j.jacc.2020.11.018 (143)

Smythe MA, Priziola J, Dobesh PP, Wirth D, Cuker A, Wittkowsky AK. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. *J Thromb Thrombolysis.* 2016;41:165–186. doi:10.1007/s11239-015-1315-2 (10)

Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC Expert Consensus Decision Pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76(5):594–622. doi:10.1016/j.jacc.2020.04.053 (43)

Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018;2(22):3257–3291. doi:10.1182/bloodadvances.2018024893 (41)

COMPLETE REFERENCES CHAPTER 11 THROMBOSIS

1. Turpie AG, Chin BS, Lip GY. Venous thromboembolism: pathophysiology, clinical features and prevention. *BMJ*. 2002;325:887–890.
2. Turpie AGG, Ensom C. Venous and arterial thrombosis—pathogenesis and the rationale for anticoagulation. *Thromb Haemost*. 2011;105:586–596.
3. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e24S–e43S.
4. Mastroiacovo D, Sala G, Dentali F. The safety of fondaparinux sodium for the treatment of venous thromboembolism. *Expert Opin Drug Saf.* 2016;15(9):1259–1265. doi:10.1080/14740338.2016.1221395
5. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e495S–e530S.
6. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e44S–e88S.
7. Lezini P, Wadelius M, Kimmel S, et al. Integration of genetic, clinical, and INR data to refine warfarin dosing. *Clin Pharmacol Ther*. 2010;87(5):572–578.
8. Ng VL. Anticoagulation monitoring. *Clin Lab Med*. 2009;28:283–304.
9. Laposata M, Green D, Van Cott EM, Barrowcliffe TW, Goodnight SH, Sosolik RC. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: the clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. *Arch Pathol Lab Med*. 1998;122:799–807.
10. Smythe MA, Priziola J, Dobesh PP, Wirth D, Cuker A, Wittkowsky AK. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. *J Thromb Thrombolysis.* 2016;41(1):165–186. doi:10.1007/s11239-015-1315-2
11. Cuker A, Raby A, Moffat KA, Flynn G, Crowther MA. Interlaboratory variation in heparin monitoring: lessons from the quality management program of Ontario coagulation surveys. *Thromb Haemost.* 2010;104:837–844.
12. Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. *Pharmacotherapy.* 2012;32:546–558.

13. College of American Pathologists. CAP Hematology and Coagulation Checklist. CAP Accreditation Program. 9.25.2012. https://webapps.cap.org/apps/docs/education/OnlineCourseContent/2012/LAP/Resources/Checklists/HEM09252012.pdf
14. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e351S–e418S.
15. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2(22):3226–3256. doi:10.1182/bloodadvances.2018024828
16. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e227S–e277S.
17. Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? *JAMA*. 2006;295(2):199–207.
18. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315–352. doi:10.1016/j.chest.2015.11.026
19. Raschke RA. The weight-based heparin dosing nomogram compared with a “standard-care” nomogram: a randomized controlled trial. *Ann Intern Med*. 1993;119:874–891.
20. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy: the emerging theme of delayed recurrence. *Arch Intern Med*. 1997;157:2317–2321.
21. Anand SS, Bates S, Ginsberg JS, et al. Recurrent venous thrombosis and heparin therapy: an evaluation of the importance of early activated partial thromboplastin times. *Arch Intern Med*. 1999;159:2029–2032.
22. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy. *Chest*. 2012;141:e152S–e184S.
23. Gunnarson PS, Sawyer WT, Montague D, Williams ML, Dupuis RE, Caiola SM. Appropriate use of heparin: empiric vs. nomogram-based dosing. *Arch Intern Med*. 1995;155:526–532.
24. Hylek EM, Regan S, Henault LE, et al. Challenges in the effective use of unfractionated heparin in the hospitalized management of acute thrombosis. *Arch Intern Med*. 2003;163:621–627.
25. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. *Chest*. 2010;137(6):1382–1390.

26. Bakchoul T, Zöllner H, Greinacher A. Current insights into the laboratory diagnosis of HIT. *Int J Lab Hematol*. 2014;36(3):296–305.
27. Cuker A. Clinical and laboratory diagnosis of heparin-induced thrombocytopenia: an integrated approach. *Semin Thromb Hemost*. 2014;40:106–114.
28. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings [see comment]. *J Thromb Haemost*. 2006;4(4):759–765.
29. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv*. 2018;2(22):3360–3392. doi:10.1182/bloodadvances.2018024489
30. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. *Thromb Haemost*. 2005;94(1):132–135.
31. Warkentin TE, Elavathil LJ, Hayward CP, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med*. 1997;127(9):804–812.
32. Landefeld CS, Beyth RJ. Anticoagulation-related bleeding: clinical epidemiology, prediction and prevention. *Am J Med*. 1993;85:315–328.
33. Barbour LA, Kick SD, Steiner JF, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. *Am J Obstet Gynecol*. 1994;170:862–869.
34. Blossom DB, Kallen AJ, Patel PR, et al. Outbreak of adverse reactions associated with contaminated heparin. *N Engl J Med*. 2008;359(25):2674–2684.
35. Suryanarayan D, Schulman S. Potential antidotes for reversal of old and new oral anticoagulants. *Thromb Res*. 2014;133(suppl 2):S158–S166.
36. Van Dongen CJ, van den Belt AG, Prins MH, Lensing AW. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev*. 2004;(4):CD001100.
37. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693–4738. doi:10.1182/bloodadvances.2020001830
38. Büller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep vein thrombosis: a randomized trial. *Ann Intern Med*. 2004;140:867–873.
39. Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute

treatment of venous thromboembolism. *JAMA*. 2006;296:935–942.
40. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. *Am J Hematol*. 2019;94:697–709. doi:10.1002/ajh.25475
41. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018;2(22):3257–3291. doi:10.1182/bloodadvances.2018024893
42. Mohammad I, Korkis B, Garwood CL. Incorporating comprehensive management of direct oral anticoagulants into anticoagulation clinics. *Pharmacotherapy*. 2017;37(10):1284–1297. doi:10.1002/phar.1991
43. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC Expert Consensus Decision Pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2020;76(5):594–622. doi:10.1016/j.jacc.2020.04.053
44. Merli G, Spiro TE, Olsson CG, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med*. 2001;134:191–202.
45. Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med*. 2006;144:673–684.
46. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low molecular weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. *Ann Pharmacother*. 2009;43:1064–1084.
47. Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use. Accessed December 30, 2020. https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-us-medical-eligibility-criteria_508tagged.pdf
48. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e278S–e325S.
49. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e195S–e226S.
50. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon*. 2005;51(2–3):70–78.
51. Spyropoulos AC, Anderson FA, Fitzgerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest*. 2011;140 (3):706–714. doi:10.1378/chest.10-1944

52. Gibson CM, Spyropoulos AC, Cohen AT, et al. The IMPROVEDD VTE risk score: incorporation of D-Dimer into the IMPROVE score to improve venous thromboembolism risk stratification. *TH Open*. 2017;1(1):e56–e65. doi:10.1055/s-0037-1603929
53. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost*. 2010;8:2450–2457.
54. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2(22):3198–3225. doi:10.1182/bloodadvances.2018022954
55. Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv*. 2019;3(23):3898–3944. doi:10.1182/bloodadvances.2019000975
56. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J*. 2019;54(3):1901647. doi:10.1183/13993003.01647-2019
57. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;23:1788–1830.
58. Wells PS. Advances in the diagnosis of venous thromboembolism. *J Thromb Thrombolysis*. 2006;21:31–40.
59. Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. *Am J Med*. 2002;113:269–275.
60. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med*. 2010;170:1383–1389.
61. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005;172:1041–1046.
62. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2004;140:175–183.
63. Erkens PM, Prins MH. Fixed dose subcutaneous low molecular weight heparins vs adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev*. 2010;(9):CD001100.

64. Büller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695–1702.
65. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129:764–772.
66. EINSTEIN–PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–1297.
67. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;11:21.
68. Agnelli G, Buller HR, Cohen A, et al Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.
69. Hokusai-VTE Investigators, Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;9:1406–1415.
70. Leech BF, Carter CJ. Falsely elevated INR results due to the sensitivity of the thromboplastin reagent to heparin. *Am J Clin Pathol*. 1998;109:764–768.
71. Kearon C, Johnston M, Moffat K, McGinnis J, Ginsberg JS. Effect of warfarin on activated partial thromboplastin time in patients receiving heparin. *Arch Intern Med*. 1998;158:1140–1143.
72. James AH, Britt RP, Raskino CL, Thompson SG. Factors affecting the maintenance dose of warfarin. *J Clin Pathol*. 1992;45:704–706.
73. Wittkowsky AK. Warfarin. In: Murphy J, ed. *Clinical Pharmacokinetics*. 5th ed. American Society of Health System Pharmacists; 2011:345.
74. Pengo V, Biasiolo A, Pegoraro C. A simple scheme to initiate oral anticoagulant treatment in outpatients with nonrheumatic atrial fibrillation. *Am J Cardiol*. 2001;88:1214–1216.
75. Siguret V, Gouin I, Debray M, et al. Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. *Am J Med*. 2005;118:137–142.
76. Tait RC, Sefcick A. A warfarin induction regimen for outpatient anticoagulation in patients with atrial fibrillation. *Br J Haematol*. 1998;101:450–454.
77. Kovacs MJ, Anderson DA, Wells PS. Prospective assessment of a nomogram for the initiation of oral anticoagulant therapy for outpatient treatment of venous thromboembolism. *Pathophysiol Haemost Thromb*. 2002;32:131–133.
78. Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10 mg and 5 mg warfarin initiation nomograms together with low molecular weight heparin for

outpatient treatment of acute venous thromboembolism. *Ann Intern Med*. 2003;138:714–719.
79. Eckhoff CD, Didomenico RJ, Shapiro NL. Initiating warfarin therapy: 5 mg versus 10 mg. *Ann Pharmacother*. 2004;38:2115–2121.
80. Crowther MA, Bracikowski J. Warfarin: less may be better. *Ann Intern Med*. 1997;127:332–333.
81. Crowther MA, Ginsberg JB, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med*. 1999;159:46–48.
82. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2020;38(5):496–520. doi:10.1200/JCO.19.01461
83. Streiff MB, Holmstrom B, Angelini D, et al. Cancer-Associated Venous Thromboembolic Disease, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;15:19(10):1181-1201. doi: 10.6004/jnccn.2021.0047.
84. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. CLOT Trial. *N Engl J Med*. 2003;349:146–153.
85. Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. *JAMA*. 2014;312:1122–1135.
86. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet*. 2014;383:955–962.
87. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet*. 1996;348:423–428.
88. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med*. 2004;141(10):745–752.
89. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart survey. *Chest*. 2010;138:1093–1100.
90. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study. *J Am Coll Cardiol*. 2011;58:395–401.
91. Borre ED, Goode A, Raitz G, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. *Thromb Haemost*. 2018;118(12):2171–2187. doi:10.1055/s-0038-1675400
92. Piovella C, Dalla Valle F, Trujillo-Santos J, et al Comparison of four scores to predict major bleeding in patients receiving anticoagulation for venous

thromboembolism: findings from the RIETE registry. *Intern Emerg Med*. 2014;98:847–852.

93. Nieto JA, Solano R, Trapero Iglesias N, et al. Validation of a score for predicting fatal bleeding in patients receiving anticoagulation for venous thromboembolism. *Thromb Res*. 2013;132:175–179.
94. Sherz N, Méan M, Limacher A, et al. Prospective, multicenter validation of prediction scores for major bleeding in elderly patients with venous thromboembolism. *J Thromb Haemost*. 2013;11:435–443.
95. Vedovati MC, Mancuso A, Pierpaoli L, et al. Prediction of major bleeding in patients receiving DOACs for venous thromboembolism: a prospective cohort study. *Int J Cardiol*. 2020;301:167–172. doi:10.1016/j.ijcard.2019.11.105
96. van Es N, Wells PS, Carrier M. Bleeding risk in patients with unprovoked venous thromboembolism: a critical appraisal of clinical prediction scores. *Thromb Res*. 2017;152:52–60. doi:10.1016/j.thromres.2017.02.016
97. Steuer AB, Cohen JM. The color of skin: purple diseases of the skin, nails, and mucosa. *Clin Dermatol*. 2019;37(5):528–547. doi:10.1016/j.clindermatol.2019.07.016
98. Hirschmann JV, Raugi GJ. Blue (or purple) toe syndrome. *J Am Acad Dermatol*. 2009;60:1–20.
99. Chiquette E, Amato MG, Bussey HI. et al. Comparison of an anticoagulation clinic with usual medical care. *Arch Intern Med*. 1998;185:1641–1647.
100. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. *Chest*. 2005;127:1515–1522.
101. Gage BF, Eby C, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther*. 2008;84(3):326–331.
102. Booth SL, Pennington JA, Sadowski JA. Food sources and dietary intakes of vitamin K-1 (phylloquinone) in the American diet: data from the FDA Total Diet Study. *J Am Diet Assoc*. 1996;96:149–154.
103. Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. *Am J Med*. 2004;116:651–655.
104. Sconce E, Khan T, Mason J, Noble F, Wynne H, Kamali F. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. *Thromb Haemost*. 2005;93:872–875.
105. Booth SL, Centurelli MA. Vitamin K: a practical guide to the dietary management of patients on warfarin. *Nutr Rev*. 1999;57(9 Pt 1):288–296.
106. Nutescu EA, Shapiro NL, Ibrahim S, West P. Warfarin and its interactions with foods, herbs and other dietary supplements. *Expert Opin Drug Saf*. 2006;5:433–451.

107. Pincus D, Gomes T, Hellings C, et al. A population-based assessment of the drug interaction between levothyroxine and warfarin. *Clin Pharmacol Ther*. 2012;92:766–770.
108. Wood MD, Delate T, Clark M, Clark N, Horn JR, Witt DM. An evaluation of the potential drug interaction between warfarin and levothyroxine. *J Thromb Haemost*. 2014;12:1313–1319.
109. Nathisuwan S, Dilokthornsakul P, Chaiyakunapruk N, Morarai T, Yodting T, Piriyachananusorn N. Assessing evidence of interaction between smoking and warfarin: a systematic review and meta-analysis. *Chest*. 2011;139:1130–1139.
110. Kuykendall JR, Houle MD, Rhodes RS. Possible warfarin failure due to interaction with smokeless tobacco. *Ann Pharmacother*. 2004;38(4):595–597.
111. Johnson JA, Cavallari LH. Warfarin pharmacogenetics. *Trends Cardiovasc Med*. 2015;25:33–41.
112. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013;369:2283–2293.
113. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2013;369:2294–2303.
114. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *N Engl J Med.* 2013;369(24):2304–2312. doi:10.1056/NEJMoa1311388
115. Gage BF, Bass AR, Lin H, et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the GIFT randomized clinical trial. *JAMA*. 2017;318(12):1115–1124. doi:10.1001/jama.2017.11469
116. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. *Am J Med*. 2000;109:481–488.
117. Wong W, Wilson Norton J, Wittkowsky AK. Influence of warfarin regimen type on clinical and monitoring outcomes in stable patients in an anticoagulation management service. *Pharmacotherapy*. 1999;19:1385–1391.
118. Hylek EM, Regan S, Go AS, Hughes RA, Singer DE, Skates SJ. Clinical predictors of prolonged delay in return of the international normalized ratio to within the therapeutic range after excessive anticoagulation with warfarin. *Ann Intern Med*. 2001;135:393–400.
119. Crowther MA, Douketis JD, Schnurr T, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy: a randomized, controlled trial. *Ann Intern Med*. 2002;137:251–254.
120. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest

Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e691S–e736S.

121. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis.* 2016;41:92–128.
122. American College of Obstetricians and Gynecologists Women's Health Care Physicians. ACOG Practice Bulletin No. 138: inherited thrombophilias in pregnancy. *Obstet Gynecol*. 2013;122(3):706–717.
123. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22):3317–3359. doi:10.1182/bloodadvances.2018024802
124. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). *Reg Anesth Pain Med*. 2018;43(3):263–309. doi:10.1097/AAP.0000000000000763
125. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154(5):1121–1201.
126. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to DC electrical conversion of atrial fibrillation. *Am J Cardiol*. 1969;23:208–216.
127. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation*. 2019;140:e125–e151.
128. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*. 2001;344:1411–1420.
129. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials [published correction appears in *Arch Intern Med*. 1994;154:2254]. *Arch Intern Med*. 1994;154:1449–1457.
130. The efficacy of aspirin in patients with atrial fibrillation: analysis of pooled data from three randomized trials. The Atrial Fibrillation Investigators. *Arch Intern Med*. 1997;157:1237–1240.
131. ACTIVE Writing Group of the ACTIVE Investigators; Connolly S, Pogue J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–1912.
132. ACTIVE Investigators; Connolly SJ, Pogue J, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*.

2009;360:2066–2078.
133. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery. *Eur Heart J*. 2021;42(5):373–498.
134. Fry E, Bollempali H, Suarez K, et al. Watchman outcomes comparing post-implantation anticoagulation with warfarin versus direct oral anticoagulants. *J Interv Card Electrophysiol*. 2020;61(1):137–144. doi:10.1007/s10840-020-00790-2
135. Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol*. 2020;75(25):3122–3135.
136. Nielsen-Kudsk JE, Korsholm K, Damgaard D, et al. Clinical outcomes associated with left atrial appendage occlusion versus direct oral anticoagulation in atrial fibrillation. *J Am Coll Cardiol Interv*. 2021;14:69–78.
137. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(1):1139–1151.
138. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
139. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
140. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
141. Kovacs RJ, Flaker GC, Saxonhouse SJ, et al. Practical management of anticoagulation in patients with atrial fibrillation. *J Am Coll Cardiol*. 2015;65(13):1340–1360.
142. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease. American College of Chest Physicians Evidence-Based Practice Guidelines (9th ed): American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e576S–e600S.
143. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2021;77(4):e25–e197. doi:10.1016/j.jacc.2020.11.018
144. Cannegeiter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briët E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med*. 1995;333:11–17.
145. Saour JN, Sieck JO, Mamo LA, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. *N Engl J Med*. 1990;322:428–432.
146. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomized, phase II study to evaluate the safety and pharmacokinetics

of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). *Am Heart J*. 2012;163:931–937.

147. Guimaraes HP, Lopes RD, de Barros e Silva PGM, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med*. 2020;383(22):2117–2126.
148. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791.
149. Dangas GD, Tijssen GP, Wohrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382(2):120–129.
150. Nijenhuis VJ, Brouwer J, Delewi R, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med*. 2020;382(18):1696–1707.
151. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e326S–e350S.
152. Steinberg BA, Peterson ED, Kim S, et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation*. 2015;131:488–494.
153. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015;373(9):823–833.
154. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2017;69(7):871–898.
155. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med*. 2019;179(11):1469–1478.
156. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165:1095–1106.
157. Wittkowsky AK. Drug interactions with oral anticoagulants. In: Colman RW, Marder VJ, Clowes AW, George JN, Goldhaber SZ, eds. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. 5th ed. Lippincott Williams & Wilkins; 2005:118.
158. Sands CD, Chan ES, Welty TE. Revisiting the significance of warfarin protein-binding displacement interactions. *Ann Pharmacother*. 2002;36:1642–1644.
159. Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin, rifabutin, and rifapentine drug interactions. *Curr Med Res Opin*. 2013;29(1):1–12.

160. Matchar DB, Jacobson A, Dolor R, et al. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med*. 2010;363:1608–1620.
161. Matchar DB, Love SR, Jacobson AK, et al. The impact of frequency of patient self-testing of prothrombin time on time in target range within VA Cooperative Study #481: The Home INR Study (THINRS), a randomized, controlled trial. *J Thromb Thrombolysis*. 2015;40(1):17–25. doi:10.1007/s11239-014-1128-8
162. Chan TY. Adverse interactions between warfarin and nonsteroidal antiinflammatory drugs: mechanisms, clinical significance, and avoidance. *Ann Pharmacother*. 1995;29:1274–1283.
163. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal antiinflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. *Arch Intern Med*. 1993;153:1665–1670.
164. Zhang Q, Bal-dit-Sollier C, Drouet L, et al. Interaction between acetaminophen and warfarin in adults receiving long term anticoagulants: a randomized, controlled trial. *Eur J Clin Pharmacol*. 2011;67:309–314.

12

Chronic Stable Angina

Angela M. Thompson and Toby C. Trujillo

CORE PRINCIPLES		CHAPTER CASES
CHRONIC STABLE ANGINA—MEDICAL MANAGEMENT		
1	Chronic stable angina is a clinical syndrome resulting from an imbalance in myocardial oxygen supply and demand. The supply–demand imbalance is typically a result of coronary atherosclerosis.	**Case 12-1 (Questions 1–3)**
2	The modification of cardiovascular disease (CVD) risk factors and adoption of healthy lifestyles is a key strategy in both the primary prevention of coronary artery disease (CAD) and slowing the progression of established CAD.	**Case 12-1 (Questions 7–9)** **Case 12-2 (Question 2)**
3	Standard therapy for all patients with chronic stable angina includes sublingual nitroglycerin, antiplatelet	**Case 12-1 (Questions 10–14, 16)** **Case 12-3 (Question 2)**

	therapy, and an anti-ischemic agent that either restores the appropriate balance of myocardial oxygen supply and demand (β-blockers, calcium channel blockers, and long-acting nitrates) or interrupts the negative consequences of myocardial ischemia on myocardial energy consumption (ranolazine).	
4	β-Blockers are the preferred initial agents for prevention of ischemic symptoms, especially in patients who have a history of myocardial infarction (MI) or heart failure.	**Case 12-1 (Questions 11–13, 15)**
5	Although effective as monotherapy, long-acting calcium channel blockers are typically added on to β-blocker therapy if additional control of ischemic symptoms is needed.	**Case 12-2 (Question 1)**
6	Long-acting nitrates should never be used as monotherapy but can be used as add-on therapy to other anti-ischemic options in chronic stable angina.	**Case 12-1 (Questions 16–19)**
7	Although ranolazine can be used as initial therapy for chronic stable angina, it is typically reserved as a second-line option. It is especially useful in patients who cannot tolerate further decreases in heart rate and blood pressure secondary to the use of traditional antianginal agents.	**Case 12-2 (Questions 3, 4)**
CHRONIC STABLE ANGINA—REVASCULARIZATION		

1	Myocardial revascularization can be accomplished either through percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). In most patients, both are equally effective in reducing myocardial ischemia.	**Case 12-1 (Question 4)** **Case 12-4 (Question 3)**
2	Certain patients who are at high risk for morbidity and mortality from CAD derive a mortality benefit with CABG as compared to PCI or medical management.	**Case 12-3 (Question 1)** **Case 12-4 (Question 3)**
3	In patients not at high risk, optimal medical management is as good as PCI in the long-term management of chronic stable angina, including the prevention of MI and death.	**Case 12-1 (Question 6)**
4	Patients who undergo myocardial revascularization either with PCI or CABG should still receive optimal pharmacotherapy for chronic stable angina.	**Case 12-4 (Question 3)**
5	Appropriate pharmacotherapy for patients undergoing elective PCI plus myocardial stent implantation should include dual antiplatelet therapy with aspirin and a $P2Y_{12}$ antagonist, in most cases clopidogrel therapy, for a minimum of 1 month (bare-metal stent) and ideally up to 1 year (bare-metal and drug-eluting stents).	**Case 12-1 (Question 5)** **Case 12-4 (Question 1, 2)**
6	Antiplatelet nonresponsiveness has	**Case 12-4 (Question**

	been demonstrated to be associated with an increased risk for cardiovascular events such as MI and death. An understanding of various testing modalities for antiplatelet response as well as potential drug–drug interactions that may lead to reduced antiplatelet activity will facilitate optimal pharmacotherapy in each patient.	**4, 5)**
PRINZMETAL ANGINA/CARDIAC SYNDROME X		
1	Patients with Prinzmetal angina and cardiac syndrome X typically present with severe chest pain despite having coronary arteries that are free from atherosclerosis.	**Case 12-5 (Question 1)**
2	Vasodilators are the primary mode of therapy for patients with Prinzmetal angina, whereas standard anti-ischemic options should be used for cardiac syndrome X.	**Case 12-5 (Question 2, 3)** **Case 12-6 (Question 1)**

INTRODUCTION

Coronary heart disease (CHD) includes heart failure (HF), arrhythmias, sudden cardiac death, and ischemic heart disease (IHD) such as myocardial infarction (MI) as well as unstable and stable angina pectoris. Because angina is a marker for underlying heart disease, its management is of great importance. Typical angina pectoris is characterized by substernal chest, jaw, shoulder, back, or arm pain triggered by exertion or stress, and it is relieved by rest or nitroglycerin (NTG); however, its presentation is variable.[1,2]

Patients who have a reproducible pattern of angina associated with a certain level of physical activity have chronic stable angina or exertional angina. In contrast, patients with unstable angina experience angina that is prolonged, occurs at rest, or at an increased intensity or frequency.[3] Angina often reflects underlying atherosclerotic narrowing of coronary arteries on coronary angiography. In contrast, Prinzmetal variant or vasospastic angina is associated with normal findings on coronary angiography and is thought to be caused by a spasm of the coronary artery that decreases myocardial blood flow. The presence of atherosclerosis also may lead to impairment of the normal vasodilatory function of the coronary arteries. As such, patients with coronary artery disease (CAD) who experience ischemia produced by an increase in myocardial oxygen demand (increased exertion) may also experience vasospasm at the site of atherosclerosis, further worsening the ischemic state. As such, patients with CAD likely experience angina because of both increased demand (exertion) and decreased supply (vasospasm), a phenomenon known as microvascular angina.[3]

Silent (asymptomatic) myocardial ischemia can result in transient changes in myocardial perfusion, function, or electrical activity and is detected on an electrocardiogram (ECG).[3] The patient, however, does not experience chest pain or other signs of angina during these episodes.

Epidemiology

It is estimated that 121.5 million adults in the United States have cardiovascular disease (CVD),[4] and 18.2 million of these adults have CHD.[4] Chronic stable angina is the first clinical sign of CHD in ~50% of patients.[1] Current estimates indicate 9.4 million American adults have angina pectoris, although the prevalence of angina is likely underestimated because of limited population-based data and because it is often unrecognized in patients.[4]

CVD is responsible for 17.8 million deaths worldwide and is the leading cause of death in the United States.[4] Although CHD is the leading cause of CVD death in the United States, individual mortality varies according to the patient's age, sex, cardiovascular risk profile, myocardial contractility, coronary anatomy, and specific anginal syndrome.[4]

In addition to the high morbidity and mortality associated with CHD, the economic cost to the U.S. health care system is substantial. Total direct and indirect costs associated with CHD were estimated to be $218.7 billion from 2014 to 2015.[4]

Pathophysiology

A brief review of coronary anatomy will facilitate a thorough understanding of the pathophysiology of chronic stable angina. **Figure 12-1** illustrates the normal distribution of the major coronary arteries, although variation is common between individuals.

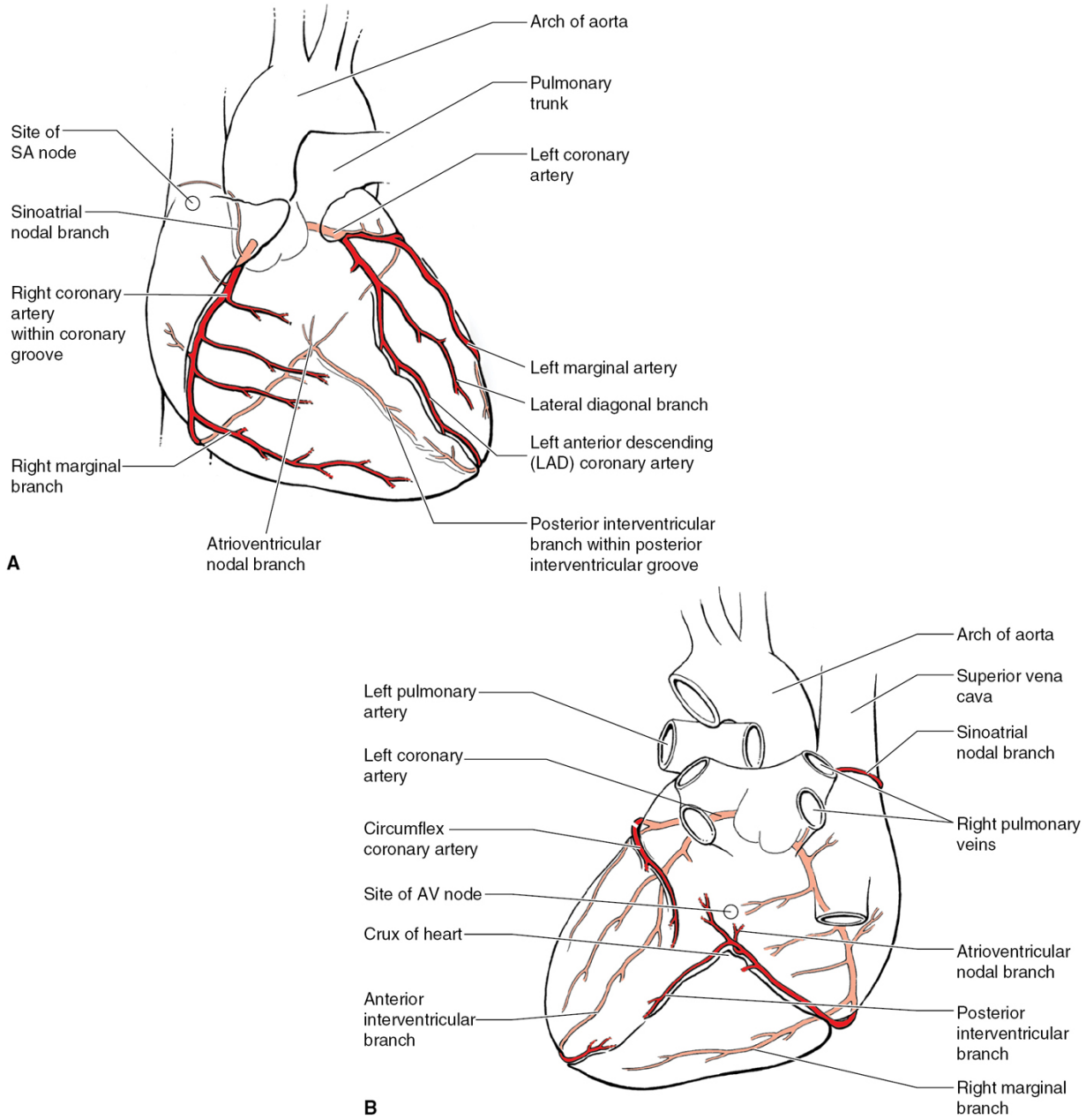


Figure 12-1 Coronary arteries. The right coronary artery (RCA) originates from the aorta and courses in the atrioventricular (coronary) groove to reach the posterior surface of the heart. The left coronary artery splits into the circumflex branch that supplies blood to the lateral and posterior walls of the left ventricle and a left anterior descending (LAD) branch that supplies blood to the anterior wall of the left ventricle. A, Anterior view. B, Posteroinferior view.

Angina pectoris typically occurs from myocardial ischemia. Ischemia in the myocardium develops when there is a mismatch between myocardial oxygen supply and demand. The underlying pathologic condition of this mismatch invariably is the presence of atherosclerosis in one or more of the coronary arteries.[3]

MYOCARDIAL OXYGEN SUPPLY AND DEMAND

The oxygen demand of the heart is determined by its workload. The major determinants of myocardial oxygen consumption are heart rate, contractility, and intramyocardial wall tension during systole (**Fig. 12-2**).[3,5] Intramyocardial wall tension, the force the heart is required to develop and sustain during contraction, is affected primarily by changes in ventricular pressures and volume. Both enlargement of the ventricle and increased pressure within the ventricle increase the systolic wall force and consequently myocardial oxygen demand. Increases in contractility and heart rate also increase oxygen demand.[6] Pharmacologic control of angina is directed toward decreasing the myocardial oxygen demand by decreasing heart rate, myocardial contractility, or ventricular volume and pressures.[3,5]

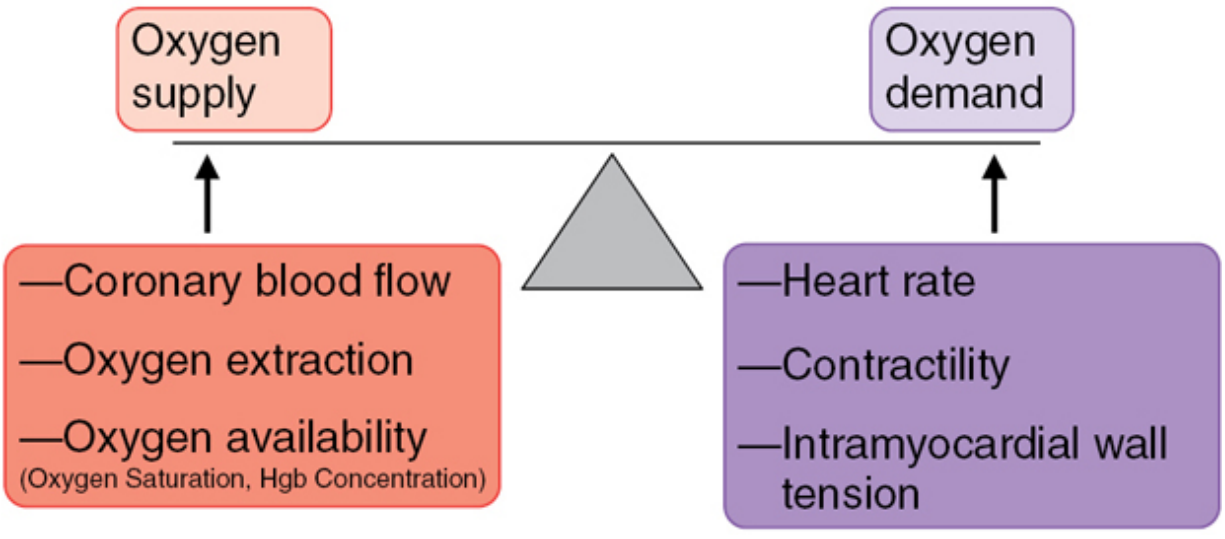


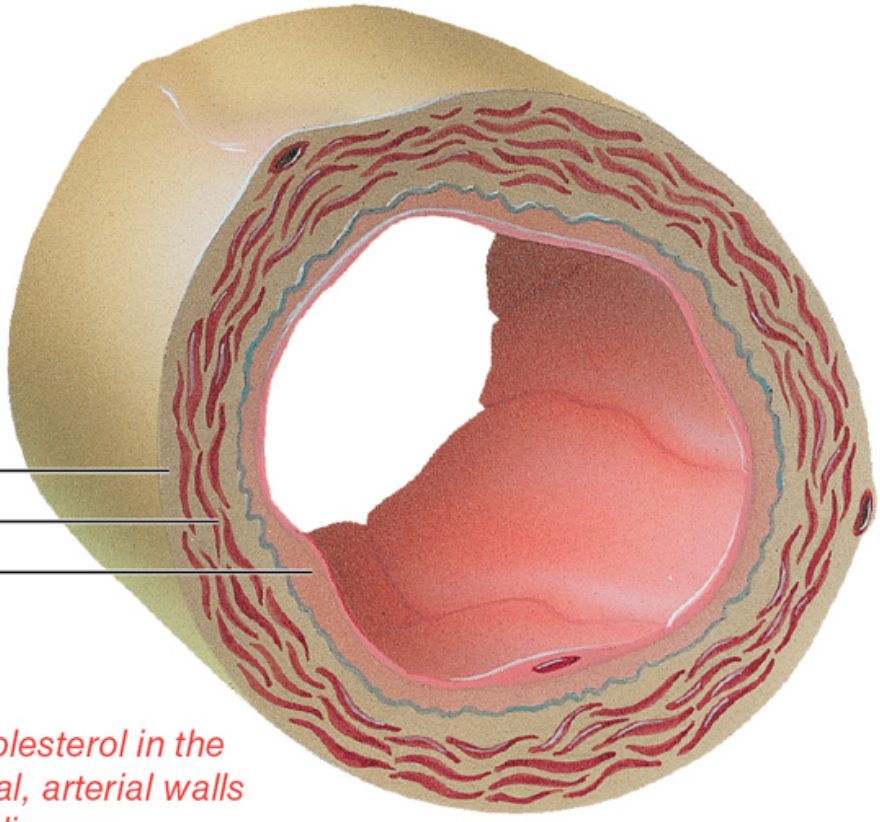
Figure 12-2 Determinants of myocardial oxygen supply and demand.

Oxygen supply to the heart is impacted by many factors, including coronary blood flow and oxygen extraction (see Fig. 12-2). Oxygen extraction by heart cells is high (~70%–75%) even at rest. When extra demand is placed on the heart, myocardial oxygen extraction increases slightly and plateaus at ~80%. Because oxygen extraction is increased only modestly when the heart is stressed, high oxygen demands must be met by increases in coronary blood flow.[7] The oxygen content of arterial blood also is important. Therefore, the hematocrit (Hct), hemoglobin (Hgb), and arterial blood gases should be monitored. In a similar fashion to targeting determinants of myocardial oxygen demand, pharmacologic control of angina is directed at improving oxygen supply through vasodilation of the epicardial coronary arteries.[5]

ATHEROSCLEROTIC VASCULAR DISEASE

Although understanding the determinants of myocardial oxygen supply and demand is important in treating CHD, of equal importance is understanding how atherosclerotic plaques develop because the underlying pathologic condition of this mismatch invariably is the presence of atherosclerosis in one or more of the coronary arteries. Understanding how the process of atherosclerosis unfolds, as well as the primary pharmacologic and nonpharmacologic interventions that help prevent progression of atherosclerosis, is an important piece in treating a patient with chronic stable angina (**Fig. 12-3**) (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease).

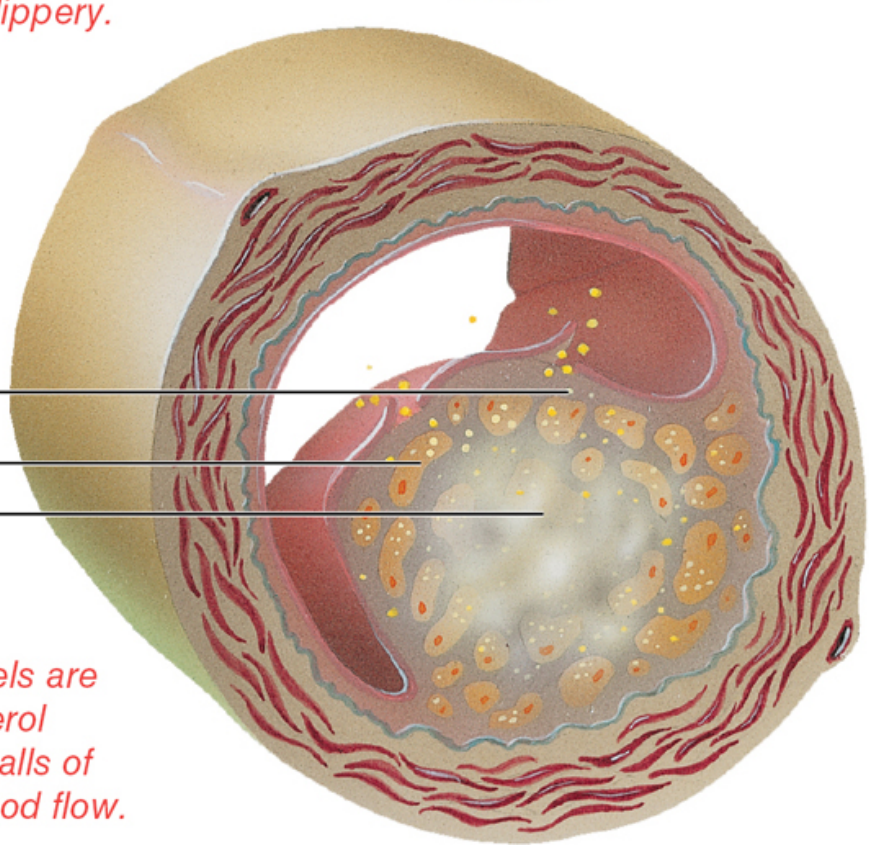
Atherosclerosis
A consequence of high cholesterol



Normal artery

Outer layer
Muscle layer
Lining

When the level of cholesterol in the bloodstream is normal, arterial walls remain smooth and slippery.



Clogged artery

LDL cholesterol
Foam cell
Plaque

When cholesterol levels are high, excess cholesterol accumulates in the walls of arteries, reducing blood flow.

Figure 12-3 Process of atherosclerosis. (Anatomical Chart Company. http://www.anatomical.com/.)

Traditional risk factors, such as smoking, hypertension, hyperlipidemia, diabetes, and obesity, are linked to the process of atherosclerosis by producing oxidative stress within the vasculature. Increased oxidative stress leads to progressive decreases in nitric oxide (NO) levels and endothelial dysfunction, enhancing atherosclerosis (**Fig. 12-4**).[8] In addition, diets typically seen in western industrialized countries have been linked to increased oxidative stress within the vasculature. This may partially explain the link between diet and atherosclerosis.[9] The role of a healthy lifestyle and diet is crucial in preventing the development or progression of CAD.

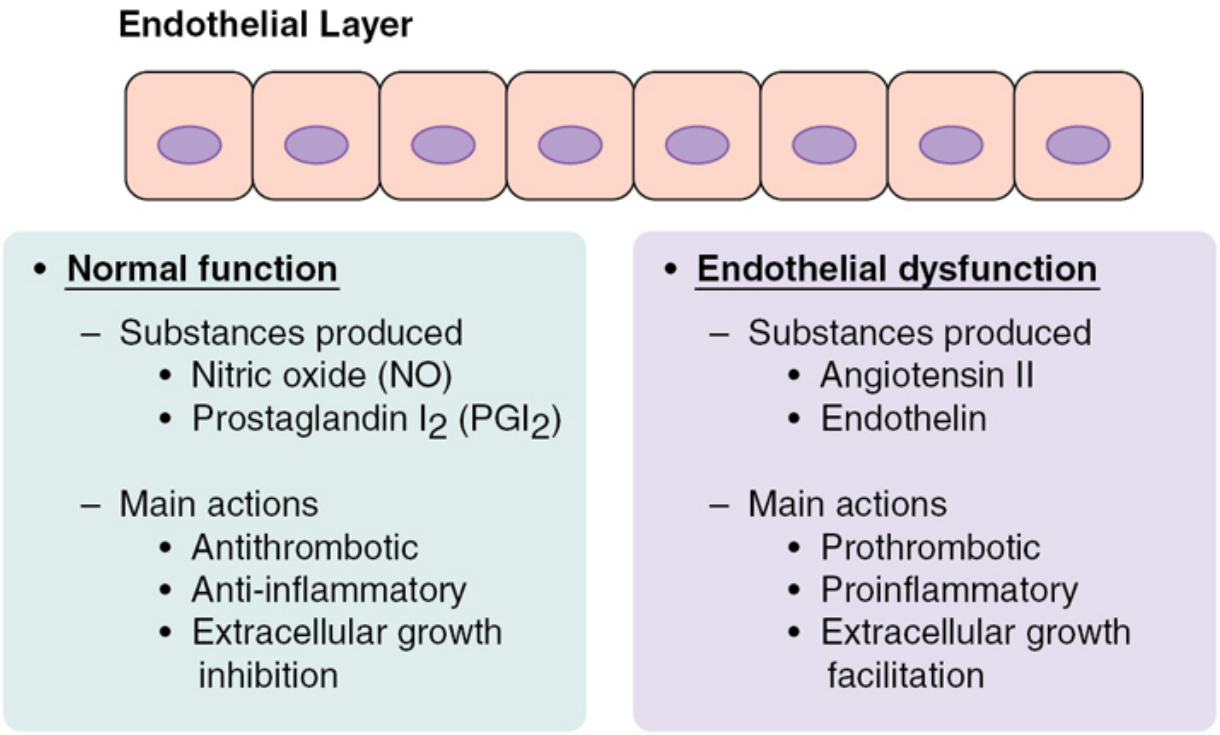


Figure 12-4 Endothelial function.

Although traditional risk factors have long been appreciated as the underlying cause for the development of CAD, continuing research efforts have attempted to identify novel risk factors to refine risk

assessment for the development of CAD. Potential candidates have included highly sensitive C-reactive protein, homocysteine, fibrinogen, and lipoprotein (a), among others.[10,11] Findings from the INTERHEART study indicate little may be gained from identifying additional risk factors.[12] In this large case–control study, nine clinical risk factors were strongly associated with the development of first-ever MI and accounted for >90% of the risk for developing CAD (**Table 12-1**). The results were consistent across sex, geographic regions, and ethnic groups, suggesting that strategies to reduce the incidence of CAD can be applied universally. Subsequent studies have verified the findings of INTERHEART, and many of these potential risk factors may indeed more accurately reflect the presence of CAD and be considered markers, as opposed to predicting who will subsequently exhibit CAD.[10,11,13]

Table 12-1

Risk Factors for First-Time Myocardial Infarction From the INTERHEART Study

Risk Factor	Adjusted Odds Ratio (99% Confidence Interval)
ApoB to apoA-1 ratio[a]	3.25 (2.81–3.76)
Current smoking	2.87 (2.58–3.19)
Psychosocial	2.67 (2.21–3.22)
Diabetes	2.37 (2.07–2.71)
Hypertension	1.91 (1.74–2.10)
Abdominal obesity	1.62 (1.45–1.80)
Moderate alcohol intake	0.91 (0.82–1.02)
Exercise	0.86 (0.76–0.97)
Vegetables and fruits daily	0.70 (0.62–0.79)
All combined	129.2 (90.2–185.0)

Apo, apolipoprotein.

[a]Risk of myocardial infarction increases with increased ratio.

Source: Reprinted from Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the

INTERHEART study): case control study. *Lancet*. 2004;364(9438): 937–952. © 2004 Elsevier. With permission.

PLATELET AGGREGATION AND THE FORMATION OF THROMBI

Although coronary atherosclerosis is the underlying mechanism for most patients with anginal syndromes, thrombotic factors commonly play a key role in the pathogenesis of myocardial ischemia. Both blood flow turbulence and stasis can cause intermittent platelet aggregation or intermittent coronary artery thrombosis. Thus, platelet-active agents are used in the treatment of chronic stable angina.[14]

INTRACELLULAR SODIUM AND CALCIUM HANDLING

The late sodium current (I_{Na}) plays a role in the development and maintenance of myocardial ischemia. Most sodium enters the myocardium in phase 0 of the action potential. Under normal conditions, however, a small amount of sodium will enter the cell during phase 2 (plateau phase) of the action potential. When ischemia is present, sodium handling is altered such that a substantial increase occurs in the late I_{Na}. The increase in intracellular sodium triggers an increase in the influx of calcium through the reverse mode of the sodium–calcium exchanger. The net result of the alterations in intracellular ion handling is intracellular calcium overload.[5] Increases in intracellular calcium impair myocardial relaxation, increase intramyocardial wall tension, decrease perfusion to the myocardium owing to compression of the small arterioles feeding the myocardium, and increase myocardial oxygen demand.[15] Ultimately, these pathologic changes in sodium and calcium handling perpetuate and worsen ischemia once it develops. Targeting this pathologic process has led to the development of new antianginal medications (eg, ranolazine) with a distinct, novel mechanism of action compared with traditional antianginal agents (ie, nitrates, β-blockers, and calcium channel blockers [CCBs]).[5]

Clinical Presentation

A detailed description of chest pain is vital in order for the clinician to determine whether chest pain represents chronic stable angina, acute coronary syndrome (ACS), or is noncardiac in origin. Five key components commonly used to characterize chest pain include the location, duration, severity, and quality of pain as well as any factors that provoke and relieve the pain (**Table 12-2**). Chest pain stemming from myocardial ischemia is often described as a sensation of pressure or heavy weight located over the sternum. Patients may also report shortness of breath (SOB), nausea, vomiting, or diaphoresis. Pain may also occur in the neck, jaw, shoulder, or arm. The precipitation of pain is typically associated with exertion and rapidly resolves with rest or the administration of NTG. Chest pain that occurs at rest, prolonged in duration, or increased in severity is likely reflective of unstable disease and warrants immediate medical attention to prevent complications such as MI, HF, and death. Importantly, some patients (females, people with diabetes) may present with atypical symptoms such as indigestion or gastric fullness, or may present with diaphoresis alone without concomitant chest pain. Last, many episodes of ischemia are asymptomatic and termed as "silent ischemia."[1–3]

Table 12-2
Characteristics of Angina Pectoris

Symptoms
Sensation of pressure or heavy weight on chest alone or with pain
Pain described variably as feelings of tightness, burning, crushing, squeezing, vicelike, aching, or "deep"
Gradual increase in intensity followed by gradual fading away (distinguished from esophageal spasm)[a]
Shortness of breath with feeling of constriction about the larynx of upper trachea
Duration of Symptoms
0.5–30 minutes
Location of Pain or Discomfort

Over the sternum or very near to it
Anywhere between epigastrium and pharynx
Occasionally limited to the left shoulder and left arm
Rarely limited to right arm
Lower cervical or upper thoracic spine
Left interscapular or suprascapular area
Radiation of Pain
Medial aspect of left arm
Left shoulder
Jaw
Occasionally, right arm
Electrocardiogram
ST-segment depression >2 mm
T-wave inversion
Precipitating Factors
Mild, moderate, or heavy exercise, depending on the patient
Effort that involves the use of arms above the head
Cold environment
Walking against the wind
Walking after a large meal
Emotions: fright, anger, or anxiety
Coitus
Nitroglycerin Relief[a]
Relief of pain occurring within 45 seconds to 5 minutes of taking nitroglycerin

[a]Esophageal spasm and other gastrointestinal disorders occasionally mimic anginal pain and also can be relieved by nitroglycerin.

Sources: Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic

Surgeons. *Circulation*. 2012;126:e354–e471. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. The task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41:407–477. Morrow DA, De Lemos JA. Stable ischemic heart disease. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt D, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 11th ed. Elsevier Saunders; 2019:1209.

Physical findings in patients with chronic stable angina are often absent or nonspecific.[1]

Diagnosis and Risk Assessment

The evaluation of a patient presenting with chest pain suspected to be because of CAD should begin with a detailed history of ischemic symptoms and physical examination. Once this information is available, an estimate can be made of the probability of CAD being present (low, intermediate, high).[1] The probability estimate will often help direct which diagnostic tests are appropriate. Given that many symptoms associated with chronic stable angina are nonspecific, several noninvasive and invasive testing modalities are available to assist in the diagnosis and risk assessment of CAD.[1,2] It is important to discern as soon as possible whether the patient's reported chest discomfort is consistent with chronic stable angina or represents the presence of ACS. Patients presenting with ACS often are at high short-term risk of MI or death and warrant hospitalization with aggressive treatment strategies.[16,17] Lipid parameters, renal function, and fasting blood glucose levels, A_{1c}, should be obtained in all patients with suspected or established CAD to screen for metabolic abnormalities. High-sensitivity C-reactive protein (hsCRP) offers some prognostic value, but its value is uncertain. Other biochemical markers such as lipoprotein(a), lipoprotein-associated phospholipase A_2, and apolipoprotein B are not routinely recommended.[3]

A 12-lead ECG reading should be obtained in all patients with symptoms suggestive of angina pectoris. Although not useful in establishing a definitive diagnosis of CAD, the ECG will be useful at

detecting important information regarding conduction abnormalities, left ventricular hypertrophy, ongoing ischemia, or evidence of a previous MI. Chest radiography is not routinely recommended, except in patients with an abnormal ECG, history of MI, symptoms of HF, or ventricular arrhythmias.[1] Cardiac computed tomography angiography (CCTA) is a reasonable option to determine risk in patients whose ECG cannot be interpreted, who are unable to exercise to an appropriate workload, unable to perform stress testing, or alternatively to invasive coronary angiography in patients at moderate-to-high risk of unknown coronary anatomy.[1]

STRESS TESTING

The induction of stress via exercise or pharmacologic means is a common and highly useful procedure in the diagnosis of CAD. The test would be indicative of CAD if angina, ECG signs of ischemia, arrhythmias, abnormal heart rate, or abnormal blood pressure (BP) response develops. The product of the heart rate and systolic BP (ie, the rate–pressure or double product) correlates well with myocardial oxygen demand. The rate–pressure product normally rises progressively during exercise, with the peak value best describing the cardiovascular response to stress. Often, patients with stable angina experience chest pain at a consistent rate–pressure product.[18]

Abnormal responses of either BP or heart rate may signal CAD. A normal BP response to exercise is a gradual rise in systolic BP with the diastolic BP remaining unchanged. A rise or fall of diastolic BP >10 mm Hg is considered abnormal. A fall in systemic BP during exercise is especially ominous because this indicates that the cardiac output cannot increase sufficiently to overcome the vasodilation in the skeletal muscle vascular bed.[18]

Stress imaging studies, either echocardiographic or nuclear, are preferred over the exercise tolerance test in patients with left bundle-branch block, electronically paced ventricular rhythm, prior revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]), preexcitation syndrome, >1

mm ST-segment depression at rest, or other ECG conduction abnormalities. In addition, many patients are not able to exhibit an appropriate level of cardiac stress through exercise; pharmacologic stress testing is preferred in these patients.[1,18]

Pharmacologic stress may be achieved through the use of dipyridamole, adenosine, or dobutamine. Each of these agents is used to induce changes in the balance between myocardial oxygen supply and demand, similar to walking on a treadmill during the exercise stress test. Vasodilators (dipyridamole and adenosine) promote vasodilation in normal coronary segments but have no effect in arteries affected by atherosclerosis. The net result is shunting of blood away from diseased coronary arteries and the development of ischemia that may be detected by changes in BP, heart rate, or ECG changes. These agents are typically used in conjunction with myocardial perfusion scintigraphy. Stress thallium-201 myocardial perfusion imaging provides a dynamic picture of the heart. The radionuclide is injected at peak stress and an image is obtained within several minutes. A defect in myocardial uptake of the thallium indicates an area of ischemia or possible infarction.[19]

Dobutamine is a positive inotrope and typically is used with echocardiography. Administration of dobutamine leads to an increase in myocardial oxygen demand secondary to increases in heart rate and contractility. If demand exceeds the available oxygen supply, ischemia develops. Subsequent to the infusion of dobutamine, defects or decreases in the wall motion or thickening of the left ventricle are indicative of ischemia.[19]

CARDIAC CATHETERIZATION

CAD can be diagnosed definitively by coronary catheterization and angiography. In addition, angiography is the most accurate means of identifying less common causes of chronic stable angina, such as coronary artery spasm.[1] Cardiac catheterization is a procedure used to provide vascular access to the coronary arteries. Once access is gained with an intravascular catheter, a number of procedures (angiography, ventriculography, PCI) can be performed. Access to

the vasculature is usually obtained percutaneously through the radial, brachial, or femoral arteries. From this point, the catheter is advanced through the vasculature until the coronary arteries are accessible. After the tip of the catheter is advanced into the coronary arteries, dye is injected into the coronary arteries and the location and extent of atherosclerosis can be determined. Approximately 75% of patients with chronic stable angina are noted to have one-vessel, two-vessel, or three-vessel disease by this procedure (equally divided).[3]

The results of angiography can be useful in determining the risk of death or MI in patients with CAD and, subsequently, the course of needed treatment. For example, patients who have a significant stenosis in the left main coronary artery are at high risk of death and should undergo CABG.[20,21]

OVERVIEW OF DRUG AND NONDRUG THERAPY

The goals of therapy for chronic stable angina are to reduce or eliminate the symptoms of angina, to maintain or improve the quality of life, halt the progression of atherosclerosis, and prevent complications of the disease, such as MI and death, while minimizing health care costs. Both pharmacologic and nonpharmacologic interventions, in addition to myocardial revascularization procedures, are utilized simultaneously to achieve each of these goals.[1]

Vasculoprotective Therapy

LIFESTYLE MODIFICATIONS

Lifestyle modifications should always constitute a significant portion of any treatment plan for patients with chronic stable angina. Lifestyle modification should include adoption of a heart-healthy diet, smoking cessation/avoidance of second-hand smoke, adequate

physical activity, weight control, and maintenance of an acceptable waist circumference.[1,22,23] Dietary recommendations typically consist of limiting saturated fat, total fat, cholesterol, sodium, sugar-sweetened beverages, and red meat while consuming a diet high in fruits, vegetables, whole grains, omega-3 fatty acids, and fiber[22] (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease). Adoption of a healthy dietary pattern reflective of these components has been demonstrated to have positive effects on cardiovascular risk factors.[1,22]

Smoking cessation is a crucial intervention as cigarette smoking (including second-hand smoke exposure) has been identified as the single most preventable cause of death because of CAD.[24] Clinicians should routinely assess the smoking status of patients with chronic stable angina and provide information regarding effective options to aid in smoking cessation. Nicotine replacement products, bupropion, and varenicline have been demonstrated as effective in assisting cessation efforts (see Chapter 91, Tobacco Use and Dependence). In addition to the avoidance of cigarette smoke, it is reasonable to recommend the avoidance of air pollution in patients with chronic stable angina. Unless contraindicated, it is appropriate to recommend one alcoholic beverage in females and one to two alcoholic beverages in males.[1]

A body mass index (BMI) of 18.5 to 24.9 kg/m^2 and a waist circumference <40 inches (101.60 cm) in males and 35 inches (88.90 cm) in females should be achieved or maintained. Adequate exercise facilitates both weight loss and better control of cardiovascular risk factors. Patients with chronic stable angina should be encouraged to engage in moderate-intensity exercise for 30 to 60 minutes per day for at least 5 days per week, but ideally each day. Weight loss can be facilitated through appropriate caloric restriction, as well as the adoption of healthy dietary eating patterns.[1]

RISK FACTOR MODIFICATION

In addition to appropriate lifestyle modifications, optimization of cardiovascular risk factors should be achieved. Although lifestyle

modifications may help improve risk factor control, pharmacotherapy may be required. **Table 12-3** provides appropriate targets for risk factor optimization. Appropriate identification and treatment of risk factors help prevent the development of CAD and disease progression in patients with existing CAD. Select drug therapies for each risk factor may be preferred because of their positive effects on the pathophysiology of atherosclerosis. Although several different classes of lipid-modifying drugs exist, 3-hydroxy-3-methylglutaryl co-enzyme A inhibitors (HMG-CoA reductase inhibitors, or statins) have been demonstrated in multiple trials to significantly reduce the progression of atherosclerosis, as well as reduce the incidence of death and MI.[25] In patients who require additional BP control after antianginal therapy has been optimized, angiotensin-converting enzyme (ACE) inhibitors may be preferred because of their theoretical potential to reduce the progression of CAD by improving endothelial function. Data suggest that angiotensin-receptor blockers (ARBs) may provide similar benefits in patients who cannot tolerate ACE inhibitors.[1,26] The presence of diabetes has been shown to be a significant risk factor for the development and progression of atherosclerosis; however, the majority of clinical trials demonstrate that tight glycemic control did not have a positive effect on the progression of atherosclerosis or reduce the risk of hard end points such as MI.[27] Information from the Diabetes Control and Complications Trial indicates that tight glycemic control with intensive insulin therapy in patients with type 1 diabetes significantly reduces the risk for MI and cardiovascular death.[28] Similar effects have not been seen in large randomized trials in patients with type 2 diabetes. In one large trial involving patients with CVD and type 2 diabetes, the use of intensive insulin therapy reduced nonfatal MI at 5 years, but total mortality was increased.[29] Given the available information, intensive glucose lowering cannot be recommended for patients with CAD and type 2 diabetes. Patients with type 2 diabetes should target a glycosylated hemoglobin (Hgb A_{1c}) <7%. The benefits in CVD of certain antihyperglycemic medications independent of A_{1c} lowering have been demonstrated and should be considered in patients with

both CVD and diabetes. Agents found to be beneficial for CVD include the sodium–glucose cotransporter 2 inhibitors empagliflozin, dapagliflozin, and canagliflozin and the glucagon-like peptide 1 receptor agonists liraglutide, semaglutide, and dulaglutide.[27]

Table 12-3

Recommendations for Risk Factor Optimization for Secondary Prevention in Patients with Coronary Heart Disease

Risk Factor	Intervention and Goal
Blood pressure	<130/80 mm Hg
	Use antihypertensives indicated for compelling indications as first-line therapy
Lipid management	High intensity, or maximally tolerated, statin
	Consider the addition of nonstatin therapy in very high-risk ASCVD when LDL-C remains ≥70 mg/dL
Diabetes	Hemoglobin A_{1c} <7%
	Sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit
Smoking	Complete cessation with the help of pharmacological and behavioral strategies
	Avoid passive smoking
Dietary intake	High intake of fruits, vegetables, and whole grains
	Limit saturated fat to <10% of total calories
Physical activity	30–60 minutes of moderate physical activity (eg, brisk walking) for most days of the week
Weight management	BMI between 18.5 and 24.9 kg/m^2

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol.

Sources: Grundy SM, Stone NJ, Bailey AL, et al. 2018 ACC/AHA/AACVPP/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350; Whelton PK, Carey RM,

Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:2199–2269; American Diabetes Association. Standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43(suppl 1):S1–S212; Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.

ANTIPLATELET THERAPY

Antiplatelet therapy has a central place in the treatment of patients with CAD. Aspirin (acetylsalicylic acid [ASA]) therapy has demonstrated a reduction in the incidence of MI and sudden cardiac death in patients with chronic stable angina. Aspirin's clinical efficacy in chronic stable angina, coupled with its minimal cost and demonstrated efficacy after MI, have made it the gold standard for antiplatelet monotherapy in patients with CAD. Current national guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) recommend an ASA dose of 75 to 162 mg daily for the prevention of MI and death. Although higher doses have been investigated in clinical studies, they have not shown increased efficacy but do increase the risk for adverse effects.[23]

Clopidogrel represents a suitable alternative antiplatelet agent to prevent MI and death in chronic stable angina patients unable to take ASA. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial demonstrated that clopidogrel significantly reduced the incidence of stroke, MI, or vascular death in patients with atherosclerotic vascular disease (previous MI, stroke, or peripheral arterial disease [PAD]) compared with ASA. In addition, clopidogrel was well-tolerated with the major adverse effects noted to be gastrointestinal (GI) intolerance and rash. Despite the significant results, the absolute difference in the primary outcome between the two strategies was quite small (0.4%, number need to treat = 200).[30] As such, clopidogrel remains a second-line choice behind ASA in patients with CAD. Clopidogrel should be administered at a dosage of 75 mg/day.

The approach of dual antiplatelet therapy (DAPT), combining ASA with a $P2Y_{12}$ antagonist (clopidogrel, prasugrel, or ticagrelor), has been demonstrated to improve morbidity and mortality in a number of patients at high risk of CVD.[16,17] Given the different mechanisms of antiplatelet effect, combining aspirin with a $P2Y_{12}$ antagonist might be expected to provide additional protection from MI and death in patients with stable CAD as compared to monotherapy. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial assessed the utility of long-term DAPT in patients with documented CAD or with multiple cardiovascular risk factors. The combination of ASA plus clopidogrel for 28 months did not reduce the risk of death, MI, stroke, or coronary revascularization as compared to ASA alone. However, dual therapy did increase the risk of bleeding.[31]

A post hoc analysis revealed a reduction in ischemic risk in patients with prior MI, suggesting that some patients may benefit from long-term DAPT.[31] The Pegasus-TIMI 54 trial evaluated the role of DAPT (low-dose ASA plus either ticagrelor 90 or 60 mg bid vs ASA alone) in patients with a prior MI in the previous 1 to 3 years.[32] The median time from MI to randomization was 1.7 years. In over 21,000 patients with a median follow-up of 33 months, ASA plus both doses of ticagrelor reduced the primary end point (cardiovascular death, MI, stroke) compared to ASA monotherapy. This reduction came at the expense of an increased risk of bleeding, with TIMI major bleeding occurring at a rate of 2.6% and 2.3% in the groups receiving ticagrelor 90 and 60 mg bid, as compared to 1.06% in patients receiving placebo.[32]

In a separate investigation, patients who received an additional 18 months of DAPT as compared to the standard duration of 12 months in patients who received drug-eluting stents (DESs) had a lower rate of stent thrombosis (0.4% vs 1.4%, $P < .001$) and major adverse cardiovascular and cerebrovascular events (4.3% vs 5.9%, $P < .001$), which included a reduction in MI.[33] There was an increase in moderate-to-severe bleeding (2.5% vs 1.6%, $P < .001$). Up to 40% of the 9961 patients underwent PCI because of chronic stable angina,

and DAPT either consisted of ASA plus clopidogrel or ASA plus prasugrel.[33] The duration of DAPT must be individualized. Whereas patients with stable IHD that are not post-MI or post-PCI do not require DAPT, some patients may receive extended durations of DAPT if they have a previous history of prior MI or are post-PCI and have received a DES.[34]

Anti-ischemic Pharmacotherapy

Historically, agents used in the treatment of patients with chronic stable angina primarily affected either determinants of myocardial oxygen supply or myocardial oxygen demand, or both. Within this paradigm, β-blockers, CCBs, and chronic nitrate therapy have demonstrated effectiveness in the prevention of ischemic symptoms. In January 2006, the U.S. Food and Drug Administration (FDA) granted approval to ranolazine. Unlike traditional anti-anginal medications, ranolazine does not affect heart rate or BP. The selection of specific anti-ischemic pharmacotherapy for patients with chronic stable angina should take into account relevant patient characteristics as well as guideline recommendations.

β-BLOCKERS

β-Blockers lower myocardial oxygen demand primarily by lowering heart rate and myocardial contractility. Neither β-selectivity nor the presence of α-1 blockade appear to vary efficacy at preventing ischemia, and, therefore, the choice of a specific agent for a given patient will likely depend on cost, number of daily doses, and the presence of other comorbid conditions. β-Blockers with intrinsic sympathomimetic activity are not routinely used in patients with stable angina because of reduced efficacy. The dose of the β-blocker should be titrated to a goal resting heart rate of 55 to 60 beats/minute and therefore will be patient-specific.[2] β-Blockers should be avoided in patients with primary vasospastic angina and may worsen symptoms in patients with reactive airway disease or PAD. The most common side effects observed with chronic therapy

include bradycardia, hypotension, fatigue, and sexual dysfunction. Other conditions that may prevent the use of β-blocker therapy include severe bradycardia or atrioventricular (AV) nodal conduction defects.[35–37]

NITRATES

Nitrates are available in a number of different formulations, and available options are listed in **Table 12-4**. Regardless of the formulation, all nitrate options are effective at preventing or relieving ischemic symptoms if used appropriately, including the use of a nitrate-free interval. Nitrates can increase myocardial oxygen supply through vasodilation of the coronary arteries, as well as reduce myocardial oxygen demand through the reduction of preload. Nitrates produce vasodilation through the biotransformation and the release of NO.[38] Long-acting nitrates are effective agents for the prevention of anginal symptoms. Sublingual NTG is a vital agent to treat acute anginal attacks. Common side effects of nitrate therapy include hypotension, dizziness, and headache. Headache often will resolve with continued therapy and may be treated with acetaminophen. Concomitant administration with phosphodiesterase type-5 inhibitors (within 24 hours for sildenafil and vardenafil, 48 hours for tadalafil) is contraindicated because of the risk of life-threatening hypotension.[38,39]

Table 12-4
Commonly Prescribed Organic Nitrates

Drug	Dosage Form	Duration	Onset (Minutes)	Usual Dosage
Short-Acting				
NTG	SL	10–30 minutes	1–3	0.4–0.6 mg[a,b]
NTG	Translingual spray	10–30 minutes	2–4	0.4 mg/metered spray[a,b]
NTG	IV	3–5 minutes[c]	1–2	Initially 5 μg/minute. Increase every 3–5 minutes until pain is relieved or hypotension occurs
Long-Acting[d]				
NTG	SR capsule	4–8 hours	30	6.5–9 mg every 8 hours
NTG	Topical ointment[e]	4–8 hours	30	1–2 inches every 4–6 hours[f]
NTG	Transdermal patch	4 to >8 hours	30–60	0.1–0.2 mg/hour to start; titrate up to 0.8 mg/hour[f]
NTG	Transmucosal	3–6 hours	2–5	1–3 mg every 3–5 hours[f]
ISDN	SL	2–4 hours	2–5	2.5–10 mg every 2–4 hours[f]
	Chewable	2–4 hours	2–5	5–10 mg every 2–4 hours[f]
	Oral	2–6 hours	15–40	10–60 mg every 4–6 hours[f]
	SR capsule	4–8 hours	15–40	40–80 mg every 6–8 hours[f]
ISMN[g]	Tablet (ISMO, Monoket)	7–8 hours	30–60	10–20 mg bid (morning and midday) to start; titrate to 20–40 mg bid[f]
	Extended-release tablet (Imdur)	8–12 hours	30–60	60 mg every day to start; titrate to 30–120 mg every day

bid, two times daily; ISDN, isosorbide dinitrate; ISMN, isosorbide monohydrate; IV, intravenous; NTG, nitroglycerin; SL, sublingual; SR, sustained release.

[a]When using sublingual or translingual spray forms of NTG, patients should administer the dose while sitting to minimize tachycardia, hypotension, dizziness, headache, and flushing. The optimal dose relieves symptoms with <10 to 15 mm Hg drop in systolic blood pressure or <10 beats/minute rise in pulse. Pain relief is rapid (onset 1–2 minutes; relief in 3–5 minutes), but up to three doses at 5-minute intervals may be given. After this, medical assistance should be summoned.

[b]Sublingual NTG tablets are degraded rapidly by heat, moisture, and light. They should be stored in a cool, dry place; do not leave the lid open or refrigerate. Tablets should be stored in the original manufacturer's container or a glass vial because the tablets volatilize and bind to many plastic vials and cotton. Previously, stinging of the tongue was an indicator of fresh tablets, but newer formulations only cause stinging in ~75% of patients.

[c]Duration after infusion discontinued.

[d]Longer-acting forms of nitrates are effective drugs, but it is important to understand their limitations to optimize effectiveness. Sublingual ISDN tablets display an onset and duration intermediate between that of sublingual NTG and oral ISDN. Because of high presystemic (first-pass) metabolism of the oral forms of both NTG and ISDN, very large doses may be required compared with SL or chewable dosage forms. Small oral doses (2.5 mg NTG, 5 mg ISDN) are probably not effective; doses as large as 9 mg NTG and 60 mg ISDN are not uncommon. Despite claims for longer activity, ointments and oral forms are often only effective for 4 to 8 hours, even when given as SR preparations. Also, continued daily use leads to rapid development of tolerance (see note f).

[e]Squeeze 1 to 2 inches of ointment onto the calibrated paper enclosed in the package with tube. Carefully spread the ointment on chest in a thin layer ~2 inches by 2 inches in size. Keep area covered with applicator paper. Wipe off previous dose before adding new dose or if hypotensive. If another person applies the ointment, avoid contact with fingers or eyes to prevent headache or hypotension.

[f]Dosage regimens should maintain a nitrate-free interval (eg, bedtime) to decrease tolerance development. Give last oral dose or remove ointment or transdermal patch at 7 PM. Give last dose of SR ISDN in early afternoon.

[g]Major active metabolite of ISDN; 100% bioavailable; no first-pass metabolism, but tolerance may still occur. Rapid-release form (ISMO, Monoket) as 10 and 20 mg tablets. Extended-release form (Imdur) as 60 mg tablets. Okay to cut Indur in half, do not crush or chew.

CALCIUM CHANNEL BLOCKERS

CCBs are highly diverse compounds. They differ markedly in chemical structure as well as specificity for cardiac and peripheral tissue. Using these characteristics, it is possible to classify CCBs into subtypes (**Table 12-5**).[40]

Table 12-5
Calcium Channel Blockers in Anginal Syndromes

Drug Name	FDA Approved[a]	Usual Dose for Chronic Stable Angina[b]	Product Availability
Dihydropyridines			
Amlodipine	Angina, hypertension	2.5–10 mg every day	2.5, 5, 10 mg tab
Felodipine	Hypertension	5–20 mg every day	5, 10 mg ER tab
Isradipine	Hypertension	2.5–10 mg bid	2.5, 5 mg IR cap
		5–10 mg every day	5, 10 mg CR tab
Nicardipine	Angina (IR only), hypertension	20–40 mg tid	20, 30 mg IR cap
		30–60 mg bid	30, 45, 60 mg SR cap
Nifedipine	Angina, hypertension	10–30 mg tid	10, 20 mg IR cap
		30–180 mg every day	30, 60, 90 mg ER tab
Nisoldipine	Hypertension	20–60 mg every day	10, 20, 30, 40 mg ER tab
Diphenylalkylamines			
Verapamil	Angina, hypertension, SVT	30–120 mg tid/qid	40, 80, 120 mg IR tab
		120–240 mg bid	120, 180, 240 mg SR tab
		120–480 mg every HS	180, 240 mg DR, ER tab
			120, 180, 240, 360 mg ER cap
			100, 200, 300 mg DR, ER tab
Benzothiazepines			
Diltiazem	Angina, hypertension, SVT	30–120 mg tid/qid	30, 60, 90, 120 mg IR tab
		60–180 mg bid	60, 90, 120, 180 mg SR cap
		120–480 mg every day	120, 180, 240, 300, 360 mg cap
			120, 180, 240 mg ER cap
			120, 180, 240, 300, 360, 420 mg ER cap

bid, two times a day; cap, capsules; CR, controlled-release; DR, delayed-release; ER, extended release; FDA, U.S. Food and Drug Administration; HS, bedtime; IR, immediate release; qid, four times a day; SR, sustained release; SVT, supraventricular including atrial fibrillation, atrial flutter, and reentry; tab, tablets; tid, three times a day.

[a]FDA-approved indications vary among IR and ER products. However, most or all have been used clinically for both angina and hypertension. Avoid IR products in hypertension.

[b]Because of short half-lives, most of these drugs are given tid if using IR tabs or caps. Amlodipine has a long half-life and is given once daily.

Both non-dihydropyridine CCBs (non-DHP CCBs), diltiazem and verapamil, exert similar effects on myocardial and peripheral tissue. They slow conduction and prolong the refractory period in the AV node (see Chapter 15, Cardiac Arrhythmias). Both agents can depress myocardial contractility and are moderate peripheral vasodilators and potent coronary artery vasodilators.[40]

In contrast to diltiazem or verapamil, the dihydropyridines (DHPs) such as nifedipine, amlodipine, felodipine, isradipine, and nicardipine do not slow cardiac conduction. They are more potent peripheral

vasodilators and may be associated with a reflex increase in the heart rate. The net effect of these actions results in no or minimal depression of myocardial function (see Chapter 14, Heart Failure).[40]

Both DHP and non-DHP CCBs produce an increase in myocardial oxygen supply through vasodilation of the coronary arteries, as well as reduce myocardial oxygen demand through lowering of intramyocardial wall tension (by lowering systemic BP). However, non-DHP CCBs would be expected to lower myocardial oxygen demand to a greater degree because of additional reductions in heart rate and contractility. Although defined as being within the same pharmacologic class, it is important to consider DHPs and non-DHPs separately when considering their use in patients with chronic stable angina. The reductions in heart rate and contractility with non-DHPs may be beneficial for some patients, although detrimental in others such as patients with compromised left ventricular (LV) function or bradycardia at baseline. Conversely, amlodipine and felodipine have been shown to be safe to use in patients with LV dysfunction and to provide a reasonable option for the prevention of ischemic symptoms in those patients.[40] CCB should be used cautiously when used in combination with cyclosporine, carbamazepine, lithium, amiodarone, and digoxin. Non-DHP CCB should be avoided in most situations because of the duplicate effects on heart rate and cardiac contractility.[1] Side effects of CCB therapy depend on the specific agent used. Use of non-DHP CCBs may result in bradycardia, hypotension, and AV block. Patients receiving DHP CCBs may experience reflex tachycardia, peripheral edema, headache, and hypotension.[3]

RANOLAZINE

Ranolazine is an anti-ischemic agent that inhibits the late sodium current, thereby reducing intracellular sodium. During myocardial ischemia, sodium influx is increased, leading to intracellular calcium overload through the sodium/calcium exchanger. An excess of intracellular calcium leads to changes that promote and worsen ischemia, such as increased intramyocardial wall tension and

reduced microvascular perfusion. By inhibiting sodium influx, ranolazine prevents ischemia-induced contractile dysfunction and delays the onset of angina. A key distinction between ranolazine and traditional antianginal agents is that it has no appreciable effect on heart rate and BP. The lack of significant hemodynamic effects makes the drug useful in patients in need of further antianginal therapy but who have low BP or heart rates preventing titration of conventional antianginal agents.[41]

Initial clinical trials demonstrated that ranolazine was an effective agent at reducing anginal episodes when added to existing therapy with CCBs or long-acting nitrates. Subsequent investigations demonstrated long-term safety and efficacy. Common adverse effects include headache, constipation, dizziness, and nausea. The drug is extensively metabolized in the liver through both cytochrome P-450 enzymes CYP3A4 and CYP2D6; therefore, attention should be paid to potential drug interactions. CYP3A4 appears to be the major pathway for metabolism and use of ranolazine is contraindicated in patients with significant hepatic dysfunction and in those receiving potent inhibitors and inducers of CYP3A4 such as ketoconazole or rifampin, respectively.[41]

Myocardial Revascularization

Revascularization of the myocardium, with CABG or PCI, is a mainstay in the treatment of patients with CAD. The goals of revascularization do not differ from the overall goals in treating patients with chronic stable angina, namely, to relieve symptoms, improve quality of life, and prevent MI and death. Historically, a great deal of focus was devoted to comparing CABG, PCI, and medical management and their relative efficacy in relieving symptoms and improving prognosis. In a broad population of patients with CAD, revascularization with either CABG or PCI was found to be superior to medical management therapy alone at relieving symptoms at 1 year, although there was no difference in overall mortality between the treatment strategies.[42] However, CABG therapy tended to be

superior at providing long-term relief of symptoms, as well as providing a lower need for repeat revascularization therapy compared to PCI. When considering subgroups of patients with more severe disease or who have manifested LV dysfunction, differences in long-term mortality can be observed among the different treatment strategies. In patients with double-vessel or triple-vessel disease, significant disease of the left main artery, or LV dysfunction, CABG therapy has been demonstrated to provide a reduced 5-year mortality rate compared with PCI or medical therapy alone.[21]

Despite the availability of data regarding the relative effects of PCI, CABG, and medical management on morbidity and mortality, there has been a dramatic increase in the use of PCI in recent years. CABG remains the preferred strategy for patients with three-vessel disease or who have multivessel disease plus LV dysfunction. In patients with less severe CAD, PCI can be expected to provide similar benefits in mortality as compared to CABG but may not be as effective at reducing symptoms or the need for repeat revascularization procedures. Recent investigations have indicated that aggressive medical treatment, including intensive lipid-lowering therapy, may be as effective as PCI at improving prognosis over the long term, but may be inferior at reducing symptoms of angina.[1,43,44] These trials are significant in that they highlight the importance of implementing effective strategies, which reduce the progression of CAD, regardless of whether revascularization therapy is utilized. Relevant issues facing pharmacists today not only include optimizing the medical management of CAD but also providing effective pharmacotherapy to prevent complications of PCI.

CASE 12-1

Question 1: J.P., a 62-year-old dairy farmer, is hospitalized for evaluation of chest pain. About 3 weeks before admission, he noted substernal chest pain brought on by lifting heavy objects or walking uphill. He describes a crushing or viselike pain that never occurs at rest and is not associated with meals, emotional stress, or a particular time of day. When J.P. stops working, the pain subsides in about 5 minutes.

J.P.'s mother and brother died of a heart attack at ages 62 and 57, respectively; his father, who is alive at age 86, has survived one heart attack and one stroke. Family history is negative for diabetes mellitus. J.P. is 70 inches (177.80 cm) tall and weighs 235 pounds (106.59 kg); he drinks two or three beers a day and does not smoke or chew tobacco.

J.P.'s other medical problems include a 10-year history of hypertension and diabetes for 4 years. Until 3 weeks ago, J.P. could perform all his farm chores without difficulty, including heavy labor. He follows a no-added-salt diet, but consistently eats at fast-food establishments with his favorite meal consisting of two cheeseburgers and French fries.

J.P.'s medication history reveals the following: lisinopril 10 mg once daily, metformin 500 mg bid, and hydrochlorothiazide 25 mg once daily. He rarely uses over-the-counter (OTC) medications. He has an allergy to sulfamethoxazole.

On admission to the cardiac ward, J.P. appears his stated age and is in no apparent distress. Resting vital signs include supine BP, 145/95 mm Hg (last ambulatory visit, 130/85 mm Hg); regular pulse, 84 beats/minute (last ambulatory visit, 78 beats/minute), and respiratory rate, 12 breaths/minute. He has no peripheral edema or neck vein distension, and lung auscultation is within normal limits. Abdominal examination is unremarkable, and he is alert and oriented three times. Cardiac auscultation reveals a regular rate and rhythm with a normal S_1 and S_2; third or fourth heart sounds and murmurs are not noted. A 12-lead ECG reveals normal sinus rhythm at a rate of 84 beats/minute without evidence of previous MI. All intervals are within normal limits.

Admitting laboratory values include the following:

Hct, 43.5%
White blood cell (WBC) count, 5000/mL
Sodium (Na), 140 mEq/L
Potassium (K), 4.7 mEq/L
Magnesium (Mg), 1.9 mEq/L
Random blood glucose, 132 mg/dL
Hgb A_{1c}, 7.4%
Blood urea nitrogen, 27 mg/dL
Serum creatinine, 1.4 mg/dL
Urinary albumin–creatinine ratio, 27 mg/mmol

Chest radiograph is within normal limits.

What signs and symptoms does J.P. exhibit that are consistent with the diagnosis of chronic stable angina?

CLINICAL PRESENTATION OF CHRONIC STABLE ANGINA

J.P.'s description of his chest pain includes several common characteristics of angina pectoris (see Table 12-2).[1–3] The substernal location of J.P.'s chest pain is typical, although some patients describe pain radiating down the left arm or pain that is referred to the shoulder area or jaw. J.P.'s pain is described as crushing or viselike in quality, which also is common; a fullness in the throat or jaw may occur simultaneously or in lieu of chest pain. In some cases, the patient may not consider these sensations as pain, describing them instead as a sense of pressure or heaviness. Many patients report SOB. J.P.'s symptoms are related to exercise and exertion—both known precipitating factors of angina. Most episodes of exertional angina last several minutes in duration and are relieved with rest. Because J.P. has never sought medical attention for his chest pain, his response to NTG cannot be determined.

After getting a detailed description of J.P.'s symptoms, his physician can characterize his chest pain and make a global assessment. Initially, the chest pain should be classified as either typical angina, atypical angina, or noncardiac chest pain. Furthermore, angina should also be classified as either stable or unstable. This distinction is important because it indicates whether his short-term risk of an acute coronary event could be life-threatening. Attempts to categorize J.P.'s anginal symptoms on an objective measurement scale (eg, Canadian Cardiovascular Society Grading Scale) can be misleading.[45] For example, a sedentary 65-year-old patient's class II symptoms may be tolerable, but the same symptoms could significantly disable an active 50-year-old patient.

J.P.'s chest pain is of a quality and duration characteristic of angina, provoked by exertion, and relieved by rest; therefore, J.P.'s constellation of symptoms can be classified as typical chest pain. J.P.'s symptoms do not occur at rest; however, they should be classified as stable angina.[1–3]

Case 12-1, Question 2: Assess J.P.'s physical examination. What signs and symptoms are relevant to the angina?

The physical examination typically provides little information about the presence of CAD. The most useful findings pertain to the cardiovascular system where heart rate and BP can be increased during an acute anginal episode. J.P.'s physical examination is characteristic of a male of his age with angina.[3] He is obese and hypertensive, but his cardiac examination is normal. The presence of murmurs would have required further workup; the absence of a third heart sound suggests that the left ventricle may be functioning normally (see Chapter 14, Heart Failure, for a description of third heart sounds). The absence of a fourth heart sound in J.P. is indicative of a low probability of cardiac end-organ damage resulting from systemic hypertension. His chest radiograph, which is normal, does not present evidence of other complications commonly associated with myocardial ischemia (eg, enlarged heart, HF).

J.P.'s physical examination should also evaluate the possibility of the presence of atherosclerosis in other major vascular beds (peripheral vascular disease, cerebrovascular disease, abdominal aortic aneurysm). The presence of xanthomas would suggest severe hypercholesterolemia, but these were not noted in J.P.

Diagnostic Procedures

Case 12-1, Question 3: What other objective diagnostic procedures are helpful to confirm CAD and angina in J.P.?

A 12-lead ECG indicates there is no ongoing ischemia at this time. As such, it does not help confirm the diagnosis of CAD. An echocardiogram could be used to better assess cardiac structure and function, including ruling out other potential causes for myocardial ischemia such as valvular dysfunction or pericardial disease, but would not definitively confirm the presence of CAD.

Electron bean computed tomography or CCTA could be used to detect the presence of coronary atherosclerosis, but in J.P. would not offer vital prognostic information available with other testing modalities.[1]

Given J.P.'s current lifestyle and activity level, he would likely be able to tolerate exercise treadmill testing. Treadmill testing would be an appropriate initial diagnostic modality in J.P. because of its noninvasive nature, reliability with established protocols, as well as the ability to offer prognostic information regarding the risk of MI and death for J.P. Therefore, stress testing, in this case with exercise treadmill versus pharmacologic means, is an excellent initial diagnostic modality to use in J.P.

Case 12-1, Question 4: Should J.P. undergo cardiac catheterization? How will the results of this invasive procedure influence future therapy?

Coronary catheterization and angiography are the best tests for the definitive diagnosis of CAD. In addition, angiography is the most accurate means of identifying less common causes of chronic stable angina, such as coronary artery spasm.[1] Although angiography is effective at identifying flow-limiting atherosclerotic plaques in the coronary vasculature, it cannot provide information on whether those lesions are causing clinical symptoms. Stress testing is often a more appropriate initial modality to first characterize the myocardial ischemia that takes place with exertion. Patients with significant ischemia via stress testing should then undergo cardiac catheterization to determine the nature and extent of disease. The results of angiography will be useful in determining the risk of death or MI in J.P. and, subsequently, the course of needed treatment. For example, patients who have a significant stenosis in the left main coronary artery are at high risk of death and should undergo CABG.[20]

Risk Stratification and Prognosis

Case 12-1, Question 5: After having a positive treadmill stress test and undergoing subsequent cardiac catheterization, J.P. is found to have two-vessel CAD with obstructive lesions of 55% and 70% in the right coronary artery (RCA) and circumflex arteries, respectively; the left anterior descending (LAD) coronary artery is not involved. What is his prognosis?

The prognosis of patients with stable angina is variable and dependent on the presence of other factors and comorbid conditions. The extent of CAD, quantification of ventricular function, the response to stress testing, and the initial clinical evaluation all help to provide an estimate of risk in a given patient. Developing a level of risk for a particular patient helps determine the appropriate treatment strategy.[1,2]

J.P.'s history and physical examination suggest he does not have HF; poor LV function would be an ominous concurrent finding. J.P. also does not have three-vessel disease or blockage of the LAD artery. J.P. does have type 2 diabetes, which elevates his risk for future cardiovascular events. The absence of other major comorbid conditions and myocardial dysfunction, along with the current extent of CAD, indicates that J.P.'s prognosis at this time is favorable provided he initiate appropriate treatment strategies demonstrated to reduce morbidity and mortality in patients with CAD.[1,2]

Medical Management of Chronic Stable Angina

Case 12-1, Question 6: How should J.P. be managed at this time? Should he undergo revascularization with PCI or CABG or be managed medically?

As discussed, goals for managing CAD and angina in J.P. include relief of symptoms and reduction of myocardial ischemia to improve quality of life, as well as prevention of major complications of CAD such as acute MI and death.[1] Depending on the patient, both goals may be accomplished through revascularization (surgical or percutaneous), medical management, or both. Regardless of the

treatment strategy chosen to relieve ischemic symptoms, therapies that prevent death (vasculoprotective agents) should receive priority.

Presently, CABG is not the best option for J.P. because the usual indications for surgical therapy include presence of left main CAD, presence of three-vessel disease (especially if LV function is impaired), or ineffectiveness of medical therapy.[1,20] However, revascularization with PCI is a potential option along with medical management alone. Although PCI would offer no mortality advantage over medical therapy at this time, it has been shown to decrease the incidence of recurrent symptoms in the short term (1 year).[1] If J.P. can implement aggressive lifestyle modifications and control of risk factors, progression of CAD and control of ischemic symptoms will be similar to PCI within a 5-year time frame.[42] Both strategies, including the pros and cons of PCI or medical management alone, should be offered to J.P. so that an informed decision can be made in accord with his wishes. Overall, J.P. will probably do well with medical therapy. His life expectancy depends on the progression of the disease and development of other complications of CHD (HF, MI, sudden cardiac death).

RISK FACTORS AND LIFESTYLE MODIFICATIONS

Case 12-1, Question 7: What independent risk factors for CAD are present in J.P.? Which of these may be altered?

The first step in the treatment of any patient with chronic stable angina or CAD should be the modification of any existing risk factors and the adoption of a healthy lifestyle. By addressing the underlying circumstances, which likely led to the development of CAD, a significant impact can be made at halting the progression of the disease and preventing complications of CAD. Current recommendations for the goals for risk factor management are listed in Table 12-3.[23,25,26] In addition to specific risk factor goals, attention should be paid to evidence that favors specific drug therapies that have evidence supporting reductions in morbidity and mortality.

Examples would include the use of HMG-CoA reductase inhibitors in the treatment of hyperlipidemia,[1,2] as well as the use of ACE inhibitors for the treatment of hypertension.[25,26]

J.P. has several risk factors for CAD, some of which cannot be altered, such as middle age, male sex, and a strong family history of CAD. Risk factors, such as hypertension, obesity, hypercholesterolemia, smoking, and possibly stress, can potentially be modified to decrease the likelihood of adverse sequelae for J.P. His hypertension should be controlled, and statin therapy should be initiated (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease). A fasting Hgb A_{1c} should be drawn with a goal of <7% (see Chapter 53, Diabetes Mellitus). Dietary modification and weight reduction for J.P. are mandatory because they positively influence several risk factors. J.P., however, does not smoke cigarettes, which would significantly increase his cardiovascular risk.[1,22] J.P.'s active lifestyle may influence his prognosis favorably.[1]

DIETARY INTERVENTIONS

CASE 12-1, QUESTION 8: Are there any dietary patterns that J.P. can adopt that have demonstrated reductions in cardiovascular end points?

Although the positive effects of lifestyle modifications on cardiovascular risk factors are well-recognized, the effect of specific lifestyle interventions on reducing hard cardiovascular end points can be underappreciated. The adoption of a healthy dietary pattern is one such example. Randomized controlled trials have demonstrated that the adoption of the Mediterranean diet (diets emphasizing whole grains, fruit, vegetables, nuts and legumes, moderate dairy intake, moderate amounts of lean protein, and polyunsaturated fats) reduced the relative risk of MI or cardiac death by 50% to 73% as compared to a diet similar in composition to the AHA Step I diet.[46] It is important to note that in one of these studies, the Lyon Diet Heart Study, the improvements in cardiovascular

morbidity and mortality occurred without significant changes in the lipid profiles of study subjects.[46] One trial found the Mediterranean diet supplemented with either nuts or olive oil reduced cardiovascular events in patients at high risk of CVD when compared to a low-fat diet.[47] Several additional trials demonstrated that patients with a history of MI who increased their intake of either fatty fish or ingested omega-3 fatty acid fish oil supplements also had reductions in cardiovascular death and MI as compared to control patients without dietary intervention.[48] Lastly, epidemiologic studies have confirmed the results from randomized controlled trials showing that adherence to a Mediterranean diet significantly reduces cardiovascular morbidity and mortality.[46] A Mediterranean diet reduces systemic inflammation as measured by C-reactive protein, reduces the incidence of insulin resistance, and improves endothelial function. Although a great deal of attention has been directed at the increased intake of omega-3 polyunsaturated acids (eicosapentaenoic acid and docosahexaenoic acid derived from fish or α-linoleic acid derived from plants) being responsible for the observed benefits in each of these trials, multiple dietary alterations were likely in play. The results should be interpreted as the result of the adoption of a healthy dietary pattern.[22]

Case 12-1, Question 9: J.P. states he had heard that antioxidants such as vitamin E could benefit him along with a daily B vitamin. Would these supplements offer significant cardiovascular benefit for J.P.?

Because oxidation of low-density lipoprotein (LDL) in the arterial wall is a key step in the atherosclerotic process, considerable interest exists in the theory that supplementation with high doses of antioxidants such as vitamin E, vitamin C, and β-carotene might mitigate this process and slow the progression of atherosclerosis. Multiple large randomized studies have shown no positive effect from supplemental intake of antioxidants such as vitamin E on the incidence of cardiovascular outcomes including MI or death.[1,49] These findings were observed in both primary and secondary

prevention of cardiovascular events. J.P. should be informed that supplemental intake of vitamin E will not have any positive effect on his CVD.

Interest in the use of supplemental intake of folic acid and B vitamins stems from their ability to lower homocysteine levels. It is well-established that elevated levels of homocysteine are associated with a higher incidence of CVD.[50] Despite this association, the great majority of appropriately designed, randomized, placebo-controlled studies have demonstrated that supplemental ingestion of folic acid and B vitamins has no impact in reducing cardiovascular outcomes such as MI or death.[1,51] Therefore, similar to the advice for vitamin E, J.P. should be counseled that folic acid and B vitamin supplementation will not provide any tangible cardiovascular benefit.

Anti-ischemic Drug Therapy

SUBLINGUAL NITROGLYCERIN

Case 12-1, Question 10: Should J.P. receive a prescription for SL NTG on discharge from the hospital? If so, what education should J.P. receive with regard to the use and storage of SL NTG?

All patients with CAD, especially those with chronic stable angina, should receive a prescription for SL NTG for the treatment of acute anginal attacks.[38,39] NTG leads to vasodilation of both veins and arteries that reduces myocardial oxygen demand, thereby relieving angina. Because response to NTG varies among patients, the dosage should be individualized (Table 12-4). Most patients, however, use a dose of 0.4 mg. The administration of sublingual NTG is also useful in patients who have a good understanding of what level of exertion produces their chest pain. About 5 to 10 minutes before J.P. is about to undergo heavy exertion, he can take a sublingual NTG tablet to prevent angina.[1]

Patient education is a crucial component of ensuring SL NTG is used appropriately to treat acute anginal attacks. When angina

occurs, J.P. should sit down immediately and utilize his SL NTG. If using tablets, he should place the NTG tablet under his tongue; he should not swallow it. If using the NTG spray, he should apply the spray on or under the tongue and not swallow or inhale it. Many patients experience dizziness and light-headedness, which is minimized by sitting. The onset of action is within 1 to 2 minutes, and pain usually is relieved within 3 to 5 minutes. If the pain persists or is unimproved 5 minutes after the first dose of NTG, the patient should call 9-1-1 as they may be experiencing an MI.[1] If he needs more than one dose, he can take a maximum of 1.2 mg in 15 minutes.

The tablets should be dispensed in the original, unopened manufacturer's container and stored in the original brown bottle. Because sublingual NTG tablets are degraded by heat, moisture, and light, they should be stored in a cool, dry place, but not refrigerated. The bottle should be closed tightly after each opening. Safety caps should not be used, although patients should be cautioned to keep all medications out of the reach of children. The cotton plug sometimes is difficult to remove. Therefore, it should be discarded on initial receipt of the prescription and should not be replaced. Use of cotton other than that supplied by the manufacturer should be discouraged because NTG tablets are volatile and are adsorbed by household cotton. This results in a significant loss in tablet effectiveness. Expiration dating should be monitored closely, and tablets should be replaced immediately if they are exposed to excessive light, heat, moisture, or air. Once a container is opened, the tablets should be used for only a limited time—usually from 6 months to 1 year.[1]

ADRENERGIC BLOCKERS

Case 12-1, Question 11: Given J.P.'s active lifestyle and recent history of frequent anginal attacks, the medical team wishes to optimize chronic preventative therapy for chronic stable angina. J.P. currently is receiving metformin 500 mg bid, lisinopril 10 mg once daily, and hydrochlorothiazide 25 mg once daily. His current resting heart rate and BP are 78 beats/minute and 135/90 mm Hg, respectively. Is a β-blocker the best initial option for chronic stable angina in J.P.?

Options for chronic prevention of anginal episodes include β-blockers, CCBs, long-acting nitrates, and ranolazine. Current guidelines recommend that β-blockers should be administered before a nitrate or a CCB when long-term therapy is indicated.[1,2] β-Blockers are very effective at reducing anginal symptoms and ischemia, including silent myocardial ischemia.[1,2] β-Blockers also significantly increase exercise tolerance and time to ST-segment depression during exercise testing.[36] Several cohort and case–control studies have shown that β-blockers improve clinical outcomes, including reductions in mortality in patients with chronic stable angina or CAD.[52–56] In addition, evidence indicates that β-blockers may also slow the progression of atherosclerosis.[57] In a meta-analysis of clinical trials that compared the three classes of anti-ischemics, no differences in long-term mortality were noted. β-Blockers, however, were more effective in lowering the incidence of anginal episodes.[58] In addition, β-blockers clearly lower morbidity and mortality in patients with CAD[17,19] and HF.[36] Overall, the body of literature available supports the recommendation that all patients with angina should receive a β-blocker as initial therapy unless contraindicated.[59] J.P. at this time does not appear to have any contraindications to β-blocker therapy, and β-blocker therapy should be initiated.

Case 12-1, Question 12: How should therapy with a β-blocker be optimized in J.P.?

All patients receiving antianginal drugs should be monitored for frequency of angina attacks and SL NTG consumption. Traditionally, clinicians have monitored the reduction in resting heart rate and have progressively increased the β-blocker dose until the resting heart rate was 55 or 60 beats/minute.[36] J.P. currently has a heart rate of 78 beats/minute and preserved BP. If J.P. continues to have preserved BP and his heart rate remains above 55 to 60 beats/minute after the initiation of β-blocker therapy, a doubling of his

dose would be a reasonable increase, with close monitoring of heart rate and BP. Additional goals with β-blocker therapy include a maximum heart rate of 100 beats/minute or less with exercise. Resting heart rate <50 beats/minute may be acceptable, provided the patient is asymptomatic and heart block is not present. Variations in resting heart rate are normal and subject to the influence of the endogenous sympathetic nervous system and other exogenous factors, such as drugs, tobacco, and caffeine-containing beverages. β-Blockers with intrinsic sympathomimetic activity (eg, pindolol) will not reduce the resting heart rate as much as β-blockers lacking this activity.[35]

Exercise stress testing is probably the most accurate, but least practical, method of documenting the adequacy of β-blocker therapy. During an exercise tolerance test, a β-blocker should substantially increase the time J.P. walks before developing angina. There also may be a reduction in ST-segment depression during exercise, indicating less myocardial ischemia. The rate–pressure product probably will be markedly lower, reflecting a decrease in both heart rate and systolic wall tension.[34] An alternative to conducting a formal stress test is to repeat the physical activity that produced angina during this hospitalization, namely, walking a few flights of stairs.

Case 12-1, Question 13: Would the decision to use β-blockers initially in J.P. be altered if he had a history of reactive airway disease such as asthma or PAD?

Although all β-blockers are equally effective in the treatment of angina, the addition of reactive airway disease or PAD to J.P.'s medical history would pose several relative contraindications to the use of some β-blockers. The concern directly relates to the potential for β-blockers to worsen either bronchoconstriction in the case of asthma by blunting β_2 receptors or worsening vasoconstriction in the peripheral arteries, again, through blunting vasodilation through β_2-receptors. Although not absolute contraindications, the presence of

these disease states warrants careful monitoring of β-blocker therapy during initiation and titration.[34]

Cardioselective β-blockers, such as metoprolol, are often considered in patients with reactive airway disease or PAD with the hope that β_2-receptors will be unaffected. In one meta-analysis, cardioselective β-blockers were better tolerated than nonselective β-blockers in patients with asthma.[60] Cardioselective β-blockers also are less likely to inhibit β_2-mediated vasodilation in the peripheral arterioles. Therefore, cardioselective β-blockers are preferred over nonselective β-blockers for patients with PAD and Raynaud disease.[2,61]

Unfortunately, cardioselectivity is not an all-or-none response; instead, it is a dose-dependent phenomenon. As the dose is increased, cardioselectivity is lost. The dose at which cardioselectivity will be lost in any given patient cannot be predicted, and even a very small dose (eg, metoprolol 50–100 mg) could cause wheezing.[35,61] If β-blocker therapy is to be initiated in a patient with reactive airway disease or PAD, close monitoring for worsening of symptoms should occur and an alternative anti-ischemic medication should be used if symptoms worsen.

In the event that β-blocker therapy is not tolerated or considered too risky, initial therapy with a heart-rate–controlling CCB is the next best option, provided there is adequate heart rate and BP to tolerate therapy. In patients who already have low heart rate and/or marginal BP, ranolazine may be considered as an initial option. Long-acting nitrates are typically reserved for add-on therapy for reasons that will be subsequently discussed.[1]

Case 12-1, Question 14: J.P. is being discharged from the hospital today with prescriptions for SL NTG 0.4 mg tablets, metoprolol succinate 100 mg once daily, metformin 500 mg bid, and lisinopril 20 mg once daily, and education regarding diet and exercise. Is there anything else J.P. should receive for his chronic stable angina?

Antiplatelet therapy is a cornerstone in the management of a patient with atherosclerotic vascular disease. Antiplatelet therapy

reduces the incidence of CVD events such as MI, stroke, and death. Although newer antiplatelet options are available, aspirin is still the first-line choice for patients with atherosclerotic vascular disease because of well-established efficacy and cost-effectiveness.[1]

The mechanism of action for aspirin's antiplatelet effect is inhibition of cyclooxygenase (see Chapter 11, Thrombosis). By acetylating the active site of cyclooxygenase, aspirin blocks the formation of prostaglandin endoperoxides from arachidonic acid. This inhibits the formation of both thromboxane and prostacyclin. Thromboxane A_2 is a potent vasoconstrictor and facilitates further activation of platelets. Prostacyclin (PGI_2) counterbalances the effect of thromboxane A_2, because it is a potent inhibitor of platelet aggregation and a vasodilator.[62]

Although it has been theorized that higher doses of aspirin would produce a higher level of efficacy than low doses, all available literature indicates that low dosages of aspirin (75–325 mg/day) are as effective as higher dosages (625–1300 mg/day) in the treatment of patients with angina.[62] Conversely, as the aspirin dosage increases, the incidence of adverse effects, especially GI bleeding, increases. Therefore, current guidelines recommend a daily dosage of 75 to 162 mg orally for the prevention of MI and death in patients with CAD.[1] Given this information, J.P. should be advised to take aspirin at a dose of 81 mg/day to maintain efficacy but decrease the risk of adverse effects.

CASE 12-1, QUESTION 15: J.P. returns to the hospital with recurrent angina 8 weeks after he was discharged. He mentioned he stopped his metoprolol 36 hours ago when he forgot to get his prescriptions refilled. He is transported to the hospital emergency department for treatment of angina unresponsive to three NTG tablets. How could J.P.'s situation have been avoided?

The β-blocker withdrawal syndrome is a rebound phenomenon resulting from heightened β-receptor density and sensitivity (ie, upregulation) subsequent to receptor blockade. It places patients with CAD at high risk for adverse cardiovascular events, which may

include acute MI and sudden cardiac death. An “overshoot” in heart rate, as a consequence of sympathoadrenal activity from abrupt β-blocker withdrawal increases myocardial oxygen demand and platelet aggregation. Withdrawal syndromes may be less severe in patients taking β-blockers with partial agonist activity.[34–36]

If β-blockers are to be discontinued, a gradual tapering schedule (preferably for 1–2 weeks) should be used. Shorter periods for β-blocker withdrawal (eg, 2–3 days) have been proposed, although the optimal strategy for discontinuation is not known. Ensuring that β-blockers are tapered and that the patient is reasonably monitored for adverse events for the duration of the taper is imperative. Patients should limit physical activity throughout the β-blocker withdrawal period and seek prompt medical attention when angina symptoms become apparent. Patients should be warned not to precipitously discontinue their β-blockers. Failure to renew prescriptions and financial hardship are common reasons for abrupt discontinuation, and clinicians need to have sufficient professional rapport with patients to understand when patients encounter difficulties in obtaining medications.

LONG-ACTING NITRATES

Case 12-1, Question 16: J.P. recovers quickly and is discharged from the hospital after 48 hours. He does well during the next several months, but he is still bothered by occasional angina episodes, two to four times a week. The attacks usually are precipitated by strenuous work and are relieved by rest and two or three NTG tablets. The quality and location of the pain are unchanged, although the duration has increased by 1 or 2 minutes. He follows a low-cholesterol, no-added-salt diet. Physical examination is unchanged except for a 20-pound (9.07 kg) weight loss. Vital signs include the following: supine BP, 119/76 mm Hg; heart rate, 60 beats/minute; and respiratory rate, 12 breaths/minute. J.P.’s cardiologist elected to start a long-acting prophylactic nitrate (isosorbide mononitrate) as well as continuing his metoprolol succinate (100 mg daily), lisinopril (20 mg daily), aspirin (81 mg daily), and metformin (500 mg twice daily). Is a long-acting nitrate the best add-on option for J.P.’s chronic stable angina?

Long-acting nitrates occupy a key role in the prevention of angina of all types. The goals of therapy are to decrease the number, severity, and duration of J.P.'s anginal attacks. A CCB could be prescribed for J.P. instead of isosorbide mononitrate because he has no contraindications to this class of drugs. A CCB would have been a good alternative if his BP had remained elevated, but for now, J.P.'s BP and pulse are within the desired range. Nitrates can also affect BP but will likely do so to a lesser extent than CCBs. Because sublingual nitrates were well-tolerated by J.P., a long-acting nitrate would be acceptable. If a CCB is considered at this point, a DHP should be used because they have no effect on heart rate, unlike diltiazem or verapamil. Lastly, ranolazine would be an option for add-on therapy, especially if J.P. experiences any adverse hemodynamic effects from either a CCB or long-acting nitrate. Ultimately, the decision for additional therapy is based on the prescriber's personal choice and past experience, as well as the entire spectrum of the patient's disease complex.[63]

Case 12-1, Question 17: Will J.P. develop tolerance to the long-acting nitrate?

Although not completely understood, several mechanisms of nitrate tolerance have been proposed, including the increased production of catecholamines, plasma volume expansion, and activation of the renin–angiotensin–aldosterone system.[64]

All organic nitrates exhibit similar hemodynamic effects through a common pharmacologic mechanism; yet, the differing pharmacokinetic profiles of the nitrate delivery systems lead to a variation in the development of tolerance.[65] Short-acting formulations (eg, SL NTG, oral NTG spray, and SL isosorbide dinitrate) are not likely to induce tolerance given their rapid onset of action and short duration of effect. Oral nitrates and transdermal products, both having an extended duration of action, are likely to induce tolerance.

Intermittent application of transdermal NTG can limit tolerance development in patients with both chronic stable angina and HF. The

effects of continuous (24 hours/day) and intermittent (16 hours/day) transdermal NTG (10 mg/day) were compared in 12 males with chronic stable angina who also were being treated with β-blockers or CCB.[66] Nitrate efficacy was maintained with intermittent treatment and an 8-hour nitrate-free interval. Tolerance to the antianginal effects occurred, however, with continuous treatment. Twelve-hour intermittent patch therapy also prevents tolerance.[67] The minimal time necessary for a nitrate-free interval is unknown. Nitrate dosing schedules should be arranged to permit a nitrate-free interval during which time the patient may receive angina protection from β-blockers, CCBs, or ranolazine. Most often, this nitrate-free interval is arranged during the night because angina is more likely to occur during the workday. Patients with nocturnal or early morning angina should arrange their nitrate-free interval during the day.[68]

Despite the availability of nitrate preparations that can be dosed once or twice a day (isosorbide mononitrate), oral isosorbide dinitrate is still commonly used in a variety of settings for the treatment of angina. Isosorbide dinitrate needs to be dosed three times a day and presents a challenge in ensuring patients have a nitrate-free interval. If J.P. were to receive isosorbide dinitrate, he should take his oral nitrate at 7 AM, noon, and 5 PM because his exercise-induced angina is likely to occur during daylight hours. If he were to take isosorbide dinitrate on a more traditional three-times-a-day or every-8-hours schedule, he would be in danger of not having an adequate nitrate-free interval. Because long-acting nitrates must be dosed intermittently to avoid tolerance, metoprolol therapy will provide J.P. with continuous protection, even during the nitrate-free interval. Although J.P. uses a long-acting nitrate, he still will respond favorably to sublingual NTG. No evidence indicates that use of long-acting nitrates leads to resistance or tolerance to the effects of sublingual NTG.

Case 12-1, Question 18: Does isosorbide mononitrate offer any distinct advantages over other nitrate preparations for angina prophylaxis?

Isosorbide mononitrate is the primary metabolite of isosorbide dinitrate. In fact, most of the clinical activity of isosorbide dinitrate is because of the mononitrate. Therefore, both drugs share a similar pharmacology. Isosorbide mononitrate does not undergo first-pass metabolism and has no active metabolites. Its oral bioavailability is almost 100%, and its overall elimination half-life is about 5 hours.[65] Maximal serum concentrations are observed 30 to 60 minutes after a dose. To minimize the potential development of nitrate tolerance, isosorbide mononitrate should be used in a twice-daily, asymmetric dosing regimen in which the first dose is taken on awakening and the second dose about 7 hours later. Because of this unconventional dosing pattern and the availability of the extended-release product, which can be taken once a day, most use of isosorbide mononitrate is in the form of the extended-release preparation. Pharmacists must be sure to recognize the difference between these two products.

General precautions and adverse reactions for isosorbide mononitrate are similar to those for the other nitrates. Potential advantages for the clinical use of isosorbide mononitrate are less dosage fluctuation because of the absence of presystemic clearance and an effective once-daily or twice-daily dosing schedule, which could perhaps lead to improved patient adherence. Nevertheless, isosorbide dinitrate is effective clinically when administered two or three times a day and is a viable alternative.

Case 12-1, Question 19: J.P. likes the idea of using topical nitrates instead of an oral agent. Are the transdermal patches a viable alternative?

Transdermal NTG patches were originally designed to provide anti-ischemic protection with once-daily application. The concept of a compact, easy-to-apply transdermal NTG patch prompted pharmaceutical manufacturers to design a number of products, which the FDA subsequently approved based on plasma level data, not clinical efficacy studies. Subsequently, the shortcomings of plasma level data have become apparent and prompted numerous clinical efficacy studies.

Transdermal NTG therapy has been shown to increase exercise duration and maintain an anti-ischemic effect for 12 hours after patch application. These beneficial responses remained consistent throughout 30 days of therapy. No significant nitrate tolerance or rebound was noted when the patch was applied for not more than 12 of 24 hours.[65]

Although the various patches use different pharmaceutical delivery systems, clear-cut advantages of one over another are not apparent. Despite variations in surface area and NTG content, the most important common denominator of the transdermal NTG systems is the amount of drug released per hour expressed as the release rate (eg, 0.2 mg/hour). Each product label includes this information. Low dosages (0.2–0.4 mg/hour) may not produce sufficient plasma and tissue concentrations to produce a clinically significant effect[3]; however, it is still recommended to start with a low-dose patch and titrate upward as needed. Because the skin is the major factor influencing NTG absorption rate, product release characteristics do not favor one system over another. Contact dermatitis has been reported with the transdermal patches. Patient instructions are included with the patches and should be reviewed with the patient, emphasizing the appropriate time for application of the patch, removal of the patch, as well as the appropriate sites on the body where the patch should be placed.

CALCIUM CHANNEL BLOCKERS

CASE 12-2

QUESTION 1: B.N., a 56-year-old male, has just undergone cardiac catheterization, which showed two-vessel CAD with obstructions of 55% and 65% in the right coronary and circumflex coronary arteries, respectively. Before catheterization, he had a 2- to 3-month history of exertional angina for which his primary care physician prescribed sublingual NTG tablets (0.4 mg) and oral isosorbide mononitrate (60 mg once daily). B.N. discontinued the use of isosorbide mononitrate after a few weeks because of intolerable headaches. His medical history includes asthma, hypertension, and hyperlipidemia. Currently, his other medications include losartan 100 mg once daily, fluticasone inhaler two puffs twice daily, albuterol inhaler two puffs as needed, aspirin 81 mg daily,

and atorvastatin 20 mg daily. Current vital signs include a resting heart rate of 75 beats/minute, BP of 125/80 mm Hg, and respiratory rate of 14 breaths/minute. His physician begins antianginal therapy with oral diltiazem 120 mg once daily.

Is this a good option for B.N. and his chronic stable angina?

CCBs are effective in both vasospastic and classic exertional angina. These drugs relieve vasospasm of the large coronary arteries and, as a result, are effective in treating Prinzmetal variant angina. Their beneficial effect in chronic stable (effort-induced) angina is the result of multiple factors. Their vasodilatory effects in the coronary circulation increase myocardial oxygen supply, whereas dilation of the peripheral arterioles leads to a reduction in myocardial oxygen demand. Because coronary vasospasm can occur at the site of an atherosclerotic plaque, a CCB is particularly useful in patients who have a vasospastic component to their angina.[40,69]

Although β-blockers are considered the drugs of choice when instituting antianginal therapy,[1] data indicate that CCB may also be a reasonable first-line choice. CCBs and β-blockers appear to provide equivalent efficacy in head-to-head trials of chronic stable angina.[70–72] In addition, the available head-to-head trials with sufficient numbers also suggest that CCBs and β-blockers produce similar effects on cardiovascular outcomes and mortality in patients with chronic stable angina.[40,73] In addition, several trials in the setting of hypertension with CAD have demonstrated that CCBs can produce meaningful reductions in mortality.[74–77] It would appear that either a CCB or a β-blocker may be considered relatively equal options and initial therapy for chronic stable angina. The selection of a particular class will likely be dictated by patient characteristics.

In the case of B.N., his asthma may be worsened by the addition of a β-blocker. Although a cardioselective β-blocker could be tried to see if B.N. could tolerate it, a heart rate–lowering CCB is a good alternative to a β-blocker for the treatment of angina in this situation. The choice of a CCB as initial therapy in this patient is appropriate because of B.N.’s previous intolerance to nitrates and because nitrate therapy requires a nitrate-free period.[1]

Given B.N.'s current heart rate and BP, the selection of a heart rate–lowering CCB seems most appropriate. However, the distinct pharmacologic and adverse event profiles of the various classes may dictate agent selection from patient to patient. Some side effects of CCBs reflect an extension of their hemodynamic and electrophysiologic profiles and, therefore, are predictable (**Table 12-6**). DHP-induced hypotension and dizziness occur in ~15% of patients. Patients also may report light-headedness, facial flushing, headache, and nausea. Swelling of the lower legs and ankles (peripheral edema) is related to the potent peripheral vasodilating effects of these agents. The non-DHPs, verapamil and diltiazem, have similar side effect profiles, although diltiazem appears to be better tolerated. The lower incidence of side effects reported with diltiazem, compared with verapamil, may reflect a true difference or, perhaps, less aggressive dosing regimens. Both drugs can cause sinus bradycardia and worsen already existing conduction defects and heart block.[40,69] Neither should be used in patients with sick sinus syndrome or advanced degrees of heart block unless a functioning ventricular pacemaker is present. Patients should be monitored for signs of worsening HF, such as SOB, weight gain, and peripheral edema. Verapamil-induced constipation can be particularly troublesome to the elderly.[3,40]

Table 12-6
Calcium Channel Blocker Hemodynamic and Electrophysiologic Profile

Effect	Dihydropyridine Derivatives[a]	Diltiazem	Verapamil
Peripheral vasodilation[b]	+++	++	++
Coronary vasodilation[b]	+++	+++	++
Negative inotropes[c]	±	++	+++
AV node suppression[c]	±	+	++
Heart rate	Increase (reflex)	Decrease or unchanged	Decrease or unchanged
Pharmacokinetics[d]			
Dosing[e]			
Side Effects			
Nausea, vomiting	+ (most)	+/1	±
Constipation	Not observed	±	+
Hypotension, dizziness[f]	++	+	+
Flushing, headache	++	+	+
Bradycardia, HF symptoms	±	+	++
Reflex tachycardia, angina	+[f]	Not observed	Not observed
Peripheral edema	+	±	±

[a]Dihydropyridine derivatives that are U.S. Food and Drug Administration approved for angina: amlodipine (Norvasc), nicardipine (Cardene), and nifedipine (Adalat, Procardia).

[b]Peripheral and coronary vasodilation helpful for angina, hypertension, and possibly HF, but peripheral dilation is the basis for side effects of flushing, headache, and hypotension.

[c]AV node suppression is helpful for controlling supraventricular arrhythmias, but this property plus the negative inotropic effect may worsen HF. Nifedipine has less negative inotropic effect than verapamil and diltiazem but still may worsen HF. Amlodipine may have the least negative inotropic effect.

[d]All have poor bioavailability owing to high first-pass metabolism and all are eliminated primarily by hepatic metabolism; intradivisional and interindividual variability in bioavailability and metabolism is extensive. Diltiazem, nifedipine, nicardipine, and verapamil have a short half-life (<5 hours) requiring frequent dosing or use of sustained-release products. Amlodipine, isradipine (8 hours), and felodipine (10–20 hours) have longer half-lives.

[e]See Table 12-5.

[f]Hypotension and reflex tachycardia most with immediate-release nifedipine, occasional with immediate-release diltiazem and verapamil, minimal with sustained-release products or intrinsically long-acting agents.

Sources: Cooper-DeHoff RM, Chang SW, Pepine CJ. Calcium antagonists in the treatment of coronary artery disease. *Curr Opin Pharmacol*. 2013;13:301–308. Opie LH. Calcium channel blockers. In: Opie LH, Gersh BJ, eds. *Drugs for the Heart*. 8th ed. Elsevier Health Sciences; 2013.

Appreciation for the individual side effect profiles helps determine preference for one CCB over another. B.N. is not likely to experience

major side effects with either verapamil or diltiazem.

Case 12-2, Question 2: On questioning, B.N. does not report any previous adverse events or tolerance issues with an ACE inhibitor. Is an ARB appropriate to use in B.N. or should he be switched to an ACE inhibitor for his CAD?

As discussed, the totality of available evidence supports the role of ACE inhibitors in reducing total mortality, cardiovascular mortality, nonfatal MI, and stroke in patients with stable IHD and preserved ventricular function. Although in theory ARBs should produce the same beneficial effects as ACE inhibitors in patients with atherosclerosis, there are far fewer clinical trials with ARBs. The best supporting evidence comes from the TRANSCEND and ONTARGET trials, both of which suggest ARBs produce similar benefits as ACE inhibitors in preventing CVD events.[77,78] Based on these trials, it would be reasonable to continue ARB therapy in B.N. at this time given he has demonstrated the ability to tolerate the medication. It would not be unreasonable though to discuss with B.N. the possibility of switching to an ACE inhibitor given the substantial body of evidence that exists for patients with CAD. The combination of an ACE inhibitor and ARB does not offer any increased benefit but does increase the risk of hyperkalemia and renal insufficiency.[78]

Case 12-2, Question 3: Six months later, B.N. returns to see his physician. His current therapy consists of SL NTG 0.4 mg tablets, losartan 100 mg once daily, fluticasone inhaler two puffs twice daily, albuterol inhaler two puffs as needed, aspirin 81 mg daily, atorvastatin 20 mg daily, and diltiazem 180 mg once daily. Current vitals include a resting heart rate of 55 beats/minute, BP of 115/65 mm Hg, and respiratory rate of 10 breaths/minute. B.N. states he still is having roughly three to four anginal attacks per week when he exerts himself doing yard work. Would ranolazine be a therapeutic option for his chronic stable angina at this time?

Although higher doses of diltiazem might be attempted in B.N., his current heart rate and BP would likely prevent further titrating of therapy. β-Blocker therapy is not a good option because of the potential reduction in heart rate and asthma. Thus, ranolazine

represents a good option for B.N. at this time because of the absence of heart rate and BP-lowering effects with ranolazine. Several large, randomized studies with ranolazine have been conducted, all demonstrating its effectiveness at reducing ischemia and angina when added to existing therapy. The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial found that compared to placebo, ranolazine significantly increased exercise duration, time to onset of angina, and 1-mm ST-segment depression during exercise treadmill testing.[79] Similar results were seen in the Combination Assessment of Ranolazine in Stable Angina (CARISA) trial where ranolazine when added to antianginal monotherapy.[80] The Efficacy of Ranolazine in Chronic Angina (ERICA) trial assessed the effects of ranolazine added to amlodipine 10 mg/day. Patients receiving 1000 mg/day of ranolazine had a significant reduction in both the number of weekly anginal attacks as well as the number of SL NTG tablets used when compared to placebo.[81] A reduction in the frequency of angina was also seen in patients with CAD and diabetes mellitus when ranolazine was added in the Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) study.[82] Ranolazine was well-tolerated in all four of these trials with the most common side effects being dizziness, constipation, nausea, and headache. The incidence of adverse effects increased with increasing doses. No other significant adverse effects were noted, although it is important to note that the duration of these trials was limited.[41]

Information regarding the safety of ranolazine in patients with longer drug exposure came from the Ranolazine Open Label Experience (ROLE) program,[83] which followed patients from the MARISA and CARISA trials who continued in an open-label extension program. A total of 746 patients initially entered the 6-year run-on safety program. At the time of publication, the mean duration of therapy was 2.82 years, with 23.3% of patients discontinuing therapy. One-half of the withdrawals were because of adverse events, but the incidence of common adverse effects did not seem to change from that seen in the randomized portions of the clinical

trials. Mortality rates at both 1 year (2.8%) and 2 years (5.6%) indicate no adverse risk of ranolazine on overall mortality.

The Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome (MERLIN)-TIMI 36 trial[84] randomly assigned patients to ranolazine or placebo in the setting of ACS. The incidence of recurrent ischemia was significantly reduced with ranolazine providing additional support for the efficacy of ranolazine in treating chronic stable angina. Although ranolazine appeared to offer no benefit in the setting of ACS, significant long-term safety data were seen in the trial. Importantly, the risk of mortality, sudden cardiac death, or symptomatic arrhythmias was not increased with ranolazine versus placebo. In fact, the incidence of arrhythmias in the first 7 days, as documented by Holter monitor, was significantly lower with ranolazine than with placebo.[85] This was an important finding given ranolazine produces a dose-dependent increase in the QT interval.[15,41] As QT prolongation activity has been associated with proarrhythmia in other medications, results from the MERLIN trial are reassuring that ranolazine appears to be safe to use for chronic treatment of patients with stable angina.

B.N. is at goal heart rate, and his BP is well controlled on his current regimen, but he continues to have anginal symptoms. Given the demonstrated efficacy in relieving anginal symptoms, as well as the safety profile in a patient like B.N., ranolazine would be an excellent option for him for additional angina control.

Case 12-2, Question 4: How should ranolazine be dosed in B.N.?

Ranolazine is marketed as an extended-release tablet formulation that should be dosed twice daily. Maximal plasma concentrations are observed 4 to 6 hours after administration of the extended-release formulation with a terminal half-life of 7 hours. With twice-daily dosing of the extended-release preparation, a more favorable peak-to-trough fluctuation of 1.6 is observed.[41] Steady state is typically reached within 3 days and oral bioavailability is 30% to 55%. Ranolazine is primarily metabolized by the liver through CYP3A4

(70%–85%) and CYP2D6 (10%–15%). Ranolazine also is a substrate for P-glycoprotein.[15,41] Patients should initially be started at an oral dose of 500 mg twice daily, which can be titrated up to a maximal dose of 1000 mg twice daily.[86]

Although ranolazine is an option in the treatment of chronic stable angina, careful patient selection is required for the drug to be used safely and effectively.[86] **Table 12-7** summarizes significant issues, which should be evaluated when the drug is being considered for a patient. For B.N., the main issue is the drug–drug interaction with diltiazem, and the maximum dose of ranolazine that should be used in patients receiving diltiazem is 500 mg twice daily. B.N. should be monitored closely for possible increased adverse effects with ranolazine.

Table 12-7
Considerations for the Use of Ranolazine in Patients With Chronic Stable Angina

Clinical Issue	Recommended Management Strategy
Renal insufficiency	Ranolazine plasma levels may increase up to 50%. Caution with dose titration to maximal recommended dose.
Hepatic insufficiency	Ranolazine is contraindicated in patients with clinically significant hepatic impairment.
Drug Interactions: Effects on Ranolazine	
Strong CYP3A4 inhibitors	Plasma concentrations of ranolazine are significantly elevated when combined with potent inhibitors of CYP3A4. Ranolazine is contraindicated in patients receiving strong CYP3A4 inhibitors (ketoconazole, clarithromycin, nelfinavir, etc).
Moderate CYP3A4 inhibitors	Limit the dose of ranolazine to 500 mg twice daily in patients receiving moderate inhibitors of CYP3A4 (diltiazem, verapamil, erythromycin, fluconazole, etc).
CYP3A4 inducers	Coadministration of ranolazine with CYP3A4 inducers is contraindicated and should be avoided.
P-glycoprotein inhibitors	Caution should be exercised when coadministering ranolazine with P-glycoprotein inhibitors, and the dose of ranolazine may need to be lowered based on clinical response.
Drug Interactions: Effects on Other Medications	

Simvastatin	Plasma levels of simvastatin are increased twofold with coadministration with ranolazine through CYP3A4 inhibition by ranolazine; limit simvastatin dose of 20 mg daily when used with ranolazine; closely monitor for adverse effects (eg, myositis) from simvastatin.
Digoxin	Ranolazine coadministration increases plasma concentrations of digoxin by 1.5 times. Adjust dose of digoxin accordingly to maintain desired therapeutic level and response.
Metformin	Limit the dose of metformin to 1700 mg daily when coadministered with ranolazine 1000 mg twice daily.
CYP2D6 substrates	Ranolazine can inhibit the activity of CYP2D6, and plasma concentrations of 2D6 substrates (β-blockers, tricyclic antidepressants, antipsychotics) may be increased and lower doses of these agents may be required.
QT prolongation	Caution is recommended if the patient is on other QT-prolonging drugs, or has QT prolongation as baseline.

Sources: Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation.* 2006;113:2462–2472. Dobesh PP, Trujillo TC. Ranolazine: a new option in the management of chronic stable angina. *Pharmacotherapy*. 2007;27:1659–1676. Ranexa (ranolazine). Prescribing information. Gilead Sciences, Inc.; 2019.

CASE 12-3

QUESTION 1: E.R. is a 58-year-old female with a history of chronic stable angina for the last several years that has been managed primarily with medical therapy. Her current medications include oral isosorbide mononitrate 120 mg daily, oral metoprolol succinate 200 mg daily, ranolazine 1000 mg twice daily, fluticasone two puffs bid, albuterol two puffs as needed, NTG spray 0.4 mg as needed for chest pain, and enteric-coated aspirin 81 mg/day. Today she returns to your pharmacy to obtain refills of her medications with her 64-year-old brother who wants to know if he should be taking an aspirin a day to prevent heart disease. His only medical history consists of hypertension for which he is taking oral hydrochlorothiazide 25 mg/day.

Is primary prevention of CAD with aspirin appropriate for E.R.'s brother?

The question of whether aspirin is valuable in the primary prevention of cardiovascular events has been debated for more than 30 years. The absolute risk–benefit ratio for aspirin in primary prevention will depend on the overall absolute risk of vascular

ischemic events. Several meta-analyses suggest that any benefit for aspirin in reducing ischemic events is offset by an increase in bleeding, resulting in no net clinical benefit.[87–90]

The 2019 ACC/AHA guideline on primary prevention of CVD provides contemporary recommendations for the use of ASA in primary prevention, incorporating more recent evidence.[91] Patients who are between the ages of 40 to 70 years, who are at high risk for atherosclerotic cardiovascular disease (ASCVD) but do not have a high bleeding risk, can be considered for the use of ASA for primary prevention. Importantly, this is a class 2b recommendation indicating that the literature supporting this recommendation is mixed. Because E.R.'s brother is 64 years old, it is appropriate for him to consider the use of aspirin for primary prevention, provided he is found to be at high risk for ASCVD and does not carry a high bleed risk. Recognizing the existing controversy surrounding the use of aspirin for primary prevention, a thorough review of the potential risk and benefits should take place with E.R.'s brother so that he may make the most informed decision possible.

CASE 12-3

QUESTION 2: E.R. buys a bottle of OTC ibuprofen. On further questioning, you learn that E.R. suffers from occasional back and knee pain and uses ibuprofen three to five times a week for pain relief.

How should E.R. be educated regarding the use of ibuprofen and aspirin concomitantly?

In 2006, the FDA released a warning statement on the concomitant use of both aspirin and ibuprofen. The impetus for the statement was the growing recognition that nonsteroidal anti-inflammatory drugs (NSAIDs), in particular ibuprofen, may attenuate the antiplatelet effects of low-dose aspirin. This FDA warning was then followed by an updated scientific statement, from the AHA.[92] The mechanism of this interaction is that both aspirin and nonselective NSAIDs bind to the same acetylation sites of the cyclooxygenase enzyme. Although aspirin does this in a

nonreversible fashion, binding by an NSAID occurs in a reversible fashion. If an NSAID, such as ibuprofen, is present, aspirin will be unable to bind to its site of action and will be rapidly cleared from the plasma. The result is the patient will not receive the antiplatelet benefit of aspirin.

E.R. should be counseled on the consequences of the interaction between her aspirin and ibuprofen. Additionally, if she can avoid or at least minimize (both dose and duration) the use of ibuprofen, the effect on her cardiovascular health would be optimized. If occasional use of ibuprofen cannot be avoided, it should be administered to minimize the potential for interacting with her aspirin. This would include taking ibuprofen at least 2 hours after her daily dose of aspirin, as well as taking her daily aspirin dose at least 8 hours after the last dose of ibuprofen. Although similar concerns exist for other nonselective NSAIDs (naproxen, diclofenac), no formal recommendations exist on how to manage concomitant use of these agents with aspirin.[92] Beyond the potential drug–drug interaction with aspirin therapy, there has emerged a large body of evidence that the use of NSAIDs in patients with underlying CVD may increase the risk of major adverse cardiovascular events. Although the underlying mechanisms remain to be determined, clinicians should minimize the use of NSAIDs if possible in patients with underlying CVD.[93]

REVASCULARIZATION

Percutaneous Coronary Intervention

Case 12-4, Question 1: Nine months later, E.R. returns to her cardiologist stating that her chronic angina has been worsening. She is experiencing chest pain more frequently and much sooner when she does any type of physical activity. Her current medications are the same as discussed previously, and it is felt that her medical management has been optimized as much as possible. After discussions with her cardiologist, she elects to undergo revascularization with PCI for symptom relief. What is the current standard for prevention of acute complications during PCI?

PCI, also known as angioplasty, involves the percutaneous insertion of a balloon catheter into the femoral or brachial artery. The catheter is advanced up the aorta and into the coronary arteries at the coronary sinus. PCI initially involved the inflation of a catheter-borne balloon that mechanically dilated a coronary artery obstruction through arterial intimal disruption, plaque fissuring, and stretching of the arterial wall. Balloon inflations were repeated until the plaque was compressed and coronary blood flow resumed. Since then, alternative devices have been developed, including rotational blades designed to remove atheromatous material, lasers to ablate plaques, and intracoronary stents that are designed to maintain the patency of the vessel after it is reopened.[94] Stents can be of the bare-metal (BMS) variety or contain a drug impregnated on the surface of the stent to prevent restenosis (DES). It is estimated that more than 1,265,000 PCI procedures are performed in the United States each year. An overwhelming majority of these procedures involve placement of a BMS or DES (**Fig. 12-5**). PCI is indicated in patients with single-vessel or multivessel disease and who are either symptomatic or asymptomatic.[20,94,95]

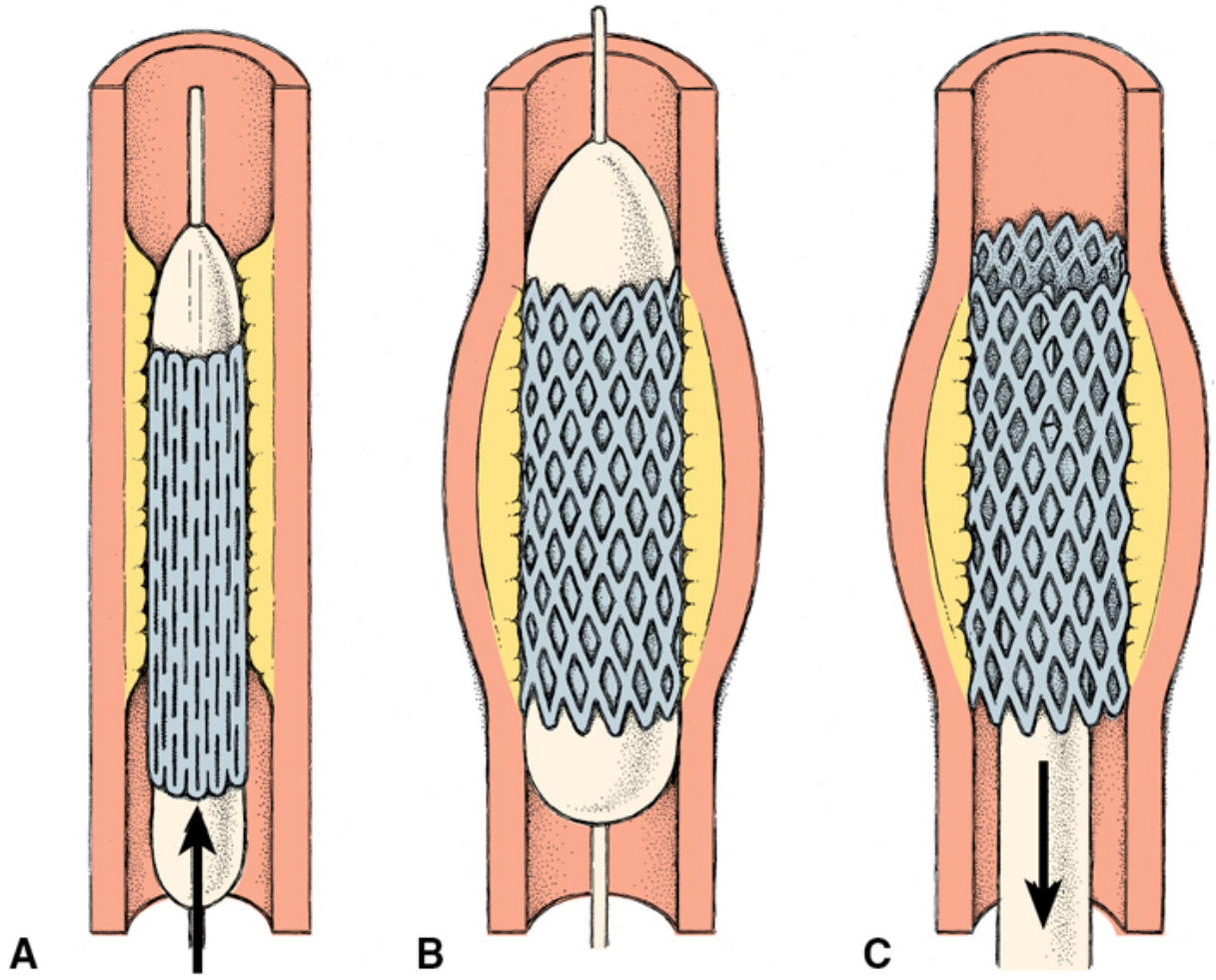


Figure 12-5 Vascular stent. A, A balloon catheter positions the stent at the site of arterial stenosis. B, Inflation of the balloon dilates the artery and expands the stent. C, The balloon is collapsed and withdrawn, leaving the expanded stent in position. (Illustration by Neil O. Hardy, Westpoint, CT.)

Because of mechanical disruption of the atherosclerotic plaques and exposure of plaque contents to the bloodstream during PCI, potent antiplatelet and antithrombotic strategies are needed to prevent acute thrombotic events such as MI and death. Current strategies in patients undergoing elective PCI involve the administration of aspirin, a $P2Y_{12}$ antagonist (clopidogrel, prasugrel, or ticagrelor), an antithrombin agent, and occasionally a glycoprotein (GP) IIb/IIIa receptor antagonist in selected patients. Although

ticagrelor and prasugrel represent alternatives to clopidogrel in patients undergoing PCI, current ACC/AHA guidelines recommend their use only in patients undergoing PCI in the setting of ACS. In patients not taking aspirin on a daily basis, 300 to 325 mg of aspirin should be given at least 2 hours before the procedure. Patients currently on daily aspirin therapy should receive 75 to 325 mg of aspirin before PCI is performed. A 600-mg loading dose of clopidogrel on or before the time of the procedure is currently recommended, producing an antiplatelet action within 2 hours.[16,17,20,95] Adequate antithrombin therapy such as unfractionated heparin, the low-molecular-weight heparin enoxaparin, or the direct thrombin inhibitor bivalirudin should be used in patients having elective PCI[20,95] (see Chapter 13, Acute Coronary Syndrome).

Case 12-4, Question 2: E.R. undergoes PCI plus placement of a DES to address a 75% lesion in her proximal left circumflex artery. What advantages and disadvantages are there in the decision to place a DES versus a BMS?

The overall success of any procedure is directly related to the experience of the operator, patient factors (such as LV function or number of vessels treated), and the equipment used. In patients receiving balloon angioplasty alone (without stent placement), repeat revascularization procedures (either repeat angioplasty or surgery) may be required in as many as 32% to 40% of cases because of lesion recurrence at the angioplasty site. The process is known as restenosis.[94] Many pharmacologic strategies have been studied in an attempt to reduce the risk of restenosis. The outcome with most methods has been disappointing. The only strategy that has been associated with a decrease in restenosis is the use of intraluminal stents.[94] Stents are essentially metal scaffolding devices placed into the vessel after balloon inflation has taken place. They provide a physical barrier to the recurrence of a significant stenosis at the site. One of the early drawbacks of the use of stents was the need for complicated antithrombotic regimens, including aspirin, heparin, dipyridamole, and warfarin, to prevent in-stent thrombosis. DAPT—a

combination of a $P2Y_{12}$ antagonist and aspirin—is effective at reducing in-stent thrombosis and is now recommended for use after stent placement.[20,95] The duration of DAPT will depend on the type of stent used as well as other clinical characteristics of the patient.

Recently, stents that elude antiproliferative agents such as sirolimus, paclitaxel, zotarolimus, or everolimus have been shown in clinical trials to reduce the incidence of restenosis compared with BMS.[96] Restenosis rates in clinical trials with these DES were in the single-digit range, as compared to 15% to 20% with traditional BMS. Soon after their introduction to the U.S. market, DES use grew to the point that >90% of stent use was DES. This trend abruptly halted in the fall of 2006 when several reports indicated a higher-than-expected incidence of stent thrombosis a year or more after DES placement. Although late stent thrombosis had previously been reported with BMS usage, the incidence was rare.[20] Shortly after these initial reports, an explosion of scientific literature emerged on the topic. Delayed endothelialization is seen with DES compared with BMS. After placement of an intracoronary stent, a healing process typically occurs resulting in growth of a protective layer of endothelial cells over the stent surface, removing the stent surface from blood exposure and drastically reducing the stimulus for thrombosis. In the case of DES coated with paclitaxel, sirolimus, or everolimus, cellular growth may be inhibited, significantly impairing endothelialization of the stent surface. In a small number of patients, endothelialization does not seem to occur at all. In this scenario, the stent structure remains continually exposed to flowing blood and is a potent stimulus for thrombosis.[97] More recent advances in percutaneous interventions and stent technology though have largely eliminated many concerns regarding late stent thrombosis, and in the setting of elective PCI shorter durations of intense antiplatelet therapy is needed to prevent thrombotic complications.[44]

One critical issue that had been identified as a cause of late stent thrombosis with DES is the premature discontinuation of DAPT. As such, consideration of whether the patient is likely to comply with aspirin and $P2Y_{12}$ antagonist therapy or afford such therapy based

on insurance status has become a significant factor in the decision process between using a BMS or DES. Previous recommendations called for varying durations of combined therapy, depending on the type of stent used. Because of the recognition of a delayed healing response to DES, current guidelines recommend at least 1 year of DAPT in patients receiving a DES if patients are not at an elevated risk of bleeding. For BMS placement, DAPT should continue for a minimum of 1 month, and up to 1 year ideally, but this extended duration is not as critical as it is in the setting of DES placement. After PCI, it is reasonable to use aspirin 81 mg daily rather than higher doses.[20] The dose of clopidogrel should be 75 mg/day.[20,95]

CASE 12-4, QUESTION 3: Would revascularization therapy with coronary artery bypass grafting have been a better option for E.R. than PCI and stent placement?

Coronary artery bypass grafting is a complicated surgical procedure during which an atherosclerotic vessel is bypassed using either a patient's saphenous vein or internal mammary artery (IMA; **Fig. 12-6**). The graft (ie, the saphenous vein or IMA) then allows blood to flow past the obstruction in the native vessel. The goals of antianginal therapy, whether medical (pharmacologic) or revascularization, remain unchanged: (a) to prolong life, (b) to prevent MI, and (c) to improve the quality of life.

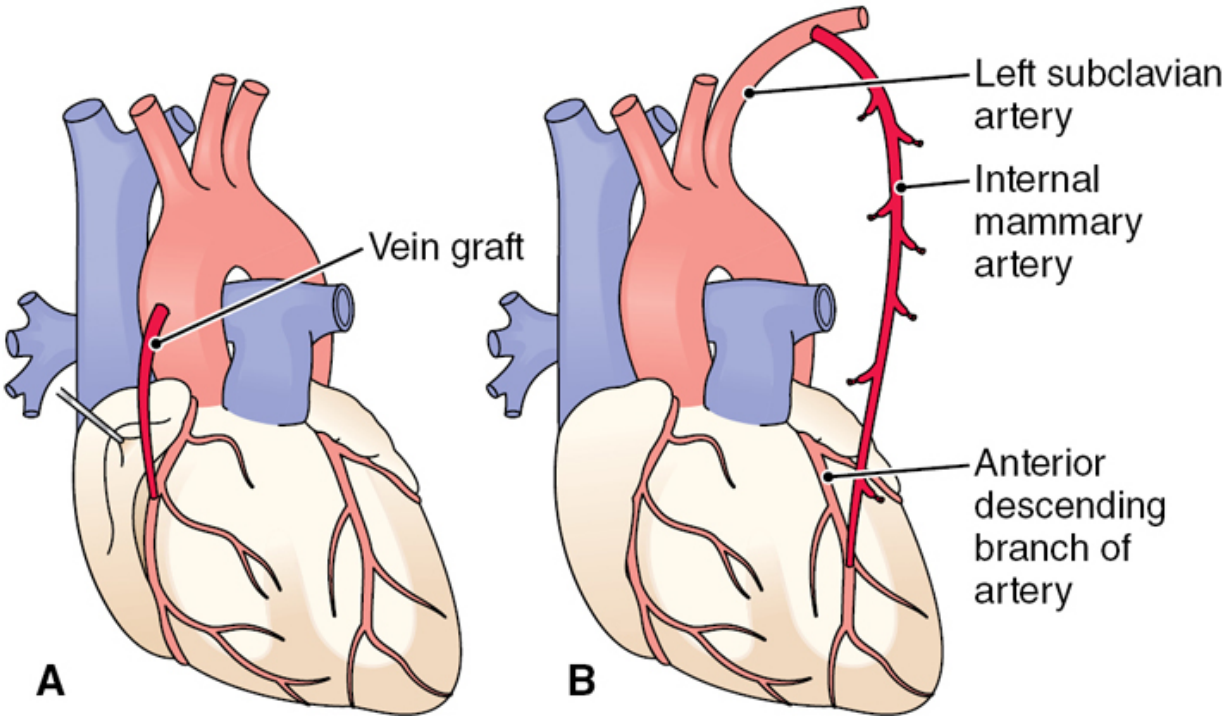


Figure 12-6 Coronary artery bypass graft (CABG). A, A segment of the saphenous vein carries blood from the aorta to a part of the right coronary artery that is distal to an occlusion. B, The mammary artery is used to bypass an obstruction in the left anterior descending (LAD) coronary artery. (Reprinted with permission from Cohen BJ. *Medical Terminology: An Illustrated Guide*. 7th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.)

The outcomes of medical therapy, PCI, and revascularization with CABG have been compared, and current guidelines are available.[1,21] When compared with medical treatment in patients who would not be considered high risk, PCI in general offers no improvement in the long-term incidence of MI or cardiovascular death, but significantly reduces symptoms.[1] Because of her escalating symptoms on triple-drug therapy, the choice of PCI for E.R. is justified.

Certain subgroups of patient at high risk clearly have an improved outcome with CABG. These include (a) patients with significant left main coronary disease; (b) patients who have three-vessel disease, especially with LV dysfunction; (c) patients with two-vessel disease with a significant proximal LAD lesion; (d) patients who have

survived sudden cardiac death; and (e) patients who are refractory to medical treatment. In patients who do not meet these criteria, either medical treatment or PCI is a viable option.[1,20] Because E.R. does not fall into one of these categories, PCI is preferable owing to the less-invasive nature of the procedure and the equivalent outcomes that are seen. These results were recently confirmed in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial.[43] Patients with CAD were randomly assigned to aggressive medical treatment with optimization of medical therapy and risk factors, or aggressive medical treatment plus PCI. During a 4.6-year period, no significant difference was noted between the groups in cardiovascular outcomes (death, MI, stroke, hospitalization for ACS). The only difference noted was better control of anginal symptoms early on with PCI, but that difference was no longer significant at the end of the study. These results highlight the crucial role of optimizing medical therapy (including diet, lifestyle changes, risk factor modification) for patients with CAD, regardless of whether revascularization is performed.[1]

Case 12-4, Question 4: E.R. undergoes PCI plus stent placement and returns to your pharmacy to have a new prescription filled. The prescription calls for clopidogrel at a dose of 150 mg once a day for 1 week, then 75 mg a day thereafter with 11 monthly refills. You have not seen clopidogrel dosed in such a manner. What is the rationale for the higher dose, and is there evidence to support its use?

Clopidogrel, a thienopyridine, inhibits platelet function as a noncompetitive antagonist of the $P2Y_{12}$ platelet adenosine diphosphate receptor. Clopidogrel is dosed at 75 mg daily, and this dose has been demonstrated to be effective and safe as monotherapy, or as a component of DAPT with aspirin, in a wide variety of settings for patients with CAD.[98] Despite proven efficacy, patients continue to experience clinical events while receiving clopidogrel.[99] It is now understood that clopidogrel does not produce a consistent antiplatelet response in many patients.[100]

Although the term clopidogrel resistance was first used to describe patients who do not have the expected antiplatelet response to standard doses of clopidogrel, a better term to describe this phenomenon is clopidogrel nonresponsiveness. Alternatively, the phrase *high on-treatment platelet reactivity* is also used commonly in the literature, especially when characterizing the clinical consequences of decreased antiplatelet response.[100] The presence of high on-treatment platelet reactivity in patients who have undergone PCI has been linked to a higher rate of stent thrombosis, MI, repeat revascularization, and death. This link has been observed in both patients with stable CAD undergoing elective PCI and patients with ACS. Although nonresponsiveness identifies an elevated risk for ischemic events, not all patients with identified clopidogrel nonresponsiveness necessarily go on to have recurrent events.[99]

There is a lack of consistency of how clopidogrel nonresponsiveness is defined. It may be defined as the presence of a recurrent ischemic event while on therapy. But, thrombosis is a complex interplay of many different factors, and recurrent clinical events do not necessarily imply a lack of antiplatelet effect. The identification of a lack of the expected biologic effect on platelet function is a more appropriate definition to work with. However, there are multiple tests available to assess the antiplatelet activity of clopidogrel (and other antiplatelet agents), and it is unclear which assay correlates best with clinical outcome and would be preferred to assess clopidogrel nonresponsiveness.[101,102] Because of the variability in available platelet function tests, as well as definitions of nonresponsiveness, estimates for the incidence of clopidogrel nonresponsiveness range anywhere from 5% to 44%.[100] **Table 12-8** lists some of the available laboratory testing modalities for antiplatelet agents, their pros and cons, as well as previously identified levels of high on-treatment platelet reactivity.[103]

Table 12-8
Commonly Used Platelet Function Tests for Assessment of

Antiplatelet Effects

Test	Pros	Cons	Monitoring Key Points
Turbidimetric aggregometry, commonly referred to as light transmission aggregometry	Historical gold standard	Large blood volume Expensive Poor reproducibility Time-consuming Technical complexity	Whole blood assay Can be used for multiple antiplatelet agents with variable reagents
VASP phosphorylation	Whole blood assay Small blood volume needed	Technical complexity Expensive Requires a flow cytometer	Specific for thienopyridines Cutoff for antiplatelet nonresponsiveness PRI >50%
VerifyNow	True point-of-care assay Large number of patients studied Whole blood assay Simple and rapid	Cartridge cost Limited ranges for hematocrit and platelet count	Can assess multiple antiplatelet agents Cutoff for antiplatelet nonresponsiveness PRU >235–240
Thromboelastography	Whole blood assay Point of care	Limited clinical studies Substantial pipetting of reagents	Can assess multiple antiplatelet agents

PRI, platelet reactivity index; PRU, platelet reaction units; VASP, vasodilator-stimulated phosphoprotein.

Sources: Michelson AD. Methods for the measurement of platelet function. *Am J Cardiol.* 2009;103(3, Suppl):20A–26A. Price MJ. Bedside evaluation of thienopyridine antiplatelet therapy. *Circulation*. 2009;119:2625–2632.

Potential reasons for clopidogrel nonresponsiveness are multifactorial. One source of nonresponsiveness is in the decreased biotransformation of clopidogrel from its prodrug form to its active metabolite. Biotransformation is a multistep process through the cytochrome P-450 system, but the most important enzyme is CYP2C19, which exhibits variable metabolic capacity. Patients with the *1/*1 CYP2C19 alleles are considered extensive metabolizers and are capable of generating sufficient levels of clopidogrel's active metabolite. Patients with one or two copies of either the *2 or *3 alleles (considered loss of function alleles) are considered either intermediate or poor metabolizers, generate lower amounts of active metabolite, and generally produce a reduced antiplatelet effect as measured with available platelet function testing.[104] Conversely, patients with one or two copies of the *17 allele (considered a gain of function allele) are considered ultrarapid metabolizers and demonstrate a heightened antiplatelet response with clopidogrel. With the unraveling of pharmacogenomic factors related to clopidogrel response, a great deal of attention has been given to the idea of identifying patients with copies of either the *2 or *3 allele and adjusting antiplatelet therapy accordingly. The FDA added language

to the clopidogrel package insert specifying that poor metabolizers have a higher cardiovascular event rate and that tests are available to identify who those patients are who carry these genes. Alternative antiplatelet agents or alternative dosing of clopidogrel should be used.[105] Expert consensus recommends against routine CYP2C19 genotyping in patients with stable CAD. Exceptions can be made in specific situations that are deemed high risk such as left main coronary artery stenting and prior stent thrombosis. Expert consensus also recommends against platelet function testing (PFT) in patients with stable CAD to determine if antiplatelet therapy should be increased, but PFT may be useful in predicting cardiovascular risk (both bleeding and ischemic events) after PCI.[106]

An alternative approach to address the issue of clopidogrel nonresponsiveness is to assess platelet function in patients receiving clopidogrel. To date, trials conducted have indicated that increasing loading or maintenance doses of clopidogrel do have the potential to convert patients deemed nonresponders to responders.[107,108] However, not all patients can be converted and no trial has demonstrated that such an approach leads to improved clinical outcomes.[109] Therefore, in chronic stable angina, increase loading and maintenance doses should not be used.

Case 12-4, Question 5: While you are filling her new clopidogrel prescription, E.R. mentions that she has been having some problems with heartburn lately and asks where she can find some OTC omeprazole. Is omeprazole appropriate to use in a patient with clopidogrel therapy?

Another source of variable clopidogrel response is through potential drug–drug interactions involving the CYP2C19 enzyme. One class of agents that has generated substantial controversy in this area are the proton-pump inhibitors (PPIs), given the likelihood of coadministration to prevent GI bleeding as a result of antiplatelet therapy. Several studies indicate there is a pharmacokinetic interaction between PPIs, in particular omeprazole, with clopidogrel resulting in reduced levels of the active metabolite. Evidence that this interaction is clinically significant is variable. Several

retrospective analyses suggest an increased risk for CVD events in patients taking PPIs with clopidogrel therapy.[110-114] However, the available evidence from randomized controlled trials does not support an increased clinical risk with this combination.[114-116] However, one study has identified that PPI use alone is associated with an elevated risk of CVD events.[117] Clinicians are faced with addressing this issue from a medical–legal aspect as the FDA has incorporated language into the clopidogrel package insert warning against the concomitant administration of omeprazole and esomeprazole with clopidogrel.[118] The recommendation applies to omeprazole and esomeprazole but not other PPIs. Drug–drug interaction studies indicated PPIs such as pantoprazole and rabeprazole have the lowest propensity for clinically significant interactions with clopidogrel. Until further information becomes available, clinicians should first validate the need for PPI therapy in clopidogrel patients. If acid-suppressive therapy is needed, the use of an H_2 antagonist (excluding cimetidine, which can inhibit CYP enzymes) or a PPI less likely to interact with clopidogrel would seem to be appropriate options to consider.[119]

VARIANT ANGINA (CORONARY ARTERY SPASM)

Clinical Presentation

CASE 12-5

Question 1: A.P., a 35-year-old female, is hospitalized for evaluation of severe chest pain, which occurs almost daily at about 5 AM. A.P. ranks the severity of pain as 7 to 8 on a scale of 1 to 10. It is associated with diaphoresis and is not relieved by change in position. A.P. has no cardiovascular risk factors, and her hobbies include triathlon competition and rock climbing, neither of which has caused chest pain. She follows a strict vegetarian diet and takes no medications. Admission ECG reveals sinus bradycardia at 56 beats/minute.

Serum electrolytes, chemistry panel, and cardiac enzymes are all within normal limits.

On day 1 of hospitalization, A.P. is awakened at 6 AM abruptly by severe chest pain. Her vital signs at this time include the following: heart rate, 55 beats/minute; supine BP, 110/64 mm Hg; and respiratory rate, 12 breaths/minute. An ECG shows sinus bradycardia with marked ST-segment elevation. The pain is relieved within 60 seconds by one NTG 0.4-mg sublingual tablet. During the day, she completes an exercise tolerance test without complication or evidence of CAD.

On the second day, A.P. undergoes cardiac catheterization, and no coronary atherosclerosis is visualized. A.P. is diagnosed as having Prinzmetal variant angina. Discharge medications include oral amlodipine 10 mg every day at 11 PM and NTG lingual spray 0.4 mg as needed for chest pain.

Is A.P.'s presentation typical for Prinzmetal variant angina?

A.P. presents with a classic picture of variant (Prinzmetal) angina, with transient total occlusion of a large epicardial coronary artery as a result of severe segmental spasm. Clinical manifestations include chest pain occurring at rest, often in the morning hours. As with A.P., patients with Prinzmetal variant angina generally are younger than patients with chronic stable angina and do not carry a high-risk profile. Other vasospastic disorders, such as migraine attacks or Raynaud phenomenon, may be present; smoking can be an important contributing factor.[120]

The hallmark of variant angina is ST-segment elevation on the ECG, which denotes rapid and complete occlusion of the coronary artery. Many patients also have asymptomatic episodes of ST-segment elevation.[120]

As documented by angiography, A.P. has vasospasm of the large RCA. This transient, reversible narrowing is probably caused by increased coronary vascular resistance. It can occur in the absence of atherosclerosis, as illustrated by A.P., and also in the presence of CAD.

Therapy

Case 12-5, Question 2: Oral amlodipine 10 mg every day was ordered for A.P. Would long-acting nitrates or β-adrenergic blockers be reasonable alternatives to amlodipine for A.P.? Is one CCB preferable to another for treatment of Prinzmetal variant angina?

Because of their antispasmodic effects and low incidence of side effects, CCBs are generally selected either alone or in combination with long-acting nitrates for nocturnal vasospastic angina. All CCBs appear equally effective in preventing Prinzmetal variant angina.[120] Intrinsically long-acting or sustained-release forms are preferred, however, and some patients may respond better to one agent than to another.

Nitrates cause vasodilation by a different mechanism than CCBs and are effective in treating Prinzmetal variant angina.[120] To avoid tolerance, the nitrate-free interval for A.P. should be scheduled during the day so that the early morning hours when vasospasm occurs are covered by NTG. For example, A.P. could apply a transdermal NTG patch at bedtime and remove it on awakening. Statin therapy is indicated for A.P.[120]

Blockade of the β_2-receptors that mediate vasodilation may allow unopposed α_1-mediated vasoconstriction with worsening symptoms. Even a cardioselective β-blocker could worsen Prinzmetal variant angina.[118] Therefore, a CCB or nitrate is preferred.

Case 12-5, Question 3: Will A.P. require treatment for the remainder of her life?

Patients often experience an acute phase of anginal episodes that occur during the first 6 months after diagnosis.[120] This occurs most often in patients who have had a short duration of symptoms or who have normal or mildly diseased coronary arteries (ie, isolated vasospasm without atherosclerosis). If A.P. is pain-free and not experiencing significant arrhythmias or silent ischemic episodes of Prinzmetal angina after 1 year, amlodipine could be tapered and discontinued. It is also possible, however, that she will require

treatment indefinitely. Modification of smoking may promote remission of Prinzmetal angina.[120]

MICROVASCULAR ANGINA

CASE 12-6

QUESTION 1: K.G., a 50-year-old female executive, has undergone an extensive cardiovascular workup for exertional angina associated with a 3-mm ST-segment depression. A recent cardiac catheterization did not reveal any atherosclerosis. The cardiologists believe K.G. has microvascular angina.

What drug therapy might be indicated for K.G.?

Microvascular angina, historically known as cardiac syndrome X, is a syndrome of angina or angina-like chest pain in the setting of a normal coronary arteriogram, and ST-segment depression during exercise. Microvascular angina is because of various coronary microvascular functional and structural abnormalities. Several subtypes exist, and subtypes respond differently to different pharmacologic options. However, currently, there is a lack of knowledge in diagnosing different microvascular anginal subtypes.[121]

By symptoms alone, K.G.'s presentation does not significantly differ from that of a patient with exercise-induced angina secondary to atherosclerosis. Of concern is the finding of a 3-mm ST-segment depression on K.G.'s ECG, which raises concern of severe CAD. The negative findings from her cardiac catheterization, however, rule against both CAD and coronary artery spasm as a cause of her symptoms, and help to confirm the diagnosis of microvascular angina.[121]

Until subtypes of microvascular angina are commonly diagnosed, traditional anginal therapy with a nitrate, CCB, or β-blocker is recommended. All appear to offer some relief, but, overall, the response to therapy in these patients is poor. Some subtypes may benefit from other agents such as ACE inhibitors, ranolazine, and

tricyclic antidepressants. The choice of agent will likely depend on specific patient characteristics. Sublingual NTG is often ineffective at treating acute attacks, although it should still be prescribed. Often a combination of anti-ischemic therapy, analgesic therapy, and lifestyle modifications is necessary.[121]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Serebrauny VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol*. 2005;45:246–251.

Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization: the Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for cardio-Thoracic Surgery (EACTS), developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2019;40:87–165

Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373:1849–1860. (87)

Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation*. 2006;113:2462–2472. (15)

Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354–e471. (1)

Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41:407–477.

Hippisley-Cox J, Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. *BMJ*. 2005;330:1059–1063. (52)

Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44–e122. (95)

Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet*. 2010;376(9748):1233–1243. (107)

Parikh P, McDaniel MC, Ashen MD, et al. Diets and cardiovascular disease: an evidence-based assessment. *J Am Coll Cardiol*. 2005;45:1379–1387. (48)

Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study. *Lancet*. 2004;364:937–952. (12)

Key Websites

American College of Cardiology. CardioSource, https://www.acc.org/education-and-meetings/products-and-resources/cardiosource-plus

American Heart Association, https://www.acc.org/education-and-meetings/products-and-resources/cardiosource-plus

FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-poor

COMPLETE REFERENCES CHAPTER 12 CHRONIC STABLE ANGINA

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354–e471.
2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41:407–477.
3. Morrow DA, De Lemos JA. Stable ischemic heart disease. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt D. eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 11th ed. Elsevier Saunders; 2019:1209.
4. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596.
5. Pepine CJ, Nichols WW. The pathophysiology of chronic ischemic heart disease. *Clin Cardiol*. 2007;30:I4–I9.
6. Duncker DJ, Canty JM. Coronary blood flow and myocardial ischemia. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt D. eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 11th ed. Elsevier Saunders; 2091:1069.
7. Kones R. Recent advances in the management of chronic stable angina I: approach to the patient, diagnosis, pathophysiology, risk stratification, and gender disparities. *Vascular Health and Risk Management*. 2010;6:635–656.
8. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685–1695.
9. Zarraga IG, Schwarz ER. Impact of dietary patterns and interventions on cardiovascular health [published correction appears in *Circulation*. 2006;114:e577]. *Circulation*. 2006;114:961–973.
10. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA*. 2009;302(1):49–57.
11. Schnabel RB, Schulz A, Messow CM, et al. Multiple marker approach to risk stratification in patients with stable coronary artery disease. *Eur Heart J*. 2010;31:3024–3031.
12. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study. *Lancet*. 2004;364:937–952.

13. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25, Suppl 2):S49–S73.
14. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med*. 2007;357:2482–2494.
15. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation*. 2006;113:2462–2472.
16. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;64(24):e139–e228.
17. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2013;127:1–64.
18. Fletcher GF, Ades PA, Kligfield P, et al Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128:873–934.
19. Amsterdam EA, Kirk JD, Bluemke DA, et al; Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1756–1776.
20. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization: the Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for cardio-Thoracic Surgery (EACTS), developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2019;40:87–165.
21. Mack MJ, Squiers JJ, Lytle BW, DiMaio JM, Mohr FW. Myocardial revascularization surgery. JACC historical breakthroughs in perspective. *J Am Coll Cardiol.* 2021;78:365–383.
22. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2014;129(25 Suppl 2):S76–S99.
23. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124:2458–2473.
24. U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. U.S.

Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014 [accessed 2015 Mar 26]. https://www.hhs.gov/sites/default/files/consequences-smoking-exec-summary.pdf

25. Grundy SM, Stone NJ, Bailey AL, et al. 2018 ACC/AHA/AACVPP/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73: e285–e350.
26. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:2199–2269.
27. American Diabetes Association. Standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43(Suppl 1):S1–S212.
28. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643–2653.
29. The Accord Study Group, Gerstein HC, Miller ME, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med*. 2011;364:818–828.
30. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk for ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348:1329–1339.
31. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717.
32. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.
33. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy and drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166.
34. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease—a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1082–1115.
35. Reiter MJ. Cardiovascular drug class specificity: beta-blockers. *Prog Cardiovasc Dis*. 2004;47(1):11–33.

36. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers. *J Am Coll Cardiol*. 2007;50:563–572.
37. Goldstein S. Beta-blocking drugs and coronary heart disease. *Cardiovasc Drugs Ther*. 1997;11:219–225.
38. Boden WE, Finn AV, Patel D, Peacock WF, Thadani U, Zimmerman FH. Nitrates as an integral part of optimal medical therapy and cardiac rehabilitation for stable angina: review of current concepts and therapeutics. *Clin Cardiol*. 2012;35:263–271.
39. Wei J, Wu T, Yang Q, Chen M, Ni J, Huang D. Nitrates for stable angina: a systematic review and meta analysis of randomized clinical trials. *Int J Cardiol*. 2011;146:4–12.
40. Cooper-DeHoff RM, Chang SW, Pepine CJ, et al. Calcium antagonists in the treatment of coronary artery disease. *Curr Opin Pharmacol*. 2013;13:301–308.
41. Dobesh PP, Trujillo TC. Ranolazine: a new option in the management of chronic stable angina. *Pharmacotherapy*. 2007;27:1659–1676.
42. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972.
43. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.
44. Serruys PW, Ono M, Garg S, et al. Percutaneous coronary revascularization. JACC historical breakthroughs in perspective. *J Am Coll Cardiol*. 2021;78:384–407.
45. Cox JJ, Naylor CD. The Canadian Cardiovascular Society grading scale for angina pectoris: is it time for refinements? *Ann Intern Med*. 1992;117:677–683.
46. Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. *Am J Med*. 2015;128:229–238.
47. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368:1279–1290.
48. Parikh P, McDaniel MC, Ashen MD, et al. Diets and cardiovascular disease: an evidence-based assessment. *J Am Coll Cardiol*. 2005;45:1379–1387.
49. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA*. 2007;297:842–857.
50. The Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA*. 2002;288:2015–2022.
51. Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trial. *JAMA*. 2006;296:2720–2726.

52. Hippisley-Cox J, Coupland C. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. *BMJ*. 2005;330:1059–1063.
53. Kernis SJ, Harjai KJ, Stone GW, et al. Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty? *J Am Coll Cardiol*. 2004;43:1773–1779.
54. Bunch TJ, Muhlestein JB, Bair TL, et al. Effect of beta-blocker therapy on mortality rates and future myocardial infarction rates in patients with coronary artery disease but no history of myocardial infarction or congestive heart failure. *Am J Cardiol*. 2005;95:827–831.
55. Go AS, Iribarren C, Chandra M, et al. Statin and beta-blocker therapy and the initial presentation of coronary heart disease. *Ann Intern Med*. 2006;144:229–238.
56. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). *Circulation*. 1994;90:762–768.
57. Sipahi I, Tuzcu EM, Wolski KE, et al. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultra-sonography trials. *Ann Intern Med*. 2007;147:10–18.
58. Heidenreich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. *JAMA*. 1999;281:1927–1936.
59. Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation*. 2007;115:2761–2788.
60. Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Adverse respiratory effect of acute β-blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials. *Chest*. 2014;145:779–786.
61. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 1991;151:1769–1776.
62. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA*. 2007;297:2018–2024.
63. Trujillo T, Dobesh PP. Traditional management of chronic stable angina. *Pharmacotherapy*. 2007;27:1677–1692.
64. Munzel T, Gori T. Nitrate therapy and nitrate tolerance in patients with coronary artery disease. *Curr Opin Pharmacol*. 2013;13:251–259.
65. Frishman WH, Sica DA. The organic nitrates and nitroprusside. In: Frishman WH, Sica DA. eds. *Cardiovascular Pharmacotherapeutics*. 3rd ed. McGraw-

Hill; 2011:205.
66. Luke R, Sharpe N, Coxon R. Transdermal nitroglycerin in angina pectoris: efficacy of intermittent application. *J Am Coll Cardiol*. 1987;10:642–646.
67. Cowan JC, Bourke JP, Reid DS, Julian DG. Prevention of tolerance to nitroglycerin patches by overnight removal. *Am J Cardiol*. 1987;60:271–275.
68. Shaw SV, Hunter WJ, Shirer AE. Selection and dosing of nitrates to avoid tolerance during sustained antianginal therapy. *Formulary*. 1999;34:590.
69. Opie LH. Calcium channel blockers. In: Opie LH, Gersh BJ, eds. *Drugs for the Heart*. 8th ed. Elsevier Health Sciences; 2013.
70. Von Arnim T. Medical treatment to reduce total ischemic burden: total ischemic burden bisoprolol study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. The TIBBS Investigators. *J Am Coll Cardiol*. 1995;25:231–238.
71. Savonitto S, Ardissiono D, Egstrup K, et al. Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris. Results of the International Multi-center Angina Exercise (IMAGE) Study. *J Am Coll Cardiol*. 1996;27:311–316.
72. Pehrsson SK, Ringqvist I, Ekdahl S, Karlson BW, Ulvenstam G, Persson S. Monotherapy with amlodipine or atenolol vs their combination in stable angina pectoris. *Clin Cardiol*. 2000;23:763–770.
73. Hjemdahl P, Eriksson SV, Held C, Forslund L, Näsman P, Rehnqvist N. Favorable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSIS). *Heart*. 2006;92:177–182.
74. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trials. *JAMA*. 2004;292:2217–2225.
75. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs. a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The international verapamil trandolapril study (INVEST): a randomized controlled trial. *JAMA*. 2003;290:2805–2816.
76. Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet*. 2004;364:849–857.
77. The Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial [published correction appears in *Lancet*. 2008;372:1384]. *Lancet*. 2008;372:1174–1183.

78. The ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
79. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol*. 2004;43:1375–1382.
80. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA*. 2004;291:309–316.
81. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L; ERICA Investigators. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol*. 2006;48:566–575.
82. Kosiborod M, Arnold SV, Spertus JA, et al. Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina). *J Am Coll Cardiol*. 2013;61:2038–2045.
83. Koren MJ, Crager MR, Sweeney M. Long-term safety of a novel antianginal agent in patients with severe chronic stable angina: the ranolazine open label experience (ROLE). *J Am Coll Cardiol*. 2007;49:1027–1034.
84. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 trial. *JAMA*. 2007;297:1775–1783.
85. Scirica BM, Morrow DA, Hod H, et al. Effect of ranolazine, an antianginal agent with novel electrophysiologic properties, on incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation*. 2007;116:1647–1652.
86. Ranexa (ranolazine). Prescribing information. Gilead Sciences, Inc.; 2019.
87. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al.Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849–1860.
88. Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *Am J Med*. 2011;124:621–629.
89. Bartolucci AA, Tendera M, Howard G. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. *Am J Cardiol*. 2011;107:1796–1801.

90. Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med*. 2012;172:209–216.
91. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646. doi:10.1161/CIR.0000000000000678
92. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115:1634–1642.
93. Danelich IM, Wright SS, Lose JM, Tefft BJ, Cicci JD, Reed BN. Safety of nonsteroidal antiinflammatory drugs in patients with cardiovascular disease. *Pharmacotherapy.* 2015;35(5):520–535.
94. Dangas GD, Mehran R. et al. Coronary arteriography and intracoronary imaging. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt D, Solomon SD eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 12th ed. WB Saunders; 2022:363.
95. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44–e122.
96. Stefanini GS, Holmes D. Drug-eluting coronary-artery stents. *N Engl J Med*. 2013;368:254–265.
97. Windecker S, Meier B. Late coronary stent thrombosis. *Circulation*. 2007;116:1952–1965.
98. White HD. Oral antiplatelet therapy for atherothrombotic disease: current evidence and new directions. *Am Heart J*. 2011;161:450–461.
99. Campo G. Poor response to clopidogrel: current and future options for its management. *J Thromb Thrombolysis*. 2010;30:319–331.
100. Serebrauny VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol*. 2005;45:246–251.
101. Michelson AD. Methods for the measurement of platelet function. *Am J Cardiol*. 2009;103(3, Suppl):20A–26A.
102. Price MJ. Bedside evaluation of thienopyridine antiplatelet therapy. *Circulation*. 2009;119:2625–2632.
103. Williams CD, Cherala G, Serebruany V. Application of platelet function testing to the bedside. *Thromb Haemost*. 2010;103:29–33.
104. Momary KM, Dorsch MP, Bates ER. Genetic causes of clopidogrel nonresponsiveness: which ones really count. *Pharmacotherapy*. 2010;30(3):265.

105. US Food and Drug Administration. FDA Drug Safety Communication: reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. Accessed October 7, 2020. http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm203888.htm
106. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2019;12:1512–1537.
107. Bonello L, Camoin-Jau L, Armero S. Tailored clopidogrel loading dose according to platelet reactivity monitoring to prevent acute and subacute stent thrombosis. *Am J Cardiol*. 2009;103:5–10.
108. Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet*. 2010;376:1233–1243.
109. Price MJ, Berger PB, Teirstein PS, et al. Standard vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention. The GRAVITAS randomized trial. *JAMA*. 2011;305:1097–1105.
110. Goodman SG, Clare R, Pieper KS, et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation*. 2012;125:978–986.
111. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009;301:937–944.
112. Wu CY, Chan FK, Wu MS, et al. Histamine2-receptor antagonists are an alternative to proton pump inhibitor in patients receiving clopidogrel. *Gastroenterology*. 2010;139:1165–1171.
113. Ortolani P, Marino M, Marzocchi A, De Palma R, Branzi A. One-year clinical outcome in patients with acute coronary syndrome treated with concomitant use of clopidogrel and proton pump inhibitors: results from a regional cohort study. *J Cardiovasc Med (Hagerstown)*. 2012;13:783–789.
114. Melloni C, Washam JB, Jones WS, et al. Conflicting results between randomized trials and observational studies on the impact of proton pump inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy. *Circ Cardiovasc Qual Outcomes*. 2015;8:47–55.
115. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010;363:1909–1917.
116. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-

pump inhibitor: an analysis of two randomised trials. *Lancet*. 2009;374:989–997.

117. Blackburn DF, Lamb DA, Mcleod MM, Eurich DT. Increased use of acid-suppressing drugs before the occurrence of ischemic events: a potential source of confounding in recent observational studies. *Pharmacotherapy*. 2010;30:985–993.
118. Plavix. Package insert. Sanofi-Aventis; 2019.
119. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018;39(3):213–260.
120. Giugliano RP, Braunwald E. Non-ST elevation acute coronary syndromes. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt D. eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 11th ed. Elsevier Saunders; 2019:1181.
121. Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. *Heart*. 2018;104:284.

13

Acute Coronary Syndrome

Brianne Dunn and Robert Lee Page II

CORE PRINCIPLES		CHAPTER CASES
ACUTE CORONARY SYNDROME		
1	Acute coronary syndrome (ACS) is an umbrella term including unstable angina (UA) or acute myocardial infarction (MI), which consists of ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation myocardial infarction (NSTEMI). Diagnosis is based on patient presentation, electrocardiographic changes, and elevated cardiac biomarkers.	**Case 13-1 (Questions 1–4)**
2	Treatment goals of ACS are to alleviate ischemic symptoms, restore blood flow to the infarct-related artery, arrest infarct expansion, minimize adverse outcomes, and prevent mortality.	**Case 13-1 (Question 5)** **Case 13-2 (Question 1)**

3	For both STEMI and non–ST-segment elevation acute coronary syndrome (NSTE-ACS), initial therapies may include oxygen, nitroglycerin (NTG), antiplatelet agents, anticoagulants, β-blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and morphine sulfate.	**Case 13-1 (Questions 14–16)**

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

1	Treatment goals of STEMI are to restore coronary blood flow by administering a fibrinolytic or performing percutaneous coronary intervention (PCI). Treatment strategy depends on the availability of catheterization laboratory and skilled staff, time of initial medical contact, and contraindication for a fibrinolytic agent.	**Case 13-1 (Questions 6, 11–13)**
2	Regardless of reperfusion strategy, patients should receive aspirin in addition to a $P2Y_{12}$ inhibitor.	**Case 13-1 (Questions 7–10)**
3	For patients receiving fibrinolytic therapy, unfractionated heparin (UFH), enoxaparin, or fondaparinux should also be initiated.	**Case 13-1 (Questions 7, 10)**
4	For patients receiving PCI, an anticoagulant strategy consisting of either UFH or low-molecular-weight heparins (LMWH) with or without a glycoprotein IIb/IIIa inhibitor or bivalirudin alone should be administered.	**Case 13-1 (Question 10)**

NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

1	For an invasive strategy, a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) and an anticoagulant (UFH, enoxaparin, or bivalirudin) should be administered along with aspirin. A glycoprotein IIb/IIIa inhibitor may be used adjunctively in select patients.	**Case 13-2 (Questions 2–5)**
2	For an ischemia-guided strategy, an anticoagulant (UFH, enoxaparin, or fondaparinux) along with dual antiplatelet therapy (DAPT) should be considered.	**Case 13-2 (Question 6)**

SECONDARY PREVENTION STRATEGIES

1	Potential long-term therapies include a β-blocker, statin, aspirin, $P2Y_{12}$ inhibitor, ACE inhibitor or ARB, aldosterone antagonist, and sublingual NTG. Unless contraindicated, ACE inhibitors or ARBs should be given to those with a left ventricular ejection fraction of <40%, hypertension, diabetes, and/or chronic kidney disease.	**Case 13-3 (Questions 1–3, 5, 6, 9)**
2	Lifestyle modifications include smoking cessation, weight management through diet and exercise to reduce body weight by 10% if body mass index exceeds 25 kg/m^2, diabetic treatment to achieve a near-normal hemoglobin A_{1c}, and	**Case 13-3 (Question 10)**

	hypertension management to achieve goal blood pressure ≤130/80 mm Hg.	
COMORBIDITIES		
1	Aldosterone antagonists and sodium–glucose-linked cotransporter-2 (SGLT2) inhibitors provide additional benefit for patients following an ACS event with a left ventricular ejection fraction <40%.	**Case 13-3 (Questions 2, 4)**
2	In patients with diabetes, an SGLT2 inhibitor or a glucagon-like peptide-1 receptor agonist (GLP1-RA) should be considered regardless of baseline A_{1c}.	**Case 13-3 (Question 4)**
3	Strategies to minimize bleeding risk for patients needing oral anticoagulation in addition to DAPT should be considered.	**Case 13-3 (Questions 7, 8)**

INTRODUCTION

Despite advances in medical intervention and pharmacotherapy, cardiovascular disease continues to be a leading killer in the United States. Acute coronary syndrome (ACS) is an umbrella term that includes patients who present with either unstable angina (UA) or acute myocardial infarction (AMI), which is further differentiated into ST-segment elevation myocardial infarction (STEMI) or non–ST-segment myocardial infarction (NSTEMI).[1–5] The terminology, non–ST-segment elevation acute coronary syndrome (NSTE-ACS) includes both UA and NSTEMI.[1] These two conditions are determined based on the presence (NSTEMI) or absence (UA) of biomarkers associated with necrosis. The etiology of ACS originates from the erosion or rupture of an unstable plaque within the coronary artery leading to the formation of an occlusive or a nonocclusive

thrombus. Although NSTE-ACS and STEMI lead to hospitalization, patients presenting with STEMI are considered medical emergencies and warrant immediate intervention.[5] Today, the management of ACS is based on reperfusion and revascularization using both pharmacologic and nonpharmacologic interventions such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).[1–5] A committee composed of representatives from the American College of Cardiology (ACC) and the American Heart Association (AHA) periodically review the literature and publish practice guidelines to aid health care practitioners in selecting the most effective treatments for patients with ACS.[1–5] These guidelines consist of graded recommendations based on the weight and quality of the evidence. Although there are local variations in practice, these guidelines serve as the foundation for care of patients with ACS.

Epidemiology

According to AHA statistics, an American has an AMI every 40 seconds, which accounts for ~720,000 new coronary events and 335,000 recurrent events. The average age at first MI is 65.6 years for males and 72.0 years for females.[6] In an analysis of >4 million Medicare beneficiaries, Krumholz et al estimated that 30-day mortality for acute MI declined from 1995 through 2014 (20.0%–12.4%). Mortality was higher in females, but, over time, the difference in 30-day mortality between males and females reduced. These trends may be reflective of application of evidence-based guidelines as well as aggressive treatment of hypertension and hypercholesterolemia.[7] Based on the 2016 estimates, the U.S. health care system spent a total of $89.3 billion for ischemic heart disease, of which nearly half was for inpatient care and almost one-quarter was for ambulatory care expenses.[8]

Pathophysiology

The majority of ACS cases results from occlusion of a coronary artery secondary to thrombus formation overlying a lipid-rich atheromatous plaque that has undergone fissuring or rupture (**Fig. 13-1**). Plaques that are susceptible to rupture have a thin fibrous cap, large fatty core, high content of inflammatory cells such as macrophages and lymphocytes, limited amounts of smooth muscle, and an eccentric shape. Triggers such as surges in sympathetic activity with a sudden increase in blood pressure (BP), pulse rate, myocardial contractility, and coronary blood flow can lead to erosion, fissuring, or rupture of the fragile fibrous cap. Once ruptured, the thrombogenic components of the plaque consisting of collagen and tissue factor are exposed. This promotes activation of the platelet cascade, ultimately leading to the formation of a thrombus as well as ischemia in the corresponding myocardial area. The extent of intracoronary thrombosis and distal embolization determines the type of ACS (see **Fig. 13-1**). In patients with UA, the coronary artery has enough blood flow such that the myocardial cells do not die. In patients with NSTEMI, there exists partial thrombotic occlusion with or without distal embolization or severe stenosis and some myocardial cells die. In STEMI, there exists total and persistent thrombotic occlusion leading to myocardial cell death.[9] Eighty percent of patients presenting with ACS have two or more active plaques.[9]

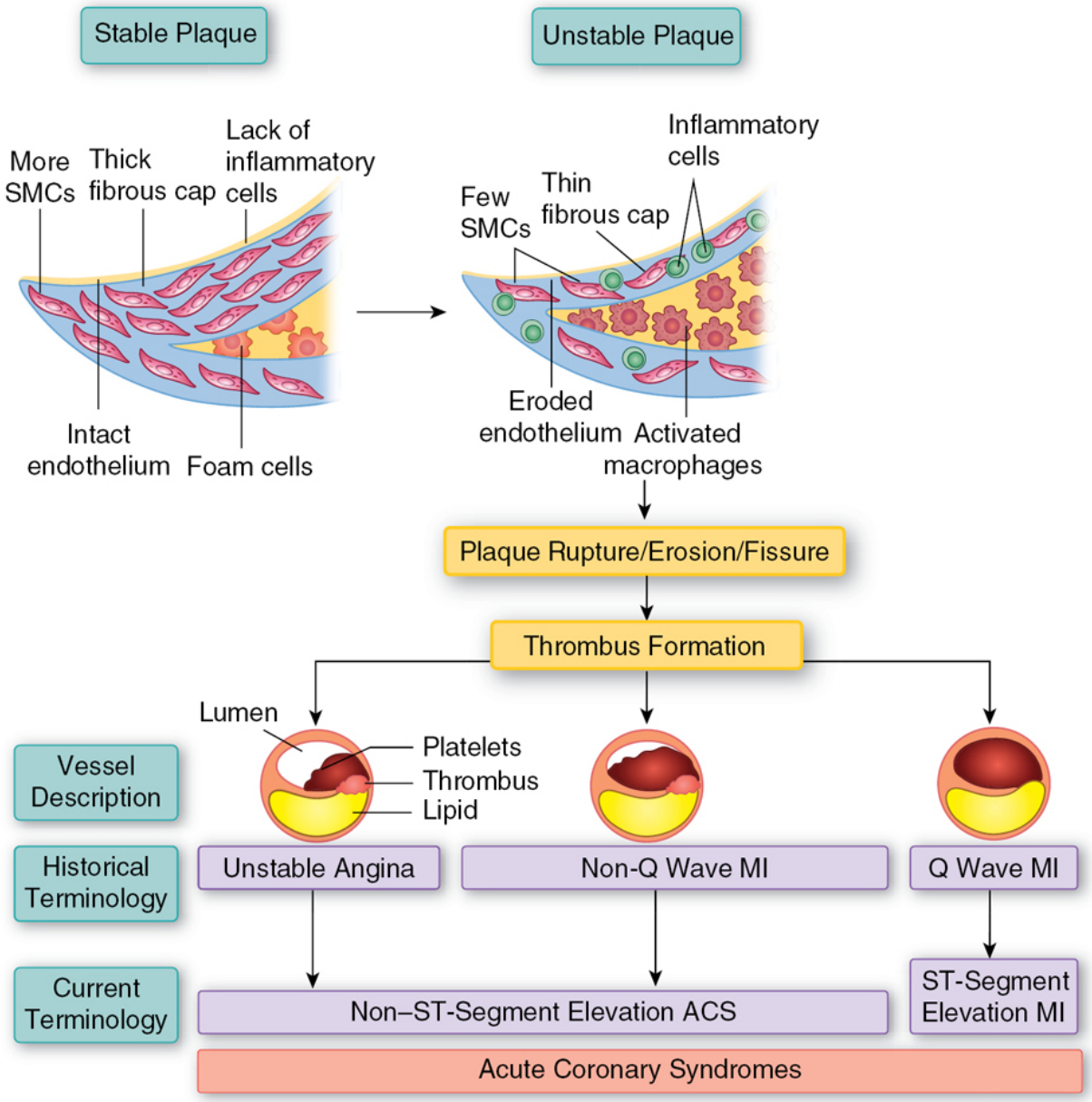


Figure 13-1 Thrombus formation and acute coronary syndrome definitions. ACS, acute coronary syndrome; MI, myocardial infarction; SMC, smooth muscle cells.

Most infarctions are located in a specific region of the heart and are described as such (eg, anterior, lateral, inferior). An anterior wall infarction carries a worse prognosis than does an inferior or lateral wall infarction because it is more commonly associated with development of left ventricular (LV) failure and cardiogenic shock.

Clinical Presentation

An important part in establishing the diagnosis of ACS is obtaining the patient's "story," which can elicit crucial hallmark symptoms such as increasing frequency of exertional angina or chest pain at rest, new-onset severe chest discomfort, or increasing angina with a duration exceeding 20 minutes. The pain is typically midline anterior chest discomfort that can radiate to the left arm, back, shoulder, or jaw and may be associated with diaphoresis, dyspnea, nausea, and vomiting, as well as unexplained syncope. Patients with STEMI will usually report unrelenting chest pain, whereas patients with NSTE-ACS will present with either angina at rest, new-onset (≤2 months) angina, or chronic angina that increases in frequency, duration, or intensity. Presentation may differ by sex, age, and presence of various comorbidities. Males commonly report chest pain, whereas females often present with nausea and diaphoresis. Elderly patients may present with hypotension or cerebrovascular symptoms rather than with chest pain. In addition, onset of ACS does not occur at random, and many episodes appear to be triggered by external factors or conditions. Myocardial infarction occurs with increased frequency in the morning, particularly within the first hour of awakening; on Mondays; during winter months or colder days; and during emotional stress and vigorous exercise.[1–5]

The physical examination is important in guiding initial therapy. Signs of severe LV or right ventricular dysfunction may be present (see Chapter 14, Heart Failure). The patient may have severe hypertension as a result of pain or, conversely, may be hypotensive. Significant tachycardia (heart rate >120 beats/minute) suggests a large area of damage. On cardiac auscultation, presence of a fourth heart sound (S_4) denotes an ischemia-induced decrease in LV compliance. New cardiac murmurs may be heard, resulting from papillary muscle dysfunction. The cerebral and peripheral vasculature should be assessed. Patients with a history of cerebrovascular disease may not be eligible for fibrinolytic therapy. Peripheral pulses should be examined to assess perfusion and to obtain a baseline before invasive procedures are instituted.

Diagnosis

In addition to the patient's history and presentation, the diagnosis of ACS is based on the electrocardiogram (ECG) and laboratory results from a cardiac injury profile. A 12-lead ECG should be obtained within 10 minutes of presenting to the emergency department (ED). The ECG is an indispensable tool in the diagnosis of ACS and has become the key point in the decision pathway (**Fig. 13-2**). Key findings on ECG consist of ST-segment elevation, ST-segment depression, or T-wave inversion.[1–5] By definition, STEMI consists of ST-segment elevation in two or more contiguous leads and either exceeding 0.2 mV (2 mm) in leads V_1, V_2, and V_3 or ≥0.1 mV (≥1 mm) in other leads. NSTE-ACS consists of ST-segment depression exceeding 0.1 mV (1 mm) in two or more contiguous leads or T-wave inversions exceeding 0.1 mV (1 mm). In addition, the 12-lead ECG is helpful in determining the location of an infarct.[10]

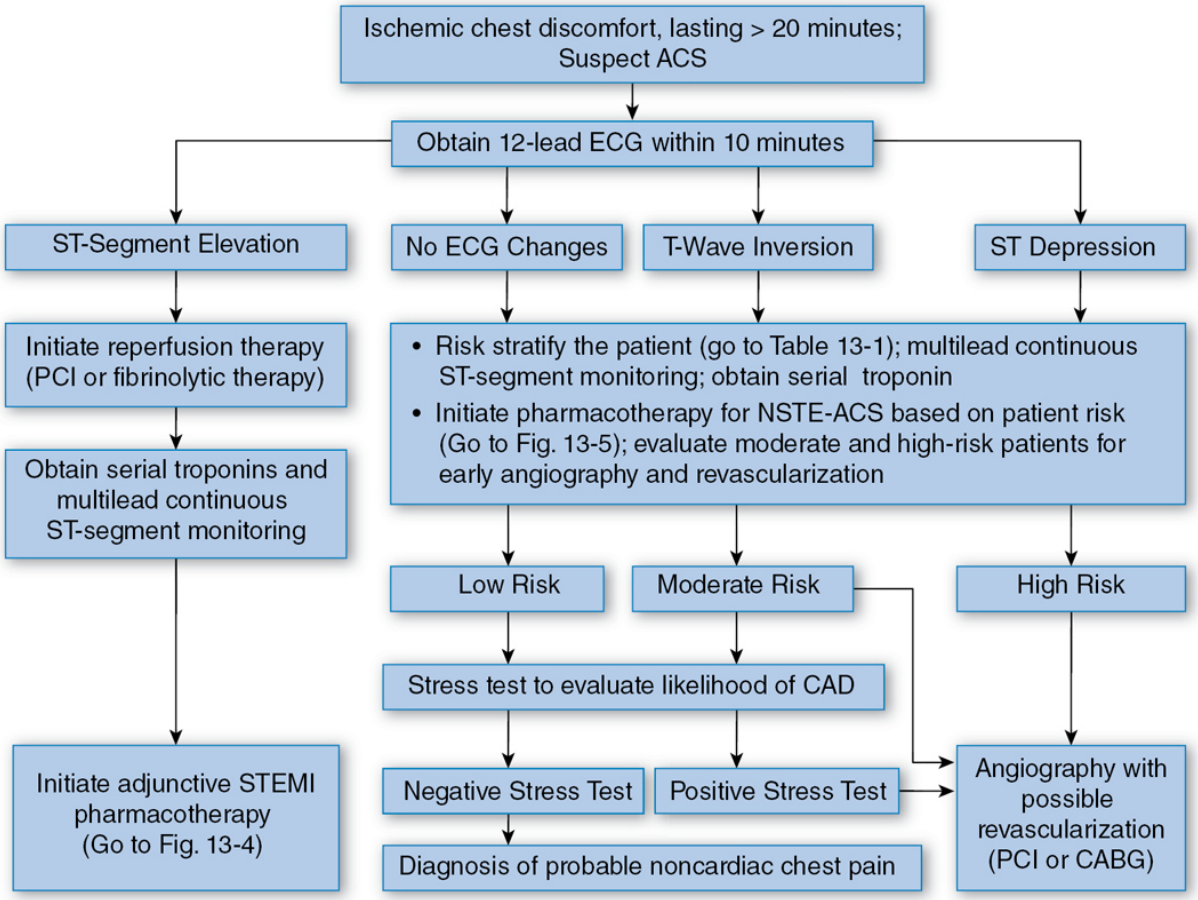


Figure 13-2 Evaluation algorithm for the patient presenting with acute coronary syndrome. ACS, acute coronary syndrome; CAD, coronary artery disease; CABG, coronary artery bypass graft; ECG, electrocardiogram; PCI, percutaneous intervention; NSTE-ACS, non–ST-segment acute coronary syndrome; STEMI, ST-segment myocardial infarction. (Adapted from Spinler SA. Evolution of antithrombotic therapy used in acute coronary syndromes. In: Richardson M, Chessman K, Chant C, Cheng J, Hemstreet B, Hume Al, eds. *Pharmacotherapy Self-Assessment Program*. 7th ed. Cardiology. American College of Clinical Pharmacy; 2010:62. Reprinted with permission from the American College of Clinical Pharmacy.)

Laboratory Changes

When a cardiac cell is injured, proteins are released into circulation. The measurement of these sensitive and specific proteins (troponins T or I and creatine kinase [CK]) is routine in establishing the diagnosis of AMI (**Fig. 13-3**). There are three isoenzymes of CK, of which the MB band is the most specific for the myocardium. Troponin is the preferred biomarker for the assessment of myocardial damage owing to its high cardiac specificity and sensitivity (90.7% and 90.2%, respectively). High-sensitivity cardiac troponin (hs-cTn) allows for more rapid detection of myocardial injury and allows for a shortened timing of serial measurements.[11] Troponins T and I are detectable in blood within 4 to 12 hours of the onset of MI, and peak values are observed at 12 to 48 hours. Troponin levels may also stay elevated for 7 to 10 days after myocardial necrosis. As seen in **Figure 13-3**, the horizontal line depicts the upper reference limit (URL) for the cardiac biomarker in the clinical chemistry laboratory.[1,2,5] The URL represents the 99th percentile of a reference control group without MI. Because cardiac troponin T and I are not normally detected in the blood of healthy people, the definition of an abnormally increased level is a value that exceeds that of 99% of a reference control group. For the diagnosis of NSTEMI or STEMI, the patient should have at least one troponin value. Cardiac biomarkers are not typically elevated in patients with UA. Presently, no current marker is detectable immediately upon onset of MI, and therefore repeated measurements of cardiac enzymes after admission are warranted. A cardiac injury profile will be measured at presentation and every 3 to 6 hours for the first 12 to 24 hours and periodically thereafter.[2–4] Unfortunately, several conditions other than AMI, such as tachyarrhythmias, heart failure (HF), myocarditis and pericarditis, hypotension or hypertension, acute pulmonary embolism, end-stage renal disease, and cardiac trauma are associated with elevated troponin. As a result, it is important to assess other diagnostic criteria such as ECG changes, chest pain, presence of atherosclerotic risk factors, and echocardiographic findings.

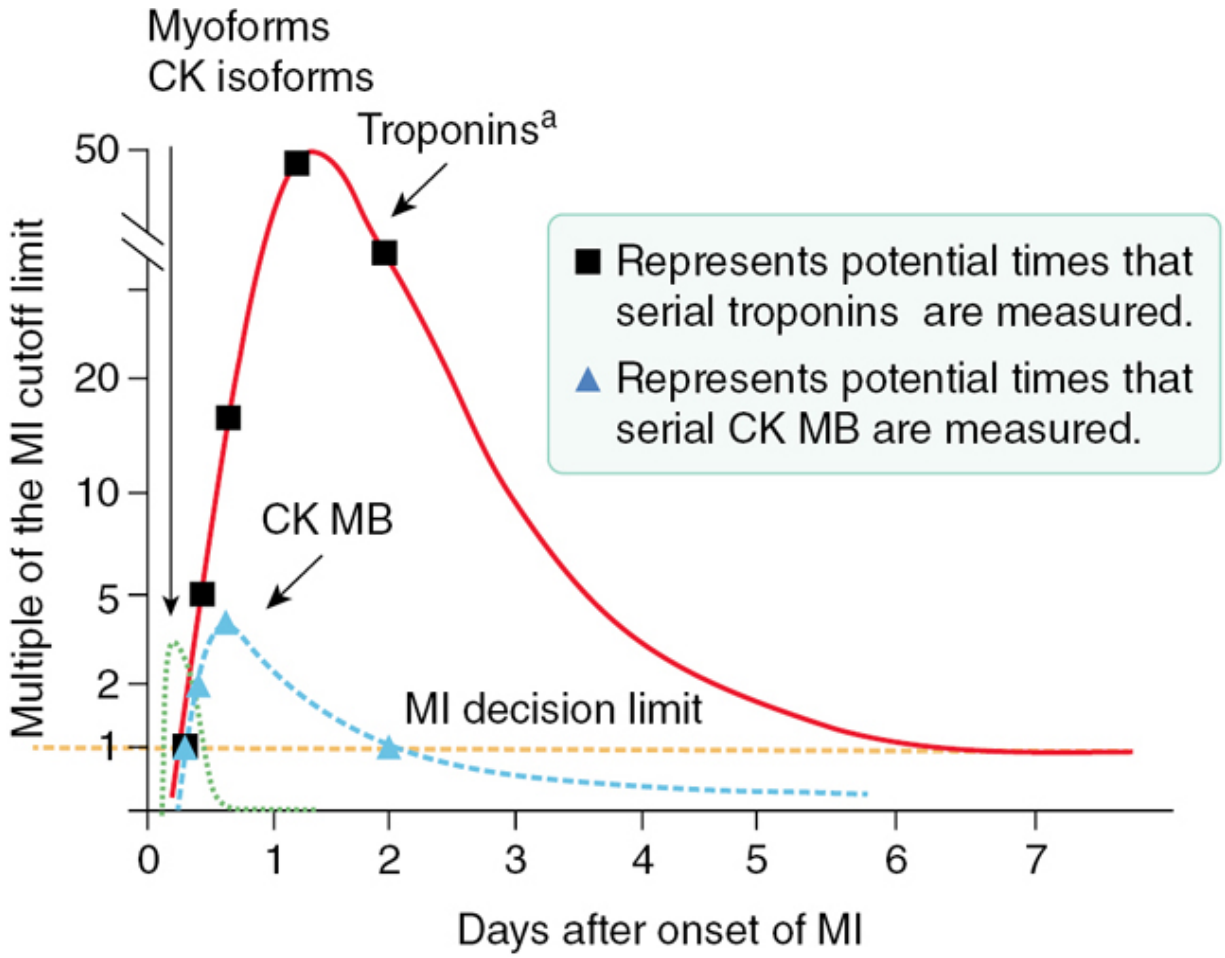


Figure 13-3 Cardiac biomarker elevation in acute coronary syndrome. CK, creatine kinase; MI, myocardial infarction.[a] Serial troponins and CK-MB are initially measured during first 12 to 24 hours of onset of chest pain and continued to be measured until the concentrations begin to decline. (Adapted from Anderson J, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular

and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50(7):e1–e157. © 2007 American College of Cardiology Foundation and the American Heart Association, Inc. With permission.)

Risk Stratification

The examination of a patient presenting with ACS begins with stratification for the risk of major adverse cardiac events (MACE), taking into account the presenting signs and symptoms, past medical history, ECG, and cardiac biomarker changes (see **Fig. 13-2**). In addition, risk scores can be used to estimate mortality and bleeding risk as well as guide decision-making for intervention. Several risk scoring systems have been validated in patients with ACS (**Table 13-1**). The two most common are the Thrombolysis in Myocardial Infarction (TIMI) risk score, which was introduced in the year 2000 and can be used with either STEMI or NSTE-ACS and the Global Registry of Acute Coronary Events (GRACE) score introduced in 2006, which estimates in-hospital and 1-year morality for patients with ACS.[12,13] The HEART score can be used as a decision aid for early discharge in low-risk patients and has been shown to better predict MACE compared to GRACE and TIMI.[14,15] Bleeding scores such as CRUSADE (*C*an *R*apid risk stratification of *U*nstable angina patients *S*uppress *AD*verse outcomes with *E*arly implementation of the ACC/AHA guidelines) can be used to estimate a patient's likelihood of major bleeding and can aid in selection of anticoagulation and antiplatelet selection.[16] Lastly, the dual antiplatelet therapy (DAPT) score was designed to identify long-term risk of extended DAPT beyond 12 months.[17] A variety of clinical tools to aid in the decision-making process can be found through the ACC and include mobile apps for ease of use. At this time, no one risk assessment strategy is preferred but, instead, is based on hospital preference and clinical experience.

Table 13-1
Risk Stratification Tools for Acute Coronary Syndrome

	TIMI Risk Score		GRACE Score		HEART Score		CRUSADE Score		DAPT Score	
Variables	Age ≥65 years	1 point	Age	0–100 points	Suspicious history	0–2 points	Heart rate	1–11 points	Age	−2 to 0 points
	≥3 risk factors for CAD	1 point	Heart rate	0–46 points	ST-segment deviation	1–2 points	Systolic BP	1–8 points	Smoking	1 point
	Prior history of CAD	1 point	Systolic BP	0–58 points	Age	0–2 points	Hematocrit	2–9 points	Diabetes	1 point
	Aspirin use in the past 7 days	1 point	Creatinine	0–28 points	1–2 risk factors for CAD	1 point	Creatinine clearance	0–35 points	MI at presentation	1 point
	≥2 anginal events in the past 24 hours	1 point	Cardiac arrest at admission	39 points	≥3 risk factors for CAD	2 points	Female gender	8 points	Prior PCI or prior MI	1 point
	ST-segment deviation ≥0.5 mm	1 point	ST-segment deviation on ECG	28 points	Elevation in cardiac markers	1–2 points	Signs of HF at presentation	7 points	Drug-eluting stent	1 point
	Elevation of cardiac markers	1 point	Abnormal cardiac enzymes	14 points			History of valvular disease	6 points	Stent diameter <3 mm	1 point
			Killip class (I–IV)	0–59 points			History of diabetes	6 points	EF < 30%	2 points
									Vein graft stent	2 points
Score Range	0–7 Low risk: 0–2 Intermediate risk: 3–4 High risk: ≥5		0–372 Low risk: <109 Intermediate risk: 109–140 High mortality risk: ≥141		0–10 Low risk: 0–3 Moderate risk: 4–6 High risk: 7–10		0–90 Very low/low risk: <31 Moderate risk: 31–40 High/very high risk: >40		−2 to 10 Favorable benefit/risk ratio: ≥2 Unfavorable benefit/risk ratio: <2	

BP, blood pressure; CAD, coronary artery disease; CRUSADE, *C*an *R*apid risk stratification of *U*nstable angina patients *S*uppress *AD*verse outcomes with *E*arly implementation of the ACC/AHA guidelines; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; EF, ejection fraction; GRACE, global registry of acute coronary events; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Sources: Collet J, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42(14):1289–1367; Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction. *Circulation.* 2000;102:2031–2037; Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J.* 2008;16(6);191–196; Mejia LAH, Betances AF, Nimmagadda M, et al. Comparison of HEART, TIMI and GRACE scores in predicting major adverse cardiac events within 120 days in patients presenting to the emergency department with chest pain in a community health system. *J Am Coll Cardiol. 2020*;75(11 suppl 1):195; Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early

implementation of the ACC/AHA Guidelines) bleeding score. *Circulation.* 2009;119:1873–1882. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA.* 2016;315:1735–1749.

Patients with STEMI are at the highest risk for death and reinfarction, and initial treatment should proceed with immediate revascularization regardless of their risk stratification score. In the case of NSTE-ACS, a TIMI risk score of 5 to 7, 3 to 4, and 0 to 2 reflect a high, moderate, and low risk for death, MI, or need for urgent coronary artery revascularization, respectively (**Table 13-1**). A low-risk patient with negative cardiac biomarkers may undergo a stress test or be discharged from the ED with a diagnostic test scheduled within 72 hours. Moderate- and high-risk patients are often admitted to the hospital for pharmacologic treatment, further diagnostic tests, and angiography with possible intervention.

Complications

The primary complications of ACS can be divided into three major groups: pump failure, arrhythmias, and recurrent ischemia and reinfarction. Depression of cardiac function after AMI is related directly to the extent of LV damage. As a result of decreased cardiac output and decreased perfusion, a number of compensatory mechanisms become activated. The levels of circulating catecholamines increase in an attempt to increase contractility and restore normal perfusion. In addition, the renin-angiotensin-aldosterone system is enhanced, leading to an increase in systemic vascular resistance and sodium and water retention. These compensatory mechanisms can eventually worsen the imbalance between myocardial oxygen supply and consumption by increasing the myocardial oxygen demand.[18]

Signs and symptoms of HF are common in patients who have abnormal wall motion affecting 20% to 25% of the LV. If ≥40% of the LV is damaged, cardiogenic shock and death may occur. Ischemia and scar formation after an AMI may lead to a decrease in

ventricular compliance, resulting in abnormally high LV filling pressures during diastole. (See Chapter 14, Heart Failure, for further discussion on HF with reduced ejection fraction [EF] and preserved EF.)

Decreased contractility and a compensatory increase in LV end-diastolic volume and pressure lead to increased wall stress within the left ventricle. LV enlargement is an important determinant of mortality after AMI. During a period of days to months after an AMI, the infarcted area may expand as a result of dilatation and thinning of the LV wall. These changes are known as ventricular remodeling. In addition, hypertrophy of the noninfarcted myocardium occurs. Administration of oral angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or aldosterone antagonists may limit remodeling and will attenuate the progression of LV dilatation.[19,20]

During the peri-infarction period, the heart is irritable and subject to ventricular arrhythmias. The continuous monitoring of patients in a coronary care unit has reduced the in-hospital mortality rate related to ventricular arrhythmias. However, patients who have had an AMI have an increased risk of sudden cardiac death for 1 to 2 years after hospital discharge. The most important predictor of sudden cardiac death is an abnormal left ventricular ejection fraction (LVEF). Other factors associated with an increased risk of sudden cardiac death are complex ventricular ectopy, frequent (>10/hour) premature ventricular complexes, and the identification of late potentials on a signal-averaged ECG.[18]

OVERVIEW OF DRUG AND NONDRUG THERAPY

Overlap exists regarding the pharmacotherapy for both STEMI and NSTE-ACS. According to the ACC/AHA guidelines, early therapies should consist of oxygen (if oxygen saturation is <90%), sublingual

(SL) and/or intravenous (IV) nitroglycerin (NTG), IV morphine, ACE inhibitor or ARB, aldosterone antagonist, antiplatelet agents, stool softener, β-blocker, statin, and anticoagulant. Adjunctive therapies such as analgesics and vasodilators can also be considered in selected patients. **Table 13-2** summarizes the evidence-based pharmacotherapies for both STEMI and NSTE-ACS. **Figure 13-4** provides an initial treatment algorithm for patients with STEMI, and **Figure 13-5** for patients with NSTE-ACS. Administration of these pharmacotherapies serves as a performance measure for health systems to ensure effective, timely, safe, and efficient patient-centered care.[1,5]

Table 13-2
Evidence-Based Pharmacotherapies for Acute Coronary Syndromes

Drug	Indication	Dose and Duration	Therapeutic End Points	Precautions	Comments
ACE inhibitors[a]	STEMI and NSTE-ACS within the first 24 hours of presentation for those with EF ≤40% or s/s of HF STEMI and NSTE-ACS for late hospital care for patients with hypertension, EF ≤40%, DM, or CKD STEMI and NSTE-ACS for indefinite use for all patients with EF ≤40%	Usual captopril dose 12–50 mg tid, then start longer acting ACE inhibitor Duration indefinite	Titrate to usual doses and maintain systolic BP >90 mm Hg.	Avoid IV therapy within 48 hours of infarct. Avoid initiation with systolic BP <100 mm Hg, pregnancy, acute renal failure, angioedema, bilateral renal stenosis, serum potassium ≥5.5 mEq/L.	
Angiotensin receptor blockers[a]	STEMI and NSTE-ACS with ACE inhibitor intolerance	Usual doses of ARBs (see Chapter 14, Heart Failure) Duration indefinite	Same as for ACE inhibitors	Same as for ACE inhibitors	
Aldosterone antagonists[a]	STEMI and NSTE-ACS with EF ≤40% and either DM or HF symptoms already receiving therapeutic doses of an ACE inhibitor and β-blocker	Spironolactone 12.5–50 mg daily or eplerenone 25–50 mg daily Duration indefinite	Titrate to HF symptom control without evidence of hyperkalemia	Hyperkalemia, hypotension Avoid if potassium ≥5 mEq/L or SCr ≥2.5 mg/dL for males and 2.0 mg/dL for females or CrCl ≤30 mL/minute	Dose can be increased every 4–8 weeks.
Aspirin[a]	STEMI and NSTE-ACS for all patients	162–325 mg during AMI, then 81–325 mg daily indefinitely (81 mg daily is preferred)		Active bleeding, thrombocytopenia	Unless clear contraindication exists, aspirin should be given to all patients with AMI.
Amiodarone	Treatment of VT, VF	150 mg IV over 10 minutes, repeat for recurrence, follow with 1 mg/minute IV infusion for 6 hours, then 0.5 mg/minute (maximum: 2.2 g/24 hours).	Cessation of arrhythmia	Bradycardia, hypotension	
β-Blockers[a]	STEMI and NSTE-ACS in all patients without contraindications	Variable Titrate to HR and BP. It is reasonable to administer an IV β-blocker at the time of presentation to patients with STEMI who are hypertensive and who do not have any of the following: (a) signs of HF, (b) evidence of a low-output state, (c) increased risk for cardiogenic shock[b], or (d) other relative contraindications to β-blockade (PR interval >0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease). Duration indefinite	Titrate to resting HR ~60 beats/minute, maintain systolic BP >100 mm Hg.	Observe HR and BP closely when given IV. Contraindicated in patients with HR <50 beats/minute; PR ECG interval >0.24 seconds, second- or third-degree heart block, persistent hypotension, pulmonary edema, bronchospasm, risk of cardiogenic shock, severe reactive airway disease	Unless clear contraindication exists, β_1-selective agents such as metoprolol and atenolol should be given to all patients with AMI. In patients with systolic dysfunction, metoprolol, carvedilol, or bisoprolol can be considered.

Bivalirudin[a]	STEMI with primary PCI and NSTE-ACS with an early invasive strategy	*STEMI with primary PCI*: 0.75 mg/kg IV bolus immediately before PCI, followed by 1.75 mg/kg/hour infusion with or without UFH. *NSTE-ACS with an early invasive strategy*: 0.1 mg/kg IV bolus followed by 0.25 mg/kg/hour infusion. Continue until diagnostic angiography or PCI is performed.		Avoid in patients with active bleeding.	Reduce infusion to 1 mg/kg/hour with estimated CrCl <30 mL/minute.
Cangrelor[a]	STEMI and NSTE-ACS before PCI in patients not treated with a $P2Y_{12}$ inhibitor and are not being given a GP IIb/IIIa inhibitor	30 μg/kg IV bolus before PCI, followed immediately by a 4 μg/kg/minute IV infusion for at least 2 hours or duration of procedure, whichever is longer		Active bleeding	After discontinuation of infusion, an oral $P2Y_{12}$ inhibitor should be administered: ticagrelor 180 mg load during or upon immediate discontinuation of infusion; prasugrel 60 mg or clopidogrel 600 mg upon immediate discontinuation of infusion.
Calcium channel blockers	STEMI and NSTE-ACS for patients with ongoing ischemia who are receiving adequate doses of nitrates and β-blockers. Consider diltiazem or verapamil for patients with contraindication to β-blocker if EF is normal.	Usual doses of calcium channel blockers are used. Duration dictated by clinical scenario	Titrate to usual doses and maintain systolic BP >90 mm Hg.	Usual calcium channel blocker contraindications. Avoid nondihydropyridines in patients with pulmonary congestion or EF <40% or AV block.	In patients with normal EF, most calcium channel blockers will exert beneficial effects. Some data support use of verapamil or diltiazem for non–Q-wave AMI.
Clopidogrel[a]	STEMI and NSTE-ACS for patients allergic to aspirin	75 mg daily		Active bleeding, thrombotic thrombocytopenia purpura (rare)	
Clopidogrel + aspirin[a]	STEMI with fibrinolytic therapy, before PCI after fibrinolytic therapy, or before primary PCI. NSTE-ACS for early invasive or ischemia-guided strategies	*STEMI with fibrinolytic therapy*: 300 mg load, then continue 75 mg daily and continue for up to 1 year; aspirin 162–325 mg on first day, then 81–325 mg daily indefinitely (81 mg daily is preferred).		Active bleeding, thrombotic thrombocytopenia purpura (rare), avoid loading dose in patients ≥75 years of age, discontinue at least 5 days for CABG.	Whether administered before fibrinolytic or PCI, clopidogrel + aspirin reduced CV death, MI, or ischemia at 30 days. The 600 mg load should be considered if a GP IIb/IIIa is not used.
		lytic, then 300 mg load and for >24 hours from fibrinolytic, 600 mg load, then continue 75 mg daily if coronary stent deployed for at least 1 year; aspirin 162–325 mg on first day, then 81–325 mg daily indefinitely (81 mg is preferred) *STEMI before primary PCI*: 600 mg load, then continue 75 mg daily if coronary stent deployed for at least 1 year; aspirin 162–325 mg on first day, then 81–325 mg/day indefinitely (81 mg daily is preferred) *NSTE-ACS for early invasive or ischemia-guided strategy*: 300–600 mg load, then continue 75 mg daily for at least 1 year; aspirin 162–325 mg on first day, then 81–325 mg/day indefinitely (81 mg daily is preferred)			
Enoxaparin[a]	STEMI (as an alternative to UFH) for patients receiving fibrinolytic therapy or for those not undergoing PCI NSTE-ACS for early invasive or ischemia-guided strategies.	*STEMI with fibrinolytic therapy*: Age <75 years, administer 30 mg IV bolus followed by 1 mg/kg SQ every 12 hours (max dose of 100 mg for patients weighing ≥100 kg). Age ≥75, administer 0.75 mg/kg SQ every 12 hours (first two doses, administer max dose of 75 mg for patients weighing ≥75 kg). Continue up to 8 days or until revascularization. *NSTE-ACS for early invasive or ischemia-guided strategies*: 1 mg/kg SQ every 12 hours. A supplemental 0.3 mg/kg IV dose should be administered at the time of PCI if the last dose of SQ enoxaparin was given 8–12 hours before PCI. Continue for duration of hospitalization or until PCI.		Avoid in patients with active bleeding, history of HIT, planned CABG, SCr ≥2.5 mg/dL in males and ≥2.0 mg/dL in females, or CrCl <15 mL/minute.	For CrCl 15–29 mL/minute, reduce to 1 mg/kg every 24 hours.

Fibrinolytic therapy[a]	STEMI presenting within 12 hours of onset of symptoms, can be considered in patients presenting within 12–24 hours of onset of symptoms with continuing s/s of ischemia	*Alteplase*: 15 mg IV bolus, 50 mg for 30 minutes, then 35 mg for 60 minutes (for patients <65 kg, reduce dose) *Reteplase*: 10-unit IV bolus, second 10-unit bolus 30 minutes later *Tenecteplase*: 30–50 mg bolus over 5–10 seconds (<60 kg: 30 mg, 60–69 kg: 35 mg, 70–79 kg: 40 mg, 80–89 kg: 45 mg, 90 kg: 50 mg)	Improved TIMI grade flow	See Table 13-3.	
Drug	**Indication**	**Dose and Duration**	**Therapeutic End Points**	**Precautions**	**Comments**
Fondaparinux[a]	STEMI: alternative to UFH or LMWH in patients receiving fibrinolytic therapy or in those not undergoing PCI NSTE-ACS: alternative to UFH or LMWH for early invasive or ischemia-guided strategies Administer additional anticoagulant with factor IIa activity in patients undergoing PCI.	*STEMI*: 2.5 mg SQ daily starting on day 2 of hospitalization, continue for 8 days or until revascularization. *NSTE-ACS for early invasive or ischemia-guided strategies*: 2.5 mg SQ daily for the duration of the hospitalization or until PCI is performed.		Avoid with active bleeding or CrCl <30 mL/minute.	In STEMI, fondaparinux reduced mortality and reinfarction without increased bleeding or strokes compared with UFH, but only in patients not undergoing PCI. In NSTE-ACS, fondaparinux was at least as effective as enoxaparin but exhibited less bleeding. Can possibly be used in HIT.
GP IIb/IIIa inhibitors[a]	STEMI: in patients undergoing PCI NSTE-ACS: in patients treated with early invasive strategy and DAPT with intermediate-/high-risk features	*Dosing for STEMI PCI*: Eptifibatide:180 μg/kg IV bolus, then begin 2 μg/kg/minute infusion followed by second IV bolus of 180 μg/kg 10 minutes after first bolus, continue infusion for 12–18 hours after PCI at the discretion of the physician. Tirofiban: 25 μg/kg IV bolus followed by an infusion of 0.15 μg/kg/minute, continue up to 18 hours at the discretion of the physician Dose for NSTE-ACS with or without PCI		Avoid with active bleeding, thrombocytopenia, prior stroke. Eptifibatide: Reduce infusion by 50% in patients with CrCl <50 mL/minute; not studied in patients with SCr >4.0 mg/dL; avoid in hemodialysis. Tirofiban: Reduce infusion by 50% in patients with CrCl <30 mL/minute.	In NSTE-ACS, eptifibatide or tirofiban is FDA approved for PCI and ischemia-guided therapy. Abciximab is only for patients undergoing PCI.
		Eptifibatide: 180 μg/kg IV bolus, then begin 2 μg/kg/minute infusion, continue infusion for 12–18 hours. Repeat bolus dose after 10 minutes for PCI. Tirofiban: 25 μg/kg IV bolus within 5 minutes followed by an infusion of 0.15 μg/kg/minutes (or 0.075 μg/kg/minutes for patients with CrCl ≤60 mL/minute), for up to 18 hours.			
Heparin[a]	STEMI: for patients undergoing PCI or treated with fibrinolytic therapy NSTE-ACS: for early invasive or ischemia-guided strategies	*STEMI with fibrinolytic therapy or NSTE-ACS with early invasive or ischemia-guided strategies*: 60 units/kg IV bolus (max 4000 units) followed by 12 units/kg/hour (max 1000 units/hour) for 48 hours or until revascularization *STEMI with PCI*: 50–70 units/kg IV bolus if a GP IIb/IIIa inhibitor planned; or 70–100 units/kg IV bolus if no GP IIb/IIIa inhibitor. Continue for 48 hours or until end of PCI.	aPTT ratio 1.5–2.5× patient's control value, aPTT should be obtained 4–6 hours after initiation of infusion if not treated with fibrinolytic therapy or PCI and within 3 hours if treated with fibrinolytic therapy.	Avoid with active bleeding, thrombocytopenia, recent stroke.	Unless clear contraindication exists, UFH should be given to all patients with AMI who do not receive fibrinolytic therapy.
Morphine and other analgesics	STEMI and NSTE-ACS for patients whose symptoms not relieved by NTG or adequate anti-ischemic therapy	Morphine: 2–5 mg IV every 5–30 minutes PRN	Decreased chest pain and HR	Avoid morphine with bradycardia, right ventricular infarct, hypotension, confusion.	Has been associated with higher risk of death; discontinue nonselective NSAIDs and COX-2 selective agents.
Nitroglycerin[a]	STEMI and NSTE-ACS with persistent ischemia, hypertension, or pulmonary congestion	Variable; titrate to pain relief or systolic BP: 5–10 μg/minute titrated to 200 μg/minute. Usually maintain IV therapy for 24–48 hours after infarct.	Titrate to pain relief or systolic BP >90 mm Hg.	Avoid with systolic BP <90 mm Hg, right ventricular infarction, sildenafil or vardenafil within 24 hours or tadalafil within 48 hours.	Use acetaminophen or narcotics for headache. NTG should be tapered gradually in patients with ischemic heart disease. Topical patches or oral nitrates are useful for patients with refractory symptoms.

Prasugrel + Aspirin[a]	STEMI: before PCI after fibrinolytic therapy or before primary PCI NSTE-ACS: before PCI with coronary stenting	60-mg loading dose, then 10 mg daily (if ≥60 kg) or 5 mg (if <60 kg) if coronary stent deployed for at least 1 year; aspirin 162–325 mg on day 1, then 81–325 mg daily indefinitely (81 mg daily is preferred)		Avoid with active bleeding, prior stroke or TIA, age ≥75 years. Do not start if urgent CABG needed; discontinue 7 days before elective CABG or other surgery.	
Ticagrelor + Aspirin[a]	ACS: previous history of AMI STEMI: before primary PCI NSTE-ACS: for early invasive or ischemia-guided strategies	*ACS with previous history of MI:* Load with 180-mg oral loading dose following an ACS event, then continue treatment with 90 mg twice daily during the first year after an ACS event. After 1 year, administer 60 mg twice daily; aspirin 162–325 mg on day 1, then 81 mg daily indefinitely. *STEMI before primary PCI:* 180 mg load, then continue 90 mg bid if coronary stent deployed for at least 1 year; aspirin 162–325 mg on day 1, then 81 mg daily indefinitely. *NSTE-ACS with early invasive or ischemia-guided strategy*: 180 mg load, then continue 90 mg bid if coronary stent deployed or for both early invasive and ischemia-guided strategies for at least 1 year; aspirin 162–325 mg on day 1, then 81 mg daily indefinitely.	No firm end points	Avoid in patients with severe hepatic impairment or active bleeding. Maintenance doses of aspirin >100 mg daily can decrease ticagrelor's effectiveness. Discontinue at least 5 days before CABG.	Monitor closely for dyspnea. For at least the first 12 months following ACS, ticagrelor was found to be superior to clopidogrel. Maximum dose of simvastatin is 40 mg with ticagrelor.
Vorapaxar	ACS for secondary prevention of thrombotic cardiovascular events	1 tablet (2.08 mg) daily.		Contraindicated in history of stroke, TIA, ICH, or active bleeding	Use with aspirin and/or clopidogrel according to their indications or standard of care. No data with ticagrelor or prasugrel or with use as a single antiplatelet agent.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AMI, acute myocardial infarction; aPTT, activated partial thromboplastin time; ARBs, angiotensin receptor blockers; bid: twice daily; BP: blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CNS, central nervous system; COX-2, cyclooxygenase-2; CrCl, creatinine clearance; CV, cardiovascular; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; FDA, U.S. Food and Drug Administration; GP IIb/IIIa, glycoprotein IIb/IIIa inhibitor; HF, heart failure; HIT, heparin-induced thrombocytopenia; HR, heart rate; INR, international normalized ratio; ICH: intracranial hemorrhage; IV, intravenously; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; NTG, nitroglycerin; PCI, percutaneous coronary intervention; PRN, as needed; SCr, serum creatinine; SQ, subcutaneously; s/s, signs and symptoms; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; tid, three times a day; TIMI, Thrombolysis in Myocardial Infarction; UHF, unfractionated heparin; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]Indicates specific drug therapies that are known to reduce morbidity or mortality.

[b]Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock) are age >70 years, systolic BP <120 mm Hg, sinus tachycardia >110 beats/minute, or heart rate <60 beats/minute.

Sources: Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task

Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64(24):e139–e228; O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127(4):e362–e425.

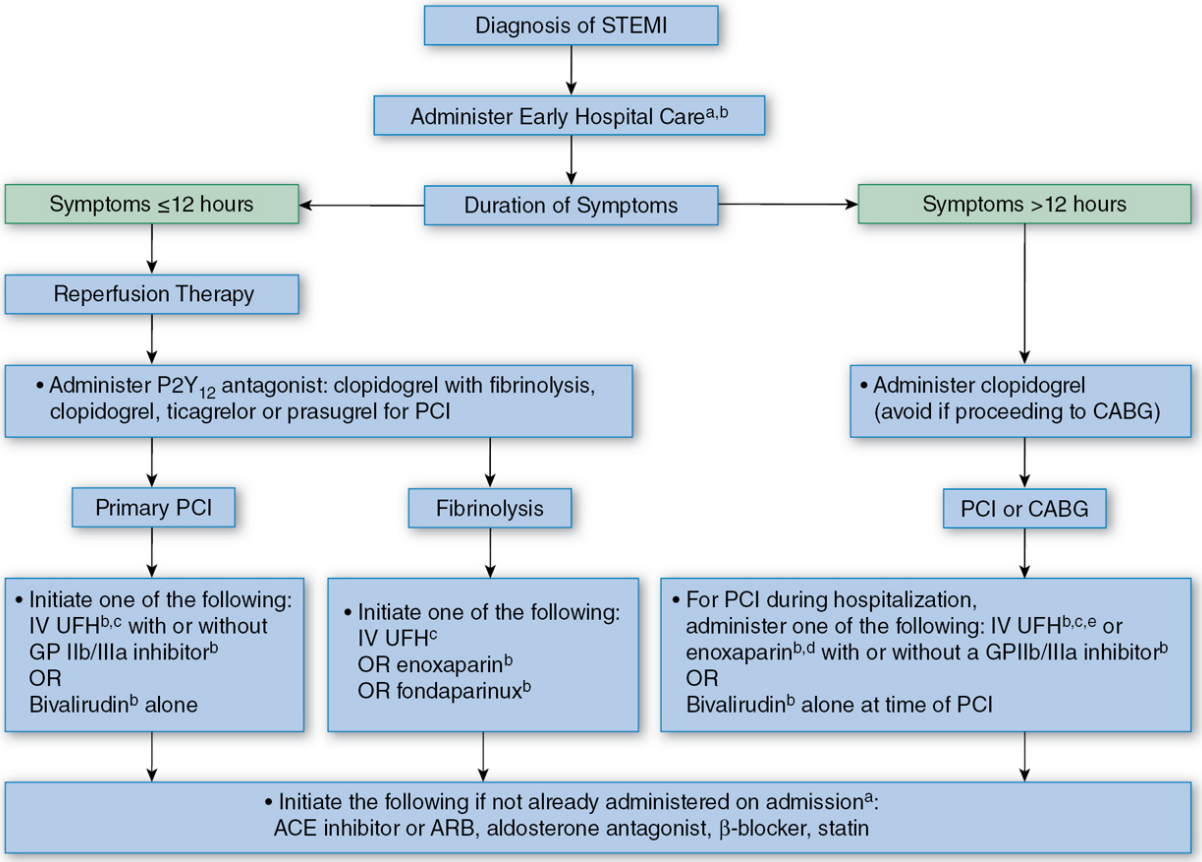


Figure 13-4 Initial treatment algorithm for STEMI.[a] Early hospital care consist of oxygen for oxygen saturation <90%, SL nitroglycerin, IV nitroglycerin, IV morphine, β-blocker, ACE inhibitor or ARB, aldosterone antagonist, stool softener, and statin.[b] Refer to Table 13-2 for indications, dosing, and contraindications.[c] For at least 48 hours.[d] For the duration of the hospitalization, up to 8 days. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; GP IIb/IIIa, glycoprotein IIB/IIIA; PCI, percutaneous coronary intervention; SL, sublingual; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin. (From Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of

patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published corrections appear in *J Am Coll Cardiol.* 2010;55:612 (dosage error in article text); *J Am Coll Cardiol.* 2009;54:2464]. *J Am Coll Cardiol*. 2009;54:2205–2241; Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine [published correction appears in *J Am Coll Cardiol.* 2008;51:974]. *J Am Coll Cardiol*. 2007;50:e1–e157; O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362–e425.)

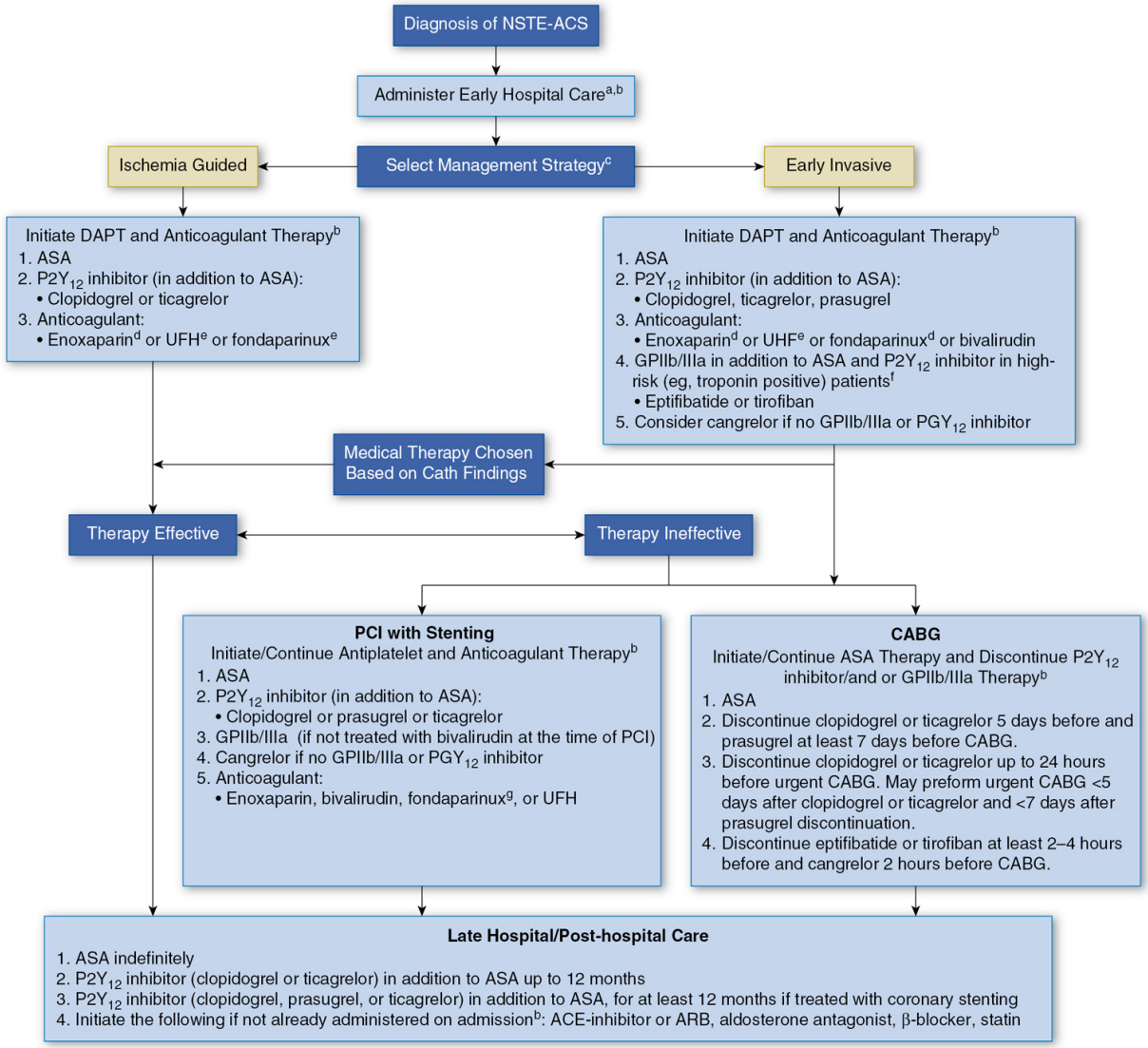


Figure 13-5 Initial treatment algorithm for NSTE-ACS.[a] Early hospital care consists of oxygen for oxygen saturation <90%, SL nitroglycerin, IV nitroglycerin, IV morphine, β-blocker, ACE inhibitor or ARB, aldosterone antagonist, stool softener, and statin.[b] Refer to Table 13-2 for indications, dosing, and contraindications.[c] An early invasive strategy would be considered if one or more of the following occurs: recurrent angina or ischemia at rest, presence of elevated cardiac biomarkers, new or presumably new ST-segment depression, signs or symptoms of HF or new worsening mitral regurgitation, hemodynamic instability, sustained ventricular tachycardia, PCI within 6 months, prior CABG, considered high risk per TIMI or GRACE risk score, LVEF <40%. An ischemia-guided

conservative strategy would be considered if the patient is classified as low-moderate risk per the TIMI or GRACE risk score or if the patient or clinician prefers this approach in the absence of high-risk features.[d] For the duration of the hospitalization, up to 8 days.[e] For at least 48 hours.[f] Factors favoring administration of a GP IIb/IIIa in addition to an ASA and a $P2Y_{12}$ inhibitor are delay to angiography, high-risk features, and early recurrent ischemia.[g] In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI owing to risk of catheter thrombosis. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, aspirin; CABG, coronary artery bypass graft; Cath, catheterization; DAPT, dual antiplatelet therapy; GP IIb/IIIa, glycoprotein IIb/IIIa; HF, heart failure; GRACE, Global Registry of Acute Coronary Events; IV, intravenous; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SL, sublingual; TIMI, Thrombolysis in Myocardial Infarction; UFH, unfractionated heparin. (Adapted from Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;64(24):e139–e228. © 2014 American Heart Association, Inc, and the American College of Cardiology Foundation. With permission.)

Fibrinolytic Drugs

Because the majority of STEMI cases result from the sudden occlusion of a coronary artery, the priority is to open the occluded artery as quickly as possible. This is accomplished by administering one of three strategies: administration of a fibrinolytic agent that enhances the body's own fibrinolytic system, mechanically reducing the obstruction with primary PCI or fibrinolysis, followed by a routine early PCI known as a pharmacoinvasive strategy or facilitated PCI.

This last strategy potentially leverages the strengths of both approaches by combining the speed and ease of fibrinolytic therapy administration with the reliability and durability of PCI, but has been studied to a more limited extent. The term *facilitated PCI* has been used when the time interval between fibrinolysis and PCI is shorter (eg, <2 hours), whereas the term *pharmacoinvasive approach* implies an intentionally longer fibrinolysis to PCI interval (eg, 2–24 hours).[21]

Large clinical trials have proved that administration of a fibrinolytic agent reduces mortality. Early mortality from STEMI was reduced by approximately one-third (from 10%–15% to 6%–10%) with fibrinolytic therapy.[5] Compared to fibrinolytic therapy, a contemporary analysis of 31 trials suggested that primary PCI reduced mortality by 27% and 21% with a pharmacoinvasive strategy.[21]

The fibrinolytic drugs currently used for patients with STEMI in the United States are fibrin-specific agents including alteplase (tissue plasminogen activator [t-PA]), reteplase (recombinant plasminogen activator [r-PA]), and tenecteplase (TNK). Alteplase, is a naturally occurring enzyme produced by recombinant DNA technology. It cleaves the same plasminogen peptide bond that urokinase cleaves. However, t-PA has a binding site for fibrin, which allows it to bind to and preferentially lyse thrombin-bound instead of circulating plasminogen. Reteplase is a genetically modified plasminogen activator that is similar to t-PA. Reteplase has a longer half-life, allowing it to be administered as two bolus injections 30 minutes apart, rather than as a bolus plus infusion. TNK is a genetically modified form of t-PA. Compared with t-PA, TNK has a longer plasma half-life, better fibrin specificity, and higher resistance to inhibition by a plasminogen activator inhibitor.[22,23] The pharmacologic properties and dosing regimens are compared in Table 13-2.

Unfortunately, an ideal fibrinolytic agent does not exist. Three problems common to all fibrinolytic drugs are the inability to open 100% of coronary artery occlusions, inconsistent ability to maintain good blood flow in the infarcted artery after it is opened, and bleeding complications. When assessing coronary artery flow after reperfusion therapy, the TIMI flow grade is used. Flow in coronary

arteries is classified as grade 0 (no flow), grade 1 (penetration without perfusion), grade 2 (partial perfusion), or grade 3 (complete perfusion).[24] When assessing an episode of bleeding, the TIMI bleeding criteria are used. TIMI major bleeding consists of overt clinical bleeding or documented intracranial or retroperitoneal hemorrhage that is associated with a drop in hemoglobin of at least 5 g/dL or hematocrit of at least 15% (absolute). TIMI minor bleeding is defined as overt clinical bleeding associated with a fall in hemoglobin of 3 to 5 g/dL or in hematocrit of 9% to 15% (absolute).[25]

To minimize the risk of bleeding complications, contraindications to the use of fibrinolytic drugs must be evaluated before administration (**Table 13-3**). There are relatively few absolute contraindications to fibrinolytic therapy, but each patient should be assessed carefully to ascertain whether the potential benefit outweighs the potential risk. Because of the serious nature of intracerebral hemorrhage, patients should be selected carefully before receiving these agents. Generally, the diagnosis of STEMI must be ensured, with a history consistent with ischemia, and presence of ST-segment elevation in two contiguous leads, or a new left bundle branch block on the ECG.[5]

Table 13-3
Risk Factors Associated With Bleeding Complications Secondary to Fibrinolytic Use[5]

Absolute Contraindications	Any prior intracranial hemorrhage
	Known structural cerebral vascular lesion (eg, arteriovenous malformation)
	Known malignant intracranial neoplasm (primary or metastatic)
	Active bleeding or bleeding diathesis (excluding menses)
	Suspected aortic dissection
	Significant closed-head or facial trauma within 3 months
	Intracranial or intraspinal surgery within 2 months
	Ischemic stroke within 3 months, except acute ischemic

	stroke within 4.5 hours
	Severe uncontrolled hypertension (unresponsive to emergency therapy)
Relative Contraindications	Uncontrolled hypertension on presentation (SBP >180 mm Hg, DBP >110 mm Hg)
	Chronic, severe, poorly controlled hypertension
	Prior ischemic stroke >3 months, dementia, or known intracranial pathology
	Puncture of a noncompressible vessel
	Major surgery (<3 weeks)
	Recent internal bleeding within 2–4 weeks
	Active peptic ulcer
	Current use of anticoagulants (the higher the INR, the greater the risk for bleeding)
	Pregnancy

DBP, diastolic blood pressure; INR, international normalized ratio; SBP, systolic blood pressure.

Source: Adapted from O'Gara PT, Kushner FG, Aschiem DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2013;61(4):e78–e140. © 2013 American College of Cardiology Foundation and the American Heart Association, Inc. With permission.

Fibrinolytic therapy is indicated in patients with STEMI who present to the hospital within 12 hours of symptom onset and are unable to undergo primary PCI within 120 minutes of first medical contact.[5] The benefit derived from fibrinolytic therapy is directly related to the time from the onset of chest pain to the time of administration. Although the guidelines recommend initiation within 12 hours of the onset of chest pain, data from clinical trials suggest that mortality reduction is greater when fibrinolytic therapy is initiated within 0 to 2 hours of symptom onset compared with treatment initiated >2 hours after symptoms have begun. The guidelines recommend a "door-to-needle time" of 30 minutes, meaning the diagnosis of STEMI and initiation of fibrinolytic therapy should ideally

take place within 30 minutes of the time the patient arrives at the hospital door. Once stabilized, the patient should be transferred to a facility capable of PCI in case reperfusion fails or reocclusion occurs.[5]

In patients with NSTE-ACS, fibrinolytic agents are not recommended. Thrombi in this population are primarily platelet-rich rather than fibrin-rich, and less responsive to fibrinolytic therapy.[26] In addition, data from the TIMI IIIB trials suggest that compared with placebo, alteplase was not associated with any improvement in death, MI, or failure of initial therapy but was associated with an increased incidence in fatal and nonfatal MI.[27]

Antiplatelet and Anticoagulant Drugs

When thrombolysis occurs, whether because of the administration of a fibrinolytic agent or through activation of the body's own fibrinolytic system, the fibrin clot begins to disintegrate. As the clot dissolves, there is a paradoxical increase in local thrombin generation and enhanced platelet aggregability, which may lead to rethrombosis. Antiplatelet agents (aspirin, $P2Y_{12}$ inhibitor: clopidogrel, prasugrel, ticagrelor, or cangrelor and the glycoprotein [GP] IIb/IIIa inhibitors) as well as parenteral anticoagulants (unfractionated heparin [UFH], low-molecular- weight heparins [LMWH] such as enoxaparin, fondaparinux, and direct thrombin inhibitors [DTIs] such as bivalirudin) have been used to minimize rethrombosis. UFH has several limitations, including a highly variable anticoagulant effect necessitating frequent monitoring and development of heparin-induced thrombocytopenia (<0.2%). LMWH may offer advantages compared with heparin owing to their ease of administration, improved bioavailability, and need for less monitoring. Unlike UFH, the DTIs offer better protection against thrombin reactivation after therapy discontinuation.

The GP IIb/IIIa receptor inhibitors, which are tirofiban, eptifibatide, and abciximab (Janssen Biologics B.V., The Netherlands), have traditionally been used; however, owing to drug shortages, Janssen

has stopped the manufacture of abciximab. GP IIb/IIIa receptors are abundant on the platelet surface. Platelets become activated when patients have an acute ischemic event or undergo PCI. With platelet activation, the GP IIb/IIIa receptor undergoes a conformational change that increases its affinity for binding fibrinogen. The binding of fibrinogen to receptors on platelets results in platelet aggregation, leading to thrombus formation. The GP IIb/IIIa receptor inhibitors prevent platelet aggregation by preventing fibrinogen from binding to GP IIb/IIIa receptor sites on activated platelets.[5]

Acute thrombocytopenia is a rare but recognized side effect of all three agents but is historically seen more often with abciximab.[28] The GP IIb/IIIa inhibitors are used in conjunction with other antiplatelet drugs and anticoagulants in patients with STEMI and those with NSTE-ACS undergoing PCI. Although effective when used in conjunction with fibrinolytic agents for patients with STEMI, the benefit is offset by high rates of bleeding. Therefore, routine use of GP IIb/IIIa inhibitors is not recommended with fibrinolytics.[5]

The $P2Y_{12}$ inhibitors, ticagrelor, prasugrel, and clopidogrel, have evolved to become an integral part in the management of ACS. By blocking the $P2Y_{12}$ adenosine diphosphate receptors, these agents decrease platelet activation and aggregation, increase bleeding time, and reduce blood viscosity.[1–5] Differences in antiplatelet potency, pharmacokinetics, pharmacodynamics, pharmacogenomics, and drug–drug interactions exist between the three agents (**Table 13-4**). Cangrelor is an IV agent approved to reduce the risk of thrombotic events in patients undergoing PCI. It is for patients who are not being treated with another $P2Y_{12}$ inhibitor or a GP IIb/IIIa inhibitor.[29] Compared with the oral agents, cangrelor has a very rapid onset (2 minutes) and offset of action (1 hour).[29] In the *Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition* (CHAMPION)-PHOENIX trial, the primary composite end point of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours occurred in significantly fewer patients treated with IV cangrelor compared to oral clopidogrel (4.7% vs 5.9%, $P = .005$). Although the benefit persisted at 30 days, it came at

the expense of an increase in bleeding, with rates of about 1 in 170 with cangrelor versus 1 in 275 with clopidogrel.[30] Controversy surrounds the use of pharmacogenomic and platelet function testing when determining whether a patient may be a "responder" or "nonresponder" to clopidogrel therapy.[31] At this time, the ACC/AHA guidelines do not recommend routine testing for genetic variants. See Chapter 12, Chronic Stable Angina, for more details about these controversies.

Table 13-4
Comparison of $P2Y_{12}$ Inhibitors

Parameter	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Class	Thienopyridine (second generation)	Thienopyridine (third generation)	Cyclopentyltriazolopyrimidine	Stabilized ATP analog
Administration	Oral	Oral	Oral	Intravenous
Dose	300–600 mg LD 75 daily	60 mg LD 10 mg daily	180 mg LD 90 mg bid (60 mg bid for years 1–3)	30 μg/kg bolus 4 μg/kg/minute infusion
Age	—	If age >75 years, not recommended unless history of DM or MI	—	—
Weight	—	If <60 kg, consider 5 mg daily	—	—
FDA Indications	ACS (NSTEMI, STEMI) Recent MI, stroke, PAD	*July 2009* NSTE-ACS + PCI STEMI + PCI	*July 2011* ACS (NSTE-ACS, STEMI)	*June 2015* PCI
Trials in ACS	CURE, PCI-CURE, CREDO, ACUITY, CLARITY, COMMIT	TRITON-TIMI 38 TRILOGY-ACS	PLATO PEGASUS TIMI-54	CHAMPION-PCI CHAMPION-PLATFORM CHAMPION-PHOENIX
Receptor Binding	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, limited by metabolism	Prodrug, *not* limited by metabolism	Active drug	Active drug
Interpatient variability	High	Low	Low	Low
Bioavailability	~50%	80%–100%	36%	NA
Onset of action	2–6 hours	30 minutes	0.5–2 hours	2 minutes
Peak platelet inhibition	300 mg LD (6 hours) 600 mg LD (2 hours)	60 mg LD (1–1.5 hours)	180 mg LD (<1 hour)	30 μg/kg bolus (2 minutes)
Duration	3–10 days	5–10 days	1–3 days	1–2 hours
Half-life	6 hours	7 hours	7 hours	3–6 minutes
Metabolism	Hepatic via CYP450 (1A2, 3A4)	Minimal	Hepatic via CYP450 (main: 3A4, 2B6) (lesser: 2C9, 2C19)	Dephosphorylation by nucleotidases
Elimination	Urine 50% Feces 46%	Urine 68% Feces 27%	Urine 26% Feces 58%	Urine 58% Feces 35%
CYP2C19 Allele	Significant	Nonsignificant	Nonsignificant	Nonsignificant

Non-CABG major bleeding	Increased	>Clopidogrel	>Clopidogrel (overall) Similar in PCI	Similar (depending on definition)
CABG major bleeding	Increased	>Clopidogrel	= Clopidogrel Mortality benefit	Similar to placebo
Safe in stroke	Yes	Contraindicated	Similar stroke rate as clopidogrel Increased intracranial hemorrhage	Similar stroke rate as clopidogrel
Dyspnea/ bradyarrhythmia	No	No	Yes	Yes
Platelet inhibition	~50%	~70%	>80%	100%
Drug–Drug Interactions	PPIs inhibit CYP 2C19 (concomitant use with omeprazole is discouraged per package labeling); enhanced bleeding with NSAIDs, oral anticoagulants, etc.	Minimal; enhanced bleeding with NSAIDs, oral anticoagulants, etc	Strong CYP 3A4 inhibitors and inducers; max of simvastatin 40 mg; may increase digoxin concentrations; limit aspirin <100 mg/day; enhanced bleeding with NSAIDs, oral anticoagulants, etc	Enhanced bleeding with NSAIDs, oral anticoagulants, etc
Drug–Disease Interactions	—	—	Careful with asthma, bradycardia, and, possibly, gout	Careful with asthma
Boxed warning	Genetic polymorphisms	Age-related bleeding Prior TIA/stroke	Prior intracranial hemorrhage Aspirin dosing >100 mg	NA
CABG hold time	5 days	7 days	5 days	1 hour

ACS, acute coronary syndrome; ATP, adenosine triphosphate; bid, twice daily; CABG, coronary artery bypass graft; CYP, cytochrome P450; LD, loading dose; MI, myocardial infarction; NA, not applicable; NSAIDs: nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSTEMI, non-ST segment elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPIs, proton-pump inhibitors; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

Sources: Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64(24):e139–e228; O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127(4):e362–e425; Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2016;37(3):267–315**.**

Vorapaxar is an oral antiplatelet that selectively inhibits the cellular actions of thrombin through antagonism of platelet protease–activated receptor-1 and is indicated for secondary prevention of cardiovascular events in patients who have a history of MI or peripheral vascular disease. In the *T*hrombin-*R*eceptor *A*ntagonist in secondary *P*revention of atherothrombotic ischemic events–*T*hrombolysis *i*n *M*yocardial *I*nfarction (TRA2P–TIMI50) trial, patients with a history of MI, ischemic stroke, or peripheral arterial disease who received vorapaxar 2.5 daily had 13% reduction in the

combined end point of death from cardiovascular causes, MI, or stroke ($P < .001$) and a 12% reduction in the combined end point of cardiovascular death, MI, stroke, or recurrent ischemia leading to revascularization ($P = .001$) compared to placebo.[32] However, patients receiving vorapaxar had an increase in moderate and severe bleeding including intracranial hemorrhage. Owing to these findings and its high cost, the use of this agent has been limited in clinical practice.

a-Blockers

β-Blockers should be administered to patients with ACS unless a contraindication is present. In patients with ACS receiving either fibrinolytic therapy or PCI, β-blockers significantly decreased the rates of cardiovascular mortality, recurrent nonfatal MI, and all-cause mortality.[1–5] The 2014 ACC/AHA guidelines recommend that oral β-blocker therapy be initiated within 24 hours of the onset of symptoms for all patients without signs of HF, evidence of low-output state, increased risk of cardiogenic shock, or other contraindications. Both β-selective and nonselective agents have been evaluated; however, β-blockers with intrinsic sympathomimetic activity should be avoided because they lack efficacy data. For patients with tachycardia or hypertension without signs of HF, IV β-blockers followed by oral administration can be considered. Unless there are contraindications to their use, β-blocking agents should be prescribed for all patients after an AMI for at least 3 years and indefinitely for those with HF.[5,33]

Lipid-Lowering Agents

β-Hydroxy-β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) reduce long-term morbidity and mortality in patients with cardiovascular disease. Beyond their lipid-lowering properties, statins are believed to exhibit pleiotropic effects, which include plaque stabilization, anti-inflammation, antithrombogenicity, enhancement of arterial compliance, and modulation of endothelial

function.[34] Data regarding early intensive statin therapy in patients with STEMI or NSTE-ACS exist with atorvastatin, simvastatin, pravastatin, rosuvastatin, and fluvastatin.[1,5,35] Recent ACC/AHA cholesterol guidelines recommend that patients receive a high-intensity statin such as atorvastatin 40 to 80 mg or rosuvastatin ≥20 mg daily to achieve a ≥50% reduction in low-density lipoprotein (LDL) levels. However, if LDL levels remain ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin therapy, adding ezetimibe followed by a proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor may be reasonable taking into account the cost benefit. The ODYSSEY OUTCOMES trial (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) and the FOURIER trial (*F*urther cardiovascular *OU*tcomes *R*esearch with PCSK9 *I*nhibition in subjects with *E*levated *R*isk), found that the addition of alirocumab or evolocumab, respectively, in patients on maximal statin ± ezetimibe with ACS, observed a 15% relative risk reduction in composite atherosclerotic cardiovascular disease (ASCVD) events. Moderate-intensity statins could be considered in patients age older than 75 years or those unable to tolerate high-intensity statins[36] (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease).

Vasodilators

Other strategies for minimizing myocardial damage include the use of vasodilators in the peri-infarction period. Progressive LV dilatation ("remodeling") occurs in some patients after an AMI and has become an important marker for prognosis. Vasodilators reduce oxygen demand and myocardial wall stress by reducing afterload or preload and can attenuate the remodeling process. Some vasodilators may increase the blood supply to the myocardium by enhancing coronary vasodilatation.[1,5]

ACE inhibitors have been assessed in a large number of clinical trials, and all trials using oral agents have demonstrated a reduction in mortality.[1,5] IV ACE inhibitors should be avoided because they

cause excessive hypotension and do not improve survival. The benefit of ACE inhibitors is greatest in patients with anterior infarction, signs of HF, or a history of previous infarction. Ideally, oral ACE inhibitors should be started within 24 hours of diagnosis, after BP and renal function have stabilized. Initial doses should be low and then titrated as quickly as possible.[1,5] The ACC/AHA guidelines recommend an ARB in patients with ACS who cannot tolerate ACE inhibitors. The combination of an ACE inhibitor and ARB should be avoided because of an increase in adverse events such as hyperkalemia.

Aldosterone antagonists such as spironolactone and eplerenone have been associated with improved LV structural remodeling and performance by increasing LVEF and decreasing LV end-diastolic and end-systolic volumes. In the *E*plerenone *P*ost Acute Myocardial Infarction *H*eart Failure *E*fficacy and *SU*rvival *S*tudy (EPHESUS), patients with AMI and LV dysfunction (LVEF <40%) with or without HF were randomized 3 to 14 days after AMI to receive eplerenone. Eplerenone was found to decrease long-term mortality as an adjunct to ACE inhibitors and β-blockers.[37] Aldosterone blockade is recommended in patients following an MI with an LVEF <40% with either diabetes or symptoms of HF, assuming they have no contraindications.[1]

Nitrates dilate venous capacitance vessels and peripheral arterioles. Their predominant effect is a decrease in preload, with a lesser effect on afterload. Consequently, nitrates lead to a decrease in both myocardial wall stress and oxygen demand. IV NTG should be used in patients who have refractory ischemic discomfort (chest pain), acute HF, and/or hypertension. Hemodynamic targets are a systolic BP 100 to 130 mm Hg with a heart rate <100 beats/minute.

Other vasodilators that have been investigated in the treatment of ACS are the calcium channel blockers. There are several proposed mechanisms whereby a calcium channel blocker might be beneficial. As a group, they dilate coronary and peripheral vessels. They also alleviate some of the coronary vasospasms present at the time of coronary thrombosis. In addition, they are effective anti-ischemic

agents through their action in improving coronary blood supply and reducing myocardial oxygen demand.[1,5]

The ACC/AHA guidelines recommend calcium channel blockers for patients with persistent or recurrent symptoms after treatment with full-dose nitrates and β-blockers, for patients with contraindications to β-blockade, and for patients with Prinzmetal or variant angina. For such patients, calcium channel blockers that slow the heart rate (eg, diltiazem or verapamil) are recommended. These nondihydropyridines should not be administered to patients with LV dysfunction or pulmonary edema. The Danish Verapamil Infarction Trial (DAVIT) evaluated the efficacy of verapamil for patients with ACS.[38] There was a trend toward lower MI and mortality rates when verapamil was given to patients with suspected ACS. Similar reductions in MI and refractory angina rates have been demonstrated with diltiazem.[39] The dihydropyridine calcium antagonists amlodipine and felodipine have not been evaluated specifically for administration to patients with ACS, but trials involving normotensive patients with coronary artery disease (CAD) or patients with hypertension and cardiovascular risk factors have demonstrated that these agents provide significant benefits in reducing cardiovascular events.[40,41]

Analgesics

It is important to abolish the patient's pain as quickly as possible because pain and anxiety associated with an AMI will contribute to increased myocardial oxygen demand. If the pain is not relieved by medications (eg, nitrates, β-blockers), then additional analgesia may be necessary. Morphine sulfate (2- to 4-mg IV with increments of 2- to 8-mg IV repeated at 5- to 15-minute intervals) is the analgesic of choice for management of pain associated with STEMI. In addition to diminishing pain and anxiety, morphine also has beneficial hemodynamic effects. By reducing pain and anxiety, the release of circulating catecholamines is diminished, possibly reducing the associated arrhythmias. Morphine also causes peripheral venous

and arterial vasodilation, which reduces preload and afterload and, consequently, myocardial oxygen demand. However, retrospective studies have suggested the potential for increased mortality in patients with NSTE-ACS receiving morphine; thus, morphine carries a Class IIb recommendation in the 2014 ACC/AHA NSTE-ACS guidelines.[42] Clinicians should be aware of potential unwanted side effects of morphine such as hypotension, nausea, and respiratory depression.

The nonselective and cyclooxygenase (COX)-2–selective nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of mortality, reinfarction, hypertension, HF, and myocardial rupture. These agents should be discontinued at the time a patient presents with ACS.[1,5]

Stool Softeners

It is common to administer agents such as docusate to prevent constipation in patients with AMI because straining causes undesirable stress on the cardiovascular system.[1,5]

Oxygen

Many patients are modestly hypoxemic during the initial hours of an AMI. Supplemental oxygen should be administered to patients with ACS with an arterial saturation <90%, respiratory distress, or other high-risk features for hypoxemia. Patients with severe hypoxemia or pulmonary edema may require intubation and mechanical ventilation.[1,5]

Antiarrhythmic Agents

Ventricular arrhythmias, including ventricular fibrillation, are common complications associated with myocardial ischemia and AMI as well as a major cause of death. More than half of the episodes of ventricular fibrillation that occur with an AMI are within 1 hour of the

onset of symptoms. If an antiarrhythmic agent is necessary, amiodarone is preferred over lidocaine (see Chapter 15, Cardiac Arrhythmias). The routine use of prophylactic lidocaine or other antiarrhythmic agents to prevent ventricular tachycardia and ventricular fibrillation is not recommended. Although lidocaine may reduce the number of episodes of ventricular fibrillation, it may contribute to an increased number of episodes of asystole.[5]

Suppression of ventricular ectopy after an AMI with the chronic use of oral antiarrhythmic agents is not recommended. Results of the Cardiac Arrhythmia Suppression Trial (CAST) showed an increase in mortality in asymptomatic patients with ventricular ectopy after an AMI who were treated with flecainide, encainide, or moricizine (see Chapter 15, Cardiac Arrhythmias).[43,44]

Nondrug Therapy

For STEMI, primary PCI is the preferred method for reperfusion as long as it can be performed in a timely manner. Specific guidelines have been published by the ACC/AHA addressing PCI and stent use in AMI.[45]

For patients presenting to a PCI-capable hospital, PCI should be performed within 90 minutes of initial medical contact (also referred to as “door-to-balloon time”). If a patient is at a non-PCI facility, immediate transfer for primary PCI is preferred only if PCI can be performed within 120 minutes of first medical contact.[5] This threshold is based on a multivariable analysis of patients undergoing PCI in which an increased door-to-balloon time exceeding 120 minutes was associated with a higher mortality rate.[46] Fibrinolytic therapy should be given to patients when the 120-minute time goal cannot be met, unless a contraindication is present.[5]

The disadvantages of PCI include the longer amount of time needed to mobilize the personnel needed to prepare the catheterization laboratory and its initial higher cost. A potential advantage of PCI is the greater ability to achieve TIMI grade 3 flow in the affected vessel compared to fibrinolytic therapy (90% vs 50%–

60%, respectively).[5] PCI is associated with fewer MACE, irrespective of patient presentation time. In addition, rates of major bleeding and intracranial hemorrhage are lower with PCI compared to fibrinolytic therapy. Unfortunately, many hospitals do not have the facilities or skilled personnel to complete this procedure in the necessary time frame.[5]

For NSTE-ACS, coronary angiography aids in defining the extent and location of the coronary lesion and in directing the definitive care strategy (eg, PCI with stent placement, CABG, or medical management). However, because angiography is an invasive procedure, there is a small risk of serious complications. Therefore, coronary angiography should be used only in patients for whom the procedure's benefits outweigh its risks. With this principle in mind, two pathways of treatment for patients with NSTE-ACS have emerged: the early invasive strategy and the ischemia-guided strategy (**Fig. 13-5**). In the early invasive strategy, all patients without contraindications undergo coronary angiography with the intent to perform revascularization within 24 hours of hospital admission. The ischemia-guided strategy consists of aggressive medical therapy for all patients and coronary angiography only for those with certain risk factors or those who fail medical therapy.

CLINICAL PRESENTATION OF ACUTE CORONARY SYNDROME

CASE 13-1

QUESTION 1: P.H., a 68-year-old, 176.37-pound (80-kg) male, is being admitted to the ED after experiencing an episode of sustained chest pain while mowing his yard. After waiting 6 hours, he called 911 and was transported to the ED to a facility without the ability to conduct PCI. Physical examination reveals an anxious and diaphoretic male. Heart rate and rhythm are regular, and no S_3 or S_4 sounds are present. Vital signs include BP 180/110 mm Hg, heart rate 105 beats/minute, and respiratory rate 32 breaths/minute. P.H.'s chest pain radiates to his left arm and jaw, and he describes the pain as "crushing" and "like an

elephant sitting on my chest." He rates it as a "10/10" in intensity. Thus far, his pain has not responded to five SL NTG tablets at home and three more in the ambulance. His ECG reveals a 3-mm ST-segment elevation and Q waves in leads I and V_2 to V_4. Based on his history and physical examination, P.H. is diagnosed with an anterior infarction. Laboratory values include the following:

Sodium (Na^+), 141 mEq/L
Potassium (K^+), 3.9 mEq/L
Chloride (Cl^-), 100 mEq/L
Carbon dioxide (CO_2), 20 mEq/L
Blood urea nitrogen (BUN), 19 mg/dL
Serum creatinine (SCr), 1.2 mg/dL
Glucose, 149 mg/dL
Magnesium (Mg), 2 mEq/L
Troponin I-Ultra, 60 ng/mL (normal, <0.02 ng/mL)
Total cholesterol, 259 mg/dL
Triglycerides, 300 mg/dL

P.H. has a prior history of CAD. A previous cardiac catheterization 2 years ago revealed lesions in his middle left anterior descending coronary artery (75% stenosis) and proximal left circumflex artery (30% stenosis). His echocardiogram at the time showed an EF of 58%. These lesions were deemed suitable for medical management. He also has a history of recurrent bouts of bronchitis associated with bronchospasm for 10 years, diabetes mellitus treated with insulin for 18 years with a hemoglobin A_{1c} of 6.8% obtained 6 months before admission, and hypertension with BP usually 140/85 mm Hg. His father died of an MI at age 53. His mother and siblings are all alive and well. P.H. has smoked one pack of cigarettes a day for 30 years, and he drinks approximately one six-pack of beer a week. He has no history of IV drug use. On admission, P.H.'s medications include insulin glargine 40 units daily; albuterol inhaler as needed (PRN) for shortness of breath; hydrochlorothiazide 25 mg daily; NTG patch 0.2 mg/hour; and NTG SL 0.4 mg PRN for chest pain.

What signs and symptoms that are consistent with the diagnosis of AMI does P.H. have?

P.H. described his pain as a pressure sensation, which is common with ischemic heart disease. The chest discomfort associated with ACS often is described as pressure or as a tight band around the chest rather than pain. Although P.H. was involved in physical exertion when his chest discomfort began, this is not always the case. It can begin at rest and, frequently, in the early morning hours. At least 20% of patients with AMI have no pain or discomfort; these

episodes are described as “silent” MIs.[5] Presentations range from no symptoms to shortness of breath, hypotension, HF, syncope, or ventricular arrhythmias. Silent or atypical infarctions occur more commonly in people with diabetes and in the elderly. P.H. is diaphoretic, a common finding, but other common symptoms such as nausea and anxiety are not present. He also describes his pain as “10/10” in intensity, or perhaps “the worst pain I’ve ever experienced,” which is typical of a STEMI. The diagnosis primarily lies in the symptoms (eg, the patient’s “story”), the ECG, and the laboratory findings.

The history of diabetes, hypertension, smoking, and a positive family history in P.H. are all risk factors for coronary disease. His admission BP is high, which could indicate poor underlying control or anxiety and stress related to his ACS. The blood sugar of 149 mg/dL is high, again indicating either poor control or a stress response. Measurement of hemoglobin A_{1c} is indicated during his hospitalization to better assess his diabetes control.

Laboratory Abnormalities

Case 13-1, Question 2: What laboratory abnormalities can you expect to see in P.H.?

P.H. has an elevated troponin, which is consistent with myocardial necrosis and consistent with laboratory abnormalities seen with both STEMI and NSTEMI. With UA, cardiac biomarkers are not elevated. Several other nonspecific laboratory findings should be monitored in P.H. Hyperglycemia may develop because P.H. has diabetes, but this can also occur in patients without diabetes. ACS is also accompanied by an acute systemic inflammatory response manifested by fever, leukocytosis, and elevation of the erythrocyte sedimentation rate and C-reactive protein, as well as a drop in LDL, high-density lipoprotein (HDL), and total cholesterol. Specifically, these lipoprotein changes may begin to decrease within 24 to 48

hours of an ACS event, reaching a nadir within 5 to 7 days and then gradually recovering during the next 30 days.[47] Therefore, it is prudent to check serum lipid profiles within the first 24 hours of the AMI to get an accurate determination of the patient's lipid values.

ST-Segment Elevation Myocardial Infarction Versus Non–ST-Segment Elevation Myocardial Infarction

Case 13-1, Question 3: P.H. was noted to have ST-segment elevation on the ECG. What are the implications of an ST-segment elevation versus non–ST-segment elevation MI?

Perhaps the most important diagnostic test in someone suspected of having an AMI is the ECG. The ECG is an important tool because it is noninvasive, can be performed rapidly, is readily available in most settings, and helps determine where the AMI is located (ie, anterior, inferior, lateral). P.H. has classic ECG changes (ST-segment elevation), and presence in the anterior ECG leads (V_2–V_4) points to the coronary artery likely to be blocked. P.H.'s previous left anterior descending lesion may have had a plaque rupture leading to thrombosis of the vessel.

The presence of ST-segment elevation in two contiguous leads indicates severe ischemia and occlusion of the coronary artery. Every effort should be made to open the infarct-related artery as soon as possible, which could consist of PCI or fibrinolytic therapy. If the ECG showed ST-segment depression (eg, NSTE-ACS), instead of elevation, P.H. would not be eligible for fibrinolytic therapy because the risks of fibrinolytic therapy outweigh the benefits in NSTE-ACS.

Anterior Versus Inferior Infarction

Case 13-1, Question 4: What are the prognostic implications of an anterior versus an inferior MI?

Damage to the anterior section of the heart is more likely to be associated with increased morbidity (eg, LV dysfunction) and mortality. The patients at highest risk for death are those with an anterior ACS, LV dysfunction, and complex ventricular ectopy. P.H. is at an increased risk because he has sustained an anterior infarction.

Risk Stratification

Therapeutic Objectives

Case 13-1, Question 5: What are the immediate and long-term therapeutic objectives in treating P.H.?

With both STEMI and NSTE-ACS, the immediate therapeutic objectives, particularly as they apply to P.H., are to restore blood flow to the infarct-related artery, arrest infarct expansion, alleviate his symptoms, and prevent death. These objectives are achieved primarily by restoring coronary blood flow (administering a fibrinolytic or performing PCI for STEMI or performing PCI with NSTE-ACS) and lowering myocardial oxygen demand with nitrates and β-blockers. Any life-threatening ventricular arrhythmias that develop must be treated. The long-term therapeutic objectives are to prevent or minimize recurrent ischemic symptoms, reinfarction, HF, and sudden cardiac death. Because P.H. is experiencing a STEMI, the specific therapeutic regimens are discussed in the questions that follow.

TREATMENT FOR ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Fibrinolytic Therapy

Case 13-1, Question 6: Is P.H. a candidate for fibrinolytic therapy? Is any one agent preferred?

STEMI is a medical emergency, and rapid administration of drug therapy is crucial to save myocardial tissue. The results of several major trials have shown unequivocally that if used appropriately, fibrinolytic agents can reduce the mortality associated with an AMI. Because mortality benefit is greatest when fibrinolytic therapy is administered within 2 hours of symptom onset, prehospital fibrinolytic therapy, in which trained paramedics administer the fibrinolytic in the field, is an attractive option to reduce total ischemic time, although it is not typically done in the United States.[48] If primary PCI cannot be performed within 120 minutes, fibrinolytic therapy should be given if no contraindications are present. For patients who present >12 hours after symptom onset, fibrinolytic therapy should be administered only if there is ongoing ischemic, hemodynamic instability or a large area of myocardium involvement. In the case of P.H., he is admitted to a hospital that is not PCI capable and cannot be transferred to a PCI-capable hospital within 120 minutes of first medical contact.

Controversy still exists about which fibrinolytic should be used, the best dosing regimen, the most appropriate adjunctive therapy, and whether the risk outweighs the benefit in some subpopulations of patients (eg, those with an inferior AMI). P.H. has a history of hypertension, and, at presentation, his BP is 180/110 mm Hg. A BP this high is a relative contraindication to fibrinolytic therapy because of an increased risk of cerebral hemorrhage; however, P.H. has an anterior MI and is likely to benefit from fibrinolytic therapy. In this case, he should receive IV NTG immediately because the onset of BP control with this agent usually occurs within minutes. Once his systolic BP is <180 mm Hg and the diastolic is <110 mm Hg, a fibrinolytic can be administered. The NTG will also reduce the workload on his heart and may provide pain relief. During and

following administration of the fibrinolytic, P.H.'s BP should be closely monitored to ensure it remains <180/105 mm Hg to reduce the risk of intracranial hemorrhage.

Because P.H. has severe pain and ECG changes consistent with an anterior AMI, he is at high risk for substantial morbidity or mortality. The argument for or against a specific fibrinolytic is probably less important than the decision to use an agent and to administer the medication as soon as possible after the onset of symptoms. P.H. is fortunate because he has presented within 1 hour of the onset of chest pain.

Reteplase was compared with t-PA in the *G*lobal *U*tilization of *S*treptokinase and *t*-PA for *O*ccluded Arteries (GUSTO)-III trial.[49] Reteplase has a slower clearance from the body, allowing the drug to be given as a bolus without the need for a constant infusion. In the GUSTO-III trial, reteplase was administered in two bolus doses of 10 million units, given 30 minutes apart. The mortality rate and incidence of stroke were the same in the two groups of patients. TNK was compared with t-PA in the second Assessment of Safety and Efficacy of a New Fibrinolytic (ASSENT-2) trial.[50] TNK was administered as a bolus of 30 to 50 mg for 5 to 10 seconds, based on body weight. No difference existed between TNK and t-PA in 30-day mortality and stroke, and TNK had fewer bleeding complications. Current guidelines do not explicitly endorse one fibrinolytic versus another, and all are acceptable first-line agents. Selection is usually based on clinician preference and hospital formulary.

ADJUNCT THERAPY

CASE 13-1, QUESTION 7: Orders are written for an infusion of t-PA along with UFH 4000 units IV bolus, followed by 960 units/hour by continuous infusion. Aspirin 325 mg is ordered stat. Are both UFH and aspirin agents necessary?

The second International Study of Infarct Survival (ISIS)-2 trial showed that the combination of aspirin and streptokinase reduced mortality in patients with an AMI by 42% compared to placebo.[51] In

doses of ≥162 mg, aspirin generates a prompt clinical antithrombotic effect as a result of its inhibition of thromboxane A_2 production. Thus, immediate administration of 162 to 325 mg of aspirin in all patients diagnosed with ACS is indicated. In the acute setting, aspirin should be chewed because it is absorbed more quickly. All patients should receive low-dose aspirin indefinitely after a diagnosis of ACS. If patients have a contraindication to aspirin, clopidogrel can be substituted.[5]

The use of UFH as adjunct therapy to prevent reocclusion has been evaluated in many studies.[5] Because P.H. will receive t-PA, an IV UFH bolus followed by a continuous infusion should be started before the end of the t-PA infusion. The ACC/AHA guidelines recommend an initial UFH bolus of 60 units/kg (maximum of 4000 units), followed by an initial infusion of 12 units/kg/hour (maximum of 1000 units/hour) for 48 hours after fibrinolysis, with a targeted activated partial thromboplastin time (aPTT) of 1.5 to 2 times the upper limit of normal, equivalent to anti-Xa concentrations of 0.4 to 0.7 units/mL assessed by anti-factor Xa determinations. UFH should always be considered in patients at high risk for systemic or venous embolism.

CASE 13-1, QUESTION 8: Would P.H. benefit from the addition of clopidogrel to his current drug regimen?

Two studies have evaluated the potential role of in-hospital clopidogrel as an integral part of fibrinolytic therapy in patients with STEMI.[52,53] The *CL*opidogrel as *A*djunctive *R*eperfus*I*on Therap*Y*–Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) evaluated patients with STEMI who received standard fibrinolytic therapy, aspirin, and UFH, and were scheduled for angiography within 2 days.[53] Patients received either clopidogrel (300 mg loading dose, followed by 75 mg daily) or placebo within 10 minutes of fibrinolytic administration. Clopidogrel was continued up to and including the day of angiography and then stopped. The primary end point was the composite of an occluded infarct-related artery on

predischarge angiography or death or an MI up to the start of coronary angiography. Compared with placebo, patients receiving clopidogrel demonstrated a 36% reduction in the primary end point ($P < .001$). By 30 days, the clopidogrel treatment group had a 20% reduction in cardiovascular death, recurrent MI, or recurrent ischemia ($P = .03$). No difference in the rate of major bleeding was seen between groups. In a substudy of patients proceeding to nonemergent PCI after fibrinolytic therapy, patients receiving pretreatment with clopidogrel demonstrated a 66% reduction in 30-day mortality compared with those receiving placebo ($P = .034$).[54]

The *C*l*O*pidogrel and *M*etoprolol in *M*yocardial *I*nfarction *T*rial (COMMIT) evaluated the effect of clopidogrel 75 mg daily (with no loading dose) or placebo in 45,852 patients presenting with STEMI.[52] In the trial population, 93% had ST-segment elevation or bundle branch block, 7% had ST-segment depression, and 54% were treated with fibrinolytic therapy. The initial clopidogrel dose was given within 24 hours of symptom onset and continued until hospital discharge or up to 4 weeks in the hospital. Compared with placebo, clopidogrel was associated with a 9% reduction in death, reinfarction, or stroke ($P = .002$) and a 7% reduction in all-cause mortality ($P = .03$). No significant excess in bleeding was noted with clopidogrel, either overall or in patients who received concomitant fibrinolytic therapy or were older than age 70 years. On the basis of these two studies, P.H. should receive clopidogrel as an inpatient.

Case 13-1, Question 9: What dose of clopidogrel should be considered?

According to the 2013 ACC/AHA guidelines, clopidogrel should be added to aspirin in patients who undergo reperfusion with fibrinolytic therapy.[5] A loading dose of clopidogrel 300 mg can be administered with fibrinolytic therapy followed by 75 mg/day for maintenance. The maintenance dose should be continued for 14 days and up to 1 year. The 1-year duration is extrapolated from experience with NSTE-ACS.[1] There are no studies evaluating a 600-mg loading dose in patients with STEMI treated with fibrinolytics. In addition, uncertainty

exists about the safety of giving a loading dose of clopidogrel in adults ages 75 years and older, particularly when they receive a fibrinolytic. Therefore, in this population, a loading dose should be avoided. A single loading dose of 300 mg of clopidogrel should be given to patients age younger than 75 years who receive a fibrinolytic agent and are subsequently proceeding to PCI within 24 hours.[5] If the patient received a fibrinolytic (with 300 mg of clopidogrel) and then proceeds to PCI after 24 hours has lapsed, then an additional 300 mg of clopidogrel should be administered. For P.H., a loading dose of 300 mg of clopidogrel should be administered at the time of fibrinolytic administration followed by 75 mg/day for 14 days to 1 year. Because P.H. has already received 325 mg of aspirin in the ED, he should continue 81 mg of daily aspirin indefinitely.

CASE 13-1, QUESTION 10: What roles do the other anticoagulant and antiplatelet agents have in P.H.'s management?

Data available with the newer $P2Y_{12}$ inhibitors when used in the setting of fibrinolytic therapy are lacking. It would be prudent to avoid giving prasugrel and other potent $P2Y_{12}$ inhibitors no sooner than 24 hours after administration of a fibrinolytic.[5] Coronary anatomy should be known to ensure that the patient is not a candidate for CABG.

The replacement of UFH with an LMWH, factor Xa inhibitor, or the addition of a GP IIb/IIIa inhibitor to fibrinolytic therapy has been evaluated in patients with STEMI.

In the *E*nox*a*parin and *T*hrombolysis *R*eperfusion for *A*cute myocardial infar*C*tion *T*reatment–Thrombolysis in Myocardial Infarction Study-25 (ExTRACT-TIMI 25), 20,506 patients with STEMI scheduled for fibrinolytic therapy were randomized to receive either enoxaparin or continuous infusion of UFH for 48 hours.[55] Enoxaparin was dosed according to age and renal function. UFH was dosed according to weight and adjusted to achieve an aPTT 1.5 to 2 times control. The composite end point of death or nonfatal MI through 30 days occurred in 12% in the UFH group and 9.9% in the enoxaparin group, representing a 17% risk reduction ($P < .001$). No difference

was noted in mortality between the two groups. Major bleeding was higher in the enoxaparin group.

The Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS) 6 was a randomized double-blind trial of 12,092 patients with STEMI assessing the effect of early initiation of fondaparinux with primary PCI and medical therapy.[56] The study compared the effects of fondaparinux with two different control arms. Patients with confirmed STEMI were assigned to one of the two following strata. Stratum 1: no indication for UFH (patients receiving streptokinase or those not receiving a thrombolytic agent were assigned to this stratum). Stratum 2: indication for UFH (patients receiving alteplase, reteplase, or TNK and those undergoing primary PCI were assigned to this stratum). Death or reinfarction at 30 days was significantly reduced in the fondaparinux group. However, fondaparinux did not benefit patients who were managed with primary PCI. Although the rates of death, MI, and severe bleeds did not differ in these patients, there was a higher rate of catheter thrombosis with fondaparinux.[56]

The TIMI-14 trial demonstrated enhanced reperfusion (TIMI 3 flow) using reduced-dose t-PA combined with abciximab compared with full-dose t-PA alone.[57] The GUSTO-V trial compared standard-dose reteplase to half-dose reteplase plus full-dose abciximab in patients with STEMI.[58] The combination group had less reinfarction and recurrent ischemia, but more episodes of moderate and severe bleeding, especially in the elderly. Similar rates of enhanced reperfusion have also been observed with the combination of a double-bolus dose of eptifibatide (180/90 μg/kg, 10 minutes apart) with a 48-hour infusion (2 μg/kg/minute) plus a half-dose of t-PA (50 mg).[59] The ASSENT-3 trial assessed three regimens: (1) full-dose TNK plus enoxaparin, (2) full-dose TNK plus UFH, or (3) half-dose TNK plus UFH with a 12-hour infusion of abciximab. The addition of either abciximab or enoxaparin to TNK reduced the composite end point of 30-day mortality, in-hospital reinfarction, or ischemia compared with UFH. More major bleeding complications were seen with abciximab compared with UFH.[60] In a meta-analysis of 11 trials involving 27,115 patients with STEMI who received adjunctive

abciximab in addition to either PCI or fibrinolytic therapy, use of abciximab was associated with a significant reduction in 30-day (*P* = .047) and 1- to 6-month mortality (*P* = .01) in patients undergoing PCI, but not in those receiving fibrinolytic therapy.[61] Despite an improvement in patency rates, the combination of GP IIb/IIIa inhibitors with either full- or half-dose fibrinolytic should be avoided, if at all possible, especially in the elderly.[5]

Based on data from ExTRACT-TIMI 25 and OASIS-6, the ACC/AHA guidelines allow for substitution of UFH with either enoxaparin or fondaparinux.[5] However, fondaparinux appeared to be superior to control therapy in the OASIS-6 trial, whereas relative benefit compared with placebo and UFH separately cannot be reliably determined.[62] If enoxaparin or fondaparinux is selected, anticoagulation should be continued for the duration of the hospitalization, up to 8 days or until revascularization. For P.H., enoxaparin would be the more appropriate choice; however, he will have a higher risk of bleeding and need to be monitored closely. Because P.H. is not undergoing PCI, the bleeding risks outweigh any benefit from the addition of a GP IIb/IIIa at this time.[5]

DETERMINATION OF REPERFUSION

Case 13-1, Question 11: How can you monitor for successful reperfusion in P.H. after he has received fibrinolytic therapy?

It is important to determine whether thrombolysis has been successful because the prognosis of the patient is related to the presence or absence of an open infarct-related artery. If fibrinolytic therapy fails to open the infarct-related artery, then the patient may benefit from PCI or a CABG. Although coronary angiography has been the standard for determining the success of reperfusion, this procedure is expensive and may be misleading because some studies have suggested that microvascular perfusion may be impaired even when TIMI grade 3 flow has been achieved. A simple and readily available technique is evaluation of ECG ST-segment

resolution. A resolution of >50% of the ST-segment elevation at 60 to 90 minutes after the initiation of fibrinolytic therapy is a good indicator of improved myocardial perfusion.[5] Relief of symptoms, maintenance or restoration of hemodynamic or electrical stability or both, and a reduction of >70% in the initial ST-segment elevation are all suggestive of adequate reperfusion. P.H. should undergo a 12-lead ECG to evaluate reperfusion.[5]

CASE 13-1, QUESTION 12: P.H. continues to have chest pain. Should the thrombolytic be readministered?

READMINISTRATION OF THROMBOLYTIC AGENTS

Reocclusion of the infarct-related artery after an initial successful thrombolysis is a major setback. If reocclusion occurs, mechanical intervention (eg, PCI) is often attempted. Several studies have evaluated whether to readminister the fibrinolytic or refer the patient for PCI. In a meta-analysis of eight trials of patients with STEMI who failed fibrinolytic therapy, those receiving rescue PCI showed no significant reduction in all-cause mortality but had a 27% risk reduction in HF (P = .05) and 42% reduction in reinfarction (P = .04) when compared with standard medical therapy. Repeat fibrinolytic therapy was not associated with significant improvements in all-cause mortality or reinfarction. Both treatment strategies demonstrated a significant increase in minor bleeding, but PCI was associated with an increase in stroke.[63] The Rapid Early Action for Coronary Treatment (REACT) study found that patients who received rescue PCI compared to repeat fibrinolytic or conservative care had a significantly lower composite of death, reinfarction, stroke, or severe HF at 6 months (event-free survival rate: 84.6% vs 70.1% vs 68.7%, respectively, P = .004).[64] The ACC/AHA guidelines recommend that patients who have failed fibrinolytic therapy undergo catheterization with appropriate antithrombotic therapy if possible.[5] Patients best suited for catheterization consist of those with high-risk features such as cardiogenic shock, significant hypotension, severe HF, or ECG evidence of an extensive area of myocardial jeopardy.

In the case of P.H., a repeat infusion with t-PA would probably be safe, but it may not be effective. If a PCI-capable institution exists, P.H. should be transferred for an invasive strategy at this time.

USE IN THE ELDERLY

CASE 13-1, QUESTION 13: If P.H. had been 85 years old, would he have still received fibrinolytic therapy?

Some of the early trials with fibrinolytic therapy excluded the elderly. Although the elderly may have a higher prevalence of relative contraindications such as severe hypertension or history of stroke at presentation, they also have a higher incidence of mortality after an AMI. The 30-day mortality rate after an AMI is 19.6% for patients between ages 75 and 85 years and 30.3% for those who are age 85 years.[65] In the ISIS-2 trial, the greatest reduction in mortality occurred in the elderly subgroup. There are no controlled trials in which fibrinolytic therapy has increased mortality in the elderly. However, in a high-risk cohort of elderly female patients (older than 75 years, <147.71 pounds [<67 kg]), the ASSENT investigators demonstrated that TNK was associated with lower rates of major bleeding and intracerebral hemorrhage compared to t-PA. Another potential strategy to reduce intracranial hemorrhage risk is a reduced dose of fibrinolytic. The *ST*rategic *R*eperfusion *E*arly *A*fter *M*yocardial infarction (STREAM) trial, evaluated prehospital fibrinolytic therapy and reduced the dose of TNK by 50% in patients age 75 years or older.[65] The intracranial hemorrhage rate was reduced to 0.5% and coronary patency rates were similar when compared to patients younger than 75 years of age who received full-dose TNK. It is also important to ensure that appropriate dosage adjustments are made for concomitant medications according to age, weight, and renal function as applicable (see **Table 13-2**).

a-Blockers

Case 13-1, Question 14: The physician wishes to write a prescription for a β-blocker. What are the benefits of administering a β-blocker to P.H.? Should it be given as IV therapy or started as oral therapy a few days after the infarction?

β-Blockers offer significant benefits to the patient with MI. Several large trials gave IV β-blockers (up to 24 hours after symptom onset) followed by oral therapy; other studies used oral therapy alone beginning days after the infarction. Early IV administration appears to be most beneficial, with a reduction in mortality of about 25% in the first 2 days when the results of these trials are pooled. However, late oral therapy alone, initiated up to 21 days after an MI in the β-Blocker in Heart Attack Trial, was also associated with a substantial reduction in mortality (around 10%).[5]

Early IV administration of propranolol, metoprolol, timolol, and atenolol has been studied. Typically, metoprolol is used in the acute setting because of its β_1 selectivity, ease of dosing and administration, and weight of evidence. Oral carvedilol, a nonselective β- and α-blocker, has been used in the peri-infarction period, specifically in patients with LV dysfunction. In the *CA*rvedilol *P*ost-infa*R*ction surv*I*val *CO*nt*R*ol in left ventricular dysfunctio*N* (CAPRICORN) trial, carvedilol 6.25 mg twice daily titrated to 25 mg twice daily reduced all-cause and cardiovascular mortality as well as recurrent nonfatal MI.[66]

It is important to tailor β-blocker therapy for each patient, as evidenced in the COMMIT trial.[67] In this study, patients were randomized to placebo or metoprolol (up to 15 mg IV of metoprolol, then oral 200 mg metoprolol succinate daily) within 24 hours of AMI. Although metoprolol reduced reinfarction and ventricular fibrillation rates compared with placebo, it was associated with a significant increase in cardiogenic shock. Patients with hemodynamic instability at randomization were at greatest risk for early cardiogenic shock associated with metoprolol. Given these concerns, oral β-blockers are generally preferred. If the patient is hypertensive or having ongoing ischemia, then IV metoprolol tartrate (5 mg IV every 5 minutes as tolerated up to three doses) can be considered (see

Table 13-2). For all other patients without contraindications, oral metoprolol tartrate 25 to 50 mg every 6 to 12 hours should be initiated. Doses should be titrated on the basis of BP and heart rate. If a patient has transient cardiac decompensation or is at risk for cardiogenic shock during the acute infarction period, early IV β-blockers should be withheld. The patient's condition may be observed for a few days; if it stabilizes, oral therapy is initiated and titrated slowly. The ACC/AHA guidelines highlight the importance of an individualized approach but do provide guidance on suggested dosing recommendations for both acute and long-term use.

In our case, P.H.'s situation is complicated by his history of intermittent pulmonary problems. In deciding whether to attempt use of β-blockers in patients with pulmonary disease, one must determine the nature of the pulmonary problem (ie, reactive airway disease). It also would be helpful to determine P.H.'s need for routine use of β-agonists to help quantify the severity of his disease. By history, P.H. does not use β-agonist bronchodilators routinely. No history is given regarding his pulmonary function tests or the degree of reversibility of his airway disease with bronchodilators. β_1-selective antagonists are the drugs of choice in these patients, but at higher doses (eg, metoprolol doses >100 mg/day), the relative β_1-selectivity may be lost. A patient would need to experience significant worsening of the pulmonary disease to justify avoiding β-blockers. A better history of P.H.'s pulmonary problems should be obtained. If they are minor and as he has experienced an uncomplicated MI, P.H. may be a candidate for early therapy with metoprolol to reduce chest pain as well as decrease the risk of reinfarction and arrhythmias.

Nitroglycerin

Case 13-1, Question 15: Despite SL NTG, P.H. continues to have chest discomfort. Would he benefit from IV NTG?

Because P.H. is exhibiting refractory ischemic discomfort despite receiving SL and topical nitrates, symptomatic management with IV NTG is indicated. NTG lowers the LV filling pressure and systemic vascular resistance, thereby reducing myocardial oxygen consumption and myocardial ischemia. At lower doses (<50 µg/minute), IV NTG preferentially dilates the venous capacitance vessels, which leads to a decrease in LV filling pressure. For patients who have signs of pulmonary congestion, IV NTG is of particular value.

CASE 13-1, QUESTION 16: How should IV NTG be administered to P.H.? How should it be monitored?

A continuous infusion of NTG is delivered in a controlled manner, starting with 5 to 10 µg/minute, which is then increased by an additional 5 to 10 µg/minute every 5 to 10 minutes if needed. Many cardiologists routinely give patients an infusion of NTG for the first 24 to 48 hours after an AMI. Increasing doses may be required during this period to maintain the desired hemodynamic effect owing to tolerance that occurs from prolonged nitrate exposure. However, if >200 µg/minute is needed to achieve the desired response, another vasodilator may be needed. NTG is typically administered in combination with fibrinolytic agents in patients who require relief from myocardial ischemia.

Patients with an inferior or a right ventricular infarct often develop hypotension (mean BP <80 mm Hg) when given NTG. P.H.'s BP should be monitored closely during this infusion. After starting NTG, we would expect to see his BP decline; the pulse rate may or may not increase. The NTG dose should be titrated to relieve pain while avoiding symptomatic hypotension. In patients with evidence of HF, NTG can reduce LV filling pressure (preload) as well as improve orthopnea and pulmonary congestion. However, excessive doses of IV NTG can reduce LV filling pressure to excess, and potentially decrease cardiac output. The systolic BP should be maintained to at least 90 mm Hg. Once P.H.'s chest pain is controlled, he may be

either transitioned to an oral agent or his transdermal delivery system increased. With either choice, a nitrate-free interval should be maintained (see Chapter 12, Chronic Stable Angina).

Treatment for Unstable Angina or Non–ST-Segment Elevation Myocardial Infarction

Invasive Versus Ischemia-Guided Strategy

CASE 13-2

QUESTION 1: J.W. is a 65-year-old male who presents to the ED with chest tightness and shortness of breath. He gives a history of similar symptoms the previous day that lasted 20 minutes. He was given aspirin 325 mg, intranasal oxygen, PO (by mouth) metoprolol tartrate, and started on an IV NTG infusion, which was increased to 80 µg/minute; at that time, his BP was 130/60 mm Hg, and his heart rate was 88. His ECG revealed ST-segment depression in the anterior leads. His shortness of breath was relieved, but he still reported chest tightness. His past medical history includes hypertension for which he takes hydrochlorothiazide 25 mg daily. His mother died of a heart attack at age 62. He has smoked a pack of cigarettes per day for the past 30 years. Laboratory values include the following:

Na^+, 135 mEq/L
K^+, 4.0 mEq/L
Cl^-, 100 mEq/L
CO_2, 20 mEq/L
BUN, 15 mg/dL
SCr, 1.1 mg/dL
Glucose, 100 mg/dL
Mg, 2 mEq/L
Troponin I-Ultra, 0.01 ng/mL (normal, <0.02 ng/mL)
Hgb, 14 g/dL
Hct, 44%
Platelets, 288 × $10^3/mm^3$

Based on his symptoms and ECG, the diagnosis is presumed to be UI.

Should J.W. receive an invasive or ischemia-guided strategy for management of his NSTE-ACS?

Although J.W. has negative biomarkers after 24 hours from his first episode of chest pain suggesting UA, the presence of new ST-segment depression may prompt the clinician to choose an early invasive approach within 24 hours (see **Fig. 13-5**). If, however, the patient is not at high or intermediate risk, then the invasive approach may be delayed and performed within 25 to 72 hours. A TIMI (or GRACE) score would also be helpful to risk stratify the patient. J.W. has a TIMI score of 4 indicating a 19.9% risk at 14 days of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization. When risk stratifying, TIMI scores of 0 to 2, 3 to 4, and 5 to 7 represent low, moderate, and high risk for death or repeat MI at 14 days. So, based on his TIMI score, he is moderate risk. As an alternative, calculating a GRACE score would indicate 137 points representing an 11% risk of in-hospital death or MI and a 19% risk at 6 months. An ischemia-guided strategy might be selected based on patient or clinician preference in the absence of high-risk features such as elevated biomarkers. In this approach, pharmacotherapy would be initiated followed by a noninvasive stress evaluation. If J.W. were to have elevated cardiac biomarkers during his presentation, his diagnosis would be NSTEMI, and an early invasive (within 24 hours) approach may be preferred. If during his hospitalization, J.W. were to experience any recurrent ischemia, arrhythmias, or signs and symptoms of HF, he would proceed directly to angiography and undergo possible PCI.

Anticoagulant Therapy

Case 13-2, Question 2: What anticoagulant regimen should J.W. receive?

The ACC/AHA guidelines recommend beginning anticoagulant therapy for all patients (without contraindications) with NSTE-ACS as soon as possible. The guidelines recommend one of four agents: UFH, enoxaparin, fondaparinux, or bivalirudin (approved only for patients managed according to an invasive strategy). **Table 13-2**

summarizes the dosing and contraindications for each of these agents.

In NSTE-ACS, UFH has been associated with lower rates of death or MI than with aspirin alone.[1] Despite its limitations, UFH is preferred if the patient is to undergo CABG because of its rapid clearance. For an invasive strategy, the guidelines give a higher level of evidence for enoxaparin but do warn about an increase in bleeding.[1] When choosing an anticoagulant, renal function, bleeding risk, and concomitant therapy should be considered.

Data supporting LMWHs in this setting come from several studies. In the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) study, enoxaparin (1 mg/kg subcutaneous [SQ] twice daily) was compared with UFH (5000 units IV bolus followed by continued infusion titrated to an aPTT of 55–86 seconds).[68] The composite outcome of death, MI, or recurrent angina at 14 days was reduced by 20% in the enoxaparin group. This benefit was maintained for 1 year.

In the *S*uperior *Y*ield of the *N*ew strategy of *E*noxaparin, *R*evascularization and *G*l*Y*coprotein IIb/IIIa inhibitors (SYNERGY) trial, 9978 high-risk patients with NSTE-ACS were randomized to enoxaparin (1 mg/kg SQ twice daily) or weight-based UFH (60 units/kg bolus followed by 12 units/kg/hour adjusted to an aPTT 1.5 to 2 times control) before undergoing an early invasive strategy.[69] Enoxaparin was found to be as efficacious as UFH in reducing 30-day all-cause mortality or nonfatal MI but was associated with a significant risk of major bleeding ($P = .008$). Bleeding was especially problematic in those patients who crossed over from one treatment to the other during the trial.

In the TIMI-11B trial, enoxaparin (30 mg IV bolus followed by 1 mg/kg SQ twice daily for 8 days) compared with UFH (70 units/kg bolus followed by 15 units/kg/hour for 3–8 days) reduced the composite end point of death, MI, or need for urgent revascularization.[70] The benefit of enoxaparin is greatest for high-risk subgroups such as those with ST-segment changes, elevated troponins, and a high TIMI risk score.[1]

Finally, enoxaparin has been compared with fondaparinux. In the OASIS-5 trial, patients with NSTE-ACS were randomized to fondaparinux (2.5 mg SQ daily) or enoxaparin (1 mg/kg SQ twice daily) for a mean of 6 days and evaluated at 9 days for the primary end point of death, MI, or refractory ischemia.[71] There was no difference between groups for the primary end point; however, compared with enoxaparin, fondaparinux had a significantly lower incidence of major bleeding at 9 days ($P < .001$) and a greater reduction in mortality at 30 days ($P = .05$). Based on these data, the guidelines give preference to fondaparinux compared with other anticoagulants for patients who are at an increased risk for bleeding and being treated with an ischemia-guided (conservative medical management) strategy. If fondaparinux is used for a patient undergoing PCI, an additional anticoagulant with factor IIa activity such as UFH is needed.[1]

Bivalirudin is given a Class I recommendation in the guidelines. In the *A*cute *C*atheterization and *U*rgent *I*ntervention *T*riage strateg*Y* (ACUITY) trial, patients with NSTE-ACS managed with an early invasive strategy were randomly assigned to receive either UFH (or enoxaparin) plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone.[72] No differences in the primary end point (composite of death, MI, unplanned revascularization for ischemia, and major bleeding at 30 days) were observed between the group receiving UFH plus a GP IIb/IIIa inhibitor and the group receiving bivalirudin plus a GP IIb/IIIa inhibitor. However, compared with those receiving UFH plus a GP IIb/IIIa inhibitor, the 30-day composite of ischemia or major bleeding was significantly lower for those receiving bivalirudin alone. This difference was attributed to reduced major bleeding with bivalirudin.

How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI) trial was a head-to-head comparison of bivalirudin versus UFH.[73] Patients who underwent emergent PCI were randomly assigned to receive either UFH or bivalirudin. At 28 days, the primary efficacy outcome of one or more MACE was significantly lower in the UFH group. When the individual components were evaluated, there was no difference in

all-cause mortality or cerebrovascular accident. The driving factors favoring heparin were new MI or reinfarction and additional unplanned target lesion revascularization. The majority of these cases were related to stent thrombosis in the bivalirudin group (0.9% vs 3.4%, *P* = .001). Major and minor bleeding events did not differ between the two groups.

Because J.W. is receiving an invasive strategy for his NSTE-ACS and he has adequate renal function, enoxaparin, UFH, or bivalirudin could be initiated and continued until the end of PCI.

Antithrombotic Therapy

Case 13-2, Question 3: What oral antithrombotic medications should be considered for J.W.?

For both ischemia-guided and invasive strategies, aspirin along with a $P2Y_{12}$ inhibitor (loading with maintenance dose) should be added as soon as possible to anticoagulant therapy unless the patient is to proceed to CABG. For an invasive strategy, prasugrel or ticagrelor can be considered in lieu of clopidogrel. The 2014 ACC/AHA guidelines recommend ticagrelor as the preferred agent (Class IIa). Prasugrel should only be used in patients undergoing PCI as long as they are not at high risk for bleeding complications.[1]

The use of clopidogrel in NSTE-ACS was evaluated in two studies.[74,75] In the *C*lopidogrel in *U*nstable angina to prevent *R*ecurrent ischemic *E*vents (CURE) trial, patients with NSTE-ACS were randomized to placebo plus aspirin (75–325 mg) or clopidogrel (300 mg, immediately followed by 75 mg daily) plus aspirin.[74] The composite of cardiovascular death, MI, or stroke was significantly reduced with clopidogrel. However, compared with placebo, an increase in major and minor bleeding was seen. On the basis of these data, clopidogrel with aspirin should be administered immediately on admission and continued ideally for 1 year in patients with ACS.[1]

The PCI–*CL*opidogrel as *A*djunctive *R*eperfus*I*on *T*herap*Y* (PCI-CLARITY) study was a planned subanalysis (*N* = 1863) of the *CL*opidogrel as *A*djunctive *R*eperfus*I*on *T*herap*Y*–Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 study (see Case 13-1, Question 8) that evaluated the effects of pretreatment with aspirin plus clopidogrel, compared with aspirin plus placebo, in patients undergoing PCI with coronary artery stenting.[76] Compared with placebo, pretreatment with clopidogrel significantly reduced the incidence of cardiovascular death, MI, or stroke as well as recurrent MI or stroke before PCI with no significant excess in TIMI major or minor bleeding.

Case 13-2, Question 4: What loading dose should J.W. receive and when should he receive it? What about his maintenance dose?

A loading dose of 600 mg of clopidogrel in patients undergoing PCI achieves greater platelet inhibition with fewer low responders and decreases the incidence of major cardiac events compared with a loading dose of 300 mg.[1] A 300-mg clopidogrel loading dose provides adequate antiplatelet activity in 6 hours, whereas a 600-mg clopidogrel loading dose provides antiplatelet activity in 2 hours. Even after a loading dose, clopidogrel requires several hours to be metabolized to its active metabolite. The current guidelines prefer 600 mg owing to a greater, more rapid and more consistent degree of platelet inhibition. Patients undergoing PCI who have previously received a loading dose of 300 mg of clopidogrel and are on a 75-mg daily maintenance dose should receive another 300-mg loading dose. Data do not exist on additional loading doses for patients currently receiving maintenance doses of prasugrel or ticagrelor.

Prasugrel has been evaluated in patients with ACS undergoing PCI. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 study, patients with moderate- to high-risk ACS, 26% of whom had STEMI, were randomized to prasugrel (60-mg loading dose followed by 10 mg

daily) or clopidogrel (300-mg loading dose followed by 75 mg daily).[77] All patients received aspirin (75–162 mg daily). The primary outcome of death from cardiovascular causes, nonfatal MI, or nonfatal stroke occurred in 9.9% of patients receiving prasugrel and 12.1% of patients taking clopidogrel ($P < .001$). However, prasugrel was associated with a significant increase in TIMI major, fatal, and life-threatening bleeding. A post hoc analysis found three subgroups that did not benefit from prasugrel: patients with a history of stroke or transient ischemic attack (TIA), age 75 years and older, or body weight <132.28 pounds (60 kg). Patients with at least one of these risk factors exhibited a higher rate of bleeding.[78] The U.S. Food and Drug Administration (FDA) recommends that a 5-mg (rather than a 10-mg) maintenance dose be considered for those patients weighing <132.28 pounds (60 kg), even though this dose has not been studied.[79]

In the *PLAT*elet inhibition and patient *O*utcomes (PLATO) trial, patients with ACS, with or without ST-segment elevation were randomized to receive ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300–600-mg loading dose, then 75 mg daily). Compared to clopidogrel, ticagrelor demonstrated a 16% reduced rate of mortality from MI, vascular causes, or stroke ($P < .001$) without an increase in the rate of major bleeding but an increased rate in CABG-related bleeding ($P = .03$).[80] However, the lowest 1-year rates of cardiovascular death, MI, or stroke were noted in patients with ACS treated with ticagrelor and maintenance low-dose aspirin (≤100 mg/day), whereas the highest rates occurred in those treated with ticagrelor and high-dose aspirin (>300 mg/day).[81] Based on these data, the maintenance dose of aspirin should not exceed 100 mg/day.[82]

When compared with clopidogrel, prasugrel and ticagrelor are more potent, exhibit a lower incidence of stent thrombosis, have fewer drug–drug interactions, and lack variable response based on pharmacogenomics (refer to Chapter 12, Chronic Stable Angina, about responders and nonresponders to clopidogrel). However, many providers have been concerned with the higher risk of bleeding. In the case of J.W., clopidogrel, prasugrel, or ticagrelor

could be added because he does not have a contraindication to any of these drugs. Ticagrelor may be preferred as long as cost is not a concern for the patient.

After PCI with coronary stent deployment with either a drug-eluting stent (DES) or a bare-metal stent, clopidogrel 75 mg, prasugrel 5 to 10 mg, or ticagrelor 90 mg twice daily should be administered for at least 12 months. It is important to highlight that clopidogrel and ticagrelor should be discontinued for 5 days and prasugrel for 7 days before surgery.

Because a rapid onset of action is needed, J.W. should receive a loading dose of 600 mg of clopidogrel as soon as possible, followed by 75 mg daily for at least 12 months. If prasugrel is chosen, a loading dose of 60 mg would be given followed by 10 mg daily as long as the patient is >132.28 pounds (60 kg). For ticagrelor, a loading dose of 180 mg is recommended followed by 90 mg twice daily. Aspirin 81 mg daily should be continued indefinitely.

Case 13-2, Question 5: Should a GP IIb/IIIa inhibitor be added? If so, which one?

In patients with NSTE-ACS, the GP IIb/IIIa inhibitors are of benefit for patients with high-risk features undergoing an early invasive strategy.[1] Analysis of GP IIb/IIIa studies suggests that those patients who obtain the greatest advantage from these agents are those who have elevated troponins, diabetes, ST-segment changes, high thrombus burden, or a TIMI risk score of ≥4 at presentation. The guidelines recommend that for patients with NSTE-ACS who will be treated initially according to an early invasive strategy, either a GP IIb/IIIa inhibitor or a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) should be added to aspirin and anticoagulant therapy before diagnostic angiography is performed.[1] The GP IIb/IIIa inhibitors tirofiban or eptifibatide are generally given for 18 to 72 hours.[1] Intracoronary administration of a GP IIb/IIIa inhibitor may be appropriate in some patients. Compared to IV, the higher local concentration achieved via intracoronary administration may result in a higher rate of thrombus

resolution and lower bleeding risk. At this time, additional trials are needed to identify the role of intracoronary use of GP IIb/IIIa inhibitors in the contemporary treatment of patients with ACS.

The guidelines recommend that in the setting of DAPT used with UFH, the adjunctive use of a GP IIb/IIIa inhibitor administered at the time of PCI cannot be recommended as routine therapy. However, a GP IIb/IIIa inhibitor may be beneficial in those with a large thrombus burden or those who have not received adequate $P2Y_{12}$ inhibitor loading.[1]

J.W. has a TIMI risk score of 4; therefore, the addition of eptifibatide or tirofiban is a reasonable choice if a large thrombus burden is demonstrated on angiography. Administration before PCI ("upstream") is not indicated unless the administration of a $P2Y_{12}$ inhibitor is delayed until the time of PCI. Platelets and signs and symptoms of bleeding should be monitored closely.

Because J.W. is not at high risk for bleeding, DAPT in addition to UFH should be adequate therapy. If a large thrombus burden is demonstrated on angiography, a GP IIa/IIIb could be initiated during PCI.

If J.W. had not received an oral $P2Y_{12}$ inhibitor or a GP IIb/IIIa inhibitor, consideration could be given to administering IV cangrelor, a direct-acting $P2Y_{12}$ inhibitor, before PCI. Based on the results of the CHAMPION-PHOENIX trial, cangrelor could be administered as a 30 µg/kg bolus followed by a 4 µg/kg/minute IV infusion for at least 2 hours or for the duration of the PCI.[30] After discontinuation of the infusion, an oral $P2Y_{12}$ inhibitor should be administered (ticagrelor 180-mg load during or upon immediate discontinuation of infusion; prasugrel 60 mg or clopidogrel 600 mg upon immediate discontinuation of infusion) followed by aspirin 81 mg daily along with a maintenance dose of the $P2Y_{12}$ inhibitor. If clopidogrel or prasugrel is administered during the infusion, they will have no antiplatelet effect until the next dose is administered.

CASE 13-2, QUESTION 6: What if an ischemia-driven strategy was decided for J.W. instead, would his antithrombotic therapy change?

Management Strategy

Ischemia-Guided Strategy

An ischemia-guided strategy avoids early invasive procedures, instead of relying on the patient's symptoms to direct the need for intervention. Similarly, J.W. would be optimized on anti-ischemic and antithrombotic regimens. At this time, prasugrel and bivalirudin are only indicated in patients undergoing PCI. In addition, the bleeding risk of GP IIb/IIIa inhibitors outweighs the benefit in this approach, and, therefore, these medications should only be used if PCI is pursued. If during his hospitalization, the patient were to experience any recurrent ischemia, refractory angina despite medical therapy, or high-risk features (eg, arrhythmias, signs or symptoms of HF, hemodynamic instability, elevated cardiac enzymes), an invasive approach would be pursued.[1]

LONG-TERM THERAPY

Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Direct Renin Inhibitors

CASE 13-3

QUESTION 1: J.S. is a 68-year-old male who presents with an NSTEMI along with signs and symptoms of HF. His past medical history includes hypertension treated with hydrochlorothiazide 25 mg daily and diabetes for which he takes metformin 500 mg twice daily. He has smoked a pack of cigarettes per day for the past 40 years. On admission, his BP was 144/86 mm Hg and his heart rate was 90 beats/minute. His weight is 200.62 pounds (91 kg), with a height of 69 inches (175.26 cm), and a body mass index (BMI) of 29.5 kg/m^2. Laboratory values include the following:

Na^+, 139 mEq/L
K^+, 4.2 mEq/L
Cl^-, 100 mEq/L
CO_2, 20 mEq/L
BUN, 15 mg/dL
SCr, 1.3 mg/dL (creatinine clearance [CrCl] ~60 mL/minute)
Glucose, 130 mg/dL
Hemoglobin A_{1c}, 7.5%
Mg, 2 mEq/L
Troponin I-Ultra, 10 ng/mL (normal, <0.02 ng/mL)

He is administered aspirin 325 mg, prasugrel 60 mg, IV NTG infusion, enoxaparin, and intranasal oxygen. J.S. is immediately sent to the catheterization laboratory where he receives a DES in his left anterior descending artery. After stabilization of his HF symptoms, J.S. is started on oral metoprolol tartrate 25 mg every 6 hours. An echocardiogram is performed before discharge and shows an LVEF of 35%. On the day before discharge, J.S. develops new-onset atrial fibrillation.

Is an ACE inhibitor appropriate for J.S.? When should an ARB be considered?

After an AMI, the heart undergoes processes that initially compensate for the loss of contractile function but may increase the long-term risk for the development of HF. This is referred to as *remodeling* of the ventricle (see Chapter 14, Heart Failure). The increase in the number of survivors of AMI has led to an increase in the number of patients with HF. A number of clinical trials that used ACE inhibitors have demonstrated reductions in HF symptoms and mortality after MI.[5]

For patients with ACS, oral ACE inhibitor therapy should be started within the first 24 hours of presentation for those with an LVEF of ≤40% (even if asymptomatic) or clinical evidence of HF. In addition, ACE inhibitors should also be considered for patients with concomitant hypertension, diabetes, and/or chronic kidney disease.[5] The use of IV ACE inhibitor therapy is not recommended. Owing to its short half-life, captopril could be given early in the hospitalization, beginning with a test dose of 6.25 mg and then titrated as tolerated. Once it is established that the patient can tolerate an ACE inhibitor, he or she can be switched to a once-daily agent such as lisinopril to

simplify the regimen. The BP should be monitored closely, with systolic BP maintained >90 mm Hg. Renal function and serum potassium levels should be monitored closely during the first few months of therapy. Because J.S. presents with clinical symptoms of HF, he is a candidate for an ACE inhibitor. In addition, J.S. has an EF of <40%, hypertension, and diabetes; therefore, the ACE inhibitor should be continued indefinitely (see Table 13-2).

If the patient cannot tolerate an ACE inhibitor because of cough, an ARB may be an alternative. In the *OP*timal *T*herapy *I*n *M*yocardial infarction with the *A*ngiotensin II *A*ntagonist *L*osartan (OPTIMAAL) trial and *VAL*sartan *I*n *A*cute myocardial i*N*farc*T*ion (VALIANT) trial, losartan and valsartan demonstrated reductions that were similar in all-cause mortality compared with captopril.[83,84] Dual therapy of ACE inhibitors with ARBs offers no additional benefits, but increases side effects. At this time, an angiotensin receptor–neprilysin inhibitor (ARNI) is indicated to reduce the risk of cardiovascular death and hospitalization for chronic HF.[85] Current guidelines suggest the use of an ARNI in patients with chronic symptomatic heart failure with reduced ejection fraction (HFrEF) who have tolerated an ACE inhibitor or ARB.[86] Since the publication of the 2017 guidelines, additional clinical studies coupled with clinical experience do support an option to initiate an ARNI de novo; however, patients should be closely monitored for tolerability specifically assessing BP, electrolytes, and renal function as well as occurrence of angioedema.[87]

Aldosterone Antagonists

Case 13-3, Question 2: Should J.S. receive an aldosterone antagonist?

As with angiotensin II, aldosterone plays an important role in LV remodeling. Inhibiting aldosterone directly in addition to ACE inhibitor therapy was first evaluated in patients with HF in the *R*andomized *AL*dactone *E*valuation *S*tudy (RALES) (see Chapter 14, Heart

Failure). Another aldosterone antagonist, eplerenone, is a selective inhibitor of the mineralocorticoid receptor with fewer sexual side effects. In the EPHESUS, patients with AMI and EF <40% receiving optimal medical therapy were randomized to eplerenone or placebo.[37] Significant reductions in mortality (15%), sudden death (13%), and cardiovascular death or hospitalization (21%) were seen with eplerenone compared to placebo.

The ACC/AHA guidelines recommend an aldosterone antagonist in patients with NSTE-ACS or STEMI who are already receiving therapeutic doses of an ACE inhibitor, have an EF <40%, and have either symptomatic HF or diabetes.[1,5] Potential contraindications to the use of an aldosterone antagonist in this setting include significant renal dysfunction (creatinine >2.5 mg/dL in males, >2.0 mg/dL in females, or CrCl <30 mL/minute) or hyperkalemia (potassium > 5 mEq/L).

Because J.S. has symptomatic HF with an EF <40% and diabetes, he is a candidate for an aldosterone antagonist. Serum potassium and renal function need to be checked in 2 to 3 days and 1 week after therapy initiation, then every month for the first 3 months. ACE inhibitor and potassium supplement doses may need to be adjusted.[86,87]

a-Blockers

Case 13-3, Question 3: Should J.S. receive a β-blocker on discharge?

The ACC/AHA guidelines recommend continued β-blocker therapy at discharge for all patients after ACS.[1,5] The benefits of β-blockers in reducing reinfarction and mortality outweigh the risk, even in patients with stable bronchospastic disease, depression, insulin-dependent diabetes, severe peripheral vascular disease, first-degree heart block, and moderate LV dysfunction. Metoprolol succinate, carvedilol, and bisoprolol are considered first-line choices in patients with HF, whereas selective β_1-blockers should be considered in

patients with chronic obstructive pulmonary disease (COPD). For patients with asthma, selective β_1-blockers may be considered once the relative risks and benefits are considered. Being discharged on a β-blocker is a quality performance measure.[88] However, debate exists surrounding the duration of use, especially in low-risk patients without compelling indications.[89–92] Data suggest that the benefits from β-blockers emerge early following an AMI and are maintained out to 1 year. Although the exact duration of benefit is unknown, high-risk patients (eg, GRACE score ≥121 and diuretic use) are likely to continue to derive benefit for up to 3 years. The 2011 AHA/ACCF (American College of Cardiology Foundation) secondary prevention guidelines recommend a 3-year treatment course for patients with normal LV function, with an option to continue indefinitely as long as the medication is well tolerated. Because J.S. has a low EF, he should be transitioned from oral metoprolol tartrate to metoprolol succinate, carvedilol, or bisoprolol, which should be continued indefinitely.

Sodium–Glucose-Linked Cotransporter-2 Inhibitors

Case 13-3, Question 4: Should J.S. be started on a sodium–glucose- linked cotransporter-2 (SGLT2) inhibitor?

SGLT2 inhibitors not only lower plasma glucose concentrations through increased urinary glucose excretion, but they also mediate osmotic diuresis and natriuresis to lower preload, pulmonary congestion, and edema. In addition, SGLT2 inhibitors exert pleiotropic effects and provide direct cardioprotective and nephroprotective effects by reducing inflammation, oxidative stress, and fibrosis.[93] Given that J.S. has underlying diabetes with new evidence of HF, the 2022 Standards of Medical Care in Diabetes would recommend use of an SGLT2 inhibitor (eg, empagliflozin, canagliflozin, dapagliflozin) in addition to metformin.[94] Clinical trials

have demonstrated a reduction in the risk of cardiovascular death and/or major cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. In addition, evidence also suggests robust effects on reducing the risk of hospitalization for HF.[95–97] Most recently, SGLT2 inhibitors have an emerging role in HF care in patients without diabetes.[98,99] Dapagliflozin and empagliflozin have an approved indication for HF.

Given a recent A_{1c} of 7.5% and new evidence of HF, J.S. should be started on an SGLT2 inhibitor. Upon initiation, the diuretic dose many need to be adjusted depending on clinical status with close monitoring to assess renal function and volume status.

Lipid-Lowering Agents

Case 13-3, Question 5: Should J.S. be started on a lipid-lowering agent? If so, which one? When should it be initiated?

A complete fasting lipid profile would be helpful and should be completed within 24 hours of presenting with an AMI.[1,5] This is often overlooked or not done because the patient is not fasting. Most patients will require a low-cholesterol, low-saturated fat diet in addition to lipid-lowering therapy. The ACC/AHA STEMI and NSTE-ACS guidelines recommend that a high-intensity statin be initiated or continued in all patients with ACS unless contraindications are present.[1,5] This would consist of atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily.[35] When triglycerides are 500 mg/dL or more, drug therapy with niacin or a fibrate is beneficial.[92]

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial evaluated patients with NSTE-ACS receiving atorvastatin 80 mg/day or placebo within 24 to 96 hours of hospitalization. A significantly lower rate of death and nonfatal major cardiac events at 4-month follow-up was seen in patients receiving atorvastatin.[100] In the *PR*avastatin *O*r Ator*V*astatin *E*valuation and *I*nfection *T*herapy (PROVE IT)-TIMI 22 trial, patients with ACS who

received atorvastatin 80 mg/day for 10 days exhibited a significantly lower risk of death, MI, UA hospitalization, stroke, and revascularization when compared with those on pravastatin 40 mg/day.[100] The A to Z trial showed a favorable trend toward major cardiovascular event reduction in patients with AMI receiving an intensive simvastatin regimen (40 mg/day for 1 month followed by 80 mg/day thereafter) when initiated within 12 hours of stabilization compared to a less intensive regimen (placebo for 4 months followed by simvastatin 20 mg/day).[101] However, based on clinical trials, observational studies, adverse event reports, and prescription use data, simvastatin 80 mg may be associated with increased muscle injury (refer to Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease).[35]

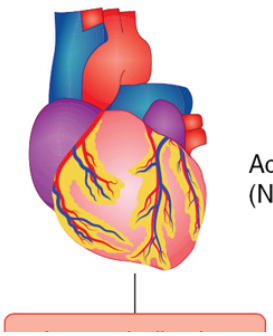
In the case of J.S., he should receive a high-intensity statin within 24 hours of his hospitalization and be discharged on a statin regardless of LDL cholesterol. This is a quality core performance measure.[88] Drug interactions, patient tolerability, and affordability should be considered. Currently, the goal LDL for patients with ACS remains controversial. The ACC/AHA guidelines do not recommend a specific goal LDL.[1,5,35] However, the National Lipid Association does recommend a goal LDL <70 mg/dL in patients with ACS.[102] For J.S., it would be reasonable to begin atorvastatin 80 mg daily and obtain an LDL reduction of ≥50%.

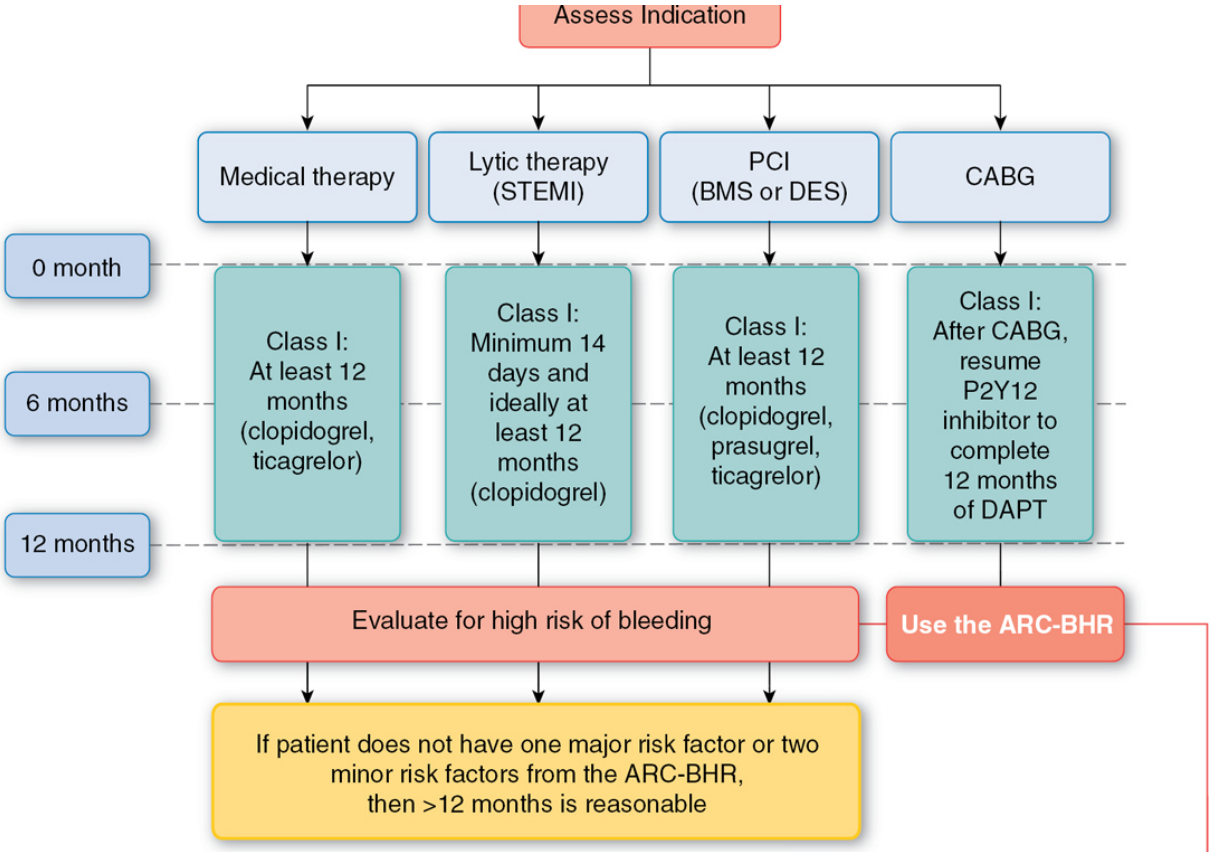
Antiplatelet Therapy

Case 13-3, Question 6: How long should J.S. continue his aspirin and prasugrel?

Antiplatelet therapy with aspirin should be lifelong for J.S. because of aspirin's beneficial effects on reinfarction. There appears to be no difference in efficacy for a wide range of aspirin doses (75–1500 mg/day), although higher doses may increase the incidence of side effects. The ACC/AHA guidelines recommend a dose of 81 to 325 mg daily indefinitely, with a preferred maintenance dose of 81 mg

daily.[1,5,103] DAPT with clopidogrel or ticagrelor, or prasugrel and with aspirin, compared with aspirin alone, reduces major cardiovascular events in patients with established ischemic heart disease.[103–105] The use of DAPT with a $P2Y_{12}$ inhibitor for patients who have undergone coronary stenting reduces the risk of future stent thrombosis.[1,5,103] In patients with ACS, the 2016 ACC/AHA guidelines recommend that, ideally, the $P2Y_{12}$ inhibitor should be continued for at least 1 year regardless of the type of coronary stent (**Fig. 13-6**).[106] Nonetheless, the duration of DAPT following PCI continues to evolve. Several randomized clinical trials have studied varying durations of DAPT to identify optimal therapy duration (**Table 13-5**). In a pooled analysis of 33,051 patients with either ACS or stable CAD undergoing PCI and received a newer generation DES, Britl et al found that compared with 3 to 6 months of DAPT, 12 months of DAPT was associated with no difference in all-cause mortality, major hemorrhage, or stent thrombosis.[107] Compared with 6 to 12 months of DAPT, 18 to 48 months of DAPT was associated with no difference in all-cause mortality but was associated with lower rates of MI and stent thrombosis. However, compared with 6 to 12 months of DAPT, 18 to 48 months was also associated with increased major bleeding. Prolonged DAPT of 18 to 48 months was associated with three fewer stent thromboses, six fewer MIs, and five more major bleeding episodes per 1000 patients. Based on these data, early discontinuation of antiplatelet therapy may be considered after 6 months if bleeding risk is high and antiplatelet therapy should be continued for >12 months if bleeding risk is low.[107] Academic Research Consortium Major and Minor-High Bleeding Risk (ARC-HBR) Criterion (**Fig. 13-6**).[12]





Academic Research Consortium Major and Minor Criterion for High Bleeding Risk (ARC-BHR)

Major	Minor
Anticipated long term use of anticoagulation	Long term use of oral NSAIDs and/or steroids
Severe or end-stage CKD (eGFR <30 mL/minute)	Moderate CKD (eGFR 30–59 mL/minute)
Hemoglobin <11 g/dL	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time if recurrent	Spontaneous bleeding requiring hospitalization or transfusion in the past 12 months not meeting major criterion
Moderate or severe baseline thrombocytopenia (platelet count <100 × 10^9/L)	Age ≥75 years
Chronic bleeding diathesis	Any ischemic stroke at any time not meeting major criterion
Liver cirrhosis with portal hypertension	
Active malignancy (excluding nonmelanoma skin cancer) within the past 12 months	
Previous spontaneous intracranial hemorrhage	
Previous traumatic intracranial hemorrhage within the past 12 months	
Presence of brain AVM	
Moderate or severe ischemic stroke (NIHSS score ≥5) in past 6 months	
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 days before PCI	

Figure 13-6 Treatment algorithm for duration of $P2Y_{12}$ inhibitor therapy in patients with ACS with DAPT. ARC-HBR, Academic Research Consortium Major and Minor Criterion for High Bleeding Risk; ACS, acute coronary syndrome; AVM, arteriovenous malformation; BMS, bare-metal stent; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; lytic, fibrinolytic therapy; eGFR, estimated glomerular filtration rate; NSAIDS, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-elevation acute coronary syndrome; NSTEMI, non–ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction. (From Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134:e123-e155; Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2021;42:1289–1397.)

Table 13-5
Summary of Major Trials Evaluating Length of DAPT Therapy

and Outcomes

Trial (Year)	DAPT Treatment Strategy	DAPT Duration (months)	N/ACS (%)	Trial Design	Primary End Point	Primary End Point Result/Major Bleeding
Standard, Extended, or No PY_{12} Inhibitor						
RESET (2012)	Clopidogrel + ASA	3 vs 12	2117 (55)	Open-label noninferiority	Cardiac death, MI, ST, revascularization, or bleeding at 1 year	4.7% vs 4.7% (P_{NI} <.001) 0.2% vs 0.6 % (P = .16)
OPTIMIZE (2013)	Clopidogrel + ASA	3 vs 12	3119 (32)	Single-blind, noninferiority	All-cause death, MI, stroke, or bleeding at 1 year	6.0% vs 5.8% (P_{NI} = .002) 0.6% vs 0.9% (P = .41)
REDUCE (2019)	Prasugrel (10.4%), ticagrelor (49.8%), or clopidogrel (40.8%) + ASA	3 vs 12	1496 (100)	Open-label, noninferiority	All-cause death, MI, ST , stroke, TVR, or bleeding at 1 year	8.2% vs 8.4% (P_{NI} < .001) 3.3% vs 4.0%, (P = .46)
EXCELLENT (2012)	Clopidogrel + ASA	6 vs 12	1443 (51)	Open-label, noninferiority	Cardiac death, MI, or ischemia-driven TVR at 1 year	4.8% vs 4.3% (P_{NI} = .001) 0.3% vs 0.6% (P = .42)
ISAR-SAFE (2015)	Clopidogrel + ASA	6 vs 12	4000 (40)	Double-blind, noninferiority	All-cause death, MI, ST, stroke, and TIMI major bleeding at 9 months	1.5% vs 1.6% (P_{NI} <.001) 0.2% vs 0.3% (P = .64)
I-LOVE-IT-2 (2016)	Clopidogrel +ASA	6 vs 12	1829 (85)	Single-blind, noninferiority	Cardiac death, target vessel MI or clinically indicated TLR at 1 year	6.8% vs 5.9% (P_{NI} = .0065) 1.3% vs 0.8% (p = .17)
IVSU-XPL (2016)	Clopidogrel + ASA	6 vs 12	1400 (49)	Open-label, superiority	Cardiac death, MI, stroke, or TIMI major bleeding at 1 year	2.1% vs 2.2% (P = .85) 0.7% vs 1.0% (P = .56)
OPTIMA-C (2018)	Clopidogrel + ASA	6 vs 12	1368 (50)	Open-label, noninferiority	Cardiac death, MI, ischemia-driven TVR at 1 year	1.2% vs 0.6%, (P_{NI} = .05)
DAPT STEMI (2018)	Prasugrel (29%), ticagrelor (29%), or clopidogrel (42%) + ASA	6 vs 12	870 (100)	Single-blind, noninferiority	All-cause mortality, revascularization, MI, stroke, and TIMI major bleeding at 18 months	4.8% vs 6.6% (P_{NI} = .004) 3.2% vs 4.3% (P = .40)
SMART-DATE (2018)	Clopidogrel + ASA	6 vs 12	2172 (100)	Single-blind, noninferiority	All-cause death, MI, or stroke at 18 months	4.7% vs 4.2% (P_{NI} = .03) 0.5% vs 0.8% (P = .33)
NIPPON (2017)	Clopidogrel (97.1%) or ticlopidine (2.7%) or prasugrel (0.2%) + ASA	6 vs 18	3773 (33)	Open-label, noninferiority	All-cause death, MI, stroke, and major bleeding at 18 months	2.1% vs 1.5% (P_{NI} < .05) 0.7% vs 0.7% (P = .99)
PRODIGY (2012)	Clopidogrel + ASA	6 vs 24	1970 (75)	Open-label, superiority	All-cause death, MI, or stroke at 2 years	10.0% vs 10.1% (P = .91) 0.6% vs 1.5% (P = .041)
ITALIC (2017)	Clopidogrel + ASA	6 vs 24	1850 (44)	Open-label, noninferiority	All-cause death, MI, urgent TVR, stroke, or major bleeding at 1 year	1.6% vs 1.5% (P_{NI} = .0002) 0.0% vs 0.4% (P = N/A)
ARTIC-Interruption (2014)	Clopidogrel (91%) or prasugrel (9%) + ASA	12 vs 18–30	1259 (26)	Open-label, superiority	All-cause death, MI, ST, stroke, or urgent revascularization at 18 months	0.4% vs 0.4% (P = .58) 0.5% vs 1% (P = .07)
DAPT (2014)	Clopidogrel (65%) or prasugrel (35%) + ASA	12 vs 30	9961 (43)	Double-blind, superiority	All-cause death, MI, or stroke at 30 months	5.9% vs 4.3% (P <.001) 1.6% vs 2.5% (P = .001)
DES LATE (2014)	Clopidogrel + ASA	12 vs 36	5045 (61)	Open-label, superiority	Cardiac death, MI, or stroke at 2 years	2.6% vs 2.4% (P = .75) 1.4% vs 1.1% (P = .20)
OPTIDUAL (2015)	Clopidogrel + ASA	12 vs 48	1385 (36)	Open-label, superiority	All-cause death, MI, stroke, or major bleeding at 3 years	7.5% vs 5.8% (P = .17) 2.0% vs 2.0% (P = .95)
PEGASUS TIMI 54 (2016)	Ticagrelor + ASA	0 vs 33	21,162 (100)	Double-blind, superiority	Cardiac death, MI, or stroke at 3 years	7.8% vs 9.0% (P = .001) 2.6% vs 1.1% (P < .001)
Aspirin Discontinuation						
Trial	**DAPT Treatment Strategy**	**ASA duration**	**N/ACS (%)**	**Trial Design**	**Primary End Point**	**Primary End Point Result/Major Bleeding**
GLOBAL LEADERS (2018)	DAPT (ticagrelor/ASA) for 1 month, followed by ticagrelor for 23 months vs DAPT (clopidogrel/ASA for stable coronary disease or aspirin/ticagrelor for unstable coronary disease) for 12 months, followed by ASA for 12 months	1 vs 12	15,968 (47)	Open-label, superiority	All-cause death or new Q-wave MI at 2 years	3.8% vs 4.4% (P = .07) 2.0% vs 2.1% (P = .77)
STOPDAPT-2 (2019)	DAPT (clopidogrel + ASA) for 1 month followed by clopidogrel monotherapy for 11 vs 12 months of DAPT	1 vs 12	3045 (38)	Open-label, noninferiority	Cardiac death, MI, stroke, ST, and TIMI major or minor bleeding at 1 year	2.4% vs 3.7% (P_{NI} < .001) 0.4% vs 1.5% (P = .004)
SMART-CHOICE (2019)	DAPT for 3 months followed by $P2Y_{12}$ inhibitor for 9 months vs DAPT for 12 months	3 vs 12	2993 (58)	Open-label, noninferiority	All-cause death, MI, or stroke at 1 year	2.9% vs 2.5% (P_{NI} = .007) 2.0% vs 3.4% (P = .02)
TICO (2020)	DAPT (ticagrelor + ASA) for 3 months followed by ticagrelor for 9 months vs DAPT for 12 months	3 vs 12	3056 (100)	Open-label, superiority	All-cause death, MI, ST, stroke, TVR, or TIMI major bleeding at 1 year	3.9% vs 5.9% (P = .01) 1.7% vs 3.0% (P = .02)
TWILIGHT (2019)	DAPT (ticagrelor + ASA) for 3 months followed by ticagrelor for 9 months vs DAPT for 12 months	3 vs 12	7119 (65%)	Open-label, superiority	BARC type 2, 3, or 5 bleeding at 1 year	4.0% vs 7.1% (P < .001)

ACS, acute coronary syndrome; ASA, aspirin; ARTIC-Interruption, assessment by a double randomisation of a conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and, of Treatment Interruption versus Continuation 1 year after stenting; BARC, Bleeding Academic Research

Consortium; DAPT STEMI, six versus twelve months of dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction; DAPT, dual antiplatelet therapy; DES LATE, optimal duration of clopidogrel therapy with DES to reduce late coronary arterial thrombotic event; EXCELLENT, Efficacy of xience/promus versus cypher to reduce late loss after stenting; GLOBAL LEADERS, long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation; I-LOVE-IT-2, evaluate safety and effectiveness of the tivoli DES and the firebird DES for treatment of coronary revascularization; ISAR-SAFE, Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC, is there a life for drug-eluting stents after discontinuation of clopidogrel; IVSU-XPL, Impact of IntraVascular UltraSound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MI, myocardial infarction; NIPPON, nobori dual antiplatelet therapy as appropriate duration; OPTIDUAL, optimal duration of dual antiplatelet therapy after drug-eluting stent implantation; OPTIMA-C, optimal duration of clopidogrel in second-generation drug-eluting stents; OPTIMIZE, Optimized duration of clopidogrel therapy following treatment with the endeavor zotarolimus-eluting stent in real-world clinical practice; PEGASUS TIMI 54, prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin–thrombolysis in myocardial infarction 54; PCI, percutaneous coronary intervention; PODIGY, prolonging dual antiplatelet treatment after grading stent-induced intimal hyperplasia; RCT, randomized control trial; REDUCE, Randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent; RESET, REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SMART-CHOICE, smart angioplasty research team: comparison between P2Y12 antagonist monotherapy versus dual antiplatelet therapy in patients undergoing implantation of coronary drug-eluting stents; SMART-DATE, smart angioplasty research team-safety of 6-month duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome; ST, stent thrombosis; STOPDAPT-2, ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2; TICO, ticagrelor monotherapy after 3 months in the patients treated with new generation sirolimus-eluting stent for acute coronary syndrome; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; TWILIGHT, ticagrelor with aspirin or alone in high-risk patients after coronary intervention.

Among patients treated with DAPT after PCI, recent trials have tested whether stopping aspirin instead of the $P2Y_{12}$ inhibitor improved outcomes (**Table 13-5**). A meta-analysis of the major randomized trials studying $P2Y_{12}$ inhibitor monotherapy after a short-term DAPT of 1 to 3 months demonstrated that this strategy was

associated with a 40% reduction in major bleeding ($P < .01$) without an associated increase in MACE, MI, or death compared with standard 12 months of DAPT.[108] These findings were consistent in the subset of patients who underwent PCI for ACS. Based on these trials, discontinuing aspirin after DAPT and continuing only the $P2Y_{12}$ inhibitor may be associated with better outcomes in patients with ACS.

Data from the DAPT trial found that DAPT with clopidogrel or prasugrel continued for 30 months after placement of a DES significantly reduced the risk of stent thrombosis and MACE compared with 12 months of therapy but were associated with an increased risk of bleeding.[109]

Because J.S. underwent PCI following his NSTEMI and received a coronary stent, a conservative approach would be to continue his aspirin 81 mg daily indefinitely. He should continue prasugrel 10 mg daily for at least 1 year. Aspirin should be prescribed at hospital discharge because it is a quality performance measure.[88] Based on the ARC-HBR criterion, J.S. does not have a high risk of bleeding; thus, based on clinical judgment and thrombosis risk, he could continue prasugrel for up to 48 months.

Oral Anticoagulation

Case 13-3, Question 7: Given the development in new-onset atrial fibrillation, is oral anticoagulation indicated for J.S. at this time?

Certain patients, particularly those with atrial fibrillation at increased risk for stroke, may have a need to add oral anticoagulation to DAPT. Data suggest that ~10% of patients with recent PCI have concomitant atrial fibrillation and up to 2% to 22% of patients may develop atrial fibrillation following an AMI.[110] Similarly, venous thromboembolism or development of an LV thrombus may warrant an indication for triple therapy (eg, aspirin, a $P2Y_{12}$ inhibitor, and oral anticoagulation). Given the significant concern for bleeding

with a two- to threefold increased risk for patients on triple therapy, clinical judgment is needed to decide whether the benefit is likely to exceed the risk.

Direct oral anticoagulants (DOACs; eg, apixaban, rivaroxaban, dabigatran, edoxaban) are typically recommended first line for patients with atrial fibrillation and venous thromboembolism, whereas warfarin is preferred for valvular heart disease. In patients with ACS and a need for oral anticoagulation, the ACC expert consensus pathway recommends DOACs in preference over warfarin because of lower risk of bleeding, simplified dosing, rapid onset of action, and lack of bridging. Furthermore, careful selection of the most appropriate $P2Y_{12}$ inhibitor is important and preference for clopidogrel should be considered.[110] Prasugrel and ticagrelor can produce a greater degree of platelet inhibition than clopidogrel and are associated with greater rates of bleeding. If a newer agent is warranted, ticagrelor would be favored over prasugrel.[110] For patients on warfarin, consideration can be given to targeting a goal international normalized ratio (INR) of 2.0 to 2.5 for those patients whose usual goal INR is between 2.0 to 3.0; however, no prospective studies have demonstrated that a target INR of 2.0 to 2.5 reduces bleeding complications.[1,5] Current ACC/AHA guidelines for the management of atrial fibrillation recommend that if triple therapy is used, the duration should be limited with consideration for discontinuation of aspirin after 4 to 6 weeks to minimize the risk of bleeding.[111] In the *W*hat is the *O*ptimal antiplat*E*let and anticoagulant therapy in patients with oral anticoagulation and coronary *S*ten*T*ing (WOEST) trial, use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in thrombotic events compared to clopidogrel with aspirin in patients undergoing PCI who were receiving oral anticoagulation.[112] Caution is required when using these agents in patients who require an anticoagulant or who are at significantly increased risk for bleeding.[1]

In the case of J.S., owing to a new diagnosis of atrial fibrillation, an assessment of thromboembolic and bleeding risk would be warranted. With a CHA_2DS_2-VASc (Congestive heart failure,

Hypertension, Age ≥75 years [doubled], Diabetes mellitus, prior Stroke or TIA or thromboembolism [doubled], Vascular disease, Age 65 to 74 years, Sex category) score of 5 and a HAS-BLED (*H*ypertension, *A*bnormal renal or liver function, *S*troke, *B*leeding, *L*abile INR, *E*lderly, *D*rugs and alcohol) score of 3, oral anticoagulation would be warranted, but caution should be exercised because of bleeding risk (see Chapter 15, Cardiac Arrhythmias). A DOAC, such as apixaban 5 mg bid, dabigatran 150 mg bid, edoxaban 60 mg/day, or rivaroxaban 20 mg/day, would be preferred. Given the risk of stent-related complications early on, consider discontinuation of aspirin after 30 days. After 12 months, the $P2Y_{12}$ inhibitor can be stopped and replaced with low-dose aspirin 81 mg/day. It would also be reasonable to consider clopidogrel instead of prasugrel in J.S.

Proton-Pump Inhibitors

Case 13-3, Question 8: Should J.S. receive a proton-pump inhibitor (PPI)?

The ACC/AHA/American College of Gastroenterology recommends using a PPI in patients receiving DAPT who have multiple risk factors for gastrointestinal bleeding such as advanced age; concomitant use of warfarin, steroids, or NSAIDs; or *Helicobacter pylori* infection.[113] The ACC expert consensus decision pathway recommends a PPI or histamine H_2 receptor antagonist in patients on two or more antithrombotic agents to minimize gastrointestinal bleeding. Once the patient is on just one antithrombotic agent, it is important to discontinue these agents to minimize long-term risks and complications specifically associated with PPI use.[110] Because omeprazole and esomeprazole are known to inhibit the isoenzyme 2C19, the FDA recommends against the use of these with clopidogrel because of the possible reduced effectiveness of clopidogrel.[1,114]

Case 13-3, Question 9: How would you summarize the long-term therapy needed by J.S. on discharge?

Appropriate discharge medications for J.S. include a β-blocker, ACE inhibitor, aldosterone antagonist, high-intensity statin, SGLT2 inhibitor, aspirin 81 mg/day, $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor), PPI (or histamine H_2 receptor antagonist), and a DOAC. He also should receive a prescription for SL NTG to carry with him for use PRN. Many of these important discharge medications are specified by the Joint Commission as national performance and quality measures for AMI. This specifically includes statin, β-blocker, aspirin, and ACE inhibitor (or ARB) and aldosterone antagonist for LVEF <40% prescribed at discharge.[35] Continuation of the $P2Y_{12}$ inhibitor beyond 1 year may be considered after careful assessment of the patient's ischemic and bleeding risk. His previous hydrochlorothiazide may be discontinued because his hypertension will likely be controlled with the β-blocker, ACE inhibitor, and aldosterone antagonist. His metformin should be continued and an SGLT2 inhibitor added, with close monitoring of blood glucose. Because J.S. will have several new medications, he will need education regarding his medications before discharge to optimize medication adherence.

LIFESTYLE MODIFICATIONS

Case 13-3, Question 10: What types of lifestyle modifications should J.S. be encouraged to pursue to reduce his risk factors?

J.S. must be encouraged to stop smoking; this may be the most important change he can make (see Chapter 91, Tobacco Use and Dependence).[115] For weight management, an initial goal weight loss should be to reduce body weight by ~10% from baseline if BMI

exceeds 25 kg/m^2.[92] Other dietary modifications should be implemented so that J.S. can maintain a hemoglobin A_{1c} <7.0% and achieve a BP goal of <140/90 mm Hg (or possibly lower) because J.S. has diabetes, and a serum LDL <100 mg/dL.[92,116,117,118] (See Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease; Chapter 9, Essential Hypertension; and Chapter 12, Chronic Stable Angina, for further information on antihypertensive and lipid-lowering drugs, as well as diet therapy.)

SUMMARY

Although mortality and incidence rates for ACS appear to be on the decline, ACS still remains a major cause of morbidity and mortality in the United States. The use of PCI has significantly improved the survival of patients with STEMI. The major risk associated with thrombolysis is bleeding, especially intracerebral hemorrhage. Another problem associated with fibrinolytic therapy is reocclusion of the artery that was initially opened. PCI is more effective than is fibrinolytic therapy; however, it is available only in hospitals with experienced invasive cardiologists, thereby limiting its availability to some patients.

Aspirin should be given to all patients with ACS unless there is a contraindication. β-Blockers and statins should be administered as well. $P2Y_{12}$ inhibitors are recommended with aspirin in all patients with ACS with or without stenting. ACE inhibitors, ARBs, and aldosterone antagonists have been shown to be beneficial in patients who have LV dysfunction (LVEF <40%) and are also recommended for secondary prevention. More recently, SGLT2 inhibitors have been shown to convey cardiovascular benefit and may be considered in patients who have diabetes and/or LV dysfunction (LVEF <40%). Nitrates are useful, but care must be taken to maintain an adequate perfusion pressure. Secondary

prevention emphasizing a healthy lifestyle and aggressive lipid lowering are important components to the overall treatment plan.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010;24:2619–2633. (113)

Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228. (1)

Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2021;42:1289–1397. (12)

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;139:e1082–e1143. (36)

Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: a report of

the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77:629–658. (110)

Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134:e123–e155. (106)

O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425. (5)

Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation.* 2011;124:2458–2473. (92)

Wilson PWF, Jacobson TA, Martin SS, et al. Lipid measurements in the management of cardiovascular diseases: practical recommendations a scientific statement from the National Lipid Association writing group. *J Clin Lipidol*. 2021;15:629–648. (102)

Key Websites

American College of Cardiology. Guidelines and clinical documents. https://www.acc.org/guidelines

American Heart Association. Guidelines & statements. https://professional.heart.org/en/guidelines-and-statements

CRUSADE Score Calculator. https://www.mdcalc.com/crusade-score-post-mi-bleeding-risk

DAPT Risk Calculator. https://tools.acc.org/daptriskapp/#!/content/calculator/

GRACE Model. https://www.mdcalc.com/grace-acs-risk-mortality-calculator

HEART Score Calculator. https://www.mdcalc.com/heart-score-major-cardiac-events

TIMI Risk Score for NSTEMI. http://www.mdcalc.com/timi-risk-score-for-uanstemi

TIMI Risk Score for STEMI. http://www.mdcalc.com/timi-risk-score-for-stemi

COMPLETE REFERENCES CHAPTER 13 ACUTE CORONARY SYNDROME

1. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64(24):e139–e228.
2. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 Guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50(7):e1–e157.
3. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 Guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2008;51(2):210–247.
4. Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI Guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2009;54(23):2205–2241.
5. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362–e425.
6. Virani SS, Alonso AA, Aparicio HJ, et al. Heart disease and stroke statistics —2021 update. *Circulation*. 2021;143(8):e254–e743.
7. Krumholz HM, Normand ST, Wang Y. Twenty-year trends in outcomes for older adults with acute myocardial infarction in the United States. *JAMA Netw Open*. 2019;2(3):e191938.
8. Dieleman JL, Cao J, Chapin A, et al. US health care spending by payer and health condition, 1996–2016. *JAMA*. 2020;323(9):863–884.

9. Riccioni G, Sblendorio V. Atherosclerosis: from biology to pharmacological treatment. *J Geriatr Cardiol*. 2012;9(3):305–317.
10. Dubin D. Infarction. In: Dubin D, ed. *Rapid Interpretation of EKGs*. 6th ed. COVER Publishing Co; 2000:290.
11. Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol*. 2017;70(8):996–1012.
12. Collet J, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289–1367.
13. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction. *Circulation*. 2000;102:2031–2037.
14. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J*. 2008;16(6);191–196.
15. Mejia LAH, Betances AF, Nimmagadda M, et al. Comparison of HEART, TIMI and GRACE scores in predicting major adverse cardiac events within 120 days in patients presenting to the emergency department with chest pain in a community health system. *J Am Coll Cardiol*. 2020;75(11 suppl 1):195.
16. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines) bleeding score. *Circulation*. 2009;119:1873–1882.
17. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749.
18. Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med*. 2005;352(25):2581–2588.
19. Burchfield JS, Xie M, Hill JA. Pathological ventricular remodeling: mechanisms: part 1 of 2. *Circulation*. 2013;128(4):388–400.
20. Xie M, Burchfield JS, Hill JA. Pathological ventricular remodeling: therapies: part 2 of 2. *Circulation*. 2013;128(9):1021–1030.
21. Gonzalez PE, Omar W, Patel KV, et al. *Circ Cardiovasc Interv*. 2020;13(6):e009622.
22. Hilleman DE, Tsikouris JP, Seals AA, Marmur JD. Fibrinolytic agents for the management of ST-segment elevation myocardial infarction. *Pharmacotherapy*. 2007;27(11):1558–1570.
23. Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part II. *Mayo Clinic Proc*. 2009;84(11):1021–1036.
24. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med*. 1985;312(14):932–936.

25. Cannon CP, Battler A, Brindis RG, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). *J Am Coll Cardiol*. 2001;38(7):2114–2130.
26. Jang IK, Gold HK, Ziskind AA, et al. Differential sensitivity of erythrocyte-rich and platelet-rich arterial thrombi to lysis with recombinant tissue-type plasminogen activator. A possible explanation for resistance to coronary thrombolysis. *Circulation*. 1989;79(4):920–928.
27. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation*. 1994;89(4):1545–1556.
28. Huxtable LM, Tafreshi MJ, Rakkar AN. Frequency and management of thrombocytopenia with the glycoprotein IIb/IIIa receptor antagonists. *Am J Cardiol*. 2006;97(3):426–429.
29. Kengreal (cangrelor). Package insert. The Medicines Company; 2015.
30. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303–1313.
31. Cohoon KP, Heit JA. Should platelet function testing guide antiplatelet therapy for patients with coronary artery stenting or acute coronary syndromes? *Clin Chem*. 2013;59(9):1299–1300.
32. Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med*. 2012;366(15):1404–1413.
33. Holt A, Blanche P, Zareini B, et al. Effect of long-term beta-blocker treatment following myocardial infarction among stable, optimally treated patients without heart failure in the reperfusion era: a Danish, nationwide cohort study. *Eur Heart J*. 2021;42(9):907–914.
34. Waters DD, Ku I. Early statin therapy in acute coronary syndromes: the successful cycle of evidence, guidelines, and implementation. *J Am Coll Cardiol*. 2009;54(15):1434–1437.
35. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889–2934.
36. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guideline. *Circulation*. 2019;139:e1082–e1143.

37. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309–1321.
38. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II—DAVIT II). *Am J Cardiol*. 1990;66(10):779–785.
39. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med*. 1988;319(7):385–392.
40. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359(23):2417–2428.
41. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292(18):2217–2225.
42. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J*. 2005;149(6):1043–1049.
43. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med*. 1992;327(4):227–233.
44. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med*. 1989;321(6):406–412.
45. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58(24):e44–e122.
46. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000;283(22):2941–2947.
47. Balci B. The modification of serum lipids after acute coronary syndrome and importance in clinical practice. *Curr Cardiol Rev*. 2011;7(4):272–276.
48. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368(15):1379–1387.
49. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med*. 1997;337(16):1118–1123.

50. Van De Werf F, Adgey J, Ardissino D, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet*. 1999;354(9180):716–722.
51. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet*. 1988;2(8607):349–360.
52. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1607–1621.
53. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005;352(12):1179–1189.
54. Gibson CM, Murphy SA, Pride YB, et al. Effects of pretreatment with clopidogrel on nonemergent percutaneous coronary intervention after fibrinolytic administration for ST-segment elevation myocardial infarction: a Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 study. *Am Heart J*. 2008;155(1):133–139.
55. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). *Am Heart J*. 2005;149(2):217–226.
56. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006;295(13):1519–1530.
57. Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 Investigators. *Circulation*. 1999;99(21):2720–2732.
58. Topol EJ, GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet*. 2001;357(9272):1905–1914.
59. Brener SJ, Zeymer U, Adgey AA, et al. Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial. *J Am Coll Cardiol*. 2002;39(3):377–386.
60. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358(9282):605–613.

61. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA*. 2005;293(14):1759–1765.
62. Peters RJ, Joyner C, Bassand JP, et al. The role of fondaparinux as an adjunct to thrombolytic therapy in acute myocardial infarction: a subgroup analysis of the OASIS-6 trial. *Eur Heart J*. 2008;29(3):324–331.
63. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol*. 2007;49(4):422–430.
64. Gershlick AH, Stephens-Lloyd A, Hughes S, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med*. 2005;353(26):2758–2768.
65. Mehta RH, Granger CB, Alexander KP, Bossone E, White HD, Sketch MH Jr. Reperfusion strategies for acute myocardial infarction in the elderly: benefits and risks. *J Am Coll Cardiol*. 2005;45(4):471–478.
66. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357(9266):1385–1390.
67. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1622–1632.
68. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation*. 1999;100(15):1602–1608.
69. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA.* 2004;292(1):45–54.
70. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation*. 1999;100(15):1593–1601.
71. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354(14):1464–1476.
72. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355(21):2203–2216.
73. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet*. 2014;384(9957):1849–1858.

74. Mehta SR, Yusuf S, Clopidogrel in Unstable angina to prevent Recurrent Events Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J*. 2000;21(24):2033–2041.
75. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527–533.
76. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA*. 2005;294(10):1224–1232.
77. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009;373(9665):723–731.
78. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet*. 2008;371(9621):1353–1363.
79. Effient (prasugrel). Package insert. Eli Lilly and Company; 2015.
80. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–1057.
81. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2011;124(5):544–554.
82. Brilinta (ticagrelor). Package insert. AstraZeneca; 2015.
83. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349(20):1893–1906.
84. Dickstein K, Kjekshus J, OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet*. 2002;360(9335):752–760.
85. Entresto (sacubitril/valsartan). Package insert. Novartis; 2021.
86. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association

Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161.

87. Maddox TM, Januzzi JL, Allen LA, et al. 2021 update to the 2017 ACC expert concensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77(6):772–810.
88. Jneid H, Addison D, Bhatt DL, et al. 2017 AHA/ACC clinical performance and quality measures for adults with ST-elevation and non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2017;10:e000032.
89. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. *Am J Med*. 2014;127(10):939–953.
90. Nakatani D, Sakata Y, Suna S, et al. Impact of beta blockade therapy on long-term mortality after ST-segment elevation acute myocardial infarction in the percutaneous coronary intervention era. *Am J Cardiol*. 2013;111(4):457–464.
91. Park KL, Goldberg RJ, Anderson FA, et al. Beta-blocker use in ST-segment elevation myocardial infarction in the reperfusion era (GRACE). *Am J Med*. 2014;127(6):503–511.
92. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124(22):2458–2473.
93. Zelniker J, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC State-of-the-Art review. *J Am Coll Cardiol*. 2020;75(4):422–434.
94. American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes. *Diabetes Care.* 2022;45(suppl 1):S125–S143.
95. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
96. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal event sin type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
97. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357.
98. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

99. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.
100. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285(13):1711–1718.
101. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292(11):1307–1316.
102. Wilson PWF, Jacobson TA, Martin SS, et al. Lipid measurements in the management of cardiovascular diseases: practical recommendations a scientific statement from the national lipid association writing group. *J Clin Lipidol*. 2021;15:629–648.
103. Kamran H, Jneid H, Kayani WT, et al. Oral antiplatelet therapy after acute coronary syndrome: a review. *JAMA*. 2021;325(15):1545–1555.
104. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348(9038):1329–1339.
105. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791–1800.
106. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134:e123–e155.
107. Bittl JA, Baber J, Bradley SM, Wijeysundera DN. Duration of dual antiplatelet therapy: a systematic review for the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1116–1139.
108. O'Donoghue ML, Murphy SA, Sabatine MS. The safety and efficacy of aspirin discontinuation on a background of a $P2Y_{12}$ inhibitor in patients after percutaneous coronary intervention: a systematic reviw and meta-analysis. *Circulation*. 2020;142:538–545.
109. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*.

2014;371(23):2155–2166.
110. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: A report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77:629–658.
111. January CT, Wann S, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151.
112. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107–1115.
113. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010;122(24):2619–2633.
114. Plavix (clopidogrel). Package insert. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2015.
115. Gerber Y, Rosen LJ, Goldbourt U, Benyamini Y, Drory Y, Israel Study Group on First Acute Myocardial I. Smoking status and long-term survival after first acute myocardial infarction a population-based cohort study. *J Am Coll Cardiol*. 2009;54(25):2382–2387.
116. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens*. 2014;32(1):3–15.
117. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507–520.
118. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267–315.

14

Heart Failure

Harleen Singh and Joel C. Marrs

CORE PRINCIPLES		CHAPTER CASES
1	Heart failure (HF) is a “clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.” This is further classified according to left ventricular ejection fraction.	**Case 14-1 (Question 1)**
2	HF symptoms, including limitations in activity, can be quantified with the use of the New York Heart Association functional classification system and the American College of Cardiology–American Heart Association classification of chronic HF. The cardinal signs and symptoms (eg, peripheral	**Case 14-1 (Questions 2, 3)**

	edema, dyspnea, fatigue) of HF must be evaluated in light of the patient's medical history, physical examination, and results of additional testing.	
3	Coexisting medical conditions that lead to HF (eg, ischemic heart disease, hypertension, atrial fibrillation [AF], diabetes mellitus, sleep apnea) or result from HF (eg, AF, cachexia, depression) may influence the overall prognosis and treatment; therefore, these should be assessed on a routine basis.	**Case 14-1 (Question 4)** **Case 14-5 (Question 3)**
4	Several categories of medications (such as nonsteroidal anti-inflammatory drugs and "glitazones") may exert unfavorable hemodynamic effects and may precipitate HF symptoms in patients with previously compensated HF. In some patients, the occurrence of HF can be attributed to the cardiotoxic effect of a particular medication (cancer chemotherapeutic drugs).	**Case 14-1 (Question 5)**
5	Treatment goals are to improve symptoms, decrease hospitalizations, and prevent premature death in patients. The cornerstone of treatment for heart failure with reduced ejection fraction (HFrEF) is to optimize life-prolonging therapies (eg, angiotensin converting enzyme inhibitors, angiotensin receptor blocking agents, angiotensin receptor–neprilysin inhibitors, β-blockers, aldosterone	**Case 14-1 (Questions 6–22)** **Case 14-2 (Question 1)** **Case 14-3 (Questions 1–9)** **Case 14-4 (Questions 1, 2)**

	antagonists, sodium–glucose cotransporter-2 inhibitors, and promote healthy lifestyle choices (eg, sodium restriction, exercise training). In selected patients, ivabradine can be added for additional heart rate lowering.	
6	Prompt recognition of symptoms and appropriate treatment are critical in the management of acute decompensated HF. The mainstay of therapy in patients with volume overload is an intravenous loop diuretic. Other therapies (eg, inotropic drugs) have failed to show long-term benefits in clinical trials.	**Case 14-5 Questions 1–3)** **Case 14-6 (Questions 1, 2)**
7	To reduce the risk of sudden cardiac death due to ventricular arrythmias an implantable cardioverter-defibrillator or amiodarone should be considered. Cardiac resynchronization therapy can be used in combination to improve symptoms and quality of life in patients with severe HF symptoms.	**Case 14-6 (Questions 3–5)** **Case 14-7 (Questions 1, 2)**
8	There is little clinical trial evidence to guide which treatments are optimal to use in heart failure with normal or preserved left ventricular ejection fraction (HFpEF).	**Case 14-8 (Question 1)**
9	Although controversial, certain patients may respond differently to drug therapy (eg, African American patients, females).	**Case 14-3 (Question 3)** **Case 14-4 (Question 2)**
10	HF is an extremely serious condition	**Case 14-9 (Question**

and requires careful diagnosis, ongoing monitoring, and the implementation of evidence-based therapy. Herbal remedies (eg, hawthorn) have some evidence to support their role in improving symptoms of HF; however, they have no evidence demonstrating improvements in mortality. Herbals can also potentially interact with other heart medications.	1)

INTRODUCTION

The definition, descriptive terminology, diagnostic techniques, and treatment of heart failure (HF) have undergone significant change in the past 20 years. Since 1994, a series of consensus- and evidence-based practice guidelines have been published in an effort to standardize HF management. Guidelines from the Heart Failure Society of America (HFSA),[1] American College of Cardiology (ACC), American Heart Association (AHA),[2] and the European Society of Cardiology[3] (ESC) have been revised over the years and updated to reflect ongoing changes in the management of HF. In March 2021, the HFSA, the Heart Failure Association of the European Society of Cardiology (HFA-ESC), and the Japanese Heart Failure Society (JHFS) released a consensus statement on the Universal Definition and Classification of Heart Failure.[4]

The proposed universal definition describes HF[4] as a “clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide (NP) levels and/or objective evidence of pulmonary or systemic congestion.” The intent of this new definition was to standardize HF management. The HF societies recognized that the textbook definition “A clinical syndrome caused by the

inability of the heart to supply blood to meet tissue metabolic requirements" has certain limitations and interpretation of the current definition can be confusing for nonspecialists, patients, and payers.

Furthermore, the HF definition by numerous guidelines differs from the textbook definition and from each other. Some guidelines utilize symptoms (dyspnea, fatigue) or physical findings, whereas others include assessment of hemodynamic, neurohormonal, or circulatory abnormalities to define HF. Unlike other disease states such as cancer, diabetes, chronic obstructive pulmonary disease (COPD), and so on, that have specific standardized criteria for diagnosis, HF diagnosis lacks specificity. Also, there are multiple etiologies associated with HF, thus adding another layer of complexity to diagnose and treat HF in clinical practice. In the past 20 years, despite advances in HF management, optimization of guideline-directed medical therapy (GDMT) continues to be suboptimal as reported by real-world registries, suggesting a lack of ability to standardize care in practice. As the burden of HF continues to increase, the need for a standardized definition that is clinically relevant, globally applicable, and allows for timely implementation of GDMT was deemed necessary.

Congestive heart failure (CHF) is a subset of HF characterized by left ventricular systolic dysfunction (LVSD) and volume excess. However, some patients may lack symptoms of congestion and still have reduced cardiac output (CO) manifesting as fatigue and reduced exercise tolerance. Therefore, the term CHF has been replaced with HF.

The ACC/AHA guidelines and updates 2, 5, and 6 provide a comprehensive review on prevention, diagnosis, risk stratification, and treatment of HF in both outpatient and inpatient settings. The updates emphasize how to implement GDMT, how to overcome barriers to safely titrate medications, and improve adherence to therapy in clinical practice.

Numerous programs and systems have been implemented in an attempt to decrease the cost and length of hospital stay for HF. It is recommended that practitioners look at least annually for the most

recently published guidelines to be aware of the rapidly evolving treatment strategies for HF.

Incidence, Prevalence, and Epidemiology

It is estimated that there are 6.2 million people (1.5%–2% of the population) with HF in the United States, and ~23 million people with HF worldwide. The prevalence of HF continues to increase, with an estimated 46% increase in prevalence by 2030.[5] Every year, 870,000 people have a new diagnosis of HF, and at 40 years of age, 1 in 5 persons has a lifetime risk of developing this syndrome. After age 65, HF incidence approaches 21 per 1000 person-years and is the most common cause of hospitalizations in the elderly population in the United States.

The incidence of HF is greater in males and in the elderly; however, the incidence in Black females is as high as that in White males. In females, coronary artery disease (CAD) and diabetes are considered the strongest risk factors for HF. African Americans present with HF at a younger age compared with White individuals. Risk factors, such as ischemic heart disease, hypertension (HTN), gender, obesity, and diabetes, among others, that predict the incidence of HF as well as its severity have been identified.[5]

In older individuals, the survival after new onset of HF has improved; however, survival benefits are not similar across all demographics, and one in nine deaths has HF mentioned on the death certificate.[5] Evidence from national databases and community-based cohorts indicates that the incidence of HF seems to be stabilizing, if not decreasing, for females, and that the length of survival in patients with HF is increasing. However, the death rate remains high; almost 50% of people diagnosed with HF will die within 5 years. The mortality risk steadily increases each year after the diagnosis of HF. The 6-month mortality rates are no different in patients with preserved versus reduced left ventricular ejection fraction (LVEF).[6] HF costs are currently estimated at $30.7 billion. If

no improvements are made to current treatment outcomes, it is expected to grow to $69.8 billion by the year 2030.

Various risk prediction models have been developed to predict HF outcomes. Given the heterogeneous nature of the HF population (ischemic vs nonischemic, low vs preserved ejection fraction [EF]), and multiple comorbid conditions, the validity of the risk prediction models is not consistent in all populations with HF. Therefore, it is important to identify patients who are at high risk for HF and how various risks factors can predict outcomes.[7] Based on the strength of these associations, prevention measures need to be designed to decrease HF hospitalizations in targeted subpopulations. The 2013 guidelines[2] emphasize that validated multivariable risk scores can be useful to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF.

Etiology

LOW-OUTPUT VERSUS HIGH-OUTPUT FAILURE

HF has been described as being either *low-output* or *high-output failure,* with a predominance of cases being low-output failure (**Table 14-1**). In both types, the heart cannot provide adequate blood flow (tissue perfusion) to meet the body's metabolic demands, especially during exercise. The hallmark of classic low-output HF is a diminished volume of blood being pumped by a weakened heart in patients who have normal metabolic needs.

Table 14-1
Classification and Etiology of Left Ventricular Dysfunction

Type of Failure	Characteristics	Contributing Factors	Etiology
Low output, systolic dysfunction (dilated cardiomyopathy)[a]	Hypofunctioning left ventricle; enlarged heart (dilated left ventricle); ↑left ventricular end-diastolic volume; EF <40%; ↓stroke volume; ↓CO; S_3 heart sound present	1 ↓Contractility (cardiomyopathy) 2 ↑Afterload (elevated SVR)	1 Coronary ischemia,[b] MI, mitral valve stenosis or regurgitation, alcoholism, viral syndromes, nutritional deficiency, calcium and potassium depletion, drug-induced, idiopathic 2 Hypertension, aortic stenosis, volume overload
Diastolic dysfunction	Normal left ventricular contractility; normal size heart; stiff left ventricle; impaired left ventricular relaxation; impaired left ventricular filling; normal EF; S_4 heart sound	1 Thickened left ventricle (hypertrophic cardiomyopathy) 2 Stiff left ventricle (restrictive cardiomyopathy) 3 ↑Preload	1 Coronary ischemia,[b] MI hypertension, aortic stenosis and regurgitation, pericarditis, enlarged left ventricular septum (hypertrophic cardiomyopathy) 2 Amyloidosis, sarcoidosis 3 Sodium and water retention
High-output failure (uncommon)	Normal or ↑contractility; normal size heart; normal left ventricular end-diastolic volume; normal or ↑EF; normal or increased stroke volume; ↑CO	1 ↑Metabolic and oxygen demands	1 Anemia and hyperthyroidism

CO, cardiac output; EF, ejection fraction; MI, myocardial infarction; SVR, systemic vascular resistance.

[a]Same as congestive heart failure if symptoms also present.

[b]Heart failure caused by coronary artery ischemia or myocardial infarction classified as ischemic etiology. All other types combined and classified as nonischemic.

In high-output failure, the heart is healthy and pumps a normal or an even higher than normal volume of blood. Because of high metabolic demands caused by other underlying medical disorders (eg, hyperthyroidism, anemia), the heart becomes exhausted from the increased workload and eventually cannot keep up with demand. The primary treatment of high-output HF is amelioration of the underlying disease. Unless otherwise stated, this chapter focuses on the treatment of low-output HF.

LEFT VERSUS RIGHT VENTRICULAR DYSFUNCTION

Low-output HF is further divided into left ventricular (LV) and right ventricular dysfunction, or a combination of the two (biventricular failure). Because the left ventricle is the major pumping chamber of the heart, *LV dysfunction* is the most common form of low-output HF and the major target for pharmacologic intervention. Right ventricular dysfunction may coexist with LV HF if the damage is sustained by

both sides of the heart or as a delayed complication of progressive left-sided HF.

Isolated right-sided ventricular dysfunction, which is relatively uncommon, is usually caused by either primary or secondary pulmonary arterial HTN. Under these conditions, elevated pulmonary artery pressure impedes emptying of the right ventricle, thus increasing the workload on the right side of the heart.[8,9] Primary pulmonary arterial HTN is idiopathic, caused by increased resistance of the pulmonary arterial vasculature of unknown etiology. Secondary causes of pulmonary HTN include collagen vascular disorders, sarcoidosis, fibrosis, exposure to high altitude, and drug and chemical exposure. Drug-induced causes include opioid overdoses (especially heroin), 5-hydroxytryptamine-2B (5HT-2B) agonists (eg, dexfenfluramine, fenfluramine, and pergolide), and pulmonary fibrosis caused by intravenous (IV) injection of poorly soluble forms of methylphenidate. Right-sided heart disease that occurs as a result of a pulmonary process is known as *cor pulmonale*.

CLASSIFICATION OF HEART FAILURE ACCORDING TO LEFT VENTRICLE EJECTION FRACTION; ISCHEMIC VERSUS NONISCHEMIC HEART FAILURE

Over the years, the classification of HF has evolved based on emerging evidence. Initially, LV dysfunction was subdivided into systolic and diastolic dysfunction, with mixed disorders also being encountered (see **Table 14-1**). In systolic dysfunction, the stroke volume (SV) (the volume of blood ejected with each contraction; normal, 60–130 mL) and the subsequent CO (SV × heart rate [HR]; normal, 4–7 L/minute) are reduced. In diagnosing HF, a critical marker differentiating systolic from diastolic dysfunction is the LVEF, defined as the percentage of LV end-diastolic volume expelled during each systolic contraction (normal, 60%–70%).

In *systolic dysfunction,* the LVEF is <40%, dropping to <20% in advanced HF. Heart failure with reduced ejection fraction (HFrEF) is a result of factors causing the heart to fail as a pump (decreased

myocardial contractility). The heart dilates as it becomes congested with retained blood, leading to an enlarged hypokinetic left ventricle.

HF caused by coronary ischemia or after myocardial infarction (MI) is classified as *ischemic,* with all other types grouped as *nonischemic*. CAD is a common cause of HF in patients with LVSD. Other causes of LV pump failure include persistent arrhythmias, poststreptococcal rheumatic heart disease, chronic alcoholism (alcoholic cardiomyopathy), viral infections, or unidentified etiology (idiopathic dilated cardiomyopathy). Chronic HTN, as well as cardiac valvular disorders (aortic or mitral stenosis), precipitate systolic HF by increasing resistance to CO (a high afterload state).

In contrast, LV diastolic dysfunction refers to impaired relaxation and increased stiffness of the left ventricle; the EF may or may not be abnormal, and the patient may or may not be symptomatic. Some patients have both systolic and diastolic dysfunction. The term *heart failure with normal or preserved left ventricular ejection fraction* (HFpEF) is used for patients who have symptoms of HF but a normal EF. These patients always have diastolic dysfunction.

Possible causes of diastolic dysfunction include coronary ischemia, chronic uncontrolled HTN, LV wall scarring after an MI, ventricular wall hypertrophy, hypertrophic cardiomyopathy, restrictive cardiomyopathy (amyloidosis and sarcoidosis), and valvular heart disease (aortic stenosis). These factors lead to LV wall stiffness (reduced wall compliance) and inability of the ventricle to relax during diastole, which result in an elevated pressure within the ventricle despite a relatively low volume of blood. In turn, the elevated pressure impedes LV filling during diastole that would normally occur by passive inflow against a low-resistance pressure gradient. Heart size is usually (but not always) normal. It is estimated that 20% to 60% of patients with HF may have normal LVEF and reduced ventricular compliance.[10] Because coronary ischemia, MI, and HTN are contributors to both systolic and diastolic dysfunction, many patients have both systolic and diastolic dysfunction.

The pathology of systolic dysfunction most closely resembles what has historically been called *congestive heart failure*. Tremendous variability exists in the clinical presentation of both systolic and

diastolic dysfunction; however, both disorders can have similar symptoms.[9,11] Most patients exhibit exercise intolerance and shortness of breath (SOB) with either systolic or diastolic dysfunction. Some exhibit significant edema, whereas others may have no edema or symptoms of congestion. It is possible to be asymptomatic in the early stages of HF. For all these reasons, it is best to avoid the abbreviation CHF because not all patients have congestion. CHF has also been used to denote "chronic heart failure." Clinicians are strongly encouraged to obtain an EF measurement in all patients. The diagnosis of HF should be based on a combination of symptoms and signs together with appropriate clinical tests.

Population studies have shown that patients with "systolic HF" also presented with LV diastolic dysfunction compared to those with so-called diastolic HF. Interestingly, LV diastolic dysfunction is present even in the absence of HF. Clinical trials defined inclusion criteria–based HFrEF or HFpEF and HF with "normal" EF. The noninvasive assessment of LV function using echocardiography became the standard of care in HF. The guidelines used a cutoff of 50% to define normal LVEF. However, these EF cutoffs became confusing when LVEF was between 40% and 50%. The 2016 European Society of Cardiology HF Guidelines[12] coined the term *HF with mid-range EF (HFmrEF)*, whereas the 2013 American College of Cardiology/American Heart Association HF Guidelines used "borderline" for LVEF of 40% to 50%, respectively. In clinical practice, things got further complicated when patients presented with improved EF, which often led to discontinuation or step-down of life-prolonging therapy. Thus, to close this gap, a new revised nomenclature based on LVEF was proposed. The rationale for standardizing the EF categories was to encourage clinicians to use life-prolonging therapies of HFrEF (such as sodium–glucose cotransporter-2 [SGLT2] inhibitors) and to highlight the expanded indication for angiotensin receptor–neprilysin inhibitor (ARNI) in EF between 45% and 57% based on new evidence.[63] See **Figure 14-1**.

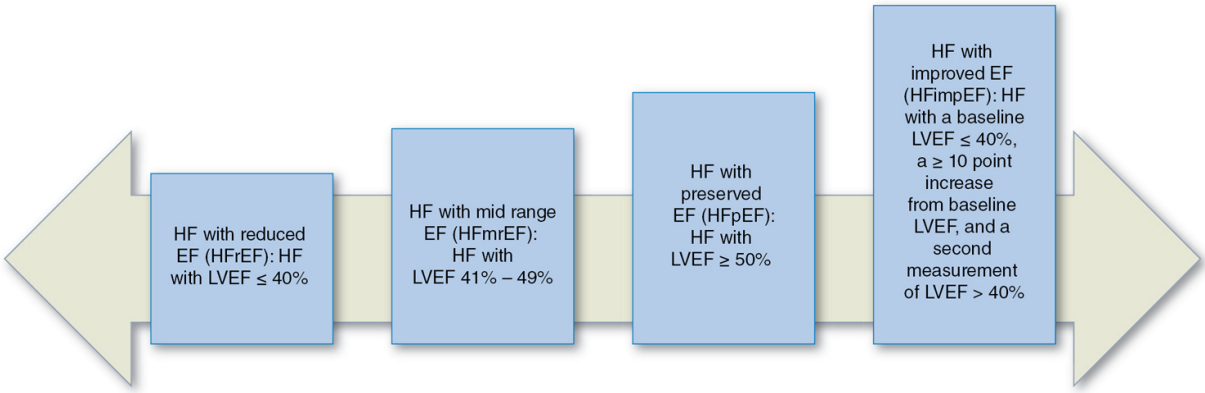


Figure 14-1 Classification of heart failure based on ejection fraction. EF, ejection fraction; HF, heart failure; LVEF, left ventricle ejection fraction.

CARDIAC WORKLOAD

A common finding of HF is increased cardiac workload. Four major determinants contribute to LV workload: preload, afterload, contractility, and HR.

Preload

Preload describes forces acting on the *venous* side of the circulation affecting myocardial wall tension. The volume is maximal when filling finishes at the end of diastole (LV end-diastolic volume). An increased volume raises the pressure within the ventricle (LV end-diastolic pressure), which in turn increases the "stretch," or wall tension, of the ventricle. Peripheral venous dilation and decreased peripheral venous volume diminish preload, whereas peripheral venous constriction and increased peripheral venous volume increase preload.

Elevated preload can aggravate HF. Rapid administration of blood plasma expanders and osmotic diuretics or administration of large amounts of sodium or sodium-retaining agents increases preload. A malfunctioning aortic valve (aortic insufficiency), resulting in regurgitation of blood back into the left ventricle, can increase the volume of blood that must be pumped. A malfunctioning mitral valve (mitral regurgitation) can cause retrograde ejection of blood from the

left ventricle back into the left atrium, with a resultant decrease in CO. In patients with systolic failure, ventricular blood is ejected less efficiently because of a hypofunctioning left ventricle; the volume of blood retained in the ventricle is thus increased, and preload becomes elevated. In HFpEF with a stiffened left ventricle, relatively small increases in end-diastolic volume from sodium and water overload can lead to exaggerated increases in end-diastolic pressure.

Afterload

Afterload is the tension developed in the ventricular wall as contraction (systole) occurs. This tension is affected by intraventricular pressure, ventricular diameter, and wall thickness. Afterload is affected by the systemic vascular resistance (SVR) or the impedance against which the ventricle must pump and is estimated by arterial blood pressure (BP). HTN, atherosclerotic disease, or a narrow aortic valve opening increases arterial impedance (afterload), thereby increasing the workload of the heart. HTN is a major factor in the development of both HFrEF and HFpEF. The Framingham group found that 75% of patients who developed HF had a history of HTN.[13] The risk of developing HF was six times greater in patients with hypertension versus that in patients with normotension.

Cardiac contractility

The terms *contractility* and *inotropic state* are used synonymously to describe the myocardium's ability to develop force and shorten its fibers independent of preload or afterload. Myocardial contractility is decreased when myocardial fibers are diminished or poorly functioning, as may occur in patients with primary cardiomyopathy, valvular heart disease, CAD, or after an MI. Defects in contractility play a major role in systolic HF but are not a factor for diastolic dysfunction. Drugs such as β-adrenergic blockers or anthracyclines precipitate HF by decreasing myocardial contractility.

Heart rate

An increased HR is a reflex mechanism to improve CO as EF declines. The sympathetic nervous system is the major mediator of this response. The workload and energy demands of a rapid HR ultimately place strain on the heart and can eventually worsen HF.

Pathophysiology

When the heart begins to fail, the body activates several complex compensatory mechanisms in an attempt to maintain CO and oxygenation. These include increased sympathetic tone, activation of the renin–angiotensin–aldosterone system (RAAS), sodium and water retention, and other neurohormonal adaptations, which lead to cardiac “remodeling” (ventricular dilatation, cardiac hypertrophy, and changes in LV shape). The consequences of these adaptive mechanisms can create more harm than good (**Fig. 14-2**). The relative balance of each of these adaptive processes varies depending on the type of HF (systolic vs diastolic dysfunction) and from patient to patient with the same disorder. An understanding of the potential benefits and adverse consequences of these compensatory mechanisms is essential to understanding the signs, symptoms, and treatment of HF.[14]

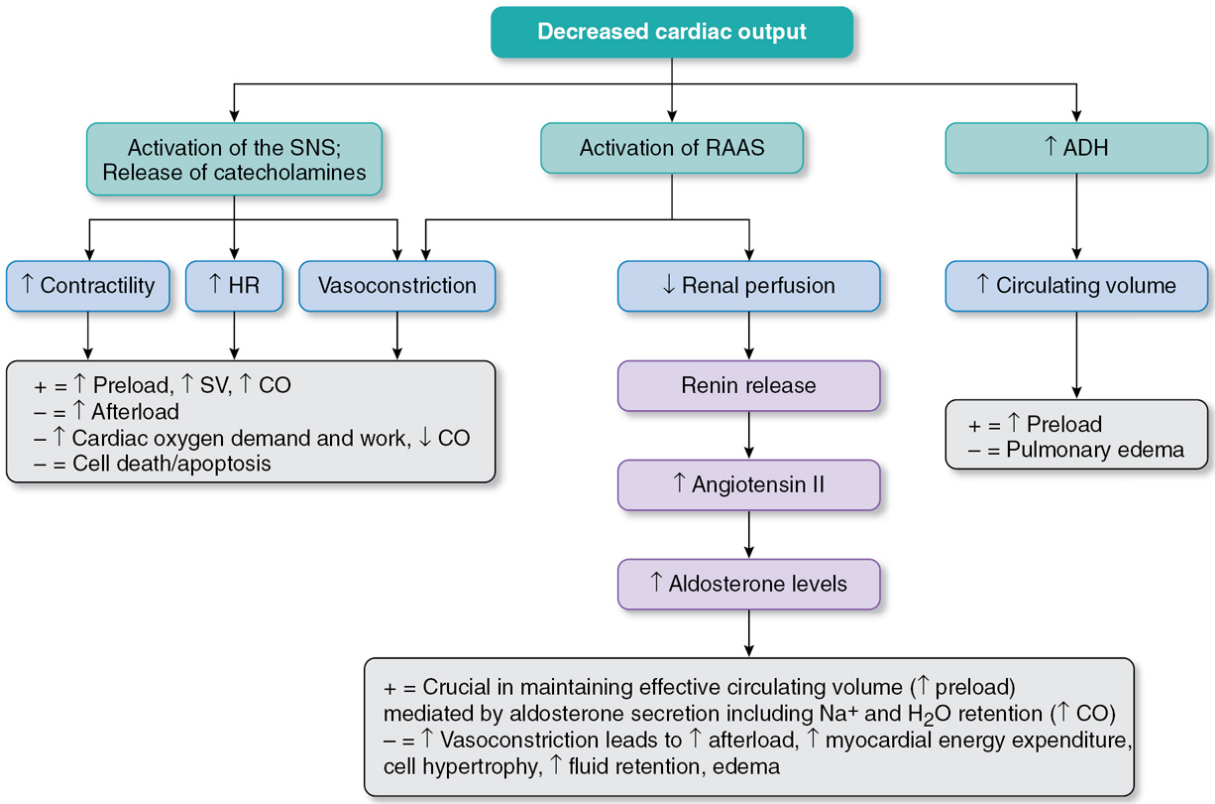


Figure 14-2 Adaptive mechanisms in systolic heart failure. +, beneficial results; –, negative (detrimental) effects; ADH, antidiuretic hormone; CO, cardiac output; HR, heart rate; H_2O, water; Na^+, sodium; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; SV, stroke volume.

SYMPATHETIC (ADRENERGIC) NERVOUS SYSTEM

The body's normal physiologic response to a decreased CO is generalized activation of the adrenergic (sympathetic) nervous system, as evidenced by increased circulating levels of norepinephrine (NE) and other catecholamines. The inotropic (increased contractility) and chronotropic (increased HR) effects of NE initially maintain near-normal CO and perfusion of vital organs such as the central nervous system (CNS) and myocardium. Adverse consequences of NE activation include impaired sodium excretion by the kidneys, restricted ability of the coronary arteries to supply blood to the ventricle (myocardial ischemia), increased

arrhythmias, hypokalemia, and oxidative stress triggering cell death (apoptosis).

Chronic high levels of catecholamines are harmful to the heart because they decrease β_1-receptor sensitivity and reduce β_1-receptor density on the surface of myocardial cells by 60% to 70% in severe HF.[15–20] The normal ratio of β_1- to β_2-receptors in the heart is ~80:20. As a response to overstimulation, this balance is shifted to a ratio of ~70:30 in the failing myocardium by downregulation of β_1-subtype receptors. This selective downregulation of β_1-receptors is accompanied by "uncoupling of the β_1- and β_2-receptor activity," whereby the number of β_2-receptors is unchanged, but the responsiveness of these receptors can be reduced by 30%.[15] Over time, this leaves the myocyte less responsive to adrenergic stimuli and further decreases contractile function. β-Blockers cause the upregulation of the downregulated β_1 receptors and the resensitization of the uncoupled β_2-receptors, protecting the heart from the deleterious effects of catecholamines.[21]

Alterations in sympathetic adrenergic receptors are partially determined by genetic phenotype. Among African American patients with HF, a disproportionately high incidence of polymorphisms for variants of the β_1-receptor that are associated with increased function is seen. In addition, the combined presence of a variant of the β_1-receptor (β_1Arg389) and α_{2C}-adrenergic receptor (α_{2c}Del322–325) results in adrenergic overstimulation and increases the risk of HF. These combined defects are found less often in Whites, perhaps partially explaining a higher incidence of HF in African Americans. A better understanding of α- and β-receptor phenotypes may someday lead to improved prevention and treatment of HF.[22]

RENAL FUNCTION AND THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

The reduced CO in HF leads to the stimulation angiotensin II, which is a potent vasoconstrictor. Angiotensin II is also a potent stimulator of the sympathetic nervous system, which increases SVR. Renal

vascular resistance is increased, and the glomerular filtration rate (GFR) is decreased. As the GFR decreases, more sodium and water are reabsorbed. A diminished effective circulating plasma volume and angiotensin II also stimulate the release of antidiuretic hormone (ADH) from the pituitary, resulting in the retention of free water in the collecting ducts.

The kidney releases renin when renal perfusion pressure is decreased. Renin converts *angiotensinogen* into *angiotensin I.* Angiotensin I is metabolized to *angiotensin II*, under the influence of angiotensin converting enzyme (ACE) (see **Fig. 14-2**). Angiotensin II has multiple effects favoring sodium and water retention. Its vasoconstricting effect decreases GFR, and it stimulates the adrenal glands to secrete aldosterone, which increases sodium reabsorption. Angiotensin II stimulates increased synthesis and release of vasopressin, thereby increasing free water retention and stimulation of thirst centers in the CNS. Finally, angiotensin II stimulates NE release. The net result of decreased renal perfusion is detrimental. Increased sodium and water retention increases preload, whereas angiotensin II–induced vasoconstriction increases SVR and afterload.

A chronic excess of aldosterone causes fibrosis in the myocardium, kidneys, and other organs.[23] Thus, aldosterone promotes remodeling of organs and fibrosis independent of angiotensin II.

OTHER HORMONAL MEDIATORS

Endothelins

Several other regulatory hormones and cytokines have been identified as playing a role in the pathogenesis and adaptation to HF. The first of these are the endothelins.[24,25] Endothelin-1 (ET-1) is the most active. ET-1 is synthesized by vascular and airway smooth muscle, cardiomyocytes, leukocytes, and macrophages. Serum concentrations of ET-1 are elevated in HF, pulmonary HTN, MI, ischemia, and shock, and cause vasoconstriction, potentiation of cardiac remodeling, and decreased renal blood flow (RBF). Although

the effects of ET-1 are detrimental in HF, its pharmacology is complex and dependent on the relative balance of two distinct G protein–coupled receptor subtypes referred to as ET_A and ET_B. As illustrated in **Table 14-2**, ET-1 can elicit opposing effects from each receptor, with the net effect being dependent on the relative density of the two receptors.

Table 14-2
Biologic Effects of Endothelin-1

Organ System	ET_A Receptor Effects	ET_B Receptor Effects	Other Effects
Blood vessels	Potent vasoconstrictor	Vasodilation mediated through nitric oxide and prostacyclin release	
	Collagen deposition		
Heart	Hypertrophy and remodeling		↑ HR
			+/– Inotropic effects
Lungs	Bronchoconstriction		
Kidney	Afferent and efferent vasoconstriction	Natriuresis and diuresis	
	Decrease in RBF and GFR		
Neuroendocrine			Release of catecholamines, renin, aldosterone, and ANH

ANH, atrial natriuretic hormone; ET_A, endothelin A; ET_B, endothelin B; GFR, glomerular filtration rate; HR, heart rate; RBF, renal blood flow; +/–, positive/negative.

From Ergul A. Endothelin-1 and endothelin receptor antagonists as potential cardiovascular therapeutic agents. *Pharmacotherapy*. 2002;22(1):54–65. Reprinted by permission of John Wiley & Sons, Inc.

Possible future therapeutic agents could be specific inhibitors of one or more of the enzymes to prevent activation of ET-1. Alternatively, selective inhibitors of ET_A receptors could shift responses toward the favorable aspects of ET_B receptor activation. Bosentan and tezosentan are nonselective dual ET_A/ET_B antagonists. Bosentan has the U.S. Food and Drug Administration (FDA) approval for the treatment of pulmonary HTN.

Natriuretic peptides

NPs are a family of peptides containing a common 17–amino acid ring. A-type NP, previously referred to as atrial NP or atrial natriuretic factor, is secreted by the atria in response to dilatation. Similarly, B-

type natriuretic peptide (BNP) is produced by the ventricular myocardium in response to elevations of end-diastolic pressure and volume. Type-C natriuretic peptide (CNP) is secreted by the lungs, kidneys, and vascular endothelium in response to shear stress. Collectively, the NPs are considered to be a favorable form of neurohormonal activation. Among their positive attributes are antagonism of the renin–angiotensin system, inhibition of sympathetic outflow, and ET-1 antagonism. The net effect is peripheral and coronary vasodilation decreasing preload and afterload. As their name implies, they also have diuretic or natriuretic properties, with improved RBF and glomerular filtration resulting from afferent arteriolar dilation and, possibly, efferent arteriolar constriction. Sodium reabsorption is blocked in the collecting duct owing to indirect aldosterone inhibition. NPs also inhibit vasopressin secretion and block salt appetite and thirst centers in the CNS, which contributes to diuresis. CNP has minimal diuretic properties.[26]

The BNP precursor is cleaved to produce the biologically active C-terminal fragment (BNP) and an inactive N-terminal fragment (NT-proBNP). Plasma level measurement of either BNP or NT-proBNP can be used as a biologic marker to differentiate HF-induced dyspnea from other causes of respiratory distress.[27–29] BNP levels <100 pg/mL usually indicate absence of HF, whereas levels >400 pg/mL are highly indicative of HF. However, the interpretation of BNP levels between 100 and 400 pg/mL can be challenging because elevated levels are also associated with renal failure, pulmonary embolism, pulmonary HTN, and chronic hypoxia.[30] Higher concentrations correlate with the severity of HF. Clinical resolution of symptoms is often accompanied by a decline in BNP concentration. The revised cutoff values for diagnosing HF according to NP levels in the ambulatory setting are ≥35 pg/mL for BNP and ≥125 pg/mL for NT-proBNP; and in the hospital setting are ≥100 for BNP and ≥300 pg/mL for NT-proBNP.[4]

Natriuretic hormone analogs or inhibitors of their metabolism have been investigated for drug therapy of HF. Nesiritide is a recombinantly produced human BNP approved by the FDA for IV management of acute HF exacerbations in hospitalized patients, but

it is no longer used in practice.[31,32] Downregulation of NP receptors, however, occurs during chronic HF, reducing the protective benefit of their actions and, possibly, limiting their usefulness as therapeutic entities.

Vasopressin receptor antagonists

Volume overload is associated with increased hospitalization. The potent vasoconstrictor ADH (arginine vasopressin) is inappropriately elevated in HF. Early studies with tolvaptan (selective vasopressin subtype V_2 receptor antagonist) demonstrated improvement in congestive symptoms of HF and overall hemodynamic profile but no improvement in long-term outcome.[33–35] Because long-term mortality benefits are lacking and the cost of the drug is high, the use of tolvaptan is restricted to patients with hypervolemic hyponatremia associated with HF despite fluid restriction and diuretic use.

Calcium sensitizers

Calcium sensitizers represent another class of drugs investigated for the treatment of acute decompensated heart failure (ADHF). They exert positive inotropic effects by stabilizing the calcium–troponin C complex and facilitating actin–myosin cross-bridging without increasing myocardial consumption of adenosine triphosphate.[36] Levosimendan, the prototype for this drug class, has a dual mechanism of action to increase myocardial contractibility and induce vasodilation. Unlike other inotropic agents, it does not affect the intracellular calcium concentrations and, therefore, has a lower potential for proarrhythmia. The safety and efficacy of levosimendan in ADHF has been evaluated in placebo-controlled trials and in comparative trials with dobutamine. In patients with decompensated HF, levosimendan significantly reduced the incidence of worsening HF and improved hemodynamic indices.[37–39] In addition, mortality was lower in the levosimendan group. These trials, however, were not powered to show a difference in mortality as an end point. A subsequent trial comparing levosimendan with dobutamine in ADHF, designed to confirm the beneficial effects on morbidity and mortality,

did not reduce all-cause mortality, which contrasts with earlier studies.[40] The most common adverse effects associated with levosimendan are headache and hypotension. Currently, levosimendan is approved in Europe for ADHF.

CARDIAC REMODELING

Progression of HF results in *cardiac remodeling*, characterized by changes in the shape and mass of the ventricles.[40] The three primary manifestations of cardiac remodeling are chamber dilatation, LV myocardial hypertrophy, and a resulting spherical shape of the left ventricle (**Fig. 14-3**). Cardiac remodeling, which starts before the appearance of clinical symptoms, contributes to the progression of the disease.

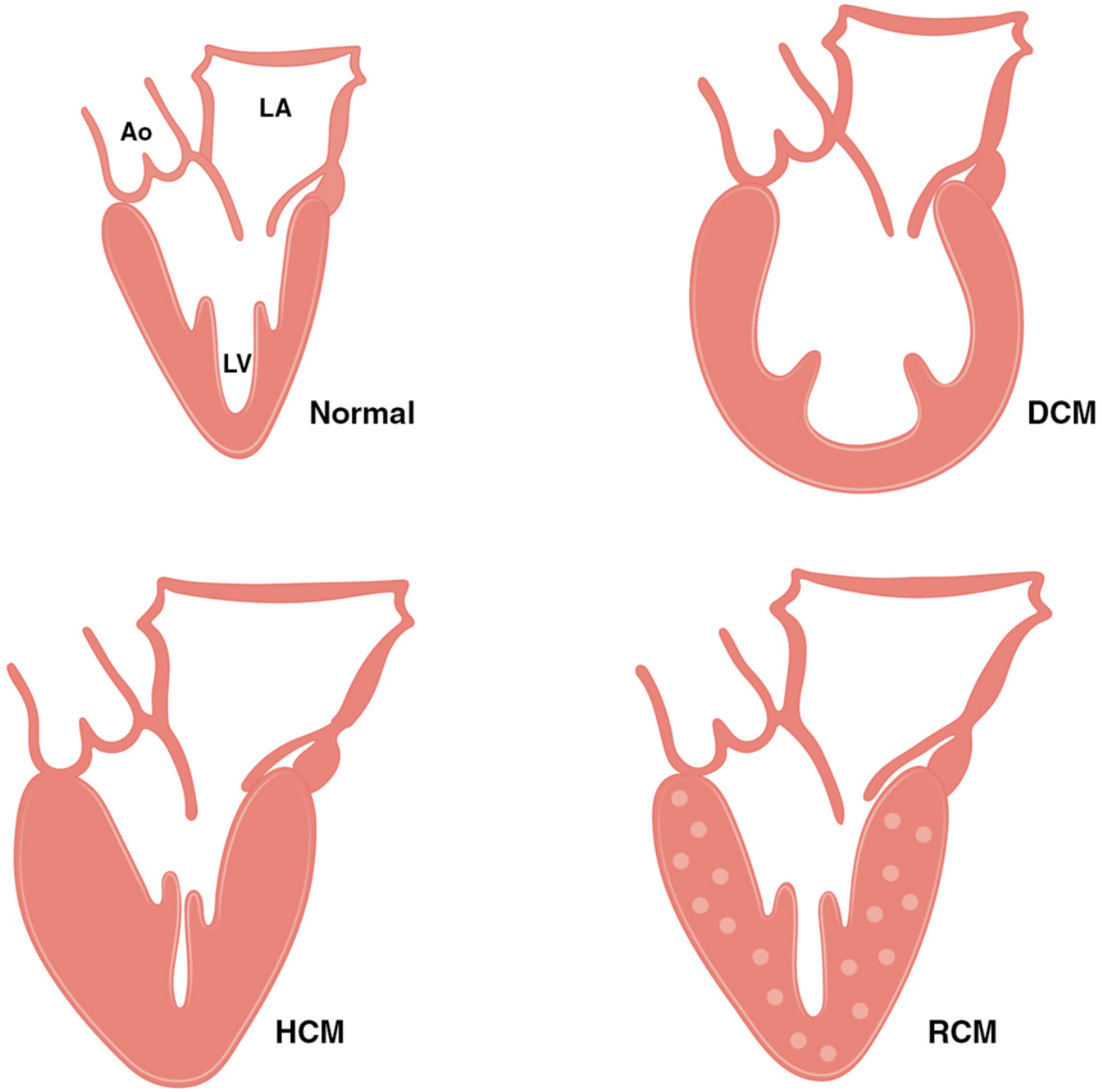


Figure 14-3 Cardiac remodeling. Dilated cardiomyopathy (DCM) results in thinning of the left ventricular walls and a decrease in systolic function; in hypertrophic cardiomyopathy (HCM), there is a marked thickening of the left ventricular walls leading to diastolic or systolic failure; and in restrictive cardiomyopathy (RCM), the left ventricular walls may be normal, hypertrophic, or slightly dilated, resulting in a decrease in diastolic compliance. Ao, aorta; LA, left articular; LV, left ventricular. (Adapted with permission from Topol EJ, Callif RM, Prystowsky EN, et al, eds. *Textbook of Cardiovascular Medicine*. 3rd ed. Lippincott Williams & Wilkins; 2006.)

Cardiac dilatation

Cardiac dilatation results from hypervolemia. End-diastolic volume increases, myocardial fibers are stretched, and the ventricle(s) become dilated. In a healthy heart, the end-diastolic volume is 110 to 120 mL. With an EF of 60%, the SV would be 70 mL, leaving an end-systolic residual volume in the ventricle of 40 to 50 mL. With HFrEF, the end-diastolic volume increases resulting in an enlarged heart. Cardiac dilatation is less evident in HFpEF because normal contractility is maintained, and the stiffened left ventricle is resistant to filling and less likely to dilate (see **Fig. 14-3**).

Frank–Starling curve

The Frank–Starling curve (**Fig. 14-4**) demonstrates a curvilinear relationship between LV myocardial muscle fiber "stretch" (wall tension) and myocardial work. As the stretch increases, the volume of blood ejected (SV) with each contraction increases. In systolic HF, the work capacity for any degree of stretch is diminished. A simple analogy is drawn using a balloon. The greater amount of air blown into a balloon, the more it stretches and, if released, the farther it flies around a room. As the balloon gets old, it loses its elasticity and thus has less recoil. Similarly, dilatation of the ventricles initially may serve as an effective compensating mechanism in systolic failure but becomes inadequate as the elastic limits of the muscle fibers are reached. HR also increases to maintain CO when SV is low. The disadvantage of cardiac dilatation is increased myocardial oxygen demand. Theoretically, as cardiac dilatation progresses beyond a certain point, CO could decrease (as visualized on the descending limb of the Starling curve), but this is rarely observed clinically.

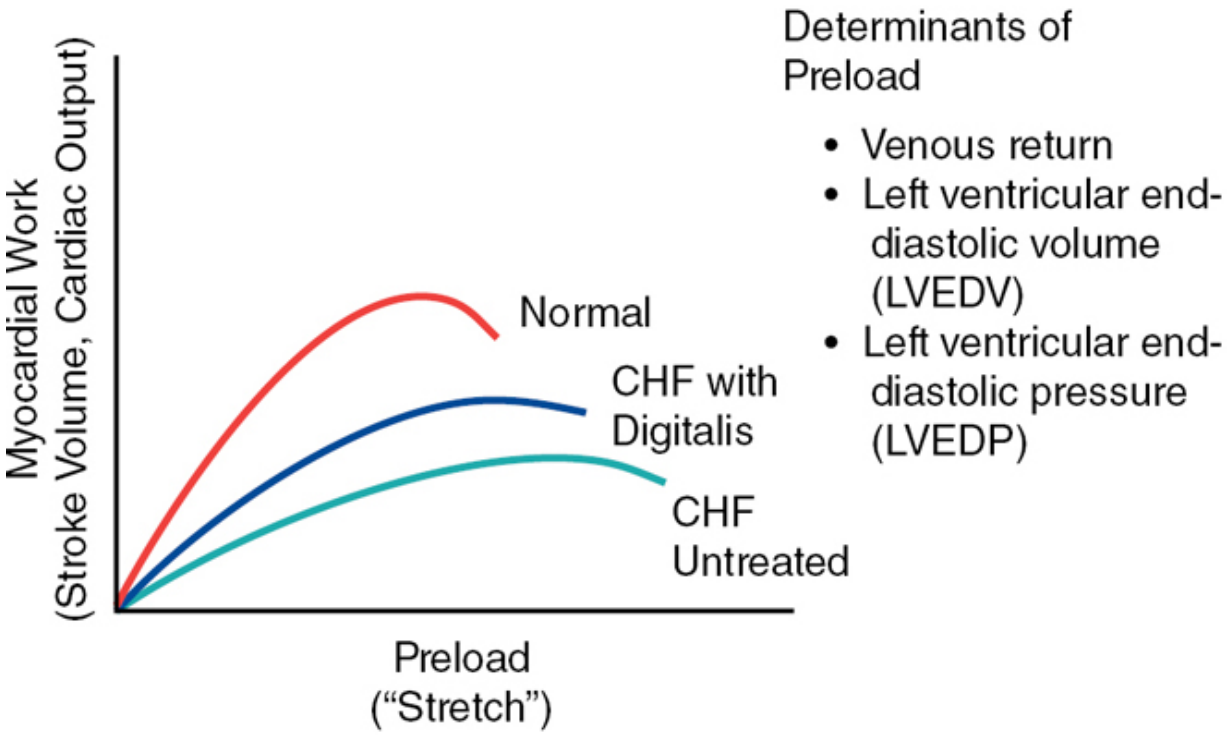


Figure 14-4 Representation of the Frank–Starling ventricular function curve.

Cardiac hypertrophy

Cardiac hypertrophy represents an absolute increase in myocardial muscle mass and muscle wall thickness (see **Fig. 14-3**). This is analogous to increased skeletal muscle mass in response to weightlifting. Cardiac hypertrophy should not be confused with cardiac dilatation.

FUNCTIONAL LIMITATION CLASSIFICATION AND STAGES OF HEART FAILURE

New York Heart Association classification

The NYHA classification scheme identifies four categories of functional disability associated with HF. Patients in class I are well compensated with no physical limitations and lack symptoms with ordinary physical activity. In class II, ordinary physical activity results in mild symptoms and imparts slight limitations on exercise tolerance. Patients in class III are comfortable only at rest; even less

than ordinary physical activity leads to symptoms. In class IV, symptoms of HF are present at rest and no physical activity can be undertaken without symptoms. Determination of class is subjective and will vary among observers.

A shortcoming of the NYHA classification scheme is that it does not include asymptomatic individuals who are at high risk for developing HF and may benefit from preemptive lifestyle changes and drug therapy.[41]

The 2001 ACC/AHA guidelines introduced a staging system that can be used in conjunction with the NYHA classifications.[42] Although this staging has been uniformly adopted by different societies, it is not widely used by nonspecialists or clearly understood by patients. Furthermore, staging gives the impression that there is only one direction for patients to progress (A–D). With this framework, the staging terminology has been revised[4] to add clarity and applicability. The new stages of HF include At risk for HF (former stage A), Pre-HF (former stage B), HF (former stage C), and Advanced HF (former stage D) (**Fig. 14-5**).

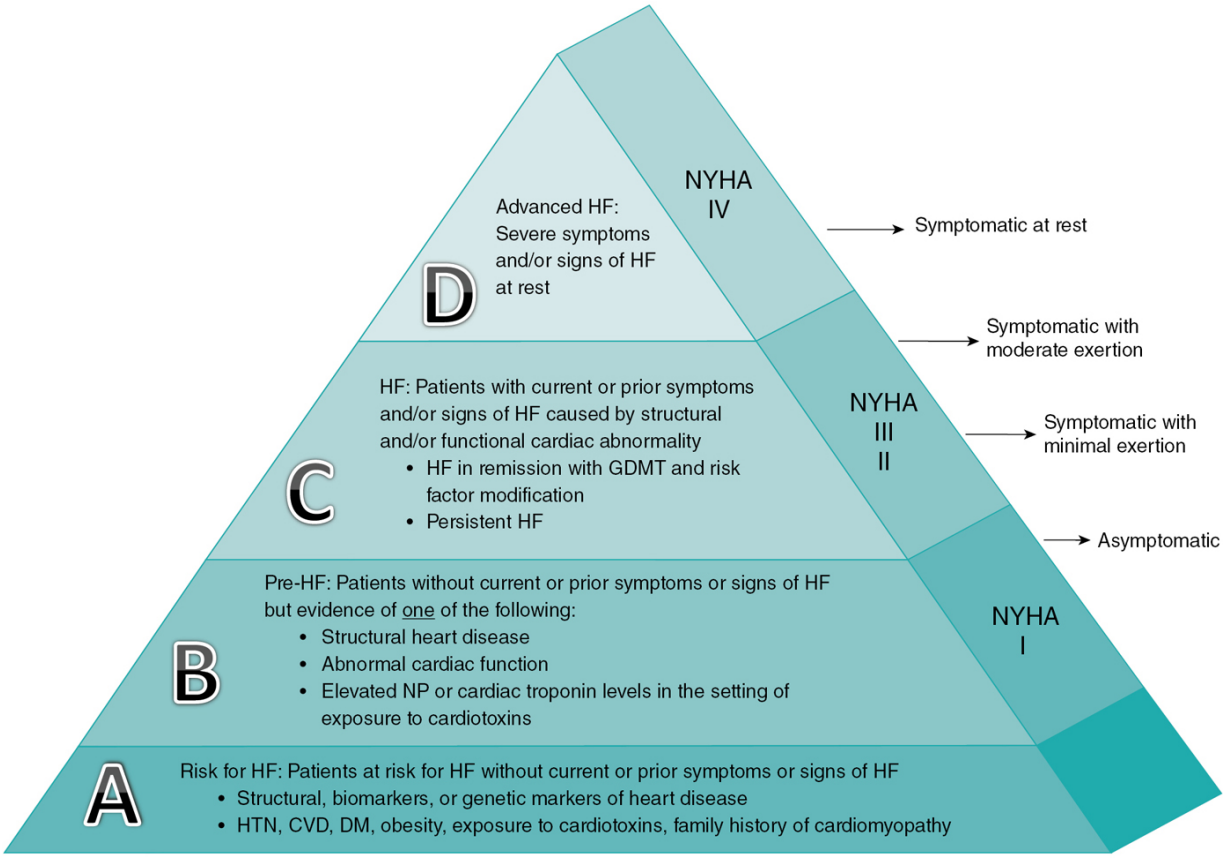


Figure 14-5 Staging and New York Heart Association (NYHA) classification of heart failure. (Data from Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79(17):e263–e421.)

In addition, staging can improve with GDMT. The intent of this change was to simplify the staging so that it is easier to translate to patients. The Pre-HF terminology raises awareness for screening and prevention treatment strategies such as precancer screening. It also allows clinicians to prescribe treatment strategies such as SGLT2 inhibitors for patients at risk for HF and Pre-HF.

The writing committee also introduced new terminology on clinical trajectories.[4] The new emphasis is on “persistent” HF rather than on “stable” HF. Even patients who are less symptomatic and not deteriorating are at significant risk for death (22% mortality at 5

years). The emphasis has also shifted to HF in “remission” rather than in “recovered HF.” Patients with HF with a resolution of signs/symptoms of HF and previous structural/functional heart disease typically do not recover. This is supported by the results of TRED-HF trial[43] that showed that withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF) resulted in a relapse in about 40% of patients, suggesting that improvement in LV function and resolution of symptoms represent remission rather than complete recovery for most patients.

In the new universal definition, the writing committee also extended the signs and symptoms of HF. In clinical trials, validation of HF diagnosis historically relies on criteria based on signs and symptoms such as Framingham criteria or episodes of care (hospitalizations and emergency department [ED] visits). But this criterion lacks specificity because similar symptoms can be caused by kidney disease or lung disease. Therefore, typical as well as less typical symptoms and specific exam findings are added for clarity.[4]

Overview of Treatment Principles

The guidelines recommend that most patients with HFrEF should receive GDMT including an angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) or an ARNI, a β-adrenergic blocker, aldosterone receptor antagonist, and an SGLT2 inhibitor. Clinical algorithms from the ACC/AHA guidelines are found in **Figures 14-6** and **14-7**. Diuretics are recommended for patients with congestion. The combination of hydralazine and nitrate should be considered in Black patients with symptoms despite receiving other GDMTs or in patients unable to tolerate an ACEI or ARB. Digoxin is potentially beneficial in symptomatic patients with HFrEF already receiving optimal medical therapy to decrease HF hospitalizations. In patients who are receiving maximally tolerated doses of β-blockers with an HR of >70 bpm, addition of ivabradine can be considered.

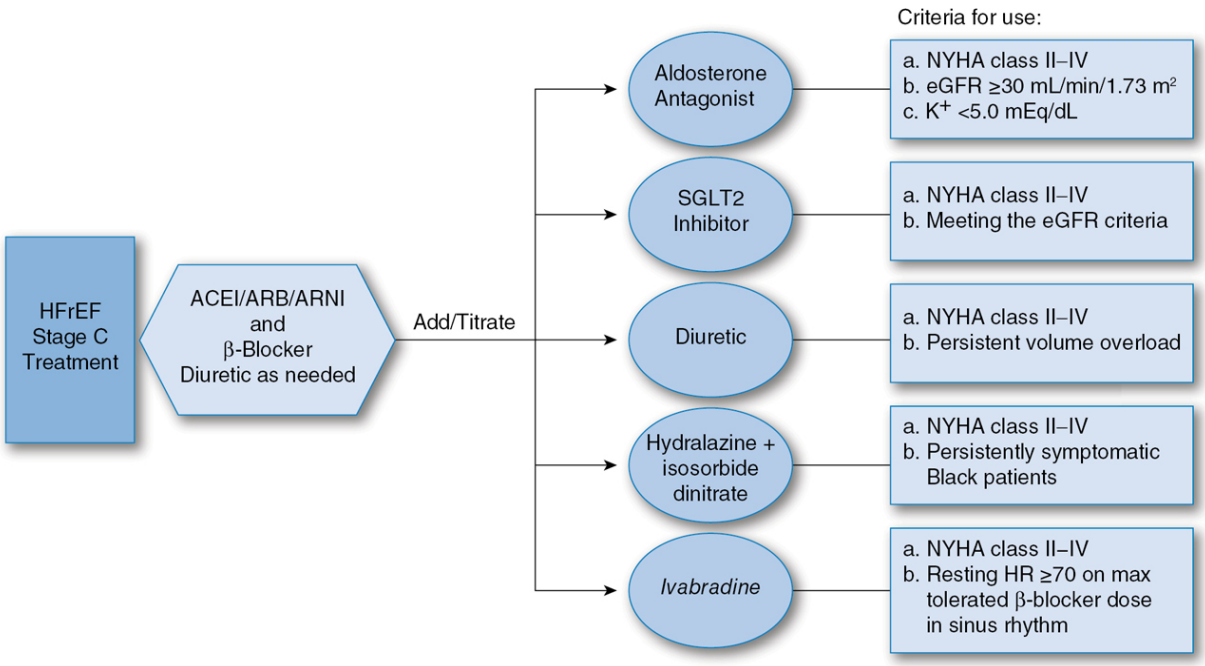


Figure 14-6 Treatment algorithm for HFrEF stage C. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; NYHA, New York Heart Association; SGLT2, sodium–glucose cotransporter-2.

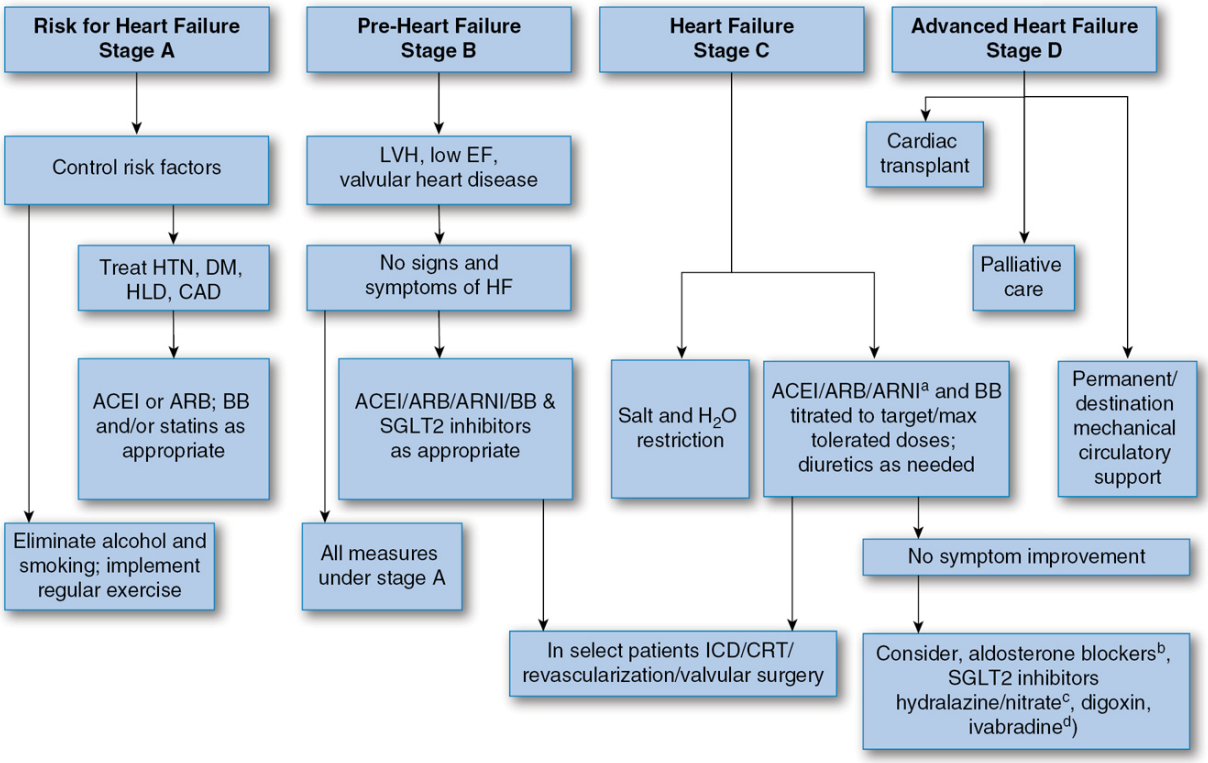


Figure 14-7 Stages in the development of heart failure and recommended therapy by stage. ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitor; BB, β-blockers; CAD, coronary artery disease; CrCl, creatinine clearance; DM, diabetes mellitus; EF, ejection fraction; HLD, hyperlipidemia; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy; SGLT2, sodium–glucose cotransporter 2 inhibitors.

[a]New York Heart Association (NYHA) II or III who tolerate angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) with adequate blood pressure (BP) and no hx of angioedema; replace with angiotensin receptor–neprilysin inhibitor (ARNI) to further reduce morbidity and mortality, must wait at least 36 hours from the last dose of ACEI.

[b]New York Heart Association (NYHA) II to IV unless est. creatinine clearance (CrCl) <30 mL/minute and serum potassium >5.0 mEq/L.

[c]New York Heart Association (NYHA) III or IV in Black patients.

[d]New York Heart Association (NYHA) II or III, left ventricular ejection fraction (LVEF) ≤35%, maximally tolerated dose of β-blocker, sinus rhythm, and heart rate

70 bpm or greater.

Despite robust evidence of HF medications in reducing mortality and morbidity, the findings from the **Cha**nge the **Ma**nagement of **P**atients with **H**eart **F**ailure (CHAMP-HF)[44] registry demonstrated major gaps in use and dosing of GDMT. Among eligible patients for GDMT (27%), 33% were not on a β-blocker and 67% were not prescribed aldosterone antagonists (AAs). Even when patients received HF medications, they were not on target doses and only 1% of patients with HFrEF were receiving target doses of indicated therapies.

Many barriers in clinical practice such as renal function, hypotension, and hyperkalemia make it challenging to initiate or uptitrate GDMT. The 2021 update to the 2017 ACC expert consensus decision pathways for optimization of HF treatment[45] addresses strategies to overcome treatment barriers, improve adherence, manage comorbidities, decide when to refer patients for advanced HF therapies, and provide team-based care. The authors provide detailed scenarios for treating HFrEF with β-blockers, ACEIs, ARBs or ARNI, and SGLT2, as well as tools to evaluate the titration and maintenance of medications.

The goals of therapy for HF are to abolish disabling symptoms, avoid complications such as arrhythmias, improve the quality of life, and prolong survival. Short of a heart transplant, none of the treatment measures are curative.

Nonspecific medical management of HF includes addressing cardiovascular (CV) risk factors, correcting underlying disease states (HTN, ischemic heart disease, arrhythmias, lipid disorders, anemia, or hyperthyroidism), performing moderate physical activity as tolerated, undergoing immunization with influenza and pneumococcal vaccines, and discontinuing possible drug-induced causes. The role of NPs, endothelin inhibitors, vasopressin receptor antagonists, and calcium sensitizers has been investigated. Non-digitalis inotropic agents and tumor necrosis factor-α (TNF-α) inhibitors, although theoretically valuable, have yielded disappointing results and significant complications, including arrhythmias and

increased mortality rates. Myosin activators (such as omecamtiv mecarbil and danicamtiv) represent another potential drug target in HF.[46]

Treatment of HFpEF historically has been less well defined, but recent data with sacubitril-valsartan and empagliflozin have shown positive findings.[47,48] A sodium-restricted diet and diuretics are indicated for symptomatic relief of SOB or edema. Because these patients typically present with comorbid conditions (atrial fibrillation [AF], HTN, diabetes mellitus, and CAD), treatment of comorbidities with available therapies should aim to decrease CV events and improve survival.[11] The guidelines[2,3,11] suggest a IIb class of recommendation consideration for angiotensin receptor antagonists and mineralocorticoid antagonists.

The new 2022 HF guidelines[2] have included both SGLT2 inhibitors and ARNI for the management of HFpEF to decrease HF hospitalizations: A 2a and 2b class of recommendation for SGLT2 inhibitors and ARNI, respectively.

The 2022 HF guidelines[2] also provide treatment recommendations for heart failure with ejection fractions between 41% and 49% considered “mildly reduced ejection fractions” (HFmrEF). These recommendations are based on secondary analysis of previous HF trials. SGLT2 inhibitors have a stronger recommendation whereas ARNI, ACEi, ARB, MRA and β-blockers are considered weaker recommendations in HFmrEF. In clinical practice, this category of patients are frequently treated similar to patients with HFrEF. Periodic assessment of LV function should be considered to determine the course of disease.

PHYSICAL ACTIVITY

Patients should be encouraged to exercise to maintain physical conditioning. Treatment goals include prolonging life and improving quality of life. The results of the Effects of Exercise Training on Health Status in Patients with Chronic Heart Failure (HF-ACTION)[49] trial showed that a highly structured exercise program in patients with HF did not reduce all-cause mortality or all-cause hospitalization

when compared with patients who were getting the usual care in which exercise was simply encouraged. However, according to the HF-ACTION substudy, the structured exercise training program improved the overall Kansas City Cardiomyopathy Questionnaire (KCCQ) score (a test that includes questions on physical limitations, symptoms, quality of life, and social limitations). The improvement occurred early on and was sustained for 3 years. The ACC/AHA HF guidelines[2,11] recommend exercise training as safe and effective for patients with HF who are able to participate in symptom control.[1,11] However, during acute exacerbations, bed rest and restricted physical activity decrease the metabolic demands and minimize gravitational forces contributing to edema. Renal perfusion is increased in the prone position, resulting in diuresis and mobilization of fluid.

SODIUM-RESTRICTED DIET

Dietary indiscretion (high salt intake) is often cited as the cause of HF exacerbations and hospital admissions. Several observational studies have demonstrated associations between lower dietary sodium intake and reduced hospitalizations and mortality.[50,51] In contrast, several randomized trials imply that dietary sodium restriction in patients with CV diseases may be deleterious. One of the largest meta-analysis in patients with HFrEF showed that compared with control groups (2800 mg/day), the sodium-restricted groups (1800 mg/day) had increased morbidity and mortality.[52] The trials included in this analysis had several limitations. High doses of diuretics were used in conjunction with strict fluid restriction, which could have resulted in intravascular volume depletion and adverse outcomes. Also, many patients were not on optimal doses of GDMT. There is limited evidence to support sodium restriction in the inpatient setting. In one trial, sodium restriction greater than the standard 2000 mg/day in patients hospitalized for HFrEF did not affect clinical stability or decrease length of stay.[53] For these reasons, further randomized trials are needed to elucidate the impact of sodium restriction on outcomes in patients with HF. Because high

sodium intake leads to HTN, LV hypertrophy, and CV disease, the ACC/AHA HF guidelines[1,11] recommend 1.5 g/daily sodium restriction for patients with stages A and B HF. In patients with advanced HF (stages C and D), <3 g/daily is recommended owing to lack of sufficient data to support any specific degree of restriction.

Even though adherence to dietary sodium restriction is considered "a cornerstone of HF disease management," there are many challenges in implementing dietary sodium restriction. Barriers such as lack of knowledge, interference with socialization, limited access to appropriate food selections, and increased taste preference for salty foods all contribute to lack of adherence to a low-sodium diet.[54,55] Although <1 g of sodium chloride (NaCl) is required to meet physiologic needs, the average U.S. diet contains 10 g. Dietary sodium can be reduced to 2 to 4 g of NaCl by eliminating cooking salt. This diet is more palatable and leads to better adherence than is a severely salt-restricted diet.

DIURETICS

Only those points salient to the treatment of HF are included in this chapter. Diuretic use is discussed in Chapter 9, Essential Hypertension, and Chapter 27, Fluid and Electrolyte Disorders.

Diuretics are indicated in patients with HF with congestion (pulmonary and/or peripheral edema). They produce rapid symptomatic relief. Because activation of the RAAS and sympathetic nervous system contributes to the progression of HF, diuretics should be combined with an ACEI and a β-blocker unless contraindications exist.[1]

Initially, the goal of diuretic therapy is symptomatic relief of HF by decreasing excess volume without causing intravascular volume depletion. Once excess volume is removed, therapy is aimed at maintaining sodium balance and preventing the accumulation of new fluid, while avoiding dehydration. The rate at which volume can be removed is limited by its rate of mobilization from the interstitial to the intravascular fluid compartment. If diuresis is too vigorous, intravascular volume depletion, hypotension, and a paradoxical

decrease in CO may result. Diuretic doses are titrated so that urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily.[1]

The effectiveness of diuretics depends on the amount of sodium delivered to their site of action and the patient's renal function.[56,57] Proximal tubular reabsorption of sodium is increased in patients with severe HF when RBF is compromised, rendering thiazide and potassium-sparing diuretics (which act primarily on the distal tubule) minimally effective. Thiazides are believed to lose their effectiveness when creatinine clearance (CrCl) decreases to <30 mL/minute. Metolazone is an exception in that its activity may be preserved in these patients. The loop diuretics (furosemide, bumetanide, and torsemide) are more potent than are thiazides and retain their effectiveness in renal insufficiency. Thus, in most patients with HF, loop diuretics are preferred. In addition to having activity in the ascending limb of the loop of Henle, furosemide has vasodilating properties that decrease renal vascular resistance. The usual recommended doses for the loop diuretics are found in **Table 14-3**.[56]

Table 14-3
Comparison of Loop Diuretics

	Furosemide	Bumetanide	Torsemide
IV dose equivalence	40 mg	1 mg	20 mg
Maximum total daily dose (IV)	600 mg	10 mg	200 mg
Bioavailability (oral)	10%–100% (average 50%)	80%–100%	80%–100%
Metabolism	50% renal	50% hepatic	80% hepatic
Average duration of action	6–8 hours	4–6 hours	6–8 hours
PO to IV conversion	2:1	1:1	1:1

IV, intravenous.

Reprinted from Felker GM, Ellison DH, Mullens W, et al. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75(10):1178–1195. © 2020 by the American College of Cardiology Foundation. With permission.

The effectiveness of diuretics depends on active secretion of the drug in the proximal tubule. Slow absorption (even if bioavailability is high) or protein binding impairs tubular delivery and compromises

diuretic response. Once the drug is in the tubule and the threshold for diuresis is met, further drug delivery produces no greater diuresis. Increasing single doses beyond the ceiling dose produces no additional diuretic response; however, improved diuresis may be obtained by giving the drug more frequently.

A combination of diuretics (a loop diuretic and thiazide) is used in patients who are refractory to high-dose loop diuretics.[56,57] Despite their effects on reducing HF symptoms, loop diuretics do not counteract the underlying cause of HF or modify mortality rates.

ALDOSTERONE ANTAGONISTS

The AAs eplerenone and spironolactone exert a mild diuretic effect by competitive binding to the aldosterone receptor site in the distal convoluted renal tubules. The *R*andomized *AL*dactone *E*valuation *S*tudy (RALES) investigators found that spironolactone reduced both morbidity and mortality in patients in NYHA classes III and IV.[58] The authors speculated that the beneficial effect of spironolactone was related to a reduction in aldosterone-induced vascular damage and myocardial or vascular fibrosis rather than in its diuretic effect. Similarly, reduced mortality and morbidity were observed in patients with LV dysfunction and NYHA class II symptoms with eplerenone.[59] The ACC/AHA HF guidelines[1,11] and the 2021 ACC expert consensus decision pathway for optimization of HF recommend the addition of an AA in all patients with HFrEF who are already on ACEIs or ARB/ARNI and β-blockers irrespective of the severity of symptoms and in patients immediately after MI who have LV dysfunction or diabetes. According to the updated HF guidelines,[2] AAs can be also considered in HFpEF and HFmrEF to reduce hospitalizations and CV mortality.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Drugs with vasodilating properties are a primary treatment for HF. Arterial dilation provides symptomatic relief of HF by decreasing arterial impedance (afterload). Venous dilation decreases LV

congestion (preload). The combination of these two properties provides additive benefits to alleviate the symptoms of HF and increase exercise tolerance. The first vasodilator drugs to be studied were hydralazine (an arterial dilator) and nitrates (predominately venous dilators). By combining these two drugs, significant reductions in HF symptoms can be achieved along with a reduction in mortality rates. With the advent of ACEIs, the use of hydralazine and nitrates has been relegated to a secondary role and mainly in patients who are African American.

ACEIs possess both afterload- and preload-reducing properties and volume-reducing potential. They produce hemodynamic effects similar to that of the hydralazine–nitrate combination as a single agent, favorably modify cardiac remodeling, have a more tolerable side effect profile, and were superior to hydralazine/ISDN in the **V**asodilator-**H**eart **F**ailure **T**rial **II** (V-HeFT 2) trial (A Comparison of Enalapril with Hydralazine– Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure). These advantages led to the recommendations that ACEIs are the drugs of choice for initial therapy, even in patients with relatively mild LVSD.[1]

The ACC/AHA guidelines[1,11] state that ACEIs should be prescribed to all patients with HFrEF unless they have a contradiction to their use or are unable to tolerate these drugs. In general, ACEIs are used with β-blockers. ACEIs should be initiated at low doses and titrated to maximum doses if well tolerated. Fluid retention can blunt the therapeutic effects, and volume depletion can potentiate the adverse effects of ACEIs. Clinicians should attempt to use doses that have been shown to reduce CV events in clinical trials, but they should not delay the initiation of β-blockers in patients because of a failure to reach clinical trial ACEI doses.[1]

The pharmacologic actions of all the ACEIs are essentially identical, but some of them have not been studied or received FDA approval for use in HF (**Table 14-4**). Their value in HFpEF still is unclear based on neutral trial findings in this population. A related class of drugs is the ARBs.[60,61] ARBs offer theoretic advantages compared with ACEIs by being more specific for angiotensin II

blockade (preferentially bind to AT_1 receptors) and having a lower risk of drug-induced cough.

Table 14-4
Signs and Symptoms of Heart Failure

Left Ventricular Failure	Right Ventricular Failure[a]
Subjective	
DOE	
SOB	
Orthopnea (2–3 pillows)	
PND, cough	
Weakness, fatigue, confusion	Peripheral edema
Weakness, fatigue	
Objective	
LVH	Weight gain (fluid retention)
↓BP	
EF <40%[b]	Neck vein distension
RALES, S_3 gallop rhythm	Hepatomegaly
Reflex tachycardia	Hepatojugular reflux
↑BUN (poor renal perfusion)	

BP, blood pressure; BUN, blood urea nitrogen; DOE, dyspnea on exertion; EF, ejection fraction; LVH, left ventricular hypertrophy; PND, paroxysmal nocturnal dyspnea; SOB, shortness of breath.

[a]Isolated right-sided failure occurs with long-standing pulmonary disease (cor pulmonale) or after pulmonary hypertension.

[b]Ejection fraction normal in patients with diastolic dysfunction.

ARBs can be used as alternatives to ACEIs in patients who are intolerant (angioedema or cough). Triple combination of an ACEI, ARB, and an aldosterone receptor antagonist is potentially harmful for patients and therefore is listed as a class III (avoid) recommendation in the ACC/AHA guidelines.[1,11] Currently, only candesartan and valsartan are FDA approved for the treatment of

HFrEF. The potential to decrease hospitalizations with ARBs in the HFpEF population has been demonstrated.

ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITOR

The NP hormones are responsible for both natriuresis and diuresis and are broken down by the neutral endopeptidase neprilysin. To augment NP, several neprilysin inhibitors (ecadotril, candoxatril) were developed in CV diseases. Disappointingly, the development of these drugs was halted owing to lack of efficacy. The most likely explanation for these findings was that neprilysin inhibition also leads to increased plasma concentrations of angiotensin II, thus counteracting the therapeutic benefits of neprilysin inhibition. The next logical step was to combine neprilysin inhibitor therapy with renin–angiotensin system inhibition, leading to the development of omapatrilat. Unfortunately, side effects such as angioedema led to discontinuation of omapatrilat. Because ARBs have a lower incidence of angioedema, a new combination sacubitril/valsartan, an ARNI, was developed and tested in HF.

A randomized, double-blind trial "*P*rospective comparison of *A*ngiotensin *R*eceptor neprilysin inhibitors with *A*ngiotensin-converting enzyme inhibitors to *D*etermine *I*mpact on *G*lobal *M*ortality and morbidity in *H*eart *F*ailure" (PARADIGM-HF)[62] compared sacubitril/valsartan (400 mg daily) to enalapril (20 mg daily) in patients with an LVEF <35%. This trial showed a 20% reduction in the primary outcome of CV death or HF hospitalization in the sacubitril/valsartan group versus the enalapril group. Based on the results of the PARADIGM-HF trial, sacubitril/valsartan received a class I recommendation in HFrEF.[11] The 2017 ACC/AHA/HFSA update on the 2013 HF guidelines recommend switching chronic symptomatic patients with HFrEF (NYHA class II or III) who tolerate an ACEI or ARB to sacubitril/valsartan, to further reduce morbidity and mortality. The 2021 ESC HF guidelines have a class I, level of evidence A recommendation for ACEIs in patients with HFrEF to reduce morbidity and mortality, but further go on to give a class I, level of evidence B recommendation to sacubitril/valsartan as a

replacement for ACEI in patients with HFrEF to reduce the risk of morbidity and mortality.[3]

Also, according to the 2021 ACC expert consensus decision pathway for patients with newly diagnosed stage C HFrEF, ARNI is preferred over ACEI/ARB for initial treatment.[45] A subgroup analysis of the PARAGON-HF[47,63] (*P*rospective comparison of *AR*NI with *A*RB *G*lobal *O*utcomes in heart failure with preserved ejectio*N* fraction) trial showed a significant reduction in HF hospitalization in subjects with LVEF below the median 57% value in the study. Based on this evidence, the FDA has granted an expanded indication to ARNI in patients with HFpEF with an LVEF at the lower end of the range 45% to 57%. The new HF guidelines[2] now recommend ARNI in patients with HFpEF and HFmrEF.

A-ADRENERGIC BLOCKING AGENTS

Until the mid-1990s, β-blockers were contraindicated in patients with HFrEF. This was based on the belief that sympathomimetic agonists and other positive inotropic drugs were the logical choices to counteract systolic failure and that negative inotropic drugs would exacerbate HF. A better understanding of the pathophysiology of HF led to a rethinking of this logic.[15–20,22] In combination with ACEIs, β-blockers are considered first-line agents in patients with HFrEF. The ACC/AHA guidelines state that β-blockers should be prescribed to all patients with HFrEF unless they have a contraindication to their use or are unable to tolerate the treatment. Intolerance or resistance to other HF therapies should not preclude or delay the initiation of β-blocker use in patients with HFrEF.[1] Although some patients can have a temporary worsening of symptoms, continued use results in improved quality of life, fewer hospitalizations, and, most importantly, a reduction in mortality by ~34% when added to other HF therapies. Extended-release (XL) metoprolol succinate, carvedilol, and bisoprolol are FDA approved for use in HFrEF. Metoprolol and bisoprolol are both partially selective β_1-blockers, and carvedilol is a mixed α_1- and nonselective β-blocking agent. Metoprolol can lose β_1-selectivity at higher doses.

IVABRADINE

There is considerable evidence of an association between elevated HRs (>80 beats/minute [bpm]) and increased risk of mortality in patients with HF. The HF trials with β-blockers demonstrated increased mortality with elevated baseline resting heart rates (RHRs) >90 bpm.[64,65] Post hoc analysis of the *C*andesartan in *H*eart failure *A*ssessment of *R*eduction in *M*orbidity and mortality (CHARM)[66] showed that increased RHR was an independent predictor of mortality regardless of LV function or use of β-blockers. A subsequent meta-analysis of HF trials[67] showed an association between the magnitude of HR reduction and survival benefit.

Ivabradine is a selective I_f ("funny current") inhibitor that lowers HR by acting on the sinoatrial node. In 2010, the *S*ystolic *H*eart failure treatment with the I_f inhibitor ivabradine *T*rial (SHIFT)[68] provided evidence for the benefit of HR lowering in patients with HFrEF. Compared to placebo, ivabradine significantly reduced the risk of hospitalization for worsening HF and death due to HF but did not have a significant effect on all-cause mortality.

In April 2015, the FDA approved ivabradine (Corlanor®) for symptomatic chronic HF with LVEF ≤35%, to reduce the risk of hospitalization for worsening HF in adults. The 2017 ACC/AHA/HFSA update on 2013 HF guidelines notes that ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA classes II–III) stable chronic HFrEF (≤35%) who are receiving maximal GDMT, including a β-blocker at maximum tolerated dose, and in sinus rhythm with an HR ≥70 bpm at rest. It received a class IIa recommendation, level of evidence B to R.[11]

DIGITALIS GLYCOSIDES (DIGOXIN)

Digoxin has several pharmacologic actions on the heart. It binds to and inhibits sodium–potassium (Na^+/K^+) adenosine triphosphatase (ATPase) in cardiac cells, decreasing outward transport of sodium and increasing intracellular concentrations of calcium within the cells. Calcium binding to the sarcoplasmic reticulum causes an increase in the contractile state of the heart.

At one time, the primary benefit of digoxin in HFrEF was assumed to be an increase in the force of contraction (positive inotropic effect). We now know that digoxin has beneficial neurohumoral and autonomic effects caused by reducing sympathetic tone and stimulating parasympathetic responses at serum concentrations below those associated with positive inotropism.[69,70] Inhibition of Na^+/K^+ ATPase in vagal afferent fibers sensitizes cardiac baroreceptors, resulting in reduced sympathetic outflow from the CNS. Similarly, inhibition of Na^+/K^+ ATPase in renal cells reduces renal tubular reabsorption of sodium and indirectly suppresses renin secretion. This has led to the suggestion that the positive benefits of digoxin can be obtained using small doses.

Digoxin decreases the conduction velocity and prolongs the refractory period of the atrioventricular (AV) node. This AV node–blocking effect prolongs the PR interval and is the basis for use of digoxin in slowing the ventricular response rate in patients with AF and other supraventricular arrhythmias (see Chapter 15, Cardiac Arrhythmias).

Several studies have confirmed a clinical benefit for digoxin in reducing HF symptoms, independent of rhythm status, but there are no data that demonstrate a beneficial effect on survival. Digoxin is used for symptom management in patients optimally treated with ACEIs, β-blockers, and AAs. In symptomatic patients in stage C or stage D, digoxin can reduce HF-related hospitalizations.[2] Digoxin can be considered in patients with HF who also have AF, although β-blockers are more effective than is digoxin in controlling the ventricular response, especially during exercise.

OTHER VASODILATING DRUGS: HYDRALAZINE AND NITRATES

Although ACEIs are drugs of choice, the first vasodilators evaluated in HFrEF were hydralazine and nitrates. Hydralazine provides symptomatic relief of HF by decreasing afterload. Nitrates have venous dilating properties that decrease preload. Used in combination, these two agents have additive benefits in alleviating the symptoms of HF and increasing exercise tolerance. Importantly,

the hydralazine–isosorbide dinitrate combination was the first treatment regimen to show improved survival in severe HF compared with placebo[70] (while patients continued their diuretic or digitalis therapy). The African American Heart Failure Trial (AHeFT)[71] showed that the addition of hydralazine combined with isosorbide dinitrate to standard HF therapy with an ACEI or a β-blocker improved survival and reduced HF hospitalizations. Based on the results of AHeFT, the FDA approved the combination product of hydralazine and isosorbide dinitrate (BiDil®) for the treatment of HFrEF as an adjunct to standard HF therapy in African American or self-identified Black patients. The combination of hydralazine and nitrate is reasonable in patients with current or prior HF symptoms and reduced LVEF who cannot tolerate ACEIs or ARBs, and is also recommended for patients self-described as Black or African American with moderate-to-severe symptoms on optimal therapy with ACEIs, β-blockers, and diuretics.[2] IV nitroglycerin (NTG) and nitroprusside (a mixed arterial and venous dilator) are also used in hospitalized patients with acute HF exacerbations. The role of these vasodilators in HFpEF is not well studied.

OTHER INOTROPIC AGENTS

IV dopamine and dobutamine, which are sympathomimetics, and milrinone (a phosphodiesterase [PDE] inhibitor) are used in ADHF (see Chapter 17, Shock). They are associated with an increased incidence of mortality but frequently used short term for ADHF. Both dobutamine and milrinone are used chronically in some stage D patients.

Initial positive hemodynamic effects during the first few weeks to months of therapy are followed by increased mortality with continued therapy when compared with placebo. This is related to proarrhythmic effects. Inotropic drugs are contraindicated in HFpEF.

CALCIUM CHANNEL BLOCKERS

Amlodipine, felodipine, isradipine, nifedipine, and nicardipine are examples of dihydropyridine calcium channel blockers (CCBs) with

arterial vasodilating effects. Compared with the non-dihydropyridine CCBs (verapamil and diltiazem), they have minimal negative inotropic properties. Only amlodipine[72] and felodipine[73] have been documented to be safe in HF, but only a small subset of patients with nonischemic dilated cardiomyopathy actually had a beneficial effect of improved survival with amlodipine.[72] Verapamil and diltiazem are safe to use in HFpEF and may improve symptoms by reducing HR and allowing more time to fill the ventricle, but should be avoided in patients with HFrEF because of their negative inotropic effects.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

Ventricular arrhythmias are common in patients with HF ranging from asymptomatic ventricular premature beats to sustained ventricular tachycardia, ventricular fibrillation, and sudden cardiac death (SCD). SCD is highest in patients with severe HF symptoms, or stage D HF.[2] Patients with previous cardiac arrest or documented sustained ventricular arrhythmias have a higher risk of future events. An implantable cardioverter-defibrillator (ICD) is indicated for secondary prevention of SCD in patients with HF who have good clinical function and prognosis, a low EF, and experience syncope of unknown origin, as well as in a small subset of patients with HF who are awaiting a planned cardiac transplant. The ACC/AHA guidelines[2] also recommend ICD for primary prevention of SCD in patients with nonischemic dilated cardiomyopathy or ischemic heart disease at least 40 days after MI, EF of ≤35% despite optimal drug therapy, with mild-to-moderate symptoms of HF, and in whom survival with good functional capacity is otherwise anticipated to extend beyond 1 year (see Case 14-6, Question 4, for a detailed discussion).

CARDIAC RESYNCHRONIZATION

Cardiac resynchronization therapy (CRT) is a therapeutic approach for treating patients with ventricular dyssynchrony (defined as a QRS duration of at least 120 ms). Selected patients with HF benefit from simultaneous pacing of both ventricles (biventricular pacing), or of one ventricle in patients with bundle branch block. The rationale for

using CRT is that dyssynchrony causes ventricular remodeling and worsens HF. CRT can be used alone or with an ICD device. Several clinical trials with CRT or CRT-D[74–77] (cardiac resynchronization defibrillator therapy) have demonstrated improvements in HF functional status, survival, and reduction in hospitalizations. The approved indication for CRT-D includes patients with NYHA class II or ischemic class I HF, with an EF of <30% and a QRS duration of >130 ms, and left bundle branch block (LBBB). These indications are based on results[75] that showed a significant reduction in HF events among patients with mild HF symptoms with CRT-D compared with ICD alone. Current guidelines[1] support the use of CRT in patients with NYHA classes II, III, or ambulatory IV symptoms on GDMT, LVEF of ≤35%, and LBBB with a QRS ≥150 ms (see Case 14-7, Questions 1 and 2).

LEFT VENTRICULAR ASSIST DEVICES

A left ventricular assist device (LVAD) is a battery-operated, mechanical pump that is surgically implanted to maintain the pumping ability of the heart. Clinical trials using LVADs have shown improvement in survival and quality of life. For patients with end-stage HF, LVADs are used as a bridge to transplant or as destination therapy, which is permanent device implantation for patients who are not candidates for a transplant.

The landmark trial REMATCH[78] (*R*andomized *E*valuation of *M*echanical *A*ssistance for the *T*reatment of *C*ongestive *H*eart failure) found that patients with end-stage HF who received an LVAD (HeartMate® XVE) had a 52.1% chance of surviving 1 year, compared with a 24.7% survival rate for patients who received optimal medical therapy. At 2 years, the survival was 23% for the patients with LVAD versus 8% for those receiving medical therapies. However, these survival rates were much lower than those seen with transplantation. Advances in technology led to the introduction of the second-generation devices, notably HeartMate® II, which was approved as a bridge to transplant in 2008.[79] In January 2010, the HeartMate® II (continuous flow), a smaller device, was approved for

destination therapy. In a head-to-head comparison with the first-generation HeartMate® XVE (pulsatile flow), 1- and 2-year survival rates were 68% and 58% with HeartMate® II versus 55% and 24% with HeartMate® XVE.[80] Adverse events were less frequent with the continuous-flow device and patients reported significant improvements in their quality of life. The novel pump called HeartWare ventricular assist device (HVAD®) was tested in patients awaiting cardiac transplantation with refractory and advanced HF.[81] There were less bleeding and fewer infections reported with HVAD; however, the incidence of stroke was higher. This LVAD was removed from the market in 2020 owing to increased neurologic adverse events and mortality compared with similar mechanical circulatory support (MCS) devices.

Patients on continuous-flow LVADs were still susceptible to hemocompatibility-related complications such as pump thrombosis, stroke, and bleeding, despite an improved survival and quality of life. In the largest LVAD study, the centrifugal flow HeartMate® 3 was compared to the axial flow HeartMate® II (HMII). The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3)trial[82] randomized 366 patients with advanced HF requiring LVAD for either bridge or destination therapy (LVEF ≤25%, NYHA III–IV, inotropic dependent or confidence interval [CI] <2.2), HeartMate® 3 centrifugal flow device, or standard-of-care axial flow LVAD (HMII). At 2 years, the HeartMate® 3 device was associated with a 19.3% absolute reduction in reoperation for device malfunction or disabling stroke. Pump replacement at 2 years occurred in 2.3% of patients who received a centrifugal flow pump and in 11.3% of patients receiving HMII. Rates of disabling stroke and death were similar in both groups, although there was a significant reduction in overall stroke ($P < .0001$). The number needed to treat (NNT) over 2 years to avert at least one hemocompatibility-related adverse event (pump thrombosis, stroke, or bleed) was <1. This trial demonstrated superior performance of the HeartMate® 3 compared to the axial flow HeartMate® II pump with respect to the following: absolute reduction in pump thrombosis rates, reduction in strokes of any type and of

any severity, and reduction in any bleeding, particularly gastrointestinal bleeds. HeartMate® 3 received FDA approval in 2017. Devise-related complications continue to be a challenge, and, for now, in patients ineligible for heart transplantation, the field of LVAD continues to grow.

NEW THERAPIES IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Vericiguat

Patients with HF often present with endothelial dysfunction resulting in decreased production of nitric oxide (NO). NO stimulates soluble guanylate cyclase (sGC) and increases the production of cyclic guanosine monophosphate (cGMP), causing vasodilation of vascular smooth muscles. Similarly, endocardial endothelium via NO regulates contractility and diastolic dysfunction; hence, any deficiency in the NO-SGc-CGMP pathway can impair diastolic relaxation and microvascular dysfunction.[83] Furthermore, experimental studies have suggested that sGC stimulators can reverse left ventricular hypertrophy (LVH) and fibrosis. Hence, pharmacologic agents that help restore the (NO)-sGC–cGMP signaling pathway have been recently developed in the treatment and prevention of HF.

Unlike the nitrates, vericiguat directly binds sGC increasing the CGMP production, which, in turn, enhances endogenous availability of NO, leading to favorable downstream effects on the CV system. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction (VICTORIA Study Group)[84] was a randomized double-blind placebo-controlled multinational study that included 5050 patients with LVEF <45%, NYHA classes II to IV HFrEF, elevated NP level in the 30 days before randomization (sinus rhythm: BNP ≥300 pg/mL or NT-proBNP ≥1000 pg/mL, AF: BNP ≥500 pg/mL or NT-proBNP ≥1600 pg/mL), and evidence of worsening HF (HF hospitalization within 6 months of randomization, or IV diuretic therapy without hospitalization in the past 3 months). Patients received vericiguat 10 mg daily versus placebo and were on excellent background therapy

with >90% on β-blockers and an ACEI, ARB, or ARNI. More than 40% of the patients had stage 3 chronic kidney disease. The primary outcome was a composite of death from CV causes or first hospitalization for heart failure. Over 10.8 months, 897 of 2526 patients (35.5%) in the vericiguat group experienced a primary outcome event, compared with 972 of 2524 patients (38.5%) in the placebo group, for a hazard ratio (HR) of 0.90, 95% CI, 0.82 to 0.98; *P* = .02. The main finding was the reduction in hospitalizations that drove the primary composite end point (HR 0.90, 95% CI 0.81–1, *P* = .048, absolute risk reduction [ARR] 2.2%, NNT 46). Generally, the drug was very well tolerated. Symptomatic hypotension occurred in 9.1% of the patients in the vericiguat group and in 7.9% of the patients in the placebo group (*P* = .12); syncope occurred in 4.0% of the patients in the vericiguat group and in 3.5% of the patients in the placebo group (*P* = .30). VICTORIA enrolled a very high-risk population with HF having significant unmet needs not well addressed by prior HF studies. Given the positive results of this trial, vericiguat will likely be added to the guidelines, particularly for high-risk patients who carry the residual risk of CV death despite receiving optimal GDMT, with a high event rate as seen in the trial. Because vericiguat is a once-daily medicine, easy to titrate, generally safe and well tolerated, without the need for monitoring renal function or electrolytes, it may play a useful role in patients with a recent worsening HF. According to the ESC and AHA/ACC/HFSA guidelines,[2,3] vericiguat may be considered, in addition to standard therapy for HFrEF, to reduce the risk of CV mortality and hospitalizations for HF.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors

Despite the many medications that have demonstrated benefits in lowering the risk of morbidity and mortality in patients with HFrEF, there remains a need to continue to further lower this risk. SGLT2 inhibitors have been utilized to help improve glycemic control in patients with type 2 diabetes mellitus, but recently have demonstrated benefit in patients with or without diabetes. There are

a number of proposed mechanisms for this benefit, which include improvement in ventricular loading by reducing preload and afterload, providing an alternative cardiac energy supply in the form of cardiac ketones, direct inhibition of sodium/hydrogen exchange in the myocardium leading to reductions in cardiac injury, reduction in LV mass, improvement in endothelial function, and stimulation of increased glucagon secretion potentially improving cardiac performance.[47] The exact mechanism of benefit has yet to be fully determined at this point.

The two SGLT2 inhibitors that have demonstrated benefit in the population with HFrEF to reduce CV death and HF hospitalization are dapagliflozin and empagliflozin. The two clinical trials were the *D*apagliflozin *A*nd *P*revention of *A*dverse outcomes in *H*eart *F*ailure (DAPA-HF)[85] and *EMP*agliflozin outcomE t*R*ial in patients with chr*O*nic hea*R*t failure and a *R*educed ejection fraction (EMPEROR-Reduced).[86] DAPA-HF was a clinical trial of NYHA classes II to IV HF with an EF <40% who were randomized to dapagliflozin 10 mg or placebo daily. The primary outcome was a composite of worsening HF (hospitalization or an urgent visit resulting in IV therapy for HF) or CV death. The study lasted a median of 18.2 months. The primary outcome occurred in 16.3% of the dapagliflozin group and in 21.2% of the placebo group (HR, 0.74; 95% CI, 0.65–0.85; $P < .001$). All individual components of the primary outcome were statistically significant as well. Based on this trial, the FDA approved dapagliflozin for the treatment of HFrEF in adults with or without diabetes in May 2020. The EMPEROR-Reduced trial was a clinical trial of NYHA classes II to IV HF with an EF <40% who were randomized to empagliflozin 10 mg or placebo daily. The primary outcome was a composite of CV death or hospitalization for worsening HF. The study lasted for a median of 16 months. The primary outcome event occurred in 19.4% of the empagliflozin group and 24.7% of the placebo group (HR, 0.75; 95% CI, 0.65–0.86; $P < .001$). Hospitalization for HF was statistically significant as an individual end point, but CV death did not reach significance as an individual outcome. Based on the findings of these studies, SGLT2 inhibitors (dapagliflozin, empagliflozin) have a class I

recommendation inhibitor for HFrEF with NYHA classes II to IV patients to reduce the risk of HF hospitalization and death. The 2022 HF guidelines[2] recommend SGLT2 inhibitors for HFpEF and HFmrEF to decrease HF hospitalizations and CV mortality. This expanded indication is based on the results of Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved).[48]

PATIENT EVALUATION

Signs and Symptoms

CASE 14-1

Question 1: A.J., a 58-year-old male, is admitted with increasing SOB and a 17.64-pound (8-kg) weight gain. Two weeks before admission, he noted the onset of dyspnea on exertion (DOE) after one flight of stairs, orthopnea, and ankle edema. Since then, his symptoms have worsened. He has also noted episodic bouts of paroxysmal nocturnal dyspnea (PND), and he has been able to sleep only in a sitting position. A.J. reports a productive cough, nocturia (two to three times a night), and edema.

A.J.'s other medical problems include a long history of heartburn, a 10-year history of osteoarthritis, depression, and poorly controlled HTN. A family history of diabetes mellitus is also present.

Physical examination reveals dyspnea, cyanosis, and tachycardia. A.J. has the following vital signs: BP, 160/100 mm Hg; pulse, 90 bpm; and respiratory rate, 28 breaths/minute. He is 71 inches (180.34 cm) tall and weighs 171.96 pounds (78 kg). His neck veins are distended. On cardiac examination, an S_3 gallop is heard; the point of maximal impulse is at the sixth intercostal space, 12 cm from the midsternal line. His liver is enlarged and tender to palpation, and a positive hepatojugular reflux is observed. He is noted to have 3+ pitting edema of the extremities and sacral edema. Chest examination reveals inspiratory rales and rhonchi bilaterally.

The medication history reveals the following current medications: hydrochlorothiazide (HCTZ) 25 mg every day, ibuprofen 600 mg four times a day (qid), ranitidine 150 mg every night at bedtime, and citalopram 20 mg every day. He has no allergies and no dietary restrictions.

Admitting laboratory values include the following:

Hematocrit, 41.1%
White blood cell count, 5300/μL
Sodium (Na^+), 132 mEq/L
Potassium (K^+), 3.2 mEq/L
Chloride (Cl^-), 100 mEq/L
Bicarbonate, 30 mEq/L
Magnesium, 1.5 mEq/L
Fasting blood sugar, 100 mg/dL
Uric acid, 8 mg/dL
Blood urea nitrogen (BUN), 40 mg/dL
Serum creatinine (SCr), 0.8 mg/dL
Alkaline phosphatase, 44 units/L
Aspartate aminotransferase, 30 units/L
BNP, 1364 pg/mL (normal <100 pg/mL)
Thyroid-stimulating hormone, 2.0 μU/mL

The chest radiograph shows bilateral pleural effusions and cardiomegaly.

What signs, symptoms, and laboratory abnormalities of HF does A.J. exhibit? How do you relate these clinical findings to the pathogenesis of the disease and to left-sided or right-sided HF?

Left-sided ventricular dysfunction primarily causes pulmonary symptoms, whereas right-sided ventricular dysfunction causes signs of systemic venous congestion. Although LV failure usually develops first, many patients present with signs of biventricular failure. The signs and symptoms of both left-sided and right-sided ventricular dysfunction are summarized in **Table 14-4**.

LEFT-SIDED HEART FAILURE (LEFT VENTRICULAR DYSFUNCTION)

Weakness, fatigue, and cyanosis result from decreased CO and compromised tissue perfusion. If the left ventricle is not emptied completely, pulmonary congestion occurs. Dyspnea (labored or uncomfortable breathing) on exertion, a productive cough, rales (crackles in the lung during auscultation), pleural effusions on chest radiograph, and hypoxemia all result from pulmonary congestion. Pulmonary symptoms are aggravated in the reclining position. Orthopnea or SOB in the supine position is quantified by the number of pillows the patient must lie on to sleep comfortably. A.J., for

example, could sleep only sitting upright. PND is characterized by SOB that awakens the patient from sleep and is alleviated by an upright position.

Cardiac dilatation is observed on chest radiography as an enlarged cardiac silhouette. The point of maximal impulse corresponds to the apex of the left ventricle and is visualized as an external pulsation on the left side of the chest. It is displaced laterally and downward from its normal location at the fifth intercostal space, <10 cm from the midsternal line. An S_3 gallop rhythm denotes a third heart sound often heard in close proximity to the second heart sound (closing of the aortic and pulmonary valves) in HF. Rapid filling of the ventricles causes the S_3 sound and, in an adult, usually indicates decreased ventricular compliance. In patients with mitral valve regurgitation, an S_3 heart sound is common and denotes systolic dysfunction and elevated filling pressure. Tachycardia is caused by compensatory increases in sympathetic tone.

Weight gain and edema reflect sodium and water retention resulting from decreased renal perfusion (see the section on Pathogenesis). As RBF and GFR decrease, a disproportionate amount of BUN may be retained. This phenomenon is termed *prerenal azotemia* and is detected by an elevated BUN-to-SCr ratio of >20:1. A.J. has a ratio of >40:1. Prerenal azotemia also can be caused by dehydration and overuse of diuretics. Frequency of urination at night (nocturia) is caused by improved perfusion of the kidney when the patient is lying down.

RIGHT-SIDED HEART FAILURE (RIGHT VENTRICULAR DYSFUNCTION)

The signs and symptoms of right ventricular dysfunction are related to hypervolemia, valvular disease, or pulmonary HTN. The overall effect is elevation in central venous pressure.

Dependent edema results from increased venous and capillary hydrostatic pressure, causing a redistribution of fluid from the intravascular to interstitial spaces. Ankle and pretibial edema are common findings after prolonged standing or sitting because fluid

tends to localize in the dependent portions of the body secondary to gravitational forces. Sacral edema can be present in patients at bed rest. Edema is subjectively quantified on a 1+ (minimal) to 4+ (severe) scale. A.J. has 3+ pitting edema.

Hepatomegaly, hepatic tenderness, and ascites (fluid in the abdomen) arise from hepatic venous congestion and increased portal vein pressure. Metabolism of drugs highly dependent on the liver for elimination can be impaired by both the retrograde venous congestion of the liver from right-sided HF and the decreased arterial perfusion of the liver from left-sided HF. Congestion of the gastrointestinal tract makes the patient anorectic.

Neck vein distension, primarily seen as internal jugular venous distension, denotes an elevated jugular venous pressure (JVP).

How high the neck veins are distended while the patient is lying down and how much the patient's head has to be raised before the jugular venous distension disappears gives the clinician a rough estimate of the patient's central venous pressure. Jugular distension in centimeters is measured as the vertical distance from the top of the venous pulsation down to the sternal angle. Neck vein distension of <4 cm when the patient is lying with the head elevated at a 45-degree angle is considered normal for an average, healthy adult. Applying pressure to the liver can cause further distension of the neck veins if hepatic venous congestion is present. This phenomenon is termed *hepatojugular reflux.*

EJECTION FRACTION MEASUREMENT

CASE 14-1, QUESTION 2: Does A.J. have LVSD?

SOB, crackles on auscultation, neck vein distension, edema, and nearly all of A.J.'s other signs and symptoms provide some important clues about the nature of the underlying cardiac abnormalities; however, they are limited in evaluating structural abnormalities. Some of these symptoms can be confused with other disorders, especially reduced exercise intolerance, which is often a gradual

process that patients may fail to recognize and report. An enlarged heart on a chest radiograph increases the suspicion of LVSD, but this finding can be absent in some patients with LVSD and present in others with normal LV function. Some patients may be asymptomatic with structural abnormalities.

The most useful method to diagnose HF with LVSD is by measuring the LVEF. All patients with suspected HF should have an EF measured before beginning therapy because the treatment strategies between HFrEF and HFpEF differ. Two-dimensional echocardiography coupled with Doppler flow studies (Doppler echocardiogram) is the diagnostic test of choice for measuring EF. This procedure uses sound waves to visualize and measure ventricular wall thickness, chamber size, valvular function, and pericardial thickness. EF is estimated based on changes in ventricular chamber size between diastole and systole. This method of EF measurement is not as technically accurate as that provided by ventriculography, but the procedure is more comfortable for the patient and the correlation of the measured EF to that of the other methods is acceptable.

Radionuclide left ventriculography (also called a multiple gated acquisition scan) uses radiolabeled technetium as a tracer to measure LV hemodynamics. Although this method is the most accurate measurement of EF, it is moderately invasive because it requires venipuncture and radiation exposure. In addition, radionuclide scanning does not provide information on the architecture of the left ventricle. Magnetic resonance imaging and computed tomography are useful in evaluating ventricular mass but do not provide EF data.

Subsequently, A.J. underwent an echocardiogram. The results were reported as LVH with mild-to-moderate depression of EF (30%–40%). Because he has systolic dysfunction and classic congestive signs, he fits the criteria for having congestive HF.

STAGES OF HEART FAILURE AND NEW YORK HEART ASSOCIATION CLASSIFICATION

Case 14-1, Question 3: What stage of HF does A.J. exhibit according to the ACC/AHA criteria? How severe is A.J.'s disability, according to the NYHA functional classification of HF?

The updated ACC/AHA staging scheme and the NYHA functional classification are summarized in **Figure 14-5**.[4,28]

PREDISPOSING FACTORS

Case 14-1, Question 4: What factors contributed to the cause of A.J.'s HF?

Age, HTN, MI, diabetes, tachycardia-induced cardiomyopathy, valvular heart disease, and obesity are well-established major risk factors associated with the development of HF. Other risk factors associated with HF are smoking, excessive intake of alcohol, dyslipidemia, anemia, and chronic kidney disease.[87] There is interest in biochemical and genetic markers that are associated with HF. CAD, and MI, in particular, is considered to be the most significant risk factor for HF in the elderly. During the past decades, there has been an increase in the incidence of HF after MI owing to the increased survival after MI.[88]

A.J. is especially vulnerable to HF because of his poorly controlled HTN, which increases afterload. HTN can lead to LVH, which is a compensatory response to increased afterload. LVH is associated with a higher risk of HF, especially in younger individuals.[6] The lifetime risk for individuals developing HF with BP of at least 160/90 mm Hg is double that for those with BP <140/80 mm Hg.[89] Preventive strategies directed toward earlier and more aggressive BP control can reduce the incidence of HF by almost 50% and its associated mortality as well.[6]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND SODIUM CONTENT

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their anti-inflammatory effects by inhibiting prostaglandins. Blocking

prostaglandins leads to sodium reabsorption and counteracts the beneficial effects of diuretics and ACEIs. The ibuprofen used for A.J.'s arthritis contributes to sodium overload. Epidemiologic studies indicate that NSAIDs exacerbate HF symptoms, resulting in hospitalizations for HF.[90–92] ACC/AHA practice guidelines recommend avoiding NSAIDs whenever possible in patients with HF.[1]

Another potential source of excess sodium is in IV formulations. Sodium chloride is often used as a diluent for IV drug administration. Some parenteral antibiotics, particularly nafcillin and ticarcillin, have high sodium content. Most prescription and nonprescription drug labels carry a disclosure of sodium content.

A.J.'s HTN and HF are both poorly controlled and he has gained 17.64 pounds (8 kg). His clinical presentation (orthopnea, dyspnea, SOB, lower extremity edema, elevated JVP) clearly indicates fluid overload. This could be a result of high-dose ibuprofen use. His HCTZ should be replaced by a loop diuretic to enhance diuresis. Also, an ACEI should be added to the current regimen for BP control. Once he is euvolemic, the addition of a β-blocker before discharge should be considered. Lowering the dose or preferably discontinuing all NSAIDs might reduce sodium retention and allow ACEI therapy to be more effective. Acetaminophen is an alternative for treating his osteoarthritis.

DIET

It is possible that A.J.'s diet contains a considerable excess of sodium from foods such as canned soups and vegetables, potato chips, or overuse of salt at mealtime. Dietary supplements and sports drinks can also be rich sources of sodium. He should follow a controlled-sodium (2–3 g/day) diet. If salt substitutes are used, he should be warned that they are high in potassium and could cause hyperkalemia if used concurrently with potassium supplements, an AA, or other potassium-sparing diuretics.

Drug-Induced Heart Failure

Case 14-1, Question 5: What are the basic mechanisms by which drugs can induce HF, and how can an understanding of these mechanisms be predictive of the drugs to avoid in A.J.?

Drug-induced HF is mediated by three mechanisms: inhibition of myocardial contractility (negative inotropic agents and direct toxins), proarrhythmic effects, or expansion of plasma volume (**Table 14-5**). The latter category includes drugs that act primarily on the kidney (to either alter RBF or increase sodium retention) or those that increase total body sodium and water because of their high sodium content.

Table 14-5
Drugs That May Induce Heart Failure

Negative Inotropic Agents	
β-Blockers[a]	Most evident with propranolol or other nonselective agents
	Less with agents with intrinsic sympathomimetic activity (acebutolol, carteolol, pindolol); can also be caused by use of timolol eye drops
Calcium channel blockers[a]	Verapamil has most negative inotropic and AV-blocking effects; amlodipine has least.
Antiarrhythmics	Disopyramide, flecainide, dronedarone
Direct Cardiotoxins	
Cocaine, amphetamines	Overdoses and long-term myopathy
HER2-Targeted Therapies	Trastuzumab, pertuzumab
Alkylating agents	Cyclophosphamide
Proarrhythmic Effects	
Class IA, class III antiarrhythmic drugs	QT interval widening
	Probable torsades de pointes
	HF develops if disturbed rhythm compromises cardiac functioning.
Nonantiarrhythmic drugs	Same mechanism as given earlier
(See Crouch et al[91] for a	Often associated with drug interactions that inhibit

complete list)	the metabolism of the offending drug, leading to higher than desired plasma levels
Expansion of Plasma Volume	
Antidiabetics	
	Na retention with pioglitazone and rosiglitazone
NSAID	Prostaglandin inhibition; Na retention
Glucocorticoids, androgens, estrogens	Mineralocorticoid effect; Na retention
Licorice	Aldosterone-like effect; Na retention
Antihypertensive vasodilators (hydralazine, methyldopa, prazosin, minoxidil)	↓Renal blood flow, activation of renin–angiotensin system
Drugs high in Na^+	Selected IV cephalosporins and penicillins
	Effervescent or bicarbonate-containing antacids or analgesics
	Also liquid nutrition supplements
Unknown Mechanism	
Tumor necrosis factor antagonists	Multiple case reports of new-onset HF or exacerbation of prior HF with etanercept and infliximab in patients with Crohn disease or rheumatoid arthritis

AV, atrioventricular; HF, heart failure; IV, intravenous; Na, sodium; NSAID, nonsteroidal anti-inflammatory drugs.

[a]β-Blockers and verapamil may be beneficial in diastolic heart failure. Carvedilol and metoprolol counteract autonomic hyperactivity in systolic dysfunction.

Because A.J. has symptoms of HF and structural changes in cardiac architecture, he is in ACA/AHA stage C. On admission, A.J. is in NYHA functional class III as evidenced by a need to sleep upright and an inability to undertake even minimal physical activity. It is important to recognize that HF can progress very slowly in some patients and very rapidly in others. A patient with MI could move from stage A to stage C.

The most recognized negative inotropic agents are the β-blockers, which decrease myocardial contractility and slow the HR. Both of these factors can compromise CO. Other well-documented negative inotropic drugs include the non-dihydropyridine CCBs (verapamil and diltiazem), and some antiarrhythmic agents (disopyramide, flecainide, and dronedarone). The anthracyclines (daunorubicin and doxorubicin) have a direct, dose-related cardiotoxicity that can be minimized by limiting total cumulative doses to 500 mg/m^2 (see Chapter 94, Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents).[93,94] Cocaine and alcohol are cardiotoxins when used chronically in large quantities or after an overdose. Drugs that increase the incidence of arrhythmias will worsen HF if the abnormal rhythm compromises cardiac functioning or output.

Drugs that promote sodium and water retention include NSAIDs, certain antihypertensive drugs, glucocorticoids, androgens, estrogens, and licorice. Weight gain and peripheral and pulmonary edema have been observed in patients on pioglitazone and rosiglitazone.[95] Worsening of HF appears to be dose dependent and presumed to be at least partly caused by fluid retention. As a consequence, the package inserts for pioglitazone and rosiglitazone recommend they not be administered to patients with NYHA class III or IV HF and that they be used cautiously in earlier stages of HF.[95] Saxagliptin has been also associated with an increased risk of HF hospitalizations. The FDA has initiated an investigation to further evaluate this risk.[96]

TREATMENT

Therapeutic Objectives

Case 14-1, Question 6: What are the therapeutic goals in treating A.J.?

Cure is not a feasible therapeutic objective in patients with most forms of HF, the exceptions being patients who are candidates for cardiac transplantation or who have certain forms of viral, alcohol-induced, or tachycardia-induced dilated cardiomyopathy. The immediate objective for A.J. is to provide symptomatic relief by reducing his SOB and PND, improve sleep quality, and increase exercise tolerance. Parameters to measure success include reduced peripheral and sacral edema, weight loss, slowing of the HR to <90 bpm, normalization of BP, reduction of BUN, reduction of heart size on chest radiograph, decreased neck vein distension, and loss of the S_3 heart sound. Long-range goals are to improve A.J.'s EF and quality of life including better tolerance of daily life activities, fewer future hospitalizations, avoidance of side effects of his therapy, and, ultimately, an increased survival time. The achievement of these goals depends on the severity of A.J.'s disease, his understanding of his disease, and his adherence to prescribed interventions.

Diuretics

FUROSEMIDE AND OTHER LOOP DIURETICS

Case 14-1, Question 7: Bed rest and a 3-g sodium diet were ordered. The medical team decides to begin furosemide for A.J. What is the rationale for using diuretics and what route, dose, and dosing schedule should be used?

Excessive volume increases the workload of a compromised heart, and diuretics are an integral part of therapy. This is especially true if volume overload is symptomatic (dyspnea) as it is in A.J. Diuretics produce rapid symptomatic improvement. They relieve pulmonary and peripheral edema within hours, whereas the effects of ACEIs, β-blockers, and digoxin take days to months to be fully realized. Diuretics, however, should not be used alone. Even when they are initially successful in controlling symptoms and reducing edema, they are ineffective in maintaining clinical stability for long periods without the addition of other drugs. More importantly,

activation of the RAAS and sympathetic nervous system in response to diuresis could lead to HF progression.

All current guidelines recommend diuretic therapy, both acutely and chronically, if clinical volume overload is evident, but further state that patients without edema can be treated either intermittently or without diuretics.[1] Diuretics used on an intermittent (as-needed) basis are titrated based on changes in weight gain, neck vein distension, peripheral edema, or SOB. Patients with a good understanding of their disease can be instructed to weigh themselves daily and start taking their diuretic if they gain >1 to 2 pounds (0.45–0.90 kg) in 1 day or 5 pounds (2.27 kg) in 1 week or have leg or abdominal swelling. Diuretics can be withheld as long as patients are at their target dry weight. In other cases, diuretic-free intervals or weekends can be arranged. Even with these options, if the patient has experienced volume overload at some time during the course of their disease, either past or present, a diuretic should always be readily available.[97] Despite remarkable initial benefits, vigorous diuretic therapy carries the risk of volume depletion, electrolyte abnormalities, and diminished CO. Abrupt worsening of renal function (increased BUN or SCr) or hypotension indicates the need to temporarily withhold diuretics.

Route of administration

Furosemide is a commonly used loop diuretic because of clinical experience and low cost. Bumetanide and torsemide are preferred in some settings because of more predictable absorption.[47,63,98,99] Ethacrynic acid, which is also a loop diuretic, is not preferred because of its ototoxic potential. However, unlike other loop diuretics, ethacrynic acid does not contain a sulfonamide moiety, and it is mainly reserved for patients with severe sulfonamide allergies to other loop diuretics.

According to one group of investigators, patients with HF treated with torsemide fare better than do those receiving furosemide.[99] During a 1-year open-label trial, patients receiving torsemide were less likely to be admitted to the hospital for HF (17% torsemide vs

32% furosemide). Admissions for all CV causes were also lower among patients taking torsemide (44%) than among patients taking furosemide (59%). Fatigue scores improved to a greater extent in patients treated with torsemide, but no difference was found in the dyspnea score. Torsemide is more expensive than is furosemide, and this may be an issue for some patients.

Erratic responses to furosemide are prevalent in persons with severe HF or diminished renal function. Some patients respond promptly and vigorously to small oral doses of furosemide, whereas others require large IV doses to achieve only minimal diuresis. Part of these differences can be explained by the drug's pharmacokinetics.[56,100] Loop diuretics are highly protein bound and have to be actively secreted into the proximal tubular lumen to elicit a response. Tubular secretion of loop diuretics can be compromised in the presence of increased levels of endogenous organic acids because of renal insufficiency and drugs (NSAIDs) that are competing for the same transporters. Also, oral absorption of furosemide is erratic and incomplete, averaging 50% to 60% in healthy subjects and 45% in those with renal failure. When taken with a meal, absorption is delayed, but the total amount absorbed does not differ. There are claims that the absorption and, therefore, effectiveness of furosemide are further diminished in patients with HF attributable to edema of the bowel and decreased splanchnic blood flow. This has been partially refuted by one investigator, who noted an average furosemide bioavailability of 61% in patients with HF, the same as in normal patients.[99] Total absorption in patients with HF varies widely (34%–80%); however, both the rate of absorption and the time to peak urinary excretion are delayed for furosemide and bumetanide.[56,57,101]

The rate and extent of absorption are not only different among individuals but intraindividual variability also exists. Ingestion of the same brand of furosemide by the same individual on multiple occasions can show up to a threefold difference in bioavailability. These differences are evident with the innovator's brand (Lasix®) or generic brands.[102,103]

Dosing

Typically, a patient's treatment is initiated with 20 to 40 mg of oral or IV furosemide given as a single dose and monitored for responsiveness (see **Table 14-3**). If the desired diuresis is not obtained, the dose can be increased in 40- to 80-mg increments to a total daily dose of 160 to 240 mg, usually divided into two or three doses. For torsemide, a usual starting dose is 10 to 20 mg/day, but a ceiling effect is noted in patients with HF at a dosage of 100 to 200 mg/day.[104] Equivalent doses of bumetanide are 0.5 to 1.0 mg once or twice daily, titrated to a maximum of 10 mg daily. Because A.J. is not in acute distress, it could be argued that oral therapy would suffice. The decision, however, is to give a single 40-mg IV dose of furosemide for immediate symptom control. Further increases in the dose or frequency (ie, twice-daily dosing) of diuretic administration may be required to maintain an active diuresis and sustain weight loss.

Another alternative in hospitalized patients is to administer loop diuretics via continuous infusion. Multiple studies have demonstrated the benefits of continuous infusions compared with intermittent infusions.[105–107] However, the results of these studies have been questioned because of a lack of methodologic rigor, and the studies have been underpowered to address the primary end points. Recently, the DOSE (Diuretic Optimization Strategies Evaluation) trial[108] showed no difference in efficacy or safety between intermittent IV bolus and continuous infusion. There are potential benefits of continuous infusion when compared with intermittent bolus dosing. Bolus diuretic dosing can cause a higher rate of diuretic resistance owing to the postdiuretic phenomenon. Continuous IV infusion results in a constant delivery to the tubule, potentially reducing this phenomenon. In addition, continuous infusions are also associated with a lower incidence of ototoxicity owing to lower peak concentrations. Patients who are candidates for continuous IV infusion should receive a loading dose before infusion to reach steady-state concentrations faster. However, if the patient has received one or more IV boluses within the previous few hours, then

an infusion can be started without a loading dose. In case of inadequate response, the loading dose should be repeated, and the infusion rate increased. The infusion rate depends on the patient's renal function and response.

ADVERSE EFFECTS

CASE 14-1, QUESTION 8: Examine A.J.'s laboratory values (see Question 1). Does A.J. have any abnormal values? What is the significance of these abnormalities?

Azotemia

A.J. has an elevated BUN (40 mg/dL) but a normal SCr (0.8 mg/dL). Worsening renal function is characterized by an elevation of BUN and creatinine. A disproportionately elevated BUN relative to creatinine is indicative of prerenal azotemia, secondary to poor renal perfusion from HF or overdiuresis. SCr will also rise in some patients with prerenal azotemia but will quickly return to normal with rehydration.

A.J.'s laboratory values reflect prerenal azotemia. The most probable cause of his azotemia is decreased RBF secondary to decompensated HF. Diuretics should not be withheld and, in fact, judicious diuresis should improve his HF and help lower his BUN. Caution must be exercised because excessive diuresis and volume depletion can cause renal ischemia, leading to true renal damage. If this happens, the SCr also will rise.

Hyponatremia

A low serum sodium of 132 mEq/L is noted. Low serum sodium, however, is not necessarily a sign of overdiuresis. A person may be significantly overdiuresed with a body deficit of sodium, but if that sodium is lost isotonically, the serum sodium concentration will be normal. Conversely, a person such as A.J. can be hypervolemic, indicating excessive body sodium, but the serum sodium concentration may be normal or even low.

Hyponatremia (low serum sodium concentration) reflects the dilutional effect of extra free water in the plasma. The most common causes of dilutional hyponatremia are excess ADH production or excessive free water intake. Individuals on severely sodium-restricted diets can experience hyponatremia. Likewise, patients given too much diuretic and who are then given salt-free fluids or who have compensatory ADH release can become hyponatremic. Patients with HF or hepatic cirrhosis are more likely to develop diuretic-induced dilutional hyponatremia because of preexisting defects in free water excretion. The exact cause of hyponatremia in A.J. is unknown, but his marginally low serum sodium does not contraindicate continued diuretic therapy. In general, levels of serum sodium concentration <120 to 125 mEq/L are associated with adverse events in patients with HF; chronic serum sodium concentrations of ≤130 mEq/L are associated with higher morbidity and mortality.[109] Asymptomatic hyponatremia can be treated with water restriction. In the setting of volume depletion, IV administration of normal saline may be effective. Vasopressin receptor antagonists can be used in patients with HF and hypervolemic hyponatremia.

Hypokalemia

A.J. has a serum potassium of 3.2 mEq/L. Hypokalemia is associated with an increased incidence of arrhythmias. Some studies showed increased ectopic activity with serum levels between 3.0 and 3.5 mEq/L.[110–112] It is estimated that the risk of arrhythmias increases by 27% with each 0.5 mEq/L reduction in the plasma potassium concentration <3.0 mEq/L.[113]

In chronic HF, potassium abnormalities are commonly seen. The risk of SCD in patients with HF may be lessened by using low doses of diuretics in combination with potassium-sparing agents, with the goal of maintaining serum potassium levels between 4.5 and 5.0 mEq/L.[114]

A.J. will be receiving increased doses of diuretics for the next several days and, therefore, may need additional potassium supplementation to prevent life-threatening hypokalemia. In addition,

if he needs digoxin therapy in the future, low serum potassium levels can predispose him to digitalis toxicity. Potassium replacement is warranted for A.J. at this time. Long-term potassium supplementation may not be necessary with concomitant administration of ACEIs. If hypokalemia persists, A.J. can be started on an AA.

Hypomagnesemia

A.J.'s serum magnesium level is 1.5 mEq/L. Severe hypomagnesemia can lead to somnolence, muscle spasms, a decreased seizure threshold, and cardiac arrhythmias, effects similar to those seen with hypokalemia. Some investigators have claimed that many of the arrhythmias previously ascribed to diuretic-induced hypokalemia were actually caused by diuretic-induced hypomagnesemia.[115] Concurrent hypokalemia and hypomagnesemia can be especially dangerous. A.J. should be given 1 g of magnesium sulfate IV and observed for changes in his magnesium level. If needed, he could be given chronic oral supplements of magnesium.

Hyperuricemia

Increases of 1 to 2 mg/dL in uric acid levels are common during thiazide administration. Rarely, 4- to 5-mg/dL elevations have been reported. A.J.'s uric acid level is 8 mg/dL, which is slightly elevated. It has been proposed that serum uric acid levels may be a valuable prognostic marker in patients with HF. One study indicates a graded relationship between serum uric acid and HF survival.[116] In HF, xanthine oxidase is upregulated, which can lead to endothelial dysfunction. Therefore, treatment with allopurinol may improve endothelial function and promote reverse remodeling. The relationship between serum uric acid and CV disease is still controversial, and the guidelines do not recommend the use of xanthine oxidase inhibitors to prevent CV disease. In patients who experience symptomatic hyperuricemia, the addition of allopurinol or other urate-lowering agents should be considered (see Chapter 45, Gout and Hyperuricemia).

B-type natriuretic peptide

A.J.'s BNP is elevated (1365 pg/mL). Various studies evaluating the diagnostic accuracy of BNP and NT-proBNP have used different lower limits to define normal values. The most commonly used plasma concentration to define the upper limit of normal for BNP is 100 pg/mL, with concentrations >400 pg/mL being considered a strong indicator of HF. The age-related NT-proBNP diagnostic upper limit of normal is 125 pg/mL for patients younger than age 75 years, and 450 pg/mL for patients older than age 75 years. If the patient has a level below the upper limit of normal for the respective assay used, then the symptoms are most likely attributable to causes other than HF. In patients with renal impairment, the clearance of these peptides is reduced; therefore, the upper limit of normal is 200 pg/mL for BNP and the corresponding value for NT-proBNP is 1200 pg/mL.[117] Moreover, concentrations of these biomarkers are influenced by age, sex, obesity, and other cardiac and noncardiac comorbidities. Asymptomatic patients with HF can also present with elevated BNP or NT-proBNP levels. This confounds the accurate interpretation of these markers and makes it challenging to integrate their usefulness into routine clinical practice. Elevated BNP and NT-proBNP have an established utility in ruling out HF in patients who present to the ED with SOB.[24] According to the ACC/AHA guidelines, measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF; however, the role of these biomarkers in reducing morbidity or mortality in HF is not well established. Several NP-guided therapy trials have been published.[118–120] The BNP- or NT-proBNP–guided HF therapy can be useful to achieve GDMT in selected clinically stable patients, but it is unclear if such an approach improves outcome. The *Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure* (GUIDE-IT) study,[121] designed to assess the effects of NP-guided therapy in high-risk patients with LVSD, did not improve clinical outcomes between biomarker-guided treatment strategy versus usual care. It is still not clear when to use biomarkers to adjust HF medications. BNP levels may be elevated in patients

receiving ARNI because BNP is a substrate for neprilysin. Therefore, the 2021 update states that the utility of NP biomarker levels should be cautiously interpreted in patients on ARNI.[45] A.J.'s elevated BNP level, along with his clinical presentation, is indicative of HF exacerbation.

POTASSIUM SUPPLEMENTATION

Case 14-1, Question 9: The physician gave A.J. one 1-g dose of magnesium sulfate and three 20-mEq doses of potassium chloride IV. This raised his serum magnesium to 2.0 mEq/L and his potassium to 3.9 mEq/L. Should he receive prophylactic magnesium or potassium supplementation? What is an appropriate dose?

At this time, A.J. does not need further magnesium replacement, but his serum magnesium level should be measured again after he has received furosemide for a few days. If the level drops again, maintenance therapy with oral magnesium oxide tablets can be started.

A fall in serum potassium concentration can be seen within hours of the first dose of a diuretic, and the maximal fall usually is reached by the end of the first week of treatment. Potassium supplementation is not required in all patients receiving diuretics. They should be monitored frequently in the first few months of diuretic therapy to determine their potassium requirements. Similarly, when diuretics are stopped, it can take several weeks for serum potassium to return to baseline. Therefore, it is possible that A.J.'s admitting potassium level of 3.2 mEq/L reflects the nadir of his response to HCTZ. His initial response to potassium supplementation shows that his hypokalemia will be easily controlled. It might be argued that he should be observed for a few days and not given further supplements; however, because his diuresis is to be increased and if digoxin may later be considered, potassium supplementation is warranted. Long-term potassium supplementation may not be necessary with concomitant administration of ACEIs and AAs.

Because A.J. is started on furosemide, HCTZ should be discontinued. If hypokalemia persists, the AA dose can be uptitrated.

Dose requirements

It is difficult to predict the dose of potassium chloride that will be required to maintain proper potassium balance. Many patients do well with 20 mEq/day, but it is questionable how many patients need any supplement at all. People with well-documented hypokalemia can require anywhere from 20 to 120 mEq of potassium chloride per day.[122–124] Those patients with disease states associated with high circulating aldosterone levels require doses of potassium in excess of 60 mEq/day. In patients who need long-term potassium supplementation, efforts should be made to increase doses of ACEIs to target doses or maximal tolerated doses, and appropriate addition of an AA should be considered. However, a few selected patients may still need to take potassium supplementation, despite the addition of an AA.

MONITORING

Case 14-1, Question 10: After a single 40-mg IV dose of furosemide, A.J. is begun on 40 mg of furosemide each morning and potassium chloride tablets 20 mEq bid. How should his therapy be monitored?

A.J. needs to be monitored for both an improvement in his HF and for side effects (see **Tables 14-4** and **14-6**). Subjectively, the clinician should monitor for decreased pulmonary distress and an increased exercise tolerance, demonstrating control of HF. Objective monitoring parameters for disease control include weight loss (ideal, 1.10–2.20 pounds [0.5–1 kg]/day until ideal dry weight is achieved), a decrease in edema, flattening of neck veins, and disappearance of the S_3 gallop and rales. Because A.J. has HTN, his BP also requires monitoring, with a goal to reduce it to <130/80 mm Hg.

Table 14-6
Monitoring Parameters With Diuretics

↓CHF symptoms (see Table 14-4)
Weight loss or gain; goal is 1- to 2-lb (0.45- to 0.90-kg) weight loss/day until "ideal weight" achieved[a]
Signs of volume depletion
Weakness
Hypotension, dizziness
Orthostatic changes in BP[b]
↓Urine output
↑BUN[c]
Serum potassium and magnesium (avoid hypokalemia and hypomagnesemia)
↑Uric acid
↑Glucose

BP, blood pressure; BUN, blood urea nitrogen; HF, heart failure.

[a]Weight loss may be greater during the first few days when significant edema is present.

[b]A ↓ in systolic BP of 10 to 15 mm Hg or a ↓ in diastolic blood pressure (BP) of 5 to 10 mm Hg.

[c]A rising blood urea nitrogen (BUN) can be caused by either volume depletion from diuretics or poor renal blood flow from poorly controlled heart failure (HF). Small boluses of 0.9% saline can be given cautiously to differentiate a rising BUN from volume depletion versus poor cardiac output. If volume depletion is present, saline will cause an ↑ in urine output and a ↓ in BUN. However, if the patient has severe HF, the saline could cause pulmonary edema.

Patients are instructed to record their weight each day and are allowed to adjust their diuretic dose based on changes observed. If they are at their ideal "dry weight," they may reduce their dose of diuretic by 50% or even hold one or more doses. If weight increases >1 or 2 pounds (0.45 or 0.90 kg) in a day or 5 pounds (2.27 kg) per week, edema increases, or SOB returns, the dose of diuretic is temporarily increased.

Dizziness and weakness are subjective indices of volume depletion, hypotension, or potassium loss. Muscle cramps and

abdominal pain could indicate rapid changes in electrolyte balance. Objectively, a lowering of BP, especially on standing, and a rising BUN (prerenal azotemia) signify overdiuresis. Serum sodium, potassium, and uric acid should be monitored routinely. Questioning the patient with regard to the onset of diuresis (relative to drug ingestion) and the duration of the diuretic effect helps develop the most convenient and effective schedule for the patient.

CASE 14-1, QUESTION 11: If A.J.'s furosemide dose was increased to 80 mg twice a day without much response, what should be the next step?

REFRACTORY PATIENTS: COMBINATION THERAPY

All loop and thiazide diuretics must reach the tubular lumen to be effective. Because these drugs are highly bound to serum proteins and endogenous organic acids, they cannot enter the tubular lumen by glomerular filtration. For diuresis to begin, they must be transported into the proximal tubule by active secretion from the blood into the tubule. If this active transport is blocked, diuretics will not reach their site of action. This can lead to a diminished diuretic response in patients with either renal insufficiency or decreased RBF associated with decompensated HF. Patients with renal insufficiency or poor RBF often require large doses of diuretics to achieve a desired response. Endogenous organic acids can accumulate during renal insufficiency, avidly binding the drug and preventing its access to the site of action.[56,57] Both the total amount of drug delivered to the tubule and the rate of delivery of the drug to the tubule determine the magnitude of diuretic response elicited.[56,57] This explains why 80 mg of furosemide yields more diuresis than a 40-mg dose and why an IV injection provides a more rapid and vigorous diuresis than an oral dose. Once a threshold concentration (ceiling dose) is achieved within the tubule, higher concentrations produce no greater intensity of effect, but the duration of action may be prolonged.

Many patients exhibit a blunted diuretic response with continued therapy for unknown reasons. Generally, alternative treatment plans are pursued when the dose given approaches the ceiling doses for

each drug listed in **Table 14-3**. Continuous infusions of furosemide (5–15 mg/hour), bumetanide (0.5–1 mg/hour), or torsemide (3 mg/hour) can be more efficacious than are intermittent bolus doses in patients with severe HF or renal insufficiency.[56,57,125–127] Even higher doses have been recommended: 0.25 to 1 mg/kg/hour for furosemide, 0.1 mg/kg/hour for bumetanide, and 5 to 20 mg/hour for torsemide.[128] An aggressive protocol of a 100-mg IV bolus of furosemide followed by a continuous IV infusion at a rate of 20 to 40 mg/hour, which is doubled every 12 to 24 hours in unresponsive patients, to a maximal infusion rate of 160 mg/hour to attain a diuresis rate of ≥100 mL/hour has been described.[129]

In some instances, switching from one loop diuretic to another can overcome the problem.[129] For example, torsemide or bumetanide might work when furosemide fails because of more reliable absorption.[98,99] If this maneuver fails, a combination of diuretics can be tried. The most effective regimens combine drugs that work at two different parts of the tubule.[128] For example, a loop diuretic is used with metolazone, which blocks sodium reabsorption in the distal tubule. Various thiazide diuretics, including chlorthalidone, chlorothiazide, and HCTZ, have been reported to effectively enhance diuresis when combined with a loop diuretic. Triple-therapy regimens of metolazone, a loop diuretic, and an AA are used to optimize diuresis and electrolyte control.

Most clinicians choose a combination of metolazone plus furosemide or bumetanide. A wide range of metolazone dosages has been investigated.[130] Typically, a low dose of metolazone (2.5–5 mg) is first added to the furosemide therapy. Metolazone can be given intermittently (two to three times/week or as needed) to relieve congestion. The longer duration of action for metolazone can cause a greater than predicted diuresis and electrolyte loss when combined with a loop diuretic. Thus, careful monitoring of weight, urine output, BP, BUN, potassium, magnesium, and SCr is required. Because no parenteral form of metolazone exists, chlorothiazide, at a dose of 500 to 1000 mg once or twice daily, is an alternative to the thiazide diuretic that can be given intravenously. Although A.J.’s furosemide dose could be increased, metolazone 2.5 mg daily was added. A.J.

may also require additional doses of potassium supplementation to avoid hypokalemia with the addition of metolazone.

Angiotensin Converting Enzyme Inhibitors

AGENTS OF CHOICE

Case 14-1, Question 12: Along with furosemide, A.J. was started on 10 mg of lisinopril daily. Are there specific ACEIs approved for use in patients with HFrEF?

As a general rule, formulary decisions are first based on comparative pharmacologic activity, efficacy, and drug safety. Other factors to consider are labeled (FDA approved) indications, convenience of dosing schedule, and—all else being equal—the cost to the institution and the patient. HTN is the primary indication for all of the ACEIs. Not all ACEIs have an indication for HF.

ACEIs inhibit ACE (also called kinase II), reducing the activation of angiotensin II, a major contributor to the undesired hemodynamic responses to HF. Decreased circulating levels of NE, vasopressin, neurokinins, luteinizing hormone, prostacyclin, and NO also have been noted after administration of ACEIs.

In addition, ACE is responsible for degradation of bradykinin, substance P, and, possibly, other vasodilatory substances unrelated to angiotensin II. Thus, part of the beneficial effects of ACEIs is caused by the accumulation of bradykinin (**Fig. 14-8**). After attaching to bradykinin-2 (B_2) receptors, vasodilation is produced by stimulating the production of arachidonic acid metabolites, peroxidases, NO, and endothelium- derived hyperpolarizing factor in the vascular endothelium. In the kidney, bradykinin causes natriuresis through direct tubular effects.

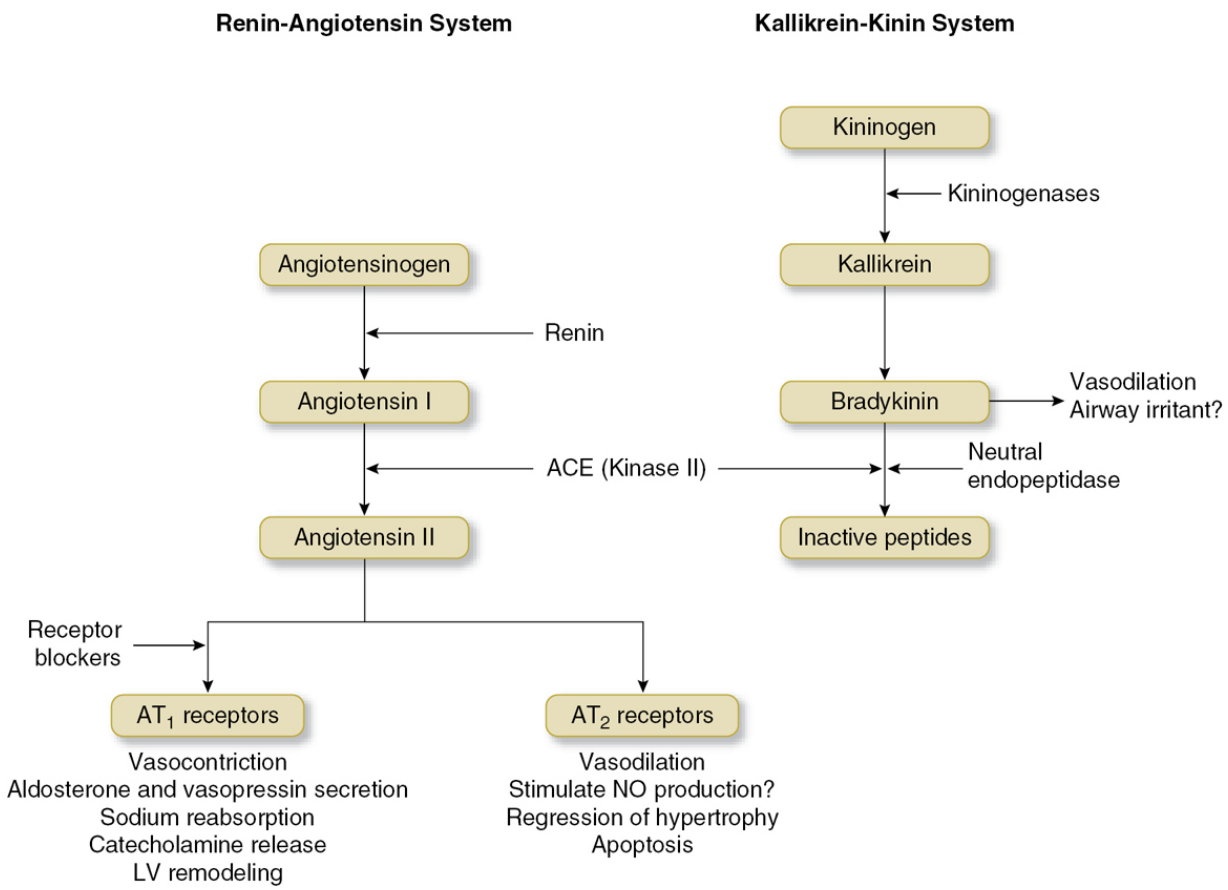


Figure 14-8 Angiotensin receptor blocker mechanism. ACE, angiotensin converting enzyme; LV, left ventricular; NO, nitric oxide.

The net effect is that ACEIs regulate the balance between the vasoconstrictive and salt-retentive properties of angiotensin II and the vasodilatory and natriuretic properties of bradykinin. The effects of ACEIs are reduced pulmonary capillary wedge pressure (PCWP; preload) and lowered SVR and systolic wall stress (afterload). CO increases without an increase in HR. ACEIs promote salt excretion by augmenting RBF and reducing the production of aldosterone and ADH. The beneficial effects on RBF, coupled with the drug's indirect inhibition of aldosterone, lead to a mild diuretic response, a distinct benefit compared to hydralazine.

Vasodilation and diuresis are not the only values of ACEIs in HF. Angiotensin II enhances vascular remodeling, whereas bradykinin impedes this process.[60,131] ACEIs impede ventricular remodeling by blocking the effects of angiotensin II on cardiac myocytes. Evidence

as to whether preserving bradykinin levels affects remodeling is inconclusive, although it might attenuate the progressive deposition of collagen during the chronic phase of post-MI cardiac remodeling.

Individual ACEIs with FDA-labeled approvals for the treatment of HF or LV dysfunction after MI are included in **Table 14-7**. There is no reason to favor one ACEI over another except in the case of optimizing dosing schedules for patients and trying to use once-daily dosing, if possible, to improve medication adherence rates.

Table 14-7

Angiotensin Converting Enzyme Inhibitor Dosing in Heart Failure With Reduced Ejection Fraction

Drug	Available Dosage Form	Initial Dose[a]	Maximal Dose
Captopril[b]	12.5, 25, 50, 100 mg tablets	6.25–12.5 mg tid	100 mg tid
Enalapril[c]	2.5, 5, 10, 20 mg tablets	2.5–5 mg every day	20 mg bid
Fosinopril	10, 20, 40 mg tablets	5–10 mg every day	40 mg every day
Lisinopril	2.5, 5, 10, 20, 40 mg tablets	2.5–5 mg every day	40 mg every day
Quinapril[c]	5, 10, 20, 40 mg tablets	5–10 mg every day	20 mg bid
Perindopril	2, 4, 8 mg tablets	2 mg every day	16 mg every day
Ramipril[c]	1.25, 2.5, 5, 10 mg capsules	1.25–2.5 mg every day	10 mg bid
Trandolapril	1, 2, 4 mg tablets	1 mg every day	8 mg every day

Benazepril, cilazapril, moexipril, perindopril, ramipril, and trandolapril are not labeled for use in heart failure.

ACE, angiotensin converting enzyme; bid, two times a day; tid, three times a day.

[a]Start with lowest dose to avoid bradycardia, hypotension, or renal dysfunction. All but captopril given every day in the morning at starting doses. Increase dose slowly at 2- to 4-week intervals to assess full effect and tolerance.

[b]Captopril is short acting. Start with a 6.25- or 12.5-mg test dose, then 6.25 to 12.5 mg three times a day (tid).

[c]Enalapril, quinapril, and ramipril could possibly be given every day instead of two times a day (bid) based on half-life.

Numerous placebo-controlled trials have documented the favorable effects of ACEI therapy on hemodynamic variables, clinical status, and symptoms of HF,[132,133] and demonstrated a consistent 20% to 30% relative reduction in HF mortality. ACEI therapy is generally better than are other vasodilator regimens, including the hydralazine–nitrate combination or ARBs after considering efficacy and tolerability.

Table 14-8 provides a brief summary of the results of the key ACEI HFrEF trials.[17,66,67,133–135] Of the five approved agents, the best evidence for improved survival is available for enalapril in both chronically symptomatic patients (NYHA classes II–IV) and asymptomatic patients with evidence of an impaired EF after an MI.[136–139]

Table 14-8
Clinical Trials of Angiotensin Converting Enzyme Inhibitors in Heart Failure With Reduced Ejection Fraction

Study	Patient Population	ACEI	Time Started After MI	Treatment Duration	Outcome
Studies in LV Dysfunction					
CONSENSUS[137]	NYHA IV (N = 253)	Enalapril vs placebo		1 day–20 months	Decreased mortality and HF
SOLVD-Treatment[134]	NYHA II/III (N = 2569)	Enalapril vs placebo		22–55 months	Decreased mortality and HF
V-HeFT II[253]	NYHA II/III (N = 804)	Enalapril vs hydralazine, isosorbide		0.5–5.7 years	Decreased mortality and sudden death
SOLVD-Prevention[315]	Asymptomatic LV dysfunction (N = 4228)	Enalapril vs placebo		14.6–62 months	Decreased mortality and HF hospitalizations
Studies in LV Dysfunction After MI					
SAVE[314]	MI, decreased LV function (N = 2331)	Captopril vs placebo	3–16 days	24–60 months	Decreased mortality
CONSENSUS II[316]	MI (N = 6090)	Enalaprilat/enalapril vs placebo	24 hours	41–180 days	No change in survival; hypotension with enalaprilat
AIRE[317]	MI and HF (N = 2006)	Ramipril vs placebo	3–10 days	>6 months	Decreased mortality
ISIS-4[318]	MI (N > 50,000)	Captopril vs placebo	24 hours	28 days	Decreased mortality
GISSI-3[319]	MI (N = 19,394)	Lisinopril vs placebo	24 hours	6 weeks	Decreased mortality
TRACE[320]	MI, decreased LV function (N = 1749)	Trandolapril vs placebo	3–7 days	24–50 months	Decreased mortality
SMILE[321]	MI (N = 1556)	Zofenopril vs placebo	24 hours	6 weeks	Decreased mortality

ACE, angiotensin converting enzyme; HF, heart failure; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association.

Source: Reprinted with permission from Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation*. 1998;97(14):1411–1420. © 1998 by American Heart Association.

The ACC/AHA guidelines recommend selecting an ACEI that has shown reductions in both morbidity and mortality in clinical trials in HFrEF. The following ACEIs are considered first-line options based on clinical trials: captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, or trandolapril.[1,11,45]

Captopril and lisinopril are both active as the parent compound and do not have active metabolites. All other ACEIs are prodrugs that require enzymatic conversion to active metabolites. Captopril has a short duration of action, necessitating three times daily administration in most patients. Although this characteristic may be advantageous when initiating therapy by allowing closer assessment of early side effects, for chronic maintenance, it is preferable to use a drug that can be given either once or twice daily. All other ACEIs meet this criterion. Package insert labeling and common standards of practice have led to twice-daily dosing, especially at higher doses, for enalapril, quinapril, and ramipril.

A.J.'s physician chooses to start lisinopril 10 mg daily based on evidence of clinical efficacy, improved survival, and availability as a generic medication. If there were concerns about hypotension, then captopril would be preferred during the initial 1 to 2 days of initiation therapy to avoid dropping the patient's BP too quickly.

Dose–response relationships

Case 14-1, Question 13: What is the target dose of lisinopril in A.J.? Do all patients need to be titrated to target doses?

Clinical evidence shows a relationship between the degree of improvement in HF symptoms and the dose of drug given. Larger doses are more likely to improve the patient's quality of life and reduce the incidence of hospital stays, but the impact of larger doses on mortality is less clear. At the same time, higher doses are associated with a greater risk of side effects. Based on these principles, proposed recommended starting and maximal doses for the ACEIs are listed in **Table 14-7**.[1]

The guidelines recommend that ACEIs be initiated at low doses and titrated to the maximal tolerated target dose. Supporting this principle are the results of the Assessment of Treatment with Lisinopril and Survival trial.[140,141] Lisinopril 2.5 to 5 mg (low dosage) or 32.5 to 35 mg (high dosage) was given to over 3000 patients. All-

cause mortality did not differ significantly between the two groups. In the high-dose group, hospitalizations and the combined end point of death and hospitalization were reduced by 24% (P = .003) and 12% (P = .002), respectively. The higher dose was tolerated by 90% of patients assigned this dose.

Despite these recommendations for using the highest tolerated doses, evidence also suggests that lower doses are beneficial. The UK Heart Failure Network Study found that 10 mg of twice-daily enalapril was no more effective than was 2.5 mg bid.[142] Mortality, evaluated separately, was 4.2%, 3.3%, and 2.9%, for low (2.5 mg bid), moderate (5 mg bid), and higher (10 mg bid) dosages, respectively, and not significantly different. The guidelines recommend prescribing doses that have reduced the risk of CV events in clinical trials, and if the trial doses cannot be achieved, then lower doses should be used.

For lisinopril, the recommended starting dosage is 2.5 to 5 mg/day. For older patients or those with other risk factors (systolic blood pressure [SBP] <100 mm Hg, those taking large doses of diuretics, or those with preexisting hyponatremia, hyperkalemia, or renal insufficiency), the starting dose of 2.5 mg/day would be more appropriate. This dose, or an equivalent with one of the other drugs, should be considered if the patient is being started directly on a long-acting drug without prior titration on captopril. For a patient such as A.J. who has already been treated with captopril for 2 days with no evidence of intolerance, a 10-mg dose is appropriate.

The long-term target maximum dosage of lisinopril for A.J. is 40 mg daily. No clear formula exists for deciding how quickly to titrate to this dose. It depends on the degree of reduction in his HF symptoms and side effects and the motivation to take the medication. Whenever dosage adjustments are made, it may take as few as 24 hours for the patient to perceive symptom reduction, but generally full hemodynamic affects are not reached for 1 to 2 months. Hypotension and other side effects are more immediate. A.J. should have his dose reassessed in 1 to 2 weeks to determine whether he can tolerate a dosage increase to 20 mg daily. An SCr and potassium should be ordered at this time to assess the safety of

titrating the ACEI. Thereafter, a doubling of the dose could occur every 2 to 4 weeks. Thus, it could take 2 months to titrate upward to 40 mg daily. If A.J.'s symptoms do not improve, but he has no side effects, titration can occur more quickly either by shortening the assessment periods (eg, every week) or by using larger dose increments.

ANGIOTENSIN RECEPTOR BLOCKERS

CASE 14-1, QUESTION 14: When should an ARB be used in A.J.?

Several clinical trials in HF have shown the therapeutic benefit of ARBs in modifying HF symptoms (**Table 14-9**).[143–150] A meta-analysis combined data on all-cause mortality and HF-related hospitalizations from a total of 17 clinical trials comparing an ARB with either placebo or an ACEI in patients with HF.[142] ARBs favorably improved exercise tolerance and EF compared with placebo. However, they were not superior to ACEIs in reducing all-cause mortality or hospitalizations for HF.

Table 14-9
Clinical Trials of Angiotensin Receptor Blockers in Heart Failure

Trial	Patient Population	ARB	Treatment Duration	Outcome
ELITE[148]	NYHA II–IV (*N* = 722) EF ≤40%	Losartan (50 mg every day) or captopril (50 mg tid)	48 weeks	No significant difference was observed for the primary end point (persistent renal dysfunction) or the secondary end point (composite of death/HF admissions). Losartan was associated with a lower mortality than was captopril.
RESOLVD[150]	NYHA II–IV (*N* = 768) EF ≤40%	Candesartan (4, 8, or 16 mg), or candesartan (4 or 8 mg) + 20 mg enalapril, or 20 mg enalapril	43 weeks	Combination has greater benefits on LV remodeling. No difference in mortality No difference in NYHA class, QoL, 6-minute walking distance
ELITEII[149]	NYHA II–IV (*N* = 3152) EF ≤40%	Losartan (50 mg every day) or captopril (50 mg tid)	48 weeks	Losartan was not superior to captopril in improving survival but was significantly better tolerated. A subgroup analysis of ELITE II found a greater risk of death when losartan was used in addition to β-blockers.
Val-Heft[151]	NYHA II–IV (*N* = 5010) EF <40%	Valsartan 160 mg bid or placebo bid	23 months	There was no difference in mortality between the two groups. In patients previously receiving both ACEI and a β-blocker (*N* = 1610), the risk of death was increased with the addition of valsartan.
CHARM[153] Alternative	NYHA II–IV (*N* = 2028) EF ≤40%	Candesartan (32 mg) vs placebo	34 months	23% reduction in CV mortality or HF hospitalization favoring the candesartan group. More side effects in the candesartan group (hypotension, hyperkalemia, ↑ SCr) vs placebo
CHARM[154] Added	NYHA II–IV (*N* = 2548) EF ≤40%	Candesartan (32 mg) + ACEI vs placebo	41 months	15% risk reduction in CV mortality or HF admissions compared with placebo. However, there were more side effects in the candesartan group (hypotension, hyperkalemia, ↑ SCr) vs placebo.
CHARM[156] Overall	NYHA II–IV (*N* = 7599)	Candesartan (32 mg) vs placebo	38 months	There was no overall difference in primary outcome of all-cause death.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; bid, two times a day; CV, cardiovascular; EF, ejection fraction; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association; QoL, quality of life; SCr, serum creatinine; tid, three times a day.

The first major clinical trial comparing an ARB with an ACEI in patients with HF was the *E*valuation of *L*osartan *I*n *T*he *E*lderly (ELITE) study.[149] Losartan was compared to captopril. For the primary end point, a sustained increase in renal function decline, the two drugs performed identically with 10.5% of subjects in each group having a >0.3 mg/dL rise in SCr. An unexpected finding was an insignificant trend toward more deaths from all causes in the captopril group (8.7%) compared with losartan (4.8%).

The follow-up ELITE II trial was specifically designed to test the hypothesis that losartan was superior to captopril in terms of reduction in mortality and morbidity in patients age 60 years and older.[145] No significant difference was seen in all-cause mortality, sudden death, or all-cause mortality plus hospitalization. Although

ARB treatment was not superior to ACEI therapy, it was better tolerated. Specifically, significantly fewer patients experienced cough with the ARB.

The Valsartan Heart Failure Trial (Val-HeFT) was a double-blind, placebo-controlled study to measure the morbidity and mortality in patients with HFrEF given valsartan.[151] Patients were randomly assigned to receive valsartan or placebo twice daily. There was no significant difference in all-cause mortality between the valsartan group (19.7%) and the control group (19.4%). Nearly 93% of patients in both groups were receiving an ACEI. Dizziness, hypotension, and renal impairment all occurred more frequently in those treated with valsartan.

Further, post hoc analysis found that within the 35% of subjects taking the combination of an ACEI and a β-blocker at baseline, the addition of valsartan as a third drug was associated with a trend toward increased morbidity and a statistically significant increase in the combined end point of mortality and morbidity. The overall study results suggested that a combination of valsartan and an ACEI reduces morbidity, but not mortality. More worrisome was the implication that the three-drug combination of valsartan, an ACEI, and a β-blocker adversely affects morbidity and mortality.[154]

The *VAL*sartan *I*n *A*cute myocardial i*N*farc*T*ion (VALIANT) trial of stable patients after MI with LV dysfunction was designed to test the hypothesis that valsartan alone and in combination with captopril (an ACEI) would improve survival. In VALIANT, 70% of the patients were also receiving β-blockers. All-cause mortality, the primary end point, was identical in all groups. In addition, an increased rate of side effects was seen in the combination ACEI/ARB group. Interestingly, among the subgroup of patients taking β-blockers, no evidence was found of harmful interaction with triple therapy.[152] As a result of the VALIANT trial, the FDA approved the use of valsartan in patients at high risk after a heart attack, and in those with HF.

The best evidence addressing the efficacy and safety of ARB in HF comes from a series of three investigations known collectively as the CHARM trial. The individual components of the CHARM Program are (a) CHARM-Alternative, (b) CHARM-Added, and (c) CHARM-

Preserved.[153–155] All three investigations were randomized, double-blind, placebo-controlled trials that enrolled adult patients (age older than 18 years) with at least a 4-week history of symptomatic (NYHA classes II–IV) HF. Subjects randomly assigned to candesartan were started on 4 mg and titrated to 32 mg once daily, as tolerated. Some standard therapy (diuretics, β-blockers, digoxin, spironolactone, and ACEI) was continued. For all three trials, the primary end point was the combined incidence of CV death, HF hospitalizations, or both. The differences in admission criteria and outcomes among the individual trials are discussed here.

CHARM-Alternative enrolled 2028 subjects who met all of the inclusion criteria defined earlier plus two additional criteria: an EF of ≤40% and intolerance of ACEIs (cough, 72%; hypotension, 13%; renal dysfunction, 12%). Thus, subjects in this group received either an ARB alone or a placebo without an ACEI. A 23% reduction was found in the primary outcome of CV death, hospital admission for HF, or both in the candesartan group compared with placebo. The overall incidence of drug discontinuations because of adverse events was not statistically different between candesartan and placebo, but there were significantly more reports of symptomatic hypotension, increased creatinine levels, and hyperkalemia in those treated with candesartan (**Table 14-10**).

Table 14-10
Adverse Events That Lead to Permanent Drug Discontinuation

Trial	Outcomes	Candesartan (%)	Placebo (%)	P Value
CHARM-Alternative[151]	Any adverse event or laboratory abnormality	21.5	19.3	.23
	Hypotension	3.7	0.9	<.0001
	Increased creatinine	6.1	2.7	<.0001
	Hyperkalemia	1.9	0.3	.0005
CHARM-Added[152]	Any adverse event or laboratory abnormality			.0003
	Hypotension	4.5	3.5	.079
	Increased creatinine	7.8	4.1	.0001
	Hyperkalemia	3.4	0.7	<.0001
CHARM-Preserved[153]	Any adverse event or laboratory abnormality	17.8	13.5	.001
	Hypotension	2.4	1.1	.006
	Increased creatinine	4.8	2.4	<.001
	Hyperkalemia	1.5	0.6	.019
CHARM-Overall[154]	Any adverse event or laboratory	21	16.7	<.001

	abnormality			
	Hypotension	3.5	1.7	<.0001
	Increased creatinine	6.2	3.0	<.0001
	Hyperkalemia	2.2	0.6	<.0001

The CHARM-Added trial attempted to determine whether the combination of an ACEI plus an ARB offered any clinical advantages compared with an ACEI alone in patients with symptomatic HF with an EF of ≤40%. At baseline, 55% of the patients were treated with β-blockers and 17% with spironolactone. The addition of candesartan to an ACEI and other usual HF treatments led to a 15% relative risk (*P* = .011) reduction in the primary outcome of CV death, hospital admission for HF in the combination group compared to the ACEI-alone group. It is interesting to compare the result of the CHARM-Added trial with those of the Val-HeFT study. In Val-HeFT, 93% of the subjects receiving the ARB valsartan were concurrently receiving an ACEI. The combined end point of morbidity and mortality was significantly reduced with combination therapy in Val-HeFT, but mortality alone was not reduced. A trend toward more deaths in the small subgroup receiving the triple combination of a β-blocker with an ACEI and ARB was observed, whereas β-blocker use had no adverse effect in CHARM-Added.

The combined results of all three CHARM components (CHARM-Added, CHARM-Alternative, and CHARM-Preserved; see discussion of CHARM-Preserved in Case 14-7, Question 1) were reported in the CHARM-Overall trial.[156] This composite analysis evaluates the benefits of candesartan in symptomatic patients with HF, regardless of LV systolic function. A different primary end point was chosen for the CHARM-Overall analysis: all-cause death. Although the combined results failed to detect a clinically significant reduction in all-cause death between candesartan and placebo (9% reduction; *P* = .32), significant reductions were seen in CV death (12%), hospital admission for HF (21%), and combined CV death or hospital

admission for HF (16%), which was the primary end point for the individual trials.

The collective results of the CHARM program reinforce the conclusion that ARBs can reduce morbidity and mortality in symptomatic patients with HFrEF, and they can be safely used in patients who are intolerant of ACEI therapy. Combination therapy (ACEI plus ARB) with concomitant use of β-blockers appears to be beneficial and safe, as long as patients are closely monitored for adverse effects. Current guidelines recommend the addition of an AA over ARB in patients receiving an ACEI and β-blockers.

Because ELITE II failed to demonstrate any survival benefits of losartan 50 mg/day, over captopril 150 mg/day in patients with HFrEF, the **H**eart failure **E**ndpoint evaluation of **A**ngiotensin II **A**ntagonist **L**osartan (HEAAL) study was designed to compare the effect of two doses of losartan (50 vs 150 mg daily) on the combined end point of all-cause mortality and hospitalizations in HFrEF. A median follow-up of 4.7 years showed losartan 150 mg daily reduced the rate of death or HF admission when compared with losartan 50 mg daily. The high-dose group experienced more renal dysfunction, hypotension, and hyperkalemia, although these results did not lead to significantly more treatment discontinuations. Old age, concomitant AA dose, and baseline levels of potassium and SCr were common predictors of adverse events and resulted in increased mortality among patients who experienced these adverse events. Therefore, dose titrations should be done with close monitoring, especially in individuals at high risk for developing adverse events.[157]

In summary, ARB HF trials demonstrate survival benefits in HFrEF in patients who are ACEI intolerant or as an add-on therapy to ACEIs and β-blockers. However, current guidelines do not recommend the routine use of triple therapy, and A.J. should not be started on an ARB in addition to his lisinopril. If A.J. develops a cough on lisinopril, he can be switched to an ARB such as candesartan.

Side Effects

ANGIOTENSIN CONVERTING ENZYME INHIBITOR–INDUCED COUGH

Case 14-1, Question 15: A.J. presents to the outpatient HF clinic with an annoying productive cough after 6 weeks of lisinopril therapy. His chest examination reveals no evidence of wheezing, with only a few crackles, his neck veins are only minimally elevated over normal, his ankle edema is 1+, and his weight is stable. All laboratory values are normal. Could the cough be a symptom of his HF or is it ACEI induced? What are the recommendations for managing an ACEI-induced cough?

Cough can be a sign of HF in patients with pulmonary congestion. In extreme cases, patients have "cardiac asthma" with severe air hunger, wheezing, and dyspnea. However, A.J.'s HF is much improved as evidenced by the objective data. The absence of wheezing and no prior history of asthma or smoking make an obstructive airways disease (asthma or COPD) unlikely. It is possible that he does have bronchitis, but he does not report having a cold or other respiratory illness preceding the cough. Without other causes, an ACEI-induced cough is most likely.

This side effect occurs with all ACEIs.[158] Cough is a well-established complication of ACEIs and presents as dry and nonproductive; sometimes described as a "tickle in the back of the throat." This complication can arise within hours of the first dose, or it can present after weeks to months of treatment. Although resolution of the cough usually occurs within 1 to 4 weeks, in some patients it can persist up to 3 months after discontinuation of therapy.

Bradykinin accumulation within the upper airway and decreased metabolism of proinflammatory mediators such as substance P or prostaglandins are proposed mechanisms of ACEI-induced cough. These chemicals then act as irritant substances in the airways to increase bronchial reactivity and induce coughing.

Various case reports have found an incidence of cough in 5% to 35% of all patients. The incidence is dose independent.[159] One investigator found a 5% to 10% incidence in White patients of European descent that rose to nearly 50% in Chinese patients.[160]

There may also be a higher incidence in females and Black populations.[157]

Because this is a pharmacologic effect rather than an allergic reaction, dose reduction or switching from one ACEI to another is generally not helpful. The only way to definitively diagnose the drug-induced cough is to discontinue therapy. Even then, false-positive results can occur if the patient had a mild case of bronchitis that spontaneously resolved at about the same time that the ACEI was discontinued. If the cough persists after drug discontinuation, other causes should be investigated such as coexisting gastroesophageal reflux disease or allergic rhinitis.

For patients with persistent cough, ARB or hydralazine–isosorbide is a safe alternative. Therefore, A.J. can continue taking lisinopril for another couple of weeks to determine whether the cough will resolve on its own. His symptoms of HF have abated since the initiation of ACEI therapy, and the cough may be no more than an annoyance. He is not at risk for experiencing asthma or other airway problems. If his cough persists, an ARB is probably the best alternative.

OTHER ANGIOTENSIN CONVERTING ENZYME INHIBITOR AND ANGIOTENSIN RECEPTOR BLOCKER SIDE EFFECTS

Hyperkalemia

Case 14-1, Question 16: What other side effects of both ACEIs and ARBs need to be monitored? Does changing from an ACEI to an ARB reduce the risk of any of these side effects?

ACEIs and ARBs have the potential to raise serum potassium concentrations via indirect aldosterone inhibition and other neurohormonal actions.[161,162] For most patients, the magnitude of increase in serum potassium concentration from ACEIs and ARBs alone is relatively small, but the risk of developing hyperkalemia is greater if the patient has compromised renal function or advanced HF. Combination therapy of an ACE or ARB with potassium

supplements, or potassium-sparing diuretics, further accentuates the risk of hyperkalemia.

Several case reports and case series have reported hyperkalemia and hospitalizations secondary to spironolactone in patients with HF. This became more evident as prescribing patterns for spironolactone dramatically increased after publication of the RALES study.[163] Not only was there a significant increase in the number of prescriptions for spironolactone for patients with HF, but doses higher than those recommended by the clinical trials were often used, especially in patients with evidence of preexisting renal dysfunction. In addition, evidence indicated inadequate monitoring of serum potassium, renal function, and concomitant drug therapy. Although concurrent use of a potassium-wasting diuretic (thiazide or loop diuretic) may counteract potassium retention from spironolactone or other drugs (ACEIs, ARBs), it is nearly impossible to predict who will exhibit hypokalemia, hyperkalemia, or remain normokalemic.[164,165] Each patient must be assessed individually for personal response to various drug combinations. Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiation of therapy known to affect potassium and at least monthly for the first 3 months (**Table 14-11**).

Table 14-11
Various Causes of Hyperkalemia and Strategies to Minimize Risk

Cause	Mechanism	Strategies to Minimize Risk
Aldosterone blockers	Decreased levels of aldosterone and subsequent potassium retention	GFR should be determined and aldosterone antagonist should be avoided if creatinine clearance is <30 mL/minute and baseline serum potassium is >5.0 mEq/L. An initial dose of spironolactone 12.5 mg

		or eplerenone 25 mg is recommended, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate. Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiation of therapy and at least monthly for the first 3 months.
RAAS blockade by ACEIs and ARBs Note: risk increases at higher doses (enalapril or lisinopril ≥10 mg/day)	Inhibition of angiotensin II production or receptor binding reduces the delivery of sodium and water to the distal nephron, which, in combination with hypoaldosteronism, promotes hyperkalemia.	Doses of drugs should be decreased as appropriate.
NSAIDs	Inhibit renal prostaglandin synthesis (PGE_2 and PGI_2), resulting in hyporeninemic hypoaldosteronism. Decreased availability of sodium for exchange with potassium at distal tubular sites	NSAIDs and cyclooxygenase-2 inhibitors should be avoided.
Potassium-sparing diuretics, cyclosporine, tacrolimus, trimethoprim, and heparin	Decreased excretion of potassium	Close monitoring of serum potassium is required. Doses of drugs known to cause hyperkalemia should be decreased as appropriate.
Patients who have increased dietary	In the presence of renal insufficiency, decreased	Potassium supplements should be discontinued

potassium intake, use salt substitutes (a rich source of potassium), or take potassium supplements in combination with aldosterone antagonists	potassium excretion occurs.	or reduced. Patients should be educated on foods rich in potassium and to avoid salt substitutes.
Patients with HF with diabetes taking aldosterone antagonists	Hyporeninemic hypoaldosteronism leading to decreased levels of aldosterone and subsequent potassium retention Insulin deficiency can stimulate the shift of potassium to the extracellular space.	Hyperglycemia should be monitored, and appropriate drug therapy should be determined to treat diabetes.
Advanced age, low muscle mass, or renal insufficiency (serum creatinine >1.6 mg/dL)	Impaired release of renin resulting in hypoaldosteronism SCr may not accurately reflect GFR. Risk of hyperkalemia increases progressively as SCr rises.	GFR should be determined and doses adjusted accordingly.

ACEIs, angiotensin converting enzymes; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate; HF, heart failure; NSAIDs, nonsteroidal anti-inflammatory drugs; PGE_2, prostaglandin E_2; PGI_2, prostaglandin I_2; RAAS, renin–angiotensin–aldosterone system; SCr, serum creatinine.

Angioedema

Angioedema (angioneurotic edema) is a severe, potentially life-threatening complication of ACEI treatment.[166–168] Characterized by facial and neck swelling, with obstruction to airflow by laryngeal and bronchial edema, this reaction resembles anaphylaxis. The mechanism of ACEI induction of angioedema is unknown but is thought to be hypersensitivity to accumulated vasodilating kinins.

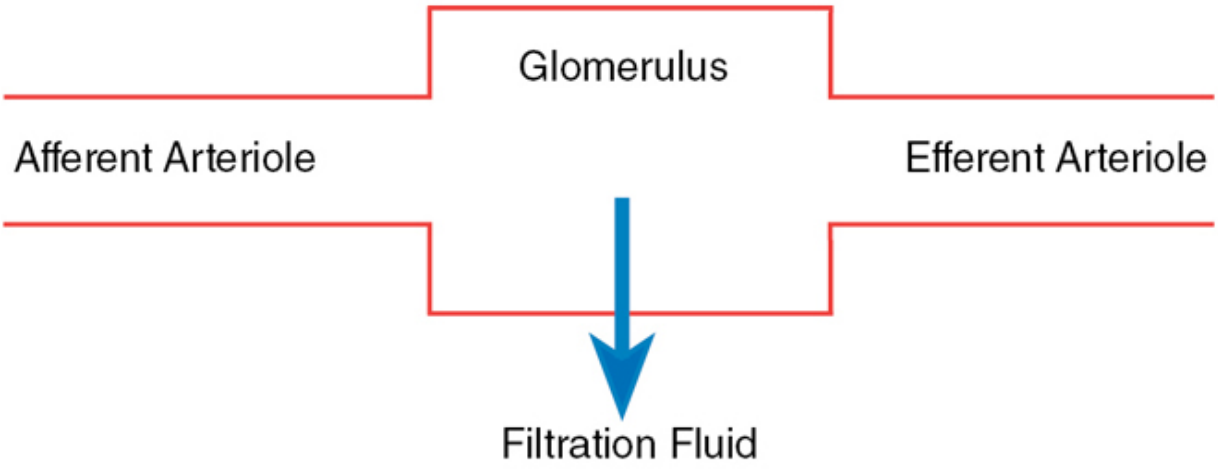
Some, but not all, persons with drug-induced angioedema have a history of familial angioedema associated with a genetic defect in their complement system. In most cases, angioedema reactions occurred within 1 month of starting therapy, but can also present after several months of therapy, although infrequent.[167] Black patients and females may have a higher prevalence. Of concern is the observation that ACEI-induced angioedema is often misdiagnosed.[168] It is prudent to avoid all ACEIs in any patient with a history of angioedema from any cause.

Because the mechanism of ACEI-induced angioedema is thought to be caused by kinin accumulation, changing to an ARB might be an option.[169] Several case reports, however, have implicated candesartan, losartan, and valsartan as possible causative agents of angioedema.[166,170–173] In some cases, the subjects had previously experienced angioedema with an ACEI (indicating possible cross-reactivity), whereas others were ACEI naive. A small but potential risk for ARB-induced angioedema in patients who are ACEI intolerant comes from the CHARM-Alternative trial.[153] Of 39 patients with a history of angioedema while taking an ACEI, 3 experienced angioedema on candesartan, although only 1 of the 3 actually discontinued taking candesartan. For now, it is prudent to assess risk–benefit, and ARBs should be used cautiously in the management of patients who have angioedema from ACEIs.

Effects of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on kidney function

As seen in **Figure 14-9**, glomerular filtration is optimal when intraglomerular pressure is normal. The balance between afferent flow into the glomerulus and efferent flow exiting the glomerulus determines the intraglomerular pressure. A drop in afferent flow or pressure occurring as a result of hypotension, volume loss, hypoalbuminemia, decreased CO, or obstructive lesions such as renal artery stenosis can significantly lower intraglomerular pressure and lead to impaired renal function. Similarly, long-standing HTN can

damage glomerular basement membrane capillaries and cause renal insufficiency.



↓ Afferent flow to glomerulus caused by:

- ↓ Cardiac output
  - Systemic hypotension
  - Blood loss
  - Overdiuresis, dehydration
- Renal artery stenosis (obstruction)
- Inhibition of PGE from NSAIDs

↑ Afferent flow to glomerulus caused by:

- Systemic hypertension

↑ Efferent pressure to maintain glomerular pressure if:

- ↑ Production of angiotensin II via activation of renin-angiotensin system

↓ Efferent pressure to protect glomerular pressure if:

- ACE inhibitors block angiotensin II production

Figure 14-9 Factors affecting renal blood flow. Glomerular filtration is optimal when adequate hydrostatic pressure is maintained in the glomerulus. Governing factors include the blood flow rate to the glomerulus and the balance of afferent and efferent arteriole dilation and constriction. ACE, angiotensin converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; PGE, prostaglandin E.

In the case of low-pressure or low-flow states, the RAAS is activated to maintain intraglomerular pressure. A key factor in preserving glomerular pressure is *efferent vasoconstriction* mediated by angiotensin II. Increased efferent pressure helps maintain intraglomerular pressure by impeding blood flow out of the glomerulus. When patients with low-pressure states are given ACEIs or ARBs, the protective mechanism of efferent vasoconstriction is inhibited and GFR decreases to a modest degree, resulting in an increase in SCr.

By decreasing afterload, CO may improve after ACEI or ARB therapy, thus preserving or even enhancing RBF. If, however, starting ACEIs or ARBs leads to a rapid decrease in systemic BP that is not followed by an increase in CO, worsening renal function may ensue. It is impossible to predict which event will occur. Therefore, ACEI or ARB therapy needs to be started with low doses, and careful monitoring of the BP and renal function should occur as dosages are increased. Renal function and BP should be checked before and 1 to 2 weeks after initiation or dose increase. Patients with risk factors such as preexisting renal insufficiency or concomitant treatment with NSAIDs or high-dose diuretics may require more frequent monitoring. Diuretics are not contraindicated, but the diuretic dosage may need to be reduced to avoid overly aggressive diuresis and the accompanying volume depletion and hypotension. The guidelines recommend caution when prescribing ACEIs/ARBs in patients who have low SBPs (80 mm Hg), increased SCr (>3 mg/dL), bilateral renal artery stenosis, or serum potassium >5.0 mEq/L.[1]

Use of a-Blockers in Heart Failure With Reduced Left Ventricular Ejection Fraction

Case 14-1, Question 17: After 3 days of furosemide and an ACEI, A.J.'s PND has resolved, but he still has difficulty walking without SOB and fatigue. His lower extremity edema has been significantly reduced. His current BP is 145/90 mm Hg, his pulse is 82 bpm, and his weight has dropped to 160.94 pounds (73

kg) after diuresis. Repeat laboratory measurements include the following results:

Na, 139 mEq/L
K, 4.3 mEq/L
Cl, 98 mEq/L
CO_2, 27 mEq/L
BUN, 27 mg/dL
SCr, 0.6 mg/dL

The medical team has decided to discharge A.J. soon. You recommend that A.J. should be started on a β-blocker before discharge. What is your rationale?

β-Blockers have been evaluated during randomized clinical trials in >20,000 patients with varying degrees of HFrEF. Five meta-analyses have arrived at the same conclusions: the use of three β-blockers (bisoprolol, metoprolol succinate, or carvedilol) is associated with a consistent 30% reduction in mortality and a 40% reduction in hospitalizations in patients with HF.[174–178]

The ACC/AHA guidelines recommend bisoprolol, metoprolol succinate, or carvedilol for all patients with HFrEF unless there is a contraindication to their use or the patient is unable to tolerate treatment with a β-blocker.[11] They should be a part of the primary treatment plan with an ACEI or ARB. Patients should receive a β-blocker to slow the rate of disease progression and reduce the risk of sudden death. Patients do not need to be taking high doses of ACEIs before being considered for treatment with a β-blocker. To the contrary, in patients taking a low dose of an ACEI, the addition of a β-blocker produces a greater reduction in symptoms and in the risk of death than an increase in the dose of an ACEI. β-Blockers should be initiated before discharge in the vast majority of patients hospitalized for HF.[179] Only those clinically unstable patients who are hospitalized in an intensive care unit, require IV positive inotropic support, have severe fluid overload or depletion, have symptomatic bradycardia or advanced heart block that is not treated with a pacemaker, or have a history of poorly controlled reactive airways disease are not candidates for a β-blocker.[180]

Based on all these factors, there is no question that A.J. should be started on a β-blocker. Treatment with a β-blocker should be initiated at low doses, followed by gradual increments in dose every 2 weeks as tolerated. Transient bradycardia, hypotension, and fatigue are common during the first 24 to 48 hours when β-blockers are first started or during subsequent increases in dosage. Thus, patients should be monitored daily for changes in vital signs (pulse and BP) and symptoms during this uptitration period. Bradycardia, heart block, and hypotension can be asymptomatic and require no intervention other than instructing the patient not to arise too quickly from a lying position to avoid postural changes. If any of these complications is accompanied by dizziness, lightheadedness, or blurred vision, it may be necessary to reduce the dose of the β-blocker, the ACEI, or both or to slow the uptitration. In patients in whom benefits are especially apparent, but bradycardia or heart block is a concern, insertion of a pacemaker should be considered.

Because initiation of β-blocker therapy can also cause fluid retention, β-blockers should only be started or uptitrated when the patient is euvolemic. Patients should be instructed to weigh themselves daily and to adjust concomitantly administered diuretics as appropriate. Diuretic doses should be decreased temporarily if patients become hypotensive or their BUN begins to rise. Planned increments in the dose of a β-blocker should be delayed until any side effects observed with lower doses are tolerable or absent.

CASE 14-1, QUESTION 18: Metoprolol succinate (12.5 mg) is prescribed for A.J. Is this a good choice of agent and starting dose? What other similar drugs have been used to treat HF?

METOPROLOL AND BISOPROLOL

Several clinical trials substantiate the clinical benefits of metoprolol, a relatively selective β_1-receptor blocker, in HF.[181–184] By blocking β_1 receptors in the myocardium, HR, contractility, and CO are reduced at rest and during exercise, without a compensatory increase in peripheral vascular resistance. The relative sparing of β_2-receptors in

the peripheral vasculature and lungs reduces vasoconstrictive and bronchospastic complications.

Effect of Metoprolol CR/XL in Chronic Heart Failure: **Me**toprolol CR/XL **R**andomized **I**ntervention **T**rial in Congestive **H**eart **F**ailure (MERIT-HF) showed a 35% reduction in all-cause mortality with sustained-release metoprolol succinate.[184] In this trial, 3991 patients, most of whom had NYHA class II or III HF, were randomly assigned to receive metoprolol succinate controlled-release (CR)/XL formulations or placebo. The starting dose of metoprolol was 12.5 to 25 mg/day, which was gradually increased every 2 weeks to the target dose of 200 mg/day. Conventional therapy with diuretics, ACEIs, and digoxin was continued. At the end of the trial, 64% of subjects assigned to the active drug had reached the target dose. Although the number of subjects was too small to detect a statistical difference, patients with severe (class IV) HF seemed to benefit as well. Up to 15% of subjects had clinical worsening of HF, even at low metoprolol doses.

Positive results have also been seen with another relatively β_1-selective drug, bisoprolol fumarate.[185,186] In the first *C*ardiac *I*nsufficiency *BI*soprolol *S*tudy (CIBIS I), 641 subjects with moderate-to- severe HF were randomly assigned to placebo or bisoprolol (starting dose, 1.25 mg/day; maximal dose, 5 mg/day) added to conventional therapy for an average of 23 months.[185] A statistically significant reduction in HF-associated hospitalization with the active drug and an insignificant trend toward reduced mortality were noted. In the larger second *C*ardiac *I*nsufficiency *BI*soprolol *S*tudy (CIBIS II), reduction in both hospitalization and mortality in the bisoprolol-treated group was significant.[186] A total of 2647 patients were included in the second trial, and doses were increased to as high as 10 mg/day. The study was stopped prematurely because of a 34% reduction in total mortality with bisoprolol. As in the MERIT-HF study, the number of patients with severe (class IV) HF was inadequate to determine the value of β-blocker therapy in this population.

Two dosage forms of metoprolol are marketed: metoprolol succinate XL and metoprolol tartrate immediate-release

formulations. Only metoprolol succinate is approved for HF in the United States. It is indicated for patients with mild-to-moderate (NYHA class II or III) HFrEF. The starting dose of 12.5 mg of metoprolol succinate prescribed for A.J. is consistent with the clinical trials and manufacturer's labeling. If the initial dose is tolerated, the dose can be doubled to 25 mg daily for an additional 2 to 4 weeks. The final target dose is 200 mg daily either as 100 mg bid or 200 mg once daily.

When choosing among the various formulations of metoprolol, pharmacokinetic and bioavailability differences should be considered.[181,182] Metoprolol succinate is available as 25-, 50-, 100-, and 200-mg tablets. Each tablet is slowly released at a constant rate for 20 hours and provides β-blockade for 24 hours. The XL formulation retains its release characteristics even if the scored tablet is divided in half, but it should not be crushed or chewed. Having the ability to split tablets is useful in the titration of metoprolol succinate when the goal is to reach target doses and sometimes patients require slower titrations.

Metoprolol has several metabolic routes of elimination that can affect dosing and drug interactions. The major routes of elimination are via α-hydroxylation, *O*-demethylation, and *N*-dealkylation.[181,182] A smaller portion is metabolized by cytochrome P450 2D6 (CYP2D6), and drugs that inhibit the metabolism of that isoenzyme may affect the drug's plasma levels. Approximately 10% of patients are poor metabolizers, resulting in higher drug plasma concentrations in these patients.

A.J. should be advised that the beneficial clinical response to metoprolol is usually delayed and may require 2 to 3 months to become apparent. Even if symptoms do not abate, long-term treatment should be maintained to reduce the risk of major clinical events. Abrupt withdrawal of treatment with a β-blocker can lead to clinical deterioration and should be avoided.[187]

Bisoprolol is FDA approved for treatment of HFrEF. Dosage size limitations, however, limit the clinical use of this drug. For example, the starting dose of bisoprolol is 1.25 mg/day, whereas the smallest

commercially available dose in the United States is a 5-mg scored tablet. Attempting to break the tablet into quarters is not practical.

CARVEDILOL

Carvedilol is a β-blocker with some blocking activity.[188] It is also theorized to possess antioxidant effects, which can protect against loss of cardiac myocytes and scavenge oxygen free radicals that are thought to potentiate myocardial necrosis. The correlation of these findings with clinical outcome is unknown.

Two pivotal studies support the use of carvedilol. The first was the U.S. Carvedilol Heart Failure Study.[189–193] Subjects were almost equally divided between NYHA classes II and III HF, and all had an EF of ≤35% despite diuretics, digoxin, and an ACEI. Subjects were stratified based on the severity of their HF and then randomly assigned to receive either placebo or carvedilol. The maximal dose given was 50 mg twice daily. During an average of 6.5 months, the mortality rate in the placebo group was 7.8% compared with 3.2% in the active treatment group, a statistically significant 65% risk reduction. The patients treated with carvedilol also had fewer HF-related hospitalizations. The most common side effect with carvedilol was dizziness.

In the Australia/New Zealand Carvedilol Study, 415 patients with chronic, stable HF were randomly assigned to receive placebo or carvedilol.[194] Those with severe symptoms were excluded. Maintenance doses in subjects randomly assigned to receive carvedilol ranged from 6.25 to 25 mg twice daily with an average follow-up of 19 months. After 12 months, EF had increased by 5.3%, and heart size was reduced in the carvedilol group. However, no differences between groups were found in treadmill exercise time, change in NYHA classification, or HF symptom scores. Most (58% in both groups) had neither improvement nor worsening of symptoms. The frequency of episodes of worsening HF was similar in the two groups. Total deaths in the carvedilol group were less than that in the placebo group, but most of the difference in mortality was attributed to non-CV deaths. There were 68% fewer hospital admissions for HF

in the carvedilol group than that for the placebo group. Overall, these findings could be interpreted as evidence for safety with either no overall benefit or a modest improvement with carvedilol.

The starting dose of carvedilol is 3.125 mg twice daily, with a doubling of the dose every 2 weeks or as tolerated up to a maximum of 25 mg twice daily in patients weighing <187.39 pounds (<85 kg) and 50 mg twice daily in larger patients. Hypotension, bradycardia, fluid retention, and worsening HF symptoms can occur in the first few weeks of therapy, necessitating additional diuretics, a reduction in dose, or discontinuation of carvedilol. Taking carvedilol with food slows the rate of absorption and reduces the incidence of orthostatic hypotension, which occurs in up to 10% of patients taking the drug. As with any β-blocker, carvedilol is not recommended for use in patients with asthma or poorly controlled diabetes.

Because carvedilol is metabolized by the CYP2D6 enzyme system, several potential drug interactions should be considered.[188,195] The best-documented ones are inhibition of metabolism by cimetidine and decreased carvedilol serum concentrations when taken with rifampin. Known inhibitors of CYP2D6 (quinidine, fluoxetine, paroxetine, and propafenone) might increase the risk of toxicity (especially hypotension). Carvedilol has been reported to increase serum digoxin levels by 15% by an unknown mechanism. Other sources of intrasubject variability in carvedilol response may be caused by differences in the extent or rate or absorption, stereospecific metabolism of the two isomers of the drug (carvedilol is a racemic mixture of *S*[−] and *R*[+] isomers), and impaired metabolism in the 10% of the population who lack CYP2D6 activity.[195]

CHOICE OF A-BLOCKER: METOPROLOL VERSUS CARVEDILOL

Case 14-1, Question 19: Would carvedilol be a better alternative than metoprolol for A.J.? What would be an appropriate dose and dosing schedule?

No consensus exists regarding the relative superiority of one β-blocker versus another. The additional α_1-blockade and antioxidant properties of carvedilol provide a theoretical basis for selecting carvedilol instead of metoprolol succinate or bisoprolol.

The *C*arvedilol *O*r *M*etoprolol *E*uropean *T*rial (COMET) was a multicenter, double-blind trial, where 3029 patients with NYHA classes II through IV HF and EF <35% were randomly assigned to receive either carvedilol (target dose, 25 mg bid) or metoprolol tartrate (target dose, 50 mg bid). Diuretics and ACEIs were continued in all subjects if tolerated. All-cause mortality was 34% for carvedilol compared with 40% with metoprolol (P = .0017).[196] The composite end point of mortality or all-cause hospital admissions were not significantly different. One major criticism of this study was the use of metoprolol tartrate instead of metoprolol succinate. Comparable doses between the two study groups have been questioned because the target dose of carvedilol was 25 mg twice daily compared with the target dose of metoprolol tartrate being 50 mg twice daily. Also, the trial used RHR to determine comparable β-blockade among study groups rather than HR response to exercise. Exercise-induced HR changes are considered a better indicator of β-blockade.

Side effects and patient tolerability are similar among β-blockers in most trials. One investigator observed that carvedilol caused more hypotension and dizziness than did metoprolol or bisoprolol, possibly owing to α_1-blockade or more rapid absorption.[197] Thus, metoprolol or bisoprolol may be preferred in patients with hypotension or dizziness. Conversely, carvedilol may be preferred in patients with inadequately controlled HTN.

Whether carvedilol is a better choice for A.J. cannot be definitely answered. A starting dosage of 3.125 mg twice daily of carvedilol could be used in place of metoprolol succinate. Both drugs are generic, although the metoprolol sustained-release product is more expensive. A.J.’s provider decided to continue metoprolol and reserve use of carvedilol if he has difficulty tolerating metoprolol.

a-Blockers in Severe Heart Failure

Case 14-1, Question 20: The original clinical trials of β-blockers excluded patients with severe (NYHA class IV) HF at the time of randomization. For this reason, the FDA limited the original approval of carvedilol for use in NYHA classes II and III HF. Likewise, the ACC/AHA guidelines strongly support the use of β-blockers in NYHA classes II and III HF, but are less definitive about severe HF. If A.J. presented with NYHA class IV HF, what evidence supports or refutes the use of β-blockers in A.J.?

The carvedilol prospective randomized cumulative survival study (COPERNICUS)[198] study demonstrated clear benefit of carvedilol in patients with severe HF. COPERNICUS was a double-blind, placebo-controlled trial assessing the clinical benefits and risks of carvedilol in patients with advanced HF (NYHA class IIIB or IV).[198] Subjects who required intensive care, had significant fluid retention, were hypotensive, had evidence of renal insufficiency, or were receiving IV vasodilators or positive inotropic drugs were excluded. The starting dose of carvedilol was 3.125 mg twice daily and increased every 2 weeks to a target dose of 25 mg twice daily. Of those in the carvedilol group, 65% achieved the target dose, with the mean dose being 37 mg at the end of the first 4 months of the trial. The trial was discontinued prematurely after an average patient follow-up of 10.4 months because of a significant survival benefit from carvedilol.

The beta-blocker evaluation of survival trial (BEST) investigators failed to demonstrate that bucindolol, a nonselective β-blocker with vasodilator properties, improved overall survival in patients with NYHA classes III and IV HF.[199] They randomly assigned 2708 patients to receive either bucindolol or placebo. Although the active drug yielded a significant decrease in NE levels and improvement in LV function, the study was stopped prematurely because of the low probability of showing any significant CV mortality benefit compared with placebo. A possible explanation is that bucindolol has intrinsic sympathomimetic activity that may counteract some of the benefits of β-blockade. Moreover, subgroup analysis suggested that Black

patients might have fared worse with bucindolol, raising concerns that β-blockers may not be effective therapy for Black patients with advanced HF (see Case 14-4, Question 2, for further discussion of possible racial differences in drug response). Bucindolol has not been approved by the FDA.

Controversy still remains about the safe and effective use of β-blockers in class IV HF. There are data to support the safe and effective use of carvedilol. Clinically, the use of β-blockers is generally continued unless the patient requires inotropic therapy or if a dose increase of the β-blockers caused the ADHF episode. If the dose titration resulted in ADHF, then most patients should receive their previous β-blocker dose, but some may require acutely holding the β-blockers and reinitiating once stabilized.

CASE 14-1, QUESTION 21: When is it appropriate to add ivabradine in HFrEF?

A meta-analysis[200] of patients with HFrEF treated with β-blockers demonstrated that the degree of HR reduction correlated with improved mortality. We also know that initiation or titration of β-blockers can be challenging because of their side effects or preexisting contraindications. Evidence also supports that for every 5 bpm reduction in HR achieved, an 18% reduction in all-cause mortality is observed. Additional HR reducing therapies in the treatment of HF, with I_f channel inhibition, were tested in clinical trials. The first of these was the mor**B**idity-mortality **E**v**A**l**U**a**T**ion of the **IF** inhibitor ivabradine in patients with coronary disease and left-ventric**UL**ar dysfunction (BEAUTIFUL) trial.[201] The BEAUTIFUL study highlighted that in certain subgroups with elevated HR, a signal for reduce admission for acute MI by 36% (fatal and nonfatal; P = .001); reduce composite admission for acute MI or unstable angina by 22% (P = .023) was observed. These findings led to trials for assessing the true effects of ivabradine in the subgroup of patients with HFrEF and HR of at least 70 bpm, the **S**ystolic **H**eart failure treatment with the **IF** inhibitor ivabradine **T**rial (SHIFT).[68]

The SHIFT tested the effect of ivabradine as add-on to standard treatment with ACEIs and β-blockers in patients with chronic HF in sinus rhythm. The SHIFT trial randomized 6558 patients with symptomatic HF to ivabradine versus placebo. Patients had an EF ≤35%, normal sinus rhythm with an HR of ≥70 bpm, NYHA FC II to IV symptoms and at least one hospitalization for HF within the previous year. In addition to background treatment, which generally included a β-blocker (89%), ACEI, and/or an ARB (93%), patients received either ivabradine at 5 mg twice daily with an increase to 7.5 mg twice daily to maintain an RHR between 50 and 60 bpm, or placebo. During a median 23 months of follow-up, patients in the ivabradine group had an 18% decrease in risk of CV death or hospitalization (HR, 0.82; *P* < .0001). Ivabradine significantly reduced the risk of hospitalization for worsening HF and death due to HF but did not have a significant effect on all-cause mortality 503 (16%) versus 552 (17%); (HR 0.90, 95% CI 0.80–1.02; *P* = .092). Ivabradine was well tolerated with relatively few adverse events, although significantly more than that with placebo. The most common adverse events were bradycardia, AF, and transient blurring of vision. Overall, ~70% of the patients in the ivabradine arm were at target dose (7.5 mg bid), and <10% had to be downtitrated to the lowest dosage (2.5 mg bid). Patients with contraindications to β-blockers, β-blocker doses of <50% of GDMT targets, and an RHR of 77 bpm benefited the most.

Ivabradine reduces HR without effects on inotropy, BP, and vascular resistance. Evidence suggests that in patients with HFrEF who cannot tolerate β-blockers because of adverse effects and in whom HRs remain elevated, the addition of ivabradine can be considered to reduce HR to <70 bpm. However, the trial results cannot be generalized to the overall HF population, particularly the elderly, with permanent AF or HFpEF. Ivabradine is best viewed by clinicians as a second-line drug for systolic dysfunction.

Ivabradine is initiated at 5 mg twice daily and titrated to 7.5 mg twice daily based on efficacy and tolerability, with a goal HR of 51 to 60 bpm. If, after initiation, there is an observed RHR <60 bpm, the dose is decreased to 2.5 mg twice per day. Ingestion with food is

recommended to increase systemic absorption by 20% to 30%. Ivabradine is metabolized by CYP3A4 enzymes in the liver and it is recommended to avoid concurrent administration with potent inhibitors of CYP3A4. In patients with mild or moderate hepatic impairment (Child–Pugh A or B), no dose adjustments are required. Ivabradine use is contraindicated in those with severe (Child–Pugh C) hepatic impairment. No dose adjustment is required for renal impairment where the CrCl is between 15 and 60 mL/minute. There are currently no data available for use in patients with CrCl <15 mL/minute.[45]

Angiotensin Receptor–Neprilysin Inhibitor

Case 14-1, Question 22: A.J. presents to the HF clinic for a follow-up visit after a recent hospitalization. His HF medications include lisinopril 20 mg daily, carvedilol 12.5 mg twice daily, and spironolactone 25 mg daily. His laboratory values are Na 141 mEq/L, K 4.1 mEq/L, SCr 1.1 mg/dL, and NT-proBNP 653 pg/mL. He denies PND, weight gain, and dizziness (SBP 138/85 mm Hg, HR 60 bpm) but reports getting short of breath while performing yard work. He is euvolemic on examination and a repeat echo shows an LVEF 30% to 35%, which has not changed from last year. The cardiologist wants to switch A.J. to sacubitril/valsartan for additional mortality benefits. What is the evidence to support this change in therapy?

The combination of sacubitril and valsartan was studied in the PARADIGM-HF[62] trial as an alternative to ACEI therapy. This was a multicenter, randomized, double-blind trial (*N* = 8422), and consisted of three phases: the screening period, a single-blind run-in period during which all patients received enalapril, and was followed by a single-blind run-in period with all patients receiving ARNI to ensure tolerability of the study drugs at target doses. Patients who tolerated the two medications were then randomized in a 1:1 ratio to either enalapril 10 mg twice daily) or ARNI (200 mg twice daily). Subjects who had LVEF <35% and elevated BNP levels were included, almost all of whom were in NYHA FC classes II to III, ACEI or ARB therapy with stable doses in the prior 4 weeks to randomization (equivalent

to enalapril ≥10 mg/day), and stable doses of β-blockers. Patients were excluded if SBP <100 mm Hg at screening or <95 mm Hg at randomization, estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2, potassium >5.2 mmol/L at screening or >5.4 mmol/L at randomization, and history of angioedema. At 3.5 years of follow-up, there was a significant reduction in the primary outcome of CV death or HF hospitalization in the S/V group (21.8%) versus the enalapril group (26.5%) (HR 0.80; 95% CI 0.73–0.87; *P* < .001; NNT 21). Patients receiving sacubitril/valsartan had lower rates of hyperkalemia, renal dysfunction, and cough but higher rates of hypotension (14.0% vs 9.2%; *P* < .001; NNT 21). Overall, fewer patients on sacubitril/valsartan stopped their study medication because of an adverse event and required treatment intensification and use of advanced therapies (inotropes, assist devices, cardiac transplantation) when compared with enalapril.

The finding that sacubitril/valsartan had a superior effect on CV mortality compared to enalapril lends support that an ARNI could replace ACEIs and ARBs in patients with HFrEF who remain symptomatic despite being on optimal GDMT. Even though ARNI met the criteria for clinical superiority when compared with conventional therapy, the benefits have to be weighed against the side effect profile. In clinical practice, the frequency of the side effects (hypotension, angioedema) may be more pronounced because of a patient population with more complications.

A.J. is currently on a target dose of lisinopril and a moderate dose of metoprolol succinate. He reports SOB with minimal activity, and weight is stable and euvolemic on physical exam. He does not report any symptomatic hypotension and has adequate SBP, 138/85, K^+ is <5.0, and SCr is stable, and EF has not improved despite being on optimal GDMT. Guidelines recommend replacing an ACEI or ARB with an ARNI in patients with HFrEF or NYHA class II or III who tolerate an ACEI/ARB. A.J. fits the guideline criteria to switch to ARNI. Dose selection should be based on patient-specific factors such as SBP, renal function, age, hepatic function, and current ACEI/ARB dose. Because all labs are within normal limits and A.J. is on a high dose of lisinopril, he can be safely switched to ARNI 49/51

mg twice daily. When making the transition from lisinopril, a 36-hour washout period between the last dose of lisinopril and the first dose of ARNI should be observed to avoid the risk of angioedema. Renal function and SBP should be monitored in 2 to 4 weeks to assess tolerability and dose uptitrated to the target dose of 97/103 twice daily if appropriate (**Table 14-12**).

Table 14-12
ARNI Dosing

Population	Initial Dose	Comments
ACEI/ARB naive	ARNI 24/26 twice daily	Allow 36-hour washout if on an ACEI. Also if SBP <100 mm Hg, initiate low dose. If patient tolerates, make every effort to increase to target dose 97/103 mg.
[a]Low- or medium-dose ACEI/ARB		
eGFr <30 mL/minute		
Elderly ≥75 years		
Hepatic impairment (Child–Pugh B classification)		
High-dose[b] ACEI/ARB	ARNI 49/51 twice daily	Evaluate SBP and rule out symptomatic hypotension before initiation.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

[a]Low/medium dose ≤ enalapril 10 mg or equivalent dose of another ACEI.

[b]High dose > enalapril 10 mg or equivalent dose of another ACEI.

[a]Low/medium dose ≤ valsartan 160 mg daily or equivalent dose of another ARB.

[b]High dose > valsartan 160 mg daily or equivalent dose of another ARB.

Yancy CW, Januzzi JL, Allen LA, et al. 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology task force on expert consensus decision pathways. *J Am Coll Cardiol*. 2018;71(2):201–230.

CASE 14-2

Question 1: S.P. is a 66-year-old male with an EF <35% and is scheduled with a pharmacy HF titration clinic. His HF medications include lisinopril 10 mg daily and metoprolol succinate 150 mg daily. He was recently initiated on ARNI 24/26 twice daily. Vitals and labs include BP 118/89 mm Hg, HR 70 bpm, SCr 1.2 mg/dL, and K 4.4 mEq/L.

What steps will you take to safely titrate the ARNI?

The common barriers to initiation and titration of GDMT are renal insufficiency and/or hyperkalemia and symptomatic hypotension. Clinical assessment of patient-specific factors is necessary to successfully titrate medications to target doses. A study was conducted to assess the safety and tolerability of initiating and uptitrating ARNI in real-world patients with HFrEF. TITRATION (Safety and Tolerability of Initiating LCZ696 in Heart Failure Patients) was a randomized,[202] double-blind study that assessed the safety and tolerability of initiating and uptitrating ARNI in a 3-week (condensed) regimen, versus a 6-week (conservative) regimen in patients with HFrEF (EF ≤35). Primary end points were the proportion of patients experiencing prespecified adverse events (symptomatic hypotension, hyperkalemia, renal dysfunction, angioedema) and laboratory outcomes including SBP <95 mm Hg, and a doubling of SCr from baseline. Secondary end points included the number of patients achieving the target dose without any downtitration or interruption over 12 weeks (defined as treatment success) and tolerating the target dose for at least 2 weeks. After 5 days of run-in with sacubitril/valsartan, patients were randomized to sacubitril/valsartan titrated up to 200 mg twice daily (50–200 mg twice daily) over 3 weeks or 6 weeks. Randomized patients were also stratified based on Renin-Angiotensin-Aldosterone System inhibitor (RAASi) use at screening, with the high-stratum group using >10 mg total daily dose of enalapril, >160 mg of valsartan, or equivalent doses of other ARBs/ACEIs. There were no differences in the primary end points between groups. Treatment success was achieved in 78% and 84% of patients in the condensed and conservative regimens, respectively (P = .07). At least 76% of

randomized patients achieved and maintained the target dose of ARNI 200 mg bid, regardless of the uptitration regimen. In the prestudy low-dose group, treatment success was achieved with the conservative approach (low RAASi, 73.6% for the condensed group, and 84.9% of the conservative group [*P* = .03]). High prestudy RAASi dose was associated with similar treatment success in both groups (82.6% vs 83.8%, respectively). Overall, there was no difference between the groups for tolerability. There was also no difference between the groups for tolerability based on high or low RAASi use. Furthermore, the target dose was achieved even in patients requiring dose interruptions. This study supports that ARNI can be safely titrated to target doses in the majority of patients in clinical practice irrespective of the speed of titration. Study limitations included the open-label design of the run-in period, the limited number of inpatients (around 11%) and those naive to ACEI/ARB at baseline (around 7%), and the absence of an active comparator arm. Nevertheless, a gradual titration should be implemented in patients who were previously receiving low doses of ACEI/ARB with diligent follow-up to attain target doses.

Given that S.P. was on a low dose of lisinopril, and his SBP is at the lower end, his dose can be titrated to target or maximum tolerated dose over 6 weeks with a 2- to 3-week follow-up after each titration to assess tolerability.

Aldosterone Antagonists

CASE 14-3

Question 1: B.D. is a 65-year-old Caucasian male with an LVEF of <25% who presents to the HF clinic today for follow-up of his recent HF hospitalization. His BP is 120/85 mm Hg, and his pulse is 70 bpm. His current medications include lisinopril 10 mg daily, metoprolol succinate 150 mg daily, and furosemide 20 mg daily. You have reviewed his chart and noted that these are the maximal tolerated doses of lisinopril and metoprolol owing to dizziness and near syncope with higher doses. Today, his laboratory results show that his SCr is 0.9 mg/dL, and his potassium level is 3.5 mEq/L.

Is this patient a candidate for AA therapy?

Aldosterone contributes to HF through the increased retention of sodium and water and contributes to the depletion of potassium. Likewise, the diuretic and potassium-sparing actions of spironolactone are attributed to inhibition of aldosterone.[203] At one time, it was believed that optimal doses of ACEIs fully suppressed the production of aldosterone. It is now recognized that aldosterone levels can remain elevated through a combination of nonadrenal production and reduced hepatic clearance. In addition, it has become clear that both angiotensin II and aldosterone have other negative effects on the CV system, including myocardial and vascular fibrosis, direct vascular damage, endothelial dysfunction, oxidative stress, and prevention of NE uptake by the myocardium.[22,204] This led the RALES investigators to test the hypothesis that low doses of spironolactone might impart a cardioprotective effect in patients with severe HF independent of diuresis or potassium retention. In this trial, 1663 patients with a history of NYHA class IV HF were randomly assigned to receive either spironolactone 25 mg or placebo. The dose of spironolactone could be increased to 50 mg if HF worsened without evidence of hyperkalemia.

The study was discontinued prematurely after a mean follow-up of 24 months when a significant reduction in mortality was observed in the spironolactone group. Hospitalization rates were lower in the patients treated with spironolactone. Hyperkalemia developed in 2% of the patients on spironolactone and 1% of those on placebo. Gynecomastia was reported in 10% of males treated with spironolactone compared with only 1% of those receiving placebo.

In 2011, the *E*plerenone in *M*ild *P*atients *H*ospitalization *A*nd *S*urv*I*val *S*tudy in *H*eart *F*ailure (EMPHASIS-HF) was published. This study evaluated eplerenone in patients with NYHA class II HF and an EF of <35%.[59] In EMPHASIS-HF, subjects were randomly assigned to receive either eplerenone or placebo. The primary outcome of the trial was CV death or HF hospitalization. During a median follow-up of 21 months, 18.3% of patients treated with eplerenone versus 25.9% of patients on placebo had a primary

outcome event ($P < .001$). This study further supported the role of AAs in HFrEF and expanded the known effectiveness to NYHA class II HF patients.

B.D. has NYHA class II HF based on his current symptom control and fits the profile of the subjects in the EMPHASIS-HF study, although he is on a low dose of ACEI. Starting B.D. on an AA is appropriate because of his relative intolerance to increasing the dose of ACEI and β-blocker. An initial spironolactone dose of 25 mg/day should be chosen for B.D. based on the dose studied in the RALES trial. Spironolactone is chosen based on the likely class effects of AAs in HF treatment and the lower cost compared with eplerenone. This dose is safe based on his current potassium level of 3.5 mEq/L and SCr of 0.9 mg/dL. He will need to be followed up to determine his potassium and SCr 2 weeks after initiation. Specific monitoring parameters for the management of hyperkalemia in patients treated with AAs can be found in **Table 14-11**.

CASE 14-3, QUESTION 2: Because BD was started on spironolactone, his K has increased to 5.0meq/L and Scr is 0.9mg/dL. The medical attending is asking you if BD should be started on a potassium binder to manage hyperkalemia?

BD is not yet a candidate for potassium binders. All causes of hyperkalemia should be evaluated and potassium should be monitored and if K levels continue to rise then the dose of spironolactone should be reduced to 12.5 mg daily. One of the barriers to optimizing RAASi is the development of hyperkalemia. In clinical practice, an increase in serum potassium levels often leads to either RAASi dose reduction or discontinuation of therapy. Clinical trials have shown a significant reduction in mortality/ morbidity benefits when patients receive target doses of RAASi therapy. Furthermore, guidelines also recommend diligent monitoring of potassium and renal function when initiating or titrating RAASi. When prescribing AA therapy, a more stringent monitoring is mandated. Consequentially AAs are underprescribed despite class 1A recommendations. In the AA landmark trials, the incidence of

hyperkalemia (K^+ >5.5 mmol/L) was low without any hyperkalemia-associated fatal events. In addition, post hoc analysis of the RALES and EMPHASIS-HF trials[58,59] have shown persistent benefits despite the development of moderate hyperkalemia (5.5–6.0 mmol/L) during treatment. Nevertheless, hyperkalemia continues to be a challenge in the real world, and clinicians are often hesitant to initiate or titrate RAASi therapy. In recent years, two potassium binders, patiromer and sodium zirconium cyclosilicate (SZC), have been approved by the FDA to facilitate continuation of RAASi therapy. Both agents remove potassium by exchanging cations for potassium in the gastrointestinal tract, binding potassium, and increasing its fecal excretion.

Three main clinical trials[205–207] have collectively demonstrated patiromer to be effective in decreasing serum potassium, preventing recurrence of hyperkalemia, and reducing RAASi discontinuation. Similarly, the HARMONIZE (Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance) trial showed a dose-dependent potassium-lowering effect of SZC.[208]

SZC acts within 1 hour of administration by permanently removing excess potassium in the gastrointestinal tract, whereas patiromer decreases potassium levels at 7 hours after administration; levels continue to decrease for at least 48 hours if treatment is continued and remain stable for 24 hours after administration of the last dose. Both these agents increase the risk of hypokalemia and patiromer increases rates of hypomagnesemia, whereas SZC is associated with increased edema in patients with HF. Patiromer can reduce the absorption of other oral medications such as ciprofloxacin, and a 3-hour separation would avoid potential drug–drug interactions. SZC can transiently increase gastric pH and should be administered at least 2 hours after or before the concomitant drug that displays pH-dependent solubility.[209]

Potassium-binding agents can certainly help optimize RAASi therapy; however, there are still many unanswered questions, such as optimal time to initiate and discontinue these medications once hyperkalemia is resolved.

Digitalis Glycosides

Case 14-3, Question 3: B.D. has tolerated spironolactone 25 mg daily for 2 months. His laboratory test results today show that his potassium is 4.4 mEq/L and his SCr is 1.0 mg/dL. His BP is 124/82 mm Hg, and his pulse is 70 bpm. He has come to the clinic today for a follow-up appointment with his cardiologist who notes that B.D. has had four HF hospitalizations in the past year. B.D. also reports increased SOB, DOE, and PND, although his weight is stable and he takes all his medications as prescribed. The medical resident who is also staffing the clinic asks whether it would be appropriate to add digoxin to B.D.'s medical treatment of HF. He was told by a colleague that in clinical trials, digoxin reduced both HF symptoms and hospitalizations for HF. What would you recommend?

Debates raged for years about whether digitalis glycosides or vasodilators should be the drug(s) of first choice for treating HFrEF. By the time the first ACC/AHA guidelines were published, a clear consensus was evident. Vasodilators are first-line therapy, with digoxin being added for patients with supraventricular arrhythmias, failure to achieve symptomatic relief with vasodilators alone, or intolerable side effects from vasodilators. ACEIs are preferred compared to other vasodilators because of proven efficacy, convenience of dosing, and fewer side effects. By 1999, experts also recommended starting β-blocker therapy earlier in the treatment plan. Digoxin, however, continues to be widely debated.

CONTROVERSY ABOUT EFFICACY OF DIGOXIN

Correction of the underlying defect is a rational approach to the treatment of any disease. When considering HF solely as "pump failure" with a weakened myocardial muscle, digitalis is the logical choice to improve cardiac contractility, CO, and renal perfusion. If focusing on symptom relief and increased exercise tolerance as markers of benefit, digoxin is effective. Critics, however, raised concerns that symptom relief was less in patients with normal sinus rhythm than in those with supraventricular arrhythmias. The most vocal critics claimed that the risk of digitalis toxicity did not warrant using this class of drugs in patients with normal sinus rhythm.

Using multivariate analysis, one group of investigators concluded that a third heart sound (S_3 gallop rhythm), an enlarged heart, and a low EF best predict those patients with normal sinus rhythm who will derive a beneficial response from digoxin.[210] Several other meta-analyses and critical reviews of the literature concurred that digoxin therapy provides a beneficial effect, especially in patients with severe symptomatic ventricular systolic dysfunction.[211,212] However these opinions were based on historical data and when many current therapies were not available.

DIGOXIN WITHDRAWAL TRIALS

In 1993, two digoxin withdrawal trials, **P**rospective **R**andomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED)[213] and **R**andomized **A**ssessment of **D**igoxin on **I**nhibitors of the **AN**giotensin **C**onverting **E**nzyme (RADIANCE),[214] were published. Both attempted to determine whether patients with HF who were already treated with digoxin would show deterioration after discontinuation. In both studies, patients had documented HFrEF (LVEF <35%), mild-to-moderate symptoms, were in normal sinus rhythm, and stable for at least 3 months with treatment of a diuretic and digoxin (baseline digoxin level, 0.9–2.0 ng/mL). Patients in the RADIANCE trial were also stabilized on an ACEI in addition to the diuretic and digoxin.[214] A 12-week, double-blind, placebo-controlled treatment period followed initial stabilization in both studies. Patients in the active treatment groups continued digoxin at their previous dose. Those in the placebo groups were withdrawn from digoxin and given placebo.

In PROVED,[213] 42 subjects continued digoxin and 46 were given placebo. There were 29% treatment failures in the withdrawal group compared with 19% in those taking digoxin. Exercise tolerance worsened in more patients taking placebo. Those taking digoxin tended to maintain lower body weight and HR as well as higher EF. In the RADIANCE study, 85 subjects continued digoxin therapy, and 93 were switched to placebo.[214] During the 12-week follow-up period, 4.7% of the subjects taking digoxin experienced worsening

symptoms compared with 24.7% of the patients on placebo. More of the patients on placebo had worsening of EF and lower quality-of-life scores. When comparing the two trials directly, fewer patients deteriorated in both arms in the RADIANCE study. Whether this is attributed to a greater benefit from combining an ACEI with a diuretic compared with using a diuretic alone (as in PROVED) cannot be established.

These studies establish a beneficial effect of digoxin, even in those patients receiving concurrent ACEIs. At least two factors, however, limit extrapolation to all patients with HF. First, the investigators only assessed the value of therapy indirectly using a withdrawal design instead of initiating therapy in patients previously untreated with digoxin. Second, the patients had advanced disease as evidenced by NYHA class II or III symptoms despite triple-drug therapy. Thus, the benefit of digoxin as initial monotherapy in early disease remains an unanswered question.

EFFECT OF DIGOXIN ON MORTALITY

The seminal study to answer the question of whether treatment with digoxin improves survival in HF was the Digitalis Intervention Group (DIG) study.[215] In this study, 6800 patients with HF were randomly assigned to receive either digoxin or placebo. Eligibility requirements included an EF of ≤45% (mean, 28% in both groups), normal sinus rhythm, and clinical evidence of HF. Most subjects were in NYHA class II or III HF, although a small number of class I and class IV subjects were included. Concurrent therapies included diuretics, ACEIs, and nitrates. In both groups, 44% were taking digoxin before randomization. The starting digoxin dose (or placebo) was based on age, weight, and renal function, with subsequent adjustments made according to plasma level measurements. Approximately 70% of subjects in both groups ended up taking 0.25 mg/day. By 1 month, 88.3% of patients receiving digoxin had serum levels between 0.5 and 2.0 ng/mL, with a mean of 0.88 ng/mL. Patients were followed up for an average of 37 months.

For the primary outcome of total mortality from any cause, 34.8% of patients on digoxin and 35.1% of those on placebo died; corresponding CV deaths were 29.9% and 29.5%, respectively. Although neither of these differences is statistically significant, a trend was seen toward fewer HF-associated deaths and statistically fewer hospitalizations (risk ratio, 0.72) with digoxin. As would be expected, cases of suspected digoxin toxicity were greater in the active treatment group (11.9% vs 7.9%), but the incidence of true toxicity was low.

The DIG trial improves on the PROVED and RADIANCE trials because it added digoxin to other therapy as opposed to being a withdrawal study and also because of the larger population. However, because nearly all patients were receiving concurrent vasodilator therapy, the value of digoxin as monotherapy on mortality rates remains unanswered.

The ACC/AHA guidelines[2] indicate that patients with HF are unlikely to benefit from the addition of digoxin in stage A or stage B HF. In stage C patients, despite receiving optimal doses of ACEIs or β-blockers, digoxin may be beneficial to reduce HF hospitalizations.

Digoxin is prescribed frequently in patients with HF and concurrent AF, but β-blockers may be more effective in controlling the ventricular response, especially during exercise. Digoxin should be avoided if the patient has significant sinus or AV block unless the block is treated with a permanent pacemaker. Digoxin should be used cautiously in patients taking other drugs that can depress sinus or AV nodal function (amiodarone or β-blockers), although patients usually will tolerate this combination.

Despite being on maximal tolerated doses of lisinopril and metoprolol, B.D. continues to have HF symptoms. In patients with persistent HF symptoms, especially as with B.D. who also presents with an EF <25%, digoxin can be used as an additional agent. However, digoxin is not indicated as primary therapy for stabilization of patients with acutely decompensated HF. Such patients should first receive appropriate treatment, including IV medications.

SEX DIFFERENCES IN RESPONSE TO DIGOXIN

CASE 14-3, QUESTION 4: If B.D. had been a female, would it have made any difference in the consideration to prescribe digoxin?

The retrospective post hoc analysis of the DIG study data reported that the death rate was lower among females in the placebo group as compared to males (28.9% vs 36.9%; $P < .001$); however, this difference was not significant between females and males taking digoxin.[205] Females taking digoxin had a higher death rate than did females taking placebo (33.1% vs 28.9%), whereas death rates in males were similar in both groups. The authors speculate that a possible mechanism for the increased risk of death among females taking digoxin is an interaction between hormone replacement therapy and digoxin. Progesterone might increase serum digoxin levels by inhibiting P-glycoprotein (PGP), thus reducing digoxin renal tubular excretion. Consistent with this hypothesis, digoxin serum concentrations after 1 month of therapy were higher in females than in males. The study investigators, however, did not gather data on estrogen and hormone replacement therapy or consistently measure serum digoxin levels later in the trial. However, subsequent reanalysis[216] of the DIG data found lower serum concentrations (0.5–0.9 ng/mL) of digoxin associated with a decreased risk of hospitalizations and mortality in females. Serum concentrations >1.2 ng/mL were associated with higher risk of death when compared with the placebo group. Higher digoxin concentrations resulted in worse clinical outcomes both in males and females. Another analysis of patients treated with digoxin in the **S**tudies of **L**eft **V**entricular **D**ysfunction (SOLVD) trial failed to demonstrate a survival difference based on gender.[217] The available data suggest that serum digoxin concentrations in the range of 0.5 to 0.9 ng/mL are safe, improve LVEF, hemodynamics, and reduce hospitalizations irrespective of gender.

MAINTENANCE DOSE

Case 14-3, Question 5: What is the appropriate maintenance dose of digoxin for B.D.?

The usual maintenance doses of digoxin have traditionally ranged from 0.125 to 0.25 mg/day. With the increased emphasis on targeting lower serum concentrations (0.5–0.9 ng/mL), more patients are now empirically started at 0.125 mg/day. It is safer to start with a conservative dose and assess B.D.'s needs after 1 to 2 weeks.

In all cases, smaller doses of digoxin are given to patients with impaired excretion rates (those with renal failure, older patients) or small-framed individuals. For example, a patient who is totally anuric may receive only 0.0625 mg 3 or 4 days/week.

Loading doses of digoxin are rarely necessary. Slow initiation of therapy with maintenance doses of digoxin is the method of choice for ambulatory or nonacutely ill patients with normal renal function. Even in the acute care setting, no indication exists for loading doses of digoxin for HF alone. The exception might be if the patient has AF, and it is desired to control ventricular response as quickly as possible. Even then, alternative drugs are likely to be used (see Chapter 15, Cardiac Arrhythmias).

MONITORING PARAMETERS

Case 14-3, Question 6: How should B.D.'s digitalis therapy be monitored? How useful are digoxin serum levels in monitoring therapy?

No clear therapeutic end point exists for digoxin therapy. Nonspecific electrocardiographic (ECG) changes (ST depression, T-wave abnormalities, and shortening of the QT interval) correlate poorly with both toxic and therapeutic effects of the drug.[218,219] Although digoxin serum levels are readily available from most clinical laboratories, no "therapeutic level" and corresponding "toxic level" are clearly defined.

A few patients, especially if they are hypokalemic or hypomagnesemic, will manifest apparent signs of toxicity when

serum digoxin concentrations are <1 ng/mL. At the other extreme, some patients tolerate concentrations >2 ng/mL with no signs of overt toxicity. Such overlap between therapeutic concentrations and toxic levels limits the value of serum level monitoring. Serum levels can be used as a guide in confirming suspected toxicity or in explaining a poor therapeutic response, but clinical evaluation ultimately remains the best therapeutic guide.

Clinical evaluation

As with diuretic and vasodilator therapy, clinical monitoring is the key to evaluating adequacy of digitalis therapy. As B.D. begins to improve, he should have less dyspnea and report less PND, and a lower HR may be observed.

TREATMENT OF SUPRAVENTRICULAR ARRHYTHMIAS IN HEART FAILURE

Case 14-3, Question 7: B.D. did well for the next 6 months until he noted the onset of palpitations, which were diagnosed by ECG as AF. A month ago, his primary care physician increased his digoxin dose to 0.25 mg every day. How should we treat his AF?

Supraventricular arrhythmias are frequently encountered in HF because volume or pressure overload can cause atrial distension and irritability. Specifically, AF is present in 10% to 30% of patients with advanced HF,[98] contributing to reduced exercise capacity, increased risk of pulmonary or systemic emboli, and worse long-term prognosis. Drug therapy should be aimed at controlling ventricular rate and preventing thromboembolic events. Cardioversion to normal sinus rhythm in patients with low EF and dilated cardiomyopathy is often unsuccessful.

Digoxin slows the ventricular response associated with AF and is a logical choice in patients with concurrent HFrEF. A potential limiting factor is that digoxin's AV-blocking properties are most evident at rest and are less effective during exercise. Hence, digoxin may be

ineffective at controlling exercise-induced tachycardia that limits the patient's functional capacity. β-Blockers are more effective than is digoxin during exercise.[220–222] If digoxin, β-blockers, or both are ineffective, amiodarone is another useful alternative. Verapamil and diltiazem are not appropriate choices for rate control in patients with HFrEF because of their negative inotropic effects.

Some studies suggest that AF is an independent predictor of mortality in patients with HF, and restoration of sinus rhythm may reduce mortality and prevent recurrences. Most patients who are electrically cardioverted revert to AF in a short time. In CHF-STAT (Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy),[223] a subset of patients who were converted to normal sinus rhythm with amiodarone treatment had significantly lower mortality than did those who remained in AF. Similar results were observed in a substudy of the DIAMOND (*D*anish *I*nvestigations of *A*rrhythmia and *M*ortality *ON D*ofetilide) trial,[224] in which patients with HF having AF treated with dofetilide had significantly improved survival if the sinus rhythm was maintained. However, AF-CHF (Atrial Fibrillation in Congestive Heart Failure)[225] showed no mortality or morbidity benefits of rhythm control compared with rate control. The lack of mortality benefits seen in the AF-CHF might be explained by the high frequency of β-blocker use (88%). Antiarrhythmic agents are frequently unsuccessful in maintaining sinus rhythm.[223] Patients who benefit the most from conversion to sinus rhythm are the hemodynamically compromised. Maintaining sinus rhythm can potentially improve their quality of life.

The use of most antiarrhythmic agents, except amiodarone and dofetilide, is associated with worse prognosis because of proarrhythmic or negative inotropic effects and should be avoided in patients with HF. Although amiodarone and dofetilide do not increase mortality in patients with HF, they are associated with increased hospitalizations.[226] Current treatment guidelines do not support the routine use of anticoagulants in HF unless patients have concomitant AF or evidence of active thrombus. Finally, AV nodal ablation may be needed if tachycardia or bothersome symptoms persist despite aggressive pharmacologic intervention.

B.D. experienced AF while already taking a relatively high dose of digoxin (0.25 mg/day) and metoprolol. If his AF-associated palpitations persist, amiodarone should be started (see Chapter 15, Cardiac Arrhythmias). Amiodarone is a PGP inhibitor. The net effect of inhibition of gut PGP by amiodarone is increased bioavailability of digoxin. B.D.'s digoxin dose will need to be lowered by ~50% if amiodarone is started.[219,227] If digoxin is continued, serum levels should be closely monitored, and patients observed for clinical evidence of toxicity.

DIGOXIN DRUG INTERACTIONS

Case 14-3, Question 8: What are the other potential drug interactions with digoxin?

Two reviews of cardiac glycoside drug interactions have been compiled.[228,229] Since publication of these early reviews, a greater understanding of PGP-mediated drug interactions has evolved.[227,230] A brief summary of all digoxin interactions is found in **Table 14-13**. Drugs recently recognized as raising digoxin serum concentrations through PGP inhibition include atorvastatin,[231] CCBs (especially verapamil and diltiazem),[232] erythromycin and clarithromycin,[233,234] and cyclosporine. Conversely, rifampin[194] and St. John's wort[235] reduce oral digoxin bioavailability and serum concentrations via induction of intestinal PGP.

Table 14-13
Digoxin Drug Interactions

Drug	Effect
Drugs Lowering Serum Digoxin Concentration	
Rifampin[194]	Probable induction of intestinal P-glycoprotein causing ↓bioavailability
	↓Serum concentration after oral, but not IV digoxin. No change in digoxin renal clearance or half-life
St. John's wort[235]	Possible induction of P-glycoprotein (33%

	reduction in digoxin trough concentrations)[322]
Sulfasalazine doses >2 g/day	Malabsorption of digoxin (decrease AUC of digoxin by 24%)[322]
Drugs Raising Serum Digoxin Concentration	
Amiodarone[219,227]	↑Serum digoxin levels inhibit intestinal P-glycoprotein (70% in 1 day)[322]
Atorvastatin[229]	20% increase in serum digoxin concentration with 80-mg dose, minimal effect with 20-mg dose. Speculated to inhibit intestinal P-glycoprotein, but not proven
Calcium channel blockers[219,227,232]	Inhibition of P-glycoprotein. Best documented with verapamil (70%–80%).[323] Diltiazem increases digoxin concentrations by 50% in some patients.[323]
Clarithromycin[233,322]	Inhibition of P-glycoprotein, decreased digoxin renal clearance. Digoxin clearance may be reduced by 60%, and plasma concentrations may increase by twofold.[322]
Cyclosporine[219,227]	Inhibition of P-glycoprotein, decreased digoxin renal clearance
Erythromycin	↑Bioavailability in persons who normally metabolize digoxin in intestinal tract. May also inhibit P-glycoprotein in the gut. Digoxin concentrations may increase by 100% in some cases.[322]
Itraconazole[324]	↑Serum digoxin levels by unknown mechanism. In one study, the AUC for digoxin was increased by 50% and renal elimination was decreased by 20%.[322]
Propafenone[212,325]	Inhibition of P-glycoprotein. Increases digoxin concentrations by 30%–60%[322]
Quinidine[219,227,228,230,326–330] (usually doses >500 mg/day may increase digoxin serum concentrations)	Inhibition of P-glycoprotein, decreased digoxin renal clearance, and increased bioavailability. Increases 25%–100% digoxin concentrations[322]

References[219,227,229] include a discussion of many of these interactions that do not include a specific reference citation.

AUC, area under the curve; IV, intravenous.

DIGITALIS TOXICITY

Signs and symptoms

Case 14-3, Question 9: If B.D. presents with digoxin toxicity, what would be the common signs and symptoms of toxicity?

Digoxin has a narrow therapeutic index, and there is concern for morbidity and death associated with its use. The most important signs of digoxin toxicity are those relating to the heart. A common misperception is that gastrointestinal or other noncardiac signs will precede cardiac toxicity. On the contrary, cardiac symptoms precede noncardiac symptoms of digitalis toxicity in up to 47% of cases. Frequently, nonspecific arrhythmias are the only manifestation of toxicity, with estimates that rhythm disturbances occur in 80% to 90% of all patients with digitalis toxicity.[236] Conversely, rhythm disturbances in patients taking digitalis are not always related to toxicity. In one study of 100 consecutive patients with suspected digitalis-induced arrhythmias, only 24 were confirmed as being toxic as defined by resolution of cardiac irritability after drug withdrawal. In the other 76 patients, the dysrhythmia persisted long after drug removal.[237]

Most arrhythmias can occur as a result of digoxin toxicity. Decreased conduction velocity through the AV node presents as a prolonged PR interval (first-degree AV block) and is seen in many patients with therapeutic concentrations of digoxin. However, higher concentrations of digoxin can impair conduction and result in bradycardia or a second-degree AV block. With severe toxicity, complete (third- degree) AV block can occur. AV block also may predispose patients to accelerated junctional rhythms. Increased automaticity of the atria can cause multifocal atrial tachycardia with block, paroxysmal atrial tachycardia with block, or AF.

Ventricular arrhythmias are among the most common rhythm disturbances caused by digoxin toxicity and include unifocal and

multifocal premature ventricular contractions (PVCs), bigeminy, trigeminy, ventricular tachycardia, and ventricular fibrillation.[236,237] In the DIG trial, 11.9% of patients in the digoxin treatment group were found to have suspected digoxin toxicity compared with 7.9% in the placebo group. Comprehensive reviews are available on the topic of digitalis- induced arrhythmias.[219]

Hyperkalemia can develop as a consequence of massive digoxin ingestion by severely poisoning the Na^+/K^+ ATPase system, causing inhibition of the uptake of potassium by the myocardium, skeletal muscle, and liver cells.[238] The shift of potassium from inside to outside the cell can result in significant hyperkalemia, especially in patients with underlying renal insufficiency. These same patients also accumulate digoxin in the body because of decreased clearance of the drug.

Vague gastrointestinal symptoms characteristic of digoxin toxicity are difficult to evaluate because anorexia and nausea are also part of clinical picture seen in patients with congestion.

CNS symptoms of digoxin are common, possibly associated with potassium depletion in neural tissue. Chronic digoxin intoxication can manifest as extreme fatigue, listlessness, or psychic disturbances in the form of nightmares, agitation, and hallucinations.[239] Visual disturbances have been described as hazy vision and difficulties in both reading and red–green color perception. Other reports included dark or moving spots, photophobia, and yellow–green vision. Disturbances in color vision returned to normal 2 or 3 weeks after discontinuation of digitalis.

Digitalis-induced visual disturbances have been reported at serum concentrations below those considered to be toxic (all <1.5 ng/mL; range, 0.2–1.5 ng/mL).[240] Five of the reactions were described as photopsia (seeing lights not present in the environment), and one person had decreased visual acuity. The symptoms resolved in all but one subject when digoxin was discontinued.

Some prospective studies have shown a good correlation between serum digoxin concentration and toxicity,[239,241,242] whereas other investigators found a poor correlation.[243,244] Once levels exceed 6 ng/mL, the risk of mortality greatly increases.[245] Patients with

hypokalemia can demonstrate digitalis toxicity at low serum digoxin concentrations.[246]

For many patients without life-threatening arrhythmias or major electrolyte imbalances, simple withdrawal of digoxin is the only treatment required. Potassium replacement should be considered in any patient with digoxin-induced ectopic beats who is hypokalemic. Digoxin-specific antibodies that bind digoxin molecules, rendering them unavailable for binding at receptors, are available.[247–252] The use of digoxin Fab products is restricted to potentially life-threatening intoxications (severe arrhythmias or hyperkalemia) that are either refractory to more conservative therapy or associated with extremely high serum digoxin concentrations.

Non–Angiotensin Converting Enzyme Inhibitor Vasodilator Therapy

CASE 14-4

Question 1: T.R. is a 57-year-old African American male (LVEF of 35%) who presents to the HF clinic for follow-up. His BP is 130/79 mm Hg and pulse is 65 bpm. Current medications include lisinopril 20 mg daily, metoprolol succinate 200 mg daily, spironolactone 25 mg daily, hydralazine 25 mg qid, and isosorbide dinitrate 20 mg tid.

Why is the patient on hydralazine and isosorbide? What other forms of nitrates can be used in place of the isosorbide? Is combination therapy rational?

T.R. is treated with an ACEI, a β-blocker, and spironolactone. Despite this therapy, he is still having HF symptoms. He was started on hydralazine and isosorbide dinitrate, which is a possible next step in treating a patient with HFrEF.

Hydralazine's predominate action is as an arteriolar dilator. Decreasing afterload improves LV function. SVR is decreased, and this leads to an increase in CO.[139,253,254] Hydralazine is a direct-acting smooth muscle relaxant with significant arteriolar dilating effects in the kidneys and limbs. It has no effect on the venous system or on hepatic blood flow.

The reflex tachycardia and hypotension that accompany hydralazine in treating HTN are minimal or absent when treating HF. In patients with end-stage cardiomyopathy, significant hypotension can occur if the heart cannot respond appropriately by increasing CO. Because hydralazine is devoid of venous dilating properties, central venous pressure and PCWP are unchanged.[139,254]

The effect of a single dose of hydralazine occurs in about 30 minutes and lasts up to 6 hours. The average maintenance dose is 50 to 100 mg every 6 to 8 hours. T.R. is receiving an initial dose at this time and may warrant a higher dose in the future. Hydralazine used as monotherapy is not associated with long-term improvement in functional status.[254] Combination therapy of hydralazine with either nitrates or ACEIs is highly effective.

Although tachyphylaxis generally is not a significant problem with prolonged courses of hydralazine, some patients require increased diuretic doses to counteract hydralazine-induced fluid retention. This latter response reflects activation of the renin–angiotensin system after vasodilation of the renal vasculature. Other side effects with hydralazine include transient nausea, headache, flushing, tachycardia, and a lupus syndrome associated with prolonged, high doses (see Chapter 9, Essential Hypertension).

ORAL NITRATES

Nitrates have effects complementary to those of hydralazine.[139,253] They primarily dilate venous capacitance vessels. Venous dilation reduces preload, resulting in reductions in PCWP and right atrial pressure. They are especially effective in reducing the symptoms of pulmonary congestion. The lack of significant arterial dilation accounts for the observations that SVR is minimally reduced and CO remains unchanged.

Isosorbide

Because sublingual NTG has a short duration of action, more attention has been focused on isosorbide dinitrate. Sublingual isosorbide dinitrate is well absorbed and does not undergo first-pass

metabolism. Its onset is rapid (5 minutes), but its effects are relatively short (1–3 hours). The usual starting dosage is 5 mg every 4 to 6 hours, but dosages may be titrated to 20 mg or more. Larger doses are associated with longer beneficial effects (~3 hours), but also have a high frequency of headaches and hypotension.

Oral isosorbide has a slower onset (15–30 minutes), but the duration of activity is longer (4–6 hours) than that of sublingual tablets. The smallest effective dose is 10 mg, with titration to dosages as high as 80 mg every 4 to 6 hours. The best dose for both sublingual and oral nitrates is that which provides the desired beneficial effect with the least side effects. Isosorbide mononitrate is frequently used because it is generally given once daily.

HYDRALAZINE–NITRATE COMBINATION

Combined afterload and preload reduction are clearly of benefit in improving symptoms and enhancing long-term survival. Compared with ACEIs, the hydralazine–isosorbide combination provides more improvement in exercise tolerance, but the side effect profile and survival statistics are better with ACEIs.[139] Generally, the use of the two drugs together is not accompanied by reflex tachycardia or hypotension.

Data supporting the use of combination hydralazine and nitrate vasodilator therapy come from two Veterans Administration (VA) Cooperative Studies (V-HeFT I and V-HeFT II).[70,139,253] These two studies confirmed symptomatic relief and improved exercise tolerance with combination therapy, and improved survival. (See Case 14-3, Question 2, for the discussion of the therapy in African American patients.)

In summary, nitrates alone are indicated for those patients with signs and symptoms of pulmonary and venous congestion. Use of an arterial dilator is beneficial in a patient with high SVR and low CO. Most patients, such as T.R., exhibit symptoms of decreased CO and elevated venous pressure, making combination therapy an attractive option. Although the hydralazine–isosorbide combination actually reduces symptoms slightly better than do ACEIs, the data on survival

are better with the ACEIs, probably owing to better adherence. A combination of an ACEI plus hydralazine, a nitrate, or both is common in patients with advanced disease.

Role of Race in the Pharmacotherapy of Heart Failure

CASE 14-4, QUESTION 2: Because T.R. is African American, would he be expected to respond differently to ACEIs or hydralazine– isosorbide dinitrate than a patient who is not African American?

In general, African American patients experience HF at an earlier age and are more likely to have HTN as a cause. The death rate of HF is higher for African American than for non–African American patients.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND HYDRALAZINE–ISOSORBIDE

Racial differences in response to drug therapy have been proposed, although this issue is far from resolved.[255–258] A post hoc analysis[256] of the V-HeFT trial data showed no difference in annual mortality between African American and non–African American patients receiving placebo. African American patients in the hydralazine–nitrate group had a significantly lower mortality rate than did those in the placebo group. This implies that African American patients, but not non–African American patients, derive benefit from the treatment with hydralazine–isosorbide. These same investigators then reanalyzed the V-HeFT II trial results for possible racial differences between response to enalapril and the hydralazine–nitrate combination.[139,256] The outcome is difficult to interpret because of the absence of a placebo group. The all-cause annual mortality rate for African American patients was identical in the two drug groups (12.8% with enalapril and 12.9% with hydralazine–isosorbide). In non–African American patients, the corresponding mortality rates

were 11% with enalapril and 14.9% with hydralazine–isosorbide. These data could be interpreted as either superior response to hydralazine–isosorbide in African Americans or inferior response to ACEIs in African Americans. The latter interpretation is consistent with the hypothesis that ACEIs might have a lesser BP-lowering effect in African American patients with HTN. A similar reanalysis of the SOLVD Prevention and Treatment trials,[134] which compared enalapril with placebo in patients with recent MI, concluded that enalapril is associated with a significant reduction in the risk of HF hospitalization among White patients (44% reduction) with LV dysfunction, but not among African American patients. Confounding variables contributing to all of these analyses include disproportionately low numbers of African American subjects in the trials, and possibly more underlying risk factors in African American subjects.

To address the effect of race on response to ACEIs, a meta-analysis of seven major ACEI studies with 14,752 patients, was conducted.[257] The authors concluded that the relative risk for mortality when taking an ACEI compared with placebo was identical (0.89) for both African American and White patients. The authors urged that ACEIs not be withheld from African American patients. Although rare, there is a higher rate of angioedema with ACEIs in Black patients compared to White patients.

The AHeFT previously mentioned was a randomized comparison trial of hydralazine–isosorbide dinitrate versus placebo in African American or self-identified Black patients with NYHA class III or IV HF who were receiving standard HF therapy (diuretics, β-blockers, ACEIs or ARBs, digoxin, and AAs).[71] The primary end point was a composite of all-cause death, first hospitalization for HF, and quality-of-life scores at 6 months. Reduction in the primary end point events was statistically significant in favor of the active drug combination. All-cause mortality declined 43% with hydralazine–isosorbide dinitrate versus placebo ($P = .012$). The study also reported a 39% reduction in first hospitalization for HF with hydralazine–isosorbide dinitrate versus placebo ($P < .001$). The results of AHeFT were also the primary factor leading the FDA to approve the combination

product of hydralazine and isosorbide dinitrate (BiDil) for adjunctive treatment in African American or self-identifying Black patients.

β-BLOCKERS

A possible racial difference in response to β-blocker drugs has also been hypothesized based on effects observed in HTN.[255,257,258] A post hoc analysis of the U.S. Carvedilol Heart Failure trials[189–193] concluded that the benefit of carvedilol was similar in both Black and non-Black patients.[258]

Contradictory evidence comes from BEST.[199] In this trial (discussed in Case 14-1, Question 20), 2708 patients with NYHA class III or IV HF were randomly assigned to either bucindolol or placebo. Bucindolol is a nonselective β-blocker with partial agonist activity that imparts weak vasodilation. A unique characteristic of this study was a preplanned subgroup analysis for racial differences. Although there was a trend toward reductions in CV mortality and hospitalization with bucindolol, the trial was terminated after 2 years. A subgroup analysis showed a mortality benefit in non-Black subjects, but no benefit in Black subjects. A meta-analysis of five major β-blockers in HF studies representing 12,727 patients has been conducted, suggesting that Black patients will derive similar benefit from β-blockers as do White patients when given carvedilol, metoprolol, or bisoprolol.[257]

Critical Care Management of Heart Failure

CASE 14-5

Question 1: L.M., a 62-year-old Black male, was admitted several days ago with severe, progressive, and debilitating symptoms of HF. His family history is significant in that his father and two brothers died of heart attack shortly after age 40. L.M. has a 5-year history of HF that is symptomatic despite treatment with furosemide 40 mg daily, lisinopril 10 mg daily, carvedilol 12.5 mg bid, digoxin 0.125 mg daily, and spironolactone 25 mg daily. His last echocardiogram showed an EF of 25%. He has a past medical history of HTN, CAD, and HF. During the past week, L.M.'s DOE became progressively worse, and he was confined to bed because of fatigue. He wakes once or twice nightly

with PND. Physical examination revealed jugular venous distension, bilateral rales, hepatomegaly, and 3+ peripheral edema. Chest radiograph showed cardiomegaly and pulmonary congestion. His BP was 154/100 mm Hg and pulse was 105 bpm.

Laboratory test results include:

Serum Na^+, 134 mg/dL
K^+, 4.3 mg/dL
BUN, 15 mg/dL
SCr, 1.3 mg/dL
Glucose, 90 mg/dL
BNP, 944 pg/mL

Hemoglobin, hematocrit, troponin, and liver enzymes were within normal limits. L.M. was admitted to the hospital with ADHF.

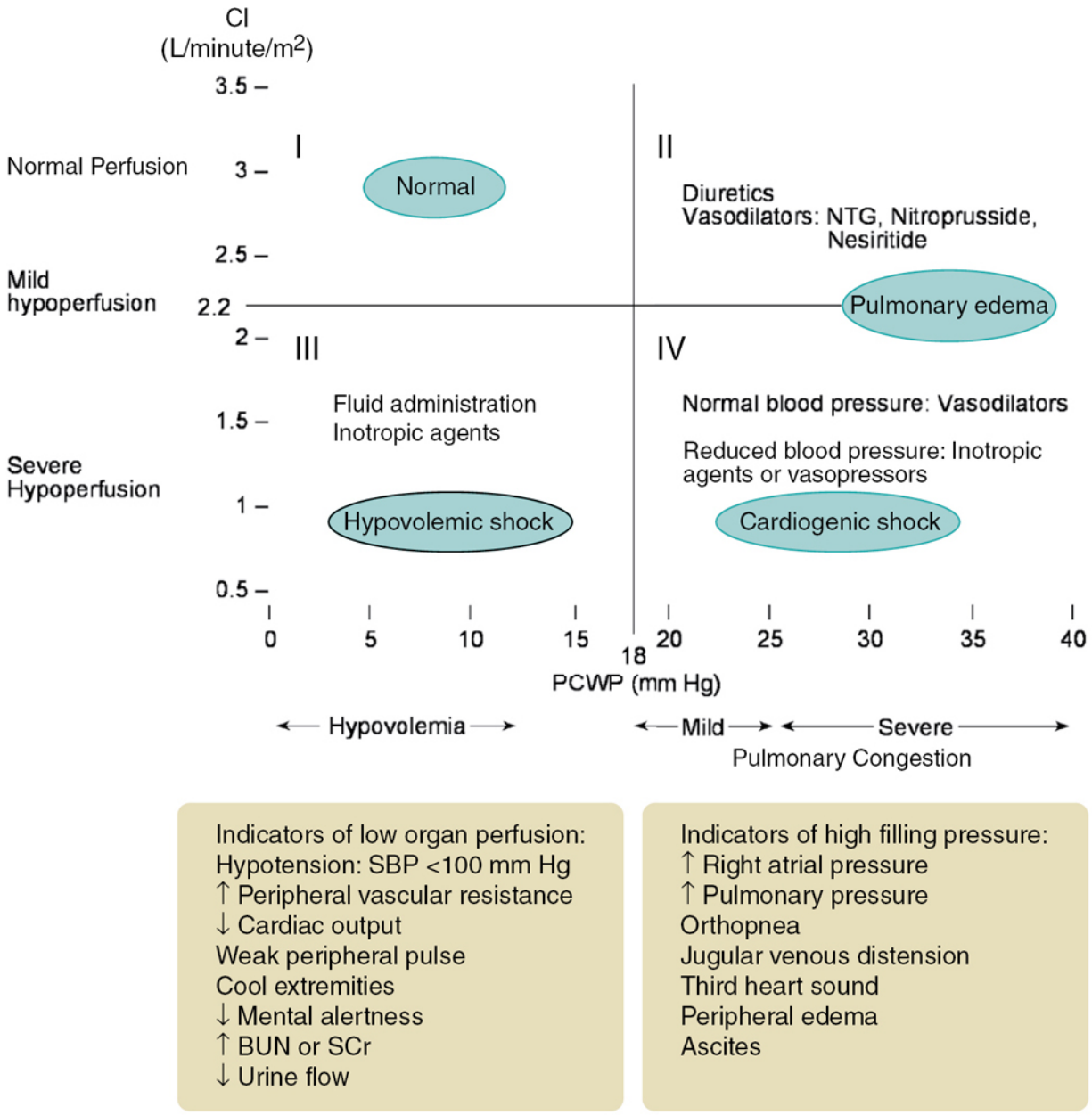
What factors are used to stratify risk for in-hospital mortality and morbidity?

ADHF is associated with high morbidity and mortality. It is the leading reason for hospitalizations among the elderly. Postdischarge mortality among patients with HF is 11% at 30 days and 37% at 1 year.[259] The most common precipitants of HF hospitalization are noncompliance (dietary or medication), acute myocardial ischemia, uncontrolled comorbidities (HTN, diabetes mellitus, chronic kidney disease, arrhythmias), and prescribing of negative inotropic agents, NSAIDs, or other inappropriate agents. Regardless of the precipitating event, the common pathophysiologic state that perpetuates the progression of HF is complex. A cascade of hemodynamic and neurohormonal derangements provoke activation of adrenergic systems and RAAS, leading to volume overload and hypoperfusion—classic symptoms of ADHF. According to the ADHF National Registry, nearly half of the patients who present with ADHF have preserved EF (>50%).[260]

In-hospital mortality remains as high as 20% for patients who present with elevated BUN and creatinine, and low SBP (SCr >2.75 mg/dL, BUN >43 mg/dL, SBP <115 mm Hg).[251] Patients presenting with hyponatremia (serum sodium <135 mEq/L) have the worst outcomes and are more likely to receive inotropic agents. After discharge, patients who continue to be hyponatremic have an 8% risk of rehospitalization per 3 mEq/L decrease in serum sodium. Uric

acid >7 mg/dL in males and >6 mg/dL in females is associated with a high admission rate for HF. Admission and discharge levels of BNP are also helpful in predicting rehospitalizations. According to studies, a 30% to 40% reduction in BNP levels during hospitalization may improve outcomes. Other biomarkers such as cardiac troponin levels, C-reactive protein, and apolipoprotein A-I levels are all linked to HF readmissions.[7] All these factors can be used to stratify risk for in-hospital mortality.

Another approach to risk stratification and therapeutic decision-making is based on hemodynamic profiles. Most patients with acute HF can be classified into one of four hemodynamic profiles using relatively simple assessment techniques (see **Fig. 14-10**).[261–264] Patients are assessed for the presence or absence of elevated venous filling pressures ("wet" vs "dry") and adequacy of vital organ perfusion ("warm" vs "cold"). Elevated filling pressure can be assessed at the bedside by observing jugular venous distension, presence of a third heart sound (S_3), peripheral edema, and ascites. Presence or absence of rales on auscultation is not considered a reliable indicator.[264] Hypotension, weak peripheral pulse, a narrow pulse pressure, cool extremities, decreased mental alertness, and rising BUN and SCr are indicators of decreased organ perfusion. Continuous BP, ECG, urine output, and pulse oximetry measurements are standard noninvasive monitoring for all patients in an intensive care unit. Invasive hemodynamic monitoring is used in critically ill patients when more precise measurements of filling pressures, SVR, and CO or cardiac index are desired. The goals are to achieve a right atrial pressure of <8 mm Hg, pulmonary artery pressure of <25/10 mm Hg, pulmonary artery wedge pressure of 12 to 16 mm Hg, SVR 900 to 1400 dyne second/m^5, and a cardiac index >2.5 L/minute/m^2. (See Chapter 17, Shock, for a more detailed discussion of hemodynamic monitoring.)



Indicators of low organ perfusion:
Hypotension: SBP <100 mm Hg
↑ Peripheral vascular resistance
↓ Cardiac output
Weak peripheral pulse
Cool extremities
↓ Mental alertness
↑ BUN or SCr
↓ Urine flow

Indicators of high filling pressure:
↑ Right atrial pressure
↑ Pulmonary pressure
Orthopnea
Jugular venous distension
Third heart sound
Peripheral edema
Ascites

Figure 14-10 Hemodynamic profile of acute heart failure. BUN, blood area nitrogen; CI, cardiac index; NTG, nitroglycerin; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; SCr, serum creatinine. (Adapted from Forrester JS, Diamond GA, Swan HJ. Correlative classification of clinical and hemodynamic function after acute myocardial infarction. *Am J Cardiol*. 1977;39(2):137–145. © 1977 Elsevier. With permission.)

CASE 14-5, QUESTION 2: From his clinical presentation, what is L.M.'s hemodynamic profile? What are the therapeutic goals for L.M.?

L.M.'s DOE, rales, peripheral edema, PND, and JVP are consistent with ADHF and volume overload. L.M. does not have signs of hypoperfusion. His hemodynamic profile is "warm and wet" (subset II, **Fig. 14-10**). According to the guidelines, a rapid diagnosis of ADHF is necessary to initiate appropriate treatment. In patients who have established HF, precipitating factors should be identified and addressed. At the time of discharge, medications that decrease morbidity and mortality in HF should be optimized. BNP levels should be considered when the diagnosis is uncertain and can be helpful in differentiating between cardiac and noncardiac causes of dyspnea.

Because volume overload is central to the pathophysiology of most episodes of ADHF, the primary goal is to relieve congestion. However, diuretics should be cautiously used in subset IV to avoid decreases in PCWP <15 mm Hg because this can compromise preload and further reduce CO. Despite diuretics being the main therapy in reducing volume overload, their routine use in ADHF is associated with worsening renal function and mortality. Mortality rates are higher in patients receiving chronic diuretic therapy compared with those not receiving diuretics. These findings are based on retrospective data. Nevertheless, they suggest an association between mortality and diuretic use in patients with ADHF (see Case 14-1, Question 7, for diuretic dosing).

ULTRAFILTRATION

Ultrafiltration is an alternative approach for treating hypervolemia. It involves the use of a small device to rapidly remove fluid (up to 500 mL/hour). Typically, ultrafiltration for HF is reserved for patients with renal failure or those unresponsive to diuretics. Studies[265,266] in patients with ADHF have shown that peripheral venovenous ultrafiltration results in greater weight loss and fluid removal, and reduced hospital length of stay and hospital readmissions compared

with medical therapy. Significant reductions in neurohormonal activation and no significant changes in SCr or electrolytes were reported with ultrafiltration.[267] The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD trial)[268] randomly assigned 200 patients to either ultrafiltration or aggressive IV diuretic therapy. The study showed that ultrafiltration significantly improved weight loss at 48 hours (5.0 vs 3.1 kg; $P < .001$), decreased the need for vasoactive drugs (3% vs 13%; $P = .02$), and reduced 90-day hospital readmission (18% vs 32%; $P = .02$) compared with diuretics alone. Ultrafiltration has a class IIb recommendation for patients with refractory HF not responsive to medical therapy. Patients with fluid overload and some degree of renal insufficiency and those refractory to diuretic therapy are candidates for ultrafiltration.[2]

Intravenous Vasodilators

Case 14-5, Question 3: L.M. received a 40-mg IV furosemide dose with no improvement in symptoms. Then he received an 80-mg IV dose with only marginal improvement. The decision is made to start nitroprusside. What is the role of IV vasodilator therapy in someone with ADHF?

The guidelines recommend the addition of vasodilators(IV NTG or nitroprusside) in conjunction with diuretics to reduce congestion in patients with fluid overload in asymptomatic hypotension. In the presence of asymptomatic hypotension, IV NTG, or nitroprusside, in combination with diuretics. In the presence of low SVR, arterial vasodilators (eg, nitroprusside, high-dose NTG) can further compromise perfusion and should be avoided, especially in patients who have preexisting hypotension.

NITROPRUSSIDE

Nitroprusside dilates both arterial and venous vessels, decreasing afterload and preload. Nitroprusside is valuable in patients who are severely congested and have HTN or severe mitral valve

regurgitation complicating LV dysfunction. Its major disadvantages include risk of hypotension, reflex tachycardia, “coronary steal” in patients with CAD, and accumulation of toxic metabolites. Thiocyanate and cyanide toxicity are most likely seen in renal insufficiency and in patients who receive >4 µg/kg/minute of nitroprusside for >48 hours. When stopping nitroprusside therapy, a slow taper is recommended because a rebound increase in HF has been observed 10 to 30 minutes after drug withdrawal (see Chapter 16, Hypertensive Crises).

Nitroprusside must be given by continuous IV infusion, with arterial line placement and intensive care unit admission in most institutions. It is unstable if exposed to heat and light after reconstitution.

INTRAVENOUS NITROGLYCERIN

NTG primarily dilates the venous capacitance vessels with a slight effect on the arterial bed. Patients with acute MI and pulmonary edema are often considered ideal candidates for IV NTG. The resulting reduction in preload reduces PCWP. Because nitrates have minimal effect on afterload, CO will likely remain unchanged or increase slightly. In some patients, NTG could decrease CO if preload is reduced to <15 mm Hg. NTG is generally initiated at 10 µg/minute and increased by increments of 10 to 20 µg, until the patient’s symptoms are improved or PCWP is <16 mm Hg. The most common side effect is headache, which can be treated with analgesics and often resolves after continuous therapy. Tachyphylaxis to NTG occurs within 24 hours of initiation of therapy. Approximately 20% of patients with HF exhibit resistance to high doses of NTG.[2] Nitroprusside is a good choice for patients such as L.M. because he has elevated BP and no history of CAD.

Inotropic Agents

DOPAMINE AND DOBUTAMINE

CASE 14-6

QUESTION 1: B.J. is a 60-year-old male who presents to the ED with worsening DOE. He reports increased SOB during the past week. His medical history includes HTN, CAD, hyperlipidemia, and HF (EF 25%). His medications include metoprolol succinate 100 mg daily, enalapril 5 mg twice daily, furosemide 40 mg bid, aspirin 81 mg daily, and lovastatin 20 mg at bedtime. His vital signs on admission include BP 100/75 mm Hg, HR 92 bpm, respiratory rate 18 breaths/minute, and O_2 saturation 94% on room air. Laboratory values were BUN 20 mg/dL and SCr 1.4 mg/dL. Physical examination reveals pulmonary and peripheral edema and JVP 10 cm. He is given 80 mg IV furosemide with minimal response. His dose was increased to 120 mg IV furosemide, and he still does not respond adequately. Within the past 24 hours, his SCr has increased to 1.8 mg/dL, and his BP is 92/70 mm Hg. The decision is made to admit him to the coronary care unit where a pulmonary artery catheter (Swan–Ganz catheter) is placed, and the hemodynamic variables are as follows: PCWP 21 mm Hg; CO 3.64 L/minute (cardiac index 1.8 L/minute/m^2); SVR 1489 dyne second/cm^5.

Is B.J. a candidate for inotropic therapy?

The hemodynamic profile of B.J. is category IV (cold and wet) because of hypoperfusion and congestion. According to the ACC/AHA guidelines,[1] IV inotropic agents (dobutamine, dopamine, milrinone) are indicated in symptomatic patients with reduced LVEF, low CO, or end-organ dysfunction (ie, worsening renal function) and in patients who are intolerant to vasodilators. They are recommended for patients with cardiogenic shock or refractory symptoms and may be used in patients requiring perioperative support after surgery or for those awaiting transplantation. Dobutamine is usually preferred in patients with low-output HF. Dobutamine improves CO, decreases PCWP, and decreases total SVR with little effect on HR or systemic arterial pressure when compared with dopamine.[269] (See Chapter 17, Shock, for further information on dopamine and dobutamine.)

PHOSPHODIESTERASE INHIBITORS: MILRINONE

Although β-agonists, such as dobutamine, have been traditionally used in patients with ADHF, the PDE inhibitor milrinone is an alternative to the catecholamines and vasodilators for the short-term parenteral treatment of severe congestive failure. This agent

selectively inhibits PDE III, the cyclic adenosine monophosphate (cAMP)-specific cardiac PDE. Enzyme inhibition results in increased cAMP levels in myocardial cells and enhances contractility. The activity is not blocked by β-blockers. PDE inhibitors are also vasodilators. It has been suggested that at low doses they act more as unloading agents rather than as inotropic agents; others refute this viewpoint. Their overall hemodynamic effect probably results from a combination of positive inotropic action plus preload and afterload reduction.

Milrinone is structurally and pharmacologically similar to inamrinone, which is no longer used.[270–272] Besides inhibiting PDE, it also may increase calcium availability to myocardial muscle. It has both inotropic and vasodilating properties. HR increase and myocardial consumption may be less with milrinone than with dobutamine.[273,274] The half-life of milrinone is 1.5 to 2.5 hours, with renal clearance accounting for ~80% to 90% of total body elimination and is prolonged in patients with renal dysfunction. Although a loading dose of 50 μg/kg is in the product labeling, it is rarely given because of resulting hypotension. Maintenance infusions are typically between 0.2 and 0.75 μg/kg/minute. The infusion is adjusted according to hemodynamic and clinical responses and should be decreased in patients with renal insufficiency. The primary concern with milrinone is ventricular arrhythmias, reported in up to 12% of patients. Supraventricular arrhythmias, hypotension, headache, and chest pain also have been reported. Thrombocytopenia is rare.

The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial assessed the in-hospital management of 951 patients with acute HF exacerbation (mean LVEF 23%) but not in cardiogenic shock.[273,274] In addition to standard diuretic and ACEI therapy, subjects were randomly assigned to receive either milrinone or placebo. The initial milrinone infusion rate was 0.5 μg/kg/minute with no loading dose. The primary end point was total numbers of days hospitalized for CV causes from the time of the start of study drug infusion to day 60. No difference was found between milrinone and placebo with mortality

at 60 days (10.3% with milrinone and 8.9% with placebo).[273] Follow-up analysis categorized subjects as ischemic versus nonischemic.[274] Within the cohort of patients with ischemia, patients treated with milrinone tended to have worse outcomes than did those treated with placebo. In contrast, patients who were nonischemic had a trend toward better outcomes with milrinone than with placebo. From these data, it can be concluded that the benefits of milrinone in patients with acute exacerbations of HF are minimal and more likely to be seen in patients with a nonischemic etiology of HF. Worse outcomes may be seen in patients with ischemic HF. However, short-term infusions of milrinone were not associated with excess mortality.

Few trials have compared dobutamine to milrinone in ADHF. One small retrospective analysis evaluated 329 patients admitted for ADHF (EF of <20%) who either received IV dobutamine or milrinone.[275] Hemodynamic response, need for additional therapies, adverse effects, length of stay, and drug cost were evaluated. Patients were similar in clinical presentation, but the milrinone group had higher mean pulmonary arterial pressure. A greater percentage of patients received dobutamine (81.7%) versus milrinone (18.3%). Only 19% of patients were taking β-blockers before admission. Clinical outcomes were similar and there was no significant difference in the in-hospital mortality rate, adverse effects, ventilator use, or length of stay. More patients in the dobutamine group required nitroprusside to achieve optimal hemodynamic response. The study concluded that both drugs have comparable efficacy.

Other factors to consider when deciding which inotropic agent should be used in ADHF are renal function, BP, and concomitant β-blocker use. Milrinone has a longer half-life than dobutamine and accumulates in cases of renal dysfunction. Milrinone is also a vasodilator, which can limit its use in patients with hypotension. The concomitant use of β-blockers may antagonize the action of dobutamine.

B.J. has responded poorly to IV furosemide, his renal function has deteriorated, and his SBP is low. Patients with advanced HF and systemic hypoperfusion often will not tolerate vasodilator therapy. Inotropic agents may be necessary to maintain circulatory function in

these patients. According to guidelines, IV inotropic drugs may be considered for patients who have symptomatic hypotension despite adequate filling pressure, who are unresponsive to diuretics and intolerant to vasodilators, or who have worsening renal function. PDE inhibitors are sometimes preferred over dobutamine for patients who are receiving concomitant β-blockers. For the abovementioned reasons, B.J. is a candidate for milrinone therapy. Patients should be on telemetry because milrinone has the potential to cause arrhythmias. Vital signs, SCr, symptom relief, and urine output should be monitored. Once the patient's hemodynamic profile improves, milrinone should be discontinued, and oral furosemide therapy can be resumed. At discharge, the outpatient HF medications should be optimized.

Outpatient Inotropic Infusions

Case 14-6, Question 2: Are there any indications for using repeated intermittent infusions of inotropic agents as part of a home care regimen?

The long-term safety and efficacy of inotropic therapy is regarded with skepticism. There are few studies assessing intermittent (eg, weekly) infusions of dobutamine or milrinone. Nearly all the data on this therapeutic approach are from open-label and uncontrolled trials that compare two inotropic agents without a placebo.[276–280] It is thought that long-term therapy may be cardiotoxic. The only placebo-controlled trial of intermittent infusion of dobutamine was terminated because of excess mortality with dobutamine.[277] Death occurred in 32% of patients treated with dobutamine versus 14% with placebo. Whether this was caused by progression of underlying heart disease, continued drug therapy, or was a cardiotoxic effect remains unknown. No corresponding data exist for milrinone, although a placebo-controlled trial with milrinone failed to support the routine use of IV milrinone as an adjunct to standard therapy in the treatment of patients hospitalized for an acute exacerbation of chronic HF.[273,274] For this reason, the ACA/AHA guidelines indicate

that intermittent infusions of dobutamine and milrinone in the long-term treatment of HF, even in advanced stages, should be avoided.[4] Chronic continuous infusions of dobutamine and milrinone are sometimes administered in patients with refractory HF as palliative therapy or in those awaiting transplant. The lowest dose possible should be administered. The HFSA identifies the limited treatment options in advanced HF and proposes patient-centered outcomes (survival vs quality of life, palliative, and hospice care) to be incorporated into care plans.[281]

Ventricular Arrhythmias Complicating Heart Failure

AMIODARONE

Case 14-6, Question 3: B.J. was stabilized during the next several days and discharged home with furosemide 40 mg daily, enalapril 5 mg twice daily, metoprolol succinate 100 mg daily, aspirin 81 mg daily, and NTG 0.4 mg sublingual to be used as needed for chest pain. His EF is 23%. Laboratory values were normal. ECG monitoring during B.J.'s hospital stay showed normal sinus rhythm, with 15 to 20 asymptomatic PVCs/hour. At that time, it was decided not to treat his arrhythmia other than with metoprolol because he was asymptomatic. For the next several months, he continued to have frequent PVCs during follow-up examinations.

It has now been 5 months and he is still having up to 12 to 15 PVCs/hour. His exercise capacity is limited by SOB after walking about a block despite having enalapril increased to 20 mg/day, metoprolol succinate to 200 mg/day, and adding digoxin 0.25 mg/day. The furosemide is at 40 mg/day because he has edema. A repeat echocardiogram shows an EF of 20%. Is an antiarrhythmic agent indicated for B.J. at this time? What is the agent of choice, and what dose should be given?

PVCs and other arrhythmias are a common complication of LV dysfunction and may be present regardless of whether the patient has had an MI. Approximately 50% to 70% of patients with HF have episodes of nonsustained ventricular tachycardia on ambulatory monitoring. This myocardial irritability may be a result of autonomic hyperactivity or ventricular remodeling. It is not clear whether these

rhythm disturbances contribute to sudden death or simply reflect the underlying disease process. Recent studies suggest that bradyarrhythmia or electromechanical dissociation may be associated with sudden death in patients with HF having nonischemic cardiomyopathy.[282,283] More importantly, suppression of ventricular ectopy in patients with HF has not been shown to lead to a reduction in sudden death in clinical trials. Neither prophylactic antiarrhythmic therapy nor treatment of asymptomatic PVC after an MI has been proved to improve outcome or survival. Because of concerns about the proarrhythmic effects of most class IA and class IC drugs, treatment with these agents is contraindicated.

Amiodarone has value in patients with HF with arrhythmias because it has antiarrhythmic and coronary vasodilating effects as well as α- and β-blocking properties. It may offer a dual benefit to reduce myocardial irritability and improve the hemodynamics of HF.

In the Grupo de Estudio de la Sobrevida en la Insuficiecia Cardiaca en Argentina (GESICA) study,[284] 516 patients with class II to IV HF symptoms (average EF 20%), and frequent PVCs were randomly assigned to receive either standard treatment (diuretics, vasodilators, digoxin) or a fixed dose of amiodarone plus standard treatment. The dose of amiodarone was 600 mg daily for 2 weeks, then 300 mg/day for at least 1 year. Fewer patients on amiodarone (33.5%) died compared with those receiving standard treatment (41.4%), a statistically significant difference. Similarly, the number of HF-related hospitalizations was reduced with amiodarone.

Somewhat different outcomes were noted in the VA Cooperative Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) study.[285,286] Entry criteria to this trial were similar to those in the GESICA study, with a primary indicator being >10 asymptomatic PVCs per hour on 24-hour monitoring, but without sustained ventricular tachycardia. A higher dose of amiodarone was used, 800 mg for 2 weeks, then 400 mg/day for 1 year. The dose was reduced to 300 mg/day after the first year, with the average follow-up being 45 months. No difference was found between groups for either all-cause mortality or SCD. EF improved more in the patients treated with amiodarone, rising from a baseline average of

24.9% to 33.7%. The corresponding change in the standard treatment group was from a baseline of 25.8% to 29.2% at follow-up. Despite the increase in EF, symptom scores did not differ between the two groups.

Amiodarone does not have a negative effect on mortality as seen with some of the other antiarrhythmic agents. Other factors to consider are the potential for significant side effects with amiodarone (see Chapter 15, Cardiac Arrhythmias) and the drug interaction with digoxin leading to the potential for digoxin toxicity.

The ACC/AHA guidelines do not recommend routine ambulatory ECG monitoring to detect asymptomatic ventricular arrhythmias and recommend against treatment if such arrhythmias are inadvertently detected.[2,11,45] If symptomatic ventricular arrhythmias should arise or there is determined to be a high risk of sudden death, one of the following should be considered: a β-blocking drug, amiodarone, or an ICD. Nearly all patients with HF should have a β-blocker as part of their regimen because these drugs reduce all-cause mortality, not just sudden death. B.J. continued to have ectopy despite continued use of a β-blocker. Nonetheless, it is decided not to use amiodarone because he is asymptomatic.

Case 14-6, Question 4: The medical resident on your team wants to switch B.J. to ARNI. What is the appropriate time to initiate or switch to sacubitril/valsartan in acute heart failure?

ADHF is associated with high rates of mortality, occurring early after discharge and 30-day rehospitalizations. β-Blockers, ACEIs, or ARBs at the time of hospital discharge for ADHF are not only associated with significant reductions in mortality and hospital readmission but also shown to improve adherence of GDMT if initiated postdischarge. The initiation of sacubitril/valsartan in the ambulatory setting has clearly shown mortality benefits; however, evidence continues to evolve in the ADHF setting. Two clinical trials[287,288] were designed to determine whether it is feasible to safely start ARNI in patients decompensated after hemodynamic

stabilization. In addition, these studies also report initiation and uptitration of sacubitril/valsartan in ACEI/ARB-naive patients, which has also been not well studied.

The safety and efficacy of initiating sacubitril/valsartan in hospitalized patients with acute decompensated HFrEF was evaluated in the com*P*ar*I*son *O*f sacubitril-valsarta*N* versus *E*nalapril on *E*ffect on NT-p*R*oBNP in patients stabilized from an acute *H*eart *F*ailure episode (PIONEER-HF) trial.[287] This was a prospective, multicenter, double-blind, randomized, controlled trial that included patients with LVEF ≤40% within the past 6 months, NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL (screening), stabilized in hospital without symptomatic hypotension (SBP >100 mm Hg) and no increased need for IV diuretics, vasodilators in the prior 6 hours, or inotropes in the prior 24 hours. Patients were either randomized to enalapril (starting at 2.5 or 5 mg, eventually ramped up to 10 mg by mouth [PO] twice daily) or sacubitril/valsartan (starting at 24/26 twice daily and uptitrated to 97/103 twice daily) with dosing determined by SBP.

Unlike the PARADIGM-HF trial, PIONEER-HF[287] included patient populations that were underrepresented: new HF (34.4%), ACEI and ARB naive (52.1%), and a higher proportion of Black (35.9%). The primary end point of time-averaged reduction in the NT-proBNP was significantly greater in the sacubitril/valsartan group than that in the enalapril group (ratio of change 0.71; 95% CI 0.63–0.81; $P < .001$) with the effect evident at 1 week. Sacubitril/valsartan advantages over enalapril were consistent throughout all predefined subgroups, including those with or without prior HF and with a history or no history of prior ACEIs or ARBs. Rates of worsening renal function, hyperkalemia, and symptomatic hypotension and angioedema did not differ between the two groups.

In the subsequent secondary analysis[289] of the PIONEER-HF trial, which was an additional 4-week follow-up in an open-label extension (weeks 8–12), during which all patients were switched to receiving S/V from enalapril at week 8. There was a further 37% reduction in NT-proBNP levels in those who were switched to S/V. Although not powered, an early in-hospital initiation of ARNI resulted in a 31% risk

reduction (RR) in incidence of HF rehospitalization or CV death compared with those who were started on enalapril in the hospital and switched to ARNI 8 weeks post hospitalization (HR, 0.69; 95% CI 0.4–0.97).

Findings from the PIONEER-HF study complement those from the comparison of pre- and postdischarge Initiation of sacubitril/valsartan in hemodynamically stabilized heart failure patients in hospital or early after discharge (TRANSITION). The TRANSITION-HF assessed the tolerability and optimal timing for the initiation of sacubitril/valsartan after stabilization of patients with ADHF either ≥12 hours predischarge or at any point postdischarge (up to 14 days). This trial demonstrated that in ADHF, sacubitril/valsartan was tolerated and maintained at the twice-daily dosage of either 100 or 200 mg in 62.5% and 68.0% of patients pre- and postdischarge, respectively (P = .07). There were no differences in the safety profiles throughout the 10-week postdischarge period. Hypotension was observed in about 12% of the predischarge initiation group and 9% of those starting the drug after discharge, but hypotension did not lead to permanent discontinuation of the therapy. Interestingly, in the trial, 24% of participants had no prior exposure to an ACEI or ARB.

The data from the PIONEER-HF and TRANSITION studies demonstrate that sacubitril/valsartan treatment can be initiated safely before discharge or soon after discharge. Secondary analysis of PIONEER-HF also demonstrates that in-hospital initiation of sacubitril/valsartan leads to an early improvement in postdischarge outcomes. The clinical benefit of sacubitril/valsartan now extends to de novo patients with HF and patients who are ACEI/ARB naive. The 2021 American College of Cardiology Expert Consensus Decision Pathway for Optimization of Heart Failure[45] Treatment makes an allowance for considering such de novo sacubitril/valsartan in "… well-informed patients who, within a framework of shared-decision making, accept the uncertainty about effectiveness and safety as well as potentially greater out-of-pocket costs."

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

CASE 14-6, QUESTION 5: Is B.J. a candidate for an ICD implantation?

Although amiodarone is the preferred antiarrhythmic agent in patients with HF with reduced EF to prevent recurrent AF and symptomatic ventricular arrhythmias, it has not improved survival. Ventricular arrhythmias are associated with a high frequency of SCD in patients with HF. Numerous trials have established the role of ICDs in primary and secondary prevention of SCD. The earliest of the primary prevention trials was the Multicenter Automatic Defibrillator Implantation Trial (MADIT).[290] This study was terminated early because of the survival benefit seen in the ICD group compared with conventional therapy. There was no evidence that amiodarone, β-blockers, or any other antiarrhythmic therapy had a significant influence on the results. Unlike MADIT, the MADIT II[291] study enrolled patients with no documented arrhythmias but with previous MI and LVEF <30%. Patients received either an ICD or a conventional medical therapy. The primary end point was death from any cause. There was a 31% relative reduction in the risk of death and an absolute reduction of 6% in the ICD group. This was the first trial to show mortality benefits of ICDs in patients with no documented history of abnormal heart rhythms.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) evaluated the efficacy of amiodarone in patients with LV dysfunction (EF ≤35%).[292] The patients (NYHA classes II–III) were receiving conventional therapy and randomly assigned to placebo, amiodarone, or an ICD. Amiodarone was no better than placebo, whereas ICD decreased mortality by 23% (P = .007). A subgroup analysis showed that patients with class II HF had a greater drop in mortality with ICD use than did class III patients, whereas amiodarone decreased survival in class III. The role of amiodarone in patients with NYHA class III needs to be further evaluated before it is routinely used in patients with LV dysfunction.

The ACC/AHA guidelines[1] recommend the use of ICDs in patients after MI with reduced LVEF and who have a history of ventricular arrhythmias. ICDs are also recommended for primary prevention in patients with nonischemic cardiomyopathy and ischemic heart disease who have an LVEF of ≤30%, those with NYHA functional class II or III symptoms while on optimal standard oral therapy, and patients who have reasonable expected survival with a good functional status of ≥1 years. Patients with ischemic heart disease should receive an ICD at least 40 days after MI. B.J. is currently on an optimal HF drug regimen, and his EF is 20%. According to guidelines, B.J. would benefit from ICD implantation.

CARDIAC RESYNCHRONIZATION THERAPY

CASE 14-7

QUESTION 1: C.M., a 49-year-old female with a history of cardiomyopathy (EF 25%), presents to the HF clinic with NYHA class III symptoms. She reports increased SOB, chest pain, and fatigue. She has been optimized on drug therapy for 3 months. Her medications include metoprolol succinate 200 mg daily, furosemide 40 mg bid, lisinopril 20 mg daily, and spironolactone 25 mg daily. An ECG showed sinus rhythm at a rate of 72 bpm and a QRS duration of 144 ms.

Is she a candidate for CRT?

Approximately one-third of the patients with advanced systolic HF exhibit intraventricular or interventricular conduction delays that cause the ventricles to beat asynchronously.[293] Ventricular desynchrony is seen on ECG as a wide QRS complex with an LBBB and can lead to deleterious effects on cardiac function. Patients may present with reduced EF, decreased CO, and presence of NYHA class III or IV HF symptoms. These are all associated with increased mortality.

CRT is the use of cardiac pacing to coordinate the contraction of the left and right ventricles.[76] Initial randomized trials of CRT show reduced HF symptoms and improved exercise tolerance and quality of life. The Comparison of Medical Therapy, Pacing, and Defibrillator

in Heart Failure (COMPANION) trial[77] enrolled 1520 patients with NYHA class II or IV (QRS interval of at least 120 ms, and LVEF ≤35%) who were treated with optimal drug therapy (ACEIs, diuretics, β-blockers, and spironolactone). Patients were randomly assigned to receive optimal drug therapy alone, optimal drug therapy and CRT with a pacemaker, or optimal drug therapy and CRT-D. The primary end point was a composite of all-cause mortality and hospitalization. Both the CRT and CRT-D groups were associated with a decreased risk of primary end point compared with optimal drug therapy alone. All-cause mortality at 1 year was decreased by 24% in the CRT group (which did not reach statistical significance) and 43% in the CRT-D group.

The results of the *CA*rdiac *RE*synchronization in *H*eart *F*ailure (CARE-HF)[76] study extended the findings of the COMPANION trial. CARE-HF demonstrated a significant all-cause mortality reduction for CRT pacing without defibrillator backup (CRT) in patients with HF who received similar medical treatment. The inclusion criteria were NYHA class III or IV, EF of ≤35%, and QRS duration of ≥120 ms. The primary end point of all-cause deaths and hospitalizations for a CV reason occurred in fewer patients with CRT compared with the optimal drug therapy (39% vs 55%; $P < .001$). Death or hospitalization for worsening HF was also significantly reduced with CRT.

The combined results of CARE-HF and COMPANION confirm the importance of CRT and CRT-D in improving ventricular function, HF symptoms, and exercise tolerance, while also reducing frequency of HF hospitalizations and death.[294] The role of CRT in patients with mild HF symptoms, narrow QRS, chronic AF, and right bundle branch block needs to be explored.

According to the ACC/AHA guidelines,[2] patients with NYHA class III and ambulatory patients with class IV HF should receive CRT (unless contraindicated) if they meet the following criteria: LVEF of ≤35%, presence of a wide QRS (>120 ms) and receiving optimal HF standard medical therapy. Despite optimal doses of HF medications, C.M. continues to have HF symptoms. CRT could provide incremental benefits beyond what is provided with drug therapy.

Case 14-7, Question 2: If C.M. presented with NYHA class I or II symptoms, would she be a candidate for CRT therapy? What is the evidence to support CRT in NYHA classes I and II patients?

As mentioned in Case 14-6, Question 1, the CARE-HF and COMPANION trials provide strong evidence that CRT induces reverse modeling in patients with symptomatic NYHA class III and ambulatory class IV HF. The next logical step was to evaluate the benefits of CRT therapy in patients with HF with milder symptoms. The Multicenter InSynch ICD Randomized Clinical Evaluation (MIRACLE-ICDII)[295] trial randomized patients with classes II through IV HF but with separate specified end points for class II patients. In this trial, 186 patients with NYHA class II HF, an LVEF of <35%, and a QRS of >130 ms received a CRT-ICD device. Subjects were randomly assigned to active CRT group (ICD activated and CRT on) or control group (ICD activated and CRT off). The primary end point was progression of HF, defined as all-cause mortality, hospitalizations for HF, and ventricular tachycardia or ventricular fibrillation requiring device intervention. A 15% reduction in HF progression was observed with active CRT but did not reach statistical significance. At 6 months, patients with active CRT had improved exercise tolerance, but this was not significantly different from that seen in the control group. However, there was a significant decrease in ventricular end-systolic volume and increased LVEF after 6 months of therapy. Even though the study results did not translate into improved exercise tolerance, it helped set the stage for future trials in patients with less symptomatic HF.

The **RE**synchronization re**VE**rses **R**emodeling in **S**ystolic left v**E**ntricular dysfunction (REVERSE) trial[74] enrolled 610 participants with NYHA class I or II HF, LVEF <40%, and with a QRS duration of >120 ms who received a CRT device (with or without ICD) in combination with optimal drug therapy. The patients in the active CRT group had significant improvement in LV end-systolic volume index, LV end-diastolic volume index, and LVEF compared to those in the control group. The primary clinical end point (the percentage of

patients with worsened clinical composite score) did not reach statistical significance at 12 months in patients enrolled in the United States; but in the European cohort,[296] a significant difference was seen at 24 months, primarily driven by the time to first hospitalization. The aggregate data from these two clinical trials provided overwhelming evidence that linked CRT with substantial reverse remodeling in patients with mild HF.

The MADIT-CRT[75] was the largest randomized trial designed to determine whether CRT-D therapy would reduce the primary end point (all-cause mortality or HF events) when compared with patients receiving ICD-only therapy. The study population involved patients with cardiac issues in NYHA functional class I or II with LVEF of ≤30% and QRS duration of >130 ms. There was a 34% ($P < .001$) reduction in the primary end point, and a 44% ($P < .001$) reduction in HF events when compared with ICD therapy. Patients with CRT-D therapy showed an 11% improvement in LVEF after 1 year, compared with a 3% improvement for patients on ICD alone. Both MADIT-CRT and REVERSE excluded patients with AF. Both studies failed to show a benefit for CRT in patients with QRS duration <150 ms.

The *R*esynchronization/defibrillation for *A*mbulatory heart *F*ailure *T*rial (RAFT)[297] confirmed that CRT benefited patients with a QRS duration of ≥150 ms and in those with LBBB. The RAFT investigators randomly assigned 1798 patients with NYHA class II or III HF, LVEF of ≤30%, and a QRS duration of at least 120 ms (or a paced QRS of at least 200 ms) to either ICD therapy alone or a CRT-D. The primary outcome was a combination of total mortality and HF hospitalization, which was significantly higher in the ICD group compared with the ICD-CRT group (40% vs 33%, respectively). These findings demonstrate that earlier intervention with CRT-D, in addition to guideline-recommended medical and ICD therapy, benefits this patient population.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

CASE 14-8

QUESTION 1: D.F., a 72-year-old White female, has a 5-year history of HF symptoms, including decreased exercise capacity, SOB, and distended neck veins. She has minimal peripheral edema. History is suggestive of rheumatic fever as a child, but she does not recall having any cardiac symptoms when she was younger, other than being told she had a murmur. Her symptoms are controlled with diuretics. She has HTN but no other medical problems, and all laboratory test findings are normal. Her BP is 155/85 mm Hg, and HR is 90 bpm. Cardiac examination reveals a prominent S_4 heart sound. Echocardiography reveals an EF of 50%. Prior treatment included furosemide, most recently at 40 mg bid. The physician is considering adding a β-blocker or CCB to control the BP and HR.

Why might this consideration be appropriate?

This case exemplifies a patient with HFpEF, previously referred to as diastolic HF. Risk factors for HFpEF include advanced age, female sex, HTN, and CAD. This diagnosis can be made on the basis of LVH, clinical evidence of HF, a normal EF, and echocardiography findings. The ideal treatment for HFpEF has not been extensively validated. A review of trials evaluating specific drug therapy in HFpEF is listed in **Table 14-14**. No drug selectively enhances myocardial relaxation without having associated effects on LV contractility or on the peripheral vasculature.[10,298]

Table 14-14
Clinical Trials of Pharmacotherapy in Heart Failure With Preserved Ejection Fraction

Study	Patient Population	Therapy Intervention	Outcome	Treatment Duration	Results
Aronow and Kronzon[331]	NYHA III; Prior MI, EF >50%; (*N* = 21)	Enalapril vs placebo	NYHA class, treadmill exercise time (seconds)	3 months	Enalapril: NYHA class from 3 ± 0 to 2.4 ± 0.5 (*P* = .005), exercise time from 224 ± 27 to 270 ± 44 (*P* < .001) vs no difference in placebo
Lang et al[332]	HF symptoms >3 months; EF >50%; (*N* = 12)	Lisinopril vs placebo crossover	Dyspnea and fatigue	5 weeks for each treatment arm	No significant differences
Cleland et al[300] PEP-CHF	Diastolic dysfunction; CV admission within 6 months; EF >40%; (*N* = 850)	Perindopril vs placebo	Primary: composite of all-cause mortality or hospitalization for HF	Mean 26.2 months	Primary: 23.6% in perindopril group vs 25.1% in placebo (HR 0.92 [0.70–1.21], *P* = .545)
Zi et al[333]	NYHA class II or III; EF ≥40%; (*N* = 74)	Quinapril vs placebo	6-minute walk test, QoL, NYHA class	6 months	No significant differences
Yusuf et al[155] CHARM-Preserved	NYHA II–IV; hospitalization for CV causes; EF >40%; (*N* = 3023)	Candesartan vs placebo	Primary: CV death or hospital admission for HF	Median 36.6 months	Primary: 22% in the candesartan group vs 24% in the placebo group (adjusted HR 0.86 [0.74–1.00], *P* = .051)
Massie et al[302] I-PRESERVE	NYHA II–IV; hospitalized for HF in last 6 months; EF ≥45%; (*N* = 4122)	Irbesartan vs placebo	Primary: all-cause death or hospitalization for CV causes	Mean 49.5 months	Primary: 36% in the irbesartan group vs 37% in the placebo group (HR 0.95 [95% CI 0.86–1.05], *P* = .35)
Yip et al[334]	NYHA II–IV; history of HF in last 2 months; EF >45%; (*N* = 151)	Ramipril vs irbesartan	QoL, 6-minute walk test, HF hospital admission	12 months	No significant differences
Warner et al[335]	Diastolic dysfunction; DOE; EF >50%; SBP >150, <200 mm Hg (*N* = 20)	Losartan vs placebo crossover	Exercise time, QoL	2 weeks for each treatment arm	Increase in exercise time (11.3 minutes at baseline, improved to 12.3 ± 2.6 minutes with losartan vs 11.0 minutes with placebo, *P* < .05) and improvement in QoL (25 at baseline, improved to 18 with losartan vs 22 with placebo); *P* < .05 for both end points
Parthasarathy et al[336]	Diastolic dysfunction; DOE; EF >40%; (*N* = 152)	Valsartan vs placebo	Primary: exercise time	14 weeks	No significant differences
Takeda et al[337]	NYHA II–III and stage C heart failure; EF ≥45%	Carvedilol vs placebo	Plasma BNP, NYHA class, exercise capacity	12 months	NYHA class improved by 0.77 (carvedilol) vs 0.25 (placebo) (*P* < .02), exercise capacity in METs improved 0.69 (carvedilol) vs worsened by 0.07 (placebo) (*P* = .01).
Flather et al[303] SENIORS	HF hospital admission in last year; EF ≤35%; subgroup EF ≥35%	Nebivolol vs placebo	Primary: composite of all-cause mortality or hospitalization for a cardiovascular cause	Mean 21 months	EF >35%, primary event rate 17.6% in nebivolol and 21.9% in placebo (HR 0.86 [95% CI 0.74–0.99], *P* = .039)
Aronow et al[338]	NYHA II–III; prior Q-wave MI; EF >40%; (*N* = 158)	Propranolol vs placebo	All-cause mortality, all-cause mortality plus nonfatal MI	32 months	All-cause mortality (56% propranolol group vs 76% placebo group, *P* = .007) and all-cause mortality plus nonfatal MI (59% propranolol vs 82% placebo, *P* = .002)
Setaro et al[339]	Abnormal diastolic filling; EF >45%; (*N* = 20)	Verapamil vs placebo	Exercise capacity	2 weeks for each crossover	Exercise capacity (10.7 minutes at baseline, improved to 13.9 minutes with verapamil vs 12.3 minutes with placebo, *P* < .05)
Ahmed et al[340] DIG	NYHA I–IV; EF >45%; (*N* = 988)	Digoxin vs placebo	Primary: composite of HF hospitalization or mortality	Mean 37 months	102 (21%) in the digoxin group vs 119 (24%) in the placebo group (HR 0.82 [0.63–1.07], *P* = .136)
Pitt et al[304] TOPCAT	Symptomatic HF; EF >45%; (*N* = 3445)	Spironolactone vs placebo	Primary: composite of CV death, HF hospitalization, or aborted cardiac arrest	Mean 39 months	320 (18.6%) in the spironolactone group vs 351 (20.4%) in the placebo group (HR 0.89 [0.77–1.04], *P* = .14)
Solomon et al. PARAGON-HF[47]	HF (NYHA classes II–IV); EF >45%; (*N* = 4822)	Sacubitril-valsartan vs valsartan	Primary: composite of total HF hospitalization and CV death	Median 35 months	894 (12.8 per 100 patient-years) in the sacubitril-valsartan group vs 1009 (14.6 per 100 patient-years) in the valsartan group (HR 0.87 [0.75–1.01])
Anker et al[48] EMPEROR-Preserved	HF (NYHA classes II–IV); EF >40%; (*N* = 5988)	Empagliflozin vs placebo	Primary: composite of HF hospitalization and CV death	Median 26.2 months	415 (13.8%) in the empagliflozin group vs 511 (17.1%) in the placebo group (HR 0.79 [0.69–0.90])

BNP, B-type natriuretic peptide; CV, cardiovascular; DOE, dyspnea on exertion; EF, ejection fraction; HF, heart failure; HR, hazard ratio; METs, metabolic equivalents; MI, myocardial infarction; NA, not available; NYHA, New York Heart Association; QoL; quality of life; SBP, systolic blood pressure.

Factors affecting HF control, such as adherence to medication and diet, including NSAID and herbal remedy use, should be appropriately managed along with drug therapy. Symptomatic HFpEF is initially treated similar to other forms of HF, by slow diuresis. Diuresis decreases preload and lessens passive congestion

of the ventricles. Excessive lowering of ventricular filling pressures, however, can decrease CO and cause hypotension.

The most common cause of HFpEF is HTN that leads to LVH and decreased cardiac compliance.[299] The ACC/AHA/HFSA guidelines recommend an SBP goal of <130 mm Hg in patients with HFpEF and persistent HTN after management of fluid overload. Drugs that cause regression of LVH (eg, ACEIs, ARBs, β-blockers) may also slow or reverse structural abnormalities associated with HFpEF.

In the *P*erindopril in *E*lderly *P*atients with *C*hronic *H*eart *F*ailure (PEP-CHF) trial,[300] the ACEI perindopril failed to reduce the incidence of the primary end point (all-cause mortality or HF hospitalizations) but did reduce symptoms and improved functional capacity. The CHARM-Preserved trial[155] also failed to show any difference in CV mortality, but fewer hospitalizations were seen in the candesartan group (see Case 14-1, Question 13).

The *VAL*sartan *I*n *D*iastolic *D*ysfunction (VALIDD)[301] trial compared the effects of valsartan or placebo added to standard antihypertensive therapy (which included diuretics, β-blockers, CCBs, or α-blockers) in patients with mild HTN and diastolic dysfunction. The hypothesis of this trial was that RAAS inhibition with an ARB would be associated with greater improvement in diastolic function because of more regression of LVH or myocardial fibrosis. Patients with a history of stage 1 or 2 essential HTN were randomly assigned to receive either valsartan 160 mg, titrated up to 320 mg, or matching placebo. Patients who did not achieve a target BP goal of <135/80 mm Hg received additional therapy starting with a diuretic followed by a CCB or a β-blocker, and then an α-blocker. ARBs, ACEIs, and aldosterone blockers were excluded. The primary end point was the change in diastolic myocardial relaxation velocity from baseline to 9 months with a secondary end point of change in LV mass. During the study, the placebo group received more concomitant antihypertensive therapy compared with the valsartan group. A small, but significant, increase was seen in diastolic relaxation velocity in both groups from baseline to follow-up, but there was no significant difference between the treatment groups. BP reduction did not differ significantly between the two treatment

groups and was associated with significant improvement in diastolic function. The authors concluded that aggressive BP control—even in mild HTN—was associated with improvement in diastolic dysfunction, irrespective of whether BP reduction was achieved with a RAAS inhibitor or another antihypertensive agent.

CHARM-Preserved[155] investigated the role of candesartan in patients with HFpEF. The trial enrolled 3023 subjects who met the overall CHARM trial inclusion criteria with an EF of >40% (mean, 54%). Subjects had symptomatic HF with normal (preserved) EF. They received either an ARB alone (*N* = 1514) or placebo; only 20% of subjects in both groups were taking an ACEI at randomization, 56% a β-blocker, and 11% spironolactone.[155] After a median follow-up of 36.6 months, a trend was noted toward reduction in the primary outcome of CV death or hospital admission for HF in the candesartan group (22%) compared with placebo (24.3%; *P* = .118). CV deaths and all-cause mortality were nearly identical in both groups, but the total number of hospitalizations for HF was significantly reduced in the candesartan group. The most common side effects with candesartan were hypotension (2.4%), increase in creatinine (4.8%), and hyperkalemia (1.5%). Discontinuation because of an adverse event occurred in 17.8% of those treated with candesartan compared with 13.5% of placebo recipients (*P* = .001) (see **Table 14-14**). Overall, in symptomatic patients with HFpEF, no significant improvement in mortality occurred with candesartan compared with placebo, but there was a significant reduction in HF-related hospitalizations.

Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) evaluated irbesartan titrated to 300 mg daily or placebo for the management of HFpEF.[302] The patient population was age 60 years or older with NYHA classes II through IV symptoms, EF of at least 45%, and hospitalized for HF within 6 months prior, or have persistent class III or IV symptoms (*N* = 4128). There was no difference in the primary end point (death from any cause or hospitalization for a CV cause) between irbesartan (36%) and placebo (37%). The irbesartan group had more patients experiencing hyperkalemia than had those on placebo. One possible reason for

the neutral results of I-PRESERVE included the high rate of dual RAAS blockade at baseline (39% ACEI use in the irbesartan group and 40% in the placebo group; 28% spironolactone use in the irbesartan group and 29% in the placebo group). Based on this high use, the study is less likely to find benefit with ARBs in addition to other RAAS agents. Another potential limitation of the study included the high study discontinuation rate (34%). Overall, irbesartan showed no benefit in reducing morbidity or mortality in patients with HFpEF.

β-Blockers or non-dihydropyridine CCBs are other classes of drugs of interest in HFpEF. Part of their value is to control HTN, a risk factor for all forms of HF. More specific to HFpEF, β-blockers and CCBs (especially verapamil) possess negative inotropic properties that may favorably influence the pathophysiology of diastolic dysfunction by (a) slowing the HR to allow more time for complete ventricular filling, particularly during exercise; (b) reducing myocardial oxygen demand; and (c) controlling BP. Both pharmacologic classes are beneficial in decreasing ischemia in patients with CAD.

Most HF trials with β-blockers demonstrating decreased morbidity and mortality have focused on HFrEF. The *S*tudy of the *E*ffects of *N*ebivolol *I*ntervention on *O*utcomes and *R*ehospitalization in *S*eniors with heart failure (SENIORS) study[303] evaluated β-blocker use in elderly patients with HF irrespective of LV function. The trial randomly assigned patients to nebivolol or placebo. Nebivolol is a selective β_1-adrenergic receptor blocker with vasodilator properties that are mediated through NO release. This effect may be beneficial in elderly patients who tend to have low reserves of endothelial vasodilation.

The primary end point of the study was the combination of all-cause mortality and CV hospital admissions. The end point was significantly reduced by 14% in the nebivolol group, regardless of the EF. Prospective subgroup analyses of the primary outcome by LVEF (≤35% or >35%), sex, or age (75 years or younger, or older than 75 years) showed benefits across all subgroups. Patients with EF

>35%, however, appeared to benefit a little more than did those with low EF%, and all-cause mortality was lower in patients older than 75 years treated with nebivolol compared with placebo. The study reinforces the current recommendations that all patients with HF with reduced EF should receive β-blockers. Only 35% of the patients had preserved LV function and were mostly males. This is not typical of patients with HFpEF, who are frequently females. Further studies are required to define the role of β-blockers in HFpEF.

No randomized controlled trials have demonstrated mortality benefits with CCBs in HFpEF. Non-dihydropyridine CCBs can be used in patients who have a contraindication to β-blockers to control BP and HR. Non-dihydropyridine CCBs should not be used in patients with HFrEF.

The role of AAs in the management of patients with HFpEF has been evaluated in the *T*reatment *O*f *P*reserved *C*ardiac function heart failure with an *A*ldosterone an*T*agonist (TOPCAT) trial.[304] This trial evaluated the impact of spironolactone versus placebo on CV morbidity and mortality in patients older than 50 years of age with an EF >45%. There was no difference in the primary end point (composite of CV death, aborted cardiac arrest, and hospitalization for HF) between the spironolactone and placebo treatment arms with an HR of 0.89 (95% CI 0.77–1.04; *P* = .14). There was a significant reduction with spironolactone versus placebo in the secondary end point of hospitalization for HF (HR 0.83 [95% CI 0.69–0.99; *P* = .04]). There has also been a subanalysis of the TOPCAT study evaluating differences in patients enrolled in the Americas compared to Russia/Georgia relative to the primary and secondary end points. When looking only at patients enrolled from North or South America, there was a significant reduction in the patients treated with spironolactone compared to those on placebo in the primary end point (HR 0.82 [95% CI 0.69–0.98]) and all secondary end points.[305] Based on these findings, the 2017 ACC/AHA/HFSA Focused Update recommend aldosterone receptor antagonists (class IIb) in HFrEF. An aldosterone receptor antagonist can be considered to decrease hospitalizations in patients with EF ≥ 45%, an elevated BNP, or recent hospitalizations. If spironolactone is initiated, then potassium

and renal function should be closely monitored (eGFR >30 mL/minute, creatinine, 2.5 mg/dL, potassium <5.0 mEq/L).[45]

The role of angiotensin–neprilysin inhibitors in the management of patients with HFpEF has been evaluated in the PARAGON-HF trial.[47] This trial evaluated the impact of sacubitril-valsartan versus valsartan along with HF hospitalizations and CV mortality in patients with NYHA classes II to IV HF and an EF of ≥45%. Patients needed to have elevated levels of NPs and have structural heart disease to be enrolled. Patients were enrolled for a median of 35 months. There were 894 primary outcomes in the sacubitril/valsartan group and 1009 primary outcomes in the valsartan arm, demonstrating a nonsignificant difference between groups (RR 0.75 [95% CI 0.75–1.10]). The two components of the primary outcome were also not statistically significant when evaluated individually. The findings of this trial demonstrate there was no difference in outcomes between sacubitril/valsartan and valsartan in the overall patient population with HFpEF; but based on the subgroup of patients[63] with an EF below normal, yet not reaching the definition of HFrEF, the FDA approved sacubitril-valsartan for use in the population with HFpEF.

The role of SGLT2 inhibitors in the management of patients with HFpEF has been evaluated in the *EMP*agliflozin outcom*E* t*R*ial in patients with chr*O*nic hea*R*t failure with *P*reserved ejection fraction (EMPEROR-Preserved) trial.[48] This trial evaluated the impact of empagliflozin versus placebo on HF hospitalizations and CV mortality in patients with NYHA classes II to IV HF and an EF of ≥40%. Patients needed to have an elevated NT-proBNP of >300 pg/mL, or if having AF, it needed to be >900 pg/mL. Patients were enrolled for a median of 26.2 months. There were 415 primary outcomes in the empagliflozin group and 511 primary outcomes in the placebo arm, demonstrating a significant difference between groups (HR 0.79 [95% CI 0.69–0.90]). The positive findings in the primary outcome were driven by the lower risk of HF hospitalizations (HR 0.71 [95% CI 0.60–0.83]). The findings of this trial demonstrate a lowering of the composite of morbidity and mortality compared to placebo in patients with HFpEF. Based on these findings, the FDA

has given empagliflozin a breakthrough designation as an investigational treatment for adults with HFpEF.

Both nitrates and PDE type 5 inhibitors have not demonstrated benefit in patients with HFpEF and thus are not recommended for use in the ACC/AHA guidelines. The lack of benefit seen with isosorbide mononitrate was demonstrated in the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) trial.[306] This trial included patients older than age 50 years with NYHA classes II to III HF and an EF of 50% or higher. The isosorbide mononitrate 120 mg group versus placebo demonstrated a nonsignificant lower daily activity level (−381 accelerometer units; 95% CI −780–17; p = .06) and a significant decrease in hours of activity per day (−0.3 hours; 95% CI −0.55 to −0.05; P = .02). Sildenafil was evaluated in the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial.[307] This trial included patients with NYHA classes II to III HF with an EF of ≥50% and a mean age of 69 years. The trial lasted for 24 weeks and demonstrated no significant difference between the groups in primary end point of peak oxygen consumption or the secondary end points of clinical status rank score and exercise tolerance. Based on these findings, it is not recommended to use nitrates or PDE 5 inhibitors for treating patients with HFpEF.

D.F. fulfills the criteria for having HFpEF, based on her history of long-standing HTN, which has been poorly controlled. Her BP is not at goal, and her HR is elevated. Therefore, antihypertensive therapy is warranted. Tachycardia alone can compromise the ventricle filling time and cause myocardial ischemia. So far, no data support the use of one agent over another for BP control in HFpEF. β-Blockers and non-dihydropyridine CCBs can each reduce BP and HR. β-Blockers are not considered first-line antihypertensive medications based on recent guidelines without a compelling indication. The use of a non-dihydropyridine CCB would be supported in patients with HFpEF to reduce both BP and HR. D.F. can be started on a non-dihydropyridine CCB such as diltiazem sustained release (120 mg daily).

Herbal Products and Nutritional Supplements

CASE 14-9

QUESTION 1: W.L., a 60-year-old male recently diagnosed by his naturopath with HF, is concerned about his decreasing exercise capacity and increasing SOB during his morning walks. The naturopath wants to initiate hawthorn and coenzyme Q10 to control his HF symptoms. The patient has uncontrolled HTN (170/85 mm Hg) and has 2+ ankle edema. He distrusts medical doctors because in the past he was given HCTZ for BP reduction but stopped taking it after a few days because he did not tolerate the urinary urgency it caused.

What is the role of herbal products and nutritional supplements in HF?

HAWTHORN

Hawthorn extracts from the leaves and flowers of *Crataegus monogyna* and *C. oxyacantha* have been reported to have beneficial effects in mild HF.[308,309] Oligomeric procyanidins and flavonoids are considered the key active ingredients. Hawthorn extracts have shown positive inotropic effects, weak ACE inhibition, vasodilating properties, and increased coronary blood flow in vitro and in animal models. In short-term (≤8 weeks), placebo-controlled trials in patients with the equivalent of NYHA class II HF, modest improvements were noted in exercise tolerance and subjective symptoms as well as decreases in HR and BP. Patients with more advanced HF were excluded. A systematic review by Pittler et al also concluded that hawthorn extract was efficacious in the treatment of HF when given with standard HF therapy.[310] Conversely, the results of the Hawthorne Extract Randomized Blinded Chronic Heart Failure (HERB-CHF) trial failed to provide any evidence that hawthorn was beneficial in patients with HF who were already receiving standard medical therapy.[311] In clinical trials, side effects of hawthorn include nausea, vomiting, diarrhea, palpitations, chest pain, and vertigo. These side effects are more common when doses exceed 900 mg/day, but, in some trials, they have not occurred more often than with placebo. The risks and benefits of using hawthorn and digoxin

together, both of which have positive inotropic effects, are not known.

To further investigate the longer term benefits of hawthorn, additive effects to conventional therapy and effect on mortality were tested in the Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in Congestive Heart Failure (SPICE) trial.[312] The trial enrolled 2681 patients with NYHA class II or III, LVEF of ≤35%, who were randomly assigned to hawthorn or placebo for 2 years. Although the study failed to show any clear benefits in the treatment of chronic HF, hawthorn was well tolerated.

COENZYME Q

Coenzyme Q, also known as ubiquinone and ubidecarenone, is an endogenously synthesized provitamin that is structurally similar to vitamin E, serves as a lipid-soluble electron transport carrier in mitochondria, and aids in the synthesis of adenosine triphosphate.[313,314] It may also have membrane-stabilizing properties, may enhance the antioxidant effects of vitamin E, and stabilize calcium-dependent slow channels. In animal models, it has positive inotropic effects, although weaker than those of digoxin. More than 18 open-label and double-blind, randomized clinical trials have been conducted of coenzyme Q in patients with HF ranging from NYHA classes II to IV.[313] Doses varied from 50 to 200 mg/day. Patients in many of these trials were also taking diuretics, ACEIs, and digoxin. Different trials used different end point measurements. Positive effects on subjective symptoms, NYHA class improvement, EF, quality of life, and hospitalization rates have all been observed. Two trials, however, failed to demonstrate significant changes in EF, vascular resistance, or exercise tolerance. None of the trials had sufficiently large sample sizes or adequate duration of assessment to detect reduction in mortality. Side effects were minimal, but included nausea, epigastric pain, diarrhea, heartburn, and appetite suppression. Mild increases in lactate dehydrogenase and hepatic enzymes have been rarely reported with coenzyme Q doses in excess of 300 mg/day.

Because no clinical trials have demonstrated improved survival with nutritional/herbal supplements, the current guidelines do not recommend these agents in patients with current or prior symptoms of HFrEF.

W.L. has poorly controlled systolic HTN and HF that is beginning to interfere with his activities of daily life. Although evidence indicates that patients with NYHA class II HF obtain symptomatic improvement with hawthorn and coenzyme Q, this does not address W.L.'s HTN. Conflicting data exist on the value of coenzyme Q in lowering BP.[313] The results of the SPICE trial did not demonstrate any mortality benefits, and no incremental benefits were seen when combined with standard therapy. Uncontrolled HTN in patients with HF leads to cardiac remodeling and worsening HF. Currently, W.L. is presenting with symptomatic HF; therefore, he should be started on a diuretic to alleviate his symptoms. Starting with a 20-mg dose of furosemide and titrating slowly may be one approach. For all of the reasons cited throughout this chapter, one must also argue strongly for starting an ACEI to control his HTN. He should be counseled that the urinary frequency he experienced previously should diminish after a few days. Once he is euvolemic, a β-blocker should be started.

The guidelines clearly state that natural products should not be used to treat symptomatic HF. Agents such as ephedra (which contain catecholamines), ephedrine metabolites, or imported Chinese herbs are contraindicated in HF because of increased risk of mortality and morbidity. No regulatory oversight, quality control, or regulations exist on the use of natural supplements. Because of the widespread use of nutritional supplements and herbal therapies and their potential to cause drug interactions, clinicians should routinely inquire about their use.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references

and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Adamczak DM, Oduah MT, Kiebalo T, et al. Heart failure with preserved ejection fraction-a concise review. *Curr Cardiol Rep*. 2020;22(*9*):82. doi:10.1007/s11886-020-01349-3 (299)

Arrigo M, Jessup M, Mullens W, et al. Acute heart failure. *Nat Rev Dis Primers.* 2020;6(1):16. doi:10.1038/s41572-020-0151-7 (261)

Bozkurt B, Coats AJ, Tsutsui H, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure [published online ahead of print, 2021 Mar 1]. J Card Fail. 2021;S1071-9164(21)00050-6. doi:10.1016/j.cardfail.2021.01.022. (4)

Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. *J Am Coll Cardiol.* 2018;72(*4*):351–366. (44)

McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(*11*):993–1004. (62)

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(*21*):1995–2008. (85)

Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383(*15*):1413–1424. (86)

Rosano GMC, Spoletini I, Agewall S. Pharmacology of new treatments for hyperkalaemia: patiromer and sodium zirconium cyclosilicate. *Eur Heart J Suppl.* 2019;21(suppl A):A28–A33. (209)

Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med.* 2019;381(*17*):1609–1620. (47)

Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639. doi:10.1161/CIR.0000000000001052 (5)

Writing Committee; Maddox TM, Januzzi JL Jr, et al. 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;77(6):772–810. (45)

Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *Circulation*.

2017;136:e137–e161. (11)

COMPLETE REFERENCES CHAPTER 14 HEART FAILURE

1. Heart Failure Society of America, Lindenfeld J, Albert NM, et al. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail*. 2010;16(6):e1–e194.
2. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):e263-e421. doi:10.1016/j.jacc.2021.12.012
3. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726.
4. Bozkurt B, Coats AJ, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure [published online ahead of print, 2021 Mar 1]. J Card Fail. 2021;S1071-9164(21)00050-6. doi:10.1016/j.cardfail.2021.01.022
5. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics —2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639. doi:10.1161/CIR.0000000000001052
6. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev*. 2011;8(1):30–41.
7. Giamouzis G, Kalogeropoulos A, Georgiopoulou V, et al. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. *J Card Fail*. 2011;17(1):54–75.
8. Pass S, Dusing M. Current and emerging therapy for primary pulmonary hypertension. *Ann Pharmacother*. 2002;36(9):1414–1423.
9. Chatterjee K, De Marco T, Alpert JS. Pulmonary hypertension: hemodynamic diagnosis and management. *Arch Intern Med*. 2002;162(17):1925–1933.
10. Zile M. Heart failure with preserved ejection fraction: is this diastolic heart failure? *J Am Coll Cardiol*. 2003;41(9):1519–1522.
11. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *Circulation*. 2017;136:e137–e161.

12. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18(8):891–975.
13. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol*. 1993;22(4, suppl A):6A–13A.
14. Schreier R, Abraham W. Hormones and hemodynamics in heart failure. *N Engl J Med*. 1999;341(8):577–585.
15. Hash TW, Prisant M. Beta-blocker use in systolic heart failure and dilated cardiomyopathy. *J Clin Pharmacol*. 1997;37(1):7–19.
16. Patterson JH, Rogers JE. Expanding role of b-blockade in the management of chronic heart failure. *Pharmacotherapy*. 2003;23(4):451–459.
17. Foody JM, Farrell MH, Krumholz HM. Beta-blocker therapy in heart failure: scientific review. *JAMA*. 2002;287(7):883–889.
18. Munger MA, Cheang KI. Beta-blocker therapy: a standard of care for heart failure. *Pharmacotherapy*. 2000;20(11, Pt 2):359S–367S.
19. Goldstein S. Benefits of beta-blocker therapy for heart failure: weighing the evidence. *Arch Intern Med*. 2002;162(6):641–648.
20. Bristow MR. Mechanistic and clinical rationales for using beta-blockers in heart failure. *J Card Fail*. 2000;6(2, suppl 1):8–14.
21. Leineweber K, Heusch G. Beta 1- and beta 2-adrenoceptor polymorphisms and cardiovascular diseases. *Br J Pharmacol*. 2009;158(1):61–69.
22. Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. *N Engl J Med*. 2002;347(15):1135–1142.
23. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med*. 2001;345(23):1689–1697.
24. Ergul A. Endothelin-1 and endothelin receptor antagonists as potential cardiovascular therapeutic agents. *Pharmacotherapy*. 2002;22(1):54–65.
25. Nguyen B, Johnson J. The role of endothelin in heart failure and hypertension. *Pharmacotherapy*. 1998;18(1):706–719.
26. Chen HH, Burnett JC Jr. C-type natriuretic peptide: the endothelial component of the natriuretic peptide system. *J Cardiovasc Pharmacol*. 1998;32(suppl 3):S22–S28.
27. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of the B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347(3):161–167.
28. Lee CR, Adams KF Jr, Patterson JH. Surrogate endpoints in heart failure. *Ann Pharmacother*. 2002;36(3):479–488.
29. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma amino terminal

brain natriuretic peptide (N-BNP) concentrations. *Lancet*. 2000;355(9210):1126–1130.
30. Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. *Rev Cardiovasc Med*. 2002;3(suppl 4):S10–S17.
31. Vichiendilokkul A, Tran A, Racine E. Nesiritide: a novel approach for acute heart failure. *Ann Pharmacother*. 2003;37(2):247–258.
32. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated heart failure. *N Engl J Med*. 2000;343(4):246–253.
33. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan a vasopressin antagonist, in patient hospitalized with worsening heart failure. *JAMA*. 2004;291(16):1963–1971.
34. Gheorghiade M, Konstam MA, Burnett JC Jr, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist in patients hospitalized for heart failure. The EVEREST Clinical Trials. *JAMA*. 2007;297(12):1332–1343.
35. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patient hospitalized with worsening heart failure. *JAMA*. 2007;297(12):1319–1331.
36. Earl GL, Fitzpatrick JT. Levosimendan: a novel inotropic agent for treatment of acute decompensated heart failure. *Ann Pharmacother*. 2005;39(11):1888–1896.
37. Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low output heart failure (the LIDO study): a randomized double-blind trial. *Lancet*. 2002;360(9328):196–202.
38. Moiseyev VS, Põder P, Andrejevs N, et al. Safety and efficacy of novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. *Eur Heart J*. 2002;23(18):1422–1432.
39. Packer M. REVIVE II: Multicenter placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure. Program and abstracts from the American Heart Association Scientific Sessions. Late Breaking Clinical Trials II, Dallas, TX, November 13–16, 2005. *Circulation.* 2005;112:3363.
40. Mebazaa A, Nieminen MS, Packer M, et al. The SURVIVE Randomized Trial: levosimendan vs dobutamine for patients with acute decompensated heart failure. *JAMA*. 2007;297(17):1883–1891.
41. O'Connell JB, Bristow M. The economic burden of heart failure. *Clin Cardiol*. 2000;23(suppl III):III6–III10.
42. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines in the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the

Evaluation and Management of Heart Failure). *Circulation*. 2001;104(24):2996–3007.

43. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet*. 2019;393(10166):61–73.
44. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. *J Am Coll Cardiol*. 2018;72(4):351–366.
45. Writing Committee; Maddox TM, Januzzi JL Jr, et al. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77(6):772–810.
46. Teerlink JR, Diaz R, Felker GM, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N. Engl. J*. Med. 2021;384:105-116. doi:10.1056/NEJMoa2025797
47. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):1609–1620.
48. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451–1461.
49. Flynn KE, Piña IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301(14):1451–1459.
50. Son YJ, Lee Y, Song EK. Adherence to a sodium-restricted diet is associated with lower symptom burden and longer cardiac event-free survival in patients with heart failure. *J Clin Nurs*. 2011;20(21/22):3029–3038.
51. Arcand J, Ivanov J, Sasson A, et al. A high-sodium diet is associated with acute decompensated heart failure in ambulatory heart failure patients: a prospective follow-up study. *Am J Clin Nutr*. 2011;93(2):332–333.
52. DiNicolantonio JJ, Di Pasquale P, Taylor RS, Hackam DG. Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis. *Heart (Br Card Soc)*. 2013;99(11):820. doi:10.1136/heartjnl-2012-302337
53. Aliti GB, Rabelo ER, Clausell N, Rohde LE, Biolo A, Beck-da-Silva L. Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. *JAMA Intern Med*. 2013;173(12):1058–1064.
54. Bentley B, De Jong MJ, Moser DK, Peden AR. Factors related to nonadherence to low sodium diet recommendations in heart failure patients. *Eur J Cardiovasc Nurs*. 2005;4(4):331–336.
55. Neily JB, Toto KH, Gardner EB, et al. Potential contributing factors to noncompliance with dietary sodium restriction in patients with heart failure.

Am Heart J. 2002;143(1):29–33.
56. Brater DC. Pharmacology of diuretics. *Am J Med Sci*. 2000;319(1):38–50.
57. Krämer BK, Schweda F, Riegger GA. Diuretic treatment and diuretic resistance in heart failure. *Am J Med*. 1999;106(1):90–96.
58. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709–717.
59. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11–21.
60. Rodgers J, Patterson JH. The role of the renin-angiotensin-aldosterone system in the management of heart failure. *Pharmacotherapy*. 2002;20(11, Pt 2):368S–378S.
61. Patterson JH. Angiotensin II receptor blockers in heart failure. *Pharmacotherapy*. 2003;23(2):173–182.
62. McMurray JJ, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004.
63. Gronda E, Vanoli E, Lacoviello M. The PARAGON-HF trial: the sacubitril/valsartan in heart failure with preserved ejection fraction. *Eur Heart J Suppl*. 2020;22(suppl L):L77–L81.
64. Gullestad L, Wikstrand J, Deedwania P, et al. What resting heart rate should one aim for when treating patients with heart failure with a beta-blocker? Experiences from the Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). *J Am Coll Cardiol*. 2005;45(2):252–259.
65. Lechat P, Hulot JS, Escolano S, et al. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. *Circulation*. 2001;103(10):1428–1433.
66. Castagno D, Skali H, Takeuchi M, et al. Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program. *J Am Coll Cardiol*. 2012;59(20):1785–1795.
67. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol*. 2008;101(6):865–869.
68. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875–885.
69. van Veldhuisen DJ, de Graeff PA, Remme WJ, Lie KI. Value of digoxin in heart failure and sinus rhythm: new features of an old drug. *J Am Coll Cardiol*. 1996;28(4):813–819.

70. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med*. 1986;314(24):1547–1552.
71. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351(20):2049–2057.
72. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med*. 1996;335(15):1107–1114.
73. Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplemental vasodilator therapy in patients with chronic heart failure treated with enalapril. V-HeFT III. *Circulation*. 1997;96(3):856–863.
74. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52(23):1834–1843.
75. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361(14):1329–1338.
76. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352(15):1539–1549.
77. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350(21):2140–2150.
78. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345(20):1435–1443.
79. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med*. 2007;357(9):885–896.
80. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361(23):2241–2251.
81. Aaronson K, Mark S, Erik M. Evaluation of the HeartWare® HVAD left ventricular assist device system for the treatment of advanced heart failure: results of the ADVANCE bridge to transplant trial. American Heart Association 2010 Scientific Sessions. Late-Breaking Clinical Trials I; November 14, 2010; Chicago, IL. *Clin Res Cardiol*. 2011;100:2.
82. Mehra MR, Naka Y, Uriel N, et al. A fully magnetically levitated left ventricular assist device. *N Engl J Med.* 2017;376:440–450.
83. Gheorghiade M, Marti CN, Sabbah HN, et al. Soluble guanylate cyclase: a potential therapeutic target for heart failure. *Heart Fail Rev*. 2013;18(2):123–

134.
84. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382(20):1883–1893.
85. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008.
86. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413–1424.
87. Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation*. 2008;117(19):2544–2565.
88. de Couto G, Ouzounian M, Liu PP. Early detection of myocardial dysfunction and heart failure. *Nat Rev*. 2010;7(6):334–344.
89. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics —2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–e209.
90. Huerta C, Varas-Lorenzo C, Castellsague J, García Rodríguez LA. Non-steroidal anti-inflammatory drugs and risk of first hospitalization admissions for heart failure in the general population. *Heart (Br Card Soc)*. 2006;92(11):1610–1615.
91. Crouch MA, LimonL, Cassano AT. Clinical relevance and management of drug-related QT interval prolongation. Pharmacotherapy. 2003;23:881.
92. Page J, Henry D. Consumption of NSAIDS and the development of congestive heart failure in elderly patients: an under-recognized public health problem. *Arch Intern Med*. 2000;160(6):777–784.
93. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. *Ann Intern Med*. 1996;125(1):47–58.
94. Singal P, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med*. 1998;339:900–905.
95. Page RL, Gozansky WS, Ruscin JM. Possible heart failure exacerbation associated with rosiglitazone: case report and literature review. *Pharmacotherapy*. 2003;23(7):945–954.
96. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317–1326.
97. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119(14):e391–e479.

98. Risler T, Schwab A, Kramer B, Braun N, Erley C. Comparative pharmacokinetics and pharmacodynamics of loop diuretics in renal failure. *Cardiology*. 1994;84(suppl 2):155–161.
99. Murray MD, Deer MM, Ferguson JA, et al. Torsemide more effective that furosemide for treatment of heart failure. *Am J Med*. 2001;111(7):513–520.
100. Cutler R, Blair A. Clinical pharmacokinetics of furosemide. *Clin Pharmacokinet*. 1979;4(4):279–296.
101. Greither A, Goldman S, Edelen JS, Benet LZ, Cohn K. Pharmacokinetics of furosemide in patients with congestive heart failure. *Pharmacology*. 1979;19(3):121–131.
102. Straughn AB, Wood GC, Raghow G, Meyer MC. Bioavailability of seven furosemide tablets in man. *Biopharm Drug Dispos*. 1986;7(2):113–120.
103. McNamara PJ, Foster TS, Digenis GA, et al. Influence of tablet dissolution on furosemide bioavailability: a bioequivalence study. *Pharm Res*. 1987;4(2):150–153.
104. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther*. 1995;57(6):601–609.
105. Rudy DW, Voelker JR, Greene PK, Esparza FA, Brater DC. Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med*. 1991;115(5):360–366.
106. Van Meyel JJ, Smits P, Dormans T, Gerlag PG, Russel FG, Gribnau FW. Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance. *J Intern Med*. 1994;235:329–334.
107. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. *J Card Fail*. 2010;16(3):188–193.
108. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797–805.
109. Haley H, Ploth DW. Dyshomeostasis of serum sodium concentration in congestive heart failure. *Am J Med Sci*. 2010;340(1):42–47.
110. Steiness E, Olesen KH. Cardiac arrhythmias induced by hypokalemia and potassium loss during maintenance digoxin therapy. *Br Heart J*. 1976;38(2):167–172.
111. Holland OB, Nixon JV, Kuhnert L. Diuretic-induced ventricular ectopic activity. *Am J Med*. 1981;770(4):762–768.
112. Hollifield JW, Slaton PE. Thiazide diuretics, hypokalemia and cardiac arrhythmias. *Acta Med Scand Suppl*. 1981;647:67–73.

113. Tsuji H, Venditti FJ Jr, Evans JC, Larson MG, Levy D. The association of levels of serum potassium and magnesium with ventricular premature complexes (the Framingham Heart Study). *Am J Cardiol*. 1994;74(3):237–235.
114. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice. *Arch Intern Med*. 2000;160(16):2429–2436.
115. Hollifield JW. Potassium and magnesium abnormalities: diuretics and arrhythmias in hypertension. *Am J Med*. 1984;77(5A):28–32.
116. Anker SD, Doehner W, Rauchhaus M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. *Circulation*. 2003;107(15):1991–1997.
117. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart Failure. *Can Med Assoc J*. 2006;175(6):611–617.
118. Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol*. 2007;49(16):1733–1739.
119. Lainchbury JG, Troughton RW, Frampton CM, et al. NTproBNP-guided drug treatment for chronic heart failure: design and methods in the "BATTLESCARRED" trial. *Eur J Heart Fail*. 2006;8(5):532–538.
120. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA*. 2009;301(4):383–392.
121. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2017;318(8):713–720. doi:10.1001/jama.2017.10565
122. Kosman ME. Management of potassium problems during long-term diuretic therapy. *JAMA*. 1974;230(5):743–748.
123. Davidson C, McLachlan MS, Burkinshaw L, Morgan DB. Effect of long-term diuretic treatment on body potassium in heart disease. *Lancet*. 1976;2(2):1044–1047.
124. Schwartz AB, Swartz CD. Dosage of potassium chloride elixir to correct thiazide-induced hypokalemia. *JAMA*. 1974;230(5):702–704.
125. Lahav M, Regev A, Ra'anani P, Theodor E. Intermittent administration of furosemide vs continuous infusion preceded by a loading dose for congestive heart failure. *Chest*. 1992;102(3):725–731.
126. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high-dose furosemide in severe heart failure: bolus injections versus continuous infusion. *J Am Coll Cardiol*. 1996;28:376–382.
127. Kramer WG, Smith WB, Ferguson J, et al. Pharmacodynamics of torsemide administered as an intravenous injection and as a continuous infusion to patients with congestive heart failure. *J Clin Pharmacol*. 1996;36(3):265–270.

128. Sica D, Gehr TW. Diuretic combinations in refractory edema states. *Clin Pharmacokinet*. 1996;30:229–249.
129. Howard P, Dunn M. Aggressive diuresis is safe and cost effective for severe heart failure in the elderly. *Chest*. 2001;119(3):807–810.
130. Rosenberg J, Gustafsson F, Galatius S, Hildebrandt PR. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. *Cardiovasc Drugs Ther*. 2005;19(4):301–306.
131. Wollert KC, Drexler H. The kallikreins-kinin system in post myocardial infarction cardiac remodeling. *Am J Cardiol*. 1997;80(3A):158A–161A.
132. White CM. Angiotensin-converting-enzyme inhibition in heart failure or after myocardial infarction. *Am J Health Syst Pharm*. 2000;57(suppl 1):S18–S25.
133. Garg R, Yusuf S. Overview of randomized trials on angiotensin-converting enzyme inhibition on mortality and morbidity in patients with heart failure. *JAMA*. 1995;273(18):1450–1456.
134. The SOLVD Investigators; Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293–302.
135. Zannad F, Chati Z, Guest M, Plat F. Differential effects of fosinopril and enalapril in patients with mild to moderate chronic heart failure. Fosinopril in Heart Failure Study Investigators. *Am Heart J*. 1998;136(4, Pt 1):672–680.
136. van Veldhuisen DJ, Brouwer J, Man in ‘t Veld AJ, Dunselman PH, Boomsma F, Lie KI. Progression of mild untreated heart failure during 6 months follow-up and clinical and neurohumoral effects of ibopamine and digoxin as monotherapy. *Am J Cardiol*. 1995;75(12):796–800.
137. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316(23):1429–1435.
138. Kjekshus J, Swedberg K, Snapinn S. Effects of enalapril on long-term mortality in severe congestive heart failure. *Am J Cardiol*. 1992;69(1):103–107.
139. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325(5):303–310.
140. Hobbs RE. Results of the ATLAS study. High or low doses of ACE inhibitors for heart failure? *Cleve Clin J Med*. 1998;65(10):539–542.
141. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100(23):2312–2318.
142. The NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *Eur Heart J*. 1998;19(3):481–489.

143. Martineau P, Goulet J. New competition in the realm of renin-angiotensin axis inhibition: the angiotensin II receptor antagonists in congestive heart failure. *Ann Pharmacother*. 2001;35(1):71–84.
144. Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2002;39(3):463–470.
145. Riegger GA, Bouzo H, Petr P, et al. Improvement in exercise tolerance and symptoms of congestive heart during treatment with candesartan cilexetil. *Circulation*. 1999;100(22):2224–2230.
146. Havranek EP, Thomas I, Smith WB, et al. Dose-related beneficial long-term hemodynamic and clinical efficacy of irbesartan in heart failure. *J Am Coll Cardiol*. 1999;33(5):1174–1181.
147. Dickstein K, Chang P, Willenheimer R, et al. Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate to severe heart failure. *J Am Coll Cardiol*. 1995;26(2):438–445.
148. Pitt B, Segal R, Martinez FA, et al. Randomized trial of losartan versus captopril in patients over 65 with heart failure. *Lancet*. 1997;349(9054):747–752.
149. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355(9215):1582–1587.
150. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation*. 1999;100(10):1056–1064.
151. Cohn J, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667–1675.
152. Solomon SD, Zelenkofske S, McMurray JJ, et al. The valsartan in acute myocardial infarction trial (VALIANT) investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med*. 2005;352(25):2581–2588.
153. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to ACEIs: the CHARM-Alternative trial. *Lancet*. 2003;362(9386):772–776.
154. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking ACEIs: the CHARM-Added trial. *Lancet*. 2003;362(9368):767–771.

155. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362(9386):777–781.
156. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. *Lancet*. 2003;362(9386):759–766.
157. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet*. 2009;374(9704):1840–1848.
158. Luque C, Ortiz M. Treatment of ACE inhibitor induced cough. *Pharmacotherapy*. 1999;19(7):804–810.
159. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1, suppl):169S–173S.
160. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin-converting enzyme inhibitors in Chinese. *Br J Clin Pharmacol*. 1995;40(2):141–144.
161. Schepkens H, Vanholder R, Billiouw JM, Lameire N. Life threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med*. 2001;110(6):438–441.
162. Wrenger E, Müller R, Moesenthin M, Welte T, Frölich JC, Neumann KH. Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. *BMJ*. 2003;327(7407):147–149.
163. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of randomized aldactone evaluation study. *N Engl J Med*. 2004;351(6):543–551.
164. Palmer BF. Managing hyperkalemia cause by inhibition of renin-angiotensin aldosterone system. *N Engl J Med*. 2004;35(6):585–592.
165. Shah KB, Rao K, Sawyer R, Gottlieb SS. The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. *J Am Coll Cardiol*. 2005;46(5):845–849.
166. Vleeming W, van Amsterdam JG, Stricker BH, de Wildt DJ. ACE inhibitor-induced angioedema. Incidence, prevention, and management. *Drug Saf*. 1998;18(3):171–188.
167. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased risk of angiotensin converting enzyme inhibitor associated angioedema. *Clin Pharmacol Ther*. 1996;60(1):8–13.
168. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin converting enzyme inhibitor associated angioedema. *JAMA*. 1997;278(3):832–833.
169. Gavras I, Gavras H. Are patients who develop angioedema with ACE inhibition at risk for the same problem with AT-1 receptor blockade? *Arch Intern Med*. 2003;163(2):240–241.

170. Abdi R, Dong VM, Lee CJ, Ntoso KA. Angiotensin II receptor blocker-associated angioedema. On the heels of ACE inhibitor angioedema. *Pharmacotherapy*. 2002;22(9):1173–1175.
171. Lo KS. Angioedema associated with candesartan. *Pharmacotherapy*. 2002;22(9):1176–1179.
172. van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. Angioneurotic edema attributed to the use of losartan. *Arch Intern Med*. 1998;158(18):2063–2065.
173. Frye C, Pettigrew T. Angioedema and photosensitive rash induced by valsartan. *Pharmacotherapy*. 1998;18(4):866–868.
174. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure: a Bayesian meta-analysis. *Ann Intern Med*. 2001;134(7):550–560.
175. Doughty RN, Rodgers A, Sharpe N, MacMahon S. Effects of beta-blocker therapy on mortality in patients with heart failure. A systematic overview of randomized controlled trials. *Eur Heart J*. 1997;18(4):560–565.
176. Avezum A, Tsuyuki RT, Pogue J, Yusuf S. Beta-blocker therapy for congestive heart failure. *Can J Cardiol*. 1998;14(8):1045–1053.
177. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure. *Circulation*. 1998;98(12):1184–1191.
178. Heidenreich PA, Lee TT, Massie BM. Effects of beta-blockade on mortality in patients with heart failure. *J Am Coll Cardiol*. 1997;30(1):27–34.
179. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M; IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol*. 2004;43(9):1534–1541.
180. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the task force for the diagnosis and treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26(11):1115–1140.
181. Gattis W. Metoprolol CR/XL in the treatment of chronic heart failure. *Pharmacotherapy*. 2001;21(5):604–613.
182. Tangeman H, Patterson JH. Extended-release metoprolol succinate in chronic heart failure. *Ann Pharmacother*. 2003;37(5):701–710.
183. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet*. 1993;342(8885):1441–1446.
184. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT HF). *Lancet*. 1999;353:2001–2007.
185. CIBIS Investigators and Committees. A randomized trial of b-blockade in heart failure: the cardiac insufficiency bisoprolol study. *Circulation*.

1994;90:1765–1773.
186. The Cardiac Insufficiency Bisoprolol Study II: a randomized trial. *Lancet*. 1999;353:9–13.
187. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long term beta-blockade in dilated cardiomyopathy: effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. *Circulation*. 1989;80(3):551–563.
188. Bleske BE, Gilbert EM, Munger MA. Carvedilol: therapeutic application and practice guidelines. *Pharmacotherapy*. 1998;18(4):729–737.
189. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334(21):1349–1355.
190. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation*. 1996;94(11):2807–2816.
191. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. *Circulation*. 1996;94(11):2793–2799.
192. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. *Circulation*. 1996;94(11):2800–2806.
193. Cohn JN, Fowler MB, Bristow MR, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *J Card Fail*. 1997;3(3):173–179.
194. Greiner B, Eichelbaum M, Fritz P, et al. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. *J Clin Invest*. 1999;104(2):147–153.
195. Meadowcroft AM, Williamson KM, Patterson JH, Pieper JA. Pharmacogenetics and heart failure: a convergence with carvedilol. *Pharmacotherapy*. 1997;17(4):637–639.
196. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol in clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET). *Lancet*. 2003;362(9377):7–13.
197. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation*. 2000;102(5):546–551.
198. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344(22):1651–1658.

199. Beta-Blocker Evaluation of Survival Trial Investigators; Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori PW. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659–1667.
200. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med*. 2009;150(11):784–794.
201. Fox K, Ford I, Steg PG, Tendera M, Ferrari R; BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9641):807–816.
202. Senni M, McMurray JJ, Wachter R, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail*. 2016;18(9):1193–1202.
203. Struthers AD. Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure? *Br J Clin Pharmacol*. 1999;47(5):479–482.
204. Jessup M. Aldosterone blockade and heart failure. *N Engl J Med*. 2003;348(14):1380–1382.
205. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372(3):211–221.
206. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J*. 2011;32(7):820–828.
207. Bakris GL, Pitt B, Weir MR, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial [published correction appears in *JAMA*. 2015 Aug 18;314(7):731. Dosage error in article text]. *JAMA*. 2015;314(2):151–161. doi:10.1001/jama.2015.7446
208. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial [published correction appears in *JAMA*. 2015 Feb 3;313(5):526. Dosage error in article text]. *JAMA*. 2014;312(21):2223–2233.
209. Rosano GMC, Spoletini I, Agewall S. Pharmacology of new treatments for hyperkalaemia: patiromer and sodium zirconium cyclosilicate. *Eur Heart J Suppl*. 2019;21(suppl A):A28–A33.
210. Lee DC, Johnson RA, Bingham JB, et al. Heart failure in outpatients. *N Engl J Med*. 1982;306(12):699–705.

211. Jaeschke R, Oxman AD, Guyatt GH. To what extent do congestive heart failure patients in normal sinus rhythm benefit from digoxin therapy? A systematic overview and meta-analysis. *Am J Med*. 1990;88(3):279–286.
212. Kulick D, Rahimtoola S. Current role of digitalis therapy in patients with congestive heart failure. *JAMA*. 1991;265(22):2995–2997.
213. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol*. 1993;22(4):955–962.
214. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. *N Engl J Med*. 1993;329(1):1–7.
215. The Digitalis Intervention Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336(8):525–533.
216. Adams KF Jr, Patterson JH, Gattis WA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. *J Am Coll Cardiol*. 2005;46(3):497–504.
217. Domanski M, Fleg J, Bristow M, Knox S. The effect of gender on outcome in digitalis-treated heart failure patients. *J Card Fail*. 2005;11(2):83–86.
218. Reuning R, Geraets DR, Rocci ML. Digoxin. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. 3rd ed. Applied Therapeutics; 1992:1–48.
219. Bauer L. Digoxin. In: *Applied Clinical Pharmacokinetics*. McGraw Hill; 2001.
220. Matsuda M, Matsuda Y, Yamagishi T, et al. Effects of digoxin, propranolol and verapamil on exercise in patients with chronic isolated atrial fibrillation. *Cardiovasc Res*. 1991;25(6):453–457.
221. David D, Segni ED, Klein HO, Kaplinsky E. Inefficacy of digitalis in the control of heart rate in patients with chronic atrial fibrillation: beneficial effects of an added beta-adrenergic blocking agent. *Am J Cardiol*. 1979;44(7):1378–1382.
222. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol*. 1999;33(2):304–310.
223. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation*. 1998;98(23):2574–2579.
224. Pedersen OD, Bagger H, Keller N, Marchant B, Køber L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with

reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation*. 2001;104(3):292–296.
225. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358(25):2667–2677.
226. Deedwania PC, Lardizabal JA. Atrial fibrillation in heart failure: a comprehensive review. *Am J Med*. 2010;123(3):198–204.
227. Yu D. The contribution of P-glycoprotein to pharmacokinetic drug interactions. *J Clin Pharmacol*. 1999;39(12):1203–1211.
228. Hooymans P, Merkus F. Current status of cardiac glycoside drug interactions. *Clin Pharm*. 1985;4(4):404–413.
229. Rodin S, Johnson B. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet*. 1988;11(4):227–244.
230. Fromm MF, Kim RB, Stein CM, Wilkinson GR, Roden DM. Inhibition of P-glycoprotein-mediated drug transport: a unifying mechanism to explain the interaction between digoxin and quinidine. *Circulation*. 1999;99(4):552–557.
231. Boyd RA, Stern RH, Stewart BH, et al. Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. *J Clin Pharmacol*. 2000;40(1):91–98.
232. Verschraagen M, Koks CH, Schellens JH, Beijnen JH. P-glycoprotein system as a determinant of drug interactions. The case of digoxin-verapamil. *Pharmacol Res*. 1999;40(4):301–306.
233. Tanaka H, Matsumoto K, Ueno K, et al. Effect of clarithromycin on steady-state digoxin concentrations. *Ann Pharmacother*. 2003;37(2):178–181.
234. Wakasugi H, Yano I, Ito T, et al. Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. *Clin Pharmacol Ther*. 1998;64(1):123–128.
235. Johne A, Brockmöller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St. John's wort (Hypericum perforatum). *Clin Pharmacol Ther*. 1999;66(4):338–345.
236. Kelly R, Smith T. Recognition and management of digitalis toxicity. *Am J Cardiol*. 1992;69(18):108G–118G; disc 118G–119G.
237. Bernabei R, Perna GP, Carosella L, et al. Digoxin serum concentration measurements in patients with suspected digitalis arrhythmias. *J Cardiovasc Pharmacol*. 1980;2(3):319–329.
238. Reisdorff EJ, Clark MR, Walters BL. Acute digitalis poisoning: the role of intravenous magnesium sulfate. *J Emerg Med*. 1986;4(6):463–469.
239. Lely AH, van Enter C. Non-cardiac symptoms of digitalis intoxication. *Am Heart J*. 1972;83(2):149–152.
240. Butler VP Jr, Odel JG, Rath E, et al. Digitalis induced visual disturbances with therapeutic digitalis concentrations. *Ann Intern Med*. 1995;123(9):675–680.
241. Beller GA, Smith TW, Abelmann WH, Haber E, Hood WB Jr. Digitalis intoxication: a prospective clinical study with serum level correlations. *N Engl*

J Med. 1971;284(18):989–997.
242. Lee T, Smith T. Serum digoxin concentration and diagnosis of digitalis toxicity. *Clin Pharmacokinet*. 1983;8(4):279–285.
243. Park GD, Spector R, Goldberg MJ, Feldman RD. Digoxin toxicity in patients with high serum digoxin concentrations. *Am J Med Sci*. 1987;30(6):423–428.
244. Shapiro W. Correlative studies of serum digitalis levels and the arrhythmias of digitalis intoxication. *Am J Cardiol*. 1978;41(5):852–859.
245. Ordog GJ, Benaron S, Bhasin V, Wasserberger J, Balasubramanium S. Serum digoxin levels and mortality in 5100 patients. *Ann Emerg Med*. 1987;16(1):32–39.
246. Jelliffe RW. Factors to consider in planning digoxin therapy. *J Chron Dis*. 1971;24:407–416.
247. Antman EM, Wenger TL, Butler VP Jr, Haber E, Smith TW. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. *Circulation*. 1990;81(6):1744–1752.
248. Woolf AD, Wenger T, Smith TW, Lovejoy FH Jr. The use of digoxin-specific Fab fragments for severe digitalis intoxication in children. *N Engl J Med*. 1992;326(26):1739–1744.
249. Borron SW, Bismuth C, Muszynski J. Advances in the management of digoxin toxicity in the older patient. *Drugs Aging*. 1997;10(1):18–33.
250. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific FAB therapy in the management of digitalis toxicity. *Clin Pharmacokinet*. 1995;28(6):483–493.
251. Ujhelyi MR, Robert S, Cummings DM, et al. Influence of digoxin immune Fab therapy and renal dysfunction on the disposition of total and free digoxin. *Ann Intern Med*. 1993;119(4):273–277.
252. Hickey AR, Wenger TL, Carpenter VP, et al. Digoxin immune Fab in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol*. 1991;17(3):590–598.
253. Rector TS, Johnson G, Dunkman WB, et al. Evaluation by patients with heart failure of the effects of enalapril compared with hydralazine plus isosorbide dinitrate on quality of life. V-HeFT II. *Circulation*. 1993;87(suppl VI):V171–V177.
254. Mulrowe J, Crawford M. Clinical pharmacokinetics and therapeutic use of hydralazine in congestive heart failure. *Clin Pharmacokinet*. 1989;16(2):86–89.
255. Kalus J, Nappi J. Role of race in the pharmacotherapy of heart failure. *Ann Pharmacother*. 2002;36(3):471–478.
256. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the Vasodilator-Heart Failure Trials. *J Card Fail*. 1999;5(3):178–187.

257. Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Cardiol*. 2003;41(9):1529–1538.
258. Yancy CW, Fowler MB, Colucci WS, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med*. 2001;344(18):1358–1365.
259. Curtis LH, Greiner MA, Hammill BG, et al. Early and long-term outcomes of heart failure in elderly persons, 2001–2005. *Arch Intern Med*. 2008;168(22):2481–2488.
260. Adams KF Jr, Fonarow GC, Emerman CL, et al. ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209-216. doi: 10.1016/j.ahj.2004.08.005. PMID: 15846257.
261. Arrigo M, Jessup M, Mullens W, et al. Acute heart failure. *Nat Rev Dis Primers*. 2020;6(1):16. doi:10.1038/s41572-020-0151-7
262. Grady KL, Dracup K, Kennedy G, et al. Team management of patients with heart failure: a statement for healthcare professionals from the Cardiovascular Nursing Council of the American Heart Association. *Circulation*. 2000;102(19):2443–2456.
263. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. *Am Heart J*. 1998;135(6, Pt 2 Su):S293–S309.
264. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart. *JAMA*. 1989;261(6):884–888.
265. Bourge RC, Tallaj JA. Ultrafiltration: a new approach toward mechanical diuresis in heart failure. *J Am Coll Cardiol*. 2005;46(11):2052–2053.
266. Bart BA, Boyle A, Bank AJ, Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J Am Coll Cardiol*. 2005;46(11):2043–2046.
267. Costanzo MR, Saltzberg M, O'Sullivan J, Sobotka P. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. *J Am Coll Cardiol*. 2005;46(11):2047–2051.
268. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49(6):675–683.
269. Leier CV, Heban PT, Huss P, Bush CA, Lewis RP. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. *Circulation*. 1978;58(3, Pt 1):466–475.

270. Hillerman D, Forbes W. Role of milrinone in the management of congestive heart failure. Drug Intelligence and Clinical Pharmacy. *Ann Pharmacother*. 1989;23(5):357–362.
271. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin and their combination in the treatment of patients with chronic heart failure. *N Engl J Med*. 1989;320(11):677–683.
272. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med*. 1991;325(21):1468–1475.
273. Cuffe MS, Califf RM, Adams KF Jr, et al. Short term intravenous milrinone for acute exacerbations of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287(12):1541–1517.
274. Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure. Results from the OPTIME-CHF study. *J Am Coll Cardiol*. 2003;41(6):997–1003.
275. Yamani MH, Haji SA, Starling RC, et al. Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: hemodynamic efficacy, clinical outcome, and economic impact. *Am Heart J*. 2001;142:998–1002.
276. Cesario D, Clark J, Maisel A. Beneficial effects of intermittent home administration of the inotrope/vasodilator milrinone in patients with end-stage congestive heart failure: a preliminary study. *Am Heart J*. 1998;135(1):121–129.
277. Elis A, Bental T, Kimchi O, Ravid M, Lishner M. Intermittent dobutamine treatment in patients with chronic refractory heart failure: a randomized, double-blind, placebo-controlled study. *Clin Pharmacol Ther*. 1998;63(6):682–685.
278. Applefeld MM, Newman KA, Sutton FJ, et al. Outpatient dobutamine and dopamine infusions in the management of chronic heart failure: clinical experience in 21 patients. *Am Heart J*. 1987;114(3):589–595.
279. Marius-Nunez AL, Heaney L, Fernandez RN, et al. Intermittent inotropic therapy in an outpatient setting: a cost-effective therapeutic modality in patients with refractory heart failure. *Am Heart J*. 1996;132(4):805–808.
280. Leier C, Binkley PF. Parenteral inotropic support for advanced congestive heart failure. *Prog Cardiovasc Dis*. 1998;41(3):207–224.
281. Fang JC, Ewald GA, Allen LA, et al. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. *J Card Fail*. 2015;21(6):519–534.
282. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J*. 1989;117(1):151–159.
283. Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure.

Circulation. 1989;80(6):1675–1680.
284. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomized trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobreivida en la Insuficiencia Cardiaca en Argentina (GESICA). *Lancet*. 1994;344(8921):493–498.
285. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med*. 1995;333(2):77–82.
286. Massie BM, Fisher SG, Radford M, et al. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure. *Circulation*. 1996;93(12):2128–2134.
287. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure [published correction appears in *N Engl J Med*. 2019 Mar 14;380(11):1090]. *N Engl J Med*. 2019;380(6):539–548. *N Engl J Med*. 1992;327(10):669–677.
288. Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail*. 2019;21(8):998–1007.
289. DeVore AD, Braunwald E, Morrow DA, et al. Initiation of Angiotensin–Neprilysin inhibition after acute decompensated heart failure: secondary analysis of the open-label extension of the PIONEER-HF Trial. *JAMA Cardiol*. 2020;5(2):202–207. doi:10.1001/jamacardio.2019.4665
290. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med*. 1996;335(26):1933–1940.
291. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346(12):877–883.
292. Bardy GH, Lee KL, Mark DB, et al. Sudden Cardiac Death in Heart failure Trial (SCD-HeFT) investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352(3):225–237.
293. Jarcho JA. Resynchronizing ventricular contraction in heart failure. *N Engl J Med*. 2005;352(15):1594–1597.
294. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricle systolic dysfunction. *JAMA*. 2007;297(22):2502–2514.
295. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol*. 2003;42(8):1454–1459.

296. Daubert C, Gold MR, Abraham WT, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol*. 2009;54(20):1837–1846.
297. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363(25):2385–2395.
298. Yamamoto K, Wilson DJ, Canzanello VJ, Redfield MM. Left ventricular diastolic dysfunction in patients with hypertension and preserved systolic dysfunction. *Mayo Clin Proc*. 2000;75(2):148–155.
299. Adamczak DM, Oduah MT, Kiebalo T, et al. Heart failure with preserved ejection fraction-a concise review. *Curr Cardiol Rep*. 2020;22(9):82. doi:10.1007/s11886-020-01349-3
300. Cleland JG, Tendera M, Adamus J, et al. The Perindopril in elderly people with Chronic Heart Failure (PEP-CHF) Study. *Eur Heart J*. 2006;27(11):2338–2345.
301. Solomon SD, Janardhanan R, Verma A, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet*. 2007;369(9579):2079–2087.
302. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359(23):2456–2467.
303. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26(3):215–225.
304. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383–1392.
305. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131(1):34–42.
306. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med*. 2015;373(24):2314–2324.
307. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309(12):1268–1277.
308. De Smet P. Herbal remedies. *N Engl J Med*. 2002;347(25):2046–2056.
309. American Botanical Council. Hawthorn leaf with flower. 2000. http://www.herbalgram.org/

310. Pittler MH, Schmidt K, Ernst E. Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. *Am J Med*. 2003;114(8):665–674.
311. Tauchert M. Efficacy and safety of crataegus extract WS 1442 in comparison with placebo in patients with chronic stable New York Heart Association class III heart failure. *Am Heart J*. 2002;143(5):910–915.
312. Holubarsch CJ, Colucci WS, Meinertz T, Gaus W, Tendera M; Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in CHF (SPICE) Trial Study Group. The efficacy and safety of Crataegus extract WS 1442 in patients with heart failure: the SPICE trial. *Eur J Heart Fail*. 2008;10(12):1255–1263.
313. Tran MT, Mitchell TM, Kennedy DT, Giles JT. Role of coenzyme Q 10 in chronic heart failure, angina, and hypertension. *Pharmacotherapy*. 2001;21(7):797–806.
314. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: the Survival and Ventricular Enlargement Trial (SAVE). *N Engl J Med*. 1992;327(10):669–677.
315. The SOLVD Investigators; Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685–691. doi:10.1056/NEJM199209033271003
316. Swedberg K, Held P, Kjekshus J, Rasmussen K, Rydén L, Wedel H. Effects of the early administration of enalapril in mortality in patients with acute myocardial infarction (CONSENSUS II). *N Engl J Med*. 1992;327(10):628–684.
317. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet*. 1993;342(8875):821–828.
318. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet*. 1995;345(8951):669–685.
319. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Soprawvenza nell infarto Miocardico. *Circulation*. 1993;88(8906):1115–1122.
320. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 1995;333(25):1670–1676. doi:10.1056/NEJM199512213332503
321. Borghi C, Cicero AFG, Ambrosioni E. Effects of early treatment with zofenopril in patients with myocardial infarction and metabolic syndrome: the SMILE Study. *Vasc Health Risk Manag*. 2008;4(3):665–671. doi:10.2147/vhrm.s2799

322. Hansten PD, Horn JR. *Drug Interactions Analysis and Management*. Wolters Kluwer Health; 2009.
323. George CF. Interactions with digoxin: more problems. *Br Med J (Clin Res Ed.)* 1982;284(6312):291–292.
324. Sachs MK, Blanchard LM, Green PJ. Interaction of itraconazole and digoxin. *Clin Infect Dis*. 1993;16(3):400–403.
325. Nolan PJ, Marcus FI, Erstad BL, Hoyer GL, Furman C, Kirsten EB. Effects of co-administration of propafenone on the pharmacokinetics of digoxin in healthy volunteer subjects. *J Clin Pharmacol*. 1989;29(1):46–52.
326. Fitchtl B, Doering W. The quinidine-digoxin interaction in perspective. *Clin Pharmacokinet*. 1983;8(2):137–154.
327. Bigger JT, Leahy E. Quinidine and digoxin: an important interaction. *Drugs*. 1982;24(2):229–239.
328. Fenster PE, Hager WD, Perrier D, Powell JR, Graves PE, Michael UF. Digoxin-quinidine interaction in patients with chronic renal failure. *Circulation*. 1982;66(6):1277–1280.
329. Doering W, Fichtl B, Herrmann M, Besenfelder E. Quinidine-digoxin interaction: evidence for involvement of an extra-renal mechanism. *Eur J Clin Pharmacol*. 1982;21(4):281–285.
330. Mordel A, Halkin H, Zulty L, Almog S, Ezra D. Quinidine enhances digitalis toxicity at therapeutic serum digoxin levels. *Clin Pharmacol Ther*. 1993;53(4):457–462.
331. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. *Am J Cardiol*. 1993;71(7):602–604.
332. Lang CC, McAlpine HM, Kennedy N, Rahman AR, Lipworth BJ, Struthers AD. Effects of lisinopril on congestive heart failure in normotensive patients with diastolic dysfunction but intact systolic function. *Eur J Clin Pharmacol*. 1995;49(1/2):15–19.
333. Zi M, Carmichael N, Lye M. The effect of quinapril on functional status of elderly patients with diastolic heart failure. *Cardiovasc Drugs Ther*. 2003;17(2):133–139.
334. Yip GW, Wang M, Wang T, et al. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. *Heart (Br Card Soc)*. 2008;94(5):573–580.
335. Warner JG Jr, Metzger DC, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. *J Am Coll Cardiol*. 1999;33(6):1567–1572.
336. Parthasarathy HK, Pieske B, Weisskopf M, et al. A randomized, double-blind, placebo-controlled study to determine the effects of valsartan on exercise

time in patients with symptomatic heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2009;11(10):980–989.

337. Takeda Y, Fukutomi T, Suzuki S, et al. Effects of carvedilol on plasma B-type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction. *Am J Cardiol*. 2004;94(4):448–453.
338. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol*. 1997;80(2):207–209.
339. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol*. 1990;66(12):981–986.
340. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation*. 2006;114(5):397–403.

15

Cardiac Arrhythmias

C. Michael White and James S. Kalus

CORE PRINCIPLES		CHAPTER CASES
ATRIAL FIBRILLATION (AF)/FLUTTER		
1	Chest palpitations, light-headedness, and reduced exercise tolerance are the most common symptoms of AF, but stroke is among the severe complications. The goals of therapy are to control the ventricular rate and reduce the risk of stroke.	**Case 15-1 (Questions 1, 2)**
2	Digoxin, β-blockers, and nondihydropyridine calcium channel blockers are appropriate rate-controlling medications. Digoxin is usually adjunctive therapy. Antiarrhythmic drugs are recommended in patients with symptoms but not needed in	**Case 15-1 (Questions 3–7)**

	asymptomatic patients (no symptoms other than palpitations).	
3	Before converting AF to sinus rhythm, assurance of a lack of clot is important but not required if someone is unconscious or hemodynamically unstable. Males with a CHA_2DS_2-VASc score of ≥2 and females with a CHA_2DS_2-VASc score of ≥3 should receive chronic anticoagulant therapy with dabigatran, rivaroxaban, edoxaban, apixaban, or warfarin. Males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2 may, but are not required to, receive chronic anticoagulant therapy.	**Case 15-1 (Questions 8, 13)**
4	Antiarrhythmic drugs convert patients out of AF 50% of the time, whereas electrical shock is successful 90% of the time. To maintain sinus rhythm after conversion, class Ib agents cannot be used, class Ic agents cannot be used in patients with structural heart disease (left ventricular hypertrophy, myocardial infarction, or heart failure), and class Ia and III agents can increase the risk of torsades de pointes. Propafenone, sotalol, dronedarone, dofetilide, and amiodarone are commonly used antiarrhythmic agents for AF.	**Case 15-1 (Questions 9–12)**
5	Atrial flutter is less common than AF, but similar rate control and antiarrhythmic	**Case 15-2 (Question 1)**

	strategies can be tried. Radiofrequency ablation can be used to terminate atrial flutter.	
	PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA (PSVT)	
1	PSVT is caused by reentry within the atrioventricular (AV) node. Palpitations and hypotension can occur. The Valsalva maneuver, adenosine, or nondihydropyridine calcium channel blockers can be used to treat arrhythmia.	**Case 15-3 (Questions 1–6)**
2	In Wolff–Parkinson–White syndrome patients with PSVT, the use of AV nodal blocking agents such as β-blockers, nondihydropyridine calcium channel blockers, and digoxin can increase the risk of cardiac arrest. Ablation can destroy the bypass tract and cure the patient.	**Case 15-4 (Questions 1, 2)**
	AV BLOCK	
1	β-Blockers, digoxin, and nondihydropyridine calcium channel blockers should be withheld in patients with type 1 second- or third-degree AV block. Atropine or β-agonists (isoproterenol, dobutamine, and epinephrine) can be used acutely to treat symptomatic occurrences.	**Case 15-5 (Questions 1, 2)**
	VENTRICULAR ARRHYTHMIAS	
1	In patients with premature ventricular complexes (PVCs) or nonsustained	**Case 15-6 (Questions 1–3)**

	ventricular tachycardia (VT) and postmyocardial infarction, β-blockers are the treatment of choice. Catheter ablation is recommended for those with a high PVC burden, and all patients should be evaluated to determine whether they should receive an implantable cardioverter-defibrillator (ICD).	
2	Patients with sustained VT should be acutely treated with intravenous antiarrhythmic agents unless they are hemodynamically unstable, in which case they should be electrically converted. To prevent death from arrhythmia recurrence, ICDs are superior to antiarrhythmic drugs. To decrease the occurrence of painful ICD shocks, antiarrhythmic drugs are first-line interventions with catheter ablation for treatment failures.	**Case 15-7 (Questions 1–4)**
TORSADES DE POINTES (TdP)		
1	TdP occurs secondary to drug-induced QTc interval prolongation. Class Ia and III antiarrhythmics, antipsychotics, citalopram, fluoroquinolones, macrolides, azole antifungals, and certain opioids (methadone, kratom, mega-dose loperamide) can prolong the QTc interval. Magnesium is the treatment of choice for hemodynamically stable TdP with electrical cardioversion reserved for the	**Case 15-8 (Questions 1–4)**

	hemodynamically unstable. Naloxone does not treat opioid-induced TdP.	
CARDIAC ARREST		
1	If electrical cardioversion fails to convert ventricular fibrillation (VF), epinephrine is used to lower the defibrillation threshold and, if that fails, amiodarone is used to hold the patient in a perfusing rhythm. You never shock pulseless electrical activity or asystole but can use epinephrine.	**Case 15-9 (Questions 1–4)** **Case 15-10 (Questions 1, 2)** **Case 15-11 (Questions 1, 2)**

INTRODUCTION

Adequate circulation depends on continuous, well-coordinated electrical activity within the heart. This chapter reviews and discusses cardiac electrophysiology, arrhythmogenesis, common arrhythmias, and antiarrhythmic treatment.

ELECTROPHYSIOLOGY

Understanding Electrophysiology

CELLULAR ELECTROPHYSIOLOGY

An electrical potential exists across the cell membrane, and the electrical potential changes in a cyclic manner that is related to the flux of K^+, Na^+, and Ca^{2+} ions across the cell membrane.[1] If the change in the membrane potential is plotted against time in a given cycle of a His–Purkinje fiber, a typical action potential results (**Fig. 15-1**).

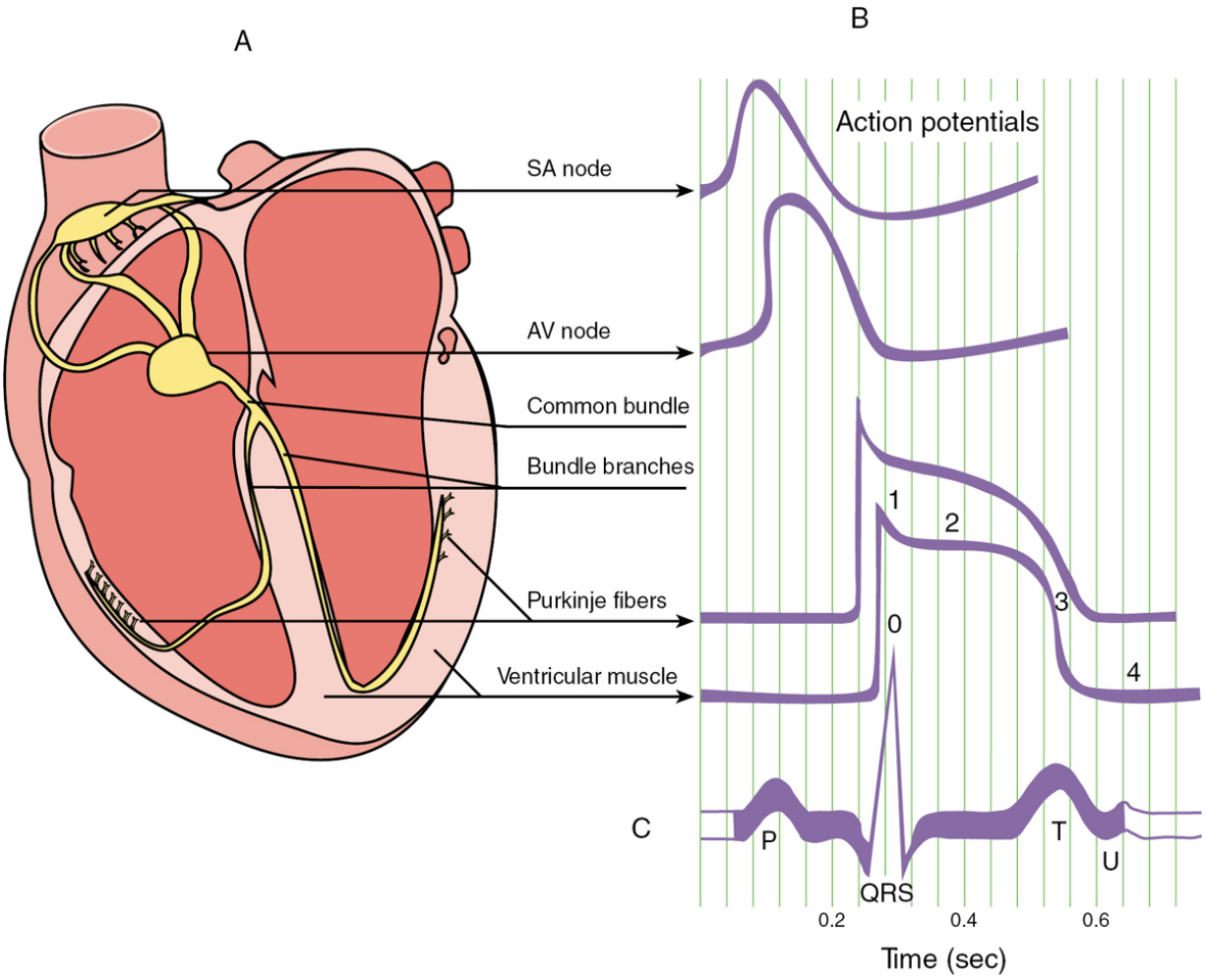


Figure 15-1 The cardiac conduction system. A, Cardiac conduction system anatomy. B, Action potentials of specific cardiac cells. C, Relationship of surface electrocardiogram to the action potential. AV, atrioventricular; SA, sinoatrial.

The action potential can be described in five phases.[1] Phase 0 is related to ventricular depolarization resulting from sodium entry into the cell through fast sodium channels. On a surface electrocardiogram (ECG), phase 0 is represented by the QRS complex. Phase 1 is the overshoot phase in which calcium enters the cell and contraction occurs. During phase 2, the plateau phase, inward depolarizing currents through slow sodium and calcium channels are counterbalanced by outward repolarizing potassium currents. Phase 3 constitutes repolarization, which on the ECG is represented by the T wave. During phase 4, sodium moves out of

the cell, and potassium moves into the cell via an active pumping mechanism. During this phase, the action potential remains flat in some cells (eg, ventricular muscle) and does not change until it receives an impulse from above. In other cells (eg, sinoatrial [SA] node), the cell slowly depolarizes until it reaches the threshold potential and again spontaneously depolarizes (phase 0). The shape of the action potential depends on the location of the cell (see Fig. 15-1). In both the SA and atrioventricular (AV) nodes, the cells are more dependent on calcium influx than sodium influx, resulting in a less negative resting membrane potential, a slow rise of phase 0, and the capability of spontaneous (automatic) phase 4 depolarization (Fig. 15-1).

The upward slope of phase 0, referred to as V_{max}, is related to the conduction velocity. The steeper the slope, the more rapid is the rate of depolarization. Another influence on V_{max} is the point at which depolarization occurs. The less negative the threshold potential, the slower V_{max} will be, and hence conduction velocity is slowed. Drugs can affect V_{max} and conduction velocity by blocking the fast sodium channels or by making the resting membrane potential less negative (eg, class I agents).

The action potential duration (APD) is the length of time from phase 0 to the end of phase 3. The effective refractory period is the length of time that the cell is refractory and will not propagate another impulse. Both of these measurements can be obtained from intracardiac recordings of the action potential. Class Ia and III agents prolong the refractoriness of the heart.[1]

NORMAL CARDIAC ELECTROPHYSIOLOGY

Automaticity

Automaticity is the ability of cells (often called pacemaker cells) to depolarize spontaneously. These cells are located in the SA and AV nodes and the His-Purkinje system. The SA node is normally the dominant pacemaker because it reaches the threshold faster than other nodes in a normal heart, resulting in 60 to 100 depolarizations per minute.[2] The innate AV node and Purkinje rate of depolarization

are 40 to 60 and 40 depolarizations per minute, respectively. In the healthy heart, the AV node and Purkinje fibers are prevented (overridden) from spontaneous depolarization by the more frequent impulses from the SA node.

Conduction

An impulse normally originates in the SA node and travels down specialized intranodal pathways to activate atrial muscle and the AV node. The AV node holds the impulse briefly before releasing it to the bundle of His. It then travels to the right and left bundle branches and out to the ventricular myocardium via the Purkinje fibers. The ECG tracing consists of a series of complexes that correspond to electrical activity in a specific location or anatomic site. By convention, these electrical deflections have been labeled the P wave, QRS complex, and T wave. The P wave represents depolarization of the atria, whereas the QRS complex reflects ventricular depolarization. The T wave reflects repolarization of the ventricles. To evaluate the intact conduction system, conduction intervals at different sites can be obtained. The normal intervals as measured by ECG or intracardiac electrodes are shown in **Table 15-1**. Drugs and ischemia can alter the conduction and hence the ECG intervals. The effects of antiarrhythmic agents on the ECG are described in **Table 15-2**.

Table 15-1

Normal Electrocardiographic Intervals

Interval	Normal Indices (milliseconds)	Electrical Activity
PR	120–200	Atrial depolarization
QRS	<140	Ventricular depolarization
QTc[a]	<400	Ventricular repolarization

[a]QTc interval is the QT interval corrected for heart rate.

Table 15-2

Pharmacologic Properties of Antiarrhythmic Agents

	Surface ECG				
Type	PR Interval	QRS Interval	QT Interval	Conduction Velocity	Refractory Period
Ia	0/↑	↑	↑↑	↑↓[a]	↑[b]
Ib	0	0	0	0/↓	↓[b]
Ic	↑	↑↑	↑	↑[b]	0[b]
II	↑↑	0	0	↓[b]	↑[b]
III	0[c]	0	↑↑	0[b]	↑[b]
IV	↑↑	0	0	↓[b]	↑[b]

ECG, electrocardiogram.

[a]Conduction increases at low dosages and decreases at higher dosages.

[b]On atrial and atrioventricular nodal tissue.

[c]May cause PR prolongation independent of class III antiarrhythmic activity.

Pathophysiology

ABNORMAL IMPULSE FORMATION

Abnormal impulse formation can arise from abnormal automaticity or triggered activity originating from the SA node (eg, sinus bradycardia) or other sites (eg, junctional or idioventricular tachycardia). Causes of abnormal automaticity include hypoxia, ischemia, or excess catecholamine activity.

Triggered activity occurs when there is an attempted depolarization before or after the cell is fully repolarized, but not by a pacemaker cell. These after-depolarizations may occur in phase 2 or 3 (early) or phase 4 (delayed) of the action potential. Early after-depolarizations (EADs) arise from a reduced level of membrane potential and may require a bradycardic state. Torsades de pointes (TdP), a form of polymorphic ventricular tachycardia (VT), is thought to be initiated by EAD. Delayed after-depolarizations, often seen with

digoxin toxicity, are thought to be secondary to an overload of intracellular free calcium.

ABNORMAL IMPULSE CONDUCTION

Reentry

The most common abnormal conduction leading to arrhythmogenesis is reentry. A reentrant circuit is formed as normal conduction occurs down a pathway that bifurcates into two pathways (eg, AV node or left and right bundle branches). The impulse travels along one pathway (**Fig. 15-2**) but encounters unidirectional antegrade block in the other pathway (see Fig. 15-2). The impulse that passed through the unblocked pathway propagates in a retrograde manner (ie, moves backward) through the previously blocked pathway. This abnormal impulse can travel down the first pathway again when it is not refractory. Supraventricular and monomorphic VT are both examples of reentrant arrhythmias.

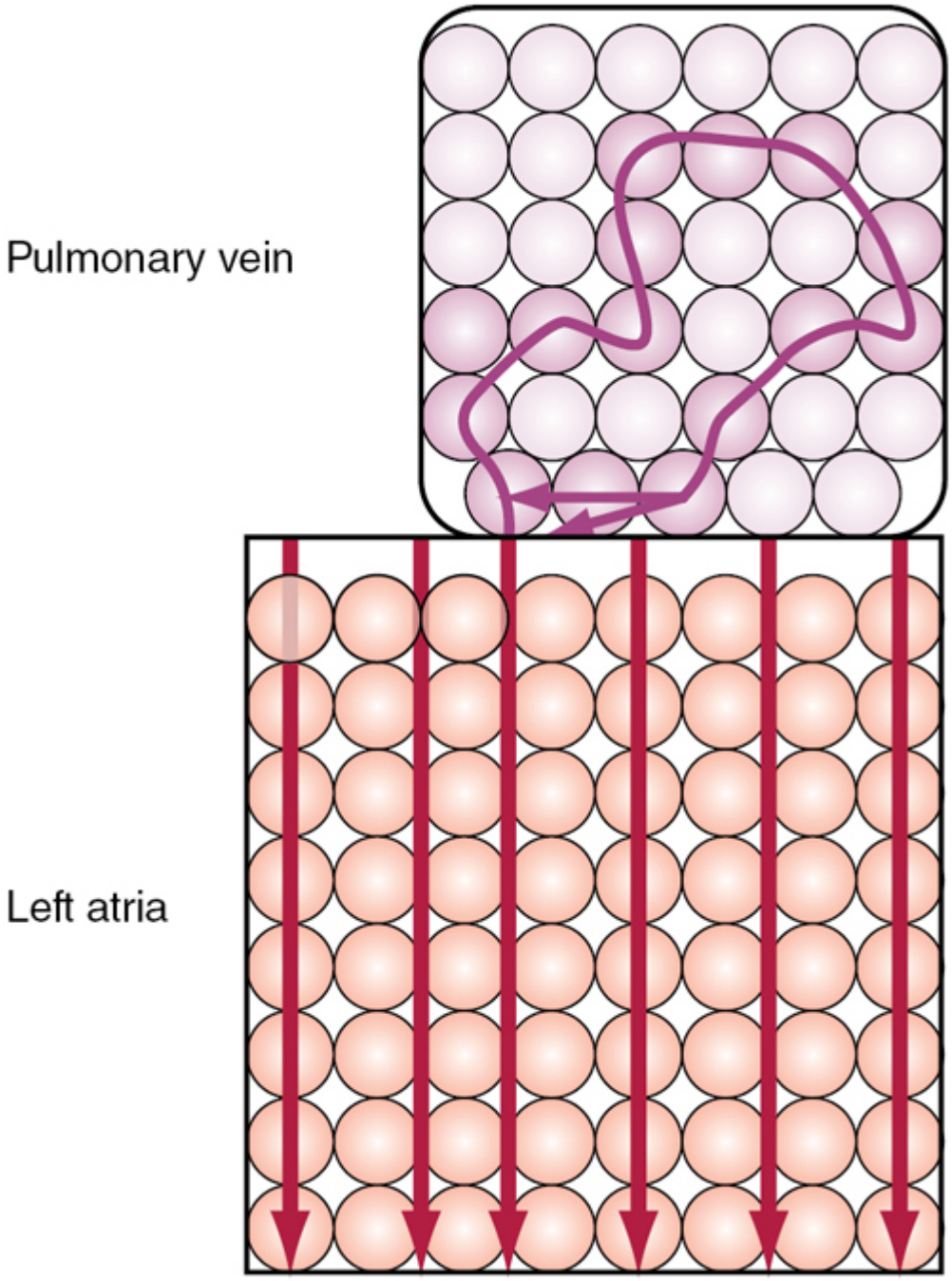


Figure 15-2 Reentrant circuit in the pulmonary vein. In the pulmonary vein, there is a mixing of electrically active cells (*shaded circles*) and electrically inactive cells (*white circles*). Although the main wave of depolarization goes homogenously down the atria, a small depolarization stimulus enters the pulmonary vein and meanders through the electrically active tissue. In this case, there is a reentrant circuit formed where the impulse can continue to rotate

through the pulmonary vein and a route for it to stimulate the atria as well.

Block

Another form of abnormal impulse conduction occurs when the normal conducting pathway is blocked and the impulse is forced to travel through nonpathway tissues to cause depolarization. Common examples are left and right bundle branch blocks in the ventricles. A block in one path necessitates retrograde conduction through the opposite bundle to stimulate both ventricles. Nonpathway tissue conducts the electrical impulse more slowly than conduction tissues do.[1]

Classification of Arrhythmias

All arrhythmias originating above the bundle of His are referred to as supraventricular arrhythmias. These may include sinus bradycardia, sinus tachycardia, paroxysmal supraventricular tachycardia (PSVT), atrial flutter, atrial fibrillation (AF), Wolff–Parkinson–White (WPW) syndrome, and premature atrial contractions (PACs). All of these arrhythmias are characterized by normal QRS complexes (ie, normal ventricular depolarization) unless there is a bundle branch block. Not all these rhythm changes are necessarily a sign of pathology. For example, athletes with a well-conditioned heart and large stroke volume commonly have slow heart rates (sinus bradycardia). Vigorous exercise is accompanied by transient sinus tachycardia.

Arrhythmias originating below the bundle of His are referred to as ventricular arrhythmias. These include premature ventricular contractions (PVCs), VT, and ventricular fibrillation (VF). Conduction blocks often are categorized separately based on their level or location, which can be a supraventricular site (eg, first-, second-, or third-degree AV block, see Case 15-6, Question 2) or in the ventricle (eg, right or left bundle branch block). An alternative method of classifying arrhythmias is based on the rate: bradyarrhythmia (<60 beats/minute) or tachyarrhythmia (>100 beats/minute). There is a

website with useful rhythm evaluation tutorials at http://www.blaufuss.org.

Antiarrhythmic Drugs

Based on their electrophysiologic (EP) and pharmacologic effects, there are four Vaughn-Williams antiarrhythmic drug classes. Class I drugs, sodium channel blockers, are subdivided further depending on the duration of blockade (class Ia: intermediate; Ib: fast; and Ic: long). Class II drugs are β-adrenergic blockers, class III drugs are potassium channel blockers, and class IV drugs are calcium channel blockers. The classification, pharmacokinetics, and adverse effects of these agents are summarized in **Table 15-3**.

Table 15-3
Vaughn-Williams Classification of Antiarrhythmic Agents

Drug and Classification	Pharmacokinetics	Indications	Side Effects
Class Ia (can cause torsades de pointes similar to class III agents)			
Quinidine sulfate (83% quinidine; SR) Quinidine gluconate (62% quinidine; SR)	$t_{1/2}$ = 6.2 ± 1.8 hours (affected by age, cirrhosis); V_d = 2.7 L/kg (↓ in HF); liver metabolism, 80%; renal clearance, 20%; C_p = 2–6 μg/mL, CYP3A4 substrate, CYP2D6 inhibitor, P-glycoprotein inhibitor	AF (conversion or prophylaxis), WPW, PVCs, VT	Diarrhea, hypotension, N/V, cinchonism, fever, thrombocytopenia, proarrhythmia
Procainamide	$t_{1/2}$ = 3 ± 0.6 hours; V_d = 1.9 ± 0.3 L/kg; liver metabolism 40%; renal clearance (GFR + possible CTS) 60%; active metabolite (NAPA)[a] C_p = 4–10 μg/mL, possible CTS substrate	AF (conversion or prophylaxis), WPW, PVCs, VT	Hypotension, fever, agranulocytosis, SLE (joint/muscle pain, rash, pericarditis), headache, proarrhythmia
Disopyramide (SR and CR forms)	$t_{1/2}$ = 6 ± 1 hours; V_d = 0.59 ± 0.15 L/kg; liver metabolism, 30%; renal clearance, 70%; C_p = 3–6 μg/mL	AF, WPW, PSVT, PVCs, VT	Anticholinergic (dry mouth, blurred vision, urinary retention), HF, proarrhythmia
Class Ib[b] (cannot be used to treat atrial arrhythmias)			
Lidocaine	$t_{1/2}$ = 1.8 ± 0.4 hours; V_d = 1.1 ± 0.4 L/kg; liver metabolism, 100%; C_p = 1.5–6 μg/mL	PVCs, VT, VF	Drowsiness, agitation, muscle twitching, seizures, paresthesias, proarrhythmia
Mexiletine	$t_{1/2}$ = 10.4 ± 2.8 hours; V_d = 9.5 ± 3.4 L/kg; liver metabolism, 35%–80%; C_p = 0.5–2 μg/mL	PVCs, VT, VF	Drowsiness, agitation, muscle twitching, seizures, paresthesias, proarrhythmia, N/V, diarrhea
Class Ic (cannot be used in patients with structural heart disease)			
Flecainide	$t_{1/2}$ = 12–27 hours; CYP2D6 substrate, 75%; renal clearance, 25%; C_p = 0.4–1 μg/mL	AF, PSVT, severe ventricular arrhythmias	Dizziness, tremor, lightheadedness, flushing, blurred vision, metallic taste, proarrhythmia
Propafenone	$t_{1/2}$ = 2 hours (extensive metabolizer); 10 hours (poor metabolizer); V_d = 2.5–4 L/kg, CYP2D6 substrate/inhibitor, P-glycoprotein inhibitor	PAF, WPW, severe ventricular arrhythmias	Dizziness, blurred vision, taste disturbances, nausea, worsening of asthma, proarrhythmia
Class III (can cause torsade de pointes similar to class Ia agents, amiodarone, and dronedarone and have lower risk)			
Amiodarone	$t_{1/2}$ = 40–60 days; V_d = 60–100 L/kg; erratic absorption; liver metabolism, 100%; oral F = 50%, C_p = 0.5–2.5 μg/mL, CYP1A2, 2D6, 2C9, 3A4 inhibitor, P-glycoprotein inhibitor	AF, PAF, PSVT, severe ventricular arrhythmias, VF	Blurred vision, corneal microdeposits, photophobia, skin discoloration, constipation, pulmonary fibrosis, ataxia, hypothyroid or hyperthyroid, hypotension, N/V
Sotalol[c]	$t_{1/2}$ = 10–20 hours; V_d = 1.2–2.4 L/kg; renal clearance, 100%	AF (prophylaxis), PSVT, severe ventricular arrhythmias	Fatigue, dizziness, dyspnea, bradycardia, proarrhythmia
Dofetilide	$t_{1/2}$ = 7.5–10 hours; V_d = 3 L/kg; renal elimination, 60% (GFR + CTS), CYP3A4 substrate	AF or atrial flutter conversion and prophylaxis	Chest pain, dizziness, headache, proarrhythmia
Ibutilide	$t_{1/2}$ = 6 (2–12) hours; V_d = 11 L/kg, C_p = undefined	AF or atrial flutter conversion	Headache, nausea, proarrhythmia
Dronedarone	$t_{1/2}$ = 13–19 hours; V_d = 20 L/kg, T_{max} = 3–6 hours, CYP3A4 substrate, CYP 2D6, 3A4 inhibitor, P-glycoprotein inhibitor, take with food for maximal absorption	AF or atrial flutter prophylaxis	Diarrhea, nausea, dermatitis or rash, bradycardia, hepatotoxicity, pregnancy category X

AF, atrial fibrillation; C_p, steady-state plasma concentration; CR, controlled release; CTS, cation tubular secretion; CYP, cytochrome P-450; F, bioavailability; GFR, glomerular filtration rate; HF, heart failure; NAPA, *N*-acetylprocainamide; N/V, nausea and vomiting; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; SLE, systemic lupus erythematosus; SR, sustained release; $t_{1/2}$, half-life; V_d, volume of distribution; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff–Parkinson–White syndrome.

[a]NAPA is 100% renally eliminated and possesses class III antiarrhythmic activity.

[b]Phenytoin is classified as a class Ib antiarrhythmic.

[c]Possesses both class II and III antiarrhythmic activities.

Class Ia and class III antiarrhythmic agents increase repolarization time, the QTc interval, and the risk of TdP. Class II and IV antiarrhythmic agents may decrease heart rate (cause bradycardia), decrease ventricular contractility (decrease stroke volume), and prolong the PR interval (cause second- or third-degree AV block). Class Ib antiarrhythmic agents work only in ventricular tissue, so they cannot be used in AF or atrial flutter. Class Ic antiarrhythmic agents are useful but should never be used after a myocardial infarction (MI) or with heart failure with reduced ejection fraction (HFrEF) or severe left ventricular hypertrophy (classified as structural heart diseases) because increased mortality can result. These drugs are discussed in greater detail later.

SUPRAVENTRICULAR ARRHYTHMIAS

The specific arrhythmias include (a) those primarily atrial in origin, such as AF, atrial flutter, paroxysmal sinus tachycardia, ectopic atrial tachycardia, and multifocal atrial tachycardia and (b) AV nodal reentrant tachycardia (AVNRT) and AV reentrant tachycardia (AVRT) involving accessory pathways within the atria or ventricle. AVNRT and AVRT often self-terminate and are paroxysmal (episodic) in nature; thus, they are commonly referred to as PSVT. The most common supraventricular arrhythmias are AF, atrial flutter, and PSVT.

Atrial Fibrillation and Atrial Flutter

AF is usually initiated when a depolarization stimulus arising from an ectopic focus or reentrant circuit impacts the atria while the tissue is in the vulnerable period. The vulnerable period in the atria and

ventricles occurs during the first half of the QRS complex; this period is vulnerable because the net charge is near normal, but the ion concentrations of sodium, calcium, and potassium inside and outside the cells are radically different. Stimulation during the vulnerable period causes multiple ectopic foci to arise and attempt to pace the atria with no single pacemaker in control, eliminating discernable P waves on the ECG (**Fig. 15-3**) and eliciting a rapid, ineffective writhing of the atrial muscle with a classic "irregularly irregular" ventricular rate. In contrast, atrial flutter (**Fig. 15-4**) is characterized by typical sawtooth atrial waves, at a rate of 280 to 320 beats/minute, and a variable ventricular rate, depending on the nature of the AV block present (eg, 2, 3, or 4 atrial beats for each ventricular beat or 2:1, 3:1, or 4:1 block). In most cases, the ventricular rate is ~150 beats/minute. Episodes of atrial flutter can progress to AF if the ectopic atrial depolarization stimulus impacts the surrounding atrial tissue in the vulnerable period. When patients initially experience AF, the episodes are usually short lived, and spontaneous conversion occurs. The pattern of erratic initiation and termination of AF is termed paroxysmal atrial fibrillation (PAF), and if enough AF events occur in close proximity to each other, the duration of subsequent AF events increases in length and the event degenerates into persistent AF. In persistent AF, the AF episode will continue until the heart is electrically or chemically converted out of the rhythm. With time, persistent AF degenerates into permanent AF, in which normal sinus rhythm cannot be achieved and sustained. An example of PAF is presented in the following section.

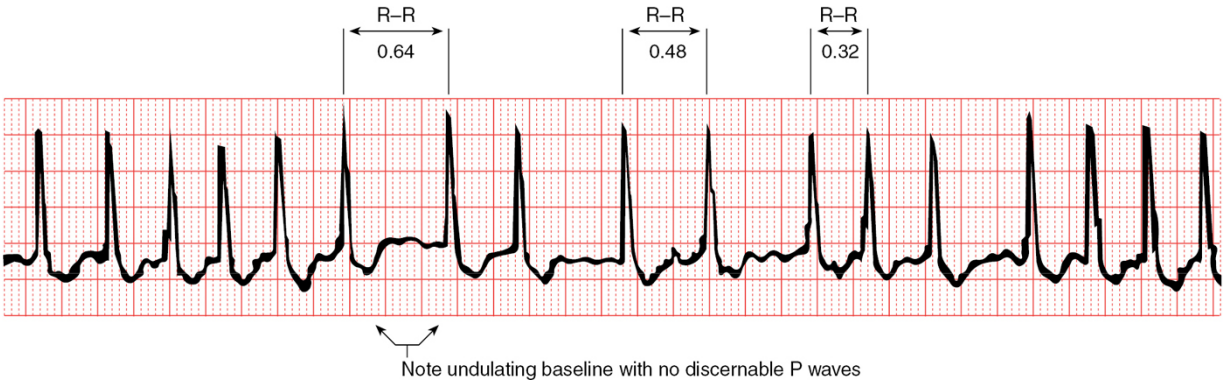


Figure 15-3 Atrial fibrillation. Note the irregularly irregular R–R intervals, undulating baseline without definitive P waves, normal width of the QRS complexes, and ventricular rate of 140 beats/min.

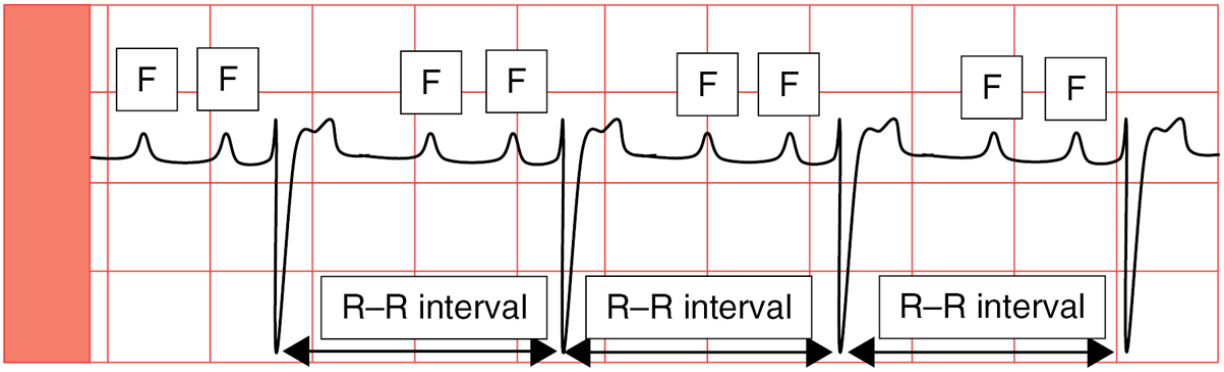


Figure 15-4 Atrial flutter. Note the sawtooth appearance of the rhythm strip. F denotes flutter waves with consistent R–R spacing.

CLINICAL MANIFESTATION AND UNDERLYING CAUSES

CASE 15-1

QUESTION 1: J.K., a 66-year-old male, presents for a routine checkup in the clinic. His medical history includes type 2 diabetes mellitus and HFrEF for the last 5 years, hypertension, and gout. There is no history of rheumatic heart disease, MI, pulmonary embolism, or thyroid disease. Medications include metformin 1 g twice daily, lisinopril 40 mg every day, furosemide 40 mg twice daily, metoprolol succinate 100 mg once daily, and allopurinol 300 mg/day. J.K. does not smoke or drink alcohol. Physical examination reveals a blood pressure (BP) of 136/84 mm Hg, pulse of 70 beats/minute in normal sinus rhythm, respiratory rate of 12 breaths/minute, and temperature of 98.2 °F (36.77 °C). His body mass index is 32 kg/m^2.

What factors in J.K.'s past medical history predispose him to the development of AF? What is his 10-year risk of developing AF?

AF is commonly associated with, or a manifestation of, other diseases or disorders (**Table 15-4**).[2,3] When treatable underlying causes are present, they should be corrected because this may resolve the AF. A risk prediction tool highlights common factors associated with the development of AF, particularly older age, male gender, hypertension, heart failure (HF), obesity, and valvular

disease.[4,5] In a small percentage of patients who do not have underlying heart disease, AF is called “lone” AF and usually has a more benign course.

Table 15-4
Causes of Atrial Fibrillation and Flutter

Alcohol	Nonrheumatic Heart Disease
Atrial septal defect	Pericarditis
Cardiac surgery	Pneumonia
Cardiomyopathy	Pulmonary embolism
Cerebrovascular accident	Sick sinus syndrome
Chronic obstructive pulmonary disease	Stimulants Thyrotoxicosis
Fever	Trauma
Hypothermia	Tumors
Ischemic heart disease	Wolff–Parkinson–White syndrome
Mitral valve disease	

J.K. has several risk factors for the development of AF within the next 10 years, including the presence of treated hypertension, HF, his age, and his sex. A detailed scoring system is described in the referenced manuscript but is beyond the scope of this chapter. Using his risk factors, his 10-year risk of developing AF would be >30%.[4]

Consequences of Atrial Fibrillation

Case 15-1, Question 2: Two years later, J.K. presents with dyspnea on exertion (DOE) and palpitations for the last 2 weeks. He experienced palpitations of shorter duration three times in the last year, but these were not associated with DOE. On physical examination, he is found to have rales. Cardiac examination reveals an irregularly irregular rhythm without murmurs, gallops, or rubs. His jugular veins are distended 4 cm, but no organomegaly is found. His extremities have 1+ pitting edema. The ECG shows AF (see Fig. 15-3), and the chest radiograph is compatible with mild pulmonary congestion. A cardiac echocardiogram reveals the atrial size to be <5 cm (normal) and a left

ventricular ejection fraction of 35%. What clinical findings demonstrated by J.K. are typically associated with AF? What are the likely consequences of his AF?

The most common issue in patients with AF, as with J.K., is palpitations (the sensation of the heart beating rapidly or unusually in the chest). This is a result of the rapid ventricular rate, which typically ranges from 100 to 160 beats/minute. The R–R interval (time from the R wave in one QRS complex to the R wave in the next complex) is irregularly irregular (random irregularity). During AF, the atrial kick or the atria's contribution to stroke volume is lost. Because the atrial kick may account for 20% to 30% of the total stroke volume, this, coupled with rapid ventricular rates and irregular R–R interval spacing during AF, can cause symptoms of inadequate blood flow such as light-headedness, dizziness, or reduced exercise tolerance. However, some patients are asymptomatic except for palpitations. Depending on the underlying ventricular function, signs of HF, such as DOE and peripheral edema, may develop, as experienced by J.K. Conversely, underlying HF may precipitate AF.

Patients with AF are at risk for thrombotic stroke (see Stroke Prevention section).[6] With the chaotic movement of the atria, normal blood flow is disrupted, and atrial mural thrombi (usually forming in a pouch called the left atrial appendage) may form. The risk of stroke increases after the restoration of normal sinus rhythm, which allows more efficient cardiac contractility and expulsion of the thrombus. Patients with nonvalvular AF have a fivefold increase in the risk of stroke; this risk increases as patients have an increased number of associated risk factors. Other concurrent diseases that may increase the risk of stroke are HF, cardiomyopathy, thyrotoxicosis, congenital heart disease, and valvular heart disease. Because of the high risk of stroke and significant impact of stroke on patient outcomes, pharmacologic stroke prophylaxis is often indicated. Selection of an appropriate antithrombotic regimen for the patient with AF must be based on the assessment of the underlying stroke and bleeding risk. Risk stratification in AF is performed with the use of the CHA_2DS_2-VASc scoring system. A CHA_2DS_2-VASc score is calculated by

assigning one point each for the presence of congestive HF, hypertension, diabetes, vascular disease, age of 65 to 74 years, or female gender and two points for the age of 75 years or older or a history of stroke. Points are totaled, and the subsequent score correlates with stroke risk.[6]

TREATMENT OF ATRIAL FIBRILLATION

Goals of therapy

CASE 15-1, QUESTION 3: What are the therapeutic goals and general approaches used to treat AF in patients like J.K.?

The two primary goals of treatment are to control the ventricular response rate and to reduce the risk of stroke. In some cases, a third therapeutic goal may be conversion to normal sinus rhythm.

Ventricular rate control

Digoxin

CASE 15-1, QUESTION 4: J.K. is given a 1-mg loading dose of digoxin, followed by a 0.25-mg every day maintenance dose. What is the purpose of administering digoxin? What are the relative advantages and disadvantages of digoxin compared with other agents to control ventricular rate?

The first treatment goal is to slow the ventricular response rate, which allows better ventricular filling with blood. **Table 15-5** displays the agents commonly used to control the ventricular response and provides typical loading and maintenance doses. Because of its direct AV node-blocking effects and vagomimetic properties, digoxin prolongs the effective refractory period of the AV node and reduces the number of impulses conducted through the AV node (negative dromotropy).[6–8]

Table 15-5
Agents Used for Controlling Ventricular Rate in

Supraventricular Tachycardias[a]

Drug	Loading Dose	Usual Maintenance Dose	Comments
Digoxin	10–15 μg/kg LBW up to 1–1.5 mg IV or PO for 24 hours (eg, 0.5 mg initially, then 0.25 mg every 6 hours)	PO: 0.125–0.5 mg/day; adjust for renal failure (see Chapter 14, Heart Failure)	Maximal response may take several hours; use with caution in patients with renal impairment.
Esmolol	0.5 mg/kg IV for 1 minute	50–300 μg/kg/minute continuous infusion with bolus between increases	Hypotension common; effects additive with digoxin and calcium channel blockers
Propranolol	0.5–1.0 mg IV repeated every 2 minutes (up to 0.1–0.15 mg/kg)	IV infusion: 0.04 mg/kg/minute PO: 10–120 mg tid	Use with caution in patients with HF or asthma; additive effects seen with digoxin and calcium channel blockers
Metoprolol	5 mg IV at 1 mg/min	PO: 25–100 mg bid	Use with caution in patients with HF or asthma; additive effects seen with digoxin and calcium channel blockers
Verapamil	5–10 mg (0.075–0.15 mg/kg) IV for 2 minutes; if response inadequate after 15–30 minutes, repeat 10 mg (up to 0.15 mg/kg)	IV infusion: 5–10 mg/hour PO: 40–120 mg tid or 120–480 mg in sustained-release form daily	Hypotension with IV route; AV blocking effects are additive with digoxin and β-blockers; may increase digoxin levels.
Diltiazem	0.25 mg/kg IV for 2 minutes; if response inadequate after 15 minutes, repeat 0.35 mg/kg for 2 minutes.	IV infusion: 5–15 mg/hour PO: 60–90 mg tid or qid or 180–360 mg in extended-release form daily	Response to IV therapy occurs in 4–5 minutes; hypotension; effects additive with digoxin and β-blockers

AV, atrioventricular; bid, two times a day; HF, heart failure; IV, intravenously; LBW, lean body weight; PO, orally; qid, four times a day; tid, three times a day.

[a]AV nodal ablation is a nonpharmacologic alternative to control the ventricular response, but the effect is permanent and may require chronic ventricular pacing afterward.

There are several limitations associated with digoxin use in AF. Digoxin has a slow onset of action. After an intravenous (IV) dose, it will take more than 2 hours for the onset of effect and 6 to 8 hours for the maximal effect, which is markedly slower than other negative dromotropic agents.[7] Digoxin is also less effective than β-blockers and nondihydropyridine calcium channel blockers during states of heightened sympathetic tone (eg, exercise or emotional stress), a common precipitant of PAF.[6–8] The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines for the management of patients with AF recommend that digoxin use be reserved for control of ventricular response rate in patients with impaired left ventricular function or HF or for use as an add-on therapy when treatment with a β-blocker or calcium channel blocker provides inadequate rate control.[6] Patients who require rate control of AF and have a lower BP may also benefit from rate control with digoxin. It should also be noted that digoxin serum concentrations may be increased when combined with P-

glycoprotein inhibitors such as verapamil, propafenone, quinidine, flecainide, and amiodarone.[9,10] Normally, P-glycoprotein in the brush border membrane of intestinal enterocytes pumps digoxin into the lumen of the gut, reducing its bioavailability and pumps digoxin out of the body via the renal tubules (see Chapter 14, Heart Failure, for discussion of digoxin and digoxin drug interactions).

Case 15-1, Question 5: J.K. has diabetes, which increases the risk for diabetic nephropathy. Would the dosing be changed if J.K. had renal dysfunction?

J.K.'s renal function is normal. If he had significant renal dysfunction, both the loading and the maintenance doses of digoxin would need to be altered. A loading dose is used to achieve a therapeutic level, and volume of distribution of digoxin is reduced in patients with renal dysfunction. The digoxin maintenance dose is highly dependent on renal clearance because digoxin is eliminated 50% to 75% unchanged in the urine (see Chapter 14, Heart Failure, for further discussion of digoxin dosing in patients with normal and impaired renal function). Although the usual digoxin target range is generally 0.5 to 1.0 ng/mL in the management of patients with HFrEF,[11] higher serum concentrations may be necessary when using digoxin as a rate control agent for J.K.

a-Adrenergic Blocking Agents

Case 15-1, Question 6: What other drugs can be used for ventricular rate control, and what are their relative advantages and disadvantages compared with digoxin?

β-Adrenergic blocking agents are another class of negative dromotropic agents used in AF. Propranolol, metoprolol, and esmolol are available for IV administration. Each agent rapidly controls the ventricular rate both at rest and during exercise. β-Blockers are the first choice in high catecholamine states such as thyrotoxicosis and

postcardiac surgery. However, given their negative inotropic effects, β-blockers should be used cautiously to acutely control the ventricular response in patients with decompensated HFrEF. Although β-blockers are used to treat HFrEF (eg, bisoprolol, carvedilol, and metoprolol), they need to be started at low doses and titrated slowly for several weeks to therapeutic doses[2] (see Chapter 14, Heart Failure). When trying to achieve rapid rate control, more aggressive dosing may be needed. β-Blockers should also be avoided in patients with asthma because of their β_2-blocking properties, and blood glucose levels should be monitored more closely in patients with diabetes mellitus because the signs and symptoms of hypoglycemia (except sweating) can be masked.

Calcium Channel Blockers

Nondihydropyridine calcium channel blockers are also effective in slowing the ventricular rate at rest and during exercise. Both verapamil and diltiazem can be administered IV for a rapid (4–5 minutes) reduction in heart rate.[8] Nondihydropyridine calcium channel blockers should not be used in patients presenting with decompensated HF.[6] They work through their effect on slow calcium channels within the AV node. Although the duration of action produced by bolus dosing is short, both agents can be administered either as a continuous drip or orally. Given the ability of calcium channel blockers to cause arteriolar dilation, a transient decrease in BP may be seen. IV calcium pretreatment can be used to attenuate the BP decrease among patients with hypotension, near-hypotensive BP, or left ventricular dysfunction. Calcium pretreatment does not appear to diminish the negative dromotropic effects of nondihydropyridine calcium channel blockers.[12-14] Verapamil is contraindicated in patients with an ejection fraction <35%, and diltiazem should be used with caution in HFrEF. Verapamil increases the concentrations of other cardiovascular drugs such as digoxin, dofetilide, simvastatin, and lovastatin. Verapamil and diltiazem are good alternatives to β-blockers in patients with asthma.[6]

For chronic therapy, oral negative dromotropic agents (usually a β-blocker or nondihydropyridine calcium channel blocker) are recommended. If higher dose monotherapy with one of these drugs is needed to control symptoms but is associated with intolerable side effects, adding lower dose digoxin to a β-blocker or calcium channel blocker is recommended.[6,15,16]

J.K. has signs of mild HF, so digoxin is a reasonable choice, although short-term IV diltiazem is often used in this type of patient as well. IV verapamil and β-blockers may worsen the signs and symptoms of HF, and the β-blockers may mask signs of hypoglycemia in J.K. The goal of rate control should be a resting heart rate between 60 and 80 beats/minute and an exercising heart rate between 90 and 115 beats/minute.[6] A study has explored the use of a more lenient target resting heart rate (<110 beats/minute) and reported similar patient outcomes as compared with a more strict target heart rate (resting heart rate <80 beats/minute).[17] This study may suggest that it could be acceptable for a patient's heart rate to be >80 beats/minute if there is difficulty in achieving this level of heart rate control in asymptomatic patients or those with HF and a preserved EF.[6,18]

Rate Control Versus Rhythm Control

Case 15-1, Question 7: After loading of digoxin, J.K.'s heart rate is still 120 beats/minute, and he continues to experience palpitations. His BP is 100/60 mm Hg, and his symptoms of HF are improving, but he still has mild shortness of breath. The decision is made to cardiovert J.K. to normal sinus rhythm. Is J.K. a good candidate for a rhythm control strategy and if so, why? What is the likelihood that J.K. will be successfully converted to normal sinus rhythm?

The use of a rhythm control strategy has become much less common during the last several years. This change is because of the completion of several studies comparing the effect of a rate or rhythm control strategy on patient outcomes.[19–24] The AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management), a randomized, multicenter study, was one of the largest to compare

rate control with rhythm control for the management of AF. AFFIRM enrolled 4060 patients with AF and a risk of stroke.[19] The primary end point was all-cause mortality. Antiarrhythmic drugs were chosen at the discretion of the treating physician, but >60% of the patients received amiodarone or sotalol as the initial antiarrhythmic agent. Rate control agents included digoxin, β-blockers, and nondihydropyridine calcium channel blockers. After a mean follow-up of 3.5 years, there was a trend toward lower overall mortality (*P* = .08) with significant reductions in hospitalizations (10% lower; *P* = .001) and TdP (300% lower; *P* = .007) in the rate control group. Therefore, using rhythm control in patients with AF rather than rate control does not improve outcomes and increases the risk of hospitalizations and TdP.

The default long-term treatment strategy for most patients should be a rate control strategy, in which heart rate is controlled and anticoagulation is provided if indicated. However, rhythm control is necessary when patients experience symptoms despite adequate rate control, when heart rate cannot be adequately controlled with currently available treatments, or if patients cannot tolerate the adverse effects of rate-controlling medications. J.K.'s heart rate is not adequately controlled with digoxin and an oral β-blocker. It is not advisable to increase his β-blocker at this time, given that he has mild symptoms of HF decompensation. A nondihydropyridine calcium channel blocker could be added to better control his heart rate; however, his BP may not tolerate the addition of a nondihydropyridine calcium channel blocker. Therefore, the pursuit of a rhythm control strategy is warranted.

Likelihood of successful conversion to, and maintenance of, normal sinus rhythm is determined by the duration of the arrhythmia, underlying disease processes, and left atrial size.[6,25] Duration of AF for more than 1 year significantly reduces the chances of maintaining a normal sinus rhythm. When the atrial size exceeds 5 cm, there is a <10% chance of maintaining normal sinus rhythm at 6 months. J.K.'s chance of being maintained in normal sinus rhythm is good because the duration of his AF is short and the echocardiogram revealed only slight enlargement of his left atrium.

Conversion to normal sinus rhythm

Case 15-1, Question 8: Warfarin treatment is begun and J.K.'s prothrombin time is to be maintained at an international normalized ratio (INR) of 2 to 3. J.K. is scheduled for a transesophageal echocardiogram (TEE) to determine whether cardioversion can be performed during this admission. How does a TEE help to determine whether cardioversion can be performed, and why is warfarin therapy being used?

When the onset of AF is <48 hours, the likelihood of atrial clot formation is low. However, if patients are at high risk for stroke, they should receive an anticoagulant (unfractionated heparin, low-molecular-weight heparin, factor Xa, or direct thrombin inhibitor) as soon as possible surrounding the cardioversion, followed by long-term anticoagulation.[6] When the duration of AF is >48 hours, or if the duration is unknown, then an oral anticoagulant agent (warfarin, dabigatran, factor Xa inhibitor) should be given for 3 weeks before cardioversion at doses providing an INR between 2 and 3 if using warfarin.[6] Studies in patients with AF showed that those who were anticoagulated with warfarin before cardioversion had a lower incidence (0.8%) of emboli than those who were not anticoagulated (5.3%).[26] Alternatively, a TEE can be used to determine whether atrial clots have formed.[6,27] Atrial clots form most often in a small side pouch on the atria called the atrial appendage.[28] Because the frequency of right atrial appendage thrombosis is half that of left atrial appendage thrombosis in patients with AF, the risk of stroke is enhanced much more than the risk of pulmonary embolism.[28]

If no clot is observed on TEE, then there is a low risk for stroke with cardioversion of AF.[27] However, if an atrial clot is evident on TEE, J.K. would need to be adequately anticoagulated for 3 weeks before cardioversion to prevent embolization of the clot and stroke. If cardioversion is successful, patients should remain on an oral anticoagulant agent for at least 4 weeks after cardioversion because normal atrial contraction may not return for up to 3 weeks, and patients may be at risk of late embolization.[29] The decision to provide long-term oral anticoagulation is dependent on the patient's

underlying stroke and bleeding risk. This will be discussed further below.

Conversion—Chemical with Ibutilide, Propafenone, Flecainide

Case 15-1, Question 9: J.K. was found to be free of atrial clots. Chemical cardioversion with ibutilide is planned for tomorrow. If J.K. fails to convert with ibutilide, he will be electrically cardioverted later in the day. How does ibutilide therapy compare with the other therapeutic choices for chemical cardioversion?

The most effective method of cardioversion is by direct current (DC) cardioversion (see Electrical Cardioversion section). However, the use of DC cardioversion may be undesirable if the patient is a poor candidate for conscious sedation or if the patient is not willing to undergo DC cardioversion. In these situations, pharmacologic cardioversion may be attempted. Many class I and III antiarrhythmic agents have been evaluated for efficacy in placebo-controlled trials for conversion of AF or atrial flutter to normal sinus rhythm. The available agents with the most positive data for chemical conversion include IV ibutilide, oral propafenone, oral flecainide, oral and IV amiodarone, and oral dofetilide. This section will focus on ibutilide, propafenone, and flecainide.

IV ibutilide, a class III antiarrhythmic agent with potassium channel blocking and slow sodium channel enhancing effects, was the first agent that the U.S. Food and Drug Administration (FDA) approved for the termination of recent-onset AF and atrial flutter.[30] Ibutilide is administered as a 1-mg infusion for 10 minutes, followed by another 1-mg infusion for 10 minutes if the conversion has not occurred by 10 minutes after the first infusion. The conversion rate for recent-onset AF is 35% to 50%; the conversion rate is 65% to 80% in atrial flutter. In a retrospective study of hospital inpatients with either AF or atrial flutter, 50% of patients converted initially (41% conversion AF, 65% atrial flutter), but only 33% of patients left the hospital in sinus rhythm. If the duration of AF or atrial flutter before cardioversion was <15 days, significantly more patients remained in sinus rhythm at

discharge compared with patients who had AF or atrial flutter for more than 15 days before cardioversion.[30] As is the case with most class III antiarrhythmic agents, the main adverse effect is TdP, which occurred in ~4% of patients. Ibutilide should be avoided in patients with hypokalemia, hypomagnesemia, QT prolongation, and a low ejection fraction (<30%). Aside from the risk of TdP, therapy is well tolerated.[31–33]

Propafenone is a class Ic agent with β-blocking properties. When given in doses of 450 to 750 mg orally (600 mg was the most common dose), the initial conversion rate in patients with AF ranged from 41% to 57%. In contrast to ibutilide, no patients experienced ventricular arrhythmias (including TdP), but a risk of hypotension, bradycardia, and QRS prolongation was noted.[34–36]

Oral flecainide is another class Ic antiarrhythmic agent. In one study, 300 mg of oral flecainide converted 68% of patients to sinus rhythm within 3 hours and 91% of patients by 8 hours. The efficacy in atrial flutter has yet to be established. Sinus node dysfunction, prolongation of intraventricular conduction, dizziness, weakness, and gastrointestinal (GI) disturbances have been reported.[37,38]

A β-blocker or nondihydropyridine calcium channel antagonist should be administered ≥30 minutes before administering the Vaughan Williams class Ic agent to prevent a rapid ventricular response owing to 1:1 AV conduction during atrial flutter.[7] J.K. is not a candidate for these agents owing to his structural heart disease.

Electrical Conversion

Case 15-1, Question 10: J.K. received two doses of IV ibutilide. After the second dose, he converted to normal sinus rhythm for only 5 minutes, then returned to AF. J.K. is scheduled for electrical cardioversion in 6 hours. What is electrical cardioversion? How efficacious and safe is it?

DC cardioversion quickly and effectively restores 85% to 90% of patients with AF to normal sinus rhythm.[29] If DC conversion alone is ineffective, it can be repeated in combination with antiarrhythmic

drugs.[6,39] In one study, the success rate of electrical cardioversion was significantly higher in AF patients (duration of AF averaged 119 days) with ibutilide pretreatment (1 mg) compared with those without pretreatment (100% vs 72%; *P* = .001).[39] This is because ibutilide pretreatment lowered the energy requirement for atrial defibrillation by 27% (*P* = .001). TdP occurred in 3% of patients receiving ibutilide, all of whom had an ejection fraction <20%. Flecainide, propafenone, amiodarone, and dofetilide could also be considered for enhancing DC cardioversion.[6]

DC cardioversion is clearly indicated for patients who are hemodynamically unstable. A reason one may wish to avoid DC conversion is that anesthesia (short-acting benzodiazepine, barbiturate, or propofol) is required for the procedure.

Maintenance of Sinus Rhythm

Case 15-1, Question 11: J.K. is discharged after successful DC conversion. However, when he returns for a follow-up visit 2 weeks later, he is found to be in AF again. He again reports frequent palpitations. His physician would like to initiate an antiarrhythmic drug to maintain normal sinus rhythm. Which agent(s) would be the best option for this patient?

To choose the best antiarrhythmic agent for J.K., the efficacy and adverse effect profiles for each agent should be reviewed. Class Ia, Ic, and III antiarrhythmic drugs (see Tables 15-2 and 15-3) prevent the recurrence of AF. Flecainide, sotalol, dofetilide, and dronedarone are approved by the FDA for the maintenance of sinus rhythm. Propafenone and amiodarone are commonly used but Ia agents are not.

Flecainide and Propafenone

The class Ic agents flecainide and propafenone are effective in suppressing AF.[40–44] The efficacy rate may be as high as 61% to 92% for flecainide.[45,46] Flecainide and possibly other class Ic agents are proarrhythmic, especially in patients with structural heart

disease, and they should be avoided in such patients. Propafenone, a class Ic agent with β-blocking properties, is as efficacious as flecainide and is relatively safe in patients without ischemic heart disease and an ejection fraction >35%; it may be preferred in patients who require additional AV blockade to control ventricular response. In a direct comparison with flecainide (200–300 mg/day), propafenone (450–900 mg/day) was equally safe and effective. Over the course of 12 months, a similar percentage of patients (~12% in each group) did not have adequate control of their arrhythmia. Adverse events were comparable and occurred in 10.3% of patients on flecainide and 7.7% of patients on propafenone. Of all the adverse events noted, only one patient who was receiving propafenone developed a ventricular arrhythmia. Another 1-year comparative study of propafenone versus flecainide demonstrated similar efficacy, but this study showed a trend toward better tolerability in the flecainide group.[47,48]

Class III Agents

Case 15-1, Question 12: J.K. is to begin dofetilide today. He is admitted to the hospital for dofetilide initiation. Why would J.K. need to be admitted for dofetilide initiation? Is it necessary to initiate all antiarrhythmic medications in the hospital?

Class III agents (sotalol, dofetilide, amiodarone, and dronedarone) prolong refractoriness in the atria, ventricles, AV node, and accessory pathway tissue and can prevent recurrence of AF. All of these agents act by blocking potassium channels; however, sotalol also has additional β-blocking properties.[49–51] Both amiodarone and dronedarone block sodium channels and calcium channels and have antiadrenergic effects in addition to potassium channel blocking properties.[49,51]

Sotalol, Amiodarone, Dofetilide, and Dronedarone

The efficacy of sotalol in delaying the recurrence of AF was evaluated in a double-blind, placebo-controlled, multicenter, randomized trial that enrolled 253 patients with AF or atrial flutter.[52] The median times to recurrence were 27, 106, 229, and 175 days with placebo, sotalol 160 mg/day (divided into two doses), sotalol 240 mg/day (divided into two doses), and sotalol 320 mg/day (divided into two doses), respectively. Sotalol is contraindicated in patients with a creatinine clearance (CrCl) <40 mL/minute because the drug is largely renally cleared and can cause TdP in high concentrations. In a comparative study versus propafenone, sotalol was similarly effective in producing ≥75% reduction in AF recurrence (79% of patients on propafenone vs 76% on sotalol). Bradycardia, dizziness, and GI disturbances were the most common intolerable side effects.[53] Sotalol should not be used in patients with HFrEF owing to the negative inotropic effects of the drug. It may be useful as a first-line agent in patients with AF and concomitant underlying coronary artery disease or in patients with no cardiovascular disease.[6]

Amiodarone is more effective at maintaining sinus rhythm than sotalol and propafenone.[54] The Canadian Trial of Atrial Fibrillation (CTAF) compared the ability of low-dose amiodarone (200 mg/day) versus propafenone (450–600 mg/day) and sotalol (160–320 mg/day) to prevent recurrence of AF.[54] After a mean follow-up of 16 months, 35% of the amiodarone-treated patients had a recurrence of AF versus 63% in the combined group with sotalol and propafenone (P = .001). Because of its unusual pharmacokinetics and potential serious adverse effects (see **Table 15-3** and Case 15-7, Question 2), amiodarone is only recommended as a first-line choice for patients with HF, for which it has specific safety data, or for patients with significant left ventricular hypertrophy.[6] Amiodarone could also be used when other agents such as sotalol, propafenone, or dofetilide have failed.[6,55]

Dofetilide is an effective pharmacologic agent for conversion to, and maintenance of, normal sinus rhythm. Two clinical trials, EMERALD (European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide)[56] and SAFIRE-D

(Symptomatic Atrial Fibrillation Investigation and Randomized Evaluation of Dofetilide),[57] have shown conversion rates of 30% in patients with AF or atrial flutter receiving higher doses of dofetilide. Patients failing chemical conversion received electrical conversion. If this conversion succeeded, they were continued on dofetilide for 1 year. At 1 year, 60% of those converted were still in sinus rhythm with the 500-µg dose. Also, dofetilide appears to exert neutral effects on mortality rates in HF and post-MI patients.[58,59]

Dofetilide dose is based on the patient's CrCl; the doses are 500, 250, and 125 µg twice daily with CrCl >60, 40 to 60, and 20 to 39 mL/minute, respectively. Drug interactions pose a significant problem with dofetilide. Cimetidine, ketoconazole, prochlorperazine, megestrol, and trimethoprim (including in combination with sulfamethoxazole) inhibit active tubular secretion of dofetilide and can elevate dofetilide plasma concentrations.[49,60] Because the incidence of TdP is directly related to dofetilide plasma concentrations, concomitant use with these agents is contraindicated. Concomitant administration of dofetilide with verapamil or hydrochlorothiazide increases the incidence of TdP by an unclear mechanism and is contraindicated as well. Concurrent use of agents that can prolong the QTc interval is not recommended with dofetilide. Dofetilide also undergoes metabolism by the cytochrome P-450 CYP3A4 isoenzyme to a minor extent. Therefore, inhibitors of this isoenzyme (eg, azole antifungal agents, protease inhibitors, serotonin reuptake inhibitors, amiodarone, diltiazem, nefazodone, zafirlukast) should be coadministered with caution with dofetilide. Other agents that can potentially increase dofetilide levels (through inhibition of tubular secretion) include metformin, triamterene, and amiloride. Hence, these agents should be cautiously coadministered with dofetilide.[49,60]

Dofetilide is considered a first-line agent for patients with HFrEF or coronary artery disease, as the impact on mortality in this patient population is neutral.[6] Dofetilide can also be considered as a first-line agent for patients without cardiovascular disease but should be avoided in patients with severe left ventricular hypertrophy.[6]

Dronedarone is structurally and pharmacologically similar to amiodarone; however, it lacks iodine, and it has a much smaller volume of distribution than amiodarone. The lack of iodine may make dronedarone less likely to cause thyroid-related or other adverse effects.[51] Dronedarone has been shown to have modest efficacy in maintaining sinus rhythm when compared with placebo. The rate of recurrence of AF at 1 year is ~40%, and the number of days to recurrence is nearly doubled with dronedarone.[61] The major clinical trial evaluating dronedarone was the A PlaceboControlled, Double-Blind, Assess the Efficacy of Dronedarone for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA) study. The primary end point of ATHENA was a composite of death or cardiovascular hospitalization, and patients received either dronedarone 400 mg twice daily or placebo for at least 1 year.[62] The primary composite end point was significantly reduced from 39.4% with placebo to 31.9% with dronedarone. This reduction in the composite was completely attributable to the reduction in cardiovascular hospitalizations, most of which were related to AF recurrence. GI events were the most common type of adverse effect with dronedarone in this study. It should be noted that patients with recent decompensated HF or New York Heart Association (NYHA) class IV HFrEF were excluded from this trial. The exclusion of patients with severe or unstable HF was related to negative findings that led to the early discontinuation of the ANDROMEDA study.[63] ANDROMEDA was designed as a safety study to evaluate the impact of dronedarone on mortality in patients with HF. Patients admitted with NYHA class III or IV HFrEF were included in this study. The study was stopped early because of an approximate doubling in the risk of death with dronedarone as compared with placebo. Therefore, dronedarone is contraindicated in a patient with severe or recently decompensated HF. Based on the findings of the PALLAS study, dronedarone should be avoided in patients with permanent AF as well.[64] This study found that the rate of stroke, HF, and cardiovascular death was increased when dronedarone was used in this patient population. Dronedarone has also been compared

directly with amiodarone.[65] In this study, dronedarone was less effective than amiodarone but was less likely than amiodarone to cause thyroid, neurologic, skin, or ocular adverse effects. GI adverse effects were more common with dronedarone.[65] Dronedarone is appropriate as a first-line agent for patients with AF and concomitant coronary artery disease, and possibly left ventricular hypertrophy or in patients with no cardiovascular disease. Dronedarone should not be used in a patient with severe HF symptoms or a recent hospitalization for HF but may be used with mild, well-controlled HF.[6]

In view of J.K.'s HF, sotalol, propafenone, and flecainide would not be indicated. Although dronedarone may be better tolerated than amiodarone, it would be contraindicated because J.K. was recently admitted with decompensated HF. Therefore, the only available options for J.K. would be either dofetilide or amiodarone, both of which have proven safe in patients with HF. Selection between dofetilide and amiodarone could be based on renal function, the presence of any major drug interactions, or the desire to avoid adverse effects with amiodarone.

Dofetilide was approved with the requirement for in-hospital initiation because of the relatively high risk of TdP in clinical trials. ECG monitoring is required for patients being initiated on dofetilide for a minimum of 3 days in a properly equipped facility. The initial regimen is determined by the patient's estimated CrCl. The QTc interval must be measured (using a 12-lead ECG) 2 to 3 hours after the first dose and each subsequent dose while the patient is hospitalized. If the QTc interval increases by >15% or if it surpasses 500 milliseconds (>550 milliseconds in patients with ventricular conduction abnormalities) after the first dose, the dofetilide regimen should be reduced by 50%. If the QTc interval exceeds the above parameters any time after the second subsequent dose, dofetilide should be discontinued.

Sotalol may also be arrhythmogenic in high doses, and the risk of inducing TdP has prompted its manufacturer to mandate a minimum of 3 days of ECG monitoring in a properly equipped facility during therapy initiation as well. Further, during initiation and titration, QTc intervals should be monitored 2 to 4 hours after each dose. In fact,

most antiarrhythmic agents for AF should probably be initiated in the inpatient setting, except amiodarone owing to the low risk of proarrhythmia with this drug.[6]

STROKE PREVENTION

Antithrombotic therapy

Case 15-1, Question 13: J.K. is discharged from the hospital on dofetilide 500 µg twice daily, which is appropriate given his CrCl of 92 mL/minute. He has been doing fine for 2 weeks after discharge. Should J.K. remain on warfarin therapy? Could any other antithrombotic options be considered?

Patients with nonvalvular and valvular AF have a 5- and 17-fold increased risk for stroke compared with patients without AF, respectively.[3,4] Stroke can lead to death or significant neurologic disability in up to 71% of patients, with an annual recurrence rate as high as 10%.[66]

In three large, randomized trials, patients with nonvalvular AF benefited from antithrombotic therapy.[66–70] In the Stroke Prevention in Atrial Fibrillation (SPAF) study, both aspirin 325 mg/day and warfarin (titrated to an INR of 2.0–4.5) reduced the risk of stroke significantly with an acceptable level of hemorrhagic complications.[69] The results of SPAF II, a direct comparison of warfarin and aspirin, indicated that warfarin was more effective than aspirin in preventing stroke.[70] These results were verified by the Copenhagen Atrial Fibrillation, ASpirin, AntiKoagulation (AFASAK) study, which found warfarin to be significantly better than aspirin and placebo at preventing cerebral emboli and overall vascular deaths (cerebral and cardiovascular).[67] An oral direct thrombin antagonist (dabigatran) and oral factor Xa antagonists (rivaroxaban, apixaban, and edoxaban) are now available for stroke prevention in AF. These newer anticoagulant agents have been shown to have similar or better efficacy and safety for AF stroke prevention compared to warfarin.[71–73]

Dabigatran is approved by the FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF.[74] In the Re-

Ly trial, dabigatran 110 mg twice daily and 150 mg twice daily was compared with warfarin in patients with a $CHADS_2$ score of 1 or more (average $CHADS_2$ score of 2.1). The $CHADS_2$ score is a tool used to estimate stroke risk and was used prior to the CHA_2DS_2-VASc score. In this study, the lower dose of dabigatran was noninferior to warfarin for stroke prevention but was associated with less bleeding. High-dose dabigatran was superior to warfarin for stroke prevention but comparable in bleeding.[75] The most common nonbleeding adverse event in this study was GI upset. It should also be noted that dabigatran capsules should not be chewed or opened.

The three oral factor Xa inhibitors that are currently approved for the prevention of stroke and systemic embolus in patients with AF include rivaroxaban, apixaban, and edoxaban. Each of these agents has been compared directly to warfarin using fairly similar study designs.[71–73] Rivaroxaban and edoxaban were found to be noninferior to warfarin in stroke/systemic embolus prevention, whereas apixaban was found to be superior to warfarin in efficacy. Major bleeding occurred less frequently with edoxaban and apixaban and at a similar rate with rivaroxaban compared to warfarin. Although efficacy and safety of all the new agents differed when compared with warfarin, there are no direct comparisons between any of the newer antithrombotic options. As such, no firm conclusions can be drawn regarding the optimal agent to choose. However, in a patient who is perceived to have a high bleeding risk, it is reasonable to select apixaban or edoxaban, given the bleeding risk advantage of these agents relative to warfarin.[72,73]

Some differences between the newer agents could be considered when selecting an anticoagulant regimen for a patient. For example, each agent has different recommendations for use with kidney dysfunction. None of the newer oral agents should be used in patients with a CrCl <15 mL/minute. The “renal doses” of rivaroxaban (15 mg/day with CrCl of 15–49 mL/minute) and edoxaban (30 mg/day with CrCl of 15–50 mL/minute) were evaluated in the ROCKET AF and ENGAGE AF TIMI 48 studies, whereas the renal dose adjustment recommended for dabigatran (75-mg twice-

daily dose for those with a CrCl of 15–30 mL/minute) was based on extrapolated pharmacokinetic data.[71,73,76] Apixaban does not require dosage adjustment specifically based on a CrCl, but adjustment should occur if the patient has two or more high-risk characteristics (body weight 132.27 pounds [<60 kg], serum creatinine >1.5 mg/dL, or age >80 years). In addition, apixaban product information suggests that this reduced dose produces drug concentrations in patients with end-stage renal disease (ESRD) on intermittent hemodialysis, comparable to the normal dose used for those without renal dysfunction in clinical trials. This suggestion is based on pharmacokinetic data, and it is unclear whether patients with ESRD derive the same efficacy and safety with the reduced dose. Interestingly, edoxaban is less effective and should not be used when CrCl is >95 mL/minute. Therefore, edoxaban, apixaban, or rivaroxaban may be a more evidence-based option than dabigatran for a patient with poor kidney function, and edoxaban would be an inappropriate choice for the patient with very good kidney function.[71–74]

The drug interaction profiles of the oral direct thrombin inhibitor or oral factor Xa inhibitors are favorable compared to that of warfarin. All of the newer anticoagulant options interact with rifampin. Rivaroxaban and apixaban also interact with other strong inhibitors and inducers of both the P-glycoprotein and CYP 3A4 systems. Dabigatran interacts with inhibitors of P-glycoprotein (ketoconazole and dronedarone); however, no change in therapy is required unless the interacting drugs are used in a patient who also has a CrCl <50 mL/minute. At this time, no notable interactions have been identified with edoxaban other than the interaction with rifampin. Although the number of interactions with the newer anticoagulants is fewer than with warfarin, it will still be important to evaluate for the presence of interactions at therapy initiation and when the drug therapy regimen is changed. An advantage of dabigatran and the oral factor Xa antagonists is that these agents do not require frequent monitoring and dosage adjustment to assure an appropriate level of anticoagulation. A potential disadvantage is that it is often not possible to monitor the extent of anticoagulation in the setting of

bleeding or when an urgent procedure or surgery is needed. In the last few years, strategies for the reversal of these agents have become available. Dabigatran can be reversed by idarucizumab, a monoclonal antibody that binds to dabigatran, rendering the anticoagulant inactive.[77] The factor Xa antagonists, rivaroxaban and apixaban, can be reversed with andexanet alfa. Andexanet alfa is a recombinant inactive factor Xa molecule that binds to the Xa antagonist, preventing anticoagulation.[78] Data do not exist to support the use of andexanet alfa for other factor Xa antagonists (edoxaban, betrixaban). Therefore, the best available evidence suggests that concentrated blood factor products (four-factor prothrombin complex concentrates and Factor Eight Inhibitor Bypassing Activity (FEIBA)) may be options for reversing the effects of these agents.[78]

Male patients with a CHA_2DS_2-VASc score of ≥2 and female patients with a CHA_2DS_2-VASc of ≥3 should receive anticoagulant therapy for stroke prophylaxis.[18] Warfarin (INR target 2–3), dabigatran, rivaroxaban, apixaban, and edoxaban are all recommended as antithrombotic agents for stroke prophylaxis.[18] Dabigatran, rivaroxaban, apixaban, and edoxaban are preferred over warfarin, except in the setting of moderate-to-severe mitral stenosis or mechanical heart valve. If CHA_2DS_2-VASc is 1 in males and 2 in females and the patient does not have moderate-to-severe mitral stenosis or a mechanical valve, anticoagulant stroke prophylaxis could be considered but is not absolutely necessary. If a patient's INR is difficult to control on warfarin, a direct thrombin inhibitor or oral Xa antagonist could be used.[7] It should be noted that patients with AF and valvular disease should only be treated with warfarin for stroke prophylaxis as data with valvular AF are either unfavorable or unavailable with the newer agents in this patient population.[18]

Even though J.K. is in normal sinus rhythm at this time, in the AFFIRM trial, only 73% and 63% of patients randomized to rhythm control remained in sinus rhythm at 3 and 5 years, respectively.[19] As such, the use of an antiarrhythmic drug does not eliminate the risk of stroke, and in fact, patients may return to AF and not be aware they are no longer in normal sinus rhythm. J.K. has a CHA_2DS_2-VASc

score of 4 and does not appear to have any factors that would suggest a high bleeding risk (no recent history of GI bleeding, etc). Therefore, he should continue to receive anticoagulation for stroke prophylaxis.[18] Although J.K. is currently taking warfarin, he could be changed to any of the other available anticoagulants if after he learns about the other options, he feels it would align with his preferences and/or lifestyle.

CASE 15-2

QUESTION 1: M.P. is a 38-year-old female who has had frequent episodes of atrial flutter for the past 2 years. She has no other medical history and is taking metoprolol 50 mg twice daily. She does not want to take the drug any longer because it reduces her exercise tolerance.

Does the treatment of atrial flutter differ from the treatment of AF, and what is the role of radiofrequency catheter ablation for M.P.?

Atrial flutter is an arrhythmia that often reverts to sinus rhythm or progresses to AF. If atrial flutter is episodic, its underlying cause should be identified and treated if possible. If a patient remains in atrial flutter, the treatment goals (control of ventricular rate, return to normal sinus rhythm) are the same as those for AF. Similar agents and doses can be used to control the ventricular response. Chemical conversion, low-energy (<50 J) DC cardioversion, or rapid atrial pacing may acutely convert atrial flutter back to sinus rhythm, but the recurrence of atrial flutter is high.

Radiofrequency catheter ablation therapy could be used as a nonpharmacologic treatment for atrial flutter and AF.[6] With both atrial flutter and AF, an EP study is performed to identify whether ablation can be performed. Various sections of the atria and pulmonary veins (where they intersect with the atria) are probed with a catheter that delivers cardiac pacing. If an area is stimulated with pacing and an atrial ectopic or reentrant focus is recognized, that area could be ablated. Ablation destroys the tissue that is integral either to the initiation or to the maintenance of the arrhythmia by delivering electrical energy through electrodes on the catheter. If the focus of the arrhythmia is in the atrial tissue (typically for atrial flutter), then

the focus itself is ablated. This procedure is successful in 75% to 90% of cases and can be recommended for patients with atrial flutter who are drug-resistant or drug-intolerant or do not desire long-term therapy. In AF, an ectopic focus originating in the pulmonary veins can often initiate arrhythmia. In this case, circumferential ablation, in which a circle of ablated tissue is made around the pulmonary veins, is performed. Circumferential ablation does not prevent the ectopic impulses from the pulmonary veins from occurring; however, it does prevent the propagation of the impulse into the atria and may reduce the recurrence of AF. Recent data comparing ablation to antiarrhythmic drug therapy in patients with PAF suggest that ablation is more effective in preventing recurrence of AF than medications.[6,78]

Radiofrequency ablation therapy may be suitable for M.P. However, if exercise intolerance is her primary issue, this might be relieved by switching M.P. to another drug such as verapamil.

Paroxysmal Supraventricular Tachycardia

CLINICAL PRESENTATION

CASE 15-3

Question 1: B.J., a 32-year-old female, presents to the emergency department (ED) with symptoms of fatigue and palpitations. She has had similar episodes ~twice a year for the past 2 years but has not sought medical attention for them. She is in no apparent distress and has a temperature of 98.0 °F (36.66 °C), heart rate of 185 beats/minute, BP of 95/60 mm Hg, and respiratory rate of 12 breaths/minute. Her ECG (**Fig. 15-5**) shows regular rhythm with a heart rate of 185 beats/minute. The P waves cannot be found, and the QRS complex is 110 milliseconds (normal, <120 milliseconds). She has no past medical history of note.

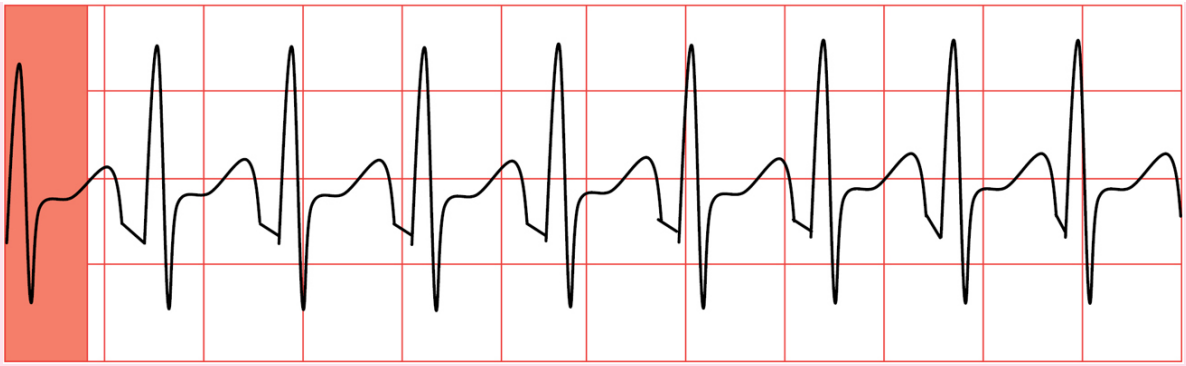


Figure 15-5 Supraventricular tachycardia. Note the lack of P waves, narrow QRS complexes, and rapid rate.

What is the clinical presentation of PSVT, and what are the consequences of this arrhythmia?

PSVT often has a sudden onset and termination. At the time of PSVT, the heart rate is usually 180 to 200 beats/minute. As illustrated by B.J., patients experience palpitations and often nervousness and anxiety. In patients with a rapid ventricular rate, dizziness and syncope can occur, and the rhythm may degenerate to other serious arrhythmias. Angina, HF, or shock may be precipitated by underlying severe atherosclerosis or left ventricular dysfunction, but this is not part of B.J.'s past medical history. There is no evidence that patients with episodes of PSVT are at an increased risk of stroke.

ARRHYTHMOGENESIS AND REENTRY

Case 15-3, Question 2: What is the arrhythmogenic mechanism of PSVT?

AV nodal reentry is the most common mechanism of paroxysmal supraventricular arrhythmias (see Fig. 15-2). Here AV nodal impulses are blocked in one of two directions in an antegrade fashion but when reaching the end, conducts in a retrograde fashion setting up a circular reentrant circuit. Reciprocating tachycardias occur when there is an accessory pathway for conduction of

impulses between the atria and ventricles, like with WPW syndrome, and PSVT results (**Fig. 15-6**).

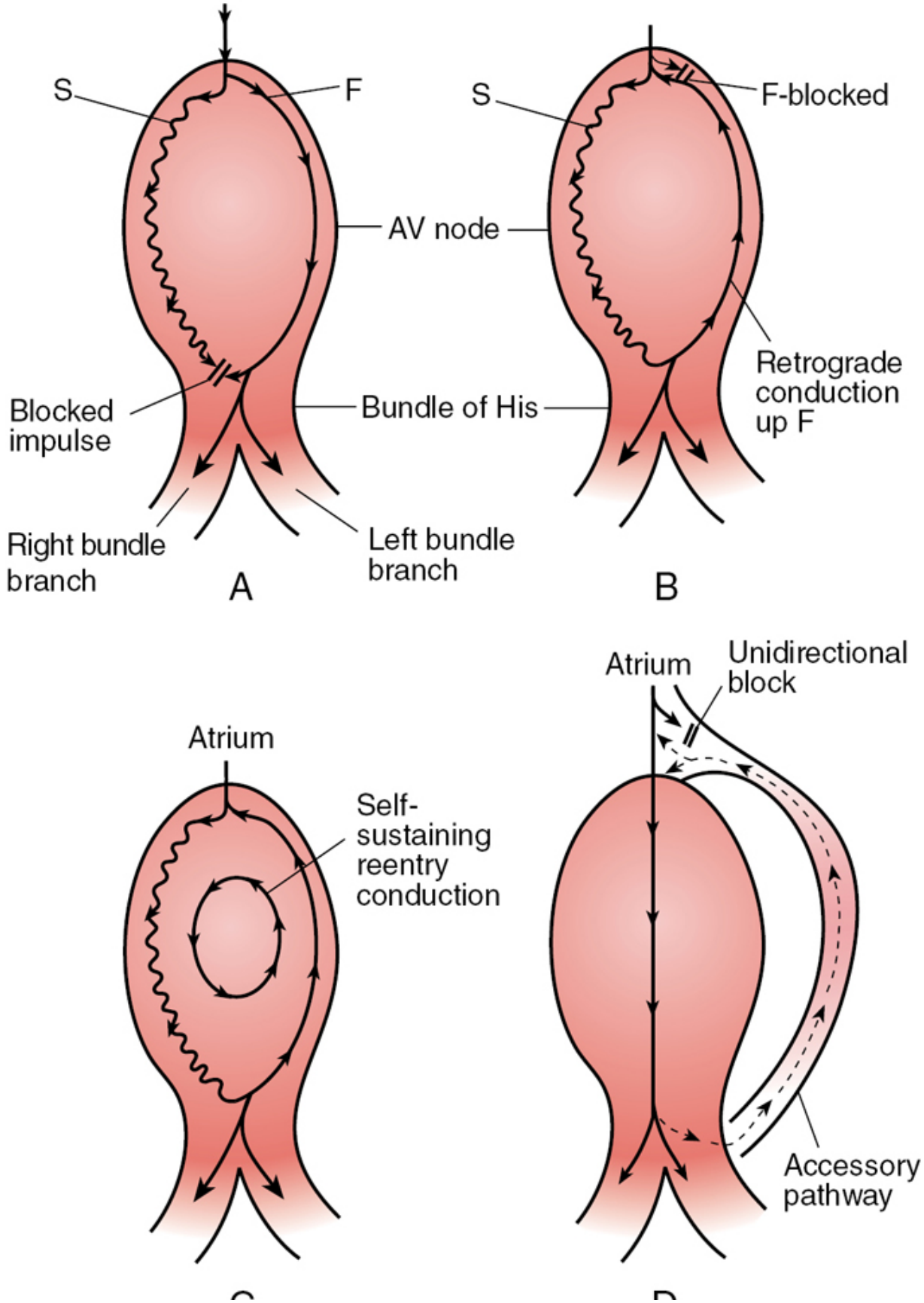

S
F
AV node
Blocked impulse
Bundle of His
Right bundle branch
Left bundle branch
A
S
F-blocked
Retrograde conduction up F
B
Atrium
Self-sustaining reentry conduction
Atrium
Unidirectional block
Accessory pathway

Figure 15-6 The atrioventricular (AV) node in paroxysmal supraventricular tachycardia and Wolff–Parkinson–White syndrome. A, A bifurcation of an impulse, one propagated fast and another slow. B, The slow impulse in (A) can send impulses in a retrograde fashion. C, The reentry from (A) to (B) can be self-sustaining. D, Normal impulse conduction through the AV node, but abnormal retrograde conduction up an accessory pathway, as would be seen in a patient with Wolff–Parkinson–White syndrome.

TREATMENT

Nondrug treatment

Valsalva Maneuver

CASE 15-3, QUESTION 3: B.J. tries the Valsalva maneuver, and her ventricular rate is reduced to 150 beats/minute; the other parameters are unchanged. She is given IV adenosine 6 mg, administered over 1 minute, with no effect on the PSVT rate. Another dose of adenosine 12 mg given over 1 minute has no effect. No side effects are noted from therapy. What treatment options can be used if B.J. is hemodynamically unstable? What is the Valsalva maneuver? What is the probable reason for B.J.'s unresponsiveness to adenosine? Are there any drug interactions that might diminish adenosine's effect?

Although her BP is low at 95/60 mm Hg, B.J. is maintaining an adequate perfusion pressure, so vagal maneuvers should be attempted first. Two common vagal techniques are pressure over the bifurcation of the internal and external carotid arteries and the Valsalva maneuver (forcible exhalation against a closed glottis, similar to bearing down to have a bowel movement). The increase in pressure induced by these maneuvers is sensed by the baroreceptors, causing a reflex decrease in sympathetic tone and an increase in vagal tone. The increase in vagal tone will terminate in 10% to 30% of cases.[79] If B.J. was hemodynamically unstable or becomes hemodynamically unstable, she should receive synchronized DC cardioversion.

Drug therapy

Adenosine

Because most PSVT episodes involve reentry in the AV node, drugs that block the AV node (negative dromotropic drugs) are generally effective. Adenosine, a purine nucleoside that exerts a transient negative chronotropic and dromotropic effect on cardiac pacemaker tissue,[80] is considered the drug of choice for the acute treatment of PSVT because of its rapid and brief effect. An initial 6-mg IV bolus is given; if this is unsuccessful within 2 minutes, it can be followed by one or two 12-mg IV boluses, up to a maximum of 30 mg. Because of its short half-life (9 seconds), adenosine should be administered as a rapid bolus (over 1–3 seconds), followed immediately by a saline flush. Adenosine begins to be metabolized immediately after entering the bloodstream; therefore, B.J.'s failure to respond is likely attributed to the prolonged (1 minute) infusion time.

Theoretically, adenosine may be ineffective or higher doses may be required in patients who are receiving theophylline because theophylline is an effective adenosine receptor blocker. Larger doses of other methylxanthines (caffeine, guarana) may also theoretically interact like theophylline. Conversely, concomitant use of dipyridamole may accentuate adenosine's effects because dipyridamole blocks the adenosine uptake (and subsequent clearance).[80]

Case 15-3, Question 4: B.J. is given 12 mg of adenosine IV for 2 seconds, followed by a 20-mL normal saline flush. Thirty seconds later, she experiences chest tightness and pressure. What is the explanation for these symptoms?

B.J. is experiencing a common side effect of adenosine. Patients receiving adenosine should be warned that they may feel transient chest heaviness, flushing, or a feeling of anxiety. Shortness of breath and wheezing may be observed in patients with asthma. The denervated heart of the patient who has undergone heart transplant is particularly sensitive to adenosine; therefore, lower doses of adenosine should be used.

Calcium Channel Blockers

Case 15-3, Question 5: B.J. is still in PSVT. What other acute therapeutic options should be considered at this time?

Nondihydropyridine calcium channel blockers, verapamil, and diltiazem can be used in patients with PSVT. Verapamil (5–10 mg or 0.075–0.15 mg/kg IV given over 2 minutes) achieves peak therapeutic effects in 3 to 5 minutes after dosing and can be repeated at 10- to 15-minute intervals to a maximal dose of 20 mg if needed. The elderly should receive the verapamil infusion over 3 minutes to minimize the risk of adverse events. Diltiazem is given as a 0.25-mg/kg IV bolus over 2 minutes, and a second bolus of 0.35 mg/kg can be given 15 minutes later if the effect is inadequate. Both of these calcium channel blockers have an 85% conversion rate.[80] However, verapamil should not be used in patients with wide complex tachycardia of unknown origin because it may lead to hemodynamic compromise and potentially VF. β-Blockers and digoxin can be used if calcium channel blockers and adenosine fail.

Case 15-3, Question 6: B.J. is given 5-mg IV verapamil, followed by an additional 5 mg 10 minutes later. She converts to normal sinus rhythm 3 minutes after the second dose. Because she has experienced symptoms that could be attributed to PSVT in the past, she may be a candidate for chronic therapy to slow conduction and increase refractoriness at the AV node. Which agents have been evaluated for this indication? Is there a role for radiofrequency catheter ablation therapy for PSVT?

Radiofrequency catheter ablation is frequently used as a definitive treatment for PSVT. EP testing is used to determine the location of the reentrant tract, which then can be ablated, thereby interrupting accessory pathways and reentrant circuits. This treatment approach is potentially curative and is performed by an electrophysiologist. Patients who are not candidates for ablation, or who do not wish to undergo the procedure, can receive medications on a chronic basis. PSVT is managed with agents that slow conduction and increase

refractoriness in the AV node, thereby preventing a rapid ventricular response. These include oral verapamil, diltiazem, β-blockers, or digoxin. Class Ic and III agents are used occasionally to slow conduction and increase refractoriness of the fast bypass tract to prevent triggering impulses such as premature atrial and ventricular contractions.

B.J. has had a few episodes of PSVT in the past and may be a candidate for curative therapy with ablation. Alternatively, because she responded to IV verapamil, if she did not want to undergo ablation, oral sustained-release (SR) verapamil could be prescribed at a dosage of 240 mg/day.

Wolff–Parkinson–White Syndrome

CASE 15-4

Question 1: M.B., a 35-year-old male, presents to the ED with a chest palpitations for 4 hours with an intermittent feeling of almost passing out (presyncope). M.B.'s vital signs are BP, 96/68 mm Hg; pulse, 226 beats/minute, irregular; respiratory rate, 15 breaths/minute; and temperature, 98.7 °F (37.06 °C). A rhythm strip confirms AF, with a QRS width varying from 0.08 to 0.14 seconds. To control the ventricular rate, 10 mg of IV verapamil is administered over 2 minutes. Within 2 minutes of completing the infusion, VF is noted on the monitor. M.B. is defibrillated, and normal sinus rhythm is restored. A subsequent ECG demonstrates a P-R interval of 100 milliseconds (normal, 120–200 milliseconds) and delta waves, compatible with WPW. He relates a past medical history of many similar self-terminating episodes since he was a teenager but he has no atherosclerotic heart disease or HF. He took an unknown medication 5 years ago that decreased the occurrence of the palpitations, but he stopped taking it because of side effects.

What is WPW syndrome?

WPW is a preexcitation syndrome in which there is an accessory bypass tract connecting the atria to the ventricles (Fig. 15-6). An impulse can travel down this pathway and excite the ventricle before the expected regular impulse through the AV node arrives. If there is antegrade conduction over the bypass tract while the patient is in normal sinus rhythm, the ECG will demonstrate a short P-R interval

(<100 milliseconds), a delta wave that represents a fused complex from preexcitation, and the regular QRS complex after AV conduction. PSVT and AF occur in these patients at a higher incidence than in the general population of the same age.[81–83] Similar to M.B., the rapid heart rate experienced during the tachycardia may cause palpitations, light-headedness, and fatigue. When patients with WPW develop AF, there is a danger that the rapid atrial impulses will be conducted directly to the ventricle through the bypass tract, causing a rapid ventricular rate that may evolve into VF. Verapamil (like diltiazem, β-blockers, adenosine, and amiodarone) can increase this risk by increasing the effective refractory period of the AV node and indirectly reducing the effective refractory period in the bypass tract.[83]

Case 15-4, Question 2: Why did verapamil cause VF in M.B.? What therapies would be appropriate for M.B., and what drugs should be avoided?

Because M.B. had AF, the rapid atrial impulses were conducted directly down the bypass tract to the ventricle, causing VF.

The antiarrhythmic drugs used to chemically convert patients with AF who have WPW, such as M.B., include procainamide, propafenone, flecainide, and dofetilide. DC cardioversion is an option for more emergent conversion of AF in patients with WPW and hemodynamic instability. Radiofrequency ablation of the bypass tract is curative for many patients with WPW and is indicated for people who maintain preexcitation during exercise stress testing, a shortest preexcited RR interval <250 milliseconds, symptoms like syncope of palpitations, or preexisting structural heart disease. M.B. has symptoms associated with AF in WPW and should undergo evaluation from a cardiologist to determine if ablation is appropriate at this time.[81–83]

Further therapy for M.B. may not be useful at this time. However, if he has recurrent AF or other symptomatology associated with WPW, radiofrequency catheter ablation could be indicated.

CONDUCTION BLOCKS

Various arrhythmias can result from blockage of impulse conduction. These can occur above the ventricle, such as first-, second-, and third-degree (complete) AV blocks. Others, such as right or left bundle branch block (RBBB or LBBB) and trifascicular block, originate below the bifurcation of the His bundle.[84]

CASE 15-5

QUESTION 1: H.T., a 63-year-old male with a history of MI treated with metoprolol tartrate 75 mg twice daily, was admitted to the hospital 12 hours ago with a low pulse rate of 50 beats/minute, BP of 89/57 mm Hg, severe dizziness, and low exercise tolerance. On admission, the rhythm strip is shown in **Figure 15-7** (Wenckebach or type I second-degree AV block).

How is second-degree AV block different from first- or third-degree AV block? Which one is the most severe?

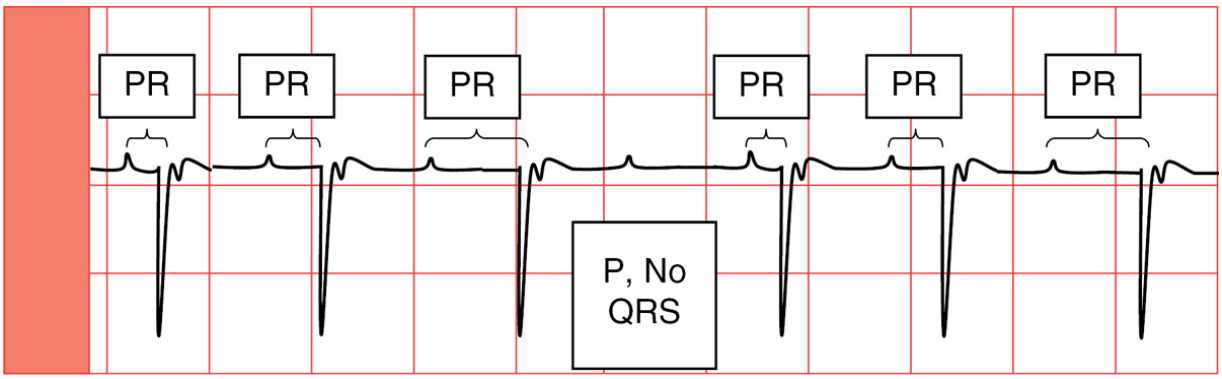


Figure 15-7 Second-degree atrioventricular block type I. The P–R interval progressively prolongs until a QRS complex is not conducted and then the cycle repeats.

First-degree AV block usually is asymptomatic. The ECG will show P waves with a prolonged P-R interval (normal, <200 milliseconds), but each P wave is followed by a normal QRS complex. First-degree AV block is a common finding in patients taking β-blockers, digoxin, nondihydropyridine calcium channel blockers, or other drugs that slow AV conduction (negative dromotropic drugs).

Second-degree heart block consists of two types. Mobitz type I (Wenckebach) is characterized by progressive lengthening of the P-R interval with each beat until an impulse is not conducted; the cycle then starts over again. Mobitz type II (**Fig. 15-8**) impulse conduction is blocked in a fixed, regular pattern (eg, 3:1 block, in which for every three P waves, only one is conducted but each available P-R interval is fixed). A major difference is that Mobitz type I can be induced by negative dromotropic drugs but not Mobitz type II.

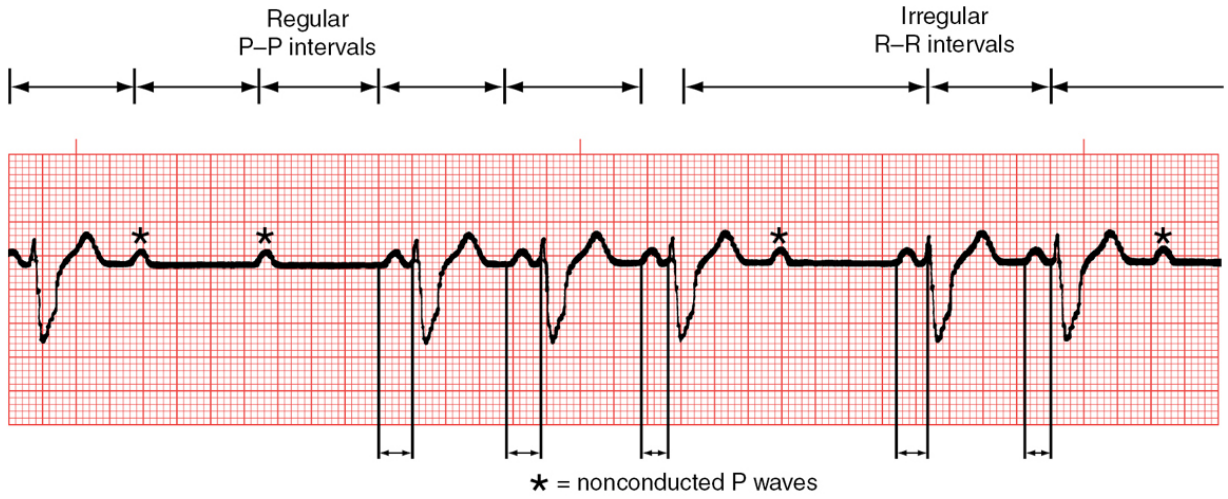


Figure 15-8 Sinus rhythm with second-degree AV block, type II; note constant PR interval. (Reprinted with permission from Smeltzer SC, Bare BG. *Textbook of Medical-Surgical Nursing*. 9th ed. Lippincott Williams & Wilkins; 2000.)

Third-degree heart block (complete heart block) occurs when none of the impulses from the SA node are conducted to the ventricles. During the third-degree block, the ventricle must develop its own pacemaker (escape rhythm), which may be too slow to provide adequate cardiac output, causing the patient to become symptomatic. A mechanical pacemaker is needed for the treatment of permanent third-degree AV block. AV blocks can be caused by negative dromotropic drugs, acute MI, amyloidosis, and congenital abnormalities.[84] Both second and third-degree AV blocks are usually symptomatic ranging from dizziness to unconsciousness. Second- or third-degree AV block with an acute inferior zone (bottom of the

ventricle) MI usually resolves on its own over time, but symptomatic cases can be acutely treated with aminophylline.[84]

Atropine

Case 15-5, Question 2: How should H.T.'s heart block be treated?

H.T. is experiencing a Wenckebach rhythm with compromised hemodynamics and symptoms. Metoprolol should be held and atropine 0.5 mg IV bolus (maximum 2 mg), β-agonists (isoproterenol, dobutamine, and epinephrine), or a temporary pacemaker can acutely increase the heart rate. Once the issue resolves, the dose of metoprolol could be reduced or β-blockers could be stopped altogether, but this could attenuate the mortality benefits postmyocardial infarction. Therefore, according to the guidelines, a permanent pacemaker should be inserted to control the heart rate while maintaining metoprolol therapy.[84]

VENTRICULAR ARRHYTHMIAS

Recognition and Definition

Impulses from ventricular ectopic foci or reentrant circuits generate wide QRS complexes leading to PVCs (**Fig. 15-9**). Three consecutive PVCs that have the same shape usually are defined as monomorphic VT, which can be nonsustained or sustained.

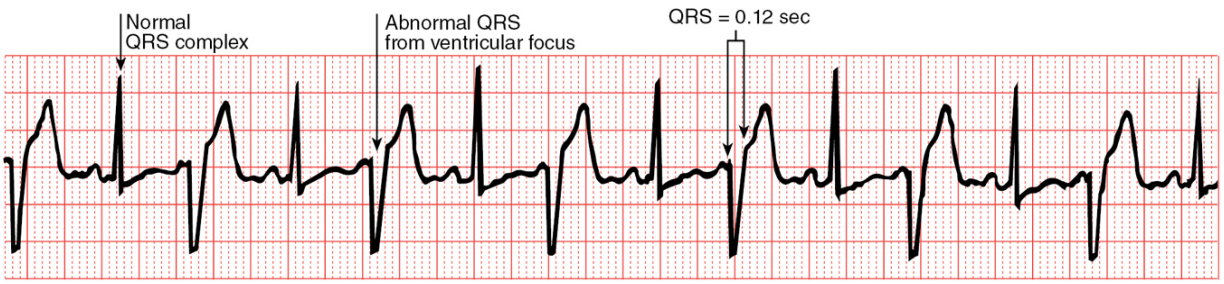


Figure 15-9 Premature ventricular contraction. Every other beat is a premature ventricular (ectopic) contraction.

Nonsustained ventricular tachycardia (NSVT) (**Fig. 15-10**) is commonly defined as three or more consecutive PVCs lasting <30 seconds and terminating spontaneously. Sustained VT (SuVT) is defined as consecutive PVCs lasting more than 30 seconds, with a rate usually in the range of 150 to 200 beats/minute. P waves are lost in the QRS complex and are indiscernible. SuVT (**Fig. 15-11**) is a serious development because it can degenerate into VF. VF (see **Fig. 15-12**) is characterized by irregular, disorganized, rapid beats with no identifiable P waves or QRS complexes. It is thought to be triggered by multiple reentrant wavelets in the ventricle. There is no effective cardiac output or pulse in patients with VF.[85,86]

Figure 15-10 Nonsustained ventricular tachycardia. (Reprinted with permission from MacDonald MG, Seshia MMK, Mullet MD. *Avery's Neonatology Pathophysiology & Management of the Newborn*. 6th ed. Lippincott Williams & Wilkins; 2005.)

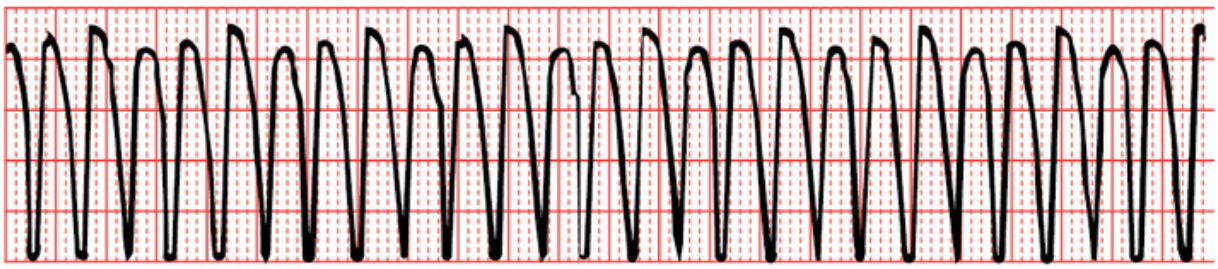


Figure 15-11 Sustained ventricular tachycardia.

Figure 15-12 Ventricular fibrillation.

Etiology

Common factors that cause VT or VF are ischemia, the presence of organic heart disease, exercise, metabolic or electrolyte imbalance (eg, acidosis, hypokalemia or hyperkalemia, hypomagnesemia), or drugs (digitalis, sympathomimetic amines, antiarrhythmic drugs). It is essential to identify and remove any treatable cause (eg, metabolic or electrolyte imbalance and proarrhythmic drugs) before initiating antiarrhythmic drug therapy.

Evaluation Potentially Serious Ventricular Arrhythmias

An episode of life-threatening ventricular arrhythmia (ie, SuVT, TdP, VF) carries a significant risk of morbidity and mortality. Adequate documentation of the arrhythmia and its suppression by either drugs or a mechanical device are essential. The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines for ventricular arrhythmias specifies that patients suspected of having, or documented to have, symptoms of a life-threatening arrhythmia (eg, syncope, out-of-hospital cardiac arrest) should be admitted to the hospital and evaluated.[85] A 12-lead ECG should be acquired in all patients undergoing evaluation for the presence of ventricular arrhythmias, prior MI (pathologic Q-waves), and long QTc intervals. Echocardiography is also conducted to detect the presence of ventricular wall thickness and structure and to assess valve function and ejection fraction. Ambulatory rhythm

monitoring and EP studies are two additional approaches used to evaluate the arrhythmia and the effectiveness of therapy.[85]

AMBULATORY MONITORING AND ELECTROPHYSIOLOGY STUDIES

Small ECG rhythm recorders called Holter monitors or Loop Recorders are worn by patients, and electrodes are attached to the chest. For more frequent arrhythmia occurrences, 48-hour Holter monitoring is an option. For less frequent arrhythmias, a 30-day Loop recorder can be used instead. Whenever a patient experiences symptoms, they press a button on the recorder and a record of the patient's heart rhythm at the time of the event is recorded. In both cases, the patient logs the symptoms they felt around the time of events.[85]

ELECTROPHYSIOLOGIC STUDIES

EP studies represent another approach to evaluating ventricular arrhythmias, especially in patients with infrequent ventricular arrhythmias that may be missed by ambulatory monitoring.[85] EP testing uses an inserted temporary pacemaker to try to induce arrhythmias which can be important in assessing the need for an implantable cardioverter-defibrillator (ICD).

Premature Ventricular Contractions and Nonsustained Ventricular Tachycardia

CASE 15-6

QUESTION 1: A.S., a 56-year-old female, is admitted to the critical care unit (CCU) with a diagnosis of acute anterior wall MI. Her vital signs are BP, 115/75 mm Hg; pulse, 85 beats/minute; and respiratory rate, 15 breaths/minute. Auscultation of the heart reveals an S_3 gallop. Her electrolytes include potassium (K) 3.8 mEq/L, and magnesium (Mg) 1.2 mEq/L. Otherwise, her examination is within normal limits. Two days later, an echocardiogram estimates her ejection fraction to be 35% (normal, >50%). During her stay in the

CCU as well as the step-down unit, multiple PVCs (15/minute) were noted on the bedside monitor.

Should A.S.'s multiple PVCs be treated with a class I antiarrhythmic drug?

PVCs are a benign, natural occurrence, even in a healthy heart, and are not an indication for class I or class III drug therapy even in patients with other cardiac diseases. However, the presence of frequent PVCs may be associated with concomitant ischemia and impaired left ventricular function, and this should be further explored.[85,87]

TYPE IC ANTIARRHYTHMIC AGENTS

The National Institutes of Health launched the Cardiac Arrhythmia Suppression Trial (CAST)[88,89] to assess the benefit of PVC suppression in survivors of MI. The CAST was a prospective, randomized, placebo-controlled trial that evaluated the class Ic agents flecainide and encainide versus placebo. Ten months after initiation of the study, CAST was discontinued because total mortality in the flecainide and encainide groups was 8.3% compared with 3.5% in the placebo group.[88] Because the patients enrolled in CAST were asymptomatic and at low risk for the development of SuVT, the risk from drug toxicity exceeded the benefit. Thus, the decision to avoid using a class I antiarrhythmic medication to treat A.S.'s PVCs was a sound one.[88,89]

CASE 15-6, QUESTION 2: What alternatives to class I antiarrhythmic drugs should be considered for A.S.?

A-BLOCKING AGENTS

Since A.S. has had an MI, β-blockers have proven benefits. In pooled analyses of numerous trials evaluating β-blockers in MI, ~20% reductions in the risks of reinfarction and cardiac arrest resulted (see Chapter 13, Acute Coronary Syndrome).[90–92] β-Blockers can modestly suppress PVCs in many patients, but only 10% to 15% of them achieve >90% PVC suppression.

In addition, because her ejection fraction is <40%, β-blockers, ACE inhibitors or angiotensin-receptor blockers (with or without neprilysin inhibitor), and aldosterone receptor antagonists—a drug from each class should be given to reduce her risk of overall mortality and Sudden Cardiac Death (SCD).[85]

CASE 15-6, QUESTION 3: While receiving carvedilol 25 mg twice daily, lisinopril 40 mg daily, and eplerenone 25 mg daily for 6 days, A.S. begins to develop nonsustained runs of VT intermingled with the frequent PVCs. The NSVT causes some palpitations but no other symptoms. Are there any additional drugs that should be added to the regimen as a result?

AMIODARONE AND RANOLAZINE

NSVT has a greater risk of inducing SuVT or VF than would PVCs, and this requires further workup and potential therapy.

In high-risk patients with MI who are not candidates for β-blockade, alternative antiarrhythmic therapy with amiodarone can be considered.[93,94] Amiodarone is a class III antiarrhythmic agent but also has antiadrenergic, class I, and class IV activities. However, given that cumulative exposure to this drug can result in damage to multiple organs, caution should be exercised before using it for PVC suppression or NSVT. An evaluation of amiodarone in post-MI patients with frequent PVCs (≥10/hour) or at least one run of VT was conducted in the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT).[93] In this trial, amiodarone significantly reduced the incidence of VF or arrhythmic death by 48.5% compared with placebo. Arrhythmic death alone was reduced by 32.6%, and all-cause mortality was reduced by 21.2%, but these differences were not statistically significant.

Similarly, the European Myocardial Infarct Amiodarone Trial (EMIAT) evaluated MI survivors with a reduced ejection fraction (<40%).[94] Amiodarone significantly reduced arrhythmic deaths by 35% compared with placebo, but no difference in mortality (13.86% with amiodarone vs 13.72% with placebo) was seen.

Ranolazine is a novel antianginal drug that does not reduce BP or heart rate but like amiodarone, possesses both class I and III

antiarrhythmic mechanisms. It is a much safer option than amiodarone for long-term administration. Unfortunately, some trials found no antiarrhythmic benefits whereas others found reductions in VT occurrence but not for SCD.[85]

Ranolazine would be a reasonable additional option for A.S.'s NSVT and frequent PVCs but only if she would benefit from an additional antianginal drug. Although amiodarone might provide more potent antiarrhythmic benefits than ranolazine, given the asymptomatic nature of these NSVT events, the adverse event profile of amiodarone would preclude its use in this patient. However, if the β-blocker could not be used, substituting amiodarone would be reasonable for A.S. Of course, if the patient has hypokalemia and hypomagnesemia, treating these underlying triggers for arrhythmias is worthwhile, but using these therapies just to attempt to suppress NSVT or PVCs is not successful and is not warranted.[85]

Catheter ablation

A better option for A.S. might be the use of ablation. The most commonly employed technique involves activation mapping, where electrophysiologists maneuver catheters to target the precise PVC origin in the heart, which is subsequently heated (radiofrequency ablation) or frozen (cryoablation) destroying the foci.[86–88] Catheter ablation is not without risk but has been shown to abolish PVCs in 74% to 100% of patients in numerous studies.[86–88] Catheter ablation is indicated for patients with reversible left ventricular dysfunction associated with frequent PVCs/NSVT, who have failed, did not tolerate, or declined medical treatment.[87]

A.S. should see an electrophysiologist to determine whether ablation is an option and to be risk stratified for SCD risk. If the risk of SCD is sufficiently high, an ICD should be placed.

Sustained Monomorphic Ventricular Tachycardia

TREATMENT

CASE 15-7

QUESTION 1: S.L., a 64-year-old female, presents to the ED with a palpitations. Her medical history includes hypertension controlled with a diuretic and an inferior wall MI 6 months ago. She is pale and diaphoretic but able to respond to commands. Her vital signs are weight, 138.89 pounds (63 kg); BP, 95/70 mm Hg; pulse, 145 beats/minute; and respiratory rate, 10 breaths/minute. When telemetry monitoring is established, S.L. is found to be in SuVT (Fig. 15-11). S.L.'s echocardiography (6 months earlier) revealed a left ventricular ejection fraction (LVEF) of 32%.

How should she be treated?

Acutely, S.L. could either receive an IV antiarrhythmic drug or undergo DC cardioversion to rapidly convert the patient back to sinus rhythm. Only patients who are hemodynamically stable should receive the antiarrhythmic option while the electrical cardioversion option can be used in either case although a short-acting benzodiazepine (eg, midazolam) should be administered before undergoing DC cardioversion.

Antiarrhythmic agents

Most hemodynamically stable patients with SuVT should receive IV procainamide as first-line therapy with IV amiodarone or sotalol reserved for refractory or recurrent cases.[95] In the randomized, open-label PROCAMIO (PROCainamide-AMIOdarone) trial, patients with SuVT received intravenous procainamide (10 mg/kg/20 minutes) or amiodarone (5 mg/kg/20 minutes). The primary end point (incidence of major cardiac adverse events within 40 minutes) occurred in 9% of procainamide and 41% of amiodarone patients (P = .006), and VT terminated within 40 minutes 67% of procainamide and 38% of amiodarone patients (P = .026).[95]

Procainamide is optimally loaded at 10 to 17 mg/kg infused at 20 to 50 mg/minutes. IV amiodarone should be loaded as a 150-mg dose for 10 minutes, followed by a 6-hour infusion at a rate of 1 mg/minute, and finally a 0.5-mg/minute infusion for 18 hours. Prolonged amiodarone infusions must be in D5W, not normal saline or lactated ringers, and must be in glass or polyolefin bags, not

polyvinyl chloride parenteral bags. For recurrent or resistant arrhythmias, supplemental infusions of 150 mg can be repeated every 10 minutes, up to a maximal total daily IV dose of 2.25 g.[125] IV sotalol 1.5 mg/kg should be infused over 5 minutes.[85] IV sotalol is approximately dose-equivalent to the oral formulation because an IV dose of 75 mg equals an 80-mg oral dose.[85] Commonly seen adverse effects for all three antiarrhythmic agents include hypotension, bradycardia, and AV block, which can be attenuated by slowing the drug infusion rate, but this can also reduce their efficacy. The propensity of sotalol to induce TdP is covered later in this chapter, but QTc interval monitoring after the infusion is important.

If this is unsuccessful and the cardiologist determines that the patient meets the criteria for idiopathic VT without structural heart disease, then intravenous β-blockers or verapamil can be utilized. Additionally, if the cardiologist determines or it is known that the patient has one of many genetically determined arrhythmia syndromes, then the specific therapy for that particular syndrome can be used (such as the selective use of quinidine in Brugada syndrome). Given the number of these syndromes and the complexity associated with their determination, they are outside the scope of this chapter but can be found within the ACC/AHA/HRS ventricular arrhythmia guidelines. A team-based approach to care is essential in complex arrhythmias with the pharmacist guiding the safe use of the drugs (drug dosing, interactions, and incompatibilities) and conducting drug monitoring.[85] S.L. received a 600-mg loading dose of procainamide over 30 minutes and converted back to normal sinus rhythm. She remains on a maintenance infusion of 2 mg/minutes while chronic therapeutic options are considered.

Implantable Cardiac Defibrillators

Case 15-7, Question 2: The next day, S.L. experiences another run of VT lasting about 2 minutes. The cardiology consult service has recommended the placement of an ICD. What is an ICD, and how does it work?

Transvenous or subcutaneous ICDs are devices implanted under the skin with wires or patches that are advanced or attached so they are in direct contact with the ventricular myocardium. The ICD is composed of a pulse generator, sensing and pacing electrodes, and defibrillation coils. The pulse generator consists of a microprocessor, a memory component capable of storing ECG data, a high-voltage capacitor, and a battery. The microprocessor controls the analysis of cardiac rhythm and delivery of therapy.[96,97] When NSVT is detected and then terminates, the ICD will turn on a pacemaker to pace at a rapid rate to overdrive and therefore suppress the ectopic foci. This can prevent the subsequent event (which could be SuVT or VF from arising). If SuVT or VF is detected, the device charges and then induces a period of asystole by shocking it, which hopefully restores normal sinus rhythm. Defibrillation threshold is classified as the minimum amount of energy needed to successfully defibrillate the heart and restore normal sinus rhythm.

Multiple clinical trials have proven the superiority of ICD treatment over antiarrhythmic therapy for the prevention of SCD.[85] ICD therapy is indicated for (a) survivors VF or hemodynamically unstable SuVT; (b) patients with LVEF ≤35% caused by a prior MI who are ≥40 days after the event and are in NYHA functional class II or III; (c) patients with LVEF ≤30% caused by prior MI who are ≥40 days after the event and are in NYHA functional class I; (d) patients experiencing spontaneous SuVT in conjunction with structural heart disease, regardless of hemodynamic stability; (e) hemodynamically compromised patients with electrophysiology study–induced SuVT or VF associated with syncope of undetermined origin; (f) patients with LVEF ≤35% associated with nonischemic dilated cardiomyopathy and are in NYHA functional class II or III; and (g) patients with LVEF ≤40% in conjunction with NSVT secondary to prior MI, who experience SuVT or inducible VF at EP study.[85]

Although ICDs have been shown to improve survival in select patient populations, the benefit may be offset by the diminished quality of life associated with painful shocks, increased mortality compared with ICD patients who do not require shocks, and incomplete protection from the occurrence of SCD (5% of patients

fail to respond).[98–102] In recent years, investigators have examined various approaches to reducing the frequency of ICD shocks. Antiarrhythmic medications and prophylactic catheter ablation have been shown to reduce the incidence of ICD firing.[98–102]

Clearly, S.L. should have an ICD implanted for the category (d) above. An MI meets the definition of structural heart disease (as does HF and left ventricular hypertrophy). It is her best chance for prolonging long-term survival.

Amiodarone

Case 15-7, Question 3: S.L.'s cardiologist would like to start amiodarone as adjunctive therapy because S.L. has expressed concern about the number of ICD discharges that may occur after ICD placement. If S.L. is to be treated with amiodarone, how should it be initiated and monitored?

Although the ICD helps the patient live longer than antiarrhythmic drugs, they are commonly used together. ICD shocks are exquisitely painful and can reduce the quality of life or even cause generalized anxiety and agoraphobia when the shock occurs too frequently.

The OPTIC (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients) trial enrolled 412 patients with an LVEF <40% who had inducible VT or VF, prior history of SuVT, VF, or cardiac arrest, or syncope of unknown cause with VF or VT. The effect of amiodarone plus β-blocker (metoprolol, carvedilol, or bisoprolol) compared with sotalol or β-blocker alone on the primary end point, the first occurrence of any shock delivered by the ICD, was assessed for a median of 359 days. One-year shock rates were 10.3%, 24.3%, and 38.5%, respectively, in amiodarone/β-blocker–treated patients, sotalol-treated patients, and β-blocker–treated patients, respectively. Of note, adverse effects such as pulmonary toxicity, thyroid effects, and symptomatic bradycardia contributed to an 18.2% discontinuation rate for amiodarone at 1 year. However, longer-term studies assessing the safety and efficacy of amiodarone for secondary prophylaxis showed higher rates of VT recurrence and

major adverse effects, compared with placebo.[121,122] Dofetilide[123] (off-label use) and the combination of mexiletine and amiodarone have shown reductions in recurrences of SuVT in other studies.[99]

Amiodarone exhibits properties of classes I, II, III, and IV antiarrhythmic agents. Although it has class II effects on the heart, amiodarone is virtually devoid of antiadrenergic effects outside the heart and is not contraindicated in patients with asthma. The antiadrenergic effects arise from inhibition of adenylate cyclase, the enzyme that catalyzes the production of the second-messenger product cyclic adenosine monophosphate.[2]

Because of the extremely long half-life of amiodarone, loading doses are used to accelerate the onset of the drug effect. The OPTIC trial used a loading dose of oral amiodarone 400 mg, given twice daily for 2 weeks, followed by a daily dose of 400 mg for the next 4 weeks, and a daily maintenance dose of 200 mg thereafter.[99] A concentration–effect relationship is hard to determine for amiodarone, given its complex pharmacokinetics.

Amiodarone has many serious adverse effects involving a variety of organ systems, the most serious and life-threatening of which is pulmonary toxicity. Amiodarone-induced pulmonary toxicity (AIPT) has been shown to account for 11% of the sum total of all reported adverse events associated with this agent.[103] AIPT presents as an acute process or a chronic condition that develops several months after starting amiodarone therapy. The pathophysiologic mechanism for AIPT has not been fully elucidated but may involve (a) heightened extracellular expression of β-hexosaminidase; (b) imbalance between T-helper 1 and 2 cells, leading to a maladaptive immune response; (c) increased tumor necrosis factor-α activity; and (d) angiotensin-mediated apoptotic effects of amiodarone on alveolar epithelial cells. It has been suggested that higher doses of amiodarone, older age, and preexisting pulmonary disease may predispose patients to develop AIPT. However, AIPT has been shown to occur after patients received low doses of amiodarone (200 mg/day). Manifestations of chronic AIPT include cough, dyspnea, impaired diffusion capacity of carbon monoxide, infiltrates on chest radiograph, weight loss, and fever. In contrast, patients presenting

with acute AIPT experience rapid decline in respiratory function, potentially culminating in the development of acute respiratory distress syndrome (ARDS) with alveolar opacities. Given the prolonged half-life of amiodarone, symptom resolution will be a slow process for patients with AIPT. Patients presenting with marked radiographic opacities and hypoxemia may need to receive prednisone 40 to 60 mg daily for several months. Mortality rates for patients with AIPT have been shown to approach 10%, with higher mortality rates seen in patients requiring hospitalization (20%–30%) or who develop ARDS (50%).[103]

A baseline chest radiograph and pulmonary function tests (diffusion capacity in particular) are recommended by the manufacturer. The chest radiograph should be repeated at 3- to 6-month intervals, and patients should be specifically questioned about pulmonary symptoms because early detection can decrease the extent of lung damage.

Liver toxicity can range from an asymptomatic elevation of transaminases (two to four times normal) to fulminant hepatitis. The mean latent period between the start of amiodarone therapy and evidence of liver injury is 10 months (onset can be as short as 3–4 days), but with rapid IV loading of amiodarone, a Reye syndrome–like fulminant hepatitis can occur as early as 1 day after starting therapy, most likely caused by the IV vehicle polysorbate-80. The precise mechanism of amiodarone-induced hepatotoxicity has not been fully elucidated. However, higher doses and prolonged drug use appear to place patients at higher risk of experiencing hepatotoxic effects of amiodarone. Thus, liver enzymes should be monitored at baseline, 1, 3, 6 months, and semiannually afterward.[104,105] The most common GI symptoms are nausea, anorexia, and constipation, which occur in 25% of patients receiving amiodarone.

Both hypothyroidism and hyperthyroidism have been reported, although hypothyroidism is more common. The thyroid complications are a consequence of amiodarone's large iodine content and its ability to block the peripheral conversion of thyroxine (T_4) to

triiodothyronine (T_3). In addition, amiodarone and its metabolite, desethylamiodarone, appear to be directly cytotoxic to the thyroid gland.[106]

Recent reports have indicated that photosensitive eruptions occur in 7% of amiodarone recipients.[107] Classical presentations of amiodarone photosensitivity involve a burning and tingling sensation in sun-exposed skin with accompanying erythema. Approximately 1% to 2% of patients receiving amiodarone for long-term use develop blue-gray pigmentation on sun-exposed skin. Resolution of amiodarone-associated photo-induced pigmentation may take up to 2 years, with gradual fading of skin discoloration.[107] In recent years, amiodarone-associated optic neuropathy has been highlighted in multiple case reports. A review of amiodarone-associated optic neuropathy (January 1993–May 2011) revealed a total of 214 cases from the FDA's Adverse Event Reporting System, 59 published cases, and 23 cases from clinical trials.[144] On average, patients received amiodarone for 9 months (range 1–84 months) before experiencing vision loss. In 20% of cases, patients progressed to legal blindness in at least one eye. Other bothersome side effects are corneal deposits (usually asymptomatic), exacerbation of HF, and central nervous system effects that include ataxia, tremor, dizziness, and peripheral neuropathy. Other than eye examination and pulmonary function tests, which should be repeated when the patient is symptomatic, other tests should be repeated every 6 months (thyroid and liver function) or annually (chest x-rays) for routine monitoring.[108] Amiodarone also blocks multiple cytochrome P-450 enzyme systems and P-glycoprotein pumps, resulting in clinically significant drug interactions.

CASE 15-7, QUESTION 4: S.L. is placed on amiodarone and dosed according to the OPTIC trial. After two months, the patient starts to get breakthrough NSVT and SuVT events requiring overdrive pacing or ICD shocks one to three times a week for 3 consecutive weeks. It is seriously reducing the patient's quality of life. What should be done to prevent this from occurring as often?

The VANISH (Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease) trial included patients with an ICD who had VT despite the use of antiarrhythmic drugs.[109] Patients were randomized to catheter ablation with continuation of baseline antiarrhythmic medications or escalated antiarrhythmic drug therapy. In the escalated therapy group, amiodarone was substituted if another agent had been used previously. If amiodarone was used previously, the dose was increased to 300 mg/day or, if the dose was already at least 300 mg/day, mexiletine was added. The primary outcome (composite of death, three or more documented episodes of VT within 24 hours [VT storm], or appropriate ICD shock) occurred in 59.1% of patients in the ablation group and 68.5% of those in the escalated therapy group (P = .04). In subgroup analysis, those patients who initially failed amiodarone did better with ablation while those failing other therapy who were switched to amiodarone did similarly as well. One confounder is that the ablations were performed in major medical centers with experienced electrophysiologists, which might have maximized the benefits versus procedures done in hospitals with lower ablation procedure volumes.[109]

Because S.L. had failed amiodarone therapy at 200 mg, it is likely that an ablation procedure with an experienced electrophysiologist would provide superior efficacy to amiodarone dosage elevation or the addition of mexiletine.

Torsades de Pointes

PROARRHYTHMIC EFFECTS OF ANTIARRHYTHMIC DRUGS AND CLINICAL PRESENTATION

CASE 15-8

Question 1: L.G. is a 69-year-old female who is taking sotalol 80 mg twice daily for a previous episode of SuVT. L.G. was admitted to the hospital 3 days ago for altered mental status. She is also taking oral citalopram 40 mg every morning for major depressive disorder. At baseline, her QTc interval was 400

milliseconds, and her CrCl was 50 mL/minute. Other laboratory values are as follows:

Potassium, 4.0 mmol/L
Blood urea nitrogen (BUN), 32 mg/dL
Serum creatinine, 1.5 mg/dL

Today, her ECG reveals a QTc interval of 502 milliseconds and TdP, with a ventricular rate of 110 beats/minute.

What is QTc interval prolongation? Why does QTc interval prolongation indicate an increased risk of TdP? Could an antiarrhythmic agent such as sotalol cause this arrhythmia?

How does CrCl affect this?

The QT interval denotes ventricular depolarization (the QRS complex in the cardiac cycle) and repolarization (from the end of the QRS complex to the end of the T wave). Certain ion channels in phases 2 and 3 of the action potential are vital in determining the QT interval (see Fig. 15-1). An abnormal increase in ventricular repolarization increases the risk of TdP. TdP is defined as a rapid polymorphic VT preceded by QTc interval prolongation. TdP can degenerate into VF and as such can be life-threatening (**Fig. 15-13**).[110]

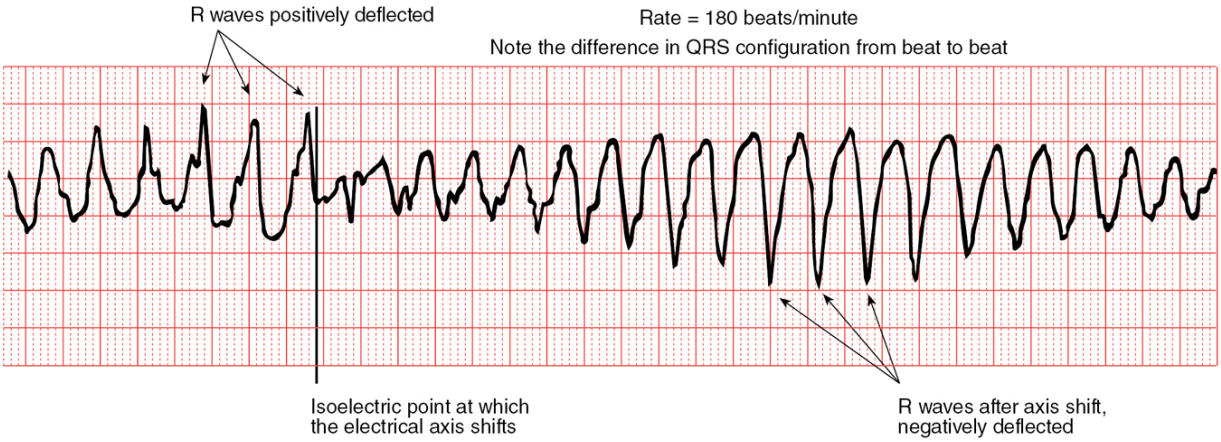


Figure 15-13 Torsades de pointes.

Because there is tremendous variability in the QT interval resulting from changes in heart rate, the QT is frequently corrected for heart rate (QTc interval). Several correction formulas for the QT interval exist and give similar results at most heart rates. The most common

correction formula uses QT and R–R intervals measured in seconds as follows: (QTc − QT/[R–$R^{0.5}$]). However, overcorrection of the QT interval may occur in persons with elevated heart rates (>85 beats/minute).[111,112] The Fridericia correction (QTc − QT/ [R–$R^{1/3}$]) represents an alternative correction method for patients with heart rates exceeding 85 beats/minute.

Any QTc interval over 500 milliseconds is a definite risk factor for the development of TdP as is an increase from the baseline QTc interval by 60 milliseconds. Increases from baseline of 30 to 60 milliseconds is a moderate risk factor for developing TdP.[110–112]

Class Ia and class III antiarrhythmic agents have been shown to induce TdP in numerous literature reports.[110,111] Of note, class Ia antiarrhythmic agents do not exhibit dose-dependent association with TdP, whereas the incidence of TdP does appear to be dose related with class III antiarrhythmic agents. QT prolongation associated with the use of class Ia antiarrhythmic agents is likely the result of blockade of outward potassium channels, but it is offset by concomitant blockade of inward sodium channels at increased drug concentrations.[2,113] TdP induced by class III antiarrhythmic agents arises from prolonged repolarization and cardiac refractoriness. All class III antiarrhythmic agents have been implicated in cases of TdP, although amiodarone and dronedarone are less likely to do so than the others.[2,114] These drugs block both multiple potassium channels, not just the rapid component of the delayed rectifier potassium channel (IKr) in the ventricle. This causes less transmural dispersion of repolarization from the endocardium, midmyocardium, and epicardium and is noted by less prolongation from the peak of the T wave to the end of the T wave (T_{peak} to T_{end}).[115]

Class Ic antiarrhythmic agents do not exert significant effects on repolarization and therefore have rarely been shown to induce TdP in patients without structural heart disease. To date, eight cases of flecainide-induced TdP have been published, along with one report of propafenone-associated TdP.[116–118]

Sotalol is known to cause QTc interval prolongation in a dose-dependent manner. Total daily doses of 160, 320, 480, and >640 mg

gave patients a steady-state QTc interval of 467, 473, 483, and 512 milliseconds, and the incidence of TdP was 0.5%, 1.6%, 4.4%, and 5.8%, respectively.

It is likely that L.G.'s reduced renal function put her at high risk for sotalol accumulation and accentuated QTc interval prolongation. In patients with a CrCl >60 mL/minute, the sotalol dose of 80 mg twice daily is appropriate, but in patients like L.G. with a CrCl <40 to 60 mL/minute, the manufacturer-recommended dose should be 80 mg daily or 40 mg twice daily owing to sotalol's predominant renal clearance.

Hypokalemia, hypomagnesemia, hypocalcemia (rare cases of TdP), concurrent use of more than one QT-prolonging drug, advanced age, female sex, heart disease (HF or MI), treatment with diuretics, impaired hepatic drug metabolism, and bradycardia are important risk factors for TdP in hospitalized patients.[111,113] Hypokalemia may prolong QT interval by modifying the function of the inwardly rectifying potassium channel, resulting in heterogeneity and dispersion of repolarization. Prolonged ventricular cycle length can assume the form of complete AV block, sinus bradycardia, or a rhythm in which long cycles may progress to arrhythmogenic EAD.

CASE 15-8, QUESTION 2: What transient conditions or other disorders can increase the risk of TdP in patients on class Ia or III antiarrhythmic agents?

Congenital long QT syndrome (LQTS) occurs in 1 in 2500 individuals and is a channelopathy associated with mutations identified in genes encoding voltage-gated sodium and potassium channels.[2,111] Since 1995, ~1000 individual LQTS-causing mutations have been detected in 12 distinct LQTS-susceptibility genes. The LQTS-susceptibility genes *KCNQ1* (encoded I_{Ks} α-subunit), *KCNH2* (encoded I_{Kr} α-subunit), and *SCN5A* (encoded Nav1.5 α-subunit) account for nearly 75% of all congenital LQTS cases.

Because L.G. did not have a family history of hereditary LQTS but was being treated with sotalol (an agent known to be associated with

TdP) in renal dysfunction, it can be assumed that sotalol therapy was responsible for her arrhythmia.

Case 15-8, Question 3: Which nonantiarrhythmic agents cause TdP? What is the mechanism of TdP initiation in this situation?

PROARRHYTHMIC EFFECTS OF NONANTIARRHYTHMIC AGENTS

Nonantiarrhythmic agents can also exhibit potassium channel inhibitory properties and can prolong the QTc interval. Most of these drugs, including arsenic trioxide, macrolide antibiotics, fluoroquinolones, azole antifungals, methadone, antidepressants, organophosphorus compounds, and antipsychotics, cause QTc interval prolongation by inhibiting the IKr potassium ion channel, just like quinidine and sotalol.[119–125] However, ranolazine and pentobarbital block multiple potassium channels like amiodarone and yield a lower TdP risk for each level of QTc interval prolongation.[2,115] Moreover, toxic concentrations of nonantiarrhythmic drugs can induce TdP as a result of large doses, impaired kidney or liver function, or other drug therapy that interferes with the metabolism of nonantiarrhythmic drugs.

The U.S. FDA alerted health care providers about new dosing recommendations for citalopram owing to concerns of QTc interval prolongation and TdP when using this agent at higher doses.[121] Key recommendations included (a) prescribing citalopram at a dose of ≤20 mg/day for patients age >60 years (also, in patients age <60 years with hepatic impairment or taking cimetidine) and (b) prescribing citalopram at a dose of ≤40 mg/day for younger patients. Hasnain and associates recently conducted a comprehensive review of published literature on QTc interval prolongation and/or TdP risk associated with antidepressants and antipsychotics.[122] The authors identified the highest number (16) of case reports implicating citalopram, relative to other antidepressants, including fluoxetine (9), escitalopram (6), venlafaxine (5), and sertraline (2). Quetiapine was the antipsychotic drug with the largest number of QTc interval

prolongation and/or TdP cases (16), followed by ziprasidone (13), risperidone (13), amisulpride, olanzapine (6), and clozapine (5). The authors of the review noted that 92% of patients had at least one additional risk factor for QTc interval prolongation.

During the past two decades, multiple case reports of methadone-induced TdP have been published. Guidelines recommend QTc interval monitoring, but some experts have questioned the necessity of screening patients.[123] Kao et al[123] reviewed the FDA Adverse Event Reporting System (FAERS) database for QTc interval prolongation or TdP events linked with methadone compared to other agents including antiarrhythmic drugs and other opioids. Between 2000 and 2011, the three most commonly implicated drugs were dofetilide (359 cases), methadone (211), and sotalol (119). The authors acknowledged limitations of their analysis (voluntary and selective reporting, along with the inability to determine incidence rates) but suggested that a Risk Evaluation and Mitigation Strategy (REMS) specific to methadone may be warranted to lower the risk of TdP.[124] Like methadone, the natural opioid kratom and massive ingestions of loperamide in patients trying to self-control their opioid addiction has also resulted in QTc interval prolongation and TdP. Naloxone does not treat TdP resulting from these opioid drugs as the IKr channel blockade is a direct action not secondary to opioid receptors.[126–128] Currently, the utility of published cardiac risk data on anti-infective agents is limited, owing to underreporting, failure to completely eliminate contributory confounding variables (cardiac disease, electrolyte abnormalities, use of other QT-prolonging drugs), and the retrospective nature of some postmarketing studies.[119] However, the propensity of antimicrobial agents to induce QT prolongation appears to be specially marked with macrolide antibiotics. All of the commercially available antifungal agents have been shown to induce TdP and QTc prolongation, with a larger number of cases attributed to fluconazole, followed by voriconazole.[125] Among the marketed quinolones in the United States, ciprofloxacin appears to display the lowest potential for causing TdP.[119,125]

A list of nonantiarrhythmic agents implicated in causing QTc interval prolongation and known pharmacokinetic drug interaction increasing the blood concentrations of these drugs is given in **Table 15-6**.

Table 15-6
Nonantiarrhythmic Agents With Known Torsades de Pointes Risk[a]

Drug Class	Agent	Drugs That Increase Blood Concentrations of These QTc Interval–Prolonging Drugs
Anesthetic, general	Propofol, sevoflurane	
Antibiotics: macrolides	Azithromycin, clarithromycin, erythromycin (lactobionate and base)	
Antibiotics: fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin	
Antibiotics: other	Pentamidine isethionate	
Anticancer	Arsenic trioxide, vandetanib	
Antidepressants	Citalopram, escitalopram	CYP3A4 or 2C19 inhibitors
Antiemetics	Chlorpromazine, droperidol, ondansetron	CYP3A4 (primary for ondansetron), 1A2 (primary for chlorpromazine), or 2D6 inhibitors
Antifungals	Fluconazole	
Antimalarials	(Hydroxy)chloroquine, halofantrine	Cimetidine (chloroquine), CYP3A4 inhibitors (halofantrine)
Antipsychotics	Haloperidol, pimozide, thioridazine	CYP2D6 (thioridazine) or 3A4 (pimozide) inhibitors
Cholinesterase inhibitors	Donepezil	CYP3A4 or 2D6 inhibitors

Narcotics	Methadone, mega-dose loperamide, kratom	CYP3A4, 2B6, and 2C19 inhibitors
Phosphodiesterase 3 inhibitor	Anagrelide, cilostazol	CYP1A2 (anagrelide), 3A4 (primary for cilostazol), or 2C19 inhibitors

[a]An up-to-date list can be found at http://www.crediblemeds.org/everyone/; Used with permission.

Because L.G. was taking citalopram in combination with sotalol, it is likely that QTc-prolonging effects resulting from concomitant use contributed to the development of TdP.

TREATMENT

Case 15-8, Question 4: How should TdP be treated? What treatments should be considered for L.G.?

If the patient is significantly hemodynamically compromised (frequently associated with a ventricular rate >150 beats/minute, unconsciousness, inability to identify who or where they are) while in TdP, DC cardioversion is the therapy of choice and should be given immediately.

Magnesium

In a hemodynamically stable patient, magnesium is frequently considered the drug of choice to restore normal sinus rhythm. It benefits patients whether they have hypomagnesemia or normal serum magnesium levels. However, magnesium is not effective for patients with polymorphic VT without TdP and with normal QT intervals. Hypokalemia should be corrected, and there is conflicting evidence on the value of achieving potassium levels in the high normal range of 4.5 to 5.0 mmol/L.[129] A common magnesium regimen is 2 g given for 60 seconds through the IV route, followed by an infusion of 2 to 4 mg/minute. The exact mechanism of action for magnesium in TdP is not known, but it reduces the occurrence of triggered activity such as EAD. In addition, magnesium blocks L-type

calcium channels in the membrane and may stabilize the membrane gradient through activation of the sodium–potassium ATPase.[129]

Other treatment options for torsades de pointes

Cardioacceleration with isoproterenol (1–4 µg/minute) or cardiac pacing has also been shown to be beneficial.[130,131] As described previously, the ability of sotalol, quinidine, and *N*-acetylprocainamide to prolong the APD is diminished at faster heart rates (reverse use dependence).[131] The more the inwardly rectifying potassium channels are activated, the less susceptible the channels are to inhibition by potassium channel blocking drugs.

Transvenous pacing is of some use in abolishing refractory TdP.[130–133] Before adjusting the ventricular rate to suppress ectopic ventricular beats, it is essential to ensure proper catheter placement and cardiac capture. In general, ventricular rates of 90 to 110 beats/minute can usually eliminate ventricular ectopy, but some patients may require rates as high as 140 beats/minute. Once control of TdP has been attained, the pacing rate can be gradually decreased to the lowest paced rate that suppresses further ectopy and dysrhythmia.

Numerous other strategies have been utilized for patients who fail to respond adequately to standard therapeutic approaches, including lidocaine and mexiletine, calcium channel blockers, and propofol.[128,134] However, the evidence supporting these alternative agents is not compelling enough to classify them as first-line options for abolishing TdP.

Because L.G. is hemodynamically stable, a bolus injection of 2 g of magnesium should be administered over 1 minute, followed by an infusion administered at a rate of 2 to 4 mg/minute. If the arrhythmia recurs, cardiac pacing should be used.

CARDIOPULMONARY ARREST

Cardiopulmonary Resuscitation

Cardiac arrest from VF, pulseless VT, pulseless electrical activity (PEA), and asystole are life-threatening emergencies. **Table 15-7**[135–140] reviews commonly used drugs for these indications. Health care practitioners treating patients during a cardiac arrest should be Advanced Cardiac Life Support (ACLS) certified. Although this section provides salient information on the diseases, treatments, and mechanisms, the reader should also review the newest national consensus guidelines under construction in 2020 and set for release in 2021.[135]

Table 15-7
Commonly Used Drugs in Cardiac Arrest

Drug	Formulation	Dosage/Administration	Rationale/Indications	Comments
Epinephrine	0.1 mg/mL (1:10,000) or 1 mg/mL (1:1000)	10 mL of a 1:10,000 solution of epinephrine (1 mg; dilute 1:1000 solution in 0.9% sodium chloride) every 3–5 minutes	Increases coronary sinus perfusion pressure through α_1 stimulation Indicated in pulseless VT, VF, asystole, and PEA	If administered through a peripheral catheter, need to flush the line to get the drug into the central compartment.
Amiodarone	50 mg/mL Vials: 3, 9, 18 mL	300 mg diluted in 20–30 mL D5W or NS; an additional 150 mg (diluted solution) can be given for recurrent or refractory VT or VF	Exhibits antiadrenergic properties and blocks sodium, potassium, and calcium channels First-line antiarrhythmic for pulseless VT and VF	Excipients (polysorbate 80 and benzyl alcohol) can induce hypotension. Failing to dilute can induce phlebitis.

D5W, 5% dextrose in water; NS, normal saline; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

Treatment

CASE 15-9

Question 1: M.N., a 52-year-old male, is visiting his wife, who is hospitalized for pneumonia. His past medical history is significant for hypertension and type 2 diabetes mellitus. He goes into the bathroom, and 2 minutes later his wife hears a dull thud. She calls out for her husband, but he does not respond. After an additional 2 minutes, health care workers open the bathroom door and find M.N. unresponsive and pulseless. CPR is initiated and a code blue is called. The ECG shows VF (Fig. 15-12), and there is no BP.

In addition to CPR, what initial therapy is available?

Determining the underlying rhythm disturbance is important because it directs health care workers to follow the ACLS algorithm for pulseless VT or VF. The algorithm calls for electrical defibrillation first, but other clinicians should work to establish IV access in case defibrillation fails.[135]

EXTERNAL DEFIBRILLATION

In VF and pulseless VT, DC cardioversion is the first corrective therapy that is attempted. Although commercially available manual defibrillators provide monophasic or biphasic waveform shocks, the biphasic defibrillator has become the preferred device owing to its high first-shock efficacy.[135] Most commercially available biphasic defibrillators display the device-specific energy dose range that should be used. However, if a health care provider operating a manual biphasic defibrillator is uncertain of the effective energy dose to terminate VF, using the maximal shock energy setting available is preferred. For second and subsequent shocks delivered by manual biphasic defibrillators, the same or higher energies should be used. For first and subsequent shocks, a shock of 360 J should be delivered if a monophasic defibrillator is used to terminate VF.

CASE 15-9, QUESTION 2: The initial shock fails to cause a return of spontaneous circulation in M.N. An IV catheter is established in a peripheral arm vein. What is the first drug that should be used?

EPINEPHRINE

If the patient's defibrillation threshold is above a monophasic 360 J shock, shocking at 360 J will be unsuccessful.[135] Shocking above 360 J might cause more people to convert out of VF or pulseless VT, but it will likely damage the ventricular myocardium so severely that the patient will die from PEA. This is why DC cardioversion machines limit the maximum shock energy.

The first drug strategy seeks to add epinephrine to lower the patient's defibrillation threshold, hopefully below the maximum shock energy the machine can provide. Although epinephrine stimulates

β_1-, β_2-, and α_1-adrenergic receptors, it is the α_1-adrenoceptor effects that are most closely associated with efficacy in VF or pulseless VT.[135] Applying α_1-adrenoceptor stimulation increases systemic vascular resistance (via vasoconstriction), which elevates coronary perfusion pressure and makes the VF waves look more coarse. These features lower the defibrillation threshold.

The recommended dose of epinephrine is 1 mg (10 mL of a 1:10,000 dilution; refer to Table 15-7) given by IV push. The dosage can be repeated at 3- to 5-minute intervals during resuscitation. If the drug is given IV through a peripheral catheter, which in this case includes a peripherally inserted central catheter, then a 20-mL flush with normal saline is recommended to ensure delivery into the central compartment. Only chest compressions cause blood circulation in VF or pulseless VT, so the movement of drugs from the periphery to the heart (where the benefit will occur) is severely impaired.[135]

Case 15-9, Question 3: M.N. is given a 1-mg bolus of epinephrine, followed by a 20-mL normal saline flush. The arm was elevated for 20 seconds to ensure adequate delivery. Thirty seconds after administration, a 200-J shock is given (via biphasic manual defibrillator), but it fails to convert VF. What can be done now?

The most recently updated ACLS guideline calls 2 additional minutes of CPR followed by the use of IV amiodarone or lidocaine in cases of VF or pulseless VT that do not respond to CPR, shocks, and epinephrine.[135] The strategy here is that giving an antiarrhythmic drug will allow a patient who converts but then immediately goes back into VF or pulseless VT to instead maintain Return of Spontaneous Circulation (ROSC) after the shock.

INTRAVENOUS AMIODARONE AND LIDOCAINE

The effect of IV amiodarone on VF or pulseless VT was studied in the ARREST (Amiodarone for Resuscitation of Refractory Sustained Ventricular Tachyarrhythmias) trial.[139] This study was conducted in

patients who experienced cardiac arrest in an out-of-hospital situation with therapy given by paramedics in the field. Patients who failed three stacked shocks and one dose of epinephrine with an electrical countershock were randomly assigned to amiodarone 300 mg IV bolus or placebo. This was followed by other antiarrhythmic agents historically used in ACLS (2000 guidelines: lidocaine, procainamide, or bretylium) if the clinicians desired. Amiodarone significantly increased the chance of survival to hospital admission (44% vs 34% of the placebo group; *P* = .03), but survival to hospital discharge was not changed. Of note, 66% of patients received antiarrhythmic drug treatment for pulseless VT or VF after amiodarone administration.

The ALIVE (Amiodarone vs Lidocaine in Ventricular Ectopy, *n* = 347) trial directly compared IV amiodarone 300 mg to lidocaine 1 to 1.5 mg/kg bolus.[141] In this trial, patients needed to fail three stacked shocks and epinephrine plus an additional shock to be eligible for randomization to either amiodarone or lidocaine. Amiodarone was given as an initial dose of 5 mg/kg followed by a shock. If unsuccessful, a dose of 2.5 mg/kg was given followed by a subsequent shock. Lidocaine was given as a 1.5 mg/kg bolus followed by a shock. If therapy failed, then a second bolus of 1.5 mg/kg was used with a subsequent shock. Patients given amiodarone were 90% more likely to experience survival to hospital admission than those given lidocaine (*P* = .009). Unfortunately, no significant advantage to hospital discharge occurred (5% vs 3%).

On the basis of these findings, amiodarone is preferable to lidocaine in its ability to improve the return of spontaneous circulation and short-term survival. However, it has not yet been shown to improve survival to hospital discharge.

Case 15-9, Question 4: M.N. is given amiodarone 300 mg diluted to 20 mL in D5W and administered with the arm subsequently elevated for 20 seconds. The next DC cardioversion shock was also unsuccessful. What should be done now?

M.N. is at serious risk of death as a result of VF. He should again receive CPR for 2 minutes and then repeat the cycle with epinephrine and if unsuccessful amiodarone 150 mg or lidocaine should be administered. As long as M.N. remains in VF, it is appropriate to continue active therapy. If M.N. degenerates into asystole after more than two or three cycles of treatment for VF, then the resuscitation efforts should be discontinued. However, if a patient only had a brief period of VF before having asystole, it is prudent to apply active asystole therapy.

Pulseless Electrical Activity

CASE 15-10

Question 1: J.D. is an 80-year-old female who experiences cardiac arrest in the hospital. J.D. was in respiratory failure upon admission to the ED, where she underwent immediate intubation, had a peripheral IV placed, and upon transfer to the medical intensive care unit (MICU), placed on assist/control mechanical ventilation with F_{IO_2} of 100%. A rhythm is noted on the monitor, but no femoral pulse is felt. J.D. is in PEA.

How should J.D. be assessed?

PEA is the clinical situation in which there is organized electrical activity on the monitor without a palpable pulse. Although electrical activity is present, it fails to stimulate the contractile process. Virtually, all patients in PEA without an identified treatable cause die. Therefore, it is imperative to rule out treatable causes in patients who appear to be in PEA. The major treatable causes are hypovolemia, hypoxia, acidosis, hyperkalemia, hypokalemia, hypothermia, cardiac tamponade, pulmonary embolism, acute coronary syndrome, trauma, and drug overdose.[135]

Case 15-10, Question 2: No treatable cause of PEA was identified for J.D. What treatment should she receive?

In the absence of an identifiable cause, the focus of resuscitation is to administer high-quality CPR, and after the initial rhythm check, resume CPR during the establishment of IV or intraosseous (IO) access.[135]

Once IV or IO access becomes available, administer epinephrine 1 mg every 3 to 5 minutes.[135,142,143] When the rhythm is PEA or asystole, you do not shock the patient as you can make the chances of survival worse, not better. Shocking could further damage the myocardial muscle in PEA and would promote asystole in the patient who already has this disorder.

Asystole

CASE 15-11

Question 1: K.K., a 73-year-old male, has a past medical history significant for hypertension and diverticulitis. Upon arrival at the operating room for surgical correction of pericardial and pleural effusions, K.K. received etomidate, fentanyl, lidocaine, and succinylcholine. During placement of a double-lumen endotracheal tube, K.K. goes into cardiac arrest. The ECG shows a flat line, and the patient is determined to be in asystole (**Fig. 15-14**).

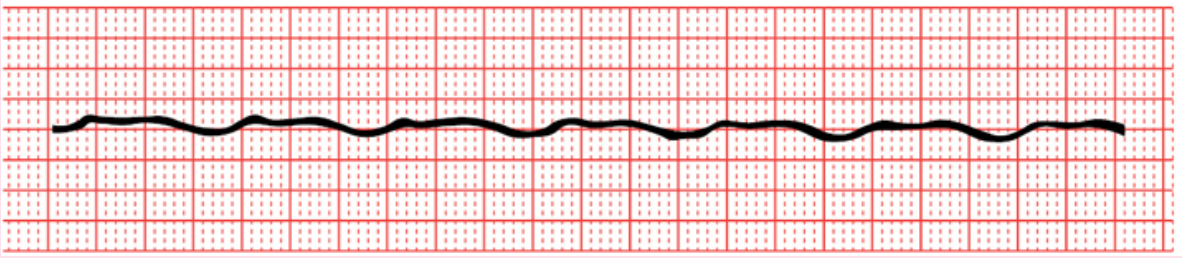


Figure 15-14 Asystole. There is no electrical activity detected in the heart resulting in a very low-amplitude undulating waveform.

Is this rhythm treatable?

Lack of electrical activity or asystole, like PEA, carries a grave prognosis. Its development usually indicates a prolonged arrest, which may explain its poor response to treatment. The tremendous death of myocardial cells with prolonged VF or pulseless VT leaches

out intracellular potassium. This raises the interstitial concentrations above the threshold level for the pacemakers to initiate an electrical depolarization. However, a few patients go directly from a sinus rhythm into asystole and may be resuscitated. Enhanced parasympathetic tone, possibly attributable to a vagal reaction, manipulation of the airway from intubation, suctioning or insertion of an oral airway, or chest compression, may play a role in inhibiting supraventricular and ventricular pacemakers.[136]

A post hoc analysis performed by Wenzel et al[136] demonstrated superior survival rates at the time of hospital admission in vasopressin-treated patients, compared with epinephrine-treated patients. However, no difference in intact neurologic survival was noted between the two treatment groups. Consequently, the guidelines recommend the use of epinephrine 1 mg IV every 3 to 5 minutes with no DC cardioversion.

CASE 15-11, QUESTION 2: Does the timing of epinephrine dosing impact survival to hospital discharge in patients with nonshockable rhythms (asystole or PEA)?

A post hoc analysis of data from the Get With the Guidelines-Resuscitation study showed a stepwise reduction in survival to hospital discharge (primary study end point) with each 3-minute delay to epinephrine: (a) 1 to 3 minutes (odds ratio [OR] 1.0, reference group); (b) 4 to 6 minutes (OR, 0.91; 95% CI, 0.82–1.00; $P = .055$); (c) 7 to 9 minutes (OR, 0.74; 95% CI, 0.63–0.88; $P < .001$); and (d) >9 minutes (OR, 0.63; 95% CI, 0.52–0.76; $P < .001$).[144]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2018;72:e91–e220. (85)

Cohen MI, Triedman JK, Cannon BC, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, Ventricular Preexcitation) Electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). *Heart Rhythm*. 2012;9:1006–1024. (83)

Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2010;55:934–947. (112)

Giugliano RP, Ruff CT, Murphy SA, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104. (73)

January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199–e267. (6)

January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol.* 2019;74:104–132. (18)

Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *J Am Coll Cardiol.* 2019;74:e51–156. (84)

Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. *J Cardiovasc Electrophysiol*. 2010;21:597–605. (65)

Sapp JL, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *N Engl J Med*. 2016;375:111–121. doi:10.1056/NEJMoa1513614 (109)

Key Website

Blaufuss Medical Multimedia Laboratories ECG Tutorial. http://www.blaufuss.org

COMPLETE REFERENCES CHAPTER 15 CARDIAC ARRHYTHMIAS

1. Anon. Arrhythmias and conduction disorders. In: Porter RS, Kaplan JL, eds. *The Merck Manual of Diagnosis & Therapy*. 19th ed. Merck & Co, Inc.; 2011 (E-book).
2. Knowllmann BC, Roden DM. Antiarrhythmic drugs. In: Brunton LL, ed. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. McGraw Hill. 2018 (E-book).
3. Menezes AR, Lavie CJ, DiNicolantonio JJ, et al. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. *Mayo Clin Proc*. 2013;88:394–409.
4. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739–745.
5. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292:2471–2477.
6. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199–e267.
7. Rawles JM, Metcalfe MJ, Jennings K. Time of occurrence, duration, and ventricular rate of paroxysmal atrial fibrillation: the effect of digoxin. *Br Heart J*. 1990;63:225–227.
8. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol*. 1999;33:304–310.
9. Woodland C, Verjee Z, Giesbrecht E, Koren G, Ito S. The digoxin-propafenone interaction: characterization of a mechanism using renal tubular cell monolayers. *J Pharmacol Exp Ther*. 1997;283:39–45.
10. Freitag D, Bebee R, Sunderland B. Digoxin-quinidine and digoxin-amiodarone interactions: frequency of occurrence and monitoring in Australian repatriation hospitals. *J Clin Pharm Ther*. 1995;20:179–183.
11. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the management of heart failure: executive summary. *Circulation*.

2013;128:1810–1852.
12. Hariman RJ, Mangiardi LM, McAllister RG Jr, Surawicz B, Shabetai R, Kishida H. Reversal of the cardiovascular effects of verapamil by calcium and sodium: differences between electrophysiologic and hemodynamic responses. *Circulation*. 1979;59:797–804.
13. Lang J, Timour-Chah Q, el Chebly M, Faucon G. Effect of gradual rise in plasma calcium concentration on the impairment of atrioventricular nodal conduction due to verapamil. *J Cardiovasc Pharmacol*. 1986;8:6–13.
14. Salerno DM, Anderson B, Sharkey PJ, Iber C. Intravenous verapamil for treatment of multifocal atrial tachycardia with and without calcium pretreatment. *Ann Intern Med*. 1987;107:623–628.
15. Falk RH, Leavitt JI. Digoxin for atrial fibrillation: a drug whose time has gone? *Ann Intern Med*. 1991;114:573–575.
16. Zarowitz BJ, Gheorghiade M. Optimal heart rate control for patients with chronic atrial fibrillation: are pharmacologic choices truly changing? *Am Heart J*. 1992;123:1401–1403.
17. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363–1373.
18. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol.* 2019;74:104–132.
19. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
20. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840.
21. Grönefeld GC, Lilienthal J, Kuck KH, et al. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. *Eur Heart J*. 2003;24:1430–1436.
22. Opolski G, Torbicki A, Kosior DA, et al. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation. The results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFÉ) Study. *Chest*. 2004;126:476–486.
23. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control inpersistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690–1696.
24. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–2677.
25. Keefe DL, Miura D, Somberg JC. Supraventricular tachyarrhythmias: their evaluation and therapy. *Am Heart J*. 1986;111:1150–1161.

26. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to DC electrical conversion of atrial fibrillation. *Am J Cardiol*. 1969;23:208–216.
27. Klein AL, Murray RD, Grimm RA. Role of transesophageal echocardiography guided cardioversion of patients with atrial fibrillation. *J Am Coll Cardiol*. 2001;37:691–704.
28. de Divitiis M, Omran H, Rabahieh R, et al. Right atrial appendage thrombosis in atrial fibrillation: its frequency and its clinical predictors. *Am J Cardiol 1999;84:1023-8*.
29. Falk RH, Podrid PJ. Electrical cardioversion of atrial fibrillation. In: Falk RH, Podrid PJ, eds. *Atrial Fibrillation: Mechanisms and Management*. Raven Press; 1992:181.
30. Dunn AB, White CM, Reddy P, Chow MS, Kluger J. Efficacy and cost-analysis of ibutilide. *Ann Pharmacother*. 2000;34:1233–1237.
31. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK, VanderLugt JT. Efficacy and safety of repeated doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Ibutilide Repeat Dose Study Investigators. *Circulation*. 1996;94:1613–1621.
32. Ellenbogen KA, Clemo HF, Stambler BS, Wood MA, VanderLugt JT. Efficacy of ibutilide for termination of atrial fibrillation and flutter. *Am J Cardiol*. 1996;78(8A):42–45.
33. Naccarelli GV, Lee KS, Gibson JK, VanderLugt JT. Electrophysiology and pharmacology of ibutilide. *Am J Cardiol*. 1996;78(8A):12–16.
34. Boriani G, Biffi M, Capucci A, et al. Oral propafenone to convert recent-onset atrial fibrillation in patients with and without underlying heart disease. A randomized, controlled trial. *Ann Intern Med*. 1997;126:621–625.
35. Azpitarte J, Alvarez M, Baún O, et al. Value of single oral loading dose of propafenone in converting recent-onset atrial fibrillation. Results of a randomized, double-blind, controlled study. *Eur Heart J*. 1997;18:1649–1654.
36. Botto GL, Bonini W, Broffoni T, et al. Conversion of recent onset atrial fibrillation with single loading oral dose of propafenone: is in-hospital admission absolutely necessary? *Pacing Clin Electrophysiol*. 1996;19(11 Pt 2):1939–1943.
37. Capucci A, Lenzi T, Boriani G, et al. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. *Am J Cardiol*. 1992;70:69–72.
38. Goy JJ, Kaufmann U, Kappenberger L, Sigwart U. Restoration of sinus rhythm with flecainide in patients with atrial fibrillation. *Am J Cardiol*. 1988;62:38D–40D.
39. Oral H, Souza JJ, Michaud GF, et al. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. *N Engl J Med*. 1999;340:1849–1854.

40. Hammill SC, Wood DL, Gersh BJ, Osborn MJ, Holmes DR Jr. Propafenone for paroxysmal atrial fibrillation. *Am J Cardiol*. 1988;61:473–474.
41. Porterfield JG, Porterfield LM. Therapeutic efficacy and safety of oral propafenone for atrial fibrillation. *Am J Cardiol*. 1989;63:114–116.
42. Pritchett EL, McCarthy EA, Wilkinson WE. Propafenone treatment of symptomatic paroxysmal supraventricular arrhythmias. A randomized, placebo-controlled, crossover trial inpatients tolerating oral therapy. *Ann Intern Med*. 1991;114:539–544.
43. Pietersen AH, Hellemann H. Usefulness of flecainide for prevention of paroxysmal atrial fibrillation and flutter. Danish-Norwegian Flecainide Multicenter Study Group. *Am J Cardiol*. 1991;67:713–717.
44. Anderson JL, Gilbert EM, Alpert BL, et al. Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy. A multicenter, double-blind, crossover study of flecainide and placebo with transtelephonic monitoring. Flecainide Supraventricular Tachycardia Study Group. *Circulation*. 1989;80:1557–1570.
45. Bolognesi R. The pharmacologic treatment of atrial fibrillation. *Cardiovasc Drugs Ther*. 1991;5:617–628.
46. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Bergmann JF. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev*. 2007;(4):CD005049.
47. Chimienti M, Cullen MT Jr, Casadei G. Safety of long-term flecainide and propafenone in the management of patients with symptomatic paroxysmal atrial fibrillation: report from the Flecainide and Propafenone Italian Study Investigators. *Am J Cardiol*. 1996;77:60A–75A.
48. Aliot E, Denjoy I. Comparison of the safety and efficacy of flecainide versus propafenone in hospital out-patients with symptomatic paroxysmal atrial fibrillation/flutter. The Flecainide AF French Study Group. *Am J Cardiol*. 1996;77:66A–71A.
49. Singh BN. Current antiarrhythmic drugs: an overview of mechanisms of action and potential clinical utility. *J Cardiovasc Electrophysiol*. 1999;10:283–301.
50. Kalus JS, Mauro VF. Dofetilide: a class III-specific antiarrhythmic agent. *Ann Pharmacother*. 2000;34:44–56.
51. Laughlin JC, Kowey PR. Dronedarone: a new treatment for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2008;19:1220–1226.
52. Benditt DG, Williams JH, Jin J, et al. Maintenance of sinus rhythm with oral D,L-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. D,L-Sotalol Atrial Fibrillation/Flutter Study Group. *Am J Cardiol*. 1999;84:270–277.
53. Lee SH, Chen SA, Tai CT, et al. Comparisons of oral propafenone and sotalol as an initial treatment in patients with symptomatic paroxysmal atrial fibrillation. *Am J Cardiol*. 1997;79:905–908.

54. Roy D, Talajic M, Dorain P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;342:913–920.
55. Gosselink AT, Crijns HJ, Van Gelder IC, Hillige H, Wiesfeld AC, Lie KI. Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. *JAMA*. 1992;267:3289–3293.
56. Greenbaum RA, Campbell TJ, Channer KS, et al. Conversion of atrial fibrillation and maintenance of sinus rhythm by dofetilide. The EMERALD (European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide) Study [abstract]. *Circulation*. 1998;98(Suppl I):1–633.
57. Singh S, Zoble RG, Yellen L, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter. The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) Study. *Circulation*. 2000;102:2385–2390.
58. Torp-Pedersen C, MØller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med*. 1999;341:857–865.
59. KØber L, Bloch Thomsen PE, MØller M, et al. Effect of dofetilide in patients with recent myocardial infarction and left ventricular dysfunction: a randomised trial. *Lancet*. 2000;356:2052–2058.
60. Song JC, White CM. Dofetilide (Tikosyn). *Conn Med*. 2000;64:601.
61. Singh BN, Connolly SJ, Crijns HJ, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987–999.
62. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360:668–678.
63. KØber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure [published correction appears in *N Engl J Med*. 2010;363:1384]. *N Engl J Med*. 2008;358:2678–2687.
64. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high risk permanent atrial fibrillation. *N Engl J Med*. 2011;365:2268–2276.
65. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. *J Cardiovasc Electrophysiol*. 2010;21:597–605.
66. Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use among patients with atrial fibrillation. *Stroke*. 1997;28:2382–2389.
67. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. 1989;1:175–179.

68. [No authors listed]. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med*. 1990;323:1505–1511.
69. [No authors listed]. Stroke Prevention in Atrial Fibrillation Investigators Study. Final results. *Circulation*. 1991;84:527–539.
70. [No authors listed]. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;343:687–691.
71. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
72. Granger CB, Alexander JH, McMurray JV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
73. Giugliano RP, Ruff CT, Murphy SA, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
74. Talati R, White CM. Dabigitran: a new orally available anticoagulant for prevention of strokes and thrombosis in patients with atrial fibrillation. *Formulary*. 2011;46:44.
75. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation [published correction appears in *N Engl J Med.* 2010;363:1877]. *N Engl J Med*. 2009;361:1139–1151.
76. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet*. 2010;49:259–268.
77. Sie P. Spotlight on idarucizumab and its potential for the reversal of the anticoagulant effects of dabigatran. *Drug Des Devel Ther.* 2016;10:1683–1689.
78. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol.* 2017;70:3042–3067.
79. Al-Zipes DP. Specific arrhythmias: diagnosis and treatment. In: Braunwald E, ed. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Vol 1. 5th ed. WB Saunders; 1997:640.
80. Zaiti SA, Magdic KS. Paroxysmal supraventricular tachycardia pathophysiology, diagnosis, and management. *Crit Care Nurs Clin North Am.* 2016;28:309–316. doi:10.1016/j.cnc.2016.04.005
81. Tijunelis MA, Herbert ME. Myth: intravenous amiodarone is safe in patients with atrial fibrillation and Wolff-Parkinson-White syndrome in the emergency department. *CJEM*. 2005;7:262–265.
82. Krahn AD, Klein GJ, Yee R. A randomized, double-blind, placebo controlled evaluation of the efficacy and safety of intravenously administered dofetilide

in patients with Wolff-Parkinson-White syndrome. *Pacing Clin Electrophysiol*. 2008;24:1258–1260.

83. Cohen MI, Triedman JK, Cannon BC, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, Ventricular Preexcitation) Electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). *Heart Rhythm*. 2012;9:1006–1024.
84. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *J Am Coll Cardiol.* 2019;74:e51–e156.
85. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2018;72:e91–e220.
86. Majorowicz K. *Clinical Management of Ventricular Arrhythmias*. CME Resource; 2008.
87. Cantillon DJ. Evaluation and management of premature ventricular complexes. *Cleve Clin J Med*. 2013;80:377–387.
88. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781–788.
89. Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. The Cardiac Arrhythmia Suppression Trial II Investigators. *N Engl J Med*. 1992;327:227–233.
90. Hjalmarson A. Effects of beta blockade on sudden cardiac death during acute myocardial infarction and the postinfarction period. *Am J Cardiol*. 1997;80(9B):35J–39J.
91. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta-blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318:1730–1737.
92. Kendall MJ, Lynch KP, Hjalmarson A, Kjekshus J. Beta-blockers and sudden cardiac death. *Ann Intern Med*. 1995;123:358.
93. Cairns JA, Connolly SJ, Roberts R, et al. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators [published correction appears in *Lancet*. 1997;349:1776]. *Lancet*. 1997;349:675–682.

94. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarction Amiodarone Trial Investigators [published corrections appear in *Lancet*. 1997;349:1776; *Lancet*. 1997;349:1180]. *Lancet*. 1997;349:667–674.
95. Ortiz M, Martín A, Arribas F, et al. Randomized comparison of intravenous procainamide vs. intravenous amiodarone for the acute treatment of tolerated wide QRS tachycardia: The PROCAMIO study. *Eur Heart J.* 2016;38:1329–1335. doi:10.1093/eurheartj/ehw230
96. Fornell D. Advances in Implantable Cardioverter Defibrillator (ICD) technology. Accessed June 14, 2015. www.dicardiology.com/article/advances-implantable-cardioverter-defibrillator-technology
97. Aziz S, Leon AR, El-Chami MF. The subcutaneous defibrillator: a review of the literature. *J Am Coll Cardiol*. 2014;63:1473–1479.
98. Steinberg JS, Martins J, Sadanandan S, et al. Antiarrhythmic drug use in the implantable defibrillator arm of the Antiarrhythmic Versus Implantable Defibrillators (AVID) study. *Am Heart J*. 2001;142:520–529.
99. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of β-blockers, amiodarone plus β-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA*. 2006;295:165–171.
100. Kowey PR, Crijns HJ, Aliot EM, et al. Efficacy and safety of celivarone, with amiodarone as calibrator, in patients with an implantable cardioverter-defibrillator for prevention of implantable cardioverter-defibrillator interventions or death: the ALPHEE study. *Circulation*. 2011;124:2649–2660.
101. Reddy VY, Reynolds MR, Neuzil P, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med*. 2007;357:2657–2665.
102. Kuck KH, Schaumann A, Eckardt L, et al. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. *Lancet*. 2010;375:31–40.
103. Van Cott TE, Yehle KS, DeCrane SK, Thorlton JR. Amiodarone-induced pulmonary toxicity: case study with syndrome analysis. *Heart Lung*. 2013;42:262–266.
104. Chan AL, Hsieh HJ, Hsieh YA, Lin SJ. Fatal amiodarone-induced hepatotoxicity: a case report and literature review. *Int J Clin Pharmacol Ther*. 2008;46:96–101.
105. Babatin M, Lee SS, Pollak PT. Amiodarone hepatotoxicity. *Curr Vasc Pharmacol*. 2008;6:228–236.
106. Padmanabhan H. Amiodarone and thyroid dysfunction. *South Med J*. 2010;103:922–930.

107. Drucker AM, Rosen CF. Drug-induced photosensitivity. Culprit drugs, management, and prevention. *Drug Saf*. 2011;34:821–837.
108. Passman RS, Bennett CL, Purpura JM, et al. Amiodarone-associated optic neuropathy: a critical review. *Am J Med*. 2012;125:447–453.
109. Sapp JL, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs, *N Engl J Med.* 2016;375:111–121. doi:10.1056/NEJMoa1513614
110. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. *Prog Cardiovasc Dis*. 2001;43(5 suppl 1):1–45.
111. Darpo B, Nebout T, Sager PT. Clinical evaluation of QT/QTc prolongation and proarrhythmic potential for nonantiarrhythmic drugs: the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E14 guideline. *J Clin Pharmacol*. 2006;46:498–507.
112. Drew B, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2010;55:934–947.
113. Camm AJ. Safety considerations in the pharmacological management of atrial fibrillation. *Int J Cardiol*. 2008;127:299–306.
114. Kao DP, Hiatt WR, Krantz MJ. Proarrhythmic potential of dronedarone: emerging evidence from Spontaneous Adverse Event Reporting. *Pharmacotherapy*. 2012;32:767–771.
115. Shah S, Kluger J, White CM. Monotherapy versus combination therapy with class III antiarrhythmic agents to attenuate transmural dispersion of repolarization: a potential risk factor for torsade de pointes. *Pharmacotherapy.* 2007;27:1297–1305. doi:10.1592/phco.27.9.1297
116. Oguayo KN, Oyetayo OO, Costa SM, Mixon TA. An unusual case of flecainide-induced QT prolongation leading to cardiac arrest. *Pharmacotherapy*. 2014;34:e30–e33.
117. Hii JT, Wyse DG, Gillis AM, Cohen JM, Mitchell LB. Propafenone-induced torsade de pointes: cross-reactivity with quinidine. *Pacing Clin Electrophysiol*. 1991;14(11 Pt 1):1568–1570.
118. Thevenin J, Da Costa A, Roche F, Romeyer C, Messier M, Isaaz K. Flecainide induced ventricular tachycardia (torsades de pointes). *Pacing Clin Electrophysiol*. 2003;26:1907–1908.
119. Owens RC Jr, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. *Clin Infect Dis*. 2006;43:1603–1611.
120. Letsas KP, Tsikrikas S, Letsas GP, Sideris A. Drug-induced proarrhythmia: QT interval prolongation and torsades de pointes. *Hosp Chron*. 2011;6:118–122.
121. Vieweg WV, Hasnain M, Howland RH. Citalopram, QT_c interval prolongation, and torsade de pointes. How should we apply the recent FDA ruling? *Am J*

Med. 2012;125:859–868.
122. Hasnain M, Vieweg WV. QT_c interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. *CNS Drugs*. 2014;28:887–920.
123. Kao D, Bucher Bartelson B, Khatri V, et al. Trends in reporting methadone-associated cardiac arrhythmia, 1997–2011: an analysis of registry data. *Ann Intern Med*. 2013;158:735–740.
124. Pimentel L, Mayo D. Chronic methadone therapy complicated by torsades de pointes: a case report. *J Emerg Med*. 2008;34:287–290.
125. Poluzzi E, Raschi E, Motola D, Moretti U, De Ponti F. Antimicrobials and the risk of torsades de pointes. The contribution from data mining of the US FDA adverse event reporting system. *Drug Saf*. 2010;33:303–314.
126. White CM. Pharmacologic and clinical assessment of kratom: an update. *Am J Health Syst Pharm.* 2019;76:1915–1925. doi:10.1093/ajhp/zxz221
127. White CM. Loperamide: a readily available but dangerous opioid substitute. *J Clin Pharmacol.* 2019;59:1165–1169. doi:10.1002/jcph.1449
128. Goodman JS, Peter CT. Proarrhythmia: primum non nocere. In: Mandel WJ, ed. *Cardiac Arrhythmias: Their Mechanisms, Diagnosis, and Management*. 3rd ed. JB Lippincott; 1995:173.
129. Charlton NP, Lawrence DT, Brady WJ, Kirk MA, Holstege CP. Termination of drug-induced torsade de pointes with overdrive pacing. *Am J Emerg Med*. 2010;28:95–102.
130. Schwartz PJ, Priori SG, Locati EH, et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na^+ channel blockade and to increases in heart rate: implications for gene-specific therapy. *Circulation*. 1995;92:3381–3386.
131. Miwa S, Inoue T, Yokoyama M. Monophasic action potentials in patients with torsades de pointes. *Jpn Circ J*. 1994;58:248–258.
132. Whalley DW, Wendt DJ, Grant AO. Basic concepts in cellular cardiac electrophysiology: part II: block of ion channels by antiarrhythmic drugs. *Pacing Clin Electrophysiol*. 1995;18(9 Pt 1):1686–1704.
133. Ellermann C, Könemann H, Wolfes J, et al. Propofol abolishes torsade de pointes in different models of acquired long QT syndrome. *Sci Rep.* 2020;10:12133. doi:10.1038/s41598-020-69193-7
134. Neuman RW, Shuster M, Callaway CW, et al. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Care Cardiovascular Care. *Circulation.* 2015;132(Supple 2):S315-S367.
135. Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med*. 2004;350:105–113.
136. Stiell IG, Hébert PC, Wells GA, et al. Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised controlled trial. *Lancet*.

2001;358:105–109.
137. Aung K, Htay T. Vasopressin for cardiac arrest: a systematic review and meta-analysis. *Arch Intern Med*. 2005;165:17–24.
138. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation in out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med*. 1999;341:871–878.
139. Somberg JC, Timar S, Bailin SJ, et al. Lack of a hypotensive effect with rapid administration of a new aqueous formulation of intravenous amiodarone. *Am J Cardiol*. 2004;93:576–581.
140. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation [published correction appears in *N Engl J Med*. 2002;347:955]. *N Engl J Med*. 2002;346:884–890.
141. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA*. 2012;307:1161–1168.
142. Khera R, Chan PS, Donnino M, et al. Hospital variation in time to epinephrine for nonshockable in-hospital cardiac arrest. *Circulation*. 2016;134:2105–2114. doi:10.1161/CIRCULATIONAHA.116.025459
143. Donnino MW, Salciccioli JD, Howell MD, et al. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. *BMJ*. 2014;348:g3028.
144. Passman RS, Bennett CL, Purpura JM, et al. Amiodarone-associated optic neuropathy: a critical review. *Am J Med.* 2012;125(5):447-453. doi:10.1016/j.amjmed.2011.09.020

16

Hypertensive Crises

Sandeep Devabhakthuni, Ryan G. D'Angelo, and Michael Armahizer

CORE PRINCIPLES		CHAPTER CASES
1	Hypertensive crisis is defined as a systolic blood pressure >180 mm Hg and/or diastolic blood pressure >120 mm Hg. This disorder can be further classified as hypertensive urgency or hypertensive emergency when there is evidence of acutely progressive end-organ damage.	**Case 16-1 (Question 1), Table 16-1**
2	Risk factors for the development of a hypertensive crisis include, but are not limited to, medication nonadherence, illicit drug use, and drug–drug and drug–food interactions.	**Case 16-1 (Question 1)**
3	Hypertensive urgency can be treated with oral antihypertensive agents including clonidine, labetalol, or	**Case 16-1 (Questions 2–6), Table 16-3**

	captopril. Caution must be taken to prevent rapid reductions in blood pressure.	
4	The organs primarily affected as a result of a hypertensive emergency are the central nervous system, eyes, heart, and kidneys.	**Case 16-2 (Question 1)**
5	Parenteral therapy should be used to manage hypertensive emergencies, and therapeutic options are dictated by the affected organ(s) and comorbidities. Mean arterial pressure should be reduced by no more than 25% within the first hour, then subsequently reduced toward a goal of 160/100–110 mm Hg, for most patients, during the next 2–6 hours. Gradually reduce blood pressure to normal, for most patients, during the next 24–48 hours.	**Case 16-2 (Questions 2–5, 9, 10)** **Case 16-3 (Questions 1–6)** **Case 16-4 (Questions 1, 2), Tables 16-2 and 16-4, Figure 16-1**
6	Nitroprusside, a therapeutic option for hypertensive emergencies, has been associated with cyanide and thiocyanate toxicity, and monitoring is required to minimize the risk of these toxicities, especially in patients with renal impairment.	**Case 16-2 (Questions 6–8)**
7	The most commonly used agents for the management of postoperative hypertension are nicardipine, clevidipine, nitroglycerin, nitroprusside, and labetalol.	**Case 16-5 (Questions 1–3)**
8	Management of aortic dissection	**Case 16-6 (Question**

requires prompt control of blood pressure without increasing the force of cardiac contraction or heart rate. | 1)

INTRODUCTION

The term *hypertensive crisis* is defined as a systolic blood pressure (SBP) >180 mm Hg and/or diastolic blood pressure (DBP) >120 mm Hg.[1] The actual blood pressure (BP) level may not be as important as the rate of BP rise because patients with chronic hypertension often tolerate higher BP compared to those who are normotensive. These disorders are divided into two general categories: *hypertensive emergency* and *hypertensive urgency* (**Table 16-1**). If left untreated, the 1-year death rate associated with hypertensive emergencies is >79%, and median survival is 10.4 months.[1–5]

Table 16-1
Hypertensive Emergency Versus Urgency

	Emergency	Urgency
Blood pressure criteria	Systolic > 180 mm Hg[a] Diastolic > 120 mm Hg[a]	
Life-threatening	Potentially	Not acutely
End-organ damage	Acute or progressing	Chronic; not progressing
Clinical manifestations	CNS (dizziness, N/V, encephalopathy, confusion, weakness, intracranial or subarachnoid hemorrhage, acute ischemic stroke) Eyes (ocular hemorrhage or funduscopic changes, blurred vision, loss of sight) Cardiac (left ventricular failure, pulmonary edema, MI, angina, aortic dissection)	Optic disc edema

	Renal failure or insufficiency	
Treatment strategy	Immediate reduction in blood pressure within hours; administer parenteral therapy (Table 16-2)	Reduction in blood pressure over several hours to days; administer oral therapy (Table 16-3)

CNS, central nervous system; MI, myocardial infarction; N/V, nausea and vomiting.

[a]Degree of blood pressure elevation is less diagnostic than the rate of pressure rise and presence of concurrent diseases or end-organ damage. See Chapter 9, Essential Hypertension, for staging of hypertension.

The term *hypertensive emergency* describes a clinical situation in which the elevated BP has caused acute progressive secondary organ damage (eg, stroke or myocardial infarction [MI]). Admission to an intensive care unit is recommended for rapid reduction in BP to a safe level (not necessarily normal) within minutes to hours.[1] *Hypertensive urgency* is not an immediately life-threatening situation; a reduction in BP to a safe level can occur more slowly over the next 24 to 48 hours.[1,6]

Acute, potentially life-threatening elevations of BP can occur in previously normotensive individuals with acute glomerulonephritis, head injury, or severe burns; during pregnancy (eclampsia); and with the use of recreational drugs such as cocaine. Other causes include abrupt medication withdrawal or medication nonadherence, drug–drug interactions (including herbal medications), erythropoietin administration, or drug–food interactions (ie, patients receiving monoamine oxidase inhibitors who ingest foods rich in tyramine).[7–9] In addition, poor systolic BP control has been identified as an independent risk factor for the development of hypertensive crisis.[10] Despite improvements in the recognition and treatment of hypertension, a recent study found that severely elevated BP was present in 18% of patients admitted to the emergency department (ED).[11] However, a recent nationwide study demonstrated the frequency of hypertensive emergency is 0.2% among all adult ED visits.[12]

CLINICAL PRESENTATION OF HYPERTENSIVE URGENCY

There are limited data describing the presentation and characteristics of those patients with hypertensive urgency. Mild symptoms may include nausea, epistaxis, fatigue, tinnitus, and psychomotor agitation.[13] Not all patients presenting with a hypertensive urgency will have symptoms.

CLINICAL PRESENTATION OF HYPERTENSIVE EMERGENCY

Similar to hypertensive urgencies, hypertensive emergencies typically occur in those with a history of hypertension. This suggests that hypertensive emergencies are almost entirely preventable.[14,15] Hypertensive emergencies tend to occur in patients with catecholamine-producing adrenal tumors (pheochromocytoma) or renal vascular disease. Additionally, hypertensive emergencies occur more often in African Americans than in Caucasians, among patients who have no primary care physician, and those who are unable adhere to treatment regimens.[14,16]

Symptoms associated with hypertensive emergency are highly variable and reflect the degree of damage to specific organ systems (eg, headache, dizziness, visual changes, and chest discomfort). Rapid, severe BP elevation is not always the hallmark of a hypertensive emergency. The primary sites of damage are the central nervous system, heart, kidneys, and eyes. Although hypertensive emergencies are much less common than hypertensive urgencies, without a thorough patient history, it is often difficult to know whether end-organ dysfunction is acute or chronic in nature.

Central Nervous System

Central nervous system abnormalities, especially cerebrovascular accidents, are the most commonly reported complications in hypertensive emergencies. Symptoms may include a severe headache with or without dizziness, nausea, vomiting, and anorexia. Mental confusion with apprehension indicates more severe damage, as does nystagmus, localized weakness, or a positive Babinski sign (ie, upward extension of the great toe and spreading of the smaller toes when moderate pressure is applied along a curve from the sole to the ball of the foot). Central nervous system damage may rapidly progress, resulting in coma or death. If a cerebrovascular accident has occurred, slurred speech or motor paralysis may be present.[14]

Other Complications

Cardiac consequences are the second most common complication of hypertensive emergency reported. Presentations may include heart failure (HF), acute pulmonary edema, acute aortic dissection, and/or an acute coronary syndrome. Ocular symptoms of hypertensive emergency usually are related to changes in visual acuity. Blurred vision or loss of eyesight are often associated with funduscopic findings of hemorrhages, exudates (yellow deposits within the retina as a result of leaks from capillaries and microaneurysms), and occasionally papilledema (edema of the optic nerve). Acute kidney injury can also develop. Markers of renal dysfunction include hematuria, proteinuria, and elevated serum blood urea nitrogen and serum creatinine levels.

OVERVIEW OF TREATMENT

Oral Versus Parenteral Therapy

Hypertensive urgency can be managed by either restarting or intensifying the patient's oral antihypertensive regimen. Practitioners should exercise caution in aggressive treatment of patients with

elevated BP in the absence of target-organ damage.[17] Aggressive dosing of antihypertensives to rapidly lower BP is not without risk and can lead to hypotension and subsequent morbidity. Some have suggested that the term *hypertensive urgency* leads to overly aggressive treatment and should be discarded in favor of a less ominous term such as *markedly elevated BP*.[1,6] In contrast, hypertensive emergencies require immediate hospitalization, generally in an intensive care unit, and the administration of parenteral antihypertensive medications to reduce arterial pressure.[18] Owing to the disturbance of autoregulation of tissue perfusion, continuous infusions of short-acting titratable antihypertensives are preferred to prevent further end-organ damage in the setting of hypertensive emergency. Effective therapy greatly improves the prognosis, reverses symptoms, and arrests the progression of end-organ damage.[19,20] Whether treatment can completely reverse end-organ damage is related to two factors: How soon treatment is initiated and the extent of damage at the initiation of therapy.

There are two fundamental concepts in the management of hypertensive emergencies. First, immediate and intensive therapy is required and takes precedence over time-consuming diagnostic procedures.[21] Second, the medication selection will depend on their onset of action and hemodynamic and metabolic effects meet the needs of the emergent situation. If encephalopathy, acute left ventricular failure, dissecting aortic aneurysm, eclampsia, or other end-organ damage is present, the BP should be lowered promptly with rapid-acting, parenteral antihypertensive medications such as clevidipine, esmolol, enalaprilat, fenoldopam, hydralazine, labetalol, nicardipine, nitroglycerin, or nitroprusside (**Table 16-2**).[1,3,4,22–26] If a slower BP reduction over several hours or days is acceptable, as in the case of a hypertensive urgency, rapid-acting oral therapy using captopril, clonidine, labetalol, or minoxidil may be used (**Table 16-3**).[3,4,26–28] An alternative option is to restart the patient's home medications and/or titrate the doses in a controlled manner so as not to drop the BP too rapidly.[29] **Figure 16-1** provides an overview of the management of a hypertensive crisis. A summary of treatment

recommendations for acutely lowering BP for selected indications is listed in **Table 16-4**.

Table 16-2
Parenteral Medications Commonly Used in the Treatment of Hypertensive Emergencies

Medication (Brand Name)/Class	Dose/Route	Onset of Action	Duration of Action
Clevidipine (Cleviprex®)/calcium channel blocker	Initial: 1–2 mg/hour; double dose at 90-second intervals until approaching goal BP, then increase by less than double every 5–10 minutes to a max of 21 mg/hour	2–4 minutes	10–15 minutes after D/C infusion
Enalaprilat[a] (Vasotec® IV)/ACE inhibitor	0.625–1.25 mg IV every 6 hours	15 minutes (peak, 1–4 hours)	6–12 hours
Esmolol[b] (Brevibloc®)/β-adrenergic blocker	500–1000 µg/kg IV loading dose, then 50–300 µg/kg/min	β-blockade: 2–10 minutes Hemodynamic effects: 10–30 minutes	10–20 minutes
Fenoldopam (Corlopam®)/dopamine-1 agonist	0.01–0.3 µg/kg/min, increase by 0.05–0.1 µg/kg/min every 15 minutes until goal BP achieved up to a max of 1.6 µg/kg/min	10 minutes	60 minutes
Hydralazine[c] (generic)/arterial vasodilator	10–20 mg IV or IM, can repeat every 20 minutes as needed	10–80 minutes	Up to 12 hours
Labetalol[d] (Normodyne®)/α- and β-adrenergic blocker	10–20 mg IV bolus at a rate of 10 mg/min, repeat every 10 minutes with escalating doses of 20, 40, and then 80 mg to a cumulative max of 300 mg or 0.5–2 mg/min IV infusion titrated at a rate of 0.5 mg/min every 15 minutes	Within 5 minutes Peak effect: 5–15 minutes	3–6 hours
Nicardipine[e] (Cardene® IV)/calcium channel blocker	Initiate at 5 mg/hour IV increased by 2.5 mg/hour every 5–15 minutes to desired BP or a max of 15 mg/hour, may decrease to 3 mg/hour after response achieved although not required	2–10 minutes (max, 8–12 hours)	40–60 minutes after D/C infusion
Nitroglycerin[f] (Tridil®, Nitro-Bid® IV, Nitro-Stat® IV)/venous vasodilator	Initiate at 5–10 µg/min IV infusion increased by 5 µg/min every 3–5 minutes to 20 µg/min then may increase by 10–20 µg/min every 3–5 minutes up to a max of 200 mg/min.	Immediate	3–5 minutes after D/C infusion
Nitroprusside[g] (Nipride®, Nitropress®)/arterial and venous vasodilator	Initiate at 0.1–0.3 µg/kg/min IV infusion increased by 0.2 µg/kg/min every 10–20 minutes to a max of 10 µg/kg/min. Doses >3 µg/kg/min are generally not recommended.	<2 minutes	1–10 minutes after D/C infusion

Medication	Major side effects (all can cause hypotension)	Avoid or use cautiously in patients with these conditions.
Clevidipine	Atrial fibrillation, nausea, vomiting, headache, acute renal failure, reflex tachycardia, and MI	Allergy to soybeans, soy products, eggs or egg products, severe aortic stenosis, defective lipid metabolism (eg, pathologic hyperlipidemia, lipid nephrosis, or acute pancreatitis), and HF
Enalaprilat	Hyperkalemia, acute kidney injury in those who are volume depleted	Hyperkalemia, bilateral renal artery stenosis, and pregnancy (teratogenic)
Esmolol	Nausea, thrombophlebitis, and painful extravasation	Asthma, bradycardia, decompensated HF, and advanced heart block
Fenoldopam	Tachycardia, headache, nausea, and flushing	Glaucoma
Hydralazine	Tachycardia, headache, and angina	Angina pectoris, MI, and aortic dissection

Labetalol	Abdominal pain, nausea, vomiting, and diarrhea	Asthma, bradycardia, and decompensated HF
Nicardipine	Headache, flushing, nausea, vomiting, dizziness, and tachycardia; local thrombophlebitis rotate peripheral infusion site every 12 hours	Angina pectoris, advanced aortic stenosis, decompensated HF, and increased intracranial pressure
Nitroglycerin	Methemoglobinemia, headache, tachycardia, nausea, vomiting, flushing, and tolerance with prolonged use	Pericardial tamponade, constrictive pericarditis, or increased intracranial pressure
Nitroprusside	Nausea, vomiting, diaphoresis, weakness, thiocyanate toxicity,[h] cyanide toxicity (rare),[i] chest pain, nausea, vomiting, dizziness, headache, nasal congestion, and arrhythmia	Renal failure (thiocyanate accumulation), hepatic impairment (cyanide toxicity), pregnancy, increased intracranial pressure, and acute coronary syndrome

ACE, angiotensin-converting enzyme; BP, blood pressure; D/C, discontinued; HF, heart failure; IM, intramuscular; IV, intravenous; MI, myocardial infarction.

[a]Not approved by the U.S. Food and Drug Administration for treatment of acute hypertension.

[b]Approved for intraoperative and postoperative treatment of hypertension.

[c]Parenteral hydralazine is an intermediate treatment between oral agents and more aggressive therapies such as nitroprusside. It can be given IV or intramuscularly, but there is no appreciable difference in onset of action (20–40 minutes) between the two routes. This slow onset minimizes hypotension.

[d]Labetalol is contraindicated in acute decompensated heart failure because of its β-blocking properties. Infusions start at 2 mg/min and are titrated until a satisfactory response or a cumulative dose of 300 mg is achieved.

[e]Indicated for short-term treatment of hypertension when the oral route is not feasible or desirable.

[f]Requires special delivery system owing to drug binding to polyvinyl chloride tubing. Also see Chapter 12, Chronic Stable Angina, and Chapter 13, Acute Coronary Syndrome, for further information regarding nitroglycerin.

[g]The container should be wrapped with metal foil to prevent light-induced decompensation once reconstituted; the product will be a red-brown solution. Under these conditions, the solution is stable for 4 to 24 hours. A rising BP may indicate a loss of potency. A change in color to yellow does not indicate effectiveness. The appearance of a dark brown, green, or blue color indicates loss in activity. When changing to a new bag, the administration rate may require adjustment.

[h]Thiocyanate levels rise gradually in proportion to the dose and duration of administration. The half-life of thiocyanate is 2.7 days with normal renal function and *9* days in patients with renal failure. Toxicity occurs after 7 to 14 days in patients with normal renal function and after 3 to 6 days in renal failure patients. Thiocyanate serum levels should be measured after 3 to 4 days of therapy, and the drug should be discontinued if levels exceed 10 to 12 mg/dL. Thiocyanate toxicity causes a neurotoxic syndrome of toxic psychosis, hyperreflexia, confusion, weakness, tinnitus, seizures, and coma.

[i]Signs of cyanide toxicity include lactic acidosis, hypoxemia, tachycardia, altered consciousness, seizures, and the smell of almonds on the breath. Concurrent administration of sodium thiosulfate or hydroxocobalamin may reduce the risk of cyanide toxicity in high-risk patients.

Table 16-3
Oral Medications Commonly Used in the Treatment of Hypertensive Urgencies

Medication[a] (Brand Name)	Dose/Route	Onset of Action	Duration of Action	Major Side Effects[a]	Avoid or Use Cautiously in Patients With These Conditions
Captopril[b] (Capoten®) 12.5-, 25-, 50-, 100-mg tablets ACE inhibitor	6.5–50 mg PO	15 minutes	4–6 hours	Hyperkalemia, angioedema, increased SCr if volume depletion, rash, pruritus, and loss of taste	Renal artery stenosis, hyperkalemia, volume depletion, acute kidney injury, and pregnancy
Clonidine (Catapres®) 0.1-, 0.2-, 0.3-mg tablets Central α_2-agonist	0.1–0.2 mg PO initially, then 0.1 mg/hour up to 0.8 mg total	0.5–2 hours	6–8 hours	Sedation, dry mouth, bradycardia, and constipation	Altered mental status and severe carotid artery stenosis
Labetalol (Normodyne®, Trandate®) 100-, 200-, 300-mg tablets α-and β-adrenergic blocker	200–400 mg PO repeated every 2–3 hours	30 minutes–2 hours	4 hours	Orthostatic hypotension, nausea, and vomiting	HF, asthma, bradycardia, and advanced heart block
Minoxidil (Loniten®) 2.5-, 10-mg tablets Arterial and venous vasodilator	5–20 mg PO	30–60 minutes; maximum response in 2–4 hours	12–16 hours	Tachycardia and fluid retention	Angina and HF

ACE, angiotensin-converting enzyme; HF, heart failure; PO, orally; SCr, serum creatinine.

[a]All may cause hypotension, dizziness, and flushing.

[b]Other oral ACE inhibitors are too slow in onset to be useful but should be used for maintenance therapy to improve adherence as captopril requires multiple daily doses.

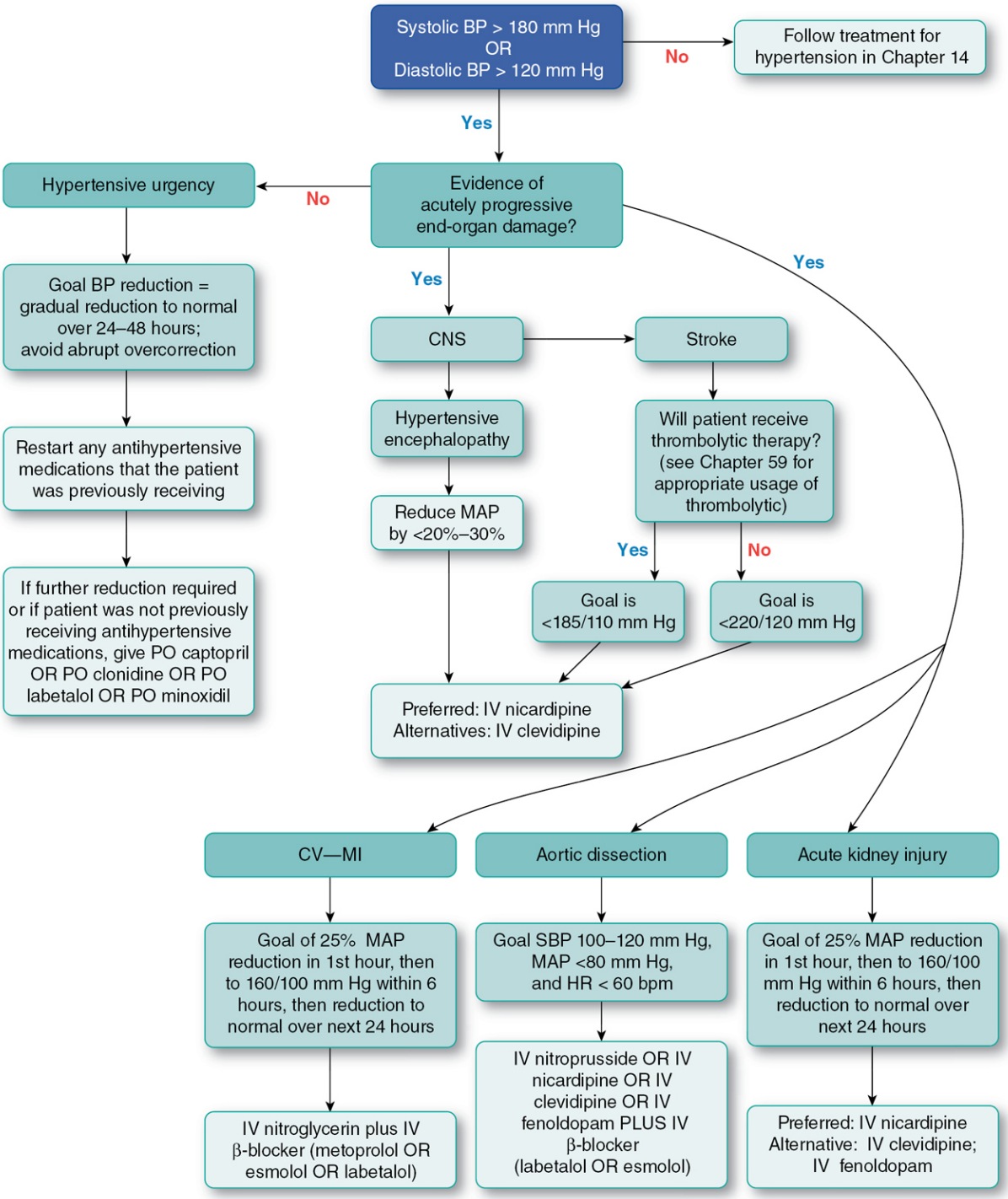


Figure 16-1 Overview of management for a hypertensive crisis. BP, blood pressure; CNS, central nervous system; CV, cardiovascular; HR, heartrate; IV, intravenous; MAP, mean arterial pressure; MI, myocardial infarction; SBP, systolic blood pressure.

Table 16-4
Treatment Recommendations for Hypertensive Emergency

Clinical Presentation	Recommendation	Rationale
Acute aortic dissection	Nitroprusside, nicardipine, clevidipine, or fenoldopam plus esmolol or IV metoprolol or labetalol; trimethaphan. Avoid inotropic therapy.	Vasodilator will decrease pulsatile stress in aortic vessel to prevent further dissection expansion. β-Blockers will prevent vasodilator-induced reflex tachycardia.
Angina and myocardial infarction	Nitroglycerin plus esmolol or metoprolol or labetalol. Avoid nitroprusside.	Coronary vasodilation, decreased cardiac output, myocardial workload, and oxygen demand. Nitroprusside may cause coronary steal.
Acute pulmonary edema and left ventricular failure	Nitroprusside or nitroglycerin and a loop diuretic. Alternative: enalaprilat. Avoid nondihydropyridines and β-blockers.	Promotion of diuresis with venous dilatation to decrease preload. Nitroprusside and enalaprilat decrease afterload. Nicardipine may increase stroke volume.
Acute kidney injury	Nicardipine, clevidipine, or fenoldopam. Avoid nitroprusside or enalaprilat.	Peripheral vasodilation without affecting renal clearance
Cocaine use	Nicardipine, clevidipine, fenoldopam, verapamil, or nitroglycerin. Alternative: labetalol. Avoid β-selective blockers.	Vasodilation effects without potential unopposed α-adrenergic receptor stimulation. CCBs controle cocaine-induced vasospasm.

Clinical Presentation	Recommendation	Rationale
Pheochromocytoma	Nicardipine, clevidipine, fenoldopam, or verapamil. Alternatives: labetalol. Avoid β-selective blockers.	Vasodilation effects without potential unopposed α-adrenergic receptor stimulation
Eclampsia or preeclampsia	Hydralazine, labetalol, or nicardipine	Requires rapid BP lowering. ACE inhibitors, ARBs, and nitroprusside are contraindicated.
Hypertensive encephalopathy, intracranial hemorrhage, subarachnoid hemorrhage, ischemic stroke, and thrombotic stroke	Nicardipine, clevidipine, or labetalol. Avoid nitroprusside, nitroglycerin, enalaprilat, and hydralazine.	Vasodilation effects without compromised CBF induced by nitroprusside and nitroglycerin; Enalaprilat and hydralazine may lead to unpredictable BP changes when carefully controlled BP management is required.

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BP, blood pressure; CBF, cerebral blood flow; CCB, calcium channel blocker; IV, intravenous.

Goals of Therapy

The rate of BP lowering must be individualized, depending on whether the patient presents with hypertensive urgency or emergency. Also, ischemic damage to the heart and brain can be provoked by a precipitous fall in BP.[28–33] As treatment is initiated, clinicians should recognize that the elderly and patients with severely defective autoregulatory mechanisms are at high risk for developing hypotensive complications. The latter group includes those with autonomic dysfunction or fixed sclerotic stenosis of cerebral or neck arteries.[34] In addition, patients who have chronically elevated BP are less likely to tolerate abrupt reductions in their BP, and the amount of reduction appropriate for those patients is somewhat less than for those whose BP is acutely elevated.

For hypertensive emergencies complicated by aortic dissection, pheochromocytoma crisis, severe preeclampsia, or eclampsia, it is recommended that the SBP is reduced to <140 mm Hg during the first hour and to 100 to 120 mm Hg in aortic dissection (Case 16-6).[1] For hypertensive emergencies with the presence of other end-organ damage, mean arterial pressure should be reduced initially by no more than 25% (within minutes to 1 hour); then if stable, this should be followed by further reduction toward a goal of 160/100–110 mm Hg within 2 to 6 hours and gradual reduction to normal during the next 24 to 48 hours.[4] A DBP of 100 to 110 mm Hg is an appropriate initial therapeutic goal.[1]

Another exception to this rule applies to patients with acute cerebrovascular accidents. Cerebral autoregulation is disrupted in this setting, and the use of antihypertensives may cause a reduction in cerebral blood flow and increased morbidity.[35] Current guidelines recommend lowering BP after acute ischemic stroke if the systolic BP is >220 mm Hg or the DBP is >120 mm Hg by 15% within 24 hours in patients ineligible for thrombolytic therapy; a lower BP goal can be achieved, if medically necessary, to manage a condition such as an MI or aortic dissection. The SBP should be lowered to <185 mm Hg and DBP to <110 mm Hg in candidates for thrombolytics or mechanical thrombectomy.[36] The systolic BP should be maintained at <180 mm Hg and the DBP at <105 mm Hg for the first 24 hours after thrombolytic therapy. A lower BP in patients undergoing thrombolytic therapy reduces the risk of intracerebral bleeding.[36] Additionally, in those with hypertensive encephalopathy, cerebral hypoperfusion may occur if the mean BP is reduced by more than 40%.[37] Thus, in the presence of hypertensive encephalopathy, it is suggested that within the first hour of treatment, the mean arterial pressure be lowered by no more than 20% or to a DBP of 100 mm Hg, whichever is greater.[37,38]

HYPERTENSIVE URGENCIES

Patient Assessment

CASE 16-1

QUESTION 1: M.M. is a 60-year-old male with a long history of HF with a preserved ejection fraction (HFpEF), poorly controlled hypertension believed to be caused by nonadherence, and a history of MI. He was referred from a community health center this morning for a thorough evaluation of his elevated BP. He has not taken his enalapril, clonidine, or carvedilol for the past 7 days. M.M. is completely asymptomatic. Physical examination reveals a BP of 198/130 mm Hg and a pulse of 92 beats/min. Funduscopic examination is pertinent for mild arteriolar narrowing, without hemorrhages or exudates. The discs are flat. His lungs are clear, and the cardiac examination is unremarkable. The electrocardiogram indicates normal sinus rhythm at a rate of 90 beats/min. The chest radiograph is interpreted as mild cardiomegaly. Serum electrolytes, blood urea nitrogen, and serum creatinine are within normal limits. A urinalysis is significant for 2+ proteinuria.

How quickly should his BP be lowered, and what therapeutic options are available?

The absolute magnitude of BP elevation does not in itself constitute a medical emergency requiring an acute reduction in BP. There is no evidence of encephalopathy, cardiac decompensation, chest pain, or rapid change in renal function. Therefore, no evidence exists to indicate a rapid deterioration in the function of target organs. One would classify M.M.'s case as a hypertensive urgency.

As is often the case, M.M.'s lack of BP control is related to medication nonadherence. M.M.'s clinical presentation requires that his BP be lowered during the next 24 to 48 hours while being careful not to induce hypotension. At this time, no specific evidence exists supporting a BP reduction goal, although a goal of reducing the mean arterial pressure by 20% to 25% over several days may be reasonable. Aggressive reductions with intravenous (IV) antihypertensives and even some oral agents are associated with the development of syncope, stroke, and MI; thus, this should be avoided. A variety of rapid-acting oral agents such as clonidine, captopril, labetalol, or minoxidil can be used for this purpose. Restarting his previously prescribed medications in a controlled

manner, so as not to drop his BP too rapidly, may also be a reasonable option for treatment. Later, he can be converted to a regimen designed to enhance adherence by selecting medications with once-daily dosing. For example, lisinopril or another long-acting angiotensin-converting enzyme (ACE) inhibitor would be preferred for maintenance instead of the enalapril previously prescribed owing to the frequency of doses required. One should also determine and address barriers to medication adherence with the patient including the cost of therapy, lack of understanding of the benefits of therapy, misconceptions of the side effect profiles, and so forth. Timely follow-up within 1 week after treatment of hypertensive urgency is of paramount importance for the appropriate management of these patients.

Oral Drug Therapy

RAPIDLY ACTING CALCIUM CHANNEL BLOCKERS

Case 16-1, Question 2: M.M.'s physician has ordered immediate-release nifedipine 10 mg to be given sublingually. Is this appropriate therapy to treat his hypertensive urgency?

Captopril, clonidine, labetalol, and minoxidil have all been used to lower BP acutely. These oral agents take several hours to adequately lower pressure and are therefore useful in treating hypertensive urgencies but not emergencies. Oral-acting ACE inhibitors, other than captopril, are not useful for acutely lowering BP because of a slower onset of action.

The immediate-release calcium channel blockers, including diltiazem, verapamil, and nicardipine, can rapidly lower BP; however, the most extensive experience is with nifedipine. Nifedipine, when given orally or by the "bite and swallow" method, was previously recommended as a rapid-acting alternative to parenteral therapy in the acute management of hypertension. However, its use has been associated with life-threatening adverse events related to ischemia,

MI, and stroke.[29–33] The cavalier use of immediate-release nifedipine to acutely lower BP is potentially dangerous and should be avoided.[39,40] M.M.'s BP can be managed safely using other oral medications.

CLONIDINE

Case 16-1, Question 3: A decision is made not to use nifedipine, but rather to give M.M. oral clonidine. What is an appropriate starting and maintenance dose?

Clonidine is considered a generally safe, and effective first-line therapy for hypertensive urgency. It is a centrally acting, α_2-adrenergic agonist that inhibits sympathetic outflow from the central nervous system. BP can be lowered gradually over several hours using oral clonidine. Traditional dosing regimens have included an initial oral loading dose (0.1–0.2 mg) followed by repeated doses of 0.1 mg/hour until the desired response is achieved or until a cumulative dose of 0.8 mg is reached.[41] Some authors, however, have cautioned against the use of sequential loading doses, citing lack of benefit over placebo and the potential for unpredictable adverse effects, particularly abrupt occurrences of significant hypotension.[42] If loading doses are to be used, it is especially important to reduce doses in patients with volume depletion, those who have recently used other antihypertensive drugs, and the elderly.[1,25,43]

The acute response to oral clonidine loading is not predictive of the daily dose required to maintain BP control. Maintenance oral therapy with clonidine is somewhat empiric; however, total daily doses should be spread between two and three times daily dosing owing to the drug's short half-life.

Adverse effects and precautions

Case 16-1, Question 4: What are the adverse effects and precautions that should be considered before recommending the use of clonidine?

Oral clonidine is generally well tolerated. Adverse effects include orthostatic hypotension, bradycardia, sedation, dry mouth, and dizziness. Clonidine can decrease cerebral blood flow by up to 28%; it should not be used in patients with severe cerebrovascular disease.[44] Clonidine also should be avoided in patients with HF, bradycardia, sick sinus syndrome, or cardiac conduction defects[25] as well as in patients at risk of medication nonadherence because of potential rebound hypertension following abrupt discontinuation.[45,46]

OTHER ORAL DRUGS

Captopril

Case 16-1, Question 5: M.M. has a history of HFpEF and normal renal function. Based on these findings, would captopril be a reasonable choice for initial treatment? What would be an appropriate initial dosing regimen? What if he had acute kidney injury?

Captopril has been used both orally and sublingually to acutely lower BP.[47,48] Although sublingual captopril has been used because of its rapid onset of action, the overall BP reduction at 60 minutes is similar between sublingual and oral administration.[49] Captopril decreases both afterload and preload and lowers total peripheral vascular resistance.[25] For this reason, captopril and other ACE inhibitors are often considered the drugs of choice in patients with HF with reduced ejection fraction as they have been shown to reduce mortality in this patient population (see Chapter 14, Heart Failure, for further discussion). M.M. has HFpEF; the evidence of using ACE inhibitors in reducing mortality in this patient population is not strong. However, given that M.M. appeared to be well controlled on his enalapril therapy before abruptly stopping his medications, it is reasonable to restart a rapid-acting ACE inhibitor and reinforce medication adherence issues. Additionally, in patients with diabetic

or nondiabetic proteinuria, ACE inhibitors can reduce the level of urinary protein excretion and progression of Chronic Kidney Disease (CKD), making these agents an optimal first-line treatment option for M.M.[1]

After oral administration, the onset of action of captopril occurs within minutes and peaks 30 to 90 minutes later.[50] Clinically, it reduces BP within 10 to 15 minutes, with effects persisting for 2 to 6 hours. Sublingual captopril is as effective as nifedipine but without reflex tachycardia in acutely reducing mean arterial pressure in both urgent and emergent conditions.[48–52]

Despite these beneficial effects, captopril, as well as long-acting ACE inhibitors, must be used with caution in patients with renal insufficiency or volume depletion. In most cases, an elevated blood urea nitrogen or serum creatinine will provide a clue to the existence of these conditions; however, captopril can also induce renal failure in patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney. Such conditions may not be easy to detect in the context of an acute hypertensive emergency. Therefore, in patients in whom these conditions can be excluded, captopril can be considered for initial therapy. First-dose hypotension is a common limiting factor with captopril use. This complication is most likely to occur in the elderly and in patients with high renin levels, such as those who are volume depleted or those receiving diuretics. Under these circumstances, initial doses should not exceed 12.5 mg, with repeat doses an hour or more later if necessary. Therefore, captopril would be a reasonable choice as initial therapy in M.M., which can later be replaced by a longer-acting ACE inhibitor.

Minoxidil and labetalol

Case 16-1, Question 6: What other oral agents can be considered in the treatment of hypertensive urgency?

Minoxidil, a potent oral vasodilator, has been used successfully in the treatment of hypertensive urgencies.[53,54] An oral loading dose of

10 to 20 mg produces a maximal BP response in 2 to 4 hours and can be followed by a dose of 5 to 20 mg every 4 hours if necessary. Unfortunately, its onset of action is slower than that of clonidine or captopril. Another complicating factor is that β-blockers and loop diuretics generally must be used concomitantly to counteract minoxidil-induced reflex tachycardia and fluid retention.[54] Because of this, minoxidil should only be prescribed by those who have experience with prescribing this agent and managing these adverse effects. These adverse effects make this agent a less preferred choice in M.M. because of his history of HF. Minoxidil should be used only in patients presenting with hypertensive urgency who are not responding to other antihypertensive therapies or who have previously been taking this agent.

Oral labetalol, a combined α- and β-receptor antagonist, is an alternative to oral clonidine or captopril for the treatment of severe hypertension, but the most appropriate dosing regimen remains to be determined.[55–58] Initial doses of 100 to 300 mg may provide a sustained response for up to 4 hours.[56] Labetalol (200 mg given at hourly intervals to a maximum dose of 1200 mg) was comparable to oral clonidine in reducing mean arterial pressure.[58] An alternative regimen using 300 mg initially followed by 100 mg at 2-hour intervals to a maximum of 500 mg was also successful in acutely lowering BP.[57] Other literature has reported that a single loading dose of 200 to 400 mg does not appear to be effective in achieving an adequate BP response.[59] Because labetalol can cause profound orthostatic hypotension, patients should remain in the supine position and should be assessed for orthostasis before ambulation. In addition, owing to its β_1- and β_2-receptor antagonism, labetalol should be avoided in patients with asthma or obstructive pulmonary disease, bradycardia, or advanced heart block.

HYPERTENSIVE EMERGENCIES

Patient Assessment

CASE 16-2

Question 1: M.R., a 55-year-old male, presents to the ED with a 3-day history of progressively increasing shortness of breath. During the past 2 days, he experienced a severe headache unrelieved by ibuprofen, as well as chest pressure, which worsened with exertion, anorexia, and nausea. His medical history includes hypertension, asthma, and chronic stable angina. His medications include albuterol via metered-dose inhaler, isosorbide dinitrate, felodipine, and lisinopril; however, he discontinued these medications on his own 3 weeks ago.

Physical examination reveals an anxious-appearing male who is alert, oriented, and in moderate respiratory distress. His vital signs include a heart rate of 125 beats/min, respiratory rate of 36 breaths/min, BP of 220/145 mm Hg without orthostasis, and a normal body temperature. Funduscopic examination shows arteriolar narrowing and arteriovenous nicking without hemorrhages, exudates, or papilledema. No jugular venous distention is observed, but bilateral carotid bruits are present. Chest examination reveals decreased breath sounds with bilateral rales extending to the tip of the scapula. M.R.'s heart is displaced 2 cm to the left of the midclavicular line with no thrills or heaves. The rhythm is regular with an S_3 and an S_4 gallop; no murmurs are noted. The remainder of M.R.'s examination is within normal limits.

Significant laboratory values include the following:

Sodium, 142 mEq/L
Potassium, 4.9 mEq/L
Chloride, 101 mEq/L
Bicarbonate, 23 mEq/L
Urea nitrogen, 30 mg/dL
Serum creatinine, 1.2 mg/dL
Hematocrit, 38%
Hemoglobin, 13 g/dL
White blood cell count and differential, within normal limits
Troponin—negative × 2

Urinalysis shows 1+ hemoglobin and 1+ protein. Microscopic examination of the urine reveals 5 to 10 red blood cells per high-power field and no casts. Pulse oximetry reveals an oxygen saturation of 88%. An electrocardiogram demonstrates sinus tachycardia and left ventricular hypertrophy but no T wave changes compared to baseline. The chest radiograph shows moderate cardiomegaly and bilateral fluffy pulmonary infiltrates.

What aspects of M.R.'s history and physical examination are characteristic of an emergent need to immediately lower his BP?

Hypertensive crisis occurs most often in males and in individuals between ages 40 and 60 years. Furthermore, many patients who present with hypertensive crisis have a recent history of discontinuing the use of their antihypertensives,[14,16] as is the case with M.R. in Case 16-2 and M.M. in Case 16-1.

Recent-onset severe headache, nausea, and vomiting are consistent with central nervous system signs of severe hypertension, as are the acute onset of angina (substernal chest pain) and acute HF (shortness of breath, increased pulse and respiratory rate, cardiomegaly, S_3, and chest radiographic findings of pulmonary edema). The absence of signs of right-sided HF such as jugular venous distention or hepatomegaly suggests an acute onset of HF caused by hypertension as opposed to a gradual worsening of chronic HF. M.R.'s urinary sediment is relatively unimpressive at this time, especially in light of his history, and his ocular complications are minimal. M.R.'s presentation is considered hypertensive emergency because of the presence of HF symptoms; M.R. should be admitted to the hospital as IV antihypertensive therapy is warranted.

Parenteral Drug Therapy

NITROPRUSSIDE

Case 16-2, Question 2: M.R. is to be started on nitroprusside. Is this an appropriate choice of drug? What alternatives to nitroprusside are available?

M.R.'s arterial pressure should be lowered with parenteral medications, which have a rapid onset of action. Nitroprusside, fenoldopam, and IV nitroglycerin all decrease total peripheral resistance rapidly with minimal effect on myocardial oxygen consumption and heart rate. Of these agents, either nitroprusside or fenoldopam would be preferred in patients with hypertension accompanied by decompensated HF in the absence of MI. Parenteral nitroglycerin is similar to nitroprusside except that it has a

relatively greater effect on venous circulation and less effect on arterioles. It is most useful in patients presenting with angina secondary to coronary insufficiency, ischemic heart disease, MI, or hypertension after coronary bypass surgery (also see Case 16-3, Question 6). In addition, both nitroprusside and IV nitroglycerin may decrease elevated left ventricular diastolic pressures in patients presenting with hypertensive emergency and pulmonary edema. Although nitroglycerin may be used preferentially for someone who is experiencing chest pain in the setting of an MI, this patient is not having an acute coronary syndrome, which is confirmed by negative troponins and electrocardiogram. Before considering nitroprusside, it is important to consider the etiology of the chest pain. As described earlier, the chest discomfort is likely caused by acute-onset HF owing to severe hypertension. Nitroprusside provides an advantage over nitroglycerin because it provides both arterial and venous vasodilation, allowing for further reduction in peripheral resistance and left ventricular diastolic pressures. Nitroglycerin has a relatively greater effect on venous circulation, especially at lower doses.

Fenoldopam and nitroprusside are equally efficacious in acutely lowering BP.[60–63] Both medications have an immediate onset, are easily titratable, have a short duration of action, and are relatively well tolerated.[64–67] Unlike nitroprusside, fenoldopam does not cause cyanide or thiocyanate toxicity. However, fenoldopam is associated with dose-related tachycardia and should be avoided in those with concern for active coronary ischemia.

Therefore, in the absence of any significant renal or liver disease, nitroprusside is the preferred treatment for M.R.

Hemodynamic effects

Nitroprusside has many pharmacologic effects that should improve M.R.'s condition. It dilates both venous and arterial vessels, thereby increasing venous capacitance and decreasing the venous return or preload on the heart (see Chapter 14, Heart Failure). A decrease in the pulmonary capillary wedge pressure and ventricular filling pressure will ultimately improve M.R.'s pulmonary edema. Afterload

is also decreased as a result of arterial dilation. This action increases cardiac output, reduces arterial pressure, and increases tissue perfusion.

Concurrent use of diuretics

Case 16-2, Question 3: Should M.R. be given a diuretic before nitroprusside therapy is begun?

Administration of potent IV diuretics is relatively ineffective in the acute treatment of hypertensive crisis except in patients with concomitant volume overload or HF. Many patients with hypertensive emergencies are vasoconstricted and have normal or reduced plasma volumes; therefore, diuretics have little effect and may actually aggravate renal impairment or cause other adverse effects.[24,68] Furthermore, when diuretics are given acutely in combination with other antihypertensive agents, profound hypotension can occur.

The immediate value of diuretics in acute HF is related more to their hemodynamic effects (venodilation) than to diuresis. Venodilation after IV diuretic administration decreases right-sided cardiac filling pressures, decreases pulmonary artery and wedge pressures, and increases cardiac output before diuresis occurs.[69] The presence of HF, pulmonary edema, and severely elevated BP in M.R. warrants IV administration of a loop diuretic (eg, furosemide [Lasix®] 40 mg, torsemide [Demadex®] 10–20 mg, or bumetanide [Bumex®] 1 mg) in addition to nitroprusside.

Dosing and administration

Case 16-2, Question 4: What dose of nitroprusside should be used initially?

Effective infusion rates range from 0.1 to 10 µg/kg/min.[70,71] For M.R., an infusion of nitroprusside should be initiated at a rate of 0.1

μg/kg/min. The dose should be increased slowly by 0.2 μg/kg/min every 10 to 20 minutes until the desired pressure is achieved. Although a maximum infusion rate of 10 μg/kg/min has been recommended, this rate should not be continued for more than 10 minutes. If adequate BP control has not been achieved within this time frame, nitroprusside should be discontinued and alternative therapy initiated.[4] The dosage must be individualized according to patient response using continuous intraarterial BP recording and observing for signs or symptoms of toxicity.

Nitroprusside decomposes on exposure to light, so the solution should be shielded with an opaque sleeve. It is not necessary to protect the tubing from light. Reconstituted solutions are stable for 24 hours at room temperature. A change in the solution's color from light brown to dark brown, green, orange, or blue indicates a loss in activity. The solution should be discarded if this change occurs.

Therapeutic end point

Case 16-2, Question 5: A nitroprusside infusion is started. What is the goal of therapy?

For most patients, BP should be reduced by no more than 25% within the first hour, then if stable, therapy can be titrated to achieve a goal BP of 160/100 mm Hg during the next 2 to 6 hours. BPs can then be reduced to 140/80 mm Hg levels within 24 to 48 hours. However, because M.R. has a cerebral occlusive disease (carotid bruits), excessive reduction of his BP should be avoided to minimize the risk of decreased cerebral blood flow causing stroke or other neurologic complications.

Normal cerebral blood flow remains relatively constant over a wide range of systemic BP measurements through autoregulatory mechanisms.[43,72] The autoregulatory effects can prevent large alterations in cerebral blood flow from either slow or rapid changes in systemic arterial pressures. In addition, the arterial BP required to maintain cerebral perfusion is higher in patients with hypertension

than in normotensive individuals. If M.R.'s BP is reduced excessively, cerebral blood flow may decrease sharply. Therefore, a DBP of 100 to 105 mm Hg would be a reasonable initial therapeutic goal for him in the first 6 hours. If hypotension occurs, nitroprusside should be discontinued, and M.R. should be placed in the Trendelenburg position, in which the head is kept lower than the trunk.

Cyanide toxicity

Case 16-2, Question 6: M.R. is being treated with nitroprusside. However, during the last 24 hours, dose titration to 7 µg/kg/min has been necessary to control his BP. His tachycardia, chest discomfort, and dyspnea have resolved. Is he at risk of developing cyanide toxicity? What indices of toxicity should be monitored? Are there agents available to prevent toxicity?

A major concern when using sodium nitroprusside is toxicity secondary to the accumulation of its metabolic by-products, cyanide, and thiocyanate. Sodium nitroprusside decomposes within a few minutes after IV infusion. Free cyanide, which represents 44% of nitroprusside by weight, is released into the bloodstream, producing prussic acid (hydrogen cyanide), which is responsible for acute toxicity.[73] The amount of hydrogen cyanide released is dose related.[74] Endogenous detoxification of cyanide occurs through a mitochondrial rhodanese system, which, in the presence of a sulfur donor such as thiosulfate, converts cyanide to thiocyanate.[73] Theoretically, cyanide can be expected to accumulate in the body when the rate of the sodium nitroprusside infusion exceeds 2 µg/kg/min for a prolonged period, or when doses exceed 4 µg/kg/min for as short as 2 to 3 hours. The presence of hepatic or renal impairment may also predispose the patient to cyanide toxicity.[75,76]

Symptomatic cyanide toxicity occurs infrequently; however, several deaths have been reported after the use of sodium nitroprusside.[77] Cyanide toxicity occurs most commonly when large doses (total dose 1.5 mg/kg) of nitroprusside are administered rapidly to patients undergoing a surgical procedure that requires induction of hypotension. However, cyanide toxicity and mortality

associated with nitroprusside exceed 1000 and 3000 cases per year, respectively, according to two sources.[77,78]

Although concurrent sodium thiosulfate administration has been recommended in high-risk patients, no clinical data are available to indicate that it reduces overall mortality.[79] Furthermore, this intervention may result in the accumulation of thiocyanate, particularly if sodium thiosulfate is given at high infusion rates or to patients with renal insufficiency. Hydroxocobalamin has also been used to reduce the risk of cyanide toxicity secondary to nitroprusside infusions, but its use is limited because of poor availability and cost considerations.[76] With the availability of safer alternatives (eg, fenoldopam, IV labetalol, IV nicardipine, and IV clevidipine) for use in high-risk patients, the use of hydroxocobalamin or thiosulfate is rarely required.

Cyanide toxicity can be detected early by monitoring M.R.'s metabolic status. Lactic acidosis is an early indicator of toxicity because the progressive inactivation of cytochrome oxidase by cyanide results in increased anaerobic glycolysis.[80,81] A low plasma bicarbonate concentration and low pH, accompanied by an increase in the blood lactate or lactate-to-pyruvate ratio could indicate cyanide toxicity.[81] Additional signs of cyanide intoxication include tachycardia, altered consciousness, coma, convulsions, and the occasional smell of almonds on the breath.[74,81] Measuring serum thiocyanate levels is of no value in detecting the onset of cyanide toxicity. If toxicity develops, the infusion should be stopped and appropriate therapy for cyanide intoxication instituted. The need for such a high-dose infusion of nitroprusside to maintain M.R.'s pressure may increase his risk for cyanide toxicity, warranting close monitoring of his acid–base balance or converting to alternative therapy.

Thiocyanate toxicity

Case 16-2, Question 7: What are the differences between cyanide toxicity and thiocyanate toxicity. What is M.R.'s risk for thiocyanate toxicity if he is continued on a dose of 7 µg/kg/min? Is monitoring of serum thiocyanate concentrations necessary?

Sodium nitroprusside is more likely to produce thiocyanate toxicity. Although this complication is also rare, patients with renal impairment who receive infusions beyond 72 hours are particularly susceptible. Conversion of cyanide to thiocyanate, via sulfation by the liver, proceeds relatively slowly. The half-life of thiocyanate is 2.7 days with normal renal function and up to 9 days in patients with renal failure.[82] When sodium nitroprusside is infused for several days at moderate dosages (2–5 µg/kg/min), toxic levels of thiocyanate can occur within 7 to 14 days in patients with normal renal function and 3 to 6 days in patients with severe renal disease.[73]

Thiocyanate causes a neurotoxic syndrome manifested by psychosis, hyperreflexia, confusion, weakness, tinnitus, seizures, and coma.[75,82] Prolonged exposure to thiocyanate can suppress thyroid function through inhibition of iodine uptake and binding by the thyroid gland.[82] Measurement of blood levels of thiocyanate is only recommended in patients with renal disease or when the duration of the nitroprusside infusion exceeds 3 or 4 days. Nitroprusside should be discontinued if serum thiocyanate levels exceed 10 to 12 mg/dL.[83,84] Life-threatening toxicity is of concern when blood thiocyanate levels exceed 20 mg/dL. In emergency cases, thiocyanate can be readily removed by hemodialysis.[82]

For M.R., the potential for thiocyanate toxicity is low because his renal function is normal and the infusion duration currently has been relatively short. Therefore, measurement of thiocyanate levels is not indicated at this time.

Other side effects associated with nitroprusside therapy include nausea, vomiting, diaphoresis, nasal stuffiness, muscular twitching, dizziness, and weakness. These effects are usually acute and associated with rapid infusion rates.

Case 16-2, Question 8: M.R.'s serum chemistries and arterial blood gas values indicate metabolic acidosis. Should the nitroprusside infusion be continued at 7 µg/kg/min? What alternatives are available?

Although the duration of M.R.'s nitroprusside therapy has been short, tolerance to the antihypertensive effect requires the use of a high-dose infusion to maintain BP control. Thus, acidosis may represent toxicity as a result of cyanide accumulation. The nitroprusside infusion should be discontinued at this time, and another rapidly acting, easily titratable parenteral antihypertensive such as fenoldopam or IV nitroglycerin should be initiated.

FENOLDOPAM

CASE 16-2, QUESTION 9: What are the advantages and disadvantages of fenoldopam compared with sodium nitroprusside?

Fenoldopam is a parenteral, rapidly acting, peripheral dopamine-1 agonist used to manage hypertensive crisis when a rapid reduction in BP is required.[85–88] Stimulation of the dopamine-1 receptors vasodilates coronary, renal, mesenteric, and peripheral arteries.[89,90] Fenoldopam has been used to control perioperative hypertension in patients undergoing cardiac bypass surgery as it had been thought to improve renal blood flow and maintain glomerular filtration.[91] This has been refuted after it was demonstrated that low-dose fenoldopam does not reduce the risk of renal replacement therapy or 30-day mortality.[66,90,92]

Fenoldopam is as effective as sodium nitroprusside for the treatment of hypertensive emergencies and does not cause either cyanide or thiocyanate toxicity.[61–63] Fenoldopam can be considered as an alternative to nitroprusside in patients who are at high risk for cyanide or thiocyanate toxicity, although its use has decreased considerably owing to its significantly higher cost.

Clearance of fenoldopam is not altered by renal or liver disease. Like nitroprusside, fenoldopam also has a short duration of action, with an elimination half-life of ~5 minutes, thus allowing for easy titration.[87,93] BP and heart rate should be monitored frequently to avoid hypotension and dose-related reflex tachycardia. Flushing and headache may occur. Serum potassium should be monitored and

repleted as necessary. Fenoldopam should be used cautiously in patients with glaucoma or intraocular hypertension owing to a dose-dependent increase in intraocular pressure.[94,95]

Case 16-2, Question 10: Which antihypertensive agents should be avoided in M.R.? Why?

Labetalol, a potent, rapidly acting antihypertensive with both α- and β-blocking activity, is very effective in the treatment of hypertensive emergencies,[95–102] but it should not be used in M.R. Hemodynamically, labetalol reduces peripheral vascular resistance (afterload), BP, and heart rate, with almost no change in the resting cardiac output or stroke volume.[103]

M.R. was experiencing chest pain and had tachycardia on admission; these signs and symptoms are most likely caused by his severely elevated BP and the presence of acute left ventricular failure. Although labetalol may have alleviated M.R.'s angina, the negative inotropic action could acutely compromise his left ventricular dysfunction, an effect that outweighs the potential benefit of afterload reduction. In addition, although labetalol is one of the safest β-blocking drugs when used in patients with asthma,[104] β-blocker therapy should be avoided as initial treatment in patients with asthma. Labetalol should be used only if alternative methods of reducing M.R.'s BP fail.

LABETALOL

CASE 16-3

Question 1: C.M., a 52-year-old male, is admitted to the hospital with a 3-day history of increasing exertional substernal chest pain (without shortness of breath), diaphoresis, nausea, and vomiting. His history is significant for poorly controlled hypertension, glaucoma, and angina pectoris. Prior medications include dorzolamide ophthalmic drops, atenolol, hydrochlorothiazide, and oral nitrates. Physical examination reveals an anxious male who is alert and oriented. He has a BP of 210/146 mm Hg without orthostasis and a regular pulse of 115 beats/min. Bilateral hemorrhages and exudates are present on

funduscopic examination. The lungs are clear, and the point of maximal impulse is displaced. There are no murmurs or gallops. Examination of the abdomen is unremarkable, and there is no peripheral edema. The neurologic examination is normal.

Significant laboratory values include the following:

Urea nitrogen, 49 mg/dL
Serum creatinine, 2.8 mg/dL

Serum creatinine was previously noted to be 1.2 mg/dL. Urinalysis shows proteinuria and hematuria. The electrocardiogram demonstrates sinus tachycardia with left-axis deviation, left ventricular hypertrophy, and nonspecific ST-T wave changes. The chest radiograph reveals mild cardiomegaly.

C.M. is given nitroglycerin sublingually, and 1 inch of nitroglycerin ointment is applied topically. He is started on IV labetalol.

Is this choice of treatment reasonable, considering C.M.'s angina and acute kidney injury?

The presence of chest pain, retinopathy, new-onset renal disease, and BP elevation in C.M. classifies his presentation as a hypertensive emergency that warrants a prompt reduction in BP. Sublingual and topical nitroglycerin may help in acutely and temporarily lowering his BP and relieve his chest pain while waiting for more definitive treatment to be implemented.

IV labetalol has been used successfully in hypertensive emergencies.[96–102] Labetalol blocks both β- and α-adrenergic receptors and also may exert a direct vasodilator effect. The β-blockade is nonselective with β-to-α potency of 3:1 for oral and 7:1 for IV. Labetalol is advantageous in C.M. because the immediate onset of action will reduce peripheral vascular resistance without causing reflex tachycardia. Myocardial oxygen demand will be reduced and coronary hemodynamics will be improved, making this agent an excellent choice for patients such as C.M., with anginal symptoms or MI. In addition, IV labetalol does not significantly reduce cerebral blood flow; therefore, it may be useful in patients with cerebrovascular disease.[1,25]

Fenoldopam or nitroprusside could also be used to treat C.M. Fenoldopam could be considered, but C.M.'s history of glaucoma would preclude its use. Additionally, fenoldopam would not be preferred because of its potential for reflex tachycardia and the risk

of worsening ischemia. Treatment with nitroprusside would expose C.M. to the potential risk of cyanide and thiocyanate toxicity with his new-onset acute kidney injury. In contrast, labetalol has been used successfully in patients with renal disease without deleterious side effects.[105,106] Labetalol is eliminated by glucuronidation in the liver, with <5% of the dose being excreted unchanged in the urine.

Contraindications and precautions

Case 16-3, Question 2: What cautions should be exercised when using labetalol in C.M.?

Labetalol's disadvantages are primarily related to its β-blocking effects. Therefore, it should not be used in patients with asthma or obstructive airway disease, heart block greater than first degree, or sinus bradycardia, and it should be used with caution in patients with decompensated HF[97,101,107,108] (see Case 16-2, Question 10). Nonselective β-blockers, such as labetalol, have been associated with an increased risk of moderate or severe asthma exacerbations, as compared with cardioselective β-blockers.[109] None of these are present in C.M. Labetalol has been effective in the treatment of hypertension associated with pheochromocytoma and excess catecholamine states as well as those with rebound hypertension from β-blocker withdrawal.[110] However, because labetalol is primarily a β-blocker, paradoxical hypertension may occur in patients with pheochromocytoma. These individuals have adrenal tumors that excrete high amounts of norepinephrine, which results in relatively unopposed α-1-receptor stimulation.[110] More clinical experience is required before labetalol can be recommended in patients with pheochromocytoma.[6,96]

Case 16-3, Question 3: How should parenteral labetalol be given to C.M.?

IV labetalol can be given by bolus administration or continuous infusion.[96–101] Bolus injections are administered, beginning with 10 to

20 mg given at a rate of 10 mg/min, followed by 20 to 80 mg every 10 minutes until the desired response is achieved or a cumulative dose of 300 mg is reached. The desired response is usually achieved with a mean dose of 200 mg in 90% of patients.[97] The maximal effect occurs within 5 to 15 minutes,[99] and the antihypertensive response may persist for more than 6 hours.[111] Because the rate of BP reduction is accelerated with an increase in infusion rate,[99] a controlled continuous infusion may provide a more gradual reduction in arterial pressure with less frequent adverse effects.[101,112] The infusion can be started at a rate of 0.5 to 2 mg/min and titrated at a rate of 0.5 mg/min every 15 minutes until a satisfactory response is achieved or until a cumulative dose of 300 mg is reached. However, it is important to note that labetalol has a long half-life, and prolonged infusions can lead to accumulation and have been associated with dangerous, potentially fatal cases of delayed hemodynamic compromise.[113] Once the cumulative dose is achieved, therapy should be transitioned to oral dosing as soon as possible.

Parenteral to oral conversion

Case 16-3, Question 4: C.M. was treated with a labetalol infusion and required a cumulative dose of 180 mg to achieve a DBP of 100 mm Hg. His anginal symptoms resolved almost immediately, but 3 hours after the infusion, C.M. became faint and dizzy while ambulating. Should oral labetalol be withheld in C.M.?

Postural hypotension and dizziness are dose related and more commonly associated with the IV route of administration.[103,107] C.M. should remain in a supine position after the IV administration of labetalol, and his ability to tolerate an upright position should be established before permitting ambulation. Oral labetalol can be given to C.M. when his symptoms resolve. There is no correlation between the oral maintenance dose and the total initial IV dose. C.M. should be started on an empiric dose of 200 mg of oral labetalol two to three times per day, and this can be titrated as necessary at ≥1-day

intervals to a range of 400 mg/day to 2.4 g/day in two to three divided doses.

Case 16-3, Question 5: What other side effects can occur with labetalol therapy?

Other side effects commonly associated with labetalol include nausea, vomiting, abdominal pain, and diarrhea in up to 15% of the patients.[107] Scalp tingling is an unusual side effect that has been reported in a few patients after IV administration; it tends to disappear with continued treatment. Other side effects include tiredness, weakness, muscle cramps, headache, and skin rashes.

NITROGLYCERIN

Case 16-3, Question 6: Would parenteral nitroglycerin be an acceptable alternative to labetalol for C.M.?

Hypertensive emergencies in the setting of unstable angina or MI requires an immediate reduction in BP. Nitroprusside has been used successfully, but IV nitroglycerin can have more favorable effects on collateral coronary flow in patients with ischemic heart disease.[114] By diminishing preload, nitroglycerin decreases left ventricular diastolic volume, diastolic pressure, and myocardial wall tension, thus reducing myocardial oxygen consumption.[115] These changes favor redistribution of coronary blood flow to the subendocardium, which is more vulnerable to ischemia. At high dosages, nitroglycerin dilates arteriolar smooth muscles, and this reduction in afterload also decreases myocardial wall tension and oxygen consumption.[116]

IV nitroglycerin has a rapid onset of action and a short duration and is easily titratable. It is generally appropriate to begin IV nitroglycerin in the dose range of 5 to 10 µg/min, increased by 5 µg/min every 3 to 5 minutes up to 20 µg/min. If no response occurs at 20 µg/min, the dose can be titrated by 10 to 20 µg/min every 3 to 5 minutes as needed to control pressure and symptoms. The usual

dose ranges from 40 to 100 µg/min. The major limiting side effects are headache and tachyphylaxis. In general, IV nitroglycerin is well suited for use in patients such as C.M. who have angina or in patients who have hypertensive emergency associated with MI or coronary artery bypass surgery.

HYDRALAZINE

CASE 16-4

QUESTION 1: T.M., a 30-year-old male with a history of chronic glomerulonephritis and poorly controlled hypertension, came to the ED for evaluation of early morning occipital headaches during the past week. He has no other symptoms. He has not taken any BP medication in a month. Physical examination revealed an afebrile male in no acute distress with a BP of 160/128 mm Hg without orthostasis and a regular pulse of 90 beats/min. Funduscopic examination revealed bilateral exudates without hemorrhages or papilledema. The lungs were clear. Cardiac examination was pertinent for cardiomegaly and an S_4 gallop. The remainder of the physical workup was normal.

Laboratory results include the following values:

Hematocrit, 32%
Blood urea nitrogen, 40 mg/dL
Serum creatinine, 2.5 mg/dL (baseline serum creatinine 1.9 mg/dL)
Bicarbonate, 18 mEq/L

Urinalysis reveals 2+ protein, 2+ hemoglobin with 4 to 10 red blood cells per high-power field. The electrocardiogram demonstrates normal sinus rhythm with left ventricular hypertrophy. The chest radiograph is unremarkable.

T.M.'s presentation meets the criteria for a hypertensive emergency (ie, DBP >120 mm Hg and presence of worsening renal function). IV antihypertensive therapy is required for T.M., and he was given 20 mg of hydralazine IV. A repeat BP after 1 hour was 150/100 mm Hg.

What are the advantages and disadvantages of parenteral hydralazine, and when should it be used to acutely lower BP?

Hydralazine is a direct vasodilator that reduces systemic resistance through relaxation of the arterial smooth muscle, with little effect on veins. It is rarely used to treat hypertensive emergencies because its antihypertensive response is less predictable than that of other parenteral agents. Additionally, hydralazine has a prolonged

half-life, which can be problematic if too fast correction or hypotension occurs.[24] It is not consistently effective in controlling crises associated with essential hypertension.

Contraindications

Hydralazine should not be used in patients with coronary heart disease because the reflex tachycardia causes an increase in myocardial oxygen demand, which may result in the development or worsening of ischemic symptoms. In addition, hydralazine should be avoided in patients with aortic dissection because of its reflex cardiostimulating effect. In contrast, hydralazine can be useful in patients such as T.M., who have a chronic renal failure because the reflex increase in cardiac output is accompanied by an increase in organ perfusion.[23]

Dosing and administration

Parenteral hydralazine should be considered an intermediate treatment between oral agents and more aggressive therapy with agents such as clevidipine, nicardipine, fenoldopam, or nitroprusside. It can be given IV or intramuscularly. The onset of action develops slowly over 10 to 80 minutes. The prolonged duration of effect up to as long as 12 hours makes additional dosing requirements unpredictable. Parenteral doses are considerably lower than oral doses because of extensive first-pass metabolism.

OTHER PARENTERAL DRUGS

Case 16-4, Question 2: What are the alternatives to hydralazine for parenteral treatment of hypertensive crisis?

Intravenous enalaprilat

Enalaprilat, the active metabolite of the oral prodrug enalapril, is approved by the U.S. Food and Drug Administration for the treatment of hypertension and has been used to treat severe

hypertension.[117–122] The initial dose is 0.625 to 1.25 mg IV given over 5 minutes and can be repeated every 6 hours, if necessary. To minimize the risk of hypotension, the initial doses should not exceed 0.625 mg in patients receiving diuretics or in patients with clinical evidence of hypovolemia or with a history of HF or hyponatremia. The onset of action is within 15 minutes, but the maximal effect may take 1 to 4 hours. Because only 60% of patients respond to BP reduction within 30 minutes, it cannot be reliably used to acutely lower BP in hypertensive emergencies.[120] Although higher initial doses have been successfully used to achieve BP control,[121] some evidence indicates that initial doses >0.625 mg do not significantly alter the magnitude of enalaprilat's antihypertensive effect.[119] Enalaprilat is also beneficial in patients with HF. Precautions for the use of enalaprilat are similar to those of captopril (see Case 16-1, Question 5). Because of the prolonged time required to achieve an adequate response, limited clinical experience, and variable response rates (especially in Black patients), enalaprilat cannot be recommended for the routine treatment of patients with hypertensive emergencies.[120,122]

Intravenous calcium channel blockers

CASE 16-5

QUESTION 1: H.C. is a 71-year-old male undergoing urgent coronary artery bypass graft surgery after an MI. H.C. has a history of cerebrovascular accident and chronic kidney disease (serum creatinine is stable at 1.6 mg/dL). Two hours after surgery, H.C.'s BP increased from 142/90 to 170/132 mm Hg. H.C. was administered IV nicardipine postoperatively for BP control.

Is nicardipine an appropriate choice for H.C.?

Nicardipine

Postoperative hypertension is typically short-lived and is most commonly seen after neurosurgical, head and neck, vascular, and cardiothoracic procedures (as is the case with H.C.). Treatment is typically only required for 6 hours postoperatively and up to 24 to 48

hours for some who may have persistent hypertension. Adequate control of BP postoperatively is necessary to minimize the risk of cardiovascular, neurologic, or surgical-site complications such as bleeding.[123] When selecting an agent, one should consider therapies with a quick onset and short duration of action as well as established efficacy and safety in the postoperative setting.

Nicardipine is a potent cerebral and systemic vasodilator and a useful therapeutic option in the management of severe hypertension. Its onset of action is within 1 to 2 minutes, and its elimination half-life is 45 minutes, with a terminal half-life of 14 hours after prolonged infusions.[124] Hemodynamic evaluations demonstrated that IV nicardipine significantly decreased mean arterial pressure and systemic vascular resistance and significantly increased cardiac index with little or no change in heart rate.[125] As a dihydropyridine, nicardipine has less negative inotropic activity compared with nondihydropyridines. Titratable IV nicardipine has been studied extensively for use in controlling postoperative hypertension[125–128] and hypertensive emergencies.[129–132]

In the treatment of postoperative hypertension,[125] IV nicardipine was administered as an infusion titrated in the following manner: 10 mg/hour for 5 minutes, 12.5 mg/hour for 5 minutes, and 15 mg/hour for 15 minutes, followed by a maintenance infusion of 3 mg/hour thereafter. The mean response times and infusion rates were 11.5 minutes and 12.8 mg/hour, respectively. The most commonly reported adverse effects included hypotension, tachycardia, and nausea and vomiting. In hypertensive emergency, the recommended initial dose of nicardipine infusion is 5 mg/hour, titrated by 2.5 to 5 mg/hour every 5 to 15 minutes to achieve goal BP with a maximum dose of 15 mg/hour.

In studies of patients receiving nicardipine versus nitroprusside for postoperative hypertension after cardiac endarterectomy and coronary artery bypass grafting, breakthrough BP was controlled more rapidly with nicardipine and required fewer overall dose titrations. In addition, nicardipine was well tolerated and did not lead to an increased risk of complications.[133,134]

Nicardipine is an appropriate choice of therapy for H.C. in the postoperative setting because this agent has a rapid onset of action and provides sustained BP control during the infusion period. It is easily titratable, with a predictable response, and is relatively free of severe adverse effects. Therapy should be titrated to achieve a BP ~10% higher than the patient's baseline. In addition to nicardipine, clevidipine, nitroprusside, nitroglycerin, and labetalol are commonly used to manage perioperative hypertension.[123,135] Nicardipine may be useful in patients with cerebral insufficiency or peripheral vascular disease. Additionally, among patients undergoing cardiac surgery, nicardipine may exert a beneficial effect on pulmonary wedge pressure and cardiac index, as compared to nitroprusside.[136] Because of the potential for reflex tachycardia, it should be used with caution in patients with ongoing coronary ischemia.

Clevidipine, a third-generation dihydropyridine, has also been shown to be useful in controlling BP in hypertensive emergencies and in the perioperative setting.[135,137,138]

Case 16-5, Question 2: What other IV forms of calcium channel blockers are available? Would any of these agents be an appropriate choice of therapy for H.C.?

Nondihydropyridines

Intravenous verapamil (5–10 mg) produces a significant reduction in BP, which occurs within 3 to 5 minutes and persists for up to 6 hours. As a cardiovascular drug, it is primarily used as a rate-controlling agent in the treatment of supraventricular tachycardias.

IV diltiazem is approved for temporary control of the ventricular rate in atrial fibrillation or atrial flutter and for rapid conversion of paroxysmal supraventricular tachycardia.[139–141] Parenteral diltiazem has also been used to control hypertension that occurs intraoperatively and postoperatively[142,143] and in patients with an acute coronary syndrome.[144,145] However, published experience with the use of IV diltiazem for the treatment of severe hypertension is limited.[146,147]

Atrioventricular nodal conduction abnormalities can occur during the administration of IV verapamil or diltiazem. Patients receiving either of these therapies require continuous monitoring by electrocardiogram and frequent BP checks. Intravenous verapamil and diltiazem should be avoided in patients with sick sinus syndrome or advanced degrees of heart block. Until additional information is available, caution should be exercised in using either agent parenterally to lower BP acutely. In addition, use of nondihydropyridines should be avoided when acutely treating any hypertensive patient with concomitant systolic HF owing to their negative inotropic effects.

CASE 16-5, QUESTION 3: What factors should clinicians consider before recommending the use of clevidipine?

Clevidipine

Clevidipine is another IV dihydropyridine calcium channel blocker with arterial-selective vasodilatory properties.[148] Clevidipine is quickly metabolized in extravascular tissue and blood by esterases, leading to a short initial elimination half-life of 1 minute and a terminal half-life of 15 minutes,[149] with complete resolution of hemodynamic effects within 5 to 15 minutes after the end of a 24-hour continuous infusion.[150] Clevidipine demonstrates a quick onset of action of 2 to 4 minutes.[151] These pharmacokinetic and pharmacodynamic properties make it an attractive agent for managing hypertensive emergencies. Clevidipine demonstrated efficacy in the treatment of hypertension in both preoperative and postoperative cardiac surgery patients.[135,152,153] In this setting, therapy was initiated at a rate of 0.3 to 0.4 μg/kg/min. Target BP was a reduction of at least 15% from baseline. The dose was titrated every 90 seconds by doubling the dose up to an infusion rate of 3.2 μg/kg/min, then increasing the dose by 1.5 μg/kg/min to a maximum rate of 8 μg/kg/min. Clevidipine demonstrated a median time of effectiveness within 6 minutes in >90% of the patients who received the study medication.

A systematic review and meta-analysis compared clevidipine with nitroglycerin, nitroprusside, and nicardipine in the management of perioperative hypertension.[135] Clevidipine was more effective in maintaining BP within the target range with a reduction in rates of treatment failure, without an increase in adverse events or atrial fibrillation. Differences in clinical outcomes have not been identified.

Based on the limited data, nondihydropyridines would not be an appropriate choice of therapy for H.C. Additionally, IV verapamil has a long duration of action, which is not an ideal characteristic in the setting of postoperative hypertension. Clevidipine, however, has a rapid onset of action and short duration of action and is effective in controlling BP in the perioperative setting.

Clevidipine infusions can induce reflexive tachycardia with an increased heart rate by up to ~20 beats/min.[150] Clevidipine is formulated in a 20% lipid emulsion and provides 2 kcal/mL of lipids. Clevidipine infusions are typically initiated at a dose of 1 to 2 mg/hour, with titration occurring by doubling the dose at 90-second intervals. When approaching goal BP, the dose may be increased by less than double every 5 to 10 minutes. In general, each 1 to 2 mg/hour increase in dose may produce an approximate reduction in BP of 2 to 4 mm Hg. The recommended maximum dose is 21 mg/hour, which provides 1000 mL (2000 kcal) in a 24-hour period, although the short-term use of doses up to 32 mg/hour has been reported. It should be avoided in patients with serum triglycerides >500 mg/dL, and any remaining drug and associated tubing should be discarded after 12 hours of use. Clevidipine is contraindicated in patients with allergies to soybeans, soy products, eggs, or egg products. This agent is also contraindicated in those with defective lipid metabolism or acute pancreatitis (if accompanied by hyperlipidemia) and in patients with severe aortic stenosis.[151]

Aortic Dissection

TREATMENT

CASE 16-6

QUESTION 1: B.S., a 68-year-old male with a long history of hypertension and nonadherence, presents to the local ED after experiencing the sudden onset of severe, sharp, diffuse chest pain that radiates to his back between his shoulder blades. Significant findings on physical examination include a pulse of 100 beats/min, BP of 200/120 mm Hg, clear lungs, and an S_4 without murmurs. The laboratory data are unremarkable. The electrocardiogram results are interpreted as sinus tachycardia with left ventricular hypertrophy, but no acute changes are noted. The chest radiograph is significant for widening of the mediastinum. An emergency chest computed tomography scan reveals a dissection at the arch of the aorta.

What antihypertensive medication(s) would be most appropriate for B.S., and why?

Dissection of the aorta occurs when the innermost layer of the aorta (the intima) is torn such that blood enters and separates its layers. The ultimate treatment for this type of hypertensive emergency depends on its location and severity; however, the first principle of therapy is to control any existing hypertension with agents that do not increase the force of cardiac contraction or heart rate. This lessens the force that the cardiac impulse transmits to the dissecting aneurysm.

The aim of antihypertensive therapy in aortic dissection is to lessen the pulsatile load or aortic stress by lowering the BP. Reducing the force of left ventricular contractions, and consequently the rate of rise of aortic pressure, retards the propagation of the dissection and aortic rupture.[154,155] The treatment of choice for aortic dissection typically consists of vasodilatory agents such as sodium nitroprusside, nicardipine, clevidipine, or fenoldopam in combination with a β-blocker titrated to a heart rate <60 beats/min.[154,156,157] Labetalol monotherapy has been used as an alternative.[158] These drugs decrease BP, venous return, and cardiac contractility, thus decreasing shear stress to the aorta.

One common regimen is a combination of IV sodium nitroprusside (0.5–2 μg/kg/min) plus IV esmolol.[22,155] This combination can be used as initial therapy for B.S. The concurrent administration of a β-

blocking agent with a vasodilator is desirable because the latter may induce reflex tachycardia in response to vasodilation.

Esmolol is a parenteral cardioselective β_1-blocker with a rapid onset and short duration of action. For the management of hypertensive emergencies, esmolol should be given as a loading dose of 500 to 1000 μg/kg over 1 minute, followed by a maintenance infusion of 50 μg/kg/min and titrated in 50 μg/kg/min increments up to a maximum rate of 300 μg/kg/min. Irritation, inflammation, and induration at the infusion site occur in 5% to 10% of patients.

Hypotension is the most commonly reported adverse event and is directly related to the duration of esmolol administration.[159] However, because of the short half-life, resolution of hypotension occurs within 10 to 30 minutes of discontinuing the infusion, although this can be prolonged with extended infusion durations. Direct vasodilators such as hydralazine should be avoided because they increase stroke volume and left ventricular ejection rate. These effects augment the pulsatile flow and accentuate the sharpness of the pulse wave, increasing mechanical stress on the aortic wall, which may further dissection.[22]

Depending on the location of the dissection, surgical intervention may be required.[156,160] However, until a definitive diagnosis is made, the primary goal is to reduce the BP and myocardial contractility to the lowest level compatible with the maintenance of adequate renal, cerebral, and cardiac perfusion.[22] Aggressive BP control is warranted to minimize target-organ damage and to prevent further dissection or hemorrhage.[155] For aortic dissection, it is generally recommended that a target heart rate <60 beats/min be achieved first, followed by a systolic BP goal of 100 to 120 mm Hg.[161–163]

In addition to nitroprusside, nicardipine and clevidipine have been evaluated as antihypertensives in the management of aortic dissection and can be considered as options. Titration recommendations in this setting are consistent with prior recommendations in Case 16-5, Question 1 and Case 16-5, Question 3.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Curran MP, Robinson DM, Keating GM. Intravenous nicardipine: its use in the short-term treatment of hypertension and various other indications. *Drugs.* 2006;66:1755–1782. (132)

Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA*. 1996;276:1328–1331. (39)

Haas CE, LeBlanc JM. Acute postoperative hypertension: a review of therapeutic options. *Am J Health Syst Pharm*. 2004;61:1661–1673. (123)

Khoynezhad A, Plestis KA. Managing emergency hypertension in aortic dissection and aortic aneurysm surgery. *J Card Surg*. 2006;21(*Suppl 1*): S3–S7. (155)

Marik PE, Rivera R. Hypertensive emergencies: an update. *Curr Opin Crit Care*. 2011;17:569–580. (22)

Patel KK, Young L, Howell EH, et al. Characteristics and outcomes of patients presenting with hypertensive urgency in the office setting. *JAMA Intern Med*. 2016;176:981–988. (29)

Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418. (36)

Rodriguez MA, Kumar SK, De Caro M. Hypertensive crisis. *Cardiol Rev*. 2010;18:102–107. (3)

Key Websites

Barkis GL. Hypertensive emergencies. Merck Manual Professional Version. Accessed October 12, 2020. http://www.merckmanuals.com/professional/cardiovascular-disorders/hypertension/hypertensive-emergencies

Erbel R, Aboyans V, Boileau C, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;35:2873–2926. Accessed October 12, 2020. http://eurheartj.oxfordjournals.org/content/ehj/35/41/2873.full.pdf

COMPLETE REFERENCES CHAPTER 16 HYPERTENSIVE CRISIS

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324.
2. Ault MJ, Ellrodt AG. Pathophysiological events leading to the end-organ effects of acute hypertension. *Am J Emerg Med*. 1985;3(6, Suppl):10–15.
3. Rodriguez MA, Kumar SK, De Caro M. Hypertensive crisis. *Cardiol Rev*. 2010;18:102–107.
4. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 report [published correction appears in *JAMA*. 2003;290(2):197]. *JAMA*. 2003;28:2560–2572.
5. Bales A. Hypertensive crisis: how to tell if it's an emergency or an urgency. *Postgrad Med*. 1999;105:119–126.
6. Vidt DG. Hypertensive crises: emergencies and urgencies. *J Clin Hypertens (Greenwich)*. 2004;6:520–525.
7. Abo-Zena RA, Bobek MB, Dweik RA. Hypertensive urgency induced by an interaction of mirtazapine and clonidine. *Pharmacotherapy*. 2000;20:476–478.
8. Patel S, Robinson R, Burk M. Hypertensive crisis associated with St. John's wort. *Am J Med*. 2002;112:507–508.
9. Novak BL, Force RW, Mumford BT, Solbrig RM. Erythropoietin-induced hypertensive urgency in a patient with chronic renal insufficiency: case report and review of the literature. *Pharmacotherapy*. 2003;23:265–269.
10. Tisdale JE, Huang MB, Borzak S. Risk factors for hypertensive crisis: importance of out-patient blood pressure control. *Fam Pract*. 2004;21:420–424.
11. Adhikari S, Mathiasen R. Epidemiology of elevated blood pressure in the ED. *Am J Emerg Med*. 2014;32:1370–1372.

12. Jenke AT, McNaughton CD, Brody AM, et al. Trends in the incidence of hypertensive emergencies in US emergency departments from 2006 to 2013. *J Am Heart Assoc*. 2016;5:e004511.
13. Bender SR, Fong MW, Heitz S, Bisognano JD. Characteristics and management of patients presenting to the emergency department with hypertensive urgency. *J Clin Hypertens (Greenwich)*. 2006;8:12–18.
14. Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P. Hypertensive urgencies and emergencies: prevalence and clinical presentation. *Hypertension*. 1996;27:144–147.
15. Bennett NM, Shea S. Hypertensive emergency: case criteria, sociodemographic profile, and previous care of 100 cases. *Am J Public Health*. 1988;78:636–640.
16. Shea S, Misra D, Ehrlich MH, Field L, Francis CK. Predisposing factors for severe uncontrolled hypertension in an inner-city minority population. *N Engl J Med*. 1992;327:776–781.
17. McRae RP Jr, Liebson PR. Hypertensive crisis. *Med Clin North Am*. 1986;70:749–767.
18. Lipari M, Moser LR, Petrovitch EA, et al. As-needed intravenous antihypertensive therapy and blood pressure control. *J Hosp Med*. 2016;11:193–198.
19. Bakir A, Dunea G. Accelerated and malignant hypertension: experience from a large American inner city hospital. *Int J Artif Organs*. 1989;12:675–676.
20. McNair A, Krogsgaard AR, Hilden T, Nielsen PE. Reversibility of cerebral symptoms in severe hypertension in relation to acute antihypertensive therapy. *Acta Med Scand Suppl*. 1985;693:107–110.
21. Winer N. Hypertensive crisis. *Crit Care Nurs Q*. 1990;13:23–33.
22. Marik PE, Rivera R. Hypertensive emergencies: an update. *Curr Opin Crit Care*. 2011;17:569–580.
23. Varon J. Treatment of acute severe hypertension: current and newer agents. *Drugs*. 2008;68:283–297.
24. Norlander M, Sjöquist P, Ericsson H, Rydén L. Pharmacodynamic, pharmacokinetic and clinical effects of clevidipine, an ultrashort-acting calcium antagonist for rapid blood pressure control. *Cardiovasc Drug Rev*. 2004;22:227–250.
25. Murphy C. Hypertensive emergencies. *Emerg Med Clin North Am*. 1995;13:973–1007.
26. McKindley DS, Boucher BA. Advances in pharmacotherapy: treatment of hypertensive crisis. *J Clin Pharm Ther*. 1994;19:163–180.
27. Gales MA. Oral antihypertensives for hypertensive urgencies. *Ann Pharmacother*. 1994;28:352–358.
28. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA*. 1995;274:620–625.

29. Patel KK, Young L, Howell EH, et al. Characteristics and outcomes of patients presenting with hypertensive urgency in the office setting. *JAMA Intern Med*. 2016;176:981–988.
30. Leavitt AD, Zweifler AJ. Nifedipine, hypotension, and myocardial injury. *Ann Intern Med*. 1988;108:305–306.
31. O'Mailia JJ, Sander GE, Giles TD. Nifedipine-associated myocardial ischemia or infarction in the treatment of hypertensive urgencies. *Ann Intern Med*. 1987;107:185–186.
32. Schwartz M, Naschitz JE, Yeshurun D, Sharf B. Oral nifedipine in the treatment of hypertensive urgency: cerebrovascular accident following a single dose. *Arch Intern Med*. 1990;150:686–687.
33. Fami MJ, Ho NT, Mason CM. Another report of adverse reactions to immediate-release nifedipine. *Pharmacotherapy*. 1998;18:1133–1135.
34. Bertel O, Marx BE, Conen D. Effects of antihypertensive treatment on cerebral perfusion. *Am J Med*. 1987;82(3B):29–36.
35. Talbert RL. The challenge of blood management in neurologic emergencies. *Pharmacotherapy*. 2006;26(8 Pt 2):123S–130S.
36. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418.
37. Dinsdale HB. Hypertensive encephalopathy. *Neurol Clin*. 1983;1:3–16.
38. Vaughan CJ, Delanty N. Hypertensive emergencies. *Lancet*. 2000;356:411–417.
39. Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA*. 1996;276:1328–1331.
40. Gemici K, Baran I, Bakar M, Demircan C, Ozdemir B, Cordan J. Evaluation of the effect of sublingually administered nifedipine and captopril via transcranial Doppler ultrasonography during hypertensive crisis. *Blood Press*. 2003;12:46–48.
41. Anderson RJ, Hart GR, Crumpler CP, Reed WG, Matthews CA. Oral clonidine loading in hypertensive urgencies. *JAMA*. 1981;246:848–850.
42. Handler J. Hypertensive urgency. *J Clin Hypertens*. 2006;8:61–64.
43. Varon J, Marik PE. Clinical review: the management of hypertensive crises. *Crit Care*. 2003;7:374–384.
44. Reed WG, Anderson RJ. Effects of rapid blood pressure reduction on cerebral blood flow. *Am Heart J*. 1986;111:226–228.
45. Stewart M, Burris JF. Rebound hypertension during initiation of transdermal clonidine. *Drug Intell Clin Pharm*. 1988;22:573–574.
46. Vernon C, Sakula A. Fatal rebound hypertension after abrupt withdrawal of clonidine and propranolol. *Br J Clin Pract*. 1979;33:112.

47. Damasceno A, Ferreira B, Patel S, Sevene E, Polónia J. Efficacy of captopril and nifedipine in black and white patients with hypertensive crisis. *J Hum Hypertens*. 1997;11:471–476.
48. Misra A, Jain P, Reddy RB. Sublingual captopril in hypertensive urgencies. *Postgrad Med J*. 1993;69:498–499.
49. Kaya A, Tatlisu MA, Kaplan Kaya T, et al. Sublingual vs. oral captopril in hypertensive crisis. *J Emerg Med*. 2016;50(1):108–115.
50. Komsuolu B, Sengün B, Bayram A, Komsuog`lu SS. Treatment of hypertensive urgencies with oral nifedipine, nicardipine, and captopril. *Angiology*. 1991;42:447–454.
51. van Onzenoort HA, Bussink M, Menheere PP, van Mook WN, van der Kuy PM. The effect of sublingual captopril versus intravenous enalaprilat on angiotensin II plasma levels. *Pharm World Sci*. 2006;28:131–134.
52. Angeli P, Chiesa M, Caregaro L, et al. Comparison of sublingual captopril and nifedipine in immediate treatment of hypertensive emergencies. A randomized, single-blind clinical trial. *Arch Intern Med*. 1991;151:678–682.
53. Wood BC, Sharma JN, Crouch TT. Oral minoxidil in the treatment of hypertensive crisis. *JAMA*. 1979;241:163.
54. Alpert MA, Bauer JH. Rapid control of severe hypertension with minoxidil. *Arch Intern Med*. 1982;142:2099–3104.
55. McDonald AJ, Yealy DM, Jacobson S. Oral labetalol versus oral nifedipine in hypertensive urgencies in the ED. Am J Emerg Med. 1993;11(5):460-463.
56. Gonzalez ER, Peterson MA, Racht EM, Ornato JP, Due DL. Dose-response evaluation of oral labetalol in patients presenting to the emergency department with accelerated hypertension. *Ann Emerg Med*. 1991;20:333–338.
57. Zell-Kanter M, Leikin JB. Oral labetalol in hypertensive urgencies. *Am J Emerg Med*. 1991;9:136–138.
58. Atkin S, Jaker MA, Beaty P, Quadrel MA, Cuffie C, Soto-Greene ML. Oral labetalol versus oral clonidine in the emergency treatment of severe hypertension. *Am J Med Sci*. 1992;303:9–15.
59. Wright SW, Hedges JR, Wright MB, Chudnofsky CR, MacCarthy EP. Ineffectiveness of oral labetalol for hypertensive urgency. *Am J Emerg Med*. 1990;8:472–473.
60. Devlin JW, Seta ML, Kanji S, Somerville AL. Fenoldopam versus nitroprusside for the treatment of hypertensive emergency. *Ann Pharmacother*. 2004;38:755–759.
61. Panacek E, Bednarczyk EM, Dunbar LM, Foulke GE, Holcslaw T. Randomized, prospective trial of fenoldopam vs sodium nitroprusside in the treatment of acute severe hypertension. Fenoldopam Study Group. *Acad Emerg Med*. 1995;2:959–965.
62. Pilmer B, Green JA, Panacek EA, et al. Fenoldopam mesylate versus sodium nitroprusside in the acute management of severe systemic

hypertension. *J Clin Pharmacol*. 1993;33:549–553.
63. Reisin E, Huth MM, Nguyen BP, Weed SG, Gonzalez FM. Intravenous fenoldopam versus sodium nitroprusside in patients with severe hypertension. *Hypertension*. 1990;15(2, Suppl):159–162.
64. Garwood S, Hines R. Perioperative renal preservation: dopexamine and fenoldopam—new agents to augment renal performance. *Semin Anesth Perioper Med Pain*. 1998;17:308–318.
65. Murphy MB, McCoy CE, Weber RR, Frederickson ED, Douglas FL, Goldberg LI. Augmentation of renal blood flow and sodium excretion in hypertensive patients during blood pressure reduction by intravenous administration of the dopamine1 agonist fenoldopam. *Circulation*. 1987;76:1312–1318.
66. Shusterman NH, Elliott WJ, White WB. Fenoldopam, but not nitroprusside, improves renal function in severely hypertensive patients with impaired renal function. *Am J Med*. 1993;95:161–168.
67. Elliott WJ, Weber RR, Nelson KS, et al. Renal and hemodynamic effects of intravenous fenoldopam versus nitroprusside in severe hypertension. *Circulation*. 1990;81:970–977.
68. McKinney TD. Management of hypertensive crisis. *Hosp Pract (Off Ed)*. 1992;27:133–137.
69. Brater DC, Chennavasin P, Dehmer GJ. Prolonged hemodynamic effect of furosemide in congestive heart failure. *Am Heart J*. 1984;4:1031–1032.
70. N*itropress (sodium nitroprusside). Package insert*. Hospira, Inc; 2008.
71. Hirschl M. Guidelines for the drug treatment of hypertensive crises. *Drugs*. 1995;50:991–1000.
72. Lavin P. Management of hypertension in patients with acute stroke. *Arch Intern Med*. 1986;146:66–68.
73. Rindone JP, Sloane EP. Cyanide toxicity from sodium nitroprusside: risks and management [published correction appears in *Ann Pharmacother*. 1992;26:1160]. *Ann Pharmacother*. 1992;26:515–519.
74. Schulz V. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. *Clin Pharmacokinet*. 1984;9:239–251.
75. Friederich JA, Butterworth JF 4th. Sodium nitroprusside: twenty years and counting. *Anesth Analg*. 1995;81:152–162.
76. Zerbe NF, Wagner BK. Use of vitamin B_{12} in the treatment and prevention of nitroprusside-induced cyanide toxicity. *Crit Care Med*. 1993;21:465–467.
77. Robin ED, McCauley R. Nitroprusside-related cyanide poisoning: time (long past due) for urgent, effective interventions. *Chest*. 1992;102:1842–1845.
78. Sarvotham S. Nitroprusside therapy in post-open heart hypertensives: a ritual tryst with cyanide death. *Chest*. 1987;91:796.
79. Hall VA, Guest JM. Sodium nitroprusside-induced cyanide intoxication and prevention with sodium thiosulfate prophylaxis. *Am J Crit Care*. 1992;1:19–25.

80. Cottrell JE, Casthely P, Brodie JD, Patel K, Klein A, Turndorf H. Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. *N Engl J Med*. 1978;298:809–811.
81. Kayser SR, Kurisu S. Hydroxocobalamin in nitroprusside-induced cyanide toxicity. *Drug Intell Clin Pharm*. 1986;20:365–366.
82. Curry SC, Arnold-Capell P. Toxic effects of drugs used in the ICU: nitroprusside, nitroglycerin, and angiotensin converting enzyme inhibitors. *Crit Care Clin*. 1991;7:555–581.
83. Stumpf JL. Drug therapy of hypertensive crises. *Clin Pharm*. 1988;7:582–591.
84. Dwyer MM, Morris CL. Toxicity of sodium nitroprusside. *Conn Med*. 1993;57:489–492.
85. [No authors listed]. Fenoldopam—a new drug for parenteral treatment of severe hypertension. *Med Lett Drugs Ther*. 1998;40:57–58.
86. Ellis DJ, Luther RR, Fellmann J, et al. Treatment of hypertensive emergencies with fenoldopam, a peripherally acting dopamine (DA_1) receptor agonist [abstract]. *Crit Care Med*. 1998;26(1, Suppl):A23.
87. Brogden RN, Markham A. Fenoldopam: a review of its pharmacodynamic and pharmacokinetic properties and intravenous clinical potential in the management of hypertensive urgencies and emergencies. *Drugs*. 1997;54:634–650.
88. Murphy MB, Murray C, Shorten GD. Fenoldopam: a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. *N Engl J Med*. 2001;345:1548–1557.
89. Nichols AJ, Ruffolo RR Jr, Brooks DP. The pharmacology of fenoldopam. *Am J Hypertens*. 1990;3:116S–119S.
90. White WB, Halley SE. Comparative renal effects of intravenous administration of fenoldopam mesylate and sodium nitroprusside in patients with severe hypertension. *Arch Intern Med*. 1989;149:870–874.
91. Oparil S, Aronson S, Deeb GM, et al. A new parenteral antihypertensive: consensus roundtable on the management of perioperative hypertension and hypertensive crises. *Am J Hypertens*. 1999;12:653–664.
92. Bovet T, Zangrillo A, Guarracino F, et al. Effect of fenoldopam on use of renal replacement therapy among patients with acute kidney injury after cardiac surgery: a randomized clinical trial. *JAMA*. 2014;312:2244–2253.
93. Yakazu Y, Iwasawa K, Narita H, Kindscher JD, Benson KT, Goto H. Hemodynamic and sympathetic effects of fenoldopam and sodium nitroprusside. *Acta Anaesthesiol Scand*. 2001;45:1176–1180.
94. Everitt DE, Boike SC, Piltz-Seymour JR, et al. Effect of intravenous fenoldopam on intraocular pressure in ocular hypertension. *J Clin Pharmacol*. 1997;37:312–320.
95. Piltz JR, Stone RA, Boike S, et al. Fenoldopam, a selective dopamine-1 receptor agonist, raises intraocular pressure in males with normal intraocular

pressure. *J Ocul Pharmacol Ther*. 1998;14:203–216.
96. Cressman MD, Vidt DG, Gifford RW Jr, Moore WS, Wilson DJ. Intravenous labetalol in the management of severe hypertension and hypertensive emergencies. *Am Heart J*. 1984;107:980–985.
97. Wilson DJ, Wallin JD, Vlachakis ND, et al. Intravenous labetalol in the treatment of severe hypertension and hypertensive emergencies. *Am J Med*. 1983;75(4A):95–102.
98. Smith WB, Clifton GG, O'Neill WM Jr, Wallin JD. Antihypertensive effectiveness of intravenous labetalol in accelerated hypertension. *Hypertension*. 1983;5:579–583.
99. Dal Palu C, Pessina AC, Semplicini A, et al. Intravenous labetalol in severe hypertension. *Br J Clin Pharmacol*. 1982;13(1, Suppl):97S–99S.
100. Lebel M, Langlois S, Belleau LJ, Grose JH. Labetalol infusion in hypertensive emergencies. *Clin Pharmacol Ther*. 1985;37:615–618.
101. Vidt DG. Intravenous labetalol in the emergency treatment of hypertension. *J Clin Hypertens*. 1985;1:179–186.
102. Patel RV, Kertland HR, Jahns BE, Zarowitz BJ, Mlynarek ME, Fagan SC. Labetalol: response and safety in critically ill hemorrhagic stroke patients. *Ann Pharmacother*. 1993;27:180–181.
103. Kanto JH. Current status of labetalol, the first alpha- and beta-blocking agent. *Int J Clin Pharmacol Ther Toxicol*. 1985;23:617–628.
104. George RB, Light RW, Hudson LD, et al. Comparison of the effects of labetalol and hydrochlorothiazide on the ventilatory function of hypertensive patients with asthma and propranolol sensitivity. *Chest*. 1985;88:815–818.
105. Walstad RA, Berg KJ, Wessel-Aas T, Nilsen OG. Labetalol in the treatment of hypertension in patients with normal and impaired renal function. *Acta Med Scand Suppl*. 1982;665:135–141.
106. Wood AJ, Ferry DG, Bailey RR. Elimination kinetics of labetalol in severe renal failure. *Br J Clin Pharmacol*. 1982;13(1, Suppl):81S–86S.
107. MacCarthy EP, Bloomfield SS. Labetalol: a review of its pharmacology pharmacokinetics, clinical uses and adverse effects. *Pharmacotherapy*. 1983;3:193–219.
108. Eisalo A, Virta P. Treatment of hypertension in the elderly with labetalol. *Acta Med Scand Suppl*. 1982;665:129–133.
109. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. *BMC Med*. 2017;15(1):18.
110. Navaratnarajah M, White DC. Labetalol and phaeochromocytoma. *Br J Anaesth*. 1984;56:1179.
111. Pearson RM, Havard CW. Intravenous labetalol in hypertensive patients treated with beta-adrenoceptor blocking drugs. *Br J Clin Pharmacol*. 1976;3(4, Suppl 3):795–798.

112. Cumming AM, Brown JJ, Lever AF, Robertson JI. Intravenous labetalol in the treatment of severe hypertension. *Br J Clin Pharmacol*. 1982;13(1, Suppl):93S–96S.
113. Fahed S, Grum DF, Papadimos TJ. Labetalol infusion for refractory hypertension causing severe hypotension and bradycardia: an issue of patient safety. *Patient Saf Surg*. 2008;2(1):13.
114. Flaherty JT, Magee PA, Gardner TL, Potter A, MacAllister NP. Comparison of intravenous nitroglycerin and sodium nitroprusside for treatment of acute hypertension developing after coronary artery bypass surgery. *Circulation*. 1982;65:1072–1077.
115. Chun G, Frishman WH. Rapid-acting parenteral antihypertensive agents. *J Clin Pharmacol*. 1990;30:195–209.
116. Francis GS. Vasodilators in the intensive care unit. *Am Heart J*. 1991;121:1875–1878.
117. Rutledge J, Ayers C, Davidson R, et al. Effect of intravenous enalaprilat in moderate and severe systemic hypertension. *Am J Cardiol*. 1988;62:1062–1067.
118. Evans RR, Henzler MA, Weber EM, DiPette DJ. The effect of intravenous enalaprilat (MK-422) administration in patients with mild to moderate essential hypertension. *J Clin Pharmacol*. 1987;27:415–418.
119. Hirschl MM, Binder M, Bur A, et al. Clinical evaluation of different doses of intravenous enalaprilat in patients with hypertensive crises. *Arch Intern Med*. 1995;155:2217–2223.
120. White CM. Pharmacologic, pharmacokinetic, and therapeutic differences among ACE inhibitors. *Pharmacotherapy*. 1998;18:588–599.
121. Misra M, Chembale J, Kankane A. Evaluation of the efficacy, safety, and tolerability of intravenous enalaprilat in the treatment of grade III essential hypertension in Indian patients. *Indian Heart J*. 2004;56:67–69.
122. DiPette DJ, Ferraro JC, Evans RR, Martin M. Enalaprilat, an intravenous angiotensin-converting enzyme inhibitor, in hypertensive crises. *Clin Pharmacol Ther*. 1985;38:199–204.
123. Haas CE, LeBlanc JM. Acute postoperative hypertension: a review of therapeutic options. *Am J Health Syst Pharm*. 2004;61:1661–1673.
124. Cheung DG, Gasster JL, Neutel JM, Weber MA. Acute pharmacokinetic and hemodynamic effects of intravenous bolus dosing of nicardipine. *Am Heart J*. 1990;119:438–442.
125. [No authors listed]. Efficacy and safety of intravenous nicardipine in the control of postoperative hypertension. IV Nicardipine Study Group. *Chest*. 1991;99:393–398.
126. Halpern NA, Sladen RN, Goldberg JS, et al. Nicardipine infusion for postoperative hypertension after surgery of the head and neck. *Crit Care Med*. 1990;18:950–955.

127. Halpern NA, Alicea M, Krakoff LR, Greenstein R. Postoperative hypertension: a prospective placebo controlled, randomized, double-blind trial with intravenous nicardipine hydrochloride. *Angiology*. 1990;41:992–1004.
128. Kaplan JA. Clinical considerations for the use of intravenous nicardipine in the treatment of postoperative hypertension. *Am Heart J*. 1990;119:443–446.
129. Wallin JD, Fletcher E, Ram CV, et al. Intravenous nicardipine for treatment of severe hypertension. A double-blind, placebo-controlled multicenter trial. *Arch Intern Med*. 1989;149:2662–2669.
130. Neutel JM, Smith DH, Wallin D, et al. A comparison of intravenous nicardipine and sodium nitroprusside in the immediate treatment of severe hypertension. *Am J Hypertens*. 1994;7:623–628.
131. Qureshi AI, Harris-Lane P, Kirmani JF, et al. Treatment of acute hypertension in patients with intracerebral hemorrhage using American Heart Association guidelines. *Crit Care Med*. 2006;34:1975–1980.
132. Curran MP, Robinson DM, Keating GM. Intravenous nicardipine: its use in the short-term treatment of hypertension and various other indications. *Drugs*. 2006;66:1755–1782.
133. Kwak YL, Oh YJ, Bang SO, Lee JH, Jeong SM, Hong YW. Comparison of the effects of nicardipine and sodium nitroprusside for control of increased blood pressure after coronary artery bypass graft surgery. *J Int Med Res*. 2004;32:342–350.
134. Dorman T, Thompson DA, Breslow MJ, Lipsett PA, Rosenfeld BA. Nicardipine versus nitroprusside for breakthrough hypertension following carotid endarterectomy. *J Clin Anesth*. 2001;13:16–19.
135. Espinosa A, Ripollés-Melchor J, Casans-Francés R, et al. Perioperative use of clevidipine: a systematic review and meta-analysis. *PLoS One*. 2016;11(3):e0150625.
136. Villarreal EG, Flores S, Kriz C, Iranpour N, Bronicki RA, Loomba RS. Sodium nitroprusside versus nicardipine for hypertension management after surgery: a systematic review and meta-analysis. *J Card Surg*. 2020;35(5):1021–1028.
137. Freiberger NA, Tellor KB, Stevens AM. Comparison of clevidipine versus sodium nitroprusside for the treatment of postoperative hypertension in cardiac surgery patients. *Hosp Pharm*. 2016;51(6):461–467.
138. Cruz JE, Thomas Z, Lee D, Moskowitz DM, Nemeth J. Therapeutic interchange of clevidipine for sodium nitroprusside in cardiac surgery. *P T*. 2016;41(10):635–639.
139. Salerno DM, Dias VC, Kleiger RE, et al. Efficacy and safety of intravenous diltiazem for treatment of atrial fibrillation and atrial flutter. *Am J Cardiol*. 1989;63:1046–1051.
140. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. A placebo-controlled trial of continuous intravenous diltiazem infusion for 24-hour heart

rate control during atrial fibrillation and atrial flutter: a multicenter study. *J Am Coll Cardiol*. 1991;18:891–897.

141. Dougherty AH, Jackman WM, Naccarelli GV, Friday KJ, Dias VC. Acute conversion of paroxysmal supraventricular tachycardia with intravenous diltiazem. IV Diltiazem Study Group. *Am J Cardiol*. 1992;70:587–592.
142. Koh H, Kimura F, Kushikata T, Satoh T, Ishihara H, Matsuki A. Clinical study of total intravenous anesthesia with droperidol, fentanyl, and ketamine: control of intraoperative hypertension with diltiazem [article in Japanese]. *Masui*. 1991;40:1376–1383.
143. Boylan JF, O'Leary G, Weisel RD, Ivanov J, Mickle DA, Teasdale SJ. A comparison of diltiazem, esmolol, nifedipine, and nitroprusside therapy of post-CABG hypertension. *Can J Anaesth*. 1990;37:S156.
144. Jaffe AS. Use of intravenous diltiazem in patients with acute coronary artery disease. *Am J Cardiol*. 1992;69:25B–29B.
145. Fang ZY, Picart N, Abramowicz M, et al. Intravenous diltiazem versus nitroglycerin for silent and symptomatic myocardial ischemia in unstable angina pectoris. *Am J Cardiol*. 1991;68:42C–46C.
146. Onoyama K, Omae T, Iimura O, et al. Effect of drip infusion or a bolus injection of intravenous diltiazem on hypertensive crisis. Curr Ther Res. 1987;42(6):1223–1231.
147. Onoyama L, Omae T, Iimura O, Yoshinaga K, Inagaki Y. Effect of a drip infusion of intravenous diltiazem on severe systemic hypertension. Curr Ther Res. 1988;43(3):361–368.
148. Aronson S, Dyke CM, Stierer KA, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment for cardiac surgery patients. *Anesth Analag*. 2008;107:1110–1121.
149. Vuylsteke A, Milner Q, Ericsson H, et al. Pharmacokinetics and pulmonary extraction of clevidipine, a new vasodilating ultra-short-acting dihydropyridine, during cardiopulmonary bypass. *Br J Anaesth*. 2008;85:683–689.
150. Ericsson H, Bredberg U, Eriksson U, Jolin-Mellgård A, Nordlander M, Regårdh CG. Pharmacokinetics and arteriovenous differences in clevidipine concentration following a short- and a long-term infusion in healthy volunteers. *Anesthesiology*. 2000;92:993–1001.
151. Clevip*rex (clevidipine butyrate). Package insert*. The Medicines Company; 2008.
152. Levy JH, Mancao MY, Gitter R, et al. Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1. *Anesth Analg*. 2007;105:918–925.

153. Singla N, Waltier DC, Gandhi SD, et al. Treatment of acute postoperative hypertension in cardiac surgery patients: an efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery-2 (ESCAPE-2), a randomized, double-blind, placebo-controlled trial. *Anesth Analg*. 2008;107:59–67.
154. Chen K, Varon J, Wenker OC, Judge DK, Fromm RE Jr, Stenbach GL. Acute thoracic aortic dissection: the basics. *J Emerg Med*. 1997;15:859–867.
155. Khoynezhad A, Plestis KA. Managing emergency hypertension in aortic dissection and aortic aneurysm surgery. *J Card Surg*. 2006;21(Suppl 1):S3–S7.
156. DeSanctis RW, Doroghazi RM, Austen WG, Buckley MJ. Aortic dissection. *N Engl J Med*. 1987;317:1060–1067.
157. Alviar CL, Gutierrez A, Cho L, et al. Clevidipine as a therapeutic and cost-effective alternative to sodium nitroprusside in patients with acute aortic syndromes. *Eur Heart J Acute Cardiovasc Care*. 2020;9(3, Suppl):S5–S12.
158. Lindsay J. Aortic dissection. *Heart Dis Stroke*. 1992;1:69–76.
159. Gray RJ. Managing critically ill patients with esmolol. An ultra short-acting beta-adrenergic blocker. *Chest*. 1988;93:398–403.
160. Gupta R, Kaufman S. Cardiovascular emergencies in the elderly. *Emerg Med Clin North Am*. 2006;24:339–370.
161. Diercks DB, Promes SB, Schuur JD, et al. Clinical policy: critical issues in the evaluation and management of adult patients with suspected acute nontraumatic thoracic aortic dissection. *Ann Emerg Med*. 2015;65(1):32–42.e12.
162. Erbel R; Task Force on Aortic Dissection, European Society of Cardiology. Diagnosis and management of aortic dissection. *Eur Heart J*. 2001;22(18):1642–1681.
163. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation*. 2010;121(13):e266–e369.

17

Shock

Jason S. Haney and Carolyn M. Bell

CORE PRINCIPLES		CHAPTER CASES
1	Shock is a syndrome with multiple etiologies characterized by an impairment of tissue perfusion which, regardless of cause, can lead to cellular dysfunction, organ failure, and death.	
2	The diagnosis of shock is made by the findings of impaired tissue perfusion on physical examination and hemodynamic and laboratory changes consistent with impaired perfusion. Hypotension may or may not be present. Hemodynamic monitoring is vital for the determination of the type of shock and assessment of response to interventions.	**Case 17-1 (Questions 1, 3, 6)** **Case 17-2 (Questions 1, 4, 6)** **Case 17-3 (Questions 1, 2, 6, 8)** **Case 17-4 (Questions 1, 4), Tables 17-2, 17-3, 17-6, Figure 17-1**
3	Hypovolemic shock is caused by a reduction in intravascular volume.	**Case 17-1 (Question 1)**

		Case 17-2 (Questions 1, 2, 4), Tables 17-1, 17-3
4	Resuscitation is required to treat hypovolemic shock to maintain adequate tissue perfusion and oxygenation. This can be achieved by administration of intravenous crystalloids, colloids, or blood products.	**Case 17-1 (Questions 2–7)** **Case 17-2 (Questions 3–6), Tables 17-4, 17-5**
5	The physiologic response to fluid loss or gain is described by the Frank–Starling curve.	**Case 17-2 (Questions 3, 4), Figure 17-2**
6	Cardiogenic shock results from a decrease in the heart's ability to maintain cardiac output that is unrelated to hypovolemia.	**Case 17-3 (Questions 1, 2), Tables 17-1, 17-3, 17-6**
7	Treatment of patients in cardiogenic shock involves stabilization of the patient, optimization of preload, increasing contractility, and reducing afterload if the blood pressure permits. In cases of acute myocardial infarction complicated by cardiogenic shock, early revascularization is priority.	**Case 17-3 (Questions 3–8), Table 17-7, Figure 17-3**
8	Septic shock is a type of distributive shock characterized by a profound vasodilatory response and decrease in blood pressure caused by a dysregulated host response to infection.	**Case 17-4 (Question 1), Tables 17-1, 17-3, 17-8, 17-9**
9	Treatment of septic shock involves stabilization with fluids, vasopressors, and inotropic agents and treatment of	**Case 17-4 (Questions 1-6), Table 17-7**

the underlying condition. Other therapies involve modification of the body's response to infection.

INTRODUCTION

Shock is defined in simple terms as a syndrome of impaired tissue perfusion and oxygenation usually, but not always, accompanied by hypotension. This impairment of tissue perfusion eventually leads to cellular dysfunction, followed by organ damage and death if untreated. Shock may result from one or more situations, causing a reduction of intravascular volume (hypovolemic shock), myocardial pump failure (cardiogenic shock), severe peripheral vasodilation (distributive shock), or obstruction of blood flow in the systemic or pulmonary circulation (obstructive shock). The type of treatment required depends on the etiology.

In recent years, medical support of patients with shock has improved because of better technologies for hemodynamic monitoring, recognition of the value of volume replacement, appropriate use of inotropic and vasoconstrictive agents, and the development of better ways to treat the underlying cause of the shock syndrome. Understanding the principles of shock should further enhance the prompt recognition of patients at risk, rapid initiation of corrective measures, and development of innovative treatment regimens.

CAUSES

Shock is common among patients in the intensive care unit (ICU) and is present in up to one-third of ICU admissions.[1] **Table 17-1** outlines the classification of shock and precipitating events.[2] Recognition of the etiology and underlying pathology of the various

forms of shock is essential for managing this condition. The distinctions among subtypes of shock only apply, however, in the relatively early stages. As the syndrome evolves and compensatory mechanisms are overwhelmed, it becomes increasingly difficult to determine the subtypes because the clinical and pathophysiologic features of advanced shock are the same for all. Also, different types of shock can occur at the same time (eg, a patient with septic shock who is also hypovolemic). The mortality rate for shock remains quite high—as high as 60% to 80% in severe cases—despite recent improvements in its early recognition and management.[1]

Table 17-1
Classification of Shock and Precipitating Events

Hypovolemic Shock
Hemorrhagic
Gastrointestinal bleeding: varices, peptic ulcer
Trauma
Internal bleeding: ruptured aortic aneurysm, iatrogenic, retroperitoneal bleeding, postoperative bleeding, hemorrhagic pancreatitis, postpartum hemorrhage, tumor or abscess erosion into major vessels
Nonhemorrhagic
Gastrointestinal losses: vomiting, diarrhea, external drainage
Renal losses: diabetes mellitus, diabetes insipidus, overuse of diuretics, salt-wasting nephropathies, hypoaldosteronism
Sequestration: ascites, third-space accumulation
Cutaneous: burns, nonreplaced perspiration, and insensible water losses
Cardiogenic Shock
Cardiomyopathic causes
Acute myocardial infarction: left or right ventricular infarction
Myocardial stunning: low cardiac output syndrome, postcardiac arrest
Myocarditis
End-stage cardiomyopathy or severe acute exacerbation of heart failure
Drug-induced: β-blockers

Arrhythmogenic causes
Tachyarrhythmia: atrial fibrillation/flutter, reentrant tachycardia, ventricular tachycardia/fibrillation
Bradyarrhythmia: Mobitz type II second-degree heart block, complete heart block
Mechanical causes
Rupture of ventricular septum or free wall
Papillary muscle or chordae tendineae rupture or dysfunction
Native valvular insufficiency, stenosis, or obstruction
Prosthetic valvular obstruction, mechanical/leaflet failure, or dehiscence
Distributive Shock
Septic: bacterial, fungal, viral, parasitic, mycobacterial
Nonseptic
Anaphylactic: IgE-mediated, nonimmunologic
Neurogenic: spinal cord injury, traumatic brain injury, cerebral damage, severe dysautonomia
Inflammatory: burns, trauma, pancreatitis, air/fat embolism, postcardiopulmonary bypass, postmyocardial infarction, postcardiac arrest
Drug- or toxin-induced: anesthesia, ganglionic and adrenergic blockers, overdoses of barbiturates and narcotics, carbon monoxide, heavy metal, cyanide
Endocrine: adrenal crisis, myxedema coma
Obstructive Shock
Pulmonary vascular: pulmonary embolism, pulmonary hypertension, severe or acute obstruction of pulmonic or tricuspid valve, venous air embolus
Mechanical
Tension pneumothorax or hemothorax
Pericardial tamponade
Constrictive pericarditis
Restrictive cardiomyopathy
Ventricular outflow tract obstruction
Abdominal compartment syndrome

IgE, immunoglobulin E.

Adapted with permission from Gaieski DF, Mikkelsen ME. Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock. In: Post TW, ed. *UpToDate*. UpToDate, Accessed November 2, 2020. © 2022 UpToDate, Inc and its affiliates and/or licensors. All rights reserved.

PATHOPHYSIOLOGY

Tissue perfusion is a complex process of oxygen and nutrient delivery as well as waste removal. When perfusion is impaired, it sets up a cascade of events that can eventually end in death. Although the etiology of shock is varied, the eventual progression (if untreated) to cell death and subsequent organ dysfunction results from a common pathway of ischemia, endogenous inflammatory cytokine release, and the generation of oxygen radicals. When cells are subjected to a prolonged period of ischemia, anaerobic metabolism begins. This inefficient process results in a decrease in adenosine triphosphate stores and causes the buildup of lactic acid and other toxic substances that can alter mitochondrial function and eventually result in cell death. In the advanced stages of shock, irreversible cellular damage leads to multiple organ system failure, also known as *multiple organ dysfunction syndrome*.

The body produces inflammatory cytokines in response to ischemia, injury, or infection. The phrase *systemic inflammatory response syndrome* (SIRS) is the recommended umbrella term to describe any acute, overwhelming inflammatory response, independent of the cause.[3] This syndrome has best been described in the sepsis literature; however, it can occur after a wide variety of insults, including hemorrhagic shock, infection (septic shock), pancreatitis, ischemia, multitrauma and tissue injury, and immune-mediated organ injury. SIRS is usually a late manifestation of hypovolemic forms of shock. It is uncommon in cardiogenic shock, but is the hallmark of septic shock. SIRS is clinically characterized by profound vasodilation, which impairs perfusion, increases capillary permeability, and can reduce intravascular volume.

CLINICAL PRESENTATION AND DIAGNOSIS

Independent of the pathophysiologic cause, the clinical syndrome of shock progresses through several stages. During each step, the body uses and exhausts various compensatory mechanisms to balance oxygen delivery ($\dot{D}o_2$) and oxygen consumption ($\dot{V}o_2$) in an effort to maintain perfusion of vital organs. Oxygen delivery is determined by the arterial concentration of oxygen multiplied by the blood flow (cardiac output [CO]) (**Fig. 17-1** and **Table 17-2**). Normally, consumption is independent of supply, except at low rates of $\dot{D}o_2$. In some critically ill patients, perfusion is inadequate to meet metabolic demands, and $\dot{V}o_2$ becomes dependent on the supply despite "normal" $\dot{D}o_2$ ranges.

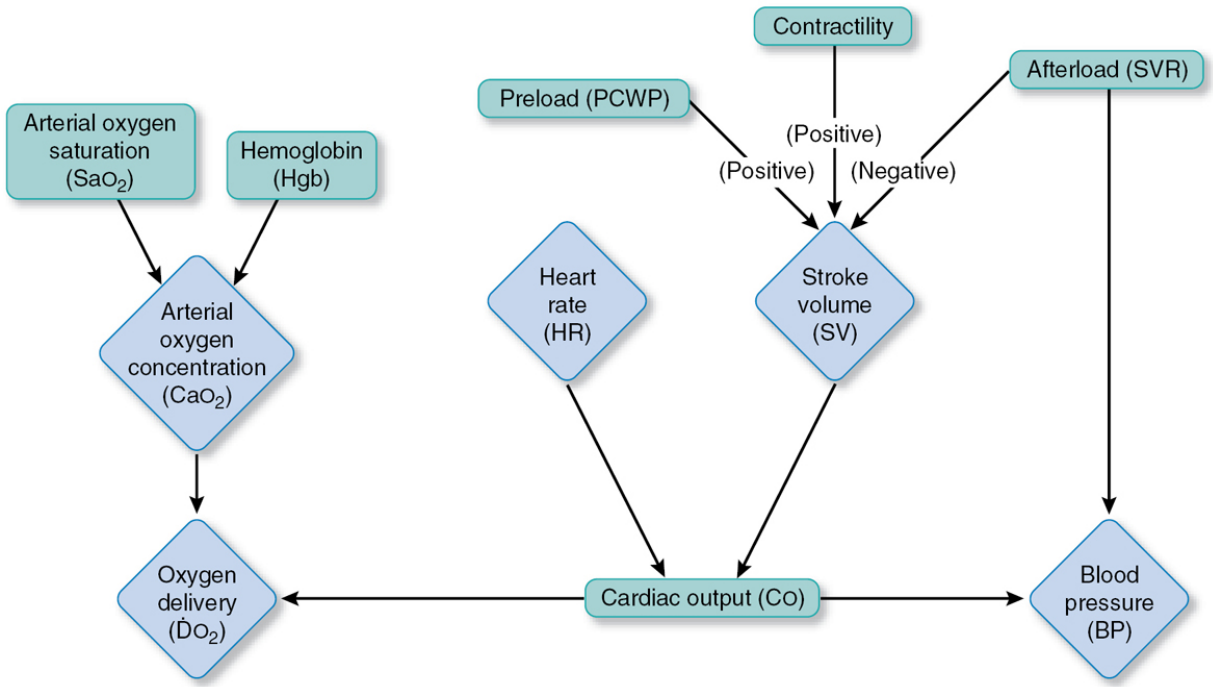


Figure 17-1 Determinants of blood pressure, cardiac output, and oxygen delivery. PCWP, pulmonary capillary wedge pressure. SVR, systemic vascular resistance.

Table 17-2
Normal Hemodynamic Values and Derived Indices

	Definition/Equation	Normal Value	Units
Directly Measured			
Blood pressure (BP) (systolic blood pressure [SBP]/diastolic blood pressure [DBP])	Pressure in the central arterial bed, determined by cardiac output and systemic vascular resistance	90–140/ 60–90	mm Hg
Cardiac output (CO)	Amount of blood ejected from the left ventricle per minute; determined by stroke volume and heart rate CO = SV × HR	4–7	L/minute
Central venous pressure (CVP)[a]	Measures mean pressure in right atrium and reflects right ventricular filling pressure and volume status. Primarily determined by venous return to the heart. The goal in most critically ill patients is 8–12 mm Hg.	2–6	mm Hg[b]
Heart rate (HR) (pulse)	Number of myocardial contractions per minute	60–100	beats/minute
Pulmonary artery pressure (PAP)	*Systolic* (PASP): measures PAP during systole; reflects pressure generated by the contraction of the right ventricle *Diastolic* (PADP): Measures PAP during diastole; reflects diastolic filling pressure in the left ventricle. May approximate PCWP; normal gradient <5 mm Hg between PADP and PCWP	20–30/8–12	mm Hg
Pulmonary capillary wedge pressure (PCWP)	Measures pressure distal to the pulmonary artery; reflects left ventricular filling pressures (*preload*). Usually lower than or within 5 mm Hg of PADP	5–12[c]	mm Hg
Central venous oxygen saturation ($Scvo_2$)	The oxygen saturation of blood returning to the heart; a reflection of oxygen extraction from the upper body	>70	%
Mixed venous oxygen saturation (Svo_2)	The oxygen saturation of blood in the pulmonary artery; a marker of the relationship between CO and total body oxygen consumption	>65	%
Derived Indices			
Cardiac index (CI)	CO per square meter of body surface area (BSA[d]) CI = CO/BSA	2.5–4.2	L/minute/m^2
Left ventricular stroke work index (LVSWI)	Amount of work the left ventricle exerts during systole; adjusted for BSA[d]. A measure of *contractility*, the inotropic state of the myocardium LVSWI = (MAP − PCWP) × SVI × 0.0136	35–85	g/m^2/beat
Mean arterial pressure (MAP)	MAP = [(2 × DBP) + SBP]/3	70–100	mm Hg
Mean pulmonary artery pressure (mPAP)	Average measure of PAP during the entire cardiac cycle; mPAP ≥25 mm Hg at rest is defined as pulmonary hypertension. mPAP = [(2 × PADP) + PASP]/3	12–15	mm Hg
Oxygen delivery ($\dot{D}o_2$)	The amount of oxygen delivered by the body per unit time $\dot{D}o_2 = CO \times Cao_2$, where $Cao_2 = (1.34 \times Hgb \times Sao_2) + (0.0031 \times Pao_2)$	700–1200	mL/minute
Oxygen consumption ($\dot{V}o_2$)	The amount of oxygen consumed by the body per unit time; the product of CO and the difference between the arterial and venous oxygen concentration $\dot{V}o_2 = CO \times (Cao_2 - Cvo_2)$, where $Cvo_2 = (1.34 \times Hgb \times Svo_2) + (0.0031 \times Pvo_2)$	200–400	mL/minute
Coronary artery perfusion pressure (CPP)	The pressure gradient between the coronary arteries and the pressure in either the right atrium or the left ventricle during diastole; a major determinant of coronary blood flow and oxygen supply to the heart CPP = DBP − PCWP	60–80	mm Hg
Pulmonary vascular resistance (PVR)	Primary determinant of right ventricular *afterload* PVR = [(mPAP − PCWP)/CO] × 80 (divide by 80 for Wood units)	20–120 (<2)	dynes·s·cm^{-5} (Wood units)
Stroke volume (SV)	Amount of blood ejected from the ventricle with each systolic contraction SV = CO/HR	60–130	mL/beat
Stroke volume index (SVI)	Stroke volume adjusted for body surface area (BSA[d]) SVI = SV/BSA	30–75	mL/beat/m^2

	Definition/Equation	Normal Value	Units
Derived Indices			
Systemic vascular resistance (SVR)	Measure of impedance applied by systemic vascular system to systolic effort of left ventricle; determined by autonomic nervous system and condition of vessels. Determinant of left ventricular *afterload* SVR = [(MAP − CVP)/CO] × 80	800–1200	dyne·s·cm^{-5}
Systemic vascular resistance index (SVRI)	SVR adjusted for body surface area (BSA[d]) SVRI = SVR × BSA	1680–2580	dyne·s·cm^{-5}·m^2

Ca_{O_2}, arterial oxygen content; Cv_{O_2}, venous oxygen content; Hgb, hemoglobin concentration; PADP, pulmonary artery diastolic pressure; Pa_{O_2}, arterial oxygen tension; PASP, pulmonary artery systolic pressure; Pv_{O_2}, mixed venous oxygen tension; Sa_{O_2}, arterial oxyhemoglobin saturation.

[a]CVP is essentially synonymous with RAP.

[b]2–6 mm Hg = 3–6 cm H_2O (conversion: 1 mm Hg = 1.34 cm H_2O).

[c]May optimally ↑ PCWP to 16–18 mm Hg in critically ill patients.

[d]BSA, body surface area = 1.7 m^2 (average male).

Shock is often first identified by the presence of arterial hypotension and reflexive tachycardia. Although hypotension is often described as the hallmark of shock, it is not necessarily present in all patients.

The diagnosis of shock is based on the findings of impaired tissue perfusion on examination.[1] These findings may include the following:

- Hypotension (systolic blood pressure [SBP] <90 mm Hg, mean arterial pressure [MAP] <65 mm Hg, or at least a 40 mm Hg decrease from baseline)
- Tachycardia (heart rate [HR] >90 beats/min)
- Tachypnea (respiratory rate [RR] >20 breaths/min)
- Cutaneous vasoconstriction: cold, clammy, blue, mottled skin; decreased capillary refill (although not typical of distributive shock)
- Abnormal mental status (agitation, confusion, stupor, or coma)
- Oliguria: urine output <0.5 mL/kg/hour
- Metabolic acidosis (usually because of an elevated blood lactate level)
- Decreased venous oxygen saturation (mixed [Sv_{O_2}], central venous oxygen saturation [Scv_{O_2}]) (reflects a mismatch between oxygen supply [$\dot{D}_{O_2}$] and demand [$\dot{V}_{O_2}$])

Not all these described findings are encountered in every patient with shock, and considerable variability exists in both the rapidity and the sequence of onset. This depends on the severity of the initiating event, the underlying mechanism, and the baseline condition of the

patient, including medications that may alter the clinical presentation. It is important to consider the patient's medical and pharmacologic history, while monitoring for subtle clinical changes that may signal impending deterioration and necessitate immediate intervention.

TREATMENT OVERVIEW

The treatment of patients in shock requires both treatment of the underlying cause of shock, as well as early, aggressive measures to maintain adequate perfusion to vital organs and minimize organ damage. The general measures used are the restoration of volume in patients with hypovolemia, the use of vasopressors or inotropic agents when volume resuscitation is inappropriate or inadequate to maintain perfusion, and careful monitoring of the hemodynamic status of the patient. In sepsis, specific hemodynamic goals have been determined.[4] In other types of shock, specific goals have not been established; however, the principles of ensuring adequate tissue perfusion are the same.

HEMODYNAMIC MONITORING

Hemodynamic monitoring in critically ill patients is mandatory to properly assess and manage various shock states. Noninvasive, minimally invasive, and invasive monitoring techniques can be used to measure or calculate cardiovascular performance and differentiate the causes of various conditions that result in hypoperfusion and organ dysfunction. Less invasive techniques are preferred to minimize risk; however, invasive devices more accurately estimate hemodynamic parameters. The values obtained with hemodynamic monitoring should always be interpreted in the context of other parameters and used in conjunction with a physical examination and clinical judgment.

Noninvasive Monitoring

Noninvasive measures are an important part of hemodynamic monitoring. Clinical examination and vital signs (specifically HR, blood pressure [BP], MAP) provide valuable information as surrogate markers of organ perfusion. An appropriately sized sphygmomanometer can estimate systemic BP, but may be inaccurate in the setting of shock owing to malperfusion of extremities. Cardiac telemetry and/or electrocardiogram (ECG) may help identify a variety of causes for shock (eg, arrhythmia, ischemia, pericarditis). Pulse oximetry is commonly used to measure peripheral arterial oxygen saturation [Sa_{O_2}], which augments respiratory assessment and can be used to determine $\dot{D}_{O_2}$.

ULTRASONOGRAPHY

Transthoracic echocardiography (TTE) can estimate the functional status of the heart and heart valves, visualize the pericardium, and assess response to therapy.[5] Transcutaneous Doppler ultrasound may be used to visualize blood flow through blood vessels or structures and provide estimates of CO, stroke volume (SV), central venous pressure (CVP), and MAP. Ultrasound imaging can also provide dynamic assessment of fluid responsiveness through the evaluation of the collapsibility of the inferior vena cava (IVC) and stroke volume variation (SVV). However, ultrasonography is an intermittent assessment and, therefore, cannot detect acute changes unless the procedure is repeated. In addition, multiple conditions may limit an echocardiogram's ability to produce quality images, such as severe obesity, emphysema, high intrathoracic pressures, and presence of foreign material in the chest cavity.[6]

OTHER NONINVASIVE MONITORING TOOLS

Additional noninvasive methods exist to objectively evaluate certain hemodynamic variables. The Non-invasive Cardiac Output (NICO®, Novametrix Medical Systems, Wallingford, CT, USA) system is able to estimate CO via Fick's principle by measuring partial C_{O_2}

rebreathing through a disposable breathing loop attached to the mechanical ventilator.[7] Bioimpedance and bioreactance technologies can estimate CO, cardiac index (CI), systemic vascular resistance (SVR), and SV by applying electrodes to the thorax and measuring electrical changes during the cardiac cycle.[7] Although each of these methods is intrinsically noninvasive, they all require the patient to be intubated and mechanically ventilated. In addition, none of these methods are currently suitable to replace the more invasive methods of estimating CO because of their inaccuracy in critical illness. Numerous factors can alter the signal quality and accuracy of these methods, including patient movement, electrical interference, arrhythmias, obesity, pleural effusion, pulmonary edema, and aortic valve disease.

Although important, noninvasive measures have limitations, and certain hemodynamic values important for the diagnosis and assessment of illness, as well as the patient's response to therapy, must be measured more invasively at the present time.

Minimally Invasive Monitoring

Indwelling monitoring devices that require insertion into various body parts may be categorized as minimally invasive or invasive. Vascular monitoring devices can be placed within the venous or arterial circulatory system and the location of the terminal end dictates the degree of invasiveness. Minimally invasive devices terminate within the peripheral vasculature, whereas the terminal end of invasive devices dwells inside or near the heart.

ARTERIAL PRESSURE LINE

The arterial line is a common tool in the ICU. It consists of a small catheter placed into an artery (usually the radial or femoral artery) under sterile conditions and attached to a pressure transducer. This allows for continuous measurement of BP and can be more accurate than is a sphygmomanometer in patients with shock, cardiac arrhythmias, calcified arteries, or high SVR. Its accuracy is

dependent on proper calibration of the transducer hub and arterial waveform, patient immobility, and absence of arterial stenosis. The arterial catheter also provides easy access for arterial blood gas (ABG) samples. Arterial lines should never be used for medication administration.

ARTERIAL PULSE WAVEFORM ANALYSIS

Pulse contour analysis devices measure hemodynamic variables such as CO, CI, SV, SVR, SVV, and pulse pressure variation (PPV) using the waveform from a conventional arterial pressure line.[7–9] These devices are increasingly being used in ICUs as an alternative to the pulmonary artery catheter (PAC). Waveform analysis is based on the hypothesis that SV is directly proportional to the area under the systolic portion of the arterial waveform and inversely proportional with impedance.

Several pulse contour methods are available in clinical practice and require various calibration techniques. Uncalibrated methods may be manually calibrated with a measured CO from another source (eg, echocardiogram). LiDCOrapid™ (Medtronic, Minneapolis, MN, USA), Pulsioflex™ (PulsioFlex™ is PULSION Medical Systems, Feldkirchen, Germany), and MostCare™ (Vytech, Padova, Italy) are uncalibrated systems that calculate CO using a detected pulse rate and calculated arterial flow from exclusive algorithms. FloTrac™ is a proprietary transducer that was part of the Vigileo™ monitor (Edwards LifeSciences, Irvine, CA, USA) and one of the earliest adopted uncalibrated methods of hemodynamic monitoring within the ICU. Vigileo™ is no longer commercially available, but FloTrac™ is still available as part of the Edwards EV1000™ clinical platform (Edwards LifeSciences, Irvine, CA, USA).

Calibrated pulse contour systems calculate CO after utilizing either a transpulmonary thermodilution or lithium dilution method for initial calibration. The PiCCO$_2$™ (Pulsion Medical Systems, Munich, Germany) and Edwards EV1000™ are thermodilution-based systems that measure temperature changes within a central artery following the injection of a cold saline bolus through a central venous

catheter. Lithium-based dilution devices, such as the LiDCOplus(™) System (LiDCO Ltd., London, UK), measure diminishing concentrations of lithium following its injection into a central or peripheral vein and a proprietary formula to calculate CO.

Proper calibration and an accurate arterial waveform are vital to the accuracy of pulse contour analysis devices. Arrhythmias, severe aortic regurgitation, cardiac shunts, aortic aneurysms, intra-aortic balloon pumps (IABPs), and extreme hemodynamic instability may limit the accuracy of these devices. Lithium-based devices may be inaccurate in patients with hyponatremia or those receiving neuromuscular blockers and should not be used in patients receiving lithium therapy. Although pulse contour analysis devices compare well with more invasive measurement techniques, an international consensus conference does not currently recommend the newer, less invasive technologies because of lack of validation in patients with shock.[1]

ULTRASONOGRAPHY

Similar to TTE, transesophageal echocardiography (TEE) may provide information to help guide the management of shock states. TEE is more invasive and may provide clearer diagnostic imaging of cardiac structures and function, valvular function, thoracic aorta, and structures surrounding the heart. Because the ultrasound probe is advanced into the esophagus and sedation is generally required for the procedure, a TEE is associated with higher risk. These risks include oversedation, respiratory depression, and physical injury to the oropharynx, esophagus, or lung. Consequently, TEE utilization is generally limited to the perioperative setting with cardiovascular surgery and situations requiring detailed evaluation of valve structure and function, including diagnostic assessments of endocarditis.

Esophageal Doppler ultrasound is an additional minimally invasive technique to monitor CO. The Doppler probe is advanced into the esophagus to continuously measure blood flow in the descending thoracic aorta. CO, CI, SV, SVR, and SVV may be calculated using these measurements. Esophageal Doppler ultrasound has been

shown to have a good correlation with invasive hemodynamic measurements. However, its use is limited by the need for mechanical ventilation, sedation, and proper positioning of the probe within the esophagus when used over extended periods.

OTHER MINIMALLY INVASIVE MONITORING TOOLS

In shock, compromised systemic perfusion and tissue gas exchange result in tissue hypoxia, ischemia, and hypercarbia. Gastric tonometry monitors partial pressure of carbon dioxide (PCO_2) levels within the gut mucosa that are directly influenced by systemic PCO_2 and a surrogate marker of systemic perfusion. Limitations to this process include a lengthy equilibration period (90 minutes) for measurement, increased gastric reflux, and interference from enteral nutrition. Sublingual capnography is a similar, yet simpler, process of tissue PCO_2 monitoring. A PCO_2 gap may be calculated by both methods such as the difference between the arterial partial pressure of carbon dioxide ($PaCO_2$) and measured tissue PCO_2. Excessive PCO_2 gaps (gastric >20 mm Hg and sublingual >25 mm Hg) have been associated with increased mortality.[10,11]

Invasive Monitoring

CENTRAL VENOUS CATHETER

Common in the ICU, the central venous catheter consists of a large-bore catheter usually inserted into a subclavian, jugular, or a femoral vein. It can be used for infusion of fluid and medications or frequent laboratory studies. When attached to a pressure transducer, it can measure the CVP, a static reflection of right ventricular (RV) preload and volume status. A recent shift in clinical practice has occurred as various guidelines call for dynamic rather than static variables (eg, CVP) to guide fluid resuscitation in patients with shock.[1,4] Central venous catheters are preferred to peripheral venous access for administration of large fluid volumes, hypertonic medications, blood products, or vasopressors in patients with shock, but resuscitative

efforts should not be delayed if only peripheral access is available. Central venous catheters that continuously measure the central venous oxygen saturation ($ScvO_2$) have been developed and are becoming more common. These catheters allow for the assessment and monitoring of tissue perfusion and the response to interventions. Low $ScvO_2$ has been associated with worse outcomes.[12–14]

PULMONARY ARTERY CATHETER

The flow-directed, balloon flotation PAC is inserted via a central venous access and positioned into the pulmonary artery (PA).[15] The essential components for hemodynamic monitoring are incorporated in a standard quadruple-lumen catheter. This catheter is composed of multiple lumens, each terminating at different points along the catheter, and enables clinicians to assess intracardiac pressures, determine CO by the thermodilution technique, measure pulmonary arterial pressures, and obtain mixed venous blood samples. These capabilities allow one to evaluate volume status and ventricular performance, derive hemodynamic indices, and determine systemic $\dot{D}o_2$ and $\dot{V}o_2$.

Although the PAC is confined to the right side of the heart and pulmonary vasculature, left ventricular (LV) pressure can be ascertained from the pulmonary capillary wedge pressure (PCWP). A balloon at the tip of the PAC becomes lodged or “wedged” after it is manually inflated. Because forward flow from the right ventricle ceases beyond the wedged PA segment, a static fluid column exists between the LV and the PAC tip during diastole when the mitral valve is open. The PCWP then equilibrates with all distal pressures and thus indirectly reflects left ventricular end-diastolic pressure (LVEDP). Based on the relationship between pressure and volume, the LVEDP is equivalent to the left ventricular end-diastolic volume (LVEDV), and thus PCWP is a surrogate for left-sided *preload.* Significant mitral valve insufficiency or stenosis, LV dysfunction, cardiomyopathy, pulmonary veno-occlusive disease, and positive end-expiratory pressure (PEEP) from respiratory support devices can alter the accuracy of PCWP measurements. Because PCWP

measurements are not always available, the diastolic pulmonary artery pressure (DPAP) may help estimate left-sided preload in the absence of pulmonary hypertension or cardiac tamponade.

The use of PAC has been decreasing in the ICU as newer and less invasive technologies become available. In addition, the PAC is not recommended for routine use in patients with shock because of its lack of a significant effect on mortality, number of days in the ICU or hospital, or cost.[1,3,16,17] In most situations, the PAC is reserved for those patients who specifically require the monitoring of pulmonary artery pressures (PAPs) and oxygenation parameters, such as patients with pulmonary hypertension, refractory shock, RV dysfunction, pericardial illness, cardiac shunts, congenital heart disease, or who are postcardiac surgery.[1,4] More studies are needed to determine the value of PAC data–driven treatment protocols. Complications associated with PAC include atrial or ventricular arrhythmias, thrombotic events, infections, pneumothorax, hemothorax, air embolus, pulmonary infarction, and, very rarely, PA perforation.[16]

INTERPRETATION OF HEMODYNAMIC MONITORING PARAMETERS

Because hypotension alone is not required to define shock, the presence of inadequate tissue perfusion on physical examination is more important than are the numbers obtained by invasive monitoring.[1] The effective interpretation and management of hemodynamic parameters requires a thorough understanding of the physiologic determinants of CO and arterial pressure. Assuming oxygen content of blood is adequate, CO and SVR are the ultimate determinants of Do_2, adequate arterial pressure, and tissue perfusion. As outlined in Figure 17-1, CO may be quantified as the product of SV and HR. SV is determined by preload, afterload, and contractility. Preload is defined as end-diastolic fiber length before contraction and is represented by LVEDV. It is approximated by LVEDP and PCWP. RV preload is reflected by CVP or right atrial pressure (RAP). Afterload is defined as ventricular wall tension developed during

contraction. It is determined by the resistance or impedance the ventricle must overcome to eject end-diastolic volume. LV and RV afterload are determined primarily by SVR and pulmonary vascular resistance (PVR), respectively. Contractility describes the inotropic state of the myocardium and affects the SV and CO independently of preload and afterload. The effects of these factors on hemodynamic parameters are interrelated and complex. Patients often present with features of combined or mixed shock states. Thus, hemodynamic parameters must be assessed carefully when selecting therapeutic interventions that will produce the desired response. A review of the determinants of cardiac performance is found in Chapter 14, Heart Failure. Table 17-2 provides definitions of terms and normal hemodynamic indices.

ETIOLOGIC CLASSIFICATION OF SHOCK AND COMMON MECHANISMS

The most common clinical conditions associated with the major forms of shock are reviewed in the subsequent sections and detailed in Table 17-1. **Table 17-3** describes the common hemodynamic findings for the various forms of shock.

Table 17-3
Hemodynamic Findings in Various Shock States

	Hypovolemic	Cardiogenic	Distributive (Septic)	Obstructive
Heart rate	↑	↑	↑	↑
Blood pressure[a]	↓	↓	↓	↓
Cardiac output	↓	↓	↑/↓[b]	↓
Preload (PCWP)	↓	↑	↔/↓	↑/↓[c]
Afterload (SVR)	↑	↑	↓	↑

PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

[a]Patients may be in a state of compensated shock in which blood pressure is normal, but clinical signs of hypoperfusion are evident.

[b]Cardiac output is increased early in sepsis, but can be decreased in late or severe sepsis.

[c]Left ventricular preload is increased in mechanical forms, but decreased in pulmonary vascular forms.

HYPOVOLEMIC SHOCK

Shock secondary to reduced intravascular volume is referred to as *hypovolemic shock*. Whether the primary insult is the external loss of fluid (eg, blood, plasma, or free water) or the internal sequestration of these fluids into body cavities (third spacing), the overall result is reduced venous return or preload (decreased CVP and PCWP) and decreased CO (Table 17-3). The severity of hypovolemic shock depends on the amount and rate of intravascular volume loss and each person's capacity for compensation. Although responses vary, a healthy person may tolerate an acute loss of as much as 30% of his or her intravascular volume.[18] Compensatory mechanisms such as increased HR, myocardial contractility, and SVR are sufficiently

effective for this loss in volume, and measurable falls in SBP are not detected. Losses in excess of 40% generally overwhelm compensatory mechanisms; venous return decreases and the patient's condition can deteriorate to overt shock with hypotension and signs of hypoperfusion. If restorative measures are not taken immediately, irreversible shock and death may result. The most common and dramatic cause of hypovolemic shock is hemorrhagic shock in which intravascular volume depletion occurs as a result of bleeding. Trauma is responsible for most cases of acute hemorrhagic shock; other significant causes are listed in Table 17-1.

Acute Hemorrhagic Shock

CASE 17-1

Question 1: N.G. is a 64-year-old female with a history of peptic ulcer disease, who arrives to the emergency department (ED) with diffuse abdominal pain and bright red blood in her stool over the past 2 days. She is confused and oriented only to person. Her skin is pale and cool, with HR 120 beats/min, SBP 80 mm Hg, and RR 28 breaths/min.

What are the physiologic changes in N.G. in response to her gastrointestinal (GI) bleeding? What are the goals of resuscitation in patients with hemorrhagic shock?

N.G. has lost a significant amount of intravascular fluid directly from her GI tract. She is hypotensive with a compensatory increase in both HR and RR. Her pale, cool skin indicates shunting of blood from the periphery to maintain perfusion of vital organs. Based on her clinical presentation, N.G. is in hypovolemic shock.

The major hemodynamic abnormality in hypovolemic shock is decreased venous return (preload) to the heart, resulting in a decrease in CO. $\dot{D}o_2$ to the tissues is reduced from this and the loss of oxygen-carrying hemoglobin (Hgb). The physiologic response of the body to a sudden decrease in volume (preload) is to activate the sympathetic nervous system to release catecholamines (epinephrine, norepinephrine). The subsequent increase in HR and contractility help maintain CO. The peripheral vasoconstriction caused by the sympathomimetic response helps maintain arterial pressure. In addition, reduction in capillary pressure leads to fluid shifts from the interstitial spaces into the vasculature to increase preload. These responses are effective in maintaining BP in patients with a loss of up to ~30% of the total blood volume. N.G.'s increased HR and signs of peripheral vasoconstriction are consistent with these compensatory changes. Her SBP is still low, however, and she has signs of decreased perfusion to her brain, manifested by confusion and disorientation. Given the severity of her condition, if intravascular losses are not rapidly replaced, myocardial dysfunction may ensue and lead to irreversible shock.

The goals of resuscitation of patients in hypovolemic shock are the correction of inadequate tissue perfusion and oxygenation and limiting secondary insults until steps are taken to control the underlying cause. HR, BP, and urine output have been traditional markers for the adequacy of resuscitation, but reliance on these end points alone is acceptable only in the initial management of hemorrhagic shock. One concern is that patients may persist in a state of compensated shock even after these parameters are normalized.[19] Ongoing deficiencies in $\dot{D}o_2$ to vital organs may progress, and if left untreated, organ dysfunction and death may result. Measurement of base (bicarbonate) deficit and lactate levels can be used to assess the global adequacy of perfusion by tracking trends, ensuring that the levels are decreasing. Metabolic acidosis can signal that resuscitation is incomplete despite normal vital signs.

TREATMENT

Choice of fluid in hypovolemic shock

Case 17-1, Question 2: Is an IV saline solution adequate to compensate for N.G.'s blood loss? What other fluid options are available to resuscitate this patient?

Once an adequate airway is established and initial vital signs are obtained, the most important therapeutic intervention in hypovolemic shock is the infusion of IV fluids. Initially, crystalloids or colloids are used to restore blood volume because blood products are limited, costly, and transfusion of these products carries a risk.[20] Blood products may not be immediately available and are frequently unnecessary to manage mild shock (<20% blood loss). Resuscitative measures should be taken until N.G. can be taken for endoscopic therapy to control bleeding.

Crystalloids versus colloids

Balanced crystalloids (eg, lactated Ringer [LR] solution, Plasma-Lyte® (Baxter Healthcare Corporation, Deerfield, IL, USA)) and isotonic saline (0.9% sodium chloride) are both recommended as resuscitation fluids (**Table 17-4**). Colloidal solutions contain high-molecular-weight molecules that are derived from natural products, such as proteins (albumin), carbohydrates (dextrans, starches), and animal collagen (gelatin), and largely remain in the intravascular space, thereby contributing to colloid oncotic pressure (COP) (**Table 17-5**).

Table 17-4
Composition and Properties of Crystalloids

Solution	Sodium (mEq/L)	Chloride (mEq/L)	Potassium (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)	Lactate (mEq/L)	Tonicity Relative to Plasma	Osmolarity (mOsm/L)
5% Dextrose	0	0	0	0	0	0	Hypotonic	253
0.9% Sodium chloride	154	154	0	0	0	0	Isotonic	308
Plasma-Lyte (Baxter)	140	103	10	5	3	8	Isotonic	312
Lactated Ringer's	130	109	4	3	0	28	Isotonic	273
Normosol™ (Hospira)	140	98	5	0	3	0	Isotonic	294
7.5% Sodium chloride	1283	1283	0	0	0	0	Hypertonic	2567

Table 17-5
Composition and Properties of Colloids

Solution	Colloid Type	MWw (kDa)	DS	Sodium (mEq/L)	Chloride (mEq/L)	Potassium (mEq/L)	Calcium (mEq/L)	Glucose (mg/L)	Osmolarity (mOsm/L)
Albumin	Blood derived	67		130–160		≤2			300
Hespan® 6%, B. Braun Medical, Inc Bethlehem, PA	Hetastarch	450	0.7	154	154				309
Hextend® 6%[a], Hospira, Inc Lake Forest, IL	Hetastarch	450	0.7	143	124	3	5	90	307
Voluven®, Fresenius Kabi Norge A.S., Halden Norway	Tetrastarch	130	0.4	154	154				308
Gentran 40, (Baxter Inc; Deerfield, IL)	Dextran 40	40		154	154			50	308
Gentran 70, (Baxter Inc; Deerfield, IL);	Dextran 70	70		154	154			50	308

DS, proportion of substituted to nonsubstituted glucose moieties (higher DS is more resistant to hydrolysis); MWn, arithmetic mean of all particle molecular weight; MWw, weight-averaged molecular weight (number of molecules at each weight multiplied by the particle weight divided by the total weight of all the molecules).

[a]Hextend also contains magnesium 0.9 mEq/L and lactate 28 mEq/L.

The choice of a crystalloid versus a colloid solution to restore blood volume in hemorrhagic shock is controversial. The controversy primarily involves the ultimate distribution of these fluids in the extracellular compartment, which, in turn, depends on their composition. Isotonic solutions (normal saline [NS] or LR) freely distribute within the extracellular fluid compartment, which is divided between the interstitial and intravascular spaces at a ratio of 3:1. This distribution is determined by the net forces of COP and hydrostatic pressure, both inside and outside the capillary vascular space. Consequently, large volumes of crystalloid fluid are required to expand the intravascular space during resuscitation. In contrast, intact capillary membranes are relatively impermeable to colloids, and, therefore, colloids effectively expand the intravascular space with little interstitial loss. Comparatively smaller volumes of colloids than of crystalloids are required for resuscitation, and their duration of action is longer. It is thought that three to four times as much volume of crystalloid compared to colloid is necessary to provide the same degree of volume expansion.

Proponents of crystalloids argue that both intravascular and interstitial fluids are depleted in hypovolemic shock because of the

rapid shifts between the extracellular compartments. Volume replacement of both fluid spaces is best accomplished using crystalloids. In addition, loss of capillary integrity in shock can cause the leak of larger molecules (including colloidal molecules) into the interstitium. This increase in the interstitial oncotic pressure would favor fluid movement out of the vascular space into the tissues, with resultant edema. Crystalloids do not produce allergic or hypersensitivity reactions as many of the colloidal agents do. Colloids can also cause coagulopathies, have been associated with an increased incidence of acute kidney injury, and are much more expensive than are crystalloids.

Proponents of colloids maintain that resuscitation with these solutions more rapidly and effectively restores intravascular volume after acute hemorrhage. For a given infusion volume, colloidal solutions (eg, albumin) will expand the intravascular space two to four times more than crystalloids do, and the intravascular effects persist longer. Traditionally, it has been contended that the larger volumes of crystalloids necessary to restore the vascular space will further dilute the plasma proteins, resulting in a decreased COP and promotion of pulmonary edema. However, clinical studies comparing colloids with crystalloids have failed to show any differences in the development of pulmonary edema. This is likely because of the relatively high alveolar capillary permeability to albumin causing a decreased transcapillary COP gradient. Research suggests that certain subgroups may be at greater risk for the development of pulmonary edema, but considerable variance remains because of differences in physiologic end points, criteria for assessing pulmonary edema, and the extent of shock.

Numerous meta-analyses have compared resuscitation with crystalloids or colloids to find a consensus among divergent clinical trial results. One meta-analysis failed to show a mortality benefit for resuscitation with colloids compared to crystalloids in patients who were critically ill who required fluid replacement as a result of sepsis, trauma, or burns.[21] Mortality outcomes in other meta-analyses reviewing various colloids across different patient groups have been comparable.[22–26] It is important to recognize that study inclusion

criteria (heterogeneity), differences in fluid management, and dosages provide several limitations to these meta-analyses. Fluid resuscitation with starches may be uniquely harmful in patients who are critically ill or undergoing elective surgeries. Multiple analyses have indicated an increase in mortality, need for transfusion of blood products, and need for renal replacement therapy in these patients when starches were used.[21,27,28] Starches should be avoided in these patients until more data are available.

A Cochrane Database meta-analysis found that volume resuscitation with albumin in hypovolemic critically ill patients did not reduce mortality compared to crystalloids and was possibly associated with an increased risk of death in patients with burns or hypoproteinemia.[29] This meta-analysis was heavily influenced by the Saline versus Albumin Fluid Evaluation (SAFE) trial, the largest randomized, prospective trial to evaluate albumin versus NS solution resuscitation in the critically ill.[30] The primary end point of the SAFE trial was 28-day mortality, which showed no difference between albumin and NS solution. No statistical differences were identified in any of the predetermined subgroups (trauma, acute respiratory distress syndrome [ARDS], severe sepsis). A trend toward increased mortality in the trauma patients who received albumin led to a post hoc follow-up study in patients who had traumatic brain injury.[31] A higher mortality rate was seen in patients with severe traumatic brain injury (Glasgow Coma Scale 3–8), who received albumin versus those receiving saline for fluid resuscitation.

More certain differences between colloids and crystalloids are availability and cost. Crystalloid solutions are readily available and remain 20 to 100 times cheaper than are colloidal solutions; therefore, treatment costs can be significantly different and must be considered when choosing between therapies with similar outcomes.[32] Because current evidence does not show mortality benefit with colloids compared to crystalloids and because colloids are more expensive, multiple sets of consensus guidelines do not recommend the routine use of colloids.[33,34] Use of crystalloid solution would be appropriate for N.G. Colloidal products are not needed at this time; instead, they should be reserved for persistent hypotension

despite an appropriate crystalloid challenge.[33] Given the severity of N.G.'s hemorrhagic shock, blood transfusion is indicated and should be transfused as soon as available.[20,35]

Crystalloids

Case 17-1, Question 3: Two large-bore IV catheters are inserted into N.G.'s arms and STAT blood samples are sent for type and cross-match, complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), and serum chemistry (blood urea nitrogen [BUN], creatinine [SCr], Na, K, Cl, and bicarbonate). Warmed LR solution (1 L) is infused rapidly, and the GI endoscopy suite is notified. N.G.'s SBP has increased to 94 mm Hg, but the bleeding has not stopped. A Foley catheter is inserted to measure urine output. LR is continued, with 500- to 1000-mL boluses ordered to maintain hemodynamic stability while waiting for fully cross-matched blood. Are the doses of LR given to N.G. appropriate? What clinical and objective parameters should be monitored to determine the success of fluid replacement?

Volume Requirements

Isotonic crystalloids equilibrate rapidly between the interstitial and the intravascular spaces at a ratio of 3:1. For every liter of fluid infused, ~750 mL will pass into the interstitium, whereas 250 mL will remain in the plasma. Because determination of blood loss is based solely on clinical assessment and not on quantitative measurements, treatment is best directed by the response to initial therapy rather than to the initial classification. Close observation of hemodynamic status with consideration of the patient's age, particular injury, and prehospital fluid therapy is essential to avoid inadequate or excessive fluid administration.

Crystalloids have been used for decades to manage bleeding. Although crystalloids can transiently expand intravascular volume, they do not provide intrinsic benefit. Large volumes of crystalloids can cause complications such as respiratory failure, compartment syndrome, and increased coagulopathy. Because of these complications, a more restrictive crystalloid resuscitation strategy is employed. A Cochrane systematic review including six randomized

trials that examined timing and volume of fluid administration in bleeding patients found no difference in mortality between restrictive fluid resuscitation and more aggressive fluid resuscitation.[36] Crystalloids are now typically limited to 3 L in the first 6 hours of arrival at the hospital in acutely bleeding patients.[37] The fluid boluses given to N.G. are an appropriate initial measure, and then assessment of her perfusion is vital to determine the need for additional boluses.

Normalization of BP, HR, and pulse pressure (difference between SBP and diastolic blood pressure [DBP]) indicates improved circulation. Signs that actual organ perfusion is normalizing and that fluid resuscitation is adequate include improvements in mental status, warmth and color of skin, improved acid–base balance, and increased urinary output. The minimal acceptable urine output is 0.5 mL/kg/hour for an adult, 1 mL/kg/hour for a child, and 2 mL/kg/hour in an infant age younger than 1 year.[18] Persistent metabolic acidosis in normothermic shock usually indicates the need for additional fluid resuscitation; sodium bicarbonate administration has not been shown to improve mortality or organ failure in patients with severe metabolic acidosis (pH < 7.2) but did decrease 28-day mortality and the composite outcome of 28-day mortality or presence of at least one major organ failure in a subgroup of patients with acute kidney injury.[38] The role of sodium bicarbonate is controversial, but is not recommended unless the pH is <7.2.[19] Monitoring serum lactate and base deficit is important to determine adequate resuscitation.[37] As perfusion improves, lactate and base deficit will decrease; thus, the actual values are not as important as the trend. It is important to note that resuscitation is not defined by just one value or number, such as BP, but by the constellation of indicators of overall perfusion.

Balanced crystalloids versus normal saline

Case 17-1, Question 4: Is there an advantage to using a balanced crystalloid solution (ie, LR) versus NS solution for N.G.?

The optimal resuscitative fluid remains controversial. Historically, intravenous (IV) NS has been the most commonly administered fluid. In recent years, there has been much interest in using balanced crystalloids (eg, LR, Plasma-Lyte, Normosol™, ICU Medical, Inc., Lake Forest, IL, USA) for resuscitation in critically ill patients. NS solution has a supraphysiologic sodium and chloride content, whereas the electrolyte content of balanced crystalloids more closely resembles extracellular fluid (Table 17-4). Large volumes of NS can cause hyperchloremic metabolic acidosis, thereby worsening the tissue acidosis from hypovolemic shock. The SALT Balanced Crystalloids versus Saline in the Intensive Care Unit, with 974 critically ill patients, demonstrated that the incidence of death, new renal replacement therapy, and persistent renal dysfunction were all lower with balanced crystalloids compared to that with NS.[39] Similarly, the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) trial showed a reduction in acute kidney injury with balanced crystalloids in 15,802 critically ill patients.[40] A meta-analysis of 13 trials demonstrated a lower hospital or 28- or 30-day mortality and less new acute kidney injury in patients given balanced crystalloid.[41]

Balanced crystalloids are buffered with a base (eg, lactate, acetate, gluconate). Sodium lactate in LR can cause a minimal increase or less than expected decrease in serum lactate concentrations following fluid resuscitation, particularly in patients with impaired hepatic function, but it does not cause lactic acidosis.[42–44] The lactate buffer is utilized for energy in ischemic conditions and may decrease cellular death.[44] Lactate and acetate are metabolized to carbon dioxide and water and later to bicarbonate. Metabolism of gluconate is not fully understood, but many studies suggest that gluconate is excreted unchanged in the urine. Adverse effects and outcomes between different balanced crystalloids are still being investigated.[45] Recent randomized controlled trials add to a growing body of evidence suggesting that balanced crystalloids decrease morbidity and mortality in critically ill patients and are preferred over NS. LR is an appropriate option for volume resuscitation in N.G.

Hypertonic Saline

CASE 17-1, QUESTION 5: What is the role of hypertonic saline (HS) solution in the setting of hemorrhagic shock?

The presumed advantage of HS (3%–7.5% NaCl) solution as a resuscitative fluid is the smaller volume of fluid required to expand the intravascular compartment compared with isotonic solutions. With a high concentration of sodium, the HS solution exerts an osmotic effect, translocating fluid from the interstitial and intracellular compartments to the intravascular space. Consequently, plasma volume is rapidly expanded to a greater extent than are similar volumes of crystalloid solutions, and systemic BP, CO, and $\dot{D}o_2$ are readily increased. Intracranial pressure is reduced, but to date HS has not been shown to improve outcomes in trauma patients with concomitant head injury.[46] Other studies have shown that HS may have beneficial effects on circulation, inflammation, and endothelial function.[46,47]

Despite these initial positive findings, hypertonic solutions are not widely used because they have failed to improve clinical outcomes. Much of the data regarding HS as a resuscitative fluid in hypovolemic shock is in trauma patients. The Resuscitation Outcomes Consortium performed a multicenter randomized controlled trial of NS, HS, and HS dextran for prehospital resuscitation in patients with hemorrhagic shock. An interim analysis showed no mortality difference between groups and worse coagulopathy with hypertonic solutions. The trial was stopped early owing to futility.[48] No high-quality trials are available in patients with GI bleeding.

Hypertonic solutions are also high-risk medications. HS is prone to dosing and administration errors, particularly when used by clinicians who are unfamiliar with the product. The osmolarity of HS can range from 1026 to 2567 mOsm/L (3%–7.5% NaCl), so infusion through a central line is preferred to minimize phlebitis. HS may cause hypernatremia and hyperchloremic metabolic acidosis, resulting in

rapid fluid shifts between cellular compartments and potentially devastating effects such as osmotic demyelination syndrome. However, most studies have not reported such events, which may be because of a lack of power or the relatively small volumes of HS used for resuscitation.

Blood replacement

Case 17-1, Question 6: N.G. has received 3 L of LR solution to maintain hemodynamic stability. Her current vital signs are BP 98/54 mm Hg, HR 108 beats/min, and RR 30 breaths/min. She is still confused and is becoming more agitated and combative. Urine output has been only 30 mL in the past 30 minutes. Laboratory results include the following:

Hematocrit (Hct), 21% (down from 26%)
Hemoglobin (Hgb), 7.1 g/dL (down from 8.9 g/dL)
pH, 7.14
P_{CO_2}, 34 mm Hg
P_{O_2}, 106 mm Hg
HCO_3^-, 16 mEq/L

Two units of packed red blood cells (PRBCs) are now available, and N.G. is being prepared for the GI endoscopy suite. What is the current status of N.G.'s resuscitation and the need for blood products?

N.G. is still exhibiting signs of inadequate tissue perfusion. Although her BP has improved and her HR has decreased, her mental status has declined, she is oliguric, and her ABG indicates metabolic acidosis. N.G. has not been adequately resuscitated from her hemorrhage, is still actively bleeding, and should receive available blood at this point.

The prior conventional approach to the transfusion of critically ill patients was to maintain the Hgb >10 g/dL or the Hct >30%. It has been argued that these liberal transfusion goals are justified in acutely ill patients, particularly those with cardiovascular disease, because the compensatory mechanisms to maintain tissue $\dot{D}o_2$ are impaired. However, randomized, controlled trials have shown that a restrictive transfusion strategy (target Hgb 7–8 g/dL or transfused if

symptomatic) is associated with equivalent or better outcomes in hemodynamically stable critical care, surgical, and medical patients.[20,35] In acute upper GI bleeding, a restrictive transfusion threshold (Hgb <7 g/dL) compared with a liberal transfusion threshold (Hgb <9 g/dL) was associated with a higher 6-week survival, lower rates of further bleeding, and less adverse effects.[49] Consensus guidelines recommend a transfusion target of 8 g/dL for nonvariceal upper GI bleeds.[34]

In acute hemorrhage, the actual degree of blood loss is not accurately reflected by the Hgb and Hct values, and it also does not take into account the body's ability to compensate for the loss of oxygen-carrying capacity. Because it takes at least 24 hours for all fluid compartments to reach equilibrium, a normal Hct (or Hgb concentration) in the setting of hemorrhagic shock does not rule out significant blood loss or indicate adequacy of transfusion. Only when equilibrium has been reached can these measures be used reliably to gauge blood loss. On the other hand, if cardiopulmonary function is normal and volume status is maintained, an increase in CO can compensate for a reduction in Hgb (O_2 content) to a certain degree (Fig. 17-1).

Because inadequacy of tissue perfusion, and hence $\dot{D}o_2$, is the primary abnormality in shock, the need for transfusion therapy is more accurately determined by the patient's symptoms and oxygen demand, rather than an arbitrary Hct or Hgb value.[20] Calculation of $\dot{D}o_2$ and $\dot{V}o_2$ can be used to determine the adequacy of perfusion. Although these values can be determined using a PAC and arterial and venous blood samples, for practical purposes the patient's response to initial fluid resuscitation and clinical signs of inadequate tissue perfusion are the primary determinants for blood transfusion. Patients who are not acutely bleeding and who do not respond to initial volume resuscitation or who transiently respond but remain tachycardic, tachypneic, and oliguric clearly are underperfused and will likely require blood transfusion. Patients who have acute bleeding or who demonstrate signs of underperfusion should be

considered for transfusion much sooner; thus, N.G. should receive a transfusion.

In acute bleeding, combinations of fresh frozen plasma (FFP), platelets, and PRBCs are needed to treat coagulopathy, but the optimal ratio is unclear. The PROPPR (Pragmatic, Randomized, Optimal Platelet and Plasma Ratios) study compared 1:1:1 versus 1:1:2 (FFP:platelets:PRBC).[50] International guidelines differ in recommendations of FFP:RBC, but agree that platelets should be transfused based on platelet counts.[51–54]

Adverse effects of transfusion

Case 17-1, Question 7: After the transfusion, N.G. has a serum potassium concentration of 4.7 mEq/L compared with 4.2 mEq/L before the transfusion. Could this be a result of the blood product? What other potential acute transfusion-related complications are associated with PRBC administration?

Possible risks of blood transfusions include febrile and allergic reactions, hemolytic reactions, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), electrolyte abnormalities, infectious disease transmission, coagulopathies, and immunosuppression.[55] Blood products are now safer than before because of improved donor screening, patient identification, hemovigilance, and increased understanding of transfusion-related adverse events. Febrile nonhemolytic, allergic reactions, and delayed serologic transfusion reactions are the most common adverse reactions. Recognition of donor–recipient ABO incompatibility and the signs and symptoms of a transfusion reaction (eg, anxiety, infusion site pain, chills, rigors, fever, hypotension, tachycardia, hemolysis, hemoglobinuria) can prevent unnecessary morbidity and mortality by stopping the infusion and providing supportive therapy.

TRALI and TACO are the most commonly fatal transfusion-related adverse events.[55,56] The pathophysiologic mechanisms of each are complex and incompletely understood. TRALI occurs owing to

activation of recipient neutrophils, which cause capillary endothelial damage and noncardiogenic pulmonary edema. TACO results in pulmonary edema in patients with limited cardiac reserve (eg, the elderly, infant, renal failure, heart failure [HF]), following suboptimal fluid management, or after massive transfusions. Both occur within 6 hours of blood transfusion.[56] No specific treatment is available for either adverse reaction, and management includes supportive care.

Hemolytic transfusion reactions can be classified as immune mediated or nonimmune mediated. Immune-mediated reactions occur when incompatible blood or blood products are transfused, normally owing to mistransfusion events. It is unlikely that N.G. is having a true hemolytic reaction. Banked blood is stored with a citrate anticoagulant additive. With multiple transfusions, the large amount of citrate can cause hypocalcemia and acid–base abnormalities. Hyperkalemia also can occur because transfusion of stored blood causes the release of potassium from hemolyzed (ruptured) red blood cells. The increase in serum potassium observed in N.G. may be from the blood product; however, the average amount of extracellular potassium ranges from <0.5 to 7 mEq/unit of blood, so the transfusion is unlikely the culprit. The increased potassium may simply reflect hemolysis of blood cells in the test tube after the blood draw. In either case, the measured serum concentration of 4.7 mEq/L is not sufficiently high to warrant immediate treatment, but should be monitored.

Blood products and donors are screened for disease; thus, transmission of bacterial or viral illness is rare. It is estimated that the transmission of human immunodeficiency virus or hepatitis C is now <1 in 2 million.[50] Protozoan infection and prion disease are also transmissible through infusion, but are an even lower risk.

Immunosuppression has also been associated with blood transfusions, as evidenced by enhanced graft survival in renal transplant recipients, tumor recurrence in patients with colorectal carcinoma, and postoperative infections. Transfusion-related immunosuppression is multifactorial, but it is most likely caused by the infusion of donor white blood cells (WBCs), which creates a competition between the donor and the recipient leukocytes.

Transfusion-related immunomodulation can be limited by leukoreducing PRBCs before transfusion. The majority of blood in the United States is leukoreduced, but it is not a universal practice primarily because of cost. Patients who are immunosuppressed, undergoing cardiac surgery, or receiving chronic transfusions should receive leukoreduced blood. This mechanism is not, however, the only cause because immunosuppression is associated with autologous blood transfusions as well as the infusion of plasma alone.

Because of the limited supply and potential adverse effects associated with blood, research is ongoing to develop blood substitutes. The ideal agent would have a longer shelf life, a reduced risk of disease transmission, and less risk of transfusion reactions. The agents in various stages of clinical research include the modified hemoglobins and the perfluorocarbons.[57] Problems have occurred with some of the products thus far, such as short half-life, vasoconstriction, GI disturbances, and flulike symptoms. The exact role the blood substitutes would play in transfusions is unclear. No agents are approved, but unlicensed blood substitutes may be available under a U.S. Food and Drug Administration Expanded Access (previously referred to as compassionate use) protocol for patients with life-threatening anemia for whom blood is not an option.

Postoperative Hypovolemia

HYPOVOLEMIA VERSUS PUMP FAILURE

CASE 17-2

Question 1: P.T. is a 58-year-old male who arrives to the ED via ambulance after a motor vehicle accident. He has remained conscious during the event, but his mental status fluctuates between somnolent and agitated with a Glasgow Coma Scale of 10 (moderate injury). Chest computed tomography (CT) reveals a type II proximal descending thoracic aortic injury. P.T. is taken for an emergent surgical repair of his aorta. He has been admitted to the ICU after surgery and is intubated and receiving 60% oxygen. His ABGs are adequate. His initial

postoperative and 2-hour postoperative hemodynamic profiles are as follows (initial parameters in parentheses):

BP (S/D/MAP), 86/44/58 mm Hg (100/52/68 mm Hg)
HR, 96 beats/min (88 beats/min)
CO, 3.2 L/min (4.8 L/min)
CI, 1.9 L/min/m^2 (3.3 L/min/m^2)
CVP, 6 mm Hg (12 mm Hg)
PAP (S/D), 18/8 mm Hg (24/14 mm Hg)
PCWP, 13 mm Hg (18 mm Hg)
SVR, 1080 dyne.sec/cm^5 (1560 dyne.sec/cm^5)
Urine output, 0.4 mL/kg/hour (1.2 mL/kg/hour)
Temperature, 99.32 °F (37.4 °C) to 94.64 °F (34.8 °C)
Hct, 32% (31%)

From the hemodynamic profile, is P.T. hypovolemic or experiencing pump failure after his surgery?

Most of P.T.'s hemodynamic changes are consistent with hypovolemia. These include a drop in BP, CVP, PAP, PCWP, CO, and urine output. The decrease in CVP and PCWP suggests that preload is reduced, resulting in a lower CO. The pulse pressure is narrowed, suggesting that either blood flow or ventricular contractility has decreased. Decreases in pulse pressure correlate with decreases in SV or left ventricular stroke work index [LVSWI]. P.T.'s HR increased slightly, but it is unclear whether he was taking any medications, such as a β-blocker, before his injury. As body temperature rises postoperatively, vasodilation decreases SVR and increases the intravascular space. If intravascular volume is inadequate and increased sympathetic tone cannot generate a sufficient CO, mean BP falls. The decline in urine output reflects a compensatory drop in renal perfusion. The most likely explanation for the hemodynamic change in P.T. is hypovolemia. The PCWP would be higher if P.T. was in cardiogenic shock; however, he also should be evaluated for the occurrence of a perioperative cardiac event (myocardial infarction [MI]). His ABG should be checked to assess oxygen requirements.

CAUSES

CASE 17-2, QUESTION 2: What are the most likely causes of hypovolemia in P.T.?

Common causes of hypovolemia in surgical patients are postoperative bleeding, third spacing, and temperature-related vasodilation. Postoperative bleeding can produce hypovolemia; however, P.T.'s initial and 2-hour postoperative Hct of 31% and 32%, respectively, do not support bleeding as a cause.

After major vascular or bowel surgery and in cases of burns or peritonitis, patients have an internal redistribution of fluids, called *third spacing*, which can result in intravascular volume depletion. It is not unusual for patients to third-space significant amounts of intravascular volume. The interstitial space and bowel walls can sequester large amounts of fluid, and this can produce a state of relative hypovolemia as is occurring with P.T. This is likely in the first 12 to 24 hours after the surgical procedure. P.T. needs a bolus of IV crystalloids for volume repletion. Mild hypothermia is common during operative procedures. Vasodilation occurs as patients warm postoperatively, expanding the intravascular space. If the amounts of IV fluids administered are insufficient to compensate for the increased venous capacitance, BP and CO will decline during the rewarming phase, which can range from 1 to 6 hours. P.T. has rewarmed from 94.64 °F (34.8 °C) to 99.32 °F (37.4 °C) in 2 hours, which is not unusual after a major operative procedure. His temperature could conceivably rise to as high as 100.04 °F (38 °C) to 101.03 °F (38.5 °C) during the first 12 to 24 hours after surgery.

Other considerations include inadequate fluid administration during the operative procedure and the effects of drugs given in the operating room or in the immediate postoperative period (eg, opioids, sedatives, inhaled anesthetics) that cause systemic vasodilation.

VOLUME REPLACEMENT AND VENTRICULAR FUNCTION

Case 17-2, Question 3: How will volume replacement improve P.T.'s CO and perfusion pressure?

The Frank–Starling mechanism indicates that the volume of blood returned to the heart is the main determinant of volume pumped by the heart. Therefore, as venous return is increased, the CO also will increase within physiologic limits until the optimal preload is achieved, at which point further volume has minimal effect on SV (Fig. 17-1). The PCWP, the best indicator of LV preload, and the CVP, a marker of RV preload and overall estimate of volume status, are low because of declining venous return in P.T.

A ventricular function curve can be constructed by plotting a measure of cardiac pumping (CO, SV, or LVSWI) against a measure of preload (**Fig. 17-2**). Two hours after surgery, P.T.'s CVP has fallen from 12 to 6 mm Hg and his CO has fallen from 4.8 to 3.2 L/min. Therefore, additional volume replacement is warranted.

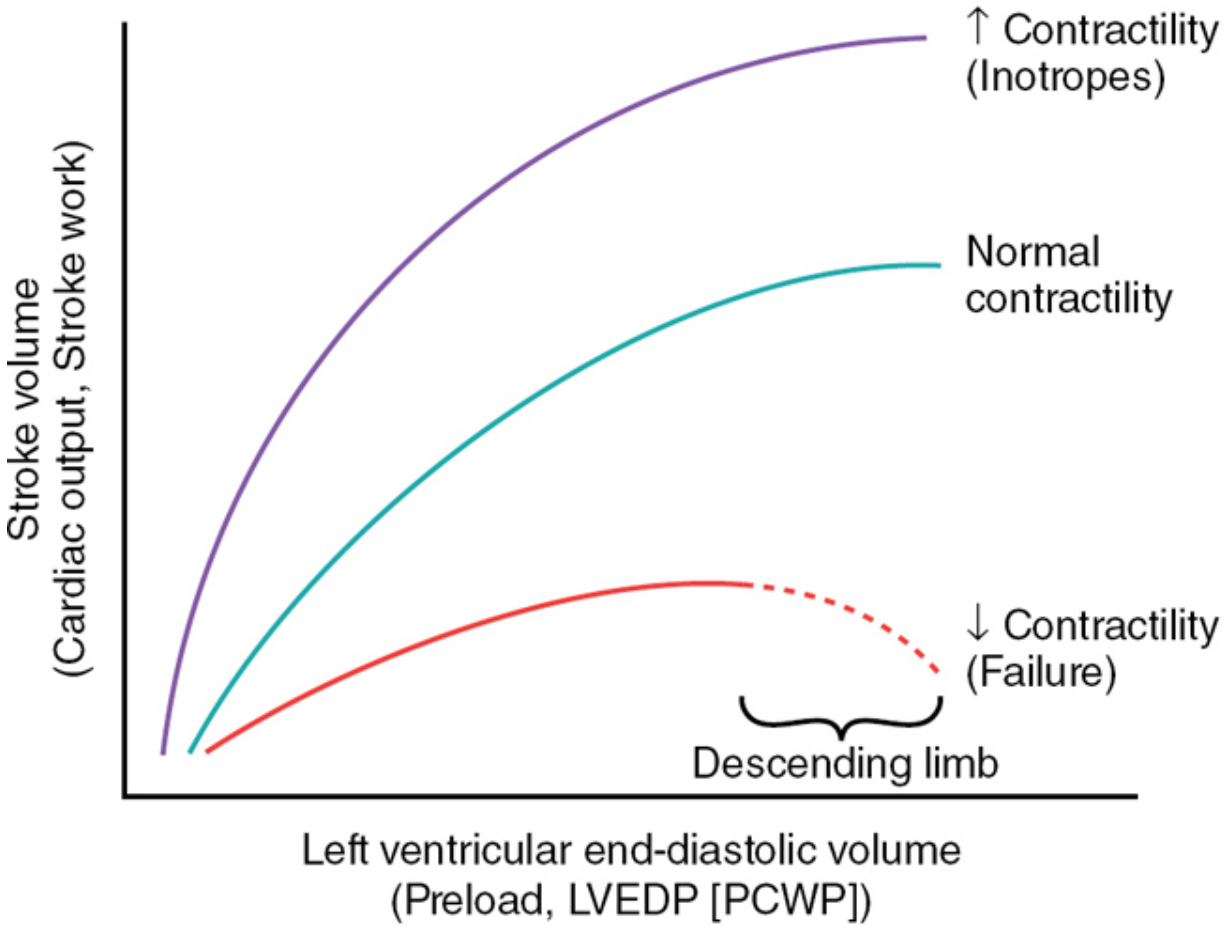


Figure 17-2 Ventricular function (Frank–Starling) curve. In the normal heart, as preload (left ventricular end-diastolic pressure [LVEDP]), measured clinically by pulmonary capillary wedge pressure (PCWP), increases, stroke volume (cardiac output, stroke work) increases until the contractile fibers reach their capacity, at which point the curve flattens. A change in contractility or afterload causes the heart to perform on a different curve. If the contractile fibers exceed their capacity, as with severe heart failure, the heart will operate on the descending limb of the curve.

CASE 17-2, QUESTION 4: P.T. is given a 500-mL bolus of LR solution in 10 minutes, and this results in the following hemodynamic profile (previous values in parentheses):

BP (S/D/M), 96/54/68 mm Hg (86/44/58 mm Hg)
HR, 88 beats/min (96 beats/min)
CO, 3.9 L/min (3.2 L/min)

CI, 2.4 L/min/m^2 (1.9 L/min/m^2)
CVP, 10 mm Hg (6 mm Hg)
PCWP, 15 mm Hg (13 mm Hg)

How can P.T.'s response to the fluid challenge be assessed (see Table 17-2 for normal values)?

According to the Frank–Starling curve, a small change in preload in response to a volume challenge with a minimal change in CO represents a ventricle on the flat portion of the ventricular function curve (Fig. 17-2). Additional fluid therapy given to these patients can increase their risk of pulmonary edema without improving CO. In contrast, a large change in preload in response to a fluid challenge with a significant increase in CO represents a ventricle on the steep portion of the curve. In P.T., the PCWP indicates that he does not have pulmonary edema, and the change in CVP from 6 to 10 mm Hg along with the increase in CO show that he is still responsive to fluid. Thus, it is reasonable to administer more fluid to enhance CO and renal perfusion.

FLUID CHALLENGE

Case 17-2, Question 5: One hour after the 500-mL NS bolus, P.T.'s hemodynamic profile returns to his postoperative state. P.T. is continuing to "third-space" intravascular volume. Based on this information, what strategies can be developed for additional fluid challenges in P.T.?

Acceptable strategies for administering additional fluid challenges to patients with hypovolemia are based on the direction and degree of change in the various hemodynamic parameters in response to a fluid load rather than to their absolute values. CVP has a poor correlation with RV end-diastolic volume because it can be affected by changes in intrathoracic pressure, venous tone, and ventricular compliance (distensibility of the relaxed ventricle or stiffness of the myocardial wall).[58] PCWP and PPV are more predictable markers of fluid status.[1] LV SV (and, thus, pulse pressure) is inversely related to intrathoracic pressures during respiration; SV is maximally affected

at lower filling pressures when the ventricles are operating on the steepest portion of the Frank–Starling curve. An SV that varies at least 12% during a respiratory cycle (between end inspiration and expiration) is highly predictive of a positive response to fluid challenge.[58]

Some practitioners argue that CVP is still an acceptable gauge of fluid responsiveness when used in conjunction with other parameters, including CO, BP, urine output, and tissue perfusion. Using CVP as a guide, an increase in the CVP of 5 mm Hg after a 250- to 500-mL fluid challenge in 10 minutes implies the LV is still functioning on the steep portion of the volume–pressure curve. If the CVP rises abruptly as fluid is given, with a small change in CO, the flat portion of the ventricular function curve has been reached and the IV infusion rate should be slowed. If signs and symptoms of inadequate tissue perfusion worsen or fail to improve and if the CVP remains >10 to 14 mm Hg, fluid challenges should be stopped and inotropic therapy initiated.

Most critically ill patients require a CI >2.5 L/min/m^2 and a PCWP of 12 to 18 mm Hg, or a CVP of 8 to 14 mm Hg to maintain an acceptable MAP of >65 mm Hg. A downward trend in the lactate and base deficit and the change in hemodynamic parameters as well as vital signs and urine output should serve as indicators for whether additional fluid is required.

COLLOIDS

Case 17-2, Question 6: P.T. has received a total of 3.5 L of LR boluses during the past 6 hours and remains hemodynamically unchanged. His urine output has averaged 0.3 mL/kg/hour for the past 4 hours, indicating that volume replacement is inadequate. Given his age and the lack of response to initial crystalloid administration, the decision is made to infuse a colloid solution. How do the colloids compare as a volume expander for P.T., and which agent should be used?

Albumin, the predominant protein in the plasma, accounts for ~80% of the COP, the force that maintains fluid in the intravascular

space.[59] Human serum albumin is the colloidal agent against which all others are compared for volume-expanding properties. It is commercially prepared from pooled donor plasma that is heat treated to eliminate the potential for disease transmission. Albumin 5% solution increases plasma volume by ~80% to 100% of the volume infused, with an initial duration of action of 16 hours.[59] At steady state (3–5 days), ~40% of albumin remains in the intravascular compartment, whereas the rest is in the interstitial compartment. Side effects involve transient clotting abnormalities and anaphylactic reactions (0.5%), both of which are rare.[60] The anaphylactoid reaction is caused by the pasteurization process, causing albumin to polymerize, which produces an antigenic macromolecule. Albumin solutions also contain citrate, which can lower serum calcium concentrations and theoretically lead to decreased LV function. The effects on coagulation and serum calcium are possibly related to the volume of fluid infused rather than to albumin administration.[59] Albumin is available as a 5% solution that is iso-oncotic with the plasma and as a 25% solution that is hyperoncotic. The 5% solution is generally preferred for routine volume expansion, whereas the 25% solution is most useful in correcting hypoproteinemia or intravascular hypovolemia in patients with excess interstitial water. Albumin is subject to availability, as ~1 L of pooled donor plasma is required to produce 20 to 25 g of albumin.

Hydroxyethyl starch (HES) is a synthetic colloid made from amylopectin, which closely resembles human serum albumin but is less expensive. Available as a 6% solution, HES expands the plasma volume by an amount greater than the volume infused because the high oncotic pressure draws water from the interstitial spaces. HES solutions have varying locations and degrees of substitutions on the glucose molecules, which slow enzymatic degradation and confer greater hydrolysis resistance (Table 17-5). HES solutions have complex pharmacokinetics because of their wide range of molecular weights; with an average molecular weight of 69,000 Da and a range of 1000 to 3,000,000 Da. Numerous clinical studies have compared albumin and hetastarch for fluid resuscitation

in patients with and without shock. However, most of these trials were underpowered and there were no significant differences in mortality.[61,62] Although HES has comparable efficacy to albumin, controversy exists regarding the use of HES owing to adverse effects seen with its use. These adverse effects include severe pruritus, coagulopathy, and renal dysfunction and appear to be class-related effects because the newer, lower molecular weight and substitution products are similar.[63–65]

Dose-related reductions in platelet count and transient increases in PT and PTT have been reported with moderate infusions of HES (up to 1500 mL/day), and coagulopathies persist for up to 7 days with larger volumes.[62,64] HES causes factor VIII and von Willebrand factor levels to be lowered beyond that which can be attributed to hemodilution and also increases fibrinolysis.[62] This places patients with von Willebrand disease at greater risk of bleeding. In critically ill patients, particularly those with sepsis, HES is also associated with a dose-related increased risk of acute kidney injury and greater probability of needing renal replacement therapy.[63,64,66–68] HES now includes warnings of excessive bleeding when used in patients undergoing cardiopulmonary bypass as well as a boxed warning that states these products are contraindicated in critically ill patients. Experts argue that HES should not be used because of the potential adverse effects and that other alternatives are available.

Dextrans are colloidal solutions that are synthesized by bacteria from sucrose and are available in 40,000- and 70,000-Da average molecular weight solutions. These products lack adequately powered randomized trials to adequately examine their efficacy or safety.[62] As with HES, dextrans can cause renal dysfunction, bleeding, and anaphylactic reactions. Dextrans can cause acute kidney injury, possibly because of accumulation of dextran molecules within the renal tubules. They increase bleeding by causing dose-related decreased platelet adhesion, increased fibrinolysis, and decreased levels of factor VIII. Dextran solutions are associated with the highest incidence of anaphylactic reactions among all of the colloids.

Because of the lack of superior clinically important outcomes and less favorable safety profiles for HES and dextrans compared to

albumin, it is decided to use albumin for further volume expansion in P.T.

CARDIOGENIC SHOCK

Shock arising primarily from an abnormality in cardiac function constitutes cardiogenic shock. The causes of cardiogenic shock can be separated largely into cardiomyopathic, arrhythmogenic, and mechanical (Table 17-1), although occasionally patients may have a combination of causes. Regardless of the source, the underlying problem in cardiogenic shock is a decrease in CO that is not caused by a reduction in circulating blood volume. This decrease in CO results in the syndrome of shock, organ dysfunction, and death if measures to restore perfusion are not successful.

The most common cause of cardiogenic shock is LV dysfunction and necrosis as a result of acute myocardial infarction (AMI) (see Chapter 13, Acute Coronary Syndrome).[69] Necrosis of the left ventricle can be the result of a single massive MI, numerous smaller events, or severe global cardiac ischemia. Increases in sympathetic tone—seen clinically as increased HR and peripheral vasoconstriction—initially serve to increase CO and maintain arterial pressure. When necrosis exceeds ~40% of the left ventricle, normal compensatory responses can no longer maintain CO, and hypotension and hypoperfusion result. In addition to decreased perfusion to vital tissues and organs, the decrease in CO leads to a reduction in the flow of blood through the coronary arteries, which can lead to infarct extension and a further worsening of cardiac performance.

Recent reports show an increased incidence of cardiogenic shock for unclear reasons, but is likely due in part to improved access to care and diagnosis.[70] Cardiogenic shock occurs in 5% to 12% of AMI cases and is twice as common with ST-elevation MI versus non–ST-segment elevation acute coronary syndrome.[69,71] Higher incidences of cardiogenic shock occur in patients older than 75 years of age,

females, Asian/Pacific Islanders, and those with end-stage renal disease.[72] Cardiogenic shock is the leading cause of death in patients hospitalized with AMI. Early revascularization has improved in-hospital mortality, but the 6- to 12-month mortality rate remains unchanged around 50%.[70,71]

Infarction involving the right ventricle can cause cardiogenic shock, even with normal LV systolic function. In this situation, the volume of blood reaching the left ventricle (preload) is reduced because of the inability of the right ventricle to move blood to the left side of the heart. In most patients with cardiogenic shock and RV infarction, significant LV dysfunction is present as well. Arrhythmias are often associated with worsening perfusion, causing or worsening cardiogenic shock, and poor outcomes.

Patients with chronic HF (see Chapter 14, Heart Failure) usually compensate for their poor cardiac function, but acute exacerbations can cause cardiogenic shock with hypotension, hypoperfusion, and organ dysfunction. Cardiac dysfunction occasionally can be seen with severe sepsis because of increases in the production of inflammatory cytokines that have a depressant effect on the myocardium. However, the cytokine-mediated vasodilation and reduction in afterload usually negates the ability to detect the cardiac dysfunction. A similar picture occurs after cardiopulmonary bypass with heart surgery through activation of the inflammatory cascade.

Mechanical problems are relatively infrequent causes of cardiogenic shock. The systolic function (contractility) of the heart may be normal in this setting, but other defects render the heart unable to eject a normal volume of blood. This limitation of CO may be caused by acute, idiopathic malfunction of cardiac valve(s) or worsening valvular heart disease, infarction (ie, papillary muscle rupture), or infection (ie, endocarditis). Ventricular septal or free wall rupture can also occur, often in the setting of AMI, with the reduction in forward flow related to the inability of the left ventricle to eject a normal volume of blood during systole. Pericardial tamponade (bleeding into the pericardial sac) and tension pneumothorax (air leakage from the lung into the chest) compress the heart, leading to acute diastolic dysfunction. These extracardiac processes are forms

of obstructive shock with physiologic end points that resemble cardiogenic shock.

The symptoms of cardiogenic shock are largely the same as those for other types of shock. Hypotension and signs of inadequate tissue perfusion, such as confusion, oliguria, tachycardia, diminished pulses, cutaneous vasoconstriction, are present in many patients. Differentiating cardiogenic shock from distributive or hypovolemic shock requires further examination. A history of coronary artery disease or symptoms of MI are important findings. Hypovolemia occurs in up to 20% of patients in cardiogenic shock, but patients frequently have signs of volume overload because the heart cannot effectively move blood through the circulation. Peripheral edema and jugular venous distension are seen; lung sounds are diminished; and dyspnea, orthopnea, and/or rales may be present as pulmonary edema develops with LV dysfunction. These findings are particularly evident in patients with severe HF and represent the classic presentation of cardiogenic shock that is termed *cold and wet* owing to the cool extremities and pulmonary congestion. Patients with a previous MI or chronic kidney disease are more likely to present euvolemic or "cold and dry."[71] The least common presentation for cardiogenic shock is "warm and wet," where vasodilation from an SIRS offsets the suppressed CO, allowing for adequate forward flow to perfuse extremities. This subtype is more likely to happen after an MI than in severe HF, but also may reflect a mixed shock state.[69,71]

Because the distinction between cardiogenic and other forms of shock can be difficult to make based on physical examination alone, further testing with invasive hemodynamic monitoring may be required to establish the diagnosis and guide therapy. **Table 17-6** lists the common laboratory, ECG, and chest radiograph findings, and Table 17-3 lists the common hemodynamic findings in cardiogenic shock. CVP may be easily attained, particularly if the patient already has a central line; other hemodynamic findings will require further monitoring tools (eg, PA catheter, echocardiography).

Table 17-6

Typical Findings of Early Cardiogenic Shock

- Arterial blood gas (ABG)
  - Hypoxemia secondary to pulmonary congestion with ventilation–perfusion abnormalities
  - Anion gap metabolic acidosis with a compensatory respiratory alkalosis
- Elevated blood lactate levels (which contribute to the acidosis)
- Complete blood count (CBC)
  - Leukocytosis
  - Thrombocytopenia (if disseminated intravascular coagulation is present)
- Elevated cardiac enzymes if myocardial infarction is present
- Electrocardiogram (ECG)–one or more of the following:
  - T-wave changes indicating infarction
  - Left bundle branch block
  - Sinus tachycardia
  - Arrhythmia
- Chest radiograph
  - Pulmonary edema or evidence of acute respiratory distress syndrome (ARDS)
- Echocardiography
  - Valvular or mechanical problems if present
  - Normal or decreased ejection fraction
- Hemodynamic monitoring—one or more of the following:
  - Reduced cardiac output
  - Arterial hypotension
  - Elevated pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP)
  - Elevated pulmonary artery pressure (PAP)
  - Elevated systemic vascular resistance (SVR)

Acute Myocardial Infarction

IMMEDIATE GOALS OF THERAPY AND GENERAL CONSIDERATIONS

CASE 17-3

QUESTION 1: J.S. is a 43-year-old male who presents to the ED with chest pain, tingling down his left arm, diaphoresis, nausea, vomiting, and shortness of breath. His pain has been ongoing for 3 hours and is not relieved by rest. He has no known history of cardiac disease and takes no home medications. His BP is 80/40 mm Hg (by cuff) with a weak pulse of 110 beats/min. His RR is 24 breaths/min, and his breathing is shallow. Heart sounds include S_3/S_4 gallops, but no murmurs are heard. The jugular venous pulse is normal.

He has diffuse rales over the lower lung fields with moderate wheezing. J.S. is cold and clammy to touch; however, his temperature is normal. He is restless, anxious, and oriented only to person and place. A 3-mm ST-segment elevation is seen on 12-lead ECG in leads I and aVL. Cardiac biomarkers are pending. ABG measurements, on 4 L/min oxygen via nasal cannula, are the following:

pH, 7.28
$Paco_2$, 32 mm Hg
Pao_2, 94 mm Hg
HCO_3^-, 15 mEq/L
Hct, 31%

What immediate goals of therapy are necessary to stabilize and treat J.S.?

J.S. has signs of "cold and wet" cardiogenic shock with decreased systemic perfusion. His BP is low, HR is elevated, and respiratory status is compromised. J.S. is restless, anxious, and confused, indicating poor cerebral perfusion. His ABG indicates a component of metabolic acidosis secondary to poor systemic perfusion. The ST elevation on the ECG is consistent with an acute anterior MI.

Cardiogenic shock after AMI occurs in only a small percentage of patients, but it carries a high mortality rate. Irreversible organ system dysfunction may rapidly ensue because the compensatory mechanisms fail to maintain tissue perfusion, so its presence can alter the interventional strategy. Treatment of these critically ill patients involves two components: stabilization and definitive treatment. Initial stabilization of the patient must be attained before further evaluation and treatment of the cause of cardiogenic shock can proceed. The goals are to maintain adequate $\dot{D}o_2$ to the tissues and to prevent further hemodynamic compromise. Stabilization includes (a) establishing ventilation and oxygenation (arterial Po_2 should be >70 mm Hg); (b) restoring arterial BP and CO with

vasopressors and inotropic agents, if needed; (c) infusing fluids, if hypovolemic; and (d) treating pain, arrhythmias, and acid–base abnormalities, if present.

While the patient is being stabilized and standard pharmacotherapies are provided as part of early hospital care as discussed in Chapter 13, Acute Coronary Syndrome, reperfusion of the occluded artery is paramount. Coronary occlusion is treated by immediate percutaneous coronary intervention (PCI) if available or, if not, fibrinolytic therapy (unless contraindicated).[69,73]

Early revascularization with PCI or coronary artery bypass grafting (CABG) is preferred in patients with cardiogenic shock complicating AMI, irrespective of time delay.[73] In the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, emergency revascularization, compared to immediate medical stabilization (fibrinolysis and IABP), resulted in significantly lower mortality at 1 and 6 years in patients with ST-elevation MI and cardiogenic shock.[74] Long-term mortality was positively correlated with time to revascularization from 0 to 8 hours, confirming that revascularization should be performed as soon as possible. However, a survival benefit for revascularization remains even as long as 54 hours after MI and 18 hours after shock onset.[74] Operator skill is also a consideration, and larger centers with greater experience may have better outcomes than do smaller centers. In settings in which interventional cardiac procedures such as percutaneous transluminal coronary angioplasty or stenting are not readily available, insertion of an IABP and thrombolytic agents should not be delayed, if indicated.

Thrombolytic therapy in AMI may reduce the incidence of subsequent cardiogenic shock, but its value may be limited in patients who have already experienced shock.[74] The effectiveness of thrombolysis is reduced in this setting, possibly because of reduced delivery of the agent to the coronary artery thrombus as a result of hypotension.[75] The use of an IABP to augment coronary artery blood flow may improve the efficacy of thrombolytic agents, but has not been shown to improve mortality.[76,77]

Administration of oxygen is appropriate for patients who have severe dyspnea, hypoxemia (oxygen saturation <90%), or persistent or worsening acidemia (pH <7.3).[71,73] Improving oxygenation may contribute to improved ventricular performance; however, supplemental oxygen could potentially be harmful by causing increased coronary vascular resistance and infarct size, particularly in normoxic patients.[73,78] Invasive mechanical ventilation is indicated when arterial oxygen saturation cannot be maintained above 90% despite 100% oxygen per face mask. Low tidal volume strategies (5–7 mL/kg ideal body weight) are preferred to lower stress and prevent RV failure.[71] Once the patient is intubated, sedation should be provided to alleviate anxiety and discomfort while cautiously monitoring hemodynamic effects.

The arterial pressure must be increased to provide adequate coronary and systemic perfusion to meet oxygen requirements. Some areas of ischemia in the infarct zone may be depressed but viable, provided myocardial oxygen supply exceeds demand. If the myocardial oxygen demands are not met, then myocardial tissue necrosis will expand into the area of ischemia. This results in further hemodynamic impairment and initiates a vicious cycle that can lead to intractable pump failure and irreversible shock. To be effective, treatment of cardiogenic shock should favorably influence the balance between oxygen supply and demand in the ischemic zone. Although correction of volume deficits and early pharmacologic support may prevent the extension of myocardial damage, it must be emphasized that exclusive use of these measures does not improve survival. Therefore, drug therapy must be considered only an interim maneuver to preserve myocardial and systemic integrity while further therapeutic interventions and definitive therapy are being considered.

Optimizing preload to improve CO and systemic perfusion is crucial, especially in patients with RV infarction, but is clinically challenging and can vary over time. In patients with severe LV impairment, increasing intravascular volume can worsen pulmonary congestion. The definitive method of volume assessment is right heart catheterization in conjunction with coronary angiography.[71]

Conservative boluses (250–500 mL) of crystalloid solution are reasonable for patients who are hypovolemic and not exhibiting signs of pulmonary vascular congestion. J.S. currently has signs of pulmonary congestion and RV infarction is not evident; thus, a fluid challenge must be administered cautiously or withheld until hemodynamic monitoring can be established.

Inotropic agents or vasopressors should be used to increase systemic BP and reestablish coronary perfusion in patients with cardiogenic shock and hypotension. However, vasoactive agents have risk because they can increase $\dot{V}o_2$ in ischemic myocardium and potentially extend the area of necrosis in patients with infarct-induced cardiogenic shock. This also exacerbates or increases the risk of ventricular arrhythmias. Therefore, careful selection and titration of agents to the minimal dose that will best preserve myocardium while sustaining systemic arterial pressure and tissue perfusion are essential. Selection of vasoactive medications in cardiogenic shock is generally based on the expected hemodynamic effects and adverse effects of each agent as few clinical outcome data are available to guide decision making. Achieving a MAP >65 mm Hg is the immediate goal of therapy, but it should be adjusted based on adequate perfusion (eg, warm extremities, adequate urine output, improved mental status).[69]

Correction of metabolic acidosis is best accomplished by treating the underlying cause. Improving tissue perfusion by optimizing oxygen content and increasing CO can eventually restore aerobic metabolism and eliminate lactic acid production. The use of sodium bicarbonate to correct lactic acidosis in cardiogenic shock and other critically ill patients is controversial. Sodium bicarbonate can have numerous adverse effects, such as hypernatremia, paradoxic intracellular acidosis, and hypercapnia; conclusive data on its efficacy are lacking. Bicarbonate therapy is recommended only, if at all, when severe acidemia (pH <7.2 or HCO_3^- <10–12 mEq/L) is present.

Postoperative Cardiac Failure

ASSESSMENT BY HEMODYNAMIC PROFILE

CASE 17-3, QUESTION 2: Cardiac catheterization reveals an acute occlusion of the proximal left circumflex artery, but it was not possible to perform a PCI for J.S. He undergoes emergent CABG and arrives in the ICU sedated, intubated, and receiving mechanical ventilation with 50% inspired oxygen. Several hours after admission to the ICU, his BP and urine output have fallen and his skin is mottled and cool. Urine output has fallen from 0.8 to 0.2 mL/kg/hour in the last hour. The chest tube output has been stable at 50 mL/hour. His current hemodynamic profile is as follows:

BP (S/D/M), 86/44/58 mm Hg
HR, 105 beats/min (sinus rhythm)
CO, 3.0 L/min
CI, 1.7 L/min/m^2
Svo_2, 48%
CVP, 14 mm Hg
PAP (S/D), 41/24 mm Hg
PCWP, 24 mm Hg
SVR, 1570 dyne·s·cm^{-5}

What is your assessment of J.S.'s clinical status and hemodynamics?

Clinically, J.S. has signs of hypoperfusion manifested by low urine output; mottled, cool skin; and metabolic acidosis. His decreased Svo_2 shows that he has impaired perfusion owing to his low $\dot{D}o_2$. Evaluation of his hemodynamics will help determine a potential cause for his hypoperfusion and assist with the decision about appropriate therapeutic interventions to prevent his condition from worsening to serious organ dysfunction and death.

Possible causes of shock following cardiac surgery include blood loss, excessive vasodilation from medications or cardiopulmonary bypass–induced inflammation, cardiac ischemia-reperfusion injury, valvular dysfunction, tamponade, HF, or perioperative MI. Another concern is "stunning" of the myocardium caused by surgical trauma, which can take hours to days to resolve.

Hypovolemia should always be evaluated first when assessing hemodynamic profiles. Using vasopressor or inotropic agents in the setting of hypovolemia is rarely effective and could cause further

hypotension or serious adverse effects (eg, cardiac arrhythmias). Also, correction of hypovolemia is relatively straightforward and can be accomplished rapidly. Most patients require no more than 2 to 3 L of crystalloid after cardiac surgery, especially once rewarming is complete. J.S.'s tachycardia, low urine output, low BP, and low CO could indicate volume depletion. However, his Hct is adequate, and he has an elevated CVP, PAP, and PCWP, suggesting that he is not hypovolemic.

Excessive vasodilation is also unlikely in J.S., given that his calculated SVR (afterload) is above normal range. Cardiac tamponade should always be considered after cardiac surgery, and it is usually manifested by very high CVP, PCWP, and PAPs, with significant decreases in CO and BP. Diminished or muffled heart sounds and an inappropriately fluctuating BP with respirations (pulsus paradoxus) will usually accompany an equalization of diastolic pressures during cardiac tamponade. J.S.'s CVP and PCWP are not as high as would be expected in pericardial tamponade, and his chest tube output has remained consistent, suggesting that blood is not accumulating within the mediastinum.

Based on this hemodynamic profile, it appears that J.S. is in shock because of acute HF, most likely from postoperative myocardial dysfunction, although he should also be evaluated for myocardial ischemia or infarction and to rule out early cardiac tamponade. This evaluation should not delay the initiation of therapy.

Patients with cardiogenic shock from an acute event (such as an MI) are usually more critical than are patients who have an acute exacerbation of chronic HF. Patients with HF have compensated over time for the increases in preload and reduced CO, but patients such as J.S. have not had time to develop compensatory mechanisms. His severely depressed CO should be treated immediately to prevent further decompensation.

THERAPEUTIC INTERVENTIONS

Case 17-3, Question 3: The chest radiograph shows moderate pulmonary edema, and rales were heard on auscultation. His ABG measurements on mechanical ventilation with 50% inspired oxygen are pH 7.3, $Paco_2$ 38 mm Hg, Pao_2 90 mm Hg, and HCO_3^- 18 mEq/L. Tamponade is not evident on the radiograph. The ECG shows ST-T-wave changes with some resolution of ST elevation in leads I and aVL, but no indication is seen of a new AMI. Cardiac biomarkers are pending. BP and CO need to be improved to increase perfusion to vital organs. Three therapeutic interventions are available: fluid challenge, vasodilators, and inotropic agents. How would these choices affect J.S.'s ventricular function?

Fluid challenge (increase preload)

Augmentation of preload with a fluid challenge to improve CO is the first option. J.S. has signs of pulmonary edema on chest radiograph, rales on auscultation, and his Pao_2 is 90 mm Hg on 50% inspired oxygen. These clinical signs plus the CVP and PCWP (14 and 24 mm Hg, respectively) indicate volume overload. In addition, increasing the PCWP >18 mm Hg usually does not result in further benefit.[79,80] Giving volume might increase the pulmonary vascular hydrostatic pressure and worsen his pulmonary edema.

Because J.S. is mechanically ventilated, dynamic markers of fluid status may be used to predict fluid responsiveness. Dynamic markers more reliably predict fluid responsiveness than do static variables. Assuming J.S. has an arterial pressure line and is not generating spontaneous breaths, a pulse contour analysis device can be used to determine SVV or PPV. One systematic review indicated that a PPV >12.5% and an SVV >11.6% predicted fluid responsiveness.[81] Ultrasound imaging may provide the degree of IVC collapsibility as an alternative dynamic marker. A >12% change in the IVC diameter predicts responsiveness to fluid administration. A simpler method of dynamic fluid assessment is the passive leg raising (PLR) test in which venous return is increased by shifting blood from the lower extremities toward the heart by lifting the patient's legs passively from the horizontal position to a 45-degree angle. This technique does not require additional equipment and is possible even if J.S. is generating spontaneous breaths. One benefit

of the PLR is predicting fluid responsiveness without giving exogenous fluids. Exogenous fluids are only given if the patient is fluid responsive. J.S. would be considered fluid responsive and a fluid challenge should be given if a 10% to 15% increase in CO is seen after the PLR test.

If a fluid challenge is attempted to enhance preload, 250 to 500 mL of crystalloid solution should be given over 20 to 30 minutes while continuously monitoring the hemodynamic profile and for volume overload. If oxygenation worsens or the PCWP rises without an improvement in CO, fluid challenges should be discontinued. Elevating the preload without appreciably improving CO increases LV wall tension, which is a major determinant of myocardial $\dot{V}o_2$; consequently, myocardial ischemia could develop. Although J.S. has signs of pulmonary edema, diuretics to reduce his volume overload can be detrimental to his CO and BP and should not be used until J.S.'s hemodynamics and signs of hypoperfusion have improved.

Vasodilators (preload and afterload reduction)

A peripheral venodilator will decrease pulmonary venous congestion by reducing preload (CVP and PCWP) and pulmonary vascular hydrostatic pressure. With myocardial ischemia, a reduction in the LV filling pressure may improve subendocardial blood flow, reduce the myocardial wall tension, and shrink the LV radius. The resultant decrease in myocardial $\dot{V}o_2$ will help prevent further depression of cardiac function.

Arterial resistance (afterload) is also elevated in patients with LV failure because of a reflexive increase in sympathetic tone following a drop in systemic arterial pressure. CO is inversely related to resistance to outflow from the left ventricle. Lowering the SVR will decrease resistance to ventricular ejection and shift the ventricular function curve up and to the left, depending on whether an arterial, venous, or mixed vasodilator is used, thereby improving cardiac performance at a lower filling pressure (**Fig. 17-3**).

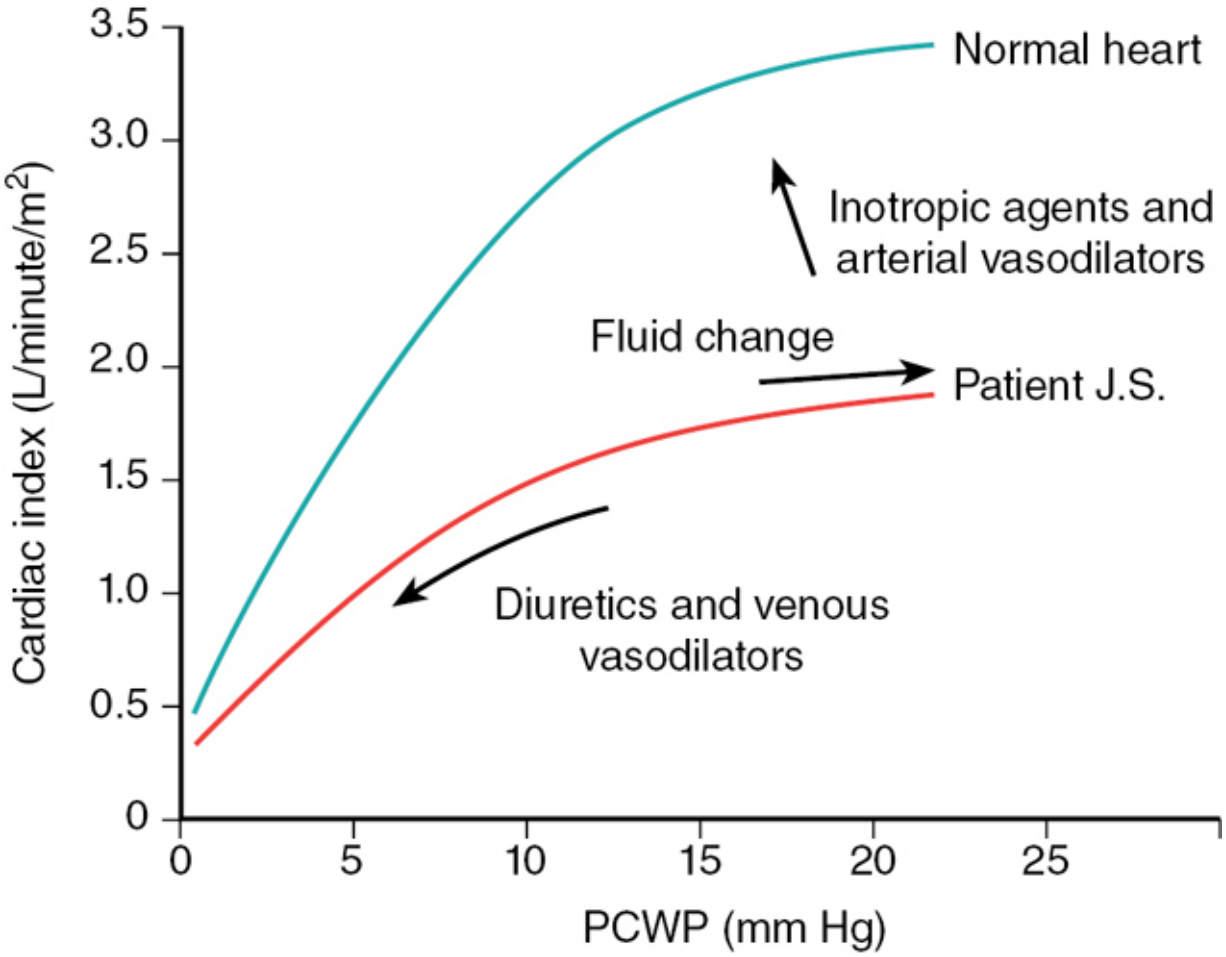


Figure 17-3 Ventricular function curve for J.S. PCWP, pulmonary capillary wedge pressure.

J.S. appears to have LV failure with clinical signs of volume overload and elevations in PCWP and SVR. Vasodilator therapy in this setting will likely improve his CO and, therefore, increase the $\dot{D}o_2$ to the tissues and prevent organ dysfunction. The major risk of vasodilator therapy in J.S., however, is further reduction of an already low MAP. Although the reduction in BP may be offset by an increase in CO, a significant drop in arterial BP could occur, which could decrease perfusion to vital organ systems and exacerbate myocardial ischemia by reducing coronary perfusion pressure. Vasodilator therapy should be reserved for situations of LV failure with elevations in PCWP and SVR and a SBP >90 mm Hg.

Inotropic support

A rapid-acting inotropic agent also can be used to increase myocardial contractility after optimization of the volume status if the CO remains low or inadequate with signs of tissue hypoperfusion.[1] This intervention shifts the ventricular function curve upward and slightly to the left (Fig. 17-3). The disadvantage is that improved CO is accompanied by increased myocardial oxygen demand. Depending on the agent selected, three of the determinants of myocardial $\dot{V}o_2$ could be elevated: HR, contractility, and ventricular wall tension. Therefore, inotropic support is directed at establishing or maintaining a reasonable arterial pressure and ensuring adequate tissue perfusion by improving the CO while minimizing ischemic complications from increased myocardial $\dot{V}o_2$. In the setting of an AMI, inotropic therapy should be considered only after revascularization.

In summary, the most appropriate therapeutic intervention for J.S. at this time would be inotropic support. Dynamic fluid assessment could be considered, but the clinical signs of volume overload and elevated static markers suggest that preload has been maximized; therefore, fluid may worsen J.S.'s pulmonary edema. Although J.S.'s SVR is elevated (1570 dyne·s·cm^{-5}), his BP is low; therefore, initial use of a peripheral vasodilator could jeopardize perfusion. Revascularization via emergent CABG is complete. Thus, inotropic support is an acceptable initial therapeutic intervention to improve CO and tissue perfusion. After a reasonable BP has been established, addition of a peripheral vasodilator could be considered to further enhance CO if needed, and diuretics added to reduce his pulmonary edema.

CASE 17-3, QUESTION 4: Which inotropic agent is the best choice for J.S.?

INOTROPIC AGENTS

Dopamine

Dopamine, a precursor of norepinephrine, has inotropic, chronotropic, and vasoactive properties, all of which are dose

dependent (**Table 17-7**). The distinct ranges noted for dopamine activity are generalizations; responses noted in clinical practice will be patient specific. At <5 μg/kg/min, dopamine stimulates dopaminergic receptors primarily in the splanchnic, renal, and coronary vascular beds. The effect on dopaminergic receptors is not blocked by β-blockers, but is antagonized by dopaminergic-blocking agents such as the butyrophenones and phenothiazines. Depending on the clinical state of the patient, low dosages of dopamine may slightly increase myocardial contractility but usually will not alter HR or SVR significantly.

Table 17-7
Inotropic Agents and Vasopressors

		Receptor Sensitivity			Pharmacologic Effect			
Drug	**Usual Dose**	**α1**	**β1**	**β2**	**VD**	**VC**	**INT**	**CHT**
Dobutamine	2–10 μg/kg/min	+	++++	++	+	+	+++[a]	+
	>10 μg/kg/min	++	++++	+++	++	+	++++[a]	++
Dopamine	<5 μg/kg/min[b]	0	+	0	+	0	++	+
	5–10 μg/kg/min[b]	0/+	++++	++	+	+	+++	++
	10–20 μg/kg/min[b]	+++	++++	+	0	+++	+++	+++
Epinephrine[c]	<0.1 μg/kg/min	+	++++	+++	+	+	++++[a]	++
	0.1–2 μg/kg/min	+++	++++	+++	0	+++	+++[a]	+++
	>2 μg/kg/min	++++	++	+	0	++++	++[a]	+++
Isoproterenol	0.01–0.1 μg/kg/min	0	++++	++++	+++	0	++++	++++
Milrinone	Possible 50 μg/kg bolus, then 0.125–0.75 μg/kg/min	0	0	0	+++[d]	0	+++	0
Norepinephrine[c]	0.02–3 μg/kg/min[f]	++++	+++	+	0	++++	+[e]	++
Phenylephrine	0.5–5 μg/kg/min[f]	++++	0	0	0	++++	0	0
Vasopressin[g]	0.03–0.04 units/min[h]	0	0	0	0	++++	0	0

CHT, chronotropic; INT, inotropic; MAP, mean arterial pressure; VC, peripheral vascular vasoconstriction; VD, peripheral vascular vasodilation.

[a]Dobutamine, milrinone, and epinephrine have more inotropic effect than does dopamine.

[b]Dopamine stimulates dopaminergic receptors at all doses, causing vasodilation in the splanchnic and renal vasculature.

[c]Epinephrine has predominant inotropic effects; norepinephrine has predominant vasoconstrictive effect. Epinephrine may vasodilate at low dosages, and vasoconstrict at high dosages.

[d]Milrinone inhibits phosphodiesterase-3, leading to increased contractility of the myocardium and vasodilation of vascular smooth muscle.

[e]Cardiac output unchanged or may decline because of vagal reflex responses that slow the heart.

[f]Highly variable, titrate to desired MAP.

[g]Vasopressin stimulates V_{1a} receptors to cause vasoconstriction in the periphery.

[h]Dosing for sepsis; in other vasodilatory conditions, it may be titrated from 0.*01* to *0.1* units/min.

At 5- to 10-μg/kg/min, the improved cardiac performance produced by dopamine is through direct stimulation of β_1-adrenergic receptors and indirectly through release of norepinephrine from nerve terminals. Increased β_1-adrenergic receptor stimulation increases SV (inotropic effect), HR (chronotropic effect), and, consequently, CO. These cardiac effects can be blocked by β-blockers. As infusion rates increase >5 μg/kg/min, the α-adrenergic receptors are activated. At this dosage, the vasoactive effects on peripheral blood vessels are unpredictable and depend on the net effect of β_1-adrenergic stimulation, α-adrenergic stimulation, and reflex mechanisms. MAP and PCWP usually will rise. The increased HR, along with the elevated PCWP in J.S., could adversely affect the myocardial oxygen supply to demand ratio. However, it is hoped that the increase in coronary blood flow (caused by the rise in arterial pressure) and the decrease in LV chamber size (associated with the increase in contractility) would tend to offset the increase in myocardial oxygen requirements.

At doses >10 μg/kg/min, dopamine primarily stimulates peripheral α-adrenergic receptors. SVR increases, splanchnic and renal blood flow decreases, and LV filling pressure is raised. Cardiac irritability is a potential complication, and the overall myocardial $\dot{V}o_2$ is increased. The increase in SVR limits CO; thus, infusion rates should be limited to <15 μg/kg/min in patients with cardiac failure.[82]

In a recent trial of 1679 patients with shock, who were randomized to dopamine or norepinephrine for BP support, there was no significant difference in the primary outcome of 28-day mortality.[83] However, patients receiving dopamine had more arrhythmic events and a prespecified subgroup analysis showed an increased mortality

rate in 280 patients with cardiogenic shock. Although these findings may have been because of chance and randomization was not stratified, these findings warrant consideration before selecting dopamine for J.S. and highlight the need for more studies comparing catecholamines in cardiogenic shock.

Dobutamine

Dobutamine, a synthetic catecholamine, is a potent positive inotropic agent with dose dependent but predominant direct β_1-agonist effects and weak β_2- and α_1-adrenergic effects (Table 17-7). With greater β_2-vasodilatory than α_1-vasoconstrictive actions, dobutamine reduces SVR and PVR. The reduction in SVR may be caused by a reflex decrease in vasoconstriction secondary to enhanced CO. Unlike dopamine, dobutamine does not release endogenous norepinephrine or stimulate renal dopaminergic receptors.[84]

Studies assessing dobutamine in cardiac failure demonstrate consistent increases in CO and SV, with reductions in PCWP and SVR. The reduction in filling pressures, as indicated by a lowered PCWP, results in a decrease in LV wall tension and myocardial $\dot{V}o_2$. Consequently, coronary perfusion pressure and myocardial oxygen supply is improved.

Compared with dopamine, dobutamine has equal or greater inotropic action. Dobutamine lowers PCWP and SVR with increasing doses, whereas dopamine may increase PCWP and SVR with increasing doses.[85] The effect on HR is variable; however, evidence suggests that dobutamine is less chronotropic than is dopamine at lower infusion rates. In the clinical setting, dobutamine may be preferred in patients with depressed CO, elevated PCWP, and increased SVR with mild hypotension (SBP >70 mm Hg) and no signs or symptoms of shock. The increase in CO may not be sufficient to raise the BP in a patient who initially is moderately to severely hypotensive (SBP <70 mm Hg) or with signs or symptoms of shock. Dopamine may be recommended in patients with mild hypotension and symptoms of shock, whereas norepinephrine is reserved for patients with an SBP <70 mm Hg.[86,87] Given the

concern of increased mortality with dopamine monotherapy in patients with cardiogenic shock, the combination of dopamine or norepinephrine with dobutamine may be preferred in patients with depressed CO, normal or moderately elevated PCWP, and moderate or severe hypotension.[82,83,87]

Epinephrine

Similar to dopamine and dobutamine, epinephrine has dose-dependent hemodynamic effects (Table 17-7). At lower infusion ranges (<0.1 μg/kg/min) epinephrine stimulates β_1-adrenergic receptors, causing increases in HR and contractility. As the dose increases, more α_1-receptor stimulation occurs, resulting in vasoconstriction and corresponding increases in SVR.

The favorable hemodynamic effects (increased CO and BP) make low-dose epinephrine an attractive option for J.S.; however, epinephrine can induce hyperglycemia through gluconeogenesis and has been shown to increase lactate levels compared with other vasopressors and inotropic agents.[88] J.S. already has signs of acidosis (pH 7.28, HCO_3^- 15 mEq/L), and increased lactic acid production by epinephrine could be detrimental to his organ function. Epinephrine should be reserved for patients with a markedly depressed CO in conjunction with severe hypotension.

In summary, very few comparable studies of inotropic agents in this setting have been conducted; thus, the selection of agent is often based on the expected clinical benefit as well as individual experience with the drugs.[69,89] None of the choices are without risk because they could adversely affect the myocardial oxygen supply to demand ratio and could further extend the area of ischemia or necrosis. J.S. would benefit from an increase in his CO, as well as in his MAP. The team elects to start J.S. on dobutamine and dopamine infusions.

SELECTION AND INITIATION OF THERAPY

Case 17-3, Question 5: At what doses should you initiate a dobutamine and dopamine infusion in J.S.? What therapeutic outcomes are anticipated at these doses and during what time? What adverse effects may be encountered with these infusions?

J.S. has a MAP of 58 mm Hg, CI of 1.7 L/min/m^2, PCWP of 24 mm Hg, and HR of 105 beats/min. Goals of therapy are to increase the CI to ≥2.5 L/min/m^2, maintain a MAP of at least 65 mm Hg (preferably >70 mm Hg, depending on clinical signs of hypoperfusion), reduce the PCWP to 12 to 18 mm Hg, and maintain an HR of <125 beats/min. A urine output of ≥0.5 mL/kg/hour is desirable. Reasonable initial infusion rates would be dopamine 5 μg/kg/min and dobutamine 2 μg/kg/min. These doses should increase cardiac contraction and CO, resulting in an increase in renal blood flow. The onset of effect is rapid and the half-life short (~2 minutes) for both agents, with steady-state conditions generally achieved within 10 minutes of initiation of therapy. This allows dose titration every 10 minutes based on patient tolerance.

Because the onsets of action are within minutes, J.S. can be reevaluated and the infusion rates can be alternately titrated upward by 1 to 2 μg/kg/min every 10 minutes, depending on the hemodynamic data. The response to both agents is highly variable among patients; thus, careful titration using the lowest effective infusion rates is advised.

Adverse effects encountered with both infusions include increased HR, angina, arrhythmias, headache, tremors, nausea, and vomiting. The increases in contractility and HR caused by dobutamine and dopamine pose additive risk of tachyarrhythmias and can increase myocardial $\dot{V}o_2$, leading to ischemia in patients with coronary artery disease.

Dobutamine could lower the MAP, adversely affecting coronary perfusion pressure. Another limiting factor to dobutamine is tolerance to its hemodynamic effects with long-term continuous use. A decline in CO and HR has been seen after prolonged infusion and is most likely caused by downregulation of β_1-receptors. Of concern,

evidence suggests that inotropic agents can be associated with an increased risk of mortality in patients with HF despite the improvement of symptoms and hemodynamic indices.[90]

Dopamine might elevate the PCWP, thereby decreasing coronary perfusion pressure. Extravasation of large amounts of dopamine during infusion can cause ischemic necrosis and sloughing. At higher dosages, α_1-adrenergic effects are more prominent, causing peripheral arterial vasoconstriction and increases in afterload, preload, and myocardial oxygen demand as well as ischemia.

CASE 17-3, QUESTION 6: Dobutamine and dopamine are titrated from 2 to 4 µg/kg/min and 5 to 6 µg/kg/min, respectively, in J.S. during the next 2 hours. A repeat chest radiograph shows slight worsening of pulmonary edema. The following hemodynamic profile is obtained (previous values are in parentheses):

BP (S/D/M), 105/60/75 mm Hg (86/44/58 mm Hg)
HR, 140 beats/min (105 beats/min)
CO, 5.3 L/min (3 L/min)
CI, 3 L/min/m^2 (1.7 L/min/m^2)
CVP, 11 mm Hg (14 mm Hg)
PCWP, 22 mm Hg (24 mm Hg)
SVR, 1493 dyne·s·cm^{-5} (1570 dyne·s·cm^{-5})
Urine output, 0.4 mL/kg/hour (0.2 mL/kg/hour)
Hct, 33% (31%)

Do these data indicate a favorable or an adverse hemodynamic effect from dobutamine and dopamine in J.S.?

Dobutamine at 4 µg/kg/min and dopamine at 6 µg/kg/min have established a trend in the desired direction for CI; however, the HR has increased significantly. The SVR and PCWP have not changed appreciably, and the urine flow has increased. The SV (CO/HR) has only increased from 28 to 38 mL/beat; thus, the increase in CO has resulted from both the chronotropic and the inotropic effects of these agents. As a net response, the dobutamine and dopamine have most likely adversely affected the myocardial oxygen supply to demand ratio; however, this cannot be established definitively. J.S. should be monitored closely for signs of myocardial ischemia.

Milrinone

Case 17-3, Question 7: The clinician decides that an HR of 140 beats/min is unacceptable in J.S., who presented with an AMI. Subsequent attempts to taper the dobutamine to lessen the induced tachycardia without dropping the CI and perfusion pressure are unsuccessful. Milrinone is suggested as an alternative to dobutamine. What hemodynamic changes would you expect with milrinone in J.S.? Does milrinone offer any advantages compared with dobutamine?

Milrinone increases intracellular adenosine monophosphate (AMP) levels by inhibiting phosphodiesterase-3 within the sarcoplasmic reticulum of cardiac myocytes and vascular smooth muscle, leading to increased contractility of the myocardium and vasodilation of vascular smooth muscle (Table 17-7). The increased CO and decreased SVR are accompanied by an increased lusitropic effect. Milrinone produces fewer chronotropic and arrhythmogenic effects than do catecholamines, but, similar to dobutamine, can decrease SVR and cause hypotension. Moreover, milrinone has a longer half-life than does dobutamine, making it difficult to use as monotherapy for cardiogenic shock. The combination of dopamine, norepinephrine, or vasopressin with milrinone would offset some of milrinone's hypotensive effects. Although milrinone has not been shown to improve outcomes in patients who are post-AMI with cardiogenic shock, it could be beneficial in patients with adequate BP, who have downregulated β-receptors (chronic HF or β-agonist use), recently received β-blockade, or with catecholamine dose-limiting arrhythmias.

Dobutamine has equivalent or greater inotropic action than does dopamine, and, as mentioned earlier, dobutamine causes less tachycardia, so it may be better to remove dopamine in this patient. A decrease of 20% of the current dopamine infusion rate (1–2 μg/kg/min) every 10 to 15 minutes is reasonable. Just as with upward titration of therapy, steady state should be achieved within 10 minutes. When tapering vasoactive agents, it is prudent to let the patient stabilize hemodynamically at new infusion rates for a period that exceeds the time to achieve a new steady-state plasma

concentration. After each reduction in the infusion rate, hemodynamic data can be assessed. The major difference between the two agents is the effect of dopamine on α_1-receptors. With dobutamine's greater clinical effect on β_2-receptors compared to α_1-receptors, J.S. may experience a decrease in the SVR. A decreased SVR should allow for an increased CI, but J.S. should be monitored carefully because his MAP is relatively low and any major reduction in SVR could lead to further BP reduction.

CASE 17-3, QUESTION 8: Dopamine is tapered off and dobutamine is increased to 5 µg/kg/min for J.S. His HR decreased to 105 to 110 beats/min within the next hour. Despite these changes and initiation of ventilatory support by tracheal intubation, J.S. continues to show signs of deterioration with progressive obtundation and loss of bowel sounds. His systemic arterial pressure has continued to decline. Preload reduction was attempted previously with nitroglycerin; however, the BP reduction was intolerable. A repeat hemodynamic profile shows the following values (previous values in parentheses):

BP (S/D/M), 86/40/55 mm Hg (105/60/75 mm Hg)
HR, 132 beats/min (105 to 110 beats/min)
CO, 3.2 L/min (5.3 L/min)
CI, 1.8 L/min/m^2 (3 L/min/m^2)
Svo_2, 42% (48%)
CVP, 16 mm Hg (11 mm Hg)
PCWP, 28 mm Hg (22 mm Hg)
SVR, 992 dyne·s·cm^{-5} (1493 dyne·s·cm^{-5})
Urine output, 0.1 mL/kg/hour (0.4 mL/kg/hour)
Pao_2, 75 mm Hg (90 mm Hg)
$Paco_2$, 42 mm Hg (38 mm Hg)
pH, 7.24 (7.3)
HCO_3^-, 17 mEq/L (18 mEq/L)

The ECG shows atrial tachycardia with occasional premature ventricular contractions. What therapeutic alternatives can be considered at this time?

J.S. is still in "cold and wet" cardiogenic shock, and his tissue perfusion continues to deteriorate as evidenced by a further reduction in urine output, a loss of bowel sounds, continuing acidosis, and obtundation. Because his systemic arterial pressure

and tissue perfusion have declined, additional support with a potent vasopressor and the insertion of an IABP or other percutaneous ventricular assist device are indicated. The combination of dopamine and dobutamine previously resulted in intolerable tachycardia, so other therapies should be considered.

Phenylephrine

Phenylephrine is a pure α-adrenergic agonist (Table 17-7) that leads to vasoconstriction and an increased SVR. The lack of β-adrenergic effects can make phenylephrine an ideal vasopressor in patients with other forms of shock who are experiencing atrial or ventricular arrhythmias. However, in cardiogenic shock, phenylephrine will further increase afterload on the weak heart without increasing cardiac contractility. Phenylephrine should only be considered in patients with certain mechanical forms of cardiogenic shock (ie, valvular issues, outflow tract obstruction).[69] Otherwise, phenylephrine should be avoided in patients such as J.S. because it will likely further decrease CO.

Norepinephrine

Norepinephrine is a potent α-adrenergic agonist that vasoconstricts arterioles at all infusion rates, thereby increasing SVR and systemic arterial and coronary perfusion pressures (Table 17-7). Unlike phenylephrine, norepinephrine also stimulates β_1-adrenergic receptors, resulting in increased contractility and SV. However, HR and CO usually remain constant or may decrease secondary to the increased afterload, and baroreceptor-mediated reflex increases in vagal tone. Although coronary perfusion pressure is enhanced as a result of the elevation in diastolic pressure, myocardial $\dot{V}o_2$ also is increased. Consequently, myocardial ischemia and arrhythmias may be exacerbated and LV function further compromised.

Infusions of norepinephrine are begun at 0.01 to 0.05 μg/kg/min and titrated upward to achieve a MAP >65 mm Hg. Adverse effects of norepinephrine are related mostly to excessive vasoconstriction and compromise of organ perfusion. Administration should be

through a central IV line because local subcutaneous necrosis and sloughing can result from peripheral IV extravasation. Prolonged infusion of larger doses will transiently exert a beneficial effect by diverting blood flow from the peripheral and splanchnic vasculature to the heart and brain; however, this ultimately can compromise capillary perfusion to the extent that end-organ failure, particularly renal failure, ensues.

Again, it must be emphasized that pharmacologic support for J.S., particularly the use of norepinephrine, is only an interim maneuver to temporarily maintain hemodynamic function. J.S. should continue to be monitored for signs of myocardial ischemia and the need for further revascularization procedures. Patients who cannot be stabilized with pharmacologic intervention, and in whom systemic or myocardial perfusion is becoming compromised, may require further support through insertion of a mechanical circulatory assist device.

Mechanical circulatory support

When drug therapy is ineffective in stabilizing patients in cardiogenic shock, mechanical intervention should be considered. Mechanical interventions can rapidly stabilize patients with cardiogenic shock, especially those with global myocardial ischemia or infarction complicated by mechanical defects, such as papillary muscle rupture or ventricular septal rupture. In fact, mechanical support has been associated with improved survival rates in patients with AMI complicated by cardiogenic shock when implanted before initiating vasoactive support or PCI.[91] Sometimes, combined inotropic support and intra-aortic balloon counterpulsation are required to maintain an acceptable BP (MAP >65 mm Hg) and CI (>2.2 L/min/m^2).

The IABP is the most commonly used mechanical assist device in cardiogenic shock.[69] It is designed to improve coronary arterial perfusion pressure and reduce afterload, providing short-term reperfusion of the ischemic myocardium.[92] A 20- to 50-mL balloon catheter is inserted into the femoral or axillary artery and advanced to the proximal descending aorta just distal to the left subclavian artery. Balloon inflation and deflation are synchronized with the ECG

to inflate at the onset of diastole and deflate at the onset of systole. The inflated balloon in diastole increases coronary perfusion by elevating the mean aortic pressure. The rapid deflation of the balloon at the onset of systole decreases afterload and modestly improving CO (<1 L/min).[92] The enhanced myocardial perfusion provided by IABP may reduce vasopressor requirements, thereby further decreasing myocardial $\dot{V}o_2$. Occasionally, IABP augmentation is sufficient to allow the institution of vasodilators (eg, nitroprusside) or inodilators (eg, milrinone). IABP support should be discontinued as soon as the patient stabilizes or complications develop. Aortic regurgitation, aortic dissection, and aortic stents are absolute contraindications to IABP use, whereas aortic aneurysm, severe peripheral arterial disease, and major arterial reconstruction surgery are relative contraindications. Complications associated with the IABP increase with longer duration of use and include vascular injury, hematoma, thrombocytopenia from the mechanical destruction of platelets, thromboembolism because of the large, thrombogenic surface area, and limb ischemia because of reduced blood flow in the artery into which the IABP catheter is inserted. A stable cardiac rhythm is necessary for proper function. Heparin anticoagulation is usually given with IABP to reduce the risk of limb ischemia and thromboembolism. Infectious complications are uncommon when the use is limited to <7 days.

The use of IABP support in cardiogenic shock has declined because of the lack of compelling evidence showing benefit.[93] The IABP- SHOCK II study randomly assigned patients with cardiogenic shock following AMI who were expected to undergo early revascularization to receive optimal medical therapy with or without IABP support.[94] The investigators found no mortality benefit at 30 days, 6 months, or 12 months and no differences between groups for all secondary end points.[94,95] Limitations to this study include multiple crossovers to the IABP group that may represent sicker patients, clinician- dependent revascularization strategy (culprit vs multivessel PCI), and the low rate of IABP insertion before PCI. Additional reviews of IABP use in cardiogenic shock have found no differences in 30-day mortality and an increase in the risk of bleeding

complications and stroke.[92,96] Guidelines recommend IABP support as reasonable to consider for patients requiring circulatory support after ST-elevation MI.[73]

Newer percutaneous devices that directly augment CO and decrease the load on the left ventricle have been developed.[92] The percutaneous versions of the Impella® axial flow pumps (Impella 2.5® Abiomed, Inc., Danvers, MA, USA/CP®/RP®) are placed in the cardiac catheterization laboratory, avoiding major cardiac surgery. The left-sided devices (Impella 2.5® Abiomed, Inc., Danvers, MA, USA and CP®) are advanced from the common femoral artery and passed retrograde across the aortic valve into the left ventricle. A CO of 2.5 to 4 L/min can be maintained as blood enters the device from the left ventricle and is ejected into the ascending aorta. In cases of RV failure, the Impella RP® can be inserted similarly to a PAC to pump blood from the IVC to the PA at flows >4 L/min. Systemic anticoagulation is required with these devices. Impella® devices are contraindicated in patients with ventricular thrombi, moderate-to-severe aortic valve disease, mechanical aortic valve, or severe peripheral artery disease. Impella®-related complications include vascular injury, thrombosis, limb ischemia, valve injury, arrhythmias, thrombocytopenia, bleeding, and hemolysis.

Unlike the IABP, the Impella® devices continuously unload the ventricle and support arterial pressure, independent of heart function and rhythm. Despite providing superior hemodynamic support, Impella® devices have not been shown to reduce mortality rates compared with IABP.[69,71] However, early implantation of the Impella® before PCI has been independently associated with improved survival to discharge.[91,97,98] They are best used for early stabilization and temporary circulatory support until revascularization or more definitive therapy is available.

The TandemHeart® (TandemLife, Pittsburgh, PA, USA) is an extracorporeal, centrifugal, continuous-flow mechanical circulatory support device.[69,71] A cannula is advanced from the femoral vein into the left atrium through an atrial septal puncture. Oxygenated blood from the left ventricle is aspirated and pumped into the systemic arterial circulation via the femoral artery. This process unloads the

left ventricle and increases peripheral tissue perfusion. A major limitation to the use of TandemHeart® is the requirement for a skilled physician to implant the device via a transseptal puncture. The TandemHeart® is approved for short-term use in cardiogenic shock because it delivers flow up to 4 L/min and achieves 80% to 90% unloading of the left ventricle. However, it has not been shown to improve mortality in these patients. Systemic anticoagulation is required for this device. Because of the unique cannular approach, the TandemHeart® can be used in patients with aortic valve disease, aortic valve prostheses, or ventricular thrombi when Impella® devices are contraindicated. Contraindications for the TandemHeart® include severe peripheral artery disease, left atrial thrombus, and ventricular septal defect. Complications of the TandemHeart® include bleeding requiring transfusions, disseminated intravascular coagulation, vascular injury, limb ischemia, cardiac tamponade, thromboembolism or air embolism, and hemolysis.

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is an additional temporary measure of cardiovascular and respiratory support.[69,71] Venous blood is drained, oxygenated, and returned to the systemic circulation using a centrifugal pump. VA-ECMO can support both ventricles with flow rates >4 L/min and may be used in combination with other therapies (ie, IABP, Impella®). Similar to other mechanical support devices, systemic anticoagulation is required for VA-ECMO. Relative contraindications include advanced age (older than 75 years), life expectancy under 1 year, severe peripheral vascular disease, advanced liver disease, and neurologic injury. Potential complications of VA-ECMO include limb ischemia, thromboembolism, stroke, bleeding, hemolysis, infection, and aortic valve insufficiency. Utilization has increased in recent years, but there are no randomized trials investigating its efficacy.[69] VA-ECMO is the device of choice for patients with cardiac arrest, refractory shock with hypoxemia, or biventricular HF. The need for experienced physicians will undoubtedly limit the use of VA-ECMO to experienced medical centers.

In summary, J.S.’s condition has continued to deteriorate since his admission to the ICU. Attempts at stabilizing his hemodynamic

parameters with dopamine and dobutamine have failed. This is evidenced by inadequate tissue perfusion, which is reflected clinically by his continued lactic acidosis, decreased urine output, reduced bowel sounds, and central nervous system obtundation. Norepinephrine and epinephrine should be considered at this point to restore intra-arterial pressure and tissue perfusion. Although early mechanical circulatory support was likely part of the optimal treatment course, synergistic support with intra-aortic counterpulsation or an Impella® device should be considered for J.S.

DISTRIBUTIVE SHOCK

Distributive shock is characterized by an overt loss of vascular tone, causing acute tissue hypoperfusion. Although numerous events such as anaphylaxis, vasoplegia, or neurogenic causes can initiate distributive shock, most cases are readily reversed by supportive measures and treatment or elimination of the underlying cause.

SEPTIC SHOCK

Distributive shock secondary to sepsis, or septic shock, is associated with a high mortality rate, reflecting the limited therapeutic options available at this time. Over 1,500,000 cases of sepsis syndrome are seen annually in the United States. Mortality rates are as high as 50%.[99] The combination of degree of organ dysfunction and number of failing organs is the strongest predictor of death. Epidemiologic studies show that ~25% of cases of sepsis syndrome eventually result in septic shock. It has been projected that the incidence of sepsis will increase 1.5% per year mainly because of the disproportionate growth of the elderly in the U.S. population, increasing burden of chronic health conditions, rising numbers of patients who are immunocompromised, and multidrug-resistant infections.[4,99–102]

The Guidelines Committee of the Surviving Sepsis Campaign—an international consortium of professional societies involved in critical

care, infectious diseases, and emergency medicine—defines *sepsis* syndrome as life-threatening organ dysfunction caused by a dysregulated host response to infection (see **Table 17-8** for definitions).[4] Organ dysfunction is identified as an acute change in total Sequential Organ Failure Assessment (SOFA) score by at least 2 points consequent to the infection (see **Table 17-9** for SOFA calculation). In patients without preexisting organ dysfunction, the baseline SOFA score is assumed to be zero. Persons with an overall SOFA score of ≥2 may have a 25 times higher risk of mortality compared to those with a score <2. Other screening tools include systemic inflammatory response syndrome (SIRS) criteria, National Early warning Score (NEWS), or Modified early warning Score (MEWS). When hypotension persists despite adequate fluid resuscitation and requires vasopressor support to maintain a MAP of ≥65 mm Hg while also having a serum lactate level <2 mmol/L, it is termed *septic shock*. Septic shock is associated with a higher risk of mortality. Persons most at risk for septic shock are those who are immunocompromised or have underlying conditions that render them susceptible to bloodstream invasion. Groups at risk include neonates, the elderly, patients with acquired immune deficiency syndrome, alcoholics, childbearing females, and those undergoing surgery or who have experienced trauma. Other predisposing factors include coexisting diseases such as diabetes mellitus, malignancies, chronic hepatic or renal failure, and hyposplenism; exposure to immunosuppressant drugs and cancer chemotherapy; and procedures such as insertion of urinary catheters, endotracheal tubes, and IV lines.

Table 17-8

Third International Consensus Definitions for Sepsis and Septic Shock

Infection	Pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. (Noted exception: *Clostridium difficile* colitis does not occur in a sterile colon.)
Bacteremia	The presence of viable bacteria in the blood.

Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection.
Organ dysfunction	Identified as an acute change in total SOFA score ≥2 points consequent to the infection.
Septic shock	A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Persistent sepsis-induced hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate level >2 mmol/L despite adequate fluid resuscitation. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Multiple organ dysfunction syndrome	Presence of progressive organ dysfunction in an acutely ill patient, such that homeostasis cannot be maintained without intervention.

MAP, mean arterial pressure; SOFA, sequential organ failure assessment.

Source: Reprinted by permission of Springer: Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707–710. © 1996 Springer-Verlag.

Table 17-9
Sequential Organ Failure Assessment Score

	Score				
System	**0**	**1**	**2**	**3**	**4**
Pao_2/Fio_2, mm Hg	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Platelets, $\times 10^3$/mL	≥150	<150	<100	<50	<20
Bilirubin, mg/dL	<1.2	1.2–1.9	2–5.9	6–11.9	>12
Cardiovascular	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	DA < 5[a] or DOB (any dose)	DA 5.1–15 or Epi ≤ 0.1 or NE ≤ 0.1[a]	DA > 15 or Epi > 0.1 or NE > 0.1[a]
GCS score[b]	15	13–14	10–12	6–9	<6
Creatinine, mg/dL	<1.2	1.2–1.9	2–3.4	3.5–4.9	>5
Urine output, mL/day				<500	<200

DA, dopamine; DOB, dobutamine; Epi, epinephrine; Fio_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; MAP, mean arterial pressure; NE, norepinephrine; Pao_2, arterial partial pressure of oxygen.

[a]Catecholamine doses are expressed as μg/kg/min for at least 1 hour.

[b]GCS scores range from 3 to *15*; higher score indicating better neurologic function.

Source: Reprinted by permission of Springer: Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707–710. © 1996 Springer-Verlag.

Septic shock is characterized initially by a normal or high CO and a low SVR (Table 17-3). Hypotension is caused by the low SVR and alterations in macrovascular and microvascular tone, which result in maldistribution of blood flow and volume. Changes in the microvasculature can lead to loss of normal microvascular autoregulatory mechanisms, resulting in constriction of capillaries, changes in cellular rheology, fibrin deposition, and neutrophil adherence. This causes vascular “sludging” and, in some cases, arteriovenous shunts that bypass capillary beds. Loss of intravascular fluid caused by increased vascular permeability and third spacing of fluid further adds to hypovolemia.[103] In an effort to compensate for the changes in volume and SVR, the body goes into a hyperdynamic state and increases CO. Most patients exhibit myocardial dysfunction as manifested by decreased myocardial compliance, reduced contractility, and ventricular dilation, but they maintain a normal CO, because of tachycardia and cardiac dilatation, which increases or maintains preload.[104] Although the cause of, and mechanism for, this abnormality is not fully understood, it is not believed to be attributable to myocardial ischemia. Rather, it is thought to be caused by one or more circulating inflammatory mediators, such as cytokines (eg, interleukin [IL]-1), tumor necrosis factor-α (TNF-α), platelet-activating factor, arachidonic acid, nitric oxide (NO), and reactive oxygen species. In late septic shock, the body is no longer able to compensate because of the cardiac effects of the inflammatory mediators and resultant myocardial edema, thus resulting in a decreased CO. The end product of this complicated pathway is cellular ischemia, dysfunction, and, eventually, cellular death unless the chain of events is interrupted.

The complex pathogenesis of sepsis is more fully understood now, but some of the exact mechanisms are still not completely clear. The

changes that take place during sepsis are caused by the immunologic host response to infection, which involves inflammatory (SIRS) and immunodepressive (compensatory anti-inflammatory response) mediators that are present from the onset of the immune response.[105]

The inflammatory stage of sepsis is initiated by an infection with a microorganism, most commonly bacterial. Organisms can either enter the bloodstream directly (producing positive blood cultures) or may indirectly elicit a systemic inflammatory response by locally releasing their toxins or structural components at the site of infection. The binding of these toxins to cell receptors promotes proinflammatory cytokine production, primarily TNF-α and IL-1. These toxins stimulate the production and release of numerous endogenous mediators that are responsible for the inflammatory consequences of sepsis. The cytokines act synergistically to directly affect organ function and stimulate the release of other proinflammatory cytokines, such as IL-6, IL-8, platelet-activating factor, complement, thromboxanes, leukotrienes, prostaglandins, NO, and others.[104]

The presence of these cytokines promotes inflammation and vascular endothelial injury, but it also causes an overwhelming activation in coagulation. Thrombin has potent proinflammatory and procoagulant activities, and its production is increased in sepsis. The human body normally counteracts these effects by increasing fibrinolysis, but the homeostatic mechanisms in the patient with sepsis are dysfunctional. There are decreases in the levels of protein C, plasminogen, and antithrombin III as well as increased activity of plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor, endogenous agents that inhibit fibrinolysis.[105] The patient is in a coagulopathic state, which promotes formation of microvascular thrombi, leading to hypoperfusion, ischemia, and, ultimately, organ failure. Multiple organ failure is responsible for about half the deaths caused by septic shock.[106]

The clinical features of sepsis are highly variable and depend on multiple factors: site of infection, causative organism, degree of organ dysfunction, baseline patient health status, and delay to initial

treatment.[107] The working definition of sepsis accounts for the presence of systemic manifestations of infection and organ dysfunction, which may be subtle (Table 17-8). Serum biomarkers are the subject of intense research because they could aid the early diagnosis of sepsis, guide treatment, and predict outcomes. Most biomarkers have not been extensively studied and few are in clinical use (eg, C-reactive protein, procalcitonin, soluble triggering receptor expressed on myeloid cells 1 [sTREM-1], CD64, pancreatic stone protein).[108] Most of these biomarkers have high negative predictive values, but lack high specificity and positive predictive value.

Characteristic laboratory findings include leukocytosis or leukopenia, thrombocytopenia with or without coagulation abnormalities, and, often, hyperbilirubinemia. These features are usually readily detectable and occur within 24 hours of sepsis developing. In extremes of age (very young or very old) or in debilitated patients, hypothermia can be present, and positive findings may be limited to unexplained hypotension, mental confusion, and hyperventilation.

Persons dying of septic shock often have a normal or elevated CO. Death within the first week of the onset of sepsis occurs as a result of intractable hypotension that is secondary to significantly depressed SVR. This causes extensive maldistribution of blood flow in the microvasculature, with subsequent tissue hypoxia and development of lactic acidosis. Death occurring beyond the first week usually is caused by multiple organ failure that began during acute circulatory failure. Severe, unresponsive hypotension as a result of a decreased CO occurs in a subpopulation of patients with septic shock; cardiogenic shock becomes superimposed on the distributive shock of sepsis, but this is a less common cause of death.[109]

Clinical and Hemodynamic Features

CASE 17-4

Question 1: E.B., a 71-year-old female, presents to the ICU with hypoxemic respiratory failure after a 4-day stay on the floor. She initially presented from home with altered mental status and a urinary tract infection that was being managed on the floor with ceftriaxone.

E.B. has a history of diabetes mellitus type 2, hypertension, chronic kidney disease stage II, dyslipidemia, coronary artery disease, obesity, and peripheral arterial disease.

Physical findings include a temperature of 101.66 °F (38.7 °C), BP 95/60 mm Hg, pulse 120 beats/min, and RR 32 breaths/min with oxygen saturation 88% on 2 L/min nasal cannula. E.B. weighs 224.87 pounds (102 kg) and is 65 inches (165.01 cm) tall. A Foley catheter is placed in her bladder and her urine output is 0.4 mL/kg/hour. The chest radiograph shows bilateral patchy opacities.

Pertinent laboratory values are as follows:

WBC count, 19,500 cells/mL
BUN, 58 mg/dL
SCr, 2.2 mg/dL
Na, 131 mEq/L
Glucose, 58 mg/dL
Albumin, 1.6 g/dL
Lactate, 4.5 g/dL

ABG measurements on 2 L/min nasal cannula (FiO_2 27%) are as follows:

PaO_2, 56 mm Hg
$PaCO_2$, 32 mm Hg
HCO_3^-, 16 mEq/L
pH, 7.31

Urine, sputum, and blood samples are sent for culture and sensitivity. A fluid bolus of 1000 mL of LR is given. An arterial pressure line was inserted, revealing the following hemodynamic profile:

BP (S/D/M), 90/48/62 mm Hg
HR, 122 beats/min

What hemodynamic and clinical features of E.B. are consistent with septic shock?

E.B. would not be classified in septic shock at this time because she has not been adequately fluid resuscitated. However, she would be classified as having sepsis because of the manifestations of infection and organ dysfunction.

E.B. has a metabolic acidosis (pH 7.31, $Paco_2$ 32 mm Hg, HCO_3^- 16 mEq/L), indicating anaerobic metabolism and lactic acidosis most likely caused by decreased perfusion, and a CO that is inadequate to meet the oxygen requirements of the tissues. Other features consistent with sepsis in E.B. include declining urine output indicating decreased renal perfusion, hypoglycemia, a rising WBC count, and a spiking fever.

Therapeutic Approach

The management of septic shock is directed toward three primary areas: (a) eradication of the source of infection, (b) hemodynamic support and control of tissue hypoxia, and (c) inhibition or attenuation of the initiators and mediators of sepsis.

ERADICATING THE SOURCE OF INFECTION

Case 17-4, Question 2: What factors should be considered in determining antimicrobial therapy in septic shock? What are the potential sources of infection in E.B.?

Systemic infection caused by either aerobic or anaerobic bacteria is the leading cause of septic shock. Fungal, mycobacterial, rickettsial, protozoal, or viral infections can also be encountered. The source of infection (ie, respiratory, intra-abdominal, genitourinary, skin/soft tissue infection) helps determine which bacteria are of concern and therefore should be empirically covered.

Eradicating the source of infection involves the early administration of antimicrobial therapy, and source control, if indicated. Antimicrobials should be administered within 1 hour of recognition for patients with septic shock or who have a high likelihood of sepsis. For patients with possible sepsis without shock, rapid assessment of non- infectious causes should occur. If concern for infection still exists after rapid investigation of other causes, antimicrobials should be administered within 3 hours of sepsis

recognition.[4] The use of an appropriate antibiotic regimen within 1 hour of diagnosis of septic shock is associated with a significant increase in survival.[110] Appropriate cultures should be obtained before starting antibiotic therapy, unless this would result in a significant (>45 minutes) delay in therapy.[4] The selection of antibiotics should take into account the presumed site of infection; whether the infection is a community associated or health care–associated one; recent invasive procedures, manipulations, or surgery; any predisposing conditions; drug intolerances; and the likelihood of drug resistance. Ideally, the primary source of infection can be determined and therapy specifically tailored to the most likely organisms. If the source of infection is unclear, however, early institution of broad-spectrum antibiotics against all likely pathogens is generally recommended while awaiting culture results. Empiric broad- spectrum therapy usually requires combinations of antimicrobials because of the increasing frequency of polymicrobial infections and antimicrobial resistance. Mortality for septic shock may be as much as fivefold higher when an empiric regimen fails to cover the offending pathogen.[4] Every hour of delay of appropriate antibiotics may lead to a 7.6% decrease in survival.[110] Because a wide range of variables must be considered in the selection of empiric regimens (eg, anatomic site of infection, pathogen prevalence, resistance patterns), a specific regimen cannot be recommended for all episodes of sepsis or septic shock (see Chapter 62, Principles of Infectious Diseases). Generally, empiric regimens target gram-positive cocci, aerobic gram-negative bacilli, as well as anaerobes and include (a) an antipseudomonal penicillin, fourth-generation cephalosporin, or carbapenem plus (b) vancomycin to cover methicillin-resistant *Staphylococcus aureus* (MRSA) for high risk patients. Combination gram-negative coverage (eg, aminoglycoside, fluoroquinolone) is recommended for critically ill patients at risk of infection with difficult-to-treat, multidrug-resistant pathogens, such as *Pseudomonas* and *Acinetobacter* spp. Additional coverage should be considered based on the presence of other risk factors (eg, *Candida* species, atypical pathogens, viremia).

The most likely potential source of sepsis in E.B. is hospital-acquired pneumonia. Other sources of infection are less likely based on her presentation. For patients with hospital-acquired pneumonia, empiric antimicrobials should cover *Pseudomonas aeruginosa*, other gram-negative bacilli, and *S. aureus*. Patients with risk factors for MRSA (ie, prior IV antibiotic use within 90 days, hospitalization in a unit with >20% or unknown rate of MRSA isolates, or high risk of mortality) should be empirically covered for MRSA. The team has chosen to start cefepime and vancomycin. Antimicrobial therapy should be adjusted once cultures are finalized.

CASE 17-4, QUESTION 3: What are the immediate goals of therapy in E.B.? How can they be achieved and assessed?

INITIAL STABILIZATION

The goals in treating septic shock, in addition to eradicating the precipitating infection, are to optimize $\dot{D}o_2$ to the tissues and to control abnormal use of oxygen and anaerobic metabolism by reducing the tissue oxygen demand. Tissue injury is widespread during sepsis, most likely because of vascular endothelial injury with fluid extravasation and microthromboses, which decrease oxygen and substrate utilization by the affected tissues. The mainstay of therapy is volume expansion to increase intravascular volume, enhance CO, and ultimately delay associated development of refractory tissue hypoxia.

Increasing CO with fluids will improve capillary circulation and tissue oxygenation by maintaining sufficient intravascular volume. Current guidelines suggest a fluid bolus of 30 mL/kg of IV crystalloid fluid should be given within the first 3 hours of resuscitation.[4] If fluids do not correct the hypoxia or if filling pressures are increased, the sequential addition of vasopressors and inotropic agents is indicated. Crystalloids should be initiated to maintain a MAP of >65 mm Hg. Balanced crystalloids are recommended over NS.[45] Although MAP is not an absolute measure of blood flow to all vital organs, it is considered the therapeutic end point that will sustain myocardial and

cerebral perfusion. After optimization with fluid therapy, vasopressor and inotropic agents are indicated if the patient remains hypotensive with a low CI or if signs of inadequate tissue perfusion persist.

The therapeutic goals used for hemodynamic resuscitation are controversial. The issue is whether therapy should be directed to physiologic end points of tissue perfusion or clinical end points, such as BP and urine output. The physiologic end points include clearance of blood lactate concentrations, base deficit, Svo_2, and increased CO. Serum lactate concentrations may be elevated through various mechanisms (eg, tissue hypoxia, excessive β-adrenergic stimulation, liver failure), but are associated with worse outcomes regardless of the source. Dynamic measures of volume responsiveness such as passive leg raise, stroke volume, stroke volume variation, pulse pressure variation, or echocardiography are suggested. Resuscitation can also be guided by decreasing serum lactate and capillary refill time. Lactate-guided resuscitation of patients in septic shock is recommended because of its association with a significantly reduced mortality rate compared with usual care.[4]

Many institutions have developed “sepsis bundles” that incorporate these same variables and therapeutic end points as early as possible in the treatment of sepsis. Sepsis bundles often include many additional issues addressed in the Surviving Sepsis Campaign Guidelines, such as ventilatory support, initial choice of antibiotics, glucose control, and stress ulcer prophylaxis.[4]

One study by Rivers et al. combined physiologic and clinical end points of resuscitation during the early stages of sepsis.[111] CVP, MAP, Hct, and $Scvo_2$ were optimized during at least 6 hours of continuous care in the ED. This was compared to conventional therapy that targeted only CVP, MAP, and urine output. In-hospital mortality was significantly lower in the early goal-directed therapy (EGDT) group (30.5% vs 46.5%, $P = .009$). EGDT was adopted as the standard of care in the treatment of sepsis and septic shock. However, there are several limitations to the EGDT approach. As noted earlier, CVP is an unpredictable marker of fluid resuscitation, and fluid overload is common after EGDT resuscitation.[58]

Furthermore, the Hct target of 30% is unnecessarily high because transfusions of PRBCs to achieve an Hgb >7 g/dL do not increase $ScvO_2$. Finally, the use of invasive monitoring with PACs has fallen out of favor because they do not improve mortality in critically ill patients and the derived data is often incorrectly measured and/or interpreted.[112]

Several large, multicenter studies have shown no improvement in patient outcomes using EGDT for severe sepsis and septic shock. Protocol-based resuscitation did not improve in-hospital mortality among 1341 patients in the ProCESS (*Protocolized Care for Early Septic Shock*) study.[113] In the ARISE (Australasian Resuscitation In Sepsis Evaluation) and ProMISe (*Pro*tocolized *M*anagement *I*n *Se*psis) studies, EGDT did not reduce all-cause mortality compared to usual care.[114,115] The mortality rates among the usual care groups from these trials (18.9%,[113] 18.8%,[114] 29.2%[115]) were similar to that of the EGDT group in the Rivers et al study. These findings could be because of an improvement in our standard of care over that time period, chiefly the early identification and treatment. Nonetheless, the most recent Surviving Sepsis Campaign Guidelines have departed from the EGDT-guided resuscitation strategy from the Rivers study.[4]

E.B. should receive fluid boluses to maintain perfusion with a MAP of at least 65 mm Hg. Reassessment of E.B.'s hemodynamic status should include a thorough clinical examination as well as assessment of available physiologic variables (eg, HR, BP, SaO_2, RR, temperature, urine output). A bolus of 30 mL/kg crystalloid fluid challenge is recommended within the first 3 hours of resuscitation. Albumin may be substituted if large volumes of crystalloids are required, but HESs should be avoided because of an increased risk of acute renal dysfunction and potential increased mortality.[4] Excessive volume administration should be avoided because substantial data have linked fluid overload with worse outcomes including acute kidney injury, days in organ failure, and mortality. This has led many investigators to study early fluid minimization strategies. Further fluid administration should be done cautiously.

The optimal amount of fluid administration is still being investigated in the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) studies.[116]

In summary, the immediate goal of therapy is to maximize $\dot{D}o_2$ to the tissues. Early, but judicious, fluid resuscitation is the mainstay of therapy and improves $\dot{D}o_2$ by increasing CO; however, vasopressor agents are often required for additional cardiovascular support. A favorable response to immediate resuscitative efforts will be reflected by a reversal or halt in the progression of the metabolic acidosis, improved sensorium, and increased urine output. In E.B., selection of appropriate antibiotics while maintaining hemodynamic support are the clinical goals of therapy.

HEMODYNAMIC MANAGEMENT

Fluid therapy versus inotropic support

Case 17-4, Question 4: E.B. is given three 1000-mL fluid boluses, and norepinephrine is begun at a rate of 0.05 µg/kg/min. During the next 2 hours, she receives 4 L of fluid in boluses, and the norepinephrine is increased to 0.3 µg/kg/min to maintain her BP. She does not have signs of pulmonary edema on chest x-ray and her Spo_2 remains 96%. E.B. has the following hemodynamic profile (previous values in parentheses):

BP (S/D/M), 95/48/64 mm Hg (90/48/62 mm Hg)
HR, 124 beats/min (122 beats/min)
Urine output, 0.25 mL/kg/hour (0.4 mL/kg/hour)
Pao_2, 85 mm Hg (98 mm Hg)
$Paco_2$, 36 mm Hg (32 mm Hg)
HCO_3^-, 17 mEq/L (16 mEq/L)
pH, 7.3 (7.31)

Bedside ultrasound reveals a noncollapsible IVC that is 2.5 cm in diameter. Which of the following therapeutic considerations would be reasonable for E.B. at this time: additional fluid boluses, an increase in the norepinephrine infusion rate, or initiation of a different vasopressor?

E.B. continues to be hypotensive despite volume resuscitation and a norepinephrine infusion rate of 0.3 μg/kg/min. Her IVC is plump, suggesting adequate volume resuscitation. The goals of therapy remain the same (ie, maximize arterial oxygen content and $\dot{D}o_2$ to reverse cellular anaerobic metabolism).

E.B.'s PaO_2 of 85 mm Hg correlates with an oxygen–hemoglobin saturation of ~96%, which should provide adequate arterial oxygen content. However, $\dot{D}o_2$ still may be inadequate. E.B.'s Hgb and Hct should be checked to ensure adequate oxygen-carrying capacity in the blood. In addition, decreased tissue oxygen utilization can contribute to the continued acidosis. Further attempts to enhance the CI and, hence, $\dot{D}o_2$ are appropriate. E.B. has a dilated heart and a history of cardiovascular disease and chronic kidney disease that will influence the choice of therapeutic options.

Although fluid administration is the mainstay of therapy in septic shock, the increased IVC diameter suggests that E.B. has been adequately volume resuscitated. Therefore, additional fluid therapy to maintain BP may cause pulmonary edema, compromise pulmonary gas exchange, and increase the risk of other complications such as acute kidney injury. Additional fluid boluses at this time should be used only to maintain the current level of intravascular volume status.

VASOPRESSORS AND INOTROPIC AGENTS

When fluid therapy fails to maintain a satisfactory MAP despite an elevated CO, the use of a vasopressor should be considered. The optimal time to initiate vasopressors is still being investigated.[116] It is now suggested to start vasopressors peripherally rather than delay initiation until central venous access is established.[4] Maintaining a goal MAP does not correlate with decreased mortality, but it helps sustain myocardial and cerebral perfusion. If it is necessary to increase CO, then inotropic agents should be used. Although the use of inotropic agents is well established, controlled comparative studies have not clearly determined which agent, or combination of agents, is most useful in the management of septic shock. Because

differences among the inotropic agents are significant, however, selection of the most appropriate drug should be guided by careful consideration of the patient's hemodynamic status. A recent observational trial hypothesized that early aggressive vasopressor titration may be preferred over low-dose initiation and slow uptitration. The investigators also suggest that a more aggressive vasopressor starting dose must also be accompanied by early and adequate volume resuscitation to prevent deleterious effects of high-dose vasopressors.[117]

Norepinephrine

Norepinephrine is predominantly an α-adrenergic agonist (Table 17-7) and is the recommended first-line vasopressor for sepsis.[4] Norepinephrine has been titrated to 0.3 μg/kg/min, but E.B.'s HR will likely limit the utility of further increases in the dose.

Vasopressin

Catecholamines have been the mainstay of treatment to support BP in patients with sepsis once adequate fluid resuscitation has been achieved. Sepsis, however, can cause a decrease in responsiveness to catecholamines, resulting in refractory hypotension, possibly because of downregulation of adrenergic receptors or altered receptor relative binding affinities in hypoxic and acidotic conditions.[82] Vasopressin is an endogenous hormone that has very little effect on BP under normal conditions, but it becomes important in maintaining BP when the baroreceptor reflex is impaired. In contrast to the catecholamines, vasopressin's effects are relatively preserved in hypoxic and acidotic states.[82] For adult patients with septic shock with inadequate MAP response to norepinephrine alone, current guidelines suggest adding vasopressin instead of increasing doses of norepinephrine.[4] The optimal dose of norepinephrine for vasopressin initiation is not yet established.

Vasopressin's direct vasoconstricting actions are mediated by the vascular V_{1a} receptors coupled with phospholipase C.[82,120] When these receptors are activated, calcium is released from the

sarcoplasmic reticulum in smooth muscle cells, leading to vasoconstriction. Vasopressin levels peak in early septic shock and decrease to low-normal levels in most patients within 48 hours. This phenomenon is called a *relative vasopressin deficiency* because higher vasopressin levels would be expected in hypotensive states.

The VASST (Vasopressin And Septic Shock Trial) study compared norepinephrine monotherapy to norepinephrine plus vasopressin in patients with septic shock, who were unresponsive to fluids and assessed mortality at 28 days.[121] Vasopressin significantly decreased the amount of norepinephrine required; however, there was no difference in mortality between the treatment groups except when the patients were stratified according to severity of sepsis. The patients with less severe septic shock benefited from vasopressin therapy. The VAsopressin vs Noradrenaline as Initial therapy in Septic sHock (VANISH) trial compared early vasopressin to norepinephrine and again found that vasopressin reduces catecholamine requirements. The study also found that fewer patients in the vasopressin group required renal replacement therapy, but this was mostly in nonsurvivors. There was no difference in renal replacement therapy–free days or mortality.[122]

Low-dose vasopressin (up to 0.03 units/min) is recommended to synergistically achieve the goal MAP with norepinephrine or allow norepinephrine dose reductions.[4] Doses >0.03 to 0.04 units/min are only recommended as salvage therapy.[4]

E.B. has a decreased MAP despite the increased titration of norepinephrine. The optimal time to consider additional or alternative therapies to norepinephrine is unknown. Because patients in septic shock have decreased endogenous levels of vasopressin, it would be reasonable to add vasopressin at 0.03 units/min to increase the MAP and renal perfusion.

Epinephrine

Epinephrine stimulates α-, β_1-, and β_2-adrenergic receptors (Table 17-7). CO is augmented via increased contractility and HR, with the contribution of each being highly variable. Blood vessels in the

kidney, skin, and mucosa constrict in response to α-adrenergic stimulation, whereas vessels in the skeletal muscle vasodilate because of β_2 effects. A biphasic response in SVR is observed as β_2-receptors are activated at the lower range and α_1-receptors are stimulated at higher infusion rates. The improvement in CO, therefore, may be negated by an increase in afterload at higher dosages.

Historically, epinephrine was reserved as a last-line therapy because of the studies that showed harmful splanchnic and renal vasculature effects and elevated lactate levels. Despite these effects, there are no clinical studies showing that epinephrine causes worse outcomes in sepsis. In fact, two prospective, double-blind, randomized controlled trials comparing epinephrine and norepinephrine in patients with septic shock found similar mortality rates, time to hemodynamic recovery, and time to vasopressor withdrawal.[118,119] Both studies showed lower arterial pH values associated with impaired serum lactate clearance in the epinephrine-treated groups. Therefore, lactate clearance would not be recommended to guide resuscitation when utilizing epinephrine.

Epinephrine is recommended as adjunctive therapy to norepinephrine and vasopressin to maintain adequate MAP.[4] However, if tachyarrhythmias are limiting the use or norepinephrine, epinephrine is likely to produce similar effects because it also stimulates β_1-receptors. Consequently, it is not appropriate to substitute epinephrine for norepinephrine at this time for E.B.

Dopamine

Dopamine previously was another initial pharmacologic agent chosen for the treatment of septic shock. A trial that randomized 1679 patients with shock to dopamine or norepinephrine for BP support found no significant difference in the primary outcome of 28-day mortality, but there was an increased risk of arrhythmic events with dopamine.[83] A meta-analysis of six randomized trials of patients with sepsis found that dopamine was associated with an increased risk of death and arrhythmias compared to norepinephrine.[123]

Similarly, another meta-analysis that included six randomized trials found norepinephrine was associated with a lower in-hospital and 28-day mortality compared to dopamine as well as a lower incidence of arrhythmias.[124]

In light of these findings, the Surviving Sepsis Campaign relegated dopamine from a first line to an alternative vasopressor. Dopamine is now reserved for patients with absolute or relative bradycardia and a low risk of tachyarrhythmias, which is difficult to predict.[4] Accordingly, dopamine is not an appropriate therapeutic option for E.B.

In addition, low-dose dopamine should not be used for renal protective purposes.[4] Dopamine does not decrease the time to recovery of renal function or the need for renal replacement therapy.

Phenylephrine

Phenylephrine is a pure α-adrenergic agonist (Table 17-7) and, thus, increases systolic, diastolic, and MAPs through vasoconstriction. Reflex bradycardia can occur secondarily because of the absence of β-adrenergic effects. The increase in afterload, while increasing myocardial $\dot{V}o_2$, correspondingly increases coronary blood flow because of increased perfusion pressure and autoregulation. In patients with myocardial hypoxia, or in those experiencing atrial or ventricular arrhythmias, phenylephrine can be beneficial because it has minimal direct cardiac effects. In situations in which the CO is decreased, phenylephrine can be detrimental. Preload is reduced because plasma fluid is lost owing to increased capillary hydrostatic pressure, forcing water and solutes from the vascular space into the interstitial spaces. This response, in addition to the increased afterload and reflex bradycardia, may significantly impair CO (Table 17-7). Therefore, phenylephrine should be reserved for treating septic shock in the following patients: (a) those with arrhythmias on norepinephrine, (b) those with high CO but persistent hypotension, or (c) those who fail to achieve the goal MAP on combination inotropes/vasopressors and low-dose vasopressin. Phenylephrine is a reasonable alternative therapy for E.B. if her hypotension and tachycardia persist despite the addition of vasopressin.

Angiotensin II

Angiotensin II is a synthetic octapeptide identical to endogenous human angiotensin II that can improve BP in patients with catecholamine- resistant distributive shock. It was approved by the U.S. Food and Drug Administration (FDA) based on the results of the Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) trial, which showed a significant increase in MAP response at 3 hours compared to placebo.[125] Patients in the angiotensin II group experienced venous thromboembolism (VTE) at a higher rate than patients on placebo. Because of the increased risk of VTE, the package insert recommends ensuring that patients are on appropriate VTE prophylaxis before administration.[126] The clinical application and place in therapy of angiotensin II have not yet been fully established. Currently, routine use is cost prohibitive.

Dobutamine

Tissue $\dot{D}o_2$ may be impaired by a suboptimal CO or decreased oxygen-carrying capacity. If tissue hypoperfusion persists after optimizing fluid status, achieving the goal MAP, and assuring an adequate Hgb concentration, then CO should be assessed. Epinephrine and dopamine are inotropic therapies with vasoconstricting properties, but dobutamine is the recommended first-line inotropic agent in the management of septic shock.[4] Dobutamine produces a greater increase in CO than does dopamine, but it also lowers SVR. In contrast to dopamine, dobutamine lowers PCWP and causes less pulmonary shunting. Because dobutamine can lower ventricular filling pressure, volume status must be monitored closely to avoid the development of hypotension and reduced MAP. Fluids should be administered as needed to maintain the PCWP at optimal and tolerated levels of 15 to 18 mm Hg. With the administration of greater amounts of fluid, CO, $\dot{D}o_2$, and systemic $\dot{V}O_2$ are significantly increased. Dobutamine increases $\dot{D}o_2$ and CI when given concurrently with or after volume resuscitation, and it may independently increase capillary perfusion regardless of systemic effects. Decreases in PaO_2 and increases in

venous P_{O_2}, as well as adverse effects on myocardium, may be evident at higher dosages (>6 μg/kg/min).[127]

Combinations of vasopressors and inotropic agents can also be used to achieve desired hemodynamic parameters. GI perfusion can be compromised owing to the vasoconstricting effects of catecholamines and may play a role in the pathogenesis of multiple organ dysfunction.[88] Currently, it is unknown whether a specific catecholamine regimen provides a significant benefit over others. There are conflicting data about which vasopressor can increase gastric perfusion and whether this increase can alter progression to organ dysfunction.

CASE 17-4, QUESTION 5: Given E.B.'s history of cardiovascular disease, what factors should you consider before initiating an inotropic or alternative vasopressor agent? Outline an overall approach to maintaining adequate hemodynamic status.

E.B. has a history of coronary artery disease and is susceptible to myocardial ischemia. Therefore, a careful balance must be achieved between myocardial $\dot{V}O_2$ and coronary perfusion pressure. Further attempts to optimize MAP and CI with norepinephrine alone could increase myocardial $\dot{V}O_2$ and precipitate ischemia. Evidence suggests that the goal of therapy in treating patients with septic shock, or any form of shock for that matter, is not to simply normalize BP but to optimize $\dot{D}O_2$ and $\dot{V}O_2$. Once anemia and hypoxia have been corrected, CO becomes the remaining parameter that can be adjusted to increase oxygen supply, but raising arterial BP and CO with inotropic agents or vasopressors before restoring adequate blood volume can actually worsen tissue perfusion. Therefore, the patient's current hemodynamic status and the individual properties of those agents that will most effectively maintain or increase the MAP and CO should be considered while selecting an inotropic agent. In many instances, because of individual variability and response, more than one inotropic agent or addition of a vasopressor is required to achieve these end points. These interventions must be made with strict monitoring of the patients' response to the interventions to

prevent any adverse consequences, especially in those patients who are predisposed to an adverse event, such as E.B.

It is important to realize that the response to exogenous catecholamines in patients with septic shock is highly variable, and a successful regimen in one patient may be unsuccessful in another. In addition, patients with sepsis often require infusion rates in the moderate-to-high range. Therefore, the goal is to use one or more agents at the dosages necessary to achieve the desired end points without unduly compromising the patient's status. The use of catecholamines, however, is only a stabilizing measure. Strict attention to all other physiologic parameters—as well as nutritional support, antibiotic modification, respiratory support, and ongoing surgical intervention—cannot be overemphasized.

CORTICOSTEROIDS

Case 17-4, Question 6: What is the rationale for the use of glucocorticoids in the treatment of septic shock, and is there evidence to support their use for this indication in E.B.?

The use of corticosteroids in sepsis and septic shock has been a controversial topic for many years. Corticosteroids were originally proposed as a treatment option because of their anti-inflammatory properties, with the hope of attenuating the body's response to infection. It has been shown that critically ill patients exhibit impaired cortisol secretion because of a relative adrenocortical insufficiency and a glucocorticoid peripheral resistance syndrome that can also be affected by multiple medications.[128] The Consensus Task Force from the Society of Critical Care Medicine and European Society of Intensive Care Medicine has defined this dysfunction of the hypothalamic–pituitary–adrenal axis as *critical illness–related corticosteroid insufficiency*.[129,130]

Diagnosis of this condition is intensely debated. Some clinicians recommend a random cortisol level that is below a certain threshold during physiologic stress (ie, shock) to diagnose adrenal

insufficiency; however, this has only been shown to be useful in diagnosing absolute adrenal insufficiency.[4] The traditional assessment method has been the adrenal corticotropin hormone (ACTH) stimulation test with administration of either 1 or 250 μg of cosyntropin. However, the ACTH test only evaluates the adrenal function, not the entire hypothalamic–pituitary–adrenal axis, and lacks sensitivity and specificity in critical illness.[128] Random cortisol levels may be useful for evaluating absolute adrenal insufficiency, but have not demonstrated a benefit in patients with septic shock. The Surviving Sepsis Campaign does not recommend the ACTH stimulation test or random cortisol levels to identify patients who should receive glucocorticoids.[4]

Clinical trials investigating the use of steroids in septic shock have been performed with varying results with respect to mortality. The trial by Annane et al. showed a shortened time to shock reversal and mortality benefit with the use of low doses of hydrocortisone and fludrocortisone in patients with severe septic shock, who exhibited a relative adrenocortical insufficiency (serum cortisol increase ≤9 μg/dL in response to ACTH stimulation).[131] The Corticosteroid Therapy of Septic Shock (CORTICUS) trial showed a faster resolution of shock for those patients on hydrocortisone, as evidenced by faster time to weaning from vasopressors; however, those patients also had a higher incidence of superinfection and new episodes of sepsis or septic shock.[132] There was no mortality benefit seen with the use of corticosteroids. The CORTICUS trial included patients with septic shock, whereas the study by Annane et al. only enrolled patients with severe septic shock unresponsive to vasopressor therapy. The HYPRESS (*Hy*drocortisone for *Pre*vention of *S*eptic *S*hock) trial randomized patients with severe sepsis and those who had not progressed to shock to hydrocortisone 200 mg/day versus placebo.[133] There was no difference in progression to shock or 28-day mortality. Patients in the hydrocortisone group experienced more hyperglycemia. Two large randomized controlled trials of over 5000 critically ill patients with sepsis were recently published and add to the clinical evidence. The ADjunctive coRticosteroid trEatment iN criticAlly ilL Patients With Septic Shock

(ADRENAL) trial randomized 3658 patients with septic shock requiring mechanical ventilation for <24 hours to receive hydrocortisone 200 mg/day or placebo.[134] There was no difference in the primary end point of 90-day mortality. Hydrocortisone was associated with reduced duration of shock, reduced duration of mechanical ventilation, and reduced ICU length of stay. The APROCCHSS (*A*ctivated *Pro*tein *C* and *C*orticosteroids for *H*uman *S*eptic *S*hock) trial randomized 1241 patients with septic shock to hydrocortisone IV 50 mg every 6 hours and fludrocortisone 50 μg orally daily versus placebo for 7 days.[135] The hydrocortisone and fludrocortisone group had lower 90-day mortality but not 28-day mortality. Vasopressor-free days at 28 days were also higher in the treatment group. It is not clear why the results of ADRENAL and APROCCHSS differ. APROCCHSS enrolled much sicker patients with a higher mortality. The results of these studies demonstrate that corticosteroid therapy likely has a small benefit of decreased mortality in patients with septic shock, particularly if more severe.[136] Adverse effects (ie, hypernatremia, hyperglycemia, increased risk of neuromuscular weakness) are likely minimal with short-term corticosteroid use in this population. Thus, corticosteroids may be a reasonable choice for those patients unresponsive to vasopressors.

The optimal dose, duration, and method of administration are still unknown. The Surviving Sepsis Campaign recommends hydrocortisone 200 mg/day.[4] Continuous infusion of hydrocortisone may avoid significant fluctuations in glucose and sodium. Because E.B. is refractory to increasing doses of norepinephrine and requires additional vasopressor support, it was decided to start hydrocortisone 50 mg IV every 6 hours.

Ascorbic acid and thiamine

Interest in hydrocortisone, ascorbic acid (vitamin C) and thiamine (HAT) as separate agents and in combination with hydrocortisone have been receiving significant attention in recent years as adjunctive therapies in multiple subpopulations of septic shock. Vitamin C is important for cellular regulation and immune system

function. Vitamin C is an essential cofactor for endogenous catecholamine and vasopressin synthesis, and is known to be depleted in critically ill patients because of consumption and reduced intake.[137] In a phase I trial, vitamin C decreased SOFA score in a dose-dependent manner.[138] Thiamine is the precursor of thiamine pyrophosphate, which is an essential component of the Krebs cycle. Serum thiamine concentrations are reduced in 20% of patients with sepsis because of increased metabolic consumption and decreased intake.[139] Thiamine has been shown to improve lactate clearance.[140,141]

The role of vitamin C and thiamine in sepsis has been evaluated in observational and randomized control trials. A retrospective before–after trial evaluated 94 patients who received vitamin C within 24 hours of ICU admission and showed a decrease in duration of vasopressors and hospital mortality in patients treated with HAT.[142] Randomized controlled trials have produced inconsistent results. The Vitamin C, Hydrocortisone and Thiamine in Patients With Septic Shoc (VITAMINS) trial, the largest randomized control trial to evaluate the use of HAT therapy, evaluated the effects of HAT therapy (*N* = 109) versus hydrocortisone (*N* = 107). The study reported no difference in median time alive and vasopressor-free days up to day 7, hospital mortality, ICU mortality, 28-day mortality, or 90-day mortality.[143] HYVCTTSSS (*Hy*drocortisone, *V*itamin *C*, and *T*hiamine combination *T*reatment for patients with *S*epsis or *S*eptic *S*hock) showed a decrease in 72-hour SOFA score in patients who received HAT.[144] In Outcomes of metabolic Resuscitation using Ascorbic acid, thiamiNe, and Glucocorticoids in the Early treatment of Sepsis (ORANGES), patients who received HAT had faster resolution of shock, defined as time to vasopressor discontinuation.[145] Neither HYVCTTSSS nor ORANGES found a difference in mortality.[144,145]

There is inconsistency in the vitamin C dosing regimens used in clinical trials, making it challenging to draw definitive conclusions on its role in sepsis. The most common doses used in clinical trials are IV ascorbic acid 1500 mg every 6 hours and thiamine 200 mg every 12 hours. In general, vitamin C appears to be safe. However,

patients should be monitored for nephropathy and glucose monitoring errors when high-dose vitamin C is administered. Thiamine also appears to be safe. Overall, there is insufficient evidence to support the routine use of vitamin C and thiamine in sepsis. Current guidelines suggest against the use of IV vitamin C for septic shock.[4]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med*. 2017;43:1751–1763. (129)

Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: Red blood cell transfusion thresholds and storage. *JAMA*. 2016;316(*19*):2025–2035. (20)

Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40:1795–1815. (1)

De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362:779–789. (83)

Evans L, Rhodes A, Alhazzani, W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021; 49:e1063-e-1143.

Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256. (30)

Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among

patients with septic shock: the VITAMINS randomized clinical trial. *JAMA*. 2020;323(*5*):423–431. (143)

Hammond DA, Lam SW, Rech MA, et al. Balanced crystalloids versus saline in critically ill adults: a systematic review and meta-analysis. *Ann Pharmacother*. 2020;54(*1*):5–13. (41)

Overgaard CB, Džavík V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. *Circulation*. 2008;118:1047–1056. (82)

Rochwerg B, Oczkowski SJ, Siemieniuk RA, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med*. 2018;46: 1411–1420. (136)

Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358:877–887. (121)

Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced crystalloids versus saline in the intensive care unit: the SALT randomized trial. *Am J Respir Crit Care Med*. 2017;195(*10*):1362–1372. (39)

Vahdatpour C, Collins D, Goldberg S. Cardiogenic shock. *J Am Heart Assoc*. 2019;8:e011991. (71)

van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e232. (69)

Key Websites

Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45:486–552. https://www.sccm.org/SurvivingSepsisCampaign/Home (4)

COMPLETE REFERENCES CHAPTER 17 SHOCK

1. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40:1795–1815.
2. Gaieski D. Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock. In: Post TW, ed. *UpToDate*. Wolters Kluwer. Accessed November 2, 2020. https://www.uptodate.com/contents/evaluation-of-and-initial-approach-to-the-adult-patient-with-undifferentiated-hypotension-and-shock

3. Balk RA. Systemic inflammatory response syndrome (SIRS). *Virulence*. 2014;5(1):20–26.
4. Evans L, Rhodes A, Alhazzani, W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021; 49:e1063-e-1143.
5. Beaulieu Y, Marik PE. Bedside ultrasonography in the ICU: part 2. *Chest*. 2005;128:1766–1781.
6. Beaulieu Y, Marik PE. Bedside ultrasonography in the ICU: part 1. *Chest*. 2005;128:881–895.
7. Sangkum L, Liu GL, Yu L, Yan H, Kaye AD, Liu H. Minimally invasive or noninvasive cardiac output measurement: an update. *J Anesth*. 2016;30:461–480.
8. Hendy A, Bubenek S¸. Pulse waveform hemodynamic monitoring devices: recent advances and the place in goal-directed therapy in cardiac surgical patients. *Rom J Anaesth Intensive Care*. 2016;23:55–65.
9. Grensemann J. Cardiac output monitoring by pulse contour analysis, the technical basics of less-invasive techniques. *Front Med (Lausanne)*. 2018;5:64.
10. Marik PE. Sublingual capnography: a clinical validation study. *Chest*. 2001;120:923–937.
11. Levy B, Gawalkiewicz P, Vallet B, Briancon S, Nace L, Bollaert PE. Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. *Crit Care Med*. 2003;31(2):474–480.
12. Collaborative Study Group on Perioperative ScvO2 Monitoring. Multicentre study on peri and postoperative central venous oxygen saturation in high-risk surgical patients. *Crit Care*. 2006;10:R158.
13. Lima A, van Bommel J, Jansen TC, Ince C, Bakker J. Low tissue oxygen saturation at the end of early goal-directed therapy is associated with worse outcome in critically ill patients. *Crit Care*. 2009;13(suppl 5):S13.
14. Boulain T, Garot D, Vignon P, et al. Prevalence of low central venous oxygen saturation in the first hours of intensive care unit admission and associated mortality in septic shock patients: a prospective multicentre study. *Crit Care*. 2014;18:609.
15. Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with the use of a flow-directed balloon-tipped catheter. *N Engl J Med*. 1970;283:447–451.
16. Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev*. 2013; (2):CD003408.
17. Marik PE. Obituary: pulmonary artery catheter 1970 to 2013. *Ann Intensive Care*. 2013;3(1):38.
18. Cothren Burlew C, Moore EE. Trauma. In: Brunicardi F, Andersen DK, Billiar TR, et al, eds. *Schwartz's Principles of Surgery*. 11th ed. McGraw-Hill; 2019.

Accessed November 29, 2020. http://accessmedicine.mhmedical.com/book.aspx?bookID=2576#208296159

19. Bonanno FG. Clinical pathology of the shock syndromes. *J Emerg Trauma Shock*. 2011;4:233–243.
20. Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA*. 2016;316(19):2025–2035.
21. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018;8:CD000567.
22. He B, Xu X, Li L, et al. Hydroxyethyl starch versus other fluids for non-septic patients in the intensive care unit: a meta-analysis of randomized controlled trials. *Crit Care*. 2015;19:92.
23. Haase N, Perner A, Hennings LI, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ*. 2013;346:f839.
24. de Crescenzo C, Gorouhi F, Salcedo ES, Galante JM. Prehospital hypertonic fluid resuscitation for trauma patients: a systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2017;82(5):956–962.
25. Qureshi SH, Rizvi SI, Patel NN, Murphy GJ. Meta-analysis of colloids versus crystalloids in critically ill, trauma and surgical patients. *Br J Surg*. 2016;103(1):14–26.
26. Eljaiek R, Heylbroeck C, Dubois MJ. Albumin administration for fluid resuscitation in burn patients: a systematic review and meta-analysis. *Burns*. 2017;43:17–24.
27. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2013;(2):CD000567.
28. Gattas DJ, Dan A, Myburgh J, et al. Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. *Intensive Care Med*. 2013;39:558–568.
29. Roberts I, Blackhall K, Alderson P, Bunn F, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev*. 2011;11:CD001208.
30. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256.
31. Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357:874–884.
32. Lyu PF, Murphy DH. Economics of fluid therapy in critically ill patients. *Curr Opin Crit Care*. 2014;20:402–407.

33. Fox DL, Vermeulen LC, et al. *Technology Assessment: Albumin, Nonprotein Colloid, and Crystalloid Solutions*. University HealthSystem Consortium; 2000. 1–76.
34. Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med*. 2010;152:101–113.
35. Mueller MM, Van Remoortel H, Meybohm P, et al. Patient blood management recommendations from the 2018 Frankfurt Consensus Conference. *JAMA*. 2019;321(10):983–997.
36. Kwan I, Bunn F, Chinnock P, Roberts I. Timing and volume of fluid administration for patients with bleeding. *Cochrane Database Syst Rev*. 2014;3:CD002245.
37. Cannon JW. Hemorrhagic shock. *N Engl J Med*. 2018;378:370–379.
38. Jaber S, Paugam C, Futier E, et al. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label randomised controlled, phase 3 trial. *Lancet*. 2018;392:31–40.
39. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced crystalloids versus saline in the intensive care unit: the SALT randomized trial. *Am J Respir Crit Care Med*. 2017;195(10):1362–1372.
40. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378:829–839.
41. Hammond DA, Lam SW, Rech MA, et al. Balanced crystalloids versus saline in critically ill adults: a systematic review and meta-analysis. *Ann Pharmacother*. 2020;54(1):5–13.
42. Ergin B, Kapucu A, Guerci P, Ince C. The role of bicarbonate precursors in balanced fluids during haemorrhagic shock with and without compromised liver function. *Br J Anaesth*. 2016;117(4):521–528.
43. Zitek T, Skaggs ZD, Rahbar A, Patel J, Khan M. Does intravenous lactated Ringer's solution raise serum lactate? *J Emerg Med*. 2018;55(3):313–318.
44. Singh S, Kerndt CC, Davis D. Ringer's lactate. In: *StatPearls*. StatPearls Publishing; 2020. Accessed November 17, 2020. https://www.ncbi.nlm.nih.gov/books/NBK500033/
45. Semler MW, Kellum JA. Balanced crystalloid solutions. *Am J Respir Crit Care Med*. 2019;199(8):952–960.
46. van Haren FM, Sleigh J, Boerma EC, et al. Hypertonic fluid administration in patients with septic shock: a prospective randomized controlled pilot study. *Shock*. 2012;37:268–275.
47. van Haren FM, Sleigh J, Cursons R, La Pine M, Pickkers P, van der Hoeven JG. The effects of hypertonic fluid administration on the gene expression of inflammatory mediators in circulating leucocytes in patients with septic shock: a preliminary study. *Ann Intensive Care*. 2011;1:44.

48. Delano MJ, Rizoli SB, Rhind SG, et al. Prehospital resuscitation of traumatic hemorrhagic shock with hypertonic solutions worsens hypocoagulation and hyperfibrinolysis. *Shock*. 2015;44(1):25–31.
49. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11–21.
50. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471–482.
51. Roback JD, Caldwell S, Carson J, et al. Evidence-based practice guidelines for plasma transfusion. *Transfusion*. 2010;50:1227–1239.
52. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guidelines from the AABB. *Ann Intern Med*. 2012;157:49–58.
53. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2015;162:205–213.
54. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*. 2016;20:100.
55. Goel R, Tobian AAR, Shaz BH. Noninfectious transfusion-associated adverse events and their mitigation strategies. *Blood*. 2019;133(17):1831–1839.
56. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood*. 2019;133(17):1840–1853.
57. Fridey JL. Oxygen carriers as alternatives to red cell transfusion. In: Post TW, ed. *UpToDate*. UpToDate. Accessed November 17, 2020. https://www.uptodate.com/contents/oxygen-carriers-as-alternatives-to-red-blood-cell-transfusion
58. Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care*. 2011;1:1.
59. Griffel MI, Kaufman BS. Pharmacology of colloids and crystalloids. *Crit Care Clin*. 1992;8:235–253.
60. Imm A, Carlson RW. Fluid resuscitation in circulatory shock. *Crit Care Clin*. 1993;9:313–333.
61. Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. *Cochrane Database Syst Rev*. 2012;7:CD001319.
62. Groeneveld AB, Navickis RJ, Wilkes MM. Update on the comparative safety of colloids: a systematic review of clinical studies. *Ann Surg*. 2011;253:470–483.
63. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–1911.
64. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367:124–134.

65. Navickis RJ, Haynes GR, Wilkes MM. Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials. *J Thorac Cardiovasc Surg*. 2012;144:223–230.
66. Dart AB, Mutter TC, Ruth CA, Taback SP. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *Cochrane Database Syst Rev*. 2010;(1):CD007594.
67. Bayer O, Reinhart K, Kohl M, et al. Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: a prospective sequential analysis. *Crit Care Med*. 2012;40:2543–2551.
68. Bayer O, Schwarzkopf D, Doenst T, et al. Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery—a prospective sequential analysis. *Crit Care Med*. 2013;41:2532–2542.
69. van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e232–e238.
70. Kolte D, Khera S, Aronow WS, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc*. 2014;3:e000590.
71. Vahdatpour C, Collins D, Goldberg S. Cardiogenic shock. *J Am Heart Assoc*. 2019;8:e011991.
72. Gupta T, Harikrishnan P, Kolte D, et al. Trends in management and outcomes of ST-elevation myocardial infarction in patients with end-stage renal disease in the United States. *Am J Cardiol*. 2015;115:1033–1041.
73. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425.
74. Van Herck JL, Claeys MJ, De Paep R, Van Herck PL, Vrints CJ, Jorens PG. Management of cardiogenic shock complicating acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2015;4:278–297.
75. Becker RC. Hemodynamic, mechanical, and metabolic determinants of thrombolytic efficacy: a theoretical framework for assessing the limitations of thrombolysis inpatients with cardiogenic shock. *Am Heart J*. 1993;125:919–929.
76. Prewitt RM, Gu S, Schick U, Ducas J. Intraaortic balloon counterpulsation enhances coronary thrombolysis induced by intravenous administration of a thrombolytic agent. *J Am Coll Cardiol*. 1994;23:794–798.
77. Unverzagt S, Buerke M, de Waha A, et al. Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock. *Cochrane Database Syst Rev*. 2015;(3):CD007398.
78. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation*. 2015;131:2143–2150.

79. Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute, myocardial infarction by application of hemodynamic subsets (first of two parts). *N Engl J Med*. 1976;295:1356–1362.
80. Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute, myocardial infarction by application of hemodynamic subsets (second of two parts). *N Engl J Med*. 1976;295:1404–1413.
81. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med*. 2009;37:2642–2647.
82. Overgaard CB, Džavík V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. *Circulation*. 2008;118:1047–1056.
83. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362:779–789.
84. McGhie AI, Golstein RA. Pathogenesis and management of acute heart failure and cardiogenic shock: role of inotropic therapy. *Chest*. 1992;102(5 suppl 2):626S–632S.
85. Loeb HS, Bredakis J, Gunner RM. Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. *Circulation*. 1977;55:375–378.
86. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004;44:E1–E211.
87. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. *Eur Heart J*. 2015;36:1223–1230.
88. Levy B, Bollaert PE, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med*. 1997;23:282–287.
89. Unverzagt S, Wachsmuth L, Hirsch K, et al. Inotropic agents and vasodilator strategies for acute myocardial infarction complicated by cardiogenic shock or low cardiac output syndrome. *Cochrane Database Syst Rev*. 2014;1:CD009669.
90. Thackray S, Easthaugh J, Freemantle N, Cleland JG. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure—a meta-regression analysis. *Eur J Heart Fail*. 2002;4:515–529.
91. Basir MB, Schreiber TL, Grines CL, et al. Effect of early initiation of mechanical circulatory support on survival in cardiogenic shock. *Am J Cardiol*. 2017;119:845–851.

92. Rihal CS, Naidu SS, Givertz MM, et al. 2015 SCAI/ACC/HFSA/STS clinical expert consensus statement on the use of percutaneous mechanical circulatory support devices in cardiovascular care: endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. *J Am Coll Cardiol*. 2015;65:e7–e26.
93. Sandhu A, McCoy LA, Negi SI, et al. Use of mechanical circulatory support in patients undergoing percutaneous coronary intervention: insights from the National Cardiovascular Data Registry. *Circulation*. 2015;132:1243–1251.
94. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367:1287–1296.
95. Thiele H, Zeymer U, Neumann FJ, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet*. 2013;382:1638–1645.
96. Ahmad Y, Sen S, Shun-Shin MJ, et al. Intra-aortic balloon pump therapy for acute myocardial infarction: a meta-analysis. *JAMA Intern Med*. 2015;175:931–939.
97. O'Neill WW, Grines C, Schreiber T, et al. Analysis of outcomes for 15,259 US patients with acute myocardial infarction cardiogenic shock (AMICS) supported with the Impella device. *Am Heart J*. 2018;202:33–38.
98. Basir MB, Schreiber T, Dixon S, et al. Feasibility of early mechanical circulatory support in acute myocardial infarction complicated by cardiogenic shock: the Detroit cardiogenic shock initiative. *Catheter Cardiovasc Interv*. 2018;91:454–461.
99. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence*. 2014;1:4–11.
100. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med*. 2003;31:1250–1256.
101. Elixhauser A, Friedman B, Stranges E. *Septicemia in U.S. Hospitals, 2009*. Agency for Healthcare Research and Quality. Accessed November 30, 2020. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb122.pdf
102. Sutton JP, Friedman B. *Trends in Septicemia Hospitalizations and Readmissions in Selected HCUP States, 2005 and 2010*. Agency for Healthcare Research and Quality. Accessed November 30, 2020. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb161.pdf
103. Lundy DJ, Trzeciak S. Microcirculatory dysfunction in sepsis. *Crit Care Clin*. 2009;25:721–731.
104. Nduka OO, Parrillo JE. The pathophysiology of septic shock. *Crit Care Clin*. 2009;25:677–702.

105. King EG, Bauzá GJ, Mella JR, Remick DG. Pathophysiologic mechanisms in septic shock. *Lab Invest*. 2014;94:4–12.
106. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med*. 2004;32:1928–1948.
107. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369:840–851.
108. Cohen J, Vincent JL, Adhikari NK, et al. Sepsis: a roadmap for future research. *Lancet Infect Dis*. 2015;15:581–614.
109. Antonucci E, Fiaccadori E, Donadello K, Taccone FS, Franchi F, Scolletta S. Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment. *J Crit Care*. 2014;29:500–511.
110. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589–1596.
111. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368–1377.
112. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA*. 2005;294;1664–1670.
113. ProCESS Investigators; Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370:1683–1693.
114. ARISE Investigators, ANZICS Clinical Trials Group; Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371:1496–1506.
115. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372:1301–1311.
116. Clinicaltrials.gov. *Crystalloid liberal or vasopressors early resuscitation in sepsis (CLOVERS*). Accessed September 9, 2020. https://clinicaltrials.gov/ct2/show/NCT03434028
117. Roberts RJ, Miano TA, Hammond DA, et al. Evaluation of vasopressor exposure and mortality in patients with septic shock. *Crit Care Med*. 2020;48:1445–1453.
118. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*. 2007;370:676–684.
119. Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34:2226–2234.
120. Russell JA. Bench-to-bedside review: vasopressin in the management of septic shock. *Crit Care*. 2011;15:226.

121. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358:877–887.
122. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. *JAMA*. 2016;316(5):509–518.
123. De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. *Crit Care Med*. 2012;40:725–730.
124. Vasu TS, Cavallazzi R, Hirani A, Kaplan G, Leiby B, Marik PE. Norepinephrine or dopamine for septic shock: a systematic review of randomized clinical trials. *J Intensive Care Med*. 2012;27:172–178.
125. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med*. 2017;377:419–430.
126. Giapreza™ (angiotensin II). Package insert. La Jolla Pharmaceutical Company; 2017.
127. Rudis MI, Basha MA, Zarowitz BJ. Is it time to reposition vasopressors and inotropes in sepsis? *Crit Care Med*. 1996;24:525–537.
128. Patel GP, Balk RA. Systemic steroids in severe sepsis and septic shock. *Am J Respir Crit Care Med*. 2012;185:133–139.
129. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med*. 2017;43:1751–1763.
130. Pastores SM, Annane D, Rochwerg B; Corticosteroid Guideline Task Force of SCCM and ESICM. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med*. 2018;46(1):146–148.
131. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288:862–871.
132. Sprung C, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111–124.
133. Keh D, Trips E, Marx G, et al. Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial. *JAMA*. 2016;316(17):1775–1785.
134. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med*. 2018;378(9):797–808.
135. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med*. 2018;378(9):809–818.

136. Rochwerg B, Oczkowski SJ, Siemieniuk RA, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med*. 2018;46:1411–1420.
137. Carr A, Shaw GM, Fowler AA, Natarajan R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? *Crit Care*. 2015;19:418.
138. Fowler AA, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med*. 2014;12:32.
139. Donnino MW, Carney E, Cocchi MN, et al. Thiamine deficiency in critically ill patients with sepsis. *J Crit Care*. 2010;25(4):576–581.
140. Woolum JA, Abner EL, Kelly A, et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. *Crit Care Med*. 2018;46(11):1747–1752.
141. Donnino MW, Andersen LW, Chase M, et al. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. *Crit Care Med*. 2016;44(2):360–367.
142. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. 2017;151(6):1229–1238.
143. Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. *JAMA*. 2020;323(5):423–431.
144. Chang P, Liao Y, Guan J, et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. *Chest*. 2020;158(1):174–182.
145. Iglesias J, Vassallo AV, Patel VV, et al. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis. *Chest*. 2020;158(1):164–173.

SECTION 3

Pulmonary Disorders

Section Editors: Timothy R. Hudd and Kathy Zaiken

18

Asthma

Cary R. Chrisman and Christopher K. Finch

CORE PRINCIPLES		CHAPTER CASES
1	Asthma is a heterogeneous disease usually characterized by chronic airway inflammation that is defined by the Global Initiative for Asthma as history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[1]	**Case 18-1 (Question 1)** **Case 18-2 (Question 1)** **Case 18-6 (Question 1)** **Case 18-7 (Question 1)**
2	There are a variety of phenotypes, and now endotypes, used to further categorize the etiology and treatment of asthma, which allows for a more personalized approach to treatment than in the past.	**Case 18-3 (Question 1)** **Case 18-6 (Question 1)** **Case 18-7 (Question 1)**
3	The clinical presentation of asthma	**Case 18-3 (Question 1)**

	includes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction that is often reversible either spontaneously or with treatment.	**Case 18-4 (Question 1)** **Case 18-5 (Question 1)** **Case 18-7 (Question 1)** **Case 18-8 (Question 1)**
4	Core management principles include environmental control, inhaled corticosteroid (ICS) maintenance therapy, simultaneous utilization of ICS whenever a β-agonist is administered, biologic treatment for the most severe asthma, and management of comorbidities that worsen asthma.	**Case 18-6 (Question 1)** **Case 18-7 (Question 1)** **Case 18-8 (Questions 1, 2)** **Case 18-9 (Question 1)**
5	Major treatments of acute exacerbations include frequent inhaled short-acting β_2-agonists and systemic corticosteroids.	**Case 18-1 (Questions 1, 3–7)** **Case 18-2 (Questions 3–9)**
6	Monitoring parameters include spirometric measures such as forced expiratory volume in 1 second (FEV_1). Patient self-monitoring includes peak expiratory flow (PEF) and symptom assessment. Acute-care monitoring includes FEV_1, PEF, arterial O_2 saturation, and arterial blood gases.	**Case 18-1 (Questions 2, 3)** **Case 18-2 (Questions 2–4, 6, 8)** **Case 18-4 (Question 4)** **Case 18-8 (Question 1)**
7	Patient education regarding correct use of inhalation devices is frequently not done but is absolutely essential for successful treatment. There are now multiple types of inhalers (including	**Case 18-2 (Questions 1, 2, 10)** **Case 18-3 (Questions 3, 4)** **Case 18-4 (Questions 3, 5)**

	smart devices), with online video demonstrations and printable patient instructions. Conveying the concept of preventative therapy to the patient, and how to achieve it, in simple and understandable terms, is of paramount importance.	**Case 18-8 (Question 3)** **Case 18-9 (Questions 2, 3)**
8	Following expert guidelines reduces airway inflammation long term, which in turn improves multiple outcomes, including reductions in emergency department visits, hospitalizations, costs, and enhances overall quality of life.	**Case 18-2 (Question 11)** **Case 18-3 (Question 2)** **Case 18-4 (Questions 2–4)** **Case 18-5 (Question 1)** **Case 18-8 (Questions 1, 2)** **Case 18-9 (Question 1)**

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role (**Fig. 18-1**). Airway inflammation also causes an increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Bronchospasm is another key feature of asthma.[2] In susceptible persons, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an increase in the existing bronchial hyperresponsiveness to a variety of stimuli.[2] In 2019, and estimated 25.1 million Americans

carried a diagnosis of asthma, a prevalence of approximately 7.8%.[3] It is an underdiagnosed and undertreated condition that is estimated to have overall costs of roughly $80 billion annually in the United States.[4] Asthma was the cause of 1.6 million emergency department (ED) visits in 2017, is one of the leading causes of lost school days in children, and is a common cause of lost workdays among adults.[2,3] Mortality from asthma has decreased in the 21st century, from 4657 (1.7 per 100,000) deaths in 1999 to 3441 (1.1 per 100,000) deaths in 2018, but has been largely stable since 2011 in the United States, according to the Centers for Disease Control and Prevention.[5] However, morbidity and mortality are still unacceptably high, especially in inner-city minority populations. This chapter emphasizes the Global Initiative for Asthma (GINA) 2020,[1] National Institutes of Health (NIH) Expert Panel Report (EPR-3)[2] including the 2020 focused updates, and European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines. Application of the principles of these guidelines by clinicians and patients is vital to further reducing asthma morbidity and mortality.

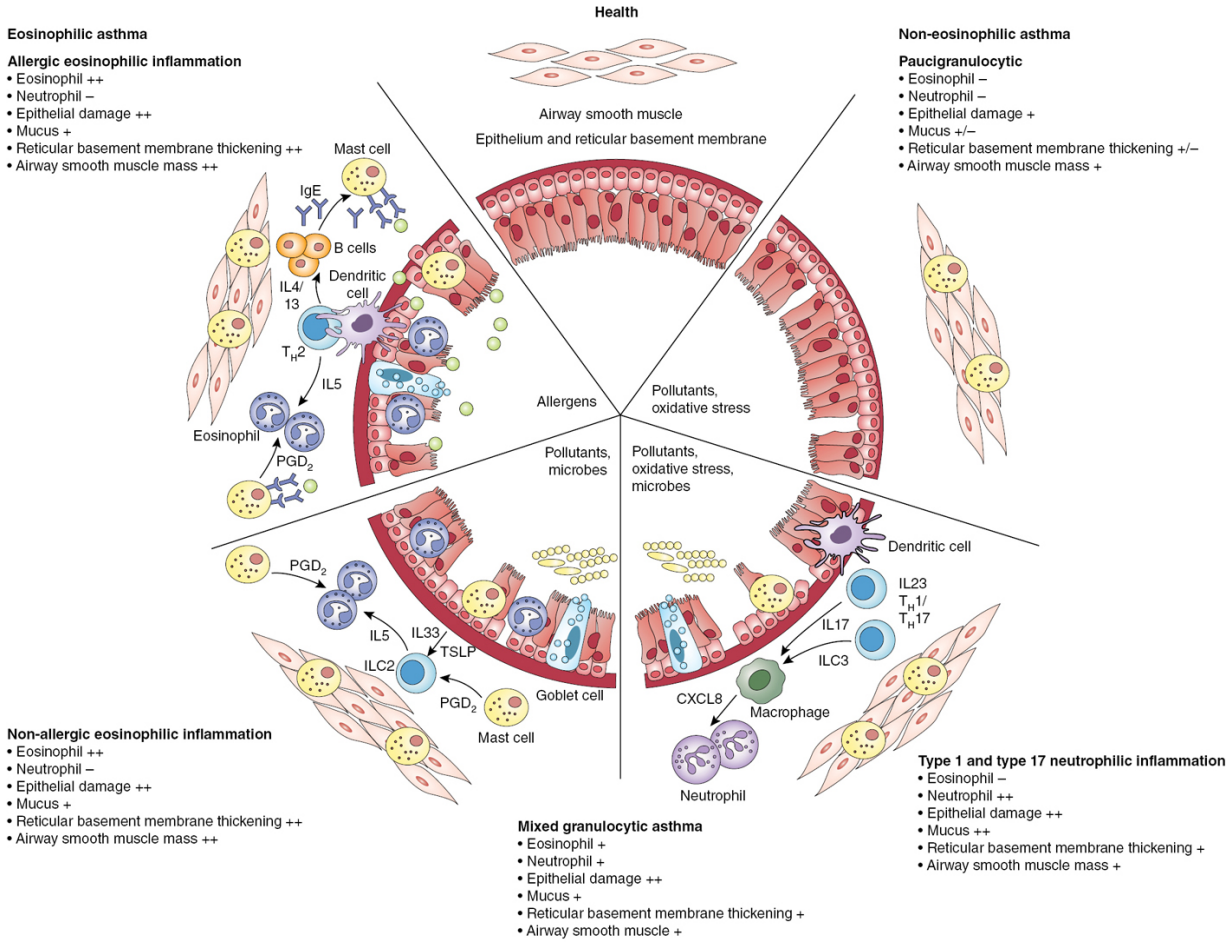


Figure 18-1 Mechanisms and characteristic pathologic features of asthma immunopathology. (Adapted from Papi A, Brightling C, Pedersen SE, et al. Asthma. *Lancet*. 2018;391(10122):783–800. © 2017 Elsevier. With permission.)

Etiology

PHENOTYPIC PRESENTATIONS

Asthma is a heterogeneous disease categorized into one of several phenotypes, which is particularly important in the workup of poorly controlled asthma. However, a given patient may have more than one phenotypic presentation (see Fig. 18-1).[1]

The most common phenotype, termed *allergic* asthma, is most often found to involve eosinophilic and immunoglobulin E (IgE)-associated inflammation, and typically responds well to inhaled

corticosteroids (ICSs).[1,6] This includes the majority of childhood-onset disease, and is usually associated with atopy, which is the genetic predisposition for the development of IgE-mediated response to common aeroallergens. Atopy is the strongest predisposing factor in the development of asthma.[2] A very common presentation of asthma is a child with a positive family history of asthma and allergy to tree and grass pollen, house dust mites, household pets, and molds.

Nonallergic asthma is a less common phenotype, where the sputum may still contain eosinophils, but may also contain neutrophils or a mix of these types. The adult-onset asthma phenotype may also be associated with atopy, but many adults with asthma have a negative family history and negative skin tests to common aeroallergens. Some of these patients may have Samter triad: nasal polyps, aspirin sensitivity, and asthma. Both nonallergic and adult-onset phenotypes are less likely to be fully responsive to ICSs.[1,7] In fact, a recent trial found that many patients with persistent asthma and low sputum eosinophils failed to respond to ICSs, which is the standard controller therapy.[8]

Occupational asthma, a subset of adult-onset asthma, results from workplace exposure to various organic and inorganic substances including chemicals, wood dust, enzymes, and metals. This should be promptly investigated in adult-onset asthma because it represents a modifiable trigger that can be eliminated in these patients.[9]

Obesity-associated asthma, which is considered by some to be a separate phenotype, is, at the very least, another modifiable factor that can be present across phenotypes. Although the mechanisms underlying obesity's role in asthma are unclear, it is increasingly apparent that obesity can make it more difficult to attain adequate control of symptoms.[10]

For unknown reasons, in some patients, the failure to adequately minimize severe airway inflammation and bronchoconstriction results in structural changes characterized by increased smooth muscle and goblet cell hypertrophy and angiogenesis. These alterations in functional bronchial anatomy, termed *airway remodeling*, may lead to persistent airflow limitation, representing another phenotype.[1,7,11]

Although not a single phenotype, asthma/chronic obstructive pulmonary disease (COPD) overlap may be present in >20% of those who have been diagnosed with asthma or COPD, depending on the subset of patients studied.[12] Associated with both symptoms of asthma and COPD, this frequently includes a history of smoking or long-term exposure to biomass fuel. Because the "asthma portion" of this disease always requires an anti-inflammatory agent, correct diagnosis is vital because it is crucial to not mistakenly treat these patients as having purely COPD.

ENDOTYPES

The current paradigm of asthma inflammatory "endotypes," which is a particular cascade of interactions with certain cells and mediators that underlie the phenotypic presentation of a disease, includes T helper (Th2), high asthma. This pathway is mapped out to a greater degree and is driven by interleukin (IL)-4, IL-5, and IL-13 cytokines and eosinophilic inflammation.[1,6,7] Type 2 (T2)-low asthma is less well defined, but more often involves noneosinophilic-associated (neutrophilic or paucigranulocytic) airway inflammation and may be linked with a number of cytokines such as IL-17 produced by Th17 cells.[1,6,7] This latter endotype has proved particularly difficult to treat, with targets for therapy of T2-low disease being a focus of active research. Moreover, it is apparent that some patients have an overlap of both endotypes.[6,7,13]

BIOMARKERS

Used as a method to phenotype and guide the treatment of severe asthma, there are currently a small number of biomarkers in routine clinical use, but more are being elucidated in the research arena. Blood (which is easier to attain) and sputum eosinophils can be helpful in both monitoring and guiding the treatment of severe asthma.[14] When IgE is bound to mast cells and basophils, the binding of an allergen to these cross-linked IgE receptors results in degranulation of these cells, resulting in the release of inflammatory mediators (see Fig. 18-1). The sensitization to this allergen–IgE

complex is strongly linked to asthma, and can be both quantified as skin testing in initial evaluation of inhalant allergens in asthma and measured as serum IgE, used to guide anti-IgE treatment. One biomarker of airway inflammation, nitric oxide, can be measured by determining the fractional concentration of exhaled nitric oxide or FeNO level.[14] Although not essential in the diagnosis of asthma, FeNO has been used as a treatment guide in asthma refractory to treatment on high-dose ICSs, has been found to be elevated during periods of exacerbations, and is measurably decreased with administration of ICSs but not β_2-agonists.[1,14–16] The ERS/ATS guidelines suggest that when combined with blood eosinophils, FeNO >19.4 ppb may help in choosing which patients with severe asthma are most likely to benefit from anti-IgE therapy,[15] whereas the NIH states that although FeNO use is not required, it may be utilized as part of a comprehensive set of diagnostic and monitoring parameters.[16] The utility of periostin, an extracellular protein associated with IL-13, is currently being evaluated as another biomarker of T2 inflammation.[17]

Pathophysiology

Recent literature has focused on the “hygiene hypothesis,” an imbalance of Th2 and Th1 type T lymphocytes, to explain the marked increase in Westernized countries. Although genetics can undoubtedly play a role in the development of some patients with asthma,[18–20] researchers have also identified that the microbiology of the environment of young children can determine the likelihood of the occurrence of asthma, providing some evidence that is supportive of this epigenetic hygiene hypothesis.[21] Whether purposeful modifications of the microbiota can be designed to lessen the chance of asthma developing in a given household is undetermined as of yet.

Asthma is caused by a complex interaction between inflammatory cells and mediators. As noted in the definition of asthma, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells are of

central importance. The bronchial epithelium in patients with asthma has been described as fragile, with various abnormalities including destruction of ciliated cells and overexpression of epidermal growth factors.[1,2] Figure 18-1 depicts the complex interaction of cells and mediators associated with airway inflammation.

After exposure to an asthma-precipitating factor (eg, aeroallergen), inflammatory mediators are released from bronchial mast cells, macrophages, T lymphocytes, and epithelial cells. These mediators direct the migration and activation of other inflammatory cells, most notably eosinophils, to the airways.[1,6,13] Eosinophils release biochemicals (eg, major basic protein and eosinophil cationic protein) that cause airway injury, including epithelial damage, mucous hypersecretion, and increased reactivity of smooth muscle.[1,2]

T2-high mediators include Th2 lymphocytes that release the cytokines IL-4, IL-5, and IL-13, which at least partially control the activation and enhanced survival of eosinophils.[1,13] The complexity of airway inflammation is indicated by the fact that >100 inflammatory and cell signaling mediators of varying types are being investigated for a role in the pathophysiology of asthma.[6] In addition, at least 18 chemokines (eg, eotaxins) that are important in the delivery of eosinophils to the airways have been identified. Studies have shown the efficacy of monoclonal antibodies against IL4, IL5, and IL13.[22] See Case 18-8 later in this chapter regarding biologics. Other potential targets for treatment of severe asthma continue to be discovered.[13,19]

Hyperreactivity (defined as an exaggerated response of bronchial smooth muscles to trigger stimuli) of the airways to physical, chemical, immunologic, and pharmacologic stimuli is pathognomonic of asthma.[2] Examples of these stimuli include inhaled allergens; respiratory viral infection; cold, dry air; smoke; other pollutants; and methacholine. Endogenous stimuli that can worsen asthma include poorly controlled rhinitis, sinusitis, and gastroesophageal reflux disease.[2] In addition, premenstrual asthma has been reported, but the exact hormonal mechanism is not known.[23] Although patients with allergic rhinitis, chronic bronchitis, and cystic fibrosis also

experience bronchial hyperreactivity, these patients do not experience bronchiolar constriction as severely as do patients with asthma. The degree of bronchial hyperreactivity correlates with the clinical course of disease, which is characterized by periods of remissions and exacerbations. During times of remission, a more intense stimulus is required to produce bronchospasm than it is during times of increased symptoms. Numerous theories have been proposed to explain the bronchial hyperreactivity found in asthma, yet none fully explains the phenomenon. Inflammation appears to be the primary process in the pathogenesis of bronchial hyperreactivity; however, neurogenic imbalances in the airways also may play a significant role.[6,7] Hyperreactivity can be measured in the physician's office by having the patient inhale small escalating concentrations of nebulized methacholine or histamine or by exercise (eg, treadmill). The concentration of aerosolized methacholine or histamine that decreases the forced expiratory volume in 1 second (FEV_1) by 20% is referred to as the *PD20* or the *PC20* (provocative dose or provocative concentration that decreases the FEV_1 by 20%).[2] An indicator of optimal anti-inflammatory therapy is an increase in the PD20 with time because the airways become less inflamed and therefore less hyperreactive. Biphasic inflammation, "late phase" versus "early phase," is another concept related to asthma (**Fig. 18-2**). The inhalation of specific allergens in patients with atopic asthma produces immediate bronchoconstriction (measured by a drop in peak expiratory flow [PEF] or FEV_1) that spontaneously improves in an hour or is reversed easily by inhalation of a β_2-agonist. Although this early asthmatic response (EAR) is blocked by the preadministration of β_2-agonists or theophylline, a second response often occurs ~4 to 8 hours later. This late asthmatic response (LAR) often is more severe, more prolonged, and more difficult to reverse with bronchodilators than is the EAR. The LAR is associated with the influx of inflammatory cells and mediators, as described previously. Bronchodilators do not block the LAR to allergen challenge; corticosteroids block the LAR, but do not affect the EAR.[2] Pathologic changes found at autopsy performed on patients with asthma include

(a) marked hypertrophy and hyperplasia of the bronchial smooth muscle, (b) mucous gland hypertrophy and excessive mucus secretion, and (c) denuded epithelium and mucosal edema owing to an exudative inflammatory reaction and inflammatory cell infiltration.[24] Hyperinflation of the lungs from air trapping with extensive mucous plugging is found at autopsy in patients who have died of acute asthma attacks,[24] but these changes also are seen at autopsy in patients with asthma dying of other causes. The bronchial smooth muscle hypertrophy and mucous hypersecretion are secondary to the chronic inflammatory response.[2,15]

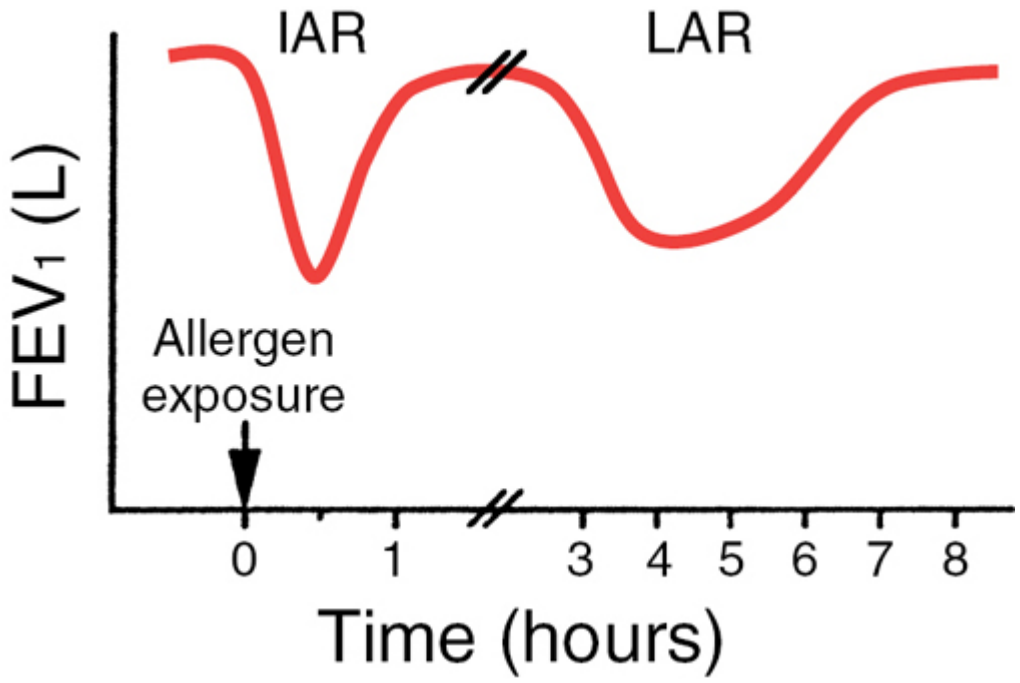


Figure 18-2 Typical immediate and late asthmatic responses seen after exposure to relevant allergen. Immediate asthmatic response (IAR) occurs within minutes, whereas late asthmatic response (LAR) occurs several hours after exposure. Patients may demonstrate isolated IAR, isolated LAR, or dual responses. FEV_1, forced expiratory volume in 1 second. (Adapted with permission from Helms RA, Quan DJ. *Textbook of Therapeutics: Drug and Disease Management*. 8th ed. Lippincott Williams & Wilkins; 2006.)

Symptoms

The heterogeneity of asthma is reflected best in its clinical presentation. Classically, patients with asthma present with intermittent episodes of expiratory wheezing, coughing, and dyspnea. Some patients, however, experience chest tightness or a chronic cough that is not associated with wheezing. There is a wide spectrum of disease severity, ranging from patients with occasional, mild bouts of breathlessness to patients who wheeze daily despite continuous high dosages of medication. In addition, the severity of asthma may be influenced by environmental factors (eg, specific seasonal allergens). Symptoms often are associated with exercise and sleep (refer to Cases 18-9).

Classification of asthma severity is of major importance in defining initial long-term treatment. Within three age groups, GINA 2020 uses the classifications of mild, moderate, and severe asthma, which are determined after a patient has been on controller treatment for several months.[1] These steps represent the level of medication required to control symptoms and minimize exacerbations. This categorization is not static and may change multiple times over months or years (**Figs. 18-3**–**18-7**). Mild asthma is defined as asthma that is well controlled with step 1 or 2 treatment. Moderate asthma is defined as asthma that is well controlled on step 3 treatment. Severe asthma is defined as asthma that requires step 4 or 5 treatment.[1] Another key concept that is of extreme significance, particularly in patients with severe asthma, is differentiating between controlled and uncontrolled asthma. There may be a large disconnect between patient perception of symptoms and the clinician's viewpoint on asthma control. A study of 8000 European patients revealed that >80% of subjects who had experienced major life disruptions owing to uncontrolled asthma (ED visits, hospitalizations, or a course of oral steroids) over the previous 12 months considered that their asthma was "controlled."[25]

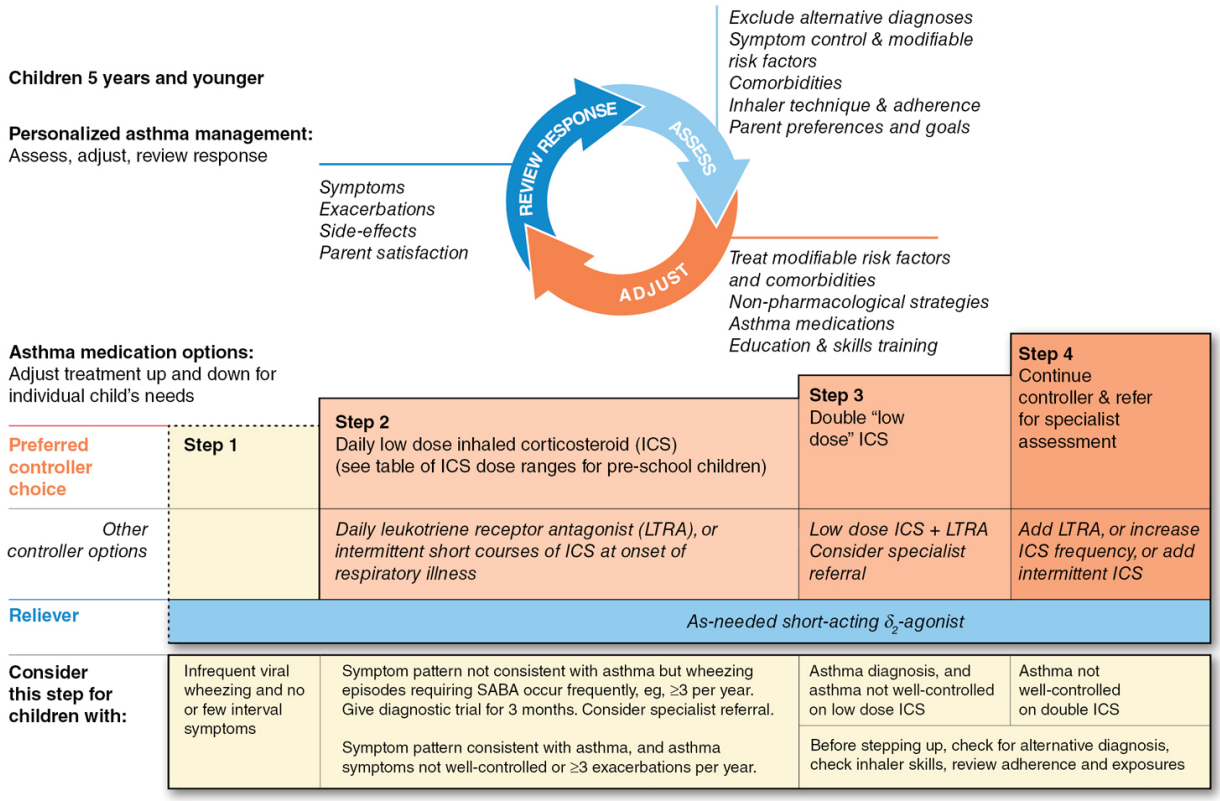


Figure 18-3 Personalized management of asthma in children ages 5 years and younger.

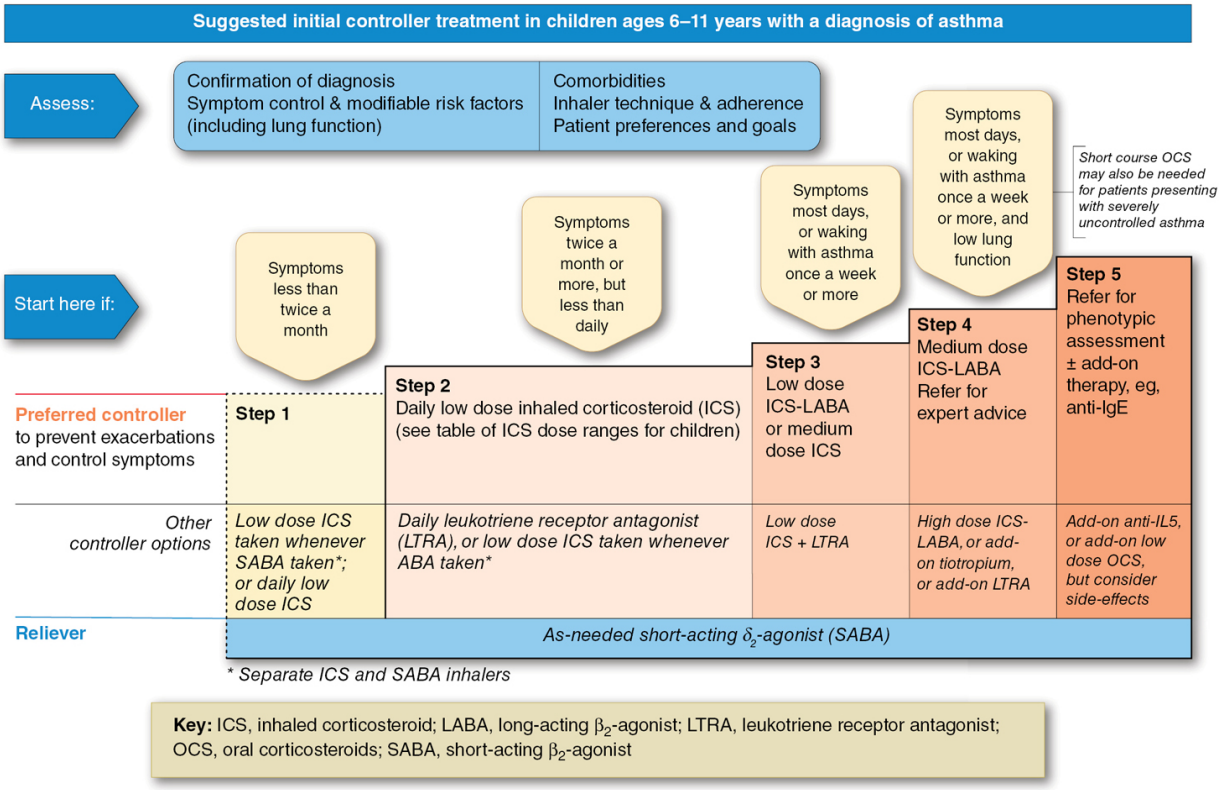


Figure 18-4 Selecting initial controller treatment in children ages 6 to 11 years with a diagnosis of asthma.

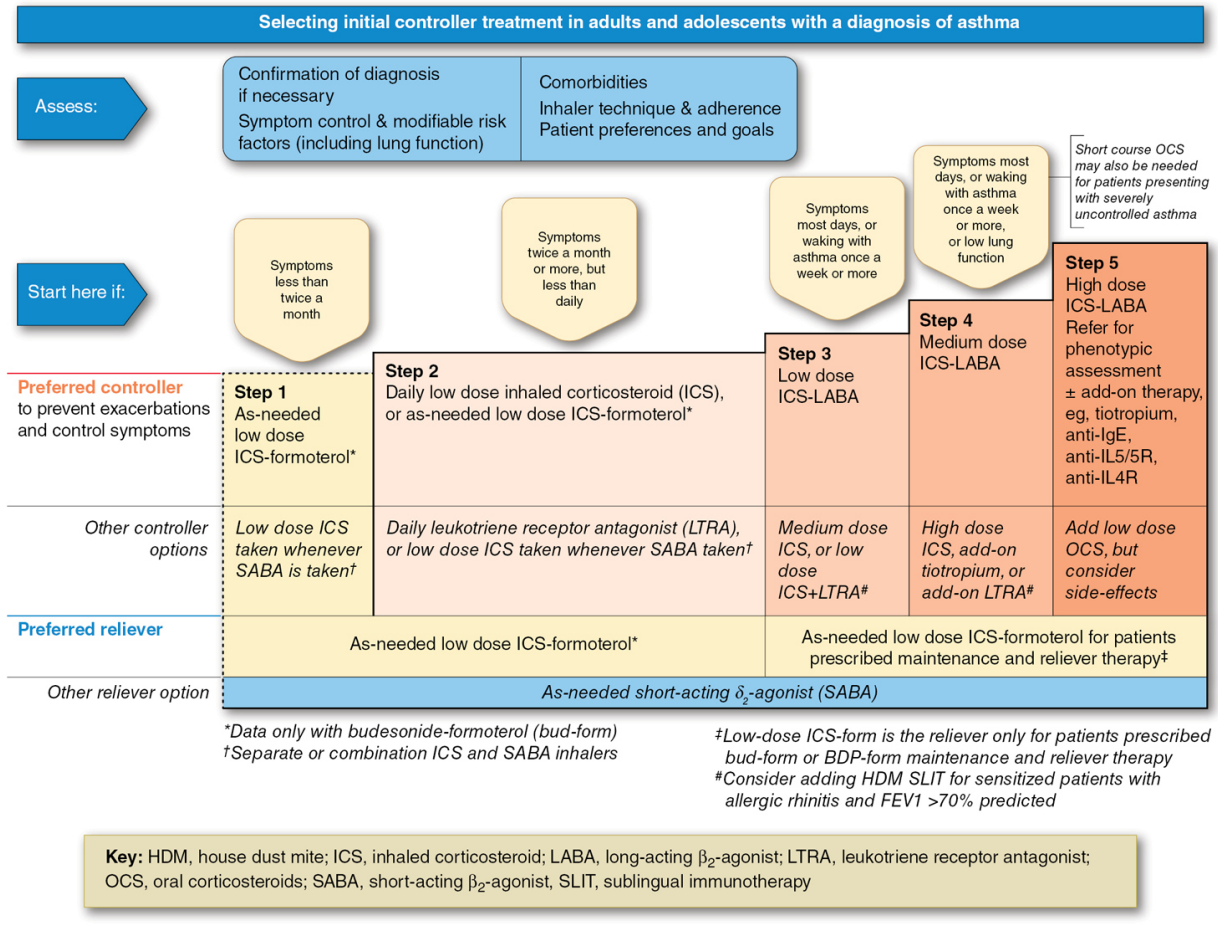


Figure 18-5 Selecting initial controller treatment in adults and adolescents with a diagnosis of asthma.

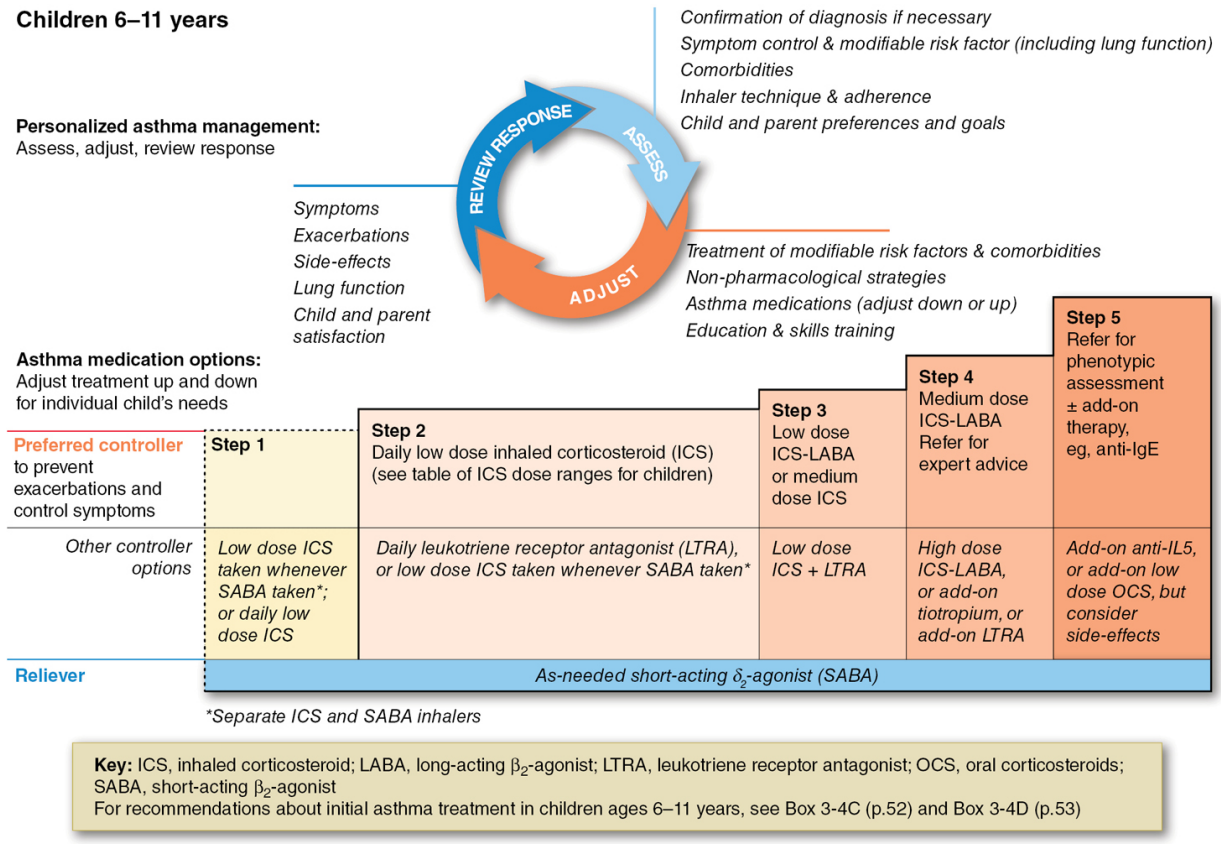


Figure 18-6 Personalized management for children ages 6 to 11 years to control symptoms and minimize future risk.

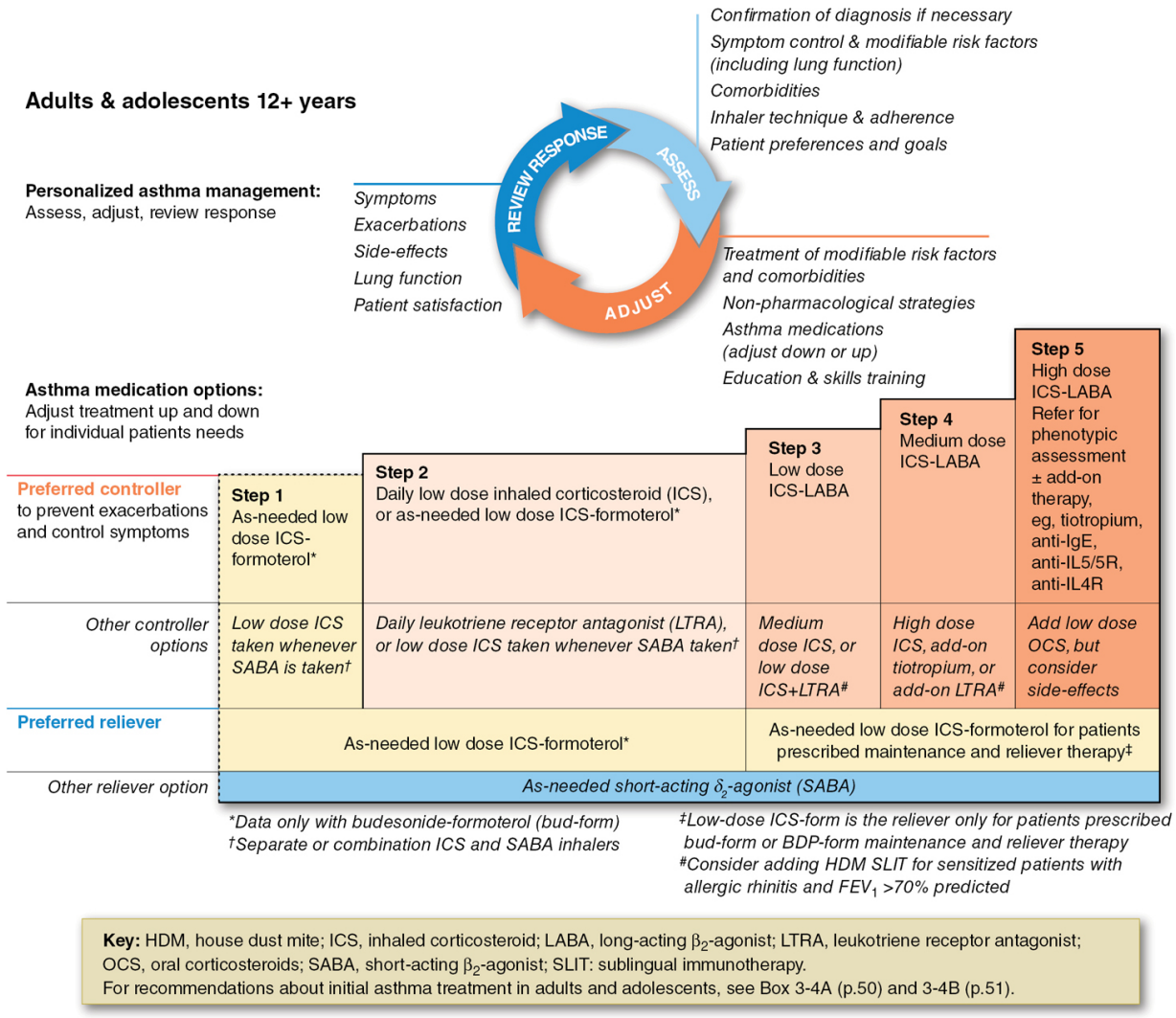


Figure 18-7 Personalized management for adults and adolescents to control symptoms and minimize future risk.

Diagnosis and Monitoring

HISTORY

The diagnosis of asthma is based primarily on a detailed history of intermittent symptoms of wheezing, chest tightness, shortness of breath, and coughing. These episodes may be worse seasonally (eg, springtime or late summer and early fall) or in association with exercise. History of nocturnal symptoms with awakening in the early morning is a critical component to assess. In addition, history of symptoms after exposure to other common triggers (eg, cats, bleach,

perfume, secondhand tobacco smoke) is typical (**Table 18-1**).[1,2] A positive family history and the presence of rhinitis or atopic dermatitis also are significant. After a careful history is obtained, skin testing may be useful in identifying triggering allergens, but it is only of supportive value in the diagnosis of asthma. A common adage, "all that wheezes is not asthma" is true, of which a prime example is the confusing term "cardiac asthma," which is not asthma at all, but is used to denote wheezing caused by cardiogenic pulmonary edema. A significant minority, up to one-third of patients in one series, may have been misdiagnosed with asthma, and instead were found to have alternate explanations for their symptoms.[26]

Table 18-1
Sample Questions for the Diagnosis and Initial Assessment of Asthma

A "yes" answer to any question suggests that an asthma diagnosis is likely.[a]
In the past 12 months:
Have you had a sudden severe episode or recurrent episodes of coughing, wheezing (high-pitched whistling sounds when breathing out), chest tightness, or shortness of breath? Have you had colds that "go to the chest" or take >10 days to get over? Have you had coughing, wheezing, or shortness of breath during a particular season or time of the year? Have you had coughing, wheezing, or shortness of breath in certain places or when exposed to certain things (eg, animals, tobacco smoke, perfumes)? Have you used any medications that help you breathe better? How often? Are your symptoms relieved when the medications are used?
In the past 4 weeks, have you had coughing, wheezing, or shortness of breath?
At night that has awakened you? On awakening? After running, moderate exercise, or other physical activity?

[a] These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions has not been assessed.

PULMONARY FUNCTION TESTS

The diagnosis of asthma is based in part on demonstration of reversible airway obstruction. A brief discussion of tests to detect reversibility of airway obstruction is important. Furthermore, a short summary of arterial blood gases (ABGs) is pertinent here in assessing the severity of asthma exacerbations.

Spirometry

Lung volumes often are measured to obtain information about the size of the patient's lungs because pulmonary diseases can affect the volume of air that can be inhaled and exhaled. The tidal volume is the volume of air inspired or expired during normal breathing. The volume of air blown off after maximal inspiration to full expiration is defined as the vital capacity (VC). The residual volume (RV) is the volume of air left in the lung after maximal expiration. The volume of air left after a normal expiration is the functional residual capacity (FRC). Total lung capacity (TLC) is the VC plus the RV. Patients with obstructive lung disease have difficulty with expiration; therefore, they tend to have a decreased VC, an increased RV, and a normal TLC. Classic restrictive lung diseases (eg, sarcoidosis, idiopathic pulmonary fibrosis) present with decrements in all lung volumes.[27,28] Patients also may have mixed lesion diseases, in which case the classic findings are not apparent until the disease has advanced considerably. The spirometer also can be used to evaluate the performance of the patient's lungs, thorax, and respiratory muscles in moving air into and out of the lungs. Forced expiratory maneuvers amplify the ventilation abnormalities produced. The single most useful test for ventilatory dysfunction is the FEV. The FEV is measured by having the patient exhale into the spirometer as forcefully and completely as possible after maximal inspiration. The resulting volume curve is plotted against time (**Fig. 18-8**) so that expiratory flow can be estimated.

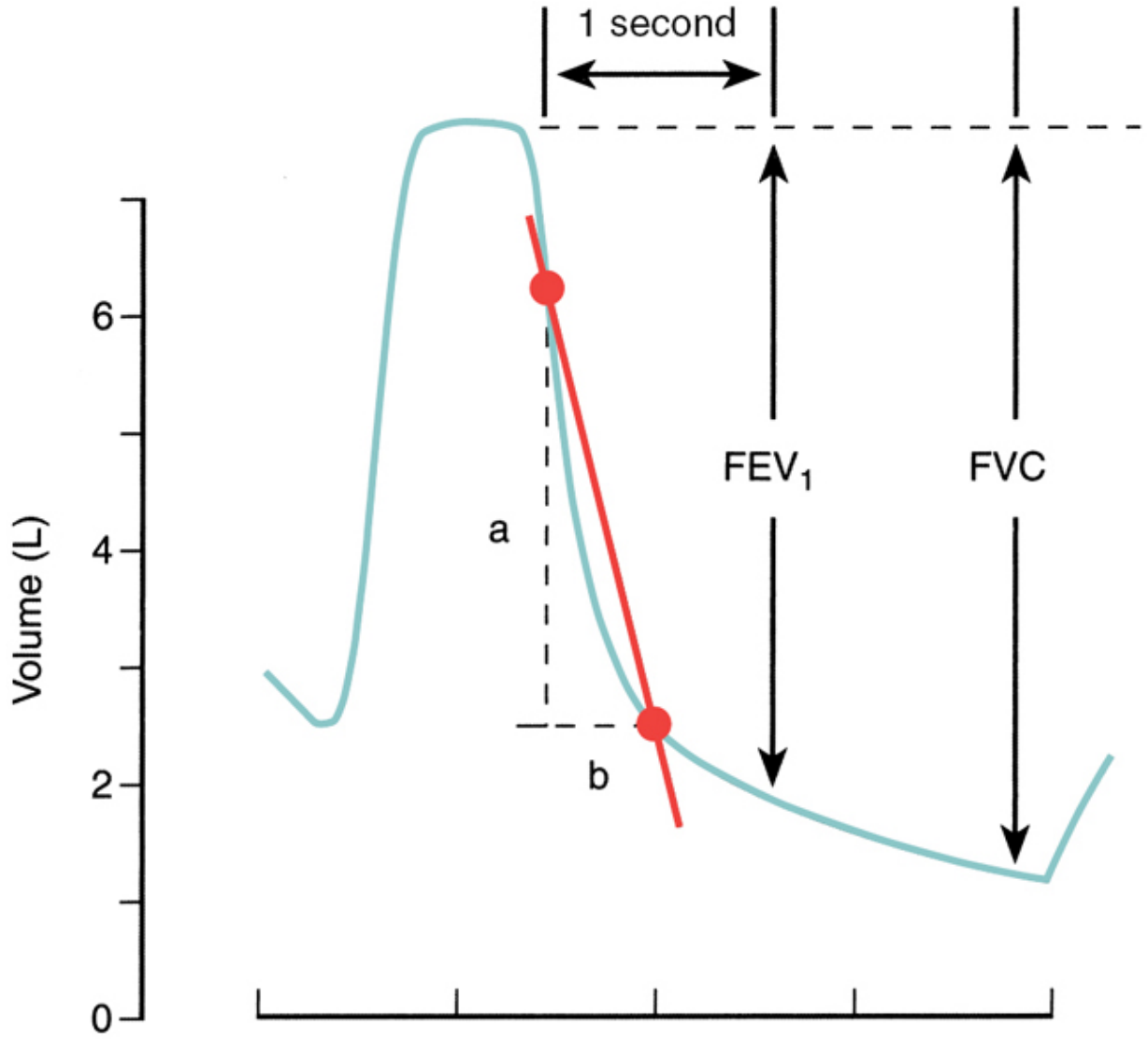


Figure 18-8 Volume–time curve from a forced expiratory maneuver. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Standard spirometers contain pneumotachographs in the mouthpieces that can measure airflow directly. A number of important measures of lung function are made from the resulting flow–volume curves. The advantages of this technique include a display of simultaneous flows at any lung volume, visual estimation of patient effort and cooperation, high reproducibility within as well as across individuals, and an analysis of the distribution of flow limitation.[28] The FEV_1 of the forced vital capacity (FVC, the maximal

volume of air exhaled with maximally forced effort from a position of maximal inspiration) commonly is measured to determine the dynamic performance of the lung in moving air. The FEV_1 usually is expressed as a percentage of the total volume of air exhaled and is reported as the FEV_1-to-FVC ratio.[27] Healthy persons generally can exhale at least 75% to 80% of their VC in 1 second and almost all of it in 3 seconds. Thus, the FEV_1 normally is 80% of the FVC. The patient's breathing ability is compared against "predicted normal" values for patients with similar physiologic characteristics because lung volumes depend on age, race, sex, height, and weight. For example, an average-sized young adult male may have an FVC of 4 to 5 L, and a corresponding FEV_1 of 3.2 to 4 L. The FEV_1 and the FVC are the most reproducible of the pulmonary function tests.

For a video that shows how to take a lung function test, see

https://www.nationaljewish.org/conditions/tests-procedures/pulmonary-physiology/pulmonary-function/spirometry.

Peak expiratory flow

The PEF is the maximal flow that can be produced during forced expiration. The PEF can be measured easily with various handheld peak flow meters and commonly is used in EDs and clinics to quickly and objectively assess the effectiveness of bronchodilators in the treatment of acute asthma attacks. The changes in PEF generally parallel those of the FEV_1; however, the PEF is a less reproducible measure than the FEV_1.[1] A healthy, average-sized middle-aged adult female typically has a PEF of 400 to 500 L/minute. Peak flow meters come with a chart for patients to determine their predicted normal PEFs based on their sex, age, and height. These devices are affordable for most, available without a prescription, and can be an essential part of home monitoring, particularly to those patients who

are not as sensitive to changes in lung function or who have a history of exacerbations requiring oral corticosteroids (OCSs). It is important to use the same device when documenting PEF because there is some variation between brands.

For a video that shows how to take a lung function test,

https://www.lung.org/lung-health-diseases/lung-disease-lookup/asthma/living-with-asthma/managing-asthma/measuring-your-peak-flow-rate.

OBSTRUCTIVE VERSUS RESTRICTIVE AIRWAY DISEASE

Generally, pulmonary disorders fall into two categories: those that restrict the lungs and thorax and those that obstruct them. In simplest terms, restrictive disease limits airflow during inspiration, and obstructive disease limits airflow during expiration. Restrictive disease results from a loss of elasticity (eg, fibrosis, pneumonia) or physical deformities of the chest (eg, kyphoscoliosis), with a consequent inability to expand the lung and a reduced TLC, although the FEV_1/FVC ratio may still be >70%. Restrictive airway diseases limit lung expansion, whereas obstructive airway diseases (eg, bronchitis, asthma) narrow air passages, create air turbulence, and increase resistance to airflow. In obstructive diseases, maximal expiration may begin at higher than normal lung volumes, and the expiratory flow is depressed.

REVERSIBLE AIRWAY OBSTRUCTION

Spirometry often is used to determine the reversibility of airway disease. Although many generally associate reversibility with bronchospasm, therapy can improve airflow by reversing any of the causative pathologic processes of asthma described previously. Significant clinical reversibility produced from bronchodilators is determined by the tests outlined in **Figure 18-9**. The FEV_1 is considered the gold standard test for determining reversibility of

airway disease and bronchodilator efficacy. Significant clinical reversibility is defined as a >200 mL and >12% improvement in FEV_1 after administration of a short-acting bronchodilator.[1] An improvement of 20% in FEV_1 provides noticeable subjective relief of respiratory symptoms in most patients. For patients with a very low baseline FEV_1 (eg, <1 L), an absolute improvement of 250 mL sometimes is considered a better indicator of therapeutic benefit than is assessing the percentage of change. In either case, the patient's subjective clinical impression also should be considered when using pulmonary function testing and drug challenges as predictors for future therapy.

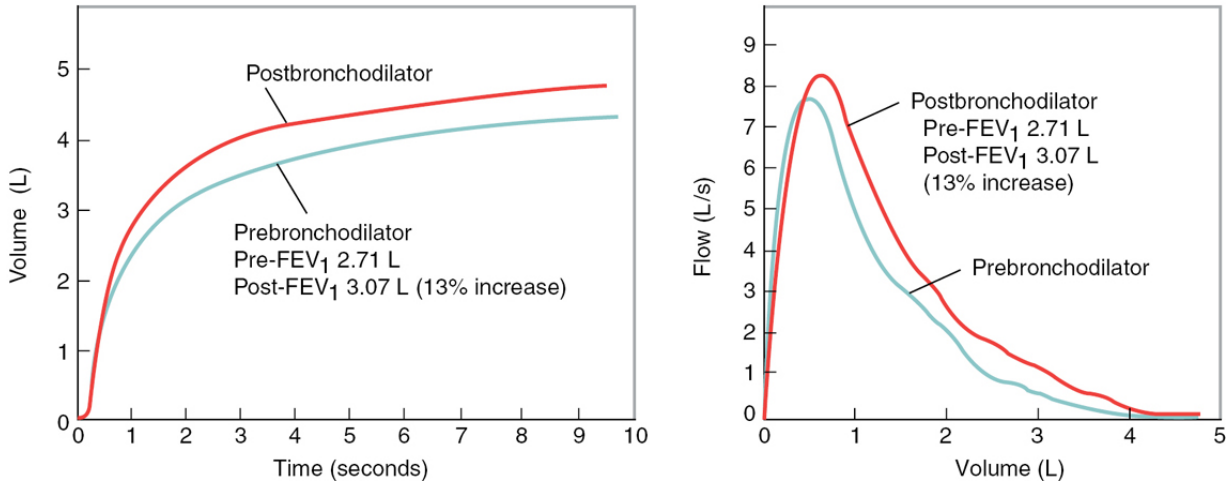


Figure 18-9 Interpretation of results of spirometry. The graphs depicted are for illustration only. The interpretation of flow rates may vary with the age of the patient. FEV_1, forced expiratory volume in 1 second. (Adapted from National Institutes of Health. *Expert Panel Report 2. Guidelines for the Diagnosis and Management of Asthma*. National Heart, Lung, and Blood Institute; 1997. NIH publication no. 97-4051.)

BLOOD GAS MEASUREMENTS

The best indicators of overall lung function (ventilation and diffusion) are the ABGs (ie, arterial partial pressure of oxygen [Pao_2], arterial partial pressure of carbon dioxide [$Paco_2$], and pH). Although ABG

measurements also are dependent on the patient's cardiovascular status, they are indispensable in assessing both acute and chronic changes in pulmonary patients (see Chapter 26, Acid–Base Disturbances, for a review of ABGs). However, obtaining ABGs is more painful for the patient than is a venous blood draw and is only required in the more severe cases. Another means of assessing the patient's ability to oxygenate tissues adequately is to measure oxygen saturation, which is described by the following equation:

$$\text{O}_2\text{ saturation} = \text{Quantity of O}_2\text{ actually bound to hemoglobin} / \text{Quantity of O}_2\text{ that can be bound to hemoglobin} \times 100. \quad \textbf{(Eq. 18-1)}$$

According to this equation, oxygen saturation is the ratio between the actual amount of oxygen bound to hemoglobin and the potential amount of oxygen that could be bound to hemoglobin at a given pressure. The denominator in the preceding equation is the oxygen capacity. The normal oxygen saturation of arterial blood at a Pao_2 of 100 mm Hg is 97.5% and that of mixed venous blood ($ScVO_2$) at a Po_2 of 40 mm Hg is about 75%.

Oxygen saturations can be measured continuously with transcutaneous monitors. This type of monitoring (pulse oximetry) is extremely helpful in determining whether supplemental oxygen therapy is indicated in patients with various chronic respiratory diseases. At a Pao_2 of <60 mm Hg, oxygen saturation begins to drop precipitously (**Fig. 18-10**). Although a significant elevation in pCO_2 (hypercapnia) may occur in severe asthma exacerbations, portending a need for intubation, a variety of acid–base and blood gas abnormalities may be seen in various stages of an asthma attack.

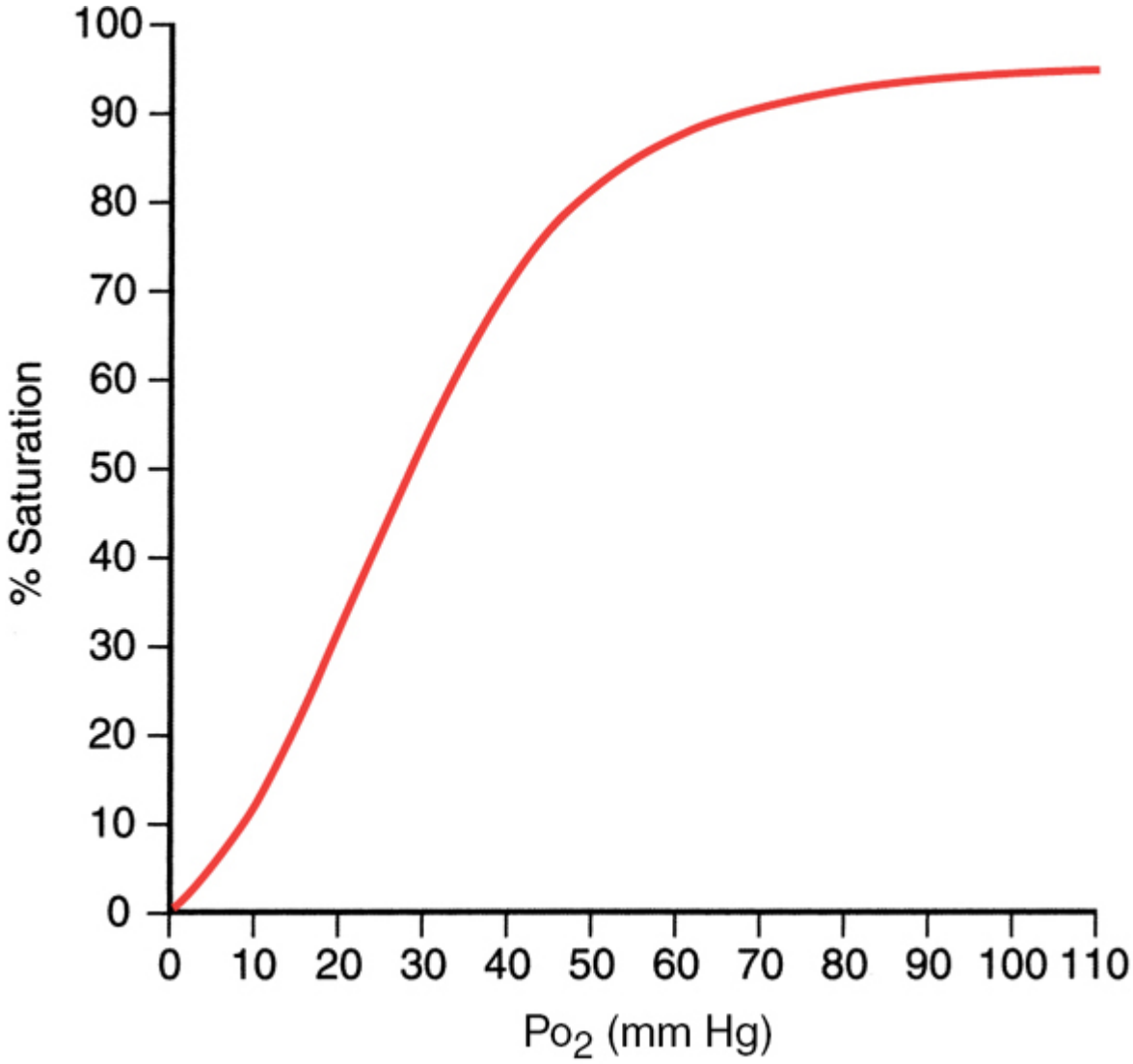


Figure 18-10 The oxygen dissociation curve reveals that the percent saturation of hemoglobin increases almost linearly with increases in the arterial O_2 tension until a partial pressure of arterial oxygen (Pao_2) of 55 to 65 mm Hg is reached. At Pao_2 values above this, the increase in hemoglobin saturation becomes proportionately less, and relatively little additional oxygen is added to the hemoglobin despite large increases in Pao_2. (Reprinted with permission from Klabunde RE. *Cardiovascular Physiology Concepts*. 3rd ed. Wolters Kluwer; 2021.)

Goals of Therapy

Reduce impairment: (a) Prevent chronic and troublesome symptoms (eg, coughing or breathlessness in the night, in the early morning, or after exertion); (b) maintain (near) "normal" pulmonary function; (c) maintain normal activity levels (including exercise, other physical activities, and attendance at work or school); and (d) meet patients' and families' expectations of and satisfaction with asthma care.[1,2]

Reduce risk: (a) Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations; (b) prevent progressive loss of lung function—for children, prevent reduced lung growth; and (c) provide optimal pharmacotherapy with minimal or no adverse effects.

CASE 18-1

QUESTION 1: Q.C., a 6-year-old 44.09-pound (20-kg) girl, presents to the ED with dyspnea and coughing that have progressively worsened during the past 2 days. These symptoms were preceded by 3 days of an upper viral respiratory infection. She has experienced several bouts of acute bronchitis in the past 2 years and was hospitalized with pneumonia 3 months ago. She is not being treated with any medications as an outpatient. Physical exam reveals an anxious-appearing young girl in moderate respiratory distress with audible wheezing, coughing, a prolonged expiratory phase, a hyperinflated chest, and obvious use of sternocleidomastoid and trapezius muscles to help her breathe. Bilateral inspiratory and expiratory wheezes are heard on auscultation. Vital signs: respiratory rate (RR) 30, blood pressure (BP) 110/83, pulse 130 beats/minute, and pulsus paradoxus measured at 18 mm Hg. Her O_2 saturation is 89%, so she is started on 1 L of oxygen by face mask, which is titrated up to maintain a saturation of 94% to 98%. Albuterol, 2.5 mg per nebulizer is administered every 20 minutes in three doses, plus budesonide 1000 µg per nebulizer in one dose. She initially feels better, but then begins to wheeze louder.

What signs and symptoms in Q.C. are consistent with acute bronchial obstruction? Does increased wheezing after albuterol indicate failure of treatment?

Asthma is an obstructive lung disease; therefore, the primary limitation to airflow occurs during expiration. This outflow obstruction leads to the classic findings of dyspnea, expiratory wheezes, and a prolonged expiratory phase during the ventilatory cycle.[1] Wheezing

is a whistling sound produced by turbulent airflow through a constricted opening and is usually more prominent on expiration as opposed to stridor, which is a pronounced high-pitched sound made on inspiration and is associated with significant large airway obstruction, as seen in viral croup or epiglottitis. Thus, the audible expiratory wheezing in Q.C. is compatible with bronchial obstruction. In fact, Q.C.'s obstruction is so severe that even inspiratory wheezes and decreased air movement were detected on auscultation. It is important to realize that the classic symptom of wheezing requires turbulent airflow; therefore, effective therapy of acute asthma may actually result in increased wheezing initially because airflow increases throughout the lung. As a result, Q.C.'s increased wheezing on auscultation is compatible with her clinical improvement after the albuterol nebulizer treatments. The coughing experienced by Q.C. is another common finding associated with acute asthma attacks. The coughing may be caused by stimulation of "irritant receptors" in the bronchi by the chemical mediators of inflammation (eg, leukotrienes) that are released from mast cells or from the mechanics of smooth muscle contraction. In the progression of an asthma attack, the small airways become completely occluded during expiration, and air can be trapped behind the occlusion; therefore, the patient must breathe at higher than normal lung volumes.[2] Consequently, the thoracic cavity becomes hyperexpanded, and the diaphragm is lowered. As a result, the patient must use the accessory muscles of respiration to expand the chest wall. Q.C.'s hyperinflated chest and her use of accessory muscles to assist in breathing also are compatible with obstructive airway diseases.

Occlusion of the small airways, air trapping, and resorption of air distal to the obstruction can lead to atelectasis (incomplete expansion or collapse of pulmonary alveoli or of a segment of a lobe of the lung). Localized areas of atelectasis often are difficult to distinguish from infiltrates on a chest radiograph, and atelectasis can be mistaken for pneumonia. Q.C.'s history of multiple bouts of "bronchitis" is significant and typical of many young patients with asthma. In any patient with recurring episodes of bronchial

symptoms (eg, bronchitis, pneumonia), the possible diagnosis of asthma should be investigated.

The increased pulse, RR, and anxiety experienced by Q.C. can be attributed to both the hypoxemia and the feeling of suffocation. The hypoxemia in acute asthma is caused principally by an imbalance between alveolar ventilation and pulmonary capillary blood flow, also known as ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatching. Each alveolus of the lung is supplied with capillaries from the pulmonary artery for gas exchange. When ventilation is decreased to an area of the lung, the alveoli in that area become hypoxic, and the pulmonary artery to that region constricts as a normal physiologic response. As a result, blood flow is shunted to the well-ventilated portions of the lung because of the need to preserve adequate oxygenation of the blood. The pulmonary arteries, however, are not constricted completely, and when a small amount of blood flows to the poorly ventilated alveoli, mismatching is the result. Conditions of diffuse bronchial obstruction (ie, acute asthma) increase the amount of mismatching. In addition, some mediators of acute bronchospasm (eg, histamine) further worsen mismatching by constricting bronchial smooth muscle while concurrently relaxing vascular smooth muscle. Q.C. also demonstrated a significant pulsus paradoxus. Pulsus paradoxus is defined as a drop in systolic BP of >10 mm Hg with inspiration. In general, pulsus paradoxus correlates with the severity of bronchial obstruction; however, it is not always present.[2]

EXTENT OF OBSTRUCTION

Case 18-1, Question 2: What additional tests would be helpful in assessing the extent of pulmonary obstruction in Q.C.?

Chest radiographs are routinely helpful in assessment of asthma but should be obtained in patients who are suspected of having a complication (eg, pneumonia).[1] Hyperinflated lungs and areas of atelectasis can be seen on a chest x-ray film; however, chest x-ray studies usually are negative and of little value in evaluating acute

asthma attacks. The finding of a local decrease in breath sounds in Q.C.'s left lung may justify the need for a chest x-ray study, particularly if a significant differential in air movement persists after initial therapy. A local decrease in breath sounds may indicate pneumonia, aspiration of a foreign object, pneumothorax, or merely thickened mucous plugging of a large bronchus.

Pulmonary function testing (eg, FEV_1, PEF) provides objective measurement of the degree of airway obstruction. Peak flow meters are helpful in the ED for assessing both the severity of airway obstruction and the response to bronchodilator therapy. Unfortunately, infants and many young children do not have the cognitive or motor skills necessary to perform pulmonary function tests. In one study, only 65% of children ages 5 to 16 years could complete either FEV_1 or PEF during an acute exacerbation. Because of Q.C.'s initial anxiety, the PEF should be measured after bronchodilator therapy has been initiated, when she may be calmer. One disadvantage of pulmonary function tests in acute asthma is that the forced expiratory maneuver commonly triggers coughing. ABG measurements are the gold standard for assessing very severe airway obstruction.[1,2] GINA suggests ABGs for evaluation of patients who have not responded to initial treatment, are in severe distress, or in whom the FEV_1 or PEF is <50%.

ABG measurements are indicated in patients who fail to respond adequately to initial therapy or in patients requiring hospitalization; they are not indicated at this time for Q.C. A repeat pulse oximetry at 1 hour after treatment initiation is warranted in Q.C. to ensure adequate arterial oxygen saturation.

NEED FOR HOSPITALIZATION

CASE 18-1, QUESTION 3: Q.C. may require hospitalization. Which clinical test is predictive of the need for admission or whether Q.C. will relapse if sent home from the ED? Are Q.C.'s signs and symptoms predictive of whether she will relapse and return to the ED if not hospitalized?

Although Q.C. is not able to perform spirometry, she is able to execute the PEF maneuver, and the plan is to check her PEF after 1 hour of therapy. Signs and symptom scores alone are not adequate to predict the outcome of ED treatment of asthma, but scores along with pulse oximetry and PEF or FEV_1 are helpful predictors.[2] There have been several predictive scores and pathways to determine the probability of hospital admission that do not rely on PEF of FEV_1 because these may be difficult to obtain, especially in pediatric patients. A decrease in O_2 saturations from 98% to 94% and an inspiratory-to-expiratory ratio of ≤1 to 3 were found to be the two strongest components of the Asthma Prediction Rule associated with the need for hospitalization.[29] Assessment of the response to treatment at regular intervals is essential. Primary care and emergency care management of children ages 5 years and younger with asthma exacerbations is listed in GINA.[1]

CASE 18-1, QUESTION 4: Why was albuterol selected as the bronchodilator of choice in preference to other bronchodilators such as levalbuterol, ipratropium, or subcutaneous (SC) terbutaline? Why did Q.C. receive inhaled budesonide?

Because of their potency and rapidity of action, short-acting β_2-agonists (SABAs) are considered the first choice for the treatment of acute asthma.[1,2] The bronchodilatory properties of SABAs are particularly effective in reversing early-phase asthma responses.[1,2] Although levalbuterol is effective, its increased cost and minimally different side effect profile as compared to albuterol make it unpractical for regular use.[30] Similarly, the bronchodilation from the anticholinergic drug ipratropium is of smaller magnitude than it is with inhaled SABAs.[2] Although SC terbutaline is effective in severe asthma, current guidelines discourage routine use of parenteral β_2-agonists, and most clinicians reserve their use in rare situations where nebulized albuterol is ineffective or unable to be administered. Early addition of inhaled ipratropium in adequate doses to SABAs has produced mixed results but may improve pulmonary function

tests in some patient populations.[31,32] Q.C.'s physician chose to use only inhaled SABAs initially because Q.C. was not severely ill.

Although ICSs are properly positioned as controller medication for asthma, there is evidence that administration of ICSs in acute asthma in addition to systemic steroids can decrease hospital admissions.[33,34] The prescriber decided that even if this dose of budesonide did not help her significantly, there was no harm. If she does not get admitted to this hospital, prescribing ICSs from the ED on discharge can expedite the patient getting started on appropriate therapy than waiting for the outpatient clinician to do so.[2]

Case 18-1, Question 5: Q.C. received albuterol by nebulization. Would metered-dose aerosol administration of the albuterol have been inferior? What is a comparable dose of albuterol given by metered-dose inhaler (MDI) versus via nebulizer?

Aerosols are mixtures of particles (eg, a drug–lipid mixture) suspended in a gas. An MDI consists of an aerosol canister and an actuation device (valve). The drug in the canister is a suspension or solution mixed with propellant. The valve controls the delivery of drug and allows the precise release of a premeasured amount of the product. A second aerosol device, the air jet nebulizer, mechanically produces a mist of drug. The drug is placed in a small volume of solute (typically 3 mL of saline) and then placed in a small reservoir (nebulizer) connected to an air source such as a small compressor pump, an oxygen tank, or a wall air hose. Air travels from the relatively large-diameter tubing of the air source into a pinhole-sized opening in the nebulizer. This creates a negative pressure at the site of the air entry and causes the drug solution in the bottom of the nebulizer reservoir to be drawn up through a small capillary tube, where it then encounters rapid airflow. The drug solution is forced against a small baffle that causes mechanical formation of a mist. An ultrasonic nebulizer is a type of nebulizer that uses sound waves to generate the aerosol.

Studies that compared nebulization with pressurized metered-dose aerosols in stable patients with chronic asthma have shown no

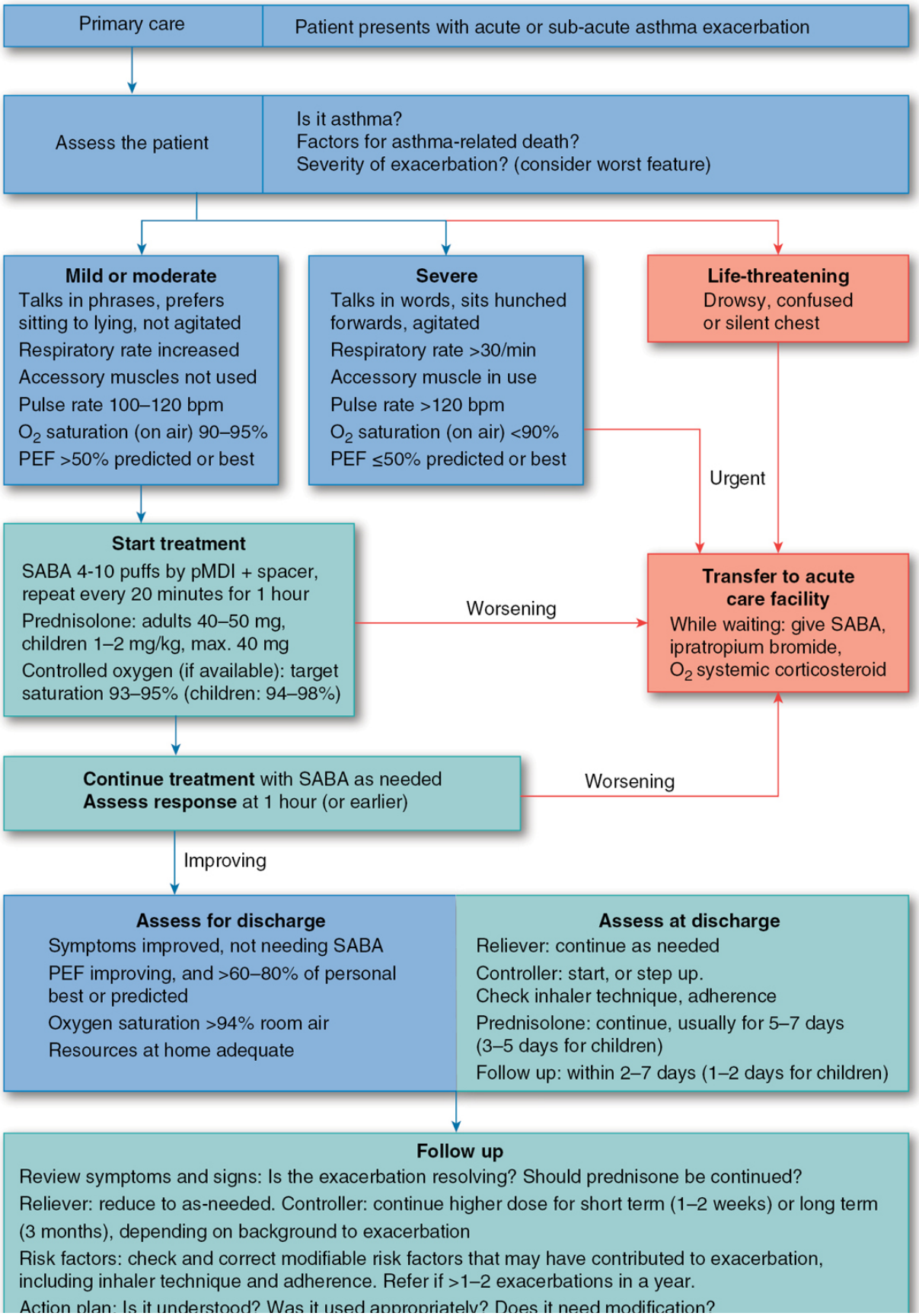
advantage among these methods of administration when equivalent doses are administered.[35] Trials comparing metered-dose aerosols of inhaled SABAs with the nebulization of those same drugs in acute asthma also have shown no significant advantage for the nebulization method of administration when the metered-dose aerosolized administration was carefully supervised by experienced personnel and a spacer device was used.[36] One pediatric randomized study from Iramain et al found that children with acute severe asthma had a significantly reduced rate of hospitalization if given ipratropium with albuterol with MDI as compared to the same drugs administered by nebulizer in the ED.[37] However, in some younger acutely ill children, it is difficult (even with supervision) to administer an effective SABA with a metered-dose canister. Because many patients and clinicians perceive that nebulizers provide more intensive therapy, it often is important psychologically to give at least the first dose of a SABA via a nebulizer. Thereafter, it is more cost effective to use the therapeutically equivalent MDI plus spacer.

An albuterol MDI contains 90 µg per actuation (puff), whereas a standard dose of albuterol given via nebulizer is 2.5 mg. Although not precise, it is generally accepted that in practical use, four to six inhalations of 90 µg per actuation of albuterol is approximately equivalent to a 2.5 mg albuterol "breathing treatment" administered via nebulizer. In a recent study of pediatric patients presenting to the ED, the investigators used four, six, or eight puffs of albuterol MDI for patients weighing <22.04 pounds (<10 kg), 22.04 to 44.09 pounds (10–20 kg), or >44.09 pounds (>20 kg) in a trial designed to increase efficiency compared to standard albuterol nebulizer treatments for mild-to-moderate asthma. The result was both a decrease in length of stay and admission rate in those patients after this albuterol MDI protocol was initiated.[38]

Case 18-1, Question 6: Starting 20 minutes after the first albuterol dose, two more doses of 2.5 mg albuterol were given via nebulizer every 20 minutes during the next 40 minutes. After three treatments, Q.C.'s breath sounds became increasingly clear. She was no longer in distress and could speak in complete sentences. Her PEF was now 70% of predicted, her O_2 saturations

were 97% on room air, with a discharge to home planned. Were the dose and interval of albuterol appropriate for Q.C.?

Schuh et al[39] were the first investigators to demonstrate that a higher dose albuterol regimen (0.15 vs 0.05 mg/kg every 20 minutes) produced significantly greater improvement with no greater incidence of adverse effects. Schuh et al[40] subsequently reported greater efficacy of albuterol in a dose of 0.3 mg/kg (up to 10 mg) hourly compared with a dose of 0.15 mg/kg (up to 5 mg) hourly in children. The larger dose was tolerated as well as the 0.15 mg/kg dose. Therefore, Q.C.'s albuterol regimen of 2.5 mg (0.13 mg/kg) nebulized 20 minutes for 40 minutes subsequent to her first dose of aerosolized albuterol could have been even more aggressive, but was appropriate. **Figures 18-11** and **18-12** provide treatment guidelines for the ED and hospital management of asthma.[1] Drug dosing recommendations are listed per GINA.[1]


Primary care
Patient presents with acute or sub-acute asthma exacerbation
Assess the patient
Is it asthma?
Factors for asthma-related death?
Severity of exacerbation? (consider worst feature)
Mild or moderate
Talks in phrases, prefers sitting to lying, not agitated
Respiratory rate increased
Accessory muscles not used
Pulse rate 100–120 bpm
O2 saturation (on air) 90–95%
PEF >50% predicted or best
Severe
Talks in words, sits hunched forwards, agitated
Respiratory rate >30/min
Accessory muscle in use
Pulse rate >120 bpm
O2 saturation (on air) <90%
PEF ≤50% predicted or best
Life-threatening
Drowsy, confused or silent chest
Urgent
Start treatment
SABA 4-10 puffs by pMDI + spacer, repeat every 20 minutes for 1 hour
Prednisolone: adults 40–50 mg, children 1–2 mg/kg, max. 40 mg
Controlled oxygen (if available): target saturation 93–95% (children: 94–98%)
Worsening
Transfer to acute care facility
While waiting: give SABA, ipratropium bromide, O2 systemic corticosteroid
Continue treatment with SABA as needed
Assess response at 1 hour (or earlier)
Worsening
Improving
Assess for discharge
Symptoms improved, not needing SABA
PEF improving, and >60–80% of personal best or predicted
Oxygen saturation >94% room air
Resources at home adequate
Assess at discharge
Reliever: continue as needed
Controller: start, or step up. Check inhaler technique, adherence
Prednisolone: continue, usually for 5–7 days (3–5 days for children)
Follow up: within 2–7 days (1–2 days for children)
Follow up
Review symptoms and signs: Is the exacerbation resolving? Should prednisone be continued?
Reliever: reduce to as-needed. Controller: continue higher dose for short term (1–2 weeks) or long term (3 months), depending on background to exacerbation
Risk factors: check and correct modifiable risk factors that may have contributed to exacerbation, including inhaler technique and adherence. Refer if >1–2 exacerbations in a year.
Action plan: Is it understood? Was it used appropriately? Does it need modification?

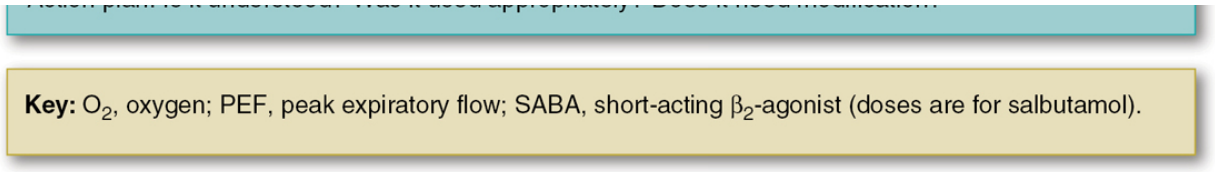
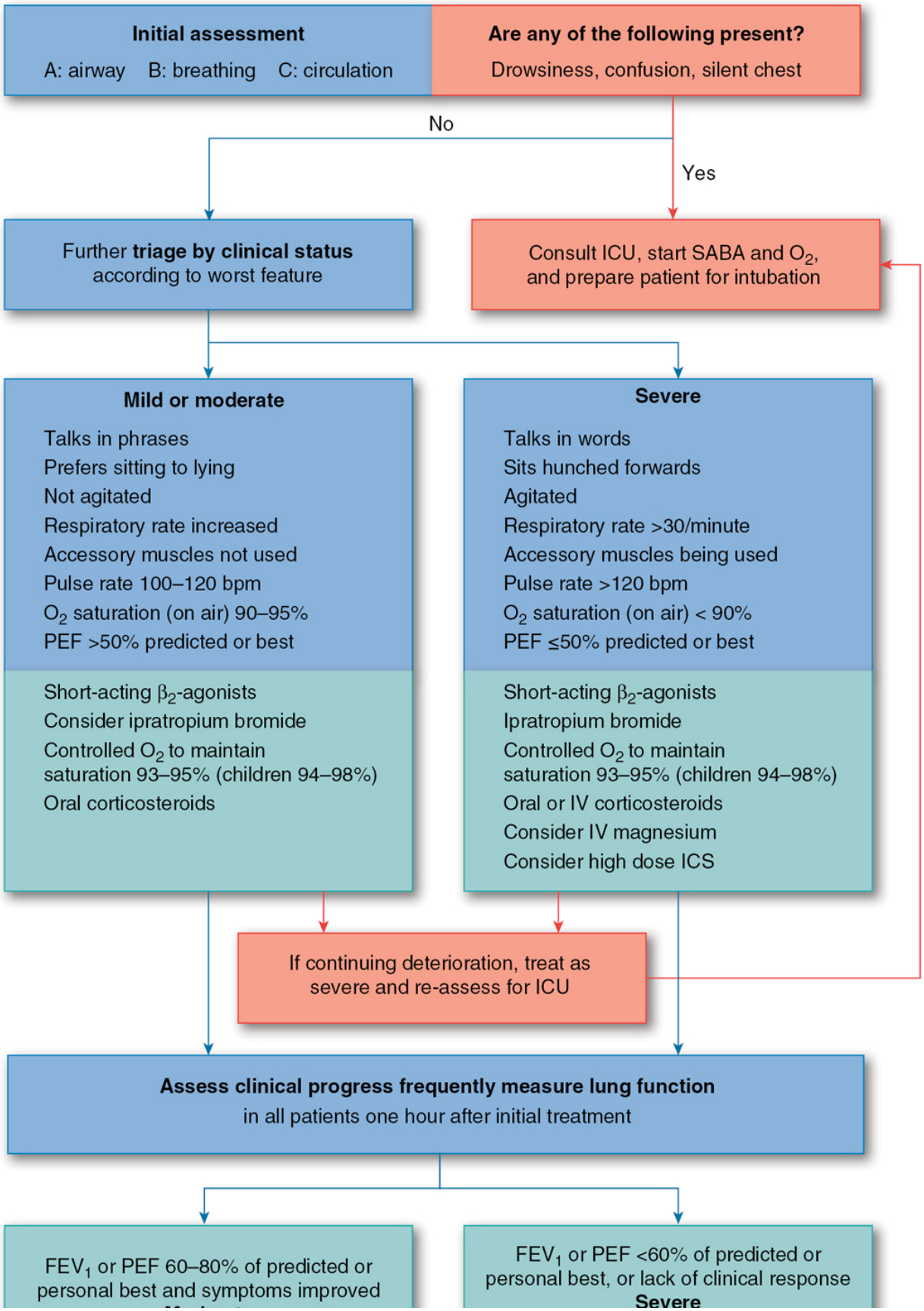


Figure 18-11 Management of asthma exacerbation in primary care (adults, adolescents, and children ages 6–11 years.)


Initial assessment
A: airway B: breathing C: circulation
Are any of the following present?
Drowsiness, confusion, silent chest
No
Yes
Further triage by clinical status according to worst feature
Consult ICU, start SABA and O_2, and prepare patient for intubation
Mild or moderate
Talks in phrases
Prefers sitting to lying
Not agitated
Respiratory rate increased
Accessory muscles not used
Pulse rate 100–120 bpm
O_2 saturation (on air) 90–95%
PEF >50% predicted or best
Short-acting β_2-agonists
Consider ipratropium bromide
Controlled O_2 to maintain saturation 93–95% (children 94–98%)
Oral corticosteroids
Severe
Talks in words
Sits hunched forwards
Agitated
Respiratory rate >30/minute
Accessory muscles being used
Pulse rate >120 bpm
O_2 saturation (on air) < 90%
PEF ≤50% predicted or best
Short-acting β_2-agonists
Ipratropium bromide
Controlled O_2 to maintain saturation 93–95% (children 94–98%)
Oral or IV corticosteroids
Consider IV magnesium
Consider high dose ICS
If continuing deterioration, treat as severe and re-assess for ICU
Assess clinical progress frequently measure lung function
in all patients one hour after initial treatment
FEV_1 or PEF 60–80% of predicted or personal best and symptoms improved
FEV_1 or PEF <60% of predicted or personal best, or lack of clinical response
Severe

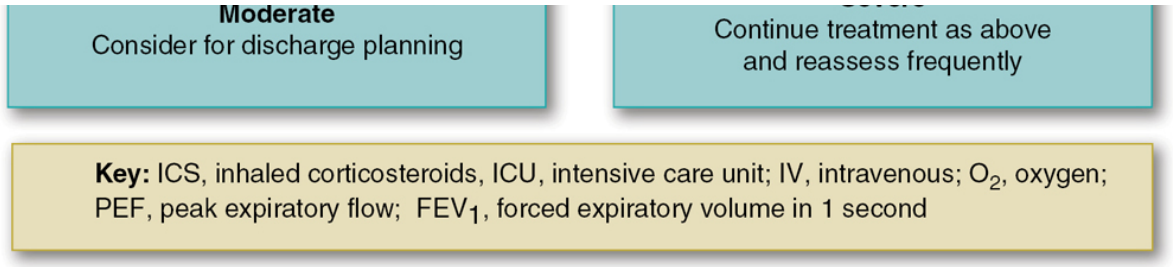


Figure 18-12 Management of asthma exacerbation in acute-care facility (eg, emergency department).

SYSTEMIC CORTICOSTEROIDS IN THE EMERGENCY DEPARTMENT FOR CHILDREN

CASE 18-1, QUESTION 7: Should Q.C. receive systemic corticosteroid therapy as part of her ED management?

Yes. Because asthma is primarily an inflammatory airway disease, the degree of inflammation associated with Q.C.'s current exacerbation should be considered. Per GINA,[1] if there is not an immediate response to inhaled β_2-agonist therapy, systemic corticosteroids should be administered (refer to further discussion of this subject in Case 18-3). Furthermore, if Q.C. had a peak flow meter at home, earlier objective detection of the development of this exacerbation might have prevented an ED visit. When the PEF is in the red zone (<50% of personal best) and poorly responsive to SABAs, early intervention with OCSs is associated with a reduction in ED visits[1] (see Fig. 18-9; refer to the Outcomes section at the end of the chapter). Q.C. and her parents should also understand that if respiratory distress is severe and nonresponsive to treatment, they should proceed to an ED or call 9-1-1. Finally, before going home from the ED, Q.C. and her parents should receive some basic education regarding asthma and its acute and long-term management. It is important to follow up with more detailed education during future clinic visits. According to GINA,[1] Q.C. should receive a short course of systemic corticosteroids as part of her discharge plan, thereby reducing her risk of reexacerbation.

Typically, oral prednisolone solution at a dose of 1 to 2 mg/kg/day to a maximum of 40 mg for 3 to 5 days is adequate. Prescribing ICSs on discharge from the ED may increase the chances of receiving appropriate therapy before the first follow-up visit in the office.[41]

Adverse effects

CASE 18-2

QUESTION 1: H.T. is a 45-year-old, 200.62-pound (91-kg) male with a long history of asthma, presenting to the ED with severe dyspnea and wheezing, tremors, and palpitations. He has been taking one inhalation of 220 µg mometasone twice daily, which has controlled his symptoms fairly well over the past year. However, after his cousin brought his two ferrets along to visit him for a few days, he immediately started wheezing, which fluctuated somewhat, but never resolved and gradually worsened. On the second day of using his Primatene Mist® (an MDI available over the counter [OTC] that he picked up at a chain drug store after losing his albuterol inhaler) eight times per day, he remembered being instructed to use his new budesonide160 µg/formoterol 4.5 µg as a reliever. Consequently, after 2 days of being exposed to the ferrets, he started using two puffs every 4 hours (around the clock) of this new budesonide/formoterol inhaler. The next morning on his way to the hospital, H.T. began using his Primatene Mist® plus his albuterol inhaler, which he found in his truck, since his breathing was becoming more labored, and he felt that no single one of his inhalers was working well.

Heart rate 120–160 s
RR 30/minute
Pulsus paradoxus 18 mm Hg
BP 160/100 mm Hg
ABGs on room air:
PH 7.3
Pao_2 60 mm Hg
Serum electrolyte concentrations were as follows:
Sodium 140 mEql/L
Potassium 3.1 mEql/L
Chloride 102 mEq/L
Bicarbonate 19 mEq/L

How would you critique his use of inhalers?

Albuterol has an acceptable safety profile and is generally considered the SABA of choice in most settings. Although the standard initial albuterol dose given via nebulizer is 2.5 mg, higher doses, up to 15 mg/hour can be given in acute asthma in the ED setting.[2] Skeletal muscle tremor, tachycardia, hypokalemia, and adverse effects related to its sympathomimetic activity may be observed, particularly at higher doses.[2] Formoterol is a long-acting β-agonist (LABA) that produces bronchodilation rapidly, similar to albuterol, but this agent is no longer commercially available as a standalone option in the United States. Mometasone/formoterol and budesonide/formoterol are the two products that the U.S. Food and Drug Administration (FDA) approved for the treatment of asthma in the United States.

However, per the FDA-approved labeling from the manufacturer, the maximum daily dose of formoterol is 18 μg (2 × 4.5 μg inhalations twice daily) as part of the combination product with budesonide, meaning that H.T. was taking a total of 12 inhalations (54 μg of formoterol daily). ICS/LABA as both the controller and quick relief therapy was shown to lower risk of asthma exacerbations in a recent meta-analysis of 16 trials when compared with traditional monotherapy with ICS and prn SABA.[42] Although the symbicort given as needed in mIld asthma (SYGMA) 2 trial[43] allowed adult subjects to take up to 12 inhalations of budesonide/formoterol, and the 2020 NIH guidelines[16] likewise lists 54 μg of formoterol as the maximum total daily dose in patients age older than 12 years, this is an unusually high dose and an indication that H.T. needs prompt evaluation. Overuse of these three different β-agonists was the most likely the etiology of the supraventricular tachycardia (SVT) and the hypokalemia and strongly emphasizes the need for education. However, H.T. gets his prescription inhalers from a mail order company in another state, so he never speaks with a pharmacist, and only glances at the enclosed education before he throws it and the box away (which displays the dosing directions).

Other additive causes of cardiac effects must also be considered, such as hypoxemia, which is also a potent stimulus for cardiac arrhythmias. Therefore, although H.T.’s tachycardia was most likely

caused by the inadvertent toxic dose of β_2-agonists, the worsening of his airway obstruction (as reflected in the increase in $Paco_2$), could have also contributed.

The decrease in the serum potassium concentration to 3.1 mEq/L could be attributed to β_2-adrenergic activation of the Na^+–K^+ pump and subsequent transport of potassium intracellularly. In fact, high-dose albuterol via nebulizer (10–20 mg) may be used in the treatment of hyperkalemia.

Case 18-2, Question 2: What is this OTC inhaler H.T. has been using?

For decades, Primatene Mist MDI® (epinephrine) has been available in the United States as an OTC option for the temporary relief of mild asthma symptoms. In 2011, it was discontinued with other MDIs, because it contained chlorofluorocarbons (CFCs), a propellant used to deliver medication, which was deemed harmful to the environment. Although epinephrine is a known efficacious bronchodilator owing to its β-agonist properties, the increased propensity to cause adverse reactions and short duration of action makes it a poor choice as a reliever. Much to the dismay of many clinicians, Primatene Mist® reemerged in 2019 in a reformulated product containing a more environmentally friendly propellant called *hydrofluoroalkane* (HFA). In addition, Asthmanefrin® (racemic epinephrine) is available OTC in a nebulized form, which is the drug of choice in the hospital setting for stridor, and likewise should not be routinely used in the treatment of asthma. He should be counseled instead to use his ICS/formoterol as a first-line reliever.

Case 18-2, Question 3: Because of the severity of the obstruction and rapid heart rate, H.T. was monitored with an electrocardiogram (ECG) that showed sinus tachycardia alternating with SVT. Albuterol 5 mg and ipratropium 0.5 mg were given via nebulizer with little improvement. Methylprednisolone 60 mg was given via intravenous (IV) administration. H.T. was then started on 4 L of oxygen per nasal cannula to maintain O_2 saturations at 93% to 95%. PEF was now 25% of his personal best. The internal medicine resident suggests adenosine to terminate the SVT. Do you agree?

Although the treatment of SVT is beyond the scope of this chapter, the use of adenosine is not an absolute contraindication in asthma. However, H.T. has severe airway obstruction, as evidenced by his vital signs and physical exam, and the potential bronchospasm from adenosine could be disastrous in this situation. You suggest to the physician that we avoid adenosine in this case, and instead use a verapamil bolus (10 mg) and drip at 5 mg/hour. This works quickly, and his heart rhythm converts to sinus tachycardia and decreases the BP to 140/90 mm Hg.

b-Adrenergic Agonist Subsensitivity

Although tolerance or tachyphylaxis to systemic effects of β_2-agonists (eg, tremor, sleep disturbances) is documented, complete tolerance to the airway response does not occur.[43] Even with long-term use, the intensity of response to β_2-agonists is usually retained (ie, the maximal percent increase in pulmonary function), but is more pronounced in those during severe bronchoconstriction.[44] Partial tolerance has been observed with LABAs, where Haney and Hancox[45] showed a 15% lower response to albuterol after using formoterol daily for 1 week. Of note, the response to ipratropium remained unaffected. Possible explanations for patient variability include downregulation of receptors, disease progression, or true drug tolerance. The exact contribution of each is not known. Therefore, H.T.'s failure to respond to the initial therapy most likely is attributable to the severity of his airway obstruction. H.T.'s history of chronic asthma, the slow progression of this attack, and the lack of response to his inhaled β_2-agonist also are largely owing to a significant inflammatory component to this attack. Thus, bronchodilators would not be expected to immediately reverse the airway obstruction in H.T.

Case 18-2, Question 4: Repeat measurements of PEF and ABGs indicate continued significant bronchial obstruction. What should be the next step in

H.T.'s therapy?

H.T. received initial therapy with a combination of inhaled SABAs and ipratropium. He should receive a third dose of albuterol 5 mg plus ipratropium 0.5 mg 20 minutes after the second dose. Because of the severity of his exacerbation, he should then receive albuterol 15 mg/hour by continuous nebulization, with close monitoring of his cardiac status. H.T.'s PEF also should be monitored. Figures 18-11 and 18-12 outline management of asthma exacerbations in primary care and in the ED, respectively.

CORTICOSTEROIDS

Case 18-2, Question 5: Why was H.T. given IV steroids?

Corticosteroids have potent anti-inflammatory activity and are indicated in H.T.[1] In patients such as H.T. with acute asthma, corticosteroids decrease airway inflammation and increase the response to β_2-selective agonists.[46] Corticosteroids are not smooth muscle relaxants (ie, not bronchodilators); however, they can relieve bronchial obstruction by improving the responsiveness of β_2-receptors and by inhibiting numerous phases of the inflammatory response (eg, cytokine production, neutrophil and eosinophil chemotaxis and migration, and release of inflammatory mediators).[46,47]

The anti-inflammatory activity of corticosteroids is delayed for about 4 hours after the dose has been administered.[1,48] Corticosteroid-induced restoration of responsiveness to endogenous catecholamines and exogenous β_2-agonists, however, occurs within 1 hour of administration of the corticosteroid in severe, chronic, and stable patients with asthma.[1,2] Significant improvement in objective measures (eg, FEV_1) occurs 12 hours after administration. Consequently, GINA advocates early initiation of corticosteroids in cases of acute severe asthma. Corticosteroids also hasten the

recovery of acute exacerbations of asthma and decrease the need for hospitalization if given early in the initial management of acute asthma in the ED.[1,2]

On the basis of his initial presentation, H.T. should be started on systemic corticosteroid therapy immediately in the ED (see Fig. 18-12). Preferably, OCSs would have been started at home before H.T.'s exacerbation escalated to this degree of severity.

Doses of corticosteroids used to treat acute asthma are largely empiric. Studies comparing very high dosages (eg, IV methylprednisolone 125 mg every 6 hours in an adult) versus moderate dosages (40 mg every 6 hours) have shown no advantage with very high dosages.[49] In addition, oral therapy is as efficacious as the IV route.[50] Dosing recommendations for systemic corticosteroids in the management of asthma exacerbations in the ED or hospital are listed in GINA.[1] Higher corticosteroid dosages may be considered in patients with impending respiratory failure. When patients cannot take oral medication, IV methylprednisolone is preferred over hydrocortisone in patients with heart disease or fluid retention or when high dosages of corticosteroids are used; this is because it has less mineralocorticoid activity.

For patients who require IV corticosteroid therapy, the dosage can usually be reduced rapidly to 50 mg/day for adults (1–2 mg/kg/day for children) because the condition improves (usually after 48–72 hours). On discharge from the hospital, GINA recommends, for example, prednisolone 50 mg/day in one dose for 5 to 7 days.[1] Although some clinicians may prescribe a tapering regimen, no taper is necessary in this situation. On the other hand, if the patient required long-term OCS therapy before hospitalization, tapering the dose to the preadmission dosage is prudent. For patients who are discharged from the ED, up to 7 days of prednisone therapy usually is sufficient.

CASE 18-2, QUESTION 6: H.T. was given one dose of 80 mg methylprednisolone on admission to the ED about 1 hour ago and says he is feeling a bit better, yet expiratory wheezes were still audible; and he is obviously using his accessory muscles, and requires 6 L of oxygen per nasal cannula to

maintain O_2 saturations >93. His PEF was now 35% of predicted, and a repeat ABG showed $Paco_2$ of 50 mm Hg. What is the next appropriate step and how should he be monitored for impending respiratory failure?

H.T. still is significantly obstructed despite intensive therapy in the ED. As a result, he should be admitted to the intensive care unit (ICU), where he can be monitored closely.

When patients continually must expand their chest wall with high lung volumes for a prolonged period, respiratory muscle fatigue may ensue, resulting in a decreased ventilatory effort. Clinical signs of impending respiratory failure include increased heart rate, decreased breath sounds, agitation from worsening hypoxia, or lethargy from increased CO_2 retention. These clinical signs and symptoms are relatively nonspecific and are affected by many variables. Thus, they should not be used to detect impending respiratory failure.

The best way to assess therapy is to monitor ABGs. The Pao_2 component of an ABG determination is not very helpful because of $\dot{V}/\dot{Q}$ mismatching and the administration of oxygen. The $Paco_2$ is the best indicator of hypoventilation in acute asthma[2]; however, there is no single value for $Paco_2$ that indicates impending respiratory failure, because different $Paco_2$ values are acceptable under different clinical circumstances. A $Paco_2$ of 55 mm Hg 1 to 2 hours after intensive bronchodilator therapy or an increase in $Paco_2$ of 5 to 10 mm Hg/hour during aggressive therapy is an ominous sign. His slow improvement is slight but encouraging.

CASE 18-2, QUESTION 7: H.T. initially received high-dose albuterol, a total of 30 mg over 2 hours, plus standard (0.5 mg) doses of ipratropium and IV methylprednisolone 80 mg. What should we do now?

H.T.'s response to inhaled albuterol also suggests that IV β-agonists are inappropriate at this time, particularly with his recent episode of SVT. Because standard therapies already administered were not sufficient, IV magnesium sulfate may benefit severely ill

patients such as H.T.[1] Recent research has found mixed results on nebulized isotonic magnesium sulfate as an adjunctive therapy to inhaled albuterol in the treatment of severe asthma exacerbations.[51,52] Further, heliox (a mixture of helium and oxygen) may also add benefit in selected cases.[1] Should he need to be intubated, both propofol and ketamine are considered safe in asthma.

Response to therapy

Case 18-2, Question 8: H.T. has continued to improve slowly during the past 72 hours. The nebulizer treatments are now every 6 hours, and he is taking oral prednisone 60 mg once per day. PEF measurements taken before and after his last albuterol treatment were 65% and 85% of predicted, respectively. Is H.T.'s long duration of recovery unusual?

No. In a patient such as H.T., whose condition progressively deteriorated during a long period, a slow reversal should be expected. The prolonged deterioration reflects an increasing inflammatory response in the lung. These patients require prolonged, intensive bronchodilator and anti-inflammatory therapy before maximal improvement is noted in pulmonary function tests. Thus, H.T. should continue to receive systemic corticosteroids for ~7 days after such a severe acute exacerbation of asthma.[1]

Adverse Effects of Short-Term Therapy

Case 18-2, Question 9: H.T. has been taking corticosteroids for a total of 7 days. Long-term corticosteroid use is associated with many adverse effects such as adrenal suppression, cataracts, and elevated blood glucose. What adverse effects are related to short-term corticosteroid use?

Short courses of daily corticosteroids are usually associated with minor side effects.[1,2] Facial flushing, appetite stimulation, gastrointestinal irritation, headache, and mood changes ranging from

a mere sense of well-being to overt toxic psychosis are the most commonly encountered adverse effects of short-term corticosteroid therapy. Acne can be exacerbated in patients susceptible to this skin problem, and weight gain also can occur because of sodium and fluid retention. In addition, hyperglycemia, leukocytosis, and hypokalemia are possible. All of these problems are transient and will disappear with time after the corticosteroids are discontinued. These short-term adverse effects are less common when small corticosteroid doses are used; however, corticosteroid doses must be adequate to prevent disease exacerbation. The minor risks of short-term use are far outweighed by the marked benefits.

Overuse of Short-Acting b_2-Agonists

Case 18-2, Question 10: Is H.T.'s history of increased use of his albuterol during the early stages of his asthma attack appropriate?

The overuse of SABAs as a possible risk factor for asthma death has been debated for decades. Because most deaths attributable to asthma occur outside the hospital setting before the patient can reach medical assistance, the primary cause of death in asthma most probably is an underestimation of the severity of the asthma attack by the patient and delay in seeking medical help. Overuse of quick reliever medication suggests inadequate asthma control and can lead to fatal asthma. Nwaru et al in the SABA us IN Asthma (SABINA) trial conducted in Sweden found an increased mortality risk directly proportional to the number of SABA inhalers obtained per patient.[53]

Although increased use of ICS/LABA inhalers as the primary reliever is expected to decrease overall need for albuterol, as-needed albuterol is still appropriate as a second-line add-on reliever.[54] The frequency of as-needed doses of albuterol is a good marker of the adequacy of inhaled anti-inflammatory therapy and environmental control measures. For example, if the patient needs

the SABA more than once a day for 2 or 3 days per week, the clinician should reassess environmental control, increase the dose of inhaled anti-inflammatory therapy, or add other controller agents per GINA.[1] Patients should be instructed verbally and in writing regarding the proper use of their inhalers during acute attacks and in recognizing when it is necessary to seek medical assistance. Patients can continue using their short-acting β-agonist inhalers on an as-needed basis until they reach medical care. H.T. should be considered at high risk because of the severity of his latest attack, and it would be reasonable to consider providing a preemptive prescription for a 5-day OCS burst to self-administer at the first sign of significant deterioration. In addition, H.T. should have a home peak flow meter so that he can objectively determine the severity of his attacks. Finally, the β_2-agonist controversy does not extend to use of high dosages in the acute-care setting. High dosages are essential in the ED and hospital and, as discussed previously, usually are tolerated very well.

CASE 18-2, QUESTION 11: How can H.T.'s outpatient therapy be optimized?

GINA 2020 step 3 and onward recommend ICS/LABA combination therapy as the preferred controller in adults and adolescents, although step 2 still leaves daily low-dose ICS as one of the primary options as a controller, the other being ICS/formoterol as needed in place of a daily controller. Although many patients seem to be adequately controlled on a home regimen similar to H.T., Single Maintenance and Reliever Therapy, or SMART, has been proved in key trials to provide a lower risk of exacerbations as compared to traditional pharmacotherapy of persistent asthma.[42,43] These and other large studies have resulted in a "sea change" in the way patients with asthma are prescribed therapy. First, that an ICS-containing inhaler should be prescribed in all patients with asthma, regardless of symptom severity or frequency. Second, that ICS/LABA inhalers are not only safe and effective but the ICS/LABA is also an integral component of the guidelines, listed in steps 1 to 5

of GINA, with either scheduled or as-needed dosing as a controller and/or reliever. In particular, budesonide/formoterol has been studied in the majority of the trials, although there is no reason to think that mometasone/formoterol would not be equally as efficacious. However, in the United States, neither budesonide nor mometasone combined with formoterol is FDA approved yet for as-needed use. Thus, the prescribing clinician may have to attain prior authorization for H.T. for allowance of more than one budesonide/formoterol inhaler per month.

CHRONIC ASTHMA

Classification of Severity

CASE 18-3

Question 1: J.B. is a 3-year-old, 35.27-pound (16-kg) boy with a 1-year history of recurrent wheezing 3 days per week and 4 nights per month. His medications include albuterol syrup 2 mg three times per day, and albuterol MDI as needed for wheezing. J.B. demonstrates the use of his inhaler with his mother's assistance. The mother holds the inhaler in J.B.'s mouth and actuates it at the end of a deep inhalation. J.B.'s mother tells the pharmacist that he acts jittery after taking the albuterol syrup.

What is the first step in deciding how to improve J.B.'s long-term asthma treatment?

While keeping in mind the goals of therapy, the first step here is to classify J.B.'s asthma severity (see Fig. 18-3). Because J.B. has symptoms 3 days per week and 4 nights per month (persistent asthma), he should be started at step 2, and unless symptoms worsen, be reevaluated after 2 to 3 months.

Selection of Appropriate Long-Term Initial Therapy

Case 18-3, Question 2: What would be a reasonable regimen for J.B.?

According to the GINA Strategy Document 2020[1] for very young children (see Fig. 18-3), low-dose ICSs with an as-needed SABA would be the choice for J.B.[1] He could receive low-dose ICS treatments via nebulizer (budesonide) or MDI plus a spacer. Most children ages 3 years and younger cannot use dry powder inhalers because of the inability to generate sufficient peak inspiratory flow (PIF). As J.B. matures, he may be able to use some dry powder inhalers (eg, Diskus®). Oral β_2-agonists are generally not recommended because of poor tolerability attributed to increased systemic exposure compared to inhaled delivery. Because J.B. is jittery and not tolerating the albuterol syrup, it should be discontinued and replaced with an inhaled formulation. Moreover, if concurrent inhaled albuterol is administered correctly, oral albuterol is not needed and would only be expected to increase the likelihood of adverse effects. J.B.'s mother must be educated about asthma, its treatment, and the appropriate use of medications (eg, proper use of inhaler devices).

Case 18-3, Question 3: It is anticipated that because of his young age, J.B. will find it difficult to use an MDI. What alternative devices are reasonable?

Children younger than age 5 years generally have a difficult time coordinating the use of standard MDIs; therefore, the ICS and SABA should be administered by another mode of delivery. For example, the as-needed β_2-agonist and scheduled ICS could be administered with an inhalational aid ("spacer" or valved holding chamber [VHC]), which is connected to an MDI. A nebulized corticosteroid preparation (budesonide) is available for very young children. Inhalation aids significantly improve the efficacy of medications that are administered by MDI in very young children or in other patients who are unable to coordinate the plain inhalers correctly.[1,2] The AeroChamber® is a widely used VHC (the medication stays in the

chamber for a few seconds until the patient inhales slowly and the inhalation valve opens). Studies have shown that many children as young as 2 and 3 years of age can use MDIs with VHC devices by modeling after a parent.[1] VHCs with face masks are required for most children age younger than 4 years. Extender device-assisted delivery of aerosolized medications is as effective as nebulization in the home management of chronic severe asthma and even in the ED treatment of asthma in children.[1,2,38] AeroChamber® is an example of a device that contains a flow indicator whistle that sounds if the patient inhales rapidly. This whistle is particularly effective in teaching the patient the appropriate slow inhalation technique. The clinician should verify the correct use of the device by observation of the patient's or caregiver's administration technique.

Alternatively, the ICS could be administered to selected children using a breath-activated dry powder inhaler (eg, budesonide [Pulmicort Flexhaler®] or fluticasone [combined with salmeterol in Advair Diskus®]). In young children, the Diskus® has the advantage of requiring a lower PIF than does Flexhaler®, and it has been used successfully in children as young as 4 years of age.[55] Another option is the Twisthaler® used for delivery of mometasone (Asmanex®) or the breath-actuated beclomethasone (QVAR Redihaler®) inhaler, but they are approved for children ages 4 years and older.

Many pediatricians may choose a nebulizer to administer SABAs to a 3-year-old child. This method is certainly acceptable and very common, but it takes longer to administer the medication (~5–15 minutes), and the device must be properly cleaned and maintained. Because J.B. recently turned 3 years old, therapy should be initiated with nebulized budesonide (Pulmicort Respules®) in a low dose of 0.25 mg bid. As mentioned previously, GINA[1] suggests an initial trial of low-dose ICS in very young children who have not previously been treated with ICSs. The plan is to switch J.B. to a steroid inhaler approved for children at least 4 years old in 12 months, as soon as he and his caregiver can demonstrate correct use. J.B.'s clinician should assess the response to low-dose budesonide within 12 weeks. Therapy can be stepped up if necessary and subsequently

stepped down in the coming months, if possible so that optimal asthma control is achieved at the lowest ICS dose possible.

Case 18-3, Question 4: J.B.'s parents are wary of their child taking corticosteroids on a continuous basis after reading about side effects on the Internet. How should his parents be counseled?

Corticosteroids reach the systemic circulation minimally via inhalation in part because they are largely inactivated through first-pass hepatic metabolism. However, a dose-dependent response is evident, and clinically significant adverse events resulting from systemic exposure can occur, albeit more commonly with doses at the high end of the range. Long-term studies in pediatric patients have examined the effects of ICS on growth reduction, bone density, and adrenal suppression.

Although ICSs can cause a mild and temporary reduction in growth velocity, final height attained in adulthood appears to be within normal limits, although longer term trials are required to confirm these findings.[56–58] Two large studies of ICSs in pediatric patients found reductions in height of 0.47 inch (1.20 cm) to 0.52 inch (1.34 cm) when compared to placebo.[59,60] Bone density and risk of fractures have not been found in the majority of investigations to be affected by ICSs.[56,58] Although a measurable reduction in serum and urinary cortisol levels is not an uncommon finding in studies of ICSs, clinically significant adrenal insufficiency solely caused by ICSs is rare, although, again, it is more likely to occur with high doses.[56,58]

In summary, these adverse effects are generally of minimal clinical significance, with the benefits of well-controlled asthma far outweighing the risks.

The most common local side effect with ICS therapy is oropharyngeal candidiasis (thrush), but this problem is rare with any delivery system and is easily treatable with nystatin oral liquid. With MDIs, it can be further minimized using a spacer device. Rinsing the mouth with water after use of any ICSs is strongly recommended.

Another possible local side effect is hoarseness (dysphonia), and spacers may not effectively reduce this problem.

Corticosteroids in Adolescents and Adults

CASE 18-4

Question 1: S.T. is a 12-year-old girl with asthma receiving step 3 care, and has not been well controlled on inhaled mometasone monotherapy. She does admit to only using it when she feels like she needs it, but uses her as-needed albuterol multiple times per day. When her symptoms worsen, she uses her home nebulizer and awakens most nights because of wheezing. She has been hospitalized four times over the past 2 years and has required bursts of prednisone with increasing frequency. S.T. is just finishing a 2-week course of prednisone 20 mg/day. Her face has the rounded appearance of chronic oral steroid use.

What actions are needed to improve S.T.'s care?

Because S.T. is suffering needlessly and requiring frequent systemic corticosteroids, all efforts must be made to optimize other therapies and to minimize systemic corticosteroid toxicities. Although S.T. is receiving an ICS, she admits to poor adherence. Therefore, with her uncontrolled asthma, one strategy would be to increase her mometasone from medium dose to high dose, although she has already demonstrated failure of compliance with a single ICS inhaler treatment. Although short bursts of prednisone (eg, 40 mg/day for 3 days) are very helpful occasionally, frequent short courses often indicate the need to optimize other therapies. Some patients require courses of 1 to 2 weeks. S.T. is requiring longer frequent bursts and is showing signs of adverse effects. Obviously, S.T. and her parents also need a concerted and persistent effort in patient education as a partnership (refer to the sections Patient Education and Outcomes).

ICSs are chemically modified to maximize topical effectiveness while minimizing systemic toxicities. GINA[1] compares the dosages of ICS products. These differences in dosages (low, medium, and high) reflect differences among ICSs in receptor-binding affinity and topical potency. There are also differences among these agents in oral

bioavailability (ie, absorption of drug that is swallowed after inhalation) and systemic availability via absorption from the lungs. Of these two variables, absorption from the lungs is the most likely contributor to possible hypothalamic–pituitary–adrenal (HPA) suppression or other systemic effects. Fortunately, the total absorption has not been shown to be clinically important, except at the higher recommended dosages. Although the various ICSs are not equipotent on a microgram-per-microgram basis, major differences in efficacy or adverse effects are not firmly established (**Table 18-2**).[1,2] For patients with severe-persistent asthma, a logical choice would be a high-potency agent that would allow for a minimum number of inhalations per day, potentially improving treatment adherence. Furthermore, the delivery system used affects pulmonary deposition, but each available delivery system has established efficacy if used correctly. The differences among the various dry powder inhalers are discussed later in this chapter. Addition of a spacer device to an MDI also enhances pulmonary deposition. In very high dosages (the equivalent of 1600 µg/day of beclomethasone dipropionate), all ICSs produce some degree of HPA axis suppression.[2] The clinical significance of this suppression has yet to be firmly established.

Table 18-2
Low, Medium, and High Daily Doses of Inhaled Corticosteroids

This is not a table of equivalence, but, instead, suggested total daily doses for the "low-," "medium-," and "high-" dose ICS options for adults/adolescents, p. 54 and children 6–11 years, p. 55, based on available studies and product information. Data on comparative potency are not readily available and, therefore, this table does *not* imply potency equivalence. Doses may be country specific depending on local availability, regulatory labeling and clinical guidelines.

Low-dose ICSs provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need **medium-dose ICS** if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). High dose ICS (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	*Total daily ICS dose (μg)—see notes earlier*		
	Low	*Medium*	*High*
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle[a], HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle[a], HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200–400		>400
Children 6–11 years—see notes earlier (for children 5 years and younger, see Box 6-6, p. 153)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle[a], HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle[a], HFA)	80	>80–160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50–100	>100–200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50–100	>100–200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI, dry powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; n.a., not applicable; pMDI, pressurized metered-dose inhaler.

[a] See product information.

Source: Gina.org. Accessed October 4, 2020. https://ginasthma.org

Although low-to-moderate dosages of ICSs are accepted as being quite safe, very high dosages continue to be scrutinized regarding the potential adverse effects.[1] Clearly, for patients who require high dosages for optimal control of asthma, the benefits of therapy with these agents far outweigh the risks.[1,2] A possible association between prolonged, very high dosages of ICSs and cataracts[61] and glaucoma[62] has been reported.

All of these risks seen with ICSs are greatly outweighed by the benefits. In a landmark study, Suissa et al demonstrated a decreased mortality rate examining ICS usage over several years in

>30,000 patients. Remarkably, this trial demonstrated a dose–response curve, which is a proportional decrease in mortality rate with each increasing number of ICS canisters used.[63]

Case 18-4, Question 2: How should S.T. be managed?

LABAs have been very successful in the prevention of "stepping up" the dose of ICSs while markedly enhancing overall asthma control, and this fact is reflected in GINA.[1,64] S.T.'s care level is escalated to step 4, and a reasonable therapeutic option for would be the combination of fluticasone 250 µg and salmeterol 50 µg via Diskus® (Advair 250/50®) one inhalation bid, the budesonide/formoterol (Symbicort®) combination inhaler (160 µg/4.5 µg) two inhalations bid, the mometasone/formoterol (Dulera®) combination inhaler (100 µg/5 µg) two inhalations bid daily. Airduo Digihaler® 113/14 µg one inhalation bid. S.T. should be reevaluated in 2 weeks. Wanting to ensure adherence and engage S.T. in the treatment plan, her physician suggested a new "smart" "inhaler. S.T. was excited to use this Airduo Digihaler® (fluticasone/salmeterol) because it involved using an application on her smartphone that tracks data including compliance and inspiratory flow rates, which is available for both her and her doctor to analyze. The plan is to step down the dose of fluticasone after excellent asthma control is achieved.

Adverse effects associated with long-acting inhaled a_2 agonists

Case 18-4, Question 3: S.T.'s parents researched their daughter's new type of medicine and found reports of fatalities associated with a very similar inhaler on the Internet. How would you educate them?

Several randomized trials[65] for more than a decade have demonstrated that LABAs have minimal adverse effects (eg, tachycardia, tremor). EPR-3[2] and GINA[1] both strongly recommend against the use of LABAs as monotherapy for long-term control of

persistent asthma. LABA therapy should only be used in the form of a combination ICS/LABA inhaler, never as separate inhalers in patients with asthma. There were previous safety concerns stemming from a signal of increased deaths from the SMART study,[66] which investigated adding salmeterol to baseline treatment, which did not always include ICSs. More recently, a meta-analysis involving over 36,000 patients enrolled in head-to-head trials of ICSs versus ICS/LABA found both a lower risk of asthma exacerbations and only two deaths in the ICS/LABA arm.[67] Based on these results, an ICS/LABA therapy is preferred for S.T.

Case 18-4, Question 4: After being adherent to her new therapy for 1 month, one inhalation twice daily of fluticasone 113 µg/14 µg salmeterol, S.T.'s asthma control has markedly improved. She has required no ED visits, sleeps through the night, and has started exercising outside again. Her PEF is staying near at least 90% of her personal best and uses her albuterol inhaler less than once per week. At the 6-month mark, with continued excellent control of symptoms, her clinician is ready to step down the dose. How does she proceed in a safe manner?

GINA[1] suggests stepping down the dose at a rate of 25% to 50% every 3 months to the lowest dose that maintains control (**Table 18-3**). A step down to fluticasone 55 µg/salmeterol 14 µg would be a reasonable reduction in therapy for S.T. If a single ICS product had been started for S.T. initially (eg, budesonide, beclomethasone, fluticasone), the dosage reduction would normally proceed at a slower pace. However, fluticasone 50 µg bid, especially in combination with salmeterol, will likely be an adequate dose for S.T. After S.T.'s dose of fluticasone was stepped down as planned, she started requiring only slightly more prn albuterol (but still was symptom free most days).

Table 18-3
Options for Stepping Down Treatment Once Asthma Is Well Controlled

General Principles of Stepping Down Asthma Treatment

- Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for ≥3 months (Evidence D). If the patient has risk factors for exacerbations (Box 2-2, p. 35), for example, a history of exacerbations in the past year,[271] or persistent airflow limitation, do not step down without close supervision.
- Choose an appropriate time (no respiratory infection, patient not traveling, not pregnant).
- Approach each step as a therapeutic trial. Engage the patient in the process; document their asthma status (symptom control, lung function, and risk factors, Box 2-2, p. 35); provide clear instructions; provide a written asthma action plan (Box 4-2, p. 117) and ensure the patient has sufficient medication to resume their previous dose if necessary; monitor symptoms and/or PEF; and schedule a follow-up visit (Evidence D).
- Stepping down ICS doses by 25%–50% at 3-month intervals is feasible and safe for most patients[277] (Evidence A).

Current Step	Current Medication and Dose	Options for Stepping Down	Evidence
Step 5	High-dose ICS–LABA plus OCSs	■ Continue high-dose ICS–LABA and reduce OCS dose ■ Use sputum-guided approach to reducing OCS ■ Alternate-day OCS treatment ■ Replace OCS with high-dose ICS	D B D D
	High-dose ICS–LABA plus other add-on agents	■ Refer for expert advice	D
Step 4	Moderate- to high-dose ICS–LABA maintenance treatment	■ Continue combination ICS–LABA with 50% reduction in ICS component by using available formulations. ■ Discontinuing LABA may lead to deterioration.[278]	B A
	Medium- to high-dose ICS–formoterol[a] as maintenance and reliever	■ Reduce maintenance ICS–formoterol[a] to low, and continue as-needed low-dose ICS–formoterol[a] reliever.	D
	High-dose ICS plus second controller	■ Reduce ICS dose by 50% and continue second controller.[227]	B
Step 3	Low-dose ICS–LABA maintenance	■ Reduce ICS–LABA to once daily. ■ Discontinuing LABA may lead to deterioration.[278]	D A
	Low-dose ICS–formoterol[a] as maintenance and reliever	■ Reduce maintenance ICS–formoterol[a] dose to once daily and continue as-needed low-dose ICS–formoterol[a] reliever.	C
	Medium- or high-dose ICS	■ Reduce ICS dose by 50%.[277] ■ Adding LTRA[b] may allow ICS dose to be stepped down.[279]	A B
Step 2	Low-dose ICS	■ Once-daily dosing (budesonide, ciclesonide, mometasone)[280,281] ■ Switch to as-needed low-dose ICS–formoterol.[171,177,180] ■ Switch to taking ICS whenever SABA is taken.[184,185,187]	A A B
	Low-dose ICS or LTRA	■ Switch to as-needed low-dose ICS–formoterol.[173,174,177,180] ■ Complete cessation of ICS in adults and adolescents is not advised because the risk of exacerbations is increased with SABA-only treatment.[276]	A A

BDP, beclometasone diproprionate; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2-agonists.

[a]ICS–formoterol maintenance and reliever treatment can be prescribed with low-dose budesonide–formoterol.

[b]Note U.S. Food and Drug Administration (FDA) warning on neuropsychiatric effects with montelukast.[205]

CASE 18-4 QUESTION 5: What education should be done with S.T. and her parents during this clinic visit?

S.T. needs to hear from the clinicians treating her that asthma does not have to dominate her life, and in the words of a title to an NIH booklet for patients, “Your asthma can be controlled: Expect

nothing less." Finally, special care should be taken in cleaning the MDI actuator. Health care professionals should stress the importance of regular MDI actuator cleaning with their patients. S.T. needs a written asthma action plan and an emergency supply of prednisone (ie, to use when her PEF is in the red zone and unresponsive to the reliever).

During follow-up evaluations, clinicians should carefully investigate factors that may contribute to poor asthma control, including exposure to inhalant allergens, indoor or outdoor irritants, medications, and tobacco smoke. Secondhand smoke exposure has been demonstrated to reduce the benefit of ICSs in children and necessitate step-up therapy, and patients with asthma who smoke have reduced response to ICS therapy.[68]

Leukotriene Modifiers

CASE 18-5

QUESTION 1: C.R. is a 53-year-old male with asthma and dysthymia (persistent depressive disorder) requiring step 2 treatment for his asthma. His asthma symptoms began when he was 2 years old, and he has never smoked. C.R. has had numerous drug regimens for his asthma over the years and would like to try life without inhalers. His coworker only takes a pill for his asthma, so C.R. would like to try that out as well, or, at the very least, minimize his reliance on inhalers.

Is this appropriate for C.R.?

In patients of any age with GINA step 2 asthma, and certainly in children or adolescents, an oral agent such as montelukast with once-daily dosing at bedtime has obvious advantages. Zileuton® is another leukotriene modifier, but it has more drug interactions and adverse effects than do the other available agents. A daily low-dose ICS or as-needed ICS/formoterol is the preferred treatment for step 2 asthma. Studies comparing ICSs with leukotriene receptor agonists have consistently demonstrated the superiority of ICSs for most asthma outcome measures,[69–71] but in patients (adults or children) who prefer oral therapy to inhaling medication every day, leukotriene

modifiers are a reasonable option. The simplest and safest possible oral controller regimen for C.R. is montelukast 10 mg at bedtime (with prn inhaled ICS/formoterol as the reliever). Bedtime dosing with montelukast is recommended because it will have peak activity late at night and in the early morning hours when asthma symptoms tend to be more frequent. However, montelukast has a boxed warning for the development of agitation, depression, and suicidal ideation, so he must be counseled carefully and agree to close monitoring for neuropsychiatric effects with his prescriber and counselor.[72] It is likely that this regimen will result in good asthma control. If C.R. does not have good control of his asthma when he returns to the clinic in a few weeks, switching to a low-dose ICS in the evening only would keep the regimen simple while enhancing efficacy.

Anticholinergics

CASE 18-6

QUESTION 1: N.C. is a 25-year-old musician with asthma requiring step 4 treatment, which has been controlled well for the past 3 years on Advair® (fluticasone propionate/salmeterol). Recently he has noticed that his asthma symptoms have worsened, he is requiring his albuterol inhaler three to four times per week, and frequently awakens feeling tightness in his chest, which is improved for a few minutes after a hot shower. He sees an online commercial for a new type of inhaler that contains three different medicines.

He comes to your clinic and asks if this new drug is “right “for him. How do you respond?

Until the past few years, antimuscarinic agents have had limited use in asthma except for ipratropium in the ED and have been used for COPD almost exclusively. However, in 2012, Kerstjens et al in a randomized, controlled trial found that tiotropium, a long-acting antimuscarinic agent (Long Acting Muscarinic Antagonist, LAMA) added to combination ICS/LABA once daily in patients with suboptimally controlled adult asthma was superior to placebo.[73] Subsequently, in patients with persistent asthma poorly controlled on

ICSs, researchers demonstrated that the addition of tiotropium to ICS therapy was noninferior to the effects of adding salmeterol to ICS therapy and was superior to doubling the inhaled steroid dose.[74] The morning and evening PEFs were significantly higher in patients receiving tiotropium than in those receiving a doubling of the ICS dose.[74] Now an option per GINA for step 4 treatment, a therapeutic trial of LAMA, perhaps even with the inhaler N.C. saw in the commercial, may be considered given these new data. In 2015, Spiriva Respimat® was approved for use as maintenance therapy in patients with asthma and is now approved in both adults and in children ages 6 years and older. Both GINA[1] and the NIH[16] guidelines position LAMA as an add-on treatment for those who remain symptomatic despite already receiving combination ICS/LABA treatment (**Fig. 18-13**). However, it must be noted that LAMA use in asthma should always be given in conjunction with ICSs. The (in) *A*ppropriate *L*AMA *P*rescribing in *A*sthma patients: A *C*ohort *A*nalysis (ALPACA) trial, an observational study that evaluated LAMA use in patients with asthma, revealed a significant increase in severe asthma exacerbations when a LAMA was used as monotherapy.[75] Trelegy Ellipta® (fluticasone furoate/umeclidinium/vilanterol) is another antimuscarinic-containing inhaler that FDA approved in 2020 for asthma in patients at least 18 years old. Although there are several inhalers containing LAMAs on the market, only a few are FDA approved for use in asthma at this point. Given his suboptimal asthma control despite good adherence and proper technique, the clinician decides to prescribe Trelegy® 100/62.5/25 µg once daily for N.C.

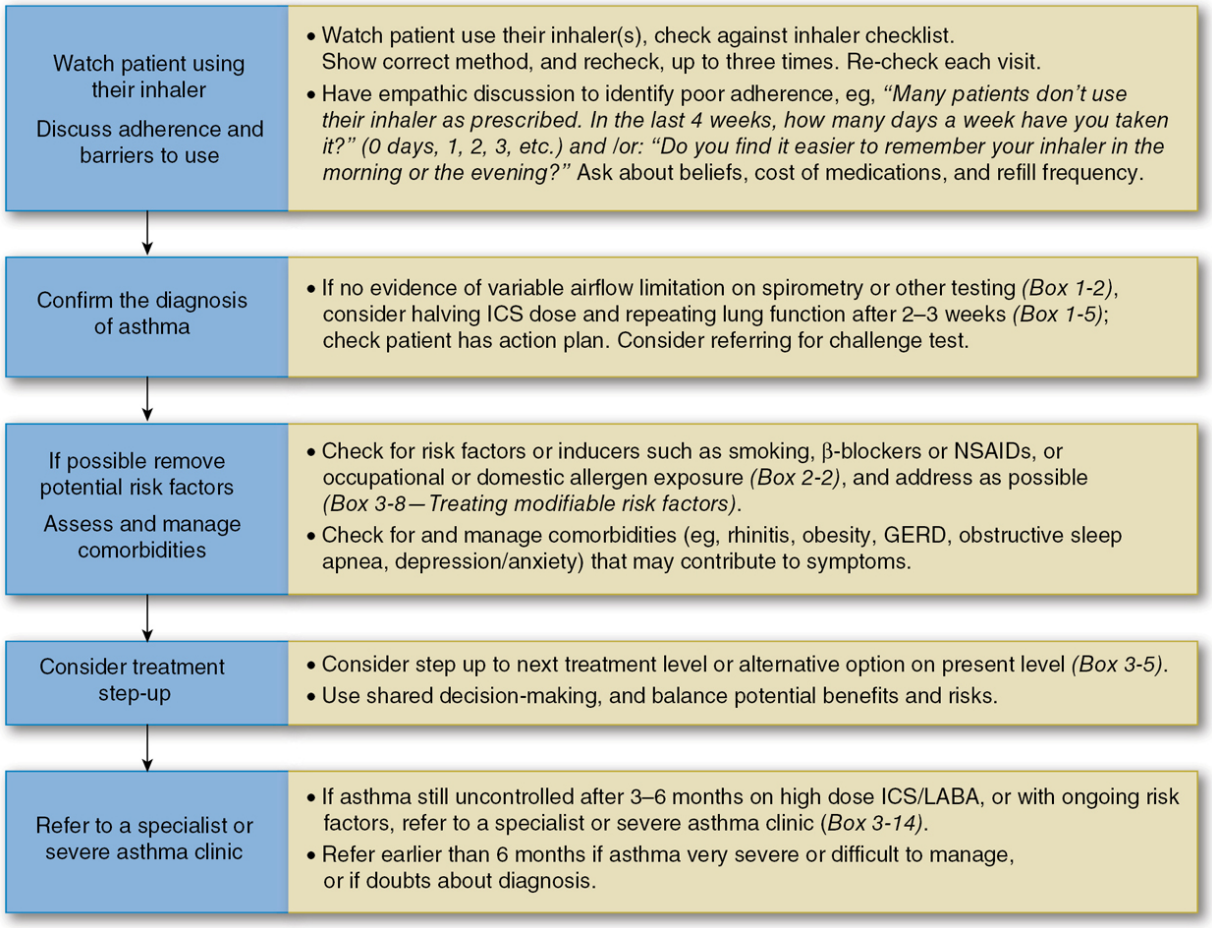


Figure 18-13 Investigating a patient with poor system control and/or exacerbation despite treatment.

Biologics

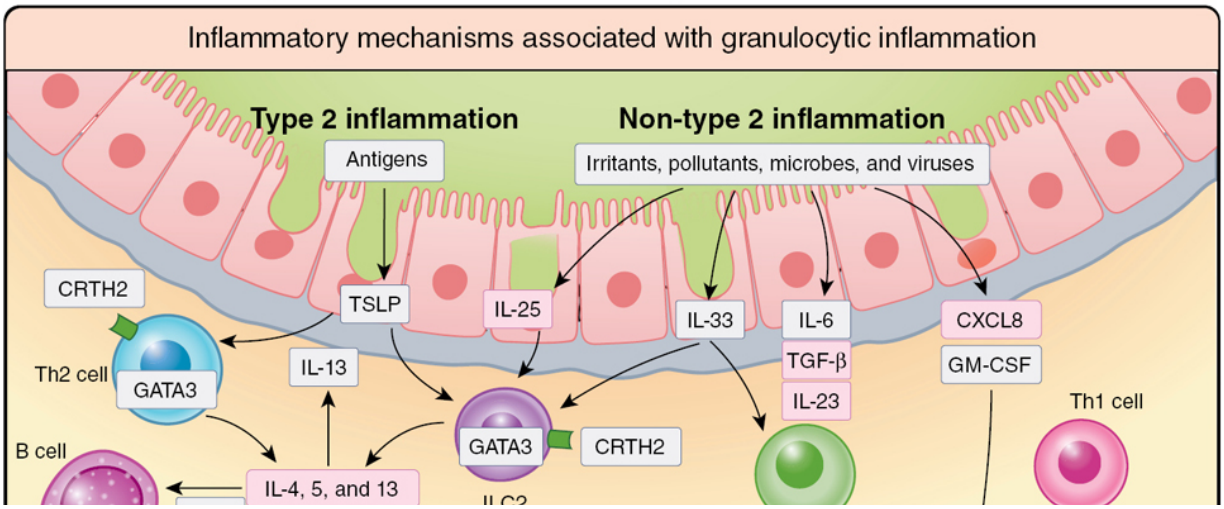
CASE 18-7

QUESTION 1: M.M. is a 30-year-old female with asthma requiring step 5 treatment who has been worsening on ICS/LABA/LAMA and environmental control around her house and workplace. In addition, she suffers from both nasal polyps and chronic rhinosinusitis, which are more prevalent in patients with asthma. She has had two recent and frightening hospitalizations for asthma. Her allergist ordered a blood eosinophil count, which is reported at 325 cells/μL, whereas FeNO was measured at 27 ppb. She is considering one of the asthma biologic treatment options in an effort to improve her quality of life and to prevent her from going on chronic OCSs.

How should she proceed in selecting from the currently available drugs?

Currently, there are five available injectable biologic (monoclonal antibody) drugs for asthma, which, at this point, are typically employed only in patients with severe asthma who are refractory to standard GINA step 5 therapies (high-dose ICS/LABA ± LAMA, low-dose OCSs). Most of the efficacy observed with the biologics likely stems from their actions blocking eosinophilic-mediated inflammation (**Fig. 18-14**). At the time of this writing, there have been no head-to-head randomized trials comparing these agents directly. In addition, because many of these drugs tend to perform better in patients with a higher baseline level of eosinophils, for most situations it is unclear which of these drugs should be tried first in a given patient, although FDA-approved indications vary slightly.[22,76] Until more evidence becomes available, the use of these very expensive agents is, in large part, determined by insurance coverage and physician preference. Because this area of asthma research is proceeding at a rapid rate and is highly specialized, GINA and the joint ERS and ATS both publish separate focused guidelines on difficult-to-treat/severe asthma.[15,77] Omalizumab was the first of these drugs available. It inhibits the binding of IgE to receptors on the surface of mast cells and basophils, reducing the activation of these cells, thereby preventing the release of proinflammatory mediators that are key components in most types of asthma.[78] It is administered 75 to 375 mg SC every 2 to 4 weeks depending on age, weight, and pretreatment IgE level.

Inflammatory mechanisms and pathobiologic features leading to severe asthma



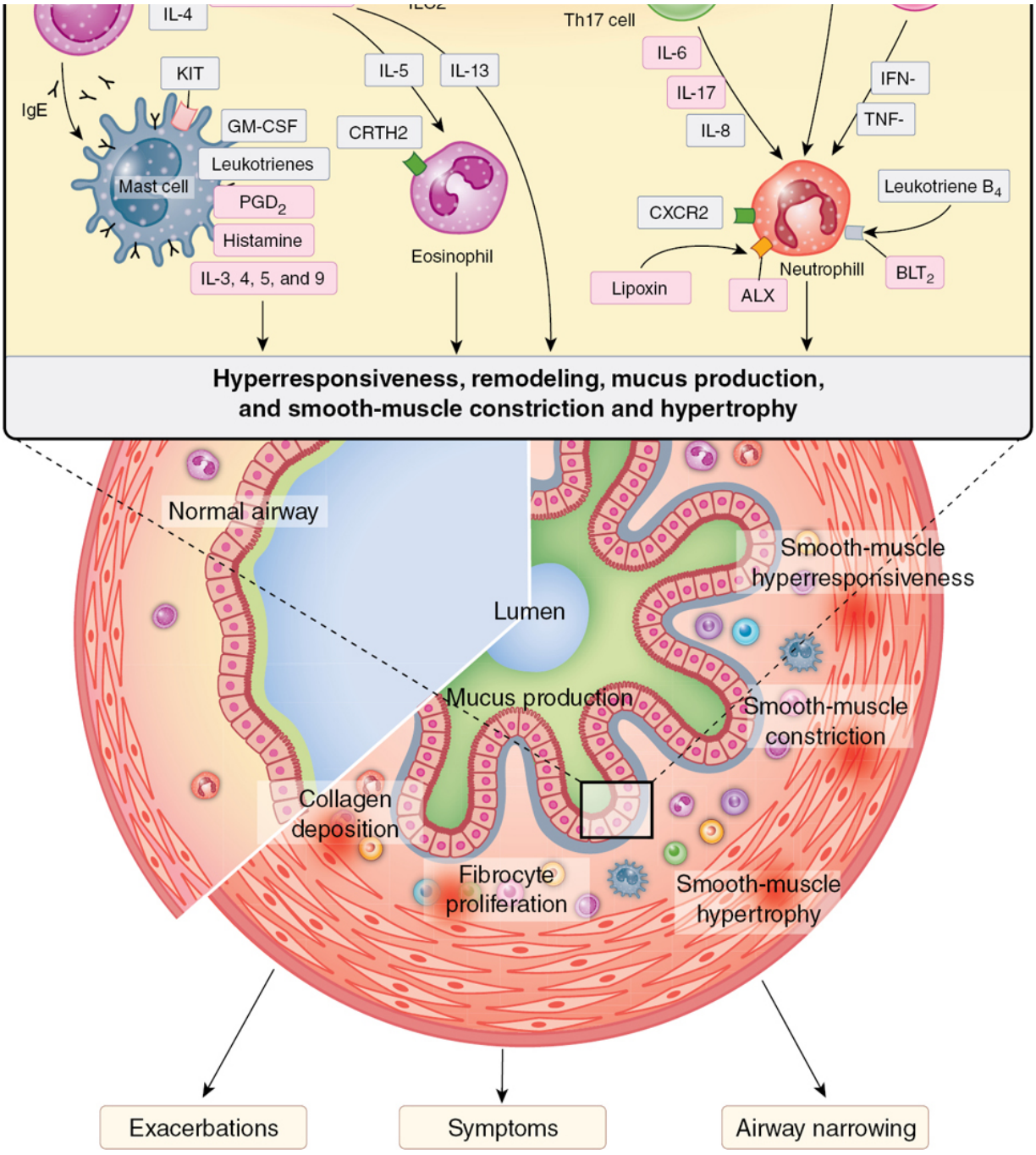


Figure 18-14 Inflammatory mechanisms and pathobiologic features leading to severe asthma (From Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med*. 2017;377(10):965–976. © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

There are three drugs that primarily affect interleukin (IL)-5. This cytokine plays an essential role in signaling, function, and recruitment of eosinophils to the airway, leading to inflammation.[6,11,79] Mepolizumab,[80] an IL-5 antagonist, is dosed at 40 mg SC every 4 weeks (ages 6–11 years) or 100 mg SC every 4 weeks (ages 12 years and older). Reslizumab,[81] an IL-5 antagonist, is dosed at 3 mg/kg actual body weight IV over 20 to 50 minutes every 4 weeks.

Benralizumab[82] binds to the α-subunit of the human IL-5 receptor, which is found on the surface of eosinophils and basophils. This activity not only prevents the interaction of IL-5 with the receptor but also results in apoptosis of these same cells. It is FDA approved for self-administration at home. The initial dose is 30 mg SC every 4 weeks in three doses; thereafter, the dose is 30 mg SC every 8 weeks.

Dupilumab[83] is an IL-4 receptor α-antagonist that binds to the IL-4 α-subunit shared by both IL-4 and IL-13, inhibiting multiple inflammatory cells that express IL-4 receptors. It is FDA approved for self-administration at home. The dose is 400 SC in one dose, then 200 mg SC every 2 weeks or 600 mg SC in one dose, then 300 mg SC every 2 weeks if the patient is on oral steroids or has moderate-to-severe atopic dermatitis.

Dupilumab is chosen for M.M. because it is also FDA approved for chronic rhinosinusitis with nasal polyps, for which M.M. has also been unsuccessfully treated for several years. Because it is a 2-hour round trip to her doctor's office, the added convenience of self-administration of the drug at home makes it a practical choice for her.

EXERCISE-INDUCED BRONCHOCONSTRICTION

CASE 18-8

QUESTION 1: J.Z. is a 35-year-old male who presents to the clinic with a history of severe coughing and chest tightening after exercise. He has recently tried to step up his weekend running to enrolling in 5K events but becomes symptomatic half way through the race.

Why is this happening?

Exercise-induced bronchoconstriction (EIB) is mostly present in those with a diagnosis of asthma but can occur in normal subjects as well. During sustained exercise, at least 90% of patients with asthma experience an initial improvement in pulmonary function quickly followed by a significant decline (**Fig. 18-15**). This phenomenon may be the only symptom of subclinical asthma.[84] Patients can be diagnosed by measuring the FEV_1 or PEF before and after exercise (6- to 8-minute treadmill or bicycle exercise test). A reduction in FEV_1 by >15% of the baseline value is a positive test result.[83,84]

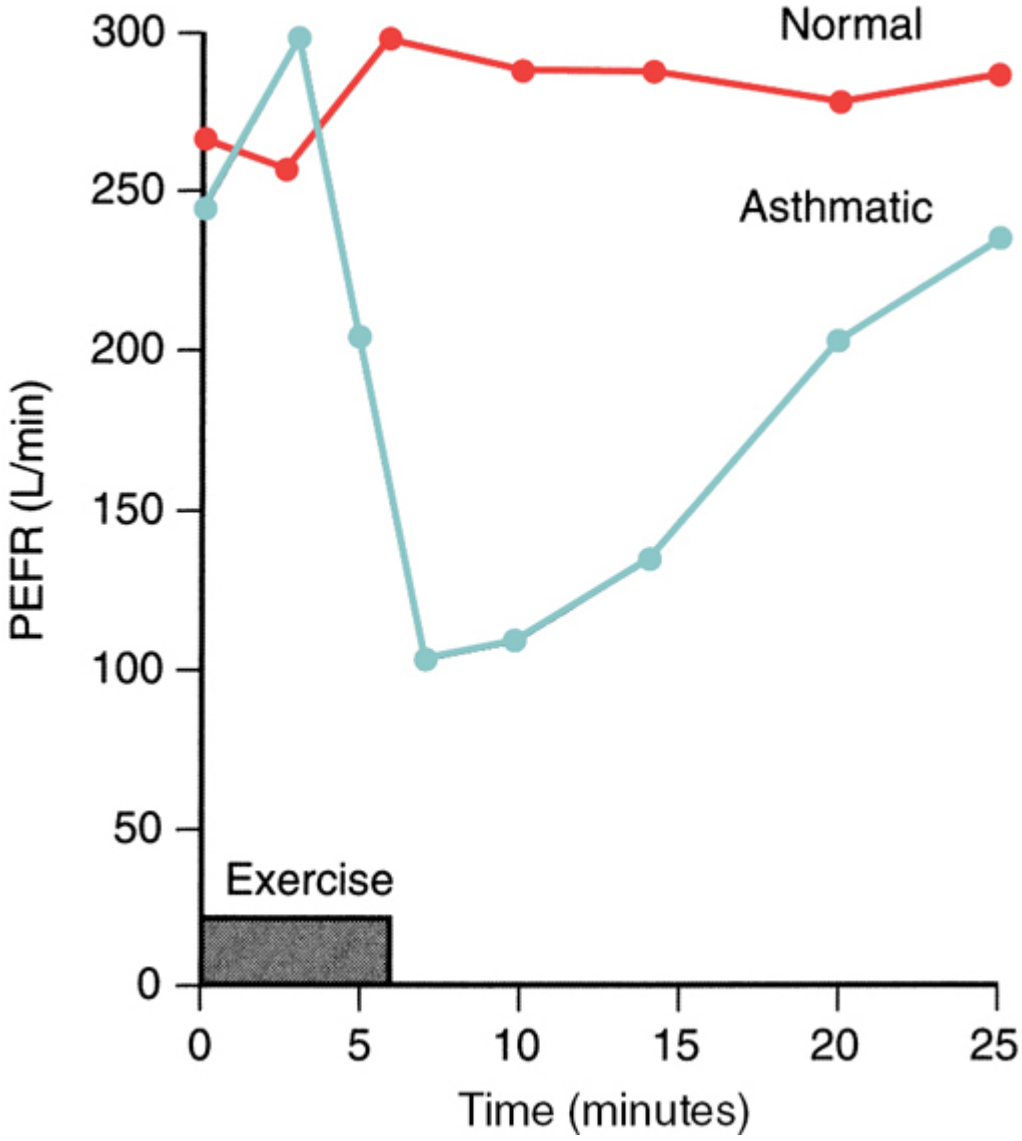


Figure 18-15 Changes in peak expiratory flow rate with exercise in a patient with asthma and a normal subject. PEFR, peak expiratory flow rate.

Hyperventilation of cold, dry air increases the sensitivity to EIB and induces bronchospasm.[84,85] The main stimulus for EIB is respiratory heat loss, water loss, or both, whereas breathing heated, humidified air completely blocks exercise-induced asthma (EIA) in many patients.[85] Masks are indicated for patients with EIA in the wintertime, and patients with severe asthma accompanied by EIB also should be encouraged to engage in other indoor exercises that do not promote EIB. A warm-up period before strenuous exercise is

helpful in some patients. With appropriate premedication, most EIB can be prevented, so virtually all patients with stable asthma should be encouraged to exercise. The mechanism of bronchoconstriction after airway heat and water loss is still incompletely understood.

Case 18-8, Question 2: What is the best course of action?

Although warming up at least 15 minutes before exercise and attempting to primarily breathe through the nose or through a scarf to warm up the inspired air may help to some degree, pharmacotherapy is the mainstay of prevention and treatment, with β-agonists playing the primary role.

About 15 minutes before exertion, either albuterol, two puffs (180 µg) or one to two puffs of formoterol-containing inhaler are highly effective in preventing significant bronchoconstriction.[85] Although any LABA-containing inhaler would be expected to work if administered at the appropriate time relative to its particular onset of action, formoterol has a faster onset of action compared to other LABAs, so it would be a reasonable choice to use either a mometasone/formoterol or budesonide/formoterol MDI at least 15 minutes before exercising. The duration would be expected to be ~10 to 12 hours with formoterol.

Other Treatments

Montelukast carries a specific indication for prevention of EIB in patients ages 6 years and older, and 5 to 10 mg (pediatric and adult doses, respectively) taken 2 hours before exercise produces a measurable but modest effect in preventing EIB. For example, Raissy et al[86] reported that EIB was prevented in 100% of the pediatric patients receiving albuterol compared with 55% receiving montelukast.

Chromones, which are mast cell stabilizers, can also be used in the prevention of EIB, but the duration of prevention is short (2–3 hours).[87] Cromolyn sodium 20 mg/2 mL nebulized solution is the only

available inhaled option from this class and should be administered 1 hour before exercise or exposure to other precipitating factors. As a controller, it needs to be taken four times per day, so consequently its overall use has fallen out of favor, making it a less attractive option.

J.Z. is prescribed mometasone/formoterol two puffs 15 minutes before exercise because this is the product on his health plan's formulary. Although this product is not specifically FDA approved for this use, he ends up using less than one inhaler per month, so his insurance company does not refuse to cover it in this situation.

CASE 18-8, QUESTION 3: Will EIB prevent J.Z. from becoming a successful 5K competitor?

No. Although J.Z. may not win any gold medals or pick up any contracts from athletic shoe manufacturers, it is not because of his EIB. There are many examples of world-class, elite athletes who have asthma and/or EIB that have competed successfully in both the Olympics and on professional sports teams such as David Beckham, Michael Phelps, and Jackie Joyner Kersee, to name just a few.

DRUG-INDUCED ASTHMA

The clinician should counsel the patient regarding the fact that patients with asthma who are aspirin sensitive often react to other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen by developing asthma symptoms with the first dose. The health care professional should suggest acetaminophen. If J.Z. says that acetaminophen does not give adequate relief of his pain, other options are salsalate or consultation with a board-certified allergist with experience in aspirin and NSAID desensitization. The clinician should also suggest consultation with an allergist regarding evidence that cyclooxygenase (COX)-2 inhibitors are safe in aspirin-sensitive asthma for a particular patient.[88] This case also points out the need

for health professionals to pay close attention to patient use of nonprescription medications. Although drug-induced asthma may present as relatively mild symptoms in some patients, fatal asthma caused by medicinal agents has been reported numerous times. The most extensive literature on drug-induced asthma involves NSAIDs and β-blockers. Other drugs and drug preservatives also can induce symptoms of asthma, but because the topic is beyond the scope of this chapter, the reader is referred to other sources[89–91] for further discussion.

The percentage of patients with asthma reported to have aspirin exacerbated respiratory disease ranges from 4% to 28%.[89–91] Clinical manifestations of aspirin sensitivity include rhinorrhea, mild wheezing, or severe, life-threatening shortness of breath. Once the reaction has occurred, there is a refractory period of 2 to 5 days.[90] If a patient with asthma is aspirin sensitive, it is likely that the patient also will react to most other NSAIDs. Aspirin and other NSAIDs share common mechanisms involving the arachidonic acid pathways, including inhibition of COX, which results in more rapid synthesis and overproduction of leukotrienes.[89–91] Montelukast has been found to at least be partially effective in blocking aspirin-induced asthma.[92] Because most patients with asthma do not react to aspirin and other NSAIDs, the NIH guidelines recommend avoiding these agents only in patients with known sensitivity.[2] In addition, patients with severe-persistent asthma or nasal polyps should be counseled regarding the risks associated with these drugs. In patients with known sensitivity, acetaminophen or salsalate is recommended for headaches and relatively minor pain.[2] For patients who are sensitive but who need to take aspirin (eg, after myocardial infarction [MI]) or an NSAID (eg, arthritis), it is possible to desensitize the patient, and daily use then prevents further reaction.[88] Prostaglandin D_2, one of the key mediators, is produced by eosinophils in aspirin-exacerbated disease.[93,94] Likewise, it has been noted that some of the biologics, omalizumab in particular, have resulted in the reversal of aspirin intolerance.[95,96] Although not as thoroughly studied, it has been noted in surveys that a significant

percentage of patients with asthma experience alcoholic drinks as a trigger.[97] In a small trial looking at alcohol sensitivity in asthma, 75% of the subset of patients with aspirin-exacerbated respiratory disease was found to have upper respiratory tract reactions with alcohol.[98]

When discussing drug-induced asthma, the other major consideration is β-blockers. These agents should be used with great caution in patients with asthma. Because even β_1-adrenergic blockers lose selectivity as dosages are increased, they, as well as nonselective β-blockers, should be avoided in most patients. Furthermore, ophthalmic timolol has been reported several times to cause fatal asthma, and should absolutely be avoided in patients with a history of asthma.[99] Other β-blocker eye drops (eg, betaxolol) have been reported to have less propensity to induce asthma, but all have some risk.[100,101]

Two notable exceptions to using β-blockers in patients with asthma are patients who are post-MI and patients with heart failure. Because β-blockers prolong life after an MI and improve the care of patients with heart failure, benefits versus risks should be weighed. Risks outweigh benefits if a patient has severe-persistent asthma. If a post-MI patient has intermittent asthma or well-controlled mild-to-persistent or moderate-to-persistent, asthma with optimal management, a low dosage of metoprolol is a reasonable consideration in which benefits may outweigh risks, with safe titration to goal dose. If the indication is hypertension, atenolol is another option and can be started at 50 mg/day, although, again, full benefits are not attained until the dose is adjusted to a goal BP. Patients with asthma have been shown to respond to inhaled β_2-agonists when receiving this dosage of atenolol.[102] For patients with heart failure, metoprolol controlled release/extended release (CR/XL) is the cardioselective β-blocker approved in the United States, whereas carvedilol, which has nonselective β-blocker as well as α-blocking properties, can worsen asthma symptoms or cause fatal asthma. A recent population-based nested case-control study comparing cardioselective β-blockers to non–cardioselective β-blockers in patients with asthma found that cardioselective β-blockers

prescribed to people with asthma and cardiovascular disease (CVD) were relatively safe and not associated with a significant increase in asthma exacerbations.[103] However, the authors did find both an overall increase in exacerbations and a dose–response effect of asthma exacerbations with non–cardioselective β-blockers, with exacerbations being more likely to occur with higher dosages.[103]

NOCTURNAL ASTHMA

CASE 18-9

QUESTION 1: R.R., a 41-year-old male, presents to the clinic with a history of coughing and shortness of breath and stuffy nose that awakens him virtually every night. Diagnosed with asthma in elementary school that has not bothered him much until recently, he is on step 1 treatment with low-dose ICSs taken whenever albuterol is taken as needed, although because he feels better instantly after the albuterol, he often fails to use the ICS. R.R.'s morning PEF is consistently in the yellow zone, usually about 400 L/minute (personal best of 600 L/minute), whereas in the early evening his PEF is consistently just <600 L/minute.

What is the next step?

Many patients with asthma experience symptoms that awaken them in the night or occur on awakening in the morning. Morning cough with or without bronchospasm may be a clue to nocturnal asthma. Although nocturnal asthma may be appropriately viewed as simply another manifestation of airway inflammation, it is so common and troublesome among patients with asthma that it deserves special note. When it occurs with any regularity, it is an indication that the asthma is not under control. Circadian rhythm in PEF is exaggerated in patients with asthma. The difference in PEF in normal subjects averages about 8% between 4 PM (maximal airflow) and 4 AM (minimal airflow), but in patients with asthma, the average variation can be as high as about 50%.[104] Several mechanisms account for this diurnal variation in PEF. The following are examples

of factors that contribute to nocturnal asthma: increased release of inflammatory mediators, increased activity of the parasympathetic nervous system, lower circulating levels of epinephrine, and lower levels of serum cortisol (lowest at about midnight).[104] In addition, for patients whose asthma is triggered by gastroesophageal reflux, this problem is worse at night, but treatment of this problem generally provides only minimal improvement in asthma management.[104]

The initial approach to managing nocturnal symptoms is the same as that for overall long-term therapy of persistent asthma, including adequate anti-inflammatory agents.[1,2] ICSs are often effective in eliminating or reducing nocturnal asthma, including symptoms and the drop in PEF. Also, the basic asthma treatment principle of good control of concomitant rhinitis and environmental control, especially in the bedroom (eg, house dust mites, household pets), should be considered in the patient with nocturnal asthma symptoms.

Because asthma is primarily an inflammatory disease and nocturnal symptoms are largely caused by airway inflammation, the first concern in R.R. is that he needs significant modifications to his regimen. By getting R.R. to change his regimen to 180 µg of budesonide (Pulmicort Flexhaler®) twice per day and switch to as-needed ICS/formoterol as the reliever (increasing his level of care to step 2), this is likely enough anti-inflammatory activity to prevent his nocturnal symptoms and provide adequate control throughout the day. Adding a daily dose of a nonsedating antihistamine (such as 10-mg loratadine or cetirizine, 5 mg of levocetirizine, or 180 mg of fexofenadine) may help with his rhinitis.

As part of optimal management of nocturnal asthma, R.R. also should be asked about avoiding or minimizing exposure to his asthma triggers (eg, if he is allergic to dogs, are there dogs in the bedroom?). Follow-up visits for R.R. should verify that the early morning and evening PEFs remain in the green zone and that symptoms, both during the night and on awakening in the morning, have been eliminated.

PATIENT EDUCATION

If optimal long-term drug therapy of asthma is prescribed, treatment may still fail or be suboptimal if the patient does not receive adequate education. Patients with asthma require special educational efforts because of the use of inhalation devices and peak flow meters. In addition, it often is a major challenge to have patients and parents understand the critical importance of long-term daily controller therapy and environmental control. Of course, an important first step in educating patients with asthma is to be caring and a good listener. Rather than sharing your knowledge initially, it is important to help establish a "partnership" with the patient by first asking the following question: "What is bothering you the most about your asthma?" Really listening to the patient and then addressing patient concerns is extremely important to successful education and long-term management.

Clinicians can be of invaluable assistance to the patient by repeatedly reinforcing education on the necessity of using anti-inflammatory therapies. Many patients underuse long-term preventive therapy because no health professional took the time to adequately instruct them that most asthma symptoms are preventable. Although underusing the most important medicines for long-term control, and recent literature and guidelines have emphasized the use of ICS/formoterol as the preferred reliever, many patients still overuse "quick relievers" (ie, SABAs). Health care providers must be able to detect these problems and intervene to enhance patient care.

Because a large percentage of patients have difficulty using inhaler devices, teaching patients the correct use of MDIs (alone or in combination with spacers) and dry powder inhalers is absolutely essential.[1,2] In one study, 89% of patients could not perform all of the steps for MDI use correctly.[105] Competent teaching requires observation of the patient using the devices initially and again on repeat visits to the clinic, hospital, or community pharmacy. Telling the patient about correct use is inadequate. Health professionals

must demonstrate the use of the devices (live or with videotapes) for patients who cannot use the devices correctly.

For videos that show proper use of many types of asthma inhalers and nebulizers, go to **https://www.nationaljewish.org/conditions/health-information/multimedia/devices-to-inhale-medication**.

Although there is more than one correct way to use an MDI, each manufacturer has gained FDA approval using one type of technique. Many asthma experts prefer to use a spacer or VHC to help ensure optimal efficacy. Spacers and VHCs are external devices that can be attached to the MDI, which may result in a larger amount of the aerosolized drug reaching the lungs instead, particularly in those who have difficulty coordinating the timing of actuation and inhalation. Proper MDI technique is difficult for many patients to master, and even those patients who display initial proficiency can experience a lapse in ability over time to correctly use an MDI. Much like a spacer, a VHC provides space in between the mouthpiece of the MDI and the mouth, but also incorporates a one-way valve that prevents exhalation into the device and may allow the patient to more easily and efficiently inhale the aerosolized drug particles. Upon actuation of the inhaler, the aerosol is suspended within the holding chamber, whereby the patient may take a single or, if needed, multiple inhalations from one actuation. Young children may particularly benefit from this device, which may also include a face mask. A VHC should be used in virtually all patients receiving ICSs via an MDI, even those with perfect MDI technique because a VHC enhances efficacy and reduces the risk of oropharyngeal candidiasis.[106–108] On the other hand, a VHC does not add efficacy to correct use of a β_2-agonist MDI. Although any VHC can be helpful, marketed devices that have a flow indicator whistle when inhalation is too fast are preferred (eg, AeroChamber®).

Some newer inhalers such as QVAR Redihaler® (beclomethasone) and ProAir RespiClick® (albuterol) are breath-actuated ones and do not need to be used with any type of VHC. In addition, there are now breath-activated "smart" inhalers (see Case 18-4) that measure inspiratory flow and patient adherence, and then upload this information to an application to be viewed by the patient and physician.

Studies have shown that health professionals, similar to some patients, generally are not competent in using MDIs.[106–108] Obviously, the clinician should practice with a placebo inhaler and gain competence before teaching a patient. Among clinicians who educate patients, pharmacists can be helpful in teaching correct use of MDIs. Unfortunately, many times, community pharmacists may not have the resources (ie, sufficient time and management support) and are not providing such teaching.

In addition to teaching the correct use of MDIs and spacers, clinicians should help patients via education regarding the correct use of breath-activated dry powder inhalers (eg, Twisthaler®, Diskus®, Flexhaler®, Ellipta®, RespiClick®) and nebulizing machines.[1,2] When using the Flexhaler®, for example, patients must clearly understand the need for a rapid (preferably 60 L/minute), deep inhalation (not slow as with an MDI). Adequate PIF rates may be difficult for some young children and elderly to generate.[109] In addition, patients need to breath-hold 10 seconds, if possible, as with an MDI.

Asthma Self-Management Plans

Objective monitoring of lung function at home with the use of peak flow meters can be very helpful to patients and health care professionals. EPR-3 discusses the debates about PEF versus symptom-based action plans.[2] Use of peak flow meters may be valuable in patients who have had severe exacerbations and those who are "poor perceivers" of deteriorating asthma control. Instructing patients on the correct use of the devices, including use of the green,

yellow, and red zones, is essential.[2] After establishing that optimal therapy has maintained the PEF in the "green zone" in the early morning, most patients can simply verify their values once daily in the early morning. Analogous to a traffic light, green, yellow, and red zones have been established to guide the patient and clinician. The green zone refers to a PEF that is 80% to 100% of "personal best" and generally indicates that therapy is providing good control. Before a course of optimal therapy to attain a personal best, the zones are set based on predicted values found in each peak flow meter package insert. The yellow zone indicates a PEF that is 50% to 79% of personal best. Patients should be instructed to call their physician or other health care provider for adjustment in preventive medication if the PEF stays in the yellow zone after using two puffs of a fast-acting β_2-agonist. The red zone indicates a PEF that is <50% of personal best. The patient should know to call his or her health care provider immediately if the use of an inhaled β_2-agonist does not bring the PEF to the yellow or green zone. **Figure 18-16** provides an example of PEF monitoring, and **Figure 18-17** gives an example of a written action plan.

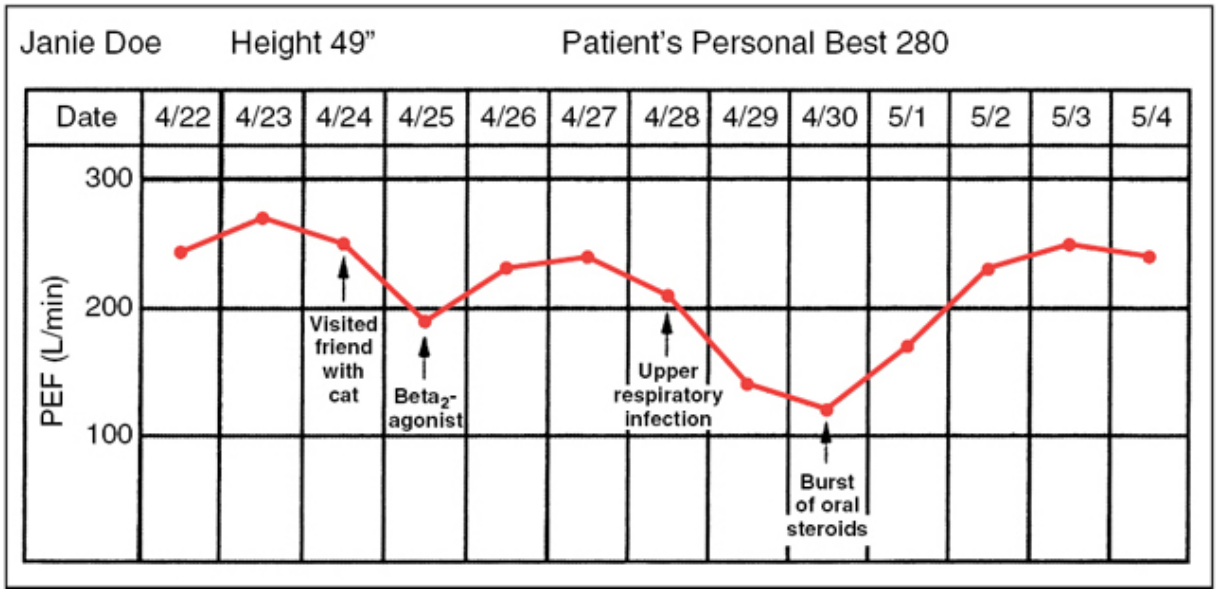


Figure 18-16 Asthma changes with time: patient monitoring and follow-up required. PEF, peak expiratory flow. (Adapted from National Institutes of Health. *Practical Guide for the Diagnosis and*

Management of Asthma. National Heart, Lung, and Blood Institute; 1997. NIH publication no. 97-4053.)

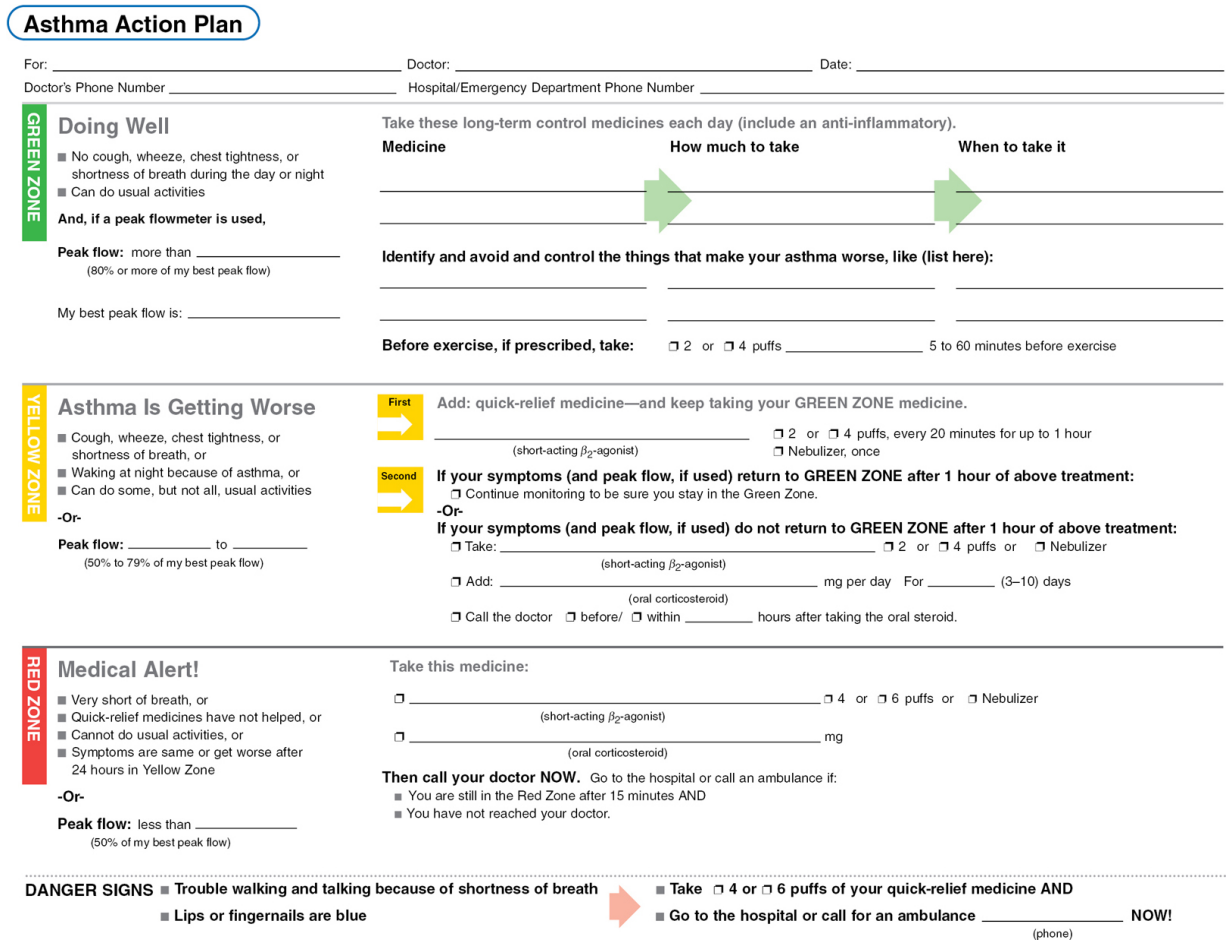


Figure 18-17 Sample asthma action plan. (Adapted from National Institutes of Health. *Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma*. National Heart, Lung, and Blood Institute; 2007. NIH Publication no. 08-4051.)

Correct use of the peak flow meter includes standing, inhaling completely, forming a tight seal with the lips around the mouthpiece, exhaling as hard and fast as possible (blast!), and repeating this maneuver twice; the best of three attempts should be recorded. Beyond giving maximal effort when using peak flow meters, patients should be instructed to place the instrument well into the mouth on top of the tongue to avoid acceleration of air in the mouth with the

tongue and buccal musculature. In essence, “spitting” into the peak flow meter causes a dramatic false elevation in PEF.[110]

All patients need education regarding the benefits of long-term inhaled anti-inflammatory therapy. The clinician should explain with enthusiasm that controller medications are extremely effective and that it is the cornerstone of asthma management. The delayed onset and safety of ICSs must be stressed as well as the requirement of regular use every day. Showing the patient colored pictures, models, or a video of inflamed airways can be very helpful—these teaching aids are available from several pharmaceutical manufacturers. Finally, MDIs need special care, and every patient requires education on cleaning the actuator.

OUTCOMES

CASE 18-9, QUESTION 2: R.R. returns to the clinic 4 weeks later, and says he feels fantastic. How do you reinforce his success to increase the likelihood of long-term improvement?

Numerous studies have documented that applying the principles of the evidence-based guidelines[1,2] results in improved clinical outcomes, and many of these studies have been summarized in GINA.[2] Several studies have documented that pharmacists who are highly knowledgeable about asthma guidelines and who work closely with patients and physicians improve outcomes, including reduced ED visits and hospitalizations.[111] These successful studies involved highly motivated pharmacists, who were asthma experts based in university-affiliated clinics or in large private health maintenance organizations.

A randomized controlled trial based in community pharmacies in Canada with specially trained pharmacists has also shown very positive outcomes for patients with asthma.[112] When assessing the effect of comprehensive management on clinical outcomes, quality-of-life measures should be assessed (a validated questionnaire [the

Asthma Control Test] is shown in EPR-3[2]) as well as reduction in ED visits and hospitalizations.[1,2] To achieve optimal outcomes, attention to each of the four major components of management is required (objective assessment, environmental control, pharmacologic therapy, and patient education as a partnership). Examples of areas that pose special challenges for inner-city patients include psychosocial factors, exposure to cockroaches and rodents, underuse of controller medications, and passive cigarette smoke.[113] As part of overall management to improve outcomes, studies have emphasized again the importance of good inhalation technique with ICSs and education in the use of peak flow meters.

Targeted educational and intervention efforts in older (older than 60 years)[114] and in preschool-age[115] patients have been proved that these types of protocols can decrease ED visits and increase the quality of life.

Emphasizing the need for annual influenza vaccination in October is important. In addition, patients with asthma age older than 19 years should receive pneumococcal vaccine, and patients age 65 years and older should receive pneumococcal conjugate vaccine (see Chapter 64, Vaccinations for more details). Reinforcement of the importance of continued preventive therapy that has given such remarkable success is appropriate for R.R. and reassuring him that he is well in control of his asthma. The clinician should continue to work with him to further tailor the therapy, including control of rhinitis, to maintain optimal outcomes at the lowest dosages and on the simplest possible regimen. Research has further emphasized the goal of simplified regimens and achieving the lowest effective doses of anti-inflammatory therapy.

NONDRUG OPTIONS

CASE 18-9, QUESTION 3: R.R. is in the clinic a few months later. He is continuing to have excellent control of his asthma and allergic rhinitis. What is

your opinion on alternative nondrug options to lessen his reliance on prescriptions?

Complementary and alternative approaches have been used in the treatment of asthma, with one study finding teas and herbs as the most commonly used alternatives to prescription medicines. As with any herbal product, although some may work to a degree, such as ma huang, which contains ephedra (a bronchodilator), they are unregulated, and not well studied in terms of drug interactions and toxicity.[116] Also, as Roy et al discovered, it is not uncommon for a patient who takes herbals to decrease their intake of their prescribed effective medication, in this case, ICSs.[117]

Although not a “complementary alternative” therapy, bronchial thermoplasty, which aims to reduce smooth muscle tissue, thereby decreasing the amount of muscle available for bronchoconstriction, has been demonstrated to be efficacious in the management of severe, refractory asthma in selected cases.[118] However, the 2020 NIH guidelines recommend against its routine use outside of clinical trials because of both short-term risk and unknown long-term adverse events. However, in an individual case, it may be used where the benefits are deemed to outweigh the risks (a conditional recommendation against its use).[15]

Although it is unlikely that one single change (such as using a high-efficiency particulate air [HEPA] vacuum) to reduce a specific allergen exposure in the household will have a significant impact in lessening symptoms, multiple changes, such as pest control plus mold removal plus using a dust mite pesticide, for example, may be beneficial. For a complete list of mitigation strategies, the reader is referred to the 2020 Focused Updates to the Asthma Management Guidelines.[16] Sublingual immunotherapy (SLIT) is relatively new and is still being trialed in the United States, and was also not generally recommended for allergic asthma in the 2020 NIH guidelines (a “conditional” recommendation against its use).[16] However, specifically in the form of sublingual tablets, SLIT could be used in patients on a case-by-case basis, particularly in patients, for example, with asthma and concomitant allergic rhinoconjunctivitis

after shared decision between clinician and patient weighing the risks and benefits.[16] In contrast, subcutaneous immunotherapy (SCIT) has a long track record and is recognized as potentially beneficial by improving quality of life in patients with asthma with a concomitant allergy to which the patient is sensitive and regularly exposed.[16]

ACKNOWLEDGMENT

The authors gratefully acknowledge Timothy H. Self for his expert guidance and contributions for many previous editions.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide–formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378(*20*):1877–1887. (43)

Busse WW, Bateman ED, Caplan AL, et al. Combined analysis of asthma safety trials of long-acting β_2-agonists. *N Engl J Med*. 2018;378(*26*):2497–2505. (67)

Kerstjens HA, Casale TB, Bleecker ER, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. *Lancet Respir Med*. 2015;3(*5*):367–376. (74)

Lazarus SC, Krishnan JA, King TS, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. *N Engl J Med*. 2019;380(*21*):2009–2019. (8)

Price D, Fletcher M, Molen TVD. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *Prim Care Respir Med*. 2014;24:14009. (25)

Key Websites

https://ginasthma.org

https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines

https://www.thoracic.org/professionals/clinical-resources/disease-related-resources/asthma.php

COMPLETE REFERENCES CHAPTER 18 ASTHMA

1. Gina.org. Accessed October 4, 2020. https://ginasthma.org
2. National Institutes of Health. *National Asthma Education and Prevention Program: Expert Panel Report III: Guidelines for the Diagnosis and Management of Asthma*. National Heart, Lung, and Blood Institute; 2007. NIH publication no. 08-4051. Accessed September 15, 2020. https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma
3. Centers for Disease Control and Prevention. Asthma. Accessed October 12, 2020. https://www.cdc.gov/nchs/fastats/asthma.htm
4. Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008–2013. *Ann Am Thorac Soc*. 2018;15(3):348–356.
5. Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying cause of death 1999–2020. CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999–2018, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed November 16, 2020. http://wonder.cdc.gov/ucd-icd10.html
6. Barnes PJ. Asthma mechanisms. *Medicine*. 2016;44(5):265–270.
7. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet*. 2018;391(10122):783–800.
8. Lazarus SC, Krishnan JA, King TS, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. *N Engl J Med*. 2019;380(21):2009–2019.

9. Tarlo SM, Lemiere C. Occupational asthma. *N Engl J Med*. 2014;370(7):640–649.
10. Mohanan S, Tapp H, McWilliams A, Dulin M. Obesity and asthma: pathophysiology and implications for diagnosis and management in primary care. *Exp Biol Med (Maywood)*. 2014;239(11):1531–1540.
11. Grainge CL, Lau LC, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma [published correction appears in *N Engl J Med*. 2018 Jun 13;378(25):2450]. *N Engl J Med*. 2011;364(21):2006–2015.
12. Krishnan JA, Nibber A, Chisholm A, et al. Prevalence and characteristics of asthma-chronic obstructive pulmonary disease overlap in routine primary care practices. *Ann Am Thorac Soc*. 2019;16(9):1143–1150.
13. Boonpiyathad T, Sözener ZC, Satitsuksanoa P, Akdis CA. Immunologic mechanisms in asthma. *Semin Immunol*. 2019;46:101333.
14. Wan XC, Woodruff PG. Biomarkers in severe asthma. *Immunol Allergy Clin North Am*. 2016;36(3):547–557.
15. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2020;55(1):1900588.
16. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, Blake KV, et al. 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217–1270.
17. Carpagnano GE, Scioscia G, Lacedonia D, et al. Looking for airways periostin in severe asthma. *Chest*. 2018;154(5):1083–1090.
18. Okada H, Kuhn C, Feillet H, Bach JF. The “hygiene hypothesis” for autoimmune and allergic diseases: an update. *Clin Exp Immunol*. 2010;160(1):1–9.
19. Grayson MH, Feldman S, Prince BT, Patel PJ, Matsui EC, Apter AJ. Advances in asthma in 2017: mechanisms, biologics, and genetics. *J Allergy Clin Immunol*. 2018;142(5):1423–1436.
20. Shrine N, Portelli MA, John C, et al. Moderate-to-severe asthma in individuals of European ancestry: a genome-wide association study. *Lancet Respir Med*. 2019;7(1):20–34.
21. Kirjavainen PV, Karvonen AM, Adams RI, et al. Farm-like indoor microbiota in non-farm homes protects children from asthma development [published correction appears in *Nat Med*. 2019 Aug;25(8):1319]. *Nat Med*. 2019;25(7):1089–1095.
22. Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the

EAACI Guidelines—recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75(5):1023–1042.
23. Murphy VE, Gibson PG. Premenstrual asthma: prevalence, cycle-to-cycle variability and relationship to oral contraceptive use and menstrual symptoms. *J Asthma*. 2008;45(8):696–704.
24. Dunican EM, Watchorn DC, Fahy JV. Autopsy and imaging studies of mucus in asthma. Lessons learned about disease mechanisms and the role of mucus in airflow obstruction. *Ann Am Thorac Soc*. 2018;15(suppl 3):S184–S191.
25. Price D, Fletcher M, Molen TVD. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med*. 2014;24:14009.
26. Aaron SD, Vandemheen KL, Fitzgerald JM, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA*. 2017;317(3):269–279.
27. Dempsey TM, Scanlon PD. Pulmonary function tests for the generalist: a brief review. *Mayo Clin Proc*. 2018;93(6):763–771.
28. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med*. 2019;200(8):e70–e88.
29. Arnold DH, Gebretsadik T, Moons KG, Harrell FE, Hartert TV. Development and internal validation of a pediatric acute asthma prediction rule for hospitalization. *J Allergy Clin Immunol Pract*. 2015;3(2):228–235.
30. Brunetti L, Poiani G, Dhanaliwala F, Poppiti K, Kang H, Suh DC. Clinical outcomes and treatment cost comparison of levalbuterol versus albuterol in hospitalized adults with chronic obstructive pulmonary disease or asthma. *Am J Health Syst Pharm*. 2015;72(12):1026–1035.
31. Cydulka RK, Emerman CL, Muni A. Levalbuterol versus levalbuterol plus ipratropium in the treatment of severe acute asthma. *J Asthma*. 2010;47(10):1094–1100.
32. Iramain R, López-Herce J, Coronel J, Spitters C, Guggiari J, Bogado N. Inhaled salbutamol plus ipratropium in moderate and severe asthma crises in children. *J Asthma*. 2011;48(3):298–303.
33. Razi CH, Cörüt N, Andıran N. Budesonide reduces hospital admission rates in preschool children with acute wheezing. *Pediatr Pulmonol*. 2017;52(6):720–728.
34. Alangari AA, Malhis N, Mubasher M, et al. Budesonide nebulization added to systemic prednisolone in the treatment of acute asthma in children: a double-blind, randomized, controlled trial. *Chest*. 2014;145(4):772–778.
35. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev*. 2013;2013(9):CD000052.

36. Nian AL, Orr RJ, Schroeder SK. A report of an asthma pathway leading to improved resource use. *J Pediatr Pharmacol Ther*. 2018;23(4):298–304. doi:10.5863/1551-6776-23.4.298
37. Iramain R, Castro-Rodriguez JA, Jara A, et al. Salbutamol and ipratropium by inhaler is superior to nebulizer in children with severe acute asthma exacerbation: randomized clinical trial. *Pediatr Pulmonol*. 2019;54(4):372–377.
38. Abaya R, Delgado EM, Scarfone RJ, et al. Improving efficiency of pediatric emergency asthma treatment by using metered dose inhaler. *J Asthma*. 2018;56(10):1079–1086.
39. Schuh S, Parkin P, Rajan A, et al. High-versus low-dose, frequently administered, nebulized albuterol in children with severe, acute asthma. *Pediatrics*. 1989;83(4):513–518.
40. Schuh S, Reider MJ, Canny G, et al. Nebulized albuterol in acute childhood asthma: comparison of two doses. *Pediatrics*. 1990;86(4):509–513.
41. Self TH, Twilla JD, Rogers ML, Rumbak MJ. Inhaled corticosteroids should be initiated before discharge from the emergency department in patients with persistent asthma. *J Asthma*. 2009;46(10):974–979.
42. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA*. 2018;319(14):1485–1496.
43. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide–formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378(20):1877–1887.
44. Haney S, Hancox RJ. Recovery from bronchoconstriction and bronchodilator tolerance. *Clin Rev Allergy Immunol*. 2006;31(2–3):181–196.
45. Haney S, Hancox RJ. Overcoming beta-agonist tolerance: high dose salbutamol and ipratropium bromide. Two randomised controlled trials. *Respir Res*. 2007;8(1):19. doi:10.1186/1465-9921-8-19
46. Beigelman A, Chipps BE, Bacharier LB. Update on the utility of corticosteroids in acute pediatric respiratory disorders. *Allergy Asthma Proc*. 2015;36(5):332–338.
47. Cooper PR, Panettieri RA Jr. Steroids completely reverse albuterol-induced beta(2)-adrenergic receptor tolerance in human small airways. *J Allergy Clin Immunol*. 2008;122(4):734–740.
48. Schuh S, Reisman J, Alshehri M, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med*. 2000;343:689–694.
49. Alangari AA. Corticosteroids in the treatment of acute asthma. *Ann Thorac Med*. 2014;9(4):187–192. doi:10.4103/1817-1737.14012
50. Cunnington D, Smith N, Steed K, Rosengarten P, Kelly AM, Teichtahl H. Oral versus intravenous corticosteroids in adults hospitalised with acute asthma.

Pulm Pharmacol Ther. 2005;18(3):207–212.
51. Hossein S, Pegah A, Davood F, et al. The effect of nebulized magnesium sulfate in the treatment of moderate to severe asthma attacks: a randomized clinical trial. *Am J Emerg Med*. 2016;34(5):883–886.
52. Schuh S, Sweeney J, Rumantir M, et al. Effect of nebulized magnesium vs placebo added to albuterol on hospitalization among children with refractory acute asthma treated in the emergency department: a randomized clinical trial. *JAMA*. 2020;324(20):2038–2047.
53. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β_2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J*. 2020;55(4):1901872.
54. Boonsawat W, Thinkhamrop B. Role of budesonide/formoterol maintenance and reliever therapy: a pragmatic study. *Asian Pac J Allergy Immunol*. 2014;32(2):160–165.
55. Stempel DA, Szefler SJ, Pedersen S, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. *N Engl J Med*. 2016;375(9):840–849.
56. Kwda A, Gldc P, Baui B, et al. Effect of long term inhaled corticosteroid therapy on adrenal suppression, growth and bone health in children with asthma. *BMC Pediatr*. 2019;19(1):411.
57. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. *Cochrane Database Syst Rev*. 2014;(7):CD009878.
58. Allen DB. Effects of inhaled steroids on growth, bone metabolism, and adrenal function. *Adv Pediatr*. 2006;53:101–110.
59. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012;367(10):904–912.
60. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet*. 2003;361(9363):1071–1076.
61. Weatherall M, Clay J, James K, Perrin K, Shirtcliffe P, Beasley R. Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis. *Respirology*. 2009;14(7):983–990.
62. Shroff S, Thomas RK, D'Souza G, Nithyanandan S. The effect of inhaled steroids on the intraocular pressure. *Digit J Ophthalmol*. 2018;24(3):6–9.
63. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000;343(5):332–336.
64. Lemanske RF, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med*. 2010;362:975–985.

65. Berger WE, Noonan MJ. Treatment of persistent asthma with Symbicort (budesonide/formoterol inhalation aerosol): an inhaled corticosteroid and long-acting beta2-adrenergic agonist in one pressurized metered-dose inhaler. *J Asthma*. 2010;47(4):447–459.
66. Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol [published correction appears in *Chest*. 2006;129:1393]. *Chest*. 2006;129:15–26.
67. Busse WW, Bateman ED, Caplan AL, et al. Combined analysis of asthma safety trials of long-acting β_2-agonists. *N Engl J Med*. 2018;378(26):2497–2505.
68. Stapleton M, Howard-Thompson A, George C, Hoover RM, Self TH. Smoking and asthma. *J Am Board Fam Med*. 2011;24(3):313–322.
69. Szefler SJ, Carlsson LG, Uryniak T, Baker JW. Budesonide inhalation suspension versus montelukast in children aged 2 to 4 years with mild persistent asthma. *J Allergy Clin Immunol Pract*. 2013;1(1):58–64.
70. Szefler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. *J Allergy Clin Immunol*. 2007;120(5):1043–1050.
71. Zhang HP, Jia CE, Lv Y, Gibson PG, Wang G. Montelukast for prevention and treatment of asthma exacerbations in adults: systematic review and meta-analysis. *Allergy Asthma Proc*. 2014;35(4):278–287.
72. Singulair. Package insert. Merck and Co Inc.; 2021.
73. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*. 2012;367(13):1198–1207.
74. Kerstjens HA, Casale TB, Bleecker ER, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. *Lancet Respir Med*. 2015;3(5):367–376.
75. Baan EJ, Hoeve CE, DeRidder MA, et al. (in)Appropriate LAMA prescribing in asthma patients: a cohort analysis (the ALPACA study). *Eur Respir J*. 2020;56:2644.
76. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med*. 2019;199(4):433–445.
77. Global Initiative for Asthma. Difficult-to-treat & severe asthma in adolescent and adult patients, diagnosis and management. 2018. Accessed March 7, 2021. https://ginasthma.org/severeasthma/
78. Strunk RC, Bloomberg GR. Omalizumab for asthma. *N Engl J Med*. 2006;354:2689–2695.
79. Pelaia C, Paoletti G, Puggioni F, et al. Interleukin-5 in the pathophysiology of severe asthma. *Front Physiol*. 2019;10:1514.
80. Nucala. Package insert. GlaxoSmithKline; 2015.

81. Cinqair. Package insert. Teva; 2016.
82. Fasenra. Package insert. AstraZeneca; 2019.
83. Dupixent. Package insert. Regeneron; 2020.
84. Weiler JM, Brannan JD, Randolph CC, et al. Exercise-induced bronchoconstriction update-2016. *J Allergy Clin Immunol*. 2016;138(5):1292–1295.
85. Backer V, Mastronarde J. Pharmacologic strategies for exercise-induced bronchospasm with a focus on athletes. *Immunol Allergy Clin North Am*. 2018;38(2):231–243.
86. Raissy HH, Harkins M, Kelly F, Kelly HW. Pretreatment with albuterol versus montelukast for exercise-induced bronchospasm in children. *Pharmacotherapy*. 2008;28(3):287–294.
87. de Benedictis FM, Tuteri G, Pazzelli P, Bertotto A, Bruni L, Vaccaro R. Cromolyn versus nedocromil: duration of action in exercise-induced asthma in children. *J Allergy Clin Immunol*. 1995;96(4):510–514.
88. Macy E, Bernstein JA, Castells MC, et al. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper. *Ann Allergy Asthma Immunol*. 2007;98:172–174.
89. Babu KS, Marshall BG. Drug-induced airway disease. *Clin Chest Med*. 2004;25:113–125.
90. Woessner KM. Update on aspirin-exacerbated respiratory disease. *Curr Allergy Asthma Rep*. 2017;17(1):2.
91. Lo PC, Tsai YT, Lin SK, Lai JN. Risk of asthma exacerbation associated with nonsteroidal anti-inflammatory drugs in childhood asthma: a nationwide population-based cohort study in Taiwan. *Medicine (Baltimore)*. 2016;95(41):e5109.
92. Lee DK, Haggart K, Robb FM, Lipworth BJ. Montelukast protects against nasal lysine-aspirin challenge in patients with aspirin-induced asthma. *Eur Respir J.* 2004;24(2):226–230.
93. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D_2: a dominant mediator of aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2015;135(1):245–252.
94. Feng X, Ramsden MK, Negri J, et al. Eosinophil production of prostaglandin D2 in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2016;138(4):1089–1097.
95. Hayashi H, Fukutomi Y, Mitsui C, et al. Omalizumab for aspirin hypersensitivity and leukotriene overproduction in aspirin-exacerbated respiratory disease. a randomized controlled trial. *Am J Respir Crit Care Med*. 2020;201(12):1488–1498.
96. Guillén D, Bobolea I, Calderon O, et al. Aspirin desensitization achieved after omalizumab treatment in a patient with aspirin-exacerbated urticaria and respiratory disease. *J Investig Allergol Clin Immunol*. 2015;25(2):133–135.

97. Vally H, Thompson PJ. Allergic and asthmatic reactions to alcoholic drinks. *Addict Biol*. 2003;8:3–11.
98. Cardet JC, White AA, Barrett NA, et al. Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease. *J Allergy Clin Immunol Pract*. 2014;2(2):208–213.
99. Odeh M. Timolol eyedrop-induced fatal bronchospasm in an asthmatic patient. *J Fam Pract*. 1991;32:97
100. Morales DR, Dreischulte T, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blocker eye drops in asthma: population-based study and meta-analysis of clinical trials. *Br J Clin Pharmacol*. 2016;82(3):814–822.
101. Dunn TL, Gerber MJ, Shen AS, Fernandez E, Iseman MD, Cherniack RM. The effect of topical ophthalmic instillation of timolol and betaxolol on lung function in asthmatic subjects. *Am Rev Respir Dis*. 1986;133:264–268.
102. Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Adverse respiratory effect of acute β-blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials. *Chest*. 2014;145(4):779–786.
103. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. *BMC Med*. 2017;15(1):18.
104. Greenberg H, Cohen RI. Nocturnal asthma. *Curr Opin Pulm Med*. 2012;18(1):57–62.
105. Self TH, Wallace JL, George CM, Howard-Thompson A, Schrock SD. Inhalation therapy: help patients avoid these mistakes. *J Fam Pract*. 2011;60:714–721.
106. Klijn SL, Hiligsmann M, Evers S, Roman-Rodriguez M, van der Molen T, van Boven JFM. Effectiveness and success factors of educational inhaler technique interventions in asthma & COPD patients: a systematic review. *NPJ Prim Care Respir Med*. 2017;27:24.
107. Giraud V, Allaert FA, Roche N. Inhaler technique and asthma: feasability and acceptability of training by pharmacists. *Respir Med*. 2011;105:1815–1822.
108. Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? *ERJ Open Res*. 2018;4(2). doi:10.1183/23120541.00065-2018
109. Vogelberg C, Kremer HJ, Ellers-Lenz B, et al. Clinical evaluation of the peak inspiratory flow generated by asthmatic children through the Novolizer®. *Respir Med*. 2004;98(10):924–931.
110. Strayhorn V, Leeper K, Tolley E, Self T. Elevation of peak expiratory flow by a “spitting” maneuver: measured with five peak flowmeters. *Chest*. 1998;113:1134–1136.
111. Garcia-Cardenas V, Armour C, Benrimoj SI, Martinez-Martinez F, Rotta I, Fernandez-Llimos F. Pharmacists interventions on clinical asthma outcomes:

a systematic review. *Eur Respir J*. 2015;47(4):1134–1143.
112. McLean W, Gillis J, Waller R. The BC Community Pharmacy Asthma Study: a study of clinical, economic and holistic outcomes influenced by an asthma care protocol provided by specially trained community pharmacists in British Columbia. *Can Respir J*. 2003;10:195–202.
113. Gergen PJ, Togias A. Inner city asthma. *Immunol Allergy Clin North Am*. 2015;35(1):101–114.
114. Federman AD, O'Conor R, Mindlis I, et al. Effect of a self-management support intervention on asthma outcomes in older adults: the SAMBA study randomized clinical trial. *JAMA Intern Med*. 2019;179(8):1113–1121.
115. Eakin MN, Zaeh S, Eckmann T, et al. Effectiveness of a home-and school-based asthma educational program for head start children with asthma: a randomized clinical trial. *JAMA Pediatr*. 2020;174(12):1191–1198.
116. Clark CE, Arnold E, Lasserson TJ, Wu T. Herbal interventions for chronic asthma in adults and children: a systematic review and meta-analysis. *Prim Care Respir J*. 2010;19(4):307–314.
117. Roy A, Lurslurchachai L, Halm EA, Li XM, Leventhal H, Wisnivesky JP. Use of herbal remedies and adherence to inhaled corticosteroids among inner-city asthmatic patients. *Ann Allergy Asthma Immunol*. 2010;104(2):132–138.
118. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med*. 2010;181:116–124

19

Chronic Obstructive Pulmonary Disease

Timothy R. Hudd and Kathy Zaiken

CORE PRINCIPLES

1 Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and a range of pathologic changes in the lung, some significant extrapulmonary effects, and important comorbidities that may contribute to the severity of the disease in individual patients. Cigarette smoking is the major risk factor for COPD, and most cases of COPD are attributed to a current or past history of cigarette smoking. Exposure to indoor and outdoor air pollution, occupational dusts and fumes, and abnormal lung growth

CHAPTER CASES

Case 19-1 (Question 1)

	and development are other significant risk factors.	
2	Inhalation of noxious particles or gases, such as cigarette smoke, leads to the activation of resident immune and parenchymal cells, which, in turn, recruit additional inflammatory cells from the systemic compartment into the lung. The exact mechanisms responsible for the pathogenesis of COPD are not entirely clear, but likely involve activation of the innate and adaptive immune system, leading to chronic inflammation.	**Case 19-2 (Question 2)**
3	As COPD progresses, additional systemic consequences can arise, including cachexia, cardiac and skeletal muscle dysfunction, osteoporosis, depression, and anemia. Pulmonary rehabilitation is recommended to address these systemic manifestations.	**Case 19-2 (Question 5)**
4	The diagnosis of COPD is based on the presence of risk factors, clinical symptoms, and airflow obstruction determined by spirometric testing. Generally, COPD manifests in the fourth or fifth decade of life with symptoms of cough, wheeze, or dyspnea on exertion. The severity of disease is based on a grading system, which then guides therapy.	**Case 19-1 (Questions 1, 2)**
5	The only interventions that have been	**Case 19-1 (Question**

	consistent shown to reduce mortality in COPD are smoking cessation, oxygen therapy for patients with severe hypoxemia at rest, and lung volume reduction surgery for very select patients with advanced emphysema. Medications are an important component of therapy and are aimed at alleviating symptoms and reducing future risk of exacerbations.	**3)**
6	Bronchodilators are central to the symptomatic management of COPD and include short-acting β_2-agonist and long-acting β_2-agonist (LABA), short- and long-acting anticholinergic agents, and theophylline.	**Case 19-2 (Questions 1, 3, 4)** **Case 19-3 (Questions 2, 3)**
7	A combined long-acting bronchodilator therapy improves lung function over monotherapy and is recommended for severe breathlessness, while daily use of an inhaled corticosteroid in combination with a LABA may be effective in patients who experience frequent or severe exacerbations and have elevated serum eosinophils or in patients with a history or findings suggestive of asthma, whereas systemic corticosteroids are only advocated for short-term use owing to the risk of adverse effects.	**Case 19-2 (Question 3)**
8	Antibiotic use in the setting of an acute exacerbation should be made based on	**Case 19-3 (Question 1)**

	the presence of the following symptoms: increased dyspnea, sputum volume, and sputum purulence.	
9	Individual patient factors should be considered before prescribing long-term oxygen supplementation in patients with stable COPD who experience mild-to-moderate desaturation while at rest or during exercise. However, long-term oxygen administration (>15 hours/day) has been shown to improve survival in patients with severe resting hypoxemia (PaO_2 ≤7.3 kPa [55 mm Hg] or SaO_2 ≤88%), when confirmed twice over a 3-week period. Supplemental oxygen should be titrated to a target saturation of ≥90% for maintenance in stable COPD.	**Case 19-4 (Question 1)**
10	Lung volume reduction surgery, which involves the surgical removal of parts of the lung to improve hyperinflation, can significantly improve quality of life, exercise tolerance, and mortality in patients with severe upper lobe emphysema and low exercise capacity despite pulmonary rehabilitation.	**Case 19-4 (Question 2)**

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable airway disorder characterized by

persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities.[1] Dyspnea is the hallmark symptom of COPD, which may be accompanied by other common symptoms such as cough and sputum production. Airflow limitation is generally not fully reversible and attributed to an enhanced chronic inflammatory response in the airways following significant exposure to cigarette smoke, biomass fuels, and other noxious particles or gases.[1,2] Host factors including abnormal lung development, genetic abnormalities, and advanced age may predispose individuals to developing COPD.[1]

Emphysema (lung parenchymal destruction) and *chronic bronchitis* (chronic cough and phlegm production) are two commonly used terms that reflect disease spectrum and are often used as pathologic subtypes or *phenotypes* of COPD. More recent definitions have transitioned away from these terms, as pathologic features from both likely contribute to airflow limitation in patients with COPD.[1]

In 2001, the National Institutes of Health (NIH) and the World Health Organization (WHO) collaborated to develop the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report.[1] This document is updated annually and offers evidence-based strategies for the diagnosis, assessment, and management of COPD. In addition, other international expert groups have developed consensus guidelines aimed toward the prevention and management of acute exacerbations associated with COPD.[3,4]

Asthma is a separate and distinct obstructive airway disorder with features similar to COPD. However, airflow limitation and symptoms such as wheezing, cough, dyspnea, and chest tightness are usually episodic and reversible. Some patients may present with clinical features from both conditions, with 15% to 32% of patients sharing a dual diagnosis of asthma and COPD.[5] The term *asthma–COPD overlap* (ACO) is a common descriptor used in clinical practice to collectively describe patients who have persistent airflow limitation along with clinical features of both asthma and COPD.[5] Patients with ACO experience more frequent exacerbations, accelerated loss of lung function, higher health care resource utilization, and greater mortality compared to patients with asthma or COPD alone.[5]

Epidemiology

COPD affects an estimated 15.7 million Americans and is the fourth leading cause of death worldwide.[1,6] However, the true prevalence of COPD is believed to be much higher with an estimated 12 million more cases undiagnosed because of the insidious onset of the disease.[7] In 2010, total U.S. health care–related expenditures were an estimated 50 billion dollars, including $32 billion in direct costs.[8] COPD exacerbations are the most significant contributor to the cost burden of the disease, accounting for ~50% to 75% of all costs.[2]

COPD is also a leading cause of disability in the United States.[6] Surveillance data from the 2013 Behavioral Risk Factor Surveillance System found that patients with COPD were more likely to be unable to work (24.3% vs 5.3%), have difficulty walking or climbing stairs (38.4% vs 11.3%), and report limitations with daily activity because of health problems (49.6% vs 16.9%) compared with adults without COPD.[6]

The prevalence of COPD and associated costs are expected to continue to rise over the next few decades, at least, in part, because of the increased life expectancy of the general population and advanced age of patients who began smoking earlier in life.[1,8] Historically, the prevalence of COPD and related mortality was reported to be greater in males than that in females.[1] However, the prevalence of COPD among females has risen steadily in recent years and may now be higher than male.[6,7] The reason for this increase is likely multifactorial and may be due to changes in smoking patterns among females over the past century, and a growing body of evidence suggests females may be more vulnerable to the adverse effects of smoking.[9]

Risk Factors

Cigarette smoking is the major risk factor for COPD, and most cases are attributed to a current or past history of smoking.[1] In susceptible individuals, smoking elicits an abnormal inflammatory response that

damages the airways and lung parenchymal tissue, which accelerates decline in lung function.[10] It should be noted that fewer than half of smokers develop clinically significant COPD, suggesting a more complex interplay between host-related factors (ie, genetics, sex, age, etc.) and other environmental exposures.[11,12] Genome-wide association studies have successfully identified multiple loci associated with lung function and COPD, but precise genetic characteristics have not yet been elucidated.[1,13] One exception is α_1-antitrypsin deficiency (AATD), which affects ~1% to 2% of patients with emphysema.[12] Affected individuals have an inherited deficiency of this protective antiprotease and are at much higher risk for developing emphysema than the general population.[14]

Abnormal lung growth and development during gestation and throughout adolescence may predispose patients to COPD later in life, particularly in chronic smokers and in those who begin smoking at an early age.[15] In developing countries, poor indoor air quality has been associated with obstructive airway diseases, including COPD.[1] Approximately 3 billion people worldwide burn biomass fuels for heating and cooking, which significantly contributes to poor indoor air quality.[16] Occupational exposures to dusts and chemicals,[11,17] childhood respiratory illnesses, and certain infections, including tuberculosis and human immunodeficiency virus, may also lead to COPD.[1] Advanced age and low socioeconomic status are other known risk factors.[1]

Pathogenesis

The exact mechanisms responsible for the pathogenesis of COPD are not entirely clear, but likely involve activation of the innate and adaptive immune system, leading to chronic inflammation. In general, inhalation of noxious agents, such as cigarette smoke, leads to the activation of resident immune and parenchymal cells, which, in turn, recruit additional inflammatory cells from the systemic compartment into the resident tissue and airway.

The activation and recruitment of immune cells is largely mediated through the production and release of cytokines and chemokines. Recent evidence also supports a role for oxidant stress as a disease mediator.[18,19] The consequences of an oxidant-rich environment include the activation of inflammatory genes, inactivation of antiproteases, stimulation of mucus secretion, and increases in plasma exudate.

The most well-studied cause of COPD, and particularly emphysema, relates to protease–antiprotease imbalance. In this setting, inflammation promotes the production and release of proteases from inflammatory and parenchymal cells. When the local concentration of antiproteases becomes overwhelmed, proteases go unchecked and destroy the major connective tissue components in the lung, such as elastin, leading to the irreversible loss of alveoli. The classic example of this occurs in patients with AATD.

Although the traditional idea of disease pathogenesis focuses on smoking-related lung *injury*, more recent hypotheses suggest that another important component of disease pathogenesis may involve inadequate lung *repair.* Indeed, there is evidence that normal lung homeostatic mechanisms are altered in COPD. This may involve inadequate production of growth factors as well as altered regulation of apoptosis, or programmed cell death.[20]

Pathophysiology

The airflow obstruction caused by COPD is usually progressive and is attributed to pathologic changes in the lung that affect the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature.[21] Alterations in tissue structure are caused by chronic inflammation that involves recruitment of inflammatory cells into the lung, as well as structural changes that result from repeated injury and tissue remodeling. The magnitude of structural changes and tissue dysfunction varies among patients and is often distinguished by two major phenotypes that include chronic bronchitis and emphysema. Chronic airflow limitation can result from both of these

processes. Recent guidelines[1,22] do not distinguish between these two entities; however, the classic definitions and pathophysiologic features are described here to aid in a better understanding of the disease process.

In the simplest view, *bronchitis* is inflammation of the bronchioles. The clinical definition from the American Thoracic Society (ATS) for *chronic bronchitis* is "the presence of chronic productive cough for 3 months in each of two consecutive years in a patient in whom other causes of chronic cough (eg, asthma, congestive heart failure, gastroesophageal reflux) have been excluded."[23] *Emphysema* is described as "abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis." The degree of impairment of the small airways (bronchioles) or the lung parenchyma (alveoli and supporting structures) directly influences tissue dysfunction and the clinical symptoms of the patient.

LARGE (CENTRAL) AND SMALL (PERIPHERAL) AIRWAYS

The large airways, which include the trachea and first generations of the bronchi, are a major site of inflammation and mucus hypersecretion. This results from an increase in numbers (hyperplasia) and enlargement (hypertrophy) of the submucosal glands and mucus-producing goblet cells within the surface epithelium.[24,25] Overproduction of mucus in the large airways results in a chronic productive cough, as observed in chronic bronchitis, but this alone does not have a major impact on airflow limitation. Mucus hypersecretion, coupled with impaired ciliary function, reduces mucociliary clearance, increases the accumulation of secretions, and enhances the risk of bacterial colonization in an otherwise sterile environment.[26] As a result, recurrent infections often occur owing to the inability to clear pathogens.

The peripheral airway is composed of the smaller bronchi down to the terminal bronchioles, the smallest branches in the lung that are not involved in gas exchange. The extent of inflammation, fibrosis, and airway exudate in the peripheral airway correlates best with the

reduction in airflow as measured by a decrease in forced expiratory volume in the first second of expiration (FEV_1) or the FEV_1 to forced vital capacity (FVC) ratio.[27] After age 35, nonsmokers experience a decline in FEV_1 of about 20 to 30 mL/year. In smokers, an accelerated decline of 50 to 120 mL/year may be observed.[28] A model of the annual decline in lung function in nonsmokers, smokers, and susceptible smokers is illustrated in **Figure 19-1**. Chronic obstruction of the peripheral airway also results in air trapping on expiration, which contributes to hyperinflation. Hyperinflation places the respiratory muscles at a mechanical disadvantage and further reduces respiratory capacity. Hyperinflation can become more pronounced during exercise, leading to dyspnea and decreased exercise capacity. It is now known that hyperinflation can occur early in the course of COPD and is an important cause of exertional dyspnea.[29]

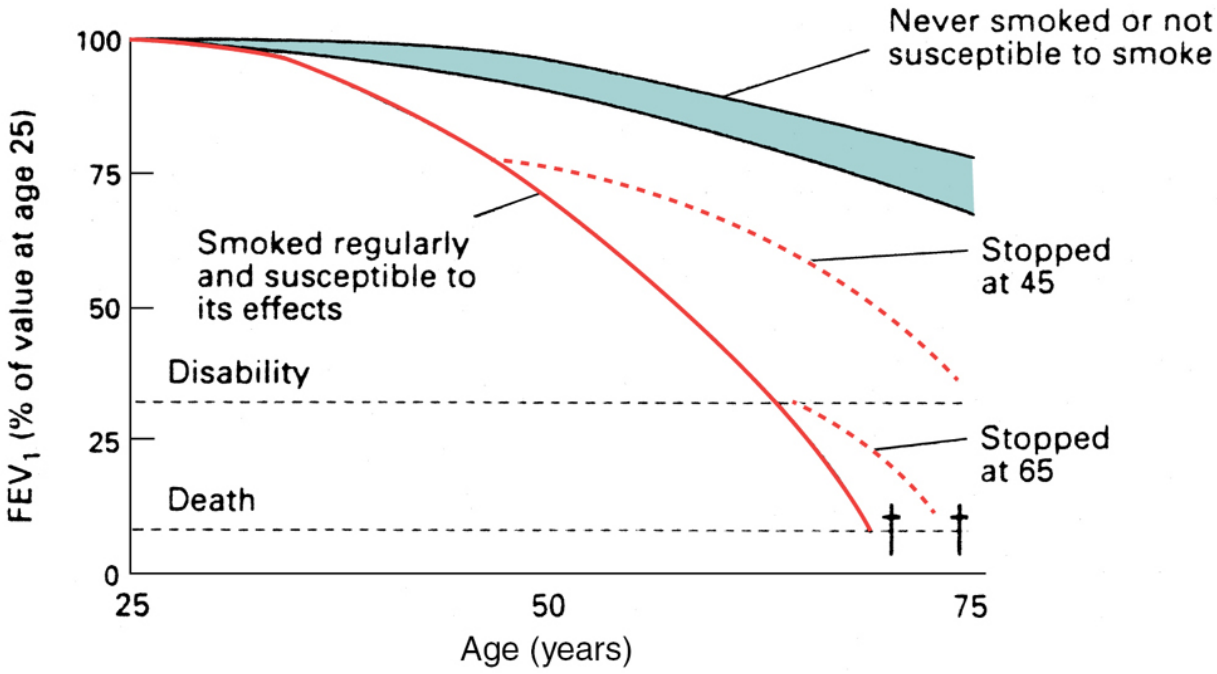


Figure 19-1 Model of annual decline in FEV_1 with accelerated decline in susceptible smokers. On stopping smoking, subsequent loss is similar to that in healthy nonsmokers. FEV_1, forced expiratory volume in the first second of expiration. (Reproduced from Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med*

J. 1977;1(6077):1645–1648; with permission from BMJ Publishing Group Ltd.)

PARENCHYMAL DESTRUCTION

The terminal bronchioles lead directly to the alveolar ducts and sacs, the major site where gas exchange occurs. Emphysema is characterized by the destructive loss of alveolar walls and enlargement of the terminal airspaces, resulting in a loss of gas-exchanging surface area.[26] In advanced cases, large, balloon-shaped bullous lesions may develop. Rupture of these bullae (pneumothorax) can lead to collapse of lung segments (pneumothorax).

SIGNIFICANT COMORBID ILLNESS

In the later stages of disease, chronic hypoxemia causes persistent vasoconstriction in the lung vascular bed, particularly the small pulmonary arteries. This can result in permanent structural alteration of the blood vessels, causing intimal hyperplasia and smooth muscle hypertrophy.[30] The loss of pulmonary capillaries in emphysema can also contribute to increased pulmonary vascular pressures. The cumulative impact of vascular changes can result in progressive pulmonary hypertension and, eventually, right-sided cardiac failure (cor pulmonale).

As COPD progresses, additional systemic consequences can arise, including cachexia, skeletal muscle dysfunction, osteoporosis, depression, and anemia. The cause of these additional systemic disease processes is not entirely clear, but likely involves the dynamic interplay of progressive respiratory dysfunction, lung and systemic inflammation, side effects from medication use, and physical debilitation. In summary, although COPD is primarily a disease of the large and small airways and adjacent alveolar structures, it also includes important systemic consequences. The clinical consequences of the morphologic and pathophysiologic alterations include progressive dyspnea on exertion, chronic cough

and sputum production, increased risk for respiratory infections, deconditioning, and an overall reduction in quality of life.

COMPARISON WITH ASTHMA

COPD and asthma are common obstructive airway disorders, and both illnesses can coexist in the same patient. Nevertheless, these conditions should be considered as separate and distinct entities (**Table 19-1**). For example, although inflammation is a key component of both conditions, the pattern of inflammation differs significantly (**Table 19-2**). As a result, the pathophysiologic consequences, patient symptoms, and response to medications typically differ. Asthma is generally not progressive, and symptoms and airflow obstruction are often completely reversible. Patients with asthma respond well to anti-inflammatory medication, including inhaled corticosteroids (ICSS). Furthermore, in the absence of an acute exacerbation, significant gas exchange abnormalities are uncommon. COPD, on the other hand, is a progressive and often fatal disorder. Although bronchodilators are helpful in COPD, the degree of bronchodilator reversibility is typically less than that seen in asthma. In addition, the beneficial effects of anti-inflammatory medication, including ICS, are much more modest. Patients with COPD, particularly those with emphysema, have substantial derangements in pulmonary gas exchange, even at baseline.

Table 19-1
Clinical Features of Asthma, COPD, and Asthma–COPD Overlap (ACO)

Clinical Feature	COPD	Asthma	Asthma–COPD Overlap
Age of onset	>40 years of age	Childhood, but can occur at any age	Usually ≥40 years of age, but may have had symptoms in childhood or adolescence
Possible symptoms	Dyspnea, chronic cough, sputum production	Dyspnea, cough, wheeze, chest tightness	Mixed symptoms
Symptom pattern	Persistent and slowly progressive Present daily, worse with exertion or exercise	Vary day to day and may be episodic based on trigger exposure Often worse at night or early morning	Persistent and worse with exertion though variability may exist
Risk factors	History of chronic exposure to cigarette smoke, biomass fuels, or noxious particles and gases α_1-Antitrypsin deficiency (<2% of cases)	Atopic conditions (ie, allergies, eczema, etc.) Family history of asthma	History of asthma with chronic exposure to cigarette smoke, biomass fuels, or noxious particles and gases
Postbronchodilator FEV_1 reversibility[a] FEV_1/FVC ratio	Usually little to no change FEV_1/FVC <70%	Reversible and may be normal between symptoms	Airflow limitation is usually not fully reversible and often varies over time
Chest x-ray	Hyperinflation	Usually normal	Hyperinflation

FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity.

[a]Reversibility is defined as an increase in FEV_1 of >200 mL and 12% from baseline measure after inhalation of a short-acting β_2-agonist.

Source: Global Initiative for Asthma. Global strategy for asthma management and prevention. 2020. www.ginasthma.org.

Table 19-2
Differences in Pulmonary Inflammation Between Asthma and Chronic Obstructive Pulmonary Disease (COPD)

COPD	Asthma	Severe Asthma
Cells		
Neutrophils++	Eosinophils++	Neutrophils+
Macrophages+++	Macrophages+	Macrophages
$CD8^+$ T cells (Tc1)	$CD4^+$ T cells (Th2)	CD4+ T cells (Th2)
		CD8+ T cells (Tc1)
Key Mediators		
IL-8, TNF-α, IL-1β, IL-6, NO+	Eotaxin	IL-8
	IL-4, IL-5, IL-13	IL-5, IL-13
	NO+++	NO++
Oxidative Stress		

+++	+	+++
Site of Disease		
Peripheral airways	Proximal airways	Proximal airways
Lung parenchyma		Peripheral airways
Pulmonary vessels		
Consequences		
Squamous metaplasia	Fragile epithelium	
Mucous metaplasia	Mucous metaplasia	
Small airway fibrosis	↑Basement membrane	
Parenchymal destruction	Bronchoconstriction	
Pulmonary vascular remodeling		
Response to Therapy		
Small bronchodilator response	Large bronchodilator response	Smaller bronchodilator response
Poor response to steroids	Good response to steroids	Reduced response to steroids

IL, interleukin; NO, nitric oxide; TNF, tumor necrosis factor.

Source: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Updated 2011. Accessed September 3, 2020. http://www.goldcopd.org.

α_1-ANTITRYPSIN DEFICIENCY

The best characterized antiprotease in the lung is α_1-antitrypsin. This serum glycoprotein is primarily produced in the liver and works by binding to and neutralizing proteases. As described previously, cigarette smoke can activate and attract inflammatory cells into the lung, thereby promoting the release of proteases, such as neutrophil elastase. Cigarette smoke can also inactivate endogenous protease inhibitors, including α_1-antitrypsin, further supporting protease activity and increasing the risk of tissue damage. This risk of tissue damage is greatly accentuated in patients with AATD.

AATD is a genetic disorder responsible for 1% to 2% of patients with COPD.[12] It is more common in patients of European ancestry and has been associated with other conditions, including liver disease.[12,31] The diagnosis of AATD is made by measuring circulating serum α_1-antitrypsin levels, followed by phenotype analysis.[31,32] The *SERPINA1* gene (also known as PI) is responsible for producing α_1-antitrypsin, and mutations in this gene can affect production. More than 120 mutations in the *SERPINA1* gene have been identified, but not all lead to AATD.[33] Inherited alleles are assigned letters to represent the migration of the molecule in an isoelectric pH gradient.[14]

The PiM allele confers production of the fully functional protein. Accordingly, a homozygous PiMM individual will produce a functional protein with normal plasma concentrations. Other gene types include, but are not limited to, PiS (normal serum levels of a poorly functioning enzyme), PiZ (an active form but poorly secreted, leading to low circulating levels), and Pi null (gene polymorphism leads to production of a truncated protein and undetectable serum levels of functional protein). Different allele pairs can exist. PiMZ and PiSZ are heterozygous disorders, and PiSS is a homozygous phenotype, all with >35% of normal enzyme activity and a relatively low risk of developing emphysema. PiZZ is a rare homozygous disorder characterized by accelerated lung destruction and serum α_1-antitrypsin levels of ~15% of normal. In these rare patients, the disease develops as early as age 20, but more typically, it occurs in the fourth to fifth decades of life.[14]

Replacement therapy is available for patients with COPD with documented AATD and emphysema. Patients who do qualify typically receive weekly intravenous infusions of α_1-antitrypsin to maintain acceptable antiprotease activity and minimize the progression of lung disease. This therapy is very expensive, and it is not well tolerated by some (fever, chills, allergic reactions, flulike symptoms). Replacement therapy may improve outcomes in patients with AATD, documented emphysema, and an FEV_1 between 30% and

65% of predicted.[32] Several formulations of α_1-antitrypsin are available: Aralast®, Prolastin®, Zemaira®, and Glassia®. No clinically significant differences exist among these preparations. Because the α_1-antitrypsin products are derived from pooled human plasma, there are also associated risks for the transmission of infectious diseases (eg, viral infections and Creutzfeldt–Jakob disease). Overall, the use of the α_1-antitrypsin replacement therapy remains controversial, and some have argued that this therapy cannot be recommended based on a lack of proven clinical benefit and high cost of treatment.[34]

DIAGNOSIS AND PATIENT ASSESSMENT

The diagnosis of COPD is based on the presence of risk factors (generally smoking), clinical symptoms, and airflow obstruction on spirometric testing.[1] Generally, individuals with COPD present in the fourth or fifth decade of life with symptoms of cough, wheeze, or dyspnea on exertion.[35] Patients usually have at least a 10-pack-year history (eg, averaging one pack of cigarettes a day for 10 years) of cigarette smoking. Because the severity of COPD is related to the cumulative exposure to cigarette smoke, patients with more severe disease are likely to be older with a heavier smoking history. Cough and sputum production may be present for many years before airflow limitation develops, but not everyone with those symptoms will develop COPD. Dyspnea is a hallmark symptom and a major cause of disability and anxiety.[1]

On physical examination, patients with early COPD may not exhibit any overt clinical signs or symptoms.[1] In more advanced stages, objective findings may include the presence of a barrel chest (defined as an increase in the anteroposterior diameter of the chest), rales (defined as intermittent, nonmusical, brief crackle sounds), rhonchi (defined as continuous, musical high- or low-pitched sounds), prolonged expiratory phase, and cyanosis.[24] Symptomatic patients may present with decreased breath sounds, wheezes, or

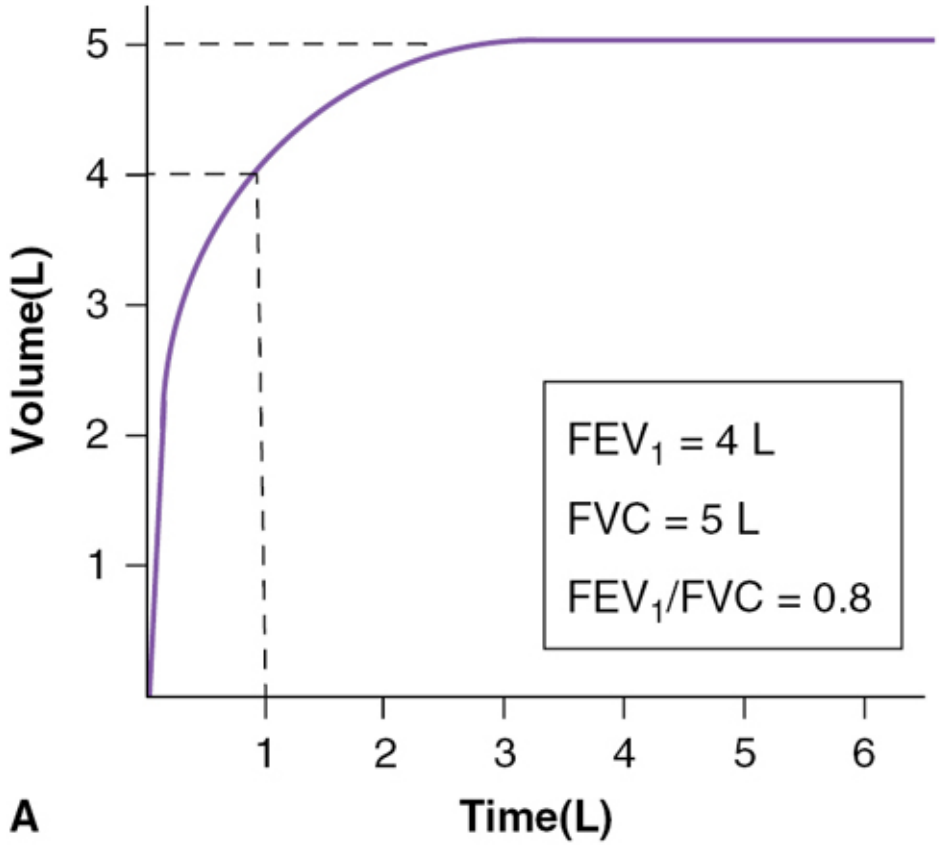
slight rales on auscultation. In advanced disease, cyanosis, edema, intercostal retractions, and pursed-lip breathing may be present.[24]

Spirometry Testing

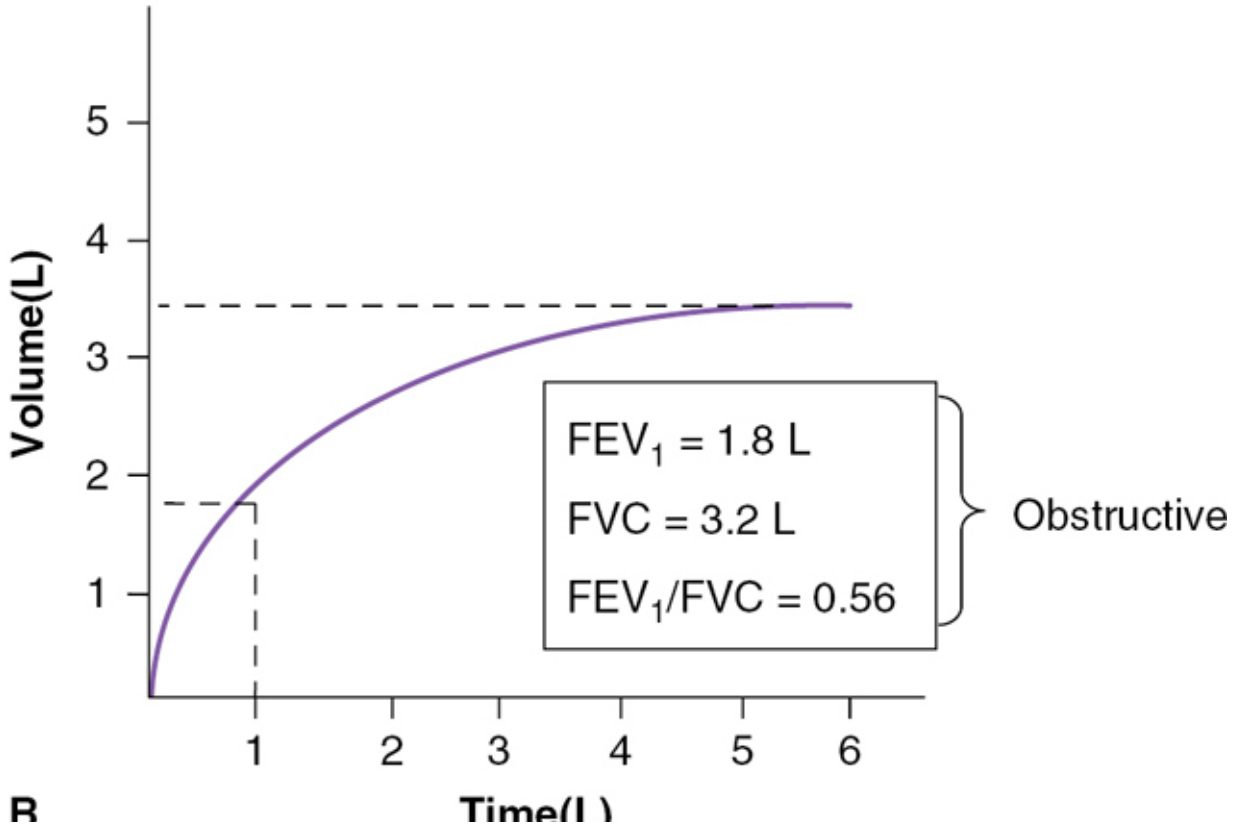
Spirometry is the gold-standard measurement in assessing and monitoring obstructive lung disease and is required for a diagnosis of COPD.[1,22] In the evaluation of COPD, spirometry testing should be performed according to published guidelines, when the patient's condition is stable and after administration of a short-acting bronchodilator, such as two to four puffs (90 µg/puff) of albuterol by metered-dose inhaler (MDI).[1,5] During spirometry, a full breath is taken, followed by a forceful exhalation of all the air that can be exhaled (FVC). Flow rates and volumes of air that are expired at different time intervals can be recorded (**Fig. 19-2**). The FEV_1 is the volume of air that can be expired within the first second of an FVC maneuver. A decrease in the FEV_1/FVC ratio indicates airflow obstruction. Although the range of normal for FEV_1/FVC depends on the age, sex, and height of the patient, a value of <0.70 indicates airflow obstruction that is compatible with COPD.[1,22] Also, patients with COPD may have some improvement in spirometry testing with an acute bronchodilator challenge. The degree of reversibility is typically less than that seen with asthma, although up to 50% of patients with moderate-to-severe emphysema will have an increase in FEV_1 with acute bronchodilator challenge that meets ATS criteria as significant. In addition to being critical for making the diagnosis of COPD, spirometry also affords the best objective way to monitor disease progression and should be considered if there has been a persistent change in clinical symptoms (eg, worsened dyspnea). Four "grades" are used to classify the degree of airflow limitation using postbronchodilator spirometric results in patients with an FEV_1/FVC <70%:

- GOLD 1 (mild): FEV_1 ≥80% predicted

- GOLD 2 (moderate): FEV_1 ≥50% to 80% predicted
- GOLD 3 (severe): FEV_1 ≥30% to 50% predicted
- GOLD 4 (very severe): FEV_1 <30% predicted[1]


5
4
3
2
1
Volume(L)
FEV1 = 4 L
FVC = 5 L
FEV1/FVC = 0.8
1
2
3
4
5
6
Time(L)

A


5
4
3
2
1
Volume(L)
FEV1 = 1.8 L
FVC = 3.2 L
FEV1/FVC = 0.56
Obstructive
1
2
3
4
5
6

B

Figure 19-2 A, A normal spirometry tracing. B, A spirometry tracing typical of a patient with obstructive disease. FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity. (From the Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2020. Copyright © 2020 Global Initiative for Chronic Obstructive Lung Disease, Inc. All rights reserved. Available from https://www.goldcopd.org.)

Deteriorating lung function is associated with increased prevalence of hospitalizations, exacerbations, and associated mortality at the population level.[1] However, FEV_1 is an unreliable clinical indicator when used alone to predict exacerbation or mortality risk at the individual patient level.[1] Although optimal frequency of spirometric testing for patients with COPD is not known, some groups recommend annual monitoring to identify patients whose lung function may be declining rapidly.[1]

Other pulmonary function testing is sometimes used to assess patients with COPD. The determination of lung volumes, including the total lung capacity (TLC) and residual volume (RV), as well as measurements of the diffusing capacity for carbon monoxide (DLCO) may provide more detail regarding lung physiology. For example, a reduction in DLCO indicates disruption or destruction of the alveolar capillary interface and correlates with the degree of emphysema. Determination of lung volumes may be used to assess the presence of concomitant restrictive lung disease (eg, idiopathic pulmonary fibrosis) in the case of diagnostic uncertainty. Patients with COPD typically have normal or increased lung volumes; a reduction in TLC may indicate a superimposed restrictive process. Furthermore, lung volumes and diffusion capacity are used to assess patients for surgical procedures, such as lung volume reduction surgery.[1,36] In most cases, however, spirometric testing is adequate to make the diagnosis of COPD and follow the course of disease.[1,22]

A chest x-ray (CXR) may be performed during the initial assessment of patients with COPD. Because the CXR lacks sensitivity

and demonstrates minimal changes until COPD is moderately severe, its main utility is in ruling out other disease processes, possibly contributing to the patient's symptoms. In severe disease, the chest radiograph may indicate hyperinflation, manifested by a flattened diaphragm, or evidence of pulmonary arterial hypertension, characterized by enlarged pulmonary arteries.

Assessing the oxygen status of a patient with COPD can be done by pulse oximetry. This should be considered in patients with dyspnea and advanced disease and patients with evidence of right ventricular pressure overload (eg, peripheral edema or jugular venous distension). Although a decrease in pulse oximetry (normal, ≥97%) is common in COPD, values of 88% or less are consistent with chronic respiratory failure and qualify the patient for supplemental oxygen. Arterial blood gas (ABG) determination is generally reserved for patients with severe disease (ie, an FEV_1 <50% of predicted). ABGs can more precisely define the oxygen status of a patient and can be used to assess whether the patient has carbon dioxide retention (normal P_{CO_2} = 35–45 mm Hg). Determining the α_1-antitrypsin concentration is indicated for patients developing COPD before age 45 and for patients who have emphysema without a significant history of cigarette smoking or who have a family history of emphysema.[1]

Classification of Severity and Clinical Presentation

Earlier guidelines categorize the severity of COPD based on the degree of airflow obstruction as assessed by the FEV_1.[23] However, lung function has been found to be a poor indicator of disease severity when used alone. Thus, the GOLD Report offers a systematic approach to better individualize patient assessment of symptom burden and exacerbation risk to guide initial therapy (**Fig. 19-3**).[1] Patients may be initially categorized into one of the following groups: group A: low risk, less symptoms; group B: low risk, more symptoms; group C: high risk, less symptoms; and group D: high risk, more

symptoms. Moreover, comorbidities, serum eosinophil counts, and other patient's related characteristics should be considered before initiating therapy.

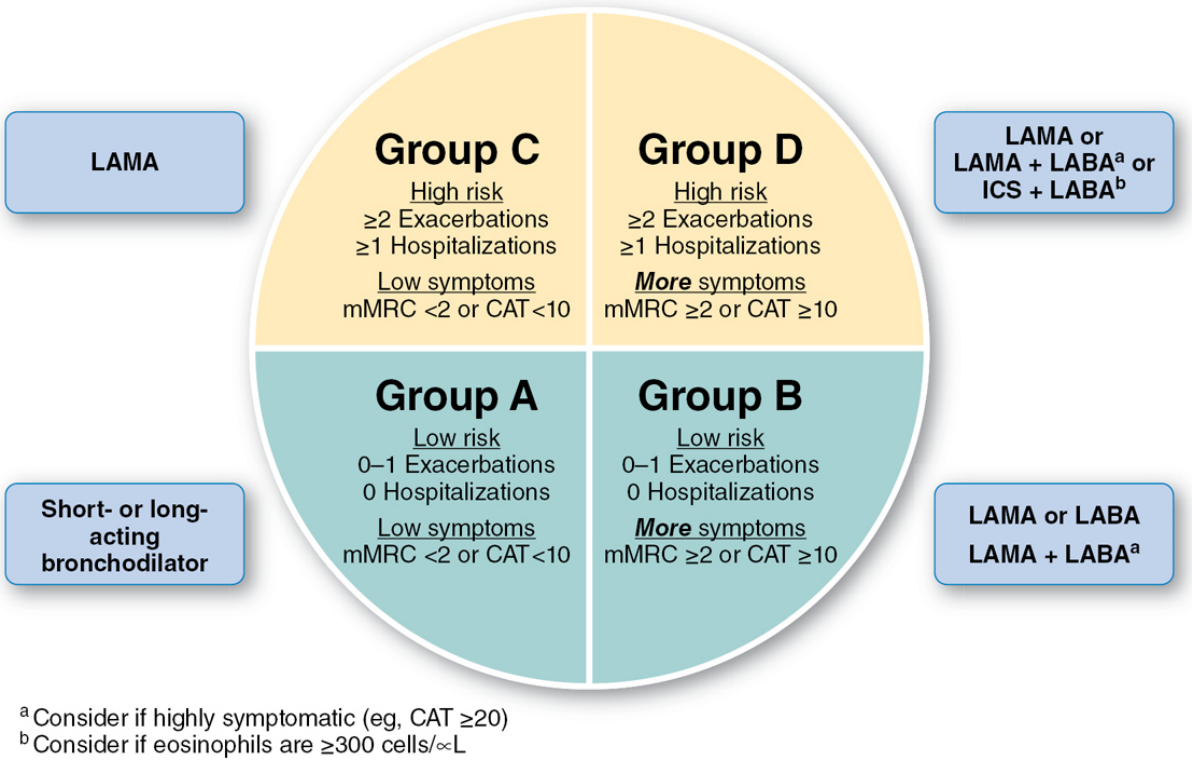


Figure 19-3 Initial pharmacologic selection by COPD group. CAT™, COPD Assessment Test; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting antimuscarinic (anticholinergic); mMRC, modified Medical Research Council Questionnaire. (From the Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2020. Copyright © 2020 Global Initiative for Chronic Obstructive Lung Disease, Inc. All rights reserved. Available from https://www.goldcopd.org.)

Two steps should be followed when using the ABCD assessment tool. The first step is to assess patient symptoms. Several reliable questionnaires such as the Modified British Medical Research Council Questionnaire (mMRC), COPD Assessment Test (CAT), and COPD Control Questionnaire (CCQ) may be used to assess symptom burden and health status. The mMRC only assesses the

impact of breathlessness on health-related quality of life. However, patients with COPD often exhibit additional symptoms, such as cough, chest tightness, and mucus production. Therefore, scales that provide a more comprehensive assessment of symptoms (eg, CAT) may be preferred by some clinicians. Nevertheless, patients are considered to have a high level of symptoms when scoring ≥2 on the mMRC or ≥10 on the CAT. Of note, it is only necessary to use one of these scales when assessing symptom burden.

The second step involves an assessment of the patient's risk for future exacerbations. Patients are considered to be in the "high-risk" category if the patient has experienced two or more exacerbations in the previous year or if the patient has had one exacerbation that led to a hospitalization within this time period.[1]

Although the GOLD management strategy can provide important prognostic information, other comprehensive assessment tools may too provide discriminating information with regard to survival in COPD. For example, a scoring system based on body mass index, obstruction on spirometry, dyspnea level, and exercise capacity (BODE) can predict survival in COPD better than the FEV_1 alone.[37]

GENERAL MANAGEMENT CONSIDERATIONS

The natural course of COPD is highly variable, generally spanning 20 to 40 years and influenced by numerous factors, including genetic predisposition, exposure to inhaled irritants (tobacco smoke, workplace, and/or environmental pollutants), and repeated infections.[38] The overarching goals of COPD management involve two main principles. First, to reduce symptoms (ie, relieve symptoms, improve exercise tolerance, and improve health status); and second, to reduce risk (ie, prevent disease progression, prevent and treat exacerbations, and reduce mortality).[1] Unfortunately, the only interventions that have been proven to reduce mortality in COPD are smoking cessation, oxygen therapy for patients with severe

hypoxemia at rest, and lung volume reduction surgery for very select patients with advanced emphysema.[36,39–41] As such, many of the interventions are aimed at alleviating symptoms and maximizing quality of life.

Because continued cigarette smoking is associated with accelerated progression of disease in susceptible smokers, smoking cessation is critical to disease treatment. Strategies for smoking cessation are detailed in Chapter 91, Tobacco Use and Dependence. The benefits of smoking cessation in COPD include decreases in respiratory symptoms, exacerbation rate, and decline in lung function.[28,42] It should also be noted that cardiovascular complications, including coronary artery disease, are more common in patients with COPD and that smoking cessation may attenuate morbidity and mortality from this complication.

Immunizations provide protection against serious illness and death in patients with COPD.[43] The efficacy, benefit, and cost-effectiveness of vaccination against influenza among this population are significant.[44] In addition, the pneumococcal polysaccharide vaccine is recommended to all patients with COPD,[1] as well as in adult patients age 19 to 64 years who smoke cigarettes or have chronic lung disease.[45]

Pulmonary rehabilitation is an exercise-based program aimed at maximizing the patient's functional status and quality of life. Multiple studies have now documented the beneficial effects of pulmonary rehabilitation, particularly with respect to improved exercise tolerance and alleviation of dyspnea.[46] In addition, cost-effective analysis suggests that pulmonary rehabilitation programs are very cost-effective.[1,46] Pulmonary rehabilitation programs are multidisciplinary programs typically running for 6 to 12 weeks, two to three sessions per week. However, no consensus on the optimal duration of pulmonary rehabilitation currently exists.[46] A number of interventions are used, including breathing retraining, psychosocial counseling, education, dietary counseling, and airway clearance techniques for patients with chronic sputum production. Arm strengthening and arm endurance exercises are important because

patients with COPD commonly have excessive dyspnea when using their upper extremities.[46] The most important component of a pulmonary rehabilitation program is lower extremity endurance training, often using a treadmill or bicycle ergometer. Because the large muscle groups have diminished oxidative capacity,[47–49] likely related to deconditioning and chronic inflammation,[50,51] patients with COPD convert to anaerobic metabolism at low levels of exercise. This leads to increased lactate production for a given level of activity[52] and, subsequently, increased CO_2 production. Lower extremity endurance training can significantly improve mitochondrial oxidative capacity in patients with COPD.[53] This physiologic benefit is believed to be an important mechanism whereby pulmonary rehabilitation exerts its effect. Other important effects, such as alleviation of depression and anxiety, may be important as well.[46]

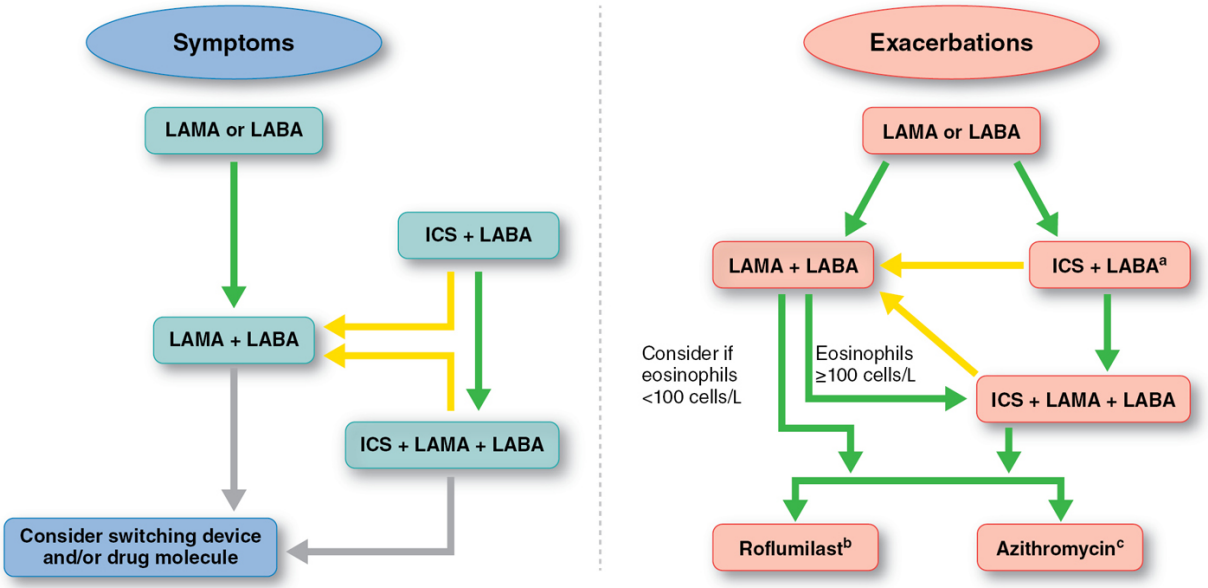
As mentioned, patients with severe resting hypoxemia have improved mortality with supplemental oxygen treatment. Long-term oxygen administration (>15 hours/day) has been shown to improve survival in patients with severe resting hypoxemia (Pa_{O_2} ≤7.3 kPa [55 mm Hg] or Sa_{O_2} ≤88%), when confirmed twice over a 3-week period.[1] Conversely, oxygen therapy does not increase the time to first hospitalization or death in patients with moderate oxygen desaturation while at rest (Sp_{O_2}, 89%–93%) or in those who experience exercise-induced desaturation.[54]

PHARMACOTHERAPY

The fundamental goals of medication use are to prevent or control symptoms, reduce the frequency and severity of exacerbations, and improve both health status and exercise tolerance.[1,22] None of the existing medications used to treat COPD have been conclusively shown to modify the long-term decline in lung function.[1] Therefore, therapy should be individualized and aimed toward symptom management and reducing future risk of exacerbations.[1] Treatment

goals should be realistic and developed jointly by the caregiver and the patient.

After medications are modified or prescribed, routine follow-up visits are recommended to evaluate treatment response. The process of "Review," "Assess," and "Adjust" may be employed as a guiding principle of pharmacologic management and offers a systematic approach to assessing response to therapy.[1] During the "Review," the emphasis is on identifying "treatable traits" in order to determine whether further treatment is necessary to manage "dyspnea" or prevent "exacerbations." Before modifying therapy, clinicians should "Assess" proper inhaler technique, medication adherence, and impact of nonpharmacologic interventions before adjusting therapy. If a change in therapy is necessary, escalation and de-escalation strategies are available to "Adjust" therapy, which may involve switching to an alternative inhaler device or drug product or both (**Fig. 19-4**).



[a] Consider ICS if serum eosinophils are ≥300 cells/L or if ≥100 cells/L AND 2+ exacerbations or 1 related hospitalization
[b] Consider if chronic bronchitis and FEV1 <50% predicted
[c] Consider in former smokers
Green arrows represent therapeutic escalation
Yellow arrows represent de-escalation of the ICS component if pneumonia, or if inappropriate original indication, or if lack of response to ICS

Figure 19-4 Follow-up pharmacologic escalation/de-escalation strategies group. *Green arrows* denote escalation strategies. *Yellow arrows* denote ICS removal, which should be considered if

pneumonia, lack of response, or if inappropriately prescribed initially. ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting antimuscarinic (anticholinergic). (Adapted from Global Initiative for Chronic Obstructive Lung Disease [GOLD]. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2020. Accessed September 3, 2020. http://www.goldcopd.org.)

Although the standard for assessing benefit from treatment has been to measure spirometric improvement in FEV_1, many patients will not demonstrate noticeable changes after either an acute or extended therapeutic trial of any therapy. Increasingly, clinicians are considering other measures to determine the benefit of therapy, including measuring improvements in quality of life, dyspnea, and exercise tolerance.[55] Other appropriate measures may include COPD exacerbation rates and utilization of health care resources. In most patients, it is important to consider the use of multiple outcome measures, both objective and subjective, to guide the therapeutic decision-making process.

Bronchodilators

Bronchodilators are central to the symptomatic management of COPD and include short-acting β_2-agonist and long-acting β_2-agonist (LABA), short- and long-acting anticholinergic agents, and theophylline. These medications, although pharmacologically distinct, improve airflow, primarily by reducing bronchial airway smooth muscle tone. In COPD, the spirometric response, as measured by FEV_1, can be variable and, in many cases, will demonstrate no change, although the patient may subjectively feel better. This can be attributed to treatment facilitating emptying of the lungs and a reduction in thoracic hyperinflation at rest and during exercise. No clear evidence exists for benefit of one bronchodilator over another in the chronic management of COPD, although inhaled therapy is generally preferred to oral therapy to achieve a more rapid

onset of action and to minimize the risk of systemic exposure and adverse events. Generally, initial treatment selection is based on the frequency and severity of symptoms, as well as future exacerbation risk (Fig. 19-3). Additional factors such as product availability, cost, and patient preference may further allow treatment to be individualized.[1]

Short-acting β_2-agonists (eg, albuterol) with or without a short-acting anticholinergic (eg, ipratropium) is usually preferred for exacerbations and acute symptoms because of their more rapid onset of action and relatively short duration of activity when compared with long-acting agents.[1] A short- or long-acting bronchodilator should be offered to patients who have few symptoms and are at a low risk for exacerbations (group A).

Long-acting bronchodilators are preferred to short-acting agents for patients with a greater symptom burden, because the bronchodilator effect is sustained for a longer duration, thus reducing the number of daily inhalations. This strategy will also likely enhance patient adherence. For group B patients presenting with severe breathlessness, a combined bronchodilator therapy may be used as initial therapy.[1] The adverse effect profile of inhaled bronchodilators, particularly β_2-agonists, is dose dependent. The most common adverse effects are an extension of stimulation of β_2-adrenergic receptors that can produce resting sinus tachycardia or provoke cardiac dysrhythmias in predisposed individuals, especially the elderly. Precipitation of somatic tremors and hypokalemia can also occur with excessive use.

The relationship between β_2-agonist use and cardiovascular complications remains somewhat controversial. It is recognized that albuterol and long-acting inhaled β_2-sympathetic agents can induce systemic sympathetic states, hypokalemia, and other metabolic derangements that can contribute to cardiac rhythm disturbances. This has led to speculation that these abnormalities could contribute to an increase in cardiovascular death among patients with COPD using β_2-agonist inhalers.[56] Nevertheless, this speculation has been

largely refuted by the TORCH (Towards a Revolution in COPD Health) study, in which >6000 patients with COPD were randomly assigned to treatment with salmeterol, fluticasone, combined salmeterol–fluticasone, or placebo.[57] Overall mortality, cardiovascular mortality, and cardiovascular-related adverse events were no greater in the salmeterol group compared with any of the other groups.

Inhaled antimuscarinics inhibit bronchoconstriction primarily by inhibiting the effects of acetylcholine on M3 receptors expressed on airway smooth muscle.[58] These agents are generally well tolerated by virtue of their minimal systemic absorption. Excessive dry mouth is the most common adverse effect reported with inhaled anticholinergic agents, both short and long acting. It has been suggested that regular use of inhaled anticholinergic agents increases the risk of cardiovascular complications.[59,60] However, more recent large prospectively performed randomized trials have found a decreased risk of cardiovascular complications among patients with COPD using the long-acting anticholinergic tiotropium on a regular basis.[61,62]

It is not unusual to find reports in the literature that suggest superiority of one bronchodilator class versus another for COPD treatment[3,63] It is difficult, however, to predict individual responses to treatment. For some patients, β_2-agonist bronchodilators will increase airflow, improve pulmonary function test results, and reduce symptoms of dyspnea.[64] Others may achieve greater improvement with an anticholinergic in comparison with a β_2-agonist.[65,66] Still others may not have a reversible component with either drug, but may perceive symptomatic benefit.[67,68] Thus, the therapeutic regimen should be reviewed with the patient at each follow-up visit to assess response. Careful review of adherence, technique, and response to therapy should be assessed before adjusting therapy.

Theophylline is a methylxanthine that induces bronchodilation by relaxing the smooth muscle of the bronchi. Although not fully understood, its pharmacologic activity has been attributed to nonselective inhibition of phosphodiesterase (PDE), inhibition of extracellular adenosine (a bronchoconstrictor), stimulation of

endogenous catecholamines, and antagonism of prostaglandins PGE_2 and $PGF_{2\beta}$.[69] Theophylline has been shown to provide greater symptomatic improvement when compared with placebo, though it is considered to be less effective and usually less well tolerated than inhaled long-acting bronchodilators.[1] Theophylline may provide additional symptomatic improvement via stimulation of diaphragmatic contractility and anti-inflammatory effects. However, the clinical significance of these findings remains to be determined.[1,58]

Currently, theophylline is reserved for patients who do not tolerate, or fail to adequately respond to, a combination of first-line bronchodilators. It is relatively inexpensive and studies showing clinical benefit have involved mostly slow-release preparations. The major limitation of theophylline is its relatively narrow therapeutic index, potential to cause significant adverse events, and requirement for blood monitoring of drug levels.[1]

Selective Phosphodiesterase 4 Inhibitors

Roflumilast (Daliresp®) is an orally administered selective PDE4 enzyme inhibitor approved to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[70] Recent guidelines recommend the use of roflumilast in patients who are not adequately controlled by long-acting bronchodilators and continue to experience frequent exacerbations. It has been recommended to use this agent in combination with at least one long-acting bronchodilator.[1] Although roflumilast has been shown to improve FEV_1 by 40 to 60 mL compared to placebo, it is not a bronchodilator and is not indicated to relieve acute bronchospasm.[70,71] In comparison with theophylline, roflumilast has much less potential for drug–drug interactions and does not require drug-level monitoring. Though it is metabolized to an active metabolite via CYP3A4 and CYP1A2 pathways, it should be used with caution in patients receiving strong inducers or inhibitors of these enzymes and should be avoided in those with significant hepatic impairment. Significant adverse effects, including diarrhea,

nausea, weight loss (~2 kg), and adverse psychiatric effects, such as anxiety and depression, have been reported.[1,70,71] A starting dose of 250 µg once a day for 4 weeks may reduce the rate of treatment discontinuation in some patients. However, roflumilast 250 µg daily is not an effective therapeutic dose.[70]

Corticosteroids

Historically, initiation of a short (2-week) course of oral corticosteroids was often advocated to identify patients with COPD who might benefit from long-term treatment. Recent evidence, however, indicates that a short course challenge is a poor method to predict patients who will benefit from long-term ICS use.[72,73] Given the lack of evidence and risk for significant side effects that include steroid myopathy and loss of bone density, chronic systemic corticosteroid therapy is not generally recommended. For patients with COPD experiencing an acute exacerbation of their disease, the short-term use of systemic corticosteroids has proven efficacy.[74]

In contrast, inhalation of corticosteroids leads to substantially less systemic absorption, thereby minimizing many of the risks associated with systemic corticosteroid therapy. On this basis, studies have been conducted to evaluate the potential benefit of ICS maintenance therapy.[75] Well-conducted clinical trials have revealed that daily treatment with an ICS alone does not delay the long-term decline in FEV_1 in patients with COPD.[75]

In recent years, the concept of “precision medicine” and the need to identify different COPD subtypes based on groups of observable characteristics (ie, phenotypes) and underlying pathophysiologic mechanisms (ie, endotypes) has been explored.[76] Biomarkers are used to identify endotypes[77] and serve as an indicator of normal and pathogenic processes, or pharmacologic responses to therapy.[1] For example, serum eosinophil is a biomarker that may help predict the likelihood of response to an ICS. According to the GOLD Report, patients with elevated serum eosinophils ≥300 cells/µL and/or those with a history of asthma are most likely to benefit from the addition of

an ICS to the regimen.[1] Combination therapy with an ICS and LABA in a single inhaler is more effective than using an ICS alone in improving lung function and health status and reducing exacerbations.[1,78–83] Patients with moderate-to-very severe airflow obstruction who continue to experience symptoms and frequent exacerbations despite dual therapy may benefit from triple therapy (ICS/long-acting antimuscarinic [LAMA]/LABA).[1] Thus, both serum eosinophils and exacerbation history should be considered when determining the likelihood of patient response to ICS therapy.[1,84]

Most trials to date involving ICS therapy have studied patients on moderate-to-high doses. Common adverse effects include oral candidiasis, dysphonia, and skin bruising. ICS either alone or in combination with a bronchodilator may increase the risk of pneumonia in some patients. However, risk estimates have varied owing to inconsistencies in how pneumonia is defined, reported, and diagnosed among trials.[85] Of note, withdrawal from ICS therapy has led to exacerbations in some patients, while other studies have conflicting results.[1] Magnussen and colleagues found a slight decrease in lung function with no increases in exacerbation risk among patients with moderate-to-severe COPD when the ICS dose was tapered over a 3-month period.[86] In a separate study, most patients were able to de-escalate triple therapy to dual bronchodilator therapy without diminished lung function or increased number of exacerbations.[87] However, a greater decline in lung function and increase in exacerbations were observed in patients with elevated serum eosinophil counts (≥300 cells/μL).[87] Given the paucity of data, patient symptoms and lung function should be monitored while gradually stepping down therapy in appropriate candidates.[1]

INITIAL PHARMACOLOGIC THERAPY BY DISEASE SEVERITY

Recent iterations of the GOLD Report now separate "initial pharmacologic management" using the ABCD assessment system from "follow-up pharmacologic treatment," which is based on certain treatable traits and overall response to the initial treatment plan.[1] Patients with infrequent or intermittent symptoms who are at a low risk for a future COPD exacerbation (group A) may be initiated on either a short- or long-acting bronchodilator. As the disease progresses and patients become more symptomatic, as-needed use of bronchodilators alone will not maintain adequate relief from symptoms. Long-acting bronchodilators have been shown to be more effective and convenient for patients experiencing more persistent symptoms. These patients may also continue to use a short-acting bronchodilator as needed for additional symptomatic relief. Combination therapy is generally indicated for patients presenting with more severe symptoms and activity limitation.[1,84] Dual bronchodilator therapy has been shown to improve lung function and symptoms and may reduce exacerbations over monotherapy,[1] likely due to complimentary effects associated with targeting bronchoconstriction through two distinct mechanisms.[58]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

An exacerbation of COPD is defined as "an acute worsening of respiratory symptoms that results in additional therapy."[1] Acute exacerbations of COPD are important events in the natural history of this disease.[88,89] Acute exacerbations are associated with considerable morbidity, whereas severe exacerbations are associated with an increased mortality.[89] Furthermore, acute exacerbations are responsible for a high percentage of the health care costs associated with COPD.[1,2]

The cause of acute exacerbations is believed to be a result of respiratory tract infections, either viral or bacterial; air pollution; or

other environmental exposures.[90,91] These triggers can initiate increased bronchospasm and airway resistance in an individual with already compromised lung function. Although mild exacerbations may be readily managed with outpatient therapy, severe exacerbations can result in respiratory failure and death, particularly if they occur in a patient with severe COPD.

Key therapeutic interventions for acute COPD exacerbations include regular bronchodilator therapy, a short course of systemic corticosteroid therapy, antibiotics, and supportive measures such as oxygen therapy. Bronchodilator therapy consisting of a short-acting β_2-agonist with or without a short-acting anticholinergic is given as needed by MDI or nebulizer every 3 to 4 hours.

For videos that show proper use of many types of inhalers, go to **http://use-inhalers.com/** or **http://www.nationaljewish.org/healthinfo/multimedia/asthma-inhalers.aspx**. For a video of how to use a nebulizer, go to **http://www.nationaljewish.org/healthinfo/medications/lung-diseases/devices/nebulizers/instructions.aspx**.

Systemic corticosteroids shorten recovery time and improve lung function and hypoxemia when added to other treatments used to manage exacerbations.[1] Although there are insufficient data to support the optimal duration of treatment, a 5-day course of prednisone has been shown as effective as a 14-day course for reducing the occurrence of a reexacerbation within a 6-month follow-up period.[74] Elevated serum eosinophil levels may predict response to oral corticosteroid therapy, but further study is needed.[1,92] Corticosteroids may be administered either orally or intravenously for severe COPD exacerbations managed in the hospital setting, because there is insufficient evidence to support one method of administration over another.[1,4] No significant difference in length of hospitalization, treatment failure, and hospital readmissions has been observed.[4,92]

Decisions about antibiotic use in the setting of an acute exacerbation should be made based on the presence of the following respiratory symptoms: increased dyspnea, sputum volume, and sputum purulence. Data suggest that if two of the three are increased, antibiotics are beneficial.[93] The optimal antibiotic regimen for acute COPD exacerbations has not been rigorously studied. For many outpatients, however, generic, low-cost antibiotics, including amoxicillin, trimethoprim–sulfamethoxazole, or doxycycline, may be very effective. Indeed, these agents can effectively cover the most common bacterial causes of acute exacerbations, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Guidelines suggest that hospitalized patients with respiratory failure should receive broad-spectrum antimicrobials that include activity against *Pseudomonas aeruginosa*, because these patients have a higher risk for more resistant organisms.[1,94]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE GROUP A (LOW RISK, LESS SYMPTOMS)

Diagnosis

CASE 19-1

QUESTION 1: T.A., a 51-year-old White male smoker, presents with daily cough and mild dyspnea on exertion with strenuous activity. He has noticed that walking up two flights of steps bothers him, when previously it did not. He has had a slight amount of wheezing, but no chest pain. He has no known chronic medical problems. He has smoked 1.5 packs/day for 34 years, and he continues to smoke that amount. His physical examination is unremarkable. COPD is suspected.

What diagnostic test should be ordered?

A clinical diagnosis of COPD should be considered in any patient presenting with persistent dyspnea, chronic cough, or sputum production with a history of exposure to risk factors such as cigarette smoking. Spirometry is the gold-standard diagnostic test and should be considered to confirm the diagnosis of COPD. The main values gleaned from spirometry will include FVC, FEV_1, and FEV_1/FVC ratio. An FEV_1/FVC ratio of <0.70 following a bronchodilator indicates obstruction to expiratory flow consistent with COPD. The FEV_1 can be used in conjunction with other clinical indicators to further determine disease severity. Repeat spirometry on a separate occasion is recommended when the postbronchodilator FEV_1/FVC ratio falls between 0.6 and 0.8, as the ratio may change as a result of biologic variation.[1]

CASE 19-1, QUESTION 2: Office spirometry demonstrates a postbronchodilator FEV_1/FVC of 0.59 and an absolute FEV_1 of 81% of predicted. T.A. has a CAT score of 7 and has had one exacerbation in the past year, which was managed at home. Using GOLD criteria, which initial COPD risk group should T.A. be assigned, and what other diagnostic tests would be necessary before initiating therapy?

Based on GOLD guidelines, this patient has clinical features most consistent with "group A." A CXR study may be performed to exclude other respiratory diagnoses contributing to the patient's symptoms; however, the abnormal spirometry, persistent symptoms, and significant exposure to cigarette smoke (51 pack-year history of smoking) are sufficient to make the diagnosis of COPD and to initiate therapy.[22]

In certain cases of diagnostic uncertainty or in patients with severe disease being considered for surgical intervention, such as lung volume reduction surgery, a complete set of pulmonary function tests, including the determination of lung volumes and DLCO, may be performed.

In patients with more severe symptoms or airflow obstruction, assessment of oxygen status by means of pulse oximetry or ABG

may be necessary. Pulse oximetry should be used to assess stable patients if the FEV_1 is <35% of predicted or with clinical signs suggestive of respiratory failure or right-sided heart failure. ABGs are recommended if peripheral saturation is <92%.[1] An α_1-antitrypsin level to rule out AATD is generally recommended for all individuals with COPD.[1,32] Especially those with early onset of disease (younger than 45 years), or in patients with a strong family history of COPD.[1]

CASE 19-1, QUESTION 3: What therapeutic interventions should be recommended for T.A. at this point?

Therapeutic Management

SMOKING CESSATION

A comprehensive smoking cessation plan with therapy should be initiated for T.A. because smoking cessation has been shown to decrease the decline in FEV_1 associated with COPD.[1,28] Although pharmacologic interventions for smoking cessation are covered elsewhere in the text (see Chapter 91, Tobacco Use and Dependence), it should be noted that a personalized message may be beneficial for this patient. Indeed, discussion of spirometry results with the patient can provide an important opportunity to deliver a personalized message.[95] It can be explained to T.A. that he is beginning to develop definite irreversible abnormalities in his pulmonary function and, therefore, is a "susceptible" smoker. It is critical for him to stop smoking and, thereby, prevent continued deterioration in lung function.

IMMUNIZATIONS

In addition to smoking cessation, this patient's immunization status should be evaluated.[96] According to the GOLD Report and in the absence of contraindications, T.A. is a candidate for vaccination against influenza and pneumococcal pneumonia, even though he is in the early stages of COPD.[1] Patients with COPD are at risk for

increased morbidity and mortality if they develop either of these infectious complications.

Individuals at highest risk for significant morbidity and mortality from influenza and pneumonia are those with chronic disease, including lung disease. Optimally, the influenza vaccine should be administered during the fall before the end of October.[97] This allows an adequate antibody response before the peak influenza season, which typically occurs within the first quarter of the year. Annual immunization is required to ensure adequate antibody protection against influenza virus and is effective in reducing morbidity and mortality from influenza.[94]

The pneumococcal polysaccharide vaccine (Pneumovax 23, PPSV23) is also recommended for patients with COPD.[1] The PPSV23 contains 23 *S. pneumoniae* serotypes and provides protection against *S. pneumoniae*.[98] PCV13 (Prevnar-13) may further protect against PCV13-type pneumonia and invasive pneumococcal disease in adults age 65 years or older without an immunocompromising condition, a cerebrospinal fluid (CSF) leak, or cochlear implant.[1,99] The Advisory Committee on Immunization Practices (ACIP) now recommends only adding the PCV13 following shared clinical decision-making between the patient and clinician.[99] These vaccines should be separated as indicated to ensure an optimal immune response.[100] To manage T.A.'s symptoms, treatment with an as-needed bronchodilator may be reasonable to start. Bronchodilators are the primary pharmacologic therapy used in the management of COPD.[1,22]

Available bronchodilator therapies include short-acting β_2-agonist or LABA, short- or long-acting anticholinergics, and methylxanthines (theophylline). For initial treatment, the most common choice for T.A. would be a short-acting inhaled β_2-agonist (eg, albuterol), a short-acting inhaled anticholinergic (eg, ipratropium), or a combination of these two agents. Either of these therapies has a relatively short onset of action and is effective in relieving symptoms. **Table 19-3** summarizes inhaled therapeutic options for COPD.

SHORT-ACTING β_2-AGONISTS

β_2-Agonists produce bronchodilation by relaxing bronchial smooth muscle through activation of cyclic adenosine monophosphate (cAMP).[101] The inhalation route of delivery for bronchodilators is recommended over oral therapy based on safety and efficacy. The dose–response curve among all available bronchodilators is relatively flat and similar. No evidence suggests that one agent is superior to another.

Albuterol is the most frequently used agent in this class. It is available as an MDI or DPI 90 µg/inhalation. It is also available as a premixed solution for nebulization (eg, adult dose 2.5 mg/0.5 mL), as well as a concentrated solution (5 mg/mL, 0.5%) that requires saline to be prescribed separately. The onset of action of short-acting β_2-agonists (eg, albuterol, levalbuterol) is rapid (within 5 minutes) and generally reaches maximal effect in 15 to 30 minutes. The duration of action is ~4 hours. Although inhaled β_2-agonists are usually well tolerated, some patients experience adverse effects (tremors, tachycardia, or nervousness) with even low dosages. Although concern has been expressed about the safety of short-acting inhaled β_2-agonists in patients with cardiac disease, a cohort study using the Saskatchewan Health Services database concluded that there was no increased risk for fatal or nonfatal myocardial infarction in patients using these agents.[102]

SHORT-ACTING ANTICHOLINERGICS

The parasympathetic (cholinergic) nervous system plays a primary role in the control of bronchomotor tone in COPD. By inhibiting cyclic guanosine monophosphate (cGMP) in the lung, aerosolized anticholinergic drugs are effective bronchodilators. The bronchodilation produced by anticholinergics in patients with stable COPD has been shown to be noninferior to that achieved by inhaled β_2-agonists.

Ipratropium bromide is the primary short-acting anticholinergic agent used in COPD. It is marketed as both an MDI (17 µg ipratropium

per puff) and as a solution for nebulization (0.5 mg ipratropium/2.5 mL). Ipratropium has an average onset of effect within 15 minutes, with a maximal bronchodilator effect in 60 to 90 minutes, although some patients may experience more rapid symptom relief. The duration of action is ~6 hours. Although some reports suggest a quicker onset of action, patients should be advised that the relief of acute symptoms will be slower compared with an inhaled β_2-agonist. A typical dose of ipratropium is two inhalations four times daily.[103] Although well tolerated, some patients experience dry mouth, nausea, and blurred vision with the use of ipratropium.

The anticholinergic actions of ipratropium are localized predominantly in the lungs, with an apparent specificity of action in the larger airways. Because it has minimal effects on sputum viscosity, there is little problem with drying of airway secretions. In addition, ipratropium's structure as a quaternary amine increases its polarity, thereby minimizing absorption from the lung and systemic side effects. These structural properties also reduce penetration across the blood–brain barrier, reducing the incidence of confusion and other central nervous system (CNS) side effects.

COMBINATION β_2-AGONISTS–ANTICHOLINERGICS

Combination therapy with two different classes of bronchodilators is appealing because it may decrease the cumulative dose of individual agents, thereby decreasing the risk of side effects while maintaining the benefits of each medication. In addition, anticholinergics and β-agonists have different mechanisms of action, and combining these two classes may provide additional benefit. Indeed, it has been demonstrated that combination therapy results in significantly greater increases in FEV_1 compared with the use of either albuterol or ipratropium alone.[104] The Combivent Respimat contains both albuterol and ipratropium in a single inhaler.[105] The respimat is a novel propellant-free inhalation device that produces a slow-moving mist from mechanical energy produced by the release of a compressed spring.

Umeclidinium plus vilanterol (Anoro Ellipta) and tiotropium plus olodaterol (Stiolto Respimat) are once-daily products that combine a long-acting anticholinergic with an LABA in a single device.[106,107] Glycopyrrolate is available in combination with indacaterol (Utibron™ Neohaler) and in combination with formoterol (Bevespi Aerosphere®), but both are dosed twice daily (bid).[108,109] Each has been approved for the maintenance treatment of airflow obstruction in patients with COPD.[106,109]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH DISEASE PROGRESSION

Therapeutic Management

CASE 19-2

QUESTION 1: J.O., a 46-year-old female with a 32-pack-year history of cigarette smoking, presents with increasing shortness of breath. She gets winded walking on level ground after about 100 yards. She quit smoking 2 years ago. The chronic cough that she previously had lessened after smoking cessation, but the dyspnea is now somewhat worse, despite the use of an albuterol inhaler on an as-needed basis. On examination, mild wheezing is noted. A CXR is unremarkable. No history of asthma or atopic conditions and serum eosinophils are unremarkable. Office spirometry demonstrates a postbronchodilator FEV_1/FVC ratio of 0.64 and an absolute FEV_1 of 2.0 L or 60% of predicted. J.O. has a CAT score of 20 and has had one exacerbation in the past year, which was managed at home. Postbronchodilator treatment demonstrated an FEV_1 increase of 100 mL, marking a 5% increase from baseline.

How should J.O. be treated?

J.O. is reporting progression of dyspnea despite smoking cessation and the use of a short-acting β_2-agonist. She is still at a low risk for an exacerbation based on her exacerbation history. Because pharmacologic management of COPD involves a stepwise approach, regular use of a long-acting bronchodilator would be the

next step in treatment, provided J.O. has been using her albuterol inhaler correctly and adherent to her initial treatment plan.

The main classes of long-acting bronchodilators currently available include β_2-agonists and anticholinergics. Both classes can be further divided into two groups according to the duration of activity—those producing bronchodilation for 12+ hours and those producing bronchodilation for 24+ hours. Both classes have been shown to improve quality of life and reduce dyspnea in patients with COPD.

LONG-ACTING β_2-AGONISTS

The role of inhaled LABAs in the chronic management of COPD has become well established in recent years. Available evidence with both salmeterol and formoterol shows improved pulmonary function, reduced dyspnea, and enhanced quality of life in patients with COPD.[1] Indacaterol, olodaterol, and vilanterol are dosed once daily and have a rapid onset of activity (eg, >5 minutes) and produce bronchodilation for 24 hours or more. Their long duration of activity and comparable safety profile may offer an added convenience to some patients. A plateau in bronchodilation is achieved for most patients at the recommended dose for each agent, so no benefits exist in exceeding the recommended dose. In addition, higher doses will increase the risk of adverse events associated with β_2-agonist excess.

LONG-ACTING ANTICHOLINERGICS

Vagal cholinergic tone is a reversible component of the airway limitation in COPD. Stimulation of the vagal parasympathetic nerves causes the release of acetylcholine, which, in turn, binds to muscarinic receptors to produce bronchoconstriction and secretion of mucus. Three muscarinic subtypes have been identified in human airways: M_1, M_2, and M_3 receptors. Tiotropium is a long-acting anticholinergic that binds to the M_1, M_2, and M_3 muscarinic receptors of bronchial smooth muscle.[110] Although tiotropium dissociates rapidly from the M_2 receptor, it dissociates much more slowly from

the M_1 and M_3 receptors. In fact, its dissociation from the M_1 and M_3 receptors is 100 times slower than that of ipratropium. M_1 receptors are located on parasympathetic ganglia, where they facilitate postganglionic transmission, thus enhancing cholinergic tone. M_3 receptors are found on airway smooth muscle and mucous glands, where activation leads to bronchoconstriction and mucus secretion. Conversely, M_2 receptors are located on postganglionic nerve endings, where they serve as autoreceptors regulating acetylcholine release and, thereby, cholinergic tone. Thus, anticholinergics, by virtue of antagonizing M_1 and M_3 receptors, relax airway smooth muscle and can reduce mucus secretion. M_2 blockade, however, augments acetylcholine release and thus enhances cholinergic tone. Therefore, the slower dissociation rate from both the M_1 and M_3 receptors enhances bronchodilation and allows the convenience of once-daily dosing.

Tiotropium has a very long duration of action and can provide effective bronchodilation with once-daily dosing. Numerous studies have documented its beneficial effect on pulmonary function and quality of life. The UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) compared 4 years of therapy with either tiotropium or placebo in nearly 6000 patients with COPD. Tiotropium was associated with improvements in lung function, quality of life, and exacerbation risk, but did not impact the rate of decline of FEV_1 or mortality.[61] Tiotropium is also a quaternary amine with limited systemic absorption; therefore, the agent is well tolerated, with dry mouth being the major side effect. Concerns have been raised, however, about tiotropium's safety. In particular, disparate sources have identified stroke, cardiovascular events, and death as possible adverse outcomes. After completion of UPLIFT, which included 17,721 patient-years of drug exposure, the Food and Drug Administration (FDA) concluded that the appropriate use of tiotropium in COPD patients does not place them at increased risk for stroke or adverse cardiovascular events.[111] In September 2014, tiotropium was also approved to be delivered via the Respimat

device. The Tiotropium Safety and Performance in Respimat (TIOSPIR) trial is the largest COPD trial to date involving >17,000 patients. This trial was designed to directly compare the safety of tiotropium respimat to tiotropium delivered via the HandiHaler device. The length of time to first COPD exacerbation was also followed to compare efficacy. Both the Respimat and HandiHaler were found to have comparable results for exacerbation frequency, as well as exacerbations associated with hospitalization. The incidence of adverse events was also similar between all treatment groups.[112]

Aclidinium bromide (Tudorza PressAir), umeclidinium bromide (Incruse Ellipta), and glycopyrrolate (Seebri Neohaler) are other long-acting anticholinergics approved for the long-term maintenance treatment of COPD. These agents have been shown to improve lung function and are well tolerated.[113–115]

J.O. should be started on a long-acting bronchodilator, such as salmeterol or tiotropium. Once-daily β-agonists such as indacaterol or olodaterol are additional options to consider. Recently approved anticholinergics such as aclidinium bromide, glycopyrrolate, or umeclidinium bromide are other potential options. It should be noted that the tolerability and efficacy of the available long-acting bronchodilators are comparable. The choice of agent is largely based on considerations such as the frequency of drug administration, the patient's ability to use the inhalation device correctly, and any out-of-pocket costs incurred by the patient. J.O. should also be instructed to continue her albuterol two puffs every 4 hours as needed for breakthrough symptoms. A follow-up visit should be scheduled to assess her response.

CASE 19-2, QUESTION 2: J.O. is started on tiotropium respimat, inhale 5 μg daily and returns to the office for a follow-up visit 3 months later. She has had significant benefit from the medication and has had decreased wheezing and a noticeable improvement in her exercise tolerance. She asks to have spirometry repeated to see whether her lung function has improved on the new medication. Spirometry is repeated, and no significant improvement is noted in her FEV_1.

How can she feel better, with improved exercise tolerance, without an improvement in her lung function?

Increasing evidence suggests that bronchodilators, including LABAs and anticholinergics, may reduce exercise-related dyspnea in patients with COPD by decreasing dynamic hyperinflation.[116] This improvement may be independent of marked changes in spirometry performed at rest. Indeed, because of flow limitation, these patients who exercise can have significant worsening of air trapping, which can worsen lung compliance and adversely affect respiratory muscle mechanics. A number of studies have shown that alleviation of such dynamic hyperinflation may be an important mechanism whereby bronchodilators improve exercise tolerance in patients with obstructive lung disease.[116]

CASE 19-2, QUESTION 3: J.O. seemed to do reasonably well for a number of years, but now, 3 years later, she has noticed progressive dyspnea on exertion. She is now having difficulty carrying laundry up from her basement, and she has noticed that her overall activity level has been curtailed. Repeat office spirometry now shows an FEV_1/FVC ratio of 0.49 and an absolute FEV_1 of 49% of predicted. She now has a CAT score of 22 and has had two exacerbations in the past year. J.O. has been adherent with her tiotropium regimen and has had no other significant changes to her medical history. She remains smoke free and is not exposed to secondhand smoke in her home and work environments. What therapeutic intervention(s) should be considered at this point?

INHALED CORTICOSTEROID THERAPY

J.O. has had significant deterioration in status and repeated COPD exacerbations despite appropriate adherence to tiotropium. Before modifying therapy, proper inhaler technique, medication adherence, and impact of nonpharmacologic interventions should be assessed. Combination therapy with either LAMA + LABA or ICS + LABA should be considered in patients with persistent symptoms or who continue to experience exacerbations despite appropriate use and adherence to long-acting bronchodilator monotherapy.[1] Fixed-dose combination products are preferred, and several options are commercially

available (Table 19-3). LAMA + LABA therapy may be preferred, given the absence of asthma or atopic conditions and without elevated serum eosinophil levels and other biomarkers associated with ICS response. Also, dual bronchodilator therapy has a lower incidence of pneumonia, when compared to regimens containing an ICS. An LAMA + LABA combination was superior to an ICS + LABA in preventing exacerbations and other patient-reported outcomes in those with a history of prior exacerbations.[117] Several corticosteroid LABA inhalers are available and indicated for COPD, including Advair (fluticasone–salmeterol), Symbicort (budesonide–formoterol), and Breo Ellipta (fluticasone–vilanterol). No convincing data suggest that one preparation is superior to the other in the treatment of COPD. However, a number of multicenter, randomized, controlled clinical trials have demonstrated the efficacy of ICS in COPD.[78,83] The data have supported the use of ICS in advanced COPD and in patients with frequent exacerbations. ICS responsiveness may be further predicted by the presence of elevated eosinophils (≥300 cells/μL) or underlying asthma.[1] Moreover, regular use of ICS can decrease the frequency of acute exacerbations and improve health-related quality of life in patients with an FEV_1 <60% of predicted.[22]

Table 19-3
Inhaled Therapeutic Options for COPD

Medication Brand Name and Strength (per Inhalation)	Chemical Name	Device	No. of Doses[a]/Device or Box
Short-Acting β_2 Agonists			
[c]ProAir HFA 90 µg, [c]Proventil HFA 90 µg, [c]Ventolin HFA 90 µg	Albuterol	MDI	200[b]
ProAir, RespiClick 90 µg	Albuterol	DPI	200
[c]AccuNeb 0.63 mg/3 mL, 1.25 mg/3 mL	Albuterol	Nebulizer	Varies
ProAir® Digihaler™	Albuterol	DPI	200
[c]Proventil 2.5 mg/3 mL (0.083%),[e]5 mg/mL (0.5%) *concentrate*	Albuterol	Nebulizer	Varies
[c]Xopenex HFA 45 µg	Levalbuterol	MDI	200[b]
[c]Xopenex 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL, [e]1.25 mg/0.5 mL *concentrate*	Levalbuterol	Nebulizer	Varies
Short-Acting Anticholinergic			
Atrovent HFA 17 µg	Ipratropium	MDI	200[b]
[c]Atrovent 0.02% (0.5 mg/2.5 mL) vial	Ipratropium	Nebulizer	25ct, 30ct, 60ct
Short-Acting Anticholinergic + β_2-Agonist Combination			
Combivent Respimat 20–100 µg	Ipratropium + Albuterol	SMI	120[b]
[c]DuoNeb 0.5–2.5 mg/3 mL vial	Ipratropium + Albuterol	Nebulizer	30ct, 60ct
Long-Acting β_2-Agonists			
Serevent Diskus 50 µg	Salmeterol	DPI	60
Brovana 15 µg/2 mL vial	Arformoterol	Nebulizer	30ct, 60ct
Perforomist 20 µg/2 mL vial	Formoterol	Nebulizer	30ct, 60ct
Arcapta Neohaler 75 µg	Indacaterol maleate	DPI	30 blister units
Striverdi Respimat 2.5 µg	Olodaterol	SMI	60[b](*30 doses*)
Long-Acting Anticholinergics			
Spiriva HandiHaler 18 µg	Tiotropium	DPI	30 blister units
[d]Spiriva Respimat 2.5 µg	Tiotropium	SMI	60[b](*30 doses*)
Tudorza Pressair 400 µg	Aclidinium bromide	DPI	60
Incruse Ellipta 62.5 µg	Umeclidinium	DPI	30
Seebri Neohaler 15.6 µg	Glycopyrrolate	DPI	60 blister units
Lonhala Magnair 25 µg/mL	Glycopyrrolate	Nebulizer	60ct
Yupelri 175 µg/3 mL	Revefenacin	Nebulizer	30ct
Long-Acting Anticholinergic + β_2-Agonist Combination			
Anoro Ellipta 62.5–25 µg	Umeclidinium + Vilanterol	DPI	60
Stiolto Respimat 2.5–2.5 µg	Tiotropium + Olodaterol	SMI	60[b](*30 doses*)
Utibron Neohaler 15.6–27.5 µg	Glycopyrrolate + Indacaterol	DPI	60 blister units
Bevespi Aerosphere 9–4.8 µg	Glycopyrrolate + Formoterol	MDI	120[b]
Duaklir Pressair 400–12 µg	Aclidinium + Formoterol	DPI	60
Inhaled Corticosteroid + Long-Acting β_2-Agonist Combination			
[c,d]Advair Diskus 250–50 µg	Fluticasone + Salmeterol	DPI	60
[c,d]Symbicort HFA 160–4.5 µg	Budesonide + Formoterol	MDI	120[b]
[d]Breo Ellipta 100–25 µg	Fluticasone + Vilanterol	DPI	60
Inhaled Corticosteroid + Long-Acting Anticholinergic + β_2-Agonist Combination			
[b,d]Trelegy Ellipta 100-62.5-25 µg	Fluticasone furoate + umeclidinium + vilanterol	DPI	60
Breztri Aerosphere 160-9-4.8 µg	Budesonide + glycopyrrolate + formoterol	MDI	120[b]

DPI, dry-powder inhaler; MDI, metered-dose inhaler; SMI, soft mist inhaler.

[a]Generic formulations available.

[b]Only FDA-approved strength for COPD other strengths may be commercially available.

[c]Institutional sizes not included.

[d]Number of doses after initial priming.

[e]Nebulized solutions marked “0.5- mL concentrate” should be diluted with 0.9% sodium chloride solution.

The TORCH study has defined the benefits and potential side effects of ICS in a broader patient population of COPD.[57] In this multicenter, randomized, placebo-controlled study, mean FEV_1 was 50% of predicted, but entry criteria did not require a history of repeated exacerbations. More than 6000 patients were randomly assigned to either an ICS (fluticasone 500 µg bid), inhaled salmeterol (50 µg bid), combined fluticasone 500 µg and salmeterol 50 µg bid, or placebo. Subjects were assessed for ~3 years. A significant benefit was seen as measured by decreased exacerbation rates in subjects taking either inhaled fluticasone or a combination of fluticasone–salmeterol therapy. Also, an improvement was found in mortality with combination therapy that approached, but did not reach statistical significance. Overall adverse side effects with ICS were similar to those with placebo. An increased risk, however, was seen for lower respiratory tract infections with inhaled fluticasone or fluticasone–salmeterol. Of note, patients did not experience an increased risk of ocular manifestations or decreased boFFIgurene density with ICS treatment.

J.O. is already taking tiotropium, so a decision must be made regarding step-up therapy. Proper inhalation technique and adherence should be confirmed before escalating therapy. LAMA + LABA is the preferred regimen for this patient, given her persistent symptom burden and high frequency of exacerbations over the past year despite LAMA monotherapy. Tiotropium + olodaterol is one possible fixed-dose combination product that may replace tiotropium. J.O. is already familiar with the Respimat device, which may help maintain adherence. If J.O. is experiencing difficulty with using the respimat, several alternative long-acting dual bronchodilator products are available in different inhaled delivery devices.

CASE 19-2, QUESTION 4: J.O. calls the next day, having read something on the Internet regarding possible increased risk of death in people with obstructive

lung disease who take long-acting bronchodilators. She is reluctant to take it. What should you tell her?

SAFETY OF LONG-ACTING BRONCHODILATORS

Although some evidence in asthma indicates that the use of long-acting bronchodilators may be associated with an increased risk of death, such evidence does not exist in patients with COPD. In fact, the TORCH study demonstrated no increased risk of death or adverse events among patients prescribed salmeterol compared with placebo.[57] Other trials designed to evaluate the safety of bronchodilator use have resulted in similar findings.[61,62,102,111] The patient should be reassured that long-acting bronchodilators are safe in COPD.

PULMONARY REHABILITATION

CASE 19-2, QUESTION 5: J.O. also wonders whether anything else other than her medication can be done for her. What advice might be given?

At this point, pulmonary rehabilitation should be strongly considered. In fact, a comprehensive multidisciplinary pulmonary rehabilitation program should be considered in any patient with COPD experiencing persistent shortness of breath despite pharmacologic management.[1,46]

Increasing evidence points to COPD as a systemic process,[118] and pulmonary rehabilitation addresses the systemic nature of the disease. Although the proximate cause of disability involves the respiratory system, leading to dyspnea on exertion, this, in turn, has systemic consequences. Although the changes may be fairly subtle to start with, most patients will gradually manifest increasing limitations in their activity. This results in substantial deconditioning. It is likely that this deconditioning, in addition to other factors such as systemic inflammation, adversely affect skeletal muscle function. Indeed, evidence is clear that oxidative capacity is diminished in patients with COPD,[47–49] which results in overall decreased aerobic

capacity and increased lactic acid production for a given level of activity.[50] The increased acid load will lead to a greater requirement for ventilation, which makes dyspnea more severe. The more dyspneic the patient is, the less activity he or she will do, leading to more deconditioning and recapitulation of the downward spiral.

Pulmonary rehabilitation is an exercise-based, multidisciplinary program that seeks to address this cycle.[1] Most programs generally last 8 to 12 weeks and involve two to three sessions per week.[46] Education, particularly about medication use, as well as psychosocial counseling and breathing retraining are important components of the program. An important component of breathing retraining involves coaching patients how to use pursed-lip breathing effectively. Pursed-lip breathing involves pursing the lips together (as in whistling) during exhalation. This helps to slow down respirations and also provides a back pressure in the small airways, preventing dynamic airway collapse and exercise-induced hyperinflation. The major intervention, however, is exercise training, especially endurance training of the lower extremities (eg, using a treadmill or bicycle ergometer). Numerous studies have demonstrated that a rehabilitation program can significantly improve exercise capacity and quality of life, as well as decrease health care utilization.[51] This may partly be related to the beneficial effects of exercise on the oxidative capacity of the skeletal muscles.

J.O. should be referred to a local outpatient pulmonary rehabilitation program. A typical program involves 2-hour sessions, two to three times per week for 8 to 12 weeks. The sessions will involve education, breathing retraining, and strength and endurance exercise training.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH DISEASE PROGRESSION

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

ANTIMICROBIAL THERAPY

CASE 19-3

QUESTION 1: R.L., a 66-year-old male with diabetes mellitus and severe COPD, presents with increased cough with productive discolored sputum after a "cold." He had been hospitalized 6 weeks earlier with community-acquired pneumonia. He is a former smoker (quit 10 years ago); his current medications include tiotropium respimat 5 µg once daily, albuterol MDI two puffs every 4 hours as needed, and theophylline 200 mg bid. He also has increased dyspnea and chest tightness. On examination, he is in no acute distress and vital signs are stable. There is increased wheezing on chest examination, and the rest of the examination is unchanged. Room air pulse oximetry is 90%, and a CXR in the office shows no infiltrates.

How should this patient be treated?

This patient has increased sputum purulence and increased dyspnea consistent with an exacerbation of COPD. It is not uncommon for such an exacerbation to be triggered by an upper respiratory viral infection. Procalcitonin is a biomarker more specific for bacterial infections and has been used to guide decisions involving antibiotic use.[1] However, the test is relatively expensive, and the clinical effectiveness of procalcitonin-guided therapy requires further study.

Given that the patient has increased dyspnea and purulent sputum production, a course of systemic corticosteroids (eg, 40 mg of prednisone daily for 5 days) and a course of antibiotics are warranted. In outpatients with low-risk factors, a low-cost antibiotic regimen is a reasonable option. Empirical treatment with an aminopenicillin with or without clavulanic acid, a macrolide, or tetracycline derivative such a doxycycline may be used.[1] Although other antibiotics are commonly prescribed, no data support superiority in this setting when compared with conventional, less expensive agents. An acute exacerbation of COPD is one of the few

instances in which antibiotic therapy is warranted to treat a respiratory infection in the absence of evidence of lower respiratory tract involvement (ie, pneumonia).

Patients with COPD and risk factors for poor outcome (severe COPD, comorbid conditions, history of frequent exacerbations) may be more susceptible to resistant pathogens. As such, guidelines recommend that a broad-spectrum antibiotic regimen be considered, including β-lactam–β-lactamase inhibitor combinations, quinolone antibiotics, or second- or third-generation cephalosporins.[1,94]

Because of his recent hospitalization, R.L. is at increased risk for resistant pathogens, including *P. aeruginosa*. He also presents with increased sputum purulence and increased dyspnea, so a broad-spectrum antimicrobial regimen, such as oral ciprofloxacin 750 mg bid or oral levofloxacin 500 mg every day for 5 to 10 days, would be appropriate. A course of oral prednisone 40 mg daily for 5 days is also indicated to improve R.L.'s lung function, reduce his hypoxemia, and hasten his recovery time.

CASE 19-3, QUESTION 2: R.L. was treated with oral ciprofloxacin 750 mg bid and demonstrated a decrease in sputum volume and purulence with less dyspnea after 3 days of therapy. However, 5 days later, he is feeling palpitations and has become nauseous. What laboratory value should be checked?

This patient has clinical evidence of theophylline toxicity. Adverse gastrointestinal reactions (eg, nausea) and CNS symptoms, including sleep difficulty and nervousness, are consistent with theophylline toxicity. Other adverse reactions associated with methylxanthines are cardiac irritability (tachycardia or arrhythmias) and seizures. All these side effects are dose related. Gastrointestinal intolerance, nervousness, and insomnia can occur at any serum concentration, but increase in frequency when serum concentrations are >15 μg/mL.

In R.L., the addition of the antibiotic ciprofloxacin to his regimen most likely resulted in a drug interaction, causing a rise in his theophylline concentration. The potential for an interaction with theophylline varies among the available fluoroquinolone antibiotics.

Drug interactions are dependent on several factors, including the dose of each agent and the baseline serum theophylline concentration. Elevations in the theophylline concentration of 25% are typical with ciprofloxacin interactions, although elevations of 50% have been observed. In R.L., a theophylline concentration should be obtained and further doses withheld until results are known.

In general, theophylline metabolism is associated with significant interpatient and intrapatient variability. Patients should be monitored closely for early signs of toxicity, as well as for the initiation of drugs that potentially may interact. Understanding and recognizing the potential for drug interactions can allow safe and effective therapy with theophylline.

CASE 19-3, QUESTION 3: A theophylline serum concentration is measured for R.L. It is reported as 21 μg/mL. What action should be taken?

The serum concentration is consistent with the interaction between theophylline and ciprofloxacin reported in the literature. His symptoms do not appear life-threatening at this point, so a conservative approach to treatment is appropriate. Theophylline should be withheld for one dose and then restarted at a lower dose (100 mg bid) until the ciprofloxacin therapy is completed. Alternatively, theophylline could be withheld until the antibiotic treatment is finished or discontinued. As mentioned, theophylline has a narrow therapeutic index and has the potential for serious toxicity as is evidenced by the current case. If the patient is unclear how beneficial the theophylline has been, a trial off of the medication is reasonable. After ~2 to 4 weeks, R.L. should be reassessed. If he feels that his chronic symptoms are no different without the drug, it should be discontinued. On the other hand, his symptoms may become more pronounced without the theophylline, and it could then be restarted. Alternatively, it would be reasonable to replace theophylline with an additional long-acting bronchodilator from a different class; in this case, a long-acting β-agonist. Evidence suggests that the combination of a long-acting anticholinergic and

LABA can increase lung function and reduce hyperinflation compared with either agent used alone.[119,120] Salmeterol, indacaterol, and olodaterol are possible stand-alone long-acting β-agonist options. In addition, formoterol and arformoterol are available in a nebulized solution. However, fixed-dose dual bronchodilator combination products may be easier for R.L. to adhere to.

COPD has a progressive course, highlighted by a worsening of symptoms with time. Because stepwise therapy is recommended, it is not uncommon to find patients on multiple medications added on in an attempt to alleviate symptoms. Nevertheless, it is important periodically to assess the patient to determine whether all the medications are continuing to provide symptomatic benefit and are still needed. This may result in a step-down approach.

Oxygen Therapy

CASE 19-4

QUESTION 1: P.J., a 62-year-old male with long-standing COPD, presents with worsening dyspnea on exertion. He is currently prescribed combination fluticasone–salmeterol (Advair 250/50 one puff bid), tiotropium (Spiriva 18 μg one puff every day), and as-needed albuterol (two to four puffs every 4 to 6 hours as needed). P.J. reports excellent adherence with his medications, and an evaluation of his inhaler technique reveals he is able to use all three devices correctly. He has undergone pulmonary rehabilitation in the past with some benefit. He is no longer exercising, however. He has smoked 1.5 packs of cigarettes a day for 40 years (60 pack-years), but quit 1 year previously. His most recent FEV_1/FVC ratio is 0.41, and his FEV_1 is 1.25 L or 38% of predicted. His room air oxygen saturation at rest is 85%. On examination, reduced breath sounds are noted in his chest, and he has lower extremity edema. His physician recommended supplemental oxygen; however, he is resistant.

How might P.J. benefit from supplemental oxygen?

The Nocturnal Oxygen Treatment Trial (NOTT), a randomized controlled study, studied patients with COPD and severe hypoxemia ($Pa_{O_2} \leq 55$ mm Hg, or $Pa_{O_2} \leq 59$ mm Hg associated with polycythemia or peripheral edema).[40] Patients were randomly

assigned to receive continuous oxygen or nocturnal oxygen. The primary outcome variable was mortality. Subjects using continuous oxygen had a significantly greater survival and improved end-organ function, including improved cognitive function. The Medical Research Council Study published in 1981, using similar entry criteria, demonstrated a significant survival benefit with continuous supplemental oxygen compared with no oxygen.[41]

On the basis of these studies, long-term oxygen administration (>15 hours/day) has been shown to improve survival in patients with severe resting hypoxemia (PaO_2 ≤ 7.3 kPa [55 mm Hg] or SaO_2 ≤ 88%), when confirmed twice over a 3-week period.[1] Individual patient factors should be considered before prescribing long-term oxygen supplementation in patients with stable COPD who experience mild-to-moderate desaturation while at rest or during exercise.[1] These guidelines (**Table 19-4**) are used by Medicare and most insurance companies as criteria to determine coverage for supplemental oxygen.[121] This patient should be encouraged to use supplemental oxygen titrated to a target saturation of ≥90% for maintenance, because it is one of the few available interventions that has been associated with improved survival in COPD.[1] In addition, a fixed-dose inhaled LAMA + LABA + ICS option (ie, triple therapy), such as Breztri™ Aerosphere™, or Trelegy® Ellipta®, may further simplify the regimen.

Table 19-4

Guidelines for Insurance Reimbursement of Oxygen Therapy in Chronic Obstructive Pulmonary Disease (COPD)

Severe hypoxemia at rest[a]:
PaO_2 ≤ 55 mm Hg
Or
PaO_2 ≤ 59 mm Hg, with polycythemia or evidence of cor pulmonale
Or
Oxygen saturation ≤ 88%
Oxygen desaturation ≤ 88% with activity or during sleep[b]

[a]Proven to improve survival.

[b]Efficacy not proven.

In addition to supplemental oxygen, the patient should be reenrolled in pulmonary rehabilitation. As mentioned, existing data suggest that this intervention can improve quality of life and exercise tolerance and decrease health care utilization.

Surgical Treatments for Chronic Obstructive Pulmonary Disease

CASE 19-4, QUESTION 2: P.J. is prescribed supplemental oxygen and enrolls in a pulmonary rehabilitation program. These interventions are successful in improving exercise tolerance; however, he presents 12 months later with worsening dyspnea. In addition, although he is compliant with the oxygen, he is wondering whether any other interventions available might improve his lung function and allow him to "get off" of oxygen.

He is reevaluated with pulmonary function studies, which demonstrate a reduced FEV_1/FVC ratio of 0.38 and an absolute FEV_1 of 29% of predicted. In addition, lung volume determinations show severe hyperinflation (TLC = 135% of predicted and air-trapping RV = 292% of predicted). His CXR shows a marked decrease in lung markings in the upper lung zones with vascular crowding in the lower lung fields. What therapeutic options are available for P.J.?

Lung volume reduction surgery, which involves the surgical removal of ~30% of the volume of each lung, can significantly improve quality of life, exercise tolerance, and mortality in selected patients with COPD. The National Emphysema Treatment Trial (NETT) demonstrated that patients with severe, upper lobe predominant emphysema who have lung volume reduction surgery have significant benefits in health-related quality of life as well as exercise tolerance.[36] Subjects who also had persistently poor exercise tolerance before surgery appeared to have the most benefit compared with control subjects with similar impairment. These patients also had a mortality benefit.[36] The rationale for the surgery is that removing the areas of the lung most involved with emphysema can improve the physiology of the remaining lung. This includes improvement in expiratory airflow and improved lung elastic

recoil as well as improved ventilation–perfusion matching. The major patient selection criteria for lung volume reduction surgery are depicted in **Table 19-5**. After a successful surgery, patients can have improved gas exchange and may no longer require supplemental oxygen.

Table 19-5
Major Selection Criteria for Lung Volume Reduction Surgery

Moderate-to-severe airflow obstruction
Hyperinflation
Upper lobe predominant emphysema
Nonsmoker
Rehabilitation potential

The CXR for this patient suggests upper lobe predominant emphysema. This would need to be confirmed with a high-resolution computed tomography scan of the chest. Furthermore, the patient would need to complete a comprehensive pulmonary rehabilitation program before surgery. Only a few centers within the United States are certified by Medicare to perform lung volume reduction surgery, and this could be an important issue for P.J., depending on where he lives. It should be stressed that lung volume reduction surgery is only appropriate for a select group of patients with advanced emphysema.

In patients with severe emphysema, another option is lung transplantation. This intervention has been shown to improve quality of life and exercise tolerance in carefully selected candidates.[122] Bilateral lung transplantation may be associated with more prolonged survival compared to single lung transplantation in some patients, but further study is necessary.[123]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. *J Am Med Assoc*. 1994;272:1497–1505. (28)

Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ*. 2000;320:1297–1303. (72)

Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775–789. (57)

Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:1005–1012. (37)

Chapman KR, Hurst JR, Frent SM, et al. Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (SUNSET): a randomized, double-blind, triple dummy clinical trial. *Am J Respir Care Med*. 2018;198(*3*):329–330. (87)

Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med*. 1980;93:391–393. (40)

Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. *N Engl J Med*. 2003;348:2059–2073. (36)

Leuppi JD, Schuetz P, Bingisser R, et al. Short term versus conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *J Am Med Assoc*. 2013;309(*21*):2223–2231. (74)

Long-Term Oxygen Treatment Trial Research Group; Albert RK, Au DH, Blackford AL, et al. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med*. 2016;375(*17*):1617–1627. (54)

Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled corticosteroids and exacerbations of COPD. *N Engl J Med*. 2014;371(*14*):1285–1294. (86)

Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543–1554. (61)

Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomized controlled trial. *Lancet*. 2016;387(*10030*):1818–1826. (82)

Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med.* 2016;374(*23*):2222–2234. (117)

Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med*. 2013;369:1491–1501. (112)

Key Websites

Global Initiative for Asthma. Global strategy for asthma management and prevention. 2020. www.ginasthma.org

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2020. Accessed September 3, 2020. http://www.goldcopd.org

Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of COPD: an official ATS clinical practice guideline. *Am J Respir Crit Care Med.* 2020;201(*9*):e56–e369. https://www.thoracic.org/statements/guideline-implementation-tools/pharmacologic-mgmt-of-copd.php

COMPLETE REFERENCES CHAPTER 19 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

1. GOLD (Global Initiative for Chronic Obstructive Lung Disease). *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease*. Updated 2020. Accessed September 3, 2020. http://www.goldcopd.org
2. Bartolome CR, Decramer M, Wedzicha JA, et al. An official American Thoracic Society/European Respiratory Society statement: research questions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;191(7):e4–e27.
3. Wedzicha JA, Calverley PM, Albert RK, et al. Prevention of COPD exacerbations: an ERS/ATS guideline. *Eur Respir J*. 2017;50:1602265.

4. Wedzicha JA, Miravitlles M, Hurst JR, et al. Management of COPD exacerbations: an ERS/ATS guideline. *Eur Respir J*. 2017;49:1600791.
5. Global Initiative for Asthma. *Global strategy for asthma management and prevention*. 2020. www.ginasthma.org
6. Wheaton AG, Ford ES, Cunningham TJ, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease—United States, 2013. *MMWR Morb Mortal Wkly Rep.* 2015;64(11):289–295.
7. Doney B, Hnizdo E, Syamlal G, et al. Prevalence of chronic obstructive pulmonary disease among US working adults aged 40 to 70 years: National Health Interview Survey Data 2004 to 2011. *J Occup Environ Med*. 2014;56(10):1088–1093. doi:10.1097/JOM.0000000000000232
8. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon Outcomes Res*. 2013;5:235–245.
9. Sin DD, Cohen SBZ, Day A, Coxson H, Paré PD. Understanding the biological differences in susceptibility to chronic obstructive pulmonary disease between men and women. *Proc Am Thorac Soc*. 2007;4(8):671–674.
10. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381:1248–1256.
11. Trupin L, Earnest G, San Pedro M, et al. The occupational burden of chronic obstructive pulmonary disease. *Eur Respir J*. 2003;22:462–469.
12. Pillai SG, Ge D, Zhu G, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. *PLoS Genet.* 2009;5(3):e1000421. doi:10.1371/journal.pgen.1000421
13. Prokopenko D, Sakornsakolpat P, Fier HL, et al. Whole-genome sequencing in severe chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2018;59(5):614–622. doi:10.1165/rcmb.2018-0088OC
14. Stoller JK, Aboussouan LS. α1-Antitrypsin deficiency. *Lancet*. 2005;365:2225–2236.
15. Lange P, Celli B, Agusti A, et al. Lung function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373(2):111–122.
16. Assad NA, Balmes J, Mehta S, et al. Chronic obstructive pulmonary disease secondary to household air pollution. *Semin Respir Crit Care Med*. 2015;36(3):408–421.
17. De Matteis S, Jarvis D, Darnton A, et al. The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort. *Eur Respir J*. 2019;54(1):1900186. doi:10.1183/13993003.00186-2019
18. Rahman I. Oxidative stress in pathogenesis of chronic obstructive pulmonary disease: cellular and molecular mechanisms. *Cell Biochem Biophys*. 2005;43:167–188.

19. Ito K, Ito M, Elliott WM, et al. Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *N Engl J Med*. 2005;352:1967–1976.
20. Henson PM, Vandivier RW, Douglas IS. Cell death, remodeling, and repair in chronic obstructive pulmonary disease? *Proc Am Thorac Soc*. 2006;3:713–717.
21. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med*. 2010;363(23):2233–2247.
22. Qaseem A, Wilt TJ, Weinberger SE, et al. American College of Physicians/American College of Chest Physicians/American Thoracic Society/European Respiratory Society (ACP/ACCP/ATS/ERS) clinical practice guideline on diagnosis and management of stable chronic obstructive pulmonary disease. *Ann Intern Med*. 2011;155:179–191.
23. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med*. 1995;152(suppl):S77–S121.
24. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J*. 1995;8:1398–1420.
25. Madison JM, Irwin RS. Chronic obstructive pulmonary disease. *Lancet*. 1998;352:467–473.
26. Jeffery PK. Structural and inflammatory changes in COPD: a comparison with asthma. *Thorax*. 1998;53:129–136.
27. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:2645–2653.
28. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *J Am Med Assoc*. 1994;272:1497–1505.
29. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;164:770–777.
30. Barberà JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21:892–905.
31. Silverman EK, Sandhaus RA. Clinical practice. Alpha-1antitrypsin deficiency. *N Engl J Med*. 2009;360:2749–2757.
32. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis*. 2016;3(3):668–682.
33. National Library of Medicine (US). Genetics Home Reference—SERPINA1 gene [Internet]. The Library; 2020. Reviewed August 2009. Accessed July 31, 2020. https://ghr.nlm.nih.gov/gene/SERPINA1
34. Gøtzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung

disease. *Cochrane Database Syst Rev.* 2016;(9):CD007851. doi:10.1002/14651858.CD007851.pub3

35. World Health Organization. *Chronic obstructive pulmonary disease (COPD)*. 2017. Accessed July 29, 2020. https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
36. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. *N Engl J Med*. 2003;348:2059–2073.
37. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:1005–1012.
38. Afonso A, Verhamme K, Sturkenboom M, Brusselle G. COPD in the general population: prevalence, incidence and survival. *Respir Med*. 2011;105:1872–1884.
39. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality. A randomized clinical trial. *Ann Intern Med*. 2005;142:233–239.
40. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med*. 1980;93:391–393.
41. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet*. 1981;1:681–686.
42. Godtfredsen N, Lam T, Hansel T, et al. COPD-related morbidity and mortality after smoking cessation: status of the evidence. *Eur Respir J*. 2008;32:844–853.
43. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination. A randomized controlled study. *Chest*. 2004;125:2011–2020.
44. Wongsurakiat P, Lertakyamanee J, Maranetra KN, Jongriratanakul S, Sangkaew S. Economic evaluation of influenza vaccination in Thai chronic obstructive pulmonary disease patients. *J Med Assoc Thai*. 2003;86:497–508.
45. Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR Morb Mortal Wkly Rep*. 2010;59:1102–1106.
46. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation [published correction appears in *Am J*

Respir Crit Care Med. 2014;189(12):1570]. *Am J Respir Crit Care Med*. 2013;188(8):e13–e64. doi:10.1164/rccm.201309-1634S

47. Maltais F, Simard AA, Simard C, Jobin J, Desgagnés P, LeBlanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med*. 1996;153:288–293.
48. Jakobsson P, Jorfeldt L, Henriksson J. Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1995;151(2 Pt 1):374–377.
49. Sauleda J, García-Palmer F, Wiesner RJ, et al. Cytochrome oxidase activity and mitochondrial gene expression in skeletal muscle of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(5 Pt 1):1413–1417.
50. Couillar D, Maltais F, Saey D, et al. Exercise-induced quadriceps oxidative stress and peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2003;167:1664–1669.
51. Rabinovich RA, Figueras M, Ardite E, et al. Increased tumour necrosis factor-alpha plasma levels during moderate-intensity exercise in COPD patients. *Eur Respir J*. 2003;21:789–794.
52. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis*. 1991;143:9–18.
53. Whittom F, Jobin J, Simard PM, et al. Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc*. 1998;30:1467–1474.
54. Long-Term Oxygen Treatment Trial Research Group; Albert RK, Au DH, Blackford AL, et al. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med*. 2016;375(17):1617–1627.
55. Gross NJ. Outcome measurements in COPD. Are we schizophrenic? *Chest*. 2003;123:1325–1327.
56. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of β-agonists in patients with asthma and COPD: a meta-analysis. *Chest*. 2004;125:2309–2321.
57. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775–789.
58. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev*. 2012;64(3):450–504.
59. Anthonisen NR, Connett JE, Enright PL, et al. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med*. 2002;166:333–339.
60. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary

disease: a systematic review and meta-analysis. *J Am Med Assoc*. 2008;300:1439–1450.
61. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543–1554.
62. Wise RA, Anzueto A, Calverley P, et al. The Tiotropium Safety and Performance in Respimat® Trial (TIOSPIR™), a large-scale, randomized, controlled, parallel group trial—design and rationale. *Respir Res*. 2013;14(40):1–7.
63. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147(4):894–942.
64. Anthonisen NR, Wright EC. Bronchodilator response in chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1986;133:814–819.
65. Gross NJ. The influence of anticholinergic agents on treatment for bronchitis and emphysema. *Am J Med*. 1991;91(suppl 4A):11S–12S.
66. Lakshminarayan S. Ipratropium bromide in chronic bronchitis/emphysema. A review of the literature. *Am J Med*. 1986;81(suppl 5A):76–80.
67. O'Donnell DE, Webb KA. Breathlessness in patients with severe chronic airflow limitation. Physiologic correlations. *Chest*. 1992;102:824–831.
68. Belman MJ, Brooks LR, Ross DJ, Mohsenifar Z. Variability of breathlessness measurement in patients with chronic obstructive pulmonary disease. *Chest*. 1991;99:566–571.
69. *Theophylline. Drug Facts & Comparisons. Facts & Comparisons eAnswers*. Wolters Kluwer Health, Inc; 2020.
70. Daliresp Oral Tablets. Prescribing information. Astra Zeneca Pharmaceuticals LP; 2020.
71. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374(9691):685–694.
72. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ*. 2000;320:1297–1303.
73. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA. Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study. *Thorax*. 2003;58:654–658.
74. Leuppi JD, Schuetz P, Bingisser R, et al. Short term versus conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *J Am Med Assoc*. 2013;309(21):2223–2231.
75. Yang IA, Clarke MS, Sim EHA, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012; (7):CD002991. doi:10.1002/14651858.CD002991.pub3

76. Corlateanu A, Mendez Y, Wang Y, Garnica RJ, Botnaru V, Siafakas N. Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art. *Pulmonology*. 2020;26(2):95–100.
77. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381:1257–1266.
78. Mahler DA, Wire P, Horstman D, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166:1084–1091.
79. Jones PW, Willits LR, Burge PS, et al. Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J*. 2003;21:68–73.
80. Calverley PM, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial [published correction appears in *Lancet.* 2003;361:1660]. *Lancet*. 2003;361:449–456.
81. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease.*Eur Respir J*. 2003;21:74–81.
82. Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomized controlled trial. *Lancet*. 2016;387(10030):1818–1826.
83. Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2013;(8):CD006826. doi:10.1002/14651858.CD006826.pub2
84. Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2020;201(9):e56–e69. doi:10.1164/rccm.202003-0625ST
85. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2014; (3):CD010115. doi:10.1002/14651858.CD010115.pub2
86. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled corticosteroids and exacerbations of COPD. *N Engl J Med*. 2014;371(14):1285–1294.
87. Chapman KR, Hurst JR, Frent SM, et al. Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (SUNSET): a randomized, double-blind, triple dummy clinical trial. *Am J Respir Care Med*. 2018;198(3):329–330.
88. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient centered outcomes. *Chest*. 2007;131:696–704.

89. Rivera-Fernández R, Navarrete-Navarro P, Fernández-Mondejar E, et al. Six-year mortality and quality of life in critically ill patients with chronic obstructive pulmonary disease. *Crit Care Med*. 2006;34:2317–2324.
90. Ko FW, Ip M, Chan PK, et al. A 1-year prospective study of the infectious etiology in patients hospitalized with acute exacerbations of COPD. *Chest*. 2007;131:44–52.
91. White AJ, Gompertz S, Stockley RA. Chronic obstructive pulmonary disease. 6: The aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2003;58:73–80.
92. Lindenauer PK, Pekow PS, Lahti MC, Lee Y, Benjamin EM, Rothberg MB. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. *J Am Med Assoc*. 2010;303:2359–2367.
93. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106:196–204.
94. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J*. 2005;26:1138–1180.
95. Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *BMJ*. 2008;336:598–600.
96. McIvor A, Little P. Chronic obstructive pulmonary disease. *BMJ*. 2007;334:798.
97. Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2020–21 Influenza Season. *MMWR Morb Mortal Wkly Rep*. 2021;69(8):1–24.
98. Pneumovax 23. Prescribing information. Merck Sharp and Dohme Corp.; 2019.
99. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68(46):1069–1075.
100. Kobayashi M, Bennett NM, Gierke R, et al. Intervals between PCV13 and PPSV23 vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2015;64(34):944–947.
101. Giembycz MA, Newton R. Beyond the dogma: novel β2-adrenoceptor signalling in the airways. *Eur Respir J*. 2006;27:1286–1306.
102. Suissa S, Assimes T, Ernst P, et al. Inhaled short acting beta agonist use in COPD and the risk of acute myocardial infarction. *Thorax*. 2003;58:43–46.

103. Atrovent HFA. Prescribing information. Boehringer Ingelheim Pharmaceuticals; 2020.
104. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group. *Chest*. 1994;105:1411–1419.
105. Combivent Oral Inhalation Aerosol. Prescribing information. Boehringer Ingelheim Pharmaceuticals; 2016.
106. Anoro Ellipta Oral Inhalation Powder. Prescribing information. GlaxoSmithKline; 2020.
107. Stiolto Respimat Oral Inhalation Spray. Prescribing information. Boehringer Ingelheim Pharmaceuticals; 2019.
108. Utibron Neohaler Oral Inhalation Powder. Prescribing information. Novartis Pharmaceutical Corp; 2019.
109. Bevespi Aerosphere. Prescribing information. AstraZeneca Pharmaceuticals LP; 2019.
110. Barnes PJ. The pharmacological properties of tiotropium. *Chest*. 2000;117(2 suppl):63S–66S.
111. Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium—the FDA's conclusions. *N Engl J Med*. 2010;363:1097–1099.
112. Wise RA, Anzueto A, Cotton D, et al. Tiotropium respimat inhaler and the risk of death in COPD. *N Engl J Med*. 2013;369:1491–1501.
113. D'Urzo A, Ferguson GT, van Noord JA, et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. *Respir Res*. 2011;12:156.
114. Kerwin EM, D'Urzo AD, Gelb AF, et al. Efficacy and safety of a 12-week treatment with twice daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD*. 2012;9(2):90–101.
115. Carter NJ. Inhaled glycopyrronium bromide: a review of its use in patients with moderate to severe chronic obstructive pulmonary disease. *Drugs*. 2013;73(7):741–753.
116. O'Donnell DE, Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. *COPD*. 2006;3:219–232.
117. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med*. 2016;374(23):2222–2234.
118. Wouters EF. Local and systemic inflammation in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;2:26–33.
119. Cazzola M, Centanni S, Santus P, et al. The functional impact of adding salmeterol and tiotropium in patients with stable COPD. *Respir Med*. 2004;98:1214–1221.
120. van Noord JA, Aumann JL, Janssens E, et al. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients

with COPD. *Chest*. 2006;129:509–517.
121. Centers for Medicare and Medicaid Services. *Decision Memo for Home Use of Oxygen*. US Government Printing Office; 2006. CMMS Publication No. CAG-00296N.
122. Patel N, Criner GJ. Transplantation in chronic obstructive pulmonary disease. *COPD*. 2006;3:149–162.
123. Thabut G, Christie J, Ravaud P, et al. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. *Lancet*. 2008;371:744–751.

20

Acute and Chronic Rhinitis

Suzanne Bollmeier and Dennis M. Williams

CORE PRINCIPLES		CHAPTER CASES
1	Rhinitis is a common disorder and refers generally to inflammation in the nasal cavity. Common manifestations can include nasal discharge, itching, sneezing, congestion, and postnasal drip. Rhinitis can be caused by allergic, nonallergic, or mixed allergic and nonallergic triggers. Distinguishing the subtype can be helpful in targeting symptomatic treatment and prevention.	**Case 20-1 (Question 1)** **Case 20-8 (Question 2)** **Case 20-9 (Question 1)**
2	Oral antihistamines are the most common therapies used for treating allergic rhinitis. They are convenient and effective for most rhinitis symptoms including rhinorrhea, sneezing, and itching.	**Case 20-1 (Question 4)**
		Case 20-1 (Question

3	Second-generation antihistamines are preferred over first-generation agents based on a superior side-effect profile and convenience of dosing.	4)
4	Intranasal antihistamines offer an alternative to oral agents, with the advantage of efficacy for congestion and symptoms from some nonallergic causes. Side effects can challenge patient acceptance, however.	**Case 20-1 (Question 5)**
5	Intranasal corticosteroids are the most effective therapies available for treating a variety of rhinitis disorders. They are safe, well tolerated, and are highly effective in reducing itching, sneezing, rhinorrhea, and congestion.	**Case 20-3 (Question 3)**
6	Proper administration technique is important for intranasal therapies to maximize effectiveness and minimize the risk of side effects and toxicities.	**Case 20-1 (Question 5)** **Case 20-2 (Question 3)** **Case 20-3 (Question 7)**
7	Leukotriene modifiers are not recommended first line for treating patients with allergic rhinitis owing to cost and other products with superior efficacy. Leukotriene modifiers may be beneficial for select patient populations (eg, those with concomitant asthma or aspirin sensitivity).	**Case 20-4 (Question 2)**
8	The duration of use of topical decongestants should be limited to 3 to 5 days.	**Case 20-7 (Question 1)**

9	Ophthalmic therapies may be indicated if ocular itching, tearing, and redness are the primary symptoms or continue to be bothersome despite appropriate therapy for nasal symptoms associated with rhinitis.	**Case 20-1 (Question 5)**
10	Many patients seek complementary and alternative therapies to treat rhinitis conditions, despite limited evidence regarding their effectiveness.	**Case 20-5 (Question 1)**

INTRODUCTION

Rhinitis is defined as an inflammatory condition affecting the mucous membranes of the nose and upper respiratory system. In clinical practice, however, the term is used broadly to encompass a heterogeneous group of nasal disorders characterized by periods of rhinorrhea (nasal discharge), pruritus (itching), sneezing, congestion, and postnasal drainage (postnasal drip). These nasal symptoms can be accompanied by ocular symptoms such as redness, itching, and discharge and can be exacerbated by the development or presence of sinusitis. The most common form of rhinitis occurs in response to an allergen, although a variety of other subtypes have been demonstrated.[1–3]

CAUSES AND CLASSIFICATIONS

Rhinitis is not a single disease but rather has multiple causes and underlying pathophysiologic mechanisms with multiple phenotypes commonly divided into allergic, nonallergic, mixed, and infectious.[2–4] **Figure 20-1**[2,3] depicts common causes of acute and chronic rhinitis

symptoms, including some conditions that mimic rhinitis (eg, nasal polyps). The most common cause of acute rhinitis is a viral upper respiratory infection, that is, the common cold.

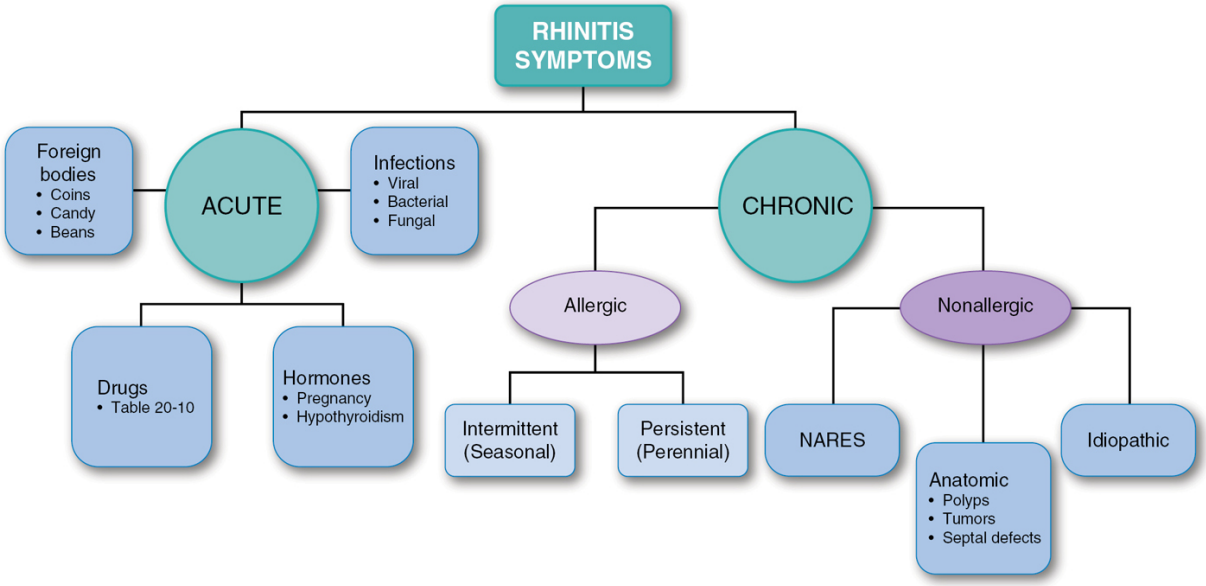


Figure 20-1 Possible causes of rhinitis symptoms. NARES, nonallergic rhinitis with eosinophilia syndrome.

In most patients, these viral infections are self-limited and require only symptomatic treatment. Nasal foreign bodies are another frequent cause and should be suspected when a pediatric patient presents with acute, unilateral symptoms.[3] Hormonal, food, and medication-related rhinitis are also common acute syndromes.[3,5]

Chronic rhinitis can be classified as allergic, nonallergic, or mixed allergic and nonallergic.[2] Allergic rhinitis, the most common subtype, is typically associated with atopy, an inherited tendency to develop a clinical hypersensitivity condition, and its symptoms are a result of immunoglobulin E (IgE)-dependent events.[5] There is not a single, uniform standard for classifying allergic rhinitis. In the past, patients were classified as having seasonal or perennial disease, based on the frequency of symptoms and potential offending allergens.[1] A newer approach categorizes allergic rhinitis based on severity (eg, mild or moderate to severe) and frequency (eg, intermittent or persistent) of symptoms.[1,6] This classification system is summarized

in **Figure 20-2**. Clinicians are likely to encounter a combination of these two classification schemes when evaluating clinical literature and participating in patient care activities. Product labeling from the Food and Drug Administration (FDA) utilizes both classification systems.

Intermittent[a] Disease	Persistent[b] Disease
Symptoms occur: Fewer than 4 days/week *or* for fewer than 4 weeks	**Symptoms occur:** At least 4 days/week *and* for at least 4 weeks
Mild	**Moderate–Severe**
All of the following:	At least *one* of the following:
• Normal sleep	• Impaired sleep
• No impairment of usual daily activities, sports, and leisure	• Impairment of daily activities, sports, and leisure
• No interference with work or school	• Interference at work or school
• No troublesome symptoms	• Troublesome symptoms

[a]Formerly "seasonal" symptoms.
[b]Formerly "perennial" symptoms.

Figure 20-2 ARIA classification of allergic rhinitis. ARIA, Allergic Rhinitis and its Impact on Asthma. (Source: Bousquet J, Khalteav N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2) LEN and AllerGen). *Allergy*. 2008;63(suppl 86):8–160. Reprinted by permission of John Wiley & Sons, Inc.)

Several categories exist for nonallergic causes of rhinitis, including drug-induced rhinitis, hormonal rhinitis (ie, pregnancy), nonallergic occupational rhinitis, idiopathic rhinitis,[7] and vasomotor rhinitis, which is the most common form.[8] Vasomotor rhinitis and nonallergic rhinitis are often used interchangeably. In vasomotor rhinitis, symptoms are often associated with environmental factors including temperature or barometric pressure changes, strong chemical odors,[8] tobacco smoke,[9] stress, or emotional factors.[10] Another form is nonallergic

rhinitis with eosinophilia syndrome (NARES) where patients have no evidence of allergic disease except the presence of >20% eosinophils in nasal smears.[11] Mixed rhinitis is a subset of allergic rhinitis in which features of both allergic and nonallergic diseases are present. These patients can be hard to differentiate but will have at least one nonallergic trigger such as temperature changes, tobacco smoke, perfumes, and cleaning products is present.[8] The presence of mixed disease should not be overlooked when evaluating the presentation of a patient or assessing the response to therapy.

EPIDEMIOLOGY AND IMPACT

Prevalence rates for rhinitis are difficult to quantify because the condition is often undiagnosed, different definitions are used, and data collection methods vary. A conservative estimate suggests that the prevalence of allergic rhinitis in the United States is ~7.7% of adults and 7.2% of children[12] (via physician diagnosis), but it may be as high as up to 30% in adults (and even more children), based on self-reported nasal symptoms,[2] making it the fifth most common chronic illness in the United States.[1] According to recent survey data, the number of children with respiratory allergies in the past 12 months was nearly 7 million, and adults reporting a diagnosis of hay fever in the past 12 months was 19.2 million.[12]

In recent decades, the prevalence in Western societies has increased, and studies from around the world are reporting similar trends.[5,13] Although studies have traditionally reported a 3:1 ratio of allergic to nonallergic rhinitis, recent data suggest that 35% to 50% of patients may experience symptoms from mixed causes.[8]

Rhinitis can lead to a worsening in sleep quality, cognitive function and mood, decreased work productivity, and a worsening of asthma or sinusitis. Also, patients with rhinitis are typically less attentive in school because of decreased concentration and difficulty learning.[14] Although many patients will self-treat their rhinitis symptoms, visits to provider offices are common.[15] A patient with allergic rhinitis will visit

the provider approximately three more times per year and fill nine more prescriptions yearly compared to a patient without rhinitis.[16]

Although rhinitis does not lead to the mortality associated with some illnesses, its prevalence and negative health impact make it an important health problem in the United States. Allergic diseases are a frequent contributor to health-related absenteeism.[17] It is estimated that 10.7 million workdays are missed because of allergic rhinitis in the United States per year.[17]

ANATOMY AND PHYSIOLOGY

The external nose is pyramidal and consists of paired nasal bones and associated cartilage. Its base has two elliptical-shaped openings called nares or nostrils. Internally, a septum divides the nasal cavity into two separate compartments and consists of bone and cartilage covered by a mucosal membrane.[18]

The membranes of the nasal cavity consist primarily of pseudostratified ciliated columnar epithelial cells with mucus-producing goblet cells interspersed among them.[19] The mucous lining serves as a protective shield against bacterial and viral infections.[19] The tiny cilia beat rhythmically to transport mucus across the upper airway membrane to the nasopharynx. In addition, respiratory secretions residing on these mucous membranes contain immunoglobulin A (IgA), which serves as an immunologic defense.[19]

The autonomic nervous system controls the vascular supply and the secretion of mucus to the nasal membrane. Sympathetic activation results in vasoconstriction, which decreases nasal airway resistance.[19] Parasympathetic stimulation results in glandular secretion and nasal congestion.[19] The mucosa is also innervated by the nonadrenergic–noncholinergic system. Neuropeptides from these nerves (eg, substance P and neurokinins) play a role in vasodilation, mucus production, and inflammation,[19] although their significance is unclear. The trigeminal nerve also provides sensory innervation.[19] The primary functions of the nose and upper airway

are smell, speech, and the exchange of air between the internal and external environments.[19] These processes are disrupted in the presence of inflammation, increased mucus, and congestion.

ETIOLOGY OF ALLERGIC RHINITIS

Genetic, environmental, and lifestyle influences are associated with the development of allergic rhinitis.[20] Candidate genes have not been identified[20]; however, atopy is a significant inheritable factor, and the risk of a child experiencing allergic symptoms is ~44% to 50% with one atopic parent[2,5] and is even more likely with two atopic parents.[5] Environmental exposures, particularly early in life, are also important in the development of symptoms.[21] In addition, lower socioeconomic status may be a risk factor for the development of allergic rhinitis.[21]

One etiologic theory, referred to as the hygiene hypothesis, suggests that the initial differentiation of lymphocytes early in life has either positive or negative influences on the development of subsequent allergies. In the normal development of the immune system, the lymphocytes differentiate into helper T (either T_H1 or T_H2) cells based on environmental stimuli. Factors associated with a T_H1 (allergy protective) response include exposures to various bacteria and viruses, the presence of older siblings, and early attendance in daycare. Factors associated with a T_H2 (predisposition to allergies) response include environmental exposures to house dust mites, cockroaches, or early, frequent antimicrobial use.[4,5]

Aeroallergens are common triggers for allergic rhinitis and are grouped into indoor, outdoor, or occupational agents. Indoor allergens include dust mites, pet dander, and insects. Outdoor allergens are pollens and mold, which create a greater risk of intermittent or seasonal symptoms as seasonal peaks and abundance in certain hot and humid areas increase their development.[22] It is postulated that global warming and climate

change also impact seasonal allergic rhinitis. Ragweed season, for example, is starting earlier and ending later in the central Midwest United States.[23] Interestingly, ragweed is intolerant to frost.[24]

PATHOPHYSIOLOGY

Allergic rhinitis is characterized by an IgE-mediated response that involves three primary steps: sensitization, early-phase events, and late-phase events.[4,25] This process is depicted in **Figure 20-3**. The nonallergic pathogenic course is less well understood. It is not IgE-mediated, although in some subtypes inflammatory cells and mediators can cause similar effects to those seen in the allergic form.[25]

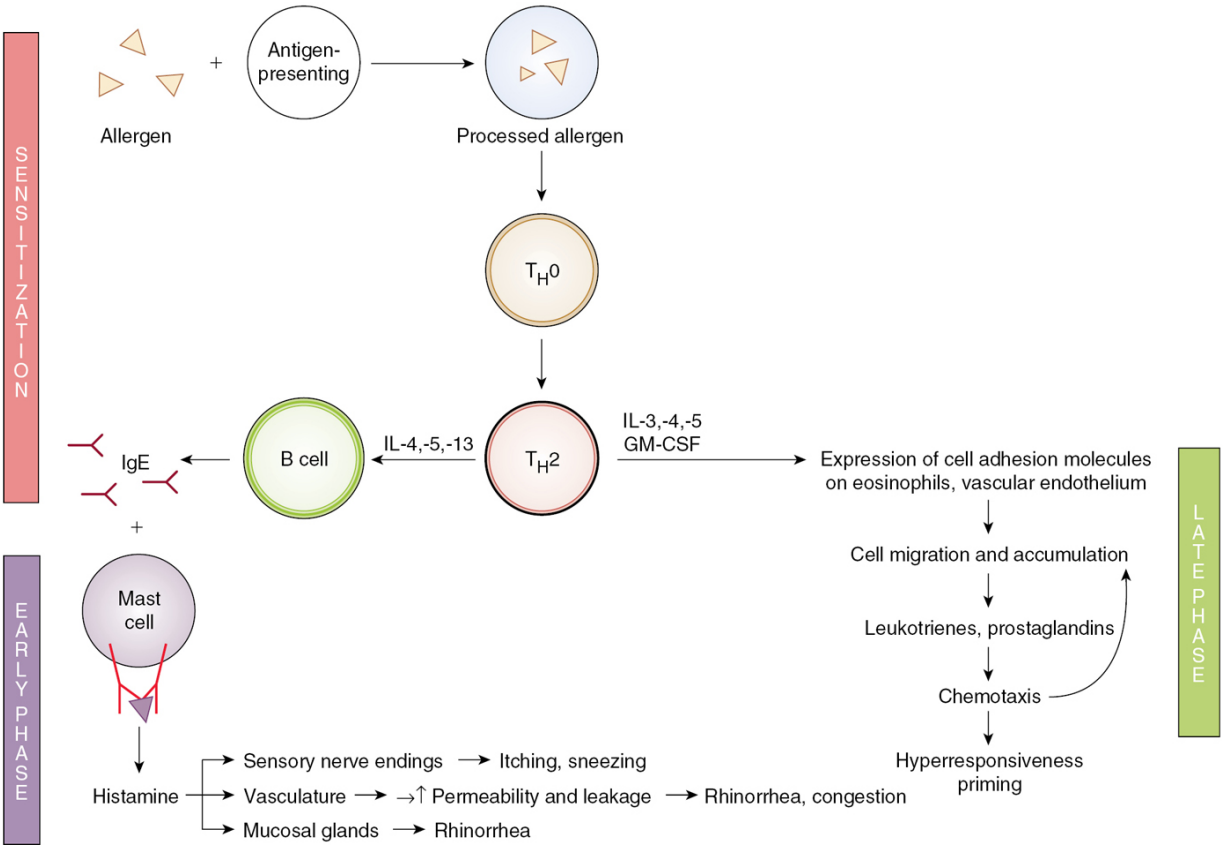


Figure 20-3 Pathophysiology of allergic rhinitis. GM-CSF, Granulocyte macrophage –colony stimulating factor; IL, interleukin.

Sensitization

In atopic patients, sensitization to an allergen occurs after initial exposure causing the production of IgE antibodies. These antibodies bind to receptors on mast cells. Upon subsequent exposure, activation of an inflammatory response is initiated because of the cross-linking of the allergen, IgE antibody, and the mast cell.[5]

Early Response

After initial exposure, antigen-presenting cells of the immune system react to allergens deposited on the nasal mucosa.[5] Mast cells and other cells, such as basophils,[26] then release both new and preformed chemotactic[26] inflammatory mediators, such as histamine, which can cause localized inflammation.[4] Symptoms associated with this early response can occur within minutes, including sneezing, rhinorrhea, and nasal itching.[5] Histamine receptors (H_1) are present throughout the nasal mucosa and airway. Their activation results in vascular engorgement, leading to nasal congestion and rhinorrhea.[26] In addition, histamine stimulates sensory nerves of the parasympathetic nervous system in the upper airway causing other inflammatory mediators such as basophils,[5] eosinophils, lymphocytes, macrophages, and dendritic cells to migrate to the upper airway, contributing to a late-phase response.[26]

Late Response

Up to one-third of patients with allergic rhinitis also experience a late response that develops ~4 hours after initial exposure and may persist for up to 8 hours.[27] In this phase, the nature of inflammation is even more complex, and nasal congestion is a prominent feature.[27] Numerous cells and mediators, including T_H2 lymphocytes, cytokines, basophils, eosinophils, neutrophils, macrophages, and leukotrienes, play important roles.[4] These additional mediators, attracted to the area through chemotaxis, sustain the inflammatory

response.[4] Also, some chemotactic proteins can cause damage to the airway epithelium and expose local nerve fibers.[4] Continued exposure to the offending allergen can also prolong the late-phase reaction.

CLINICAL PRESENTATION AND ASSESSMENT OF RHINITIS

The diagnosis of rhinitis is not defined by one specific laboratory test; rather, it is related to the coordinated results of a thorough patient interview, including medication history, pertinent physical examination, and a limited number of relevant laboratory assessments.

Risk Factors

Several elements increase the risk of developing allergic rhinitis. Atopy, parental history, introduction of formula in infancy, exposure to maternal smoking at age younger than 1 year, serum IgE levels >100 IU/mL before age 6 years, ethnic origin other than White European, environmental pollution, birth during pollen season, no older siblings, late entry into nursery or preschool, and exposure to indoor allergens such as animal dander and dust mites as well as concomitant food allergies[26] are risk factors.[5]

History, Signs, and Symptoms

A history should be obtained from the patient that includes details of the onset (including seasonality),[3] character, frequency, duration, and severity of the patient's symptoms and any identifiable factors that provoke or relieve these symptoms.[5] Past medical history (including the age of onset of symptoms) and family history (eg, atopy) are also helpful.[5] Other symptoms such as sleep problems,

snoring, repeated sniffing, and allergic salute and shiner should also be noted.[3]

Both allergic and nonallergic forms of rhinitis are common and can potentially coexist.[2] Diagnostic criteria suggestive of allergic rhinitis include nasal discharge, itching, sneezing, and nasal congestion.[3] Occasionally, patients will present with a decreased sense of smell.[5] Symptoms of allergic conjunctivitis include itchy, watery eyes,[5] which occur in ~50% to 70% of patients with allergic rhinitis. Their presence can be used to differentiate allergic rhinitis from other forms.[5] Persistent congestion and/or rhinorrhea[25] like changes in temperature, air conditioning, pollutants, tobacco smoke, and other irritants suggest that nonallergic triggers may be involved. The negative impact of rhinitis on a patient's quality of life can be substantial, and it is important to assess this during the patient interview. Symptoms and symptom-induced interference with necessary (ie, work, school) and enjoyable (eg, hobbies, family events) activities can lead to patient anger, sadness, irritation, and withdrawal.[5] The questions listed in **Figure 20-4** provide a guide to collecting the information needed to initiate and modify therapy based on the underlying causes of the rhinitis symptoms.

1. Which of the common symptoms of rhinitis is the patient experiencing?
   - Sneezing, nasal itching, runny nose, nasal congestion, postnasal drip, altered sense of smell, watery eyes, itching eyes, ear “popping”

2. What color are the nasal secretions?
   - Clear, white, yellow, green, blood-streaked, rusty brown

3. When did the symptoms first appear?
   - Infancy, childhood, adulthood

4. Were the symptoms associated with a change in state/environment?
   - After a viral upper respiratory infection, after a traumatic blow to the head or face, upon moving into/visiting a new dwelling, after obtaining a new pet

5. How often do the symptoms occur?
   - Daily, episodically, seasonally, constantly

6. For how long has this symptom pattern persisted?
   - Days, weeks, months, years

7. Which factors or conditions precipitate symptoms?
   - Specific allergens, inhaled irritants, climatic conditions, food, drinks

8. Which specific activities precipitate symptoms?
   - Dusting, vacuuming, mowing grass, raking leaves

9. Are other members of the family experiencing similar symptoms?

10. Which of the following are prevalent in the household?
    - Carpeting, heavy drapes, foam or feather pillows, stuffed toys, areas of high moisture (basements, bathrooms), tobacco use (by patient or others), pets

11. Does the patient have other medical conditions that can cause similar symptoms?

12. Is the patient taking any medications that might cause or aggravate these symptoms?

13. What prescription and nonprescription medications have been used for these symptoms in the past? Were they effective? Did they cause any unwanted effects?

14. What is the patient's occupation?

15. What are the patient's typical leisure activities?

16. To what extent have the symptoms interfered with the patient's lifestyle (ie, are they disabling or merely annoying)?
    - Greatly, somewhat, not much

Figure 20-4 Patient history interview.

Diagnosis

PHYSICAL EXAMINATION

During a physical examination for rhinitis, the patient's nose should be inspected for the position of the septum, appearance of the nasal mucosa, secretions, and any growths.[3] Common physical characteristics of patients with allergic rhinitis are clear nasal discharge, swollen nasal membranes,[4] allergic shiners (discoloration under the lower eyelids owing to vasodilation or venous congestion), and allergic salute (horizontal nasal crease across the bridge of the nose as a result of repeated upward rubbing of the tip of the nose by the palm).[8] The patient's eyes, ears, throat, lung, and skin should also be examined.[8] Chronic mouth breathing because of nasal obstruction can cause recognizable facial characteristics (eg, adenoid face and dental abnormalities).[1] Many patients with chronic rhinitis will have a decreased sense of smell or taste and may also experience ear popping and pressure owing to auditory tube dysfunction.[8]

Laboratory Tests

Several diagnostic tests are available for confirming a diagnosis of allergic rhinitis in patients who present with a suggestive history and symptoms. Microscopic examination of nasal secretions can be performed, but consensus on their usefulness is lacking.[1] In allergic conditions, the clinician would expect numerous eosinophils to be present in the sample; however, this could also be true of NARES or nasal polyps.[28]

Immediate hypersensitivity skin tests are used to demonstrate an IgE-mediated response of the skin to an allergen.[1] A variety of skin test methods are available; however, the skin-prick/puncture technique (in which the wheal-and-flare reaction is evaluated 15–20 minutes after allergen administration) is preferred.[1] A primary point of differentiation between pure allergic versus nonallergic disease is the presence of a serum IgE level >100 international units/mL

(especially before age 6), which is consistent with atopy.[5] However, a clinical diagnosis of either allergic or nonallergic disease is often made in the absence of a serum IgE and is based on the nature of symptoms and triggers.

OVERVIEW OF TREATMENT

There are two primary guideline resources available that summarize the evidence and expert opinion regarding the diagnosis and management of allergic rhinitis. The first, from the American Academy of Otolaryngology, Head and Neck Surgery Foundation, was published in early 2015 by a panel consisting of 20 members representing experts in the field of allergy and immunology.[1] The British Society of Allergy and Clinical Immunology has also developed a revised guideline for the diagnosis and management of both allergic and nonallergic rhinitis that was last updated in 2017.[3] In addition, evidence linking asthma and allergic rhinitis epidemiologically, pathologically, and physiologically has been published, suggesting that upper respiratory allergic disorders and asthma represent components of a single inflammatory airway syndrome.[4] This prompted the development and subsequent updates of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines most recently in 2010 and a brief update was published in 2017, which provide direction for clinicians caring for patients with both conditions.[6] The 2010 document includes information about the use of complementary and alternative therapies, rhinitis in athletes, and grading the evidence used to establish the guidelines.[29] Guidelines for the treatment of seasonal allergic rhinitis were published in 2017 by the Joint Council of AAAAI and ACAAI and are evidence based.[30]

The treatment goals for rhinitis are to prevent or relieve symptoms and improve quality of life without adverse drug effects or excessive cost. These goals should be achievable through the establishment of a therapeutic partnership with a competent and caring clinician. With

appropriate treatment, the patient should be able to maintain a normal lifestyle and perform desired activities. Common management strategies include patient education, allergen and irritant avoidance, and pharmacotherapy.[1,3,4,26] **Figures 20-5** and **20-6** depict algorithms for the general management of intermittent and persistent allergic rhinitis.

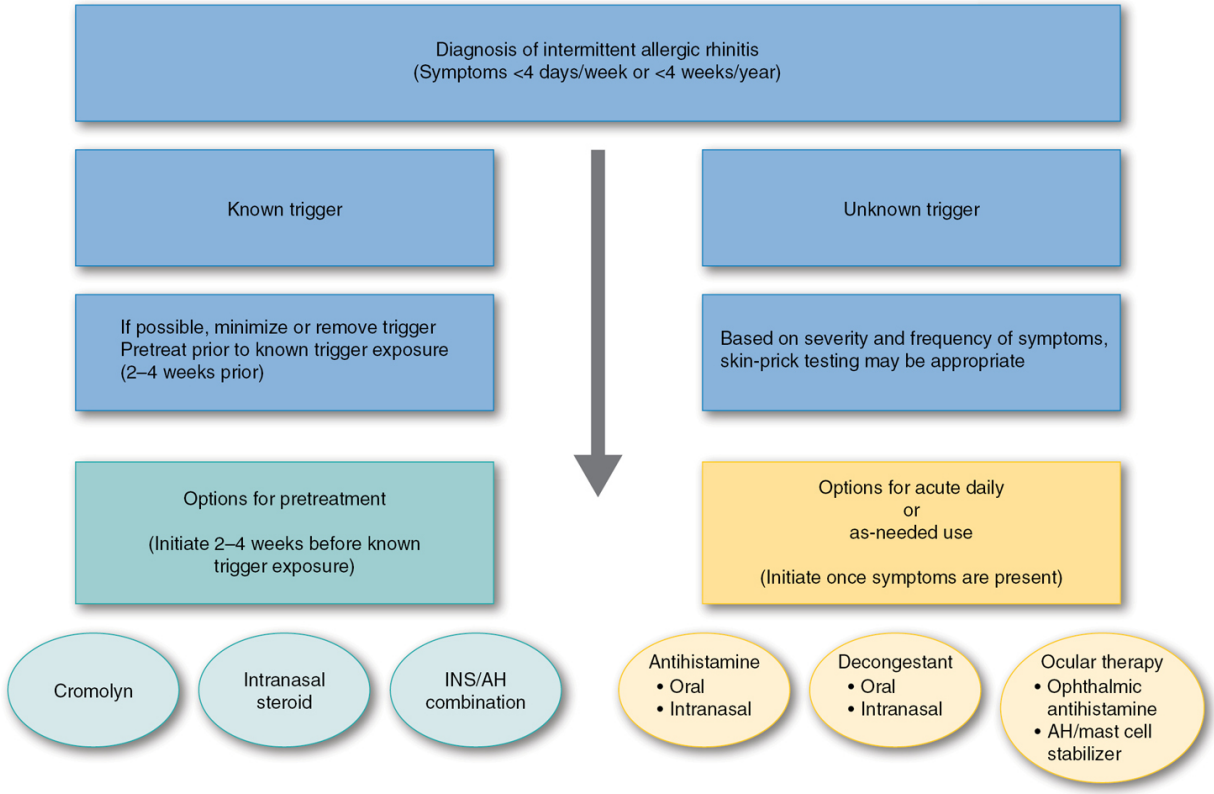


Figure 20-5 Treatment algorithm for persistent allergic rhinitis. Treatment should be directed at predominant symptoms (eg, for eye symptoms in the absence of other symptoms use ophthalmic preparation). Prevention strategies are just as important and effective as treatment strategies. INS/AH, intranasal steroid/intranasal antihistamine combination. (From Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol.* 2017;140(4):950–958; Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg.* 2015;152(1S):S1–S43; Scadding GK, Kriyawasan HH, Scadding G, et al. BSACI guideline for the diagnosis and

management of allergic and non-allergic rhinitis (Revised edition 2017: First edition 2007). *Clin Exp Allergy.* 2017;47:856–889.)

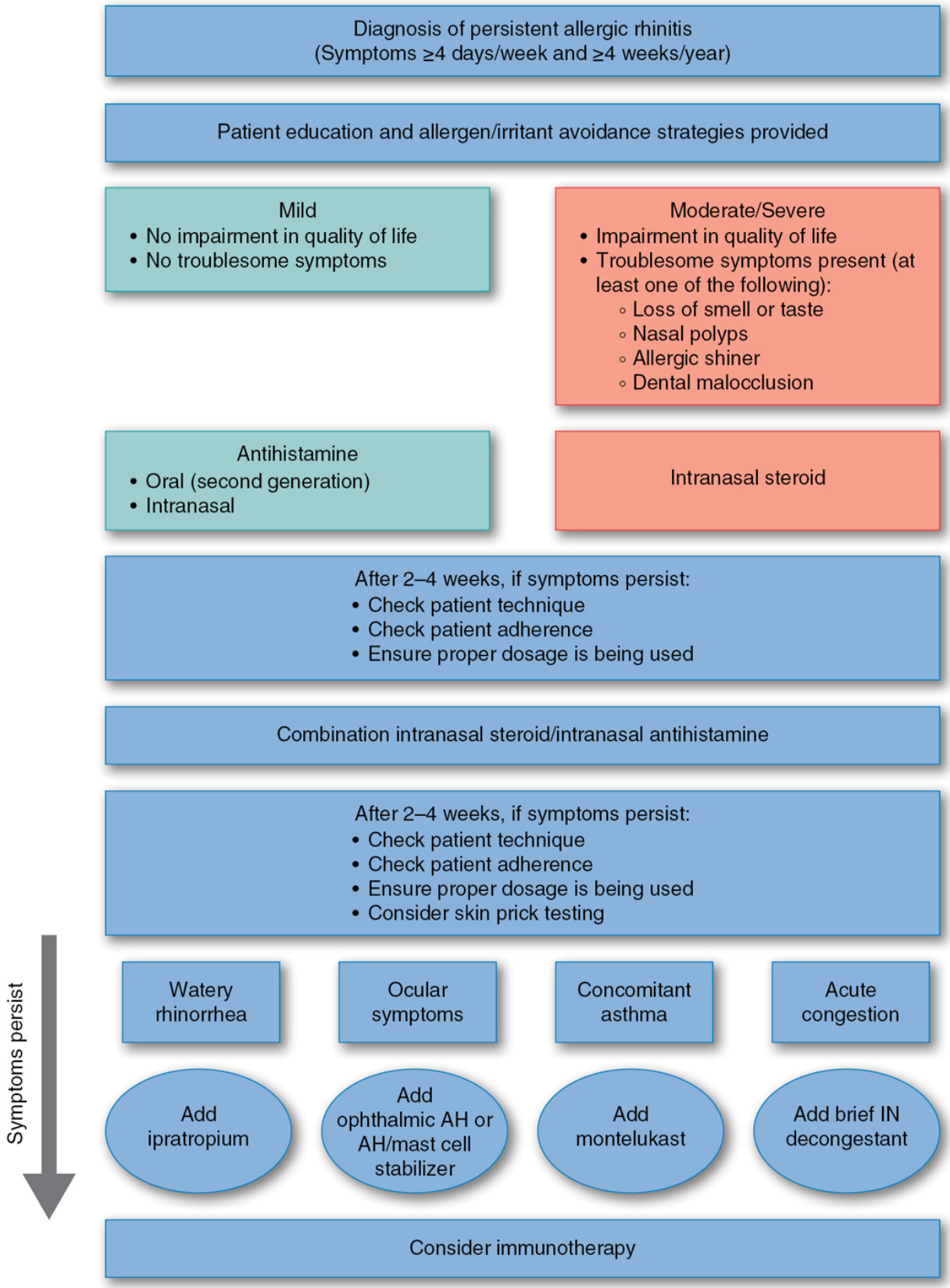

Diagnosis of persistent allergic rhinitis
(Symptoms ≥4 days/week and ≥4 weeks/year)
Patient education and allergen/irritant avoidance strategies provided
Mild
• No impairment in quality of life
• No troublesome symptoms
Moderate/Severe
• Impairment in quality of life
• Troublesome symptoms present (at least one of the following):
◦ Loss of smell or taste
◦ Nasal polyps
◦ Allergic shiner
◦ Dental malocclusion
Antihistamine
• Oral (second generation)
• Intranasal
Intranasal steroid
After 2–4 weeks, if symptoms persist:
• Check patient technique
• Check patient adherence
• Ensure proper dosage is being used
Combination intranasal steroid/intranasal antihistamine
After 2–4 weeks, if symptoms persist:
• Check patient technique
• Check patient adherence
• Ensure proper dosage is being used
• Consider skin prick testing
Symptoms persist
Watery rhinorrhea
Ocular symptoms
Concomitant asthma
Acute congestion
Add ipratropium
Add ophthalmic AH or AH/mast cell stabilizer
Add montelukast
Add brief IN decongestant
Consider immunotherapy

Figure 20-6 Treatment algorithm for intermittent allergic rhinitis. antihistamine; INS, intranasal steroid. (From Wallace DV, Dykewicz MS, Oppenheimer J, Portnoy J, Lang DM. Pharmacologic treatment of seasonal allergic rhinitis: Synopsis of guidance from the 2017 Joint Task Force on Practice Parameters. *Ann Intern Med.* 2017;167:876–881.)

Patient Education

Patients should be educated about their rhinitis. Considerations for patient education include instruction about the disease and specific triggers, the range of symptoms, the role of various treatments, and suitable technique for nasal drug delivery.[5] A discussion of allergen and trigger avoidance is also important.

Allergen and Irritant Avoidance

Although the benefit of allergen avoidance has proved difficult to document, this strategy is considered central in a comprehensive management plan for allergic rhinitis.[1,5,9,26] Various strategies for minimizing exposure to known allergens (eg, pollens, house dust mites, molds, animal dander, and cockroaches) are commonly used for prevention. Because little evidence supports a single physical or chemical intervention to reduce allergen exposure, a multifaceted approach should be used.[1] Efforts to reduce exposure to irritants (eg, tobacco smoke, indoor, or outdoor pollutants) should also be recommended because it is anticipated that this would have similar benefits as allergen avoidance.[3]

Pharmacotherapy

Several classes of medications are used in the management of rhinitis disorders. Choices should be based on goals of treatment, safety, efficacy, cost-effectiveness, adherence, severity, comorbidity, and patient preferences. Common therapies are administered either

orally or topically and used on a regular schedule or on an as-needed basis.[1] Few cost-effectiveness data exist comparing the classes of therapy, except the second-generation antihistamines (SGAs),[31] nasal corticosteroids,[32] and subcutaneous immunotherapy,[33] which are cost-effective. **Table 20-1** summarizes the effectiveness of agents for specific symptoms used in the treatment of allergic rhinitis.

Table 20-1
Effectiveness of Agents[a] Used in the Management of Allergic Rhinitis

	Rhinorrhea	Nasal Pruritus	Sneezing	Nasal Congestion	Eye Symptoms	Onset
Antihistamines						
Nasal	Moderate	High	High	Moderate	0	Rapid
Ophthalmic	0	0	0	0	Moderate	Rapid
Oral	Moderate	High	High	0/Low	Low	Rapid
Decongestants						
Nasal	0	0	0	High	0	Rapid
Ophthalmic	0	0	0	0	Moderate	Rapid
Oral	0	0	0	High	0	Rapid
Corticosteroids						
Nasal	High	High	High	High	High	Slow (days)
Ophthalmic	0	0	0	0	High	Slow (days)
Mast-Cell Stabilizers						
Nasal	Low	Low	Low	0/Low	Low	Slow (weeks)
Ophthalmic	Low	Low	Low	Low	Moderate	Slow (weeks)
Anticholinergics						
Nasal	High	0	0	0	0	Rapid
Leukotriene Modifiers						
Oral	Low	0/Low	Low	Moderate	Low	Rapid

High, significant effect; moderate, moderate effect; low, low effect; 0, no effect.

[a]Immunotherapy can lead to significant responses in all symptom categories; however, the onset of action is delayed (months).

Sources: van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. *Allergy.* 2000;55:116–134; Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA[2]LEN and AllerGen). *Allergy.* 2008;63(suppl 86):8–160; Facts and Comparisons. Accessed October 5, 2020. https://fco.factsandcomparisons.com/lco/action/home.

ANTIHISTAMINES

Antihistamines are the most common treatment for allergic rhinitis and are effective for relieving sneezing, itching, and rhinorrhea. They also diminish eye symptoms but, when taken orally, have minimal effects on nasal congestion.[2,3] Although first-generation antihistamines (FGAs) are efficacious, their use is limited by anticholinergic, sedative, and performance-impairing effects, which challenge their cost-effectiveness.[9] As a result, SGAs are preferred over FGAs in most cases where an antihistamine is desired.[1] Antihistamines are available in oral, ophthalmic, and intranasal formulations and can also be found in combinations with oral decongestants. They are most effective when administered before allergen exposure.

Although oral antihistamines (**Table 20-2**) represent the most commonly used therapy for allergic rhinitis, there is evidence that intranasal antihistamines are equal or superior in efficacy to oral agents. Further, they appear to relieve symptoms of mild congestion, which is not a feature of oral antihistamines.[1] Intranasal antihistamines work quickly, within 15 to 30 minutes, but may be complicated by a bitter taste.[1] The improved efficacy of intranasal antihistamines over oral agents in certain rhinitis conditions may be because of direct administration to the affected site. Olopatadine 0.6% is FDA approved for treating seasonal allergic rhinitis in patients age older than 6 years.[1] Azelastine 0.1% and 0.15% are FDA approved for treating both intermittent (0.1% age older than 6 months to age younger than 6 years) and persistent allergic rhinitis (0.15% in those age older than 6 years).[34]

Table 20-2
Oral Antihistamines[a,b] Commonly Used in Allergic Rhinitis

Generic Name (Example Brand Product)	Adult Dose	Pediatric Dose[c]	Other Effects		
First generation			Sedative	Antiemetic	Anticholinergic
Chlorpheniramine (Chlor-Trimeton®)	4 mg every 4–6 hours	Children 6–12 years: 2 mg every 4–6 hours Children 2–6 years: 1 mg every 4–6 hours	+	0	++
Clemastine (Tavist®)	1 mg every 12 hours	Children 6–11 years: 0.67 mg every 12 hours	++	++	+++
Diphenhydramine (Benadryl®)	25–50 mg every 4–8 hours	Infants and children 12.5–25 mg every 6-8 hours Adolescents: 25-50 mg every 6-8 hours	+++	++	+++
Second generation			Sedative	Antiemetic	Anticholinergic
Cetirizine (Zyrtec Allergy®)	5–10 mg once daily	Children ≥6 years: 5–10 mg once daily Children 2–5 years: 2.5 mg once daily, 2.5 mg twice daily, or 5 mg once daily Children 6–11 months: 2.5 mg once daily Children 12–23 months: 2.5 mg once daily (max 5 mg daily)	+	0	±
Fexofenadine (Allegra®)	60 mg every 12 hours or 180 mg once daily	Children 2 to ≤12 years: 30 mg every 12 hours	±	0	±
Loratadine (Claritin®)	10 mg once daily	Children ≥6 years: 10 mg once daily or 5 mg twice daily Children ≥2 to ≤6 years: 5 mg once daily	±	0	±
Levocetirizine (Xyzal®)	5 mg once daily in the evening	Children 6–11 years: 2.5 mg once daily in the evening Children 6 months–5 years: 1.25 mg once daily in the evening	±	0	±
Desloratadine (Clarinex®)	5 mg once daily	Children 6–11 years: 2.5 mg once daily Children 1–5 years: 1.25 mg once daily Children 6–11 months: 1 mg once daily	±	0	±

[a]Many oral antihistamines are sold as combination products with the oral decongestants pseudoephedrine and phenylephrine. The addition of the decongestant may alter the dosing scheme for the product. As of 2005, pseudoephedrine products have been placed behind the pharmacy counter in the United States. Federal law limits the quantity available for purchase and requires a signature and photo identification. Individual states may have additional restrictions regarding the sale of pseudoephedrine. Consult local boards of pharmacy for details.

[b]Some oral antihistamines are available in both short-acting and extended- or sustained-release formulations. Refer to package insert for specific dosing instructions for long-acting products.

[c]In 2008, the Food and Drug Administration (FDA) issued an advisory alert recommending that over-the-counter (OTC) cough and cold agents (eg, products containing antitussives, expectorants, decongestants, and antihistamines) not be used in infants and children age younger than 2 years because of the potential for serious and possibly life-threatening adverse events (https://www.fda.gov/consumers/consumer-updates/should-you-give-kids-medicine-coughs-and-colds). More recently, in October 2008, leading pharmaceutical manufacturers voluntarily modified product labels on OTC cough

and cold preparations to state “do not use” in children age younger than 4 years (https://www.fda.gov/consumers/consumer-updates/should-you-give-kids-medicine-coughs-and-colds). Furthermore, in 2011, the FDA removed unapproved prescription allergy products from the market because they had not been proven to meet standards for safety, effectiveness, and quality (https://www.duanemorris.com/alerts/FDA_removes_unapproved_prescription_cough_cold_allergy_drugs_initiative_3985.html).

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

INTRANASAL CORTICOSTEROID AGENTS

Intranasal corticosteroids are the most effective medication class for the treatment of allergic rhinitis and are particularly useful for more severe or persistent symptoms.[1,3] Although achieving optimal outcomes depends on the patient’s ability to use the device correctly, if administered as intended, these agents are appropriate for all symptoms, are generally well tolerated, and have few adverse effects.[29] They are most beneficial when dosed on a regular schedule; some evidence indicates, however, that they are effective when used on an as-needed basis.[1,9] Intranasal corticosteroids are also useful for treating nonallergic rhinitis[28] and several are available over the counter (OTC).

LEUKOTRIENE MODIFIERS

Leukotriene modifiers are effective in relieving many of the nasal symptoms of allergic rhinitis such as daytime congestion, rhinorrhea, pruritis, sneezing, and improving sleep as well as congestion on awakening.[4] Current guidelines recommend against utilizing this class of drugs as first line.[1] They may have a role as an alternative option for preschool-aged children[30] with seasonal allergic rhinitis but are not recommended for adult patients with perennial allergic rhinitis.[29] In addition, selected patients might benefit from the combination of an antihistamine and a leukotriene modifier,[26] such as those with concomitant asthma and allergic rhinitis.[1,35] There is no evidence that these agents are helpful for symptoms from nonallergic causes.

CROMOLYN

Intranasal cromolyn, a nonsteroidal agent, acts as a mast-cell stabilizer and, although safe, it is generally less efficacious than other therapies and only useful for symptoms related to allergic causes. It should be administered multiple times daily and requires several weeks to be effective.[5] It is best reserved for prophylaxis before exposure to a known allergen[26,35] and, because of its excellent safety profile,[35] for use by children or in pregnancy.[34]

DECONGESTANTS

Oral and nasal decongestants (**Table 20-3**) can effectively reduce nasal congestion by activation of α-adrenergic receptors.[35] Oral agents are often combined with antihistamines and are generally well tolerated, but their use can lead to insomnia, nervousness, urinary retention, hypertension, and even palpitations that may be problematic for some patients.[36] Subsequently, these agents should be used with caution in elderly patients and in those with hyperthyroidism, cardiovascular disease, diabetes, glaucoma, or those who are pregnant.[36] Nasal agents are not typically associated with these effects but should be limited to short-term use to avoid rebound nasal congestion.[35] Because pseudoephedrine is used in the illegal manufacture of methamphetamine, there are now restrictions on the sale of nonprescription formulations.[36] Also, questions regarding the efficacy of phenylephrine[36] have resulted in challenges to the optimal use of oral decongestants.

Table 20-3

Decongestants[a,b] Commonly Used in Allergic Rhinitis

Generic Name (Example Brand Product)	Adult Dose	Pediatric Dose[c]
Oral[a]		
Pseudoephedrine (Sudafed®)	60 mg every 4–6 hours (max 240 mg/day) 120 mg SR every 12 hours 240 mg CR every 24 hours	Children 6–12 years: 30 mg every 4–6 hours (max 120 mg/day)

		Children 2–5 years: 15 mg every 4–6 hours (max 60 mg/day)
Phenylephrine (Sudafed PE®)	10 mg every 4 hours (max 60 mg/day)	Children ≥12 years of age and adolescents: 10 mg every 4 hours (max 60 mg/day) Children 6–11 years: 5 mg every 4 hours (max 30 mg/day) Children 4–5 years: 2.5 mg every 4 hours (max 15mg/day)
Topical[d]		
Phenylephrine (Neo-Synephrine®)	0.25%–1.0% solution: 2–3 sprays or drops/nostril not more than every 4 hours for not more than 3 days.	Children 6–11 years: 2–3 sprays or drops (0.25% solution)/ nostril not more than every 4 hours for not more than 3 days. Children 2–5 years: 2–3 drops (0.125% solution) into each nostril not more than every 4 hours for not more than 3 days.
Oxymetazoline (Afrin®)	0.05% solution: 2–3 sprays/nostril every 12 hours	Children 6–12 years: 2–3 sprays/nostril every 12 hours

CR, Controlled release; SR, sustained release.

[a]Many oral decongestants are sold as combination products with oral antihistamines. The addition of the antihistamine may alter the dosing scheme for the product. As of 2005, pseudoephedrine products have been placed behind the pharmacy counter in the United States. Federal law limits the quantity available for purchase to 9 g/month, 3.6 g/day with signature and photo identification. Individual states may have additional restrictions regarding the sale of pseudoephedrine. Consult local boards of pharmacy for details.

[b]Some oral decongestants are available in both short-acting and extended- or sustained-release formulations. Refer to package insert for specific dosing instructions for long-acting products. Note that some extended-release formulations are not recommended for children age younger than 12 years.

[c]In 2008, the FDA issued an advisory alert recommending that over-the-counter (OTC) cough and cold agents (eg, products containing antitussives, expectorants, decongestants, and antihistamines) not be used in infants and children age

younger than 2 years because of the potential for serious and possibly life-threatening adverse events (https://www.fda.gov/consumers/consumer-updates/should-you-give-kids-medicine-coughs-and-colds). More recently, in October 2008, leading pharmaceutical manufacturers voluntarily modified product labels on OTC cough and cold preparations to state “do not use” in children age younger than 4 years. Furthermore, in 2011, the FDA removed unapproved prescription allergy products from the market because they had not been proven to meet standards for safety, effectiveness, and quality.

[d]Limit duration of treatment to 5 days to minimize the risk of rebound congestion. Topical decongestants should never be used in preschoolers[24] or infants because of possible toxicity.[14]

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

ANTICHOLINERGIC AGENTS

Intranasal ipratropium bromide is an anticholinergic agent effective in reducing watery, nasal secretions in allergic rhinitis, nonallergic rhinitis, and viral upper respiratory infections.[35] Anticholinergic agents have no significant effects on other symptoms.

OPHTHALMIC THERAPIES

Ophthalmic products used to treat symptoms of allergic conjunctivitis include antihistamines, decongestants, mast-cell stabilizers, and nonsteroidal anti-inflammatory agents. These agents are effective in reducing ocular symptoms and may be used in combination with oral and intranasal agents.

IMMUNOTHERAPY

Specific allergen immunotherapy (SIT) should be considered for patients with IgE-mediated disease,[3] who have severe symptoms despite optimal pharmacotherapy,[2,5] those who experience side effects from drugs restricting their treatment choices,[5] or those who cannot avoid allergen exposure.[3] The clinical efficacy of immunotherapy by subcutaneous injection (SCIT), sometimes called “allergy shots,” is well established[2] and is the only treatment that can offer the potential for disease remission.[1–3] Traditional SCIT presents some disadvantages, such as cost, adherence, and rare adverse

systemic reactions.[1,37] More recently, the efficacy of immunotherapy given sublingually (SLIT) has been documented and the tablet form received FDA approval in April 2014.[1,38] See **Table 20-4** for details. There are potential adverse effects including local reactions such as oral itching[1] and swelling of the lips and mouth.[39] Systemic reactions can occur from both SCIT and SLIT and include urticaria, gastrointestinal upset, wheezing, and anaphylaxis.[1] Because of the potential for these reactions, SCIT is to be administered in the provider's office; however, after the first dose of SLIT, it may be given at home (on a daily basis).[2] Providers are urged to prescribe and educate patients on how to use injectable epinephrine for emergency use, and SLIT should not be given to patients with uncontrolled asthma or those on β-blocking agents.[34]

Table 20-4
Sublingual Tablet Immunotherapy

Drug Name	Allergen	Ages Approved for (in years)	Dosing	Dosing Considerations
Ragwitek®	Ragweed pollen	≥5–65	1 tablet SL once daily	Initiate treatment at least 12 weeks before the expected onset of each ragweed pollen season and continue throughout the pollen season.
Oralair®	Mixed grasses: sweet vernal, orchard, perennial rye, Timothy and Kentucky bluegrass	5–65	Adults: 300 IR SL once daily 5–17 years of age: 100 IR SL on day 1, then 200 IR on day 2, and then 300 IR once daily thereafter Remove sublingual tablet from blister immediately prior to administration	Initiate treatment 4 months before the expected onset of each grass pollen season and continue throughout the pollen season.
Grastek®	Timothy grass	5–65	5 and older: 2800 BAU SL once daily Remove sublingual tablet from blister immediately prior to administration	Initiate treatment at least 12 weeks before the expected onset of each grass pollen season and continue throughout the pollen season. May be taken daily for 3 consecutive years (including intervals between grass pollen seasons) In clinical trials, treatment interruptions of up to 7 days were allowed.
Odactra®	House dust mites	18–65	1 tablet SL once daily	Administer first dose in health care setting and monitor for at least 30 minutes. Subsequent doses may be given at home.

Administer first dose in a health care setting because of the potential for allergic reactions; monitor patient for 30 minutes after first dose. If well tolerated, subsequent doses may be taken at home. Autoinjectable epinephrine should be made available to patients. Place tablet(s) under tongue until completely dissolved (at least 1 minute) and then swallow. Wash hands after handling the tablet. Avoid

food or beverage for 5 minutes following dissolution of tablet (to prevent the swallowing of allergen extract).

BAU, bioequivalent allergy unit; IR, index of reactivity; SL, sublingually.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

BIOLOGIC THERAPY FOR ALLERGIC RHINITIS

There are currently no biologic therapies with an approved indication for allergic rhinitis. Biologic therapies are FDA approved for the add-on treatment of very poorly controlled persistent asthma despite the use of conventional therapies such as inhaled corticosteroids and long-acting bronchodilators. Several biologic agents exist that interfere with the inflammatory cascade and include anti-IgE, anti-IL-5, and anti-IL-4.

Anti-IgE Therapy

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds free circulating IgE in the body preventing binding to receptors on mast cells and basophils.[40] Currently, this therapy is FDA approved only for people age 6 years or older with moderate-to- severe allergy-related asthma inadequately controlled with inhaled corticosteroids; however, off-label use is allergic rhinitis. Omalizumab has shown efficacy at decreasing serum IgE levels, improvement in daily nasal symptom scores and quality of life, and a decrease in rescue antihistamine use.[40] Omalizumab is also approved for patients age 12 years or older with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment. This product has a high cost (estimated to be between $6400 and $32,000 per patient per year).[35] The product has a boxed label warning to alert users that it can cause potentially life-threatening allergic reactions after any dose, up to 24 hours after the dose is given, and even if there was no reaction to the first dose. Ongoing monitoring is recommended to better determine rates of malignancies related to long-term use of omalizumab.[41]

Anti-IL-5 and Anti-IL-4

Reslizumab, mepolizumab, benralizumab (anti-IL-5), and dupilumab (anti-IL-4) have all been studied in small allergic rhinitis studies. These agents have promise, but further investigation is needed[40] as the efficacy and safety of these drugs for the treatment of allergic rhinitis need to be confirmed. Also, a pharmacoeconomic perspective must be carefully considered when identifying patients in whom these therapeutic targets will be options in the future.

Special Considerations of Medications in Pregnancy

The majority of data about the fetal risks of various pharmacotherapies are derived from animal studies. There are limited human data; however, cohort and case-control studies have been used to support therapeutic decision-making. Antihistamines, intranasal steroids, and cromolyn are considered safe to use during pregnancy.[3] Oral decongestants should generally be avoided,[3] although topical decongestants may be used on a short-term basis.[35] With limited human data available, oral montelukast is categorized as “probably compatible” with pregnancy[35]; however, generally, topical drugs are recommended over systemic therapy. Pregnant patients currently using immunotherapy may continue; however, initiation or an increased dose of immunotherapy during pregnancy is contraindicated.[3]

Nondrug Therapies

Supportive care is the foundation of treatment for patients with symptoms of rhinitis.[1] These strategies can be helpful during an acute worsening of symptoms as well as for the patient who suffers chronically. Supportive care can ameliorate discomfort, relieve mild symptoms, and assist with side effects from pharmacotherapies. Examples include the application of compresses to the sinuses or

external nasal passages and humidification of mucous membranes with artificial tears or nasal saline solutions. Many patients with chronic symptoms of rhinosinusitis report subjective improvement with nasal saline douching[3,5] or irrigation.

SPECIFIC THERAPEUTIC OPTIONS

Antihistamine Therapy

DIAGNOSIS OF ALLERGIC RHINITIS

CASE 20-1

QUESTION 1: L.B. is a 57-year-old male with a history of hypertension for 10 years and intermittent allergic rhinitis since childhood (confirmed sensitivity to birch tree pollen via skin testing). L.B. presents with nasal itching, sneezing, and clear rhinorrhea. He states he also has occasional stuffiness. He usually experiences similar symptoms, as well as ocular itching every spring, but has noticed that the problem has become persistent since he moved into an older home in the historic district of town 6 months ago. In the past, L.B. has successfully self-medicated his seasonal symptoms with an OTC antihistamine and decongestant (diphenhydramine 50 mg and pseudoephedrine 60 mg twice a day to four times a day as needed for symptoms), although "nothing seems to help much with the itchy eyes." L.B.'s hypertension has been well controlled with hydrochlorothiazide 25 mg and amlodipine 10 mg every morning. He denies any other medical problems, is afebrile, and his blood pressure is 128/82 mm Hg. He has no history of adverse drug reactions or drug allergies. He does not smoke but drinks alcohol socially.

What elements of L.B.'s presentation indicate a probable diagnosis of allergic rhinitis?

L.B. is exhibiting the classic symptoms of persistent (perennial) allergic rhinitis with intermittent (seasonal) exacerbations: nasal itching, sneezing, watery (often profuse) rhinorrhea, and congestion.[4] His history of positive skin tests and that his symptoms previously responded to antihistamine or decongestant[2] also support the diagnosis. In the past, L.B. has experienced symptoms predictably at

the onset of the tree pollination season, with only minimal symptoms during the remainder of the year. Moving into an older home, however, has likely triggered latent sensitivities to dust mite allergens and mold spores. A treatment approach can be developed based on these presumptions. If this strategy is not effective, skin-prick testing or additional laboratory assessments are warranted.

ALLERGEN AVOIDANCE MEASURES

Case 20-1, Question 2: What allergen avoidance strategies could L.B. use to minimize his exposure to triggers?

Allergen avoidance is important for reducing symptoms in patients with known sensitivities. Avoiding these triggers should lead to an improvement of symptoms; however, the use of a single physical or chemical method is not recommended.[29] To achieve effective control, a multifaceted approach to the control of environmental triggers is usually needed.[29] Although total allergen avoidance is often impractical to implement, simple changes that can reduce exposure to many perennial triggers, such as house dust mites, animal dander, and mold, may assist with symptom control.[1,9]

Dust mite avoidance (eg, the use of impermeable covers on box springs, mattresses, and pillows) has traditionally been used as a method of reducing allergen exposure. Although this practice continues to be recommended frequently, it is controversial. Studies have shown less dust mite levels in mattresses with impermeable covers, but this has not been correlated to improvement in symptoms.[1] Other methods of reducing antigen exposure include washing bedding at least weekly in hot water >130 °F (>55 °C) and dried under high heat in an electric dryer,[42] removing upholstered furniture, and washing floors daily.[1] Also, reducing humidity in the house to <50% and replacing carpets with linoleum, tile, or wood floors are commonly recommended.[42]

Mold avoidance is difficult when outdoor humidity levels are high, but covering cold, moist surfaces such as water pipes with insulation

and increasing ventilation can help reduce humidity. Also, visible mold should be removed from surfaces with detergent and water, and any embedded mold should also be removed.[42] Because L.B. has recently moved into an older home, he may not have used these avoidance strategies. These should be recommended and explained during the initial clinical consultation.

THERAPEUTIC OBJECTIVES FOR ALLERGIC RHINITIS

CASE 20-1, QUESTION 3: What are the therapeutic goals in treating L.B.?

The therapeutic goals for the treatment of allergic rhinitis are to control symptoms and permit all usual daily activities with no adverse effects of therapy. In patients with seasonal exacerbations, another goal is to prevent the onset of symptoms by anticipating the patient's season of sensitivity. In L.B.'s case, he should use daily environmental measures to reduce exposure to dust mites and mold and also begin chronic treatment. He may benefit from add-on therapy instituted 2 weeks before the start of birch tree pollen season.

CHOICE OF THERAPEUTIC AGENT

CASE 20-1, QUESTION 4: L.B. has used diphenhydramine for many years with good symptom relief and, as he recalls, only minimal daytime sedation. He asks your opinion regarding whether this is the best treatment for his allergy symptoms. He specifically requests an oral option that is the most cost-effective treatment available, because he must pay cash out-of-pocket for any medications. What therapy do you recommend and how should it be initiated?

Based on effectiveness and convenience, including nonprescription availability, oral antihistamines are the most frequent initial therapy recommended for patients with allergic rhinitis, particularly those with mild symptoms.[1] They reduce symptoms of nasal itching, sneezing, and rhinorrhea,[3] as well as ocular symptoms but offer no benefit for nasal congestion. FGAs (eg,

diphenhydramine, brompheniramine, chlorpheniramine, and clemastine) lack specificity for the H_1 receptor and can cause significant sedation, various anticholinergic side effects, can impair performance,[34] and are dosed multiple times per day, all of which limit their usefulness. Although at times these effects are considered desirable (eg, to aid in sleep and dry nasal secretions), the SGAs (eg, loratadine, fexofenadine, cetirizine, desloratadine, and levocetirizine)[35] are preferable in most instances.[1–3,43]

Antihistamines block the effects of histamine by one of two mechanisms: (a) as an H_1-receptor antagonist and (b) as an inverse agonist of the H_1-receptor.[4] FGAs cross the blood–brain barrier (BBB) leading to unwanted adverse effects. The nonsedating antihistamines (second- and third-generation agents) do not cross the BBB[4] and therefore are less sedating and preferred for small children and the elderly. L.B. has experienced a good response to an FGA without excessive drowsiness. However, sedation includes both drowsiness (ie, the subjective state of sleepiness or lethargy) and impairment (ie, an objective decrease in specific physical or mental abilities),[4] and cognitive impairment can occur[4] even in the absence of overt drowsiness. Although patients can exhibit tolerance to sedative properties of FGAs, they may not perceive the performance impairment that is still present. This has led to a consensus opinion among experts that SGAs are preferred to FGAs when treating allergic rhinitis.[1,3,5]

Essentially, all the antihistamines listed in Table 20-2 are equally effective.[2] Therefore, the choice of agent is based on the duration of action, side-effect profile (especially drowsiness and anticholinergic effects), risk of drug interactions, and cost.[1] Some patients claim that a kind of “tolerance” to the therapeutic effects occurs with antihistamines, in that with consistent use over time they perceive less symptomatic relief. Although no pharmacologic explanation exists to support these observations, patients may experience benefit from switching therapies if this perception presents.[1]

The major advantages of SGAs are their selectivity to the H_1-receptor and their reduced central nervous system sedative

effects.[9,35] Desloratadine, fexofenadine, loratadine, and levocetirizine—at recommended doses—are reported to have no sedating effects.[9] Loratadine and desloratadine can cause sedation at higher than recommended doses.[9] Cetirizine[9] and levocetirizine[1] have more sedation potential than the other second-generation agents.[9] Another advantage of SGAs is that most products can be dosed once daily[9] to improve patient adherence to therapy. Specific antihistamines are compared in Table 20-2. Maximum benefit is seen with continued use of oral antihistamines, but intermittent use may provide relief for many individuals.[1] In the case of L.B., it would be reasonable to begin therapy with loratadine 10 mg daily because as an SGA it has demonstrated efficacy with minimal side effects and is also available as an oral option without a prescription (as he requested) and as a generic formulation, which will further control costs.

INTRANASAL ANTIHISTAMINES

Case 20-1, Question 5: L.B. reports that a friend with similar symptoms had experienced relief from an antihistamine nasal spray. Is it possible to give antihistamines by this route, or is L.B. confusing this with other topical therapies such as decongestants or corticosteroids? Are intranasal antihistamines appropriate for L.B.?

Topical formulations are available for intranasal use. These are considered to be equal in efficacy to oral SGAs[1,26] with a quicker onset of action.[3] Also, they may improve congestion.[1,3] The intranasal antihistamines (azelastine and olopatadine) have a faster onset of action than oral agents[1] but unfortunately require twice-daily dosing.[9] Intranasal azelastine can also cause local side effects, including nasal irritation, dry mouth, sore throat, and mild epistaxis. An objectionable bitter aftertaste is a significant problem, occurring in up to 20% of patients.[3]

A potential role for intranasal antihistamines is for patients who do not respond adequately to oral antihistamines.[1] In addition, some patients may prefer the intranasal route of administration or benefit

from concomitant therapy with intranasal antihistamines and intranasal corticosteroids. As a prescription-only product, an intranasal antihistamine (even if available generically) would be more expensive than many oral alternatives. Because of the expense associated with prescription-only status, increased risk of side effects, and possibly objectionable taste, topical azelastine is not an optimal therapeutic option for L.B. at this time.

Decongestant Therapy

Case 20-1, Question 6: What role do decongestants have in L.B.'s treatment?

Nasal congestion is often much less severe in patients who experience only intermittent symptoms, but as L.B.'s symptoms have become persistent since his move, the exact frequency and severity of his nasal congestion should be assessed before recommending drug therapy. In patients with only mild, intermittent symptoms, saline irrigation (administered as frequently as needed) is helpful in soothing and moisturizing irritated nasal mucosa but may be impractical. Oral antihistamines do little to relieve nasal congestion; therefore, patients with moderate-to-severe congestion may require a combination of an antihistamine with a decongestant. The combination of an oral antihistamine and an oral decongestant is more effective than either component alone in the treatment of allergic rhinitis.[1]

Both the topical (intranasal) and the oral decongestants are sympathomimetics that directly stimulate α_1-adrenergic receptors, resulting in vasoconstriction.[35] Local effects on the nasal mucosa include reduced turbinate swelling and congestion[4] and improved nasal airway patency.[1] Oral decongestants include phenylephrine and pseudoephedrine. Until 2005, pseudoephedrine was the more popular agent; however, because of the potential to use it in the manufacture of illicit substances (eg, methamphetamine), restrictions

on the allowable quantity and methods for purchasing pseudoephedrine-containing products have been implemented at both the state and federal levels. These restrictions have resulted in the reformulation of many oral decongestant products to include phenylephrine as an alternative decongestant. These agents have no effect on sneezing, pruritis, or ocular symptoms.[4] The available oral and topical decongestants, some of which are available without a prescription, are compared in Table 20-3.

Oral decongestants can cause systemic side effects, particularly those associated with central nervous system stimulation (eg, nervousness, insomnia, tremor, anxiety, and panic attacks).[35] Cardiovascular stimulation (eg, tachycardia, palpitations, and increased blood pressure) can also occur, so patients with hypertension should be monitored carefully while taking oral decongestants.[25] Because oral decongestants are not associated with the development of rebound congestion, in most patients they are appropriate for intermittent short-term use but not chronic use.[29] Topical administration of decongestants generally does not lead to systemic side effects; however, these agents are not appropriate for chronic use in rhinitis because of their potential for causing rebound congestion (see Case 20-7 [Question 1]).

Because L.B. states occasional nasal congestion, he will require a decongestant in addition to the loratadine. He may choose to use a once-daily fixed-dose combination product (eg, loratadine 10 mg plus pseudoephedrine extended-release 240 mg), or it may be best for L.B. to supplement the daily loratadine with as needed pseudoephedrine. Although L.B. has used pseudoephedrine in the past without a problem, he may require education regarding procedures for purchasing this product, while assuring him that the restrictions are not related to the drug's safety as a decongestant. In addition, although his hypertension is controlled, his blood pressure should be monitored regularly to detect any effect. If L.B. is ready to consider a nonoral option, an intranasal steroid (discussed subsequently) would also be a reasonable option for him.

Ocular Therapies

RELATIONSHIP BETWEEN OCULAR AND NASAL SYMPTOMS

Case 20-1, Question 7: L.B.'s new therapies are effective for his persistent nasal symptoms; however, in the spring, he states that his eyes are itchy and watery and that the loratadine and pseudoephedrine do not seem to be helping. How are L.B.'s ocular symptoms related to his allergic rhinitis?

The most common forms of allergic ocular disorders are intermittent (seasonal) allergic conjunctivitis (SAC) and persistent (perennial) allergic conjunctivitis (PAC).[44] The symptoms of both SAC and PAC are identical in that they are caused by allergic response in the conjunctiva to airborne allergens. SAC symptoms are often linked to temporal exposure patterns of airborne environmental allergens like tree pollen (early spring), grasses (May–July), and weed pollens and outdoor molds (August–October).[44] Symptoms from PAC are triggered by single or multiple indoor allergens including animal dander, molds, and dust mites. The symptoms of allergic conjunctivitis are itchy eyes, redness, and swelling of the conjunctiva.[44]

Because of the potential for long-term damage to vision, persistent ocular conditions should always be assessed by an eye care professional. Other ocular problems that can be confused with allergic conjunctivitis include atopic keratoconjunctivitis and vernal keratoconjunctivitis, giant papillary conjunctivitis, and contact blepharoconjunctivitis[44] (see Chapter 54, Eye Disorders).

CHOICE OF THERAPEUTIC AGENT

Case 20-1, Question 8: What are the treatment options for L.B.'s allergic conjunctivitis, and how does the clinician choose between the available options?

Seasonal and perennial allergic conjunctivitis are treated similarly with only the duration of the treatment course differing (ie, episodic

vs chronic treatment). Nonpharmacologic treatment includes avoidance of aeroallergens to the extent possible, cold compresses,[45] and lubrication with frequent application of artificial tear substitutes to provide a barrier to and dilute various allergens and inflammatory mediators on the ocular surface.[46] The available therapeutic options for the management of allergic conjunctivitis include topical ocular administration of antihistamines, decongestants (vasoconstrictors), mast-cell stabilizers, and nonsteroidal anti-inflammatory drugs (**Table 20-5**).[45] These ocular medications act by the mechanisms similar to their nasal counterparts. In addition, topical ophthalmic corticosteroids have a limited role in the acute management of allergic conjunctivitis; however, they are not indicated for prolonged use because of the risk of serious infectious complications in the eye.[46]

Table 20-5
Topical Ophthalmic Medications Commonly Used for Allergic Conjunctivitis

Generic Name (Example Brand Product)	Available Dosage Forms/Strength	Dose
Antihistamines		
Azelastine (Optivar®)	Ophthalmic solution: 0.05%	Adults and children 3 years or older: 1 drop in the affected eye(s) every 12 hours
Emedastine (Emadine®)	Ophthalmic solution: 0.05%	Adults and children 3 years or older: 1 drop in the affected eye(s) up to four times daily
Epinastine (Elestat®)	Ophthalmic solution: 0.05%	Adults and children 2 years or older: 1 drop in the affected eye(s) twice daily
Antihistamine/Decongestant Combinations		
Pheniramine + Naphazoline (Naphcon-A®, Opcon-A®, Visine-A®)[a]	Ophthalmic solution: naphazoline HCl 0.025% + pheniramine maleate 0.3%	Adults and children 6 years or older: 1–2 drops in the affected eye(s) up to four times/day for up to 3 days

Antihistamine/Mast-Cell Stabilizers		
Ketotifen (various brand names)[a]	Ophthalmic solution: 0.025%	Adults and children 3 years or older: 1 drop in the affected eye(s) every 8–12 hours
Olopatadine (Pataday®, Patanol®, Pazeo®)	Ophthalmic solution: 0.1%, 0.2%, 0.7%	0.1%: Adults and children 3 years or older: 1 drop in affected eye(s) twice daily at an interval of 6–8 hours 0.2% and 0.7%: Adults and children 2 years or older: 1 drop in the affected eye(s) once daily
Alcaftadine (Lastacaft®)	Ophthalmic solution: 0.25%	Adults and children 2 years or older: 1 drop in each eye once daily
Bepotastine (Bepreve®)	Ophthalmic solution: 1.5%	Adults and children 2 years or older: 1 drop in the affected eyes(s) twice daily
Mast-Cell Stabilizers		
Cromolyn Sodium (Crolom®)	Ophthalmic solution: 4%	Adults and children 4 years or older: 1–2 drops in the affected eye(s) four to six times daily
Lodoxamide (Alomide®)	Ophthalmic solution: 0.1%	Adults and children 2 years or older: 1–2 drops in the affected eye(s) four times daily
Nedocromil (Alocril®)	Ophthalmic solution: 2%	Adults and children 3 years or older: 1–2 drops in the affected eye(s) twice a day
Nonsteroidal Anti-Inflammatory Drugs[b]		
Ketorolac (Acular®)	Ophthalmic solution: 0.5%	Adults and children 2 years or older: 1 drop in the affected eye(s) four times daily
Corticosteroids[c]		
Loteprednol (Alrex®)	Ophthalmic suspension: 0.2%	Adults: 1 drop in the affected eye(s) four times daily

[a]Available without a prescription.

[b]Other ophthalmic nonsteroidal anti-inflammatory drugs (diclofenac, flurbiprofen, and suprofen) indicated for intraoperative miosis and for postcataract surgery but not approved for allergic conjunctivitis.

[c]Other ophthalmic corticosteroids (dexamethasone, difluprednate, triamcinolone, and fluorometholone) indicated for ocular inflammation but not approved for allergic conjunctivitis.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

In the case of L.B., a trial of antihistamine plus vasoconstrictor combination eye drops (eg, pheniramine maleate 0.3% plus naphazoline hydrochloride 0.025%) one to two drops in the affected eye(s) up to four times a day for the management of acute symptoms is an appropriate recommendation for short-term use. Note that the overuse of ocular vasoconstrictors can lead to rebound conjunctivitis, similar to that occurring with nasal decongestants (see Drug-Induced Nasal Congestion: Rhinitis Medicamentosa section). As a result, the use of a topical ophthalmic decongestant should be limited to 3 to 5 days. If the patient exhibits chronic symptoms, consider a switch to an intranasal corticosteroid (which may have better efficacy for combination symptoms)[1] or refer to specialist care.

Cromolyn Therapy

CASE 20-2

Question 1: J.C. is a 10-year-old girl who has been experiencing rhinorrhea and sneezing during visits to her father's home in another state for 3 weeks at a time a couple of times each year. On questioning, J.C.'s mother reveals that although J.C. has not had symptoms in the past, her father adopted a puppy from the local animal shelter about a year ago, and the symptoms only correspond to the times that the child spends with the dog. J.C. will be visiting her father again next month, and she is hoping to purchase something without a prescription to prevent her from "getting sick and missing out on her summer vacation."

What options are available to treat J.C.'s intermittent symptoms of allergic rhinitis?

These symptoms may reflect mild, intermittent allergic rhinitis triggered by exposure to animal dander. When it is possible to anticipate symptoms, as in J.C.'s case, initiating prophylactic therapy

can help lessen the impact of allergen exposure.[42] Although intermittent use of antihistamines or intranasal corticosteroids are commonly selected options, intranasal cromolyn sodium administered regularly beginning several weeks before each trip may also offer benefit in this situation. Because the mother indicates that she wants to select an OTC product, allergen avoidance strategies plus cromolyn nasal spray would be a reasonable choice for initial therapy. The drawbacks to this are its out-of-pocket cost, its technique-dependent administration, its multiple daily dosing requirements (up to six times daily),[29] and its reduced effectiveness compared with other treatments.[3]

Case 20-2, Question 2: What strategies should J.C.'s father use to minimize exposure to the allergic triggers?

To minimize J.C.'s exposure to allergens, the dog should be kept out of the child's bedroom at all times and, when possible, kept outside or confined to an uncarpeted area of the home.[47] J.C.'s father should vacuum the home with a HEPA filter and double thickness bag vacuum system while J.C. is out of the house. Although evidence of benefit is unclear, it may be helpful to wash the dog at least twice a week while the child visits.[47] Similarly, after touching or playing with the dog, J.C. should wash her hands especially before touching her face[48] and should change and wash clothes regularly.[47] The additional expense of regular, commercial cleaning of air ducts is not cost justified.

INSTRUCTIONS FOR USE

Case 20-2, Question 3: How should J.C. be advised to use cromolyn nasal spray to prevent her symptoms?

To be effective, cromolyn nasal spray must be dosed several times each day, which can hinder adherence.[43] The initial dose for the cromolyn sodium nasal spray (5.2 mg/actuation) is one spray in each

nostril three to four times a day up to six times daily.[34] In some patients, symptom control can be maintained with dosing two to three times per day. J.C. should be instructed to begin therapy at least 2 weeks before her planned visit because of the delay in the onset of action for this agent with a known trigger exposure (dog dander).[49]

The clinician should ensure that both parent and child can demonstrate appropriate administration technique before therapy is initiated. On first use, the device should be primed until a consistent fine mist spray is achieved. J.C. should be instructed to gently blow her nose and then spray the cromolyn sodium solution into each nostril in a slightly upward direction, parallel to the nasal septum.

Topical nasal cromolyn has an excellent safety profile, including minimal incidence of adverse effects. Local irritation with burning, stinging, and sneezing are the most common manifestations. The safety of cromolyn[49] has made it widely used as initial therapy for children with allergic rhinitis and for treating rhinitis during pregnancy. **Table 20-6** includes information about intranasal cromolyn dosing and availability.

Table 20-6
Additional Oral and Intranasal Agents for Rhinitis

Generic (Brand Product)	Available Dosage Forms/Strength	Adult Dose	Pediatric Dose
Oral			
Leukotriene modifiers Montelukast (Singulair®)	Tablets: 10 mg Tablets, chewable: 4 mg, 5 mg Oral granules: 4 mg	10 mg once daily	Children ≥6 to <15 years: 5 mg once daily Children 6 months to <6 years: 4 mg once daily (chewable tablet or granules)
Intranasal			
Antihistamine Azelastine (Astepro®)	Nasal spray: 0.1% 0.15%	Perennial: 0.15%: 2 sprays/nostril twice daily Seasonal: 0.1%: 1–2 sprays/nostril twice daily 0.15%: 1–2 sprays/nostril twice daily or 2 sprays/nostril once daily	Perennial: Children 6 months–5 years (0.1%) 1 sp each nostril (EN) bid Children 6–11 years: 0.1% or 0.15%: 1 spray/nostril twice daily Seasonal: Children 6–11 years: 0.1% or 0.15%: 1 spray/nostril twice daily Children 2–5 years: 0.1%: 1 spray/nostril twice daily
Olopatadine (Patanase®)	Nasal solution: 0.6%	Seasonal: 2 sprays/nostril twice daily	6 to <12 years: 1 spray/nostril twice daily
Mast-cell stabilizer Cromolyn sodium (Nasalcrom®)[a]	Nasal spray: 5.2 mg/spray	1 spray/nostril three to four times/day (every 4–6 hours; max six times daily)	Children 2 years or older: 1 spray/nostril three to four times/day (every 4–6 hours; max six times daily)
Anticholinergic Ipratropium bromide (Atrovent®)[b]	Nasal spray: 21 µg/spray (for perennial symptoms), 42 µg/spray (for seasonal symptoms)	2 sprays/nostril 3 to 4 times daily (max 672 µg/day)	Children 6 years or older: 42 µg/spray: 2 sprays/nostril two to three times/day Children 5–11 years: 84 µg/spray: 2 sprays/nostril three times daily

[a]Available without a prescription.

[b]Optimum dosage varies with the response of the individual patient. It is always desirable to titrate an individual to the minimum effective dose to reduce the risk of side effects. In addition, the safety and efficacy of the use of ipratropium 42 µg nasal spray beyond 3 weeks in patients with seasonal allergic rhinitis not been established.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

Intranasal Corticosteroid Therapy

CASE 20-3

QUESTION 1: A.R. is an 8-year-old girl with allergic rhinitis and asthma. She is being treated with inhaled budesonide for asthma and oral loratadine for rhinitis. Her mother reports that she frequently sneezes, has an itchy nose and eyes, and does not sleep well at night because of nasal congestion. She also reports that she cannot give her cetirizine daily because it "makes her drowsy at school." Her asthma has been well controlled in the past; however, lately, she is concerned that she is experiencing some shortness of breath, and it may be related to her allergies. While you are talking to her, you note that A.R. breathes

exclusively through her mouth, sniffs frequently, and rubs her nose. You also notice dark circles under her eyes.

What signs and symptoms of allergic rhinitis is A.R. displaying?

A.R. is showing the classic signs of allergic airways disease in children. She is sniffing and snorting in response to nasal itching and discharge. The frequent upward rubbing of the nose (generally with the palm) is known as the "allergic salute"[1] and is caused by nasal itching. Long-standing symptoms can lead to facial abnormalities, including the formation of a transverse crease across the bridge of the nose.[3] Dark circles under the eyes are commonly known as "allergic shiners," and they can be further aggravated by the frequent rubbing of the eyes associated with severe ocular itching.[1,3]

CASE 20-3, QUESTION 2: Given her concomitant asthma, are there any special considerations for treating A.R.'s allergic rhinitis?

Based on the relationship between inflammation in the upper and lower airways, and the similar immunologic mechanisms involved in allergic rhinitis and asthma, it is a reasonable assumption that poor control of upper airway allergies can have a negative impact on asthma control.[29] In fact, rhinitis is a risk factor for asthma development,[43] and poorly controlled rhinitis can aggravate asthma control.[4] In a patient with asthma, like A.R., treatment of allergic rhinitis can also reduce airway hyperresponsiveness and symptoms of asthma.[1,43] Historically, the use of antihistamines (FGAs) was considered problematic for patients with asthma because of a theoretic concern about excessive drying of airway secretions caused by the anticholinergic properties of these agents. It is now clear that most patients with asthma can take any of the antihistamines without adverse pulmonary effects as AR has done in the past. Intranasal corticosteroids should be considered for A.R. as they are considered first line for patients with concomitant allergic rhinitis and asthma.[6]

ROLE IN THERAPY

Case 20-3, Question 3: What would be the role of intranasal corticosteroids in A.R.?

Based on the frequency and severity of symptoms, the lack of control/side effects with oral antihistamine therapy, and concomitant asthma, intranasal corticosteroids are appropriate consideration for A.R. Intranasal corticosteroids are the most effective therapy available for the treatment of allergic rhinitis. They are safe, well tolerated, and are highly effective in reducing itching, sneezing, rhinorrhea, and congestion in both adults and children.[1] In addition to improving all nasal symptoms, evidence suggests that intranasal administration of corticosteroids effectively relieves ocular symptoms.[43] These agents also have demonstrated efficacy for nonallergic rhinitis,[9] rhinitis medicamentosa (RM),[50] and nasal polyps.[51] The currently available intranasal corticosteroids are listed in **Table 20-7**.

Table 20-7
Intranasal Corticosteroids[a] Commonly Used for Rhinitis

Generic Name (Example Brand Product)	Available Dosage Forms/Strengths	Adult Dose[a]	Pediatric Dose[a]
Beclomethasone dipropionate (Beconase AQ®), QNASL (HFA)®, QNasal (Children's)®	42 µg/spray 80 µg/spray 40 µg/spray	42 µg: 1–2 sprays/nostril twice daily 80 µg: 2 sprays/nostril once daily	Children 6–12 years: 42 µg: 1 spray/nostril twice daily (max 2 sprays/nostril daily) Children 4–11 years: 40 µg: 1 spray/nostril once daily
Budesonide (Rhinocort Aqua®, Rhinocort Allergy®, Children's Rhinocort®)	32 µg/spray	1 spray/nostril once daily (max 4 sprays/nostril daily)	Children 6 to <12 years: 1 spray/nostril once daily (max 2 sprays/nostril daily)
Ciclesonide (Omnaris®), Zetonna (HFA®)	50 µg/spray 37 µg/spray	50 µg: 2 sprays/nostril once daily 37 µg: 1 spray/nostril once daily	50 µg: Children 6 to <12 years: 2 sprays/nostril once daily (approved for seasonal symptoms in ages older than 6 years and for perennial symptoms for ages older than 12 years) 37 µg: do not use in children younger than 12 years.
Fluticasone propionate (Flonase Allergy Relief®, Clarispray®, Children's Flonase®, GoodSense Nasoflow®, Ticaspray®)	50 µg/spray	2 sprays/nostril once daily or 1 spray/nostril twice daily	Children 4–11 years: 1–2 sprays/nostril once daily (max 2 sprays/nostril daily)
Fluticasone furoate (Flonase Sensimist® and Veramyst®)	27.5 µg/spray	2 sprays/nostril once daily	Children 2–11 years: 1 spray/nostril once daily (max 2 sprays/nostril daily)
Flunisolide (no brand product available)	0.025%	Older than 15 years: 2 sprays/nostril two or three times daily (max 8 sprays/nostril daily)	Children 6–14 years: 1 spray/nostril three times daily or 2 sprays/nostril twice daily (max 4 sprays/nostril daily)
Mometasone furoate (Nasonex®)	50 µg/spray	2 sprays/nostril once daily	Children 2–11 years: 1 spray/nostril once daily
Triamcinolone acetonide (Nasacort AQ®, Nasacort Allergy®)	55 µg/spray	2 sprays/nostril once daily	Children 2–5 years: 1 spray/nostril once daily (max 1 spray/nostril daily) Children 6–11 years: 1–2 sprays/nostril once daily (max 2 sprays/nostril daily)
Azelastine HCl/fluticasone propionate (Dymista®)	137/50 µg/spray	1 spray/nostril twice daily	Children 6 years or older: 1 spray/nostril twice daily

[a]It is always desirable to titrate an individual patient to the minimum effective steroid dose to reduce the risk of side effects. When the maximum benefit has been achieved and symptoms have been controlled, reducing the steroid dose might be effective in maintaining control of rhinitis symptoms.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

Intranasal corticosteroids are the most effective agents to treat allergic rhinitis regardless of concomitant asthma. They are more effective than other available therapeutic options. They are frequently rated as more effective than antihistamines,[1] although the benefit from therapy requires correct use of the administration device.[3] Intranasal corticosteroids improve congestion, sneezing, rhinorrhea, itching,[42] and ocular symptoms[52] with no difference in efficacy among the available options.[1]

MECHANISM OF ACTION

Case 20-3, Question 4: How do intranasal corticosteroids work to reduce the symptoms of allergic rhinitis?

Corticosteroids readily diffuse across cell membranes, where they bind to a specific steroid receptor in the cytoplasm of a cell, and the steroid–receptor complex then moves into the cell nucleus, where it influences protein synthesis and inhibits the breakdown of phospholipids to arachidonic acid.[52] This, in turn, inhibits the formation of prostaglandins and leukotrienes. Topical corticosteroids reduce the number of eosinophils, basophils, and mast cells in the nasal mucosa and epithelium; directly inhibit the release of mediators from mast cells and basophils; reduce mucosal edema and vasodilation; and stabilize the endothelium and epithelium, resulting in decreased exudation.[1] Topical corticosteroids inhibit both the early-phase and late-phase reactions to antigen challenge,[35] and therefore pretreatment and continued use are recommended.[1]

CHOICE OF THERAPEUTIC AGENT

Case 20-3, Question 5: What intranasal corticosteroid products are appropriate to manage A.R.'s allergic rhinitis?

Currently marketed intranasal corticosteroid products vary in the pharmacologic characteristics that can influence patient acceptance and adherence; however, there do not appear to be significant advantages with regard to efficacy among them.[1] Primary differences among products include potency, dosing regimens, delivery systems, spray volume,[34] and patient preference. For sensitive patients, there may be some theoretical advantage to products that are preservative or alcohol-free.

The ideal intranasal corticosteroid agent should exhibit high topical potency and low systemic activity. After topical administration, the corticosteroid may reach the systemic circulation by absorption across the nasal mucosa or through gastrointestinal absorption of the swallowed portion of the dose.[44] Studies have shown that varying

sensory attributes (eg, aftertaste, nose runout, and smell) affect acceptability of, and preference for, particular nasal corticosteroid products.[1] Some degree of experimentation may be required to find the optimal product for A.R.

SAFETY

Case 20-3, Question 6: How safe are intranasal corticosteroids in this situation?

The corticosteroids currently available for intranasal administration are listed in Table 20-7. Among available products, intranasal corticosteroids have similar efficacy in clinical trials.[1] Budesonide, beclomethasone, ciclesonide, and flunisolide are indicated for age 6 years or older. Beclomethasone HFA and fluticasone propionate are labeled for age 4 years or older, and mometasone, triamcinolone, and fluticasone furoate are indicated in children age 2 years or older.[34] Triamcinolone (Nasacort Allergy 24 hour®), fluticasone propionate (Flonase Allergy Relief®), budesonide (Rhinocort®), and fluticasone furoate (Flonase Sensimist®) are available OTC. Because A.R. is 8 years old, theoretically she is a candidate for any of the OTC intranasal steroids; however, given her concomitant asthma, a prescription agent may be a better choice. Because poor control of upper airway allergies can have a negative impact on asthma control,[29] proper monitoring by her provider is important.

A common concern regarding the use of corticosteroids in children is the risk of growth suppression. Current U.S. FDA labeling for inhaled and intranasal corticosteroid preparations include wording that use of these products in children may reduce their rate of growth. Although beclomethasone may be associated with reduced growth velocity,[34] numerous studies have shown no growth delay in children treated long term with newer intranasal steroids.[1] Specifically, studies with mometasone, fluticasone, budesonide, ciclesonide, and triamcinolone have shown little clinical effect on growth at recommended doses.[53] It is always judicious to

recommend and utilize the lowest effective dose of intranasal corticosteroids especially in a pediatric population also on a concomitant inhaled corticosteroid agent. Because A.R. has concomitant asthma, this may be the case in this patient.

Other potential adverse effects of chronic intranasal corticosteroids have been investigated. Severe local effects such as nasal mucosal atrophy or septal ulceration are rarely seen and can be prevented with appropriate technique.[53] Changes in bone mineral density, intraocular pressure, or cataracts do not appear to be of concern.[53]

INSTRUCTIONS FOR USE

CASE 20-3, QUESTION 7: A.R. is given a prescription for budesonide, two actuations in each nostril twice daily. How should she be counseled to use this drug?

Although intranasal corticosteroids have an excellent safety profile, some local adverse effects can occur. The currently available products are all aqueous solutions delivered via a manual spray pump; these are much less drying than the original propellant-based aerosol formulations of the same products. The most commonly reported side effect is epistaxis.[51] Local irritation, burning, stinging, and dryness are also possible.[1] Proper technique in using nasal corticosteroid products can reduce the risks for these side effects.[1]

Patient education is important to ensure proper use of, and response to, the intranasal corticosteroids.[5] A.R. should be instructed to blow her nose gently before using the nasal spray as severe blockage of the nasal passage may prevent deposition of the drug at the intended site of action. The patient should be instructed to direct the spray away from the nasal septum.[42] This technique is facilitated by using the contralateral hand during administration to each nostril. This results in pointing the applicator nozzle straight and back to ensure application is parallel to the septum.[3]

Therapeutic benefit to intranasal steroids is generally evident in a few days,[3] although some newer agents may begin to relieve symptoms within hours because of a quick onset of effect.[1] Fluticasone has been effective when used on an as-needed basis.[1] Nonetheless, it is reasonable to advise patients that full benefit may not be realized for up to 2 weeks.[3]

Systemic Corticosteroids

Case 20-3, Question 8: What is the role of systemic corticosteroid therapy in the management of A.R.'s allergic rhinitis?

In contrast to the minimal side effects of the topical corticosteroids, systemic administration of these drugs can cause numerous, and at times serious, side effects. Systemic administration, therefore, must be reserved for only short-term, adjunctive therapy in cases of severe, debilitating rhinitis. In such cases, a short course of relatively high-dose corticosteroid, so-called burst therapy, can be administered. Prednisone 40 mg/day for adults or 1 to 2 mg/kg/day for children (or an equivalent dose of a comparable compound) every morning for up to 7 days effectively relieves acute, severe rhinitis symptoms. If A.R. were to have a particularly severe exacerbation of her allergic rhinitis such that it interfered with sleep or ability to attend school, an oral corticosteroid burst would be indicated. More likely, A.R. would require a short course of systemic corticosteroids for an acute asthma exacerbation, which should also result in improved nasal symptoms.

Combination Therapy

Case 20-3, Question 9: Would there be an advantage in combining various therapies for allergic rhinitis in A.R.?

The rationale for combining agents to treat allergic rhinitis is based on the theoretic benefit of additive or synergistic reactions. Various combinations have been studied. Concomitant use of antihistamines and decongestants has been shown to relieve individual nasal symptoms compared with either agent alone. Combining intranasal antihistamines and intranasal corticosteroids also is beneficial.[1] However, the combination of intranasal corticosteroids with oral antihistamines has not been shown to offer clinical benefit over use of intranasal steroids alone.[1] Similarly, the combination of oral antihistamines and leukotriene modifier therapy is generally not recommended.[1] As A.R. has concomitant asthma, recent guidelines concur that an intranasal corticosteroid is preferred monotherapy over combinations with oral agents. However, the addition of montelukast may be considered, given her asthma history.[6] When combination therapy of any kind is used, once symptoms are controlled, one agent should undergo a trial for discontinuation.

Leukotriene-Modifying Agent Therapy

CASE 20-4

Question 1: K.H. is a 58-year-old male with allergic rhinitis. He has experienced symptoms during ragweed pollen season (<4 weeks out of the year) for several years. He has used various antihistamines including clemastine and diphenhydramine for his symptoms during these times with moderate success. This year, he initiated therapy with diphenhydramine 1 week before the pollen season but began experiencing symptoms of urinary retention after 10 days. His physician advised him that this might be related to the antihistamine aggravating his enlarged prostate, and he was advised to use fexofenadine 60 mg twice daily. After 1 week, K.H. states that the medication is not working. After seeing an advertisement on television, he enquires about the use of a leukotriene modifier for his allergic rhinitis.

What is the mechanism for K.H.'s urinary discomfort attributed to the diphenhydramine?

K.H. is exhibiting symptoms of urinary outflow obstruction or prostatism. Common features of this are frequency, hesitancy, slow

urine stream, dribbling, and bladder fullness after voiding. The most common cause of obstruction is benign prostatic hyperplasia (BPH). Because the prostate is located anatomically around the urethra, enlargement of the gland can obstruct urine flow.[54]

The bladder and urethra are made up of smooth muscle tissue that is innervated by the sympathetic and parasympathetic divisions of the autonomic nervous system. The detrusor musculature is predominantly innervated by β-adrenergic and cholinergic receptors, whereas the bladder neck (or outlet) is innervated predominately by α-adrenergic receptors.[55] Sympathetic stimulation causes relaxation of the detrusor muscle to allow bladder filling, closure of the urethra, and decreased bladder emptying. Cholinergic stimulation of the detrusor causes contraction of the detrusor to cause bladder emptying. Initially, the detrusor musculature can compensate for the urethral obstruction in BPH. Eventually, however, the detrusor muscle fibers hypertrophy and decompensate, resulting in urinary retention and detrusor hyperreflexia manifesting as urinary frequency, urgency, urge incontinence, and nocturia.[56]

When K.H. took diphenhydramine, the anticholinergic properties of the drug blocked detrusor contraction and precipitated acute urinary retention.[55] In this case, switching therapy to an SGA (ie, fexofenadine) is more appropriate because these agents have little to no anticholinergic side effects.

EFFICACY

Case 20-4, Question 2: What are the rationale and evidence that a leukotriene modifier might be beneficial in the management of K.H.'s allergic rhinitis?

Leukotrienes are important inflammatory mediators in the upper and lower airways and are present in nasal secretions of patients with allergic rhinitis. They serve as inflammatory mediators that attract eosinophils and increase microvascular leakage, edema, and mucus gland secretion.[4] These actions lead to the symptoms of

allergic rhinitis as well as those of asthma.[29] In clinical trials, leukotriene modifiers relieve nasal symptoms in patients with allergic rhinitis however not as well as nasal corticosteroids.[1]

In actual use, the benefit of leukotriene modifiers has been modest; therefore, their role is typically adjunctive to the use of first-line agents (eg, intranasal steroids), and these are not recommended first line for allergic rhinitis.[1] Other therapies are more effective and less costly. There are, however; certain patient scenarios where leukotriene modifiers have a role in therapy. Clinical decisions about the value of combining treatments regimens that include a leukotriene-modifying agent should be based on the specific clinical situation. Specifically, a patient with both mild asthma and concomitant allergic rhinitis may benefit from therapy with a leukotriene modifier[6] with or without an antihistamine.[35] If used, however, a risk exists of a rare complication known as eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss). This syndrome is characterized by eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and neuropathy.[34] Table 20-6 includes information about the use and availability of montelukast, which is currently the only leukotriene modifier approved for allergic rhinitis. Montelukast carries a boxed warning related to mental health adverse events including completed suicides. This strengthens the recommendation that montelukast not be considered first line for allergic rhinitis.[34] K.H. has intermittent (seasonal) allergic rhinitis with a known trigger (ragweed pollen). The best option at this time would be to ideally start before ragweed season with an intranasal steroid. Since ragweed season has already hit, and patient is symptomatic, the use of Intranasal steroid (INS) is still recommended first line. The use of montelukast should be discouraged for K.H. as it plays a limited role in seasonal allergic rhinitis, and is not generally recommended for patients with persistent disease either.

Complementary and Alternative Therapies

CASE 20-5

QUESTION 1: C.L., a 25-year-old female, presents in mid-August stating that her allergies are worsening daily. Symptoms are nasal discharge and obstruction, repetitive sneezing, and itching of the nose, eyes, and throat. She is fatigued and has difficulty concentrating. Her symptoms have been occurring in late spring and summer since high school, and she has used a variety of medications intermittently (clemastine, fexofenadine, beclomethasone nasal, and ketotifen ophthalmic) over the years. C.L. is a competitive runner but has been unable to run as far or as often as usual because of bothersome allergy symptoms. She is also reluctant to use traditional Western medications as they may be prohibited by her race sponsors. A running partner mentioned that she could control her allergy symptoms with diet, exercise, and herbal remedies purchased at a local nutritional supplement shop.

What, if any, alternative treatments are efficacious in allergic rhinitis?

Alternative treatments such as yoga, massage, acupuncture, homeopathy, and herbal therapy are common among adults with rhinitis and should be taken into account by health care providers. Literature indicates that 25% to 50% of the general population and up to 70% of children have used an alternative method at least once.[57] The estimated lifetime prevalence of complementary and alternative medicine (CAM) use among patients with allergic rhinitis is high; between 27% and 46%. Acupuncture is used by ~18% of patients with allergic rhinitis. Still, because allergic rhinitis is largely a self-managed disease, it is likely that reported use of these agents is underestimated. A survey found that only 43% of subjects who had used alternative methods had informed their provider about it.[57] For these reasons, patients should always be questioned specifically about the use of alternative therapies during the patient interview. Although some alternative approaches such as acupuncture have been deemed to be safe,[1,51] the safety and efficacy of herbal remedies has not been clearly established and cannot be recommended at this time[1] although their use is quite popular.[58] In addition, some complementary therapies have been associated with side effects and potential drug interactions.[57] Because of C.L.'s reluctance to use traditional Western medications, other strategies are appropriate to consider to help manage her rhinitis symptoms.

Camphor and menthol-delivered rubs (Vicks VapoRub®, Breathe Right Colds Nasal Strips®) have been shown to have an ameliorating effect on nasal congestion[59]; however, the effects are short-lived.[34] Other forms of aromatherapy suggested to relieve nasal congestion are lacking data related to efficacy.[59] Saline nasal irrigation (eg, neti pot) is simple, inexpensive, and has been shown to have some efficacy.[60]

PHYSICAL TECHNIQUES

Acupuncture

Clinical trial data show patients with allergic rhinitis who use acupuncture have seen an improvement in quality of life and antihistamine use.[61] The clinical significance of these findings remains uncertain; however, some experts do recommend that clinicians offer this treatment modality to patients who are interested.[1]

HERBAL MEDICINES

It has been suggested that some herbs have anti-allergy, immune modulation, and anti-inflammatory effects that may be helpful to ease symptoms of allergy.[62] With this in mind, *Echinacea* has become one of the top-selling herbal products in the United States. *Echinacea*, also known as the purple cornflower, however, is a member of the daisy Compositae (Asteraceae) family.[63] Although *Echinacea* is often used for immune-related disorders, patients with known allergy to these plants should be cautioned regarding the use of *Echinacea* products.

A few herbal therapies, including butterbur, biminne, Chinese herbal mixture,[1] and spirulina[64] potentially hold some promise because of positive results in trials on clinical symptoms and quality of life in patients with allergic rhinitis, but more investigation is needed before they can be included in recommended treatment algorithms.[1]

OTHER

Reports regarding the use of intranasal zinc for upper respiratory symptoms, particularly those associated with the common cold, and congestion associated with allergies have been conflicting. Although zinc gels and sprays are popular OTC products, studies show inconsistent results[65] and may be associated with zinc-induced anosmia syndrome.[65] Some products have been removed from the market because of this problem. By giving patients minuscule amounts of allergen, homeopathic medicines are designed to mimic and augment a patient's own immune responses and natural defenses.[66] Some studies have shown that patients with allergic rhinitis who received homeopathic dilutions of allergens had significantly better nose running scores than those in the placebo group.[66] Further investigation is needed before homeopathy can be recommended for allergic rhinitis.

Although a variety of alternative remedies are widely available and used frequently in self-treatment, based on the evaluation of these data, there is no firm recommendation for C.L. regarding the use of alternative therapies in allergic rhinitis.[1] C.L. should be advised to consult with the specific regulating agency that governs her sporting activities (eg, the World Anti-Doping Agency for Olympic events) to gain a clear understanding of medicines that are banned in all cases as compared to those that may be used with medical exemptions or used outside of the competitive window. This may allow her to use many conventional treatments (eg, intranasal steroids) with confidence. Saline irrigation or acupuncture would also be a safe, noncontroversial option that may offer some efficacy.

Immunotherapy

EFFICACY

CASE 20-6

Question 1: R.C. is a 25-year-old schoolteacher who has experienced allergic symptoms since childhood, but noticed a worsening after she graduated from college and moved to a new area of the country. Although she has mild

symptoms year-round, she has severe exacerbations during April through June and August through October each year. During these periods, she feels that exposure to cut grass and weeds provokes profound nasal symptoms. She also notes that when she spends more time outdoors in spring and early fall, the regular therapy that she buys OTC, fluticasone (Flonase®) nasal spray (two sprays per nostril once daily), is less effective. She has added loratadine (10 mg daily) during this time but is frustrated by having to take so many medications while continuing to experience symptoms. Her administration technique and adherence to the INS are both good. R.C. asks your opinion about allergy shots, remarking that she started them as a child with some relief, but moved after a year and never resumed treatment.

Is allergen immunotherapy effective for reducing symptoms of allergic rhinitis?

Allergen-specific immunotherapy has long-standing and long-term efficacy, induces clinical and immunologic tolerance, and may prevent the progression of allergic disease.[67] Immunotherapy is available via SCIT (sometimes called “allergy shots”) or sublingual tablets (SLIT).[68] Sublingual aqueous drops[68] are also sometimes used but are not FDA approved in the United States.[1] Immunotherapy is unique and capable of changing the course of the disease.[1] By giving dilute solutions of allergen-containing extracts in repeated and increasing doses, immunologic tolerance is provided.[67] Therefore, subsequent exposure to those allergens elicits no or mild symptoms. Immunotherapy has been shown to improve symptom scores and quality of life.[69]

Immunotherapy administered via SCIT has been used empirically since the early 1900s, and its efficacy has been documented in many controlled trials.[70] SIT is effective in the treatment of allergic rhinitis and may even prevent the onset of asthma.[1] In addition, the benefit of immunotherapy is long-lived. Even after discontinuation, studies show continued beneficial effects up to 10 years later.[1] SCIT and SLIT should be considered a supplement to drug therapy in specific patients and possibly be used earlier in the course of allergic disease to achieve maximal benefit.[1,71]

ALLERGEN TESTING

Case 20-6, Question 2: How can the clinician determine R.C.'s specific sensitivities?

Skin testing using the modified prick test method or a prick-puncture method is used to confirm the diagnosis of allergic rhinitis[72] and to determine specific allergen sensitivities. Skin testing is a highly sensitive and relatively inexpensive objective measurement of allergen sensitivity. Small quantities of allergen are introduced into the skin by pricking or puncturing the skin in the immediate presence of the diluted allergen extract. Fifteen to 35 tests are placed on the upper portion of the back or the palmar surface of the forearms. A positive skin test produces a wheal-and-flare reaction at the site within 10 to 20 minutes of application and should be read after 15 minutes.[73] An experienced clinician, usually an allergist, should conduct skin testing using high-quality allergen extracts and should interpret the results.[73]

The allergens tested vary with geographic location, emphasizing the most common offending plant species that generate airborne particles. Pollen, the primary particle, is produced by trees, grasses, and weeds. Each of these plant groups generally pollinates at about the same time each year: trees in the spring, grasses from early to midsummer, and weeds from late summer into fall before the first killing frost. The onset and potency of the pollen season vary with geographic location and weather, particularly with respect to temperature and moisture. It is postulated that climate change is also affecting pollen and weed seasons. For example, ragweed is projected to have a much greater impact on patients living across the eastern United States in the future owing to increases in climate variability.[24] Seasonality of symptoms can be misleading because settled pollen particles from a previous season may be resuspended in the air following the spring snowmelt or periods of heavy winds.

Mold spores are also common airborne allergens. The outdoor molds release their spores from early spring through late fall. Within this long season, spore counts increase and decrease, depending on the presence of local flora on which these molds grow (eg, grain and

other crops, forests, and orchards). Some perennial allergens (eg, house dust mites, insect and animal dander, and some indoor molds) occur consistently across all geographic distributions.

In addition to skin-prick testing, clinicians can detect allergen-specific IgE antibodies in the blood.[74] Results are reported quantitatively and total serum IgE can be useful in determining if atopy is present[75] and will help determine which allergen extracts should be utilized if allergen immunotherapy is desired.[75] In each case, skin test results[62] or IgE serum levels[63] must be correlated with the patient's clinical history as it may help assess prognosis and inform treatment decisions[75.] R.C.'s perennial symptoms with seasonal exacerbations indicate sensitivity to the common perennial allergens such as dust mite, with a particular sensitivity to seasonal allergens such as tree, grass, and weed pollen. These subjective relationships should be confirmed with skin-prick testing.

Case 20-6, Question 3: R.C. is currently using medications (fluticasone nasal spray and loratadine) for her symptoms. Should these be discontinued before skin testing?

Antihistamines blunt the wheal-and-flare reaction by blocking the effects of histamine on capillaries. Different antihistamines vary in the extent to which they can inhibit wheal formation and in the duration of the inhibitory effect with older first-generation agents being the worst offenders.[73] Other agents that may interfere with skin-prick testing include long-term systemic corticosteroids, topical (dermal) corticosteroids, tricyclic antidepressants,[76] phenothiazine-type antipsychotics, antiemetics,[73] and possibly some herbal preparations.[76] Depending on the agent selected, antihistamines must be discontinued from 24 hours to 10 days before skin testing,[73] and even then considerable interpatient variability exists in blocking effects. For best results, R.C.'s loratadine should be discontinued 10 days before her skin testing. Recommendations for discontinuing antihistamines before allergen skin testing are listed in **Table 20-8**.

Table 20-8

General Recommendations for Discontinuation of Antihistamines Before Allergen Skin Testing

1. Remind the patient that allergic symptoms may return during the antihistamine-free period, but that reliable skin tests cannot be performed in a patient currently taking antihistamines.
2. Discontinue any short-acting antihistamine (ie, those in Table 20-2 with a duration of suppression ≤4 days) 4 days before skin testing.
3. Discontinue longer-acting antihistamines (ie, those in Table 20-2 with a duration of suppression >4 days) at an interval appropriate to their duration of effect (eg, hydroxyzine should be discontinued 10 days before skin testing).
4. Before applying the full battery of skin tests, apply histamine (positive) control and glycerinated diluent (negative) control tests. Application of a 1 mg/mL histamine base equivalent should yield wheal-and-flare diameters of 2–7 mm and 4.5–32.5 mm, respectively, to be considered a normal histamine reaction. A normal cutaneous reaction to histamine control suggests that accurate skin testing can be performed.

Source: Bousquet J, Khalteav N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2) LEN and AllerGen). *Allergy*. 2008;63(suppl 86):8-160. Reprinted by permission of John Wiley & Sons, Inc.

Other allergy medications, including cromolyn and nasal corticosteroids, have no effect on skin tests. Likewise, most asthma medications, including leukotriene modifiers, inhaled β_2-agonists, cromolyn, theophylline, and inhaled and short-course systemic (burst) corticosteroids have no effect on skin tests.[73] R.C. can continue the use of fluticasone nasal spray as she waits to be skin tested.

Case 20-6, Question 4: Is R.C. a candidate for immunotherapy injections and/or sublingual tablets?

Immunotherapy via SCIT or SLIT should be offered to patients who have an inadequate response to pharmacologic treatment for AR with or without environmental controls.[1] Further considerations are the patient's preference, adherence, response to avoidance measures, adverse drug effects, and coexistence of allergic asthma.[1]

It has also been shown that the clinical benefits of immunotherapy are similar if not better than standard therapy with intranasal steroids, montelukast, or antihistamines.[71] In the case of R.C., she has year-round symptoms with seasonal exacerbations, she has not experienced symptom relief when using appropriate therapies, and she is motivated to try immunotherapy. In addition, a previous trial in childhood was beneficial. For these reasons, skin-prick testing and a trial of immunotherapy with specific allergens are reasonable.

LENGTH OF THERAPY

Case 20-6, Question 5: If R.C. decides to proceed with immunotherapy, how long should her therapy continue and how long will the effects last?

After identifying the offending allergens via skin testing, subcutaneous immunotherapy is generally administered in two phases. During the build-up phase, increasing doses of allergen are given once or twice a week until a predetermined target or maintenance dose is achieved. Once this maintenance dose is reached, shots are usually administered every 2 to 3 weeks for the ensuing several years of treatment. Clinical improvement with immunotherapy usually occurs in the first year. In a small percentage of patients, there is no improvement, and immunotherapy is discontinued. If symptoms are reduced, however, injections are usually continued for 3 to 5 years of maintenance therapy.[77]

Although immunotherapy can lead to long-term remission of symptoms, one drawback is the lengthy treatment period. SCIT and SLIT have disease-modifying properties, and clinical benefits can persist 2 to 3 years after discontinuation of therapy.[78] Both SLIT and SCIT are effective for allergic rhinitis. They both reduce symptoms and the need for medication. Both SLIT and SCIT are being studied to determine their effectiveness for preventing other atopic disease states like asthma.[79] Immunotherapy via sublingual tablet involves placing the tablet under the tongue for 1 to 2 minutes before swallowing. There is no titration schedule. See Table 20-4 for dosing

information and when best to initiate therapy in relation to the allergen season. A benefit of the sublingual tablet form of immunotherapy is only the first dose needs to be administered in the provider's office, compared to every dose with SCIT.[77] Patients, however, need to be adherent because these sublingual tablets require daily dosing. Choice of formulation often is determined by patient convenience, availability of resources (ability to travel to allergist office), and personal preference,[78] so RC would need to discuss these with her provider.

RISKS

Case 20-6, Question 6: What are the risks associated with either the shot or the sublingual tablet?

Local adverse reactions (ie, redness, local itching, and swelling of the mouth)[78] to SCIT can be common, but the risk of severe reaction (ie, anaphylaxis) is low.[1] Sublingual tablets are FDA approved for self-administration after the first dose because of the perceived safety profile. Because of the risk of anaphylaxis, patients should have access to and be taught the proper technique for an epinephrine autoinjector.[1] Because of the occasional occurrence of systemic side effects, it is important that if R.C. receives SCIT, it should be administered by office personnel who are fully trained and experienced in the early recognition and treatment of such reactions.[78]

Case 20-6, Question 7: Should R.C. also have a prescription for an epinephrine injector for use in case of anaphylaxis? If so, how should it be used?

Yes, if R.C. decides to use SLIT, she will need a prescription for and education on how to administer injectable epinephrine. She should be educated to use the injection of epinephrine if signs or symptoms (such as facial itching, tongue swelling, difficulty

swallowing, or shortness of breath) occur after a dose of SLIT. The autoinjector is given intramuscularly into the thigh, through clothing if necessary. R.C. can repeat the injection with an additional epinephrine autoinjector as necessary.[34] See **Table 20-9** for available injectable epinephrine products.

Table 20-9
Available Injectable Epinephrine Products

Product Name	Dosage Form and Strength	Injection Site	Injection Hold Time	Adult Dose	Pediatric Dose	Generic Available?
EpiPen (2 Pak)®	Solution autoinjector 0.3 mg/0.3 mL	Outer middle of thigh	3 seconds	≥30 kg: 0.3 mg IM or SQ	0.15 mg for 33–66 pounds (15–30 kg)	Yes
Auvi-Q®	0.1 mg/0.1 mL 0.15 mg/0.15 mL 0.3 mg/0.3 mL auto injector (includes voice prompts)		2 seconds	≥30 kg: 0.3 mg IM or SQ	0.1 mg for 16.5–33 lb (7.5–15 kg) 0.15 mg for 33–66 lb (15–30 kg)	No
Symjepi®	0.3 mg/0.3 mL prefilled syringe 0.15 mg/0.3 mL prefilled syringe		2 seconds	≥30 kg: 0.3 mg IM or SQ	0.15 mg for 33–66 pounds (15–30 kg)	No
EpiPen Jr (2 Pak)®	Solution autoinjector 0.15 mg/0.3 mL		3 seconds	N/A	0.15 mg for 33–66 pounds (15–30 kg)	Yes

IM, intramuscularly; SQ, subcutaneously.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

DRUG-INDUCED NASAL CONGESTION: RHINITIS MEDICAMENTOSA

CASE 20-7

Question 1: L.K. is a 27-year-old male who has intermittent allergic rhinitis. He reports that his symptoms are most bothersome in the spring and associated with blooming of various grasses. During these past periods, he has used oral chlorpheniramine (4 mg every 6 hours), which relieves his symptoms but makes him drowsy at work. This season, he reports that his symptoms have been more severe, with sneezing, runny nose, and extreme itching in his nose. He tried oral loratadine (10 mg daily) with partial relief of symptoms. He also states that nasal congestion has been more of an issue with this episode and to address

this he has used oxymetazoline nasal spray (0.05% solution) for the past 3 weeks. Despite increasing the use of nasal spray from the OTC recommended dosages of two sprays per nostril twice daily to three sprays per nostril four times a day, he reports that the congestion is getting worse.

What might be an explanation for L.K.'s increasing need for nasal decongestant?

Selected medications and some drugs of abuse can cause nasal congestion through a variety of mechanisms.[50] **Table 20-10** lists agents associated with drug-induced nasal symptoms. In this case, L.K. is likely experiencing rebound nasal congestion because of a specific form of drug-induced rhinitis called rhinitis medicamentosa (RM).

Table 20-10

Drugs Capable of Causing Nasal Symptoms

Local Inflammatory Mechanisms
Aspirin
Nonsteroidal anti-inflammatory drugs
Neurogenic Mechanisms
Centrally Acting Sympatholytics
Clonidine
Methyldopa
Reserpine
Peripherally Acting Sympatholytics
Prazosin
Guanethidine
Doxazosin
Phentolamine
Vasodilators
Sildenafil
Tadalafil
Vardenafil

Idiopathic Mechanisms
Antihypertensives
Amiloride
Angiotensin-converting enzyme inhibitor class
β-Blocker class
Calcium channel blockers
Chlorothiazide
Hydralazine
Hydrochlorothiazide
Hormonal Products
Exogenous estrogens
Oral contraceptives
Neuropsychotherapeutic Agents
Alprazolam
Amitriptyline
Chlordiazepoxide
Chlorpromazine
Gabapentin
Risperidone
Perphenazine
Thioridazine

Sources: Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol*. 1998;81(5 Pt 2):478–518; Ramey JT, Bailen E, Lockey RF. Rhinitis medicamentosa. *J Investig Allergol Clin Immunol*. 2006;16:148–155; Varghese M, Glaum MC, Lockey RF. Drug-induced rhinitis. *Clin Exper Allergy*. 2010;40:381–384.

Topical decongestants are indicated for short-term use. When used acutely, these drugs cause vasoconstriction by acting on α-adrenergic receptors on blood vessels.[80] This serves to relieve nasal congestion associated with edematous, congested blood vessels, but, when these agents are used chronically, this can result in

overstimulation of α-adrenergic receptors leading to tachyphylaxis and decreased production of endogenous norepinephrine through a negative feedback mechanism.[80] RM has also been associated with the presence of benzalkonium chloride as a preservative in some nasal products.[80]

When RM occurs, many patients will attempt to treat the rebound congestion by using the offending topical decongestant more frequently and/or at increased doses, creating a vicious cycle. L.K.'s description of using the oxymetazoline for an extended period of time (3 weeks), more frequently (from twice daily to four times daily), and at high doses (from two sprays per nostril to three sprays per nostril) support the diagnosis of RM.

Case 20-7, Question 2: How should L.K.'s RM be managed?

Strategies for Resolution

The best strategy for managing RM is prevention by limiting the duration of topical decongestant use to no more than 3 to 5 days.[34] When these medications must be used for longer than 5 days, the patient should be advised to take a 1- to 2-day holiday during which the topical agent is not used before resuming treatment. Patients should be counseled about this whenever topical decongestants are recommended or purchased. When preventative strategies fail, several options for treatment exist.[80]

The first step is to discontinue the offending topical decongestant. L.K. should be counseled to stop the oxymetazoline. Because abrupt discontinuation may cause discomfort or worsening of congestion, L.K. should be educated to not restart the topical decongestant.[80] Intranasal corticosteroids (any available product) should be recommended to patients with RM and may need 6 weeks to reach full effect.[80] Because L.K. is experiencing RM plus symptoms (sneezing, runny, and itchy nose) that occur seasonally, an IN corticosteroid such as mometasone nasal spray (two sprays in each nostril daily) should be recommended. Saline nose drops or spray

can be added to moisturize and alleviate any nasal irritation. In refractory cases, a short course of systemic corticosteroids (prednisone) may be necessary.[80] Note that if the patient has used the topical decongestant continuously for many months or even years, the nasal mucosa may have undergone irreversible changes.

IDIOPATHIC RHINITIS

Diagnosis

CASE 20-8

Question 1: M.S. is a 29-year-old male with profuse watery rhinorrhea that has been a chronic and progressively worsening problem for the past 5 years. He also experiences some nasal congestion with the rhinorrhea but denies nasal itching or sneezing. Although the symptoms tend to remit and exacerbate, they do not occur in any definable seasonal pattern. His symptoms are worsened by exposure to tobacco smoke, strong fumes such as paint or ammonia, and cold air. These often are associated with headaches. M.S. has no other medical problems and no family history of allergies. He does not smoke and rarely drinks alcohol. His only medication, mometasone (50 µg/spray, two sprays in each nostril once daily as needed), only partially relieves the symptoms. M.S. sniffs and blows his nose several times during the medical history taking. Physical examination reveals a mildly erythematous nasal mucosa and a minimally edematous inferior turbinate. Copious nasal discharge is clear and watery and air movement through the nose is relatively good. There is no sinus tenderness. The remainder of his physical examination is normal. Microscopic examination of a nasal smear demonstrates only a few neutrophils and no eosinophils.

What information about M.S. supports the diagnosis of idiopathic rhinitis?

Idiopathic rhinitis is a diagnosis of exclusion encompassing those patients with nasal mucous membrane inflammation with no clinical signs of infection (colored secretions) and no systemic signs of allergic inflammation (IgE in blood or nasal smear).[7] The syndrome is sometimes called nonallergic rhinitis or “vasomotor rhinitis,” but using this terminology can be confusing because the cause of the

symptoms has still not been clearly identified.[9] The prevailing theories involve local atopy, dysfunction of both or either the autonomic nervous system or nociceptive nerve sensor and ion channel proteins.[10] Theoretically, this is the reason that stimuli that normally increase parasympathetic activity in the nose, such as cold air and inhaled irritants, aggravate symptoms.[10] Still, substantial debate exists over whether idiopathic rhinitis represents a localized allergic response in the absence of systemic atopic markers as well as the evidence for inflammatory pathophysiology in the disease.[9]

Case 20-8, Question 2: What causes idiopathic rhinitis, and what can be done to alleviate M.S.'s symptoms?

The symptoms of idiopathic rhinitis are variable. Most patients experience perennial nasal obstruction accompanied by profuse, watery nasal, and postnasal discharge. Many patients have nasal obstruction as the primary symptom, whereas for others it is rhinorrhea. Sneezing, nasal itching, and conjunctival symptoms are rare.[10] Headache may occur and usually is frontal or localized over the bridge of the nose. Symptoms may also appear or worsen in response to climatic changes such as temperature, barometric pressure, and humidity.[10] Similarly, irritant triggers such as tobacco smoke, industrial pollutants, strong odors and perfumes, newsprint, and chemical fumes may worsen or aggravate symptoms.[10]

The appearance of the nasal mucosa also is variable. The turbinates are usually erythematous and, during an exacerbation, considerable quantities of nasal secretions, which can lead to crusting and dryness, may be present.[9] Nasal eosinophilia is not present, and skin-prick testing results are usually negative.[10]

M.S.'s symptoms of bothersome watery rhinorrhea, nasal congestion, and headache without itching or sneezing are typical. His worsening symptoms with exposure to noxious inhalants and cold air support the diagnosis of idiopathic rhinitis. The nasal smear, which notably lacks large numbers of eosinophils, initially differentiates this disease from NARES. This disorder has similar

symptoms but also is marked by nasal eosinophilia (5%–20%) in the setting of negative skin-prick testing and negative IgE levels.[10]

Choice of Therapeutic Agent

Case 20-8, Question 3: What nonpharmacologic and pharmacologic treatments are appropriate to manage M.S.'s idiopathic rhinitis?

Patients should be instructed to avoid as many aggravating factors as possible, such as strong odors (perfumes, soaps, and paints) and air pollutants (smoke and tobacco fumes).[9] Saline irrigation is valuable as a general soothing and moisturizing treatment.[9] Pharmacotherapy for idiopathic rhinitis should be directed toward the predominant symptoms of the individual patient. For patients with predominant nasal congestion and minimal rhinorrhea, intranasal corticosteroids may be helpful.[7] The addition of oral decongestants may improve nasal obstruction in some patients with idiopathic rhinitis but should be considered adjunctive therapy because side effects can be problematic and data regarding efficacy are lacking.[9]

M.S.'s case is typical of the often frustrating course in treating idiopathic rhinitis. Commonly, multiple therapeutic plans fail, and M.S. has responded incompletely and unsatisfactorily to intranasal corticosteroids. There is some older evidence suggesting topical nasal capsaicin may be effective, but this option has not garnered widespread support.[9] Surgical treatments have been attempted for patients in whom medical management fails, although it is typically reserved for patients with concomitant nasal septal deviation or turbinate hypertrophy.[9]

In patients such as M.S., who have rhinorrhea as their predominant symptom, FGAs may be helpful because of their anticholinergic drying effects.[9] The topical antihistamine, azelastine, has been shown to be efficacious for symptoms including congestion, postnasal drip, and sleeping difficulty in those with idiopathic rhinitis.[9] Another option for decreasing nasal secretions is nasal ipratropium bromide, a topical anticholinergic agent with

minimal adverse effects[9] (see Table 20-6 for dosing information). In the case of M.S., because he has been comfortable using an intranasal product (mometasone) in the past, it would be reasonable to initiate a trial of ipratropium bromide 0.03% two sprays in each nostril three times daily. Once the rhinorrhea is controlled, he should be advised to reduce the dosage to twice daily. Nasal saline can also be used as needed if excessive dryness occurs during dosage optimization.

CASE 20-9

QUESTION 1: D.W. is a 56-year-old female with a long-standing history of allergic rhinitis related to triggers with seasonal ragweed. Her primary symptoms are rhinorrhea and sneezing, which she has relieved by using various oral antihistamines (clemastine 1 mg daily and, more recently, cetirizine 10 mg daily) that she takes several weeks each autumn. Recently (during winter), she has experienced new rhinitis symptoms associated with the weather and various odors that were not a problem in the past, specifically, perfumes and food spices. When she encounters these, she exhibits watery rhinorrhea and profound congestion. She has tried a combination of cetirizine with pseudoephedrine for these episodes but reports that it "doesn't seem to help much and it makes me feel jumpy."

Are D.W.'s new symptoms the result of breakthrough (uncontrolled) allergic rhinitis or do they represent something new?

MIXED ALLERGIC–NONALLERGIC RHINITIS

Distinguishing between allergic rhinitis and nonallergic rhinitis may be difficult in clinical practice, and the presence of concomitant allergic and nonallergic rhinitis in some patients confounds the diagnosis further.[8] A careful history should be gathered from the patient and an assessment made of the temporal nature of the symptoms and various exposures. The Clinical Presentation and Assessment of Rhinitis section in this chapter can be helpful to review to help distinguish between allergic and nonallergic causes of rhinitis. When a patient presents with characteristics suggestive of

both types, especially in the case of new symptoms or triggers despite optimized therapy, mixed rhinitis should be considered.

Although D.W. has a confirmed history of ragweed pollen sensitivity (supporting the allergic rhinitis diagnosis), the timing of the more recent symptoms and the new triggers (ie, odors) suggest that she may have developed sensitivities of a nonallergic (non–IgE-based) nature. The patient's age also is consistent with the development of vasomotor rhinitis (nonallergic), which can present around the time of menopause. This, combined with the lack of efficacy from a previously successful therapy (ie, oral antihistamine), suggests that D.W. may be exhibiting a mixed allergic–nonallergic rhinitis presentation.

Case 20-9, Question 2: How should D.W.'s mixed rhinitis be treated? How is this different from the management of allergic rhinitis?

The important point about nonallergic triggers, or new onset triggers such as those present in D.W., is that oral antihistamines and other therapies directed primarily at allergic responses may be ineffective in relieving all symptoms. Good clinical evidence suggests that intranasal steroids are an effective option, as well as intranasal antihistamine therapy or a combination of the two.[1] Avoidance or minimization of exposure to the triggers is also an important strategy. For D.W., a 4-week therapeutic trial of a benzalkonium chloride-free intranasal steroid (eg, ciclesonide two sprays in each nostril once daily) with counseling about appropriate administration is warranted. Intranasal steroid therapy may improve the response to both allergic and nonallergic triggers.[1]

SUMMARY

The initial management of rhinitis should be directed at preventing symptoms, which can be achieved through a variety of pharmacologic and nonpharmacologic methods. Treatment plans for

allergic rhinitis, the most common subtype, should include patient education, allergen or irritant avoidance, and the appropriate medications, including immunotherapy if indicated. Control of the disease process is the expected outcome so that patients can live their lives comfortably without symptoms or impairment. Customizing therapy for each patient based on symptom history and response to treatments is important. Rhinitis can be controlled, and effective management can greatly improve the quality of patients' lives.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol.* 2017;140(*4*):950–958. (6)

Scadding GK, Kriyawasan HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised edition 2017: First edition 2007). *Clin Exp Allergy.* 2017;47:856–889. (3)

Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg*. 2015;152*(1S*):S1–S43. (1)

Tran NP, Vickory J, Blaiss MS. Management of rhinitis: allergic and non-allergic. *Allergy Asthma Immunol Res.* 2011;3:148–158. (9)

Wallace DV, Dykewicz MS, Oppenheimer J, Portnoy J, Lang DM. Pharmacologic treatment of seasonal allergic rhinitis: synopsis of guidance from the 2017 Joint Task Force on Practice Parameters. *Ann Intern Med.* 2017;167:876–881. (30)

COMPLETE REFERENCES CHAPTER 20 ACUTE AND CHRONIC RHINITIS

1. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg*. 2015;152(1S):S1–S43.

2. Wheatley LM, Togias A. Allergic rhinitis. *N Engl J Med*. 2015;372:456–463.
3. Scadding GK, Kriyawasan HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised edition 2017: First edition 2007). *Clin Exp Allergy.* 2017;47:856–899.
4. Mandhane SN, Shah JH, Thennati R. Allergic rhinitis: an update on disease, present treatments and future prospects. *Int Immunopharmacol*. 2011;11:1646–1662.
5. Greiner AN, Hellings PW, Rotiroti G, Scadding GL. Allergic rhinitis. *Lancet.* 2011;378:2122–2222.
6. Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol.* 2017;140(4):950–958.
7. Hellings PW, Klimek L, Cingi C, et al. Non-allergic rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy.* 2017;72:1657–1665.
8. Greiwe JC, Bernstein JA. Allergic and mixed allergic rhinitis: diagnosis and natural evolution. *J Clin Med.* 2019. Accessed October 5, 2020. doi:10.3390/jcm8112019.
9. Tran NP, Vickory J, Blaiss MS. Management of rhinitis: allergic and non-allergic. *Allergy Asthma Immunol Res*. 2011;3:148–158.
10. Settipane RA, Kaliner MA. Nonallergic rhinitis. *Am J Rhinol Allergy*. 2013;27(3):S48–S51.
11. Becker S, Rasp J, Eder K, et al. Non-allergic rhinitis with eosinophilia syndrome is not associated with local production of specific IgE in nasal mucosa. *Eur Arch Otorhinolaryngol.* 2016;273:1469–1475.
12. National Center for Health Statistics. Allergies and hay fever. Accessed February 10, 2021. https://www.cdc.gov/nchs/fastats/allergies.htm
13. Cibella F, Ferrante G, Cuttitta G, Bucchieri S, Melis MR, La Grutta S, Viegi G. The burden of rhinitis and rhinoconjunctivitis in adolescents. *Allergy Asthma Immunol Res*. 2015;7:44–50.
14. Vandenplas O, Vinnikov D, Blanc PD, et al. Impact of rhinitis on work productivity: a systematic review. *J Allergy Clin Immunol Pract*. 2018;6(4):1274–1286.
15. National Ambulatory Medical Care Survey 2010: Summary Tables. (Table 13). Accessed April 8, 2015. http://www.cdc.gov/nchs/data/ahcd/namcs_summary/2010_namcs_web_tables.pdf.
16. Bhattacharyya N. Incremental healthcare utilization and expenditures for allergic rhinitis in the United States. *Laryngoscope*. 2011;121:1830–1833.
17. Bhattacharyya N. Functional limitations and workdays lost associated with chronic rhinosinusitis and allergic rhinitis. *Am J Rhinol Allergy*. 2012;26:120–122.

18. Mete A, Akbudak IH. Functional anatomy and physiology of airway. 2018. Accessed October 5, 2020. doi:10.5772/intechopen.77037
19. Sahin-Yilmaz A. Anatomy and physiology of the upper airway. *Proc Am Thorac Soc*. 2011;8:31–39.
20. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(suppl 86):8–160.
21. Rook GW, Raison CL, Lowry CA. Microbial “old friends,” immunoregulation and socioeconomic status. *Clin and Exp Immunol*. 2014;177:38–46.
22. Passali D, Cingi C, Staffa P, et al. The International Study of the Allergic Rhinitis Survey: outcomes from 4 geographical regions. *Asia Pac Allergy.* 2018;8(1):e7.
23. Dhar MG, Portnoy JM, Barnes CS. Increasing length of ragweed season in the central midwest. *J Allergy Clin Immunol.* 2018;141:AB84.
24. Case MJ, Stinson KA. Climate change impacts on the distribution of the allergenic plant, common ragweed (*Ambrosia artemisiifolia*) in the eastern United States. *PLoS One*. 2018;13(10):e0205677. doi:10.1371/journal.pone.0205677. Accessed October 5, 2020.
25. Aarif E. Pathogenesis of rhinitis. *Clin Exp Allergy*. 2016. Accessed October 5, 2020. https://spiral.imperial.ac.uk/bitstream/10044/1/37061/2/Accepted%20version%2016%207%2016.pdf
26. Schmitt T, Palma L. Allergic rhinitis in children. *Austin J Nurs Health Care*. 2014;1:1006.
27. Dispenza MC. Classification of hypersensitivity reactions. *Allergy Asthma Proc*. 2019;40:470–473.
28. Campo P, Eguiluz-Gracia I, Bogas G, et al. Local allergic rhinitis: implications for management. *Clin Exp Allergy*. 2019;49:6–16.
29. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466–476.
30. Wallace DV, Dykewicz MS, Oppenheimer J, Portnoy J, Lang DM. Pharmacologic treatment of seasonal allergic rhinitis: synopsis of guidance from the 2017 Joint Task Force on Practice Parameters. *Ann Intern Med.* 2017;167:876–881.
31. Rodrigues-Martinez CE, Sossa-Briceño MP, Vladimir Lemos E. Cost effectiveness analysis of mometasone furoate versus beclomethasone dipropionate for the treatment of pediatric allergic rhinitis in Columbia. *Adv Ther*. 2015;32(3):254–269.
32. Hay JW, Kaliner MA. Costs of second-generation antihistamines in the treatment of allergic rhinitis: US perspective. *Curr Med Res Opin*. 2009;25(6):1421–1431.

33. Kennedy JL, Robinson D, Christophel J, Borish L, Payne S. Decision-making analysis for allergen immunotherapy versus nasal steroids in the treatment of nasal-steroid responsive allergic rhinitis. *Am J Rhinol Allergy*. 2014;28(1):59–64.
34. Facts and Comparisons. Accessed October 5, 2020. https://fco.factsandcomparisons.com/lco/action/home
35. Melvin TN, Patel AA. Pharmacotherapy for allergic rhinitis. *Otolaryngol Clin North Am*. 2011;44:727–739.
36. Kushnir NM. The role of decongestants, cromolyn, guaifenesin, saline washes, capsaicin, leukotriene antagonists, and other treatments on rhinitis. *Immunol Allergy Clin North Am*. 2011;31:601–617.
37. Bahceciler NN. Mucosal immunity and sublingual immunotherapy in respiratory disorders. *J Asthma*. 2012;2012:725719. doi:10.1155/2012/725719
38. U.S. Food and Drug Administration. Fighting allergy season with medications. Accessed Jan 5, 2022. https://www.thelakewoodscoop.com/news/2014/05/fighting-allergy-season-with-medications.html
39. Hochfelder JL, Ponda P. Allergen immunotherapy: routes, safety, efficacy, and mode of action. *Immunotargets Ther*. 2013;2:61–71.
40. Ghadersohi S, Tan BK. Contemporary pharmacotherapy for allergic rhinitis and chronic rhinosinusitis. *Otolaryngol Clin North Am.* 2017;50(6):1135–1151.
41. Xolair. Prescribing information. Accessed October 5, 2020. https://www.gene.com/download/pdf/xolair_prescribing.pdf
42. Mucci T, Govindaraj S, Tversky J. Allergic rhinitis. *Mt Sinai J Med*. 2011;78:634–644.
43. Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2013;68:1102–1116.
44. Ackerman S, Smith LM, Gomes PJ. Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. *Ther Adv Chronic Dis*. 2016;7(1):52–67.
45. Bielory L, Meltzer EO, Nichols KK, Melton R, Thomas RK, Bartlett JD. An algorithm for the management of allergic conjunctivitis. *Allergy Asthma Proc*. 2013;34:408–420.
46. La Rosa M, Lionetti E, Reibaldi M, et al. Allergic conjunctivitis: a comprehensive review of the literature. *Ital J Pediatr*. 2013;39:18.
47. Cosme-Blanco W, Arce-Ayala Y, Malinow I, Nazario S. Primary and secondary environmental control measures for allergic diseases. *Allergy and Asthma*. 2018. Accessed October 5, 2020. https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-58726-4_36-1

48. Reisacher WR. Allergy treatment: environmental control strategies. *Otolaryngol Clin North Am*. 2011;44:711–725.
49. Strauss RA. Nasal cromolyn in the treatment of rhinitis. *J Allergy Clin Immunol Pract*. 2020;8(8):2841–2842.
50. Mortuaire G, de Gabory L, François M, et al. Rebound congestion and rhinitis medicamentosa: nasal decongestants in clinical practice. Critical review of the literature by a medical panel. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2013;130:137–144.
51. Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. *J Investig Allergol Clin Immunol*. 2012;22:1–12.
52. Watts AM, Cripps AW, West NP, Cox AJ. Modulation of allergic inflammation in the nasal mucosa of allergic rhinitis sufferers with topical pharmaceutical agents. *Front Pharmacol.* 2019;10:294.
53. McDonnell J, Weller K, Pien LC. Safety of intranasal steroids: an updated perspective. *Curr Allergy Asthma Rep.* 2020;20:69.
54. Hollingsworth JM, Wilt TJ. Lower urinary tract symptoms in men. *BMJ*. 2014;349:4474–4485.
55. Pearson R, Williams PM. Common questions about the diagnosis and management of benign prostatic hyperplasia. *Am Fam Physician*. 2014;11:769–774.
56. Roehrborn CG. Pathology of benign prostatic hyperplasia. *Int J Impot Res*. 2008;20:S11–S18.
57. Sayin I, Cingi C, Oghan F, Baykal B, Ulusoy S. Complementary therapies in allergic rhinitis. *ISRN Allergy*. 2013;2013:938751. doi:10.1155/2013/938751.
58. Moradi B, Heidari-Soureshjani S, Asadi-Samani M, Yang Q, Saeedi-Boroujeni A. Efficacy and mechanisms of medicinal plants as immunotherapy in treatment of allergic rhinitis: a systematic review. *IJPSR.* 2017;8(5):1892–1899.
59. Mihara S, Shibamoto T. The role of flavor and fragrance chemicals in TRPA1 (transient receptor potential cation channel, member A1) activity associated with allergies. *Allergy Asthma Clin Immunol*. 2015;11:11–23.
60. Liang J, Lane AP. Topical drug delivery for chronic rhinosinusitis. *Curr Otorhinolaryngol Rep*. 2013;1:51–60.
61. Brinkhaus B, Ortiz M, Witt CM, et al. Acupuncture in patients with seasonal allergic rhinitis. *Ann Intern Med*. 2013;158:225–234.
62. Zhang X, Lan F, Zhang Y, Zhang L. Chinese herbal medicine to treat allergic rhinitis: evidence from a meta-analysis. *Allergy Asthma Immunol Res.* 2018;10(1):34–42.
63. Kumar A, Rinwa P, Chhabra MK. Pharmacotherapeutics of Echinacea purpurea: gardening shelf to clinic. *J Pharm Educ Res*. 2011;2:45–54.
64. Ceylan ME, Kuzucu I, Mulu NB. Herbal remedy alternatives for allergic rhinitis. 2019. Accessed Jan 5, 2022. https://link.springer.com/chapter/10.1007/978-3-030-21217-9_37

65. Hulisz D. Efficacy of zinc against common cold viruses: an overview. *J Am Pharm Assoc*. 2004;44:594–603.
66. Liu LL, Wan K-S, Cheng C-F, Tsai M-H, Wu Y-L, Wu W-F. Effectiveness of MORA electronic homeopathic copies of remedies for allergic rhinitis: a short-term, randomized, placebo-controlled PILOT study. *Eur J Integr Med*. 2013;5:119–125.
67. Jensen-Jarolim E, Bachmann MF, Bonini S, et al. State of the art marketed adjuvants and formulations in allergen immunotherapy: a position paper of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy.* 2019;75:746–760.
68. Mahler V, Esch RE, Kleine-Tebbe J, et al. Understanding differences in allergen immunotherapy products and practices in North America and Europe. *J Allergy Clin Immunol.* 2019;143(3):813–828.
69. Dhami S, Nurmatov U, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. *Allergy.* 2017;72:1597–1631.
70. Aboshady OA, Elghanam KM. Sublingual immunotherapy in allergic rhinitis: efficacy, safety, adherence, and guidelines. *Clin Exp Otorhinolaryngol*. 2014;7:241–249.
71. Devillier P, Dreyfus JF, Demoly P, Calderón MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med*. 2014;12:71. doi: 10.1186/1741-7015-12-71.
72. Nevis IF, Binkley K, Kabali C. Diagnostic accuracy of skin-prick testing for allergic rhinitis: a systematic review and meta-analysis. *Allergy Asthma Clin Immunol.* 2016;12:20.
73. Bousquet J, Heinzerling L, Bachert C, et al. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy*. 2012;67:18–24.
74. Ciprandi G, Comite P, Ferrero F, et al. Serum allergen-specific IgE, allergic rhinitis severity, and age. *Rhinology.* 2016;54:231–238.
75. Corsico AG, De Amici M, Ronzoni V, et al. Allergen-specific immunoglobulin E and allergic rhinitis severity. *Allergy Rhinol.* 2017;8:1–4.
76. Qureshi TA, Qadri Q, Shafi T, Shah ZA, Kundanger A, Rasool R. Pre skin prick testing: a curfew required on herbals too. *J Cell Immunother.* 2018;4:83–86.
77. Walker SM, Durham SR, Till SJ, et al. Immunotherapy for allergic rhinitis. *Clin Exp Allergy*. 2011;41:1177–1200.
78. Durham SR, Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis? *J All Clin Immunol.* 2016;137(2):339–349.
79. Cardona V, Luengo O, Labrador-Horrilo M. Immunotherapy in allergic rhinitis and lower airway outcomes. *Allergy*. 2016;72:35–42.
80. Wahid NWB, Shermetaro C. Rhinitis medicamentosa. Accessed October 5, 2020. https://www.ncbi.nlm.nih.gov/books/NBK538318/?report=printable

21

Cystic Fibrosis

Paul M. Beringer and Michelle Condren

CORE PRINCIPLES		CHAPTER CASES
1	Cystic fibrosis (CF) is a genetic disorder affecting ~30,000 individuals in the United States that is caused by a defect in the CF transmembrane conductance regulator protein, which is a chloride channel that regulates fluid and electrolyte transport within secretory epithelial cells throughout the body.	**Case 21-1 (Question 1), Figures 21-1, 21-2**
2	The principal manifestations of CF include malnutrition secondary to pancreatic insufficiency and pulmonary dysfunction resulting from chronic airway obstruction, infection, and inflammation.	**Case 21-1 (Question 1), Table 21-1**
3	Diagnosis of CF is based on newborn screening or the presence of the typical	**Case 21-1 (Questions 1, 2), Table 21-2**

	signs and symptoms of the disease, and either documented abnormalities in ion transport or identification of two CF mutations.	
4	Administration of pancreatic enzymes and fat-soluble vitamins is prescribed to correct malabsorption and vitamin deficiencies and improve nutritional status.	**Case 21-1 (Question 2), Table 21-3**
5	Key therapies for the management of CF pulmonary disease include cystic fibrosis transmembrane regulator (CFTR) modulator therapies to correct the basic defect, inhaled dornase alfa and hypertonic saline in combination with mechanical airway clearance techniques to combat airway obstruction, inhaled antibiotics to combat airway infection, and oral azithromycin for airway inflammation.	**Case 21-2 (Questions 1–3)** **Case 21-3 (Question 3)** **Case 21-3 (Question 6)**
6	Periodically, patients will experience acute pulmonary exacerbations characterized by increased pulmonary symptoms, acute loss of lung function, and loss of weight, which require intensification of airway clearance, administration of systemic antibiotics, and nutritional supplements.	**Case 21-3 (Questions 1, 2, 4), Table 21-4**
7	Key monitoring parameters in patients with CF include trends in pulmonary function tests to determine response to therapies and identify possible acute	**Case 21-1 (Question 3)**

	pulmonary exacerbations, and body mass index to assess nutritional status.	
8	Therapy for patients with CF should include attention to complications including CF-related diabetes mellitus, osteoporosis, hepatobiliary disease, constipation, and anxiety/depression.	**Case 21-3 (Question 5)**

INTRODUCTION

Cystic fibrosis (CF) is a severe, complex, hereditary disease that affects one in every 3200 Caucasian births, or ~30,000 children and adults in the United States. One in 31 Americans carries the autosomal recessive gene for CF, which arises from a mutation in coding for the CF transmembrane regulator (CFTR) protein. This genetic mutational error results in the complex, multisystem disease of CF, which is characterized by malabsorption and a state of chronic lung obstruction, inflammation, and infection.

The course and severity of CF are variable and unpredictable. The median predicted survival age has increased from 34 to 46 years over the past two decades owing to advances in the management of this disorder.[1] The recent availability of highly active CFTR modulators (eg, elexacaftor, tezacaftor, and ivacaftor) has created significant excitement in the CF community because of the dramatic improvements in clinical outcomes (eg, lung function and nutritional status) and is expected to significantly increase the life expectancy of people with CF.

GENETIC BASIS

CF is caused by mutations in the *CFTR* gene, which is a member of the ATP-binding cassette family. CFTR is dependent on cyclic adenosine monophosphate for chloride transport: defective coding for CFTR inhibits the normal regulation of ion transport in and out of the cell on the apical surface of secretory epithelial cells.[2] CFTR also regulates the transport of bicarbonate and sodium ions, mucous rheology, pulmonary inflammation, and bacterial adherence.[3–7]

CF is an autosomal recessive disorder, which means there is a 25% chance of inheriting the malfunctioning genes from both parents and developing the disease, a 50% chance of inheriting one abnormal gene (ie, carrier), and a 25% chance of inheriting two normal genes. Approximately 5% of Whites are asymptomatic carriers of the CF mutation. More than three decades have passed since the identification and cloning of the gene responsible for CF, and >2000 *CFTR* mutations have been discovered (https://www.cftr2.org). These mutations have been grouped into six major classes according to the functional consequence of the defect (**Fig. 21-1**).[8–10] However, this classification scheme is an oversimplification owing to the potential for multiple molecular defects caused by a single or combination of mutant alleles.[11] For example, the most common variant, F508del, exhibits impaired protein folding, leading to degradation within the endoplasmic reticulum consistent with a class II mutation. Administration of CFTR rescue therapies (eg, lumacaftor) allows the protein to reach the airway epithelial surface, where it exhibits a channel gating defect, consistent with a class III mutation. This complex molecular pathology is the basis for combination therapy with CFTR modulators (eg, elexacaftor, tezacaftor, and ivacaftor). In vitro models representing these complex mutations to test various combination therapies, “theratyping,” is an active area of drug discovery and development designed to identify the optimal treatment of people with rare CF mutations.

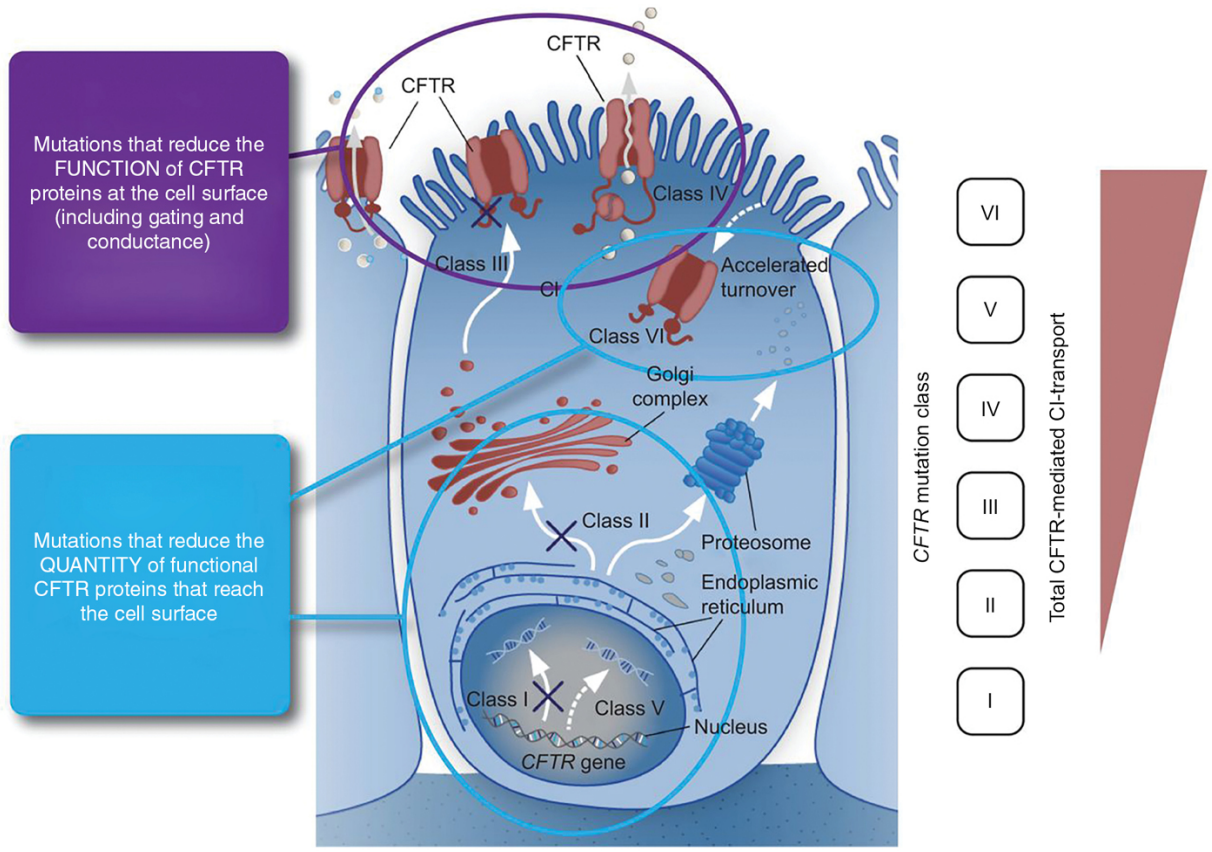


Figure 21-1 Classification of mutations. Class I mutations include those in which the production of the cystic fibrosis transmembrane regulator (CFTR) protein is blocked owing to *stop mutations.* Defective protein processing is responsible for the class II mutations. In this class, the protein is made, but it is unable to make its way from the endoplasmic reticulum to the apical membrane, where it is needed for proper operation. This includes the most common mutation, ΔF508, which is caused by improper folding of the protein. Class III mutations disrupt the channel to open properly. Class IV mutations are unable to achieve proper ion conduction. Class V is a milder form of class I mutations and includes mutations that cause reduced production of functional CFTR. Class VI mutations are characterized by a high turnover of CFTR at the cell surface. (Source: From Derichs N. Targeting a genetic defect: cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. *Eur Respir Rev.* 2013;22(127):58–65.

doi:10.1183/09059180.00008412. Reproduced with permission of the © ERS 2022.)

Interestingly, even among individuals with identical genotypes, a broad spectrum of disease severity is seen.[12,13] The contribution of genetic factors other than the misfunctioning CFTR can have a great influence on disease severity.[14]

CLINICAL MANIFESTATIONS

Genotype, environmental factors, and modifier gene status all contribute to the highly variable clinical course of CF. The linking of the loss of CFTR function to clinical manifestations of the disease, however, has been central to gaining an understanding of the disease and in the discovery of new therapies. Normally, CFTR is highly expressed on the membranes of epithelial cells of the lungs, sweat glands, salivary glands, male genital ducts, pancreas, kidney tubules, and digestive tract. The CFTR performs different functions in specific tissues; therefore, a dysfunctional or absent CFTR has different effects on different organs, resulting in multiorgan clinical manifestations of CF (**Table 21-1**).

Table 21-1
Clinical Manifestations of Cystic Fibrosis

	Approximate Incidence (%)	
Manifestation	**Children (Infants)**	**Adults**
Pancreatic		
Insufficiency	85 (80–85)	90
Pancreatitis	1–2	2–4
Abnormal glucose tolerance	38	75
Diabetes mellitus	14	40–50
Hepatobiliary		

Biliary cirrhosis	10–20	>20
Cholelithiasis	5	5–10
Biliary obstruction	1–2	5
Intestinal		
Meconium ileus	20	
Meconium ileus equivalent	1–5	10–20
Rectal prolapse	10–15	1–2
Intussusception	1–5	1–2
Gastroesophageal reflux	1–5	>10
Appendiceal abscess	0–1	1–2
Respiratory		
Nasal polyps	4–10 (<1)	15–20
Pansinusitis		90–100
Bronchiectasis	30–50	>90
Pneumothorax	1–2	10–15
Hemoptysis	5–15	50–60
Reproductive		
Delayed puberty		85
Infertility		
Males		98
Females		70–80

Sweat Glands

Fluid secreted by the sweat glands in patients with CF is normal, but a defect in the reabsorption of electrolytes leads to sweat with high salt content. CFTR, in the apical membrane of the resorptive area of the sweat gland, functions as an ion channel for chloride transport and also activates an associated epithelial sodium channel.[15] Normally, these channels efficiently reabsorb sodium chloride from sweat. In people with CF, loss of these functioning channels blocks the ability of the sweat ducts to reabsorb salt, leading to elevated

sweat sodium chloride concentrations (**Fig. 21-2**). The loss of these sodium and chloride ion channels serves as the basis for the diagnostic sweat chloride test.

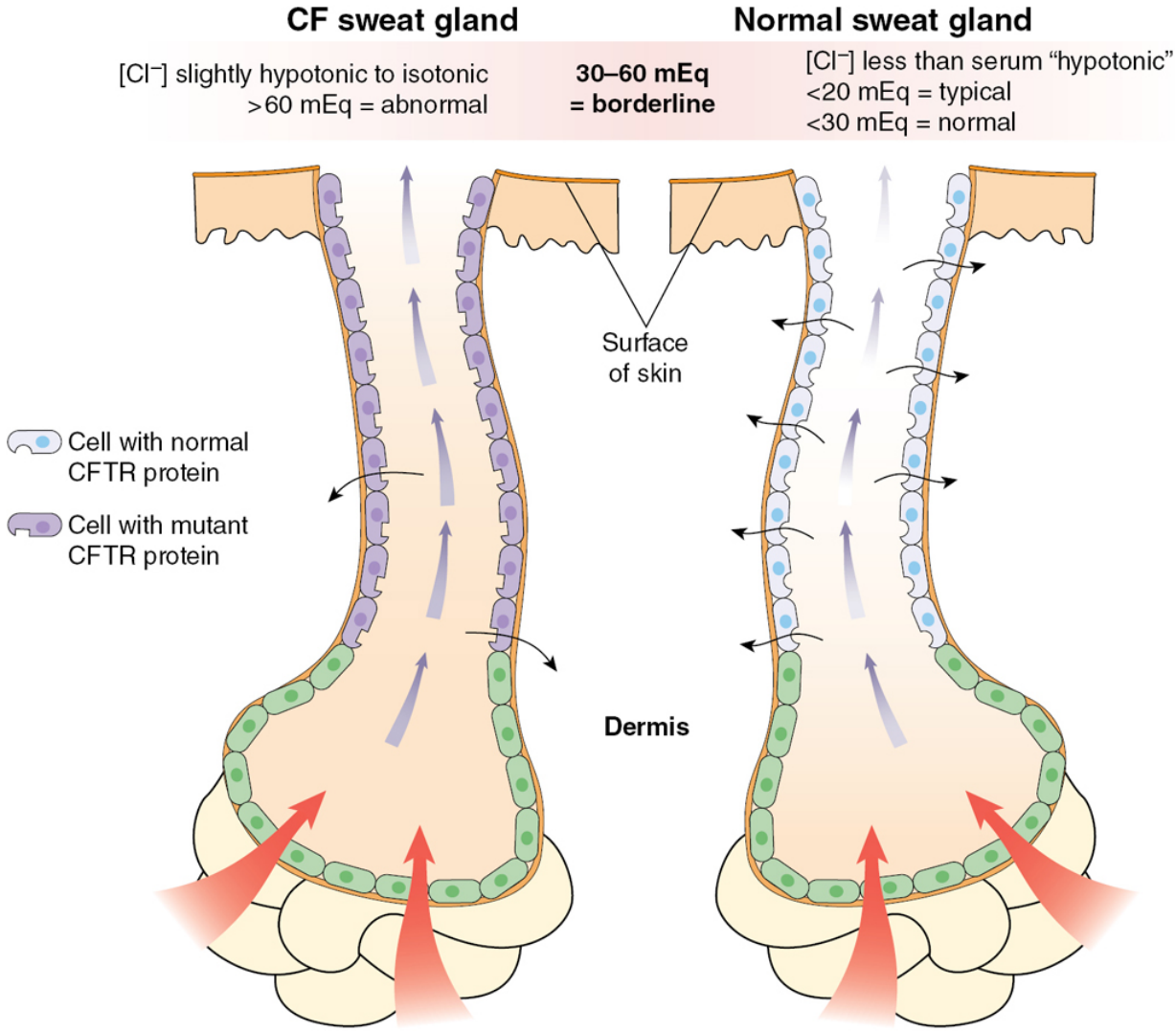


Figure 21-2 Chloride transport in sweat glands of normal and cystic fibrosis individuals. CFTR, cystic fibrosis transmembrane regulator. (Adapted with permission of American Society for Microbiology from Lyczak JB, Cannon CL, Pier GB. Lung infections associated with cystic fibrosis. *Clin Microbiol Rev*. 2002;15(2):194–222; permission conveyed through Copyright Clearance Center, Inc.)

Pancreatic Involvement

The exocrine and ultimately the endocrine functions of the pancreas are affected in CF. Pancreatic enzymes normally are secreted into bicarbonate-rich fluid from the pancreatic duct. The loss of CFTR function inhibits the secretion of digestive enzymes and bicarbonate into the duodenum, resulting in ductal obstruction. With time, these enzymes (lipase, protease, and amylase) accumulate and eventually begin to digest the pancreatic tissue.[5,16] The term *cystic fibrosis* arises from the fibrotic scar tissue that replaces the destroyed pancreas. Without these enzymes, there is poor digestion of fats and, to a lesser extent, proteins and carbohydrates. As a result, 90% of patients with CF experience pancreatic insufficiency characterized by steatorrhea (fatty stools), decreased absorption of the fat-soluble vitamins (A, D, E, and K), malnutrition, and failure to thrive. Early in life, serum concentrations of amylase and lipase are increased secondary to pancreatic autodigestion. This destructive process can result in either painful or asymptomatic chronic pancreatitis.

Eventually, the progressive destruction of the pancreas affects its endocrine function, leading to CF-related diabetes mellitus in 15% to 20% of adolescents and nearly 40% of adults ages 20 to 30 years.[17] The additional diagnosis of diabetes in CF is associated with more rapid decline in lung function and shortened survival. Early aggressive insulin therapy can result in improved clinical outcomes.

Gastrointestinal Involvement

Meconium ileus, an intestinal obstruction at birth, occurring in 20% of newborns with CF, is an inheritable trait of this disease.[18] Outside the neonatal period, distal intestinal obstruction syndrome (DIOS, also called *meconium ileus equivalent*) can occur at any age and results from the complete or partial obstruction of the intestine. Intestinal obstruction occurs in 10% to 20% of patients and results from the inspissation of intestinal secretions and incompletely digested intestinal contents. A right lower quadrant mass, abdominal distension, failure to pass stools, and vomiting can accompany DIOS.

Gastroesophageal reflux disease (GERD) is common in both children and adults with CF.[19–21] Children with CF should be screened for GERD and treated if diagnosed. Other intestinal complications include rectal prolapse, intussusception, and appendiceal abscesses.

Hepatic Involvement

Located on the apical surfaces of the cells lining the intrahepatic and extrahepatic bile ducts and the gallbladder, CFTR functions to facilitate ion transport.[22] In people with CF, the abnormal chloride efflux across the cells results in the reduction in water and sodium movement into the bile. The resulting decrease in the volume and flow of bile leads to stasis and obstruction of the biliary tree. With chronic obstruction, inflammation gives rise to the characteristic lesion of focal biliary cirrhosis.[23]

Liver disease develops in the first decade of life. Significant liver disease is seen in 13% to 25% of children with CF.[24–26] Prevalence rates may be underestimated. Progressive cirrhosis is associated with portal hypertension, hypersplenism, esophageal varices, ascites, and, in a small number of patients, complete hepatic failure requiring transplantation. Approximately 30% of adult patients with CF have abnormal gallbladder function and size (absent or small gallbladder) with 5% to 10% of patients forming gallstones.[27]

Genitourinary Involvement

Approximately 98% of male patients with CF are infertile secondary to in utero obstruction of the vas deferens or related structures. Hormonal secretion and secondary sexual characteristics are normal. In a small number of patients, infertility can be the only manifestation of disease, and CF may go undiagnosed until fertility testing is performed. The prevalence of infertility is higher in females with CF and is hypothesized to be related to the production of thick and tenacious cervical mucus.

Bone and Joint Involvement

Patients with CF have low bone mineral density, slower rate of bone formation, an accelerated rate of bone loss, and arthritis.[28,29] Osteoclastic precursors are elevated during acute pulmonary exacerbation.[30] Although early, aggressive treatment of pulmonary exacerbations can improve bone health, sufficient intake and absorption of the fat-soluble vitamins, D and K, are important, and oral bisphosphonates may also be indicated.[31]

Patients with CF often suffer from intermittent arthritis symptoms, but only about 2% of patients have persistent symptoms. The three types of intermittent CF arthritis are (a) hypertrophic osteoarthropathy, (b) immunoreactive, and (c) CF arthropathy. The first two types are associated with pulmonary disease flare-up. The third type, CF arthropathy, affects large joints and may be accompanied by fever and erythema nodosum.[32–35]

Sinus Involvement

Nasal polyps, which are outgrowths of normal sinus epidermis, can be found in up to 20% of older patients with CF and may become sufficiently large to block nasal passages. The pathogenesis of these polyps is unknown, but the obstruction of nasal passages can lead to infection. The faulty ionic transport of chloride across the apical membrane of epithelial cells lining exocrine glands leads to dehydration of extracellular fluids and the development of thickened inspissated mucus in nasal and sinus passages. Nearly all patients with CF (90%–100% of patients age >8 months) develop sinus disease. On radiographic examination, >90% of adult-age patients have pansinusitis, which can contribute to pulmonary exacerbations.[36,37] The impact of sinusitis on the CF population is significant.

Pulmonary Involvement

Respiratory disease is of major importance in patients with CF because it is the principal cause of repeated hospitalizations, decline in pulmonary function, and death. Although the exact pathophysiologic mechanisms leading from the *CFTR* cellular defect to the development of bronchiectasis and loss of pulmonary function are not completely understood, recent research in animal models and infants with CF has greatly expanded our understanding of this process.[38]

AIRWAY OBSTRUCTION, INFECTION, AND INFLAMMATION

The lower airways of a normal lung are maintained free of pathogens through various lung defense mechanisms. For example, a thin film of liquid on the airway surfaces called the *airway surface layer* (*ASL*) contains antimicrobials, antioxidants, proteases, and other substances that work to eliminate pathogens. In addition, the ASL can remove invading microbes from the lung by moving a mucous gel toward the mouth through ciliary motion. Mucociliary clearance of microbes and debris is aided by the cough reflex to keep the airways clear. Because coughing is an important defense mechanism, cough suppressants should not be used in patients with CF.

In patients with CF, the CFTR defect reduces the ASL, resulting in markedly thickened mucus and impaired mucociliary clearance. Continued mucus hypersecretion leads to mucus plugging and airway obstruction. Additionally, the CFTR defect causes acidification of the ASL secondary to reduced bicarbonate secretion, resulting in reduced host antimicrobial protein activity and increased susceptibility to infection.[39] Hypoxic gradients within the mucus lead to adaptations of *P. aeruginosa* to the anaerobic environment by increasing alginate production and the formation of biofilms. In response to infection, proinflammatory cytokines (eg, tumor necrosis factor-α, interleukin [IL] 1), chemokines (eg, IL-8), and other inflammatory mediators (eg, leukotriene B_4) are released from airway epithelial cells and alveolar macrophages, resulting in neutrophil recruitment into the airways. Recent evidence from infants with CF indicates airway inflammation may precede evidence of infection and

contribute to early lung injury.[40] As the neutrophils undergo apoptosis, they release their DNA, which accumulates and contributes to airway obstruction. In the normal host, proteases (eg, neutrophil elastase) are released in response to an infectious insult and digest the bacteria, while lung tissue is protected by the presence of antiproteases. In patients with CF, the intense neutrophilic infiltration in response to IL-8 results in an imbalance between airway proteases and antiproteases.[41] The excess proteases cause degradation of elastin, a structural component of the airways. In addition, airway proteases can degrade cell-surface receptors (eg, CXCR1 from neutrophils), leading to impaired bactericidal activity contributing to the persistence of *P. aeruginosa* within the airways despite a robust inflammatory response.[42] The chronic cycle of airway obstruction, infection, and inflammation leads to bronchiectasis, progressive loss of lung function with eventual respiratory failure, and death.

MICROBIOLOGY

The microbiology of airways in patients with CF changes as a function of age. In infants and toddlers, the principal organisms include nontypeable *Haemophilus influenzae* and *Staphylococcus aureus.* In older children and adults, *P. aeruginosa* becomes the predominant pathogen (60% of adults). Other pathogens in CF include *Achromobacter xylosoxidans, Aspergillus fumigatus, Burkholderia cepacia, nontuberculous mycobacteria, and Stenotrophomonas maltophilia.*

Pseudomonas aeruginosa

Infections with *P. aeruginosa* occur in three distinct phases. First, the patient acquires the organism and presents with initial infection. Treatment often leads to eradication; however, reinfection eventually occurs and leads to chronic infection. Under pressure from hypoxic gradients within the mucus, *P. aeruginosa* within the airways converts to the mucoid phenotype. Observational studies have noted significant structural as well as functional changes within the lung in

patients with sputum cultures that grow mucoid *P. aeruginosa* when compared with patients with nonmucoid strains or who are not infected with *P. aeruginosa.* Specifically, when compared with patients with nonmucoid *P. aeruginosa,* those with mucoid *P. aeruginosa* had significant abrupt declines in the percentage of predicted forced expiratory volume in 1 second (FEV_1).[43] The median time to acquisition of nonmucoid and mucoid strains is 1 and 13 years, respectively; however, there is tremendous variability in the initial acquisition and development of chronic infection. Patients with delayed acquisition of *P. aeruginosa* typically have minimal lung disease and few hospital admissions when compared with children who acquire *P. aeruginosa* (in particular mucoid *P. aeruginosa*) earlier in life. The relatively long period between nonmucoid and mucoid *P. aeruginosa* offers an opportunity for intervention with pharmacologic therapy (eg, inhaled and/or oral antibiotics) designed to eradicate the organism from the airways. The mucoid strains create a significant therapeutic challenge because they can develop into biofilms. A biofilm is a community of bacteria that adheres to tissues (eg, airway epithelial cells) and secretes a slimy coating (mucoid exopolysaccharide), which protects it from the hostile environment within which it resides. *P. aeruginosa* biofilms create a therapeutic challenge when compared with their planktonic (freely motile) bacterial counterparts because they evade local defense mechanisms, are slow-growing, and can sequester β-lactamase.

Methicillin-resistant *Staphylococcus aureus*

The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased dramatically in recent years and has been associated with a more rapid decline in pulmonary function and increased mortality.[44,45] A randomized controlled clinical trial of rifampin in combination with trimethoprim-sulfamethoxazole for 21 days was successful in eradicating new-onset MRSA infection in 63% of treated versus 39% of controls. In addition, treatment was associated with significant improvements in lung function and nutritional status.[46]

Burkholderia cepacia

Occasionally, infections involve atypical organisms, including *B. cepacia* (2.8%). *B. cepacia* is actually a complex consisting of several distinct species. *Burkholderia cenocepacia* is the most frequently isolated and clinically relevant species in patients with CF. *B. cepacia* is easily transmitted via inhalation or contact with a reservoir of *B. cepacia,* including other patients with CF, health care professionals, or contaminated medical instruments. Colonization with *B. cepacia* can manifest as chronic asymptomatic carriage, progressive deterioration of lung function, or fatal decline during a short interval often associated with septicemia (known as *B. cepacia* syndrome) and is associated with a 50% reduction in life expectancy.[47] *B. cepacia* is intrinsically resistant to many antibiotics, including aminoglycosides and β-lactams, which limits treatment options. Because of the adverse health outcomes and limited treatment options, chronic infection with *B. cenocepacia* is a relative contraindication to lung transplantation at many centers, emphasizing the importance of preventing the acquisition of this organism through active infection control measures.

Aspergillus fumigatus

Aspergillus species present a unique challenge in patients with CF. The presence of this organism often ignites an immunologic response characterized by an increase in serum immunoglobulin E and eosinophilic infiltration of the alveoli. This syndrome is referred to as allergic bronchopulmonary aspergillosis (ABPA). The typical symptoms of this syndrome include wheezing, shortness of breath, low-grade fever, and production of thick, brownish, or bloody sputum. This disease is not invasive; however, chronic eosinophilic infiltration can lead to bronchiectasis and lung scarring. ABPA is present in ~10% of patients with CF and accounts for 10% of acute pulmonary exacerbations. The diagnosis of ABPA can be challenging owing to the overlap in clinical features with acute pulmonary exacerbations. A consensus conference sponsored by the Cystic Fibrosis Foundation (CFF) provides guidelines for the diagnosis and

treatment of ABPA in patients with CF.[48] The minimal diagnostic criteria include clinical deterioration, elevated total serum immunoglobulin E (>500 international units/mL), positive immediate *A. fumigatus* skin test or serum immunoglobulin E antibodies, and *A. fumigatus* serum precipitins or immunoglobulin G antibodies or radiographic changes. Annual screening of serum immunoglobulin E concentrations is recommended for patients with CF age 6 years or older. Treatment of ABPA includes oral corticosteroids and azole antifungals.

DIAGNOSIS

The diagnosis of CF can be made soon after birth through newborn screening or later in life based on the presentation of symptoms. A newborn screening test based on the measurement of trypsinogen concentrations in blood is performed for early diagnosis of CF. Trypsinogen is normally produced in the pancreas and is carried to the small intestine, where it changes from an inactive proenzyme to the active enzyme trypsin, which is used in the digestion of proteins. In infants with CF, mucus can block the ducts from the pancreas into the small intestine. The mucus prevents trypsinogen from reaching the intestines, resulting in accumulation in the blood. This process can be detected and measured because immunoreactive trypsin (IRT) levels increase in the blood of the infant. The IRT testing is a screening test; confirmatory testing including a sweat chloride test and DNA analysis for CF mutations should be performed in infants with a positive IRT.[49]

When the pilocarpine iontophoresis test (ie, sweat chloride test) is conducted at a certified CF center and is positive (≥60 mM), the diagnosis of CF can be applied, a value of 40 to 59 mM indicates possible CF and should be repeated in conjunction with DNA analysis.

DNA analysis is recommended and is expected to identify 90% of CFTR mutations. The DNA analysis used for population screening is

not as sensitive at detecting CFTR mutations in non-White populations. Prenatal screening for the presence of a CF carrier state in the parents is recommended by the American College of Medical Genetics and the American College of Obstetrics and Gynecology.[50]

Symptoms Suggestive of Cystic Fibrosis

For those in whom CF may not have been detected by newborn screening, the suspicion for CF is raised by clinical symptoms. Infants born with meconium ileus, an intestinal obstruction attributable to thickened meconium, at birth are highly likely to have CF. Other clinical symptoms that require further diagnostic testing are listed in **Table 21-2**. Presence of these symptoms warrants obtaining a sweat chloride and DNA analysis.

Table 21-2
Phenotypic Features Consistent With Diagnosis of Cystic Fibrosis

Persistent colonization or infection with typical CF pathogens (eg, *Staphylococcus aureus,* nontypeable *Haemophilus influenzae, Pseudomonas aeruginosa,* and *Burkholderia cepacia*)
Chronic cough and sputum production
Persistent chest radiograph abnormalities
Airway obstruction manifested by wheezing and air trapping
Nasal polyps; radiographic or computed tomographic abnormalities of paranasal sinuses
Digital clubbing
Meconium ileus, distal intestinal obstruction syndrome, and rectal prolapse
Pancreatic insufficiency and recurrent pancreatitis
Chronic hepatic disease
Failure to thrive, hypoproteinemia and edema, and complications secondary to fat-soluble vitamin deficiency
Salt loss syndromes: acute salt depletion and chronic metabolic alkalosis

Male urogenital abnormalities resulting in obstructive azoospermia (CBAVD)

CBAVD, congenital bilateral absence of the vas deferens.

Reprinted from Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153(2):S4–S14. © 2008 Elsevier. With permission.

CASE 21-1

QUESTION 1: K.M. is a 1-week-old girl weighing 6.39 pounds (2.9 kg) who presents for routine follow-up. Her birth weight was 5.95 pounds (2.7 kg). She is growing well on breast milk every 3 hours. Areview of systems reveals no abnormalities. K.M.'s newborn screening panel has returned with an elevated IRT concentration.

What further testing is recommended to determine whether this infant has CF?

At this time, it is recommended that K.M. have a sweat chloride test and DNA analysis performed. If K.M. has a positive sweat chloride, additional testing is recommended to determine whether she has pancreatic insufficiency. The preferred testing method is fecal elastase, which is measured in a single stool sample. Fecal elastase is not degraded during intestinal transit and has been shown to correlate well with duodenal lipase, amylase, trypsin, and bicarbonate concentrations. A low value indicates the presence of pancreatic insufficiency necessitating enzyme supplementation. Although 25% of infants with CF are pancreatic sufficient at the time of diagnosis, most will become pancreatic insufficient in the first year of life.[49] For those age 8 years or older, a serum trypsinogen may be used to assess pancreatic function.

EARLY INTERVENTIONS AND THERAPY

CASE 21-1, QUESTION 2: K.M. returns to the clinic 2 weeks later. Testing has revealed a sweat chloride of 84 mM and the presence of homozygous F508del

mutations. Fecal elastase is low, and the diagnosis of pancreatic insufficiency is made. What therapy should be initiated at this time?

K.M. now meets the diagnostic criteria for CF with pancreatic insufficiency. Early nutritional therapy to ensure appropriate growth is essential as good nutritional status has been associated with improved pulmonary outcomes.[51] Patients with CF are hypermetabolic and do not absorb fats and proteins normally. Therefore, the CF diet must be high in calories, fat, and protein. It is recommended that those with CF have an energy intake of 110% to 200% of that recommended for the general population.[52] If K.M. has difficulty gaining weight, the frequency of breastfeeding may need to increase or she will need to be changed to high-calorie infant formula.

Vitamin and Mineral Supplementation

The malabsorption of fats in patients with CF with pancreatic insufficiency also results in decreased gastrointestinal absorption of the fat-soluble vitamins (A, D, E, and K). Approximately 45% of the CF population is deficient in one of these vitamins, even when pancreatic enzymes are being used appropriately.[53] The current recommendations for replacement therapy are listed in **Table 21-3**.[54] Concerns about inadequate supplementation of vitamins D and K resulting in poor bone health have arisen.[55,56] Calcium supplementation will be needed for those receiving inadequate calcium in their diet. Iron supplements might also be needed if iron-deficiency anemia occurs.

Table 21-3

Daily Recommended Doses of Fat-Soluble Vitamins for Patients With Cystic Fibrosis and Vitamin Content in Specialty Vitamin Formulations

Age	Vitamin A[a] (μg)	Vitamin E[b] (mg)	Vitamin D[c] (μg)	Vitamin K (mg)
0–12 months	450	27–33.6	10–12.5	0.3–0.5
1–3 years	1500	54–100	20–25	0.3–0.5
4–8 years	1500–3000	67–134	20–25	0.3–0.5
>8 years	3000	134–268	20–50	0.3–0.5
Chewable Vitamins				
AquaDEK	2725 (92% β-carotene)	33.6	15	0.35
Complete formulation	4800 (88% β-carotene)	134	37.5	1
Complete formulation D3000	4800 (88% β-carotene)	134	75	
Complete formulation D5000	4800 (88% β-carotene)	134	125	1
DEKAs plus	5450 (92% β-carotene)	67	50	1
Liquid Vitamins				
AquADEK (per mL)	1725 (87% β-carotene)	33.6	15	0.4
Complete formulation (per mL)	2777 (75% β-carotene)	67	37.5	1
DEKAs plus (per mL)	1727 (84% β-carotene)	33.6	18.8	0.5
Softgel Products				
Complete formulation	4800 (88% β-carotene)	134	37.5	0.8
Complete formulation minis	2400 (88% β-carotene)	67	18.75	0.5
Complete formulation D3000	4800 (88% β-carotene)	134	75	0.8
Complete formulation D5000	4800 (88% β-carotene)	134	125	0.8
DEKAs plus	5450 (92% β-carotene)	101	75	1

[a]1 international unit = 0.3 μg

[b]1 international unit = 0.67 mg

[c]1 international unit = 0.025 μg

K.M. should be started on a CF-specific liquid multivitamin preparation. Additional vitamins may be supplemented if laboratory monitoring reveals an abnormality. Additionally, K.M. should receive 1/8 teaspoon of table salt per day to account for sodium loss in sweat.[57] At age 6 months, the dose increases to 1/4 teaspoon. For bottle-fed infants, a small amount of salt is added to each feeding. For K.M., who is breastfed, the parents should attempt pumping and bottle-feeding with breast milk twice a day to add salt. If K.M. does not tolerate bottle-feeding, the salt is not supplemented, and they should ensure K.M. is not exposed to warm conditions for a prolonged time.

Enzyme Supplementation

The mainstay of treatment for pancreatic insufficiency is the exogenous replacement of pancreatic digestive enzymes. The goals of pancreatic enzyme supplementation are to (a) improve weight

gain, (b) minimize steatorrhea, and (c) eliminate abdominal cramping and bloating. Supplementation with currently available therapies does not fully restore fat absorption, and the absorption of sufficient fat-soluble vitamins continues to be problematic.[58] The digestive enzymes (lipase, protease, and amylase) are available in a mixture of approximately one part lipase to three parts protease and three parts amylase in capsules that contain enteric-coated microspheres of these enzymes. The enteric coating protects these enzymes from gastric acid. Because the breakdown of fat is the most important function of these enzymes, dosing is based on the lipase content, and the dose varies according to weight, age, dietary fat intake, and symptom severity. The initial dose for infants is 2000 to 5000 units of lipase per breastfeeding or per 120 mL of bottle-feeding. Infants eating solid food begin at a dose of 1000 units/kg/meal.[57] For children age >4 years, 500 units of lipase/kg/meal is the initial dose for enzyme supplementation.[52] A full dose is taken with meals, and half the prescribed dose is taken with snacks. Subsequent dosing adjustments are titrated to response. Lack of weight gain, smelly, greasy stools, and abdominal pain or bloating might be indicative of insufficient enzyme supplementation.[59,60]

High-strength pancreatic enzymes have been associated with colonic strictures, which are accompanied by symptoms similar to that of DIOS. Although cause and effect have not been firmly established, doses >6500 units of lipase/kg/meal have been associated with stricture formation. As a result, most recommend that the daily dose of lipase not exceed 10,000 units of lipase/kg or 2500 units of lipase/kg/meal.[52]

When patients require unusually high doses of enzyme supplements, it sometimes can be attributable to high gastric acidity. The enteric coating on the pancreatic enzyme microspheres dissolves at a pH of 5.8, and the enzymes are destroyed at a pH of 4.0. Patients with CF have longer postprandial periods when the pH is <4.0 in the bowel and also have significantly less time when the pH is >5.8. Because enzymes may be less effective when the bowel pH is very low,[61,62] adding a histamine type H_2 antagonist or a

proton-pump inhibitor to increase gastric pH might help lower the enzyme dosing requirement.[63–65]

K.M. should receive a pancreatic enzyme supplement of 2000 to 5000 units per feeding. Although K.M. is not yet eating solid food, the capsule may be opened and the contents sprinkled on a small amount (eg, a baby's spoonful) of rice cereal, baby food, or applesauce and given before each feeding. K.M.'s caregivers should ensure that no beads are left in her mouth after the feeding is complete.

Pulmonary Interventions

Although data on the benefits of airway clearance and bronchodilator therapy in infants are sparse, these interventions are recommended by the CFF.[57] Generally, albuterol may be administered before percussion and postural drainage (P&PD; see Treatment of Cystic Fibrosis Airway Disease: Mechanical Methods section) once daily in infants with CF. The frequency of treatments may be increased if symptoms become evident. Respiratory syncytial virus affects most infants and may more adversely affect those with CF. Therefore, palivizumab is recommended in those with CF age 2 years or younger.[57] K.M. should receive albuterol by nebulizer or metered-dose inhaler and spacer once daily before airway clearance. She should also receive palivizumab 15 mg/kg intramuscularly once a month during respiratory syncytial virus season.

Case 21-1, Question 3: What monitoring is recommended for K.M.?

K.M.'s head circumference, height, and weight should be plotted on standard growth charts every month for the first year. The goal is for her to have a weight-for-length status of the 50th percentile.[52] After the first year, quarterly growth evaluations are recommended. From ages 2 to 20 years, the goal for growth is to achieve at least the 50th percentile for body mass index (BMI). An experienced, knowledgeable registered dietitian should meet with the family to

help them understand the importance of appropriate nutrition and help develop a plan for K.M. Fasting blood glucose, liver function tests, albumin, serum electrolytes, complete blood count, prothrombin time, and vitamins A, D, and E levels should be determined now, at age 1 year, and at least annually. An abdominal examination should be done to determine liver and spleen size and consistency at each office visit.

Pulmonary status is monitored based on clinical symptoms, auscultation of the chest, and chest radiographs until about age 5 years, when pulmonary function testing may be performed. Oropharyngeal cultures are recommended at least quarterly to detect the presence of pathogenic bacteria.

Those with CF are at risk for CF-related diabetes, warranting annual oral glucose tolerance testing (OGTT) starting at age 10 years.[17] They are also at increased risk for osteoporosis and should be assessed annually for risk factors. Bone densitometry is recommended for all adults and starting at age 8 years in those with risk factors including low vitamin D, FEV_1 <50%, oral corticosteroid use >90 days in a year, diabetes, delayed puberty, and BMI <25th percentile.[66] K.M. currently does not have any known risk factors for osteoporosis and is too young for bone densitometry. Her risk should be reevaluated annually starting at age 8 years.

Treatment of Cystic Fibrosis Airway Disease

In addition to CFTR, modulator therapies are directed against the basic defect (see Cystic fibrosis transmembrane regulator modulator therapy section below), treatment of CF airway disease involves the use of medications and techniques to mobilize pulmonary secretions, antibiotics to manage infection, and anti-inflammatory agents to reduce airway inflammation.[67]

MUCOCILIARY CLEARANCE

Sputum in patients with CF is difficult to mobilize because pulmonary secretions are thick as a result of the CFTR defect, the large

amounts of viscous DNA from the breakdown of white blood cells, and the bacterial debris left over from chronic infections. Mechanical clearance methods, inhaled mucolytics, and airway hydration therapies can help mobilize pulmonary secretions.

Mechanical methods

Methods used to mechanically break up and mobilize mucus in the pulmonary tree include traditional hand P&PD, oscillating positive-end pressure (OPEP) with the flutter valve, high-frequency chest-wall oscillation (HFCWO), intrapulmonary percussive ventilation, and autogenic drainage (a technique of deep-breathing exercises).

See **https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Airway-Clearance/Airway-Clearance-Techniques/.**

These mechanical approaches for mobilizing mucus are about equal in efficacy, and the selection of the most appropriate one for a patient depends on the ability, motivation, preference, and resources of the patient.[68] When the traditional P&PD was compared with HFCWO and OPEP, clinical efficacy and safety were comparable, but 50% of patients preferred the HFCWO, 37% preferred OPEP, and 13% preferred P&PD.[69]

Dornase alfa

Dornase alfa is an inhaled recombinant form of human deoxyribonuclease I, which breaks up the extracellular DNA formed by apoptotic neutrophils that contributes to airway obstruction in patients with CF. The pivotal clinical trial demonstrated improvement in pulmonary function (FEV_1 5.8% vs placebo, $P < .01$) and a reduction in exacerbation frequency (28% vs placebo, $P = .04$) in patients receiving dornase alfa.[70] Based on these benefits, the use of dornase alfa is recommended in all patients age 5 years or older.[67] Consideration can be given to treating infants and toddlers as well if

their clinical symptoms support the presence of airway disease. Dornase alfa is expensive, with costs averaging about $3600/month, and the cost–benefit ratio for its use continues to be debated.[71,72] A reasonable approach is to provide a brief trial of dornase alfa (1–2 months) to determine whether there is improvement in pulmonary function, and the medication is well tolerated. A longer trial (up to 1 year) may be necessary to assess its effect on the hospitalization rate.

Dornase alfa is available in 2.5 mg vials and is administered once daily via a vented jet nebulizer or eRapid™ nebulizer system. The drug must be stored in the refrigerator and protected from light. Patients should be instructed on the proper use and maintenance of the nebulizer and compressor system. In addition, patients should be instructed not to dilute or mix dornase alfa with other drugs in the nebulizer.

Airway hydration therapies

Hypertonic Saline

Inhalation of hypertonic saline (IHS) improves mucociliary clearance.[73] Hypertonic saline rehydrates the airways through osmotic flow of water. When twice-daily inhaled normal saline was compared with 7% (hypertonic) sodium chloride, no difference was noted in the primary outcome, which was the linear rate of pulmonary function decline during the 48-week study period.[74] However, patients randomly assigned to receive IHS experienced a significant reduction in exacerbations (56% decrease vs placebo, P = .02). In two small, randomized, crossover trials, dornase alfa provided a greater improvement in lung function, albeit at a much higher financial cost than IHS ($70/month). One approach is to consider the use of IHS in patients who are intolerant or do not respond to a trial of dornase alfa. In addition, IHS should be considered as add-on therapy in patients with airway congestion despite optimal standard therapy (ie, dornase alfa and chest physiotherapy). A short-acting β_2-agonist should be given before IHS treatment because IHS has been associated with bronchospasm.[75]

IHS is available commercially, and its use is recommended to improve lung function and reduce exacerbations in all patients age 6 years or older.[67] Recent data on the efficacy of IHS in infants during the first month of life demonstrate improved lung clearance index and weight.[76]

Inhaled Mannitol

The dry powder formulation of mannitol is an inhaled hyperosmotic agent designed to increase mucus clearance. To date, a total of 784 people with CF have been enrolled to assess the safety and efficacy of inhaled mannitol.[77] Overall, results showed a small but statistically significant improvement in lung function in treated patients when compared with a placebo. The rates of pulmonary exacerbations in patients receiving inhaled mannitol were not significantly different than placebo.

Considering the modest improvement in lung function and lack of effect on pulmonary exacerbation frequency, the use of inhaled mannitol may be considered in patients who are intolerant of inhaled hypertonic saline.

The dose is 400 mg of mannitol, administered through oral inhalation of ten 40-mg hard gelatin capsules twice daily using the inhaler. Each inhaler is used for 1 week and is then discarded. Prior to treatment initiation, patients are required to undergo a tolerance test to evaluate if the treatment will cause bronchospasm.

Bronchodilation

The chronic use of inhaled β_2-agonists improves lung function in patients with bronchial hyperresponsiveness or a positive bronchodilator response and is recommended for use.[67] In addition, they may assist in airway clearance when administered before chest physiotherapy. No clear consensus exists for the use of other bronchodilators. Studies in support of inhaled anticholinergic medications for the treatment of CF also are limited, and the results have been mixed.[78]

Cystic fibrosis transmembrane regulator modulator therapy

The role of CFTR modulation is rapidly evolving and significantly impacting the quality of life and clinical outcomes for people with CF. There are currently four molecular entities utilized in various combinations and for specific CF genotypes; ivacaftor, lumacaftor, tezacaftor, and elexacaftor. Ivacaftor, a *CFTR* potentiator, improves chloride transport at the cell surface and is used in people age 4 months or older, with at least one gating (class III) or residual function (class IV or class V) defect. Ivacaftor is considered a highly effective therapy owing to the magnitude of response seen in clinical trials. A phase 3 trial in people with at least one copy of a *G551D* mutation demonstrated improvements in pulmonary function (absolute change of 10% in FEV_1), and a 55% reduction in risk for acute pulmonary exacerbations over the 48-week study period.[79]

Ivacaftor is a substrate for CYP3A and coadministration with moderate or strong inducers is not recommended. In addition, dosage adjustment is necessary when coadministered with moderate or strong inhibitors of CYP3A or when used in patients with moderate or severe hepatic disease. Monitoring of liver function tests as well as ophthalmologic examinations for potential lens opacities is recommended for all drug regimens that include ivacaftor.

Lumacaftor is a *CFTR* corrector, correcting misfolded CFTR protein so that it can be presented to the cell surface. However, that corrected CFTR protein is not fully functional without adding a *CFTR* potentiator. The combination product containing lumacaftor and ivacaftor is recommended starting at age 2 for people homozygous for the *F508del* mutation. Lumacaftor/ivacaftor has a modest effect on CF outcomes. A phase 3 study evaluating the combination of lumacaftor/ivacaftor in patients homozygous for the *F508del* mutation demonstrated some improvement in pulmonary function (absolute improvement in FEV_1 of 2.6%–4%) and a 30% to 39% reduction in the rate of pulmonary exacerbations.[80]

Tezacaftor is also a *CFTR* corrector that, when combined with ivacaftor, has a modest effect on CF outcomes. Tezacaftor/ivacaftor

combination therapy is recommended for people age 6 years or older, who are homozygous for the *F508del* mutation, and those with one *F508del* and a residual function mutation (class IV or class V). Phase 3 studies demonstrated a 6.8% absolute improvement in FEV_1 compared to placebo and a 35% reduction in the rate of pulmonary exacerbations for both the homozygous and heterozygous groups.[81,82]

Elexacaftor is also a *CFTR* corrector with a different binding site than that of tezacaftor. When combined with tezacaftor and ivacaftor, it is considered a highly effective modulator therapy. The triple combination of elexacaftor/tezacaftor/ivacaftor is recommended for people age 6 years or older with at least one *F508del* mutation. This inclusion of all people heterozygous for *F508del*, regardless of the second genotype, has made a therapy available to a larger population of people with CF, many of who were not candidates for previous *CFTR* modulator therapies. A phase 3 study comparing elexacaftor/tezacaftor/ivacaftor for people homozygous for the *F508del* mutation demonstrated a 10% absolute improvement in FEV_1 for triple therapy compared to tezacaftor/ivacaftor.[83] For people heterozygous for the *F508del* mutation who did not previously qualify for *CFTR* modulator therapy, a phase 3 study demonstrated a 13.8% absolute improvement in FEV_1 compared to placebo and a 63% reduction in pulmonary exacerbations.[84] This triple combination therapy is now approved for children aged 6 years and older by the Food and Drug Administration (FDA).

Starting *CFTR* modulator therapy early in life is anticipated to significantly impact long-term survival. Based on K.M.'s CF mutations, she will qualify for lumacaftor/ivacaftor therapy once she is 2 years old. Lumacaftor/ivacaftor is available as a granule formulation allowing for administration to young children.

CASE 21-2

Question 1: J.P. is a 12-year-old girl who was seen for a routine quarterly visit at the CF center. J.P. was diagnosed with CF at age 2 months as a result of newborn screening. Genotyping revealed she is homozygous for *F508del*. At

this visit, she has increased cough and chest congestion when compared with her visit 3 months ago. She has a history of hemoptysis but has not had an episode recently. She has had no pulmonary exacerbations in the last 12 months. Her current medications include pancreatic enzymes (~2000 units of lipase/kg/meal) with all meals, a fat-soluble vitamin supplement, two puffs of albuterol inhaler before airway clearance treatment once daily, tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg at night, dornase alfa 2.5 mg via nebulization once daily, and fluticasone 44 µg inhaler two puffs daily. She performs airway clearance using HFCWO for 30 minutes once daily and reports she is tolerating this therapy well. Microbiological cultures of her oropharyngeal tract grow *S. aureus*; she has not grown *P. aeruginosa* in the past. J.P.'s BMI is in the 60th percentile (stable from the last visit), and her lung function tests show an FEV_1 of 1.99 L (89% predicted), which is down from her baseline of 2.05 L (92% predicted). A recent chest computed tomography revealed mild bronchiectatic changes in all lobes as well as mucus plugging and air trapping.

What steps should be taken to improve J.P.'s airway clearance?

Methods of mechanical assistance to remove pulmonary secretions are all equally effective, and the decision about which device to use should be individualized. J.P. is currently using HFCWO and appears to be tolerating this well. One advantage to this treatment is the independence it provides when compared with manual percussion and drainage, which requires the assistance of another individual. It also is efficient as the patient can perform some nebulization treatments while on the therapy vest (eg, hypertonic saline).[67] This is an especially important consideration to improve adherence. The typical frequency and duration of treatment with HFCWO is 30 minutes twice daily. J.P. is currently using the therapy vest only once daily and could benefit from increasing the frequency of treatment to twice daily.

Dornase alfa improves sputum viscosity in patients with CF and provides benefits early during lung disease.[85] In the Pulmozyme Early Intervention Trial, the risk of pulmonary exacerbations was reduced by 34% in young patients with mild lung function abnormalities, and pulmonary function tests improved even in patients with close to normal pulmonary function. J.P. is currently receiving dornase alfa and should continue this therapy to improve pulmonary function and reduce the risk of pulmonary exacerbations.

Hypertonic saline (7%) twice daily should also be considered for J.P. to enhance the mucociliary clearance and improve pulmonary function. The albuterol should be increased to twice daily to provide bronchodilation to prevent potential bronchospasm from the hypertonic saline. The recommended sequence of the treatments is albuterol for bronchodilation, hypertonic saline to hydrate the airways, and dornase alfa to liquefy the mucus, followed by airway clearance therapy to clear the mucus.[67] If adherence is an issue, the hypertonic saline can be administered during airway clearance treatment.

Based on her age, J.P. can be changed to triple *CFTR* modulator therapy with elexacaftor/tezacaftor/ivacaftor. Because triple therapy is considered highly effective compared with other therapies, it is recommended to make this change. J.P. should be counseled on the potential to have increased mucus productivity during the first few days of therapy. Once changed, the liver function will need to be monitored every 3 months for the first year of therapy. Additional common adverse effects may include rash, gastrointestinal upset, and headache. Many patients experience an increase in appetite which is typically desired, but in some cases may lead to excess weight gain.

Control of Inflammation

The inflammatory response in CF airways contributes significantly to the destruction of the airways and eventual pulmonary function decline. Pharmacologic intervention to block the intense neutrophilic inflammatory response is a key strategy to reducing pulmonary disease progression. Corticosteroids, nonsteroidal anti-inflammatory drugs, and macrolides have all been used to control the inflammation seen in CF lung disease. Although leukotriene modifiers have improved lung function in small studies, the overall data are insufficient to support a recommendation for their use.[86] Cromolyn use also is not routinely recommended because of limited evidence of positive outcomes with this drug.[67]

CASE 21-2, QUESTION 2: Is J.P. a candidate for anti-inflammatory therapy?

CORTICOSTEROIDS

Oral corticosteroids are not recommended in the treatment of CF. Although prednisone 1 to 2 mg/kg every other day demonstrated a significant reduction in the decline of lung function and decreased pulmonary exacerbations in patients with *Pseudomonas* infections, long-term use was associated with unacceptable adverse effects including cataracts, glucose intolerance, osteoporosis, and persistent growth retardation.[87–89] Although inhaled corticosteroids are widely prescribed to patients with CF, there are limited data supporting their use in this population. In particular, a randomized controlled trial of withdrawal of inhaled corticosteroids demonstrated no change in pulmonary function after discontinuation; therefore, they are not recommended for routine use in patients with CF in the absence of concomitant asthma.[67,90] Fluticasone should be discontinued in J.P., and pulmonary function testing should be performed at the next clinic visit. In addition, J.P. should be questioned about wheezing or shortness of breath.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs have been used to slow lung function decline. High-dose ibuprofen (20–30 mg/kg twice daily with doses titrated to a peak concentration of 50–100 mg/L) can significantly slow the annual rate of FEV_1 decline in children ages 5 to 13 years.[91] Ibuprofen serum concentrations must be measured and monitored closely to stay in the therapeutic range because lower concentrations can paradoxically increase neutrophil infiltration. Because these doses are much higher than the recommended doses to treat pain or fever, concerns about long-term side effects, including gastrointestinal bleeding and renal toxicity, together with the need for frequent blood draws have not made this method of treatment common. For patients age 6 years or older with an FEV_1 >60% of predicted, chronic oral ibuprofen is recommended to reduce

the loss of lung function.[67] Considering J.P.'s history of hemoptysis, the use of high-dose ibuprofen is not recommended.

AZITHROMYCIN

Azithromycin is an antibiotic with anti-inflammatory properties. Although its use is established in patients with CF with chronic *P. aeruginosa* infection (see Case 21-3, Question 3), a study conducted in children and young adults who were not infected with *P. aeruginosa* demonstrated a significant reduction in exacerbation frequency (50%) and increased weight (1.27 pounds [0.58 kg]) during the 24-week study period; however, no improvement in pulmonary function was noted.[92]

Because J.P. has not experienced any pulmonary exacerbations during the past year, there would be little advantage to adding azithromycin unless she becomes infected with *P. aeruginosa*.[67]

ANTIBIOTIC THERAPY

Treatment of pulmonary infections in patients with CF has undoubtedly contributed to the improved survival observed in patients with CF in the past 30 years. Antibiotics are indicated in patients with CF for (a) early eradication of *P. aeruginosa* at the time of the first detection with the intent to prevent or delay chronic infection, (b) treatment of acute pulmonary exacerbations, and (c) chronic maintenance therapy with inhaled antibiotics to control the bacterial burden within the airways to slow the progression of pulmonary function decline.

Early eradication of *Pseudomonas aeruginosa*

CASE 21-2, QUESTION 3: J.P. returns to the clinic 6 weeks later for a follow-up visit to evaluate response to changes made at the previous visit. Subjectively, she reports less chest congestion and cough. Spirometry demonstrates her FEV_1 has returned to baseline. A throat culture is obtained and reveals *P. aeruginosa*. What additional therapies should be considered for J.P. at this time?

Because of the increased rate of pulmonary function decline and shortened survival in patients chronically infected with *P. aeruginosa*, early treatment with the goal of eradication is recommended.[67] Results of two studies guide the optimal treatment approach. The Early Inhaled Tobramycin for Eradication trial demonstrated that treatment with inhaled tobramycin 300 mg twice daily for 28 or 56 days was similar in terms of eradication at 1 month (93% vs 92%) and time to recurrence of *P. aeruginosa* (66% vs 69% culture-free at 27 months).[93] The Early *Pseudomonas* Infection Control trial demonstrated that therapy (inhaled tobramycin 300 mg twice daily for 28 days with or without ciprofloxacin twice daily for 14 days) initiated when quarterly respiratory cultures are positive for *P. aeruginosa* was not different in eradication or recurrence when compared with a similar antibiotic regimen cycled for 28 days followed by 56 days off for a period of six quarterly cycles.[94] Alternatively, results from a recent study conducted with aerosolized aztreonam 75 mg three times daily for 28 days in children age older than 6 years with CF demonstrated eradication in 89.1% at the end of treatment and 58.2% remained culture negative at 28 weeks.[95] A recent study evaluated oral azithromycin 10 mg/kg up to 500 mg three times weekly in combination with inhaled tobramycin for eradication of *P. aeruginosa* in children with CF.[96] The risk of an acute pulmonary exacerbation was reduced by 44% in patients receiving azithromycin in addition to inhaled tobramycin. Based on the results of these two studies, it would be appropriate to start J.P. on inhaled tobramycin 300 mg twice daily (or aztreonam 75 mg three times daily) in combination with oral azithromycin for 28 days. Cultures should be obtained on completion of the therapy to confirm eradication and quarterly thereafter to monitor for recurrence of *P. aeruginosa.*

Acute Pulmonary Exacerbation

Acute pulmonary exacerbations are an inevitable consequence of pulmonary disease in most patients with CF. A pulmonary

exacerbation is defined as a change in respiratory signs and symptoms from the patient's baseline that necessitates treatment with antibiotics and augmented airway clearance. Key indicators include increased cough or sputum production, decreased exercise tolerance, loss of weight or appetite, decrease in FEV_1 or forced vital capacity (FVC) by more than 10%, or onset of new or increased crackles.[97] Approximately one-third of patients experience at least one pulmonary exacerbation annually; however, the onset and frequency vary widely in the population. The frequency of exacerbations is correlated with the severity of the pulmonary disease. Traditional management for an acute CF exacerbation includes nutritional repletion, antibiotics, and chest physiotherapy.[98] For mild exacerbations, the patient can typically be managed in the outpatient setting using oral antibiotics and intensification of airway clearance and nutritional therapies. For moderate-to-severe exacerbations, patients are typically hospitalized and receive a 14-day course of intravenous (IV) antibiotics, as well as airway clearance and nutrition therapies. If the patient demonstrates a significant improvement in signs and symptoms, he or she may be a candidate to complete treatment at home before completion of the 14-day course.[99]

ANTIBIOTIC DRUG SELECTION

Antibiotic drug selection is based on sputum or throat culture and susceptibility data. Combination therapy with two antibiotics with different mechanisms of action is often prescribed for treating acute pulmonary exacerbations involving *P. aeruginosa* to prevent the development of resistance and provide potential synergistic activity. Therefore, the combination of an antipseudomonal β-lactam and an aminoglycoside or fluoroquinolone is frequently used. Results of a controlled trial comparing β-lactam monotherapy versus β-lactam plus an aminoglycoside demonstrated similar improvement in pulmonary function, but a greater reduction in bacterial density in sputum and a longer duration before readmission for a new pulmonary exacerbation in the patients receiving combination

therapy.[100] Multidrug-resistant (MDR) strains, defined as resistance to all agents within two of the three major classes of antipseudomonal therapies (eg, β-lactams, aminoglycosides, and fluoroquinolones), are reported in 15% to 20% of patients. The recent availability of ceftolozane–tazobactam and ceftazidime–avibactam provide new treatment options for infections involving MDR *P. aeruginosa*.

ANTIBIOTIC DOSING

The antibiotics used most commonly to treat acute pulmonary exacerbations and their dosage ranges are listed in **Table 21-4**. Typical dosage regimens used in other populations may not be adequate in patients with CF owing to reduced lung penetration, decreased activity in sputum, presence of bacteria within biofilms, heavy inocula, and reduced susceptibility. Altered pharmacokinetics of drugs in patients with CF is also frequently cited in the published literature. In particular, both the volume of distribution and clearance of a number of antibiotics (eg, β-lactams and aminoglycosides) are reported to be higher in patients with CF when compared with healthy control subjects. One potential explanation for the observed differences in pharmacokinetics in CF is related to differences in body composition. Patients with CF have reduced adipose tissue and lean mass owing to nutritional deficiencies. If the pharmacokinetic parameters are normalized to body weight (eg, L/kg and L/kg/hour), then the parameters would appear to exceed that of normal healthy individuals. This observation was recently demonstrated in a clinical trial evaluating the pharmacokinetics of ceftazidime in CF. The intersubject variability in pharmacokinetic parameters was significantly reduced when the parameters were normalized to fat-free mass, indicating that fat-free mass is a better metric for normalization.[101] Importantly, the authors observed that the pharmacokinetic parameters appeared higher when normalized to body weight; however, when normalized to fat-free mass, there was no significant difference.

Table 21-4
Antibiotic Doses for Cystic Fibrosis

Systemic Antibiotics			
Drug	**Pediatric Dose**	**Adult dose**	**Maximum daily dose**
Amikacin	30 mg/kg q24h	30 mg/kg q24h	TDM
Aztreonam	150 mg/kg/day divided q6–8h	2 g q6h	12 g/day
Cefepime	150 mg/kg/day divided q6–8h	2 g q6h	8 g/day
Ceftazidime	150–300 mg/kg/day divided q6–8h	2 g q6h	12 g/day
Ceftazidime–avibactam	50 mg/kg–12.5 mg/kg q8h	2.5 g infused over 2h q8h	6 g/day (ceftazidime)
Ceftolozane–tazobactam	30–40 mg/kg q8h	3 g q8h	12 g/day
Ciprofloxacin IV	30 mg/kg divided q8h	400 mg q8h	1.2 g/day
Ciprofloxacin PO	40 mg/kg divided q8–12h	750 mg q8–12h	2.25 g/day
Colistimethate	2.5–5 mg/kg/day divided q8h	2.5–5 mg/kg/day divided q8h	300 mg/day colistin base
Gentamicin	10 mg/kg q24h	10 mg/kg q24h	TDM
Imipenem	100 mg/kg/day divided q6h	1 g q6h	4 g/day
Linezolid	10 mg/kg q8h	600 mg q8–12h	600 mg q8h
Meropenem	60–120 mg/kg/day divided q8h	2 g q8h	6 g/day
Piperacillin–tazobactam	400 mg/kg/day divided q6h	4.5 g q6h	16 g/day (piperacillin)
Ticarcillin/clavulanate	400 mg/kg/day divided q6h	3.1 g q6h	18.6 g/day (ticarcillin)
Tobramycin	10 mg/kg q24h	10 mg/kg q24h	TDM
TMP/SMZ	15–20 mg/kg/day divided q8h	15–20 mg/kg/day divided q8h	800 mg/day
Vancomycin	15–20 mg/kg q6h	15–20 mg/kg q8–12h	TDM
Inhaled Antibiotics			
Drug	**Dosage (mg)**	**Interval**	**Comments**
Aztreonam	75	tid	28 days on, 28 days off
Tobramycin nebulized	300	bid	28 days on, 28 days off
Tobramycin Podhaler	112 (four 28-mg capsules)	bid	28 days on, 28 days off
Colistin	37.5–75	bid	28 days on, 28 days off

bid, twice daily; TDM, therapeutic drug monitoring (gentamicin/tobramycin desired maximal concentration is 25–35 mg/L, AUC_{24h} = 70–100 mg/L × h; once-daily dosing); tid, three times daily; TMP/SMZ, trimethoprim/sulfamethoxazole.

Adapted from Zobell JT, Young DC, Waters C, et al. Optimization of anti-pseudomonal antibiotics for cystic fibrosis pulmonary exacerbations: VI. Executive summary. *Pediatr Pulmonol*. 2013;48(6):525–537. © 2013 Wiley Periodicals, Inc. Reprinted by permission of John Wiley & Sons, Inc.

β-Lactam antibiotics can be administered as an intermittent, prolonged, or continuous infusion. Prolonged or continuous infusions are designed to maximize the time the concentrations exceed the minimum inhibitory concentration.[101] This is particularly important in patients with CF because of the rapid clearance (excellent renal function) and reduced susceptibility of the organisms within the airways.[102]

Extended-interval dosing of aminoglycosides (every 24 hours compared with every 8 hours) is easier and less costly to administer and potentially limits toxicity. A randomized clinical trial in children and adults with CF (*N* = 244) demonstrated equivalent efficacy as evidenced by a change in FEV_1 in ~10% in patients receiving tobramycin 10 mg/kg/day either as a single dose or in three divided doses. However, the once-daily regimen provided improved renal safety in children as evidenced by serum creatinine and urinary *N*-acetyl-β-D-glucosaminidase, a biomarker of renal proximal tubular injury.[103] An evidence-based review conducted by the CFF concluded that once-daily dosing of aminoglycosides is preferable to three times-daily dosing for treatment of an acute exacerbation of the pulmonary disease.[99]

Routine monitoring of serum aminoglycoside concentrations is recommended to maximize efficacy and minimize the risk of toxicity. Because many patients with CF receive multiple courses of aminoglycosides, sometimes for extended durations, they are particularly predisposed to the toxicities. With once-daily dosing, the trough concentrations are expected to be unmeasurable by design (eg, dosing interval exceeds 5 half-lives). Therefore, serum concentrations are typically obtained between 1 to 2 and 6 to 8 hours after the end of the infusion. The two levels can then be used to determine the extrapolated peak concentration (target 20–30 mg/L) and the area under the serum concentration–time curve (target 72–100 mg/L × hour).[104]

CASE 21-3

QUESTION 1: B.W., a 19-year-old male, was diagnosed with CF at age 3 years after a history of chronic pneumonias. His CFTR genotype is *F508del/R117H*. He presents to the pulmonary clinic with increasing cough and sputum production during the past 2 weeks, with a change in sputum color from white to green. He was last admitted for treatment of an acute pulmonary exacerbation 6 months ago. He currently weighs 99.64 pounds (45.2 kg) and states he has lost 4 pounds (1.81 kg). B.W. is a slightly thin adult male whose breathing is labored. Pulmonary function tests reveal an FEV_1 of 75% of predicted and an FVC of 70% (his usual baselines are FEV_1, 85%, and FVC, 80%). *P. aeruginosa*

grew out of his sputum sample taken at the clinic 4 weeks ago and demonstrated susceptibility to ceftazidime, piperacillin, imipenem, tobramycin, and colistin and intermediate susceptibility to ciprofloxacin. Other pertinent laboratory findings are as follows:

White blood cell count, 17,000/μL, with 4% bands, 35% segmented neutrophils, 50% lymphocytes, and 11% eosinophils
Blood urea nitrogen (BUN), 7 mg/dL
Creatinine, 0.5 mg/dL

All other blood work, liver function tests, and electrolytes are within normal limits. Heart rate and blood pressure are normal. Temperature is 99.2 °F (37.33 °C), respiratory rate is 25 breaths/minute with an oxygen saturation of 95%. A number of new pulmonary infiltrates are seen on chest radiograph. His current medications include the following: one fat-soluble vitamin twice daily, two microencapsulated pancreatic enzyme capsules (16,000 units of lipase/capsule) with meals, and one or two capsules with snacks as needed, dornase alfa 2.5 mg nebulized daily, and elexacaftor 100 mg, tezacaftor 50 mg, ivacaftor 75 mg two tablets in the morning and ivacaftor 150 mg in the evening.

What subjective and objective findings does B.W. exhibit that would lead to the diagnosis of a pulmonary exacerbation?

B.W. demonstrates an increase in sputum production (purulent), increased cough, dyspnea, weight loss, and a 10% decline in pulmonary function tests from baseline. B.W. also has a mild fever and elevated white blood cell count; however, an increase in white blood cell count, fever, or appearance of a new infiltrate on chest radiograph may or may not be present in all cases of pulmonary exacerbations.

Case 21-3, Question 2: B.W. is admitted to the hospital for treatment of an acute pulmonary exacerbation. What would be an appropriate antimicrobial treatment plan for B.W. based on his current laboratory data?

Based on these findings and the in vitro susceptibility results, it would be reasonable to initiate a regimen of ceftazidime or piperacillin–tazobactam in combination with tobramycin. Ciprofloxacin is not optimal in this instance because of reduced susceptibility. Imipenem and colistin are typically reserved for the treatment of resistant *P. aeruginosa* infections.

Ceftazidime 2 g IV every 6 hours could be administered to B.W. by intermittent, 3-hour prolonged infusion, or a 2-g loading dose administered for 30 minutes followed by 6 g as a continuous infusion. Data from a large randomized trial demonstrated similar efficacy and safety between intermittent and continuous infusion ceftazidime in patients with CF; however, the continuous infusion treatment was associated with greater improvement in pulmonary function in those infected with resistant strains. In addition, continuous infusion resulted in a significantly prolonged interval between exacerbations.[102]

In B.W., the preferred initial dosing regimen of IV tobramycin would be 440 mg (10 mg/kg) every 24 hours. Target peak concentrations of 20 to 30 mg/L should be verified after the first or second dose. Target area under the concentration–time curve should be 72 to 100 mg/L × hour. Tobramycin concentrations should be measured at least every 7 days while B.W. is on therapy. In addition, serum concentrations of BUN and creatinine should be measured three times weekly for early detection of acute kidney injury.

The antibiotics should be administered for 2 weeks. After the initiation of antibiotics in this hospitalization, home IV antibiotic therapy should be a consideration for B.W.[105] The decision as to whether a patient is a good candidate for home IV antibiotic therapy is based on initial response as well as the expected level of support provided to the patient at home. In particular, the ability of the patient to maintain nutritional and intensive airway clearance programs established in the hospital needs to be assessed. The duration of B.W.'s antibiotic therapy should be based on his clinical response. Ideally, his pulmonary function (eg, FEV_1) should improve by 10% to 20% and should be evaluated weekly. The purulent nature and volume of the sputum should decrease, and a gradual overall improvement in subjective feeling should be noted. Improved appetite and increased weight gain should be assessed daily to reach baseline weight (increase of 1–2 kg/week). For patients receiving repeated courses of IV aminoglycosides, periodic audiometric testing is recommended.

CHRONIC MAINTENANCE THERAPY WITH ORAL OR INHALED ANTIBIOTICS

Recognition of the progressive decline in pulmonary function despite aggressive treatment of acute exacerbations and the availability of oral and inhaled therapies with activity against typical CF pathogens have led to increased use of chronic maintenance antibiotic therapy. The goal of chronic maintenance therapy is to suppress bacterial infection to reduce the frequency and severity of pulmonary exacerbations and to slow the progressive deterioration in lung function. Inhaled antibiotics include tobramycin, aztreonam, and colistimethate. Inhaled antibiotics are desirable because of the relatively high sputum concentrations and low systemic bioavailability, which maximizes efficacy and minimizes toxicity.

Tobramycin for inhalation

Results of phase 3 studies of inhaled tobramycin conducted during a 6-month interval demonstrated significant improvement in pulmonary function (relative difference in FEV_1 of 10%), a reduction in the risk of hospitalization (37%), and a reduced need for IV antipseudomonal antibiotics (32%).[106] A significantly greater proportion of patients in the treatment arm reported hoarseness; however, this did not require discontinuation and improved with time. In addition, some patients report a bitter taste to this preparation; however, this typically does not result in discontinuation of the medication. The recommended dosage of tobramycin nebulizer solution is 300 mg twice daily in a cycle of 28 days on and 28 days off. Tobramycin for inhalation is provided as a premixed solution contained in unit dose vials and requires refrigeration before use. Tobramycin for inhalation is administered via a vented jet nebulizer system (Pari LC Plus) to ensure consistent particle size and outflow characteristics. Based on the results of the phase 3 studies, inhaled tobramycin is indicated in patients age older than 6 years with repeated sputum cultures demonstrating *P. aeruginosa* and FEV_1 between 25% and 75% of predicted.[67] A dry powder formulation of tobramycin for inhalation (TOBI® podhaler®) also exists, which offers the advantages of

shortened administration time, no need for refrigeration, and easy portability. TOBI® podhaler® is provided in 28-mg capsules and is administered as four capsules twice daily in a cycle of 28 days on and 28 days off. Several retrospective analyses have demonstrated a potential drug interaction between tobramycin and azithromycin. In particular, a retrospective cohort study using the CFF registry data found that patients receiving inhaled aztreonam and azithromycin experienced a slower rate of lung function decline when compared with matched controls receiving inhaled tobramycin and azithromycin.[107] Potential issues with selection bias preclude the determination of a direct cause and effect relationship. A prospective controlled trial (https://clinicaltrials.gov/ct2/show/NCT02677701) is currently being conducted and is expected to provide definitive evidence of the significance of this potential drug interaction.

Aztreonam lysine solution for inhalation

Two phase 3 trials evaluated the short-term safety and efficacy of aztreonam lysine solution for inhalation.[106,108] The results of these trials demonstrated a significant improvement in respiratory symptoms assessed using a patient-reported outcome instrument, and a significant delay in the need for inhaled or IV antipseudomonal antibiotics is determined by the presence of pulmonary exacerbation symptoms. The most common adverse effects are cough and wheezing. Bronchodilator use is recommended before each dose to reduce these symptoms. The recommended dosage of aztreonam lysine is 75 mg three times daily for 28 days. Aztreonam is provided in a powder form that requires reconstitution with saline before administration. Aztreonam requires refrigeration before use. A special nebulizer device is required for administration (Altera), which delivers the drug in a relatively short time (eg, 2–3 minutes). Based on the results of these studies, aztreonam lysine is indicated in patients age 6 years or older with *P. aeruginosa* to improve respiratory symptoms. Aztreonam is particularly useful in patients who are intolerant of inhaled tobramycin or as add-on therapy in

those with frequent exacerbations or continued decline in pulmonary function.

Colistimethate

Colistimethate is a prodrug of colistin, an antibiotic in the polymyxin family. Colistimethate is available only in an IV powder formulation in the United States and requires reconstitution before nebulization. Clinical trials evaluating the safety and efficacy of colistimethate in CF are limited by the small number of patients enrolled in the trials. Based on the lack of data, colistimethate is not recommended for routine use.[67] Colistimethate may be useful in patients infected with MDR *P. aeruginosa* or those intolerant to other inhaled antibiotics. Adverse effects associated with inhaled colistimethate include cough and bronchospasm. Bronchodilators should be used before each dose. In addition, colistimethate tends to foam on nebulization, resulting in incomplete drug administration. The typical dose of colistimethate is 75 mg twice daily.

The cost of inhaled antibiotics is relatively high (tobramycin solution for inhalation $3800/month, https://www.drugs.com/price-guide/tobi); aztreonam lysine solution for inhalation $4900/month, https://www.drugs.com/price-guide/cayston; however, use of inhaled antibiotics reduces hospital days, leading to substantial savings in direct medical costs that may offset its acquisition price. The cost-effectiveness of inhaled antibiotics would be expected to be greatest in patients experiencing relatively frequent exacerbations (two or more hospital admissions per year). A short-term trial (eg, 1–2 months) is warranted in patients with CF chronically colonized with *P. aeruginosa* to assess improvement in pulmonary function. A longer trial period (eg, up to 1 year) may be necessary to assess the impact on hospitalizations. Patients should be instructed in the proper use and maintenance of the nebulizer and compressor system used in its delivery. In particular, it is important to wash reusable nebulizers between uses to avoid the buildup that can reduce their effectiveness. The nebulizers can be hand washed with liquid dish soap or placed in the top rack of a dishwasher for cleaning. After

each cleaning, the nebulizer should be allowed to dry before reusing to reduce bacterial contamination. Regular sterilization is required to reduce the potential for bacterial contamination. In addition, the patient should be instructed not to dilute or mix antibiotic solutions with other drugs in the nebulizer, which can alter the delivery characteristics. Inhaled antibiotics are typically administered after the bronchodilator, dornase alfa, and airway clearance therapies to maximize retention time within the airways.

Azithromycin

Oral azithromycin is frequently prescribed to patients with CF owing to its anti-inflammatory and antivirulence properties. The macrolide antibiotics do not exhibit significant antibacterial activity against *P. aeruginosa* using conventional susceptibility testing methods; however, they do inhibit alginate production, the principal component of biofilms. Because of its favorable pharmacokinetics and reduced potential for drug interactions, most studies have evaluated azithromycin. Results of a multicenter randomized controlled trial demonstrated treatment with azithromycin was associated with a significant improvement in FEV_1 (6%) and a reduction in hospitalizations for acute pulmonary exacerbations (44%).[109] The beneficial effect of azithromycin on pulmonary function was additive with other chronic therapies such as aerosolized tobramycin and dornase alfa. Azithromycin is generally well tolerated. Nausea, vomiting, and wheezing are the most common adverse effects reported. Based on current data, azithromycin is indicated in patients older than 6 years who are colonized with *P. aeruginosa.*[95] Based on the pivotal trial, the dose of azithromycin is 500 mg three times/week for patients weighing >88.18 pounds (40 kg) and 250 mg three times weekly for patients weighing <88.18 pounds (40 kg). One contraindication to treatment with azithromycin is colonization with mycobacteria because of the potential for the development of resistance.

Case 21-3, Question 3: B.W. comes to the outpatient clinic 2 weeks after hospital discharge for a follow-up visit and reports a significant reduction in cough and sputum production, and no shortness of breath. Spirometry reveals an FEV_1 of 85% of predicted. He has resumed his outpatient treatment regimen, which includes one multiple vitamin every day, two microencapsulated pancreatic enzyme capsules (16,000 units of lipase/capsule) with meals, and one or two capsules with snacks as needed, dornase alfa 2.5 mg nebulized daily, and elexacaftor 100 mg, tezacaftor 50 mg, ivacaftor 75 mg two tablets in the morning, and ivacaftor 150 mg in the evening. What changes, if any, should be made to B.W.'s treatment regimen?

Because B.W. has had two exacerbations in the last 6 months, he would benefit from the addition of medications to reduce the frequency of exacerbations. In addition to the disruption to his life, frequent exacerbations are associated with a more rapid decline in pulmonary function and reduced survival.[110] Key pharmacologic therapies demonstrated to improve pulmonary function and reduce the frequency of pulmonary exacerbations include dornase alfa, inhaled tobramycin or aztreonam, IHS, and azithromycin. B.W. is already receiving dornase alfa but is not on inhaled tobramycin or aztreonam, IHS, or azithromycin. One important consideration when adding new therapies is the treatment burden, particularly with inhaled therapies. Inhaled tobramycin 112 mg twice daily via the podhaler cycled for 28 days on and 28 days off and oral azithromycin 500 mg every Monday, Wednesday, and Friday would be appropriate additions to the treatment regimen because B.W. is chronically infected with *P. aeruginosa,* and these particular agents demonstrated the greatest improvement in pulmonary function when compared with IHS. In addition, azithromycin has a minimal effect on treatment burden as it can be administered orally 3 days a week. IHS would also be of benefit by reducing exacerbation frequency; however, it could be added in the future if B.W. demonstrates a decline in pulmonary function or increased frequency of exacerbations despite the new additions.

Oral antibiotics

Case 21-3, Question 4: One year later, B.W. returns to the clinic exhibiting signs and symptoms of a mild exacerbation but refuses IV antibiotics or hospitalization, because he is in the middle of final examinations. What alternative to IV therapy is available to treat B.W.?

The quinolone family of antibiotics is currently the only option for oral treatment of *P. aeruginosa.* Emergence of resistant strains of *Staphylococcus* and *Pseudomonas* species has led the CF medical community to restrict the use of quinolones in the treatment of acute CF exacerbations.[111,112] Oral fluoroquinolones (eg, ciprofloxacin) have become widely used in patients with CF because they are less expensive, easy to administer, and as effective as IV therapy in an acute exacerbation.[113,114]

Because of the past sensitivities of B.W.'s organisms and his refusal to be admitted to the hospital, ciprofloxacin 1000 mg orally twice daily for 1 week can be initiated in addition to the aerosolized tobramycin and oral azithromycin.[115] After 1 week of the combined aerosol and oral therapies, B.W. should be reevaluated for hospital admission if his condition worsens, or his therapy can be continued if his condition improves.

Case 21-3, Question 5: B.W. returns to the outpatient clinic 3 months later for his annual comprehensive visit. Results of laboratory studies, dual-emission X-ray absorptiometry (DXA) scan, spirometry, and an OGTT are as follows:

BUN, 10 mg/dL
Creatinine, 0.6 mg/dL
Urine microalbumin/creatinine, 12 µg/mg
2-hour OGTT plasma glucose, 220 mg/dL
Glycosylated hemoglobin, 7.8%
DXA Z-score, –2.1 (pelvis)
FEV_1, 83% of predicted

How should these laboratory studies be interpreted and what new therapies would you recommend?

The elevated 2-hour OGTT plasma glucose indicates B.W. has CF-related diabetes mellitus. This is confirmed by the elevated

glycosylated hemoglobin. The urine microalbumin testing indicates that B.W. is not spilling protein into the urine as a result of the CF-related diabetes mellitus. Treatment with insulin should be initiated in B.W. to improve nutritional status and prevent microvascular complications. The DXA scan results indicate B.W. has osteopenia and should be initiated on calcium 500 mg orally twice daily, and his vitamin D status should be determined. Treatment of osteopenia is recommended to prevent progression to osteoporosis, which would put the patient at risk for fractures. In addition, osteoporosis is a relative contraindication for lung transplantation because of the risk for fractures after transplantation that may impair adequate recovery.

B.W.'s spirometry results indicate that his pulmonary function is stable, and his current pharmacotherapeutic regimen should be continued.

CASE 21-3, QUESTION 6: During his clinic visit, B.W. is noted to have oral thrush and is prescribed fluconazole 200 mg on the first day and 100 mg daily for a 14-day treatment course. Are any adjustments needed to B.W.'s treatment regimen with the addition of fluconazole?

Fluconazole is a moderate CYP3A inhibitor and therefore would be expected to reduce the metabolism of elexacaftor, tezacaftor, and especially ivacaftor. The dose should be reduced to two elexacaftor/tezacaftor/ivacaftor tablets and one ivacaftor tablet on alternate days when coadministered with fluconazole. The evening dose of ivacaftor should not be taken.

LUNG TRANSPLANTATION

Pulmonary disease progression leading to eventual respiratory failure is an inevitable consequence of the chronic cycle of airway obstruction, infection, and inflammation. End-stage lung disease (defined by an FEV_1 of <30% of predicted) significantly affects the quality of life for patients with CF as a result of reduced exercise

tolerance, heavy treatment burden, need for oxygen therapy, and frequent hospitalizations for pulmonary exacerbations. Lung transplantation is a potential therapeutic option for CF patients with end-stage lung disease.[116] The optimal time to refer a patient for lung transplantation is not precisely defined; however, patients are typically referred when their FEV_1 is ~40% to maximize the chances of obtaining new lungs before the patient experiences respiratory failure. Transplant evaluation includes assessments of pulmonary disease severity, patient adherence to therapies, and concomitant illnesses. Once accepted into the program, the patient is placed on the transplant list awaiting the availability of potential organs. The waiting time to receive a lung transplant is highly variable and depends on the Lung Allocation Score, a score that distributes organs based on model-predicted benefit from transplantation. The mean survival after lung transplantation is ~50% at 5 years. Importantly, the quality of life for many lung transplant recipients improves significantly.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187:680–689.

Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H.. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc*. 2008;108:832–839. doi:10.1016/j.jada.2008.02.020 (52)

Key Websites

Clinical and Functional Translation of CFTR. https://cftr2.org

Cystic Fibrosis Foundation. Drug Development Pipeline. https://www.cff.org/trials/pipeline

Johns Hopkins Cystic Fibrosis Center. https://hopkinscf.org/knowledge/cftr/

COMPLETE REFERENCES CHAPTER 21 CYSTIC FIBROSIS

1. Cystic Fibrosis Foundation. Patient Registry 2020 Annual Data Report. Bethesda, MD. https://www.cff.org/medical-professionals/patient-registry
2. Welsh MJ. Abnormal regulation of ion channels in cystic fibrosis epithelia. *FASEB J.* 1990;4:2718–2725.
3. Ballard ST, Trout L, Bebok Z, Sorscher EJ, Crews A. CFTR involvement in chloride, bicarbonate, and liquid secretion by airway submucosal glands. *Am J Physiol.* 1999;277(4 Pt 1):L694–L699.
4. Boucher RC, Stutts MJ, Knowles MR, Cantley L, Gatzy JT. Na+ transport in cystic fibrosis respiratory epithelia. Abnormal basal rate and response to adenylate cyclase activation. *J Clin Invest.* 1986;78(5):1245–1252. doi:10.1172/jci112708
5. Lee MG, Choi JY, Luo X, Strickland E, Thomas PJ, Muallem S. Cystic fibrosis transmembrane conductance regulator regulates luminal Cl-/HCO3- exchange in mouse submandibular and pancreatic ducts. *J Biol Chem.* 1999;274:14670–14677.
6. Schwiebert EM, Benos DJ, Egan ME, Stutts MJ, Guggino WB. CFTR is a conductance regulator as well as a chloride channel. *Physiol Rev.* 1999;79(Suppl):S145–S166.
7. Smith JJ, Welsh MJ. cAMP stimulates bicarbonate secretion across normal, but not cystic fibrosis airway epithelia. *J Clin Invest.* 1992;89:1148–1153.
8. Derichs N. Targeting a genetic defect: cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. *Eur Respir Rev.* 2013;22(127):58–65. doi:10.1183/09059180.00008412
9. Welsh MJ, Ramsey BW. Research on cystic fibrosis: a journey from the Heart House. *Am J Respir Crit Care Med.* 1998;157(Pt 2):S148–S154.
10. Zielenski J, Tsui LC. Cystic fibrosis: genotypic and phenotypic variations. *Annu Rev Genet.* 1995;29:777–807.
11. Veit G, Avramescu RG, Chiang AN, et al. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. *Mol Biol Cell.* 2016;27(3):424–433. doi:10.1091/mbc.E14-04-0935

12. Kerem E, Corey M, Kerem BS, et al. The relation between genotype and phenotype in cystic fibrosis: analysis of the most common mutation (delta F508). *N Engl J Med.* 1990;323:1517–1522.
13. Zielenski J. Genotype and phenotype in cystic fibrosis. *Respiration.* 2000;67:117–133.
14. Drumm ML, Konstan MW, Schluchter MD, et al. Genetic modifiers of lung disease in cystic fibrosis. *N Engl J Med.* 2005;353(14):1443–1453. doi:10.1056/NEJMoa051469
15. Reddy MM, Light MJ, Quinton PM. Activation of the epithelial Na+ channel (ENaC) requires CFTR Cl–channel function. *Nature.* 1999;402:301–304.
16. Sohma Y, Gray MA, Imai Y, Argent BE. HCO3-transport in a mathematical model of the pancreatic ductal epithelium. *J Membr Biol.* 2000;176:77–100.
17. Moran A, Pillay K, Becker DJ, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes.* 2014;(15 suppl 20):65–76. doi:10.1111/pedi.12178
18. Blackman SM, Deering-Brose R, McWilliams R, et al. Relative contribution of genetic and nongenetic modifiers to intestinal obstruction in cystic fibrosis. *Gastroenterology.* 2006;131(4):1030–1039. doi:10.1053/j.gastro.2006.07.016.
19. Brodzicki J, Trawinska-Bartnicka M, Korzon M. Frequency, consequences and pharmacological treatment of gastroesophageal reflux in children with cystic fibrosis. *Med Sci Monit.* 2002;8(7):CR529–CR537.
20. Heine RG, Button BM, Olinsky A, Phelan PD, Catto-Smith AG. Gastro-oesophageal reflux in infants under 6 months with cystic fibrosis. *Arch Dis Child.* 1998;78:44–48.
21. Ledson MJ, Tran J, Walshaw MJ. Prevalence and mechanisms of gastro-oesophageal reflux in adult cystic fibrosis patients. *J R Soc Med.* 1998;91:7–9.
22. Cohn JA, Strong TV, Picciotto MR, Nairn AC, Collins FS, Fitz JG. Localization of the cystic fibrosis transmembrane conductance regulator in human bile duct epithelial cells. *Gastroenterology.* 1993;105(6):1857–1864.
23. Kopelman H. Cystic fibrosis. 6. Gastrointestinal and nutritional aspects. *Thorax.* 1991;46:261–267.
24. Akata D, Akhan O. Liver manifestations of cystic fibrosis. *Eur J Radiol.* 2007;61(1):11–17. doi:10.1016/j.ejrad.2006.11.008.
25. Colombo C, Apostolo MG, Ferrari M, et al. Analysis of risk factors for the development of liver disease associated with cystic fibrosis. *J Pediatr.* 1994;124(3):393–399.
26. Gaskin KJ, Waters DL, Howman-Giles R, et al. Liver disease and common-bile-duct stenosis in cystic fibrosis. *N Engl J Med.* 1988;318:340–346.
27. Sokol RJ, Durie PR. Recommendations for management of liver and biliary tract disease in cystic fibrosis. Cystic Fibrosis Foundation Hepatobiliary

Disease Consensus Group. *J Pediatr Gastroenterol Nutr.* 1999;28:S1–S13.
28. Elkin SL, Vedi S, Bord S, Garrahan NJ, Hodson ME, Compston JE. Histomorphometric analysis of bone biopsies from the iliac crest of adults with cystic fibrosis. *Am J Respir Crit Care Med.* 2002;166(11):1470–1474. doi:10.1164/rccm.200206-578OC.
29. Haworth CS, Selby PL, Horrocks AW, Mawer EB, Adams JE, Webb AK. A prospective study of change in bone mineral density over one year in adults with cystic fibrosis. *Thorax.* 2002;57:719–723.
30. Shead EF, Haworth CS, Gunn E, Bilton D, Scott MA, Compston JE. Osteoclastogenesis during infective exacerbations in patients with cystic fibrosis. *Am J Respir Crit Care Med.* 2006;174:306–311.
31. Haworth CS. Impact of cystic fibrosis on bone health. *Curr Opin Pulm Med.* 2010;16(6):616–622. doi:10.1097/MCP.0b013e32833e2e94
32. Dixey J, Redington AN, Butler RC, et al. The arthropathy of cystic fibrosis. *Ann Rheum Dis.* 1988;47(3):218–223.
33. Newman AJ, Ansell BM. Episodic arthritis in children with cystic fibrosis. *J Pediatr.* 1979;94:594–596.
34. Phillips BM, David TJ. Pathogenesis and management of arthropathy in cystic fibrosis. *J R Soc Med.* 1986;79(suppl 12):44–50.
35. Rush PJ, Shore A, Coblentz C, Wilmot D, Corey M, Levison H. The musculoskeletal manifestations of cystic fibrosis. *Semin Arthritis Rheum.* 1986;15:213–225.
36. Ramsey B, Richardson MA. Impact of sinusitis in cystic fibrosis. *J Allergy Clin Immunol.* 1992;90(Pt 2):547–552.
37. Umetsu DT, Moss RB, Lewiston NJ, King VV. Sinus disease in patients with severe cystic fibrosis: relation to pulmonary exacerbation. *Lancet.* 1990;335:1077–1078.
38. Mall MA, Hartl D. CFTR: cystic fibrosis and beyond. *Eur Respir J.* 2014;44(4):1042–1054. doi:10.1183/09031936.00228013.
39. Pezzulo AA, Tang XX, Hoegger MJ, et al. Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung. *Nature.* 2012;487(7405):109–113. doi:10.1038/nature11130
40. Rosenow T, Mok LC, Turkovic L, et al. The cumulative effect of inflammation and infection on structural lung disease in early cystic fibrosis. *Eur Respir J.* 2019;54(1):1801771. doi:10.1183/13993003.01771-2018
41. Griese M, Kappler M, Gaggar A, Hartl D. Inhibition of airway proteases in cystic fibrosis lung disease. *Eur Respir J.* 2008;32(3):783–795. doi:10.1183/09031936.00146807
42. Hartl D, Latzin P, Hordijk P, et al. Cleavage of CXCR1 on neutrophils disables bacterial killing in cystic fibrosis lung disease. *Nat Med.* 2007;13(12):1423–1430. doi:10.1038/nm1690
43. Li Z, Kosorok MR, Farrell PM, et al. Longitudinal development of mucoid Pseudomonas aeruginosa infection and lung disease progression in children

with cystic fibrosis. *JAMA.* 2005;293(5):581–588. doi:10.1001/jama.293.5.581

44. Dasenbrook EC, Checkley W, Merlo CA, Konstan MW, Lechtzin N, Boyle MP. Association between respiratory tract methicillin-resistant *Staphylococcus aureus* and survival in cystic fibrosis. *JAMA.* 2010;303(23):2386–2392. doi:10.1001/jama.2010.791
45. Dasenbrook EC, Merlo CA, Diener-West M, Lechtzin N, Boyle MP. Persistent methicillin-resistant *Staphylococcus aureus* and rate of FEV1 decline in cystic fibrosis. *Am J Respir Crit Care Med.* 2008;178(8):814–821. doi:10.1164/rccm.200802-327OC
46. Dolce D, Neri S, Grisotto L, et al. Methicillin-resistant *Staphylococcus aureus* eradication in cystic fibrosis patients: a randomized multicenter study. *PloS One.* 2019;14(3):e0213497. doi:10.1371/journal.pone.0213497
47. Courtney JM, Dunbar KE, McDowell A, et al. Clinical outcome of *Burkholderia cepacia* complex infection in cystic fibrosis adults. *J Cyst Fibros.* 2004;3(2):93–98. doi:10.1016/j.jcf.2004.01.005
48. Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis.* 2003;37(suppl 3):S225–S264. doi:10.1086/376525
49. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr.* 2008;153(2):S4–S14. doi:10.1016/j.jpeds.2008.05.005
50. Farrell PM, Fost N. Prenatal screening for cystic fibrosis: where are we now? *J Pediatr.* 2002;141:758–763.
51. Konstan MW, Butler SM, Wohl ME, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr.* 2003;142(6):624–630. doi:10.1067/mpd.2003.152
52. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc.* 2008;108(5):832–839. doi:10.1016/j.jada.2008.02.020
53. Feranchak AP, Sontag MK, Wagener JS, Hammond KB, Accurso FJ, Sokol RJ. Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. *J Pediatr.* 1999;135(5):601–610.
54. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2002;35(3):246–259.
55. Boyle MP, Noschese ML, Watts SL, Davis ME, Stenner SE, Lechtzin N. Failure of high-dose ergocalciferol to correct vitamin D deficiency in adults

with cystic fibrosis. *Am J Respir Crit Care Med.* 2005;172(2):212–217. doi:10.1164/rccm.200403-387OC

56. Conway SP, Wolfe SP, Brownlee KG, et al. Vitamin K status among children with cystic fibrosis and its relationship to bone mineral density and bone turnover. *Pediatrics.* 2005;115:1325–1331.
57. Cystic Fibrosis Foundation, Borowitz D, Robinson KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr.* 2009;155(6 suppl):S73–S93. doi:10.1016/j.jpeds.2009.09.001
58. Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. *Pediatr Pulmonol.* 2006;41:35–49.
59. Baker SS, Borowitz D, Duffy L, Fitzpatrick L, Gyamfi J, Baker RD. Pancreatic enzyme therapy and clinical outcomes in patients with cystic fibrosis. *J Pediatr.* 2005;146(2):189–193. doi:10.1016/j.jpeds.2004.09.003
60. Borowitz D. Update on the evaluation of pancreatic exocrine status in cystic fibrosis. *Curr Opin Pulm Med.* 2005;11(6):524–527.
61. Guarner L, Rodríguez R, Guarner F, Malagelada JR. Fate of oral enzymes in pancreatic insufficiency. *Gut.* 1993;34:708–712.
62. Robinson PJ, Smith AL, Sly PD. Duodenal pH in cystic fibrosis and its relationship to fat malabsorption. *Dig Dis Sci.* 1990;35:1299–1304.
63. Heijerman HG, Lamers CB, Dijkman JH, Bakker W. Ranitidine compared with the dimethylprostaglandin E2 analogue enprostil as adjunct to pancreatic enzyme replacement in adult cystic fibrosis. *Scand J Gastroenterol Suppl.* 1990;178:26–31.
64. Heijerman HG, Lamers CB, Bakker W. Omeprazole enhances the efficacy of pancreatin (Pancrease) in cystic fibrosis. *Ann Intern Med.* 1991;114:200–201.
65. Hendriks JJ, Kester AD, Donckerwolcke R, Forget PP, Wouters EF. Changes in pulmonary hyperinflation and bronchial hyperresponsiveness following treatment with lansoprazole in children with cystic fibrosis. *Pediatr Pulmonol.* 2001;31:59–66.
66. Aris RM, Merkel PA, Bachrach LK, et al. Guide to bone health and disease in cystic fibrosis. *J Clin Endocrinol Metab.* 2005;90(3):1888–1896. doi:10.1210/jc.2004-1629
67. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2013;187(7):680–689.
68. Varekojis SM, Douce FH, Flucke RL, et al. A comparison of the therapeutic effectiveness of and preference for postural drainage and percussion, intrapulmonary percussive ventilation, and high-frequency chest wall compression in hospitalized cystic fibrosis patients. *Respir Care.* 2003;48:24–28.

69. Oermann CM, Sockrider MM, Giles D, Sontag MK, Accurso FJ, Castile RG. Comparison of high-frequency chest wall oscillation and oscillating positive expiratory pressure in the home management of cystic fibrosis: a pilot study. *Pediatr Pulmonol.* 2001;32:372–377.
70. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med.* 1994;331(10):637–642. doi:10.1056/nejm199409083311003
71. Cramer GW, Bosso JA. The role of dornase alfa in the treatment of cystic fibrosis. *Ann Pharmacother.* 1996;30(6):656–661.
72. Grieve R, Thompson S, Normand C, Suri R, Bush A, Wallis C. A cost-effectiveness analysis of rhDNase in children with cystic fibrosis. *Int J Technol Assess Health Care.* 2003;19:71–79.
73. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med.* 2006;354(3):241–250. doi:10.1056/NEJMoa043891
74. Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med.* 2006;354(3):229–240. doi:10.1056/NEJMoa043900
75. Taylor LM, Kuhn RJ. Hypertonic saline treatment of cystic fibrosis. *Ann Pharmacother.* 2007;41:481–484.
76. Stahl M, Wielputz MO, Ricklefs I, et al. Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS). A randomized, double-blind, controlled study. *Am J Respir Crit Care Med.* 2019;199(10):1238–1248. doi:10.1164/rccm.201807-1203OC
77. Nevitt SJ, Thornton J, Murray CS, Dwyer T. Inhaled mannitol for cystic fibrosis. *Cochrane Database Syst Rev.* 2020;5:CD008649. doi:10.1002/14651858.CD008649.pub4
78. Ziebach R, Pietsch-Breitfeld B, Bichler M, Busch A, Riethmüller J, Stern M. Bronchodilatory effects of salbutamol, ipratropium bromide and their combination: double-blind, placebo-controlled cross-over study in cystic fibrosis. *Pediatr Pulmonol.* 2001;31:431–435.
79. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med.* 2011;365(18):1663–1672. doi:10.1056/NEJMoa1105185
80. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for phe508del CFTR. *N Engl J Med.* 2015;373(3):220–231. doi:10.1056/NEJMoa1409547
81. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for phe508del. *N Engl J Med.* 2017;377(21):2013–2023. doi:10.1056/NEJMoa1709846

82. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med.* 2017;377(21):2024–2035. doi:10.1056/NEJMoa1709847
83. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet.* 2019;394(10212):1940–1948. doi:10.1016/S0140-6736(19)32597-8
84. Middleton PG, Mall MA, Dr˘evínek P, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single phe508del allele. *N Engl J Med.* 2019;381(19):1809–1819. doi:10.1056/NEJMoa1908639
85. Quan JM, Tiddens HA, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr.* 2001;139:813–820.
86. Conway SP, Etherington C, Peckham DG, Whitehead A. A pilot study of zafirlukast as an anti-inflammatory agent in the treatment of adults with cystic fibrosis. *J Cyst Fibros.* 2003;2:25–28.
87. Auerbach HS, Williams M, Kirkpatrick JA, Colten HR. Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. *Lancet.* 1985;2(8457):686–688.
88. Eigen H, Rosenstein BJ, FitzSimmons S, Schidlow DV. A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. Cystic Fibrosis Foundation Prednisone Trial Group. *J Pediatr.* 1995;126(4):515–523.
89. Lai HC, FitzSimmons SC, Allen DB, et al. Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *N Engl J Med.* 2000;342:851–859.
90. Balfour-Lynn IM, Lees B, Hall P, et al. Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis. *Am J Respir Crit Care Med.* 2006;173(12):1356–1362. doi:10.1164/rccm.200511-1808OC
91. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med.* 1995;332:848–854.
92. Saiman L, Anstead M, Mayer-Hamblett N, et al. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA.* 2010;303(17):1707–1715. doi:10.1001/jama.2010.563
93. Ratjen F, Döring G, Nikolaizik WH. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. *Lancet.* 2001;358:983–984.
94. Mayer-Hamblett N, Burns JL, Khan U, Retsch-Bogart G, Treggiari M, Ramsey BW. Predictors of *Pseudomonas aeruginosa* recurrence in cystic fibrosis: results from the EPIC trial. *Pediatr Pulmonol.* 2010;45(S33):326–327.

95. Tiddens HA, De Boeck K, Clancy JP, et al. Open label study of inhaled aztreonam for Pseudomonas eradication in children with cystic fibrosis: the ALPINE study. *J Cyst Fibros.* 2015;14(1):111–119. doi:10.1016/j.jcf.2014.06.003
96. Mayer-Hamblett N, Retsch-Bogart G, Kloster M, et al. Azithromycin for early Pseudomonas infection in cystic fibrosis. The OPTIMIZE randomized trial. *Am J Respir Crit Care Med.* 2018;198(9):1177–1187. doi:10.1164/rccm.201802-0215OC
97. Rosenfeld M, Emerson J, Williams-Warren J, et al. Defining a pulmonary exacerbation in cystic fibrosis. *J Pediatr.* 2001;139(3):359–365. doi:10.1067/mpd.2001.117288
98. Ramsey BW. Management of pulmonary disease in patients with cystic fibrosis. *N Engl J Med.* 1996;335:179–188.
99. Flume PA, Mogayzel PJ Jr, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med.* 2009;180(9):802–808. doi:10.1164/rccm.200812-1845PP
100. Smith AL, Doershuk C, Goldmann D, et al. Comparison of a beta-lactam alone versus beta-lactam and an aminoglycoside for pulmonary exacerbation in cystic fibrosis. *J Pediatr.* 1999;134(4):413–421. doi:10.1016/s0022-3476(99)70197-6
101. Bulitta JB, Landersdorfer CB, Huttner SJ, et al. Population pharmacokinetic comparison and pharmacodynamic breakpoints of ceftazidime in cystic fibrosis patients and healthy volunteers. *Antimicrob Agents Chemother.* 2010;54(3):1275–1282. doi:10.1128/aac.00936-09
102. Hubert D, Le Roux E, Lavrut T, et al. Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis. *Antimicrob Agents Chemother.* 2009;53(9):3650–3656. doi:10.1128/AAC.00174-09
103. Smyth A, Tan KH, Hyman-Taylor P, et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis—the TOPIC study: a randomized controlled trial. *Lancet.* 2005;365(9459):573–578. doi:10.1016/S0140-6736(05)17906-9
104. Kirkpatrick CM, Duffull SB, Begg EJ. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. *Br J Clin Pharmacol.* 1999;47(6):637–643. doi:10.1046/j.1365-2125.1999.00938.x
105. Balaguer A, Gonzalez de Dios J. Home intravenous antibiotics for cystic fibrosis. *Cochrane Database Syst Rev.* 2008;(3):CD001917. doi:10.1002/14651858.CD001917.pub2
106. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med.* 1999;340:23–30.
107. Nichols DP, Odem-Davis K, Cogen JD, et al. Pulmonary outcomes associated with long-term azithromycin therapy in cystic fibrosis. *Am J Respir Crit Care Med.* 2020;201(4):430–437. doi:10.1164/rccm.201906-1206OC

108. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med.* 2008;178(9):921–928. doi:10.1164/rccm.200712-1804OC
109. Saiman L, Mayer-Hamblett N, Campbell P, et al. Heterogeneity of treatment response to azithromycin in patients with cystic fibrosis. *Am J Respir Crit Care Med.* 2005;172:1008–1012.
110. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol.* 2001;153(4):345–352.
111. Blumberg HM, Rimland D, Carroll DJ, Terry P, Wachsmuth IK. Rapid development of ciprofloxacin resistance in methicillin-susceptible and -resistant Staphylococcus aureus. *J Infect Dis.* 1991;163(6):1279–1285.
112. Radberg G, Nilsson LE, Svensson S. Development of quinolone-imipenem cross resistance in Pseudomonas aeruginosa during exposure to ciprofloxacin. *Antimicrob Agents Chemother.* 1990;34:2142–2147.
113. Bosso JA, Black PG, Matsen JM. Ciprofloxacin versus tobramycin plus azlocillin in pulmonary exacerbations in adult patients with cystic fibrosis. *Am J Med.* 1987;82(4A):180–184.
114. Hodson ME, Roberts CM, Butland RJ, Smith MJ, Batten JC. Oral ciprofloxacin compared with conventional intravenous treatment for Pseudomonas aeruginosa infection in adults with cystic fibrosis. *Lancet.* 1987;1:235–237.
115. Rubio TT, Miles MV, Lettieri JT, Kuhn RJ, Echols RM, Church DA. Pharmacokinetic disposition of sequential intravenous/oral ciprofloxacin in pediatric cystic fibrosis patients with acute pulmonary exacerbation. *Pediatr Infect Dis J.* 1997;16:112–117.
116. Adler FR, Aurora P, Barker DH, et al. Lung transplantation for cystic fibrosis. *Proc Am Thorac Soc.* 2009;6(8):619–633. doi:10.1513/pats.2009008-088TL

SECTION 4

Gastrointestinal Disorders

Section Editor: Carrie A. Sincak

22

Nausea and Vomiting

Lisa M. DiGrazia and J. Todd Carter

CORE PRINCIPLES		CHAPTER CASES
MOTION SICKNESS		
1	Motion sickness is caused by discordant information about body position or motion received from visual, vestibular, or body proprioceptors. Acetylcholine is thought to be the primary neurotransmitter involved.	**Case 22-1 (Question 1)**
2	Transdermal scopolamine is recommended for prophylaxis of motion sickness for moderate-to-severe stimuli. Dimenhydrinate or promethazine is recommended for treatment of breakthrough symptoms. The most common adverse effects of these agents include drowsiness, confusion, and dry mouth.	**Case 22-1 (Questions 2, 3), Table 22-1**

CORE PRINCIPLES		CHAPTER CASES
CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING		
1	Nausea and vomiting are initiated by several stimuli and mediated by several neurotransmitters in the central nervous system, peripheral nervous system, and gastrointestinal tract. Because of the multiple neurotransmitter receptors involved, successful prophylaxis and treatment of chemotherapy-induced nausea and vomiting will almost always require medications with more than one mechanism of action.	**Case 22-2 (Question 1)**
2	The likelihood of nausea and vomiting depends on patient risk factors and, most importantly, on the emetogenicity of the chemotherapy agents prescribed. The antiemetic regimen should be appropriate for the chemotherapy agent with the highest emetogenicity level.	**Case 22-2 (Question 1), Table 22-2**
3	Patients receiving moderate to highly emetogenic chemotherapy should receive prophylaxis with an aprepitant-, netupitant-, or olanzapine-containing regimen. The backbone of these regimens includes a 5-hydroxytryptamine receptor type 3 (5-HT_3) antagonist and dexamethasone.	**Case 22-2 (Question 2), Tables 22-3, 22-4, Figures 22-2, 22-3**

CORE PRINCIPLES		CHAPTER CASES
4	For breakthrough symptoms, patients should receive rescue antiemetics with a mechanism of action different from the prophylactic medications and receive more aggressive antiemetics before the next cycle of chemotherapy.	**Case 22-2 (Question 3), Tables 22-3, 22-4, Figures 22-2, 22-3**
RADIATION-INDUCED NAUSEA AND VOMITING		
1	Radiation can cause nausea and vomiting by the same pathways as chemotherapy. The risk depends on the area and size of the radiation field as well as the fractional dose of radiation and whether the patient has had chemotherapy in the past.	**Case 22-3 (Question 1), Table 22-5**
2	The recommended prophylaxis for radiation-induced nausea and vomiting includes a 5-HT_3 antagonist with dexamethasone for high-risk patients and with or without dexamethasone for patients at moderate risk. Breakthrough symptoms may be treated with a 5-HT_3 antagonist or dopamine antagonist.	**Case 22-3 (Question 1), Table 22-5**
POSTOPERATIVE NAUSEA AND VOMITING		
1	The risk of postoperative nausea and vomiting depends on several patient-related, surgical, and anesthetic factors. The antiemetic regimen should be proportional to the risk factors.	**Case 22-4 (Question 1), Table 22-6**

CORE PRINCIPLES		CHAPTER CASES
2	The most active agents in preventing postoperative nausea and vomiting are 5-HT_3 antagonists. For patients at moderate to high risk, a 5-HT_3 antagonist should be combined with dexamethasone or droperidol. Antiemetics used for rescue therapy should be of a class different from the prophylactic agents used.	**Case 22-4 (Question 1), Table 22-6**

INTRODUCTION

Nausea and vomiting are unpleasant symptoms caused by self-limiting disorders or serious conditions such as cancer. These symptoms can range from mild, short-lived nausea to continuing severe emesis and retching. The emetic response can be described in three phases: nausea, vomiting, and retching. *Nausea* is the subjective feeling of the need to vomit. It includes an unpleasant sensation in the mouth and stomach and can be associated with salivation, sweating, dizziness, and tachycardia. *Vomiting* is the forceful expulsion of the stomach contents through the mouth but is preceded by the relaxation of the esophageal sphincter, contraction of the abdominal muscles, and temporary suspension of breathing. *Retching* is the rhythmic contraction of the abdominal muscles without actual emesis. It can accompany nausea or occur before or after emesis.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

Nausea and vomiting are caused by many disorders. Central nervous system (CNS) causes include increased intracranial pressure, migraine headaches, brain metastases, vestibular dysfunction, alcohol intoxication, and anxiety. Infectious disease causes include viral gastroenteritis, food poisoning, peritonitis, meningitis, and urinary tract infections. Metabolic causes include hypercalcemia, uremia, hyperglycemia, and hyponatremia. Gastrointestinal (GI) disorders, such as gastroparesis, bowel obstruction, distension, and mechanical irritation, can cause nausea and vomiting. Among the many medications that can cause nausea and vomiting are cancer chemotherapy, antibiotics, antifungals, and opiate analgesics.

In addition to the suffering involved, uncontrolled vomiting can lead to dehydration, electrolyte imbalances, malnutrition, aspiration pneumonia, and esophageal tears. Nausea and vomiting often reduce food intake and can impair a person's ability to care for himself or herself. Significant reductions in quality-of-life scores have been demonstrated in patients with cancer having chemotherapy-induced nausea and vomiting (CINV) compared with patients who did not have those symptoms.[1]

PATHOPHYSIOLOGY

The CNS, the peripheral nervous system, and the GI tract are all involved in initiating and coordinating the emetic response. In the CNS, the vomiting center (VC) receives incoming signals from other parts of the brain and the GI tract and then coordinates the emetic response by sending signals to the effector organs. The VC is located in the medulla oblongata of the brain, near the nucleus tractus solitarius (NTS). The VC is stimulated by neurotransmitters released from the chemoreceptor trigger zone (CTZ), the GI tract, the cerebral cortex, the limbic system, and the vestibular system (**Fig. 22-1**). The major neurotransmitter receptors associated with the emetic response include serotonin (the 5-hydroxytryptamine type

3 [5-HT_3]) receptors, neurokinin 1 (NK1) receptors, and dopamine receptors. Other receptors involved include corticosteroid, acetylcholine, histamine, cannabinoid, gabaminergic, and opiate receptors. Many of these receptors are targets for antiemetic therapy.

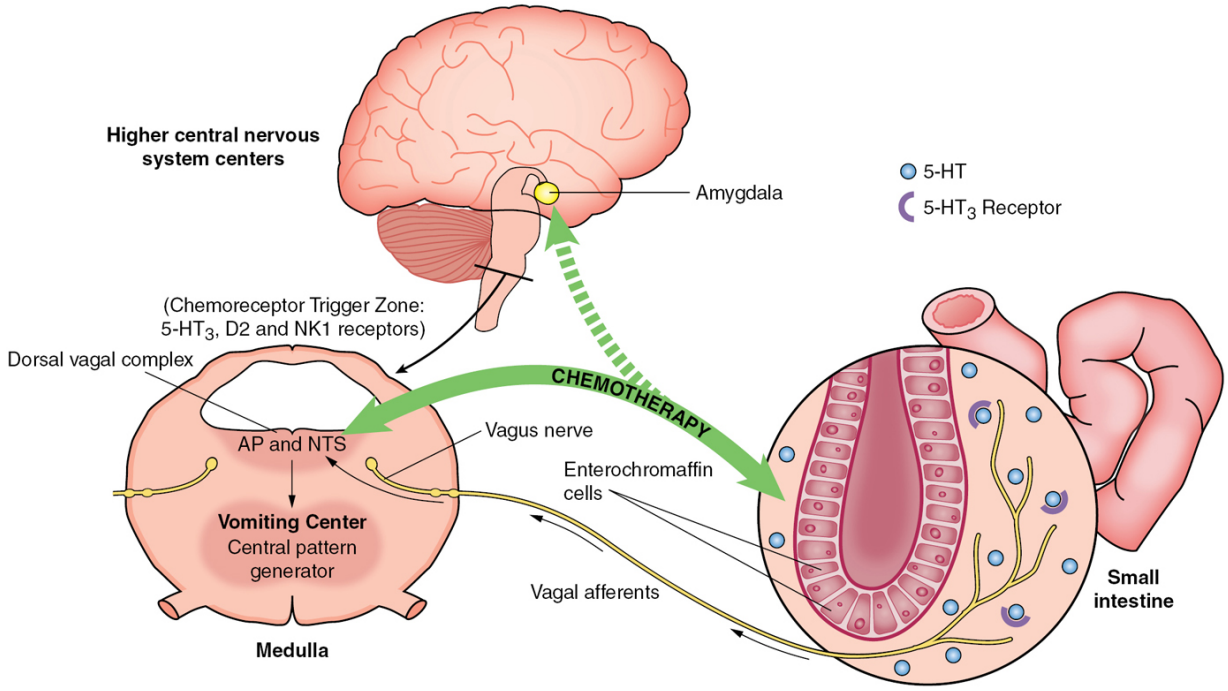


Figure 22-1 Pathways by which chemotherapeutic agents may produce an emetic response. 5-HT, 5-hydroxytryptamine; 5-HT_3, 5-hydroxytryptamine type 3 receptor; AP, anterior pituitary; D, days; NTS, nucleus tractus solitarius.

In the CNS, the CTZ is located in the area postrema on the floor of the fourth ventricle in the brainstem; it lies outside the blood–brain barrier. When the CTZ senses toxins and noxious substances in the blood or cerebrospinal fluid, it triggers the emetic response by releasing neurotransmitters that travel to the VC and NTS. The major neurotransmitter receptors include serotonin, dopamine, and NK1.

The GI system also plays a large part in the initiation of the emetic response. The GI tract contains enterochromaffin cells in the GI mucosa. When these cells are damaged by chemotherapy, radiation, anesthetics, or mechanical irritation, serotonin is released, which can

stimulate the vagal afferents as well as directly stimulate the VC and NTS. The VC then initiates the emetic response.

The cerebral cortex and limbic system can stimulate the emetic center in response to emotional states, such as anxiety, pain, and conditioned responses (anticipatory nausea and vomiting). The neurotransmitters involved in this pathway are less well understood. Disorders of the vestibular system, such as vertigo and motion sickness, stimulate the VC through acetylcholine and histamine release.

DIAGNOSIS

The initial evaluation of the patient with nausea and vomiting should include the onset of symptoms, the severity and duration of symptoms, hydration status, precipitating factors, current medical conditions and medications, and food and infectious contacts. The etiology of nausea and vomiting should be determined, if possible, so that underlying conditions can be treated specifically. Supportive treatment should be initiated, if needed, including fluid and electrolyte replacement. If the nausea and vomiting is mild and self-limited, antiemetic therapy may not be required. For others, however, the appropriate antiemetic therapy will depend on the patient and the etiology of the nausea and vomiting.

MOTION SICKNESS

Clinical Presentation and Risk Factors

CASE 22-1

QUESTION 1: P.C. is a 27-year-old female who has no significant medical history, with the exception of moderate dysmenorrhea and motion sickness

associated with travel by air. Previously, she has taken dimenhydrinate before airplane trips with moderate success. She is engaged to be married, and she and her fiancé have decided on a weeklong Caribbean cruise for their honeymoon. P.C. is concerned that she may also develop seasickness and that dimenhydrinate may not control her symptoms, particularly in the event of rough weather at sea.

Will P.C. be at higher risk for motion sickness?

The symptoms of motion sickness occur in response to an unusual perception of real or apparent motion. In these situations, there is sensory conflict about body position or motion through the visual, vestibular, or body proprioceptors. Acetylcholine is thought to be the primary neurotransmitter involved in signaling the VC, as is histamine, but to a lesser extent. Adrenergic stimulation can block this transmission. Although nausea may be the first symptom recognized by the patient, other mild symptoms often proceed including an awareness of the stomach (ie, a sensation of fullness), hypersalivation, facial pallor, belching, yawning, and heartburn.[2] The milder symptoms may then progress to diaphoresis, flushing, hyperventilation, increased body warmth, and, ultimately, emesis. The risk of motion sickness varies between ages and genders. The risk is lowest in children younger than 2 years old and highest in children 2 to 12 years old and is more likely to occur in biologic females than in biologic males.[3] In some individuals, sensitivity to motion sickness diminishes with time.[4] Boat travel is most likely to cause symptoms with air, car, and train travel occurring less frequently.[5,6] Severity of the motion sickness is highly dependent on the individual and the circumstances at the time (eg, consumption of food or alcohol). Other contributing factors include weather and the patient's position in the plane, vehicle, or boat. Because of P.C.'s history and her travel plans, she is at high risk for recurrence of her motion sickness symptoms.

Nonpharmacologic Measures

Case 22-1, Question 2: What nonpharmacologic methods could P.C. employ to reduce her chance of developing motion sickness?

Nonpharmacologic measures or natural remedies may be useful for reducing motion sickness.[4] These include riding in the middle of the boat or plane where the motion is less dramatic, lying in a semirecumbent position, driving the vehicle or sitting in the front passenger seat, choosing a window seat, maintaining hydration while avoiding carbonated beverages or alcohol, fixing the vision on the horizon, avoiding reading, and closing the eyes if below deck, in the backseat, or in the cabin.[3] Many people recommend keeping active on a ship to "get their sea-legs" faster through habituation. The effectiveness of acupressure at the P6 point of the wrist (about three fingerbreadths above the wrist) is unclear. A controlled-stimulus trial compared two brands of wristbands with placebo; neither band was more effective than was placebo in preventing symptoms of motion sickness.[7] Studies of ginger preparations also are equivocal. The action of ginger may be through enhanced gastric emptying and not on the vestibular system.[8,9]

Overview of Treatment

Case 22-1, Question 3: For P.C., what medications are available to prevent and treat motion sickness symptoms?

Anticholinergic agents and antihistamines that cross the blood–brain barrier effectively prevent and treat motion sickness.[5,6] Antihistamines frequently used include dimenhydrinate, meclizine, cyclizine, and promethazine.[10] In general, these medications are more effective in preventing than in treating established symptoms. Sympathomimetics and amphetamines have shown effectiveness in the treatment of motion sickness, but owing to addictive potential and or controlled status, they are not used as often.[11] Benzodiazepines have been used but are not as effective as other

treatments. Diazepam has been shown to prevent motion sickness, but the sedative effects may limit its use.[11] The 5-HT_3 receptor antagonists and NK1 receptor antagonists have not been shown to be effective in preventing motion sickness.[4,8] Nonsedating antihistamines are not as effective as other antihistamines because they do not sufficiently cross the blood–brain barrier.[4,5] Scopolamine has been well studied for the prevention of motion sickness and is highly effective.[4,12] In a controlled trial, scopolamine was more effective than was promethazine, and both were more effective than placebo, meclizine, or lorazepam.[13] Scopolamine is available as a topical patch, which bypasses the problem of GI symptoms associated with motion sickness. **Table 22-1** summarizes medications effective for the prevention and treatment of motion sickness.

Table 22-1
Medications for Prevention or Treatment of Motion Sickness in Adults

Medication (Trade Name)	Dosage	Recommended Use	Adverse Effects
Scopolamine (Transderm-Scop®)	1 mg TOP behind the ear every 3 days Apply at least 4 hours before exposure.	Prevention of nausea/vomiting associated with motion sickness and recovery from anesthesia and surgery	Xerostomia, dizziness, agitation, drowsiness, blurred vision, confusion, fatigue
Dimenhydrinate (Dramamine®)	50–100 mg PO every 4–6 hours (max 400 mg/day). May be taken PRN or on a scheduled basis if required.	Prevention and treatment of nausea, vomiting, or dizziness associated with motion sickness	Drowsiness or excitement, dry mouth, thickening of secretions, dizziness, blurred vision, tachycardia, fatigue
Promethazine (Phenergan®)	12.5–25 mg PO every 4–6 hours. May be taken PRN or on a scheduled basis if required. (Some experts recommend a maximum dose of 50 mg/day to avoid intolerable side effects.)	Although included as an FDA-approved use in the manufacturer's prescribing information, other therapies are available without the risks associated with promethazine use.[2]	Drowsiness, bradycardia, xerostomia, confusion, dizziness
Meclizine (Dramamine® Less Drowsy [OTC], Bonine® [OTC], Motion-Time® [OTC], Travel Sickness® [OTC], Travel-Ease® [OTC])	25–50 mg PO 1 hour before travel. Repeat every 24 hours if needed.	Prevention and treatment of nausea, vomiting, or dizziness associated with motion sickness	Drowsiness, dizziness, fatigue, xerostomia, headache, blurred vision

OTC, over the counter; PO, oral; PRN, as needed; TOP, topical patch.

Source: Data from Facts & Comparisons. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

Because P.C. is susceptible in a moderate-to-severe stimulus situation, prevention with a scopolamine patch applied behind the

ear every 3 days, starting at least 4 hours before departure, should be recommended. If she experiences breakthrough symptoms, dimenhydrinate or promethazine may be useful. She should be advised about the potential adverse effects of these agents, which include drowsiness, confusion, and dry mouth.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

CINV occurs in many patients receiving chemotherapy for cancer.[1] The mechanisms of the emetic response described at the beginning of this chapter apply to CINV as well. The major neurotransmitter receptors involved in these pathways include 5-HT_3, NK1, and dopamine receptors. CINV can occur in different phases. Acute-onset CINV symptoms occur within a few minutes to hours of the administration of chemotherapy. These symptoms often peak several hours after administration and can last for the first 24 hours. Some antineoplastic agents can also cause nausea and vomiting symptoms for a longer time after chemotherapy administration. These delayed-onset CINV symptoms peak in about 2 to 3 days and can last 6 to 7 days. Some patients may experience acute symptoms without delayed symptoms or delayed symptoms without acute symptoms, whereas others experience CINV in both. Some patients who have received previous chemotherapy treatments may experience a conditioned response in which they have symptoms even before chemotherapy begins. This is called *anticipatory nausea and vomiting* and is difficult to treat because it is primarily triggered by poor nausea and vomiting control in previous cycles. Breakthrough nausea and vomiting occur if the primary prophylactic antiemetics fail to work completely. Of course, regardless of the time course and cause, these are very distressing, unpleasant, and disruptive symptoms for the patient.

The likelihood of CINV depends on several factors.[1] Patient-related factors that increase the risk of acute-onset CINV include age younger than 50 years, female sex, previous history of CINV, history of motion sickness or nausea with pregnancy, anxiety, or depression. A significant history of alcoholism actually protects against CINV. Delayed symptoms are more common in females, in those who have had poor emetic control in the acute phase, and in patients with anxiety or depression.

Chemotherapy-related factors also predict the likelihood of symptoms. Factors such as shorter infusion time, higher dose, and more chemotherapy cycles increase the risk of CINV. With multiday chemotherapy regimens, the symptoms usually peak around the third to the fourth day of chemotherapy, when the acute symptoms caused by the later days' doses overlap with the delayed symptoms from the first days' doses. The most predictive factor, however, is the chemotherapy agent's inherent ability to cause CINV, or its emetogenicity.[1,14,15] Antineoplastics that are most likely (>90% of patients) to cause symptoms are classified as highly emetogenic chemotherapy. Agents that cause nausea and vomiting in 30% to 90% of patients are classified as moderate-risk agents. Low emetogenicity agents cause symptoms in 10% to 30% of patients. Other chemotherapy agents have a minimal risk, causing CINV in <10% of patients. **Table 22-2** lists selected chemotherapy agents in the various emetogenicity classes, noting that references differ in the estimation of emetic risk for some antineoplastic agents. The emetogenicity risk also depends on the dosage used and the route of administration.

Table 22-2
Emetogenicity of Selected Intravenous and Oral Antineoplastic Agents With Prophylaxis Options

Potential	Chemotherapy		Prophylaxis Options
Intravenous high emetic risk (>90% frequency of emesis)	AC combination defined as anthracycline with cyclophosphamide Carboplatin AUC ≥4 Carmustine >250 mg/m^2 Cisplatin Cyclophosphamide >1500 mg/m^2 Dacarbazine Doxorubicin ≥60 mg/m^2 Epirubicin >90 mg/m^2 Ifosfamide ≥2 g/m^2 per dose Mechlorethamine Streptozocin		Four-drug–containing regimen (preferred) *or* Three-drug regimen (containing olanzapine) *or* Three-drug regimen (containing NK1RA)
Intravenous moderate emetic risk (30%–90% frequency of emesis)	Aldesleukin >12–15 million IU/m^2 Amifostine >300 mg/m^2 Azacitidine Bendamustine Busulfan Carboplatin AUC <4 Carmustine ≤250 mg/m^2 Clofarabine Cyclophosphamide ≤1500 mg/m^2 Cytarabine >200 mg/m^2 Dactinomycin Daunorubicin Dual-drug liposomal encapsulation of cytarabine and daunorubicin Dinutuximab Doxorubicin <60 mg/m^2	Epirubicin ≤90 mg/m^2 Enfortumab vedotin-ejfv Fam-trastuzumab deruxtecan-nxki Idarubicin Ifosfamide <2 g/m^2 per dose Interferon α ≥10 million IU/m^2 Irinotecan Irinotecan (liposomal) Melphalan Methotrexate ≥250 mg/m^2 Oxaliplatin Temozolomide Trabectedin	Three-drug regimen (containing olanzapine) *or* Three-drug regimen (containing NK1RA) *or* 5-HT$_3$RA (choose one: dolasetron, granisetron, ondansetron, or palonosetron) + dexamethasone
Intravenous low emetic risk (10%–30% frequency of emesis)	Ado-trastuzumab emtansine Aldesleukin ≤12 million IU/m^2 Amifostine ≤300 mg/m^2 Arsenic trioxide Axicabtagene ciloleucel Brentuximab vedotin Cabazitaxel Carfilzomib Copanlisib Cytarabine 100–200 mg/m^2 Docetaxel Doxorubicin (liposomal) Eribulin Etoposide 5-Fluorouracil Floxuridine Gemcitabine Gemcitabine ozogamicin Inotuzumab ozogamicin Interferon α >5 million ≤10 million IU/m^2	Ixabepilone Methotrexate >50 to 249 mg/m^2 Mitomycin Mitoxantrone Necitumumab Olaratumab Omacetaxine Paclitaxel Paclitaxel-albumin Pemetrexed Pentostatin Polatuzumab vedotin Pralatrexate Romidepsin Tagraxofusp Thiotepa Tisagenlecleucel Topotecan Ziv-aflibercept	Dexamethasone *or* Metoclopramide *or* Prochlorperazine *or* 5-HT$_3$RA (choose one: dolasetron, granisetron, ondansetron, or palonosetron)

Intravenous minimal emetic risk (<10% frequency of emesis)	Alemtuzumab Atezolizumab Asparaginase Avelumab Bevacizumab Bleomycin Bortezomib Cetuximab Cladribine Cytarabine <100 mg/m^2 Daratumumab Decitabine	Nelarabine Nivolumab Obinutuzumab Ofatumumab Panitumumab Pegaspargase Peginterferon Pembrolizumab Pertuzumab Ramucirumab Rituximab Siltuximab	No routine prophylaxis
	Denileukin diftitox Dexrazoxane Durvalumab Elotuzumab Fludarabine Interferon α ≤5 million IU/m^2 Ipilimumab Methotrexate ≤50 mg/m^2	Temsirolimus Trastuzumab Valrubicin Vinblastine Vincristine Vincristine (liposomal) Vinorelbine	
Oral moderate to high emetic risk (≥30% frequency of emesis)	Altretamine Avapritinib Binimetinib Busulfan (≥4 mg/day) Ceritinib Crizotinib Cyclophosphamide (≥100 mg/m^2/day) Dabrafenib Enasidenib Encorafenib Estramustine Etoposide	Lenvatinib (>12 mg/day) Lomustine (single day) Mitotane Niraparib Olaparib Procarbazine Rucaparib Selinexor Temozolomide (>75 mg/m^2/day)	5-HT$_3$RA
Minimal to low emetic risk (≤30% frequency of emesis)	Abemaciclib Acalabrutinib Afatinib Alectinib Alpelisib Axitinib Bexarotene Brigatinib Bosutinib Busulfan (<4 mg/day) Cabozantinib Capecitabine Chlorambucil Cobimetinib Cyclophosphamide (<100 mg/m^2/day) Dacomitinib Dasatinib Duvelisib Entrectinib Erdafitinib Erlotinib Everolimus Fludarabine Gefitinib	Loratinib Melphalan Mercaptopurine Methotrexate Nilotinib Neratinib Osimertinib Palbociclib Panobinostat Pazopanib Pomalidomide Ponatinib Regorafenib Ribociclib Ruxolitinib Sonidegib Sorafenib Sunitinib Talazoparib tosylate Temozolomide (≤ 75mg/m^2/day) Thalidomide Thioguanine Topotecan Trametinib	As needed

	Gilteritinib Glasdegib Hydroxyurea Ibrutinib Idelalisib Imatinib Ixazomib Ivosidenib Lapatinib Larotrectinib Lenalidomide	Tretinoin Trifluridine/tipiracil Vandetanib Vemurafenib Venetoclax Vismodegib Vorinostat Zanubrutinib	

5-HT_3RA, 5-hydroxytryptamine type 3 receptor antagonist; NK1RA, neurokinin 1 receptor antagonist.

Sources: Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—an update. *Support Care Cancer*. 2005;13:80–84; Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update [published correction appears in *J Clin Oncol*. 2014;32(19):2117. Dosage error in article text]. *J Clin Oncol*. 2011;29:4189–4198; Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(Suppl 5):v232–v243.

Certain antineoplastic agents are more likely to cause delayed CINV symptoms. These include cisplatin, carboplatin, cyclophosphamide, doxorubicin, epirubicin, ifosfamide, and (to a lesser degree) irinotecan and methotrexate. Patients receiving more than one of these agents are at high risk for delayed symptoms.

Most chemotherapy agents are given in combination rather than as single agents. Estimating the emetogenicity of chemotherapy combinations has always been difficult. The primary literature of the regimen should always be consulted to determine the emetic risk. Should that not be available, the antiemetic regimen should be geared toward the chemotherapy agent with the highest emetogenicity level given on that day.[1,16,17] For example, in a chemotherapy combination with one high-risk agent and one with a moderate risk, the antiemetic regimen should be appropriate for the high-risk chemotherapy agent.

Antiemetic efficacy, or complete emetic response, is usually defined as no emesis and no nausea or only mild nausea in the first 24 hours after chemotherapy administration. With currently recommended antiemetic regimens, most, but not all, patients will be

protected from emesis in the acute onset (first 24 hours). Nausea is more difficult to control, whereas delayed-onset CINV symptoms are more difficult to prevent.

Overview of Treatment

Appropriate antiemetic therapy is based on the emetogenicity of the chemotherapy regimen and patient risk factors. Because the pathophysiologic response of nausea and vomiting involves many neurotransmitters, combinations of antiemetics from different therapeutic classes will be more effective in most situations than is a single agent. The predominant classes of antiemetics used for CINV include 5-HT_3 antagonists, the NK1 antagonist, and corticosteroids.

5-HYDROXYTRYPTAMINE TYPE 3 ANTAGONISTS

The 5-HT_3 antagonists inhibit the action of serotonin in the GI tract and CNS, and thereby block the transmission of emetic signals to the VC. The 5-HT_3 antagonists are both highly effective and have minimal side effects. Several agents and dosage forms in this class are now available: ondansetron, granisetron, dolasetron, and palonosetron. Dosages of these agents are shown in **Table 22-3**. The route of administration should be matched to the clinical status of the patient. Oral tablets are appropriate for most patients, but intravenous (IV), topical, or oral dissolving tablet formulations may be needed in patients who cannot take oral medications.

Table 22-3
Antiemetic Agents for Chemotherapy-Induced Nausea and Vomiting

Medication (Trade Name)	Class	Indication
Aprepitant (Emend®)	NK1RA	Acute and delayed
Dexamethasone (Decadron®)	Corticosteroid	Acute (high emetogenicity)

Medication (Trade Name)	Class	Indication
		Acute (moderate emetogenicity)
		Acute (low emetogenicity)
		Delayed
Dolasetron (Anzemet®)	5-HT_3RA	Acute Breakthrough
Dronabinol (Marinol®) capsules	Cannabinoid	Breakthrough
Dronabinol (Syndros®) oral solution	Cannabinoid	Breakthrough
Droperidol (Inapsine®)	Butyrophenone	Breakthrough
Fosaprepitant (Emend®)	NK1RA	Acute
Granisetron (Kytril®)	5-HT_3RA	Acute Breakthrough
Haloperidol (Haldol®)	Butyrophenone	Breakthrough
Metoclopramide (Reglan®)	Dopamine antagonist	Breakthrough
Lorazepam (Ativan®)	Benzodiazepine	Breakthrough
Nabilone (Cesamet®)	Cannabinoid	Refractory symptoms
Netupitant and palonosetron (Akynzeo®)	NK1RA + 5-HT_3RA	Acute (moderate or high emetogenicity)
Olanzapine (Zyprexa®)	Serotonin/dopamine antagonist	Acute (moderate or high emetogenicity)/delayed
		Breakthrough (preferred breakthrough drug of choice)
Ondansetron (Zofran®)	5-HT_3RA	Acute (moderate or high emetogenicity) Delayed
Palonosetron (Aloxi®)	5-HT_3RA	Acute/delayed
Prochlorperazine (Compazine®)	Dopamine antagonist	Breakthrough Acute

Medication (Trade Name)	Class	Indication
Promethazine (Phenergan®)	Dopamine antagonist	Breakthrough
Rolapitant (Varubi®)	NK1RA	Acute and delayed

5-HT_3RA, 5-hydroxytryptamine type 3 receptor antagonist; bid, two times daily; IM, intramuscular; IV, intravenous; NK1RA, neurokinin 1 receptor antagonist; PO, oral; PR, rectal; PRN, as needed; qid, four times daily; SL, sublingual; tid, three times daily; q6h, every 6 hours.

Sources: Adapted with permission from: Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol*.1997;15:103-109; Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—state of the art. *Support Care Cancer*. 2011;19:S43-S47; Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update [published correction appears in *J Clin Oncol*. 2014 Jun 1;32(19):2117. Dosage error in article text]. *J Clin Oncol*. 2011;29:4189–4198; Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(Suppl 5):v232–v243.

These agents have been widely studied, and some commonalities have emerged. All of the 5-HT_3 antagonists are considered to have equivalent efficacy.[18–23] All of these agents have a threshold effect, and so a sufficiently large dose must be given to block the relevant receptors. In addition, the dose–response curve is relatively flat, such that escalating the dose beyond the threshold dose does not enhance efficacy. When given in appropriate doses, all of these agents have similar efficacy for acute CINV, with response rates of 60% to 80%, depending on the study design.[1,16,18–23] The effectiveness of the 5-HT_3 receptor antagonists is enhanced by the addition of dexamethasone. The response rate increases by about 15% to 20% in regimens that include dexamethasone and a 5-HT_3 antagonist.[21,24] Oral and IV 5-HT_3 administration are equally effective assuming that the patient can take oral medications. The side effects of the 5-HT_3 antagonists are similar and fairly mild, and include

headache and constipation. The 5-HT_3 antagonists are one component of optimal antiemetic prophylaxis for acute CINV. However, they are not more effective than are agents from other classes (notably dexamethasone, aprepitant, or prochlorperazine) for delayed CINV.[21,25–27] The 5-HT_3 antagonists, therefore, are not generally recommended for delayed CINV. The 5-HT_3 antagonists are metabolized by different cytochrome P-450 (CYP) enzymes, including CYP1A2, CYP2D6, and CYP3A4. Differences in the metabolic rate of 5-HT_3 antagonists attributable to CYP2D6 polymorphisms might account for differences in efficacy among individual patients.[21] However, these differences are not used clinically to choose initial antiemetic therapy at this time.

Ondansetron, granisetron, and dolasetron are first-generation 5-HT_3 antagonists and have similar pharmacokinetic parameters. Palonosetron, the newest member of the 5-HT_3 antagonist family, is distinguished by a longer elimination half-life (~40 hours) than are others in its class.[28] One group of researchers described a three-drug combination of palonosetron, dexamethasone, and aprepitant in a noncomparative, phase 2 study with moderately emetogenic chemotherapy and found that the three-drug combination was safe and effective.[29]

Ondansetron, granisetron, and dolasetron have been associated with an increased risk of prolonging electrocardiographic intervals, such as QT.[30] It is not recommended to exceed maximum dosages to decrease this risk. In addition, patients should be monitored if they have an underlying cardiac disease, electrolyte abnormalities, or are concurrently taking other medications that also prolong electrocardiographic intervals.

CORTICOSTEROIDS

The mechanism of action of corticosteroids as antiemetics has not been fully determined. Some suggest that corticosteroids may decrease serotonin release, antagonize 5-HT_3, or activate corticosteroid receptors in the NTS of the medulla in the CNS.[24]

Many studies validate the effectiveness of corticosteroids in the prophylaxis of CINV symptoms. Efficacy with both dexamethasone and methylprednisolone has been described, but dexamethasone is much more widely studied and almost exclusively used. Dexamethasone improves the antiemetic control of 5-HT_3 antagonists by about 15% to 20%.[24] In addition to its use in acute-onset CINV, dexamethasone is one of the cornerstone agents used to prevent delayed-onset CINV. It is inexpensive and available in both IV and oral formulations.

The optimal dose of dexamethasone with different emetic stimuli has been studied in controlled trials.[24] For moderately emetogenic chemotherapy in the acute phase, a single 8-mg dose was as effective as larger 24 mg doses or prolonged administration. In the setting of highly emetogenic cisplatin-based chemotherapy, higher doses of 12 or 20 mg were superior to doses of 4 and 8 mg. If dexamethasone is used with aprepitant in acute onset, the lower 12-mg prechemotherapy dose is recommended because of inhibition of steroid metabolism by aprepitant (see the section on Neurokinin 1 Receptor Antagonists).[16] For prevention of delayed CINV symptoms, the most commonly used dose of dexamethasone is 8 mg twice daily on days 2 and 3 after chemotherapy without aprepitant. The dose for delayed CINV should be reduced to 8 mg daily when used with aprepitant.

Corticosteroids are sometimes underused because of the potential risk of side effects. The adverse effects of corticosteroids include insomnia, jitteriness, increased appetite, GI distress, and perineal irritation if the IV dexamethasone is infused too quickly.[22,24,31] For most patients, however, dexamethasone is well tolerated, especially because the therapy is typically short term at lower doses. Tapering the corticosteroid dose after the end of treatment for CINV is usually unnecessary because the duration of therapy is short. Patients who experience rare steroid withdrawal-like symptoms may, however, benefit from a short taper on repeated corticosteroid courses.

Corticosteroids also have antitumor properties and are a part of the antineoplastic regimen for some malignancies, such as

lymphoma, lymphoid leukemia, and myeloma, and additional dexamethasone for antiemetic protection is not necessary. In these cases, the corticosteroid should be administered just before chemotherapy to provide antiemetic activity. If aprepitant is part of an antiemetic regimen in a situation where the corticosteroid is given for antitumor reasons, the dose of the corticosteroid should not be reduced.[16]

NEUROKININ 1 RECEPTOR ANTAGONISTS

The potential use of NK1 receptor antagonists as antiemetics became apparent when the role of substance P in the peripheral nervous system and CNS was recognized in the emetic stimulus pathway. Aprepitant, the first NK1 receptor antagonist available, is active in both the acute and delayed phases of CINV caused by moderately and highly emetogenic chemotherapy. Aprepitant is usually given as a 3-day oral regimen, 125 mg on day 1 and 80 mg on days 2 and 3. Early trials determined that aprepitant could not replace a 5-HT_3 antagonist, but that it would be used best in conjunction with corticosteroids and a 5-HT_3 antagonist.[32]

Aprepitant has been studied in the prevention of CINV with highly and moderately emetogenic chemotherapy.[21,32] These studies showed improved response rates when aprepitant was added to antiemetic regimens containing a 5-HT_3 antagonist plus dexamethasone.

Although CINV symptoms tend to worsen from cycle to cycle, the effects of aprepitant seem to be maintained during four cycles of chemotherapy in patients receiving moderately emetogenic chemotherapy.[33] The addition of aprepitant to the antiemetic regimen during cycle two (even when omitted from cycle one) also seems to improve control of CINV symptoms.[34,35] For patients who have had an inadequate response to an antiemetic regimen that did not include aprepitant, it may be useful to add it in later cycles.

There is growing evidence that the prechemotherapy dose of aprepitant (or fosaprepitant) provides the majority of benefit compared with postchemotherapy doses.[21,36] The first dose of

aprepitant blocks about 80% of the NK1 receptors in the CNS.[21,36] One study compared a single 150-mg IV dose of fosaprepitant with the standard 3-day oral regimen (along with ondansetron and dexamethasone) in patients receiving highly emetogenic chemotherapy. No difference was found in the antiemetic efficacy between the two groups.[37]

Aprepitant is generally well tolerated and has mild side effects, including fatigue, hiccups, headache, and diarrhea.[32,38] The overall adverse effects in standard aprepitant-containing regimens are not appreciably different from regimens without aprepitant. Several NK1 antagonists are now available: fosaprepitant, an IV prodrug of aprepitant; an oral fixed combination capsule of an NK1-antagonist, netupitant plus palonosetron; and oral rolapitant. Netupitant and palonosetron combination therapy is recommended as an option for patients receiving highly or moderately emetogenic regimens. Trials comparing its efficacy against aprepitant have not yet been done. Rolapitant, the newest NK1 antagonist, is an oral drug with an extended half-life and should not be administered at <2-week intervals.

Aprepitant is metabolized by the CYP3A4 enzyme system. It is a moderate inhibitor and inducer of CYP3A4 and an inducer of CYP2C9.[1,32] Consequently, several drugs potentially interact with aprepitant. The most commonly encountered interaction occurs with corticosteroids. Aprepitant increases the area under the curve (AUC) of dexamethasone such that the dexamethasone dose (when used as an antiemetic) should be reduced by about one-half of the usual dose when these drugs are used together.[1,21,32] The interaction is greatest when the corticosteroid is administered orally (PO). However, when the corticosteroid is also given as part of the antitumor regimen, the corticosteroid dose should not be reduced because of concern that the antineoplastic activity might be compromised.[16] Aprepitant, fosaprepitant, and netupitant inhibit the metabolism of dexamethasone. Rolapitant does not share this interaction with dexamethasone. Aprepitant may also enhance warfarin metabolism by inducing CYP2C9. International normalized ratio (INR) values in patients treated with warfarin and the standard

aprepitant regimen are significantly reduced, especially on day 8 of the chemotherapy cycle.[21,32,39,40] The patient's coagulation status after aprepitant administration should be monitored, especially during the 7- to 10-day period after aprepitant. The dosage of warfarin should be adjusted if the INR is out of range. Several chemotherapy agents (paclitaxel, etoposide, ifosfamide, irinotecan, imatinib, vinca alkaloids, and others) are metabolized by the CYP3A4 enzyme system, and the metabolism of these agents may be altered by aprepitant. Aprepitant was used in clinical trials with some of these agents. Caution is warranted because the clinical relevance of this potential interaction is not known.[32,41] On comparing NK1-antagonists, there are fewer drug interactions with rolapitant when compared with aprepitant, fosaprepitant, and netupitant.

OLANZAPINE

Olanzapine is an atypical antipsychotic agent that antagonizes several serotonin and dopamine receptors as well as other neurotransmitter receptors.[42] Its antiemetic action was first described in patients with refractory nausea or vomiting and advanced cancer. Olanzapine has activity both in the prevention of CINV in patients at high and moderate risk and in rescue treatment for patients with refractory nausea and vomiting. Studies have demonstrated its efficacy in preventing CINV in the setting of highly and moderately emetogenic chemotherapy. Newer, controlled trials show improved response rates when added to an antiemetic regimen of a 5-HT_3 antagonist plus dexamethasone as well as comparable activity to aprepitant.[27,39,42,43] The typical dose of olanzapine used in these trials was 10 mg PO daily on days 1 through 5.

Olanzapine is also active as a rescue agent for patients with refractory CINV. In this setting, the usual dose of olanzapine is 2.5 to 10 mg daily in one to four divided doses. The common side effects of olanzapine include sleepiness, dry mouth, and dizziness, although these were not significant in preliminary reports.[27,39,42,43] Olanzapine is an option for the prevention of CINV in patients receiving highly to

moderately emetogenic regimens and a good choice for control of highly refractory CINV symptoms.

OTHER ANTIEMETICS

Medications from other drug classes have also been used as antiemetics for CINV. These include dopamine antagonists (prochlorperazine, promethazine), benzodiazepines (lorazepam), butyrophenones (droperidol, haloperidol), benzamides (metoclopramide), and cannabinoids. Many of these agents were used widely until more effective antiemetic agents became available. These agents remain useful for breakthrough symptoms or for patients who are refractory to standard therapy. The dosages and indications for these agents are shown in Table 22-3. Many of these agents have more side effects than contemporary agents do, especially sedation and extrapyramidal side effects, such as dystonia and akathisia. Lorazepam is commonly used as a rescue antiemetic. Its mechanism of action as an antiemetic is not completely understood, but it may involve disruption of the cortical impulses to the VC, as well as anxiolytic activity.

Cannabinoids have long been used for refractory nausea and vomiting. This is based on the effect of the CNS cannabinoid receptors on the CTZ, the NTS, and the VC.[44] Small trials have shown conflicting effectiveness in the prevention of CINV.[45,46] An oral cannabinoid, nabilone, was approved for the treatment of CINV in patients who do not respond adequately to other antiemetics.[44] Cannabinoids are associated with side effects, such as drowsiness, dry mouth, dysphoria, vertigo, and euphoria.[44,45] Although some patients have a clear preference for, and good response to, cannabinoids, side effects and a lack of pronounced efficacy limit their use in the general population of chemotherapy patients. These agents are usually reserved for patients who do not have adequate relief from other rescue medications.

The optimal prophylactic antiemetic regimens depend on the emetic risk of the chemotherapy regimen. Treatment guidelines have been developed by several groups, including the American Society

of Clinical Oncology (ASCO; http://jco.ascopubs.org/content/24/18/2932.full.pdf+html)[16]; and the Multinational Association of Supportive Care in Cancer (MASCC; https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-by-air-land-sea/motion-sickness).[17] These evidence- and consensus-based guidelines, which are similar in regard to the roles of the various antiemetics, are summarized in **Table 22-4** and **Figure 22-2**.

Table 22-4
Recommended Antiemetic Regimens for Chemotherapy-Induced Nausea and Vomiting by Emetogenicity of Chemotherapy Regimen

Emetogenicity Potential	Acute-Phase CINV (Doses Should Be Given 30–60 Minutes Before Chemotherapy) Day 1	Delayed-Phase CINV	Breakthrough CINV
High-risk IV chemotherapy regimens	**Four-Drug Regimen (Preferred)**		
	Olanzapine 5–10 mg PO once + NK1RA (select one) + 5-HT_3RA (select one) + dexamethasone 12 mg PO/IV once	Olanzapine 5–10 mg PO on days 2–4 + aprepitant 80 mg PO daily on days 2–3 (if aprepitant is the NK1RA used on day 1) + dexamethasone 8 mg PO/IV on days 2–4	Two agents for PRN use
	Three-Drug Regimen (Containing Olanzapine)		
	Olanzapine 5–10 mg PO once + palonosetron 0.25 mg IV once + dexamethasone 12 mg IV once	Olanzapine 5–10 mg PO daily on days 2–4	Two agents for PRN use
	Three-Drug Regimen (Containing NK1RA)		
	NK1RA (select one) + 5-HT_3RA (select one) + dexamethasone 12 mg PO/IV once	Aprepitant 80 mg PO daily on days 2–3 (if aprepitant is the NK1RA used on day 1) + dexamethasone 8 mg PO/IV on days 2–4	Two agents for PRN use
Moderate-risk IV chemotherapy regimens	**Three-Drug Regimen (Containing Olanzapine)**		
	Olanzapine 5–10 mg PO once + palonosetron 0.25 mg IV once + dexamethasone 12 mg PO/IV once	Olanzapine 5–10 mg PO daily on days 2–3	Two agents for PRN use
	Three-Drug Regimen (Containing NK1RA)		
	NK1RA (select one) + 5-HT_3RA (select one) + dexamethasone 12 mg PO/IV once	Aprepitant 80 mg PO daily on days 2–3 (if aprepitant is the NK1RA used on day 1) + dexamethasone 8 mg PO/IV on days 2–3	Two agents for PRN use
	5-HT_3RA + Dexamethasone		
	5-HT_3RA (select one) + dexamethasone 12 mg PO/IV once	Olanzapine 10 mg PO daily on days 2–3	Two agents for PRN use
Low-risk IV chemotherapy regimens	Single-dose dexamethasone or metoclopramide or prochlorperazine or 5-HT_3RA (ondansetron, granisetron, or dolasetron)	None	Either none or one agent for PRN use
Minimal-risk IV chemotherapy regimens	None	None	Usually none
High- to moderate-risk PO chemotherapy regimens	5-HT_3RA (ondansetron, granisetron, or dolasetron)	None	One agent for PRN use
Low-risk PO chemotherapy regimens	None	None	One agent for PRN use

5-HT_3RA, 5-hydroxytryptamine type 3 receptor antagonists; CINV, chemotherapy-induced nausea and vomiting; IV, intravenous; PO, oral; PRN, as needed; NK1RA, neurokinin 1 receptor antagonists.

Sources: National Cancer Institute https://www.cancer.gov/about-cancer/treatment/side-effects/nausea/nausea-hp-pdq# 66; Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update [published correction appears in J Clin Oncol. 2014 Jun 1;32(19):2117. Dosage error in article text]. *J Clin Oncol*. 2011;29:4189–4198; Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(suppl 5):v232–v243.

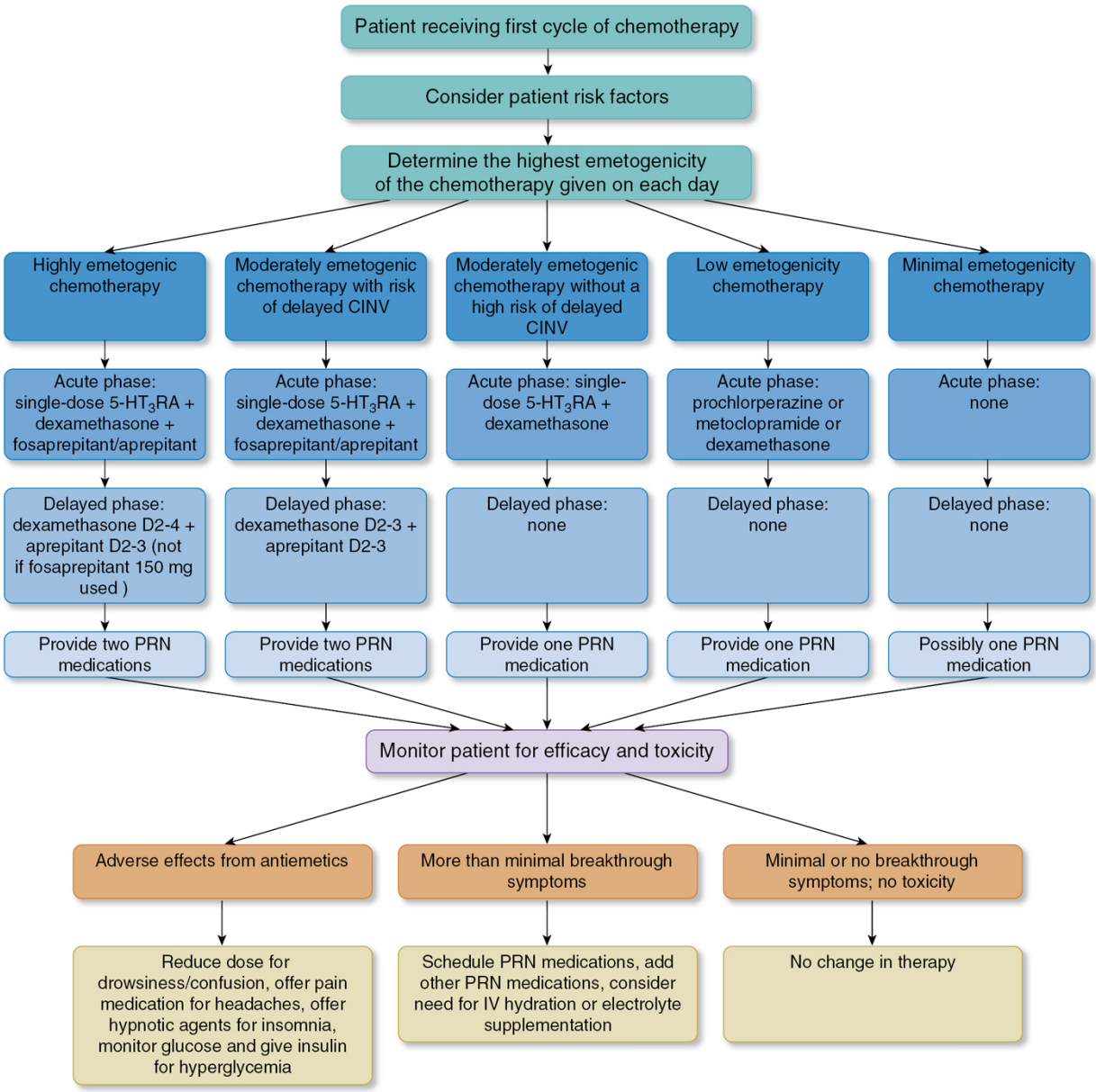


Figure 22-2 Algorithm for antiemetic selection of an *initial* chemotherapy cycle. 5-HT_3-RA, 5-hydroxytryptamine type 3 receptor antagonist; CINV, chemotherapy-induced nausea and vomiting; PRN, as needed.

Many patients may benefit from nondrug therapy for CINV symptoms, especially for anticipatory nausea and vomiting and anxiety. Techniques include guided imagery, hypnosis, relaxation techniques, systematic desensitization, and music therapy.[47] Acupuncture and acupressure techniques have been investigated for

use in CINV, and some patients benefit from their use. The use of acupressure devices that stimulate the P6 point on the wrist has been proposed; however, in a controlled trial in patients with breast cancer, it was not found to be helpful.[48] If patients are troubled by CINV symptoms, it is recommended that they refrain from heavy meals for 8 to 12 hours before chemotherapy. They should also avoid heavy, greasy foods and food with strong aromas. Chewing gum can mask the metallic taste that some patients perceive. Dry, salty foods can also help settle the stomach.

Clinical Presentation and Risk Factors

CASE 22-2

Question 1: M.C., a 54-year-old female with breast cancer, is in the clinic today to receive her first cycle of chemotherapy. Her chemotherapy will consist of docetaxel 75 mg/m^2 IV, carboplatin dosed to achieve an AUC of 6 mg/mL × minute. This will be repeated every 21 days. In addition, she will receive trastuzumab 4 mg/kg IV for one dose, then 2 mg/kg/week for 17 weeks. M.C. does not drink alcohol or smoke. Her only other medical condition is adult-onset diabetes, which is controlled with metformin and diet. She has had four children, now all grown, and had substantial morning sickness with each of her pregnancies. M.C.'s neighbor told her that all chemotherapy causes severe nausea and vomiting.

How likely is M.C. to experience nausea and vomiting? What are her risk factors?

M.C. is at moderate risk for acute CINV. Her personal risk factors include female sex, history of morning sickness with pregnancy, and being a nondrinker. The docetaxel has a low risk of acute CINV, the carboplatin has a moderate risk of acute CINV with a high risk of delayed CINV, and the trastuzumab has a minimal risk of acute CINV. A moderate-risk prophylactic regimen should be recommended for M.C.

Case 22-2, Question 2: What antiemetics are available for M.C.?

For moderate-risk prophylaxis, a two- to three-drug–containing regimen is recommended. For a single-day chemotherapy regimen, the aprepitant-containing regimen includes a single dose of 5-HT_3 antagonist plus dexamethasone 8 to 12 mg oral or IV plus oral aprepitant 125 mg on day 1, then oral dexamethasone 8 mg on days 2 through 4, and oral aprepitant 80 mg on days 2 and 3. The olanzapine-containing regimen includes olanzapine 10 mg oral on days 1 to 3, dexamethasone 20 mg IV once on day 1, and palonosetron 0.25 mg IV once on day 1. The two-drug–containing regimen includes a single dose of 5-HT_3 antagonist plus dexamethasone 8 to 12 mg oral on day 1, then dexamethasone 8 mg oral or IV daily on days 2 to 3, or 5-HT_3 antagonist monotherapy on days 2 and 3.

CASE 22-2, QUESTION 3: M.C. is at moderate risk for acute nausea and vomiting and at high risk for delayed CINV symptoms as a result of her chemotherapy regimen of docetaxel, carboplatin, and trastuzumab. What would be the most appropriate antiemetic regimen for M.C.?

For M.C., the best regimen would be a two- to three-drug–containing regimen. She should be offered medications for breakthrough CINV symptoms, such as prochlorperazine and lorazepam. She should be warned of the potential adverse effects of dexamethasone or olanzapine, especially hyperglycemia, and counseled to check her blood sugar levels more frequently and contact her physician if they remain elevated. M.C. should be advised to maintain a record of her symptoms and contact her physician if the breakthrough medications are not working or if she cannot keep fluids down.

If M.C. had been prescribed a multiday chemotherapy regimen, prophylaxis with a 5-HT_3 antagonist and dexamethasone should be offered for each day that moderately or highly emetogenic chemotherapy is administered.[1,16,17,49] If multiday chemotherapy regimens have a high risk of delayed symptoms, then therapy (eg, dexamethasone plus prochlorperazine or metoclopramide, if

aprepitant was already administered) for the delayed symptoms should be continued for at least 2 to 3 days after the last chemotherapy administration.

Modern antiemetic regimens achieve complete emetic control in about 70% to 90% of patients, but the response rate is lower for delayed CINV symptoms. If CINV symptoms are not adequately controlled, alterations in the prophylactic antiemetic regimen should be made for the next cycle (**Fig. 22-3**). Suggestions include upgrading to the next higher emetogenicity level recommendation, adding aprepitant if not already given, and scheduling antiemetic agents from other pharmacologic classes.

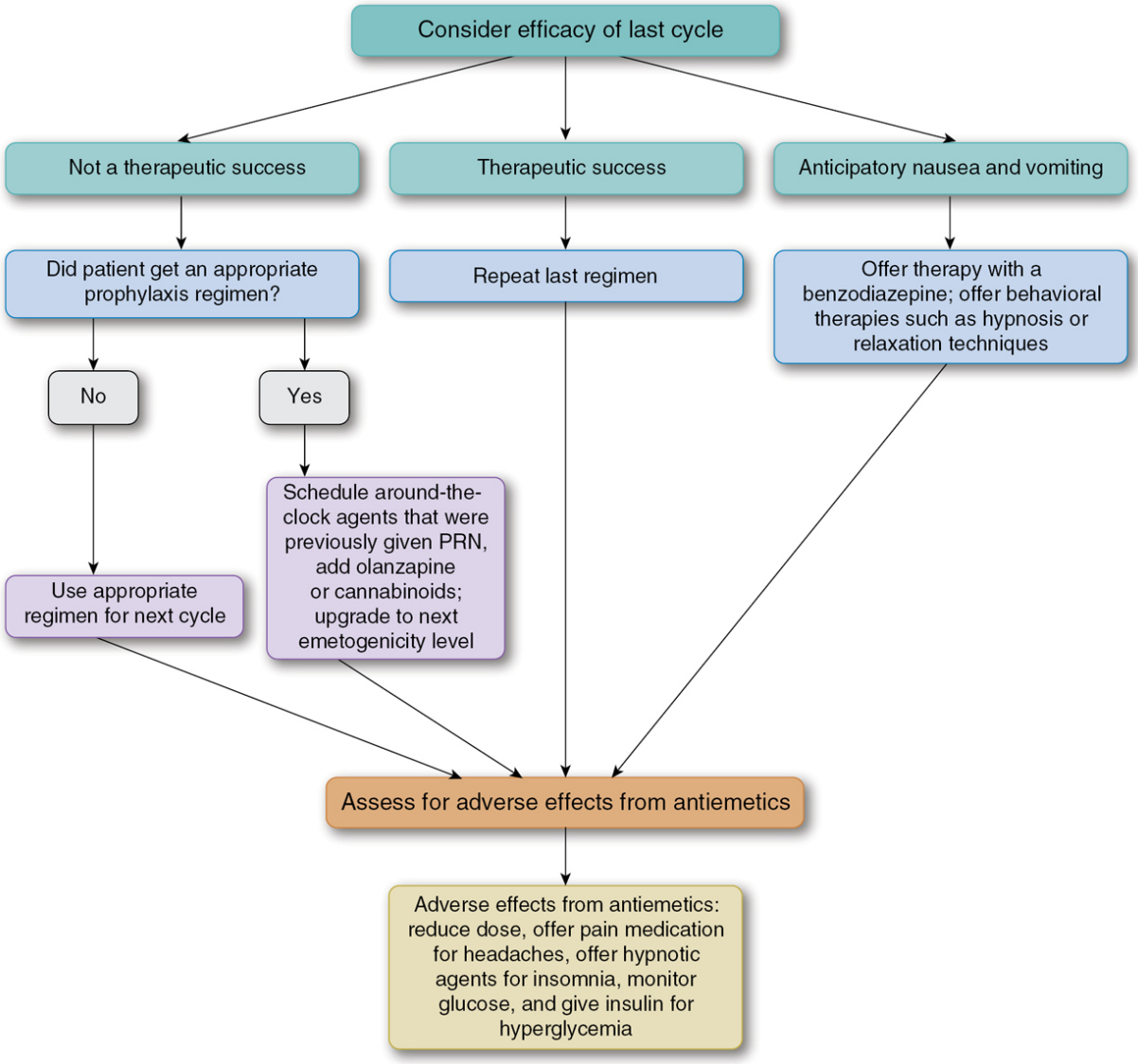


Figure 22-3 Algorithm for selection of antiemetic regimens for subsequent chemotherapy cycles. PRN, as needed.

RADIATION-INDUCED NAUSEA AND VOMITING

Clinical Presentation and Risk Factors

CASE 22-3

QUESTION 1: E.G. is a 54-year-old male with newly diagnosed head and neck cancer who will receive radiation therapy concurrently with cisplatin and fluorouracil chemotherapy. His daily (Monday through Friday) radiation treatments will last for 6 weeks. He has a heavy smoking history (35 pack-years) and "quit" last week, although it is not going well.

After nausea and vomiting from the chemotherapy subsides, is E.G. at risk for experiencing radiation-induced nausea and vomiting (RINV)? What antiemetic prophylaxis is appropriate?

Radiation therapy can cause nausea and vomiting through the same basic pathways that chemotherapy does. RINV affects 40% to 80% of patients receiving radiation therapy. The risk of RINV depends on several factors, namely, the size and area to be irradiated, larger fractional doses of radiation, and whether the patient has had previous chemotherapy.[1,50,51] Patients with radiation areas >400 cm^2 are more likely to have significant RINV symptoms. The radiation therapy oncologist will determine the size of the radiation field and fractional doses of radiation to maximize the efficacy of the radiation therapy. The high dose used in total body irradiation (associated with hematopoietic stem cell transplantation) causes RINV in >90% of patients. Patients receiving radiation to the upper abdominal area experience nausea and vomiting about 50% to 80% of the time. Radiation to other areas of the body is less likely to cause nausea and vomiting.

Overview of Treatment

Just as with CINV, symptoms caused by radiation can be prevented with 5-HT_3 antagonists, corticosteroids, or both. Evidence- and consensus-based recommendations have been published by several multidisciplinary groups, and are shown in **Table 22-5**. High-risk RINV is best treated with a combination of a 5-HT_3 antagonist and a corticosteroid.[1,50-53] Patients receiving concomitant chemotherapy and radiation should receive antiemetics appropriate for the chemotherapy regimen.[1] Patients receiving radiotherapy in the moderate RINV risk group can receive either prophylaxis or rescue therapy with a 5-HT_3 antagonist.

Table 22-5
Prophylaxis for Radiation-Induced Nausea and Vomiting for Adults

Emetic Risk	Radiation Area	Recommendation
High risk	Total body irradiation	Prophylaxis with a 5-HT_3RA (eg, ondansetron 8 mg PO bid–tid or granisetron 2 mg PO daily) ± dexamethasone 4 mg PO daily
Moderate risk	Upper abdomen	Prophylaxis with a 5-HT_3 antagonist (eg, ondansetron 8 mg PO bid or granisetron 2 mg PO daily) ± dexamethasone 4 mg PO daily

5-HT_3RA, 5-hydroxytryptamine type 3 receptor antagonist; bid, twice daily; PO, oral; tid, three times daily.

Sources: McDonagh M, Peterson K, Thakurta S. Consideration of Evidence on Antiemetic Drugs for Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy in Adults. Rockville (MD); 2010; Adapted with permission from: Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol*. 1997;15:103-109; Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—state of the art. *Support Care Cancer*. 2011;19:S43-S47; Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—an update. *Support Care Cancer*. 2005;13:80–84; Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus

conference. *Ann Oncol*. 2010;21(Suppl 5):v232–v243; Feyer P, Maranzano E, Molassiotis A, et al. Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: update 2009. *Support Care Cancer*. 2011;19 Suppl 1:S5-S14; Abdelsayed GG. Management of radiation-induced nausea and vomiting. *Exp Hematol*. 2007;35(4 Suppl 1):34–36.

Although E.G. is receiving concurrent chemotherapy, he is at low risk for experiencing RINV because his radiation site will be in the head and neck region, it is not likely to be >400 cm^2, and he will likely receive a smaller fractional dose. Because E.G. is at low risk for having RINV symptoms, he does not need prophylaxis with a 5-HT_3 antagonist. If he experiences symptoms, rescue therapy with a dopamine antagonist or a serotonin antagonist should be offered.

POSTOPERATIVE NAUSEA AND VOMITING

Clinical Presentation and Risk Factors

CASE 22-4

QUESTION 1: E.W. is a 48-year-old female who is scheduled for a laparoscopic cholecystectomy. The scheduled duration of her surgery is less than an hour. Her medical history includes hypertension. She does not have a history of motion sickness and is a nonsmoker. E.W. has never had surgery before. Her sister-in-law had severe nausea and vomiting after an outpatient surgical procedure last year, and E.W. is worried that she too may have it.

What is E.W.'s risk of having postoperative nausea and vomiting (PONV)? What can be done to reduce her risk, and how can symptoms be treated if they occur?

PONV is a common complication of surgery affecting 25% to 30% of all patients, but up to 80% of patients in high-risk groups.[54] In surgical patients, PONV can lead to hospitalizations, stress on the surgical closure, hematomas, and aspiration pneumonitis. Patient-related, surgical, and anesthetic factors can increase the risk of PONV.[54–58] Patient risk factors include female sex, history of motion

sickness, nonsmoking status, age younger than 50 years, and a history of PONV.[11] Some surgical risk factors for PONV include type of surgical procedure (eg, laparoscopy, gynecologic surgeries, intra-abdominal surgery, and neurosurgery) and prolonged surgical time.[11] Anesthesia-related risk factors include the use of volatile anesthetics, nitrous oxide, prolonged duration of anesthesia, increased doses of neostigmine (>3 mg), and the use of intraoperative or postoperative opioids.[11] Children are twice as likely to have PONV as do adults, but the risk declines after puberty.[55,59]

Certain anesthesia practices may reduce the risk of PONV. These include use of regional anesthesia (instead of general anesthesia); use of total IV anesthesia with propofol; use of intraoperative oxygen; adequate hydration; and avoidance of nitrous oxide, volatile anesthesia therapy, and intraoperative or postoperative opiates.[54–56,58–60] Using propofol for anesthesia (or sedation) is associated with a 3.5-fold reduction in the incidence of PONV in adults and 5.7-fold reduction in children.[11]

Antiemetics to treat nausea and vomiting produce major side effects ranging from mild headache to severe arrhythmia due to QTc prolongation. Therefore, it is essential to calculate the risk of developing PONV and post discharge nausea and vomiting (PDNV) in each patient to reduce excessive use of antiemetics for prophylaxis.[11] Several risk factor models have been studied to correlate these factors into recommendations for prevention and therapy.[54,56] One model, the Apfel risk scoring system, is both simple and practical. A study by White et al[61] reported that an Apfel risk score of 3 or 4 (vs a score of 1–2) is associated with a higher incidence of emesis in the first 24 hours after surgery irrespective of administration of multiple antiemetics as prophylaxis.[11] This model uses the following risk factors: biologic sex, history of PONV or motion sickness, smoking status, and the use of postoperative opioids.[11] The PONV risk increases by 10%, 21%, 39%, 69%, and 79% when 0, 1, 2, 3, and 4 factors are present, respectively. Apfel's risk scoring system is more sensitive and specific compared to predicting PONV based on history of PONV or type of surgery alone. E.W. has at least two risk factors (female, nonsmoker) that may

increase if her surgery lasts longer than expected, or if she receives intraoperative or postoperative opioids. She has a moderate to high risk of PONV.

The Apfel risk scoring system is not directly applicable to children. Instead, the Eberhart classification scoring system is more often used for children and incorporates the following risk factors: age older than 3 years, duration of surgery >30 minutes, strabismus surgery, and personal or family history of PONV.[11] The risk of PONV for children undergoing strabismus surgery with 0 to 1, 2, 3, or 4 of these risk factors is 10%, 30%, 50%, and 70%, respectively.[11] This scoring system has also been validated for children having surgery other than for strabismus, and PONV was observed in 3%, 11%, 30%, and 40% of children who had 0, 1, 2, or 3 risk factors, respectively.

Overview of Treatment

The management strategy for each individual patient should be based on the level of risk for PONV, the patient's preexisting condition, patient preference, and cost efficiency.[11] Patients with zero or one risk factor typically will not need prophylaxis. Patients with moderate risk (two to three risk factors) should receive one to two antiemetics. Appropriate choices for monotherapy include droperidol, a 5-HT_3 antagonist, or dexamethasone. Patients at the highest risk for PONV (at least four risk factors) should be given prophylaxis with a combination of two to three antiemetics. Dual-therapy choices include a 5-HT_3 antagonist plus either droperidol or dexamethasone. Triple therapy would combine a 5-HT_3 antagonist plus dexamethasone plus droperidol. Because E.W. has a moderate to high risk for PONV, a combination of a 5-HT_3 antagonist (such as ondansetron 4–8 mg at the end of surgery) and dexamethasone (4–10 mg after induction of anesthesia)[11] would be a good choice for prophylactic therapy.

The most effective and commonly used medications for the prevention of PONV include 5-HT_3 antagonists, dexamethasone,

droperidol, and combinations of these agents. 5-HT_3 antagonists have differences regarding its efficacy and duration of action. Granisetron, a more selective 5-HT_3 antagonist, has been suggested to provide more sustained antiemesis for prophylaxis.[62] Ramosetron has a greater affinity for the 5-HT_3 receptor and a longer duration of antiemetic action. This results in a similar or greater prophylactic antiemetic effect than that of the older 5-HT_3 receptor antagonists (eg, ondansetron), and provides better antiemetic efficacy in patients at moderate to high risk.[11] Droperidol has long been used for PONV, but concerns have been raised about the rare occurrence of QTc prolongation and torsades de pointes.[63,64] Most clinicians believe droperidol to be safe, especially when doses are not excessive (up to 1.25–2.5 mg/dose for adults).[55,64,65] Multiple well-controlled, randomized, comparative clinical trials have validated droperidol to be as safe and effective than are the more costly 5-HT_3 and NK1 antagonists.[66,67] The mechanism by which dexamethasone protects against PONV is unclear, but its efficacy has been shown in many trials.[55,59,63] Ormel et al found that dexamethasone 4 to 5 mg was equally as effective as 8 to 10 mg in terms of antiemetic efficacy.[68] Combinations of medications with different mechanisms of action are more effective than is monotherapy. Aprepitant has been studied in the prevention of PONV.[32,54,55] Studies have shown similar activity of aprepitant compared with ondansetron.[32,54,55] Aprepitant, however, is significantly more expensive than is generic ondansetron or dexamethasone, which is a consideration. The use of aprepitant is also limited by the potential for drug interactions.[58] Dexamethasone and 5-HT_3 antagonist combinations have been well studied and are highly effective.[54,55,59,63,65] Transdermal scopolamine is also effective, but can have side effects.[54] Dosages for the prophylaxis and treatment of PONV are shown in **Table 22-6**. The 5-HT_3 antagonists and droperidol seem to be more effective when given at the end of surgery. Corticosteroids are best given after the induction of anesthesia.[11] Although not a first-line agent, the dopamine (D_2) receptor antagonist amisulpride (Barhemsys®) has been found to be

effective in treating PONV after failed prophylaxis[69] for patients at low-to-moderate risk of PONV who received no prior PONV prophylaxis.[70]

Table 22-6
Prophylactic Doses and Timing for the Administration of Antiemetic Drugs

Drug Group	Drugs	Dose	Timing	Adverse Effect
Serotonin (5-HT_3 receptor) antagonists	Ondansetron	4–8 mg IV every 4–8 hours	End of surgery	Headaches, constipation, flushing, fatigue, malaise, raised liver enzymes
	Granisetron	1–2 mg IV		
	Ramosetron	0.3 mg IV 0.1 mg PO		
	Palonosetron	0.075–0.25 mg IV		
Corticosteroids	Dexamethasone	4–10 mg IV	After induction of anesthesia	Elevated blood glucose level, diabetes mellitus, hypotension/hypertension
Butyrophenone	Droperidol	0.625–1.25 mg IV	After induction of anesthesia	Psychomimetic effects, extrapyramidal side effects, Parkinson disease, sedation, lightheadedness, prolonged QT interval
Neurokinin antagonists (NK-1 receptors)	Aprepitant	40 mg orally	1–2 hours before induction	Headaches, constipation, fatigue
	Fosaprepitant	150 mg IV	After induction of anesthesia	
Anticholinergics	Scopolamine	Transdermal patch[a] 1.5 mg for 24 hours	Evening before[a] surgery or at least 1–2 hours before operation	Dizziness, dry mouth, visual disturbances, tachycardia, confusion, urinary retention
Dopamine antagonists	Metoclopramide	10–25 mg IV	15–30 minutes before end of surgery	Sedation, hypotension (fast injection), headache, extrapyramidal symptoms
	Amisulpride IV	5–10 mg IV	At induction of anesthesia	

IV, intravenous; PO, oral.

[a]UpToDate, Inc. Lexi-Drugs. UpToDate, Inc.; December 8, 2021.

From Elvir-Lazo OL, White PF, Yumul R, Cruz Eng H. Management strategies for the treatment and prevention of postoperative/postdischarge nausea and vomiting: an updated review. *F1000Res*. 2020;9:F1000 Faculty Rev-983. https://creativecommons.org/licenses/by/4.0/

Ginger root contains the active ingredients gingerol (Ginjervel) and shogaol (Chagall). They reduce stomach contractions and increase GI tract motility via anticholinergic and antiserotonergic actions.[11] There has been conflicting information reported concerning the effectiveness, but it may be an option for E.W.

Nonpharmacologic techniques for the prevention of PONV have been studied and shown to be effective in some patient populations. These include acupuncture, transcutaneous nerve stimulation,

acupressure at the P6 wrist point, hypnosis, and aromatherapy with isopropyl alcohol.

Even with appropriate prophylaxis for PONV, some patients will experience breakthrough symptoms and require rescue therapy.[54] Patients who have not received prophylaxis with a 5-HT_3 antagonist can be offered it as rescue therapy. Only one-quarter of the typical 5-HT_3 prophylaxis dose is needed.[55] For all patients who have breakthrough symptoms, it is important to choose an antiemetic from a different pharmacologic class than the agents used for prophylaxis.[54,56,63] Droperidol, promethazine, metoclopramide, and prochlorperazine are commonly used as rescue medications. If E.W. had breakthrough nausea, droperidol (0.625–1.25 mg IV or intramuscular every 4–6 hours as needed) would be a good choice for rescue therapy.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Basch E, Prestrud AA, Hesketh PJ, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2011. *J Clin Oncol.* 2011;29:4189–4198. (16)

Feyer P, Maranzano E, Molassiotis A, Roila F, Clark-Snow RA, Jordan K. Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: update 2009. *Support Care Cancer.* 2011;19(suppl 1):S5–S14. (51)

Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2020;131(2):411–448. (60)

Golding JF, Gresty MA. Motion sickness. *Curr Opin Neurol*. 2005;18: 29–34. (8)

Ignoffo RJ. Current research on PONV/PDNV: practical implications for today's pharmacist. *Am J Health Syst Pharm.* 2009;66*(1 suppl 1*):S19–S24. (58)

Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(suppl 5):v232–v243. (17)

Shupak A, Gordon CR. Motion sickness: advances in pathogenesis, prediction, prevention, and treatment. *Aviat Space Environ Med*. 2006;77:1213–1223. (5)

COMPLETE REFERENCES CHAPTER 22 NAUSEA AND VOMITING

1. McDonagh M, Peterson K, Thakurta S. Consideration of Evidence on Antiemetic Drugs for Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy in Adults. Rockville (MD); 2010.
2. Brainard A, Gresham C. Prevention and treatment of motion sickness. *Am Fam Physician.* 2014;90:41–46.
3. Erskine SK. *Travelers' Health—Motion Sickness*. Centers for Disease Control and Prevention. Yellow Book. Chapter 8. 2020:1. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-by-air-land-sea/motion-sickness
4. Priesol AJ. Motion sickness. *Up To Date*. Accessed December 10, 2021. http://www.uptodate.com/contents/motion-sickness
5. Shupak A, Gordon CR. Motion sickness: advances in pathogenesis, prediction, prevention, and treatment. *Aviat Space Environ Med*. 2006;77:1213–1223.
6. Committee to Advise on Tropical Medicine and Travel. Statement on motion sickness. *Can Commun Dis Rep*. 2003;29:101–112.
7. Miller KE, Muth ER. Efficacy of acupressure and acustimulation bands for the prevention of motion sickness. *Aviat Space Environ Med*. 2004;75:227–234.
8. Golding JF, Gresty MA. Motion sickness. *Curr Opin Neurol*. 2005;18:29–34.
9. Lien HC, Ming Sun W, Chen YH, Kim H, Hasler W, Owyang C. Effects of ginger on motion sickness and gastric slow-wave dysrhythmias induced by circular vection. *Am J Physiol Gastrointest Liver Physiol*. 2003;284:G481–G489.
10. Brainard A, Gresham C, et al. Motion sickness treatment & management. Medication. Medscape: Drugs & Diseases—Neurology. Published October 22, 2018.
11. Elvir-Lazo OL, White PF, Yumul R, Cruz Eng H. Management strategies for the treatment and prevention of postoperative/postdischarge nausea and

vomiting: an updated review. *F1000Research.* 2020;9(Faculty Rev):983. doi:10.12688/f1000research.21832.1

12. Spinks A, Wasiak J, Villanueva EV, Bernath V. Scopolamine (hyoscine) for preventing and treating motion sickness. *Cochrane Database Syst Rev*. 2007;(3):CD002851.
13. Dornhoffer J, Chelonis JJ, Blake D. Stimulation of the semicircular canals via the rotary chair as a means to test pharmacologic countermeasures for space motion sickness. *Otol Neurotol*. 2004;25:740–745.
14. Petrella T, Clemons M, Joy A, et al. Identifying patients at high risk for moderate to severe nausea and vomiting following chemotherapy: the development and validation of a prediction tool for the practicing oncologist. *Support Care Cancer*. 2006;14:683.
15. Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—an update. *Support Care Cancer*. 2005;13:80–84.
16. Basch E, Prestrud AA, Hesketh PJ, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2011. *J Clin Oncol*. 2011;29:4189–4198.
17. Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(suppl 5):v232–v243.
18. Hamadani M, Padmanabhan R, Chaudhary L, Tfayli A. Relative efficacy of various 5-hydroxytyptamine receptor antagonists in the prevention and control of acute nausea and vomiting associated with platinum-based chemotherapy. *J Clin Oncol*. 2006;24(18 suppl):8623.
19. Jordan K, Schmolla HJ, Aaprob MS. Comparative activity of antiemetic drugs. *Crit Rev Oncol Hematol*. 2007;61:162–175.
20. Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT_3-receptor antagonists for acute chemotherapy-induced emesis. *Support Care Cancer*. 2007;15:1023–1033.
21. Frame DG. Best practice management of CINV in oncology patients: 1. Physiology and treatment of CINV. Multiple neurotransmitters and receptors and the need for combination therapeutic approaches. *J Support Oncol*. 2010;8(2 suppl 1):5–9.
22. Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. *Cochrane Database Syst Rev*. 2010; (1):CD006272.
23. Hamadani M, Chaudhary L, Awan FT, et al. Management of platinum-based chemotherapy-induced acute nausea and vomiting: is there a superior serotonin receptor antagonist? *J Oncol Pharm Pract*. 2007;13:69–75.
24. Grunberg SM. Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis. *Ann Oncol*.

2007;18:233–240.
25. Lindley C, Goodin S, McCune J, et al. Prevention of delayed chemotherapy-induced nausea and vomiting after moderately high to highly emetogenic chemotherapy. *Am J Clin Oncol*. 2005;28:270–276.
26. Hickok JT, Roscoe JA, Morrow GR, et al. 5-Hydroxytryptamine-receptor antagonists versus prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomised controlled trial. *Lancet Oncol*. 2005;6:765–772.
27. Gelling O, Eichler HG. Should 5-hydroxytryptamine-3 antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systemic re-evaluation of clinical evidence and drug cost implications. *J Clin Oncol*. 2005;23:1289–1294.
28. Navari RM. Pharmacological management of chemotherapy-induced nausea and vomiting: focus on recent developments. *Drugs*. 2009;69:515–533.
29. Grote T, Hajdenberg J, Cartmell A, Ferguson S, Ginkel A, Charu V. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. *J Support Oncol*. 2006;4:403–408.
30. Brygger L, Herrstedt J. Academy of Geriatric Cancer Research (AgeCare). 5-Hydroxytryptamine 3 receptor antagonists and cardiac side effects. *Expert Opin Drug Saf*. 2014;13:1407–1422.
31. Einhorn LH, Grunberg SM, Rapoport B, Rittenberg C, Feyer P. Antiemetic therapy for multiple-day chemotherapy and additional topics consisting of rescue antiemetics and high-dose chemotherapy with stem cell transplant: review and consensus statement. *Support Care Cancer*. 2011;19(suppl 1):S1–S4.
32. Curran MP, Robinson DM. Aprepitant: a review of its use in the prevention of nausea and vomiting. *Drugs*. 2009;69:1853–1878.
33. Herrstedt J, Muss HB, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer*. 2005;104:1548–1555.
34. Hesketh PJ, Younger J, Sanjay R, et al. Aprepitant as salvage antiemetic therapy in breast cancer patients receiving doxorubicin and cyclophosphamide (AC). *J Clin Oncol*. 2006;24:(suppl):8618.
35. Oechsle K, Müller MR, Hartmann JT, Kanz L, Bokemeyer C. Aprepitant as salvage therapy in patients with chemotherapy-induced nausea and emesis refractory to prophylaxis with 5-HT(3) antagonists and dexamethasone. *Onkologie*. 2006;29:557–561.
36. Grunberg SM, Chua DT, Maru A, et al. Phase III randomized double-blind study of single-dose fosaprepitant for prevention of cisplatin induced nausea and vomiting. *J Clin Oncol*. 2010;28(suppl):9021.

37. Grunberg S, Chua D, Maru A, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol-EASE. *J Clin Oncol*. 2011;29:1495–1501.
38. Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. *Ann Oncol*. 2006;17:1000–1006.
39. Navari RM. Antiemetic control: toward a new standard of care for emetogenic chemotherapy. *Expert Opin Pharmacother*. 2009;10:629–644.
40. Depre M, Van Hecken A, Oeyen M, et al. Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. *Eur J Pharmacol*. 2005;61:341–346.
41. Aapro MS, Walko CM. Aprepitant: drug–drug interactions in perspective. *Ann Oncol*. 2010;21:2316–2323.
42. Tan L, Liu J, Liu X, et al. Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. *J Exp Clin Cancer Res*. 2009;28:131.
43. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV): a randomized phase III trial. *J Clin Oncol*. 2010;28(15_suppl):9020.
44. Slatkin NE. Cannabinoids in the treatment of chemotherapy induced nausea and vomiting: beyond prevention of acute emesis. *J Support Oncol*. 2007;5(5 suppl 3):1–9.
45. Meiri E, Jhangiani H, Vredenburgh J, et al. Dronabinol treatment of delayed chemotherapy-induced nausea and vomiting (CINV). *J Clin Oncol*. 2005;23(suppl):8018.
46. Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin*. 2007;23:533–543.
47. Roscoe JA, Morrow GR, Aapro MS, Molassiotis A, et al. Anticipatory Nausea and Vomiting. *Support Care Cancer*. 2011;19(10): 1533–1538. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136579/
48. Roscoe JA, Matteson SE, Morrow GR, et al. Acustimulation wrist bands are not effective for the control of chemotherapy-induced nausea in women with breast cancer. *J Pain Symptom Manage*. 2005;29:376–384.
49. Ellebaek E, Herrstedt J. Optimizing antiemetic therapy in multiple-day and multiple cycles of chemotherapy. *Curr Opin Support Palliat Care*. 2008;2:28–34.
50. Maranzano E, De Angelis V, Pergolizzi S, et al. A prospective observational trial on emesis in radiotherapy: analysis of 1020 patients recruited in 45 Italian radiation oncology centres. *Radiother Oncol*. 2009;94:36–41.

51. Feyer P, Maranzano E, Molassiotis A, Roila F, Clark-Snow RA, Jordan K. Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: update 2009. *Support Care Cancer*. 2011;19(suppl 1):S5–S14.
52. Wong RKS, Paul N, Ding K, et al. 5-Hydroxytryptamine-3 receptor antagonist with or without short-course dexamethasone in the prophylaxis of radiation induced emesis: a placebo-controlled randomized trial of the National Cancer Institute of Canada Clinical Trials Groups (SC19). *J Clin Oncol*. 2006;24:3458–3464.
53. Abdelsayed GG. Management of radiation-induced nausea and vomiting. *Exp Hematol*. 2007;35(4 suppl 1):34–36.
54. Le TP, Gan TJ. Update on the management of postoperative nausea and vomiting and postdischarge nausea and vomiting in ambulatory surgery. *Anesthesiol Clin*. 2010;28:225–249.
55. Gan TJ, Meyer T, Apfel CC, et al. Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg*. 2020;97:62–71.
56. Golembiewski J, Chernin E, Chopra T. Prevention and treatment of postoperative nausea and vomiting. *Am J Health Syst Pharm*. 2005;62:1247–1260.
57. Kloth D. New pharmacologic findings for the treatment of PONV and PDNV. *Am J Health Syst Pharm*. 2009;66(1 suppl 1):S11–S18.
58. Ignoffo RJ. Current research on PONV/PDNV: practical implications for today's pharmacist. *Am J Health Syst Pharm*. 2009;66(1 suppl 1):S19–S24.
59. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs*. 2000;59:213–243.
60. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2020;131(2):411–448.
61. White PF, Sacan O, Nuangchamnong N, Sun T, Matthew R. The relationship between patient risk factors and early versus late postoperative emetic symptoms. *Anesth Analg*. 2008;107(2):459–463.
62. White PF, Tang J, Hamza MA, et al. The use of oral granisetron versus intravenous ondansetron for antiemetic prophylaxis in patients undergoing laparoscopic surgery: the effect on emetic symptoms and quality of recovery. *Anesth Analg*. 2006;102(5):1387–1393.
63. Wilhelm SM, Dehoorne-Smith ML, Kale-Pradhan PB. Prevention of postoperative nausea and vomiting. *Ann Pharmacother*. 2007;41:68–78.
64. McKeage K, Simpson D, Wagstaff AJ. Intravenous droperidol: a review of its use in the management of postoperative nausea and vomiting. *Drugs*. 2006;66:2123–2147.
65. Leslie JB, Gan TJ. Meta-analysis of the safety of 5-HT_3 antagonists with dexamethasone or droperidol for prevention of PONV. *Ann Pharmacother*. 2006;40:856–872.

66. Fortney JT, Gan TJ, Graczyk S, et al. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. *Anesth Analg*. 1998;86(4):731–738.
67. Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. *Anesthesiology*. 2000;92(4):958–967.
68. Ormel G, Romundstad L, Lambert-Jensen P. Dexamethasone has additive effect when combined with ondansetron and droperidol for treatment of established PONV. *Acta Anaesthesiol Scand*. 2011;55(10):1196–1205.
69. Habib AS, Kranke P, Bergese SD, et al. Amisulpride for the rescue treatment of postoperative nausea or vomiting in patients failing prophylaxis: a randomized, placebo-controlled phase III trial. *Anesthesiology*. 2019;130(2):203–212.
70. Candiotti KA, Kranke P, Bergese SD, et al. Randomized, double-blind, placebo-controlled study of intravenous amisulpride as treatment of established postoperative nausea and vomiting in patients who have had no prior prophylaxis. *Anesth Analg*. 2019;128(6):1098–1105.

23

Upper Gastrointestinal Disorders

Elaine J. Law and Ricky B. Thumar

CORE PRINCIPLES	CHAPTER CASES
PEPTIC ULCER DISEASE	
1 Chronic peptic ulcer disease (PUD) is causally linked to *Helicobacter pylori* infection or the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and is usually characterized by epigastric pain or discomfort, sometimes accompanied by heartburn, bloating, and belching.	**Case 23-1 (Questions 1, 2) Case 23-2 (Question 1) Case 23-4 (Question 3)**

CORE PRINCIPLES		CHAPTER CASES
2	Treatment for PUD is aimed at relieving ulcer symptoms, healing the ulcer, eradicating *H. pylori* (if finding is positive), preventing ulcer recurrence, and reducing ulcer-related complications; eradication is recommended for all patients with an *H. pylori*–positive active ulcer or a history of a previous ulcer or ulcer-related complication; proton-pump inhibitors (PPIs) are the drugs of choice for healing and reducing the risk of an NSAID ulcer; patients with a peptic ulcer should be recommended lifestyle modifications.	**Case 23-1 (Questions 3–10) Case 23-2 (Questions 2–10)**
3	Treatment for an *H. pylori* ulcer should be initiated with a clarithromycin-based three-drug eradication regimen; the regimen should be effective, well tolerated, easy to comply with, cost-effective, and should take into consideration antibiotic resistance; if a second course of therapy is necessary, it should contain different antibiotics.	**Case 23-1 (Questions 3, 4, 6–10)**

CORE PRINCIPLES		CHAPTER CASES
4	PPIs are the preferred agents for healing an *H. pylori*–negative NSAID ulcer because they accelerate ulcer healing and provide more effective symptom relief than do histamine-2 receptor antagonists (H_2RAs); the duration of treatment should be extended if the NSAID is continued; if the patient is *H. pylori* positive, a clarithromycin-based three-drug regimen should be used.	**Case 23-2 (Questions 2, 3, 10)**
5	Prophylactic risk reduction therapy with a PPI or misoprostol or switching to an NSAID with greater cyclooxygenase-2 (COX-2) selectivity is recommended for patients at risk for exhibiting an ulcer or ulcer-related complication; when selecting a PPI, its gastrointestinal benefits must be weighed against the cardiovascular risks associated with COX-2 inhibitors and concomitant antiplatelet therapy.	**Case 23-2 (Questions 4–7) Case 23-5 (Question 2)**
6	Patients receiving an *H. pylori* eradication regimen, those undergoing treatment for an active NSAID ulcer, and individuals receiving prophylactic risk reduction therapy require patient education regarding ulcer risk, potential ulcer complications, and drug therapy.	**Case 23-1 (Question 5) Case 23-2 (Questions 8, 9)**

GASTROESOPHAGEAL REFLUX DISEASE

CORE PRINCIPLES		CHAPTER CASES
1	The classic symptoms associated with gastroesophageal reflux disease (GERD) are usually very specific and include heartburn and acid regurgitation; however, not all patients will present with these typical symptoms and may present with more serious “alarm symptoms” or extra esophageal manifestations, warranting referral for further evaluation.	**Case 23-3 (Question 1)**
2	Appropriate management of the patient with GERD is focused on the relief of symptoms, promotion of healing of the esophageal mucosa, and prevention of relapse or the development of complicated disease. This is accomplished with lifestyle modification and pharmacotherapy directed at reducing esophageal mucosal exposure to gastric acid.	**Case 23-3 (Questions 2–4)**
3	Diagnostic testing strategies for patients with more severe GERD include empiric acid suppression test, upper endoscopy and biopsy (in the presence of alarm symptoms), ambulatory esophageal reflux monitoring, and esophageal manometry.	**Case 23-4 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
4	Mild-to-moderate GERD can be managed acceptably with antacids, sucralfate, and H_2RAs; however, for more severe, frequent, or complicated GERD, the drugs of choice are PPIs, which have demonstrated superiority over these other agents in terms of symptom relief and esophageal healing.	**Case 23-4 (Question 2)**
5	GERD can be associated with numerous manifestations that occur outside the esophagus, including noncardiac chest pain, asthma, hoarseness, laryngitis, and chronic cough.	**Case 23-5 (Question 1)**
UPPER GASTROINTESTINAL BLEEDING		
1	Stress-related mucosal bleeding (SRMB) is a serious complication that can occur in critically ill patients under severe physiologic stress. Appropriate prophylactic management includes identification of risk factors for SRMB, such as mechanical ventilation and coagulopathy, and then implementation of an appropriate pharmacotherapy strategy (eg, PPIs, H_2RAs) aimed at reducing the risk of exhibiting SRMB.	**Case 23-6 (Questions 1–4)**

INTRODUCTION

Upper gastrointestinal (GI) disorders are a subset of GI diseases that vary in severity from simple discomfort to life-threatening illness, and include dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), Zollinger–Ellison syndrome (ZES), and upper GI bleeding. Most are acid related, whereby gastric acid plays an important role in their development, progression, and treatment. Common pharmacotherapeutic options include antacids, histamine-2 receptor antagonists (H_2RAs), and proton-pump inhibitors (PPIs).

Total annual U.S. health care expenditures for all GI diseases ($135.9 billion) exceed those for heart disease ($113.4 billion), trauma-related disorders ($102.7 billion), and mental disorders ($98.8 billion); of those expenditures, upward of $12.4 billion is spent on prescription H_2RAs and PPIs.[1] Management and treatment of these diseases place a substantial burden on both patients and the health care system.

PHYSIOLOGY OF THE UPPER GASTROINTESTINAL TRACT

The upper GI tract consists of the mouth, esophagus, stomach, and duodenum (**Fig. 23-1**). Ingested food or liquids pass from the mouth through the esophagus and into the stomach. As these substances enter into the esophagus, the lower esophageal sphincter (LES), an area of smooth muscle near the distal end of the esophagus, relaxes to allow their entry into the stomach. The LES usually remains contracted to prevent the reflux of gastric contents into the esophagus. However, peristaltic contractions of the esophageal muscles allow the LES to remain open until all food has entered the stomach.[2]

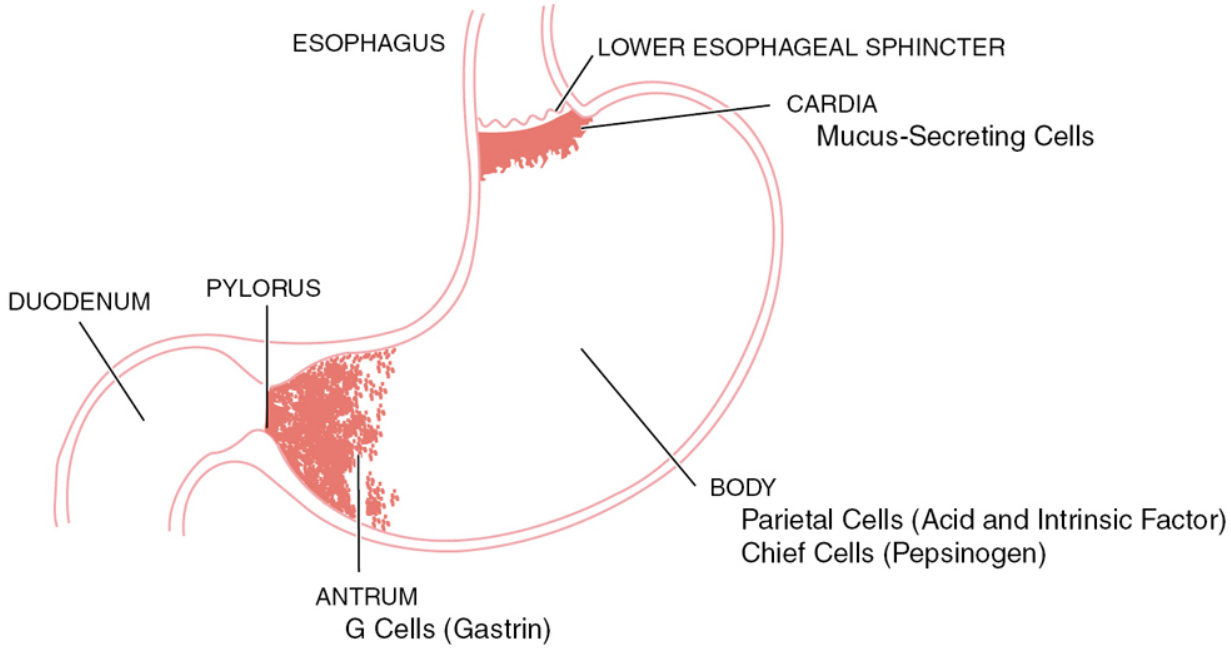


Figure 23-1 Gastrointestinal anatomic regions.

The stomach consists of three distinct anatomic regions, each responsible for a variety of specialized functional processes (see Fig. 23-1). The cardia is the uppermost portion of the stomach (~5% of its surface area), and is responsible for the mucous secretion that protects against the stomach's acidic environment. The body of the stomach makes up the majority of its surface area (80%–90%) and contains parietal cells, which secrete gastric acid and intrinsic factor, as well as peptic (chief) cells, which secrete pepsinogen. Intrinsic factor is required for vitamin B_{12} absorption. Under acidic conditions in the stomach, pepsinogen is converted to pepsin, which is a proteolytic enzyme responsible for breaking down protein. The antrum is the lower portion of the stomach (10%–20% of its surface area) and contains G cells which secrete gastrin. The final portion of the upper GI tract is the duodenum, which begins just after the pylorus and extends to the ligament of Treitz (at which point the jejunum begins the first portion of the lower GI tract).

Three stimuli (neurologic, physical, and hormonal) trigger the parietal cell to secrete gastric acid. Neurologic impulses, from the central nervous system (CNS) and initiated by the sight, smell, and taste of food, travel along cholinergic pathways to stimulate the

release of acetylcholine, which arrives via nerve endings and activates the muscarinic receptor on the parietal cell.[3] Ingested food causes gastric distension, which triggers the release of acetylcholine and also stimulates G cells within the antrum to produce gastrin. Elevated intragastric pH also stimulates the production of gastrin; low gastric pH provides a feedback mechanism to inhibit its production. The stomach is also protected from overproduction of gastric acid by the release of somatostatin from antral D cells, which signals the G cells to stop the production of gastrin.[3] Gastrin enters the blood and arrives at the parietal cell, where it binds to the gastrin receptor. Acetylcholine and gastrin promote the release of histamine from the mast cell or enterochromaffin- like (ECL) cells, which then binds to the histamine H_2 receptor on the parietal cell. Histamine release is associated with both postprandial and nocturnal acid secretion.

The gastrin, histamine H_2, and muscarinic receptors are located on the basolateral membrane of the parietal cell (**Fig. 23-2**). Activating any of these receptors leads to a cascade of events that increase and activate intracellular protein phosphokinases. This, in turn, activates the hydrogen–potassium adenosine triphosphatase (H^+/K^+-ATPase) pump, better known as the *proton pump*. The proton pump is an ion transport pathway that transports hydrogen ions out of the cytoplasm, in exchange for potassium ions, and into the secretory canaliculus of the parietal cell. Here, the hydrogen ions combine with chloride from the blood to form hydrochloric acid, which is then released into the gastric lumen. The proton pump is the final common pathway for gastric acid secretion.[3]

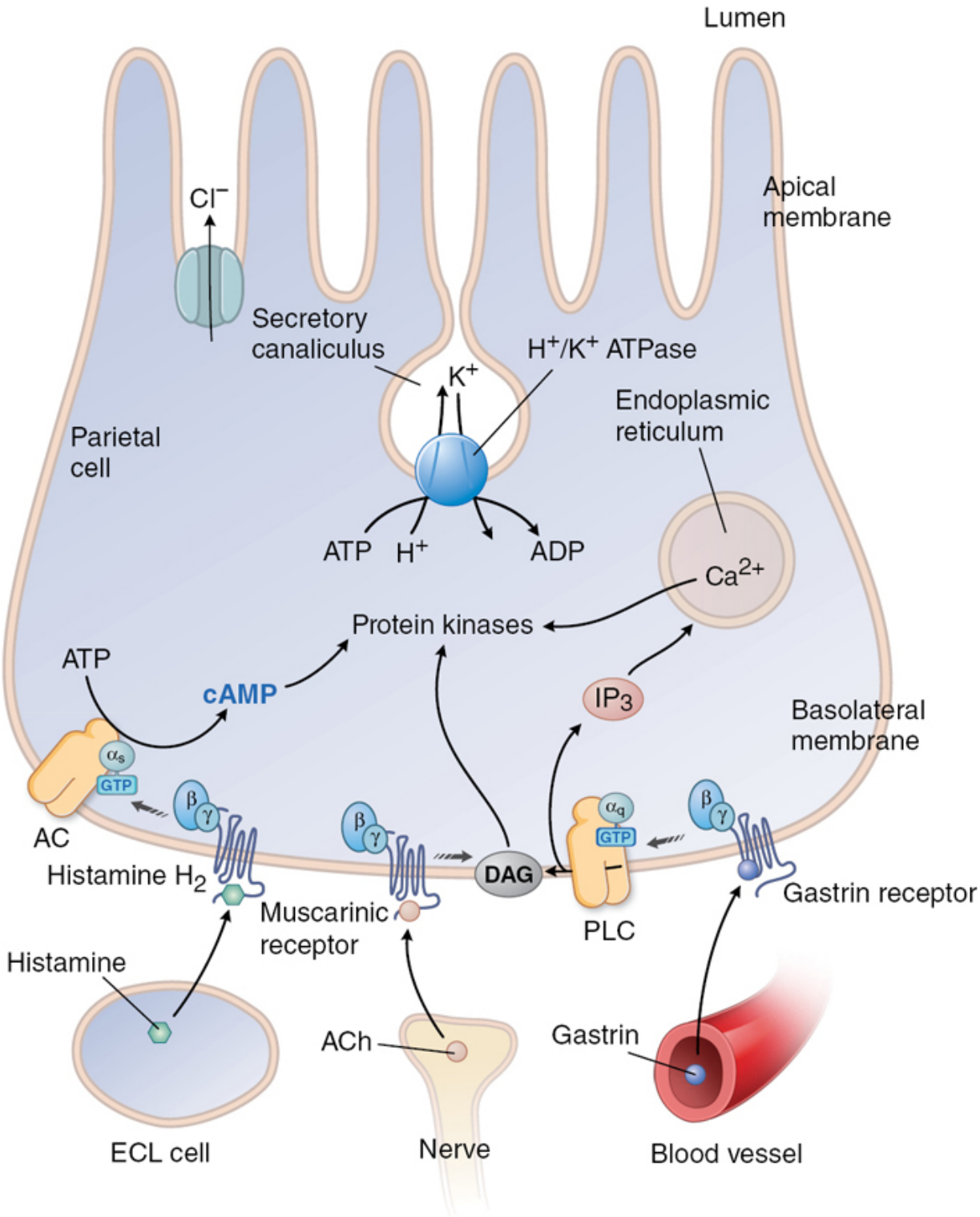


Figure 23-2 Parietal cell. DAG, diacylglycerol; ECL, enterochromaffin like; PCL, phospholipase C. (Adapted with permission from Golan DE, Tashjian AH, Armstrong EJ. *Principles of*

Pharmacology: The Pathophysiologic Basis of Drug Therapy. 3rd ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.)

PHARMACOTHERAPY OF DRUGS USED TO TREAT ACID-RELATED DISORDERS

The following section briefly reviews the drugs used to treat acid-related disorders (**Table 23-1**). Their therapeutic use is discussed under each specific GI disorder.

Table 23-1
Oral Medications Used to Treat Upper Gastrointestinal Disorders

	Gastric and Duodenal Ulcer Healing	Maintenance of Gastric and Duodenal Ulcer Healing	Reduction of Gastric Ulcer Risk Associated With NSAIDs	Relief of Heartburn and Indigestion (OTC Use)	Relief of GERD Symptoms (Rx Use)	Esophageal Healing[a]	Maintenance of Esophageal Healing[a]	Hypersecretory Diseases[a,b]
H_2 Receptor Antagonists								
Cimetidine	300 mg qid	400–800 mg at bedtime	Not indicated	200 mg bid prn	300 mg qid	400 mg qid	400–800 mg at bedtime	[a]
	400 mg bid					800 mg bid		
	800 mg daily							
Famotidine	20 mg bid	20–40 mg at bedtime	Not indicated	10 mg bid prn	20 mg bid	40 mg bid	20–40 mg bid	[a]
	40 mg at bedtime			20 mg bid prn				
Nizatidine	150 mg bid	150–300 mg at bedtime	Not indicated	75 mg bid prn	150 mg bid	300 mg bid	150–300 mg bid	[a]
	300 mg at bedtime							
Ranitidine	150 mg bid	150–300 mg at bedtime	Not indicated	75 mg bid prn	150 mg bid	300 mg bid	150–300 mg bid	[a]
	300 mg at bedtime			150 mg bid prn				
Proton-Pump Inhibitors								
Esomeprazole	20–40 mg daily	20 mg daily	20 mg daily	20 mg daily[c]	20 mg daily	20–40 mg daily	20 mg daily	40 mg bid
Dexlansoprazole	Not indicated	Not indicated	Not indicated	Not indicated	30 mg daily	60 mg daily	30 mg daily	Not indicated
Lansoprazole	15–30 mg daily	15–30 mg daily	15–30 mg daily	15 mg daily[c]	15–30 mg daily	30 mg daily	15–30 mg daily	60 mg daily
Omeprazole	20 mg daily	20 mg daily	20 mg daily	20 mg daily[c]	20 mg daily	20–40 mg daily	20 mg daily	60 mg daily
Pantoprazole	40 mg daily	40 mg daily	40 mg daily	Not indicated	20 mg daily	40 mg daily	40 mg daily	80 mg daily
Rabeprazole	20 mg daily	20 mg daily	20 mg daily	Not indicated	20 mg daily	20 mg daily	20 mg daily	60 mg daily
Other Agents								
Sucralfate	1 g qid	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
	2 g bid							
Misoprostol	Not indicated	Not indicated	200 μg tid–qid	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated

bid, two times daily; qid, four times daily; tid, three times daily.

[a]Although U.S. Food and Drug Administration (FDA) labeled for this indication, H_2 receptor antagonists (H_2RAs) are not recommended because they are not as effective as the proton-pump inhibitors (PPIs).

[b]Initial starting dose; daily dosage must be titrated to gastric acid–secretory response.

[c]Duration of treatment should not exceed 14 consecutive days; if needed, repeat 14-day treatment every 4 months.

Antacids

Antacids are available over the counter (OTC) and widely used to relieve mild and infrequent GI symptoms. They work by partially neutralizing gastric acid, thus increasing gastric pH and inhibiting pepsin. Options include salts or combinations of calcium, magnesium, aluminum, or sodium salts.[4] Because their therapeutic and adverse effects are dose dependent and large doses are required to raise gastric pH, their value in certain acid-related GI disorders has diminished with the advent of H_2RAs and PPIs. Their effect is quick in onset (within minutes), but relatively short in duration (up to 1 hour on an empty stomach; up to 3 hours with or 1 hour after a meal).[4] Beyond their acid-neutralizing capacity, antacids have mechanisms by which they benefit other GI and non-GI disorders, which are discussed elsewhere.[4]

Antacids are generally well tolerated. When used alone, magnesium-containing antacids may cause a dose-related osmotic diarrhea, whereas aluminum- and calcium-containing antacids may cause constipation. Aluminum is often coformulated with magnesium to offset the diarrhea (which still predominates at higher doses of the combination).[4,5] Antacid use in renal insufficiency warrants caution. Small amounts of aluminum and magnesium are absorbed systemically and have the potential to accumulate in patients with renal insufficiency and lead to toxicity. As such, magnesium-containing antacids should be avoided in patients with a creatinine clearance <30 mL/minute; and chronic use of aluminum-containing antacids should be avoided in patients with renal failure.[4,5] Hypercalcemia from calcium carbonate has been described in patients with renal failure taking as little as 4 g/day; patients with normal renal function generally are at lower risk unless using prolonged, large doses (>20 g/day).[4] Sodium bicarbonate should not be used for long periods of time (especially in renal impairment) because systemic alkalosis can result from the accumulation of

bicarbonate. Further, the high sodium content (274 mg sodium per gram sodium bicarbonate) has been associated with sodium retention, and may pose a problem in patients with hypertension, ascites, severe renal dysfunction, or heart failure.[4,5]

Drug interactions must also be considered with antacids. Because all of them change gastric pH, they can reduce acid hydrolysis of drugs, alter dissolution of drug dosage forms, or reduce urinary pH and thus alter elimination. Apart from sodium bicarbonate, antacids can also decrease absorption of other drugs through chelation.[4,6] Orally administered drugs that require an acidic environment for dissolution and absorption (eg, digoxin, phenytoin, isoniazid, ketoconazole, itraconazole, iron preparations) will have reduced bioavailability when improperly used with antacids, leading to potential therapeutic failures. An increase in gastric pH may also prematurely break down the enteric coating of relevant dosage forms because the coating is usually designed to dissolve at a higher pH than does gastric acid.[5,6] Urinary alkalinization may result in either increased urinary excretion (eg, salicylates) or decreased excretion (eg, amphetamines and quinidine), leading to decreased or increased blood concentrations, respectively.[4–6] Certain drugs (eg, tetracyclines, fluoroquinolones, levothyroxine) can bind/chelate with calcium, aluminum, or magnesium (as divalent and trivalent cations) to form an insoluble and inactive complex, thereby reducing bioavailability.[5,6] Almost all of these drug interactions can be avoided by separating the antacid from the interacting drug by a minimum of 2 hours.[5,6]

Histamine-2 Receptor Antagonists

The four H_2RAs approved for use in the United States include famotidine, ranitidine, nizatidine, and cimetidine, with varying prescription and OTC availability as well as differences in oral and parenteral formulations. They competitively and selectively inhibit the action of histamine on the H_2 receptors of the parietal cells, thus reducing both basal and stimulated gastric acid secretion (Fig. 23-2).

Standard oral doses across the class have been adjusted to account for varying potency within the class, whereby each H_2RA has approximately equipotent antisecretory effects (Table 23-1).[7] Compared to antacids, onset of symptom relief with H_2RAs is not as rapid (30–45 minutes), although duration of effect is longer (4–10 hours).[5] The oral bioavailability of nizatidine is considered nearly 100% because this agent does not undergo first-pass metabolism; cimetidine, famotidine, and ranitidine undergo first-pass metabolism, resulting in 40% to 65% bioavailability. All four drugs are eliminated by a combination of hepatic metabolism, glomerular filtration, and tubular secretion.[7,8] Hepatic metabolism is the principal pathway for the elimination of cimetidine, famotidine, and ranitidine, whereas renal excretion is the major route for elimination of nizatidine.[7–9] The pharmacokinetics appear to be unaffected by hepatic dysfunction; however, in patients with combined hepatic failure and renal insufficiency, dose reduction is likely necessary.[9] Dose reductions for all four agents are recommended for patients with moderate-to-severe renal insufficiency.[5]

H_2RAs are well tolerated with low incidence of mostly nonspecific adverse effects (ie, headache, diarrhea, constipation, dizziness, and drowsiness). Cimetidine has been shown to have a mild antiandrogenic effect, whereby high doses may result in decreased libido, impotence, or gynecomastia in males; this is reversible upon discontinuation, and has not been shown with famotidine, ranitidine, or nizatidine.[5,10] Although rare and also reversible upon discontinuation, thrombocytopenia may occur with any of the four H_2RAs; although more commonly reported with intravenous (IV) administration, it is likely that the overall incidence of H_2RA-associated thrombocytopenia is overestimated.[11,12] Hepatotoxicity, although uncommon, has also been described, but primarily in patients receiving IV H_2RAs.[13] Patients at highest risk for experiencing any of these adverse effects include the elderly, those requiring higher doses (usually parenteral), and those with altered renal function.[10,14]

Similar to antacids, all four H_2RAs can potentially alter the absorption and reduce the bioavailability of drugs that require an acidic environment for absorption. Taking into account the longer time to peak effect as well as longer duration of effect with H_2RAs as compared to antacids, various mitigation strategies can be considered including avoidance, monitoring change in effects, and possible dose adjustments.[6] Of the four, cimetidine has the greatest potential to cause drug interactions because of its ability to inhibit several hepatic cytochrome P-450 (CYP450) isozymes, including CYP1A2, CYP2C19, CYP2D6, and CYP3A4.[6] Ranitidine is less inhibitory than is cimetidine, and thus has less interaction concerns, whereas famotidine and nizatidine do not bind appreciably to the CYP450 system and do not interact with drugs that are metabolized through this hepatic system.[6] Organic cation transporters (OCTs) in the kidney support drug excretion. Not only can H_2RAs inhibit these transporters, specifically OCT2, but they can also compete with other drugs that use OCTs to undergo renal tubular excretion, resulting in reduced drug excretion.[6,15,16] Tachyphylaxis, or tolerance, to the antisecretory effect has been described with all H_2RAs, and appears to occur more frequently with high-dose parenteral formulations as well as daily (vs as-needed) oral use.[6,14,17,18]

Reports of contaminants in various medications have been on the rise in recent years, prompting inquiry, investigation, and action by the U.S. Food and Drug Administration (FDA). The contaminants seem related to excipient and/or manufacturing rather than to the actual medications, but investigations are ongoing. One of the main contaminants in question is N-Nitrosodimethylamine (NDMA), which is considered a probable human carcinogen. With ranitidine being implicated, the FDA has requested manufacturers to withdraw all prescription and OTC products from the market as of April 1, 2020.[19] At the time of this writing, the investigation is still ongoing, and other H_2RAs have not been implicated.

Proton-Pump Inhibitors

PPIs are highly specific inhibitors of gastric acid secretion, and include omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole. These agents act by irreversibly binding to the aforementioned H^+/K^+-ATPase (proton pump). PPIs are the most potent inhibitors of gastric acid secretion in that they inhibit the terminal step in the acid production cycle.[20–22] They inhibit both basal and stimulated gastric acid secretion in a dose-dependent and sustained manner.[21] Despite most of them having short plasma elimination half-lives (~1–2 hours), their antisecretory effect lasts 48 to 72 hours because of covalent (irreversible) binding to the proton pump.[22,23] PPIs are prodrugs that require an acidic environment for conversion to the active moiety. They are absorbed in the small intestine (protected from the acidic milieu of the stomach by enteric coating) and taken via the bloodstream to the acidic secretory canaliculus of the parietal cell for protonation to the active form (**Fig. 23-2**).[20,22] This conversion requires an actively secreting proton pump; thus, PPIs are most efficacious when taken 30 to 60 minutes before a meal.[22] Of note, although it does not suggest clinical superiority to other PPIs, dexlansoprazole uses a unique dual delayed- release technology that extends the duration of its antisecretory effect, thus allowing it to be taken without regard to meal times.[24]

Although the benefits and risks with PPI use are mostly the same across the class when used in equivalent doses (**Table 23-1**), PPIs are superior to H_2RAs in reducing gastric acid secretion and improving mucosal healing.[23,25–31] Dose reduction is not required in patients with renal insufficiency, but is recommended for patients with severe hepatic impairment due to reduced clearance.[32] All PPIs are available for oral use as tablets, capsules, disintegrating tablets, or oral suspensions and via slightly differing technologic mechanisms of drug absorption/delivery.[25] The immediate-release formulation of omeprazole contains sodium bicarbonate, requiring precautions as noted in the section on Antacids of this chapter. Only pantoprazole and esomeprazole are available for IV use in the United States; oral options may be prescription or OTC, although

specific dosage forms or compounding options are also available (**Table 23-12**; see section on Upper Gastrointestinal Bleeding).

Drug interaction profiles for PPIs warrant particular clinical attention, especially when evaluating evidence-based benefits and risks. Because PPIs increase intragastric pH, they can alter the absorption of various medications, leading to possible toxicity or therapeutic failure.[22,33] All PPIs are metabolized by the hepatic CYP450 enzyme system, although each has its own profile that must be considered with regard to being a substrate, inhibitor, or inducer of particular CYP450 isozymes; for example, omeprazole and esomeprazole have been described as inhibiting CYP2C19.[22,33] Further, it remains important to evaluate the relative strength of any inhibitory or inductive CYP450 PPI effects (mild, moderate, strong) to prevent possible toxicity or therapeutic failure.

The potential CYP2C19 interaction with PPIs and clopidogrel (a thienopyridine antiplatelet drug) has generated a substantial amount of interest and debate. In 2009, the FDA issued a labeling change for clopidogrel and a safety warning recommending providers to avoid the coadministration of omeprazole, omeprazole/sodium bicarbonate, or esomeprazole with clopidogrel.[34] In 2010, the American College of Gastroenterology (ACG), American College of Cardiology Foundation (ACCF), and the American Heart Association (AHA) released a consensus statement on the concomitant use of PPIs and thienopyridine antiplatelet drugs. Core recommendations advocate for joint use in patients with a history of upper GI bleeding or in patients at high risk for GI bleeding with multiple risk factors; routine concomitant use of PPIs with thienopyridine antiplatelet drugs is not recommended in patients at low risk for GI bleeding.[35]

Before this 2010 consensus statement, numerous reports suggested an interaction between PPIs and clopidogrel that reduces the antiplatelet effects of clopidogrel and potentially increases the risk of adverse cardiovascular outcomes.[36–40] The hypothesis for this interaction is based on clopidogrel being a prodrug that must undergo biotransformation through CYP2C19 to be converted to its active metabolite. In addition to potential enzyme inhibitory properties, PPIs may be substrates of this enzyme (for their own

metabolism), suggesting a possible competition for the same enzyme binding site as clopidogrel.[37–40] Both hypotheses describe a reduction in the conversion of clopidogrel to its active metabolite and, therefore, a reduction in its efficacy toward platelet inhibition. One important confounding variable involved in the evaluation of this interaction is the role played by genetic polymorphisms in CYP2C19. These can result in loss of functional alleles, which has been related to decreased clopidogrel effectiveness as a result of reduced ability to convert clopidogrel to its active metabolite.[41]

Subsequent ACC/AHA guideline and consensus statements such as the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction mentions a potential interaction between clopidogrel and omeprazole, but state that the interaction might not be clinically relevant in terms of worsening cardiovascular outcomes.[42] Meta-analyses and systematic reviews are mostly limited to observational data, and have not demonstrated clear or consistent results regarding the clinical relevance of this interaction on cardiovascular outcomes (composite ischemic end points, all-cause mortality, nonfatal myocardial infarctions, stroke, and stent thrombosis).[43–52] One meta-analysis found conflicting results, although aggregate results from randomized controlled trials showed no difference in cardiovascular outcomes.[53] Until more comprehensive evidence becomes available, the most important aspects to consider are to ensure that patients have an appropriate indication for the use of a PPI, to determine that on a case-by-case basis the benefit outweighs the risk, and, if possible, to avoid concomitant use of omeprazole or esomeprazole, PPIs known to be potent inhibitors of CYP2C19, with clopidogrel unless absolutely necessary. Pantoprazole or rabeprazole might be an alternative option given that they have the weakest inhibitory effect on CYP2C19 in the PPI class.[54]

Advancing age, high doses, and longer durations of use (especially for potentially inappropriate indications) have contributed to a growing list of possible side effects and clinical concerns that have unclear causal relationships and mixed, low-quality data.[55,56] The short-term adverse effects of PPIs are relatively infrequent,

tolerable, and comparable to H_2RAs or placebo. The most common side effects include GI discomfort (eg, nausea, diarrhea, abdominal pain), CNS effects (eg, headache, dizziness), and rare isolated reactions (eg, skin rash, increased liver enzymes).[20,57] Long-term PPI use in older patients on high doses has been associated with an increased risk of hip fractures (as well as spine, forearm, and wrist fractures, albeit to a lesser extent).[55,58] The presumed mechanism is inhibition of calcium absorption by PPI-induced hypochlorhydria or through inhibition of proton pumps within the osteoclastic vacuole, resulting in decreased bone resorption.[55,58] A large retrospective cohort study suggested that PPI users had lower baseline bone mineral density than did nonusers, particularly at the femoral neck and total hip, but that PPI therapy was not associated with significant acceleration in bone mineral density loss after 5 and 10 years of follow-up.[59] Although additional research is required to confirm a causal relationship between long-term PPI use and bone fractures, additional bone density testing and calcium supplementation are not suggested beyond age-related recommendations.[59–63]

In addition to fractures, micronutrient deficiencies and infection risk remain among the more pressing and appreciable clinical considerations surrounding long-term PPI use.[55,58] Vitamin B_{12} (cyanocobalamin) deficiency has been described in PPI users, and may occur because gastric acid is required to liberate the vitamin from dietary sources.[55,56,63,64] In a large retrospective case-controlled study, longer duration PPI use (>2 years) as well as higher doses suggested a significant association between either variable and the presence of vitamin B_{12} deficiency.[63] Hypomagnesemia may occur in adults taking PPIs for >1 year, but cases have been reported after 3 months of treatment; the exact mechanism by which PPIs increase the risk of hypomagnesemia is uncertain, but may be associated with altered intestinal absorption of magnesium.[65–67] Malabsorption of iron secondary to long-term gastric acid suppression has been suggested, but has not been confirmed in clinical trials.[55,56] PPIs have also been associated with interstitial nephritis, although an extremely rare finding.[56,68] Pneumonias and enteric infections from

PPIs may stem from the ability of the microorganisms to survive in a less acidic environment.[55,56,60,64,69] Risk considerations and management surrounding PPI use and potential acute nosocomial infections (pneumonia) in critically ill patients is described later (see section on Upper Gastrointestinal Bleeding). The risk of developing community-acquired pneumonia in patients treated with PPIs has also been evaluated in numerous retrospective studies; however, causality has been very difficult to establish and remains controversial.[1,56] Malignancies and enteric (ie, intestinal) infections, most notably *Clostridioides difficile* infection (CDI), have also been described as likely a result of bacterial overgrowth.[1] A retrospective database study of PPI use describes a near-threefold increase in the risk of *C. difficile*–associated diarrhea in patients receiving a PPI versus patients not receiving a PPI.[70] Results from two large meta-analyses suggest that PPI users have upward of a 65% increased risk of developing *C. difficile*–associated diarrhea than do nonusers.[70,71] Although available data may seem compelling, it is mostly observational and of low quality. The true risk seems modest compared to traditional risk factors such as antibiotic use.[1] Because the overall risk of developing CDI remains low, it should not be considered a contraindication to therapy.

Although the long-term adverse effects associated with PPIs are relatively uncommon, the benefit of long-term use must always be weighed against potential risks in each individual patient.

Sucralfate

Sucralfate (an aluminum salt of a sulfated disaccharide) promotes gastric mucosal protection by shielding ulcerated tissue from aggressive factors, such as acid, pepsin, and bile salts.[72] At a pH of 2 to 2.5, sucralfate binds to damaged and ulcerated mucosa, forming a physical barrier against injury from these aggressive factors. The drug has minimal systemic absorption, and does not possess antisecretory activity. It may also have other protective actions related to the stimulation of mucosal prostaglandins.[72] The most

common side effect associated with sucralfate is constipation, which occurs in ~1% to 3% of patients.[72] This is most likely attributable to the aluminum content of the compound, which can also accumulate in patients with renal insufficiency; therefore, long-term use should be avoided.[72] In addition, aluminum salts can bind with dietary phosphate in the GI tract, increasing the potential for hypophosphatemia (see section on Antacids). Sucralfate tablets are large, and some patients, particularly the elderly, may have difficulty swallowing them; a liquid formulation is available for patients with swallowing difficulties. Drug interactions are thought to be caused by binding of the interacting medication with sucralfate in the GI tract, thereby limiting the medication's absorption.[72] Fluoroquinolone antibiotics are most notably associated with this interaction, and concomitant use with sucralfate should be avoided. Single doses of other medications have shown substantial reductions in absorption and bioavailability when given at the same time as sucralfate; often, however, impact on bioavailability was diminished if the interacting drug was given 2 hours before sucralfate.[72] Because of these interactions and findings, sucralfate should be given at least 2 hours after these medications (and avoided altogether with fluoroquinolones). The lack of an antisecretory effect from sucralfate limits its correlation to acid-sensitive drug interactions, as may normally be considered with aluminum-containing antacids.

Misoprostol

Misoprostol is a synthetic prostaglandin E_1 analog that acts primarily by enhancing mucosal defense mechanisms, offering possible value in ulcer management.[73,74] It produces cytoprotective effects by stimulating the production of mucus and bicarbonate, improving mucosal blood flow, and reducing mucosal cell turnover similar to the effects of endogenous prostaglandin.[73] Misoprostol also produces a dose-dependent inhibition of gastric acid, but even at high doses, the inhibition is less than that of H_2RAs. The use of misoprostol is limited because of its potential to cause dose-dependent diarrhea (in up to

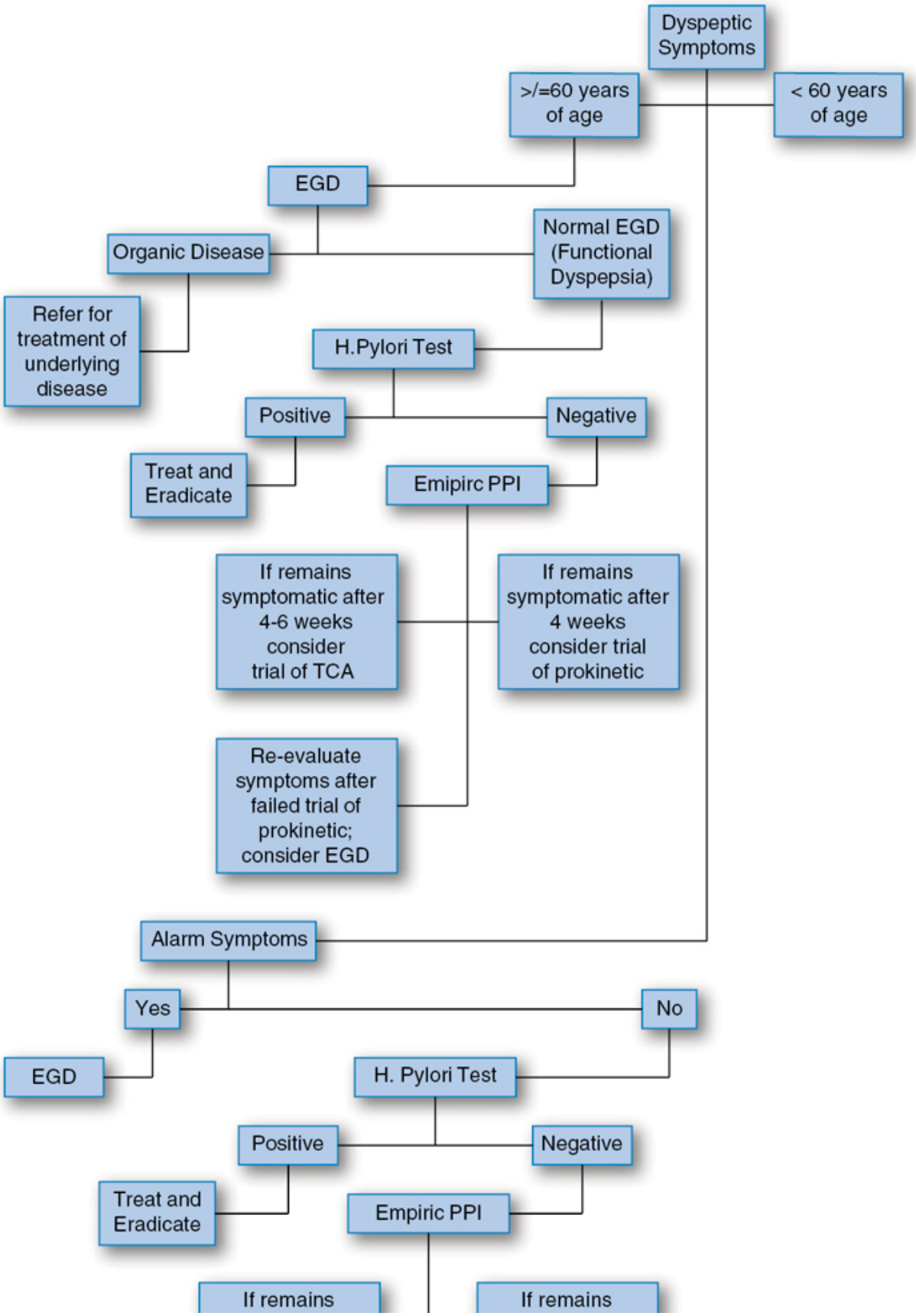
30% of patients) and abdominal cramping.[73] Taking the drug with meals may help reduce the incidence of diarrhea. Decreasing the daily dose may also reduce diarrhea, but efficacy may be compromised.[74] Other troublesome side effects include nausea, flatulence, and headaches. Misoprostol is an abortifacient because of its uterotropic effects that also may be used for cervical ripening during labor induction. It is contraindicated in pregnant females; use in females of child-bearing age requires a negative serum pregnancy test result and adequate contraception.[73,74]

Bismuth Salts

Bismuth subsalicylate has been used for years as an OTC option for many GI ailments. Although its mechanism of action is not completely understood, it is thought to work by binding to and protecting mucosal lesions and enhancing cellular protective mechanisms. Bismuth lacks acid-inhibitory effects, but has an antimicrobial effect, primarily against *H. pylori*, and is available as both subsalicylate and subcitrate salts.[75] These salts have few side effects, but may have reduced elimination in patients with renal impairment. They are associated with a harmless black coloring of the stools because of colonic conversion of bismuth to bismuth sulfide and a potential black discoloration of the tongue with liquid dosage forms.[5] Bismuth subsalicylate should be used with caution in patients on concomitant salicylates because of the potential for salicylate toxicity or increased bleeding risk; it is generally not recommended for children and patients with salicylate allergies or sensitivities, and long-term use is not advised.[5] At the time of this writing, bismuth subcitrate is only available in the United States by prescription in a combination product with metronidazole and tetracycline for the treatment of *H. pylori* infection; it lacks salicylate, but otherwise presents benefits and risks similar to that of bismuth subsalicylate.[76]

DYSPEPSIA

Dyspepsia refers to a subjective feeling of pain or discomfort located primarily in the upper abdomen. It is a common problem that affects about 25% of the U.S. population accompanied by substantial costs to the health care system.[77–79] The etiology of dyspepsia in ~25% of patients seems to be secondary to an organic disease, such as PUD, GERD with or without esophagitis, or gastric malignancy (uncommon in North America), or otherwise drug-induced disease from medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics such as erythromycin and tetracycline, iron and potassium supplements, digoxin, theophylline, and bisphosphonates.[80,81] Smoking or a stressful lifestyle can also play a role in dyspepsia (**Fig. 23-3**). The other 75% of patients are defined to have functional dyspepsia (idiopathic) who have undergone diagnostic evaluation (usually upper endoscopy) to rule out any organic pathology.[80] Heartburn may coexist with dyspepsia, but is usually suggestive of GERD.


Dyspeptic Symptoms
>/=60 years of age
< 60 years of age
EGD
Organic Disease
Normal EGD (Functional Dyspepsia)
Refer for treatment of underlying disease
H.Pylori Test
Positive
Negative
Treat and Eradicate
Emipirc PPI
If remains symptomatic after 4-6 weeks consider trial of TCA
If remains symptomatic after 4 weeks consider trial of prokinetic
Re-evaluate symptoms after failed trial of prokinetic; consider EGD
Alarm Symptoms
Yes
No
EGD
H. Pylori Test
Positive
Negative
Treat and Eradicate
Empiric PPI
If remains
If remains

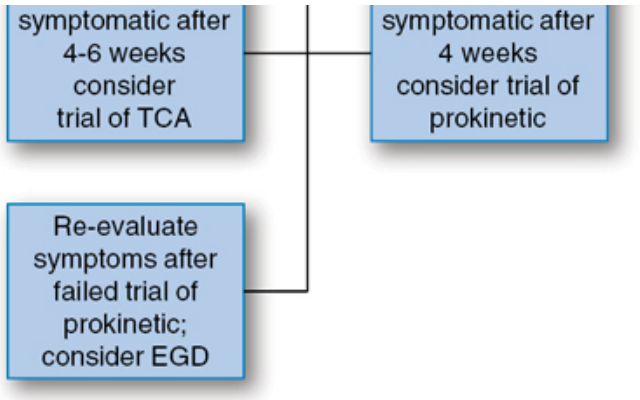


Figure 23-3 Management of dyspeptic symptoms. EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; H_2RA, H_2 receptor antagonist; IBS, irritable bowel syndrome; NSAID, nonsteroidal anti-inflammatory drug; OTC, over the counter; PPI, proton-pump inhibitor; PUD, peptic ulcer disease. (Longstreth GF, Lacy BE. Approach to the adult with dyspepsia. *UpToDate*. UpToDate; 2020. Accessed November 8, 2020. www.uptodate.com)

Functional dyspepsia, also known as idiopathic or nonulcer dyspepsia (NUD), is a clinical syndrome in which there is no evidence of mucosal damage related to PUD, GERD, or malignancy found at endoscopy. Functional dyspepsia is defined based on the Rome IV diagnostic criteria.[81–83] It includes the presence of one or more of the following for the past 3 months, with symptom onset 6 months before diagnosis, and without evidence of structural anatomic symptoms.[84,85]

- Postprandial fullness (classified as postprandial distress syndrome)
- Early satiation (inability to finish a normal-sized meal, also classified as postprandial distress syndrome)
- Epigastric pain or burning (classified as epigastric pain syndrome)

It should be noted that any of these criteria can overlap.[82] A cross-sectional population-based study performed in the United States, United Kingdom, and Canada found that about 10% of the adult population meets Rome IV criteria to be diagnosed with functional dyspepsia.[83]

Pathophysiology

Acute, infrequent dyspepsia is most often related to food, alcohol, smoking, or stress. Chronic dyspepsia may be related to an underlying cause, such as PUD, GERD, or malignancy, or may not have any known cause (endoscopy-negative, functional, idiopathic dyspepsia). Functional dyspepsia may involve delayed gastric emptying; there is also evidence that the esophagus, stomach, duodenum, and other regions of the GI tract are hypersensitive, and may be associated with irritable bowel syndrome, especially in females.[85] However, a pathologic association between functional dyspepsia and gastroduodenal motility, hypersensitivity, or any other GI abnormality remains to be more clearly elucidated because psychological disturbances seem to also be an important contributing factor. Although *H. pylori* infection has been identified in 20% to 60% of patients with functional dyspepsia, its pathophysiologic relevance remains uncertain.[84]

Clinical Assessment and Diagnosis

Acute, infrequent dyspepsia is usually self-limiting and generally requires no further investigation. Chronic dyspeptic symptoms cannot be used to predict endoscopic findings of PUD, GERD, or malignancy in patients with uninvestigated dyspepsia.[85–87] In addition, individual symptoms or symptom subgroups, such as PUD-like, GERD-like, or dysmotility-like dyspepsia, are not useful in distinguishing organic disease from functional dyspepsia, nor do they aid in management. This is because there is considerable overlap of symptoms among patients with PUD, GERD, malignancy, and functional dyspepsia.

The clinical assessment of uninvestigated dyspepsia in patients younger than 60 years of age with no alarm signs or symptoms includes a test-and-treat *H. pylori* option (**Fig. 23-3**).[81] Testing for *H. pylori* should be conducted using a nonendoscopic-validated test (see section on Tests for Detecting *Helicobacter pylori*). New-onset dyspepsia in an older individual is considered an independent risk

factor for an underlying malignancy such as gastric cancer.[85] As such, all patients ages 60 years and older with dyspepsia should undergo upper endoscopy (**Fig. 23-3**).[81] Guidelines do not recommend endoscopy in patients younger than age 60 unless they present with clinically significant weight loss (>5% body weight over the past 6–12 months), overt GI bleeding, or multiple or rapidly progressive alarm symptoms (**Fig. 23-3**).[81] It should be noted that the age threshold was increased from 55 to 60 years based on economic analyses showing only borderline cost-effectiveness of endoscopy at age 55.[88] Owing to seemingly limited value in using alarm symptoms to pursue upper endoscopy, it should not solely be used to rule out malignancy.[81,89] Other alarm features that assist in identifying serious underlying disease, especially malignancy, include early satiety, anorexia, worsening dysphagia or odynophagia, unexplained weight loss (>10% body weight), vomiting, anemia, GI bleeding, lymphadenopathy, jaundice, a history of PUD, a family history of upper GI tract cancer, previous gastric surgery, or other malignancy.[85]

Treatment

The recommended strategies for managing dyspepsia in adults are presented in **Figure 23-3**. Individuals with acute dyspepsia can be effectively treated with self-directed therapy using antacids or OTC antisecretory drugs if they are unable or unwilling to avoid offending foods and beverages, stop smoking, or discontinue offending medications. The initial management of patients younger than 60 years of age with uninvestigated chronic dyspepsia and no alarm features depends on the presence or absence of *H. pylori* (**Table 23-2**; **Fig. 23-3**).[81] Empiric therapy with the lowest PPI dose is considered first line if patients are *H. Pylori* negative or otherwise remain symptomatic after *H. Pylori* eradication therapy.[81] Studies have not shown a significant difference in using once-daily versus twice-daily PPI therapy for dyspepsia; as such, the lowest dose should be trialed first and titrated to symptom improvement.[85–87,90]

PPIs should be discontinued after 1 month if the patient's symptoms respond to treatment. H_2RAs are an appropriate substitute to PPIs in patients with dyspepsia because randomized controlled trials found no statistically significant difference between them with regard to providing symptom relief.[81] However, patients who are *H. pylori* positive should receive treatment for eradication (see section on *Helicobacter pylori*–Related Ulcers).[84–87]

Table 23-2
Indications for Testing and Treating *Helicobacter pylori* Infection

Recommended (Evidence Established)
Uninvestigated dyspepsia (depending on *H. pylori* prevalence)
PUD (active gastric or duodenal ulcer)
History of PUD (confirmed ulcer not previously treated for *H. pylori*)
Gastric MALT lymphoma
After resection of early gastric cancer
Reduce the risk of recurrent bleeding from gastroduodenal ulcer
Controversial (Evidence Not Well Established)
NUD
Individuals using NSAIDs (no signs/symptoms of peptic ulcer)
GERD
Individuals at risk for gastric cancer
Individuals with unexplained iron deficiency anemia

GERD, gastroesophageal reflux disease; MALT, mucosa-associated lymphoid tissue; NSAID, nonsteroidal anti-inflammatory drug; NUD, nonulcer dyspepsia; PUD, peptic ulcer disease.

Adapted with permission from Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102(8):1808–1825. © 2007 The American College of Gastroenterology.

Early endoscopy with biopsy for *H. pylori* is recommended for all patients 60 years of age or older with uninvestigated chronic dyspepsia; it is also recommended for those younger than 60 years of age, but only if they present with the aforementioned symptoms (**Fig. 23-3**).[81] In the event that an abnormality (such as PUD, GERD,

or malignancy) is found, it should be treated accordingly. If no abnormality is identified, the treatment algorithm for those younger than age 60 years who are otherwise not candidates for endoscopy should be utilized (**Fig. 23-3**).[81] The medical management of functional dyspepsia (eg, NUD) is challenging and, when possible, should take into consideration the cost-effectiveness of treatment.[85–87] Although pharmacotherapy is considered for most patients, evidence of benefit is limited because of the lack of well-designed studies and an incomplete understanding of the disorder. Meta-analyses have demonstrated the efficacy of H_2RAs and PPIs, but there is no evidence to support the use of antacids, sucralfate, and misoprostol.[91,92] Antidepressants, particularly tricyclic antidepressants, are often recommended for patients with functional dyspepsia. Although they may have some benefit, the mechanism for this finding is unclear, and published clinical trials are small and of poor quality, resulting in uncertain efficacy.[85,87,91] Although benefit from prokinetic agents has been reported, most studies were conducted with cisapride, which was withdrawn from the U.S. market.[91] The use of available prokinetic agents (eg, metoclopramide) should be reserved for difficult-to-treat patients or those with gastroparesis because of side effects and relatively limited efficacy; they should also not be used for >12 weeks.[85,87] Guidelines recommend against the combination of prokinetic agents and H_2RAs in functional dyspepsia because the combination was not shown to be more effective than using either agent alone.[81] Alternative therapies, including herbal products, remain unproved.[85] Patients with persistent dyspepsia despite a negative endoscopy finding, in whom PPI therapy and *H. pylori* eradication fails, should have their diagnosis reevaluated.

PEPTIC ULCER DISEASE

PUD is one of the most common diseases affecting the upper GI tract.[93] Chronic peptic ulcers are defects in the gastric (gastric ulcer) or duodenal (duodenal ulcer) mucosa that require gastric acid for their formation. Chronic peptic ulcers differ from erosions and gastritis in that the ulcer extends deeper into the muscularis mucosa.[93,94]

Stress ulcer is an acute form of peptic ulcer, but it occurs primarily in critically ill patients and differs in its underlying pathogenesis (see section on Stress-Related Mucosal Bleeding).

Epidemiology

It is difficult to estimate the epidemiology of PUD because of the different methods used to diagnose peptic ulcers (eg, symptom-based, ulcer-related complications, radiology, or endoscopy) along with differences in NSAID use, *H. pylori* prevalence, and cigarette smoking. Improved medical treatment, changes in the criteria and coding for hospitalizations and mortality, and the evolution from hospital-based to ambulatory care have also altered the epidemiology of PUD.[93] Current data suggest a shift in the prevalence of PUD in the United States from predominantly males to a comparable rate in males and females.[93] A declining ulcer rate in younger individuals and an increasing rate for older adults reflect a decline in *H. pylori* infection and an increased use of NSAIDs in the United States. Office visits, hospitalizations, and deaths have modestly declined during the past four decades, but deaths among older patients (older than 75 years) have increased and are most likely related to NSAID use.[93]

Etiology and Risk Factors

H. pylori and NSAIDs are the two most common causes of chronic PUD, and influence the chronicity of the disease.[93] Less common causes include hypersecretory states, such as ZES (see section on Zollinger–Ellison Syndrome), viral infections (eg, cytomegalovirus),

radiation, and chemotherapy (eg, hepatic artery infusion). Factors that may increase the risk of a peptic ulcer include alcohol ingestion, cigarette smoking, psychological stress, corticosteroid use, organ transplantation, and certain conditions such as renal failure, cirrhosis, pancreatitis, obstructive pulmonary disease, or Crohn disease.[93]

HELICOBACTER PYLORI–RELATED ULCERS

H. pylori infection is causally linked to chronic gastritis, PUD, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer (**Table 23-2**).[93–98] The lifetime risk of exhibiting an endoscopic ulcer in *H. pylori*–positive individuals is 10% to 20%.[93,94] Worldwide, infected individuals have a two- to sixfold increased risk of developing gastric cancer and MALT lymphoma when compared to noninfected individuals.[99] Differences in strains and host-specific factors account for the variable pathogenesis of the organism.[94,97] There is increasing evidence that iron deficiency anemia and idiopathic thrombocytopenia are associated with *H. pylori* infection, but cause and effect remain unproved.[95,100] The association between *H. pylori* and PUD bleeding remains unclear, but *H. pylori* eradication decreases recurrent bleeding (see section on Upper Gastrointestinal Bleeding).[95]

Table 23-3
Risk Factors for Nonsteroidal Anti-inflammatory Drug–Induced Ulcer and Ulcer-Related Upper Gastrointestinal Complications

Established
Confirmed prior ulcer or ulcer-related complication Age >65 years Multiple or high-dose NSAID use Concomitant use of aspirin (including low cardioprotective dosages, eg, 81 mg) Concomitant use of an anticoagulant, corticosteroid, bisphosphonate, clopidogrel, or SSRI Selection of NSAID (selectivity of COX-1 vs COX-2)
Controversial

Established
Helicobacter pylori Alcohol consumption Cigarette smoking

COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Sources: From Soll AH, Graham DY. Peptic ulcer disease. In: Yamada T, Podolsky, Daniel K, et al, eds. *Textbook of Gastroenterology*. 5th ed. Wiley-Blackwell; 2009:936; Chey WD, Wong BCY, Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102:1808–1825; Scarpignato C, Hunt RH. Nonsteroidal anti-inflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis and prevention. *Gastroenterol Clin North Am*. 2010;39:433–464; Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104:728–738; Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet*. 2009;374:1449–1461; Vonkeman H, Meek I, van de Laar M. Risk management of risk management: combining proton pump inhibitors with low-dose aspirin. *Drug Healthc Patient Saf*. 2010;2: 191–204; Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *Am J Gastroenterol*. 2009;104:1475–1482; Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hallas J. There is an association between selective serotonin reuptake inhibitor use and uncomplicated peptic ulcers: a population-based case-control study. *Aliment Pharmacol Ther*. 2010;32: 1383–1391; Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review of clinicians and a reconsideration of mechanisms. *J Clin Psychiatry*. 2010;71:1565–1575.

The prevalence of *H. pylori* varies by geographic location, socioeconomic status, ethnicity, and age, and is more common in developing countries than in industrialized nations.[94] The overall prevalence in the United States is estimated to be 30% to 40%, but is higher in older individuals (50%–60%) than in children (10%–15%).[94] In general, rates are lower in those born in North America than in other parts of the world.[99]

Transmission occurs usually during childhood from the infected person by either the gastro-oral (vomitus) or fecal–oral (diarrhea) route, or from fecal-contaminated water or food.[94,96] Individuals living in the same household with an *H. pylori*–positive person, especially

when there is household crowding, are at increased risk for acquiring the infection.[94,96]

Nonsteroidal Anti-inflammatory Drug–Induced Ulcers

There is considerable evidence linking the chronic use of NSAIDs with GI injury.[93,101–104] Endoscopically confirmed gastric and duodenal ulcers develop in 15% to 30% of chronic NSAID users, 2% to 4% of whom experience ulcer-related bleeding or perforation.[101,102] Gastric ulcer is most common, and develops primarily in the antrum. NSAIDs may also cause ulcers in the esophagus and the colon, but these ulcers occur less frequently and differ in their underlying pathogenesis.[101,104] It is estimated that NSAIDs account for ~100,000 hospitalizations and 7000 to 10,000 deaths annually in the United States, although mortality may be overstated because of a recent decline in hospitalizations.[102] A national prescription audit in the United States revealed an annual NSAID cost of $4.9 billion, with additional nonprescription NSAID sales of $3 billion.[105,106] Risk factors for NSAID-induced ulcers and upper GI complications are listed in **Table 23-3**. Combinations of factors confer an additive risk.

Pathophysiology

A physiologic balance exists in healthy individuals between gastric acid secretion and gastroduodenal mucosal defense. Peptic ulcers occur when the balance between aggressive factors (gastric acid, pepsin, bile salts, *H. pylori*, and NSAIDs) and mucosal defensive mechanisms (mucosal blood flow, mucus, mucosal bicarbonate secretion, mucosal cell restitution, and epithelial cell renewal) are disrupted.[93,103] Increased acid secretion may occur in patients with duodenal ulcer, but most patients with gastric ulcer have normal or reduced rates of acid secretion.[3] Pepsin is an important cofactor that plays a role in the proteolytic activity involved in ulcer formation. Mucosal defense and repair mechanisms protect the gastroduodenal

mucosa from noxious endogenous and exogenous substances.[93] The viscous nature and near-neutral pH of the mucus–bicarbonate barrier protect the stomach from the acidic contents in the gastric lumen. The maintenance of mucosal integrity and repair are mediated by the production of endogenous prostaglandins. When aggressive factors alter mucosal defense mechanisms, back diffusion of hydrogen ions occurs with subsequent mucosal injury. *H. pylori* and NSAIDs cause alterations in mucosal defense by different mechanisms, and are important factors in the formation of peptic ulcers.

HELICOBACTER PYLORI–RELATED ULCERS

H. pylori is a gram-negative, spiral-shaped bacillus that thrives in a microaerophilic environment. The bacterium resides between the mucous layer and surface epithelial cells in the stomach or in any location where gastric-type epithelium is found.[94] Flagella enable it to move from the lumen of the stomach, where the pH is low, to the mucous layer, where the pH is neutral. Acute infection is accompanied by transient hypochlorhydria, which enables the organism to survive the acidic gastric juice. Although the exact method by which *H. pylori* induces hypochlorhydria is uncertain, it is hypothesized that its urease-producing ability hydrolyzes urea in the gastric juice and converts it to ammonia and carbon dioxide, which creates a neutral microenvironment that surrounds the bacterium.[94,103] Adherence pedestals attach to gastric-type epithelium and prevent the bacterium from being shed during cell turnover and mucous secretion.

Disease outcome depends on the patterns of *H. pylori* colonization and inflammation within the stomach.[94,103] Colonization of the antrum and acid-secreting body of the stomach (corpus) is associated with gastric ulcer and gastric adenocarcinoma, and is typically accompanied by gastric atrophy and decreased acid secretion. When *H. pylori* colonizes, the antrum and the body of the stomach are spared, the risk of duodenal ulcer is increased, and gastric acid is normal or slightly increased. Ulcers in the duodenum arise from

the colonization by antral organisms of gastric-type epithelium that develops in the duodenum in response to changes in duodenal pH.[94] Direct mucosal damage is produced by virulence factors (eg, cytotoxin-associated gene, vacuolating cytotoxin), elaborating bacterial enzymes (eg, urease, lipases, proteases), and adherence.[94,103,107] *H. pylori* infection may also cause alterations in the host immune response.[94,107] Host polymorphisms related to interleukin (IL)-1β and its receptor antagonist, tumor necrosis factor α (TNF-α), and IL-10, may be associated with increased gastric acid secretion and duodenal ulcer or acid suppression and gastric cancer.[94,107]

Nonsteroidal Anti-inflammatory Drug–Induced Ulcers

Nonselective NSAIDs (**Table 23-4**), including aspirin, cause peptic ulcers and upper GI complications by systemically inhibiting protective prostaglandins in the gastric mucosa.[93,101,103] NSAIDs inhibit cyclooxygenase (COX), the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins. There are two COX isoforms: COX-1, which is found in the stomach, kidney, intestine, and platelets; and COX-2, which is induced with acute inflammation.[93,101] The inhibition of COX-1 is associated with upper GI (including ulcers) and renal toxicity, and the inhibition of COX-2 is related to anti-inflammatory effects.[93,101] Nonselective NSAIDs, including aspirin, inhibit both COX-1 and COX-2 to varying degrees and decrease platelet aggregation, which may increase the risk of upper GI bleeding.[93,101] The coadministration of selected NSAIDs (eg, ibuprofen) with aspirin also reduces the antiplatelet effects of aspirin.[108] Although prostaglandin inhibition is regarded as the major cause of gastric ulcers, diversion of arachidonate through the lipoxygenase pathway enhances leukotriene synthesis and results in vasoconstriction and release of oxygen free radicals, which may also contribute to impairment of mucosal defense.[101] Further, there is increasing evidence that NSAIDs may cause gastric damage by

interfering with the mucosal synthesis of nitric oxide and hydrogen sulfide, important mediators in maintaining gastric mucosal integrity.[101]

Table 23-4
Selected Nonsteroidal Anti-inflammatory Drugs

Salicylates
Acetylated: aspirin
Nonacetylated: trisalicylate, salsalate
Nonsalicylates[a]
Nonselective (traditional) NSAIDs: ibuprofen, naproxen, tolmetin, fenoprofen, sulindac, indomethacin, ketoprofen, ketorolac, flurbiprofen, piroxicam
Partially selective NSAIDs: etodolac, diclofenac, meloxicam, nabumetone
Selective COX-2 inhibitors: celecoxib[b], rofecoxib[c], valdecoxib[c]

COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.

[a]Based on COX-1/COX-2 selectivity ratio in vitro.

[b]Initially marketed as a COX-2 inhibitor, but current U.S. Food and Drug Administration (FDA) labeling is consistent with nonselective and partially selective NSAIDs.

[c]Withdrawn from the U.S. market.

The relative COX selectivity among NSAIDs varies, and is thought to be an important factor in determining the propensity for ulcer formation.[93,101] Partially selective NSAIDs that inhibit COX-2 more than COX-1 (**Table 23-4**) may be associated with less GI toxicity, but there are few controlled trials to support this claim.[93,101,109,110] The selective COX-2 inhibitors rofecoxib and valdecoxib do not inhibit gastric mucosal prostaglandin synthesis or serum thromboxane A_2, which accounts for their improved GI safety; however, they were withdrawn from the U.S. market in 2004 because of concerns about cardiovascular safety.[93,101,110] Celecoxib, an NSAID originally marketed as a selective COX-2 inhibitor, currently remains available in the United States despite similar concerns about cardiovascular risk, especially at higher doses.[93] However, the risk of gastric ulcer

and upper GI complications with celecoxib seems lower than that with rofecoxib and valdecoxib, suggesting it may not be as selective for COX-2 as originally hypothesized.[93]

Aspirin and nonaspirin NSAIDs also have a topical (direct) irritating effect on the gastric mucosa, but the resulting inflammation and erosions usually heal within a few days. Gastric damage is associated with the acidic properties of aspirin and nonaspirin NSAIDs and their ability to decrease the hydrophobicity of the mucous gel layer in the gastric mucosa.[101,111] Thus, direct mucosal injury appears to correlate with the pK_a of a compound—suggesting the lower the acidity of the drug, the less the short-term topical damage.[101] Formulations, such as enteric-coated aspirin, buffered aspirin, NSAID prodrugs, and parenteral or rectal preparations, may spare topical effects on the gastric mucosa, but all have the potential to cause a gastric ulcer because of their systemic inhibition of endogenous prostaglandins.[93,112]

Clinical Presentation

SIGNS AND SYMPTOMS

The signs and symptoms associated with a peptic ulcer range from mild epigastric pain to life-threatening upper GI complications.[93,103] A change in the character of the pain may indicate an ulcer-related complication. The absence of epigastric pain, especially in older adults who are taking NSAIDs, does not exclude the presence of an ulcer or related complications. Although the reasons for this are unclear, they may be related to the analgesic effect of the NSAID. There is no one sign or symptom that differentiates an *H. pylori*–related ulcer from an NSAID-induced ulcer. Ulcer-like symptoms may occur in the absence of peptic ulceration in association with *H. pylori*–related gastritis or duodenitis.

COMPLICATIONS

The most serious life-threatening complications associated with chronic PUD are upper GI bleeding, perforation into the abdominal

cavity or penetration into an adjacent structure (eg, pancreas, liver, or biliary tract), and obstruction.[93,103,113] Ulcer-related bleeding is the most frequent complication and occurs with all types of ulcers (see section on Upper Gastrointestinal Bleeding). The incidence of ulcer-related upper GI bleeding and perforation is highest in individuals taking NSAIDs who are older than age 60 years.[101,103] The bleeding may be occult (hidden) or present as melena (black-colored stools) or hematemesis (vomiting of blood). Mortality is higher in patients who continue to bleed or who rebleed after the initial bleeding has stopped and in patients with a perforated ulcer.[2,114] The pain associated with perforation is typically sudden, sharp, and severe, beginning in the epigastric area but quickly spreading throughout the upper abdominal area. Gastric outlet obstruction, the least frequent complication, is caused by previous ulcer healing and scarring or edema of the pylorus or duodenal bulb and can lead to symptoms of gastric retention, including early satiety, bloating, anorexia, nausea, vomiting, and weight loss.

Clinical Assessment and Diagnosis

TESTS FOR DETECTING HELICOBACTER PYLORI

The detection of *H. pylori* infection can be made through gastric mucosal biopsies in patients undergoing upper endoscopy or by nonendoscopic tests (**Table 23-5**).[94,95,115] Any patient who tests positive for *H. pylori* should be offered treatment. Patients indicated for testing include any individual with active or previous confirmed history of PUD (not previously treated for *H. pylori*), history of low-grade gastric MALT lymphoma, or a history of endoscopic resection of early gastric cancer. Recent guidelines also recommend that clinicians consider testing in individuals starting on long-term NSAID therapy, those with unexplained iron deficiency anemia, and adults with idiopathic thrombocytopenic purpura.[95] The selection of a specific method is influenced by the clinical circumstance and the availability and cost of the individual test. Endoscopic tests require a mucosal biopsy for the rapid urease test, histology, or bacterial

culture (which is less common). Medications that reduce urease activity or the density of *H. pylori* may decrease the sensitivity of the rapid urease test by up to 25%.[95] For this reason, when possible, antibiotics and bismuth salts should be withheld for 4 weeks, whereas H_2RAs and PPIs should be withheld for 1 to 2 weeks before endoscopic testing. Patients who are taking these medications at endoscopy will require histology in addition to the rapid urease test. At least three biopsies are taken from different areas of the stomach because patchy distribution of *H. pylori* can result in false-negative results. Acute ulcer bleeding at the time of testing is likely to decrease the sensitivity of the rapid urease test and histology and increase the likelihood of false-negative results.[95,116]

Table 23-5

Diagnostic Tests for *Helicobacter pylori* Infection

Tests Using Gastric Mucosal Biopsy in Patients Undergoing Endoscopy
Rapid Urease Test
Tests for active *H. pylori* infection; >90% sensitivity and specificity In the presence of *H. pylori* urease, urea is metabolized to ammonia and bicarbonate resulting in an increase in pH, which changes the color of a pH-sensitive indicator. Results are rapid (within 24 hours), and test is less expensive than is histology or culture. Withhold H_2RAs and PPIs 1–2 weeks before testing and antibiotics and bismuth salts 4 weeks before testing to reduce the risk of false negatives.
Histology
"Gold standard" for detection of active *H. pylori* infection and associated lesions; >95% sensitive and specific Permits further histologic analysis and evaluation of infected tissue (eg, gastritis, ulceration, adenocarcinoma); tests for active *H. pylori* infection Results are not immediate; not recommended for initial diagnosis; more expensive than is rapid urease test.
Culture
Permits sensitivity testing to determine antibiotic choice or resistance; tests for active *H. pylori* infection. High specificity, but low sensitivity due to difficulty culturing *H. pylori* Use usually limited to patients who fail initial course of eradication therapy

Tests Using Gastric Mucosal Biopsy in Patients Undergoing Endoscopy

Nonendoscopic Tests That Do Not Use Gastric Mucosal Biopsy

Urea Breath Test

Tests for active *H. pylori* infection; >95% sensitive and specific

Radiolabeled urea with either ^{13}C or ^{14}C is given orally; urease secreted by *H. pylori* in the stomach (if present) hydrolyzes radiolabeled urea to produce radiolabeled CO_2, which is exhaled and then quantified from the expired breath; radiation exposure is minimal.

Withhold H_2RAs and PPIs 1–2 weeks before testing and antibiotics and bismuth salts 4 weeks before testing to reduce the risk of false negatives.

Used to detect *H. pylori* before treatment and to document posttreatment eradication

Results usually take about 2 days; less expensive than are tests that utilize gastric mucosal biopsy, but more expensive than serologic tests; availability and reimbursement is inconsistent.

Antibody Detection (In-Office or Near Patient)

Qualitative test; detects IgG antibodies to *H. pylori* in whole blood or finger stick.

Effective for primary diagnosis, but not of benefit in confirming eradication because antibodies to *H. pylori* remain positive for years after successful eradication of the infection.

Results obtained quickly (usually within 15 minutes) but reduced sensitivity and specificity compared with laboratory-based tests; widely available and inexpensive.

Results not affected by H_2RAs, PPIs, or bismuth; antibiotics given for other indications may result in a positive antibody test.

Antibody Detection (Laboratory)

Quantitative test; detects IgG antibodies to *H. pylori* in serum using laboratory-based ELISA tests and latex agglutination techniques.

More accurate than in-office tests; similar sensitivity and specificity to rapid urease biopsy and urea breath tests.

Unable to determine whether antibody is related to active or cured infection; antibody titers vary between individuals and take up to 6 months to 1 year to return to the uninfected state.

Results not affected by H_2RAs, PPIs, or bismuth; antibiotics given for other indications may result in a positive antibody test.

Fecal Antigen Test

Tests Using Gastric Mucosal Biopsy in Patients Undergoing Endoscopy
An enzymatic immunoassay test that identifies *H. pylori* antigen in stool; sensitivity and specificity comparable to the UBT for initial diagnosis
H_2RAs, PPIs, antibiotics, and bismuth may cause false-negative results, but to a lesser extent than is the UBT.
Considered an alternative to detecting *H. pylori* before treatment and documenting posttreatment eradication; patients may have a reluctance to obtain stool samples.

ELISA, enzyme-linked immunosorbent assay; H_2RA, H_2 receptor antagonist; IgG, immunoglobulin G; PPI, proton-pump inhibitor; UBT, urea breath test.

Sources: Washington MK, Peek RM. Gastritis and gastropathy. In: Yamada T, Podolsky, Daniel K, et al, eds. *Textbook of Gastroenterology*. 5th ed. Wiley-Blackwell; 2009:1005; Chey WD, Wong BCY, Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102:1808–1825; Calvet X, Lehours P, Lario S, Mégraud F. Diagnosis of *Helicobacter pylori* infection. *Helicobacter*. 2010;15(suppl 1):7–13; Francis M, Lehours P. *Helicobacter pylori* detection and antimicrobial susceptibility testing. *Clin Microbiol Rev*. 2007;20(2):280–322.

Nonendoscopic tests include the urea breath test (UBT), stool antigen, or serology to identify active infection or detect antibodies to *H. pylori.*[94,95,115] The UBT, the most accurate noninvasive test, detects active *H. pylori* infection and is also effective after eradication treatment.[94,95,115] The ^{13}C (nonradioactive isotope) and ^{14}C (radioactive isotope) tests require that the patient ingest radiolabeled urea, which is then hydrolyzed by *H. pylori* (if present in the stomach) to ammonia and radiolabeled bicarbonate. The radiolabeled bicarbonate is absorbed in the blood and detected in expired breath. The in-office and laboratory antibody tests are a cost-effective method to initially diagnose *H. pylori* infection, but because they do not differentiate between active infection and previously eradicated *H. pylori*, they should not be used to confirm eradication.[94,95,115] The fecal antigen test identifies *H. pylori* antigens in the stool, and is less expensive and easier to perform than is the UBT.[94,95,115] Although usually comparable with the UBT in the initial detection of *H. pylori,* the fecal antigen test may be less accurate when used to document eradication posttreatment.

LABORATORY TESTS, RADIOGRAPHY, AND ENDOSCOPY

Generally, laboratory tests are not helpful in the diagnosis of PUD. Fasting serum gastrin concentrations are only recommended for patients who are unresponsive to therapy or those suspected of having a hypersecretory disease. Serum hematocrit (Hct) and hemoglobin (Hgb), as well as guaiac fecal occult blood tests, assist in the evaluation of ulcer-related bleeding.

Gastric acid–secretory studies are not routinely performed in patients suspected of having an uncomplicated peptic ulcer. However, measurements of acid secretion are instrumental in the evaluation of patients with severe, recurrent PUD that is unresponsive to standard drug therapy. Acid secretion is expressed as basal acid output (BAO), in response to a meal (meal-stimulated acid secretion), or as maximal acid output (MAO).[3] These tests estimate the acid-secretory response under various circumstances, and are measured by inserting a nasogastric tube into the stomach and aspirating the gastric contents.[3] The aspirate is estimated by titration with a basic solution of known concentration and expressed as milliequivalents of H^+ per hour. Results obtained for an individual patient are then compared with standard ranges for each test. The BAO, meal-stimulated acid secretion, and MAO vary according to age, sex, health, and time of day. The BAO follows a circadian rhythm, with the highest acid secretion occurring at night and the lowest in the morning. An increase in the BAO/MAO ratio suggests a basal hypersecretory state such as ZES.

Confirmation of a peptic ulcer requires visualizing the ulcer by either GI radiography or upper endoscopy.[93] Radiography is sometimes the initial diagnostic procedure because it is less expensive than is endoscopy and more widely available, although small ulcers are often difficult to detect and false positives may result from trapped barium.[93] Fiberoptic upper endoscopy (esophagogastroduodenoscopy [EGD]) is the gold standard because it detects >90% of peptic ulcers and permits direct inspection, biopsy, and visualization of superficial erosions and sites of active bleeding. Upper endoscopy is preferred if complications are suspected or if an

accurate diagnosis is required. If a gastric ulcer is found on radiography, malignancy should be excluded by direct endoscopic visualization and histology.

Clinical Course and Prognosis

The natural history of PUD is characterized by periods of exacerbations and remissions unless the underlying cause is removed.[93] *H. pylori* and NSAIDs are the two most important risk factors for the development of peptic ulcer.[93] Successful eradication of *H. pylori* heals ulcers and dramatically decreases ulcer recurrence and GI complications.[93] The risk of NSAID-induced ulcer and life-threatening GI complications is greatest in the elderly and those with a history of PUD. Prophylactic co-therapy and/or the use of a more COX-2–selective inhibitor markedly decreases ulcer risk and complications.[101,102] Gastric cancer in *H. pylori*–infected individuals develops slowly over 20 to 40 years, and is associated with a slightly higher lifetime risk when compared with that in patients with duodenal ulcer or in the general population.[94,97,98]

Treatment

THERAPEUTIC GOALS

The therapeutic goals for treating PUD in adults depend on whether the ulcer is related to *H. pylori* or associated with an NSAID. Treatment goals may differ depending on whether the ulcer is initial or recurrent and whether complications have occurred. Treatment is aimed at relieving ulcer symptoms, healing the ulcer, preventing ulcer recurrence, and reducing ulcer-related complications. When possible, the most cost-effective drug regimen should be utilized.

NONPHARMACOLOGIC THERAPY

Patients with PUD should discontinue NSAIDs (including aspirin) if possible. Patients unable to tolerate certain foods and beverages (eg, spicy foods, caffeine, and alcohol) may benefit from dietary

modifications. Lifestyle modifications such as stress reduction and decreasing or stopping tobacco use should be encouraged. Probiotics, particularly strains of lactic acid–producing bacteria such as *Lactobacillus* and *Bifidobacterium,* lactoferrin, and certain foods (eg, cranberry juice, ginger, chili, oregano, some milk proteins) have been used as adjuvant *H. pylori* therapy.[93,117–119] Probiotics can help reduce the side effects of the antibiotics used for eradication; however, most studies related to probiotic effectiveness in cure rates were performed in China with no optimal dose, timing, or duration of therapy that could be established. Current guidelines indicate that more research is needed before widespread recommendations can be made.[120,121] Patients with ulcer-related complications may require surgery for bleeding, perforation, or obstruction.[93] Surgery for medical treatment failures (eg, vagotomy with pyloroplasty or vagotomy with antrectomy) is rarely performed because of effective medical management and the risk of postoperative complications from surgery.

PHARMACOTHERAPY

Drug regimens used to eradicate *H. pylori* are identified in **Table 23-6**. As previously noted, all patients with a positive *H. pylori* test finding should be offered treatment.[95] Recommended first-line treatment in the United States includes a clarithromycin-based three-drug regimen (standard triple therapy) for 14 days or a bismuth-based four-drug regimen (standard quadruple therapy) for 10 to 14 days (**Fig. 23-4**). Treatment selection should be based on a patient's previous antibiotic exposure and current resistance rates. Another treatment option is sequential therapy; however, its effectiveness has not been validated in North America.[95] If initial eradication fails, a second course of therapy (ie, salvage therapy) should be offered based on the selection of antibiotics that have not been previously used. Successful treatment eradicates the infection and heals the ulcer. Treatment of *H. pylori*–positive patients with a conventional antiulcer drug or combining an antisecretory drug with sucralfate is not recommended because of high rates of ulcer recurrence and

complications. Maintenance therapy with a PPI or H_2RA (Table 23-1) should only be necessary in high-risk patients with a history of ulcer complications, those with *H. pylori*–negative ulcers, and patients with other concomitant acid-related diseases (eg, GERD).

Table 23-6
Oral Drug Regimens Used to Eradicate *Helicobacter pylori* Infection

Drug Regimen	Dose	Frequency	Duration
Clarithromycin-Based Three-Drug Regimens			
PPI	Standard dose[a]	bid[a]	14 days[b]
Clarithromycin	500 mg	bid	14 days[b]
Amoxicillin[c]	1 g	bid	14 days[b]
Or			
PPI	Standard dose[a]	bid[a]	14 days[b]
Clarithromycin	500 mg	bid	14 days[b]
Metronidazole[c]	500 mg	bid	14 days[b]
Bismuth-Based Four-Drug Regimens			
Bismuth subsalicylate[d]	525 mg	qid	10–14 days
Metronidazole[c]	250–500 mg	qid	10–14 days
Tetracycline plus	500 mg	qid	10–14 days
PPI	Standard dose[a]	Daily or bid[a]	10–14 days
Or			
H_2RA[e]	Standard dose[e]	bid[e]	4–6 weeks
Sequential Therapy[f]			
PPI	Standard dose[a]	bid[a]	Days 1–10
Amoxicillin[c]	1 g	bid	Days 1–5
Clarithromycin	250–500 mg	bid	Days 6–10
Metronidazole[c]	250–500 mg	bid	Days 6–10
Salvage Therapy			
Bismuth subsalicylate[d]	525 mg	qid	14 days
Metronidazole[c]	500 mg	qid	14 days
Tetracycline	500 mg	qid	14 days
PPI	Standard dose[a]	Daily or bid[a]	14 days
Or			
PPI	Standard dose[a]	bid[a]	14 days
Amoxicillin[c]	1 g	bid	14 days
Levofloxacin	500 mg	Daily	14 days

bid, two times a day; H_2RA, H_2 receptor antagonist; PPI, proton-pump inhibitor; qid, four times a day.

[a]Omeprazole 20 mg bid, lansoprazole 30 mg bid, pantoprazole 40 mg bid, rabeprazole 20 mg bid, esomeprazole 20 mg bid.

[b]Although 7- to 10-day regimens may provide acceptable eradication rates, the preferred treatment duration in the United States is 14 days.

[c]Use amoxicillin in non–penicillin-allergic individuals; substitute metronidazole for amoxicillin in true penicillin-allergic patients.

[d]Pylera, a prepackaged U.S. Food and Drug Administration (FDA)-approved *Helicobacter pylori* regimen, contains bismuth subcitrate potassium (biskalcitrate) 140 mg as the bismuth salt in place of bismuth subsalicylate, metronidazole 125 mg, and tetracycline 125 mg per capsule. The patient is directed to take three capsules per dose with each meal and at bedtime. A standard dose of a proton-pump inhibitor (PPI) is added to the regimen and taken twice daily. All medications are taken for a 10-day period.

[e]See Table 23-1 for standard peptic ulcer healing dosage regimens.

[f]Requires validation in the United States.

Sources: From Soll AH, Graham DY. Peptic ulcer disease. In: Yamada T, Podolsky, Daniel K, et al, eds. *Textbook of Gastroenterology*. 5th ed. Wiley-Blackwell; 2009:936; Washington MK, Peek RM. Gastritis and gastropathy. In: Yamada T, Podolsky, Daniel K, et al, eds. *Textbook of Gastroenterology*. 5th ed. Wiley-Blackwell; 2009:1005; Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet*. 2009;374:1449–1461; Gisbert JP, Calvet X, O'Connor A, Mégraud F, O'Morain CA. Sequential therapy for *Helicobacter pylori* eradication: a critical review. *J Clin Gastroenterol*. 2010;44:313–325; Gisbert JP, Gisbert JL, Marcos S, Olivares D, Pajares JM. *Helicobacter pylori* first-line treatment and rescue options in patients allergic to penicillin. *Aliment Pharmacol Ther*. 2005;22:1041–1046; Gisbert JP, Pérez-Aisa A, Castro-Fernández M, et al. *Helicobacter pylori* first-line treatment and rescue option containing levofloxacin in patients allergic to penicillin. *Dig Liver Dis*. 2010;42:287–290; Vergara M, Vallve M, Gisbert JP, Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2003;18:647–654; Gisbert JP, Khorrami S, Calvet X, Gabriel R, Carballo F, Pajares JM. Meta-analysis: proton pump inhibitors vs. H_2-receptor antagonists—their efficacy with antibiotics in *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2003;18:757–766; Gisbert JP. Review: second-line rescue therapy of *Helicobacter pylori* infection. *Therap Adv Gastroenterol*. 2009;2:331–356. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2017;112(2):212–239.

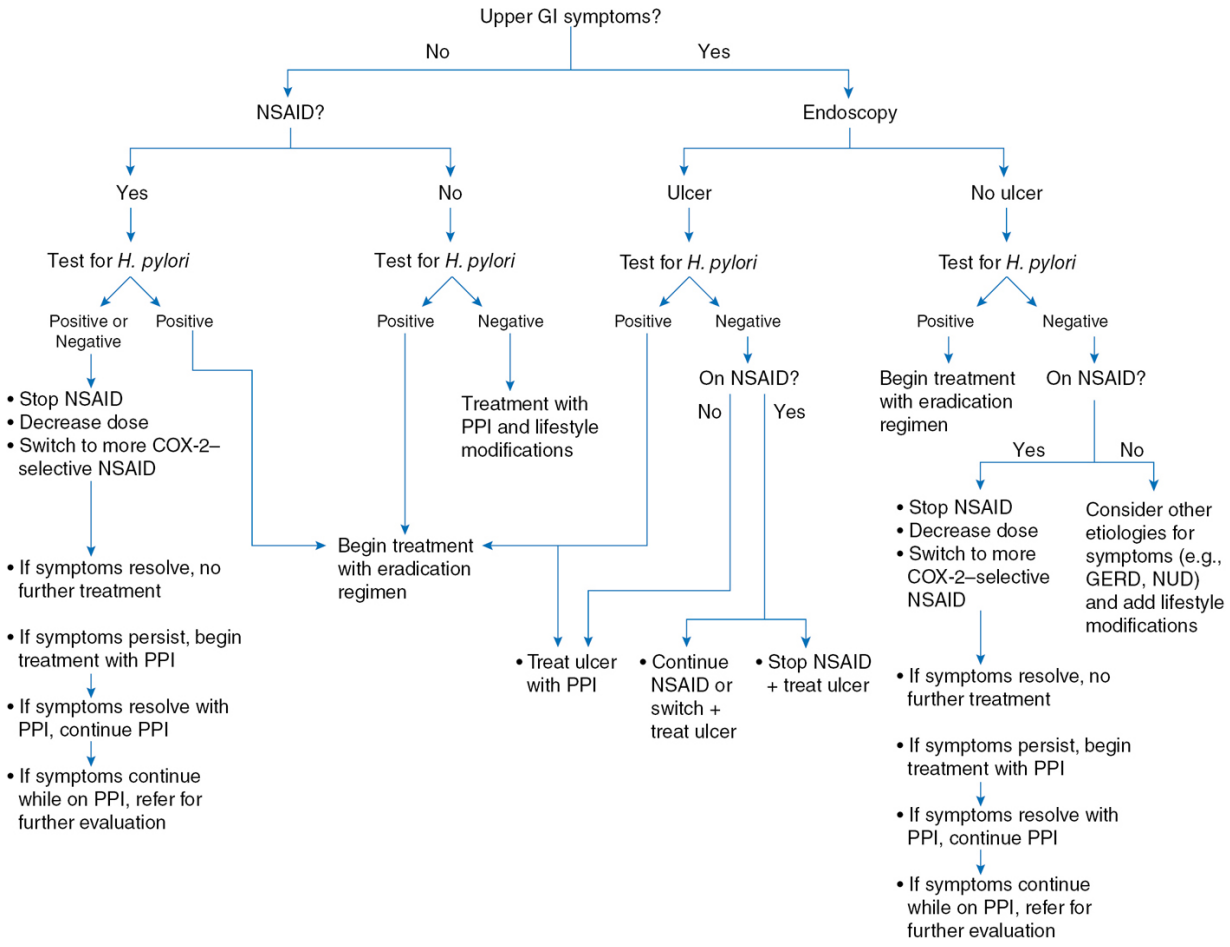


Figure 23-4 Management of peptic ulcer disease. COX-2, cyclooxygenase-2; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drug; NUD, nonulcer dyspepsia; PPI, proton-pump inhibitor. (Lamont JT. Treatment regimens for Helicobacter pylori in adults. *UpToDate*. UpToDate; 2020. Accessed November 11, 2020. www.uptodate.com)

Drug regimens used to treat and prevent NSAID-induced ulcers are identified in **Table 23-1**. Patients with NSAID-induced ulcers should be tested to determine their *H. pylori* status. If the patient is *H. pylori* negative, the NSAID should be discontinued, and treatment should be initiated with antiulcer medications. The duration of treatment should be extended if the NSAID is continued. Prophylactic co-therapy with a PPI or misoprostol, or switching to an

NSAID with greater COX-2 selectivity, is recommended for patients at risk for exhibiting ulcer-related upper GI complications.

CASE 23-1

QUESTION 1: R.L. is an otherwise healthy 45-year-old male who works in a high-stress job as an air traffic controller at a major airport. He reports 2 weeks of "burning stomach pain," sometimes accompanied by "indigestion and bloating." The pain initially occurred several times a day, usually between meals, and sometimes awakened him at night, but it has increased in frequency during the past week. Initially, the pain was temporarily reduced by food or antacids. Last week, R.L. tried an OTC H_2RA that "lasted longer," but did not provide adequate symptom relief. R.L. states that he experienced a similar type of pain about 12 years ago when he was treated with omeprazole for a suspected peptic ulcer. He has smoked one pack of cigarettes daily for the past 20 years, has an occasional glass of red wine with dinner, and usually drinks four to six cups of caffeinated coffee throughout the day. R.L. takes acetaminophen when needed for occasional headaches and a daily multivitamin, but denies the use of any other OTC or prescription medications, including NSAIDs and the previous use of clarithromycin or metronidazole. He denies nausea, vomiting, anorexia, weight loss, and changes in stool consistency or color. A review of other body systems is noncontributory. He has no known food or drug allergies.

Physical examination is normal except for epigastric tenderness on palpation of the upper abdomen. Vital signs include a temperature of 98.8 °F (37.11 °C), blood pressure of 132/80 mm Hg, and a heart rate of 78 beats/minute. Pertinent laboratory values include the following:

Hgb, 14.0 g/dL
Hct, 44%
Stool guaiac test, negative
All other laboratory values are within normal limits.

What signs and symptoms are suggestive of a recurrent peptic ulcer?

HELICOBACTER PYLORI–RELATED PEPTIC ULCER

The diagnosis of PUD cannot be made based on symptoms alone, and requires visualization of the ulcer crater because the symptomology, severity of pain, and timing of the pain (eg, seasonal,

intermittent, or pain-free periods lasting from weeks to years) can differ for each patient and encompass a wide variety of symptoms. Most patients with PUD present with abdominal pain that is epigastric and often described as burning or gnawing, whereas others describe abdominal discomfort, fullness, or cramping. Epigastric pain, however, does not necessarily correlate with an ulcer because patients with ulcer-like symptoms may have NUD, and asymptomatic patients may have an NSAID-induced ulcer; heartburn, bloating, and belching may accompany the pain. Ulcer pain typically occurs during the day, but can also awaken the patient from sleep (nocturnal pain). In patients with a duodenal ulcer, epigastric pain frequently occurs between meals and is often relieved by food, but this varies from patient to patient. Alternatively, food may precipitate or accentuate pain in patients with a gastric ulcer.

Antacids and antisecretory medications usually provide relief of ulcer pain in most patients. Pain usually diminishes or disappears during treatment, but epigastric pain after healing often suggests an unhealed or recurrent ulcer. Changes in the character of the pain may suggest the presence of complications. Nausea, vomiting, anorexia, and weight loss are more common with gastric ulcer, but may also be suggestive of ulcer-related complication.

CASE 23-1, QUESTION 2: R.L. underwent EGD, which revealed a single 0.5-cm ulcer in the duodenal bulb. The ulcer base was clear without evidence of active bleeding. Antral gastritis was biopsy positive for *H. pylori.* What risk factors may have contributed to ulcer recurrence in this patient?

R.L. indicates that he had a similar type of abdominal pain about 12 years ago for which he was treated with omeprazole for a suspected peptic ulcer. When conventional antiulcer therapy (ie, PPI) is discontinued after ulcer healing, the ulcer tends to recur. The most important etiologic factors that influence ulcer recurrence are *H. pylori* infection and NSAID use. It is not known whether R.L. underwent testing for *H. pylori* 12 years ago. The patient denies the use of OTC and prescription NSAIDs. The long-term use of

maintenance therapy with a conventional antiulcer medication (**Table 23-1**) to maintain remission after initial ulcer healing was standard practice for years, and may have been an option for this patient at the time.[103] However, successful eradication of *H. pylori* (in a patient who is *H. pylori* positive) cures the infection, heals the ulcer, and eliminates the need for long-term maintenance therapy in most patients.[95,103]

Other factors, such as cigarette smoking, psychological stress, and diet, may have contributed to ulcer recurrence in this patient. There is strong epidemiologic evidence indicating that cigarette smoking is a major risk factor for PUD and that the risk is proportional to the number of cigarettes smoked per day.[93] Although cigarette smoking exacerbates PUD, there is insufficient evidence to conclude that it causes a peptic ulcer; however, it is hypothesized that smoking or nicotine might provide an environment for *H. pylori* infection.

R.L. works as an air traffic controller, which is a high-stress job. The importance of psychological stress and how it affects PUD is complex and multifactorial. Results from controlled trials are conflicting, and have failed to demonstrate a cause-and-effect relationship.[93,103] However, the clinical observation of patients with ulcer having high-stress jobs and a stressful lifestyle suggest that they are adversely affected.

Caffeine-containing coffee, tea, and cola beverages, constituents in decaffeinated coffee or tea, caffeine-free carbonated beverages, and alcoholic beverages, such as beer and wine, all increase gastric acid secretion; however, there is no evidence that they increase the risk of PUD. Certain foods (eg, spicy) may cause dyspepsia or worsen ulcer symptoms, but do not cause peptic ulcers. In high concentrations, alcohol is associated with acute gastric mucosal damage and upper GI bleeding, but there is insufficient evidence to confirm that alcohol causes ulcers.[93] Dietary restrictions and bland diets do not alter the frequency of ulcer recurrence.

CASE 23-1, QUESTION 3: What are the goals of therapy when treating this patient?

The goals of therapy in an *H. pylori*–positive patient with an active ulcer, a previously documented ulcer, or a history of an ulcer-related complication are to render the patient asymptomatic, heal the ulcer, eradicate the infection, and cure the disease. Treatment should be effective, well-tolerated, easy to comply with, and cost-effective. Drug regimens should have an eradication rate of at least 80% (intention-to-treat [ITT]) or 90% (per protocol analysis) and should minimize the potential for antimicrobial resistance.[122]

Primary Treatment for *Helicobacter pylori* Infection

Case 23-1, Question 4: What factors should be taken into consideration when selecting a first-line eradication regimen? What are the therapeutic options for first-line *H. pylori* eradication in the United States? Which is the preferred *H. pylori* eradication regimen for R.L.?

The selection of a first-line *H. pylori* eradication regimen should be based on proven effectiveness, and should take into consideration antibiotic combinations that permit second-line treatment (if necessary) with different antibiotics, treatment duration, the likelihood of antibiotic resistance, and the ability to adhere to the drug regimen. The antibiotics that have been most extensively studied in the United States and found to be effective in various combinations include clarithromycin, amoxicillin, metronidazole, and tetracycline (**Table 23-6**).[93,95,103]

Current treatment guidelines in the United States and Europe recommend two first-line eradication therapy combinations for patients with an *H. pylori*–positive peptic ulcer: standard triple therapy (clarithromycin-based) for 14 days or standard quadruple therapy (bismuth-based) for 10 to 14 days (**Table 23-6**).[95] Despite these recommendations, there are recent concerns about the efficacy of these regimens because of declining eradication rates thought to be related to antibiotic resistance, particularly with

clarithromycin, and the potential for nonadherence, especially with standard quadruple therapy (see Case 23-1, Question 8).[95,123–127] Clarithromycin should be avoided where resistance rates are >15% or in patients who recently received macrolide antibiotics.[122] Controversy exists as to whether standard triple therapy should remain as first-line treatment in the United States.[95,123–127] Some clinicians believe that sequential therapy should replace the clarithromycin-based three-drug regimens because of superior eradication rates or that the bismuth-based four-drug regimen should be used exclusively as first-line treatment.[123,127] Others believe that more robust clinical trials involving a broader range of patients is needed before sequential therapy replaces standard triple therapy in the United States, and that medication adherence remains problematic with standard quadruple therapy.[95,124,125]

When combined with a PPI and clarithromycin, the inclusion of either amoxicillin or metronidazole for standard triple therapy provides similar eradication rates.[95] Amoxicillin is usually preferred initially because it is associated with little or no bacterial resistance, has fewer adverse effects, and leaves metronidazole as an option for second-line therapies.[93] Recent data suggest that eradication rates with clarithromycin-based triple therapy have been declining, with global eradication rates below 80%.[128] This low eradication rate was also observed in several meta-analyses completed in the United States and Canada when treatment with clarithromycin-based triple therapy was prescribed for 7 or 10 days. The superiority of the 14-day regimen over a 7- or 10-day treatment course has been confirmed, and is less likely to be associated with antimicrobial resistance.[95] Because of this data, when standard triple therapy is chosen, guidelines now recommend it should be given for 14 days.[95] Increasing the antibiotic daily dose or extending antibiotic treatment beyond 14 days usually does not improve eradication rates. The PPI may be extended to 28 days if needed for ulcer healing. Twice-daily dosing of the PPI appears to be more effective than is a single daily dose.[129] Pretreatment with a PPI before initiating *H. pylori* eradication does not decrease the rate of eradication.[130]

Bismuth-based quadruple therapy containing a bismuth salt, metronidazole, tetracycline, and either a PPI or an H_2RA has been advocated as first-line treatment because it usually yields satisfactory eradication rates despite increased resistance to clarithromycin.[95,127] The complexity of this regimen and the potential for increased side effects often relegate it to preferred second-line status if not previously used. However, eradication rates, tolerability, and medication adherence were reported to be similar to that of standard triple therapy when used as first-line treatment, although both regimens yielded eradication rates of <80% ITT.[131] Using a PPI instead of an H_2RA permits a shorter duration of treatment (10 vs 14 days), and may provide increased efficacy in patients with metronidazole-resistant strains of *H. pylori.*[95] Increasing the duration of quadruple therapy to 1 month does not substantially increase eradication, although the antisecretory drug may be continued for an additional 2 (PPI) or 4 weeks (H_2RA) in patients with an active ulcer.

Sequential therapy was introduced in the year 2000 as a potential alternative to standard triple and quadruple therapy, with evidence arising from small studies primarily conducted in Italy. Sequential therapy, described as a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and an imidazole for an additional 5 days, achieved eradication rates (>80% ITT). The rationale for sequential therapy is to initially treat the patient with antibiotics that rarely promote resistance (eg, amoxicillin) to reduce the bacterial load and preexisting resistant organisms, and then to follow with different antibiotics to eradicate the remaining organisms. Although the precise mechanism for the success of sequential therapy is uncertain, the increased efficacy may be related to the number of antibiotics to which the organism is exposed. Originally, this made a compelling case to switch to sequential therapy as the preferred first-line treatment in the United States.[123–125] A meta-analysis looking at previously untreated adults comparing sequential therapy with preexisting or emerging therapies demonstrated that sequential therapy is superior to a 7-day course of the clarithromycin-based three-drug regimens.[95,123–127,132–134] However, sequential therapy was

only marginally superior to the 10-day course, not superior to the 14-day course, and not superior to 10 to 14 days of bismuth-based quadruple therapy.[126] In addition, sequential therapy is more complex than is standard PPI triple therapy because it requires a midcourse change in medications.

The therapeutic options available for the eradication of *H. pylori* should be carefully considered in each individual patient. The PPI–amoxicillin–clarithromycin regimen is an acceptable first-line management strategy for R.L. because he has not previously received clarithromycin and has no known allergies to penicillin. Posttreatment testing should be considered, but may not be necessary if R.L. remains asymptomatic. Although sequential therapy may overcome clarithromycin resistance, it is unclear, at this time, whether it would provide any increased benefit in this patient.

Patient Education

Case 23-1, Question 5: R.L. is prescribed a 14-day clarithromycin three-drug eradication regimen containing amoxicillin. What instructions should R.L. be provided regarding his medications?

R.L. should be informed of the importance of taking his medications as prescribed to minimize treatment failure and the development of antibiotic resistance. He should be advised that the PPI is an integral part of the three-drug regimen and should be taken twice daily 30 to 60 minutes before breakfast and dinner (see section on Pharmacotherapy) along with amoxicillin and clarithromycin.

R.L. should also be informed of the most common side effects associated with his treatment regimen. All antibiotics included in the *H. pylori* eradication regimens are usually associated with mild side effects including nausea, abdominal pain, and diarrhea. *C. difficile*–associated diarrhea, a serious antibiotic-related complication, occurs occasionally. Oral thrush and vaginal candidiasis (in females) may also occur. Clarithromycin and metronidazole may cause taste disturbances.

R.L., as well as all other patients receiving *H. pylori* eradication therapy, should be advised of the risk of clinically important drug–drug interactions that may occur with the medications included in their eradication regimen. Special attention should be given to metronidazole and clarithromycin (inhibitors of CYP3A4), as well as to substrates of CYP2C9 (inhibited by metronidazole).[135] Drug–drug interactions may also occur with H_2RAs and PPIs (see section on Pharmacotherapy).

Regimens for the Management of *Helicobacter pylori* Infection in Patients With Penicillin Allergies

CASE 23-1, QUESTION 6: What would have been the preferred initial *H. pylori* eradication regimen if R.L. had a documented allergy to penicillin?

Before selecting alternative therapies, R.L.'s penicillin allergy should be investigated and defined as a true penicillin hypersensitivity. There are two first-line treatment options if R.L. has a true allergy to penicillin. Metronidazole can be substituted for amoxicillin in the clarithromycin-based three-drug regimen, because similar eradication rates are achieved (**Table 23-6**).[95,136] Bismuth-based quadruple therapy may also be used, because it provides similar eradication rates.[95,131]

If R.L.'s medications included metronidazole, tetracycline, or a bismuth salt, he should be provided additional information on these medications. Metronidazole-containing regimens increase the frequency of side effects (especially when the dose is >1 g/day) and may be associated with a disulfiram-like reaction in patients who consume alcohol. Tetracycline may cause photosensitivity, and should not be used in children because it may cause tooth discoloration. Bismuth salts may cause darkening of the tongue and stool.

Regimens that substitute levofloxacin for amoxicillin in clarithromycin-based triple therapy have been used with success, although there are fewer studies supporting their efficacy.[137] The most common sequential therapy contains amoxicillin and, therefore, is not suitable for a penicillin-allergic patient.

CASE 23-1, QUESTION 7: What drug substitutions are acceptable in the standard clarithromycin-based three-drug and bismuth-based four-drug eradiation regimens?

There are insufficient data to support the substitution of ampicillin for amoxicillin, doxycycline for tetracycline, and azithromycin or erythromycin for clarithromycin. Substitution of clarithromycin 250 to 500 mg four times a day for tetracycline in the bismuth-based four-drug regimen (**Table 23-6**) yields similar results, but substitution of amoxicillin for tetracycline lowers the eradication rate and is not recommended.[93,103]

CASE 23-1, QUESTION 8: What are the most important predictors of *H. pylori* treatment outcomes, and how may they alter R.L.'s response to treatment?

The two most important factors in predicting *H. pylori* treatment outcomes are antibiotic resistance and medication adherence.[95,123,124,127] Antibiotic resistance rates are highly variable throughout the United States and the world, and thus are difficult to compare.[95,124,127] However, there is evidence that clarithromycin resistance is increasing in North America and Europe, which is thought to be the most important reason for the decreasing efficacy of clarithromycin-containing eradication regimens.[95,123,124,127] Because treatment with clarithromycin may increase the likelihood of *H. pylori* resistance, clinicians should ask about previous macrolide antibiotic use when deciding upon an eradication regimen.[95]

The clinical importance of metronidazole resistance is unclear because higher metronidazole doses and the synergistic effect of combining metronidazole with other antibiotics appear to render

resistance to metronidazole more relative.[95,124,127,135] Resistance to amoxicillin and tetracycline is uncommon. Levofloxacin is emerging as a component of eradication therapy, but there are reports of increasing resistance to fluoroquinolones.[123–127,135]

Medication adherence decreases with multiple medications, increased frequency of administration, increased duration of treatment, intolerable adverse effects, and costly drug regimens.[95,123] Although most eradication studies report >95% adherence to medications, this high rate must be questioned because it is very difficult to accurately assess the level of compliance in clinical trials where patients take their own medications.[123] In addition, medication adherence is usually more problematic in clinical practice. A longer treatment duration may contribute to nonadherence, but missed doses in a shorter regimen may also lead to failed eradication. Most bismuth-based four-drug regimens require the patient to take medications four times per day, with as many as 18 tablets or capsules total per day. The complexity of this regimen, as well as a mid-treatment change in medications with sequential therapy, should be considered when selecting an eradication regimen. Although mild side effects are common with all of the eradication regimens, some patients will experience clinically important effects that lead to discontinuation of a specific drug or of the entire regimen.

Other factors that may contribute to treatment failure include high bacterial load, the specific *H. pylori* strain, low intragastric pH, and genetic polymorphism (eg, CYP2C19 polymorphism) when PPIs are used as part of the eradication regimen.[95,124,127,135,138,139] There are limited data to suggest that smoking, alcohol consumption, and diet may negatively affect eradication.

Case 23-1, Question 9: What parameters should be monitored to determine R.L.'s response to treatment?

Testing to confirm eradication should be performed in all patients treated for *H. pylori* because of increasing rates of antibiotic resistance (**Table 23-5**).[95,122] The term *eradication* or *cure* is used

when posttreatment tests, conducted 4 weeks after the end of treatment, do not detect the organism. PPIs should be held for 1 to 2 weeks before testing to prevent false-negative results.

Upper endoscopy should only be used to confirm eradication and ulcer healing if indicated (eg, severe or frequent recurrent symptoms or current or previous ulcer complication) because the procedure is costly and invasive. When endoscopic follow-up is necessary, testing to prove eradication includes a biopsy for the rapid urease test and histology (**Table 23-5**). Ulcer healing can also be confirmed at that time.

Secondary or Rescue Therapy for *Helicobacter pylori* Infection

Case 23-1, Question 10: What other drug regimens can be used if R.L. fails clarithromycin-based triple therapy? What regimens can be used when secondary treatment fails?

All initial eradication regimens require that there be an effective second-line treatment. Eradicating *H. pylori* is more difficult after initial treatment fails, and attempts to eradicate the organism are extremely variable.[95] Second-line regimens should (a) avoid using antibiotics that were used during initial therapy, (b) use antibiotics that have less problems with resistance, (c) use drugs that have a topical effect (eg, bismuth), and (d) use a 10- to 14-day treatment duration.[95,123,127,140] If R.L. was not successfully eradicated initially with the PPI–amoxicillin–clarithromycin, he should receive second-line therapy with bismuth subsalicylate, metronidazole, tetracycline, and a PPI for 10 to 14 days.[95,123,127,140,141]

Bismuth-based regimens are the most frequently used second-line treatments in the United States when standard clarithromycin-based triple therapy fails (**Table 23-6**).[95] A number of alternatives have been evaluated in small studies utilizing fluoroquinolone, rifabutin (an antibiotic used to treat tuberculosis), or furazolidone (no longer marketed in the United States).[95,123] Levofloxacin-based therapy for

14 days has shown eradication rates of 76% after clarithromycin-based triple therapy failure and 81% after sequential therapy failure.[142] The results from the levofloxacin-based clinical trials look promising and suggest that these regimens may be an alternative to second-line bismuth quadruple therapy, especially for patients who have no prior use of a fluoroquinolone.[95,123,137,140] However, increasing fluoroquinolone resistance, which appears to be easily acquired, is of concern and may limit the use of these agents for *H. pylori* eradication.[140] Various rifabutin-based regimens are effective in treating patients with *H. pylori* strains resistant to clarithromycin or metronidazole.[95,140] Regimens that include rifabutin should be the last option, and only used for patients with multiple eradication failures because of concerns about major hematologic side effects and the possibility of resistance.[140]

CASE 23-2

QUESTION 1: A.D. is a 70-year-old female who retired from teaching 5 years ago. A few days ago, she noticed black "tarry" stools and was hospitalized for an upper GI bleed most likely secondary to NSAID use. She reports of "feeling tired" and occasional dizziness for ~1 week. A.D. presents with a 5-year history of osteoarthritis for which she takes naproxen 250 mg every morning and 500 mg every evening. Other active medications include hydrochlorothiazide 25 mg daily and lisinopril 20 mg daily for hypertension, self-directed treatment with enteric-coated aspirin 81 mg daily, calcium carbonate, and a multivitamin. When questioned, she denies the use of corticosteroids, bisphosphonates, anticoagulants, clopidogrel, or selective serotonin reuptake inhibitors (SSRIs). She does not have a history of a previous ulcer or related complication. A.D. does not use tobacco or drink caffeinated beverages, but does have an occasional glass of wine. She denies epigastric pain, nausea, vomiting, anorexia, and weight loss, but notes the recent change in stool color. A review of other body systems is noncontributory other than previously indicated. There are no known food or drug allergies.

Physical examination reveals a well-developed weak female in no acute distress. The abdomen is normal, with no pain on palpation. Bowel sounds are normal, with no guarding, masses, hepatomegaly, or splenomegaly. The rectum is normal, but with guaiac-positive stool. Vital signs include a temperature of 98.9 °F (37.17 °C), blood pressure of 118/75 mm Hg, and a heart rate of 90 beats/minute. Pertinent laboratory values include the following:

Hgb, 11.0 g/dL

Hct, 35%
Blood urea nitrogen (BUN), 40 mg/dL
Serum creatinine (SCr), 1.5 mg/dL
All other laboratory values are within normal limits.

What factors placed A.D. at increased risk for experiencing an NSAID-induced ulcer and related upper GI bleeding?

NONSTEROIDAL ANTI-INFLAMMATORY DRUG–INDUCED PEPTIC ULCER

Risk factors for NSAID-induced ulcers and related complications are presented in **Table 23-3**. A.D.'s age (70 years) is an independent risk factor for NSAID-induced ulcers.[101,102] The increased incidence in older patients may be explained by age-related changes in gastric mucosal defense. A.D.'s self-treatment with cardioprotective/antiplatelet doses (81–325 mg/day) of aspirin, combined with her twice-daily NSAID use (naproxen) increases her risk of upper GI events to a greater extent than is the use of either drug alone.[101–103] The use of buffered or enteric-coated aspirin does not confer added protection from ulcer or upper GI complications.[103,112,143] The use of nonselective NSAIDs (eg, naproxen) is linked to a threefold to fourfold increase in upper GI complications, compared to a twofold to threefold increase with selective and partially selective COX-2 inhibitors (**Table 23-4**).[110] Upper GI events can occur at any NSAID dose, including low OTC doses, and at any time during treatment.[101–103] The risk of upper GI bleeding is markedly increased when NSAIDs are taken with anticoagulants, corticosteroids, bisphosphonates, antiplatelets, or SSRIs.[35,101–103,110] Corticosteroids do not increase ulcer risk when used alone, but the risk is increased twofold in corticosteroid users who are also taking concurrent NSAIDs.[101–103] SSRIs independently increase the risk of upper GI bleeding, and although the magnitude of the risk is variable, it is increased in patients taking NSAIDs.[144,145] The pharmacologic mechanism underlying this adverse effect is

thought to be related to SSRI inhibition of platelet aggregation, which may interfere with ulcer healing, but it remains unknown if SSRIs have a direct ulcerogenic effect.[144,145] Although A.D. did not have a history of an ulcer or an ulcer-related complication before admission, the history of an NSAID-related upper GI event further increases the risk of NSAID-related GI injury.[101–103] It is uncertain whether *H. pylori* is a risk factor for NSAID-induced ulcers, but a higher incidence of PUD in *H. pylori*–positive patients taking NSAIDs suggests an additive effect, which may increase the risk of NSAID-related GI complications.[101–103]

CASE 23-2, QUESTION 2: A.D. was admitted for further evaluation and treatment. An EGD revealed two bleeding antral ulcers (0.2 and 0.4 cm), and endoscopic hemostasis was performed. An antral biopsy finding was reported to be *H. pylori* negative. All medications were discontinued before endoscopy. Oral oxycodone was instituted after endoscopy at 5 mg every 6 hours as needed to control A.D.'s arthritic pain while she was hospitalized. Consideration was given to decreasing the naproxen dose and switching to acetaminophen, a non-acetylated salicylate, or a partially selective NSAID, but none of these options were satisfactory for this patient. Treatment was initiated with a continuous infusion of IV pantoprazole for 3 days and then switched to oral pantoprazole 40 mg twice daily. A.D. was discharged on pantoprazole 40 mg daily and naproxen 250 mg in the morning and 500 mg in the evening. Hydrochlorothiazide, lisinopril, calcium carbonate, and the multivitamin were resumed upon discharge from the hospital. Will A.D.'s gastric ulcer heal if she continues to take the naproxen?

The naproxen should be discontinued, if possible, in the presence of an active ulcer in favor of alternative osteoarthritis therapy.[93,103] Despite A.D. being discharged on naproxen, a PPI such as pantoprazole is the preferred treatment to heal A.D.'s gastric ulcer because its potent acid suppression provides a more rapid rate of ulcer healing (4 weeks) and symptom relief than does an H_2RA or sucralfate (6–8 weeks).[93,101,103] Because A.D. will be continuing the naproxen, the duration of PPI therapy should be extended from 4 weeks to 8 to 12 weeks, because continuing the offending NSAID will interfere with ulcer healing.[93,103] Cardiovascular risk and the need for low-dose aspirin must be determined by the patient's primary

care physician or cardiologist, and, if not needed, the aspirin should be discontinued. Three large randomized control trials were conducted in patients with diabetes, elderly patients, and patients without diabetes at moderately increased cardiovascular risk to interpret the benefits versus risks of aspirin in primary prevention; all showed significantly elevated bleeding rates compared to placebo, with only marginal benefit seen in patients with diabetes.[146–148] Updated guidelines for the primary prevention of cardiovascular disease advocate against the use of low-dose aspirin in A.D. because of her age and associated bleeding risk that outweigh the potential benefits; its use in secondary prevention is still well documented.[148] Also, it may be advisable to continue low-dose aspirin after endoscopic hemostasis in patients at elevated cardiovascular risk.[93,149] Of note, the risk of GI bleed is not reduced by substituting clopidogrel for low-dose aspirin.[35,102]

CASE 23-2, QUESTION 3: Which ulcer-healing regimen would be recommended if A.D. was reported to be *H. pylori* positive?

All patients with NSAID-induced GI events should be tested for *H. pylori* (**Fig. 23-4**). An eradication regimen (either clarithromycin-based triple therapy or bismuth-based quadruple therapy) is recommended in an *H. pylori*–positive patient with an active ulcer who is also taking an NSAID. One reason for this is that it is not possible to determine whether the *H. pylori,* the NSAID, or both actually caused the ulcer. If an individual is tested and found to be *H. pylori* positive, he or she should be offered eradication therapy whether or not there is a documented ulcer. The selection of a specific regimen (Table 23-6) depends on a number of factors, including whether the individual is allergic to penicillin.

Strategies to Reduce the Risk of Nonsteroidal Anti-inflammatory Drug–induced Peptic Ulcers

CASE 23-2, QUESTION 4: Three months later, A.D. returned to her gastroenterologist for a follow-up EGD, which confirmed that the gastric ulcers were healed. On return to her primary care physician, the pantoprazole was changed to famotidine 20 mg twice daily, and the patient was advised to discontinue low-dose aspirin. Current medications include naproxen 250 mg in the morning and 500 mg in the evening, hydrochlorothiazide 25 mg daily, lisinopril 20 mg daily, calcium carbonate, and multivitamins. What pharmacologic options are available to reduce the risk of an NSAID-induced ulcer now that A.D.'s initial ulcer is healed and that she continues to take the naproxen?

Strategies to reduce the risk of NSAID-induced ulcers and upper GI complications during continued NSAID use in patients with an ulcer history include co-therapy with a PPI or misoprostol, the use of a COX-2 inhibitor, or various combinations of a PPI, misoprostol, and a COX-2 inhibitor.[93,101–103,105,108,113] All PPIs, when used in standard doses, are effective for this indication. Standard H_2RA doses should not be recommended as prophylactic co-therapy to reduce the risk of NSAID ulcers because they are not effective in reducing the risk of gastric ulcers, which is the most common ulcer associated with NSAIDs; higher H_2RA doses reduce the risk of gastric and duodenal ulcer, but are less effective than are standard PPI doses (**Table 23-1**).[101–103] Famotidine 20 mg twice daily may be an alternative to a PPI in patients at risk who are taking low-dose aspirin,[150] but comparative trials with PPIs are needed to support the use of standard-dose H_2RAs for this indication. There are no studies that have evaluated the use of H_2RAs in reducing the risk of ulcer-related upper GI complications.

Misoprostol reduces the risk of NSAID-induced gastric and duodenal ulcers as well as the risk of upper GI complications in high-risk patients.[101–103,149] Initially, the recommended dose was 200 μg four times daily, but diarrhea and abdominal cramping limited its use. A lower daily dose of 600 μg/day should be used because it reduces GI side effects and is comparable in efficacy; dose reductions to 400 μg/day or less minimize GI side effects, but compromise gastroprotective effects.[102,103] When used as co-therapy, misoprostol

and PPIs have comparable efficacy in preventing gastric ulcer, but PPIs have fewer side effects.[102,103]

Two large randomized clinical trials compared the GI safety in patients taking COX-2 inhibitors versus nonselective and partially selective NSAIDs, and reported a reduction of 50% to 60% in upper GI events with the COX-2 inhibitors.[151,152] A 6-month trial of celecoxib in patients who were not taking low-dose aspirin revealed a statistically lower rate of ulcer complications when compared with that of ibuprofen or diclofenac,[152] but evaluation at 1 year found no GI safety advantage among those taking celecoxib.[102] Further, a post hoc analysis at 6 months indicated that patients taking celecoxib and concomitant cardioprotective doses of aspirin had a rate of upper GI events similar to those taking either diclofenac or ibuprofen, thus negating the beneficial effects of celecoxib.[152] This explains why celecoxib contains the same GI warnings as the nonselective and partially selective NSAIDs (**Table 23-4**).[153]

Because A.D. continues to take naproxen, she remains at high risk for another NSAID-related complication even though gastric ulcer healing was confirmed. Co-therapy with a PPI or misoprostol is preferred for this patient because both are effective in reducing the risk of NSAID-related upper GI events. A.D.'s osteoarthritis is well controlled with naproxen, so there is no need to switch her to celecoxib or another more costly NSAID. Combining PPI therapy with misoprostol is not necessary, but some physicians prefer to use combination therapy for older patients with multiple risk factors. Standard H_2RA doses (eg, famotidine 20 mg bid) should not be used as prophylactic co-therapy for A.D. because they are not effective in reducing the risk of NSAID-related gastric ulcer. Although higher H_2RA doses (eg, famotidine 40 mg bid) reduce the risk of gastric ulcer, they are less effective than is a PPI. Famotidine should be discontinued, and a standard PPI prophylaxis dose should be instituted (eg, pantoprazole 40 mg daily). All PPIs, when used in standard doses, are effective for this indication, but A.D.'s out-of-pocket cost should be taken into consideration when selecting a PPI.

Cyclooxygenase-2 Inhibitors and Cardiovascular Toxicity

Case 23-2, Question 5: What is the concern regarding the use of COX-2 inhibitors and the risk of cardiovascular toxicity?

The risk of cardiovascular events in patients taking COX-2 inhibitors increases with a number of factors, including increased COX-2 selectivity, higher doses, a longer duration of treatment, and preexisting cardiovascular risk.[102,103,153–155] Although ulcers and related GI complications were less likely with rofecoxib than with naproxen in the vioxx gastrointestinal outcomes research study (VIGOR) trial, the number of myocardial infarctions and thrombotic strokes were increased with rofecoxib.[151] Similar cardiothrombotic events were observed in other rofecoxib studies of longer duration.[156] In 2004, rofecoxib was withdrawn from the U.S. market, and soon thereafter valdecoxib was withdrawn amid concerns about cardiovascular risk.[102]

The cardiovascular safety of celecoxib has been evaluated, but the risk of myocardial infarction and thrombotic stroke is less certain.[102,157] Although there was no difference in cardiovascular events when celecoxib was compared with diclofenac and ibuprofen in the celecoxib Long-term Arthritis Safety Study (CLASS) trial,[152] cardiovascular events were significantly higher in a clinical trial where patients were taking higher doses of celecoxib (400 mg twice daily).[158] Similarly, no difference in cardiovascular events was noted when comparing moderate celecoxib doses to below standard doses of ibuprofen and naproxen in treating arthritis, although a dose-dependent risk remains likely.[157] Emerging data has suggested that celecoxib actually has a safer cardiovascular profile than does ibuprofen, comparable to naproxen, while demonstrating less GI and renal toxicity than do both ibuprofen and naproxen; when coadministered with cardioprotective doses of aspirin, similar results were seen.[159] Celecoxib remains available in the United States, but the underlying cardiovascular risk of the patient must be assessed

when considering the use of this drug. The lowest effective celecoxib dose should always be used for the shortest duration of time.[153]

The risk of cardiovascular events is also increased in patients taking nonselective and partially selective NSAIDs, with the possible exception of naproxen.[102,103,160–162] Naproxen is usually the preferred NSAID, especially in patients with increased cardiovascular risk.[102,103,160–162] If possible, NSAIDs and COX-2 inhibitors should be avoided in patients at very high GI and cardiovascular risk.[102] Consideration should be given to using less risky therapeutic options including acetaminophen, tramadol, or narcotics.[163] Thus, the selection of a drug regimen to reduce the risk of NSAID ulcers and GI complications should not only be based on the GI safety of the NSAID or COX-2 inhibitor but must also be weighed against the cardiovascular risk of each patient.[102,103,162]

Stratification of Future Risk for Nonsteroidal Anti-inflammatory Drug–Induced Peptic Ulcers

Case 23-2, Question 6: How does a COX-2 inhibitor compare with a PPI and a nonselective or partially selective NSAID when used to decrease ulcer risk and related complications? Have any studies evaluated GI safety in patients taking a COX-2 inhibitor plus a PPI?

There have been very few randomized controlled trials in *H. pylori*–negative patients at high risk for NSAID-related complications that compared the combined therapy of celecoxib with a PPI versus a partially selective NSAID with a PPI or celecoxib alone.[102,164,165] Results from these trials suggest that in high-risk, *H. pylori*–negative patients, combined therapy with a COX-2 inhibitor and PPI may be more efficacious than is a partially selective NSAID plus a PPI or celecoxib monotherapy in reducing NSAID-related ulcer complications. Combining a COX-2 inhibitor with a PPI may be considered in very high-risk patients; however, long-term outcomes beyond 1 year are unclear based on available evidence.[102,164,165]

Case 23-2, Question 7: What factors should be considered when evaluating management strategies for patients at risk for experiencing an NSAID-induced ulcer? What risk reduction strategies are considered acceptable for A.D.?

Strategies to reduce the risk of NSAID ulcers and related complications depend on the assessment of upper GI (**Table 23-3**) and cardiovascular risks. Although there are no universally accepted definitions, the levels of risk can be arbitrarily stratified into low, moderate, and high GI risk and low or high cardiovascular risk.[102,103] High cardiovascular risk implies a physician-recommended requirement for low-dose aspirin to prevent serious cardiothrombotic events.[102] In general, individuals younger than age 65 years, and those taking NSAIDs in the short term who do not require low-dose aspirin, are considered to be at low GI and cardiovascular risk and usually do not require GI risk reduction therapy.[102,103]

Patients at moderate GI risk typically have one to two risk factors that include age older than 65 years, a history of a prior uncomplicated ulcer, treatment with high-dose NSAIDs, or the concurrent use of aspirin (including low-dose), corticosteroids, or anticoagulants. The recommended risk reduction strategy in this group is co-therapy with either a PPI or misoprostol, but misoprostol is usually considered a secondary option because of its GI adverse events and the need for more frequent daily dosing.[102,103] If the patient requires low-dose aspirin, naproxen is the NSAID of choice. Although celecoxib provides gastroprotective effects similar to that of a nonselective or partially selective NSAID plus a PPI or misoprostol, its use may be limited by cost, prescription-only availability, and concerns related to myocardial infarction and thrombotic events.[102]

Patients at very high GI risk include those with a prior history of an ulcer-related complication or multiple (more than two) risk factors (**Table 23-3**).[102,103] If cardiovascular risk is low, alternative therapies such as oxycodone are preferred, but a COX-2 inhibitor plus a PPI or misoprostol may be used.[102] Although it is best to avoid an NSAID if the patient had a complicated ulcer, some physicians will continue the same NSAID that provided the most effective anti-inflammatory

effect. This should be done with extreme caution and with maximally effective co-therapy. All COX inhibitors should be avoided in patients at high GI risk and high cardiovascular risk, and alternative therapy should be used.[102,103]

Patients such as A.D., who have a history of a recent ulcer and related upper GI bleed, are at high risk for future NSAID-related ulcers and complications and require an effective risk reduction strategy. In addition, A.D. has other factors that contribute to her high-risk status, including her age (70 years) and the continued use of a nonselective NSAID (naproxen). Famotidine should be discontinued immediately, and A.D. should be switched to an evidence-based risk reduction regimen. If celecoxib is used, the risk of cardiovascular effects must be weighed against the gastroprotective benefits, especially because A.D. has a history of hypertension. If A.D. had renal dysfunction (specifically creatinine clearance <30 mL/minute), NSAIDs and COX-2 inhibitors should be avoided, and the patient should be treated with other analgesics (eg, tramadol, narcotics), keeping in mind that NSAIDs and COX-2 inhibitors are associated with fluid retention, hypertension, and renal failure. Although switching naproxen to celecoxib plus a PPI or continuing the oxycodone may be preferred by some, the selection of the optimal strategy for a high-risk patient such as A.D. is debatable and should take into consideration the risks, benefits, patient preferences, continued analgesic relief, and cost of treatment. Co-therapy with a PPI or misoprostol is an acceptable risk reduction strategy given A.D.'s GI and cardiovascular risk. Combination therapy of celecoxib and PPI may represent the greatest GI risk reduction and may be considered in this patient.

Case 23-2, Question 8: What information should be conveyed to A.D. regarding the combined use of OTC aspirin and NSAIDs?

Remind A.D. that her physician has recommended that she discontinue taking the enteric-coated aspirin and that she should not restart it without his/her consent. Explain to A.D. that enteric-coated

aspirin may protect against the topical mucosal damage in the stomach and minimize dyspepsia, but the enteric coating does not prevent an ulcer. Even low-dose aspirin (eg, 81 mg/day) is capable of causing an ulcer, especially when used in conjunction with an NSAID (naproxen). Buffered aspirin may cause less dyspepsia, but buffering does not prevent ulcers. Taking food, milk, or an antacid with aspirin or NSAIDs may minimize dyspepsia, but does not prevent an ulcer. Inform A.D. that she should not take OTC NSAIDs in conjunction with her naproxen unless advised to do so by her physician, because combining NSAIDs will increase the risk of ulcers and GI bleeding. Advise A.D. that even though NSAIDs available for self-treatment may have different generic names (eg, ibuprofen, naproxen), they all belong to the same drug class and have similar side effects.

Case 23-2, Question 9: A.D.'s physician decides to maintain her on naproxen, but changes the famotidine to lansoprazole 30 mg daily. What instructions should you provide A.D. regarding her medications?

A.D. should be advised of the major signs and symptoms of upper GI bleeding and cardiovascular disease and what action should be taken if these signs or symptoms develop. She should be instructed to take the lansoprazole daily, 30 to 60 minutes before breakfast, and continue taking naproxen twice daily. The importance of adhering to PPI co-therapy must be stressed, especially because A.D. may not have accompanying dyspeptic or ulcer-like symptoms. There is a strong relationship between the level of adherence to gastroprotective medication and the risk of ulcers and serious GI complications in patients such as A.D. who are high-risk NSAID users.[166] Older patients, such as A.D., who are at risk for osteoporosis and hip fractures and who require long-term PPI therapy should be counseled to take age-related recommended doses of a calcium salt and vitamin D and have periodic bone density examinations (see section on Pharmacotherapy of Drugs Used to Treat Acid-Related Disorders).

CASE 23-2, QUESTION 10: What parameters should be monitored to determine A.D.'s response to treatment?

High-risk patients such as A.D. who continue to take an NSAID daily should be closely monitored for upper abdominal pain and signs or symptoms associated with bleeding, obstruction, or perforation. The presence of upper abdominal pain or a change in the severity of the pain may suggest an upper GI complication. Every effort should be made to monitor A.D.'s compliance with her PPI regimen because of the strong relationship between nonadherence and the risk of upper GI complications in high-risk NSAID users.

ZOLLINGER–ELLISON SYNDROME

ZES is an uncommon gastric acid hypersecretory disease characterized by severe recurrent peptic ulcers that result from a gastrin-producing tumor (gastrinoma).[141,167] The primary tumor is usually located in the duodenum or pancreas, but other locations (eg, mesenteric lymph nodes, spleen, stomach, liver) have been described.[141,167] Although most gastrinomas occur sporadically, ~25% occur in association with multiple endocrine neoplasia type 1 (MEN 1), which is an autosomal dominant inherited syndrome.[167] Most gastrinomas are malignant and tend to be slow growing, but a small number grow and metastasize rapidly to the regional lymph nodes, liver, and bone. Abdominal pain is the most predominant symptom, and is usually related to persistent peptic ulcers, which are less responsive to antisecretory therapy. Duodenal ulcers occur most often, but ulcers may also occur in the stomach or jejunum. Diarrhea, which is present in more than half of patients, may precede ulcer symptoms and results from massive gastric acid hypersecretion, which activates pepsinogen and contributes to mucosal damage.[141,167] Steatorrhea may also occur, and results from inactivation of pancreatic lipase by low duodenal pH resulting from

excessive acid load.[167] This leads to the precipitation of bile acids, which, in turn, reduces micelle formation necessary for fatty acid absorption. Vitamin B_{12} deficiency may develop secondary to malabsorption related to reduced intrinsic factor activity. GERD often occurs, and is complicated by esophageal ulcers and strictures. Other symptoms include nausea, vomiting, upper GI bleeding, and weight loss. Upper GI bleeding is related to duodenal ulceration and may be the presenting symptom.

Epidemiology

The incidence of ZES in the United States is 0.1% to 1.0% among patients with duodenal ulcers.[167] The majority of patients are diagnosed between the ages of 30 and 50 years, with males being slightly more affected than are females.[167] The morbidity and mortality of ZES have decreased because of improved medical and surgical management.

Pathophysiology

The pathophysiology of ZES is related to a non-β islet cell gastrin-secreting tumor that stimulates the parietal cells of the stomach to hypersecrete gastric acid.[141,167] Large amounts of gastrin are produced by the gastrinoma cells, usually resulting in a profound hypergastrinemia. The gastric parietal cell mass is expanded in response to the trophic effects of hypergastrinemia and causes an increase in basal and stimulated acid output. Hypersecretion of gastric acid results in severe mucosal ulceration, diarrhea, and malabsorption, and is responsible for the signs and symptoms associated with ZES.

Clinical Assessment and Diagnosis

The diagnosis of ZES is established when the fasting serum gastrin is >1000 pg/mL and the BAO is >15 mEq/hour in patients with an

intact stomach (or >5 mEq/hour in the postgastric surgery patient) or when hypergastrinemia is associated with a gastric pH value <2.[167] When serum gastrin is between 100 and 1000 pg/mL and gastric pH is <2, a provocative test (secretin or calcium) is recommended to assist in the diagnosis. Imaging techniques are performed to localize the tumor, and are useful in evaluating metastatic disease. Upper endoscopy is performed to confirm mucosal ulcerations. The use of PPIs may mask the clinical presentation and complicate the diagnosis.[141]

Treatment

The goal of treatment for ZES is to pharmacologically control gastric acid secretion and to surgically resect the tumor, if possible. Oral PPIs are the drugs of choice for controlling acid secretion because of their potent and prolonged antisecretory effect. Treatment should be initiated with omeprazole 60 mg/day or an equivalent oral dose of lansoprazole, pantoprazole, esomeprazole, or rabeprazole (see **Table 23-1**), and should be titrated to maintain a BAO <10 mEq/hour (1 hour before next dose) in patients with no complications or <5 mEq/hour in patients with complicated disease.[167] Once adequate control of acid secretion has been achieved, the daily PPI dose should be gradually reduced and administered every 8 to 12 hours. In most patients, an omeprazole dose of 60 to 80 mg/day reduces the BAO to target levels. IV PPIs should be reserved for those patients who are not able to take oral medications. H_2RAs are no longer used to treat ZES, despite proving efficacy at higher doses, because they are not as effective as PPIs (see **Table 23-1**).

Somatostatin analogs are used with varying success to treat gastrinomas, but they are only available parenterally and rarely used as first-line treatment.[167] Octreotide, a synthetic somatostatin analog, inhibits gastric acid secretion and decreases serum gastrin concentrations; however, its subcutaneous route of administration, frequent dosing, and side effect profile (abdominal pain, diarrhea, gallstones, and pain at the injection site) make it less desirable for

use in treating ZES. The long-acting depot formulation of octreotide can be administered less frequently, and may be useful in controlling temporal growth. Patients with metastatic gastrinomas can be treated with chemotherapeutic agents to inhibit tumor growth, or may require resection of the tumor. Localization and surgical removal of the gastrinoma should be considered in all patients unless widespread metastases exist.

GASTROESOPHAGEAL REFLUX DISEASE

GERD is a common acid-related GI disorder associated with a wide array of symptoms, the most frequent of which is heartburn and acid regurgitation. Gastroesophageal reflux (GER) is defined as the retrograde passage of gastric contents from the stomach into the esophagus. It is primarily the result of transient relaxation of the LES. When the LES is relaxed, the esophagus is exposed to small amounts of acidic stomach contents. This normal physiologic event occurs many times throughout the day in healthy individuals.[168–170] Protective mechanisms, such as esophageal peristalsis and bicarbonate-rich saliva, quickly return the acidic pH to normal. GERD develops when alterations in reflux result in symptoms, mucosal injury, or both.[62] Esophageal injury occurs with continued exposure of the mucosa to gastric acid and results in inflammation that can progress to ulceration (erosive esophagitis).[168,171] Complications associated with long-standing GERD include esophageal strictures, Barrett metaplasia (replacement of normal esophageal squamous epithelium by specialized intestinal-like columnar epithelium), and adenocarcinoma of the esophagus.[3] Male sex and advanced age (males and females) are associated with an increase in the prevalence of esophageal complications, presumably as a result of refluxed acidic contents damaging the mucosa over time.[168]

Epidemiology

GERD is a chronic disease that affects patients across all age groups, with equal distribution between males and females.[3] In Western populations, 25% of patients report heartburn monthly, 12% weekly, and 5% describe daily symptoms, whereas symptoms of regurgitation were reported in 16% of patients.[172] GERD is the second most common GI disease diagnosed in the outpatient setting.[1] It has been estimated that 7% of the U.S. population has complicated GERD associated with erosive esophagitis; however, this finding is difficult to validate because most patients do not undergo diagnostic esophageal endoscopy.[3] Many patients with erosive esophagitis are asymptomatic on diagnosis, which suggests that symptoms do not correlate with the degree of esophageal injury. Up to 75% of patients who undergo endoscopic procedures as a result of symptoms associated with GERD have normal esophageal findings.[173] These patients are identified as having functional heartburn, nonerosive reflux disease (NERD), or endoscopy-negative reflux disease (ENRD). Other patients with GERD have symptoms that occur outside the esophagus, which are considered atypical or extraesophageal manifestations of GERD. Extraesophageal manifestations may be present with or without accompanying typical symptoms (eg, heartburn) and have been estimated to occur in about 80% of patients with at least weekly symptoms of GERD (see section on Extraesophageal Manifestations).[174]

Childhood GERD appears to continue into adolescence and adulthood.[175] Although most infants exhibit physiologic regurgitation, or spitting up, the majority (95%) will have abatement of symptoms by 1 year of age.[176] Pregnancy has also been associated with an increased incidence of GERD, with an overall incidence of 30% to 50% depending on other risk factors and trimester. GERD can begin in any trimester, but is less likely to start in the third trimester (8% of patients).[62,177,178] The mechanisms for GERD in pregnancy are related to the hormonal effects of progesterone and estrogen, which lower LES pressure, and increase intra-abdominal pressure (see Chapter 49, Obstetric Drug Therapy, for a complete discussion

related to the management as well as the risks and benefits associated with treating GERD in the pregnant patient).[168,179]

Etiology and Risk Factors

The causes of GERD are associated with factors that increase the frequency or duration of GER leading to increased contact of the acidic refluxate with the esophageal mucosa. Risk factors associated with GERD include dietary and lifestyle factors, drugs, and certain medical and surgical conditions (**Table 23-7**).[3,169–171,180,181] These factors may precipitate or worsen GERD symptoms by lowering the LES pressure (eg, nitrates, progesterone, foods high in fat, mint, chocolate) or by having a direct irritating effect on the esophageal mucosa (eg, citrus, tomatoes, bisphosphonates). Stress reflux from increased intra-abdominal pressure has been associated with overeating, coughing, and bending or straining to lift heavy objects, as well as tight-fitting clothing.[168] Conditions such as gastroparesis, scleroderma, ZES, and long-term placement of nasogastric tubes may also be associated with GERD.[168]

Table 23-7
Risk Factors Associated With Gastroesophageal Reflux Disease

Drugs	Dietary
α-Adrenergic agonists	Foods high in fat
Anticholinergics	Spicy foods
Aspirin	Carminatives (peppermint, spearmint)
Barbiturates	Chocolate
Benzodiazepines	Caffeine (coffee, tea, colas)
β_2-Adrenergic agonists	Garlic or onions
Bisphosphonates	Citrus fruits and juices
Calcium channel blockers	Tomatoes and juice
Dopamine	Carbonated beverages
Estrogen	

Drugs	Dietary
Isoproterenol	**Lifestyle**
Iron	Cigarette/cigar smoke
Narcotics	Obesity
Nitrates	Supine body position
NSAIDs	Tight-fitting clothing
Progesterone	Heavy exercise
Potassium	
Prostaglandins	**Medical/Surgical Conditions**
Quinidine	Pregnancy
Tetracycline	Scleroderma
Theophylline	ZES
Tricyclic antidepressants	Gastroparesis
Zidovudine	Nasogastric tube intubation

NSAID, nonsteroidal anti-inflammatory drug; ZES, Zollinger–Ellison syndrome.

Sources: Roman S, Pandolfino JE, Kahrilas PJ. Gastroesophageal reflux disease. In: Yamada T, Podolsky, Daniel K, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:906–928; Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. *Lancet*. 2006;367(9528):2086–2100; Armstrong D, Sifrim D. New pharmacologic approaches in gastroesophageal reflux disease. *Gastroenterol Clin North Am*. 2010;39(3): 393–418; Storr M, Meining A. Pharmacologic management and treatment of gastroesophageal reflux disease. *Dis Esophagus.* 2004;17(3):197–204; Fock KM, Poh CH. Gastroesophageal reflux disease. *J Gastroenterol*. 2010;45(8):808–815; Benamouzig R, Airinei G. Diet and reflux. *J Clin Gastroenterol*. 2007;41:S64–S71.

Pathophysiology

The pathophysiology of GERD is associated with defects in transient relaxations of the LES, esophageal acid clearance and buffering capabilities, anatomic abnormalities, mucosal resistance, and exposure of the esophageal mucosa to aggressive factors (gastric acid, pepsin, and bile salts) leading to esophageal damage.[168]

TRANSIENT RELAXATIONS OF THE LOWER ESOPHAGEAL SPHINCTER

The LES, when in a resting state, remains at a high pressure (10–30 mm Hg) to prevent the gastric contents from entering into the esophagus.[168] Pressures are lowest during the day and with meals, and highest at night.[168] Transient relaxations of the LES are short periods of sphincter relaxation that are different from those that occur with swallowing or peristalsis.[3,182] They occur as a result of vagal stimulation in response to gastric distension from meals (most common), gas, stress, vomiting, or coughing, and can persist for >10 seconds.[3] These transient relaxations of the LES are associated with virtually all GER events in healthy individuals, but account for 50% to 80% of occurrences in patients with pathogenic GERD.[3] Thus, not all transient relaxations of the LES are associated with GERD.

A small percentage of patients may also have a continuously weak and hypotensive LES (decreased LES resting tone). Stress reflux increases intra-abdominal pressure and may blow open the hypotensive LES.[3] When LES pressures remain constantly low, the risk of serious complications (eg, erosive esophagitis) increases dramatically. Scleroderma, which is related to fibrosis of smooth muscle, may reduce LES tone and increase the potential for GERD.[168]

ESOPHAGEAL ACID CLEARANCE AND BUFFERING CAPABILITIES

Although the number of reflux events and quantity of refluxate are notable, it is the duration of time the mucosa is in contact with these noxious substances that determines esophageal damage and complications. More than 50% of patients diagnosed with severe esophagitis have decreased acid clearance from the esophagus.[168] Peristalsis is the primary mechanism by which acid refluxate is removed from the esophagus. Other mechanisms include swallowing, esophageal distension in response to refluxate, and gravity (which is only effective when the patient is in an upright position).

Saliva plays an important role in the neutralization of gastric acid within the esophagus. Its bicarbonate-rich content buffers the residual acid that remains in the esophagus after peristalsis.[168] However, saliva is only effective on small amounts of gastric acid because patients with larger volumes of acid refluxate may not have the neutralizing capacity in saliva necessary to protect the esophagus.[168] Swallowing increases the rate of saliva production and esophageal acid clearance. The reduction of swallowing that occurs during sleep is associated with nocturnal GERD. Patients with decreased saliva production (eg, elderly, patients taking medication with antimuscarinic effects, and those with certain medical conditions such as xerostomia or Sjögren syndrome) may also be at increased risk for experiencing GERD.[168]

ANATOMIC ABNORMALITIES

Hiatal hernia (protrusion of the upper portion of the stomach into the thoracic cavity because of weakening in the diaphragmatic muscles) is frequently described as a cause of GERD, but its causal relationship remains uncertain.[168] Although hiatal hernia is associated with a greater degree of esophagitis, strictures, and Barrett metaplasia, not all patients with hiatal hernia exhibit symptoms or complications. This may be related to the size of the hiatal hernia and its effect on LES pressure.[168] An increase in the size of the hernia may decrease its ability to remain below the diaphragm during swallowing, and, thus, reduces LES pressure. Hypotensive LES in combination with hiatal hernia increases the likelihood of reflux and complicated disease.[168]

MUCOSAL RESISTANCE

The capability of the esophageal mucosa to endure contact with and withstand injury from gastric refluxate (acid and pepsin) is a substantial determinate for the development of GERD. When considering the mucosal resistance within the esophagus compared with that of the stomach and duodenum, the esophagus is less resistant to damage from gastric acid.[168] However, mucosal

resistance in the esophagus is composed of many defensive factors working in tandem to prevent esophageal injury. An increase in mucosal cell thickness and intracellular junctional complexes prevents the diffusion of hydrogen ions from penetrating into the esophageal epithelium, leading to cell death.[168] The esophagus also secretes a protective mucous layer and bicarbonate.[168,183] Enhanced blood flow in response to an acidic environment within the esophagus improves tissue oxygenation, provides nutrients, and helps maintain a normal acid–base balance.[168] Esophageal injury also occurs when the concentration of acid and pepsin exceed the protection afforded by mucosal resistance mechanisms.

AGGRESSIVE FACTORS ASSOCIATED WITH ESOPHAGEAL DAMAGE

The gastric refluxate, which is composed primarily of gastric acid and pepsin, is the primary aggressive factor associated with GERD. The development and degree of mucosal damage is dependent on the pH and contents of the refluxate as well as the total exposure time of refluxate with the esophageal mucosa. A pH <4 is usually required to produce injury to the esophageal mucosa, but as the refluxate becomes more acidic, the mucosal damage is accelerated.[168] The duration of total exposure time of the esophagus to the refluxate is the primary mechanism involved in the development of GERD and its complications. The longer the duration of exposure time, the greater the possibility of severe disease, including progression to Barrett metaplasia. The addition of pepsin (which is converted from secreted pepsinogen in an acidic pH) to the acidic refluxate will markedly increase the propensity of the refluxate to compromise mucosal resistance, which increases the potential for esophageal bleeding.[168,184] Duodenogastric reflux or alkaline reflux containing bile acids and pancreatic juices may also contribute to esophagitis.[168] Because gastric and duodenogastric reflux are often concomitantly present, their actions may be additive in causing esophageal damage.

ERADICATION OF HELICOBACTER PYLORI

There is currently no data proving a causal relationship between *H. pylori* infection and GERD. In a community-based study from the United Kingdom, it was concluded that treatment for *H. pylori* infection was not associated with an increase in heartburn or other GERD symptoms.[95,184] Routine *H. pylori* testing in patients with GERD is not standard practice; if the patient is tested and found to be *H. pylori* positive, eradication is recommended (see section on Primary Treatment for *Helicobacter pylori*).[95]

Clinical Presentation

SIGNS AND SYMPTOMS

CASE 23-3

QUESTION 1: W.J. is a 39-year-old, 286.60-pound (130-kg), 66.93-inch (170-cm)-tall male who presents with indigestion. He describes a burning sensation behind his breastbone and some belching that is often associated with an acid taste in the back of his mouth. He indicates that his symptoms began a few months ago, and they only occur a few times a month, especially after eating large or spicy meals. Also, if he eats too close to bedtime, the burning keeps him up at night. He has used liquid antacids in the past for these symptoms and states they work fairly well, but he has to take frequent doses, because the symptoms return quickly. He does not take any other medications.

Which of W.J.'s symptoms are consistent with GERD?

Symptoms that are typically associated with GERD include heartburn, pyrosis (a retrosternal burning that occurs in the upper esophagus and travels up through the throat), regurgitation of gastric contents into the throat, or a combination of the three.[62,168] These symptoms may be episodic or meal related, and are often alleviated by antacids.[168] Heartburn, the most frequent typical symptom, is caused by the contact of acidic refluxate with nerve endings within the esophageal mucosa.[168] Other symptoms include water brash (salty or sour fluid occurring abruptly within the mouth), early satiety, belching, hiccups, nausea, and vomiting.[168] Worrisome symptoms

(alarm signs or symptoms) include dysphagia (trouble swallowing), odynophagia (painful swallowing), vomiting of blood, bloody or tarry stools, unexplained weight loss, and anemia.[62,168] These symptoms suggest complicated disease, such as erosive esophagitis, esophageal stricture, malignancy, or GI bleeding, and require immediate evaluation by a health care professional. Some patients, such as the elderly, may not have typical GERD symptoms, but present initially with alarm symptoms.[168,185] This is attributable in part to older patients having a reduced pain perception and a possible reduction in the acidity of the refluxate.[168] Other patients may present with only extraesophageal or atypical symptoms (see section on Treatment for the Extraesophageal Manifestations of Gastroesophageal Reflux Disease). Despite the lack of esophageal symptoms, the potential for serious esophageal damage exists, because there is no correlation between symptoms and the degree of esophageal injury.[168] W.J.'s symptoms of a burning sensation (heartburn), regurgitation soon after eating spicy or large meals, and the association of symptoms with eating a meal near his bedtime are all consistent with GERD. The fact that his symptoms are relieved by his use of antacids is also suggestive of GERD.

Treatment

THERAPEUTIC GOALS

Case 23-3, Question 2: What are the therapeutic goals for the treatment of W.J.'s GERD?

The therapeutic goals for the management of GERD are to alleviate symptoms, promote esophageal healing, prevent recurrence, provide cost-effective pharmacotherapy, and avoid long-term complications.[168] One long-term consequence is Barrett esophagus, or Barrett metaplasia, which is identified in 5% to 15% of patients with GERD upon endoscopic evaluation.[168,186,187] This premalignant condition may predispose the patient to esophageal

adenocarcinoma. Patients with Barrett esophagus have a risk of developing esophageal cancer that is 30 to 40 times higher than do patients without this disorder.[186]

NONPHARMACOLOGIC MEASURES AND SELF-DIRECTED TREATMENT

CASE 23-3, QUESTION 3: What lifestyle and dietary changes may potentially reduce W.J.'s GERD symptoms?

Lifestyle and dietary modifications comprise the initial step in managing patients with GERD (**Table 23-8**).[62,181,188,189] Strategies should be discussed with the patient and tailored to his or her specific needs. The paucity of evidence to date suggests that although many patients may benefit from these modifications, they are unlikely to completely alleviate symptoms in most patients.[62,189] Lifestyle modifications are aimed at reducing acid exposure within the esophagus by increasing LES pressure, decreasing intragastric pressure, improving esophageal acid clearance, and avoiding specific agents that irritate the esophageal mucosa. There is evidence to support several modifications that reduce esophageal gastric acid exposure and symptoms.[62,189] These include raising the head of the bed 6 to 8 inches, sleeping in a left lateral decubitus position, and weight loss, which also decreases intragastric pressure.[62,189]

Table 23-8
Dietary and Lifestyle Modifications Used to Manage Gastroesophageal Reflux Symptoms

Dietary	Medication	Lifestyle
Avoid foods listed in Table 23-7	Avoid medications with a potential to relax the lower esophageal sphincter or that have a direct irritant effect on the esophageal mucosa (Table 23-7)	Stop or decrease smoking/tobacco

Dietary	Medication	Lifestyle
Avoid eating large meals	Medications with the potential to irritate the esophagus should be taken with a full glass of water	Avoid alcohol
Avoid eating within 3 hours of bedtime		Lose weight[a]
		Elevate the head of bed 6–8 inches or use a foam wedge[a]
		Sleep in the left lateral decubitus position[a]

[a]Sufficient evidence exists to support lifestyle modification.

Sources: Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3): 308–328; Benamouzig R, Airinei G. Diet and reflux. *J Clin Gastroenterol*. 2007;41:S64–S71; Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med*. 2008;359(16):1700–1707; Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med*. 2006;166(9):965–971.

Patients with GERD symptoms should avoid foods and beverages known to trigger symptoms (see **Table 23-7**); however, the evidence suggesting benefit remains uncertain.[62,189] Individualized lifestyle and dietary modifications should be recommended to all patients with GERD symptoms. When appropriate, OTC or prescription medications should be recommended.[62]

W.J. has a body mass index (BMI) of 45, which is considered class 3 obesity. Because obesity is a large risk factor for Barrett esophagus, particularly an abnormal waist-to-hip ratio, he should be counseled to lose weight.[190] Further, he should be advised to wear loose-fitting clothing and avoid eating spicy meals that he knows will exacerbate his symptoms. He should also be advised to avoid eating

at least 3 hours before bedtime and consider raising the head of his bed 6 to 8 inches because these efforts may help decrease nocturnal symptoms.

CASE 23-3, QUESTION 4: Which OTC treatment options (if any) would you recommend for W.J.?

Many patients with mild, infrequent symptoms can be managed with OTC medications (**Fig. 23-5**).[168,191–193] First, a determination must be made as to the suitability of the patient for self-treatment. This determination is based on the absence of the following: alarm signs or symptoms, severe or frequent (2 or more days a week) heartburn lasting >3 months, presence of extraesophageal manifestations (see Case 23-5), or symptoms that persist despite appropriate drug therapy. If the patient does not meet the criteria for self-treatment, he or she should be referred for further medical evaluation.[168,192,193] OTC antacids and H_2RAs are the drugs of choice for patients with mild, infrequent heartburn; OTC PPIs should be reserved for patients who experience more frequent heartburn (see Table 23-1).[62]

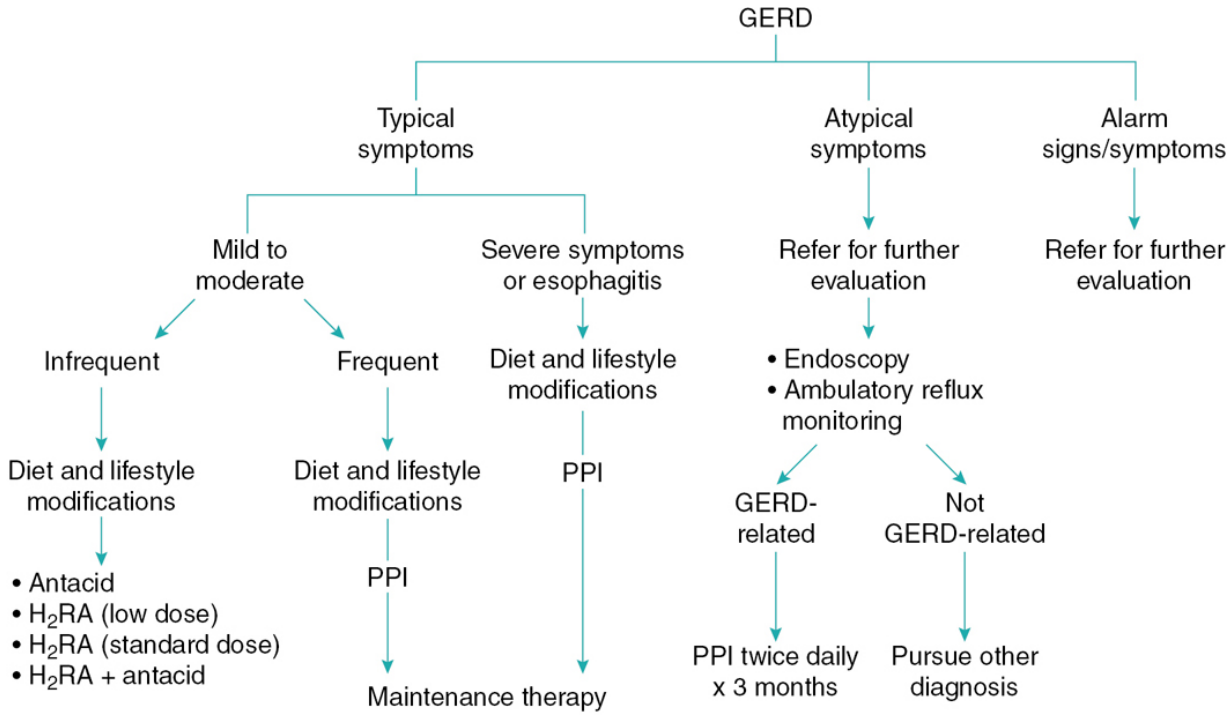


Figure 23-5 Management of GERD. GERD, gastroesophageal reflux disease; H_2RA, H_2 receptor antagonist; PPI, proton-pump inhibitor.

Antacids remain an effective option for treating mild, infrequent heartburn (occurring less than once weekly) because they rapidly (within minutes) relieve symptoms, although the duration of symptom relief only lasts about 30 minutes when taken on an empty stomach (see section on Antacids in Pharmacotherapy of this chapter).[62] They are available in tablet and liquid forms, and are usually interchangeable when used in recommended doses. Although doses can be repeated multiple times per day as needed, the maximum recommended daily dose should not be exceeded. Patients requiring frequent or regular antacid use for more than 2 weeks should be reevaluated because an H_2RA or a PPI may be needed.[62,192,193] About 20% of patients will achieve symptom relief with the use of antacids; however, they are not effective in healing erosive esophagitis, nor do they prevent GERD.[3,168]

The OTC H_2RAs are indicated for mild-to-moderate infrequent GERD symptoms.[192] When compared with antacids, their onset of

symptom relief is slower, but they have a longer duration of action (up to 10 hours).[168] One benefit of the H_2RAs is that they can be used prophylactically for postprandial GERD symptoms.[168] They also have a beneficial effect on reducing nocturnal acid secretion. Tachyphylaxis (tolerance) has been reported with continued use of H_2RAs within 2 to 6 weeks of initiation, although this effect can be overcome with intermittent or as-needed use.[194] The four H_2RAs (cimetidine, famotidine, ranitidine, nizatidine) are interchangeable when used in recommended doses (see Table 23-1). When used for self-treatment, the H_2RA dose should not exceed two doses per day, and the treatment duration should not exceed 2 weeks. Use beyond 2 weeks should be under the care of a health care provider.[168]

OTC PPIs are potent inhibitors of gastric acid, and are indicated for use in patients with frequent heartburn (≥2 days a week) or in patients who have failed twice-daily H_2RA therapy.[62] The onset of symptom relief is slower (2–3 hours) than it is with H_2RAs, and complete relief may not be realized until up to days after therapy initiation. PPIs are superior to H_2RAs with regard to symptom relief and duration of acid suppression. Patients should take the OTC PPIs 30 to 60 minutes before a meal (breakfast is preferable) and not take more than one dose daily for up to 2 weeks. Another course of therapy should not be taken more than every 4 months unless directed by a health care provider, because this may indicate more serious disease.[168,192,193]

W.J. is an appropriate candidate for self-treatment because his symptoms are mild, occur infrequently, and are not classified as alarm symptoms. Although antacids are an acceptable option for W.J., he has tried these and is unhappy with the frequency of dosing needed to relieve his heartburn. Because W.J. has requested a medication to specifically “prevent” meal-related symptoms, he should take an OTC H_2RA 30 to 60 minutes before eating or drinking. If symptoms remain infrequent and unrelated to meals, as-needed use of an OTC H_2RA is reasonable. He can increase the dose to twice daily if symptom relief is not optimal, and may consider

an OTC PPI if symptoms occur >2 days a week. If he continues to have symptoms beyond 2 weeks, they become more severe, or they are accompanied by alarm symptoms, he should be referred for further evaluation.

SEVERE DISEASE WITH COMPLICATIONS

CASE 23-4

QUESTION 1: L.F. is a 48-year-old female who presents to her primary care provider reporting recurrent heartburn occurring daily for the past 6 weeks. She states that the heartburn occurs frequently after meals and often wakens her at night. Lately, she has been experiencing difficulty swallowing solid foods. L.F. currently smokes two packs of cigarettes per day and likes to have two glasses of wine each night with her dinner. She states that she occasionally uses OTC ranitidine 150 mg orally up to twice daily, which temporarily relieves her symptoms.

What diagnostic modalities are available for the evaluation of her GERD?

Clinical Assessment and Diagnosis

Numerous diagnostic options exist for the evaluation of the patient with presumed GERD. The medical history should include the identification of specific symptoms and an assessment of symptom frequency, severity, and duration as well as risk factors or triggers. An empiric diagnosis can be made in the majority of patients based on the symptoms of heartburn and regurgitation. However, patients who present with severe symptoms, alarm symptoms, or long-standing GERD or who do not respond to empiric therapy warrant further diagnostic evaluation.

ACID SUPPRESSION EMPIRIC TEST

A trial of a PPI is commonly used to empirically diagnose typical GERD-like symptoms in patients without alarm symptoms or symptoms of complicated disease. Doses used in clinical trials range from 20 to 80 mg of omeprazole (or equivalent) once daily for up to 4 weeks.[168,195] If symptoms are relieved after a short trial of a PPI (7–

14 days), an empiric diagnosis of GERD may be made and other invasive and costly diagnostic methods may be avoided.[168,169,191,195,196] However, this methodology is not without its limitations. The test cannot differentiate between other acid-related disorders, such as PUD, and studies evaluating its ability to detect GERD versus other diagnostic options have been equivocal.[168,195,196]

UPPER ENDOSCOPY AND BIOPSY

Upper endoscopy, although not required to make a GERD diagnosis, is the primary diagnostic method for evaluating the esophageal mucosa for injury or cellular changes. It is usually recommended in the presence of alarm symptoms or in patients suspected to be at high risk for developing Barrett esophagus.[62] There are four primary reasons why endoscopy is performed in patients suspected of having GERD[168]: (a) to rule out significant disease (eg, adenocarcinoma of the esophagus) or complications (eg, stricture); (b) to screen for Barrett metaplasia; (c) to evaluate and grade the severity of esophagitis; and (d) to allow the provider to optimize treatment and predict the long-term course of the disease. Endoscopic grading of the esophagus is based on the level of inflammation and mucosal damage; two classification systems are used for the grading of esophagitis (**Table 23-9**).[197]

Table 23-9
Classification Systems for Endoscopically Determined Esophagitis

The Savary–Miller Classification System of Esophagitis	
Grade 0	Normal esophageal mucosa
Grade 1	Erythema or diffusely red mucosa, edema causing accentuated folds
Grade 2	Isolated round or linear erosions extending from the gastroesophageal junction upward, not involving entire circumference
Grade 3	Confluent erosions extending around entire circumference or superficial ulceration without erosions
Grade 4	Complicated cases; erosions as in grade 3 plus deep ulcerations, strictures, or columnar epithelium-lined esophagus

The Savary–Miller Classification System of Esophagitis	
Grade 5	Presence of Barrett metaplasia
The Los Angeles Classification System of Esophagitis	
Grade A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break >5 mm long that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but that involves <75% of the circumference
Grade D	One (or more) mucosal break that involves at least 75% of the esophageal circumference

Reproduced from Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut*. 1999;45(2):172–180; with permission from BMJ Publishing Group Ltd.

Biopsy of the esophageal mucosa is performed during endoscopy, and tissue samples are evaluated by microscopy for evidence of Barrett metaplasia or neoplastic disease. In patients with suspected Barrett metaplasia, the biopsy is obtained after the esophagus has healed to prevent misinterpretation of the inflammatory markers for dysplastic syndrome. Mucosal biopsy for inflammatory markers in nonerosive disease remains debatable.

AMBULATORY ESOPHAGEAL REFLUX MONITORING

Ambulatory pH monitoring is indicated before endoscopic or surgical interventions in patients with NERD, in patients where a diagnosis of GERD is not clear, or in patients with persistent symptoms who have trialed twice-daily PPI therapy.[62,198] A small (2–3 mm diameter) pH electrode is threaded through the patient's nostril (similar to placing a nasogastric tube), past the patient's larynx, to ~5 cm above the LES in the distal esophagus.[168] Once it is connected to a logging device, which documents pH measurements every few seconds, it allows for the determination of reflux events (defined as esophageal pH <4), duration of reflux events, and percentage of time within a 24-hour

period that the patient's pH is <4. The patient is asked to keep a diary to record symptomatic events that can be correlated with a decrease in esophageal pH. This is especially important when correlating extraesophageal manifestations with reflux events.

RADIOLOGIC TESTING

Barium radiography is no longer recommended for GERD diagnosis.[62]

ESOPHAGEAL MANOMETRY

Esophageal manometry is used to evaluate the patient's LES pressure and esophageal peristalsis.[3] This procedure does not have a specific role in the diagnosis of GERD, because it does not detect the presence of acid within the esophagus. It is used primarily to evaluate patients before 24-hour continuous ambulatory pH monitoring and antireflux surgical procedures (eg, Nissen fundoplication) to determine the location of the LES.[3,199]

Case 23-4, Question 2: L.F.'s frequent severe symptoms continue despite OTC ranitidine 150 mg orally twice daily, and the presence of warning signs warranted that she undergo endoscopy, which revealed moderate esophagitis (Los Angeles grade C), the presence of an esophageal stricture, and no evidence of Barrett metaplasia. Esophageal dilation was performed during the procedure to widen the lumen of the esophagus. What treatment options exist for L.F.?

Pharmacotherapy

ANTACIDS

Antacids are useful only in the relief of mild symptoms associated with GERD (see section on Nonpharmacologic Measures and Self-Directed Treatment). Because of their short duration of action and inability to heal erosive esophagitis, they are not an option for treating moderate-to-severe GERD.[62,168]

HISTAMINE-2 Receptor Antagonists

H_2RAs are effective in treating patients with mild-to-moderate GERD, but response rates vary with the severity of disease, the dose of the drug, and the duration of therapy. H_2RAs are considered equally effective when used in equipotent doses for symptomatic relief and esophageal healing (**Table 23-1**). They are effective in reducing nocturnal symptoms, but only modestly effective in relieving meal-related symptoms because they only block one mechanism of parietal cell activation (the H_2 receptor).[168] H_2RAs relieve symptoms in about 50% to 60% of patients treated after 12 weeks of continuous therapy.[200] Increasing the H_2RA dose may not improve symptoms, but may lead to tachyphylaxis (tolerance). Esophageal healing requires higher doses (eg, famotidine 40 mg bid) compared with those used for symptom relief (**Table 23-1**). Esophageal healing rates with H_2RAs are reported to be about 50% after 8 to 12 weeks of treatment, but rates will vary depending on the degree of esophagitis.[200] For example, endoscopic healing rates in trials with high-dose H_2RAs were ~60% to 90% in patients with grades 1 and 2 esophagitis, but were only 30% to 50% in patients with more severe disease (grades 3 and 4 esophagitis).[168,200]

PROTON-PUMP INHIBITORS

PPIs are the drugs of choice for patients with frequent, moderate- to-severe GERD symptoms and esophagitis because they provide more rapid relief of symptoms and esophageal healing than do H_2RAs. When used in recommended doses, all of the PPIs provide similar rates of symptom relief and esophageal healing (see **Table 23-1**). Their superior efficacy when compared with H_2RAs is related to their ability to maintain an intragastric pH <4 for a longer duration time (up to 24 hours/day vs up to 10 hours with an H_2RA).[201] Typically, PPIs are taken once daily 30 to 60 minutes before breakfast, but if a second dose is required, it should be taken before the evening meal.

A large meta-analysis of 16 trials confirms that PPIs are superior to H_2RAs for achieving rapid and complete relief of GERD symptoms. Complete symptom relief (within 4–12 weeks) was achieved in 77.4% of patients taking a PPI versus 47.6% of those taking an H_2RA ($P < .0001$).[200] PPIs have also been shown to heal esophagitis more quickly and effectively than do H_2RAs. In the same meta-analysis, which evaluated 43 double-blinded or single-blinded, randomized studies (including patients with severe esophagitis), PPIs (83.6%) were more effective than were H_2RAs (51.9%) at healing erosive esophagitis at 12 weeks.[200] Healing also occurred more quickly with PPI therapy in that by the second week, 63.4% of patients had healed with the PPI, whereas it took 12 weeks with the H_2RAs for 60.2% of patients to heal.[200] Another large meta-analysis, which evaluated >33 randomized trials, demonstrated similar results, with 81.7% of patients healed at 8 weeks with a PPI versus 52.0% with an H_2RA.[31]

Esophageal healing among PPIs appears to be equivalent because about 85% to 90% of patients achieved complete healing at 8 weeks in numerous head-to-head trials with equivalent doses.[26–29] One meta-analysis, which compared esophageal healing rates among omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and rabeprazole 20 mg (each given once daily), reported no statistically significant difference.[25] However, all of the PPIs were superior to ranitidine 300 to 600 mg/day. Esomeprazole 40 mg once daily has been reported to be superior to omeprazole 20 mg once daily, at both 4 and 8 weeks, when used to heal erosive esophagitis.[202] However, the esomeprazole 40 mg and omeprazole 20 mg doses are not equipotent, and this study has been heavily criticized based on this fact. Another study, which compared equipotent doses of esomeprazole (40 mg) and lansoprazole (30 mg), also suggests that esomeprazole has statistically significant greater healing rates (92.6% vs 88.8%, respectively, $P = .0001$).[28] In contrast, a similar study comparing lansoprazole 30 mg with esomeprazole 40 mg showed no statistical difference in esophageal healing, albeit with a smaller population.[29] Dexlansoprazole modified

release (MR) 60 mg once daily has been compared with lansoprazole 30 mg once daily in randomized, double-blind clinical trials to assess healing of erosive esophagitis.[203] The results using life-table analysis reveal similar healing rates with dexlansoprazole MR 60 mg and lansoprazole 30 mg (92%–93% vs 86%–92%, respectively), but the results were not statistically significant.[203] A higher dose of dexlansoprazole MR (90 mg daily) was superior to lansoprazole (30 mg daily) in patients with more severe disease, but these are not equipotent doses. In spite of the lack of supportive evidence, some clinicians prefer to use esomeprazole 40 mg/day or dexlansoprazole MR 60 mg/day for patients with severe erosive esophagitis.

The ability of a high-dose PPI to reverse Barrett metaplasia remains controversial.[168,204] Although studies have demonstrated islands of normal squamous epithelium returning, no data have determined that this is associated with a risk reduction in adenocarcinoma.[168,204] In fact, others have suggested that this return of normal mucosa may actually mask carcinogenic changes occurring deeper in the gastric mucosa.[205]

PROKINETIC AGENTS

Metoclopramide in addition to PPI therapy may be effective in the management of GERD by increasing LES pressure and stimulating the motility of the upper GI tract without altering gastric acid secretion.[168] Combination therapy of metoclopramide and an H_2RA was not shown to be effective.[206] Although prokinetic agents combined with a PPI may provide symptomatic relief, there is no clear role in the absence of gastroparesis, and they are associated with numerous side effects (eg, sedation, anxiety, extrapyramidal symptoms, etc.).[62,168]

PPIs are considered the drugs of choice for patients with frequent or severe GERD symptoms, or who have complicated disease, because of their potent inhibition of gastric acid secretion (**Fig. 23-5**).[62,169,191–193] In this case, L.F. presents with severe esophagitis and will require a once-daily PPI to relieve her symptoms and heal the

esophagus (Table 23-1). A reasonable option for L.F. would be lansoprazole 30 mg daily to be taken 30 to 60 minutes before breakfast each morning for the next 8 weeks; however, if the cost of therapy is an issue, generic omeprazole 40 mg daily would also be an acceptable alternative. L.F. should also be counseled regarding lifestyle and dietary modifications, including smoking cessation and abstinence from alcohol. She should avoid eating large meals before bedtime and may wish to elevate the head of her bed by 6 to 8 inches.

Maintenance Therapy

Case 23-4, Question 3: L.F.'s symptoms resolved in about 2 weeks after starting PPI therapy, and she remained asymptomatic after 8 weeks. She then underwent endoscopy again, which revealed that the esophagus had healed completely. Her primary care physician then stopped the PPI. Now, 2 weeks later, she is experiencing mild heartburn. Is L.F. a candidate for long-term maintenance therapy?

GERD is a chronic disease. Up to 80% of patients with severe esophagitis and 15% to 30% with less severe disease have a symptomatic relapse within 6 months of discontinuing treatment.[168] The goal of maintenance therapy is to keep the patient symptom free and prevent potentially life-threatening complications. Continuous maintenance therapy with a daily PPI is more effective than is an H_2RA, with reported relapse rates of 25% and 50%, respectively.[168] Thus, PPIs are the drugs of choice for maintaining remission in patients with healed esophagitis. An H_2RA may be considered for patients with mild nonerosive disease. Although half of the PPI dose used for esophageal healing has been suggested, guidelines indicate that the recommended maintenance dose should be the dose that is required to render the patient asymptomatic.[62,192] Maintenance therapy, to reduce the risk of morbidity associated with chronic, relapsing disease, should be initiated with lansoprazole 15 to 30 mg once daily or an equivalent PPI dose given the severity of

L.F.'s esophagitis and symptomatic recurrence after discontinuing the PPI.

On-Demand Pharmacotherapy

The use of intermittent (on-demand) courses of PPI therapy (2–4 weeks) has been suggested as being potentially beneficial in patients with GERD.[207–212] One trial, which compared continuous maintenance therapy with esomeprazole 20 mg daily versus on-demand therapy with the same drug and dose in patients with healed erosive esophagitis, reported that continuous therapy was superior to on-demand therapy (81% vs 58%, respectively) in maintaining endoscopic remission at 6 months.[212] The ability to maintain remission with on-demand therapy was reduced as the severity in esophagitis increased. Although numerous studies with a variety of PPIs have demonstrated patient satisfaction with on-demand therapy, a systemic review of 17 trials evaluating the use of on-demand therapy indicates that intermittent therapy should only be considered in patients with mild, nonerosive disease.[207–211]

Combination of a Proton-Pump Inhibitor and Histamine-2 Receptor Antagonists

The addition of an H_2RA at bedtime to a once- or twice-daily PPI regimen is sometimes used for patients who continue to have nocturnal symptoms, although the evidence to support this combination remains inconclusive and current guidelines do not endorse this type of antisecretory management strategy at this time.[62] The rationale for this practice is based on evidence that suggests a period of nocturnal acid breakthrough (defined as intragastric pH <4 for >1 hour during the night) in a significant number of patients despite twice-daily PPI therapy, suggesting that histamine release may have an important function in nocturnal acid secretion.[213] One study suggests that the addition of an H_2RA to a twice-daily PPI regimen resulted in a statistically significant reduction

in nocturnal acid breakthrough during the sleeping hours.[213] This trial, however, evaluated only a single bedtime dose of an H_2RA and did not consider the tachyphylaxis that can occur with continuous use. A subsequent trial using a twice-daily PPI regimen with continuous use of an H_2RA for 4 weeks demonstrated no difference in nocturnal acid suppression, suggesting that tolerance does play an important role in the use of H_2RAs for this indication.[14] It has been theorized that one way to possibly avoid this occurrence is to use the H_2RA on only an as-needed basis when lifestyle and dietary modifications are not effective for preventing nocturnal symptoms.[168]

Nonerosive Reflux Disease

Up to 75% patients with typical GERD symptoms who undergo endoscopy will not have evidence of esophagitis or complicated disease.[173] These patients are described as having functional heartburn, NERD, or ENRD, and often undergo 24-hour ambulatory pH monitoring to determine whether abnormal reflux is present despite a negative endoscopy finding. A trial of a PPI is usually indicated, despite no esophageal findings, because many patients will respond to this therapy.[173] Further medical evaluation is required if a patient does not respond to PPI therapy despite a doubling of the daily dose.

Extraesophageal Manifestations

CASE 23-5

Question 1: S.P. is a 71-year-old retired male who was eating dinner with his wife when he experienced a sudden onset of chest pain described as crushing, burning, and squeezing. His wife notified emergency personnel, who transported S.P. to the emergency department. His past medical history reveals some cardiovascular risk factors, including age, hypertension, hyperlipidemia, and a sedentary lifestyle. His medications before admission include aspirin 81 mg daily, hydrochlorothiazide 25 mg daily, and atorvastatin 40 mg at bedtime. He also takes OTC famotidine 20 mg daily as needed for dyspepsia. On

examination, he reports substernal crushing chest pain that has lasted >1 hour. He is diaphoretic and extremely anxious. He denies any shortness of breath, pain radiating to the upper extremities or jaw, or cough. His vital signs include a temperature of 99.1 °F (37.28 °C), blood pressure of 155/95 mm Hg, and heart rate of 115 beats/minute. Pertinent laboratory results at this time are as follows:

White blood cell (WBC) count, 7700/μL
Hgb, 14.2 g/dL
Hct, 45%
Platelets, 270,000/μL
SCr, 1.1 mg/dL
BUN, 11 mg/dL
Total cholesterol, 161 mg/dL
Low-density lipoprotein, 93 mg/dL
High-density lipoprotein, 30 mg/dL
Triglycerides, 190 mg/dL
Sodium, 141 mEq/L
Potassium, 4.1 mEq/L
Troponin I, 0.3 ng/mL

Electrocardiogram reveals sinus tachycardia with no evidence of ST-segment elevation, depression, or T-wave inversion or new left bundle branch block. Because of S.P.'s cardiovascular risk factors and indeterminate troponin, he underwent immediate diagnostic cardiac catheterization, which showed normal coronary angiography and an ejection fraction of 65%. S.P. was diagnosed with noncardiac chest pain (NCCP).

Could S.P.'s chest pain be associated with an extraesophageal manifestation of GERD?

Extraesophageal (atypical) manifestations of GERD are those signs and symptoms that occur outside of the esophagus, yet are presumed to be associated with GERD. The extraesophageal manifestations of GERD include NCCP; pulmonary symptoms; problems related to the ear, nose, and throat; as well as hypersalivation and dental erosions (**Table 23-10**). Interestingly, these symptoms are often the only problem that a patient has when he or she presents to the health care provider.[168,214]

Table 23-10
Atypical Manifestations of Gastroesophageal Reflux Disease

Noncardiac Chest Pain	Pulmonary

Noncardiac Chest Pain	Pulmonary
Ear, Nose, and Throat	Chronic cough
Laryngitis/pharyngitis	Nonallergic, nonseasonal asthma
Hoarseness	Aspiration
Globus sensation	Bronchiectasis/bronchitis
Laryngeal cancer	Sleep apnea
Sinusitis	Idiopathic pulmonary fibrosis
Otitis	Pneumonia
Other	
Hypersalivation	
Dental erosions	

Sources: Roman S, Pandolfino JE, Kahrilas PJ. Gastroesophageal reflux disease. In: Yamada T, Podolsky, Daniel K, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:906–928; Richter JE. Review article: extraoesophageal manifestations of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2005;22(suppl 1):70–80.

NONCARDIAC CHEST PAIN

About 30% of patients with angina-like chest pain have normal coronary arteries or minimal microvascular disease, as demonstrated by cardiac angiography.[215] Up to 60% of these patients will have concomitant GERD, as demonstrated by an abnormal esophageal endoscopy or ambulatory pH monitoring.[168,215] The symptoms associated with NCCP are very similar to those associated with cardiac angina. The chest pain is usually described as crushing, squeezing, or burning, retrosternal in location, and with or without lateral radiation to the upper extremities, back, neck, or jaw. The pain is often temporarily related to a meal or occurs nocturnally, usually awakening the patient and continuing for hours. An appropriate workup for coronary artery disease must be performed in all patients presenting with chest pain before considering a GI cause or trial of antireflux therapy.[62,215] This is especially important in females, the elderly, and patients with diabetes because their initial presentation may be similar to that of

GI symptoms when, in fact, an acute coronary syndrome is present. In patients with NCCP presenting with GERD symptoms, it is recommended to do diagnostic evaluation with endoscopy and ambulatory pH monitoring before an empiric PPI trial because data suggest no difference in this patient population in response to PPI versus placebo.[62,216]

ASTHMA AND GASTROESOPHAGEAL REFLUX DISEASE

Respiratory symptoms commonly associated with asthma such as cough, dyspnea, wheezing, and chest tightness are also seen in patients with GERD.[217] Reflux symptoms are common among patients with asthma, with reports ranging from 30% to 90%. One pathogenic theory is the vagal reflex theory, which proposes that symptoms result from the direct irritation of the vagus nerve when refluxate comes into contact with the esophageal mucosa, resulting in reflex bronchospasm.[218,219] In contrast, the microaspiration or reflux theory proposes that aspiration of refluxed acid into the lungs causes caustic injury of tissue within the bronchial tree, resulting in asthmatic symptoms.[219,220]

Although epidemiologic studies have suggested an association between GERD and asthma, a causal relationship remains to be established.[221] Significant controversy exists regarding the benefit of antireflux pharmacotherapy in patients with asthma, especially in those patients who do not endorse typical GERD symptoms. An important meta-analysis of trials that evaluated the effects of antireflux therapy on patients with asthma indicates that asthma symptoms improved in 69% of patients, that the use of asthma medications was reduced by 62%, and that only 26% of the subjects showed improvement in evening peak expiratory flow rate; all other pulmonary function tests showed little or no change with antireflux therapy.[222,223] However, this meta-analysis only evaluated studies of up to 8 weeks in duration. A large randomized, double-blind trial evaluated esomeprazole 40 mg twice daily versus placebo for 6 months in patients with poorly controlled asthma who were managed with inhaled corticosteroids and who lacked typical GERD

symptoms; results revealed no benefit in asthma control with the addition of a PPI, despite 40% of subjects demonstrating GERD by ambulatory reflux monitoring.[224] The American Gastroenterological Association guidelines accepts the use of an empiric trial of twice-daily PPI for patients with asthma and with typical GERD symptoms, but that reflux monitoring should be considered before PPI trial in patients with asthma and atypical GERD symptoms.[62]

OTOLARYNGOLOGY SYMPTOMS AND GASTROESOPHAGEAL REFLUX DISEASE

GERD is the most common etiologic factor in 60% of patients with chronic laryngitis and in 25% to 50% of patients with a globus sensation (the feeling that something is caught in the throat).[225] Symptoms relating to GERD are responsible for up to 10% of the patients seen by otolaryngologists.[225] The most likely mechanism for the pathophysiology of GERD-related laryngitis is that damage and inflammation occur at night while the patient is sleeping. It is during this time when upper esophageal sphincter pressures are especially low and the protective or neutralizing mechanisms of cough and salivation are suppressed.[226] This damage may be in addition to injury or laryngeal inflammation sustained from other causes, such as excessive voice usage, smoking, chronic throat clearing or cough, vomiting, or injury from endotracheal tubes.[214,227] The extent of injury in GERD-related hoarseness is directly related to the exposure time of the pharyngeal mucosa to the refluxate as well as the pH. Patients with GERD- related hoarseness usually do not have any other GERD-related symptoms.[214] The diagnostic procedure of choice is laryngoscopy, and should be considered in all patients presenting with GERD-related hoarseness. Once the diagnosis of GERD-related hoarseness or laryngitis is established, the patient will likely require extended high-dose PPI therapy, with the understanding that the majority of patients will relapse within 6 weeks once therapy is discontinued.[228]

TREATMENT FOR THE EXTRAESOPHAGEAL MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX DISEASE

Experts suggest that treatment should be initiated with a high-dose (twice-daily) PPI, but if there is no response in 2 to 3 months, then the patients should be evaluated and managed as having refractory GERD.[62]

S.P.'s chest pain is not of cardiac origin based on angiographic findings. Therefore, it is reasonable to presume that he is having an extraesophageal manifestation of GERD. S.P.'s symptoms were meal related, and he has a history of dyspepsia for which he takes an OTC H_2RA. The H_2RA should be discontinued, and S.P. should be given a trial of empiric twice-daily PPI therapy for a period of 2 to 4 weeks. If symptoms are severe, the use of endoscopy (to determine whether esophageal damage is present) or 24-hour esophageal pH monitoring (to correlate reflux events with symptomatic chest pain) is appropriate.

Antireflux Surgery

Case 23-5, Question 2: S.P. responded well to the trial of omeprazole 40 mg orally twice daily and has not had chest pain in 2 months. He has heard that surgical options that may eliminate his need for medications exist, because they are very expensive for him. Is S.P. a candidate for antireflux surgery?

Numerous surgical and endoscopic procedures exist for patients with GERD, but they vary by efficacy, adverse effects, and long-term durability. Examples include laparoscopic Nissen fundoplication, laparoscopic Hill gastropexy, transoral incisionless fundoplication, and magnetic sphincter augmentation. Obese patients being evaluated for GERD surgical intervention should be considered for bariatric surgery.[3] The primary goal of these procedures is to restore LES pressure by repairing a hiatal hernia or diaphragmatic hiatus. Appropriate candidates include patients who are in good health and request another treatment option as a result of poor medication adherence, patients who are unable to afford their medication,

patients who suffer from side effects or worry about risks with long-term therapy, patients with extraesophageal symptoms who have responded well to antireflux therapy, or patients experiencing volume regurgitation and aspiration of gastric contents who have not responded to PPI therapy.[62,163,168,199] Despite the availability of these surgical options, the consideration of antireflux surgery is one in which the benefits should be heavily weighed against the risks of such an invasive approach because these procedures are not without potential complications. The effectiveness of these procedures has been questioned, because many patients will still require drug therapy.[62,168] S.P. has responded well to high-dose PPI therapy for his NCCP, but he describes some financial difficulties with affording his medications. In addition, he is 64 years old, which may increase the risk associated with surgery. S.P. should be referred for further medical evaluation to determine whether he is a candidate for antireflux surgery.

UPPER GASTROINTESTINAL BLEEDING

Upper GI bleeding is a common medical emergency that occurs in up to 160 cases per 100,000 adults annually, and is associated with increased morbidity and mortality as well as substantial costs to the health care system.[229,230] Despite advances in endoscopic hemostatic therapy and pharmacotherapy, the mortality rate associated with upper GI bleeding remains at 5% to 15%, which is the same as it has been for the past 20 to 40 years.[229–232] Upper GI bleeding can be categorized as either variceal or nonvariceal bleeding. Variceal bleeding is caused by esophageal or gastric varices, and is discussed in a separate chapter (see Chapter 25, Complications of End-Stage Liver Disease). Nonvariceal bleeding most commonly describes bleeding associated with peptic ulcers (including stress ulcers), mucosal erosions (esophagitis, gastritis, duodenitis), or Mallory–Weiss tears (a tear near the gastroesophageal junction associated with retching or coughing);

other causes include malignancy and malformation.[114] The term *stress ulcer* offers a simplified nomenclature for the more apt description of stress-related mucosal bleeding (SRMB); although peptic ulcer bleeding and SRMB generally stem from acid-related disorders, their pathophysiology, presentation, risk assessment, and clinical management differ.[233–235]

Peptic Ulcer Bleeding

EPIDEMIOLOGY

The majority of upper, nonvariceal GI bleeding is caused by PUD.[114,229,230,232] Bleeding ulcers account for >400,000 hospitalizations in the United States each year.[230] As mentioned, the mortality rate for peptic ulcer bleeding can be as high as 15%. It has been suggested that an older presenting patient population (>60 years of age) with a greater number of comorbidities may account for this continued high mortality rate.[229–231] Fortunately, the vast majority (80%) of upper GI bleeding events are self-limited and require only minimal intervention.[231] National data derived from a U.S. database demonstrate a decreasing mortality rate (3.54%) in elderly patients with complications during 2001 to 2009.[236] Length of stay has been dramatically reduced in the majority of patients who receive early endoscopy (within 24 hours of admission).[229,230] However, in the 20% to 25% of patients who continue to bleed or rebleed after appropriate intervention, mortality increases to nearly 40%.[114,237]

PATHOPHYSIOLOGY

The most common causes of upper GI bleeding in patients with PUD are NSAID use and *H. pylori* infection.[93] Bleeding occurs when an ulcer extends deeper into the mucosa and erodes the wall of a blood vessel.[238] The incidence of *H. pylori* infection in bleeding ulcers is 15% to 20% lower than in patients with nonbleeding ulcers.[238] Bleeding associated with PUD is generally not caused by the hypersecretion of gastric acid, with the exception of patients with ZES.[238] The pathophysiology and risk factors associated with PUD

are described earlier in this chapter (see section on Peptic Ulcer Disease).

CLINICAL ASSESSMENT AND DIAGNOSIS

The clinical presentation of a patient with a bleeding peptic ulcer usually includes the presence of melena (dark, tarry stools), which occurs in 20% of patients, hematemesis (vomiting of blood) in 30%, and both in ~50% of patients. Up to 5% of patients present with hematochezia (bloody diarrhea) indicative of rapid and substantial blood loss.[238] The primary step in evaluating the patient is to assess hemodynamic status and the degree of urgency for rapid medical management.[238,239] Two validated prognostic scales exist for early risk stratification into high-risk or low-risk adverse outcomes for patients presenting with upper GI bleeding: the pre-endoscopic Rockall score and the Glasgow– Blatchford score.[239] The pre-endoscopic Rockall score only uses clinical patient data at presentation (eg, blood pressure, pulse, age, comorbidities), whereas the Blatchford score utilizes both laboratory (eg, Hgb, BUN) and clinical patient data (typically available early after admission); both are used to determine which patients are at higher risk for further bleeding or death, and also may assist in determining the need for and emergent nature of endoscopy, time of discharge, and level of care in the individual patient.[114,229,230,239] After endoscopy, the complete Rockall score incorporates endoscopic data to predict the likelihood of rebleeding and mortality.[114,229,230] Hypovolemia owing to substantial blood loss can rapidly lead to shock. The initial management of these patients should focus on volume resuscitation and improving the patient's hemodynamic status. Clinical features suggestive of high risk for rebleeding or mortality include patients older than 65 years, serious comorbidities (eg, hepatic or renal dysfunction, cardiac or pulmonary disease), hemodynamic instability (eg, hypotension, tachycardia), shock, poor health, continued bleeding, mental status changes, and prolonged prothrombin/activated partial thromboplastin time (aPTT) (or elevated international normalized ratio [INR]).[114,229,231,237,238,240,241]

These patients should immediately be transferred to an intensive care setting.

Most patients should receive early diagnostic endoscopic evaluation within 24 hours of presentation to determine the source of the bleeding, to predict the risk for rebleeding, and, when required, to perform endoscopic interventions directed at stopping the bleeding ulcer and restoring hemostasis.[229,230] Risk of rebleeding may be predicted based on the presenting lesion(s) identified on endoscopy.[114,238] The most common ulcer identified on endoscopy is a clean-base ulcer found in ~42% of patients. This ulcer has a very low risk of rebleeding (5%), and the patient can usually be discharged immediately after recovery from the endoscopy and managed with appropriate oral antisecretory therapy.[229,239] Intermediate stigmata of bleeding include lesions identified as flat-spot ulcers and/or adherent clots, which have a risk of rebleeding of 10% and 22%, respectively. Although endoscopic procedures are not usually necessary with flat-spot ulcers, adherent clots remain an area of controversy and usually require the endoscopist to attempt to remove the clot and manage the underlying lesion.[229] Patients identified with high-risk ulceration (nonbleeding visible vessel or active bleeding) will require endoscopic intervention and have a high risk of rebleeding (43% and 55%, respectively) despite intervention. Nonbleeding visible vessel and active bleeding are associated with an 11% mortality on initial presentation.[238] Ulcer size is also predictive of mortality and rebleeding, because ulcers >1 or 2 cm in diameter confer greater risk.[238] Despite appropriate endoscopic hemostasis, ~20% of patients with peptic ulcer bleeding will rebleed within 48 to 72 hours of treatment.[114,229,237,238] Mortality associated with rebleeding is ~30% to 37%.[237] Patients undergoing endoscopy should be tested for *H. pylori* infection with biopsy (rapid urease test), because infection with this organism is associated with an increased risk of rebleeding.[229,230] Because false negatives can occur in the presence of active bleeding, all patients who are *H. pylori* positive should have a confirmatory follow-up test with serologic antibody testing on discharge to ensure that the patient is not infected.[229]

TREATMENT

Patients with upper GI bleeding require rapid risk stratification based on the presenting signs and symptoms. Patients with hemodynamic instability require immediate institution of resuscitative measures.[114,229,230,239,242] IV access should be obtained with two large-bore (eg, 16–18 gauge) catheters to facilitate the administration of fluids and blood products.[114,230] Intravascular volume should initially be replenished with normal saline to prevent the patient progressing into hypovolemic shock. During this time, blood can be typed and crossed in the event a transfusion is required. Guidelines recommend the transfusion of packed red blood cells for patients with an Hgb level of <7 g/dL; however, consideration is warranted in the patient with tachycardia or hypotension and an Hgb level of 10 g/dL.[229,230] Although not required, a nasogastric tube may be placed to allow for lavage and determination of the upper GI tract as the source of the bleed and evaluation of continued bleeding.[114,229,230,239,242]

Endoscopic evaluation with hemostatic techniques (when required) should be performed as soon as safely possible.[229,230] Endoscopic hemostasis is the cornerstone of management of patients with serious bleeding ulcers, because it reduces the incidence of rebleeding, the need for surgery, and mortality when compared with placebo or drug therapy.[229,230] Endoscopic procedures include thermocoagulation, laser therapy, injection therapy (epinephrine, ethanol, or saline), injection with sclerosing agent, or placement of endoscopic clips.[229,239] Despite initial hemostasis, however, the potential for rebleeding remains high, especially in patients with high-risk lesions.[114,229,230,236–239]

Improvements in hemostatic parameters (eg, platelet aggregation, inactivation of pepsin, and correction of coagulation) leading to clot stabilization correlate directly with an intragastric pH >6. Therefore, treatment with an antisecretory drug is beneficial in patients after endoscopy to promote healing of the lesion.[230,236,239,240] After the acute phase, the patient should be placed on appropriate drug therapy to continue healing and prevent ulcer recurrence (see

section on Peptic Ulcer Disease). Patients who are *H. pylori* positive should receive appropriate eradication pharmacotherapy and confirmation of eradication at a later time.[229,239]

Histamine-2 receptor antagonists

Once widely used to manage upper GI bleeding, H_2RAs are now considered inferior to PPIs for reducing the incidence of rebleeding and the need for surgery.[229,230] This is likely related to the inability of H_2RAs to achieve an intragastric pH ≥6 (even with continuous IV administration) and the rapid development of tachyphylaxis (especially with high IV doses).[17,229,240] Thus, H_2RAs are no longer recommended for the prevention of rebleeding associated with a peptic ulcer.[229,230,239]

Proton-pump inhibitors

PPIs are the drugs of choice to reduce recurrence of upper GI bleeding ulcers and the need for surgical intervention.[114,229,230,239,243–245] However, no clinical trials were able to show a mortality benefit with PPIs when entire treatment cohorts were evaluated.[243–245] Two meta-analyses performed by the Cochrane Collaborative group evaluating PPIs administered IV or orally against H2RAs or placebo showed a reduction in rebleeding, surgery, and repeat endoscopic treatment.[243,244] Based on these available data, PPI therapy for peptic ulcer bleeding is superior to H_2RAs and placebo.[230] Although no reduction in the number of deaths were identified when all patients were considered, PPI treatment of patients at the highest risk of mortality, as evidenced by endoscopically determined active bleeding or nonbleeding visible vessel, did impart a mortality benefit.[244] All-cause mortality was also reduced in Asian trials, with a concomitant greater reduction in the incidence of rebleeding and need for surgery than in trials performed elsewhere in the world. This may be explained by the inclusion of a younger patient population, more potent acid suppression because of genetic polymorphism in

CYP450 metabolism leading to a slower clearance of PPIs, a lower parietal cell mass, and a greater incidence of *H. pylori* infection.[243]

Despite the data, important questions remain as to the most appropriate dose and route of administration for PPIs in patients with peptic ulcer bleeding. A pre-endoscopic PPI bolus plus continuous infusion has been shown to reduce the proportion of patients with active bleeding at endoscopy, reduce the requirements for endoscopy, and reduce hospital stay.[239,246] However, this strategy should not replace early endoscopic management in high-risk patients, because combination PPI therapy with endoscopic maneuvers has been proved to be more effective than is monotherapy with an IV PPI.[229,230,247] Evidence suggests that most patients with low-to-intermediate risk lesions (clean-base or flat-spot ulcers) and who are hemodynamically stable may be treated with a once-daily oral PPI and immediately discharged after endoscopy, because rebleeding is infrequent in this population.[229,239,243,248]

After successful endoscopic hemostasis, patients with adherent clots and high-risk bleeding ulcers (active bleeding and nonbleeding visible vessels) are typically managed with high-dose IV bolus and continuous IV infusion of a PPI (omeprazole 80 mg or equivalent PPI followed by 8 mg/hour for 72 hours).[229,239] Some patients may be switched to an oral PPI if rapid stabilization occurs, but careful clinical assessment should be performed to ensure the patient is stable.[248] Of note, a recent meta-analysis has called into question the need for high-dose, continuous PPI therapy, suggesting that intermittent PPI therapy may be noninferior.[249] Further, another meta-analysis has suggested that PPI therapy is associated with reduced blood transfusion requirements.[250] To more effectively assess the validity of the findings from these meta-analyses, a carefully designed prospective randomized controlled trial would need to take place.

Once the high-risk patient has stabilized and is considered safe for discharge after endoscopy and 72 hours of IV PPI, the patient should be discharged with a prescription for at least once-daily PPI pharmacotherapy for continued healing of the lesion and further prevention of rebleeding.[229,239] The actual dose and duration,

however, should be decided based on the patient's severity of disease and identified complications, with more severe disease warranting consideration of twice-daily therapy.[229,239] Patients with *H. pylori*–associated bleeding ulcers should receive standard therapy for eradication, although maintenance PPI therapy is not necessary unless the patient also requires NSAIDs or antithrombotics.[229,239] Patients who are required to remain on long-term NSAID therapy require long-term secondary prophylaxis with daily oral PPI therapy in an attempt to prevent future upper GI bleeding events; patients should consider a more COX-2–selective NSAID at the lowest effective dose plus daily PPI for this situation (see section on Nonsteroidal Anti-inflammatory Drug–Induced Peptic Ulcer).[229,239] When considering the role of cardioprotective aspirin in patients with previous ulcer bleeding, risks often outweigh benefits in primary prevention and benefits often outweigh risks in secondary prevention.[148] As such, aspirin therapy should only be restarted if the risk of cardiovascular complication outweighs the bleeding risk and only in combination with daily PPI therapy (the same concept applies to dual antiplatelet and anticoagulation therapy); for secondary prevention, aspirin should be resumed with daily PPI therapy as soon as possible after bleeding cessation (ideally 1–3 days but no more than 7 days).[229,239]

Other agents

Despite being commonly used in the management of variceal bleeding (see Chapter 25, Complications of End-Stage Liver Disease), the use of somatostatin or octreotide is not recommended for the management of nonvariceal upper GI bleeding because of insufficient supporting evidence.[229,230]

Stress-Related Mucosal Bleeding

Acute SRMB is a type of erosive gastritis that occurs in critically ill patients with severe physiologic stress (eg, surgery, trauma, organ failure, sepsis, severe burns, and neurologic injuries).[244,251–254] The

term *stress ulcer* is a misnomer in that SRMB may range from numerous diffuse superficial erosive mucosal lesions (those that do not penetrate the muscularis mucosa) to major deep ulceration (penetration of the muscularis mucosa and potentially submucosa).[233,234] Initial lesions occur early (<24 hours) and appear as subepithelial petechiae that can develop into superficial erosions and ulcerations.[234,254] Early stress-related mucosal lesions are multiple, usually asymptomatic, without perforation, and commonly bleed from superficial mucosal capillaries.[233,253] The gastric fundus is the most likely anatomic region of the stomach to be involved. Distal lesions involving the gastric antrum and duodenum have also been described, but tend to appear later in the hospital course and are often deeper and associated with a greater probability for bleeding.[233] SRMB from these lesions may be categorized into three distinct types based on clinical presentation.[233–235,253,254] Occult (hidden) bleeding is defined as aspirated gastric fluid or stool that is guaiac positive for the presence of occult blood and without other signs or symptoms.[235] Overt bleeding is defined as frank hemorrhage identified by hematemesis (bloody vomitus or the appearance of coffee grounds in gastric aspirates or vomitus), hematochezia (bloody diarrhea), or melenic stools.[235] Clinically important bleeding or life-threatening bleeding is the presence of overt bleeding that is associated with hemodynamic changes (tachycardia, hypotension, orthostatic changes, or Hgb concentration decline of >2 g/dL) and the requirement of transfusion of blood products.[235] Endoscopic therapy is generally not a viable option because of the extensive distribution of lesions associated with SRMB.[251]

EPIDEMIOLOGY

The majority (>75%) of the critically ill patients admitted to intensive care units (ICUs) will exhibit mucosal lesions consistent with SRMB within 24 hours of admission.[233–235,251,253,254] Only a small percentage (up to 6%) of these patients will progress to clinically important GI bleeding.[233–235,253,254] Clinically important SRMB has been associated with an increased length of stay in the ICU by up to 11 days, and

results in substantial increases in the cost of health care.[233,235,251,253,254] The mortality of clinically important SRMB approaches 50%, but mortality may also be associated with underlying comorbidities related to the critical illness.[244,254]

PATHOPHYSIOLOGY

Numerous factors have been identified in the pathogenesis of SRMB and resultant bleeding. These include gastric acid and pepsin secretion, disruptions to the normal homeostatic mechanisms that protect the gastric mucosa against the highly acidic environment (decreases in prostaglandin, bicarbonate, and GI mucous formation as well as impaired turnover of gastric epithelium), GI motility disturbances, and mucosal ischemia resulting from decreased blood flow.[234,235,251,253,254] Gastric acid and disruption of the mucosal barrier seem to be central factors associated with development of SRMB.[233,235,251] Because of the absence of protective defenses, substantial amounts of acid are not required for the formation of lesions, but some acid is required for damage to occur.[234] Although some patients may have increased acid secretion (eg, sepsis, CNS injuries, small bowel resections), the majority of critically ill patients have normal or decreased acid secretion.[233–235,252] Pepsin secretion is associated with the lysis of clots owing to its proteolytic action on fibrin.[251,255] Gastric prostaglandins play a key role in the cellular defense against gastric acid.[251] These prostaglandins are responsible for maintaining the integrity of the mucosal barrier by stimulating mucous and bicarbonate production, regulating blood flow, and, to some degree, inhibition of acid production. Mucosal ischemia secondary to splanchnic hypoperfusion also plays a large role in the pathogenesis of SRMB.[234,251,253] Mucosal ischemia is associated with reduced ability to neutralize hydrogen ions, leading to intracellular acidosis within the mucosa and subsequent cell death. These factors all contribute to an imbalance by increasing injurious factors and reducing the protective mechanisms within the gastric fundus.

RISK FACTORS

CASE 23-6

QUESTION 1: J.S., a 58-year-old, 242.51-pound (110-kg) male was admitted to the medical ICU for severe necrotizing pancreatitis identified on abdominal computed tomography. The patient was immediately made "nothing by mouth" (NPO) and started on imipenem/cilastatin 1000 mg intravenous piggyback (IVPB) every 6 hours. He was given hydromorphone 1 mg IV every 3 hours as needed for pain. He subsequently exhibited shortness of breath on his third day after admission, required intubation, and was placed on a ventilator. A chest x-ray showed a left lower lobe infiltrate suggestive of hospital-acquired pneumonia. Antibiotic coverage was increased with the addition of ciprofloxacin 400 mg IVPB every 8 hours and linezolid 600 mg IV every 12 hours. He has a temperature of 103.5 °F (39.72 °C), heart rate of 115 beats/minute, and blood pressure of 70/40 mm Hg. Pertinent laboratory results at this time include the following:

WBC count, 38,000/μL
Hgb, 13.6 g/dL
Hct, 40%
Platelets, 150,000/μL
SCr, 1.3 mg/dL
BUN, 24 mg/dL
INR, 1.0
aPTT, 39 seconds
Aspartate aminotransferase (AST), 292 units/L
Alanine aminotransferase (ALT), 305 units/L
Amylase, 508 units/L
Lipase, 624 units/L

In addition to the antimicrobials and initiation of fluid resuscitation, the critical care team is considering stress ulcer prophylaxis.

What risk factors does J.S. have (if any) for SRMB, and is he a candidate for stress ulcer prophylaxis?

Numerous risk factors have been associated with SRMB (**Table 23-11**).[233,235,251–254] However, a large landmark, multicenter, prospective study involving >2200 critically ill patients admitted to a medical ICU identified only the requirement of mechanical ventilation (respiratory failure) or coagulopathy as independent risk factors for development of clinically important bleeding.[239] Considering the cost

associated with the reduction of risk related to SRMB, the authors concluded that only these two risk factors warrant the use of prophylactic therapy. Because not all risk factors impose the same level of risk, clinical guidelines and most practitioners recommend prophylaxis only when the patient is mechanically ventilated, has a coagulopathy, or when two or more of the remaining risk factors are present (**Table 23-11**).[235,251,252,254,256,257] J.S.'s risk factors include septic shock as evidenced by hemodynamic instability and mechanical ventilation. Therefore, a prophylactic regimen to reduce the risk of SRMB is appropriate.

Table 23-11

Risk Factors for Stress-Related Mucosal Bleeding

Mechanical ventilation
Coagulopathy
Respiratory failure
Hepatic failure
Acute renal failure
Renal replacement therapy
Head/brain injury
Hypotension
Sepsis
Shock
Enteral feeding
High-dose corticosteroids[a]
Organ transplant
Anticoagulants
Severe burns (>35% of body surface area)
Intensive care unit stay >7 days
History of previous GI hemorrhage

GI, gastrointestinal.

[a]Greater than 250 mg/day hydrocortisone or equivalent.

Sources: Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. *Chest.* 2001;119(4):1222–1241; Cook D, Guyatt G. Prophylaxis against upper gastrointestinal bleeding in hospitalized patients. *N Engl J Med*. 2018;378(26):2506–2516; Ali T, Harty RF. Stress-induced ulcer bleeding in critically ill patients. *Gastroenterol Clin North Am.* 2009;38(2):245–265; ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. *Am J Health Syst Pharm*. 1999;56(4): 347–379; Stollman N, Metz DC.

Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *J Crit Care*. 2005;20(1):35–45; Jung R, MacLaren R. Proton-pump inhibitors for stress ulcer prophylaxis in critically ill patients. *Ann Pharmacother*. 2002;36(12):1929–1937.

TREATMENT

CASE 23-6, QUESTION 2: What options exist to prevent SRMB in J.S.?

Not all patients admitted to the ICU will require prophylaxis for SRMB. However, because mortality can be high in patients when bleeding occurs, evaluation of risk is of absolute importance to ensure that protective pharmacotherapy is initiated in appropriate patients.[233–235,251–254,256,257] Because acid is required for mucosal injury, the inhibition of gastric acid is the primary target when pharmacotherapy is used to reduce the risk of SRMB. An intragastric pH >4 is the recommended goal of therapy.[233,234,244,251–254] Therapeutic options include the use of antacids, sucralfate, H_2RAs, and PPIs (**Table 23-12**). When determining whether medication therapy is warranted, risk of pneumonia must also be assessed.[235,257] Beyond medications, enteral nutrition may provide protection against bleeding while increasing gastric pH to a similar or even greater extent than does acid suppression.[235,256] Within 48 hours of ICU admission, initiation of enteral nutrition has been evaluated as a means of prophylaxis against SRMB.[258] A meta-analysis of 17 studies suggested that patients who require enteral tube feedings may not require additional forms of SRMB prophylaxis and may also have a reduced risk of pneumonia or death when compared with patients receiving an H_2RA-based SRMB prophylaxis regimen.[258] This meta-analysis, however, was only hypothesis generating and should be interpreted with care until a large controlled study is available to confirm these findings.

Table 23-12
Stress-Related Mucosal Bleeding Prevention: Regimens and

Doses

Agent	Dose and Frequency of Administration	FDA Approval[a]
Antacid	30 mL PO/NG every 1–2 hours	No
Cimetidine	300 mg IV loading dose, then 50 mg/hour continuous IV infusion[b]	Yes
Famotidine	20 mg IV every 12 hours *or*	No
	1.7 mg/hour continuous infusion	No
Ranitidine	50 mg IV every 6–8 hours *or*	No
	6.25 mg/hour continuous infusion	No
Sucralfate	1 g PO/NG every 6 hours	No
Omeprazole	20–40 mg PO/NG[c] every 12–24 hours	No
Omeprazole/sodium bicarbonate powder for oral suspension	40 mg PO/NG initially, followed by 40 mg 6–8 hours later, then 40 mg PO/NG every 24 hours	Yes
Lansoprazole	30 mg PO/NG[c,d] every 12–24 hours	No
Pantoprazole	40 mg IV/PO/NG[c] every12–24 hours	No
Esomeprazole	40 mg IV/PO/NG every 12–24 hours	No

IV, intravenous; NG, nasogastric; PO, by mouth.

[a]For prevention of stress-related mucosal bleeding.

[b]Not available in the United States.

[c]Extemporaneously compounded in sodium bicarbonate.

[d]Oral disintegrating tablet.

Antacids

The use of aggressive antacid therapy is superior to placebo in reducing clinically important SRMB when an intragastric pH >3.5 is maintained.[251,253,254] Although antacids are effective in preventing SRMB, their use has fallen out of favor because of difficult administration regimens (every 1–2 hours) along with the continuous requirement of intragastric pH monitoring for dose titration, electrolyte abnormalities (especially in patients with renal dysfunction), diarrhea, constipation, and the potential risk of

aspiration pneumonia.[233,251,253,254] These issues, coupled with the fact that potent acid suppression is available in far more convenient dosage forms, have all but eliminated the use of antacids as SRMB prophylaxis.[251]

Sucralfate

Despite the fact that antisecretory therapy is preferred, sucralfate remains an available therapeutic option. Sucralfate is effective in preventing SRMB, but does not have an important effect on intragastric pH.[259,260] Early studies suggested a reduction in nosocomial pneumonia with sucralfate when compared with ranitidine or antacids; however, a subsequent randomized trial involving 1200 mechanically ventilated patients revealed no increase in pneumonia with H_2RAs when compared with sucralfate or antacids.[259–261] The usual dose of 1 g four times daily can present problems within the critical care setting because of multiple daily dosing, binding of other enterally administered drugs, and occlusion of nasogastric tubes (may be reduced with suspension formulation). Other potential issues include the risk of aluminum toxicity in patients with renal failure, constipation, and electrolyte imbalances. The concomitant use of sucralfate with antisecretory therapy may reduce the effectiveness of sucralfate because an intragastric pH <4 is needed for conversion to its active form, which binds to the gastric mucosa.[254]

Histamine-2 receptor antagonists

H_2RAs are effective in preventing SRMB; although previously the most widely used for this indication, PPIs now predominate.[235,256,257,262,263] Although only cimetidine continuous infusion has been FDA labeled for the prevention of SRMB, continuous or intermittent infusions of ranitidine and famotidine are preferred because of the adverse effect and drug interaction profile of cimetidine.[240,251,253] Continuous infusions have been suggested as being more effective than are intermittent infusions in maintaining a

pH >4, but there are no data comparing these two treatment options with respect to clinical outcomes.[233,251] Despite this, intermittent dosing of H_2RAs is used more commonly than are continuous infusions for the prophylaxis of SRMB.[240,253,262,263]

Numerous trials and meta-analyses have evaluated the effectiveness of H_2RAs for prophylaxis of SRMB.[235,264,265] Cook et al reviewed 63 randomized trials and determined that prophylaxis with H_2RAs was associated with a statistically significant reduction in overt and clinically important upper GI bleeding when compared with no therapy and a significant reduction in overt bleeding when compared with antacids.[264] A trend toward reduced clinically important bleeding was identified when H_2RAs were compared with sucralfate, but this was not statistically significant. In another meta-analysis, ranitidine was shown to be of no benefit in preventing SRMB while increasing the risk of pneumonia.[265] However, neither of these meta-analyses included the large study involving 1200 mechanically ventilated patients that compared sucralfate, ranitidine, and placebo.[261] Despite these conflicting results, H_2RAs remain an option, and are still sometimes used for the prophylaxis of SRMB.[262,263] One shortcoming of H_2RAs is that tolerance may develop (within 72 hours), which may theoretically lead to prophylaxis failure.[17]

Proton-pump inhibitors

PPIs, because of their profound ability to inhibit gastric acid secretion and the lack of tolerance to their antisecretory effect, have emerged as the preferred option for preventing SRMB. However, there is very little evidence to confirm their clinical superiority to H_2RAs for this indication. Numerous studies have compared PPIs with H_2RAs or placebo in critically ill patients in small populations using varied predetermined end points.[254,266] These studies suggest that PPIs provide greater acid suppression compared with H_2RAs and are likely to be as effective in preventing SRMB.[254,266] Alternative administration options exist for patients in the critical care setting

who cannot take medications by mouth, have nasogastric tubes in place, or have difficulty swallowing[254,267] (**Table 23-13**). One study in 359 critically ill patients evaluated the use of immediate-release omeprazole suspension in bicarbonate given via nasogastric tube versus IV cimetidine; results suggested that the PPI-bicarbonate suspension was associated with a greater mean time of intragastric pH >4 than was the cimetidine infusion, but that the rate of clinically important bleeding did not significantly differ between treatment arms.[268] Further, an extremely important analysis aimed at identifying the most appropriate dose for IV PPIs in SRMB prophylaxis was performed in >200 critically ill patients.[269] This analysis included five different dosing approaches of IV pantoprazole intermittent infusions (40 mg given every 8, 12, or 24 hours or 80 mg given every 12 or 24 hours) compared with cimetidine given as a 300-mg IV bolus immediately followed by a 50 mg/hour continuous infusion. The patients received a minimum of 48 hours of therapy with a maximum of 7 days. In all the study arms, pH control was achieved (defined as intragastric pH ≥4); however, in all the pantoprazole arms, pH control continued to improve from day 1 to 2, whereas a decline was noted in the cimetidine group, suggesting the occurrence of tachyphylaxis. No upper GI bleeding was noted in any patient during the trial regardless of treatment group assigned. The conclusions of this study demonstrated that patients may have adequate pH control with an initial IV dose of pantoprazole 80 mg followed by 40 mg IV every 12 hours.[269] A 2013 meta-analysis that included 14 studies totaling ~1700 patients evaluating the efficacy and safety of PPIs compared with H_2RAs demonstrated a statistically significant difference between the two options (favoring PPIs) with respect to the important end points of overt or clinically important bleeding; there were no differences with regard to mortality or incidence of pneumonia.[266] The incidence of nosocomial pneumonia in patients receiving PPI therapy for SRMB prophylaxis undergoing cardiothoracic surgery has been evaluated in two retrospective cohort studies.[267,270] Both studies demonstrated that patients receiving PPIs were at an

increased risk for developing pneumonia even after data adjustments for various risk factors.

Table 23-13

Alternative Proton-Pump Inhibitor Administration Options

	Omeprazole	Lansoprazole	Pantoprazole	Esomeprazole	Rabeprazole	Dexlansoprazole
Capsule granules sprinkled on selected soft foods (ie, applesauce)		✓[a]		✓[a]	✓[a]	✓[a]
Capsule granules mixed in water and flushed down NG tube				✓		✓[a]
Capsule granules mixed in juice (can be administered via NG tube if required)	✓[a]	✓[a]		✓[a]	✓[a]	✓[a]
Extemporaneous compound of PPI in bicarbonate for NG tube	✓	✓	✓			
Package for oral suspension	✓[a,b]	✓[a,c]		✓[a]		
Oral disintegrating tablet		✓[a]				
IV formulation	Not available in the United States	Removed from U.S. market	✓[a]	✓[a]		

IV, intravenous; NG, nasogastric; PPI, proton-pump inhibitor.

[a]Labeled by the U.S. Food and Drug Administration (FDA) for this administration option.

[b]Omeprazole suspensions available in 20- and 40-mg packets with bicarbonate (1680 mg); both contain same amount of bicarbonate, and two 20-mg packets cannot be substituted for one 40-mg packet.

[c]Not to be administered via nasogastric (NG) tube, because occlusion of tube is possible.

Sources: Jung R, MacLaren R. Proton-pump inhibitors for stress ulcer prophylaxis in critically ill patients. *Ann Pharmacother*. 2002;36(12):1929–1937; Bateman BT, Bykov K, Choudhry NK, et al. Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. *BMJ*. 2013;347:f5416.

More recently, a large randomized controlled trial compared pantoprazole to placebo in adult patients at risk for GI bleeding in the ICU; 90-day mortality and the number of clinically important events (GI bleeding, pneumonia, CDI, or myocardial ischemia) were similar in both arms.[256] This important trial further puts into question the

benefits and risks of widespread use of acid suppression therapy for SRMB prophylaxis. Although PPIs have become predominantly first-line therapy for the prevention of SRMB, additional studies are needed to confirm the most effective dose and route of administration to obtain optimal clinical outcomes in patients at risk for SRMB.[253,262] Recent data has prompted reevaluation of system-wide approaches to SRMB prevention and management; evidence also supports a broad and significant impact of pharmacist-led management programs for SRMB prophylaxis to reduce inappropriate prescribing/use of acid suppression therapy.[235,256,257]

MONITORING

CASE 23-6, QUESTION 3: J.S. has been started on famotidine 20 mg IV every 12 hours. How should this pharmacotherapy be monitored for safety and efficacy?

The famotidine dose should be adjusted to maintain an intragastric pH >4 and should be based on severity of the patient's illness, renal function, and intragastric pH measurements. The intragastric pH can be determined with an indwelling probe or by measuring the pH of nasogastric aspirates. The patient should be monitored for signs of bleeding (eg, presence of blood or coffee-ground material in nasogastric aspirates, hematemesis, hematochezia, or melena), hypotension, reductions in Hgb or Hct, and thrombocytopenia.

CASE 23-6, QUESTION 4: During the next 6 days, J.S. improves and is subsequently removed from mechanical ventilation and transferred to the medical ward. He is now able to eat normally. Should J.S. be continued on SRMB prophylaxis?

Patients receiving prophylaxis for SRMB should be evaluated for the continued presence of risk factors. As the patient improves, the risk factors should, in turn, be reversed, and the need for SRMB prophylaxis should diminish. Factors such as extubation, correction of coagulopathies, discharge from the intensive care setting, and the

ability to take oral feeding advocate for the discontinuation of prophylaxis. Numerous studies have suggested that up to 54% of patients were ordered SRMB prophylaxis outside the ICU setting and without a compelling indication.[271] Erstad and colleagues surveyed 153 institutions within the United States and found that in 65% of the hospitals, >25% of patients remained on SRMB prophylaxis after discharge from the ICU.[272] This can lead to increased costs, the potential of the patient being discharged on medication for which there is no indication, and future potential adverse effects from the medication.[271] Of note, pharmacist-led programs designed to reduce inappropriate acid suppression for SRMB prophylaxis in ICU and non-ICU populations safely reduced prescribing by 58% and 84%, respectively.[257] Because J.S. does not possess any risk factors for SRMB, famotidine should be discontinued at this time.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Abraham NS, Klatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Am J Gastroenterol.* 2010;105(12):2533–2549. (35)

Armstrong D, Sifrim D. New pharmacologic approaches in gastroesophageal reflux disease. *Gastroenterol Clin North Am*. 2010;39:393–418. (170)

Barkun AN, Almadi M, Kuipers EJ, et al. Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the international consensus group. *Ann Intern Med*. 2019;171(11s):805–822. (230)

Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* Infection. *Am J Gastroenterol*. 2017;112(2):212–239. (95)

Cook D, Guyatt G. Prophylaxis against upper gastrointestinal bleeding in hospitalized patients. *N Engl J Med*. 2018;378(26):2506–2516. (236)

Gisbert JP, Calvet X, O'Connor A, Mégraud F, O'Morain CA. Sequential therapy for *Helicobacter pylori* eradication: a critical review. *J Clin Gastroenterol*. 2010;44(5):313–325. (124)

Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3):308–328. (62)

Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012;107(3):345–360. (240)

Lanza FL, Chan FK, Quigley EM. Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104(3): 728–738. (102)

Li B-Z, Threapleton DE, Wang J-Y, et al. Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: systematic review and network meta-analysis. *BMJ*. 2015;351:h4052. (128)

Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet*. 2009;374(9699):1449–1461. (103)

Moayyedi P, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia [published correction appears in *Am J Gastroenterol*. 2017 Sep;112(9):1484]. *Am J Gastroenterol*. 2017;112(7):988–1013. (81)

Patel D, Bertz R, Ren S, Boulton DW, Någård M. A systematic review of gastric acid-reducing agent-mediated drug-drug interactions with orally administered medications. *Clin Pharmacokinet*. 2020;59(4):447–462. (6)

Scarpignato C, Hunt RH. Nonsteroidal anti-inflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis and prevention. *Gastroenterol Clin North Am*. 2010;39(3):433–464. (101)

Sherwood MW, Melloni C, Jones WS, Washam JB, Hasselblad V, Dolor RJ. Individual proton pump inhibitors and outcomes in patients with coronary artery disease on dual antiplatelet therapy: a systematic review. *J Am Heart Assoc*. 2015;4(11):e002245. (46)

COMPLETE REFERENCES CHAPTER 23 UPPER GASTROINTESTINAL DISORDERS

1. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update

2018. *Gastroenterology*. 2019;156(1):254–272.e11.
2. Kahrilas PJ, Pandolfino JE, Katzka DA. Esophageal motor function. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:330–347.
3. Wolfe MM, Lowe RC. Gastric secretions. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:399–419.
4. Maton PN, Burton ME. Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. *Drugs*. 1999;57(6):855–870.
5. Whetsel T, Garofoli G. Chapter 13: Heartburn and dyspepsia. In: Krinsky DL, Ferreri SP, Hemstreet BA, Hume AL, Newton GF, eds. *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care*. 20th ed. American Pharmacists Association; 2020. doi: 10.21019/9781582123172.ch13
6. Patel D, Bertz R, Ren S, Boulton DW, Någård M. A systematic review of gastric acid-reducing agent-mediated drug-drug interactions with orally administered medications. *Clin Pharmacokinet*. 2020;59(4):447–462.
7. Lin JH. Pharmacokinetic and pharmacodynamic properties of histamine H2-receptor antagonists. Relationship between intrinsic potency and effective plasma concentrations. *Clin Pharmacokinet*. 1991;20(3):218–236.
8. Feldman M, Burton ME. Histamine2-receptor antagonists. Standard therapy for acid-peptic diseases 1. *N Engl J Med*. 1990;323(24):1672–1680.
9. Feldman M, Burton ME. Histamine2-receptor antagonists: standard therapy for acid-peptic diseases 2. *N Engl J Med*. 1990;323(25):1749–1755.
10. Jensen RT, Collen MJ, Pandol SJ, et al. Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med*. 1983;308(15):883–887.
11. Aymard JP, Aymard B, Netter P, Bannwarth B, Trechot P, Streiff F. Haematological adverse effects of histamine H2-receptor antagonists. *Med Toxicol Adverse Drug Exp*. 1988;3(6):430–448.
12. Wade EE, Rebuck JA, Healey MA, Rogers FB. H2-antagonist-induced thrombocytopenia: is this a real phenomenon? *Intensive Care Med*. 2002;28(4):459–465.
13. Lewis JH. Hepatic effects of drugs used in the treatment of peptic ulcer disease. *Am J Gastroenterol.* 1987;82(10):987–1003.
14. Poh CH, Navarro-Rodriguez T, Fass R. Review: treatment of gastroesophageal reflux disease in the elderly. *Am J Med*. 2010;123(6):496–501.
15. Nazario M. The hepatic and renal mechanisms of drug interactions with cimetidine. *Drug Intell Clin Pharm*. 1986;20(5):342–348.
16. Kosoglou T, Vlasses PH. Drug interactions involving renal transport mechanisms: an overview. *DICP*. 1989;23(2):116–122.

17. Merki HS, Wilder-Smith CH. Do continuous infusions of omeprazole and ranitidine retain their effect with prolonged dosing? *Gastroenterology*. 1994;106(1):60–64.
18. Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. *Gastroenterology*. 2002;122(3):625–632.
19. U.S. Food & Drug Administration. FDA news release: FDA requests removal of all Ranitidine products (Zantac) from the market. Published April 1, 2020. Accessed October 1, 2020. https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market
20. Boparai V, Rajagopalan J, Triadafilopoulos G. Guide to the use of proton pump inhibitors in adult patients. *Drugs*. 2008;68(7):925–947.
21. Jones R, Bytzer P. Review article: acid suppression in the management of gastro-oesophageal reflux disease—an appraisal of treatment in primary care. *Aliment Pharmacol Ther*. 2001;15(6):765–772.
22. Welage LS. Pharmacologic properties of proton pump inhibitors. *Pharmacotherapy*. 2003;23(10 Pt 2):74S–80S.
23. Hatlebakk JG. Review article: gastric activity—comparison of esomeprazole with other proton pump inhibitors. *Aliment Pharmacol Ther*. 2003;17(suppl 1):10–15.
24. Metz DC, Vakily M, Dixit T, Mulford D. Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy. *Aliment Pharmacol Ther*. 2009;29(9):928–937.
25. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. *Clin Ther*. 2001;23(7):998–1017.
26. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Comparison of rabeprazole 20 mg versus omeprazole 20 mg in the treatment of active duodenal ulcer: a European Multicentre Study. *Aliment Pharmacol Ther*. 1999;13(2):179–186.
27. Mossner J, Holscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Aliment Pharmacol Ther*. 1995;9(3):321–326.
28. Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. *Am J Gastroenterol*. 2002;97(3):575–583.
29. Howden CW, Ballard ED 2nd, Robeison W. Evidence for therapeutic equivalence of lansoprazole 30 mg and esomeprazole 40 mg in the treatment of erosive oesophagitis. *Clin Drug Investig*. 2002;22(2):99–109.

30. Horn JR, Howden CW. Review article: similarities and differences among delayed-release proton-pump inhibitor formulations. *Aliment Pharmacol Ther*. 2005;22(suppl 3):20–24.
31. Wang WH, Huang JQ, Zheng GF, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. *World J Gastroenterol*. 2005;11(26):4067–4077.
32. Stedman CA, Barclay ML. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. *Aliment Pharmacol Ther*. 2000;14(8):963–978.
33. Ogawa R, Echizen H. Drug-drug interaction profiles of proton pump inhibitors. *Clin Pharmacokinet*. 2010;49(8):509–533.
34. U.S. Food & Drug Administration. Information for healthcare professionals: update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). Accessed Feb 28, 2022. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-poor
35. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Am J Gastroenterol*. 2010;105(12):2533–2549.
36. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) Study. *J Am Coll Cardiol*. 2008;51(3):256–260.
37. Last EJ, Sheehan AH. Review of recent evidence: potential interaction between clopidogrel and proton pump inhibitors. *Am J Health Syst Pharm*. 2009;66(23):2117–2122.
38. Norgard NB, Mathews KD, Wall GC. Drug-drug interaction between clopidogrel and the proton pump inhibitors. *Ann Pharmacother*. 2009;43(7):1266–1274.
39. Liu TJ, Jackevicius CA. Drug interaction between clopidogrel and proton pump inhibitors. *Pharmacotherapy*. 2010;30(3):275–289.
40. Laine L, Hennekens C. Proton pump inhibitor and clopidogrel interaction: fact or fiction? *Am J Gastroenterol*. 2010;105(1):34–41.
41. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360(4):354–362.

42. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Catheter Cardiovasc Interv*. 2013;82(1):E1–E27.
43. Hu W, Tong J, Kuang X, Chen W, Liu Z. Influence of proton pump inhibitors on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: a meta-analysis. *Medicine (Baltimore)*. 2018;97(3):e9638.
44. Bundhun PK, Teeluck AR, Bhurtu A, Huang W-Q. Is the concomitant use of clopidogrel and proton pump inhibitors still associated with increased adverse cardiovascular outcomes following coronary angioplasty?: a systematic review and meta-analysis of recently published studies (2012–2016). *BMC Cardiovasc Disord*. 2017;17(3):1–11.
45. Serbin MA, Guzauskas GF, Veenstra DL. Clopidogrel-proton pump inhibitor drug-drug interaction and risk of adverse clinical outcomes among PCI-treated ACS patients: a meta-analysis. *J Manag Care Spec Pharm*. 2016;22(8):939–947.
46. Sherwood MW, Melloni C, Jones WS, Washam JB, Hasselblad V, Dolor RJ. Individual proton pump inhibitors and outcomes in patients with coronary artery disease on dual antiplatelet therapy: a systematic review. *J Am Heart Assoc*. 2015;4(11):e002245.
47. Kwok CS, Jeevanantham V, Dawn B, Loke YK. No consistent evidence of differential cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: meta-analysis. *Int J Cardiol*. 2013;167(3):965–974.
48. Huang B, Huang Y, Li Y, et al. Adverse cardiovascular effects of concomitant use of proton pump inhibitors and clopidogrel in patients with coronary artery disease: a systematic review and meta-analysis. *Arch Med Res*. 2012;43(3):212–224.
49. Siller-Matula JM, Jilma B, Schrör K, Christ G, Huber K. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. *J Thromb Haemost*. 2010;8(12):2624–2641.
50. Farhat N, Fortin Y, Haddad N, et al. Systematic review and meta-analysis of adverse cardiovascular events associated with proton pump inhibitors used alone or in combination with antiplatelet agents. *Crit Rev Toxicol*. 2019;49(3):215–261.
51. Focks JJ, Brouwer MA, Oijen MGHV, Lanas A, Bhatt DL, Verheugt FWA. Concomitant use of clopidogrel and proton pump inhibitors: impact on platelet function and clinical outcome-a systematic review. *Heart*. 2012;99(8):520–527.
52. Gerson LB, Mcmahon D, Olkin I, Stave C, Rockson SG. Lack of significant interactions between clopidogrel and proton pump inhibitor therapy: meta-analysis of existing literature. *Dig Dis Sci*. 2011;57(5):1304–1313.
53. Melloni C, Washam JB, Jones WS, et al. Conflicting results between randomized trials and observational studies on the impact of proton pump

inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy: systematic review. *Circ Cardiovasc Qual Outcomes*. 2015;8(1):47–55.

54. Zvyaga T, Chang SY, Chen C, et al. Evaluation of six proton pump inhibitors as inhibitors of various human cytochromes P450: focus on cytochrome P450 2C19. *Drug Metab Dispos*. 2012;40(9):1698–1711.
55. Ali T, Roberts DN, Tierney WM. Long-term safety concerns with proton pump inhibitors. *Am J Med*. 2009;122(10):896–903.
56. Yang YX, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology*. 2010;139(4):1115–1127.
57. Ramakrishnan A, Katz PO. Overview of medical therapy for gastroesophageal disease. *Gastrointest Endosc Clin N Am*. 2003;13(1):57–68.
58. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. 2006;296(24):2947–2953.
59. Targownik LE, Leslie WD, Davison KS, et al. The relationship between proton pump inhibitor use and longitudinal change in bone mineral density: a population-based study [corrected] from the Canadian Multicentre Osteoporosis Study (CaMos) [published correction appears in *Am J Gastroenterol*. 2013 Jan;108(1):157]. *Am J Gastroenterol*. 2012;107(9):1361–1369.
60. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA*. 2005;294(23):2989–2995.
61. Gray SL, LaCroix AZ, Larson J, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med*. 2010;170(9):765–771.
62. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3):308–328.
63. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *JAMA*. 2013;310(22):2435–2442.
64. Laine L, Ahnen D, McClain C, Solcia E, Walsh JH. Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther*. 2000;14(6):651–668.
65. U.S. Food & Drug Administration. FDA drug safety communication: low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs). Published March 2, 2011. Accessed October 1, 2020. http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm
66. Danziger J, William JH, Scott DJ, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int*. 2013;83(4):692–699.

67. Markovits N, Loebstein R, Halkin H, et al. The association of proton pump inhibitors and hypomagnesemia in the community setting. *J Clin Pharmacol*. 2014;54(8):889–895.
68. Sierra F, Suarez M, Rey M, Vela MF. Systematic review: proton pump inhibitor-associated acute interstitial nephritis. *Aliment Pharmacol Ther*. 2007;26(4):545–553.
69. Williams C, McColl KE. Review article: proton pump inhibitors and bacterial overgrowth. *Aliment Pharmacol Ther*. 2006;23(1):3–10.
70. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazi R, Loke YK. Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol*. 2012;107(7):1011–1019.
71. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. *Clostridium difficile*-associated diarrhea and proton pump inhibitor therapy: a meta analysis. *Am J Gastroenterol*. 2012;107(7):1001–1010.
72. McCarthy DM. Sucralfate. *N Engl J Med*. 1991;325(14):1017–1025.
73. Walt RP. Misoprostol for the treatment of peptic ulcer and antiinflammatory-drug-induced gastroduodenal ulceration. *N Engl J Med*. 1992;327(22):1575–1580.
74. Graham DY, Agrawal NM, Roth SH. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. *Lancet*. 1988;2(8623):1277–1280.
75. Wagstaff AJ, Benfield P, Monk JP. Colloidal bismuth subcitrate. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in peptic ulcer disease. *Drugs*. 1988;36(2):132–157.
76. Hussar DA. New drugs: retapamulin, bismuth subcitrate potassium, and rotigotine. *J Am Pharm Assoc*. 2007;47(4):539–543.
77. Lacy BE, Weiser KT, Kennedy AT, Crowell MD, Talley NJ. Functional dyspepsia: the economic impact to patients. *Aliment Pharmacol Ther*. 2013;38(2):170–177.
78. Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. *Gastroenterology*. 2005;129(5):1756–1780.
79. Tack JF. Approach to the patient with dyspepsia and related functional gastrointestinal complaints. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:651–656.
80. Bytzer P, Talley NJ. Dyspepsia. *Ann Intern Med*. 2001;134(9 Pt 2):815–822.
81. Moayyedi P, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia [published correction appears in *Am J Gastroenterol*. 2017 Sep;112(9):1484]. *Am J Gastroenterol*. 2017;112(7):988–1013.
82. Futagami S, Yamawaki H, Agawa S, et al. New classification Rome IV functional dyspepsia and subtypes. *Transl Gastroenterol Hepatol*. 2018;3(70):1–3.

83. Aziz I, Palsson OS, Törnblom H, Sperber AD, Whitehead WE, Simrén M. Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study. *Lancet Gastroenterol Hepatol*. 2018;3(4):252–262.
84. Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders [published correction appears in *Gastroenterology*. 2006 Jul;131(1):336]. *Gastroenterology*. 2006;130(5):1466–1479.
85. Talley NJ; American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology*. 2005;129(5):1753–1755.
86. Harmon RC, Peura DA. Evaluation and management of dyspepsia. *Therap Adv Gastroenterol*. 2010;3(2):87–98.
87. Camilleri M, Tack JF. Current medical treatments of dyspepsia and irritable bowel syndrome. *Gastroenterol Clin North Am*. 2010;39(3):481–493.
88. Barton PM, Moayyedi P, Talley NJ, Vakil NB, Delaney BC. A second-order simulation model of the cost-effectiveness of managing dyspepsia in the United States. *Med Decis Making*. 2008;28(1):44–55.
89. Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? *JAMA*. 2006;295(13):1566–1576.
90. Talley NJ, Lauritsen K. The potential role of acid suppression in functional dyspepsia: the BOND, OPERA, PILOT, and ENCORE studies. *Gut*. 2002;50(suppl 4):iv36–iv41.
91. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev*. 2006;(4):CD001960.
92. Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. *Gastroenterology*. 2004;127(5):1329–1337.
93. Ingram RJ, Ragunath K, Atherton JC. Peptic ulcer disease. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:1032–1077.
94. Washington MK, Peek RM. Gastritis and gastropathy. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:1103–1120.
95. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2017;112(2):212–239.
96. Ford AC, Axon AT. Epidemiology of *Helicobacter pylori* infection and public health implications. *Helicobacter*. 2010;15(suppl 1):1–6.
97. El-Omar EM, McLean MH. Tumors of the stomach. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:1121–1140.

98. Selgrad M, Bornschein J, Rokkas T, Malfertheiner P. Clinical aspects of gastric cancer and *Helicobacter pylori*—screening, prevention, and treatment. *Helicobacter*. 2010;15(suppl 1):40–45.
99. Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of *Helicobacter pylori* infection. *Helicobacter*. 2014;19:1–5.
100. Figura N, Franceschi F, Santucci A, Bernardini G, Gasbarrini G, Gasbarrini A. Extragastric manifestations of *Helicobacter pylori* infection. *Helicobacter*. 2010;15(suppl 1):60–68.
101. Scarpignato C, Hunt RH. Nonsteroidal anti-inflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis and prevention. *Gastroenterol Clin North Am*. 2010;39(3):433–464.
102. Lanza FL, Chan FK, Quigley EM. Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104(3):728–738.
103. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet*. 2009;374(9699):1449–1461.
104. Lanas A, Sopeña F. Nonsteroidal anti-inflammatory drugs and lower gastrointestinal complications. *Gastroenterol Clin North Am*. 2009;38(2):333–352.
105. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology*. 2001;120(3):594–606.
106. Fine M. Quantifying the impact of NSAID-associated adverse events. *Am J Manag Care*. 2013;19(14 suppl):S267–S272.
107. Costa AC, Figeuiredo C, Touati E. Pathogenesis of *Helicobacter pylori* infection. *Helicobacter*. 2009;14(suppl 1):15–20.
108. Chan FK, Abraham NS, Scheiman JM, Laine L. Management of patients on nonsteroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. *Am J Gastroenterol*. 2008;103(11):2908–2918.
109. Naesdal J, Brown K. NSAID-associated adverse effects and acid control aids to prevent them: a review of current treatment options. *Drug Saf*. 2006;29(2):119–132.
110. García Rodríguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. *Gastroenterology*. 2007;132(2):498–506.
111. Bjarnason I, Scarpignato C, Takeuchi K, Rainsford KD. Determinants of the short-term gastric damage caused by NSAIDs in man. *Aliment Pharmacol Ther*. 2007;26(1):95–106.
112. Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet*. 1996;348(9039):1413–1416.

113. Cryer B. Management of patients with high gastrointestinal risk on antiplatelet therapy. *Gastroenterol Clin North Am*. 2009;38(2):289–303.
114. Thai A, Leung JW. Endoscopic diagnosis and treatment of nonvariceal upper gastrointestinal hemorrhage. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:2664–2677.
115. Calvet X, Lehours P, Lario S, Mégraud F. Diagnosis of *Helicobacter pylori* infection. *Helicobacter*. 2010;15(suppl 1):7–13.
116. Gisbert JP, Abraira V. Accuracy of *Helicobacter pylori* diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis. *Am J Gastroenterol*. 2006;101(4):848–863.
117. Kim MN, Kim N, Lee SH, et al. The effects of probiotics on PPI-triple therapy for *Helicobacter pylori* eradication. *Helicobacter*. 2008;13(4):261–268.
118. Zou J, Dong J, Yu X. Meta-analysis: lactobacillus containing quadruple therapy versus standard triple first-line therapy for *Helicobacter pylori* eradication. *Helicobacter*. 2009;14(5):97–107.
119. Zou J, Dong J, Yu XF. Meta-analysis: the effect of supplementation with lactoferrin on eradication rates and adverse events during *Helicobacter pylori* eradication therapy. *Helicobacter*. 2009;14(2):119–127.
120. Wang Z-H, Gao Q-Y, Fang J-Y. Meta-analysis of the efficacy and safety of lactobacillus-containing and bifidobacterium-containing probiotic compound preparation in *Helicobacter pylori* eradication therapy. *J Clin Gastroenterol*. 2013;47(1):25–32.
121. Zhang M-M. Probiotics in *Helicobacter pylori* eradication therapy: a systematic review and meta-analysis. *World J Gastroenterol*. 2015;21(14):4345–4357.
122. Malfertheiner P, Megraud F, O'morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence Consensus Report. *Gut*. 2012;61(5):646–664.
123. O'Connor A, Gisbert JP, McNamara D, O'Morain C. Treatment of *Helicobacter pylori* infection 2010. *Helicobacter*. 2010;15(suppl 1):46–52.
124. Gisbert JP, Calvet X, O'Connor A, Mégraud F, O'Morain CA. Sequential therapy for *Helicobacter pylori* eradication: a critical review. *J Clin Gastroenterol*. 2010;44(5):313–325.
125. Moaayyedi P, Malfertheiner P. Editorial: sequential therapy for eradication of *Helicobacter pylori*: a new guiding light or a false dawn? *Am J Gastroenterol*. 2009;104(12):3081–3083.
126. Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. *BMJ*. 2013;347:f4587.
127. Graham DY, Fischback L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut*. 2010;59(8):1143–1153.
128. Li B-Z, Threapleton DE, Wang J-Y, et al. Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: systematic review and

network meta-analysis. *BMJ*. 2015;351:h4052.
129. Vallve M, Vergara M, Gisbert JP, Calvet X. Single vs. double dose of a proton pump inhibitor in triple therapy for *Helicobacter pylori* eradication: a meta-analysis. *Aliment Pharmacol Ther*. 2002;16(6):1149–1156.
130. Janssen MJ, Laheij RJ, de Boer WA, Jansen JB. Meta-analysis: the influence of pretreatment with a proton pump inhibitor on *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2005;21(4):341–345.
131. Luther J, Higgins PD, Schoenfeld PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs. triple therapy for primary treatment of *Helicobacter pylori* infection: systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol*. 2010;105(1):65–73.
132. Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. *Ann Intern Med*. 2008;148(12):923–931.
133. Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. *Am J Gastroenterol*. 2009;104(12):3069–3079.
134. Paoluzi OA, Visconti E, Andrei F, et al. Ten and eight-day sequential therapy in comparison to standard triple therapy for eradicating *Helicobacter pylori* infection: a randomized controlled study on efficacy and tolerability. *J Clin Gastroenterol*. 2010;44(4):261–266.
135. Furuta T, Graham DY. Pharmacologic aspects of eradication therapy for *Helicobacter pylori* infection. *Gastroenterol Clin North Am*. 2010;39(3):465–480.
136. Gisbert JP, Gisbert JL, Marcos S, Olivares D, Pajares JM. *Helicobacter pylori* first-line treatment and rescue options in patients allergic to penicillin. *Aliment Pharmacol Ther*. 2005;22(10):1041–1046.
137. Gisbert JP, Pérez-Aisa A, Castro-Fernβndez M, et al. *Helicobacter pylori* first-line treatment and rescue option containing levofloxacin in patients allergic to penicillin. *Dig Liver Dis*. 2010;42(4):287–290.
138. Suzuki T, Matsuo K, Sawaki A, et al. Systematic review and meta-analysis: importance of CagA status for successful eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2006;24(2):273–280.
139. Padol S, Yuan Y, Thabane M, Padol IT, Hunt RH. The effect of CYP2C19 polymorphisms on *H. pylori* eradication rate in dual and triple first-line PPI therapies: a meta-analysis. *Am J Gastroenterol*. 2006;101(7):1467–1475.
140. Gisbert JP. Second-line rescue therapy of *Helicobacter pylori* infection. *Therap Adv Gastroenterol*. 2009;2(6):331–356.
141. Napolitano L. Refractory peptic ulcer disease. *Gastroenterol Clin North Am*. 2009;38(2):267–288.
142. Marin AC, Mcnicholl AG, Gisbert JP. A review of rescue regimens after clarithromycin-containing triple therapy failure (for *Helicobacter pylori*

eradication). *Expert Opin Pharmacother*. 2013;14(7):843–861.
143. Vonkeman H, Meek I, van de Laar M. Risk management of risk management: combining proton pump inhibitors with low-dose aspirin. *Drug Healthc Patient Saf*. 2010;2:191–204.
144. Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *Am J Gastroenterol*. 2009;104(6):1475–1482.
145. Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry*. 2010;71(12):1565–1575.
146. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med*. 2018;379(16):1519–1528.
7Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;392(10152):1036–1046.
148. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines [published correction appears in *J Am Coll Cardiol*. 2019 Sep 10;74(10):1429–1430] [published correction appears in *J Am Coll Cardiol*. 2020 Feb 25;75(7):840]. *J Am Coll Cardiol*. 2019;74(10):e177–e232.
149. Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med*. 2010;152(1):1–9.
150. Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9684):119–125.
151. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med*. 2000;343(21):1520–1528.
152. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA*. 2000;284(10):1247–1255.
153. U.S. Food & Drug Administration. COX-2 selective (includes Bextra, Celebrex, and Vioxx) and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). Accessed Feb 28, 2022. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/cox-2-selective-includes-bextra-celebrex-and-vioxx-and-non-selective-non-steroidal-anti-inflammatory
154. White WB. Cardiovascular effects of the cyclooxygenase inhibitors. *Hypertension*. 2007;49(3):408–418.

155. Abraham NS, El-Serag HB, Hartman C, Richardson P, Deswal A. Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident. *Aliment Pharmacol Ther*. 2007;25(8):913–924.
156. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial [published correction appears in *N Engl J Med*. 2006 Jul 13;355(2):221]. *N Engl J Med*. 2005;352(11):1092–1102.
157. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375(26):2519–2529.
158. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med*. 2006;355(9):873–884.
159. Reed GW, Abdallah MS, Shao M, et al. Effect of aspirin coadministration on the safety of celecoxib, naproxen, or ibuprofen. *J Am Coll Cardiol*. 2018;71(16):1741–1751.
160. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ*. 2005;330(7504):1366–1373.
161. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet*. 2005;365(9458):475–481.
162. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332(7553):1302–1308.
163. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115(12):1634–1642.
164. Chan FK, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial [published correction appears in *Lancet*. 2011 Jul 16;378(9787):228]. *Lancet*. 2010;376(9736):173–179.
165. Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet*. 2007;369(9573):1621–1626.
166. van Soest EM, Sturkenboom MC, Dieleman JP, Verhamme KM, Siersema PD, Kuipers EJ. Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal ulcers and haemorrhage. *Aliment Pharmacol Ther*. 2007;26(2):265–275.

167. Jenson R. Zollinger-Ellison syndrome. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016.
168. Roman S, Pandolfino JE, Kahrilas PJ. Gastroesophageal reflux disease. In: Yamada T, et al, eds. *Textbook of Gastroenterology*. 6th ed. Wiley-Blackwell; 2016:906–928.
169. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. *Lancet*. 2006;367(9528):2086–2100.
170. Armstrong D, Sifrim D. New pharmacologic approaches in gastroesophageal reflux disease. *Gastroenterol Clin North Am*. 2010;39(3):393–418.
171. Storr M, Meining A. Pharmacologic management and treatment of gastroesophageal reflux disease. *Dis Esophagus*. 2004;17(3):197–204.
172. Camilleri M, Dubois D, Coulie B, et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. *Clin Gastroenterol Hepatol*. 2005;3(6):543–552.
173. DeVault KR. Review article: the role of acid suppression in patients with non-erosive reflux disease or functional heartburn. *Aliment Pharmacol Ther*. 2006;23(suppl 1):33–39.
174. Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*. 1997;112(5):1448–1456.
175. El-Serag HB, Gilger M, Carter J, Genta RM, Rabeneck L. Childhood GERD is a risk factor for GERD in adolescents and young adults. *Am J Gastroenterol*. 2004;99(5):806–812.
176. Nelson SP, Kothari S, Wu EQ, Beaulieu N, McHale JM, Dabbous OH. Pediatric gastroesophageal reflux disease and acid-related conditions: trends in incidence of diagnosis and acid suppression therapy. *J Med Econ*. 2009;12(4):348–355.
177. Chatila AT, Nguyen MTT, Krill T, Roark R, Bilal M, Reep G. Natural history, pathophysiology and evaluation of gastroesophageal reflux disease. *Dis Mon*. 2020;66(1):100848.
178. Olans LB, Wolf JL. Gastroesophageal reflux in pregnancy. *Gastrointest Endosc Clin N Am*. 1994;4(4):699–712.
179. Richter JE. Review article: the management of heartburn in pregnancy. *Aliment Pharmacol Ther*. 2005;22(9):749–757.
180. Fock KM, Poh CH. Gastroesophageal reflux disease. *J Gastroenterol*. 2010;45(8):808–815.
181. Benamouzig R, Airinei G. Diet and reflux. *J Clin Gastroenterol*. 2007;41:S64–S71.
182. Dent J, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. *Gut*. 1988;29(8):1020–1028.

183. Orlando RC. Pathophysiology of gastroesophageal reflux disease. *J Clin Gastroenterol*. 2008;42(5):584–588.
184. Kahrilas PJ. GERD pathogenesis, pathophysiology, and clinical manifestations. *Cleve Clin J Med*. 2003;70(suppl 5):S4–S19.
185. Pilotto A, Franceschi M, Leandro G, et al. Clinical features of reflux esophagitis in older people: a study of 840 consecutive patients. *J Am Geriatr Soc*. 2006;54(10):1537–1542.
186. Sharma P. Clinical practice. Barrett's esophagus [published correction appears in *N Engl J Med*. 2010 Apr 15;362(15):1450]. *N Engl J Med*. 2009;361(26):2548–2556.
187. Westhoff B, Brotze S, Weston A, et al. The frequency of Barrett's esophagus in high-risk patients with chronic GERD. *Gastrointest Endosc*. 2005;61(2):226–231.
188. Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med*. 2008;359(16):1700–1707.
189. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med*. 2006;166(9):965–971.
190. El-Serag HB, Kvapil P, Hacken-Bitar J, Kramer JR. Abdominal obesity and the risk of Barrett's esophagus. *Am J Gastroenterol*. 2005;100(10):2151–2156.
191. Tytgat GN. Review article: treatment of mild and severe cases of GERD. *Aliment Pharmacol Ther*. 2002;16(suppl 4):73–78.
192. Tytgat GN, McColl K, Tack J, et al. New algorithm for the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2008;27(3):249–256.
193. Haag S, Andrews JM, Katelaris PH, et al. Management of reflux symptoms with over-the-counter proton pump inhibitors: issues and proposed guidelines. *Digestion*. 2009;80(4):226–234.
194. Komazawa Y, Adachi K, Mihara T, et al. Tolerance to famotidine and ranitidine treatment after 14 days of administration in healthy subjects without *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2003;18(6):678–682.
5. Numans ME, Lau J, de Wit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. *Ann Intern Med*. 2004;140(7):518–527.
196. Vakil N. Review article: how valuable are proton-pump inhibitors in establishing a diagnosis of gastro-oesophageal reflux disease? *Aliment Pharmacol Ther*. 2005;22(suppl 1):64–69.
197. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut*. 1999;45(2):172–180.
198. Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. *Gastroenterology*.

1996;110(6):1982–1996.
199. Rice TW, Blackstone EH. Surgical management of gastroesophageal reflux disease. *Gastroenterol Clin North Am*. 2008;37(4):901–919.
200. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology*. 1997;112(6):1798–1810.
201. Hunt RH. Importance of pH control in the management of GERD. *Arch Intern Med*. 1999;159(7):649–657.
202. Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol*. 2001;96(3):656–665.
203. Sharma P, Shaheen NJ, Perez MC, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation—results from two randomized controlled studies. *Aliment Pharmacol Ther*. 2009;29(7):731–741.
204. Wang KK, Sampliner RE; Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol*. 2008;103(3):788–797.
205. Falk GW. Barrett's esophagus. *Gastroenterology*. 2002;122(6):1569–1591.
206. Richter JE, Sabesin SM, Kogut DG, Kerr RM, Wruble LD, Collen MJ. Omeprazole versus ranitidine or ranitidine/metoclopramide in poorly responsive symptomatic gastroesophageal reflux disease. *Am J Gastroenterol*. 1996;91(9):1766–1772.
207. Pace F, Tonini M, Pallotta S, Molteni P, Porro GB. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken "on-demand". *Aliment Pharmacol Ther*. 2007;26(2):195–204.
208. Bytzer P, Blum A, De Herdt D, Dubois D, Trial Investigators. Six-month trial of on-demand rabeprazole 10 mg maintains symptom relief in patients with non-erosive reflux disease. *Aliment Pharmacol Ther*. 2004;20(2):181–188.
209. Talley NJ, Venables TL, Green JR, et al. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative gastro-oesophageal reflux disease: a placebo-controlled trial of on-demand therapy for 6 months. *Eur J Gastroenterol Hepatol*. 2002;14(8):857–863.
210. Scholten T, Dekkers CP, Schütze K, Körner T, Bohuschke M, Gatz G. On-demand therapy with pantoprazole 20 mg as effective long-term management of reflux disease in patients with mild GERD: the ORION trial. *Digestion*. 2005;72(2–3):76–85.
211. Bigard MA, Genestin E. Treatment of patients with heartburn without endoscopic evaluation: on-demand treatment after effective continuous

administration of lansoprazole 15 mg. *Aliment Pharmacol Ther*. 2005;22(7):635–643.
212. Sjöstedt S, Befrits R, Sylvan A, et al. Daily treatment with esomeprazole is superior to that taken on-demand for maintenance of healed erosive oesophagitis. *Aliment Pharmacol Ther*. 2005;22(3):183–191.
213. Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects. *Gastroenterology*. 1998;115(6):1335–1339.
214. Richter JE. Review article: extraoesophageal manifestations of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2005;22(suppl 1):70–80.
215. Oranu AC, Vaezi MF. Noncardiac chest pain: gastroesophageal reflux disease. *Med Clin North Am*. 2010;94(2):233–242.
216. Hirano I, Richter JE. ACG practice guidelines: esophageal reflux testing. *Am J Gastroenterol*. 2007;102(3):668–685.
217. Parsons JP, Mastronarde JG. Gastroesophageal reflux disease and asthma. *Curr Opin Pulm Med*. 2010;16(1):60–63.
218. Mansfield LE, Hameister HH, Spaulding HS, Smith NJ, Glab N. The role of the vague nerve in airway narrowing caused by intraesophageal hydrochloric acid provocation and esophageal distention. *Ann Allergy*. 1981;47(6):431–434.
219. Moore JM, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease: real or imagined? *Curr Opin Gastroenterol*. 2010;26(4):389–394.
220. Bretza J, Novey HS. Gastroesophageal reflux and asthma. *West J Med*. 1979;131(4):320.
221. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. *Gut*. 2007;56(12):1654–1664.
222. Field SK, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux?: a critical review of the literature. *Chest*. 1998;114(1):275–283.
223. Chan WW, Chiou E, Obstein KL, Tignor AS, Whitlock TL. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. *Arch Intern Med*. 2011;171(7):620–629.
224. American Lung Association Asthma Clinical Research Centers, Mastronarde JG, Anthonisen NR, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med*. 2009;360(15):1487–1499.
225. Richter JE. Ear, nose and throat and respiratory manifestations of gastro-esophageal reflux disease: an increasing conundrum. *Eur J Gastroenterol Hepatol*. 2004;16(9):837–845.
226. Klinkenberg-Knol EC. Otolaryngologic manifestations of gastro-oesophageal reflux disease. *Scand J Gastroenterol Suppl*. 1998;225:24–28.

227. Wong RK, Hanson DG, Waring PJ, Shaw G. ENT manifestations of gastroesophageal reflux. *Am J Gastroenterol*. 2000;95(8 suppl):S15–S22.
228. Kamel PL, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis. *Am J Med*. 1994;96(4):321–326.
229. Barkun AN, Almadi M, Kuipers EJ, et al. Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the international consensus group. *Ann Intern Med*. 2019;171(11):805–822.
230. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. *N Engl J Med*. 2008;359(9):928–937.
231. Imperiale TF, Dominitz JA, Provenzale DT, et al. Predicting poor outcome from acute upper gastrointestinal hemorrhage. *Arch Intern Med*. 2007;167(12):1291–1296.
232. Chiu PW, Ng EK. Predicting poor outcome from acute upper gastrointestinal hemorrhage. *Gastroenterol Clin North Am*. 2009;38(2):215–230.
233. Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. *Chest*. 2001;119(4):1222–1241.
234. Fennerty MB. Pathophysiology of the upper gastrointestinal tract in the critically ill patient: rationale for the therapeutic benefits of acid suppression. *Crit Care Med*. 2002;30(6 suppl):S351–S355.
235. Cook D, Guyatt G. Prophylaxis against upper gastrointestinal bleeding in hospitalized patients. *N Engl J Med*. 2018;378(26):2506–2516.
236. Laine L, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol*. 2012;107(8):1190–1196.
237. van Leerdam ME. Epidemiology of acute upper gastrointestinal bleeding. *Best Pract Res Clin Gastroenterol*. 2008;22(2):209–224.
238. Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med*. 1994;331(11):717–727.
239. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012;107(3):345–360.
240. Devlin JW, Welage LS, Olsen KM. Proton pump inhibitor formulary considerations in the acutely ill. Part 2: clinical efficacy, safety, and economics. *Ann Pharmacother*. 2005;39(11):1844–1851.
241. Elmunzer BJ, Inadomi JM, Elta GH. Risk stratification in upper gastrointestinal bleeding. *J Clin Gastroenterol*. 2007;41(6):559–563.
242. Pisegna JR. Treating patients with acute gastrointestinal bleeding or rebleeding. *Pharmacotherapy*. 2003;23(10 Pt 2):81S–86S.
243. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: cochrane collaboration meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2007;82(3):286–296.
244. Leontiadis GI, Sharma VK, Howden CW. WITHDRAWN: proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev*. 2010;(5):CD002094.

245. Bardou M, Toubouti Y, Benhaberou-Brun D, Rahme E, Barkun AN. Meta-analysis: proton-pump inhibition in high-risk patients with acute peptic ulcer bleeding. *Aliment Pharmacol Ther*. 2005;21(6):677–686.
246. Lau JY, Leung WK, Wu JC, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med*. 2007;356(16):1631–1640.
247. Sung JJ, Chan FK, Lau JY, et al. The effect of endoscopic therapy in patients receiving omeprazole for bleeding ulcers with nonbleeding visible vessels or adherent clots: a randomized comparison. *Ann Intern Med*. 2003;139(4):237–243.
248. Leontiadis GI, Howden CW. Pharmacologic treatment of peptic ulcer bleeding. *Curr Treat Options Gastroenterol*. 2007;10(2):134–142.
249. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. *JAMA Intern Med*. 2014;174(11):1755–1762.
250. Leontiadis GI, Sharma VK, Howden CW. Systematic review and meta-analysis: proton-pump inhibitor treatment for ulcer bleeding reduces transfusion requirements and hospital stay—results from the Cochrane Collaboration. *Aliment Pharmacol Ther*. 2005;22(3):169–174.
251. Ali T, Harty RF. Stress-induced ulcer bleeding in critically ill patients. *Gastroenterol Clin North Am*. 2009;38(2):245–265.
252. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. *Am J Health Syst Pharm*. 1999;56(4):347–379.
253. Stollman N, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *J Crit Care*. 2005;20(1):35–45.
254. Jung R, MacLaren R. Proton-pump inhibitors for stress ulcer prophylaxis in critically ill patients. *Ann Pharmacother*. 2002;36(12):1929–1937.
255. Wei KL, Tung SY, Sheen CH, Chang TS, Lee IL, Wu CS. Effect of oral esomeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *J Gastroenterol Hepatol*. 2007;22(1):43–46.
256. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*. 2018;379(23):2199–2208.
257. Buckley MS, Park AS, Anderson CS, et al. Impact of a clinical pharmacist stress ulcer prophylaxis management program on inappropriate use in hospitalized patients. *Am J Med*. 2015;128(8):905–913.
258. Marik PE, Vasu T, Hirani A, Pachinburavan M. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med*. 2010;38(11):2222–2228.
259. Tryba M. Risk of acute stress bleeding and nosocomial pneumonia in ventilated intensive care unit patients: sucralfate versus antacids. *Am J Med*. 1987;83(3B):117–124.
260. Bresalier RS, Grendell JH, Cello JP, Meyer AA. Sucralfate suspension versus titrated antacid for the prevention of acute stress-related

gastrointestinal hemorrhage in critically ill patients. *Am J Med*. 1987;83(3B):110–116.

261. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med*. 1998;338(12):791–797.
262. Daley RJ, Rebuck JA, Welage LS, Rogers FB. Prevention of stress ulceration: current trends in critical care. *Crit Care Med*. 2004;32(10):2008–2013.
263. Lam NP, Lê PD, Crawford SY, Patel S. National survey of stress ulcer prophylaxis. *Crit Care Med*. 1999;27(1):98–103.
264. Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA*. 1996;275(4):308–314.
265. Messori A, Trippoli S, Vaiani M, Gorini M, Corrado A. Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ*. 2000;321(7269):1103–1106.
266. Alhazzani W, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Crit Care Med*. 2013;41(3):693–705.
267. Bateman BT, Bykov K, Choudhry NK, et al. Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. *BMJ*. 2013;347:f5416.
268. Conrad SA, Gabrielli A, Margolis B, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Crit Care Med*. 2005;33(4):760–765.
269. Somberg L, Morris J Jr, Fantus R, et al. Intermittent intravenous pantoprazole and continuous cimetidine infusion: effect on gastric pH control in critically ill patients at risk of developing stress-related mucosal disease. *J Trauma*. 2008;64(5):1202–1210.
270. Miano TA, Reichert MG, Houle TT, MacGregor DA, Kincaid EH, Bowton DL. Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs ranitidine in cardiothoracic surgery patients. *Chest*. 2009;136(2):440–447.
271. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected] [published correction appears in *Am J Gastroenterol*. 2009;104(4):1072] [published correction appears in *Am J Gastroenterol*. 2009;104(2 suppl):S39]. *Am J Gastroenterol*. 2009;104(suppl 2):S27–S32.
272. Erstad BL, Barletta JF, Jacobi J, Killian AD, Kramer KM, Martin SJ. Survey of stress ulcer prophylaxis. *Crit Care*. 1999;3(6):145–149.

24

Lower Gastrointestinal Disorders

Charmaine Rochester-Eyeguokan, Divita Singh, and Abigail Klutts

CORE PRINCIPLES	CHAPTER CASES
INFLAMMATORY BOWEL DISEASE	
1 Inflammatory bowel disease (IBD) is a generic classification for a group of chronic, idiopathic, relapsing inflammatory disorders of the gastrointestinal tract. Symptoms of IBD are thought to result from dysregulation of the mucosal immune system. By convention, IBD is divided into two major disorders, ulcerative colitis (UC) and Crohn disease (CD).	**Case 24-1(Question 1)** **Case 24-2 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
2	UC is a continuous, superficial mucosal disease isolated to the colon, whereas CD presents in patches, or “skip lesions,” anywhere from the mouth to anus, but more commonly localized to the ileum and large intestine. Extraintestinal manifestations and complications requiring surgery are more common in CD than in UC.	**Case 24-1 (Question 1)** **Case 24-2 (Question 1)**
3	Treatment for both UC and CD are divided into either induction treatment, which controls symptoms, or maintenance treatment, which prevents recurrences. Therapy selection depends on disease severity, location, medication safety profile, cost, and failed or intolerable treatments.	**Case 24-1 (Questions 2, 4, 5, and 8)** **Case 24-2 (Questions 2–6)**
4	Topical 5-aminosalicylic acid (5-ASA) agents, mesalamine and sulfasalazine, are effective for induction and maintenance of mild UC, confined to the rectum (proctitis), or distal colon. They have proved ineffective for CD, but oral sulfasalazine may be used for mild-to-moderate CD with colonic involvement.	**Case 24-1 (Questions 6 and 10)** **Case 24-2 (Question 2)**

CORE PRINCIPLES		CHAPTER CASES
5	Corticosteroids can be used for induction in CD and UC. However, long-term use for maintenance of remission is associated with well-known risks, so alternative therapy is recommended. In no particular order, maintenance therapies for CD include azathioprine, mercaptopurine, methotrexate, adalimumab, certolizumab, infliximab, natalizumab, vedolizumab, and ustekinumab. Maintenance therapies for UC include sulfasalazine, mesalamine, olsalazine, balsalazide, azathioprine, mercaptopurine, infliximab, adalimumab, golimumab, vedolizumab, and tofacitinib.	**Case 24-1 (Questions 3, 7, 9–11)** **Case 24-2 (Questions 3 and 4)**
6	All immunosuppressive medications increase infection risk; therefore, it is necessary to screen for infection before, during, and following discontinuation. Active infections should be treated before starting immunosuppressive therapy. Individuals who need live vaccines should receive them before starting immunosuppressive therapy.	**Case 24-1 (Question 12)** **Case 24-2 (Questions 4–6)**
7	Therapeutic approaches to IBD are rapidly evolving with the advent of biosimilars and novel small-molecule agents, many of which are currently under investigation.	**Case 24-2 (Questions 2 and 3)**

CORE PRINCIPLES		CHAPTER CASES
IRRITABLE BOWEL SYNDROME		
1	Irritable bowel syndrome (IBS) is a common and often debilitating condition that involves abdominal pain, bloating, and defecation associated with a change in bowel habits (usually constipation or diarrhea). Clinicians should reassure patients that the diagnosis is correct, and the condition is benign and treatable.	**Case 24-3 (Questions 1 and 2)**
2	Nonpharmacologic interventions target stress relief and lifestyle modifications. These include patient reassurance, creating a strong physician–patient relationship, improving sleep habits, increasing exercise, and subscribing to a low-FODMAP diet (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols). Psychological interventions can reduce overall symptom burden and should be considered early in IBS management.	**Case 24-3 (Questions 3 and 4)**
3	The treatment goal of IBS management is to improve the predominant symptom type and severity. Treatments for irritable bowel syndrome with constipation (IBS-C) include soluble fiber (psyllium), polyethylene glycol (PEG) laxatives, linaclotide, plecanatide, lubiprostone, tenapanor, and tegaserod.	**Case 24-3 (Question 5)**

CORE PRINCIPLES		CHAPTER CASES
4	Abdominal pain, bloating, or visceral hypersensitivity associated with IBS may respond to antispasmodic agents or tricyclic antidepressants, but the use of selective serotonin-reuptake inhibitors is not recommended.	**Case 24-4 (Question 1)**
5	Treatments for irritable bowel syndrome with diarrhea (IBS-D) include loperamide, eluxadoline, rifaximin, and alosetron. Retreatment with rifaximin in patients who relapsed after initial response is strongly recommended.	**Case 24-4 (Question 2)**

INTRODUCTION

Definition of Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a nonspecific classification for a group of chronic, idiopathic, noninfectious, relapsing inflammatory disorders of the gastrointestinal (GI) tract. By convention, IBD is divided into two major disorders: ulcerative colitis (UC) and Crohn disease (CD).[1–3]

Epidemiology

The incidence of IBD is increasing globally, particularly among high-income countries and in urban areas.[1-,2,4,5] An estimated 6.8 million people have IBD worldwide,[4] and 3.1 million cases are attributed to the United States, where prevalence is highest.[6] Approximately 10% of patients with IBD are classified as having indeterminate colitis

because they do not present with the distinct clinical features of UC or CD.[7] There is a greater prevalence of IBD among females and Caucasians.[1–4,8] Both UC and CD are considered diseases of the young, with peak incidence from ages 15 to 30 years.[2,5]

Pathophysiology

Under normal conditions, the mucosal immune system interacts with luminal antigens and mucosal bacteria on a continuous basis to maintain a state of controlled inflammation. In IBD, genetic predisposition leads to immune response dysfunction. Proinflammatory cytokines in the gut trigger an "attack" on the colonic mucosa by leukocytes and other factors, leading to edema, ulceration, and destruction of the tissue. Normal immune regulators do not halt this process, and the disease progresses. This can be attributable to a lack of regulatory or suppressor cells, an enhanced numbers of T cells, or both.[9] Studies have demonstrated that an increase of proinflammatory cytokines, chemokines, prostaglandin, and reactive oxygen species leads to increased inflammation and tissue destruction.[1]

IBD has an unclear etiology, but hypotheses include a combination of genetic abnormalities, chronic infection, environmental factors (bacterial, viral, temperate climate, prior appendectomy, and dietary antigens), host or intestinal microbiome interactions, and other abnormalities of immunoregulatory mechanisms.[1] Symptoms result from dysregulation of the mucosal immune system and from an interplay between genetic expression and the environment.[2,10–13]

Several environmental exposures have been associated with IBD. Smoking has been the most consistently studied environmental factor associated with IBD, with smokers having a decreased risk of developing UC but an increased risk of developing CD.[14] The theory of an infectious etiology for IBD remains controversial. Patients may be genetically predisposed to mucosal immune dysregulation, and either normal flora or bacterial pathogens may trigger the inflammatory response that leads to IBD.[15–20] Finally, dietary habits

are thought to play a role in the composition of gut flora and inflammation, particularly with high intake of inflammatory foods such as red meat and highly processed, fatty, or sugary foods.[13] Although no clear causal relationship has yet been established, further investigation on the role of gut flora is ongoing.[21]

Clinical Presentation

A careful patient history, physical examination, and endoscopic and radiologic findings are necessary to diagnose and assess IBD. Blood tests and stool examination help exclude other causes linked to infection, allergies and intolerances, or irritable bowel syndrome (IBS). Erythrocyte sedimentation rate (ESR), fecal calprotectin, and C-reactive protein (CRP) can also aid in the diagnosis, but no single marker is pathognomonic.[22],-[23] Endoscopy is particularly useful to understand the extent of the disease and to differentiate between UC and CD.[24]

Extraintestinal manifestations of IBD can cause significant morbidity and include reactive arthritis, uveitis, ankylosing spondylitis, pyoderma gangrenosum, and primary sclerosing cholangitis. Although their incidence varies, many of the extraintestinal manifestations of UC and CD are similar.[23] Other pathophysiologic similarities and differences are outlined in **Table 24-1**.

Table 24-1
Pathophysiologic Differences Between Ulcerative Colitis and Crohn Disease

Characteristic	Ulcerative Colitis	Crohn Disease
Incidence (per 100,000 person years)	19.2	20.2
Anatomic location	Colon and rectum	Mouth to anus
Distribution	Continuous, superficial, diffuse, mucosal	Segmental, focal, transmural

Characteristic	Ulcerative Colitis	Crohn Disease
Bowel wall	Shortened, loss of haustral markings, generally not thickened	Rigid, thick, edematous, and fibrotic
Gross rectal bleeding	Common	Infrequent
Crypt abscesses	Common	Infrequent
Fissuring with sinus formation	Absent	Common
Noncaseating granulomas	Absent	Common
Strictures	Absent	Common
Abdominal mass	Absent	Common
Abdominal pain	Infrequent	Common
Toxic megacolon	Occasional	Rare
Bowel carcinoma	Greatly increased	Slightly increased
Fistulas	Absent	Advanced complication

Sources: Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361(21):2066–2078. doi:10.1056/NEJMra0804647; Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384–413; Bernstein CN, Eliakim A, Fedail S, et al. World Gastroenterology Organization Global Guidelines inflammatory bowel disease: update August 2015. *J Clin Gastroenterol*. 2016;50(10):803–818; Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in *Am J Gastroenterol*. 2018;113(7):1101]. *Am J Gastroenterol*. 2018;113(4):481–517. doi:10.1038/ajg.2018.27.

ULCERATIVE COLITIS DIAGNOSIS

Patients with UC usually present with proctitis, with symptoms such as bleeding, urgency, tenesmus (urge to defecate), and abdominal pain. The disease cycles between relapsing and remitting, with periods of remission. The inflammation is limited to the mucosa, which presents as friable, granular, and erythematous, with or without ulceration. Despite medical therapy, some patients experience a rapid onset of a progressive type of colitis known as

fulminant disease.[22-,23,25] Long-standing untreated UC is associated with an increased risk of dysplasia and colorectal cancer, which is believed to be due to the chronic inflammation.[26]

After diagnosing UC, the next step is to determine disease severity (see **Table 24-2**). UC activity can be categorized as remission, mild, moderately severe, or fulminant.[22] Acute severe UC is defined in the guidelines as six or more bowel movements a day in the presence of at least one of the following systemic signs of toxicity: tachycardia, fever, anemia (hemoglobin [Hgb] <10.5 g/dL), or elevated inflammatory markers (ESR > 30 mm/hour).[22] Proctitis is usually considered a separate type of UC in which treatment is occasionally needed for constipation.

Table 24-2

Ulcerative Colitis Severity Classification

	Remission	Mild	Moderate-to-Severe	Fulminant
Stools (number/day)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
Erythrocyte sedimentation rate	<30	<30	>30	>30
C-reactive protein (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (μg/g)	<150–200	>150–200	>150–200	>150–200
Endoscopy (Mayo subscore)	0–1	1	2–3	3
Ulcerative Colitis Endoscopic Index of Severity	0–1	2–4	5–8	7–8

Reprinted with permission from Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384–413. © 2019 by The American College of Gastroenterology.

CROHN DISEASE DIAGNOSIS

The cardinal symptoms of CD include diarrhea, abdominal pain, and fatigue. Anemia and weight loss may occur because of slow intestinal bleeding and malabsorption, respectively. There is no single objective criterion that confirms CD diagnosis, but ileocolonoscopy is a key tool for diagnosing and assessing disease activity.[27] Classification of disease severity is included in **Table 24-3**.

Table 24-3
Crohn Disease Severity Classification

	Remission	Mild-to-Moderate	Moderate-to-Severe	Severe-to-Fulminant
Crohn's Disease Activity Index	<150	150–220	220–450	>450
Symptoms	None	May have diarrhea, abdominal pain	Intermittent nausea or vomiting, abdominal pain, or tenderness	Persistent vomiting, significant peritoneal signs such as involuntary guarding or rebound tenderness
Weight loss	None	<10%	≥10%	May be cachectic
Endoscopy		Mild, superficial erosions or ulcers (<10% of the surface area)	Moderate to severely active endoscopic mucosal disease	Severe endoscopic lesions (large >2 cm confluent and deep ulcers)
Simple Endoscopic Score for Crohn's Disease (SES-CD)		≤6	>6	
Crohn's Disease Endoscopic Index of Severity (CDEIS)	<3	≤8	>8	
Complications	None	Not present; can eat and drink without complications	Present, including fever, but no obstruction or significant anemia	Present including intestinal obstruction, anemia, intra-abdominal abscess; frequently hospitalized.
C-reactive protein (mg/L)	May be normal	Usually elevated	Elevated	Elevated
Treatment response	May have responded to medical or surgical therapy (eg, resection). Does not include patients who are steroid dependent	Responds to conventional therapy; surgery is uncommon.	Inadequate response or intolerance to conventional therapy; surgery is common.	Persistent symptoms despite aggressive therapy; surgery is most common.

Sources: Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in *Am J Gastroenterol*. 2018;113(7):1101]. *Am J Gastroenterol*. 2018;113(4):481–517. doi:10.1038/ajg.2018.27; Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110(9):1324–1338; Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14(1):4–22. doi:10.1093/ecco-jcc/jjz180.

Although UC is restricted to the colon, CD can exist anywhere along the digestive tract, but areas from the ileum to anus are more common. Unlike UC, ulcerations in CD are patchy and discontinuous, appearing as "skip lesions" with alternating areas of normal and diseased tissue. Penetrating disease is common and includes colonic ulcers, strictures, and fistulas. Abscesses or sepsis can occur because of these complications.[28,29]

As with UC, CD is also a relapsing and remitting disease, where remission involves the resolution of symptoms and objective

inflammatory markers with normalization of bowel habits.[30] An estimated 19% to 38% of individuals have evidence of penetrating disease upon diagnosis, such as enterocutaneous, enterorectal, or enterovaginal fistulae, whereas up to 88% may experience these complications within 20 years of disease.[31]

Overview of Treatment

Treatment of IBD is dependent on disease characteristics (severity, anatomic location, complications), medication characteristics (safety, effectiveness), and individual characteristics (coexisting conditions, adherence, insurance coverage, lifestyle, health literacy, therapy response, and preference). Clinicians should consider failed or intolerable treatments when selecting therapy.[22,28,32]

The goals of IBD therapy include sustained steroid-free remission, mucosal healing, prevention of complications, decreased hospitalizations, and improved quality of life with psychosocial support.[22,28,33] **Table 24-4** displays a list of medications used to treat UC and CD. Although UC and CD share common treatment options, they are often used under different circumstances. **Table 24-5** lists recommendations for pharmacologic use, according to the most recent guidelines from the American College of Gastroenterology. A comparison of aminosalicylate compounds is provided in **Table 24-6**. The treatment algorithms for UC and CD are depicted in **Figures 24-1** and **24-2**, respectively. There are several novel agents in development for IBD, some of which are already approved for other immunologic conditions, such as psoriasis, rheumatoid arthritis, or multiple sclerosis. Novel agents include biosimilars and sphingosine-1 phosphate receptor modulators.[34] Similar to Janus kinase 1, this is a signaling molecule implicated in downstream inflammatory effects. As a small-molecule drug, it is also poised to overcome barriers to biologic use, such as loss of effectiveness over time due to immunogenicity.[35,36]

Table 24-4
Pharmacologic Treatment Options for Irritable Bowel Disease

Drug Class	Mechanism of Action	Warnings	Adverse Drug Reactions	Monitoring
Aminosalicylates				
Mesalamine Enema (Rowasa®) Suppository (Canasa®) Controlled-release microspheres (Pentasa®) Multimatrix, pH-sensitive coating and delayed release (Lialda®) pH-dependent coating, dissolves at pH >7 (Asacol HD®) (Delzicol®) Polymer Matrix/enteric coating, dissolves at pH 6 (Apriso®)	Modulates local chemical mediators of the inflammatory response, especially leukotrienes A free radical scavenger and TNF inhibitor	Hepatitis Pericarditis Myocarditis Acute intolerance syndrome Photosensitivity Renal impairment Hematologic abnormalities Pneumonitis	Headache Burping Abdominal pain Constipation	Renal function CBC Hepatic function Signs and symptoms of worsening, acute intolerance syndrome
Sulfasalazine (Azulfidine®) (Sulfazine®) Oral tablet		Blood dyscrasias Neuromuscular changes Stevens–Johnson syndrome Toxic epidermal necrolysis Fibrosing alveolitis	Skin rash Nausea/vomiting Dyspepsia Anorexia	CBC with differential and liver function tests (before therapy, then every other week for first 3 months of therapy, followed by every month
		Folate deficiency Nausea/vomiting Abdominal pain Hepatic necrosis Drug rash with eosinophilia and systemic symptoms Nephritis Pneumonitis Serious infections Sulfonamide allergy	Oligospermia Headache	for the second 3 months, then once every 3 months thereafter or as clinically indicated) Periodic urinalysis and renal tests Signs of infection, dermatologic toxicity, or hypersensitivity reactions
Olsalazine (Dipentum®) Oral capsule		Colitis, diarrhea	Diarrhea Nausea Abdominal pain	CBC and hepatic function at baseline Renal function at baseline, 6 and 12 months during treatment, and annually thereafter
Balsalazide (Colazal®) Oral capsule		Colitis Acute intolerance syndrome Nephrolithiasis	Headache Abdominal pain Teeth/gum staining Nausea/vomiting	Renal function at baseline, within 6 months of initiation, then annually thereafter LFTs in patients with liver disease
Corticosteroids				
Conventional steroids Oral tablet	Decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and reversing potent inhibitors of T-cell activation and proinflammatory cytokines	Contraindications: Hypersensitivity to prednisone or any component of the formulation Administration of live or live attenuated vaccines with immunosuppressive doses of prednisone Systemic fungal infections Adrenal suppression Anaphylactoid reactions Immunosuppression Kaposi sarcoma	Hyperglycemia Dyslipidemia Hypertension Infection Osteoporosis Psychosis	Blood pressure Weight Chemistries Signs of infection BMD HPA axis suppression Leukopenia and thrombocytopenia (every 6 months when used in combination with AZA) IOP with therapy > 6 weeks Eye examination

		Myopathy Psychiatric disturbances such as euphoria, insomnia, mood swings, personality changes, severe depression, or frank psychotic manifestations		
Budesonide Controlled ileal release, time dependent and pH release ≥5.5 (Entocort EC®) (Ortikos®) Multimatrix structure with gastric acid–resistant coating, pH release ≥7 (Uceris®) Rectal foam (Uceris foam®)	Depresses the activity of endogenous chemical mediators of inflammation		As given earlier, with reduced risk of systemic effects because of local site of action and high first-pass hepatic metabolism	
Immunomodulators				
Thiopurines				
Azathioprine (Imuran®) Oral tablet	Imidazolyl derivative of mercaptopurine, metabolites are incorporated into replicating DNA and halt replication; also block the pathway for purine synthesis	**Malignancy** Leukopenia Thrombocytopenia Neoplasia Infection	Allergic reaction Pancreatitis Myelosuppression Nausea/vomiting Infection Hepatotoxicity	TPMT testing before use CBC with differential (weekly for 1 month, then twice monthly for 2 months); monthly thereafter (monitor more frequently with dosage modifications)
				Total bilirubin LFTs (every 3 months) CrCl Signs of infection and malignancy
6-Mercaptopurine (Purixan®) Oral tablet	Purine antagonist Inhibits DNA and RNA synthesis, specific for the S phase of the cell cycle	Malignancy BMS Hepatotoxicity Immunosuppression Macrophage activation syndrome Photosensitivity		CBC with differential weekly for 1 month, then every 2 weeks for 1 month, then every 1–2 months thereafter LFTs every 3 months Signs of infection and malignancy
Methotrexate (Otrexup®) (Rasuvo®) Subcutaneous injection	Folate antimetabolite that inhibits DNA synthesis, repair, and cellular replication Methotrexate targets the S phase of the cell cycle.	**Serious adverse reactions including death** **BMS** **Serious infections** **Secondary malignancy** **Tumor lysis syndrome** **Renal toxicity and increased toxicity with renal impairment** **GI toxicity** **Hepatotoxicity** **Pneumonitis Hypersensitivity dermatologic reactions** **Opportunistic infections** Increased risk of malignancy, including skin cancer and lymphoma	Pancreatitis Nausea/vomiting Hepatotoxicity Pulmonary toxicity BMS	Pregnancy: Contraindicated in pregnancy due to embryo-fetal toxicity, including fetal death

Calcineurin Inhibitor				
Cyclosporine (Gengraf®) (Neoral®) (Sandimmune®) Oral tablet	Inhibits the production and release of IL-2 and inhibits IL-2-induced activation of resting T lymphocytes	**Infections** **Immunosuppression** **Hypertension** **Nephrotoxicity** **Malignancy** **Neurotoxicity** Gingival hyperplasia Hepatotoxicity Hyperkalemia Hyperuricemia	Nausea Headache Hypertension Nephrotoxicity Edema Paresthesia Hirsutism Elevated triglycerides	Renal function Blood pressure periodically and following medication changes Signs and symptoms of: Infection Hepatotoxicity Secondary malignancy Diabetes mellitus Hypersensitivity reactions (IV) Progressive cognitive or motor deficits MRI may be required to diagnose posterior reversible encephalopathy syndrome (PRES).
Biologics				
TNF Blockers				
Adalimumab (Humira®) Subcutaneous injection Adalimumab-atto (Amjevita®) Adalimumab-adbm (Cyltezo®) Adalimumab-adaz (Hyrimoz®)	Binds to TNF-α and blocks the interaction with p55 and p75 cell-surface TNF receptors	**Serious infection leading to hospitalization or death** **Lymphoma and other malignancies, particularly in combination with thiopurines** Hepatitis B reactivation New or worsening demyelinating disease New or worsening CHF Lupus-like syndrome Hypersensitivity reaction Cytopenias	URI Headache Rash Injection site reaction	Perform test for latent TB; if positive, start treatment for TB before initiating. Monitor all patients for active TB during treatment, even if the initial latent TB test result is negative.
Certolizumab pegol (Cimzia®) Subcutaneous injection	Binds to and selectively neutralizes TNF-α to inhibit receptor binding		URI Rash UTI Injection site reaction	
Golimumab (Simponi®) Subcutaneous injection	Binds to and inhibits TNF-α		URI Nasopharyngitis Injection site reaction	
Infliximab (Remicade®) IV infusion Infliximab-axxq (Avsola®) Infliximab-dyyb (Inflectra®) Infliximab-qbtx (Ixifi®) Infliximab-abda (Renflexis®)	Binds to and selectively neutralizes TNF-α to inhibit receptor binding		URI Infusion-related reactions Headache Abdominal pain	

Anti-Integrins				
Natalizumab (Tysabri®) IV infusion	Binds to α4-subunit of αβ1 and αβ integrins to inhibit leukocyte binding to receptors	**PML** Infection Hypersensitivity reaction Hepatotoxicity	Headache Fatigue Arthralgia Pain in extremities UTI Lower respiratory infection Gastroenteritis Vaginitis Depression Abdominal discomfort Diarrhea Rash Nausea	Testing for anti-JCV before initiation and every 6 months until treatment is stopped, or the result is positive Signs and symptoms of hepatotoxicity
Vedolizumab (Entyvio®) IV infusion	Selectively binds to α4 β7 integrin to interrupt cell signaling and inhibit T-cell migration	PML cannot be ruled out. Infection Hypersensitivity reaction Hepatotoxicity	Headache Fatigue Arthralgia Pain in extremities URI Lower respiratory infection Nasopharyngitis Nausea Pyrexia Cough Back pain Rash Pruritus Sinusitis Oropharyngeal pain	Signs and symptoms of hepatotoxicity
Interleukin Antagonist				
Ustekinumab (Stelara®) IV infusion for induction Subcutaneous injection for maintenance	Selectively binds to the p40 subunit on IL-12 and IL-23 cytokines to interrupt natural killer cell and CD4+ T-cell activation	Serious infection requiring hospitalization Malignancy Hypersensitivity reaction RPLS (rare)	Vomiting Nasopharyngitis Injection site erythema Vulvovaginal candidiasis Mycotic infection Bronchitis Pruritus UTI Sinusitis	TB screen before and throughout treatment
Novel Small Molecules				
Janus Kinase Inhibitor				
Tofacitinib (Xeljanz®) Oral tablet	Inhibits JAK1 and JAK3 signaling to modulate intracellular activity like gene expression	**Serious infection requiring hospitalization** **Lymphoma and other malignancies**	Nasopharyngitis Elevated cholesterol Headache URI	Perform test for latent TB; if result is positive, start treatment for TB before initiating.
		EBV-associated post-(renal) transplant lymphoproliferative disorder, with concomitant immunosuppressive medications GI perforation	Increased blood creatinine phosphokinase Rash Diarrhea Herpes zoster	Monitor all patients for active TB during treatment, even if the initial latent TB test result is negative. Laboratory monitoring recommended to detect changes in lymphocytes, neutrophils, Hgb, LFTs, and lipids
Bold indicates boxed warning				

AZA, azathioprine; BMD, bone mineral density; BMS, bone marrow suppression; CBC, complete blood count; CHF, congestive heart failure; CrCl, creatinine

clearance; DNA, deoxyribonucleic acid; EBV, Epstein–Barr virus; GI, gastrointestinal; Hgb, hemoglobin; HPA, hypothalamic–pituitary–adrenal axis; IL, interleukin; IOP, intraocular pressure; IV, intravenous; JAK, Janus kinase; JCV, John Cunningham virus; LFT, liver function test; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; RNA, ribonucleic acid; RPLS, reversible posterior leukoencephalopathy syndrome; TB, tuberculosis; TNF, tumor necrosis factor; URI, upper respiratory infection; UTI, urinary tract infection.

Source: Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in *Am J Gastroenterol*. 2018;113(7):1101]. *Am J Gastroenterol*. 2018;113(4):481–517. doi:10.1038/ajg.2018.27. See also references 37–72.

Table 24-5
Pharmacotherapy for Inflammatory Bowel Disease

Drug	Indication	Quality of Evidence per ACG	Recommendation per ACG	Dose	Therapeutic Considerations
	UC: Mildly active maintenance of remission	Moderate	Strong	Apriso®: 1.5 g PO every morning Delzicol®: 1.6 g PO in 2–4 divided doses Lialda®: 2.4 g PO daily Pentasa®: 1 g PO qid	
	UC: Moderate to severely active induction of remission (do not recommend combination with TNF blocker therapy)	Conditional	Low	Mesalamine Enema Rowasa® 4 g rectal enema at bedtime, retained overnight for 8 hours. Asacol HD®: 1.6 g PO tid Delzicol®: 800 mg PO tid Lialda®: 2.4 or 4.8 g PO daily Pentasa®: 1 g PO qid	
	CD: Not recommended	Strong	Moderate		
Olsalazine Dipentum®	UC: Mildly active induction of remission	Moderate	Strong	2–3 g/day PO in 2–4 divided doses	
	UC: Mildly active maintenance of remission	Moderate	Strong	500 mg PO bid	
	UC: Moderate to severely active induction of remission (do not recommend combination with TNF blocker therapy)	Conditional	Low	2–3 g/day PO in 2–4 divided doses	
	UC: Moderate to severely active maintenance of remission (do not recommend combination with TNF blocker therapy)	Conditional	Low	500 mg PO bid	
Balsalazide Colazal®	UC: Mildly active induction of remission	Moderate	Strong	2.25 g PO tid	Not recommended in combination with TNF blockers for moderate to severely active UC
	UC: Mildly active maintenance of remission	Moderate	Strong		
	UC: Moderate to severely active induction of remission	Conditional	Low	1.5–3 g PO bid	
	UC: Moderate to severely active maintenance of remission	Conditional	Low		
Corticosteroids					
Conventional oral steroids	UC: Mildly active induction of remission	Low	Strong	Prednisone PO 40–60 mg/day	Use in patients who failed 5-ASA. Goal to avoid chronic use in IBD Expect clinical response in 5–7 days.

	UC: Mildly active maintenance of remission—**not recommended**	Strong	Moderate		
	UC: Moderate to severely active induction of remission	Strong	Moderate	Prednisone PO 40–60 mg/day	
	UC: Moderate to severely active maintenance of remission—**not recommended**	Strong	Moderate		
	UC: Severely active UC in hospitalized patient induction of remission	Strong	Low	Methylprednisolone 60 mg/day or Hydrocortisone 100 mg three to four times per day	Goal to avoid chronic use in IBD Expect clinical response in 3–5 days.
	CD: Moderate to severely active symptom relief for short-term use	Strong	Moderate	Oral prednisone equivalent 40–60 mg daily tapered weekly. Not to exceed 60 mg equivalent or 3-month duration	Goal to avoid chronic use or steroid dependence
	CD: Intravenous use for severe or fulminant disease	Conditional	Moderate	Equivalent to hydrocortisone 300–400 mg/day or methylprednisolone 48–60 mg/day	
	CD: Not recommended for long-term maintenance	Strong	Moderate		
Budesonide Entocort EC® Ortikos® Uceris®	UC: Mildly active induction of remission	Strong	Moderate	Uceris®: 9 mg PO daily Uceris Foam®: 2 mg per rectum bid	Consider in patients who failed 5-ASA. Rectal formulations can be considered for symptoms of diarrhea and rectal bleeding.
	UC: Moderate to severely active induction of remission	Strong	Moderate		Rectal formulations can be considered for symptoms of diarrhea and rectal bleeding.
	CD: Mild to moderately active and low-risk ileocecal disease for induction of symptomatic remission	Strong	Low	Uceris®: 9 mg PO daily	Not recommended to maintain remission beyond 4 months
Immunomodulators					
Thiopurines (AZA and 6-MP) AZA Imuran® 6-MP Purixan®	UC: Moderate to severely active induction of remission	Low	Strong	6-MP: 50 mg PO once daily; titrate up to 1.5 mg/kg/day AZA: 2.5 mg/kg/day PO	**Do not use monotherapy in UC.** Recommended in combination with infliximab Pharmacogenomic testing for TPMT polymorphism now commonly performed before initiating drug Avoid use with xanthine oxidase inhibitors.

	UC: Mildly active maintenance of remission—**not recommended**	Strong	Moderate		
	UC: Moderate to severely active induction of remission	Strong	Moderate	Prednisone PO 40–60 mg/day	
	UC: Moderate to severely active maintenance of remission—**not recommended**	Strong	Moderate		
	UC: Severely active UC in hospitalized patient induction of remission	Strong	Low	Methylprednisolone 60 mg/day or Hydrocortisone 100 mg three to four times per day	Goal to avoid chronic use in IBD Expect clinical response in 3–5 days.
	CD: Moderate to severely active symptom relief for short-term use	Strong	Moderate	Oral prednisone equivalent 40–60 mg daily tapered weekly. Not to exceed 60 mg equivalent or 3-month duration	Goal to avoid chronic use or steroid dependence
	CD: Intravenous use for severe or fulminant disease	Conditional	Moderate	Equivalent to hydrocortisone 300–400 mg/day or methylprednisolone 48–60 mg/day	
	CD: Not recommended for long-term maintenance	Strong	Moderate		
Budesonide Entocort EC® Ortikos® Uceris®	UC: Mildly active induction of remission	Strong	Moderate	Uceris®: 9 mg PO daily Uceris Foam®: 2 mg per rectum bid	Consider in patients who failed 5-ASA. Rectal formulations can be considered for symptoms of diarrhea and rectal bleeding.
	UC: Moderate to severely active induction of remission	Strong	Moderate		Rectal formulations can be considered for symptoms of diarrhea and rectal bleeding.
	CD: Mild to moderately active and low-risk ileocecal disease for induction of symptomatic remission	Strong	Low	Uceris®: 9 mg PO daily	Not recommended to maintain remission beyond 4 months
Immunomodulators					
Thiopurines (AZA and 6-MP) AZA Imuran® 6-MP Purixan®	UC: Moderate to severely active induction of remission	Low	Strong	6-MP: 50 mg PO once daily; titrate up to 1.5 mg/kg/day AZA: 2.5 mg/kg/day PO	**Do not use monotherapy in UC.** Recommended in combination with infliximab Pharmacogenomic testing for TPMT polymorphism now commonly performed before initiating drug Avoid use with xanthine oxidase inhibitors.

	UC: Moderate to severely active maintenance of remission	Low	Conditional	6-MP: 1–1.5 mg/kg/day PO AZA: 2.5 mg /kg/day PO	Recommended for patients who achieved remission with corticosteroid
	UC: Severely active UC in hospitalized patient maintenance of remission	Low	Conditional	6-MP: 1–1.5 mg/kg/day PO AZA: 2.5 mg /kg/day PO	Use in patients who achieved remission through cyclosporine treatment.
	CD: Moderate to severely active as steroid-sparing agents	Strong	Low	6-MP: 0.75–1.5 mg/kg/day PO AZA: 1.5–2.5 mg/kg/day PO	Effective steroid-sparing option, or in the case of steroid dependence, with or without TNF blocker therapy
					Not to be used for induction because of slow time to clinical response, up to 12 weeks If used in combination with infliximab, dose may be reduced to minimize adverse effects.
	CD: Moderate to severely active for maintenance of remission, particularly following induced remission using steroids	Strong	Moderate		
	CD: Moderate to severely active, in combination with infliximab is more effective than is monotherapy in naive patients	Strong	High		
	CD: Fistulizing disease	Strong	Low		
Methotrexate Otrexup® Rasuvo®	UC: Moderate to severely active induction of remission (do not use monotherapy)	Low	Strong	25 mg IM/SQ weekly for 4 months	Usually reserved for patients who have failed 6-MP/AZA UC data extrapolated from CD studies (use in combo with a TNF blocker) Known teratogen: Administer to females only if highly effective contraception is in place. Males should avoid unprotected sex with a female of reproductive potential during and at least 3 months after use. Administer with folic acid 1 mg PO daily to reduce GI, hepatic, and hematologic adverse effects associated with methotrexate.

	UC: Moderate to severely active maintenance of remission **(do not recommend)**	Low	Conditional		
	CD: Moderate to severely active for alleviating signs and symptoms in steroid-dependent CD for maintaining remission	Conditional	Low	25 mg IM/SQ weekly for 4 months, then consider 15 mg weekly thereafter	
	CD: Combined with a TNF blocker to reduce immunogenicity and loss of response	Strong	Moderate	12.5 mg PO weekly	
Cyclosporine Gengraf® Neoral® Sandimmune®	UC: Severely active UC in hospitalized patient induction of remission (use if not responding to 3–5 days of IV corticosteroids)	Moderate	Strong	2 mg/kg/day continuous infusion over 25 hours Switch to cyclosporine PO 2.3–3 mg/kg every 12 hours.	IV route preferable in hospitalized patients
	UC: Severely active UC in hospitalized patient maintenance of remission (do not use cyclosporine—switch to thiopurines or vedolizumab)	Low	Conditional		
	CD: Not recommended	Strong	Moderate		
Biologics					
Infliximab Avsola® Inflectra® Ixifi® Remicade® Renflexis®	UC: Moderate to severely active induction of remission	High	Strong	5 mg/kg IV at weeks 0, 2, and 6; then every 8 weeks thereafter	Scheduled treatment preferred to episodic treatment to maintain response and decrease delayed infusion reactions Pediatrics: Use has not been studied in children younger than 6 years. Pregnancy: Use only if benefit outweighs risk. Drug has been found in infant serum up to 6 months post birth. May be reserved in CD for steroid-resistant or refractory cases and those refractory to thiopurines or methotrexate May be used in combination with thiopurines, but with increased risk of adverse effects Combination use is not recommended for other TNF blockers.

	UC: Moderate to severely active maintenance of remission (continue medication)	Moderate	Strong		
	UC: Severely active UC in hospitalized patient induction of remission (use if not responding to 3–5 days of IV corticosteroids)	Moderate	Strong		
	UC: Severely active UC in hospitalized patient maintenance of remission (continue if achieved remission via Infliximab treatment)	Moderate	Strong		
	CD: Moderate to severely active for induction and maintenance of TNF blocker–induced remission	Strong	Moderate-to-high	5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks thereafter; dose may be increased to 10 mg/kg for initial responders who later lose response	
	CD: Fulminant disease	Conditional	Low		
	CD: Perianal fistulas	Strong	Moderate		
	CD: Enterocutaneous and rectovaginal fistulas	Strong	Moderate		
Adalimumab Amjevita® Cyltezo® Humira® Hyrimoz®	UC: Moderate to severely active induction of remission	High	Strong	160 mg SQ day 1, 80 mg SQ day 14, 40 mg SQ day 29 then every other week thereafter	Available as a prefilled pen for self-administration Pediatrics: Use has not been studied in children younger than 4 years. Pregnancy: Use only if benefit outweighs risk. Consider enrollment in pregnancy registry. May be reserved for steroid-resistant CD or cases refractory to thiopurines or methotrexate
	UC: Moderate to severely active maintenance of remission (continue medication)	Moderate	Strong	40 mg SQ every other week	
	CD: Moderate to severely active for induction and maintenance of TNF blocker–induced remission	Strong	Moderate-to-high	Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week	
	CD: Perianal fistulas	Strong	Low		

Certolizumab pegol Cimzia®	CD: Moderate to severely active for induction and maintenance of TNF blocker–induced remission	Strong	Moderate-to-high	400 mg SQ at weeks 0, 2, and 4; then every 4 weeks thereafter	Pediatrics: Not indicated Pregnancy: Use only if benefit outweighs risk. Consider enrollment in pregnancy registry. May be reserved for steroid-resistant CD or cases refractory to thiopurines or methotrexate
	CD: Perianal fistulas	Strong	Low		
Golimumab Simponi®	UC: Moderate to severely active induction of remission	High	Strong	200 mg SQ at week 0, then 100 mg at week 2	Test for latent TB; if result is positive, start treatment for TB before starting golimumab.
	UC: Moderate to severely active maintenance of remission (continue medication)	Moderate	Strong	100 mg SQ every 4 weeks	
Natalizumab Tysabri®	CD: Moderate to severely active for induction of symptomatic response and remission	Strong	High	300 mg IV over 1 hour every 4 weeks	Requires TOUCH Prescribing Program, which is a restricted distribution program because of cases of PML
					Pediatrics: Not indicated Pregnancy: Animal reproductive studies have shown adverse effects on the fetus. Use only if benefit outweighs risk. Consider enrollment in pregnancy registry.
	CD: Moderate to severely active maintenance in natalizumab-induced remission; only if serum antibody to John Cunningham virus is negative	Strong	Moderate		
Vedolizumab Entyvio®	UC: Moderate to severely active induction of remission	Moderate	Strong	300 mg IV over 30 minutes at weeks 0, 2, and 6, and every 8 weeks thereafter	No cases of PML were observed in clinical trials; and does not currently require a restricted distribution program. Favorable side effect profile when compared to other systemic immunosuppression

					Pediatrics: Not indicated Pregnancy: Use only if benefit outweighs risk. Consider enrollment in pregnancy registry.
	UC: Moderate to severely active maintenance of remission (continue medication)	Moderate	Strong	300 mg IV every 8 weeks	
	UC: Severely active UC in hospitalized patient maintenance of remission (use in patients who achieved remission through cyclosporine treatment)	Low	Conditional	300 mg IV every 8 weeks	
	CD: Moderate to severely active and objective evidence of active disease with or without an immunomodulator for induction of symptomatic remission	Strong	High	300 mg IV over 30 minutes at weeks 0, 2, and 6	
	CD: Maintenance of remission of vedolizumab-induced remission	Conditional	Moderate	300 mg IV over 30 minutes every 8 weeks	
Ustekinumab Stelara®	CD: Moderate-to-severe disease in patients who have failed previous treatment with corticosteroids, thiopurines, methotrexate, or TNF blockers or who have no prior experience with TNF blockers	Strong	High	Weight-based induction dosing, administered IV as a single dose: ≤55 kg: 260 mg >55–85 kg: 390 mg >85 kg: 520 mg	Pediatrics: Not indicated Pregnancy: Use only if benefit outweighs risk. Consider enrollment in pregnancy registry.
	CD: Maintenance of remission of ustekinumab-induced remission	Conditional	Moderate	90-mg SQ injection every 8 weeks starting 8 weeks after the induction dose	
JAK Inhibitor					
Tofacitinib Xeljanz®	UC: Moderate to severely active induction of remission	Moderate	Strong	10 mg PO bid for 8 weeks; based on therapeutic response, may continue 10 mg bid for up to 16 weeks XR: 2 mg PO once daily for at least 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed, continue 22 mg q day for up to 16 weeks.	Test for latent TB; if result is positive, start treatment for TB before starting tofacitinib.
	UC: Moderate to severely active maintenance of remission (continue medication)	Moderate	Strong	5 mg PO bid XR: 11 mg PO daily	For patients with loss of response during maintenance treatment, a dosage of 10 mg bid (or XR 22 mg daily) may be considered and limited to the shortest duration.

5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; ACG, American College of Gastroenterology; ADR, adverse drug reaction; AZA azathioprine; BID, two times daily; CD, Crohn disease; CNS, central nervous system; GI, gastrointestinal; HA, headache; IM, intramuscularly; IV, intravenously; JAK, Janus kinase; N/V, nausea/vomiting; PML, progressive multifocal leukoencephalopathy; PO, orally; PR, per rectum; q day, daily; qid, four times daily; SQ, subcutaneously; TB, tuberculosis; tid, three times daily; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase; UC, ulcerative colitis; XR, extended release.

Sources: Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3): 384–413; Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in *Am J Gastroenterol*. 2018;113(7):1101]. *Am J Gastroenterol*. 2018;113(4):481–517. doi:10.1038/ajg.2018.27. See also references 37–88.

Table 24-6
Comparison of Aminosalicylate Compounds

Generic (Trade)	Delivery System	Intestinal Site of Release
Balsalazide (Colazal®)	Bacterial cleavage of azo bond	Colon
Mesalamine (Apriso®)	Polymer matrix/enteric coating that dissolves at pH 6	Ileum (distal), colon
Mesalamine (Asacol HD®)	pH-dependent coating (Eudragit® S) dissolves at pH ≥7	Ileum (distal), colon
Mesalamine (Delzicol®)	pH-dependent coating (Eudragit® S) dissolves at pH ≥7	Ileum (distal), colon
Mesalamine (Lialda®)	Multimatrix (pH-sensitive coating and delayed release)	Ileum (distal), colon
Mesalamine (Pentasa®)	Controlled-release microspheres	Duodenum, jejunum, ileum, colon
Mesalamine suppository (Canasa®)	Direct topical therapy	Rectum
Mesalamine enema (Rowasa®)	Direct topical therapy	Descending colon/rectum
Olsalazine (Dipentum®)	Bacterial cleavage of azo bond	Colon

Generic (Trade)	Delivery System	Intestinal Site of Release
Sulfasalazine (Azulfidine®) (Sulfazine®)	Bacterial cleavage of azo bond	Colon

Adapted from Fernandez-Becker NQ, Moss AC. Improving delivery of aminosalicylates in ulcerative colitis: effect on patient outcomes. *Drugs*. 2008;68:1089; Drug Facts and Comparisons 4.0 [on-line] 2015. Accessed August 26, 2015. http://www.wolterskluwercdi.com/facts-comparisons-online/

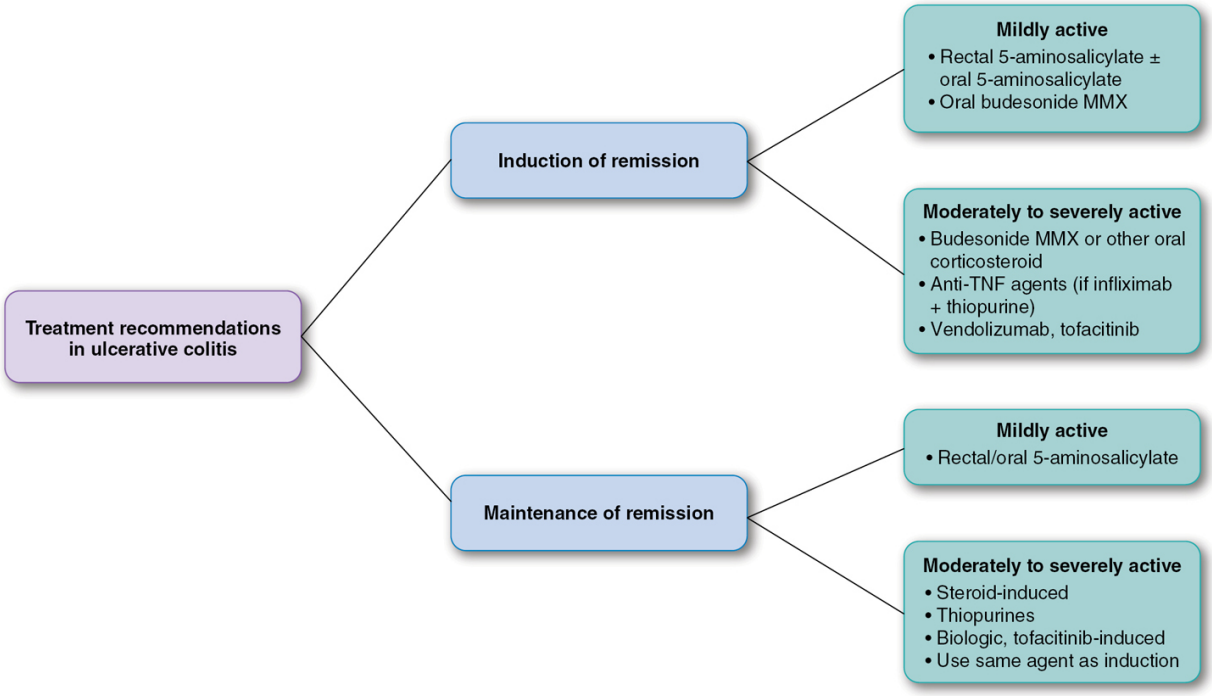


Figure 24-1 Ulcerative colitis treatment algorithm. MMX, multimatrix system; TNF, tumor necrosis factor. (Reprinted with permission from Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384–413. © 2019 by The American College of Gastroenterology.)

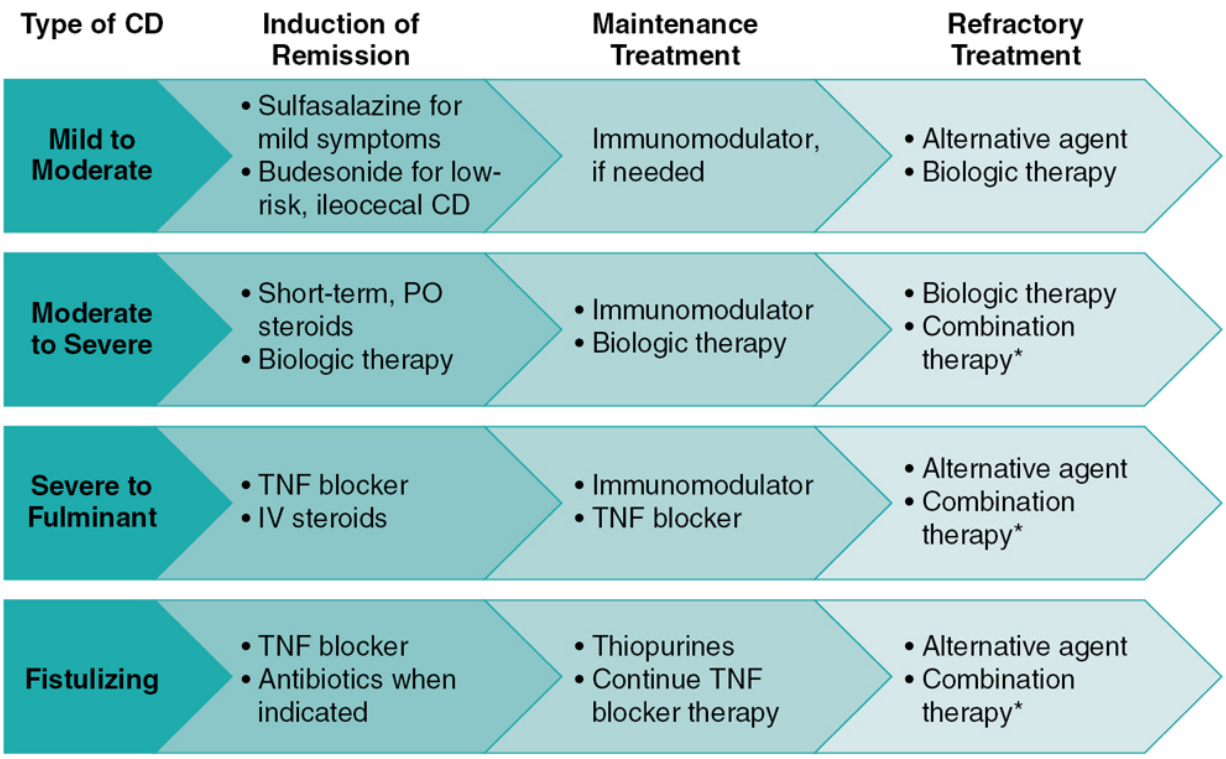


Figure 24-2 Crohn disease treatment algorithm. Biologic therapy includes TNF blocker (infliximab, adalimumab, certolizumab pegol), anti-integrin (natalizumab, vedolizumab), and anti-interleukin (ustekinumab) therapies. Thiopurines include AZA and 6-MP. Immunomodulators include thiopurines and methotrexate. Fistulizing disease may require intervention besides those listed, including seton placement or surgery. The figure displays a simplified version of therapeutic considerations and should be considered in combination with information in Tables 24-4 and 24-5. 6-MP, 6-mercaptopurine; AZA, azathioprine; CD, Crohn disease; IV, intravenous; PO, oral; TNF, tumor necrosis factor. *Combination therapy indicates, infliximab with reduced doses of a thiopurine or methotrexate. Studies are ongoing to explore safety and effectiveness. (From Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in *Am J Gastroenterol*. 2018;113(7):1101]. *Am J Gastroenterol*. 2018;113(4):481–517. doi:10.1038/ajg.2018.27; Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on

therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14(1):4–22. doi:10.1093/ecco- jcc/jjz180.)

Although it has been theorized that an abnormal immune response to normal flora can lead to inflammation in genetically susceptible individuals, the American College of Gastroenterology guidelines for CD recommend against using probiotics and long-term antibacterial therapy for treatment.[28,88] The American College of Gastroenterology guidelines for UC do not make a recommendation about probiotic use.[22] Antibiotics are still recommended where otherwise indicated, for example, in the case of pyogenic complications. [22,28] Metronidazole is often used to treat, or, in unique cases, prevent bacterial infections in the GI tract. Common adverse effects with chronic, high-dose metronidazole include metallic taste and peripheral neuropathy.[89]

NUTRITION

There is no single diet recommended for all patients with IBD,[22,28] although specific protein requirements are recommended for adults with an active flare (1.2–1.5 g/kg/day).[88] Evidence is insufficient to suggest that diet alone can induce or maintain remission,[90] except for pediatric patients with CD where guidelines may recommend exclusive enteral nutrition.[88,91,92] Total parenteral and enteral nutrition for adults is only recommended in accordance with the American Society for Parenteral and Enteral Nutrition Guidelines (ASPEN).[93] Individuals with IBD should meet with a dietician as part of a holistic approach to avoid nutritional deficiencies, dehydration, and exacerbation of flares.[22,28,32] General dietary guidance includes eating a healthy, well-balanced diet rich in fruits, vegetables, and omega-3 fatty acids, while limiting foods that promote intestinal inflammation or discomfort such as caffeine, alcohol, sugar, saturated fats, and insoluble fiber.[88,94] Patients should be screened for malnutrition at diagnosis and regularly thereafter. Vitamin deficiencies are common, especially if ileal involvement is extensive or resection has been performed.

SUPPORTIVE CARE

Symptomatic management of IBD is important to the patient's quality of life. This includes pain relief and diarrhea control. For pain relief, patients should avoid medications that upset the GI tract such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Loperamide or diphenoxylate with atropine may be used to treat mild symptoms provided that alternative causes for diarrhea have been ruled out, including obstruction or toxic megacolon. Severe worsening of symptoms and abdominal distension may indicate toxic megacolon caused by the inability to rapidly empty secretory products of the bowel.[3] Patients with active IBD are more likely to have feelings of distress or lack of self-control compared to the general population.[2] Therefore, psychosocial support may be needed to improve overall quality of life.

SURGERY

Surgery is indicated when the patient fails to respond to medical management; demonstrates intestinal complications such as perforation, obstruction, hemorrhage, stricture, toxic megacolon, or fistula formation; fails to grow and develop at a normal rate; or exhibits carcinoma on biopsy.[22,95] The surgical procedure of choice depends on the indication, but may include a subtotal or a total colectomy with end ileostomy. For patients with UC, surgery is often curative. In contrast, in patients with CD, the disease recurrence after surgery is common and anatomically correlates with the original pattern of the disease.[23]

ULCERATIVE COLITIS

Pathophysiology and Clinical Presentation

CASE 24-1

QUESTION 1: A.C., a 24-year-old female college student, has had episodic, watery diarrhea, and colicky abdominal pain relieved by defecation for the past 9 months. Eight weeks before admission, the diarrhea increased to three to five semiformed stools daily. The frequency of the stools gradually increased to 7 to 10 times a day 1 week ago. At that time, A.C. noted bright red blood in the stools. Stool frequency has now increased to 12 to 15 per day, although the volume of each stool is estimated to be only "one-half cupful." She feels a great urgency to defecate, even though the volume is small. She has not traveled outside the United States, has not been camping, and has not taken any antibiotics within the past 6 months. She is allergic to sulfa.

A.C. reports of anorexia and a 10-pound (4.53-kg) weight loss during the previous 2 months. For the past 4 months, she has had intermittent swelling, warmth, and tenderness of the left knee, which is unassociated with trauma. She denies any skin rashes or any difficulties with her vision. A review of other body systems and social and family history are noncontributory.

A.C. appears to be slightly anxious and fatigued, with normal body habitus. She is 65 inches (165.01 cm) tall and weighs 112.44 pounds (51 kg). Her temperature is 100 °F (37.78 °C); her pulse rate is 105 beats/minute. Physical examination is normal except for swelling, warmth, and tenderness of the left knee, suggestive of arthritis.

Stool examination shows a watery effluent that contains numerous red and white cells with no trophozoites. Stool cultures and an amebiasis indirect hemagglutination test result are negative. Other laboratory values include the following results:

Hematocrit (Hct), 30%
Hgb, 8.1 g/dL
White blood cell (WBC) count, 17,500/μL with 82% polymorphonuclear neutrophils (PMNs)
ESR, 72 mm/hour
Serum albumin, 2.8 g/dL
Alanine aminotransferase (ALT), 33 units/mL
Sigmoidoscopy showed evidence of granular, edematous, and friable mucosa with continuous ulcerations extending from the anus throughout the colon.

What is the most probable cause of A.C.'s diarrheal illness, and what is the evidence for this?

A.C.'s presentation is typical of a patient with new-onset UC. Drug-induced (pseudomembranous colitis) and infectious (parasitic) causes of diarrhea have been ruled out by history, including no travel outside the United States, no antibiotic use, and stool examination. As discussed previously, UC is characterized by inflammation of the

mucosal layer of the colon and rectum.[1] The inflammation does not extend beyond the submucosa, so transmural ulcers are rare. On examination, the mucosa appeared erythematous and friable. Differentiation from CD is made by endoscopic and radiologic evidence of continuous distribution of pathologic disease (as opposed to segmental or skip lesions), as well as the anatomic location (confined to the colon and rectum).

A.C. presents with the classic triad of UC clinical symptoms: chronic diarrhea, rectal bleeding, and abdominal pain. Diarrhea is secondary to decreased colonic absorption of water and electrolytes and diminished colonic segmental contractions that normally serve to decrease the flow of bowel content. A good indication of disease severity is the volume of stool passed per day.[22] Incontinence and nocturnal diarrhea commonly occur as disease severity progresses. Stools are usually soft, mushy, formed, and often contain small amounts of mucus mixed with blood. In addition to diarrhea, the malabsorption of water and electrolytes causes dehydration, weight loss (as observed in A.C.), and electrolyte disturbances.

A.C.'s rectal bleeding is secondary to colonic mucosal erosions and occurs in most patients with UC. Bright red blood mixed in the stools indicates a colonic origin, whereas blood-streaked stools indicate an anal or a rectal origin. The anemia associated with UC is secondary to rectal bleeding. It presents as a hemorrhagic or an iron-deficiency anemia, depending on the acuteness of the bleeding. Hgb and Hct laboratory values often are decreased, as in A.C.'s case. Chronic inflammatory disease–induced hypoalbuminemia is often exacerbated by malnutrition.

A.C.'s abdominal pain and cramping are caused by spasm of the irritated and inflamed colon. This abdominal pain is commonly associated with an urgency to defecate. As illustrated by A.C., the pain is usually relieved with defecation, even though the stool volume may be small.

A.C.'s arthritis and elevated ALT are indicative of the extraintestinal manifestations that occur in IBD.[96] Her nonspecific symptoms (ie, anorexia, fatigue, weight loss, anxiety, tachycardia) could become profound during an exacerbation of UC. Fever,

leukocytosis, and increased ESR are also systemic manifestations of an inflammatory disease. Rehydration is important to ensure fluid balance and maintain good renal function. Given her frequency of stools, Hgb, tachycardia, and elevated ESR, A.C.'s disease would be classified as acute severe UC. Patients with acute severe UC should be admitted to the hospital for inpatient management.

Case 24-1, Question 2: How should A.C.'s diarrhea be managed?

Treatment of the diarrhea associated with UC is often difficult. For patients with mild-to-moderate disease, antidiarrheals, such as loperamide or diphenoxylate with atropine, used as needed, may help minimize chronic diarrhea. Extreme caution must be used, especially in patients with severe disease because of the chance of inducing toxic megacolon, a life-threatening condition, and medical emergency. For this reason, antidiarrheals are best avoided in patients with severe active disease, such as with A.C. Bulk-forming agents (ie, psyllium) may be helpful for patients with constipation caused by ulcerative proctitis.[97]

Case 24-1, Question 3: What agents can be used to induce disease remission in A.C.?

Systemic intravenous (IV) corticosteroids are the most effective agents to induce remission of acute severe UC. Patients with acute severe UC should be started on methylprednisolone 60 mg IV per day or hydrocortisone 100 mg IV three to four times a day to induce remission. Up to 67% of patients with acute severe UC respond to steroid treatment.[98] Topical corticosteroids can be added for symptom control with distal involvement.

Infliximab or cyclosporine should be considered for induction of remission as rescue therapy in patients with acute severe UC who are hospitalized and not responding to 3 to 5 days of IV corticosteroid therapy. Notably, additional response is unlikely after 7 days of IV corticosteroid therapy.[22] When choosing between

infliximab and cyclosporine for rescue therapy, it is important to keep in mind that rates of treatment failure and colectomy are higher in patients receiving cyclosporine who have previously failed immunomodulator therapy; therefore, infliximab may be a preferred agent in such patients. In addition, in patients with albumin <2.3 g/dL, infliximab is the preferred agent because of more favorable treatment results.[99]

Given that A.C. is of childbearing age, a pregnancy test should be obtained, and results taken into consideration when choosing current and future drug therapy, particularly if pregnant or breastfeeding (see Chapter 49, Obstetric Drug Therapy).[100]

Case 24-1, Question 4: Methylprednisolone at a dosage of 40 mg IV every 6 hours is ordered. What are the treatment goals for A.C.?

The goal of parenteral corticosteroid therapy for A.C. is to achieve a rapid therapeutic response. Monitoring should include assessment of vital signs and physical examination to assess abdominal distension, abdominal tenderness, frequency of bowel movements, presence of visible blood, abdominal pain, and systemic symptoms.

The Oxford Criteria is used to identify patients who are not responding to IV corticosteroid therapy and includes the following parameters: having more than eight bowel movements per day on day 3 of IV corticosteroid treatment, or three to eight bowel movements per day, and CRP >45 mg/L. Patients who are nonresponders to IV corticosteroid therapy are more likely to require colectomy than do patients with partial or complete response. Additional parameters that can be used to predict nonresponders to IV corticosteroid therapy include patients with elevated ESR >75 mm/hour, elevated temperature, and hypoalbuminemia.[101,102]

Patients who are poor responders to IV corticosteroid therapy should be evaluated for surgical intervention. Surgery is indicated in patients who develop toxic megacolon, perforation, or massive hemorrhage. It is important not to delay a surgical consultation in patients who are poor responders because that can lead to poor

clinical outcomes. Surgical treatment options include a subtotal or total colectomy with end ileostomy. It is important not to delay surgical interventions in patients who otherwise are initiated on infliximab or cyclosporine rescue therapy.[103]

Poorly nourished patients in whom oral intake is expected to be absent for >7 days should receive parenteral nutrition, and treatment should be continued until oral feeding is tolerated.[104] An adequate response is defined as resolution of fever and tachycardia, improved patient well-being, and less abdominal tenderness on palpation. Diarrhea is usually considered to be resolved with four bowel movements or more daily. Usually by this point, stools are rarely formed, and the patient is no longer observing bloody stools. Once A.C.'s symptoms are controlled, the goal should be to switch to oral corticosteroids and discharge her from the hospital.

Case 24-1, Question 5: A.C. is responding well to methylprednisolone. She is afebrile, her abdominal pain is reduced (to a score of 4 on a 1–10 scale), and her diarrhea is decreasing. When is the oral route of corticosteroid administration indicated in UC? What are the most appropriate dosages?

Oral corticosteroids are effective for the initial treatment of mild-to-moderate acute UC.[105] In addition, patients on parenteral corticosteroids for severe exacerbation should be switched to oral corticosteroids once a satisfactory initial response has been achieved. The usual dose of oral prednisone is 40 to 60 mg/day because doses >60 mg/day have shown to provide no additional therapeutic value, while causing more adverse effects.

Case 24-1, Question 6: What if A.C.'s UC was limited to the distal colon or rectum? Would topical corticosteroids be indicated? When should other topical agents be considered for A.C.?

It is important to select organ-specific treatment options compared to systemic therapies when symptoms are limited to the distal colon or rectum. Topically administered 5-aminosalicylic acid (5-ASA) and corticosteroids, in the form of suppositories, foams, and retention

enemas, are effective in the management of acute, mild-to-moderate UC that is limited to the distal colon and rectum.[106]

The desired outcome for medications administered via this topical route is to provide a higher concentration of drug to the diseased mucosal area, exerting a local anti-inflammatory effect, while minimizing systemic side effects. Unfortunately, variable but significant systemic absorption (up to 90%) and adrenal suppression occur from the topical administration of corticosteroid to the rectum and distal colon.[107] Therefore, the beneficial effects produced by topical use of these agents may accrue from both systemic and local effects. The low incidence of corticosteroid side effects associated with topical administration may be related to both the low doses and the infrequent administration (daily to twice daily) needed to control mild acute UC.

5-ASA suppositories and enemas are preferred over topical corticosteroids for the treatment of distal UC and proctitis because they produce higher remission rates in proctitis and effectively maintain remission of distal UC.[107] For distal UC, therapy is initiated with a nightly enema (4 g of mesalamine), and the response should be evaluated in 3 to 4 weeks. For mild acute proctitis, administering one suppository of 5-ASA twice daily for 3 to 6 weeks is sufficient to induce disease remission. Improvement should be seen in 2 to 3 weeks, and therapy should be maintained until complete remission is achieved. If remission is reached, therapy can then be tapered to one suppository or enema, two to three times weekly. Therapy with oral plus topical mesalamine showed greater efficacy than either alone in achieving remission of distal UC or proctitis.[106]

CASE 24-1, QUESTION 7: What corticosteroid adverse effects should the clinician monitor in A.C.?

Corticosteroid side effects and precautions for use often limit the therapeutic effectiveness of these agents and should never be overlooked.[108] Certain glucocorticoid adverse effects are of particular importance in patients with IBD in that they may mimic, mask, or

intensify symptoms and complications of this disease. For example, the symptoms of peritonitis, one of the major complications of intestinal perforation, may be masked by corticosteroids. Other deleterious effects of corticosteroids include hyperglycemia, avascular necrosis, cataract formation, and central nervous system effects, including mood disorders, insomnia, psychoses, and euphoria.

Patients with IBD are at risk for decreased bone mineral density, which is exacerbated by prolonged use of corticosteroids.[109,110] This is an often-overlooked side effect of these drugs. Thus, calcium, vitamin D supplements, and bisphosphonates are recommended to minimize metabolic demineralization in all patients with IBD taking corticosteroids for longer than 3 months. Given the patient's family history (mother with osteoporosis) and her elevated risk of bone loss, alendronate 35 mg weekly with 1500 mg daily of calcium and 800 international units (IU) of vitamin D intake should be initiated.

Case 24-1, Question 8: A.C. is still responding well to oral prednisone; however, her blood glucose concentrations have ranged from 226 to 445 mg/dL (normal, 70–110 mg/dL). Her physician would like to try another modality for active treatment. What other drugs could be used for remission induction?

Previously, sulfasalazine was considered the drug of choice in UC exacerbation because of its demonstrated efficacy and reduced toxicity when compared with corticosteroids. However, controlled trials have shown that corticosteroids may act more promptly than does sulfasalazine alone for severe acute UC.[111] Sulfasalazine use has declined significantly because of the availability of better-tolerated 5-ASA formulations. Sulfasalazine use is often limited by its side effect profile including headache and nausea, as well as multiple daily dosing. In addition, as in the case of A.C., patients with a sulfa allergy should avoid sulfasalazine.

For patients with mildly active extensive UC, oral 5-ASA, also known as mesalamine, at a dose of 2 g/day is the preferred treatment for inducing remission.[112] Meta-analyses have shown that patients with moderately active UC may benefit from higher doses of

5-ASA at 4.8 g/day.[113] Single daily oral 5-ASA administration is found to be as effective as multiple daily doses and can be advantageous in increasing compliance.[113]

Patients with mildly active UC who are unable to reach remission with a 5-ASA should not be switched to an alternative 5-ASA formulation, because there is no therapeutic benefit between different formulations. Instead, they should be switched to corticosteroids for induction of remission.[75] In such patients requiring corticosteroid therapy, oral budesonide multimatrix system (MMX) 9 mg for 8 weeks would be preferred, and has been found to be more effective than continuing the oral 5-ASA. Budesonide is a long-acting corticosteroid with high first-pass metabolism and minimal side effects, and is therefore preferred over systemically active glucocorticoids in patients with mildly active UC.

For patients with moderately active UC, 5-ASA monotherapy for induction of remission is an option; however, it was not found to be effective in patients with severely active UC. Nonsystemic corticosteroids such as budesonide MMX are also preferred treatment options in patients with moderately active UC compared to systemic corticosteroids.

Infliximab, adalimumab, and golimumab are tumor necrosis factor (TNF) blockers that are effective for the induction of remission of moderate to severely active UC.[22] Patients with moderate to severely active UC, who fail TNF blockers, can be started on vedolizumab, which has a favorable safety profile and lower risk of infections compared to systemic immunosuppressive treatment options. Another treatment choice in patients who fail TNF blockers is tofacitinib, an orally administered small molecule that nonselectively inhibits the Janus kinase enzyme administered at a dose of 10 mg twice daily for 8 weeks. It is important to remember that infectious complications are more common in patients receiving tofacitinib including herpes zoster.[114]

In summary, oral 5-ASA compounds are considered first-line therapy for mildly active UC, with systemic corticosteroids reserved for more severely active UC or refractory disease. Because A.C. has improved symptomatically and is suffering significant adverse effects

from corticosteroid treatment, switching to oral mesalamine is a reasonable choice at this time.

Case 24-1, Question 9: A.C. feels much better and claims to be "back to normal." Her abdominal pain is gone, and she currently has two formed, nonbloody stools daily. Most of her laboratory parameters have returned to normal (ESR, 19 mm/hour; blood glucose, 95 mg/dL; WBC, 8300/μL). She is currently taking mesalamine 800 mg PO (orally) tid. What drug regimen should be used to maintain disease remission in A.C.?

5-ASA agents significantly reduce the incidence of relapse in patients with UC who are in remission.[105,115] As discussed previously, the anatomic site of disease is an important consideration in the selection of a 5-ASA preparation.[116] Data also suggest that, if tolerated, higher doses have higher rates of treatment success. In contrast, oral and topical corticosteroids do not prevent relapse of UC once remission has occurred.

Based on this information, A.C.'s mesalamine should be titrated to a total dose of 4.8 g in divided doses. If she experiences a relapse, a course of oral corticosteroids may be needed to reachieve remission. Prophylactic therapy should be continued indefinitely unless intolerable adverse effects develop.

Case 24-1, Question 10: A.C.'s mesalamine has been increased to 1200 mg tid for UC maintenance therapy. Several days after starting this higher dose of mesalamine, A.C. experienced anorexia, nausea, and epigastric pain. What is the possible cause of A.C.'s symptoms? How can they be minimized?

A.C. appears to be experiencing adverse effects of mesalamine. Although usually better tolerated than is sulfasalazine, unwanted adverse effects occur in 10% to 45% of patients. Most 5-ASA adverse reactions are dose related and tend to occur early during therapy.

Dose-related 5-ASA adverse effects can be minimized by initiating the patient on a low dosage (1–2 g/day) and gradually increasing the amount to tolerated therapeutic doses.[117] If dose-related reactions do

occur, the drug should be discontinued until the symptoms subside, and then it may be reinstituted at a lower dosage. A.C.'s symptoms are probably dose-related adverse reactions to mesalamine. The dosage should be decreased, or the drug temporarily withheld. If tolerated, the dosage can be increased slowly as necessary, or she can be switched to another agent to maintain disease remission, such as an immunomodulator.

Case 24-1, Question 11: A.C.'s dose of mesalamine was decreased to 800 mg tid. After 2 weeks, A.C. continued to have nausea, diarrhea, and headache severe enough to cause her to miss classes and call in sick from her part-time job. She lost 11.02 pounds (5 kg) (now 101.41 pounds [46 kg]) in the past week because of anorexia and nausea. What alternative therapies should be considered at this point?

For patients with previous moderate to severely active UC who are now in remission owing to induction with corticosteroids, such as A.C., or who have failed mesalamine or sulfasalazine, there is limited and conflicting evidence that thiopurines may provide clinical benefit.[118–120]

Methotrexate should not be used in patients with previous moderate to severely active UC because it has not been found to be therapeutically effective in maintaining remission after steroid induction.[80]

Patients who achieved remission with TNF blockers including infliximab, adalimumab, and golimumab, integrin inhibitor vedolizumab, or Janus kinase inhibitor tofacitinib should continue therapy for maintenance with the same pharmacologic agent.[22]

Because A.C. achieved remission with corticosteroids but is now unable to tolerate mesalamine, thiopurine therapy can be considered. In A.C., a reasonable choice would be azathioprine (AZA) 2.5 mg/kg/day. AZA is typically dosed in 50-mg increments; therefore A.C. should receive 100 to 150 mg/day of AZA. Clinicians should monitor WBC counts, liver function testing, and periodic assessment for any signs and symptoms of pancreatitis.

Case 24-1, Question 12: One year has passed since A.C. last had an acute attack of UC. She has been taking AZA 2.5 mg/kg/day. Today, she presented to her primary health care provider for her annual physical examination. She asked about receiving the yearly influenza vaccination as well as the pneumococcal vaccination she has been reading about online. Her primary care provider is unsure whether A.C. is a candidate for either vaccination. Should A.C. receive both vaccinations? What vaccinations, if any, is A.C. a candidate for?

Immunomodulators and biologic drugs are the mainstay of IBD treatment. However, some of the most important adverse effects are infectious complications. Some of these infections are preventable with immunizations.[121] Unfortunately, data exist that immunization strategies are significantly underutilized in the IBD population.[122] It is essential that patients with IBD receive age-appropriate vaccines, with additional vaccine considerations for patients initiated on immunosuppressive therapies. However, delaying certain live vaccinations may be necessary to ensure prompt administration of immunosuppressive therapy.[123] Nonlive vaccines are still administered according to recommendations from the Centers for Disease Control and Prevention.[124]

When considering live vaccine administration for patients with IBD, it is important to consider the patient's level of immunosuppression. Low-level immunosuppression includes patients receiving any of the following: daily dose of systemic corticosteroids for ≥14 days (prednisone 20 mg/day equivalent and within 3 months of stopping) or alternate-day corticosteroid therapy, methotrexate ≤0.4 mg/kg/week and within 3 months of stopping, AZA ≤3.0 mg/kg/day, or 6-mercaptopurine ≤1.5 mg/kg/day and within 3 months of stopping. Patients receiving TNF blockers are classified to have high-level immunosuppression. For patients receiving vedolizumab, live vaccines may be administered if the benefits outweigh the risks.[124]

All patients with IBD should undergo serologic testing for varicella, and if nonimmune, should be vaccinated against this virus. Because the varicella vaccine is a live vaccine, it should be avoided in

patients with high-dose immunosuppression; however, administration can be considered in patients on low-dose immunosuppression such as A.C., who is receiving AZA <3 mg/kg/day.[124]

Because patients with IBD who are immunosuppressed may have reactivation of hepatitis B infection, it is essential to test for hepatitis B before starting TNF blockers and vaccinate patients who are found to be nonimmune.[124]

Specifically, concerning A.C., she should receive the seasonal inactivated influenza and the 23-valent pneumococcal polysaccharide vaccines. Many patients with IBD would also be candidates for the human papilloma virus vaccine.[124]

CASE 24-2

Question 1: C.J. is a 30-year-old male who was well until 18 days ago when he experienced crampy right lower quadrant abdominal pain associated with an increased frequency of semiformed stools (4–5/day) that are streaked with fat. He has not taken any medications to prevent diarrhea. He describes the pain as "moderate," and it was episodic at first, exacerbated by meals, and relieved with defecation. He reports increased fatigue, which he attributes to recent anorexia and a 17.63-pound (8-kg) weight loss over the past 3 months. He denies any extraintestinal findings including arthralgias, changes in vision, or the appearance of skin rashes. He denies recent antibiotic use, travel outside the United States, or a personal or family history of food allergies or intolerance. He describes his general well-being as "poor."

Physical examination is normal, except for abdominal tenderness in the right lower quadrant when palpated. Vital signs include a temperature of 100.04 °F (37.8 °C), pulse of 100 beats/minute, and blood pressure of 135/75 mm Hg. He is 71 inches (180.34 cm) and weighs 176.37 pounds (80 kg).

Pertinent objective data are as follows:

Hct, 28%
Hgb, 9 g/dL
WBC count, 14.0 × 10^9/L
ESR, 60 mm/hour
CRP, 65 mg/L
Fecal calprotectin, 250 µg/g
Occult blood, positive
Stool culture/toxin findings negative for *Clostridioides difficile* and intestinal parasites
Crohn's Disease Activity Index score: 358 points

A barium enema shows an edematous ileocecal valve and a terminal ileum that has a nodular irregularity of the mucosa. Follow-up ileocolonoscopy reveals a cobblestone-appearing terminal ileum with areas of normal tissue separated by diseased mucosa. Results of sigmoidoscopy and rectal biopsy are negative. Which of C.J.'s signs, symptoms, and laboratory data are consistent with CD? What is the pathophysiologic basis for his clinical presentation?

C.J. presents with the classic symptom triad of abdominal pain, diarrhea, and fatigue, in addition to weight loss.[28] His abdominal pain is secondary to inflammation in the ileocecal area. Diarrhea is common, and in contrast to UC, the stools are usually partly formed, without overt rectal bleeding, although possible with diseased sigmoid or rectal tissue. For colonic disease, the quality and quantity of diarrhea may be similar to that of UC. Significant ileal inflammation can result in bile malabsorption, resulting in fatty streaks called *steatorrhea*.[88] Weight loss may be pronounced in patients with long-standing CD because of anorexia and malabsorption. In addition, vitamin deficiencies are common given the extent of intestinal involvement.[88] The patient interview should include questions related to quality of life, although limited by subjectivity, because they contribute to the Crohn's Disease Activity Index score.[27] In addition, differential diagnoses should be excluded, such as traveler's diarrhea, infection risk, and food intolerance.

Rectal bleeding in CD is less common than in UC, but it may occur with colonic involvement. It can be detected using an occult blood test, with a positive result indicating the presence of blood. Slow blood loss over time can result in anemia, but altered iron metabolism in the presence of inflammation is another common cause.[125]

C.J.'s inflammatory markers demonstrate that, similar to UC, CD has systemic effects. Elevated WBC, ESR, CRP, and fecal calprotectin are common, and studies are ongoing to determine how they might be used to diagnose the disease, assess severity, and monitor response to therapy. For example, fecal calprotectin is a noninvasive tool that can differentiate IBD from other causes, including IBS, and may correlate well with endoscopic findings to assess mucosal healing.[28,126]

Most patients with CD have recurrent, symptomatic episodes of pain and diarrhea with progressively shorter asymptomatic periods. Although the clinical course is progressive, 10% of patients will remain asymptomatic after a few acute episodes.[126] Other patients may only manifest a slight fever for years until a late complication of the disease, such as fistula formation, develops. Alternatively, CD may be rapidly progressive, in the case of fulminant disease.

CASE 24-2, QUESTION 2: What agents can be used to induce remission of C.J.'s CD?

Based on C.J.'s subjective and objective findings, including a Crohn's Disease Activity Index score between 220 and 450, he likely has moderate-to-severe CD for which budesonide and sulfasalazine are not indicated.[28,32] Immunomodulators including thiopurines and methotrexate are also inappropriate at this time given their delayed onset of action and limited utility for induction.[28,51–53] C.J. has no complications that might warrant the use of infliximab or another TNF blocker in favor of other therapies. Considerations for therapy selection include safety, effectiveness, cost, and patient preference.

Corticosteroids are widely used therapeutic agents for the treatment of active, symptomatic CD.[127,128] They may be recommended for short-term, symptomatic relief during an active flare, but are not recommended for maintenance therapy because they cannot promote mucosal healing, and they have well-known adverse effects associated with long-term use (see Table 24-5).[128–130] There are no head-to-head trials to compare effective steroid regimens, but they generally include tapering prednisone, prednisolone, or methylprednisolone from doses not to exceed 40 to 60 mg prednisone equivalents per day.[129] Studies suggest that oral budesonide is about as equally effective as conventional steroids for mild-to-moderate IBD flares localized to the ileum and ascending colon.[47–49,130] Budesonide has a pH-dependent controlled ileal release formulation that acts locally and topically to reduce inflammation.[47–49] This formulation is preferred to conventional

steroids in mild cases because of reduced systemic exposure and adverse effects, but is not appropriate for C.J. given his disease severity.

Although used extensively in the past for mild-to-moderate CD, trial data and expert opinion have limited the role of 5-ASA to mild active colonic CD.[28,75] Oral mesalamine has not consistently demonstrated benefit over placebo, but sulfasalazine may benefit individuals with mild-to-moderate colonic CD who require symptomatic relief.[28] Sulfapyridine is the component of sulfasalazine that helps deliver 5-ASA to the colon; therefore, it remains largely ineffective for CD in other intestinal areas.[28] C.J. is not an appropriate candidate for sulfasalazine based on disease severity and his intestinal location of disease.

The immunomodulators AZA, 6-mercaptopurine (6-MP), and methotrexate have delayed clinical benefit, up to 12 weeks or more, which minimizes their utility for induction therapy. However, biologic agents are considerations for induction.[28] Infliximab and adalimumab are thought to be superior to certolizumab pegol for remission induction.[131–133] Uniquely, certolizumab pegol contains only the antibody receptor for TNF-α bound to polyethylene glycol (PEG) to increase its duration in the body,[63] but the impact on clinical outcomes is unknown. Studies suggest a roughly equivalent response between adalimumab and infliximab[134] but large, head-to-head studies including certolizumab pegol are lacking.[133] Infliximab has the most data to support its use for fistulizing disease,[135] but guidelines state that adalimumab and certolizumab pegol may still be considered to treat perianal fistulas.[128] Despite the high relative efficacy of TNF blockers, nearly a third of treated individuals are primary nonresponders, meaning they receive no benefit from the drug. Over time, about half of the primary responders become secondary nonresponders within the first year, requiring dose escalation or therapy change because of the development of antidrug antibodies.[35,36] Because immunomodulator adjunct therapy can reduce the development of antidrug antibodies, these agents can be used in combination, regardless of prior failed therapy to immunomodulators.[136,137] Data are developing regarding combined

use, and risks should be evaluated before choosing combined therapy. Infliximab is only administered IV, so one potential advantage of adalimumab or certolizumab pegol is the ability to self-administer them subcutaneously at home. Infliximab and adalimumab have approved biosimilars available, whereas a biosimilar for certolizumab pegol is currently under development.

Natalizumab may be beneficial for induction and maintenance of remission for moderate-to-severe CD, but at the increased risk of developing progressive multifocal leukoencephalopathy (PML), a potentially fatal infection of the nervous system.[70,138] For individuals with positive John Cunningham virus antibody, an estimated 1 in 100 will develop the disease; thus, testing is required before therapy initiation and at least every 6 months during continued use to ensure safety.[70,139] Furthermore, patients are required to be enrolled in a mandatory patient registry program (TOUCH, TYSABRI Outreach: Unified Commitment to Health) to receive the drug and should avoid concomitant immunosuppressive therapies.[70] As a result, natalizumab has fallen out of favor compared to alternative therapies.[140] In 2014, vedolizumab was approved for inducing and maintaining remission of moderate-to- severe UC and CD in patients who have failed TNF-α therapy or demonstrated corticosteroid dependence.[71] Vedolizumab differs from natalizumab because it is gut-selective, thereby reducing the risk of PML, for which no cases were observed in clinical trials.[141,142] Although gut-selective, some studies still suggest improvement in extraintestinal manifestations.[143,144] Vedolizumab is known for its relatively favorable safety profile without a black box warning for increased risk of infection or malignancy.[71,140] Anti-integrin therapy works better among TNF blocker–naive individuals,[140–142] but guidelines do not require failed TNF blocker therapy before considering their use.[28,32]

Ustekinumab is typically reserved for moderate-to-severe CD in patients who have failed or were intolerant to prior therapies, regardless of prior TNF blocker use.[28,72,145] However, it has emerged as a first-line treatment option for moderate-to-severe CD owing to its relatively low immunogenicity and high safety profile compared to other biologics.[146] Data are limited regarding its comparison to

alternative therapies, particularly its ability to reduce surgical necessity or hospitalization.[146] Similar to anti-integrin agents, ustekinumab maintenance therapy is only approved following induction with the same agent.[72] Clinical benefit is expected within 3 weeks of initiation.[145]

Case 24-2, Question 3: C.J. and his provider chose corticosteroid therapy to induce remission, because of cost, route of administration, and effectiveness. After 3 weeks of using prednisone 40 mg daily, C.J. experiences fewer symptoms of CD. He passes one to two well-formed stools daily, has increased appetite and weight, decreased abdominal pain and tenderness, and normal body temperatures. Despite attempts to taper the dose, C.J. states he is unable to tolerate a dose decrease. What therapies are effective for maintaining remission?

Once prednisone has induced remission of active symptomatic CD, attempts should be made to taper the drug over a duration long enough for maintenance therapy to take effect, if needed.[129] Studies suggest that corticosteroids do not impact mucosal healing and are not effective in maintaining remission.[28] Up to one-third of patients with CD require chronic administration of corticosteroids to prevent recurrence of symptoms (termed steroid-dependent CD).[126] Because C.J. has not tolerated tapering and long-term high-dose treatment is unsafe, alternative maintenance therapy is warranted.

With the advent of biologics, some experts advocate for a "top-down" approach, in which biologic therapy is introduced upfront for high-risk patients with moderate-to-severe CD.[147] TNF blockers may be appropriate at this time. Typically, anti-integrin and anti-interleukin therapies are reserved for maintenance therapy if used for induction.[70–72] In this case, a conventional approach is also acceptable, particularly given that the cost of thiopurines and methotrexate is often favorable. Guidelines recommend considering thiopurines for steroid-dependent disease and maintenance in relapsing cases, regardless of anatomic site or severity.[28] Methotrexate is another conventional option, typically reserved where other treatments have failed (see Table 24-5). C.J. can take 6-MP 120 mg (1.5 mg/kg/day) or AZA 200 mg (2.5 mg/kg/day). He will

continue prednisone upon thiopurine initiation because it may take several weeks to take effect, but the steroid will soon be tapered. C.J.'s WBC counts should be monitored regularly, and he should be counseled regarding the signs and symptoms of severe infection and pancreatitis (see Table 24-4).

Case 24-2, Question 4: Six weeks into initiating AZA and tapering prednisone (currently, 10 mg/day), C.J. returns to the clinic for routine laboratory monitoring. His WBC count is 1800/μL with an absolute neutrophil count of 1100/μL. He is afebrile. His physical examination finding is negative for any sign of infection. This is in keeping with the current person-first terminology.

AZA is a prodrug that is converted to the active moiety, 6-MP, in the liver, which is then metabolized by xanthine oxidase, hypoxanthine- guanine phosphoribosyltransferase, or thiopurine-S-methyltransferase (TPMT).[51,137,148] Genetic polymorphisms determine the extent of TPMT activity, which varies by ethnicity.[148] An estimated 90% of adults have normal enzymatic activity, but those with reduced TPMT activity are predisposed to myelosuppression because of drug accumulation. Pharmacogenomic testing to assess TPMT activity may inform the appropriate use of thiopurines to minimize the incidence of bone marrow suppression.[137,148]

For patients such as C.J. who experience neutropenia from AZA therapy, the primary treatment is to discontinue use and monitor for signs and symptoms of infection. Upon discontinuation, the WBC count should be monitored regularly until it exceeds 3000/μL. This may take several days to weeks. In extreme cases, the use of granulocyte colony-stimulating factor may be considered. The clinician should avoid initiating another thiopurine in the future, including 6-MP.

Case 24-2, Question 5: C.J.'s leukocyte count returned to normal after 3 weeks. Unfortunately, he experienced a flare of his CD symptoms, specifically, an increase in diarrhea and abdominal pain that C.J. has noted during the past 2 weeks. He states that he and his wife are preparing to start a family soon, and he would like to control his symptoms before new stressors confound his symptoms. He lives in a rural area, far from an infusion clinic, so he prefers the

autonomy of home medication use. What other agents should be considered at this time?

Methotrexate induces and maintains remission in patients with refractory disease and can be used in the case of failed or intolerable thiopurine use. Clinical improvement or reduction in corticosteroid doses have been observed with 15 mg/week subcutaneous methotrexate or 25 mg/week of intramuscular methotrexate, but its effect on endoscopic healing has not been assessed.[149] Folic acid is required in combination with methotrexate because of its inhibition of dihydrofolate reductase.[53,54] Reasons for methotrexate discontinuation include GI toxicity, neutropenia, and hepatotoxicity. For C.J., however, this option is not appropriate because methotrexate is teratogenic. Therefore, pregnancy should be avoided when either partner is using methotrexate, up to 3 months following discontinuation for males, and after completion of at least one ovulatory cycle following discontinuation for females.[53,54,150]

C.J. has been experiencing new symptoms for 2 weeks, so it would be appropriate to reconsider induction at this time, followed by maintenance. Natalizumab is not preferred based on safety, convenience, and route of administration (see Table 24-5). Infliximab and vedolizumab are also not self-administered at home. Ustekinumab is administered IV but only for the induction dose, followed by subcutaneous injections every 8 weeks thereafter. Adalimumab and certolizumab pegol are self-administered every 2 or 4 weeks, respectively, following induction treatment. TNF blockers have boxed warnings for increased risk of infection and malignancy, whereas ustekinumab has similar but less pronounced risks, in addition to a rare risk for reversible posterior leukoencephalopathy syndrome.

C.J. and his provider learn that adalimumab is the preferred agent on his insurance formulary, and C.J. does not meet prior authorization criteria for alternative therapies. He will start adalimumab 160 mg subcutaneously (four 40-mg injections for 1 day or two 40-mg injections for 2 days) followed by 80 mg in 2 weeks.

Two weeks after the second dose, he will initiate a 40-mg maintenance injection every other week. C.J. must test negative for hepatitis B, tuberculosis, and all other active infections before starting treatment. Periodic tuberculosis screenings must also return negative results. He will monitor for signs and symptoms of hypersensitivity, and infection throughout its use.

Case 24-2, Question 6: C.J. has developed an enterocutaneous fistula with his latest disease exacerbation, and nothing is helping him achieve remission. Does this new development require C.J. to change his therapy?

Adalimumab may be effective for treating perianal fistulas, but infliximab is now firmly established as an integral treatment for fistulizing disease.[28] Hypersensitivity reactions may be severe or delayed, but typically include urticaria, dyspnea, and/or hypotension within 2 hours of infusion.[65–69] Pretreatment with diphenhydramine, acetaminophen, and/or corticosteroids is common to mitigate these reactions.

Like all TNF blockers, infliximab should be avoided in patients with active infection. Screening and/or monitoring for tuberculosis and hepatitis are recommended before and throughout treatment. Current data concerning a link between TNF-α blocker use and malignancy are conflicting.[35] To date, the data suggest a small risk of developing lymphoma when using TNF-α blockers, but the benefits of increased quality of life may outweigh the risk.

Case 24-2, Question 7: C.J. was initiated on infliximab 400 mg IV every 8 weeks, and it was successful in keeping him symptom free. However, after 2 years of remission, C.J. is hospitalized for an acute exacerbation of right lower quadrant pain associated with abdominal distension, lack of bowel movements, and vomiting during the past 24 hours. Radiographic studies indicate partial small bowel obstruction at the terminal ileum. Is surgery indicated at this time?

Owing to the natural progression of disease, medical therapy may be inadequate. Most patients with CD require at least one surgical resection throughout the course of disease.[151] In contrast to UC,

surgical removal of the involved bowel in CD is not a definitive form of therapy, as indicated by the risk of recurrence even after extensive resection.[126] Depending on the amount and site of the bowel removed during surgery, specific malabsorption syndromes can occur (eg, vitamin B_{12} malabsorption with removal of the terminal ileum). If an ileostomy is necessary, the patient may need psychological support. Surgery is indicated only for specific complications that are unresponsive to medical therapy, and it should be avoided if possible.

IRRITABLE BOWEL SYNDROME

IBS is one of the most highly prevalent disorders of the gut–brain interaction, in which a patient has recurrent abdominal pain associated with defecation, bloating, and disordered bowel habits.[152]

The prevalence of IBS in the United States is 10% to 20%, with a higher incidence in patients younger than 50 years.[153] Patients with IBS have a poor quality of life, and there are significant gender differences and variability among IBS subtypes.[153,154] Compared to males, females are almost three times more likely to have IBS, have a higher incidence of irritable bowel syndrome with constipation (IBS-C), and report more fatigue, depression, anxiety, and a lower quality of life.[154,155] In contrast, males with IBS report a higher incidence of irritable bowel syndrome with diarrhea (IBS-D).[155,156] Patients with IBS-C are more likely to report avoiding sex, difficulty concentrating, and feeling self-conscious compared to those with IBS-D. Patients with IBS-D more frequently report avoiding places without bathrooms, having difficulty making plans, and being reluctant to travel, compared to those with IBS-C.[157] The U.S. health care burden exceeds $20 billion for IBS management.[158] Despite patients' frequent use of health care services and decrease in their quality of life, IBS is non–life-threatening with a good prognosis.[159]

Pathophysiology

The pathophysiology of IBS remains complex and poorly understood.[159] There are multiple influencing factors, including an interaction between the brain–gut axis, psychosocial factors, visceral hypersensitivity, GI dysmotility, altered microbiota, and immune dysregulation. Other factors include intestinal permeability, postinfectious low-grade inflammation, bacterial overgrowth, and food sensitivity.[152,159,160]

The brain and gut communicate with each other using complex pathways between the enteric nervous system, the autonomic nervous system, the hypothalamus–pituitary–adrenal axis, and the central nervous system.[161] This brain–gut communication affects GI motility, secretion, and immune regulation, which influences food intake, digestion, gut sensation, and bowel movement. In IBS, this communication between the brain and gut is disrupted.[159] For example, genetics, culture, and the environment (trauma, infection, parental behaviors) influence psychosocial development. Psychosocial development includes coping skills, personality traits, psychological state, cognition, and social support. Genetics, culture, and environment also influence gut physiology (motility, sensation, altered microflora, immune dysfunction, inflammation, and the effect of food/diet).[162] Scientists believe that IBS results from the dysfunctional interactions between psychosocial development and physiologic factors.[162]

Visceral hypersensitivity is a mechanism for abdominal pain in IBS. Studies show that patients with IBS have dysregulation with activation of certain brain regions affecting pain during rectal distension.[159,163]

Experts suggest that the interstitial cells of Cajal (ICC) produce, propagate, and regulate waves affecting GI motility, causing high-amplitude propagating contractions resulting in an urge to defecate, abdominal cramps, and pain. Having less ICC results in fewer contractions, leading to constipation in IBS-C. Alternatively, with more ICC, there are more contractions, leading to diarrhea in IBS-D.[152,160]

The gut microbiota play a major role in digestion, homeostasis, and immunity, but early life stresses alter its composition.[161] Patients with altered microbiota can develop immune dysregulation, mucosal membrane permeability, altered tight cell junction, activated mast cells, increased inflammatory cytokine release, and inflammation leading to visceral hypersensitivity.[162] Patients who had an acute gastroenteritis, with a large bacterial load, lengthy disease duration, psychosocial condition, high life stress, sexual or physical abuse history, and/or poor coping skills can develop severe postinfectious IBS with poor outcomes.[162]

Clinical Presentation

The symptoms of IBS include abdominal bloating, distension, recurrent abdominal pain associated with defecation, and disordered bowel habits (ie, constipation, diarrhea, or both). Notably, these symptoms cannot be explained by structural or biochemical abnormalities.[154] Stress and food aggravate the symptoms, which vary in frequency and severity, resulting in a chronic debilitating relapsing and remitting disorder.[164] Patients may also commonly report extra-GI symptoms of headache, dysmenorrhea, dyspareunia, and fatigue. In addition, patients commonly present with comorbidities such as stress, anxiety, depression, dyspepsia, interstitial cystitis, and fibromyalgia.[162,164]

Diagnosis

There are no objective diagnostic tests for IBS, and the condition is diagnosed based on clinical presentation and exclusion of other causes as listed in **Table 24-7**.[154,165,166] The Rome IV criteria is used for IBS diagnosis, and is made when the patient presents with recurrent abdominal pain, at least 1 day per week in the past 3 months, associated with any two or more of the following:

Table 24-7

Differential Diagnoses to Consider Before Making an Irritable Bowel Syndrome Diagnosis

Inflammatory bowel disease
Food intolerance or sensitivity
Small intestinal bacterial overgrowth
Bile acid diarrhea
Pancreatic exocrine deficiency
Medication side effects
Functional diarrhea
Colon cancer
Chronic parasitic infection
Microscopic colitis
Thyroid disease
Celiac disease

Sources: Reprinted with permission from Kurin M, Cooper G. Irritable bowel syndrome with diarrhea: Treatment is a work in progress. *Cleve Clin J Med*. 2020;87(8):501-511. doi:10.3949/ccjm.87a.19011. Copyright © 2022 Cleveland Clinic Foundation. All rights reserved.

1. related to defecation, and/or
2. associated with a change in frequency of stool, and/or
3. associated with a change in form (appearance) of the stool.

IBS is diagnosed if any of the abovementioned three criteria is fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis.[154]

The Bristol Stool Form Scale, **Figure 24-3**, is used as an aid to help patients describe their stool form (eg, hard/lumpy or loose/watery stool) without the use of laxatives or antidiarrheal medications.[154,167] Because there are no organic or structural observations in patients with IBS, a colonoscopy is not generally required, and reserved only for patients older than 50 years, or those who present with alarm symptoms, which include[154,158]:

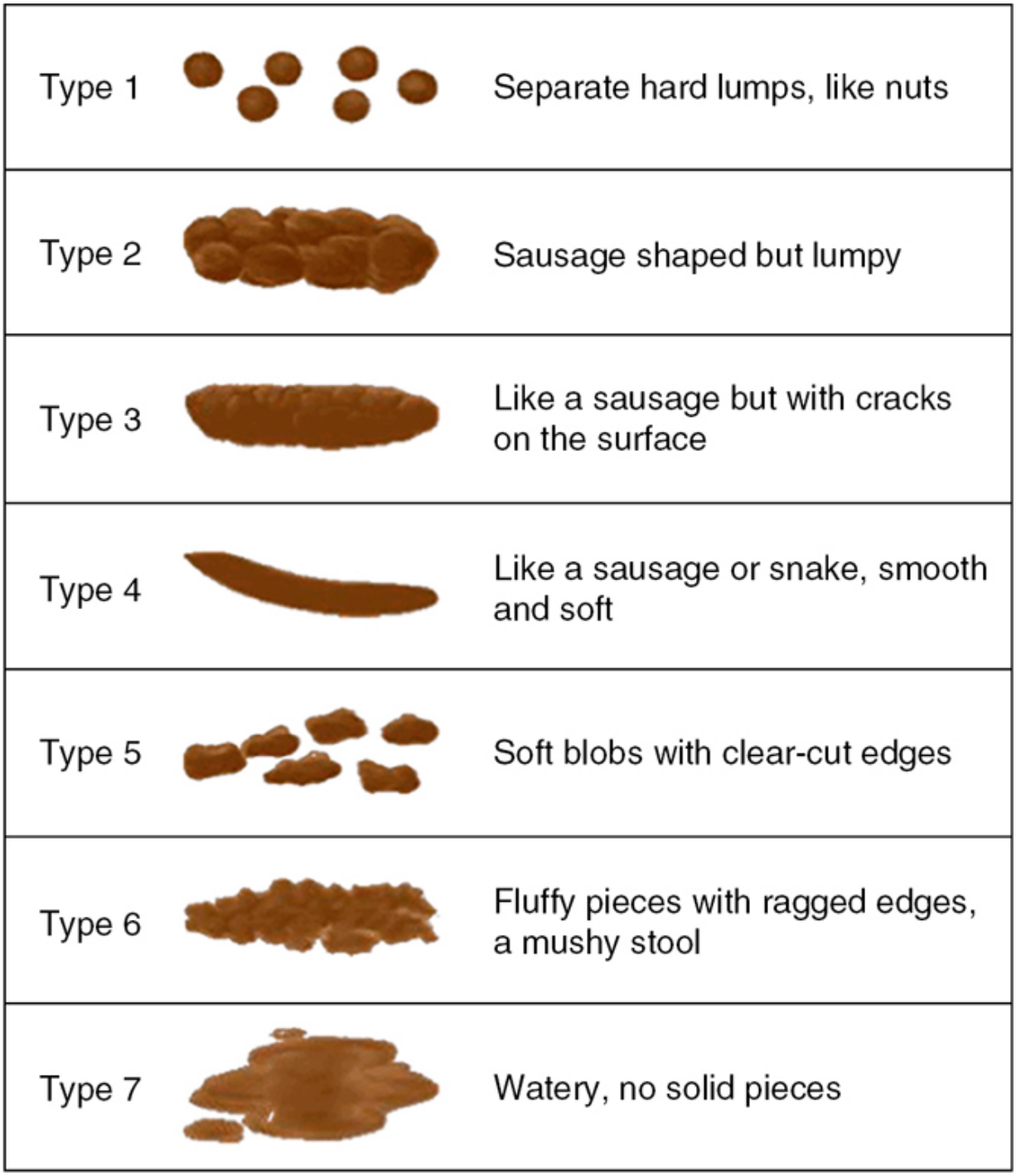


Figure 24-3 Bristol Stool Form Scale. (Reprinted with permission from the Rome Foundation. All rights reserved.)

- Abdominal pain and cramping not relieved by bowel movement
- Nocturnal symptoms (abdominal pain and cramping, which awakes the sufferer from sleep)

- Palpable abdominal mass
- Fatigue
- GI or rectal bleeding
- Iron-deficient anemia
- Weight loss (significant, unintentional, and unexplained)
- Fever
- Night sweats
- Age of onset older than 50 years
- Family history of IBD, colorectal cancer, or organic GI disease
- Symptoms that persist when fasting
- Low fecal osmotic gap

Once diagnosed, IBS is differentiated into subtypes based on the predominant symptom: IBS-C, IBS-D, irritable bowel syndrome mixed (IBS-M), or unclassified irritable bowel syndrome (IBS-U) defined in **Table 24-8**.[154]

Table 24-8
Diagnostic Criteria for Irritable Bowel Subtypes

Subtypes	Diagnostic Criteria
IBS-C	>25% of bowel movements with Bristol Stool Form types 1, 2 and <25% of bowel movements with Bristol Stool Form types 6, 7
IBS-D	>25% of bowel movements with Bristol Stool Form types 6, 7 and <25% of bowel movements with Bristol Stool Form types 1, 2
IBS-M	>25% of bowel movements with Bristol Stool Form types 1, 2 and >25% of bowel movements with Bristol Stool Form types 6, 7
IBS-U	Patients meet diagnostic criteria for IBS, but their bowel habits cannot be accurately categorized in any of the abovementioned subtypes.

IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, mixed irritable bowel syndrome; IBS-U, unsubtyped irritable bowel syndrome.

Reprinted from Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterolog y*. 2016;150(6):1393–1407.e5. © 2016 The AGA Institute. With permission.

Overview of Treatment

Treatment should target the predominant symptom such as constipation, diarrhea, bloating, or abdominal pain. There are currently no available agents that treat the entire spectrum of IBS symptoms, so multiple interventions may be warranted. Nonpharmacologic interventions target stress relief and lifestyle modifications. These include reassuring the patient, creating a strong physician–patient relationship, improving sleep habits, increasing exercise, and subscribing to a low-FODMAP diet (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols).[154] Soluble dietary fibers, such as psyllium, act as stool bulking agents and improve stool consistency, but there are few studies to evaluate their role in IBS-D.[158] Osmotic laxatives and stool softeners treat constipation, although not specifically U.S. Food and Drug Administration (FDA) approved for IBS-C. According to the American College of Gastroenterology, tricyclic antidepressants are recommended for abdominal pain and IBS global symptoms, but antispasmodics are not recommended.[168] No medications are FDA approved to treat IBS-M or IBS-U.[169] Clinicians can use the suggested treatment algorithm depicted in **Figure 24-4** for IBS management.[158,164,165,168,170,171]

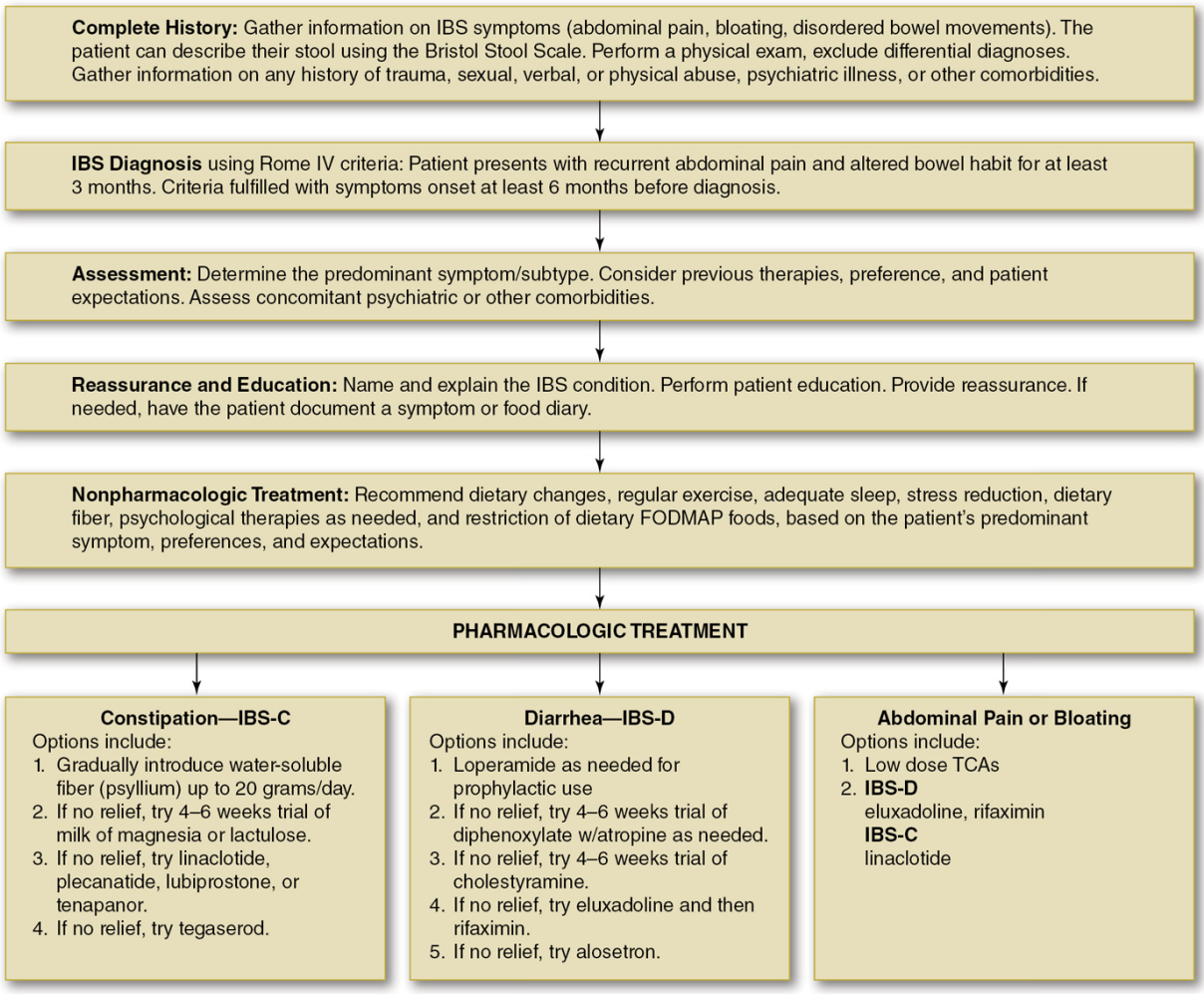


Figure 24-4 Irritable bowel syndrome management algorithm. FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; TCA, tricylic antidepressants. Source: See references 157, 163, 164, 167, 169, 170.

PATIENT EDUCATION

CASE 24-3

QUESTION 1: V.H. is a 28-year-old female who presents with severe abdominal pain (rated 7 on a scale of 0–10) and bloating with the passage of hard, pellet-like stools every 3 days for the past 7 months. She notices that an "attack" normally occurs after a large meal. Her past medical history is significant for

generalized anxiety disorder for which she takes buspirone. She denies using alcohol, tobacco, or illicit drugs.

What subjective data in the case is consistent with IBS?

V.H. presents with recurrent abdominal pain at least 1 day per week in the past 3 months that is associated with defecation and constipation. The symptoms started at least 6 months ago, consistent with the diagnosis of IBS. Although common in IBS, bloating and symptoms exacerbated by meals are not criteria for diagnosis.

CASE 24-3, QUESTION 2: V.H. is concerned that her symptoms are indicative of cancer. How should the clinician respond to V.H.'s concerns?

Many patients are fearful that their symptoms are indicative of cancer. Clinicians should reassure V.H. that the diagnosis is accurate, benign, and treatable.[154] An effective physician–patient relationship is important to maintain patient satisfaction, adherence to therapy, and symptom reduction.[172] Involving patients at the earliest stages in their treatment plan is vital for patient acceptance to avoid "doctor shopping," where patients seek second opinions from other providers. Initial interventions may be multidisciplinary to provide reassurance and provide interactive patient education.

CASE 24-3, QUESTION 3: After educating V.H. on IBS, she seems less worried and suggests making lifestyle modifications to "cure" IBS. What evidence-based, nonpharmacologic recommendations can be provided?

NONPHARMACOLOGIC: LIFESTYLE MODIFICATIONS

Many patients believe their symptoms are diet related.[165] The mechanisms by which food can worsen IBS symptoms include gastrocolic reflex, food maldigestion or malabsorption, food allergy, and visceral hypersensitivity.[173] More than 40% of patients with IBS have lactose intolerance and experience pain, bloating, and diarrhea after ingesting milk-based products. Some experts recommend

avoiding lactose, whether intolerant or not.[158] However, exclusion diets are generally not recommended because most patients with IBS have difficulty complying or will not achieve significant symptomatic relief.[165] Current experts recommend against following a gluten-free diet, because trials did not demonstrate a positive impact on IBS symptoms.[165]

Patients with IBS can have poor absorption of FODMAP diets because fermentation by gut bacteria produces gas, luminal distension, bloating, and worsening abdominal pain.[173] Some researchers believe a low-FODMAP diet can have detrimental effects on the normal gut microbiota, and thus only recommend it for symptomatic patients.[174] However, the American College of Gastroenterology recommends a low-FODMAP diet for overall symptom improvement and pain reduction in patients with IBS.[165]

Prebiotics and synbiotics lack efficacy in treating IBS symptoms, and probiotic use is now restricted to clinical trials only.[165,175] Patients with IBS-C may benefit from increased consumption of soluble fiber up to 20 g daily. Psyllium significantly improved IBS symptoms, stool viscosity, and frequency in trials.[165,176] However, large doses of fiber can lead to abdominal gas and bloating, so patients should introduce fiber gradually. Insoluble fiber (wheat bran) is not effective and can worsen symptoms of bloating, cramping, or flatulence.[177] Exercise improves physical and mental health, but needs rigorous studies as a treatment choice.[165]

V.H. should be reminded that IBS has no cure. She should be encouraged to keep a food diary to identify any food intolerances and avoid those foods. Whether she is lactose intolerant or not, she can omit dairy products. She should avoid prebiotics, synbiotics, probiotics, insoluble fiber, and gluten-free diets, which are not evidence based, and can increase unnecessary cost. To reduce bloating and gas, she should eat small, frequent meals, gradually introduce soluble fiber (eg, psyllium), and follow a low-FODMAP diet. She should incorporate exercise and adequate sleep to bolster physical and mental health.

Case 24-3, Question 4: Several months have passed since V.H. was first diagnosed with IBS-C. She still reports of some constipation and abdominal pain. She wants to try other nonpharmacologic therapies. What other nonpharmacologic options are available?

PSYCHOLOGICAL THERAPIES

Psychological disorders are present in a sizable number of patients with IBS. Treating comorbid psychological disorders and identifying overlooked sexual abuse or posttraumatic stress disorder are important components to successfully treat IBS.[178] Some patients exhibit a phenomenon known as *somatization*, which is a tendency to experience and communicate somatic distress in response to psychosocial stress. Patients with IBS should be encouraged to seek health care for their condition.[179] Educational sessions and psychological techniques are thought to decrease the risk of developing somatization, but data are limited.[180]

In a recent meta-analysis, cognitive behavioral therapy, relaxation therapy, multicomponent psychological therapy, hypnotherapy, and dynamic psychotherapy have all been shown to reduce overall symptom burden in patients with IBS.[181] For patients with psychiatric comorbidities, poor social support, traumatic life events, and dysfunctional relationships, clinicians should consider psychotherapy very early in IBS management.[181] An expert consensus recommends psychological therapies for patients who have not responded to first- or second-line treatments after 3 to 6 months, or for those with a significant association between stress and IBS symptoms.[182]

Case 24-3, Question 5: V.H. has since changed her diet and had therapeutic trials of several over-the-counter agents that were either poorly tolerated or lacked effectiveness. What other options are available for treating V.H.'s IBS-C?

Pharmacotherapy for Irritable Bowel Syndrome With Constipation

For patients with IBS-C in whom soluble fiber fails, osmotic laxatives

(e.g, milk of magnesia, lactulose, PEG without electrolytes), or stool softeners may be tried. However, the ACG recommends against the use of PEG products to relieve global IBS symptoms in those with IBS-C.[168,183] Few well-designed trials assess the use of any laxative for IBS. Laxatives are usually well tolerated and provide constipation relief, but may cause bloating, diarrhea, taste disturbances, and hypermagnesemia (especially in patients with renal impairment). Thus, other treatments will be needed in many patients.

The agents lubiprostone, linaclotide, plecanatide, and tenapanor are indicated for the treatment of IBS-C, and they all share the same contraindication of avoiding in patients with mechanical GI obstructions.[184–187] Although lubiprostone is indicated only for adults age 18 years and older, all the other agents have additional documented contraindications for avoiding in children younger than 6 years. In addition, clinicians should avoid use of all four agents in children ages 6 to 17 years because of death from dehydration in younger juvenile mice.[184–187]

LUBIPROSTONE (AMITIZA®)

Lubiprostone is a GI chloride channel activator that enhances chloride influx into the intestinal lumen, resulting in increased intestinal fluid secretion and small and large bowel intestinal transit.[184] The FDA approved lubiprostone for females older than 18 years with IBS-C, at a dose of 8 µg orally twice daily with food to reduce the adverse effects of nausea and vomiting.[184]

Two studies found that lubiprostone was moderately effective in improving patient perception of constipation.[188,189] Very few males with IBS-C were enrolled in the clinical trials with lubiprostone to draw any conclusions about its effectiveness in males. Lubiprostone is associated with teratogenic effects in animals, so females of childbearing age need a negative pregnancy test result before beginning therapy and must use contraception during therapy.[184] Lubiprostone is more expensive than are traditional laxatives, and should be reserved for patients with IBS-C who have failed cheaper alternatives. Acute-onset dyspnea, syncope, and hypotension may

occur, but typically resolve within a few hours or upon discontinuation.[184] Monitor patients for dyspnea, hypotension, and syncope, especially if patients are taking concomitant antihypertensives or high doses of lubiprostone.[184]

LINACLOTIDE (LINZESS®)

Linaclotide is a guanylate cyclase-C agonist and, together with its active metabolite, acts locally on the luminal surface of the intestinal epithelium to stimulate and increase chloride and bicarbonate secretions into the intestinal lumen, increase GI motility, decrease pain, and improve stool consistency. Linaclotide is approved for adult male and female patients with IBS-C at an oral dose of 290 µg daily taken 30 minutes before breakfast to reduce the side effects of diarrhea, abdominal pain, and gas.[185]

Patients receiving linaclotide in trials reported statistically significant improvements in abdominal pain, discomfort, bloating, bowel straining, constipation, and stool consistency.[190,191] Upon discontinuation, abdominal pain returned and bowel movements decreased to levels similar to the placebo group, but there was no rebound effect noted.[190,191] The main side effects of linaclotide are diarrhea, abdominal pain, and flatulence.[185]

PLECANATIDE (TRULANCE®)

Plecanatide is a guanylate cyclase-C agonist with a mechanism of action similar to that of linaclotide, but whereas linaclotide acts throughout the entire GI tract, plecanatide affects only the proximal small bowel.[192] Plecanatide is similar to endogenous uroguanylin, except for a single amino acid substitution for greater binding affinity, and activates guanylate cyclase-C receptors in a pH-sensitive manner in the small intestine to stimulate fluid secretion, maintain stool consistency, and decrease visceral pain. Experts believe that this difference results in less diarrhea with plecanatide compared to that with linaclotide.[192] Plecanatide is approved for adult male and female patients older than 18 years with IBS-C at an oral dose of 3 mg daily without regard to food.[186]

Patients taking plecanatide in clinical trials demonstrated significant improvements in bowel movements, stool consistency, pain reduction, satisfaction, and a desire to continue therapy, with a low incidence of diarrhea.[193,194]

TENAPANOR (IBSRELA®)

Tenapanor inhibits the sodium/hydrogen exchanger isoform 3 on the apical enterocytes of the small intestine and colon, reducing sodium absorption from the colon and intestines. This inhibition results in increased intestinal lumen secretions and accelerated gut transit time, resulting in a softer stool consistency and normalized bowel movement frequency.[195] Tenapanor is FDA approved for treating IBS-C in adult male and female patients older than 18 years at a dose of 50 mg orally twice daily to be taken immediately before breakfast and dinner.[187]

Patients on tenapanor for IBS-C had significant improvement in abdominal and global IBS symptoms in clinical trials.[196] Diarrhea was the most reported adverse effect. Clinicians and patients should monitor for signs and symptoms of diarrhea, which can lead to dehydration. Patients with renal impairment should be carefully monitored because they may be at greater risk for adverse reactions including diarrhea and hyperkalemia, requiring subsequent hospitalizations.[187]

In the absence of head-to-head trials, a meta-analysis was designed to compare the efficacy of linaclotide, lubiprostone, tenapanor, and plecanatide for treating IBS-C.[197] Study results show that all therapies were efficacious and superior to placebo. Linaclotide was ranked highest in efficacy by achieving significant abdominal pain reduction and complete spontaneous bowel movements. A complete spontaneous bowel movement occurs without the use of rescue medication and the sensation of complete evacuation. Tenapanor was ranked first for decreasing bloating, and plecanatide was ranked first for safety. Diarrhea was common among all therapies except lubiprostone, with which nausea was more common.[197] Current guidelines strongly recommend linaclotide

because of high certainty of evidence, but cautions its use in patients who want to avoid diarrhea and high drug cost. Plecanatide and lubiprostone are recommended over no drug treatment, but the evidence is moderate.[168] Tenapanor is not addressed in current guidelines because of recent FDA approval.[168] At a minimum, patients should monitor for treatment efficacy by quantifying stool frequency, the number of complete spontaneous bowel movements per week, and abdominal pain scores.[198]

TEGASEROD (ZELNORM®)

Tegaserod is a partial neuronal 5-HT4 receptor agonist that accelerates colonic peristalsis, decreases transit time, increases intestinal secretion, and reduces visceral hypersensitivity and pain.[199] Tegaserod is approved for females younger than 65 years with IBS-C, without a history of cardiovascular ischemic disease, and who have zero or one risk factor for cardiovascular disease. A dose of 6 mg orally twice daily should be administered on an empty stomach >30 minutes before a meal because its bioavailability decreases by 40% to 65% when taken with food.[200]

Tegaserod demonstrates modest but significant benefits in reducing abdominal pain, discomfort, bloating, and constipation with overall improvement in well-being in clinical trials.[199] Headache, abdominal pain, and diarrhea were the main adverse effects in trials.[200] Postmarketing analyses revealed increased incidence of heart attack, stroke, and unstable angina, resulting in halting all sales in 2007, followed by restricted use in 2009.[201] After a safety review, tegaserod was reintroduced for treating IBS-C in females.[201] Tegaserod is contraindicated in patients with a history of ischemic colitis, bowel obstruction, myocardial infarction, stroke, transient ischemic attack, angina, severe renal or hepatic impairment, or symptomatic gallbladder disease.[200] Tegaserod should be discontinued and not rechallenged in patients with new or sudden worsening abdominal pain, rectal bleeding, or bloody diarrhea indicative of ischemic colitis or other forms of intestinal ischemia.[200]

Clinicians should reserve tegaserod use for when other options for IBS-C have been exhausted.

Given that V.H. is not responding to over-the-counter laxatives, she needs a more efficacious agent. If cost and the fear of diarrhea are not significant factors, she can consider a trial of linaclotide to reduce her abdominal pain and increase complete spontaneous bowel movements. If diarrhea is a concern, trials of plecanatide or lubiprostone are reasonable choices for this patient because they may produce less diarrhea. Although tenapanor is not addressed by current guidelines, it is a viable alternative, when available in pharmacies, if linaclotide, plecanatide, or lubiprostone therapies fail. Owing to reported significant adverse effects, tegaserod can be withheld until safer therapeutic options are exhausted.

Irritable Bowel Syndrome–Associated Pain and Bloating

CASE 24-4

Question 1: L.K. is a 38-year-old female with a history of abdominal pain and episodic diarrhea. She works as a college professor. Just before teaching, she experiences "attacks" of abdominal pain and diarrhea. Her past medical history is significant for fibromyalgia and IBS-D. She takes no medications and has no known drug allergies. She denies alcohol, tobacco, or illicit drug use. She currently has two loose stools daily, with bouts of abdominal pain (severity of 7 on a 0–10 pain scale) described as "cramping" several times daily.

What pharmacologic options are available for L.K.'s abdominal pain?

ANTISPASMODICS

Antispasmodics (eg, hyoscyamine, dicyclomine, and peppermint oil) decrease GI spasticity, abdominal pain, cramping, and motility.[202,203] Clinical trials that have examined the use of these agents in IBS have been plagued by small numbers and methodologic problems. Systematic reviews have found that smooth muscle relaxants were superior to placebo in improving abdominal pain, but less effective in treating other IBS symptoms.[204] Current treatment guidelines

recommend against antispasmodics as options for pain or bloating associated with IBS.[168] If prescribed, an as-needed strategy of use has been advocated as opposed to continuous dosing owing to anticholinergic adverse effects.

ANTIDEPRESSANTS

Current treatment guidelines recommend using low-dose tricyclic antidepressants because of their analgesic effects, but selective serotonin-reuptake inhibitors are not recommended.[168] A recent meta-analysis found low-dose tricyclic antidepressants significantly improved abdominal pain, bloating, and other IBS symptoms compared with placebo.[205] A 3-month trial at a target dose should be attempted before confirming therapeutic failure. As-needed secondary amine tricyclic antidepressants (eg, doxepin, nortriptyline, desipramine) are better tolerated than are tertiary amines (eg, amitriptyline, imipramine) owing to decreased anticholinergic adverse effects such as sedation, dry mucous membranes, urinary retention, and weight gain. Clinicians can reserve tricyclic antidepressants for moderate-to-severe cases of abdominal pain and choose agents with the least anticholinergic effects for patients with IBS-C. Imipramine or amitriptyline can be recommended for patients with IBS-D.[205]

For L.K., amitriptyline 10 mg orally at bedtime can be initiated with titration to symptom relief for her moderately severe abdominal pain because she has IBS-D.

Irritable Bowel Syndrome With Diarrhea

Case 24-4, Question 2: Two weeks after L.K. was initiated on amitriptyline, she reports significant abdominal pain relief. She is sleeping better, and now rates her pain as a 2 on a 0–10 scale. Her diarrhea has improved, but she still experiences a "diarrhea attack" before each lecture. What other treatments are available for IBS-D? What are the risks and benefits of these treatments?

STANDARD ANTIDIARRHEALS

Loperamide, an opioid agonist that penetrates poorly into the central nervous system and slows accelerated small bowel and colonic transit, is the preferred agent for IBS-D because of its efficacy, cost, availability, and safety profile.[206] Loperamide improves diarrhea and global well-being.[207] As-needed dosing is preferred to scheduled dosing (eg, 2–4 mg PO up to qid as needed up to 16 mg daily), especially as prophylaxis before an identified stressful situation. Diphenoxylate with atropine is a second-line agent because of its increased risk of anticholinergic adverse effects. Cholestyramine is occasionally used in refractory cases of IBS-D, especially when bile acid malabsorption is suspected or confirmed, but it is poorly tolerated and has a substantial number of drug interactions.[208]

ALOSETRON (LOTRONEX®)

Alosetron is a highly potent 5-HT3 receptor antagonist that slows colonic motility and transit time, increases intraluminal sodium absorption, and decreases small intestinal secretions and abdominal pain.[209] Alosetron is FDA approved for females with severe IBS-D with chronic symptoms lasting 6 months or longer, who do not have anatomic or biochemical abnormalities of the GI tract, and who have not responded to conventional therapy. The starting dose for alosetron is 0.5 mg orally twice daily with or without food for 1 month. If, after 4 weeks, alosetron is well tolerated but does not control IBS symptoms, then the dosage can be increased to 1 mg twice daily.[210]

In clinical trials, alosetron was effective in improving stool consistency, frequency, and abdominal pain and discomfort as well as decreasing fecal urgency in females with IBS compared to placebo.[211] Constipation was the most frequently reported adverse effect.[211] Postmarketing reports of severe constipation with cases of bowel obstruction and ischemic colitis were reported.[212] Bowel perforation and, rarely, death were also reported, leading to withdrawal from the market in 2000. After extensive lobbying by patient groups, alosetron was reintroduced to the U.S. market in 2002 with restricted conditions for use. Prescribers must be registered with a risk evaluation and mitigation program before

prescribing alosetron, and patients must sign a patient–physician agreement and be provided with a printed medication guide. Patients must not start alosetron if they have a history of constipation, bowel obstruction, ischemic colitis, IBD, or a thromboembolic disorder.[210] A review of the mandatory postmarketing surveillance system found an overall low rate of ischemic colitis.[213] Patients must discontinue therapy if they experience constipation, new or worsening abdominal pain, or bloody stool.[210] A provider should be contacted if there is no symptom improvement after 4 weeks of use.

RIFAXIMIN (XIFAXAN®)

Rifaximin is an antibiotic that is theorized to inhibit bacterial translocation across the GI mucosa, alters the bacterial composition of gut microbiota, modulates the brain–gut axis, and reduces local inflammation.[214,215] Rifaximin is approved for the treatment of IBS-D in adults at a dose of a 550-mg tablet orally three times a day for 14 days with or without food. Patients who experience recurrence can be retreated up to two times with the same regimen.[216]

Because some evidence exists concerning an association of bacterial GI infection and IBS symptoms, some investigators suggest that small bowel flora overgrowth may contribute to IBS symptoms. Rifaximin was shown in trials to improve global symptoms in patients with IBS.[214,215,217] The size of improvement was small, but was considered clinically relevant. The most common side effects include nausea and an increase in ALT. Caution should be used when using rifaximin in patients with severe liver impairment.[216] American College of Gastroenterology guidelines recommend rifaximin to treat global IBS-D symptoms.[168] Patients should monitor for worsening diarrhea after therapy given increased risk of *C. difficile* with its use.[216]

ELUXADOLINE (VIBERZI®)

Eluxadoline is a minimally absorbed μ-opioid receptor agonist and δ-opioid receptor antagonist, in which the combination causes decreased abdominal pain, intestinal motility, and diarrhea.[218]

Eluxadoline is FDA approved for IBS-D in adults at a dose of 100 mg orally twice daily taken with food. The dose is reduced to 75 mg twice daily in patients who are unable to tolerate the original dose, have no gallbladder, have mild-to-moderate liver impairment, or are taking organic anion transporting polypeptide (OATP1B1) inhibitors.[219]

In trials, patients treated with eluxadoline had decreased abdominal pain and increase in stool consistency without significant risk of constipation.[218] The most common side effects in patients treated with eluxadoline include constipation, nausea, and abdominal pain, but the most serious is the risk of sphincter of Oddi spasm and pancreatitis among patients with a history of alcohol abuse or cholecystectomy.[219] Eluxadoline should not be used in patients with a history of bile duct obstruction, pancreatitis, severe liver impairment, and in patients who drink more than three alcoholic beverages daily.[219]

Patients should be counseled to avoid alosetron or loperamide in combination with eluxadoline use on a chronic basis because of the concern for constipation, although they can be infrequently used together as needed. Loperamide should be discontinued at once if constipation occurs. Similarly, eluxadoline requires discontinuation for constipation lasting for more than 4 days. Patients should also be recommended to avoid concomitant use of any drugs that can cause constipation (eg, anticholinergics, ferrous compounds, or opioids with eluxadoline). Pharmacists should counsel patients that eluxadoline has a potential for drug abuse.[219] At a minimum, patients should monitor for therapeutic efficacy by assessing stool consistency using the Bristol Stool Form Scale and rate their abdominal pain when it occurs.

In L.K.’s case, if dietary and other nonpharmacologic interventions fail, initiation of loperamide 2 mg as needed before lectures would be a cost-effective approach to address her symptoms. Should diarrhea worsen, or loperamide lose effectiveness, eluxadoline 100 mg twice daily with food is an alternative, whereas a course of rifaximin 550 mg tid for 14 days would be considered thereafter. The patient should combine these therapies for chronic treatment and

discontinue eluxadoline if she experiences constipation for 4 days. Alosetron is reserved only for severe cases of IBS-D.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361(21):2066–2078. doi:10.1056/NEJMra0804647 (1)

Bernstein CN, Eliakim A, Fedail S, et al. World Gastroenterology Organization Global Guidelines inflammatory bowel disease: update August 2015. *J Clin Gastroenterol*. 2016;50(10):803–818. (23)

Farmer AD, Wood E, Ruffle JK. An approach to the care of patients with irritable bowel syndrome. *CMAJ*. 2020;192(11):E275–E282. (163)

Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology Monograph on management of irritable bowel syndrome. *Am J Gastroenterol*. 2018;113:1–18. (164)

Lacy, BE, Pimentel, M, Brenner, DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome, *Am J Gastroenterol*. 2021;116(1):17-44 doi: 10.14309/ajg.0000000000001036

Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in *Am J Gastroenterol*. 2018;113(7):1101]. *Am J Gastroenterol*. 2018;113(4):481–517. doi:10.1038/ajg.2018.27 (28)

Pietrzak A, Skrzydło-Radoman´ska B, Mulak A, et al. Guidelines on the management of irritable bowel syndrome. *Gastroenterol Rev.* 2018;13(4): 259–288. (166)

Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol.* 2019;114(3): 384–413. (22)

Talley NJ, Abreu MT, Achkar JP, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol*. 2011;106(suppl 1):S2–S26. doi:10.1038/ajg.2011.58 (2)

Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14(1):4–22. doi:10.1093/ecco-jcc/jjz180 (32)

COMPLETE REFERENCES CHAPTER 24 LOWER GASTROINTESTINAL DISORDERS

1. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361(21):2066–2078. doi:10.1056/NEJMra0804647
2. Talley NJ, Abreu MT, Achkar JP, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol*. 2011;106(suppl 1):S2–S26. doi:10.1038/ajg.2011.58
3. Sairenji T, Collins KL, Evans DV. An update on inflammatory bowel disease. *Prim Care*. 2017;44(4):673–692.
4. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(1):17–30.
5. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012;142(1):46–54.e42.
6. Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of inflammatory bowel disease among adults aged ≥18 years—United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(42):1166–1169.
7. Tremaine WJ. Review article: indeterminate colitis—definition, diagnosis, and management. *Aliment Pharmacol Ther*. 2007;25(1):13–17.
8. Shi HY, Levy AN, Trivedi HD, Chan FKL, Ng SC, Ananthakrishnan AN. Ethnicity influences phenotype and outcomes in inflammatory bowel disease: a systematic review and meta-analysis of population-based studies. *Clin Gastroenterol Hepatol*. 2018;16(2):190–197.e11.
9. Eastaff-Leung N, Mabarrack N, Barbour A, Cummins A, Barry S. Foxp3+ regulatory T cells, Th17 effector cells, and cytokine environment in inflammatory bowel disease. *J Clin Immunol*. 2010;30(1):80–89.
10. Brant SR. Update on the heritability of inflammatory bowel disease: the importance of twin studies. *Inflamm Bowel Dis*. 2011;17(1):1–5.
11. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012;491(7422):119–124.
12. Franke A, McGovern DP, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci.

Nat Genet. 2010;42(12):1118–1125.
13. Khalili H, Chan SS, Lochhead P, Ananthakrishnan AN, Hart AR, Chan AT. The role of diet in the aetiopathogenesis of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2018;15(9):525–535.
14. Higuchi LM, Khalili H, Chan AT, Richter JM, Bousvaros A, Fuchs CS. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. *Am J Gastroenterol*. 2012;107(9):1399–1406.
15. Khan I, Ullah N, Zha L, et al. Alteration of gut microbiota in Inflammatory bowel disease (IBD): cause or consequence? IBD treatment targeting the gut microbiome. *Pathogens.* 2019;8(3):1–28.
16. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol*. 2016;13(1):13–27.
17. Wright EK, Kamm MA, Teo SM, Inouye M, Wagner J, Kirkwood CD. Recent advances in characterizing the gastrointestinal microbiome in Crohn's disease: a systematic review. *Inflamm Bowel Dis*. 2015;21(6):1219–1228.
18. Walker AW, Sanderson JD, Churcher C, et al. High-throughput clone library analysis of the mucosa-associated microbiota reveals dysbiosis and differences between inflamed and non-inflamed regions of the intestine in inflammatory bowel disease. *BMC Microbiol*. 2011;11:1–12.
19. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology.* 2014;146(6):1489–1499.
20. Nagalingam NA, Lynch SV. Role of the microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2011;18(5):968–984.
21. Ni J, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol*. 2017;14(10):573–584.
22. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384–413.
23. Bernstein CN, Eliakim A, Fedail S, et al. World Gastroenterology Organization Global Guidelines inflammatory bowel disease: update August 2015. *J Clin Gastroenterol*. 2016;50(10):803–818.
24. American Society for Gastrointestinal Endoscopy Standards of Practice Committee, Shergill AK, Lightdale JR, et al. The role of endoscopy in inflammatory bowel disease. *Gastrointest Endosc*. 2015;81(5):1101–1121.e1-13.
25. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural history of adult ulcerative colitis in population-based Cohorts: a systematic review. *Clin Gastroenterol Hepatol*. 2018;16(3):343–356.e3.
26. Rubin DC, Shaker A, Levin MS. Chronic intestinal inflammation: inflammatory bowel disease and colitis-associated colon cancer. *Front Immunol*. 2012;3:1–10.

27. D'Incà R, Caccaro R. Measuring disease activity in Crohn's disease: what is currently available to the clinician. *Clin Exp Gastroenterol*. 2014;7:151–161.
28. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published correction appears in *Am J Gastroenterol*. 2018;113(7):1101]. *Am J Gastroenterol*. 2018;113(4):481–517. doi:10.1038/ajg.2018.27
29. Lewis RT, Maron DJ. Efficacy and complications of surgery for Crohn's disease. *Gastroenterol Hepatol*. 2010;6(9):587–596.
30. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110(9):1324–1338.
31. Louis E. Epidemiology of the transition from early to late Crohn's disease. *Dig Dis*. 2012;30(4):376–379.
32. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14(1):4–22. doi:10.1093/ecco-jcc/jjz180
33. Strong S, Steele SR, Boutrous M, et al. Clinical practice guideline for the surgical management of Crohn's disease. *Dis Colon Rectum*. 2015;58(11):1021–1036.
34. Pérez-Jeldres T, Tyler CJ, Boyer JD, et al. Cell trafficking interference in inflammatory Bowel disease: therapeutic interventions based on basic pathogenesis concepts. *Inflamm Bowel Dis*. 2019;25(2):270–282.
35. Adegbola SO, Sahnan K, Warusavitarne J, Hart A, Tozer P. Anti-TNF therapy in Crohn's disease. *Int J Mol Sci.* 2018;19(8):1–21.
36. Yarur AJ, Rubin DT. Therapeutic drug monitoring of anti-tumor necrosis factor agents in patients with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2015;21(7):1709–1718.
37. Rowasa (mesalamine). Package insert. MEDA Pharmaceuticals; Revised June 2017.
38. Canasa (mesalamine). Package insert. Allergan; Revised July 2017.
39. Pentasa (mesalamine). Package insert. Shire US; Revised July 2013.
40. Lialda (mesalamine). Package insert. Shire US; Revised June 2009.
41. Asacol HD (mesalamine). Package insert. Procter & Gamble Pharmaceuticals; Revised April 2009.
42. Delzicol (mesalamine). Package insert. Actavis Pharma; Revised September 2015.
43. Apriso (mesalamine). Package insert. Salix Pharmaceuticals; Revised October 2008.
44. Azulfidine (sulfasalazine). Package insert. Pfizer; Revised August 2019.
45. Dipentum (olsalazine sodium). Package insert. Alaven Pharmaceutical; Revised February 2009.

46. Colazal (balsalazide disodium). Package insert. Salix Pharmaceuticals; Revised February 2007.
47. Entocort EC (budesonide). Package insert. Perrigo; Revised April 2016.
48. Ortikos (budesonide). Package insert. Sun Pharmaceutical Industries; Revised June 2019.
49. Uceris (budesonide). Package insert. Santarus; Revised January 2013.
50. Uceris rectal foam (budesonide). Package insert. Salix Pharmaceuticals; Revised October 2014.
51. Imuran (azathioprine). Prescribing information. Sebela Pharmaceuticals; Revised December 2018.
52. Purixan (mercaptopurine). Package insert. AnovoRx Distribution; Revised April 2014.
53. Otrexup (methotrexate injection). Package insert. Antares Pharma; Revised December 2019.
54. Rasuvo (methotrexate). Package insert. Medac Pharma; Revised March 2018.
55. Gengraf (cyclosporine). Package insert. AbbVie; Revised October 2018.
56. Neoral (cyclosporine). Package insert. Novartis; Revised September 2009.
57. Sandimmune (cyclosporine). Package insert. Novartis; Revised February 2020.
58. Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology*. 2003;125(4):1025–1031.
59. Humira (adalimumab). Package insert. AbbVie; Revised March 2020.
60. Amjevita (adalimumab-atto). Package insert. Amgen; Revised September 2016.
61. Cyltezo (adalimumab-adbm). Package insert. Boehringer Ingelheim Pharmaceuticals, Revised August 2017.
62. Hyrimoz (adalimumab-adaz). Package insert. Sandoz; Revised October 2018.
63. Cimzia (certolizumab pegol). Package insert. UCB; Revised January 2017.
64. Simponi (golimumab). Package insert. Janssen Biotech; Revised September 2019.
65. Remicade (infliximab). Package insert. Janssen Biotech; Revised March 2020.
66. Renflexis (infliximab-abda). Package insert. Merck; Revised April 2017.
67. Avsola (infliximab-axxq). Package insert. Amgen; Revised December 2019.
68. Inflectra (infliximab-dyyb). Package insert. Pfizer; Revised June 2019.
69. Ixifi (infliximab-qbtx). Package insert. Pfizer; Revised December 2017.
70. Tysabri (natalizumab). Package insert. Biogen Idec; 2013.
71. Entyvio (vedolizumab). Package insert. Takeda Pharmaceuticals America; 2014.

72. Stelara (ustekinumab). Package insert. Janssen Biotech; Revised July 2020.
73. Xeljanz/Xeljanz XR (tofacitinib). Package insert. Pfizer; Revised December 2019.
74. Kruis W, Brandes JW, Schreiber S, et al. Olsalazine versus mesalazine in the treatment of mild to moderate ulcerative colitis. *Aliment Pharmacol Ther*. 1998;12(8):707–715.
75. Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(4):601–616.
76. Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med*. 2011;365(18):1713–1725.
77. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology.* 2014;146(2):392–400.e3.
78. Chande N, Wang Y, MacDonald JK, MacDonald JWD. Methotrexate for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2014;8:1–17.
79. Jani M, Barton A, Warren RB, Griffiths CEM, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology (Oxford).* 2014;53(2):213–222.
80. Herfarth H, Barnes EL, Valentine JF, et al. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. *Gastroenterology.* 2018;155(4):1098–1108.e9.
81. DeSaussure P, Soravia C, Morel P, Hadengue A. Low-dose oral microemulsion ciclosporin for severe, refractory ulcerative colitis. *Aliment Pharmacol Ther*. 2005;22(3):203–208.
82. Weber A, Fein F, Koch S, et al. Treatment of ulcerative colitis refractory to steroid therapy by oral microemulsion cyclosporine (Neoral). *Inflamm Bowel Dis*. 2006;12(12):1131–1135.
83. Danese S, Fiorino G, Peyrin-Biroulet L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. *Ann Intern Med*. 2014;160(10):704–711.
84. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. *Aliment Pharmacol Ther*. 2014;39(7):660–671.
85. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699–710.
86. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2014;146(1):85–95.

87. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2014;146(1):96–109.
88. Bischoff SC, Escher J, Hébuterne X, et al. ESPEN practical guideline: clinical nutrition in inflammatory bowel disease. *Clin Nutr*. 2020;39(3):632–653.
89. Flagyl (metronidazole). Package insert. G.D. Searle; Revised August 2003.
90. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2019;2(2):1–35.
91. Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis*. 2014;8(10):1179–1207.
92. Sandhu BK, Fell JM, Beattie RM, et al. Guidelines for the management of inflammatory bowel disease in children in the United Kingdom. *J Pediatr Gastroenterol Nutr*. 2010;50(suppl 1):S1–S13.
93. Mueller C, Compher C, Ellen DM; American Society for Parenteral and Enteral Nutrition (ASPEN) Board of Directors. ASPEN clinical guidelines: nutrition screening, assessment, and intervention in adults. *JPEN J Parenter Enteral Nutr*. 2011;35(1):16–24.
94. Schreiner P, Martinho-Grueber M, Studerus D, et al. Nutrition in inflammatory Bowel disease. Digestion. 2020;101(suppl 1):120–135.
95. Cohen JL, Strong SA, Hyman NH, et al. Practice parameters for the surgical treatment of ulcerative colitis. Dis Colon Rectum. 2005;48:1997–2009.
96. Juillerat P, Mottet C, Froehlich F, et al. Extraintestinal manifestations of Crohn's disease. Digestion. 2007;76:141–148.
97. Hanai H, Kanauchi O, Mitsuyama K, et al. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. Int J Mol Med. 2004;13:643–647.
98. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol. 2007;5:(1)103–110.
99. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open label randomised controlled trial. Lancet. 2012;380(9857):1909–1915.
100. Briggs GG, Freeman RK, Yaffe SJ, eds. Mesalamine. In: *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 8th ed. Lippincott Williams & Wilkins; 2008:1146–1301.
101. Ho GT, Mowat C, Goddard CJ, et al. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther*. 2004;19(10):1079–1087.

102. Benazzato L, D'Inca R, Grigoletto F, et al. Prognosis of severe attacks in ulcerative colitis: effect of intensive medical treatment. *Dig Liver Dis*. 2004;36(7):461–466.
103. Nelson R, Liao C, Fichera A, Rubin DT, Pekow J. Rescue therapy with cyclosporine or infliximab is not associated with an increased risk for postoperative complications in patients hospitalized for severe steroid-refractory ulcerative colitis. *Inflamm Bowel Dis*. 2014;20(1):14–20.
104. Borrelli O, Cordischi L, Cirulli M, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol*. 2006;4(6):744–753.
105. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W, American Gastroenterological Association. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology.* 2006;130(3):940–987.
106. Regueiro M, Loftus EV, Steinhart AH, Cohen RD, Inflammatory Bowel Disease Center. Clinical guidelines for the medical management of left-sided ulcerative colitis and ulcerative proctitis: summary statement. *Inflamm Bowel Dis*. 2006;12(10):972–978.
107. Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2006;23(7):841–855.
108. Irving PM, Gearry RB, Sparrow MP, Gibson, PR. Review article: appropriate use of corticosteroids in Crohn's disease. *Aliment Pharmacol Ther*. 2007;26(3):313–329.
109. Ali T, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. *Am J Med*. 2009;122(7):599–604.
110. Cino M, Greenberg GR. Bone mineral density in Crohn's disease: a longitudinal study of budesonide, prednisone, and nonsteroid therapy. *Am J Gastroenterol*. 2002;97(4):915–921.
111. Podolsky DK. Inflammatory bowel disease. *N Engl J Med*. 2002;347(6):417–429.
112. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;10:1–2.
113. Wang Y, Parker CE, Bhanji T, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2016;4:1–32.
114. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723–1736.
115. Hoentjen F, Sakuraba A, Hanauer S. Update on the management of ulcerative colitis. *Curr Gastroenterol Rep*. 2011;13(5):475–485.

116. Fernandez-Becker NQ, Moss AC. Improving delivery of aminosalicylates in ulcerative colitis: effect on patient outcomes. *Drugs.* 2008;68(8):1089–1103.
117. Gisbert JP, Gollomon F, Mate J, Pajares JM. Role of 5-aminosalicylic acid (5-ASA) in treatment of inflammatory bowel disease: a systematic review. *Dig Dis Sci*. 2002;47(3):471–488.
118. Khan KJ, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(4):630–642.
119. Gisbert JP, Linares PM, McNicholl AG, Mate J, Gomollon F. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. *Aliment Pharmacol Ther*. 2009;30(2):126–137.
120. Timmer A, McDonald JW, Tsoulis DJ, McDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;9:1465–1858.
121. Melmed GY, Ippoliti AF, Papadakis KA, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. *Am J Gastroenterol*. 2006;101(8):1834–1840.
122. Selby L, Kane S, Wilson J, et al. Receipt of preventive health services by IBD patients is significantly lower than by primary care patients. *Inflamm Bowel Dis*. 2008;14(2):253–258.
123. Rubin LG, Levin MJ, Ljungman P, et al. IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):e44–e100.
124. Freedman MS, Hunter P, Ault K, Kroger A. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older: United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(5):133–135.
125. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet.* 2012;380(9853):1590–1605.
126. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol*. 2010;105(2):289–297.
127. Coward S, Kuenzig ME, Hazlewood G, et al. Comparative effectiveness of mesalamine, sulfasalazine, corticosteroids, and budesonide for the induction of remission in Crohn's disease: a Bayesian network meta-analysis [published correction appears in *Inflamm Bowel Dis*. 2017;23(5):E25]. *Inflamm Bowel Dis*. 2017;23(3):461–472.
128. De Cassan C, Fiorino G, Danese S. Second-generation corticosteroids for the treatment of Crohn's disease and ulcerative colitis: more effective and less side effects? *Dig Dis*. 2012;30(4):368–375.
129. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2008;2008(2):1465–1858.

130. Rezaie A, Kuenzig ME, Benchimol EI, et al. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2015;(6):1465–1858.
131. Kestens C, van Oijen MG, Mulder CL, et al. Adalimumab and infliximab are equally effective for Crohn's disease in patients not previously treated with anti-tumor necrosis factor-α agents. *Clin Gastroenterol Hepatol*. 2013;11(7):826–831.
132. Osterman MT, Haynes K, Delzell E, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12(5):811–817.e3.
133. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther*. 2014;39(12):1349–1362.
134. Patil SA, Rustgi A, Langenberg P, Cross RK. Comparative effectiveness of anti-TNF agents for Crohn's disease in a tertiary referral IBD practice. *Dig Dis Sci*. 2013;58(1):209–215.
135. Lee MJ, Parker CE, Taylor SR, et al. Efficacy of medical therapies for Fistulizing Crohn's disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16(12):1879–1892.
136. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362(15):1383–1395.
137. Axelrad JE, Roy A, Lawlor G, Korelitz B, Lichtiger S. Thiopurines and inflammatory bowel disease: current evidence and a historical perspective. *World J Gastroenterol*. 2016;22(46):10103–10117.
138. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med*. 2012;366(20):1870–1880.
139. Nelson SM, Nguyen TM, McDonald JW, MacDonald JK. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2018;8(8):1465–1858.
140. Park SC, Jeen YT. Anti-integrin therapy for inflammatory bowel disease. *World J Gastroenterol*. 2018;24(17):1868–1880.
141. Chandar AK, Singh S, Murad MH, Peyrin-Biroulet L, Loftus EV Jr. Efficacy and safety of natalizumab and vedolizumab for the management of Crohn's disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2015;21(7):1695–1708.
142. Moc´ko P, Kawalec P, Smela-Lipin´ska B, Pilc A. Effectiveness, and safety of vedolizumab for treatment of Crohn's disease: a systematic review and meta-analysis. *Arch Med Sci*. 2016;12(5):1088–1096.
143. Feagan BG, Sandborn WJ, Colombel JF, et al. Incidence of arthritis/arthralgia in inflammatory bowel disease with long-term Vedolizumab

treatment: post hoc analyses of the GEMINI trials. *J Crohns Colitis*. 2019;13(1):50–57.
144. Fleisher M, Marsal J, Lee SD, et al. Effects of Vedolizumab therapy on extraintestinal manifestations in inflammatory bowel disease. *Dig Dis Sci*. 2018;63(4):825–833.
145. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375(20):1946–1960.
146. Hindryckx P, Vande Casteele N, Novak G, et al. The expanding therapeutic armamentarium for inflammatory bowel disease: how to choose the right drug[s] for our patients? *J Crohns Colitis*. 2018;12(1):105–119.
147. Amezaga AJ, Assche GV. Practical approaches to "Top-Down" therapies for Crohn's disease. *Curr Gastroenterol Rep*. 2016;18(7):1–9.
148. van Gennep S, Konté K, Meijer B, et al. Systematic review with meta-analysis: risk factors for thiopurine-induced leukopenia in IBD. *Aliment Pharmacol Ther*. 2019;50(5):484–506.
149. Nielsen OH, Steenholdt C, Juhl CB, Rogler G. Efficacy and safety of methotrexate in the management of inflammatory bowel disease: a systematic review and meta-analysis of randomized, controlled trials. *EClinicalMedicine*. 2020;20:1–10.
150. Gutierrez JC, Hwang K. The toxicity of methotrexate in male fertility and paternal teratogenicity. *Expert Opin Drug Metab Toxicol*. 2017;13(1):51–58.
151. Cheifetz AS. Management of active Crohn disease. *JAMA*. 2013;309(20):2150–2158.
152. Lee YJ, Park KS. Irritable bowel syndrome: emerging paradigm in pathophysiology. *World J Gastroenterol*. 2014;20(10):2456–2469.
153. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(7):712–721.
154. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology.* 2016;150(6):1393–1407.
155. Lovell RM, Ford AC. Effect of gender on prevalence of irritable bowel syndrome in the community: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107:991–1000.
156. Kim YS, Kim N. Sex-gender differences in irritable bowel syndrome. *J Neurogastroenterol Motil*. 2018;24(4):544–558.
157. Ballou S, Lee H-N, Katon J, et al. The impact of irritable bowel syndrome on quality of life and daily activities, a comparison between subtypes: insight from the IBS in America survey. *Clin Gastroenterol Hepatol*. 2019;156(17):2471–2478.
158. Kurin M, Cooper G. Irritable bowel syndrome with diarrhea: treatment is a work in progress. *Cleve Clin J Med.* 2020;87(8):501–511.
159. Fichna J, Storr MA. Brain-gut interactions in IBS. *Front Pharmacol*. 2012;3:1–12.

160. Eshraghian A, Eshraghian H. Interstitial cells of Cajal: a novel hypothesis for the pathophysiology of irritable bowel syndrome. *Can J Gastroenterol*. 2011;25(5):277–279.
161. Mukhtar K, Nawaz H, Abid S. Functional gastrointestinal disorders, and gut-brain axis: what does the future hold? *World J Gastroenterol*. 2019;25(5):552–566.
162. Drossman D. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. *Gastroenterology.* 2016;150:1262–1279.
163. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. *Gastroenterology.* 2011;140(1):91–100.
164. Farmer AD, Wood E, Ruffle JK. An approach to the care of patients with irritable bowel syndrome. *CMAJ*. 2020;192(11):E275–E282.
165. Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology Monograph on management of irritable bowel syndrome. *Am J Gastroenterol*. 2018;113:1–18.
166. Grad S, Dumitrascu DL. Irritable bowel syndrome subtypes: new names for old medical conditions. *Dig Dis*. 2020;38:122–127.
167. Pietrzak A, Skrzydło-Radoman´ska B, Mulak A, et al. Guidelines on the management of irritable bowel syndrome. *Gastroenterol Rev*. 2018;13(4):259–288.
168. Lacy, BE, Pimentel, M, Brenner, DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome, *Am J Gastroenterol*. 2021;116(1):17-44 doi: 10.14309/ajg.0000000000001036
169. Whitehead WE, Palsson OS, Simrén M. Irritable bowel syndrome: what do the new Rome IV diagnostic guidelines mean for patient management? *Expert Rev Gastroenterol Hepatol*. 2017;11(4):281–283.
170. Moayyedi P, Mearing F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: a simplified algorithm for clinical practice. *United European Gastroenterol J*. 2017:5(6):773–788.
171. Horwitz BJ, Fisher RS. The irritable bowel syndrome. *N Engl J Med*. 2001;344:1–15.
172. Occhipinti K, Smith JW. Irritable bowel syndrome: a review and update. *Clin Colon Rectal Surg*. 2012;25(1):46–52.
173. Patcharatrakul T, Juntrapirat A, Lakananurak N, Gonlachanvit S. Effect of structural individual low-FODMAP dietary advice vs. brief advice on a commonly recommended diet on IBS symptoms and intestinal gas production. *Nutrients.* 2019;11(12):1–12.
174. Marsh A, Eslick EM, Eslick GD. Does a diet low in FODMAPs reduce symptoms associated with functional gastrointestinal disorders? A comprehensive systematic review and meta-analysis. *Eur J Nutr*. 2016;55(3):897–906.

175. Su GL, Ko CW, Bercik P, et al. AGA clinical practice guidelines on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology.* 2020;159(2):1–9.
176. Bijkerk CJ, de Wit NJ, Muris JWM, Whorwell PJ, Knottnerus JA, Hoes AW. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo-controlled trial. *BMJ.* 2009;339:1–7.
177. Ford A, Moayyedi P, Lacy BE, et.al. American college gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014:109:S2–S26.
178. Fass R, Longstreth GF, Pimentel M, et al. Evidence and consensus-based practice guidelines for the diagnosis of irritable bowel syndrome. *Arch Intern Med*. 2001;161:2081–2088.
179. Choung RS, Locke GR III, Zinsmeister AR, Schleck CD, Talley NJ. Psychosocial distress and somatic symptoms in community subjects with irritable bowel syndrome: a psychological component is the rule. *Am J Gastroenterol*. 2009;104:1772–1779.
180. Creed F, Guthrie E, Ratcliffe J, et al. Does psychological treatment help only those patients with severe irritable bowel syndrome who also have a concurrent psychiatric disorder? *Aust N Z J Psychiatry*. 2005;39:807–815.
181. Hetterich L, Stengel A. Psychotherapeutic interventions in irritable bowel syndrome. *Front Psychiatry*. 2020;11:1–12.
182. Ford AC, Lacy BE, Harris LA, Lucinda A, Quigley EMM, Moayyedi, P. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. *Am J Gastroenterol*. 2019;114:21–39.
183. Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2006;23:191–196.
184. Amitiza. Package insert. Takeda Pharmaceuticals; 2013.
185. Linzess. Package insert. Ironwood Pharmaceuticals; 2014.
186. Trulance. Package insert. Salix Pharmaceuticals; 2020.
187. Ibsrela. Package insert. Ardelyx; 2019.
188. Carter NJ, Scott LJ. Lubiprostone in constipation predominant irritable bowel syndrome. *Drugs.* 2009;69:1–8.
189. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther*. 2009;29:329–341.
190. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012;107:1702–1712.

191. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol*. 2012;107:1714–1724.
192. Love B. Plecanatide for treatment of chronic constipation and irritable bowel syndrome. *Am J Med*. 2019;132(5):572−575.
193. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. *Am J Gastroenterol*. 2018;113(5):735–745.
194. Barish CF, Crozier RA, Griffin PH. Long-term treatment with plecanatide was safe and tolerable in patients with irritable bowel syndrome with constipation. *Curr Med Res Opin*. 2019;35(1):81–85.
195. Markham A. Tenapanor: first approval. *Drugs.* 2019;79(17):1897–1903.
196. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo-controlled phase 3 trial (T3MPO-1). *Am J Gastroenterol*. 2020;115(2):281–293.
197. Black CJ, Burr NE, Quigley EM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. *Gastroenterology.* 2018;155:1753–1763.
198. FDA. Irritable bowel syndrome—clinical evaluation of products for treatment guidance document. Accessed August 19, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irritable-bowel-syndrome-clinical-evaluation-products-treatment
199. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2002;16:1877–1888.
200. Zelnorm (tegaserod). Package prescribing information. Sloan Pharma; March 2019.
201. Drugs.com. Zelnorm approval history. Accessed August 12, 2020. https://www.drugs.com/history/zelnorm.html
202. Merat S, Khalili S, Mostajabi P, Ghorbani A, Ansari R, Malekzadeh R. The effect of enteric-coated, delayed-release peppermint oil on irritable bowel syndrome. *Dig Dis Sci*. 2010;55:1385–1390.
203. Tack J, Fried M, Houghton LA, Spicak J, Fisher G. Systematic review: the efficacy of treatments for irritable bowel syndrome—a European perspective. *Aliment Pharmacol Ther*. 2006;24:183–205.
204. Camilleri M. Management of the irritable bowel syndrome. *Gastroenterology* 2001;120:652–668.
205. Rahimi R, Nikfar S, Rezaie A, Abdollahi M. Efficacy of tricyclic antidepressants in irritable bowel syndrome: a meta-analysis. *World J*

Gastroenterol. 2009;15:1548–1553.
206. Hanauer SB. The role of loperamide in gastrointestinal disorders. *Rev Gastroenterol Disord*. 2008;8:15–20.
207. Akehurst R, Kaltenthaler E. Treatment of irritable bowel syndrome: a review of randomised controlled trials. *Gut* 2001;48:272–282.
208. Wedlake L, A'hern R, Russell D, Thomas K, Walters JRF, Andreyev HJN. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2009;30:707–717.
209. Talley N. Serotoninergic neuroenteric modulators. *Lancet*. 2001;358:2061–2068.
210. Lotronex. Package insert. Prometheus Labs; 2014.
211. Lucak SL. Optimizing outcomes with alosetron hydrochloride in severe diarrhea-predominant irritable bowel syndrome. *Therap Adv Gastroenterol*. 2010;3(3):165–172.
212. Moynihan R. Alosetron: a case study in regulatory capture, or a victory for patients' rights. *BMJ*. 2002;325:592–595.
213. Chang L, Chey MD, Harris L, Olden K, Surawicz C, Schoenfeld P. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. *Am J Gastroenterol*. 2006;101:1069–1079.
214. Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med*. 2006;145:557–563.
215. Koo HL, DuPont HL. Rifaximin: a unique gastrointestinal-selective antibiotic for enteric diseases. *Curr Opin Gastroenterol*. 2010;26:17–25.
216. Xifaxan. Package insert. Salix Pharmaceuticals; 2015.
217. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med*. 2011;364:22–32.
218. Lembo AJ, Lacy Be, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med*. 2016;374:242–253.
219. Viberzi. Package insert. Pantheon Pharmaceuticals; 2015.

25

Complications of End-Stage Liver Disease

Yasar O. Tasnif and Mary F. Hebert

CORE PRINCIPLES	CHAPTER CASES
ASCITES	
1 Cirrhosis is defined as fibrosis of the hepatic parenchyma, resulting in altered hepatic function, restricted venous outflow, and portal hypertension. Cirrhosis results in an overall vasodilated state, activation of the renin–angiotensin–aldosterone system, altered hepatic synthetic function, and development of complications such as ascites and other complications of cirrhosis.	**Case 25-1 (Question 2)**

CORE PRINCIPLES		CHAPTER CASES
2	Physical findings of ascites can include the presence of an enlarged fluid-filled abdomen, increased abdominal girth, a positive fluid wave, increased body weight, and often accompanied by peripheral edema. The goals of treatment for ascites are to mobilize ascitic fluid, diminish abdominal discomfort, as well as to prevent complications such as bacterial peritonitis and respiratory distress.	**Case 25-1 (Questions 1, 3)**
3	The treatment for ascites involves sodium restriction (2 g/day), water restriction for severe dilutional hyponatremia, and the use of spironolactone and furosemide (100:40 mg ratio). Management and monitoring of ascites includes ensuring adequate weight loss, maintaining electrolyte balance, and preventing complications of diuretic therapy.	**Case 25-1 (Questions 4–8)**

CORE PRINCIPLES		CHAPTER CASES
4	In cases of refractory ascites (diuretic-resistant), large-volume paracentesis, along with albumin replacement, is often indicated. Transjugular intrahepatic portosystemic shunt (TIPS), surgical shunts, and liver transplantation are the options for the treatment of refractory ascites when paracentesis is deemed ineffective, or in patients who are intolerant or who have a contraindication to paracentesis.	**Case 25-1 (Questions 9–11)**
5	Spontaneous bacterial peritonitis (SBP) is a common complication of ascites. Prophylactic regimens include the long-term administration of oral antibiotics such as fluoroquinolones to prevent the recurrence of SBP. Recommendations also include the administration of antibiotic prophylaxis with ceftriaxone for the prevention of SBP in patients with variceal hemorrhage.	**Case 25-2 (Question 4)**

ESOPHAGEAL VARICES

CORE PRINCIPLES		CHAPTER CASES
1	Because esophageal varices are directly related to the severity of portal hypertension, the treatment is aimed at primary prevention of bleeding by reduction of portal pressure with the use of nonselective β-blockers, such as carvedilol, and/or elimination of the varices with endoscopic variceal ligation (EVL). Treatment approaches depend on the risk of hemorrhage.	**Case 25-2 (Question 5)**
2	Secondary prophylaxis to prevent recurrent bleeding episodes includes the combination of nonselective β-blockers and EVL. TIPS may be an option in patients who experience recurrent variceal hemorrhage despite combination of pharmacologic and endoscopic therapy.	**Case 25-2 (Question 6)**

CORE PRINCIPLES		CHAPTER CASES
3	Acute variceal bleeding is considered a medical emergency and should be treated immediately. Treatment goals include volume resuscitation, acute treatment of bleeding, and prevention of recurrence of variceal bleeding. For the control and management of acute hemorrhage, the combination of pharmacologic therapy and variceal ligation is the preferred approach. In cases of acute variceal bleeding uncontrolled by pharmacologic and endoscopic therapy, TIPS can be an effective option. In certain high-risk patients, early TIPS may also be an option.	**Case 25-2 (Questions 1–3)**

HEPATIC ENCEPHALOPATHY

CORE PRINCIPLES		CHAPTER CASES
1	Hepatic encephalopathy is a metabolic disorder of the central nervous system that occurs in patients with either advanced cirrhosis or fulminant hepatic failure. The clinical features include altered mental status and asterixis. Several theories exist about the pathogenesis of hepatic encephalopathy; however, it is likely multifactorial. Precipitating causes can include gastrointestinal (GI) bleeding, diuretic-induced hypovolemia and/or electrolyte abnormalities, metabolic alkalosis, as well as sedating drugs.	**Case 25-3 (Questions 1–3)**
2	After identifying and removing precipitating causes of hepatic encephalopathy, therapeutic management is aimed primarily at reducing the amount of ammonia or nitrogenous products in the circulatory system by limiting protein intake and by the use of lactulose. Other therapeutic options include rifaximin and neomycin.	**Case 25-3 (Questions 4, 5)**
3	Monotherapy with lactulose should be tried first. If satisfactory results do not occur, switching to another option (rifaximin or neomycin) or combination therapy should be considered.	**Case 25-3 (Question 6)**

HEPATORENAL SYNDROME

CORE PRINCIPLES		CHAPTER CASES
1	Hepatorenal syndrome (HRS) is a complication of advanced cirrhosis and is diagnosed by exclusion of other known causes of kidney disease. The definitive treatment for hepatorenal syndrome-acute kidney injury (HRS-AKI, type 1 HRS) and non-AKI-HRS (type 2 HRS) is liver transplantation, which is the only treatment that assures long-term survival. The main goal of pharmacologic therapy is to reverse HRS sufficiently so that appropriate liver transplant candidates can survive until suitable donor organs can be procured.	**Case 25-3 (Questions 7, 8)**

INTRODUCTION

According to the National Vital Statistics Report published by the Centers for Disease Control and Prevention, chronic liver disease with cirrhosis is the 11th leading cause of death in the United States in non-Hispanic White, 14th in non-Hispanic Black, and 7th in Hispanic patients and accounts for ~41,571 deaths each year.[1] Cirrhosis, or end-stage liver disease, can be defined as fibrosis of the hepatic parenchyma resulting in nodule formation and altered hepatic function, which results from a variety of causes. Although there are other common causes of cirrhosis, most cases of cirrhosis worldwide result from chronic viral hepatitis or chronic alcohol consumption.[2] This chapter describes the pathogenesis of cirrhosis and the associated complications of portal hypertension (esophageal varices, gastric varices, ascites, spontaneous bacterial peritonitis

[SBP], hepatic encephalopathy [HE], and hepatorenal syndrome [HRS]) and their treatment.

PATHOGENESIS OF CIRRHOSIS

The liver consists of the hepatic parenchyma (hepatocytes) and a large proportion of nonparenchymal cells, including sinusoidal endothelial cells, Ito cells, and macrophages. Most of the liver's role in detoxification takes place within the hepatocytes. Also within the liver is the biliary tree in which bile drains from the liver and some substances are actively transported into the bile.[3] The liver has the capacity to regenerate; however, ethanol and hepatitis viruses can impair regeneration.[4]

Liver injury leading to cirrhosis impairs hepatic function. Steatosis from ethanol is characterized by lipid deposition in the hepatocytes, which is followed by liver inflammation (steatohepatitis), hepatocyte death, and collagen deposition leading to fibrosis.[5] Oxidative stress appears to play a role in alcohol-induced liver injury. It is important to note that not all heavy drinkers experience liver cirrhosis.[6] Factors such as sex, genetic risk factors, diabetes, obesity, cigarette smoking, and chronic viral infection may also play a role in the development and progression of alcohol-related liver disease.[7]

Hepatitis C virus (HCV) affects millions of people worldwide. If left untreated, approximately a half to two-thirds of those chronically infected are predicted to progress to cirrhosis, and about 3% of patients with cirrhosis progress to hepatocellular carcinoma.[8] The progression of liver disease in patients with HCV is dependent on both patient and viral factors. Multiple mechanisms are proposed to play a role in liver injury associated with HCV infection, such as diminished immune clearance of HCV, oxidative stress, hepatic steatosis, increased iron stores, and increased rate of hepatocyte apoptosis.[9] Because not all patients infected with HCV experience cirrhosis, factors other than viral clearance, such as individual immune response, age, sex, hepatic iron content, alcohol

consumption, and HCV genotype, are all implicated as cofactors in the development of cirrhosis.[10]

Among other causes, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia, metabolic disorders (eg, Wilson disease and hemochromatosis), chronic inflammatory conditions (eg, sarcoidosis), and vascular derangements can lead to hepatic fibrosis and cirrhosis.[2] Approximately 20% of Americans have nonalcoholic fatty liver disease (NAFLD), which in most cases has no symptoms. Risk factors commonly associated with the development of NAFLD include obesity, hyperlipidemia, and diabetes. Although corticosteroids can cause fatty liver, NAFLD diagnosis excludes corticosteroids and other causes of fatty liver. Nonalcoholic steatohepatitis (NASH) is a more serious form of NAFLD, which can lead to cirrhosis. Evidence suggests that insulin resistance and lipid peroxidation play a role in the pathogenesis of this condition.[11,12] Regardless of the cause of end-stage liver disease, the most frequent complications of portal hypertension are esophageal or gastric varices, ascites, HE, and HRS.[13]

COMPLICATIONS OF CIRRHOSIS

Portal Hypertension

The portal vein begins as a confluence of the splenic, superior mesenteric, inferior mesenteric, and gastric veins and ends in the sinusoids of the liver (**Fig. 25-1**). Blood in the portal vein contains substances absorbed from the intestine and delivers these substances to the liver to be metabolized before entering the systemic circulation. Once the portal blood reaches the liver, it crosses through a high-resistance capillary system within the hepatic sinusoids.

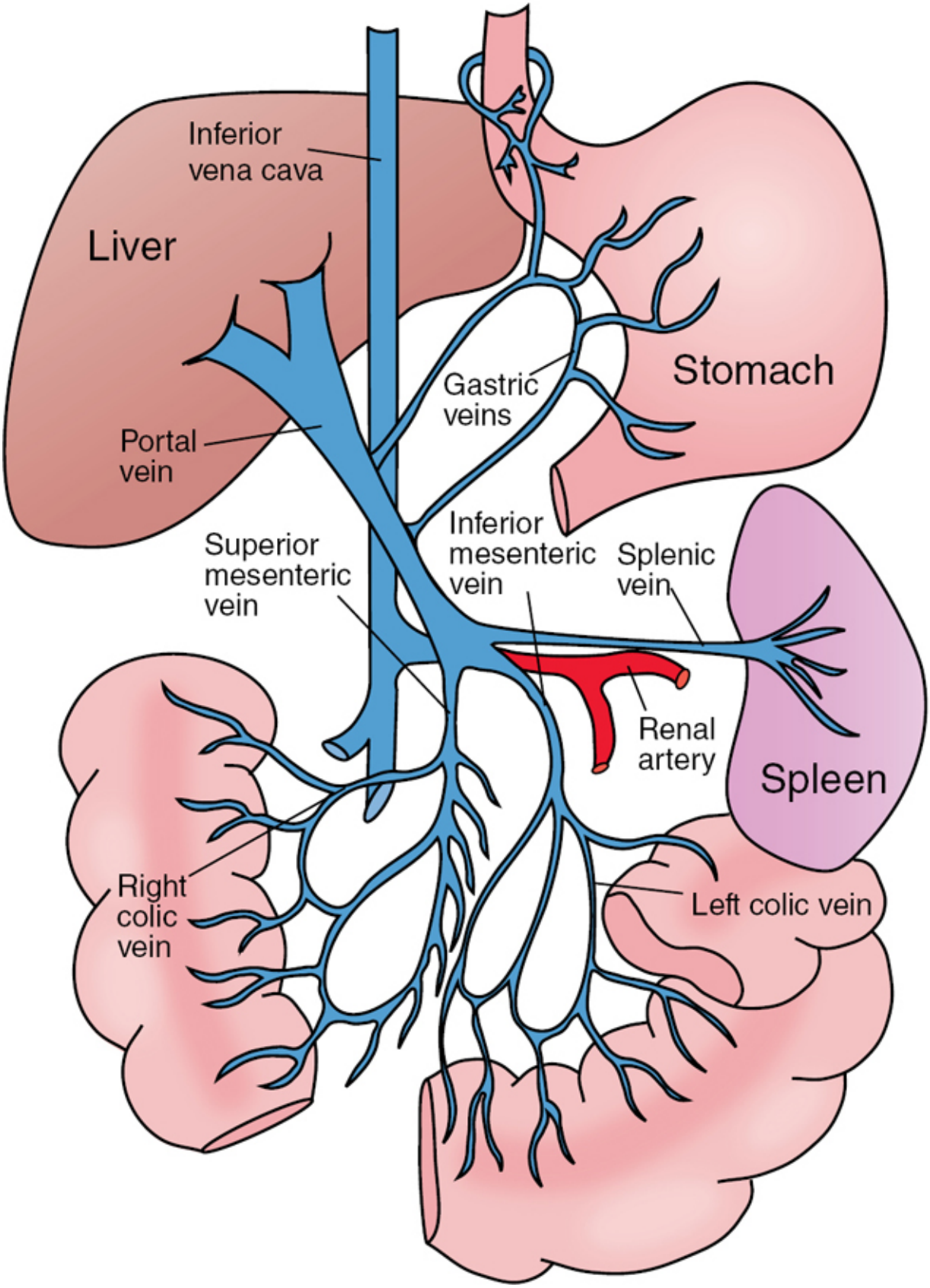

Inferior
vena cava
Liver
Stomach
Gastric
veins
Portal
vein
Superior
mesenteric
vein
Inferior
mesenteric
vein
Splenic
vein
Renal
artery
Spleen
Right
colic
vein
Left colic vein

Figure 25-1 Schematic diagram of the portal venous system.

In cirrhosis, increased intrahepatic resistance results from intrahepatic vasoconstriction that is hypothesized to be caused by a deficiency in intrahepatic nitric oxide (NO).[14] Increased intrahepatic resistance also results from an enhanced activity of vasoconstrictors and structural changes from liver regeneration, sinusoidal compression, and fibrosis.

Portal hypertension results from both an increase in resistance to portal flow and an increase in portal venous inflow because of splanchnic vasodilation from increased NO production in the extrahepatic circulation.[15]

Direct portal pressure measurement is invasive and not routinely performed. The hepatic venous pressure gradient (HVPG), which reflects the gradient between the portal vein and vena cava pressure, is another accurate, safe, and less invasive procedure, widely accepted as the portal venous pressure gradient.[16–18] Normal portal pressure is generally <6 mm Hg, and in patients with cirrhosis, it may increase to 7 to 9 mm Hg. Clinically significant portal hypertension develops when portal pressure exceeds 10 to 12 mm Hg, resulting in complications such as esophageal varices and ascites.[17,19] Portal hypertension can be further classified as prehepatic (eg, splenic, portal vein thrombosis), intrahepatic (eg, hepatic cirrhosis and fibrosis), or posthepatic portal hypertension (eg, inferior vena cava obstruction, right-sided heart failure).[20–22] Persistent portal hypertension may (a) change both blood flow and the lymphatic circulation and lead to ascites formation; (b) increase pressure in the vessels that branch off the portal vein, such as the coronary veins, leading to the formation of esophageal varices; and (c) lead to the development of increased abdominal collateral circulation. HE and HRS are other complications associated with advanced cirrhosis and portal hypertension.[20–22] The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) Single-Topic Conference classified cirrhosis into two main categories, compensated and decompensated. Patients can be cirrhotic with a

portal pressure <10 mm Hg and an absence of the complications of cirrhosis (eg, ascites, variceal hemorrhage, or encephalopathy) and thus would be considered to be compensated. This is in contrast to a patient presenting with ascites, esophageal hemorrhage, HE, and/or HRS, which are present in decompensated cirrhosis.[23] Patients with compensated cirrhosis are managed by treatment of the underlying cause as well as prevention (primary prophylaxis) and early diagnosis of the complications. For patients with decompensated cirrhosis, the aim is to treat the complications and prevent sequela (secondary prevention).[24]

LABORATORY FINDINGS

Laboratory evaluations in cirrhosis may not reflect the extent of the parenchymal necrosis, regeneration, and fibrotic nodular scarring. Conventional liver "function" tests, such as the serum aminotransferases (aspartate aminotransferase [AST, formerly known as SGOT], alanine aminotransferase [ALT, formerly known as SGPT]) and alkaline phosphatase, are actually better characterized as liver "injury" tests and are modestly helpful to the clinician screening for hepatobiliary disease and monitoring injury progression. These tests, however, do not quantitatively measure the functional capacity of the liver. The aminotransferases are released during the normal turnover of liver cells (see Chapter 2, Interpretation of Clinical Laboratory Tests). High serum concentrations of aminotransferases suggest enzyme release from injured hepatocytes. Serum concentrations of AST and ALT may initially rise very high with acute liver injury and then fall when the etiology is removed or necrosis is so severe that few hepatocytes remain.

Because alkaline phosphatase is present in high concentrations in biliary canaliculi (as well as bone, intestines, kidneys, placenta, and white blood cells [WBCs]), its concentration increases more with biliary than hepatocellular injury. High serum concentrations of γ-glutamyl transpeptidase, alkaline phosphatase and bilirubin are suggestive of biliary injury. Elevated serum concentrations of AST

and/or ALT may suggest hepatocyte injury, but because they are also found in other tissues, their elevation is not diagnostic for liver disease.[25,26]

Serum concentrations of proteins (eg, albumin), clotting factors, prothrombin time (PT), and international normalized ratio (INR) provide some insight into liver function. Albumin is synthesized entirely by the liver; therefore, concentrations reflect hepatocellular function to some degree. However, changes in albumin concentration are nonspecific, because they are influenced by other factors, including poor nutrition, renal wasting (proteinuria), and gastrointestinal (GI) losses. PT is also nonspecific, because it is prolonged in vitamin K deficiency from poor nutrition or fat malabsorption as well as biliary obstruction (cholestasis).[27]

A number of the factors described earlier are included in the Child–Turcotte–Pugh classification of liver disease severity (**Table 25-1**).[28,29] This scoring system helps clinicians grade disease severity, and predicts the long-term risk of mortality and quality of life. A person with Child–Turcotte–Pugh class A cirrhosis may survive 15 to 20 years, whereas those with class C may survive only 1 to 3 years.[30] The main limitation of the Child–Turcotte–Pugh classification is the subjective nature of some factors, such as ascites and HE, which are subject to clinical interpretation and may be altered by therapy.[31,32] As a general guide, and not a rule, class A patients are considered to be compensated, and classes B and C decompensated.[24]

Table 25-1
Child–Turcotte–Pugh Classification of Severity of Liver Disease

	Score[a]		
	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild to moderate	Severe
Encephalopathy (grade)	None	Mild to moderate (1 and 2)	Severe (3 and 4)

INR, international normalized ratio.

[a]Class A, 5–6 points; class B, 7–9 points; class C, 10–15 points.

Sources: Reprinted from Gitto S, Lorenzini S, Biselli M, Conti F, Andreone P, Bernardi M. Allocation priority in non-urgent liver transplantation: an overview of proposed scoring systems. *Dig Liver Dis*. 2009;41(10):700–706. © 2009 Editrice Gastroenterologica Italiana S.r.l. With permission; Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med*. 2010;362(9):823–832.

An alternate method for assessing survival in patients with liver disease is the Model for End-Stage Liver Disease (MELD) score, which is calculated by the following formula[32]:

$$\begin{aligned}\text{MELD score} = {} & 9.6 \times \log(\text{serum creatinine mg/dL}) + 3.8 \\ & \times \log(\text{serum bilirubin mg/dL}) \\ & + 11.2 \times \log(\text{INR}) + 6.4\end{aligned}$$

(Eq. 25-1)

Because of the good correlation between the MELD score and short-term (3-month) mortality, as well as the objective nature of the system, it replaced the Child–Turcotte–Pugh score in the United Network for Organ Sharing (UNOS) prioritization of organ allocation of cadaveric livers for transplantation.[33–35] Hyponatremia is common in patients with cirrhosis. Because lower serum sodium levels are a marker of the severity of cirrhosis, in January 2016, UNOS adopted serum sodium as a factor in the calculation of the MELD score[32]:

$$\text{MELD-Na} = \text{MELD} + 1.32 \times (137 - \text{Na}) - [0.033 \times \text{MELD} \times (137 - \text{Na})]$$

(Eq. 25-2)

The UNOS policy states that candidates with an initial MELD score >11 have their score recalculated utilizing the MELD-Na equation. Candidates with hyponatremia may benefit from this recalculation, because it can increase their MELD score and, therefore, priority for transplantation.[32]

MELD scores range from 6 (less ill) to 40 (gravely ill), with highest scores given priority for organ allocation with the exception of Status 1A adult patients (acute and severe onset of liver failure, who have a life expectancy of hours to a few days without liver transplantation) who are given highest priority.[36]

CLINICAL PRESENTATION

CASE 25-1

QUESTION 1: R.W. is a 54-year-old male with a 2-week history of nausea, vomiting, and lower abdominal cramps without diarrhea. Despite chronic anorexia, he has managed to drink a fifth of vodka (750 mL) and eat about two meals a day for the past 2 years. During this time, he experienced a 30-pounds (13.60 kg) weight loss. He began drinking 9 years ago when his wife became disabled after diagnosis of a brain tumor. Two years ago, his alcohol consumption increased from one pint to a fifth daily. Recently, he has noted bilateral edema of his legs, an increased tenseness and girth of his abdomen, jaundice, and scleral icterus. His medical history is noncontributory, other than a history of SBP 6 months ago. He is not taking any medications and has no known drug allergies.

Physical examination reveals an afebrile, jaundiced, and cachectic male in moderate distress. Spider angiomas were found on his face and upper chest. In addition, palmar erythema was noted.

Abdominal examination reveals prominent veins on a very tense abdomen. The liver edge is percussed below the right costal margin and ascites is noted by shifting dullness and a fluid wave. The spleen is not palpable. On neurologic examination, R.W. is awake and oriented to person, place, and time. Cranial nerves II to XII are grossly intact, but a decrease in vibratory sensation of the lower extremities is noted bilaterally. Admission laboratory data are as follows:

Sodium, 135 mEq/L
Chloride, 95 mEq/L

Potassium, 3.8 mEq/L
Bicarbonate, 25 mEq/L
Blood urea nitrogen (BUN), 15 mg/dL
Serum creatinine (SCr), 1.4 mg/dL
Glucose, 136 mg/dL
Hemoglobin (Hgb), 11.2 g/dL
Hematocrit (Hct), 33.4%
AST, 212 IU
ALT, 110 IU
Alkaline phosphatase, 954 IU
PT, 13.5 (INR, 1.1)
Total/direct bilirubin, 18.8/10.7 mg/dL
Albumin, 2.3 g/dL
Guaiac-positive stools

On admission to the hospital, the impression is alcoholic cirrhosis, ascites, and heme-positive stools.

What subjective and objective evidence are compatible with alcoholic cirrhosis in R.W.?

R.W.'s liver function tests (elevated ALT, AST, alkaline phosphatase, and bilirubin) and physical findings (enlarged, palpable liver edge; jaundice; spider angiomas; palmar erythema; and cachexia) are consistent with advanced alcoholic cirrhosis in a patient with a history of chronic alcohol abuse. The prolonged PT and hypoalbuminemia suggest impaired hepatic synthesis of both albumin and vitamin K–dependent clotting factors. The low albumin contributes to both ascites and edema. The bilirubin of 18.8 mg/dL suggests that vitamin K absorption may be a factor in the prolonged PT. The presence of ascites (an enlarged fluid-filled abdomen) and prominent abdominal veins is suggestive of portal hypertension. A biopsy of the liver may establish the presence and severity of cirrhosis. R.W.'s prolonged PT, however, will increase the risk of bleeding from a liver biopsy. His positive guaiac finding could be indicative of bleeding esophageal varices or from another GI source. This needs to be confirmed by endoscopy. He is oriented to person, place, and time, but full HE evaluation is needed. R.W.'s calculated MELD score is 23, which predicts a 90-day mortality of ~20%.[33] A patient's MELD score may increase or decrease for a period of time depending on the patient's clinical status and treatment. A number of

MELD scores will be calculated if R.W. is listed as a transplantation candidate to determine his status for organ allocation.[36] Muscle wasting and poor nutrition are the most common causes of weight loss in patients with alcohol-related cirrhosis (see Chapter 90, Substance Use Disorders).

ASCITES

Pathogenesis of Ascites

Case 25-1, Question 2: What physiologic mechanism predisposes R.W. to fluid accumulation in the peritoneal cavity?

Ascites, or accumulation of fluid in the peritoneal cavity, is the most commonly encountered clinical symptom of cirrhosis.[24,37] This complication can be detected during physical examination when >3 L of fluid has accumulated. In addition to an obviously enlarged abdomen, R.W. was found to have a positive fluid wave and shifting dullness, indicating that the abdominal enlargement is not simply obesity. If the diagnosis is in doubt, which sometimes occurs in patients with obesity, ascites can be confirmed with ultrasound. Generally speaking, in obesity the abdomen enlarges over time (months to years), in contrast to ascites where abdominal enlargement can occur over a few weeks.[38] Once ascites develops, the 1-year patient survival rate falls to ~50%.[24]

In cirrhosis, high hepatic venous pressure leads to high intrasinusoidal pressure and development of ascites across the hepatic capsule.[39] The systemic compensation to the generalized vasodilation in cirrhosis is increased cardiac output as well as sodium and water retention through activation of the renin–angiotensin–aldosterone system (RAAS).[40] R.W.'s hypoalbuminemia (2.3 g/dL), RAAS activation, exudation of fluid from the splanchnic capillary bed and the liver surface when the drainage capacity of the

lymphatic system is exceeded, and decreased ability of fluid to be contained within the vascular space owing to impaired hepatic albumin synthesis contribute to the development of ascites.

Goals of Therapy

Case 25-1, Question 3: What are the therapeutic goals in the treatment of R.W.'s ascites?

The goals of treatment for R.W.'s ascites are to treat the cause of cirrhosis by ceasing alcohol consumption; mobilize ascitic fluid; diminish abdominal discomfort, back pain, and difficulty ambulating; as well as prevent complications (eg, bacterial peritonitis, hernias, pleural effusions, HRS, and respiratory distress).[38] After the initial resolution of significant edema, the weight loss goal is 1.10 pounds/day (0.5 kg/day), which corresponds to a net fluid volume loss of ~0.5 L/day. Treatment of ascites in R.W. should be undertaken cautiously and gradually because acid–base imbalances, hypokalemia, or intravascular volume depletion caused by overly aggressive therapy can lead to compromised renal function, HE, and death.[41,42] The initial medical management of ascites involves restriction of sodium intake and the use of diuretics to promote salt and water excretion.[38]

Fluid and Electrolyte Balance

URINARY Na:K RATIO

Case 25-1, Question 4: The 24-hour urinary electrolytes for R.W. were as follows:

Na, 10 mEq/L
K, 28 mEq/L

Why would sodium or water restriction be appropriate (or inappropriate) for R.W.?

Normally, urine electrolytes mirror serum electrolytes (ie, sodium concentration is greater than that of potassium). A reversal of this pattern (ie, potassium exceeding sodium) may indicate a relative hyperaldosteronism secondary to diminished renal blood flow and low oncotic pressure. A small study by Trevisani et al[43] evaluated renal sodium and potassium handling and plasma aldosterone in a 24-hour period in cirrhotic patients without ascites, with ascites, and healthy controls. Plasma aldosterone was significantly higher in patients with ascites, resulting in reduced renal sodium excretion and more than doubling renal potassium excretion in comparison to healthy controls.[43] For urine electrolyte monitoring to be meaningful, the first sample must be obtained before initiating diuretics.[44,45]

SODIUM RESTRICTION

Although serum sodium in patients with ascites is often low, they are total body sodium overloaded. Sodium restriction has been shown to enhance mobilization of ascites, because fluid loss and weight change are directly related to sodium balance in patients with portal hypertension–related ascites.[46] This finding has been incorporated into the AASLD guidelines for the treatment of ascites. The AASLD recommends that dietary sodium should be restricted to 2000 mg/day (88 mmol/day) and R.W. should be advised to limit his sodium intake accordingly.[38] Historically, bed rest has been advocated; however, no controlled trials support this practice.[38,42]

WATER RESTRICTION

A large prospective, observational study[47] reported that hyponatremia (sodium <135 mEq/L) is common in patients with cirrhosis, associated with poor ascites control and a greater frequency of HE, HRS, and SBP compared to patients with normal serum sodium concentrations.[47] In addition, very low serum sodium concentrations (<120 mEq/L) are independent from the MELD score in predicting 3- to 6-month mortality. The AASLD recommends that water restriction should be implemented in patients with cirrhosis who have severe dilutional hyponatremia (serum Na <125 mEq/L).[38]

Water restriction is not indicated for R.W. at this time because his serum sodium concentration is within normal limits (135 mEq/L).

VASOPRESSIN RECEPTOR ANTAGONISTS

A complete discussion of vasopressin receptor antagonists can be found in Chapter 27, Fluid and Electrolyte Disorders. The AASLD guidelines do not recommend the use of vasopressin (V2) receptor antagonists because of the lack of evidence of efficacy in patients with cirrhosis, side effects, as well as the low cost-effectiveness of these medications.[38] However, it is possible that with more evidence from clinical trials, this class of medications may find a niche in the treatment of hyponatremia in patients with cirrhosis.

Diuretic Therapy

CHOICE OF AGENT

Case 25-1, Question 5: R.W. was prescribed sodium restriction after initial evaluation. Spironolactone 100 mg/day and furosemide 40 mg/day were ordered to induce diuresis. Why is spironolactone preferred over other diuretics in the treatment of ascites?

Most patients with cirrhosis have elevated plasma concentrations of aldosterone.[48] High serum concentrations of aldosterone may be attributed to both increased production and decreased excretion of the hormone. Increased portal pressure, ascites, depletion of intravascular volume, and decreased renal perfusion can lead to activation of the RAAS.[49] In addition, hepatic shunting also increases aldosterone production by decreasing renal blood flow.[50] The liver metabolizes aldosterone, and hepatic impairment prolongs the physiologic half-life of aldosterone.[51] The AASLD consensus guidelines recommend the use of spironolactone as the initial diuretic of choice in the treatment of ascites.[38] Although no large comparative studies have evaluated different diuretics as first-line treatment of ascites, spironolactone is a rational diuretic choice for

R.W. based on its aldosterone antagonist activity. Perez-Ayuso et al[52] conducted a small randomized trial to study the efficacy of furosemide versus spironolactone in non-azotemic cirrhotic patients with ascites. They reported a higher response to spironolactone than furosemide (18/19 vs 11/21; $P < .01$). Of the 10 nonresponders to furosemide, 9 responded to spironolactone. The authors also found that patients with higher renin and aldosterone levels did not respond to furosemide and required higher doses of spironolactone to achieve a diuretic response.[52]

Some clinicians may initiate spironolactone at a dose of 25 mg once or twice daily; however, much larger doses (100–400 mg/day) are generally necessary to antagonize the high circulating levels of aldosterone in patients with ascites.[38] The diuretic effect is enhanced when spironolactone is combined with sodium restriction.[42] In addition, furosemide can be started to minimize the risk of hyperkalemia and enhance diuresis. The AASLD guidelines recommend starting spironolactone 100 mg and furosemide 40 mg/day simultaneously and maintaining a 100:40 mg ratio. The doses of both oral diuretics can be increased simultaneously every 3 to 5 days (maintaining the ratio) to achieve adequate response. Usual maximal doses are 400 mg/day of spironolactone and 160 mg/day of furosemide.[38] In patients without renal failure, sodium restriction and diuretic therapy are effective in 90% of patients with ascites.[38,53]

Triamterene and amiloride can be used as alternatives to spironolactone if intolerable side effects (eg, gynecomastia) occur with spironolactone.[54,55] In a small trial,[56] non-azotemic cirrhotic patients with ascites were randomly assigned to receive amiloride (20–60 mg/day) or potassium canrenoate (150–500 mg/day, an active metabolite of spironolactone not available in the United States). A higher response rate was seen in the canrenoate group versus the amiloride group (14/20 vs 7/20; $P < .025$). The authors also assessed plasma aldosterone activity and found that all responders to amiloride had normal plasma aldosterone concentrations, and all nonresponders to amiloride who later

responded to potassium canrenoate had increased levels of plasma aldosterone.[56]

Eplerenone (a selective aldosterone blocker, more specific for the aldosterone receptor with a lower affinity for progesterone and androgen receptors than spironolactone) has been studied in patients with heart failure, hypertension, and renal disease.[57,58] The usual dose for eplerenone is 25 to 50 mg/day, with no dosage adjustment needed in mild-to-moderate liver disease. However, severe liver disease has not been studied.[59] Interestingly, a study by Sehgal et al utilized a higher dose of eplerenone (100 mg/day) in patients with cirrhosis and showed significantly higher weight reduction compared to patients taking 50 mg/day ($P < .001$).[60] Approximately 10% of patients treated with spironolactone develop gynecomastia or breast pain, with 2% requiring drug discontinuation.[61] In contrast, gynecomastia occurs at a similar rate with eplerenone as with placebo (0.5%).[62,63] Unfortunately, eplerenone is much more expensive than spironolactone.[63] The lower risk of gynecomastia with eplerenone may make it a useful alternative to spironolactone; however, given its higher cost and the lack of data in the treatment of ascites in patients with severe liver disease, its role in ascites treatment remains unclear.

R.W. should receive spironolactone 100 mg and furosemide 40 mg simultaneously (maintaining a 100:40 mg ratio) as recommended by the AASLD.[38] R.W. should be carefully monitored for diuretic complications and clinical response (see Case 25-1, Questions 6–8).

MONITORING

Clinical responses

Case 25-1, Question 6: What clinical responses should be monitored to ensure the therapeutic effectiveness of spironolactone therapy for R.W.?

Because ascitic fluid is slow to reequilibrate with vascular fluid, diuresis >0.5 to 1 kg/day (>0.5–1 L) may be associated with volume depletion, hypotension, and compromised renal function.[38] Patients

may tolerate a faster diuresis if peripheral edema is present. Once edema has resolved, a scaled-back weight loss, not to exceed 1.10 pound/day (0.5 kg/day), can be used as a rule of thumb to minimize the risk of renal insufficiency induced by plasma volume contraction and other diuretic-induced complications.[38,64] Body weight and abdominal girth are routinely monitored in both the inpatient and outpatient settings. Fluid intake and urine output are monitored primarily for inpatients, owing to practical constraints in the outpatient setting. Ideally, urine output should exceed fluid intake by about 300 to 1000 mL/day. These measurements do not account for nonrenal fluid losses; therefore, total fluid loss will be somewhat higher. Abdominal girth measurement (circumference around the abdomen) is subject to error, because of its dependence on patient position and measurement location on the abdomen.[65] Attempts should be made to standardize patient position (eg, sitting at a 45° angle) and location of measurement (level of umbilicus) to minimize variability in abdominal girth measurements.

Laboratory parameters

Case 25-1, Question 7: What laboratory parameters could be monitored to assess the therapeutic efficacy of R.W.'s spironolactone treatment?

Serum concentrations of creatinine and urine chemistries (sodium and potassium) can be monitored to define and guide the need for dosage adjustment of spironolactone. A low baseline urine Na:K ratio (<1.0) suggests high intrinsic aldosterone activity and that a larger dosage of spironolactone may be needed, as is the case for R.W. If necessary, the dosage of diuretic therapy may be doubled after a few days.[49] AASLD recommends increasing both spironolactone and furosemide simultaneously every 3 to 5 days (maintaining a 100:40 mg ratio) to achieve adequate diuresis and maintain a normal serum potassium.[38]

DIURETIC COMPLICATIONS AND MANAGEMENT

Case 25-1, Question 8: The spironolactone and furosemide dosages were increased to 200 and 80 mg/day (maintaining a 100:40 mg ratio). What potential complications from the diuretic therapy might arise in R.W. and how can they be minimized?

Electrolyte and acid–base disturbances

Hyponatremia, hyperkalemia, metabolic alkalosis, and, uncommonly, hypokalemia occur as side effects of diuretic therapy in patients with ascites. Hyponatremia results from a reduction in free water clearance (dilutional hyponatremia). Diuresis exacerbates hyponatremia by causing volume depletion and antidiuretic hormone (ADH) release. Hyponatremia usually can be corrected by temporary withdrawal of diuretics and free water restriction.[53,66–68] Although serum sodium may be low, these patients are total body sodium overloaded. Hyperkalemia is common in patients with refractory ascites and impaired renal function requiring high doses of diuretics such as spironolactone. Hyperkalemia can be approached in multiple ways, depending on the clinical situation (see Chapter 27, Fluid and Electrolyte Disorders). Furosemide is added to spironolactone to maintain normal serum potassium.[38] Decreasing or holding spironolactone may be appropriate depending on the patient's renal function and serum potassium.[24] Metabolic alkalosis, a result of loop diuretics, occurs because of increased urinary hydrogen loss from enhanced distal hydrogen secretion. Hypokalemia often accompanies metabolic alkalosis owing to loop diuretics.[67] Furosemide can be temporarily withheld in patients presenting with hypokalemia.[38] R.W. has some degree of renal impairment (SCr, 1.4 mg/dL) and is receiving spironolactone and furosemide. Therefore, his electrolytes and renal function tests should be monitored daily while hospitalized. After hospital discharge, monitoring will be dictated by the stability of the patient and need for diuretic dosage adjustments. For example, outpatients may need electrolytes and renal function monitoring once or twice weekly early after hospital discharge to as infrequently as every 3 months for very stable patients.[38]

Prerenal azotemia

Prerenal azotemia usually results from overdiuresis with subsequent compromise of intravascular volume and decreased renal perfusion. In addition to looking for clinical signs of hypovolemia, such as dizziness, orthostatic hypotension, and increased heart rate, frequent measurements of BUN and SCr concentrations provide a relatively simple means of assessing the intravascular volume. A gradual rise in SCr, BUN, as well as the BUN:SCr ratio can serve as a warning to slow the rate of diuresis.[69] In a small study,[64] serial measurements of plasma volume and ascites volume were made during treatment with diuretics in patients with cirrhosis. Patients with ascites and no edema were able to mobilize >1 L/day during rapid diuresis, but at the expense of plasma volume contraction and renal insufficiency. Patients with peripheral edema appear to be somewhat protected from these effects and may safely undergo diuresis at a more rapid rate (>2 kg/day) until edema resolves.[64] Others suggest, however, that the maximal daily fluid loss should not exceed >0.5 L/day (>0.5 kg/day) for patients with ascites alone or 1 L/day (>1 kg/day) for those with both ascites and edema to prevent plasma volume depletion and decreased renal perfusion. If faster removal of ascites is required because of respiratory distress, large-volume paracentesis may be more effective than rapid diuresis (see Case 25-1, Question 9).[38,45,70,71] In patients with cirrhosis, azotemia may also occur because of nonsteroidal anti-inflammatory drugs (NSAIDs). All NSAIDs should be discontinued, except low-dose aspirin in patients at high risk for a cardiac or neurologic event.[38]

Because R.W. presented with both edema and ascites, an initial weight loss of up to 2.20 pounds/day (1 kg/day) would be reasonable with slowing to 1.10 pound/day (0.5 kg/day) when the edema resolves. Gradual diuresis avoids diuretic-induced depletion of intravascular fluid volume by permitting ascitic fluid to equilibrate with intravascular fluid. Long-term management of ascites is done in the outpatient setting. Severe cases with respiratory distress or impaired ambulation as well as patients with SBP (see Chapter 70, Intra-Abdominal Infections) require hospitalization. If outpatient therapy is

an option, a weekly evaluation initially would be prudent to prevent overdiuresis and electrolyte disturbances.[38]

Refractory Ascites

Case 25-1, Question 9: Over the next several days, R.W.'s spironolactone dosage was increased to 400 mg/day. Furosemide was simultaneously increased to 80 mg bid without major improvement in diuresis. Laboratory data revealed that R.W.'s SCr had increased to 3.2 mg/dL (estimated creatinine clearance: 26 mL/minute) and his BUN had increased to 45 mg/dL. Serum electrolytes were as follows:

K, 3.1 mEq/L
Na, 130 mEq/L
Cl, 88 mEq/L
Bicarbonate, 32 mEq/L

R.W. became progressively short of breath because of restricted diaphragmatic movement secondary to his significantly enlarged abdomen. What therapeutic measures are appropriate for R.W.'s refractory (diuretic-resistant) ascites?

The AASLD guidelines mention a few treatment options for refractory ascites. Midodrine 7.5 mg given three times daily to increase blood pressure (BP) in patients with hypotension could possibly convert diuretic-resistant patients to diuretic-sensitive ones. In addition, discontinuation of β-blockers is recommended because these drugs are associated with increased mortality in patients with refractory ascites. The guidelines also mention avoiding angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) because of the risk of hypotension.[38]

Because of the increase in SCr and respiratory distress, R.W.'s ascites treatment needs modification. Patients with cirrhosis experiencing respiratory distress despite diuretic therapy, sodium restriction, and appropriate management of hypotension (discontinuation of β-blockers and adding midodrine) may warrant more aggressive second-line treatment, including large-volume paracentesis, shunting procedures, or both.[38] Paracentesis involves

the removal of ascitic fluid from the abdominal cavity with a needle or a catheter. Although paracentesis can remove large amounts of ascitic fluid (eg, 10 L), removal of as little as 1 L of fluid may provide considerable relief from the painful stretching of skin and the respiratory distress that occurs with massive ascites. The ascitic fluid often reaccumulates rapidly after paracentesis. The major complications of overly aggressive, large-volume paracentesis include hypotension, shock, oliguria, encephalopathy, and renal insufficiency. Other potential complications of paracentesis are hemorrhage, perforation of the abdominal viscera, infection, and protein depletion.[38]

ALBUMIN

Case 25-1, Question 10: R.W. continues to reaccumulate ascitic fluid and is exhibiting signs of declining renal function. A 6 L paracentesis coupled with a 50 g albumin infusion is ordered. Why are albumin infusions used in conjunction with paracentesis?

Large-volume (>4 L) paracentesis should be performed for patients with tense ascites, resulting in respiratory distress or impaired ambulation. However, large-volume paracentesis is associated with paracentesis-induced circulatory dysfunction (PICD), which manifests as ascites recurrence, development of HRS, hyponatremia, and decrease in survival.[72,73] Intravenous (IV) albumin infusions are commonly administered to prevent PICD after large-volume paracentesis.[38] Use of albumin in combination with large-volume paracentesis increases circulatory function, prevents the subsequent reactivation of vasoconstrictors, and reduces the incidence of PICD.[73] Although albumin is costly and sometimes in short supply, for some patients it is appropriate with paracentesis.[74] In one study, patients requiring large-volume paracentesis (≥6 L/day) received either concomitant IV albumin (40 g) or saline. The incidence of PICD was significantly higher in the saline than the albumin group (33.3% vs 11.4%, respectively). The prevalence of PICD after paracentesis depends on the volume of ascites removed

such that albumin infusion may not be necessary for a single paracentesis <4 to 5 L.[38,74] For large-volume paracentesis ≥6 L, 6 to 8 g of albumin is typically administered for each liter of ascites removed.[38]

Bernardi et al[73] conducted a meta-analysis of 17 randomized controlled trials (total of 1225 patients) evaluating albumin versus alternative therapies (dextran, gelatin, saline, etc.) in the acute treatment of cirrhotic patients undergoing large-volume paracentesis. The odds of death were lower by 36% in the albumin group (*P* = .038).[73] In addition, a trial evaluating albumin administered to patients with SBP showed a lower incidence of renal impairment (10% vs 33%; *P* = .002), lower overall mortality at 3 months (22% vs 41%; *P* = .03), and lower hospital mortality (10% vs 29%; *P* = .01) than the group that did not receive albumin.[75] A previous meta-analysis by Wilkes and Navickis[76] evaluating albumin and mortality found no improvement in mortality with albumin administration. However, only part of the analysis focused on ascites (five trials).[76]

DEXTRAN 70 AND OTHER PLASMA EXPANDERS

The use of synthetic plasma expanders with large-volume paracentesis has also been explored in patients with refractory ascites.[77] Ginès et al[78] studied patients with ascites refractory to diuretic therapy, who required paracentesis. More patients treated with dextran 70 (34.4%) or polygeline (37.8%) experienced PICD than those receiving albumin (18.5%).[78] Hydroxyethyl starch, an effective colloid agent for intravascular volume expansion, should not be used in patients with cirrhosis, because repeated administration in this population has been reported to accumulate in the hepatocytes, causing severe portal hypertension and acute liver failure.[79]

R.W. should be given 50 g of 25% albumin administered at a rate of 3 mL/minute, for the 6 L of ascitic fluid removed. Albumin 25% infusion is preferred because 5% solution has fivefold the sodium load and a larger volume to give the same amount of protein.[38] More rapid administration than 3 mL/minute in patients with

hypoproteinemia can cause circulatory overload and pulmonary edema. R.W. should be monitored for anaphylactic reactions (rare), hypotension, hypertension, and signs of pulmonary edema.[80–82]

Alternative Therapy

Case 25-1, Question 11: What alternative treatments are available for the management of refractory ascites? How would these alternatives be applied in R.W.'s case?

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Transjugular intrahepatic portosystemic shunt (TIPS) is another option for patients who are refractory to the pharmacologic interventions described previously. It is a nonsurgical technique for establishing a shunt in patients with portal hypertension (**Fig. 25-2**).[83] The TIPS procedure involves opening a conduit between the hepatic vein and the intrahepatic segment of the portal vein with an expandable metal stent placed during an angiographic procedure. This low-resistance channel allows blood to return to the systemic circulation and reduces portal pressure. In addition, TIPS may improve urinary sodium excretion. The major complications of TIPS include severe encephalopathy and shunt occlusion. HE (see Case 23-5, Question 1) occurs in ~20% of patients after TIPS.[83] Because of poor prognosis, liver transplantation should be considered for appropriate candidates refractory to pharmacologic treatment and/or shunt placement.[38] Selection of surgical shunt procedures may include evaluation of liver transplantation candidacy because some procedures may complicate the feasibility of a future liver transplantation procedure.

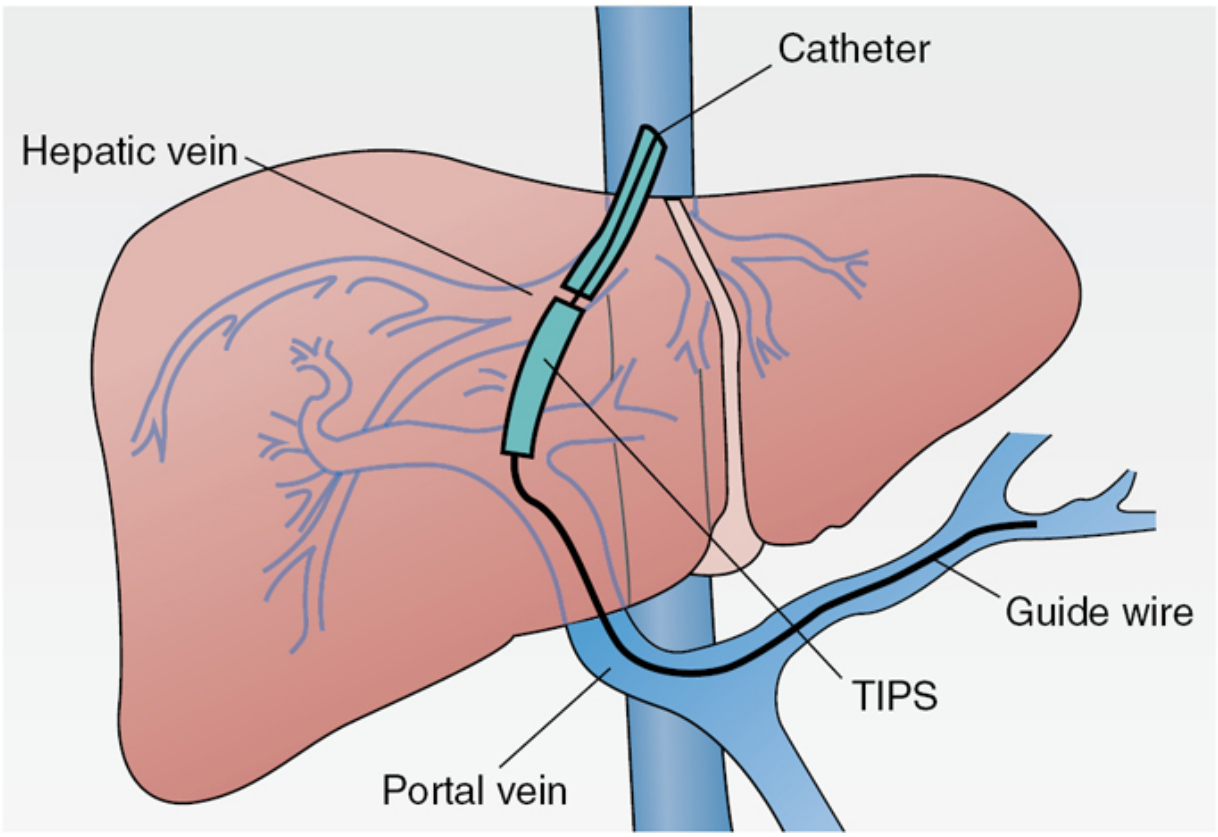


Figure 25-2 Transjugular intrahepatic portosystemic shunt (TIPS). A stent is inserted via catheter to the portal vein to divert blood flow and reduce portal hypertension. (Adapted with permission from Smeltzer SC, Bare BG. *Brunner and Suddarth's Textbook of Medical-Surgical Nursing*. 9th ed. Lippincott Williams & Wilkins; 2000.)

Salerno et al[84] conducted a meta-analysis of cirrhotic patients with refractory ascites and found that transplant-free survival was higher in the TIPS group (38.1% vs 28.7% at 3 years; $P = .035$) and the recurrence of ascites was lower (42% vs 89%; $P < .0001$) than in the large-volume paracentesis group. The average number of HE episodes was significantly higher in the TIPS group ($P = .006$). However, the probability of developing the first episode of HE was similar between the groups ($P = .19$).[84] Bureau et al[85] conducted a randomized controlled trial to determine the effects of TIPS with stents covered with polytetrafluoroethylene in patients with refractory ascites. Covered stents reflect a more current practice as compared

to previous literature that analyzed the outcomes of bare metal stents. Patients were randomly assigned to groups that received covered TIPS (*N* = 29) versus large-volume paracenteses and albumin as necessary (LVP+A; *N* = 33). The results of the study found that a higher proportion of patients in the TIPS group survived without a liver transplant for 1 year as compared to those in the LVP+A group (93% vs 52%; *P* = .03). Patients in the TIPS group also had a lower number of paracenteses (32 vs 320), lower portal hypertension–related bleeding (0% vs 18%; *P* = .01), and lower hospitalization rate (35 vs 17 days; *P* = .04) as compared to the LVP+A group. The 1-year probability of remaining free of encephalopathy was similar for each group (65%).[85]

The AASLD guidelines mention that as experience and technology with TIPS improves, the outcomes associated with TIPS in future trials may also improve.[38] Currently, the AASLD treatment guidelines continue to recommend TIPS for the treatment of refractory ascites in patients for whom paracentesis is contraindicated, deemed ineffective as determined by the frequency of repeated paracentesis (more than three times per month), or intolerant of repeated large-volume paracentesis.[86]

PERITONEOVENOUS SHUNT

A peritoneovenous shunt consists of a surgically implanted valve in the abdominal wall, an intra-abdominal cannula, and an outflow tube tunneled subcutaneously from the valve to a vein that empties directly into the superior vena cava. In this manner, ascitic fluid can be withdrawn from the abdominal cavity and be returned to the vascular space. Multiple contraindications exist to a surgical shunt procedure, and as hepatic function worsens, surgical risks significantly increase in likelihood.[87] The lack of survival benefit, surgical complications, including fibrous adhesions complicating future liver transplantation, and the high risk of shunt occlusion have led to the reserving of peritoneovenous shunt procedures for patients with refractory ascites that are not candidates for paracentesis, liver transplantation, or TIPS.[38]

CLONIDINE

It has been shown that the activation of the sympathetic nervous system leads to renal hypoperfusion and sodium retention. The activated sympathetic nervous system stimulates renal α_1-adrenoreceptors and causes decreases in renal blood flow and glomerular filtration rate. Additionally, norepinephrine increases proximal tubular reabsorption of sodium and enhances renin, aldosterone, and vasopressin secretions.[88–90] Preliminary evidence suggests that clonidine may be of benefit in refractory ascites and an activated sympathetic nervous system. Lenaerts et al[91] conducted a very small study in patients randomly assigned to receive repeated large-volume paracentesis (4–5 L every 48 hours) plus IV albumin (7 g/L ascites) until ascites disappeared, or a combination of clonidine 0.075 mg bid for 8 days and then clonidine 0.075 mg bid with spironolactone 200 to 400 mg daily for 10 days. Both groups were discharged with spironolactone adjusted according to individual response. During the first hospitalization, the mean weight loss in the paracentesis group was higher than in the clonidine group, but the mean hospital stay was shorter in the clonidine group ($P \leq .01$). Clonidine decreased sympathetic activity and increased glomerular filtration rate. During the follow-up, the number of rehospitalizations for ascites was higher and the mean time to the first readmission was shorter in the paracentesis group than in the clonidine group ($P \leq .01$).[91] Yang et al. conducted a study in Chinese patients with refractory ascites. Patients were randomized to receive clonidine 0.075 mg twice daily in addition to spironolactone and furosemide ($N = 135$) versus diuretics alone ($N = 135$) for 3 months. The study found that 55% to 60% of patients in the clonidine group responded to the addition of clonidine. Patients in the clonidine group also had a significantly higher 1-year survival rate ($P = .0001$) compared to patients with diuretics alone. Interestingly, this study also found that a therapeutic response of clonidine can be predicted by certain genetic polymorphisms. The authors stated a possibility of polymorphism analysis to identify patients with cirrhosis that can benefit from the addition of clonidine to diuretics for the treatment of

refractory ascites.[90] The addition of clonidine to diuretic therapy may be an effective therapeutic modality; however, more trial data are needed to establish the role of clonidine in the treatment of ascites. Currently, the use of clonidine is considered experimental by the AASLD guidelines.[38]

In consideration of R.W.'s increasing SCr concentration, rising BUN, and the grave prognosis of HRS, TIPS is a reasonable therapeutic alternative if R.W. cannot tolerate or requires frequent large-volume paracentesis. Patients with a history of SBP and ascites with advanced liver failure or renal impairment appear to benefit from SBP prophylaxis. R.W. would benefit from the addition of SBP prophylaxis because of his history of SBP (see Chapter 70, Intra-Abdominal Infections).

ESOPHAGEAL VARICES

Treatment

CASE 25-2

QUESTION 1: C.V., a 55-year-old, pale-looking female with alcohol- induced cirrhosis, was admitted for hematemesis. C.V. has a history of recurrent upper GI bleeding and documented esophageal varices. She has no other significant medical history. She is not taking any medications and has no known drug allergies. On examination, her BP was 78/40 mm Hg, pulse rate was 110 beats/minute, and respiratory rate was 22 breaths/minute. Her skin was cold; chest and cardiac examinations were within normal limits and abdominal examination revealed ascites and a palpable spleen. Bowel sounds were normal. Laboratory values included the following:

Hgb, 6.8 g/dL
Hct, 22%
Albumin, 3.0 g/dL
AST, 160 IU
ALT, 250 IU
Alkaline phosphatase, 40 IU
Creatinine, 2.0 mg/dL
PT, 18 seconds (INR, 1.5)

Serum electrolytes, all within normal limits
An electrocardiogram revealed sinus tachycardia.

What are the immediate goals of therapy and treatment measures of the highest priority in managing C.V.'s hematemesis?

GOALS OF THERAPY

Most patients with cirrhosis develop portal hypertension, which can progress to bleeding varices (dilated veins in the upper GI tract that protrude into the esophageal or gastric lumens). Of patients with Child–Turcotte–Pugh class A cirrhosis, 40% develop esophageal varices, as compared with 85% of those with Child–Turcotte–Pugh class C cirrhosis.[24,92] Unless varices bleed, they do not cause significant complications or symptoms.

The progression and severity of varices is directly related to the severity of portal hypertension. The major site of concern in portal hypertension is the coronary vein, draining the bottom of the esophagus and upper stomach. The scarring and fibrosis associated with cirrhosis initially lead to an increase in portal vein pressure (PVP), which may eventually rise, causing backflow of blood supply and subsequent increased pressure in the veins coming off the portal vein. Hyperkinetic circulation in the branches of the portal vein raises the esophageal transmural pressure and increases the risk of upper GI bleeding. Because the veins are designed for low-pressure circulation (5–8 mm Hg) and generally cannot tolerate a sustained hyperdynamic circulation, the shunting of high portal pressure blood results in gastric and esophageal varices. When PVP exceeds 12 mm Hg, patients are at increased risk of variceal hemorrhage.[93]

Varices can only be visualized during a diagnostic endoscopy. Esophageal varices are graded as small or large (>5 mm). The presence or absence of red signs (red wale marks or red spots) on varices is also noted.[92]

Despite improvement in the management of portal hypertension, massive bleeding from esophageal or gastric varices is the leading cause of death in patients with cirrhosis.[94] Prevention of variceal bleeding is critical because the mortality rate remains at 32% in

Child–Turcotte–Pugh class C patients.[94] New varices develop at a rate of 5% to 10% per year in patients with cirrhosis. Once varices develop, they enlarge by 4% to 10% each year.[95] Acute variceal bleeding is considered a medical emergency and should be treated immediately. Treatment goals include volume resuscitation, acute treatment of bleeding, and prevention of recurrence of variceal bleeding. Approximately 10% to 20% of patients are refractory to endoscopic and medical intervention and may require life-saving portal decompressive shunt surgery or TIPS.[24]

GENERAL MANAGEMENT

Resuscitation is the first priority in patients with acute bleeding episodes. An indwelling nasogastric tube (NG) should be placed, then saline or tap-water lavage of the stomach, with suctioning of the gastric contents, should be initiated promptly to prevent airway complications such as aspiration pneumonia.[83,96] Obtunded or unconscious patients should be intubated to maintain and protect the airway. Pharmacologic treatment should be initiated immediately to reduce bleeding and the risk of hypotension-induced renal failure. The patient should also be monitored for any abnormal electrolyte and metabolic chemistries (eg, potassium, sodium, bicarbonate), hypoxia (eg, PO_2, pH), SCr, and decreased urinary output.[96]

Rebleeding is most likely to occur within the first 2 to 5 days in patients with large varices and in patients with advanced liver disease (ie, Child–Turcotte–Pugh class C, Table 25-1).[24,97] Factors associated with early rebleeding include age older than 60 years, acute renal failure, and severe initial bleeding defined by Hgb <8 g/dL at presentation. Risk factors for late rebleeding are severe liver failure, continued alcohol abuse, large variceal size, renal failure, and hepatocellular carcinoma.[97]

HYPOVOLEMIA/BLOOD LOSS

Care should be taken when correcting hypovolemia so as not to increase the degree of portal hypertension by overtransfusion, which can increase the risk of further bleeding. Hypovolemia should be

immediately managed to maintain a systolic BP of 90 to 100 mm Hg and the Hgb between 7 and 9 g/dL.[24,98] C.V.'s pallor, cold and clammy skin, rapid pulse, and a systolic BP <80 mm Hg suggest significant hypotension and hypovolemia needing correction with whole blood or packed red cell transfusion and cryoprecipitate.[27,92,97]

Patients with liver disease and elevated bilirubin frequently develop some level of vitamin K deficiency. Prolongation of the PT because of vitamin K deficiency usually improves within 12 hours after a 10-mg parenteral or oral dose of vitamin K. In contrast, a prolonged PT caused by poor liver function is not responsive to the administration of vitamin K. If no improvement is seen in INR after a 1-mg dose of vitamin K, repeated administration is unlikely to have therapeutic benefit.[27] Although vitamin K is often administered in the treatment of acute variceal bleeding, there are no data to support this practice.[99] For rapid correction of INR because of bleeding or a planned invasive procedure, fresh frozen plasma has been used. However, this may lead to increased portal pressure. Cryoprecipitate may be a viable alternative because of lower infusion volume and less impact on portal pressure.[27]

CASE 25-2, QUESTION 2: Three units of whole blood and eight units of cryoprecipitate were transfused initially. C.V.'s stomach was lavaged with saline, and the gastric aspirate from the NG tube continued to be strongly positive for blood. Four hours later, her bleeding still persisted. What other pharmacologic interventions can be used to control C.V.'s bleeding esophageal varices?

OCTREOTIDE

Octreotide is a synthetic analog of somatostatin, with similar pharmacologic properties and a slightly longer half-life. Somatostatin is available in Europe, but is substituted with octreotide or vapreotide (orphan drug status) in the United States (**Table 25-2**).[100–103] Octreotide is shown to be effective for controlling acute variceal bleeding and appears comparable in efficacy to vasopressin and balloon tamponade, with fewer side effects. Octreotide is administered as a 50-100 µg bolus followed by an infusion of 50 µg/hour for 2 to 5 days.[92] In one study, complete bleeding control

was achieved in all patients receiving octreotide after 48 hours of therapy compared with 64% of patients who are treated with vasopressin, and 59% in the omeprazole group ($P < .005$). Patients receiving vasopressin also experienced more side effects (abdominal cramps, nausea, tremor, decreased cardiac output, myocardial ischemia, and bronchial constriction) than those receiving octreotide or omeprazole ($P < .01$). In patients with bleeding not controlled within 48 hours in the vasopressin and omeprazole groups, complete bleeding control was subsequently achieved by octreotide.[104] In a meta-analysis assessing the efficacy of vasopressin, octreotide, and somatostatin administered to patients with acute variceal bleeds, studies found that control of acute hemorrhage was significantly greater with octreotide when compared with vasopressin ($N = 2$; risk ratio [RR] 1.31, 95% confidence interval [CI] 1.10–1.56), whereas mortality was not significantly different ($N = 1$; RR 1.00, 95% CI 0.54–1.85). Hemostasis was significantly lower with vasopressin when compared with somatostatin (RR 0.75, CI 0.61–0.92), whereas no significant difference in mortality or rebleeding was detectable.[105] In general, octreotide is fairly well tolerated.[104] Although some centers may still initiate therapy with vasopressin, most will use octreotide as first-line therapy and reserve vasopressin for treatment failures.

Table 25-2
Treatment of Acute Bleeding

Therapy	Mechanism	Side Effects and Risks
Octreotide	Selective and potent vasoconstrictor that reduces portal and collateral blood flow by constricting splanchnic vessels	Diarrhea, hyperglycemia, hypoglycemia, constipation, rectal spasms, abnormal stools, headache, dizziness, fat malabsorption

Therapy	Mechanism	Side Effects and Risks
Vasopressin	Nonspecific vasoconstrictor of all parts of the vascular bed	Abdominal cramping, nausea, tremor, skin blanching, phlebitis, hematoma at the site of the infusion, worsening of hypertension, angina, arrhythmias, myocardial infarction, bowel necrosis, gangrene, dilutional hyponatremia
Endoscopic variceal ligation (EVL)	An elastic band is placed around the mucosa and submucosa of the esophageal area containing the varix, leading to strangulation, fibrosis, and ideally obliteration of the varix.	Moderate bleeding, hypotension, gastrointestinal discomfort, esophageal ulceration, perforation
Sclerotherapy	Injection of 0.5–5 mL of a sclerosing agent (eg, concentrated saline: 11.5% NaCl or ethanolamine oleate) into each varix at points about 0.79 inch (2 cm) apart to induce immediate hemostasis (cessation of bleeding within 2–5 minutes)	Esophageal ulceration, stricture formation, esophageal perforation, retrosternal chest pain, temporary dysphagia
Balloon tamponade	Bleeding is controlled by direct compression of the varices at the gastroesophageal junction or at the bleeding site by a Sengstaken–Blakemore tube or Linton tube (gastric varices only). The tube is passed through the mouth and into the stomach. A balloon is then inflated, which applies direct compression to the varices.	Aspiration (>10% incidence), pressure necrosis, pneumonitis, esophageal ulceration and rupture, bleeding on balloon deflation, chest pain, asphyxia (aspiration may be minimized by endotracheal intubation and continued aspiration of oropharyngeal secretions)

Therapy	Mechanism	Side Effects and Risks
Transjugular intrahepatic portal systemic shunt (TIPS)	A conduit between the hepatic vein and the intrahepatic segment of the portal vein with an expandable metal stent placed during an angiographic procedure. This channel allows blood to return to the systemic circulation and reduces portal pressure.	Bleeding, thrombosis, stenosis, severe encephalopathy, hepatic failure, shunt occlusion, shunt migration

Sources: Goulis J, Burroughs AK. Role of vasoactive drugs in the treatment of bleeding oesophageal varices. *Digestion.* 1999;60(suppl 3):25–34; Wao T, Toyonaga A, Oho K, et al. Effect of vasopressin on esophageal varices blood flow in patients with cirrhosis: comparisons with the effects on portal vein and superior mesenteric artery blood flow. *J Hepatol.* 1996;25:491–497; Law AW, Gales MA. Octreotide or vasopressin for bleeding esophageal varices. *Ann Pharmacother.* 1997;31:237–238; de Franchis R. Longer treatment with vasoactive drugs to prevent early variceal re-bleeding in cirrhosis. *Eur J Gastroenterol Hepatol.* 1998;10:1041–1044.

VASOPRESSIN

Vasopressin, a naturally occurring hormone (also known as 8-arginine vasopressin, ADH), is produced by the posterior pituitary and was originally derived for the treatment of diabetes insipidus in persons with pituitary insufficiency.[100,101] Its use to control variceal bleeding is a non–Food and Drug Administration (FDA)-labeled use that takes advantage of its intense smooth muscle vasoconstrictive properties. Vasopressin (Table 25-2) is effective in reducing or terminating bleeding in ~60% of patients with variceal hemorrhage.[100,101] Of concern are reports of patients developing hypertension, angina, arrhythmias, gangrene, and, rarely, myocardial infarction while receiving vasopressin. Vasopressin is given as a continuous IV infusion because of its short half-life. To minimize dose-related adverse effects, the lowest effective dosage should be used. Vasopressin may be administered by peripheral IV infusion, but use of a central vein is preferred because of the risk of tissue necrosis if extravasation occurs. Most commonly, vasopressin is initiated as a continuous IV infusion of 0.2 to 0.4 units/minute, and

increased by 0.2 units/minute every hour until control of bleeding is obtained (maximal dose 0.8 units/minute).[92] Approximately 12 hours after the control of bleeding, the infusion rate can be decreased by half. Higher doses should be avoided because dosages exceeding 1 unit/minute fail to control hemorrhage in patients who are unresponsive to lower dosages.[106] Because of the potential for serious cardiovascular and dermatologic complications caused by nonspecific vasoconstriction, vasopressin should be used only when necessary and for a duration necessary to control bleeding. The duration of infusion should not exceed 24 hours.[92] Interestingly, a meta-analysis of four randomized controlled trials comparing vasopressin for the acute treatment of variceal bleeding with nonactive treatment or placebo found no difference in mortality.[100] Because the efficacy of vasopressin for the treatment of esophageal bleeding is limited and adverse effects (eg, abdominal cramping, arrhythmias, and gangrene) are of great concern (Table 25-2), it has largely been replaced by octreotide. Nonetheless, some clinicians still prescribe vasopressin.

Nitroglycerin can help to minimize the adverse vascular and cardiac effects of vasopressin and enhance the reduction in portal pressure. When given by IV infusion, the nitroglycerin dosage is 40 to 200 µg/minute.[100,102,107] A randomized trial by Gimson et al[108] found a lower rate of complications in the vasopressin and nitroglycerin group compared with vasopressin alone. At the end of the 12-hour study period, variceal hemorrhage was controlled in 68% receiving combined therapy versus 44% in those given vasopressin alone ($P < .05$). Major complications requiring cessation of therapy were less common in those given nitroglycerin with vasopressin compared with those given vasopressin alone ($P < .02$).[108]

TERLIPRESSIN

Terlipressin, a synthetic analog of vasopressin and a prodrug of lypressin (currently not available in the United States), effectively controls acute bleeding from esophageal varices in 80% of patients. Fewer cardiovascular side effects have been associated with

terlipressin than with vasopressin.[109] Octreotide, vapreotide, vasopressin, and terlipressin have been shown to be effective in the control of acute variceal hemorrhage.[110,111] Seo et al[112] conducted a large prospective, multicenter, randomized, noninferiority trial comparing the effects of terlipressin, somatostatin, and octreotide followed by endoscopic treatment in patients with acute variceal bleeding. Similar rates of control of bleeding and reduction in mortality were achieved in all groups (NS). However, terlipressin was used at doses lower than recommended.[92,112]

Pharmacologic therapy for C.V. (somatostatin or its analogs [octreotide or vapreotide] or terlipressin) should be initiated as soon as variceal hemorrhage is suspected and continued for 2 to 5 days after diagnosis is confirmed.[92]

ENDOSCOPIC VARICEAL LIGATION AND BALLOON TAMPONADE

Case 25-2, Question 3: Octreotide and vasopressin are nonspecific vasoconstrictors that require continuous IV infusion and carry a risk of systemic side effects. What place does endoscopic variceal ligation (EVL) have in the management of C.V.'s hemorrhage? What is a balloon tamponade? Are alternative therapies such as TIPS appropriate?

After successful resuscitation, endoscopy should be performed within 12 hours to establish the cause of bleeding.[92] Fiberoptic endoscopy allows direct visualization of the esophagus and location of the bleeding. Those with actively bleeding varices can be treated with EVL or balloon tamponade. Sclerotherapy has also been used in some cases (Table 25-2). EVL is a well-tolerated procedure (Table 25-2).[110,113–117] Villanueva et al,[118] in a randomized controlled trial, found that the use of variceal ligation instead of sclerotherapy had a lower failure rate (4% vs 15%; P = .02) and a lower transfusion requirement (P = .05). No statistically significant differences were found in mortality. Adverse effects (eg, aspiration pneumonia, esophageal bleeding, ulceration, and chest pain) occurred in 28% of patients receiving sclerotherapy and 14% with ligation (RR 1.9, 95%

CI 1.1–3.5; *P* = .03).[118] In another similar but smaller study, Sarin et al[119] found that the rate of rebleeding was lower in the EVL group than in the sclerotherapy group (6.4% vs 20.8%; *P* < .05). EVL is the recommended form of therapy for acute esophageal variceal bleeding, although sclerotherapy has been used in the acute setting if ligation is technically difficult. Endoscopic treatments are best used in combination with pharmacologic therapy, which preferably should be started before endoscopy.[111] The AASLD Practice Guidance on Portal Hypertensive Bleeding in Cirrhosis recommend that for the control and management of acute hemorrhage, the combination of vasoconstrictive pharmacologic therapy and variceal ligation is the preferred approach.[92] Therefore, C.V. should immediately be treated with octreotide for 2 to 5 days, and EVL to control the esophageal variceal bleeding.[24,92]

BALLOON TAMPONADE

Balloon tamponade is used to control bleeding by direct compression to the site of origin in massive hemorrhage cases (Table 25-2). It is important to remember that balloon tamponade is only a temporary measure and can cause pressure necrosis after 48 to 72 hours. Thus, the balloon should be deflated after 12 to 24 hours. Deflation and removal of the tube can result in removal of the fibrin scab at the bleeding site, resulting in rebleeding. Balloon tamponade has been used in rebleeding episodes refractory to vasoconstrictive pharmacologic therapy and EVL. This modality may achieve temporary control of the bleeding and allow time for other measures such as TIPS to be undertaken.[92,110,120,121]

ALTERNATIVE TREATMENT MODALITIES

Transjugular intrahepatic portal systemic shunt

Although the combination of pharmacotherapy (octreotide, terlipressin, or somatostatin) and EVL has been shown to be beneficial in controlling acute bleeding, rebleeding episodes can occur.[92,110] Poor responders to initial therapy may require further intervention to lower portal pressure and control the bleeding.

Henderson et al[122] conducted a prospective, multicenter trial comparing distal splenorenal shunt (DSRS) to TIPS for variceal bleeding refractory to medical treatment with β-blockers and endoscopic therapy. Patients with Child–Turcotte–Pugh class A and class B cirrhosis and refractory variceal bleeding were randomly assigned to DSRS or TIPS. No significant differences were found in survival at 2 and 5 years (DSRS, 81% and 62%; TIPS, 88% and 61%, respectively). Thrombosis, stenosis, and reintervention rates were significantly higher in the TIPS group (DSRS, 11%; TIPS, 82%; $P < .001$). Rebleeding, encephalopathy, ascites, need for transplantation, quality of life, and costs did not significantly differ between groups.[122] TIPS has the advantage of being less invasive and faster than surgical portal systemic shunts. Long-term patency of the TIPS remains problematic (Table 25-2). TIPS can be used as a bridge to liver transplantation and might be an effective option for nonsurgical patients or in recurrent bleeding uncontrolled by pharmacologic and endoscopic therapy.[86,92,110,123,124] "Early" or preemptive TIPS (within 72 hours from endoscopy and EVL) may be considered in those at high risk for rebleeding. High risk may be classified as those with Child–Turcotte–Pugh class B/C with active bleeding on endoscopy despite vasoactive therapy.[92] Patients with successful TIPS do not require specific therapy for portal hypertension or varices.[92] TIPS would be an option for C.V. if EVL and pharmacologic therapy fail.

Surgery

Surgical creation of a portacaval shunt has been effective in reducing portal pressure and in preventing recurrent bleeding. These shunts, however, are associated with a high incidence of HE and may exacerbate hepatic parenchymal dysfunction by shunting blood away from the liver. Mesocaval shunts and DSRSs are also effective in preventing variceal rebleeding and may be associated with a lower incidence of HE.[125]

INFECTION PROPHYLAXIS: SHORT-TERM ANTIBIOTICS

Case 25-2, Question 4: Should CV receive prophylaxis for bacterial infections?

Variceal hemorrhage is a risk factor for the development of severe bacterial infections, which increase mortality.[92] Short-term administration of antibiotics for the prevention of bacterial infections in patients with variceal hemorrhage has demonstrated favorable results.[126,127] In a prospective, randomized trial comparing norfloxacin 400 mg bid for 7 days (N = 60) with no treatment controls (N = 59), the norfloxacin group had a significantly lower incidence of SBP (3.3% vs 16.9%; P < .05), although the decrease in mortality (6.6% vs 11.8%) did not reach statistical significance.[126] Because of the emergence of infections caused by quinolone-resistant bacteria, Fernandez et al[127] compared oral norfloxacin with IV ceftriaxone in the prophylaxis against bacterial infection in cirrhotic patients with GI hemorrhage. Patients were randomly assigned to oral norfloxacin 400 mg bid or IV ceftriaxone 1 g/day for 7 days. Antibiotics were initiated after emergency endoscopy and within 12 hours of hospital admission. The probability of developing proven infections (26% vs 11%; P < .03), and bacteremia or SBP (12% vs 2%, P < .03) was significantly higher in patients receiving norfloxacin as compared with ceftriaxone. No significant difference was seen between groups in mortality at 10 days.[127] A Cochrane review of 12 trials evaluating the role of antibiotic prophylaxis with placebo or no antibiotic prophylaxis to prevent bacterial infections in cirrhotic patients with upper GI bleeding reported that antibiotic prophylaxis was associated with a significant decrease in mortality from bacterial infections (RR 0.43, 95% CI 0.19–0.97).[128]

The AASLD guidelines recommend 7 days of antibiotic prophylaxis for the prevention of SBP in patients with variceal hemorrhage. Antibiotic recommendations should be based on local antimicrobial susceptibility patterns, with ceftriaxone (1 g/24 hour) being the first choice in patients with advanced cirrhosis, in those with prior quinolone prophylaxis use, and in hospital settings with high

prevalence of quinolone-resistant bacterial infections.[92] C.V. should be treated with ceftriaxone 1 g/day for 7 days to prevent SBP.

PRIMARY PROPHYLAXIS

Case 25-2, Question 5: All variceal hemorrhage interventions up to this point were aimed at terminating the acute bleeding episode. Could drug therapy have helped prevent the first episode of bleeding from C.V.'s esophageal varices?

Preventing the initial occurrence of variceal bleeding is referred to as primary prevention or primary prophylaxis. Pharmacologic prophylaxis is aimed at reducing the HVPG to ≤12 mm Hg, or a decrease from baseline of ≥20%.[129,130] In a small study by Vorobioff et al[129] none of the patients with HVPG ≤12 mm Hg bled from portal hypertension–related causes as compared to 42% in the HVPG >12 mm Hg group. In addition, only one of the six patients with a HVPG <12 mm Hg as compared with 16 (of 24) in the HVPG >12 mm Hg group died during the study period ($P < .06$).[129] In addition, Escorsell et al[130] confirmed that a fall of HVPG by 20% or more from baseline was associated with a decreased risk of variceal bleeding (6% vs 45%; $P = .004$).

β-Blockers

Nonselective β-adrenergic blockers decrease portal pressure through a reduction in portal venous inflow as a result of a decrease in cardiac output (β_1-adrenergic blockade) and splanchnic blood flow (β_2-adrenergic blockade). Only nonselective β-blockers have an adrenergic vasoconstrictive effect on mesenteric arterioles, resulting in a decrease in portal pressure. In addition to nonselective β-adrenergic blockers, carvedilol has additional α_1-antiadrenergic (vasodilator) activity. It decreases portal flow, but also acts as a vasodilator within intrahepatic circulation. It has been shown to be effective in the primary prevention of variceal bleeding compared to EVL for patients with medium/large varices. However, it is limited by its systemic hypotensive effects.

Usual starting dosages of propranolol are 20 mg twice daily, nadolol 20 mg daily, and carvedilol 6.25 mg once daily. Selective β-blockers (eg, atenolol and metoprolol) have little effect on mesenteric arterioles and have not been shown to be effective in primary prophylaxis.[92,131]

Propranolol or nadolol, given in dosages to reduce the resting heart rate to 55 to 60 beats/minute or by 25%, have been shown to prevent or delay the first episode of variceal bleeding.[15] Nonselective β-blockers are considered first-line drug therapy in the prevention of variceal hemorrhage based on numerous randomized, placebo-controlled trials and meta-analyses.[110,132] For example, Pascal and Cales[133] conducted a prospective, randomized, multicenter, single-blinded trial of propranolol compared with placebo in the prevention of bleeding in patients with large esophageal varices without previous bleeding. Patients received either propranolol or placebo, with the endpoints of the study being bleeding and death. The dosage of propranolol was progressively increased to decrease the heart rate by 20% to 25%. The cumulative percentages of patients free of bleeding 2 years after inclusion in the study (74% vs 39%; $P < .05$) and cumulative 2-year survival (72% vs 51%; $P < .05$) were higher in the propranolol group compared to the placebo group.[133]

Sarin et al[134] conducted a prospective, randomized, controlled trial comparing EVL plus propranolol with EVL alone as primary prophylaxis for the prevention of first variceal bleeding among patients with high-risk varices. The mean duration of follow-up for both groups was about 12.2 months (±10.7 months). EVL was performed at 2-week intervals until obliteration of varices. Propranolol was administered at a dosage sufficient to reduce heart rate to 55 beats/minute or 25% reduction from baseline, and continued after obliteration of varices. No significant differences were seen in the rates of bleeding or survival between groups, although more patients in the EVL alone group had recurrence of varices ($P = .03$).[134]

In a prospective, randomized, double-blind, placebo-controlled trial of propranolol for the primary prevention of variceal hemorrhage, Abraczinskas et al[135] found that when propranolol was tapered off,

the risk of variceal hemorrhage increased from 4% (while on propranolol therapy) to 24% (after propranolol withdrawal) and was comparable to the risk of bleeding in an untreated population (22% in the placebo group from the previous study). Importantly, patients who abruptly discontinued β-blockers experienced increased mortality compared with the untreated population (48% vs 21%; $P < .05$).[135] Therefore, avoiding sudden discontinuation of β-blockers in this population is essential.

The AASLD guidelines recommend nonselective β-blockers for primary prophylaxis in patients with small varices that have not bled, but are at increased risk of hemorrhage (presence of red wale marks and/or occurring in a Child–Turcotte–Pugh class C patient). For patients with medium or large varices that have not bled, nonselective β-blockers, carvedilol or EVL, may be recommended. Choice of treatment may be based on patient preference and characteristics, contraindications to therapy, and adverse events. The β-blocker should be titrated to the maximal tolerated dose.[92]

Isosorbide-5-mononitrate

Isosorbide-5-mononitrate monotherapy for primary prophylaxis for variceal hemorrhage has not proven to be effective.[136,137] Garcia-Pagan et al[137] conducted a prospective, multicenter, double-blind, randomized, controlled trial evaluating whether isosorbide-5-mononitrate prevented variceal bleeding in cirrhotic patients with gastroesophageal varices, who had contraindications or could not tolerate β- blockers. Patients received isosorbide-5-mononitrate or placebo. No significant differences were noted in the 1- and 2-year actuarial probability of bleeding or survival between the two treatment groups.[137] When combined with a β-blocker, isosorbide-5-mononitrate lowers the HVPG more than a β-blocker alone. However, trial data show a higher rate of withdrawal with combination therapy than with β-blocker monotherapy because of side effects.[138]

The AASLD guidelines suggest that nonselective β-blockers in combination with EVL, nitrates (either alone or in combination with β-

blockers), TIPS, or sclerotherapy should not be used in the primary prophylaxis of variceal hemorrhage.[92,139]

Depending on the size of C.V.'s varices on endoscopy and the risk of hemorrhage, C.V. should have been given propranolol 20 mg two times a day, nadolol 20 mg daily, or carvedilol 6.25 mg daily titrated to reduce the resting heart rate to 55 to 60 beats/minute (or by 25%), or EVL to prevent or delay the first episode of variceal bleeding.

SECONDARY PROPHYLAXIS

CASE 25-2, QUESTION 6: C.V.'s hepatologist would like to start treatment to prevent further variceal hemorrhage. What are the long-term objectives for the treatment of C.V.? What treatment approaches can be used to prevent a recurrence of bleeding (secondary prevention)?

Secondary prevention or secondary prophylaxis is therapy used to prevent rebleeding. All patients who survive a variceal bleeding episode should receive therapy to prevent recurrent episodes. It is important that the initiation of β-blockers be delayed until after recovery of the initial variceal hemorrhage. Initiation of a β-blocker during the treatment of an acute bleed would block the patient's acute tachycardia in response to his or her hypotension, which may adversely impact survival. The benefit of nonselective β-blockers in the prevention of rebleeding episodes has been demonstrated by a number of trials.[113,140,141] For example, Colombo et al[140] randomized cirrhotic patients with a history of variceal hemorrhage to propranolol, atenolol, or placebo. Oral propranolol was titrated until the resting pulse rate was reduced by ~25%, and atenolol was given at a fixed dose of 100 mg daily. The incidence of rebleeding was significantly lower in patients receiving propranolol than those receiving placebo (P = .01). Bleeding-free survival was higher for patients on active drugs than for those on placebo (propranolol vs placebo, P = .01; atenolol vs placebo, P = .05).[140]

Eradication of varices by endoscopic procedures is also effective in preventing recurrent variceal bleeding.[15,141] A study by de la Pena et al[141] showed that nadolol plus EVL (N = 43) reduced the incidence

of variceal rebleeding compared with EVL alone (*N* = 37). Variceal bleeding recurrence rate was 14% in the EVL plus nadolol group and 38% in the EVL alone group (*P* = .006). Mortality was similar in both groups, and the actuarial probability of variceal recurrence at 1 year was lower in the EVL plus nadolol group than in the EVL alone group (54% vs 77%; *P* = .06). The adverse effects in the β-blocker group were higher, which led to the withdrawal of the β-blocker in 20% to 30% of the patients.[141]

A meta-analysis of randomized trials[142] reported that compared with EVL alone, EVL combined with β-blockers and/or isosorbide-5-mononitrate reduced overall rebleeding (32% vs 17%, respectively; *P* < .01) with no significant difference in mortality or complications. When comparing drug therapy alone to combination therapy with EVL and β-blockers and/or isosorbide-5-mononitrate, combination therapy showed a trend toward lower rebleeding (29% vs 37%, respectively; NS), but with no effect on mortality. Combination therapy with EVL plus β-blockers and/or isosorbide-5-mononitrate is effective in preventing rebleeding. Drug therapy alone is an alternative.[142]

TIPS is an option for those patients who fail both EVL and prophylaxis with β-blocker therapy. In a randomized study of Child–Turcotte–Pugh class B and C cirrhotic patients surviving their first episode of variceal hemorrhage, Escorsell et al[143] reported a lower rate of rebleeding (13% vs 39%; *P* = .007) and higher rate of encephalopathy (38% vs 14%, *P* = .007) in patients treated with TIPS versus those treated with the combination of propranolol and isosorbide-5-mononitrate. The 2-year rebleeding probability was also lower in the TIPS group (13% vs 49%; *P* = .01). Of note, drug therapy improved the Child–Turcotte–Pugh class more frequently than with TIPS (72% vs 45%; *P* = .04) and at lower costs.[143]

The AASLD guidelines suggest the combination of a nonselective β-blocker plus EVL as first-line therapy for secondary prophylaxis. TIPS should be considered in patients who experience recurrent variceal hemorrhage despite combination pharmacologic and endoscopic therapy.[86,92]

Because C.V. has a history of recurrent upper GI bleeding, the best option to prevent further bleeding is to initiate a nonselective β-blocker and begin EVL. The β-blocker should be titrated to reduce the resting heart rate to 55 to 60 beats/minute or by 25%. EVL should be repeated every 1 to 4 weeks until obliteration, with a repeat endoscopy performed 3 to 6 months after obliteration, and then every 6 to 12 months to check for variceal recurrence.[92] If this combination fails to prevent variceal hemorrhage, then TIPS would be considered as a therapeutic option.[86,92]

HEPATIC ENCEPHALOPATHY

CASE 25-3

Question 1: R.C., a 57-year-old male, was admitted to the hospital because of nausea, vomiting, and abdominal pain. He had a long history of alcohol abuse, with multiple hospital admissions for alcoholic gastritis and alcohol withdrawal. Physical examination revealed a cachectic male patient (weighing 121.25 pounds [55 kg]) with clouded mentation, who was not responsive to questions about name and place. Tense ascites and edema were noted, and the liver was percussed at 3.54 inches (9 cm) below the right costal margin. The spleen was not palpated, and no active bowel sounds were heard. Laboratory results on admission included the following:

Na, 132 mEq/L
K, 3.7 mEq/L
Cl, 98 mEq/L
Bicarbonate, 27 mEq/L
BUN, 24 mg/dL
SCr, 1.4 mg/dL
Hgb, 9.2 g/dL
Hct, 24.1%
AST, 520 IU
Alkaline phosphatase, 218 IU
Lactate dehydrogenase (LDH), 305 IU
Total bilirubin, 3.5 mg/dL
PT, 22 seconds (INR, 1.8)

A 70-g protein, 2000 kcal diet was ordered. Furosemide 40 mg IV every 12 hours was ordered in an attempt to reduce the edema and ascites. Morphine

sulfate and prochlorperazine were ordered for his abdominal pain and nausea, respectively. Two days after admission, R.C. had an episode of hematemesis. He became mentally confused and at times nonresponsive to verbal command. An NG tube was inserted and coffee-ground material was produced on continuous suctioning. Saline lavage was continued until the aspirate became clear. The next morning, R.C. was still in a confused mental state. He demonstrated prominent asterixis, and fetor hepaticus was noted on his breath. On the second day of his hospitalization, laboratory data were as follows:

Hgb, 7.4 g/dL
Hct, 21.2%
K, 3.1 mEq/L
SCr, 1.4 mg/dL
BUN, 36 mg/dL
PT, 22 seconds (INR, 1.8)
Guaiac-positive stool
HE and upper GI bleeding were added to his problem list.

What aspects of R.C.'s history are compatible with a diagnosis of HE? What classification of HE does he fall into?

HE is a spectrum of central nervous system (CNS) abnormalities ranging from subclinical alterations to coma and caused by advanced liver disease and/or portosystemic shunting of blood. According to the guidelines by the AASLD and the EASL for HE in Chronic Liver Disease, HE is classified according to four criteria: (1) underlying disease (acute liver failure [type A]; resulting from portosystemic bypass or shunting [type B]; from cirrhosis [type C]), (2) severity of manifestations, (3) according to time course (episodic, recurrent, or persistent HE), and (4) according to precipitating factors (nonprecipitated or precipitated).[144]

The gold standard to measure the severity of HE is by the West Haven Criteria (WHC), and patients with significantly altered consciousness by the Glasgow Coma Scale (GCS). For more details on WHC and GCS, please refer to the AASLD/EASL 2014 guidelines at aasld.org (https://www.aasld.org/sites/default/files/2019-06/hepaticencephalopathy82014.pdf). The ISHEN (International Society for Hepatic Encephalopathy and Nitrogen Metabolism) consensus classifies patients as having minimal HE and Grade I hepatic encephalopathy (WHC) as covert HE, whereas those with

apparent clinical abnormalities as overt hepatic encephalopathy (OHE). The ISHEN consensus defines the onset of disorientation or asterixis as the onset of OHE.[145] This chapter will focus on the treatment of OHE in cirrhosis.

During the early phase of HE, the altered mental state may present as a slight derangement of judgment and change in personality, sleep pattern, or mood. Drowsiness and confusion become more prominent as the HE progresses. Finally, unresponsiveness to arousal and deep coma ensue. Asterixis, or flapping tremor, is often present in the early to middle stages of HE that precede stupor or coma.[144]

The clinical features (as seen in R.C.) include altered mental state and asterixis. He is classified as having OHE, type C, grade III, episodic, precipitated (by upper GI bleed; see Case 25-3, Question 3).

Asterixis can be demonstrated by having the patient hyperextend his or her wrist with the forearms outstretched and fingers separated. It is characterized by bilateral, synchronous, repetitive, arrhythmic motions occurring in bursts of one flap (twitch) every 1 to 2 seconds. Asterixis is not specific for HE and may also be present in uremia, hypokalemia, heart failure, ketoacidosis, respiratory failure, and sedative overdose.[144]

As discussed in the questions that follow, the pharmacologic management of HE is guided by both an understanding of the pathogenesis of this disorder and the stage of severity demonstrated by the individual patient. In most cases, HE is fully reversible; therefore, it is likely a metabolic or neurophysiologic rather than an organic disorder.[144] Severe, progressive HE can lead to irreversible brain damage (caused by increased intracranial pressure), brain herniation, and death.[144,146,147]

Pathogenesis

Case 25-3, Question 2: What is the pathogenesis of HE?

Several theories exist about the pathogenesis of HE. The most widely referenced theories involve abnormal ammonia metabolism; altered ratio of branched chain to aromatic amino acids; imbalance in brain neurotransmitters, such as γ-aminobutyric acid (GABA) and serotonin; derangement in the blood–brain barrier; and exposure of the brain to accumulated "toxins."[148] The pathogenesis of HE is likely multifactorial.

AMMONIA

Ammonia is a by-product of dietary protein metabolism or digestion of protein-rich blood in the GI tract (eg, bleeding esophageal varices). Bacteria present in the GI tract digest protein into polypeptides, amino acids, and ammonia. These substances are then absorbed across the intestinal mucosa. Ammonia is readily metabolized in the liver to urea, which is then renally eliminated. However, when blood flow and hepatic metabolism are impaired by cirrhosis, serum and CNS concentrations of ammonia are increased. The ammonia that enters the CNS combines with α-ketoglutarate to form glutamine, an aromatic amino acid. Ammonia has been considered central to the pathogenesis of HE. An increased ammonia level raises the amount of glutamine within astrocytes, causing an osmotic imbalance, cell swelling, and ultimately brain edema. Although high serum ammonia and cerebrospinal glutamine concentrations are characteristic of encephalopathy, they may not be the actual cause of this syndrome.[147,149] According to the AASLD/EASL guidelines, high ammonia levels alone may not add any diagnostic, staging, or prognostic value.[144] However, if a level is normal, the diagnosis of HE should be questioned. In the case where ammonia-lowering drugs are used (eg, lactulose), repeated measurements of ammonia would be beneficial to assess their efficacy.[144]

AMINO ACID BALANCE

In both acute and chronic liver failure, the ratio of the branched chain to aromatic amino acids is altered. Because of the higher

permeability of aromatic amino acids across the blood–brain barrier and into the cerebrospinal fluid, some aromatic compounds can lead to production of “false neurotransmitters” that can lead to HE with altered mental status (see Chapter 38, Adult Parenteral Nutrition).[148,149]

Γ-AMINOBUTYRIC ACID

Schafer and Jones[150] proposed that in liver disease, gut-derived GABA escapes hepatic metabolism, crosses the blood–brain barrier, binds to its postsynaptic receptor sites, and causes the neurologic abnormalities associated with HE. Others hypothesize that endogenous benzodiazepine-like substances, via their agonist properties, contribute to the pathogenesis of HE by enhancing GABAergic neurotransmission. The role of GABA and endogenous benzodiazepines in HE is still not clearly defined.[151,152] Of all the toxins suspected to cause hepatic coma, ammonia and certain aromatic amino acids are most commonly studied. Other precipitating factors include infections, electrolyte disorders, GI bleeding, constipation, and overdiuresis. These factors may increase the serum ammonia and precipitate an exacerbation of HE.[144,153,154]

Case 25-3, Question 3: What are the probable precipitating causes of HE in R.C.?

The main precipitating cause of HE in R.C. was the sudden onset of upper GI bleeding. The bacterial degradation of blood in the gut results in absorption of large amounts of ammonia and possibly other toxins into the portal system. Other important contributory factors in this case are diuretic-induced hypovolemia (BUN:SCr ratio >20), hypokalemia (potassium, 3.1 mEq/L), and potentially metabolic alkalosis (continuous NG suctioning and furosemide). Overzealous diuretic therapy increases HE by inducing prerenal azotemia, hypokalemia, and metabolic alkalosis. Alkalosis promotes diffusion of nonionic ammonia and other amines into the CNS. The associated

intracellular acidosis “traps” the ammonia by converting it back to ammonium ion (NH_4^+).[155,156]

Sedating drugs such as opioids (eg, morphine, methadone, meperidine, codeine), sedatives (eg, benzodiazepines, barbiturates, chloral hydrate), and tranquilizers (eg, phenothiazines) can also precipitate HE. Encephalopathy precipitated by most drugs can be explained by increased CNS sensitivity and decreased hepatic clearance with subsequent drug and, in some cases, active metabolite accumulation. For R.C., the morphine and prochlorperazine might have contributed to the worsening of his HE. Although not applicable to this case, excessive dietary protein, infections, and constipation can also contribute to excess nitrogen load and hepatic coma.

Treatment and General Management

Case 25-3, Question 4: What nondrug steps should be taken to manage R.C.’s HE?

Correcting the precipitating factor underlying the episode of OHE can improve mental status in 90% of patients.[144] After identifying and removing precipitating causes of HE, therapeutic management is aimed primarily at reducing the amount of ammonia or nitrogenous products in the circulatory system, even though ammonia alone is not particularly useful for staging or determining prognosis for HE.[144] The 2013 ISHEN and 2014 AASLD/EASL guidelines recommend an energy intake of 35 to 40 kcal/kg of body weight/day and a protein intake of 1.2 to 1.5 g/kg of ideal body weight/day for patients with cirrhosis and those awaiting liver transplantation surgeries.[144,157–161] A study conducted by Córdoba et al[162] randomized patients with cirrhosis and HE to two dietary groups for 14 days. The first group followed a progressive increase in the dose of protein receiving 0 g of protein for the first 3 days, then increased progressively every 3 days (12, 24, and 48 g) up to 1.2 g/kg/day for the last 2 days. The

second group received 1.2 g/kg/day from the first day. Results showed that the course of HE was not significantly different between groups. The patients in the first group, however, experienced a higher degree of protein breakdown.[162]

R.C. is a cachectic male, and care should be taken in providing nutrition to malnourished patients. The 70-g protein, 2000-kcal diet ordered for R.C. is appropriate because it falls within the recommended weight-based ranges established by the ISHEN and AASLD/EASL guidelines. R.C. should be offered small meals or liquid nutritional branched chain amino acids and leucine-enriched amino acid supplements evenly distributed throughout the day along with a late-night snack.[157,159] Oral branched chain amino acids can improve episodic HE and may allow for achieving recommended nutritional target when dietary protein is not tolerated.[144,163] Vegetable and dairy proteins may be better tolerated than animal proteins.[157]

Case 25-3, Question 5: Which pharmacologic interventions are appropriate to manage R.C.'s HE?

LACTULOSE

Lactulose is broken down by GI bacteria to form lactic, acetic, and formic acids, which acidify colonic contents converting ammonia into the less readily absorbed ammonium ion. Back-diffusion of ammonia from the plasma into the GI tract can also occur. The net result is a lower plasma ammonia concentration. The absorption of other protein breakdown products (eg, aromatic amino acids) may also be reduced. Lactulose-induced osmotic diarrhea decreases intestinal transit time available for ammonia production and absorption, and it may help clear the GI tract of blood. Lactulose syrup (10 g/15 mL) has been used successfully for the treatment of HE. For OHE, lactulose 25 mL is administered every 1 to 2 hours until catharsis occurs. Doses are then titrated downward to maintain two to three bowel movements daily and clear mentation in order to avoid complications of overuse of lactulose (aspiration, dehydration,

severe perianal skin irritation, and precipitation of HE).[144] When the oral route of administration is not possible, as in the treatment of a comatose patient, it may be necessary to administer the drug through an NG tube. Alternatively, a rectal retention enema compounded with 300 mL of lactulose in 700 mL water can be prepared. The lactulose water mixture (125 mL) is retained for 30 to 60 minutes, although this is difficult in patients with altered mental status. The beneficial clinical effect of lactulose occurs within 12 to 48 hours. Patients may need long-term administration of lactulose as maintenance therapy, especially in patients with recurring HE. For prevention of recurrence of OHE, oral daily prophylactic dosing of lactulose should be maintained. If precipitating factors have been removed or liver function improved, prophylactic therapy may be tapered and potentially discontinued.[144] The administration of lactulose permits better dietary protein tolerance and is well tolerated if dosages are kept sufficiently low to avoid diarrhea.[164]

Although lactulose is the mainstay of HE treatment,[144,165] very limited data exist evaluating its efficacy. Care should be taken not to induce excessive diarrhea that could lead to dehydration and hypokalemia, both of which have been associated with exacerbation of HE. Although lactulose is generally well tolerated, 20% of patients report symptoms of gaseous distention, flatulence, or belching. Dilution with fruit juice, carbonated beverages, or water can reduce the excessive sweetness of the syrup.[146]

RIFAXIMIN

Rifaximin is a synthetic antibiotic structurally related to rifamycin. It has a wide spectrum of antibacterial activity against gram-negative and gram-positive bacteria, both aerobic and anaerobic.[166] Of note, 96.6% of the drug is recovered in the feces as unchanged drug, and what is absorbed undergoes metabolism with minimal renal excretion of unchanged drug.[82,167] It was introduced in the United States for the treatment of travelers' diarrhea,[168] but also is indicated for HE.[167] Although dosages used in HE trials ranged from 550 mg twice daily to 400 mg every 8 hours,[169,170] the FDA-approved dose

for HE is 550 mg twice daily.[167] Rifaximin is well tolerated, but can cause flatulence, nausea, and vomiting. Some urticarial skin reactions have been reported with prolonged use.[171] Bacterial superinfections (*Clostridium difficile*–associated diarrhea) with >2 months of rifaximin have also been reported.[82,167]

NEOMYCIN

Neomycin is also an antibiotic effective in reducing plasma ammonia concentrations (presumably by decreasing protein-metabolizing bacteria in the GI tract). Approximately 1% to 3% of the neomycin dose is absorbed. Chronic use in patients with severe kidney disease can cause ototoxicity and nephrotoxicity. Routine monitoring of SCr, presence of protein in the urine, and estimation of creatinine clearance are advisable for patients receiving high dosages for >2 weeks.[164] Neomycin therapy can also produce a reversible malabsorption syndrome that not only suppresses the absorption of fat, nitrogen, carotene, iron, vitamin B_{12}, xylose, and glucose but also decreases the absorption of some drugs, such as digoxin, penicillin, and vitamin K.[146] Typical HE dosage for neomycin ranges from 500 to 1000 mg four times daily, or as a 1% solution (125 mL) given as a retention enema (retained for 30–60 minutes) four times daily.[164]

FLUMAZENIL

Based on the theory of accumulation of endogenous benzodiazepine- like substances in HE, flumazenil, a benzodiazepine antagonist, has been evaluated for its role in the treatment of HE. Several trials have demonstrated both clinical and electrophysiologic improvement in patients with HE.[172] However, an IV product with modest benefits in the treatment of HE is not an ideal treatment option.

Lactulose versus rifaximin

An extensive review of rifaximin for the treatment of HE conducted by Lawrence and Klee[173] found that rifaximin was equally effective, and in some studies superior to lactulose in mild-to-moderate

disease. Patients treated with rifaximin required fewer, shorter, and less costly hospitalizations than patients who are treated with lactulose.[173] Bucci and Palmieri[174] conducted a double-blind study comparing rifaximin (1200 mg/day) and lactulose (30 g/day) for 15 days in patients with moderate-to-severe HE. After 7 days, ammonia concentrations normalized and at the end of the treatment period, cognitive function test scores improved in both groups. Rifaximin therapy was better tolerated.[174] Although the data reported from these and other trials suggest a benefit with rifaximin for the treatment of HE, larger trials must be conducted to determine its superiority over lactulose. In addition, the current cost of rifaximin is considerably higher than both lactulose and neomycin (estimated cash price: lactulose [60–100 g daily] ~$75–$120/month; neomycin [500 mg four times daily] ~$150/month; and rifaximin [550 mg twice daily] ~$2660/month; data per goodrx.com).

Rifaximin versus neomycin

Miglio et al[175] conducted a randomized, controlled, double-blind study to evaluate the efficacy and tolerability of rifaximin (400 mg three times daily) in comparison to neomycin (1 g three times daily) treatment for 14 days each month over 6 months. During the study, blood ammonia concentrations in both the rifaximin and neomycin groups decreased similarly.[173] Pedretti et al[176] compared rifaximin 400 mg every 8 hours to neomycin 1 g every 8 hours in patients with cirrhosis and reported a higher rate of adverse events (increases in BUN, creatinine, nausea, abdominal pain, and vomiting) in the neomycin group after 21 days of therapy. Both drugs significantly decreased blood ammonia concentrations. However, rifaximin produced an earlier reduction of blood ammonia.[176] Because of the lower adverse effect profile and considerable efficacy, rifaximin has taken over as second-line therapy for HE over neomycin at many institutions.

Lactulose versus neomycin

Orlandi et al[177] found that lactulose and neomycin appear to have similar efficacy for the acute treatment of HE. However, in the treatment of an acute exacerbation, particularly in an acute GI bleed, lactulose may produce a faster response than neomycin. Interestingly, although lactose therapy is considered the standard of practice in OHE treatment and prevention, a meta-analysis evaluating the efficacy of lactulose in patients with HE questions its benefit.[178] Large randomized controlled trials are needed to determine the optimal treatment for HE management.[147] The AASLD/EASL guidelines consider neomycin as an alternative choice for the treatment of OHE.[144]

Lactulose would be the preferred option to treat R.C.'s HE because it would shorten the time to clear the blood from his GI tract and hopefully lead to a rapid resolution of his confusion. Although neomycin is not contraindicated for R.C., the potential for worsening of his coagulopathy (by interfering with vitamin K absorption) and risk of nephrotoxicity (SCr, 1.4 mg/dL) makes this a less optimal choice. If R.C.'s renal function continues to decline, neomycin may become contraindicated. Lactulose can be initiated at 25 mL every 1 to 2 hours until at least two soft or loose stools per day are produced. The dose can then be reduced to maintain two to three soft stools per day and improved mental status. R.C. may receive lactulose by NG tube if necessary in the early treatment period.

COMBINATION THERAPY WITH LACTULOSE

Case 25-3, Question 6: Would combination therapy provide any additive beneficial effect for R.C.?

A randomized, double-blind, placebo-controlled trial by Bass et al[169] compared rifaximin versus placebo in the prevention of HE and hospitalization in patients recovering from recurrent HE (at least two episodes within the previous 6 months). Patients were assigned to either rifaximin at a dose of 550 mg twice daily or placebo for 6 months. The study allowed the use of lactulose (~90% of patients

received concomitant therapy). The results of the study showed that a breakthrough episode of HE occurred in 22.1% with rifaximin and 45.9% with placebo. Hospitalization involving HE was lower with rifaximin (13.6%) than with placebo (22.6%). Adverse events were similar among the two groups.[169] A randomized controlled trial compared the efficacy of rifaximin and lactulose combination with lactulose monotherapy for the treatment of OHE. Neurologic status improved in the lactulose monotherapy group than in the combination therapy group.[179] In contrast, a systematic review of five randomized and five observational studies reported better efficacy and lower mortality with the combination of lactulose and rifaximin than lactulose alone in their overall analysis. However, in their pooled analysis, they reported similar efficacy outcomes in their combination therapy and lactulose monotherapy groups.[180] The AASLD/EASL considers rifaximin as an effective add-on therapy to lactulose for the prevention of OHE recurrence.[144] Previous HE guidelines (American College of Gastroenterology) stated that combination therapy of lactulose and neomycin may be reasonable in patients who do not respond to monotherapy.[164] The current AASLD/EASL guidelines do not address this combination.[144] Combination therapy would not be appropriate for R.C. at this time.

HEPATORENAL SYNDROME

Case 25-3, Question 7: Lactulose treatment was initiated at 25 mL every hour and titrated to effect with some improvement in R.C.'s mental status. A few days after resolution of his GI bleeding, his SCr increased from 1.4 to 2.7 mg/dL and he became progressively oliguric. His BP was 85/65 mm Hg, pulse rate was 70 beats/minute, and respiratory rate was 16 breaths/minute. Furosemide was discontinued, and R.C. was treated with albumin infusions to allow volume expansion and improve urine output. A renal ultrasound did not reveal any specific abnormalities. Minimal improvement occurred in his BP and urine output. Laboratory results included the following:

Na, 123 mEq/L
K, 3.6 mEq/L

Cl, 98 mEq/L
Bicarbonate, 25 mEq/L
BUN, 96 mg/dL
SCr, 2.7 mg/dL
Hgb, 8.4 g/dL
Hct, 27.1%
AST, 640 IU
Alkaline phosphatase, 304 IU
LDH, 315 IU
Total bilirubin, 4.1 mg/dL
PT, 22 seconds (INR, 1.8)
A 24-hour urinalysis showed the following:
Protein, 50 mg/day
Red blood cells, 1 to 2 per high-power field
Negative for WBC, glucose, and ketones

After exclusion of other possible causes of kidney disease, R.C. is diagnosed with HRS. What are potential treatment options for R.C.'s HRS?

Pathogenesis

HRS is a complication of advanced cirrhosis characterized by cholestasis, worsening inflammation and/or microcirculatory dysfunction, bile salt direct tubular damage, increased proinflammatory cytokines and chemokines, splanchnic vasodilation, impaired cardiac function, activation of RAAS and an intense renal vasoconstriction, which leads to a very low renal perfusion and glomerular filtration rate, as well as a severe reduction in the ability to excrete sodium and free water.[181,182] A summary of the pathogenesis of HRS can be found in the EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis.[183] HRS is diagnosed by exclusion of other known causes of kidney disease in the absence of parenchymal disease. The International Ascites Club (IAC) has revised criteria for the diagnosis and classification of HRS.[183–185] In the revised classification of HRS, the former type 1 HRS is now referred to as HRS-acute kidney injury (AKI) and type 2 HRS is now referred to as non-AKI-HRS, although the criteria are somewhat different.[183]

HRS can be classified into two categories. HRS-AKI (type 1 HRS) was previously characterized by an acute and progressive kidney failure defined by doubling of the initial SCr concentrations to a level >2.5 mg/dL in <2 weeks. The new criteria require an increase in SCr of 0.3 mg/dL and/or ≥50% increase from baseline within 48 hours along with the presence of cirrhosis and ascites, no improvement in SCr after 2 days of discontinuation of diuretics and plasma expansion with albumin, no shock, no nephrotoxic medications, and no parenchymal kidney disease.[183] HRS-AKI (type 1 HRS) is precipitated by factors such as SBP or large-volume paracentesis, but can occur without a precipitating event. This usually occurs within the setting of an acute deterioration of circulatory function characterized by hypotension and activation of endogenous vasoconstrictor systems. It may be associated with impaired cardiac and liver functions as well as HE. The prognosis of patients exhibiting HRS-AKI (type 1 HRS) is very poor.[186,187] In contrast, non-AKI-HRS (type 2 HRS) is a progressive deterioration of kidney function, which fulfills criteria for HRS, but not for AKI. The prior definition of type 2 HRS was SCr between 1.5 and 2.5 mg/dL.[183] Non-AKI-HRS (type 2 HRS) is often associated with refractory ascites and has a better survival rate than that of patients with HRS-AKI (type 1 HRS).[184,186,188] HRS develops in ~30% of patients with SBP.[182]

Treatment

HRS is associated with a high mortality rate with median overall survival being 3 months (~2 weeks for HRS-AKI [type 1 HRS] and 6 months for non-AKI-HRS [type 2 HRS]).[182] The definitive treatment for HRS is liver transplantation, which is the only treatment that ensures long-term survival.[68] The main goal of pharmacologic therapy is to manage HRS sufficiently so that the patient can survive long enough to obtain a suitable donor liver.[184,186] Diuretic therapy worsens HRS and should be discontinued.[188] Excessive fluid

administration should be avoided to prevent fluid overload and dilutional hyponatremia.

Solanki et al[189] randomized patients with HRS-AKI (type 1 HRS) to terlipressin 1 mg IV every 12 hours or placebo. Both groups also received albumin. Urine output, creatinine clearance, mean arterial pressures, and survival (42% vs 0%) were significantly better with terlipressin than with placebo ($P < .05$). All survivors in the terlipressin group had a reversal of HRS.[189] Sanyal et al[190] conducted a prospective, double-blind, placebo-controlled clinical study in which patients with HRS-AKI (type 1 HRS) were randomly assigned to terlipressin (1 mg IV every 6 hours) or placebo. If, after 3 days of therapy, the SCr level had not decreased by ≥30% from baseline, the dose was increased to 2 mg every 6 hours. All patients in this study also received albumin. The primary endpoint on day 14 was SCr ≤1.5 mg/dL on two occasions at least 48 hours apart, without dialysis, death, or recurrence of HRS-AKI (type 1 HRS). The primary endpoint was achieved twice as often with terlipressin than with placebo (25% vs 12.5%, respectively), although this did not reach statistical significance. In addition, terlipressin did not improve survival. However, terlipressin was superior to placebo for HRS-AKI (type 1 HRS) reversal as defined by SCr ≤ 1.5 mg/dL (34% vs 13%; $P = .008$). Adverse events were similar between groups.[190] Continuous infusions are being studied to try and reduce side effects and maintain stable effects on portal pressure. In 2009, the FDA accepted the final section of the New Drug Application seeking marketing approval for terlipressin for the treatment of HRS-AKI (type 1 HRS) and granted priority review and fast-track designation. In 2013, terlipressin was granted Orphan Drug Status.

A meta-analysis of four randomized controlled trials reported similar efficacy for norepinephrine (initial dose 0.5 mg/hour, max dose 3 mg/hour) and terlipressin for the treatment of HRS.[191] Other nonrandomized studies suggest that vasoconstrictor therapy with norepinephrine (combined with albumin and furosemide) or midodrine (combined with octreotide and albumin) improves renal function in patients with HRS-AKI (type 1 HRS).[192–194] Duvoux et al[194] conducted a pilot study describing the efficacy and safety of

norepinephrine in combination with IV albumin and furosemide in patients with HRS-AKI (type 1 HRS). Norepinephrine was given for 10 ± 3 days, at a mean dosage of 0.8 ± 0.3 mg/hour. Reversal of HRS was observed in 83% of patients after a median of 7 days, with a reduction in SCr (358 ± 161 to 145 ± 78 μmol/L; $P < .001$), a rise in creatinine clearance (13 ± 9 to 40 ± 15 mL/minute; $P = .003$), an increase in mean arterial pressure (65 ± 7 to 73 ± 9 mm Hg, $P = .01$), and a marked reduction in active renin and aldosterone plasma concentrations ($P < .05$).[194] Two small, open-label, randomized, pilot studies evaluated the efficacy and safety of norepinephrine compared to terlipressin in the treatment of HRS.[195,196] All subjects also received albumin. Both drugs significantly improved renal function and had similar effects with respect to efficacy and safety. These preliminary data suggest that norepinephrine may be a safe, effective, and less costly alternative to terlipressin in the treatment of HRS-AKI (type 1 HRS). Both terlipressin and norepinephrine can cause ischemic and cardiovascular events. Patient screening prior to their use is recommended. Optimum albumin dosage for the treatment of HRS has not been determined. However, a meta-analysis has demonstrated a dose–response relationship for albumin cumulative dose and survival such that the 30-day survival with a cumulative dose of 200 g is 43.2%, 400 g is 51.4% and 600 g is 59.0%.[197]

Esrailian et al[198] conducted a retrospective chart review of HRS-AKI (type 1 HRS) patients who received a combination of octreotide, midodrine, and albumin compared to untreated controls who received albumin only. Octreotide administration started at 100 μg subcutaneous TID, with the goal to increase the dose to 200 μg subcutaneous TID. Midodrine administration started at 5, 7.5, or 10 mg TID orally, with the goal to increase the dose to 12.5 or 15 mg TID if necessary. Adjustment in medication dose was based on a goal of increasing the mean arterial pressure by ≥15 mm Hg from baseline. All patients received IV expansion of plasma volume with 1.5 L of saline combined with an average of 120 g of human albumin after diuretic withdrawal. The authors found that at 30 days, 40% of treated patients had a sustained reduction in SCr compared with

10% of the concurrent untreated controls (P = .01). In that same time period, 43% of patients in the treatment group had died, compared with 71% of controls (P = .03).[198]

The IAC and EASL guidelines recommend vasoconstrictors and albumin for first-line treatment of HRS-AKI (type 1 HRS).[183,186] They advocate for the use of terlipressin (2–12 mg/day) in combination with albumin (20–40 g/day after 1 g/kg on the first day) with 64% to 76% having complete or partial response and 46% to 56% a complete response.[183,186] The IAC and EASL recommend norepinephrine as an alternative to terlipressin, although there are much less data to support norepinephrine for HRS.[183,186] The AASLD guidelines also recommend albumin plus norepinephrine as a treatment option of HRS-AKI (type 1 HRS); however, this approach requires an intensive care unit.[38] Midodrine, octreotide, and albumin are alternative options if terlipressin and norepinephrine are not available, as this combination is much less effective than terlipressin with albumin.[183,199] The latest AASLD recommendation is to consider the use of albumin plus octreotide and midodrine (largely because of the lack of availability of terlipressin in the United States).[38] Studies mention that the combination of both octreotide and midodrine is required to be effective.[200,201] Vasoconstrictor efficacy and safety requires further evaluation in large, randomized clinical trials.[192–194]

Non-AKI-HRS (type 2 HRS) manifests itself as a progressive disease and, therefore, patients do not present acutely with deterioration in kidney function. Although vasoconstrictors with albumin improve SCr concentrations in patients with non-AKI-HRS (type 2 HRS), following discontinuation of treatment, non-AKI-HRS (type 2 HRS) returns. There are also some concerns regarding the potential impact of non-AKI-HRS (type 2 HRS) treatment on post–liver transplantation outcomes.[183,202,203] The main clinical problem in non-AKI-HRS (type 2 HRS) is refractory ascites, which can be controlled by large-volume paracentesis along with IV albumin or TIPS.[188,192,204] Studies are needed to determine the place in therapy for vasoconstrictors and other potential treatments in patients with non-AKI-HRS (type 2 HRS).[186]

R.C. should continue to receive albumin 20–40 g IV per day and either norepinephrine or terlipressin IV should be initiated. Norepinephrine or terlipressin along with albumin is more effective than albumin, octreotide, and midodrine for HRS-AKI and therefore the preferred treatment for R.C. However, because of the recent variceal hemorrhage, careful monitoring of BP is necessary to avoid rebleeding. Albumin, octreotide, and midodrine could be considered. Because of the poor prognosis associated with HRS, R.C. should be evaluated for liver transplantation.

CASE 25-3, QUESTION 8: Why should liver transplantation be considered in patients with end-stage liver disease such as R.C.?

Liver transplantation for appropriate candidates may be the best option for end-stage liver disease and its complications leading to improved quality and duration of life. Transplantation is generally considered in patients with refractory ascites, severe HE, esophageal or gastric varices, and HRS.[205] Because of the shortage of organs available and significant complications associated with transplantation, therapeutic alternatives should be considered to avoid the necessity for transplantation. For patients such as R.C., who are candidates for transplantation, therapeutic strategies to improve outcomes after transplantation should be considered in therapeutic decision-making before transplantation (see Chapter 34, Kidney and Liver Transplantation, for further information on the indications for liver transplantation).[204]

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol.* 2015;62:986–974. (184)

Boyer TD, Haskal ZJ, American Association for the Study of Liver Diseases. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009. *Hepatology.* 2010;51(1):306. (86)

European Association for Study of Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol.* 2018;69:406–460. (183)

European Association for Study of the Liver. EASL clinical practice guidelines on nutrition in chronic liver disease. *J Hepatol.* 2019;70:172–193. (157)

Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases [published correction appears in *Hepatology.* 2017;66:304]. *Hepatology.* 2017;65:310–335. (92)

Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology.* 2013;57:1651–1653. (38)

Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology.* 2014;60(2):715–735. (144)

COMPLETE REFERENCES CHAPTER 25 COMPLICATIONS OFEND-STAGE LIVER DISEASE

1. Heron M. Deaths: leading causes for 2017. *Natl Vital Stat Rep*. 2019;68:1–77.
2. Friedman SL. Liver fibrosis—from bench to bedside. *J Hepatol*. 2003;38(suppl 1):S38–S53.
3. Roberts RA, Ganey PE, Ju C, Kamendulis LM, Rusyn I, Klaunig JE. Role of the Kupffer cell in mediating hepatic toxicity and carcinogenesis. *Toxicol Sci*. 2007;96:2–15.
4. Tarla MR, Ramalho F, Ramalho LNZ, et al. Cellular aspects of liver regeneration. *Acta Cir Bras*. 2006;21(suppl 1):63–66.

5. Pritchard MT, Nagy LE. Ethanol-induced liver injury: potential roles for egr-1. *Alcohol Clin Exp Res*. 2005;29(suppl 11):146S–150S.
6. Zhu H, Jia Z, Misra H, Li YR. Oxidative stress and redox signaling mechanisms of alcoholic liver disease: updated experimental and clinical evidence. *J Dig Dis*. 2012;13(3):133–142.
7. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol*. 2018;69(1):154–181.
8. World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. 2018. Accessed August 4, 2020. https://www.who.int/publications/i/item/guide-care-treat-persons-diagnosed-chronic-hepatitis-c-978-92-4-155034-5
9. Safdar K, Schiff ER. Alcohol and hepatitis C. *Semin Liver Dis*. 2004;24:305–315.
10. Ramalho F. Hepatitis C virus infection and liver steatosis. *Antiviral Res*. 2003;60:125–127.
11. Liangpunsakul S, Chalasani N. Treatment of nonalcoholic fatty liver disease. *Curr Treat Options Gastroenterol*. 2003;6:455–463.
12. Cave M, Deaciuc I, Mendez C, et al. Nonalcoholic fatty liver disease: predisposing factors and the role of nutrition. *J Nutr Biochem*. 2007;18:184–195.
13. Heidelbaugh JJ, Sherbondy M. Cirrhosis and chronic liver failure: part II. Complications and treatment. *Am Fam Physician*. 2006;74:767–776.
14. Hu LS, George J, Wang JH. Current concepts on the role of nitric oxide in portal hypertension. *World J Gastroenterol*. 2013;19(11):1707–1717.
15. Turco L, Garcia-Tsao G. Portal hypertension: pathogenesis and diagnosis. *Clin Liver Dis*. 2019;23:573–587.
16. Groszmann R, Vorobioff JD, Gao H. Measurement of portal pressure: when, how, and why to do it. *Clin Liver Dis*. 2006;10:499–512.
17. Wadhawan M, Dubey S, Sharma BC, Sarin SK, Sarin SK. Hepatic venous pressure gradient in cirrhosis: correlation with the size of varices, bleeding, ascites, and Child's status. *Dig Dis Sci*. 2006;51:2264–2269.
18. Laleman W, Landeghem L, Wilmer A, Fevery J, Nevens F. Portal hypertension: from pathophysiology to clinical practice. *Liver Int*. 2005;25:1079–1090.
19. Rodriguez-Vilarrupla A, Fernández M, Bosch J, García-Pagán JC. Current concepts on the pathophysiology of portal hypertension. *Ann Hepatol*. 2007;6:28–36.
20. Lata J, Hulek P, Vanasek T. Management of acute variceal bleeding. *Dig Dis Sci*. 2003;21:6–15.
21. Yeung E, Wong FS. The management of cirrhotic ascites. *MedGenMed*. 2002;4:1–8.

22. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. *Am J Kidney Dis*. 2003;41:269–278.
23. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding: unresolved issues. Summary of an American Association for the Study of Liver Diseases and European Association for the Study of the Liver Single-Topic Conference. *Hepatology.* 2008;47:1765–1772.
24. Garcia-Tsao G, Lim JK, Members of Veterans Affairs Hepatitis C Resource Center Program. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program [published correction appears in *Am J Gastroenterol*. 2009;104:1894]. *Am J Gastroenterol*. 2009;104:1803–1829.
25. Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and monitoring of hepatic injury. II. Recommendations for use of laboratory tests in screening, diagnosis, and monitoring. *Clin Chem*. 2000;46:2050–2068.
26. Lee TH, Kim WR, Poterucha JJ. Evaluation of elevated liver enzymes. *Clin Liver Dis*. 2012;16(2):183–198.
27. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: coagulation in cirrhosis. *Gastroenterology* 2019;157:34–43.e1.
28. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis [published correction appears in *N Engl J Med.* 2011;364:490]. *N Engl J Med*. 2010;362:823–832.
29. Gitto S, Lorenzini S, Biselli M, Conti F, Andreone P, Bernardi M. Allocation priority in non-urgent liver transplantation: an overview of proposed scoring systems. *Dig Liver Dis*. 2009;41:700–706.
30. Riley TR III, Bhatti AM. Preventive strategies in chronic liver disease: part II. Cirrhosis. *Am Fam Physician*. 2001;64:1735–1740.
31. Dangleben DA, Jazaeri O, Wasser T, Cipolle M, Pasquale M. Impact of cirrhosis on outcomes in trauma. *J Am Coll Surg*. 2006;203:908–913.
32. Bambha K, Kamath PS. Model for End-stage Liver Disease (MELD). In: Runyon BA, ed. UpToDate. [Internet]. UpToDate; 2014. Accessed August 5, 2020. https://www.uptodate.com
33. Dunn W, Jamil LH, Brown LS, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology.* 2005;41:353–358.
34. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33:464–470.
35. Heuman DM, Mihas AA, Habib A, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. *Liver Transpl*. 2007;13:30–37.
36. United Network for Organ Sharing. Talking about transplantation: questions and answers for transplant candidates about liver allocation [online brochure]. Accessed August 5, 2020. https://unos.org/wp-content/uploads/Brochure-104-Liver-allocation.pdf

37. Krige JE, Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system: portal hypertension-2. Ascites, encephalopathy, and other conditions. *BMJ*. 2001;322:416–418.
38. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology.* 2013;57:1651–1653.
39. Bekheirnia MR, Schrier RW. Pathophysiology of water and sodium retention: edematous states with normal kidney function. *Curr Opin Pharmacol*. 2006;6:202–207.
40. Hou W, Sanyal AJ. Ascites: diagnosis and management. *Med Clin North Am*. 2009;93(4):801–817.
41. Suzuki H, Stanley AJ. Current management and novel therapeutic strategies for refractory ascites and hepatorenal syndrome. *QJM*. 2001;94:293–300.
42. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003;38:258–266.
43. Trevisani F, Bernardi M, De Palma R, et al. Circadian variation in renal sodium and potassium handling in cirrhosis. The role of aldosterone, cortisol, sympathoadrenergic tone, and intratubular factors. *Gastroenterology.* 1989;96:1187–1198.
44. Biswas KD, Jain AK. Hepatorenal syndrome. *Trop Gastroenterol*. 2002;23:113–116.
45. Gentilini P, Vizzutti F, Gentilini A, Zipoli M, Foschi M, Romanelli RG. Update on ascites and hepatorenal syndrome. *Dig Liver Dis*. 2002;34:592–605.
46. Lenz K, Buder R, Kapun L, Voglmayr M. Treatment and management of ascites and hepatorenal syndrome: an update. *Therap Adv Gastroenterol*. 2015;8(2):83–100.
47. Angeli P, Wong F, Watson H, Gines P, CAPPS Investigators. Hyponatremia in cirrhosis: results of a patient population survey. *Hepatology.* 2006;44:1535–1542.
48. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis: potential role of natriuretic doses of mineralocorticoid antagonist? *Circ Heart Fail*. 2009;2(4):370–376.
49. Runyon BA. Albumin infusion for spontaneous bacterial peritonitis. *Lancet.* 1999;354:1838–1839.
50. Javlé P, Yates J, Kynaston HG, Parsons KF, Jenkins SA. Hepatosplanchnic haemodynamics and renal blood flow and function in rats with liver failure. *Gut.* 1998;43:272–279.
51. Coppage WS Jr, Island DP, Cooner AE, Liddle GW. The metabolism of aldosterone in normal subjects and in patients with hepatic cirrhosis. *J Clin Invest*. 1962;41:1672–1680.
52. Perez-Ayuso RM, Arroyo V, Planas R, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with

ascites. *Gastroenterology.* 1983;84:961–968.
53. Runyon BA. Treatment of patients with cirrhosis and ascites. *Semin Liver Dis*. 1997;17:249–260.
54. Runyon BA, AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2004;39:841–856.
55. Yamamoto S. Disappearance of spironolactone-induced gynecomastia with triamterene. *Intern Med*. 2001;40:550–550.
56. Angeli P, Dalla Pria M, De Bei E, et al. Randomized clinical study of the efficacy of amiloride and potassium canrenoate in nonazotemic cirrhotic patients with ascites. *Hepatology.* 1994;19:72–79.
57. Delyani JA, Rocha R, Cook CS, et al. Eplerenone: a selective aldosterone receptor antagonist (SARA). *Cardiovasc Drug Rev*. 2001;19:185–200.
58. Zillich AJ, Carter BL. Eplerenone—a novel selective aldosterone blocker. *Ann Pharmacother*. 2002;36:1567–1576.
59. Inspra (eplerenone). Product information. Pfizer; 2020.
60. Sehgal R, Singh H, Sing IP. Comparative study of spironolactone and eplerenone in management of ascites in patients of cirrhosis of liver. *Eur J Gastroenterol Hepatol*. 2020;32:535–539.
61. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.
62. Pitt B, Williams G, Remme W, et al. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. *Cardiovasc Drugs Ther*. 2001;15:79–87.
63. Tang WH, Parameswaran AC, Maroo AP, Francis GS. Aldosterone receptor antagonists in the medical management of chronic heart failure. *Mayo Clin Proc*. 2005;80:1623–1630.
64. Pockros PJ, Reynolds TB. Rapid diuresis in patients with ascites from chronic liver disease: the importance of peripheral edema. *Gastroenterology.* 1986;90:1827–1833.
65. Runyon BA. Management of adult patients with ascites caused by cirrhosis. *Hepatology*. 1998;27:264–272.
66. Runyon BA. Historical aspects of treatment of patients with cirrhosis and ascites. *Semin Liver Dis*. 1997;17:163–173.
67. Ahya SN, Soler MJ, Levitsky J, Batlle D. Acid-base and potassium disorders in liver disease. *Semin Nephrol*. 2006;26:466–470.
68. Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology.* 1993;105:229–236.
69. Antes LM, Fernandez PC. Principles of diuretic therapy. *Dis Mon*. 1998;44:254–268.

70. Wong F. Liver and kidney diseases. *Clin Liver Dis*. 2002;6:981–1011.
71. Wong F, Blendis L. New challenge of hepatorenal syndrome: prevention and treatment. *Hepatology.* 2001;34:1242–1251.
72. Ruiz-del-Arbol L, Monescillo A, Jimenèz W, Garcia-Plaza A, Arroyo V, Rodès J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology*. 1997;113:579–586.
73. Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. *Hepatology.* 2012;55:1173–1181.
74. Sola-Vera J, Miñana J, Ricart E, et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. *Hepatology.* 2003;37:1147–1153.
75. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341:403–409.
76. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2001;135:149–164.
77. Terg R, Berreta J, Abecasis R, Romero G, Boerr L. Dextran administration avoids hemodynamic changes following paracentesis in cirrhotic patients. *Dig Dis Sci*. 1992;37:79–83.
78. Ginès A, Fernández-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology.* 1996;111:1002–1010.
79. Christidis C, Mal F, Ramos J, et al. Worsening of hepatic dysfunction as a consequence of repeated hydroxyethylstarch infusions. *J Hepatol*. 2001;35:726–732.
80. Flexbumin 25% (Albumin Human, USP, 25% Solution). Product information. Baxalta US; 2019.
81. Plasbumin-25 (Albumin, Human). Product information. Grifols Therapeutics; 2018.
82. Lexi-Comp Online™, Lexi-Drugs Online™. Lexi-Comp; August 20, 2020.
83. Therapondos G, Hayes PC. Management of gastroesophageal varices. *Clin Med*. 2002;2:297–302.
84. Salerno F, Cammà C, Enea M, Rössle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data [published correction appears in *Gastroenterology*. 2007;133:1746]. *Gastroenterology.* 2007;133:825–834.
85. Bureau C, Thabut D, Oberti F, et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites [published correction appears in *Gastroenterology*. 2017;153(3):870]. *Gastroenterology.* 2017;152:157–163.

86. Boyer TD, Haskal ZJ, American Association for the Study of Liver Diseases. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009. *Hepatology.* 2010;51(1):306.
87. Tueche SG, Pector JC. Peritoneovenous shunt in malignant ascites. The Bordet Institute experience from 1975–1998. *Hepatogastroenterology.* 2000;47:1322–1324.
88. Arroyo V, Planas R, Gaya J, et al. Sympathetic nervous activity, renin-angiotensin system and renal excretion of prostaglandin E2 in cirrhosis. Relationship to functional renal failure and sodium and water excretion. *Eur J Clin Invest*. 1983;13:271–278.
89. Henriksen JH, Ring-Larsen H. Hepatorenal disorders. Role of the sympathetic nervous system. *Semin Liver Dis*. 1994;14:35–43.
90. Yang YY, Lin HC, Lee WP, et al. Association of the G-protein and α2-adrenergic receptor gene and plasma norepinephrine level with clonidine improvement of the effects of diuretics in patients with cirrhosis with refractory ascites: a randomised clinical trial. *Gut.* 2010;59:1545–1553.
91. Lenaerts A, Codden T, Henry J-P, Legros F, Ligny G. Comparative pilot study of repeated large volume paracentesis vs the combination on clonidine-spironolactone in the treatment of cirrhosis-associated refractory ascites. *Gastroenterol Clin Biol*. 2005;29:1137–1142.
92. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases [published correction appears in *Hepatology*. 2017;66:304]. *Hepatology*. 2017;65:310–335.
93. Sarin SK, Agarwal SR. Gastric varices and portal hypertensive gastropathy. *Clin Liver Dis*. 2001;5:727–767.
94. Carbonell N, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology.* 2004;40:652–659.
95. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis*. 2001;5:645–663.
96. Chung S. Management of bleeding in the cirrhotic patient. *J Gastroenterol Hepatol*. 2002;17:355–360.
97. Bhasin DK, Malhi NJ. Variceal bleeding and portal hypertension: much to learn, much to explore. *Endoscopy.* 2002;34:119–128.
98. Thabut D, Bernard-Chabert B. Management of acute bleeding from portal hypertension. *Best Pract Res Clin Gastroenterol*. 2007;21:19–29.
99. Marti-Carvajal AJ, Solà I. Vitamin K for upper gastrointestinal bleeding in patients with acute or chronic liver diseases. *Cochrane Database Syst Rev*. 2012;9:CD004792.

100. Goulis J, Burroughs AK. Role of vasoactive drugs in the treatment of bleeding oesophageal varices. *Digestion*. 1999;60(suppl 3):25–34.
101. Iwao T, Toyonaga A, Oho K, et al. Effect of vasopressin on esophageal varices blood flow in patients with cirrhosis: comparisons with the effects on portal vein and superior mesenteric artery blood flow. *J Hepatol*. 1996;25:491–497.
102. Law AW, Gales MA. Octreotide or vasopressin for bleeding esophageal varices. *Ann Pharmacother*. 1997;31:237–238.
103. de Franchis R. Longer treatment with vasoactive drugs to prevent early variceal re-bleeding in cirrhosis. *Eur J Gastroenterol Hepatol*. 1998;10:1041–1044.
104. Zhou Y, Qiao L, Wu J, Hu H, Xu C. Comparison of the efficacy of octreotide, vasopressin, and omeprazole in the control of acute bleeding in patients with portal hypertensive gastropathy: a controlled study. *J Gastroenterol Hepatol*. 2002;17:973–979.
105. Wells M, Chande N, Adams P, et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. *Aliment Pharmacol Ther*. 2012;35:1267–1278.
106. Stump DL, Hardin TC. The use of vasopressin in the treatment of upper gastrointestinal haemorrhage. *Drugs*. 1990;39:38–53.
107. Anderson JR, Johnston GW. Development of cutaneous gangrene during continuous peripheral infusion of vasopressin. *Br Med J (Clin Res Ed)*. 1983;287:1657–1658.
108. Gimson AE, Westaby D, Hegarty J, Watson A, Williams R. A randomized trial of vasopressin and vasopressin plus nitroglycerin in the control of acute variceal hemorrhage. *Hepatology*. 1986;6:410–413.
109. Bruha R, Marecek Z, Spicak J, et al. Double-blind randomized, comparative multicenter study of the effect of terlipressin in the treatment of acute esophageal variceal and/or hypertensive gastropathy bleeding. *Hepatogastroenterology.* 2002;49:1161–1166.
110. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension [published correction appears in *J Hepatol*. 2005;43:547]. *J Hepatol*. 2005;43:167–176.
111. Cales P, Masliah C, Bernard B, et al. Early administration of vapreotide for variceal bleeding in patients with cirrhosis. *N Engl J Med*. 2001;344:23–28.
112. Seo YS, Park SY, Kim MY, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. *Hepatology*. 2014;60:954–963.
113. Dib N, Oberti F, Calès P, et al. Current management of the complications of portal hypertension: variceal bleeding and ascites. *CMAJ*. 2006;174:1433–1443.

114. Lay CS, Tsai Y-T, Lee F-Y, et al. Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis. *J Gastroenterol Hepatol*. 2006;21:413–419.
115. Tatemichi M, Nagata H, Sekizuka E, et al. Differences in hemostasis among sclerosing agents in endoscopic injection sclerotherapy. *Dig Dis Sci*. 1996;41:562–570.
116. Dagher L, Burroughs A. Variceal bleeding and portal hypertensive gastropathy. *Eur J Gastroenterol Hepatol*. 2001;13:81–88.
117. Goff JS. Endoscopic variceal ligation. In: Basow DS, ed. *UpToDate*. UpToDate; 2011.
118. Villanueva C, Piqueras M, Aracil C, et al. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. *J Hepatol*. 2006;45:560–567.
119. Sarin SK, Govil A, Jain AK, et al. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. *J Hepatol*. 1997;26:826–832.
120. Helmy A, Hayes PC. Review article: current endoscopic therapeutic options in the management of variceal bleeding. *Aliment Pharmacol Ther*. 2001;15:575–594.
121. Gow PJ, Chapman RW. Modern management of oesophageal varices. *Postgrad Med J*. 2001;77:75–81.
122. Henderson JM, Boyer T, Kunter MH, et al. Distal splenorenal shunt versus transjugular intrahepatic portal systematic shunt for variceal bleeding: a randomized trial. *Gastroenterology.* 2006;130:1643–1651.
123. Tripathi D, Therapondos G, Jackson E, Redhead DN, Hayes PC. The role of the transjugular intrahepatic portosystemic stent shunt (TIPSS) in the management of bleeding gastric varices: clinical and haemodynamic correlations. *Gut.* 2002;51:270–274.
124. Hidajat N, Stobbe H, Hosten N, et al. Transjugular intrahepatic portosystemic shunt and transjugular embolization of bleeding rectal varices in portal hypertension. *AJR Am J Roentgenol*. 2002;178:362–363.
125. Jovine E, Cescon M, Ercolani G, Masetti M, Mazziotti A, Cavallari A. Splenoadrenal shunt. An original portosystemic decompressive technique. *Hepatogastroenterology.* 2001;48:107–108.
126. Soriano G, Guarner C, Tomás A, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. *Gastroenterology.* 1992;103:1267–1272.
127. Fernandez J, del Arbol LR, Gómez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology.* 2006;131:1049–1056.

128. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding—an updated Cochrane review. *Aliment Pharmacol Ther*. 2011;34:509–518.
129. Vorobioff J, Groszmann RJ, Picabea E, et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: a 10-year prospective study. *Gastroenterology*. 1996;111:701–709.
130. Escorsell A, Bordas JM, Castaneda B, et al. Predictive value of the variceal pressure response to continued pharmacological therapy in patients with cirrhosis and portal hypertension. *Hepatology.* 2000;31:1061–1067.
131. Ge PS, Runyon BA. The changing role of beta-blocker therapy in patients with cirrhosis. *J Hepatol*. 2014;60:643–653.
132. Talwalkar JA, Kamath PS. An evidence-based medicine approach to beta-blocker therapy in patients with cirrhosis. *Am J Med*. 2004;116:759–766.
133. Pascal JP, Cales P. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices [published correction appears in *N Engl J Med*. 1988;318:994]. *N Engl J Med*. 1987;317:856–861.
134. Sarin SK, Wadhawan M, Agarwal SR, Tyagi P, Sharma BC. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. *Am J Gastroenterol*. 2005;100:797–804.
135. Abraczinskas DR, Ookubo R, Grace ND, et al. Propranolol for the prevention of first esophageal variceal hemorrhage: a lifetime commitment? *Hepatology.* 2001;34:1096–1102.
136. Angelico M, Carli L, Piat C, Gentile S, Capocaccia L. Effects of isosorbide-5-mononitrate compared with propranolol on first bleeding and long-term survival in cirrhosis. *Gastroenterology.* 1997;113:1632–1639.
137. Garcia-Pagan JC, Villanueva C, Vila MC, et al. Isosorbide mononitrate in the prevention of first variceal bleed in patients who cannot receive beta-blockers. *Gastroenterology.* 2001;121:908–914.
138. Merkel C, Marin R, Enzo E, et al. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Gruppo-Triveneto per L'ipertensione portale (GTIP). *Lancet.* 1996;348:1677–1681.
139. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD. Practice Guidelines Committee of American Association for Study of Liver Diseases; Practice Parameters Committee of American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis [published correction appears in *Am J Gastroenterol*. 2007;102:2868]. *Am J Gastroenterol*. 2007;102:2086–2102.
140. Colombo M, de Franchis R, Tommasini M, Sangiovanni A, Dioguardi N. Beta-blockade prevents recurrent gastrointestinal bleeding in well-compensated

patients with alcoholic cirrhosis: a multicenter randomized controlled trial. *Hepatology.* 1989;9:433–438.
141. de la Pena J, Brullet E, Sanchez-Hernández E, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. *Hepatology.* 2005;41:572–578.
142. Puente A, Hernández-Gea V, Graupera I, et al. Drugs plus ligation to prevent rebleeding in cirrhosis: an updated systematic review. *Liver Int*. 2014;34:823–833.
143. Escorsell A. TIPS versus drug therapy in preventing variceal rebleeding in advanced cirrhosis: a randomized controlled trial. *Hepatology*. 2002;35:385–392.
144. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology.* 2014;60:715–735.
145. Bajaj JS, Cordoba J, Mullen KD, et al. Review article: the design of clinical trials in hepatic encephalopathy—an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. *Aliment Pharmacol Ther*. 2011;33:739–747.
146. Abou-Assi S, Vlahcevic ZR. Hepatic encephalopathy. Metabolic consequence of cirrhosis often is reversible. *Postgrad Med*. 2001;109:52–54.
147. Wright G, Jalan R. Management of hepatic encephalopathy in patients with cirrhosis. *Best Pract Res Clin Gastroenterol*. 2007;21:95–110.
148. Gluud LL, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2015;(2):CD001939.
149. James JH. Branched chain amino acids in hepatic encephalopathy. *Am J Surg*. 2002;183:424–429.
150. Schafer DF, Jones EA. Potential neural mechanisms in the pathogenesis of hepatic encephalopathy. *Prog Liver Dis*. 1982;7:615–627.
151. Jones EA, Basile AS. The involvement of ammonia with the mechanisms that enhance GABA-ergic neurotransmission in hepatic failure. *Adv Exp Med Biol*. 1997;420:75–83.
152. Basile AS, Jones EA. Ammonia and GABA-ergic neurotransmission: interrelated factors in the pathogenesis of hepatic encephalopathy. *Hepatology.* 1997;25:1303–1305.
153. Butterworth RF. Hepatic encephalopathy: a neuropsychiatry disorder involving multiple neurotransmitter systems. *Curr Opin Neurol*. 2000;13:721–727.
154. Haussinger D, Kircheis G, Fischer R, Schliess F, vom Dahl S. Hepatic encephalopathy in chronic liver disease: a clinical manifestation of astrocyte swelling and low-grade cerebral edema? *J Hepatol*. 2000;32:1035–1038.
155. Gerber T, Schomerus H. Hepatic encephalopathy in liver cirrhosis: pathogenesis, diagnosis and management. *Drugs*. 2000;60:1353–1370.

156. Blei AT. Diagnosis and treatment of hepatic encephalopathy. *Baillieres Best Pract Res Clin Gastroenterol*. 2000;14:959–974.
157. European Association for Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;70(1):172–193.
158. Amodio P, Bemeur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: international Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. *Hepatology.* 2013;58:325–336.
159. Plauth M, Merli M, Kondrup J, et al. ESPEN guidelines for nutrition in liver disease and transplantation. *Clin Nutr*. 1997;16:43–55.
160. Marsano LS, Martin AE, Randall HB. Current nutrition in liver disease. *Curr Opin Gastroenterol*. 2002;18:246–253.
161. Heyman JK, Whitfield CJ, Brock KE, McCaughan GW, Donaghy AJ. Dietary protein intakes in patients with hepatic encephalopathy and cirrhosis: current practice in NSW and ACT. *Med J Aust*. 2006;185:542–543.
162. Córdoba J, López-Hellín J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol*. 2004;41:38–43.
163. Gluud LL, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2017;5(5):CD001939.
164. Blei AT, Córdoba J, Practice Parameters Committee of the American College of Gastroenterology. Hepatic encephalopathy. *Am J Gastroenterol*. 2001;96:1968–1976.
165. de Melo RT, Charneski L, Hilas O. Rifaximin for the treatment of hepatic encephalopathy. *Am J Health Syst Pharm*. 2008;65(9):819–822.
166. Festi D, Vestito A, Mazzella G, Roda E, Colecchia A. Management of hepatic encephalopathy: focus on antibiotic therapy. *Digestion.* 2006;73(suppl 1):94–101.
167. Xifaxan (rifaximin). Product information. Salix Pharmaceuticals; 2019.
168. Williams R, Bass N. Rifaximin, a nonabsorbed oral antibiotic, in the treatment of hepatic encephalopathy: antimicrobial activity, efficacy, and safety. *Rev Gastroenterol Disord*. 2005;5(suppl 1):S10–S18.
169. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362(12):1071–1081.
170. Mas A, Rodés J, Sunyer L, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. *J Hepatol*. 2003;38(1):51–58.
171. Phongsamran PV, Kim JW, Abbott JC, Rosenblatt A. Pharmacotherapy for hepatic encephalopathy. *Drugs*. 2010;70(9):1131–1148.
172. Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. *Cochrane Database Syst Rev*. 2004;(2):1465–1858.

173. Lawrence KR, Klee JA. Rifaximin for the treatment of hepatic encephalopathy. *Pharmacotherapy*. 2008;28(8):1019–1032.
174. Bucci L, Palmieri GC. Double-blind, double-dummy comparison between treatment with rifaximin and lactulose in patients with medium to severe degree hepatic encephalopathy. *Curr Med Res Opin*. 1993;13:109–118.
175. Miglio F, Valpiani D, Rossellini SR, Ferrieri A. Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. A double-blind, randomised trial. *Curr Med Res Opin*. 1997;13:593–601.
176. Pedretti G, Calzetti C, Missale G, Fiaccadori F. Rifaximin versus neomycin on hyperammoniemia in chronic portal systemic encephalopathy of cirrhotics. A double-blind, randomized trial. *Ital J Gastroenterol*. 1991;23(4):175–178.
177. Orlandi F, Freddara U, Candelaresi MT, et al. Comparison between neomycin and lactulose in 173 patients with hepatic encephalopathy: a randomized clinical study. *Dig Dis Sci*. 1981;26:498–506.
178. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. *BMJ*. 2004;328:1–6.
179. Hasan S, Datta S, Bhattacherjee S, Banik S, Saha S, Bandyopadhyay D. A randomized controlled trial comparing the efficacy of a combination of rifaximin and lactulose with lactulose only in the treatment of overt hepatic encephalopathy. *J Assoc Physicians India*. 2018;66:32–36.
180. Wang Z, Chu P, Wang W. Combination of rifaximin and lactulose improves clinical efficacy and mortality in patients with hepatic encephalopathy. *Drug Des Devel Ther*. 2018;13:1–11.
181. Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. *J Hepatol.* 2019;71:811-822.
182. European Association for Study of the Liver. EASL clinical practice guideline on the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis. *J Hepatol*. 2010;53:397–417.
183. European Association for Study of Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69:406–460.
184. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *Gut.* 2015;64:986–974.
185. Bucsics T, Krones E. Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. *Gastroenterol Rep*. 2017;5:127–137.
186. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. A consensus workshop of the international ascites club. *Gut.* 2007;56:1310–1318.
187. Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation.

Hepatology. 2005;41:1282–1289.
188. Cárdenas A, Ginès P. Therapy insight: management of hepatorenal syndrome. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3:338–348.
189. Solanki P, Chawla A, Garg R, Gupta R, Jain M, Sarin SK. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. *J Gastroenterol Hepatol*. 2003;18:152–156.
190. Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology.* 2008;134(5):1360–1368.
191. Mattos AZ, de Mattos AA, Ribeiro RA. Terlipressin versus noradrenaline in the treatment of hepatorenal syndrome: systematic review with meta-analysis and full economic evaluation. *Eur J Gastroenterol Hepatol*. 2016;28:345–351.
192. Moreau R, Lebrec D. Diagnosis and treatment of acute renal failure in patients with cirrhosis. *Best Pract Res Clin Gastroenterol*. 2007;21:111–123.
193. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology.* 1999;29:1690–1697.
194. Duvoux C, Zanditenas D, Hézode C, et al. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. *Hepatology.* 2002;36:374–380.
195. Alessandria C, Ottobrelli A, Debernardi-Venon W, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol*. 2007;47:499–505.
196. Sharma P, Kumar A, Shrama BC, Sarin SK. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. *Am J Gastroenterol*. 2008;103:1689–1697.
197. Salerno F, Navickis RJ, Wilkes MM. Albumin treatment regimen for type 1 hepatorenal syndrome: a dose-response meta-analysis. *BMC Gastroenterol.* 2015;15:1–11.
198. Esrailian E, Pantangco ER, Kyulo NL, Hu K-Q, Runyon BA. Octreotide/midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. *Dig Dis Sci*. 2007;52(3):742–748.
199. Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. *Hepatology.* 2015;62:567–574.
200. Kiser TH, Fish DN, Obritsch MD, Jung R, MacLaren R, Parikh CR. Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. *Nephrol Dial Transplant*. 2005;20:1813–1820.

201. Pomier-Layrargues G, Paquin SC, Hassoun Z, Lafortune M, Tran A. Octreotide in hepatorenal syndrome: a randomized, double-blind, placebo-controlled, crossover study. *Hepatology.* 2003;38:238–243.
202. Restuccia T, Ortega R, Guevara M, et al. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. *J Hepatol*. 2004;40:140–146.
203. Rodriguez E, Pereira GH, Solà E, et al. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: effects on kidney function and transplantation outcomes. *Liver Transpl*. 2015;21:1347–1354.
204. Gines P, Guevara M, Arroyo V, Rodés J. Hepatorenal syndrome. *Lancet.* 2003;362:1819–1827.
205. Francoz C, Belghiti J, Durand F. Indications of liver transplantation in patients with complications of cirrhosis. *Best Pract Res Clin Gastroenterol*. 2007;21:175–190.

SECTION 5

Renal Disorders

Section Editors: Susan A. Krikorian and Oussayma Moukhachen

26

Acid–Base Disturbances

Mary P. Kovacevic, Jeremy R. DeGrado, and Kevin E. Anger

CORE PRINCIPLES		CHAPTER CASES
1	Acquisition and interpretation of diagnostics and laboratory tests used in acid–base analysis is key to identifying and managing acid–base disturbances.	**Case 26-1 (Question 1) Case 26-2 (Questions 1, 3, 4) Case 26-3 (Question 1) Case 26-4 (Questions 1, 2)Case 26-5 (Questions 1–3) Case 26-6 (Question 1)**
2	Acid–base status assessment in patient care should be conducted using a stepwise approach.	**Case 26-1 (Question 1) Case 26-2 (Questions 1, 3, 4) Case 26-3 (Question 1) Case 26-4 (Questions 1, 2) Case 26-5 (Questions 1–3) Case 26-6 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
3	A metabolic acidosis with a normal anion gap (or “non-anion gap”) is associated with a loss of bicarbonate. The decrease in serum bicarbonate in non–anion gap metabolic acidosis can be secondary to gastrointestinal loss or alterations in reabsorption. A urine anion gap can be used to determine the cause of a normal anion gap metabolic acidosis.	**Case 26-1 (Questions 1, 2)**
4	A metabolic acidosis with an elevated anion gap (“anion gap acidosis”) is associated with a decrease in bicarbonate related to the buffering of acids. An anion gap develops because of the increase in unmeasured anions. Common causes of anion gap metabolic acidosis include increased production of endogenous acids (eg, lactic acid, ketoacids) and exposure to toxins that produce acids (eg, methanol and ethylene glycol).	**Case 26-2 (Questions 1–4)**
5	Metabolic alkalosis can be classified according to a patient’s volume status and responsiveness to the administration of chloride-containing solutions.	**Case 26-3 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
6	A respiratory acidosis can be acute, chronic, or acute-on-chronic. The best way to differentiate these disturbances is with a careful patient history and review of previous blood gas values.	**Case 26-4 (Questions 1–3) Case 26-5 (Questions 1, 2)**
7	Respiratory alkalosis stems from a small number of conditions that increase either the rate or depth of respirations leading to decreased $Paco_2$.	**Case 26-6 (Questions 1–3)**

INTRODUCTION

Acid–base disturbances are common in patients who are acutely ill and in some chronic diseases such as chronic bronchitis. Severe acid–base disturbances can contribute significantly to morbidity and mortality. Although most cases of acid–base disturbances are mild and self-limiting, extreme changes in pH can have a significant impact on organ function.[1,2] Generally, acidemia is defined as a serum pH <7.35 and is associated with disturbances or process of acidosis, whereas alkalemia is a pH >7.45 and associated with disturbances or process of alkalosis.[1–3] In this chapter, we discuss basic physiology, stepwise assessment, etiologies, and (briefly) various management strategies for acid–base disturbances.

NORMAL ACID–BASE PHYSIOLOGY

The human body is constantly working to maintain homeostasis of many physiologic parameters. Under normal conditions, the balance between extracellular acid load and baseload is tightly controlled to

maintain arterial pH between 7.35 and 7.45.[4–6] Maintenance of this pH range is needed to protect many physiologic/organ functions within the body. Acid–base balance is maintained by complex buffer systems that control ventilation to expel carbon dioxide (CO_2) through the respiratory system and renal elimination of acids and reabsorption of bicarbonate (HCO_3^-) and other extracellular buffers. The renal system is recognized as the metabolic pathway.[4,7–9] **Figure 26-1** summarizes the buffer systems in the body that are responsible for maintaining acid–base homeostasis.

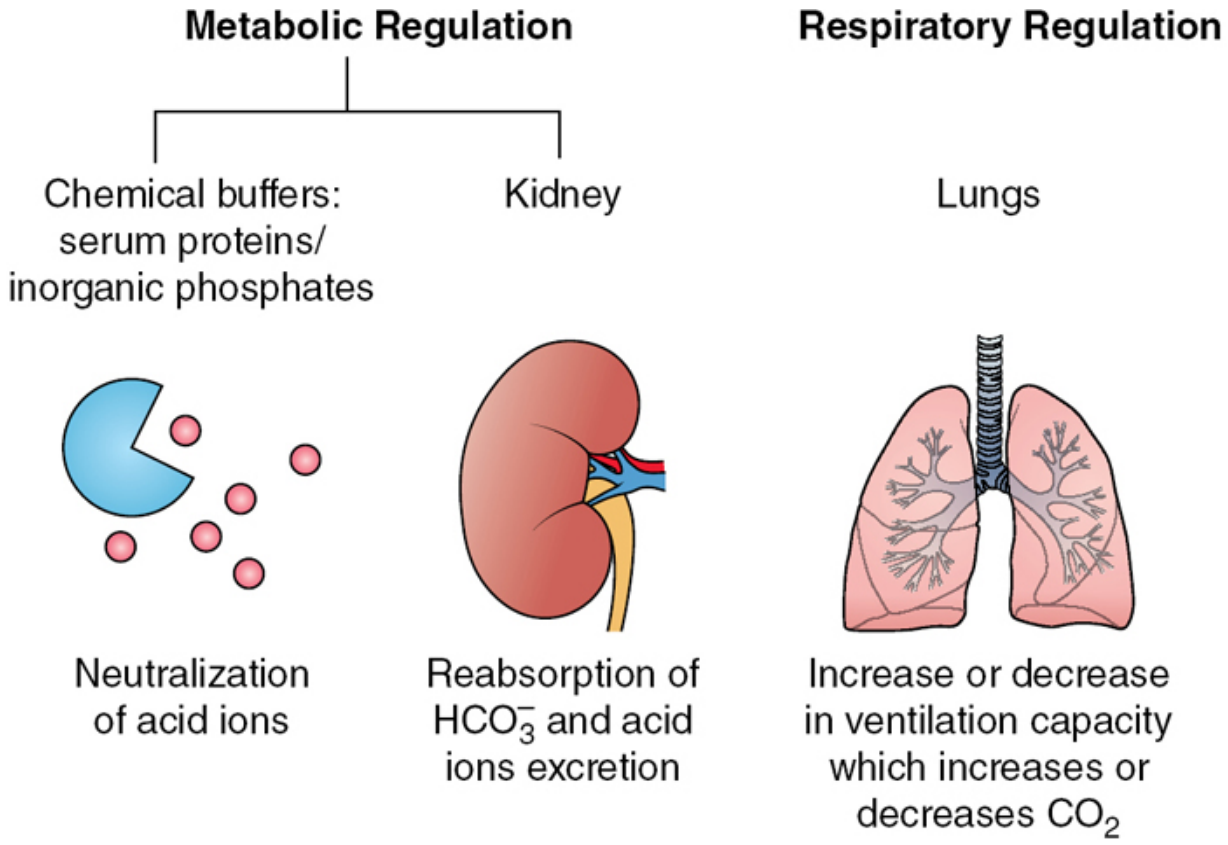


Figure 26-1 Acid–base buffering systems. Regulation/buffering of acid–base balance is rooted in metabolic and respiratory regulation mechanisms. Respiratory regulation is rooted in ventilation and subsequent CO_2 elimination. The speed and quantity of carbon dioxide make respiratory regulation a powerful buffering system in the body. Renal regulation is another important regulatory system that involves acid ion secretion and bicarbonate

excretion/reabsorption. Chemical buffers are a lower capacity buffering system involving serum proteins such as albumin that bind acid ions.

Figure 26-2 depicts the application of the Henderson–Hasselbalch principles to acid–base physiology and the principles by which the body maintains its acid and baseload. The major acid–base buffering system in the blood involves the bicarbonate–carbon dioxide buffering system.[1,3,7,8] Carbon dioxide, bicarbonate, and carbonic acid are interconverted according to the following equation ($H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$) in which changes in pH shift the direction of the equation toward more production of CO_2 (considered as the acid, because in this equation it gave a hydrogen ion (H^+) or HCO_3^- (considered as the base, because it accepted an [H^+]). Although CO_2 is not an acid itself, it diffuses out of cells into plasma to combine with water to form carbonic acid (H_2CO_3).[10–12] When conceptualizing, it is easy to link CO_2 as an acid that is associated with the respiratory system, and given that HCO_3^- is eliminated through the kidneys, HCO_3^- is linked to the renal system and to the metabolic pathway.

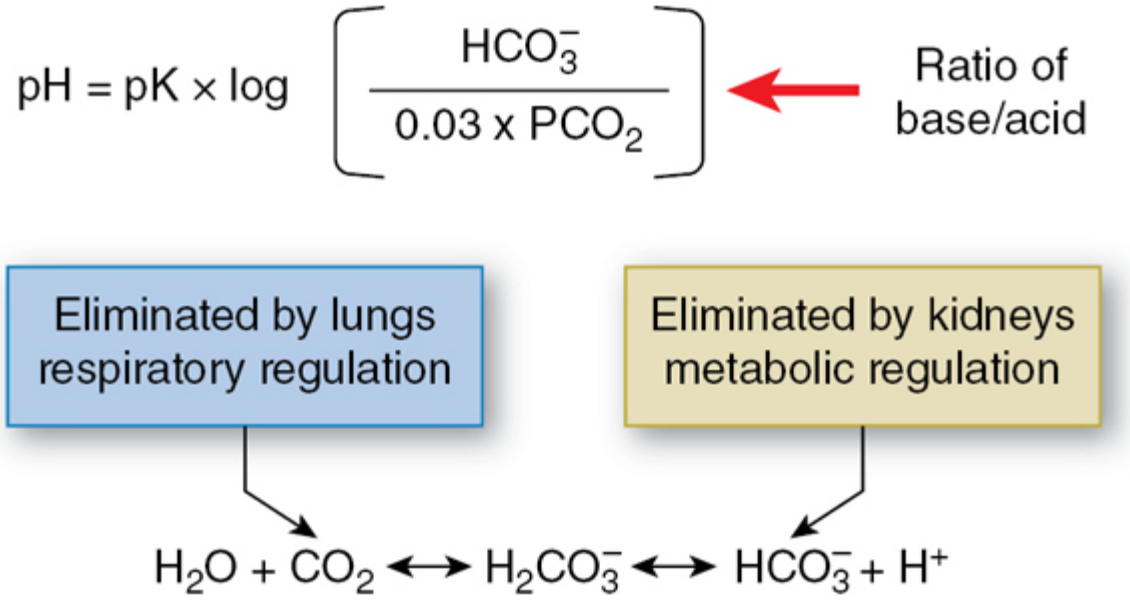


Figure 26-2 Applying Henderson–Hasselbalch principles to blood gas analyzers that measure pH and PCO_2 and calculate bicarbonate. Simply, blood pH is largely driven by the ratio of base upon the blood pH, and shifts in pH swing the direction of dissociation. This sets up the core principles by which the body regulates CO_2 (acid) elimination and HCO_3^- (base) elimination by respiratory and metabolic mechanisms to maintain target pH. Note: $[HCO_3^-]$ is the concentration of bicarbonate in the blood (mEq/L or mmol/L), and $Paco_2$ (Pco_2) is the partial pressure of carbon dioxide in the arterial blood (mm Hg); pK = 6.1.

Respiratory buffering involves changes in ventilation and CO_2 concentrations in the blood in response to changes in pH. Ventilation is regulated by central and peripheral chemoreceptors that are sensitive to arterial pH, arterial carbon dioxide tension ($Paco_2$), and arterial oxygen tension (Pao_2) concentrations.[6,11,13] Ventilation can be altered in a matter of minutes, resulting in the ability to excrete or retain high amounts of CO_2 (acid) in response to pH changes.[1,2,12]

Metabolic regulation of acid–base balance is rooted in the kidneys reclaiming filtered bicarbonate by secreting hydrogen ions and other acid salts by glomerular filtration.[3,5] Under normal conditions, proximal tubule carbonic anhydrase converts CO_2 and water into protons and bicarbonate ions, which are then reclaimed into the blood while the hydrogen is secreted into the proximal tubule.[5,6,13] The kidney can retain or excrete large amounts of bicarbonate under normal conditions; however, the speed of its mechanism results in a much slower response compared to respiratory buffering.[6,13]

Approaches to Acid–Base Balance

Approaches to acid–base balance vary in their incorporation of buffering capacity, hydrogen ion balance, and weak versus strong ion effect.[1,2,13–15] Newer approaches to assessing acid–base status such as the base excess and physiochemical approaches are

gaining popularity in routine clinical use among specialists; however, discussion of these approaches is beyond the scope of this chapter. The traditional physiologic approach is the current predominant means of assessing acid–base status in clinical practice and is discussed throughout this chapter.

Classification of Acid–Base Disturbances

Acid–base disturbances can be simply classified into four disturbances of either respiratory or metabolic origins (**Table 26-1**). Simple (single) acid–base disturbances involve one acid–base abnormality, whereas mixed disturbances involve two or three simple disturbances.[1,12,16] Patients with a double mixed disturbance can have a respiratory and metabolic disturbance or a mixture of two different metabolic disturbances that complete or synergize the patient's imbalance. Although rare, triple mixed disturbances involved two metabolic imbalances with a respiratory imbalance. Patients can have one respiratory and multiple metabolic disturbances at the same time; however, they cannot have two respiratory disturbances at the same time.[1,16]

Table 26-1
Simple Acid–Base Disturbances

Acid–Base Disorder	Pathophysiologic Associated System	Compensating System and Response
Metabolic acidosis	↓HCO_3^- to <22 mmol/L	↓$Paco_2$
Respiratory acidosis	↑$Paco_2$ to >42 mm Hg	↑HCO_3^-
Metabolic alkalosis	↑HCO_3 to >26 mmol/L	↑$Paco_2$
Respiratory alkalosis	↓$Paco_2$ to <38 mm Hg	↓HCO_3

Note: Simple acid–base disturbances are often referred to as single acid–base disturbances.

Laboratory Assessment

Depending on the patient's clinical status and established disease physiology, a variety of laboratory tests are used to evaluate acid–base status.[12,17,18] Arterial pH, arterial carbon dioxide tension ($Paco_2$), and serum bicarbonate (HCO_3^-) are the laboratory values needed for the traditional approach assessment. These values are obtained routinely with an arterial blood gas (ABG) determination. Normal ABG values are listed in **Table 26-2**. ABG is the gold standard for acid–base assessment; however, availability of ABG may be limited to patients with respiratory distress or low oxygenation states. Familiarity with venous blood gas (VBG) parameters is also important, because this may be the first laboratory data available on patient presentation. The VBG provides useful information for assessment of acid–base balance, and can be used clinically because the arteriovenous differences in pH and PCO_2 are relatively consistent.[1,5,19] Although oxygen does not directly impact the blood pH, low oxygenation status of the blood does drive acid–base disturbances or is a result of ventilatory compensation of an acid–base disturbance.[19] In clinical practice, the serum HCO_3- concentration is either estimated from the total carbon dioxide content on electrolyte panels (such as the basic metabolic panel [BMP] or the complete metabolic panel [CMP]), or it is calculated from the pH and $Paco_2$ from an ABG using the Henderson–Hasselbalch equation shown in Figure 26-2. It is important to note that the estimated serum HCO_3^- from the electrolyte panels is a more accurate estimate of the total carbon dioxide concentration (TCO_2) than is the calculated bicarbonate obtained from the ABG. In this chapter, the serum bicarbonate concentration obtained from the electrolyte panels is referred to as TCO_2. Serum TCO_2 from the electrolyte panels should be used when assessing acid–base status.[2] In addition, in clinical practice and in all the equations used when referring to bicarbonate in this chapter, the

value used in these equations will be obtained from the electrolyte panel rather than the HCO_3^- from the ABG.

Table 26-2
Normal Arterial and Venous Blood Gas Values

Variable	Arterial	Venous
pH	7.4 (7.35–7.45)	7.36 (7.33–7.43)
Pco_2 mm Hg	40 (35–45)	41–51
TCO_2 mEq/L	24 (22–26)	24–28
O_2 mm Hg	80–100	35–40
O_2 saturation, %	≥95	70–75

A stepwise approach to acid–base assessment is discussed later in the chapter, and highlights how specific laboratory testing works its way through the assessment as the patient's acid–base status is evaluated. Secondary laboratory tests for acid–base assessment involve looking at a variety of whole blood, plasma, and urine samples.

STEPWISE APPROACH TO THE EVALUATION OF SIMPLE ACID–BASE DISTURBANCES

Acid–base assessment is a complex clinical task in which a systematic approach is warranted.[1,2] A stepwise approach to the evaluation of simple acid–base disturbances can be summarized as follows:

1. Evaluate pH as acidosis or alkalosis.
2. Evaluate $Paco_2$ and HCO_3^- levels.
3. Identify the dominant acid–base disorder, presence of compensation, and potential for mixed disorder status.

4. If a respiratory disorder, determine whether acute or chronic.
5. For metabolic acidosis or metabolic alkalosis, further assess laboratory parameters:
   - If the disorder is a metabolic acidosis, determine whether it is a normal- or high-anion gap (AG) acidosis:
     - Winter formula
     - Calculate corrected AG
     - If high AG, check Delta (δ) gap
   - If high-AG metabolic acidosis, assess clinically for anion source:
     - Lactate, serum osmolality, serum ketones, serum/urine toxicology screen
   - If normal-AG metabolic acidosis, assess clinically:
     - Serum K^+, renal function, urine osmolality, urine pH, urine NH_4^+, renal bicarbonate reabsorption
   - If the disorder is metabolic alkalosis, determine if Cl^- sensitive or Cl^- resistant
     - Urine chloride assessment

Evaluation of a patient's acid–base status involves looking at their medical history, current physical examination/findings, and laboratory data. Clinicians should be mindful to follow through on the stepwise assessment and avoid channeling toward prior history or certain laboratory variables that will mislead the assessment. **Table 26-3** outlines the predicted degree of compensation for the simple acid–base disturbances.[1,5,6] The expected degree of compensation is important for delineating acute versus chronic disturbances as well as the presence of mixed disturbances.

Table 26-3
Predicted Degrees of Compensation

Acid–Base Disturbance	Primary Change	Compensatory Response
Metabolic acidosis	1 mEq/L ↓ HCO_3^-	1.2 mm Hg ↓ $Paco_2$
Respiratory acidosis	10 mm Hg↑ $Paco_2$	1 mEq/L (acute) or 3.5 mEq/L (chronic) ↑ HCO_3^-

Acid–Base Disturbance	Primary Change	Compensatory Response
Metabolic alkalosis	1 mEq/L ↑ HCO_3^-	0.7 mm Hg ↑ $Paco_2$
Respiratory alkalosis	10 mm Hg↓ $Paco_2$	2 mEq/L (acute) or 4 mEq/L (chronic) ↓ HCO_3^-

METABOLIC ACIDOSIS

Metabolic acidosis is a condition defined by a pH <7.35 with low serum bicarbonate.

Metabolic acidosis is caused by a reduction in serum bicarbonate or an increased acid load from endogenous or exogenous sources.[10] The body compensation for a metabolic acidosis is typically by an attempt of the lungs to expel CO_2, thus lowering the $Paco_2$ to balance the pH. Depending on the underlying cause of the acid–base disturbance, metabolic acidosis can be classified into two categories: normal AG versus increased or elevated AG.[1,9,12,20] The AG represents the concentration of unmeasured negatively charged substances (anions) in excess of the concentration of unmeasured positively charged substances (cations) in the extracellular fluid (Eq. 26-1). The concentrations of total anions and cations in the body are equal, to allow the body to remain electrically neutral.[21–23] Other unmeasured anions in serum include phosphate, urate, and sulfate. Unmeasured cations include potassium (in the United States, where potassium is not included in the AG calculation), ionized calcium, magnesium, and certain abnormal proteins.[1,9,10,20] For this chapter, all AG calculations use the equation provided in Eq. 26-1. The concentration of unmeasured anions normally exceeds the concentration of unmeasured cations by 6 to 12 mEq/L, and the AG can be calculated as follows:

Anion gap **(Eq. 26-1)**

$$\text{Anion gap (AG)} = Na^+ - (Cl^- + HCO_3^-)$$

Adjusted anion gap

$$\text{Adjusted AG} = \text{AG} + 2.5 \times (\text{normal albumin [mg/dL]} - \text{measured albumin [mg/dL]})$$

(Eq. 26-2)

Of the unmeasured anions, albumin is perhaps the most important.[21–23] In patients with hypoalbuminemia, the calculated AG should be adjusted using Eq. 26-2. A normal albumin concentration is assumed to be 4.0 g/dL.[2,24,25] For example, a patient with hypoalbuminemia (serum albumin, 2.0 g/dL) with early sepsis and lactic acidosis might have a calculated AG of 11 mEq/L; however, after the calculation is corrected for the effect of the abnormal serum albumin concentration, the presence of elevated AG acidosis is more prominent (the calculated AG = 11 mEq/L + 2.5 × [$4.0_{(\text{normal albumin})}$ − $2.0_{(\text{measured albumin})}$]), or a calculated AG of 16 mEq/L.

Increased-AG and normal-AG metabolic acidosis etiologies are displayed in **Tables 26-4** and **26-5**. The compensation equations for both can be found in Table 26-3. Metabolic acidosis with a normal AG (eg, hyperchloremic metabolic acidosis) usually is caused by loss of bicarbonate and can be further characterized as hypokalemic or hyperkalemic.[6,10,11,26,27] Bicarbonate loss can be secondary to gastrointestinal (GI) loss (diarrhea, pancreatic fistula, laxative use) or alterations in reabsorption related to renal (proximal or distal renal tubular acidosis [RTA] or use of carbonic anhydrase inhibitors) or exogenous (administration of chloride-rich solutions such as 0.9% sodium chloride) etiologies.[1,10–12] The serum chloride concentration usually increases in proportion to the decrease in bicarbonate in normal-AG metabolic acidosis, and the urine anion gap (UAG) can be used to determine the etiology.[28,29] The UAG = urine ($Na^+ + K^+ - Cl^-$) and has a normal range of ~20 to 90 mEq/L.[28,29] In patients with significant diarrhea, sodium and potassium are bound to bicarbonate that is lost. Urine chloride is largely bound to ammonium ($NH4^+$) and exceeds the urine concentration of sodium and potassium, leading to a negative UAG. In contrast, patients with RTA have reduced $NH4^+$

excretion (in addition to a lack of loss of Na^+ and K^+ through the GI tract), resulting in an elevated UAG.[1,2,28]

Table 26-4
Etiologies of Anion Gap Metabolic Acidosis

Etiology	Associated Acid
Renal failure	Phosphoric, sulfuric acid
Ketosis Diabetic ketoacidosis Alcoholic ketoacidosis Starvation ketosis	Acetoacetate, acetone, β-hydroxybutyrate
Lactic acidosis Type A: septic shock, mesenteric ischemia, hypovolemic shock, carbon monoxide poisoning, cyanide Type B: medications (metformin, isoniazid, nonnucleoside reverse transcriptase inhibitors, β-1 agonists) thiamine deficiency, seizure, liver dysfunction	Lactic acid
Ingestions Methanol Ethylene glycol Salicylates Toluene[a]	Formic acid, oxalic acid, glyoxylic acid, salicylic acid
Rhabdomyolysis	Uric acid, lactic acid
Glutathione deficiency	Pyroglutamic acid (5-oxoproline)

[a]Toluene may also cause a non-AG acidosis (see Table 26-5).

Table 26-5
Common Etiologies of Non–Anion Gap Metabolic Acidosis

Loss of bicarbonate
Gastrointestinal conditions Diarrhea Ureteral diversions Biliary or pancreatic drainage Renal conditions Type 2 (proximal) RTA

Toluene ingestion Medications (tenofovir, topiramate, carbonic anhydrase inhibitors)
Decreased renal acid excretion
Type 1 (distal) RTA Type 4 RTA Early uremic acidosis
Other
Fluid resuscitation with saline Hyperalimentation with HCl-containing amino acid solutions Cholestyramine

RTA, renal tubular acidosis.

In contrast to non-AG acidosis, elevated-AG metabolic acidosis is usually associated with an excess in either endogenous or exogenous acids (see Table 26-4).[1,5,9] Acids present because of increased production (eg, ketoacids, lactic acid) or exposure (eg, formic acid, glycolic acid) are buffered by extracellular bicarbonate, with resultant consumption of bicarbonate and appearance of an unmeasured anion (eg, formate, lactate).[1,5,9] In simple AG metabolic acidosis, the decrease in serum bicarbonate approximates the increase in the AG, the latter being a good estimate of the circulating anion level. Common etiologies of increased endogenous acid production include tissue hypoxemia (lactic acid), hyperglycemic emergencies (ketoacids), and renal failure (sulfate and phosphate).[1,5,9,27] Table 26-4 further highlights common causes of elevated-AG metabolic acidosis, along with the associated acids.

Normal-Anion Gap Hyperchloremic Metabolic Acidosis

EVALUATION

CASE 26-1

Question 1: M.N. is a 35-year-old, 62-inch (157.48-cm), 121.25-pound (55-kg) female with a history of a recent enterococcal urinary tract infection (UTI) who

was recently prescribed amoxicillin for 10 days. She presents to the emergency department with several days of significant diarrhea, and her admission laboratory values are as follows:

Na^+: 136 mEq/L
K^+: 3.2 mEq/L
Cl^-: 112 mEq/L
TCO_2: 14 mEq/L
Blood urea nitrogen (BUN): 25 mg/dL
Serum creatinine (SCr): 1.2 mg/dL (baseline 0.8 mg/dL)
Glucose: 123 mg/dL
Albumin: 4.2 g/dL
ABGs: pH 7.33; $Paco_2$ 27 mm Hg; Pao_2 91 mm Hg; HCO_3^- 14 mmol/L
Assess M.N.'s acid–base status.

What are possible etiologies and what compensatory response (laboratory and physical exam) would you expect?

We can begin using the stepwise approach.

Step 1: Evaluate pH as acidemia or alkalemia—M.N. has a low pH, indicating that she is acidemic.

Step 2: Evaluate $Paco_2$ and bicarbonate—She has a low $Paco_2$ and a low bicarbonate.

Step 3: Identify the dominant acid–base disorder, presence of compensation, and potential for mixed disorder status—A decrease in the bicarbonate can be linked to the presence of an acidosis, whereas a decrease in $Paco_2$ would not primarily drive a decrease in pH. Therefore, M.N. has a metabolic acidosis because a low bicarbonate is the primary factor. To evaluate the degree of respiratory compensation and determine whether there is a secondary primary respiratory disturbance, we should evaluate the $Paco_2$ and compare the observed value to what we would "expect" based on the change in bicarbonate. This can be accomplished using the ratio in Table 26-3, or utilizing the Winter formula to calculate the compensatory response (Eq. 26-3). If we use the ratio approach, we would expect a decrease of 1.2 mm Hg for every 1-point drop in bicarbonate (1.2 × 10 = 12); therefore, an expected $Paco_2$ would be ~28 mm Hg (40 − 12 = 28). Utilizing the

Winter formula ([1.5 × HCO_3^-] + 8 ± 2), we obtain a similar answer for the expected $Paco_2$: ([1.5 × 14] + 8 ± 2 = 27–31). Therefore, we can determine that M.N. has appropriately compensated for her metabolic acidosis, and there is no secondary respiratory acid–base disturbance. If M.N.'s $Paco_2$ had been <27, she would have an additional respiratory alkalosis due to breathing out more $Paco_2$ than would be expected from a purely compensatory perspective. On the other hand, if her $Paco_2$ was >31, we can determine that she has an additional respiratory acidosis secondary to the buildup of $Paco_2$. An additional respiratory acidosis would have produced a higher than expected $Paco_2$, whereas an additional respiratory alkalosis would have produced a lower than expected $Paco_2$.

Winter formula **(Eq. 26-3)**

$$\text{Expected } Paco_2 = (1.5 \times HCO_3^-) + 8 \pm 2$$

Step 4: For metabolic acidosis, further assess laboratory parameters. Determine whether it is normal- or high-AG acidosis. Calculate the AG to determine the type of metabolic acidosis— M.N.'s AG = 136 − (112 + 14) = 10, which is within the normal range. Therefore, M.N.'s acid–base disturbance is a normal-AG metabolic acidosis. Because her albumin is normal, we do not need further adjustment of the AG calculation. Etiologies of normal-AG metabolic acidosis are displayed in Table 26-5. M.N.'s recent history and clinical presentation support this diagnosis because diarrhea results in the loss of bicarbonate and retention of chloride to maintain ionic neutrality, leading to hyperchloremia.[30] A UAG could be measured to confirm the etiology of M.N.'s non-AG metabolic acidosis. A negative UAG usually indicates increased NH_4^+ excretion and would be expected if the etiology was secondary to GI losses, such as diarrhea. A positive UAG indicates low or normal NH_4^+ excretion, and likely is secondary to RTA.[1,2,30]

RTA is characterized by the kidney's failure to adequately excrete acids into the urine. Many medical conditions and chemical substances have been associated with RTA. The recognized forms are type 1 (distal), type 2 (proximal), and type 4 (distal, hypoaldosteronism).[1,5,9,11] Type 3 has features of both proximal and distal RTA. Type 1 RTA is caused by a defect in the distal tubule's ability to acidify the urine. The most common causes in adults are autoimmune disturbances, toluene sniffing in recreational drug users, and marked volume depletion.[1,5,9] Type 2 RTA may be caused by a specific deficiency in bicarbonate reabsorption (eg, acetazolamide use), but is more commonly noted with a defect in proximal tubular function, leading to impaired reabsorption of solutes such as phosphate, glucose, uric acid, and amino acids. Type 4 is characterized by hypoaldosteronism, leading to hyperkalemia, impaired ammonium excretion, and subsequent hyperchloremic (normal-AG) metabolic acidosis.[1,5,9]

TREATMENT

Case 26-1, Question 2: What treatment should be considered for M.N.?

As with all acid–base disturbances, the cornerstone of management is to treat the underlying cause.[1,5] M.N. has signs of intravascular and total body fluid depletion, likely secondary to severe diarrhea. The type of fluid to administer should be carefully considered. She already has a hyperchloremic metabolic acidosis, and the administration of a chloride-rich solution (eg, 0.9% sodium chloride) would likely further precipitate that. If intravenous (IV) fluids are needed, a balanced solution (lactated Ringer) would be preferred to 0.9% sodium chloride (known as normal saline).[5,9]

The use of alkali therapy for the treatment of normal-AG metabolic acidosis is controversial and largely depends on the etiology, severity, and patient presentation. Alkali therapy in the form of isotonic sodium bicarbonate may be reasonable for the treatment of M.N.'s normal-AG acidosis because she is also hypovolemic.

Sodium bicarbonate, or organic acids such as sodium acetate that are converted to bicarbonate, may be administered IV or enterally depending on the available formulations as well as the nature of the non-AG acidosis (ie, chronic or acute).

There is no consensus approach to the administration of sodium bicarbonate in a patient with metabolic acidosis. Generally, the goal is to estimate the bicarbonate deficit and administer the amount that will correct the serum bicarbonate level to the desired goal concentration. The goal bicarbonate concentration should generally be a modest increase from baseline to avoid complications such as hypernatremia and should be reassessed following sodium bicarbonate therapy. Alternatively, a goal of 24 mEq/L can be chosen, but it may be necessary to slowly administer sodium bicarbonate to avoid electrolyte abnormalities. Sodium bicarbonate rapidly distributes to the extracellular space following IV administration. This distribution is estimated at ~50% of the total body weight, and therefore the approximate total dose of sodium bicarbonate to administer can be calculated by the following equation:

$$\begin{aligned}\text{Bicarbonate dose (mEq)} = {} & 0.5\ (\text{L/kg}) \times \text{total body weight (kg)} \\ & \times \text{desired increase in serum} \\ & \text{HCO}_3^-\ (\text{mEq/L})\end{aligned}$$

For M.N., the dose of sodium bicarbonate would be ~250 mEq (0.5 L/kg × 55 kg × [24–14]). This could be replaced by administering isotonic sodium bicarbonate (150 mEq/1000 mL) at a rate of 100 to 125 mL/hour for ~12 to 15 hours.

Elevated Anion Gap Metabolic Acidosis

EVALUATION

CASE 26-2

Question 1: K.S. is a 45-year-old, 143.30-pound (65-kg) female with hypertension, type 1 diabetes (T1D), and hyperlipidemia who presents to the emergency department with generalized weakness, polyuria, polydipsia, altered mental status, and signs of dehydration on physical exam. K.S. reports having fever, chills, frequent urination, and abdominal pain over the past 4 days. K.S. is suspected to have a UTI. Her vital signs are as follows: heart rate 115 *beats/minute*, blood pressure 85/55 mm Hg (mean arterial pressure [MAP] 65), respiratory rate 31 breaths/minute, temperature 100.8 °F (38.22 °C). K.S. receives 1000 mL of 0.9% sodium chloride, and her laboratory results are as follows:

Na^+: 130 mEq/L
K^+: 4.9 mEq/L
Cl^-: 95 mEq/L
TCO_2: 10 mEq/L
BUN: 27 mg/dL
SCr: 1.5 mg/dL
Glucose: 412 mg/dL
Albumin: 3.1 g/dL
β-Hydroxybutyrate: 10.9 mmol/L
Lactate: 4.5 mmol/L
ABGs: pH 7.12; $Paco_2$ 22 mm Hg; Pao_2 85 mm Hg; HCO_3^- 10 mmol/L
Assess K.S.'s acid–base status.

What are possible etiologies, and what compensatory response (laboratory and physical exam) would you expect?

We use the stepwise approach.

Step 1: Evaluate pH as acidemia or alkalemia—K.S. is acidemic given the low pH (pH = 7.12).

Step 2: Evaluate $Paco_2$ and bicarbonate—The stepwise approach highlights the low bicarbonate and low $Paco_2$.

Step 3: Identify the dominant acid–base disorder, presence of compensation, and potential for mixed disorder status—Given the abovementioned information, we can conclude that K.S. has a metabolic acidosis secondary to low serum bicarbonate. To evaluate the respiratory compensation, we apply the Winter formula (expected $Paco_2$ = [1.5 × 10] + 8 ± 2 = 21–25). Because K.S. has a $Paco_2$ of 22 within the range of the expected $Paco_2$ by

the Winter formula, we can determine that there is no secondary respiratory disturbance on top of the primary metabolic acidosis.

Step 4: For metabolic acidosis, further assess laboratory parameters. Determine whether it is normal- or high-AG acidosis. Calculate the AG to determine the type of metabolic acidosis—The next step is to evaluate the AG (130 − [95 + 10] = 25). After correction for hypoalbuminemia (AG = 25 + 2.5 × [4 − 3.1]), K.S. has an elevated AG of ~27. There are several possible etiologies for the elevated AG. K.S. has a history of T1D and presents with a blood glucose >400 mg/dL. Diabetic ketoacidosis (DKA), therefore, needs to be on the differential. K.S.'s β-hydroxybutyrate was positive at 10.9 mmol/L, confirming the presence of ketones. Common causes of DKA include infection and insulin nonadherence, both of which may be possible with K.S. In DKA, a relative or absolute deficiency of insulin leads to an inability to utilize glucose for adenosine triphosphate (ATP) production. In this state, fatty acids are metabolized to ketone bodies, specifically acetoacetate, acetone, and β-hydroxybutyrate.[1,2,9,27] Serum levels of bicarbonate decrease secondary to buffering of these acids, particularly acetoacetic acid and β-hydroxybutyric acid. Although the presence of acetone and acetoacetate can be detected through urine studies, β-hydroxybutyrate can only be assessed through serum levels. As with all etiologies of elevated-AG metabolic acidosis, treatment of the underlying cause is critical. If DKA is suspected or confirmed, fluid resuscitation and insulin therapy are required to allow the clearance of ketones and prevent further ketone body formation.[5,9–11]

However, other causes should be ruled out. K.S. clearly has signs of organ dysfunction and shock, with altered mental status and elevated SCr and a serum lactate level of 4.5 mmol/L. A lack of perfusion of oxygen to tissues leads to anaerobic metabolism and, subsequently, the production of lactic acid.

CASE 26-2, QUESTION 2: Does K.S. have a separate metabolic process in addition to her elevated-AG metabolic acidosis?

To further evaluate K.S.'s metabolic acidosis, we can use the δ ratio and compare the change in her AG to the change in her bicarbonate. The δ ratio can be calculated using Eq. 26-4. If the bicarbonate decreases in proportion with the elevation in AG, the decreased bicarbonate is likely secondary to acid buffering, and there is no additional metabolic process.[1,5,9] If the bicarbonate is lower or higher than expected, a concurrent metabolic acidosis or alkalosis may be present. Physiologically, this occurs because the amount of acid buffered by the carbonic acid buffer system is in proportion with the amount of bicarbonate lost (see Fig. 26-1). Therefore, if the drop in the bicarbonate is out of proportion with the increase in AG from normal, there is likely a secondary metabolic process going on to cause a higher (alkalosis) or lower (non-AG acidosis) bicarbonate concentration than is expected from a purely AG acidosis. Interpretation of the δ ratio can be found in **Table 26-6**. For K.S., her δ ratio is calculated to be 1.1 ([27–12] ÷ [24–10]). A δ around 1 indicates the presence of a pure high-AG metabolic acidosis.

$$\delta \text{ ratio} = \frac{\text{AG} - 12}{24 - \text{HCO}_3^-} \qquad \text{(Eq. 26-4)}$$

Table 26-6
Delta Ratio

Ratio	Acid–Base Disturbance
<0.8	Normal anion gap acidosis or respiratory alkalosis
0.8–1.2	Pure high anion gap acidosis
>1.2	High anion gap acidosis and metabolic alkalosis, or a preexisting compensated respiratory acidosis

TREATMENT

CASE 26-2, QUESTION 3: Should K.S. receive sodium bicarbonate for her elevated-AG metabolic acidosis?

The administration of alkali therapy, such as sodium bicarbonate, in elevated-AG metabolic acidosis is controversial and debated, and often is determined by the overall severity of the acidosis.[31,32] Adverse effects of severe acidosis (pH <7.1), such as impaired cardiac contractility, decreased responsiveness to catecholamines, and increased likelihood of arrhythmias, may warrant consideration of alkali therapy. Sodium bicarbonate is usually preferred given its immediate onset of action, as opposed to salts of organic acids (eg, sodium acetate) that require metabolism for activation.[5,9,31] However, the use of sodium bicarbonate is controversial for several reasons. Although it may improve arterial pH, the effects are often temporary given its lack of effect on the underlying problem causing metabolic acidosis. In addition, sodium bicarbonate may be limited owing to the volume of fluid that accompanies administration, particularly in some patient populations such as those with reduced ejection fraction. Also, there are limited data demonstrating the clinical benefits of utilizing sodium bicarbonate in elevated-AG metabolic acidosis. Finally, bicarbonate is converted to carbonic acid, leading to an increase in $Paco_2$, thus potentially worsening the acidosis if the patient is unable to increase ventilation adequately.[5,9] Although arterial pH may improve transiently, intracellular pH likely is unchanged or potentially even worsened secondary to changes in the intracellular ratio of HCO_3^- to CO_2. Tromethamine (THAM) is a proton acceptor that may have theoretical benefits over sodium bicarbonate, including increased buffering capacity and the ability to significantly reduce $Paco_2$.[31–36] However, data demonstrating the role of THAM are limited. Although there are no consensus dose recommendations, the approximate dose of THAM to administer for metabolic acidosis can be calculated by the following equation:

$$\text{THAM volume (mL)} = \text{body weight (kg)} \times \text{base deficit (mEq/L)}$$

35

THAM, unlike sodium bicarbonate, may also be effective in the treatment of respiratory acidosis because it acts a proton acceptor. Dosing strategies for dosing of THAM acetate 0.3 mol/L in respiratory acidosis differ, but a daily dose limit of ~15 mmol/kg is recommended.[35]

CASE 26-2, QUESTION 4: K.S. receives 6 L of normal saline total for the management of her possible DKA and septic shock. Her updated laboratory values are:

Na^+: 142 mEq/L
K^+: 3.8 mEq/L
Cl^-: 115 mEq/L
TCO_2: 18 mEq/L
BUN: 22 mg/dL
SCr: 0.7 mg/dL
Glucose: 197 mg/dL
Albumin: 3 g/dL
ABGs: pH 7.32; $Paco_2$ 22 mm Hg; HCO_3^- 19 mmol/L; Pao_2 95 mm Hg

What is her current acid–base disturbance?

K.S. has received treatment for her DKA in the form of isotonic fluid administration and IV insulin. Using the stepwise approach, we see that she continues to have an acidosis with a pH <7.35. With a low $Paco_2$ and a low bicarbonate, we can further classify it as a metabolic acidosis. The AG (142 − [115 + 18] = 9) is normal even after correction for hypoalbuminemia (9 + (2.5 × [4 − 3]) = 12.5). Potential etiologies for normal-AG metabolic acidosis include diarrhea and RTA; however, the most likely cause here is the administration of isotonic chloride-containing fluid in the form of 6 L of normal saline.

METABOLIC ALKALOSIS

Metabolic alkalosis is a condition defined by an elevated pH (>7.45) with a high plasma bicarbonate concentration. Compensation for metabolic alkalosis is demonstrated by hypoventilation by the lungs in an attempt to increase the $Paco_2$ to balance the pH.

Metabolic alkalosis can be caused by either an accumulation of bicarbonate or a loss of hydrogen ions (**Table 26-7**). The most common etiologies include vomiting or gastric suction (loss of chloride-rich fluid), diuresis (secondary to loss of both chloride and potassium), or an excess in mineralocorticoid activity (eg, Cushing syndrome and hyperaldosteronism).[1,2] Another less-common cause of metabolic alkalosis is through ingestion of large amounts of bicarbonate-containing products (eg, antacids).

Table 26-7
Metabolic Alkalosis

Chloride Status	Urine Chloride	Etiology
Chloride sensitive	<10–20 mEq/L	Gastrointestinal Vomiting Nasogastric suctioning Cl^- wasting diarrhea Diuretic therapy Post hypercapnia Cystic fibrosis
Chloride resistant	>20 mEq/L	Adrenal disorders Hyperaldosteronism Cushing disease Exogenous steroids Licorice Bartter syndrome Milk alkali syndrome

The cause of metabolic alkalosis can typically be determined based on the patient's presentation, but a urinary chloride concentration can further classify the disturbance.[1,2,5,9] Chloride-responsive metabolic alkalosis refers to disturbances that are secondary to loss of chloride-rich fluid. Urinary chloride is typically

<20 mEq/L in patients with chloride-responsive disturbances. Metabolic alkalosis secondary to severe hypokalemia or excessive mineralocorticoid activity often presents with urinary chloride concentrations >20 mEq/L.[1,5]

Evaluation

CASE 26-3

Question 1: D.K. is a 62-year-old male with a history of hypertension and systolic heart failure who presented to the emergency department 5 days ago with shortness of breath and signs of volume overload consistent with a heart failure exacerbation thought to be secondary to stopping his loop diuretic regimen of furosemide 80 mg daily. He has been receiving IV furosemide during his hospitalization (doses ranging from 80 to 160 mg once or twice daily) and has been 1 to 2 L net negative each day. On day 5 of his hospital admission, he is experiencing some dizziness and slowed breathing. His laboratory values are:

Na^+: 138 mEq/L
K^+: 2.5 mEq/L
Cl^-: 92 mEq/L
TCO_2: 34 mEq/L
BUN: 28 mg/dL
SCr: 0.9 mg/dL
Glucose: 167 mg/dL
Albumin: 3.9 g/dL
Urine chloride: 15 mEq/L
ABGs: pH 7.49; $Paco_2$ 46 mm Hg; HCO_3^- 33 mmol/L; Pao_2 92 mm Hg
Assess D.K.'s acid–base status.

What are possible etiologies, and what compensatory response (laboratory and physical exam) would you expect?

Use the stepwise approach.

Step 1: Evaluate pH as acidemia or alkalemia—D.K. has an elevated pH >7.45, indicating that DK is alkalemic.

Step 2: Evaluate $Paco_2$ and bicarbonate—An elevated bicarbonate is consistent as the primary cause, and the increased $Paco_2$ can

be attributed to compensation.

Step 3: Identify the dominant acid–base disorder, presence of compensation, and potential for mixed disorder status— Based on the abovementioned information, D.K. has a metabolic alkalosis. Referring to Table 26-3 to assess compensation, we see that D.K. has appropriate respiratory compensation (expected $Paco_2$ ~45.6 mm Hg), indicating there are no secondary respiratory disturbances present. Physical findings, such as dizziness or orthostatic hypotension, may accompany metabolic alkalosis.

Step 4: For metabolic alkalosis, further assess laboratory parameters and the etiology. Determine whether it is chloride sensitive or chloride resistant—D.K. has a metabolic alkalosis with appropriate respiratory compensation. Given D.K.'s acute increase in diuretic dose, significant loss of volume during the hospital admission, and his current electrolytes, it seems likely that his alkalosis is secondary to diuresis. In addition, his urine chloride is <20 mEq/L, indicating a chloride-responsive metabolic alkalosis.[1,5,9] In a "contraction alkalosis," total body HCO_3^- remains relatively constant. However, an increase in serum HCO_3^-, and subsequently pH, is seen due to extracellular fluid contraction.

Treatment

Case 26-3, Question 2: How can D.K.'s acid–base disturbance be treated?

Because we believe D.K. has a metabolic alkalosis secondary to loss of chloride-rich volume, cessation of (or at least slower) diuresis should be attempted. In addition, because the urine chloride is <20 mEq/L, D.K. likely will respond to chloride administration.[5,9–11] Chloride administration should help restore balance to the extracellular fluid and allow for adequate bicarbonate clearance. The form of chloride repletion should be based on the patient's overall volume status. In patients who are hypovolemic, chloride

administration with 0.9% sodium chloride is warranted. In patients who are euvolemic or hypervolemic, or who may not tolerate large volumes of fluid because of renal failure or decreased ejection fraction, use of potassium chloride is indicated.[1,2,30] Other chloride-containing therapeutic options, such as diluted hydrochloric acid and arginine hydrochloride, may be considered as options in certain patients with chloride-responsive metabolic alkalosis. Because both agents contain similar amounts of chloride, dosing can be approximated by the following equation: mEq HCl = 0.5 L/kg × actual body weight (kg) × (observed bicarbonate − 24).[37] Hydrochloric acid has been shown to be relatively safe; however, challenges in operational compounding and administration limit its use to extreme and severe conditions. The administration of hydrochloric acid requires central line access and pharmaceutical compounding in glass containers. Acetazolamide, a carbonic anhydrase inhibitor, decreases the breakdown of HCO_3^- to CO_2 and H_2O, leading to an increase in bicarbonate excretion via the urine.[1,2] Although acetazolamide may decrease serum bicarbonate levels, it likely will not “fix” the metabolic alkalosis.[1,5,9,20] In addition, it may lead to hypokalemia secondary to increased potassium excretion. Patients with chronic obstructive pulmonary disease (COPD) may additionally have more difficulty to expel CO_2, and administration of acetazolamide in these patients is controversial.

RESPIRATORY DISTURBANCES

Respiratory acidosis or alkalosis results from $Paco_2$ retention or enhanced gas exchange.[1,2,5,6] The compensatory response to respiratory disturbances occurs in the kidneys via bicarbonate absorption or excretion. An inverse relationship exists between the $Paco_2$ and pH (as $Paco_2$ increases, the pH will decrease), as seen in Table 26-1.

Respiratory Acidosis

Respiratory acidosis can manifest from hypoventilation or impaired gas exchange of CO_2 (hypercapnia) in the lungs. When the lungs cannot excrete CO_2 effectively, the $Paco_2$ rises. This elevation in $Paco_2$ causes a decrease in pH. Common causes and the management of respiratory acidosis can be found in **Table 26-8**. Generally, causes of respiratory acidosis can be categorized into conditions of airway obstruction, central nervous system (CNS) depression leading to reduction in the respiratory drive, failure of the heart or lungs, and disturbances of the peripheral nerves or skeletal muscles that impair or weaken the diaphragm.[1,5,11]

Table 26-8
Respiratory Acidosis

Mechanism	Pathophysiology	Treatment Modalities
Central nervous system Depression	Central sleep apnea CNS depressant drugs Opiates Benzodiazepines Barbiturates Sedatives Status epilepticus Cerebral vascular accident Tumor	Invasive/noninvasive ventilation Antidotal reversal (eg, naloxone for opioid overdose)
Airway obstruction	Foreign body aspiration Tumor Bronchospasm COPD	Invasive/noninvasive ventilation Steroids Bronchodilators

Mechanism	Pathophysiology	Treatment Modalities
Neuromuscular dysfunction	Guillain–Barré syndrome Amyotrophic lateral sclerosis Myasthenia gravis Brainstem or spinal cord injury Severe hypophosphatemia	Invasive/noninvasive ventilation
Cardiopulmonary disorders	COPD ARDS Pulmonary edema Cystic fibrosis Pulmonary fibrosis Pulmonary embolism Cardiac arrest/circulatory collapse	Invasive/noninvasive ventilation Steroids Antimicrobials Antifibrinolytics/ anticoagulants

ARDS, acute respiratory distress syndrome; CNS, central nervous system; COPD, chronic obstructive pulmonary disease.

Patients who present with acute respiratory acidosis will have an elevated $Paco_2$ and a decline in the pH. The kidneys will begin to retain HCO_3^- as a compensatory mechanism. Compensation will begin 6 to 12 hours after the development of academia, with only modest increases in serum HCO_3^- and full metabolic compensation after 48 to 72 hours.[1,5,12]

Patients with chronic respiratory conditions, such as COPD or neuromuscular dysfunction, may present with stably elevated $Paco_2$; however, the pH will be maintained at a near-normal value because of full metabolic compensation.[38]

EVALUATION

CASE 26-4

Question 1: B.G. is a 69-year-old male who was brought to the emergency department after being found with new altered mental status at home. B.G. has a past medical history of insomnia, anxiety, and chronic pain for which he takes extended-release oxycodone, and he was recently was started on diazepam for back spasms. Upon arrival at the hospital, his vital signs were the following: temperature 99.8 °F (37.67 °C), heart rate 95 beats/minute, blood pressure 100/65 mm Hg, respiratory rate 10 breaths/minute, O2 saturation 90% on 5 L/minute of oxygen via nasal cannula.

The patient is noted to have the following laboratory values:

Na^+: 135 mEq/L
K^+: 4.4 mEq/L
Cl^-: 98 mEq/L
TCO_2: 29 mEq/L
BUN: 20 mg/dL
SCr: 1.25 mg/dL
Glucose: 124 mg/dL
Albumin: 3.5 g/dL

What type of acid–base disturbance is present?

B.G. has a respiratory acidosis. Acidemia is present as the pH < 7.35 (pH is 7.15). Given the Paco2 > 42, with bicarbonate slightly increased, the primary process is respiratory acidosis.

Case 26-4, Question 2: Is this an acute or chronic process?

Acute: $\Delta Paco_2 = 90 - 40 = 50$; $\Delta HCO_3^- = 29 - 24 = 5$

Using the compensation ratios seen in Table 26-3, we can see that this is an acute process. Comparing the change in $Paco_2$ to the change in bicarbonate, we calculate a ratio of 10:1.

Case 26-4, Question 3: What is most likely to contribute significantly to B.G.'s acid–base abnormality?

As seen in Table 26-8, CNS depressant medications can lead to CO_2 retention and respiratory acidosis.[1,2,5,12] The addition of diazepam to B.G.'s chronic pain management can cause respiratory

depression, leading to B.G.'s low respiratory rate and $Paco_2$ accumulation.

TREATMENT

The treatment for respiratory acidosis should focus on identifying and correcting the underlying cause of the patient's decompensation, which is further discussed in Table 26-8.[2,10,11] Supplemental oxygen for patients presenting with hypoxemia may be necessary to maintain tissue oxygenation. In the event of severe or worsening respiratory acidosis, mechanical ventilation may be necessary to reduce the $Paco_2$. Reductions in $Paco_2$ should be made gradually and, in patients with chronic $Paco_2$ elevations, should be reduced to baseline levels.[2,5,10,11] The administration of exogenous bicarbonate therapy (such as sodium bicarbonate) is not recommended, because there is not a total body deficit of bicarbonate.[31,39,40]

EVALUATION

CASE 26-5

QUESTION 1: J.A. is an 87-year-old male who presents to his primary care provider for a routine follow-up. J.A.'s past medical history includes hypertension, hyperlipidemia, type 2 diabetes, and COPD for which he is on home oxygen. J.A. does not endorse any new shortness of breath or changes in sputum production. He does note that he was recently babysitting his grandson who had cold-like symptoms. The patient is noted to have the following laboratory values: temperature 98.7 °F (37.05 °C), heart rate 90 beats/minute, blood pressure 145/90 mm Hg, respiratory rate 16 breaths/minute, O_2 saturation 92% on 2 L/minute of oxygen via nasal cannula. From his previous outpatient pulmonologist appointments, J.A.'s baseline blood gases are:

Na^+: 146 mEq/L
K^+: 4.1 mEq/L
Cl^-: 107 mEq/L
TCO_2: 31 mEq/L
BUN: 16 mg/dL
SCr: 1.2 mg/dL

Baseline ABGs: pH: 7.34; $Paco_2$: 60 mm Hg; Pao_2: 67 mm Hg; HCO_3^- 31 mEq/L

Does J.A. have an acid–base disorder?

Using the stepwise approach, we can see that J.A. has a respiratory acidosis. Acidemia is detected, because the pH is <7.35 (pH 7.34, although relatively normal, is still on the low side of normal). The PCO_2 is elevated, with an increase in bicarbonate as a potential metabolic compensation.

CASE 26-5, QUESTION 2: Is this an acute or a chronic process?

$$\text{Chronic: } \Delta Paco_2 = 60 - 40 = 20; \Delta HCO_3^- = 31 - 24 = 7$$
$$\text{Compensation ratio: } \Delta Paco_2 \text{ to } \Delta HCO_3^- = 10{:}3.5$$

Although J.A. has a significantly elevated $Paco_2$, this is an example of a fully compensated chronic respiratory acidosis. Although J.A.'s $Paco_2$ is elevated, the compensation of the kidneys and retention of bicarbonate maintains close to normal pH.

EVALUATION

CASE 26-5, QUESTION 3: Five days later, J.A. presents to the emergency department with cough, shortness of breath, and increased sputum production. A chest x-ray reveals a left lower lobe consolidation, and J.A. has the following vital signs: temperature 101.2 °F (38.44 °C), heart rate 102, and a respiratory rate of 16. J.A. is noted to be more confused and has an O_2 saturation of 87% for which the physician orders a STAT ABG and initiates him on 5 L supplemental oxygen.

ABGs: pH 7.25; $Paco_2$ 75 mm Hg; Pao_2 63 mm Hg; HCO_3^- 33 mEq/L

What type of acid–base disturbance is now present?

J.A. has a respiratory acidosis. Acidosis is present, because the pH is <7.35, and the $Paco_2$ is elevated, with an increase in bicarbonate. As we know from admission and J.A.'s past medical history, his current $Paco_2$ of 75 is elevated from his baseline (60 mm Hg).[38] J.A.'s new blood gas is exhibiting an acute-on-chronic respiratory acidosis, most likely due to a COPD exacerbation based on his chest x-ray and presenting symptoms.

Evaluating his new acidosis on top of his baseline, we can see the acute nature of his respiratory acidosis.

$$\Delta Paco_2 = 75 - 60 = 15; \Delta HCO_3^- = 33 - 31 = 2;$$
$$\Delta Paco_2 \text{ to } \Delta HCO_3^- = 15{:}2$$

As seen in the calculation, J.A.'s "normal" $Paco_2$ of 60 mm Hg and HCO_3^- of 31 mEq/L are elevated as compared to standardly accepted values ($Paco_2$ 35–45 mm Hg and HCO_3^- 22–26 mEq). In patients with chronic acid–base disorders, patient-specific baseline values should be used to evaluate changes in acid–base status, because new homeostasis has been achieved.

Respiratory Alkalosis

Respiratory alkalosis typically results from excessive rate or the depth of respiration leading to increased pulmonary gas exchange and elimination of carbon dioxide. The fall in $Paco_2$ causes a rise in arterial pH. Dyspnea, chest pain, and palpitations are the most common presenting symptoms in patients with respiratory alkalosis.[1,2,11,12,40] Both acute and chronic conditions can lead to a respiratory alkalosis with common causes, as listed in **Table 26-9**. As with respiratory acidosis, the treatment for respiratory alkalosis is the treatment of the underlying cause.[1,6,12]

Table 26-9
Respiratory Alkalosis

Mechanism	Pathophysiology	Treatment Modality
Respiratory rate stimulation	Anxiety Severe pain Sepsis Pregnancy Tumor Salicylate overdose	Rebreathe into a closed system (paper bag) Urinary alkalization or dialysis (salicylate toxicity)
Impaired oxygen extraction or carrying capacity	Pneumonia Pulmonary embolism Congestive heart failure Pulmonary fibrosis High altitude/acute altitude changes Anemias	Supplemental oxygen Invasive/noninvasive ventilation Steroids Thrombolysis Bronchodilators Carbonic anhydrase inhibitors (altitude changes)
Iatrogenic	Excessive mechanical ventilation	Ventilation changes

EVALUATION

CASE 26-6

QUESTION 1: R.W. is a 35-year-old female who presents to the emergency department with severe shortness of breath and cough since the previous night. R.W. has no noted past medical history. She appears to be in respiratory distress, using accessory muscles to breathe. A chest radiograph shows bilateral lower lung infiltrates. Her current vital signs are temperature 101.2 °F (38.44 °C), heart rate 104 beats/minute, blood pressure 110/83, respiratory rate 35 breaths/minute, and O_2 saturation 90% on room air. The patient is noted to have the following laboratory values:

Na^+: 145 mEq/L
K^+: 4.5 mEq/L
Cl^-: 110 mEq/L
TCO_2: 23 mEq/L
BUN: 10 mg/dL
SCr: 0.6 mg/dL
ABGs: pH: 7.54; $Paco_2$: 21 mm Hg; Pao_2: 77 mm Hg; HCO_3^- 19 mEq/L

What type of acid–base disturbance is present?

R.W. has a respiratory alkalosis. Alkalemia is present, because the pH is >7.35 (pH 7.54, and the $Paco_2$ is <38), with bicarbonate slightly decreased. The primary process is respiratory.

CASE 26-6, QUESTION 2: What is the most likely cause of R.W.'s acid–base abnormality?

R.W.'s chest x-ray with bilateral infiltrates, severe shortness of breath, and cough are consistent with pneumonia. R.W. also presents with a fever and an elevated white blood cell count, which are consistent with a bacterial infection.

TREATMENT

CASE 26-6, QUESTION 3: What is the appropriate treatment for R.W.'s respiratory alkalosis?

Similar to respiratory acidosis, treatment of respiratory alkalosis usually involves correcting the underlying disturbance. Initiation of appropriate antibiotic therapy for a community-acquired pneumonia is indicated in this case. If R.W. were to become hypoxic, supplemental oxygen therapy may be indicated.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Adrogue HJ. Metabolic acidosis: pathophysiology, diagnosis and management. *J Nephrol.* 2006;19(suppl 9):S62–S69. (10)

Al-Jaghbeer M, Kellum JA. Acid–base disturbances in intensive care patients: etiology, pathophysiology and treatment. *Nephrol Dial Transplant.* 2015;30(7):1104–1111. (11)

Ayers P, Dixon C, Mays A. Acid–base disorders: learning the basics. *Nutr Clin Pract.* 2015;30(1):14–20. (12)

Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. *N Engl J Med.* 2014;371(15):1434–1445. (1)

Dzierba AL, Abraham P. A practical approach to understanding acid-base abnormalities in critical illness. *J Pharm Pract.* 2011;24(1):17–26. (2)

Kellum JA. Disorders of acid-base balance. *Crit Care Med.* 2007;35(11): 2630–2636. (4)

Marino PL. *The ICU Book.* 4th ed: Wolters Kluwer Health; 2013. (5)

Montague J, Clive D. Metabolic acidosis and metabolic alkalosis. In: Irwin RS, Rippe JM, eds. *Manual of Intensive Care Medicine*. 5th ed. Wolters Kluwer Health; 2012. (9)

Sacks GS. The ABC's of acid–base balance. *J Pediatr Pharmacol Ther.* 2004;9(4):235–242. (6)

Story DA. Stewart acid–base: a simplified bedside approach. *Anesth Analg.* 2016;123(2):511–515. (13)

COMPLETE REFERENCES CHAPTER 26 ACID–BASE DISTURBANCES

1. Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid–base disturbances. *N Engl J Med.* 2014;371:1434–1445.
2. Dzierba AL, Abraham P. A practical approach to understanding acid–base abnormalities in critical illness. *J Pharm Pract.* 2011;24:17–26.
3. Hood VL, Tannen RL. Protection of acid–base balance by pH regulation of acid production. *N Engl J Med.* 1998;339:819–826.
4. Kellum JA. Disorders of acid–base balance. *Crit Care Med.* 2007;35:2630–2636.
5. Marino PL. *The ICU Book.* 4th ed. Wolters Kluwer Health; 2013.
6. Sacks GS. The ABC's of acid–base balance. *J Pediatr Pharmacol Ther.* 2004;9:235–242.
7. Kellum JA. Determinants of blood pH in health and disease. *Crit Care.* 2000;4:6–14.

8. Kellum JA. Determinants of plasma acid–base balance. *Crit Care Clin.* 2005;21:329–346.
9. Montague J, Clive D. Metabolic acidosis and metabolic alkalosis. In: Irwin RS, Rippe JM. *Manual of Intensive Care Medicine*. 5th ed. Wolters Kluwer Health; 2012.
10. Adrogue HJ. Metabolic acidosis: pathophysiology, diagnosis and management. *J Nephrol.* 2006;19(suppl 9):S62–S69.
11. Al-Jaghbeer M, Kellum JA. Acid–base disturbances in intensive care patients: etiology, pathophysiology and treatment. *Nephrol Dial Transplant.* 2015;30:1104–1111.
12. Ayers P, Dixon C, Mays A. Acid–base disorders: learning the basics. *Nutr Clin Pract.* 2015;30:14–20.
13. Story DA. Stewart acid–base: a simplified bedside approach. *Anesth Analg.* 2016;123:511–515.
14. Adrogue HJ, Madias NE. Assessing acid–base status: physiologic versus physicochemical approach. *Am J Kidney Dis.* 2016;68:793–802.
15. Kurtz I, Kraut J, Ornekian V, Nguyen MK. Acid–base analysis: a critique of the Stewart and bicarbonate-centered approaches. *Am J Physiol Renal Physiol.* 2008;294:F1009–F1031.
16. Adrogue HJ. Mixed acid–base disturbances. *J Nephrol.* 2006;19(suppl 9):S97–S103.
17. Adrogue HJ, Gennari FJ, Galla JH, Madias NE. Assessing acid–base disorders. *Kidney Int.* 2009;76:1239–1247.
18. Narins RG, Emmett M. Simple and mixed acid–base disorders: a practical approach. *Medicine (Baltimore).* 1980;59:161–187.
19. Williams AJ. ABC of oxygen: assessing and interpreting arterial blood gases and acid–base balance. *BMJ.* 1998;317:1213–1216.
20. Jung B, Martinez M, Claessens YE, et al. Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care.* 2019;9:92.
21. Feldman M, Soni N, Dickson B. Influence of hypoalbuminemia or hyperalbuminemia on the serum anion gap. *J Lab Clin Med.* 2005;146:317–320.
22. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol.* 2007;2:162–174.
23. Winter SD, Pearson JR, Gabow PA, Schultz AL, Lepoff RB. The fall of the serum anion gap. *Arch Intern Med.* 1990;150:311–313.
24. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. *Crit Care Med.* 1998;26:1807–1810.
25. Story DA, Poustie S, Bellomo R. Estimating unmeasured anions in critically ill patients: anion-gap, base-deficit, and strong-ion-gap. *Anaesthesia.* 2002;57:1109–1114.

26. Schoolwerth AC, Kaneko TM, Sedlacek M, Block CA, Remillard BD. Acid–base disturbances in the intensive care unit: metabolic acidosis. *Semin Dial.* 2006;19:492–495.
27. Gabow PA. Disorders associated with an altered anion gap. *Kidney Int.* 1985;27:472–483.
28. Batlle D, Ba Aqeel SH, Marquez A. The urine anion gap in context. *Clin J Am Soc Nephrol.* 2018;13:195–197.
29. Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. *N Engl J Med.* 1988;318:594–599.
30. Kraut JA, Kurtz I. Treatment of acute non-anion gap metabolic acidosis. *Clin Kidney J.* 2015;8:93–99.
31. Kraut JA, Kurtz I. Use of base in the treatment of severe acidemic states. *Am J Kidney Dis.* 2001;38:703–727.
32. Rehm M, Finsterer U. Treating intraoperative hyperchloremic acidosis with sodium bicarbonate or tris-hydroxymethyl aminomethane: a randomized prospective study. *Anesth Analg.* 2003;96:1201–1208.
33. Holmdahl MH, Wiklund L, Wetterberg T, et al. The place of THAM in the management of acidemia in clinical practice. *Acta Anaesthesiol Scand.* 2000;44:524–527.
34. Kallet RH, Jasmer RM, Luce JM, Lin LH, Marks JD. The treatment of acidosis in acute lung injury with tris-hydroxymethyl aminomethane (THAM). *Am J Respir Crit Care Med.* 2000;161:1149–1153.
35. Nahas GG, Sutin KM, Fermon C, et al. Guidelines for the treatment of acidaemia with THAM. *Drugs.* 1998;55:191–224.
36. Bleich HL, Schwartz WB. Tris buffer (THAM). An appraisal of its physiologic effects and clinical usefulness. *N Engl J Med.* 1966;274:782–787.
37. Sierra CM, Hernandez EA, Parbuoni KA. Use of arginine hydrochloride in the treatment of metabolic alkalosis or hypochloremia in pediatric patients. *J Pediatr Pharmacol Ther.* 2018;23:111–118.
38. Bruno CM, Valenti M. Acid–base disorders in patients with chronic obstructive pulmonary disease: a pathophysiological review. *J Biomed Biotechnol.* 2012;2012:915150.
39. Adrogue HJ, Madias NE. Alkali therapy for respiratory acidosis: a medical controversy. *Am J Kidney Dis.* 2020;75:265–271.
40. Mountain RD, Heffner JE, Brackett NC Jr, Sahn SA. Acid–base disturbances in acute asthma. *Chest.* 1990;98:651–655.

27

Fluid and Electrolyte Disorders

Priscilla P. How and Alan H. Lau

CORE PRINCIPLES		CHAPTER CASES
FLUID AND SODIUM DISORDERS		
1	Plasma osmolality is maintained within normal limits through a delicate balance between water intake and excretion. Antidiuretic hormone (ADH) plays an important role in maintaining fluid balance in the body.	**Case 27-1 (Question 1), Figure 27-1**
2	Signs of volume depletion include orthostatic hypotension, dry mucous membranes, and poor skin turgor. Because water and sodium are inherently linked, the assessment of volume status and selection of replacement fluid require examination of sodium concentration.	**Case 27-2 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
3	Aldosterone is the main regulatory hormone for sodium homeostasis. A patient may have hypotonic, isotonic, or hypertonic hyponatremia depending on the plasma osmolality. Normal serum sodium concentration is 135 to 145 mEq/L.	**Case 27-4 (Question 1) Case 27-5 (Questions 1, 2) Case 27-6 (Question 1) Case 27-7 (Questions 1, 2, 3, 4)**
4	Hypovolemic hypotonic hyponatremia can occur with volume depletion and decreased extracellular fluid. Calculation of sodium deficit will determine how much sodium replacement is required.	**Case 27-5 (Questions 1, 2)**
5	Hypervolemic, hypotonic hyponatremia is caused by a disproportionate accumulation of ingested water relative to sodium. It is also observed in patients with heart failure, liver and kidney failure, and nephrotic syndrome. Management includes sodium and water restriction, as well as the use of diuretics.	**Case 27-6 (Question 1) Case 27-3 (Questions 1, 2)**
6	Syndrome of inappropriate ADH is a common cause of normovolemic hypotonic hyponatremia. Persistent ADH secretion together with water ingestion results in hyponatremia.	**Case 27-7 (Question 1) Case 27-7 (Question 2)**

CORE PRINCIPLES		CHAPTER CASES
7	Neurologic symptoms may be manifested in acute or severe hyponatremia. Low plasma osmolality causes water to move into the brain, resulting in cerebral edema, increased intracranial pressure, and central nervous system symptoms. Rapid or overly aggressive correction of hyponatremia can result in osmotic demyelination.	**Case 27-7 (Questions 1-4)**
POTASSIUM DISORDERS		
1	The sodium–potassium adenosine triphosphatase pump plays a pivotal role in maintaining potassium homeostasis. Normal serum potassium concentration is 3.5 to 5.0 mEq/L. Clinical manifestations of hypokalemia include muscle weakness and electrocardiography (ECG) changes.	**Case 27-8 (Questions 1, 2)**
2	Potassium repletion should be guided by close monitoring of serum potassium. Oral supplementation is usually preferred. Patients who cannot tolerate oral potassium or who have severe/symptomatic hypokalemia can receive intravenous potassium. In general, the rate of potassium infusion administered via a peripheral vein should not exceed 10 mEq/hour to prevent phlebitis.	**Case 27-8 (Question 3)**

CORE PRINCIPLES		CHAPTER CASES
3	Hyperkalemia can be caused by chronic kidney disease and medications that inhibit the renin–angiotensin–aldosterone system. Intravenous calcium is administered to antagonize the cardiac effects (ECG changes and ventricular arrhythmias) of hyperkalemia. Other treatment strategies include the use of insulin and glucose, β_2-agonists, sodium polystyrene sulfonate, patiromer, sodium zirconium cyclosilicate, sodium bicarbonate, and dialysis.	**Case 27-9 (Question 1)** **Case 27-10 (Questions 1, 2), Table 27-3**

CALCIUM DISORDERS

CORE PRINCIPLES		CHAPTER CASES
1	Normal serum calcium is 8.5 to 10.5 mg/dL (corrected for serum albumin because calcium is protein bound). Hypercalcemia can be caused by dehydration, malignancy, hyperparathyroidism, vitamin D intoxication, sarcoidosis, and other granulomatous diseases. Clinical presentation of hypercalcemia includes signs and symptoms involving the neurologic, cardiovascular, pulmonary, kidney, gastrointestinal, and musculoskeletal systems. First-line treatment for hypercalcemia is hydration and diuresis. Calcitonin and bisphosphonates are alternative agents used in the management of hypercalcemia.	**Case 27-11 (Questions 1–3), Table 27-4**
PHOSPHATE DISORDERS		
1	Hypophosphatemia can develop as a result of impaired intestinal phosphorus absorption, increased kidney elimination, or shift of phosphorus from extracellular to intracellular compartments. Normal serum phosphorus concentration is 2.7 to 4.7 mg/dL.	**Case 27-12 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
2	Clinical effects of hypophosphatemia can involve multiple organ systems and are attributed to impaired cellular energy stores and tissue hypoxia secondary to ATP depletion. Phosphorus supplementation can be administered orally or intravenously, depending on the signs and symptoms, and severity of hypophosphatemia. Kidney function, serum phosphorus, calcium, and magnesium need to be monitored closely. Diarrhea is a common dose-related side effect of oral phosphorus replacement.	**Case 27-12 (Questions 3, 4)**
MAGNESIUM DISORDERS		
1	Magnesium depletion (normal serum magnesium, 1.8–2.4 mEq/L) can result in abnormal function of the neurologic, neuromuscular, and cardiovascular systems. Typical findings include Chvostek and Trousseau signs, muscle fasciculation, tremors, muscle spasticity, convulsions, and, possibly, tetany. Because serum magnesium does not reflect total body stores, symptoms are more important determinants of the urgency and aggressiveness of magnesium replacement.	**Case 27-13 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
2	Oral magnesium replacement is indicated in asymptomatic patients with mild depletion. Urinary excretion of magnesium increases during intravenous replacement. Thus, replenishment of magnesium stores usually takes several days. After intravenous magnesium administration, the patient should be monitored for hypotension, marked suppression of deep tendon reflexes, ECG and respiration changes, as well as hypermagnesemia.	**Case 27-13 (Questions 3, 4)**
3	A common cause of hypermagnesemia is the use of magnesium-containing laxatives and antacids by patients with kidney impairment. Potentially life-threatening complications of severe hypermagnesemia include respiratory paralysis, hypotension, and complete heart block. Intravenous calcium should be administered to antagonize the respiratory and cardiac manifestations of magnesium. Diuretics may be given to patients with good kidney function to enhance urinary magnesium excretion.	**Case 27-14 (Questions 1–3)**

INTRODUCTION

Body Water Compartments and Electrolyte Composition

In newborns, ~75% to 85% of body weight is water. After puberty, the percentage of water per kilogram of weight decreases as the amount of adipose tissue increases with age. Body water constitutes 50% to 60% of the lean body weight (LBW) in adult males but only 45% to 55% in females because of their greater proportion of adipose tissue. The water content per kilogram of body weight further decreases with advanced age. Total body water (TBW) is usually calculated as 0.6 × LBW in males and 0.5 × LBW in females.[1]

Two-thirds of the TBW resides in the cells (intracellular water). The extracellular water can be divided into different compartments—the interstitial fluid (12% LBW) and plasma (5% LBW) are the two major compartments. Other compartments of the extracellular fluid (ECF) include the connective tissues and bone water, the transcellular fluids (eg, glandular secretions), and other fluids in sequestered spaces, such as the cerebrospinal fluid.

The electrolyte composition differs between the intracellular and extracellular compartments. Potassium, magnesium, and phosphate are the major ions in the intracellular compartment, whereas sodium, chloride, and bicarbonate are predominant in the extracellular space. Water travels freely across the cell membranes of most parts of the body. The cell membrane, however, is only selectively permeable to solutes. The impermeable solutes are osmotically active and can exert an osmotic pressure that dictates the distribution of water between fluid compartments. Water moves across the cell membrane from a region of low osmolality to one of high osmolality. Net water movement ceases when osmotic equilibrium occurs. Each fluid compartment contains a major osmotically active solute: potassium in the intracellular space and sodium in the ECF. The volumes of the two compartments reflect the asymmetrically larger number of solute particles or osmoles inside the cells.[1]

The capillary wall separates the interstitial fluid from plasma. Because sodium moves freely across the capillary wall, its

concentration is identical across both sides of the wall. Therefore, no osmotic gradient is generated, and water distribution between these two spaces is not affected. Plasma proteins, which are confined in the vascular space, are the primary osmoles that affect water distribution between the interstitium and the plasma. In contrast, urea, which traverses both the capillary walls and most cell membranes, is osmotically inactive.

Plasma Osmolality

Osmolality is defined as the number of particles per kilogram of water (mOsm/kg). It is determined by the number of particles in solution and not by particle size or valence. Nondissociable solutes, such as glucose and albumin, generate 1 mOsm/mmol of particles; and dissociable salts, such as sodium chloride, liberate two ions in solution to produce 2 mOsm/mmol of salt. The osmolality of body fluid is maintained between 280 and 295 mOsm/kg. Because all body fluid compartments are iso-osmotic, plasma osmolality reflects the osmolality of TBW. Plasma osmolality can be measured by the freezing point depression method, or estimated by Eq. 27-1, which takes into account the osmotic effect of sodium (Na), glucose, and blood urea nitrogen (BUN):

$$P_{osm} = 2(Na)(mmol/L) + Glucose\,(mg/dL)/18 + BUN\,(mg/dL)/2.8 \quad \textbf{(Eq. 27-1)}$$

This equation predicts the measured plasma osmolality within 5 to 10 mOsm/kg. Although BUN contributes to the measured osmolality, it is an ineffective osmole because it readily traverses cell membranes and, therefore, does not cause a significant fluid shift within the body. Hence, the effective plasma osmolality (synonymous with tonicity, the portion of total osmolality that has the potential to induce transmembrane water movement) can be estimated by Eq. 27-2:

$$P_{osm} = 2(Na)(mmol/L) + Glucose\,(mg/dL)/18 \quad \textbf{(Eq. 27-2)}$$

An osmolal gap exists when the measured and calculated values differ by >10 mOsm/kg; it signifies the presence of unidentified particles. When the individual solute has been identified, its contribution to the measured osmolality can be estimated by dividing its concentration (mg/dL) by 1/10 of its molecular weight. Calculating the osmolal gap is used to detect the presence of substances, such as ethanol, or antifreeze ingredients (methanol and ethylene glycol) that have high osmolality. Occasionally, the osmolal gap can also result from an artificial decrease in the serum sodium secondary to severe hyperlipidemia or hyperproteinemia.[1]

CASE 27-1

QUESTION 1: J.F., a 31-year-old male, is admitted to the inpatient medicine service for methanol intoxication. Routine laboratory analysis reveals the following:

Serum sodium (Na^+), 145 mEq/L
Serum potassium (K^+), 3.4 mEq/L
BUN, 10 mg/dL
Serum creatinine (SCr), 1.1 mg/dL
Serum glucose, 90 mg/dL
The blood methanol concentration was 108 mg/dL and the measured plasma osmolality was 333 mOsm/kg.

What is J.F.'s calculated osmolality? Are other unidentified osmoles present?

Using Eq. 27-1, J.F.'s total calculated osmolality is

$$P_{osm} = 2(145\ mEq/L) + 90\ mg/dL/18 + 10\ mg/dL/2.8 \quad \text{(Eq. 27-3)}$$
$$= 290 + 5 + 3.6$$
$$= 299\ mOsm/kg$$

$$\text{Osmolal gap} = 333\ mOsm/kg - 299\ mOsm/kg = 34\ mOsm/kg \quad \text{(Eq. 27-4)}$$

In J.F., the entire osmolal gap calculated in Eq. 27-4 can be accounted for by the presence of the methanol (because 108 mg/dL

of methanol will provide 108/3.2 = 33.7 mOsm/kg). It is unlikely, therefore, that other unmeasured osmoles are present (eg, ethylene glycol, isopropanol, and ethanol). The laboratory determination of osmolality measures the total number of osmotically active particles but not their permeability across the cell membrane. Methanol increases plasma osmolality but not tonicity because the cell membrane is permeable to methanol. Therefore, no net water shift occurs between the intracellular and extracellular compartments.

Tubular Function of Nephron

The kidney plays an important role in maintaining a constant extracellular environment by regulating the excretion of water and various electrolytes. The volume and composition of fluid filtered across the glomerulus are modified as the fluid passes through the tubules of the nephron.[1]

The kidney tubule is composed of a series of segments with heterogeneous structures and functions: the proximal tubule, the medullary and cortical thick ascending limb of the Henle loop, the distal convoluted tubule, and the cortical and medullary collecting duct (**Fig. 27-1**). The mechanism for sodium reabsorption is different for each nephron segment, but it is generally mediated by carrier proteins or channels located on the luminal membrane of the tubule cell. Na^+/K^+-ATPase (sodium–potassium adenosine triphosphatase) actively pumps sodium out of the kidney tubule cell in exchange for potassium in a 3:2 ratio. Hence, the intracellular sodium concentration is kept at a low level. The potassium that is pumped into the cell leaks back out through potassium channels in the membrane, rendering the cell interior electronegative. The low intracellular sodium concentration and a negative intracellular potential produce a favorable gradient for passive sodium entry into the cell. Na^+/K^+-ATPase also indirectly provides the energy for active sodium transport and the reabsorption and secretion of other solutes across the luminal membrane of the kidney tubule. The distal

segments are mainly involved in the reabsorption of sodium and chloride ions and the secretion of hydrogen and potassium ions.

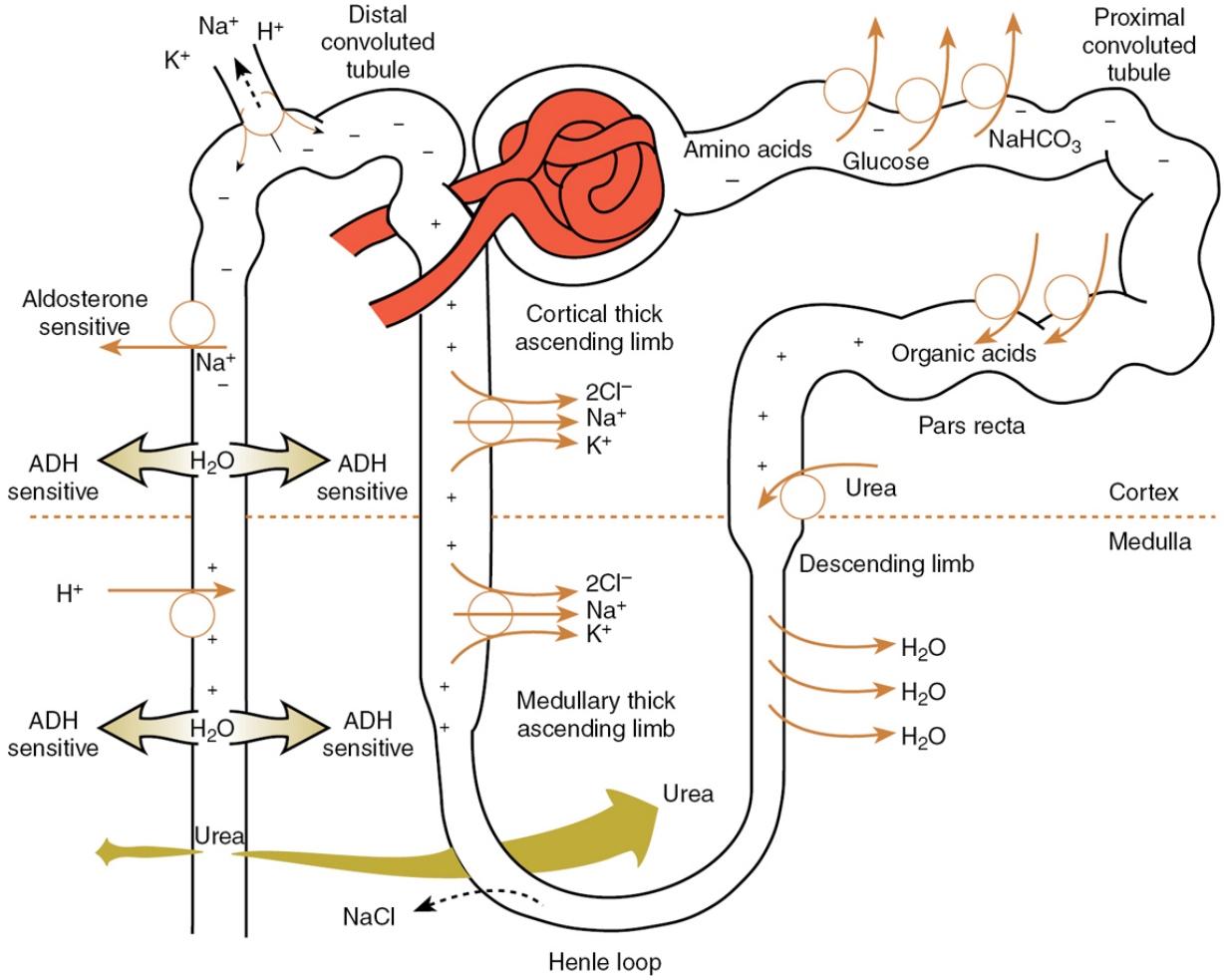


Figure 27-1 Sites of tubule salt and water absorption. Sodium is reabsorbed with inorganic anions, amino acids, and glucose in the proximal tubule against an electrical gradient that is lumen negative. In the distal part of the proximal tubule (pars recta), sodium and water are reabsorbed to a lesser extent and organic acids (hippurate, urate) and urea are secreted into the urine. The electrical potential is lumen positive in the pars recta. Water, but not salt, is removed from tubule fluid in the thin descending limb of the Henle loop; but in the ascending portion, salt is reabsorbed without water, rendering the tubule fluid hyposmotic with respect to the interstitium. Sodium, chloride, and potassium are reabsorbed by the medullary and cortical portions of the ascending limb; the lumen potential is

positive. Sodium is reabsorbed and potassium and hydrogen ions are secreted in the distal tubule and collecting ducts. Water absorption in these segments is regulated by antidiuretic hormone (ADH). The electrical potential is lumen negative in the cortical sections and positive in the medullary segments. Urea is concentrated in the interstitium of the medulla and assists in the generation of maximally concentrated urine. (Used with permission of McGraw Hill LLC from Chonko AM et al. Treatment of edema states. In: Narins RG, ed. *Maxwell & Kleeman's Clinical Disorders of Fluid and Electrolyte Metabolism*. 5th ed. McGraw-Hill, 1994:545; permission conveyed through Copyright Clearance Center, Inc.)

Iso-osmotic reabsorption of the glomerular filtrate occurs in the proximal tubule such that two-thirds of the filtered sodium and water and 90% of the filtered bicarbonate are reabsorbed. The Na^+/H^+ antiporter (exchanger) in the luminal membrane is instrumental in the reabsorption of sodium chloride, sodium bicarbonate, and water. The reabsorption of most nonelectrolyte solutes, such as glucose, amino acids, and phosphates, are coupled to sodium transport.

Both the thick ascending limb of the Henle loop and the distal convoluted tubule serve as the diluting segments of the nephron because they are impermeable to water. Sodium chloride is extracted from the filtrate without water. Sodium transport in both of these segments is flow dependent and varies with the amount of sodium ions delivered from the proximal segments of the nephron. Decreased sodium ions in the tubular fluid will limit sodium transport in the thick ascending limb of the Henle loop and the distal convoluted tubule.

Reabsorption of sodium in the thick ascending limb of the Henle loop accounts for ~25% of the total sodium reabsorption. Sodium, chloride, and potassium are reabsorbed by the medullary and cortical portions of the ascending limb, but the leakage of reabsorbed potassium ions back into the tubular lumen, via potassium channels, makes the tubular lumen electropositive. This electrical gradient promotes the passive reabsorption of cations, such as sodium, calcium, and magnesium, in the distal convoluted

tubules. Because the thick ascending limb of the Henle loop is impermeable to water, it contributes to the interstitial osmolality in the medulla. This high osmolality is key to the reabsorption of water by the medullary portion of the collecting duct under the influence of antidiuretic hormone (ADH), or vasopressin. Therefore, the thick ascending limb of the Henle loop is important for both urinary concentration and dilution.

Because, as noted previously, the distal convoluted tubule is also impermeable to water, the osmolality of the filtrate continues to decline as sodium is being reabsorbed. In the distal convoluted tubule and collecting duct, sodium is reabsorbed in exchange for hydrogen ions and potassium. When sodium ions are reabsorbed, the tubule lumen becomes electronegative, which promotes potassium secretion in the lumen via potassium channels. Aldosterone enhances sodium reabsorption in the collecting duct by increasing the number of opened sodium channels.

The collecting duct is usually impermeable to water. Under the influence of ADH, however, water permeability is increased through an increase in the number of water channels along the luminal membrane. The amount of water reabsorbed depends on the tonicity of the medullary interstitium, which is determined by the sodium reabsorbed in the thick ascending limb of the Henle loop and urea.

Osmoregulation

A reduction in intracellular volume often increases effective plasma osmolality; conversely, decreased effective plasma osmolality is associated with cellular hydration. Water homeostasis is important in the regulation of plasma osmolality, and plasma tonicity is maintained within normal limits through a delicate balance between the rates of water intake and excretion.[1]

The amount of daily water intake includes the volume of water ingested (sensible intake), the water content of ingested food, and the metabolic production of water (insensible intake). To maintain homeostasis, these should be equal to the amount of water excreted

by the kidney and the gastrointestinal (GI) tract referred to as *sensible losses* plus water lost from the skin and respiratory tract known as *insensible losses*.

Changes in plasma tonicity are detected by osmoreceptors in the hypothalamus, which also houses the thirst center and is the site for ADH synthesis. When the plasma tonicity falls <280 mOsm/kg as a result of water ingestion, ADH release is inhibited, water is no longer reabsorbed in the collecting duct, and a large volume of dilute urine is excreted. Conversely, when the osmoreceptors in the hypothalamus sense an increased plasma osmolality, ADH is released to increase water reabsorption. A small volume of concentrated urine is then excreted. The threshold for ADH release is 280 mOsm/kg, and maximal ADH secretion occurs when the plasma osmolality is 295 mOsm/kg. Thus, urine osmolality varies from 50 mOsm/kg in the absence of ADH to 1200 mOsm/kg during maximal ADH release. As predicted, the volume of urine produced depends on the solute load to be excreted, as well as the urine osmolality:

$$\text{Urine volume (L)} = (\text{Solute load (mOsm)}/\text{Urine osmolality (mOsm/kg)}) \times (1/\text{Density of water (kg/L)}) \quad \textbf{(Eq. 27-5)}$$

Therefore, for a typical daily solute load of 600 mOsm:

$$= (600\ \text{mOsm}/50\ \text{mOsm/kg})(1/1\ \text{kg/L}) = 12\ \text{L (No ADH)} \quad \textbf{(Eq. 27-6)}$$

$$= (600\ \text{mOsm}/1200\ \text{mOsm/kg})(1/1\ \text{kg/L}) = 0.5\ \text{L (Max ADH)} \quad \textbf{(Eq. 27-7)}$$

Although the kidney has a remarkable ability to excrete free water, it is not as efficient in conserving water. ADH minimizes further water loss, but it cannot correct water deficits. Therefore, optimal osmoregulation requires increased water intake stimulated by thirst. Both ADH and thirst can be stimulated by nonosmotic stimuli. For

example, volume depletion is such a strong nonosmotic stimulus for ADH release that it can override the response to changes in plasma osmolality. Nausea, pain, and hypoxia are also potent stimuli for ADH secretion.[1]

Volume Regulation

The afferent sensors for the changes in the effective circulating volume are the intrathoracic volume receptors, the baroreceptors in the carotid sinus and aortic arch, and the afferent arteriole in the glomerulus.

When the effective circulating volume is decreased, both the renin– angiotensin–aldosterone and the sympathetic nervous systems are activated. Angiotensin type 2 (AT_2) and norepinephrine enhance sodium reabsorption at the proximal convoluted tubule. In addition, aldosterone stimulates sodium reabsorption at the collecting tubule. The decrease in effective arterial volume also stimulates ADH release, which enhances water reabsorption at the collecting duct. Conversely, after a salt load, the increases in atrial pressure and kidney perfusion pressure suppress the production of renin and, subsequently, AT_2 and aldosterone. The release of atrial natriuretic peptide secondary to increased atrial filling pressure and intrarenal production of urodilators increase urinary excretion of the excess sodium.[2]

Although the kidney can excrete a 20-mL/kg water load in 4 hours, only 50% of the excess sodium is excreted on the first day.[3] Sodium excretion continues to increase until a new steady state is reached after 3 to 4 days when intake equals output. It is important to recognize that osmoregulation and volume regulation occur independently of each other.[2,3] The two homeostatic systems regulate different parameters and possess different sensors and effectors. However, both systems can be activated simultaneously.

DISORDERS IN VOLUME REGULATION

Volume Depletion

CASE 27-2

QUESTION 1: A.B., a 17-year-old female, presented to the emergency department (ED) with anorexia, nausea, vomiting, and generalized weakness for the past 3 days. She denied other medical problems and had not used any medications. On examination, her supine blood pressure (BP) was 105/70 mm Hg, with a pulse of 80 beats/minute. Her standing BP was 85/60 mm Hg, with a pulse of 100 beats/minute, and she felt dizzy when she stood up. Her mucous membranes were dry, but her skin turgor was normal. Her jugular venous pressure was not elevated and peripheral or sacral edema was not present. Laboratory blood tests showed the following:

Na^+, 134 mEq/L
K^+, 3.5 mEq/L
Chloride (Cl^-), 95 mEq/L
Total CO_2, 35 mEq/L
BUN, 18 mg/dL
Creatinine, 0.8 mg/dL
Glucose, 70 mg/dL

Random urinary sodium was 40 mEq/L, potassium was 40 mEq/L, and chloride was <15 mEq/L. The hemoglobin was 14 g/dL, and white cell and platelet counts were normal.

Based on the clinical and laboratory data, what is the most probable explanation for A.B.'s presentation?

The signs and symptoms in A.B. are consistent with volume depletion. The loss of gastric fluid owing to vomiting and decreased oral intake secondary to anorexia led to moderate-to-severe volume depletion. She exhibits orthostatic changes in both her BP (a drop in systolic BP of 20 mm Hg) and pulse (an increase of 20 beats/minute). The dry mucous membranes, the nonelevated jugular vein pressure, and the absence of edema support volume depletion as well, and dizziness on standing indicates extracellular volume depletion. Her hypochloremic metabolic alkalosis was probably

initiated by the loss of acidic gastric contents through vomiting. Her volume depletion increased bicarbonate reabsorption by the kidneys, perpetuating the metabolic alkalosis. The decreased kidney perfusion brought about by volume depletion enhanced proximal tubular reabsorption of urea, resulting in an increased BUN-to-creatinine ratio suggestive of prerenal azotemia. When kidney perfusion is decreased and the renin–angiotensin–aldosterone system is activated, the proximal reabsorption of sodium and chloride is increased. Excretion of the poorly permeable bicarbonate ions, however, results in obligatory urinary sodium loss to maintain luminal electroneutrality. A.B.'s urinary sodium was therefore elevated (40 mEq/L). In this situation, the urinary chloride remained low, and this is a better index of volume status.[3] Both urinary sodium and chloride are elevated, however, in patients using diuretics, in those undergoing osmotic diuresis, and in those with underlying kidney disease or hypoaldosteronism, even in the face of volume depletion. Physical examination should therefore be conducted as part of the volume status assessment. A.B.'s volume depletion increased the concentration of red blood cells, which could explain her slightly elevated hemoglobin concentration of 14 g/dL.

CASE 27-2, QUESTION 2: How should A.B.'s volume depletion be managed?

The etiology of A.B.'s vomiting should be sought, and the cause removed. Because the patient is neither hypernatremic nor hyponatremic, 0.9% sodium chloride should be administered via intravenous (IV) infusion to replenish the extracellular volume and improve tissue perfusion. If the patient is hypernatremic (having a greater deficit of water than of solute), 0.45% sodium chloride or dextrose in 5% water (D5W), which contains more free water, should be administered. In contrast, patients with hyponatremic hypovolemia have a greater deficit of solute than of water; 0.9% sodium chloride or hypertonic saline such as 3% sodium chloride should then be given. The amount of volume deficit is often difficult to ascertain. Because A.B. was severely orthostatic, 1 or 2 L of 0.9

% sodium chloride can be given over the course of 2 to 4 hours. The subsequent rate of infusion will depend on A.B.'s response and the prevailing symptoms. The clinician should monitor her body weight, skin turgor, supine and upright BP, jugular venous pressure, urine output, and urine chloride concentration to assess the adequacy of volume repletion. Because the treatment goal is to achieve a positive fluid balance where fluid intake is more than fluid output, the infusion rate should be 50 or 100 mL/hour in excess of the sum of urine output, insensible losses, and other losses, such as emesis and diarrhea (eg, 200–300 mL/hour), until the patient is hemodynamically stable.[4]

Volume Excess

CASE 27-3

Question 1: L.J., a 45-year-old male, presented to the clinic with swollen legs and puffy eyelids. He also noticed that his urine had been foamy recently. On examination, his BP was 180/100 mm Hg, and his pulse was 80 beats/minute. Bilateral periorbital edema and 2+ bilateral pitting edema up to the thigh were noted. On auscultation, his heart was normal, and his lungs had bilateral crackles. His jugular venous pressure was elevated at 10 cm H_2O. Laboratory blood tests revealed the following:

Serum Na^+, 132 mEq/L
K^+, 3.8 mEq/L
Cl^-, 100 mEq/L
Total CO_2, 26 mEq/L
BUN, 40 mg/dL
Creatinine, 2.5 mg/dL
Glucose, 120 mg/dL
Albumin, 2 g/dL
Serum cholesterol, 280 mg/dL,
Triglycerides, 300 mg/dL

The serum transaminases, alkaline phosphatase, and bilirubin were within normal limits. Urinalysis showed the following:

Specific gravity, 1.015
Random urinary sodium, 20 mEq/L
pH, 7.0

Protein, >300 mg/dL
24-hour urinary protein excretion, 6 g
Creatinine clearance (CrCl), 40 mL/minute

Urinalysis also showed oval fat bodies and fatty casts. L.J. was taking no medications and he denied illicit drug use. Hepatitis B serology and human immunodeficiency virus (HIV) antibody test results were negative. The impression was anasarca (total body edema) secondary to nephrotic syndrome.

What is nephrotic syndrome? What could be the cause of L.J.'s volume excess state?

Nephrotic syndrome is characterized by hypoalbuminemia, urine protein excretion >3.5 g/day, hyperlipidemia, lipiduria, and edema.[5] The heavy proteinuria is a result of damage to the selective barrier of the glomerulus. The causes of nephrotic syndrome are multiple and diverse. The causes can be idiopathic (primary glomerular disease) or secondary to chronic systemic diseases (eg, diabetes mellitus, amyloidosis, sickle cell anemia, lupus), cancer (eg, multiple myeloma, Hodgkin disease), infections (eg, HIV, hepatitis B, syphilis, malaria), IV drug abuse, and medications (eg, gold, penicillamine, captopril, nonsteroidal anti-inflammatory drugs [NSAIDs]).

A heavy urinary protein loss results in various extrarenal complications.[6] Hypoalbuminemia reduces plasma oncotic pressure and contributes to the increased hepatic synthesis of both albumin and lipoproteins. This, coupled with the decreased catabolism of lipoproteins, resulted in L.J.'s hyperlipidemia. Urinary loss of inhibitors of coagulation predisposes these patients to thromboembolism.

Specific therapy of nephrotic syndrome ranges from simple removal of the offending medication and treatment of the underlying comorbidities to the use of immunosuppressive agents in specific glomerular diseases.

L.J.'s anasarca results from changes in both capillary hemodynamics and sodium and water retention.[6] The hypoalbuminemia (2 g/dL) and proteinuria (>300 mg/dL) produce an imbalance in the Starling forces across the capillary wall, namely, the hydrostatic and oncotic pressures in the capillary and interstitial compartments. The reduced capillary oncotic pressure favors the

movement of fluid from the vascular space into the interstitium. This leads to contraction of the effective arterial blood volume, which in turn activates humoral, neural, and hemodynamic mechanisms that signal the kidney to retain sodium and water. This underfill hypothesis has been challenged by data, suggesting that hypoalbuminemia plays a minor role in nephrotic edema and the observation that patients with nephrotic syndrome can have increased, normal, or decreased plasma volumes.

A defect in the intrarenal sodium handling mechanism that causes inappropriate sodium retention also contributes to nephrotic edema.[6] According to this overflow hypothesis, proteinuric kidney disease leads to increased sodium reabsorption in the distal nephron. The mechanism is not well defined but may be related to cellular resistance to atrial natriuretic peptide. It is likely that the interaction between the underfill and overflow mechanisms results in the production of nephrotic edema. Patients with severe hypoalbuminemia (ie, serum albumin level <1.5 g/dL), who have a severe reduction in plasma oncotic pressure, are most likely to exhibit evidence of the underfill phenomenon.

CASE 27-3, QUESTION 2: How should L.J.'s volume excess state be managed?

DIURETICS

Usually, loop diuretics are the mainstay of therapy in the management of nephrotic edema.[6] In most of these patients, the edema can be removed safely with rapid diuresis without compromising the systemic circulation, probably because of the rapid refilling of the plasma volume by interstitial fluid. IV diuretics are usually initiated in severe edema. As the edema resolves, the rate of fluid removal and weight loss should be decreased to avoid compromising the effective circulating volume, and IV diuretics may be switched to the oral route. The patient should be monitored for the development of orthostatic hypotension while on diuretic therapy.

Infusions of albumin can expand the plasma volume; however, it is expensive, the relief is temporary, and it should therefore be used

only for resistant edema.[6] In patients who are resistant to the aforementioned measures, extracorporeal fluid removal, namely, ultrafiltration, may be necessary.

In addition, bed rest reduces orthostatic stimulation of the renin–angiotensin–aldosterone and sympathetic systems, thereby favoring the movement of interstitial fluid into the vascular space. The central blood volume is thus increased, and natriuresis and diuresis are facilitated. Prolonged bed rest might, however, predispose these patients who are hypercoagulable to thromboembolism. Similarly, use of support stockings may reduce the stimulation for sodium retention by redistributing blood volume to the central circulation.

L.J. was initially treated with IV furosemide 60 mg twice daily and placed on a low-sodium (50 mEq), low-fat, high–complex carbohydrate diet that consisted of 0.8 g/kg protein of high biologic value with additional protein to match gram-per-gram of urinary protein loss. Fluid was restricted to 1000 mL/day.[7] He had 5 L of diuresis in 2 days, with resolution of respiratory symptoms and a reduction in the anasarca. Parenteral furosemide was discontinued on the fifth day of hospitalization and oral furosemide 120 mg twice daily was started (conversion of IV to oral furosemide is often done based on a 1:2 conversion ratio). After a total weight loss of 24.45 pounds (12 kg), he was discharged with instructions to maintain strict water and dietary sodium intake, as well as daily weight monitoring for further adjustment in his furosemide dose.

SODIUM DISORDERS

Sodium resides almost exclusively in the ECF; the amount of total body sodium, therefore, determines the extracellular volume.[1] Because daily sodium intake varies from 100 to 250 mEq, the body must rely on adjustments in urinary sodium excretion to maintain the extracellular volume and tissue perfusion. The ability of the kidney to retain sodium is so remarkable that a person can survive with a daily sodium intake of as low as 20 to 30 mEq.

Hyponatremia

Serum sodium concentration reflects the ratio of total body sodium to TBW and is not an accurate indicator of total body sodium.

Because the kidney can excrete >12 to 16 L of free water daily, hyponatremia does not occur unless the water intake overwhelms the kidney's ability to excrete free water (eg, psychogenic polydipsia),[1] or free-water excretion is impaired.

Free-water formation requires a normal glomerular filtration rate (GFR), the reabsorption of sodium chloride without water in the thick ascending limb of the Henle loop and the distal convoluting tubule, and the excretion of dilute urine in the absence of ADH (see Fig. 27-1). Therefore, hyponatremia can occur when the kidney's diluting ability is exceeded or impaired owing to volume depletion and nonosmotic stimulation of ADH release or inappropriate stimulation of ADH production.

Although plasma sodium is the primary determinant of plasma tonicity, hyponatremia does not always represent hypotonicity. In patients with severe hyperlipidemia or hyperproteinemia (eg, multiple myeloma), pseudohyponatremia can occur because the increased amounts of lipids and proteins displace plasma water, in which sodium ions dissolve, resulting in a lower concentration of sodium per unit volume of plasma. Normally, water accounts for 93% of the plasma volume, and lipids and proteins make up the rest. The increase in plasma lipid and protein contents expands plasma volume, displaces water, and increases the percentage of solids in plasma, resulting in isotonic hyponatremia. Hyponatremia resulting from severe hyperlipidemia and hyperproteinemia is sometimes also referred to as *pseudohyponatremia*. Another example of isotonic hyponatremia can be found when a large volume of isotonic sodium-free solution is infused (eg, when mannitol irrigant is used during prostate surgery); see **Table 27-1**.

Table 27-1
Clinical Presentation and Treatment of Hyponatremia

Na^+ and H_2O Status	Clinical Presentation/Cause	Treatment
Edematous, Fluid Overload (Hypervolemic, Hypotonic)		
↑ Total body Na^+–↑↑ Total body H_2O	Cirrhosis/HF/nephrotic syndrome: A ↓ in kidney blood flow activates renin–angiotensin system. ↑ Aldosterone leads to ↑ Na^+, and ↑ ADH leads to free H_2O retention. Urine Na^+ is low (0–20 mEq/L) and urine osmolality ↓. Diuretics can induce paradoxical effects on urine Na^+ and osmolality. This form can also occur in patients with renal failure who drink excessive amounts of water. Patients have symptoms of fluid overload (ascites, distended neck veins, edema).	Fluid and Na^+ restriction. Correct underlying disorder (eg, paracentesis for ascites). Diurese cautiously[a]; avoid ↓ ECF and accompanying ↓ tissue perfusion. ↑ BUN may indicate overly rapid diuresis. Conivaptan: Loading dose of 20 mg IV for 30 minutes, followed by 20 mg IV as continuous infusion for 24 hours for an additional 1–3 days; may titrate up to maximal dose of 40 mg/day; maximal duration is 4 days after the loading dose. Dedicated IV line is recommended and site of peripheral IV lines should be changed every 24 hours. Caution if used together with fluid restriction. Tolvaptan: Start 15 mg PO once daily. Dose may be increased at intervals of at least 24 hours to 30 mg PO once daily and then to a maximum of 60 mg PO once daily as needed. Caution if used together with fluid restriction. Initiate therapy in a hospital setting.
Nonedematous Hypovolemic (Hypotonic With Extracellular Fluid Depletion)		

Na^+ and H_2O Status	Clinical Presentation/Cause	Treatment
↓↓ Total body Na^+ ↓ Total body H_2O	Occurs in GI fluid loss (eg, diarrhea) with hypotonic electrolyte-poor fluid replacement, overdiuresis, "third spacing," Addison disease, renal tubular acidosis, osmotic diuresis. Replacement of fluid losses with solute-free fluid predisposes these patients to hyponatremia. Kidneys concentrate urine to conserve fluid (urine Na^+ < 10 mEq/L). Symptoms: nonedematous; ECF depletion (collapsed neck veins, dehydration, orthostasis). Neurologic symptoms (see sections Hyponatremia and Neurologic Manifestations in text).	Discontinue diuretics. Replace fluid and electrolyte (especially K^+) losses. Saline 0.9% preferred unless Na^+ deficit[a] severe, then use 3%–5% saline.
Nonedematous, Normovolemic (Euvolemic, Hypotonic)		
↓ Total body Na^+ ↑ Total body H_2O	SIADH[b]: Hyponatremia, hypo-osmolality, kidney Na^+ wasting (>40 mEq/L), absence of fluid depletion, U_{osm} > P_{osm}, normal kidney and adrenal function. Free H_2O retained while Na^+ lost. *Causes:* (a) ADH production (infectious disease, vascular disease, cerebral neoplasm, cancer of lung, pancreas, duodenum); (b) exogenous ADH administration; (c) drugs; (d) psychogenic polydipsia.	See earlier text for dosing of VRA (conivaptan and tolvaptan) Chronic treatment: Restrict fluids to less than urine loss. Demeclocycline (300–600 mg bid) induces reversible diabetes insipidus. Emergency treatment for unresponsive patients includes furosemide diuresis to achieve negative H_2O balance with careful replacement of Na^+ and K^+ using hypertonic saline solutions.[c]

ADH, antidiuretic hormone; bid, twice daily; BUN, blood urea nitrogen; ECF, extracellular fluid; GI, gastrointestinal; HF, heart failure; IV, intravenous; NS, normal saline (0.9% sodium chloride); PO, orally; SIADH, syndrome of inappropriate antidiuretic hormone; TBW, total body weight; VRA, vasopressin receptor antagonist.

[a]Remove estimated excess free water with intravenous (IV) furosemide (1 mg/kg). Repeat as necessary. Because furosemide generates urine that resembles 0.5% NaCl, urine losses of sodium and potassium must be carefully measured and replaced hourly with hypertonic salt solutions. Correction rate: 1 to 2 mEq Na/hour in symptomatic patients; 0.5 mEq/hour in asymptomatic patients.

[b]Estimate sodium deficit: (mEq) = total body water (TBW) (sodium desired − sodium observed). Rate of sodium and fluid repletion used depends on severity. Mild: replace with normal saline (NS). First one-third for 6 to 12 hours at a rate of <0.5 mEq/L/hour, remaining two-thirds for 24 to 48 hours. Severe (eg, seizures): Use 3% to 5% saline, rate gauged by patient's ability to tolerate sodium and volume load. Monitor central nervous system function, skin turgor, blood pressure (BP), urine sodium, signs of sodium or water overload, especially in patients with cardiovascular, kidney, and pulmonary disease.

[c]Total body water (TBW) = 0.6 L/kg × weight in kg (for males) and 0.5 L/kg × weight in kg (for females).

TBW excess = TBW − [TBW (observed serum sodium)/(desired serum sodium)].

Neurologic Manifestations

As the plasma osmolality declines, the osmotic gradient created across the blood–brain barrier favors the movement of water into the brain and other cells. Water movement from the cerebrospinal fluid into the cerebral interstitium results in cerebral edema. Brain swelling is limited by the meninges and cranium, however, giving rise to increased intracranial pressure and neurologic symptoms. The degree of cerebral overhydration and the rapidity of its development appear to correlate with the severity of symptoms.

When hyponatremia develops in <2 to 3 days or the rate of decline in serum sodium is >0.5 mEq/L/hour, the situation is regarded as acute.[8,9] The patient often becomes symptomatic when serum sodium concentration falls to 125 mEq/L; early presentation include nausea, vomiting, and malaise.[8,9] Severe symptoms occur more commonly when the serum sodium falls to <120 mEq/L and the rate of decline is >0.5 mEq/L/hour. The patient may present with headache, tremors, incoordination, delirium, lethargy, and obtundation. As the serum sodium drops <110 to 115 mEq/L, seizure and coma may result.[9] On occasion, severe brain edema leads to

transtentorial herniation and, eventually, death. Females, especially those who are premenopausal, apparently are more susceptible to the development of severe neurologic symptoms and irreversible neurologic damage than are males.[10]

In contrast to acute hyponatremia, patients who are chronically hyponatremic are usually asymptomatic. If present, symptoms are usually vague and nonspecific and tend to occur at lower serum sodium concentrations than do those associated with symptomatic acute hyponatremia.[9] The patient may experience anorexia, nausea, vomiting, muscle weakness, and cramps. Irritability, hostility, confusion, and personality changes may also be seen. At extremely low sodium levels, stupor and, rarely, seizures have been reported.

Brain Adaptation to Hyponatremia

The difference in symptoms between acute and chronic hyponatremia is related to cerebral adaptation to hypotonicity.[8,9] Two adaptive mechanisms are important in minimizing cerebral edema. First, cerebral overhydration increases the hydrostatic pressure in the cerebral interstitium, which results in the movement of fluid from the cerebral interstitial space to the cerebrospinal fluid. Second, the extrusion of intracellular solutes reduces cellular osmolality, which in turn enhances water movement out of the cells. Sodium and potassium ions are the initial solutes extruded, followed over a period of hours to days by osmolytes such as inositol, glutamine, glutamate, and taurine.[11] Therefore, when the serum sodium concentration falls faster than the onset of brain osmotic adaptation processes, serious and permanent neurologic damage can occur.[8,9,11] On the other hand, when hyponatremia develops over the course of 2 to 3 days, symptoms are not usually seen unless the serum sodium concentration is reduced markedly.

It is often difficult to determine the acuity and chronicity of hyponatremia. Unless an obvious cause for acute hyponatremia is found, assume that the condition is chronic. A rapid decline in serum sodium concentration usually suggests that hypotonic fluid was

administered to a patient with a condition that overwhelms or impairs water excretion. These conditions include psychogenic polydipsia[12]; postoperative hyponatremia[10]; postprostatectomy syndrome[13]; and administration of thiazide diuretics,[14] parenteral cyclophosphamide,[15] oxytocin,[16] and arginine vasopressin (AVP) or its analogs.[17]

CASE 27-4

QUESTION 1: T.T., a 63-year-old male with kidney failure secondary to diabetic kidney disease, is receiving chronic ambulatory peritoneal dialysis. Because of dietary and fluid noncompliance, T.T. reported shortness of breath (SOB), and his dialysis prescription was adjusted to include six cycles of 2.5% peritoneal dialysis solutions daily. Today, his blood laboratory values are as follows:

Na^+, 128 mEq/L
K^+, 4 mEq/L
Cl^-, 98 mEq/L
Total CO_2, 24 mM
BUN, 50 mg/dL
Creatinine, 6 mg/dL
Glucose, 600 mg/dL
Evaluate T.T.'s plasma osmolality.

What is T.T.'s plasma osmolality?

T.T.'s effective plasma osmolality is calculated to be 289 mOsm/L, according to Eq. 27-1, of which 33 mOsm/L is contributed by hyperglycemia. The slow utilization of glucose, because of the lack of insulin, causes water to move from the intracellular compartment into the plasma space because of the increased tonicity, thereby lowering the plasma sodium concentration.[4] Despite the lowered plasma sodium concentration, the plasma osmolality is normal because of hyperglycemia. Hence, no symptoms attributable to hypo-osmolality are observed. Indeed, when serum glucose is normalized with insulin and hydration, the serum sodium level will increase to ~136 mEq/L. For each 100-mg/dL increment in serum glucose, serum sodium decreases by 1.3 to 1.6 mEq/L.[4]

Hypotonic Hyponatremia With Decreased Extracellular Fluid

CASE 27-5

Question 1: Q.B., a 30-year-old male athlete who has had multiple bouts of diarrhea for the past several days, has been drinking a sports drink to keep himself from getting dehydrated. His vital signs include supine BP, 145/80 mm Hg, and pulse, 70 beats/minute; standing BP, 128/68 mm Hg, and pulse, 90 beats/minute. Respiratory rate (RR) is 12 breaths/minute, and he is afebrile. His skin turgor is mildly decreased, and laboratory blood data are the following:

Na^+, 128 mEq/L
K^+, 3.0 mEq/L
Cl^-, 100 mEq/L
Total CO_2, 17 mEq/L
BUN, 27 mg/dL
Creatinine, 1.2 mg/dL

Urinary sodium and chloride were both <10 mEq/L. Assess Q.B.'s electrolyte and fluid status.

What is the etiology of Q.B.'s hyponatremia?

Q.B. has true hypotonic hyponatremia with ECF depletion, suggesting that his total body sodium deficit is greater than that of TBW. His poor skin turgor, orthostasis, prerenal azotemia, and low urinary sodium are consistent with volume depletion. The urinary sodium concentration helps distinguish between kidney and non-kidney losses that result in sodium and water deficits. When the plasma volume is depleted, the urinary sodium concentration is <10 mEq/L, suggesting appropriate sodium conservation. This is usually seen in patients such as Q.B. with GI fluid loss as in vomiting, diarrhea, or profuse sweating.

Other causes of hypotonic hyponatremia are less likely in Q.B. They include surreptitious cathartic abuse and "third spacing," or accumulation of ECF in the abdominal cavity during acute pancreatitis, ileus, or pseudomembranous colitis.[4] If the urinary sodium is <20 mEq/L in the face of volume depletion, salt wastage should be considered.[4] The potential causes of this latter problem

include diuretic use,[14,18] adrenal insufficiency,[18] and salt-wasting nephropathy[12] (eg, chronic interstitial nephritis, medullary cystic disease, polycystic kidney disease, obstructive uropathy, and cisplatin toxicity).[18] In patients with kidney insufficiency, neither the urinary sodium nor chloride concentration is a reliable index of volume status.[3]

Volume depletion leads to increased reabsorption of sodium and water in the proximal tubule and, thus, decreased sodium delivery to the diluting segments for free-water formation.[4] Decreased effective arterial volume is also a potent nonosmotic stimulus for ADH release. These factors combine to dampen the ability of the kidney to form dilute urine and result in high urine osmolality despite a low serum sodium concentration. Although the fluid lost in diarrhea is hypotonic, it is the replacement of fluid lost with an even more hypotonic fluid such as the sports drink or tap water that causes hyponatremia in patients such as Q.B.

Q.B.'s diarrhea probably caused loss of potassium and bicarbonate through the GI tract, resulting in hypokalemia and hyperchloremic metabolic acidosis. The potassium depletion can sensitize ADH secretion in response to hypovolemic stimuli, and the hypokalemia can also lead to hyponatremia. The cellular efflux of potassium causes cellular uptake of sodium, further reducing the serum sodium concentration.

Case 27-5, Question 2: How should Q.B.'s hyponatremia be treated?

The treatment of hypovolemic hyponatremia involves sodium replacement to correct the deficit. The sodium deficit can be estimated by the following formula:

$$\text{Na deficit} = \text{TBW} \times (\text{Desired} - \text{Current Na concentration})$$

$$= 0.6\frac{\text{L}}{\text{kg}} \times 70\ \text{kg} \times (140 - 125\ \text{mEq/L})$$

$$= 630\ \text{mEq}$$

(Eq. 27-8)

Recall that TBW = 0.6 L/kg × weight in kg for males and 0.5 L/kg × weight in kg for females.

Approximately one-third of the deficit can be replaced over the course of the first 12 hours at a rate of <0.5 mEq/L/hour. The remaining amounts can be administered over the course of the next several days.

The use of isotonic sodium chloride solution is ideal for the treatment of hyponatremia associated with volume depletion. As kidney perfusion is restored, free water will be excreted with appropriate retention of sodium. Because Q.B. has only mild volume depletion, oral rehydration salts may also be considered. Oral rehydration salts contain a mixture of electrolytes (salts) and carbohydrates (in the form of glucose) and are ideal for the management of persistent fluid loss in the outpatient setting. Glucose not only provides calories but also promotes the intestinal absorption of ingested sodium.

When hypokalemia occurs concurrently with hyponatremia, potassium replacement should be given to correct hypokalemia because this will help correct and reverse the accompanying hyponatremia. When this happens, the serum sodium concentration may rise faster than expected because as tissue perfusion is restored, sodium delivery to the distal tubules will increase and ADH secretion will be suppressed appropriately. In the absence of ADH, increased free-water excretion will improve the serum sodium concentration faster than is initially estimated.

In patients with chronic kidney salt wasting resulting in hyponatremia, the ongoing daily sodium loss should also be taken into consideration when estimating the amount of replacement.

Hypervolemic Hypotonic Hyponatremia

CASE 27-6

QUESTION 1: T.W., a 55-year-old male with a longstanding history of alcoholic liver cirrhosis, is admitted to the hospital for worsening SOB. His medical history includes portal hypertension, esophageal varices, and noncompliance with dietary restriction and medications. His BP is 120/60 mm Hg; pulse, 100 beats/minute; and RR, 20 breaths/minute. He is afebrile. Physical examination reveals a jaundiced male in respiratory distress. His jugular vein is flat and lung examination reveals bilateral basal rales. Abdominal examination shows tense ascites with hepatomegaly and spider angiomas (telangiectasias resembling a spider). He has 1+ pedal edema bilaterally. Laboratory data on admission are as follows:

Serum Na^+, 127 mEq/L
K^+, 3.4 mEq/L
Cl^-, 95 mEq/L
Total CO_2, 24 mEq/L
BUN, 10 mg/dL
SCr, 1.2 mg/dL
Albumin, 2.5 g/dL
Urine Na, <10 mEq/L
Urine osmolality, 380 mOsm/L

Identify the possible causes of hyponatremia in T.W. and discuss its pathophysiology.

How should he be treated?

T.W. had no history of vomiting or diarrhea and had stopped using diuretics before admission. The physical findings of ascites and bilateral edema are not consistent with volume depletion but indicate a sodium- excess state. Both sodium and water retention occur, but the disproportionate accumulation of ingested water relative to sodium leads to hyponatremia.

Patients with cirrhosis who are susceptible to developing hyponatremia have a decreased effective arterial blood volume.[19,20] The low urinary sodium concentration suggests that the effective arterial blood volume was decreased. The high urinary osmolality in the face of hypotonic hyponatremia suggests, however, that the

release of ADH has been stimulated, impairing free-water excretion. Peripheral vasodilation causes decreases in systemic arterial BP despite a normal-to-high cardiac output. This, along with splanchnic venous pooling and decreased oncotic pressure secondary to hypoalbuminemia, decreases kidney perfusion in patients with cirrhosis, such as T.W.[19] Decreased kidney perfusion activates the renin–angiotensin–aldosterone system, the sympathetic nervous system, and the release of ADH. Reabsorption of sodium and water in the proximal tubules is enhanced, diminishing sodium and water delivery to the distal segments of the nephron. The diluting capacity of the kidney is thus impaired. Increased secretion of ADH also promotes free-water reabsorption at the collecting tubule and contributes to the hyperosmolality of urine and hyponatremia. Hypervolemic hyponatremia is also seen in patients with heart failure (HF) and nephrotic syndrome and in patients with chronic kidney disease who drink excessive amounts of water[4] (see Chapter 14, Heart Failure). As the GFR decreases, distal delivery of sodium is reduced and the ability to generate free water is impaired. In addition, the capacity to conserve sodium is impaired in these patients.[3]

Most patients who are edematous and hyponatremic are asymptomatic, but the degree of hyponatremia probably reflects the severity of the underlying disease.[19,20] Unless an acute decrease in serum sodium occurs, rapid therapeutic correction is not warranted.[19,20] Water restriction, the mainstay of therapy, is determined by the degree of hyponatremia and the severity of symptoms. Sodium restriction and judicious use of diuretics may help reduce the edematous state, but the patient must be monitored closely to avoid prerenal azotemia, which suggests overaggressive diuresis. Furthermore, diuretics can induce or worsen hyponatremia and volume depletion by impairing the diluting capacity of the kidney.[19,20]

T.W. had abdominal paracentesis to relieve respiratory discomfort with no sequelae. He was then prescribed a 1000-mg sodium diet, and water was restricted to 500 mL/day. Diuretic therapy was resumed.

CASE 27-7

Question 1: C.C., a 50-year-old male who was diagnosed recently with small-cell lung carcinoma, was brought to the ED by his family because he had become progressively lethargic and stuporous during the past week. Laboratory data revealed the following:

Serum Na^+, 110 mEq/L
K^+, 3.6 mEq/L
Cl^-, 78 mEq/L
Total CO_2, 22 mEq/L
BUN, 10 mg/dL
SCr, 0.9 mg/dL
Glucose, 90 mg/dL
Serum osmolality, 230 mOsm/kg
Urine osmolality, 616 mOsm/kg
Urine Na, 60 mEq/L

Arterial blood gas (ABG) examination at room air showed pH, 7.38; $Paco_2$, 38 mm Hg; and Pao_2, 80 mm Hg. On physical examination, C.C. was normotensive, appeared to be euvolemic, and had no edema detected. Review of his medical records showed normal adrenal and thyroid function. C.C. was currently not using any medications. On admission to the ward, C.C. weighed 132.28 pounds (60 kg) and was given 1 L of 0.9 % sodium chloride (normal saline), after which his serum sodium concentration was 108 mEq/L. Identify the cause of hyponatremia in C.C.

What is its pathophysiology?

Euvolemic Hypotonic Hyponatremia

In a patient with hypotonic hyponatremia with a volume status that is apparently normal, the differential diagnosis includes hypothyroidism, cortisol deficiency, a reset osmostat, psychogenic polydipsia, and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, which is a diagnosis of exclusion.[4] C.C.'s normal thyroid and adrenal function tests exclude hypothyroidism and cortisol insufficiency as causes of his hyponatremia. The inappropriately elevated urine osmolality (>100 mOsm/kg) is inconsistent with psychogenic polydipsia or a reset osmostat, because free-water excretion is usually not impaired in these disorders. These findings, in addition to a urine sodium concentration

>40 mEq/L and a normal acid–base and potassium balance, are consistent with SIADH.

In SIADH, the ADH secretion is considered inappropriate because of its persistence in the absence of appropriate osmotic and hemodynamic stimuli. Water ingestion is essential to the development of hyponatremia in SIADH because persistent ADH activity impairs water excretion, resulting in the expansion of body fluids and hypotonic hyponatremia. Edema rarely is apparent because only one-third of the retained water resides in the extracellular space and the sodium homeostatic mechanisms are intact. The ECF expansion activates volume receptors and results in natriuresis. At steady state, urinary sodium excretion reflects sodium intake and is usually >40 mEq/L, as in C.C.'s case. Nonetheless, if sodium intake is reduced severely, the urinary sodium concentration may become <40 mEq/L.

The causes of SIADH are diverse and are shown in Table 27-1. Drug-induced SIADH may occur in patients taking certain medications. These include selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine; antiepileptics, such as phenytoin, carbamazepine, and oxcarbazepine; chlorpropamide; indomethacin; diuretics; and clofibrate.[4,21] Mechanisms for drug-induced SIADH include ADH-like action on the collecting tubule, central stimulation of ADH release, and potentiation of the ADH effect.[21]

The most likely cause of C.C.'s SIADH is his small-cell lung carcinoma that results in ADH production.

Case 27-7, Question 2: Why was C.C.'s serum sodium concentration lower after the 0.9% sodium chloride infusion?

Isotonic sodium chloride solution contains 154 mEq/L each of sodium and chloride ions, or 308 mOsm/L. Initially, it will increase the plasma sodium concentration because its osmolality is higher than that of C.C.'s. C.C., however, has a relatively fixed urine osmolality of 616 mOsm/kg owing to persistent ADH activity; thus, he must excrete an osmolar load of 616 mOsm in a volume of 1000 mL of

urine at steady state. Because a total of 1 L of fluid containing 308 mOsm was administered, all the solutes were excreted in 500 mL of urine output, and 500 mL of free water was retained to cause a further dilution of sodium and a reduction in serum sodium concentration.

Rate of Correction of Hyponatremia

CASE 27-7, QUESTION 3: How should C.C.'s hyponatremia be managed?

C.C.'s symptoms appear to have developed over the course of 7 days and are consistent with chronic hyponatremia. C.C.'s water excess should be calculated to estimate the amount of water that should be removed to achieve the desired sodium concentration.

$$\text{Water excess} = \text{TBW} - \text{TBW}\,(\text{Observed serum Na}/\text{Desired serum Na}) = 36\ \text{L} - 36\ \text{L}\,(110\ \text{mEq/L}/120\ \text{mEq/L}) = 3.0\ \text{L} \quad \textbf{(Eq. 27-9)}$$

where

$$\text{TBW} = 0.6\ \text{L/kg} \times 60\ \text{kg} = 36\ \text{L} \quad \textbf{(Eq. 27-10)}$$

The treatment of hyponatremia has been controversial. Severe hyponatremia is associated with high rates of morbidity and mortality, but its treatment can also result in morbidity. The rate of correction has been implicated as the main cause of complications.[4,22–25]

It takes time for the brain to lose osmolytes to reduce cerebral swelling during hyponatremia; conversely, the rate of reaccumulation of these osmolytes must keep pace with the rise in serum sodium concentration to avoid brain dehydration and damage. Indeed, rapid correction of hyponatremia can cause a constellation of neurologic findings known as *osmotic demyelination syndrome (ODS)*. Clinical manifestations usually are delayed and occur 1 day to several days after the treatment has been started. Neurologic findings include

transient behavioral changes, seizures, akinetic mutism in mild cases, and features of a pontine disorder in severe cases (pseudobulbar palsy, quadriparesis, and coma). In some patients, the damage is irreversible, and central pontine myelinolysis can be documented in fatal cases. Patients at greatest risk for osmotic demyelination are those with severe hyponatremia lasting >2 days and those in whom the rate of correction of hyponatremia is >12 mEq/L in any 24-hour period.[4,22–25] Hypokalemia, which was found in about 90% of patients with ODS associated with rapid hyponatremia correction, has been suspected as a predisposing factor in the development of ODS.[26] This is because correction of hypokalemia often increases serum sodium concentration; and if clinicians do not take this into consideration when determining the rate and amount of sodium repletion, overcorrection may occur, resulting in ODS. The increase in serum sodium concentration from potassium repletion alone thus needs to be factored in when treating hyponatremia.

Retrospective reviews suggest that acute hyponatremia can be treated safely at a rate of 1 mEq/L/hour initially until the serum sodium concentration reaches 120 mEq/L. Thereafter, the rate of correction should be reduced to ≤0.5 mEq/L/hour, such that an increment in sodium concentration does not exceed 12 mEq/L in the first 24 hours.[4] Although limited, more recently available literature also suggests that an increase in serum sodium of 4 to 6 mEq/L in 1 to 2 hours is adequate to reverse serious complications associated with acute hyponatremia.[4,27] Slow correction is indicated for severe chronic hyponatremia. No neurologic complications were seen in patients with severe hyponatremia when the average rate of correction to serum sodium was <0.55 mEq/L/hour or when the increase in serum sodium was <12 mEq/L in 24 hours or <18 mEq/L in 48 hours. For patients at high risk for developing ODS such as patients with chronic hyponatremia or quickly rising serum sodium, a slower correction in serum sodium of 4 to 6 mEq/L in 24 hours is recommended.[22]

C.C.’s symptoms appear to have developed over the course of 7 days and are consistent with chronic hyponatremia. Thus, his serum sodium concentration should be raised to ~120 mEq/L at a

correction rate of ~0.5 mEq/L/hour, using 3% sodium chloride and furosemide. Serum sodium concentrations should be monitored closely because the equation for calculating water excess does not take into account insensible loss, which can increase the rate of sodium correction.[28]

The use of normal saline is not suitable for C.C. because he excretes salt normally (urine sodium, 60 mEq/L). C.C.'s sodium deficit is as follows:

$$(0.6\ \mathrm{L/kg})(60\ \mathrm{kg})(120 - 110\ \mathrm{mEq/L}) = 360\ \mathrm{mEq} \qquad \textbf{(Eq. 27-11)}$$

Because 1 L of 3% sodium chloride solution contains 513 mEq of sodium, ~700 mL of 3% sodium solution, which contains 360 mEq of sodium, will be required to correct the sodium deficit. The recommended serum sodium concentration correction rate is 0.5 mEq/L/hour; therefore, a minimum of 20 hours will be needed to raise the serum sodium concentration by 10 mEq/L (from 110 to 120 mEq/L). The amount of sodium replacement to safely increase the serum sodium concentration can be determined by the product of the rate of replacement (0.5 mEq/L/hour) and TBW (36 L, Eq. 27-10)—that is, 18 mEq/hour. The maximal rate of infusion of 3% saline, which contains 0.513 mEq/mL of sodium, is therefore 35 mL/hour (18 mEq/hour)/(0.513 mEq/mL). A rate of 30 mL/hour, therefore, is appropriate to safely replace C.C.'s sodium deficit.

Although current guidelines on the management of severe symptomatic hyponatremia recommend administering 3% sodium chloride as a small, fixed bolus rather than as a continuous infusion, there have been few good-quality comparative trials studying the safety and efficacy between these two methods of administration. However, a recently published randomized controlled trial comparing rapid intermittent bolus versus slow continuous infusion therapy with hypertonic saline demonstrated that both methods were effective and safe, with similar risk in overcorrection.[28] However, rapid intermittent bolus administration was found to have a lower incidence

of relowering treatment and thus deemed to be the preferred way of treating symptomatic hyponatremia.

Because calculations for water excess and sodium deficits are only approximations, the patient's serum osmolality, serum sodium, and clinical response must be monitored closely, such as every 4 to 6 hours initially and daily afterward, until the serum sodium concentration has stabilized.[29] In addition, urinary losses can be replaced with 3% sodium chloride solution and appropriate amounts of potassium.

When treating hyponatremia, patients should also be monitored closely for excessive free-water losses from diuresis. Desmopressin has been shown to be effective in minimizing urinary free-water losses and avoiding rapid autocorrection of serum sodium concentration during the correction of hyponatremia.[30]

Management of the Syndrome of Inappropriate Antidiuretic Hormone Secretion

Case 27-7, Question 4: How should C.C.'s SIADH be managed long term?

SIADH is usually transient if the underlying cause can be removed. Chronic SIADH can occur, however, as illustrated by C.C. Water restriction sufficient to create a negative water balance is the primary therapy and should be attempted first.[22] In general, all fluids, not just water, should be included in the restriction. Salt intake, however, should not be reduced or solute depletion can occur. The extent of fluid restriction depends on urine output, the amount of insensible water loss, and urine osmolality. For a given amount of solute excretion, patients with a high urine osmolality require a smaller volume of urine (ie, more water retained) than those with a lower urine osmolality (ie, less water retained). Hence, more stringent water restriction is required in patients with a high urine osmolality. Commonly, several days of restriction are needed before a significant increase in plasma osmolality is observed.

When fluid restriction fails to reverse the hypo-osmolar state or when the patient is unwilling or unable to comply with the severe fluid restriction, urea, vasopressin receptor antagonists (VRAs), and other drugs that antagonize the effect of ADH can be used.[22] These include loop diuretics and demeclocycline. Furosemide (20–40 mg/day) reduces urine osmolality by blocking the concentrating ability of the kidney. Demeclocycline directly impairs the response to ADH at the collecting tubule, inducing nephrogenic diabetes insipidus, and may be used at a dose of 300 to 600 mg twice daily. Its effect on water excretion is delayed for a few days, and it dissipates over a similar period of time after the drug is stopped. Nephrotoxicity has been reported after its use in patients with cirrhosis.[31] Limited data suggest that phenytoin may inhibit ADH secretion, but its questionable effectiveness and toxicity limit its use in clinical practice.[32] Urea can correct hypo-osmolality by increasing solute-free water excretion and reducing urinary sodium excretion.[33] It has been used effectively, at 30 to 60 g/day, both short term and long term, to reduce the need for fluid restriction. For oral administration, 30 g of urea crystals can be dissolved in 10 mL of aluminum–magnesium antacid and 100 mL of water. Orange juice or other strongly flavored liquids can be used to improve palatability.

VASOPRESSIN RECEPTOR ANTAGONISTS

Nonpeptide VRAs, also known as the “vaptans” or “aquaretic agents,” constitute a class of agents used for the treatment of hyponatremia. AVP, a neuropeptide hormone, plays an important role in maintaining serum osmolality, as well as circulatory and sodium homeostasis.[34,35] AVP exerts its physiologic effects by acting on V1A, V1B, and V2 receptors, causing effects such as vasoconstriction,[36,37] corticotropin release,[38] and water excretion,[39] respectively. V2 receptors are located in the kidney collecting tubules and mediate the antidiuretic effects of AVP. Antagonism of the V2 receptors results in aquaresis, which is a unique solute-free and electrolyte-sparing (sodium and potassium) water excretion process in the kidneys. Because circulating levels of AVP are elevated in

SIADH, cirrhosis, and HF, VRA can be beneficial in the management of hyponatremia associated with these conditions.

Conivaptan, a mixed V1A and V2 receptor antagonist, was the first VRA approved by the U.S. Food and Drug Administration (FDA) for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients.[40] Randomized, double-blind, placebo-controlled trials demonstrated its efficacy in increasing serum sodium concentrations in patients with euvolemic and hypervolemic hyponatremia associated with SIADH and HF, respectively.[40,41] It is administered as an IV infusion and its use is restricted to a short-term (4 days) inpatient use only. Close monitoring of serum sodium concentration is necessary to prevent overly rapid correction of hyponatremia and central pontine myelinolysis that may ensue. Because conivaptan is a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) enzyme, drug interactions with medications that undergo CYP3A4-mediated metabolism are possible.[34] There are also concerns with conivaptan's effects on antagonizing the V1 receptors, which can result in hypotension and splanchnic vasodilation.[22]

In addition, patients may experience infusion site reactions with conivaptan caused by the organic solvent, polypropylene glycol.

Tolvaptan, a selective oral VRA, was approved by the FDA in 2009 for the treatment of hypervolemic and euvolemic hyponatremia in patients with HF, cirrhosis, and SIADH. Because of its selectivity for the V2 receptor, tolvaptan increases urinary excretion of free water (aquaresis) and has less of a BP-lowering effect. As such, it may be more suitable for use in patients with low to normal BP, such as those with HF or cirrhosis. Tolvaptan has been shown to increase serum sodium concentration significantly and correct hyponatremia in patients with SIADH, chronic HF, or cirrhosis.[42] It has also been studied extensively in chronic HF where improvement in signs and symptoms such as reduction of edema and weight, as well as normalization of serum sodium concentrations, were shown.[43,44] However, the use of tolvaptan in HF had no effect on long-term cardiovascular mortality or hospitalization for HF.[45] Tolvaptan is also approved for use in patients with autosomal dominant polycystic

kidney disease (ADPKD), at higher doses than that used in hyponatremia.[46,47] Hepatic injury was noted in some patients in earlier trials of tolvaptan in ADPKD, thus resulting in the release of a safety announcement by the FDA to limit tolvaptan's use to no more than 30 days for the treatment of hyponatremia and the removal of the indication for use in patients with cirrhosis.[48] It should not be used also in patients with underlying hepatic disease.

Common adverse effects of VRAs include thirst, dry mouth, polyuria, and BP reduction. Aquaretics increase thirst by increasing blood tonicity and urine volume; orthostatic hypotension has been reported.[35,49] These agents are thus contraindicated in hypovolemic hyponatremia. The risk of excessive correction of hyponatremia and the resultant neurologic complications from osmotic demyelination exists with VRAs, especially when used in combination with fluid restriction. These agents should therefore be initiated in the inpatient setting at the lowest possible dose and titrated slowly, with close monitoring of serum sodium concentrations and volume status. In addition, the VRAs are substrates and inhibitors of the CYP3A4 enzyme. As a result, there is a potential for clinically significant drug interactions, particularly with concomitant administration of moderate or strong CYP3A4 inducers or inhibitors.

The VRAs should be used in patients with hyponatremia who are refractory to or cannot take other therapies. Not only have they been shown to maintain normal serum sodium concentrations both in the short and long term but their aquaretic effect could also reduce or eliminate the need for fluid restriction normally required of patients.[42,50] The effectiveness of VRAs to correct serum sodium concentration in euvolemic and hypervolemic hyponatremia has been shown. However, their long-term safety with chronic use and their potential benefits on morbidity and mortality still need to be assessed. The high cost of using these agents remains a major barrier to routine clinical use.

Hypernatremia

Hypernatremia can occur under the following conditions: (a) normal total body sodium with pure water loss, (b) low total body sodium with hypotonic fluid loss, and (c) high total body sodium as a result of pure salt gain.[22,51] Therefore, as in hyponatremia, it is important to assess the volume status of the ECF when evaluating hypernatremia.

Pure water loss can result from the inability of the kidney to conserve water (diabetes insipidus) or from extrarenal water loss through the respiratory tract or the skin. Usually, pure water loss does not cause hypernatremia unless the thirst center is damaged or access to free water is limited.

Hypotonic fluid loss can occur via the kidneys as a result of osmotic diuresis, use of loop diuretics, postobstruction diuresis, or intrinsic kidney disease. Extrarenally, hypotonic fluid loss can result from diarrhea, vomiting, burns, and excessive sweating.

Pure salt gain can result from the use of hypertonic saline during abortion, sodium bicarbonate administration during cardiopulmonary resuscitation, hypertonic feedings in infants, and, rarely, mineralocorticoid excess.

The management of hypernatremia includes correcting the underlying cause of the hypertonic state, replacing the water deficits, and administering adequate water to match ongoing losses.[22,51] The pure water deficit can be estimated as follows:

$$\text{Water deficit} = \text{TBW}\left(\frac{\text{Observed serum Na}}{\text{Desired serum Na}}\right) - \text{TBW} \qquad \textbf{(Eq. 27-12)}$$

$$= \text{TBW}\left(\frac{\text{Observed serum Na}}{\text{Desired serum Na}} - 1\right)$$

where desired serum sodium is usually 140 mEq/L.

The rate at which hypernatremia should be corrected depends on the severity of symptoms and degree of hypertonicity. Too rapid a correction can precipitate cerebral edema, seizures, and irreversible neurologic damage, and can be fatal. For asymptomatic patients, the rate of correction probably should not exceed changes of 0.5

mEq/L/hour in plasma sodium. Less aggressive correction is also recommended in patients at risk for developing neurologic complications. A rule of thumb is to replace half the calculated deficit with hypotonic solutions over the course of 12 to 24 hours, depending on the severity of hypernatremia. Any ongoing water loss, including insensible loss, should also be replenished while carefully monitoring the patient's neurologic status. The remaining deficit can then be replaced during the ensuing 24 to 48 hours. Concomitant solute deficits and ongoing solute losses should also be replaced as appropriate. If hypernatremia is caused only by pure water loss, free water can be administered as 5% dextrose in water. Half-normal saline or quarter-normal saline is used if a sodium deficit is also present. In patients with hypotension or shock, the effective arterial blood volume should be restored with normal saline or colloids before the plasma tonicity is corrected.

POTASSIUM

Homeostasis

The total amount of potassium stored in the body is ~45 to 55 mEq/kg and varies with age, sex, and muscle mass. Lower total body potassium is found in older adults, females, and individuals with a low lean body mass to fat ratio. Potassium is distributed unevenly between the intracellular and extracellular compartments; 98% of the total body potassium resides in the intracellular compartment, predominantly in the muscle, and only 2% is found in the extracellular space.[52] The disproportionate intracellular distribution of potassium is maintained by the Na^+/K^+-ATPase pump, which transports sodium out of the cell in exchange for potassium. The cell membrane resting potential is determined by the ratio of intracellular/extracellular potassium concentrations. As this ratio increases, hyperpolarization of the cell membrane occurs.

Conversely, cellular depolarization results when the ratio decreases. In both situations, generation of the action potential is impaired.

The plasma potassium concentration is maintained within a narrow range of 3.5 to 5.0 mEq/L. Although the plasma potassium concentration can be affected by the total body potassium store, total body potassium excess or deficit cannot be estimated accurately based solely on the plasma concentration. In fact, a normal plasma potassium concentration does not imply normal total body potassium because multiple factors affect the plasma potassium concentration independent of total body potassium.[52]

Potassium homeostasis is maintained by both the kidney and extrarenal processes. The kidney process regulates total body potassium by matching potassium excretion to dietary intake (external balance), whereas the extrarenal process regulates potassium distribution across the cell membrane (internal potassium balance).[52]

The normal daily intake of potassium ranges between 50 and 100 mEq. Approximately 90% of the ingested potassium is eliminated by the kidneys and ~10% is eliminated via the GI tract.[52] Potassium is filtered freely through the glomerulus and then reabsorbed. By the time the filtrate reaches the distal convoluted tubule, ~90% of filtered potassium has already been reabsorbed. The amount of potassium excreted is determined by the distal tubular potassium secretion in the principal cells of the cortical collecting duct, which is under the influence of aldosterone. Hyperkalemia, increased potassium load, and AT_2 can all stimulate aldosterone secretion.

Factors that affect kidney potassium excretion include tubular flow, sodium delivery to the distal segments of the nephron, the presence of poorly absorbable anions that increase luminal electronegativity, acid–base status, and aldosterone activity. Potassium excretion increases during hyperkalemia and decreases during potassium depletion. Excretion of an acute potassium load is a slow process, with only half the potassium load excreted in the first 4 to 6 hours. Lethal hyperkalemia would ensue without the extrarenal process that regulates intracellular/extracellular potassium distribution.

The Na^+/K^+-ATPase pump, which extrudes sodium from the cell in exchange for potassium, is pivotal in maintaining internal potassium balance. Different hormonal factors regulate the activity of the Na^+/K^+-ATPase pump, namely, insulin, catecholamines, and aldosterone. Insulin, the most important regulator, enhances potassium uptake by the muscle, liver, and adipose tissue by stimulating Na^+/K^+-ATPase. Indeed, basal insulin secretion is essential for potassium homeostasis. β_2-adrenergic agonists activate the Na^+/K^+-ATPase pump via cyclic adenosine monophosphate and cause hypokalemia, whereas α-adrenergic stimulation promotes hepatic potassium release and causes hyperkalemia. Epinephrine, an α- and β-agonist, causes a transient increase in plasma potassium (α-agonism) followed by a more sustained decrease in plasma potassium (β-agonism). Besides its kaliuretic effect and enhanced potassium secretion in the colon, aldosterone also stimulates Na^+/K^+-ATPase.[52]

Other factors that affect the transcellular distribution of potassium include systemic pH, plasma tonicity, and exercise. The effect of the acid–base balance on potassium distribution is not readily predictable and depends on both the nature and the direction of the underlying disorder.[53] The concomitant effect of the acid–base disorder on potassium excretion further complicates the relationship between plasma potassium concentration and pH. In acute non–anion gap metabolic acidosis, plasma potassium concentration increases by 0.2 to 1.7 mEq/L per 0.1 unit decrease in pH. Chronic non–anion gap metabolic acidosis usually is associated, however, with hypokalemia because of the urinary potassium loss associated with both proximal (type 2) and distal (type 1) renal tubular acidosis. In contrast, anion gap metabolic acidosis commonly has no effect on potassium distribution.

Other associated factors in anion gap acidosis may, however, affect cellular potassium distribution.[53] For example, hyperglycemia in diabetic ketoacidosis may increase the serum potassium concentration because of the hypertonic effect of glucose.[54] Hypertonicity causes cell shrinkage and increases the intracellular to

ECF potassium gradient, favoring potassium egress from the cell. Acute metabolic alkalosis only modestly decreases the plasma potassium concentration: 0.3 mEq/L for each 0.1 unit pH increment.[53] As with chronic metabolic acidosis, chronic metabolic alkalosis causes profound kidney potassium wasting and is associated with hypokalemia. Respiratory acid–base disorders usually are associated with less significant changes in plasma potassium concentration than are metabolic acid–base disorders. Exercise often causes an increase in the serum potassium concentration to a degree that varies with the intensity of the exercise.[55]

Hypokalemia

ETIOLOGY

CASE 27-8

Question 1: J.P., a 60-year-old female, presents to the ED with malaise, generalized weakness, nausea, and vomiting for 3 days. Her medical history includes hypertension for 20 years. J.P.'s current medications include hydrochlorothiazide 25 mg/day and nifedipine XL 30 mg/day. She has not been able to take her medications in the past few days, however, because of vomiting. J.P. denies recent diarrhea or use of laxatives. Her BP is 130/70 mm Hg with a pulse of 80 beats/minute while sitting and 120/70 mm Hg with a pulse of 95 beats/minute on standing. Physical examination reveals a thin, older female with poor skin turgor, dry mucous membranes, and a flat jugular vein. T-wave flattening is noted on the electrocardiogram (ECG). Laboratory tests show the following:

Serum Na^+, 138 mEq/L
K^+, 2.1 mEq/L
Cl^-, 100 mEq/L
Total CO_2, 32 mEq/L
BUN, 30 mg/dL
Creatinine, 1.2 mg/dL
Glucose, 100 mg/dL

ABG shows pH, 7.50; $PaCO_2$, 45 mm Hg; and PaO_2, 70 mm Hg at room air. Urine electrolytes are sodium, 30 mEq/L; potassium, 60 mEq/L; and chloride,

<15 mEq/L. J.P.'s presentation is consistent with gastroenteritis.
What are the causes of J.P.'s hypokalemia?

When evaluating hypokalemia, the clinician should determine whether the hypokalemia is a result of low intake, increased cellular uptake of potassium, or excessive loss of potassium via the kidneys, GI tract, or skin.[56] History and physical evidence of potassium depletion, medication history (including use of over-the-counter medicines), and assessment of the patient's BP, extracellular volume, and concurrent acid–base status can provide clues to the causes of hypokalemia.[56] Concomitant magnesium deficiency is often associated with hypokalemia because it can augment potassium wasting by increasing distal potassium secretion.[57] It may therefore aggravate hypokalemia and render it refractory to treatment. Correction of hypomagnesemia before potassium replacement is thus necessary.

Because J.P. has been unable to eat for the past few days, decreased oral intake may have contributed to her hypokalemia. Because most foods are rich in potassium, however, inadequate intake rarely is the sole cause of potassium depletion unless inappropriate and continued kidney or extrarenal losses occur, or potassium intake is severely restricted to <10 to 15 mEq/day.[52,56] Alkalosis insulin administration, hypertonic solution administration, periodic paralysis, β_2-agonists, barium poisoning, and treatment of megaloblastic anemia with vitamin B_{12} all have been associated with increased cellular potassium uptake (**Table 27-2**). Although the relationship between the degree of hypokalemia and increase in blood pH varies widely,[53] J.P.'s metabolic alkalosis probably enhances the cellular uptake of potassium. However, the transcellular shift of potassium should not result in total body potassium depletion.

Table 27-2
Drugs That Most Commonly Induce Hypokalemia

Drug	Mechanism	Predisposing Factors

Drug	Mechanism	Predisposing Factors
Acetazolamide	Marked ↑ in kidney K^+ loss	Most profound with short-term therapy
Amphotericin	Kidney K^+ loss (renal tubular acidosis)	Concurrent piperacillin, ticarcillin
β_2-Agonists	Intracellular shift of K^+	
Cisplatin	Kidney K^+ loss secondary to renal tubular damage	May be dose related but can occur after a single 50-mg/m^2 dose
Corticosteroids	Kidney K^+ loss. Enhanced Na^+ reabsorption at distal tubule and collecting ducts in exchange for K^+ and H^+	Supraphysiologic doses of agents with moderate to strong mineralocorticoid activity (eg, prednisone, hydrocortisone)
Insulin with glucose	Intracellular shift of K^+	Predictable effect when insulin administered to patients with diabetic ketoacidosis combination used to treat hyperkalemia
Penicillins (piperacillin, ticarcillin)	High Na^+ load and nonresorbable anions can ↑ K^+ loss	Was more common with carbenicillin when it was available; newer penicillins are used in lower doses; less likely to produce hypokalemia
Thiazide and loop diuretics	Kidney K^+ loss. ↑ Na^+ delivery to the late distal tubule, resulting in Na^+ resorption in exchange for K^+	Patients with hyperaldosteronism (eg, cirrhosis, HF) predisposed; may be dose related

HF, heart failure.

The GI tract is an important site of potassium loss, particularly through vomiting and diarrhea. Because the potassium content of gastric secretion (5–10 mEq/L) is much less than that of the intestinal secretion (up to 90 mEq/L),[52,56] loss of a large volume of gastric secretion is needed to produce substantial potassium depletion. Potassium deficit induced by vomiting, however, is commonly secondary to kidney potassium loss, especially within the initial 24 to 48 hours. The loss of hydrogen ion in gastric juice results

in an elevated plasma bicarbonate concentration. The increased amount of bicarbonate ion, as a nonresorbable anion, increases water delivery to the distal nephron and enhances sodium reabsorption and potassium secretion, resulting in hypokalemia. The potassium wasting is often transient because increased proximal reabsorption of sodium and bicarbonate will result in diminished bicarbonate delivery to the distal site. Reduced potassium excretion will ensue, commonly within 48 to 72 hours. Subsequent potassium loss will then be primarily consequent to gastric secretion removal.

The absence of diarrhea in J.P. excludes the GI tract as the source of potassium loss. Potassium loss through the skin is also unlikely in J.P. because the potassium concentration of sweat is <10 mEq/L. Therefore, profuse sweating, such as that induced by vigorous exercise in a hot, humid environment, or severe burns are needed to cause substantial loss.

J.P.'s inappropriately high urinary potassium concentration indicates that the kidney is the source of the potassium loss.[52,56] The urinary potassium concentration is a good marker for differentiating various hypokalemic syndromes. A urinary potassium excretion of <20 mEq/day suggests extrarenal potassium loss. Kidney potassium wastage cannot be excluded, however, unless the low urinary potassium excretion is accompanied by a sodium intake of at least 100 mEq/day, because a low-sodium diet can reduce kidney potassium excretion. In J.P., metabolic alkalosis and hypovolemia promote kidney potassium wastage.[53] The distal delivery of a large sodium bicarbonate load and increased aldosterone activity (from hypovolemia) enhance potassium secretion and severely impair the kidney's ability to conserve potassium. The hydrochlorothiazide, which J.P. had been taking until 3 days before admission, could also have induced hypokalemia through volume depletion, hypochloremic metabolic alkalosis, and kidney potassium wastage. The diuretic is unlikely, however, to be the cause of J.P.'s hypokalemia because she has stopped taking the medication, and this is reflected by the low urinary chloride concentration.[52] Bartter syndrome, which presents as normotension, hypokalemia, hypochloremic metabolic alkalosis, and kidney potassium wastage, is characterized by impaired kidney

sodium and chloride reabsorption.[58] The low urinary chloride concentration in J.P. can rule out Bartter syndrome. Other causes of hypokalemia are listed in Table 27-2.

In a patient with asymptomatic hypokalemia with no apparent causes for potassium depletion or transcellular redistribution, pseudohypokalemia should be excluded before pursuing an intensive evaluation. Spurious hypokalemia can occur in patients with leukemia whose leukocyte count ranges from 100,000 to 250,000 cells/μL.[59] The potassium in serum is taken up by the large number of leukemic cells when the blood specimen is allowed to stand at room temperature.

CASE 27-8, QUESTION 2: What clinical manifestations of hypokalemia are evident in J.P.?

CLINICAL MANIFESTATIONS

The clinical presentation of hypokalemia, which depends on the severity of potassium depletion, is a result of changes in cell membrane polarization.[52,56] Patients are usually asymptomatic when the plasma potassium level is 3.0 to 3.5 mEq/L, but they may present with malaise, weakness, fatigue, and myalgia. J.P.'s muscle weakness and ECG changes reflect the muscular and cardiac manifestations of hypokalemia, respectively.

Potassium depletion can lead to hyperpolarization of myocardial cells and a prolonged refractory period. When serum potassium concentrations fall <3 mEq/L, T-wave flattening, straight tubule segment depression, and prominent U waves are seen on the ECG.

Mild hypokalemia (potassium concentration of 3.0–3.5 mEq/L) is potentially arrhythmogenic in patients with underlying coronary artery disease. The incidence of ventricular arrhythmia increases with the degree of hypokalemia. Patients without underlying heart disease may be susceptible to these myocardial effects during exercise, especially if the patient's pre-exercise potassium concentration is <3.5 mEq/L, because the potassium concentration may drop to <3.0 mEq/L as a result of β_2-adrenergic receptor–mediated cellular

potassium uptake. Potassium depletion may also increase the BP, which can be lowered with potassium supplementation.[56]

When the serum potassium concentration is <2.5 to 3.0 mEq/L (moderate hypokalemia), muscle weakness, cramps, general malaise, fatigue, restless leg syndrome, and paresthesia can occur, probably because potassium is necessary for vasodilation in skeletal muscle. In addition, severe potassium depletion (<2.5 mEq/L) can result in elevation of serum creatine phosphokinase, aldolase, and aspartate aminotransferase levels. Rhabdomyolysis can ensue when the serum potassium concentration falls <2.0 mEq/L.[56]

Chronic potassium depletion can alter kidney function and structure, which can manifest as decreased GFR and kidney blood flow, disturbance in tubular sodium handling, impaired urinary concentrating ability with polydipsia, and ADH-resistant nephrogenic diabetes insipidus.[56] Reversible pathologic changes include kidney hypertrophy and epithelial vacuolization of the proximal convoluted tubule. Interstitial scarring and tubular atrophy have been reported with prolonged potassium depletion.

Other effects of hypokalemia and potassium depletion include decreased insulin secretion resulting in carbohydrate intolerance, metabolic alkalosis, and increased kidney ammoniagenesis, which may play a role in the development of hepatic encephalopathy.

TREATMENT

CASE 27-8, QUESTION 3: How should J.P.'s hypokalemia be treated?

J.P.'s protracted vomiting should be corrected, and fluids and electrolytes (sodium, potassium, and chloride) should be replaced to correct the volume deficit, hypokalemia, and hypochloremic metabolic alkalosis. Hydrochlorothiazide should continue to be withheld.

The amount of potassium deficit and the rate of continued potassium loss should be determined to guide replacement therapy. It has been estimated that a 1-mEq/L fall in serum potassium from 4

to 3 mEq/L represents a total body deficit of ~200 mEq. When the serum potassium falls to <3 mEq/L, the total body deficit increases by 200 to 400 mEq for each 1 mEq/L reduction in serum concentration. Other data suggest that even greater degrees of potassium loss can occur—a deficit of 100 mEq per 0.27-mEq/L fall in the serum potassium concentration.[52,56] Transcellular redistribution of potassium may, however, significantly alter the relationship between serum concentration and total body deficit. Therefore, potassium repletion should be guided by close monitoring of serum concentrations and analysis of J.P.'s urine for potassium content to help assess the need for additional replacement.

The route of potassium administration depends on the acuity and severity of hypokalemia,[56] but oral supplementation is usually preferred. The parenteral route is indicated for patients who cannot tolerate high dosages of oral potassium supplements and for those with severe or symptomatic hypokalemia. J.P.'s potassium deficit is estimated to be 300 to 500 mEq. With the ECG T-wave flattening, immediate treatment is necessary with parenteral potassium supplementation.

For severe hypokalemia, parenteral potassium can be given as chloride, acetate, or phosphate. The chloride salt is preferred in J.P., who has concurrent hypochloremic metabolic alkalosis. The acetate preparation is useful in cases of concomitant metabolic acidosis. Potassium phosphate is indicated if hypophosphatemia coexists. In the latter condition, the serum calcium concentration should also be monitored because hypocalcemia may ensue. IV potassium chloride in normal saline as diluent is preferred because dextrose-containing solutions may trigger insulin release, shifting potassium into cells, and result in hypokalemia.[56]

Potassium chloride–containing infusions must be administered slowly, commonly at 10 mEq/hour and should not exceed 20 mEq/hour.[60] Rates >20 mEq/hour are highly irritating to the peripheral veins and should be given via a large central vein instead. When potassium is given as maintenance fluid to a peripheral vein, the concentration should not exceed 60 to 80 mEq/L. Exceptions may be considered when severe hypokalemia is associated with

cardiac arrhythmias or diabetic ketoacidosis, where extreme caution would be needed for concentrations of 40 to 60 mEq/L. When given to a central vein, the rate should be 20 mEq/hour, with a maximum concentration of 20 mEq/50 mL. IV potassium should never be given as IV push, even during an emergency, because it always needs to be diluted.

Continuous ECG monitoring and serial measurements of plasma potassium concentrations every 4 hours are essential during IV potassium administration, especially when the rate of administration is >20 mEq/hour.

Parenteral potassium solutions should be given only in well-hydrated patients with adequate urine flow and very cautiously in postsurgical patients and those with kidney impairment, including geriatric patients, owing to the risk of hyperkalemia with excessive correction. In addition, serum magnesium concentration should be obtained when the potassium concentration is <2.8 mEq/L. If the patient has concomitant hypomagnesemia, magnesium supplementation should first be given. Refer to the section on Hypomagnesemia: Treatment for the suggested dosing of magnesium supplementation.[57,61]

For mild and moderate hypokalemia, potassium repletion may be given orally. Potassium chloride may be given orally as medications or salt substitutes. Salt substitutes, containing 50 to 65 mEq of potassium per level teaspoon, are widely available, safe, well tolerated, and much less expensive than are the medicinal preparations.[62] Potassium chloride is also available as liquid or slow-release tablet or capsule. The liquid preparations are unpalatable, albeit being inexpensive. Slow-release preparations are commonly well tolerated but may cause GI ulceration and bleeding, owing to local exposure to high potassium concentrations. The risk is generally low with the wax matrix tablets and is further lower with the microencapsulated preparations. Potassium chloride is most often used because chloride depletion is common in the presence of metabolic alkalosis, secondary to diuretic therapy or vomiting. As such, non–chloride potassium salts are not as effective in restoring body potassium. In contrast to bicarbonate, chloride does not enter

cells to the same extent, thereby helping to maintain potassium in the ECF. In addition, potassium bicarbonate may exacerbate metabolic alkalosis, thus reducing the efficacy of potassium administration. However, potassium bicarbonate is preferred in patients with concurrent hypokalemia and metabolic acidosis. Potassium chloride tablets may be given as 10 to 40 mEq two to four times daily, depending on the severity of the hypokalemia.[60]

For J.P., IV potassium replacement should first be initiated at 10 to 40 mEq/hour and adjusted based on frequent serum potassium, as well as continuous ECG monitoring. Once her potassium levels are replenished to a concentration of >3 mEq/L, she has no more ECG abnormalities, and she is no longer vomiting, oral potassium chloride can be started.[60]

Hyperkalemia

ETIOLOGY

CASE 27-9

Question 1: A.B., a 25-year-old female with type 1 diabetes and hypertension, returns to the clinic for follow-up. Her BP is 170/90 mm Hg with a pulse of 80 beats/minute, and her physical examination is remarkable for 2+ pedal edema. Laboratory tests show the following:

Plasma Na^+, 135 mEq/L
K^+, 5.8 mEq/L
Cl^-, 108 mEq/L
Total CO_2, 20 mEq/L
BUN, 28 mg/dL
Creatinine, 2 mg/dL
Glucose, 200 mg/dL

Current medications include oral captopril 25 mg three times daily, hydrochlorothiazide 25 mg/triamterene 37.5 mg one capsule daily, human isophane insulin 30 units subcutaneously every morning, and ibuprofen 200 mg as needed for menstrual cramps. She uses a salt substitute occasionally.

What is the etiology of her hyperkalemia?

Before conducting any extensive evaluation to identify the etiology of hyperkalemia, the serum potassium concentration ought to be repeated to confirm the presence of hyperkalemia. Also to be ruled out are the different causes of spurious hyperkalemia, which can result from severe leukocytosis (>500,000/μL), thrombocytosis (>750,000/μL), or hemolysis within the blood collection tube.[56] Pseudohyperkalemia is a test-tube phenomenon that occurs when potassium is released from lysis of leukocytes, platelets, or erythrocytes during blood coagulation. The laboratory normally reports this as a hemolyzed sample. These disorders can be confirmed easily by comparing serum (clotted) and plasma (unclotted) potassium concentrations from the same blood sample. The two values should agree within 0.2 to 0.3 mEq/L. Improper tourniquet technique, causing strangulation of the patient's arm before blood sampling, may also result in spurious hyperkalemia.

Identifying the etiology of hyperkalemia can be approached systematically by considering possible disturbances in internal and external potassium balance. The former involves transcellular flux of potassium from the intracellular to the extracellular space, whereas the latter involves either increased intake, including increased endogenous potassium load (eg, rhabdomyolysis, tumor lysis syndrome, or decreased elimination).[52,56] A thorough medication history is important to identify drugs associated with hyperkalemia.[56] (Also see Chapter 28, Chronic Kidney Disease, for additional information on hyperkalemia.)

A dietary history should ascertain whether A.B.'s consumption of potassium-rich foods, salt substitutes, or potassium supplements has increased. Dietary intake alone will not induce hyperkalemia unless kidney excretion is impaired. Usually, the GFR must be <10 to 15 mL/minute, unless there is concurrent hypoaldosteronism or distal tubular potassium secretory defects. A.B.'s kidney insufficiency is mild, with an estimated CrCl of 40 mL/minute.

Conditions associated with low renin and aldosterone, which usually present as hyperkalemia and hyperchloremic metabolic acidosis,[53] decrease potassium excretion by the kidneys. These include diabetes, obstructive uropathy, sickle cell disease, lupus

nephritis, and various tubulointerstitial diseases (eg, gouty nephropathy, analgesic nephropathy). Adrenal insufficiency presents commonly with hyperkalemia because of mineralocorticoid deficiency.[56] A.B.'s hyperglycemia because of poorly controlled diabetes may cause movement of potassium-rich fluid from the intracellular space to the extracellular space because of the increased tonicity. Elevating the plasma tonicity by 15 to 20 mOsm/kg will increase the plasma potassium concentration by 0.8 mEq/L.[52,56] Patients with diabetes, mineralocorticoid deficiency, or end-stage kidney failure, which commonly results in hyporeninemic hypoaldosteronism, are particularly susceptible.

A.B. is also taking several medications that may impair her ability to excrete potassium. Captopril, as with all angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, indirectly decreases aldosterone secretion by decreasing the formation of AT_2.[56,63] Ibuprofen and all other NSAIDs inhibit prostaglandin production as well as renin and aldosterone secretion. Other drugs that cause hyperkalemia by impairing renin and aldosterone production include AT_2 receptor antagonists, β-adrenergic blockers, lithium, chronic heparin administration, and pentamidine. Triamterene, a component of her diuretic, inhibits tubular potassium secretion, as do amiloride, spironolactone, high-dose trimethoprim, cyclosporine, tacrolimus, and digoxin. By inhibiting Na^+/K^+-ATPase, digoxin decreases tubular potassium secretion and reduces cellular potassium uptake. Arginine, succinylcholine, β-blockers, α-agonists (such as phenylephrine), and hypertonic solutions also cause hyperkalemia by impairing transcellular potassium distribution into the intracellular space.

CLINICAL MANIFESTATIONS

CASE 27-10

QUESTION 1: V.C., a 44-year-old female with chronic kidney failure, returns to the outpatient unit for routine hemodialysis with severe muscle weakness. Her vital signs are BP, 120/80 mm Hg; pulse, 90 beats/minute; RR, 20

breaths/minute; and temperature, 98 °F (36.67 °C). Laboratory data are as follows:

Serum K^+, 8.9 mEq/L
Total CO_2, 15 mEq/L
BUN, 60 mg/dL
Creatinine, 9 mg/dL
Glucose, 100 mg/dL

The ECG reveals an increased PR interval and a widened QRS complex. What clinical manifestations of hyperkalemia are evident in V.C.?

Hyperkalemia decreases the intracellular/extracellular potassium ratio. Hence, the resting membrane potential becomes less negative and moves closer to the threshold excitation potential. Muscle weakness and flaccid paralysis result when the resting membrane potential approaches the threshold potential, rendering the excitable cells unable to sustain an action potential.

The cardiac toxicity of hyperkalemia is a major cause of morbidity and mortality, with ECG findings paralleling the degree of hyperkalemia. When plasma potassium is >5.5 to 6.0 mEq/L, narrow, peaked T waves and a shortened QT interval are seen. As the plasma potassium concentration increases further, the QRS complex widens and the P-wave amplitude decreases. As the level reaches 8 mEq/L, the P wave disappears and the QRS complex continues to widen and merge with the T wave to form a sine wave pattern. If these ECG changes are not recognized and no treatment is initiated, ventricular fibrillation and asystole will ensue. Hyponatremia, hypocalcemia, and hypomagnesemia all reduce the threshold potential, thereby increasing the patient's susceptibility to the cardiac effects of hyperkalemia.[52,56,57] V.C.'s muscle weakness, ECG, chronic kidney failure, and serum potassium concentration all are consistent with severe hyperkalemia.

TREATMENT

Case 27-10, Question 2: How should V.C.'s hyperkalemia be treated?

Hyperkalemia with ECG changes requires urgent treatment.[56,64] Three therapeutic modalities are available: (a) agents that antagonize the cardiac effects of hyperkalemia, (b) agents that shift potassium from the extracellular into the intracellular space, and (c) agents that enhance potassium elimination. A combination of these modalities is often used because it mitigates the potassium cardiac effect without affecting its concentration, while it reduces serum potassium concentration by shifting into cells. Agents that actually increase potassium elimination are necessary for long-term control. Considering V.C.'s severe ECG changes, 10% calcium gluconate IV should be administered at a dose of 10 to 20 mL over the course of 1 to 3 minutes. Calcium counteracts the depolarizing effect of hyperkalemia by increasing the threshold potential, thus making it less negative and moving it away from the resting potential. The onset of action occurs in a few minutes, but the effect is short-lived, lasting ~15 to 60 minutes. The dose can be repeated in 5 minutes if ECG changes do not resolve and as needed afterward for recurrence. With no response after the second dose, additional attempts, however, are not beneficial. When hyperkalemia presents with a digitalis overdose, calcium should be used cautiously because it can worsen the cardiotoxic effects of digoxin. In the absence of ECG changes, there is no justification for using calcium for hyperkalemia treatment.

Because the serum potassium concentration is not affected by calcium administration, maneuvers should be used to shift potassium from plasma into the cells. Three modalities are available: insulin and glucose, β_2-agonists, and sodium bicarbonate.

Insulin rapidly shifts potassium into the cell in a dose-dependent manner. The maximal effect occurs at insulin concentrations >20 to 40 times the basal levels. Therefore, endogenous insulin secreted in response to dextrose administration is insufficient, and exogenous insulin must be administered.[64] Although high concentrations of dextrose may worsen hyperkalemia, particularly in patients with diabetes because intracellular potassium may be shifted to the extracellular space owing to the elevated plasma tonicity, it is always

administered with insulin to prevent hypoglycemia. Regular insulin (5–10 units) can be given with 50 mL of 50% dextrose as IV boluses. The insulin– dextrose combination lowers serum potassium by direct stimulation of cellular potassium uptake and potentiates the potassium-lowering effect of β_2-adrenergic stimulation. The reduction in potassium is apparent 15 to 30 minutes after administering insulin and persists for 4 to 6 hours. In a patient with diabetes who is both hyperkalemic and hyperglycemic, insulin alone may be insufficient. If the patient has end-stage kidney disease, the insulin–glucose combination is more predictable in lowering plasma potassium concentrations than is sodium bicarbonate.

β_2-Agonists, by binding with the β_2-adrenoreceptor to activate adenylate cyclase, have an additive effect with the insulin–dextrose combination in decreasing serum potassium.[64] When albuterol nebulization is used alone, the hypokalemic effect may be inconsistent. Although side effects of albuterol nebulization are minimal, these agents can cause tachycardia and should be used cautiously in patients with underlying coronary artery disease. Nebulization is easy to set up and is less likely to be associated with tachycardia, but multiple doses are often necessary to attain an adequate response. In conjunction with the insulin–dextrose combination, albuterol (20 mg dissolved in 4 mL of saline) can be administered by nebulization and inhaled over the course of 10 minutes to further decrease serum potassium, if necessary.

Although sodium bicarbonate has long been recommended for the acute treatment of hyperkalemia, its efficacy in this setting has been questioned.[64] The usual dose, 50 mEq, is infused slowly over the course of 5 minutes and repeated in 30 minutes when necessary. Alternatively, it can be added to dextrose and saline solution to form an isotonic sodium bicarbonate infusion. The hypokalemic effect is variable and may be delayed up to 4 hours, and it is reportedly ineffective in patients on maintenance hemodialysis. Although bicarbonate therapy is not a reliable option in the acute management of hyperkalemia, it may be beneficial in patients with severe

metabolic acidosis (pH < 7. 20). Potential complications of sodium bicarbonate therapy are volume overload and metabolic alkalosis.

The definitive treatment of hyperkalemia is the removal of potassium from the body. Sodium polystyrene sulfonate (SPS) is an ion-exchange resin that binds potassium in the bowel and enhances its excretion in the stools.[64] Calcium polystyrene sulfonate is also available and is especially useful in patients with HF. It can be administered without the concern for fluid retention secondary to SPS sodium content. Each gram of SPS exchanges 0.5 to 1.0 mmol of potassium for an equal amount of sodium. SPS can be administered orally or rectally; the latter route is preferred in the symptomatic hyperkalemic patient because intestinal potassium exchange occurs mainly in the ileum and colon. A dose of 50 g of SPS in sorbitol can be given as an enema, retained for at least 30 to 60 minutes, at 4- to 6-hour intervals. For nonemergent removal of body potassium, 15 to 60 g of SPS suspension can be given orally, which can be repeated as needed. The onset of action is ~1 to 2 hours after administration. The major side effects are GI intolerance, including constipation, diarrhea, and sodium overload. Potentially fatal intestinal necrosis, although rare, has been reported with the use of SPS with sorbitol.[65] It is unclear if intestinal injury is caused by SPS or sorbitol, but the FDA has released a safety warning against the use of SPS in individuals with impaired bowel function.[66] In fact, sorbitol is no longer recommended together with SPS.

Hemodialysis is the most efficient way to remove potassium; potassium clearance by peritoneal dialysis is lower than that for hemodialysis.[64] The hypokalemic effect is immediate and lasts for the duration of dialysis; however, the amount of potassium removed is variable. Dialysis with a glucose-free dialysate will remove 30% more potassium than one containing 200 mg/dL of glucose. **Table 27-3** summarizes the treatment alternatives for hyperkalemia. Although V.C. is receiving chronic maintenance hemodialysis, the severe cardiac effects of hyperkalemia she experienced warrant immediate institution of the aforementioned measures while awaiting preparation for dialysis. Loop diuretics, which enhance kaliuresis, are

rarely useful in managing severe hyperkalemia, especially in patients with kidney dysfunction.

Table 27-3
Treatment of Hyperkalemia

Drug	Mechanism	Dose	Comment
Calcium gluconate	Reverse cardiotoxicity caused by K^+	10–20 mL 10% calcium gluconate IV over 1–3 minutes; may repeat once	*Onset:* 1–3 minutes *Duration:* 30–60 minutes. (K^+) remains unchanged
Insulin and glucose[a]	Redistribution of K^+ intracellularly	5–10 units regular insulin with 50 mL 50% dextrose (if hypoglycemic, may need supplemental dextrose afterward)	*Onset:* 15–30 minutes *Duration:* several hours Watch for hypoglycemia and hypokalemia. Does not ↓ total body K^+
β_2-Agonists (eg, albuterol)	Redistribution of K^+ intracellularly	Inhalation: 20 mg in 4 mL saline via nebulizer	*Onset:* 30–60 minutes *Duration:* 2 hours
Sodium polystyrene sulfonate	Cationic binding resin. 1 g of resin binds 0.5–1 mEq K^+ in exchange for Na^+.	Oral: 15–20 g every 4–6 hours; PRN preferred Retention enema: 50 g in 50 mL. Retain 30 minutes and follow with nonsaline irrigation.	*Onset:* slow; 50 g will lower (K^+) by 0.5–1 mEq/L over 4–6 hours; watch for Na^+ overload (100 mg Na^+/1 g SPS).
Patiromer	Nonabsorbed, cation exchange polymer containing a calcium–sodium cation	Recommended starting dose is 8.4 g PO daily; dose can be adjusted at 1-week or longer intervals, as needed to reach desired K target range; maximum oral dose of 25.2 g/day	*Onset:* generally slow, but may start to see effect in 1 hour *Duration*: shown to provide significant reductions in serum K within 7 hours of dosing and maintained for 48 hours
Sodium zirconium cyclosilicate	Nonabsorbed zirconium silicate that binds potassium in exchange for hydrogen and sodium	Initial treatment dose: 10 g tid for up to 48 hours Continued treatment: 10 g once daily; dose can be adjusted at 1-week or longer intervals, as needed to reach desired K^+ target range Recommended maintenance dose: 5 g every other day to 15 g daily	*Onset:* generally slow, but may start to see effect in 1 hour
Sodium bicarbonate	Redistribution of K^+ intracellularly	50 mEq IV over 5 minutes. Repeat as needed.	*Onset:* variable, ≈30 minutes May work best in acidosis Watch for Na^+ overload and hyperosmolar state. No change in total body K^+.
Dialysis	Removal of K^+		Use as last resort

bid, twice daily; IV, intravenous; PRN, as needed; SPS, sodium polystyrene sulfonate; tid, three times daily.

[a]Glucose unnecessary in patients with high glucose concentrations.

Two newer oral agents, patiromer and sodium zirconium cyclosilicate (SZC), were approved by the FDA in 2015 and 2018, respectively, for the treatment of mild-to-moderate hyperkalemia.[67,68] Patiromer binds to potassium in exchange for calcium in the GI tract, increasing fecal excretion of potassium. SZC binds to potassium in exchange for hydrogen and sodium. Both agents have been shown

to be effective in reducing serum potassium concentrations consistently and safely, thus allowing the continued use of renin–angiotensin–aldosterone antagonists in patients with HF and chronic kidney disease while minimizing the side effect of hyperkalemia.[69] However, their effects on clinical outcomes such as cardiac arrhythmias and all-cause mortality are still lacking. Both agents need to be administered separately from other medications by 2 to 6 hours because of their binding effect. The agents are generally considered safe because studies have not revealed any serious adverse effects.

Patiromer has been evaluated for acute hyperkalemia (>6.0 mEq/L) treatment. Single 25.2-g oral patiromer dose with standard of care (SOC) was found to reduce serum potassium within 2 hours, but did not show any difference at 6 hours, when compared with SOC. The observation needs to be confirmed by more rigorous studies because this was an open-label, convenience sampling study with no standardization of SOC. In addition, there were only 15 subjects in both study groups.[70]

SZC 10 g or placebo, up to three times during a 10-hour period, with insulin and glucose, were evaluated for acute treatment of blood potassium ≥5.8 mmol/L. This pilot study suggested that SZC with insulin and glucose may provide an incremental benefit in the emergency treatment of hyperkalemia over insulin and glucose alone. The serum potassium reduction was greater at 2 hours but not later. The study might be underpowered to delineate the effect of SZC because the subjects received different therapies that might affect serum potassium.[71]

Because new agents with novel mechanisms of action and improved efficacy and safety data become available, older and more traditional agents such as SPS are becoming less popular.

After V.C.’s condition stabilized, she admitted to eating a lot of fruits in the past few days. Because noncompliance with dietary potassium restriction is the most common cause of acute and chronic hyperkalemia in a patient on dialysis, V.C. should be counseled to consume potassium-rich foods in moderation. Medications that impair V.C.’s extrarenal potassium handling should

be avoided. If V.C. remains chronically hyperkalemic, an exchange resin such as SPS will then be needed, probably three or four times weekly. There is a growing preference to use newer agents such as patiromer and SZC that have more data on efficacy and safety, albeit being more expensive. For V.C., patiromer may be used at a dose of 8.4 g orally three to four times weekly. Alternatively, SZC 5 g every other day may be considered. In the case of V.C., either agent is appropriate, and thus the final choice may be based on her preference and cost. If hyperkalemia is associated with metabolic acidosis, however, an alkalinizing agent, such as sodium bicarbonate, should be added to maintain a serum bicarbonate concentration of about 24 mEq/L.

CALCIUM

Homeostasis

Healthy adults have ~1400 g of calcium in the body, of which >99% is stored in bone. Nonetheless, the 0.1% of the total body calcium that is in the plasma and extravascular fluid plays a critical role in many physiologic and metabolic processes.[72,73] Calcium is important in maintaining nerve tissue excitability and muscle contractility. It regulates the secretory activities of exocrine and endocrine glands and serves as a cofactor for enzyme systems and the coagulation cascade. It is also an essential component of bone metabolism.

Plasma calcium concentration is normally maintained within a relatively narrow range: 8.5 to 10.5 mg/dL. This is accomplished through a complex interaction between parathyroid hormone (PTH), vitamin D, and calcitonin, as well as the effect of these hormones on calcium metabolism in bone, the GI tract, and the kidneys.

Normally, about 40% of the plasma calcium is protein bound, primarily to albumin, and is nondiffusible.[72] Of the 60% that is diffusible, about 13% is complexed to various small ligands: phosphate, citrate, and sulfate. The remaining 47% is ionized, free,

and physiologically active. Changes in serum protein concentration will alter the concentrations of both protein-bound and total calcium. Therefore, the serum albumin concentration needs to be monitored to adequately interpret the total serum calcium concentration. Each 1-g/dL increase in serum albumin concentration is expected to increase the protein-bound calcium by 0.8 mg/dL, thus increasing the total serum calcium concentration by the same amount. The total serum calcium therefore can be corrected by Eq. 27-13:

$$\text{Correct Ca} = \text{Observed Ca} + 0.8\,(\text{Normal albumin} - \text{Observed albumin}) \quad \textbf{(Eq. 27-13)}$$

where normal albumin = 4 g/dL.

Calcium is also bound to plasma globulins at the rate of 0.16 mg of calcium for each gram of globulin. When the total globulin concentration exceeds 6 g/dL, moderate hypercalcemia may be seen. Changes in pH have an effect on calcium protein binding; acidosis decreases calcium binding, resulting in an increase in free-calcium fraction, whereas an increase in pH reduces the amount of ionized calcium. Changes in serum phosphate and sulfate concentrations are expected to alter the fraction of ionized calcium because of the formation of calcium complexes with these anions. The presence of abnormal plasma proteins with a high affinity for calcium binding, as in patients with multiple myeloma, also affects Eq. 27-13 for serum calcium concentration correction.

Serum calcium concentration is regulated by the combined effect of GI absorption and secretion, kidney reabsorption, and turnover of the skeletal calcium pool. Several hormones, such as PTH, 1,25-dihydroxyvitamin D_3, and calcitonin, have significant effects on these processes. Balanced diets generally contain 600 to 1000 mg of calcium, although the minimum daily requirement is 400 to 500 mg. Calcium is primarily absorbed in the duodenum and jejunum via saturable and nonsaturable processes. The nonsaturable process is diffusive in nature and varies with luminal calcium concentration. The saturable carrier-mediated component is stimulated by 1,25-

dihydroxyvitamin D_3. Absorption of calcium is enhanced when the calcium intake is low and also when the demand is increased, such as in pregnancy and when total body calcium is depleted. Conversely, protein deficiency can reduce intestinal calcium absorption, presumably because of the reduced amount of specific calcium-binding protein. Calcium is also secreted into the bowel lumen, which may account for the presence of a negative calcium balance when there is no oral calcium intake.

The portion of plasma calcium that is not bound to protein is filtered by the glomerulus. Approximately 97% to 99.5% of the filtered calcium is reabsorbed: 60% in the proximal tubule, 20% in the ascending limb, 10% in the distal tubule, and 3% to 10% in the collecting duct. Approximately 20% of the calcium in the kidney tubule is ionized, whereas the remainder is bound to anions such as citrate, sulfate, phosphate, and gluconate. The extent of calcium reabsorption depends on the presence of specific anions and also on the urine pH, which affects the fraction of calcium bound to anions. Passive reabsorption at the proximal convoluted tubule is linked closely to sodium transport and is increased by ECF contraction and decreased by volume expansion. At the proximal straight tubule, the transport process is active and dissociable from sodium and water transport. PTH increases the calcium reabsorption at the distal tubule and also at the collecting duct independent of sodium reabsorption. Acidosis can also increase kidney calcium excretion by inhibiting tubular reabsorption and by increasing the ultrafiltrable calcium through reduced binding of calcium to plasma proteins. Conversely, alkalosis promotes calcium protein binding, thus reducing the amount of ultrafiltrable calcium. It also induces hypocalciuria independent of PTH. Phosphorus administration reduces kidney calcium excretion, whereas phosphorus depletion increases urinary calcium elimination. Normally, ~50 to 300 mg of calcium is excreted by the kidneys daily, but this can be increased to 600 mg/day.

The other important factor regulating plasma calcium concentration is bone metabolism. The rate of bone turnover and

calcium resorption is influenced by PTH, 1,25-dihydroxyvitamin D_3, and calcitonin.

Hypocalcemia

ETIOLOGY

Hypocalcemia may be caused by factors such as PTH abnormalities or PTH resistance, vitamin D deficiency or resistance, abnormal magnesium metabolism, and extravascular calcification.[72,73]

Hypoparathyroidism secondary to parathyroidectomy, thyroidectomy, radiation therapy, congenital defects of the parathyroid glands, or autoimmune disease can result in low serum calcium concentrations.[74–77] In such cases, administration of oral calcium and vitamin D is necessary to increase GI calcium absorption. Conversely, hyperparathyroidism in the setting of vitamin D deficiency, vitamin D resistance, or chronic kidney disease is another common cause of hypocalcemia. Furthermore, patients with kidney impairment often present with hyperphosphatemia due to reduced phosphate excretion. The elevated serum phosphate concentration in turn binds with calcium, causing hypocalcemia. Hypomagnesemia causes PTH resistance and hypocalcemia.[72] In such cases, repletion of magnesium is necessary to correct the calcium disorder. Severe hypermagnesemia can also result in hypocalcemia by suppressing PTH secretion.[78]

Medications such as bisphosphonates,[79] denosumab,[80] calcimimetics,[81] foscarnet,[82] and certain chemotherapeutic agents such as cisplatin[83] can also cause hypocalcemia. Other causes of hypocalcemia include bone metastases,[84] acute pancreatitis,[85] sepsis,[86] and the use of citrate as an anticoagulant in blood transfusions.[87]

Regardless of the cause, the diagnosis of hypocalcemia should be confirmed either by repeated measurements of its laboratory value, correction for hypoalbuminemia, or direct measurement of ionized calcium.

CLINICAL MANIFESTATIONS

The clinical presentation of hypocalcemia depends on its severity and chronicity.[72] Most patients with mild hypocalcemia are asymptomatic, but those with significant or abrupt changes in calcium concentrations may be symptomatic. The most common symptoms of severe or acute hypocalcemia involve the neuromuscular system such as parasthesias, carpopedal spasms, and seizures and may progress to tetany. Neuromuscular signs of hypocalcemia include the Chvostek and Trousseau signs. The Chvostek sign is contraction of the ipsilateral facial muscles elicited by tapping the facial nerve anterior to the ear. The Trousseau sign is the induction of carpal spasm by inflation of a sphygmomanometer above systolic BP for 3 minutes. Of these two signs, the Trousseau sign is more specific. It is recommended that both clinical signs be confirmed with a measurement of ionized calcium.

Other than the neuromuscular system, cardiovascular and psychiatric manifestations such as hypotension, ECG changes (eg, QT prolongation, emotional instability, anxiety, depression, and confusion) may also be evident.

TREATMENT

The management of hypocalcemia depends on the severity of symptoms.[73] IV calcium therapy is recommended in patients with acute symptomatic hypocalcemia (serum-corrected calcium concentration <7.5 mg/dL), whereas oral calcium and vitamin D supplements are usually adequate in mildly symptomatic or chronic hypocalcemia (serum-corrected calcium concentration >7.5 to 8.0 mg/dL).

IV calcium gluconate is preferred over calcium chloride because of its lower propensity to cause extravasation and tissue necrosis. It may be given as 1 or 2 g calcium gluconate (equivalent to 90 or 180 mg elemental calcium) in 50 mL of D5W or normal saline over 10 to 20 minutes. The infusion rate should not be faster because of the risk of cardiac complications. Subsequently, a slow calcium infusion can be continued in patients whose hypocalcemia persists. Oral

calcium and vitamin D (eg, calcitriol) should be initiated, and the IV calcium supplementation stopped after achieving optimal serum calcium concentration. Patients with concurrent hypomagnesemia should be treated with IV and/or oral magnesium repletion before correcting hypocalcemia. Refer to the section on magnesium disorders for the management of hypomagnesemia.

Patients with mild hypocalcemia, are mildly symptomatic (eg, oral paresthesias), or have chronic hypocalcemia can receive oral calcium supplementation. Elemental calcium 1500 to 2000 mg in the form of calcium salts (eg, calcium carbonate or calcium citrate) may be given daily in divided doses. In addition, patients with hypoparathyroidism or vitamin D deficiency will require vitamin D supplementation in the form of nutritional (vitamin D_2, ergocalciferol or vitamin D_3, cholecalciferol) or active vitamin D (calcitriol) therapy. An advantage of vitamin D is that it enhances gut absorption of calcium and thus can possibly reduce the dose requirement of calcium.

Hypercalcemia

ETIOLOGY

CASE 27-11

Question 1: A.C., a 62-year-old female, is brought to the hospital by family members because she has become increasingly lethargic and unresponsive during the past several days. Approximately 4 years ago she underwent a radical mastectomy and node dissection followed by radiation and chemotherapy for breast carcinoma. Despite several courses of chemotherapy, she developed metastasis to the bone. About 1 week before this admission, A.C. experienced fatigue, muscle weakness, and anorexia. Since then, she has spent most of her time in bed and has had very limited oral intake. Medications taken before admission included hydrochlorothiazide, oral morphine sulfate, and tamoxifen. Physical examination reveals a dehydrated, cachectic female responsive only to painful stimuli. Vital signs include BP, 100/60 mm Hg, and RR, 16 breaths/minute. Pertinent laboratory values are as follows:

Na^+, 138 mEq/L

K^+, 4.5 mEq/L
Cl^-, 99 mEq/L
Total CO_2, 33 mEq/L
BUN, 40 mg/dL
Creatinine, 1.2 mg/dL
Calcium, 19 mg/dL
Phosphate, 4.5 mg/dL
Albumin, 3.0 g/dL
The ECG revealed a shortened QT interval.

What are the common causes of hypercalcemia? Which of these might be responsible for the hypercalcemia seen in A.C.?

Malignancy and primary hyperparathyroidism are the most common causes of hypercalcemia.[88] Hematologic malignancies, such as multiple myeloma, tend to be responsible for more hypercalcemia than are solid tumors. Cancer of the breast, lung, head and neck, and kidney cell carcinoma are solid tumors commonly associated with hypercalcemia. Malignancy can cause paraneoplastic hypercalcemia secondary to bone metastasis, which results in increased bone resorption. Alternatively, patients may exhibit hypercalcemia in the absence of bone metastasis owing to the production of osteolytic humoral factors by the tumor. The mediators secreted may be PTH, PTH-like substances, prostaglandins, cytokines, transforming growth factor-α, and tumor necrosis factor.[88]

Hyperparathyroidism is the other common cause of hypercalcemia.[89] Although the etiology of primary hyperparathyroidism is unclear, females tend to experience the condition more frequently, especially in the fourth to sixth decades of life. Approximately 75% of patients have a single adenoma, whereas much smaller percentages of patients have multiglandular disease, hyperplasia, or carcinoma.[88] Other conditions that can result in hypercalcemia include post–kidney transplantation, immobilization, vitamin A intoxication, hyperthyroidism,[72] Addison disease, and pheochromocytoma. Hypercalcemia can also occur secondary to increased intestinal calcium absorption because of vitamin D intoxication, sarcoidosis, and other granulomatous diseases. Use of

thiazide diuretics, lithium, estrogens, and tamoxifen, as well as excessive calcium ingestion together with alkali (milk–alkali syndrome), may result in hypercalcemia.

A.C.'s breast cancer bone metastasis, volume contraction, and use of hydrochlorothiazide and tamoxifen may all contribute to her hypercalcemia.

CLINICAL MANIFESTATIONS

CASE 27-11, QUESTION 2: How is hypercalcemia manifested in A.C.?

The clinical presentations of hypercalcemia vary substantially among patients, but the severity of the symptoms correlates well with free-calcium concentrations.[72] The specific presentation depends on the rate of serum calcium concentration elevation, the presence of malignancy, the PTH concentration, and the patient's age. Concurrent electrolyte and metabolic abnormalities and underlying diseases will also have an effect. Because calcium is an important regulator of many cellular functions, hypercalcemia can produce abnormalities in the neurologic, cardiovascular, pulmonary, kidney, GI, and musculoskeletal systems. As seen in A.C., the signs and symptoms can be nonspecific: fatigue, muscle weakness, anorexia, thirst, polyuria, dehydration, and a shortened QT interval on the ECG.

The effect of hypercalcemia on the central nervous system includes lethargy, somnolence, confusion, headache, seizures, cerebellar ataxia, altered personality, acute psychosis, depression, and memory impairment. The neuromuscular manifestations include weakness, myalgia, hyporeflexia or areflexia, and arthralgia.

Symptoms of impaired kidney function include polyuria, nocturia, and polydipsia. These may reflect a defective concentrating ability, possibly because of resistance to the effects of ADH. The GFR may be decreased because of afferent arteriolar vasoconstriction, and if hypercalcemia is prolonged, nephrolithiasis, nephrocalcinosis, chronic interstitial nephritis, and renal tubular acidosis may be

present. Hypermagnesuria and metabolic alkalosis may also be observed.

Calcium has a positive inotropic effect and reduces heart rate, similar to cardiac glycosides. ECG changes indicative of slow conduction, with prolonged PR and QRS intervals and shortened QT intervals, are commonly seen. In severe hypercalcemia, increased QT intervals, widened T waves, and arrhythmia may be present.

The GI symptoms of hypercalcemia are related primarily to the depressive action of calcium on smooth muscle and nerve conduction. Constipation, anorexia, nausea, and vomiting result from reduced GI motility and delayed gastric emptying. Duodenal ulcer can occur because of increased acid and gastrin secretion. Pancreatitis can occur during acute hypercalcemia owing to the blockade of the pancreatic ducts caused by intraductal calcium deposits. Proteolytic enzymes may also be activated by calcium, causing tissue damage. Both ulcer disease and pancreatitis are more common in hypercalcemia associated with primary hyperparathyroidism; they are less likely to be seen in patients with malignancy-induced hypercalcemia.

Treatment

Case 27-11, Question 3: After vigorous fluid resuscitation with IV saline at a regimen of normal saline 75 to 100 mL/hour and increased by 50 to 100 mL/hour every 6 to 8 hours to a goal rate of 200 to 300 mL/hour, combined normal saline and furosemide diuresis at a furosemide dose of 40 mg IV every 4 hours was instituted in A.C. Her serum calcium concentration declined very slowly, prompting the use of calcitonin. Despite initial success, the serum calcium concentration rose to pretreatment values within 24 hours. Higher dosages of calcitonin could have been attempted at this point; however, pamidronate 90 mg IV infused over 4 hours was used instead. Her serum calcium concentration finally stabilized at 8 mg/dL after several days of therapy. What was the rationale for each of these regimens? What other agents are available for hypercalcemia treatment?

Several therapeutic approaches are used to lower serum calcium concentration: increasing urinary calcium excretion, inhibiting release

of calcium from bone, reducing intestinal calcium absorption, and enhancing calcium complex formation with chelating agents. The underlying disease that causes hypercalcemia should also be treated, if possible. The specific treatment used depends on the serum ionized calcium concentration, the presenting signs and symptoms, and the severity and duration of hypercalcemia. Immediate therapy was needed for A.C., who had symptoms consistent with severe hypercalcemia.

Specific interventions are described in the subsequent paragraphs, but as an overview, hydration and diuresis with furosemide in patients at risk for fluid overload are generally the first steps in the acute treatment of hypercalcemia. If these measures fail to reduce the serum calcium concentration adequately, several other agents can be added. Calcitonin provides a rapid onset of hypocalcemic effect, but its duration of action is relatively short. Thus, a bisphosphonate could be used to elicit a longer hypocalcemic response. Other agents, such as denosumab, calcimimetics, and glucocorticoids also have been used to treat hypercalcemia and may be used as alternatives (**Table 27-4**).

Table 27-4
Treatment of Hypercalcemia

Intervention	Dose	Comment

Intervention	Dose	Comment
Normal saline (NS) and furosemide	1–2 L NS; then furosemide 80–100 mg every 2–4 hours. Establish and maintain normovolemia. Replace other electrolytes as needed. Alternatively, administer NS alone at an initial rate of 200–300 mL/hour followed by titration in rate to maintain urine output of 100–150 mL/minute, to treat dehydration and restore euvolemia, along with the use of other agents such as calcitonin and bisphosphonates.	Saline diuresis and volume expansion depresses Ca^{2+} reabsorption in tubules. Lowers Ca^{2+} within 24 hours. Treatment of choice in patients without HF or kidney failure. Use loop diuretics with NS hydration in patients with kidney or heart failure.
Calcitonin	4 IU/kg SQ or IM every 12 hours. ↑ Dose or use another therapy if unresponsive after 24 hours (Max: 8 IU/kg every 6 hours).	Inhibits osteoclast resorption and kidney reabsorption of calcium. Preferred second-line agent because it has a rapid onset (6 hours) and is nontoxic. It can be used safely in HF and kidney failure. Nausea is the major adverse effect. Tolerance occurs in 24–72 hours. Concomitant plicamycin can lead to hypocalcemia. Only the salmon-derived product is available.

Intervention	Dose	Comment
Bisphosphonates (pamidronate, zoledronic acid, ibandronate)	Pamidronate: 60–90 mg IV for 4 hours × 1. Repeat in 7 days PRN. Zoledronic acid: 4 mg IV administration for 15 minutes. Repeat in 7 days PRN. Ibandronate: 2 mg IV administered over 2 hours. Doses up to 6 mg shown to be safe and well tolerated	Potent effect on bone resorption. Inhibits osteoclast reabsorption in malignancy state. Efficacy 75%–100%. Onset 48 hours. Duration, days. Concomitant hydration is imperative. Use with caution in kidney failure; adjustment in dose and infusion rate recommended. Adverse effects: ↑ phosphorus, ↑ SCr, osteonecrosis of jaw
Denosumab	120 mg SQ every 4 weeks, with additional doses on days 8 and 15 during the first month of therapy. In kidney impairment, recommend lower starting dose of 0.3 mg/kg SQ followed by a second dose if goal calcium is not attained within a week.	Recommended in patients refractory to or in whom bisphosphonate therapy is contraindicated (eg, severe kidney impairment). Monitor serum calcium and vitamin D levels, and repeat with oral/IV calcium and/or vitamin D as needed; closer monitoring needed in kidney impairment
Corticosteroids	Prednisone: 60–80 mg/day Hydrocortisone: 5 mg/kg/day IV × 2–3 days	Impair GI absorption and bone resorption. Onset several days. Best in patients with multiple myeloma, vitamin D intoxication, granulomatous conditions. Can be used in HF, kidney failure

GI, gastrointestinal; HF, heart failure; IM, intramuscularly; IV, intravenously; PO, orally; PRN, as needed; SQ, subcutaneously; SCr, serum creatinine.

HYDRATION AND DIURESIS

As noted, the first-line emergency treatment for hypercalcemia is hydration and volume expansion.[90] Most patients with hypercalcemia are volume depleted because of the accompanying polyuria, nausea, and vomiting. Normal saline 1 to 2 L/day is commonly given to correct the fluid deficit and to expand extracellular volume, which will

increase urinary calcium excretion by increasing the GFR and inhibiting calcium reabsorption in the proximal tubule. Because both sodium and calcium are reabsorbed at the same site in the proximal tubule, saline hydration will reduce the reabsorption of both cations simultaneously. A.C. was hypotensive and appeared dehydrated; therefore, saline hydration was used initially to treat hypercalcemia.

In patients who have kidney failure or HF, saline hydration alone should be used with caution to avoid fluid overload. Alternatively, a loop diuretic may be used in conjunction with saline hydration to prevent volume overload in these patients. Careful monitoring of these patients is recommended.

After adequate volume repletion has been established, IV furosemide can be administered to augment calciuresis. Furosemide blocks the reabsorption of sodium, chloride, and calcium at the thick ascending limb of the Henle loop. Doses of 80 to 100 mg every 2 to 4 hours can be used until a sufficient decline of the serum calcium concentration is attained. Smaller doses (20–40 mg) commonly are given to avoid the significant loss of fluid and electrolytes caused by the more aggressive regimen. Adequate amounts of sodium, potassium, magnesium, and fluid should be used to replace any therapy-induced electrolyte abnormalities. Fluid balance as well as serum and urine concentrations of these electrolytes must be monitored closely. Urine flow must be maintained, and the kidney loss of sodium chloride must be replaced to preserve the calciuric effect of furosemide. In A.C., the decline in serum calcium concentration was slow, possibly because of inadequate restoration of plasma volume, replacement of kidney sodium loss, or both. More aggressive hydration with adequate sodium replacement ensures that the efficacy of furosemide is not compromised.

In current practice, the use of loop diuretics together with saline hydration is less common except in patients with reduced kidney function and HF. As such, administration of normal saline alone at an initial rate of 200 to 300 mL/hour followed by a titration in rate to maintain urine output of 100 to 150 mL/minute, to treat dehydration and restore euvolemia, along with the use of other agents such as

calcitonin and bisphosphonates, should be reasonable and sufficient in most patients.

CALCITONIN

Calcitonin is useful when used in combination with saline hydration for the initial management of moderate-to-severe hypercalcemia and can result in a rapid reduction in serum calcium concentration.[90] Calcitonin reduces serum calcium concentration by inhibiting osteoclastic bone resorption. It may also increase the excretion of calcium and phosphorus by the kidneys. Only the salmon-derived calcitonin product is available in the United States.

The serum calcium concentration is often reduced several hours after calcitonin is administered, and the response may last ~6 to 8 hours. The drug is relatively nontoxic compared with organic phosphates and may be used in patients with dehydration, HF, or kidney failure. Nausea, vomiting, diarrhea, and facial flushing are the more common side effects; soreness and inflammation at the injection site may also be seen. Because of the potential for developing a hypersensitivity reaction to salmon calcitonin, the manufacturer recommends skin testing with 1 IU of the salmon calcitonin before the first dose. As seen in A.C., tolerance to the hypocalcemic effect of calcitonin can develop after 24 to 72 hours of therapy. This “escape phenomenon” may be secondary to the altered responsiveness of the hormone receptors and might be prevented by concurrent use of corticosteroids. After long-term therapy, antibodies may develop as well resulting in tachyphylaxis.

The dosage of salmon calcitonin is 4 IU/kg given subcutaneously or intramuscularly (IM) every 12 hours; the maximal dosage is 8 IU/kg every 6 hours. The hypocalcemic response is often limited, and serum calcium concentration seldom drops to the normal range.

BISPHOSPHONATES

Bisphosphonates are synthetic analogs of pyrophosphate that form stable bonds that are resistant to phosphatase degradation during osteoclast-mediated bone mineralization and resorption. The

compounds adsorb to the hydroxyapatite crystals of the bone, inhibiting their growth and dissolution. In addition, the compounds may have a direct effect on osteoclasts.[90] The two distinct pharmacologic classes of bisphosphonates that exist have different mechanisms of action. Etidronate, which does not contain any nitrogen atom, is metabolized to cytotoxic, nonhydrolyzable adenosine triphosphate (ATP) analogs. In contrast, nitrogen-containing bisphosphonates, such as pamidronate, zoledronic acid, and ibandronate inhibit the prenylation of proteins and have potent inhibitory effects on osteoclast-mediated bone resorption. In addition, they induce apoptosis of osteoclasts as well as certain tumor cells. Further antitumor activities may be mediated through their inhibitory effect on angiogenesis, stimulation of the γ-T-cell fraction in blood, and reduction of cancer cells' adherence to bone matrix. At present, etidronate, pamidronate, zoledronic acid, and ibrandronate are approved in the United States for the treatment of hypercalcemia secondary to malignancy. However, etidronate use has resulted in kidney failure, which probably is caused by the formation of bisphosphonate–calcium complexes in the serum. Furthermore, its relatively weak potency and its inconvenient IV dosing schedule have made it a less preferred agent among the other newer bisphosphonates. As such, it will not be elaborated on in this chapter. Osteonecrosis of the jaw is a concern with long-term, high-dose IV bisphosphonate therapy. However, this concern may not be of critical importance because acute hypercalcemia does not usually require long-term treatment. Patients with elevated SCr concentration and reduced kidney function would benefit from dosage adjustment of IV bisphosphonates because of their potential for nephrotoxicity. As such, caution should be exercised when using IV bisphosphonates to treat hypercalcemia in such patients. Sufficient normal saline hydration and the use of a lower dose accompanied by a slower infusion rate (eg, pamidronate 30–45 mg IV over 4 hours, zoledronic acid 4 mg IV over 30–60 minutes, and ibandronate 2 mg IV over 1–2 hours) may be considered to reduce the risk.

Pamidronate

For moderate hypercalcemia (albumin-corrected serum calcium concentration of 12.0–13.5 mg/dL), a single dose of 60 to 90 mg of pamidronate is commonly infused over the course of 3 to 4 hours. For severe hypercalcemia (albumin-corrected serum calcium concentration >13.5 mg/dL), the dose is 90 mg. The advantages of pamidronate are that it requires only a single dose and produces a superior response compared with three doses of etidronate.

If the hypercalcemia recurs, the pamidronate regimen may be repeated after an interval of ≥7 days. Long-term treatment may result in osteomalacia; however, the limited life expectancy of most patients may diminish the significance of this adverse effect. Dosing adjustment is recommended in patients with kidney impairment (SCr <30 mL/minute), as described in the section on Bisphosphonates.

Zoledronic acid

Among the bisphosphonates approved for the treatment of hypercalcemia of malignancy, zoledronic acid has the most potent effect on bone resorption. It is superior to pamidronate with respect to the number of complete responses, time needed to attain calcium normalization, and duration of effect.[91] Because 8-mg doses are not superior to 4-mg doses, 4-mg doses are administered IV over the course of 15 minutes. The drug is well tolerated at 4-mg doses. Furthermore, the lower dose accompanied by longer infusion duration (4 mg IV over 30–60 minutes) makes it safer for patients with reduced kidney function such as SCr >4.5 mg/dL. Zoledronic acid's superior efficacy and convenience of administration make it the preferred bisphosphonate for hypercalcemia of malignancy. Emerging studies show that zoledronic acid may also have promising effects in reducing skeletal complications secondary to bone metastasis associated with breast cancer, prostate cancer, non-small-cell lung cancer, and multiple myeloma.[92]

Ibandronate

Ibandronate has been shown to be effective in the treatment of hypercalcemia of malignancy. When administered as a 2- or 4-mg IV dose, it demonstrated efficacy similar to that of pamidronate and is thus a suitable option if zoledronic acid or pamidronate is not available.[93] Doses up to 6 mg were also safe and well tolerated.[94,95] Just like the other bisphosphonates, a reduction in dose and/or infusion rate is recommended in patients with impaired kidney function (CrCl <30 mL/minute).

DENOSUMAB

Denosumab is a monoclonal antibody that binds to the nuclear factor-κ ligand (RANKL) and inhibits the interaction between RANKL and RANK (a receptor found on surfaces of osteoclasts).[96] Its actions include preventing osteoclast formation or decreasing osteoclastic activity, and ultimately decreasing bone mass and bone-related adverse events.

Because denosumab is not cleared by the kidneys, its use is especially useful for patients with kidney impairment in whom bisphosphonates are contraindicated. It can also be considered in patients with hypercalcemia who do not respond to other therapies.

Unlike bisphosphonates that are administered IV, denosumab is given subcutaneously at a dose of 120 mg on days 8 and 15 during the first month, followed by every 4 weeks for the treatment of hypercalcemia of malignancy. However, because patients with kidney failure are at a higher risk for developing hypocalcemia when treated with denosumab, a lower starting dose of 0.3 mg/kg followed by a second dose if goal calcium is not attained within a week is recommended.[97,98] In addition, closer monitoring of serum calcium and vitamin D levels and repletion with oral/IV calcium and/or vitamin D may be necessary.

CALCIMIMETICS

Cinacalcet and etelcalcetide are the oral and IV forms of calcimimetic agents, respectively, currently available in the United States. Cinacalcet is used in the treatment of hypercalcemia

secondary to primary hyperparathyroidism and parathyroid carcinoma, whereas both agents are approved for use in secondary hyperparathyroidism in hemodialysis patients.[99] Their use in hypercalcemia of malignancy is less well established.

CORTICOSTEROIDS

Several possible mechanisms that may explain the hypocalcemic effect of corticosteroids exist. Vitamin D_3–mediated intestinal calcium absorption may be impaired[100] and the action of osteoclast-activating factor, which mediates bone resorption in malignancy, may be inhibited. Corticosteroids may also have a direct cytolytic effect on tumor cells and inhibit the synthesis of prostaglandins. Prednisone in daily doses of 60 to 80 mg is given initially, with subsequent dosage reduction based on the calcemic response. Alternatively, hydrocortisone (5 mg/kg/day for 2–3 days) may be given. The hypocalcemic effect will not be apparent for at least 1 to 2 days. Patients with hematologic malignancies and lymphomas tend to have a better response than do those with solid tumors. Corticosteroids are also effective in treating hypercalcemia associated with vitamin D intoxication, sarcoidosis, and other granulomatous conditions.[101] They are not generally used for long-term therapy because of their potential for serious adverse reactions.

DIALYSIS

Kidney replacement therapy such as hemodialysis and peritoneal dialysis may be considered in patients with severe malignancy who do not respond to other therapies or in those with kidney or HF who do not tolerate saline hydration therapy. Of note, the use of low-calcium or calcium-free dialysate is necessary to avoid exacerbating hypercalcemia.

PHOSPHORUS

Homeostasis

Phosphorus is found primarily in bone (85%) and soft tissue (14%); <1% of the total body store resides in the ECF.[71] Virtually, all of the "free" or active phosphorus exists as phosphates in the plasma. Most clinical laboratories, however, measure and express the concentrations of elemental phosphorus contained in the phosphate molecules. Phosphate of 1 mmol contains 1 mmol of phosphorus, but 1 mmol of phosphate is three times the weight of 1 mmol of phosphorus. Therefore, it is incorrect to equate a certain milligram weight of phosphorus as the same milligram weight of phosphate. Of the total plasma phosphorus, 70% exists as the organic form and 30% as the inorganic form. Organic phosphorus, primarily phospholipids and small amounts of esters, is bound to proteins. About 85% of inorganic phosphorus, or orthophosphate, is unbound or "free." The relative amounts of the two orthophosphate components, $H_2PO_4^-$ and HPO_4^{2-}, vary with pH. At pH 7.40, the ratio of the two species is 1:4, giving rise to a composite valence of 1.8 for the orthophosphate. Serum phosphate concentrations reported by clinical laboratories reflect only the inorganic portion of the total plasma phosphate. To avoid confusion related to the pH effect on valence, phosphate concentrations are reported as mg/dL or mmol/dL rather than mEq/volume.

The normal range of serum phosphate concentration in healthy adults is 2.5 to 4.5 mg/dL. The value is higher in children, possibly because of the increased amount of growth hormone and the reduced amount of gonadal hormones.[72,101] In postmenopausal females, the range is slightly higher; it is lower in older males. The serum phosphate concentration is also affected by dietary intake. Phosphate-rich foods can transiently increase the serum phosphate concentration. In contrast, glucose decreases the serum phosphate concentration because of the flux of sugar and phosphate into cells and because of the phosphorylation of glucose. Similarly, administration of insulin and epinephrine decreases the serum phosphate concentration because of their effects on glucose. The

serum concentration of phosphate is reduced in alkalosis and increased in acidosis.[101]

A balanced diet contains 800 to 1500 mg/day phosphorus. Both the organic and inorganic forms of phosphorus are present in food substances. Most of the phosphorus in milk is the organic form; the phosphorus in meat, vegetable, and other nondairy sources represents organic forms bound to proteins, lipids, and sugars, which usually are hydrolyzed before absorption. In general, 60% to 65% of the phosphorus ingested is absorbed, mostly in the duodenum and jejunum through an energy-dependent, saturable, active process. Phosphorus absorption is linearly related to the dietary intake when the intake is 4 to 30 mg/kg/day. The amount of phosphorus ingested probably is the most important factor in determining net absorption. Phosphorus absorption is also stimulated during periods of increased demand, such as active growth and pregnancy. Increased intake of calcium and magnesium and concurrent use of aluminum hydroxide antacids may reduce phosphorus absorption owing to formation of a nonabsorbable complex. In addition, absorption is also affected by vitamin D, PTH, and calcitonin.[72]

Phosphorus excretion by the kidneys depends on the dietary phosphorus intake. Normally, >85% of the filtered phosphate load is reabsorbed; however, the fractional urinary excretion can vary from 0.2% to 20%. Phosphate excretion by the kidneys is also affected by acid–base balance, ECF volume, and calcium and glucose concentrations.[72,101] In addition, PTH, thyroid hormone, thyrocalcitonin, vitamin D, insulin, glucocorticoid, and glucagon can also alter phosphate excretion.

Hypophosphatemia

ETIOLOGY

CASE 27-12

Question 1: M.R., a 72-year-old female, was admitted to the hospital with a 1-week history of increasing malaise, confusion, and decreased activity. M.R. has

a history of HF, hypertension, type 2 diabetes, and peptic ulcer disease. She was receiving hydrochlorothiazide, aluminum–magnesium antacid, sucralfate, and insulin. She is febrile and in significant respiratory distress. ABG results at admission were pH, 7.5; PaO_2, 42 mm Hg; and $PaCO_2$, 20 mm Hg. Respiratory function continued to deteriorate, requiring intubation and mechanical ventilation. Serum electrolyte concentrations were as follows:

Na^+, 128 mEq/L
K^+, 3.2 mEq/L
Cl^-, 96 mEq/L
Total CO_2, 23 mEq/L
Glucose, 320 mg/dL
Phosphorus, 0.9 mg/dL

What may have contributed to the low serum phosphorus concentration in M.R.?

Hypophosphatemia can develop as the result of a phosphorus deficiency or secondary to a net flux of phosphorus out of the plasma compartment without a total body deficit. Moderate hypophosphatemia is defined as a serum phosphorus concentration of 1 to 2 mg/dL. A concentration of <1 mg/dL, as in M.R., is considered severe.[102] The extent of hypophosphatemia may not be assessed accurately by a single plasma phosphorus concentration determination because of diurnal variation. Patients receiving large doses of mannitol may have pseudohypophosphatemia owing to the binding of mannitol with molybdate, which is used in the calorimetric assay for phosphorus.

Hypophosphatemia is commonly caused by conditions that impair intestinal absorption, increase kidney elimination, or shift phosphorus from the extracellular to the intracellular compartments. Hypophosphatemia secondary to low dietary phosphorus is exceedingly rare because phosphorus is ubiquitous.[71,102] In addition, phosphorus excretion is reduced and intestinal phosphorus absorption is increased to prevent a deficiency state. Starvation in itself does not result in severe hypophosphatemia because the phosphorus content in plasma and muscles is often normal. Hypophosphatemia, however, can develop during refeeding with a high-calorie diet low in phosphorus. Therefore, hyperalimentation

without phosphorus supplementation is likely to cause severe hypophosphatemia.

Impaired phosphorus absorption secondary to malabsorptive conditions, prolonged nasogastric suction, and protracted vomiting can also result in hypophosphatemia. In M.R., the use of aluminum-containing and magnesium-containing antacids may further reduce phosphorus absorption. The antacids bind with endogenous and exogenous phosphorus in the GI tract and cause severe hypophosphatemia in patients with or without kidney failure.[103] In addition, M.R. was taking sucralfate, which contains aluminum and can bind phosphorus in the GI tract.[103] Similarly, iron preparations can bind phosphorus.[104]

Hyperglycemia-induced osmotic diuresis and diuretic use may have increased the kidney loss of phosphorus in M.R. Other conditions associated with phosphorus wasting include renal tubular acidosis, hyperparathyroidism, hypokalemia, hypomagnesemia, and extracellular volume expansion.[72,101,102] None of these situations, however, was evident in M.R. Shifting of phosphorus into the intracellular compartment by glucose or insulin and profound respiratory alkalosis may also have contributed to M.R.'s hypophosphatemic state.[101,102]

Case 27-12, Question 2: What other conditions are commonly associated with hypophosphatemia?

Diabetic ketoacidosis, chronic alcoholism, chronic obstructive airway disease, and extensive thermal burns are other conditions commonly associated with hypophosphatemia.[72,101,102] They are characterized by a combination of factors that result in phosphate loss and intracellular phosphate use. In patients with diabetic ketoacidosis, metabolic acidosis enhances the movement of phosphate from the intracellular compartment to plasma, whereas the concurrent osmotic diuresis secondary to hyperglycemia increases the kidney elimination of extracellular phosphate. The net result is a depletion of total body stores. Correction of the acidosis

and administration of insulin then promotes the rapid uptake of phosphorus by tissues, and volume repletion dilutes the extracellular concentration. This sequence of events can ultimately lead to severe hypophosphatemia. The hypophosphatemia associated with chronic alcoholism and acute alcohol intoxication is also thought to be related to several factors, including reduced intestinal phosphorus absorption caused by vomiting, diarrhea, and antacid use; repeated acidosis that results in increased urinary phosphate excretion; and a shift of phosphorus into cells because of respiratory alkalosis. Phosphorus wasting can also result from hypomagnesemia or as a direct effect of alcohol.[102]

CLINICAL MANIFESTATIONS

Case 27-12, Question 3: What are the signs and symptoms associated with hypophosphatemia?

The clinical effects associated with chronic phosphorus depletion are often insidious and gradual in onset. In contrast, a rapid decline in plasma phosphorus concentrations results in sudden and serious organ dysfunction. Most of the effects can be attributed to impaired cellular energy stores and tissue hypoxia secondary to depletion of ATP or erythrocyte 2,3-diphosphoglycerate.[72,102] Severe hypophosphatemia can result in generalized muscle weakness, confusion, paresthesias, seizures, and coma. In addition, reduced cardiac contractility, hypotension, respiratory failure, and rhabdomyolysis have been observed with acute severe hypophosphatemia. Chronic phosphorus depletion has been associated with decreased mentation; muscle weakness; osteomalacia; rickets; anorexia; dysphagia; cardiomyopathy; tachypnea; reduced sensitivity to insulin; and dysfunction of red blood cells, white blood cells, and platelets. Kidney function is altered, as manifested by hypophosphaturia, hypercalciuria, hypermagnesuria, bicarbonaturia, and glycosuria. M.R.'s decreased

mentation, weakness, and respiratory failure are consistent with severe hypophosphatemia.

CASE 27-12, QUESTION 4: How can phosphate depletion be assessed? Outline a treatment regimen that would effectively and safely correct the phosphorus deficit in M.R. How should her therapy be monitored?

TREATMENT

Phosphorus resides primarily in the intracellular space; the amount in the ECF is only a small percentage of the total body store. Because the patient's pH, blood glucose concentration, and insulin availability may affect phosphorus distribution, it is difficult to determine the magnitude of the phosphorus deficit based on the serum concentration alone. As discussed, a patient may have hypophosphatemia secondary to a rapid shift of phosphorus into the intracellular space without a total body deficit. The duration of the hypophosphatemia is often limited because it may be corrected by kidney phosphorus conservation and oral intake of phosphorus-containing foods. Aside from serum phosphorus concentrations, urinary phosphorus excretion may be used to further assess the phosphorus deficit. Typically, phosphorus excretion is severely limited in patients with significant deficits. A phosphorus excretion of <100 mg/day (fractional phosphorus excretion < 10%) confirms appropriate phosphorus conservation when the serum phosphorus is <2 mg/dL. It also suggests a non-kidney etiology (eg, impaired GI absorption) or some type of internal redistribution (eg, respiratory alkalosis).

Prophylactic supplementation should be used in situations that predictably increase the risk of developing hypophosphatemia. These include patients who are receiving total parenteral nutrition or large doses of antacids for an extended period, patients who are alcoholic, and those with diabetic ketoacidosis.

The specific treatment of hypophosphatemia depends on the presence of signs and symptoms, as well as the anticipated duration and severity of hypophosphatemia. In an asymptomatic patient with

mild hypophosphatemia (2–2.5 mg/dL), who has no evidence of phosphorus depletion, phosphorus supplementation is generally not necessary because the condition is usually self-limited. In other patients with mild and moderate hypophosphatemia who have evidence of phosphorus deficit, oral supplementation is the safest and preferred mode of replacement. Skim or low-fat milk is a convenient source of phosphorus and calcium. Whole milk, because of its high fat content, can cause diarrhea if a large amount is consumed. Several oral phosphorus preparations can be used in patients who cannot tolerate milk products.

When hypophosphatemia is severe, as in M.R.'s case, or when the patient is vomiting or unable to take oral medication, parenteral phosphorus replacement is needed.

Either potassium phosphate or sodium phosphate injection may be used for parenteral phosphate replacement. Owing to its propensity to cause adverse consequences such as hyperkalemia or phlebitis and risk of medication errors if inadequately diluted or administered too rapidly, potassium phosphate is less preferred nowadays, unless the patient has combined hypokalemia and hypophosphatemia. Sodium phosphate injection provides the same phosphate content and is a safer alternative in patients without concurrent hypokalemia.

Several empiric regimens have been evaluated. Because potassium phosphate is less commonly used for reasons mentioned earlier, the following dosing recommendations refer to sodium phosphate preparations. IV administration of 0.08 to 0.5 mmol/kg body weight of phosphorus is safe and effective in restoring the serum phosphorus concentration.[102] Rates of administration ranging from 1 to 3 mmol/hour are suggested to be safe. More aggressive regimens using higher doses have also been suggested for patients who are critically ill or have undergone surgery because lower doses may not be effective.[102,105] If parenteral phosphate replacement is necessary, the dose used will depend on the severity of the hypophosphatemia and the patient's weight. A suggested regimen is to give 0.08 to 0.24 mmol/kg over 6 hours (up to a maximum total dose of 30 mmol) if serum phosphate concentration is at least 1.25 mg/dL and to give 0.25 to 0.50 mmol/kg over 8 to 12 hours (up to a

maximum dose of 80 mmol) if the serum phosphate is <1.25 mg/dL.[106,107] Parenteral phosphorus replacement should be stopped once the serum phosphorus concentration reaches 1.5 to 2 mg/dL and also when oral supplementation could be started. Regardless of the regimen used, serum phosphorus, calcium, and magnesium concentrations should be monitored closely because IV phosphorus administration can induce hyperphosphatemia quite rapidly as well as hypocalcemia and hypomagnesemia. In particular, serum phosphate, calcium and magnesium concentrations should be monitored 6 hours after parenteral phosphate is given. Kidney function should also be checked daily. Metastatic soft tissue calcification, hypotension, and, depending on the preparation used, potassium, sodium, or volume overload may occur. This could be significant in patients such as M.R. who have a history of HF and hypertension. Therefore, kidney function and volume status should be monitored during therapy.

Phosphorus can be administered orally in doses of 30 to 60 mmol/day, usually given in two to four divided doses to minimize GI adverse events.[102] Oral phosphate supplements contain varying ratios of sodium and potassium phosphate. Therefore, a product should be selected based on its sodium and potassium content, as well as the patient's serum concentrations of these electrolytes. Any commercially available oral supplement such as Fleet®, Neutra-Phos®, or Neutra-Phos K® may be used. Each packet of Neutra-Phos® contains 8 mmol of phosphorus and can be given four times daily and at bedtime, whereas Fleet Phospho-Soda® can be given as 5 mL twice daily), both of which deliver 40 mmol/day of phosphorus. Skim milk, the preferred agent for diluting the supplement, contains ~7 mmol of phosphorus/cup and provides calcium and potassium as well. Diarrhea, a common dose-related side effect of oral phosphorus replacement, can be minimized by diluting the supplement and slowly titrating the dose. Large doses can also result in metabolic acidosis. Regardless of whether it is given orally or via IV, phosphate supplementation should also be avoided or used with caution in patients with kidney disease because of the risk

of developing hyperphosphatemia and calcium phosphate precipitation.

In M.R., oral supplementation was not feasible because she had intermittent diarrhea and vomiting. Potassium phosphate 15 mmol (providing 22 mEq of potassium) was therefore infused IV in 250 mL of normal saline over the course of 3 to 6 hours, in view of both hypokalemia and hypophosphatemia. The regimen was repeated once until the serum phosphorus concentration reached 2 mg/dL. Oral supplementation with Fleet Phospho-Soda® then was begun by adding 1 tsp twice daily to her enteral tube feeding.

Hyperphosphatemia

Refer to the section on Mineral and Bone Disorders in Chapter 28, Chronic Kidney Disease.

MAGNESIUM

Homeostasis

Magnesium is an intracellular cation found primarily in bone (65%) and muscle (20%). Only 2% of the total body store of 21 to 28 g (1750–2400 mEq) is located in the extracellular compartment. Serum magnesium concentrations, therefore, do not reflect the total magnesium body store accurately. In healthy adults, the serum magnesium concentration is 1.5 to 2.4 mEq/L, with ~20% of the serum magnesium bound to proteins.

Magnesium plays an important role in different metabolic processes, particularly in energy transfer, storage, and utilization. Cation deficiency can impair many ATP-mediated energy-dependent cellular processes as well as the action of phosphatases.[72] Magnesium is necessary for many enzymes involved in the metabolism of carbohydrates, fat, and protein, as well as RNA aggregation, DNA transcription, and degradation. The normal

operation of many sodium, proton, and calcium pumps and the regulation of potassium and calcium channels are all dependent on the availability of intracellular magnesium.[72,108] In addition, adequate magnesium stores are needed to maintain normal neuronal control, neuromuscular transmission, and cardiovascular tone.

The average diet in North America contains about 20 to 30 mEq of magnesium. The daily requirement is ~18 to 33 mEq for young persons and 15 to 28 mEq for females. Normally, 30% to 40% of the elemental magnesium is absorbed, primarily in the jejunum and ileum. However, absorption may be increased to 80% in deficiency states and reduced to 25% during high magnesium intake. In patients with uremia, GI absorption of magnesium is decreased; however, absorption in the jejunum can be normalized by physiologic doses of 1α,25-dihydroxyvitamin D_3. In addition, PTH also modulates magnesium absorption.[72,108]

Magnesium is eliminated primarily by the kidneys; only 1% to 2% of the endogenous magnesium is eliminated by the fecal route.[72,108] The magnitude of kidney removal is determined by GFR and tubular reabsorption. Approximately 20% to 30% of the tubular reabsorption takes place in the proximal tubule, whereas the Henle loop, primarily the thick ascending limb, is responsible for up to 65% of the total reabsorption. Only about 5% to 6% of the filtered magnesium is generally eliminated in the urine. The extent of magnesium reabsorption changes in parallel with sodium reabsorption, which is affected by the ECF volume. The kidney threshold for urinary magnesium excretion is 1.3 to 1.7 mEq/L, which is similar to the normal plasma magnesium concentration. Slight changes in plasma magnesium concentration, therefore, may substantially alter the amount of magnesium excreted in the urine.

Urinary magnesium reabsorption is affected by many factors, including sodium balance; ECF volume; serum concentrations of magnesium, calcium, and phosphate; and metabolic acidosis and alkalosis.[72,108] Concurrent use of loop and osmotic diuretics will also modulate the reabsorption. Hormones, such as PTH, and, possibly,

calcitonin, glucagon, and mineralocorticoids may affect the routine maintenance of magnesium balance as well.

Hypomagnesemia

ETIOLOGY

CASE 27-13

QUESTION 1: R.J., a 61-year-old male, is admitted to the hospital because of trauma to his forehead after falling at home. He has a long history of conditions related to his alcohol abuse: liver disease, ascites, seizures, pancreatitis, and malabsorption. R.J. reported abdominal pain, nausea, vomiting, and diarrhea for the past several days. At admission, R.J. was confused, apprehensive, and combative, and he had marked tremors. He also had delirium, as evidenced by hallucinations, screaming, and delusions, and he was having multiple tonic–clonic seizures. The medical record revealed that R.J. had been taking furosemide for the past 2 months. Pertinent laboratory test results obtained at admission were as follows:

K^+, 2.5 mEq/L
Magnesium, 0.8 mEq/L
Creatinine, 0.8 mg/dL

Phenytoin was administered for seizure control, and R.J. was placed on nasogastric suction. Fluid restriction was instituted, and furosemide therapy was continued to control his ascites.

What circumstances have contributed to R.J.'s hypomagnesemia?

Magnesium body stores are difficult to assess because magnesium is primarily an intracellular ion, and serum magnesium concentrations do not provide an accurate indication of the total body load. In fact, cellular magnesium depletion may be present with low, normal, or even high serum magnesium concentrations. Conversely, hypomagnesemia may be seen without a net loss of body magnesium. Refeeding after starvation will result in increased trapping of magnesium by newly formed tissue, resulting in hypomagnesemia. Similarly, acute pancreatitis and parathyroidectomy can cause hypomagnesemia without a net loss of the cation.

The prevalence of hypomagnesemia in ambulatory and hospitalized patients is ~6% to 12%.[109,110] The incidence increases to 40% to 60% in patients who are hypokalemic. Diuretic treatment and diarrhea may result in both hypokalemia and hypomagnesemia. In addition, hypomagnesemia induces potassium wasting by increasing potassium secretion into the kidney tubules.

As many as 60% to 65% of patients in the intensive care unit may develop hypomagnesemia, resulting in increased mortality.[109,110]

Magnesium depletion and hypomagnesemia can develop owing to GI, kidney, and endocrinologic causes. Depletion can occur in patients whose dietary magnesium intake is severely restricted and in those who have protein-calorie malnutrition.[72,108–110] Also at risk are patients who receive prolonged parenteral nutrition and those who undergo prolonged nasogastric suction. Hypomagnesemia may be present in patients who have increased magnesium requirements, such as pregnant females and infants. Conditions associated with steatorrhea, such as nontropical sprue and short bowel syndrome, can result in reduced GI magnesium absorption. Insoluble magnesium soaps may be formed in the GI tract because of the presence of unabsorbed fat. Hypomagnesemia can also occur in patients with a bowel resection and severe diarrhea. A rare genetic disorder has also been reported in patients with defective GI magnesium absorption. An impaired carrier- mediated magnesium transport system is believed to be responsible for the symptomatic deficiency, which requires high oral magnesium intake to overcome the defect.

Magnesium wasting can be caused by a primary defect or be secondary to systemic factors. A rare form of magnesium wasting is congenital. Various drugs can induce hypomagnesemia through increased kidney loss: cisplatin,[111] aminoglycosides,[112] cyclosporine,[113] proton-pump inhibitors (PPIs),[114] and amphotericin B.[115] Use of loop and thiazide diuretics can also result in hypomagnesemia, which can be reversed with the concurrent use of amiloride or triamterene. Magnesium depletion can be associated with phosphate depletion, calcium infusion, and ketoacidosis.[109,110] Acute and chronic ingestion of alcohol will result in increased

magnesium loss. Various endocrinologic disorders, such as SIADH, hyperthyroidism, hyperaldosteronism, and post-parathyroidectomy, are also associated with hypomagnesemia.[109,110]

R.J. could be hypomagnesemic for many reasons. His long history of alcohol use, malnutrition, and malabsorption may all have contributed to his magnesium deficit. The vomiting and diarrhea that he experienced could have reduced GI magnesium absorption. Use of furosemide and nasogastric suction while in the hospital could also have exacerbated his magnesium depletion through kidney and GI losses, respectively.

CLINICAL MANIFESTATIONS

CASE 27-13, QUESTION 2: What are the clinical manifestations of hypomagnesemia in R.J.?

Magnesium depletion can result in abnormal function of the neurologic, neuromuscular, and cardiovascular systems.[72,107–110] Hypomagnesemia lowers the threshold for nerve stimulation, resulting in increased irritability. Typical findings include Chvostek and Trousseau signs, muscle fasciculation, tremors, muscle spasticity, generalized convulsions, and, possibly, tetany. The patient may experience weakness, anorexia, nausea, and vomiting, as seen in R.J. Hypokalemia, hypocalcemia, and alkalosis may be present as well. In patients who are moderately depleted, changes in the ECG include widening of the QRS complex and a peaking T wave. In severe depletion, a prolonged PR interval and a diminished T wave may be seen. Ventricular arrhythmias have also been reported in some patients.

TREATMENT

CASE 27-13, QUESTION 3: Outline a regimen to replenish the body stores of magnesium for R.J. What monitoring plan could you develop to assess efficacy and potential adverse effects?

As discussed in Case 27-13, Question 1, serum magnesium concentration is a poor reflection of total body magnesium store. The specific regimen and the route of magnesium replenishment depend on the clinical presentation of the patient and the severity of the manifestations. Symptomatic patients require more aggressive parenteral therapy, whereas oral replacement may suffice for asymptomatic hypomagnesemia. Patients with life-threatening symptoms, such as seizures and arrhythmias, need immediate magnesium infusion. Because serum magnesium concentrations do not reflect total body stores, symptoms are more important determinants of the urgency and aggressiveness of therapy. As such, severity of clinical presentations is used instead of serum magnesium concentration to determine therapeutic regimens. However, the following classification of severity of hypomagnesemia based on serum concentrations may be used to guide replacement therapy in stable patients: mild (1.6–1.9 mg/dL), moderate (1–1.5 mg/dL), and severe (<1 mg/dL).[116]

The body stores of magnesium must be replenished slowly. Serum magnesium concentrations may return to the normal range within the first 24 hours, but total replenishment of body stores may take several days. Furthermore, ~50% of the administered IV dose of magnesium will be excreted in the urine.[107] Because the threshold for urinary magnesium excretion is low, the abrupt increase in serum magnesium after an IV dose will result in increased urinary magnesium excretion despite a total body magnesium deficit. Conversely, in patients with kidney impairment, decreased excretion of magnesium will place the patient at risk for hypermagnesemia. A reduced rate of magnesium administration and frequent monitoring of serum magnesium concentrations are therefore necessary in patients with kidney dysfunction.

Oral replacement of magnesium is indicated for asymptomatic patients with mild depletion.[107] Magnesium-containing antacids, milk of magnesia, and magnesium oxide are effective choices for replacement. Sustained-release preparations, such as Slow Mag® (magnesium chloride) or Mag-Tab® SR (magnesium lactate), are preferred to minimize magnesium elimination by avoiding high serum

concentration. With 5 to 7 mEq (2.5–3.5 mmol or 60–84 mg) of magnesium per tablet, six to eight tablets should be given daily in divided doses for severe magnesium depletion. For mild and asymptomatic disease, two to four tablets per day may be sufficient. A diet high in magnesium (chocolate, cereals, nuts, meat, fruits, fish, legumes, and vegetables) will also help replenish body stores and prevent depletion.

For patients with symptomatic hypomagnesemia, such as R.J., parenteral magnesium replacement is indicated.[107] The magnesium deficit in patients with chronic alcoholism is estimated to be 1 to 2 mEq/kg. Because up to half of the IV magnesium dose will be excreted in the urine during replacement, ~2 to 4 mEq/kg will be needed to replenish R.J.'s body store. Magnesium of 1 mEq/kg, as magnesium sulfate 10% solution, should be administered IV in the first 24 hours. This dose may be repeated to keep the serum magnesium concentration >1.0 mg/dL. Later, 0.5 mEq/kg of magnesium may be replenished daily for up to 4 additional days. Magnesium levels should be checked several hours after the completion of infusion to allow distribution to take place. Magnesium sulfate 1 g contains 98.6 mg (8.12 mEq or 4.06 mmol) of elemental magnesium. Magnesium can be given IM as 50% solution, but the injections are painful and potentially sclerosing, and multiple administrations are needed. Therefore, the IV route is the preferred mode of parenteral administration. For patients with symptomatic hypomagnesemia who are unstable, such as those experiencing seizures or life-threatening arrhythmias, 1 to 2 g (8–16 mEq or 4–8 mmol) of magnesium sulfate may be administered as a short IV infusion over the course of 2 to 15 minutes. The dose may be repeated if the patient remains hemodynamically unstable. If the patient is hemodynamically stable with severe symptomatic hypomagnesemia (<1 mg/dL [0.4 mmol/L or 0.8 mEq/L]), 1 to 2 g of magnesium sulfate (8–16 mEq [4–8 mmol]) in 50 to 100 mL of 5% dextrose in water can be given initially over 5 to 60 minutes followed by an infusion of 4 to 8 g of magnesium sulfate (32–64 mEq [16–32 mmol]) administered slowly over 12 to 24 hours. This dose can be repeated as needed to maintain plasma magnesium concentration

>1 mg/dL (0.4 mmol/L or 0.8 mEq/L) if the patient continues to be symptomatic. In patients who are normomagnesemic with hypocalcemia, this dose may be repeated daily for 3 to 5 days.[116]

If rapid IV magnesium administration is necessary, the patient should remain in a supine position to avoid hypotension.[107] The patient should also be monitored carefully for marked suppression of deep tendon reflexes (magnesium, 4–7 mEq/L); ECG, BP, respiration changes, and serum magnesium levels should be frequently monitored. Facial flushing, a sensation of warmth, and sweatiness may result from vasodilation secondary to a rapid magnesium infusion.

Typically, patients with kidney dysfunction should not receive magnesium-containing medications. However, magnesium repletion would be needed for those with severe hypomagnesemia (<1 mg/dL). The repletion should be administered with caution because there is no published data to guide therapy. It has been suggested that for symptomatic patients with moderate kidney impairment (GFR 15–30 mL/minute/1.73 m^2) and severe hypomagnesemia, 2 to 4 g of IV magnesium sulfate would be administered slowly over 4 to 12 hours. Serum magnesium concentration should be monitored after each dose or daily if doses are given less frequently. If the patient is asymptomatic, oral treatment at half of the doses for normal kidney function may be given. Serum magnesium concentration should be monitored afterward before subsequent doses. Particular caution is warranted in patients with renal impairment, in whom the rate of magnesium repletion should be reduced. These patients should be monitored frequently to avoid toxicities related to hypermagnesemia.

IV magnesium should also be administered cautiously in patients with severe atrioventricular heart block or bifascicular blocks because magnesium possesses pharmacologic properties similar to that of calcium channel blockers.[107]

In patients who exhibit hypomagnesemia secondary to a thiazide or loop diuretic, amiloride may be added to reduce magnesium loss by increasing reabsorption in the cortical collecting tubule.[117]

Long-term use of PPIs can cause hypomagnesemia by reduced intestine active magnesium absorption.[114] Patients at risk for serious

complications associated with hypomagnesemia (cardiac arrhythmias, underlying heart disease, etc) should be monitored closely or use H_2 antagonists instead of PPIs. For those patients who develop hypomagnesemia but require continued PPI treatment, oral magnesium supplementation can restore plasma concentrations to normal by increasing GI absorption via the passive paracellular pathway.

Case 27-13, Question 4: For the initial 2 days of hospitalization, R.J. received 3 mEq/kg of IV magnesium sulfate. However, his serum magnesium concentration remained <1.5 mEq/L. What might have contributed to the lack of favorable response to the magnesium therapy?

The total amount of magnesium administered to R.J. during the past 2 days was higher than the usual recommended rate (4–5 days) of magnesium replenishment, leading to kidney excretion of a large portion of the dose. Furthermore, the use of nasogastric suction and furosemide has increased the magnesium loss during the replacement period, and hypokalemia may have reduced the effectiveness of magnesium replacement. In a patient whose serum magnesium concentration does not increase after appropriate magnesium therapy, a 24-hour urine collection to assess magnesium excretion can be helpful. A low urinary magnesium concentration is consistent with magnesium depletion, whereas a high urinary magnesium excretion in the presence of hypomagnesemia suggests magnesium wasting.[72,108–110]

Hypermagnesemia

ETIOLOGY

CASE 27-14

Question 1: J.O., a 63-year-old male with kidney insufficiency, was admitted to the hospital because of increasing weakness during the past several days. J.O. began taking a magnesium–aluminum hydroxide antacid several times daily 2

weeks ago when he exhibited stomach upset. Physical examination reveals hypotension and depressed deep tendon reflexes. The ECG reveals prolonged PR and QRS intervals. The serum magnesium concentration is 6.5 mEq/dL.

What is the most likely cause of hypermagnesemia in J.O.?

Because the kidney is the primary route of magnesium elimination, kidney impairment is a virtual requisite for hypermagnesemia (see Chapter 28, Chronic Kidney Disease). A common cause of hypermagnesemia is the use of magnesium-containing medications, such as antacids and laxatives, by patients with impaired kidney function, including older adults. When a patient with kidney failure, such as J.O., takes magnesium-containing medications, the serum magnesium concentration can increase substantially, resulting in toxicities.[118] Hypermagnesemia may be seen when the CrCl drops to <30 mL/minute; an inverse relationship is observed between the serum magnesium concentrations and the CrCls. Hypermagnesemia is also seen in patients with acute kidney failure during the oliguric phase, but not the diuretic phase. Other potential causes of hypermagnesemia include adrenal insufficiency, hypothyroidism, lithium, magnesium citrate used as a cathartic for drug overdose, and parenteral magnesium given for preeclampsia.[72]

CLINICAL MANIFESTATIONS

Case 27-14, Question 2: What is the usual clinical presentation of a patient with hypermagnesemia?

An elevated magnesium serum concentration alters the normal function of the neurologic, neuromuscular, and cardiovascular systems. When the serum magnesium concentration is >4 mEq/L, deep tendon reflexes are depressed; they are usually lost at >6 mEq/L. Flaccid quadriplegia can develop when the concentration is >8 to 10 mEq/L. Respiratory paralysis, hypotension, and difficulty talking and swallowing may also be present. Changes in the ECG may include a prolonged PR interval and widening of the QRS complex. Complete heart block may be seen at concentrations of

~15 mEq/L. In mild hypermagnesemia, the patient may experience nausea and vomiting.

Drowsiness, lethargy, diaphoresis, and altered consciousness may be present at higher serum magnesium concentrations. J.O.'s increasing weakness, hypotension, depressed deep tendon reflexes, and ECG findings are consistent with hypermagnesemia.

TREATMENT

CASE 27-14, QUESTION 3: How should J.O.'s hypermagnesemia be treated?

If magnesium-containing medications are discontinued in patients with hypermagnesemia, the serum magnesium concentration will usually return to the normal range through kidney elimination. When potentially life-threatening complications are present, as in J.O., 5 to 10 mEq of IV calcium chloride should be administered to antagonize the respiratory and cardiac manifestations of magnesium.[72] The dose of the calcium can be repeated as necessary because its effect is short-lived. In patients with good kidney function without life-threatening complications, IV furosemide, plus 0.45% sodium chloride to replace lost urine volume, will enhance urinary magnesium excretion while preventing volume depletion. Hemodialysis or peritoneal dialysis is indicated for patients with significant kidney function impairment and possibly for those with severe hypermagnesemia.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Baek SH, Jo YH, Ahn S, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia—the SALSA randomized trial. *JAMA Intern Med*. 2021;18:81–92. (28)

Bianchi S, Giuseppe R. Pivotal clinical trials, meta-analyses and current guidelines in the treatment of hyperkalemia. *Nephrol Dial Transplant*. 2019;34:iii51–iii61. (69)

Felsenfeld AJ, Levine BS. Approach to treatment of hypophosphatemia. *Am J Kidney Dis.* 2012;60:655–661. (102)

Lehrich RW, Ortiz-Melo DI, Patel MB, Greenberg A. Role of vaptans in the management of hyponatremia. *Am J Kidney Dis*. 2013;62:364–376. (35)

Megapanou E, Florentin M, Milionis H, Elisaf M, Liamis G. Drug-induced hypophosphatemia: current insights. *Drug Saf.* 2020;43:197–210. (103)

Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. *BMJ.* 2015;350:h2723. (90)

Palmer BF, Carrero JJ, Clegg DJ, et al. Clinical management of hyperkalemia. *Mayo Clin Proc.* 2021;96:744–762. (64)

Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis: core curriculum 2019. *Am J Kidney Dis*. 2019;74:682–695. (52)

Peacock WF, Rafique Z, Vishnevskiy K, et al. Emergency potassium normalization treatment including sodium zirconium cyclosilicate: a phase II, randomized, double-blind, placebo-controlled study (ENERGIZE). *Acad Emerg Med.* 2020;27:475–486. (71)

Pepe J, Colangelo L, Biamonte F, et al. Diagnosis and management of hypocalcemia. *Endocrine.* 2020;69:485–495. (73)

Perazella MA. Proton pump inhibitors and hypomagnesemia: a rare but serious complication. *Kidney Int.* 2013;83:553–556. (114)

Seay NW, Lehrich RW, Greenberg A. Diagnosis and management of disorders of body tonicity—hyponatremia and hypernatremia: core curriculum 2020. *Am J Kidney Dis*. 2019;752:272–286. (22)

Sterns RH. Treatment of severe hyponatremia. *Clin J Am Soc Nephrol*. 2018;13:641–649. (9)

Yu ASL. Hypomagnesemia: evaluation and treatment. In: Post TW, ed. *UpToDate*. UpToDate; 2022. (116)

COMPLETE REFERENCES CHAPTER 27 FLUID AND ELECTROLYTE DISORDERS

1. Rose BD, Post T. Regulation of the effective circulating volume. In: Rose BD, Post T, eds. *Clinical Physiology of Acid-Base and Electrolyte Disorders*. 5th ed. McGraw-Hill; 2000:258–284.
2. Goetz K, Drummer C, Zhu JL, Leadley R, Fiedler F, Gerzer R. Evidence that urodilatin, rather than ANP, regulates renal sodium excretion. *J Am Soc Nephrol*. 1990;1:867–874.
3. Rose BD, Post T. Meaning and application of urine chemistries. In: Rose BD, Post T, eds. *Clinical Physiology of Acid-Base and Electrolyte Disorders*. 5th ed. McGraw-Hill; 2000:405.
4. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med*. 2013;126(10 Suppl 1):S1–S42.
5. Kaysen GA. Proteinuria and the nephrotic syndrome. In: Schrier RW, ed. *Renal and Electrolyte Disorders*. 6th ed. Lippincott Williams & Wilkins; 2003:580.
6. Politano SA, Colbert GB, Haniduzzaman N. Nephrotic syndrome. *Prim Care*. 2020;47:597–613.
7. Yeun JY, Zakari M, Kaysen GA. Nephrotic syndrome: nutritional consequences and dietary management. In: Mitch WE, Klahr S, eds. *Handbook of Nutrition and the Kidney*. 4th ed. Lippincott Williams & Wilkins; 2002:132–147.
8. Gross P. Treatment of severe hyponatremia. *Kidney Int*. 2001;60:2417–2427.
9. Sterns RH. Treatment of severe hyponatremia. *Clin J Am Soc Nephrol*. 2018;13:641–649.
10. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med*. 1992;117:891–897.
11. Lien Y, Shapiro JI, Chan L. Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia: implications for the pathogenesis of central pontine myelinolysis. *J Clin Invest*. 1991;88:303–309.
12. Goldman MB, Luchins DJ, Robertson GL. Mechanisms of altered water metabolism in psychotic patients with polydipsia and hyponatremia. *N Engl J Med*. 1988;318:397–403.
13. Rothenberg DM, Berns AS, Ivankovich AD. Isotonic hyponatremia following transurethral prostate resection. *J Clin Anesth*. 1990;2:48–53.
14. Ashouri OS. Severe diuretic-induced hyponatremia in the elderly. A series of eight patients. *Arch Intern Med*. 1986;146:1355–1357.
15. DeFronzo RA, Braine H, Colvin M, Davis PJ. Water intoxication in man after cyclophosphamide therapy. Time course and relation to drug activation. *Ann Intern Med*. 1973;78:861–869.
16. Morgan DB, Kirwan NA, Hancock KW, Robinson D, Ahmad S. Water intoxication and oxytocin infusion. *Br J Obstet Gynaecol*. 1977;84:6–12.
17. Marchioli CC, Graziano SL. Paraneoplastic syndromes associated with small cell lung cancer. *Chest Surg Clin N Am*. 1997;7:65–80.

18. Vassal G, Rubie H, Kalifa C, Hartmann O, Lemerle J. Hyponatremia and renal sodium wasting in patients receiving cisplatinum. *Pediatr Hematol Oncol*. 1987;4:337–344.
19. Vaamonde CA. Renal water handling in liver disease. In: Epstein M, ed. *The Kidney in Liver Disease*. 3rd ed. Williams & Wilkins; 1988:67.
20. Papadakis MA, Fraser CL, Arieff AI. Hyponatraemia in patients with cirrhosis. *Q J Med*. 1990;76:675–688.
21. Ramos-Levi AM, Rodriguez-Hervada AD, Mendez-Bailon M, Marco-Martinez J. Drug-induced hyponatremia: an updated review. *Minerva Endocrinol*. 2014;39:1–12.
22. Seay NW, Lehrich RW, Greenberg A. Diagnosis and management of disorders of body tonicity—hyponatremia and hypernatremia: core curriculum 2020. *Am J Kidney Dis*. 2019;752:272–286.
23. Filippatos T, Elisaf M, Liamis G. Pharmacological management of hyponatremia. *Expert Opin Pharmacother*. 2018;19(12):1337–1344.
24. Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: compilation of the guidelines. *J Am Soc Nephrol*. 2017;28:1340–1349.
25. Human T. Current therapeutic options for hyponatremia: indications, limitations and confounding variables. *Pharmacotherapy*. 2011;31:18S–24S.
26. Lohr JW. Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia. *Am J Med*. 1994;96:408–413.
27. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. *Semin Nephrol*. 2009;29:282–299.
28. Baek SH, Jo YH, Ahn S, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia—the SALSA randomized trial. *JAMA Intern Med*. 2021;18:81–92.
29. Spasovki G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatremia. *Eur J Endocrinol*. 2014;170:G1–G47.
30. Achinger SG, Ayus JC. Use of desmopressin in hyponatremia: foe and friend. *Kidney Med.* 2019;1:65–70.
31. Miell J, Dhanjal P, Jamookeeah C. Evidence for the use of demeclocycline in the treatment of hyponatraemia secondary to SIADH: a systematic review. *Int J Clin Pract*. 2015;69:1396–1417.
32. Decaux G, Przedborski S, Soupart A. Lack of efficacy of phenytoin in the syndrome of inappropriate antidiuretic hormone secretion of neurological origin. *Postgrad Med J*. 1989;65:456–458.
33. Decaux G, Prospert F, Penninckx R, Namias B, Soupart A. 5-year treatment of the chronic syndrome of inappropriate secretion of ADH with oral urea. *Nephron*. 1993;63:468–470.
34. Ali F, Guglin M, Vaitkevicius P, Ghali JK. Therapeutic potential of vasopressin receptor antagonists. *Drugs*. 2007;67:847–858.

35. Lehrich RW, Ortiz-Melo DI, Patel MB, Greenberg A. Role of vaptans in the management of hyponatremia. *Am J Kidney Dis*. 2013;62:364–376.
36. Verbalis JG. Vasopressin V2 receptor antagonists. *J Mol Endocrinol*. 2002;29:1–9.
37. Thibonnier M, Coles P, Thibonnier A, Shoham M. The basic and clinical pharmacology of nonpeptide vasopressin receptor antagonists. *Annu Rev Pharmacol Toxicol*. 2001;41:175–202.
38. Knepper MA. Molecular physiology of urinary concentrating mechanism: regulation of aquaporin water channels by vasopressin. *Am J Physiol*. 1997;272:F3–F12.
39. Burrell LM, Risvanis J, Johnston CI, Naitoh M, Balding LC. Vasopressin receptor antagonism—a therapeutic option in heart failure and hypertension. *Exp Physiol*. 2000;85:259S–265S.
40. Verbalis JG, Bisaha JG, Smith N. Novel vasopressin V_{1A} and V_2 antagonist (conivaptan) increases serum sodium concentration and effective water clearance in patients with hyponatremia. *Circulation*. 2004;110:723.
41. Ghali J. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab*. 2006;91:2145–2152.
42. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099–2112.
43. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation*. 2003;107:2690–2696.
44. Konstam MA, Gheorghiade M, Burnett JC, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome trial. *JAMA*. 2007;297:1319–1331.
45. Gheorghiade M, Konstam MA, Burnett JC, et al. Short term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA*. 2007;297:1332–1343.
46. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *NEJM*. 2012;367:2407–2418.
47. Boertien WE, Meijer E, de Jong PE, et al. Short-term effects of tolvaptan in individuals with autosomal dominant polycystic kidney disease at various levels of kidney function. *Am J Kidney Dis*. 2015;65:833–841.
48. U.S. Food and Drug Administration. FDA drug safety communication: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death. Accessed June 16, 2015. http://www.fda.gov/Drugs/DrugSafety/ucm350062.htm
49. Decaux G, Soupart A, Vassart G. Non-peptide arginine-vasopressin antagonists: the vaptans. *Lancet*. 2008;371:1624–1632.

50. Verbalis JG, Ghali, JK, Gross P, Long WA, Smith N. Conivaptan, a novel arginine vasopressin antagonist, produced aquaresis and increased serum sodium concentration in patients with euvolemic or hypervolemic hyponatremia. *Crit Care Med*. 2005;33(Suppl):A170.
51. Liamis G, Filippatos TD, Elisaf MS. Evaluation and treatment of hypernatremia: a practical guide for physicians. *Postgrad Med*. 2016;128(3):299–306.
52. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis: core curriculum 2019. *Am J Kidney Dis*. 2019;74:682–695.
53. Lee HL, Hering-Smith KS, Nakhoul NL. Acid-base and potassium homeostasis. *Semin Nephrol*. 2013;33:257–264.
54. Long B, Willis GC, Lentz S, Koyfman A, Gottlieb M. Evaluation and management of the critically ill adult with diabetic ketoacidosis. *J Emerg Med*. 2020;59:371–383.
55. Lindinger MI, Cairns SP. Regulation of muscle potassium: exercise performance, fatigue and health implications. *Eur J Appl Physiol*. 2021;121:721–748.
56. Viera AJ, Noah W. Potassium disorders: hypokalemia and hyperkalemia. *Am Fam Physician*. 2015;92:487–495.
57. Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol*. 2007;18:2649–2652.
58. Bokhari SRA, Zulfiqar H, Mansur A. Bartter syndrome. In: *StatPearls [Internet]*. StatPearls Publishing; 2021.
59. Adams PC, Woodhouse KW, Adela M, Parnham A. Exaggerated hypokalaemia in acute myeloid leukaemia. *Br Med J (Clin Res Ed)*. 1981;282:1034–1035.
60. Potassium chloride. *Lexi-Drugs. Lexicomp*. Wolters Kluwer Health, Inc. Accessed February 6, 2022. http://online.lexi.com
61. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect*. 2018;7:R135–R146.
62. Sopko JA, Freeman RM. Salt substitutes as a source of potassium. *JAMA*. 1977;238:608–610.
63. Ben SC, Badreddine A, Fathallah N, Slim R, Hmouda H. Drug-induced hyperkalemia. *Drug Saf*. 2014;37:677–692.
64. Palmer BF, Carrero JJ, Clegg DJ, et al. Clinical management of hyperkalemia. *Mayo Clin Proc*. 2021;96:744–762.
65. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J Am Soc Nephrol*. 2010;21:733–735.
66. U.S. Food and Drug Administration. Kayexelate (sodium polystyrene sulfonate) powder. Accessed June 17, 2015. http://www.fda.gov/Safety/MedWatch/default.htm

67. Weir MR, Bakris GL, Bushinsky DA. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372:211–221.
68. Packham DK, Rasmussen HS, Lavin PT. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med*. 2015;372:222–231.
69. Bianchi S, Giuseppe R. Pivotal clinical trials, meta-analyses and current guidelines in the treatment of hyperkalemia. *Nephrol Dial Transplant*. 2019;34:iii51–iii61.
70. Rafique Z, Liu M, Staggers KA, Minard CG, Peacock WF. Patiromer for treatment of hyperkalemia in the emergency department: a pilot study. *Acad Emerg Med*. 2020;27:54–60.
71. Peacock WF, Rafique Z, Vishnevskiy K, et al. Emergency potassium normalization treatment including sodium zirconium cyclosilicate: a phase II, randomized, double-blind, placebo-controlled study (ENERGIZE). *Acad Emerg Med*. 2020;27:475–486.
72. Moe SM. Disorders involving calcium, phosphorus, and magnesium. *Prim Care*. 2008;35:215–237, v–vi.
73. Pepe J, Colangelo L, Biamonte F, et al. Diagnosis and management of hypocalcemia. *Endocrine*. 2020;69:485–495.
74. Goltzman D, Cole DEC. Hypoparathyroidism. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Bone Metabolism*. 6th ed. American Society of Bone and Mineral Research; 2006:216–219.
75. Fitzpatrick LA, Arnold A. Hypoparathyroidism. In: DeGroot LJ, ed. *Endocrinology*. 3rd ed. Saunders; 1995:1123.
76. Blizzard RM, Chee D, Davis W. The incidence of parathyroid and other antibodies in the sera of patients with idiopathic hypoparathyroidism. *Clin Exp Immunol*. 1966;1:119–128.
77. Neufeld M, Maclaren NK, Blizzard RM. Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. *Medicine (Baltimore)*. 1981;60:355–362.
78. Cholst IN, Steinberg SF, Tropper PJ, et al. The influence of hypermagnesemia on serum calcium and parathyroid hormone levels in human subjects. *N Engl J Med*. 1984;310:1221–1225.
79. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol*. 2006;17:897–907.
80. Laskowski LK, Goldfarb DS, Howland MA, et al. A RANKL wrinkle: denosumab-induced hypocalcemia. *J Med Toxicol*. 2016;12:305–308.
81. Floege J, Tsirtsonis K, Iles J, Drueke TB, Chertow GM, Parfrey P. Incidence, predictors and therapeutic consequences of hypocalcemia in patients treated with cinacalcet in the EVOLVE trial. *Kidney Int*. 2018;93:1475–1482.
82. Jacobson MA, Gambertoglio JG, Aweeka FT, et al. Foscarnet-induced hypocalcemia and effects of foscarnet on calcium metabolism. *J Clin Endocrinol Metab*. 1991;72:1130–1135.

83. Lyman NW, Hemalatha C, Viscuso RL, Jacobs MG. Cisplatin-induced hypocalcemia and hypomagnesemia. *Arch Intern Med*. 1980;140:1513–1514.
84. Smallridge RC, Wray HL, Schaaf M. Hypocalcemia with osteoblastic metastases in patient with prostate carcinoma. A cause of secondary hyperparathyroidism. *Am J Med*. 1981;71:184–188.
85. McKay C, Beastall GH, Imrie CW, Baxter JN. Circulating intact parathyroid hormone levels in acute pancreatitis. *Br J Surg*. 1994;81:357–360.
86. Zaloga GP, Chernow B. The multifactorial basis for hypocalcemia during sepsis. Studies of the parathyroid hormone-vitamin D axis. *Ann Intern Med*. 1987;107:36–41.
87. Rutledge R, Sheldon GF, Collins ML. Massive transfusion. *Crit Care Clin*. 1986;2:791–805.
88. Goldner W. Cancer-related hypercalcemia. *J Oncol Pract*. 2016;12:426–432.
89. Zagzag J, Hu MI, Fisher SB, Perrier ND. Hypercalcemia and cancer: differential diagnosis and treatment. *CA Cancer J Clin*. 2018;68:377–386.
90. Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. *BMJ*. 2015;350:h2723.
91. Major P, Lortholary A, Hon J. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. 2001;19:558–567.
92. Berenson JR. Advances in the biology and treatment of myeloma bone disease. *Am J Health Syst Pharm*. 2001;58(Suppl 3):S16–S20.
93. Pecherstorfer M, Steinhauer EU, Rizzoli R, et al. Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. *Support Care Cancer*. 2003;11:539–547.
94. Ralston SH, Thiébaud D, Herrmann Z, et al. Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. *Br J Cancer*. 1997;75:295–300.
95. Pecherstorfer M, Herrmann Z, Body JJ, et al. Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcemia of malignancy. *J Clin Oncol*. 1996;14:268–276.
96. Thosani S, Hu MI. Denosumab: a new agent in the management of hypercalcemia of malignancy. *Future Oncol*. 2015;11(21):2865–2871.
97. Cicci JD, Buie L, Bates J, van Deventer H. Denosumab for the management of hypercalcemia of malignancy in patients with multiple myeloma and renal dysfunction. *Clin Lymphoma Myeloma Leuk*. 2014;14:e207–e211.
98. Bech A, de Boer H. Denosumab for tumor-induced hypercalcemia complicated by renal failure. *Ann Intern Med*. 2012;156:906–907.
99. Bilezikian JP. Primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2018;103:3993–4004.

100. Tebben PJ, Singh RJ, Kumar R. Vitamin D-mediated hypercalcemia: mechanisms, diagnosis, and treatment. *Endocr Rev*. 2016;37:521–547.
101. Christov M, Jüppner H. Phosphate homeostasis disorders. *Best Pract Res Clin Endocrinol Metab*. 2018;32:685–706.
102. Felsenfeld AJ, Levine BS. Approach to treatment of hypophosphatemia. *Am J Kidney Dis*. 2012;60:655–661.
103. Megapanou E, Florentin M, Milionis H, Elisaf M, Liamis G. Drug-induced hypophosphatemia: current insights. *Drug Saf*. 2020;43:197–210.
104. Zoller H, Schaefer B, Glodny B. Iron-induced hypophosphatemia: an emerging complication. *Curr Opin Nephrol Hypertens*. 2017;26:266–275.
105. Brown KA, Dickerson RN, Morgan LM, et al. A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. *JPEN J Parenter Enteral Nutr*. 2006;30:209–214.
106. Taylor BE, Huey WY, Buchman TG, et al. Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit. *J Am Coll Surg*. 2004;198:198–204.
107. Subramanian R, Khardori R. Severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. *Medicine (Baltimore)*. 2000;79:1–204.
108. Gröber U, Schmidt J, Kisters K. Magnesium in prevention and therapy. *Nutrients*. 2015;7:8199–8226.
109. Agus ZS. Hypomagnesemia. *J Am Soc Nephrol*. 1999;10:1616–1622.
110. Agus ZS. Mechanisms and causes of hypomagnesemia. *Curr Opin Nephrol Hypertens*. 2016;25:301–307.
111. Lajer H, Daugaard G. Cisplatin and hypomagnesemia. *Cancer Treat Rev*. 1999;25:47–58.
112. von Vigier RO, Truttmann AC, Zindler-Schmocker K, et al. Aminoglycosides and renal magnesium homeostasis in humans. *Nephrol Dial Transplant*. 2000;15:822–826.
113. Farouk SS, Rein JL. The many faces of calcineurin inhibitor toxicity—what the FK? *Adv Chronic Kidney Dis*. 2020;27:56–66.
114. Perazella MA. Proton pump inhibitors and hypomagnesemia: a rare but serious complication. *Kidney Int*. 2013;83:553–556.
115. Wazny LD, Brophy DF. Amiloride for the prevention of amphotericin B-induced hypokalemia and hypomagnesemia. *Ann Pharmacother*. 2000;34:94–97.
116. Yu ASL. Hypomagnesemia: evaluation and treatment. In: Post TW, ed.*UpToDate*; 2022. Accessed February 15, 2022. https://www.uptodate.com/contents/hypomagnesemia-evaluation-and-treatment?csi=40872868-e231-42e2-9ac5-37e5f941c989&source=contentShare
117. Liamis G, Hoorn EJ, Florentin M, Milionis H. An overview of diagnosis and management of drug-induced hypomagnesemia. *Pharmacol Res Perspect*.

2021;9:e00829.
118. Wyskida K, Witkowicz J, Chudek J, Wie¸cek A. Daily magnesium intake and hypermagnesemia in hemodialysis patients with chronic kidney disease. *J Ren Nutr*. 2012;22:19–26.

28

Chronic Kidney Disease

Adinoyi Garba

CORE PRINCIPLES		CHAPTER CASES
1	Chronic kidney disease (CKD) is progressive, irreversible kidney damage characterized by decreased estimated glomerular filtration rate (eGFR) or evidence of kidney damage for at least 3 months.	**Case 28-1 (Question 1)**
2	Classification of CKD staging should be determined based on kidney function, defined by the Kidney Disease: Improving Global Outcomes (KDIGO). Each stage is associated with certain action plans.	**Case 28-1 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
3	Many equations exist for calculating creatinine clearance (CrCl) or eGFR. The Modification of Diet in Renal Disease (MDRD) equation is used to quantify glomerular filtration rate (GFR) to detect or stage the degree of CKD and to follow progression. The Cockcroft–Gault (CG) equation is used to adjust the doses of medications that are eliminated by the kidneys.	**Equation 28-3**
4	Diabetes is the number one cause of CKD in the United States. Optimal control of blood glucose levels and albuminuria is essential to slow the progression of CKD and reduce morbidity and mortality.	**Case 28-1 (Questions 2–4)**
5	Fluid accumulation and electrolyte abnormalities secondary to CKD often complicate the treatment of hypertension and can have cardiotoxic effects.	**Case 28-1 (Questions 5, 6)**
6	Metabolic acidosis presents in late stages of CKD from reduced hydrogen ion excretion and bicarbonate production. Metabolic acidosis can worsen bone disease and other metabolic processes.	**Case 28-1 (Question 7)**

CORE PRINCIPLES		CHAPTER CASES
7	Treating anemia of CKD is essential to reducing cardiovascular disease (CVD) complications. Management of anemia includes administration of iron supplementation and erythropoiesis-stimulating agents.	**Case 28-1 (Questions 8, 9)**
8	CVD is the number one cause of morbidity and mortality in CKD. Cardioprotective measures should be addressed at all stages.	**Case 28-2 (Question 1)**
9	Hypertension is the second leading cause of CKD in the United States. Treating hypertension to target goals is necessary to slow the progression of CKD and reduce mortality.	**Case 28-2 (Question 2)**
10	Treating dyslipidemia in CKD reduces the risk of major cardiovascular events but does not affect the risk of progression of kidney disease	**Case 28-2 (Question 3)**
11	Mineral and bone disorders (MBD) characterized by biochemical abnormalities in calcium, phosphate, parathyroid hormone, and vitamin D metabolism may occur and lead to alterations of bone morphology or vascular calcification as CKD progresses. Vascular calcification increases the risk for cardiovascular mortality.	**Case 28-3 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
12	Hyperphosphatemia is managed with dietary phosphorus restriction and phosphate-binding agents.	**Case 28-3 (Question 2)**
13	Activated forms of vitamin D (calcitriol, paricalcitol, and doxercalciferol) or a calcimimetic agent (cinacalcet) may be necessary to achieve proper biochemical balance and bone metabolism.	**Case 28-3 (Question 2)**
14	Glomerulonephropathies (GNs) are a collection of glomerular diseases caused by a variety of immunologic mechanisms and the third leading cause of CKD. Patients with GN may present with nephrotic syndrome and require treatment with immunosuppressant therapy.	**Case 28-4 (Questions 1) Case 28-5 (Questions 1, 2) Case 28-6 (Question 1)**

INTRODUCTION

Chronic kidney disease (CKD) is the continuum of kidney dysfunction from early to late-stage disease. It is generally defined as an estimated glomerular filtration rate (eGFR) <60 mL/minute/1.73 m^2 persisting for more than 3 months. The most advanced stage of CKD formerly referred to as end-stage kidney disease will be referred to as kidney failure within this chapter. At this stage, chronic kidney replacement therapy (KRT) in the form of dialysis or kidney transplantation is necessary to sustain life.[1] There are several complications associated with CKD, including fluid and electrolyte abnormalities, anemia, cardiovascular disease (CVD),

mineral and bone disorders (MBDs), and malnutrition. The optimal management of CKD is best achieved using a multidisciplinary approach to slow its progression and address the concurrent medical problems and complex pharmacotherapeutic regimens.

Implementation of clinical practice guidelines in the diagnosis, monitoring, and treatment of CKD leads to improved patient outcomes and reduced variability in patient care.[2] In the United States, the National Kidney Foundation (NKF) established the Kidney Disease Outcomes Quality Initiative (K/DOQI) to provide evidence-based clinical practice guidelines for all stages of CKD and related complications. However, because CKD is a worldwide public health issue and the problems faced by patients with CKD around the world are universal, the Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003. The mission of KDIGO is to improve the care and outcomes of patients with CKD worldwide by promoting coordination, collaboration, and integration of initiatives. KDIGO is managed by the NKF. Contact information for K/DOQI and KDIGO and corresponding web addresses for clinical practice guidelines can be found in **Table 28-1**.

Table 28-1

Resources for Kidney Disease Clinical Practice Guidelines

National Kidney Foundation Kidney Disease Outcomes Quality Initiative 30 East 33rd Street New York, New York 10016 Phone: 1-800-622–9010 Website: https://www.kidney.org/professionals/guidelines
Kidney Disease: Improving Global Outcomes 30 East 33rd Street, Suite 900 New York, New York 10016 Phone: 212-889-2210 x288 Website: http://kdigo.org/home/

Definition and Classification of Chronic Kidney Disease

CKD is characterized by a progressive deterioration in kidney function over months to years, characterized by irreversible structural damage to existing nephrons. The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease defines CKD as abnormalities or damage to kidney structure or function that persists for at least 3 months with implications for the patient's health. Structural abnormalities or damage are often determined by imaging studies, kidney biopsy, or the excretion of plasma proteins like albumin in the urine (albuminuria) (**Table 28-2**). Glomerular filtration rate (GFR) is a measure of the amount of blood filtered across the glomerulus each minute. The eGFR is the widely accepted measure of kidney function. KDIGO classifies kidney function based on eGFR into five broad categories (G1–G5) (**Table 28-3**). Unlike previous K/DOQI guidelines, KDIGO divides category G3 GFR into two subcategories, G3a (GFR of 45–59 mL/minute/1.73 m^2) and G3b (GFR 30–44 mL/minute/1.73 m^2), to better stratify patients based on the different outcomes and risks associated with these levels of GFR.[1]

Table 28-2

Criteria for Chronic Kidney Disease

Markers of Kidney Damage
Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])
Urine sediment abnormalities
Electrolyte and other abnormalities because of tubular disorders
Abnormalities detected by histology
Structural abnormalities detected by imaging
History of kidney transplantation

Must be at the defined GFR range or damage persisting for 3 months or greater.

AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate.

Reprinted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2011;2013;3(1): 1–163. © 2013 International Society of Nephrology. With permission.

Table 28-3

KDIGO Staging of Chronic Kidney Disease Based on eGFR Category

GFR Categories (mL/minute/1.73 m^2)	Description	Range
G1	Normal or high	≥90
G2	Mildly decreased	60–89
G3a	Mildly to moderately decreased	45–59
G3b	Moderately to severely decreased	30–44
G4	Severely decreased	15–29
G5	Kidney failure	<15

eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes

Reprinted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2011;2013;3(1): 1–163. © 2013 International Society of Nephrology. With permission.

Estimation of GFR alone may not be sufficient for identifying early stages of CKD because GFR may be normal or borderline normal. In such cases, kidney damage is indicated by pathologic abnormalities of the kidneys or markers of kidney injury like albuminuria could add help to assess overall kidney status.[1] There are three categories of albuminuria (A1–A3) (**Table 28-4**). A comprehensive classification of CKD should include CGA (**c**ause of CKD, **G**FR, **a**lbuminuria).[1] For examples of CKD classification using CGA categories, see **Table 28-5**. The GFR and albuminuria categories can be used to evaluate the CKD risk. For instance, an individual with G1A1 is placed in low CKD risk category, whereas another individual with G1A3 is considered to be in high CKD risk category.[3] (For risk categories, see **Table 28-6**.)

Table 28-4

Albuminuria Categories: Description and Range

	A1	A2	A3
Description	Normal to mildly increased	Moderately increased	Severely increased
Albumin-to-creatinine ratio (mg/g)	<30	30–300	>300
Albumin excretion rate (mg/24 hours)	<30	30–300	>300

Reprinted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2011;2013;3(1): 1–163. © 2013 International Society of Nephrology. With permission.

Table 28-5
Examples of Chronic Kidney Disease Staging

Cause	GFR Category	Albuminuria Category	Criterion for CKD
Diabetic kidney disease	G5	A3	Decreased GFR, albuminuria
Idiopathic focal sclerosis	G2	A3	Albuminuria
Kidney transplant recipient	G2	A1	History of kidney transplantation
Polycystic kidney disease	G2	A1	Imaging abnormality
Vesicoureteral reflux	G1	A1	Imaging abnormality
Distal renal tubular acidosis	G1	A1	Electrolyte abnormalities
Hypertensive kidney disease	G4	A2	Decreased GFR and albuminuria
CKD presumed because of diabetes and hypertension	G4	A1	Decreased GFR
CKD presumed because of diabetes and hypertension	G2	A3	Albuminuria
CKD presumed because of diabetes and hypertension	G3a	A1	Decreased GFR
CKD cause unknown	G3a	A1	Decreased GFR

CKD, chronic kidney disease; GFR, glomerular filtration rate.

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2011;2013;3(1):1–163. © 2013 International Society of Nephrology. With permission.

Table 28-6
KDIGO Chronic Kidney Disease Risk Categories

		Albuminuria Category		
		A1	A2	A3
GFR Category	G1	Low risk	Moderate risk	High risk
	G2			
	G3a	Moderate risk	High risk	Very high risk
	G3b	High risk	Very high risk	
	G4	Very high risk		
	G5			

GFR, glomerular filtration rate.

A substantial decline in kidney function leads to *azotemia*, which is the accumulation of nitrogenous wastes in the blood, and uremia, which is an accumulation of urea in the blood. These lead to a myriad of complications affecting most major organ systems. Laboratory biochemical abnormalities, oftentimes present in late-stage CKD, may lead to hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism, hyperkalemia, gout, metabolic acidosis, and anemia. Clinical signs of CKD and its associated complications, including hypertension, uremic symptoms (eg, nausea, anorexia, itching), fatigue, bone disease, swelling in extremities, and bleeding, are observed as the disease advances to categories G3a through G5. Interventions to slow the progression of CKD are critical. Patients with eGFR of <30 mL/ minute/1.73 m^2 will ultimately progress to kidney failure with or without KRT and are referred to as CKD G5 without KRT and KFRT, respectively. The stage of CKD G1–G5 after transplantation is referred to CKD G1T–G5T.[3]

Epidemiology of Chronic Kidney Disease

The United States Renal Data System (USRDS) is a national data system that collects, analyzes, and distributes information about all

categories of CKD in the United States. Data describing CKD incidence and prevalence are made available annually by the USRDS, and the USRDS provides the latest pertinent data on CKD. The 2018 USRDS reports that the overall prevalence of CKD in the U.S. population was about 14%.[4] Over the period between 2001 and 2016, there was a small increase in the prevalence of stage 3 CKD that rose from 6.1% to 6.4%. The NKF's Kidney Early Evaluation Program (KEEP) screens high-risk individuals at high risk across the United States with high blood pressure (BP), diabetes mellitus, or a family history of kidney failure. Based on the high-risk participants from the KEEP screenings from 2000 to 2011, 24% of the participants had CKD. According to 2019 USRDS data, the 2017 prevalence and incidence of kidney failure were 746,557 and 124,500, respectively.[5,6] The African American population had the highest prevalence per million of the population that was 2-fold higher than Native Americans, 2.5-fold higher than Asians, and 4-fold higher than Whites.[5]

CKD is a health priority identified as a disease prevention target for the Healthy People 2020 (HP2020) national health initiative; one of the specific CKD-related objectives is to reduce the number of cases of kidney failure.[7] The HP2020 target rate of kidney failure cases is 13.3% of the population. Current data suggest that this target will not be met. A new target of 12.8% of the adult population was set for Healthy People 2030.[8] Recent data from the 2020 USRDS annual data report show that 14.9% of U.S. adults surveyed between 2016 and 2018 had CKD.[9] Additional objectives such as increasing awareness, improving cardiovascular care, and reduction of mortality in patients with CKD can be found at the HealthyPeople.gov website.

ETIOLOGY

In CKD, the progressive loss or damage to functioning nephrons as a function of time is the result of a primary disorder or disease of the kidney, a secondary complication of certain systemic diseases (eg, diabetes mellitus or hypertension), or an acute injury to the kidney

that results in irreversible kidney damage. The leading causes of kidney failure in American patients were diabetes mellitus (38%), hypertension (26%), and chronic glomerulonephritis (GN) (16%).[10] The remaining cases of kidney failure can be attributed to a variety of other pathologies; examples include polycystic kidney disease, congenital anomalies of the kidney and urinary tract (CAKUT), kidney stones, interstitial nephritis, kidney artery stenosis, carcinoma of the kidney, and human immunodeficiency virus–associated kidney disease.

A variety of risk factors associated with development, initiation, and progression of CKD have been identified. Initiation factors are medical conditions that directly cause kidney damage. Risk factors for the progression of CKD exacerbate kidney damage and are related to an accelerated decline in kidney function with time. Most susceptibility factors are not modifiable but may identify people who are at high risk for developing CKD. In contrast, pharmacotherapy and lifestyle interventions have been shown to modify CKD-related initiation and progression factors (see Prevention of Chronic Kidney Disease and Its Progression section). A summary of risk factors associated with CKD can be found in **Table 28-7**.

Table 28-7
Risk Factors for Chronic Kidney Disease

Susceptibility	Initiation	Progression
Advanced age Reduced kidney mass Low birth weight Racial/ethnic minority Family history Low income or education Systemic inflammation Dyslipidemia	Diabetes mellitus Hypertension Glomerulonephritis Drug-induced kidney toxicity Smoking Obesity	Hyperglycemia Hypertension Proteinuria Smoking Obesity

KDOQI. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2, Suppl 1):S73.

MORBIDITY, MORTALITY, AND ECONOMIC IMPACT

According to the USRDS annual data report, ~73.7% of patients with CKD were enrolled in the Medicare Part D program (including both standalone and Medicare Advantage plans) in 2016 compared to 69.5% in the general Medicare population.[4] Based on 2019 USRDS data, rates of hospitalizations and mortality are much greater in those with CKD compared with the non-CKD population.[4,6] Patients with CKD had a mortality rate of 122.6 per 1000 patient-years. After adjusting for sex, age, and race, this rate remained double that of patients without CKD.[4] The adjusted mortality rate in male patients with CKD was higher than in females, 114.4 versus 94.9 per 1000 person years, respectively. When adjusting for age and sex, the mortality rate was 106.6 per 1000 patient-years for Black patients versus 104.2 per 1000 patient-years for White patients. When stratified by stages, there was no difference between Black and White patients with CKD G1–G3; however, Black patients have a higher mortality rate than White patients with CKD G4–G5, 183 versus 170 per 1000 patient-years, respectively. Overall, the morbidity and mortality risk tend to increase with progressing stages of CKD, patient health complexity, and age.

Patients with CKD not on dialysis are typically on 6 to 8 medications on average, whereas those with kidney failure can be prescribed as many as 12 medications to manage the comorbidities of CKD. These patterns of medication use are reflective of the higher prevalence of complications and comorbidities in the latter stages of CKD, which require additional drug therapies. The extent of medication use and the complexity of prescribed drug regimens contribute to nonadherence and medication-related problems (MRPs) in the kidney failure population.[11] To manage MRPs, some dialysis units use a clinical pharmacist as part of the multidisciplinary health care team to provide pharmaceutical care to patients with kidney failure. Services provided by a clinical pharmacist have been shown to be cost-effective and associated with maintenance of health-related quality of life.[12,13]

PATHOPHYSIOLOGY

Progression of CKD to kidney failure generally occurs over the course of months to years and is assessed by the rate of GFR decline. Each kidney contains approximately one million nephrons (the functional units of the kidney), and every nephron maintains its own single-nephron GFR. In the face of nephron loss, the remaining functional nephrons maintain renal function by increasing their single-nephron GFR via compensatory glomerular hemodynamic changes.[13] With time, this compensatory increase in single-nephron GFRs eventually leads to hypertrophy and an irreversible loss of nephron function from sustained increases in glomerular pressure. Furthermore, glomerulosclerosis (glomerular arteriolar damage) develops from prolonged elevation of glomerular capillary pressure and increased glomerular plasma flow, resulting in a continuous cycle of nephron destruction. Regardless of the cause, a predictable and continuous decrease in kidney function occurs in patients when the eGFR drops below a critical value, approximately one-half of normal.[14] Usually, the rate of decline in kidney function remains fairly constant for an individual, but can vary substantially among patients and disease states. A rapid rate of decline in kidney function has been associated with Black race, proteinuria, male sex, older age, and smoking.[15–17] Rapid progression of CKD is defined as persistent decline in GFR >5 mL/minute/1.73 m^2/year.[1] Although early changes in kidney function can be detected through routine laboratory monitoring (eg, urine albumin-to-creatinine ratio [ACR], serum creatinine [SCr]), most patients are asymptomatic and do not develop signs and symptoms of uremia until they have progressed to the more severe stages of the disease (ie, CKD categories G4 and G5).

As the leading causes of kidney failure in the United States, diabetes mellitus, hypertension, and glomerular diseases have been the focus of research to identify their associated mechanisms of kidney damage. In the case of diabetes mellitus, excess filtration of glucose, excessive glucose contact with the glomerular and tubular cells leads to increased cellular osmotic pressure and thickening of the capillary basement membrane and other anatomic changes. Systemic hypertension is a potent stimulus for the development and

progression of CKD caused by the association with increased single-nephron GFRs.[13,17] Hypertension, whether as the primary cause of CKD or a as coexisting disease in the presence of other etiologies, can promote kidney damage through transmission of elevated systemic pressure to glomeruli. The result is glomerular capillary hyperperfusion and hypertension leading to progressive kidney damage as nephron destruction continues. Glomerular ischemia induced by damage to the preglomerular arteries and arterioles also occurs. People with coexistent diabetes mellitus and hypertension increase the risk of developing kidney failure by fivefold to sixfold compared with those with hypertension alone.[14] In contrast, glomerular diseases responsible for GN are mediated by immune mechanisms. The deposition and formation of immune complexes in the glomerulus cause injury, resulting in increased glomerular permeability to macromolecules (eg, proteins).[18] As stated above, the presence of albumin in urine is one of the diagnostic signs of kidney damage. Albuminuria is associated with progression of CKD.[19] Immunologic and hemodynamic mechanisms have been identified to explain the glomerular injury. Inflammatory cytokines may be responsible for fibrosis and kidney scarring, ultimately resulting in loss of nephron function.

Dyslipidemia is common in patients with CKD and often observed concurrently with proteinuria. Increased low-density lipoprotein (LDL) cholesterol, total cholesterol, and apolipoprotein B, as well as decreased high-density lipoprotein (HDL) cholesterol, have been observed in patients with progressive CKD.[18] Hypercholesterolemia has been associated with loss of kidney function in patients with and without diabetes.[20,21] LDL is thought to promote glomerular damage by initiating a series of cellular events in mesangial cells and through oxidation to a more cytotoxic derivative once within these cells. Although serum total cholesterol, triglycerides, and apolipoprotein B, all correlate with the rate of decline in eGFR, it is not clear that they directly increase the rate of progression of CKD, particularly when present with concomitant conditions that also cause kidney damage. Some evidence, however, suggests that treatment of

hypercholesterolemia with statin therapy in patients with CKD may reduce albuminuria and progression of CKD.[21]

CLINICAL ASSESSMENT OF KIDNEY FUNCTION

Quantifying Glomerular Filtration Rate

The estimation of GFR (eGFR) is the most widely used clinical tool for assessing baseline kidney function and for monitoring the progression of CKD. The ideal marker of eGFR should be a nontoxic substance that is freely filtered at the glomerulus and not secreted, reabsorbed, or metabolized by the kidney. Inulin and exogenous radioactive markers, such as ^{125}I-iothalamate or ^{51}CrEDTA, have been used to assess GFR because they meet these criteria; however, they are not readily available to clinicians, require intravenous (IV) administration, and are costly. So, other endogenous biomarkers like creatinine are used to estimate GFR in the clinical setting.

Creatinine is a substance that is produced at a relatively constant rate by nonenzymatic hydrolysis of muscle stores of the amino acid derivatives creatine and phosphocreatine. Under steady-state conditions, the urinary excretion of creatinine equals the creatinine production rate, and the SCr concentration remains relatively stable. Creatinine is excreted primarily by glomerular filtration—thus, creatinine clearance (CrCl) has been used as a reasonable surrogate for eGFR. There are limitations to consider when using methods to assess eGFR that incorporate creatinine. Creatinine is eliminated not only through glomerular filtration but also by tubular secretion. Consequently, the CrCl overestimates the true GFR by 10% to 20%. As nephron function declines, tubular secretion of creatinine contributes more substantially to overall elimination such that CrCl overestimates true GFR. Elimination of creatinine by other organs besides the kidney, like the gastrointestinal (GI) tract may

also lead to overestimation of actual GFR.[22] As a result of these processes, disease progression may be underestimated. Commonly used drugs also need to be taken into consideration when interpreting SCr values. For example, drugs like trimethoprim and cimetidine can inhibit the secretion of creatinine, increase SCr, and decrease CrCl without affecting GFR.[19]

The use of SCr alone as an index of kidney function has several limitations. In the initial stages of CKD, SCr may remain within the normal range and is relatively insensitive in detecting early CKD or estimating the progression of the disease. The generation of creatinine is proportional to the total muscle mass; it is also affected by diet (notably by the ingestion of meats), age, and gender. Generally, muscle mass declines with age and is lower in females. Thus, an SCr that is in the upper limit of normal (eg, 1.2 mg/dL) for a young male athlete is likely to be associated with a high CrCl, whereas the same SCr in a 70-year-old female could indicate compromised kidney function. Because of the substantial variation seen in the calibration of SCr among laboratories, the National Kidney Disease Education Program Laboratory Working Group initiated the creatinine standardization program to improve and normalize SCr results, reduce interlaboratory variability, and enable more accurate eGFR determinations.[23] Although SCr can provide a rough estimate of kidney function, other markers of early kidney damage, such as albuminuria, should also be evaluated in patients at risk for CKD.

Estimations of CrCl and eGFR will be compared, next. Several equations have been developed to calculate CrCl or eGFR.

The Cockcroft–Gault (CG) equation (Eq. 28-1) has been the most commonly used method to estimate kidney function for drug dosing, which provides an estimated CrCl in patients with stable kidney function.[22,24]

$$\mathrm{CrCl} = \frac{(140 - \mathrm{Age})(\mathrm{IBW})}{(72)} \qquad \textbf{(Eq. 28-1)}$$

where age is in years, IBW is ideal body weight in kg (male IBW = 50 + [2.3 × height >60 inches (152.4 cm)]; female IBW = 45.5 + [2.3 × height >60 inches (152.4 cm)]); and SCr is the serum creatinine concentration (mg/dL). For females, the CG equation is multiplied by 0.85 to account for decreased muscle mass. The recommended weight used in the CG equation is the IBW. The exception to this rule is when the actual body weight is less than the IBW, then use actual body weight. For individuals where the actual body weight is 1.3 times or more higher than the IBW, use the *adjusted* IBW (IBW + 0.4 × [actual body weight – IBW]).[25]

The CG equation is not reliable for estimating GFR in patients with rapidly changing SCr concentrations because it was derived from normal, healthy subjects with stable kidney function. The CG equation is also inaccurate in populations that have low muscle mass—such as elderly, obese, or cachectic patients. Equations have been studied for estimating GFR in older individuals like the Berlin Initiative Study 1 (BIS1) equation, which is a tool for estimating kidney function in older adults (>70 years old), and the full age spectrum (FAS) equation.[26] These equations will not be addressed in detail in this chapter.

There are several creatinine-based equations for calculating eGFR in children 1 to 16 years old; however, the updated “bedside” Schwartz equation (Eq. 28-2) from the 2009 Chronic Kidney Disease in Children (CKiD) study is currently the recommended equation for estimating GFR.[27]

$$\text{Cr Cl (mL/minute)} = \frac{(k \times \text{length [in cm]})}{\text{SCr}} \qquad \textbf{(Eq. 28-2)}$$

The most commonly used method for kidney function assessment in adults is the prediction equation developed using data from the Modification of Diet in Renal Disease (MDRD) study, a multicenter trial that evaluated the effects of dietary protein restriction and BP control on progression of CKD. The MDRD equation was derived using GFR measured directly by urinary clearance of a radiolabeled marker ^{125}I-iothalamate as opposed to creatinine and included a

relatively large and diverse population (>500 White and Black individuals with varying degrees of CKD) for derivation and validation of the equation.[28] To address the lack of validation in other populations, modifications to the MDRD equation to account for other populations are being explored.[29] An abbreviated version was developed and is referred to as the four-variable MDRD equation. This version is the widely used equation and does not require blood urea nitrogen (BUN) or serum albumin. Subsequently, this equation was further revised in 2005 for use with a standardized SCr assay enabling consistent results across clinical laboratories to improve accuracy in eGFR determinations (Eq. 28-3).[22]

$$\text{Estimated GFR}$$

$$(\text{mL/minute/1.73 m}^2) = 175 \times (\text{standardized SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

(Eq. 28-3)

The MDRD equation was found to be biased and imprecise at higher GFRs with the potential of misidentifying patients with high GFR as having poor kidney function.[1] The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) research group established by the National Institute of Diabetes and Digestive and Kidney Diseases pooled studies of different populations to develop and validate a new estimating equation for GFR that is more complex but uses the same variables as the MDRD equation.[1,30] This equation was found to be more accurate than the MDRD equation, especially at high GFRs >60 mL/minute/1.73 m^2. These two approaches estimate GFR using serum creatinine ($eGFR_{cr}$).

Cystatin C is another endogenous marker of kidney function that is freely filtered at the glomerulus. Subsequently, it is reabsorbed and catabolized by proximal tubular epithelial cells. Unlike SCr, cystatin C is not influenced by gender, age, body mass, and nutritional status. Although cystatin C has gained wider acceptance and utility in

clinical practice, it is still relatively under-utilized because of its longer turnaround time from laboratories. CKD-EPI equations based on serum cystatin C levels either alone ($eGFR_{cys}$) or in combination with SCr and other demographic variables have been developed.[1] The CKD-EPI creatinine–cystatin C equation that uses a combination of both SCr and cystatin C ($eGFR_{cr\text{-}cys}$) has shown to be a better estimate of kidney function in CKD than equations using either biomarker alone.[31] Because of the complexity of these equations, several online calculators and apps are used by clinicians to estimate renal function. Some examples of calculators are included on the NKF and the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) websites. Others include MDCalc, GlobalRPH, ClinCalc, and so on.

%

The results from the MDRD, CKD-EPI, and CG equations are not interchangeable. eGFR calculated from the MDRD and CKD-EPI equations are used to quantify GFR, to classify or stage the degree of CKD, and to follow progression, whereas CrCl calculated from the CG equation is still the most frequently used estimation used to evaluate the appropriate doses of drugs that are eliminated by the kidney. Both CrCl and eGFR are approved by the Food and Drug Administration (FDA) for drug dosing labels. (See Chapter 31, for more on Dosing of Drugs in Kidney Failure.)

ALBUMINURIA

The term “albuminuria,” which was briefly discussed earlier in this chapter, is often used interchangeably with “proteinuria,” which technically refers to the total protein excreted (including albumin). In this chapter, we will focus mainly on albuminuria and discuss proteinuria only in the context of glomerular disease. Large molecules like proteins, such as albumin, are not normally filtered across the glomerulus; thus, only trace amounts are present in the urine of individuals without CKD. The amount of protein present in the urine has been shown to be a predictor of CKD progression. As a result, protein excretion should be annually screened using a

semiquantitative urine test strip or dipstick in patients at risk for CKD. A dipstick positive for albuminuria should be followed by a quantitative assessment of albuminuria, which is a better indicator of early CKD because it is primarily indicative of glomerular damage as opposed to total protein, which is not specific for glomerular damage.[1]

There are several tests to quantify albuminuria. Determination of albuminuria can be done using timed urine samples (see Table 28-2). The gold standard is a 24-hour urine collection period used to determine albumin excretion rate (AER). A timed sample collected overnight may be more reliable because albumin excretion can vary throughout the day and with postural changes (ie, orthostatic proteinuria). Both tests are inconvenient and prone to miscalculations because of potential urine spillage or incomplete collections by the patient. Untimed or “spot” urine samples for measurement of ACR are more convenient. A first morning urine sample is preferable because it correlates best with 24-hour albumin excretion. Albuminuria is present when two out of three spot urine ACR samples are >30 mg/g. Thereafter, KDIGO has provided recommended frequency of ACR test according to CKD stage. The AER can also be performed but has limitations as indicated above. The KDIGO Guidelines for Evaluation and Management of CKD provide criteria for albuminuria categories (see Table 28-4).[1]

Because of the importance of albuminuria in the progression of CKD, several strategies have been recommended to decrease albuminuria to decrease progression of CKD, such as a renin–angiotensin–aldosterone system (RAAS) blockade should be instituted when albuminuria occurs. Aldosterone antagonists (spironolactone and eplerenone) have also been shown to decrease albuminuria when used in combination with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in adults who has mild-to-moderate CKD but could increase the risk of hyperkalemia.[32] In phase 2 clinical trials, finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist reduced albuminuria and progression of CKD in patients with type 2 diabetes

(T2D) compared to placebo. ACEI and ARBs will be discussed in detail later in the chapter.[33]

Although albuminuria is the most common biomarker for assessing kidney damage in CKD, newer biomarkers are being studied. Some of these novel biomarkers include asymmetric and symmetric dimethylarginine (ADMA and SDMA), uromodulin, kidney injury molecule 1 (KIM-1), neutrophil gelatinase-association lipocalin (NGAL), miRNA, and proteomic and metabolomic biomarkers.[34] The validation and clinical utility of these biomarkers remains a key area requiring further research.

COMPLICATIONS OF CHRONIC KIDNEY DISEASE

Complications specific to CKD begin to develop as kidney disease progresses, most often when patients reach CKD G3 (eGFR <60 mL/minute/1.73 m^2). These complications include fluid and electrolyte abnormalities, metabolic acidosis, anemia, MBD, CVD, and poor nutritional status. Often, these complications go unrecognized or are inadequately managed during the earlier stages of CKD, leading to poor outcomes by the time a patient requires dialysis. As CKD progresses into the later stages (G4 and G5), patients develop more severe clinical signs and symptoms. For some manifestations and metabolic consequences of advanced CKD, see **Table 28-8**. Low serum albumin levels and anemia were identified in more than 50% of a population of patients with CKD new to dialysis therapy, and these findings were associated with a decreased quality of life.[35] Late referral to a nephrologist to manage CKD and its associated complications has also been associated with increased mortality in the kidney failure population.[35]

Table 28-8
Metabolic Effects of Progressive Kidney Disease

Cardiovascular
Hypertension Congestive heart failure Pericarditis Atherosclerosis Arrhythmias
Dermatologic
Altered pigmentation Pruritus
Endocrine
Calcium–phosphorous imbalances Hyperparathyroidism Metabolic bone disease Altered thyroid function Altered carbohydrate metabolism Hypophyseal-gonadal dysfunction Decreased insulin metabolism Erythropoietin deficiency
Fluid, Electrolyte, and Acid–Base Effects
Fluid retention Hyperkalemia Hypermagnesemia Hyperphosphatemia Hypocalcemia Metabolic acidosis
Gastrointestinal (GI)
Anorexia Nausea, vomiting Delayed gastric emptying GI bleeding Ulcers
Hematologic
Anemia Bleeding complications Immune suppression
Musculoskeletal
Mineral and bone disease Amyloidosis

Cardiovascular
Neurologic
Lethargy Depressed sensorium Tremor Asterixis Muscular irritability and cramps (ie, restless legs syndrome) Seizures Motor weakness Peripheral neuropathy Coma
Psychological
Depression
Anxiety
Psychosis
Miscellaneous
Reduced exercise tolerance

The KDIGO guidelines recommend referral of patients to a nephrologist in any of the following circumstances: acute kidney injury (AKI) or an abrupt fall in GFR, a GFR <30 mL/minute/1.73 m^2, persistent albuminuria (ACR ≥ 300 mg/g), progression of CKD, unexplained persistence of red blood cell (RBC) casts and >20 RBCs per high-power field in urinalysis (UA), persistent abnormalities in potassium, extensive kidney stones, hereditary kidney disease, CKD with resistant hypertension on four or more antihypertensive agents, and in all patients in whom the risk of progression to kidney failure in the next year is estimated at 10% to 20% or greater.[1]

Complications of CKD will be presented in more detail throughout this chapter, and complications associated with dialysis therapy are discussed in Chapter 30, Dialysis Treatment for Chronic Kidney Failure.

PREVENTION OF CHRONIC KIDNEY DISEASE AND ITS PROGRESSION

Appropriate management of CKD includes measures to slow progression of the disease and regular evaluation of kidney function to assess changes in disease severity and to monitor therapy. This includes aggressive strategies to manage the disorders that cause CKD or are known to accelerate the disease process, such as diabetes mellitus, hypertension, high protein intake, and dyslipidemias (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease; Chapter 9, Essential Hypertension; and Chapter 53, Diabetes Mellitus). Systematic reviews and meta-analyses have shown that a protein-restricted diet might delay the progression of CKD but does not significantly reduce the overall mortality rates.[36–38] KDIGO Guidelines for Evaluation and Management of CKD currently recommends lowering protein intake to 0.8 g/kg/day while avoiding high protein intake (ie, >1.3 g/kg/day) in adults at risk for progression.[1] The potential benefits of protein restriction in patients with CKD must be weighed against the potential for malnutrition, which is prevalent in patients with CKD.[39] As mentioned, inflammatory cytokines may be responsible for fibrosis and kidney scarring, ultimately resulting in the progression of CKD. Anti-inflammatory drugs like pentoxifylline and pirfenidone, which exhibit antifibrotic properties have been studied for slowing the progression of CKD. Studies have demonstrated that pentoxifylline in combination with ACEI or ARBs slowed the progression of CKD.[40,41] Pirfenidone has been shown to slow progression of CKD in patients with focal segmental glomerulosclerosis.[42] A phase 2 clinical trial looking at the effect of pirfenidone on the progression of advanced CKD to kidney failure, Trial of Pirfenidone to Prevent Progression in Chronic Kidney Disease (TOP-CKD), is currently in progress.[43]

Antihypertensive Therapy

Antihypertensive therapy prevents kidney damage and slows the rate of progression of CKD in both diabetic and nondiabetic patients.[44] In addition, the added benefit of reduced cardiovascular mortality further supports the use of antihypertensive therapy in patients at risk for progressive CKD. The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (commonly referred to as JNC-8) and the KDIGO/Management of Blood Pressure in Chronic Kidney Disease Guideline recommends a BP <140/90 mm Hg.[44,45] Controversy exists as to the optimal BP target in patients with CKD with albuminuria (ACR > 30 mg/g in 24 hours or equivalent). Furthermore, the KDIGO guidelines recommend a BP target of ≤130/80 mm Hg in patients with CKD with albuminuria (ACR > 30 mg/g in 24 hours or equivalent), whereas JNC-8 suggest a target of 140/90 mm Hg for patients with albuminuria. In 2017, the American College of Cardiology (ACC), the American Heart Association (AHA), and several other organizations released new guidelines for the management of hypertension in adults.[46] These guidelines recommend a BP goal of <130/80 mm Hg in patients with CKD with or without albuminuria. These recommendations were made based on three trials. The combined previous analyses of cohorts from the African American Study on Kidney Disease (AASK) and MDRD trials suggested strict BP control was kidney-protective in patients with albuminuria but a mortality benefit was not reported.[47,48] In contrast, the Systolic Blood Pressure Intervention Trial (SPRINT) showed aggressive BP control (systolic BP of <120 mm Hg) was associated with better cardiovascular events and all-cause mortality compared to the standard control (systolic BP of <140 mm Hg).[49] Recent analysis of the MDRD study and AASK study suggests that like the SPRINT there is an all-cause mortality benefit to intensive BP control in individuals with CKD.[50]

ACEIs and ARBs are the most commonly recommended as first-line treatment options for hypertension in those with CKD, especially those with albuminuria by the KDIGO hypertension guidelines.[44] In individuals with decreased eGFR, angiotensin II primarily causes compensatory vasoconstriction of the efferent arteriole, thereby

increasing glomerular capillary pressure (P_{GC}) and eGFR (**Fig. 28-1**). This effect is beneficial in conditions of AKI; however, sustained increases in P_{GC} cause hypertrophy of individual nephrons and progressive CKD. ACEI and ARB therapy prevents the chronic increase in glomerular pressure mediated by angiotensin II. Benefits of ACEIs have been demonstrated in patients with diabetes with some degree of proteinuria, suggesting that ACEI use be considered in this population regardless of BP.[44] In patients without diabetes mellitus, ACEIs have been shown to reduce BP, decrease proteinuria, and slow the progression of CKD when compared with other agents. ARBs offer similar benefits to ACEIs based on their ability to decrease efferent arteriolar resistance by blockade of the angiotensin type 1 (AT_1) receptor.[51–53]

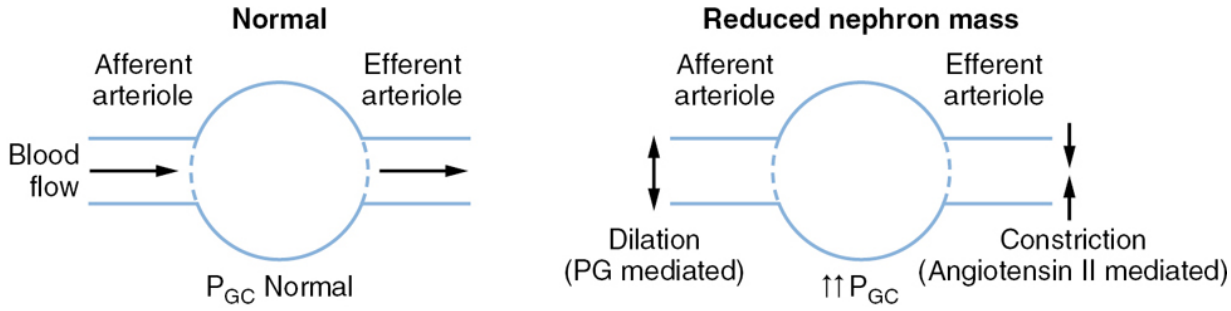


Figure 28-1 Kidney hemodynamics are dependent on afferent and efferent arteriolar tone and glomerular capillary pressure (P_{GC}). With reduced nephron mass, afferent arteriolar vasodilation (mediated primarily by prostaglandins [PG] I_2 and E_2) and efferent arteriolar constriction (mediated primarily by angiotensin II) occur within remaining functioning nephrons to compensate. This leads to an increase in blood flow, intraglomerular capillary filtration pressure (P_{GC}), and hyperfiltration (increased single-nephron effective GFR). Sustained increases in plasma flow and hydrostatic pressure lead to hyperfiltration injury and glomerular sclerosis. With time, these changes contribute to continued loss of nephron function (ie, progression of kidney disease). Angiotensin converting enzyme inhibitors and angiotensin receptor blockers prevent vasoconstriction of the efferent arteriole and reduce the P_{GC}.

The optimal kidney-protective doses of ACEI/ARBs in CKD have been an area of controversy. In a study looking into optimization of ACEI (benazepril) and ARB (losartan) in CKD, higher doses of >20 mg for benazepril and >50 mg for losartan had better kidney-protective outcomes than conventional doses.[54] Patients must be closely monitored when using doses of ACEI/ARB above the antihypertensive doses because of the potential for adverse effects. An initial and mild decrease in eGFR is expected with ACEI/ARB therapy; therefore, an increase in SCr of 30% within the first 2 months of therapy is acceptable.[55] Hypotension, AKI, and severe hyperkalemia are reasons to consider temporarily stopping or discontinuing therapy (also see Chapter 14, Heart Failure). Another controversial issue is the use of ACEI/ARBs in patients with advanced CKD (categories G4 and G5). A study looking at the effect of stopping RAAS blockage in patients with advanced CKD (eGFR < 30 mL/minute/1.73 m^2) found that compared to continuing RAAS inhibitors, stopping RAAS inhibitors increased the 5-year absolute risk of mortality and major adverse cardiovascular events, but lowered the risk of initiation of KRT.[56] Another study showed that discontinuing RAAS blockage in advanced CKD significantly increased mortality and major adverse cardiovascular events without improving the risk of kidney failures.[57] The STOP-ACEI trial, currently in progress, is also looking at the effect of discontinuing RAAS blockage in advanced CKD.[58]

Aliskiren is a direct renin inhibitor. However, its role as monotherapy for BP control or kidney protection is unclear.[59] Aliskiren has been associated with a reduction in GFR and filtration fraction in patients receiving optimal heart failure therapy.[60] The therapy that involves the combination of ACEIs with ARBs or ACEIs/ARBs with aliskiren is not recommended because of the increased risk of CKD progression to kidney failure, hyperkalemia, and AKI.[46,60–62]

Because fluid or volume overload is usually part of clinical presentation in CKD, diuretics are often a part of BP control in most patients with CKD. Thiazides and thiazide-like diuretics are typically used in patients with eGFR >30 mL/minute/1.73 m^2, as their efficacy

in reducing fluid retention diminishes as the GFR drops to 30 to 50 mL/minute/73 m^2. For patients with CKD with eGFR <30 mL/minute/1.73 m^2, loop diuretics can be used as an alternative.[63]

Calcium channel blockers have been considered for preventing progression of CKD owing to their effects on kidney hemodynamics and cytoprotective and antiproliferative properties (prevention of mesangial expansion and kidney scarring). Non-dihydropyridine agents (eg, diltiazem and verapamil) have been beneficial in reducing albuminuria when compared with dihydropyridines (eg, amlodipine), which was found to worsen albuminuria.[64,65] Dihydropyridine calcium channel blockers have the effect of increasing albuminuria and should not be used alone in patients with albuminuria, but can be used safely in combination with an ACEI or ARB. Combination therapy with an ACEI and non-dihydropyridine agents has resulted in greater reductions in albuminuria in patients with diabetes mellitus than with either agent alone, suggesting that it may be rational to use multiple agents in this population.[64]

β-Blockers may offer benefits in the treatment of diabetic kidney disease (DKD) as demonstrated by the United Kingdom Prospective Diabetes Study, which showed similar effects of atenolol and captopril on decreasing the incidence of albuminuria in patients with diabetes.[66] β-Blockers offer several benefits to patients with CKD, such as attenuation of excessive sympathetic output and reduction in sudden cardiac death seen in patients on dialysis.[67] β-Blocker selection should take into account the dialyzability of the drug and/or the risk for drug accumulation.[68]

DIABETIC KIDNEY DISEASE

CASE 28-1

QUESTION 1: G.B. is a 44-year-old, African American female (weight, 175 pounds [79.38 kg]; height, 65 inches [165.1 cm]) with a 20-year history of T2D. She presents to the diabetes clinic for her quarterly checkup. She has been

noncompliant with appointments, and her blood glucose has generally remained >200 mg/dL. She had a hemoglobin A_{1c} of 10.1% (goal, <7%) and a urine ACR of 200 mg/g (albumin category A2) obtained 3 months ago. Lately G.B. reports general nausea, fatigue, and poor appetite.

Medications: Metformin ER 500 mg PO daily and a multivitamin daily.

The workup reveals the following pertinent laboratory values:
Serum sodium (Na^+), 143 mEq/L
Potassium (K^+), 4.9 mEq/L
Chloride (Cl^-), 106 mEq/L
Total CO_2, 18 mEq/L
Serum creatinine (SCr), 2.1 mg/dL
eGFR, 31 mL/minute/1.73 m^2
BUN, 30 mg/dL
Random blood glucose, 289 mg/dL
Additional laboratory studies show the following results:
Serum phosphate, 6.6 mg/dL
Calcium (Ca), 8.8 mg/dL
Albumin (Alb), 3.6 g/dL
Magnesium (Mg), 2.1 mEq/L
Uric acid, 6.8 mg/dL
Hematologic studies show the following results:
Hematocrit (Hct), 28%
Hemoglobin (Hgb), 10.3 g/dL
Reticulocyte count, 0.5%.
Mean corpuscular volume (MCV), 95 fL
White blood cell (WBC) count, 9600/μL
Platelet count, 155,000/μL
Iron studies show the following results:
Serum ferritin, 250 ng/mL
Serum iron, 45 μg/dL
Total iron-binding capacity (TIBC), 302 μg/dL
Transferrin saturation (TSAT), 15%
Urinalysis (UA) findings: urine dipstick showed 4+ proteinuria, spot urine sample showed an ACR of 500 mg/g
Physical examination reveals a BP of 158/92 mm Hg, 2+ pedal edema, and a 10-pound (4.54 kg) weight gain.

What subjective and objective data in G.B. are consistent with a diagnosis of advanced CKD?

G.B.'s abnormal values for SCr, BUN, serum potassium, magnesium, phosphate, uric acid, total CO_2, and hemoglobin are all consistent with CKD progression and its associated complications.

Assuming relatively stable kidney function (ie, no acute changes in kidney function; has her SCr remained the same?), her eGFR is ~31 mL/minute/1.73 m^2 based on the MDRD equation, placing her in CKD category G3b (eGFR 30–44) mL/minute/1.73 m^2. As the eGFR declines, normal regulation of fluids and electrolytes is impaired. Elevations in SCr, BUN, potassium, and phosphate as well as signs of fluid accumulation are observed. G.B.'s serum potassium is slightly elevated, and the risk of hyperkalemia increases with CKD.[69] The albuminuria observed in G.B. is consistent with glomerular damage. G.B. has an ACR of 500 mg/g on today's UA, which places her in category A3, thus making her CKD stage G3b/A3 based on the KDIGO CKD classification system placing her in very high CKD risk category. Volume overload from continued intake and decreased sodium and water excretion leads to weight gain, hypertension, and edema. Metabolic acidosis results from impaired synthesis of ammonia by the kidney, which normally buffers hydrogen ions and facilitates acid excretion. Anemia associated with CKD is caused primarily by decreased erythropoietin (EPO) production by the kidneys, but it also can be caused by shortened half-life of RBCs from uremia, and iron deficiency. G.B.'s recent onset of nausea and malaise may be a consequence of the accumulation of uremic toxins (azotemia) from the decline in kidney function.

CASE 28-1, QUESTION 2: What is the cause of G.B.'s kidney disease?

Given G.B.'s presentation, her CKD is most likely caused by DKD from her 20-year history of T2D. Based on the history of present illness (HPI), her hyperglycemia is poorly controlled (A_{1c}: 10.1%), she is also African American. These are risk factors for DKD. African Americans, Native Americans, and Hispanics have an increased risk of developing kidney failure from diabetes relative to Whites.[5] Poor adherence with regular appointments, poor medication adherence, or inadequate selection or dose of antidiabetic agents may contribute to DKD. Uncontrolled diabetes associated with elevated glucose concentration and hemoglobin A_{1c} values, and albuminuria serve as

the primary causes. DKD rarely develops within the first 10 years after the onset of type 1 diabetes (T1D); however, 5% to 20% of patients with T2D have some degree of albuminuria at diagnosis.

DKD is a microvascular complication of diabetes resulting in albuminuria, hemodynamic changes in kidney microcirculation, glomerular structural changes, and a progressive decline in kidney function. DKD develops in 20% to 40% of patients with T1D or T2D within 25 years of onset.[1] With the increased prevalence and incidence of diabetes, it is likely that DKD will remain the leading cause of kidney failure in the United States. The exact mechanisms leading to the development of DKD are not clearly defined. Advanced glycosylation end products (AGEs) that form because of uncontrolled hyperglycemia have been implicated as a cause of end-organ damage. The accumulation of multiple AGE is associated with the severity of CKD in patients with DKD.[70] AGEs increase the formation of reaction oxygen species (ROS) thereby triggering inflammation, endothelial dysfunction, and interstitial fibrosis, ultimately leading to kidney damage.[71] Uncontrolled hyperglycemia alters the balance between vasoconstriction and vasodilation of the afferent and efferent arterioles.[72] It causes a shift in hemodynamics to afferent arteriole vasodilation and efferent arteriole vasoconstriction leading to increased intraglomerular pressure and consequently glomerular hyperfiltration. Certain genes and polymorphisms have also been associated with the development of DKD, and further exploration into this area may prove beneficial in identifying high-risk patients.[73,74]

Case 28-1, Question 3: What is the significance of G.B.'s albuminuria?

Albuminuria, the earliest sign of kidney involvement in patients with diabetes, correlates with the rate of progression of CKD. Albuminuria not only indicates kidney damage but is also a powerful predictor of cardiovascular morbidity and mortality.[1] For most patients, eGFR begins to decline once albuminuria is established. Because of this association, annual testing of ACR is indicated in

patients who have had T1D for more than 5 years and in all patients with T2D starting at diagnosis. The presence of severely increased albuminuria, A3, indicates irreversible kidney damage. G.B. has likely reached the point at which such damage is inevitable because her ACR exceeds ranges normally observed at the earlier stages of CKD. G.B.'s current laboratory data suggest that she has substantial CKD and has developed associated complications of the disease. Although progression to kidney failure is generally beyond prevention at this stage, appropriate intervention can slow the progression of CKD.

Management

Case 28-1, Question 4: How should G.B.'s kidney disease be managed?

Because reversal of G.B.'s kidney disease is not possible, the primary goals are to delay the need for dialysis therapy as long as possible and to manage complications. The three main risk factors for the progression of incipient CKD to clinical DKD are poor glycemic control, systemic hypertension, and high dietary protein intake (>1.3 g/kg/day). G.B.'s current random blood glucose concentration of 289 mg/dL, history of elevated glucose on prior visits, and elevated hemoglobin A_{1c} indicate poorly controlled diabetes, which will accelerate the progression of DKD and time to kidney failure. Thus, her blood glucose concentrations should be maintained within target goals while avoiding hypoglycemia. G.B.'s elevated BP is likely the result of CKD and changes in intravascular volume; reduction in BP may prevent further damage to functioning nephrons and slow the progression to kidney failure. Similarly, reductions in dietary protein intake (dietary protein intake of ~0.8 g/kg body weight/day) should be initiated to reduce the rate of further progression, although this needs to be evaluated in the context of her overall nutritional status.

INTENSIVE GLUCOSE CONTROL

Strict glycemic control can improve diabetic management, reduce albuminuria, and slow the rate of decline in eGFR. A landmark clinical trial, the UK Prospective Diabetes Study (UKPDS) demonstrated the beneficial effects of intensive glycemic control in patients with T2D. During a 10-year treatment period, intensive glucose control (fasting glucose <108 mg/dL) with either insulin or an oral sulfonylurea reduced microvascular complications (eg, retinopathy and nephropathy), including albuminuria by 33%, when compared with conventional dietary therapy (fasting glucose <270 mg/dL).[75] This benefit of intensive glucose control on development of microvascular complications was similar to the findings of another landmark study, the Diabetes Control and Complications Trial (DCCT), which was conducted in patients with T1D. This study showed that intensive glucose control slows the progression of CKD compared to conventional therapy.[76]

Other diabetes trials such as Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) evaluated the macrovascular and microvascular outcomes associated with intensive glucose control in T2D. The ACCORD trial showed a 21% reduction in the development of moderately increased albuminuria cases and a 32% reduction in severely increased albuminuria cases.[77] In the ADVANCE trial, there was a 9% reduction in moderately increased albuminuria and 30% reduction in progression to severely increased albuminuria.[78]

Recently, the role and benefit of newer anti-glycemic medications like the sodium-glucose cotransporter-2 (SGLT-2) inhibitors (eg, canagliflozin, empagliflozin, dapagliflozin) in the reduction of death and CVD in T2D have been reported. Additionally, both glycemic control and kidney protection were shown in several studies.[79,80] The Canagliflozin Cardiovascular Assessment Study (CANVAS) and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials showed that canagliflozin when added to baseline T2D therapy significantly

reduced the risk of progression to kidney failure in patients with T2D.[81,82] Dapagliflozin was recently approved to reduce the risk of CKD progression because of findings of the DAPA-Kidney trial. In this trial involving patients with CKD (with or without T2D), dapagliflozin significantly delayed the decline of eGFR compared to placebo.[83] Empagliflozin is currently in a clinical trial (EMPA-Kidney) to investigate the effect of empagliflozin on kidney disease progression or cardiovascular death versus placebo on top of standard of care in patients with pre-existing CKD.[84] The potential kidney and cardioprotective properties of these agents place them in a vital position in managing patients with CKD with T2D.[79,80] Initiation of SGLT-2 inhibitors is not recommended in patients with advanced CKD (eGFR <30 mL/minute/1.73 m^2).[85–87] KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD recommends an individualized hemoglobin A_{1c} from <6.5% for CKD G1 to <8% for CKD G5.[88] For detailed recommendations on antidiabetic management, refer to the American Diabetes Association (ADA) standards of medical care diabetes centered on evolving evidence, technology, and individualized care.

G.B. will benefit from a multifactorial approach addressing glycemic control and hypertension to slow her progression of CKD from diabetes mellitus. Appropriately dosed oral hypoglycemic can achieve these goals despite her advanced CKD. Adding an SGLT-2 inhibitor (eg, canagliflozin 100 mg daily) to the metformin could have the added benefit of reducing her albuminuria. We will discuss SGLT-2 inhibitors later in the chapter. (Also, see Chapter 53, Diabetes Mellitus for other antidiabetic therapeutic options.)

ANTIHYPERTENSIVE THERAPY

Systemic hypertension usually occurs with the development of normal to moderately increased albuminuria in patients with T1D. It is also present in about one-third of patients at the time of diagnosis of T2D and hastens the progression of CKD in both groups. The coexistence of these disorders further increases the risk of cardiovascular events. Hypertension may be a result of underlying

diabetic nephropathy and increased plasma volume or increased peripheral vascular resistance. Regardless of the etiology, virtually any level of untreated hypertension (either systemic or intraglomerular) is associated with a reduction in eGFR.[89]

Patients with diabetes and hypertension exhibit elevated systemic vascular resistance and increased vasoconstriction from angiotensin II, which are in large part responsible for the glomerular damage characteristic of diabetic nephropathy. Although the management of hypertension with virtually any agent can attenuate the progression of CKD, ACEIs, which inhibit the synthesis of angiotensin II, and ARBs, which block angiotensin II AT1 receptors, are preferred owing, in part, to the effects of these agents on kidney hemodynamics (see Fig. 28-1). KDIGO guidelines recommend an ACEI or ARB for the treatment of hypertension in all CKD patients with AER >300 mg/24 hours and diabetic CKD adults with AER ≥30 mg/24 hours. Both the JNC-8 and 2017 ACC/AHA guidelines recommend ACEI or ARB as first-line antihypertensive agents in patients with CKD regardless of race and the presence of albuminuria.[45,46]

The primary goal in G.B. is to delay the development of kidney failure and to reduce the risk of cardiovascular complications and death. Treatment with an ACEI (eg, lisinopril) should be initiated because she has substantial albuminuria (ACR of 500 mg/g) and an elevated BP (158/92 mm Hg). An ARB is a reasonable alternative to an ACEI in patients with ACEI-induced cough or other adverse effects that do not cross-react with an ARB. The initial agent selected is generally based on tolerance to therapy and cost. A goal BP for G.B., given the fact that she has diabetes and CKD, is a BP <130/80 mm Hg.[44–46] G.B. must be monitored on a long-term basis for changes in kidney function and albuminuria and for side effects of therapy, such as hyperkalemia. A moderate increase in SCr is acceptable with the initiation of therapy with ACEIs or ARBs. Contraindications for the use of ACEIs or ARBs include bilateral kidney artery stenosis and pregnancy. The risk of hyperkalemia must also be weighed against the potential beneficial effects of these agents. So, when using them for their anti-proteinuria effect, ACEI/ARBs should be started at low doses and titrated cautiously

with no effect while monitoring BP, kidney function, and potassium. Some evidence suggests that a non-dihydropyridine calcium channel blocker (eg, diltiazem, verapamil) may be beneficial alone or in combination with an ACEI.[90]

FLUID AND ELECTROLYTE COMPLICATIONS

Sodium and Water Retention

CASE 28-1, QUESTION 5: Assess G.B.'s sodium and water balance. What interventions may be used to address this problem?

As illustrated in G.B., patients in the latter stages of CKD commonly retain sodium and water. This is supported by G.B.'s elevated BP and 2+ pedal edema. Sodium and water retention also lead to weight gain. Early in CKD, glomerular and tubular adaptive processes develop as an increase in the fractional excretion of sodium (FENa). These mechanisms enable patients to maintain relatively normal sodium and water homeostasis. As G.B.'s normal serum sodium concentration indicates, this value is of little use in establishing the diagnosis of total body sodium and fluid excess because retention of sodium and water usually occurs in an isotonic fashion, leaving the serum sodium concentration relatively normal. Eventually, patients with advanced kidney dysfunction exhibit signs of sodium and fluid retention because sodium balance is maintained at the expense of increased extracellular volume, which results in hypertension. Expansion of blood volume, if not controlled, can cause peripheral edema, heart failure, and pulmonary edema. Thus, management of sodium and water retention is essential. To achieve control, most patients with advanced CKD are placed on sodium restriction (2 g/day) and fluid restriction (~1–2 L/day). These restrictions will depend on the current dietary intake, extent of

volume overload, and urine output and should be altered according to the special needs of the patient.

Diuretics may be considered for patients with diabetic nephropathy and edema, depending on their degree of kidney function. G.B.'s eGFR is 31 mL/minute/1.73 m^2, so she can be started on chlorthalidone 12.5 mg daily. Thiazide diuretics as single agents are generally not effective when the eGFR is <30 mL/minute/1.73 m^2. A possible exception is the use of thiazide-like diuretic, metolazone, which may retain its effect at reduced eGFRs.[44] Alternatively, a loop diuretic could be used in patients with eGFR <30 mL/minute/1.73 m^2. (See Chapter 27, Fluid and Electrolyte Disorders, and Chapter 9, Essential Hypertension.)

Hyperkalemia

Case 28-1, Question 6: G.B. serum potassium concentration is now 5.3 mEq/L after starting lisinopril. Describe the mechanisms by which potassium imbalance occurs in patients, such as G.B. who have progressive CKD. Is treatment of G.B.'s potassium indicated? How should chronic hyperkalemia be managed?

Hyperkalemia can result from a combination of factors, including diminished kidney potassium excretion, redistribution of potassium into the extracellular fluid owing to metabolic acidosis, excessive potassium intake or supplementation, and medications like ACEI/ARBs and potassium-sparing diuretics. The combination of CKD complication and lisinopril are both contributing to hyperkalemia in G.B.

Potassium normally is filtered at the glomerulus and undergoes nearly complete reabsorption throughout the kidney tubule. Distal tubular secretion is the primary mechanism by which potassium is excreted in the urine. A variety of factors affect this distal secretion of potassium, including aldosterone, sodium load presented to the distal tubule, hydrogen ion secretion, the amount of nonresorbable anions, urinary flow rate, diuretics, mineralocorticoids, and

potassium intake.[91,92] Serum potassium concentrations are relatively well maintained within normal limits in patients with CKD, so hyperkalemia is rare without an endogenous or exogenous load of potassium. This balance is maintained despite a decreasing nephron population and an overall drop in eGFR because the remaining nephrons undergo adaptive changes to enhance the distal tubular secretion of potassium per nephron (ie, increased fractional excretion of potassium, FEK).[91] GI excretion of potassium is also important because increased GI excretion and fecal losses may account for up to 35% of the daily potassium loss in patients with severe CKD. Additional factors that alter potassium homeostasis include metabolic or respiratory acidosis. Acidemia can cause a redistribution of intracellular potassium to the extracellular fluid. G.B. has metabolic acidosis as indicated by serum bicarbonate of 18 mEq/L, which could contribute to her mildly elevated potassium concentration.

G.B. has a mild elevation in potassium to 5.3 mEq/L; therefore, no specific treatment is required for now. Although this serum potassium concentration does not require immediate intervention, close monitoring for hyperkalemia and its manifestations is necessary. Manifestations of hyperkalemia include weakness, confusion, and muscular or respiratory paralysis. These symptoms may be absent, especially if hyperkalemia develops rapidly. Chronic management involves prevention of hyperkalemia by limiting potassium intake and avoiding the use of medications that could elevate potassium levels. Sodium polystyrene sulfonate (SPS; Kayexalate, Kionex) is a cation-exchange resin that has long been used for the chronic management of hyperkalemia.[93] Recently, two newer ion-exchange resins, patiromer (Veltassa®) and sodium zirconium cyclosilicate (SZC; Lokelma®).[94,95] These ion-exchange resins remove potassium ions from the lumen of the large intestines in exchange for sodium, sodium and hydrogen, and calcium ions, respectively. Data suggest that in spite of their comparable efficacy, tolerability is a major disadvantage. SPS has been associated with intestinal necrosis, fluid overload (because of sodium content), and other GI side effects. Patiromer and SZC have more favorable adverse effect

profiles than SPS, even though SZC has also been associated with edema.[96] Acute management of hyperkalemia is addressed in Chapter 27, Fluid and Electrolyte Disorders.

In several studies, patiromer and SZC have been shown to be effective in managing hyperkalemia in patients with CKD on RAAS inhibitors. A study investigating the safety and efficacy of patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors (OPAL-HK trial) found that patiromer was effective in reducing potassium in patients on RAAS inhibitors.[97] Another study that investigated the safety and efficacy of SZC in patients with hyperkalemia (HARMONIZE GL trial) also showed that SZC was effective in reducing potassium in patients with CKD on RAAS inhibitors.[98] To optimize the use of lisinopril in G.B., she can be initiated on patiromer 8.4 g once daily, titrated as needed weekly up to a maximum of 25.2 g daily if her potassium continues to rise.

Metabolic Acidosis

Case 28-1, Question 7: Assess G.B.'s acid–base status. How should her acid–base disorder be managed?

G.B.'s low total blood CO_2 and high chloride concentration are consistent with metabolic acidosis. Normal buffering of hydrogen ions by the bicarbonate–carbonic acid system as well as other extracellular and intracellular buffers, including proteins, phosphates, and hemoglobin, is essential for maintaining normal acid–base balance (ie, normal pH). Normal metabolism of ingested food produces ~1 mEq/kg of metabolic acid daily, which must be excreted by the kidneys (primarily as ammonium ion) to maintain acid–base balance. The kidney is responsible for reabsorption of bicarbonate and excretion of hydrogen ions through buffering by ammonia (produced by the kidney) and filtered phosphates. Reduced bicarbonate reabsorption and impaired production of ammonia by the kidneys are the major factors responsible for development of

metabolic acidosis in advanced CKD. As nephron function declines, production of ammonia is increased to compensate for a decrease in secretion of hydrogen ions; however, once the maximal capacity for ammonia production is reached, acidosis develops. As kidney disease progresses, metabolic acidosis with an elevated anion gap is observed owing to accumulation of organic acids (see Chapter 26, Acid–Base Disturbances).

G.B.'s mild acidosis should be treated with a goal of normalizing the plasma bicarbonate concentration or at least achieving bicarbonate levels of at least 22 mEq/L. Treatment options includes use of oral preparations containing sodium bicarbonate or sodium citrate. Each 650-mg tablet of sodium bicarbonate provides ~8 mEq of bicarbonate. Sodium citrate/citric acid (Bicitra, Shohl solution) orally delivers 1 mEq of bicarbonate/mL. These latter agents may be used in patients who experience excessive GI distress with sodium bicarbonate because of production and elimination of carbon dioxide. If a patient such as G.B. is sodium and fluid overloaded, it is important to consider that sodium bicarbonate or sodium citrate can exacerbate this problem. Polycitra, or potassium citrate, is a possible alternative; however, the potassium content limits its use in patients with more severe CKD. Citrate also promotes aluminum absorption and should not be used in patients taking aluminum-containing agents. Typical starting regimens can be two to four 650-mg sodium bicarbonate tablets/days (divided into two to three doses). Afterward, doses should be titrated to desired bicarbonate levels. This could be a new option for managing metabolic acidosis in CKD.

Once in kidney failure, dialysis can be used to chronically manage metabolic acidosis. Bicarbonate is added to the dialysate solution and is delivered through the process of diffusion from the dialysate bath into the plasma (see Chapter 30, Dialysis Treatment for Chronic Kidney Failure).

ANEMIA OF CHRONIC KIDNEY DISEASE

CASE 28-1, QUESTION 8: What findings in G.B. are consistent with the diagnosis of anemia of CKD, and what is the etiology of this disorder?

G.B.'s hemoglobin of 10.3 g/dL is substantially lower than the normal range for females, indicating that she has anemia. Her normal MCV suggests her red cells are of normal size, but the absence of an elevated reticulocyte count suggests an impaired bone marrow response for her degree of anemia. Her fatigue is consistent with the symptoms of anemia.

Characteristics and Etiology

Anemia, defined as a hemoglobin concentration of <13 g/dL (in males) and <12 g/dL (in females), affects most patients with CKD.[99] It is primarily caused by a decreased production of erythropoietin (EPO), a glycoprotein that stimulates RBC production in the bone marrow and is released in response to hypoxia. Approximately 90% of the total EPO is produced in the peritubular cells of the kidney; the remainder is produced by the liver. EPO concentrations in patients with kidney failure are lower than in individuals with normal kidney function who have the same degree of anemia and the same stimulus for EPO production and release.[99]

Anemia can appear as early as category G3a in CKD and is characterized by normochromic (normal color) and normocytic (normal size) RBCs unless a concomitant iron, folate, or vitamin B_{12} deficiency exists. A higher prevalence of anemia occurs in the population with an eGFR <60 mL/minute/1.73 m^2.[1] Pallor and fatigue are the earliest clinical signs, with other manifestations developing as anemia progresses with declining kidney function. A significant consequence of anemia is development of left ventricular hypertrophy (LVH), further contributing to cardiovascular complications and mortality in patients with CKD. LVH has been observed in ~30% of patients with eGFR 50 to 75 mL/minute/1.73 m^2 (CKD G2 and G3) and in up to 74% of patients at the start of

dialysis.[100] These findings support the need for early and aggressive treatment of anemia of CKD.

A complete workup for anemia of CKD is recommended for patients with an eGFR of <60 mL/minute/1.73 m^2.[99] This workup includes a complete blood count, including hemoglobin, assessment of iron indices, and evaluation for sources of blood loss. This workup should be done annually to every three months depending on the stage of CKD because of the association between anemia and the progressive decline in eGFR.[99]

IRON STATUS

Iron deficiency substantially contributes to anemia development even in the presence of adequate EPO. The two tests that best evaluate iron status are the TSAT percent and serum ferritin.[99] Transferrin is a carrier protein for iron within the blood. The TSAT indicates the saturation of the transferrin with iron and is determined as follows (Eq. 28-4):

$$\%\ \text{TSAT} = \frac{\text{serum iron}\ (\mu g/dL)}{\text{TIBC}\ (\mu g/dL)} \times 100 \qquad \textbf{(Eq. 28-4)}$$

where TIBC is the total iron-binding capacity of the transferrin protein. The TSAT is considered iron readily available for RBC production. Serum ferritin is a marker for iron reserves, which are stored primarily in the mononuclear phagocytic system. The goal of iron supplementation therapy is to maintain the TSAT >30% and a serum ferritin >500 ng/mL for CKD to provide sufficient iron for erythrocyte production. A low ferritin level in CKD is usually indicative of absolute iron deficiency. On the other hand, patients with CKD also can present with functional iron deficiency, which is a state where the total iron stores are normal but not effectively mobilized from the storage sites in the reticuloendothelial macrophages. It is postulated that chronic inflammation in CKD plays a major role in functional iron deficiency. Hepcidin, a 25-amino acid hepatic peptide, is upregulated during inflammation, which increases

in prevalence in the later stages of CKD.[101] Hepcidin suppresses the release of iron from the stores in to circulation, which contributes to functional iron deficiency. It has been explored as a possible measure of iron status, but the diurnal variation associated with hepcidin makes it an unreliable biomarker.[101]

Other tests, including the percentage of hypochromic RBCs, reticulocyte hemoglobin content, serum transferrin receptor, RBC ferritin, and zinc protoporphyrin, have been proposed as indicators of iron status, but further investigation is warranted to determine their utility and to make such testing procedures readily available.[99]

TREATMENT

Case 28-1, Question 9: What are the goals of therapy for anemia in G.B.? Describe the options available to treat anemia of CKD and achieve the goals of therapy in G.B.

The main goals of therapy in a patient with anemia of CKD include prevention/improvement of anemia-related symptoms, avoidance of blood transfusions, and preventing long-term cardiovascular effects of anemia. G.B.'s iron status should be evaluated first and corrected if necessary. If achieving an adequate iron status does not improve hemoglobin, erythropoiesis-stimulating agent (ESA) therapy may be started (see Treatment section, and Chapter 92, Anemia).

IRON THERAPY

The KDIGO guidelines suggest a 1- to 3-month trial of oral iron supplementation for CKD patients not on dialysis; however, given the poor bioavailability of oral iron and patient noncompliance, oral iron is usually inadequate for repletion of iron in patients with advanced CKD.[99,102] Therefore, a trial of oral iron is reasonable for G.B. Oral iron supplementation should be started to treat iron deficiency. Patients may not tolerate oral iron therapy because of GI side effects, so it might be desirable to start at a low dose (65 mg of elemental iron) and titrate up to the optimal daily dose of 200 mg, as

tolerated. Many oral iron preparations are available, and their iron content varies, as will the number of tablets or capsules that must be taken per day to provide the required elemental iron (see **Table 28-9**). An acidic environment is needed for adequate iron absorption, and acid-suppression therapies (eg, proton-pump inhibitors) may limit the absorption of oral iron.

Table 28-9
Oral Iron Preparations

Preparation	Common Brand Names	Commonly Prescribed Unit Size (Amount Elemental Iron in mg)[a]	Number of Units/Day to Yield 200 mg Elemental Iron
Ferrous sulfate	Slow FE, Fer-In-Sol	325 (65)	3 tablets
Ferrous gluconate	Feratab	325 (36)	5 tablets
Ferrous fumarate	Femiron, Feostat	200 (66)	3 capsules
Iron polysaccharide	Niferex, Nu-Iron	150 (150)	2 capsules
Heme iron polypeptide	Proferrin-ES	12 (12)	17 tablets
Carbonyl iron	Fesol	45 (45)	4 tablets

[a]Unit size reflects common tablet or capsule sizes prescribed and not necessarily that of the brand names listed.

G.B. should be advised to take oral iron on an empty stomach to maximize absorption unless side effects prevent this strategy. She also should be counseled on how to avoid potential drug interactions with oral iron (eg, antacids, quinolones) and to take 2 hours apart and GI side effects (eg, nausea, abdominal pain, diarrhea, constipation, dark stools). Also, nonadherence to therapy because of side effects is a common cause of therapeutic failure with oral iron. She should be counseled to contact her physician if these adverse effects persist.

If G.B.'s condition does not respond to oral therapy, as indicated by either persistent iron deficiency based on iron indices or inadequate response to the treatment dose, IV iron might be necessary. The IV iron preparations currently available include iron dextran, iron sucrose, sodium ferric gluconate, ferric carboxymaltose, ferumoxytol, and ferric derisomaltose.[103–108] See **Table 28-10**, for a comparison of several parenteral iron preparations to assist in making appropriate choices for treating iron deficiency anemia associated with CKD in patients on dialysis and

not on dialysis.[103,107,109,110] Additionally, soluble ferric pyrophosphate citrate was approved by the FDA in 2015; this iron product is added to the dialysate used for hemodialysis.[111] Parenteral iron preparations pose the risk of hypersensitivity reactions, including anaphylactoid and sometimes fatal anaphylactic reactions.[102] These serious reactions are more commonly associated with iron dextran; however, patients on parenteral iron should be monitored for at least 30 minutes after administration of any parenteral iron preparation. A test dose is required for iron dextran because of a higher incidence of anaphylactoid and anaphylaxis reactions.[103] Monitoring protocols must be put in place during and after the administration of all IV iron preparations.

Table 28-10
Intravenous Iron Preparations

Preparation	Common Brand Name(s)	Adult Dosing Information for Labeled Indication(s)	Labeled CKD Indication(s) in Adults
Iron dextran	INFed, 50 mg/mL (2 mL)	Requires test dose of 0.5 mL (25 mg) administered over 30 seconds about an hour prior to first dose Total dose (mL) = 0.0442 (Desired Hb – Observe Hb) × LBW + (0.26 × LBW) Administered in divided doses (max daily dose 100 mg)	Iron deficiency anemia (no longer favored in CKD but could still be an option)
Iron sucrose	Venofer® 20 mg/mL (2.5, 5, 10 mL)	HDD-CKD: 100 mg administered during each hemodialysis session (up to 10 doses) PDD-CKD: Two infusions of 300 administered 14 days apart followed by 400 mg 14 days after (total cumulative dose of 1000 mg) NDD-CKD: 200 mg administered on 5 different days within a 14-day period (total cumulative dose of 1000 mg)	For anemia in CKD G1–G5, CKD G5D
Sodium ferric gluconate	Ferrlecit 12.5 mg/mL (5 mL)	125 mg per dialysis session up to a cumulative dose of 1000 mg	For anemia in CKD G5D (hemodialysis)
Ferumoxytol	Feraheme® 510 mg/17 mL (17 mL)	Two-dose regimen: 510 mg over at least 15 minutes; repeat dose after 3–8 days	For anemia in CKD
Ferric carboxymaltose	Injectafer® 750 mg/15 mL (15 mL)	<50 kg: administer 15 mg/kg on day 1; repeat dose after at least 7 days (maximum: 750 mg per single dose; 1500 mg per course) ≥50 kg: administer 750 mg on day 1; repeat dose after at least 7 days (maximum: 750 mg per single dose; 1500 mg per course) May repeat course of therapy if anemia reoccurs	For anemia in CKD
Ferric derisomaltose	Monoferric 1000 mg/10 mL (10 mL)	<50 kg: 20 mg/kg as a single dose ≥50 kg: 1000 mg as a single dose May repeat if iron deficiency anemia reoccurs	For anemia in CKD G1–G5

Sources: InFeD. Package insert. Watson Pharmaceuticals, Inc; 2009; Venofer (iron sucrose). Package insert. Vifor (Int) Inc; 2020; Ferrlecit (sodium ferric gluconate). Package insert. Sanofi-Aventis US, Inc; 2020; Injectafer (ferric carboxymaltose). Package insert. American Regent, Inc; 2020; Feraheme (ferumoxytol). Package insert. AMAG Pharmaceuticals, Inc; 2020; Monoferric (ferric derisomaltose). Package insert. Pharmacosmos A/S, Inc; 2020.

ERYTHROPOIESIS-STIMULATING AGENT THERAPY

If there is no response in the hemoglobin levels after iron indices (TSAT and ferritin) are improving or normalized, then recombinant human EPO should be initiated for anemia of CKD in G.B.

The treatment target for patients on ESA therapy has been a controversial issue over the years. The KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease recommends a target hemoglobin of up to 11.5 g/dL.[99] Furthermore, for nondialysis CKD patients with a hemoglobin <10.0 g/dL, the decision to start ESA therapy is based on the rate of fall of the hemoglobin. Normalization of hemoglobin (ie, ≥13 g/dL) in CKD is not recommended. Three trials have evaluated the efficacy and safety of hemoglobin targets in patients with CKD not on hemodialysis (HD). In each study, the higher target hemoglobin groups (hemoglobin ≥13 g/dL) experienced increased cardiovascular events, stroke, or mortality rates; thus, the boxed warnings in CKD.[112–114] Partial correction of anemia to ~11 g/dL is shown to offer improvements in quality of life, reduction in hospitalizations, and improvement in LVH.[115,116] It is at these targets that benefits such as increased survival, exercise capacity, quality of life, cardiac output, cognitive function, and decreased risk of LVH were observed in the CKD population. As a result, FDA mandated a Black Box warning for ESA products and recommends to individualize treatment and use the lowest sufficient dose to reduce the need for blood transfusions.

It should be noted that iron deficiency is the leading cause of ESA hypo-responsiveness and must be corrected before ESA therapy is initiated. Iron deficiency can develop as a result of increased requirements for RBC production with ESA administration and from chronic blood loss owing to bleeding or HD. Identification and management of iron deficiency through regular follow-up testing and

iron supplementation is essential for adequate RBC production (see Chapter 92, Anemias).[99]

Human erythropoietin–epoetin alfa

Human EPO or epoetin alfa, the exogenous form of EPO, is produced using recombinant technology. Epoetin alfa is available in the United States, whereas epoetin beta is available primarily outside the United States. Since it became available in 1989, epoetin alfa (Epogen®, Procrit) has provided an effective treatment option for anemia in patients with CKD on dialysis and not on dialysis and has substantially decreased the need for RBC transfusions. Epoetin alfa stimulates the proliferation and differentiation of erythroid progenitor cells, increases hemoglobin synthesis, and accelerates the release of reticulocytes from the bone marrow.

For patients such as G.B. who do not yet require dialysis and for patients receiving peritoneal dialysis (PD), epoetin alfa is generally administered subcutaneously. However, patients on HD often receive epoetin alfa intravenously because intravenous (IV) access is already established. Subcutaneous administration of epoetin is preferred in patients not on dialysis because lower doses can be administered less frequently, and cost is lower than with IV administration. Starting doses for epoetin alfa IV administration are 50 to 100 units/kg three times weekly.[117] For patients being converted from IV to subcutaneous administration (half-life of epoetin alfa is 8.5 hours IV vs 24.4 hours subcutaneous) whose hemoglobin is within the target range, the dose given subcutaneously is usually two-thirds the IV dose. For patients not yet at the target hemoglobin, a subcutaneous dose equivalent to the IV dose is recommended.

The FDA recently approved epoetin alfa-epbx, Retacrit®, a biosimilar to epoetin alfa for use in the United States. Based on the results of randomized clinical trials EPOE-10-01 and EPOE-10-13 and the subsequent open-labeled supportive trials EPOE-11-03 and EPOE-11-04 conducted in patients on hemolysis, epoetin alfa-epbx showed similar efficacy and safety profiles compared to the

reference product, epoetin alfa.[118] The dosing of epoetin alfa-epbx is similar to that of epoetin alfa.[119]

Darbepoetin alfa

Darbepoetin alfa (Aranesp®) was approved in 2001 for the treatment of anemia of CKD, regardless of dialysis requirements. Darbepoetin is a hyperglycosylated analog of epoetin alfa that stimulates erythropoiesis by the same mechanism. Instead of the three N-linked carbohydrate chains on epoetin alfa, darbepoetin has five, which increase the capacity for sialic acid residue binding on the protein. The increased protein binding slows total body clearance and increases the terminal half-life to 25.3 and 48.8 hours after IV and subcutaneous administration, respectively. Darbepoetin alfa's longer half-life relative to epoetin alfa offers the potential advantage of less frequent dosing to maintain target hemoglobin values.[120]

Studies in patients with CKD G3 and G4 determined that starting subcutaneous doses of 0.45 µg/kg administered once per week and 0.75 µg/kg once every other week were both effective in achieving target hemoglobin and hematocrit values in patients who had not previously received erythropoietic therapy.[121] The approved starting dose of darbepoetin alfa in patients who have not previously received epoetin therapy is 0.45 µg/kg given either intravenously or subcutaneously once weekly.[120] Patients who are already receiving epoetin therapy may be converted to darbepoetin alfa based on the current total weekly epoetin dose (**Table 28-11**).[120]

Table 28-11
Estimated Darbepoetin Alfa Starting Doses Based on Previous Epoetin Alfa Dose

Previous Weekly Epoetin Alfa Dosage (units per week)	Weekly Starting Darbepoetin Alfa Dosage (µg/week)	
Adults	**Children**	
<1,500	6.25	[a]
1,500–2,499	6.25	6.25

Previous Weekly Epoetin Alfa Dosage (units per week)	Weekly Starting Darbepoetin Alfa Dosage (µg/week)	
2,500–4,999	12.5	10
5,000–10,999	25	20
11,000–17,999	40	40
18,000–33,999	60	60
34,000–89,999	100	100
≥90,000	200	200

[a]For children receiving a weekly epoetin alfa dosage of <1500 units per week, the available data are insufficient to determine a darbepoetin alfa conversion dosage.

Source: Facts & Comparisons. Accessed September 28, 2022. https://fco.factsandcomparisons.com/lco/action/home.

Epoetin alfa and darbepoetin alfa are generally well tolerated, with hypertension being the most common adverse event reported. BP should be monitored closely, and adjustment to antihypertensive therapy is made, if justified. Failure to elicit a response to erythropoietic therapy requires evaluation of factors that cause resistance, such as iron deficiency, infection, inflammation, chronic blood loss, aluminum toxicity, malnutrition, and hyperparathyroidism. Resistance to erythropoietic therapy has been observed in patients receiving ACEI, although data are conflicting.[122] Rare cases of antibody formation to epoetin therapy have been reported primarily with one epoetin alfa product manufactured outside the United States. Neutralizing anti-EPO antibodies were identified in patients with pure RBC aplasia who required blood transfusions after a course of therapy with epoetin alfa or beta.[123]

Iron supplementation is indicated, not only if G.B. is iron deficient but also to maintain adequate iron stores while receiving erythropoietic therapy (see Iron Therapy section). Although administration of iron alone may improve her anemia, epoetin alfa or darbepoetin alfa may likely be required when Hgb falls below 10 g/dL. G.B. may start darbepoetin alfa administered subcutaneously at a dose of 25 µg (0.45 µg/kg) once per week, assuming her iron status is appropriate (see Iron Status section). Another option would

be epoetin alfa at a dose of 4000 units (~50 units/kg) administered subcutaneously three times a week. She also should be counseled to administer subcutaneous epoetin alfa or darbepoetin alfa in the outer area of the upper arm, in the abdomen (2 inches or away from the navel), front middle thigh, or outer area of the buttocks.[117,120] Patient should also be counseled to change the site of injection. Dose adjustments should not be made more frequently than once every 4 weeks for either agent because of the time course for response (ie, the pharmacodynamic effects on RBC homeostasis). The time it takes to reach a new steady- state, when RBC production is equal to RBC destruction, depends on the life span of the RBC, which is ~60 days in patients with kidney failure. Therefore, it will take ~2 to 3 months to reach a plateau in measured hemoglobin. Dose adjustments should be made on the basis of G.B.'s hemoglobin, which should be monitored every 1 to 2 weeks after initiation of therapy or after a dose change. If a rapid increase in hemoglobin is observed (hemoglobin >1.0 g/dL during any 2-week period) or approaching 11.5 g/dL, then doses of either agent should be decreased by ~25%. If response is inadequate (hemoglobin increase <1 g/dL in 2–4 weeks), then the doses should be increased by 25%. Once stable, the hemoglobin should be monitored every 2 to 4 weeks. If a response is not observed despite appropriate dose titration, G.B. should be evaluated for possible reasons for nonresponse (ie, iron deficiency, bleeding, aluminum intoxication, hyperparathyroidism, infection).

OTHER ERYTHROPOIESIS-STIMULATING AGENTS

Methoxy polyethylene glycol-epoetin beta (Mircera®) is a long-acting epoetin. Continuous-erythropoietin receptor activator (CERA) has twice the molecular weight of EPO because of the addition of a single 30-kDa polymer chain into the EPO molecule resulting in a considerably longer elimination half-life compared with EPO (130 vs 4–28 hours). This allows for extended-interval dosing biweekly or once monthly, either intravenously or subcutaneously. It has an efficacy and safety profile comparable to other available ESAs.[124]

CARDIOVASCULAR COMPLICATIONS

CASE 28-2

QUESTION 1: H.B. is a 65-year-old White male with a history of autosomal dominant polycystic kidney disease (ADPKD) leading to CKD, which has progressed to G5D and has just started chronic HD. He comes in today for his third HD session (intermittent dialysis scheduled three times per week, 4-hour duration). He has a history of hypertension, which has been poorly controlled during the past 4 months (BP ranges 150–190/85–105 mm Hg) and has experienced shortness of breath and a significant weight gain during the past month. His pertinent medical history includes hypertension for the past 14 years.

Current medications: Iron sucrose 100 mg IV #8 of 10 total doses (during HD sessions), epoetin alfa 3500 units IV three times a week (during dialysis), metoprolol tartrate 50 mg bid, furosemide 80 mg bid, calcium carbonate 500 mg tid with meals, sevelamer carbonate 800 tid with meals, and Nephrocaps one by mouth (PO) every day.

Vital signs: predialysis BP was 195/100 mm Hg, and his postdialysis BP was 168/90 mm Hg. Weight 154.32 pounds (70 kg), height 70 inches (177.8 cm)
A recent echocardiogram showed evidence of LVH.
Predialysis laboratory values were as follows:
Serum sodium (Na^+), 140 mEq/L
Potassium (K^+), 5.1 mEq/L
Chloride (Cl^-), 101 mEq/L
CO_2 content, 23 mEq/L
SCr, 8.8 mg/dL
BUN, 84 mg/dL
Phosphorus, 6.5 mg/dL
Calcium, 8.6 mg/dL
Serum albumin, 3.0 g/dL
Cholesterol (nonfasting), 345 mg/dL
Triglycerides, 285 mg/dL
TSAT, 18%
Ferritin, 250 ng/mL
Hct, 27%
Hgb, 9.0 g/dL
H.B. has a urine output of 50 mL/day.

What conditions evident in H.B. place him at increased risk of cardiovascular complications and mortality?

H.B. has uncontrolled hypertension that is not adequately managed with his current drug therapy or HD. Hypertension is associated with LVH, ischemic heart disease, and heart failure, all of which are contributing factors to overall mortality in patients with CKD 5D who are undergoing dialysis.[125] H.B.'s echocardiogram shows evidence of LVH and should trigger additional evaluation to determine the extent of cardiac involvement and diagnosis of heart failure, which is associated with increased mortality in both diabetic and nondiabetic patients (see Chapter 14, Heart Failure).[100] LVH can develop early in the course of CKD and progresses as kidney disease progresses. H.B. is in the most severe stage of CKD. Anemia contributes substantially to the development of LVH and heart failure as well. H.B.'s hemoglobin of 9.0 g/dL is below the target value and requires treatment based on evaluation of his iron indices (see the section on Anemia).

Additional factors that increase the risk of cardiovascular complications and mortality in H.B. include anemia of CKD, elevated cholesterol and triglycerides levels, as well as hypoalbuminemia (serum albumin, 3.0 g/dL). Because elevated concentrations of homocysteine have been observed in conjunction with decreased folate and vitamin B_{12} levels, more aggressive supplementation of these vitamins in this population has been suggested. Because H.B.'s total corrected calcium (corrected for hypoalbuminemia; see Case 28-3, Question 2, for an explanation of this correction) is 9.4 mg/dL, his calcium will need to be monitored frequently. Metastatic calcification is common in patients with CKD on calcium-containing phosphate binders and is a risk factor associated with CVD. It has been reported that ~80% of patients with kidney failure have detectable coronary artery calcification.[126] CVD and complications continue to be the leading cause of mortality in patients with kidney failure.[1]

Hypertension

CASE 28-2, QUESTION 2: What options are available to treat H.B.'s hypertension considering his other cardiac complications and BP goal?

Hypertension is a unique complication of CKD because it is also a risk factor for CKD. We have previously discussed the pathogenesis of hypertension in CKD.

Because H.B. is just beginning dialysis therapy, it is difficult to assess the degree to which volume removal will ultimately affect his BP. (See Chapter 30, Dialysis Treatment for Chronic Kidney Failure.) H.B. has had recent findings consistent with worsening volume status (shortness of breath, weight gain) that should be considered when modifying his dialysis prescription; further workup is needed to determine whether H.B. has systolic or diastolic heart failure. It is also important to counsel H.B. on the importance of salt and fluid intake restriction between HD sessions to minimize weight gain, volume expansion, and hypertension. Restriction of salt intake to <2.4 g/day and fluid to 1 L/day is appropriate and will require regular follow-up by a dietitian.

ANTIHYPERTENSIVE THERAPY

Currently, there are no published guidelines for the management of hypertension in patients receiving hemodialysis. For some patients, initiation of dialysis alone may achieve BP target goal, and antihypertensive therapy may be withdrawn. The aim of the BP goal in patients with kidney failure on dialysis is to minimize cardiovascular complications, but it should not increase the risk for hypotension and its associated complications during dialysis. The choice of an agent is based on the patient's comorbid conditions because no single agent has a consistently proven mortality benefit in patients on HD. The complexity of managing hypertension in patients on HD is enhanced by the apparent U-shaped relationship between BP and mortality.[127] Another cohort study found a systolic BP between 100 and 125 mm Hg was associated with the lowest risk of death, and systolic BP >150 mm Hg associated with increased death.[127]

Diuretics are commonly used in patients in the early stages of CKD. As discussed, the effectiveness of diuretics depends on the amount of sodium delivered to their site of action in the kidney tubule and on the patient's kidney function. For example, a decrease in the eGFR from 125 to 25 mL/minute/1.73 m^2, theoretically, could result in an approximate 80% decrease in the amount of sodium filtered. Early during CKD, thiazides or thiazide-like diuretics are effective antihypertensive agents. As eGFR drops below 30 mL/minute/1.73 m^2, they become less effective. Potassium-sparing diuretics are also ineffective and may increase the risk of hyperkalemia. Loop diuretics, which act more proximally in the nephron, are indicated in patients with GFR <30 mL/minute/1.73 m^2.[128] They can be effective for BP and volume control in patients with advanced CKD if residual kidney function is substantial (urine output >100 mL/day). Their effect must be frequently reevaluated based on urine output and any effect on volume control. H.B.'s urine output should be assessed to determine the rationale for continued use of furosemide, and the current dose should be assessed because doses higher than his current dose of 80 mg bid are often required in patients with this degree of kidney dysfunction. It is likely that furosemide will need to be discontinued as H.B.'s residual kidney function declines.

Given the role of the RAAS in the development of hypertension in patients with CKD, ACEIs or ARBs are logical choices for antihypertensive therapy in CKD G1 to G4. Several studies have demonstrated that the initiation of ACEI, ARBs, or both in patients in CKD G5D improved BP control, lowered LVH, and reduced the cardiovascular mortality risk.[129] Most of these agents can be administered once daily; however, because of the kidney elimination of the parent drug or active metabolite, dosage adjustments are necessary in patients with CKD. ARBs offer an alternative to ACEIs in patients experiencing kinin-mediated adverse effects; however, similar side effects have been reported with ARBs.

β-Adrenergic blockers inhibit release of renin and may be useful in hypertension associated with CKD. β-Blockers can counteract the elevated sympathetic activity observed in patients on dialysis, lower the risk of sudden cardiac death, and improve survival in heart

failure.[130] Risk versus benefit should be evaluated when β-blockade is considered in conjunction with other comorbid conditions such as asthma, heart failure, and lipid abnormalities. Calcium channel blockers are effective antihypertensive agents in patients with CKD. Other agents used to treat hypertension in the CKD population include centrally acting agents (eg, clonidine, methyldopa), vasodilators (eg, minoxidil, hydralazine), and α1-adrenergic blockers (prazosin, terazosin, doxazosin). However, these agents are generally reserved as last-line therapies.

H.B. is currently taking the β-blocker metoprolol and the loop diuretic furosemide. Metoprolol is a β-blocker considered to be removed by dialysis and should be monitored closely for H.B. clinical response to the therapy while starting dialysis. It is likely that his diuretic will need to be discontinued as his residual kidney function decreases and response to therapy is inadequate. If changes imposed in H.B.'s HD prescription can improve volume control and achieve his dry weight but do not reduce his BP, another antihypertensive regimen should be selected. A reasonable antihypertensive regimen would include an ACEI or ARB. Because the agents in these drug classes have similar mechanisms of action, the choice of specific agents would depend on patient-specific factors like the ability to pay and adherence. The selection of agent will depend substantially on follow-up results of his cardiac disease, BP control with HD, and the potential for adverse effects (see Chapter 9, Essential Hypertension, and Chapter 14, Heart Failure).

Dyslipidemia

Case 28-2, Question 3: How should H.B.'s lipid abnormalities be treated?

Dyslipidemia is quite common in CKD. There is limited evidence that lowering lipids slows the progression of CKD, but studies show that the benefit of treating dyslipidemia in CKD is to reduce the cardiovascular risk. The Study of Heart and Renal Protection

(SHARP) assessed the effect of lowering LDL cholesterol in 9270 patients with CKD with ezetimibe 10 mg daily and simvastatin 20 mg daily or matching dummy placebo tablets for an average of 5 years. The results showed a 25% risk reduction in major atherosclerotic events in the treatment group. However, there was no effect on the progression of CKD. The KDIGO Clinical Practice Guidelines for Lipid Management in CKD offers some guidance for the management of dyslipidemia. For patients with CKD aged 50 years and older and not on dialysis, KDIGO recommends treatment with a statin or statin/ezetimibe combination. Patients with CKD aged 18 to 49 years with additional CVD risk factors such as known coronary disease (myocardial infarction [MI] or coronary revascularization), diabetes, prior ischemic stroke, or estimated 10-year coronary heart disease risk >10% are recommended to initiate statin therapy. The KDIGO guidelines suggest measuring a full lipid profile 6 weeks to 3 months after initiation of a statin in order to identify patients with an inadequate response to moderate-intensity statins and who require dose titration.[131] The Die Deutsche Diabetes Dialyse Studie (4D) and AURORA are two large multicenter, double-blind, placebo-controlled, randomized controlled trials that examined the effects of lowering the level of LDL-C on cardiovascular events and mortality with atorvastatin or rosuvastatin, respectively. The results of these studies along with the negative effects in patients on dialysis from the SHARP study have largely driven KDIGO recommendations to avoid initiating statin therapy in patients on dialysis unless initiated prior to starting dialysis.[132]

H.B. has elevated serum cholesterol and triglyceride concentrations, a common finding in patients with CKD. Dyslipidemia and increased oxidative stress contribute to premature atherogenesis in these patients. Several atherogenic factors in patients with CKD have been postulated, including arterial wall injury, platelet activation and adherence, smooth muscle cell proliferation, and intra-arterial accumulation of cholesterol. Lowering of serum lipids has not been shown to improve morbidity and mortality in patients on hemodialysis. Furthermore, current KDIGO Guidelines for Lipid Management in CKD do not recommend using cholesterol

values to determine who to treat or as treatment targets. Currently, H.B. is not receiving a statin that has not demonstrated the ability to reduce mortality or morbidity in dialysis. Dietary and lifestyle changes could be beneficial in reducing triglyceride and cholesterol concentrations in patients with kidney failure on dialysis.

Statins are preferred over fibrates for management of dyslipidemia in CKD.[132] Fibrates should be used cautiously in patients with CKD; all agents in this class are metabolized by the kidney and are eliminated primarily via the kidney, which may lead to an increased risk of rhabdomyolysis. However, fibric acid derivatives may be considered in patients presenting with extremely high triglycerides (>1000 mg/dL). Fenofibrate is not recommended in patients with mild-to-moderate CKD (CrCl between 30 and 80 mL/minute) and contraindicated in individuals with CrCl <30 mL/minute.[133] Gemfibrozil is to be used with caution in mild-to-moderate kidney dysfunction and not recommended in CKD G5.[134]

MINERAL AND BONE DISORDERS

CASE 28-3

QUESTION 1: W.K. is a 24-year-old Hispanic female who has an 18-year history of T1D with complications of DKD, retinopathy, and neuropathy. She was diagnosed with kidney failure, CKD G5D 2 years ago. She started PD at that time.

Current medications: Insulin aspart 10 units subcutaneous with meals; insulin glargine 25 units subcutaneous nightly; docusate 100 mg PO every day; calcium acetate 2001 mg (three tablets, 667 mg each) PO tid with meals; epoetin alfa (Procrit, Epogen) 10,000 units subcutaneous once weekly; iron sucrose 300 mg IV (repeat in 2 weeks, then 400 mg 2 weeks later), calcitriol 0.25 PO three times weekly, and Nephrocaps one capsule every day. W.K. has a history of medication nonadherence.

At a recent clinic visit, findings on physical examination included a BP of 128/84 mm Hg, diabetic retinopathic changes with laser scars bilaterally, and diminished sensation bilaterally below the knees.

Her laboratory values were as follows:

Normal serum electrolytes
Random blood glucose, 250 mg/dL
BUN, 45 mg/dL
SCr, 8.9 mg/dL
eGFR, 5 mL/minute/1.73 m^2
Hgb, 10 g/dL
WBC count, 6200/μL
Calcium, 9.2 mg/dL
Phosphorus, 6.8 mg/dL
Intact parathyroid hormone (iPTH), 950 pg/mL
Thyroid-stimulating hormone, 5 mIU/L
Total serum protein, 5.0 g/dL
Serum albumin, 2.5 g/dL
Uric acid, 8.9 mg/dL

What is the etiology of W.K.'s abnormal calcium, phosphorus, and parathyroid hormone (PTH) findings?

Etiology

Mineral bone disease of CKD (CKD-MBD) is the term used to collectively describe the dysregulation of serum phosphorus, calcium, and PTH, leading to the demineralization of bone and soft tissue calcification as a complication of CKD.[135]

Hyperphosphatemia, hypocalcemia, hyperparathyroidism, and decreased production of active vitamin D are frequent problems in CKD. Although the interrelationships among phosphorus, calcium, vitamin D, and PTH have been reviewed extensively, fibroblast growth factor 23 (FGF23), a phosphaturic hormone, has added some new insight.[136] Increased dietary phosphorus intake stimulates FGF23 secretion. FGF23 increases phosphorus excretion via the proximal tubules, inhibits vitamin D activation, increases activated vitamin D catabolism, and is associated with CKD progression.

At a GFR above 30 mL/minute/1.73 m^2, elevations in FGF23 and PTH maintain normal serum phosphorus. This concept is referred to as the trade-off hypothesis, where the ability to maintain normal phosphorus concentrations occurs at the expense of developing secondary hyperparathyroidism (SHPT), the excessive secretion of PTH and elevated FGF23.[137,138] However, FGF23 is not typically

measured in the clinical setting. Clinically significant increases in serum phosphorus are not usually seen until the late stages of CKD, GFR <30 mL/minute/1.73 m^2, when compensatory mechanisms within the kidney are compromised.

The kidney is the principal organ responsible for systemic vitamin D production, and, as such, vitamin D metabolism is altered in the presence of uremia. Persistent hyperphosphatemia stimulates the release of excessive FGF23, which inhibits the normal conversion of 25-hydroxyvitamin D3 to its biologically active metabolite, 1,25-dihydroxyvitamin D3, by the enzyme 1-α-hydroxylase (**Fig. 28-2**). This enzyme is present in proximal tubular cells of the kidney and is necessary for the conversion of vitamin D to the active form. This active form of vitamin D, also known as calcitriol, increases gut absorption of calcium and interacts with vitamin D receptors (VDRs) on the parathyroid gland to suppress PTH release. As a result of decreased calcitriol production, the absorption of dietary calcium in the gut is diminished. Decreased suppression of PTH release by vitamin D in conjunction with hypocalcemia promotes continued stimulus for mobilization of calcium from bone and plays a major role in the development of renal osteodystrophy. Furthermore, patients who are uremic require a higher extracellular calcium concentration to suppress the secretion of PTH. This is also described as an increase in the calcium “set point” or the concentration of calcium required to inhibit 50% of maximal PTH secretion.[139]

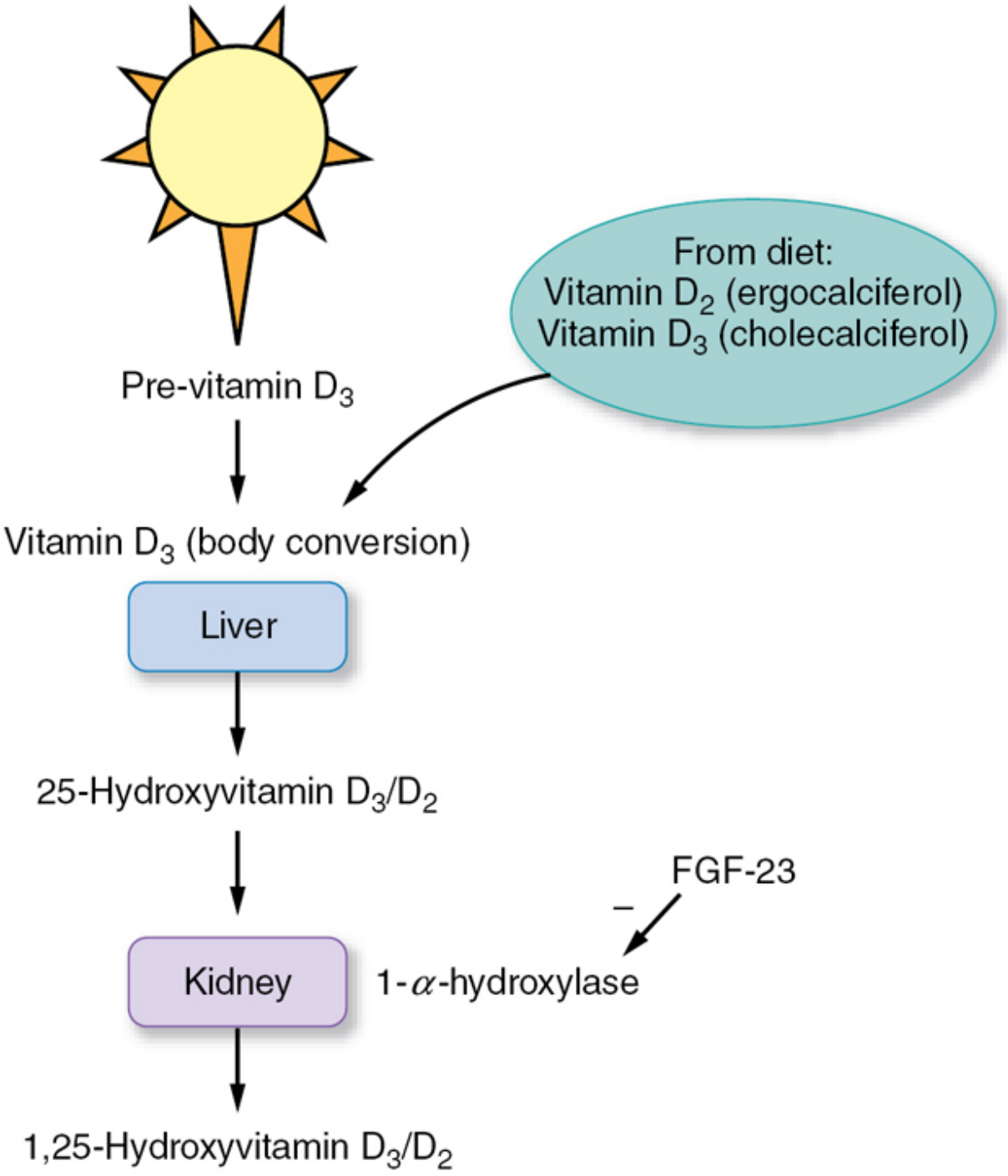


Figure 28-2 Vitamin D biotransformation.

The chronic effects of SHPT on the skeleton lead to bone pain, fractures, and myopathy. In children, these effects may be particularly severe and usually retard growth. The metabolic acidosis of CKD also contributes to a negative calcium balance in the bone.

W.K.'s presentation is consistent with CKD-MBD based on abnormalities in serum phosphorus, calcium, and PTH; all can be attributed to her CKD.

Vitamin D levels (ie, 25-hydroxyvitamin D) should be monitored in patients with CKD. Insufficient (<30 ng/mL) and deficient (<15 ng/mL) vitamin D levels are prevalent in the majority of patients with CKD and kidney failure. Several studies have linked depressed vitamin D levels to increased vascular calcification, CVD, and mortality.[140]

Treatment

Case 28-3, Question 2: What are the goals of therapy for W.K.'s calcium, phosphorus, and PTH abnormalities? What options are available to treat these disorders in late-stage CKD?

Serum calcium and phosphorus have an inverse relationship. When phosphorus levels rise, calcium levels fall, and vice versa. The management objectives for W.K. are to (a) manage serum calcium and phosphorus concentrations, (b) prevent or manage SHPT, and (c) restore normal skeletal development without inducing adynamic bone disease (or low bone turnover). These goals are best achieved with dietary phosphorus restriction, appropriate use of phosphate-binding agents, vitamin D therapy, calcimimetic agents, and dialysis.

DIETARY RESTRICTION OF PHOSPHORUS

In general, serum phosphorus should be lowered toward near-normal levels. The KDIGO recommends normal levels for all stages of CKD. Dietary phosphorus restriction can prevent hyperphosphatemia and maintain target phosphorus concentrations. Dietary phosphorus should not exceed 800 to 1000 mg/day.[135] Predominant sources of phosphorus are protein-rich foods, which presents a challenge in tailoring a diet that lowers dietary phosphorus intake while providing adequate nutrition. However, efforts should be made to distinguish between organic (eg, plant

seeds, nuts, legumes, and meats) and inorganic phosphorus (eg, preservatives and additive salts found in processed foods) sources. Inorganic phosphorus sources are absorbed to a greater extent than organic phosphorus (90% vs 50%, respectively) and should be minimized in the diet.[141]

Additionally, the type of organic phosphorus sources, plant versus meat, has varying effects with plant sources associated with lower serum phosphorus levels and decreased FGF23 levels. Although phosphorus is removed to some extent by dialysis, neither conventional HD nor PD removes adequate amounts to warrant complete liberalization of phosphorus in the diet. Nocturnal HD is an exception where patients may require phosphate supplements because of the prolonged dialysis duration. Regular dietary counseling by a kidney dietitian specialist is necessary to reinforce the importance of phosphorus restriction and other dietary recommendations.

PHOSPHATE-BINDING AGENTS

A significant reduction in serum phosphorus is difficult to achieve with dietary intervention alone, particularly in patients with more advanced CKD (eGFR <30 mL/minute/1.73 m^2). For these patients, phosphate-binding agents used in conjunction with dietary restriction are necessary. Phosphate-binding agents limit phosphorus absorption from the GI tract by binding with the phosphorus present in dietary sources. Therefore, these agents must be administered with meals. Phosphate binders can be classified into two broad categories: calcium-based and non-calcium–based preparations.

CALCIUM-CONTAINING PREPARATIONS

Calcium-containing preparations, especially calcium carbonate and calcium acetate, are effective and frequently used to prevent hyperphosphatemia in patients with CKD. Other calcium-containing phosphate binders are available, and they vary in their calcium content and pill burden (**Table 28-12**). Correction of hypocalcemia is an added beneficial effect of the calcium-containing preparations;

however, a risk exists of hypercalcemia and cardiac calcification associated with the prolonged use of these agents.[12] Additionally, the higher bioavailable calcium in calcium carbonate may lead to a positive calcium balance.[142]

Table 28-12
Recommended Phosphate Binders in Chronic Kidney Disease

Agent	Availability (Daily Pill Burden)	Comments	Adverse Effects and Warnings
Aluminum-Based Binder			
Aluminum hydroxide	320 mg/5 mL suspension	Not recommended as first line because of potential aluminum toxicity	Constipation and sodium overload Aluminum toxicity: CNS, anemia, and bone disease Warnings: perforation, fecal impaction, ileus
Calcium-Based Binders			
Calcium acetate	667 mg caplets (3–12 caplets) 667 mg/5 mL (15–20 mL with meal)	Oral solution associated with higher diarrhea risk	N/V/D; hypercalcemia; vascular calcification; oral solution associated with greater diarrhea
Calcium carbonate	500–1250 mg tablets (3–6 tablets)	Over-the-counter	N/V/D; hypercalcemia; vascular calcification
Iron-Based Agents			
Ferric citrate	210 mg ferric iron tablet (6–12 tablets)	210 mg of ferric iron—1 g ferric citrate	N/V/D; discolored feces; iron overload Precautions: gastric/hepatic disorders CI: hemochromatosis
Sucroferric oxyhydroxide	500 mg chewable tablet (3–6 tablets)	500 mg ferric iron—2500 mg sucroferric oxyhydroxide	N/D; discolored feces; iron overload Precautions: gastric/hepatic disorders; hemochromatosis
Lanthanum-Based Binder			
Lanthanum carbonate	500, 750, and 1000 mg chewable tablets (3–6 tablets)	Chewed and crushed have similar efficacy	Accumulation in bone, brain, and liver; visible on abdominal x-ray; hypercalcemia CI: bowel obstruction, ileus, and fecal impaction
Resin Binders			
Sevelamer carbonate	800 mg caplet (3–12 caplets) 0.8 g/2.4 g powder packets	Reduces low-density lipoprotein cholesterol	N/V/D; hypercalcemia CI: bowel obstruction Warnings: perforation, fecal impaction
Sevelamer hydrochloride	400, 800 mg caplets 1–2 tablets tid (6–12 caplets)	Reduces low-density lipoprotein cholesterol	N/V/D; hypercalcemia CI: bowel obstruction Warnings: perforation, fecal impaction; risk of metabolic acidosis

CI, contraindications; N/V/D, nausea, vomiting, diarrhea.

Persistent hypocalcemia must be managed to prevent SHPT and its complications. Simultaneous administration of vitamin D preparations and calcium also increases the risk of hypercalcemia. A corrected serum calcium should be determined before therapy is started and at regular intervals thereafter.

Many clinicians often correct calcium levels for low albumin. Calculating corrected calcium adjusts for the change in the ratio of free (unbound) versus protein-bound calcium owing to reduced serum albumin concentrations (Eq. 28-5). W.K.'s corrected serum calcium concentration is 10.4 mg/dL.

$$\text{Corrected calcium (mg/dL)} = \text{measured Ca (mg/dL)} + 0.8 \times (4\ \text{g/dL} - \text{measured albumin [g/dL]})$$

(Eq. 28-5)

Calcific uremic arteriolopathy (CUA), or calciphylaxis, is characterized by calcification of the arterioles and small arteries with intimal proliferation and endovascular fibrosis. CUA manifests visually as necrosis of the skin and is most frequently seen in patients on dialysis, affecting up to 5% of patients. Calcium-based phosphate binders are one of the triggering factors associated with the development of CUA. If the patient experiences hypercalcemia or evidence of advanced calcification, the patient should be switched to a non- calcium–based phosphate binder. Although avoiding hypercalcemia should reduce the risk of cardiac calcification, calcifications still can occur because of other contributing factors in the CKD population (eg, hyperphosphatemia).

Nausea, diarrhea, and constipation are other side effects of calcium-containing products. Because calcium-containing phosphate binders may interact with other drugs, the timing of their administration relative to other agents must be considered. Fluoroquinolones and oral iron, for example, should be taken at least 1 or 2 hours before calcium-containing phosphate binders. Starting doses of common calcium-containing phosphate binders are listed in Table 28-12.

NON-CALCIUM–CONTAINING PHOSPHATE BINDERS

Sevelamer

Sevelamer is a polymer-based product that binds phosphorus in the GI tract. It exists in two salt formulations, sevelamer hydrochloride (Renagel®) and sevelamer carbonate (Renvela®).[143,144] The benefit of lowering phosphorus without significantly affecting serum calcium has led to the increased use of sevelamer in patients with CKD G5 on HD. Sevelamer also lowers LDL and total serum cholesterol, a benefit considering the increased risk of cardiovascular events in this population.[135]

Sevelamer has the potential benefit of attenuating the progression of coronary calcification, which may be related to its LDL and total serum cholesterol-lowering effects and a benefit from reduced calcium loading. The actual benefit of sevelamer on mortality is controversial. The post hoc analysis of the Renagel in New Dialysis (RIND) trial showed a survival advantage with sevelamer compared with calcium acetate; however, the Dialysis Clinical Outcomes Revisited (DCOR) trial failed to show a difference in mortality between the two agents.[145] One explanation for the disparity in results may be the difference in the population of patients on HD between the two trials. The RIND trial included incident patients on HD, whereas the DCOR trial included prevalent patients on HD who likely would have advanced CVD. Sevelamer hydrochloride showed comparable efficacy to calcium acetate for managing hyperphosphatemia in kidney failure patients on PD.[146]

The starting dose is variable and depends on the baseline serum phosphorus concentration (800 mg tid with meals if serum phosphorus is <7.5 mg/dL; 1600 mg tid with meals if serum phosphorus is >7.5 mg/dL).[143,144] Gradual adjustments can be made at 2-week intervals, based on serum phosphorus levels. The drug manufacturer of sevelamer recommends dosing guidelines when switching from calcium acetate to sevelamer. For instance, the dose of sevelamer is 2.4 g (3 × 800-mg tablets) PO tid with meals when switching from calcium acetate 2001 mg PO tid with meals.

Lanthanum carbonate

Lanthanum carbonate (Fosrenol®) is another non–calcium phosphate binder preparation indicated in patients with CKD G5. When ingested, it dissociates into a trivalent cation with a similar binding capacity as aluminum salts. Lanthanum also has been found to be as effective and tolerable as standard treatment. Both calcium and iPTH were lower in the lanthanum group.[147] Lanthanum is mainly excreted via the biliary route, with minimal kidney elimination. A prospective trial of patients on HD receiving lanthanum for 1 year found minimal deposition of lanthanum within the bone and less likelihood of adynamic bone histology compared with patients receiving calcium carbonate.[148] Lanthanum is available in 500, 750, and 1000 mg oral or chewable tablets. The starting dose is 500 mg tid with meals.

Lanthanum retains the same phosphorus-binding capabilities irrespective of whether it is chewed or crushed into powder.[149] Drug interactions with lanthanum include a reduction in the bioavailability of ciprofloxacin (approximate 50% reduction) and levothyroxine. The most frequent adverse events reported in clinical trials are nausea and vomiting.[150]

Iron-based phosphate binders

Sucroferric oxyhydroxide and ferric citrate are iron-based phosphate binders with proven efficacy at reducing serum phosphate levels in patients on HD. The newer iron-based binder ferric citrate has the advantage of providing supplemental iron and is also indicated for iron deficiency anemia of CKD in patients not on dialysis.[151] Early studies of ferric citrate demonstrate a reduction in IV iron and ESA use.[152] However, sucroferric oxyhydroxide as a chewable tablet is not systemically absorbed and not indicated for iron deficiency anemia, thus not affecting anemia management.[153]

Other phosphate binders

Aluminum preparations are very potent dietary phosphorus binders. Although these products were once used as first-line agents to decrease phosphorus, aluminum accumulation and toxicities in

patients with CKD have restricted their use. Aluminum toxicity occurs in patients on dialysis because absorbed aluminum is not removed by the diseased kidney and enters various tissues where it binds to tissue and plasma proteins. Aluminum accumulation in the bone, brain, and other organs leads to toxicities such as osteomalacia (aluminum-related bone disease), microcytic anemia, and a fatal neurologic syndrome referred to as dialysis encephalopathy.

Magnesium agents (magnesium hydroxide, magnesium carbonate) may be beneficial, but as with aluminum, their use should be limited because at the high doses required to control serum phosphorus concentrations, severe diarrhea and hypermagnesemia invariably result.

More aggressive control of W.K.'s serum phosphorus is needed to lower serum phosphorus toward normal levels. Currently, W.K. is taking a high dose of calcium-based phosphate binder, calcium acetate. Although presumably much of this calcium will be bound to phosphorus in the GI tract, a potential exists for calcium absorption. Furthermore, her corrected serum calcium levels borderline high at 10.4 mg/dL. Discontinue calcium acetate. Lanthanum carbonate, a non-calcium–containing phosphate binder, should be started to limit her calcium exposure and decrease her phosphorus levels to a target of 3.5 to 5.5 mg/dL recommended in dialysis. The recommended starting dose is 500 mg tid with meals, titrated based on follow-up phosphorus values up a maximum of 4500 mg daily. Adjustments should also be considered in conjunction with vitamin D therapy (see Vitamin D section). W.K. should be instructed to take her phosphate binder with meals. This regimen should be implemented in conjunction with a restricted phosphorus diet. Regular reinforcement of adherence with prescribed dietary phosphorus restriction and drug therapy is one of the most significant factors associated with treatment failure. Although lanthanum is more costly than sevelamer, it is preferred in W.K. because of patient's history of medication nonadherence. Lanthanum is available in chewable tablets and has a lower pill burden than sevelamer.

VITAMIN D

Nutritional vitamin D (NVD) is usually in the form of ergocalciferol (vitamin D_2) or as cholecalciferol (vitamin D_3) obtained from dietary sources and activated in the skin by sunlight in mammals. Both are inactive precursors of vitamin D. An intermediate activation step (25-hydroxylation) occurs in the liver to produce 25-hydroxy vitamin D (25-hydroxycalciferol), which is also relatively inactive. Final activation (1-hydroxylation) occurs in the kidney, yielding calcitriol (l,25-dihydroxycholecalciferol), the active form of vitamin D. Thus, the response to vitamins D_2 and D_3 in patients with compromised kidney function can vary, depending on the degree of kidney dysfunction and the ability of the kidney to metabolize 25-hydroxyvitamin D to calcitriol. Decreased levels of 25-hydroxyvitamin D occur in the early stages of CKD, reducing substrate for producing calcitriol.[135] Altered vitamin D metabolism that occurs in this population warrants measurement of 25-hydroxyvitamin D and supplementation with NVD. Another inactive form of vitamin D is calcifediol, which is available as extended-release capsules and is approved for treatment of SHPT in adults with CKD stage G3a, G3b, and G4 with 25-hydroxyvitamin D levels <30 ng/mL.[154]

Oral therapy with active vitamin D (oral calcitriol) or an analog is likely warranted only when PTH remains elevated despite normal 25-hydroxyvitamin D levels.[135] As the final, active metabolite of vitamin D, calcitriol (or another activated form of vitamin D) is usually required in patients with more severe CKD (CKD stage G4–G5). Several small studies have shown that the benefits of NVD administration extend beyond bone and mineral metabolism. Reduction in ESA doses, improved glycemic control, reduced activated vitamin D administration, and inflammation modulation have been observed from NVD supplementation in patients on dialysis.[155]

Vitamin D receptor agonist

Administration of VDR agonist, active vitamin D, in conjunction with control of serum phosphorus and calcium, is necessary in many

patients with CKD to manage CKD-MBD.

Calcitriol

Calcitriol interacts with the VDR located in the parathyroid gland, intestines, bone, and kidney. It is thought to decrease PTH messenger RNA, resulting in decreased PTH secretion. In addition, calcitriol stimulates calcium absorption from the GI tract to correct hypocalcemia and prevent SHPT. To avoid hypercalcemia, the lowest effective dose should be used, and the patient's serum calcium should be monitored at least every 2 weeks for 1 month and then monthly thereafter. Furthermore, control of serum phosphorus is critical before calcitriol is initiated, as vitamin D increases GI phosphorus absorption.

Calcitriol is available as an oral formulation or IV formulation. Administration of calcitriol by either the oral or IV route may be based on conventional dosing (usually 0.25–0.5 μg/day) or pulse dosing (intermittent dosing of 0.5–2.0 μg two to three times per week). Daily dosing of 0.25 to 0.5 μg may be preferred in patients with hypocalcemia, because this regimen primarily works to stimulate calcium absorption from the GI tract. Intermittent dosing of IV calcitriol is routine in the HD population because administration is coordinated with dialysis. In contrast, oral dosing is more convenient in patients on PD or those with CKD not on dialysis. iPTH and serum calcium concentrations are used to determine starting doses and dosing adjustments for calcitriol.

Although there have been some suggestions for PTH targets in various stages of CKD, these have been mostly from expert opinion. The 2017 updates to the KDIGO guidelines recommend iPTH that treatment should be based on rising PTH trends and not determined by any specific levels.[135]

Dose adjustments of calcitriol are generally made in 0.5- to 1.0-μg increments every 2 to 4 weeks in the early stages of therapy until iPTH and serum calcium are maintained at target levels. If hypercalcemia develops, the decision to withhold therapy or to switch to a less hypercalcemic VDR agonists must be made. Serum

iPTH should be monitored every 3 to 6 months and adjustments of calcitriol doses made to maintain the goal iPTH and to prevent hypercalcemia and hyperphosphatemia.

Vitamin analogs

The unique interactions of vitamin D with the VDR led to the development of designer vitamin D analogs, which vary in their affinity for the VDR. In the case of treatment for SHPT, some were developed to retain the suppressive effect on PTH release while decreasing the potential for hypercalcemia relative to calcitriol.

Paricalcitol

The currently approved agents for managing SHPT in the United States are paricalcitol (Zemplar®), also referred to as 19-nor-1,25-dihydroxyvitamin D_2, and doxercalciferol (Hectorol®), or 1-α-hydroxyvitamin D_2. Doxercalciferol requires conversion to the active form (1-α-25-dihydroxyvitamin D_2) by the liver.

In patients with SHPT, paricalcitol significantly decreases iPTH without significantly increasing calcium or phosphorus. Paricalcitol is ~10-fold less hypercalcemic and hyperphosphatemic than calcitriol.[156,157] The recommended conversion ratio for calcitriol to paricalcitol is 1:4 (ie, for every 1 µg of calcitriol, 4 µg of paricalcitol should be administered). This information is based on similar efficacy observed when patients treated for SHPT with calcitriol were switched to paricalcitol using this dosing strategy.[156,157]

Doxercalciferol

Doxercalciferol, another vitamin D analog, is another alternative to calcitriol and has been studied in patients with CKD 5D.[158] Doxercalciferol has similar effects on PTH as the other vitamin D analogs; however, it increases phosphorus and calcium to a greater degree than paricalcitol. Doxercalciferol is available as a capsule and IV injection. Both oral and IV therapy are effective in reducing iPTH levels in patients with SHPT; however, some evidence

indicated that intermittent IV therapy may result in less hypercalcemia and hyperphosphatemia than oral intermittent therapy.[159]

Vitamin D analogs offer an alternative for patients in whom persistent hypercalcemia develops with calcitriol therapy. Use of these agents is increasing in clinical practice because of the concerns of hypercalcemia and its adverse consequences. Repeated observational reports overall indicate lower cardiovascular-related mortality rates with activated vitamin D therapy, regardless of the agent received, than in those not receiving vitamin D therapy.[160]

CALCIMIMETICS

Calcimimetic agents increase the sensitivity of the calcium-sensing receptors (CaSR) to extracellular calcium ions and inhibit the release of PTH, lowering PTH levels within hours after administration. The discovery of extracellular CaSR prompted research with calcimimetic agents that allosterically modulate CaSR. CaSR are located in the parathyroid gland, thyroid, nephron, brain, intestine, bone, lung, and other tissues.[161] There are currently two calcimimetic agents approved for use in the United States: cinacalcet and etelcalcetide.

Cinacalcet is the first agent in this class to be approved by the FDA to treat SHPT in kidney failure.[162] Cinacalcet is an effective agent at reducing and sustaining iPTH within target concentrations in patients on HD.[163] Cinacalcet offers an additional choice of agent to lower PTH when vitamin D cannot be increased because of elevated calcium or phosphorus. The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial was a randomized clinical trial comparing cinacalcet to placebo in 3883 patients on dialysis with a primary outcome of death, cardiovascular events, or hospitalizations. Patients were eligible to receive phosphate binders or vitamin D analogs in either arm. There was a 7% nonsignificant reduction in primary end points in the cinacalcet group.[164] However, issues plagued the large trial as several patients in the placebo arm received cinacalcet therapy. The survival benefits

of cinacalcet remained undetermined. Calcimimetics are not approved for use in patients with CKD not receiving dialysis because of the risk of hypocalcemia.[165]

Appropriate treatment for W.K. should be based on the assessment of her serum calcium, phosphorus, and PTH values. If these remain elevated after optimizing the current treatment regimen and after the addition of lanthanum carbonate, cinacalcet could be initiated. The decision to start cinacalcet as opposed to titrating the dose of calcitriol will depend on if the W.K. has persistent hyperphosphatemia even after optimizing the dose of the phosphate binder and if her adherence to her medications has been ascertained. Cinacalcet can then be initiated at a dose of 30 mg daily, with dosage titrations occurring every 2 to 4 weeks to 60, 90, 120, or a maximum of 180 mg daily to achieve target iPTH levels. While on cinacalcet, she should be maintained on low-dose calcitriol. Her current calcitriol regimen should be increased to 0.25 μg daily. Serum calcium and phosphorous levels should be drawn within 1 week after initiation or dosage increase and plasma PTH levels drawn within 4 weeks after initiation of therapy or dosage adjustment. The potential for hypocalcemia is an important factor to consider when giving a patient cinacalcet.

In phase III clinical trials, 66% of patients receiving cinacalcet experienced at least one episode of hypocalcemia (serum calcium <8.4 mg/dL), although <1% of patients discontinued treatment.[166] The high incidence of hypocalcemia is not solely caused by lowered PTH activity but is also attributed to the mechanism of action of cinacalcet. It is thought that activation of CaSR in bone, intestine, and other tissues may contribute to hypocalcemia. Most episodes of hypocalcemia occur during the initiation of cinacalcet therapy, and slowly titrating the dose reduces the risk. Seizures caused by hypocalcemia have been reported. Vitamin D or calcium-based phosphate binders can be used to increase serum calcium levels between 7.5 and 8.4 mg/dL. If serum calcium falls below 7.5 mg/dL and is associated with symptoms of hypocalcemia and vitamin D cannot be increased further, cinacalcet should be withheld until serum calcium normalizes or the patient is asymptomatic.[162]

Etelcalcetide is a drug that also modulates CaSR and is approved by the FDA for use to treat SHPT in adult patients with CKD on HD.[154] Etelcalcetide was shown to be noninferior to cinacalcet for serum PTH in patients with levels higher than 500 pg/mL.[167] In this study, the most common adverse effect was hypocalcemia.

PARATHYROIDECTOMY

The parathyroid glands enlarge as a compensatory response to disturbances of phosphorus, calcium, and calcitriol metabolism in patients with CKD. Timely administration of vitamin D therapy to prevent parathyroid hyperplasia is crucial as treatment with vitamin D cannot adequately reverse established hyperplasia. A parathyroidectomy is often reserved for patients with severe hyperparathyroidism, concomitant hypercalcemia, and failure to respond to pharmacologic therapy.[135] Parathyroidectomy can be subtotal, total, or total with auto-transplantation. One of the major complications of parathyroidectomy is the early development of postsurgical hypocalcemia.[168] Clinical symptoms of hypocalcemia include muscle irritability, fatigue, depression, and memory loss. Patients should be monitored closely after parathyroidectomy, and all patients with signs or symptoms of hypocalcemia should be treated with calcium supplementation (see Chapter 27, Fluid and Electrolyte Disorders). In patients who have had subtotal parathyroidectomy, the remaining parathyroid tissues will start functioning adequately, so the acute hypocalcemia is transient, lasting only a few days. Total parathyroidectomy requires long-term treatment with calcitriol and oral calcium supplements (1–1.5 g/day of elemental calcium). Studies investigating SHPT management with cinacalcet report reduced rates of parathyroidectomy surgeries.[164,169]

OTHER COMPLICATIONS OF CHRONIC KIDNEY DISEASE

Altered Glucose and Insulin Metabolism

Uremia often is associated with glucose intolerance early in the course of CKD in patients who are nondiabetic. Specifically, patients with CKD often exhibit an abnormal response to an oral glucose challenge and have sustained hyperinsulinemia.[170] The fasting blood glucose is typically within normal limits. Diminished tissue sensitivity to the action of insulin is also observed. Inflammation and oxidative stress are likely contributors predisposing patients with CKD to insulin resistance.[171] Most patients who are nondiabetic with CKD do not require therapy for hyperglycemia.

A decreased clearance of insulin by muscle tissue also can occur in patients with uremia.[172] Thus, in patients who are diabetic with progressive CKD, blood glucose concentrations should be monitored and insulin doses adjusted to avoid hypoglycemia. W.K. has CKD G5D and is receiving her insulin in the peritoneal dialysate solution. Hyperglycemia is also a concern in W.K. because the glucose present in her continuous ambulatory peritoneal dialysis (CAPD) fluid to promote fluid removal will be absorbed systemically. Intraperitoneal insulin administration in the dialysis fluid can lead to delayed or sub-optimal activity.[173] So, insulin dosage adjustments should be made based on repeated home blood glucose measurements, changes in the CAPD prescription, and glycated hemoglobin determinations.

Other Endocrine Complications

Disturbances in thyroid function are frequently encountered in patients with CKD because the kidney is involved in all aspects of peripheral thyroid hormone metabolism. Common laboratory abnormalities include reduced serum concentrations of total thyroxine (T4) and 3,5,3′-triiodothyronine (T3) and a low free thyroxine index (FTI). The thyroid-stimulating hormone (TSH) concentration is usually normal, but peripheral conversion of T4 to T3 is reduced in patients who are uremic.[174]

Other endocrine abnormalities that have been observed in patients with CKD include gonadal dysfunction leading to impotence, diminished testicular size, menstrual abnormalities, and cessation of ovulation.[175] Decreased libido and infertility occur in both sexes. Uremic females of childbearing age should be counseled on the risk of becoming pregnant because of the multiple complications of pregnancy in kidney failure, including high termination rates.[176]

GASTROINTESTINAL COMPLICATIONS

GI abnormalities are extremely common in patients with CKD and include anorexia, nausea, vomiting, hiccups, abdominal pain, GI bleeding, diarrhea, and constipation. Diminished gastric motility can occur from uremia; however, this problem may improve with adequate dialysis. Dyspepsia and gastroparesis may be more prevalent in the PD population than in the HD population and in the earlier stages of CKD.[177]

UREMIC BLEEDING

Patients with CKD are at risk for bleeding from mucosal surfaces such as the stomach. Angiodysplasia of the stomach and duodenum, as well as erosive esophagitis, are the most common causes of bleeding in patients with CKD.[178] Treatment of upper GI bleeding in patients who are uremic usually consists of cautious use of H_2-receptor antagonists, which should be given in reduced doses according to the degree of kidney dysfunction. Proton-pump inhibitors are primarily eliminated by non-kidney routes and can be administered at standard doses (see Chapter 23, Upper Gastrointestinal Disorders).

Dermatologic Complications

Several dermal abnormalities have been observed in patients with CKD, including hyperpigmentation, abnormal perspiration, skin dryness, and persistent pruritus. Of these, uremic pruritus can be the most bothersome for the patient and may lead to repeated

scratching and skin excoriation. Uremic pruritis occurs in about 46% of patients with CKD on dialysis.[179] Hyperparathyroidism, hypervitaminosis A, and dermal mast cell proliferation with subsequent histamine release have been suggested as causes of pruritus.[180]

Treatment of pruritus often is a frustrating experience for the patient and clinician. Although many therapies have been advocated, few have provided sustained benefit. A trial-and-error approach is recommended. Efficient dialysis therapy relieves pruritus in some patients and pharmacologic therapy may be avoided. When necessary, initial pharmacologic treatment usually consists of oral antihistamines (eg, hydroxyzine). Topical emollients or topical steroids may provide benefit if antihistamine therapy is not completely successful. Some other options include cholestyramine, ultraviolet B phototherapy, and oral administration of activated charcoal.[180] Studies have shown that gabapentin might provide relief in patients with CKD 3 and higher, including those on dialysis.[179] Control of calcium, phosphorus, and PTH concentrations is also advocated to reduce pruritus in patients with CKD.

GLOMERULAR DISEASES

Glomerular diseases lead to many complications that result from disruption of normal glomerular structure and function. Several clinical syndromes of glomerular disease exist; however, GN, characterized as proliferation and inflammation of the glomerulus, is observed most frequently. According to the most recent USRDS report, GN as a broad category remains the third leading cause of kidney failure in the United States.[5]

Nephrotic Syndrome

Nephrotic syndrome is characterized by proteinuria >3.5 g/day, hypoalbuminemia, edema, and hyperlipidemia.[181] In more severe

conditions, hypercoagulable conditions are increased from a loss of hemostasis control proteins, including antithrombin III, protein S, and protein C. This syndrome can occur with or without a change in GFR. Nephrotic syndrome may be caused by a primary disease, such as membranous glomerulopathy, which is characterized by deposition of immune complexes, or other systemic diseases including diabetic glomerulosclerosis and amyloidosis. Elevated serum cholesterol and triglycerides are observed in patients with this degree of proteinuria (>3.5 g/day). This hyperlipidemic condition also predisposes patients with nephrotic syndrome to accelerated atherosclerosis. Hyperlipidemia itself can also contribute to progression of CKD. Because nephrotic syndrome is associated with numerous causes, further evaluation of the patient for systemic causes is required to determine the course of therapy and prognosis.

Chronic Glomerulopathies

GN can occur as a primary disease that is idiopathic in origin (eg, focal segmental glomerulosclerosis [FSGS]) or as a secondary manifestation of other systemic diseases (eg, lupus nephritis [LN], granulomatosis with polyangiitis [GPA]). Kidney biopsy is often required for definitive diagnosis. Glomerular lesions associated with glomerulopathies are characterized as diffuse, focal, or segmental, depending on the extent of involvement of individual glomeruli. Pathologic changes are characterized as proliferative, membranous, and sclerotic based on the pattern observed. Proliferative changes usually involve an overgrowth of the epithelium or mesangium, whereas membranous changes are typically described as a thickening of the glomerular basement membrane. Signs and symptoms of GN include hematuria, proteinuria, and decreased kidney function. An autoimmune reaction is the predominant pathogenic process leading to most forms of primary and secondary GN. Although a number of autoantibodies are associated with GN, their exact role in the pathogenesis of GN is still unclear.[181]

Glomerular damage generally occurs in two phases: acute and chronic. During the acute phase, immune reactions occur within glomeruli that stimulate the complement cascade, ultimately resulting in glomerular damage. Nonimmune mechanisms that occur in response to loss of nephron function and hyperfiltration of remaining nephrons are characteristic of the chronic phase.

GN often causes AKI. Patients with damage to more than 50% of glomeruli in the presence of rapid loss in kidney function (over the course of days to weeks) are classified as having rapidly progressive glomerulonephritis (RPGN).[182] If kidney involvement is severe, signs and symptoms of uremia may develop. RPGN may be classified based on the immunopathogenic etiology of the glomerular damage: (a) immune complex deposition (eg, LN); (b) nonimmune deposit-mediated mechanism (eg, GPA); and (c) sclerotic lesions of the glomerulus (eg, FSGS).[181] This chapter focuses on the treatment of the more common forms of chronic GN (ie, LN, GPA, FSGS).

LUPUS NEPHRITIS

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by abnormalities in cell-mediated immunity, such as B-cell hyperresponsiveness and defective T-cell-mediated suppressor activity. In certain predisposed individuals, SLE can lead to the development of LN, a secondary form of GN. LN is the prototypical immune complex–mediated CKD, characterized by deposition or in situ formation of autoantibody–antigen complexes along the glomerular capillary network. LN remains an important cause of mortality. Up to 60% of adults with SLE have some degree of kidney involvement later in the course of their disease, discernible from clinical evidence of kidney damage: heavy proteinuria, hematuria, decreased eGFR, and hypertension. Early in the disease, laboratory abnormalities indicative of kidney involvement are seen in ~25% to 50% of patients.[181] See also Chapter 33, Systemic Lupus Erythematosus.

CASE 28-4

Question 1: S.L., a 34-year-old Black female with a 7-year history of SLE, presents to the nephrology clinic for follow-up of LN.

Current medications: none
Vital signs: BP 160/95
Pertinent laboratory values are as follows:
Serum Na^+, 146 mEq/L
K^+, 4.2 mEq/L
Cl^-, 100 mEq/L
CO_2 content, 25 mEq/L
SCr, 2.0 mg/dL
eGFR, 37 mL/minute/1.73 m^2
BUN, 20 mg/dL
WBC count, 9600/μL
RBC indices are normal.
Platelet count is 175,000/μL.
Her urinalysis shows 12 RBCs/high-power field (HPF; normal, 0–3). Urine ACR was 1145 mg/g.

Compared with her visit a week ago, S.L.'s kidney function and urinary indices (proteinuria, hematuria) show substantial worsening of LN. S.L. was hospitalized, and a kidney biopsy showed inflammation of 40% of the glomeruli and pathologic findings suggestive of LN class III with endocapillary hypercellularity.

S.L. has clinical evidence of kidney damage as demonstrated by her proteinuria, hematuria, and a slightly increased SCr concentration. Glomerular damage is evident by the presence of RBC or red cell casts in the urine. Her current labs place her in CKD category G3b/A3, which is very high CKD risk.

Should S.L.'s LN be treated?

Treatment

Unlike non-kidney manifestations of SLE, serologic markers of disease correlate poorly with LN. Therefore, elevations in SCr, hypertension, proteinuria, and hematuria, as seen in S.L., are used as primary markers of disease activity.

Treatment of LN must address both management of the acute disease process and maintenance therapy for the more stable chronic disease process. The consensus is that patients, such as S.L., who present with endocapillary hypercellularity (class III or IV) should be treated aggressively, with the primary goal of preventing irreversible kidney damage. The prognosis of kidney function in

patients with SLE has improved. However, the prognosis is worse in Blacks when compared with the White population treated for SLE.[183] Elevated SCr, heavy proteinuria, anemia, and disease onset during childhood or in those older than 60 years of age are other predictors of a worse prognosis. Advances in pharmacologic therapy (ie, safer immunosuppressive regimens and antihypertensives) have improved prognosis.

The treatment of LN is primarily empiric but is based, to some extent, on histologic findings. The KDIGO Clinical Practice Guideline for Glomerulonephritis provides recommendations for treatment based on disease activity.[181] Although appropriate treatment can improve patient outcomes, vigorous attempts to suppress SLE activity may lead to serious drug-related complications. The primary strategy in the treatment of LN involves immunosuppression with corticosteroids and cytotoxic agents, such as cyclophosphamide (CYC), azathioprine (AZA), calcineurin inhibitor (CNI) therapy (cyclosporine [CYA] or tacrolimus [TAC]), and mycophenolate mofetil (MMF).[184] Clinicians need to be aware of the potential complications associated with these therapies and carefully monitor patients to determine the indication for treatment and improved prognosis. Toxicities associated with immunosuppressive agents depend on both the dose and the duration of therapy. Abnormalities in hematopoiesis, such as neutropenia and thrombocytopenia, are the most common adverse effects associated with cytotoxic agents. Immunosuppression, in general, increases a patient's susceptibility to a vast array of infections and to lymphocytic malignancies. In addition, the alkylating agent CYC can cause nausea and vomiting, gonadal toxicity, hemorrhagic cystitis, and alopecia. The risk versus benefit of CYC use has to be weighed in young females who are considering pregnancy in the future. The antimetabolite AZA can cause, leukopenia, pancytopenia, myelosuppression, pancreatitis, and abnormalities in liver function. The selective inhibitor of inosine monophosphate dehydrogenase, MMF, although relatively benign compared with the other agents, can cause GI disturbances.

Induction Therapy

Therapy for LN is usually not indicated in patients with normal kidney function and proteinuria <1 g, because these patients have a good prognosis. Corticosteroids represent the cornerstone of therapy in patients with a mild form of LN. Prednisone (1 mg/kg or methylprednisolone) should be initiated for patients with class II LN with proteinuria >3 g/day or CNI. In patients with a more severe form (class III and IV), prednisone 1 mg/kg/day combined with either CYC or MMF should be initiated. For the treatment of acute exacerbations of LN, high-dose pulse therapy with methylprednisolone may be warranted. Given that S.L.'s LN has worsened, she should receive pulse methylprednisolone (0.5–1 g IV, not to exceed 1 g) for 3 days in an attempt to reduce the degree of proteinuria and improve kidney function.[181] Although generally well tolerated, rapid methylprednisolone injections can cause transient tremor, flushing, and altered taste sensation. To reduce the risk of adverse effects associated with the rate of injection, S.L. should receive methylprednisolone for 30 minutes. After a course of pulse methylprednisolone therapy, oral prednisone at a dose 10 to 20 mg daily may be initiated.[181] Suppression of S.L.'s active LN should be demonstrated by a reduction in proteinuria and hematuria and an increase in her eGFR.

The addition of cytotoxic agents is reserved for patients who do not respond to corticosteroids alone or those who have unacceptable toxicity to corticosteroids, worsening kidney function, severe proliferative lesions, or evidence of sclerosis on kidney biopsy. Induction therapy with six monthly pulse doses of IV CYC 0.5 to 1 g/m^2 or six doses of CYC given every 2 weeks at a dose of 0.5 g/m^2 along with steroid therapy was shown to have improved kidney outcomes with fewer flares and relapses.[181] Before and for 24 hours after initiating IV CYC, the patient must be well hydrated to prevent bladder toxicity. Alternatively, MMF (2000–3000 mg/day times 6 months) or TAC (0.06–0.1 mg/kg/day) has been proven to be as effective as CYC in the induction treatment for LN.[185,186] Given the significant toxicities associated with CYC (eg, gonadal toxicity and

hemorrhagic cystitis), MMF or TAC are attractive options given their anti-inflammatory properties and the lower side effect profile. Recently, rituximab, an anti-CD20 monoclonal antibody, has demonstrated similar efficacy as MMF and CYC.[187]

Maintenance Therapy

Once the acute flare resolves (generally in up to 12 weeks), low-dose, maintenance steroid therapy with 5 to 15 mg/day of prednisone can be initiated in combination with cytotoxic therapy, if indicated, based on the severity of LN. In a meta-analysis assessing the efficacy of therapeutic agents used to treat LN, improved outcomes (total mortality and kidney failure) were associated with use of oral prednisone in combination with IV CYC. As a result, the National Institutes of Health recommends the use of IV CYC pulse therapy (0.5–1 g/m^2) every 3 months for up to 2 years for maintenance therapy of LN.[181] An additional benefit of combination therapy with immunosuppressive agents is their steroid-sparing effect and, potentially, lower risk of steroid toxicity.

Steroid- and CYC-free regimens are often desired to avoid steroid and CYC adverse events. Studies have evaluated other immunosuppressive agents (AZA, MMF) for maintenance therapy considering the toxicities associated with CYC or steroids. The KDIGO Clinical Practice Guideline for Glomerulonephritis recommends AZA (1.5–2.5 mg/kg/day) or MMF (1–2 g/day) and low-dose corticosteroids (≤10 mg/day prednisone equivalent) for maintenance therapy.[181]

A multiregimen trial compared maintenance therapy with AZA (1–3 mg/day) and MMF (500–3000 mg/day) with CYC along with steroids after induction with CYC in patients with severe LN. Patients receiving AZA had a lower mortality rate than those treated with CYC, and the MMF treatment group had fewer relapses than the CYC treatment group.[188] MMF and AZA may be indicated in patients resistant to CYC therapy or with a more severe type of LN (class III and IV). The addition of AZA or MMF, along with corticosteroid therapy, should be considered in S.L. once the acute lupus flare

resolves. Once suppression of S.L.'s LN is documented, initiation of either AZA or MMF and steroids is indicated because of the severity of her LN (class III). The duration of therapy is dictated by the individual's response, but typically patients will require up to 2 years of maintenance therapy. Patients with thiopurine *S*-methyl transferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency may be at an increased risk of severe and life-threatening myelotoxicity if receiving conventional doses of AZA. Based on the genotype of a patient deficient of TPMT and NUD15 (homozygous or heterozygous), the recommendation is either to find an alternative agent like MMF or to use AZA at a reduced dose.[189]

Alternative Agents

The KDIGO practice guidelines recommend reserving CNI for those intolerant to MMF or AZA as maintenance therapy.[181] Rituximab, a monoclonal antibody that inhibits B-cell production, is being studied because B-cell hyperactivity is one of the major pathophysiologic mechanisms of LN. Small studies in patients with LN resistant to therapy have shown rituximab to be of benefit. CYA, in doses of 5 mg/kg/day, may also provide an alternative therapy to treat lupus in the maintenance phase in patients unresponsive to treatment.[181] Belimumab (Benlysta®), a monoclonal antibody blocking the binding of B-lymphocyte stimulator protein (BLyS) to receptors on the B-lymphocytes, was recently approved for maintenance treatment of LN in adults.[190] Similarly, voclosporin (Lupkynis®), a novel calcineurin inhibitor, was also approved for the treatment of LN in combination with other immunosuppressive therapy.[191]

GRANULOMATOSIS WITH POLYANGIITIS

CASE 28-5

Question 1: J.M. is a 42-year-old White male who presents to the clinic with a 1-month history of cough, nasal congestion, facial pain with headache, fever, and lethargy. During the past week, he has noted bright red blood in his phlegm,

which has worsened in the past 3 days. Pertinent laboratory values are as follows:

Serum Na, 143 mEq/L
K^+, 5.1 mEq/L
Cl^-, 102 mEq/L
CO_2 content, 24 mEq/L
SCr, 2.8 mg/dL
BUN, 41 mg/dL

This compares with last year's physical checkup visit when his SCr and BUN were within the normal range. Hematologic studies reveal an Hct of 35%, an Hgb of 11.7 g/dL, an MCV of 69 μL, a mean corpuscular Hgb concentration of 24%, and a reticulocyte count of 1.8%. RBC indices are normal, and the platelet count is 175,000/μL. His 24-hour urine contains 3.8 g of albumin (normal, <30 mg), and his eGFR is calculated to be 27 mL/minute/1.73 m^2. His urine also contains many RBC casts and 16 RBCs/HPF (normal, 0–3 RBCs/HPF). Chest radiograph shows alveolar shadowing spreading from the hilar region. The result of J.M.'s cytoplasmic-staining, antineutrophil cytoplasmic antibody (c-ANCA) is positive.

Based on his subjective and objective data, which of the chronic glomerulopathies is J.M. likely to have?

GPA, formerly called Wegener granulomatosis, is a primary systemic vasculitis characterized by granulomatous inflammation of the upper and lower respiratory tract and secondary GN. Primary systemic vasculitides, such as GPA, often cause GN. Although vasculitis involves inflammation of blood vessels of any size, the small- and medium-size vessels are most commonly affected.[192] The etiology of GPA is unclear; however, an autoimmune response is suspected for two reasons. First, GPA is a systemic inflammatory disease without a known infectious etiology. Second, good treatment response can be obtained with immunosuppressive therapy.

The clinical features of GPA include upper airway disease, such as sinusitis, epistaxis, and nasopharyngitis, as well as otitis media caused by blockage of the eustachian tube. Constitutional symptoms include fever, night sweats, arthralgia, anorexia, and malaise. After a few months, weakness may progress, severely limiting physical activity. Although the lungs are invariably affected, most patients remain asymptomatic; however, cough and hemoptysis may be

present. J.M.'s presenting symptoms are consistent with the above clinical features. The laboratory signs also are nonspecific and indicate the presence of a systemic inflammatory process. They include an elevated erythrocyte sedimentation rate in virtually all patients, anemia of chronic disease, and thrombocytosis.[192,193] Hematuria and proteinuria can be prominent features of GPA and are present on initial presentation in 80% of patients. The presence of severely diminished kidney function, seen in ~10% of patients, is an ominous sign, with nearly one-third of these patients progressing to kidney failure. All patients with GPA are at risk of developing irreversible, rapidly progressive kidney failure. Kidney histologic findings are nonspecific, with most patients exhibiting necrotizing crescentic GN.[192,193]

GPA is diagnosed primarily by the presenting signs and symptoms. According to the American College of Rheumatology 1990 classification, a person is diagnosed with GPA if any two of the following four criteria are present: (a) nasal or oral inflammation, (b) abnormal chest radiograph, (c) microhematuria (>5 RBCs/HPF) or RBC casts in the urine sediment, or (d) granulomatous inflammation on biopsy.[192] J.M. has satisfied three of the four criteria for diagnosing GPA.

Treatment

Case 28-5, Question 2: How should J.M.'s GPA be treated?

The discovery of c-ANCA and its strong association with GPA has permitted a more certain diagnosis. Because of the substantial rise in titer that commonly precedes relapse of GPA, the c-ANCA test is best used to follow the course of disease activity and guide induction of therapy. Treatment with CYC and corticosteroids results in improvement in kidney function in ~80% to 85% of patients, versus 75% with pulse steroids alone.[181] The main predictive factors for treatment success are the extent of kidney damage before therapy starts and how long therapy is delayed after symptoms develop.

Cyclophosphamide

Because GPA is considered an autoimmune inflammatory disease, immunosuppressive therapy is the mainstay of treatment. **Table 28-13** lists KDIGO guidelines-recommended treatment regimens. Therapy is generally indicated for 6 months if remission occurs and up to 12 months in resistant cases.[192] J.M. should be started on oral CYC 2 mg/kg/day, as a single morning dose, and corticosteroids to prevent irreversible glomerular scarring. High fluid intake (>3 L/day) and Mesna reduce the risk of hemorrhagic cystitis. Regular UA should be performed (every 3–6 months) to detect hematuria caused by hemorrhagic cystitis.

Table 28-13

Recommended Treatment Regimens for ANCA Vasculitis With Glomerulonephritis

Agent	Route	Initial Dose
Cyclophosphamide[a]	IV	0.75 g/m^2 q 3–4 weeks Decrease initial dose to 0.5 g/m^2 if age >60 years or GFR <20 mL/minute/1.73 m^2 Adjust subsequent doses to achieve a 2-week nadir leukocyte count >3000/mm^3
Cyclophosphamide[b]	PO	1.5–2 mg/kg/day, reduce if age >60 years or GFR <20 mL/minute/1.73 m^2 Adjust the daily dose to keep leucocyte count >3000/mm^3
Corticosteroids	IV	Pulse methylprednisolone: 500 mg IV daily × 3 days
Corticosteroids	PO	Prednisone 1 mg/kg/day for 4 weeks, not exceeding 60 mg daily Taper down over 3–4 months
Rituximab[b]	IV	375 mg/m^2 weekly × 4
Plasmapheresis[c]		60 mL/kg volume replacement Vasculitis: 7 treatments over 14 days. If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments Vasculitis in association with anti-GBM antibodies: Daily for 14 days or until anti-GBM antibodies are undetectable

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GFR, glomerular filtration rate; IV, intravenous; PO, orally.

[a]Given with pulse and oral steroids. An alternative IV cyclophosphamide dosing schema is 15 mg/kg given every 2 weeks for three pulses, followed by 15 mg/kg given every 3 weeks for 3 months beyond remission, with reductions for age and estimated GFR.

[b]Given with pulse and oral steroids.

[c]Not given with pulse methylprednisolone. Replacement fluid is 5% albumin. Add 150 to 300 mL fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.

Reprinted from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2(2):139–274. © 2012 International Society of Nephrology. With permission.

Corticosteroids

The main role of corticosteroids is to induce remission of the disease. J.M. should receive prednisone 1 mg/kg/day in addition to CYC. The combined regimen should be continued for 2 to 4 weeks until the immunosuppressive effect of CYC becomes evident. Then, during the next 2 months, the prednisone dose can be tapered to 60 mg every other day to reduce the risk of infection. Then, the dose can be tapered by 5 mg/week to discontinue prednisone over the course of 3 to 6 months. For patients with a more fulminant form of the disease, pulse methylprednisolone 500 mg/day for three doses is administered. The dose can be repeated in 1 to 2 weeks if disease progression is uncontrolled.

Alternative Therapies

Rituximab as an induction agent has been evaluated in two randomized controlled trials. The Randomized Trial of Rituximab versus Cyclophosphamide for ANCA-associated Renal Vasculitis (RITUXVAS) trial randomized 44 subjects to rituximab (375 mg/m^2 weekly × 4) plus IV CYC or to IV CYC alone.[194] Each group received IV methylprednisolone followed by oral corticosteroids. Remission rates were 76% for the rituximab group and 82% for CYC. The

Rituximab for ANCA-associated Vasculitis (RAVE) trial rituximab was compared to oral CYC (2 mg/kg/day) for up to 3 months plus AZA (2 mg/kg/day) for 4 to 6 months.[195] IV methylprednisolone plus oral corticosteroid were given to both groups. Rituximab proved noninferior to the CYC regimen with similar rates, 64% versus 53%, respectively. There were no significant differences in adverse events rates in either trial. Although rituximab has performed well in comparison studies, the high cost limits its acceptance and applicability in clinical practice.

Azathioprine and Mycophenolate Mofetil

AZA (1–2 mg/kg/day) and MMF (up to 1000 mg/day) are effective as maintenance therapy once remission has been achieved with CYC. However, a comparative study demonstrated mycophenolate to be less effective at maintaining remissions compared with AZA; thus, AZA is the preferred maintenance therapy.[196] Maintenance therapy should be continued for a minimum of 18 months for patients in complete remission. Note the pharmacogenomic considerations for AZA stated previously.[189]

Alternative Agents

Methotrexate (MTX) may be beneficial for patients with milder disease, although one study demonstrated high relapse rates in patients treated initially with weekly MTX and daily prednisone; disease was controlled in only select patients.[197] However, MTX should be reserved for patients intolerant of AZA and MMF and GFR >60 mL/minute/1.73 m^2.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

CASE 28-6

Question 1: A.G. is a 37-year-old morbidly obese (body mass index, 40 kg/m^2), Black female who presents to the clinic with increased swelling in her extremities for the last 2 weeks, decreased urine output, and dark “foamy” urine. Her medical history is significant only for hypertension, which is well controlled

with amlodipine 5 mg PO every day. She takes no other prescription or over-the-counter medications. Pertinent laboratory values are as follows:

SCr, 2.1 mg/dL (normal, 0.6–1.2 mg/dL)
Spot urine ACR, 1200 mg/g (normal, <30 mg/g)
UA, 18 RBCs/HPF (normal, 0–3)
eGFR; 34 mL/minute/1.73 m^2

The nephrologist schedules a biopsy to obtain a definitive diagnosis for her new-onset CKD. Biopsy results are as follows: light micrograph shows a moderately large segmental area of sclerosis with capillary collapse on the upper left side of the glomerular tuft; the lower right segment is relatively normal. Electron micrograph shows diffuse epithelial cell foot process fusion with occasional loss of the epithelial cells. The other major finding is massive subendothelial hyaline deposits under the glomerular basement membrane. The pathologist's impression is FSGS.

What is the relevance of FSGS, and what are the management strategies for FSGS?

FSGS is characterized by sclerotic lesions of the glomerulus, which can be either focal or segmental in nature. The development of FSGS may be idiopathic (primary) or secondary to other diseases (ie, morbid obesity, sickle cell disease, congenital heart disease, AIDS). Currently, FSGS is the leading cause of idiopathic nephrotic syndrome and accounts for 15% to 20% of the cases. Black patients are two to four times more likely to experience idiopathic FSGS than White patients, and they have a higher incidence of kidney failure caused by FSGS.[198] Genetic variants of the apolipoprotein L1 (APOL1) gene predominate in patients of African ancestry and have been identified as a major risk factor.[199]

Most patients with FSGS will present with proteinuria, but only about half of them will initially present with the nephrotic syndrome. Patients with the nephrotic syndrome will also likely present with hypertension, increased SCr levels, and hematuria. During the early stages of FSGS, the symptoms may be indistinguishable from minimal-change nephrotic syndrome, a glomerulopathy characterized by similar lesions within the glomeruli. A kidney biopsy is necessary for diagnosis. Predictors of increased risk of progression to kidney failure include massive proteinuria (>10 g/day), higher SCr level (>1.3 mg/dL), and Black race.[198,200]

Treatment

Corticosteroids

A.G. should be placed on steroids, in addition to an ACEI or ARB and a loop diuretic, because she has FSGS and nephrotic syndrome.[181] A course of corticosteroids 1 mg/kg/day (maximum 80 mg) or 2 mg/kg every other day (maximum 120 mg) for at least 4 weeks and for up to 4 months with tapering of the dose over the course of 6 months after complete remission is achieved. Complete remission is defined as reduction of albuminuria <0.3 g/day, normal urine and SCr, and serum albumin >3.5 g/dL.[181] The median time to remission is 3 to 4 months. Patients whose proteinuria does not respond after a 4-month trial of therapy should be considered resistant to steroids and be rapidly tapered off over the course of 6 weeks.[181]

Steroid-Resistant Treatment

Calcineurin Inhibitors

The addition of cytotoxic agents (CYA, TAC) may be considered for A.G. if she is steroid resistant, intolerant of long-term steroid therapy, severely nephrotic, frequently relapsing, or steroid dependent. The data supporting the use of these agents in FSGS are limited. Retrospective studies have shown that the use of cytotoxic drugs can produce complete remission in 50% of cases. Length of therapy of these agents may predict the remission rates of FSGS. Recent prospective studies support a longer duration of therapy.

Evidence supporting the efficacy and safety of CYA in FSGS stems from randomized controlled trials. In addition to being options for steroid-resistant patients, CNIs provide a steroid-sparing effect in FSGS steroid-sensitive patients. CYA studies are the most prevalent of the CNIs. CYA response is highly dependent on the previous steroid response. Complete remission rates of 73% can be seen with CYA in steroid-sensitive patients.[200] Conversely, therapy with CYA doses of 5 mg/kg/day for 6 to 12 months has been found to be effective and can result in remission rates of up to 69% in patients

resistant to steroids.[201] The current recommendation is CYA of 3 to 5 mg/kg/day in two divided doses. If remission is achieved, continue treatment for 1 year.

However, if no remission is achieved by 6 months, discontinue CYA. Limitations of CYA therapy include high relapse rate (23%–100%) after withdrawal, side effect profile (nephrotoxicity, hypertension), and resistance to therapy. Studies evaluating TAC as a treatment option for FSGS are few and lack randomized controlled trials. Current TAC therapy should be initiated at 0.1 to 0.2 mg/kg/day in two divided doses. TAC has a similar side effect profile to that of CYA.[200] Sirolimus is associated with nephrotoxicity in FSGS and is not recommended for treatment.

Mycophenolate Mofetil

MMF has the potential for a steroid-sparing effect; however, relapses are common. MMF and high-dose dexamethasone are recommended for steroid-resistant patients intolerant to CYA therapy. A small study of patients with FSGS resistant to steroids, cytotoxic agents, or both and CYA received MMF for 6 months.[181] At the end of 6 months, 44% of patients had improved proteinuria, but no patient achieved complete remission. Other studies examining MMF therapy at doses of up to 2000 mg/day have found no clinically significant effect on remission rates.[202]

DRUG-INDUCED CAUSES OF CHRONIC KIDNEY DISEASE

Analgesic Nephropathy

Analgesic nephropathy results from habitual ingestion of analgesics for many years. Particularly, agents containing at least two antipyretic analgesics and usually caffeine or codeine are commonly associated with the development of analgesic nephropathy. It is a

tubulointerstitial kidney disease characterized by kidney papillary necrosis as a primary lesion and chronic interstitial nephritis as a secondary lesion.[203] Analgesic nephropathy is a slowly progressive disease, and the clinical signs and symptoms are like the nonspecific presentation of CKD attributable to any other etiology.

Currently in the United States, most cases are caused by long-term use or misuse of compound analgesics containing acetaminophen and aspirin along with caffeine or codeine. Similar findings in terms of the effect on kidney function have also been observed with chronic nonsteroidal anti-inflammatory drug (NSAID) therapy.[204] The uses of acetaminophen and NSAIDs have been associated with the progression of kidney disease in patients with CKD in a dose-dependent manner.[204] The cumulative amount (at least 1–2 kg of acetaminophen), rather than the duration of analgesic intake, is a primary risk factor for developing chronic analgesic nephropathy.[205,206] Thus, analgesics should be used with caution in the CKD population, and chronic analgesic therapy should be discouraged. KDIGO guidelines recommend discontinuation of NSAIDs in people with a GFR <60 mL/minute/1.73 m^2.[1]

At presentation, patients may have a reduced GFR and findings consistent with CKD, such as elevated SCr, BUN, and proteinuria. However, during acute necrosis, patients may experience flank pain, pyuria, and hematuria. As necrosis progresses, cellular debris may cause ureteral obstruction. Kidney dysfunction is characterized as a salt-wasting kidney disease, with a substantial reduction in urine-concentrating and urine-acidifying capabilities. The exact mechanism for kidney damage by acetaminophen is uncertain, but it is thought that its oxidative metabolite produced by the medullary cytochrome P-450 enzyme system may bind to macromolecules, causing cellular necrosis. Conversely, NSAIDs attenuate prostaglandin-mediated vasodilatation and may induce an ischemic state within the kidney medulla, leading to papillary necrosis.[207]

Data on the chronic kidney effects of selective cyclooxygenase-2 (COX-2) inhibitors are limited compared to traditional NSAIDs. In a meta-analysis, that of 114 randomized, double-blind clinical trials evaluated the adverse kidney events of COX-2 inhibitors, of the six

agents evaluated, only rofecoxib was associated with adverse kidney effects. In contrast, celecoxib was associated with a lower risk of kidney dysfunction.[207] A cohort study of 19,163 newly diagnosed patients with CKD examined the association between analgesic use and the risk of progression to kidney failure. Among the COX-2 inhibitors, only rofecoxib use was significantly associated with an increased risk of progression to kidney failure.[204] Rofecoxib was voluntarily withdrawn from the U.S. market in 2004 because of the increased risk for serious cardiovascular events, including MI and stroke.[208]

The long-term management of analgesic nephropathy is generally supportive and primarily involves discontinuation of the offending agent and subsequent abstinence from the use of NSAIDs and combination analgesics. For patients requiring analgesics, acetaminophen as a single agent may be safe, although habitual use can contribute to progression of CKD as well as to liver toxicity.[204] Patients with CKD requiring chronic analgesic therapy should use the lowest dose to control pain, avoid combination products when possible, and maintain adequate hydration.

Lithium-Induced Nephropathy

Lithium use has been associated with alterations in kidney function secondary to acute functional and histologic changes and has been associated with the development of chronic pathologic changes to the kidneys (eg, chronic interstitial nephritis). The role of lithium as a causative agent in the development of CKD has been suggested in a variety of epidemiologic, clinical, and histopathologic studies.[209] The concentrating ability within the kidney and GFR have been shown to decline with long-term lithium use.[210] Lithium-induced CKD has a slow progression (average latency between onset of lithium use and kidney failure is 20 years) in which the rate of progression is related to the duration of lithium therapy and the concomitant use of nephrotoxic drugs or other risk factors for CKD.

Patients with lithium-induced kidney disease are generally asymptomatic. They typically present with an insidious decline in kidney function over the course of many years, and proteinuria is usually absent or minimal.[209] In patients taking chronic lithium therapy, close monitoring of serum lithium concentrations is advised, and regular measurements of SCr should be obtained to detect changes in kidney function. Higher lithium concentrations are associated with an increased risk of kidney damage.[210] Current clinical practice guidelines recommend monitoring SCr every 2 to 3 months during the first 6 months of chronic lithium therapy, followed by yearly measurements thereafter.[209] The decision to discontinue lithium and to initiate another mood stabilizer should be a mutual decision made by the psychiatrist, the nephrologist, and the patient. The diuretic amiloride has been suggested to reduce lithium-induced kidney adverse effects in mild cases.[209]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2:279–335. (99)

Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int*. 2021;99(3S):S1–S87. (63)

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl (2011)*. 2013;3(1):1–163. (1)

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis,

evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). *Kidney Int Suppl (2011)*. 2017;7(1):1–59. (135)

Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2020;98(4S):S1–S115. (88)

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2:139–274. (181)

Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl*. 2013;3:259–305. (132)

Key Websites

Healthy People 2030, http://www.healthypeople.gov/

Kidney Disease: Improving Global Outcomes, http://kdigo.org/home/

National Kidney Disease Education Program, http://nkdep.nih.gov/

NKF eGFR Calculators, https://www.kidney.org/professionals/kdoqi/gfr_calculator

US Renal Data System, http://www.usrds.org/

COMPLETE REFERENCES CHAPTER 28 CHRONIC KIDNEY DISEASE

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl (2011)*. 2013;3(1):1–163.
2. Steinberg EP. Improving the quality of care—can we practice what we preach? *N Engl J Med*. 2003;348(26):2681–2683.
3. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int*. 2020;97(6):1117–1129.
4. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2019;73(3 Suppl 1):A7–A8.
5. United States Renal Data System. *2014 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.

6. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2019 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2020;75(1 Suppl 1):A6–A7.
7. Healthy People 2020. Chronic kidney disease. Accessed January 16, 2021. http://www.healthypeople.gov/2020/topics-objectives/topic/chronic-kidney-disease/objectives
8. Heathy People 2030. Chronic kidney disease. Reduce the proportion of adults with chronic kidney disease—CKD-01. Accessed January 2021. https://health.gov/healthypeople/objectives-and-data/browse-objectives/chronic-kidney-disease/reduce-proportion-adults-chronic-kidney-disease-ckd-01
9. United States Renal Data System. *2020 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.
10. Centers for Disease Control and Prevention. Chronic kidney disease initiative. 2019. Accessed January 21, 2021. https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html
11. Cardone KE, Bacchus S, Assimon MM, Pai AB, Manley HJ. Medication-related problems in CKD. *Adv Chronic Kidney Dis*. 2010;17(5):404–412.
12. Aspinall SL, Cunningham FE, Zhao X, et al. Impact of pharmacist-managed erythropoiesis-stimulating agents clinics for patients with non-dialysis-dependent CKD. *Am J Kidney Dis*. 2012;60(3):371–379.
13. Pai AB, Boyd A, Chavez A, Manley HJ. Health-related quality of life is maintained in hemodialysis patients receiving pharmaceutical care: a 2-year randomized, controlled study. *Hemodial Int*. 2009;13(1):72–79.
14. Zandi-Nejad K, Brenner BM. Strategies to retard the progression of chronic kidney disease. *Med Clin North Am*. 2005;89(3):489–509.
15. Hogan SL, Vupputuri S, Guo X, et al. Association of cigarette smoking with albuminuria in the United States: the third National Health and Nutrition Examination Survey. *Ren Fail*. 2007;29(2):133–142.
16. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med*. 2003;139(4):244–252.
17. Parsa A, Kao WH, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med*. 2013;369(23):2183–2196.
18. Segelmark M, Hellmark T. Autoimmune kidney diseases. *Autoimmun Rev*. 2010;9(5):A366–A371.
19. Andreev E, Koopman M, Arisz L. A rise in plasma creatinine that is not a sign of renal failure: which drugs can be responsible? *J Intern Med*. 1999;246(3):247–252.

20. Appel GB, Radhakrishnan J, Avram MM, et al. Analysis of metabolic parameters as predictors of risk in the RENAAL study. *Diabetes Care*. 2003;26(5):1402–1407.
21. Bianchi S, Bigazzi R, Caiazza A, Campese VM. A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am J Kid Dis*. 2003;41(3):565–570.
22. Nyman HA, Dowling TC, Hudson JQ, Peter WL, Joy MS, Nolin TD. Comparative evaluation of the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) study equation for drug dosing: an opinion of the Nephrology Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy*. 2011;31(11):1130–1144.
23. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem*. 2006;52(1):5–18.
24. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
25. Thongprayoon C, Cheungpasitporn W, Akhoundi A, Ahmed AH, Kashani KB. Actual versus ideal body weight for acute kidney injury diagnosis and classification in critically ill patients. *BMC Nephrol*. 2014;15:176.
26. Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant*. 2016;31(5):798–806.
27. Mian AN, Schwartz GJ. Measurement and estimation of glomerular filtration rate in children. *Adv Chronic Kidney Dis*. 2017;24(6):348–356.
28. Levey AS, Adler S, Caggiula AW, et al. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis*. 1996;27(5):652–663.
29. Praditpornsilpa K, Townamchai N, Chaiwatanarat T, et al. The need for robust validation for MDRD-based glomerular filtration rate estimation in various CKD populations. *Nephrol Dial Transplant*. 2011;26(9):2780–2785.
30. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612.
31. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367(1):20–29.
32. Chung EY, Ruospo M, Natale P, et al. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2020;10:CD007004.
33. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383(23):2219–2229.
34. Rysz J, Gluba-Brzozka A, Franczyk B, Jablonowski Z, Cialkowska-Rysz A. Novel biomarkers in the diagnosis of chronic kidney disease and the

prediction of its outcome. *Int J Mol Sci*. 2017;18(8):1702. doi:10.3390/ijms18081702

35. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis*. 2003;41(2):310–318.
36. Rhee CM, Ahmadi SF, Kovesdy CP, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. *J Cachexia Sarcopenia Muscle*. 2018;9(2):235–245.
37. Yan B, Su X, Xu B, Qiao X, Wang L. Effect of diet protein restriction on progression of chronic kidney disease: a systematic review and meta-analysis. *PLoS One*. 2018;13(11):e0206134.
38. Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease. *Cochrane Database Syst Rev*. 2018;10:CD001892.
39. Fouque D, Pelletier S, Mafra D, Chauveau P. Nutrition and chronic kidney disease. *Kidney Int*. 2011;80(4):348–357.
40. Liu D, Wang LN, Li HX, Huang P, Qu LB, Chen FY. Pentoxifylline plus ACEIs/ARBs for proteinuria and kidney function in chronic kidney disease: a meta-analysis. *J Int Med Res*. 2017;45(2):383–398.
41. Carrion C, Morales MM, Llopis A. Perfil epidemiológico en pacientes infectados por el virus de la inmunodeficiencia humana (VIH) [Epidemiological profile of patients infected by Human Immunodeficiency Virus (HIV)]. *An Sist Sanit Navar*. 1999;22(1):33–41.
42. Cho ME, Smith DC, Branton MH, Penzak SR, Kopp JB. Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2007;2(5):906–913.
43. Veterans Medical Research Foundation. Trial of Pirfenidone to Prevent Progression in Chronic Kidney Disease (TOP-CKD). Identifier NCT04258397. February 6, 2020. https://clinicaltrials.gov/ct2/show/NCT04258397
44. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl*. 2012;2:337–414.
45. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507–520.
46. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American

Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13–e115.

47. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288(19):2421–2431.
48. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994;330(13):877–884.
49. Group SR, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103–2116.
50. Sarafidis P, Loutradis C, Ortiz A, Ruilope LM. Blood pressure targets in patients with chronic kidney disease: MDRD and AASK now confirming SPRINT. *Clin Kidney J*. 2020;13(3):287–290.
51. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861–869.
52. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851–860.
53. Suzuki K, Souda S, Ikarashi T, Kaneko S, Nakagawa O, Aizawa Y. Renoprotective effects of low-dose valsartan in type 2 diabetic patients with diabetic nephropathy. *Diabetes Res Clin Pract*. 2002;57(3):179–183.
54. Hou FF, Xie D, Zhang X, et al. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol*. 2007;18(6):1889–1898.
55. Hart PD, Bakris GL. Hypertensive nephropathy: prevention and treatment recommendations. *Expert Opin Pharmacother*. 2010;11(16):2675–2686.
56. Fu EL, Evans M, Clase CM, et al. Stopping renin-angiotensin system inhibitors in patients with advanced CKD and risk of adverse outcomes: a nationwide study. *J Am Soc Nephrol*. 2021;32(2):424–435.
57. Qiao Y, Shin JI, Chen TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. *JAMA Intern Med*. 2020;180(5):718–726.
58. Bhandari S, Ives N, Brettell EA, et al. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial. *Nephrol Dial Transplant*. 2016;31(2):255–261.
59. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204–2213.

60. Schroten NF, Damman K, Hemmelder MH, et al. Effect of additive renin inhibition with aliskiren on renal blood flow in patients with chronic heart failure and renal dysfunction (additive renin inhibition with aliskiren on renal blood flow and neurohormonal activation in patients with chronic heart failure and renal dysfunction). *Am Heart J*. 2015;169(5):693–701.e3.
61. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892–1903.
62. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372(9638):547–553.
63. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int*. 2021;99(3S):S1–S87.
64. Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int*. 2004;65(6):1991–2002.
65. Smith AC, Toto R, Bakris GL. Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy. *Kidney Int*. 1998;54(3):889–896.
66. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ*. 1998;317(7160):713–720.
67. Chiu DY, Sinha S, Kalra PA, Green D. Sudden cardiac death in haemodialysis patients: preventative options. *Nephrology (Carlton)*. 2014;19(12):740–749.
68. Weir MA, Dixon SN, Fleet JL, et al. beta-Blocker dialyzability and mortality in older patients receiving hemodialysis. *J Am Soc Nephrol*. 2015;26(4):987–996.
69. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med*. 2009;169(12):1156–1162.
70. Rabbani N, Thornalley PJ. Advanced glycation end products in the pathogenesis of chronic kidney disease. *Kidney Int*. 2018;93(4):803–813.
71. Vallon V, Komers R. Pathophysiology of the diabetic kidney. *Compr Physiol*. 2011;1(3):1175–1232.
72. Tuttle KR. Back to the future: glomerular hyperfiltration and the diabetic kidney. *Diabetes*. 2017;66(1):14–16.
73. Breyer MD, Qi Z, Tchekneva EE, Harris RC. Insight into the genetics of diabetic nephropathy through the study of mice. *Curr Opin Nephrol Hypertens*. 2008;17(1):82–86.

74. McKnight AJ, Duffy S, Maxwell AP. Genetics of diabetic nephropathy: a long road of discovery. *Curr Diab Rep*. 2015;15(7):41.
75. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837–853.
76. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977–986.
77. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet*. 2010;376(9739):419–430.
78. Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560–2572.
79. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2019;7(11):845–854.
80. Kluger AY, Tecson KM, Lee AY, et al. Class effects of SGLT2 inhibitors on cardiorenal outcomes. *Cardiovasc Diabetol*. 2019;18(1):99.
81. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295–2306.
82. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657.
83. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436–1446.
84. Boehringer Ingelheim. A Multicentre International Randomized Parallel Group Double-blind Placebo-controlled Clinical Trial of EMPAgliflozin Once Daily to Assess Cardio-renal Outcomes in Patients With Chronic KIDNEY Disease. Identifier NCT03594110. January 31, 2019–November 23, 2022. https://clinicaltrials.gov/ct2/show/NCT03594110
85. Invokana (canagliflozin). Package insert. Hospira, Inc; 2018.
86. Jardiance (empagliflozin). Package insert. Boehringer Ingelheim Pharmaceuticals, Inc; 2020.
87. Farxiga (dapagliflozin). Package insert. AstraZeneca Pharmaceuticals LP; 2020.
88. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2020;98(4S):S1–S115.
89. Strippoli GF, Craig MC, Schena FP, Craig JC. Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy

and delay its progression. *J Am Soc Nephrol*. 2006;17(4 Suppl 2):S153–S155.
90. Steuber TD, Lee J, Holloway A, Andrus MR. Nondihydropyridine calcium channel blockers for the treatment of proteinuria: a review of the literature. *Ann Pharmacother*. 2019;53(10):1050–1059.
91. DuBose TD Jr. Regulation of potassium homeostasis in CKD. *Adv Chronic Kidney Dis*. 2017;24(5):305–314.
92. Palmer BF, Clegg DJ. Treatment of abnormalities of potassium homeostasis in CKD. *Adv Chronic Kidney Dis*. 2017;24(5):319–324.
93. Kayexalate (sodium polystyrene sulfonate). Package insert. Sanofi-Aventis, U.S. LLC; 2009.
94. Valtessa (patiromer). Prescribing information. Relypsa, Inc; 2015.
95. Lokelma (sodium zirconium cyclosilate). Prescribing information. AstraZeneca Pharmaceuticals LP; 2018.
96. Palmer BF. Potassium binders for hyperkalemia in chronic kidney disease—diet, renin-angiotensin-aldosterone system inhibitor therapy, and hemodialysis. *Mayo Clin Proc*. 2020;95(2):339–354.
97. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372(3):211–221.
98. Zannad F, Hsu BG, Maeda Y, et al. Efficacy and safety of sodium zirconium cyclosilicate for hyperkalaemia: the randomized, placebo-controlled HARMONIZE-Global study. *ESC Heart Fail*. 2020;7(1):54–64.
99. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2:279–335.
100. Cerasola G, Nardi E, Palermo A, Mule G, Cottone S. Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review. *J Nephrol*. 2011;24(1):1–10.
101. Agarwal AK. Iron metabolism and management: focus on chronic kidney disease. *Kidney Int Suppl (2011)*. 2021;11(1):46–58.
102. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant*. 2006;21(2):378–382.
103. InFeD. Package insert. Watson Pharmaceuticals, Inc; 2009.
104. Venofer (iron sucrose). Package insert. Vifor (Int) Inc; 2020.
105. Ferrlecit (sodium ferric gluconate). Package insert. Sanofi-Aventis US, Inc; 2020.
106. Injectafer (ferric carboxymaltose). Package insert. American Regent, Inc; 2020.
107. Feraheme (ferumoxytol). Package insert. AMAG Pharmaceuticals, Inc; 2020.

108. Monoferric (ferric derisomaltose). Package insert. Pharmacosmos A/S, Inc; 2020.
109. Larson DS, Coyne DW. Update on intravenous iron choices. *Curr Opin Nephrol Hypertens*. 2014;23(2):186–191.
110. Wang C, Graham DJ, Kane RC, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA*. 2015;314(19):2062–2068.
111. Triferic (ferric pyrophosphate citrate). Package insert. Rockwell Medical, Inc; 2020.
112. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361(21):2019–2032.
113. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355(20):2085–2098.
114. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355(20):2071–2084.
115. Foley RN, Curtis BM, Parfrey PS. Erythropoietin therapy, hemoglobin targets, and quality of life in healthy hemodialysis patients: a randomized trial. *Clin J Am Soc Nephrol*. 2009;4(4):726–733.
116. Collins AJ. Influence of target hemoglobin in dialysis patients on morbidity and mortality. *Kidney Int Suppl*. 2002(80):44–48.
117. Epogen (epoetin alfa). Package insert. Amgen Inc; 2018.
118. Wish JB, Rocha MG, Martin NE, et al. Long-term safety of epoetin alfa-epbx for the treatment of anemia in ESKD: pooled analyses of randomized and open-label studies. *Kidney Med*. 2019;1(5):271–280.
119. Retacrit (epoetin alfa-epbx). Package insert. Pfizer Inc; 2018.
120. Aranesp (Darbepoetin alfa). Prescribing information. Amgen, Inc.; 2019.
121. Suranyi MG, Lindberg JS, Navarro J, Elias C, Brenner RM, Walker R. Treatment of anemia with darbepoetin alfa administered de novo once every other week in chronic kidney disease. *Am J Nephrol*. 2003;23(2):106–111.
122. Vlahakos DV, Marathias KP, Madias NE. The role of the renin-angiotensin system in the regulation of erythropoiesis. *Am J Kidney Dis*. 2010;56(3):558–565.
123. Casadevall N, Nataf J, Viron B, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med*. 2002;346(7):469–475.
124. Schmidt RJ. Methoxy polyethylene glycol-epoetin beta: worth waiting for or a novelty worn off? *Expert Opin Pharmacother*. 2009;10(9):1509–1514.
125. National Kidney Foundation. Kidney Early Evaluation Program (KEEP) 2012 Summary Figures. *Am J Kidney Dis*. 2013;61(4 Suppl 2):S33–S56.
126. Kalpakian MA, Mehrotra R. Vascular calcification and disordered mineral metabolism in dialysis patients. *Semin Dial*. 2007;20(2):139–143.

127. Park J, Rhee CM, Sim JJ, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. *Kidney Int*. 2013;84(4):795–802.
128. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol*. 2002;13(3):798–805.
129. Georgianos PI, Agarwal R. Blood pressure control in conventional hemodialysis. *Semin Dial*. 2018;31(6):557–562.
130. Masuo K, Lambert GW, Esler MD, Rakugi H, Ogihara T, Schlaich MP. The role of sympathetic nervous activity in renal injury and end-stage renal disease. *Hypertens Res*. 2010;33(6):521–528.
131. Sarnak MJ, Bloom R, Muntner P, et al. KDOQI US commentary on the 2013 KDIGO clinical practice guideline for lipid management in CKD. *Am J Kidney Dis*. 2015;65(3):354–366.
132. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl*. 2013;3:259–305.
133. Triglide (fenofibrate). Package insert. Casper Pharma, LLC; 2018.
134. Gemfibrozil. Package insert. Parke-Davis; 2010.
135. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). *Kidney Int Suppl (2011)*. 2017;7(1):1–59.
136. Quarles LD. Role of FGF23 in vitamin D and phosphate metabolism: implications in chronic kidney disease. *Exp Cell Res*. 2012;318(9):1040–1048.
137. Gutierrez OM. Fibroblast growth factor 23 and disordered vitamin D metabolism in chronic kidney disease: updating the “trade-off” hypothesis. *Clin J Am Soc Nephrol*. 2010;5(9):1710–1716.
138. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. *Kidney Int*. 2012;82(7):737–747.
139. Valle C, Rodriguez M, Santamaria R, et al. Cinacalcet reduces the set point of the PTH-calcium curve. *J Am Soc Nephrol*. 2008;19(12):2430–2436.
140. Nigwekar SU, Bhan I, Thadhani R. Ergocalciferol and cholecalciferol in CKD. *Am J Kidney Dis*. 2012;60(1):139–156.
141. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, et al. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(3):519–530.
142. Hill KM, Martin BR, Wastney ME, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3–4 chronic kidney disease. *Kidney Int*. 2013;83(5):959–966.
143. Renvela (sevelamer). Package insert. Genzyme Corporation; 2020.

144. Renagel (sevelamer hydrochloride). Prescribing information. Genzyme Corporation; 2021.
145. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int*. 2007;71(5):438–441.
146. Evenepoel P, Selgas R, Caputo F, et al. Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. *Nephrol Dial Transplant*. 2009;24(1):278–285.
147. Finn WF, Group SPDLS. Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. *Clin Nephrol*. 2006;65(3):191–202.
148. D'Haese PC, Spasovski GB, Sikole A, et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. *Kidney Int Suppl*. 2003;(85):S73–S78.
149. How PP, Mason DL, Arruda JA, Lau AH. Efficacy of chewed vs. crushed lanthanum on phosphorus binding in healthy volunteers. *Clin Nephrol*. 2010;73(5):370–373.
150. Fosrenol (lanthanum carbonate). Package insert. Shire Pharmaceuticals Inc; 2011.
151. Auryxia (ferric citrate) Triferic. Package Insert. Keryx Biopharmaceuticals, Inc; 2021.
152. Lewis JB, Sika M, Koury MJ, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. *J Am Soc Nephrol*. 2015;26(2):493–503.
153. Velphoro (sucroferric). Package insert. Fresenius Medical Care North America; 2020.
154. Rayaldee (calcifediol). Package insert. OPKO Pharmaceuticals, LLC; 2016.
155. Matias PJ, Jorge C, Ferreira C, et al. Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. *Clin J Am Soc Nephrol*. 2010;5(5):905–911.
156. Wu-Wong JR. Potential for vitamin D receptor agonists in the treatment of cardiovascular disease. *Br J Pharmacol*. 2009;158(2):395–412.
157. Valdivielso JM, Ayus JC. Role of vitamin D receptor activators on cardiovascular risk. *Kidney Int Suppl*. 2008;(111):S44–S49.
158. Joist HE, Ahya SN, Giles K, Norwood K, Slatopolsky E, Coyne DW. Differential effects of very high doses of doxercalciferol and paricalcitol on serum phosphorus in hemodialysis patients. *Clin Nephrol*. 2006;65(5):335–341.
159. Andress DL. Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation. *Kidney Int*. 2006;69(1):33–43.
160. Kalantar-Zadeh K, Kovesdy CP. Clinical outcomes with active versus nutritional vitamin D compounds in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4(9):1529–1539.

161. Rodriguez M, Goodman WG, Liakopoulos V, Messa P, Wiecek A, Cunningham J. The use of calcimimetics for the treatment of secondary hyperparathyroidism: a 10 year evidence review. *Semin Dial*. 2015;28(5):497–507.
162. Sensipar (cinacalcet). Package insert. Amgen Inc; 2014.
163. Lazar E, Hebert K, Poma T, Stankus N. Long-term outcomes of cinacalcet and paricalcitol titration protocol for treatment of secondary hyperparathyroidism. *Am J Nephrol*. 2007;27(3):274–278.
164. Investigators ET, Chertow GM, Block GA, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*. 2012;367(26):2482–2494.
165. Chonchol M, Locatelli F, Abboud HE, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet HCl in participants with CKD not receiving dialysis. *Am J Kidney Dis*. 2009;53(2):197–207.
166. Block GA, Martin KJ, de Francisco AL, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med*. 2004;350(15):1516–1525.
167. Block GA, Bushinsky DA, Cheng S, et al. Effect of etelcalcetide vs cinacalcet on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: a randomized clinical trial. *JAMA*. 2017;317(2):156–164.
168. Ishani A, Liu J, Wetmore JB, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. *Clin J Am Soc Nephrol*. 2015;10(1):90–97.
169. Cunningham J, Danese M, Olson K, Klassen P, Chertow GM. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int*. 2005;68(4):1793–1800.
170. Akalin N, Koroglu M, Harmankaya O, Akay H, Kumbasar B. Comparison of insulin resistance in the various stages of chronic kidney disease and inflammation. *Ren Fail*. 2015;37(2):237–240.
171. Banerjee D, Recio-Mayoral A, Chitalia N, Kaski JC. Insulin resistance, inflammation, and vascular disease in nondiabetic predialysis chronic kidney disease patients. *Clin Cardiol*. 2011;34(6):360–365.
172. Bailey JL. Insulin resistance and muscle metabolism in chronic kidney disease. *ISRN Endocrinol*. 2013;2013:329606.
173. Quellhorst E. Insulin therapy during peritoneal dialysis: pros and cons of various forms of administration. *J Am Soc Nephrol*. 2002;13(Suppl 1):S92–S96.
174. Leavey SF, Weitzel WF. Endocrine abnormalities in chronic renal failure. *Endocrinol Metabol Clin North Am*. 2002;31(1):107–119.

175. Holley JL, Schmidt RJ. Sexual dysfunction in CKD. *Am J Kidney Dis*. 2010;56(4):612–614.
176. Hladunewich MA, Hou S, Odutayo A, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. *J Am Soc Nephrol*. 2014;25(5):1103–1109.
177. Shirazian S, Radhakrishnan J. Gastrointestinal disorders and renal failure: exploring the connection. *Nat Rev Nephrol*. 2010;6(8):480–492.
178. Galbusera M, Remuzzi G, Boccardo P. Treatment of bleeding in dialysis patients. *Semin Dial*. 2009;22(3):279–286.
179. Simonsen E, Komenda P, Lerner B, et al. Treatment of uremic pruritus: a systematic review. *Am J Kidney Dis*. 2017;70(5):638–655.
180. Mettang T, Kremer AE. Uremic pruritus. *Kidney Int*. 2015;87(4):685–691.
181. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2:139–274.
182. Greenhall GH, Salama AD. What is new in the management of rapidly progressive glomerulonephritis? *Clin Kidney J*. 2015;8(2):143–150.
183. Somers EC, Marder W, Cagnoli P, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. *Arthritis Rheumatol*. 2014;66(2):369–378.
184. Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis. *Nat Rev Dis Primers*. 2020;6(1):7.
185. Mok CC, Ying KY, Yim CW, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. *Ann Rheum Dis*. 2016;75(1):30–36.
186. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med*. 2005;353(21):2219–2228.
187. Moroni G, Raffiotta F, Trezzi B, et al. Rituximab vs mycophenolate and vs cyclophosphamide pulses for induction therapy of active lupus nephritis: a clinical observational study. *Rheumatology (Oxford)*. 2014;53(9):1570–1577.
188. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. *N Engl J Med*. 2004;350(10):971–980.
189. Imuran (azathioprine). Package insert. Sabela Pharmaceuticals, Inc; 2018.
190. Benlysta (belimumab). Package insert. GlaxoSmithKline LLC; 2021.
191. Voclosporin (lupkynis). Package insert. Aurinia Pharmaceuticals, Inc; 2021.
192. Schilder AM. Wegener's granulomatosis vasculitis and granuloma. *Autoimmun Rev*. 2010;9(7):483–487.
193. Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. *Autoimmun Rev*. 2014;13(11):1121–1125.

194. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363(3):211–220.
195. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363(3):221–232.
196. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA*. 2010;304(21):2381–2388.
197. Walters GD, Willis NS, Craig JC. Interventions for renal vasculitis in adults. A systematic review. *BMC Nephrol*. 2010;11:12.
198. Lavin PJ, Gbadegesin R, Damodaran TV, Winn MP. Therapeutic targets in focal and segmental glomerulosclerosis. *Curr Opin Nephrol Hypertens*. 2008;17(4):386–392.
199. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329(5993):841–845.
200. Meyrier A. An update on the treatment options for focal segmental glomerulosclerosis. *Expert Opin Pharmacother*. 2009;10(4):615–628.
201. Cattran DC. Cyclosporine in the treatment of idiopathic focal segmental glomerulosclerosis. *Semin Nephrol*. 2003;23(2):234–241.
202. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int*. 2011;80(8):868–878.
203. Henrich WL, Agodoa LE, Barrett B, et al. Analgesics and the kidney: summary and recommendations to the Scientific Advisory Board of the National Kidney Foundation from an Ad Hoc Committee of the National Kidney Foundation. *Am J Kidney Dis*. 1996;27(1):162–165.
204. Kuo HW, Tsai SS, Tiao MM, Liu YC, Lee IM, Yang CY. Analgesic use and the risk for progression of chronic kidney disease. *Pharmacoepidemiol Drug Saf*. 2010;19(7):745–751.
205. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis*. 2016;75(3):552–559.
206. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1994;331(25):1675–1679.
207. Bennett WM, Henrich WL, Stoff JS. The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. *Am J Kidney Dis*. 1996;28(1 Suppl 1):S56–62.
208. Sibbald B. Rofecoxib (Vioxx) voluntarily withdrawn from market. *CMAJ*. 2004;171(9):1027–1028.
209. Grunfeld JP, Rossier BC. Lithium nephrotoxicity revisited. *Nat Rev Nephrol*. 2009;5(5):270–276.

210. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet*. 2015;386(9992):461–468.

29

Acute Kidney Injury

Susan A. Krikorian, Oussayma Moukhachen, and Alexander H. Flannery

CORE PRINCIPLES		CHAPTER CASES
1	Acute kidney injury (AKI) is characterized clinically by an abrupt decrease in kidney function over a period of hours to days, resulting in the accumulation of nitrogenous waste products (azotemia) and the inability to maintain and regulate fluid, electrolytes, and acid–base balance.	**Case 29-1(Questions 1, 2), Tables 29-1, 29-2**

CORE PRINCIPLES		CHAPTER CASES
2	Risk factors for the development of AKI include older age, higher baseline serum creatinine (SCr), chronic kidney disease (CKD), diabetes, chronic respiratory illness, underlying cardiovascular disease, prior heart surgery, dehydration resulting in oliguria, acute infection, and exposure to nephrotoxins.	**Case 29-1 (Questions 1, 2) Case 29-2 (Questions-3) Case 29-3 (Questions 1, 4), Tables 29-5, 29-6 Case 29-5 (Questions 1, 2) Case 29-6 (Question 1)**
3	AKI is classified according to the physiologic event leading to AKI: prerenal azotemia—decreased blood flow to the kidney; functional—impairment of glomerular ultrafiltrate production or intraglomerular hydrostatic pressure; intrinsic—damage to the kidneys; and postrenal—outflow obstruction in the urinary tract. The urinalysis and urine microscopy with sediment examination are important diagnostic tools for differentiating the various AKI types.	**Case 29-1 (Questions 1, 2) Case 29-2 (Questions 1, 3, 4) Case 29-3 (Questions 1, 2) Case 29-5 (Question 1) Case 29-6 (Questions 1, 2) Case 29-7 (Question 1) Case 29-8 (Question 1), Tables 29-2–29-4, Equation 29-1**
4	All medications that are excreted in the kidneys should be dosed according to kidney function and monitored closely in patients with AKI. Nephrotoxic medications should be avoided.	**Case 29-6 (Question 3) Case 29-9 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
5	Hydration therapy is useful to increase kidney perfusion and avert the conversion of prerenal azotemia to acute tubular necrosis (ATN), to reduce the risk of contrast-induced acute kidney injury (CI-AKI) in high-risk patients, and to prevent and treat kidney stones.	**Case 29-5 (Question 3)** **Case 29-8 (Question 1), Table 29-5**
6	Few treatment options are available in established AKI; therefore, prevention is key. Supportive therapy is aimed at preventing the morbidity and mortality of AKI: close patient monitoring; strict fluid, electrolytes, and nutritional management; treatment of life-threatening conditions, such as pulmonary edema, hyperkalemia, and metabolic acidosis; avoidance of nephrotoxic drugs; and initiation of kidney replacement therapy (KRT).	**Case 29-1 (Question 3)** **Case 29-2 (Questions 3)** **Case 29-4 (Question 1)** **Case 29-5 (Question 4)** **Case 29-7 (Question 2)** **Case 29-9 (Question 1)**
7	Although diuretics have not been shown to improve patient outcomes in AKI, they can be used to prevent complications from fluid overload. Sodium restriction, daily monitoring of volume status, laboratory chemistries, urine output, and gastrointestinal (GI) losses should be measured during diuretic therapy.	**Case 29-3 (Question 3)** **Case 29-4 (Question 1)** **Case 29-9 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
8	KRT is reserved for patients with severe acid–base disorders, fluid overload, hyperkalemia, or symptomatic uremia as a result of AKI. The benefits to initiate KRT should be assessed by the risk of complications associated with KRT. Dosage adjustments are necessary for drugs that are removed during KRT.	**Case 29-9 (Questions 1, 2), Table 29-7**

INTRODUCTION

Acute kidney injury (AKI) is characterized clinically by an abrupt decrease in kidney function over a period of hours to days, resulting in the accumulation of nitrogenous waste products, urea and creatinine (azotemia), and the inability to maintain and regulate fluid, electrolyte, and acid–base balance.[1] AKI is a devastating syndrome with multiple risk factors or causes. It is associated with multiorgan dysfunction, increased resource utilization, and increased mortality.[2] Not only is underlying chronic kidney disease (CKD) a risk factor for AKI but AKI also contributes to CKD development and may result in dialysis dependency. Minimizing causes of AKI and increasing awareness of the importance of early detection and treatment are associated with improved outcome in AKI. Clinicians recognize that a rapid approach to treatment is essential because the causes and complications of AKI do not allow much time to initiate management and reversal.[3–6]

Many attempts have been made to objectively quantify AKI based on laboratory data, daily urine output, or the need for kidney replacement therapy (KRT). Over the past decade, the working definition of AKI has evolved. Currently, expert opinion and consensus recommend assessing quantitative serum creatinine

(SCr) changes from baseline and/or urinary output as clinical parameters in the detection, diagnosis, and classifying the severity of AKI. Urine production of <400 mL/day is termed *oliguria*, whereas urine production <50–100 mL/day is termed *anuria*.

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO)[7] guidelines proposed a uniform practical clinical definition of AKI. AKI is defined as an increase in SCr ≥0.3 mg/dL within 48 hours *or* an increase in SCr >1.5 times baseline in 7 days or less *or* a decrease in urine output <0.5 mL/kg/hour for ≥6 hours. The most recent guideline provides a useful staging tool for severity to assist clinicians in managing AKI (**Table 29-1**).

Table 29-1
Kidney Disease: Improving Global Outcomes Classification/Staging System for Acute Kidney Injury

Category	SCr and GFR Criteria	Urine Output Criteria
Stage 1	Increased SCr ≥0.3 mg/dL within 48 hours or increased SCr × 1.5–1.9-fold in ≤7 days	<0.5 mL/kg/hour × 6–12 hours
Stage 2	Increased SCr × 2 to 2.9-fold	<0.5 mL/kg/hour × ≥12 hours
Stage 3	Increased SCr × ≥3-fold or SCr ≥4 mg/dL or need for KRT or eGFR <35 mL/minute/1.73 m^2	<0.3 mL/kg/hour × ≥24 hours or anuria × ≥12 hours

GFR, glomerular filtration rate; SCr, serum creatinine.

EPIDEMIOLOGY

Multivariable models have identified risk factors for the development of AKI, including older age, higher baseline SCr, underlying CKD, diabetes, hypertension, chronic respiratory illness, underlying cardiovascular disease, prior heart surgery, dehydration resulting in oliguria, acute infection, and exposure to nephrotoxins.[8]

According to the KDIGO definition, one in five adults and one in three children worldwide experience AKI during hospitalization.[9] Furthermore, the incidence of hospital-acquired acute kidney injury (HA-AKI) in the intensive care unit (ICU) is ~20% to 50%.[10] Sepsis, a dysregulated immune response to infection resulting in life-threatening organ dysfunction, is the most commonly identified risk factor in 26% to 50% of all cases of AKI.[11–14] Other common causes include cardiac surgery, acute liver failure, hepatorenal syndrome, cardiorenal syndrome, and malignancy.[15]

Community-acquired acute kidney injury (CA-AKI), the development of AKI outside the hospital setting, is also common, and is usually detected in the first hospital assessment when SCr can be measured.[16,17] Data on risk factors are limited, but older age and higher comorbidities, especially diabetes and cardiovascular disease, seem to be more common in patients with CA-AKI.[18,19]

In a meta-analysis, patients with CA-AKI showed less severe clinical manifestations, a better prognosis, a reduced rate of ICU treatment, a shorter hospital stay, and a lower mortality rate compared to patients with HA-AKI. However, the rate of kidney recovery and need for KRT were similar.[20]

PROGNOSIS

Patients with AKI may experience incomplete recovery of kidney function, or worsening CKD or even irreversible loss of kidney function requiring KRT referred to as *kidney failure with replacement therapy* (KFRT). Patients who remain with persistent AKI (from 7 to 90 days following AKI) are classified as having acute kidney disease (AKD). Although many patients with stage 3 AKI or AKD may require KRT in the hospital, some will develop KFRT, requiring long-term dialysis.[6]

AKI is an independent risk factor for death in patients in the ICU. Moreover, a 40% to 55% mortality rate has been reported in patients requiring KRT. The mortality rate has declined minimally during the

past 50 years. The most common causes of death are sepsis, cardiovascular disease as a result of heart failure (HF) and ischemic heart disease, malignancy, and withdrawal of life support.[21] Even stage 1 AKI in patients in the ICU is associated with significantly lower 28-day, 1-year, 5-year, and 10-year survival rates compared to critically ill patients with no AKI at any time.[22]

PATHOGENESIS

The production and elimination of urine requires three basic physiologic events:

- Blood flow to the glomeruli
- The formation and processing of ultrafiltrate by the glomeruli and tubular cells
- Urine excretion through the ureters, bladder, and urethra

Many conditions and drugs can alter these physiologic events leading to AKI. These are classified as prerenal azotemia, and functional, intrinsic, and postrenal AKI (**Table 29-2**). It is possible for more than one of these categories to coexist.[23,24]

Table 29-2
Causes of Acute Kidney Injury

Classification	Common Clinical Disorders
Prerenal azotemia	**Intravascular Volume Depletion**
	Hemorrhage (surgery, trauma) Dehydration (gastrointestinal losses, aggressive diuretic administration) Severe burns Hypovolemic shock Sequestration (peritonitis, pancreatitis)
	Decreased Effective Circulating Volume
	Cirrhosis with ascites Heart failure

Classification	Common Clinical Disorders
	Hypotension, Shock Syndromes
	Antihypertensive vasodilating medications Septic shock Cardiomyopathy
	Increased Renal Vascular Occlusion or Constriction
	Bilateral kidney artery stenosis Unilateral kidney stenosis in solitary kidney Renal artery or vein thrombosis (embolism, atherosclerosis) Vasopressor medications (phenylephrine, norepinephrine)
Functional acute kidney injury	**Afferent Arteriole Vasoconstrictors**
	Cyclosporine NSAIDs
	Efferent Arteriole Vasodilators
	Angiotensin-converting enzyme inhibitors Angiotensin II receptor antagonists
Intrinsic acute kidney injury	**Glomerular Disorders**
	Glomerulonephritis Systemic lupus erythematosus Malignant hypertension Vasculitic disorders (granulomatosis with polyangiitis)
	Acute Tubular Necrosis
	Prolonged prerenal states Drug-induced (iodinated contrast media, cisplatin, aminoglycosides, amphotericin B, vancomycin with or without piperacillin/tazobactam, adefovir, cidofovir, tenofovir, HMG CoA reductase inhibitors, bisphosphonates) Tubular crystal obstruction (eg, ethylene glycol, drugs such as acyclovir, methotrexate, indinavir, atazanavir, sulfonamide antibiotics)
	Acute Interstitial Nephritis
	Drug induced (penicillins, β-lactam antibiotics, fluoroquinolones, proton-pump inhibitors, NSAIDs, sulfonamides)
Postrenal acute kidney injury	**Ureter Obstruction (Bilateral or Unilateral in Solitary Kidney)**

Classification	Common Clinical Disorders
	Malignancy (prostate or cervical cancer) Benign prostate hypertrophy Anticholinergic drugs (affect bladder outlet muscles) Kidney stones

HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; NSAIDs, nonsteroidal anti-inflammatory drugs.

Normal kidney function depends on adequate perfusion. The kidneys receive up to 25% of cardiac output, which is >1 L/minute of blood flow. Blood enters the glomerulus via the afferent arteriole. The intraglomerular hydrostatic pressure leads to ultrafiltration across the glomerulus into the proximal tubule. The unfiltered blood leaves the glomerulus via the efferent arteriole. In conditions of decreased kidney perfusion, efferent arteriolar vasoconstriction occurs to increase intraglomerular hydrostatic pressure and maintain ultrafiltrate production. Afferent arteriolar vasodilation also occurs to improve blood flow into the glomerulus.[23,24]

Prerenal azotemia, the most common form of AKI, occurs when blood flow to the kidney is reduced. Major causes include decreased intravascular volume (eg, hemorrhage or dehydration [including overdiuresis]), decreased effective circulating volume states (eg, cirrhosis or HF), hypotensive events (eg, shock or medication-related hypotension), and renovascular occlusion or vasoconstriction. Because no structural damage occurs to the kidney parenchyma per se, correcting the underlying cause rapidly restores glomerular filtration rate (GFR). Sustained prerenal conditions can result, however, in glomerular ischemia causing acute tubular necrosis (ATN).[25]

Functional AKI results when medical conditions or drugs impair glomerular ultrafiltrate production or intraglomerular hydrostatic pressure as a result of impaired autoregulation. Blood travels through the afferent arteriole and enters the glomerulus, where it is filtered, and exits through the efferent arteriole (**Fig. 29-1**). The afferent and efferent arterioles work in concert to maintain adequate glomerular capillary hydrostatic pressure to form ultrafiltrate. Many

medications can drastically reduce intraglomerular hydrostatic pressure and GFR by producing afferent arteriolar vasoconstriction or efferent arteriolar vasodilation.

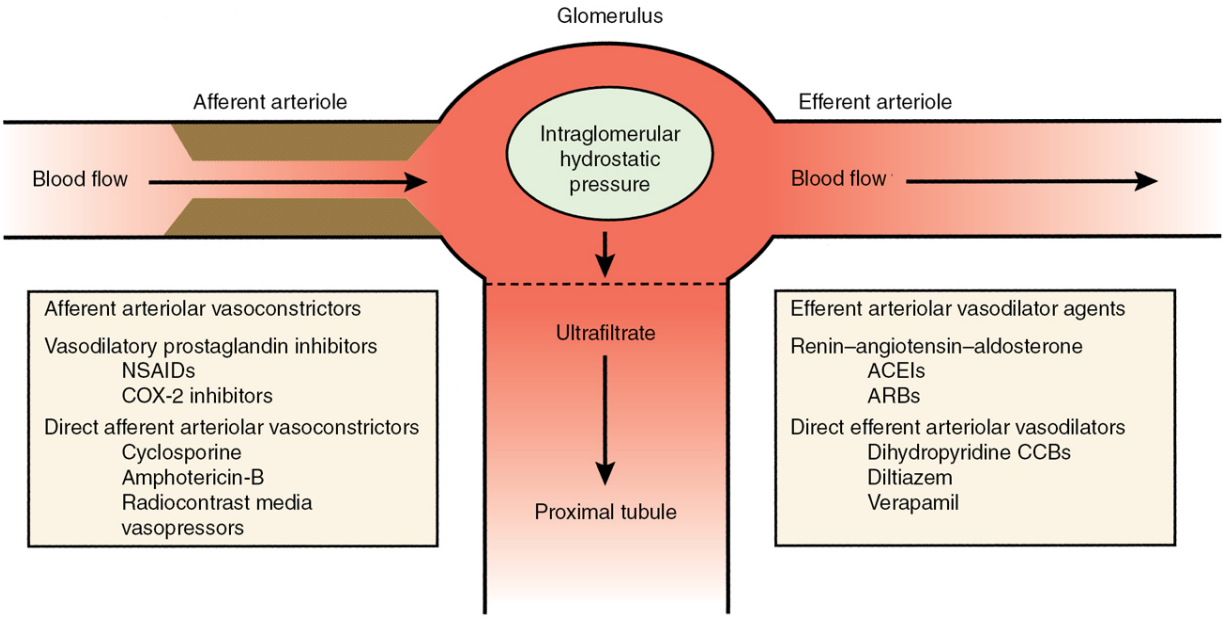


Figure 29-1 Drugs that alter renal hemodynamics by causing afferent arteriole vasoconstriction or efferent arteriole vasodilation. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; COX-2, cyclo-oxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

Intrinsic AKI can occur at the microvascular level of the nephron, glomeruli, kidney tubules, or interstitium. Vasculitic diseases (eg, granulomatosis with polyangiitis, cryoglobulinemic vasculitis) involve the small vessels of the kidney. Glomerulonephritis and systemic lupus erythematosus, although relatively uncommon, result in glomerular damage. ATN is by far the most common cause of intrinsic AKI. ATN occurs in part because the kidney tubules require high oxygen delivery to maintain their metabolic activity. Consequently, any condition that causes ischemia to the tubules (eg, hypotension, decreased blood flow) can induce ATN. Drugs (eg, acyclovir, methotrexate) can cause crystal deposition and also lead to obstruction. Moreover, the tubules may be exposed to exceedingly high concentrations of nephrotoxic drugs (eg, aminoglycosides,

intravenous [IV] contrast). Interstitial nephritis or inflammation within the kidney parenchyma is most often associated with drug administration (eg, penicillins, β-lactam antibiotics).[26,27]

Postrenal AKI occurs when there is an outflow obstruction in the upper or lower urinary tract. Lower tract obstruction is most common, and can be caused by prostatic hypertrophy, prostate or cervical cancer, anticholinergic drugs that cause bladder sphincter spasm, or kidney stones. Upper tract obstruction is less common and occurs when both ureters are obstructed or when one is obstructed in a patient with a single functioning kidney. Postrenal AKI usually resolves rapidly after the obstruction has been removed. Postobstructive diuresis can be dramatic (eg, 3–5 L/day).[24]

CLINICAL EVALUATION

History and Physical Examination

Patients with AKI have a variety of different clinical presentations. Patient symptoms vary, and clinical presentation is largely dependent on the underlying etiology. Symptoms typically include changes in urine output, signs of fluid overload or sudden weight gain, signs of dehydration, or mental status changes. However, many patients are asymptomatic; and are incidentally found to have an elevated SCr concentration, abnormal urine studies (such as proteinuria or microscopic hematuria), or abnormal radiologic imaging of the kidneys.[23]

A detailed history and physical examination often reveal the cause(s) of AKI. The clinician's responsibility is to ask specific, open-ended questions regarding the patient's chief concern; history of present illness; medical history; family, social, and allergy history; and current prescription and nonprescription medication use. Probing for pertinent information regarding recent surgery, nephrotoxin exposure, or concurrent medical conditions can aid in rapidly determining the etiology of AKI. For example, does the

patient have preexisting conditions that point toward prerenal azotemia, such as HF or liver disease? Did the patient receive nephrotoxic medications? Did the patient hemorrhage or have protracted hypotension during surgery? Does the patient report a change in weight, blood pressure (BP), fluid intake, or urine output?

A thorough physical examination, when used in conjunction with the history, can be invaluable in confirming the cause of AKI. The patient's volume status should be evaluated first. Evidence of dehydration (eg, syncope, weight loss, orthostatic hypotension) or decreased effective circulating volume (eg, ascites, pulmonary edema, peripheral edema, jugular venous distension) usually indicates prerenal azotemia. Concurrent rash and AKI associated with recent antibiotic exposure suggest drug-induced allergic interstitial nephritis (AIN). The clinician should suspect rhabdomyolysis in a patient with trauma or crush injuries and AKI. In a patient with suspected AKI, the purpose of kidney ultrasonography early in the diagnostic workup is to rule out obstructive causes of oliguria. An enlarged prostate, painful urination, or wide deviations in urine volume can suggest obstructive AKI causes. Flank and lower abdominal pain suggest upper obstruction, whereas urinary frequency, hesitancy, dribbling, and abdominal fullness indicate lower obstruction.

Laboratory Evaluation

QUANTIFYING GLOMERULAR FILTRATION RATE

GFR is measured with estimating equations that require a steady-state SCr value. No estimating equations can provide an accurate estimate of GFR in AKI because the SCr is fluctuating and not at steady state. Hence, these equations cannot be used during AKI because alterations in SCr may lag several days behind actual changes in GFR.[15] In Chapter 28, Chronic Kidney Disease, the Modification of Diet in Renal Disease (MDRD) equation, the Cockcroft–Gault (CG) equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation are reviewed, and

all three require an SCr value at steady state. The MDRD and CKD-EPI equations are used to quantify baseline GFR, to detect or stage the degree of CKD, and to follow progression. The CG equation is most commonly used to evaluate the appropriate doses of drugs that are eliminated by the kidney.[7] The CG equation may significantly overestimate the kidney function in the early stages of AKI and may underestimate the kidney function when AKI is resolving.[28]An example of this is a patient who develops ATN and anuria. Within the first few days, the SCr level may increase slightly because it takes time for the SCr concentration to achieve a new steady state. In fact, the calculated creatinine clearance (ClCr) may even remain in the normal range, although the true GFR is substantially lower. The converse is true with patients recovering from ATN. As the diuretic phase of ATN begins, urine output can be dramatic, but patients may remain markedly azotemic for several days. Using the CG equation in this setting will produce a falsely low ClCr estimate. The CG equation is also inaccurate in populations that have low muscle mass, such as the elderly, obese, or cachectic patients. Use of SCr to assess kidney function in patients with liver disease may also lead to overestimation of GFR.[29] This may be attributed to decreased production of creatine (the precursor of creatinine) by the liver or increased tubular secretion of creatinine by the kidney.

Therefore, clinicians should be aware that estimating equations have potential limitations and pitfalls. Cystatin C (CysC), a nongylcosylated protein, is an endogenous biomarker of kidney function, produced at a constant rate by all nucleated cells. Its concentration is not influenced by age, gender, and muscle mass. The interindividual variability in CysC production is less than that for SCr. CysC is freely filtered by the glomerulus and then reabsorbed by the proximal tubules, where it is catabolized. Limited evidence suggests that the concentration of CysC is an early AKI biomarker because it peaks earlier than does SCr during AKI, and it may detect AKI earlier than does SCr.[30,31] Even though CysC is not in widespread use, it is a good marker of kidney function and potentially could be used to predict the dose of drugs excreted by the kidneys.

In the past, many clinicians advocated the collection of timed urine specimens to measure urine creatinine excretion and calculate ClCr in AKI. Although this may seem relatively simple, it is susceptible to serious errors, particularly the timing of the collection and ensuring that the patient has not voided urine in the commode, resulting in an incomplete urine collection. For these reasons, the practice of collecting timed urine specimens is not routinely performed. Populations in whom estimation of GFR using a 24-hour urine collection is more reasonable include patients with variation in dietary intake of creatine sources (such as vegetarians) or persons with poor muscle mass (eg, malnourished individuals or amputees).[32] Alternatively, shorter collection times or spot untimed urine samples are sometimes used to determine creatinine excretion.

SERUM AND URINARY TESTS

The lag in SCr rise compared to the decline in kidney function[33] encouraged scientific research on discovering biomarkers that could help with the early identification and diagnosis of AKI. Early AKI identification is extremely important because it could lead to prevention of disease progression or it could help identify patients who may benefit from early interventions. Indeed, various low-molecular weight (MW) molecules, proteins, and enzymes are released by tubular epithelial cells and are secreted in the urine as a response to the AKI constituting the novel biomarkers to identify AKI.[34,35] Examples of such biomarkers include the neutrophil gelatinase associated lipocalin (NGAL), tissue injury metalloproteinase 2 (TIMP-2), and insulin-like growth factor binding protein 7 (IGFBP-7), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), and liver-type fatty acid–binding protein (L-FABP). In the near future, some of these novel biomarkers will most likely be incorporated in definitions of AKI; however, these biomarkers are not yet routinely used in most clinical practice sites. The combination product of TIMP-2 and IFGBP-7 is approved by the U.S. Food and Drug Administration (FDA) for the identification of patients at high

risk for developing KDIGO stage 2 or 3 AKI during the next 12 to 24 hours. These two biomarkers are marketed as the Nephrocheck® Test (Astute Medical Inc, San Diego, CA, USA).[36] The Nephrocheck® Test has been validated as the first point-of-care device to detect early AKI. The Nephrocheck® Test is not used as a stand-alone test for the diagnosis of AKI; however, it should be used as an adjunct tool to clinical findings and other diagnostics. The test results are revealed as an AKI risk score, with scores >0.3 ng/mL^2/1000 indicating a high risk of developing moderate-to-severe AKI within 12 hours of testing.[36,37] Lastly, real-time noninvasive measurement of GFR using fluorescently labeled markers have been proposed to estimate kinetic GFR, and these tests may be available in the future. Real-time monitoring of GFR in critically ill patients will allow for earlier diagnosis of AKI.[38] Future clinical trials are needed to identify and validate their prognostic role in AKI and estimating GFR.[39]

Assessment of both blood urea nitrogen (BUN) and SCr concentrations is crucial for guiding the diagnosis, treatment, and monitoring of AKI. Measurement of SCr and BUN are discussed in Chapter 2, Interpretation of Clinical Laboratory Tests. The BUN:SCr ratio can delineate prerenal causes from intrinsic and postrenal causes. Urea reabsorption is inversely proportional to the urine flow rate. The normal steady-state BUN:SCr ratio is ~10:1. In prerenal conditions, the BUN:SCr ratio is >20:1 because sodium and water are actively reabsorbed in the kidney tubules to expand the effective circulating volume. Urea, an ineffective osmole, is reabsorbed as a result of increased water reabsorption, whereas creatinine is not reabsorbed. Although SCr may increase owing to decreased glomerular filtration, BUN increases to a greater degree as a result of increased proximal reabsorption.

The presence of hypercalcemia, hyperkalemia, and hyperuricemia could indicate the tumor lysis syndrome (TLS) in patients with malignancy.[40] TLS is a condition that occurs in patients with some cancers particularly after chemotherapy administration. The destruction of cancerous cells results in the release of large quantities of cellular contents (eg, potassium, uric acid) into the

bloodstream, which can overwhelm the kidney's functional ability, especially in dehydrated states.

Other elevated enzymes may also aid in the diagnosis of AKI. An increased level of creatine kinase or myoglobin in the face of AKI usually indicates rhabdomyolysis. Eosinophilia may suggest acute AIN from drug exposure. High levels of circulating immune complexes in the presence of AKI suggest glomerulopathies.[23]

URINALYSIS

The urinalysis is an important diagnostic tool for differentiating AKI into prerenal azotemia, intrinsic AKI, or obstructive AKI (**Table 29-3**).[41] The presence of highly concentrated urine, as determined by elevated urine osmolality and specific gravity, suggests prerenal azotemia. During dehydrated states, vasopressin (antidiuretic hormone) is secreted, and the renin–angiotensin–aldosterone system (RAAS) is activated. These mechanisms promote the reabsorption of water and sodium at the collecting duct of the nephron, which serves to expand the effective circulating volume in an attempt to restore kidney perfusion. As a result of diminished urine volume, the urine osmolality and specific gravity increase dramatically. Patients with prerenal azotemia and oliguria often have a urine osmolality >500 mOsm/kg. The maximal urine osmolality can exceed 1200 mOsm/kg.

Table 29-3
Urinary Indices in Acute Kidney Injury

Component	Prerenal Azotemia	Acute Tubular Necrosis	Postrenal Obstruction
Urine Na^+ (mEq/L)	<20	>40	>40
FE_{Na} (%)	<1	>2	>1
FE_{Urea} (%)	<35	>50	
Urine/plasma creatinine	>40	<20	<20
Specific gravity	>1.010	<1.010	Variable
Urine osmolality (mOsm/kg)	Up to 1200	<300	<300

The presence of proteinuria or hematuria can indicate glomerular damage.[42] Nephrotic syndrome is characterized by urinary protein losses >3.5 g/1.73 m^2/day. Proteinuria can also result from tubular

damage; however, that protein loss is rarely >2 g/day. The protein content can be used to differentiate glomerular versus tubular damage. The low-MW protein β_2-microglobulin is freely filtered at the glomerulus and reabsorbed at the proximal tubule. Therefore, the presence of excessive β_2-microglobulin in the urine suggests a tubular source of AKI, such as ATN. Conversely, albumin is not readily filtered at the glomerulus; hence, the presence of heavy albuminuria suggests a glomerular source of AKI.

Microscopic examination of the urine provides helpful clues for determining the source of AKI (**Table 29-4**). Pigmented granular casts are generally seen with ischemic- or nephrotoxin-induced AKI. White blood cells (WBCs) and WBC casts can indicate an inflammatory process in the glomerulus, such as AIN or pyelonephritis. Red blood cells (RBCs) and RBC casts can result from strenuous exercise or can indicate glomerulonephritis. AIN can be detected by the presence of urinary eosinophils. Obstructive AKI causes, such as kidney stones, can be identified by the presence of crystals in the urine. Cystine, leucine, and tyrosine crystals are considered pathologic. The presence of calcium oxalate crystals may suggest toxic ingestion of ethylene glycol.

Table 29-4

Clinical Significance of Urinary Sediment in Acute Kidney Injury

Cellular Debris	Clinical Significance
Red blood cells	Glomerulonephritis IgA nephropathy Lupus nephritis
White blood cells	Infection (pyelonephritis) Interstitial nephritis Glomerulonephritis Acute tubular necrosis
Eosinophils	Drug-induced acute interstitial nephritis Pyelonephritis Renal transplant rejection

Cellular Debris	Clinical Significance
Hyaline casts	Glomerulonephritis Pyelonephritis Heart failure
Red blood cell casts	Acute tubular necrosis Glomerulonephritis Interstitial nephritis
White blood cell casts	Pyelonephritis Interstitial nephritis
Granular casts	Dehydration Interstitial nephritis Glomerulonephritis Acute tubular necrosis
Tubular cell casts	Acute tubular necrosis
Fatty casts	Nephrotic syndrome
Myoglobin	Rhabdomyolysis
Crystals	Nonspecific, kidney stones

Note: Hyaline casts may also be detected in normal kidney function.

IgA, immunoglobulin A.

URINARY CHEMISTRIES

Analyzing urine electrolyte concentrations and simultaneously comparing them with serum sodium and creatinine concentrations is useful for differentiating between prerenal azotemia and ATN (Table 29-3). The fractional excretion of sodium (FE_{Na}) is a measurement of how actively the kidney is reabsorbing sodium, and it is calculated as the fraction of filtered sodium excreted in the urine using creatinine as a measure of GFR. Under normal conditions, the proximal tubule reabsorbs 99% of filtered sodium. The FE_{Na} formula is listed as follows:

$$FE_{Na^+}(\%) = \frac{(U_{Na})\,(SCr)}{(U_{cr})\,(S_{Na})} \times 100\% \qquad \text{(Eq. 29-1)}$$

where U_{Na} is the urine sodium concentration (mEq/L), SCr is the serum creatinine concentration (mg/dL), U_{Cr} is the urine creatinine concentration (mg/dL), and S_{Na} is the serum sodium concentration (mEq/L).[43,44] In prerenal azotemia, the functional ability of the proximal kidney tubule remains intact. In fact, its sodium-reabsorbing abilities are markedly enhanced because of the effects of circulating vasopressin and activation of the RAAS. Both the FE_{Na} and urine sodium concentration become markedly low (<1% and <20 mEq/L, respectively) in prerenal conditions. In contrast, these indices are elevated in ATN because the kidney tubules lose their ability to reabsorb sodium; the FE_{Na} is >2%, and the urine sodium is >40 mEq/L. FE_{Na} values between 1% and 2% are generally inconclusive. The clinician should ensure that the patient is not receiving scheduled thiazide or loop diuretic therapy when the FE_{Na} is calculated. These diuretics increase natriuresis, thereby making the results difficult to interpret. Urea excretion is not affected by diuretics. The fractional excretion of urea (FE_{Urea}) appears more accurate in detecting prerenal azotemia, particularly in patients taking diuretics. Serum and urine sodium concentrations are replaced by blood urea and urine urea concentrations in the FE_{Na} formula. A FE_{Urea} of <35% and >50% are used to distinguish prerenal azotemia and ATN, respectively.[45]

PRERENAL AND FUNCTIONAL ACUTE KIDNEY INJURY

Chronic Heart Failure and Nonsteroidal Anti-inflammatory Drug Use

CASE 29-1

Question 1: A.W. is a 71-year-old White male, 72 inches (182.88 cm) tall and weighing 194 pounds (87.99 kg) who had an ST-segment elevation myocardial infarction (STEMI) 2 months ago. His ejection fraction is currently 15% (normal, 50%–60%). He presents today for his 2-month follow-up clinic appointment with shortness of breath, dyspnea on exertion, and inability to produce much urine. His medical history is significant for long-standing hypertension, coronary artery disease, osteoarthritis, and recent-onset HF after his MI. His home medications include furosemide 40 mg daily, lisinopril 20 mg daily, metoprolol succinate 100 mg daily, digoxin 0.125 mg daily, atorvastatin 40 mg daily, and naproxen sodium 550 mg twice daily (bid), all of which are taken orally (PO). With the exception of naproxen, A.W. often forgets to take his medications. Physical examination reveals lower leg 3+ pitting edema, pulmonary crackles and wheezes, positive jugular venous distension, and an S_3 heart sound. His vital signs are significant for a BP of 198/97 mm Hg and a weight gain of 8.82 pounds (4 kg) since his last visit 2 months ago. Last week, his BUN and SCr were 23 and 1.2 mg/dL, respectively.

What are A.W.'s risk factors for AKI?

A.W.'s risk factors for AKI are HF with poor cardiac output (ejection fraction, 15%) that resulted from his STEMI and his medication, naproxen sodium. HF is a major cause of prerenal AKI.[46] A.W.'s diminished cardiac output has resulted in decreased effective circulating volume and activation of the RAAS, which are impairing his kidney perfusion. In states of decreased kidney perfusion, prostaglandins E2 and I2 compensate for the afferent arteriole vasoconstriction by stimulating afferent arteriole vasodilation, thereby enhancing kidney blood flow. Prostaglandin synthesis is mediated predominantly by cyclooxygenase-1 (COX-1) and perhaps cyclooxygenase-2 (COX-2). Nonsteroidal anti-inflammatory drugs (NSAIDs), which act by inhibiting COX-1 and COX-2 and selective COX-2 inhibitors, should be considered as causes of AKI in high-risk patients. They exert their pharmacologic effect by inhibiting prostaglandin synthesis, thereby negating compensatory vasodilation. The drugs induce abrupt decreases in GFR in at-risk patient populations, specifically those with HF, liver disease, the elderly, or dehydrated patients. Figure 29-1 illustrates common medications that alter kidney hemodynamics by causing either afferent arteriole vasoconstriction or efferent arteriole vasodilation.

The term *triple whammy* refers to the risk of AKI when an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is combined with a diuretic and an NSAID. This combination might be seen in a patient with hypertension, HF, or CKD who has arthritis or mild-to-moderate pain.[47,48]

Celecoxib is currently the only COX-2 inhibitor available in the United States. The NSAIDs naproxen, piroxicam, ketorolac, etodolac, indomethacin, sulindac, ibuprofen, and salsalate were associated with a higher risk of AKI, whereas meloxicam, diclofenac, and the selective COX-2 inhibitor, celecoxib, were not associated significantly with AKI.[49] The highest risk was found in those using more than one NSAID, and in those switching from one agent to another. The lowest risk was found in those using the same agent continuously.[50,51] AKI risk was highest in the first 45 days of treatment initiation.[49] Sulindac may offer a "kidney-sparing" effect. Sulindac is a prodrug that is converted to its active sulfide metabolite by the liver and then becomes reversibly oxidized back to its parent compound in the kidney; kidney prostaglandin synthesis is essentially unaltered by sulindac. Cases of sulindac-induced kidney dysfunction have been reported when the drug was administered to patients with cirrhosis and ascites.

Case 29-1, Question 2: A.W.'s cardiologist obtains a stat digoxin level, serum and urine electrolyte panels, and urinalysis. The digoxin level is reported as "not detectable" (target, 0.5–0.8 ng/mL). Other significant serum laboratory values include:

Na+, 140 mEq/L
BUN, 56 mg/dL
SCr, 1.8 mg/dL

The urinalysis is significant for a urinary osmolality of 622 mOsm/kg and specific gravity of 1.092. The urine electrolytes are significant for Na+ of 12 mEq/L and creatinine of 102 mg/dL. What laboratory findings suggest prerenal AKI? Define the criteria used for the detection of AKI and staging of AKI in this patient?

A.W. has classic laboratory findings associated with poor kidney perfusion (Table 29-3). It is important to compare the current and

previous laboratory data to assess acute changes in kidney function. Compared with last week, A.W.'s kidney function has deteriorated based on substantial increases in BUN and SCr concentrations; BUN has increased nearly twofold and creatinine by 50% (SCr increased × 1.5-fold within 7 days). According to the KDIGO criteria, the patient has stage 1 AKI (see Table 29-1). Kidney demise is most likely owing to prerenal AKI because the BUN:SCr ratio is >20:1, suggesting poor kidney blood flow, which is corroborated by other urinary indices such as the urinary Na+ 12 mEq/L; specific gravity, 1.090 (elevated); urine osmolality, 622 mOsm/kg; and the calculated FE_{Na}, 0.1%. These values reflect the ability of the kidney tubules to respond to vasopressin and aldosterone to expand effective circulating volume and restore kidney perfusion.

Another consideration is furosemide-induced volume depletion; however, the nondetectable serum digoxin level indicates likely noncompliance with his medications. A more likely explanation is poor kidney perfusion because of his HF in combination with NSAID therapy.

CASE 29-1, QUESTION 3: How should A.W.'s prerenal azotemia be treated?

The presence of volume overload in the face of prerenal azotemia suggests a decreased effective circulating volume, most likely from poorly controlled HF. Restoring and improving A.W.'s cardiac output and kidney perfusion will rapidly correct the prerenal azotemia. This can be achieved by (a) optimizing doses and assuring adherence to his HF medications (furosemide, lisinopril, metoprolol succinate, and digoxin); (b) controlling BP by decreasing both preload and afterload; and (c) modifying any drug therapy that has deleterious effects on the kidney hemodynamics (eg, NSAID). The specific therapies for controlling hypertension and improving cardiac output are presented in Chapter 9, Essential Hypertension, and Chapter 14, Heart Failure. Naproxen should be discontinued and substituted with acetaminophen to treat his osteoarthritis. Normal kidney function should return in a few days after correction of the underlying causes.

Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker–Induced Acute Kidney Injury

CASE 29-2

Question 1: G.B. is a 53-year-old White female, 63 inches (160.02 cm) tall and weighing 170 pounds (77.11 kg) with hypertension, coronary artery disease, peripheral vascular disease, and diabetes, for which she had been taking hydrochlorothiazide 25 mg PO daily, atorvastatin 10 mg PO daily, aspirin 81 mg PO daily, and insulin glargine 30 units subcutaneously once daily every morning. At last week's clinic visit, she had two consecutive BP readings of 187/96 and 193/95 mm Hg, respectively, measured 20 minutes apart. At that time, G.B.'s primary care physician started her on lisinopril 5 mg PO daily. Other notable laboratory values at the time included HgA_{1c} 7.5% and urine albumin to creatinine ratio (ACR) 50 mg/g. The region was in the midst of a protracted heat wave with temperatures >95 °F (35 °C) and she claims she is not drinking enough liquids. She returns to the clinic today for her 1-week follow-up appointment with dizziness, dry mouth, and very little urine production during the past week. Laboratory values and vital signs obtained at this visit include the following:

BP, 98/43 mm Hg
Hg, 15 g/dL
Hct, 45%
Na, 145 mEq/L
K, 5.2 mEq/L
BUN, 62 mg/dL
SCr, 2.7 mg/dL (baseline SCr, 1 mg/dL)

Why is G.B. experiencing AKI?

According to the KDIGO criteria, G.B. is diagnosed with stage 2 AKI most likely because of prerenal azotemia. Inhibition of the RAAS in patients with compromised kidney blood flow is a common cause of functional AKI. A basic understanding of the effects of the RAAS on kidney hemodynamics is necessary in this situation (**Fig. 29-2**). When kidney perfusion is impaired, the juxtaglomerular cells of the kidney secrete renin into the plasma and lymph. Renin cleaves circulating angiotensinogen to form angiotensin I (AT I), which is

further cleaved by ACE and converted to angiotensin II (AT II). AT II induces two physiologic events to improve kidney perfusion. First, it directly causes systemic vasoconstriction, which shunts blood to the major organs, and indirectly increases intravascular volume through aldosterone- and vasopressin-mediated activity. Second, it preferentially vasoconstricts the efferent kidney arteriole to maintain adequate intraglomerular hydrostatic pressure. Under conditions of decreased arterial pressure or effective circulating volume, the RAAS is activated and plasma renin and AT II activity are increased.[52,53]

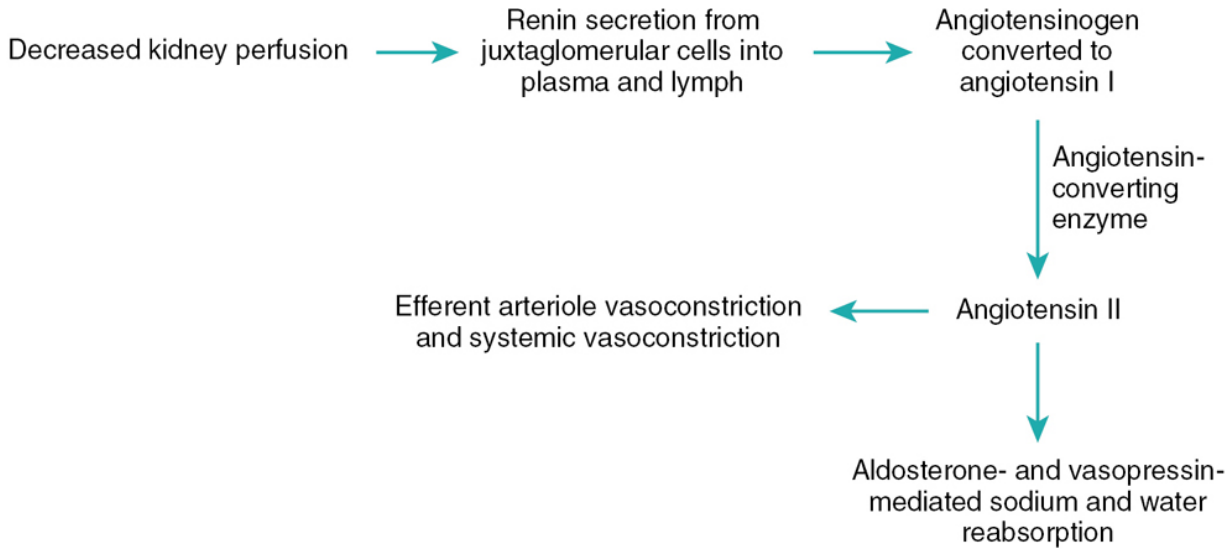


Figure 29-2 Compensatory hormonal mechanisms of decreased renal perfusion.

CASE 29-2, QUESTION 2: Are there other factors that predispose patients to ACE inhibitor–induced AKI?

G.B. has extensive atherosclerotic disease indicated by the presence of coronary artery and peripheral vascular disease. Atherosclerosis may affect the macro- and microvasculature of the kidney and potentially could cause kidney artery occlusion and decreased kidney perfusion. This activates the RAAS, which causes sodium and water reabsorption and AT II–mediated efferent arteriole

vasoconstriction, to restore normal kidney perfusion and intraglomerular hydrostatic pressure.

The administration of ACE inhibitors directly inhibits the formation of AT II, which is necessary for efferent arteriole vasoconstriction. Consequently, the compensatory physiologic event that maintains G.B.'s kidney blood flow is inhibited, thereby reducing her intraglomerular hydrostatic pressure and GFR. ACE inhibitors are contraindicated in patients with bilateral kidney artery stenosis or unilateral stenosis in patients with a single functioning kidney.[54] In addition to the previous situation, three other general scenarios will result in the development of AKI with ACE inhibitors. First, conditions of sodium and water depletion (eg, dehydration, overdiuresis, poor fluid intake, low-sodium diet) can increase the dependency of the efferent arteriole on AT II. Dehydration from diuretic use and decreased fluid intake during the heat spell may have compromised effective circulating volume and led to decreased kidney blood flow in G.B. When ACE inhibitors are given in these situations, GFR can fall dramatically, and SCr rises. AKI can be averted by withholding the ACE inhibitor (or diuretic, or both) for a day and repleting the intravascular fluid volume with normal saline infusion. The ACE inhibitor can be restarted at the same dose after adequate hydration when SCr returns to baseline. Second, ACE inhibitors can decrease the mean arterial pressure to such a degree that kidney perfusion cannot be sustained. This is more likely to occur with long-acting agents or in situations in which the pharmacologic half-life of the ACE inhibitor is prolonged (eg, preexisting kidney disease). Finally, ACE inhibitors may precipitate AKI in patients who are taking concomitant drugs with kidney afferent arteriole vasoconstricting effects, most notably cyclosporine and NSAIDs.

CASE 29-2, QUESTION 3: How should G.B.'s ACE inhibitor–induced AKI be managed?

Patients who are receiving ACE inhibitors should be monitored judiciously regarding their SCr and electrolyte concentrations. Once

an ACE inhibitor is initiated, an increase in SCr of 20% to 30% can be expected.[53] This slight increase should not worry clinicians, because SCr typically normalizes within 2 to 3 months. However, SCr increases greater than this along with reduced urine output signal AKI. AKI related to ACE inhibitors is usually reversible, principally because the AKI is caused by inadequate glomerular capillary pressure, which is restored as soon as sufficient AT II is produced. This normally takes 2 to 3 days to re-equilibrate. AKI appears to develop more commonly in patients with hypotension or in those with intravascular volume depletion (eg, patients with HF receiving high-dose diuretics, inadequate fluid intake with diuretic use). Under these conditions, it is prudent to replete the intravascular fluid volume or temporarily discontinue diuretic therapy until kidney function improves. G.B.'s ACE inhibitor therapy should be temporarily discontinued and reinstituted when she has a normalized intravascular volume and is hemodynamically stable, and kidney function has returned to baseline or stabile kidney function is established. See Chapter 14, Heart Failure, for a discussion on the use of ACE inhibitors and concurrent diuretic therapy in patients with HF.

CASE 29-2, QUESTION 4: Do ARBs cause less AKI compared with ACE inhibitors?

The ARBs competitively inhibit the angiotensin II receptor. At least two subtypes of the AT II receptors exist: AT1-R and AT2-R. The ARBs exert their pharmacologic effect at the AT1-R, which is responsible for most, if not all, of the cardiovascular effects of angiotensin II, such as vasoconstriction, aldosterone release, and β-adrenergic stimulation. Few differences are seen in the incidence of AKI between ACE inhibitors and ARBs[54] and one should not be interchanged with the other to decrease AKI risk. See Chapter 14, Heart Failure, for further discussion. After AKI resolves in G.B., an ACE inhibitor is appropriate to consider treating hypertension and delay the progression of CKD.

INTRINSIC ACUTE KIDNEY INJURY

Intrinsic AKI is a general term that connotes damage at the parenchymal level of the kidney. Pragmatically, intrinsic AKI can be subdivided into vascular, microvascular, glomerular, or tubulointerstitial disorders.

Vascular disorders involving the large kidney vessels are relatively uncommon. Acute kidney artery or vein occlusion can be caused by vasculitis, atherothromboembolism, dissection, or clamping of the ascending aorta during surgery. To affect BUN and SCr, occlusion must be bilateral, or it can be unilateral in patients with reduced kidney function or one functioning kidney. Disorders such as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, scleroderma, and preeclampsia can cause thrombotic microangiopathies, reducing the blood flow to the kidney microvasculature resulting in AKI. Kidney injury associated with systemic lupus erythematosus, human immunodeficiency virus, multiple myeloma, vasculitis, and rapidly progressing glomerulonephritis (RPGN) are examples of glomerular causes of intrinsic AKI. Tubulointerstitial disorders are commonly caused by medications, crystal precipitation, infections, and rhabdomyolysis. ATN is the most common type of AKI, and it is typically caused by nephrotoxins and any disorder that produces tubular ischemia, such as prolonged hypotension or shock syndromes.[55] In the 2020 COVID-19 pandemic caused by the SARS-CoV-2 virus, AKI was a complication noted in hospitalized patients.[56–59] Future studies are needed to evaluate the impact of COVID-19 on kidney function. Residual kidney dysfunction in patients who have recovered from COVID-19 is concerning and the impact of COVID-19 on glomerular disease is unclear.[60]

Acute Glomerulopathies

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

CASE 29-3

QUESTION 1: B.M. is an 18-year-old white male college freshman 68 inches (172.72 cm) tall and weighing 150 pounds (68.03 kg) in otherwise good health who recently developed strep throat. He received a 10-day course of amoxicillin, which cleared the infection. He returns to the student health center after completing his 10-day course with "puffy eyes," swelling in his legs, a cough productive of clear sputum, and decreased urine output that appears "tea colored." Other than the recent course of amoxicillin, he is not on any other medications. Baseline records from a routine physical examination 2 months ago reveal a BUN and SCr of 10 and 0.8 mg/dL, respectively, and a BP of 120/80 mm Hg. Today, the physical examination is significant for a BP of 176/95 mm Hg, 2+ peripheral edema, and bilateral pulmonary rales. The urinalysis is significant for gross hematuria, nephritic-range proteinuria, RBC and WBC casts, and epithelial cells. B.M.'s BUN and SCr have increased to 85 and 7.1 mg/dL, respectively.

Based on the history, physical examination, and laboratory findings, what is the most likely cause of AKI in this patient?

B.M.'s recent history of a streptococcal infection with the development of AKI suggests poststreptococcal glomerulonephritis (PSGN), which results from the formation of antibodies against streptococcal antigens.[61,62] The streptococcal–antigen immune complexes are deposited in the glomerulus, resulting in complement, cytokine, and clotting cascade activation; neutrophils and monocytes attack the glomerulus causing glomerulonephritis. The onset of PSGN is usually 7 to 21 days after the start of the pharyngeal infection. PSGN is the most common acute-onset, immune-mediated, diffuse glomerulopathy. It primarily affects children, although it can affect any age group and is more prevalent in males than in females. Certain serologic subtypes of group A β-hemolytic streptococci, known as *nephritogenic strains*, cause PSGN. Positive diagnosis of PSGN requires identification of a nephritogenic strain; objective urinalysis findings suggestive of glomerular damage, such as proteinuria, hematuria, and casts; and elevated streptococcal antibody titers.

B.M. exhibits the classic physical and laboratory findings associated with PSGN. The pertinent positive physical findings include periorbital, pulmonary, and peripheral edema; tea-colored

urine; hypertension; and decreased urine output. Edema is a common manifestation, with periorbital edema typically being the first to appear. Reduced GFR, proteinuria, and sodium retention by the kidney all contribute to edema formation. When protein, principally albumin, is lost in the urine, the intravascular oncotic pressure declines, causing a shift of fluid into the extravascular space. The loss of intravascular volume stimulates sodium and water reabsorption by the kidney via aldosterone and vasopressin leading to hypertension.

Pertinent laboratory data in B.M. include elevated SCr, and urinalysis positive for hematuria, proteinuria, WBC casts, and epithelial cells. Hematuria, which is found in almost all patients with PSGN, accounts for the reddish brown, tea-colored urine. Other commonly found urine sediments include cellular casts and hyaline and granular casts. Oliguria is common in PSGN, but anuria is rare.

Case 29-3, Question 2: Are there other tests that can be used to confirm this diagnosis?

Kidney biopsy is rarely needed, but it may be prudent in patients who present with atypical symptoms, such as anuria, prolonged oliguria, marked azotemia, hematuria for >3 weeks, or in those who have no streptococcal antibody titers.

Case 29-3, Question 3: What are the therapeutic goals and treatment options for PSGN?

The therapeutic goals are to minimize further kidney damage and to provide symptomatic relief for B.M. The underlying streptococcal infection should be treated with appropriate antibiotics, but as illustrated by B.M., this has no effect in preventing PSGN. Family members and close contacts of the patient who was infected should receive antibiotic prophylaxis as well. Restriction of protein to 0.8 g/kg/day may be beneficial in patients with marked proteinuria, and antihypertensive drugs can be used on a short-term basis to control

BP. Sodium and water restriction is beneficial in reducing edema, and loop diuretics may be used as needed for symptomatic pulmonary or peripheral edema. Close monitoring of electrolytes is warranted if diuretics are used. KRT is rarely required. Given his age and previous health, B.M.'s prognosis is very good. In general, prognosis is excellent in youth, but significantly worse in the elderly and in patients with other risk factors for CKD, such as diabetes and hypertension.[62]

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

CASE 29-3, QUESTION 4: Are there other glomerulopathies that cause AKI?

Yes; RPGN, also called crescentic glomerulonephritis, is a clinical syndrome of rapid decline in kidney function (from days to weeks) combined with the hallmark findings of gross hematuria, nephritic syndrome with proteinuria, and the presence of extensive glomerular crescents (>50% of glomeruli) on kidney biopsy. It is not uncommon for patients with RPGN to have a 50% decline in GFR in only a few weeks. RPGN is a medical emergency, and treatment success depends on how early therapy is initiated. If left untreated, progression to kidney failure or death is almost certain.

Idiopathic RPGN is divided into three categories based on immunofluorescence microscopy. Type I idiopathic RPGN is characterized by linear deposition of immunoglobulins (Igs), primarily IgG, along the glomerular basement membrane (GBM) indicating anti-GBM antibodies. Type II idiopathic RPGN is identified by granular Ig and complement depositions in the glomerular microvasculature and mesangium, suggesting immune complex deposition. Type III idiopathic RPGN is also called pauci-immune because there are no hallmark Ig or complement findings on immunofluorescence microscopy. Type III idiopathic RPGN is identified by the presence of circulating antineutrophil cytoplasmic antibodies (ANCA). Type IV, known as *double-antibody disease*, is

characterized by anti-GBM antibodies and ANCA seen in types I and III RPGN.[63]

Multisystem vasculitic disorders that result in glomerular capillary inflammation are the most common cause of RPGN.[64] Many of these patients present with nonspecific flulike symptoms such as fever, weight loss, myalgia, and malaise with proteinuria and hematuria.[65] Uremic symptoms can occur with severe disease. The presence of AKI with pulmonary congestion, cough, hemoptysis, or dyspnea suggests granulomatosis with polyangiitis (formerly known as *Wegener's granulomatosis*).[66] The treatment for autoimmune RPGN generally involves various regimens of immunosuppressive agents. Corticosteroid monotherapy (oral or "pulse" IV) or combined with either cyclophosphamide or rituximab, is often used. Plasmapheresis is also a nonpharmacologic treatment option in selected patients.[67] A more detailed discussion of glomerulonephritis is presented in Chapter 28, Chronic Kidney Disease.

Tubulointerstitial Diseases

ACUTE TUBULAR NECROSIS

ATN arises most often from ischemia or drug-induced causes.[26] Prolonged prerenal conditions, such as hypotension, surgery, overwhelming sepsis, or major burns, can lead to ischemic ATN. Unlike prerenal azotemia, tubular cell death occurs in ATN, and immediate volume resuscitation will not reverse the damage. The pathophysiology of ATN is complex and remains unclear. It is currently thought that when tubular cells die, they slough off into the tubule lumen and contribute to cast formation. The casts completely obstruct the tubule lumen and increase intratubular pressure, which causes a back leak of ultrafiltrate across the tubular basement membrane (**Fig. 29-3**). The aforementioned processes are mediated by a variety of substances, including calcium, phospholipases, and, perhaps, growth factors as well as free radical and protease activation.

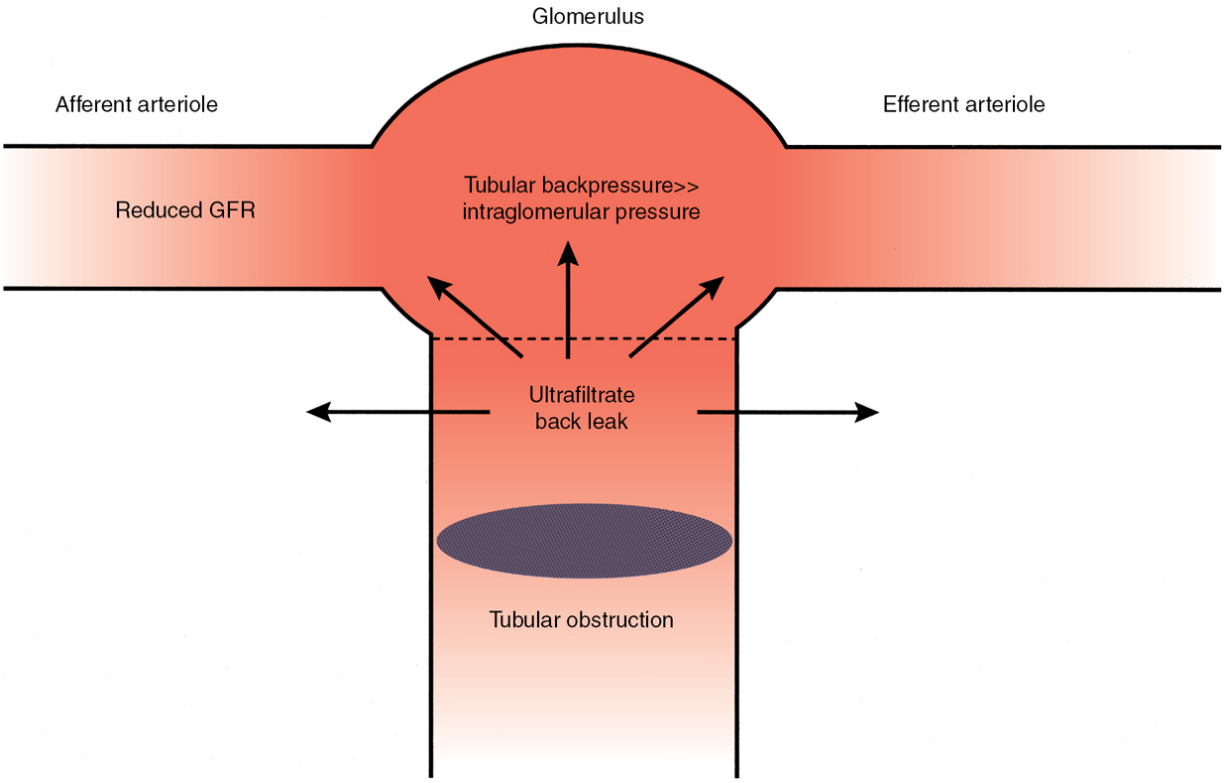


Figure 29-3 Schematic of acute tubular necrosis (ATN). The process is initiated by ischemia or nephrotoxin exposure that leads to tubular cell death. The cellular debris sloughs off and obstructs the proximal tubule lumen. Once the nephron is obstructed, a back leak of the glomerular ultrafiltrate occurs across the tubular basement membrane and impairment of glomerular filtration is seen. During the recovery phase of ATN, the obstructive cellular casts are released into the urine and filtration begins to normalize. GFR, glomerular filtration rate.

CLINICAL COURSE

There are three distinct phases of ATN: oliguric, diuretic, and recovery.[25] The oliguric phase generally occurs over the course of 1 to 2 days and is characterized by a progressive decrease in urine production. The oliguric stage may last from days to several weeks. Strict fluid and electrolytes monitoring are required during this phase until kidney function normalizes.

After the oliguric phase, a period of increased urine production occurs for several days; this is called the *diuretic phase*. This phase

signals the initial repair of the kidney insult. The diuretic phase can result, in part, from a return to normal GFR before tubular reabsorptive capacity has fully recovered. The elevated osmotic load from uremic toxins and the increased fluid volume retained during the oliguric phase may also contribute to the diuretic phase. Despite the increased urine production, patients may remain markedly azotemic for several days. The increase in urine output may lead to volume depletion and electrolyte loss if patients are not given adequate replacement therapy. Daily modifications in the fluid and electrolyte requirements are necessary based on urine output.

The recovery phase occurs over the course of several weeks to months, depending on the severity of the patient's AKI. This phase signals the return to the patient's baseline kidney function, normalization of urine production, and the return of the diluting and concentrating abilities of the kidneys.

TREATMENT WITH DIURETICS AND DOPAMINE

CASE 29-4

QUESTION 1: V.B. is an 86-year-old White male, 62 inches (157.48 cm) tall and weighing 138 pounds (62.59 kg) who was admitted for elective aortic valve replacement secondary to severe aortic stenosis. He became hypotensive during surgery, requiring aggressive fluid resuscitation. He is now in the ICU and requires vasopressors for hemodynamic support. His BUN is 88 mg/dL and his SCr is 3.5 mg/dL today, stable over the past 3 days. His baseline SCr before surgery was 1.2 mg/dL. Despite IV fluids, V.B. is oliguric with a urine output of 15 mL/hour (350 mL/day).

Do diuretics and dopamine have a role in treating ATN?

It is well documented that patients with nonoliguric kidney failure have significantly better outcomes compared to those with oliguria. This is probably because patients who are nonoliguric have less extensive kidney damage and are better able to maintain fluid and electrolyte balance. Loop diuretics have been used in established ATN to convert patients with oliguria to a nonoliguric state despite the lack of conclusive evidence for their benefits. Numerous clinical

trials, however, have failed to demonstrate improved mortality or duration of azotemia in patients with oliguria who receive loop diuretics, despite improved urine output.[7] Two large systematic reviews of the primary literature convincingly showed that diuretic therapy plays little role in altering the course of AKI, decreasing length of hospitalization, or helping recover kidney function.[68,69] These data suggest that although patients who are nonoliguric generally have better outcomes, converting a patient from oliguria to nonoliguria through pharmacologic intervention does not improve patient outcomes. According to KDIGO, the diuretic administration in patients with established ATN should be limited to managing fluid overload.[7]An interesting approach is the use of loop diuretics as a test to predict the potential subset of patients with ATN who would need KRT. Based on findings from small clinical studies, patients who respond to a loop diuretic challenge are hypothesized to have an intact tubular function and are less likely to need KRT and hence assist with KRT allocation management, particularly if KRT availability is limited. The challenge consists of administering 1 to 1.5 mg/kg furosemide in euvolemic patients and measuring their urine output over the next following 2 hours. A positive response is deemed if the urine output increases significantly (>200 mL/hour).[70]

Another controversy that has been debated extensively in the literature is the use of dopamine in patients with established ATN. Dopamine is a catecholamine that stimulates dopaminergic receptors at low dosages (1–3 μg/kg/minute), and α- and β-receptors at higher dosages (5–20 μg/kg/minute). Animal and human studies have demonstrated that low-dose dopamine improves kidney blood flow by inducing afferent arteriolar vasodilation. A meta-analysis of 61 clinical trials including nearly 3500 patients failed to detect any significant improvement in variables such as occurrence of AKI, need for KRT, or mortality.[71] Unequivocally, dopamine has no role in preventing or treating AKI.

AT II may have beneficial effects on kidney-related outcomes in vasodilatory shock with kidney failure caused by its ability to constrict the efferent arteriole more selectively than does the afferent arteriole, but further research is needed to confirm these findings of

a post hoc analysis.[72] Other modalities such as fenoldopam or atrial natriuretic peptide (ANP) have not been shown to be conclusively beneficial to treat AKI and hence are not recommended to be used.[7] KRT would be the most appropriate to use if life-threatening changes in fluid, electrolytes, or acid–base balance are noted.

Contrast-Induced Acute Kidney Injury

CASE 29-5

Question 1: K.S., a 74-year-old Black male, 69 inches (175.26 cm) tall and weighing 210 pounds (95.25 kg), presents to the emergency department with chest pain. His medical history is significant for advanced type 2 diabetes mellitus with retinopathy, peripheral vascular disease, and advanced coronary artery disease. Based on cardiac enzymes, K.S. is ruled in for STEMI. He is taken to the cardiac catheterization laboratory for a percutaneous coronary intervention. Immediately before the procedure, K.S. is given iopamidol[73] a nonionic, low-osmolar radiocontrast to enhance visualization of his cardiac arteries. His admission BUN is 37 mg/dL and SCr is 1.5 mg/dL. Two days later, pertinent laboratory findings include a BUN and an SCr of 60 and 2.0 mg/dL, respectively, and his urine output is 700 mL/day.

Why did AKI develop in K.S.? How is his diagnosis substantiated by his clinical findings?

Contrast administration is one of the most common causes of drug-induced ATN. Although no set criteria exist for its diagnosis, it is generally considered after contrast exposure when an increase in SCr of 0.5 mg/dL or 25% greater than baseline occurs in 24 to 48 hours, peaks at 3 to 5 days, and returns to baseline in 1 to 3 weeks.[74–76] Contrast-induced acute kidney injury (CI-AKI) usually presents as a nonoliguric ATN, as observed in K.S., whose urine output is >400 mL/day. Oliguria can develop in more severe cases of CI-AKI. It is also differentiated from other forms of ATN in that the FE_{Na} is usually <1% (vs the typical >2%). The degree of creatinine rise and urine output are widely variable. Because of the lack of an accepted CI-AKI definition and differences in both clinical trial design and populations studied, estimating the true prevalence of CI-AKI is

unknown. Nevertheless, patients without risk factors have a relatively minute risk of developing CI-AKI; for those with recognized risk factors, prevalence may approach 50%.[77]

The mechanisms by which contrast agents induce AKI are complex. Initially, the contrast agent produces kidney vasodilation and an osmotic diuresis. This, however, is followed by intense vasoconstriction in the medullary portion of the kidney, which has been demonstrated by significant decreases in medullary oxygen tension (pO_2) after contrast administration.[78] The ischemia is compounded by the increased medullary oxygen consumption because of the osmotic diuresis. Consequently, disequilibrium exists between oxygen supply and demand, creating ischemic ATN. Various vasoactive substances are suspected of decreasing medullary blood flow, including oxygen free radicals, prostaglandins, endothelin, nitric oxide, AT II, and adenosine. Endothelin and adenosine are potent vasoconstrictors that are directly released from endothelial cells on exposure to contrast.

CASE 29-5, QUESTION 2: What risk factors did K.S. have for developing CI-AKI?

The documented risk factors for CI-AKI are listed in **Table 29-5**. Any condition that decreases kidney blood flow increases the risk of kidney failure. Patients with diabetes and CKD, estimated glomerular filtration rate (eGFR) <60 mL/minute/1.72 m^2, HF, volume depletion, or those receiving aggressive diuretic regimens are at high risk for developing CI-AKI. Contrast volume administered during the imaging procedure as well as type of contrast remain additional risk factors.[76,79] The use of the ionic high-osmolar or ionic low-osmolar contrast products increases the risk of kidney failure as well as the previously discussed medications that markedly reduce kidney perfusion (eg, diuretics, NSAIDs, COX-2 inhibitors, ACE inhibitors, and ARBs). However, newer nonionic low-osmolar agents may be less nephrotoxic than are older agents, but still can cause

nephrotoxicity in patients at risk. Nonionic iso-osmolar contrast appears to be better tolerated.[80]

Table 29-5
Proven Risk Factors for Developing Contrast-Induced Acute Kidney Injury

Diabetic kidney disease
Chronic kidney disease
Severe heart failure
Diabetes and multiple myeloma
Volume depletion and hypotension
Dosage and frequency of intravenous radiocontrast administration
Ionic radiocontrast agents

Based on the published literature, gadolinium-based contrast agents (GBCAs) are less nephrotoxic than is iodinated radiocontrast; however, when GBCAs are used in high dosage with arterial injection in patients with advanced kidney disease, AKI can occur. More concerning is the development of debilitating nephrogenic systemic fibrosis (NSF), which is sometimes fatal.[81,82] There is no cure for NSF. Patients with AKI or CKD with GFR <30 mL/minute, who have had imaging studies (eg, magnetic resonance angiography) with GBCAs are at high risk for developing NSF. The FDA has issued an advisory Black Box Warning to avoid using these currently approved GBCAs in AKI and CKD stages G4 and G5.[83]

K.S. is at high risk for developing CI-AKI. It is very likely that K.S. has underlying diabetic-associated CKD, as evidenced by his elevated admission SCr. The presence of retinopathy, coronary artery disease, and peripheral vascular disease suggest long-term uncontrolled diabetes mellitus, a risk factor for kidney failure.

PREVENTION

Case 29-5, Question 3: What strategies could have been performed in K.S. to prevent the occurrence of CI-AKI?

Attempts have been made to minimize or prevent CI-AKI using a variety of approaches. Decreasing contact time and the concentration of contrast within the kidney tubule lumen may reduce its direct toxic effects. A higher urine output is associated with a lower incidence of CI-AKI in high-risk patients.[84,85] Volume expansion is a rational approach to prevent kidney dysfunction in this population because human and animal data have revealed dehydration as a major risk factor for developing CI-AKI. IV hydration with normal saline can prevent CI-AKI in high-risk patients. Infusion rates usually start at 1 mL/kg/hour to maintain a goal urine output of 150 mL/hour. Data suggest normal saline should be infused at least 6 hours before and 6 to 12 hours after the imaging study to adequately reduce the risk of developing kidney failure.

Sodium bicarbonate infusion may be of value.[85] Notably, sodium bicarbonate may be beneficial in decreasing the incidence of CI-AKI because it reduces oxygen free radicals in the kidney medulla and, therefore, increases the medullary pH. However, sodium overload is problematic and sodium bicarbonate should be avoided in compromised cardiac states. The antioxidant N-acetylcysteine (NAC) has also been used for its kidney-sparing effects relative to contrast, but its role in preventing CI-AKI remains unclear.[86] NAC is believed to work by protecting kidney tubule cells from apoptosis related to reactive oxygen species.[87] Although much data has been generated with NAC, many of these studies have significant pitfalls, including relatively small sample size; single-center design; heterogeneity of patient populations; differing doses, dosage forms, and schedules of NAC therapy; and differing hydration regimens.

The prevention of serious adverse events following angiography (PRESERVE) trail set out to enroll 8680 high-risk patients undergoing angiography with contrast. Investigators compared the effectiveness of IV sodium bicarbonate infusion versus normal saline infusion and oral NAC versus oral placebo for prevention of CI-AKI.

The sponsor stopped the trial after the interim analysis of 4993 patients. Among patients at high risk for kidney complications who were undergoing angiography, sodium bicarbonate, and oral NAC were not superior to normal saline infusion for the prevention of CI-AKI, need for KRT or persistent decline in kidney function, or death at 90 days. Routine use of sodium bicarbonate infusion and/or oral NAC is no longer recommended to prevent CI-AKI in patients at risk. More studies are needed in patients undergoing diverse procedures requiring imaging with contrast.[88]

When possible, alternative imaging studies that do not require contrast should be attempted. If this is not practical, the lowest effective dose of nonionic low-osmolar or iso-osmolar contrast should be used. Concomitant drug therapy that can impair kidney perfusion, such as diuretics, NSAIDs, COX-2 inhibitors, ACE inhibitors, and ARBs, should be discontinued 1 day before and 1 day after contrast administration. Metformin is also a risk factor. It is not a nephrotoxin; however, its use has been associated with the development of lactic acidosis, systemic complications, and death in rare cases. It is recommended to temporarily discontinue metformin before the administration of contrast to prevent lactic acidosis in patients at risk such as K.S. with underlying CKD.

Case 29-5, Question 4: What treatment options are available for established CI-AKI?

Few data exist regarding treatment of existing CI-AKI. The acute management largely involves supportive care that includes strict fluid and electrolyte management to prevent undue sequelae. Approximately 25% of patients will require temporary KRT. In more severe cases, patients generally require long-term KRT. As already noted, attempts to convert oliguria to nonoliguria with furosemide and mannitol have been largely unsuccessful.

Aminoglycoside-Induced Acute Tubular Necrosis

CASE 29-6

QUESTION 1: T.G. is an 81-year-old, 176.37 pounds (80 kg) White male 70 inches (177.80 cm) tall being treated for *Streptococcus bovis* prosthetic valve endocarditis. T.G. is known to have systolic congestive HF with an ejection fraction of 25%. T.G. has a low BP at 90/50 mm Hg, pulse 110 beats/minute. Since admission, T.G. has received ceftriaxone 2 g IV daily, and gentamicin 80 mg IV every 8 hours. Today, (hospital day 7), significant laboratory values are as follows:

BUN, 67 mg/dL
SCr, 5.4 mg/dL (baseline 0.9 mg/dL)
WBC count, 16,700 cells/μL with continued left shift
FE_{Na}, 3%

During the past 2 days, T.G.'s urine output has steadily declined, and today it is 700 mL/24 hours. A urinalysis revealed many WBCs, 3% RBC casts, brush-border cells, and granular casts with an osmolality of 250 mOsm/kg. A serum trough gentamicin concentration obtained with the last dose is 6 mg/L (target, <1.0 mg/L).

Given the history and laboratory data, what is the likely source of T.G.'s AKI?

The source of AKI in this situation is likely multifactorial (Table 29-2). Low kidney perfusion secondary to low ejection fraction can result in prolonged kidney ischemia. Second, T.G. has received 1 week of gentamicin, a well-known nephrotoxic antibiotic. The risk factors for developing aminoglycoside nephrotoxicity are listed in **Table 29-6**. The latest gentamicin trough concentration of 6 mg/L is far higher than is the target value of <1 mg/L for a traditional three times daily dosing regimen used for synergy for bacterial endocarditis.[89] Given the laboratory data (Table 29-3), the clinical course of prolonged hypotension, and aminoglycoside administration, nonoliguric ATN is the most likely diagnosis.

Table 29-6
Risk Factors for Developing Aminoglycoside Nephrotoxicity

Patient Factors
Elderly
Underlying kidney disease

Patient Factors
Dehydration
Hypotension and shock syndromes
Hepatorenal syndrome
Aminoglycoside Factors
Aminoglycoside choice: gentamicin > tobramycin > amikacin
Therapy >3 days
Multiple daily dosing
Serum trough >2 mg/L
Recent aminoglycoside therapy
Concomitant Drug Therapy
Amphotericin B
Cisplatin
Cyclosporine
Foscarnet
Furosemide
Intravenous contrast agents
Vancomycin

PRESENTATION

CASE 29-6, QUESTION 2: How does aminoglycoside-induced ATN present, and what are the mechanisms of toxicity?

T.G. illustrates the typical presentation of aminoglycoside-induced nephrotoxicity. Generally, the onset occurs after 5 to 7 days of treatment and presents as a hypo-osmolar, nonoliguric kidney failure with a slow rise in SCr.[90] Because of the tubular necrosis that occurs, the urinalysis is often positive for low-MW proteins, tubular cellular casts, epithelial cells, WBCs, and brush-border cells.[91] T.G.'s plasma and urinary laboratory indices are consistent with those listed for ATN in Table 29-3.

The mechanism of aminoglycoside-induced ATN is complex. Approximately 5% of filtered aminoglycoside is actively reabsorbed by the proximal tubule cells. These agents are polycationic and bind to the negatively charged brush-border cells within the tubule lumen. Once attached, these agents undergo pinocytosis and enter the intracellular space, setting off complex biochemical events that result in the formation of myeloid bodies. With continued formation of myeloid bodies, the brush-border cells swell and burst, releasing large concentrations of aminoglycoside and lysosomal enzymes into the tubule lumen, thereby beginning a cascade of further tubular destruction.[90,92] The following rank order of nephrotoxicity has been collated from human and animal data: neomycin > gentamicin > tobramycin > amikacin > netilmicin > streptomycin.[91]

EXTENDED-INTERVAL DOSING

Case 29-6, Question 3: Is "extended-interval" aminoglycoside dosing less nephrotoxic than are multiple daily dosing regimens?

Extended-interval aminoglycoside dosing entails the administration of one large daily aminoglycoside dose instead of multiple daily dosing. This dosing scheme takes advantage of the concentration-dependent killing activity and postantibiotic effect observed with aminoglycosides while minimizing time-dependent toxicity. The net effect of this dosing scheme, purportedly, is greater efficacy with reduced toxicity. Aminoglycoside nephrotoxicity is a function of drug exposure, and it might be minimized with extended-interval dosing because of saturable uptake kinetics in the proximal tubule. That is, only a maximal amount of aminoglycoside is transported into the tubule cell, no matter how much aminoglycoside is present in the tubule. Consequently, once saturation occurs, the remaining aminoglycoside concentration passes through the proximal tubule without being absorbed and is excreted in the urine. Accumulation is therefore averted.[93] Aminoglycosides, such as gentamicin 1 mg/kg every 8 hours or 3 mg/kg once daily, adjusted for kidney function are

recommended by the American Heart Association for the management of selected cases of bacterial endocarditis for their synergistic activity with the β-lactams. The extended-interval dosing is less well studied for endocarditis.[89] In summary, extended-interval aminoglycoside dosing appears to result in similar or greater efficacy, with similar or reduced toxicity. This dosing schedule is also less costly when considering therapeutic drug monitoring, preparation, and administration costs.

Drug-Induced Acute Interstitial Nephritis

Drug-induced acute interstitial nephritis (DI-AIN) accounts for ~1% to 3% of all AKI cases.[94–98] A variety of antibiotics, such as penicillins, cephalosporins, quinolones, particularly ciprofloxacin, sulfonamides, and rifampin, as well as NSAIDs, loop diuretics, thiazide-like diuretics, and proton-pump inhibitors, have been implicated as common drug causes of AIN. The pathophysiology of this reaction is not well understood; it is suspected that either humoral or cell-mediated immune mechanisms or both are involved.[99] Humoral immune reactions occur within minutes to hours of drug exposure and involve the drug or its metabolite acting as a hapten that binds to host proteins, making them antigenic. The drug–protein antigens become lodged in the kidney tubules, which initiate the inflammatory cascade. Cell-mediated injury can occur days to weeks after drug exposure and is identified by the presence of mononuclear inflammation and the lack of detectable immune complexes. This suggests a delayed hypersensitivity rather than a direct cytotoxic effect from a given drug. Both immune mechanisms probably contribute to the development of DI-AIN.

PENICILLIN-INDUCED ACUTE INTERSTITIAL NEPHRITIS

CASE 29-7

QUESTION 1: J.S. is a 50-year-old Hispanic female, 63 inches (160.02 cm) tall and weighing 160 pounds (72.57 kg), who exhibited cellulitis 3 days after a car

door was closed on her right hand. She was admitted to the hospital, where blood and wound cultures were found to be positive for methicillin-sensitive *Staphylococcus aureus*. She received 2 full days of nafcillin 2 g IV every 4 hours before being discharged to complete a 14-day course with dicloxacillin 500 mg PO four times daily (qid). Ten days after discharge, J.S. returned to the emergency department with weakness, fever, diffuse rash, blood in the urine, and reduced urine output. The following laboratory values were significant:

BUN, 39 mg/dL
SCr, 2.3 mg/dL
WBC count, 18,500 cells/μL with 18% eosinophils
The urinalysis was positive for elevated specific gravity, WBCs, RBCs, eosinophils, and an FE_{Na} of 3%.

What objective data suggest DI-AIN?

J.S.'s onset of symptoms suggests antibiotic-induced AIN. As illustrated by this case, the median onset of penicillin-induced AIN generally occurs 6 to 10 days after drug exposure. Hallmark symptoms of antibiotic-associated AIN include fever, macular rash, and malaise. Fever is present in nearly all patients with antibiotic-induced AIN, and rash occurs in 25% to 50% of patients. In contrast, NSAIDs, proton-pump inhibitors, and rifampin are less commonly associated with rash, fever, eosinophilia, and eosinophiluria, and the onset of AIN may occur several weeks to months or longer following drug exposure.[27,94,98,99] J.S.'s objective laboratory data that suggest AIN include azotemia, elevated SCr, proteinuria, cellular urinary sediment, eosinophilia, and eosinophiluria. Her FE_{Na} of 3% suggests intrinsic kidney disease, and her eosinophiluria and eosinophilia indicate an immune-mediated allergic reaction. DI-AIN is generally nonoliguric, but oliguria can develop in severe cases of AIN.

Case 29-7, Question 2: How should J.S.'s penicillin-induced AIN be treated?

Treatment of AIN includes eliminating the precipitating drug, leading to kidney inflammation from an enhanced immune response. The dicloxacillin should be stopped immediately because most patients recover normal kidney function once the offending agent is

discontinued. A non–penicillin antibiotic, clindamycin or doxycycline, may be chosen to finish the course of treatment for cellulitis. However, J.S. has completed 12 out of 14 days of antibiotic therapy, and alternative agents would be optional. General supportive measures that maintain fluid and electrolyte balance are necessary. Kidney recovery may take weeks to months. Use of steroids to treat AIN has been reported in retrospective trials and case reports, but randomized controlled trials are needed to evaluate their benefits versus risks.

KRT may be needed in patients who are oliguric, but it is usually not required for those who are nonoliguric. The clinician should document J.S.'s allergic reaction to penicillins in her medical record, and not rechallenge the patient to antibiotics with similar chemical structures because repeated exposure is likely to result in similar reactions.

Crystal-Induced AKI

Crystal-induced AKI most commonly occurs as a result of uric acid kidney injury or following the administration of drugs or toxins that are poorly soluble or have metabolites that are poorly soluble in urine. Other drugs or toxins (eg, ascorbic acid, ethylene glycol) may be metabolized to insoluble products such as oxalate, which are associated with precipitation of calcium oxalate crystals in the urine within the tubular lumen resulting in kidney injury.[100,101]

PRESENTATION AND TREATMENT

CASE 29-8

Question 1: T.C., a 45-year-old male with a past medical history of schizophrenia treated with aripiprazole, was seen in an outpatient clinic 7 days before admission where he was started on a 7-day course of oral acyclovir 800 mg five times a day for a diagnosis of herpes zoster. He presents to the emergency department with sharp flank pain, gross hematuria, and dysuria. Serum chemistries are ordered and are significant only for an elevated BUN of 34 mg/dL and an SCr of 1.5 mg/dL, compared to his baseline values of 7 and

0.9 mg/dL, respectively. A urine sample was obtained and visualized with microscopy. Birefringent needle-shaped crystals were seen on polarizing light microscopy. It was consistent with acyclovir-induced kidney injury. On questioning, he admits that he has not been drinking enough fluid during the past week owing to a busy work schedule, and his urine volume has been markedly lower than usual.

Which drugs can crystallize in the urine and cause AKI?

Many commonly prescribed drugs such as acyclovir used in T.C. are insoluble in urine and crystallize in the distal tubule.[102] Some of the risk factors that predispose patients to crystalluria include severe volume contraction, underlying kidney dysfunction, or acidotic or alkalotic urinary pH. In conditions of kidney hypoperfusion, high concentrations of drug become stagnant in the tubule lumen.[102] Drugs that are weak acids (eg, methotrexate, sulfonamide antibiotics) precipitate in acidic urine; drugs that are weak bases (eg, ciprofloxacin, indinavir, and other protease inhibitors) precipitate in alkaline urine. Patients with drug-related crystal-induced AKI are usually asymptomatic, and kidney injury is detected by an increased SCr. Occasionally, as in the case of T.C., patients present within 1 to 7 days after initiation of the offending drug with kidney colic symptoms such as flank or abdominal pain, nausea, or vomiting. Urinalysis often reveals hematuria, pyuria, and crystalluria. The diagnosis is suggested by the appearance of crystals in the urine, the morphology of which depends on the specific causative drug. Prevention of crystal-induced AKI is targeted at dosage adjustment for patients with underlying kidney dysfunction, volume expansion to increase urinary output, and urine alkalization to enhance kidney elimination of drugs that are weak acids or urine acidification to enhance kidney elimination of drugs that are weak bases. KRT may be necessary in a small percentage of patients. With appropriate pharmacotherapy, crystal-induced AKI is usually reversible without long-term complications.[102]

Kidney Stones

Calcium stones constitute ~70% to 80% of all kidney stones,[103] with calcium oxalate and calcium phosphate stones making up most of these. Genetic factors appear to play an important role in the development of kidney stones; the stereotypical patient is a male in his third to fifth decade of life. Other risk factors for developing calcium kidney stones are low urine output, inadequate hydration (eg, living in a hot climate and not drinking adequate fluids), hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, and distal kidney tubular acidosis. Generally, more than one of these conditions are present simultaneously. The diagnosis and management of kidney stones are beyond the scope of discussion in this chapter. However, pharmacists can be instrumental in providing proper counseling on hydration and preventive measures.

SUPPORTIVE MANAGEMENT OF ACUTE KIDNEY INJURY

CASE 29-9

QUESTION 1: J.W. is a 75-year-old Native American male, 74 inches (187.96 cm) tall and weighing 200 pounds (90.72 kg), who presents to the emergency room with shortness of breath and progressive worsening edema in both lower extremities. His medical history includes nephrotic syndrome secondary to diabetic nephrosclerosis, type 1 diabetes, hypertension, and chronic obstructive pulmonary disease. His surgical history includes a right-sided nephrectomy many years ago. His chronic medications are furosemide 80 mg PO twice a day, metolazone 10 mg PO once a day, lisinopril 5 mg PO once a day, diltiazem extended-release 120 mg PO once a day, albuterol, inhaler as needed, and subcutaneous 20 units of insulin glargine at bedtime, and insulin aspart as directed before meals. Vital signs are temperature 97.34 °F (36.3 °C), pulse 77 beats/minute, respirations 16 breaths/minute, and BP 179/86 mm Hg. Physical examination reveals periorbital edema, jugular venous distension at a 45-degree angle to the jaw, dullness to percussion halfway up the lungs bilaterally, and 4+ pitting edema in the extremities. Admitting laboratory tests reveal the following:

Sodium, 140 mEq/L
Potassium, 5.5 mEq/L

Chloride, 103 mEq/L
Bicarbonate, 19 mEq/L
Glucose, 249 mg/dL
BUN, 67 mg/dL
SCr, 5.2 mg/dL
Serum albumin, 2.0 g/dL
Spot urine albumin:creatinine ratio, 350 mg/g

Baseline kidney function tests 1 month ago are BUN 45 mg/dL and SCr 3 mg/dL. J.W. is oliguric with a urine output of 10 mL/hour. The nephrologist wants to use supportive management of AKI by first optimizing diuretic therapy. If no increase in urine output occurs during the next several hours, then the patient will undergo KRT.

What is the supportive management of AKI?

Despite years of study, no pharmacologic "cure" for AKI exists. Supportive management is therefore directed at preventing its morbidity and mortality. This is achieved by close patient monitoring; strict fluid, electrolyte, and nutritional management; treatment of life-threatening conditions such as pulmonary edema, hyperkalemia, and metabolic acidosis; avoidance of nephrotoxic drugs; and the initiation of dialysis or continuous renal replacement therapy (CRRT).[7]

An assessment of volume status should be performed in all patients who present with AKI, because correction of volume depletion or volume overload may reverse or ameliorate AKI. The underlying cause dictates management of AKI. For example, prerenal AKI because of volume-depleted states, such as the initial phase of septic shock, requires administration of fluids and vasopressors to restore kidney perfusion and increase urine output. On the other hand, diuretic administration for preload reduction to increase cardiac output would be required for prerenal AKI owing to volume-overload states such as HF.

As discussed earlier, diuretics currently have no role in preventing AKI progression or reducing mortality, but they can prevent complications, such as pulmonary edema in patients with fluid overload.[7] For pulmonary edema, IV furosemide (eg, 80–120 mg) is preferred because of its potency and pulmonary vasodilation properties. Oral furosemide therapy should be avoided because gut edema may limit its bioavailability. Torsemide and bumetanide are

two other loop diuretics that have excellent oral bioavailability and are unaffected by gut edema. The dosage of diuretic needed is highly patient specific, especially in those with frank proteinuria, glomerulonephritis, or nephrotic syndrome. Patients who do not respond therapeutically to an effective loop diuretic dose are labeled as diuretic resistant. Many hypotheses have been postulated to explain the lack of response to loop diuretics.[104] For example, low serum albumin could limit drug transport to the kidneys where the loop diuretics exert their action in the ascending loop of Henle to block sodium and water reabsorption. Coadministration of furosemide with albumin (FUR-ALB), to enhance furosemide's effectiveness has been evaluated in a recent meta-analysis[105] and been found to transiently increase the diuresis volume at 8 hours after a FUR-ALB dose. Unfortunately, the effect was not sustained beyond 24 hours questioning the clinical significance of the combination. Albumin is an expensive therapy, and the combination with loop diuretic benefit–risk ratio should be carefully weighed until large randomized clinical trials provide further evidence. In addition, under some conditions such as glomerulonephritis and nephrotic syndrome, furosemide binds to filtered proteins negating its pharmacologic effect.[104] Other tools to overcome loop diuretic resistance include combining the loop diuretic with a thiazide diuretic such as parenteral chlorothiazide or oral metolazone. This combination acts synergistically to block sodium and water reabsorption in both the Henle loop and the distal convoluted tubule.[106] In patients with diuretic resistance, compensatory reabsorption of sodium by the distal tubule is postulated to be the culprit, and to get the optimal benefit of the combination, it is important to administer the thiazide diuretic 30 minutes before the IV loop diuretics. Other alternatives include continuous loop diuretic infusions, such as furosemide 10–40 mg/hour.[106] The infusion rate should not exceed 4 mg/minute because these rates are associated with ototoxicity, especially when given in combination with aminoglycoside antibiotics. Close monitoring of serum bicarbonate, potassium, magnesium, and calcium is necessary when administering large doses of loop diuretics. Diuresis should aim for a

weight loss of 0.5 to 1 kg/day. If diuretics fail to achieve the desired fluid overload reduction, dialysis or KRT can be considered.

Hyperkalemia commonly occurs in patients with AKI because the kidneys regulate potassium homeostasis. It can be life-threatening. It is prevalent in patients with oliguria who are catabolic or have evidence of active cellular breakdown, such as rhabdomyolysis and TLS. J.W. is mildly hyperkalemic, but his serum potassium may decrease after furosemide therapy. Management of hyperkalemia is discussed in Chapter 27, Fluid and Electrolyte Disorders. In cases of severe hyperkalemia in which conventional pharmacologic treatment is not feasible, or not working, emergency KRT should be performed. Medications that can cause hyperkalemia such as ACE inhibitors, ARBs, or trimethoprim should be avoided.

Metabolic acidosis is a common manifestation of AKI because the kidneys are responsible for excreting organic acids. Other factors also contribute to severe acidosis among patients with AKI, who are often critically ill. For example, patients with AKI because of septic shock, trauma, and multiorgan failure often have increased production of lactic acid or ketoacids. J.W.'s serum bicarbonate concentration reveals slight acidemia that does not require correction at this time. Commonly used treatments for metabolic acidosis include bicarbonate administration and KRT. Bicarbonate therapy may be administered as first corrective therapy, in non–life-threatening and non–fluid-overloaded metabolic acidosis. Severe metabolic acidosis (pH <7.1) in the presence of anuria or oliguria and a fluid overload state should be corrected with KRT, because worsening volume overload can occur with the administration of sodium bicarbonate therapy.

Uremia can interfere with platelet aggregation resulting in hemorrhagic diathesis. Patients with uremia display increased bleeding sensitivity to aspirin compared to normal patients taking aspirin. Patients with uremia and major hemorrhagic bleed may benefit from using desmopressin (dDAVP) 0.3 μg/kg intravenously or subcutaneously for one or two doses. Desmopressin produces a dose-related increase in von Willebrand factor VII and tissue-type plasminogen activator (t-PA) levels; this shortens activated

antithromboplastin time (aPTT) as well as bleeding time. The improvement in bleeding time typically begins within about 1 hour to 4 to 8 hours. Tachyphylaxis typically develops after the second dose. Other modalities that can improve platelet function and reduce bleeding in a patient with AKI include KRT, conjugated estrogens, and cryoprecipitate.[107] Severe uremia may also signal buildup of several toxic compounds and contribute to metabolic encephalopathy.

Clinicians should closely monitor the patient's vital signs (eg, weight, temperature, BP, pulse, and respirations) several times per day. The patient's volume status should be assessed daily, and all fluids should be adjusted based on laboratory chemistries to detect fluid and electrolyte abnormalities, urine output, and gastrointestinal (GI) and insensible losses. Pharmacists should pay attention to nutritional support for patients with AKI to provide adequate amounts of energy, protein, and nutrients, while being sensitive to the electrolytes, acidosis, and volume balance issues. The patient's medication profile should be reviewed daily to assess for appropriate dosage adjustment in kidney dysfunction. Preventive measures to reduce the likelihood of AKI should be used, such as monitoring volume status to ensure adequate kidney perfusion, using dosing strategies or products that are associated with less nephrotoxicity, and avoiding drug therapy combinations that enhance nephrotoxicity (eg, NSAID, aminoglycosides, vancomycin and piperacillin/tazobactam).[108,109]

Drug Dosing in Acute Kidney Injury

Many drugs are eliminated at least in part by the kidneys and must be dosed according to kidney function. A more detailed discussion of drug dosing in the presence of compromised kidney function is provided in Chapter 31, Dosing of Drugs in Kidney Failure. Thus, standard doses and dosing intervals of many agents in the presence of AKI may lead to increased drug exposure of the active drug or metabolites. It is important to recommend appropriate drug doses in

the presence of AKI. Some clinicians make dosing recommendations based on eGFR <15 mL/minute as an initial guide for drug therapy in a patient with AKI not receiving CRRT when no other information is available. Drugs not essential for care should be discontinued to avoid potential drug-induced toxicity in the presence of AKI.

Careful monitoring of clinical and biochemical surrogate parameters associated with efficacy and toxicity and therapeutic drug monitoring, especially for drugs with a narrow therapeutic index eliminated by the kidneys, are required. High-risk medications such as aminoglycosides, vancomycin, and piperacillin/tazobactam, and calcineurin inhibitors (eg, cyclosporine, tacrolimus), those with known nephrotoxicity, or other potential toxicities associated with supratherapeutic serum concentrations should be closely monitored. It is also important to note the volume of distribution (V_d) of drugs such as aminoglycosides, vancomycin, β-lactams (eg, most cephalosporins, carbapenems) is dramatically increased in the presence of AKI. Therefore, larger loading doses may need to be administered to avoid subtherapeutic responses from lower than desired serum concentrations.[27,110,111] For most drugs, clinically useful serum drug assays are unavailable. Therefore, trends in kidney function indices (eg, SCr and urine output) along with volume status and response to therapy should be utilized to guide drug dosing. Further dose adjustments may be necessary when KRT is provided.

Kidney Replacement Therapy

INDICATIONS

KRT is not always indicated in AKI. The A-E-I-O-U mnemonic is used to help remember the indications for KRT, where “A” stands for intractable refractory acidosis, “E” refers to electrolyte abnormalities, specifically potassium with EKG changes, “I” refers to ingestion of toxins such as salicylates and ethylene glycol, “O” stands for fluid overload causing pulmonary edema, and “U” refers to symptomatic uremia with confusion, platelet dysfunction and severe bleed, and

seizures. Particularly in the hospitalized patient, these may be considered emergency indications to proceed with KRT.

TIMING

The timing of KRT initiation for AKI without these emergency indications has been more controversial. A landmark trial, the STandard versus accelerated initiation of renal-replacement therapy in acute kidney injury (STARRT-AKI), found no difference in 90-day mortality when comparing an early approach to KRT with a more conservative "watch and wait" approach.[112] KRT also has risks that must be weighed in the decision to initiate KRT, including acute risks such as hypotension, arrhythmias, and vascular access placement complications, as well as long-term considerations including an increased risk of kidney failure and the need for KRT chronically.

MODALITIES

KRT utilized for AKI can be divided into either intermittent hemodialysis (IHD) or CRRT.[3] CRRT runs continuously over 24 hours as opposed to IHD that may last a few hours. Extended daily dialysis (EDD) or sustained low-efficiency dialysis (SLED) or prolonged intermittent KRT are alternatives to both CRRT and IHD. These are typically done daily over 6 to 12 hours using a traditional IHD machine. CRRT may be preferred in patients who are hemodynamically unstable or requiring vasopressor support. Over the years, several CRRT modalities have been developed to treat patients with AKI. Not all CRRT are alike[113]; many variations exist and include modalities such as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), continuous venovenous hemodiafiltration (CVVHDF), slow continuous ultrafiltration (SCUF), and continuous venovenous high-flux hemodialysis (CVVHFD). The decision to use one modality over another is most often decided by resources available, institutional guidelines, or the nephrologist's experience and comfort level.[37,113]

Refer to Chapter 30, Dialysis Treatment for Chronic Kidney Failure for a complete overview of peritoneal dialysis (PD) and IHD.

PRINCIPLES OF SOLUTES AND WATER REMOVAL IN CONTINUOUS RENAL REPLACEMENT THERAPY

CRRT treatments are currently performed using a double-lumen catheter as vascular access, with a venovenous technique, whereby the blood driven from a vein returns to the same vein after being purified in an external circuit/filter. This process generates an ultrafiltrate or an effluent that is pumped out of the body (**Fig. 29-4**). Solutes and water transport occur through a semipermeable membrane in the external circuit via three different mechanisms: diffusion, convection, and membrane adsorption.[113] The effluent rate in CRRT is often referred to as the *dose* of CRRT. A typical CRRT prescription for AKI will be 20 to 25 mL/kg/hour effluent volume[7] and is important to consider in evaluation of drug dosing.[114]

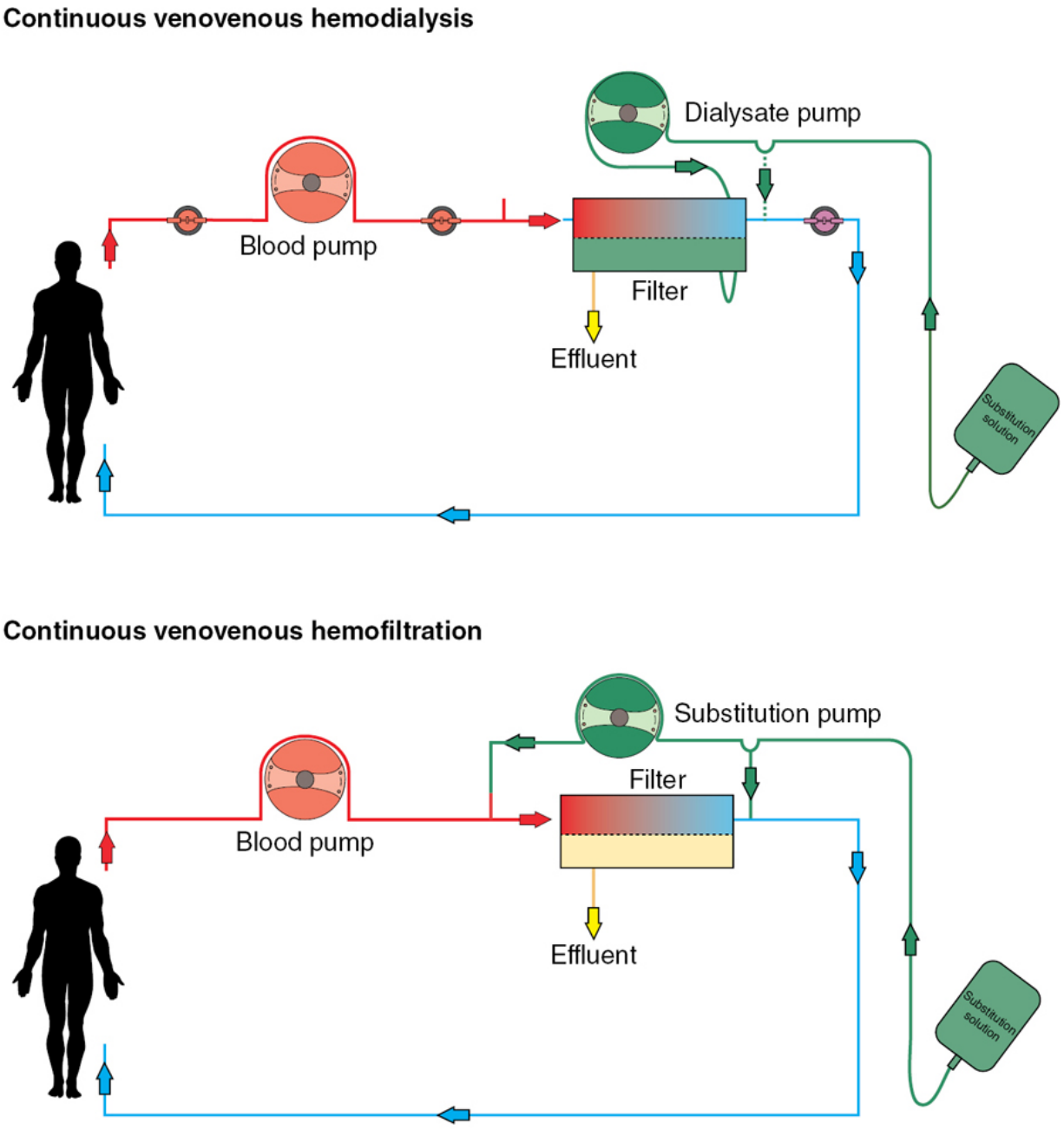


Figure 29-4 Continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHD) modalities of continuous renal replacement therapy (CRRT).

Continuous Venovenous Hemofiltration and Convection

CVVH uses convection for solute transport. In convection, water is pushed through the membrane using hydrostatic pressure. As the water passes through the membrane, it drags toxins and other

wastes. This process is referred to as *solvent drag*, and is effective in removing molecules that are <15,000 Da. In addition, solute removal by convection is influenced by ultrafiltration rates, protein binding, and blood solute concentration. The ability of molecules to pass through a membrane by convection is termed *sieving coefficient* (SC). The SC ranges from 0 to 1 with an SC of 1 representing free movement, whereas an SC of 0 represents no movement across the membrane. The effluent rate in CVVH is the ultrafiltration rate.[113–115]

Continuous Venovenous Hemodialysis and Diffusion

CVVHD uses diffusion for solute transport. Diffusion is the movement of solutes from an area of higher solute concentration to an area of lower concentration (dialysate). A concentration gradient is produced by running an electrolyte solution (known as *dialysis fluid* with a flow rate of 17–40 mL/minute) countercurrent to the flow of blood. The rate of diffusion of a solute is also inversely related to its molecular radius. Low-weight molecules (<500 Da) will diffuse faster than do higher MW ones. The effluent rate in CVVHD is the dialysate rate.[113,114]

Continuous Venovenous High-Flux Hemodialysis and Hemodiafiltration

CVVHDF combines convection and diffusion, which can enhance solute and water removal rates. The effluent flow rate is the sum of the ultrafiltrate and dialysate.[113]

Slow Continuous Ultrafiltration

SCUF is another type of KRT used for volume overload in patients needing fluid removal without the need for removal of metabolic waste products such as BUN or other toxins. The removal of fluid occurs via ultrafiltration.[113]

COMPLICATIONS OF CONTINUOUS RENAL REPLACEMENT THERAPY

CRRT has many complications that should be considered in the benefit–risk analysis before initiation of and for continuation of therapy.[3,115] **Table 29-7** lists encountered complications with CRRT. Owing to the slower blood flow rate used in CRRT, blood remains in contact with an exogenous catheter for prolonged periods of time, which predisposes to clotting that would impact functioning of the filter or dialyzer. The preferred anticoagulation in CRRT is often regional citrate (ie, within the extracorporeal circuit only), but systemic unfractionated heparin continuous infusion may also be used.[7] When regional citrate is used, it is important to monitor serum ionized calcium levels to prevent hypocalcemia induced by the formation of the citrate–calcium complex, which is behind the anticoagulant effect of the regional citrate. Ionized calcium is an important cofactor in the anticoagulation cascade. By complexing with calcium, citrate reduced circulating ionized calcium available to form a blood clot.[113,115]

Table 29-7
Complications of Continuous Renal Replacement Therapy

Vascular Access Malfunction	Circuit/Filter Clotting	Venous Thrombosis
Air embolism	Hypothermia	Bleeding
Hemolysis	Thrombocytopenia	Hypotension
Arrhythmias	Infection	Acidemia and electrolytes abnormalities (hypernatremia, hypokalemia, hypophosphatemia, hypocalcemia, hypomagnesemia)
Allergic reactions to hemodialyzer/hemofilter	Suboptimal medications dosing, especially antimicrobials	Nutritional deficiencies

Reprinted from Tandukar S, Palevsky PM. Continuous renal replacement therapy: who, when, why, and how. *Chest*. 2019;155(3):626–638. © 2019 The American College of Chest Physicians. With permission.

ESTIMATING DRUG REMOVAL

CASE 29-9, QUESTION 2: Are there ways to calculate drug removal in CRRT modalities?

Recent reviews provide an excellent background on dosing drugs in patients receiving CRRT.[7,110,114,116–118] The principles for drug removal in hemofiltration are basically identical with those for removal in hemodialysis. Drug removal during CRRT may occur by convection, diffusion, and adsorption. Convection and diffusion have the greatest influence on drug removal. Drug removal is inversely proportional to the percentage of drug that is protein bound. If a drug is >80% plasma protein bound, little will be removed. This principle holds true for convection and diffusion. Ultrafiltration rates and dialysis flow rates (UFRs/DFRs) also affect drug clearance. Because CRRT uses highly permeable membranes, the MW of most drugs has little impact on overall clearance. During convection, clearance of an unbound drug can be dramatic because CVVH can easily remove compounds with MW <15,000 Da. The impact of MW on drug removal during CVVHD is greater than the impact seen during CVVH. Solute clearance during CVVHD is dependent on diffusion, and given that diffusion is inversely proportional to MW, the greatest impact is seen with drugs having an MW <500 Da. Many drugs have low MW, and hence CVVHD can impact their removal significantly. Clearance of unbound drugs during CVVH can be dramatic, and dose adjustments are required to prevent underdosing. Drug dosing can be difficult in patients receiving these therapies, especially in those who are undergoing both dialysis and hemofiltration modalities (ie, CVVHDF).

Given the complexity of dosing in CRRT, pharmacists should use specific CRRT dosing modifications derived from primary or tertiary references. Extrapolating dose adjustments from IHD/PD literature is

not considered appropriate. Drug references such as “Demystifying Drug Dosing in Renal Dysfunction” provide useful guidelines in a concise tabular format.[119]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138. (7)

Massicotte A. Contrast medium-induced nephropathy: strategies for prevention. *Pharmacotherapy*. 2008;28:1140–1150. (85)

Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80:1122–1137. (110)

Rahman M. Acute kidney injury: a guide to diagnosis and management. *Am Fam Physician.* 2012;86:631–639. (23)

Ronco C, Bellomo R, Kellum JA. Acute kidney injury. *Lancet*. 2019;394(10212):1949–1964. (1)

Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int.* 2015;87:62–73. (4)

Key Website

KDIGO Clinical Practice Guideline for Acute Kidney Injury. http://www.kidney-international.org

COMPLETE REFERENCES CHAPTER 29 ACUTE KIDNEY INJURY

1. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. *Lancet*. 2019;394(10212):1949–1964.
2. Lewington AJ, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int*. 2013;84(3):457–467.
3. Tandukar S, Palevsky PM. Continuous renal replacement therapy: who, when, why, and how. *Chest*. 2019;155(3):626–638.
4. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int*. 2015;87(1):62–73.
5. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014;371(1):58–66.
6. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13(4):241–257.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
8. Waikar SS, Liu KD, Chertow GM. The incidence and prognostic significance of acute kidney injury. *Curr Opin Nephrol Hypertens*. 2007;16(3):227–236.
9. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol*. 2013;8(9):1482–1493.
10. Case J, Khan S, Khalid R, Khan A. Epidemiology of acute kidney injury in the intensive care unit. *Crit Care Res Pract*. 2013;2013:479730.
11. Bagshaw SM, Uchino S, Bellomo R, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clin J Am Soc Nephrol*. 2007;2(3):431–439.
12. Bagshaw SM, George C, Bellomo R, Committee ADM. Early acute kidney injury and sepsis: a multicentre evaluation. *Crit Care*. 2008;12(2):R47.
13. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005;294(7):813–818.
14. Cruz DN, Bolgan I, Perazella MA, et al. North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury (NEiPHROS-AKI): targeting the problem with the RIFLE Criteria. *Clin J Am Soc Nephrol*. 2007;2(3):418–425.
15. Griffin BR, Liu KD, Teixeira JP. Critical care nephrology: Core Curriculum 2020. *Am J Kidney Dis*. 2020;75(3):435–452.
16. Emmett L, Tollitt J, McCorkindale S, Sinha S, Poulikakos D. The evidence of acute kidney injury in the community and for primary care interventions.

Nephron. 2017;136(3):202–210.
17. Hazara AM, Elgaali M, Naudeer S, Holding S, Bhandari S. The use of automated electronic alerts in studying short-term outcomes associated with community-acquired acute kidney injury. *Nephron*. 2017;135(3):181–188.
18. Mesropian PD, Othersen J, Mason D, Wang J, Asif A, Mathew RO. Community-acquired acute kidney injury: a challenge and opportunity for primary care in kidney health. *Nephrology (Carlton)*. 2016;21(9):729–735.
19. Talabani B, Zouwail S, Pyart RD, Meran S, Riley SG, Phillips AO. Epidemiology and outcome of community-acquired acute kidney injury. *Nephrology (Carlton)*. 2014;19(5):282–287.
20. Huang L, Xue C, Kuai J, et al. Clinical characteristics and outcomes of community-acquired versus hospital-acquired acute kidney injury: a meta-analysis. *Kidney Blood Press Res*. 2019;44(5):879–896.
21. Selby NM, Kolhe NV, McIntyre CW, et al. Defining the cause of death in hospitalised patients with acute kidney injury. *PLoS One*. 2012;7(11):e48580.
22. Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. *Am J Respir Crit Care Med*. 2014;189(9):1075–1081.
23. Rahman M, Shad F, Smith MC. Acute kidney injury: a guide to diagnosis and management. *Am Fam Physician*. 2012;86(7):631–639.
24. Hilton R. Acute renal failure. *BMJ*. 2006;333(7572):786–790.
25. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. *Compr Physiol*. 2012;2(2):1303–1353.
26. Taber SS, Mueller BA. Drug-associated renal dysfunction. *Crit Care Clin*. 2006;22(2):357–374.
27. Perazella MA. Drug use and nephrotoxicity in the intensive care unit. *Kidney Int*. 2012;81(12):1172–1178.
28. Bouchard J, Macedo E, Soroko S, et al. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. *Nephrol Dial Transplant*. 2010;25(1):102–107.
29. Beben T, Rifkin DE. GFR estimating equations and liver disease. *Adv Chronic Kidney Dis*. 2015;22(5):337–342.
30. Herget-Rosenthal S, Marggraf G, Hüsing J, et al. Early detection of acute renal failure by serum cystatin C. *Kidney Int*. 2004;66(3):1115–1122.
31. Deng Y, Chi R, Chen S, et al. Evaluation of clinically available renal biomarkers in critically ill adults: a prospective multicenter observational study. *Crit Care*. 2017;21(1):46.
32. Eknoyan G, Lameire N, Eckardt K, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;3(1):5–14.
33. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. *Clin Biochem Rev*. 2016;37(2):85–98.

34. Srisawat N, Kellum JA. The role of biomarkers in acute kidney injury. *Crit Care Clin*. 2020;36(1):125–140.
35. Vaidya VS, Ramirez V, Ichimura T, Bobadilla NA, Bonventre JV. Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury. *Am J Physiol Renal Physiol*. 2006;290(2):F517–F529.
36. NEPHROCHECK® Test Kit. Package Insert. San Diego, CA: Astute Medical, Inc.;2020.
37. Moore PK, Hsu RK, Liu KD. Management of acute kidney injury: Core Curriculum 2018. *Am J Kidney Dis*. 2018;72(1):136–148.
38. Huang J, Li J, Lyu Y, Miao Q, Pu K. Molecular optical imaging probes for early diagnosis of drug-induced acute kidney injury. *Nat Mater*. 2019;18(10):1133–1143.
39. Duff S, Murray PT. Defining early recovery of acute kidney injury. *Clin J Am Soc Nephrol*. 2020;15(9):1358–1360.
40. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med*. 2011;364(19):1844–1854.
41. Palmer BF, Clegg DJ. The use of selected urine chemistries in the diagnosis of kidney disorders. *Clin J Am Soc Nephrol*. 2019;14(2):306–316.
42. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care*. 2016;20(1):299.
43. Makris K, Spanou L. Acute kidney injury: diagnostic approaches and controversies. *Clin Biochem Rev*. 2016;37(4):153–175.
44. Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. The comparative benefits of the fractional excretion of urea and sodium in various azotemic oliguric states. *Nephron Clin Pract*. 2010;114(2):c145–c150.
45. Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int*. 2002;62(6):2223–2229.
46. Chittineni H, Miyawaki N, Gulipelli S, Fishbane S. Risk for acute renal failure in patients hospitalized for decompensated congestive heart failure. *Am J Nephrol*. 2007;27(1):55–62.
47. Loboz KK, Shenfield GM. Drug combinations and impaired renal function—the ‘triple whammy’. *Br J Clin Pharmacol*. 2005;59(2):239–243.
48. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ*. 2013;346:e8525.
49. Schneider V, Lévesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: a population-based, nested case-control analysis. *Am J Epidemiol*. 2006;164(9):881–889.

50. Lafrance JP, Miller DR. Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. *Pharmacoepidemiol Drug Saf*. 2009;18(10):923–931.
51. Winkelmayer WC, Waikar SS, Mogun H, Solomon DH. Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. *Am J Med*. 2008;121(12):1092–1098.
52. Gradman AH. Evolving understanding of the renin-angiotensin-aldosterone system: pathophysiology and targets for therapeutic intervention. *Am Heart J*. 2009;157(6 suppl):S1–S6.
53. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS. Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation*. 2001;104(16):1985–1991.
54. Mangrum AJ, Bakris GL. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in chronic renal disease: safety issues. *Semin Nephrol*. 2004;24(2):168–175.
55. Fenoglio R, Sciascia S, Baldovino S, Roccatello D. Acute kidney injury associated with glomerular diseases. *Curr Opin Crit Care*. 2019;25(6):573–579.
56. Fisher M, Neugarten J, Bellin E, et al. AKI in hospitalized patients with and without COVID-19: a comparison study. *J Am Soc Nephrol*. 2020;31(9):2145–2157.
57. Peleg Y, Kudose S, D'Agati V, et al. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. *Kidney Int Rep*. 2020;5(6):940–945.
58. Sharma Y, Nasr SH, Larsen CP, Kemper A, Ormsby AH, Williamson SR. COVID-19-associated collapsing focal segmental glomerulosclerosis: a report of 2 cases. *Kidney Med*. 2020;2(4):493–497.
59. Xia P, Wen Y, Duan Y, et al. Clinicopathological features and outcomes of acute kidney injury in critically ill COVID-19 with prolonged disease course: a retrospective cohort. *J Am Soc Nephrol*. 2020;31(9):2205–2221.
60. Farouk SS, Fiaccadori E, Cravedi P, Campbell KN. COVID-19 and the kidney: what we think we know so far and what we don't. *J Nephrol*. 2020;33(6):1213–1218.
61. Rodríguez-Iturbe B, Batsford S. Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. *Kidney Int*. 2007;71(11):1094–1104.
62. Rodriguez-Iturbe B, Musser JM. The current state of poststreptococcal glomerulonephritis. *J Am Soc Nephrol*. 2008;19(10):1855–1864.
63. Levy JB, Hammad T, Coulthart A, Dougan T, Pusey CD. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int*. 2004;66(4):1535–1540.

64. Papiris SA, Manali ED, Kalomenidis I, Kapotsis GE, Karakatsani A, Roussos C. Bench-to-bedside review: pulmonary-renal syndromes—an update for the intensivist. *Crit Care*. 2007;11(3):213.
65. Couser WG. Glomerulonephritis. *Lancet*. 1999;353(9163):1509–1515.
66. Berden AE, Jones RB, Erasmus DD, et al. Tubular lesions predict renal outcome in antineutrophil cytoplasmic antibody-associated glomerulonephritis after rituximab therapy. *J Am Soc Nephrol*. 2012;23(2):313–321.
67. Greenhall GH, Salama AD. What is new in the management of rapidly progressive glomerulonephritis? *Clin Kidney J*. 2015;8(2):143–150.
68. Davis A, Gooch I. Best evidence topic report. The use of loop diuretics in acute renal failure in critically ill patients to reduce mortality, maintain renal function, or avoid the requirements for renal support. *Emerg Med J*. 2006;23(7):569–570.
69. Bagshaw SM, Delaney A, Haase M, Ghali WA, Bellomo R. Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. *Crit Care Resusc*. 2007;9(1):60–68.
70. Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. *Crit Care*. 2013;17(5):R207.
71. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med*. 2005;142(7):510–524.
72. Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med*. 2018;46(6):949–957.
73. Isovue® (Iopamidol Injection). Package insert. Monroe Township, NJ: Bracco Diagnostics, Inc.; 2019.
74. Lakhal K, Ehrmann S, Chaari A, et al. Acute Kidney Injury Network definition of contrast-induced nephropathy in the critically ill: incidence and outcome. *J Crit Care*. 2011;26(6):593–599.
75. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol*. 2008;51(15):1419–1428.
76. Davenport MS, Perazella MA, Yee J, et al. Use of intravenous iodinated contrast media in patients with kidney disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. *Radiology*. 2020;294(3):660–668.
77. Lameire NH. Contrast-induced nephropathy—prevention and risk reduction. *Nephrol Dial Transplant*. 2006;21(6):i11–i23.
78. Heyman SN, Rosen S, Khamaisi M, Idée JM, Rosenberger C. Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. *Invest Radiol*. 2010;45(4):188–195.

79. Marenzi G, Assanelli E, Campodonico J, et al. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med*. 2009;150(3):170–177.
80. Aqeel I, Garcha AS, Rudnick MR. Relative nephrotoxicity of different contrast media. *Interv Cardiol Clin*. 2014;3(3):349–356.
81. Idée JM, Fretellier N, Robic C, Corot C. The role of gadolinium chelates in the mechanism of nephrogenic systemic fibrosis: a critical update. *Crit Rev Toxicol*. 2014;44(10):895–913.
82. Deo A, Fogel M, Cowper SE. Nephrogenic systemic fibrosis: a population study examining the relationship of disease development to gadolinium exposure. *Clin J Am Soc Nephrol*. 2007;2(2):264–267.
83. U.S. Food and Drug Administration website. FDA drug safety communication: new warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. Published December 2010. Accessed October 10, 2020. www.fda.gov/Drugs/DrugSafety/ucm223966.htm
84. Solomon R, Dauerman HL. Contrast-induced acute kidney injury. *Circulation*. 2010;122(23):2451–2455.
85. Massicotte A. Contrast medium-induced nephropathy: strategies for prevention. *Pharmacotherapy*. 2008;28(9):1140–1150.
86. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. *Kidney Int*. 2004;65(4):1366–1374.
87. Romano G, Briguori C, Quintavalle C, et al. Contrast agents and renal cell apoptosis. *Eur Heart J*. 2008;29(20):2569–2576.
88. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med*. 2018;378(7):603–614.
89. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435–1486.
90. Mingeot-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. *Antimicrob Agents Chemother*. 1999;43(5):1003–1012.
91. Barclay ML, Kirkpatrick CM, Begg EJ. Once daily aminoglycoside therapy. Is it less toxic than multiple daily doses and how should it be monitored? *Clin Pharmacokinet*. 1999;36(2):89–98.
92. Swan SK. Aminoglycoside nephrotoxicity. *Semin Nephrol*. 1997;17(1):27–33.
93. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother*. 1999;43(7):1549–1555.
94. Praga M, González E. Acute interstitial nephritis. *Kidney Int*. 2010;77(11):956–961.

95. Ray S, Delaney M, Muller AF. Proton pump inhibitors and acute interstitial nephritis. *BMJ*. 2010;341:c4412.
96. Blank ML, Parkin L, Paul C, Herbison P. A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. *Kidney Int*. 2014;86(4):837–844.
97. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician*. 2008;78(6):743–750.
98. Rossert J. Drug-induced acute interstitial nephritis. *Kidney Int*. 2001;60(2):804–817.
99. Sierra F, Suarez M, Rey M, Vela MF. Systematic review: proton pump inhibitor-associated acute interstitial nephritis. *Aliment Pharmacol Ther*. 2007;26(4):545–553.
100. Goldfarb DS. In the clinic. Nephrolithiasis. *Ann Intern Med*. 2009;151(3):Itc2.
101. Brent J. Current management of ethylene glycol poisoning. *Drugs*. 2001;61(7):979–988.
102. Frassetto L, Kohlstadt I. Treatment and prevention of kidney stones: an update. *Am Fam Physician*. 2011;84(11):1234–1242.
103. Manthey DE, Teichman J. Nephrolithiasis. *Emerg Med Clin North Am*. 2001;19(3):633–654, viii.
104. Hoorn EJ, Ellison DH. Diuretic resistance. *Am J Kidney Dis*. 2017;69(1):136–142.
105. Kitsios GD, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. *J Crit Care*. 2014;29(2):253–259.
106. Asare K. Management of loop diuretic resistance in the intensive care unit. *Am J Health Syst Pharm*. 2009;66(18):1635–1640.
107. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ. Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol*. 2007;3(3):138–153.
108. Balcı C, Uzun Ö, Arıcı M, Hayran SA, Yüce D, Ünal S. Nephrotoxicity of piperacillin/tazobactam combined with vancomycin: should it be a concern? *Int J Antimicrob Agents*. 2018;52(2):180–184.
109. Rivosecchi RM, Kellum JA, Dasta JF, et al. Drug class combination-associated acute kidney injury. *Ann Pharmacother*. 2016;50(11):953–972.
110. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80(11):1122–1137.
111. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med*. 2009;37(3):840–851.
112. Bagshaw SM, Wald R, Adhikari NKJ, et al. Timing of initiation of renal-replacement therapy in acute kidney injury. *N Engl J Med*. 2020;383(3):240–251.

113. Cerdá J, Ronco C. Modalities of continuous renal replacement therapy: technical and clinical considerations. *Semin Dial*. 2009;22(2):114–122.
114. Hoff BM, Maker JH, Dager WE, Heintz BH. Antibiotic dosing for critically ill adult patients receiving intermittent hemodialysis, prolonged intermittent renal replacement therapy, and continuous renal replacement therapy: an update. *Ann Pharmacother*. 2020;54(1):43–55.
115. Karkar A, Ronco C. Prescription of CRRT: a pathway to optimize therapy. *Ann Intensive Care*. 2020;10(1):32.
116. Churchwell MD, Mueller BA. Drug dosing during continuous renal replacement therapy. *Semin Dial*. 2009;22(2):185–188.
117. Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy*. 2009;29(5):562–577.
118. Schetz M. Drug dosing in continuous renal replacement therapy: general rules. *Curr Opin Crit Care*. 2007;13(6):645–651.
119. Nemecek BD, Hammond DA. *Demystifying Drug Dosing in Renal Dysfunction*. American Society of Health-System Pharmacists; 2019.

30

Dialysis Treatment for Chronic Kidney Failure

Michelle M. Richardson

CORE PRINCIPLES		CHAPTER CASES
1	Chronic kidney failure requiring dialysis occurs when there is progressive loss of kidney function over months to years resulting in the kidneys being unable to remove wastes; concentrate urine; maintain acid–base homeostasis; and regulate fluid, electrolytes, and other important bodily functions.	**Case 30-1 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
2	Hemodialysis (HD) is a process that attempts to mimic the excretory function of a healthy kidney by facilitating removal of excess water and solutes from the body, both of which accumulate as a result of inadequate kidney function. Solutes from the blood are removed through diffusion and convection. Accumulated water is removed by ultrafiltration.	**Case 30-1 (Questions 1, 6), Figures 30-1, 30-2**
3	HD requires vascular access. Different types of vascular access include arteriovenous (AV) fistula, AV graft, and double-lumen or tunneled central venous catheter (CVC). In most circumstances, an AV fistula is preferred because of its longer survival rates and lower rates of complications.	**Case 30-1 (Question 1), Figures 30-3–30-5**
4	Dialysate is an electrolyte-containing solution that is used to facilitate removal of metabolic end products and excess electrolytes and fluid. The concentration of electrolytes in dialysate can be manipulated to control the diffusion of electrolytes from the blood into the dialysate to maintain homeostasis. Metabolic acidosis is controlled with the addition of a buffering agent such as bicarbonate or lactate to the dialysate.	**Case 30-1 (Question 1), Table 30-1**

CORE PRINCIPLES		CHAPTER CASES
5	The ability of a dialyzer membrane to remove solutes and water is determined by its composition, pore size, surface area, and configuration.	**Case 30-1 (Question 2)**
6	Anticoagulation is necessary during HD to prevent clotting in the extracorporeal circuit. Several methods have been used to provide adequate anticoagulation without increasing the risk of bleeding.	**Case 30-1 (Questions 3–5)**
7	Complications can arise during HD. The most common complications are hypotension and skeletal muscle cramping, along with vascular access thrombosis and infection.	**Case 30-1 (Questions 7–10)** **Case 30-2 (Question 1)**
8	The process of peritoneal dialysis (PD) is similar to that of HD; in this process, however, the peritoneal membrane covering the abdominal contents serves as an endogenous dialysis membrane and the vasculature embedded in the peritoneum serves as the blood supply. Fluid is removed by manipulating the dextrose concentration in dialysate to control the osmotic pressure gradient for fluid and electrolyte removal.	**Case 30-3 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
9	Continuous ambulatory peritoneal dialysis (CAPD) is performed by instilling sterile dialysate into the peritoneal cavity through a surgically placed catheter. The dialysate dwells within the peritoneal cavity for a prescribed amount of time (typically 4–8 hours) and is drained and replaced with fresh dialysate. This process of fill, dwell, and drain is performed three to four times during the day, with a longer dwell overnight.	**Case 30-3 (Question 1), Figure 30-6**
10	Preventing PD catheter exit-site infections (and decreasing the risk of peritonitis) is the primary goal of exit-site care. Routine care consists of hand cleansing with antiseptics or antibacterial soap before touching the exit site, washing the exit site daily with antibacterial soap, and using antimicrobial creams around the exit site.	**Case 30-3 (Question 2)**
11	The most significant complication among patients receiving PD is peritonitis. Empiric antibiotics can be administered by the intraperitoneal (IP) route and must cover both gram-positive and gram-negative organisms.	**Case 30-3 (Questions 3–7)**

CORE PRINCIPLES		CHAPTER CASES
12	Other medications can be administered IP. Heparin can be added to dialysate to prevent fibrin clots from forming and obstructing outflow from the peritoneal cavity. Regular insulin can be administered IP to patients with diabetes mellitus.	**Case 30-3 (Questions 5, 6, 8)**

INTRODUCTION

Kidney failure affects all aspects of bodily functioning. Failed kidneys can no longer remove wastes, maintain acid–base homeostasis, regulate fluid and electrolytes, and perform endocrine functions.

Without replacing the excretory function of a healthy kidney, patients with kidney failure will die from metabolic complications. The international organization, Kidney Disease: Improving Global Outcomes (KDIGO) published findings from a consensus conference proposing standardized nomenclature to describe kidney function and disease. Kidney failure is defined as having an estimated glomerular filtration rate (eGFR) <15 mL/minute/1.73 m^2 for ≥3 months or requiring dialysis. Dialysis and kidney transplantation (discussed in Chapter 34, Kidney and Liver Transplantation) as treatments for kidney failure are called *kidney replacement therapy* (KRT).[1] Hemodialysis (HD) and peritoneal dialysis (PD) are the two types of dialysis. Both remove metabolic waste products and water from the blood and use dialysate to create concentration gradients to promote diffusion across a semipermeable membrane. Choosing which type of dialysis to use takes into account many factors including clinical, lifestyle, patient preference, and local availability and expertise.

Despite improved survival over the past two decades, all-cause mortality rates are higher for patients treated with dialysis compared to the general population, and highest in the second and third months after starting dialysis. In 2018, adjusted mortality rates for those 66 to 74 years of age receiving dialysis were >10-fold higher for males and >15-fold higher for females compared to those not receiving dialysis.[2] Annually, the United States Renal Data System (USRDS) publishes an extensive report on KRT using data from the Centers for Medicare and Medicaid Services. In 2017, the most recent year complete data are available, 124,500 incident, or new to KRT, patients started dialysis. The incidence rate has been stable since 2015. In contrast, since 2006 the standardized prevalence rate (ie, the total number of patients treated with dialysis in 1 year), has continued to increase, and in the setting of stable incident patient rates, is likely due to improved care and decreased mortality. In 2017, there were 746,557 prevalent, or the number of existing, patients receiving dialysis in the United States.[2]

According to the USRDS, kidney failure requiring dialysis disproportionally affects patients 45 years of age and older; diabetes and hypertension continue to be the leading causes of kidney failure; and racial and ethnic differences persist. A gap in care also exists. Nearly one-third of patients treated by dialysis receive little or no care for their kidney disease before starting dialysis.[2]

A large percentage (86.9%) of incident, or new, patients choose HD as their initial type of KRT. Only 10.1% of patients start KRT with PD and even fewer patients (2.9%) have preemptive kidney transplantation before starting dialysis. Taking the entire dialysis patient population as a whole (ie, prevalent patients), 62.7% of patients receive HD and 7.1% of patients receive PD. However, the number of patients with functioning kidney transplants increases dramatically to 29.9%.[2] Increasing home dialysis and early kidney transplants is a goal of the Advancing American Kidney Health initiative through the U.S. Department of Health and Human Services. By 2025, the initiative aims for 80% of new patients to receive home dialysis or a kidney transplant.[3] Improved care for patients with chronic kidney disease (CKD) before their needing KRT

may help achieve the goal of more patients treated with home-based therapies and receiving preemptive or early kidney transplants.

The increasing numbers of patients with kidney failure treated with dialysis, racial and ethnic disparities, and the high mortality rate necessitate practitioners who understand the processes and therapies for these patients. This chapter addresses the fundamental clinical aspects of both HD and PD, including principles, common treatment complications, and management. Throughout the chapter, reference is made, when appropriate, to kidney-specific clinical practice guidelines. There are three main sources of KRT-specific clinical guidelines. International clinical practice guidelines and consensus conferences on controversial topics are sponsored by KDIGO. The U.S. National Kidney Foundation supports the Kidney Disease Outcomes Quality Initiative (KDOQI), and the International Society of Peritoneal Dialysis (ISPD) produces clinical guidelines specific to PD.

GENERAL PRINCIPLES OF DIALYSIS

There are no hard and fast rules or specific eGFR for starting dialysis. The decision to begin dialysis is based on the patient's clinical status and symptoms. Severe or intractable hyperkalemia or metabolic acidosis and intolerable uremic symptoms such as nausea, pruritus, malaise, or diuretic-resistant fluid overload are generally considered indications to start dialysis. Once the eGFR is ~10 to 15 mL/minute/1.73 m^2, most patients will exhibit signs and symptoms of kidney failure. However, there is significant variation in the level of eGFR at which patients experience clinical status decline or symptoms.[4,5]

Dialysis is a process that facilitates the removal of wastes, along with excess water, metabolic end products, and electrolytes from the body that accumulate because of inadequate kidney function. The process of dialysis requires three components—a semipermeable membrane, dialysate, and blood flow. The principles of diffusion,

convection, and ultrafiltration interplay with the three components in an attempt to replicate normal kidney excretory function.

Diffusion

Diffusion describes a property of the movement of substances (or solutes) from an environment of higher concentration across a semipermeable membrane to an environment of lower concentration. During dialysis, solutes in the blood component (the area of higher concentrations of electrolytes that have accumulated because of kidney failure) flow along one side of the semipermeable membrane (ie, the dialyzer in HD or the peritoneal lining in PD), into an area of lower electrolyte concentrations, known as the dialysate compartment. Dialysate is a physiologic solution with controlled concentrations of electrolytes and for PD, dextrose. In HD, the semipermeable membrane is a thin layer of synthetic material that contains pores that allow for diffusion to occur. The rate and amount of diffusion is dependent on the difference in solute concentrations between the blood and dialysate compartments, the molecular weight (MW) of the solute (ie, size), and characteristics of the semipermeable membrane including surface area, thickness, and porosity.[6] Regardless of the semipermeable membrane characteristics, the clearance of solutes by diffusion decreases rapidly as the MW of the solute increases. Smaller solutes and fluid pass through, but the semipermeable membrane blocks the passage of larger molecules such as red blood cells and large proteins. This mimics the filtering process that takes place in the kidneys when the blood enters the kidneys, and the larger molecules are separated from the smaller ones in the glomerulus.

Once the concentration of a solute nears equilibrium on both sides of the semipermeable membrane, the net rate of diffusion becomes zero because the rate of movement from the blood to the dialysate compartment is equal to the rate of movement from the dialysate to the blood compartment.[6]

The process of diffusion applies in both directions across the semipermeable membrane. The movement of unwanted electrolytes and metabolic end products in the blood into the dialysate for removal can be promoted by low concentrations of those solutes in the dialysate. Conversely, solutes with higher concentrations in the dialysate can move across the semipermeable membrane into the blood to achieve increased concentrations in the blood compartment.[6]

Convection

Convection also contributes to solute clearance during the process of dialysis. Convection is the mass transport of solutes along with the fluid in which they are dissolved, across a semipermeable membrane. The rate of convection depends on the pressure difference across the semipermeable membrane and the pore size of the membrane. In contrast to diffusion, the process of convection is not dependent on concentration gradient and is relatively independent of solute size. Solute clearance by convection tends to be more constant over a wide range of MWs; and convection contributes more to clearance of larger molecules than it does to smaller molecules, which are preferentially removed by difffusion.[6]

Ultrafiltration

Ultrafiltration is a process that aids in removing excess water only and maintaining extracellular volume at desired levels. The ultrafiltration rate for HD is determined by the transmembrane pressure—the difference in hydrostatic pressure between the blood and dialysate compartments across the dialyzer membrane. It is controlled through settings on the HD machine. The principle of ultrafiltration in PD is discussed in more detail later in the chapter.

Clearance Based on Molecular Weight and Dose of Hemodialysis

The clearance or removal of a substance during dialysis is dependent on its molecular MW, water solubility, and protein binding. To a lesser degree, molecule shape and charge also influence clearance. Historically, the categories of small MW (<500 Da), medium (500–2000 or 3000 Da), or large (>3000 Da) molecules were used to describe MW and the ability of a molecule to be cleared by dialysis.[7] Conventional dialyzer membranes only removed small MW substances. Small MW substances are primarily cleared by diffusion, and the amount of clearance is dependent on blood flow rates. Urea, a 60 Da molecule, is the typical example of a small MW substance and is used to define the dose of dialysis because of its small size, ease of measurement of the blood urea nitrogen (BUN) concentration, and its ability to diffuse readily across dialysis membranes.[6,8]

Advanced dialyzer membrane technology removes larger MW substances, and the traditional categories have been updated. The European Uremic Toxin Work Group kept the small MW classification, but created two new categories: protein-bound solutes and middle molecules. Middle molecules are defined as toxins in the MW range of 500 to 60,000 Da.[9,10]

HD efficiently removes small MW molecules. Molecules such as β_2-microglobulin (11,800 Da), are removed less efficiently by HD, as are low MW compounds that are protein bound, have a large volume of distribution, or are located intracellularly. Larger MW substances (>15,000 Da) are not removed by conventional dialyzer membranes, but newer dialyzer membranes may remove them to a significant degree.[11] Current dialyzer technology does not efficiently remove protein-bound substances.[10,12]

The amount, or dose, of dialysis is determined by calculating the clearance of the small MW molecule urea. The equation used is Kt/V, where K is the clearance of urea in mL/minute; t is the time in minutes of the dialysis treatment; and V is the volume of distribution

of urea. This equation assumes that urea clearance is constant throughout the treatment time. The volume of distribution of urea (V) is equal to total body water, which can be determined by either estimating it from a patient's weight (60% for males or 55% for females) or calculated using the Watson formula.[6,7] The urea reduction ratio (URR), expressed as a percentage, can also be used to assess the removal of urea during dialysis. URR = $(C_{pre} - C_{post})/C_{pre} \times 100$, where C_{pre} is the BUN before the start of dialysis and C_{post} is the BUN at the completion of dialysis.[6] However, KDOQI clinical guidelines state that URR should be phased out because its measurement is error prone, and more precise measures are preferred.[5]

HEMODIALYSIS

During HD, one large-bore needle or catheter is placed into a special vascular access site, an arteriovenous (AV) fistula or graft or central venous catheter (CVC). Tubing connecting the vascular access site to the dialyzer delivers the patient's blood containing metabolic end-products, excessive electrolytes, and water to the dialyzer. This side of the system is referred to as the *arterial line* or *arterial side*. Blood delivered to the arterial side comes into contact with the semipermeable membrane inside the dialyzer cartridge that has dialysate flowing on the other side of the membrane. Inside the dialyzer cartridge is where diffusion, convection, and ultrafiltration occur. The HD machine can be programmed to adjust the rate of ultrafiltration. Cleaned blood exits the dialyzer cartridge and is returned to the patient's access site through tubing attached to a second large-bore needle or catheter, referred to as the *venous line* or *venous side*. The tubing on both sides of the system and the dialyzer is called the *extracorporeal circuit*.[4,6] **Figure 30-1** illustrates a patient receiving HD, and **Figure 30-2** describes the extracorporeal system in HD.

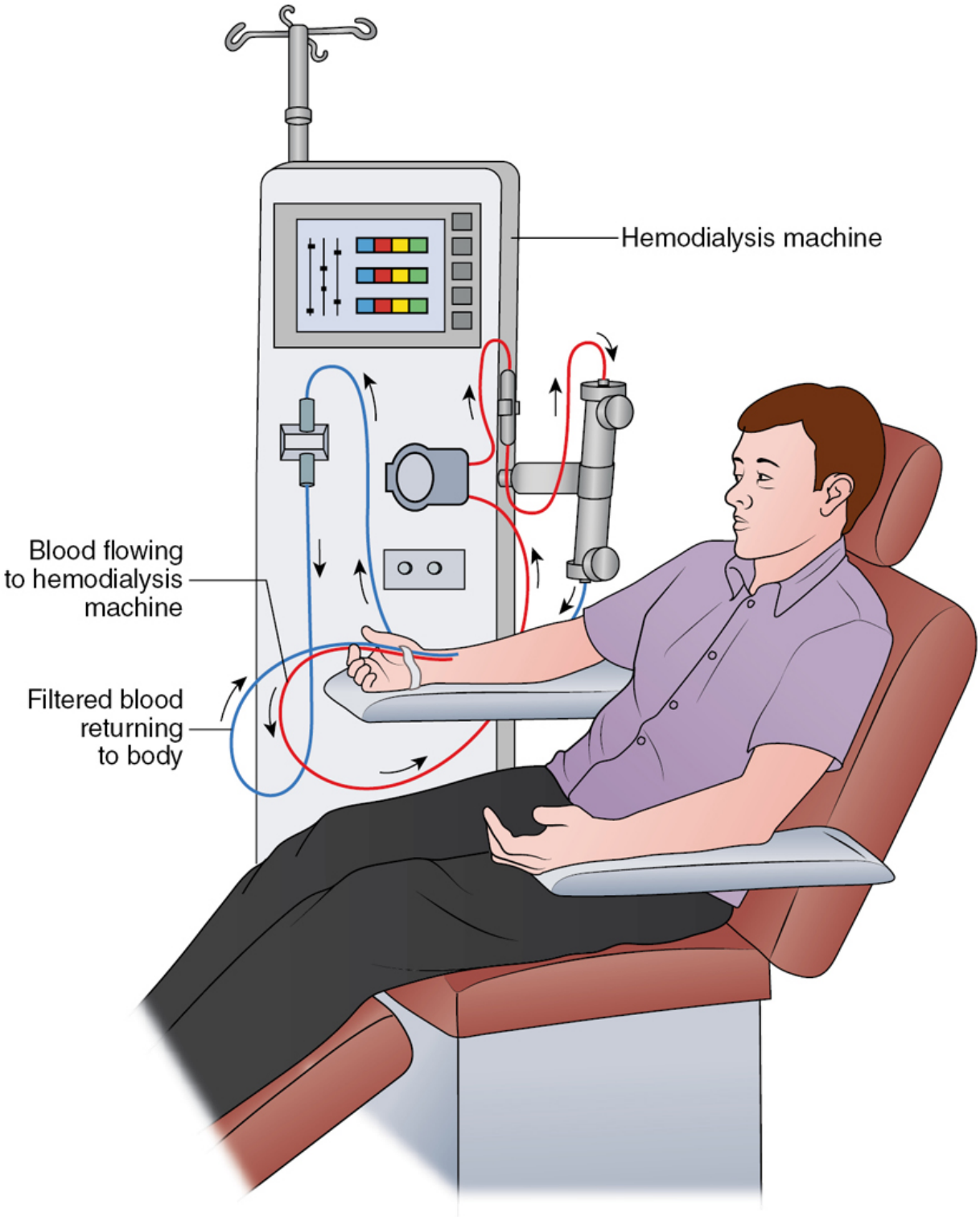


Figure 30-1 Person receiving HD using an arteriovenous (AV) access in an outpatient hemodialysis (HD) facility. Needles, inserted into the AV access in the patient's forearm, are attached to the extracorporeal circuit through which blood flows from the patient to

the HD machine where it is filtered through the dialyzer (vertical cylinder between the machine's right-hand side and the patient) and then returned through venous-side tubing into the patient's AV access. (Redrawn with permission from Patient education: Hemodialysis (The Basics). In: Post TW, ed. UpToDate. UpToDate. Accessed March 15, 2021. © 2022 UpToDate, Inc and its affiliates and/or licensors. All rights reserved.)

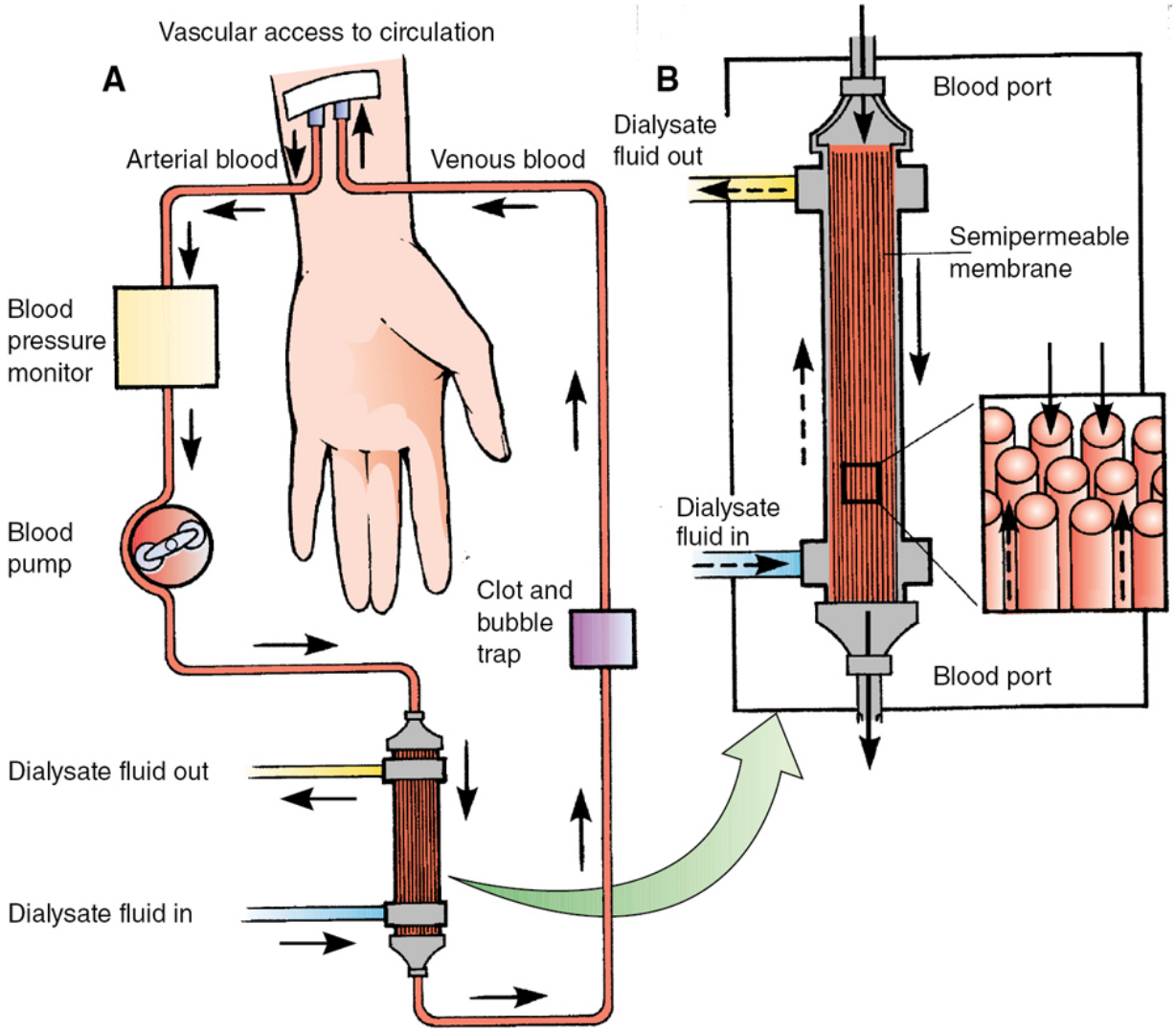


Figure 30-2 Hemodialysis system. A, Blood from an artery is pumped into (B), a dialyzer where it flows through tubes made of semisynthetic polymers, which act as the semipermeable membrane (inset). The dialysate, which has the same chemical composition as the blood except for urea and waste products, flows around the

outside of the semisynthetic polymer tubes. The waste products in the blood diffuse through the semipermeable membrane into the dialysate. (Adapted with permission from Smeltzer SC, Bare BG. *Textbook of Medical-Surgical Nursing*. 9th ed. Lippincott Williams & Wilkins; 2000.)

Hemodialysis Vascular Access

CASE 30-1

QUESTION 1: R.W., a 70-year-old male with stage G4 CKD as a result of long-term, poorly controlled hypertension, presents to clinic for reassessment of his kidney function. He is 68 inches (172.72 cm) tall and weighs 154 pounds (69.85 kg). He first saw a nephrologist 6 months ago. He reports feeling tired, but otherwise does not describe any other symptoms. His wife reports that he is not eating very much even when she prepares his favorite foods. On physical examination, his blood pressure is slightly elevated but not different from previous readings, his lungs are clear, and moderate ankle edema is noted. Since his last visit to the kidney clinic 3 months ago, his eGFR has decreased from 17 to 13 mL/minute/1.73 m^2 (now stage G5), and the BUN concentration has increased to 89 mg/dL. The serum potassium is 4.8 mEq/L, and serum bicarbonate (HCO_3) is 17 mEq/L.

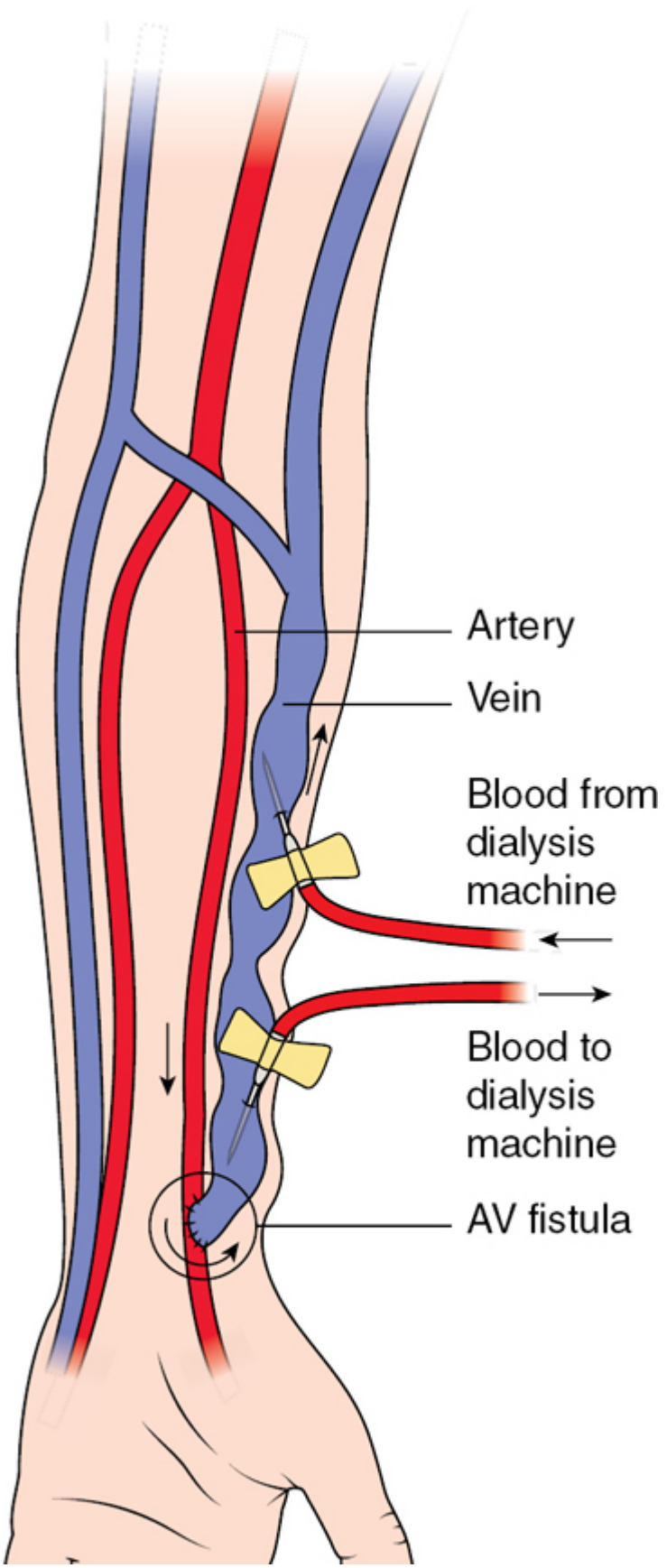
R.W. has participated in a dialysis modality patient education program. He informs his nephrologist today that he has selected HD as his choice of dialysis. Given the findings from today's clinic visit, it is anticipated that he will need to begin HD within the next 1 to 3 months.

The next step to prepare for the start of HD is to have a permanent vascular access surgically created. An AV vascular access site is necessary to achieve a sufficient blood flow rate for HD.

What are the options for permanent vascular access in R.W.? Which one is the best option for R.W.?

Ideal vascular access for HD allows high blood flow rates necessary for chronic HD, endures frequent cannulation, and has a low rate of complications (eg, infection, stenosis, thrombosis, aneurysm, and limb ischemia). The typical prescribed blood flow rates of 400 to 500 mL/minute from the patient's venous access through the extracorporeal circuit cannot be achieved through routine venipuncture that uses small-bore needles.[6] The achieved

blood flow rate is dependent on the type of AV vascular access and the cardiovascular status of the patient. Some patients are not able to tolerate high blood flow rates, and a lower blood flow rate may be necessary. Three main types of vascular access that allow for high blood flow rates are available for patients treated with HD: (a) AV fistula, (b) AV graft, and (c) CVC. The access types are illustrated in **Figures 30-3**, **30-4**, and **30-5**, respectively:


Artery
Vein
Blood from dialysis machine
Blood to dialysis machine
AV fistula

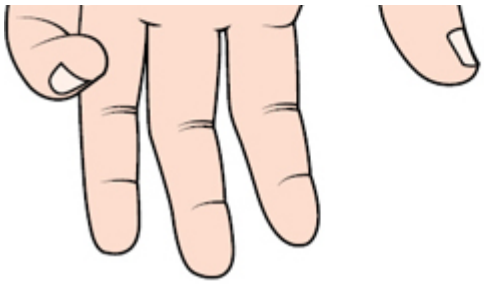
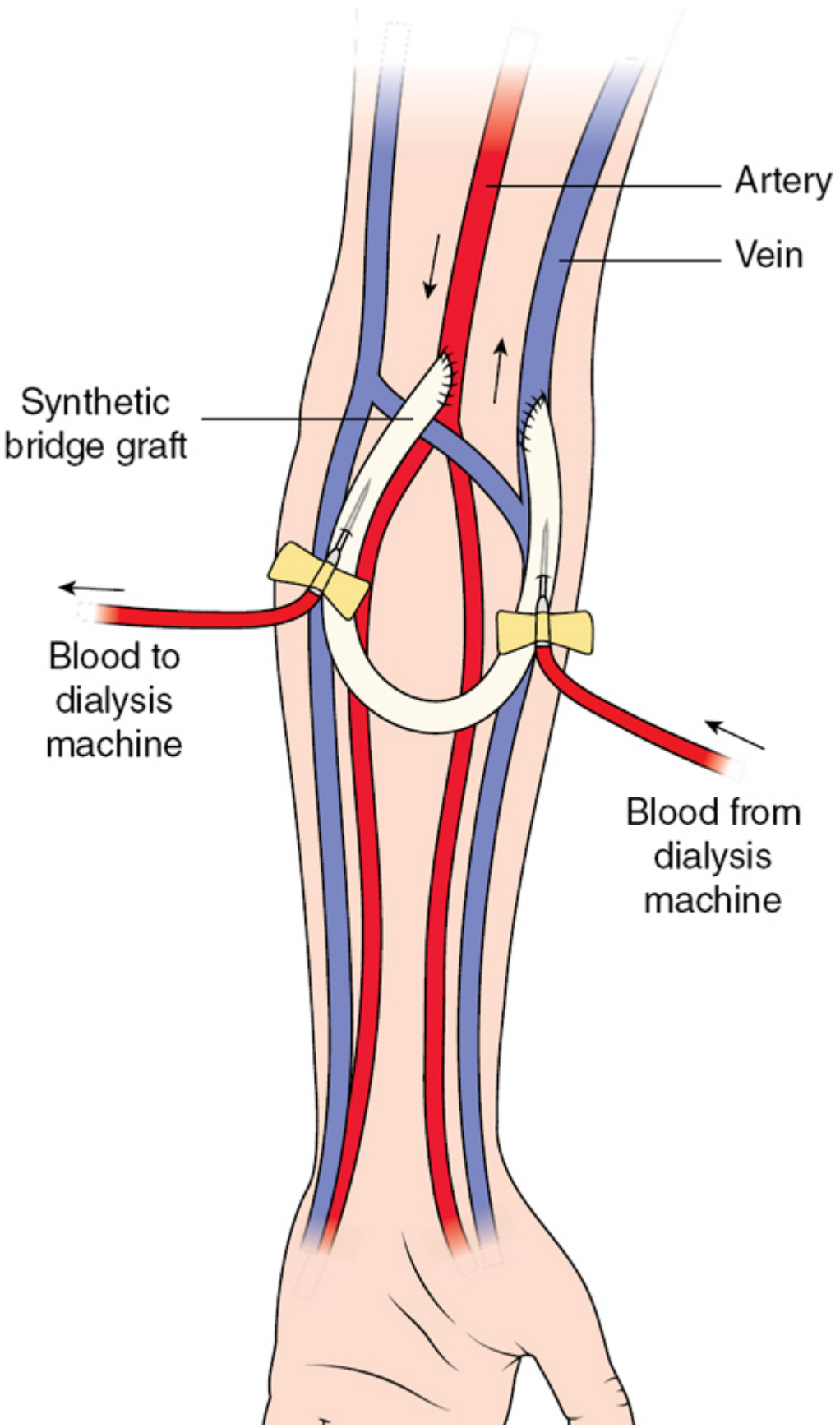


Figure 30-3 AV fistula vascular access for hemodialysis (HD). AV fistula in a person's arm. An AV fistula is placed surgically under the skin, typically in the forearm, but it can be done in the upper arm. The surgeon connects an artery directly to a vein. During HD, two large-bore needles are put into the access to remove and return blood to the body. AV, arteriovenous. (Redrawn with permission from Patient education: Hemodialysis (The Basics). In: Post TW, ed. *UpToDate*. UpToDate. Accessed March 15, 2021. © 2022 UpToDate, Inc and its affiliates and/or licensors. All rights reserved.)


Artery
Vein
Synthetic bridge graft
Blood to dialysis machine
Blood from dialysis machine

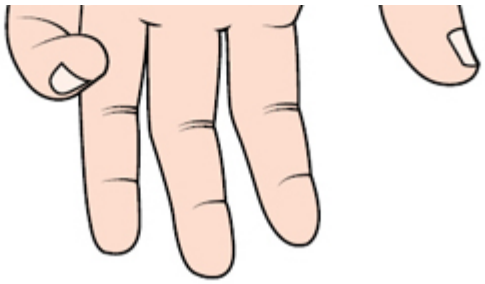


Figure 30-4 Arteriovenous (AV) graft vascular access for hemodialysis (HD). An AV graft is placed surgically under the skin, typically in the forearm, but it can be done in the upper arm. The surgeon uses a flexible rubber tube to connect an artery and a vein. During HD, two large-bore needles are put into the access to remove and return blood to the body. (Redrawn with permission from Patient education: Hemodialysis (The Basics). In: Post TW, ed. *UpToDate*. UpToDate. Accessed March 15, 2021. © 2022 UpToDate, Inc and its affiliates and/or licensors. All rights reserved.)

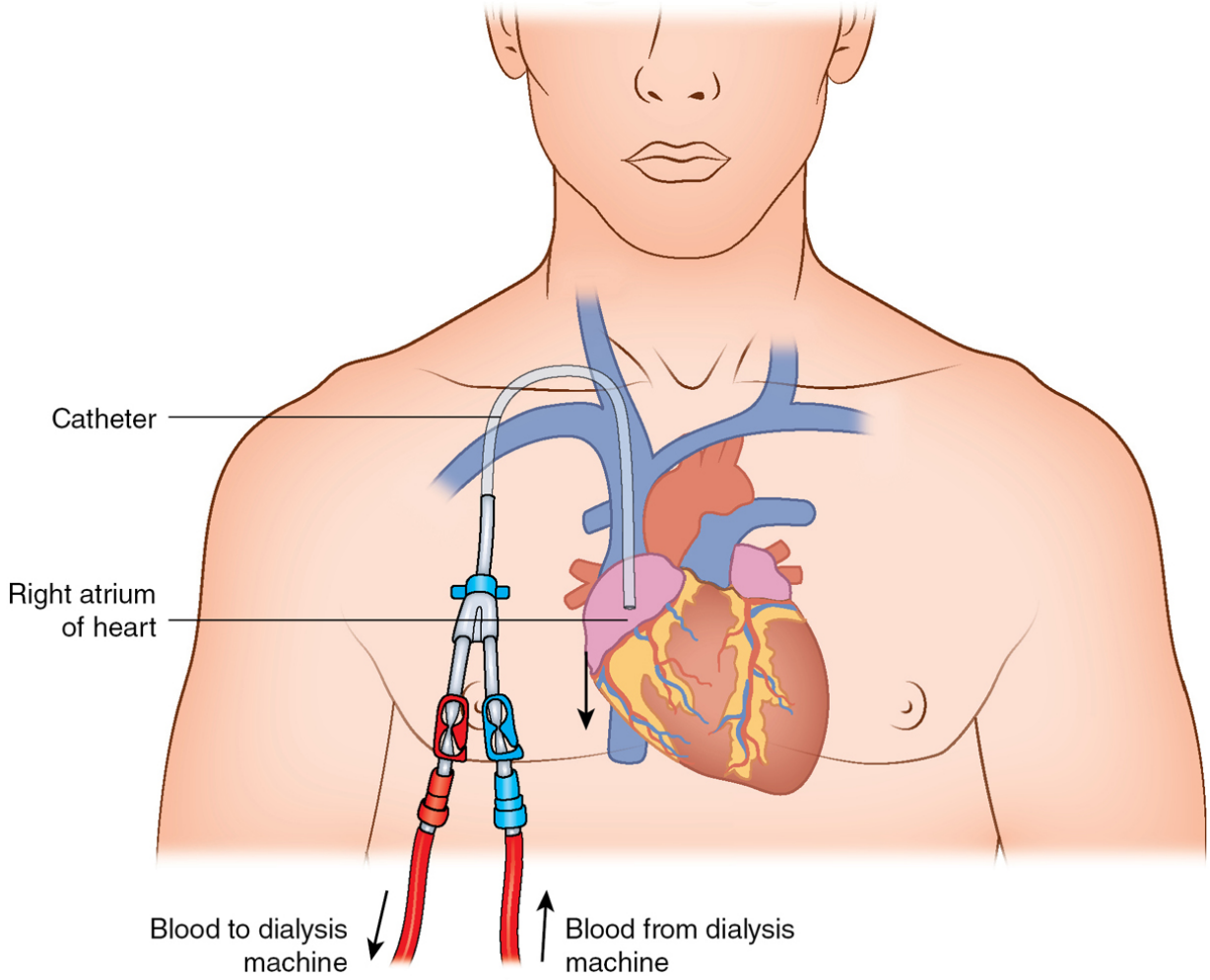


Figure 30-5 Central venous catheter access for hemodialysis (HD). A central venous catheter (CVC) is a thin, flexible tube. One end is inserted into a large vein, usually in the neck. The other end stays outside the body. During HD, the end outside of the body is connected to tubing from the dialysis machine. Note that the red clamp and cap indicate the "arterial side" of blood leaving the patient's body going toward the HD machine, and the blue clamp and cap indicate the "venous side," where blood exits the dialyzer and is returning to the patient. (Redrawn with permission from Patient education: Hemodialysis (The Basics). In: Post TW, ed. *UpToDate*. UpToDate. Accessed March 15, 2021. © 2022 UpToDate, Inc and its affiliates and/or licensors. All rights reserved.)

1. AV fistula made by surgically joining a patient's native (ie, their own) artery and a vein
2. AV graft, a soft tube made of polytetrafluoroethylene surgically placed as a connection between the patient's artery and a vein
3. CVC, a double-lumen, tunneled, cuffed catheter placed in a large vein, usually in the neck[6,13]

In the 2019 USRDS Annual Data Report, HD was initiated in 80% of patients utilizing a tunneled, double-lumen, or cuffed catheter. Patients of Hispanic ethnicity and those who are Black/African American have the lowest proportion of AV fistulas used at HD initiation. For prevalent patients, the rate of AV fistula use is 63%, and this has grown over the past decade.[2]

ARTERIOVENOUS FISTULA

An AV fistula is created surgically by subcutaneous anastomosis of a patient's native (ie, own) artery to an adjacent vein most often in the nondominant forearm, but it can also be placed in the upper arm. Once created, an AV fistula ideally requires 4 to 8 weeks to mature before it can be used for HD. During this time, the anastomosed vein is subject to arterial pressures and vein hypertrophies. This physiologic change allows the vein to tolerate frequent cannulation. In most circumstances, an AV fistula is the preferred access type because of lower infection and thrombosis rates. However, an AV fistula may be difficult to create in patients with poor vasculature, such as in elderly patients or those with diabetes, atherosclerosis, or small vessels.[4,6,13]

ARTERIOVENOUS GRAFT

An AV graft is considered a suitable alternative to an AV fistula. An AV graft is also created surgically, but the connection between the artery and vein is made by inserting a soft synthetic (eg, polytetrafluoroethylene) tube to create a connection between an artery and a vein. Like AV fistulas, AV grafts are placed in the nondominant forearm, but can also be placed in the upper arm. AV

grafts take less time to mature and can be used soon after surgery, although waiting 2 weeks to use an AV graft allows for healing at the anastomosis sites and prolongs patency. AV fistulas fail to mature at a higher rate than do AV grafts; however, AV grafts may require more interventions per year (eg, elective angioplasty, thrombectomy, or surgical revision) to maintain their long-term patency for HD.[6,13] The AV graft tubing is made of synthetic material, which may predispose patients to infection or thrombosis at higher rates than does an AV fistula. The synthetic tubing acts as a foreign body to which a biofilm created by some bacteria (eg, *Staphylococcus epidermidis, S. aureus*, and *Pseudomonas aeruginosa*) attaches. The presence of the biofilm encapsulates bacteria, allows it to adhere more tightly to the graft, and limits the effectiveness of host defenses and antibiotic therapy.[14,15] The pathophysiology of AV graft thrombosis is complex and includes endothelial and smooth muscle cell injury, proinflammatory mediators, inflammation, oxidative stress, endothelial dysfunction, and genetics.[16]

CENTRAL VENOUS CATHETERS

CVCs are often used at the start of HD either because patients did not have nephrology care before starting dialysis or their AV access is not yet ready to use.[6] The 2019 KDOQI Vascular Access Clinical Guidelines consider short-term catheter use to be reasonable in situations where HD is necessary but permanent access is not available for use (eg, AV fistula or graft did not mature, acute kidney transplant rejection). Long-term use of CVCs is discouraged as permanent vascular access because of much higher rates of infection and occlusion. The KDOQI clinical guidelines only consider long-term catheter use to be reasonable in situations of last resort (eg, multiple prior failed AV accesses with no other available options, limited life expectancy).[13]

Given the options of AV fistula, AV graft, or CVC, R.W.'s best option for permanent HD vascular access is a surgically created AV fistula in the forearm of his nondominant arm. His current symptoms are tolerable. His physical examination and laboratory results do not

suggest an urgent need to start HD. There is ample time for an AV fistula to be surgically created and mature, which will minimize the risk of needing a CVC to begin urgent HD. Also, his past medical history does not suggest he would be likely to have poor vasculature (eg, diabetes), hence an AV fistula is the preferred option for R.W.

Hemodialysis Dialysate

HD dialysate is a physiologic solution typically containing standardized concentrations of electrolytes that can be individualized, if necessary. The dialysate prescription takes into account goals of therapy, expected solute clearance needs, volume removal needs, and logistical concerns. Bicarbonate is added as a buffer to the dialysate to control metabolic acidosis associated with kidney failure that occurs because the daily obligatory load of acid cannot be excreted.[6]

The HD dialysate concentrate is diluted with tap water that is specially treated for HD use. Dialysate water does not require sterilization because the dialyzer membrane separates the blood and dialysate compartments. Nevertheless, pyrogen reactions may occur and a greater risk may exist with certain types of semipermeable membranes such as high-flux membranes because of their increased pore size.[7]

The prescribed dialysate is prepared in the HD machine by proportioning a dialysate concentrate that typically contains those elements listed in **Table 30-1** and mixing with specially treated tap water. Before HD starts, the dialysate is heated to 98.60 °F (37 °C) to maintain the patient's body temperature and avoid hemolysis, which can occur with excessive heating. Dialysate is also deaerated under vacuum to remove dissolved air.[7] The patient-specific dialysate prescription takes into account serum electrolyte concentrations. For example, if the patient is hyperkalemic, the dialysate will contain a lower potassium concentration to facilitate diffusion of potassium from the blood compartment into the dialysate compartment. Conversely, a patient with a normal serum potassium

concentration at the start of HD will have the potassium concentration of the dialysate set at a normal physiologic concentration to minimize movement of potassium across the dialyzer membrane. If the concentration of a solute is higher in the dialysate than in the blood, the net movement will be into the blood, not out.

Table 30-1
Electrolyte Composition of Hemodialysis and CAPD Dialysate

Solute	Hemodialysis (mEq/L)	CAPD (mEq/L)
Sodium	135–145	132
Potassium	0–4	0
Calcium	2.5–3.5	3.5
Magnesium	0.5–1.0	1.5
Chloride	100–124	102
Bicarbonate	30–38	NA
Lactate	NA	35
pH	7.1–7.3	5.5

CAPD, continuous ambulatory peritoneal dialysis; NA, not applicable.

Dialysate flow rates through the dialyzer cartridge are also prescribed and generally range from 500 to 800 mL/minute depending on the type of dialyzer used. Higher dialysate flow rates promote increased clearance of solutes, especially small MW solutes. Dialysate flows in a countercurrent direction to blood flow, which enhances the process of diffusion.[6]

Hemodialysis Dialyzer Membrane Characteristics

The type of semipermeable dialyzer membrane used in HD is also prescribed. Dialyzers are characterized by many factors including membrane composition, size, and ability to clear solutes. The dialyzer membrane can be made of cellulose, substituted cellulose, or synthetic polymer, each of which differs in its degree of

biocompatibility. KDOQI clinical guidelines recommend biocompatible membranes composed of synthetic polymers.[5] Cellulose dialyzers are not recommended in the United States because contact between blood and the dialyzer surface activates the complement pathway, producing proinflammatory cytokines that cause hypotension, fever, and platelet activation.[17]

Dialyzer membranes also differ in fiber configuration, surface area, pore size, and thickness. The most common fiber configuration is the hollow fiber dialyzer in which thousands of hollow fibers run the length of the dialyzer. Blood flows through the hollow fibers and dialysate flows in the space surrounding the fibers within the dialyzer cartridge. The result is an extremely large surface area for diffusion, which is functionally maximized by blood and dialysate moving in opposite directions (ie, countercurrent flow) so that equilibrium is never fully achieved.

The efficiency of a dialyzer membrane is also related to its surface area. High-efficiency membranes have a large surface area and are able to clear larger quantities of small molecules, such as urea.

Most dialyzer membranes have pore sizes that allow small molecules to freely diffuse. Blood flow through the dialyzer is the rate-limiting step in removing small molecules. Large molecules do not easily cross through the pores of conventional dialyzer membranes and their clearance is less dependent on blood flow. Instead, the overall removal of larger molecules depends more on membrane characteristics (ie, thickness and pore size) and the duration of dialysis.[7] Dialyzer membrane pore size and the ability to remove β_2-microglobulin (MW 11,800 Da) is used to characterize membranes as low flux or high flux. High-flux dialyzer membranes have larger pores and are able to clear larger sized molecules (eg, middle molecules such as β_2-microglobulin and leptin) and drugs (eg, vancomycin or vitamin B_{12}) more effectively than do low-flux membranes. High-flux dialysis membranes are defined as providing β_2-microglobulin clearances of at least 20 mL/minute[5] and have a higher rate of water transfer (ultrafiltration coefficient) compared to that of low-flux membranes. In most developed countries, high-flux

membranes are the standard of care. The 2015 update to the KDOQI Clinical Guidelines on Hemodialysis Adequacy recommended either low- or high-flux biocompatible HD membranes, with preference given to high-flux membranes depending on local considerations.[5]

Relative in vitro and in vivo solute clearance rates varying MW substances are typically printed on the outside of the dialyzer or in the dialyzer specification chart (ie, the equivalent of the package insert).

Drug clearance during HD is also influenced by dialyzer membrane surface area and pore size. The amount of drug actually removed by dialysis is dependent on dialyzer and drug characteristics along with blood and dialysate flow rates. Just like with other solutes, larger dialyzer surface area and pore size promote increased removal of drugs. The MW, protein binding (ie, amount of unbound drug available to cross the dialyzer membrane), and volume of distribution (V_d) (ie, a large V_d indicates that a relatively small amount of drug will be available in the blood for dialysis) of a drug will also determine the amount of drug removed.[18] Small MW drugs (ie, MW <500 Da such as aminoglycosides and theophylline) are likely to be significantly cleared by all dialyzer membranes. Drugs with an MW between 500 and 1000 Da (eg, morphine and digoxin) are less well dialyzed by conventional dialyzer membranes, but may be cleared by high-flux membranes. For digoxin, its large V_d and relatively low serum concentrations make it less likely to be significantly removed. Even if digoxin in the blood is effectively removed, tissue-bound drug will quickly redistribute back into the blood as soon as HD is completed, a phenomenon known as *rebound*. Finally, large MW drugs, such as vancomycin, are poorly dialyzed by conventional dialyzer membranes, but are well known to be significantly removed with high-flux dialyzer membranes.[19] Refer to Chapter 31, Dosing of Drugs in Kidney Failure, for a more detailed explanation. Many tertiary resources are available to aid in drug dosing in patients receiving dialysis. One recently published source is “Demystifying

Drug Dosing in Renal Dysfunction"[20] published by the American Society of Health-System Pharmacists, and an older publication by the American College of Physicians is *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*.[21]

Case 30-1, Question 2: R.W.'s nephrologist is developing an initial outpatient HD plan. Using a polysulfone, high-flux, high-efficiency dialyzer, he will be dialyzed 2 hours on Monday, 3 hours on Wednesday, and 4 hours on Friday for the first week of treatment. Blood flow rates and dialysate flow rates that week will be titrated upward based on R.W.'s tolerance of HD. Assuming a successful first week of HD, his routine schedule will be HD three times a week for 4 hours each treatment, using the same dialyzer with blood flow rate of 400 mL/minute and bicarbonate-containing dialysate with a flow rate of 500 mL/minute. What characteristics of the dialyzer membrane make it a good choice for R.W.? How will the success of R.W.'s HD treatment be determined?

The plan recommended by R.W.'s nephrologist is a typical start to HD to minimize complications discussed later in the chapter and allow patients to become accustomed to longer HD treatments.[8] In accordance with the KDOQI guidelines,[5] R.W.'s nephrologist is prescribing a biocompatible membrane made of polysulfone.

Advances in HD dialyzers have produced semipermeable membranes that have increased clearance of small molecules and also the ability to remove larger MW substances as compared to conventional dialyzers. High-efficiency dialyzers have increased clearance of urea and other small molecules, but their clearance of larger MW substances is variable. High-flux dialyzers, by definition, always have membrane pore sizes that allow clearance of larger MW molecules compared to conventional dialyzer membranes. They also have a higher ultrafiltration coefficient. High-efficiency and high-flux dialyzers are not mutually exclusive, and there is often overlap.[7] R.W. is being prescribed a high-efficiency, high-flux dialyzer, which means the dialyzer membrane has an increased urea clearance, and there are larger pores that will aid in removing larger sized solutes.

Once R.W. is stable on his HD schedule, KDOQI recommends assessing the amount of his dialysis or dose using the Kt/V equation. In accordance with KDOQI guidelines, the target Kt/V for patients

receiving HD three times weekly is 1.4 per HD treatment with a minimum acceptable *Kt*/*V* of 1.2 per treatment.[5] R.W.'s initial treatment goals also include adequately controlling or relieving his symptoms (fatigue and anorexia), achieving adequate fluid balance, and controlling blood pressure. Long-term goals include prolonging survival while achieving good quality of life.[7]

Anticoagulation for Hemodialysis

Case 30-1, Question 3: What is an appropriate anticoagulation regimen for R.W. when he initiates HD? Based on careful review of his past medical history, other than his recent surgery to place his AV fistula, he has no known bleeding risks. What are alternative anticoagulation regimens for patients at high risk for bleeding?

During HD, the patient's blood comes into contact with foreign surfaces in the extracorporeal circuit (ie, tubing, dialyzer) that immediately trigger the coagulation cascade, upregulate proinflammatory and procoagulant pathways, and activate coagulation factor XII and platelets.[17] Anticoagulation during HD is critical to inhibit these pathways and minimize the risk of thrombosis in the dialyzer. Dialyzer membrane clotting reduces surface area for diffusion, and clots in the circuit can cause blood loss because blood in the circuit cannot be returned to the patient via the venous side tubing. Anticoagulation goals in HD are to prevent clotting in the dialyzer, minimize the risk of bleeding, and avoid prolonged bleeding once the large-bore needles are removed from the AV fistula or graft at the end of HD.[22] Most commonly, HD anticoagulation consists of low doses of unfractionated heparin (UFH) by either intermittent bolus injections or an initial bolus followed by a continuous infusion. UFH has a rapid onset of action and short half-life. It is also affordable, reliable, reversible, and requires minimal dialysis staff intervention once an effective dose has been determined.[22] Modern HD delivery systems have incorporated heparin infusion devices that can be programmed to provide the desired infusion rate during HD.

Although not supported by extensive studies or standardized dosing protocols,[23] a common anticoagulation regimen is UFH 40 to 50 units/kg as an initial bolus immediately after vascular access cannulation followed by a continuous infusion of ~10 to 15 units/kg/hour. It is essential to wait 3 to 5 minutes between the initial bolus of UFH and the arrival of blood into the extracorporeal circuit to avoid clotting within the dialyzer.[22] Typically, most U.S. dialysis facilities rely on clinical signs and symptoms to monitor HD anticoagulation. Visual inspection of the circuit and/or the dialyzer and/or prolonged bleeding at the venipuncture sites at the end of HD are clinical clues that the anticoagulation therapy needs to be modified. It is uncommon to use laboratory parameters to monitor UFH during HD.[6,22]

In patients with AV fistulas or grafts, UFH should be discontinued 30 to 60 minutes before the end of HD to prevent excessive bleeding from the vascular access site. Patients with CVCs should receive UFH until the end of HD to minimize the risk of clotting at the tip of the catheter.[6,22]

Heparin-free HD is an alternative for patients who are at a moderate-to-high risk of bleeding or who are actively bleeding. This approach requires priming the HD circuit with UFH 2000 to 5000 units/L in normal saline to coat the extracorporeal surfaces.[22] The UFH-containing priming fluid is drained by filling the circuit with either the patient's blood or normal saline alone at the outset of HD. Next, the blood flow rate is set at 250 to 500 mL/minute if the patient tolerates it. During HD, the dialyzer is flushed with 25 to 30 mL of normal saline every 15 to 30 minutes to rinse away microclots that may have formed. The incidence of clotting with this approach is ~2% to 5%. This anticoagulation approach requires significant dialysis facility staff effort and close observation, which may not be ideal in certain outpatient settings.[22]

The regional administration of trisodium citrate through the arterial line is a potential alternative to UFH. Trisodium citrate binds free calcium, which is necessary for the coagulation process, and the calcium citrate complex is removed by dialysis. Based on serum calcium concentrations, a second infusion containing calcium

chloride is administered on the venous side to prevent hypocalcemia. A portion of the administered citrate is returned to the patient and is metabolized to bicarbonate, potentially leading to metabolic alkalosis. Hypernatremia is also a potential adverse effect. Regional citrate anticoagulation is technically difficult to administer and requires extensive monitoring to safely use. Therefore, it is reserved for patients who are at high risk for bleeding in whom other anticoagulation methods are not an option.[22] Trisodium citrate regional anticoagulation is rarely used in outpatient HD facilities, and is more commonly used in acutely ill, hospitalized patients requiring HD.[22]

Case 30-1, Question 4: R.W. is afraid to start HD, in particular the risk of bleeding has him very concerned. He talked about his fear of receiving UFH during HD with his long-time pharmacist in the outpatient general medicine clinic. As the pharmacist in the outpatient dialysis facility, you call R.W. to conduct a pre-HD medication history. During that call, he tells you that the pharmacist in his outpatient general medical clinic asked if low-molecular-weight heparins (LMWHs) are an alternative to prevent clotting during HD. What should you tell R.W. about the risk of bleeding with UFH and the role of LMWH in HD?

R.W. should be educated about UFH during HD and its risks. Typically, the UFH doses used during HD are relatively low. R.W. will be closely monitored during HD and any signs or symptoms of bleeding will be addressed by the trained dialysis staff. The effect of UFH can be reversed with protamine. In addition, UFH will be stopped 30 to 60 minutes before the end of the HD so that the anticoagulant effect will be gone by the time R.W. leaves the dialysis facility.

LMWHs are considered at least as effective and safe as UFH in HD. However, LMWH use in the United States is very limited because studies haven't shown superiority to UFH in HD-related bleeding. In addition, their effect is not completely reversible with protamine, and LMWHs are significantly more expensive than UFH. These reasons make LMWH a far less desirable alternative to UFH.[22] A meta-analysis comparing the efficacy of LMWH with UFH in patients undergoing either HD or hemofiltration found no

difference in the rate of thrombosis.[24] A second meta-analysis that focused on the safety of LMWH versus UFH found no significant difference in the primary outcome of minor and major bleeding.[25]

If used in patients with kidney failure, dose adjustments along with careful patient monitoring are necessary for LMWHs because they are eliminated by the kidneys. Patients on HD may exhibit greater sensitivity to LMWH effect compared to healthy volunteers.[26] Although LMWHs inhibit several factors (factor X_a, factor XII_a, and kallikrein), antifactor X_a activity is the only available laboratory monitoring parameter. The antifactor X_a test's clinical utility is unclear in this patient population because active heparin metabolites can accumulate and are not detected by the assay.[26–28]

Case 30-1, Question 5: Although it is unlikely that R.W. will develop heparin-induced thrombocytopenia (HIT), which anticoagulants are options for patients on HD who do develop HIT?

Up to 10% of patients on HD who are receiving UFH experience HIT.[29] Antithrombotic treatment guidelines for patients with HIT from the American Society of Hematology[30] and the American College of Chest Physicians[31] recommend immediately discontinuing all forms of UFH, including "heparin-free" dialysis, UFH flush, and LMWH in patients diagnosed with HIT. Both guidelines discuss the lack of high-quality evidence to guide non-UFH anticoagulant use in HD. There are no studies comparing one non-UFH anticoagulant to another in HD patients with HIT. The direct thrombin inhibitors argatroban and bivalirudin are the agents of choice.[32]

Several small studies show that argatroban is safe and effective in HD patients with HIT.[33–35] Argatroban is eliminated by the liver, and hence dosing adjustments are not required for patients receiving HD.[34] Approximately 20% of argatroban is removed during HD, but is not considered clinically significant to suggest dose adjustments.[34] A reported dosing regimen for argatroban is 2 μg/kg/hour continuous infusion with a goal-activated partial thromboplastin time (aPTT) of 1.5 to 3 times baseline.[32] Some regimens include an initial bolus

dose of 250 µg/kg or 20 mg at the start of HD followed by a continuous infusion.[35] In clinical practice, the actual doses needed for anticoagulation may be less than those used in studies.[35,36] Argatroban infusions are discontinued 1 hour before the end of the HD.[33]

Bivalirudin is also a safe and effective HD anticoagulant in patients with HIT.[29,32] Among the direct thrombin inhibitors, in patients without kidney function, it has the shortest half-life of 25 minutes. Appropriate dosing is still being evaluated,[29,37,38] but doses of 0.03 to 0.05 mg/kg/hour have been suggested.[32] Bivalirudin infusion should be stopped before the end of HD to prevent excessive bleeding from the AV site.

Any anticoagulation infusion regimen that requires complicated dosing changes or adjusting doses based on aPTT or other laboratory results may be technically difficult in an outpatient HD facility.

Fondaparinux, a heparinoid, has also been evaluated for HD anticoagulation in patients with HIT but is not recommended for several reasons. Fondaparinux is removed substantially by high-flux dialyzers, resulting in inadequate anticoagulation and increased risk of thrombosis.[39] Also, its half-life is significantly prolonged in patients with kidney failure and is contraindicated in patients with creatinine clearance <30 mL/minute. Lastly, fondaparinux does not have a U.S. Food and Drug Administration (FDA)-approved label for HD anticoagulation.[22,40]

Hemodialysis Process

Case 30-1, Question 6: R.W. visits the outpatient HD facility a week in advance of his expected HD treatment initiation date. What is actually going to happen during HD is among the questions he has about how the dialysis facility works?

Typically, patients receiving chronic, in-center HD are dialyzed for 3 to 4 hours, three times a week on either Monday, Wednesday,

Friday or Tuesday, Thursday, Saturday. Patients have an appointment time during the morning, middle, or evening shift on those set of days. Upon entry to the HD facility, patients are weighed, their blood pressure is taken, and then starts the process of access cannulation and being connected to the HD machine. During the HD treatment, the dialysis unit staff check on the patient routinely and automatic blood pressure measurements are taken at prescribed intervals. As HD ends, the patient's blood is flushed out of the extracorporeal circuit back into the body using normal saline, the large-bore needles are carefully removed, and compression dressings applied to the access site to promote clotting and prevent bleeding. Just before leaving the HD facility, patients are weighed again. The difference in weight from the start and end of HD is an estimate of the amount of fluid removed during HD. In the absence of kidney function, fluids ingested and produced through metabolic processes accumulate. Although patients generally are on fluid restriction, 1 to 5 L of fluid (translating into 2.20–10 pounds [1–5 kg] weight gain) can accumulate between HD treatments. The accumulated fluid must be removed during each HD treatment to avoid the complications of fluid overload.

Hemodialysis Complications

INTRADIALYTIC HYPOTENSION

Case 30-1, Question 7: R.W.'s prescribed target or dry weight at the end of HD is 152.12 pounds (69 kg). During his most recent HD, he complained of nausea and light-headedness 3 hours into his 4-hour treatment. His systolic blood pressure dropped from 135 mm Hg at the start of HD to 80 mm Hg measured shortly after he reported his symptoms. This was the first time R.W. experienced a symptomatic and significant drop in systolic blood pressure during HD. His postdialysis weight was 153.22 pounds (69.5 kg). What are the possible etiologies for his hypotension? How should R.W.'s symptoms and low blood pressure be managed?

In addition to solute removal, HD is used to maintain fluid balance in patients with kidney failure. Most patients will become anuric once

stabilized on HD and will need to limit fluid intake between HD treatments. In patients who are anuric, no appreciable amount of fluid ingested in between HD treatments is eliminated, and HD then becomes the primary way extracellular fluid volume is controlled. Patients on HD have an individualized prescribed target weight to be achieved at the end of HD that is thought to represent appropriate fluid balance. This target weight is referred to as the dry weight. Ending HD below the dry weight may result in the patient becoming symptomatic from extracellular volume depletion. Ending HD too much above the dry weight, the patient may be at risk for extracellular fluid overload. Achieving the desired dry weight is accomplished through the ultrafiltration prescription and adjusting the HD machine transmembrane pressure settings. The prescribed target weight at the end of HD for R.W. was 152.12 pounds (69 kg). R.W.'s signs and symptoms of hypotension 3 hours into today's HD suggest that too much fluid was being removed through ultrafiltration and that his prescribed dry weight is too low.

Although this was the first time R.W. experienced symptomatic hypotension during HD, it is important to monitor for intradialytic hypotension (IDH), which is a common complication related to HD. IDH is associated with increased morbidity such as vascular access thrombosis, inadequate dialysis dose, and mortality. Hypotension impairs end-organ perfusion and can lead to permanent damage. Multiple definitions of IDH exist, but a nadir systolic blood pressure drop <90 mm Hg for >30% of HD treatments strongly correlates with increased mortality.[41] The reported incidence of IDH is 10% to 30%, and even higher in patients with specific risk factors, such as autonomic dysfunction associated with diabetes or cardiac disease.[42] The pathogenesis of IDH is poorly understood. One proposed mechanism is excessive extracellular fluid removal from the vascular compartment at a rate exceeding mobilization of fluid from the interstitial space. As a consequence, patients with an inadequate hemodynamic response to intravascular volume depletion exhibit a decrease in blood pressure and related symptoms.[42] An ultrafiltration rate >10 mL/hour/kg is associated with a statistically significant higher odds of IDH and a statistically significant higher risk of

mortality.[43] Clinical symptoms of IDH include nausea and vomiting, dizziness, muscle cramping, and headache.[42] Increasing the patient's prescribed dry weight may be appropriate if the patient is volume depleted and symptomatic after HD, especially if the patient has lost lean body mass over time. Loss of lean body mass is common in the later stages of CKD, and may not be recognized because total body weight remains the same or increases owing to retained water not being effectively removed by the kidneys.

Other causes of IDH relate to increases in core body temperature. Sympathetic nervous system activity increases in response to ultrafiltration, leading to vasoconstriction of the dermal circulation and impaired heat dissipation. Increased central heat production can occur during the HD procedure. The increase in core body temperature can overcome peripheral vasoconstriction, resulting in hypotension. Excessive heating of dialysate can also produce vasodilation and resultant hypotension. Cooling of the dialysate to slightly below body temperature may correct this problem, although many patients are uncomfortable and do not tolerate the cooling effect. Eating during HD can also cause a fall in blood pressure because of vasodilation of the splanchnic vessels. Although eating is usually prohibited during HD, patients prone to IDH should also avoid eating just before HD. Taking antihypertensive medications before HD may exacerbate hypotensive episodes as well; in some patients, these medications may need to be withheld until after HD has ended. Immediate treatment of IDH can be accomplished by several methods including (a) reclining the patient and raising the level of the lower extremities higher than the head (ie, Trendelenburg position), (b) administering a small (100–250 mL) bolus of normal saline into the venous blood line, and/or (c) reducing the ultrafiltration rate.[42]

In addition to the changes to HD ultrafiltration rates, several pharmacologic agents have been proposed to manage IDH, including ephedrine, fludrocortisone, caffeine, desmopressin, vasopressin, L-carnitine, sertraline, midodrine, and droxidopa with varying degrees of efficacy.[44] Preventing IDH is an area of active

study. Of the pharmacologic options, midodrine, an oral prodrug that is converted to desglymidodrine, a selective α_1-agonist, has shown the most promise. Midodrine studies to treat IDH have been small and of short duration and used hemodynamic end points instead of hard clinical end points. Midodrine 10 to 20 mg given 30 minutes before HD improves hemodynamic parameters in the short term, but negative long-term outcomes have been reported.[45] Droxidopa, a prodrug that is converted to norepinephrine, was studied for treatment of IDH, but neither 400- nor 600-mg doses showed statistically significant benefit compared with placebo, and more patients treated with droxidopa experienced adverse events such as nausea, fatigue, and headache.[46]

R.W.'s symptoms and low blood pressure during HD were managed by placing him in the Trendelenburg position and stopping ultrafiltration, which improved his symptoms and blood pressure. Continuing the last hour of HD without ultrafiltration allows for continued removal of unwanted metabolic end products and electrolytes without appreciable removal of additional water. If his symptoms and blood pressure did not improve with those interventions, a bolus of 100 to 250 mL normal saline could have also been given.

R.W.'s care should also include an accurate assessment of R.W.'s dry weight. Accurate dry weight estimate is essential, but difficult to obtain. Typically, the estimate is made by an experienced dietician in consultation with a physician. There is a potential role for bioimpedance or relative blood volume measurements to guide the process.[6] R.W.'s episode of hypotension could be related to too much fluid being removed during HD, an overestimate of the target weight because of a change in lean body mass or a combination of both. After reviewing his HD records for the presence of fluid balance–related signs and symptoms, the dietitian asks R.W. detailed questions about his diet. R.W. states that he is very careful to follow his HD fluid restrictions. He also reports an improved appetite since starting HD. He thinks it odd that he is eating more yet his clothes seem larger, and he needs to tighten his belt more than

before. Assessing all the information, the dietician concludes that it is likely that since starting HD R.W. has gained muscle mass along with losing excess fluid from his CKD stage 5 kidney failure. It is important to consider "real" weight changes when assessing the patient's dry weight and volume status. Without appropriately increasing the dry weight goal to compensate for his real weight gain perhaps that is more reflective of gained "fat/protein" weight as opposed to "water" weight, R.W. had too much fluid removed, which resulted in volume depletion and hypotension. His dry weight should be adjusted gradually upward over a period of weeks to the point at which he is no longer symptomatic and yet does not show symptoms of fluid overload.

CASE 30-1, QUESTION 8: What other HD-related complications must be monitored in R.W., and if they happen, how can they be treated?

SKELETAL MUSCLE CRAMPS

The pathophysiology of skeletal muscle cramping in patients treated with dialysis is not known. Proposed mechanisms include excessive ultrafiltration resulting in altered perfusion of the affected tissues, electrolyte disturbances, or deranged neurobiologic pathways. Skeletal muscle cramping related to HD is extremely painful, interferes with sleep and activities of daily living, and adversely affects patients' quality of life. A wide range of treatment strategies such as behavioral interventions (eg, exercise, stretching, massage), pharmacologic treatments (eg, hypertonic saline or dextrose in water 10% or 50%), dietary supplements, and changes to the HD treatment (eg, reduced ultrafiltration, changes in treatment time) have been tried with little success.[47]

DIALYSIS DISEQUILIBRIUM

Dialysis disequilibrium is a syndrome that has been recognized since the initiation of HD >40 years ago. Patients new to HD are at greatest risk because urea accumulates over time as the kidneys begin to fail. Urea's V_d is the same as that of body water, and it

distributes in tissues throughout the body. Rapid removal of urea from the extracellular space by HD lowers plasma osmolality, thereby leading to a shift of free water into the brain. Lowering intracellular pH, as can occur during HD, has also been suggested as a cause of dialysis disequilibrium. Clinical manifestations occur during or shortly after HD and include central nervous system effects, such as headache, nausea, altered vision, and, in some rare cases, seizures, and coma. Prevention is the treatment of choice and is accomplished by initiating HD gradually, including shorter treatment times with lower blood flow rates in new patients.[6]

PREVENTING AND TREATING HEMODIALYSIS VASCULAR ACCESS FLOW DYSFUNCTION

Preventing and treating vascular access flow dysfunction is important for both clinical and economic reasons. Maintaining adequate vascular access in HD is extremely important. Complications associated with vascular access flow dysfunction are significant clinical events and are a major cause of hospitalization. Thrombosis is the most common type of vascular access flow dysfunction and is usually the result of venous stenosis.[13] If not treated, thrombosis will result in loss of vascular access.

Routine hemodialysis vascular access function monitoring

Trained dialysis staff prospectively and routinely monitor vascular access function, which is paramount to preventing thrombosis. KDOQI clinical practice guidelines recommend routine inspection, palpation, and auscultation of the AV access. In addition, clinical scenarios such as a decrease in delivered HD dose, difficulty in cannulation, prolonged bleeding after needle removal, or altered character of the pulse or thrill may indicate access malfunction.[13] For routine CVC monitoring, KDOQI considers it reasonable to assess CVC function during each HD treatment by evaluating if the prescribed extracorporeal blood flow to meet the target HD dose can be maintained without lengthening the prescribed HD treatment time.[13]

Preventing hemodialysis vascular access flow dysfunction

Inconsistent definitions and study methodologies make comparing AV fistula and AV graft patency rates difficult. However, stenosis can cause thrombosis and loss of function in both. Stenosis may be corrected by percutaneous transluminal angioplasty, stent placement, or, if necessary, surgical revision of the vascular access site. Correcting stenosis to maintain patency is effective in preventing future thrombosis.[13]

Case 30-1, Question 9: Do fish oil supplements and oral anticoagulant or antiplatelet agents have a role in preventing thrombosis in R.W.'s AV fistula?

A functioning AV fistula is essential to R.W.'s HD treatment, and many studies have attempted to identify a treatment to effectively prevent vascular access thrombosis. Most recently, fish oil, simvastatin-ezetimibe, and clopidogrel-prostacyclin have been evaluated for preventing AV fistula thrombosis.

A study of Fish Oils and Aspirin in Vascular Access Outcomes in Renal Disease (FAVOURED) evaluated fish oil 4 g/day in patients undergoing AV fistula placement. Aspirin 100 mg/day was compared to placebo in a subset of patients. Neither fish oil nor aspirin was better than was placebo for preventing AV fistula failure or thrombosis.[48] Another analysis of the FAVOURED study assessed additional outcomes. This exploratory analysis found that fish oil and aspirin reduced AV fistula intervention rates but had no effect on other outcomes.[49]

A secondary analysis of the Study of Heart and Renal Protection (SHARP) trial found that simvastatin-ezetimibe was no better than was placebo in preventing the need for intervention, access thrombosis, or the rate of any vascular occlusive event in patients with a preexisting AV fistula or graft.[50]

One small, randomized, placebo-controlled trial evaluated clopidogrel-prostacyclin to prevent AV fistula flow dysfunction. At 1 year, the rate of primary AV fistula failure was significantly lower in the clopidogrel-prostacyclin–treated group, and primary patency,

adverse effects, and bleeding were not significantly different between groups.[51] Although this study's results seem promising, because of its sample size and methods, KDOQI does not recommend the clopidogrel-prostacyclin to prevent AV fistula flow dysfunction.[13]

Maintaining R.W.'s vascular access function is of ultimate importance. However, based on the evidence, KDOQI does not recommend the routine use of fish oil or aspirin to prevent AV fistula flow dysfunction and states that there is inadequate evidence to recommend simvastatin-ezetimibe or clopidogrel-prostacyclin.[13] Therefore, none of these agents are appropriate for R.W. In addition to lack of evidence, the risks of bleeding with antiplatelet or oral anticoagulant agents to prevent AV access thrombosis may be increased in the elderly population and those patients with high bleeding risks, such as those with kidney failure.[13]

Preventing thrombosis in other vascular access types (eg, AV graft and CVC) is also important. As with AV fistulas, preventing AV graft thrombosis and maintaining longevity of use is a major consideration. Up to 80% of AV graft failures are due to thrombosis caused by stenosis at the venous anastomosis.[13]

There is no role for low-dose warfarin in achieving a targeted international normalized ratio of 1.4 to 1.9 to prevent AV graft thrombosis or prolong AV graft survival.[52] As with AV fistulas, KDOQI determined that there is inadequate evidence to recommend using simvastatin- ezetimibe to reduce AV graft interventions and thrombosis.[13]

However, unlike with AV fistulas, there may be a role for antiplatelet agents or fish oil in preventing AV graft thrombosis. In one study,[53] the combination of dipyridamole 200 mg and aspirin 25 mg twice daily in HD patients with low bleeding risk showed statistically significant improvement in AV graft primary patency. Despite statistical significance, the difference of essentially 6 weeks in the median time to AV graft failure may not be clinically significant.[53] As a result, KDOQI suggests carefully considering individual patient benefits, risks, and circumstances before using dipyridamole and aspirin to prevent AV graft thrombosis.[13] Fish oil

supplements may have a role in reducing short-term AV graft thrombosis and corrective interventions,[54,55] but there is inadequate evidence to recommend their use for prolonging long-term AV graft patency.[13]

Both systemic and intraluminal agents have been evaluated to prevent CVC thrombosis. Owing to inadequate evidence of benefit and increased risk of harm, KDOQI does not recommend the routine use of prophylactic systemic anticoagulants for the sole purpose of maintaining or improving CVC patency. However, KDOQI suggests that low-dose aspirin 81 mg may be used in patients with low bleeding risk to maintain CVC patency.[13] For intraluminal agents, KDOQI's expert opinion is that either citrate or UFH CVC locking solutions are reasonable options. Available data do not show that one is better than the other. KDOQI does not suggest low-concentration citrate (<5%) or tissue plasminogen activator once per week as prophylactic CVC locking solutions to reduce CVC dysfunction.[13]

Treatment of hemodialysis vascular access flow dysfunction owing to thrombosis

A thrombosed AV fistula or AV graft is considered a medical emergency in patients on HD and requires immediate attention. Once thrombosis occurs in an AV fistula or AV graft, it can be managed by surgical or mechanical thrombectomy with or without stent placement, and/or use of thrombolytic agents. Interventional radiologists typically use alteplase instilled at the vascular access site and allowed to dwell for 1 hour before mechanical intervention. Thrombolytic therapy should be avoided in those patients with an increased risk of bleeding. For CVC occlusion due to thrombosis, KDOQI recommends intraluminal administration of alteplase 2 mg by the dwell or push method in each CVC port.[13]

ARTERIOVENOUS ACCESS INFECTION

Case 30-1, Question 10: HD vascular access sites are assessed by trained dialysis personnel at every treatment to identify any signs and symptoms of infection. In addition to routine assessment, should R.W. be given prophylactic antibiotics (eg, cefazolin with each HD) to avoid HD AV access site infection? Why?

Patients are taught to monitor their own vascular access site, and at each HD treatment, trained staff examine the access site before cannulation. Examination includes signs of infection such as erythema, skin breakdown, purulent discharge, and presence of exposed graft material.[13] In the absence of signs or symptoms of vascular access infection, prophylactic antibiotics offer no benefit. On the contrary, indiscriminate use of antibiotics could lead to colonization with resistant organisms. Thus, R.W. should not receive a prophylactic antibiotic with HD.

Vascular access infections are a serious complication of HD, often leading to hospitalization and increased mortality.[13] If signs and symptoms of infection are present, prompt treatment is necessary to preserve the vascular access and to prevent serious morbidity and mortality. Vascular access infections can range from localized (eg, mild cellulitis) to systemic (eg, bacteremia or sepsis). Vascular access infections are predominantly caused by *S. aureus* or *S. epidermidis*. Infections with gram-negative organisms as well as *Enterococcus* species occur less frequently.[13]

In patients with suspected vascular infections, before starting antibiotics, KDOQI recommends obtaining cultures and sensitivities of the blood and any available infected AV access vessel/material, surrounding tissue, or drainage. Empiric broad-spectrum antibiotics should be initiated quickly along with timely referral to a vascular access surgeon. As with all empiric antibiotic therapy, culture results should be strictly followed up, and the antibiotic regimen adjusted based on microorganism sensitivities. Treatment duration is based on the extent of the vascular access infection. There is a role for surgical incision and resection of infected AV grafts. AV fistula infections are rare, but when they occur, they should be treated as

subacute bacterial endocarditis (Refer to Chapter 66, Endocarditis) with 6 weeks of antibiotic therapy.[13]

CASE 30-2

Question 1: D.B. is a 56-year-old, 168-lb (76.20-kg) female who started HD 3 weeks ago and had no predialysis care. She is dialyzed through a CVC three times a week with 4-hour treatments using a high-flux dialyzer. Upon arrival at the dialysis facility for her routine HD, she reports having chills. Her temperature is 100.40 °F (38 °C), her blood pressure is normal, and her heart rate is slightly elevated. The catheter insertion site appears normal (ie, not red, purulent, or warm to the touch). Blood is drawn both from the catheter and a peripheral vein and sent to the laboratory for white blood cell (WBC) count and cultures. Her WBC count is 22,000 cells/mm^3, and the blood cultures and sensitivities are pending.

What are your recommendations for empiric antibiotic therapy for D.B.'s suspected HD catheter–related bacteremia?

Intravenous empiric antibiotic therapy for suspected CVC bacteremia should cover the predominant pathogens involved (*S. aureus*, *S. epidermidis*, and gram-negative organisms). Usually, the combination of intravenous vancomycin and an agent that covers gram-negative bacilli according to the local antibiogram is prescribed as empiric therapy. Intravenous cefazolin 20 mg/kg after each HD can be used instead of vancomycin in settings with a low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA).[56] High-flux dialyzer membranes result in greater removal of vancomycin during HD than do conventional dialyzer membranes. Intradialytic dosing of vancomycin is convenient, and it avoids the need for additional intravenous access, longer stays in the HD facility, and home antibiotic administration. For patients such as D.B. receiving high-flux HD, prior guidelines advised a vancomycin loading dose of 20 mg/kg of actual body weight (ie, D.B. weighs 165.35 pounds [75 kg]; therefore, she should receive a vancomycin loading dose of 1500 mg) administered during the last 60 to 90 minutes of HD followed by a dose of 500 mg administered during the last 30 minutes of each subsequent HD.[56] However, more recent dosing guidelines recommend individualized vancomycin dosing along with therapeutic

drug monitoring.[57] In patients on HD, vancomycin dosing should be based on actual weight at the time the dose is given; loading doses range from 25 to 35 mg/kg, and empiric maintenance doses range from 7.5 to 15 mg/kg, depending on dialyzer type and timing of vancomycin administration; a maximum loading dose of 3 g in patients with obesity; and an efficacy target of a 24-hour area under the curve (AUC):mean inhibitory concentration (MIC) of 400 to 600 mg•h/L, assuming an MIC of ≤1 mg/L. The new guidelines acknowledge the lack of evidence in HD, the absence of Bayesian models for dosing in dialysis, and the logistic challenges in implementing the recommendations in an outpatient dialysis facility.[57,58] As an alternative to the goal AUC:MIC, they suggest predialysis vancomycin concentration monitoring, with a goal concentration of 15 to 20 mg/L.

Antibiotic choice for gram-negative bacilli is based on the local antibiogram. Third- or fourth-generation cephalosporins or aminoglycosides can be used. Intravenous gentamicin (or tobramycin) 1 mg/kg, not to exceed 100 mg, infused over 30 minutes after each HD can be used for empiric gram-negative coverage[56] with appropriate serum concentration monitoring. However, aminoglycoside serum concentration monitoring in some outpatient hemodialysis facilities may not be practical, and aminoglycoside use in patients on HD is associated with an increased risk of irreversible vestibular and ototoxicity.[56] Subsequent antibiotic therapy should be tailored based on culture and sensitivity results. D.B. should receive antibiotic treatment for 4 to 6 weeks for uncomplicated *S. aureus* infection or 7 to 14 days for bacteremia caused by gram-negative bacilli or *Enterococcus* species.[13,56] D.B.'s CVC infection treatment will also include assessing if the CVC needs to be removed or replaced.[13,56]

PERITONEAL DIALYSIS

PD, an alternative to HD, relies on principles similar to those described with HD. The peritoneal lining acts as the semipermeable membrane, the peritoneal cavity is the location for dialysate to flow into and remain (ie, dwell) for a prescribed amount of time, and the capillary network in the peritoneum is the blood source. The process of PD differs from that of HD in that there is no external dialyzer membrane, no extracorporeal circuit, and no ability to change transmembrane pressure. PD is performed daily, and the dialysate is exchanged multiple times after each prescribed dwell time. With appropriate training, patients can perform PD in non–health care settings.

Conceptually, the process of PD is similar to that of HD in that uremic toxins and other solutes are removed by diffusion and convective transport down a concentration gradient from the capillary system across a semipermeable membrane, the peritoneal lining, into the dialysate. A primary difference is that blood flow rates and dialysate flow rates cannot be manipulated in PD to improve the removal of water and solutes. The result is a very slow dialysate flow rate of ~7 mL/minute when 10 L of fluid is drained per day. Solute loss occurs by diffusion for small molecules and through convection for middle molecules. Osmosis is the process by which fluid removal takes place in PD.[59]

PD can be performed using different techniques: continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD). The most common method is CAPD during which a patient, using sterile technique, instills and withdraws dialysate through a PD catheter placed in the abdomen (**Fig. 30-6**). Scientific advances have resulted in specialized devices or machines (ie, cycler) to perform APD that facilitate the exchange process and improve patient convenience. Types of APD include continuous cycling peritoneal dialysis (CCPD) and nocturnal intermittent peritoneal dialysis (NIPD).[59] APD methods have grown in popularity, especially in children requiring dialysis. Although lower rates of peritonitis are observed in APD compared with that in CAPD,[60] other outcomes measures, such as mortality rates and need for transition to HD, are similar between the two modalities.

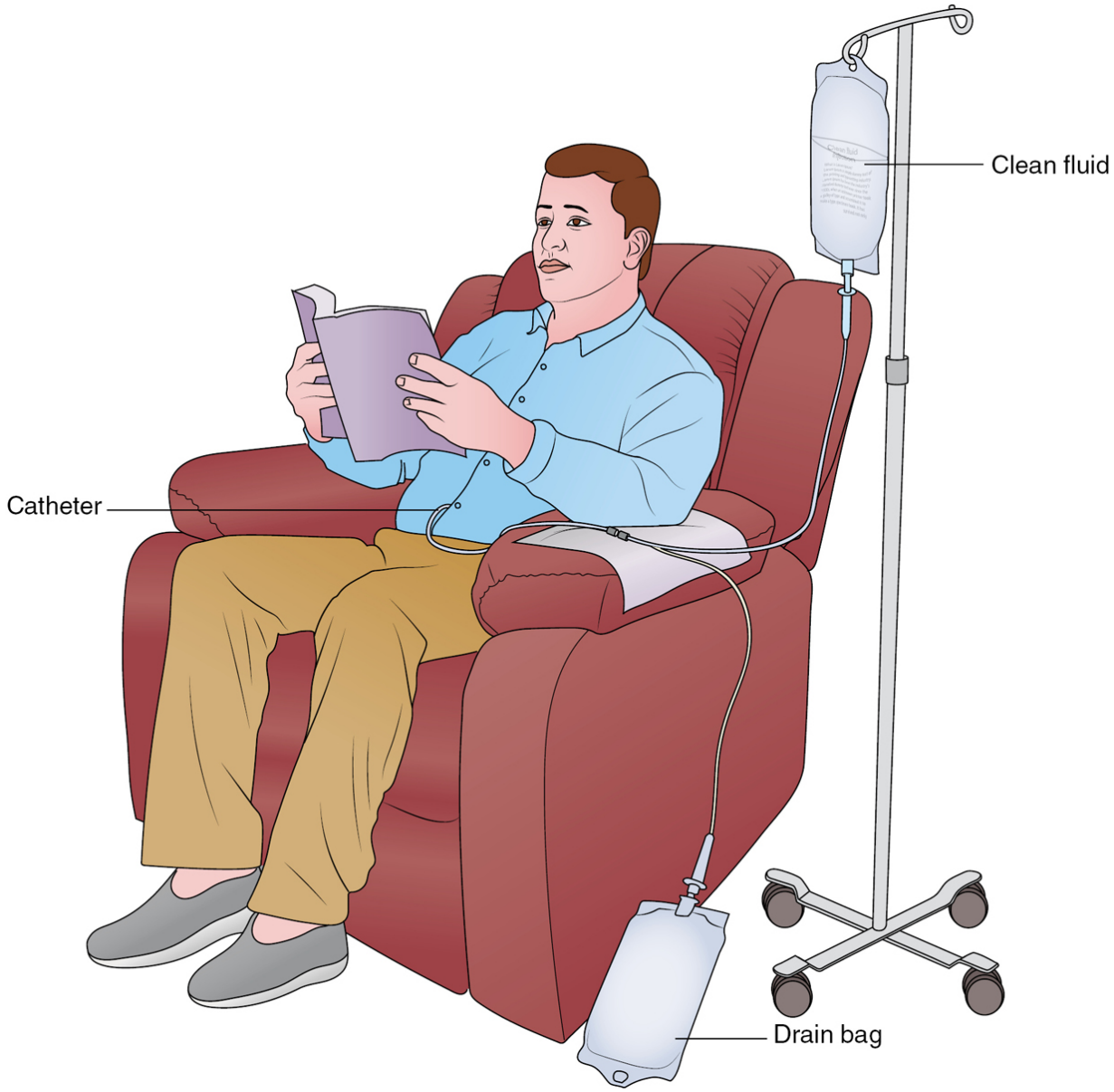


Figure 30-6 Person having continuous ambulatory peritoneal dialysis. The fresh dialysate (shown as clean fluid hanging from the intravenous [IV] pole) flows into the person's abdomen through the PD catheter, where it dwells for a prescribed amount of time and then is drained into the drain bag (shown on the floor). The transfer set is the tubing that connects the peritoneal dialysis catheter surgically placed in the patient to the dialysate bags. (Redrawn with permission from Patient education: Peritoneal dialysis (The Basics). In: Post TW, ed. *UpToDate*. UpToDate. Accessed March 15, 2021. ©

2022 UpToDate, Inc and its affiliates and/or licensors. All rights reserved.)

Peritoneal Dialysis Access

PD access is achieved via an indwelling catheter surgically inserted through the abdominal wall. The most common design is the Tenckhoff® catheter, made of silicone rubber or polyurethane. It consists of a tube, straight or curled, with many holes in the distal end for fluid inflow and outflow. The catheter also has a single or double cuff, which anchors the catheter internally and externally by promoting fibrous tissue growth; the cuff also serves as a barrier to bacterial migration. Maintaining an unobstructed outlet port is essential for successful PD.[59]

Peritoneal Dialysis Dialysate

CASE 30-3

Question 1: K.M., a 27-year-old female, has a 20-year history of type 1 diabetes mellitus (T1DM). She is 64 inches (162.56 cm) tall and weighs 121 pounds (54.88 kg). She has kidney failure requiring dialysis due to her diabetes and has been treated with CAPD for 1 year. Her CAPD prescription is three exchanges with 1.5% dextrose during the day and a fourth, overnight exchange with 4.25% dextrose. She has a double-cuff Tenckhoff® catheter and uses a Y-transfer set for her exchanges. Her blood pressure is controlled, and she shows no evidence of edema. She has no residual kidney function.

What is the purpose of the dextrose in K.M.'s dialysate? Why would the dextrose concentration be different in the overnight dwell compared to the daytime dwell?

The composition of PD dialysate is different from the composition used for HD (refer to Table 30-1). The process of HD has the advantage of adjusting the transmembrane pressure to vary the amount of fluid removed by ultrafiltration. In PD, the amount of fluid removed, or ultrafiltration, is dependent on the hyperosmolality of the dialysate, the length of time the dialysate dwells, and the individual

characteristics of the patient's peritoneal lining.[59] Commercially available PD dialysate has 1.5%, 2.5%, and 4.25% dextrose concentrations, with net fluid losses during a 4-hour dwell period of 200 and 400 mL for the 1.5% and 2.5% solutions, respectively, and ~700 mL for the 4.25% solution after an overnight dwell. In addition to dextrose, CAPD dialysate contains electrolytes (see Table 30-1). Bicarbonate is not compatible with the calcium and magnesium in PD dialysate; therefore, PD dialysate contains lactate. Acid–base balance is achieved through the absorption of lactate from the dialysate, which subsequently is metabolized to bicarbonate in vivo.[59,61]

As dextrose is absorbed through the peritoneal lining into the patient's bloodstream, the osmotic gradient between the dialysate and the blood progressively dissipates, reducing ultrafiltration. Toward the end of the long dwell (typically overnight for CAPD and during the day for APD with a prescribed day dwell), more dialysate fluid may be absorbed than fluid ultrafiltered, resulting in a negative net ultrafiltration volume where the drained volume is less than the infused volume. A negative net ultrafiltration volume is undesirable. Greater ultrafiltration and fluid management are predictors of survival.[59,61]

K.M. is prescribed a very common CAPD regimen that would be expected to achieve fluid removal of ~1300 mL, based on 200 mL of ultrafiltration from each daytime exchange and 700 mL overnight. At this time, K.M. is not showing signs of altered fluid status, her blood pressure is normal, and there is no edema; hence, adjustments to the CAPD are not needed. If adjustments are needed, the dialysate prescription can be changed to achieve fluid balance. Fluid retention is addressed by increasing the dextrose concentration used in the daytime exchanges, beginning with 2.5% in place of one of the 1.5% solutions. This change is expected to result in an additional removal of 200 mL, and therapy can be further adjusted as necessary. For patients with signs and symptoms of excessive fluid removal, the number of exchanges per day may be decreased as long as adequate solute removal is achieved. If four exchanges are needed

to manage solute removal, oral fluid intake can be liberalized to maintain fluid balance.[61]

Icodextrin is an alternative to dextrose as the osmotic agent in the peritoneal dialysate, and is superior to 4.25% dextrose for ultrafiltration.[62] Icodextrin is a starch-derived, water-soluble, nondextrose polymer, and is labeled for use in the United States during the long-dwell period in patients receiving CAPD or APD. Unlike glucose, icodextrin does not readily diffuse across the peritoneal membrane, but it is slowly removed from the peritoneal cavity via convective uptake into the peritoneal lymphatic system.[63] Other advantages of icodextrin compared to glucose-containing PD dialysate include less glucose absorption, carbohydrate exposure, fat accumulation, and weight gain. Its main disadvantage is a higher acquisition cost.[59,61]

Factors to be considered when icodextrin is used for PD include decreased insulin requirements in patients with diabetes and false elevations in glucose concentrations with certain glucose-monitoring devices unable to distinguish glucose from maltose. False readings may result in doses of glucose-lowering medications being increased unnecessarily, resulting in iatrogenic hypoglycemia. Other undesirable effects of icodextrin include skin rash, mild hyponatremia, sterile peritonitis, and false reductions of serum amylase concentrations.[64]

Process of Peritoneal Dialysis Ultrafiltration

Most PD is done in non–health care environments such as the home or the workplace. CAPD exchanges are performed by instilling 2 to 3 L of sterile dialysate into the peritoneal cavity through a surgically placed permanent catheter. Dialysate is delivered and returned through the catheter using Y-sets and double-bag systems. The Y-transfer set uses three limbs of tubing, with fresh dialysate attached to the upper arm of the Y, an empty bag to the lower arm, and the stem connected to the catheter (see Fig. 30-6). One limb of the Y-shaped tubing is the inflow arm, which is used to transfer clean

dialysate into the peritoneal cavity. The other limb of the Y-shaped tubing is the outflow arm and is used to remove spent dialysate from the peritoneal cavity. Clamping the inflow arm and opening the stem and outflow arm allow spent (or used) dialysate to drain from the peritoneum into the empty bag. Reversing the clamps then permits fresh dialysate to enter the peritoneum after a small rinse of the line is performed with the fresh dialysate. Clamping the PD catheter allows the patient to remove the Y-transfer set and bags. The double-bag system uses preattached bags to both limbs and the patient, and makes only a single connection to the catheter.[59] Use of the Y-transfer set has reduced episodes of peritonitis from ~1 for every 9 to 12 patient-months to 1 for every 24 to 36 patient-months. PD performed with the cycler involves only two disconnections of the system, compared with four for CAPD.

In CAPD, the dialysate dwells within the peritoneal cavity for 4 to 8 hours, and then it is drained and replaced with fresh dialysate. The drained, used dialysate is called spent dialysate. This process of fill, dwell, and drain is performed three to four times during the day, with an overnight dwell. The patients can perform any of these exchanges in their normal home or work environment.[59]

In APD, the cycler machine is programmed and automatically cycles dialysate into and out of the peritoneal cavity typically during nighttime hours. Patients receiving CCPD will generally have three to five exchanges at night using the cycler, each lasting ~2 hours. During the daytime hours, the patient maintains a reservoir of dialysate in the peritoneal cavity, resulting in a long dwell. The cycler process then repeats at night. Patients with NIPD have six to eight exchanges performed every night. However, there is no dialysate left to dwell in the peritoneum, and PD is not continued during the day. Nightly dwell times with NIPD are generally 1 to 2 hours for each exchange, resulting in higher small-molecule clearance because of the increased dialysate flow rate. The benefits of APD are that the patient is free from doing exchanges during the day, and the number of connections to the PD catheter is significantly reduced.[59]

PERITONEAL DIALYSIS UREA CLEARANCE

The process of HD maintains a large concentration gradient across the semipermeable membrane throughout the treatment. Unlike HD, during a typical dwell period for CAPD, concentrations of urea and other substances increase in the dialysate dwelling in the peritoneum relative to unbound plasma concentrations. During a 4-hour dwell, dialysate urea concentration achieves near equilibrium with plasma; therefore, the rate of elimination over the dwell time decreases significantly. Instilling fresh dialysate reestablishes the diffusion gradient and increases urea clearance. Urea clearance with PD is substantially lower than is urea clearance achieved with three times a week HD; therefore, multiple CAPD exchanges must be performed daily to achieve adequate urea clearance.[61]

Unlike HD, many patients on peritoneal dialysis have significant residual kidney function that typically lasts longer than that in patients receiving HD. Calculating urea clearance or the dose of PD takes into account both urea and creatinine clearance from PD and residual kidney function (creatinine clearance), reported as a weekly value.[59,61]

The 2006 KDOQI guidelines for PD dose recommend a target minimum Kt/V_{urea} of 1.7 and the target total weekly clearance of 50 L.[65] More recently, the solitary focus of a target dose of PD is being replaced with a comprehensive approach to assess broadly the effectiveness of the entire PD treatment. The newer approach takes into account clinical assessments, solute clearance measurements, prevention or treatment of PD-related complications, nutritional status, fluid removal, and the patient's quality of life.[59,61]

Residual kidney function, especially in patients on peritoneal dialysis, significantly contributes to solute and fluid clearance. Preserving whatever kidney function is present at the start of PD is extremely important; therefore, nephrotoxins such as aminoglycosides, nonsteroidal anti-inflammatory agents, and radiocontrast dye should be avoided if possible.[59,61]

Peritoneal Dialysis Complications

PERITONEAL DIALYSIS EXIT-SITE INFECTION: PROPHYLAXIS

CASE 30-3, QUESTION 2: PD catheter exit-site infections (ESIs) are a significant risk factor for developing peritonitis. Routine retraining on PD technique is recommended to reduce the risk of ESI and peritonitis.[66] K.M. arrives to her retraining clinic visit. What information should be reviewed with K.M. about her routine catheter care to prevent an ESI infection? Recommend an appropriate topical antimicrobial for K.M. to administer around the catheter exit-site.

The primary goal of exit-site care is to prevent PD catheter ESI and thus peritonitis. Preventative measures for initial catheter placement include prophylactic perioperative antibiotics; adequate catheter placement; dedicated postoperative catheter care; and, once healed, routine daily care of the exit site. Prophylactic antibiotics at the time of catheter placement are effective, and either a first-generation cephalosporin or vancomycin, depending on local antibiotic resistance, is recommended.[66] Dialysis nurses use sterile technique to change dressings around a new PD catheter until the exit site is well healed, which can take up to 2 weeks. After that, patients are trained to do routine exit-site care by closely following steps essential to avoid infection. First, K.M. should meticulously clean her hands by rubbing both hands for at least 15 seconds using antibacterial soap or antiseptics that contain at least 70% alcohol. Then, she should wash the exit site daily with antibacterial soap, although use of an antiseptic (eg, povidone iodine or chlorhexidine) is a reasonable option as long as concentrations are noncytotoxic. Hydrogen peroxide should be avoided because of its drying effect. After cleaning her hands and the exit site, K.M. can apply mupirocin or gentamicin cream around the catheter exit site daily using a cotton swab.[68]

Mupirocin 2% cream and gentamicin sulfate 0.1% cream are equally effective in preventing *S. aureus* infections. Mupirocin cream is typically the antimicrobial cream of choice, but gentamicin cream is an acceptable alternative. Unlike mupirocin cream, gentamicin cream is highly effective in reducing *P. aeruginosa* and other gram-

negative catheter infections. However, daily use of gentamicin cream may allow for an emergence of infections caused by other organisms. Mupirocin ointment, not the cream, can cause structural damage to polyurethane PD catheters and should be avoided. The final step in daily PD catheter care is to immobilize the catheter with a small gauze dressing and tape to prevent pulling and trauma to the exit site, which may lead to infection.[68]

CASE 30-3, QUESTION 3: During retraining, the PD nurse reminds K.M. that she needs to take prophylactic antibiotics before any extensive dental work. What is the PD nurse concerned about, and why are prophylactic antibiotics necessary?

Preventing peritonitis is critical to avoiding high rates of morbidity and mortality. Antibiotic prophylaxis for colonoscopy, invasive gynecologic procedures, dental procedures, and esophagogastroduodenoscopy have reduced rates of peritonitis.[69] These invasive procedures result in contiguous spread of bacteria or fungi or seeding the peritoneum during bacteremia, which then can cause peritonitis. The ISPD guidelines recommend prophylactic antibiotics for invasive gynecologic procedures and colonoscopy.[66] Although the optimal regimen has not been clinically studied, a systematic review suggests that an intravenous regimen of ampicillin plus an aminoglycoside, with or without metronidazole, may be used.[66,70] The guidelines also state that it would be reasonable for K.M. to receive a single dose of amoxicillin before extensive dental work.[66]

PERITONEAL DIALYSIS EXIT-SITE INFECTION: TREATMENT

CASE 30-3, QUESTION 4: If K.M. were to have signs and symptoms of an ESI, would oral antibiotic therapy be appropriate?

ESI is diagnosed when there is purulent drainage, with or without erythema of the skin, at the catheter–epidermal interface. Peritoneal dialysis catheter ESIs are most often caused by *S. aureus* and/or

Pseudomonas species. Exit-site drainage should be sent for Gram stain, culture, and sensitivity to direct antibiotic therapy. Empiric oral antibiotic treatment should start immediately with appropriate coverage for *S. aureus*. A penicillinase-resistant penicillin (eg, dicloxacillin or flucloxacillin) or first-generation cephalosporin is recommended unless there is a prior history of infection or colonization with MRSA or *Pseudomonas* species. Recommendations for those patients include a glycopeptide or clindamycin, or appropriate antipseudomonal antibiotic, respectively.[68]

If the Gram stain demonstrates the presence of gram-positive organisms, continue the empiric coverage for *S. aureus* for at least 2 weeks.[68] Oral antibiotic therapy has been shown to be as effective as intraperitoneal (IP) antibiotic therapy except for documented MRSA infections.[68] If gram-negative pathogens are present, the clinical guidelines recommend prolonged dual therapy including oral fluoroquinolone therapy. Fluoroquinolone monotherapy is not recommended because resistance develops rapidly. Oral fluoroquinolones should be separated by 2 hours from calcium-containing products, iron, multivitamins, antacids, zinc, or sucralfate because of chelation of the antibiotic and the potential for subtherapeutic effect. Antibiotic therapy for pseudomonal ESI should be continued for a minimum of 3 weeks.[68]

PERITONEAL DIALYSIS–ASSOCIATED PERITONITIS

Case 30-3, Question 5: Six months later (18 months of PD), K.M. presents to the PD clinic with moderate abdominal pain and cloudy effluent (ie, spent dialysate). She does not report a fever. K.M. reports an accidental catheter disconnection 2 days ago. On physical examination, her weight today is 143 pounds (64.86 kg), her vital signs are normal, lungs are clear to auscultation, abdominal tenderness is generalized, and the catheter tunnel and exit site appear normal. K.M. brought the cloudy dialysate with her and it is sent to the laboratory for cell count and differential, Gram stain, and cultures. Early laboratory results show an effluent WBC count of 330 cells/μL with 62% neutrophils. The Gram stain and culture results are pending. What is the most likely diagnosis for K.M.? Recommend appropriate treatment and monitoring.

K.M.'s clinical presentation of abdominal pain, recent accidental catheter disconnection, and cloudy dialysate strongly suggest the possibility of peritonitis. The 2022 ISPD Practice Guidelines recommend a diagnosis of peritonitis be made if two of the following are present: dialysate WBC >100/μL with >50% neutrophils after a two hour dwell; clinical features consistent with peritonitis; or positive dialysis effluent culture.[67] Although not present in K.M., peritonitis can also present with nausea and vomiting and fever. Cloudy dialysate effluent is not always present.[66]

Because K.M. has normal vital signs and her abdominal tenderness is not severe, she can be treated as an outpatient with IP antibiotic therapy. K.M. would be hospitalized for treatment if she were showing signs of sepsis or had severe abdominal pain. Peritonitis is a significant complication, and empiric antibiotic therapy should be started as soon as possible. Empiric therapy must cover both gram-positive and gram-negative organisms, and the choice of agents should be based on local microbial sensitivity data.[67]

The ISPD Practice Guidelines recommend empiric antibiotic therapy be started as soon as possible and include vancomycin or a first-generation cephalosporin (eg, cefazolin) to treat gram-positive organisms and an antipseudomonal cephalosporin (eg, ceftazidime, cefepime) or an aminoglycoside (eg, gentamicin) to treat gram-negative organisms.[67] The goal of antibiotic therapy is to rapidly resolve inflammation and preserve peritoneal membrane function.[68]

General principles of treating PD-associated peritonitis include (a) IP antibiotics are the preferred route of administration unless the patient has signs and symptoms of sepsis; (b) daily intermittent IP aminoglycoside and avoid prolonged courses of IP aminoglycoside; (c) intermittent IP vancomycin and serum vancomycin concentrations maintained >15 μg/mL; and (d) IP cephalosporin administered either continuously (in each exchange) or on a daily intermittent basis. Intravenous administration of antibiotics is recommended for patients experiencing signs and symptoms of systemic infection.[68]

The ISPD clinical guidelines list antimicrobial dosing for both intermittent and continuous dosing; however, intermittent dosing is preferred. In CAPD, IP vancomycin dosing for intermittent

administration is 15 to 30 mg/kg added to 1 exchange of dialysate every 5 to 7 days and aminoglycoside (eg, gentamicin) dose 0.6 mg/kg added to 1 exchange of dialysate daily. Antibiotics should be allowed to dwell for at least 6 hours. Both agents can be coadministered IP in the same dialysate, but separate syringes must be used to add the antibiotics to dialysate.[66] If K.M., who weighs 143 pounds (64.86 kg), is prescribed vancomycin and gentamicin, a 1- to 2-g dose of vancomycin IP and 40-mg dose of gentamicin IP would be appropriate. Doses should be rounded to an easily measurable quantity for patients to self-administer. For instance, K.M.'s original vancomycin dose calculation comes to 975 to 1950 mg. Vancomycin for injection is available in 1-g vials, and hence the dosing recommendation of a 1- to 2-g dose. The calculated dose of gentamicin would be 39 mg, but rounding up to 40 mg results in an easier to measure dose because the concentration of gentamicin for injection is 40 mg/mL.

A registry-based study of patients with peritonitis concluded that aminoglycosides did not adversely affect residual kidney function, but there was high systemic absorption across an inflamed peritoneal membrane, and the half-life of gentamicin was prolonged.[71] In this instance, gentamicin can accumulate and cause adverse effects. Short-term use appears to be safe and effective, but there is a potential risk of oto- and/or vestibular toxicity with prolonged therapy. If possible, aminoglycoside use should be limited.[61,67] Subsequent antibiotic therapy should be based on culture and sensitivity results, incorporating specific dosage regimens based on the consensus recommendations.[67]

K.M. is instructed to return to the clinic in 3 days. Her PD catheter site will be reexamined, her clinical signs and symptoms will be reevaluated, and the effluent appearance observed and cell count repeated. When the culture and sensitivity results are available, K.M.'s antimicrobial therapy should be targeted as soon as possible. Assuming clinical improvement, K.M. will receive IP antibiotics as an outpatient for 14 to 21 days depending on the culture results.[66]

Case 30-3, Question 6: In addition to empiric antibiotics, IP UFH is prescribed. What is the indication for UFH? While teaching K.M. how to administer her antibiotics, the pharmacist notices that K.M.'s diabetes has been effectively treated with 10 units of regular insulin IP with each daytime exchange and 15 units in the overnight exchange. What is the best route of administration for insulin administration during her peritonitis episode?

K.M.'s PD effluent was cloudy, and she may benefit from adjunctive IP UFH in addition to empiric antibiotics. Heparin 500 units/L can be added to each dialysate exchange to prevent fibrin clots from forming, which could obstruct dialysate outflow from the peritoneal cavity and occlude the catheter.[66]

During peritonitis, an inflamed peritoneal lining has increased permeability to water, glucose, and proteins, often resulting in hyperglycemia and fluid overload.[66] Insulin absorption will also be increased. As a result, K.M.'s blood glucose concentrations and insulin doses require close attention during the peritonitis.[66] Temporarily switching insulin administration from IP to subcutaneous will simplify treating the variable blood glucose concentrations that are likely to occur as the course of peritonitis resolves. Also see Case 30-3, Question 8, for other considerations regarding insulin dosing.

Case 30-3, Question 7: If K.M. was using APD instead of CAPD, how would the treatment of her presumed peritonitis infection be different?

For patients using APD, the choice of first-line antibiotics is the same as that for CAPD because the likely organisms are similar. Drug dosage regimens, however, can differ because patients having CCPD or NIPD undergo PD only during the nighttime hours, and those treated with NIPD do not have peritoneal dialysate dwelling during the day. The rapid exchanges in APD may lead to inadequate time to achieve therapeutic drug concentrations.[66] The dose of cefazolin in APD is 15 to 20 mg/kg (rounded to the nearest 500 mg) every day, in the long day dwell. If K.M. were treated with APD, she would receive cefazolin 1000 to 1500 mg IP in the long day dwell. A

concern is that patients given a single dose of a cephalosporin during the long day dwell may have IP antibiotic concentrations at night that are below the MIC of most organisms, allowing biofilm-associated organisms to survive, resulting in relapsing peritonitis. A more conservative approach is to add the cephalosporin to each APD exchange. Because of the lack of clinical trials with other antibiotics in APD, extrapolation from the CAPD literature is often necessary.[72,73]

Case 30-3, Question 8: K.M.'s peritonitis resolved with antibiotic therapy, and she has resumed her routine monthly clinic visits. K.M.'s only question today is about an increase in her body weight. Her vital signs and physical examination are normal. K.M.'s body weight has increased 26 pounds (11.79 kg) since starting PD. Fluid retention is possibly the cause of the weight gain, but it is unlikely that K.M. would be asymptomatic (eg, difficulty breathing, swelling) or not have signs of fluid overload (eg, hypertension, crackles on lung examination, edema). What is another cause for K.M.'s weight gain? How might this affect her insulin requirements?

PERITONEAL DIALYSIS–ASSOCIATED WEIGHT GAIN

Dextrose is present in peritoneal dialysate and serves as an osmotic agent for ultrafiltration. Higher dextrose concentrations in peritoneal dialysate result in greater fluid removal. Approximately 500 to 1000 kcal/day are absorbed as glucose from PD dialysate, which, in the absence of decreased oral caloric intake, leads to weight gain.[61] Insulin requirements increased in patients with diabetes because of the additional calories absorbed through the peritoneum. Insulin doses administered IP usually are two to three times the normal subcutaneous dose because of reduced bioavailability of 20% to 50% by this route.[74] Also see Case 30-3, Question 6, for other considerations regarding insulin dosing.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Davenport A. What are the anticoagulation options for intermittent hemodialysis? *Nat Rev Nephrol.* 2011;7(9):499–508. doi:10.1038/nrneph.2011.88 (38)

Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int.* 2020;97(6):1117–1129. doi:10.1016/j.kint.2020.02.010 (1)

Lok CE, Huber TS, Lee T, et al. KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update. *Am J Kidney Dis.* 2020;75(4 suppl 2):S1–S164. doi:10.1053/j.ajkd.2019.12.001 (13)

Mancini A, Piraino B. Review of antibiotic dosing with peritonitis in APD. *Perit Dial Int.* 2019;39(4):299–305. doi:10.3747/pdi.2018.00209 (72)

Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2011;80(11):1122–1137. doi:10.1038/ki.2011.322 (18)

McIntyre CW, Burton JO. Dialysis. *BMJ.* 2014;348:g2. doi:10.1136/bmj.g2 (4)

Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2020;77(11):835–864. Accessed May 25, 2021. doi:10.1093/ajhp/zxaa036 (57)

Silver SA, Harel Z, Perl J. Practical considerations when prescribing icodextrin: a narrative review. *Am J Nephrol.* 2014;39(6):515–527. doi:10.1159/000363417 (64)

Szeto CC, Li PK, Johnson DW, et al. ISPD Catheter-Related Infection Recommendations: 2017 Update. *Perit Dial Int.* 2017;37(2):141–154. doi:10.3747/pdi.2016.00120 (68)

Key Websites

ISPD Clinical Practice Guidelines. https://ispd.org/ispd-guidelines/

Kidney Disease: Improving Global Outcomes (KDIGO). https://kdigo.org/

NFK KDOQI Guidelines. Guidelines and commentaries. https://www.kidney.org/professionals/guidelines/guidelines_commentaries

COMPLETE REFERENCES CHAPTER 30 DIALYSIS TREATMENT FOR CHRONIC KIDNEY FAILURE

1. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int*. 2020;97(6):1117–1129. doi:10.1016/j.kint.2020.02.010
2. *US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States*. National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases; 2019.
3. U.S. Department of Health and Human Services. *Advancing American Kidney Health*. 2019. Accessed April 2, 2021. www.aspe.hhs.gov/system/files/pdf/262046/AdvancingAmericanKidneyHealth.pdf
4. McIntyre CW, Burton JO. Dialysis. *BMJ*. 2014;348:g2. doi:10.1136/bmj.g2
5. National Kidney Foundation. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. *Am J Kidney Dis*. 2015;66(5):884–930. doi:10.1053/j.ajkd.2015.07.015
6. Misra M. Hemodialysis and hemofiltration. In: Gilbert SJ, Weiner DE, eds. *National Kidney Foundation's Primer on Kidney Diseases*. 7th ed. Elsevier; 2018:528–538.
7. Yeun JY, Depner TA, Ananthakrishnan S. Principles of hemodialysis. In: Himmelfarb J, Ikizler TA, eds. *Chronic Kidney Disease, Dialysis, and Transplantation—A Companion to Brenner and Rector's the Kidney*. 4th ed. Elsevier; 2018:339–360.e337.
8. Brunelli S. The dialysis prescription. In: Nissenson AR, Fine RE, eds. *Handbook of Dialysis Therapy*. 5th ed. Elsevier; 2017:274–280.e271.
9. Winchester JF, Audia PF. Extracorporeal strategies for the removal of middle molecules. *Semin Dial*. 2006;19(2):110–114. doi:10.1111/j.1525-139X.2006.00135.x
10. Vanholder R, De Smet R, Glorieux G, et al. Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney Int*. 2003;63(5):1934–1943. doi:10.1046/j.1523-1755.2003.00924.x
11. Wolley M, Jardine M, Hutchison CA. Exploring the clinical relevance of providing increased removal of large middle molecules. *Clin J Am Soc*

Nephrol. 2018;13(5):805–814. doi:10.2215/CJN.10110917

12. Lesaffer G, De Smet R, Lameire N, Dhondt A, Duym P, Vanholder R. Intradialytic removal of protein-bound uraemic toxins: role of solute characteristics and of dialyser membrane. *Nephrol Dial Transplant*. 2000;15(1):50–57. doi:10.1093/ndt/15.1.50. Accessed March 25, 2021.
13. Lok CE, Huber TS, Lee T, et al. KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update. *Am J Kidney Dis*. 2020;75(4 suppl 2):S1–S164. doi:10.1053/j.ajkd.2019.12.001
14. Gharamti A, Kanafani ZA. Vascular graft infections: an update. *Infect Dis Clin North Am*. 2018;32(4):789–809. doi:10.1016/j.idc.2018.06.003
15. Vicaretti M. Pathophysiology of vascular graft infections. In: Fitridge R, Thompson M, eds. *Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists*. University of Adelaide Press; 2011:537–548.
16. Viecelli AK, Mori TA, Roy-Chaudhury P, et al. The pathogenesis of hemodialysis vascular access failure and systemic therapies for its prevention: optimism unfulfilled. *Semin Dial*. 2018;31(3):244–257. doi:10.1111/sdi.12658
17. Uda S, Mizobuchi M, Akizawa T. Biocompatible characteristics of high-performance membranes. *Contrib Nephrol*. 2011;173:23–29. doi:10.1159/000328941
18. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80(11):1122–1137. doi:10.1038/ki.2011.322
19. Pallotta KE, Manley HJ. Vancomycin use in patients requiring hemodialysis: a literature review. *Semin Dial*. 2008;21(1):63–70. doi:10.1111/j.1525-139X.2007.00333.x
20. Nemecek BD, Hammond DA. *Demystifying Drug Dosing in Renal Dysfunction*. American Society of Health-System Pharmacists; 2019.
21. Aronoff GR, Bennett WM, Berns JS, Brier ME, Kasbekar N, Mueller BA, eds. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*. 5th ed. American College of Physicians; 2007.
22. Ortiz-Melo DI, Kovalic EC. Methods of hemodialysis anticoagulation. In: Nissenson AR, Fine RE, eds. *Handbook of Dialysis Therapy*. 5th ed. Elsevier; 2017:191–204.e191.
23. Kato C, Oakes M, Kim M, et al. Anticoagulation strategies in extracorporeal circulatory devices in adult populations. *Eur J Haematol*. 2021;106(1):19–31. doi:10.1111/ejh.13520
24. Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: a meta-analysis of randomized trials. *J Am Soc Nephrol*. 2004;15(12):3192–3206. doi:10.1097/01.ASN.0000145014.80714.35

25. Lazrak HH, Rene E, Elftouh N, Leblanc M, Lafrance JP. Safety of low-molecular-weight heparin compared to unfractionated heparin in hemodialysis: a systematic review and meta-analysis. *BMC Nephrol*. 2017;18(1):187. doi:10.1186/s12882-017-0596-4
26. Brophy DF, Carr ME Jr, Martin EJ, Venitz J, Gehr TW. The pharmacokinetics of enoxaparin do not correlate with its pharmacodynamic effect in patients receiving dialysis therapies. *J Clin Pharmacol*. 2006;46(8):887–894. doi:10.1177/0091270006289975
27. Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. *J Thromb Haemost*. 2004;2(4):547–550. doi:10.1111/j.1538-7933.2004.00647.x
28. Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. *J Thromb Haemost*. 2004;2(4):551–554. doi:10.1111/j.1538-7933.2004.00648.x
29. Al-Ali FS, Elsayed M, Khalifa S, et al. Successful use of a bivalirudin treatment protocol to prevent extracorporeal thrombosis in ambulatory hemodialysis patients with heparin-induced thrombocytopenia. *Hemodial Int*. 2016;20(2):204–207. doi:10.1111/hdi.12379
30. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv*. 2018;2(22):3360–3392. doi:10.1182/bloodadvances.2018024489
31. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e495S–e530S. doi:10.1378/chest.11-2303
32. Gameiro J, Jorge S, Lopes JA. Haemodialysis-related-heparin-induced thrombocytopenia: case series and literature review. *Nefrologia (Engl Ed)*. 2018;38(5):551–557. doi:10.1016/j.nefro.2018.02.010
33. Murray PT, Reddy BV, Grossman EJ, et al. A prospective comparison of three argatroban treatment regimens during hemodialysis in end-stage renal disease. *Kidney Int*. 2004;66(6):2446–2453. doi:10.1111/j.1523-1755.2004.66022.x
34. Tang IY, Cox DS, Patel K, et al. Argatroban and renal replacement therapy in patients with heparin-induced thrombocytopenia. *Ann Pharmacother*. 2005;39(2):231–236. doi:10.1345/aph.1E480
35. Hursting MJ, Murray PT. Argatroban anticoagulation in renal dysfunction: a literature analysis. *Nephron Clin Pract*. 2008;109(2):c80–c94. doi:10.1159/000139993
36. Davenport A. Antibodies to heparin-platelet factor 4 complex: pathogenesis, epidemiology, and management of heparin-induced thrombocytopenia in hemodialysis. *Am J Kidney Dis*. 2009;54(2):361–374. doi:10.1053/j.ajkd.2009.03.012

37. Tsu LV, Dager WE. Bivalirudin dosing adjustments for reduced renal function with or without hemodialysis in the management of heparin-induced thrombocytopenia. *Ann Pharmacother*. 2011;45(10):1185–1192. doi:10.1345/aph.1Q177
38. Davenport A. What are the anticoagulation options for intermittent hemodialysis? *Nat Rev Nephrol*. 2011;7(9):499–508. doi:10.1038/nrneph.2011.88
39. Sombolos KI, Fragia TK, Gionanlis LC, et al. Use of fondaparinux as an anticoagulant during hemodialysis: a preliminary study. *Int J Clin Pharmacol Ther*. 2008;46(4):198–203. doi:10.5414/cpp46198
40. Arixtra. Prescribing information. Accessed March 15, 2021. www.accessdata.fda.gov/drugsatfda_docs/label/2005/021345s010lbl.pdf
41. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26(3):724–734. doi:10.1681/ASN.2014020222
42. Timofte D, Tanasescu MD, Balan DG, et al. Management of acute intradialytic cardiovascular complications: updated overview (review). *Exp Ther Med*. 2021;21(3):282. doi:10.3892/etm.2021.9713
43. Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int*. 2006;69(7):1222–1228. doi:10.1038/sj.ki.5000186
44. Perazella MA. Pharmacologic options available to treat symptomatic intradialytic hypotension. *Am J Kidney Dis*. 2001;38(4 suppl 4):S26–S36. doi:10.1053/ajkd.2001.28092
45. Chang TI. Impact of drugs on intradialytic hypotension: antihypertensives and vasoconstrictors. *Semin Dial*. 2017;30(6):532–536. doi:10.1111/sdi.12633
46. Vannorsdall MD, Hariachar S, Hewitt LA. A randomized, placebo-controlled, phase 2 study of the efficacy and safety of droxidopa in patients with intradialytic hypotension. *Postgrad Med*. 2015;127(2):133–143. doi:10.1080/00325481.2015.1015393
47. Flythe JE, Hilliard T, Lumby E, et al. Fostering innovation in symptom management among hemodialysis patients: paths forward for insomnia, muscle cramps, and fatigue. *Clin J Am Soc Nephrol*. 2019;14(1):150–160. doi:10.2215/CJN.07670618
48. Irish AB, Viecelli AK, Hawley CM, et al. Effect of fish oil supplementation and aspirin use on arteriovenous fistula failure in patients requiring hemodialysis: a randomized clinical trial. *JAMA Intern Med*. 2017;177(2):184–193. doi:10.1001/jamainternmed.2016.8029
49. Viecelli AK, Polkinghorne KR, Pascoe EM, et al. Fish oil and aspirin effects on arteriovenous fistula function: secondary outcomes of the randomised omega-3 fatty acids (fish oils) and Aspirin in vascular access outcomes in

renal disease (favoured) trial. *PLoS One*. 2019;14(3):e0213274. doi:10.1371/journal.pone.0213274

50. Herrington W, Emberson J, Staplin N, et al. The effect of lowering LDL cholesterol on vascular access patency: post hoc analysis of the study of heart and renal protection. *Clin J Am Soc Nephrol*. 2014;9(5):914–919. doi:10.2215/CJN.10371013
51. Abacilar AF, Atalay H, Dogan OF. Oral prostacycline analog and clopidogrel combination provides early maturation and long-term survival after arteriovenous fistula creation: a randomized controlled study. *Indian J Nephrol*. 2015;25(3):136–142. doi:10.4103/0971-4065.139490
52. Crowther MA, Clase CM, Margetts PJ, et al. Low-intensity warfarin is ineffective for the prevention of PTFE graft failure in patients on hemodialysis: a randomized controlled trial. *J Am Soc Nephrol*. 2002;13(9):2331–2337. doi:10.1097/01.asn.0000027356.16598.99
53. Dixon BS, Beck GJ, Vazquez MA, et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. *N Engl J Med*. 2009;360(21):2191–2201. doi:10.1056/NEJMoa0805840
54. Lok CE, Moist L, Hemmelgarn BR, et al. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: a randomized controlled trial. *JAMA*. 2012;307(17):1809–1816. doi:10.1001/jama.2012.3473
55. Bowden RG, Wilson RL, Gentile M, Ounpraseuth S, Moore P, Leutholtz BC. Effects of omega-3 fatty acid supplementation on vascular access thrombosis in polytetrafluorethylene grafts. *J Ren Nutr*. 2007;17(2):126–131. doi:10.1053/j.jrn.2006.07.009
56. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(1):1–45. doi:10.1086/599376
57. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864. doi:10.1093/ajhp/zxaa036. Accessed May 25, 2021.
58. Lewis SJ, Nolin TD. New Vancomycin Dosing Guidelines for Hemodialysis Patients: Rationale, Caveats, and Limitations. *Kidney360*. 2021;2(8):1313–1315. doi:10.34067/kid.0000192021
59. Vardhan A, Hutchison AJ. Peritoneal dialysis. In: Gilbert SJ, Weiner DE, eds. *National Kidney Foundation's Primer on Kidney Disease*. 7th ed. Elsevier; 2018:539–552.
60. Rabindranath KS, Adams J, Ali TZ, Daly C, Vale L, Macleod AM. Automated vs. continuous ambulatory peritoneal dialysis: a systematic review of

randomized controlled trials. *Nephrol Dial Transplant*. 2007;22(10):2991–2998. doi:10.1093/ndt/gfm515

61. Wang AY-M. Peritoneal dialysis solutions, prescription and adequacy. In: Himmelfarb J, Ikizler TA, eds. *Chronic Kidney Disease, Dialysis, and Transplantation a Companion to Brenner and Rector's the Kidney*. 4th ed. Elsevier; 2018:480–508.e489.
62. Finkelstein F, Healy H, Abu-Alfa A, et al. Superiority of icodextrin compared with 4.25% dextrose for peritoneal ultrafiltration. *J Am Soc Nephrol*. 2005;16(2):546–554. doi:10.1681/ASN.2004090793
63. Moberly JB, Mujais S, Gehr T, et al. Pharmacokinetics of icodextrin in peritoneal dialysis patients. *Kidney Int Suppl*. 2002(81):S23–S33. doi:10.1046/j.1523-1755.62.s81.5.x
64. Silver SA, Harel Z, Perl J. Practical considerations when prescribing icodextrin: a narrative review. *Am J Nephrol*. 2014;39(6):515–527. doi:10.1159/000363417
65. Peritoneal Dialysis Adequacy Work Group. Clinical practice guidelines for peritoneal adequacy, update 2006. *Am J Kidney Dis*. 2006;48(suppl 1):S91–S97. doi:10.1053/j.ajkd.2006.05.016
66. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. *Perit Dial Int*. 2016;36(5):481–508. doi:10.3747/pdi.2016.00078
67. Li PK, Chow KM, Cho Y, et al. ISPD Peritonitis Recommendations: 2022 Update on Prevention and Treatment. *Perit Dial Int*. 2022;42(2):110–153. doi:10.1177/08968608221080586
68. Szeto CC, Li PK, Johnson DW, et al. ISPD Catheter-Related Infection Recommendations: 2017 Update. *Perit Dial Int*. 2017;37(2):141–154. doi:10.3747/pdi.2016.00120
69. Dhruve MJ, Bargman JM. Antibiotic prophylaxis in peritoneal dialysis patients. *Adv Perit Dial*. 2017;33(2017):55–58. https://www.ncbi.nlm.nih.gov/pubmed/29668433
70. Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Antimicrobial agents to prevent peritonitis in peritoneal dialysis: a systematic review of randomized controlled trials. *Am J Kidney Dis*. 2004;44(4):591–603. https://www.ncbi.nlm.nih.gov/pubmed/15384009
71. Badve SV, Hawley CM, McDonald SP, et al. Use of aminoglycosides for peritoneal dialysis-associated peritonitis does not affect residual renal function. *Nephrol Dial Transplant*. 2012;27(1):381–387. doi:10.1093/ndt/gfr274
72. Manley HJ, Bailie GR. Treatment of peritonitis in APD: pharmacokinetic principles. *Semin Dial*. 2002;15(6):418–421. doi:10.1046/j.1525-139x.2002.00103.x
73. Mancini A, Piraino B. Review of antibiotic dosing with peritonitis in APD. *Perit Dial Int*. 2019;39(4):299–305. doi:10.3747/pdi.2018.00209

74. Quellhorst E. Insulin therapy during peritoneal dialysis: pros and cons of various forms of administration. *J Am Soc Nephrol*. 2002;13(suppl 1):S92–S96. https://www.ncbi.nlm.nih.gov/pubmed/11792768

31

Dosing of Drugs in Kidney Failure

David J. Quan

CORE PRINCIPLES		CHAPTER CASES
1	The pharmacokinetics and pharmacodynamics of many drugs are altered in patients with impaired kidney function (eg, declining glomerular filtration rate) or who are on kidney replacement therapy.	**Case 31-1 (Questions 1, 2)** **Case 31-2 (Question 1)** **Case 31-3 (Questions 1, 3)** **Case 31-4 (Questions 1, 2)** **Case 31-5 (Questions 1)** **Case 31-8 (Questions 1, 3)**
2	Clinicians should be aware of drugs that require dosage adjustment in the setting of kidney dysfunction to avoid adverse drug events and poor patient outcomes.	**Case 31-1 (Questions 1, 2)** **Case 31-3 (Questions 1, 3)** **Case 31-4 (Question 1,2)** **Case 31-5 (Questions 1)**

CORE PRINCIPLES		CHAPTER CASES
3	Dosages of drugs that are cleared by the kidneys should be adjusted according to the patient's kidney function (eg, creatinine clearance or glomerular filtration rate). The initial dose can be determined using the manufacturer's prescribing information, published guidelines, or published literature.	**Case 31-1 (Questions 1, 4)** **Case 31-3 (Question 3)** **Case 31-4 (Question 1)** **Case 31-5 (Questions 1)**
4	Many drugs have a narrow therapeutic window (range of drug concentrations that will achieve the desired effect), for which there may be lack of efficacy with subtherapeutic levels and adverse events associated with elevated levels. Therapeutic drug concentration monitoring should be performed to achieve the desired target concentration.	**Case 31-1 (Questions 2, 3)** **Case 31-5 (Question 2)** **Case 31-7 (Question 1)** **Case 31-8 (Question 3)**
5	Kidney replacement therapy (eg, hemodialysis, continuous venovenous hemofiltration) can have a significant influence on the extracorporeal removal of drug. Clinicians should be aware of the method of kidney replacement therapy and its impact on drug dosing.	**Case 31-1 (Questions 5–8)** **Case 31-2 (Questions 1, 2)** **Case 31-3 (Questions 1, 4)** **Case 31-5 (Question 3)** **Case 31-6 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
6	Biotransformation of drugs may be altered in patients with kidney failure. Active or toxic metabolites may accumulate in patients with kidney failure, leading to adverse effects. Excipients such as diluents can also accumulate in the setting of kidney failure, resulting in toxicity.	**Case 31-3 (Question 2)** **Case 31-8 (Questions 1, 2)**

INTRODUCTION

The kidneys play an important role in the disposition of many drugs. It is important to design specific pharmacotherapeutic regimens for patients with kidney impairment. Without careful dosing and therapeutic drug monitoring for select medications in these patients, accumulation of drugs or toxic metabolites can occur, resulting in serious adverse effects. Many patients are treated with multiple medications, which may require even greater attention to dosage adjustment.

In addition to altered drug elimination, numerous other factors associated with kidney disease predispose patients to potential drug toxicity by altering the pharmacokinetic disposition and the pharmacodynamic effects of drugs. For example, the physiologic changes associated with uremia can change drug absorption, protein binding, distribution, or elimination. These physiologic effects can alter drug concentrations in the plasma or blood, and at the targeted tissue site of activity, thereby affecting drug efficacy and toxicity.

Less is known about the effect of kidney disease on drug pharmacodynamics (ie, the pharmacologic or toxicologic effects produced relative to the drug concentration). Patients with kidney

disease can be more sensitive to some drugs and experience an increased frequency of adverse drug reactions.

Effect of Kidney Failure on Drug Disposition

BIOAVAILABILITY

Several factors can potentially affect drug absorption in patients with kidney disease. Limited data are available describing altered bioavailability. For example, drug absorption could be impaired in uremia because of nausea, vomiting, diarrhea, gastritis, or edema of the gastrointestinal (GI) tract, the latter condition being a complication of nephrotic syndrome. Gastric and intestinal motility, as well as gastric emptying time, can be altered by the neuropathy associated with uremia. Uremia also can increase gastric ammonia, leading to an increased gastric pH, which may affect the bioavailability of drugs that require an acidic environment for absorption such as ferrous sulfate.[1] Similarly, calcium-containing antacids used by patients with kidney failure for GI symptoms and hyperphosphatemia can neutralize hydrochloric acid in the stomach and increase gastric pH. Patients with late-stage chronic kidney disease (CKD) often take oral phosphate binders, such as sevelamer and lanthanum carbonate, which can impair the absorption of other medications.[2,3]

The bioavailability of orally administered drugs also depends on the extent to which the drug is eliminated by first-pass (pre-systemic) metabolism. The first-pass hepatic metabolism of oral propranolol was found to be reduced in patients with kidney disease, leading to increased bioavailability.[4] Subsequent studies have attributed the observed increased concentrations of propranolol in kidney failure to a significant increase in the blood to plasma ratio.[5] Intestinal P-glycoprotein activity may be decreased as well.[6] Other drugs exhibiting increased bioavailability in kidney disease include zidovudine (AZT) and erythromycin.[7]

PROTEIN BINDING AND VOLUME OF DISTRIBUTION

Kidney disease can change the volume of distribution (Vd) of various drugs. The Vd or “apparent volume of distribution” is the “volume” or size of a compartment necessary to account for the total amount of drug in the body if it were present throughout the body at the same concentration as that found in plasma.

The extent to which a drug exerts its pharmacologic effects is related to the amount of free or unbound drug available for distribution to target tissues. Patients with kidney failure often have alterations in plasma protein binding, which can increase the amount of unbound drug. Clinically, this is most important for highly protein-bound (>80%) acidic drugs, whereas the binding of basic drugs is usually unchanged or possibly decreased in kidney disease.[8]

Hypoalbuminemia is a common complication of kidney failure. Because acidic rather than basic drugs are bound to albumin, their protein binding tends to be altered in patients with kidney failure **(Table 31-1)**.[9] Patients with uremia accumulate acidic metabolic byproducts that may inhibit binding or displace acidic drugs from albumin binding sites. This is supported by the observed improvement in protein binding after removal of uremic byproducts by hemodialysis. Finally, the structural conformation of albumin is altered in kidney disease, which may reduce the number or affinity of binding sites for drugs. Studies have demonstrated differences in the amino acid composition of albumin between healthy people and patients with uremia.[10] The anticonvulsant, phenytoin, is an example of a drug whose protein binding is altered in kidney disease.[11] This is discussed in more detail later in this chapter.

Table 31-1

Plasma Protein Binding (%) of Acidic Drugs in Kidney Failure

Drug	Normal	Kidney Failure
Cefazolin	85	69
Clofibrate	97	91
Diazoxide	94	84
Furosemide	96	94

Drug	Normal	Kidney Failure
Pentobarbital	66	59
Phenytoin	88–93	74–84
Salicylate	87–97	74–84
Sulfamethoxazole	66	42
Valproic acid	92	77
Warfarin	99	98

Drugs that are not highly protein bound (eg, gentamicin, isoniazid) have little change in their Vd in kidney disease. Digoxin is a unique exception in that its Vd is decreased in kidney disease. This is attributed to a decrease in myocardial tissue uptake of digoxin, leading to a decrease in the myocardial or tissue to serum concentration ratio.[12]

ELIMINATION

The extent to which kidney disease affects the elimination of a drug depends on the amount of drug normally excreted unchanged in the urine and the degree of kidney impairment. As kidney disease progresses, the kidney's capacity to excrete uremic toxins diminishes. Consequently, the ability to eliminate certain drugs that are excreted by the kidneys also decreases. If the dose of these drugs is not modified for the patient's degree of kidney dysfunction, these drugs will accumulate, potentially leading to an increase in the pharmacologic effect and toxicity.

The kidney eliminates drugs primarily by filtration or active secretion. Characteristics of a drug that determine its ability to be filtered include its affinity for protein binding and its molecular weight (MW). Drugs with low protein binding or those that are displaced from proteins in the setting of kidney disease are filtered more readily. Molecules with a high MW (>20,000 Da) are not readily filtered because of their large size. The reasons for how kidney disease selectively alters the process of glomerular filtration or tubular secretion of specific drugs are not well understood. The

elimination of drugs by the kidneys in patients with kidney disease usually can be estimated by measuring the ability of the kidney to eliminate substances such as creatinine (ie, creatinine clearance [CrCl]) (see Chapter 28, Chronic Kidney Disease).

Organic anion transporters (OATs) are predominantly found in the basolateral membrane of the renal tubules. OATs facilitate the uptake of small organic anions into renal tubular cells. Decreased OAT activity as a result of acute kidney injury can decrease the secretion of various drugs such as methotrexate, nonsteroidal anti-inflammatory drugs, and acetylsalicylic acid.[13]

Kidney disease can also have an important impact on the elimination of drugs that are primarily metabolized by the liver.[14] Metabolic processes, such as hydroxylation and glucuronidation, often produce inactive, more polar compounds that can be eliminated by the kidney. The metabolites of some drugs (eg, meperidine, morphine, procainamide) are pharmacologically active or toxic. In the setting of decreased kidney function, these metabolites may accumulate, leading to an increase in pharmacologic activity and adverse effects.[15] For example, the central nervous system (CNS) toxicity observed in kidney disease has been attributed to accumulation of the morphine metabolite, morphine-6-glucuronide.[16] Therefore, careful dosing modifications or avoidance of these drugs is warranted in patients with kidney impairment. Metabolic enzymes have been found within kidney tissue and may play a role in the metabolism of some drugs.[17] For example, the non-kidney clearance of drugs (eg, acyclovir) decreases in patients with kidney impairment and is believed to be caused by a decrease in “kidney” metabolism.[18]

Excipients used to formulate medications should also be considered. For example, the pharmacokinetics of antifungal agents such as posaconazole and voriconazole are not significantly altered in the setting of kidney dysfunction.[19,20] However, the parenteral formulations of itraconazole, posaconazole, voriconazole, and remdesivir contain the solubilizing agent, β-cyclodextrin, which is normally rapidly eliminated by glomerular filtration but can accumulate in patients with kidney impairment.[21,22] Hemodialysis and

continuous renal replacement therapy (CRRT) removes β-cyclodextrin but not voriconazole or posaconazole, therefore allowing standard intravenous (IV) doses to be given.[23–25]

Drug Removal by Dialysis

The effect of hemodialysis on the removal of a specific drug must be considered when using medications in patients undergoing dialysis. Patients may need supplemental doses of a medication after each hemodialysis session or alteration in their dosage to maintain therapeutic drug concentrations. Hemodialysis can also be initiated to hasten drug removal from the body in some cases of drug overdose.

The primary literature should be used to determine whether any information is available about the ability of hemodialysis to remove the drug. The application of data from the literature to a specific clinical situation often is difficult, as information pertaining to the removal of a specific drug by hemodialysis may be limited.

When applying information from the primary literature to a specific patient, the specifics of the dialyzer (eg, type of machine, membrane surface area, pore size, and blood and dialysis flow rates) must be considered (see Chapter 30, Dialysis Treatment for Chronic Kidney Failure). Furthermore, patient-specific information (eg, time of drug ingestion and liver and kidney function) from case reports in the literature also should be evaluated appropriately. The method used to calculate dialysis clearance also should be considered. In addition, clinical investigators often use predialysis and postdialysis serum drug concentrations for estimating drug dialyzability.[26]

The contributing effects of drug metabolism and excretion on drug elimination should also be taken into account.

DRUG-SPECIFIC PROPERTIES

The physical and chemical characteristics of drugs can be used to predict the effectiveness of dialysis on drug removal.[27–29] Low-MW compounds are more readily dialyzed by conventional hemodialysis

procedures because they can pass with greater ease across the dialysis membrane. Using cuprophane dialysis membranes, compounds with an MW of 500 or less are more likely to be significantly dialyzed than compounds with a high MW (eg, vancomycin, MW ~1400). Newer high-flux dialyzers using polysulfone-based membranes more effectively remove large chemical compounds (see Dialyzer Characteristics section and Chapter 30, Dialysis Treatment for Chronic Kidney Failure). In addition, water-soluble drugs (eg, aminoglycosides, lithium) are removed more readily by dialysis than are lipid-soluble compounds (eg, diazepam) or those that partition into red blood cells (eg, tacrolimus).

Pharmacokinetic characteristics (eg, Vd, protein binding) also can affect drug dialyzability. A drug with a large Vd that distributes widely into the peripheral tissues resides minimally in the plasma and, therefore, is not substantially removed by dialysis. This is particularly true for highly lipid-soluble drugs such as digoxin (Vd 300–500 L) and amiodarone (Vd 60 L/kg). In addition, drugs that are highly protein bound, such as warfarin (99%) and ceftriaxone (83%–96%), are not significantly removed by dialysis because the large protein–drug complex is unable to pass through the dialysis membrane.

Because clearance values are additive, the hepatic and other non-kidney plasma clearance of a drug should be considered in relation to the dialysis clearance. Only when dialysis clearance contributes a substantially additive effect to the patient's own clearance is drug elimination enhanced. For example, AZT has a large non-kidney plasma clearance in patients with severe kidney disease (~1200 mL/minute). Therefore, despite a hemodialysis clearance of 63 mL/minute, the contribution of dialysis to total AZT removal is negligible.

HIGH-FLUX HEMODIALYSIS

High-flux hemodialysis uses higher blood and dialysate flow rates compared with conventional methods. The enhanced efficiency of high-flux dialysis and the larger pore size of membranes made from

a variety of materials, such as polysulfone and polysulfone blends, allow for small- and mid-MW compounds (eg, vancomycin) to be partially removed. Drugs such as gentamicin and foscarnet, which are removed by conventional dialysis, are also efficiently removed by high-flux hemodialysis.[30,31] In many cases, the net amount of drug removed during a high-flux dialysis session is greater than the amount removed during conventional dialysis because of the larger pore size allowing for greater diffusion of solute. The principal difference is the greater efficiency and the ability to clear drugs of larger MW compared with conventional dialysis.

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

Continuous ambulatory peritoneal dialysis (CAPD) uses the patient's peritoneum as the dialysis membrane. Patients maintained with CAPD undergo infusion of a dialysate solution via a catheter inserted into the peritoneal cavity or the solution is allowed to dwell in the cavity for several hours. The accumulated fluid and uremic byproducts diffuse from the blood into the dialysate solution, which is exchanged every 4 to 8 hours (see Chapter 30, Dialysis Treatment for Chronic Kidney Failure).

Some drugs, such as antibiotics, can be administered intraperitoneally (IP) in patients on CAPD by directly adding them to the dialysate solution. This is particularly useful for patients with peritonitis who require high intraperitoneal concentrations of antimicrobial agents to treat this infection. After intraperitoneal administration of drugs, such as the aminoglycosides, plasma and intraperitoneal drug concentrations will eventually reach equilibrium. Despite systemic absorption of these drugs from the peritoneal fluid, peritoneal dialysis (PD) usually is inefficient at removing drugs from the plasma.[32] Because CAPD contributes little to the overall elimination of most drugs, dosage modifications are not always necessary in patients having this procedure.

CONTINUOUS RENAL REPLACEMENT THERAPY

Continuous venovenous hemofiltration (CVVH) is a form of continuous renal replacement (CRRT) therapy used in patients who are critically ill with kidney failure. CRRT is typically reserved for patients who are unable to tolerate hemodialysis because of hemodynamic instability. Refer to Chapter 29, Acute Kidney Injury, for a discussion on the indications for and various modalities of kidney replacement therapy.

Data concerning the removal of drugs by hemodialysis cannot be extrapolated to CRRT because of differences in the membranes, blood flow rates, ultrafiltration rate, dialysate flow rate, and the continuous nature of the procedure compared with intermittent hemodialysis. Limited data are available on the effect of CRRT on the removal of drugs. Drugs that have a high sieving coefficient (permeability of a drug through a semipermeable membrane), such as aminoglycosides, ceftazidime, and vancomycin, are readily removed by CVVH.[33–35] CVVH clearance can be estimated to determine the appropriate dosage regimen based on the pharmacologic characteristics of a specific drug (see Case 31-1, Question 8). A literature search should be conducted for estimated drug removal based on modality, flow rates, and the most current recommendations for drug dosing.[27]

HEMOPERFUSION

Hemoperfusion is another method of drug removal that may be used to facilitate the elimination of a drug in the setting of an overdose such as phenytoin.[36,37] During the hemoperfusion procedure, blood is passed through a column of adsorbent material (eg, activated charcoal or resin) to bind toxins and drugs. Hemoperfusion can be particularly useful for removing large MW compounds or highly protein-bound drugs that are not removed efficiently by hemodialysis. Large compounds and drug–protein complexes are adsorbed onto the high-surface-area resin as blood passes through the adsorbent column.

Pharmacodynamics and Kidney Disease

Few studies have investigated the pharmacodynamics of drugs in patients with kidney disease. Clinical observations report that patients with kidney disease are more sensitive to various drugs. For example, morphine has been associated with increased neurologic depression in patients with kidney failure. The ability of morphine to potentiate the CNS-depressant effects of uremia may result from an alteration in the permeability of the blood–brain barrier that results in higher CNS levels of morphine and morphine-6-glucuronide.[38]

Another example of altered drug response in uremia is that of nifedipine, which at similar unbound plasma concentrations has an increased antihypertensive effect in patients with kidney disease.[39] Therefore, the dose of nifedipine may need to be adjusted in patients with kidney disease because of changes in drug effects rather than pharmacokinetic alterations.

The pharmacokinetics of warfarin is not significantly altered in kidney failure. However, patients with kidney failure who are prescribed warfarin have a higher incidence of hemorrhagic complications, likely because of platelet dysfunction from uremia, and drug–drug interactions from concomitant medications.[40,41]

PHARMACOKINETICS AND PHARMACODYNAMICS OF SPECIFIC DRUGS IN KIDNEY FAILURE

Ceftazidime

DOSAGE MODIFICATION: FACTORS TO CONSIDER

CASE 31-1

QUESTION 1: G.G., a 31-year-old, 154.32-pound (70-kg) female with a 3-year history of systemic lupus erythematosus (SLE) presents to the emergency department (ED) with a 5-day history of fatigue, weakness, and nausea as well as worsening of her facial rash and a fever of 104 °F (40 °C). Her SLE had been

moderately controlled until this acute flare. Her admission laboratory workup now reveals the following pertinent values:

Potassium (K^+), 6.0 mEq/L
Sodium (Na^+), 142 mEq/L
Serum creatinine (SCr), 3.4 mg/dL
Blood urea nitrogen (BUN), 38 mg/dL

Complete blood count (CBC) reveals a hematocrit of 32% and a hemoglobin of 9.2 g/dL. The platelet count is 50,000/μL, and her erythrocyte sedimentation rate is 35 mm/hour. Physical examination is significant for a blood pressure of 136/92 mm Hg and 2+ pedal edema. Prednisone is started at a dose of 1.5 mg/kg/day.

During her hospital course, G.G.'s condition worsens, and signs of sepsis develop. *Pseudomonas aeruginosa* is cultured from her urine. Therapy with ceftazidime is initiated at a dose of 2 g every 8 hours, a dose commonly used for patients with normal kidney function.

Considering that G.G.'s kidney function has remained stable and that she has an estimated CrCl of 27 mL/minute, what factors should be considered before modifying her dose? What would be an appropriate dose of ceftazidime for G.G.?

Before modifying the dose of any drug, its route of elimination should be established. As a general rule, the degree to which kidney impairment affects elimination depends on the percentage of unchanged drug that is excreted by the kidney. Thus, the elimination of most drugs that are primarily cleared by the kidneys will be decreased in the setting of kidney impairment. For many drugs dependent on the kidney for elimination, relationships between some measurements of kidney function (eg, CrCl) and some parameters of drug elimination (eg, plasma clearance or half-life) have been established to help clinicians determine the appropriate dosing modifications in patients with kidney disease.

In contrast, the clearance of drugs that are eliminated primarily by non-kidney mechanisms (eg, hepatic metabolism) may not be altered significantly in patients with kidney disease. However, some drugs have water-soluble metabolites that have either pharmacologic activity or potential toxicity and that may accumulate with kidney dysfunction, warranting dosage adjustment or avoidance of the drug entirely (eg, meperidine; see Case 31-8, Question 1).

Enzymes with metabolic capacity have also been found within kidney tissue, which can result in the kidneys playing a limited role in the metabolism of certain drugs (see Case 31-3, Question 2).

Another important factor to consider is the “therapeutic window” for a given drug (ie, the range of drug concentrations thought to be most effective). Drug concentrations below this range are usually subtherapeutic, whereas concentrations above this range can lead to a greater incidence of adverse effects. For drugs with a wide therapeutic window, the difference between toxic and therapeutic concentrations is large. Although many drugs that are cleared primarily by the kidney may require dosing modifications in patients with kidney dysfunction, aggressive dose reduction may not be necessary for drugs with a large therapeutic window, particularly if the adverse effects of the drug (eg, fluconazole) are relatively mild. This is in contrast to drugs (eg, aminoglycosides, vancomycin, or foscarnet) that are eliminated primarily by the kidney and have narrow therapeutic windows. For these drugs, the toxic plasma concentrations are very close to the therapeutic drug concentrations, with little room for dosing error.

Ceftazidime is a cephalosporin that has excellent activity against most strains of *Pseudomonas* species. As with most cephalosporins, ceftazidime primarily is cleared by the kidneys, with little nonrenal or hepatic elimination.[42] The clearance of ceftazidime correlates with CrCl.

Because her sentinel clearance is approximately one-third of normal, she would require about one-third of the normal daily dose (ie, 2 g every 24 hours). As with other cephalosporins, ceftazidime has a large therapeutic window.[43] Failure to reduce the dose from a normal dose of 2 g every 8 hours, although likely safe, might lead to accumulation of ceftazidime, predisposing G.G. to seizures and other adverse effects associated with toxic β-lactam antibiotic plasma levels.[44,45] This is in contrast to the aminoglycosides, which must be dosed based on specific pharmacokinetic calculations.

Aminoglycosides

CASE 31-1, QUESTION 2: G.G.'s medical team decides that the addition of an aminoglycoside antibiotic is necessary to treat her infection. Considering that her kidney function has remained stable, how should gentamicin be dosed in G.G.? Is it best to alter the dose or the dosing interval for this drug?

ALTERATION OF DOSE VERSUS DOSING INTERVAL

The aminoglycosides (eg, tobramycin, gentamicin, amikacin) are effective in the treatment of serious systemic infections caused by gram-negative organisms such as *Pseudomonas* species. Unlike the cephalosporins and penicillins, however, the aminoglycosides have a relatively narrow therapeutic window. Using pharmacokinetic principles, a dose regimen can be designed to produce specific peak and trough serum concentrations. Peak serum concentrations (Cp_{peak}) (eg, gentamicin or tobramycin 5–8 mg/L) correlate best with therapeutic efficacy, whereas toxicity tends to correlate with elevated trough levels (Cp_{trough}), which reflects prolonged exposure to high drug concentrations. To minimize the risk of toxicity, trough levels of <2 mg/L should be maintained. In patients with normal kidney function, these target serum aminoglycoside concentrations are usually obtained after standard doses (eg, 1.5 mg/kg) administered every 8 hours. Peak and trough levels are typically measured once steady state is achieved, which is typically within 24 hours.[46–48]

The discussion regarding aminoglycoside dosing in kidney impairment that follows is based on the traditional every 8 hours dosing regimen.

Aminoglycosides are almost completely eliminated by the kidneys; thus, the clearance of these drugs essentially is equal to the glomerular filtration rate (GFR). The pharmacokinetic properties of gentamicin and tobramycin are similar. A close correlation also exists between CrCl (a surrogate for GFR) and gentamicin total body clearance. As kidney function deteriorates, aminoglycoside doses must be modified to achieve the desired peak and trough plasma concentrations. Failure to appropriately adjust the dosage of aminoglycosides in kidney insufficiency can lead to high drug plasma levels that can result in ototoxicity and nephrotoxicity.

In many cases, the aminoglycoside dose can be modified by extending the dosing interval rather than simply reducing the dose. This permits maintenance of adequate peak plasma concentrations to ensure efficacy while allowing for sufficient elimination between doses to produce trough levels <2 mg/L. The advantages and disadvantages of adjusting the dosing interval versus reducing the dose are summarized in **Table 31-2**. **Figure 31-1** illustrates the effect of increasing the dosing interval in a patient such as G.G. with kidney function that is 30% of normal. Although this is the preferred method for adjusting the dose of aminoglycosides, for many other drugs requiring dose adjustments in kidney disease, simple dosage reduction is sufficient.

Table 31-2

Advantages and Disadvantages of General Approaches to Dosing Adjustments in Kidney Disease

Method	Advantages	Disadvantages
Variable Frequency		
Use the same dose but increase the dosing interval.	Same Cp_{ave}, Cp_{max}, Cp_{min} Normal dose	Levels may remain subtherapeutic for prolonged periods in patients requiring dosing intervals >24 hours.
Variable Dose With Fixed Cp_{ave}		
Decrease dose to maintain a target Cp_{ave}; keep the dosing interval the same.	Same Cp_{ave} Normal dosing interval	Decrease peak levels, which may be subtherapeutic; increase trough levels, which may increase potential for toxicity.

Cp_{ave}, average plasma concentration; Cp_{max}, maximum plasma concentration; Cp_{min}, minimum plasma concentration.

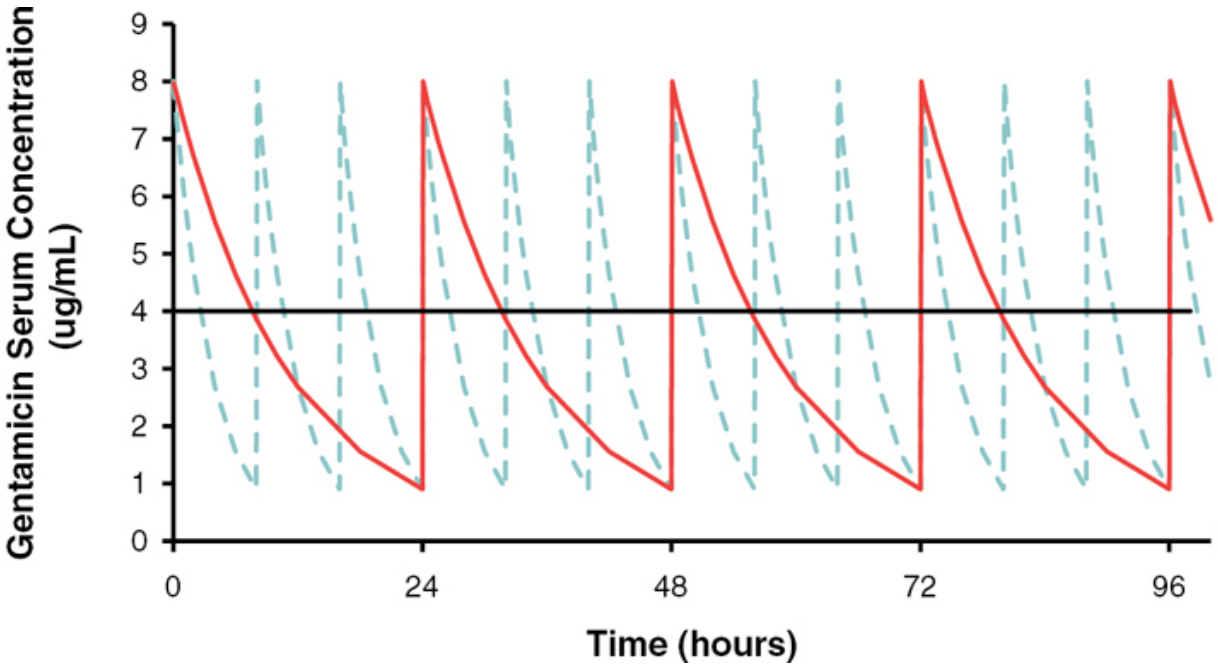


Figure 31-1 Serum concentration versus time profile for a patient with normal kidney function (*dotted line*), and for patient G.G. (Case 31-1) whose estimated creatinine clearance is 27 mL/minute (*solid lines*).

Many clinicians now use extended interval dosing of the aminoglycosides (eg, 7 mg/kg every 24 hours) for patients with normal kidney function in an attempt to minimize aminoglycoside accumulation and nephrotoxicity. The rationale for this regimen is based on the aminoglycosides' concentration-dependent killing and postantibiotic effect. This approach is not recommended for patients with advanced kidney impairment, however. When extended interval dosing is used, peak concentrations are less helpful; however, trough concentrations should be monitored with a target of being below the limit of analytic detection (<1 mg/L).[49,50] Commonly used drug references can be used for dosing guidelines for drugs used in patients with kidney failure.[51,52]

DETERMINATION OF APPROPRIATE DOSE

A number of methods have been developed to determine the appropriate aminoglycoside dose for patients.[53] One method is

Bayesian forecasting, in which pharmacokinetic data obtained in the individual patient are integrated with population parameters. Initially, a dose is used that is based on population parameter values adjusted for characteristics such as increased SCr. Drug concentrations for the individual patient are measured at specific times (eg, peak and trough measurements), and these are compared with the expected values from the population data. Individualized pharmacokinetic parameter estimates are subsequently derived using Bayes theorem to calculate a more patient-specific dosing regimen.[54]

Because of the wide interpatient variability in aminoglycoside pharmacokinetic parameters and the narrow therapeutic index for these drugs, doses should be adjusted based on pharmacokinetic principles (eg, Bayesian calculations or methods described later in this chapter) and plasma concentrations that are specific for this patient.

Patient-specific methods

Sawchuk et al developed a method to derive patient-specific estimates of Vd and clearance based on the patient's size and estimated CrCl.[47] These parameters can be used to calculate a specific dose for G.G. that will produce the desired gentamicin peak and trough concentrations. If steady-state serum concentrations of gentamicin are known, they can be used to calculate patient-specific parameters. To initiate gentamicin therapy, pharmacokinetic parameters should first be estimated from population values.

The clearance of gentamicin (Cl_{gent}) can be calculated based on G.G.'s CrCl. Using the Cockcroft–Gault equation,[55] the CrCl can be estimated as follows:

$$\text{CrCl (males)} = \frac{(140 - \text{age})(\text{IBW})}{(\text{SCr})(72)} \qquad \textbf{(Eq. 31-1)}$$

$$\text{CrCl (females)} = \frac{(140 - \text{age})(\text{IBW})}{(\text{SCr})(72)}(0.85) \quad \textbf{(Eq. 31-2)}$$

where IBW is ideal body weight in pounds (kilograms), age is measured in years, and SCr is serum creatinine in mg/dL.

With an SCr of 3.4 mg/dL, an ideal body weight of 154.32 lb (70 kg), and an age of 31 years, G.G.'s estimated CrCl is 27 mL/minute.

For practical purposes, Cl_{gent} is usually considered equivalent to CrCl. Therefore, Cl_{gent} also is ~27 mL/minute or 1.6 L/hour. The Vd of gentamicin (Vd_{gent}) is ~0.25 L/kg in patients with normal or impaired kidney function.[47,56]

The Vd_{gent} will be different in patients who are obese or those who have fluid overload. Although G.G. does have some fluid retention, this is minimal and should not affect her Vd_{gent} significantly. Therefore, the Vd_{gent} for G.G. is as follows:

$$\begin{aligned} Vd_{gent} &= (0.25\ \text{L/kg})(\text{body weight}) \\ &= (0.25\ \text{L/kg})(70\ \text{kg}) \\ &= 17.5\ \text{L} \end{aligned} \quad \textbf{(Eq. 31-3)}$$

For treatment of infections caused by *Pseudomonas* species, a peak level of ~6 to 8 mg/L is desired.

The loading dose of gentamicin (LD_{gent}) can be determined using the following equation:

$$LD_{gent} = (Vd_{gent})(\text{desired } Cp_{peak}) \quad \textbf{(Eq. 31-4)}$$

$$\begin{aligned} LD_{gent} &= (17.5\ \text{L})(7\ \text{mg/L}) \\ &= 122.5\ \text{mg or round off to } 120\ \text{mg} \end{aligned}$$

Using Cl_{gent} and Vd_{gent}, the elimination rate constant (Kd) and half-life for gentamicin can be estimated as follows:

$$\text{Kd} = \frac{\text{Cl}_{\text{gent}}}{\text{Vd}_{\text{gent}}} \quad \text{(Eq. 31-5)}$$

$$= \frac{1.6\ \text{L/hour}}{17.5\ \text{L}}$$

$$= 0.091\ \text{hour}^{-1}$$

$$t_{1/2} = \frac{0.693}{\text{Kd}} \quad \text{(Eq. 31-6)}$$

$$= \frac{0.693}{0.091\ \text{hour}^{-1}}$$

$$= 7.6\ \text{hours}$$

For the aminoglycosides, the dosing interval (τ) is determined by doubling the half-life, because by the end of two half-lives, 75% of the drug will have been eliminated. This will usually lead to a desired trough level of <2 mg/L. Therefore, gentamicin should be administered at least every 16 hours. For convenience, an interval of 24 hours can be used, which also will achieve the desired trough concentration.

Gentamicin is usually infused over 30 minutes. To determine the peak gentamicin concentration, serum samples are drawn 30 minutes after the infusion has been completed. Because the estimated elimination half-life of gentamicin in G.G. (7.6 hours) is much longer than the infusion time (0.5 hours), the intravenous bolus model can be used to calculate an appropriate maintenance dose.

To achieve the peak concentration of 7 mg/L, the following equation can be used:

$$\text{Dose} = \frac{(Cp_{peak})(1 - e^{-Kd\tau})(Vd_{gent})}{(e^{-Kdt_{sample}})} \quad \text{(Eq. 31-7)}$$

$$= \frac{(7\ \text{mg/L})(1 - e^{-(0.091\ \text{hour}^{-1})(24\ \text{hour})})(17.5\ \text{L})}{(e^{-(0.091\ \text{hour}^{-1})(1\ \text{hour})})}$$

$$= 119.2\ \text{mg}$$

$$= \text{or round off to } 120\ \text{mg}$$

where t_{sample} usually equals 1 hour (30 minutes after a 30-minute infusion).

The expected trough level in G.G. can now be estimated by the following equation:

$$Cp_{trough} = (Cp_{peak})(e^{-Kd\tau_{sample}}) \quad \text{(Eq. 31-8)}$$

$$= (7\ \text{mg/L})(e^{-(0.091\ \text{hour}^{-1})(24\ \text{hours})})$$

$$= 0.8\ \text{mg/L}$$

REVISED PARAMETERS

CASE 31-1, QUESTION 3: After 72 hours of gentamicin therapy, G.G.'s peak and trough levels are 7.6 and 2.6 mg/L, respectively. Her physician attributes this to a gradual decline in kidney function. (Her most recent SCr has increased 4.8 mg/dL.) How would you revise G.G.'s dosing regimen based on these levels?

A gentamicin trough level of >2 mg/L suggests that G.G.'s dosing interval is too short. Although her peak concentration is within the normal range of 5 to 8 mg/L, her trough concentration indicates that she is at a potentially toxic level. Her pharmacokinetic parameters can be revised based on these values, and a new Kd can be estimated from the following equation:

$$Kd = \frac{\ln\left(\frac{CP_1}{CP_2}\right)}{\Delta t} = \frac{\ln\left(\frac{7.6\ mg/L}{2.6\ mg/L}\right)}{23\ hours} = 0.047\ hour^{-1} \quad \textbf{(Eq. 31-9)}$$

Because little change in G.G.'s Vd_{gent} is expected, a new Cl_{gent} ($Cl_{revised}$) can be estimated from her revised elimination constant (while a revised Vd_{gent} could be calculated, keeping Cl_{gent} constant, the clearance is more likely to change than the volume of distribution):

$$\begin{aligned} Cl_{revised} &= (Vd_{gent})(Kd) \\ &= (17.5\ L)(0.047\ hour^{-1}) \\ &= 0.82\ L/hour \end{aligned} \quad \textbf{(Eq. 31-10)}$$

These revised values by increasing the dosing interval to 484 for Kd and Cl can now be used to calculate a revised maintenance dose to maintain the Cp_{trough} at <2 mg/L using Equation 31-7:

$$\begin{aligned} Dose &= \frac{(7\ mg/L)(1 - e^{-(0.047\ hour^{-1})(48\ hours)})(17.5\ L)}{e^{-(0.047\ hour^{-1})(1\ hour)}} \\ &= 115\ mg \\ Cp_{trough} &= (7\ mg/L)(e^{-(0.047\ hour^{-1})(48\ hours)}) \\ &= 0.73\ mg/L \end{aligned} \quad \textbf{(Eq. 31-11)}$$

The revised dose is now 115 mg (or ~110 mg) every 48 hours.

CASE 31-1, QUESTION 4: What are some limitations in calculating G.G.'s CrCl based on her SCr? Can this estimate safely be used to predict gentamicin clearance?

See Chapter 28, Chronic Kidney Disease, for information about equations used to calculate CrCl and estimate GFR. For patients with stable kidney function, CrCl can be estimated from SCr using the Cockcroft–Gault equation (see Equations 31-2 and 31-3). In a patient such as G.G., however, whose kidney function continues to decline during the hospital course, estimation of kidney function based on her increasing SCr becomes more difficult. Because her SCr does not reflect a steady-state level, the previous equations can no longer be used to accurately estimate her kidney function. Because G.G.'s SCr has increased rapidly from 3.4 to 4.8 mg/dL during the past few days, her CrCl is probably much lower than that estimated using the Cockcroft–Gault method. A rising SCr may represent a decline in kidney function manifesting as an accumulation of creatinine.

Although prediction equations such as the Modification of Diet in Renal Disease (MDRD) equations are a good measure of GFR,[57] they were developed in patients with chronic kidney disease, therefore limiting its use in healthy patients. In addition, the MDRD equation has not been validated for the dosing of most drugs in the setting of kidney dysfunction.[58,59] There can be significant differences in drug dosing regimens when the MDRD and Cockcroft–Gault methods are used to estimate kidney function.[60,61] The Cockcroft–Gault equation has been the standard method to estimate kidney function to determine if drug dosage adjustments are necessary. It also should be noted that the units for the Cockcroft–Gault equation for CrCl is mL/minute, whereas the units for the MDRD equation for estimated GFR is mL/minute/1.73 m^2. The manufacturer's prescribing information and available literature should be evaluated to determine the appropriate dosage regimen based on the patient's kidney function.

Effect of Hemodialysis

CONVENTIONAL HEMODIALYSIS

Gentamicin

CASE 31-1, QUESTION 5: G.G.'s kidney function continues to deteriorate to the extent that she requires hemodialysis. What additional alterations in her gentamicin dosing regimen are necessary when she is having hemodialysis?

Gentamicin has an MW of about 500 and a relatively low Vd (averaging 0.25 L/kg) and is about 10% bound to proteins, all favoring effective removal by conventional hemodialysis.[48] For a given patient, the observed dialysis clearance of gentamicin using conventional methods also depends on factors such as the physical properties of the dialysis filter, the blood and dialysate flow rates, and the length of dialysis. Studies indicate that dialysis clearance of gentamicin averages 45 mL/minute compared with an average plasma clearance of 5 mL/minute in patients with CKD.[62,63] Therefore, G.G.'s gentamicin dose must be adjusted to compensate for the amount of drug that will be removed by hemodialysis. Because drug removal represents a combination of drug elimination by the body and hemodialysis, the following equation can be used:

$$Cl_{total} = Cl_{dial} + Cl \qquad \textbf{(Eq. 31-12)}$$

where Cl_{total} is the total clearance of the drug during dialysis, Cl_{dial} is the clearance by dialysis, and Cl is plasma clearance. If dialysis clearance is high relative to plasma clearance, drug removal will be enhanced by the dialysis procedure. The total clearance of gentamicin in a patient with severe kidney dysfunction during hemodialysis is 50 mL/minute (45 + 5 mL/minute) or 10 times the clearance while off hemodialysis. Plasma clearance and hemodialysis clearance are related to the elimination half-life by the following equation:

$$t_{1/2} = \frac{(0.693)(Vd)}{Cl_{dial} + Cl} \qquad \textbf{(Eq. 31-13)}$$

Thus, assuming a constant Vd of 17.5 L (ie, 0.25 L/kg × 70 kg), the elimination half-life on hemodialysis is ~4 hours compared with 40 hours off hemodialysis. In addition, the extent (fraction) of drug removal (FD) during a timed dialysis run can be predicted from the following equation:

$$FD = 1 - e^{-(Cl + Cl_{dial})(t/Vd)} \quad \textbf{(Eq. 31-14)}$$

where t is the duration of dialysis. Therefore, the fraction of gentamicin removed (FD) during a 4-hour conventional hemodialysis procedure is ~50%. If specific data are not available for hemodialysis and plasma clearance, the following equation will predict fraction removed using the elimination half-life data alone obtained during hemodialysis:

$$FD = 1 - e^{-(0.693/t_{1/2on})(t)} \quad \textbf{(Eq. 31-15)}$$

The estimated value of 50% removal is consistent with literature values indicating that 50% to 70% of a dose of gentamicin is removed during a 4-hour hemodialysis procedure. A limitation of this equation, however, is that it does not consider the redistribution of drug from the tissues back into the plasma after the hemodialysis procedure.

It is generally difficult to calculate an appropriate maintenance dose for patients having hemodialysis that will maintain peak and trough concentrations similar to patients with normal kidney function, in part because of the large variability found in aminoglycoside pharmacokinetic parameters.[63,64] Sustained plasma concentrations >2 mg/L can increase the risk of toxicity; however, dosing gentamicin to achieve trough concentrations of <2 mg/L may lead to prolonged periods of subtherapeutic peak concentrations because one would have to use smaller doses with lower peak concentrations to allow the troughs to decrease before the next dose. Another practical consideration is that unless one expects the patient to recover kidney function in the future, kidney toxicity of the drug is less of a concern. As a compromise in patients receiving hemodialysis,

gentamicin doses are given to achieve a predialysis trough concentration of ~3 mg/L. This can generally be achieved with a loading dose of 2 mg/kg, followed by a maintenance dose of 1 mg/kg after each hemodialysis session.

Ceftazidime

Case 31-1, Question 6: Why does the dose of ceftazidime in G.G. have to be adjusted because of her hemodialysis when this drug has such a large therapeutic window?

Because only 21% is protein bound and its Vd is 0.2 L/kg, ceftazidime should be readily removed by hemodialysis. The mean dialysis clearance of ceftazidime is 55 mL/minute, with 55% of the drug removed during 4 hours of conventional hemodialysis.[65] A supplemental dose of ceftazidime should be given to G.G. after each hemodialysis session to maintain a therapeutic concentration. Alternatively, giving a larger dose (such as 1 g) three times a week (after each hemodialysis session) would be more convenient.

HIGH-FLUX HEMODIALYSIS

Case 31-1, Question 7: G.G.'s physician is considering changing her from a conventional dialysis system to a high-flux system that uses high-efficiency polysulfone membranes. How does the dialyzability of gentamicin and ceftazidime differ with high-flux hemodialysis compared with conventional hemodialysis?

High-flux hemodialysis is more effective than conventional hemodialysis at removing certain pharmacologic agents (see Chapter 30, Dialysis Treatment for Chronic Kidney Failure) because the membranes are more efficient and there is greater blood flow through the dialyzer. Although limited data are available, a greater fraction of drugs, such as aminoglycosides, ceftazidime, and vancomycin, are removed by high-flux versus conventional hemodialysis.[66,67] Approximately 50% to 70% of gentamicin is

removed during a 2.5-hour, high-flux dialysis session.[30] The clearance of ceftazidime by high-flux hemodialysis is 75 to 240 mL/minute compared with 55 mL/minute for conventional hemodialysis.[66] Thus, further dosage adjustments for gentamicin and ceftazidime may be necessary if G.G. is converted from conventional hemodialysis to high-flux hemodialysis.

CONTINUOUS VENOVENOUS HEMOFILTRATION

CASE 31-1, QUESTION 8: What changes would be necessary in G.G.'s gentamicin dosing if she were to start a CRRT such as CVVH?

Because of the continuous nature of CVVH, the extent of drug eliminated will differ from intermittent modes such as hemodialysis. The clearance of a drug in a patient receiving CVVH can be described in a fashion similar to Equation 31-12, where Cl_{dial} is replaced with Cl_{cvvh}.

$$Cl_{total} = Cl + Cl_{cvvh} \quad \textbf{(Eq. 31-16)}$$

In G.G., the $Cl_{revised}$ from Equation 31-10 can be used for the plasma clearance (Cl). The clearance by CVVH can be described by the following equation:

$$Cl_{cvvh} = Fu + UFR \quad \textbf{(Eq. 31-17)}$$

where Fu is the fraction of drug unbound and UFR is the ultrafiltration rate. Gentamicin exhibits low plasma protein binding (Fu ~0.95). Typical ultrafiltration rates for CVVH are ~1 L/hour but can vary.

$$\begin{aligned} Cl_{cvvh} &= Fu \times UFR \quad \textbf{(Eq. 31-18)} \\ &= 0.95 \times 1\ L/hour \\ &= 0.95\ L/hour \end{aligned}$$

$$\begin{aligned} Cl_{total} &= Cl_{revised} + Cl_{cvvh} \\ &= 0.82\ L/hour + 0.95\ L/hour \\ &= 1.77\ L/hour \\ &= 29.5\ mL/minute \end{aligned} \quad \text{(Eq. 31-19)}$$

Because the clearance of gentamicin approximates that of CrCl, G.G.'s total clearance is approximately one-third the normal clearance of 100 mL/minute. Therefore, the gentamicin dose should be approximately one-third of the normal dose. G.G. should be given 1.5 mg/kg/day or 100 mg of gentamicin every 24 hours. Gentamicin trough concentrations should be monitored and her dose adjusted to maintain a trough concentration of <2 mg/L.

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

CASE 31-2

QUESTION 1: J.J., a 24-year-old male with CKD, is maintained with CAPD. He presents to the ED with a fever of 100.76 °F (38.2 °C) and severe abdominal pain. He also reports that his peritoneal dialysate has become cloudy in the past few days. All these symptoms are consistent with peritonitis, a frequent complication of CAPD. His culture results reveal *Escherichia coli*, sensitive to gentamicin.

How should gentamicin be dosed in this patient?

Management of dialysis-related peritonitis can vary from one institution to another. Antibiotics often are administered intraperitoneal (IP) with or without systemic antibiotic therapy. For less severe cases, IP administration is often considered sufficient. With IP administration, the goal is to deliver a concentration of drug similar to the desired plasma concentration for the treatment of systemic infections. Therefore, 8 mg of gentamicin into each liter of dialysate (or 16 mg into a 2-L bag of dialysate) is recommended. Once equilibrium or steady state is achieved, the dialysate concentration will be comparable to the concentration of gentamicin

in the plasma. Despite a more rapid transfer of drug into the plasma because of increased permeability of the peritoneal membrane in patients with peritonitis, there will still be a substantial lag time before a steady state is reached. For more serious cases of peritonitis, concomitant systemic antibiotics should be given.

Case 31-2, Question 2: Is gentamicin removed by CAPD?

In general, most drugs are not well removed via CAPD. This is particularly true for drugs that are highly protein bound or for drugs with a large Vd. Gentamicin and other aminoglycosides, on the other hand, are effectively removed by CAPD because they have low protein binding and a small Vd. It is estimated that 10% to 50% of gentamicin is removed by CAPD.[68]

Acyclovir

KIDNEY CLEARANCE

CASE 31-3

Question 1: D.M., a 28-year-old male with acquired immune deficiency syndrome, presents with a severe herpetic infection requiring IV acyclovir. Because of other complications associated with his human immunodeficiency virus (HIV) infection, D.M. has developed kidney insufficiency during his hospital course prior to initiating acyclovir. His current SCr is 4.5 mg/dL (baseline SCr = 0.9 mg/dL), and his estimated CrCl is <15 mL/minute.

What are important considerations for dosing acyclovir in D.M. now and also if he requires hemodialysis in the future?

Acyclovir is used to prevent or treat a variety of viral infections, such as those caused by herpes simplex and varicella-zoster viruses.[69] It is cleared primarily by the kidneys, with ~70% to 80% excreted unchanged in the urine. Dosage adjustment is necessary in patients with kidney disease.[18,70] Tubular secretion by the kidneys in addition to filtration contributes to the elimination of acyclovir, which

explains why the clearance of acyclovir by the kidneys is about three times greater than the estimated CrCl.

In patients with normal kidney function, the clearance of acyclovir ranges from 210 to 330 mL/minute; however, in patients with CKD, the clearance is 29 to 34 mL/minute. Although this change in clearance primarily results from decreased clearance of the drug by the kidneys. Non-kidney clearance of acyclovir also decreases in these patients.[18,71,72] As a result, the elimination half-life increases significantly from ~3 hours in patients with normal kidney function to 20 hours in patients with CKD. For D.M., with a creatinine clearance of <15 mL/minute, the acyclovir dose should be 5 mg/kg IV every 24 hours.

Acyclovir is moderately removed by conventional hemodialysis, with plasma concentrations decreasing by 60% after 6 hours of hemodialysis.[73] The elimination half-life on-and-off dialysis is 6 and 20 hours, respectively, whereas the dialysis clearance averages 80 mL/minute. Therefore, when giving acyclovir, it is best to administer it after hemodialysis, on hemodialysis days. If D.M. were to start hemodialysis, the dose of acyclovir would be 2.5 mg/kg IV every 24 hours.

EFFECT OF KIDNEY DYSFUNCTION ON METABOLISM

Case 31-3, Question 2: Does D.M.'s kidney dysfunction affect the metabolism of acyclovir? Are other drugs affected similarly?

Approximately 20% of acyclovir is cleared by non-kidney mechanisms.[18,71] The only significant metabolite that has been isolated is 9-carboxymethoxymethylguanine, which accounts for 9% to 14% of an administered dose. It is believed that this metabolite is a product of hepatic metabolism; however, the kidney may also play an important role.[18] Whether kidney dysfunction alters hepatic metabolism or metabolic enzymes present within the kidney is unclear. Kidney tissue contains many of the same metabolic enzymes found in the liver. Mixed-function oxidases have been

found in segments of the proximal tubule, whereas other metabolic processes, such as glucuronidation, acetylation, and hydrolysis, also occur within the kidney.[17,74]

Kidney failure can affect hepatic metabolic enzyme activity and drug transporter function.[75,76] Kidney dysfunction substantially alters the nonrenal clearance of certain antibiotics, such as cefotaxime, and imipenem-cilastatin,[77,78] as well as benzodiazepines such as diazepam and its metabolite, desmethyldiazepam.[79]

Tenofovir

Case 31-3, Question 3: D.M. also is being treated with tenofovir disoproxil as part of antiretroviral regimen for his HIV disease. Will his tenofovir disoproxil dose need to be adjusted?

DOSAGE ADJUSTMENT

Tenofovir is a nucleotide analog of adenosine monophosphate. Tenofovir disoproxil is a prodrug that is converted to tenofovir, which undergoes activation by phosphorylation to the active form, tenofovir diphosphate. Tenofovir diphosphate inactivates HIV reverse transcriptase and hepatitis B virus (HBV) DNA polymerase by causing chain termination.[80] It is used as part of an antiretroviral regimen in the treatment of HIV infection and can also be used for the treatment of chronic hepatitis B infection.[81] Approximately 70% to 80% of tenofovir is excreted unchanged in the urine. The elimination half-life is ~17 hours, and the clearance is significantly reduced in the setting of kidney dysfunction. Nephrotoxicity, including cases of acute kidney injury and Fanconi syndrome (renal tubular injury and hypophosphatemia) have been reported. Organic transporters in the proximal tubule are believed to mediate kidney toxicity.[82] The dose of tenofovir disoproxil must be adjusted in the setting of kidney dysfunction to prevent accumulation, and the potential to worsen kidney dysfunction. For his degree of kidney function, the dose of tenofovir disoproxil is 300 mg by mouth every 72 hours.[81] Tenofovir alafenamide is another prodrug formulation of tenofovir that remains

stable in the plasma and is only converted intracellularly to the active tenofovir diphosphate. Tenofovir alafenamide results in lower circulating plasma tenofovir levels compared to tenofovir disoproxil. The lower plasma levels of tenofovir lead to lower rates of kidney and bone toxicity. Because <1% of tenofovir alafenamide is excreted unchanged in the urine, no dosage adjustment is needed in patients with kidney impairment, including hemodialysis.[83]

Both tenofovir disoproxil and alafenamide are also available in combination with other antiretrovirals in a single-dose formulation for the treatment of HIV infection. The specific dosing recommendation should be consulted in the setting of kidney dysfunction for tenofovir disoproxil or the combination products. It is important to keep in mind that while tenofovir is the same parent compound, however, the different salt forms have their own pharmacokinetic disposition and therefore dosing.

HEMODIALYSIS

Case 31-3, Question 4: Is tenofovir disoproxil significantly removed by hemodialysis?

Tenofovir disoproxil is effectively removed by hemodialysis, with an extraction coefficient of ~54%. Approximately 10% of a 300-mg tenofovir disoproxil dose is removed after 4 hours of hemodialysis. The recommended dose of tenofovir disoproxil is 300 mg orally every 7 days (after ~12 hours of hemodialysis or three 4-hour sessions).[81] If tenofovir alafenamide is used, the dose is 25 mg once a day (on days of hemodialysis, it should be administered after completion of hemodialysis).[83]

Penicillin

DOSAGE ADJUSTMENT

CASE 31-4

Question 1: T.H., a 57-year-old, 187.39-pounds (85-kg) male with CKD secondary to poorly controlled hypertension, presents to the ED with a 24-hour history of fever 102.20 °F (39 °C), altered mental status, nausea, and vomiting. On physical examination, he is found to have nuchal rigidity and a positive Brudzinski sign. Laboratory analysis reveals the following:

White blood cell (WBC) count, 22,000/μL with 89% neutrophils
BUN, 45 mg/dL
SCr, 4.4 mg/dL

A lumbar puncture yields cerebrospinal fluid (CSF) with a WBC count of 2000/μL (90% polymorphonuclear neutrophils), a glucose concentration of 36 mg/dL, and a protein concentration of 280 mg/dL. Gram-positive diplococci are seen on CSF smear. A diagnosis of meningococcal meningitis is made, and potassium penicillin G is ordered.

What dose should be used?

Meningococcal meningitis can be treated with 24 million units/day (4 million units every 4 hours) of IV penicillin G in patients with normal kidney function. As with many β-lactam antibiotics, penicillin is primarily excreted unchanged in the urine with little or no hepatic metabolism. Thus, the elimination half-life, which averages <1 hour in patients with normal kidney function, increases to 4 to 10 hours in patients with CKD.[84,85]

Using the Cockcroft–Gault method, T.H.'s CrCl is ~20 mL/minute. Therefore, his daily dose of penicillin should be 16 million units. A dose of 4 million units every 6 hours would be appropriate for T.H.[51] Penicillin G is often given as the potassium salt (penicillin G potassium), which contains ~1.7 mEq of potassium per 1 million units of penicillin. Accumulation of potassium because of kidney impairment may lead to hyperkalemia. Penicillin G sodium is an alternative formulation that would be appropriate.

PENICILLIN-INDUCED NEUROTOXICITY

Case 31-4, Question 2: The prescriber fails to consider T.H.'s kidney dysfunction when he orders penicillin and begins a dose of 4 million units every 4 hours. Four days later, T.H. is encephalopathic (confused, disoriented, and difficult to arouse), with some twitching noted on the right side of his face. Are

these toxic symptoms associated with high-dose penicillin? What predisposing factors may contribute to this neurotoxicity?

T.H. is experiencing signs of neurotoxicity that are consistent with elevated penicillin concentrations in the plasma and CSF. Penicillin usually produces few serious adverse effects. When large doses are used in patients with kidney impairment, toxic symptoms such as those exhibited by T.H. can result. Signs and symptoms of penicillin-induced CNS toxicity include myoclonus, complex or generalized seizure activity, and encephalopathy progressing to coma.[44,86]

Predisposing factors

Penicillin neurotoxicity frequently occurs in patients with decreased kidney function.[86] Several possible explanations for this observation exist. Penicillin accumulates in patients with kidney failure. The binding of acidic drugs (such as penicillin) to albumin is decreased, resulting in an increased fraction of free or active drug that can pass into the CSF. Alterations in the blood–brain barrier have been observed in patients with uremia, which can lead to further increases in CSF drug levels. High plasma concentrations of penicillin per se may contribute to changes in the blood–brain barrier permeability of this drug.[44] All these factors, together with the increased sensitivity of patients with kidney failure to centrally acting agents, make CNS toxicity more likely. Previous neurotrauma, history of seizures, elderly age, and concurrent drugs that lower the seizure threshold can also contribute to neurotoxicity. As with penicillin, the carbapenem antibiotic combination, imipenem–cilastatin, is associated with a higher incidence of seizures in patients with kidney dysfunction.[87,88] Other β-lactam antibiotics such as ceftazidime, cefepime, and piperacillin/tazobactam have also been associated with seizures.[89,90]

Antipseudomonal Penicillins

PIPERACILLIN/TAZOBACTAM

CASE 31-5

QUESTION 1: E.R., a 44-year-old, 154.32 pounds (70-kg) female with acute nonlymphocytic leukemia, was admitted to the oncology ward for placement of a Hickman catheter for her chemotherapy. Seven days after treatment with cytarabine and daunorubicin, her temperature spiked to 102.92 °F (39.4 °C). Other physical findings consistent with sepsis included a blood pressure of 102/68 mm Hg, pulse rate of 112 beats/minute, and a respiratory rate of 27 breaths/minute. E.R. is neutropenic with a WBC count of 1400/μL (3% polymorphonuclear leukocytes, 70% lymphocytes, and 22% monocytes). Her platelet count is 16,000/μL. E.R. also has kidney dysfunction as reflected by an SCr of 2.6 mg/dL (baseline = 1.2 mg/dL) and BUN of 38 mg/dL (baseline = 18 mg/dL). Empiric therapy for sepsis is started with tobramycin, piperacillin/tazobactam, and vancomycin.

How should piperacillin/tazobactam be dosed in E.R.?

Doses of piperacillin/tazobactam can be as high as 4.5 g IV every 6 hours for the treatment of serious *Pseudomonas* species infections. In patients with CKD, mean piperacillin clearance and half-life values are 0.7 mL/minute/kg and 3.3 hours, respectively.[91–93] Although these parameters are significantly different, they are less than those expected for a drug primarily cleared by the kidneys, suggesting that some other compensatory mechanism for elimination must be present. Piperacillin is partially cleared by biliary excretion, a route of elimination that is increased in patients with kidney failure.[92,94] Therefore, aggressive dosage reductions in E.R. are unnecessary. An appropriate dose of piperacillin/tazobactam for E.R. would be 3.375 g IV every 8 hours. Widely used drug references can be used for dosing guidelines for drugs commonly used in patients with kidney failure.[51]

Vancomycin

PHARMACOKINETIC DOSAGE CALCULATIONS

CASE 31-5, QUESTION 2: In addition to the aforementioned regimen for E.R., vancomycin therapy is initiated at 500 mg every 24 hours to cover the possibility

of an infection resistant to antistaphylococcal penicillins, such as nafcillin. Is this an appropriate dosing regimen for E.R.?

As with many other antibiotics, vancomycin primarily is cleared by the kidneys.[95] Significant toxicities have been associated with elevated serum concentrations, making careful dosing modification in kidney failure necessary.[96]

As with the aminoglycosides, pharmacokinetic calculations can be used to individualize a dosing regimen to produce the desired plasma levels. For patients with serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections, individualizing the dose to achieve a target AUC/MIC_{BMD} ratio of 400:600 (assuming an MIC_{BMD} of 1 mg/L measured by broth microdilution) is recommended, and trough only monitoring targeting levels of 15 to 20 mg/L should no longer be used.[97] Bayesian forecasting software can be used to optimize the dose by calculating the vancomycin area under the concentration-time-curve (AUC).[98]

Vancomycin has an elimination half-life of 3 to 9 hours in patients with normal kidney function.[99] This increases to 129 to 189 hours in patients with CKD.[100,101] Using pharmacokinetic principles and considering that the plasma clearance of vancomycin is ~60% to 70% of CrCl[102] and the Vd averages 0.7 L/kg,[99,103] the estimated Vd_{vanco} and Cl_{vanco} can be calculated using the following equation:

$$\begin{aligned} Cr_{Cl} &= 30.5\ \text{mL/minute (calculated from Eq. 31-2)} \\ Cl_{vanco} &= (0.65)(CrCl) \\ &= (0.65)(30.5\ \text{mL/minute}) \\ &= 19.8\ \text{mL/minute or rounded off to 1.2 L/hour} \end{aligned} \qquad \text{(Eq. 31-20)}$$

$$\begin{aligned} Vd_{vanco} &= (0.7\ L/kg)(\text{body weight}) \\ &= (0.7\ L/kg)(70\ kg) \\ &= 49\ L \end{aligned} \qquad \textbf{(Eq. 31-21)}$$

Based on estimated values for Cl_{vanco} and Vd_{vanco}, the elimination rate constant can be calculated using the following equation:

$$\begin{aligned} Kd &= \frac{Cl_{vanco}}{Vd_{vanco}} \\ &= \frac{1.2\ L/hour}{49\ L} \\ &= 0.024\ hour^{-1} \end{aligned} \qquad \textbf{(Eq. 31-22)}$$

$$\begin{aligned} Cp &= \frac{\dfrac{Dose}{Vd_{vanco}}}{1 - e^{-Kdt}} \\ &= \frac{\dfrac{500\ mg}{49\ L}}{1 - e^{-(0.024\ hour^{-1})(24\ hours)}} \\ &= 23\ mg/L \end{aligned} \qquad \textbf{(Eq. 31-23)}$$

$$\begin{aligned} Cp_{trough} &= Cp_{peak}\,(e^{-Kdt}) \\ &= 23\ mg/L\,(e^{-(0.024/hour^{-1})(24\ hours)}) \\ &= 13\ mg/L \end{aligned} \qquad \textbf{(Eq. 31-24)}$$

Routine monitoring of plasma vancomycin concentrations in patients with normal kidney function is controversial because the

likelihood that toxicity will develop in this group is relatively low. However, in patients with kidney failure, such as E.R., it is advisable to measure vancomycin levels after initiating therapy to ensure that they are within an acceptable range or if toxicity is suspected.[97]

Fluconazole

DOSING

Case 31-5, Question 3: E.R. continues to be febrile despite her triple antimicrobial regimen. One blood culture grew out *Candida albicans*. Fluconazole is started to treat candidemia. How should fluconazole be administered such as E.R. with kidney dysfunction?

Fluconazole is an azole antifungal agent with activity against *C. albicans*.[104] Fluconazole is eliminated primarily by the kidneys, has an MW of 306 Da, and exhibits low protein binding.[105] A loading dose of 800 mg (12 mg/kg) followed by 400 mg (6 mg/kg) daily can be used in patients with normal kidney function.[106] Based on E.R.'s degree of kidney function, the fluconazole dose of 200 mg/day would be reasonable.

FLUCONAZOLE DOSING IN KIDNEY REPLACEMENT THERAPY

Approximately 20%–40% is removed by a single session of hemodialysis.[107,108] In patients receiving hemodialysis, the normal dose is given after each hemodialysis session. Fluconazole is readily removed by continuous venovenous hemofiltration to the degree that regular doses can be given, and doses up to 800 mg/day should be used in patients with serious infections.[109] Fluconazole is a good example of the dose needing to be adjusted based on the degree of kidney dysfunction as well as the mode of kidney replacement therapy.

Cefazolin

CASE 31-6

QUESTION 1: M.J., a 65-year-old female with CKD, is awaiting a kidney transplant. She has been managed with PD for the past 8 years. She presents with a cloudy effluent and abdominal pain. Analysis of the effluent reveals a WBC count of 323/μL and gram-positive cocci in clusters on Gram stain. The patient has a history of *S. aureus* peritonitis that was readily treated with cefazolin previously. The patient has no allergies and weighs 114.64 pounds (52 kg).

How should M.J.'s PD-related infection be managed?

Gram-positive cocci such as *S. aureus* are common causes of PD-related infections. The selection of empiric antibiotics should be made based on the patient's and institution's history of microorganisms and sensitivities. A first-generation cephalosporin such as cefazolin would be a reasonable choice for M.J. At institutions with a high rate of methicillin-resistant organisms, vancomycin should be used.

IP antibiotics can be given with each exchange (continuous dosing). In this situation, a single 500-mg/L loading dose of cefazolin is given followed by a maintenance dose of 125 mg/L with subsequent exchanges. Antibiotics can also be given intermittently (once daily per exchange). With intermittent dosing, the antibiotic-containing dialysis solution should dwell for at least 6 hours to allow for adequate absorption. Cefazolin 15 mg/kg (rounded off to 750 mg) is typically given in one exchange. For patients on automated PD, the dose of cefazolin is 20 mg/kg every day in a long-day dwell. In patients with residual kidney function (eg, >100 mL/day of urine output), empirically, the dose is increased by 25%. The management of PD-related infections and dosing of various antibiotics is discussed in the International Society for Peritoneal Dialysis guidelines.[110]

Phenytoin

PROTEIN BINDING

CASE 31-7

QUESTION 1: R.S., a 24-year-old male with CKD from rapidly progressive glomerulonephritis, is treated by hemodialysis three times weekly. He has a 7-year history of generalized tonic–clonic seizures and has been treated with phenytoin. He presents to the ED after having had a seizure lasting about 5 minutes. His mother states that he ran out of phenytoin 2 weeks ago. Because his plasma phenytoin concentration on admission was <2.5 mg/L, R.S. is given an IV loading dose of fosphenytoin: 15 mg/kg phenytoin sodium equivalents (PE) over 30 minutes. Additional admission laboratory work includes the following:

SCr, 8.6 mg/dL
BUN, 110 mg/dL
Potassium, 5.4 mEq/L
Calcium, 9 mg/dL
Albumin, 2.9 g/dL

Eight hours after administration, his phenytoin level is 5 mg/L.
Is this level subtherapeutic?

R.S. has severe kidney disease, which will affect the total (bound plus free) phenytoin concentration achieved and how this concentration is interpreted. Decreased plasma protein binding will result in lower measured total phenytoin concentrations, and the calculated apparent Vd may increase. In patients with normal kidney function, ~90% of the measured phenytoin is bound to albumin, and 10% is free. The free fraction of phenytoin is increased to about 20% to 25% in patients with uremia.[11,111,112] Because the free fraction for phenytoin is increased in patients with uremia, lower plasma concentrations will produce therapeutic effects that will be equivalent to those produced by higher phenytoin concentrations in patients with normal kidney function.[113–115] Phenytoin is an acidic drug that is bound primarily to albumin. A number of mechanisms have been proposed that account for the decreased binding, including (a) decreased albumin concentration, (b) accumulation of uremic byproducts that displace acidic drugs from their binding sites, and (c) alteration in the conformation or structure of albumin in uremic

patients, resulting in a reduced number of binding sites or decreased affinity for drugs (see Chapter 60, Seizure Disorders). Other acidic drugs with altered protein binding in kidney disease are listed in Table 31-1.

The following equation should be used to correct for R.S.'s altered binding owing to his kidney dysfunction and hypoalbuminemia[116]:

$$Cp_{\text{Normal Binding}} = \frac{Cp'}{(0.48)(1-\alpha)\left(\frac{P'}{P_{NL}}\right)+\alpha} \quad \textbf{(Eq. 31-25)}$$

where Cp′ is the measured plasma concentration reported by the laboratory, and $Cp_{\text{Normal Binding}}$ is the corrected plasma concentration that would be seen if the patient had normal kidney function and normal albumin. Alpha (α) is the normal free fraction (0.1), P′ is the patient's serum albumin, and P_{NL} is normal albumin (4.4 g/dL). The factor 0.48 was derived from patients on hemodialysis and represents the decreased affinity of phenytoin for albumin.

For R.S., a total plasma phenytoin concentration of 5 mg/L is comparable to 13 mg/L in a patient without kidney failure. Because this falls within the phenytoin's therapeutic range of 10 to 20 mg/L, his measured level is not considered to be subtherapeutic.

The factor 0.48 should be used only to estimate changes in protein binding for patients with CKD receiving hemodialysis. Data for patients with moderate kidney disease are limited, and it is unclear what changes exist in the binding of phenytoin to albumin.[117] For patients with normal or moderate kidney impairment, the following equation should be used only if the serum albumin is low; the factor 0.48 should be omitted:

$$Cp_{\text{Normal Binding}} = \frac{Cp'}{(1-\alpha)\left(\frac{P'}{P_{NL}}\right)+\alpha} \quad \textbf{(Eq. 31-26)}$$

Fosphenytoin, a prodrug of phenytoin, does not need to be dissolved in propylene glycol, and therefore can be administered more quickly. This offers an important advantage for seizures that must be controlled quickly. In patients with kidney failure, the conversion of fosphenytoin to phenytoin was equally efficient to healthy subjects.[118] Once fosphenytoin is converted to phenytoin, the impact of kidney disease on protein binding is expected to be similar to that seen with phenytoin and thus the same considerations should be made for patients with kidney failure.

EFFECT OF KIDNEY FAILURE ON METABOLIZED DRUGS

Meperidine

CASE 31-8

Question 1: F.G., a 56-year-old female, is admitted for a cervical laminectomy. She has a history of CKD (CrCl 20 mL/minute) and arrhythmias that are treated with amiodarone. Her admission laboratory values are as follows:

SCr, 4.4 mg/dL
BUN, 66 mg/dL
Hematocrit, 34%
Hemoglobin, 12.6 g/dL

After surgery, she reports severe pain and is treated with meperidine 50 to 100 mg intramuscularly every 3 to 4 hours. Three days postoperatively, F.G. experiences a generalized tonic–clonic seizure. She has no history of seizures.

What might be responsible for this sudden event?

Meperidine is a narcotic analgesic that is metabolized by the liver via *N*-demethylation to normeperidine, a metabolite known to accumulate in kidney insufficiency.[15,119] Although meperidine has both CNS excitatory and depressant properties, normeperidine is a very potent CNS stimulant that can cause seizures in patients with

kidney insufficiency who are receiving multiple doses of the parent drug.[120] The kidney clearance of normeperidine correlates with CrCl, and kidney dysfunction can lead to its accumulation, resulting in neurologic toxicity. Because of these safety issues, meperidine is not generally recommended for use as an analgesic. Table 31-3 lists examples of additional drugs that have active or toxic metabolites that may accumulate in kidney disease.

Table 31-3
Drugs With Active or Toxic Metabolites Excreted by the Kidney

Drug	Metabolite
Allopurinol	Oxypurinol
Bupropion	Threo/erythro-hydrobupropion
Cefotaxime	Desacetylcefotaxime
Chlorpropamide	Hydroxy metabolites
Cyclophosphamide	4-Ketocyclophosphamide
Daunorubicin	Daunorubicinol
Meperidine	Normeperidine
Methyldopa	Methyl-*O*-sulfate-α-methyldopamine
Midazolam	α-Hydroxymidazolam
Morphine	Morphine-3-glucuronide
	Morphine-6-glucuronide
Phenylbutazone	Oxyphenbutazone
Primidone	Phenobarbital
Procainamide	*N*-acetylprocainamide (NAPA)
Rifampicin	Deacetylated metabolites
Sodium nitroprusside	Thiocyanate
Sulfonamides	Acetylated metabolites
Tramadol	*O*-Demethyl-*N*-demethyl tramadol

Narcotic Analgesics

MORPHINE

Case 31-8, Question 2: Are the pharmacokinetics or pharmacodynamics of other narcotic analgesics altered in patients with kidney insufficiency?

The pharmacokinetic disposition of morphine does not appear to be altered in patients with kidney failure[121]; however, its active metabolite, morphine-6-glucuronide, as well as its principal metabolite, morphine-3-glucuronide, do accumulate in kidney disease. The elimination half-life of morphine-6-glucuronide increases from 3 to 4 hours in normal subjects to 89 to 136 hours in subjects with kidney failure.[16] This metabolite penetrates the blood–brain barrier more readily, has a greater affinity for CNS receptors, and has analgesic activity that is 3.7 times greater than morphine.[122] Therefore, accumulation of morphine-6-glucuronide may be responsible for the morphine-induced narcosis reported in patients with severe kidney disease.[123,124] Codeine is metabolized to morphine and can cause narcosis in those with kidney dysfunction if the dose is not adjusted for kidney impairment.[125]

HYDROMORPHONE

Hydromorphone is metabolized in the liver to hydromorphone-3-glucuronide, dihydroisomorphone, dihydromorphine, and small amounts of hydromorphone-3-sulfate, norhydromorphone, and nordihydroisomorphone.[126] All metabolites that are eliminated are excreted by the kidneys. Hydromorphone can be used in patients with kidney failure; however, smaller initial doses may be warranted.[127]

Enoxaparin

Case 31-8, Question 3: Because F.G. is not ambulating well after her surgery, her physician would like to initiate deep vein thrombosis prophylaxis with enoxaparin. Are there any dosing considerations for enoxaparin in this patient?

Enoxaparin is a low-MW heparin that is used to prevent and treat various thromboembolic disorders. The kidneys play a major role in the clearance of enoxaparin,[128] and a higher incidence of bleeding complications is associated with the use of enoxaparin in patients with kidney dysfunction.[129] The elimination half-life of enoxaparin is prolonged in patients with CKD, although the other pharmacokinetic parameters are similar to those in healthy subjects.[130] The increased incidence of bleeding complications cannot be completely attributed to pharmacokinetic changes, but may also be related to the effects of enoxaparin on factor IIa and antithrombin III, as well as the effects of uremia on hemostasis.[131]

Enoxaparin should be used cautiously in patients with a CrCl <30 mL/minute. A lower dose of 30 mg subcutaneously once daily for prophylaxis in hip or knee replacement or abdominal surgery is recommended.[132,133] Although monitoring of the anticoagulant effect by anti-Xa activity is not necessary in clinically stable patients, it may be warranted in patients with kidney dysfunction as well as in those who have other factors that may increase the risk of bleeding complications.

ASSESSING KIDNEY FUNCTION IN THE ELDERLY

Kidney function declines physiologically with advancing age and as the result of comorbidities such as hypertension and diabetes.[134] This decrease in kidney function can have significant consequences on drug excretion, metabolism, and the potential for adverse drug reactions, particularly in the elderly population that is often prescribed multiple medications.[135] Antithrombotic and antidiabetic drugs are high-risk medications that are often implicated as a cause for hospitalizations because of adverse drug events in elderly patients. CKD is a risk factor for hypoglycemia in patients with diabetes.[136] Glycemic control in patients with CKD is challenging

because of physiologic changes and alterations in the disposition medications to treat diabetes. Sulfonylurea antidiabetic agents such as glyburide that are eliminated primarily by the kidneys can lead to prolonged hypoglycemia in patients with decreased kidney function.[137] Dipeptidyl peptidase-4 (DPP-4) inhibitors have a similar mechanism of action but differ in their pharmacokinetic disposition. For example, sitagliptin is 80% excreted by the kidneys, and its dose should be adjusted in the setting of kidney dysfunction, whereas only 5% of linagliptin is excreted in the urine and does not need any dose adjustment.[138–140]

Formulas that estimate kidney function use serum creatinine. In elderly adults, a low serum creatinine may not always be indicative of normal kidney function. Older adults tend to have lower muscle mass than younger people, and a low serum creatinine may not be indicative of normal kidney function, but rather reduced muscle mass. Differences in the estimated GFR between the MDRD and Cockcroft–Gault formulas may result in discordant dosing recommendations in an elderly population[141] (see Chapter 28, Chronic Kidney Disease).

This highlights the importance of obtaining a comprehensive medication history, assessment of the patient's kidney function, and evaluation of the available drug-information resources for appropriate dosing recommendations for each patient.

SUMMARY

The kidneys play a vital role in maintaining homeostasis by regulating the excretion of water, electrolytes, and metabolic byproducts. In addition, the kidneys are the primary route of elimination for many drugs. Pharmacokinetic changes, such as altered bioavailability, protein binding, drug distribution, and elimination, can occur with many drugs in patients with kidney failure. Pharmacodynamic changes, such as altered sensitivity or response to medications, can also occur in this patient population.

Kidney replacement therapies, such as hemodialysis, CAPD, and CRRT, will aid in the removal of fluid, electrolytes, metabolic byproducts, and drugs as well. Data from clinical trials provide valuable information about the disposition of drugs in patients with kidney failure. Pharmacokinetic principles should be applied when appropriate to determine the optimal dose of drugs for patients with kidney failure.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Daugirdas JT, Blake PG, Ing TS. *Handbook of Dialysis*. 5th ed. Wolters Kluwer; 2015.

Guidance for Industry. Pharmacokinetics in Patients With Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing. 2020. http://www.fda.gov/downloads/Drugs/Guidances/UCM204959.pdf

Matzke GR, Arnoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80:1122–1137. (26)

Nemecek BD, Hammond DA; American Society of Health-System Pharmacists. *Demystifying Drug Dosing in Renal Dysfunction*. American Society of Health-System Pharmacists; 2019. (52)

Winter's Clinical Pharmacokinetics. 6th ed. Lippincott Williams & Wilkins; 2017.

Key Websites

2022 Dialysis of Drugs. http://www.renalpharmacyconsultants.com/publications/

Cockcroft–Gault calculator. http://www.nephron.com/cgi-bin/CGSI.cgi

MDRD GFR calculator. http://nephron.org/mdrd_gfr_si

National Kidney Disease Education Program. http://nkdep.nih.gov/

COMPLETE REFERENCES CHAPTER 31 DOSING OF DRUGS IN KIDNEY FAILURE

1. O'Neil-Cutting MA, Crosby WH. The effect of antacids on the absorption of simultaneously ingested iron. *JAMA*. 1986;255(11):1468–1470.
2. Kays MB, Overholser BR, Mueller BA, Moe SM, Sowinski KM. Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. *Am J Kidney Dis*. 2003;42(6):1253–1259.
3. How PP, Fischer JH, Arruda JA, Lau AH. Effects of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. *Clin J Am Soc Nephrol*. 2007;2(6):1235–1240.
4. Bianchetti G, Graziani G, Brancaccio D, et al. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin Pharmacokinet*. 1976;1(5):373–384.
5. Wood AJ, Vestal RE, Spannuth CL, Stone WJ, Wilkinson GR, Shand DG. Propranolol disposition in renal failure. *Br J Clin Pharmacol*. 1980;10(6):561–566.
6. Joy MS, Frye RF, Nolin TD, et al. In vivo alterations in drug metabolism and transport pathways in patients with chronic kidney diseases. *Pharmacotherapy*. 2014;34(2):114–122.
7. Sun H, Huang Y, Frassetto L, Benet LZ. Effects of uremic toxins on hepatic uptake and metabolism of erythromycin. *Drug Metab Dispos*. 2004;32(11):1239–1246.
8. Reidenberg MM, Drayer DE. Alteration of drug-protein binding in renal disease. *Clin Pharmacokinet*. 1984;9(Suppl 1):18–26.
9. Keller F, Maiga M, Neumayer HH, Lode H, Distler A. Pharmacokinetic effects of altered plasma protein binding of drugs in renal disease. *Eur J Drug Metab Pharmacokinet*. 1984;9(3):275–282.
10. Klammt S, Wojak HJ, Mitzner A, et al. Albumin-binding capacity (ABiC) is reduced in patients with chronic kidney disease along with an accumulation of protein-bound uraemic toxins. *Nephrol Dial Transplant*. 2012;27(6):2377–2383.
11. Reidenberg MM, OdarCederlof I, von Bahr C, Borga O, Sjoqvist F. Protein binding of diphenylhydantoin and desmethylimipramine in plasma from patients with poor renal function. *N Engl J Med*. 1971;285(5):264–267.
12. Jusko WJ, Weintraub M. Myocardial distribution of digoxin and renal function. *Clin Pharmacol Ther*. 1974;16(3):449–454.
13. Sun H, Frassetto L, Benet LZ. Effects of renal failure on drug transport and metabolism. *Pharmacol Ther*. 2006;109(1–2):1–11.
14. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. *Expert Opin Drug Metab Toxicol*. 2008;4(8):1065–

1074.
15. Szeto HH, Inturrisi CE, Houde R, Saal S, Cheigh J, Reidenberg MM. Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure of cancer. *Ann Intern Med*. 1977;86(6):738–741.
16. Osborne RJ, Joel SP, Slevin ML. Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *Br Med J (Clin Res Ed)*. 1986;292(6535):1548–1549.
17. Gibson TP. The kidney and drug metabolism. *Int J Artif Organs*. 1985;8(5):237–238.
18. Laskin OL, Longstreth JA, Whelton A, et al. Acyclovir kinetics in end-stage renal disease. *Clin Pharmacol Ther*. 1982;31(5):594–601.
19. Abel S, Allan R, Gandelman K, Tomaszewski K, Webb DJ, Wood ND. Pharmacokinetics, safety and tolerance of voriconazole in renally impaired subjects: two prospective, multicentre, open-label, parallel-group volunteer studies. *Clin Drug Investig*. 2008;28(7):409–420.
20. Courtney R, Sansone A, Smith W, et al. Posaconazole pharmacokinetics, safety, and tolerability in subjects with varying degrees of chronic renal disease. *J Clin Pharmacol*. 2005;45(2):185–192.
21. Hoover RK, Alcorn H Jr, Lawrence L, et al. Clinical pharmacokinetics of sulfobutylether-beta-cyclodextrin in patients with varying degrees of renal impairment. *J Clin Pharmacol*. 2018;58(6):814–822.
22. Veklury. Package insert. Gilead Sciences Inc; 2020.
23. Luke DR, Wood ND, Tomaszewski KE, Damle B. Pharmacokinetics of sulfobutylether-beta-cyclodextrin (SBECD) in subjects on hemodialysis. *Nephrol Dial Transplant*. 2012;27(3):1207–1212.
24. Kiser TH, Fish DN, Aquilante CL, et al. Evaluation of sulfobutylether-beta-cyclodextrin (SBECD) accumulation and voriconazole pharmacokinetics in critically ill patients undergoing continuous renal replacement therapy. *Crit Care*. 2015;19:32.
25. Morris AA, Mueller SW, Rower JE, Washburn T, Kiser TH. Evaluation of sulfobutylether-beta-cyclodextrin exposure in a critically ill patient receiving intravenous posaconazole while undergoing continuous venovenous hemofiltration. *Antimicrob Agents Chemother*. 2015;59(10):6653–6656.
26. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80(11):1122–1137.
27. Hoff BM, Maker JH, Dager WE, Heintz BH. Antibiotic dosing for critically ill adult patients receiving intermittent hemodialysis, prolonged intermittent renal replacement therapy, and continuous renal replacement therapy: an update. *Ann Pharmacother*. 2020;54(1):43–55.
28. Gibson TB, Nelson HA. Drug kinetics and artificial kidneys. *Clin Pharmacokinet*. 1977;2(6):403–426.

29. Mac-Kay MV, Fernandez IP, Herrera Carranza J, Sancez Burson J. An in vitro study of the influence of a drug's molecular weight on its overall (Clt), diffusive (Cld) and convective (Clc) clearance through dialysers. *Biopharm Drug Dispos*. 1995;16(1):23–35.
30. Amin NB, Padhi ID, Touchette MA, Patel RV, Dunfee TP, Anandan JV. Characterization of gentamicin pharmacokinetics in patients hemodialyzed with high-flux polysulfone membranes. *Am J Kidney Dis*. 1999;34(2):222–227.
31. Aweeka FT, Jacobson MA, Martin-Munley S, et al. Effect of renal disease and hemodialysis on foscarnet pharmacokinetics and dosing recommendations. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999;20(4):350–357.
32. Keller E, Reetze P, Schollmeyer P. Drug therapy in patients undergoing continuous ambulatory peritoneal dialysis. Clinical pharmacokinetic considerations. *Clin Pharmacokinet*. 1990;18(2):104–117.
33. Pea F, Viale P, Pavan F, Furlanut M. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. *Clin Pharmacokinet*. 2007;46(12):997–1038.
34. Pistolesi V, Morabito S, Di Mario F, Regolisti G, Cantarelli C, Fiaccadori E. A guide to understanding antimicrobial drug dosing in critically ill patients on renal replacement therapy. *Antimicrob Agents Chemother*. 2019;63(8):e00583-19.
35. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis*. 2005;41(8):1159–1166.
36. Ghannoum M, Bouchard J, Nolin TD, Ouellet G, Roberts DM. Hemoperfusion for the treatment of poisoning: technology, determinants of poison clearance, and application in clinical practice. *Semin Dial*. 2014;27(4):350–361.
37. Kawasaki C, Nishi R, Uekihara S, Hayano S, Otagiri M. Charcoal hemoperfusion in the treatment of phenytoin overdose. *Am J Kidney Dis*. 2000;35(2):323–326.
38. Bodd E, Jacobsen D, Lund E, Ripel A, Morland J, Wiik-Larsen E. Morphine-6-glucuronide might mediate the prolonged opioid effect of morphine in acute renal failure. *Hum Exp Toxicol*. 1990;9(5):317–321.
39. Kleinbloesem CH, van Brummelen P, van Harten J, Danhof M, Breimer DD. Nifedipine: influence of renal function on pharmacokinetic/hemodynamic relationship. *Clin Pharmacol Ther*. 1985;37(5):563–574.
40. Brinkman WT, Williams WH, Guyton RA, Jones EL, Craver JM. Valve replacement in patients on chronic renal dialysis: implications for valve prosthesis selection. *Ann Thorac Surg*. 2002;74(1):37–42; discussion 42.
41. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest*. 2001;119(1 Suppl):108S–121S.

42. Welage LS, Schultz RW, Schentag JJ. Pharmacokinetics of ceftazidime in patients with renal insufficiency. *Antimicrob Agents Chemother*. 1984;25(2):201–204.
43. Gentry LO. Antimicrobial activity, pharmacokinetics, therapeutic indications and adverse reactions of ceftazidime. *Pharmacotherapy*. 1985;5(5):254–267.
44. Nicholls PJ. Neurotoxicity of penicillin. *J Antimicrob Chemother*. 1980;6(2):161–165.
45. Ong CY, Qin Y. Myoclonus from antibiotic therapy (ceftazidime-induced neurotoxicity): a case report and review. *Cureus*. 2018;10(3):e2250.
46. Dahlgren JG, Anderson ET, Hewitt WL. Gentamicin blood levels: a guide to nephrotoxicity. *Antimicrob Agents Chemother*. 1975;8(1):58–62.
47. Sawchuk RJ, Zaske DE, Cipolle RJ, Wargin WA, Strate RG. Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin Pharmacol Ther*. 1977;21(3):362–369.
48. Zaske DE, Cipolle RJ, Rotschafer JC, Solem LD, Mosier NR, Strate RG. Gentamicin pharmacokinetics in 1,640 patients: method for control of serum concentrations. *Antimicrob Agents Chemother*. 1982;21(3):407–411.
49. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995;39(3):650–655.
50. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother*. 1999;43(7):1549–1555.
51. *Drug Facts and Comparisons, Facts & Comparisons eAnswers* [online]. Wolters Kluwer Health Inc; 2020. Accessed October 4, 2020. https://fco.factsandcomparisons.com/lco/action/home
52. Nemecek BD, Hammond DA; American Society of Health-System Pharmacists. *Demystifying Drug Dosing in Renal Dysfunction*. American Society of Health-System Pharmacists; 2019.
53. Beringer P. *Winter's Basic Clinical Pharmacokinetics*. 6th ed. Wolters Kluwer; 2018.
54. Sheiner LB, Beal S, Rosenberg B, Marathe VV. Forecasting individual pharmacokinetics. *Clin Pharmacol Ther*. 1979;26(3):294–305.
55. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
56. Aronoff GR; American College of Physicians. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*. 5th ed. American College of Physicians; 2007.
57. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461–470.

58. Bailie GR, Uhlig K, Levey AS. Clinical practice guidelines in nephrology: evaluation, classification, and stratification of chronic kidney disease. *Pharmacotherapy*. 2005;25(4):491–502.
59. Kuan Y, Hossain M, Surman J, El Nahas AM, Haylor J. GFR prediction using the MDRD and Cockcroft and Gault equations in patients with end-stage renal disease. *Nephrol Dial Transplant*. 2005;20(11):2394–2401.
60. Golik MV, Lawrence KR. Comparison of dosing recommendations for antimicrobial drugs based on two methods for assessing kidney function: Cockcroft–Gault and modification of diet in renal disease. *Pharmacotherapy*. 2008;28(9):1125–1132.
61. Hermsen ED, Maiefski M, Florescu MC, Qiu F, Rupp ME. Comparison of the Modification of Diet in Renal Disease and Cockcroft–Gault equations for dosing antimicrobials. *Pharmacotherapy*. 2009;29(6):649–655.
62. Danish M, Schultz R, Jusko WJ. Pharmacokinetics of gentamicin and kanamycin during hemodialysis. *Antimicrob Agents Chemother*. 1974;6(6):841–847.
63. Halpren BA, Axline SG, Coplon NS, Brown DM. Clearance of gentamicin during hemodialysis: comparison of four artificial kidneys. *J Infect Dis*. 1976;133(6):627–636.
64. Dager WE, King JH. Aminoglycosides in intermittent hemodialysis: pharmacokinetics with individual dosing. *Ann Pharmacother*. 2006;40(1):9–14.
65. Nikolaidis P, Tourkantonis A. Effect of hemodialysis on ceftazidime pharmacokinetics. *Clin Nephrol*. 1985;24(3):142–146.
66. Toffelmire EB, Reymond JP, Brouard R, et al. Dialysis clearance in high flux hemodialysis with reuse using ceftazidime as the model drug. *Clin Pharmacol Ther*. 1988;45:160.
67. Lanese DM, Alfrey PS, Molitoris BA. Markedly increased clearance of vancomycin during hemodialysis using polysulfone dialyzers. *Kidney Int*. 1989;35(6):1409–1412.
68. Somani P, Shapiro RS, Stockard H, Higgins JT. Unidirectional absorption of gentamicin from the peritoneum during continuous ambulatory peritoneal dialysis. *Clin Pharmacol Ther*. 1982;32(1):113–121.
69. Richards DM, Carmine AA, Brogden RN, Heel RC, Speight TM, Avery GS. Acyclovir. A review of its pharmacodynamic properties and therapeutic efficacy. *Drugs*. 1983;26(5):378–438.
70. Blum MR, Liao SH, de Miranda P. Overview of acyclovir pharmacokinetic disposition in adults and children. *Am J Med*. 1982;73(1A):186–192.
71. Laskin OL, Longstreth JA, Whelton A, et al. Effect of renal failure on the pharmacokinetics of acyclovir. *Am J Med*. 1982;73(1A):197–201.
72. Jayasekara D, Aweeka FT, Rodriguez R, Kalayjian RC, Humphreys MH, Gambertoglio JG. Antiviral therapy for HIV patients with renal insufficiency. *J Acquir Immune Defic Syndr*. 1999;21(5):384–395.

73. Krasny HC, Liao SH, de Miranda P, Laskin OL, Whelton A, Lietman PS. Influence of hemodialysis on acyclovir pharmacokinetics in patients with chronic renal failure. *Am J Med*. 1982;73(1A):202–204.
74. Lohr JW, Willsky GR, Acara MA. Renal drug metabolism. *Pharmacol Rev*. 1998;50(1):107–141.
75. Vilay AM, Churchwell MD, Mueller BA. Clinical review: drug metabolism and nonrenal clearance in acute kidney injury. *Crit Care*. 2008;12(6):235.
76. Yeung CK, Shen DD, Thummel KE, Himmelfarb J. Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport. *Kidney Int*. 2014;85(3):522–528.
77. Ings RM, Fillastre JP, Godin M, Leroy A, Humbert G. The pharmacokinetics of cefotaxime and its metabolites in subjects with normal and impaired renal function. *Rev Infect Dis*. 1982;4 Suppl:S379–S391.
78. Gibson TP, Demetriades JL, Bland JA. Imipenem/cilastatin: pharmacokinetic profile in renal insufficiency. *Am J Med*. 1985;78(6A):54–61.
79. Ochs HR, Greenblatt DJ, Kaschell HJ, Klehr U, Divoll M, Abernethy DR. Diazepam kinetics in patients with renal insufficiency or hyperthyroidism. *Br J Clin Pharmacol*. 1981;12(6):829–832.
80. Pham PA, Gallant JE. Tenofovir disoproxil fumarate for the treatment of HIV infection. *Expert Opin Drug Metab Toxicol*. 2006;2(3):459–469.
81. Viread. Package insert. Gilead Sciences, Inc; 2019.
82. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat*. 2011;2011:354908.
83. Vemlidy. Package insert. Gilead Sciences Inc; 2020.
84. Barza M, Weinstein L. Pharmacokinetics of the penicillins in man. *Clin Pharmacokinet*. 1976;1(4):297–308.
85. Melikian DM, Flaherty JF. Antimicrobial agents. In: Schrier RW GJ, Gambertoglio JG, eds. *Handbook of Drug Therapy in Liver and Kidney Disease*. Little Brown and Company; 1991:1445.
86. Fossieck B Jr, Parker RH. Neurotoxicity during intravenous infusion of penicillin. A review. *J Clin Pharmacol*. 1974;14(10):504–512.
87. Calandra G, Lydick E, Carrigan J, Weiss L, Guess H. Factors predisposing to seizures in seriously ill infected patients receiving antibiotics: experience with imipenem/cilastatin. *Am J Med*. 1988;84(5):911–918.
88. Norrby SR. Carbapenems in serious infections: a risk-benefit assessment. *Drug Saf*. 2000;22(3):191–194.
89. Chow KM, Szeto CC, Hui AC, Wong TY, Li PK. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy*. 2003;23(3):369–373.
90. Lin CS, Cheng CJ, Chou CH, Lin SH. Piperacillin/tazobactam-induced seizure rapidly reversed by high flux hemodialysis in a patient on peritoneal dialysis. *Am J Med Sci*. 2007;333(3):181–184.

91. Aronoff GR, Sloan RS, Brier ME, Luft FC. The effect of piperacillin dose on elimination kinetics in renal impairment. *Eur J Clin Pharmacol*. 1983;24(4):543–547.
92. Thompson MI, Russo ME, Matsen JM, Atkin-Thor E. Piperacillin pharmacokinetics in subjects with chronic renal failure. *Antimicrob Agents Chemother*. 1981;19(3):450–453.
93. Welling PG, Craig WA, Bundtzen RW, Kwok FW, Gerber AU, Madsen PO. Pharmacokinetics of piperacillin in subjects with various degrees of renal function. *Antimicrob Agents Chemother*. 1983;23(6):881–887.
94. Giron JA, Meyers BR, Hirschman SZ. Biliary concentrations of piperacillin in patients undergoing cholecystectomy. *Antimicrob Agents Chemother*. 1981;19(2):309–311.
95. Moellering RC Jr, Krogstad DJ, Greenblatt DJ. Pharmacokinetics of vancomycin in normal subjects and in patients with reduced renal function. *Rev Infect Dis*. 1981;3 suppl:S230–S235.
96. Farber BF, Moellering RC Jr. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrob Agents Chemother*. 1983;23(1):138–141.
97. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864.
98. Turner RB, Kojiro K, Shephard EA, et al. Review and validation of Bayesian dose-optimizing software and equations for calculation of the vancomycin area under the curve in critically ill patients. *Pharmacotherapy*. 2018;38(12):1174–1183.
99. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. *Clin Pharmacokinet*. 1986;11(4):257–282.
100. Tan CC, Lee HS, Ti TY, Lee EJ. Pharmacokinetics of intravenous vancomycin in patients with end-stage renal failure. *Ther Drug Monit*. 1990;12(1):29–34.
101. Golper TA, Noonan HM, Elzinga L, et al. Vancomycin pharmacokinetics, renal handling, and nonrenal clearances in normal human subjects. *Clin Pharmacol Ther*. 1988;43(5):565–570.
102. Rotschafer JC, Crossley K, Zaske DE, Mead K, Sawchuk RJ, Solem LD. Pharmacokinetics of vancomycin: observations in 28 patients and dosage recommendations. *Antimicrob Agents Chemother*. 1982;22(3):391–394.
103. Krogstad DJ, Moellering RC Jr, Greenblatt DJ. Single-dose kinetics of intravenous vancomycin. *J Clin Pharmacol*. 1980;20(4):197–201.
104. Graninger W, Presteril E, Schneeweiss B, Teleky B, Georgopoulos A. Treatment of *Candida albicans* fungaemia with fluconazole. *J Infect*.

1993;26(2):133–146.
105. Debruyne D, Ryckelynck JP. Clinical pharmacokinetics of fluconazole. *Clin Pharmacokinet*. 1993;24(1):10–27.
106. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1–50.
107. Toon S, Ross CE, Gokal R, Rowland M. An assessment of the effects of impaired renal function and haemodialysis on the pharmacokinetics of fluconazole. *Br J Clin Pharmacol*. 1990;29(2):221–226.
108. Oono S, Tabei K, Tetsuka T, Asano Y. The pharmacokinetics of fluconazole during haemodialysis in uraemic patients. *Eur J Clin Pharmacol*. 1992;42(6):667–669.
109. Bergner R, Hoffmann M, Riedel KD, et al. Fluconazole dosing in continuous veno–venous haemofiltration (CVVHF): need for a high daily dose of 800 mg. *Nephrol Dial Transplant*. 2006;21(4):1019–1023.
110. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016;36(5):481–508.
111. Odar-Cederlof I, Borga O. Kinetics of diphenylhydantoin in uraemic patients: consequences of decreased plasma protein binding. *Eur J Clin Pharmacol*. 1974;7(1):31–37.
112. Tiula E, Tallgren LG, Neuvonen PJ. Serum protein binding of phenytoin, diazepam and propranolol in chronic renal diseases. *Int J Clin Pharmacol Ther Toxicol*. 1987;25(10):545–552.
113. Letteri JM, Mellk H, Louis S, Kutt H, Durante P, Glazko A. Diphenylhydantoin metabolism in uremia. *N Engl J Med*. 1971;285(12):648–652.
114. Browne TR. Pharmacokinetics of antiepileptic drugs. *Neurology*. 1998;51(5 Suppl 4):S2–S7.
115. Reidenberg MM. The binding of drugs to plasma proteins and the interpretation of measurements of plasma concentrations of drugs in patients with poor renal function. *Am J Med*. 1977;62(4):466–470.
116. Liponi DF, Winter ME, Tozer TN. Renal function and therapeutic concentrations of phenytoin. *Neurology*. 1984;34(3):395–397.
117. Allison TB, Comstock TJ. Temperature dependence of phenytoin-protein binding in serum: effects of uremia and hypoalbuminemia. *Ther Drug Monit*. 1988;10(4):376–381.
118. Aweeka FT, Gottwald MD, Gambertoglio JG, et al. Pharmacokinetics of fosphenytoin in patients with hepatic or renal disease. *Epilepsia*. 1999;40(6):777–782.
119. Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. *Clin Pharmacokinet*. 1996;31(6):410–422.
120. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol*. 1983;13(2):180–185.

121. Chan GL, Matzke GR. Effects of renal insufficiency on the pharmacokinetics and pharmacodynamics of opioid analgesics. *Drug Intell Clin Pharm*. 1987;21(10):773–783.
122. Shimomura K, Kamata O, Ueki S, et al. Analgesic effect of morphine glucuronides. *Tohoku J Exp Med*. 1971;105(1):45–52.
123. Bigler D, Eriksen J, Christensen CB. Prolonged respiratory depression caused by slow release morphine. *Lancet*. 1984;1(8392):1477.
124. Shelly MP, Park GR. Morphine toxicity with dilated pupils. *Br Med J (Clin Res Ed)*. 1984;289(6451):1071–1072.
125. Matzke GR, Chan GL, Abraham PA. Codeine dosage in renal failure. *Clin Pharm*. 1986;5(1):15–16.
126. Zheng M, McErlane KM, Ong MC. Hydromorphone metabolites: isolation and identification from pooled urine samples of a cancer patient. *Xenobiotica*. 2002;32(5):427–439.
127. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage*. 2004;28(5):497–504.
128. Buckley MM, Sorkin EM. Enoxaparin. A review of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disorders. *Drugs*. 1992;44(3):465–497.
129. Gerlach AT, Pickworth KK, Seth SK, Tanna SB, Barnes JF. Enoxaparin and bleeding complications: a review in patients with and without renal insufficiency. *Pharmacotherapy*. 2000;20(7):771–775.
130. Cadroy Y, Pourrat J, Baladre MF, et al. Delayed elimination of enoxaparin in patients with chronic renal insufficiency. *Thromb Res*. 1991;63(3):385–390.
131. Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? *Blood*. 1999;94(8):2569–2574.
132. Lachish T, Rudensky B, Slotki I, Zevin S. Enoxaparin dosage adjustment in patients with severe renal failure: antifactor xa concentrations and safety. *Pharmacotherapy*. 2007;27(10):1347–1352.
133. Lovenox. Package insert. Sanofi-Aventis U.S. LLC; 2020.
134. Weinstein JR, Anderson S. The aging kidney: physiological changes. *Adv Chronic Kidney Dis*. 2010;17(4):302–307.
135. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA*. 2008;300(24):2867–2878.
136. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365(21):2002–2012.
137. Krepinsky J, Ingram AJ, Clase CM. Prolonged sulfonylurea-induced hypoglycemia in diabetic patients with end-stage renal disease. *Am J Kidney Dis*. 2000;35(3):500–505.
138. Herman GA, Stevens C, Van Dyck K, et al. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in

healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. *Clin Pharmacol Ther*. 2005;78(6):675–688.

139. Chan JC, Scott R, Arjona Ferreira JC, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. *Diabetes Obes Metab*. 2008;10(7):545–555.
140. McGill JB, Sloan L, Newman J, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2013;36(2):237–244.
141. Hudson JQ, Bean JR, Burger CF, Stephens AK, McFarland MS. Estimated glomerular filtration rate leads to higher drug dose recommendations in the elderly compared with creatinine clearance. *Int J Clin Pract*. 2015;69(3):313–320.

SECTION 6

Immunologic Disorders

Section Editor: Steven Gabardi

32

Drug Hypersensitivity Reactions

Mariana C. Castells, Kathleen Marquis, and Kylie Marie Besz

CORE PRINCIPLES		CHAPTER CASES
1	Drug allergies are a subset of adverse drug reactions that are usually mediated by the immune system. Although typically unpredictable, there are several factors known to influence the frequency of allergic reactions including age, sex, genetics, prior drug exposure, and drug dose and route. A detailed drug history is key to assisting in the diagnosis of a drug allergy.	**Case 32-1 (Questions 1, 2), Table 32-1**

CORE PRINCIPLES		CHAPTER CASES
2	Skin testing for allergy to penicillin is an important diagnostic tool that assists in determining whether a patient is truly allergic to this class of drug. Patients presenting with a history of penicillin allergy but who have a negative penicillin scratch test and a negative intradermal test should be challenged with penicillin and if no reaction can be safely given β-lactam antibiotics.	**Case 32-1 (Question 3), Table 32-4**
3	There are varying degrees of cross-reactivity between various β-lactam antibiotics. Understanding the frequency of cross-reactivity is important in making treatment decisions if skin testing is not available. The frequency of cross-reaction between penicillins and cephalosporins appears to be very low except for aztreonam and ceftazidime. The risk of a cephalosporin reaction in a patient with a penicillin allergy decreases with increasing cephalosporin generation, being lowest with the third- and fourth-generation drugs. The frequency of cross-reaction between penicillins and carbapenems or monobactams appears to be very low (~1%).	**Case 32-1 (Question 4)**

ANAPHYLAXIS

CORE PRINCIPLES		CHAPTER CASES
1	Anaphylaxis is a serious allergic reaction that has a rapid onset and might cause death. It is caused by the rapid release of immune mediators from tissue mast cells and peripheral blood basophils. Symptoms such as pruritus of the hands, feet, and groin; flushing; light-headedness; hypotension; tachycardia; and difficulty breathing can begin within minutes of exposure to the precipitating agent, which is most commonly foods, insect stings, and drugs. Prompt recognition and treatment are critical to ensure a favorable outcome.	**Case 32-2 (Questions 1, 2), Table 32-2**

CORE PRINCIPLES		CHAPTER CASES
2	Epinephrine is the drug of choice for treatment of anaphylaxis and should be given immediately upon suspicion of an anaphylactic reaction. Epinephrine should be given intramuscularly into the lateral thigh as often as every 5 minutes to treat symptoms. Intramuscular injection is preferred over the subcutaneous and intravenous (IV) routes because of rapid absorption and ease of administration. The patient should be placed in the Trendelenburg position and second-line treatments including oxygen, IV fluids, and a nebulized β-agonist initiated as needed. Antihistamines and corticosteroids are also commonly used to treat anaphylaxis, although there are no data showing an impact on outcome from these therapies.	**Case 32-2 (Question 3), Table 32-5**
GENERALIZED REACTIONS		
1	Generalized hypersensitivity reactions can manifest in a number of ways including drug fever, serum sickness, hemolytic anemia, vasculitis, and autoimmune disorders. Specific organ systems such as the lungs, liver, kidneys, and the hematopoietic system can also be the target of allergic drug reactions.	**Case 32-3 (Questions 1-3)** **Case 32-4 (Questions 1-3)** **Case 32-5 (Questions 1-4), Tables 32-6 to 32-8**

CORE PRINCIPLES		CHAPTER CASES
NON-IGE HYPERSENSITIVITY REACTIONS		
1	Non–IgE hypersensitivity reactions are drug reactions that exhibit clinical signs and symptoms of an allergic response but are not immunologically mediated. Non–IgE mediated reactions can be relatively benign (such as red man syndrome from vancomycin) or potentially life-threatening, clinically resembling immune-mediated anaphylaxis as from radiocontrast media. Several drugs are associated with non-IgE reactions including aspirin and nonsteroidal anti-inflammatory drugs, opiates, angiotensin-converting enzyme inhibitors, and injectable iron products.	**Case 32-6 (Questions 1, 2, 5)** **Case 32-7 (Questions 1-3), Table 32-9**
2	The management of non–IgE mediated reactions is the same as for true allergic reactions.	**Case 32-6 (Questions 3, 4)** **Case 32-7 (Question 2)**
PREVENTION AND MANAGEMENT OF ALLERGIC REACTIONS		
1	The keys to preventing an allergic reaction in a patient with a history of allergy are a good description of the reaction and its causes, distinguishing between drug allergy and drug intolerance, and good documentation and communication of the reaction.	**Case 32-1 (Questions 1, 2)** **Case 32-8 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
2	In some cases, it is necessary to treat a patient with a drug to which they have a significant allergic reaction. To accomplish this, the process of tolerance induction and desensitization should be used for acute IgE and non-IgE reactions and for nonsevere delayed reactions but not for hepatitis, hemolytic anemia, Stevens–Johnson syndrome, or toxic epidermal necrolysis. Tolerance induction starts with administration of a suballergenic dose of the drug to which a patient is allergic and the progressive administration of larger doses with the goal of modifying the patient's response. Once tolerance has been successfully induced, the patient must remain on the drug to maintain the state of tolerance.	**Case 32-9 (Questions 1-5)**
3	All routes can be used for desensitization including oral, IV, and SQ. The oral route of tolerance induction is preferred over the IV route. Patients may experience a mild reaction during desensitization, although severe reactions are rare. Even after successful desensitization, patients may experience an allergic reaction during full-dose therapy.	**Case 32-9 (Questions 2, 3)**

CORE PRINCIPLES		CHAPTER CASES
4	A graded drug challenge (also called test dosing) is a process of giving subtherapeutic doses of a drug to a patient to determine whether they are allergic. A graded drug challenge generally uses larger starting doses than tolerance induction and involves fewer steps. The graded drug challenge may be appropriate in patients with a distant or unclear history of drug allergy, when the reaction seems minor or when diagnostic testing is unavailable, or in cases where cross-reactivity is expected to be low. It should not be used in patients with a history of a severe non–IgE-mediated reaction such as hepatitis, hemolytic anemia, Stevens–Johnson syndrome, or toxic epidermal necrolysis.	**Case 32-9 (Question 1)**

INTRODUCTION

Adverse drug reactions occur in up to 20% of hospitalized patients and in up to 25% of ambulatory patients. Studies have found that up to 6% of all hospitalizations are caused by an adverse drug event. Immunologically mediated adverse drug reactions (also commonly referred to as drug allergy or hypersensitivity) account for about one-third of all adverse drug reactions and may affect 10% to 15% of hospitalized patients.[1–4] In one study of >36,000 hospitalized patients, 731 adverse events were identified, with 1% being severe, life-threatening, allergic reactions.[5] The potential morbidity and mortality associated with allergic drug reactions can be significant.

DEFINITION

Adverse drug reactions resembling an immune response are called drug hypersensitivity reactions (DHRs). True drug allergies show evidence of either drug-specific antibodies or T cells.[1] Clinically, DHRs are commonly classified as immediate or delayed depending on their onset during treatment. Immediate reactions occur within a few hours of exposure and usually are mediated by IgE. Delayed reactions will occur a few days after starting therapy and are typically mediated by T cells. New reactions have been recently described such as infusion reactions, cytokine release reactions (CRR), and mixed reactions (IgE and CRR).[6] See **Table 32-1**.

Table 32-1
Immunologic Classification of Allergic Drug Reactions

Type	Type of Immune Response	Pathophysiology	Clinical Symptoms	Typical Chronology of the Reaction
I	IgE	Mast cell and basophil degranulation	Anaphylactic shock Angioedema Urticaria Bronchospasm	Within 1–6 hours of the last intake of the drug
II	IgG and complement	IgG- and complement-dependent cytotoxicity	Cytopenia	5–15 days after the start of the eliciting drug
III	IgM or IgG and complement or FcR	Deposition of immune complexes	Serum sickness Urticaria Vasculitis	7–8 days for serum sickness/urticaria 7–21 days after the start of the eliciting drug for vasculitis
IVa	Th1 (IFN-γ)	Monocytic inflammation	Eczema	1–21 days after the start of the eliciting drug
IVb	Th2 (IL-4 and IL-5)	Eosinophilic inflammation	MPE, DRESS	1 to several days after the start of the eliciting drug for MPE 2–6 weeks after the start of the eliciting drug for DRESS
IVc	Cytotoxic T cells (perforin, granzyme B FasL)	Keratinocyte death mediated by CD4 or CD8	MPE, pustular exanthema, SJS/TEN	1–2 days after the start of the eliciting drug for fixed drug eruption 4–28 days after the start of the eliciting drug for SJS/TEN
IVd	T cells (IL-8/CXCL8)	Neutrophilic inflammation	Acute generalized exanthematous pustulosis	Typically 1–2 days after the start of the eliciting drug (but could be longer)

DRESS, drug rash with eosinophilia and systemic symptoms; FasL, Fas ligand; FcR, Fc receptor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; MPE, maculopapular exanthema; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Source: Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69(4):420–437. © 2014 John Wiley & Sons A/S. Reprinted by permission of John Wiley & Sons, Inc.

PATHOGENESIS

DHRs cannot be attributed to a single immunopathologic mechanism. Traditionally, an allergic drug reaction was thought to occur in two phases, initial sensitization and subsequent elicitation.[7] Most drugs are small molecules (<1000 Da) and are unable to stimulate an immune response. Sensitization occurs as a result of covalent binding of a drug or a metabolite to a carrier protein in a process referred to as *haptenation*.[1,8] This drug–protein (or drug metabolite–protein) complex is sufficiently large to induce the production of drug-specific T or B lymphocytes and IgM, IgG, and IgE. On reexposure to the drug, the patient is likely to present with allergic symptoms.[8] Allergic reactions to β-lactam antibiotics occur by this mechanism. This theory, however, cannot explain several allergic phenomena. For instance, some chemically inert drugs (ie, drugs that cannot form stable covalent bonds and do not have reactive metabolites) can still elicit an allergic response. Lidocaine and mepivacaine are examples. Furthermore, some patients have a strong allergic reaction to a drug on initial exposure, and some allergic reactions rapidly occur after drug exposure, a time period shorter than expected for the development of new antibodies. For example, infusion reactions causes by the release of cytokines, namely IL-6, during infusion of platins (oxaliplatin) and monoclonal antibodies.[9-11] To account for some of these observations, other models for explaining allergic reactions have been proposed. The direct pharmacologic interaction concept offers one explanation for these observations. This model suggests that some drugs are able to bind directly to T-cell receptors in a reversible, noncovalent manner.[12] The drug–T-cell receptor complex interacts with major histocompatibility complex (MHC) molecules, leading to activation and expansion of T cells that are directed against the drug.[13]

Recent studies have demonstrated an additional mechanism whereby abacavir and carbamazepine can alter the shape and chemistry of the antigen-binding cleft via noncovalent interactions in patents with specific human leucocyte antigen (HLA) variants. These

alterations cause endogenous peptide to be viewed as foreign and lead to the activation of T cells. This process is referred to as the *altered repertoire model*.[14,15] Undoubtedly, the processes involved in allergic reactions are complex and might include some combination of each theory. The three models of hapten sensitization, direct pharmacologic interaction, and altered repertoire are not mutually exclusive. Interested readers are referred to more in-depth reviews.[16]

PREDISPOSING FACTORS

Factors known to affect the incidence of allergic reactions can be categorized as being drug-related or patient-related ones.[3] Patients with histories of allergic rhinitis, asthma, or atopic dermatitis who experience a systemic drug reaction tend to react more severely than do others.[3,17,18]

Age and Sex

Children are less likely to become sensitized than are adults, presumably because children typically have less cumulative drug exposure.[1,17] More female than male patients experience allergic reactions (up to 2.3:1), although this may vary by type of reaction, drug, patient age, and setting.[3,18]

Genetic Factors

Familial occurrences of allergic reactions, although rare, have been reported.[19] A patient's ability to metabolize a drug is influenced by his or her genetic makeup and may affect the incidence of DHRs.[16,20–22] In humans, the MHC is encoded by a group of genes on chromosome 6 called the *HLA system*. Variations in HLA are probably the most important genetic determinant of drug allergies.[16]

Genetic differences in drug-metabolizing enzymes can explain the predisposition to drug allergy and hypersensitivity of some

individuals.[16] Examples of the phenotypic expression of these polymorphisms include poor metabolizers (who possess nonfunctional alleles and have reduced metabolic activity) and ultrarapid metabolizers (who have multiple copies of functional genes and have enhanced metabolic activity).[22,23]

Slow acetylators are at risk for sulfonamide hypersensitivity and are also more likely to develop antinuclear antibodies (ANAs) and symptoms of systemic lupus erythematosus (SLE) when treated with procainamide or hydralazine.[24] Anticonvulsant hypersensitivity syndrome, characterized by fever, generalized rash, lymphadenopathy, and internal organ involvement, is most associated with aromatic anticonvulsants (eg, phenytoin, phenobarbital, and carbamazepine). Oxidation of these compounds by cytochrome P-450 enzymes results in arene oxides that are antigenic. Patients with a heritable deficiency in epoxide hydrolase cannot clear the formed antigen and are at increased risk for a drug sensitivity syndrome, also known as DRESS (drug rash with eosinophilia and systemic symptoms).[25] A polymorphism might also be responsible for a serum sickness–like reaction to cefaclor.[23]

Although polymorphism in drug-metabolizing enzymes is responsible for some allergic reactions, variation in MHC appears to be more important.[16,20] HLA polymorphisms mostly map to the antigen-binding cleft, thereby diversifying the repertoire of peptide antigens selected by different HLA allotypes. Several important DHRs are associated with specific HLA alleles.[16] For example, HLA-B*1502 is associated with increased risk (odds ratio [OR] 17.6) of Stevens–Johnson syndrome (SJS) with carbamazepine (CBZ), phenytoin, and lamotrigine.[20] HLA-B*1502 occurs in 10% to 15% of individuals from southern China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan and has a prevalence rate of 2% to 4%, or higher, in other southern Asian groups, including Indians. It is uncommon in Japan and Korea (<1%) and in European Caucasians (0%–0.1%).[21]

The potentially life-threatening hypersensitivity syndrome seen with abacavir is strongly associated with the HLA-B*5701 haplotype.[16,26–29] HLA-B*5701 in patients predicted abacavir

hypersensitivity 100% of the time, and its absence had a 97% negative predictive value.[29] This haplotype appears more commonly in White patients than in other ethnic groups and explains the predisposition of White patients to this severe reaction. Genetic screening of patients for this haplotype before initiating abacavir therapy has significantly reduced the occurrence of hypersensitivity reactions.[29] In the future, it is hoped that screening tests for HLA haplotypes associated with a variety of allergic reactions will become widely available.

A more comprehensive and up-to-date listing of alleles associated with immunologically mediated adverse drug reactions can be found at https://www.pharmgkb.org/.

Associated Illness

Although genes clearly play a role in hypersensitivity reactions, environmental factors (eg, concomitant illness) also are implicated. For example, the incidence of maculopapular rash with ampicillin therapy is significantly higher in patients with Epstein–Barr virus infections (eg, infectious mononucleosis), lymphocytic leukemia, or gout.[30] Infection with herpes virus or Epstein–Barr virus has also been linked to DRESS syndrome,[30] and the occurrence of reactions to trimethoprim–sulfamethoxazole in patients who are human immunodeficiency virus (HIV) positive is about 10-fold higher than in the HIV-negative population.[26] Liver or kidney disease may alter the metabolism or elimination of reactive drug metabolites, increasing the risk of an allergic response.

Previous Drug Administration

A history of an allergic reaction to a drug being considered for treatment, or one that is immunochemically similar, is the most reliable risk factor for the development of a subsequent allergic reaction.[1,30] A commonly encountered example is the patient with a history of a severe allergic reaction to penicillin, in whom all

structurally related penicillin compounds should be avoided, and in whom the possibility of a hypersensitivity reaction should be considered when using other β-lactam antibiotics.[1,30]

Drug-Related Factors

The dose, frequency of exposure, and route of administration can influence the incidence of drug allergy. For example, penicillin-induced hemolytic anemia requires high and sustained drug concentrations.[31] In β-lactam antibiotic IgE sensitivity, frequent intermittent courses, rather than continuous therapy, are more likely to result in drug sensitization.[25] The route of administration is important in terms of the risk of both sensitization and allergic reaction in a previously sensitized person. Topical administration carries the greatest risk of sensitization, followed by subcutaneous, intramuscular (IM), and oral routes. The intravenous (IV) route is the least sensitizing route of administration.[32] However, in a patient who is already sensitized to a specific medication, the risk of an allergic reaction to that medication is greatest when it is given IV and least when given orally. This is thought to be a function of the rate of drug delivery.[32] Multiple drug therapy is associated with a greater risk of allergic reactions. This may be related to increased demands on metabolic pathways from multiple drugs, leading to the accumulation of reactive metabolites.[32]

Drugs as Allergens and Immunologic Classification

Although there are proposed changes to the nomenclature and classification of drug allergies,[33] the Gel and Coombs classification is the most common. In this system, allergic drug reactions can be classified into one of four types (Table 32-1).[1]

TYPE I: IMMEDIATE HYPERSENSITIVITY REACTIONS

Type I reactions are typically mediated by IgE. Initial exposure to an antigen results in the production of specific IgE antibodies that are expressed on the surface of mast cells in the tissue and basophils in the blood. On reexposure, the antigen cross-links with two or more surface-bound IgE antibodies, causing the release of several chemical mediators including histamine, tryptase, leukotrienes, prostaglandins, and cyotkines.[32]

A period of several weeks is required after initial exposure and sensitization before a type I reaction can be elicited; once sensitized, however, a type I response can be elicited within minutes as a result of existing antibodies. In addition, a type I reaction can occur on reexposure to small amounts of drug administered by any route.[32,34] Immune-mediated anaphylaxis is a classic example of a type I reaction. Acute non–IgE mediated reactions involve direct activation of mast cells and basophils through the recently discovered mast cell-specific receptor called Mas-related G protein-coupled receptor X2 (MGRPRX2 receptor), CRR, mixed reactions, and COX-1 inhibition induced reactions.[35] Reactions that clinically resemble anaphylaxis, but do not involve immunologic mediators (antibodies), are termed *anaphylactoid* or *pseudoallergic* reactions (see Case 32-6, Question 1).

TYPE II: CYTOTOXIC REACTIONS

Cytotoxic reactions involve the interaction of IgG or IgM and can occur by three different mechanisms (Table 32-1). Common clinical manifestations of cytotoxic reactions include hemolytic anemia, thrombocytopenia, and granulocytopenia. Penicillin-induced hemolytic anemia is the best-known example of a cytotoxic drug reaction. This reaction typically appears after 7 days of high-dose therapy.[31]

TYPE III: IMMUNE COMPLEX–MEDIATED REACTIONS

Immune complex–mediated reactions result from the formation of drug–antibody complexes in serum, which often deposit in blood vessel walls, resulting in activation of complement and endothelial

cell injury.[34] Also referred to as serum sickness, these reactions typically manifest as fever, urticaria, arthralgia, and lymphadenopathy 7 to 21 days after exposure.[30,34]

TYPE IV: CELL-MEDIATED (DELAYED) REACTIONS

In cell-mediated (delayed) reactions, an antigen binds with sensitized T cells. Contact dermatitis is the most common manifestation of cell-mediated reactions, although systemic reactions can occur. The variety of clinical manifestations of delayed hypersensitivity has been attributed to distinct patterns of cytokine release and effector-cell recruitment, based on the type of T cells stimulated. Each pattern of cytokine release recruits specific effector cells, such as macrophages, neutrophils, or other T cells, and is responsible for the unique clinical manifestations of the reaction. Based on this understanding, type IV reactions have been further subclassified as types IVa, IVb, IVc, and IVd, corresponding to four unique patterns of T-cell and effector-cell involvement.[36]

An understanding of the immunologic mechanism can be helpful in the diagnosis and treatment of an allergic reaction; however, the exact immunologic mechanism is unknown for many allergic reactions to drugs.[30] In addition, patients often present with several symptoms characteristic of more than one of the reactions described herein. The use of many drugs concurrently also makes it difficult to identify the drug responsible for the reaction. Therefore, a careful drug history and diagnostic tests are often necessary for an appropriate diagnosis and treatment of a patient.

DIAGNOSIS

Distinctive Features of Allergic Reactions

The first step in the diagnosis of an allergic drug reaction is to recognize and differentiate it from other adverse drug reactions. This

can be accomplished by having a good understanding of the distinctive features of allergic drug reactions (**Table 32-2**).[30]

Table 32-2
Clinical Features of Allergic Drug Reactions

- Are unpredictable
- Occur only in susceptible individuals
- Have no correlation with known pharmacologic properties of the drug
- Reactions can occur at first exposure or may need a sensitization period.
- Can occur with doses far below therapeutic range
- Can affect most organs, but commonly involves the skin
- Most commonly manifests as an erythematous or maculopapular rash, but includes angioedema, serum sickness syndrome, anaphylaxis, and asthma
- Occur in a small proportion of the population (10%–15%)
- Disappear on cessation of therapy and reappear after readministration of a small dose of the suspected drug(s) of similar chemical structure . Many patients are labeled as penicillin allergic while once tested they are able to tolerate penicillin. Delabeling patients with a history of penicillin allergy is recommended to avoid usage of more expensive and complication prone medications and the generation of antibiotic resistance.
- Desensitization may be possible.

Sources: Schnyder B. Approach to the patient with drug allergy. *Immunol Allergy Clin North Am*. 2009;29:405–418; Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69:420.

CASE 32-1

QUESTION 1: J.A., a 73-year-old female, is admitted with an infected decubitus ulcer. Cultures reveal *Staphylococcus aureus*, which is sensitive to oxacillin, cefazolin, and vancomycin. On questioning, J.A. reports having experienced a rash to penicillin in the past. Her current medications include oral docusate 100 mg twice daily, oral enalapril 5 mg every morning, oral prednisone 20 mg daily, and oral ibuprofen 800 mg three times daily.

What information should be obtained to determine whether J.A.'s rash represents an allergic drug reaction?

The single most informative diagnostic procedure for allergic drug reactions is a detailed drug history (**Table 32-3**), which is helpful in obtaining the information necessary to determine whether a reaction represents a drug allergy and in identifying the culprit drug. In inquiring about prior allergic and medication encounters, it is important to document the drugs to which the patient has or has not previously reacted. This can alert the clinician about certain types of compounds to which the patient is likely to react. The acquired information allows the clinician to characterize the drug reaction and to appreciate how such a reaction might be manifested in the patient on exposure to the same, or an immunologically similar, compound in the future.

Table 32-3
Detailed Drug History

- Name of the medication
- Route of administration
- Reason medication was prescribed
- Nature and severity of reaction
- Temporal relationships between drugs and reaction (dose, date initiated, duration, when during the course of treatment did the reaction occur)
- Prior allergy history
- When did the reaction occur (days to weeks vs months to years)?
- Similar reactions in family members
- Prior exposure to the same or structurally related medications
- Concurrent medications
- Management of the reaction (effect of drug discontinuation; therapies required to treat the reaction)

- Response to treatment
- Prior diagnostic testing or rechallenge
- Other medical problems (if any)

Sources: Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S126–S137; Celik G. Drug allergy. In: Adkinson NF, ed. *Middleton's Allergy: Principles and Practice*. 7th ed. Mosby; 2008:1205.

The temporal relationship between drugs and reactions is often the strongest piece of evidence implicating an allergic reaction to a particular agent. Drugs that the patient has received for long continuous periods before the onset of a reaction are less likely to be implicated than are drugs that have been recently initiated or restarted.[30] Equally important is to determine when an adverse reaction has occurred. Many compounds have been reformulated over the years, resulting in removal of sensitizing impurities (eg, penicillin and vancomycin). Therefore, it is possible that reexposure to the agent will not result in an adverse event. Inquiring about whether the patient has received the drug since the first episode by asking the patient about other brands or names of other drugs in the same class (eg, amoxicillin and ampicillin) will assist in determining whether the patient is likely to react to the drug on reexposure. It is usually helpful to chart all the drugs the patient is currently taking, their dose, and start and stop dates of use. This can be compared with the onset and disappearance of the reaction.

CASE 32-1, QUESTION 2: On further questioning, J.A. reports having experienced an urticarial rash in the past when given ampicillin for a kidney infection ~2 years ago. The rash developed over her entire body less than a day after starting the antibiotic and disappeared 2 days after discontinuation. Her treatment course was completed with ciprofloxacin. She denies having had a viral infection at the time of the rash to ampicillin. She does not recall having experienced any adverse effects when she received penicillin before this reaction. No other recent changes in her treatment regimen were made before the occurrence of the rash. Why is it likely that J.A. is allergic to penicillin?

Several pieces of information in the drug history obtained from J.A. can be used to determine the likelihood of an allergic reaction to penicillin. J.A.'s rash appeared less than a day after initiation of ampicillin and other drugs had not been added; therefore, the rash probably was caused by ampicillin. Additionally, since the reaction occurred 2 years prior, it is likely that the patient may still be allergic. Time is important, and patients with a history of penicillin allergy over 20 years are unlikely to be allergic because the rate of penicillin allergy decreases every 10 years.[37]

Another important method of identifying a potential drug-induced allergic reaction is to examine the patient's medication list to determine whether the patient is receiving an agent that commonly is implicated in causing the exhibited allergic manifestation. For example, amoxicillin and ampicillin are two of the top three drugs implicated in drug-induced rash.[31]

J.A. received penicillin previously without experiencing any adverse effects until an urticarial rash (a relatively common allergic manifestation) developed on subsequent exposure. This sequence of events follows the typical pattern of an allergic reaction. Allergic reactions commonly require an induction period to sensitize the person to the antigen; however, once sensitized, allergic symptoms typically occur immediately on reexposure.[30] Therefore, a prior exposure to the same or structurally related compounds needs to be documented.

Finally, it is important to evaluate other medical problems that can elicit or mimic a reaction resembling drug allergy (see the section on "Associated Illness"). Rashes to ampicillin commonly occur in patients with concurrent Epstein–Barr virus infection.[38] J.A. denies having a viral infection at the time of her rash, thereby strengthening the case that the rash was likely a manifestation of an allergic reaction.

Skin Testing

Case 32-1, Question 3: Would skin testing for penicillin allergy be appropriate for J.A.?

Although J.A.'s medication history strongly suggests that she is allergic to penicillin, a skin test and a drug rechallenge would more firmly establish her drug allergy. Penicillin degrades to major determinants (95%) and minor determinants (5%). Penicilloyl, the primary metabolite of penicillin, is referred to as the *major determinant*. The other derivatives are referred to as *minor determinants*. Of these, the parent compound (penicillin), penicilloate, and penilloate are the minor determinants most associated with allergic reactions. The terms *major determinant* and *minor determinant* refer to the frequency of antibody formation to these antigenic penicillin metabolite–protein complexes. These terms do not describe the severity of the allergic reaction. Indeed, the major determinant is thought to be responsible for accelerated reactions, but not anaphylaxis. The minor determinants are responsible for anaphylaxis and immediate systemic reactions.

Skin testing with these determinants is used to identify which patients have IgE antibodies to penicillin and which do not. The skin testing antigen for the major determinant of penicillin is commercially available as penicilloyl polylysine (PPL; Pre-Pen®), which was recently reintroduced into the United States after several years of absence.[39] Skin testing using Pre-Pen® is a safe and effective procedure (**Table 32-4**), with <1% of positive responders developing systemic reactions.[40] In those in whom a false-negative response occurred, reactions were mild after penicillin administration and, in most cases, did not require drug discontinuation.[30,40] Skin testing with PPL identifies 80% of patients allergic to penicillin. When PPL is supplemented with skin tests for the minor determinants of penicillin, 99.5% of patients with allergy to penicillin can be identified.[30] Of the minor determinants, only penicillin G is available in the United States, although a minor determinant mixture is marketed in Europe and Australia.[41]

Table 32-4
Overview of Penicillin Allergy Skin Testing

Skin Testing Reagents	Epicutaneous/Puncture	Testing Intradermal Testing
Controls		
Positive: Histamine		
Negative: Normal saline	1 mg/mL 0.9%	0.9%
Major Determinanta		
Benzylpenicilloyl polylysine (Pre-Pen®)	6 x 10-5 M	6 x 10-5 M
Minor Determinants[a]		
Benzylpenicillin (Penicillin G)	10,000 units/mL	10,000 units/mL
Benzylpenicilloate	0.01-0.02 M	0.01-0.02 M
Benzylpenilloate	0.01-0.02 M	0.01-0.02 M

Penicillin Skin Testing Procedure	Interpretation
Epicutaneous/puncture testing ▪ Apply a drop of the following and then prick/puncture the skin using a skin prick/puncture device. ▪ Histamine (positive control) ▪ Normal Saline (negative control) ▪ Pre-PenR ▪ Diluted penicillin G (10,000 units/mL) ▪ Wait 15.20 minutes to read, measure, and record	Histamine test site must measure at least 5 mm ▪ If not, do not proceed with skin testing Criteria for negative prick/puncture skin test: ▪ No reaction at testing site or no reaction greater than control site ▪ Proceed with intradermal testing Criteria for positive prick/puncture skin test: ▪ Induration 3 mm greater than diluent control ▪ Do not proceed to intradermal testing ▪ Choose alternative agent, consider desensitization if no other alternatives exist

Skin Testing Reagents	Epicutaneous/Puncture	Testing Intradermal Testing

Intradermal testing
▪ Inject sufficient volume of the following to create a bleb of 2.3 mm under skin:
  ▪ Test in duplicate Pre-PenR
  ▪ Test in duplicate penicillin G (10,000 units/mL)
  ▪ Diluent control
▪ Mark perimeter of bleb at placement
▪ Wait 15.20 minutes to read, measure, and record
	Criteria for positive intradermal skin test:
	▪ Increase in size of original bleb of 3 mm or more; itching and flare are commonly present
	Criteria for negative intradermal skin test:
	▪ No increase in size of original bleb and no reaction greater than control site
	Equivocal intradermal skin test:
	▪ Weal only slightly larger than initial injection bleb and control site, with or without erythematous flare or duplicates are discordant	

[a]Approximately 95% of penicillin degrades to form a penicilloyl complex, which is called the major determinant. The remaining penicillin remains in its native form (benzylpenicillin) or degrades further to form minor determinants, which include benzylpenicilloate and benzylpenilloate.

Source: Broyles AD, Banerji A, Barmettler S, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs [published correction appears in *J Allergy Clin Immunol Pract*. 2021 Jan;9(1):603] [published correction appears in *J Allergy Clin Immunol Pract*. 2021 Jan;9(1):605]. *J Allergy Clin Immunol Pract*. 2020;8(9S):S16-S116. doi:10.1016/j.jaip.2020.08.006; Pre-Pen (benzylpenicilloyl polylysine injection solution). Package insert. ALK-Abelló, Inc; 2013. Accessed July 2022.

The negative predictive value of skin testing was demonstrated when 34 patients purportedly allergic to penicillin needed β-lactam antibiotics during hospitalization. Each subsequently tested negative to penicillin skin testing and no allergic drug reactions occurred.[42]

Penicillin and its metabolites become antigenic when combined with proteins and can precipitate a hypersensitivity reaction in a patient on reexposure. In patients with a history of penicillin hypersensitivity, skin test reactivity is affected by the length of time since the allergic reaction and by the nature of the past reaction. Skin test positivity is greatest 6 to 12 months after a reaction and decreases with time. Skin test positivity in one study was found to be only 40% of patients with a history of anaphylaxis, 17% with urticaria,

and 7% for maculopapular rashes.[43] Skin testing should not be performed in patients receiving antihistamines because they block the response to the antigen and can result in misinterpretation. In patients receiving antihistamines (ie, H_1- or H_2-receptor antagonists) or when skin testing is not possible because of severe skin disease, in vitro assays to detect drug-specific IgE antibodies have been developed for the major and minor determinants of penicillin.

To determine whether skin testing is appropriate for J.A., the risks and benefits must be weighed. Because the time of the last reaction was ~2 years ago, J.A. may still retain some skin test positivity if the previous reaction was truly an allergic response to ampicillin. Testing with PPL (major determinant) and penicillin G (minor determinant) could be useful in determining whether J.A. is likely to experience an urticarial or anaphylactic reaction to penicillin or its derivatives. That J.A. is currently receiving prednisone should not alter the interpretation of the skin test results because the corticosteroids minimally affect the IgE-mediated immediate hypersensitivity reactions. The risks of developing serious systemic reactions to penicillin skin testing are minimal.

In patients with demonstrated penicillin allergy in need of penicillin, desensitization should be the first treatment choice. Avoidance with usage of alternative second-line antibiotics will generate antibiotic resistance, provide more complications, increase resource utilization, and increase hospital stay.[44]

Cross-Reactivity

Case 32-1, Question 4: J.A. received a scratch test with PPL, the result of which was negative; however, an intradermal test result was positive. What treatment options are available to J.A. for her infection?

All penicillin derivatives should be avoided because J.A. had a positive skin test reaction. Skin tests are not commercially available for cephalosporins and other β-lactam antibiotics. Although cephalosporin skin testing (ie, prick followed by intradermal

instillation) has been proposed, no prospective studies have evaluated this approach and this practice is not without risk.[45,46] Therefore, clinicians must rely on cross-reactivity data to determine whether a non-penicillin β-lactam antibiotic (eg, a cephalosporin) can be used in a patient with allergy to penicillin.

Cross-reactivity (ie, cross-antigenicity) between penicillin and cephalosporins has been reported in 5% to 15% of patients[40,43]; however, the true incidence of cross-reactivity is considerably less because these initial percentages were based on the recollection of patients about an allergic history rather than by objective skin tests.

The risk of a cephalosporin reaction in a patient with a penicillin allergy decreases with increasing cephalosporin generation: 5% to 16.5% for first-generation, 4% for second-generation, and 1% to 3% for third-generation and fourth-generation cephalosporins.[47] The risk of a serious allergic reaction with the use of an advanced-generation cephalosporin in a patient with allergy to penicillin might be no greater than the risk of any alternative antibiotic.[48] The cross-reactivity between penicillins and cephalosporins formerly was attributed primarily to their common β-lactam chemical-ring structure; however, side-chain–specific reactions are now recognized to be responsible for a significant portion of allergic reactions within and between the penicillin and cephalosporins families.[45,48,49] In a study of 30 patients with immediate allergic reactions to cephalosporins, <20% reacted to penicillin determinants (ie, skin test positivity, radioallergosorbent testing positivity, or both).[49] (Radioallergosorbent testing is a radioimmune test to detect IgE antibodies responsible for hypersensitivity.) This cross-reactivity between penicillin and cephalosporins is significantly less than earlier reports (up to 50%); however, the results of this study could be attributable to the greater use of third-generation, rather than the first-generation cephalosporins, which share more chemical structure similarities with the penicillins. Additional support for the importance of side-chain–specific reactions of β-lactams comes from observational data noting that 30% of patients with immediate reactions to penicillins were selective for amoxicillin.[50] In patients with allergy to amoxicillin, studies have found 2% to 38% cross-reactivity with the

cephalosporin cefadroxil; both drugs share the same side chain.[34] Patients allergic to ampicillin may also have a greater risk of allergic reaction to cephalosporins that share the same side chain, such as cephalexin, cefaclor, cephradine, and loracarbef. Some patients also have multiple drug allergies and could manifest an allergic reaction to these drugs (and others that are not β-lactams) in a manner similar to their penicillin reaction.[43]

Cross-reactivity between penicillins and carbapenems (imipenem, meropenem, ertapenem, doripenem), and monobactams (eg, aztreonam) has also been studied. One hundred and twelve patients with a history of immediate reactions to penicillin and a positive skin test result to penicillin underwent skin testing with imipenem–cilastatin. One patient (0.9%) had a positive skin test result. One hundred and ten of the remaining 111 patients received gradually increasing IM doses of imipenem–cilastatin with no reactions observed.[51] Similarly, 108 children with a history of an immediate hypersensitivity reaction to a penicillin and a positive skin test underwent intradermal skin testing to meropenem. One child (0.9%) had a positive skin test. The remaining 107 subjects received increasing doses of IM meropenem with no reactions reported.[52] There also does not appear to be significant cross-reactivity between penicillins and the monobactam aztreonam.[53] Ceftazidime and aztreonam have an identical side chain, however, and there is evidence of cross-reactivity between these two antibiotics.[54]

Although desensitization with an appropriate cephalosporin is a potential option for J.A. (see Case 32-9, Question 1), her infection is not life-threatening, and the organism is probably sensitive to another antimicrobial agent. In this case, it would be prudent to treat J.A. with a non–β-lactam antibiotic. If J.A.'s skin tests to cephalosporin were undertaken, and results had been negative, she could receive a cephalosporin despite her positive history beginning with a cautiously administered small (ie, "test") initial dose.[43]

GENERALIZED REACTIONS

Drug allergies can be grouped into three categories: generalized reactions, organ-specific reactions, and non–IgE mediated hypersensitivity reactions. Generalized reactions involve multiple organ systems and variable clinical manifestations. Anaphylactic reactions, serum sickness reactions, drug-induced fever, hypersensitivity vasculitis, drug-induced vasculitis, and autoimmune drug reactions are the generalized drug reactions presented in this chapter.

Anaphylaxis

CASE 32-2

Question 1: L.P., a 187.39-pound (85-kg), 29-year-old male, presents to the emergency department with a cat bite to the forearm 2 days prior. Physical examination reveals a male in moderate distress with multiple puncture wounds on the volar aspect of the right arm. The area surrounding the wounds is swollen, erythematous, and tender to the touch. L.P.'s history is notable for exercise-induced asthma, controlled with an albuterol metered-dose inhaler as needed, and a history of a laparoscopic appendectomy 3 years prior. He has no known allergies. The wound is cleansed with a germicidal soap and 3 g ampicillin/sulbactam is started via IV route. Three minutes after starting the ampicillin/sulbactam, L.P. notes tingling and pruritus of both his hands and feet, and appears flushed. One minute later he reports feeling light-headedness, difficulty breathing, and a lump in his throat. His vital signs at this time are blood pressure (BP) 100/60 mm Hg (normal, 125/85), heart rate 70 beats/minute (normal, 60), and respiratory rate 27 breaths/minute (normal, 12). Chest auscultation reveals restricted airflow and stridor. Anaphylaxis is the diagnosis and emergency treatment is started.

What subjective and objective evidence support the diagnosis of anaphylaxis in L.P.?

Anaphylaxis is a serious allergic reaction that has a rapid onset and can cause death.[55] The diagnosis is considered probable if one of three clinical criteria are met[56]:

1. An acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least one of the following:
   a. Respiratory compromise

b. Reduced BP or symptoms of end-organ dysfunction

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient:

a. Involvement of the skin/mucosal tissue

b. Respiratory compromise

c. Reduced BP or associated symptoms

d. Persistent gastrointestinal (GI) symptoms

3. Reduced BP, after exposure to a known allergen

Anaphylaxis results from the rapid release of immunologic mediators from tissue mast cells and peripheral blood basophils.

The symptoms of anaphylaxis vary widely, depending on the route of exposure, rate of exposure, and dose of allergen.[34] Symptoms often begin within minutes of exposure, as in L.P., and most reactions occur within 1 hour. On rare occasions, anaphylaxis can appear several hours after exposure, and late phase or biphasic attacks have occurred 1 to 72 hours after the initial attack (most commonly within 8 hours). In general, the severity of the anaphylaxis is directly proportional to the speed of onset. L.P. displays symptoms in many of the organs commonly involved in anaphylaxis. Although almost any organ system can be affected, the cutaneous, GI, respiratory, and cardiovascular systems are involved most frequently, either singly or in combination.[34] These “shock organs” contain the largest number of mast cells and are the most highly affected.

L.P. exhibits erythema (flushed appearance) and pruritus of his hands and feet, both common initial symptoms of anaphylaxis; the groin is also commonly affected. These symptoms can progress to urticaria and angioedema, especially of the palms, soles, periorbital tissue, and mucous membranes. L.P. describes the early manifestations of angioedema (laryngeal edema) with a feeling of a lump in his throat (this may also be described as throat tightness or constriction by some patients).

The upper and lower respiratory tracts can also be involved during an anaphylactic event. L.P. exhibits stridor, indicating upper airway

involvement. Hoarseness is another sign of upper respiratory tract involvement. In addition, L.P. is tachypneic with poor airflow, suggesting his lower airway also is affected. L.P. does not display wheezing or acute emphysema, which are further clues of lower airway involvement. Respiratory symptoms can lead to suffocation and death. In one autopsy series, laryngeal edema accounted for 25% of the fatalities and acute emphysema for another 25% of the deaths.[57] Cardiovascular symptoms also are ominous. Cardiovascular collapse and hypotensive shock (anaphylactic shock) are caused by peripheral vasodilation, enhanced vascular permeability, leakage of plasma, low cardiac output, and intravascular volume depletion. Thus, hypotension, as seen with L.P., is a common cardiac manifestation. Tachycardia also commonly occurs in patients with cardiac complications of anaphylaxis. L.P. does not show a significant increase in heart rate; however, he is taking the β-blocker atenolol. Other cardiac manifestations of anaphylaxis include a direct cardiodepressant effect and various electrocardiographic changes, including arrhythmias and ischemia.

Although not demonstrated by L.P., common GI manifestations such as abdominal cramping, diarrhea (which can be bloody), nausea, and vomiting are also manifested during an anaphylactic reaction.[34] In summary, L.P.'s rapid onset and progression of symptoms involving multiple organ systems (ie, cutaneous, respiratory, and cardiovascular systems) are consistent with an anaphylactic reaction. L.P.'s anaphylaxis is a severe reaction given its speed of onset, the number of organ systems involved, and the degree of involvement. In particular, his respiratory and cardiovascular symptoms indicate a potentially life-threatening reaction.

CASE 32-2, QUESTION 2: What is the mechanism behind anaphylaxis, and what is the likely cause of L.P.'s anaphylactic event?

Anaphylaxis occurs through one of three mechanisms.[34] In the first type of reaction, exposure to a foreign protein, either in its native

state or as a hapten conjugated to a carrier protein, causes IgE antibody formation. The IgE antibodies then bind to receptors on mast cells and basophils. On reexposure, the antigen stimulates cellular degranulation through both antigen-IgE antibody formation and cross-linking, which result in massive release of preformed immunologic mediators from the mast cells and basophils. Tryptase is the major biomarker of anaphylaxis and is released into the peripheral blood within 30 minutes of the start of the symptoms. Measuring tryptase during an anaphylactic reaction and at baseline provides evidence of mast cell/basophil activation can rule out clonal and non-clonal mast cell activation disorders associated with an increased frequency of anaphylaxis, such as systemic mastocytosis and hereditary α-tryptasemia (HαT).[58] Whether drugs that activate MRGPRX2 receptors on mast cells such as general anesthetics, rocuronium, atracurium quinolones, and others can induce anaphylaxis has not been demonstrated. Histamine is the major mediator of anaphylaxis and the primary preformed cellular constituent. Histamine has multiple effects and is likely responsible for vasodilation, urticaria, angioedema, hypotension, vomiting, abdominal cramping, and changes in coronary flow.[34] Leukotrienes (eg, leukotrienes C_4 and D, also known as slow-reacting substance of anaphylaxis), platelet activating factor, and prostaglandins are generated rapidly as a result of cellular degranulation, and other mediators of anaphylaxis (eg, tryptase, chymase, carboxypeptidase A, tumor necrosis factor, and other cytokines and chemokines) are released as well.[34] Anaphylactic reactions to *Hymenoptera* venom (eg, bee stings), insulin, streptokinase, penicillins, cephalosporins, local anesthetics, and sulfonamides occur through this IgE-mediated mechanism.

Anaphylaxis also can occur via the formation of immune complexes that activate the complement system and the subsequent formation of anaphylatoxins C3a, C4a, and C5a. Such anaphylatoxins can directly stimulate mast cell and basophil degranulation and mediator release. In 2008, cases resembling anaphylaxis in patients receiving heparin, particularly those also

undergoing dialysis, were reported, with almost 100 deaths occurring internationally. The culprit was found to be a contaminant (oversulfated chondroitin sulfate) that caused symptoms by this mechanism.[59,60]

The third mechanism by which substances, such as radiocontrast media and other hyperosmolar agents, can cause anaphylaxis is by the direct stimulation of mediator release (primarily histamine). The pathway by which this occurs is as yet unknown, but it is independent of IgE and complement.

In addition, when no distinct mechanism can be associated with an anaphylactic event, the term idiopathic anaphylaxis is applied.[34]

Foods, insect stings, and drugs are the most common causes of anaphylaxis.[61] Antibiotics (particularly β-lactams and fluoroquinolones), nonsteroidal anti-inflammatory drugs (NSAIDs), neuromuscular blocking agents, radiocontrast media, chemotherapeutic agents, and monoclonal antibodies are the most common causes of drug-induced anaphylaxis. L.P.'s anaphylactic episode most likely is related to the first mechanism (ie, IgE antibody formation). L.P. is receiving a drug from a class of antibiotics well known to cause anaphylaxis. Specifically, L.P. may have received a prophylactic β-lactam antibiotic before his appendectomy, a standard of practice. Exposure to the antibiotic at that time stimulated IgE antibody formation. After exposure to the β-lactam ampicillin/sulbactam in the emergency department, antibody–antigen complexes were formed, resulting in cellular degranulation and anaphylaxis. The temporal relationship of L.P.'s anaphylactic reaction to the administration of the antibiotic also strongly implicates ampicillin/sulbactam as the precipitating agent. Furthermore, L.P. was not exposed to agents known to cause anaphylaxis by one of the other known mechanisms. A review of L.P.'s surgical records is necessary to confirm his prior exposure to a sensitizing antibiotic.

Case 32-2, Question 3: Given L.P.'s signs and symptoms and the presumed cause of his anaphylactic reaction, how should he be treated?

Effective management of anaphylaxis requires quick recognition and aggressive therapeutic intervention because of the immediate life-threatening nature of the reaction, as illustrated by L.P. The severity of the anaphylactic reaction must be assessed quickly, the probable causative agent determined, the administration of the offending substance discontinued, and the absorption of the offending agent minimized if possible. Recent guidelines on the management of anaphylaxis list the following treatments in order of importance: epinephrine, patient position, oxygen, IV fluids, nebulized therapy, vasopressors, antihistamines, corticosteroids, and other agents.[56] All of these interventions must be undertaken promptly and the clinical status of the patient closely monitored. Vital signs, cardiac and pulmonary function, oxygenation, cardiac output, and tissue perfusion in particular must be immediately and continuously assessed.[34,56]

Although not definitively known to be the cause, the infusion of ampicillin/sulbactam should be stopped to prevent further exposure to the presumed precipitating agent. In addition, the forearm wounds should be flushed with normal saline to remove any residual cleansing agent in the event that this is the cause of the reaction.

Pharmacologic treatment of anaphylaxis has traditionally involved several drugs and drug classes such as epinephrine, antihistamines, and corticosteroids aimed at reversing the clinical manifestations of anaphylaxis and interrupting the biologic pathways involved. Recent literature reviews, however, failed to find well-designed and well-conducted randomized controlled trials to support the use of these drugs.[62–64] Recommendations for use are based on tradition, case reports, case series, and expert opinion.

L.P. is showing early signs of anaphylactic shock that must be managed immediately. Epinephrine is the drug of choice for the pharmacologic management of anaphylaxis, and all national and international anaphylaxis guidelines recommend epinephrine as first-line treatment.[34,56,65] Studies have shown that failure to use epinephrine early in anaphylaxis is a risk factor for a poor outcome. Use of standard order sets and autoinjectors by emergency

departments has been shown to increase epinephrine utilization for patients experiencing anaphylaxis.[66]

The α-adrenergic effects of epinephrine increase systemic vascular resistance and increase BP while decreasing mucosal edema and relieving upper airway obstruction, angioedema, and hives. These actions counter the vasodilating and hypotensive effects of histamine and the other mediators of anaphylaxis. In addition, the β-adrenergic effects of epinephrine promote bronchodilation and increase cardiac rate and contractility. Epinephrine also inhibits the release of mediators from basophils and mast cells.

The route of epinephrine administration is important. Most guidelines recommend IM epinephrine, 0.01 mg/kg of a 1 mg/mL (1:1000) solution to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child injected into the lateral aspect of the thigh every 5 to 10 minutes as needed.[66,67] Epinephrine doses should be expressed in mass concentration (eg, 1 mg in 1 mL) instead of ratios such as 1:1000, which have been confused with epinephrine concentrations used in cardiac arrest (1:10,000) and caused dosing errors.[65] Epinephrine is vasodilatory in skeletal muscle, and because the skeletal muscle is highly vascular, absorption is rapid. Although some guidelines propose the subcutaneous route for epinephrine administration, subcutaneous tissue is less vascular than is skeletal muscle; thus, there is less rapid absorption of epinephrine. In addition, epinephrine causes vasoconstriction in subcutaneous tissue, thereby slowing its own absorption. Studies have shown that IM epinephrine injections into the thigh achieve higher blood concentrations more rapidly than do subcutaneous or IM injections into the arm in healthy subjects.[56] The rate and extent of absorption from IM and subcutaneous routes of epinephrine administration, however, have not been studied in patients experiencing anaphylaxis, and there is no evidence that epinephrine is ineffective when given IM or subcutaneously into the arm.[56] Epinephrine should be administered via the IV route in cases of anaphylaxis that have not responded to repeated doses of IM epinephrine and/or are progressing to shock, or in cases where cardiorespiratory arrest

appears imminent. Low cardiac output and intravascular volume depletion from shock decrease tissue perfusion and, possibly, the absorption of subcutaneous or IM injections. In animal studies, the benefits of intermittent IV boluses of epinephrine are short-lived and a continuous infusion of epinephrine provides optimal results.[67] In L.P.'s case, an initial dose of 0.5 mg of 1 mg/1 mL epinephrine solution should be injected IM into his lateral thigh. This should be repeated every 5 minutes until symptoms improve.

Some evidence suggests poor outcomes in patients who are in an upright position during anaphylactic shock.[68] Placing L.P. in the Trendelenburg position (patient supine, inclined ~45 degrees with head at the lower end and legs at the upper end) might improve survival by enhancing perfusion to vital organs. After repositioning, oxygen should be started and normal saline infused at a rate sufficient to maintain perfusion to vital organs. Normal saline is the preferred crystalloid because it stays in the intravascular space longer than does dextrose and does not contain lactate (eg, lactated Ringer solution), which could worsen metabolic acidosis. Circulating blood volume can decrease by as much as 35% in the first 10 minutes of anaphylactic shock because of vasodilation and fluid shifting from the intravascular to the extravascular space.[56] Therefore, vigorous fluid resuscitation might be necessary (eg, 1–2 L of normal saline at a rate of 5–10 mL/kg in the first 5 minutes). Cerebral perfusion, as evidenced by adequate mentation, must always take precedence over BP readings when managing shock.

The effect of L.P.'s atenolol must also be considered. Patients taking a β-blocker, whether cardioselective or not cardioselective, could experience more severe episodes and more refractory episodes of anaphylaxis than do patients not taking a β-blocker. This effect might be caused by a blunted response to epinephrine when given to treat anaphylaxis, resulting in refractory hypotension, bradycardia, and bronchospasm.[56] If L.P.'s BP and heart rate do not substantially improve shortly after initiating epinephrine, IV glucagon, which can stimulate heart rate and cardiac contractility independent of β-adrenergic blockade, should be given (**Table 32-5**). Airway protection is important because glucagon may cause emesis and

there is a risk of aspiration, especially in drowsy or obtunded patients. Methylene blue, through its ability to reduce nitric oxide production (a known potent vasodilator), has been found to be effective in a small number of cases of anaphylaxis with refractory hypotension.[61,68] Other vasopressors such as dopamine (2–20 µg/kg/minute) may be needed to maintain BP if there is a poor response to epinephrine and glucagon. Second-line treatment for anaphylaxis includes inhaled β-agonists, H_1 and H_2 antihistamines, and corticosteroids. In light of L.P.'s severe pulmonary reaction, he should receive a nebulized β-agonist (eg, albuterol). If L.P.'s respiratory status fails to improve after pharmacologic intervention, intubation must be considered. Atenolol would not be expected to diminish the effect of albuterol because atenolol is a β_1 cardioselective β-blocker and the dose is low. Because histamine is the primary mediator of anaphylaxis, IV administration of an H_1 antihistamine such as diphenhydramine (50 mg every 6 hours until the reaction resolves) should be considered. Similarly, giving an H_2 antihistamine is a common practice. Both therapies present little acute risk to the patient, but as already noted, there are few data supporting their efficacy in treating anaphylaxis.[63]

Table 32-5
Drug Therapy of Anaphylaxis

Drug	Indication	Adult Dosage	Complications
First-Line Therapy			
Epinephrine	Hypotension, bronchospasm, laryngeal edema, urticaria, angioedema	0.01 mg/kg to a maximum of 0.5 mg of a 1 mg/1 mL solution IM every 5 minutes prn; if progressing to cardiorespiratory arrest 1–3 mL of 1:10,000 (0.1–0.3 mg) IV for 3 minutes	Arrhythmias, hypertension, nervousness, tremor
		1 mL of 1 mg/mL (1:1000) in 250 mL of normal saline IV at a rate of 4–10 μg/minute	
		3–5 mL of 0.1 mg/mL (1:10,000) intratracheally every 10–20 minutes prn	
Oxygen	Hypoxemia	40%–100%	None
Albuterol		0.5 mL of 0.5% solution in 2.5 mL of saline via nebulizer (ie, 2.5 mg)	Arrhythmias, hypertension, nervousness, tremor
IV fluids	Hypotension	1 L of normal saline every 20–30 minutes prn (rates as high as 1–2 mL/kg/minute may be necessary)	Pulmonary edema, CHF
Second-Line Therapy			
Antihistamines	Hypotension, urticaria		
H_1 receptor antagonists[a]		Diphenhydramine 25–50 mg IV over 10–15 minutes Oral H_1 antagonists may be used in less severe cases.	Drowsiness, dry mouth, urinary retention; may obscure symptoms of continuing reaction
H_2 receptor antagonists[a]		Famotidine 20 mg IV over 10–15 minutes	
Corticosteroids[a]	Bronchospasm; patients undergoing prolonged resuscitation or severe reaction	Hydrocortisone sodium succinate 100 mg IV every 3–6 hours for two to four doses or Methylprednisolone sodium succinate 40–125 mg IV every 6 hours for two to four doses	Hyperglycemia, fluid retention
Dopamine	Hypotension refractory to epinephrine	400 mg in 500 mL dextrose 5% at 2–20 μg/kg/minute	Hypertension, tachycardia, palpitations, arrhythmias
Norepinephrine	Hypotension refractory to epinephrine	4 mg in 1 L dextrose 5% IV at a rate of 2–12 μg/minute	Arrhythmias, hypertension, nervousness, tremor
Glucagon[b]	Refractory hypotension	1 mg IV for 5 minutes, followed by 5–15 μg/minute in fusion	Nausea, vomiting

CHF, congestive heart failure; IM, intramuscularly; IV, intravenously; prn, as needed.

[a]Agents in these classes may be used as adjuncts to epinephrine. Controlled studies demonstrating a clear benefit in anaphylaxis are lacking. Do not delay the administration of epinephrine, supplemental oxygen, or IV fluid resuscitation by taking time to draw up and administer a second-line medication.

[b]Glucagon may be particularly useful in patients taking β-adrenergic blockers, because it can increase both cardiac rate and contractility regardless of β-adrenergic blockade. Choice of agent and starting doses should be patient specific, weighing safety and efficacy.

Lastly, given the severity of his reaction and his pulmonary involvement, L.P. is a candidate for IV corticosteroids. Methylprednisolone, 125 mg every 6 hours for four doses, might be beneficial and is associated with minimal risk. Although commonly

used, corticosteroids will not affect the acute course of the reaction because of their delayed onset of action (typically 4–6 hours after administration). Corticosteroids may impact a prolonged episode of anaphylaxis and could prevent or minimize the occurrence of a biphasic reaction, although this has not been proved in well-controlled trials. The effect of methylprednisolone on L.P.'s diabetes is not a factor because his condition is potentially life-threatening. Once stabilized, L.P. should be transferred to a critical care setting and monitored for a minimum of 24 hours because relapses of the anaphylactic reaction can occur.[34,56] Complications of anaphylaxis include Kounis syndrome with chest pain and coronary spasm with clean coronary arteries, which typically resolved after the resolution of symptoms but can lead to elevated troponins. Takotsubo is a severe complication that can lead to death and associates with inefficient cardiac output during hypotension and epinephrine treatment.

Serum Sickness

Serum sickness is a type III hypersensitivity reaction that results from the production of antibodies directed against heterologous protein or drug haptens with subsequent tissue deposition. The typical presentation of serum sickness includes fever, cutaneous eruptions (95%), lymphadenopathy, and joint symptoms (10%–50%).[69-72] Symptoms usually occur 1 to 2 weeks after exposure, but accelerated reactions can occur within 2 to 4 days in previously sensitized persons. Laboratory data are relatively nonspecific and are of little diagnostic value. For example, the erythrocyte sedimentation rate (ESR) and the serum concentration of circulating immune complexes usually are increased. Complements C3 and C4 are often low, whereas activation products C3a and C3a desarginine are elevated. Urinalysis might reveal proteinuria, hematuria, or an occasional cast.[69-72]

In most cases, serum sickness reactions are mild and self-limiting and resolve within a few days to weeks after withdrawal of the

inciting agent. Antihistamines and aspirin can be used to relieve pruritus and arthralgias. In severe cases, corticosteroids might be used and can be tapered during 10 to 14 days.[69-72] At one time, heterologous serum (eg, anti-thymocyte globulin made from rabbit or equine serum) was a leading cause of serum sickness. With the decline in the use of these products, however, the most common causes of serum sickness today are penicillins and cephalosporins, although biologic agents such as rituximab, infliximab, and natalizumab are increasingly associated with serum sickness.[73,74]

CASE 32-3

Question 1: M.M., a 57-year-old ill-appearing female, is hospitalized with a 3-day history of difficulty breathing, left-sided chest pain on inspiration, fever, chills, and a productive cough. Her medical history is significant only for hypertension, well controlled on hydrochlorothiazide; she has no known drug allergies. M.M.'s physical findings on admission are temperature, 100.4 °F (38 °C); respirations, 20 breaths/minute; left-sided crackles heard on auscultation; oxygen saturation 85% on room air; and heart rate, 85 beats/minute. A chest radiograph reveals an infiltrate in her left lower lobe. Her white blood cell (WBC) count is 17,500 cells/μL with the following differential:

Polymorphonuclear neutrophil leukocytes (PMN), 83% (normal, 45%–79%)
Bands, 12% (normal, 0%–5%)
Lymphocytes, 10% (normal, 16%–47%)
Basophils, 0% (normal, 0%–1%)
Eosinophils, 1% (normal, 1%–2%)

Community-acquired pneumonia is the diagnosis, and M.M. is empirically started on ceftriaxone 1 g IV daily, azithromycin 500 mg IV daily, and oxygen at 2 L/minute. Other medications include oral acetaminophen 325 mg every 4 to 6 hours as needed for temperature >100.4 °F (38 °C), oral famotidine 20 mg bid, and oral hydrochlorothiazide 12.5 mg daily. Seventy-two hours later, M.M. is breathing without pain at a respiratory rate of 12 breaths/minute, her lungs are clear to auscultation, and her oxygen saturation is 98% on room air. She appears much better and offers no new symptoms. Her temperature during the previous 48 hours has ranged from 101.48 °F (38.6 °C) to 104 °F (40 °C), her pulse has ranged from 90 to 100 beats/minute, and her WBC count is 22,000 with the following differential: PMN, 89%; bands, 5%; lymphocytes, 12%; basophils, 0%; and eosinophils, 7%. Drug-induced fever is considered.

What evidence supports this diagnosis? What is the mechanism for drug fever?

Drug Fever

Drug fever is described as a febrile reaction to a drug without cutaneous symptoms and is estimated to occur in 3% to 5% of inpatients.[75] Drug fever can be challenging to identify and can be misinterpreted as a new infectious process or failure of an existing infection to respond to treatment. Such failure to recognize a drug fever can lead to prolonged hospitalization and unnecessary tests or medications.[76] **Table 32-6** lists the characteristics of hypersensitivity drug-induced fever. The most important finding in the case of M.M. is her clinical improvement with respect to her pulmonary status despite a high-grade fever and persistent leukocytosis; she also appears healthier than expected if she had an untreated infection. Although a drop in her WBC count would be anticipated given her improving respiratory function, her WBC count remains elevated, consistent with hypersensitivity drug fever. Notably, her eosinophil count is increased, a frequent sign of hypersensitivity reactions. Despite her high-grade fever, she has a relative bradycardia; that is, her heart rate is not as elevated as expected if an infectious process were ongoing. Further, the timing of the symptoms favors a drug-induced fever (ie, within days of starting a new medication). A definitive diagnosis can be made only by stopping the suspected offending agent, however, because fever generally resolves within 48 to 72 hours if a rash is not present. When a rash is present, on the other hand, the fever may persist for several days after stopping the implicated drug.

Table 32-6
Hypersensitivity Reactions to Drugs: Drug-Induced Fever

Frequency	True frequency is unknown because fever is a common manifestation and almost any drug can cause fever. Estimate is that 3%–5% of hospitalized patients experiencing adverse drug reaction suffer from drug fever alone or as part of multiple symptoms.
Clinical manifestations	Temperatures may be ≥100.4 °F (38 °C) and do not follow a consistent pattern. Although patients may have high fevers with shaking chills, patients generally have few symptoms or

	serious systemic illness. Skin rash (18%), eosinophilia (22%), chills (53%), headache (16%), myalgias (25%), and bradycardia (11%) can occur in patients with drug fever. Onset of fever after exposure to the offending agent is highly variable, ranging from an average of 6 days for antineoplastics to 45 days for cardiovascular agents. Occurrence of fever is independent of the dose of the offending agent.
Treatment	Although drug fever can be treated symptomatically (eg, with antipyretics, cooling blankets), stopping the offending agent is the only therapy that will eliminate fevers. Patients generally defervesce within 48–72 hours of stopping the suspect drug.
Prognosis	Drug fever is usually benign, although one review[57] found a mean increased length of hospitalization of 9 days per episode of drug fever. Rechallenge with the offending drug usually results in rapid return of the fever. Although reexposure to the suspect drug was previously thought to be potentially hazardous, there is little risk of serious sequelae.

Sources: Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010;30:57–69; Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med*. 1987;106:728–733; Cunha BA, Shea KW. Fever in the intensive care unit. *Infect Dis Clin North Am*. 1996;10:185–209.

Drug fever can be caused by various mechanisms, although it is ascribed most commonly to a hypersensitivity reaction. Other mechanisms include the pharmacologic action of the drug (eg, cell destruction from antineoplastic agents releases endogenous pyrogens); altered thermoregulatory function (eg, increased metabolic rate from thyroid hormone); decreased sweating from drugs with anticholinergic properties (eg, atropine, tricyclic antidepressants, and phenothiazines); drug administration–related fever (eg, amphotericin B and bleomycin); and idiosyncratic reactions (eg, neuroleptic malignant syndrome from haloperidol, malignant hyperthermia from inhaled anesthetics).[75]

Case 32-3, Question 2: What agent is the most likely cause of drug fever in M.M.?

Most of the information available on drug fever is based on case reports or small case series and reviews of the literature.[76,77] Unfortunately, the literature is inconsistent with regard to the frequency of drug fever (eg, very common, common, uncommon) and such descriptions are not supported by good clinical data. Nevertheless, some drugs are more commonly associated with drug fever than are others. These include anti-infectives as a class (especially β-lactam antibiotics), antiepileptics, and antineoplastics. Drug fever has also been reported frequently with amphotericin B, azathioprine, hydroxyurea, methyldopa, procainamide, quinidine, and quinine.[76–78]

In M.M.'s case, ceftriaxone or azithromycin is the most likely cause of her ongoing fever, given the timing of the reaction relative to beginning the antibiotics and the frequency of febrile reactions attributed to them, especially to β-lactam antibiotics. Febrile reactions have not been associated with acetaminophen, and famotidine is rarely a cause of fever without other symptoms of an allergic reaction. Although diuretics such as hydrochlorothiazide can cause fever, M.M. was taking this medication before admission without any ill effects, making this drug an unlikely culprit.

Case 32-3, Question 3: How should M.M.'s drug fever be treated? Can M.M. receive cephalosporins in the future?

Because M.M. has responded clinically, her antibiotics should be discontinued and her fever curve, WBC count, heart rate, and respiratory status followed up. An oral antibiotic from another drug class (eg, a fluoroquinolone) should be started to complete a 7- to 10-day antibiotic course of therapy. Acetaminophen and other antipyretics should be avoided unless M.M. becomes uncomfortable from the fever because they can mask the response to the discontinuation of her antibiotics.

As with any hypersensitivity reaction, rechallenge with the offending drug can cause a similar, or sometimes greater, response.

In M.M.'s case, reexposure to ceftriaxone (or another β-lactam antibiotic) or a macrolide might cause a febrile reaction. It is unclear, however, how large the risk of reexposure truly is. Although drug fever sometimes precedes more serious hypersensitivity reactions, evidence suggests that there may be little risk of reexposure. Should M.M. require ceftriaxone (or another β-lactam or macrolide antibiotic) in the future, it would be prudent to administer the drug in a setting where M.M. can be monitored, at least initially, to ensure prompt treatment if an immediate hypersensitivity reaction develops.

Hypersensitivity Vasculitis

CASE 32-4

Question 1: M.G., a 26-year-old female with cystic fibrosis, is admitted for treatment of pneumonia. Sputum cultures obtained before admission reveal *Alcaligenes xylosoxidans* sensitive only to minocycline and chloramphenicol. M.G. is initiated on appropriate doses of these two antibiotics for a 2-week course. On day 8 of therapy, M.G. begins to develop a rash on her legs. Physical examination reveals palpable purpura and a maculopapular rash on both lower extremities. Laboratory data reveal an elevated ESR and leukocytosis.

What is the likely cause of M.G.'s rash and laboratory abnormalities?

M.G.'s presentation is suggestive of a diagnosis of hypersensitivity vasculitis.

Hypersensitivity vasculitis, also called cutaneous leukocytoclastic angiitis, is characterized by inflammation of the small blood vessel walls. These reactions occur when immune complex deposition within the small veins and arterioles activates complement, causing the release of chemotactic factors. These factors attract polymorphonuclear cells that cause vessel damage.[79–82]

Drug-Induced Vasculitis

Approximately 10% of cases of cutaneous vasculitis are believed to be drug related.[81] Approximately 100 drugs have been identified as causing vasculitis, including β-lactams, fluoroquinolones, NSAIDs, antiepileptics, and tumor necrosis factor blockers.[80–83] Interested readers are referred to more in-depth reviews.[82–84] The diagnosis of hypersensitivity vasculitis is based on five clinical criteria (**Table 32-7**), three of which must be present.[84] M.G. meets three of the five criteria, including age older than 16 years, palpable purpura, and a maculopapular rash. In addition, minocycline, a medication that she was taking at the onset of the rash, has been associated with serum sickness and vasculitic-type reactions. Onset of symptoms typically occurs 7 to 10 days after initiation of drug therapy but can occur sooner on reexposure. Purpuric papules and macular eruptions, the most commonly observed findings, are usually symmetric and occur on the extremities (**Table 32-8**).[79] Hypersensitivity vasculitis can involve multiple organ systems. Renal damage, ranging from microscopic hematuria to nephrotic syndrome and acute renal failure, is common in patients with disseminated disease.[84] An enlarged liver with elevated enzymes is indicative of hepatocellular involvement. Although the lungs and ears can be involved as well, clinical manifestations are usually mild.[79] Arthralgia is also commonly observed. Laboratory examinations usually show nonspecific abnormalities of inflammation such as an elevated ESR and leukocytosis. In patients with cystic fibrosis experiencing acute pneumonia, these laboratory abnormalities could already be present and, therefore, will not be helpful in establishing the diagnosis of hypersensitivity vasculitis in M.G.

Table 32-7
Criteria for the Classification of Hypersensitivity Vasculitis

Development of symptoms after age 16
Medication at disease onset that may have been a precipitating factor
Slightly elevated purpuric (hemorrhagic) rash over one or more areas of the skin that does not blanch with pressure and is not related to thrombocytopenia
Maculopapular rash over one or more areas of the skin

Biopsy showing granulocytes around an arteriole or venule

The diagnosis of hypersensitivity vasculitis can be made if a patient exhibits at least three of these criteria.

Source: Adapted from Calabrese LH, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. *Arthritis Rheum*. 1990;33(8):1108–1113. Copyright © 1990 American College of Rheumatology. Reprinted by permission of John Wiley & Sons, Inc.

Table 32-8
Hypersensitivity Reactions to Drugs: Clinical Manifestations of Drug-Induced Vasculitis

▪ Palpable purpura and maculopapular rash occurring symmetrically predominantly on the lower extremities
▪ Multiple organ systems may be involved:
▪ *Renal:* microscopic hematuria to nephrotic syndrome and acute renal failure
▪ *Liver:* enlarged liver, elevated enzymes
▪ *Joints:* arthritis
▪ *Gastrointestinal:* abdominal pain
▪ Laboratory data usually show nonspecific abnormalities of inflammation: elevated erythrocyte sedimentation rate and leukocytosis. Peripheral eosinophilia may be present and serum complement concentrations can be low. Histologic findings on biopsy reveal small blood vessels with leukocytoclastic or necrotizing vasculitis
▪ Onset typically 7–21 days after initiation of therapy

Source: Valeyrie-Allanore L, Sassolas B, Roujeau JC. Drug-induced skin, nail and hair disorders. *Drug Saf*. 2007;30:1011–1030.

CASE 32-4, QUESTION 2: What additional workup could be performed to confirm the diagnosis of drug-induced vasculitis in M.G.?

In addition to the previous workup, other laboratory and diagnostic procedures might demonstrate peripheral eosinophilia and low serum complement concentrations. A biopsy, which typically reveals

granulocytes in the wall of a venule or arteriole and eosinophils at any location, would provide more definitive information.

Case 32-4, Question 3: How should M.G.'s hypersensitivity vasculitis be treated?

The first step is to discontinue the minocycline therapy. Drug-induced vasculitic reactions typically resolve on their own without additional interventions. If the reaction is severe, corticosteroids can be used.

Autoimmune Drug Reactions

CASE 32-5

Question 1: R.F., a 24-year-old White male medical student, has been treated for 5 months with isoniazid because of a positive skin test result for tuberculosis. He now is in the clinic presenting with new-onset myalgias and arthralgias. Laboratory values obtained the morning of the visit are within normal limits except for a positive ANA titer and an elevated ESR.

What is the likely cause of R.F.'s symptoms and laboratory abnormalities?

Some drugs can induce an autoimmune process characterized by the presence of autoantibodies and, in some instances, clinical features of an autoimmune disorder. A drug-induced syndrome resembling SLE is usually characterized by myalgias, arthralgias, positive ANA titer results, and an elevated ESR (see Chapter 33, Systemic Lupus Erythematosus). All of these characteristics are manifested by R.F.

The first case of drug-induced lupus erythematosus (DILE) was recognized >60 years ago and was associated with sulfadiazine.[85] Subsequently, >80 drugs have been associated with DILE including isoniazid, chlorpromazine, quinidine, methyldopa, and minocycline; however, hydralazine and procainamide are the drugs most frequently associated with this syndrome.[86–88] As with idiopathic SLE, DILE can be separated into systemic, subacute cutaneous, and

chronic cutaneous lupus. An exact incidence of DILE is difficult to ascertain because of changing patterns of drug use; however, it is estimated that 10% of SLE cases are drug induced, with 15,000 to 30,000 cases in the United States annually.[81]

Case 32-5, Question 2: How can the diagnosis of drug-induced lupus be differentiated from SLE in R.F.?

In contrast to idiopathic SLE, DILE is less likely to affect females and Black patients.[87] On average, patients with DILE are twice as old as those with idiopathic SLE at the time of diagnosis. Individuals with a slow acetylator phenotype have a greater tendency to exhibit DILE; ANA after exposure to lupus-inducing drugs also appears more rapidly.[89] In general, DILE is a milder disease than is idiopathic SLE. Many patients with DILE, however, could fulfill the diagnostic criteria for SLE according to the American Rheumatism Association.[89–91] Arthralgias or myalgias accompanied by a positive ANA test result can be the only clinical features for some patients with drug-induced lupus. Symptoms usually appear abruptly after several months to years of continuous therapy with the offending drug. Common symptoms include fever, malaise, arthralgias, myalgias, pleurisy, and slight weight loss. Mild splenomegaly and lymphadenopathy have been reported occasionally. The skin is affected in about 25% of cases, manifesting as photosensitivity on light-exposed surfaces. The classic butterfly malar rash, discoid lesions, oral mucosal ulcers, Raynaud phenomenon, and alopecia are unusual features in DILE in contrast to idiopathic SLE. In addition, the central nervous system and kidneys rarely are affected.[92] Laboratory abnormalities commonly include anemia and an elevated ESR. The evidence supporting a diagnosis of drug-induced lupus in R.F. includes White male predominance, abrupt onset and relatively mild symptomatology, and lack of the classic butterfly malar rash. More definitive tests include determining whether antibodies to single-stranded (indicative of drug-induced lupus) or double-stranded DNA (indicative of SLE) are present.

Case 32-5, Question 3: Should ANA have been monitored in an effort to detect drug-induced lupus at an earlier stage in this patient?

No. Although all patients with symptomatic drug-induced lupus test positive for ANA (which consists predominantly of single-stranded DNA and antihistone antibodies),[92] many patients taking lupus-inducing drugs become ANA positive without going on to experience lupus. In patients treated with procainamide, about 50% to 75% are positive for ANA after 12 months and 90% after 2 years or more of continuous therapy; only 10% to 20% of those patients actually experience lupus symptoms.[92–94] Similarly, up to 44% of patients are ANA positive after 3 years of hydralazine therapy, but DILE occurs in only 6.7% of patients after 3 years of treatment.[92] It is not necessary to discontinue therapy in asymptomatic patients with positive ANA because most of them will never exhibit clinical symptoms.[87]

Case 32-5, Question 4: How should R.F.'s drug-induced lupus be treated?

Musculoskeletal symptoms can be treated with aspirin or an NSAID. More severe symptoms from pleuropulmonary or pericardial involvement may require the use of corticosteroids. Clinical features of DILE usually subside and disappear in days to weeks with discontinuation of the offending drug. Occasionally, these symptoms linger or recur over a course of several months before eventually disappearing. Serologic tests tend to resolve more slowly: ANA may persist for a year or longer.[87,95] Drug-induced lupus does not predispose patients to the subsequent development of idiopathic SLE.[96] In most instances, lupus-inducing drugs do not increase the risk of exacerbation of idiopathic SLE[97]; however, long-term treatment with isoniazid may worsen preexisting SLE.[98] Because R.F. has not yet completed his 6- to 9-month course of isoniazid therapy, an alternative agent should be prescribed for R.F. with appropriate monitoring (see Chapter 68, Tuberculosis).

ORGAN-SPECIFIC REACTIONS

The drug allergies in this chapter have been grouped into categories of generalized reactions, organ-specific reactions, and non–IgE mediated reactions. The generalized reactions have been described first, the organ-specific hypersensitivity drug reactions affecting the blood, liver, lung, kidney, and skin are described next, and non–IgE reactions follow.

Blood: Immune Cytopenias

Drug-induced immune cytopenias (eg, granulocytopenia, thrombocytopenia, and hemolytic anemia) result from type II–mediated allergic reactions (Table 32-1). A drug or drug metabolite binds to the surface of blood elements such as granulocytes, platelets, and red blood cells. IgG or IgM antibodies are formed and are directed against the drug or drug metabolite bound to the cell (ie, hapten–cell reaction).[31] Typical symptoms associated with immune thrombocytopenia include chills, fever, petechiae, and mucous membrane bleeding. Granulocytopenia generally manifests with chills, fever, arthralgias, and a precipitous drop in the leukocyte count. Symptoms of hemolytic anemia can be subacute or acute and can be sufficiently severe to cause renal failure. The Coombs test is useful in identifying antibodies bound to red cells or circulating immune complexes directed against red cells. Antibiotics are the most commonly implicated class of drugs causing either neutropenia or hemolytic anemia.

Liver

Hypersensitivity reactions involving the liver can be classified as cholestatic or cytotoxic. Jaundice is usually the first sign of a cholestatic reaction, in addition to pruritus, pale stools, and dark urine. Cholestatic reactions usually are reversible on discontinuation

of the offending agent. Cytotoxic reactions can involve hepatocellular necrosis or steatosis and can result in irreversible damage if not recognized early.

Lung

Pulmonary manifestations of drug hypersensitivity include asthma and infiltrative reactions. Asthma typically occurs as part of a generalized systemic reaction. Most reactions to drugs that involve asthma alone represent a pharmacologic side effect rather than a true allergic reaction.

Infiltrative reactions typically develop 2 to 10 days after exposure and manifest with cough, dyspnea, fever, chills, and malaise.[30] Infiltrative reactions vary in presentation from eosinophilic pneumonitis to acute pulmonary edema.

Kidney

The most common hypersensitivity reaction involving the kidney is interstitial nephritis. Typical findings include fever, rash, and eosinophilia. Methicillin is the drug most commonly associated with interstitial nephritis, although penicillins, sulfonamides, and cimetidine also have been implicated in renal hypersensitivity reactions.[31] (See Chapter 29, Acute Kidney Injury, for hypersensitivity reactions to specific drugs that adversely affect the kidney.)

Skin

Adverse reactions involving the skin are the most common clinical manifestation of drug allergy. Although several different types of cutaneous reactions are possible, most drug-induced skin eruptions can be classified as erythematous, morbilliform, or maculopapular in appearance.[31] In a surveillance study of drug-induced skin reactions, amoxicillin was the most common cause, followed by trimethoprim–

sulfamethoxazole and ampicillin. Overall, allergic skin reactions were identified in 2% of hospitalized patients.[18]

Treatment of skin reactions includes discontinuation of the offending drug and general supportive care (see Chapter 39, Dermatotherapy and Drug-Induced Skin Disorders).

NON-IGE REACTIONS

CASE 32-6

QUESTION 1: C.C., a 37-year-old male with no known allergies, is hospitalized for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia associated with an infected central line. His medical history is significant for short bowel syndrome requiring parenteral nutrition and one previous episode of MRSA line infection successfully treated with vancomycin. Similar to his last admission, vancomycin 750 mg IV for 60 minutes every 12 hours is begun. A trough level taken after the fifth dose, however, is 8 mg/L and the vancomycin dose is doubled to 1500 mg IV every 12 hours, to be administered at the same rate. Fifteen minutes after the new dose of vancomycin is begun, C.C. experienced hypotension (100/70 mm Hg), tachycardia (85 beats/minute), generalized pruritus, and facial flushing. C.C. is diagnosed as having a non–IgE mediated hypersensitivity reaction to vancomycin.

What subjective and objective data in C.C. are important in differentiating vancomycin non-IgE reaction from a true allergic reaction?

Non–IgE mediated reactions (also called nonallergic hypersensitivity reactions) are drug reactions that exhibit clinical signs and symptoms of an allergic response but are not immunologically mediated.[99] They can manifest as relatively benign symptoms or as severe, life-threatening events indistinguishable from anaphylaxis (**Table 32-9**).[99] The latter response is described as an anaphylactoid reaction because it resembles true anaphylaxis, but it does not involve IgE antibody formation.[31,99] The risk of such potentially severe reactions needs to be considered when prescribing agents known to be associated with anaphylactoid reactions. For example, the prophylactic use of antibiotics such as

ciprofloxacin to prevent meningococcal infections during an outbreak was associated with a relatively high rate (1:1000) of serious anaphylactoid reactions.[100] This would be of potentially greater importance in the setting of a mass prophylaxis program to combat exposure to anthrax. Unlike true allergic reactions, which require an induction period during which a patient becomes sensitized to an antigen, non–IgE mediated hypersensitivity reactions can occur on the first exposure to a drug. The development of non-IgE reactions can be dose related, manifesting when large doses of the drug are administered, when the dose is increased, or when the rate of IV administration is increased.[30]

Table 32-9
Hypersensitivity Reactions to Drugs: Acute Non-IgE Mediated Reactions

Frequency	Highly variable, depending on the agent involved. For example, up to 30% of patients taking aspirin exhibit a cutaneous non-IgE response. On the other hand, non–IgE mediated reactions to other agents, such as phytonadione and thiamine, are rare.
Clinical manifestations	Range from benign reactions (eg, pruritus and flushing) to a life-threatening clinical syndrome indistinguishable from anaphylaxis. Commonly require a higher drug dose to elicit the response than a true IgE-mediated reaction. May arise less quickly (>15 minutes after exposure) than a true allergic reaction.
Diagnostic workup	Skin test results and identification of specific antibodies are negative.
Treatment	Non–IgE mediated reactions are treated the same as true allergic reactions (ie, according to the clinical presentations of the patient). Thus, some reactions simply may require removal of the suspect agent, whereas some reactions may require aggressive therapy (eg, epinephrine, antihistamines, and corticosteroids).
Prognosis	As with true allergic reactions, patients who have experienced a non-IgE mediated drug reaction may have a similar reaction to reexposure. The severity of response may lessen, however, with repeated administration. Furthermore, for some drugs, the frequency and severity of the reaction also

	may be influenced by the dose or rate of intravenous administration. Pretreatment regimens to reduce the frequency and the severity of responses have been developed for some drugs well known to cause non–IgE mediated reactions (eg, radiocontrast media).

IgE, immunoglobulin E.

Sources: Pichler WJ, Adam J, Daubner B, Gentinetta T, Keller M, Yerly D. Drug hypersensitivity reactions: pathomechanism and clinical symptoms. *Med Clin North Am*. 2010;94:645–664; Schnyder B. Approach to the patient with drug allergy. *Immunol Allergy Clin North Am*. 2009;29:405–418; Sanchez-Borges M. NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). *Med Clin North Am*. 2010;94:853–864.

C.C. has experienced a common non–IgE mediated hypersensitivity reaction to vancomycin, usually referred to as the *red man syndrome* or *red neck syndrome*, which primarily occurs when large doses of vancomycin are administered rapidly. Differentiating between a true allergic response (IgE mediated) and a non–IgE mediated response can be difficult because the signs and symptoms can be indistinguishable. For example, each of the symptoms experienced by C.C. (flushing, tachycardia, pruritus, and hypotension) is caused by histamine release and can occur during an anaphylactic episode (see Case 32-2, Question 2). To conclusively determine the cause of the reaction would require immunologic testing for antibodies to the suspect drug or agent, which is not always possible or practical. In this case, C.C. had uneventfully received vancomycin previously and has tolerated five doses during this hospitalization; therefore, it is unlikely that the reaction is immunologically mediated (ie, a true allergic reaction). Furthermore, the reaction occurred after an increase in his vancomycin dose, which further supports the diagnosis of non–IgE mediated reaction.

CASE 32-6, QUESTION 2: Why did vancomycin cause a non-IgE hypersensitivity reaction in C.C.?

Non-IgE reactions from vancomycin occur because of a drug-induced histamine release that occurs through an as-yet-unknown pathway. Direct drug-induced release of histamine does not involve complement activation or IgE antibody formation. Several other drugs (eg, deferoxamine, opiates, pentamidine, phytonadione protamine, radiocontrast media) are known to directly stimulate histamine release.[17,99]

Some drugs (eg, radiocontrast media and protamine) cause non–IgE mediated reactions via both complement activation and direct-histamine release mechanisms. Furthermore, some drugs (eg, vancomycin, quaternary ammonium muscle relaxants, and ciprofloxacin) can cause both true allergic reactions (IgE mediated) and non–IgE mediated reactions.[8]

Case 32-6, Question 3: How should C.C.'s non-IgE reaction be treated? Does treatment of non–IgE mediated reactions differ from that of true allergic reactions?

The first step in treating C.C.'s reaction is to eliminate the underlying cause. Thus, his vancomycin infusion should be held until the reaction resolves. Because the reaction is histamine mediated, administration of an antihistamine such as diphenhydramine 50 mg IV is warranted. Observation of his BP and heart rate is mandatory. IV fluids should be administered if his BP continues to fall or fails to stabilize. Patients with allergic reactions should be treated based on their clinical signs and symptoms, regardless of the mechanism behind the reaction. Thus, for all intents and purposes, non–IgE mediated reactions are treated in the same manner as true allergic reactions.

Case 32-6, Question 4: Can C.C. continue to receive vancomycin? How can future reactions be prevented?

The patient should be diagnosed with red man syndrome, a non–IgE mediated hypersensitivity reaction. It is not necessary to

discontinue vancomycin therapy in C.C. This reaction can be prevented by administering smaller doses of the drug more frequently (eg, 1000 mg every 8 hours rather than 1500 mg every 12 hours) or infusing the dose for a longer interval, typically 2 hours. Alternatively, pretreatment with an antihistamine 1 hour before vancomycin administration is effective. In addition, tachyphylaxis to vancomycin-induced red man syndrome is independent of pretreatment with antihistamine and is another characteristic that differentiates a non–IgE mediated hypsersentivity reaction from a true allergic reaction. Pretreatment regimens to prevent non–IgE mediated hypersensitvity reactions to various other drugs (eg, radiocontrast media) are also well described and can be effective.

CASE 32-6, QUESTION 5: What other drugs are commonly associated with non–IgE mediated hypersensitivity reactions?

Many other agents have been associated with non–IgE mediated reactions.[8] Some of the agents more commonly associated with non-IgE reactions are described next.

Aspirin/Nonsteroidal Anti-inflammatory Drugs

After penicillins, aspirin is the drug most commonly reported as causing “allergic” reactions. Reactions to aspirin can be divided into three broad categories: respiratory reactions, cutaneous manifestations, and anaphylaxis. None of these reactions has been consistently associated with IgE and are thus non-IgE mediated reactions.[26,101]

RESPIRATORY

The prevalence of bronchospasm with rhinoconjunctivitis is 0% to 28% in children with aspirin sensitivity. In adult asthmatics, the prevalence of aspirin sensitivity ranges from 5% to 20%. The prevalence of aspirin sensitivity during aspirin challenge in adult asthmatics with a history of aspirin-induced respiratory reaction

ranges from 66% to 97%.[102] Symptoms usually occur within 30 minutes to 3 hours of ingestion. The triad seen in many sensitive patients is aspirin sensitivity, nasal polyps, and asthma. All potent inhibitors of cyclo-oxygenase (COX) can cause respiratory symptoms in patients with aspirin sensitivity. Thus, patients who react to aspirin should be considered sensitive to NSAIDs, and vice versa. Weak COX inhibitors, such as acetaminophen, choline magnesium salicylate, salicylamide, salsalate, and sodium salicylate, are generally well tolerated in patients with aspirin sensitivity.[101]

CUTANEOUS

The prevalence of cutaneous reactions to aspirin depends on the type of reaction and the population studied. For example, urticaria/angioedema occurs in 0.5% of children, 3.8% of the general adult population, and in 21% to 30% of patients with a history of chronic urticaria. Disease activity at the time of aspirin challenge plays an important role in those with a history of chronic urticaria. In one study, 70% of patients whose urticaria was active at the time of challenge reacted to aspirin, compared with only 6.6% of patients whose urticaria was not active at the time of challenge. Furthermore, aspirin or NSAIDs may aggravate preexisting urticaria.[101–103] Other dermatologic reactions to aspirin occur with less frequency; for example, eczema, purpura, and erythema multiforme occur in 2.4%, 1.5%, and 1% of the population, respectively.

ANAPHYLAXIS

The true prevalence of aspirin-induced or NSAID-induced anaphylaxis is unknown, but it may range from 0.07% of the general population to 10% of patients with anaphylactic symptoms. Although IgE is not consistently associated with aspirin or NSAID-related reactions (including anaphylaxis), aspirin-induced or NSAID-induced anaphylaxis shares three characteristics with immune-mediated anaphylaxis that point to IgE as a cause. First, the reaction occurs after two or more exposures to the offending agent, suggesting that preformed IgE antibodies are responsible. Second, patients do not

have underlying nasal polyposis, asthma, or urticaria. Third, the patient who reacts to aspirin or a single NSAID can tolerate a chemically unrelated NSAID, suggesting that a drug-specific IgE antibody has been formed.[101,104]

The NSAIDs that selectively inhibit COX-2 while sparing COX-1 include celecoxib, rofecoxib, and valdecoxib, among others. Celecoxib is the only COX-2 inhibitor currently marketed in the United States. Selective inhibition of COX-2 provides anti-inflammatory effects while minimizing the renal effects, GI toxicity, and antiplatelet effects seen with inhibition of COX-1. Aspirin and older NSAIDs are nonselective inhibitors of cyclo-oxygenase, inhibiting both COX-1 and COX-2. Anaphylactoid or hypersensitivity reactions have been reported with celecoxib, and it appears that the rate of hypersensitivity is comparable to that of traditional NSAIDs.[104] Notably, celecoxib prescribing information states that, as with any NSAID, use is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Several reports, however, describe successful administration of celecoxib and other COX-2 selective agents to patients with aspirin-sensitive asthma or a history of hypersensitivity reactions to traditional NSAIDs, and evidence suggests that inhibition of COX-1 rather than COX-2 is key to initiating these events.[105–108] Nevertheless, COX-2 selective agents can still elicit allergic responses by other means (eg, IgE-mediated hypersensitivity). Thus, appropriate precautions and monitoring should be followed when initiating therapy in any patient with a history of allergic reactions to aspirin or other NSAIDs.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

CASE 32-7

Question 1: K.J., a 48-year-old female, seeks care at an urgent care center. She presents with impaired speech but is able to swallow; she has red and

swollen lips and tongue, and puffy eyes. Her medical history includes hypertension, atrial fibrillation, and a new diagnosis of hypercholesterolemia (plasma cholesterol, 290 mg/dL). Although her BP had been well controlled on hydrochlorothiazide, her diuretic was discontinued about 3 weeks ago because of its effect on cholesterol, and enalapril 5 mg daily was started. K.J. also takes a multivitamin (one tablet each day) and warfarin (5 mg daily). Her physical examination shows BP, 130/87 mm Hg; heart rate, 70 beats/minute; lungs clear to auscultation and percussion; respirations, 12 breaths/minute; and skin without rash or urticaria. Her condition is attributed to angioedema induced by enalapril.

What is angioedema, and what evidence supports this diagnosis? What is the mechanism behind angioedema?

Angioedema refers to a localized, transient swelling of the deep skin layers or the upper respiratory or GI mucosa. Angioedema commonly manifests as localized erythematous edema, involving the tongue, lips, eyelids, and mucous membranes of the mouth, nose, and throat. However, in rare cases, it can occur in the lower GI tract. Angioedema can be caused by a variety of mechanisms involving complement, histamine, substance P, and bradykinin that can be hereditary, immunologically acquired, or pharmacologic. Angiotensin-converting enzyme (ACE) inhibitors are the most common pharmacologic cause and have been associated with this adverse effect in about 0.1% to 0.7% of individuals treated with this drug class and account for up to 60% of cases of angioedema that present to emergency departments.[109] The reaction is not dose related and occurs with all ACE inhibitors. ACE inhibition causes accumulation of excess bradykinin leading to capillary leakage. Bradykinin receptor B2 is a G protein–coupled receptor found in blood vessels and encoded by the *BDKRB2* gene in humans.[110]

K.J. presents with classic symptoms of angioedema and does not have symptoms of a true anaphylactic reaction, further strengthening the diagnosis of drug-induced angioedema. Symptoms of angioedema usually occur within the first week of starting therapy, although they can occur at any time, even years later. Thus, although angioedema developed 3 weeks after K.J. began enalapril, the temporal relationship is reasonable.

Case 32-7, Question 2: How should K.J. be treated? Would an angiotensin receptor blocker (ARB) be an appropriate substitute for her ACE inhibitor?

Although angioedema can be life-threatening, symptoms are usually mild and resolve within hours to days of stopping the offending drug. The most common life-threatening complication of angioedema is airway obstructions. More severe reactions affecting the upper airway must be treated emergently with appropriate measures to maintain airway patency. A small clinical trial of ACE-induced angioedema comparing treatment with corticosteroid and antihistamine (prednisolone 500 mg IV and clemastine 2 mg IV) to treatment with icatibant (30 mg subcutaneous injection) found that the time to initial relief and complete symptom resolution were significantly shorter with icatibant.[110] Additional trials are currently evaluating icatibant and hopefully will help define which patients will be most likely to benefit from this drug.

K.J. does not need to be hospitalized because her respirations are not compromised and she is not experiencing swallowing difficulty; however, she should be kept under observation at the urgent care center to ensure that her angioedema does not worsen. She can be treated with icatibant 30 mg subcutaneously or she can be observed and later sent home with instructions to seek emergent help if her breathing or swallowing becomes difficult. She should be instructed to discontinue her enalapril, follow up with her primary physician as soon as possible, and to request her community pharmacist to record this adverse reaction to enalapril into her drug profile at the pharmacy. Because angioedema occurs with all ACE inhibitors, K.J. must avoid all drugs in this class.

Angioedema with ARBs has also been reported,[111,112] although with less frequency than with ACE inhibitors. Many of the cases of ARB-induced angioedema involved patients with a history of ACE inhibitor–induced angioedema, but this is not consistently the case. Similar to the ACE inhibitors, angioedema to ARBs can occur at any time during treatment. In K.J.'s case, it would be best to avoid ARBs and ACE inhibitors. Instead, other antihypertensive agents that have

little effect on cholesterol (eg, calcium channel blockers) should be used.

Several other drugs have been associated with angioedema including aspirin, NSAIDs, antibiotics, radiocontrast media, and dipeptidyl peptidase (DPP)-4 inhibitors (eg, sitagliptin and saxagliptin).[109] The causes of angioedema with these drugs are less well understood but often occur after having ACE inhibitor–induced angioedema. These drugs should be used with caution if K.J. needs them in the future.

Case 32-7, Question 3: Are there other non-IgE reactions that occur with ACE inhibitors and ARBs?

Besides angioedema, cough is a non-IgE reaction caused by ACE inhibitors. It may occur in up to 39% of patients after 1 week to 6 months of therapy. Interestingly, it is more common in nonsmokers than in smokers; the incidence does not increase in patients with chronic airway disease or asthma. Cough is more common in females than in males, is not dose related, and, as with angioedema, occurs with all ACE inhibitors.[101,109,113] Several mechanisms appear to be responsible, including inhibition of the breakdown of bradykinin in the lung and increases in local mediators of inflammation such as prostaglandins and substance P. Although many approaches to the management of ACE-induced cough have been proposed,[113] angiotensin II receptor blocking agents are the most promising alternative. Cough can occur with an ARB, but the frequency appears to be no more than that of placebo. Furthermore, most direct comparative trials between ARBs and ACE inhibitors demonstrate that the frequency of cough with ARBs is much lower than that with ACE inhibitors.[113]

Radiocontrast Media

Radiocontrast media are widely used diagnostic agents, exceeding 75 million administrations annually.[114] Adverse reactions to

radiocontrast media can be divided into immediate reactions (occurring within 1 hour of administration and include nausea, flushing, BP changes, bronchospasm, urticaria, angioedema, cardiac arrhythmias, convulsions, angina, and symptoms indistinguishable from true anaphylaxis) and nonimmediate reactions (occurring 1 hour to 10 days after administration and include pruritus, maculopapular drug eruption, Stevens–Johnson syndrome, toxic epidermal necrolysis, and vasculitis). The cause of radiocontrast media reactions remains unknown, although histamine release, complement activation, and direct toxic effects on end organs might all play a role. Many of the adverse effects to radiocontrast media have historically been classified as non–IgE mediated reactions because the evidence did not support IgE mediation of these reactions. Recently, however, skin tests and laboratory evidence suggest an immunologic mechanism for radiocontrast media reactions.[114] The overall incidence of reaction to radiocontrast media is 0.7% to 13%, depending on the type of agent selected and whether the patient was pretreated before administration.[115] Conventional, ionic, high-osmolality contrast media produce reactions in 4% to 13% of recipients, whereas nonionic, low-osmolality agents produce fewer reactions (0.7%–3.1%). The mortality rate from radiocontrast media is 1 to 2 cases per 100,000 procedures and is the same for ionic and nonionic agents.[116]

Female sex, a history of asthma, and a history of reaction to contrast media are risk factors for reactions to radiocontrast media. Of these, a history of reaction is the most important; 21% to 60% of patients with a history of reaction to radiocontrast media will have a reaction on reexposure.[114] Several pretreatment regimens have been developed to minimize such occurrences. For example, 32 mg of oral methylprednisolone given 12 hours and 2 hours before a procedure involving a high-osmolality contrast medium can reduce the reaction rate by up to 45%.[115] Another pretreatment regimen uses oral prednisone 50 mg taken 13 hours, 7 hours, and 1 hour before the procedure, plus diphenhydramine 50 mg orally or IM 1 hour before the examination.[117] This latter regimen lowers the occurrence of non–IgE mediated reactions to high-osmolality

contrast media, even in high-risk patients (ie, those with a history of severe anaphylactoid reactions). Note that a “seafood allergy” is not a risk factor for a reaction to radiocontrast media. Patients with food allergies do not require special pretreatment before procedures involving these agents.[116,118]

Narcotic Analgesics

Some opiates stimulate histamine release and, thereby, cause hypotension, tachycardia, facial flushing, increased sweating, or pruritus. However, severe reactions are uncommon. In many cases, the opiate can be continued with the administration of an antihistamine to treat the symptoms. If the reaction is significant, a nonnarcotic alternative analgesic may be considered, or an opiate that does not cause histamine release can be substituted. Morphine and meperidine cause the greatest histamine release in both in vitro and in vivo studies. Codeine, hydromorphone, oxycodone, and butorphanol stimulate histamine release less commonly; and levorphanol, fentanyl, sufentanil, methadone, and oxymorphone have little to no effect on histamine levels. One of the more frequent reactions to epidurally or intrathecally administered opiates is pruritus, which does not appear to be mediated by histamine because narcotics that do not release histamine (eg, fentanyl and sufentanil) still cause pruritus after spinal administration. Furthermore, pruritus tends to develop several hours after the opiate has been administered, when serum levels of histamine are insignificant. The cause of pruritus from spinal opiates remains unclear. The reaction can be managed with antihistamines and low-dose naloxone or nalbuphine while continuing with the spinal narcotic.[99]

Iron-Dextran Injection

Parenteral iron is used in the treatment of iron deficiency when oral iron preparations cannot be used or are ineffective. This is most

commonly seen in patients with anemia of chronic renal failure, particularly those treated with epoetin alfa or darbepoetin and undergoing hemodialysis (Chapter 28, Chronic Kidney Disease). Iron preparations are associated with a wide spectrum of adverse events (eg, chest pain, hypotension, hypertension, abdominal pain, nausea, vomiting, weakness, syncope, backache, arthralgias, myalgias, and hypersensitivity reactions). Hypersensitivity reactions can manifest as urticaria, sweating, dyspnea, rash, fever, and as anaphylactoid reactions, which can be fatal. Consistent with a nonimmunologic mechanism, hypersensitivity reactions to iron are not dose related and can occur with the first drug exposure.[119]

Iron preparations differ in regard to the salt or carbohydrate carrier used, molecular weight, and rate of hypersensitivity reactions. The first commonly used iron preparations were iron dextran, available as a high-molecular-weight ferric oxyhydroxide and dextran solution (Dexferrum®) and later as a low-molecular-weight ferric hydroxide and dextran solution (INFeD). Adverse events occur more often with iron dextran preparations compared to non-dextran preparations and are highest with high-molecular-weight iron dextran. Data reported to the FDA MedWatch program between 2001 and 2003 were used to determine the odds of adverse events between iron dextran products and two non-dextran products: sodium ferric gluconate and iron sucrose (also known as iron saccharate). Relative to the INFeD brand of iron dextran, patients receiving sodium ferric gluconate or iron sucrose were half as likely to experience an allergic reaction or any adverse reaction. An equal risk existed of experiencing an allergic reaction, or any adverse reaction, between sodium ferric gluconate and iron sucrose. Although sodium ferric gluconate and iron sucrose were safer than was iron dextran, at least one death and five life-threatening reactions were reported with each of the four agents studied.[120] Ferumoxytol, an agent approved in 2009, was designed with a modified dextrose shell to reduce hypersensitivity reactions. In a comparison trial, there was a comparable safety profile but it did include one anaphylactoid reaction, although no deaths compared to iron sucrose.[121] Since approval, postmarketing FDA surveillance has demonstrated several reports of life-

threatening and serious anaphylactoid reactions, including six deaths in a 10-month reporting period.[122] The prescribing information has been updated to include a black box warning for fatal and serious hypersensitivity reactions.[123] The newest iron product is ferric carboxymaltose complex, which releases iron from a carbohydrate polymer. Hypersensitivity reactions are expected to be lower because it does not contain a dextran or modified dextran component. In comparison to iron sucrose, no significant difference was found in the rate of hypersensitivity reactions or anaphylactoid reactions.[124,125] Although FDA approval was initially delayed because of a potential safety imbalance in the risk of death, subsequent pooled analysis has not validated the early findings, and the product was approved with only a warning for hypersensitivity reactions.[126,127]

All patients receiving iron dextran should receive a test dose to assess tolerance; the other iron preparations do not require a test dose per their prescribing information. It appears that patients tolerant toward iron dextran have little risk of experiencing a serious hypersensitivity or anaphylactoid reaction to sodium ferric gluconate or iron sucrose injection and can safely be given one of these products without a prior test dose. Similarly, patients who have never received any parenteral iron product can be administered sodium ferric gluconate or iron sucrose for injection without a prior test dose. Although studies support the safety of both sodium ferric gluconate and iron sucrose for injection in patients with sensitivity to iron dextran, such patients may be at increased risk for an anaphylactoid reaction or other serious hypersensitivity response, and test dosing in this population may be reasonable. Because of the risks associated with any of the parenteral iron products, close monitoring of the patient for at least 30 minutes after drug administration is necessary and the availability of resuscitative medication and personnel trained to evaluate and address anaphylaxis is prudent.

PREVENTION AND MANAGEMENT OF ALLERGIC REACTIONS

CASE 32-8

QUESTION 1: A.M., a 40-year-old female, is hospitalized with a diagnosis of community-acquired pneumonia. Her medical history is noncontributory except for an uneventful course of ampicillin 6 months before admission for an ear infection. A.M. is empirically treated with cefuroxime 0.75 g IV every 8 hours. On day 2 of therapy, she develops a raised pruritic maculopapular rash on her back, abdomen, and upper extremities. Antacid, docusate sodium, albuterol by metered-dose inhaler, and multivitamins were initiated on the same day as the cefuroxime.

How should A.M.'s allergic reaction be managed? How might her allergic reaction have been prevented?

When examining methods to prevent allergic reactions, three possibilities exist: (a) the patient has unknowingly been sensitized to a drug and experiences an allergic reaction on receiving the same or a similar drug again; (b) the patient has a history of an allergic reaction to a medication and mistakenly receives the same or a similar medication a second time and again develops an allergic reaction; and (c) the patient has a history of an allergic reaction to a medication and intentionally receives the same or similar medication again. As in the first situation, A.M.'s allergic reaction was unpredictable and, therefore, could not be prevented. To prevent future allergic reactions (ie, the second situation), however, A.M.'s reaction should be well-documented in the medical chart and pharmacy records. In addition, all patients should undergo a thorough drug history on hospitalization. Careful attention should be paid to differentiating drug intolerance (eg, stomach upset) from true allergic reactions, and any allergic reactions elicited during an interview should be documented appropriately. Adequate communication of allergic reactions is the single most important method of preventing their occurrence.

As described earlier, the first step in managing an allergic reaction is to determine its cause. Given A.M.'s history of exposure to ampicillin, the timing of the reaction, and the low frequency of allergic reactions to her other medications, cefuroxime is the most likely candidate. Second, a decision regarding whether to stop the suspect drug should be made. This decision must be based on the severity of the reaction, the condition being treated, and the availability of suitable alternatives. When possible, an equally effective alternative drug should be substituted for the suspect agent, preferably one that is immunologically distinct to avoid cross-sensitivity (see Case 32-1, Question 4, for a discussion of cross-reactivity).[128] If a suitable alternative exists, the offending agent should be stopped and the reaction treated symptomatically if necessary. In the case of A.M., another antimicrobial (eg, azithromycin, clarithromycin, trimethoprim–sulfamethoxazole) could be substituted for cefuroxime (Chapter 67, Respiratory Tract Infections) and her symptoms treated with an oral or a parenteral antihistamine, as well as a low-potency topical corticosteroid if necessary.

Some cases are described by the third situation: a patient develops an allergic reaction (or has a well-documented history of drug allergy), and it is inappropriate or not possible to change to an alternative drug. If the sensitivity reaction is severe or life-threatening, desensitization should be considered (Case 32-9, Questions 1 and 2); premedication to prevent or minimize anaphylaxis is not effective.[33] If the reaction is minor (eg, pruritus, rash, or GI symptoms), premedication or management of the reaction with antiallergy medications (eg, antihistamines) might be sufficient to allow completion of therapy. It is rare in such cases for the reaction to progress to more serious allergic symptoms such as anaphylaxis[128]; however, suppression of allergic symptoms should be undertaken cautiously because many immunologic reactions are not IgE mediated and may progress to serious reactions, despite treatment. In general, allergy suppression should be reserved for the prevention of mild reactions that are known or strongly suspected to be IgE mediated.[8,128]

Desensitization

β-LACTAMS

CASE 32-9

QUESTION 1: K.A. is a 24-year-old primigravida in her eighth week of pregnancy with a history of angioedema secondary to penicillin. Her initial pregnancy screening revealed a positive Venereal Disease Research Laboratory reaction and a fluorescent treponemal antibody absorption titer of 1:64. K.A. denies a history of genital lesions, currently does not exhibit clinical signs or symptoms of syphilis, and denies previous treatment for syphilis. Based on the serologic evidence and her history, a diagnosis of early latent syphilis is made. Current treatment guidelines indicate that penicillin is the drug of choice for K.A.

How can a possible reaction to penicillin be prevented in K.A.? Is premedication an alternative to preventing a reaction?

There are situations where a drug is medically necessary in a patient with a known or suspected allergy to the drug, alternative therapy is not available, and diagnostic testing does not exist. In such cases, there are two options: induction of tolerance (also called desensitization) or a graded challenge. Desensitization is the process of administering gradually increasing doses of a drug in an effort to modify a patient's response to the drug so that it can then be safely administered.[116] This process has been used successfully to manage both immune-mediated and non–immune-mediated reactions. A graded challenge (also called incremental test dosing) is the process of careful administration of subtherapeutic doses of drug to determine whether a patient is truly allergic. Although similar sounding, there are distinct differences between the two processes.[116] For example, unlike induction of tolerance, a graded challenge does not alter a patient's response to the drug. The initial drug doses used for inducing tolerance are suballergenic—as low as 1/10,000th of the final dose and the process can take several hours involving multiple doses, each slightly larger than the preceding dose. Starting doses for a graded challenge may be 1/100th of the final dose. The process generally involves fewer steps (as few as two) and can be typically accomplished more rapidly. If the graded

challenge is completed and a therapeutic course of drug tolerated, a graded challenge is not required before future courses of the drug. Tolerance induction, on the other hand, is only maintained as long as the patient receives the suspect drug; any interruption of therapy will require the desensitization procedure to be repeated (see Case 32-9, Question 4).

The choice of drug desensitization or using a graded challenge depends on the likelihood of the patient having a true allergic reaction. A graded challenge may be appropriate in patients with a distant or an unclear history of drug allergy; when the reaction seems minor or for which diagnostic testing is unavailable; or in cases where cross-reactivity is expected to be low. For example, a patient with a maculopapular rash to ceftriaxone may undergo a graded challenge to imipenem–cilastatin to assess tolerance. On the other hand, a patient with a well-described, severe IgE-mediated reaction to a drug may be better suited for tolerance induction. Importantly, graded challenge or tolerance induction should not be used in patients with a history of a severe non–IgE-mediated reaction such as hepatitis, hemolytic anemia, Stevens–Johnson syndrome, toxic epidermal necrolysis, or DRESS syndrome because of the risk of provoking a potentially life-threatening reaction.[116] Because K.A.'s reaction to penicillin may be potentially severe, premedication is not an option and desensitization to penicillin should be started. (See Chapter 72, Sexually Transmitted Diseases, for alternative therapy.)

Case 32-9, Question 2: How should K.A. be desensitized? Why should she be skin tested before desensitization?

If possible, before tolerance induction is begun, K.A. should be skin tested (see Case 32-1, Questions 3 and 4) to confirm her penicillin allergy.[8,40,128] Patients who have a positive history of penicillin allergy, but whose skin test results are negative, can receive full therapeutic doses without desensitization with little risk of developing an allergic reaction. One author, for example, reported

only one case of acute anaphylaxis in a patient whose skin test result was negative and was given full therapeutic doses of penicillin in >1500 skin tests; similar results have been reported by other investigators.[40,128] If skin testing cannot be performed or if K.A.'s skin test result is positive, desensitization should be initiated. Acute oral desensitization to penicillin and other β-lactam antibiotics is well established.[129]

The oral route for β-lactam desensitization is preferred to the parenteral route because (a) exposure by the oral route is less likely to cause a systemic allergic reaction than is parenteral exposure; (b) fatal anaphylaxis from oral β-lactam drug therapy is rare; (c) preformed polymers and conjugates of penicillin major and minor determinants to *Penicillium* proteins are not well absorbed after oral administration; (d) blood levels rise gradually, favoring univalent haptenation; and (e) fatal or life-endangering reactions have not occurred using current methods. In addition, oral desensitization can be accomplished over several hours.[8] If oral desensitization is not possible (eg, if oral absorption is questionable), parenteral desensitization can be instituted. Although the subcutaneous and IM routes have been used, the IV route is quicker and allows better control over the rate and concentration of drug administered, and any untoward reaction can be detected promptly and treated rapidly.[8,130] However, oral and parenteral desensitization methods have not been compared formally. Patients should not be premedicated before desensitization, because this may prevent detection of minor allergic responses that may precede more serious reactions. In addition, only experienced personnel should undertake desensitization in an appropriate setting where emergency resuscitative equipment is readily available because severe reactions can develop.[128] Thus, K.A. should undergo oral desensitization if her skin test result is positive or if skin testing cannot be performed.

Case 32-9, Question 3: Is K.A. at risk for an allergic reaction during tolerance induction? If tolerance induction is successful, is she at risk for a reaction during full-dose penicillin therapy?

Acute β-lactam desensitization, regardless of the route or protocol chosen, is not without risk. Approximately 5% of patients experience mild cutaneous reactions during desensitization, although one study reported reactions in 20% of patients during oral desensitization.[8,131] If a reaction occurs during the desensitization procedure itself, the reaction may be treated and desensitization continued using lower doses, increased intervals between doses, or both, after the reaction has abated. Severe, fatal reactions during desensitization are rare.[130]

Uneventful β-lactam desensitization, however, does not guarantee that patients will be without reaction during full-dose therapy. Approximately 25% to 30% of patients experience a mild reaction during therapy, and 5% experience more severe reactions, including drug-induced serum sickness, hemolytic anemia, or urticaria.[8] Reaction rates are no different in severely ill or pregnant patients compared with stable or nonpregnant patients, although those with cystic fibrosis may be more difficult to desensitize because of their high frequency of allergic reactions.[131,132] Despite the occurrence of reactions, full-dose therapy is possible for most tolerance induction procedures, but suppression of the reaction (eg, by diphenhydramine) may be required.[130] Tolerance induction is also dose dependent because allergic symptoms can appear after a substantial increase in the dose after tolerance has been achieved.[8]

Case 32-9, Question 4: If K.A. requires penicillin at a later date, will she need to undergo desensitization again? What is chronic desensitization?

The desensitized state, once achieved, will persist for ~48 hours after the last full dose of antibiotic; after this time, drug sensitivity will return.[8,130] Thus, if K.A. requires future courses of penicillin, she will need to undergo desensitization once again. In some cases, those requiring long-term antibiotic therapy (eg, for endocarditis), those who may require β-lactams at a future date (eg, those with cystic fibrosis), or those who have occupational exposure to β-lactams, maintenance of the desensitized state can be considered. Chronic

twice-daily dosing of oral penicillin has safely resulted in “chronic desensitization.” Similar to acute desensitization, once therapy is interrupted, the allergic state returns.[8,31]

OTHER DRUGS

Case 32-9, Question 5: Have patients allergic to drugs besides β-lactams been desensitized successfully?

Although most experience with desensitization is with penicillin and other β-lactams, desensitization also has been accomplished with numerous other drugs, including allopurinol, vancomycin, antineoplastic agents, aspirin, and monoclonal antibodies.[74,131,132] Interestingly, not all of these cases represent IgE-mediated hypersensitivity reactions. For example, reactions to trimethoprim–sulfamethoxazole commonly occur in patients infected with HIV and may not be IgE mediated. Yet, given its role in treating and preventing *Pneumocystis jiroveci* pneumonia, successful desensitization to trimethoprim–sulfamethoxazole is commonly used.[132]

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Antonov D, Kazandjieva J, Etugov D, Gospodinov D, Tsankov N. Drug-induced lupus erythematosus. *Clin Dermatol*. 2004;22:157–166. (77)

Baile GR. Comparison of rates of reported adverse events associated with IV iron products in the United States. *Am J Health Syst Pharm*. 2012;69: 310–320.

(114)
Barbarino JM, Kroetz DL, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for human leukocyte antigen B. *Pharmacogenet Genomics*. 2015;25:205–221. (17)
Bas M, Greve J, Stelter K, et al. A randomized trial of icatibant in ACE-inhibitor–induced angioedema. *N Engl J Med*. 2015;372:418–425. (102)
Dedeoglu F. Drug-induced autoimmunity. *Curr Opin Rheumatol*. 2009;21: 547–551. (73)
Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69:420–437. (1)
Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother*. 2009;43:304–315. (46)
Kemp SF, Lockey RF, Simons FE. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy*. 2008;63:1061–1070. (57)
Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update [published correction appears in *J Allergy Clin Immunol*. 2010;126:1104]. *J Allergy Clin Immunol*. 2010;126:477–480.e1–e42. (49)
Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010;30:57–69. (68)
Sanchez-Borges M. NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). *Med Clin North Am*. 2010;94:853–864. (95)
Schnyder B. Approach to the patient with drug allergy. *Immunol Allergy Clin North Am*. 2009;29:405–418. (66)
Solensky R. Drug desensitization. *Immunol Allergy Clin North Am*. 2004;24: 425–443. (122)

COMPLETE REFERENCES CHAPTER 32 DRUG HYPERSENSITIVITY REACTIONS

1. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69:420–437.
2. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348:1556–1564.
3. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol*. 2005;5:309–316.
4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*.

1998;279:1200–1205.
5. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients [published correction appears in *JAMA*. 1992;267:1922]. *JAMA*. 1991;266:2847–2851.
6. Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol*. 2017;140:321–333. doi:10.1016/j.jaci.2017.06.012
7. de Weck A. Pharmacologic and immunochemical mechanisms of drug hypersensitivity. *Immunol Allergy Clin North Am*. 1991;11:461–474.
8. Celik G. Drug allergy. In: Adkinson NF, ed. *Middleton's Allergy: Principles and Practice*. 7th ed. Mosby; 2008:1205.
9. Silver J, Garcia-Neuer M, Lynch DM, Pasaoglu G, Sloane DE, Castells M. Endophenotyping oxaliplatin hypersensitivity: personalizing desensitization to the atypical platin. *J Allergy Clin Immunol Pract*. 2020;8:1668–1680.e2. doi:10.1016/j.jaip.2020.02.013
10. Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: phenotypes and endotypes. *J Allergy Clin Immunol*. 2018;142:159–170.e2. doi:10.1016/j.jaci.2018.02.018
11. Castells M. Drug hypersensitivity and anaphylaxis in cancer and chronic inflammatory diseases: the role of desensitizations. *Front Immunol.* 2017;8:1472. doi: 10.3389/fimmu.2017.01472.
12. Pichler WJ, Beeler A, Keller M, et al. Pharmacological interaction of drugs with immune receptors: the p-i concept. *Allergol Int*. 2006;55:17–25.
13. Gerber BO, Pichler WJ. Cellular mechanisms of T cell mediated drug hypersensitivity. *Curr Opin Immunol.* 2004;16:732–737.
14. Illing PT, Vivian JP, Dudek NL, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature*. 2012;486:554–558.
15. Wei CY, Chung WH, Huang HW, Chen YT, Hung SI. Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens–Johnson syndrome. *J Allergy Clin Immunol*. 2012;129:1562–1569.e5.
16. Pavlos R, Mallal S, Phillips E. HLA and pharmacogenetics of drug hypersensitivity. *Pharmacogenomics*. 2012;13:1285–1306.
17. Adkinson NF Jr. Risk factors for drug allergy. *J Allergy Clin Immunol*. 1984;74(4 Pt 2):567–572.
18. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA*. 1986;256:3358–3363.
19. Johnson-Reagan L, Bahna SL. Severe drug rashes in three siblings simultaneously. *Allergy*. 2003;58:445–447.
20. Man CB, Kwan P, Baum L, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia*.

2007;48(5):1015–1018.
21. Barbarino JM, Kroetz DL, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for human leukocyte antigen B. *Pharmacogenet Genomics*. 2015;25:205–221.
22. Ma MK, Woo MH, McLeod HL. Genetic basis of drug metabolism. *Am J Health Syst Pharm*. 2002;59:2061–2069.
23. Evans WE, McLeod HL. Pharmacogenomics—drug disposition, drug targets, and side effects. *N Engl J Med*. 2003;348:538–549.
24. Breathnach SM. Mechanisms of drug eruptions: part I. *Australas J Dermatol*. 1995;36:121–127.
25. Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. *Pharmacol Rev*. 2001;53:357–379.
26. Pirmohamed M. Genetic factors in the predisposition to drug-induced hypersensitivity reactions. *AAPS J*. 2006;8:E20–E26.
27. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B* 5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002;359:727–732.
28. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol [published correction appears in *Proc Natl Acad Sci U S A*. 2005;102:6237]. *Proc Natl Acad Sci U S A*. 2005;102:4134–4139.
29. Lucas A, Nolan D, Mallal S. HLA-B*5701 screening for susceptibility to abacavir hypersensitivity. *J Antimicrob Chemother*. 2007;59:591–593.
30. Chirac A, Demoly P. Drug allergy diagnosis. *Immunol Allergy Clin North Am*. 2014;34:461–471.
31. Anderson JA. Allergic reactions to drugs and biological agents. *JAMA*. 1992;268:2844–2857.
32. Scherer K, Bircher AJ. Danger signs in drug hypersensitivity. *Med Clin North Am*. 2010;94:681–689.
33. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004;113:832–836.
34. Kuruvilla M, Khan D. Anaphylaxis to drugs. *Immunol Allergy Clin North Am*. 2015;35:303–319.
35. McNeil BD. MRGPRX2 and adverse drug reactions. *Front Immunol*. 2021;12:676354. doi:10.3389/fimmu.2021.676354
36. Meth MJ, Sperber KE. Phenotypic diversity in delayed drug hypersensitivity: an immunologic explanation. *Mt Sinai J Med*. 2006;73:769–776.
37. Castells M, Khan DA, Phillips EJ. Penicillin allergy. *N Engl J Med*. 2019;381:2338–2351. doi:10.1056/NEJMra1807761
38. Shiohara T, Kano Y. A complex interaction between drug allergy and viral infection. *Clin Rev Allergy Immunol*. 2007;33:124–133.

39. PRE-PEN (benzylpenicilloyl polylysine injection solution). Package insert. ALK-Abello, Inc; 2010. Accessed July 20, 2017. https://penallergytest.com/wp-content/uploads/PRE-PEN-Package-Insert.pdf
40. Lin RY. A perspective on penicillin allergy. *Arch Intern Med*. 1992;152:930–937.
41. Kranke B, Aberer W. Skin testing for IgE-mediated drug allergy. *Immunol Allergy Clin North Am*. 2009;29:503–516.
42. Perencevich EN, Weller PF, Samore MH, Harris AD. Benefits of negative penicillin skin test results persist during subsequent hospital admissions. *Clin Infect Dis*. 2001;32:317–319.
43. Shepherd G. Allergy to β-lactam antibiotics. *Immunol Allergy Clin North Am*. 1991;11:611–634.
44. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. *J Allergy Clin Immunol*. 2015;135(3):745–752.e5. doi:10.1016/j.jaci.2014.07.062
45. Romano A, Torres MJ, Namour F, et al. Immediate hypersensitivity to cephalosporins. *Allergy*. 2002;57(*Suppl 72*):52–57.
46. Riezzo I, Bello S, Neri M, Turillazzi E, Fineschi V. Ceftriaxone intradermal test-related fatal anaphylactic shock: a medico-legal nightmare. *Allergy*. 2010;65:130–131.
47. Greenberger PA. 8. Drug allergy. *J Allergy Clin Immunol*. 2006;117(*2 Suppl Mini-Primer*):S464–S470.
48. Robinson JL, Hameed T, Carr S, et al. Practical aspects of choosing an antibiotic for patients with a reported allergy to an antibiotic. *Clin Infect Dis*. 2002;35:26–31.
49. Romano A, Mayorga C, Torres MJ, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. *J Allergy Clin Immunol*. 2000;106:1177–1183.
50. Blanca M, Mayorga C, Torres MJ, et al. Side-chain-specific reactions to betalactams: 14 years later. *Clin Exp Allergy*. 2002;32:192–197.
51. Romano A, Viola M, Guéant-Rodriguez RM, Gaeta F, Pettinato R, Guéant JL. Imipenem in patients with immediate hypersensitivity to penicillins. *N Engl J Med*. 2006;354:2835–2837.
52. Atanaskovic-Markovic M, Gaeta F, Medjo B, Viola M, Nestorovic´ B, Romano A. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. *Allergy*. 2008;63:237–240.
53. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother*. 2009;43:304–315.
54. Perez Pimiento A, Gómez Martínez M, Mínguez Mena A, Trampal González A, de Paz Arranz S, Rodríguez Mosquera M. Aztreonam and ceftazidime: evidence of in vivo cross allergenicity. *Allergy*. 1998;53:624–625.

55. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
56. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update [published correction appears in *J Allergy Clin Immunol*. 2010;126:1104]. *J Allergy Clin Immunol*. 2010;126:477–480.e1–e42.
57. Delage C, Irey NS. Anaphylactic deaths: a clinicopathologic study of 43 cases. *J Forensic Sci*. 1972;17:525–540.
58. Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. *Immunol Allergy Clin North Am*. 2018;38(3):483–495. doi:10.1016/j.iac.2018.04.003
59. Kishimoto TK, Viswanathan K, Ganguly T, et al. Contaminated heparin associated with adverse clinical events and activation of the contact system [published correction appears in *N Engl J Med.* 2010;362:1056]. *N Engl J Med*. 2008;358:2457–2467.
60. Liu H, Zhang Z, Linhardt RJ, et al. Lessons learned from the contamination of heparin. *Nat Prod Rep*. 2009;26:313–321.
61. Ben-Shoshan M, Clarke AE. Anaphylaxis: past, present and future. *Allergy*. 2011;66:1–14.
62. Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev*. 2008;2008(4):CD006312.
63. Sheikh A, ten Broek Vm, Brown SG, Simons FE. H1-antihistamines for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev*. 2007;2007(1):CD006160.
64. Choo KJ, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy*. 2010;65:1205–1211.
65. Kemp SF, Lockey RF, Simons FE. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy*. 2008;63:1061–1070.
66. Manivannan V, Hess EP, Bellamkonda VR, et al. A multifaceted intervention increases epinephrine use in adult emergency department anaphylaxis patients. *J Allergy Clin Immunol Pract*. 2014;2:294–299.e1.
67. Brown SG. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol*. 2005;5:359–364.
68. Evora PR, Simon MR. Role of nitric oxide production in anaphylaxis and its relevance for the treatment of anaphylactic hypotension with methylene blue. *Ann Allergy Asthma Immunol*. 2007;99:306–313.
69. Buhner D, Grant JA. Serum sickness. *Dermatol Clin*. 1985;3:107–117.

70. Lawley TJ, Bielory L, Gascon P, Yancey KB, Young NS, Frank MM. A study of human serum sickness. *J Invest Dermatol*. 1985;85(1 Suppl):129s–132s.
71. Erffmeyer JE. Serum sickness. *Ann Allergy*. 1986;56:105–109.
72. Lin RY. Serum sickness syndrome. *Am Fam Physician*. 1986;33:157–162.
73. Pichler WJ, Adam J, Daubner B, Gentinetta T, Keller M, Yerly D. Drug hypersensitivity reactions: pathomechanism and clinical symptoms. *Med Clin North Am*. 2010;94:645–664.
74. Schnyder B. Approach to the patient with drug allergy. *Immunol Allergy Clin North Am*. 2009;29:405–418.
75. Johnson DH, Cunha BA. Drug fever. *Infect Dis Clin North Am*. 1996;10:85–91.
76. Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010;30:57–69.
77. Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med*. 1987;106:728–733.
78. Cunha BA, Shea KW. Fever in the intensive care unit. *Infect Dis Clin North Am*. 1996;10:185–209.
79. Calabrese LH. Differential diagnosis of hypersensitivity vasculitis. *Cleve Clin J Med*. 1990;57:506–507.
80. Semble EL, Chmelewski WL, Pisko EJ. Vasculitis. A practical approach to management. *Postgrad Med*. 1991;90:161–170.
81. Dedeoglu F. Drug-induced autoimmunity. *Curr Opin Rheumatol*. 2009;21:547–551.
82. Wiik A. Drug-induced vasculitis. *Curr Opin Rheumatol*. 2008;20:35–39.
83. Bircher AJ, Scherer K. Delayed cutaneous manifestations of drug hypersensitivity. *Med Clin North Am*. 2010;94:711–725.
84. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. *Am J Dermatopathol*. 2005;27:504–528.
85. Antonov D, Kazandjieva J, Etugov D, Gospodinov D, Tsankov N. Drug-induced lupus erythematosus. *Clin Dermatol*. 2004;22:157–166.
86. Perry HM Jr, Tan EM, Carmody S, Sakamoto A. Relationship of acetyl transferase activity to antinuclear antibodies and toxic symptoms in hypertensive patients treated with hydralazine. *J Lab Clin Med*. 1970;76:114–125.
87. Skaer TL. Medication-induced systemic lupus erythematosus. *Clin Ther*. 1992;14:496–506.
88. Valeyrie-Allanore L, Sassolas B, Roujeau JC. Drug-induced skin, nail and hair disorders. *Drug Saf*. 2007;30:1011–1030.
89. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*.

1982;25:1271–1277.
90. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64:2677–2686.
91. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. *J Autoimmun*. 2014;48–49:10–13.
92. Cameron HA, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. *Br Med J (Clin Res Ed)*. 1984;289(6442):410–412.
93. Henningsen NC, Cederberg A, Hanson A, Johansson BW. Effects of long-term treatment with procaine amide. A prospective study with special regard to ANF and SLE in fast and slow acetylators. *Acta Med Scand*. 1975;198:475–482.
94. Kosowsky BD, Taylor J, Lown B, Ritchie RF. Long-term use of procaine amide following acute myocardial infarction. *Circulation*. 1973;47:1204–1210.
95. Blomgren SE, Condemi JJ, Bignall MC, Vaughan JH. Antinuclear antibody induced by procainamide. A prospective study. *N Engl J Med*. 1969;281:64–66.
96. Solinger AM. Drug-related lupus. Clinical and etiologic considerations. *Rheum Dis Clin North Am*. 1988;14:187–202.
97. Machold KP, Smolen JS. Interferon-gamma induced exacerbation of systemic lupus erythematosus. *J Rheumatol*. 1990;17:831–832.
98. Alarcon-Segovia D, Wakim KG, Worthington JW, Ward LE. Clinical and experimental studies on the hydralazine syndrome and its relationship to systemic lupus erythematosus. *Medicine (Baltimore)*. 1967;46:1–33.
99. VanArsdel P. Pseudoallergic drug reactions. Introduction and general review. *Immunol Allergy Clin North Am*. 1991;11:635–644.
100. Burke P, Burne SR. Allergy associated with ciprofloxacin. *BMJ*. 2000;320:679.
101. deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. *JAMA*. 1997;278:1895–1906.
102. Manning M, Stevenson DD. Pseudoallergic drug reactions. Aspirin, non-steroidal anti-inflammatory drugs, dyes, additives, and preservatives. *Immunol Allergy Clin North Am*. 1991;11:659–678.
103. Sanchez-Borges M. NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). *Med Clin North Am*. 2010;94:853–864.
104. Berkes EA. Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. *Clin Rev Allergy Immunol*. 2003;24:137–148.
105. Pacor ML, Di Lorenzo G, Biasi D, Barbagallo M, Corrocher R. Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or non-steroidal anti-inflammatory drugs. *Clin Exp Allergy*. 2002; 32:397–400.

106. Quiralte J, Sáenz de San Pedro B, Florido JJ. Safety of selective cyclooxygenase-2 inhibitor rofecoxib in patients with NSAID-induced cutaneous reactions. *Ann Allergy Asthma Immunol*. 2002;89:63–66.
107. Szczeklik A, Nizankowska E, Bochenek G, Nagraba K, Mejza F, Swierczynska M. Safety of a specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy*. 2001;31:219–225.
108. Woessner KM, Simon RA, Stevenson DD, et al. The safety of celecoxib in patients with aspirin-sensitive asthma. *Arthritis Rheum*. 2002;46:2201–2206.
109. Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P. Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. *Clin Exp Allergy*. 2010;40:50–61.
110. Bas M, Greve J, Stelter K, et al. A randomized trial of icatibant in ACE-inhibitor–induced angioedema. *N Engl J Med*. 2015;372:418–425.
111. Sica DA, Black HR. Angioedema in heart failure: occurrence with ACE inhibitors and safety of angiotensin receptor blocker therapy. *Congest Heart Fail*. 2002;8:334–345.
112. Kyrmizakis DE, Papadakis CE, Liolios AD, et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists. *Arch Otolaryngol Head Neck Surg*. 2004;130:1416–1419.
113. Pylypchuk GB. ACE inhibitor-versus angiotensin II blocker-induced cough and angioedema. *Ann Pharmacother*. 1998;32:1060–1066.
114. Brockow K. Immediate and delayed reactions to radiocontrast media: is there an allergic mechanism? *Immunol Allergy Clin North Am*. 2009;29:453–468.
115. Laser EC. Pseudoallergic drug reactions. Radiographic contrast media. *Immunol Allergy Clin North Am*. 1991;11:645.
116. Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S126–S137.
117. Greenberger PA, Patterson R, Radin RC. Two pretreatment regimens for high-risk patients receiving radiographic contrast media. *J Allergy Clin Immunol*. 1984;74(4 Pt 1):540–543.
118. Schabelman E, Witting M. The relationship of radiocontrast, iodine, and seafood allergies: a medical myth exposed. *J Emerg Med*. 2010;39:701–707.
119. Fishbane S, Ungureanu VD, Maesaka JK, Kaupke CJ, Lim V, Wish J. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis*. 1996;28:529–534.
120. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant*. 2006;21:378–382.
121. MacDougall IC, Strauss WE, McLaughlin J, Li Z, Dellanna F, Hertel J. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clin J Am Soc Nephrol*. 2014;9:705–712.

122. Baile GR. Comparison of rates of reported adverse events associated with IV iron products in the United States. *Am J Health Syst Pharm*. 2012;69:310–320.
123. FERAHEME (ferumoxytol injection). Package insert. AMAG Pharmaceuticals Inc; 2015. Accessed June 1, 2015. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=32b0e320-a739-11dc-a704-0002a5d5c51b
124. Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. *Nephrol Dial Transplant*. 2014;29(4):833–842.
125. Onken JE, Bregman DB, Harrington RA, et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Transfusion*. 2014;54(2):306–315.
126. INJECTAFER (ferric carboxymaltose injection). Package insert. American Regenet, Inc; 2013. Accessed June 1, 2015. https://daiichisankyo.us/prescribing-information-portlet/getDocument?product=IF&inline=true
127. Bregman DB, Goodnough LT. Experience with intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Ther Adv Hematol*. 2014;5(2):48–60.
128. Wedner HJ. Drug allergy prevention and treatment. *Immunol Allergy Clin North Am*. 1991;11:679–694.
129. Castells M. Rapid desensitization for hypersensitivity reactions to medications. *Immunol Allergy Clin North Am*. 2009;29:585–606.
130. Solensky R. Drug desensitization. *Immunol Allergy Clin North Am*. 2004;24:425–443.
131. Stark BJ, Earl HS, Gross GN, Lumry WR, Goodman EL, Sullivan TJ. Acute and chronic desensitization of penicillin-allergic patients using oral penicillin. *J Allergy Clin Immunol*. 1987;79:523–532.
132. Earl HS, Sullivan TJ. Acute desensitization of a patient with cystic fibrosis allergic to both beta-lactam and aminoglycoside antibiotics. *J Allergy Clin Immunol*. 1987;79:477–483.

33

Systemic Lupus Erythematosus

Jerika T. Lam, Ann M. Lynch, and Mary A. Gutierrez

CORE PRINCIPLES		CHAPTER CASES
1	Systemic lupus erythematosus (SLE) affects multiple organ systems with diagnoses based on clinical findings and objective criteria from the American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) guidelines.	**Case 33-1 (Questions 1–4)** **Case 33-2 (Question 1), Table 33-1, Figure 33-1**
2	Management of SLE is complex, and involves many specialists, including cardiologists and rheumatologists.	**Case 33-2 (Question 2)**

CORE PRINCIPLES		CHAPTER CASES
3	SLE treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimalarials, and immunosuppressants. The goals of SLE treatment should be considered when devising a treatment plan.	**Case 33-2 (Question 3)** **Case 33-3 (Questions 1–3, 5, 6), Table 33-3**
4	Pregnancy considerations should be applied when selecting drug treatments for female patients with SLE.	**Case 33-3 (Questions 7, 8)**
5	Hydroxychloroquine and cyclophosphamide could cause bothersome side effects. Monitoring parameters and management of hydroxychloroquine and cyclophosphamide side effects should be considered for patients with SLE.	**Case 33-3 (Questions 4, 9–11), Table 33-3**
6	Belimumab is the first U.S. Food and Drug Administration (FDA)-approved biologic treatment for SLE. The appropriate use and monitoring parameters should be considered to optimize its efficacy.	**Case 33-3 (Questions 12–17), Tables 33-2, 33-3**
7	There are several drug–drug interactions pertaining to the treatments for SLE. Concomitant use of hydroxychloroquine and antacids could have a potential adverse effect.	**Case 33-4 (Questions 1, 2), Table 33-4**

CORE PRINCIPLES		CHAPTER CASES
8	Pharmacists can play an important role in the education regarding SLE, management of side effects, and monitoring of drug–drug interactions.	**Case 33-3 (Questions 2, 3, 5–9, 13)** **Case 33-4 (Questions 2, 3), Tables 33-3–33-5**

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, inflammatory disease that affects multiple organ systems and primarily the connective tissue. Its presentation and disease progression are unpredictable and highly variable. This multiorgan disease is characterized by inflammation, autoantibody production, the deposition of complement-fixing immune complexes, and a clinical pattern alternating between disease flares and periods of remission.[1] In essence, the immune system attacks the body's own cells and tissue, resulting in a continuous inflammatory response and tissue and/or organ damage over time. Although SLE can eventually affect any organ such as the lungs and the nervous and cardiovascular systems, it mainly affects the skin, joints, and kidneys.[2] The 10-year survival rate is ~70% for patients with SLE.[3]

EPIDEMIOLOGY

SLE is more common among females than males (9:1), and generally occurs during childbearing age, with a peak age of onset between 15 and 45 years.[4,5] It is estimated that >16,000 new cases of SLE are reported annually in the United States, with an average prevalence of 1.5 million Americans. Approximately 5 million people are afflicted with SLE globally, and 90% are females.[6] Progression of

SLE is usually slow. It typically begins as a benign disease without signs or symptoms (preclinical phase) to disease with mild-to-moderate symptoms with exacerbations or flares, resulting in the involvement of additional organs and sustained damage (clinical phase). Over time the disease will progress, continually relapsing and remitting until eventually reaching severe potentially fatal disease (comorbidities phase).[7] Isolated skin and musculoskeletal involvement are associated with a milder course of disease and a higher survival rate over patients with renal and central nervous system (CNS) involvement, which indicate more severe and progressive disease conditions.

PATHOPHYSIOLOGY

The specific cause of SLE is unknown. Many genetic, ethnic, environmental, and hormonal factors are identified as potential causative risk factors. As part of the genetic component involved in the development of SLE, there is no clear Mendelian pattern of inheritance. Siblings of patients with SLE have a risk of disease of ~2%.[8] Identical twins have an ~10-fold higher risk of SLE than do dizygotic twins.[4] First-degree relatives of patients with SLE have a 20-fold increased risk of developing SLE when compared to the healthy population.[9,10] The genetic risk for the disease is more likely associated with multiple genes than with the deficiency of a single gene. Interestingly, genome-wide association studies have identified risk alleles shared between SLE and other autoimmune disorders such as rheumatoid arthritis, Graves disease, multiple sclerosis, type 1 diabetes, and psoriasis.[11] SLE is more likely to develop in females of color, at a rate two to three times higher than the rate for Caucasian females.[6] Furthermore, the symptoms are found to be more severe in African American, Asian, Native American, and Hispanic females.[4,12] However, individuals of all ages, genders, and ancestral backgrounds are susceptible to having the disease.

The association of environmental factors to SLE remains unclear. Some of the exposure-related factors that have been implicated for causing SLE include smoking and ultraviolet (UV) radiation.[13] The proposed hypothesis behind cigarette smoke is that it is associated with the indirect generation of anti-double-stranded DNA (anti-dsDNA) and related to immunoregulatory effects of tobacco exposure. Thus, in genetically predisposed individuals with a smoking-related decreased ability to clear apoptotic cells, the excess levels of intracellular antigens may lead to the production of autoantibodies such as anti-dsDNA.[14]

Ultraviolet Radiation

Exposure to sunlight may cause the occurrence of SLE, and could exacerbate preexisting symptoms. UV radiation has been implicated in cutaneous manifestations of SLE, such as macular, papular, or bullous lesions, and erythema.[15] Systemic disease is rarely induced by UV radiation. Possible mechanisms that may link the pathogenesis of UV radiation and SLE include circulating antibodies to the Ro/Sjögren syndrome type A (anti-Ro/SSA) and anti-La Sjögren syndrome type B (anti-La/SSB) antigen particles that result in an autoimmune response.[2,15] Nevertheless, both anti-Ro/SSA and anti-La/SSB are more commonly associated with Sjögren syndrome than with SLE.

Viral Infection

It has been considered for many years that viruses, particularly the Herpesvirus family and the Epstein–Barr virus (EBV) may trigger SLE via polyclonal immune activation, resulting in an activation of the autoimmune system.[16] EBV may reside in and interact with B cells, promoting interferon (IFN)-α production and contributing to the inflammatory process.

Female Hormones

The increased prevalence in the female gender proposes that hormones such as estrogen or progesterone may play a role in aggravating the disease. Both estrogen and progesterone levels are increased during pregnancy and at conception. These hormones can lead to an increase in mature, high-affinity autoreactive B cells, resulting in an autoimmune reaction.[17] Evidence that SLE worsens during pregnancy ironically does not contribute to this theory because levels of estrogen and progesterone are lower in second- and third-trimester pregnant patients with SLE compared to healthy pregnant individuals.[17] Interestingly, hormone replacement therapy is linked to worsening SLE symptoms in postmenopausal females.[18] The X chromosome may also independently contribute to the incidence of SLE, where the combination of two X chromosomes increases the severity of SLE over an X,Y combination.[19] The gene *CD40* is located on the X chromosome and has been known to contribute to the pathogenesis of the disease.[13]

Immunologic Abnormalities

SLE is a disease of an overall dysregulated, aberrant immune function, indicated by a large number of autoantibodies involved. Abnormalities of the immune system include immune complexes, T lymphocytes, cytokines, and antibodies.[13] Antigen receptor–mediated activation is changed in T and B cells for patients with SLE. B cells play a pivotal role in the disease. They produce autoantibodies, which amplify inflammation and mediate tissue damage. The autoantibodies are immunoglobulin (Ig)G mediated, and T lymphocytes help stimulate B cells to produce antibodies. Moreover, B cells process and present antigen and autoantigen to T cells and contribute to disease manifestation.[20] The innate immune system (ie, toll receptors, plasmacytoid dendritic cells, and IFN-α) and the adaptive immune network also contribute to the production of autoreactive B cells and autoantibodies.[21] Similarly, cellular debris from apoptosis further stimulate activation of the immune system. The decreased clearance of cellular debris may be related to low-

complement levels, such as C1q, C2, and C4, which normally function to help phagocytes and macrophages eliminate apoptotic material and self-reactive B cells. As a result, deposits of immune complexes can lead to organ damage, systemic inflammation, and pain.[5,13]

CLASSIFICATION CRITERIA

In 1971, the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology (ACR) developed a disease classification criteria system. Because there is no single test to diagnose SLE, the classification criteria have been used for the diagnosis of SLE. The original classification criteria system and definitions were revised in 1982, 1997, 2012, and, most recently, in 2019 (**Table 33-1**).[22–24] In 2019, the European League Against Rheumatism (EULAR) and the ACR together revised and validated the SLE classification criteria to improve its sensitivity and specificity. SLE classification comprises of one entry criterion followed by scoring of weighted additive criteria.

Table 33-1
American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) Revised Criteria for Classification of Systemic Lupus Erythematosus (SLE), 2019 Updates

Entry Criterion	■ Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended. ■ If absent, do NOT classify as SLE. ■ If present, apply additive criteria.		
Additive Criteria	■ Do not count a criterion if there is a more likely explanation than SLE. ■ Occurrence of a criterion on at least one occasion is sufficient. ■ SLE classification requires at least one clinical criterion and ≥10 points. ■ Criteria need not occur simultaneously. ■ Within each domain, only the highest weighted criterion is counted toward the total score.		
Clinical Domains		**Definition**	**Weight**
Constitutional			
	Fever	Temperature >100.94 °F (>38.3 °C)	2
Hematologic			
	Leukopenia	White blood cell count <4000/mm^3	2
	Thrombocytopenia	Platelet count <100,000/mm^3	4
	Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, and positive Coombs (direct antiglobulin) test	4
Neuropsychiatric			
	Delirium	Characterized by (1) change in consciousness or level of arousal with reduced ability to focus, (2) symptom development over hours to <2 days, (3) symptom fluctuation throughout the day, (4) either (4a) acute/subacute change in cognition (eg, memory deficit or disorientation), or (4b) change in behavior, mood, or affect (eg, restlessness, reversal of sleep/wake cycle)	2
	Psychosis	Characterized by (1) delusions and/or hallucinations without insight and (2) absence of delirium	3
	Seizure	Primary generalized seizure or partial/focal seizure	5
Mucocutaneous			
	Nonscarring alopecia	Nonscarring alopecia observed by a clinician	2
	Oral ulcers	Oral ulcers observed by a clinician[a]	2
	Subacute cutaneous *or* discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician: [a]Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted) *or* Discoid lupus erythematosus observed by a clinician: Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate; in the scalp, follicular keratin plugs may be seen; in long-standing lesions, mucin deposition may be noted).	4

	Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician[a] if skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted; perivascular neutrophilic infiltrate may be present early in the course).	6
Serosal	Pleural or pericardial effusion	Imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both	5
	Acute pericarditis	≥2 of (1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), (2) pericardial rub, (3) ECG with new widespread ST elevation or PR depression, (4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI)	6
Musculoskeletal			
	Joint involvement	*Either* (1) synovitis involving two or more joints characterized by swelling or effusion *or* (2) tenderness in two or more joints and at least 30 minutes of morning stiffness	6
Renal			
	Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to-creatinine ratio	4
	Renal biopsy Class II or V lupus nephritis	***Class II:*** Mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy ***Class V:*** Membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations	8
	Renal biopsy Class III or IV lupus nephritis	***Class III:*** Focal lupus nephritis: active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations ***Class IV:*** Diffuse lupus nephritis: active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation	10
Immunology Domains and Criteria			
Antiphospholipid Antibodies			
	Anti-cardiolipin antibodies *or* Anti-β2GP1 antibodies *or* Lupus anticoagulant	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or > the 99th percentile) or positive anti-β_2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant	2
Complement Proteins			
	Low C3 *or* low C4	C3 *or* C4 below the lower limit of normal	3
	Low C3 *and* low C4	Both C3 *and* C4 below their lower limits of normal	4
SLE-Specific Antibodies			
	Anti-dsDNA antibody *or* anti-Sm antibody	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls *or* anti-Sm antibodies	6
Total Score:			
Classify as SLE with a score of 10 or more if entry criterion is fulfilled.			

Anti-DNA, anti-deoxyribonucleic acid; anti-Sm, anti-Smith antibodies; IgG and IgM, immunoglobulins G and M.

[a]This may include physical examination or review of a photograph.

Sources: Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol*. 2019;71:1400–1412; Petri M, Orbai A-M, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64:2677–2686; Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:1725.

CLINICAL PRESENTATION

The clinical features of the disease are diverse and vary among patients. Signs and symptoms may be subtle early in the course of the disease; and the spectrum of mild-to-severe symptoms may fluctuate, with periods of remission, throughout the disease process.[25] Clinical patterns of the disease can be categorized as constitutional, musculoskeletal, and mucocutaneous.

Constitutional symptoms usually include fatigue, general malaise, fever, and weight loss. These may occur in the early stages of the disease. Fatigue is the most common and can be a debilitating symptom early on.[26,27] Musculoskeletal symptoms include arthritis, arthralgia, and myalgia. Early in the course of the disease, the symptoms may be confused with rheumatoid arthritis, especially with intermittent symmetric arthritic and joint pain. Arthritis associated with SLE is nonerosive and does not damage the joint even though it affects the joints of the hands, wrist, knees, and feet. Myopathy may also be present during periods of active disease, or secondary to treatment of hydroxychloroquine and corticosteroids.[28]

Mucocutaneous manifestations occur frequently in patients with SLE. The malar or butterfly rash across the face is one of the classic cutaneous signs; however, it may not be present in all patients with SLE. It is an erythematous skin rash distributing over the cheeks and

the bridge of the nose, but spares the nasolabial folds. It can persist for weeks and resolves without scarring. The malar rash should be differentiated from flushing, glucocorticoid-induced dermal atrophy, rosacea, and seborrheic, atopic, and contact dermatitis.[2] Other cutaneous signs may include alopecia, discoid lesions, photosensitivity reactions, periungual erythema, nail fold infarcts, and splinter hemorrhages.[29,30] In comparison, mucosal symptoms can include vasculitis and painful, recurrent ulcers in the mouth, nose, and genital cavity.[28] Raynaud phenomenon may also occur in patients with SLE. It is described as a vasospastic disorder of the extremities, commonly affecting the hands, and is characterized by color changes as a result of decreased temperature or intense stress.[18] It can also lead to avascular bone necrosis, which is a major cause of disability in patients with SLE.[2]

Additional clinical presentation of SLE may include the development of antiphospholipid antibodies (eg, lupus anti-β_2-glycoprotein, IgG and IgM anticardiolipin antibodies, and IgG and IgM anti-β_2- glycoprotein I) in the blood, and places patients with SLE at increased risk for developing blood clots.[31] Livedo reticularis is a common feature of antiphospholipid syndrome (APS), which is further discussed in the section Hematologic System. Common symptoms of SLE are described in **Figure 33-1**. Other major organ systems may also be affected by SLE, including the nervous, cardiovascular, pulmonary, gastrointestinal (GI), renal, and hematologic systems.

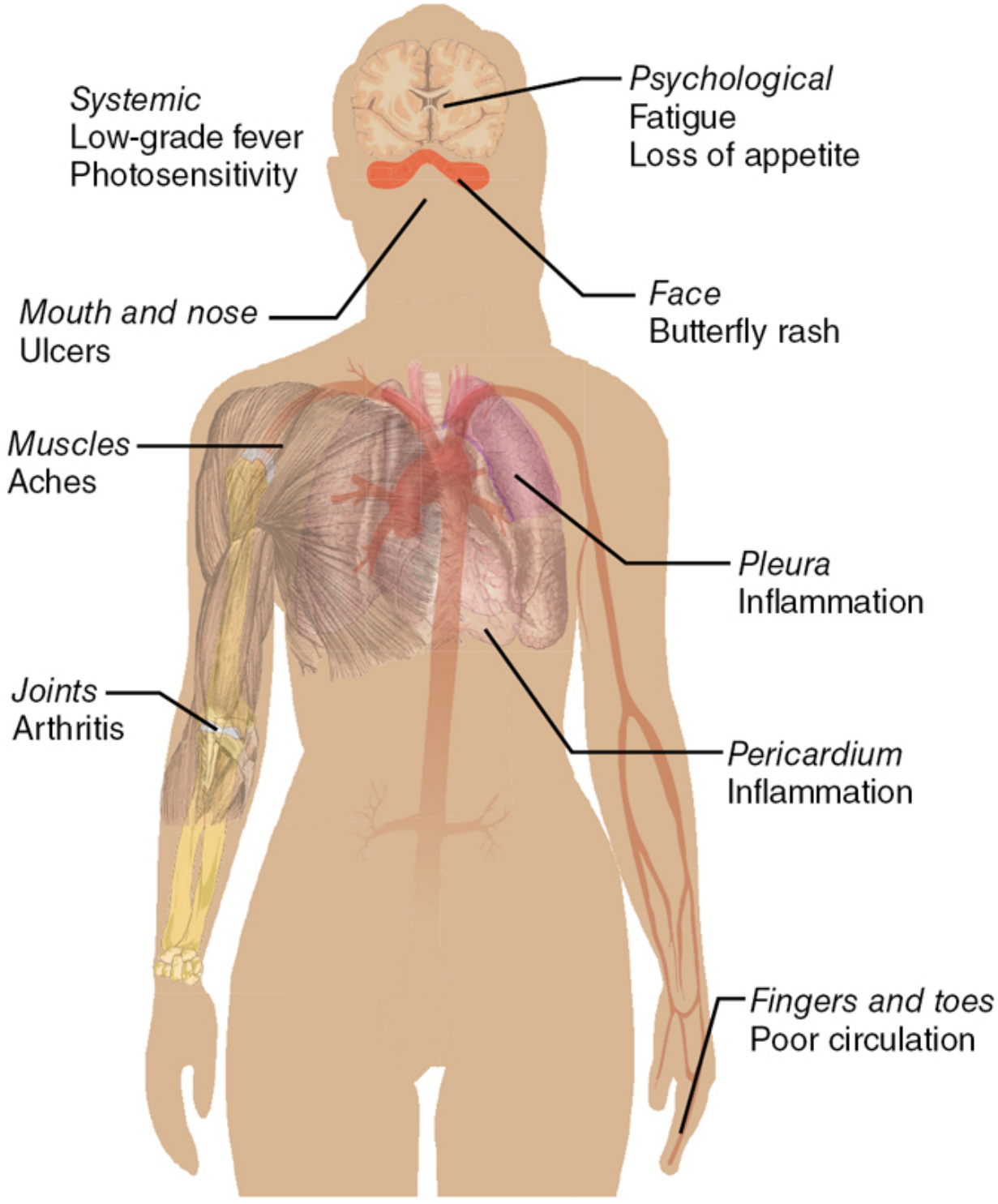


Figure 33-1 Common symptoms of systemic lupus erythematosus. (Modified from Häggström, Mikael/Wikipedia Commons/Public Domain.)

Nervous System

SLE affects both the CNS and peripheral nervous system. The CNS manifestations affect approximately two-thirds of patients with SLE.[31] Collectively, both have been described as neuropsychiatric syndromes. The pathology of the syndromes is not well understood. The syndromes may be ascribed to the autoimmune nature of SLE, where the immune antineuronal antibodies attack the neurons, causing neuronal damage and leading to cognitive dysfunction, or the production of antiphospholipid antibodies that damage blood vessels and may cause clots in the brain.[29] Neuropsychiatric manifestations are nonspecific and variable. They may occur in <40% of patients with SLE, whereas the remaining events represent complications of the disease, therapies and therapy-related side effects, infections, and metabolic abnormalities.[32] Patients with SLE can present with higher rates of anxiety and depression. Depression is more common in those experiencing changes in appearance and limitations from complications and medication-related side effects.[33] Other manifestations include migraine headaches, memory loss, and seizures. Less common symptoms may also occur, such as psychosis, confusion, peripheral neuropathy, mood disorders, autonomic dysfunction, movement disorders, Guillain–Barré syndrome, and cerebrovascular disease.[28] Diagnosis and laboratory tests for neuropsychiatric events related to SLE continue to be challenging, as well as the therapies used for them.[34]

Cardiovascular System

Patients with SLE are at increased risk for morbidity and mortality from cardiovascular disease, especially associated with atherosclerosis. Premature atherosclerosis is associated with longer lupus disease duration, more damage, and less aggressive immunosuppressive therapy.[35,36] They are at higher risk for myocardial infarction or stroke compared to the healthy population. In addition, pericarditis and pericardial effusion are the most common cardiac complications associated with SLE, occurring in

~45% of patients.[29–31,37] They range from mild-to-severe symptomatology. Patients may present with fever, dyspnea, tachycardia, and congestive heart failure. Other clinical features that may occur in >80% of patients with SLE include left ventricular dysfunction, segmental wall motion abnormalities, nonspecific ST-T wave changes, and decreased ejection fraction.[2] Valvular abnormalities can also be common and are linked to antiphospholipid antibodies. The most common abnormality is diffuse thickening of the mitral and aortic valves followed by the presence or absence of nonbacterial vegetations (Libman–Sacks), valvular regurgitation, and stenosis.[2] Modifiable risk factors, in addition to comorbid disease screening, include reducing long-term steroid use because it is linked to the development of hypertension, smoking cessation, reducing homocysteine levels with folate supplementation, and preventing thrombosis with aspirin or anticoagulation in patients with APS.[28] These will help reduce cardiovascular risk and control disease activity by reducing the inflammatory atherogenic effects.

CASE 33-1

QUESTION 1: T.C. is a 45-year-old Hispanic female with hypertension, hypercholesterolemia, and an 18-year history of SLE. For the first 10 years after the diagnosis of SLE, she had frequent SLE flares, and was treated with high doses of prednisone. As a result, she developed steroid-induced diabetes and osteoporosis. Although her SLE has been relatively stable over the past 2 years, she has not been feeling well for 1 month. T.C. denies symptoms consistent with her usual SLE flares, but she reports a sharp chest pain that worsens when lying down and improves when leaning forward, significant fatigue, and shortness of breath with minor activity. She feels better after resting, but has not returned to her previous energy level. She reports good adherence with her medications, which include the following:

Alendronate 70 mg weekly
Hydrochlorothiazide 25 mg every morning
Hydroxychloroquine 400 mg daily
Lisinopril 40 mg daily
Metformin 1000 mg twice daily
Simvastatin 40 mg daily
Acetaminophen 650 mg prn for pain

Findings from an examination of the patient are unremarkable, except for elevated blood pressure. Lupus anticoagulant antibodies are within normal limits.

What is the most likely cause of T.C.'s fatigue and positional chest pain?

Patients with long-standing SLE are at increased risk for cardiovascular disease. Given that T.C.'s SLE is stable, cardiovascular disease is the most likely cause of her current symptoms.

Case 33-1, Question 2: What tests would best confirm your suspicion?

Electrocardiograms (ECGs), exercise stress tests, and echocardiograms. Cardiac stress test is also considered the best way to determine the presence and extent of her cardiovascular disease, especially for symptomatic patients.

Case 33-1, Question 3: Along with a referral to a cardiologist, which of the following treatments would you recommend that T.C. initiate at this time?

Aspirin is recommended because her most likely diagnosis is cardiovascular disease. She has no evidence of active SLE, so aspirin would be the most appropriate treatment at this time to prevent risk of thrombosis. Premature atherosclerosis with cardiovascular events tends to manifest as a late complication for patients with SLE. Oral anticoagulants may be considered for T.C. if she has developed antiphospholipid antibodies and APS.

Case 33-1, Question 4: Late in the disease course of SLE, what is the most common cause of high mortality rates?

Early in the disease course, mortality is primarily from inflammation affecting organ systems. Over time, mortality tends to be mostly from coronary artery disease and complications of chronic steroid therapy and immunosuppression. SLE disease could elevate

the low-density lipoprotein (LDL) and reduce the high-density lipoprotein (HDL) levels in addition to treatment with systemic steroids that could worsen the cholesterol profile.

Pulmonary System

Pulmonary involvement occurs in 30% of patients with SLE.[31] Pleuritis or pleural inflammation is the most common pulmonary manifestation of SLE. It is associated with chest pain, cough, and dyspnea. Pleural effusions are typical findings and are usually linked with antinuclear antibody (ANA)-positive exudates with low complement.[38] Alveolar hemorrhage is a common occurrence in patients with SLE, particularly in those with high titers of anti-dsDNA antibodies and active extrapulmonary disease.[31] Another respiratory complication is identified as the “shrinking lung syndrome,” which can occur in 25% of patients with SLE.[2] It is characterized as progressive dyspnea (worse in the supine position) and weakness of the diaphragm and respiratory muscles. Acute lupus pneumonitis and pulmonary hypertension, although rare, could also develop as pulmonary complications.

Gastrointestinal System

Nonspecific GI symptoms include abdominal pain, nausea, vomiting, diarrhea, and stomach upset. These are reported in 25% to 40% of patients with SLE, which could be disease related or from medication side effects.[2] Other clinical manifestations include dyspepsia and peptic ulcers.

Renal System

Up to 70% of all patients with SLE will develop some form of renal complication, which is a poor prognostic indicator. Approximately 60% will have kidney involvement in the first 10 years of the disease.[18] Thirty-five percent of patients will develop nephrotic

syndrome or lupus nephritis (LN) by the time of SLE diagnosis.[39] It is a serious kidney complication, which increases the risk of renal failure, cardiovascular disease, and mortality.[40] LN is caused by inflammation and deposits of immune complexes consisting of anti-dsDNA in the glomeruli. It includes proteinuria (>0.5 g/24 hours) and/or hematuria, described as active urinary sediment (>5 red blood cells [RBCs] per high-power field, pyuria, or cell casts), in addition to a significant creatinine clearance reduction. For patients with an inactive sediment and >500 mg/day of proteinuria, monitoring is recommended with urinalysis every 3 to 6 months for 3 years. More frequent monitoring, such as every 3 months, is preferred for patients with anti-dsDNA antibodies and/or hypocomplementemia.[41]

Aside from performing a urinalysis, a renal biopsy is required in all patients with lupus with evidence of kidney involvement to determine the histologic subtype of LN and the extent of disease severity.[42,43] Pathology reports can elucidate the extent of inflammatory (reversible) and chronic (irreversible scarring) changes. LN can be an ongoing disease, with flares often requiring repeat biopsy and repeat treatment (refer to Chapter 28, Chronic Kidney Disease, for Lupus Nephritis, Case 28-4).

Hematologic System

Hematologic disorders can occur in patients with SLE. The most common hematologic manifestation is normochromic, normocytic anemia, which is often overlooked in young menstruating females. Iron deficiency may also develop. A common cause of anemia is suppressed erythropoiesis from chronic inflammation. Patients may have a positive Coombs test finding without apparent hemolysis.[43] Leukopenia and thrombocytopenia are also common manifestations that can develop as part of the disease process, or may be a side effect of the pharmacologic treatment for SLE. Oftentimes, leukopenia consists of lymphopenia, not granulocytopenia.[44] Patients with SLE may also develop a thrombotic disorder known as

antiphospholipid syndrome (APS). APS is characterized by the development of autoantibodies to phospholipids present in the serum. Antiphospholipid antibodies interfere with the coagulation system, particularly protein C and the function of endothelial cells.[13] APS features are described as venous or arterial thrombosis, miscarriages or spontaneous abortions, and thrombocytopenia from antiphospholipid antibodies.[28] The EULAR recommends low-dose aspirin in individuals with SLE and antiphospholipid antibodies as primary prevention of thrombosis and pregnancy loss.[7] Long-term use of oral anticoagulants is considered as secondary prevention of thrombosis in nonpregnant patients with SLE and thrombosis associated with APS. On the other hand, unfractionated or low-molecular-weight heparin and aspirin should be used in pregnant patients with SLE and APS.

Lymphadenopathy could be a common presentation in SLE, where it may occur in 15% to 26% in patients. Diffuse lymphadenopathy, however, is a very rare occurrence.[45,46] Lymph node biopsy may be considered to exclude alternative diagnoses.

DIAGNOSIS

Based on the 2019 EULAR/ACR updated criteria classification system, diagnosis of SLE is based on the presence of 1 or more of the entry criteria in conjunction with ≥1 additional clinical criterion and scoring of the weighted additive criteria equaling ≥10. Entry criterion should not be counted in the event there is a more likely explanation other than SLE. Occurrence of criterion on at least one occasion is sufficient to consider SLE as a diagnosis. Criteria do not require simultaneous occurrence. If multiple criteria within one domain are met, only the highest scoring criterion should be counted toward the total score. For instance, many patients with biopsy-proven LN do not meet the criteria. However, the classification can be made from a biopsy confirming LN and presence of ANA, or anti-dsDNA antibodies. Both anti-Smith (anti-Sm) and anti-dsDNA

antibodies are highly specific for SLE, but anti-Sm antibodies lack sensitivity.[1] Anti-dsDNA and anti-Sm antibodies are found in ~70% and 30% of patients with SLE, respectively.[47] Other markers, such as the lupus anticoagulant and IgG and IgM antibodies to anticardiolipin, are specific for APS. Their presence may increase the risk of thrombosis or miscarriages. When compared to the 2012 SLICC, the EULAR/ACR 2019 criteria have slightly lower sensitivity (96% vs 97%), but a much higher specificity (93.4% vs 84%) (**Table 33-1**).[18,22]

The diagnostic workup can be challenging because of the complexity of the disease and overlapping features of many other autoimmune diseases, such as polymyositis, rheumatoid arthritis, and scleroderma. The workup includes an assessment of the clinical presentation, physical examination, and diagnostic and laboratory tests. Approximately 80% of patients have skin involvement manifesting as photosensitivity, alopecia, malar and discoid rash (thick, red, scaly patches on the skin), and ulcers in the oral and nasal cavities or in the vagina, all of which are part of the ACR criteria.[22]

CASE 33-2

QUESTION 1: D.S., a 30-year-old, obese African American female, weighing 176.37 pounds (80 kg) and 60 inches (152.40 cm) tall, presents to the emergency department with chest pain. It is a sharp and substernal pain, but with a component that is diffuse and aggravated by deep aspiration. Two months ago, she presented to the emergency department with a 6-week history of fatigue, low-grade fevers, hair loss, joint pain, and oral ulcers. Her laboratory tests showed a positive ANA test result. Blood culture findings were negative for infection. The urinalysis study result was negative for blood, and the urine culture was negative for infection. A chest x-ray showed nonpulmonary infiltrates. Her symptoms improved after a 10-day tapering course of prednisone. Feeling better, D.S. decided not to follow up with her physician's appointment last week. Today, the medical resident's examination reveals an ill-appearing female, with a temperature of 100.5 °F (38.06 °C), oral ulcers, alopecia, and tachycardia with distant heart sounds.

What signs and symptoms exhibited by D.S. are consistent with SLE?

According to the "2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus," the diagnosis of SLE is satisfied when 1 entry criterion and at least 1 clinical criterion with a weighted score of at least 10 are met. The criteria contain one constitutional, three hematologic, three neuropsychiatric, four cutaneous, two serosal, one musculoskeletal, three renal, and three immunologic components (**Table 33-1**). D.S. meets criteria with the presence of a positive ANA test result, oral ulcers, presumed pericarditis, and presumed arthritis (joint pain). Furthermore, her clinical features are consistent with SLE including fatigue, alopecia, and low-grade fevers (infection ruled out).

CASE 33-2, QUESTION 2: After D.S. has started treatment and further laboratory tests are performed, what other specialists would you involve in her care at this time?

A rheumatologist and cardiologist because of D.S.'s pericarditis. The cardiologist could evaluate the patient's modifiable cardiovascular risk factors, such as hypertension, dyslipidemia, and obesity. Pericarditis with pericardial effusion is most commonly associated with cardiovascular involvement and SLE. Symptoms could include sharp chest pain and fluid around the heart, worsened with deep breathing and certain body positions. Endocarditis, myocarditis, and valvular disease are less common. Over time, other specialists including gastroenterologist, neurologist, pulmonologist, and nephrologist may be considered as part of D.S.'s multidisciplinary team.

PHARMACOLOGIC AND NONPHARMACOLOGIC TREATMENTS

The management approach for SLE will depend on the severity of the disease and organ involvement. A therapeutic plan is created

based on clinical guidelines for the management, treatment, and monitoring of SLE. It should include considerations for pharmacologic and nonpharmacologic approaches with clearly defined goals. Because there is currently no cure for SLE, the goals of therapy are to prevent flares, treat active symptoms of disease, minimize drug toxicity, and reduce risk of complications and organ damage. An effective and successful therapeutic plan is individualized based on the patient's needs, symptoms, lifestyle, and disease complications. Patients should be regularly monitored by their providers every 3 to 6 months.

Nonsteroidal Anti-inflammatory Drugs and Selective Cyclooxygenase-2 Inhibitor

Treatment options will differ depending on the level of severity of SLE. For mild disease, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitor, such as celecoxib, are used. Because of their ability to inhibit the release of prostaglandins and leukotrienes, NSAIDs and the COX-2 inhibitor possess anti-inflammatory, analgesic, and antipyretic properties. They are effective in reducing swelling, relieving muscle and joint pain, fever, and pleuritic chest pain.[27,48] Patients with antiphospholipid antibodies are at increased risk for thrombosis or atherosclerotic disease, and may benefit from low-dose aspirin for primary prevention or long-term anticoagulation therapy for secondary prevention.[7] Long-term use of NSAIDs is encumbered with GI, cardiovascular, and renal issues. Common GI side effects include dyspepsia, heartburn, and nausea. More serious GI symptoms such as stomach bleeding and mucosal lesions may occur. Cardiovascular side effects associated with NSAIDs may include hypertension and the risk of myocardial infarction. Fluid retention and acute tubular necrosis with kidney failure may also occur with long-term use, especially in elderly patients.

As a class, NSAIDs work in the same manner; however, not every agent has the same effect on every patient. When an NSAID is used,

it needs to be titrated to its maximal dose over 1 to 2 weeks. The agent should not be discontinued until the patient has been on the maximal dose for at least 2 weeks, which is the amount of time NSAIDs reach maximal efficacy.[28] Although all NSAIDs appear to work in the same way, not every agent has the same effect on every person. In addition, patients may do well with one NSAID for a period of time, and then may not derive further benefit from it for some unknown reason. Switching the patient to a different NSAID could produce the desired effects. NSAIDs may be appropriate for chronic pain management in aspirin users provided that appropriate GI prophylactic measures are used in high-risk patients. Patients should use only one NSAID at any given time to really know its benefits.

Celecoxib, a COX-2 inhibitor, is more selective in the inhibition of COX, which is involved in the transformation of arachidonic acid to prostaglandin precursors. Celecoxib has the same efficacy as NSAIDs; however, it possesses a milder GI side effect profile. It does not have a direct effect on platelets.[49] Therefore, it is preferred over NSAIDs in patients with thrombocytopenia. There have been many studies and case reports correlating COX-2 inhibitors with cardiovascular risks (eg, stroke and heart attack), especially with rofecoxib (Vioxx), which was removed from the U.S. market.[49–51]

Case 33-2, Question 3: Which of the following treatments would D.S. benefit from using at this time?

D.S. could benefit from high-dose NSAIDs. Traditionally, the initial treatment for SLE pericarditis (inflammation of the lining of the heart or pericardium) is high-dose NSAIDs such as ibuprofen. Patients with SLE are at increased risk for coronary heart disease from increased cardiovascular risk factors (ie, chronic inflammation, dyslipidemia, obesity, and physical inactivity). Patients with SLE with recurrent pericarditis will need to be on immunosuppressive medications.

Antimalarials

Antimalarials are currently the mainstay systemic therapy for SLE, in particular hydroxychloroquine sulfate (Plaquenil) and chloroquine. Both are 4-aminoquinoline antimalarial drugs and function through immunomodulation by downregulating the production of tumor necrosis factor (TNF)-α and other pro-inflammatory cytokines.[52] Chloroquine is not used in the United States for treatment of SLE. Hydroxychloroquine is preferred over chloroquine because it has a better safety profile. It is associated with less corneal deposition (opacities) and retinopathy risks.[34] Ocular side effects occur in a dose-dependent manner, where the risk is low when hydroxychloroquine's dose is <400 mg daily and <6.5 mg/kg/day based on total body weight. It has anti-inflammatory effects, and is used to reduce the time to flare-ups, constitutional (ie, fever and rashes), skin, fatigue, and joint symptoms.[53] In addition, hydroxychloroquine has antithrombotic and lipid-lowering effects, which can help patients with SLE.[54] Other ocular symptoms may include blurred vision, night blindness, missing or blanched out areas in the central or peripheral fields, light flashes and streaks, and photophobia. Hydroxychloroquine-related side effects may also include a bull's eye appearance in the macular region.[34] The manufacturer recommends that eye exams should be performed at baseline and subsequently every 3 months with long-term hydroxychloroquine treatment. In contrast, the American Academy of Ophthalmology (AAO) proposes more flexible eye exam criteria. The AAO recommends that patients who are at low risk (those taking hydroxychloroquine <6.5 mg/kg/day dose for a treatment duration of <5 years) be checked at baseline and then, if normal, every 5 years. Patients who are at high risk (those taking hydroxychloroquine >6.5 mg/kg/day dose for >5 years, age older than 60 years or pediatric patients, or those with existing retinal disease and kidney or liver disease) should be evaluated at baseline and then annually.[55] Patients should be screened for the presence of "premaculopathy" antimalarial retinopathy, or retinal toxicity during scheduled eye exams because it is a reversible stage as long as hydroxychloroquine is discontinued.

A rare, but severe adverse effect associated with hydroxychloroquine is cardiomyopathy and/or conduction abnormalities (eg, atrioventricular block, sick sinus syndrome, bundle branch block). The risk factors for hydroxychloroquine-associated cardiac adverse effects could include longer duration of hydroxychloroquine therapy, higher cumulative doses, preexisting cardiac condition, older age, female sex, and renal impairment.[56] Monitoring of certain laboratory biomarkers and imaging may be necessary for those at highest risk.

Patients may need to take hydroxychloroquine for months to experience the maximal effect. For SLE, the initial oral hydroxychloroquine dose is 400 mg given daily for 3 to 6 months depending on patient response, and then tapered to 200 mg daily for maintenance therapy. If the patient does not have any benefit from hydroxychloroquine after 6 months, the drug should be discontinued.

CASE 33-3

QUESTION 1: J.B., a 49-year-old Caucasian female with a 30-year history of SLE, returns to her rheumatologist for evaluation. She has received prednisone, hydroxychloroquine, and azathioprine in the past. Her SLE has been stable for 2 years. Feeling well, J.B. discontinued all of her medications >1 year ago. She recently returns from a family vacation in the Caribbean. Having been out in the sun for a few hours on the first day, she developed an erythematous eruption over photoexposed areas of her face, ears, and legs despite the application of sunscreen. J.B. returns home, and the lesions are healing. Although she is fatigued, she feels well enough to return to work. You determine that her rash is because of photosensitivity.

What would be the best next step in the management of J.B.?

The next appropriate step is to initiate a short course of low-dose prednisone because it can be used to treat a photosensitive rash from SLE. The rash may occur because, with SLE, the body's immune system does not function properly, and the inflammatory response works to damage the patient's own tissues. Prednisone is a corticosteroid that helps reduce the inflammation and immune response, thereby preventing further damage to the tissues in the body.

Case 33-3, Question 2: The rash resolves, however, J.B. continues to have fatigue and arthralgia. No other clinical signs or symptoms consistent with SLE flare emerge. Laboratory test results reveal continued elevation of anti-dsDNA antibody titers and suppressed complement levels. What is your next step in managing J.B.?

Hydroxychloroquine should be initiated because it is effective for long-term treatment of SLE with rash, fatigue, and arthralgias. Hydroxychloroquine is often prescribed in combination with steroids to reduce the dose of the steroids required. It is prescribed for skin rashes, mouth ulcers, and joint pain. Hydroxychloroquine improves SLE by decreasing autoantibody production, protecting against the damaging effects of UV light from the sun and other sources, and improving skin lesions. Several studies have reported the benefits of hydroxychloroquine in treating symptoms of SLE, preventing disease flares, and its association with less organ damage.[57]

Case 33-3, Question 3: J.B. is initiated on hydroxychloroquine 400 mg orally daily. How long should she be on the initial treatment dose?

Three to 6 months of the initial treatment dose of hydroxychloroquine is recommended unless J.B. does not tolerate the side effects or does not benefit from the medication. After J.B. has responded to the initial dose, hydroxychloroquine can be tapered to 200 mg daily for maintenance therapy.

Case 33-3, Question 4: How often should eye exams be performed for J.B.?

At high doses and over time, hydroxychloroquine may damage the retina of the eye (retinal toxicity), causing vision problems. Eye exams should be performed at baseline before initiating hydroxychloroquine and every 3 months based on the manufacturer's recommendation. If based on the AAO, an eye exam should be performed at baseline and then every 5 years. If low doses of hydroxychloroquine are used in the treatment of SLE, the

risk of retinal toxicity is low. Long-term users of high-dose hydroxychloroquine will need to monitor their eye health regularly to prevent retinal toxicity.

Case 33-3, Question 5: What are the goals of SLE treatment?

Because there is no cure for SLE, the goals of treatment are to reset the patient's immune system to a state of remission, reduce the incidence of drug toxicity, and prevent multiorgan damage.

Corticosteroids

Systemic corticosteroid treatment is considered for patients with SLE who have not responded to NSAIDs and hydroxychloroquine. Corticosteroids possess anti-inflammatory effects and work by inhibiting T- and B-cell responses.[58] They provide immediate relief for mild-to-moderate symptoms compared to immunosuppressant treatments. Low-dose corticosteroids, such as prednisone, may be effective for mild-to-moderate symptoms. For instance, low-dose oral prednisone (6–10 mg daily) over a duration of 4 to 6 weeks is recommended for mild disease activity. Short-term use of tapered courses of prednisone will help reduce acute flares with or without systemic symptoms starting at adult doses of 0.5 to 1 mg/kg/day, up to 60 mg daily, and tapered over 8 weeks with the aim of discontinuing treatment.[59] Short-term treatment can minimize risks of developing side effects associated with long-term corticosteroid use, such as weight gain, decreased bone mineral density, muscle wasting, hypercholesterolemia, and hyperglycemia. More severe adverse effects associated with long-term use of high-dose corticosteroids may include diabetes, osteoporosis, mood changes (eg, anxiety, insomnia, depression, and delirium), Cushing syndrome, and risks of cardiovascular events. Topical corticosteroids are recommended for cutaneous SLE manifestations, such as 1% hydrocortisone and 0.05% fluocinonide. Treatment with topical corticosteroids should be intermittent and not exceed a treatment

duration of a few weeks.[59] Adjunctive treatments with NSAIDs or celecoxib may be combined with prednisone to reduce its dose and side effects, or allow it to be administered as an every other day therapy. High-dose oral corticosteroids (eg, prednisone 40–60 mg daily) or intravenous (IV) corticosteroids (eg, methylprednisolone 0.5–1.0 g daily) are considered for more severe disease.[28]

Case 33-3, Question 6: If J.B. is to be initiated on chronic, high-dose corticosteroid therapy for management of her SLE symptoms, what should she be monitored for?

With the use of high-dose corticosteroids, it is important to monitor for weight gain, hyperglycemia, osteoporosis, glaucoma, cataracts, hypercholesterolemia, mood changes, and premature atherosclerosis. Steroid medications can have serious long-term side effects, and the risk of the side effects increases with higher doses and chronic therapy.

Disease-Modifying Antirheumatic Drugs

Disease-modifying antirheumatic drugs (DMARDs) are immunosuppressive medications that are used to treat pain and swelling of the arthritis that could accompany SLE. They could also reduce the long-term damage to the joints. Methotrexate ([MTX], Rheumatrex®, Trexall®) is an antimetabolite or folate antagonist that inhibits dihydrofolate reductase, an essential enzyme for DNA synthesis. MTX induces apoptosis of inflammatory cells and reduces levels of inflammatory cytokines, particularly interleukin (IL)-1, IL-6, and TNF-α.[60,61] Moreover, MTX increases IL-10 and IL-4 levels, which promote T helper type 2 (Th2) cytokine effects that may be protective against autoimmune manifestations.[61] MTX is usually considered for treatment of rheumatoid arthritis, particularly for arthritis and skin manifestations. It is an effective alternative agent to hydroxychloroquine and corticosteroids for patients with SLE with arthritis, rash, or serositis.[53,62,63] When used with or without

corticosteroids, MTX is dosed between 7.5 and 15 mg weekly, orally or subcutaneously, not to exceed 25 mg/week. Subcutaneous injection is recommended for patients who experience drug-induced nausea. Side effects are dose dependent and can range from mild to severe. Mild side effects include GI effects (eg, nausea and vomiting) versus mucosal ulcerations, leukopenia, thrombocytopenia, and infections that are more severe side effects. Concomitant use of folic acid is recommended with MTX to reduce the side effects, especially nausea and vomiting. Hepatotoxicity could occur from MTX use. Patients should receive baseline liver function tests, and this should continue periodically throughout therapy. They should also be screened for preexisting liver disease, excessive alcohol use, or diabetes. Patients with liver disease (eg, hepatitis B or C) should avoid MTX because of liver toxicity risk. Similarly, MTX should be used cautiously in patients with renal disease because of increased risk of renal toxicity. Other adverse effects may include lung toxicities, such as cough, shortness of breath, and pulmonary infiltrates.[53,62] MTX is teratogenic and contraindicated in pregnant females (pregnancy category X). Adequate contraception should be used while on MTX treatment. Males and females who take MTX should stop 1 to 3 months before trying to conceive. The 3-month period allows the complete elimination of MTX from the body.

Leflunomide (Arava®) is a pyrimidine synthesis inhibitor that inhibits the formation of DNA in the cells of the body, particularly the immune cells that contribute to the inflammation, swelling, stiffness, and joint pain. Leflunomide can be used as a steroid-sparing treatment for patients with SLE with photosensitive rashes and arthritis. It is also administered either as monotherapy or in combination with MTX. Treatment may be initiated with or without a loading dose, depending on the balance between the patient's tolerability of the medication and rapid efficacy associated with a loading dose and their risk for leflunomide-associated hepatotoxicity and myelosuppression.[64] Of note, the serum half-life of teriflunomide, the active metabolite of leflunomide, is between 18 and 19 days.[65] Therefore, a loading dose of leflunomide may be needed for eligible patients because it will take a long time for leflunomide to reach

steady-state plasma concentrations. For patients who are at a low risk for leflunomide-associated hepatotoxicity and myelosuppression, the oral loading dose is 100 mg daily for the first 3 days, followed by a maintenance oral dose of 20 mg daily. Alternatively, an oral loading dose of 100 mg once a week for 3 weeks, in addition to the maintenance dose have been used to reduce the increased incidence of diarrhea and other GI adverse effects. If diarrhea persists to be a bothersome side effect, in spite of the use of antidiarrheal medication, then the dose can be reduced to 10 mg daily. In contrast, patients who are at a high risk for leflunomide-associated hepatotoxicity (ie, concomitant MTX use) or leflunomide-associated myelosuppression (ie, concomitant immunosuppressant use) should receive an oral dose of 20 mg daily without a loading dose.[64] Similar to MTX screening, patients initiated on leflunomide should receive baseline liver function tests and complete blood count tests every 3 to 4 months. Furthermore, they should also be screened for preexisting liver disease and excessive alcohol use. Leflunomide is teratogenic and contraindicated in pregnant females (pregnancy category X). Females should use oral contraceptives or other forms of effective birth control methods while taking the drug. More importantly, they should continue to do so until 2 years after discontinuation of leflunomide because teriflunomide remains in the plasma. Cholestyramine (Questran®) can be used to accelerate the elimination of leflunomide and reduce the plasma levels of teriflunomide.[65]

Immunosuppressants

Azathioprine (Imuran®, Azasan®) is a derivative of 6-mercaptopurine that acts as an antimetabolite agent by inhibiting DNA synthesis and blocking cell proliferation.[62] It is used to treat LN and nonrenal SLE manifestations, such as photosensitive rashes and cutaneous lupus erythematosus. Before starting azathioprine treatment, genotyping or phenotyping of the thiopurine S-methyltransferase (TPMT) is strongly recommended.[66] Caution is recommended for patients with

reduced TPMT activity because they may be at increased risk for bone marrow suppression.[58,67] Patients who are homozygous, or carry two nonfunctional TPMT alleles, will experience life-threatening myelosuppression when treated with azathioprine because of high concentrations of thioguanine nucleotides. Bone marrow suppression can occur in any patient, is dose dependent, and reversible by reducing the dose of azathioprine.[68] Taking azathioprine with food could help reduce the GI side effects (eg, nausea, vomiting, diarrhea, and stomach pain). Leukopenia, anemia, and thrombocytopenia may result from high doses of azathioprine or from poor metabolizers of the drug. The dosage of azathioprine ranges between 1 and 3 mg/kg/day given orally and in two to three divided doses. Azathioprine has an acceptable benefit-to-risk profile in controlling SLE symptoms during pregnancy.[69]

Mycophenolate mofetil ([MMF] Cellcept®, Myfortic®) inhibits inosine monophosphate dehydrogenase, an essential enzyme for DNA synthesis in lymphocytes. Its active metabolite inhibits the proliferation of T and B cells.[58] Similar to methotrexate, MMF treatment could be used to treat patients with SLE with arthritis. It is also used for patients with SLE with renal symptoms. It has been demonstrated to be superior to azathioprine as maintenance therapy of LN.[70] Patients with SLE and nephritis have a much better response with a 6-month induction trial of mycophenolate versus azathioprine for prolonging time to treatment failure, time to renal flare, and time to rescue therapy. MMF belongs to the Risk Evaluation and Mitigation Strategy (REMS) drug safety program and cannot be prescribed by those who are not REMS certified. MMF is teratogenic (pregnancy category D) and should not be used in pregnant females or in those who plan to become pregnant. It could cause birth defects and reduces the effectiveness of oral contraceptives. Females who take this drug should wait at least 1 to 3 months after stopping the drug before trying to conceive. Common side effects are dose dependent and may include GI symptoms (eg, nausea, vomiting, and diarrhea), risk of infection, hepatotoxicity, and decreased white blood cell counts.[53] Monthly laboratory monitoring

for hematologic, hepatic, and renal toxicities is mandatory for patients taking MMF.

Case 33-3, Question 7: J.B.'s daughter has also been diagnosed with SLE. She is 25 years old and is married. She and her husband want to start a family. J.B. heard about MMF as one of the treatment options for SLE. She asks you if her daughter can benefit from taking MMF.

MMF is not an option because it is teratogenic and has been associated with infertility even though it is classified as pregnancy category D. Furthermore, MMF has risk of causing birth defects if taken during pregnancy (ie, cleft lip/palate or ear malformations). Females who take this drug should wait at least 1 to 3 months after stopping the drug before trying to conceive.

Cytotoxic Drug

Cyclophosphamide (Cytoxan®) is an alkylating agent. Its active metabolite, aldophosphamide, interferes with DNA links and causes cell death.[52] It is the agent of choice for treatment of LN, severe CNS, lung, or hematologic manifestations.[53,71] It is teratogenic (pregnancy category D) and should not be used in pregnant females or in those who plan to become pregnant. Cyclophosphamide has been reported to cause birth defects, especially if taken during the first trimester. Birth defects may include growth restriction, ear and facial abnormalities, hypoplastic limbs, and absence of digits.[72] Cyclophosphamide has a serious adverse effect profile that includes hemorrhagic cystitis, bacterial and viral (herpes zoster) infections, and infertility. Its metabolite, acrolein, is toxic to the bladder. Hemorrhagic cystitis and bladder cancer risks can be minimized by hydrating the patient (orally and via IV), frequent bladder emptying, and using mesna (sodium 2-mercaptoethane sulfonate) as a protectant before IV use.[53] Mesna is a sulfhydryl donor that binds and detoxifies acrolein.[73] Urinalysis testing and monitoring for hematuria should be performed regularly. If the patient develops hemorrhagic cystitis, cyclophosphamide therapy should be

discontinued. The risk of bladder cancer is increased after receiving a total dose of 30 g.[62]

Because immunosuppressants and cyclophosphamide can increase the prevalence of secondary malignancies, such as cervical cancer in female patients with SLE, the ACR recommends annual Papanicolaou (Pap) exams as part of laboratory monitoring.[53,74] Infertility, from ovarian failure in females or azoospermia in males, can occur in patients with SLE and of childbearing age.[7] Gonadotropin-releasing hormone analogs may preserve gonadal protection and can be considered for patients who are concerned with infertility associated with cyclophosphamide.

Case 33-3, Question 8: J.B. asks you what other commonly used drugs for SLE treatment should her daughter avoid taking if she wanted to become pregnant?

Other than MMF, her daughter should avoid taking leflunomide (pregnancy category X), MTX (pregnancy category X), and cyclophosphamide (pregnancy category D) for treatment of her SLE if she plans to get pregnant. Females should use oral contraceptives or other forms of effective birth control methods while taking leflunomide. More importantly, they should continue to do so until 2 years after discontinuation of leflunomide because its active metabolite, teriflunomide, remains in the plasma. Cholestyramine (Questran®) can be used to accelerate the elimination of leflunomide and reduce the plasma levels of teriflunomide.[65] Males and females who take MTX should stop 1 to 3 months before trying to conceive. The 3-month period allows the complete elimination of MTX from the body. Cyclophosphamide has been reported to cause birth defects, especially if taken during the first trimester. Birth defects may include growth restriction, ear and facial abnormalities, hypoplastic limbs, and absence of digits.[70]

Case 33-3, Question 9: Over the next couple of months, J.B. continues to have mild-to-moderate flares of her skin and joints because of SLE, despite

hydroxychloroquine therapy. Her primary care physician is considering cyclophosphamide for her. What common toxicity should J.B. be monitored for?

J.B. should be monitored for bladder toxicity. Acrolein, a compound of one of cyclophosphamide's active metabolite aldophosphamide, is toxic to the bladder epithelium and could cause hemorrhagic cystitis.[75] Hemorrhagic cystitis is associated with hematuria and occasional dysuria.

Case 33-3, Question 10: How is the risk of bladder toxicity reduced?

By administering mesna and plenty of fluids (orally and via IV), the risk of bladder toxicity is reduced. Pulsed or intermittent dosing of cyclophosphamide can decrease the cumulative drug dose and reduce bladder exposure to acrolein.

Case 33-3, Question 11: Considering her present symptoms, should J.B. be initiated on cyclophosphamide?

Because her symptoms are still mild to moderate without signs of CNS, lung, or renal complications, cyclophosphamide is not recommended. Cyclophosphamide is primarily reserved for treatment of LN and severe CNS associated with SLE, lung, or hematologic manifestations.

Biologic Therapies

Rituximab (Rituxan®) is a chimeric monoclonal antibody that has activity against protein CD20. CD20 is expressed from early pre-B cells to those later in differentiation; however, it is absent in terminally differentiated plasma cells. The proposed mechanism of action of rituximab includes its Fc portion that mediates antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, resulting in apoptosis of $CD20^+$ cells.[76] Efficacy of rituximab against SLE was studied in two phase III randomized

placebo-controlled trials, The Lupus Nephritis Assessment with Rituximab (LUNAR) and The Exploratory Phase II/III SLE Evaluation of Rituximab"(EXPLORER), which did not meet the studies' primary end point.[77,78] Data regarding the use of rituximab in managing SLE manifestations, particularly cutaneous lupus erythematosus, are limited. Rituximab is currently used by international expert groups for the off-label management of severe renal disease, CNS involvement, or severe autoimmune thrombocytopenia associated with SLE.[79]

Belimumab (Benylsta®) is the first biologic agent approved for adjunctive treatment of SLE in patients with active, autoantibody-positive SLE. It is a human IgG1 lambda monoclonal antibody against the B lymphocyte stimulator (BLyS). Belimumab is also referred to as a B-cell–activating factor (BAFF)-specific inhibitor. B cells have three membrane receptors: B-cell maturation antigen, transmembrane activator and calcium modulator and cyclophilin ligand interactor, and the BAFF receptor.[18] BAFF is involved in B-cell survival, activation, and differentiation. It is elevated in patients with B-cell–mediated autoimmune diseases, such as SLE.[80] Belimumab is hypothesized to decrease the amount of abnormal B cells ($CD20^+$ B cells).

Phase II clinical trials reported that belimumab combined with standard therapy offered a better response to patients with active SLE versus standard therapy alone.[80,81] Belimumab's efficacy was further demonstrated in two phase III randomized placebo-controlled clinical trials Belimumab in Subjects with Systemic Lupus Erythematosus (BLISS-52 and BLISS-76). A total of 1684 patients were randomized to receive either belimumab or placebo in combination with standard therapy.[82,83] The combination of belimumab and standard therapy was found to be superior to placebo plus standard therapy. Furthermore, the combination of belimumab and standard therapy was well tolerated, improved SLE Responder Index response rates, and reduced disease activity and severe flares.[82,83] Belimumab has not been studied in patients with severe active LN or severe active CNS lupus; therefore, it cannot be recommended for use in patients with these symptoms. More importantly, it is not recommended to be administered in combination

with other biologics or IV cyclophosphamide because it has not been studied in these settings.

Possible side effects (≥5%) of belimumab may include diarrhea, nausea, fever, insomnia, nasopharyngitis, pharyngitis, bronchitis, extremity pain, migraine, and depression.[84,85] More common side effects reported from the belimumab study group were serious infections, primarily upper respiratory tract infections.[84] Therefore, patients being treated for chronic infections should not start belimumab therapy. If an infection develops while receiving belimumab, temporary discontinuation of the drug is recommended. From clinical trials, mortality (resulting from infection, cardiovascular disease, and suicide) was increased in patients receiving belimumab versus those on placebo therapy.[80–83] Hypersensitivity reactions, including infusion reactions and anaphylaxis, may occur. Patients should be closely monitored for potential side effects and reactions.

Belimumab is administered parenterally as an IV infusion over 1 hour (**Table 33-2**). Premedication with an antihistamine for prophylaxis against infusion-related reactions and hypersensitivity reactions is recommended as part of the therapy. No dosage adjustments are required for patients with hepatic and renal impairment.

Table 33-2

Preparation and Administration Instructions of Belimumab

Reconstitution

Reconstitution
Remove belimumab vial from refrigerator and allow it to stand for 10–15 minutes to reach room temperature. Reconstitute belimumab powder with Sterile Water for Injection, USP, as follows, with reconstituted solution to make a concentration of 80 mg/mL belimumab. Reconstitute 120-mg vial with 1.5-mL sterile water. Reconstitute 400-mg vial with 4.8-mL sterile water. Direct the stream of sterile water to the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow vial to sit at room temperature during reconstitution, gently swirling the vial every 5 minutes until powder is dissolved. *Do not shake.* It usually takes 10–15 minutes, but it may take up to 30 minutes. Protect solution from light. If a mechanical reconstitution device (swirler) is used to reconstitute belimumab, it should not exceed 500 rpm, and the vial should not be swirled for longer than 30 minutes. Once reconstitution is complete, the solution should be opalescent and colorless to pale yellow and without particles. Small bubbles can occur and are acceptable.
Dilution Instructions
Belimumab should only be diluted with 0.9% sodium chloride injection, USP (normal saline). Dextrose IV solutions are incompatible with belimumab. Dilute the reconstituted product to 250 mL in normal saline for IV infusion. From a 250-mL infusion bag or bottle of normal saline, withdraw and discard a volume equal to the volume of the reconstituted solution of belimumab required for the patient's dose. Then add the required volume of reconstituted solution into the infusion bag or bottle. Discard any unused solution. Inspect visually for any particular matter and discoloration before administration. Discard if present. Use reconstituted solution immediately, otherwise it should be stored protected from sunlight and refrigerated at 36–46 °F (2–8 °C). Solutions of belimumab diluted in normal saline may be stored at 36–46 °F (2–8 °C) or room temperature. The time from reconstitution to completion of infusion should not exceed 8 hours. No incompatibilities exist between belimumab and polyvinyl chloride or polyolefin bags.
Administration Instructions
Administer the diluted solution of belimumab by IV infusion only, over a period of 1 hour. Belimumab should be administered by health care professionals prepared to manage anaphylaxis. Do not infuse belimumab concomitantly in the same IV line with other agents.

IV, intravenous; USP, US Pharmacopoeia.

Sources: Benylsta (belimumab). Package insert. GlaxoSmithKline; 2012; https://www.rheumatology.org/Learning-Center/Medication-Guides/Medication-Guide-Belimumab-Benlysta.

Case 33-3, Question 12: Over the next year, J.B. continues to have bothersome symptoms associated with her SLE, despite hydroxychloroquine therapy. She resists the recommendation to use steroids because of risks of weight gain, osteoporosis, and vision problems. She is excited to hear about a recently approved drug for SLE, belimumab. J.B. asks you, "What is the mechanism of action of belimumab?"

Belimumab is a monoclonal antibody that inhibits the B-cell survival factor, BLyS. As a BLyS-specific inhibitor, belimumab blocks the binding of BLyS to receptors on B cells, thus inhibiting the survival of B cells including autoreactive B cells. It also reduces the differentiation of B cells into immunoglobulin-producing plasma cells. Belimumab reduces disease activity and, possibly, a number of severe flares and steroid use when administered in combination with standard therapy. It is approved for treatment of patients with active, autoantibody-positive lupus in combination with standard therapies (ie, hydroxychloroquine, azathioprine, and MTX).

Case 33-3, Question 13: How is belimumab dosed and administered?

Belimumab is given at a recommended dose of 10 mg/kg that is administered via IV as an infusion over 1 hour, 2 weeks apart for the first three doses, and 4 weeks apart thereafter.

Case 33-3, Question 14: What are the necessary precautions taken before administration of belimumab?

Antihistamine premedication is recommended as a prophylaxis to prevent infusion reactions and hypersensitivity reactions. Patients should be monitored before and after drug administration. Belimumab should be used with caution in patients with chronic infections. Infections were the most common adverse events

associated with belimumab in BLISS-52 and BLISS-76 clinical trials. Upper respiratory tract infections were the most common type, occurring in >5% of patients taking belimumab.

Case 33-3, Question 15: When is belimumab not recommended for use in patients with SLE?

Belimumab is not recommended in patients with severe active LN, or in those with severe active CNS lupus because its efficacy has not been evaluated in these types of patients. Furthermore, depression and suicidality have been reported in clinical trials; therefore, it is not recommended for patients with uncontrolled psychiatric disorders. Belimumab is not recommended in combination with other biologics or IV cyclophosphamide because it has not been studied with these drugs.

Case 33-3, Question 16: Are there drug–drug interactions between belimumab and other combination treatments for SLE?

No clinically significant drug–drug interactions have been identified with belimumab in the clinical trials. It was administered concomitantly with corticosteroids, antimalarial drugs, statins, NSAIDs, angiotensin-converting enzyme inhibitors, and immunomodulatory and immunosuppressive agents.

Case 33-3, Question 17: Can J.B. receive immunizations while receiving belimumab treatment?

Live vaccines should not be administered in the 30 days before treatment starts or during treatment. Belimumab may interfere with J.B.'s response to immunizations.

Table 33-3 summarizes the current medications used for treating SLE.[53,58,74,84,85] There are drug interactions with the medications used for treating SLE symptoms. **Table 33-4** summarizes the possible significant drug–drug interactions.[86,87]

Table 33-3
Medications Used for the Treatment of Systemic Lupus Erythematosus (SLE)

Medication	FDA-Approved for SLE	Dose	Side Effects/Toxicities	Monitoring Parameters
Anifrolumab	Yes	300 mg given IV over 30 minutes every 4 weeks	Upper respiratory tract infection, bronchitis, infusion-related reactions, herpes zoster, cough, and serious infections (rare)	Signs and symptoms of infections and hypersensitivity reactions, including anaphylaxis
Azathioprine	No; off label	1–3 mg/kg/day	Bone marrow suppression, liver toxicity, elevated lymphocytes	Clinical: symptoms of infection Laboratory: CBC and platelet count every 1–2 weeks with initiation and dosage changes, then every 1–3 months; monitor LFTs and Scr; Pap test at regular intervals
Belimumab	Yes	IV: 10 mg/kg every 2 weeks for the first three doses and then administer monthly	Serious infusion and anaphylactic reactions; depression with suicidal ideation	Clinical: symptoms of allergic reaction, including hypotension, angioedema, rash, urticarial, pruritus, and difficulty breathing Symptoms of common infusion reactions, including headache, nausea, and skin reactions Symptoms of infection, including fever, nausea, diarrhea; chest pain or shortness of breath Laboratory: CBC monthly
Corticosteroids	No; off label	Prednisone (or equivalent) 0.125–1 mg/kg/day	Elevated blood pressure, glucose and cholesterol levels; low potassium or reduced potassium levels; reduced bone density; cataracts; weight gain; infections; and fluid retention	Clinical: symptoms of high blood sugar, edema, shortness of breath, high blood pressure, visual changes, bone pain. CNS symptoms of depression, suicidal ideation, insomnia, or other mood changes can occur at higher doses (eg, prednisone >60 mg). Laboratory: glucose every 3–6 months, cholesterol annually, BP at each visit, bone density

Cyclophosphamide	No; off label	IV: 0.5–1 g/m^2 monthly; Oral: 1–2 mg/kg/day	Bone marrow suppression, malignancy, immunosuppression, hemorrhagic cystitis, secondary infertility	Clinical: symptoms of infection and presence of blood in urine Laboratory: CBC and urinalysis monthly, urine cytology and Pap test annually for life
Hydroxychloroquine	Yes	200–400 mg twice daily	Ophthalmic damage, conduction abnormalities, cardiomyopathy	Clinical: visual changes Laboratory: funduscopic and visual field examination, frequency determined by risk; creatine kinase, lactate dehydrogenase, and/or troponins
Leflunomide	No; off label	Loading dose: 100 mg daily × 3 days, followed by 20 mg daily; *or* 100 mg weekly × 3 weeks, then 20 mg daily Leflunomide-associated hepatotoxicity or leflunomide-associated myelosuppression: 20 mg daily without a loading dose	Diarrhea, nausea, rash, liver toxicity, myelosuppression	Clinical: frequency and severity of diarrhea Laboratory: LFTs, CBC
Methotrexate	No; off label	Oral: 5–15 mg as a single weekly dose or can be given as three divided doses/week given every 12 hours (ie, 2.5 mg × 3 doses with 12 hours apart)	Bone marrow suppression, lung and liver toxicity, infection	Clinical: symptoms of infection, shortness of breath, nausea, vomiting Laboratory: initial chest x-ray, CBC and platelet count monthly, LFTs, albumin, Scr every 4–8 weeks
Mycophenolate mofetil	No; off label	1000–3000 mg daily	Bone marrow suppression, liver toxicity and infection	Clinical: symptoms of infection Laboratory: CBC and platelet count every 1–2 weeks with initiation and changes in dosage (then every 1–3 months), monitor LFTs and Scr, monitor changes in BP.
NSAIDs	No; off-label[a]	Product dependent	Gastrointestinal bleeding, liver and kidney toxicity, elevated blood pressure	Clinical: dark/black stool, upset stomach, nausea, vomiting, abdominal pain, edema Laboratory: CBC, LFTs and Scr annually; BP at each visit

BP, blood pressure; CBC, complete blood count; CNS, central nervous system; IV, intravenous; LFTs, liver function tests; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine.

[a]Aspirin is approved for treatment of SLE.

Sources: Tassiulas I, Boumpas D. Clinical features and treatment of systemic lupus erythematosus. In: Firestein G, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, Koretzky G. *Kelley's Textbook of Rheumatology*. 8th ed. Saunders Elsevier; 2009:1263–1300; Yildirim-Toruner C, Diamond B. Current and novel therapeutics in the treatment of systemic lupus erythematosus. *J Allergy Clin Immunol*. 2011;127:303–312; [No authors listed]. Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum*. 1999;42:1785–1796; Merrill JT, Ginzler EM, Wallace DJ, et al. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2012;64:3364–3373; Benylsta (belimumab). Package insert. GlaxoSmithKline; 2012; Saphnelo (anifrolumab). Package insert. AstraZeneca;2021.

Table 33-4
Summary of Drug Interactions With Medications for Systemic Lupus Erythematosus

Medication	Possible Interaction With Concomitant Drugs
Azathioprine	Allopurinol, ACE inhibitors, cyclosporine, etanercept, everolimus, febuxostat, infliximab, leflunomide, mycophenolate sodium, mercaptopurine, ribavirin, sulfamethoxazole/trimethoprim
Belimumab	Tofacitinib
Corticosteroids	Erythromycin, ketoconazole, mifepristone, hormonal contraceptives, NSAIDs, protease inhibitors, rifampin, tacrolimus
Cyclophosphamide	Carbamazepine, ceritinib, cyclosporine, doxorubicin, etanercept, fosphenytoin, nevirapine, nilotinib, protease inhibitors, St John's wort, phenytoin, tamoxifen, tofacitinib, warfarin
Hydroxychloroquine	Antacids, cyclosporine, digoxin, haloperidol, quinidine, other QT-prolonging drugs, tacrolimus
Leflunomide	Acyclovir, atorvastatin, baricitinib, bosentan, ciprofloxacin, elagolix, furosemide, glyburide, grazoprevir, irinotecan, methotrexate, montelukast, paclitaxel, pitavastatin, rosuvastatin, simvastatin, sulfasalazine, tenofovir alafenamide, topotecan, valacyclovir, warfarin
Methotrexate	Amoxicillin, aspirin, diclofenac, doxycycline, fosphenytoin, indomethacin, leflunomide, levetiracetam, NSAIDs, penicillin, phenytoin, piperacillin, probenecid, proton-pump inhibitors, sulfamethoxazole/trimethoprim, sulindac, tamoxifen, warfarin
Mycophenolate mofetil and mycophenolate sodium	Antacids, amoxicillin/clavulanate, azathioprine, colestipol, cholestyramine, colesevelam, ciprofloxacin, isavuconazonium, metronidazole, oral contraceptives, proton-pump inhibitors, tofacitinib
NSAIDs	ACE inhibitors, angiotensin receptor blockers, β blockers, diuretics, other antihypertensives, lithium

Sources: Belimumab (Benylsta) for systemic lupus erythematous. *Med Lett Drugs Ther* 2011;53 (1366):45-46; Hussaini MA, Hammouda EI, Hammouda AE. Optimizing pharmacotherapy of systemic lupus erythematosus: the pharmacist role. *Int J Clin Pharm*. 2014;36:684-692.

Anifrolumab (Saphnelo™) is the latest human IgG1κ monoclonal antibody approved for the treatment of SLE. It binds to type 1 IFN receptor subunit 1 and inhibits the signaling activity of all type 1 IFNs.[76] Between 60% and 80% of adults with SLE show increased IFN-induced genes, which reflect an overproduction of the immune protein type 1 IFN. Anifrolumab's efficacy was investigated in a phase III, randomized, double-blind, placebo-controlled, parallel-group clinical trial Treatment of Uncontrolled Lupus via Interferon Pathway-2 (TULIP-2).[88] TULIP-2 followed the Treatment of Uncontrolled Lupus via Interferon Pathway-1 (TULIP-1) trial, which failed to meet its primary end point. The second trial used a different end point, the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response that measures both partial and complete improvement within an organ system. TULIP-2 was completed at the end of 2019 and involved 362 patients with moderate-to-severe disease who received a fixed dose of anifrolumab 300 mg by IV administration or a placebo once every 4 weeks for 48 weeks. TULIP-2 demonstrated that the anifrolumab group was superior to the placebo group in achieving the primary end point and disease–activity response. There was a significant percentage of patients in the anifrolumab group who had a reduction in overall disease activity in all active organs, improvement in lupus skin disease, a reduction in glucocorticoid drug doses, and a reduced annual rate of flare-ups over a period of 52 weeks.[88] Regarding the adverse events from the trial, there was one death from pneumonia in the anifrolumab group. Adverse events that occurred in at least 10% of the patients in the anifrolumab group included bronchitis and upper respiratory infection. Herpes zoster was reported to be more frequent in patients receiving anifrolumab than did placebo.

Nonpharmacologic Therapy

Both the ACR and EULAR recommend nonpharmacologic treatments as part of the management of SLE.[22,89] Sunscreens with a

sun protective factor of ≥15 should be used daily, preferably with a high protection factor (SPF 60) to prevent UV-induced skin lesions.[90] There are patients who are sensitive to UVA light and may require broader spectrum sunscreens (UVA and UVB). Patients are advised to apply broad-spectrum sunscreen each morning and before sun exposure. Vitamin D supplementation may be included in photoprotective methods. A randomized controlled trial of healthy adults showed that vitamin D supplementation helped reduce the expression of pro-inflammatory mediators, such as TNF-α and increased skin expression of the anti-inflammatory mediator arginase-1 and other genes related to skin barrier repair.[91] In short, photoprotection of patients with SLE includes wearing protective clothing, minimizing sun exposure, applying broad-spectrum sunscreen, and supplementing with vitamin D. Sunbathing and the use of sunbeds in tanning parlors are discouraged. Patients with SLE should also be educated about lifestyle modifications, such as smoking cessation, weight control, and regular exercise to reduce comorbidities of atherosclerosis, hypertension, and diabetes.[7] A meta-analysis showed an increased risk of developing SLE among patients who smoke as compared with nonsmokers.[92] Furthermore, smoking is found to be associated with reduced efficacy among patients with SLE receiving belimumab.[93] Psychosocial support is also an important aspect of management because the disease and several of the medications may cause depression and anxiety. The medications' side effects can also affect a patient's adherence to treatment and medical office visits.

DRUG-INDUCED LUPUS ERYTHEMATOSUS

Drugs can cause subacute cutaneous lupus erythematosus or drug-induced lupus (DIL) (<1%) by inducing autoantibodies.[4] For as many patients who develop these antibodies, a surprisingly low number of them do not develop signs of an autoantibody-associated condition.[2] Over 38 drugs have been implicated with causing the disease (**Table**

33-5).[43,94–96] However, most DIL cases have been associated with the following medications: hydralazine, procainamide, and quinidine.

Table 33-5
Drugs That May Cause Systemic Lupus Erythematosus

Drug Class	Very Low Risk	Low-to-Moderate Risk	High Risk
Antiarrhythmics	Disopyramide, propafenone	Quinidine	Procainamide
Antimicrobials/antibiotics	Nitrofurantoin	Isoniazid, minocycline	
Anticonvulsants	Phenytoin, primidone, ethosuximide	Carbamazepine	
Antihypertensives	Enalapril, clonidine, atenolol, labetalol, pindolol, minoxidil, prazosin, chlorthalidone, hydrochlorothiazide	Captopril, methyldopa, acebutolol	Hydralazine
Anti-inflammatories	Phenylbutazone	Sulfasalazine, D-penicillamine	
Antipsychotics	Perphenazine, phenelzine, chlorprothixene, lithium	Chlorpromazine	
Anti-thyroids		Propylthiouracil	
Miscellaneous	Lovastatin, levodopa, interferon-α, timolol eye drops		

Sources: Vedove CD, Giglio MD, Schena D, Girolomoni G. Drug-induced lupus erythematosus. *Arch Dermatol Res*. 2009;301:99–105; Marzano A, Vezzoli P, Crosti C. Drug-induced lupus: an update on its dermatologic aspects. *Lupus*. 2009;18:935–940; Hussaini MA, Hammouda EI, Hammouda AE. Optimizing pharmacotherapy of systemic lupus erythematosus: the pharmacist role. *Int J Clin Pharm*. 2014;36:684–692.

The symptoms of DIL may present as arthralgia or myalgias, fatigue, malar rash, erythema multiforme-like, and the presence of anti-histone antibodies. The symptoms are similar to those of SLE; however, they are generally not as severe. Typically, the symptoms are self-limiting and resolve after discontinuing the offending drug. NSAIDs may be used to help speed up the healing process. Corticosteroids may also be used if more severe symptoms of DIL are present. The development of DIL occurs over the long term and from chronic use of medications that have high risk for causing lupus.

The mechanism by which these drugs exert their effect is not well understood. However, it may be attributed to a patient's genetic predisposition as a slow acetylator, which decreases the metabolism of some drugs such as procainamide and hydralazine. Gene expression is regulated by DNA methylation and histone modifications.[95,96] Procainamide and, particularly, hydralazine are hypothesized to inhibit DNA methylation, which alters gene expression in T lymphocytes. Subsequently, this process induces an

overexpression of lymphocyte function-associated antigen 1 (LFA-1 antigen), thereby resulting in autoreactivity.[29,94]

INVESTIGATIONAL AGENTS

Aside from the current therapies used for the treatment and management of SLE symptoms, newer therapeutic agents are being investigated for their activities against the immune system, such as the B cells, T cells, IFN, and cytokines that are involved in patients with SLE. Investigational biologic agents are being developed and undergoing phase I, II, and III clinical trials. These newer biologic agents specifically target different phases of the pathogenesis of SLE, have different mechanisms of action, and possess milder adverse effect profiles. The investigational drug classes include immune cell–targeted therapies, anti-cytokine therapy, therapies targeting costimulatory signaling pathways, and neutralizing monoclonal antibody against IFN-α.[58]

TREATMENT APPROACHES

The primary goal of treatment for SLE is to control acute flares, and maintenance strategies are used to suppress symptoms and to prevent further organ damage. NSAIDs, hydroxychloroquine, and low-dose corticosteroids are considered maintenance therapy to control mild-to-moderate symptoms of arthritis, dermatitis, and constitutional symptoms. High-dose systemic corticosteroids, DMARDs, immunosuppressants, belimumab, and anifrolumab are used for patients with more serious active disease, including those with more life-threatening forms such as LN.[71] Certain DMARDs and immunosuppressants (ie, leflunomide, MTX, cyclophosphamide, and MMF) should be used with extreme caution in females of childbearing age and in those who are planning to get pregnant

because of teratogenic effects.[7] MMF is the preferred maintenance therapy for LN in patients who can tolerate the medication, who are not pregnant, and who respond to it. It can reduce the effectiveness of oral contraceptives and, thus, additional or alternative nonhormonal methods of birth control should be considered. Currently, only hydroxychloroquine, belimumab, and anifrolumab are FDA approved for the treatment of SLE. Immunosuppressants and DMARDs (ie, azathioprine, cyclophosphamide, leflunomide, MTX, and MMF) have been used off label for managing SLE symptoms for years. Prophylaxis with aspirin or long-term anticoagulation should be considered in patients with antiphospholipid antibodies and who are at an increased risk for thrombosis.[18] Patients with mild disease require frequent medical evaluations every 3 to 6 months. On the contrary, patients with inactive disease may benefit from being monitored every 6 to 12 months.

ROLE OF PHARMACISTS

SLE disease is very complex, and the symptoms are variable. Successful and effective management of SLE requires the involvement of a multidisciplinary health care team comprising many specialists (eg, rheumatology, cardiology, nephrology, dermatology, psychology, and ophthalmology) and pharmacists. Pharmacists have an important role in caring for patients with SLE, especially with education, management of their medications, and the monitoring of drug–drug or drug–herbal interactions. As part of the health care team, pharmacists can provide drug education and counseling to patients with respect to proper administration of the medications, common side effects, management of the side effects, and reinforcement of adherence to their medications and office visits. Education and counseling of the teratogenic effects of certain DMARDs and immunosuppressants should be offered, as well as the information that the disease should remain inactive for at least 6 months before attempting to conceive.[53] More importantly,

pharmacists can provide education to help patients with SLE maintain a healthy lifestyle and better quality of life (eg, regular weight-bearing exercise, sufficient dietary vitamin intake, smoking cessation, and limited alcohol intake to a minimum of two drinks daily).[97,98]

CASE 33-4

Question 1: S.P., a 35-year-old Asian female with a 10-year history of SLE, sees you for follow-up management of her medications. She currently takes hydroxychloroquine 200 mg orally (PO) daily as part of her maintenance regimen. S.P. reports experiencing some heartburn and bloating symptoms over the past several days and purchases an over-the-counter antacid, calcium carbonate. Calcium carbonate has helped alleviate her GI symptoms; however, she notices feeling more fatigued lately.

What is the potential drug interaction between hydroxychloroquine and calcium carbonate?

Antacids that contain calcium carbonate, magnesium, or aluminum (ie, Tums®, Maalox®) can interfere with the absorption of hydroxychloroquine and reduce its effectiveness when taken at the same time.

Case 33-4, Question 2: As her pharmacist, what advice would you provide to S.P. regarding the appropriate administration of hydroxychloroquine and calcium carbonate?

S.P. should be advised to separate the administration of hydroxychloroquine and calcium carbonate by at least 4 hours to reduce the risk of a drug interaction. No clinically significant drug–drug interactions have been reported for concomitant use of hydroxychloroquine and histamine (H_2) receptor antagonists.

Case 33-4, Question 3: What other counseling points could you offer to S.P. about her health?

S.P. should be advised to incorporate a heart-healthy exercise regimen (low-impact aerobic exercise, such as walking, swimming, or Pilates) and diet (a low-sodium, low-fat, and low-carbohydrate regimen) to reduce modifiable cardiovascular risk factors and on approaches to maintain adequate rest. Counseling should also be provided regarding the use of sunscreen, vitamin D supplementation and adequate calcium intake, smoking cessation, maintenance of schedule immunizations, and prompt management of infections.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol*. 2019;71: 1400–1412. (22)

Bertsias G, Cervera R, Boumpas DT. Systemic lupus erythematosus: pathogenesis and clinical features. In: Bijlsma WJ, Hachulla E, eds. *EULAR Textbook on Rheumatic Diseases*. 20th ed. EULAR; 2012:476–505. (2)

Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and pediatric lupus nephritis. *Ann Rheum Dis*. 2012;71:1771–1782. (39)

Krikorian S. Systemic lupus erythematosus In: Helms RA, Quan DJ eds. *Textbook of Therapeutics: Drug and Disease Management*. 8th ed. Lippincott Williams & Wilkins; 2006:1767–1787. (27)

Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64:2677–2686. (23)

Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011;365: 2110–2121. (13)

Key Websites

American College of Rheumatology (ACR). Position Statement: screening for hydroxychloroquine retinopathy. ACR website. Accessed September 15, 2020. https://www.rheumatology.org/Portals/0/Files/Screening-for-Hydroxychloroquine-Retinopathy-Position-Statement.pdf

Lupus Foundation of America. What is lupus? Accessed September 15, 2020. http://www.lupus.org/answers/entry/what-is-lupus

COMPLETE REFERENCES CHAPTER 33 SYSTEMIC LUPUS ERYTHEMATOSUS

1. Kalunian K, Merrill JT. New directions in the treatment of systemic lupus erythematosus. *Curr Med Res Opin*. 2009;25:1501–1514.
2. Bertsias G, Cervera R, Boumpas DT. Lupus erythematosus: pathogenesis and clinical features. In: Bijlsma WJ, Hachulla E, eds. *EULAR Textbook on Rheumatic Diseases*. 20th ed. EULAR; 2012:476–505.
3. Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum*. 2010;39:257–268.
4. Ghodke-Puranik Y, Niewold TB. Immunogenetics of systemic lupus erythematosus: a comprehensive review. *J Autoimmun*. 2015;64:125–136.
5. Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med*. 2008;358:929–939.
6. Lupus Foundation of America. What is lupus? Accessed July 21, 2015. http://www.lupus.org/answers/entry/what-is-lupus
7. Bertsias G, Ioannidis JPA, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis*. 2008;67:195–205.
8. Mohan C, Putterman C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. *Nat Rev Nephrol*. 2015;11:329–341.
9. Harley JB, Kelly JA, Kaufman KM. Unraveling the genetics of systemic lupus erythematosus. *Springer Semin Immunopathol*. 2006;28:119–130.
10. Niewold TB. Advances in lupus genetics. *Curr Opin Rheumatol*. 2015;27:440–447.
11. Deng Y, Tsao BP. Genetic susceptibility to systemic lupus erythematosus in the genomic era. *Nat Rev Rheumatol*. 2010;6:683–692.
12. Fessel WJ. Systematic lupus in the community. Incidence, prevalence, outcome and first symptoms; the high prevalence in black women. *Arch*

Intern Med. 1974;134:1027–1035.
13. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011;365:2110–2121.
14. Majka DS, Holers VM. Cigarette smoking and the risk of systemic lupus erythematosus and rheumatoid arthritis. *Ann Rheum Dis*. 2006;65:561–563.
15. Cohen MR, Isenberg DA. Ultraviolet irradiation in systemic lupus erythematosus: friend or foe? *Br J Rheumatol*. 1996;35:1002–1007.
16. Kang I, Quan T, Nolasco H, et al. Defective control of latent Epstein-Barr virus infection in systemic lupus erythematosus. *J Immunol*. 2004;172:1287–1294.
17. Doria A, Cutolo M, Ghirardello A, et al. Steroid hormones and disease activity during pregnancy in systemic lupus erythematosus. *Arthritis Rheum*. 2002;47:202–209.
18. Olenak JL, Russell TM. Introduction to systemic lupus erythematosus (SLE) for the practicing pharmacist. Power-Pak C. E.; October 20, 2012:1–26. http://www.powerpak.com/course/content/108689
19. Smith-Bouvier DL, Divekar AA, Sasidhar M, et al. A role for sex chromosome complement in the female bias in autoimmune disease. *J Exp Med*. 2008;205:1099–1108.
20. Odendahl M, Jacobi A, Hansen A, et al. Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. *J Immunol*. 2000;165:5970–5979.
21. Christensen SR, Shlomchik MJ. Regulation of lupus-related autoantibody production and clinical disease by Toll-like receptors. *Semin Immunol*. 2007;19:11–23.
22. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol*. 2019;71:1400–1412.
23. Petri M, Orbai A-M, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64:2677–2686.
24. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:1725.
25. Gill JM, Quisel AM, Rocca PV, Walters DT. Diagnosis of systemic lupus erythematosus. *Am Fam Physician*. 2003;68:2179–2186.
26. Wallace DJ, Hahn BH, eds. *Dubois' Lupus Erythematous*. 6th ed. Lippincott Williams & Wilkins; 2002.
27. Lahita RG, ed. *Systemic Lupus Erythematosus*. 4th ed. Elsevier Academic Press; 2004.
28. Krikorian S. Systemic lupus erythematosus. In: Helms RA, Quan DJ, eds. *Textbook of Therapeutics: Drug and Disease Management*. 8th ed. Lippincott Williams & Wilkins; 2006:1767–1787.

29. Schur PH, Gladman DD. Overview of the clinical manifestations of systemic lupus erythematosus in adults. In: Basow DS, ed. *UpToDate*. Wolters Kluwer Health; 2012.
30. Hellmann DB, Imboden Jr JB. Musculoskeletal and Immunologic Disorders. In: McPhee SJ, Papdakis MA. Current Medical Diagnosis and Treatment. 48th ed. McGraw-Hill;2009:708-743.
31. Buyon JP. Systemic lupus erythematosus: clinical and laboratory features. In: Klippel JR, Stone JH, Crofford LJ, White PH. *Primer on the Rheumatic Diseases*. 13th ed. Springer; 2008:303–313.
32. Hanly JG, Urowitz MB, Su L, et al. Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis*. 2010;69:529–535.
33. Auerbach C, Beckerman N. What social workers in health care should know about lupus: a structural equation model. *Health Soc Work*. 2011;36:269–278.
34. Bertsias GK, Salmon JE, Boumpas DT. Therapeutic opportunities in systemic lupus erythematosus: state of the art and prospects for the new decade. *Ann Rheum Dis*. 2010;69:1603–1611.
35. Roman MJ, Crow MK, Lockshin MD, et al. Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum*. 2007;56:3412–3419.
36. Salmon JE, Roman MJ. Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. *Am J Med*. 2008;121(10, suppl 1):S3–S8.
37. Bourre-Tessier J, Huynh T, Clarke AE, et al. Features associated with cardiac abnormalities in systemic lupus erythematosus. *Lupus*. 2011;20:1518–1525.
38. Paran D, Fireman E, Elkayam O. Pulmonary disease in systemic lupus erythematosus and the antiphospholipid syndrome. *Autoimmun Rev*. 2004;3:70–75.
39. Gordon C, Jayne D, Adu D, et al. European consensus statement on the terminology used in the management of lupus glomerulonephritis. *Lupus*. 2009;18:257–263.
40. Bertsias GK, Tektonidou M, Amoura Z, et al. European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and pediatric lupus nephritis. *Ann Rheum Dis*. 2012;71:1771–1782.
41. Falk RJ. Treatment of lupus nephritis—a work in progress. *N Engl J Med*. 2000;343:1182–1183.
42. Faurschou M, Starklint H, Halberg P, Jacobsen S. Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. *J Rheumatol*. 2006;33:1563–1569.

43. Bernknopf A, Rak K, Bailey T. A review of systemic lupus erythematosus and current treatment options. *Formulary*. 2011;46:178–194.
44. Sultan SM, Begum S, Isenberg DA. Prevalence, patterns of disease and outcome in patients with systemic lupus erythematosus who develop severe haematological problems. *Rheumatology (Oxford)*. 2003;42:230–234.
45. Kitsanou M, Andreopoulou E, Bai MK, Elisaf M, Drosos AA. Extensive lymphadenopathy as the first clinical manifestation in systemic lupus erythematosus. *Lupus*. 2000;9:140–143.
46. Shapira Y, Weinberger A, Wysenbeek AJ. Lymphadenopathy in systemic lupus erythematosus. Prevalence and relation to disease manifestations. *Clin Rheumatol*. 1996;15:335–338.
47. Benito-Garcia E, Schur PH, Lahita R, The American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: anti-Sm and anti-RNP antibody tests. *Arthritis Rheum*. 2004;51:1030–1044.
48. Hahn BH. Systemic lupus erythematosus. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. 15th ed. McGraw-Hill; 2001:1922–1928.
49. Funk CD, FitzGerald GA. COX-2 inhibitors and cardiovascular risk. *J Cardiovasc Pharmacol*. 2007;50:470–479.
50. Martinez-Gonzalez J, Badimon L. Mechanisms underlying the cardiovascular effects of COX-inhibition: benefits and risks. *Curr Pharm Des*. 2007;13:2215–2227.
51. Ross JS, Madigan D, Hill KP, Egilman DS, Wang Y, Krumholz HM. Pooled analysis of rofecoxib placebo-controlled clinical trial data: lessons for post-market pharmaceutical safety surveillance. *Arch Intern Med*. 2009;169:1976–1985.
52. Mirabelli G, Cannarile F, Bruni C, Vagelli R, De Luca R, Carli L. One year in review 2015: systemic lupus erythematosus. *Clin Exp Rheumatol*. 2015;33:414–425.
53. Tassiulas I, Boumpas D. Clinical features and treatment of systemic lupus erythematosus. In: Firestein G, Budd RC, Harris ED Jr, McInnes IB, Ruddy S, Sergent JS, eds. *Kelley's Textbook of Rheumatology*. 8th ed. Saunders Elsevier; 2009:1263–1300.
54. Wallace DJ, Gudsoorkar VS, Weisman MH, Venuturupalli SR. New insights into mechanisms of therapeutic effects of antimalarial agents in SLE. *Nat Rev Rheumatol*. 2012;8:522–533.
55. American College of Rheumatology (ACR). Position Statement: screening for hydroxychloroquine retinopathy. https://www.rheumatology.org/portals/0/files/acr%202015%20ra%20guideline.pdf.
56. Fein C, Ness T, Weseloh C, et al. Safety management in treatment with antimalarials in rheumatology. Interdisciplinary recommendations on the

basis of a systematic literature review. *Z Rheumatol*. 2021;80(suppl 1):1–9.
57. Akhavan PS, Su J, Lou W, Gladman DD, Urowitz MB, Fortin PR. The early protective effect of hydroxychloroquine on the risk of cumulative damage in patients with systemic lupus erythematosus. *J Rheumatol*. 2013;40:831–841.
58. Yildirim-Toruner C, Diamond B. Current and novel therapeutics in the treatment of systemic lupus erythematosus. *J Allergy Clin Immunol*. 2011;127:303–312.
59. Kuhn A, Aberer E, Bata-Csörgo˝ Z, et al. S2k guideline for treatment of cutaneous lupus erythematosus. *J Eur Acad Dermatol Venereol*. 2016;31:389–404.
60. Nakazawa F, Matsuno H, Yudoh K, et al. Methotrexate inhibits rheumatoid synovitis by inducing apoptosis. *J Rheumatol*. 2001;28:1800–1808.
61. Barrera P, Boerbooms AM, Janssen EM, et al. Circulating soluble tumor necrosis factor receptors, interleukin-2 receptors, tumor necrosis factor alpha, and interleukin-6 levels in rheumatoid arthritis. Longitudinal evaluation during methotrexate and azathioprine therapy. *Arthritis Rheum*. 1993;36:1070–1079.
62. McCune WJ, Marder W, Riskalla M. Immunosuppressive drug therapy. In: Wallace DJ, Hahn BH. *Dubois' Lupus Erythematosus*. 7th ed. Lippincott Williams & Wilkins; 2007:1124–1198.
63. Fortin PR, Abrahamowicz M, Ferland D, et al. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2008;59:1796–1804.
64. Brent RL. Teratogen update: reproductive risks of leflunomide (Arava™); a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. *Teratology*. 2001;63:106–112.
65. Arava (Leflunomide). Package insert. Sanofi-Aventis; 2011.
66. Azathioprine tablet. Package insert. Glenmark Pharmaceuticals; 2015.
67. Askanase AD, Wallace DJ, Weisman MH, et al. Use of pharmacogenetics, enzymatic phenotyping, and metabolite monitoring to guide treatment with azathioprine in patients with systemic lupus erythematosus. *J Rheumatol*. 2009;36:89–95.
68. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. *Clin Pharmacol Ther*. 2013;93:324–325.
69. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis*. 2017;76:476–485.

70. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med*. 2011;365:1886–1895.
71. Houssiau FA, Ginzler EM. Current treatment of lupus nephritis. *Lupus*. 2008;17:426–430.
72. Vaux KK, Kahole NCO, Jones KL. Cyclophosphamide, methotrexate, and cytarabine embropathy: is apoptosis the common pathway? *Birth Defects Res A Clin Mol Teratol*. 2003;67:403–408.
73. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. *Arthritis Rheumatol*. 2010;62:9–21.
74. [No authors listed]. Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum*. 1999;42:1785–1796.
75. Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. *Nat Rev Clin Oncol*. 2009;6:638–647.
76. Chasset F, Francès C. Current concepts and future approaches in the treatment of cutaneous lupus erythematosus: a comprehensive review. *Drugs*. 2019;79:1199–1215.
77. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. 2012;64:1215–1226.
78. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum*. 2010;62:222–233.
79. Kleinmann J-F, Tubach F, Le Guern V, et al. International and multidisciplinary expert recommendations for the use of biologics in systemic lupus erythematosus. *Autoimmun Rev*. 2017;16:650–657.
80. Wallace DJ, Stohl W, Furie RA, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum*. 2009;61:1168–1178.
81. Jacobi AM, Huang W, Wang T, et al. Effect of long-term belimumab treatment on B cells in systemic lupus erythematosus: extension of a phase II, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum*. 2010;62:201–210.
82. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377:721–731.
83. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B

lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2011;63:3918–3929.
84. Merrill JT, Ginzler EM, Wallace DJ, et al. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2012;64:3364–3373.
85. Benlysta (belimumab). Package insert. GlaxoSmithKline; 2012.
86. Belimumab (Benlysta) for systemic lupus erythematosus. *Med Lett Drugs Ther* 2011;53 (1366):45-46.
87. Hussaini MA, Hammouda EI, Hammouda AE. Optimizing pharmacotherapy of systemic lupus erythematosus: the pharmacist role. *Int J Clin Pharm*. 2014;36:684-692.
88. Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus (TULIP-2 trial). *N Engl J Med*. 2020;382:211–221.
89. Mosca M, Tani C, Aringer M, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis*. 2010;69:1269–1274.
90. Kuhn A, Gensch K, Haust M, Meuth A-M. Photoprotective effects of a broad-spectrum sunscreen in ultraviolet-induced cutaneous lupus erythematosus: a randomized, vehicle-controlled, double-blind study. *J Am Acad Dermatol*. 2011;64:37–48.
91. Scott JF, Das LM, Ahsanuddin S, et al. Oral vitamin D rapidly attenuates inflammation from sunburn: an interventional study. *J Invest Dermatol*. 2017;137:2078–2086.
92. Jiang F, Suyun L, Jia C. Smoking and the risk of systemic lupus erythematosus: an updated systematic review and cumulative meta-analysis. *Clin Rheumatol*. 2015;34:1885–1892.
93. Parodis I, Sjöwall C, Jönsen A, et al. Smoking and pre-existing organ damage reduce the efficacy of belimumab in systemic lupus erythematosus. *Autoimmun Rev*. 2017;16:343–351.
94. Zandmann-Goddard G, Solomon M, Rosman Z, Peeva E, Shoenfeld Y. Environment and lupus related diseases. *Lupus*. 2012;21:241–250.
95. Vedove CD, Giglio MD, Schena D, Girolomoni G. Drug-induced lupus erythematosus. *Arch Dermatol Res*. 2009;301:99–105.
96. Marzano A, Vezzoli P, Crosti C. Drug-induced lupus: an update on its dermatologic aspects. *Lupus*. 2009;18:935–940.
97. Hussaini MA, Hammouda EI, Hammouda AE. Optimizing pharmacotherapy of systemic lupus erythematosus: the pharmacist role. *Int J Clin Pharm*. 2014;36:684–692.
98. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)*. 2010;62:1515–1526.

34

Kidney and Liver Transplantation

David J. Taber, Robert E. Dupuis, Nicole A. Pilch, and Kristen Szempruch

CORE PRINCIPLES		CHAPTER CASES
1	Successful kidney transplantation involves rigorous evaluation of both donor and recipient. This results in immunologic categorization as either a high-risk or low-risk transplant and determines the immunosuppressive regimen an individual recipient should receive. The majority of these patients will receive combination therapy, which includes a calcineurin inhibitor, an antiproliferative agent, and a corticosteroid.	**Case 34-1 (Question 1), Table 34-1**

CORE PRINCIPLES		CHAPTER CASES
2	Induction therapy is used in most kidney transplant cases. Rabbit antithymocyte globulin (rATG), alemtuzumab, and basiliximab are common agents. Differences among these agents include dosing regimen and side effect profile. rATG and alemtuzumab are often used in high-risk patients, including those with delayed graft function, whereas basiliximab is frequently used in low-risk recipients.	**Case 34-1 (Questions 2–6)**
3	Immunosuppressive combination therapy is directed at prevention of rejection. Acute rejection can be either T-cell mediated or B-cell mediated. T-cell–mediated rejection can be successfully treated, whereas B-cell–mediated rejection is much more resistant. Despite success in reducing acute rejections, chronic rejection and chronic graft dysfunction are major causes of graft loss.	**Case 34-1 (Questions 7–9)**

CORE PRINCIPLES		CHAPTER CASES
4	The calcineurin inhibitors cyclosporine and tacrolimus and steroids have significant toxicity profiles, particularly with chronic long-term use. Tacrolimus and cyclosporine are calcineurin inhibitors with a complex pharmacokinetic profile associated with multiple adverse effects and requires therapeutic drug monitoring (TDM). Calcineurin inhibitor–induced nephrotoxicity is a major problem. Steroids have a negative impact on the cardiovascular, bone, and endocrine systems. Several strategies have been developed in an attempt to either avoid or minimize these adverse effects.	**Case 34-2 (Questions 1, 2)** **Case 34-3 (Question 1)** **Case 34-5 (Question 2)**
5	The mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, have complex pharmacokinetic profiles, significant adverse effects, and require TDM. These agents appear to be most useful in minimizing or avoiding the use of calcineurin inhibitors or other agents.	**Case 34-4 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
6	Liver transplantation is considered the treatment of choice for patients with end-stage liver disease. Common early posttransplant complications include surgical (biliary leaks and bleeding), neurologic (continued hepatic encephalopathy, drug toxicity), and infectious complications.	**Case 34-5 (Question 1)**
7	Acute rejection of the transplanted liver is a common, but usually reversible, consequence after this surgery. It is usually asymptomatic, but can be identified early through serial monitoring of serum transaminases and bilirubin, and definitively diagnosed only through liver biopsy. Treatment usually consists of pulse-dose corticosteroids, followed by a taper, or the use of rATG for more severe rejections or those refractory to steroid therapy.	**Case 34-5 (Questions 3–5)**

CORE PRINCIPLES		CHAPTER CASES
8	Mycophenolate is considered the adjuvant agent of choice in solid organ transplantation and is used to reduce calcineurin inhibitor exposure or augment immunosuppressant regimen potency. TDM is not common and has yet to prove effective in optimizing therapy. Common side effects of this agent include gastrointestinal issues (nausea, vomiting, and diarrhea) and cytopenias (leukopenia and thrombocytopenia).	**Case 34-6 (Question 1)**
9	Drug interactions with immunosuppressants are numerous and are commonly encountered clinical dilemmas in the transplant recipient. Pharmacists should prospectively screen for these interactions and, depending on their magnitude, may need to prospectively adjust medication regimens. Closer TDM or clinical monitoring is warranted when adding or removing an interacting medication to a patient on immunosuppression.	**Case 34-6 (Question 2), Table 34-2**

CORE PRINCIPLES		CHAPTER CASES
10	Cardiovascular complications, including hypertension, hyperlipidemia, and diabetes, are prevalent among kidney transplant recipients. These contribute to poor patient survival and graft loss. Other complications such as osteoporosis are frequently observed. Monitoring and treatment of these complications, which may be drug induced, are an important part of the posttransplant care plan.	**Case 34-7 (Questions 1–3)**
11	Posttransplant lymphoproliferative disorder (PTLD), which is usually a B-cell lymphoma, is the most common cancer encountered after organ transplant. Early PTLD is generally responsive to reductions in immunosuppression; advanced PTLD is usually not responsive to this nor to traditional chemotherapy. The use of rituximab, a monoclonal antibody directed against B cells, has shown promise in the treatment of this disease.	**Case 34-8 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
12	Infections, including opportunistic infections, are common complications after transplant. Prophylaxis with antimicrobial agents is critical for the most common and severe pathogens. Hepatitis B and hepatitis C are problematic after liver transplant and require immunoprophylaxis or treatment in certain circumstances.	**Case 34-9 (Question 1), Table 34-3**
13	Cytomegalovirus is the most common and debilitating opportunistic infection after solid organ transplantation. Reactivation or new infection with this virus can lead to severe tissue-invasive disease and, potentially, death. Indirect effects include acute rejection, chronic rejection, graft loss, and, potentially, lymphoma. Prophylaxis with potent antivirals (ganciclovir or valganciclovir) is the cornerstone of prevention. Treatment involves a long course of antiviral therapy, usually in conjunction with reductions in immunosuppression.	**Case 34-10 (Questions 1–3)**
14	BK polyomavirus is almost exclusively seen in kidney transplantation and is associated with graft loss. The best approach to reducing its occurrence is viral surveillance. If it is present, then reduction of immunosuppression appears to be the most effective treatment.	**Case 34-11 (Questions 1–3)**

INTRODUCTION

Solid organ transplantation, adult and pediatric, is an established therapeutic option for patients with end-stage kidney, liver, heart, and lung disease. For many of these patients, it is the only option. Pancreas or combined pancreas–kidney transplantation is available as a treatment for patients with diabetes with or without end-stage renal failure.

Unfortunately, many more patients are in need of transplantation than there are organs available. In 2021, about 30,000 organ transplants were performed by August 2021, whereas 117,260 people were waiting for all organs and over 97,000 for kidneys as of September 29, 2021 (UNOS.org). The donor pool has been expanded beyond traditional contraindications. Specifically, now hepatitis C–positive donors are frequently used for non-hepatitis C–positive recipients because of the potency of the new direct-acting antivirals (DAAs). Despite expansion of the donor pool and the focus on getting more living donors, about 6000 patients annually will die while on the waiting list.

Immunosuppression strategies continue to evolve. During the 1960s, azathioprine, prednisone, antilymphocyte serum, and antilymphocyte globulin made the success of kidney transplantation possible. In the 1980s, the introduction of cyclosporine had a remarkable impact on solid organ transplantation, and the first monoclonal antibody approved for human use, OKT3, was introduced, but is no longer available.

Since the 1990s, a number of other agents have been approved. These include tacrolimus, mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS), sirolimus (formerly rapamycin), and everolimus; monoclonal antibodies, such as basiliximab; a polyclonal antibody, antithymocyte globulin (ATG) (eg, rabbit antithymocyte globulin [rATG]); and belatacept. More recently, several agents, such as alemtuzumab, intravenous immunoglobulins (IVIGs), rituximab, eculizumab, and bortezomib, have been

incorporated into transplant protocols. Several new agents are undergoing investigation.

Although transplantation has a significant positive impact on the quality of life in most patients, rehospitalizations, retransplantation because of graft failure or disease recurrence, donation source (living-related and -unrelated organs), and costs to individuals, insurers, and society are major issues. For example, the average Medicare cost during the first year after kidney transplantation is $83,000 and during the second year is $25,000. After liver transplantation, first-year average Medicare cost is $190,000 (adjusted for inflation in 2021, this would convert to $219,299) and second year $30,000 (adjusted for inflation in 2021, this would convert to $34,626).[1,2] The ability of transplant recipients to pay for their medications or insurance denial or termination of coverage is another major issue.

The goal of immunosuppressive therapy is to prevent organ rejection, prolong graft and patient survival, and improve quality of life by helping to maintain graft function. Short-term (ie, 1- to 2-year) survival after transplantation has improved dramatically. Long-term survival also has improved, but not to the same degree.[3] As patients live longer after transplantation, the focus of therapy has shifted to survival and management of long-term complications. Immunosuppressive agents are associated with significant long-term complications. These include nephrotoxicity, hypertension, hyperlipidemia, osteoporosis, diabetes, infection, and malignancy. Many patients also have several pre- and posttransplant comorbidities and complicated drug regimens, which must be evaluated and managed. Pharmacists play an important role in these patient care activities.[4] Although acute rejection rates are significantly lower, this remains a problem, along with chronic rejection and/or chronic allograft injury (CAI) and long-term outcomes. The search for safer and more effective immunosuppressive regimens continues, along with a better understanding of optimal long-term immunosuppression to promote improved outcomes after 1 year posttransplant.[5] This chapter addresses the immunology of transplantation and rejection,

indications for kidney and liver transplantation, appropriate use of immunosuppressive agents, and the management of postoperative and long-term complications in these patients. Many of these issues are similar for the various types of solid organ transplantations, but there can also be significant differences. This chapter addresses some of these issues because they relate to kidney and liver transplantation.

TRANSPLANTATION IMMUNOLOGY

Successful organ transplantation has evolved from a greater understanding and application of pharmacology, microbiology, molecular and cellular biochemistry and biology, genetics, and immunology. Suppression of the host's immune system and prevention of rejection are vital for host acceptance of the transplanted organ. The ultimate goal is permanent acceptance or tolerance, a situation in which the new organ is seen as "self" by the host's immune system. In general, the currently used immunosuppressive drugs provide a nonpermanent form of tolerance and lifelong immunosuppression is required. A basic understanding of the immune system and the mechanisms of rejection is key to the effective use of immunosuppressive drugs in organ transplantation.

Major Histocompatibility Complex and Human Leukocyte Antigen

The degree to which allogeneic grafting (eg, donor and recipient from same species) is successful depends on the genetic similarities or differences between the donor organ and the recipient's immune system. The recipient recognizes the transplanted graft as either self or foreign. This recognition is based on the recipient's reaction to alloantigens or antigens (ie, substances that initiate an immune

response that can lead to rejection of the transplanted organ). These substances, also known as histocompatibility antigens, play a very important role in organ transplantation. The ABO blood group system of red blood cells is also important, and, in most cases, the donor and recipient should be ABO compatible; otherwise, immediate graft destruction can occur because of antibodies directed against the ABO antigens.

Histocompatibility antigens are glycoproteins that are located on the surface of cell membranes. These are encoded by the major histocompatibility complex (MHC) genes located on the short arm of chromosome 6. In humans, the MHC is called the human leukocyte antigen (HLA). The gene products encoded on the HLA are divided into classes I, II, and III based on their tissue distribution, antigen structure, and function. Class I antigens (HLA-A, HLA-B, and HLA-C) are present on all nucleated cell surfaces and are the primary targets for cytotoxic T-lymphocyte reactions against transplanted cells and tissues. The three class II antigens (HLA-DR, HLA-DQ, and HLA-DP) have a more limited distribution and are found on macrophages, B lymphocytes (B cells), monocytes, activated T lymphocytes (T cells), dendritic cells, and some endothelial cells, all of which can act as antigen-presenting cells (APCs). Individual HLA loci are extensively polymorphic. Each transplant recipient possesses two A, B, and DR antigens, one from each parent. This is called a haplotype. Recognition of these polymorphic loci by recipient T cells appears to account for rejection events. Class III antigens (C4, C2, and Bf) are part of the complement system.

Rejection of a transplanted organ is the outcome of the natural response of the immune system, innate and adaptive immunity, to a foreign substance, or an antigen, and is a complex process, the understanding of which continues to evolve. This process involves an array of interactions between antigens, T cells, macrophages, cytokines (soluble mediators secreted by lymphocytes, also called lymphokines [the interleukins or ILs]), adhesion molecules (also referred to as costimulatory molecules), and membrane proteins expressed on a wide variety of cells that enhance binding of T and B cells. This process of organ rejection ultimately can involve all

elements of the immune response, but it is predominantly T-cell mediated. This process can be divided into several important steps, which include antigen presentation, T-cell recognition, activation, proliferation, and differentiation of the various components of the immune response. For foreign antigens to interact with recipient T cells and B cells, they must be prepared for presentation by APCs. These APCs usually are recipient macrophages or dendritic cells (indirect pathway of allorecognition), although initially donor cells—dendritic cells or passenger leukocytes and graft endothelial cells—also can serve as APCs (direct pathway of allorecognition). This phase takes place within the blood, lymph nodes, spleen, and the transplanted organ.

Once antigens are prepared and presented, the next step (signal one) involves T-lymphocyte cell recognition of the antigen presented on the surface of the APC. The primary site for this to occur is at the CD3 (clusters of differentiation)–T-cell receptor (TCR) complex on recipient T cells. This step involves the binding of the antigen, MHC, and TCR for T-cell activation. These T cells also express other molecules on their surfaces that, along with CD3, recognize and respond to different types of antigens. These T cells are known as $CD4^+$ cells (T_H, helper or inducer T cells) and $CD8^+$ cells (T cells, cytotoxic or suppressor T cells). $CD4^+$ cells interact with class II antigens. $CD8^+$ cells interact with class I antigens.

In addition (signal two), proteins known as adhesion molecules or costimulatory molecules promote T-cell signaling and activation. For T-cell activation to occur, binding of these costimulatory molecules as well as binding of the TCR with the presented antigen and MHC is required. Examples of these molecules include intercellular adhesion molecule (ICAM)-1 found on APCs, which bind with the lymphocyte function–associated antigen expressed on the surface of T cells; ICAM-1 and ICAM-3 on APCs with CD2 on T cells; B7 (now called CD80 and CD86) on APCs with either CD28 or CTLA4 on T cells; and CD40 on APC with CD40 ligand (now called CD154) on T cells. The binding of costimulatory molecules is critical to T-cell activation.

Without this costimulation, T cells undergo abortive activation or programmed T-cell death (apoptosis).

Once recognition and costimulatory binding occur, T-cell activation and proliferation are initiated. After interacting with class II antigens and stimulation from IL-1 secreted from macrophages, T_H cells produce and secrete cytokines IL-2 and interferon (IFN)-γ. T_H cells are classified, according to their cytokine secretion pattern, into either T_{H1} or T_{H2} cells. T_{H1} cells secrete IL-2, IFN, and tumor necrosis factor (TNF), which stimulate cytotoxic T cells. T_{H2} cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13, which stimulate B cells. T_H cells, along with cytotoxic T cells, are stimulated to express cell-surface IL-2 receptors (IL-2R) and other cytokines. Once these T cells express IL-2R, they bind to IL-2 and other cytokines, which leads to signal transduction that results in proliferation, division, and stimulation of more T cells (signal 3). These committed cytotoxic T cells bind directly to allogeneic cells and produce cell lysis. T_H-secreted cytokines recruit other T cells, which results in further cytotoxicity. During this process, T_H cells also produce cytokines that trigger a cascade of events involving B cells and antibody production, complement fixation, increased macrophage infiltration, neutrophil involvement, fibrin deposition, platelet activation and release, prostaglandin release, and inflammatory response at the graft site. These delayed-type hypersensitivity and humoral responses occur in conjunction with one another and are not mutually exclusive. This results in cellular and tissue injury and graft destruction.

The antibodies produced by plasma cells, which are transformed B cells under the influence of cytokines, bind to the target antigenic cells. This leads to local deposition of complement and results in immune complexation and injury to the graft (complement-mediated cell lysis). The newly formed antibodies cause a series of interactions to occur with T cells, which lead to cytotoxicity (antibody-dependent, cell-mediated cytotoxicity). These cell-mediated and humoral immunologic events can impair organ function so significantly that without therapeutic intervention, complete organ

graft dysfunction may occur. Under certain circumstances, which are not clear, certain T cells cells, known as suppressor T cells, downregulate the immune response to alloantigen.[6]

Human Leukocyte Antigen Typing

The genetic compatibility between donor and recipient can have a major impact on acute rejection, graft function, graft survival, and patient survival. The liver is unique; however, blood type matching is the only immunologic matching that is done pretransplant currently. The liver has the unique ability to promote tolerance, allowing many patients to be on minimal immunosuppression long term.[7] However, in kidney transplantation, the closer the HLA matching is between recipient and donor, the better the outcome, particularly over the long term. To determine this compatibility, a number of laboratory tests, including serologic, flow cytometric, genetic-DNA based, and cellular assessments of donor and recipient serum and lymphocytes, are performed before organ transplantation. This process is referred to as *tissue typing*. Lymphocytes are typed for HLA-A, HLA-B, and HLA-DR. Typing for HLA is performed using the donor and recipient lymphocytes for serology-based techniques or tissue- or fluid-containing nucleated cells.[8]

The panel-reactive antibody (PRA) test is commonly used to assess organ compatibility because recipients may have HLA antibodies from previous exposure to antigenic stimuli (eg, blood transfusions, previous transplantation, and pregnancy). In this test, the recipient's serum is tested against a cell panel of known HLA specificities that are representative of possible donors in the general population. The percentage of cell reactions (recipient with potential donor) determines a recipient's PRA. It is done periodically on patients in the waiting list to determine their immunologic reactivity. The potential recipient with a higher percentage of PRA (>99%) is at higher risk for rejection and will generally a have longer wait time for a kidney than do patients with lower PRAs. In December 2014, that kidney allocation system was changed to provide additional priority

points to those patients with a PRA >99% to ensure they would be included in more offers with the intent of reducing their wait times.

A cytotoxic and/or flow cytometry lymphocyte cross-match is also performed before transplantation. In this case, the potential recipient's serum is cross-matched to determine whether preformed antibodies to the donor's lymphocytes are present. A positive cross-match indicates the presence of recipient cytotoxic IgG antibodies to the donor. In kidney transplantation, a positive cross-match is usually considered a contraindication. Recently, a number of transplant programs have utilized desensitization strategies to reduce the level of HLA antibodies present in potential recipients as a mechanism to reduce the likelihood of a positive cross-match with either identified living donors or future potential deceased donors. Common strategies to reduce these preformed HLA antibodies include serial delivery of plasmapheresis coupled with IVIG, rituximab, and bortezomib.[9] In liver transplantation, a positive cross-match is not an absolute contraindication because the need is urgent and because the liver appears to be more resistant immunologically to this type of reaction. These liver transplant recipients can, however, experience significant complications and early graft dysfunction. In kidney transplantation, organ allocation and matching now utilize a virtual cross-match in which potential recipients are listed with known unacceptable HLA antigens (those that have been preidentified in the patient). If a potential donor is identified with a specific HLA antigen that the recipient has known antibodies directed against, they will be skipped on the list.

ABO blood typing is one of the most critical of all evaluations when determining the genetic compatibility for all solid organ transplants. Transplantation of an organ with ABO incompatibility typically results in a hyperacute rejection and destruction of the graft, although in kidney transplant, newer therapeutic approaches to overcome ABO incompatibility have been successful.[8]

IMMUNOSUPPRESSIVE AGENTS AND MECHANISM OF ACTION

Immunosuppressives, based on an improved understanding of their mechanisms of action and the mechanisms of rejection, have had the most significant impact on patient and graft survival. The currently used immunosuppressives are shown in **Table 34-1**. These agents can be categorized as induction or maintenance therapy.[10] Sites of action and the role of the currently used agents are discussed here.

Table 34-1
Currently Used Immunosuppressive Agents

Drug (Brand Name)	Usual Dose/Route (How Supplied)	Therapeutic Use(s)	Major Adverse Effects
Alemtuzumab (Campath-H1)	IV or SC 0.3 mg/kg or 30 mg × 1 dose (30-mg vial for injection)	Prevention and treatment of acute cellular and antibody-mediated rejection; steroid-free protocols	Lymphopenia, leukopenia, infection
Azathioprine (Imuran)[a]	IV or oral 1–3 mg/kg/day (50-mg tablet; 100-mg vial for injection)	As maintenance agent to prevent acute rejection	Leukopenia, thrombocytopenia, hepatotoxicity, nausea and vomiting, diarrhea, pancreatitis, infection
Antithymocyte globulin, equine (Atgam)	IV 10–20 mg/kg/day (250 mg/5-mL ampoule for injection)	Treat acute rejection (including severe or steroid-resistant forms); as induction agent in high-risk patient to prevent acute rejection	Anemia, leukopenia, thrombocytopenia, arthralgia, myalgias, nausea and vomiting, diarrhea, fevers, chills, hypotension, tachycardia, anaphylaxis, infection
Antithymocyte globulin, rabbit (Thymoglobulin)	IV 1.5 mg/kg/day given daily for 4–10 days (25 mg/5-mL vial for injection)	Treat acute rejection (including severe or steroid-resistant forms); as induction agent in high-risk patient to prevent acute rejection	Fever, chills, nausea and vomiting, hypotension, neutropenia, flushing, rash, itching, joint pain, myalgias, thrombocytopenia, infection
Basiliximab (Simulect)	IV 20 mg × 2 doses 10 mg; 2 doses for children if <35 kg (10- and 20-mg vial for injection)	As induction agent to prevent acute rejection	Abdominal pain, dizziness, insomnia, hypersensitivity reaction (rare)
Belatacept (Nulojix)	IV initial maintenance: 10 mg/kg on days 0, 4, 14, and 28; and weeks 8 and 12 and monthly thereafter Conversion from CNI: 5 mg/kg q 2 weeks for five doses, then q 4 weeks thereafter	As maintenance agent to prevent acute rejection; conversion agent from CNIs in patients with intolerances	Anemia, neutropenia, diarrhea, UTIs, headaches, peripheral edema, PTLD
Cyclosporine[a] (Sandimmune)	Oral 5–10 mg/kg/dose bid IV 1.5–2.5 mg/kg/dose (100 mg/mL oral solution; 25- and 100-mg capsule; 250 mg/5-mL ampoule for injection)	As maintenance agent to prevent acute rejection	Nephrotoxicity, hypertension, neurotoxicity, hair growth, gingival hyperplasia, hyperglycemia, hyperkalemia, dyslipidemia, hypomagnesemia, infection, neoplasm
Cyclosporine (Neoral, Gengraf, various others)[a]	Oral 4–8 mg/kg/day bid (100-mg solution; 25-, 50-, and 100-mg capsules)	As maintenance agent to prevent acute rejection; conversion agent from tacrolimus in patients with intolerance	Same as given earlier
Everolimus (Zortress)	Oral 0.5–1.5 mg bid (0.25-, 0.5-, 0.75-mg tablets)	As maintenance agent to prevent acute rejection; conversion agent from CNI in patients with intolerance or poor response	Dyslipidemia, thrombocytopenia, neutropenia, impaired healing, mouth ulcers, proteinuria, pneumonitis (rare)
Methylprednisolone[a] sodium succinate (Solu-Medrol, various others)	10–1000 mg/dose (40-, 125-, 250-, 500-, 1000-, and 2000-mg vial for injection)	As induction and maintenance agent to prevent acute rejection; to treat acute rejection	Hyperglycemia, psychosis, euphoria, impaired wound healing, osteoporosis, acne, peptic ulcers, gastritis, fluid, electrolyte disturbances, hypertension, dyslipidemia, leukocytosis, cataracts, cushingoid state, infection, insomnia, irritability

Mycophenolate[a] mofetil (CellCept)	1.5–3.0 g/day bid IV/PO (250-mg capsule; 500-mg tablet; 200 mg/mL oral suspension; 500-mg vial for injection)	As maintenance agent to prevent acute rejection; conversion agent from azathioprine and sirolimus in patients with intolerance or poor response	Diarrhea, nausea and vomiting, neutropenia, dyspepsia, ulcers, infection, thrombocytopenia, anemia
Mycophenolate[a] sodium (Myfortic)	360–720 mg PO bid (180- and 360-mg tablets)	As maintenance agent to prevent acute rejection. Alternative to MMF	Similar side effect profile as MMF
Prednisone[a] (Deltasone)	Oral 5–20 mg/day (1-, 2.5-, 5-, 10-, 20-, 50-, and 100-mg tablet)	As maintenance agent to prevent acute rejection	See methylprednisolone
Sirolimus[a] (Rapamune)	Oral 2–10 mg/day (0.5-, 1-, and 2-mg tablet; 1 mg/mL oral solution)	As maintenance agent to prevent acute rejection; conversion agent from CNI or mycophenolate or azathioprine in patients with intolerance or poor response	Dyslipidemia, thrombocytopenia, neutropenia, anemia, diarrhea, impaired healing, mouth ulcers, proteinuria, pneumonitis (rare)
Tacrolimus (Prograf, Astagraf XL, Envarsus XR)[a]	Oral 0.15–0.3 mg/kg/day bid IV 0.025–0.05 mg/kg/day as continuous infusion (0.5-, 1-, and 5-mg capsule; 5 mg/mL ampoule for injection) Astagraf XL: oral 0.1–0.2 mg/kg/day once daily (0.5-, 1-, and 5-mg capsules) Envarsus XR: oral 0.1–0.2 mg/kg/day once daily 80% of total daily dose of tacrolimus when converting from immediate-release formulation (0.75-, 1-, and 4-mg tablets)	As maintenance agent to prevent acute rejection; conversion agent from cyclosporine in patients with intolerance or poor response	Nephrotoxicity, hypertension, neurotoxicity, alopecia, hyperglycemia, hyperkalemia, dyslipidemia, hypomagnesemia, infection, neoplasm
Bortezomib (Velcade)	1.3 mg/m^2 on days 1, 4, 8, and 11 IV bolus or SC (3.5-mg single-use vial)	Inhibits plasma cells	Bone marrow suppression, thrombocytopenia, neuropathy, hypotension, gastrointestinal
Eculizumab (Soliris)	600- to 1200-mg IV infusion (300-mg single-use vial [30 mL of 10 mg/mL solution])	Inhibits complement	Infusion reaction, headache, hypertension, leukopenia, infections
Rituximab (Rituxan)	375 mg/m^2 × 1–5 doses or 500 mg/m^2 single-dose IV infusion (100- and 500-mg single-use vial, in 10-mg/mL concentration)	Inhibits B-cell production	Infusion reactions (fever, chills, rigors); pain at infusion site, infections
Intravenous Immunoglobulin (Carimune NF, Flebogamma, Gammagard S/D, Gamunex, Iveegam EN, Octagam, Polygam)	100 mg/kg to 2-g/kg IV infusion (vial size varies based on manufacturer, ranging from 1, 2.5, 5, 6, 10, 12, 20, 30, and 40 g; usually concentrations are 5% and 10%)	Immunomodulation of T and B cells and/or immunoglobulin replacement	Infusion reactions (fever, chills, rigors); pain at infusion site, thrombosis, hemolytic anemia, acute renal failure, septic meningitis

bid, twice daily; CNI, calcineurin inhibitor; IV, intravenous; MMF, mycophenolate mofetil; PO, orally; PTLD, posttransplant lymphoproliferative disorder; q, every; SC, subcutaneous; UTI, urinary tract infection.

[a]Generic products available.

Maintenance

AZATHIOPRINE

Azathioprine is a prodrug of 6-mercaptopurine (6-MP). Azathioprine and 6-MP are purine antagonist antimetabolites. The introduction of cyclosporine, tacrolimus, mycophenolate, and sirolimus has led to a significant reduction in azathioprine use or its elimination altogether in immunosuppressive protocols. It can be useful in some cases, because it is inexpensive, or in patients who cannot tolerate other agents. It continues to be used in other countries.[10]

Azathioprine, a nonspecific antimetabolite immunosuppressive agent, affects both cell-mediated (ie, T cell) and antibody-mediated (ie, B cell) immune responses. Because it inhibits the early stages of cell differentiation and proliferation, azathioprine is useful for preventing rejection, but it is ineffective for the treatment of acute rejection. 6-MP, an active metabolite, is incorporated into DNA and RNA, thereby interfering with the intracellular formation of thioguanine nucleotides (TGNs). 6-MP is intracellularly converted by hypoxanthine phosphoribosyltransferase to thioinosinic acid and then to TGNs. 6-MP may have two separate immunosuppressive effects: inhibition of cellular proliferation and cytotoxicity. A decrease in the levels of intracellular purine ribonucleotides decreases cellular proliferation, and incorporation of TGN into DNA mediates cytotoxicity.

The major metabolic conversion of azathioprine to 6-MP is via nucleophilic attack by glutathione. The liver and red blood cells are thought to be major tissue sites for this metabolic conversion. The 6-MP formed by this reaction can be metabolized further to thiopurine ribonucleosides and ribonucleotides such as 6-TGN. These active metabolites, which have longer half-lives, are responsible for immunosuppressive activity. Azathioprine pharmacokinetics are not affected by renal dysfunction, but 6-TGN metabolite concentrations can accumulate in this situation.[11]

The most common adverse effect of azathioprine is bone marrow suppression. Bone marrow suppression may be related to a genetic deficiency of the enzyme, thiopurine methyltransferase. Low activity of this enzyme is rare, but, in some individuals, it leads to greater

availability of 6-MP, elevated 6-thioguanine levels, and susceptibility to myelosuppression. Low levels of thiopurine methyltransferase and specific genetic polymorphisms of this enzyme have been associated with severe azathioprine myelotoxicity and reduced efficacy.[11,12] Testing for this polymorphism has been advocated. However, few transplant centers perform genetic testing before use.

MYCOPHENOLIC ACID DERIVATIVES (MYCOPHENOLATE MOFETIL AND MYCOPHENOLATE SODIUM)

As a result of several multicenter comparative registry trials in kidney transplant recipients, MMF and EC-MPS have replaced azathioprine in many transplant protocols. MPA derivatives are used as adjunctive therapy in combination with cyclosporine or tacrolimus, prednisone, mammalian target of rapamycin (mTOR) inhibitors, and monoclonal and polyclonal antibodies to prevent acute rejection and are also used for calcineurin inhibitor (CNI) withdrawal and minimization. It is also used as rescue therapy when patients have not responded to, or cannot tolerate, the side effects of other immunosuppressive agents.

MPA derivatives are antiproliferative antimetabolites that inhibit purine synthesis, but in a more selective manner than does azathioprine. Unlike azathioprine, MPA derivatives interfere with the de novo pathway for purine synthesis. MMF is the morpholinoethyl ester prodrug of MPA, which is the active component. MPA selectively, noncompetitively, and reversibly blocks an enzyme known as inosine monophosphate dehydrogenase (IMPDH) found primarily in actively proliferating T and B cells. T and B cells rely on this enzyme and the de novo purine pathway to produce purine nucleotides for DNA and RNA synthesis. Thus, MPA interferes with T-cell and B-cell proliferation. It is more selective than is azathioprine. MPA also may affect cytokine production. Other secondary effects include inhibition of B-lymphocyte antibody production, decreased adhesion molecule expression, decreased smooth muscle proliferation and recruitment, and infiltration of neutrophils.[13]

Another oral formulation of MPA, EC-MPS, is also approved by the U.S. Food and Drug Administration (FDA) to prevent rejection in kidney transplantation, when used in combination with a CNI and corticosteroids. The original purpose of designing the enteric-coated formulation was to reduce or prevent the gastrointestinal (GI) side effects commonly seen with MMF. However, most data suggest that the efficacy rates and side effect profiles of MMF and EC-MPS are nearly identical. These two agents are not bioequivalent.[13]

CORTICOSTEROIDS

Prednisone, methylprednisolone, and prednisolone—all synthetic analogs of hydrocortisone—are the primary corticosteroids used to prevent and treat rejection of transplanted organs. These agents usually are given in fixed doses or dosing is based on body weight (milligram/kilogram) despite the pharmacokinetic differences. Although they are an important part of immunosuppression, a goal of most transplantation programs is to minimize, eliminate, or avoid corticosteroid use because of their numerous and significant side effects.

Corticosteroids have multiple effects on most cells and tissues of the body, but it is their anti-inflammatory and, more importantly, their immunosuppressive properties that serve as the basis for their use in organ transplant recipients. The corticosteroids bind with specific intracellular glucocorticoid receptors and interfere with RNA and DNA synthesis as well as transcription of specific genes. Cell function is altered, resulting in suppression or activation of gene transcription. Corticosteroids also affect RNA translation, protein synthesis, cytokine production and secretion, and protein and cytokine receptor expression.

Even after a single dose, corticosteroids cause marked lymphocytopenia by redistribution of circulating lymphocytes to other lymphoid tissues, such as the bone marrow, rather than by cell lysis; however, they also transiently increase the number of peripherally circulating neutrophils. Corticosteroids inhibit IL-1 and IL-6 production from APC, a number of events associated with T-cell

activation, and IL-2 and IFN-γ production. They interfere with the action of IL-2 and IL-2R on activated T cells, resulting in the inhibition of T_{H1} function. They can enhance IL-10 regulatory function and enhance T_{H2} cell function. Moderate-dose to high-dose corticosteroids also inhibit cytotoxic T-cell function by inhibiting cytokine production and lysis of T cells. They can inhibit early proliferation of B cells but have a minimal effect on activated B cells and immunoglobulin (Ig)-secreting plasma cells. The corticosteroids affect most cells and substances associated with acute allograft rejection and inflammatory reactions. They inhibit accumulation of leukocytes at sites of inflammation; inhibit macrophage functions, including migration and phagocytosis; inhibit expression of class II MHC antigens induced by INF-γ; block the release of IL-1, IL-6, and TNF; inhibit the upregulation and expression of costimulatory molecules and neutrophil adhesion to endothelial cells; inhibit secretion of complement protein C3; inhibit phospholipase A_2 activity; and decrease production of prostaglandins.[14]

CALCINEURIN INHIBITORS

Cyclosporine

The activity of cyclosporine is mediated through a reversible inhibition of T-cell function, particularly T_H cells. Its major effect is inhibiting the production of IL-2 and other cytokines, including INF-γ. These actions result in an inhibition of the early events of T-cell activation, sensitization, and proliferation. Cyclosporine has little effect on activated mature cytotoxic T cells. Therefore, it has little usefulness in the treatment of acute rejection. Its site of action is within the cytoplasm of T cells after antigenic recognition and signaling occurs. Cyclosporine binds to an intracellular protein (immunophilin) called *cyclophilin*. Although binding to cyclophilin is required, it alone is not sufficient for immunosuppression. This cyclosporine–cyclophilin complex then binds to a protein phosphatase, calcineurin. This is thought to prevent activation of nuclear factors involved in the gene transcription for IL-2 and other cytokines, including IFN. Also, because of this inhibition,

cyclosporine indirectly impairs the activity of other cells, macrophages, monocytes, and B cells in the immune response. Cyclosporine has no effect on hematopoietic cells or neutrophils. Cyclosporine is metabolized extensively in the liver to >25 metabolites. Two of these metabolites elicit a lower immunosuppressive effect in vitro. The role of these metabolites in the development of toxicity with cyclosporine is unclear.[15]

Tacrolimus

Tacrolimus is a macrolide with a molecular structure different from that of cyclosporine. Tacrolimus is more effective than cyclosporine in liver and kidney transplant recipients as the primary immunosuppressant in combination with corticosteroids or mycophenolate, azathioprine, mTOR inhibitors, and antibodies. It also is effective in some patients as rescue treatment in liver and kidney recipients experiencing acute or chronic rejection resulting from failure of standard immunosuppressive therapy. Tacrolimus is the preferred CNI over cyclosporine in most transplant centers.[2]

The activity of tacrolimus is similar to that of cyclosporine, but the concentrations of tacrolimus needed to inhibit the production of IL-2 are 10 to 100 times lower than those of cyclosporine. Tacrolimus also inhibits production of other cytokines, including IL-3, IL-4, INF-γ, TNF, and granulocyte-macrophage colony-stimulating factor. It has variable effects on B-cell response and also has anti-inflammatory effects. As with cyclosporine, tacrolimus binds to an intracellular, although different, protein: FK binding protein 12. This protein, which interacts with calcineurin, inhibits gene transcription of cytokines and interferes with T-cell activation.[16]

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

Sirolimus, formerly known as rapamycin, is an FDA-approved agent for the prevention of acute rejection and for withdrawal of cyclosporine in kidney transplantation. Positive results for sirolimus also have been observed in other transplant populations; in situations in which it is used in combination with other agents,

including antibodies, tacrolimus, mycophenolate, and prednisone; and when it has been used for rescue therapy. Its major use, as has been traditionally published, is in CNI avoidance, withdrawal, or minimization protocols but more recently is used in patients with solid tumors or other indications such as resistant CMV.

Unlike CNIs, which work earlier in the T-cell activation cycle and inhibit cytokine production, sirolimus is an inhibitor of late T-cell activation. It does not block cytokine production; rather, it inhibits signal transduction, which blocks the response of T cells and B cells to cytokines, such as IL-2. Sirolimus binds to the same immunophilin bound by tacrolimus, FK binding protein. This complex interferes with the action of certain enzymes or proteins involved in cell proliferation signaling. Both cyclosporine and tacrolimus inhibit calcineurin, whereas sirolimus influences a protein called the mTOR. Sirolimus also inhibits an enzyme called P7056 protein kinase, which is involved in microsomal protein synthesis. These effects result in cell-cycle arrest, blockage of messenger RNA production, and blockage of cell proliferation. Sirolimus also inhibits the proliferation of smooth muscle cells and may, although it is too early to tell, reduce the development of chronic rejection and cancer.

Sirolimus exhibits significant pharmacokinetic variability. Its average bioavailability is 15%; C_{max} and area under the curve (AUC) are linear over a wide range of doses. Sirolimus is extensively distributed. It distributes primarily into red blood cells and is highly plasma protein bound, ~92%. It also binds to lipoproteins. Sirolimus is extensively metabolized in the gut and liver by cytochrome P450 (CYP) 3A4 and 3A5 isoenzymes, and it is a substrate for P-glycoprotein. Its drug interaction profile is similar to that of cyclosporine and tacrolimus. Renal elimination accounts for 2% of a dose. The terminal half-life is ~57 to 63 hours and the time to steady state is 10 to 14 days in adults and shorter in children.

Everolimus is the newest FDA-approved mTOR inhibitor for use in both kidney and liver transplantation. Its mechanism of action is similar to that of sirolimus. Everolimus is hepatically metabolized through the CYP3A4 and CYP3A5 but has a shorter half-life,

average 30 hours, and a different dose and frequency schedule than does sirolimus. Similar to sirolimus, it requires monitoring of trough blood concentrations. Its role in transplantation is generally similar to that of sirolimus, but direct comparison to sirolimus is needed.[17]

BELATACEPT

This agent is the first FDA-approved intravenous (IV) maintenance agent. Belatacept is a CTL4-Ig that blocks the costimulatory pathway of CD28 or CTL-A4:CD80/CD86 binding interactions. CTLA4-Ig binds to CD80/CD86 to a greater degree than does CD28, resulting in inhibition of costimulation and T-cell activation. Belatacept is given once every few weeks in combination with other agents, such as mycophenolate and prednisone, and generally well tolerated. It has been used as initial therapy, or for CNI avoidance or withdrawal (conversion) to reduce development or progression of CNI-induced reduction in renal function. Benefits on renal function have been demonstrated as well as other CNI-associated adverse effects. However, it should be noted that there is an increased risk of acute rejection when belatacept is used in combination with mycophenolate, as compared to a cyclosporine- and mycophenolate-based regimen. There are no large-scale studies comparing it to tacrolimus-based regimens or in combination with cytolytic induction therapy. In clinical practice, some transplant centers utilize belatacept as a conversion agent in patients who cannot tolerate CNIs. There is an ongoing multicenter study to assess the efficacy of this. Other small studies that utilize belatacept with mTOR therapy have been published. It should be noted that belatacept is contraindicated in patients who are Epstein–Barr virus (EBV) antibody negative because of the risk of posttransplant lymphoproliferative disorder (PTLD). The phase III studies that demonstrated a higher risk of PTLD in those who received belatacept noted this was the case only in EBV-naive recipients, and CNS PTLD was of particular concern. Recent data presented in abstract form, which followed up patients from the phase III studies out for >7 years posttransplant, have now demonstrated improved

graft survival in the belatacept arm, as compared to the cyclosporine group. Thus, this agent may offer beneficial outcomes for certain low-risk kidney transplant recipients. Use in other organs, particularly in liver transplant recipients, is not recommended because of previous studies demonstrating inferior outcomes, as compared to CNI-based therapy.[18]

Induction

POLYCLONAL ANTIBODIES

Antithymocyte globulins

Polyclonal antibody products have been used for decades to prevent and treat acute rejection. Polyclonal products used today are administered IV and include equine (lymphoglobulin) and rATG, which is considered the polyclonal antibody of choice.

ATG preparations have also been made in goats and sheep for investigational study. However, the following discussion is limited to the products produced in horses and rabbits. Regardless of the species from which they are produced, all ATG products have similar pharmacologic effects. Their potency and antibody specificity vary, however, from batch to batch and between products. The production of polyclonal equine or rabbit antibody begins with the injection of homogenized human spleen or thymus preparations into the animals. This injection induces an immune response in the animals directed against human T lymphocytes; serum containing antibodies to T cells is collected from the animals and purified. However, other antibodies to human cells are produced as well. These antibodies bind to all normal blood mononuclear cells in addition to T lymphocytes and B lymphocytes, resulting in depletion of lymphocytes, platelets, and leukocytes from the peripheral circulation. The mechanism of action of these agents is thought to be linked to lysis of peripheral lymphocytes, uptake of lymphocytes by the reticuloendothelial system, masking of lymphocyte receptors, apoptosis, and immunomodulation. These agents contain antibodies to a number of cell-surface markers on lymphocytes, including CD2,

CD3, CD4, CD8, CD11a, CD25, CD44, CD45, HLA-DR, and HLA class I antigens. They also interfere with leukocyte adhesion and trafficking and have effects against $CD20^+$ B cells. ATG preparations can produce a rapid and profound depletion of circulating T cells, often within 24 hours of the initial dose. The duration of the effect can last several weeks after a course of therapy, particularly with rATG. Antibodies can be produced to these products as well. This, however, does not appear to influence clinical outcomes.[19]

MONOCLONAL ANTIBODIES

Basiliximab

Basiliximab is an IL-2R antagonist, monoclonal antibody approved for use in combination with other immunosuppressives to prevent acute cellular rejection in kidney transplantation. Basiliximab is a chimeric antibody that contains both murine and human antibody sequences. This agent prevents episodes of acute rejection in kidney transplant recipients. It has been used, although not as frequently, in liver transplants. Comparative studies between basiliximab and other antibodies, such as rATG, have been conducted. Advantages over these other agents include ease of administration, minimal side effects, low immunogenicity, no greater infections or malignancy rates, and fewer required doses. It is well tolerated, although there are rare reports of anaphylaxis. Basiliximab appears to be most effective in immunologically low-risk patients, whereas in high-risk patients, its use may be limited. It binds to the α-subunit of the IL-2R, also known as CD25 or the tacrolimus (TAC) subunit, which is expressed only on the surface of activated T cells; this subunit is critical to IL-2 activation of T cells in the acute rejection process. Basiliximab prevents the IL-2R from binding with IL-2, thereby blocking T-cell activation. It does not cause lymphocyte depletion. Basiliximab, with the two-dose IV regimen, on days 0 and 4 posttransplant, saturates the receptor for ~30 to 50 days in kidney transplants.[20]

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against CD52 proteins on the surface of T cells and B cells, natural killer cells, macrophages, and granulocytes. Binding of CD52 elicits antibody-dependent lysis of these cells. It is approved for use in certain types of blood cancers, but not in organ transplant. Because it causes a profound reduction or depletion in lymphocytes, especially T_H lymphocytes, a number of studies have evaluated its effect as induction therapy to prevent acute rejection after kidney transplant. Several studies have investigated its use in low and high immunologic risk transplants and in steroid avoidance or withdrawal regimens and CNI avoidance or withdrawal regimens. Short-term studies have indicated a role for this agent in these situations. It is rarely used in liver transplantation. Most protocols with this agent give a single IV or subcutaneous (SC) dose in the operating room. With this dose, significant neutropenia and lymphopenia can occur, lasting for months to years in some patients. This single-dose regimen has been successful in reducing the incidence of fungal and viral infections as compared with multiple-dose regimens, although infection is still a concern with a single dose.[21,22]

OTHER AGENTS

These agents, although not indicated for kidney transplantation, are being used and studied primarily in kidney transplantation. IVIG and rituximab, an anti–B-cell CD20 monoclonal antibody, are being used pre- and posttransplant in order to transplant patients with ABO incompatibility or who are highly sensitized. Use of immunosuppression to reduce circulating antibodies is a process called *desensitization*. Desensitization is used to facilitate transplant across traditionally prohibitive immunologic barriers. Care is needed following transplant to ensure that appropriate immunologic monitoring is done to prevent rejection and graft loss. Eculizumab, a C5 complement inhibitor, and bortezomib, a proteasome inhibitor, are also being used and studied in these situations, as well as for the treatment of antibody-mediated acute cellular rejection.[23,24]

KIDNEY TRANSPLANTATION

Indications and Evaluation

All patients with end-stage renal disease (ESRD) are potential candidates for kidney transplantation unless contraindicated. The contraindications (absolute or relative) are determined by the individual transplant center. Absolute contraindications include current malignancy, active infection, active liver disease, hepatitis B surface antigen (HbsAg)-positive, severe or symptomatic cardiac or pulmonary disease, specific renal diseases with an accelerated recurrence rate, substance abuse, and abnormal psychosocial and noncompliant behavior. Relative contraindications for the recipient of a kidney transplant include chronic liver disease, active infection, current hepatitis C viremia, human immunodeficiency virus (HIV) positive if uncontrolled on antiviral therapy, morbid obesity, current positive cross-match, and older age, which may vary based on center. The relative contraindication for the elderly with ESRD is controversial because ~40% of the ESRD population is older than 65 years, and an increasing number of these patients are undergoing kidney transplantation. Patients with ESRD need not wait until they are receiving dialysis before being considered for a kidney transplant because early transplantation is associated with lower cost, better quality of life, and longer survival than patients on dialysis awaiting transplantation. The primary diseases leading to ESRD and transplant are diabetes, hypertension, glomerulonephritis, and polycystic kidney disease.

Diabetes and hypertension are the most likely causes of ESRD. A kidney transplant should return renal function to near normal (ie, a glomerular filtration rate between 50 and 80 mL/minute), improve quality of life, and correct the complications of ESRD such as anemia, hypocalcemia, and hyperphosphatemia, but not diabetes, hypertension, or hyperlipidemia.

The risk–benefit ratio must be considered when evaluating a patient for any organ transplantation. In general, kidney transplants

are performed to improve the quality of life and avoid the complications and outcomes associated with dialysis and renal failure. It is also more cost-effective than is dialysis. On the other hand, patients who are candidates for liver transplantation will die if the transplanted liver fails. Therefore, the criteria established for organ transplantation must be evaluated carefully before it is offered to any patient.

Donor and Recipient Matching

HLA matching of donor and recipient at the HLA-A, HLA-B, and HLA-DR loci is associated with better graft survival and longer half-lives for both living-related and deceased-donor kidney transplants. A six-antigen match is ideal, whereas a zero-antigen match is less favorable. The half-life refers to the time it takes for half of the grafts that survive the first year to fail. Organ half-lives are longer with living donors (average 15.9 years) compared with deceased donors (average 11.9 years).[25] For kidney recipients, the 1- and 3-year graft survival for a first deceased-donor transplant is >94% and 85%, respectively.[2] These positive factors may be offset, however, by ethnicity. Patient and graft survival after kidney transplantation is reduced in the African American population compared with others because of immunologic, medical, pharmacologic, pharmacokinetic, pharmacogenomic, and socioeconomic reasons. Along with African American race, other risk factors associated with decreased survival include advanced donor age, donation after cardiac death, recipient age younger than 15 years and older than 50 years, retransplantation, a high PRA, and delayed graft function. Recipients who fall into these categories are referred to as high-risk patients.

Because of a limited number of donors, the organ transplant community has devised methods to increase the donor pool by attempting to safely utilize marginal donors. In its most current form, this allocation system has incorporated the use of a predictive tool that determines the degree of marginality, termed the Kidney Donor Profile Index (KDPI). The KDPI uses donor information, including

age, height, weight, ethnicity, hypertension, diabetes, cause of death, serum creatinine (SCr), hepatitis C status, and circulatory death status to rate kidneys from 0% to 100%. Those in the higher percentile are more likely to fail, as compared to kidneys with lower KDPIs. In the current allocation system, donors with a high KDPI (≥85%) are reserved for older recipients who consent to receive these organs.[26]

CASE 34-1

Question 1: G.P. is a 52-year-old, 158.73-pound (72-kg) African American male with ESRD secondary to type 2 diabetes mellitus, hypertension, and hyperlipidemia. He has been undergoing hemodialysis three times a week for 4 years. Other medical problems include anemia, hypocalcemia, and hyperphosphatemia. G.P.'s medications include amlodipine 10 mg daily, ramipril 10 mg twice daily (bid), atorvastatin 20 mg daily, calcium carbonate two tablets with meals and at bedtime, sevelamer 800 mg with meals, glargine insulin 30 units daily, insulin aspart 8 units with meals, and erythropoietin 8000 IU IV three times weekly. He has been on the kidney transplant waiting list for 4 years. He is called by the transplant coordinator and admitted for a possible deceased-donor (formerly called cadaveric) kidney transplant. G.P. has the same blood type as the donor. His most recent calculated panel-reactive antibody (cPRA) is 99%. Cross-match is negative, and HLA typing reveals a three-antigen match (A1, A2, and B35) between donor and recipient. On admission to the hospital, his laboratory values are as follows:

Na^+, 141 mEq/L
Potassium (K^+), 4.7 mEq/L
Cl^-, 102 mEq/L
Bicarbonate (Hco_3), 23 mEq/L
Blood urea nitrogen (BUN), 44 mg/dL
SCr, 13.9 mg/dL
Calcium (Ca^{2+}), 7.8 mEq/L
Phosphorus, 6.2 mg/dL
Glucose, 225 mg/dL
Albumin, 3.5 g/dL
White blood cell (WBC) count, 8.4 cells/mL
Hemoglobin (Hgb), 10.8 g/dL
Hematocrit (Hct), 32%

His serology is negative for HIV, HbsAg, hepatitis C, and cytomegalovirus (CMV), and is positive for antibody to the surface antigen of hepatitis B (anti-Hbs) and positive for EBV antibody.

Before the transplant procedure, G.P. receives MMF 1 g orally (PO) and cefazolin 1 g IV. During surgery, just before reperfusion of his new kidney, he received methylprednisolone 500 mg IV and rATG 1.5 mg/kg IV. He is also given furosemide 100 mg IV after the kidney has been transplanted. Methylprednisolone 250 mg IV is to be given on the day after surgery. The methylprednisolone dose is to be decreased to 100 mg IV on the second postoperative day for one dose. Prednisone 60 mg (1 mg/kg/day) PO is to be given on the subsequent day for one dose and tapered by 0.3 mg/kg/day to 20 mg daily by day 7 after surgery and further tapered to 5 mg daily within a month. Tacrolimus nasogastric (NG) or PO 0.1 mg/kg/day or 3 mg every 12 hours will be started within 12 hours of surgery if renal function improves. The dosage will be adjusted according to tacrolimus whole-blood trough concentrations. MMF will be continued at 1 g PO bid. He will also continue with antibody induction with rATG 100 mg IV on days 1, 2, and 3 after surgery.

Why is G.P. being treated with this immunosuppressive regimen?

Immunosuppressive Therapy

The major goal of immunosuppressive therapy is to prevent rejection and balancing the risk of infection from overimmunosuppression with minimal adverse effects and to ensure long-term patient and graft survival as well as improve quality of life. Overall acute rejection rates are <10% during the first year after kidney transplantation. Most of these episodes respond to acute antirejection therapy.

No consensus exists on the best induction and maintenance immunosuppressive regimen, and selection primarily depends on the program and the specific organ to be transplanted. Although studies have evaluated the various regimens, comparisons are influenced by differences in donor selection and condition, organ preservation and procurement, organ ischemic (cold and warm) time, recipient's pretransplant conditions, comorbid and high-risk or low-risk immunologic factors, surgical procedures, postoperative management and monitoring, and length of follow-up. Another important consideration is that many of these agents show significant effects during the first year, but fail to show a significant impact on long-term effects such as chronic rejection and graft survival.[3] The choice of a particular regimen generally depends on the risk factors present at the time of transplantation. During this early time period,

because the risk of acute rejection is highest in the first few weeks to months, the number of agents, doses, and target drug concentrations are higher than later on after transplantation.

Most initial combination immunosuppressive drug regimens rely on two to three maintenance agents, although in some cases monotherapy has been used, depending on organ type and risk factors. Common combination regimens include a CNI (tacrolimus and cyclosporine) with MPA or sirolimus/everolimus, and prednisone. The most common regimen is tacrolimus, mycophenolate, and prednisone along with short-term administration of a monoclonal antibody (alemtuzumab, basiliximab) or a polyclonal antibody (rATG). Regimens that avoid steroids and CNIs, or use a short course, in the early transplantation period, or are withdrawn some time (usually several months) after transplantation in an attempt to avoid the long-term side effects of these agents, are another option. In HLA-identical, living-related kidney transplants, dual therapy (eg, tacrolimus or mycophenolate, and prednisone) gives excellent results; however, acute rejection may still occur, as with other regimens. Combination therapy is used to take advantage of different mechanisms of action and to reduce drug toxicity by using sequential therapy and smaller doses of multiple agents rather than larger doses of any agent used alone. These multidrug combinations can lead, however, to increased drug costs, compliance issues, a higher incidence of infection and malignancy, and difficulty in assessing and managing adverse effects.[11]

Because G.P. is receiving a deceased-donor transplant and is considered an immunologically high-risk recipient (he is African American with a high PRA), an antibody plus several maintenance agents would be appropriate. He is started on tacrolimus, mycophenolate, and prednisone. This combination, based on the literature, is the most effective.[16]

Depending on the transplant center, drug dosages are reduced over time. In G.P., tacrolimus doses are adjusted based on target trough concentration ranges, which are reduced over time as well. MMF may be discontinued later. Although the discontinuation of a drug may reduce adverse effects, it must be counterbalanced

against the risk of rejection and potential graft loss. Monotherapy, generally with tacrolimus or cyclosporine, may be achieved in low-risk kidney and liver transplant recipients at some time after transplantation. Most patients require lifetime immunosuppression, and nonadherence in the setting of reduced immunosuppression may predispose the recipient to acute and, subsequently, chronic rejection.

Case 34-1, Question 2: What is induction therapy, and which is the preferred agent for G.P.?

Induction therapy at the time of transplantation refers to the use of an antibody, typically at time of transplant and during the first few days after transplant. rATG, alemtuzumab, and basiliximab are induction agents. Acute rejection and delayed graft function (need for dialysis during the first 7 days after transplant) can occur in the early transplant period. Both of these have a negative impact on graft survival. Antibody induction reduces the incidence of early acute rejection, delayed graft function, and has typically been used in immunologically high-risk patients. They allow the use of lower doses, or slower introduction or sequential use of maintenance immunosuppression. They are a major component of early therapy in high-risk patients. Their use in patients at low-to-moderate risk has increased, often as a means of reducing or avoiding the use of CNI and steroids. Currently, ~80% of all kidney transplants receive induction therapy, with rATG making up about 60%.[2,27]

rATG was chosen as induction because G.P. is African American and is at higher risk for acute rejection. In general, rATG appears to be more effective than is equine antithymocyte globulin (horse ATG) and is the antibody of choice. rATG, when used for induction, results in reduced acute rejection, improved survival, and manageable side effect profile. In kidney transplants, this agent is effective in reducing acute rejection and improving short- and long-term graft survival compared to horse ATG and especially in high-risk patients.[27]

ANTITHYMOCYTE GLOBULINS

Dosing and administration

Case 34-1, Question 3: How would rATG be administered and monitored in G.P.?

Both rATG and horse ATG are effective as induction therapy, and rATG was recently FDA approved for induction. Both rATG and horse ATG are effective treatments for severe acute rejection. The dose of rATG ranges from 1 to 6 mg/kg but is typically 1.5 mg/kg/day for four to six doses, and the dose of horse ATG is 10 to 20 mg/kg/day but is typically 15 mg/kg/day. These drugs can be diluted in 0.9% NaCl for injection and administered for 4 to 6 hours. Both are usually infused into a high-flow central vein to reduce pain, erythema, and phlebitis at the injection site. Peripheral administration has been used successfully with rATG.[28] Skin testing is recommended before horse ATG use, but not before rATG. Patients previously sensitized to horse serum are at risk for an anaphylactoid reaction, but the prevalence of anaphylaxis has diminished with improved purification of this product. Patients with a positive pretherapy skin test could undergo desensitization, but alternatives, such as rATG, may be substituted.[19]

Dose regimen and duration of therapy

The first dose of rATG is usually given intraoperatively. Intraoperative administration of rATG reduces the incidence and severity of delayed graft function as compared with postoperative administration. Duration of therapy with rATG or horse ATG is variable (3–10 days), but, more recently, shorter courses have been employed for induction therapy. Protocols used to treat rejection commonly use a 7- to 10-day course of therapy. In patients such as G.P., a four-dose prophylactic regimen has been shown to be as effective as a longer regimen.[19]

Adverse effects

A number of adverse effects have been related to the use of rATG or horse ATG. Local phlebitis and pain usually can occur. Anaphylaxis is rare. Chills and fever, erythema, rash, hives, pruritus, headache, leukopenia, and thrombocytopenia are commonly encountered. Fever, chills, hypotension, nausea, and vomiting may be caused by the release of cytokines, such as TNF and IL-6, from lysed lymphocytes. These symptoms can be minimized by premedication with acetaminophen and diphenhydramine before each dose.

Methylprednisolone, up to 500 mg, is given 1 hour before rATG typically for the first one to two doses to minimize infusion reactions. Opportunistic viral (CMV and EBV) and fungal infections are the predominant delayed side effects. Susceptibility to malignancy, such as PTLD, is also a concern. Because of the increased risk of CMV infection, patients are often given oral valganciclovir or IV ganciclovir during therapy and then oral valganciclovir, which is continued up to several months after induction.[19]

Monitoring

Vital signs should be monitored hourly during infusion, and WBC and platelet counts should be monitored daily. If the patient's WBC count drops to <3000 cells/mL or if the platelet count drops to <75,000 cells/mL, the dose of drug is decreased by 50% or held entirely for WBC <2000 cells/mL or platelets <50,000 cells/mL until the counts return to desired levels. Patients who receive rATG for the treatment of acute rejection may have doses held or decreased based on the degree of leukopenia and thrombocytopenia; however, the need for and response to therapy would be carefully considered in this decision.

Dosages also can be adjusted based on absolute lymphocyte counts or lymphocyte subsets as a way of maximizing efficacy and minimizing infectious complications. For example, the dose can be adjusted using a target absolute T-lymphocyte count (CD2 or CD3) of <25 to 50 cells/mL, particularly if used for treatment of acute rejection. It is less common to adjust doses based on CD2 of CD3 counts when used for induction as in G.P.'s case. Using CD2 and

CD3 counts results in a lower dose, less frequent dosing (eg, every other day instead of daily), lower costs, and a lower rate of viral infection. rATG produces a more profound and longer duration of effect on lymphocytes than does horse ATG; however, it does not result in a greater risk of infection and malignancy, although still a concern.[19]

Case 34-1, Question 4: Could basiliximab or alemtuzumab be used as an alternative to rATG?

Basiliximab is approved for use as induction therapy in kidney transplantation; however, it is also used in other organ transplant recipients. It is administered in combination with cyclosporine or tacrolimus and steroids with or without MMF or sirolimus. It has a similar safety profile compared to placebo and better safety profile than does rATG. It has a limited role in high-risk populations such as G.P., or patients with high PRA or long ischemic times, delayed graft function, or patients who have received a previous transplant. In these patients, induction with polyclonal antibodies is used in most centers. The large initial trials with this IL-2R antibody included very few high-risk patients or excluded them altogether. More potent agents, such as rATG, are still preferred in high-risk patients. A prospective study comparing rATG with basiliximab in high-risk kidney transplants demonstrated that acute rejection rates were lower in patients receiving rATG.[21] Basiliximab is often used for low-risk to intermediate-risk patients and in patients where CNI minimization or steroid avoidance is implemented.

Alemtuzumab is another alternative and is used by some centers for low- and intermediate- to high-risk patients. It has been shown to be no less effective than is rATG in high-risk patients and more effective in reducing acute rejection than is basiliximab in low-risk patients.[29] Adverse effects include frequent and prolonged neutropenia, lymphopenia, thrombocytopenia, anemia, nausea, vomiting, and diarrhea. Infusion reactions can occur although it is given, as a single dose and under anesthesia, in the operating room

during the transplant. As with rATG, there is an increased risk of opportunistic infections and malignancy. Rituximab has also been studied as potential induction therapy in nonsensitized or ABO-compatible transplants and found not to be very effective in this population, unlike that in ABO-incompatible recipients.[23]

Postoperative Course and Delayed Graft Function

Case 34-1, Question 5: G.P. is admitted to the transplant ward for initial posttransplantation management. His urine output during the next 3 hours has decreased from 300 to 40 mL/hour. He is receiving IV fluids at a rate equivalent to his urine output. He received 3 L of fluids in the operating room. His blood pressure (BP) is 140/83 mm Hg, heart rate is 87 beats/minute, and temperature is 98.42 °F (36.9 °C); he has no signs of dehydration. His BUN is 56 mg/dL and his SCr is 12.8 mg/dL. Another dose of furosemide 100 mg IV increased his urine output to 140 mL/hour, but his urine output returned to <40 mL/hour in a few hours. Fluids and IV furosemide were given again with similar results. Renal ultrasound indicates no urine leaks, fluid collections, or ureteral obstruction. A diethylenetriamine penta-acetic acid renal scan result indicates good perfusion, but decreased accumulation and clearance. During the next 2 days, G.P.'s BP is 150/93 mm Hg, weight is 167.55 pounds (76 kg; 8.82 pounds [4 kg] higher than in pretransplantation), urine output has fallen to <200 mL/day, and relevant laboratory values are as follows:

BUN, 85 mg/dL
SCr, 13.2 mg/dL
K^+, 5.8 mEq/L

The decision is made to institute hemodialysis. What has happened to G.P.'s renal function? What is the most likely diagnosis?

The initial renal function after kidney transplantation can reflect excellent, moderate, or delayed graft function. In recipients with excellent function, a good diuresis begins immediately and continues; the SCr rapidly declines to <2.5 mg/dL within the first few days of transplantation. Most living-related transplants and between 30% and 50% of deceased-donor transplants generally experience this pattern. Kidney transplant recipients with moderate or slow graft

function usually experience a slower decline in SCr, which stabilizes within the first week. Recipients with delayed graft function usually have anuria or oliguria, require dialysis in the early period, and take days to weeks to recover. Delayed graft function is most common in recipients of organs from deceased transplant donors, occurring in between 10% and 50% of cases.[30] The diagnosis of delayed graft function is based on clinical, laboratory, and diagnostic criteria that may vary among centers. Traditionally, delayed graft function has been defined as the need for dialysis within the first 7 days posttransplant. *Slow graft function* is another term that has been used to describe a lag in improvement and does not involve dialysis. Delayed graft function is influenced by the donor (age, condition of organ, prolonged ischemic time), intraoperative conditions (hypotension, fluid imbalance, ischemia, or reperfusion injury), and recipient characteristics such as prior transplantation, postoperative hypovolemia or hypotension, and use of nephrotoxic drugs.[30]

In G.P., poor urine output in the first hours after transplantation and subsequent oliguria, the exclusion of other causes of acute tubular necrosis, the results of the renal scan, the lack of improvement in BUN and SCr, and the need for dialysis are indicative of delayed graft function. Delayed graft function reduces kidney long-term graft survival, increases the risk of acute rejection, and influences a patient's early management by requiring dialysis, increasing the length of hospital stay, and increasing the costs of therapy. It also may make the assessment of acute rejection more difficult because the patient already has impaired renal function. In delayed graft function, a renal biopsy may be obtained if no improvement in SCr is seen by day 7 unless there are risk factors present to indicate that delayed graft function was expected, such as donation after cardiac death or prolonged cold ischemia time.[30]

Case 34-1, Question 6: What adjustments should be made in G.P.'s immunosuppressive regimen at this time? Are there any therapies that can prevent or treat delayed graft function?

The adverse renal effects of CNIs may contribute to the onset of delayed graft function as well as prolong its duration. Therefore, tacrolimus may be discontinued temporarily if appropriate T-cell depleting induction was provided or its dose significantly reduced. Because of this effect, some protocols do not include CNIs, use them only in low doses for the first week, or delay their use until kidney function improves. These protocols often include induction therapy and provide more intense immunosuppression early after transplantation when the risk of delayed graft function and acute rejection is highest. rATG is commonly used in patients with delayed graft function because it may shorten the duration and the need for dialysis when compared with the CNI. Another potential option would be to use basiliximab, which has been shown to reduce acute rejection rates and extend the time to first rejection. One concern with the use of basiliximab is that a CNI may be required sooner than with rATG because this agent does not provide as long a duration of protection from rejection. One should also confirm that MPA doses be maintained and continue prednisone taper. In G.P., rATG would be administered for 5 to 10 days, depending on improvement in his SCr and urine output, along with his current regimen of prednisone and mycophenolate. A typical dose would be 1.5 mg/kg/day or every other day, depending on his $CD3^+$ level and WBC and platelet counts.

Recent studies have focused on developing therapies that prevent or reverse delayed graft function, with mixed results. There are several therapies being tested within this context, which include therapies to inhibit p53 (I5NP), complement (eculizumab), TLR2 (OPN-305), and hepatocyte growth factor (BB3). Other therapies that have been tested include alteplase, etanercept, ischemic preconditioning, erythropoietin, and dopamine, with the latter showing reduced dialysis requirements but none demonstrating improved graft survival. Because this is a common and important clinical dilemma, it continues to be a significant area of research and discovery.[30]

Rejection

Case 34-1, Question 7: G.P. was started on rATG 1.5 mg/kg as a 6-hour IV infusion on days 0, 1, 2, and 3 for induction, but because of his delayed graft function, he received an additional dose on day 5. He received this along with his prednisone taper and MMF. Tacrolimus PO 3 mg bid was initiated on day 2 after transplant. G.P.'s urine output has increased gradually to 1600 mL/day after stopping rATG. His weight has decreased to 160.94 pounds (73 kg), and the following is recorded:

BP, 142/84 mm Hg
Heart rate, 82 beats/minute
Temperature, 98.06 °F (36.7 °C)
BUN, 23 mg/dL
SCr, 3.2 mg/dL
K^+, 4.6 mEq/L

Sixty days after stopping rATG, he is on a regular diet and taking all oral medications. His current medications include MMF 750 mg bid, prednisone 5 mg daily, tacrolimus 5 mg bid, ranitidine 150 mg at bedtime, dioctyl sodium sulfosuccinate 100 mg bid, amlodipine 10 mg daily, metoprolol 50 mg PO bid, glargine insulin 40 IU daily, insulin aspart 10 IU with meals, valganciclovir 450 mg daily, and trimethoprim–sulfamethoxazole (TMP-SMX) double-strength, one tablet on Mondays, Wednesdays, and Fridays. His weight increased to 166.67 pounds (75.6 kg); and note the following:

BP, 160/94 mm Hg
Heart rate, 98 beats/minute
Temperature, 99.68 °F (37.6 °C)
BUN, 30 mg/dL
SCr, 3.4 mg/dL
K^+, 4.8 mEq/L
Trough whole-blood tacrolimus concentration, 5 ng/mL (target range 8–10 ng/mL)
Urine output decreased during the past 24 hours to 750 mL.

He feels tired and has a decreased appetite, but his fluid intake has been adequate during the past day. What evidence is consistent with rejection in G.P.?

Although significant improvements in reduction in acute rejection and improved graft survival have occurred over the past decade, certain types of acute rejection and chronic rejection continue to be a major reason for graft loss in kidney transplants. Rejection episodes

can be categorized as cellular and/or antibody mediated, hyperacute, accelerated, acute, or chronic. Kidney biopsy is considered the gold standard for making the diagnosis of rejection after kidney transplant. Approved criteria are used to classify and grade the type and severity of rejection.

HYPERACUTE REJECTION

Hyperacute rejection, which occurs within minutes to hours of transplantation of the allograft, is the result of preformed cytotoxic antibodies against donor-specific class I antigens. This type of rejection is rare because of ABO matching and improved HLA typing before transplant, but it remains associated with a poor prognosis. Clinically, the patient presents with anuria, hyperkalemia, hypertension, metabolic acidosis, pulmonary edema, and, in some cases, disseminated intravascular coagulopathy. A perfusion scan of the kidney would indicate no uptake. If other causes of anuria are excluded and this diagnosis is made, then the transplanted kidney must be removed.

ACCELERATED REJECTION

Accelerated rejection usually occurs within a few days of organ transplantation. This is a result of prior sensitization to antigens that are similar to those of the donor and newly developed donor-specific antibodies (DSAs) to the donor graft. Accelerated rejections of transplanted kidneys occur primarily in recipients who have had prior transplantation, multiple pregnancies, or blood transfusions. These patients usually maintain good renal function for a few days before developing acute renal failure. Accelerated organ rejections generally are more resistant to pharmacologic therapy.

ACUTE REJECTION

Acute rejection is the most common type of kidney rejection in transplant recipients and most episodes respond to therapy. Most episodes of acute rejection are T-cell mediated (cellular), although some can be B-cell (antibody or humoral) mediated, and others are a

combination of both types. Acute rejection of a transplanted kidney is associated with reduced half-life and survival of both living-donor and deceased-donor transplants. Acute rejection often occurs in the first week to months after kidney transplantation. The prophylactic use of antibody induction may, however, delay the onset for several weeks, as illustrated by G.P.'s case. If acute rejection occurs, its onset is generally within the first year, with most episodes occurring within the first 60 days of transplantation. Acute rejection can, however, also occur at any time after transplant and can be a result of patient nonadherence (also called noncompliance) to medications and monitoring. The clinical presentation of patients with acute rejection of a kidney ranges from an asymptomatic patient with mild renal dysfunction as indicated by an elevated SCr, which is common, to patients presenting with a flulike illness, hypertension, and acute oliguric renal failure. G.P. presents with subjective reports of malaise or tiredness and lack of appetite. Such nonspecific symptoms occur often in patients with rejection and can be accompanied by myalgias. Objectively, G.P.'s increased weight, hypertension, decreased urine output, and increase in SCr are consistent with acute kidney rejection. In addition, the tacrolimus trough concentration is low, suggesting inadequate immunosuppression. Acute rejection of a transplanted kidney must be distinguished from CNI nephrotoxicity, and infections (eg, pyelonephritis, CMV, polyomavirus BK) also must be ruled out. Although the clinical evidence in G.P. probably represents an acute cellular rejection, a kidney biopsy is the gold standard for establishing the diagnosis. Biopsy results usually are available within 6 to 8 hours. If there is acute rejection, the biopsy will show an interstitial infiltration of mononuclear cells with tubulitis or intimal arteritis in more severe cases. The severity of acute rejection will be classified and graded according to standardized pathologic criteria and is important in determining treatment. Less severe grades will receive high-dose steroids, whereas more severe grades will often receive rATG.[6]

ANTIBODY-MEDIATED REJECTION

Antibody-mediated rejection (AMR; previously called humoral) can be either acute or chronic rejection mediated by antibodies. Over the past several years, there has been an increased recognition of the importance and detrimental impact of this type of rejection on graft outcomes. AMR is ≤10% of acute rejection episodes but graft loss is near 30%. Histologically, criteria for AMR differ from that for acute cellular rejection (ACR). Presence of positive staining for the complement component C4d indicates AMR, although this type of rejection can also occur with negative C4d. Many patients either before transplant or after have DSAs that can occur hours to years after transplantation. AMR often is associated with hemodynamic compromise and is more resistant to drug therapy.[31]

CHRONIC REJECTION

Chronic rejection is a major cause of long-term kidney graft loss after the first year. It can be either a cellular- or an antibody-mediated graft loss. It occurs slowly in most cases over several years. The characteristic signs of chronic rejection are hypertension, proteinuria, and a progressive decline in renal function leading to renal failure. Because no specific treatment exists, therapy is supportive (eg, dialysis in the case of kidney transplantation). Ultimately, retransplantation is needed. Data suggest that some patients may benefit from some of the newer agents, such as mycophenolate and sirolimus, that are considered non-nephrotoxic, but this requires further study. The diagnosis of chronic rejection is determined by clinical signs and biopsy findings indicative of fibrosis of hollow structures and vessels within the graft. The chronic rejection of a kidney must be distinguished from chronic CNI nephrotoxicity, chronic infection, recurrence of the original kidney disease, and other causes of CAI, and further causes.

CHRONIC ALLOGRAFT INJURY

Chronic allograft injury (CAI) is a term that has been used, generally, as a diagnosis of exclusion that indicates a slow deterioration in renal function over months to years after kidney transplant, where

the exact cause is unknown and results in graft loss. Immunologic and nonimmunologic mechanisms play a role in CAI. Immunologic factors that increase the likelihood of CAI include a history of acute rejection, inadequate immunosuppression, nonadherence to immunosuppressive therapy, and previous infection, such as CMV. Nonimmunologic factors are donor related (age, hypertension, diabetes), increased ischemic times, recipient hypertension, hyperlipidemia, CNI nephrotoxicity, and elevated body mass index (BMI). Another term, *interstitial fibrosis/tubular atrophy (IF/TA)* is used to describe this deterioration. It is often considered irreversible and unaffected by increased immunosuppressive therapy.[32]

Acute Rejection Treatment

Case 34-1, Question 8: A biopsy of G.P.'s transplanted kidney shows grade 1A, moderate acute cellular rejection. G.P. is started on methylprednisolone 500 mg daily IV for three doses. His next level of baseline immunosuppression is increased by increasing his MPA and TAC doses as well as continuing his prednisone dose. His maintenance oral prednisone is discontinued and MPA and TAC doses will be increased. Why is methylprednisolone therapy of G.P.'s first acute episode of rejection appropriate?

High-dose or "pulse" IV methylprednisolone, IV rATG, and IV and oral prednisone are options to treat acute rejection in all types of solid organ transplants. A high-dose corticosteroid (usually IV methylprednisolone) is considered first-line therapy because it works very quickly in decreasing lymphocyte responsiveness, is easy to administer, and reverses at least 75% of acute rejection episodes. rATG is usually reserved for steroid-resistant rejection or more severe grades of rejection. IVIG has also been used as an alternative for resistant rejection. The ideal corticosteroid dosage, route, and regimen are unknown. Corticosteroid protocols vary among transplant programs. IV methylprednisolone and oral prednisone are equally effective in reversing rejection, but oral corticosteroids are given for a longer period and have been associated with a higher incidence of adverse effects. Even though

50 mg of IV methylprednisolone has a lymphocyte suppressive effect similar to that of a 1-g IV dose, most programs use methylprednisolone 250 to 1000 mg (most commonly 500 mg) IV every day for three doses and may adjust the prerejection oral prednisone regimen for a period of time. An example of an oral prednisone regimen is 100 to 200 mg/day tapered for 1 to 3 weeks to baseline maintenance dose. For G.P., IV methylprednisolone is appropriate because corticosteroids are considered first-line therapy for acute rejection of a transplanted kidney, and first rejection episodes (such as G.P.'s) are very responsive. In addition, G.P. has received a prophylactic course of rATG recently and additional doses should be avoided, if possible. rATG is associated with a higher risk of CMV infection and malignancy; it is more difficult to administer, requires more intensive monitoring, is more expensive, and usually is held in reserve for corticosteroid-resistant or more severe forms of rejection.

Nevertheless, high-dose corticosteroids are not without risk. They increase the risk of infection, and long-term therapy can induce ocular, bone, cardiovascular, and endocrine abnormalities. Although G.P. will be receiving high-dose IV methylprednisolone for only 3 days, because he is diabetic, he should be monitored for hyperglycemia, and a change in his insulin requirements should be anticipated because corticosteroids can alter glucose metabolism. Short-course methylprednisolone also can mask signs of infection (eg, fever, changes in WBC counts, pain associated with inflammation) and delay the diagnosis. Insomnia, nervousness, euphoria, mood shifts, acute psychosis, and mania also can occur with short-term corticosteroid use. If the methylprednisolone regimen is effective in reversing G.P.'s acute rejection, his SCr concentration should decline within 2 to 5 days and his urine output should increase.

In addition, it would be appropriate to increase G.P.'s tacrolimus dosage to 7 mg twice a day because the concentration is low (5 ng/mL) and low trough has been associated with a higher risk of acute rejection. Because small changes in tacrolimus dose can increase levels disproportionately, a trough whole-blood

concentration should be reevaluated in 2 to 3 days. The MMF dose could be increased to 1 g bid and up to 1.5 g bid, because this dose in combination with a CNI has reduced acute rejection in African American patients, particularly if the patient was on cyclosporine therapy. There are limited data supporting the increase of the MMF dose beyond 1 g bid with tacrolimus-based regimens.[33,34] If G.P. had been on cyclosporine, another option would be to change cyclosporine to tacrolimus, which has been shown to reduce future episodes of acute rejection. Another important aspect for prevention of future rejection would be to assess G.P.'s adherence to, and understanding of, his medication regimen. Nonadherence is a major cause of acute rejection and graft loss.[35]

CASE 34-1, QUESTION 9: Six months later, G.P. is noted to have another elevation in SCr. In addition, DSAs are also detected in the blood. Did kidney biopsy indicate it as AMR? How would this type of acute rejection be treated?

AMR is more difficult to treat, and approaches vary. It may not respond to steroids and rATG, which are used initially. The most common treatment is plasmapheresis or immunoadsorption. These modalities are used to remove circulating antibodies and low- or high-dose IVIG for residual antibody inhibition, given after these procedures. Because of increased recognition and diagnosis, and resistance to treatment, a number of approaches are being used and investigated. Along with plasmapheresis and IVIG, rituximab may be used to treat acute AMR. Other agents, not currently approved for transplantation, are being utilized and studied as treatment, including bortezomib, which causes plasma cell apoptosis/depletion, and eculizumab, which is an anti-C5 antibody. Given the sparsity of large-scale, randomized trials assessing which agents to utilize to treat AMR, there is no consensus regarding which should be considered first-line therapy to treat AMR, although most clinicians do utilize plasmapheresis with IVIG as a starting point, and add on the aforementioned therapies at various stages or severities of AMR.[36]

Calcineurin Inhibitor–Induced Nephrotoxicity

CASE 34-2

Question 1: C.C. is a 60-year-old male who received a deceased-donor kidney transplant 3 years ago. His SCr at 1 year after transplant was 1.5 mg/dL; at 2 years, it was 1.7 mg/dL; now it is 1.9 mg/dL. He says he feels fine. His BP is controlled, and urinalysis is negative for protein. A kidney biopsy conducted at this time indicates that he has no signs of acute or chronic rejection but has evidence of CNI nephrotoxicity. His current regimen is cyclosporine 275 mg bid, MMF 500 mg bid, and prednisone 5 mg daily. His current labs show the following:

Cyclosporine blood trough, 220 ng/mL (target 100–150 ng/mL)
K^+, 5.5 mEq/mL
Mg, 2.3 mg/dL
Uric acid, 8.0 mg/dL

Why does C.C. have CNI nephrotoxicity?

CNI nephrotoxicity is one of the most common adverse effects and occurs to some degree in all patients. The rise in the SCr concentration is more gradual than, and not as high as, that seen with rejection. CNI concentrations may be elevated, although some patients may experience CNI nephrotoxicity even with levels below or within the targeted therapeutic range. Two forms of CNI nephrotoxicity have been identified: functional or acute renal dysfunction and chronic nephrotoxicity.[37]

Acute CNI nephrotoxicity is more likely to occur in the first months after transplantation and associated with high CNI doses and levels. Functional renal dysfunction or acute nephrotoxicity, the most common form of renal dysfunction, is characterized by rapid reversal when the CNI dose is held or reduced. This syndrome typically is not associated with histopathologic abnormalities. Repeated episodes of transient acute renal dysfunction can result in protracted acute renal dysfunction. Recovery of renal function after repeated episodes may not be complete even if the CNI is withdrawn. Protracted acute renal dysfunction can lead to direct tubular toxicity and can be associated

with the development of thrombosis of glomerular arterioles or diffuse IF.

Chronic nephrotoxicity is associated with proteinuria and tubular dysfunction. Renal biopsies in patients who had allograft and have chronic CNI-related nephropathy show tubulointerstitial abnormalities, sometimes with focal glomerular sclerosis. These findings are considered nonspecific. Recently, the role of CNI chronic nephrotoxicity in the development of irreversible chronic renal dysfunction has been challenged and thought to be overdiagnosed in many patients. However, long-term use can result in chronic nephrotoxicity, is usually seen after 6 months of therapy, and may be irreversible. In this situation, renal function progressively declines to a point that dialysis or retransplant is required. The pathophysiology of cyclosporine- or tacrolimus-induced transient acute renal failure is not understood completely but seems to be related to its effects on renal vessels. For example, CNI can induce glomerular hypoperfusion secondary to vasoconstriction of the afferent glomerular arterioles, thereby reducing glomerular filtration. One possible explanation for these effects is that cyclosporine alters the balance of prostacyclin and thromboxane A_2 in renal cortical tissue. Increased thromboxane A_2 results in renal vasoconstriction. Endothelin release from renal vascular cells stimulated by CNI also may contribute to this acute effect through its potent vasoconstrictive properties. Activation of the renin–angiotensin–aldosterone system may also play a significant role. CNI also can cause a reversible decrease in tubular function. The alterations in tubular function reduce magnesium reabsorption and decrease potassium and uric acid secretion. This may be a result of direct tubular toxicity and possibly the result of thromboxane A_2 stimulation of platelet activation and aggregation.

C.C.’s rise in SCr in conjunction with an elevated cyclosporine level suggests acute cyclosporine toxicity as the most likely cause of his findings. In this case, the total cyclosporine dose should be lowered by ~25% to 225 mg twice a day, to keep the level in target range, and C.C. should be monitored closely for resolution of any

symptoms and decrease in SCr or worsening if rejection results from lowering the dose. His elevated potassium and uric acid and low magnesium should correct themselves with this dose reduction if it is acute CNI toxicity. If the nephrotoxicity is caused by cyclosporine, a decrease in the SCr may be evident when the cyclosporine dose is reduced. If no such reduction occurs or if the SCr continues to increase, then other nonimmunologic or immunologic causes should be considered and CNI will also need to be substituted with an agent such as sirolimus, everolimus, or belatacept.

Calcineurin Inhibitor Avoidance, Withdrawal/Conversion, or Minimization

Case 34-2, Question 2: Would it be appropriate to withdraw cyclosporine in C.C.? If attempted, how could this be accomplished?

Cyclosporine and tacrolimus are associated with a number of metabolic, cardiovascular, neurologic, and cosmetic side effects, but the most concerning is nephrotoxicity, which is a contributor to graft loss. The potential benefit of withdrawing cyclosporine would be to reduce toxicity, but this has to be weighed against the risk of rejection, graft loss, and toxicities of replacement agents.

Concern for chronic nephrotoxicity, as well as other long-term side effects, has led to the development of cyclosporine or tacrolimus minimization, withdrawal or substitution/conversion protocols, using agents such as mycophenolate or sirolimus, everolimus, and belatacept, or protocols using low doses of cyclosporine or tacrolimus.

Antibody induction, sirolimus, everolimus, mycophenolate, and belatacept, which are not associated with nephrotoxicity, have been evaluated in combination protocols that attempt to avoid, minimize, or withdraw CNI. Protocols completely avoiding CNIs usually contain combinations of these agents. Studies, which were usually done in low-risk populations, observed lower SCr levels and fewer CNI-

induced toxicities, but were associated with higher rates of acute rejection, especially when CNI is not used at all. Other trials that compared combinations of rATG, alemtuzumab, or basiliximab, sirolimus, everolimus, mycophenolate, and steroids with either cyclosporine or tacrolimus withdrawal, or minimization protocols have shown equal effectiveness compared to standard therapy.[38,39]

In the case of early cyclosporine withdrawal, there is a 10% to 20% increased risk of acute rejection, but no change in graft survival. Protocols that withdraw the CNI or at least reduce the dose to a minimal level are used. Many attempts are within the first 3 to 12 months of transplantation in the hope that the nephrotoxic effects can be reversed before significant chronic damage occurs. These approaches add mycophenolate, sirolimus, or both as the CNI is withdrawn or reduced in dose, but they have been primarily tested in low-risk patients. Data with sirolimus suggest that patients without proteinuria and an estimated glomerular filtration rate (eGFR) >40 mL/minute in the first year had better renal function. Whether this applies to other agents remains to be determined. Usually, when sirolimus is added to the CNI regimen, the CNI dose is reduced by 50% initially and in some cases slowly withdrawn altogether during several weeks to months. Improvement in SCr may be seen initially, which may be attributed to the diminution of the CNI vasoconstrictive effects.

CNI minimization or withdrawal may not reverse the nephrotoxicity observed in C.C.'s biopsy, but it may slow the rate of deterioration of his renal function. Because C.C. is currently receiving mycophenolate, one approach would be to continue to reduce his cyclosporine, increase his mycophenolate, and maintain steroids. Another approach would be to replace the mycophenolate with sirolimus/everolimus because he has no proteinuria and his eGFR is >40 mL/minute, maintain steroids, and reduce or withdraw slowly the cyclosporine. Belatacept could also be used as replacement for cyclosporine while continuing mycophenolate and steroids. Some studies indicate better eGFR, lower incidence of new-onset diabetes after transplant, lower BP, lower cholesterol, but no difference in survival compared to CNI.[38] The best regimen for someone such as

C.C. has not been established, because the long-term consequences of these changes are not known. If this approach is attempted, C.C. should be watched carefully for acute rejection, and side effects of these agents, which some patients do not tolerate, and infections should be closely monitored. In addition, BP control as well as control of hyperlipidemia and hyperglycemia could improve with reduction or withdrawal of cyclosporine, depending on the agent used, and could also be important in minimizing renal injury.

Steroid Avoidance or Withdrawal

CASE 34-3

Question 1: D.T., a 65-year-old Caucasian female, will receive a deceased-donor kidney transplant today. She has a negative cross-match to this donor, and her previous cPRA was <10%. She will be given alemtuzumab 30 mg IV × 1 and methylprednisolone 500 mg IV × 1, intraoperatively. After transplant, she will be started on tacrolimus 0.05 mg/kg bid, adjusted to trough levels of 8 to 10 ng/mL for the first 3 months, along with MMF 750 mg bid. Methylprednisolone IV will be given as 250 mg IV on postoperative day 1, 125 mg IV on postoperative days 2 and 3, and no maintenance steroids thereafter.

Is D.T. a good candidate for steroid avoidance or withdrawal?

Another important issue after kidney transplantation is the role of short-term and long-term steroid use. Most transplant protocols incorporate steroid therapy, although ~30% of transplant centers use steroids only in the early postoperative period.[2] The concept of either avoiding or discontinuing corticosteroids is appealing because they cause significant adverse effects such as diabetes, cataracts, infection, hypertension, hyperlipidemia, osteoporosis, avascular necrosis, and psychiatric, neurologic, and cosmetic effects. Steroid withdrawal or avoidance, however, may increase the risk of acute rejection, compromise long-term graft function, and necessitate higher doses of the other immunosuppressives. Steroid avoidance is defined as either no steroid use or steroid use only for the first few days after transplant. Short-term studies, generally in low-risk patients, suggest that no adverse impact on short-term graft survival

exists and no need is seen for higher doses of other immunosuppressives when corticosteroids are not included in maintenance regimens. These protocols have included regimens such as using induction agents, alemtuzumab, basiliximab, or rATG along with tacrolimus and cyclosporine, mycophenolate, sirolimus, or everolimus.[40]

Steroid withdrawal is the complete discontinuation of prednisone, typically a few months posttransplant. In the era of cyclosporine (Sandimmune) and azathioprine-based regimens, withdrawal was associated with a high rate of acute rejection and late graft loss. With the introduction of newer agents, steroid avoidance or withdrawal has been viewed with renewed interest. Steroid withdrawal has been successful in at least 50% of kidney transplant recipients, resulting in reductions in BP and lipid levels. Some protocols withdraw corticosteroids within the first few days to weeks of the initial transplantation period, whereas others withdraw them in 3 to 6 months or later after transplantation. The rate of success depends not only on the immunosuppressives used but also on the population (high risk vs low risk) and timing of the withdrawal. Most success takes place in low-risk patients receiving antibody induction, such as rATG, with tacrolimus and mycophenolate with short-term steroids (≤1 week). African Americans, pediatric patients, patients who have retransplants, highly sensitized patients, patients with a high SCr (>2.5 mg/dL), and those who have had a recent rejection episode are more difficult to withdraw from steroids. This is particularly true early (<3 months) after transplantation. Withdrawal in these cases is associated with a higher rate of rejection. Later withdrawal may be attempted, but the benefits in terms of side effect profile may not be as great. Not all studies have demonstrated significant differences in side effect profiles between steroid withdrawal and continuation. Long-term outcomes are also limited using this approach. Low-risk populations are candidates for steroid avoidance or early withdrawal. First-time transplantation, living-donor, well-matched transplantation, older age, and stable graft function without rejection are factors associated with a positive benefit to steroid withdrawal.[40]

D.T. would be considered a low-risk patient because of her low immunologic activity evidenced by first-time transplant, a living donor, low PRA, older age, and ethnicity. Therefore, a steroid avoidance protocol, such as the one indicated here, would be appropriate. As with other transplant recipients, she must be closely monitored for rejection and adverse effects.

CASE 34-4

Question 1: B.B. is a 27-year-old African American male who received a kidney transplant for focal segmental glomerulosclerosis (FSGS). Shortly following transplant, he developed GI intolerance, nausea, vomiting, and diarrhea, to both mycophenolate products and cannot take either one anymore. A decision is made to use an mTOR inhibitor, sirolimus or everolimus, instead.

What would be important pharmacokinetic considerations, an appropriate regimen, and monitoring parameters for this agent?

Mammalian Target of Rapamycin Inhibitors

Sirolimus, and, more recently, everolimus, could be used as a substitute for other immunosuppressives. Experience and literature are more extensive with sirolimus.[17] Sirolimus can be used in the immediate posttransplant period, although impaired wound healing and lymphocele development in kidney transplantation have limited its use in the early period. In the case of liver transplantation, its use is contraindicated in the early posttransplantation period because of hepatic artery thrombosis. Sirolimus can be added later, as is the practice in many centers, as replacement for or minimization of cyclosporine, tacrolimus, steroids, or mycophenolate. In addition, sirolimus may be used as a substitute for these agents in patients predisposed to or with evidence of malignancy.[41] Early experience advocated an initial loading dose followed by a once-daily maintenance dose; however, because of its adverse effect profile, not all centers use loading doses. The starting maintenance dose is 2 to 5 mg. The typical loading dose is 6 mg followed by 2 mg every day. In high-risk patients, such as African Americans, a 15-mg

loading dose and 5-mg daily dose are recommended along with cyclosporine. Other centers have used loading doses of 10 to 15 mg, followed by 5 to 10 mg/day for the first week with target troughs of 10 to 15 ng/mL for the first month and 5 to 10 ng/mL thereafter when used with tacrolimus. Sirolimus is often given 4 hours after the morning dose of cyclosporine. If administered at the same time as cyclosporine, sirolimus concentrations are on average 40% higher.[42]

As with other immunosuppressives, sirolimus is associated with a number of side effects, including impaired wound healing, lymphedema, oral ulcerations, hypercholesterolemia, hypertriglyceridemia, diarrhea, arthralgias, epistaxis, rash, acne, leukopenia, thrombocytopenia, nausea and vomiting, lymphocele, hypokalemia, anemia, hypertension, pneumonitis, reproductive endocrine disorders, and infection. Dose-related hypertriglyceridemia, as well as hypercholesterolemia, occurs within the first few weeks of therapy and is sufficiently significant to require intervention with lipid-lowering agents, although it may respond to dosage reduction to some degree. Leukopenia and thrombocytopenia are also dose related. Sirolimus is associated with the development of proteinuria in kidney transplant recipients. The exact mechanism is unknown, but many transplant centers are now routinely monitoring for proteinuria in patients on sirolimus therapy and generally avoid its use in patients with preexisting proteinuria. Unfortunately, adverse effects are often the reason for discontinuing this agent in many patients.[43]

Trough blood concentration monitoring plays an important role in the dosing of sirolimus. Trough concentrations correlate well with sirolimus AUC. Because it has a longer half-life than does the CNI, concentrations are obtained less frequently and only 5 to 7 days after a dose change. The target trough is usually 5 and 15 ng/mL; however, this continues to be refined with more experience. Early studies achieved concentrations >15 ng/mL, especially when used without a CNI, which were associated with a greater immunosuppression and adverse events. Because sirolimus is synergistic with CNIs, the target concentrations of the CNIs are also reduced when these agents are used together. Target tacrolimus

trough targets are 5 to 10 ng/mL, and the cyclosporine trough targets are 75 to 100 ng/mL, and in some patients, lower when used with sirolimus.[43]

B.B. could be started on sirolimus at 2 to 5 mg daily. Sirolimus blood trough concentration should be obtained 5 to 7 days after initiation. B.B.'s cyclosporine may need to be reduced if concentrations exceed 100 ng/mL. Monitoring parameters should include a fasting lipid panel, complete blood count, chemistries, and electrolytes. If everolimus was used, the starting regimen would be 0.75 mg twice daily. Everolimus blood concentrations should be obtained in 3 to 4 days after initiation. Target trough goal would be 3 to 8 mg/mL. Monitoring parameters and side effect profile are similar to those of sirolimus.

LIVER TRANSPLANTATION

CASE 34-5

QUESTION 1: B.T. is a 52-year-old, 200.62-pound (91-kg) male with a history of chronic liver disease secondary to nonalcoholic fatty liver disease (NAFLD). His chronic liver disease course was complicated by hepatorenal syndrome, hepatic encephalopathy, and ascites. He received an offer call for a potential liver transplant. Later that evening, he received an orthotopic liver transplantation (OLT). He received basiliximab and IV methylprednisolone for induction in the operating room. His Model for End-stage Liver Disease (MELD) at the time of transplant was 38. CMV serology for B.T. was positive, and the donor liver was CMV positive (CMV D+/R+). His SCr at the time of transplant was 2.5 mg/dL.

After the transplantation, B.T. was started on continuous renal replacement therapy. His immunosuppression included IV methylprednisolone taper to an oral steroid taper that is expected to end at 1-month posttransplant, MMF 500 mg NG bid with the plan to give the second dose of basiliximab and start tacrolimus on postoperative day 4. An antimicrobial regimen consisted of perioperative piperacillin/tazobactam to continue postoperatively for 48 hours with valganciclovir, fluconazole, and trimethoprim/sulfamethoxazole.

How should B.T. be monitored in the initial postoperative period?

Indications and Evaluation for Liver Transplant

B.T. was diagnosed with end-stage liver failure (cirrhosis) caused by NAFLD. Each center varies with respect to the most common causes of cirrhosis leading to liver transplant, but nationwide, alcohol-induced liver disease is one of the highest reported causes of liver transplantation. In recent years, hepatitis C virus (HCV) etiology has declined, whereas it used to be higher than alcohol-induced liver disease (OPTN/SRTR 2018 Annual Data Report: Liver). Nonalcoholic steatohepatitis (NASH), which is a type of NAFLD, has been increasing in incidence and is expected to become the most common indication within the next 10 years. Indications for liver transplantation in adults include cholestatic liver disease (eg, primary biliary cirrhosis and primary sclerosing cholangitis), hepatocellular liver disease (eg, chronic viral hepatitis B or C, autoimmune, drug induced, NASH, cryptogenic cirrhosis), vascular disease (eg, Budd–Chiari), hepatic malignancy, inherited metabolic disorders, and fulminant hepatic failure (eg, viral hepatitis, Wilson disease, drug induced, or toxin induced). Controversial indications include alcohol-induced disease and some types of hepatic malignancies. The concern with these indications is either recurrence of disease, as in the case of hepatic malignancies, or recidivism in the case of patients with alcoholism.[44,45]

Contraindications to transplantation have decreased over the past few years. Current contraindications to liver transplantation include malignancy outside the liver, cholangiocarcinoma (unless the center has a United Network for Organ Sharing [UNOS]-approved protocol), active uncontrolled infection outside the biliary system, patients with alcoholic liver disease who continue to abuse alcohol, psychosocial instability and noncompliance, severe neurologic disease, and advanced cardiopulmonary disease. Patients with active infections are considered candidates after the infection has been eradicated.[45] HIV infection is not considered an absolute contraindication to transplantation.[46]

B.T. was within the age limitations for transplantation (in general, up to age 75 years is considered, although exceptions are common).

The graft survival continues to improve with graft survival of 91.2% at 1 year and 84% at 3 years for deceased-donor liver transplants.

The liver allocation system is based on the MELD, in which higher MELD scores move patients higher on the waitlist. Some patients qualify for MELD exception scores, which will raise their native MELD score and allow them to be more competitive to receive organ offers. Patients who have an acute liver failure and their life expectancy is only a few days or less without a transplant are considered for Status 1a and are prioritized first. Blood type compatibility, body size, wait time in current urgency status, and how close their transplant hospital is to the donor hospital are other factors involved in the matching process.[47]

Patient Monitoring

Ideally, B.T. should be awake and alert within 12 to 24 hours of the operation, transferred from the intensive care unit to a regular bed in 1 to 2 days, and discharged home within 5 to 10 days. Because function of the transplanted liver is essential for the survival of the patient, extensive clinical, laboratory, and radiologic monitoring are necessary. B.T. has three Jackson–Pratt (JP) abdominal drains that must be monitored for output production. The serum concentrations of BUN, creatinine, liver function tests (LFTs), potassium, sodium, magnesium, calcium, phosphate, and glucose should be monitored every 6 hours on the first postoperative day.[48] The surgical transplantation of a liver has been associated with coagulopathies and bleeding. Therefore, platelets, prothrombin time, fibrinogen, and factor V levels also should be monitored and deficiencies rapidly corrected when clinically indicated.[48] Initial LFT results are highly variable; they can either increase for the first day or two after transplantation because of ischemic and reperfusion injury to the allograft or they can decrease because of initial dilution by high-volume blood replacement. If the liver is functioning well, the LFTs, bilirubin, and prothrombin time all should begin to trend toward normal within a few days of the transplant.

Magnesium, phosphate, and calcium levels may fall in the early postoperative period and should be monitored closely. Ionized calcium serum concentrations are often monitored rather than total calcium because most patients have low serum albumin concentrations. Hypocalcemia can occur because these patients may receive large amounts of citrate through blood transfusions, which can lower serum calcium concentrations. Magnesium deficiency is common in patients with end-stage liver disease and may be exacerbated in the early posttransplantation period by tacrolimus or diuretics. Why patients experience hypophosphatemia is not fully known, but increased demand for phosphate for incorporation into adenosine triphosphate is a possible explanation. Hypokalemia or hyperkalemia can occur, depending on renal function and fluid status.

Hyperglycemia, which is a good indication of a properly functioning liver because of its role in glucose homeostasis (gluconeogenesis and glycolysis), may need to be controlled with a continuous IV infusion of insulin initially, and then SC insulin dosed on the basis of periodic glucose measurements. In contrast, persistent refractory hypoglycemia indicates a poorly functioning liver. Hypertension, which is multifactorial, also is sometimes seen during this time and usually is treated with calcium channel blockers (CCBs) or β-blockers. Renal dysfunction and neurologic complications can also occur.[48] Neurologic complications, including those that are drug induced, include oversedation, acute psychosis, depression, tremor, headaches, peripheral neuropathy, cortical blindness, paresthesias, paresis, and seizures.[49]

Additional complications that are common within the first 3 days to 3 months of liver transplantation include respiratory distress, intra-abdominal hemorrhage, biliary tract leaks and strictures, hepatic artery thrombosis, and primary graft nonfunction. Because infection is another early postoperative concern, B.T. should be monitored for bacterial, fungal, and viral infections.[48]

Case 34-5, Question 2: Ten days after his liver transplantation, B.T.'s renal function had improved and he is off renal replacement therapy. Unfortunately,

he was noted to be altered with some hallucinations mainly in the evening and an increase in tremors in his hands throughout the day. His tremors became worse a couple days later with shaking in his legs as well. Antipsychotic medications were started, with minimal improvement in his altered mental status.

Current immunosuppression medications include tacrolimus 9 mg bid, MMF 500 mg bid, and prednisone 20 mg PO daily. B.T.'s current laboratory values include the following:

BUN, 24 mg/dL
SCr, 1.2 mg/dL
Aspartate aminotransferase (AST), 32 IU/L
Alanine aminotransferase (ALT), 92 IU/L
γ-Glutamyl transferase (GGT), 106 IU/L
Total bilirubin, 1.5 mg/dL
Tacrolimus, 8.2 ng/dL

The transplant team decided to convert B.T. to cyclosporine from tacrolimus because of the continued neurotoxicity. What pharmacokinetic and monitoring parameters and adverse effects should be considered when using cyclosporine?

Cyclosporine

Cyclosporine pharmacokinetic parameters exhibit significant intrapatient and interpatient variability. A number of factors are known to influence its pharmacokinetic behavior and outcomes. These include age, ethnicity, transplant type, underlying disease, time after transplantation, GI metabolism and motility; biliary and liver function; metabolism, body weight, cholesterol, albumin, and red blood cell mass; and drug interactions and formulation.[50] For example, children, African Americans, and patients with cystic fibrosis tend to have reduced absorption, increased clearance of cyclosporine, or both. Patients who are obese or who have decreased liver function will have reduced clearance. Oral absorption of cyclosporine, which has been characterized as slow, incomplete, and highly variable, is the parameter that is most significantly affected. Absorption can depend on the type of transplant, time after transplantation, presence of food and its composition, intestinal function (eg, diarrhea, ileus), small bowel

length, and the presence or absence of external bile drainage. Bioavailability ranges from <5% to 90%.[51] In most transplant recipients, cyclosporine absorption increases over time. The original cyclosporine (Sandimmune) is rarely used today because of its poor and erratic absorption compared to newer formulations. Cyclosporine can be given IV as a continuous infusion (2–3 mg/kg/day) or intermittently (2.5 mg/kg/day) over 2 to 6 hours divided into two equal doses.

Cyclosporine is extensively distributed into red blood cells, whereas, in plasma, it is highly bound to lipoproteins. It is extensively metabolized by both the gut and liver CYP3A4 enzymes and transported by P-glycoprotein. The average half-life is about 15 to 20 hours. Cyclosporine is an inhibitor of CYP3A4 and PGP, so it can interact with other drugs.[51]

Cyclosporine can cause a number of adverse effects, of which nephrotoxicity is the most frequent and worrisome. Other major effects include hypertension, hyperlipidemia, tremors, headaches, seizures, paresthesias, hypomagnesemia, hypokalemia or hyperkalemia, hyperuricemia, hyperglycemia, gout, gingival hyperplasia, hirsutism, hemolytic–uremic syndrome, and hepatotoxicity. Hyperlipidemia and hypertension are more common with cyclosporine than with tacrolimus, whereas neurotoxicity (tremors, headaches, seizures) and hyperglycemia are more common with tacrolimus. If adverse effects occur, usually a dose reduction/reduction of goal trough concentration or discontinuation of the agent is needed.[52]

Cyclosporine concentrations are monitored to prevent toxicity, optimize efficacy, and assess patient compliance to the prescribed regimen. Most institutions monitor trough cyclosporine levels. During the early postoperative period, cyclosporine levels are often measured daily, keeping in mind these may not reflect steady-state concentrations. The target trough therapeutic concentration of cyclosporine during the first 6 months posttransplant will vary based on institution and patient-specific factors and range from 150 to 300 ng/mL, with a usual reduction in goal around 2 to 3 months. After 6 months, the targeted cyclosporine trough concentration is lowered

even further to 50 to 150 ng/mL. The range is reduced over time, given less immunosuppression is required after transplantation and the pharmacokinetics change over time. A few programs may monitor cyclosporine level at 2 hours post-dose, obtained 2 hours after a dose, or determine AUC; however, these are more cumbersome.[53]

B.T. was started on Neoral 300 mg bid. Because he was on a higher dose of tacrolimus, he may require further dose increases to reach his goal trough concentration of 200 to 250 ng/mL. His trough concentration will be monitored closely along with signs of improved neurotoxicity. Other adverse effects due to cyclosporine and signs of rejection should be monitored.

Rejection

Case 34-5, Question 3: B.T. was discharged from the hospital on cyclosporine with improved neurotoxicity. He went to stay with his brother and was followed up with laboratory tests obtained three times a week. He reported feeling great and no longer had any altered mental status/hallucinations or tremors. The following laboratory values were obtained 2 weeks later:

AST, 31 IU/L; ALT, 52 IU/L; GGT, 65 IU/L; total/direct (T/D) bilirubin, 1.0/0.3 mg/dL
Cyclosporine tough concentration, 123 ng/mL
And another week later:
AST, 450 IU/L; ALT, 364 IU/L; GGT, 321 IU/L; T/D bilirubin, 2.5/2 mg/dL
Cyclosporine trough concentration, 116 ng/mL

B.T. was readmitted because of rise in LFTs and bilirubin, which are suggestive of acute liver dysfunction. A liver ultrasound and a percutaneous needle liver biopsy were obtained. On admission, he reported lethargy and some mild abdominal pain. He endorsed poor nutritional intake for the past 2 to 3 days. The pathologist interpreted the liver biopsy as moderate rejection, and B.T. was given a 500-mg IV bolus of methylprednisolone daily for three doses followed by tapered doses of IV methylprednisolone: 50 mg every 6 hours for four doses; 40 mg every 6 hours for four doses; 30 mg every 6 hours for four doses; 20 mg every 6 hours for four doses; 20 mg every 12 hours for two doses; and then back to the pretaper oral prednisone dose. What subjective and objective evidence for acute cellular rejection is present in B.T.?

HYPERACUTE REJECTION

Hyperacute rejection rarely occurs with liver transplantation; when this occurs, treatment is supportive and retransplantation is required.[54] Unlike other organs, however, the liver may function adequately, but survival is lower when the organ is transplanted across blood types (ABO incompatible) or in patients who are presensitized to the HLA antigens.[55]

ACUTE CELLULAR REJECTION

Although acute cellular liver rejection can occur at any time after the transplantation, it is most commonly experienced within the first 3 to 6 months of transplant and in ~20% to 50% of patients treated with either cyclosporine or tacrolimus and prednisone.[56] Data in patients treated with tacrolimus, mycophenolate, and prednisone indicate lower rejection rates.[57] Late acute rejections often are a result of either nonadherence, a reduction in dose, or a discontinuation of immunosuppressive agents. These rejection episodes, although somewhat common, rarely lead to graft loss.

B.T. presented with some of the subjective symptoms of rejection. Commonly, patients feel unwell and report anorexia, abdominal discomfort, and headache. Other symptoms, such as a low-grade fever, back pain, or respiratory distress, may rarely occur. With the use of more potent immunosuppression, symptoms are no longer commonly present with acute rejection and cannot be relied upon for early indication of rejection. Objective evidence of rejection in B.T. included an abrupt rise in transaminases and bilirubin and a liver biopsy that was interpreted as “moderate rejection.” These observations led to a diagnosis of rejection. Acute rejection is associated with mononuclear cell infiltration of the graft, edema, and parenchymal necrosis. Rejection should be diagnosed by biopsy using histologic criteria. Areas commonly damaged by rejection are the bile ducts, veins, and arteries, known as *portal triaditis*.[58]

TREATMENT OF REJECTION

Case 34-5, Question 4: Was the treatment of B.T.'s rejection of his transplanted liver appropriate?

The treatment decision was reasonable because high-dose corticosteroids reverse the majority of acute rejection episodes.[54] Acute cellular rejection in liver transplant patients is usually treated with 200 to 1000 mg/day of IV methylprednisolone (usually 500 mg IV for 3 days) and tapered rapidly, similar to B.T.'s. A high-dose corticosteroid (usually IV methylprednisolone) is considered first-line therapy because it works very quickly in decreasing lymphocyte responsiveness and is easy to administer. The ideal corticosteroid dosage, route, and regimen are unknown, and corticosteroid protocols vary among transplant programs. IV methylprednisolone and oral prednisone are equally effective in reversing rejection, but oral corticosteroids are given for a longer period and have been associated with a higher incidence of adverse effects.

Nevertheless, high doses of corticosteroids are not without risk. They increase the risk of infection, and long-term therapy can induce ocular, bone, cardiovascular, and endocrine abnormalities. Although B.T. will be receiving high-dose IV methylprednisolone for a short period of time, it can result in euphoria, mood shifts, acute psychosis, and even mania. Short-course methylprednisolone also can mask signs of infection (eg, fever, changes in WBC counts, pain associated with inflammation) and delay the diagnosis. If the methylprednisolone regimen is effective in reversing B.T.'s acute rejection, his LFTs and bilirubin should start to decline within 2 to 5 days.

Case 34-5, Question 5: After 3 days into the high-dose IV methylprednisolone course, B.T.'s liver enzyme values had not improved.

AST, 431 IU/L; ALT, 344 units/L; GGT, 351 units/L; T/D bilirubin, 3/2.5 mg/dL
The 12-hour cyclosporine trough level at the end of the treatment course was 168 ng/mL.

What other treatment options are available for B.T.?

High-dose or “pulse” IV methylprednisolone, IV rATG, and oral prednisone are options to treat acute rejection in all types of solid organ transplants. The decision to determine B.T.’s response to the initial bolus steroid dosage and the severity of rejection by biopsy also was appropriate before proceeding with further treatment. Subsequent therapy would include rATG. Most centers use rATG as a second-line agent if there is no response to high-dose corticosteroids or as a first-line agent for severe rejection. The typical dose is 1.5 mg/kg/day given as an infusion for 4 to 6 hours and is continued for 7 to 14 days. The duration will depend on clinical response, such as improvement in LFTs and bilirubin as well as the lowering of his absolute lymphocyte count. Treatment of corticosteroid-resistant rejection with rATG is effective in about 70% to 80% of liver transplant patients. rATG is associated with a higher risk of CMV infection and malignancy; it is more difficult to administer, requires more intensive monitoring, is more expensive, and usually is held in reserve for corticosteroid-resistant or more severe forms of rejection. Another alternative agent that could be used in both kidney and liver transplant patients with severe or resistant acute cellular rejection is alemtuzumab, although this is considered more of a last-line option.

In addition to starting rATG in B.T., changes to the maintenance immunosuppression regimen can be made to assist in further suppressing the immune system. B.T.’s cyclosporine level has been consistently lower than his initial goal of 200 to 250 ng/mL, and low trough concentrations have been associated with a higher risk of acute rejection. Continued dose adjustments are needed for B.T. to reach a therapeutic concentration, and in some rejection cases, a higher goal trough concentration than the patient was on prior is targeted. For example, B.T.’s goal trough concentration could increase to 250 to 300 ng/mL, but first he would need to at least reach his prior goal concentration. The prednisone dose may also be increased or added to the maintenance regimen. The MMF dose could be increased to 1 g bid, and, in some abdominal transplant patients, up to 1.5 g bid because this dose in combination with a CNI has reduced acute rejection in African American patients, particularly

if the patient was on cyclosporine therapy. There is limited data supporting the increase of the MMF dose beyond 1 g bid with tacrolimus-based regimens.[33,34] Another important aspect for prevention of future rejection would be to assess B.T.'s adherence with, and understanding of, his medication regimen. Nonadherence is a major cause of acute rejection and graft loss.[35]

CHRONIC LIVER REJECTION

Chronic liver rejection, also called ductopenic rejection, usually develops months to years after the transplant in <5% of recipients. Characteristics of chronic liver rejection include occlusive arterial lesions, destruction of small intrahepatic bile ducts (often referred to as *vanishing bile duct syndrome*), intense cholestasis, accumulation of foamy macrophages within the portal sinusoids, and fibrosis, which can lead to the development of cirrhosis.[58] Chronic rejection is almost always irreversible and unaffected by increased immunosuppressive therapy. Retransplantation has been considered the only viable alternative. Some patients with early ductopenic rejection unresponsive to cyclosporine-based therapy have responded to tacrolimus.[59]

CASE 34-6

QUESTION 1: D.C. received a liver transplant roughly 4 months ago for autoimmune hepatitis. At the time of transplant, he was started on tacrolimus 0.05 mg/kg bid and MMF 500 mg bid along with a steroid taper to his prior prednisone dose of 5 mg daily.

What are MMF's pharmacokinetic characteristics and adverse effects?

How will these characteristics affect the dosing and monitoring of MMF in this patient?

Mycophenolic Acid Derivatives

In the vast majority of transplant centers, MPA derivatives (MMF, EC-MPS) have replaced azathioprine as the antiproliferative agent used in maintenance immunosuppression. Liver transplant patients,

similar to D.C., with an autoimmune etiology for their liver disease are at higher risk of acute cellular rejection and are at risk for graft failure due to recurrent disease.[60] It is important to ensure these individuals are adequately immunosuppressed, and in many cases, they require more immunosuppression than do other liver transplant patients.

PHARMACOKINETICS

MMF is a prodrug for the active form, MPA. MMF is well absorbed (bioavailability 94%) and is rapidly hydrolyzed to MPA. The C_{max} for MPA occurs between 1 and 3 hours, and it is hepatically and renally glucuronidated to inactive MPAG, which is eliminated by the kidney, but mainly excreted into the bile. Once MPAG is excreted into the bile, it then may undergo enterohepatic recycling in the GI tract, where it is deconjugated to MPA (which is reabsorbed back into the systemic circulation). This recycling produces a second peak around 6 to 12 hours after dosing; however, this is blocked when coadministered with cyclosporine. As a result, the MPA AUC is significantly lower. MPA has an elimination half-life of 17 hours on average; the volume of distribution is 4 L/kg, and it is highly protein bound to albumin (98%). Protein binding correlates well with albumin, and free MPA concentrations somewhat correlate with the immunosuppressive effect. Renal impairment, liver dysfunction, and elevated MPAG concentrations in transplant recipients can reduce protein binding. This may be a function of low albumin concentrations seen in these patients.[13]

ADVERSE EFFECTS

The most commonly reported side effects for MMF are GI (anorexia, nausea, vomiting and diarrhea, gastritis), hematologic (leukopenia, thrombocytopenia, anemia), and infections. GI side effects are common, and all side effects are more common with higher dosages. Patients with GI problems may respond to administering the dose without other medications, smaller more frequent doses, or lowering of the dose and titrating upward as tolerated.[61] If the WBC count is

<3000 or the absolute neutrophil count is <1300 cells/mL, the MMF dose should be reduced or discontinued.

DOSING

The MMF starting dose in adults will vary based on type of transplant and institution-specific protocols. Doses usually range from 500 to 1000 mg bid. There is a drug–drug interaction between MMF and cyclosporine owing to cyclosporine inhibiting the enterohepatic recycling of MPAG. Several studies and some practices may dose MMF higher when administered with cyclosporine compared to tacrolimus.[13,33]

THERAPEUTIC DRUG MONITORING

Monitoring MPA plasma concentrations is controversial and not generally recommended at this time because of the lack of data demonstrating improved outcomes with therapeutic drug monitoring (TDM). In kidney transplant recipients, low MPA AUCs and troughs have been shown to correlate with acute rejection. In centers routinely performing MPA monitoring, typical $AUC_{0–12}$ targets are 30 to 60 µg/hour/mL and troughs are 1 to 3.5 µg/mL. MPA monitoring appears to be more beneficial in protocols where CNI sparing, withdrawal, or minimization is used. Once started on MMF, D.C. should be monitored for GI and hematologic side effects as well as for any signs and symptoms of infection and rejection.[34]

Case 34-6, Question 2: D.C. was admitted to the hospital with fevers, chest pain, cough, shortness of breath, and consistent leukopenia. His immunosuppression therapy was recently increased to prednisone 20 mg daily, MMF 750 mg bid, and tacrolimus 8 mg bid with a goal trough concentration close to 8 ng/mL (the most recent tacrolimus trough concentration was 8.9 ng/mL) because of concern for a mild rise in LFTs. Cultures were obtained and a chest x-ray was performed. On chest x-ray, there was concern for a fungal mass, possible aspergilloma. The infectious disease team was consulted and voriconazole was initiated. Owing to D.C.'s leukopenia and infection, his MMF was held. What drugs interact with immunosuppressive agents? Will the initiation of voriconazole require any adjustments in current medication doses?

Drug Interactions With Immunosuppressives

Some immunosuppressants, such as tacrolimus, have a highly variable pharmacokinetic profile, with a narrow therapeutic index highlighting the importance of managing their drug–drug interactions. Drug interactions can be separated into two main categories: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions occur when one medication alters the absorption, distribution, metabolism, or elimination of the immunosuppressant agent.[62,63] **Table 34-2** displays the most clinically relevant pharmacokinetic drug interactions that are likely to be encountered in transplant patients and how to manage these interactions. These include drugs that alter either the absorption or metabolism of the immunosuppressants. Note that this table is not comprehensive.

Table 34-2
Immunosuppressant Drug Interactions

Immunosuppressant	Interacting Drugs	Mechanism	Consequence	Clinical Management
CNIs (cyclosporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus)	Clarithromycin,[a] erythromycin,[a] telithromycin,[a] ketoconazole,[a] itraconazole,[a] fluconazole, posaconazole,[a] voriconazole,[a] fluoxetine, fluvoxamine, citalopram, nefazodone,[a] diltiazem,[a] verapamil,[a] delavirdine,[a] ritonavir,[a] cimetidine,[a] grapefruit juice,[a] amiodarone, saquinavir, nelfinavir, indinavir, amprenavir, chloramphenicol[a]	Inhibit CYP3A isoenzyme in the liver and intestines	Increase the blood concentration of the IS	Either prospectively decrease the IS dose or monitor trough concentrations and AUC more closely and adjust doses accordingly.
CNIs (cyclosporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus)	Carbamazepine,[a] dexamethasone, phenobarbital,[a] phenytoin,[a] St. John wort,[a] rifampin,[a] rifabutin,[a] efavirenz,[a] nevirapine,[a] nafcillin, clindamycin	Induce CYP3A4 isoenzyme in the liver and intestines	Decrease the blood concentration of the IS	Either prospectively increase the IS dose or monitor trough concentrations and AUC more closely and adjust doses accordingly.
CNIs (cyclosporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus), mycophenolic acid derivatives	Cholestyramine, colestipol, probucol, sevelamer, antacids (magnesium and aluminum containing)	Bind to IS and prevent absorption	Decrease the blood concentration of the IS	Avoid concomitant administration with IS and monitor trough concentrations.
Azathioprine	Allopurinol, febuxostat	Inhibit metabolism by inhibiting xanthine oxidase	Increase the blood concentration of azathioprine	Avoid use together or prospectively reduce azathioprine dose to one-third or one-fourth normal dose and monitor for increased toxicity.

AUC, area under the curve; CNI, calcineurin inhibitor; CYP, cytochrome P450; IS, immunosuppressant; mTOR, mammalian target of rapamycin.

[a]These are considered either potent inhibitors or inducers.

Pharmacodynamic interactions occur when one medication either potentiates an adverse effect or alters the pharmacologic effects of the immunosuppressant agent.[63] An example is the use of CNI in combination with angiotensin converting enzyme (ACE) inhibitors. Because both classes of agents can cause hyperkalemia and potentially decrease renal function, toxicity may be more pronounced when given in combination.[64] Pharmacodynamic drug interactions are usually more difficult to identify and require a thorough knowledge of the pharmacologic effects of the agents. Often, little or no information in the literature on these types of interactions exists to guide the clinician in determining whether this drug interaction will occur. As a general rule, if an agent is known to cause a particular toxicity similar to a toxicity associated with the immunosuppressant agent, then there is a high likelihood a pharmacodynamic interaction will occur. Another example is an interaction between metoclopramide and MMF. Both agents are known to cause diarrhea, and a higher incidence or severity of diarrhea likely occurs when these agents are used together.[63]

It is important to be alert for drugs with pharmacologic effects that may alter the efficacy of an immunosuppressant.[63] For example, a drug with immunosuppressant properties, such as cyclophosphamide, could lead to overimmunosuppression of the transplant patient and a higher incidence or severity of opportunistic infections. Conversely, a drug with immunostimulant properties, such as the herbal medication echinacea, may reduce the efficacy of the immunosuppressant agent and increase the risk of rejection in the transplant patient.[62,63] Although agents that have pharmacodynamic drug interactions with the immunosuppressants are not absolutely contraindicated, transplant patients should be closely monitored for either increased risk of drug toxicity or decreased drug efficacy when these agents are used in combination. When a transplant patient adds any new medication—whether prescription, over the counter, or herbal—it should be thoroughly researched to determine whether there is a potential interaction with the immunosuppressant regimen.

In D.C., the addition of voriconazole will lead to a pharmacokinetic drug interaction by inhibiting the CYP3A4 and CYP3A5 system and will increase tacrolimus trough concentrations.[65] Therefore, D.C.'s tacrolimus dose should be empirically reduced when voriconazole is started. The package insert for voriconazole mentions reducing the tacrolimus dose by 66%.[66] A more recent study found, owing to the patients' polymorphisms in CYP3A4, that the dose reduction of 66% may not be enough, whereas a reduction of 75% may be more appropriate if there is more concern for the patient having supratherapeutic levels rather than subtherapeutic levels.[67] Tacrolimus and voriconazole trough concentrations should be monitored, as should signs and symptoms of toxicity of these agents. In general, drug interactions can be managed and, in some cases, may only require separate administration times. In other cases, an alternative agent that does not interact with the immunosuppressant regimen can be used.

Posttransplant Complications

CASE 34-7

Question 1: J.V. is a 52-year-old African American female who received a deceased kidney transplant 4 months ago for hypertension. Her medical history is also significant for gout and depression. She currently weighs 202.83 pounds (92 kg) and is 66 inches (167.64 cm) tall, with a BMI of 32.7 kg/m^2. Before the transplant, she was taking lisinopril 20 mg PO daily, hydralazine 100 mg PO tid, amlodipine 10 mg daily, and carvedilol 25 mg PO bid to control her BP. After the transplant, amlodipine 10 mg PO daily, carvedilol 25 mg PO bid, and hydralazine 50 mg PO tid were continued. J.V. is on tacrolimus 8 mg PO bid, MMF 750 mg PO bid, and prednisone 5 mg PO daily. Her tacrolimus trough concentrations have been between 8 and 11 ng/L, with a recent goal of 6 to 8 ng/L.

After transplant, she was discharged on an insulin regimen including correctional insulin lispro at mealtimes and insulin glargine at bedtime. Currently, she is on two oral antiglycemic agents to maintain adequate blood glucose. Her BP readings during the past 2 weeks have ranged between 150/85 and 164/90 mm Hg. Fasting lipid panel is a total cholesterol, 265 mg/dL; low-density lipoprotein (LDL), 173 mg/dL; high-density lipoprotein (HDL), 45 mg/dL; and triglycerides, 220 mg/dL.

Why would J.V. have issues with controlling her blood glucose levels, BP, and lipid levels?

POSTTRANSPLANT DIABETES MELLITUS

Posttransplant diabetes mellitus (PTDM) has also been referred to as new-onset diabetes after transplant (NODAT). Diabetes significantly affects morbidity and mortality in transplant patients. It is often a preexisting condition in kidney transplant patients and a cause of ESRD. In recipients of other organs, such as livers, diabetes is common as well, both as a preexisting condition and as a posttransplantation complication. The definition of PTDM varies among studies. It has been based on symptoms, plasma glucose and HbA_{1c} levels, oral glucose challenge results, or the need for insulin or oral antidiabetic drugs after transplantation. It is recommended that diagnosis occurs once transplant patients have been discharged from the hospital and is on their maintenance immunosuppression. Within the first year posttransplant, diagnosis should not be made based on HbA_{1c} alone. Reported rates are 3% to >40%, with most cases of PTDM occurring within the first year of transplantation. Risk factors, besides pretransplantation diabetes, include advanced age, family history, CMV infection, certain HLA phenotypes, race (African American or Hispanic), increased BMI, and hepatitis C infection in the liver transplant population. One of the most critical factors in the development of PTDM is the immunosuppressive regimen. Cyclosporine, tacrolimus, and prednisone are all associated with PTDM. The CNIs appear to have a direct toxic effect on the pancreatic β cells, leading to decreased insulin synthesis and secretion; this effect seems to be dose related and generally reversible. Although still debated, the literature suggests that tacrolimus is more likely to cause PTDM than cyclosporine. In addition, conversion from tacrolimus to cyclosporine or belatacept has been beneficial. Prednisone is a major contributor to PTDM via multiple effects on β-cell sensitivity to glucose and ability to release insulin, and insulin resistance in multiple tissues. Sirolimus has also been implicated in the development of PTDM,

although its role and mechanism are unclear. Other risk factors, such as CNI drug concentrations, steroid doses, transplant type, and time lapsed after transplantation, must also be considered.[68] As with diabetes in the general population, a similar intensive approach in controlling blood glucose should be undertaken. Also, other conditions (eg, hypertension and hyperlipidemia) should be managed aggressively to reduce cardiovascular and kidney damage. Reducing or withdrawing diabetes-inducing immunosuppression as much as possible without jeopardizing graft function or using agents that are nondiabetogenic (such as mycophenolate) may be beneficial. One important aspect of posttransplant diabetes management is to realize the differences in pharmacologic management in this population, as compared with patients who are not transplant recipients. Often, in the immediate posttransplant period, because of the rapidly changing organ function and the dramatic tapering of corticosteroids, a patient's antidiabetic medicines may need frequent adjustment. During the first several weeks posttransplant, insulin is the agent of choice owing to the ability of the clinician to use sliding scales, the availability of several insulin products, and the ease in changing doses. Once patients are stabilized on their immunosuppressant regimen, and their organ function also, the use of oral antidiabetic agents can be introduced or restarted. Metformin, glitazones, gliptins, and sulfonylureas have been used in kidney transplants, but the use of oral agents is often dictated by renal function. Other considerations would be liver function and weight gain.[69] Newer antiglycemic agents, dipeptidyl peptidase-4 inhibitor (DPP-4) inhibitors and sodium–glucose cotransporter-2 (SGLT2) inhibitors have been studied in the transplant population, whereas, to date, there are no studies examining the use of glucagon-like peptide-1 (GLP-1) agonists in this population.[70] Limitations to the use of SGLT2 inhibitors are increased risk of urinary tract infections; however, both DDP-4 inhibitors and SGLT2 inhibitors have been found to lower HbA_{1c} with either no change in kidney markers or kidney graft survival, respectively.[70] Both SGLT2 inhibitors and GLP-1 agonists have been

shown in other populations to provide cardioprotective and nephroprotective effects.[71]

J.V. was not diabetic pretransplant but required insulin at her initial discharge; she is currently on two oral antiglycemic agents to manage her glucose levels and would classify for PTDM. Some would classify her as having PTDM. Risk factors J.V. has for PTDM are being African American, having a higher BMI, advanced age, and the use of tacrolimus and prednisone. The risks and benefits of changing immunosuppressant regimens to reduce PTDM must always be weighed. For instance, changing her tacrolimus to cyclosporine, or reducing or removing prednisone, may reduce her blood glucose level and may prevent PTDM, but it also will put J.V. at higher risk for developing acute rejection.

POSTTRANSPLANT HYPERTENSION

Case 34-7, Question 2: What pharmacologic options would be used for J.V.'s hypertension?

Cardiovascular disease is very common in patients with ESRD and after kidney transplantation. These patients with prior ESRD can have coronary artery disease (CAD), left ventricular hypertrophy (LVH) and congestive heart failure (CHF), and arrhythmias and valvular heart disease. Cardiovascular disease after transplant is associated with graft loss and lower patient survival. In those patients who die with a functioning graft, 40% die secondary to a cardiovascular event. Some immunosuppressives, including cyclosporine, tacrolimus, and steroids, contribute to the development of hypertension. Studies have indicated BP is higher, with high nighttime systolic BP, and more difficult to manage in patients on cyclosporine compared with tacrolimus.[72] The appropriate BP goals are similar to those in the general population, that is, <140/90 mm Hg in patients without proteinuria, as seen in this case. Nonpharmacologic therapies should be implemented; however, in

transplant patients, pharmacologic management is a key, often requiring multiple antihypertensives similar to J.V.

Pharmacologic agents used in transplant patients are the same as those used in the general population. In the transplant patient, one must consider the drug interaction profile and comorbidities. For example, non-dihydropyridine CCBs, such as amlodipine, are less likely to interact with CNIs than does diltiazem or verapamil. CCBs may also ameliorate some of the vasoconstrictive effects produced by the CNIs. In many programs, CCBs are considered first-line therapy. β-Blockers such as metoprolol are also frequently used in transplant patients. Many patients have or are at risk for CAD, and these agents can be effective in these situations. ACE inhibitors and angiotensin receptor blockers (ARBs) can be used in transplant patients, those with LVH. Historically, these agents were avoided because of concern for their association with impaired kidney function. However, these have significant cardiovascular and renal benefits in patients with comorbidities such as diabetes, proteinuria, and CHF. Their use in transplant patients has increased and is introduced usually months after transplant when renal function is more stable. If an ACE inhibitor or ARB is used, SCr and potassium levels must be monitored closely. Diuretics are useful in patients with evidence of fluid overload. In refractory patients, agents such as clonidine, hydralazine, and minoxidil may be required. In J.V.'s case, she could increase her hydralazine dose and, if needed, restart lisinopril with close monitoring and follow-up.

POSTTRANSPLANT HYPERLIPIDEMIA

Case 34-7, Question 3: What would be an appropriate lipid-lowering therapy for J.V.'s hyperlipidemia?

Hyperlipidemia is another cardiovascular issue to be addressed in transplant patients. As with hypertension, it is fairly common pre- and posttransplant. It is associated with negative cardiac outcomes and reduced graft and patient survival. Immunosuppressives including

cyclosporine, tacrolimus, steroids, sirolimus, and everolimus can cause elevations in total cholesterol, LDL, and triglycerides and reduce HDL. Goals of treatment and the level of intensity of statin therapy needed are based on individual risk factors, such as diabetes and age, along with the calculation of American College of Cardiology/American Heart Association (ACC/AHA) atherosclerotic cardiovascular disease risk to assess risk for heart disease and stroke in individuals. Application of the cholesterol clinical practice guidelines is also followed in this population.[73]

Treatment involves diet, which alone appears to have a minimal effect; therefore, pharmacologic treatment is usually required. Agents utilized in the nontransplant population are effective in reducing lipids in transplant patients. Considerations in selecting treatments for hyperlipidemia include drug interactions with the immunosuppressives and the side effect profile. Statins are considered first-line treatment and have substantial evidence to support their use. With the drug interaction of cyclosporine and statins, there is an increase in the concentration of statins, such as simvastatin and rosuvastatin. Therefore, there are recommended maximum statin doses when used in combination to limit adverse events. Atorvastatin and pravastatin are often used and appear to be safe and effective in this population. PCSK9 inhibitors are also effective in lowering cholesterol levels with minimal side effects; however, its affordability may be a challenge for some individuals. Fibrates, ezetimibe, bile acid binders, and niacin are considered second-line agents.[72] In J.F., atorvastatin would be an appropriate choice.

POSTTRANSPLANT OSTEOPOROSIS

Rapid bone loss with the subsequent development of osteopenia or osteoporosis is another common posttransplantation disorder. Osteoporosis increases bone fragility and eventually leads to fracture. Studies estimate that osteoporosis occurs in 11% to 56% and fractures in 5% to 44%, and increases in time in the transplant population. Osteoporosis risk factors for transplant patients are

similar to those in the general population. Additional risk factors in kidney transplant include time on hemodialysis before transplant, vitamin D deficiency, pretransplant parathyroid hormone (PTH) and fibroblast growth factor (FGF)-23 levels, diabetes, and steroid dose. Patients with ESRD commonly have at least some evidence of renal osteodystrophy, which includes hyperparathyroidism, osteomalacia, osteosclerosis, and adynamic or aplastic bone disease. Therapy options to prevent organ rejection predispose patients to osteoporosis, especially corticosteroids. The most dramatic reduction in bone loss after transplantation occurs within the first 3 to 6 months, when high doses of steroids are tapered off or to a lower maintenance prednisone dose. Most studies suggest a minor effect of CNI on bone. Other currently used agents appear to have little or no effect. Most recommendations are based on the American College of Rheumatology's guidelines for the prevention and treatment of corticosteroid-induced osteoporosis. These recommendations focus on providing calcium and vitamin D (variable dosing depending on kidney and liver functions) to patients who will be receiving continuous corticosteroid therapy. Patients with osteopenia or osteoporosis with bone mineral density scans using dual-energy x-ray absorptiometry (DEXA) scans, calcium, and vitamin D analogs are recommended in conjunction with a bisphosphonate, calcitonin, or teriparatide.[74–77] Bisphosphonate use is limited by patients' renal dysfunction, resulting in the need for alternative therapies. The use of denosumab has also been found to improve bone density in solid organ transplant recipients.[76]

MALIGNANCY

As a percentage of all malignancies, PTLD occurs more commonly in thoracic than in other types of solid organ transplants and is even more common in children. Lymphomas develop in about 1% of kidney transplantations and 2% of liver transplantations. These tumors often appear early and progress rapidly. The overall prevalence of malignancies in the transplantation population averages about 6%, and the risk of cancer increases with time after

a transplantation. Major organ transplant recipients are 100 times more likely to have cancer than the general population. Furthermore, the most common types of cancer observed in transplant recipients (eg, lymphomas, and cancer of the skin and lips) are uncommon in the general population. The development of skin and lip cancers in the transplant population has been attributed partially to exposure to sunlight and sensitization of skin to sunlight by an azathioprine metabolite, methylnitrothioimidazole.[78]

CASE 34-8

QUESTION 1: A.L., a 16-year-old, 92.59-pound (42-kg) female, underwent liver transplant 1 year ago secondary to biliary atresia with a failed Kasai procedure. She now presents with low-grade fever, malaise, pain, and a 1-week history of decreased appetite. She has experienced two episodes of rejection that were treated with 1 to 2 g of methylprednisolone each time, with the last rejection episode requiring rATG therapy. She received tacrolimus and prednisone after transplantation and had MMF added to her immunosuppressant regimen after the second rejection episode. She has just finished a course of IV ganciclovir (4 weeks) for CMV infection. The donor was CMV-positive, and she is CMV-positive. Her EBV DNA polymerase chain reaction (PCR) is now 18,000 copies/mL (normal, <500 copies/mL); this value was negative at the time of transplant. On physical examination, she was noted to have mediastinal adenopathy. She denies chills, sweats, nausea, vomiting, or diarrhea. A chest computed tomography scan revealed a mediastinal mass. Vital signs and all laboratory tests are within normal limits. Her tacrolimus trough is 9.8 ng/mL (goal is 8–10 ng/mL). Seven days after admission, a biopsy of this mass shows a thoracic lymphoproliferative lesion identified as a thoracic immunoblastic lymphoma adherent to the right side of the heart. Ten days later, she developed tachy/brady syndrome, and a pacemaker was implanted. Given the location of her lymphoma and symptoms, surgery and radiation therapy are not viable options, and chemotherapy is started the next day.

What clinical signs and risk factors in A.L. are associated with lymphoma?

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER

Risk factors

A.L. has developed a PTLD, one of many types of malignancies reported after solid organ transplantation. The exact etiology of this condition is unclear and probably multifactorial. The presentation of

PTLD varies significantly. Patients can present asymptomatically, with mild mononucleosis-like symptoms or with multiorgan failure. A.L. presents with fever, lymphadenopathy, malaise, and lack of appetite. Although these symptoms are consistent with PTLD, they also are consistent with infection. Because PTLD can involve various organ systems, patients can present with organ-specific symptoms (eg, acute abdominal pain, perforation, obstruction). Depending on its location, a tumor can impinge on the function of other organs, as seen in A.L.[78] Besides immunosuppression, two factors associated with PTLD are the presence of EBV and the age of the patient. Children have a higher incidence of PTLD.[79] A.L. developed EBV DNA viremia, indicating she had been exposed to this virus at the time of transplantation or afterward. EBV also can be transmitted from the donor liver and/or blood products. Also, EBV-positive recipients at the time of transplantation can experience reactivation of this virus as a result of immunosuppression.

A.L. received a significant amount of immunosuppression. This could lead to an inability to suppress an active viral infection by cytotoxic T cells and result in uncontrolled B-cell proliferation and polyclonal and monoclonal expansion. In addition to this T-cell defect, an imbalance or alteration in cytokine production in response to EBV, which infects B lymphocytes, may contribute to the exaggerated B-cell expansion and transformation; most are classified as non-Hodgkin lymphomas primarily of B-cell origin. Small percentages are of T-cell origin, however, and are harder to treat.[78]

Newer, more potent immunosuppressive agents used in different combinations, increased numbers of transplantation procedures, and closer monitoring contribute to the increase in incidence and detection of PTLD. When cyclosporine-based regimens were compared with azathioprine- or cyclophosphamide-based regimens, lymphomas made up 26% and 11% of all cancers, respectively. The lymphomas occurred, on average, within 15 months of transplant in the cyclosporine group versus 48 months in the azathioprine group. One-third of these malignancies occurred in the first 4 months in the cyclosporine group compared with only 11% in the latter group.[78] The incidence of PTLD increases with rATG therapy and appears to be

related to a cumulative dose and multiple courses. PTLD is not caused by any single agent but probably reflects the intensity of immunosuppression as a whole and the combination usually of multiple agents. Chronic antigenic stimulation by foreign antigens, repeated infections, genetic predisposition, and indirect or direct damage to DNA are other variables that might affect the development of PTLD.[80] A.L. had a recent CMV infection, which also could have contributed to this process.

Treatment and outcomes

Case 34-8, Question 2: What are the therapeutic maneuvers and outcomes that would be expected in A.L.?

Treatment of a PTLD depends on timing, presentation, symptoms, extent of involvement, histologic type, and transplant type. Early experiences with PTLD indicated that a reduction in or discontinuation of immunosuppression led to the regression of the cancer. Therefore, the first step in treating PTLD is to consider the reduction in or discontinuation of immunosuppressive agents, with the potential exception of discontinuing the corticosteroids. This course of action is not feasible for all transplant patients based on prior course of the transplanted organ (eg, rejection history) or the life-saving need to ensure functioning of the transplanted organ. Therefore, A.L.'s MMF probably should be discontinued to minimize the potential for severe bone marrow toxicity. In addition, A.L. will likely have a small reduction in her tacrolimus doses, with the goal of achieving trough concentrations on the lower end of her therapeutic range (4–6 ng/mL); her prednisone should also be reduced to the lowest dose possible. If her immunosuppressive drug therapy is diminished, she should be monitored closely for rejection. A.L. will also need to pursue chemotherapy for treatment.

Antiviral therapy with IV acyclovir or ganciclovir has been used to inhibit EBV replication in an effort to treat PTLD. Response is variable and may depend on the type and extent of PTLD. A.L.

already has received ganciclovir for 4 weeks during which time she presented with PTLD. Surgery, radiation therapy, and chemotherapy are used to treat PTLD depending on the situation. IFN and Ig have been effective in a few cases that appeared unresponsive to other therapies. Monoclonal or immunoblastic, disseminated, rapidly progressive PTLD responds poorly to traditional therapy and has a mortality rate as high as 70%. Rituximab (an anti-B-cell, anti-CD20 antibody) is considered first-line therapy for CD20-positive B-cell PTLD along with a reduction in or withdrawal of immunosuppression if possible. Patients usually get 375 mg/m^2 weekly for 4 weeks; some groups have used prolonged therapy. Patients may have relapse or disease progression that may respond to chemotherapy regimens such as cyclophosphamide, adriamycin, vincristine, prednisone, or dexamethasone (CHOP); CHOP plus rituximab (CHOP-R); and cyclophosphamide, doxorubicin, etoposide, prednisone, cytarabine, bleomycin, vincristine, and methotrexate (PROMACE-cytaBOM). Transplant recipients have a higher risk of myelotoxic side effects, depending on their maintenance immunosuppression. A.L.'s prognosis is poor given the type and extent of her PTLD, which would have been more responsive to therapy if it had been diagnosed early. Polyclonal PTLD responds well to reduction in or discontinuation of immunosuppression and high-dose acyclovir or ganciclovir therapy for several weeks to months. The roles of prophylactic antivirals, Igs, and EBV PCR monitoring in the prevention of PTLD are currently controversial, with mixed results in current literature.[81]

Infection Prophylaxis

CASE 34-9

Question 1: M.C. is a 61-year-old male who underwent liver transplantation for end-stage liver disease secondary to alcoholic cirrhosis. His MELD at the time of transplant was 22, CMV serology was D+/R−, and he received an HCV Ab+ nucleic acid amplification testing (NAT)+ organ. Besides his immunosuppressives, he received ampicillin-sulbactam 1.5 g every 8 hours for

24 hours perioperatively. After transplantation, he also was started on TMP-SMX single-strength (SS, 400/80 mg) one tablet Mondays, Wednesdays, and Fridays; micafungin 100 mg daily; and valganciclovir 900 mg daily.

What is the rationale for the aforementioned agents? Should other measures be considered to prevent infection?

Infection continues to be a major source of morbidity and mortality in transplant patients. Transplant patients have the same risk of infection from transplant surgery as any other patient having a surgical procedure. The incidence of infections has decreased since the advent of cyclosporine. Infection rates, however, remain high—upward of 50% in transplant patients.[82] Infections can occur at any time after transplantation, but there are predictable time patterns for certain kinds of infections.[82] The time of highest risk for infection in transplant patients is during the first 6 months, because they are receiving the highest doses of immunosuppressive agents during this period. Another time of high risk is during and after treatment of acute rejection with high-dose immunosuppression. Patients can acquire new infections, reactivate old infections, or experience recurrence of underlying disease.

PERIOPERATIVE AND POSTOPERATIVE ANTIBACTERIAL THERAPY

Prophylactic antimicrobial therapy decreases the risk of surgical infections; however, prophylactic regimens and antibiotic therapies are highly institution dependent.[83] Kidney transplant recipients typically receive a first-generation cephalosporin, such as cefazolin, to cover uropathogens and staphylococci. Usually, antibiotic prophylaxis is given preoperatively, before skin incision and continued for one to three doses posttransplant. Owing to how severely ill a patient with cirrhosis is going into transplant and with the surgery requiring multiple anastomoses in a nonsterile environment (the bowel), liver transplantations are associated with the highest rate of life-threatening bacterial infection. Piperacillin–tazobactam is commonly used to cover staphylococci, enterococci, and *Enterobacteriaceae.* Duration of therapy in these patients is

individualized based on the patient's postoperative recovery, but usually lasts from 24 to 96 hours posttransplant.[83]

DONOR-DERIVED INFECTIONS

Donor-derived infections are any infection present in the donor that is transmitted to one or more recipients. There are numerous pathogens that could be transmitted, whether expected or unexpected. Some expected transmissions are CMV, syphilis, and hepatitis B virus (HBV; core antibody-positive donors) because there is knowledge before the transplant of the infection in the donor. These infections potentially require monitoring, prophylaxis, and/or treatment.[84] With a continued shortage of available organs and the need to expand the donor pool along with advances in antiviral therapy for these disease states, there is a more recent use of HIV-positive organs to HIV-positive recipients and organs from HCV Ab+ NAT+/– donors to HCV-negative recipients.[85–87] Some unexpected infections are bacteremic donors or those with positive donor urine cultures.

M.C. received an HCV Ab+ NAT+ donor. He will require monitoring of his HCV RNA PCR and obtain an HCV genotype. Usually, a test to predict the presence of fibrosis in the liver, if any, is also completed. These labs will assist in obtaining antiviral therapy for the patients to achieve a sustained virologic response (HCV is not detected in blood ≥12 weeks after completing treatment) posttransplant.

PNEUMOCYSTIS JIROVECI PNEUMONIA

Pneumocystits jiroveci is an opportunistic fungus that infiltrates the lungs causing pneumonia. *P. jiroveci* pneumonia (PJP) is associated with a high mortality rate in transplant patients, and routine prophylaxis is required for usually the first six months posttransplant. First-line prophylaxis therapy is TMP/SMX, which can be dosed as SS daily or double strength with a frequency of three times weekly. For patients with sulfa allergies, alternatives such as dapsone 50 to

100 mg PO daily, inhaled monthly doses of pentamidine 300 mg, and atovaquone 1500 mg daily are used.[88,89]

OTHER OPPORTUNISTIC INFECTIONS

Because the opportunistic infections shown in **Table 34-3** occur at such a high rate, it is routine to provide specific prophylaxis for many of them. Similar to PJP, CMV and herpes virus infections should be covered by universal or preemptive prophylaxis postoperatively.

Table 34-3
Common Opportunistic Infections After Transplantation

Organisms	Usual Time of Onset After Transplantation
Cytomegalovirus	1–6 months
Herpes simplex virus	2 weeks–2 months
Epstein–Barr virus	2–6 months
Varicella-zoster virus	2–6 months
Fungal	1–6 months
Mycobacterium	1–6 months
Pneumocystis jiroveci pneumonia	1–6 months
Listeria	1 month–indefinitely
Aspergillus	1–4 months
Nocardia	1–4 months
Toxoplasma	1–4 months
Cryptococcus	4 months–indefinitely

ANTIFUNGAL

Thrush prevention with the use of nystatin suspension 500,000 to 1,000,000 IU by “swish and swallow” three to four times a day is commonly used in abdominal transplant patients during their inpatient stay or for a duration of 1 to 3 months posttransplant. Other antifungal prophylaxis such as fluconazole can be used to reduce fungal colonization of the GI tract in liver and pancreas transplant patients. For high-risk liver transplant patients, there are several

studies assessing the use of fluconazole, echinocandins, and even amphotericin B posttransplant to reduce the incidence of invasive fungal infections, in particular, aspergillosis.[90–92]

HEPATITIS B

HBV can be acute or chronic, and some patients may have a recovered HBV infection. As mentioned earlier, transplant patients who have not been exposed to HBV may be candidates to receive a donor who is HBV core positive. To treat and prevent HBV recurrence, antiviral therapy is used, such as lamivudine, entecavir, tenofovir, and others. In liver transplant patients with acute or chronic HCV, the use of hepatitis B immune globulin (HBIG) with oral antiviral therapy is used postoperatively. Dual therapy is used because monotherapy with HBIG is associated with a higher recurrence rate (in 10%–50% of patients). HBIG 10,000 IU IV is commonly given intraoperatively and daily for the first week. After the first week, there are a variety of redosing methods based on the risk of hepatitis B recurrence and on hepatitis B surface Ab titers. Because HBIG is expensive (up to $50,000 per patient per year) and with the newer, more potent oral antivirals available, more transplant centers now target lower titers (>100 IU/L rather than >500 IU/L) and HBIG doses of 1500 IU intramuscularly every 3 to 4 weeks.[93]

HEPATITIS C

Another virus of concern is hepatitis C and the recurrence of hepatitis C viral replication after transplantation.[94] Overimmunosuppression can have a significant detrimental effect on this disease after transplantation. Survival rates are significantly lower at 5 years after transplant compared with patients who received liver transplants for non-hepatitis C causes.[94] Recently, there have been dramatic advances in the treatment of hepatitis C, with the advent of non-IFN–based DAA therapies. In addition, the newer DAA therapies have a much-improved tolerability profile and are able to be used in patients with renal dysfunction. They have less cytopenias and limited constitutional symptoms, thus

substantially reducing the need to hold or discontinue therapy, as compared to IFN and ribavirin.[95,96]

CASE 34-10

QUESTION 1: R.S., a 42-year-old, 149.91-pound (68-kg) female with end-stage liver disease caused by alcoholic cirrhosis, received an orthotopic liver transplant 6 months ago. She presents to the clinic with general fatigue, diarrhea, and nausea. At the time of transplantation, both the donor and the recipient were positive for CMV antibodies (D+/R+). Her maintenance immunosuppression regimen postoperatively included a taper to prednisone 5 mg daily and tacrolimus 8 mg PO bid for a goal trough concentration of 8 to 10 ng/mL. She was also on valganciclovir prophylaxis for 3 months posttransplant. Last month, her postoperative course was complicated by acute cellular rejection likely due to her nonadherence to taking her medications, resulting in a consistent subtherapeutic tacrolimus concentration. For her rejection, she received high-dose methylprednisolone with a prednisone taper. MMF was also initiated at this time at a dose of 1 g bid. Since this episode, her liver has functioned well. It was decided to admit the patient from clinic because of her symptoms and lab values. A physical examination was remarkable for an oral temperature of 102.02 °F (38.9 °C), a BP of 121/82 mm Hg, a heart rate of 98 beats/minute, and a respiratory rate of 23 breaths/minute. All other findings on her examination were benign. Pertinent laboratory findings during admission include the following:

WBC count, 1800 cells/μL
Platelet count, 52,000 cells/μL
BUN, 20 mg/dL
SCr, 0.96 mg/dL
Total bilirubin, 1 mg/dL
AST, 23 IU/L
ALT, 25 IU/L
CMV PCR, 342,000 copies/mL (normal <500 copies/mL)
12-hour tacrolimus concentration, 12.1 ng/mL

What is the most likely diagnosis for R.S.?

CYTOMEGALOVIRUS

A major concern for R.S. is her CMV infection, which is commonly encountered within 1 to 6 months of solid organ transplant. It is a ubiquitous virus belonging to the herpes virus group. In healthy immunocompetent adults, infection with the virus is usually

asymptomatic, whereas in immunocompromised patients, CMV can cause significant morbidity and mortality. CMV can potentiate the risk of developing bacterial and fungal infections and induce chronic injury to the transplanted organ (arteriosclerosis in the heart, obliterative bronchiolitis in the lungs, vanishing bile duct syndrome in the liver, and chronic arteriopathy in the kidneys).[97] Also, CMV infection and disease can result in dysregulation of the immune system, increasing the risk of rejection.

Etiology

CMV infection in transplant recipients usually occurs when latent viruses from a seropositive donor organ are reactivated owing to immunosuppression. Without prophylaxis, transmission of CMV from a positive donor to a negative recipient leads to an 80% to 100% infection rate and a 40% to 50% disease rate; a positive donor to a positive recipient leads to a 40% to 60% reactivation rate and a 20% to 30% disease rate; and a negative donor to a negative recipient leads to a 0% to 5% infection rate. Transplant recipients at highest risk for developing the disease are (a) those who are or have a serologically positive donor and negative recipient (D+/R−) at the time of transplant, (b) elderly, (c) those who received antilymphocyte antibodies, (d) those who received a retransplantation because of acute rejection, and (e) those who received larger amounts of immunosuppressive agents.[97] R.S. is at risk for CMV infection and disease because she was treated for rejection and is currently on a more intense immunosuppression regimen, which is likely oversuppressing her immune system.

Diagnosis

Diagnosis of CMV is based on both clinical and laboratory findings. CMV may be detected by culturing body fluids, such as bronchoalveolar lavage, urine, blood, ophthalmologic examination, and tissue biopsies. CMV is contained within the host's leukocytes, which appear to have large intranuclear inclusion bodies. CMV PCR is primarily used for measuring viral loads in the patient's blood and

is called *CMV DNAemia*. The lower and upper limit of quantification of the assay will vary among tests, and a CMV PCR (of the whole blood or plasma) result of >1000 IU/mL is probably concerning for CMV DNAemia. Depending on the sensitivity of the assay, R.S. has laboratory findings consistent with CMV infection: evidence of CMV replication in any body fluid or tissue specimen regardless of symptoms. R.S. is also presenting with CMV disease: evidence of CMV infection with attributed symptoms. CMV disease can be either a viral syndrome where symptoms are present or a tissue-invasive disease (confirmed by tissue biopsy). She has leukopenia, thrombocytopenia, and clinical symptoms consistent with CMV infection and disease, including fatigue, nausea, and diarrhea.[98]

Clinical manifestations

In healthy immunocompetent adults, the CMV-infected individual is usually asymptomatic but may present with mild malaise, fever, and myalgias as well as abnormal liver enzymes and lymphocytosis. More severe reactions are rare.[96,97] CMV may, however, be life-threatening in the immunocompromised. The actual CMV course may be limited to fever and mononucleosis, or it may extend to organs presenting as pneumonitis, hepatitis, gastroenteritis, colitis, disseminated infection, encephalopathy, or leukopenia.

At this time, it is unclear whether R.S. has any end-organ involvement/disease. She presents with GI symptoms, such as diarrhea and nausea, which may be indicative of CMV gastroenteritis or CMV colitis. These symptoms could also be caused by side effects of her MMF or other medications. To fully differentiate between CMV tissue-invasive disease and medication side effects, a tissue biopsy should be obtained and/or an altering of immunosuppression/medications that are likely a cause of her symptoms.

Case 34-10, Question 2: What is the duration of therapy and treatment options?

Duration of therapy

CMV viral load should be monitored weekly to determine duration of therapy. CMV viral load should be below a threshold (usually <200 IU/mL for sensitive assays) on one or two consecutive tests drawn several days apart (minimum of 2-week duration) and resolution of clinical signs of CMV disease before discontinuing treatment.[98]

Ganciclovir

Before ganciclovir was available, CMV infection was "treated" by reducing the level of immunosuppression. This may be one of the explanations for an increased prevalence of rejection associated with CMV infections. Treatment has been largely unsuccessful with acyclovir, adenine arabinoside, and immune globulin. Ganciclovir is the first-line agent for the treatment of CMV disease in solid organ transplant recipients. Ganciclovir, a virostatic agent, is a nucleoside analog phosphorylated in infected cells to its active form and is then incorporated into replicating viral DNA. R.S. should receive ganciclovir IV or oral valganciclovir for mild CMV disease. Ganciclovir IV is recommended for life-threatening and severe cases of CMV disease.[98]

The usual dose of ganciclovir is a 5 mg/kg/dose every 12 hours, and the dose of valganciclovir is 900 mg PO bid. Both require renal dosage adjustments, which is the only recommended reason for altering the dose.[98] The most common adverse effect associated with ganciclovir therapy is neutropenia, occurring in up to 27% of patients.[99] Neutropenia is defined as an absolute neutrophil count of <500 to 1000 cells/mL. The use of a granulocyte colony-stimulating factor, such as filgrastim, to improve neutropenia and/or the discontinuation of other potential medications causing neutropenia is recommended before changing treatment therapy.[98,100] Because CMV has a propensity to cause neutropenia as well, it is often difficult to distinguish the cause. If laboratory findings and clinical signs and symptoms of CMV disease are resolving and the patient remains neutropenic, the most likely cause is ganciclovir. Thrombocytopenia occurs in ~20% of ganciclovir recipients. Patients

with initial platelet counts <100,000/mL appear to be at greatest risk. Other adverse effects include CNS effects, fever, rash, and abnormal LFT findings.[97,99] R.S.'s WBC with differential and platelet counts should be assessed every 3 to 4 days during therapy.

Immunoglobulins

The use of Igs to treat CMV disease in solid organ transplantation is controversial. They are expensive and sometimes in short supply. Igs provide passive immunization by potentiating an antibody-dependent, cell-mediated cytotoxic reaction. Basically, the Igs modify the immunologic response that damages host tissue. Some evidence suggests that Igs may have synergistic or additive effects with current antiviral drugs in the treatment of CMV disease.[100] Both unselective Igs and CMV hyperimmune globulin have been studied in combination with ganciclovir, although not usually recommended. CMV hyperimmune globulin is prepared from high-titer pooled sera that have a fourfold to an eightfold enrichment of CMV titers compared with unscreened Ig.

CMV Ig may be given as a 100 mg/kg/dose every other day for 14 days. This is the dose recommended for the treatment of CMV when used in combination with ganciclovir. The most common adverse effects associated with the administration of Igs are infusion related and include fever, chills, headache, myalgia, light-headedness, and nausea and vomiting.

Foscarnet

Foscarnet is a virostatic pyrophosphate analog that inhibits DNA synthesis; however, unlike ganciclovir, no phosphorylation is required for activation. Because this drug has a high nephrotoxicity propensity and because most transplant recipients are already receiving drugs that are nephrotoxic, experience with the use of foscarnet in solid organ transplantation is limited. At most centers, foscarnet is a second- or third-line agent to be used only if intolerance or resistance develops with ganciclovir therapy.

The usual dosage of foscarnet is 60 mg/kg/dose every 8 hours and should be dose adjusted for renal dysfunction. The most serious adverse effect with foscarnet is nephrotoxicity, which occurs in up to 50% of patients and is probably induced by acute tubular necrosis. Therefore, prehydration is suggested to help minimize or avoid nephrotoxicity. GI effects, a decrease in hemoglobin and hematocrit, an increase in LFTs, and an alteration of serum electrolyte concentrations are other side effects of foscarnet. All of these appear to be reversible on discontinuation of the drug. SCr should be monitored daily during therapy.[99]

Cidofovir

Similar to foscarnet, cidofovir inhibits DNA synthesis and does not require phosphorylation for its activity. It is approved for CMV retinitis in patients with acquired immunodeficiency syndrome. Cidofovir may be used for CMV treatment as salvage therapy in the setting of ganciclovir and foscarnet resistance. Its use is limited because of its nephrotoxic side effect, and the addition of probenecid is used to competitively inhibit the uptake of cidofovir in the proximal tubular epithelial cells to lessen its nephrotoxicity.

Letermovir

A CMV UL56 terminase inhibitor with specific activity for CMV and not for other herpesviruses, letermovir may be useful for salvage therapy in combination with reduced immunosuppression; however, its overall efficacy for treatment is still to be determined and limited by its mechanism of action. It has undergone a phase IIa randomized, controlled study for a potential treatment option for preemptive CMV strategy in kidney transplant recipients at lower doses than that approved for prophylaxis in hematopoietic stem cell transplant (HSCT). It is available in both IV and PO formulations. Adverse effects tend to be more favorable and uncommon, with mainly GI (gastritis, nausea), dyspnea, and hepatitis.[101,102]

Cytomegalovirus resistance to antiviral therapies

Although uncommon, CMV resistance to antiviral therapies, as defined by continued viral replication despite prolonged treatment, may be present in 5% to 12% of patients who have a high-risk serostatus (D+/R−). There have been two primary gene mutations associated with this resistance, one to the UL97 kinase and the other to the UL54 DNA polymerase gene. The vast majority (90%) of resistant strains to ganciclovir contain mutations to the *UL97* gene, which usually does not confer cross-resistance to other antiviral therapies, including cidofovir or foscarnet.[103] As illustrated by R.S.'s case, a patient who has received prophylactic therapy does not preclude the development of CMV infection or disease after the prophylaxis is withdrawn or, in rare instances, during prophylactic therapy.[104–106]

Prophylaxis

Case 34-10, Question 3: What are the methods and therapy options to prevent CMV in transplant patients?

Because of its significant consequences, efforts should be made to prevent CMV infection and disease. Many studies have tried to ascertain the easiest, most cost-effective regimen to prevent CMV. CMV-specific immune monitoring assays are currently being used and studied to monitor CMV-specific T-cell responses to assist with determining a patient's risk for CMV disease. These assays may be valuable to assist with clinical decisions regarding the need for and duration of secondary prophylaxis along with treatment duration. Duration of universal prophylaxis is for 3 months posttransplant for intermediate risk (D− or +/R+) and recommended for 3 to 6 or 6 months in CMV high-risk (CMV D+/R−) liver and kidney patients, respectively.[98]

Universal Prophylaxis

Ganciclovir

The use of both the IV and oral formulations of ganciclovir to prevent CMV disease has been studied in liver and kidney recipients.[107] Very few large trials have been conducted, and most of the data in the solid organ transplantation population are from small uncontrolled trials. Another difficulty lies in the large discrepancies that exist between the trials with regard to the terminology used to define prophylaxis and high-risk patients. Until the introduction of valganciclovir, ganciclovir was the most widely used prophylactic agent. In the United States, oral ganciclovir therapy has not been commercially available for a number of years. Thus, most transplant centers are now solely using valganciclovir therapy as their first-line agent. IV ganciclovir is still available and can be used for short periods if the patient is not able to tolerate oral therapy.

Valganciclovir

Valganciclovir was developed because oral ganciclovir has a very low bioavailability (<10%). Valganciclovir is the L-valyl ester of ganciclovir, which is a prodrug that is rapidly and completely converted into ganciclovir by hepatic and intestinal esterases once absorbed across the GI tract. The absolute bioavailability of valganciclovir is ~60%, so that a 900-mg single PO dose given with food is an AUC equivalent to a 5 mg/kg IV dose of ganciclovir. This is roughly twice the AUC achieved by 1000 mg of ganciclovir given PO tid. Valganciclovir is currently FDA approved for the treatment of HIV-associated CMV retinitis and to prevent CMV disease in heart, kidney, and pancreas transplantation.[104,105] Valganciclovir is not FDA approved for the prevention of CMV disease in liver transplantation, although it is often used in such cases. Several small studies have demonstrated that valganciclovir is effective in treating CMV infection preemptively and potentially preventing CMV disease.[104]

Because valganciclovir is very expensive and has a high potential for causing hematologic toxicities, several studies have been conducted using reduced dosing strategies. Some centers use half the recommended dose of 900 mg PO daily in patients with good renal function and have shown equivalent clinical outcomes with the

potential of reducing cost and toxicities. These studies were conducted in kidney transplant patients, and the dosing of this agent is transplant center specific based on institutional protocols.[106]

Valacyclovir

One published meta-analysis of 12 trials that included 1574 patients evaluated valacyclovir as a prophylactic agent in transplant recipients.[108] Valacyclovir was found to be more effective than acyclovir in preventing herpes viruses, including CMV. Most transplantation centers, however, do not use valacyclovir for routine prophylaxis of CMV, and still consider valganciclovir as first line. The use of valacyclovir or acyclovir is commonly used for prophylaxis for low-risk patients with CMV (CMV D–/R–).

Letermovir

This drug is currently approved for CMV prophylaxis in patients with CMV-seropositive allogeneic HSCT, with a dosing of 480 mg daily. When administered with cyclosporine, a dose of 240 mg daily is recommended because of drug–drug interaction. Because letermovir has a narrow antiviral effect, is active against CMV, and has no activity against other herpesviruses, other antiviral drugs should be used for the prevention of herpes simplex virus, such as acyclovir. Studies are under way evaluating its use in solid organ transplant patients.[109]

Preemptive Therapy

Owing to recent advances in the laboratory tests used to identify and quantify CMV, possible ineffectiveness of prophylactic therapy, and the toxicity and cost of valganciclovir, preemptive therapy may be used to prevent CMV. The technique involves withholding prophylactic therapy and using weekly laboratory tests to identify presymptomatic CMV DNAemia, mainly using serum CMV DNA PCR. Once a patient develops CMV DNAemia, he/she receives treatment. This strategy has been prospectively studied and is as

effective as universal prophylaxis, with some potential drug cost advantages. However, a few recent studies have demonstrated a higher incidence of the indirect effects of CMV in the preemptive group—graft loss being the most concerning in one study. Thus, the preemptive therapy role is controversial, with many centers still using universal CMV prophylaxis in all solid organ transplant recipients.[100]

Role of mammalian target of rapamycin inhibitors

mTOR inhibitors have been found to inhibit viral cell growth and enhance memory T-cell function, such as CMV-specific memory cells, CD4+ helper T cells, and CD8+ killer T cells. Its use has been studied to reduce the incidence of CMV events, and its benefit has been found to be more evident in reducing CMV events in CMV moderate-risk patients (CMV R+) than in high-risk patients (CMV D+/R−).[110–113] R.S. is CMV moderate risk (R+) and may be a candidate for use of an mTOR inhibitor, especially if she had CMV recurrence or is unable to tolerate CMV prophylaxis if requiring prophylaxis again posttransplant.

BK POLYOMAVIRUS INFECTION

CASE 34-11

Question 1: G.H. is a 41-year-old Caucasian male 20 months' post deceased kidney transplant. His posttransplant course has been more recently complicated by an episode of mixed antibody-mediated and cellular rejection, which was treated with IVIG, Plasma exchange (PLEX), high-dose steroids, and ATG therapy. His current immunosuppressant regimen consists of tacrolimus 8 mg PO bid (tacrolimus goal 8–10 ng/mL), MMF 1 g PO bid, and prednisone 5 mg PO daily. Today, he is in the transplant clinic for a routine follow-up visit. He presents with some mild pain when urinating and a slight brownish red color to his urine. Pertinent results are as follows: BUN, 36 mg/dL, SCr, 2.4 mg/dL (baseline 1.5 mg/dL), and tacrolimus trough concentration of 9.6 ng/mL. A urinalysis finding showed negative for bacteria, moderate for blood, and a urine test result showed "decoy" cells. In addition, his BK virus PCR was >10.

What is BK virus? How is it diagnosed and what are its clinical manifestations?

BK virus is a human polyomavirus, first isolated in 1971. Polyomaviruses are small, nonenveloped viruses with a closed, circular, double-stranded DNA sequence. Little is known about the transmission or about the primary infection of BK virus. It is believed that viremia during the initial exposure results in systemic seeding and subsequently becomes a latent infection. The kidney is the main site of BK virus latency in healthy people. More than 50% of the general population express BK virus antibodies by age 3 years. Immunosuppression after transplantation probably leads to the reactivation of the virus, but other factors, such as organ ischemia and coinfection with other pathogens, may contribute to reactivation. Reactivation inevitably leads to viruria or viral shedding into the urine. Asymptomatic viruria occurs in ~10% to 45% of kidney transplant patients.[114]

Decoy cells in the urine and BK virus PCR in blood are used as screening tools. Blood or plasma BK virus PCR is a more sensitive and stable test, and correlates better with renal dysfunction than do decoy cells. The American Society of Transplantation recommends screening for BK virus in all kidney transplants, by measuring serial BK PCRs monthly for the first 3 to 6 months posttransplant, then every 3 months until the end of the first year posttransplant, whenever there is an unexplained risk in SCr, and after treatment of acute rejection. If the BK PCR is consistently >10,000 copies/mL, it is recommended to reduce immunosuppression.[115] Most cases of BK virus occur within the first 3 months of transplantation, although a number of cases have been reported as long as 2 years after transplantation. The major risk factor is the degree of immunosuppression. G.H., like many patients with BK virus, is mildly symptomatic with an elevated SCr along with a change in urine color and painful urination. Other more common symptoms are difficulty urinating, increased frequency of urination, fever, muscle pain, or weakness. Because G.H. has recently received higher doses of immunosuppression, he is at higher risk of having BK virus, whether BK viruria, viremia, or even BK virus–associated nephropathy.

Treatment

Case 34-11, Question 2: G.H. is told to discontinue his MMF and to reduce his tacrolimus dose to 4 mg PO bid with a lower target trough goal of 5 to 7 ng/mL. Why was G.H.'s immunosuppressive regimen significantly reduced?

Because BK virus reactivation and BK virus–associated nephropathy (BKVAN) are strongly associated with the degree of immunosuppression, the reduction in or discontinuation of immunosuppressant agents is considered first-line therapy, and the most effective approach. Beneficial clinical responses have been demonstrated in some patients when the dose of the CNI is reduced and/or other agents are removed. Not all patients, however, respond to this maneuver. In addition, reduction in immunosuppression places patients at higher risk for rejection. Close clinical follow-up after reduction of immunosuppression is important, and monitoring viral loads from both the urine and the serum has been shown to correlate with clinical disease.[116]

Case 34-11, Question 3: With his initial lab results and rejection history, a kidney biopsy was completed and displayed no rejection. However, intranuclear inclusion bodies and IF was observed and its immunohistochemistry was consistent with BKVAN. During the month with reduced immunosuppression, G.H.'s SCr remains unchanged, and his serum and urine viral loads also remain approximately the same. What is BKVAN? Are there any additional treatment options for G.H.'s BKVAN at this time?

BK virus–associated nephropathy and antiviral therapy

Diagnosis of BKVAN is made by careful review of clinical, laboratory, and histologic findings. Patients are often asymptomatic, although hematuria has been noted in some patients. Clinically, BK virus nephritis mimics acute rejection, with an increase in SCr often leading to a tissue biopsy. Tissue histology is similar to cases of acute rejection and BK virus nephritis, with mononuclear infiltration as the predominant finding. The abundance of plasma cells, prominent tubular cell apoptosis, collecting duct destruction, and

absence of endarteritis are features that may distinguish BKVAN from acute cellular rejection. Although BK virus has been implicated in up to 5% of all cases of interstitial nephritis (of which 30% go on to graft failure), it is still unclear whether asymptomatic biopsy findings in the kidney transplant patients are a prognostic indicator. In addition, accelerated graft loss has been demonstrated in patients who received antilymphocyte antibodies in the presence of BKVAN nephropathy misdiagnosed as an acute rejection episode.

For antiviral therapy, there is cidofovir, which inhibits polyomavirus replication in vitro; however, to date, no well-conducted clinical trials have proved this agent to be effective in treating or preventing BKVAN in the transplant population. In a small number of case reports and case series, this agent was beneficial, but the appropriate dose and frequency are still undetermined. Most reports have used very small doses (0.25–1.0 mg/kg/dose) to minimize nephrotoxicity. It is given IV either weekly or every other week and usually continued until renal dysfunction is resolved and a decrease in the viral load occurs. Cidofovir is associated with a high incidence of nephrotoxicity, especially at much higher doses; therefore, patients usually receive pre- and postdose hydration with 0.9% NaCl boluses. Per the package insert, probenecid should be administered with high doses of cidofovir; however, this should be avoided with the low doses used to treat BKVAN to promote excretion of the drug into the kidney. Close clinical monitoring of the patient is advised if this treatment option is used. Other therapies that have been tried with mixed success are IVIG and leflunomide in place of the discontinued antimetabolite, such as mycophenolate.[117] Retransplantation has also been conducted with some success.[116]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references

and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9 Suppl 3:S1–S155. (5)

Manitpisitkul W, McCann E, Lee S, Weir MR. Drug interactions in transplant patients: what everyone should know. *Curr Opin Nephrol Hypertens*. 2009;18:404–411. (62)

Marino Z, Londoño MC, Forns X. Hepatitis C treatment for patients post liver transplant. *Curr Opin Organ Transplant.* 2015;20:251–258. (95)

Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2011 annual data report: kidney. *Am J Transplant.* 2013;13 Suppl s1:11–46.

Nankivell BJ, Alexander SI. Rejection of the kidney allograft. *N Engl J Med*. 2010;363:1451–1462. (6)

Parker A, Bowles K, Bradley JA, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients—BCSH and BTS Guidelines. *Br J Haematol.* 2010;149:693–705. (81)

Key Websites

www.ustransplant.org

www.srtr.org

www.unos.org

COMPLETE REFERENCES CHAPTER 34 KIDNEY AND LIVER TRANSPLANTATION

1. US Inflation Calculator. Inflation calculator. Accessed September 30, 21. https://www.usinflationcalculator.com
2. OPTN/SRTR 2019 annual data report. *Am J Transplant*. 2021;21:1–604.
3. Stegall MD, Gaston RS, Cosio FG, Matas A. Through the looking glass darkly: seeking clarity in preventing late kidney failure. *J Am Soc Nephrol*. 2015;26:20–29.
4. Maldonado AQ, Tichy EM, Rogers CC, et al. Assessing pharmacologic and nonpharmacologic risks in candidates for kidney transplantation. *Am J Health*

Syst Pharm. 2015;72(10):781–793.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guidelines for the care of kidney transplant recipients. *Am J Transplant*. 2009;9 Suppl 3:S1–S155.
6. Nankivell BJ, Alexander S. Rejection of the kidney allograft. *N Engl J Med*. 2010;363:1451–1462.
7. Thomson AW, Vionnet J, Sanchez-Fueyo A. Understanding, predicting and achieving liver transplant tolerance: from bench to bedside. *Nat Rev Gastroenterol Hepatol*. 2020;17(12):719–739. doi:10.1038/s41575-020-0334
8. Graff RJ, Lentine KL, Xiao H, Duffy B. The role of the crossmatch in kidney transplantation: past, present and future. *J Nephrol Therap*. 2012;S4. doi:10.4172/2161-0959.S4-002
9. Bassan G, Jawbeh A. Desensitization in kidney transplantation: review and future perspectives. *Clin Transplant*. 2014;28:494–507.
10. Lee RA, Gabardi S. Current trends in immunosuppressive therapies for renal transplant recipients. *Am J Heath Syst Pharm*. 2012;69:1961–1975.
11. Lennard L. The clinical pharmacology of 6-mercaptopurine. *Eur J Clin Pharmacol*. 1992;43:329–339.
12. Kurzawski M, Dziewanowski K, Gawron´ska-Szklarz B, Doman´ski L, Droz ´dzik M. The impact of thiopurine s-methyltransferase polymorphism on azathioprine-induced myelotoxicity in renal transplant recipients. *Ther Drug Monit.* 2005;27:435–441.
13. Staatz CE, Tett SE. Pharmacology and toxicology of mycophenolate in organ transplant recipients: an update. *Arch Toxicol*. 2014;88:1351–1389.
14. Bergmann TK, Barraclough KA, Lee KJ, Staatz CE. Clinical pharmacokinetics and pharmacodynamics of prednisolone and prednisone in solid organ transplantation. *Clin Pharmacokinet*. 2012;51:711–741.
15. Faulds D, Goa KL, Benfield P. Cyclosporine. A review of its pharmacodynamics and pharmacokinetic properties, and therapeutic use in immunoregulatory disorders. *Drugs.* 1993;45:953–1040.
16. Rath T. Tacrolimus in transplant rejection. *Exp Opin Pharmacother*. 2013;14:115–122.
17. Moes DJ, Guchelaar HJ, de Fijter JW. Sirolimus and everolimus in kidney transplantation. *Drug Disc Today.* 2015;20(10):1243–1249.
18. Satyananda V, Shapiro R. Belatacept in kidney transplantation. *Curr Opin Organ Transplant.* 2014;19:573–577.
19. Thiyagarajan UM, Ponnuswamy A, Bagul A. Thymoglobulin and its use in renal transplantation: a review. *Am J Nephrol*. 2013;37:586–601.
20. McKeage K, McCormack PL. Basiliximab: a review of its use as induction therapy in renal transplantation. *Biodrugs*. 2010;24(1):55–76.
21. Hanaway MJ, Woodle ES, Mulgaonkar S, et al. Alemtuzumab induction in renal transplantation. *N Engl J Med*. 2011;368:1909–1919.

22. Cianco G, Burke GW 3rd. Alemtuzumab (Campath 1H) in kidney transplantation. *Am J Transplant*. 2008;8:15–20.
23. Macklin PS, Morris PJ, Knight SR. A systematic review of the use of rituximab as induction therapy in renal transplantation. *Transplant Rev*. 2015;29:103–108.
24. Salvadori M, Bertoni E. Impact of donor specific antibodies on the outcomes of kidney graft: pathophysiology, clinical therapy. *World J Transplant*. 2014;4:1–17.
25. Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2013 annual data report: kidney. *Am J Transplant*. 2015;15(s2):1–34.
26. https://optn.transplant.hrsa.gov/media/1235/kas_faqs.pdf. Accessed May 30, 2022
27. Hardinger KL, Brennan DC, Klein CL. Selection of induction therapy in kidney transplantation. *Transpl Int.* 2013;26:662–672.
28. Erickson Al, Roberts K, Malek SK, Chandraker AK, Tullius SG, Gabardi S. Analysis of infusion site reactions in renal transplant recipients receiving peripherally administered rabbit antithymocyte globulin. *Transpl Int*. 2010;23:636–640.
29. Morgan RD, O'Callaghan JM, Knight SR, Morris PJ. Alemtuzumab induction therapy in kidney transplantation: a systematic review and meta-analysis. *Transplantation*. 2012;93:1179–1188.
30. Schroppel B, Legendre C. Delayed graft function. *Kidney Int*. 2014;86:251–258.
31. Djamali A, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M. Diagnosis and management of antibody—mediated rejection: current status and novel approaches. *Am J Transplant*. 2014;14:255–271.
32. Solez K, Colvin RB, Racusen LC, et al. BANFF 05 meeting report; differential diagnosis of chronic allograft injury and elimination of chronic graft nephropathy (CAN). *Am J Transplant*. 2007;7:518–526.
33. Neylan J. Immunosuppressive therapy in high-risk transplant patients: dose dependent efficacy of mycophenolate mofetil in African American renal allograft recipients. *Transplantation*. 1997;64:1277–1282.
34. Van Gelder T, Shaw LM. The rationale for and limitations of therapeutic drug monitoring for mycophenolate mofetil in transplantation. *Transplantation*. 2005:80:s244–s253.
35. Prendergast MB, Gaston RS. Optimizing medication adherence: an ongoing-opportunity to improve outcomes after kidney transplantation. *Clin J Am Soc Nephrol*. 2010;5:1305–1311.
36. Burton SA, Amir N, Asbury A, Lange A, Hardinger KL. Treatment of antibody-mediated rejection in renal transplant patients: a clinical practice survey. *Clin Transplant*. 2015;29:118–123.
37. Issa N, Kukla A, Ibrahim HN. Calcineurin inhibitor nephrotoxicity; a review and perspective of the evidence. *Am J Nephrol*. 2013;37:602–612.

38. Mulgaonkar S, Kaufman DB. Conversion from calcineurin inhibitor based immunosuppression to mammalian target of rapamycin inhibitors or belatacept in renal transplant recipients. *Clin Transplant*. 2014;28:1209–1224.
39. Snanoudji R, Tinel C, Legendre C. Immunological risks of minimization strategies. *Transpl Int*. 2015;28(8):901–910.
40. Adesina S, Alkhudhayri A, Patel JK, Naufal M, Geara A, Azzi J. Steroid withdrawal in kidney allograft recipients. *Expert Rev Clin Immunol*. 2014;10:1229–1239.
41. Knoll GA, Kokolo MB, Mallick R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation; systematic review and meta-analysis of individual patient data. *BMJ*. 2014;349:6679.
42. Augustine JJ, Bodziak KA, Hricik DE. Use of sirolimus in solid organ transplantation. *Drugs*. 2007;67:369–391.
43. Kaplan B, Qazi Y, Wellen JR. Strategies for the management of adverse drug events associated with mTOR inhibitors. *Transplant Rev*. 2014;28:126–133.
44. Tran TT, Nissen N, Poordad FF, Martin P. Advances in liver transplantation. New strategies and current care expand access, enhance survival. *Postgrad Med*. 2004;115:73–85.
45. Neuberger J. Developments in liver transplantation. *Gut*. 2004;53:759–768.
46. Roland ME, Stock PG. Review of solid-organ transplantation in HIV-infected patients. *Transplantation*. 2003;75:425.
47. https://optn.transplant.hrsa.gov/patients/by-organ/liver/questions-and-answers-about-liver-allocation. Accessed May 30, 2022
48. Keegan MT, Plevak DJ. Critical care issues in liver transplantation. *Int Anesthesiol Clin.* 2006;44:1–16.
49. Wijdidicks EFM. Neurotoxicity of immunosuppressive drugs. *Liver Transpl*. 2001;7:937–942.
50. Lindholm A, Kahan BD. Influence of cyclosporine pharmacokinetics, trough concentrations, and AUC monitoring on outcome after kidney transplantation. *J Clin Pharm Ther*. 1993;54:205–218.
51. Dunn CJ, Wagstaff AJ, Perry CM, Plosker GL, Goa KL. Cyclosporine: an updated review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (neoral)1 in organ transplantation. *Drugs*. 2001;61:1957–2016.
52. Jose M. Calcineurin inhibitors in renal transplantation: adverse effects. *Nephrology*. 2007;12:S66–S74.
53. Kuypers DRJ. Immunosuppressive drug monitoring—what to use in clinical practice today to improve renal graft outcome. *Transpl Int*. 2005;18:140–150.
54. Shaked A, Ghobrial RM, Merion RM, et al; A2ALL Study Group. Incidence and severity of acute cellular rejection in recipients undergoing adult living donor or deceased donor liver transplantation. *Am J Transplant*. 2009;9:301–308.

55. Neumann UP, Lang M, Moldenhauer A, et al. Significance of a T-lymphocytotoxic crossmatch in liver and combined liver-kidney transplantation. *Transplantation*. 2001;78:1163–1168.
56. Kuypers DR, Peeters PC, Sennesael JJ, et al; ADMIRAD Study Team. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. *Transplantation*. 2013;95:333–340.
57. Fisher RA, Ham JM, Marcos A, et al. A prospective randomized trial of mycophenolate mofetil with neoral or tacrolimus after orthotopic liver transplantation. *Transplantation*. 1998;66:1616–1621.
58. Demetris AJ, Adams D, Bellamy C, et al. Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. An international panel. *Hepatology*. 2000;31:792–799.
59. Sher LS, Cosenza CA, Michel J, et al. Tacrolimus as rescue therapy in liver transplantation. *Transplantation*. 1997;64:258–263.
60. Edmunds C, Ekong UD. Autoimmune liver disease post-liver transplantation: a summary and proposed areas of future research. *Transplantation*. 2016;100:515–524.
61. Behrend M. Adverse gastrointestinal effects of mycophenolate mofetil. Aetiology, incidence, and management. *Drug Saf*. 2001;24:645–663.
62. Manitpisitkul W, McCann E, Lee S, Weir MR. Drug interactions in transplant patients: what everyone should know. *Curr Opin Nephrol Hypertens*. 2009;18:404–411.
63. Dresser GK. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet*. 2000;38:41–57.
64. Campana C, Regazzi MB, Buggia I, Molinaro M. Clinically significant drug interactions with cyclosporine. An update. *Clin Pharmacokinet*. 1996;30:141–179.
65. Yamazaki H, Nakamoto M, Shimizu M, Murayama N, Niwa T. Potential impact of cytochrome P450 3A5 in human liver on drug interactions with triazoles. *Br J Clin Pharmacol*. 2010;69(6):593–597.
66. VFEND (voriconazole). Package insert. Pfizer Inc; 2019.
67. Vanhove T, Bouwsma H, Hilbrands L, et al. Determinants of the magnitude of interaction between tacrolimus and voriconazole/posaconazole in solid organ recipients. *Am J Transplant*. 2017;17:2372–2380.
68. Sharif A, Hecking M, de Vries AP, et al. Proceedings from an international consensus meeting on post transplantation on diabetes mellitus: recommendations and future directions. *Am J Transplant*. 2014;14:1992–2000.
69. Palepu S, Prasad GV. New onset diabetes mellitus after kidney transplantation: current status and future directions. *World J Diabetes*.

2015;6(3):445–455.
70. Lo C, Toyama T, Oshima M, et al. Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. *Cochrane Database Sys Rev*. 2020;8:DC009966.
71. Sarafidis P, Ferro CJ, Morales E, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patient with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrol Dial Transplant*. 2019;34(2):208–230.
72. Syoumpos S, Jardine AG, Mark PB. Cardiovascular morbidity and mortality after kidney transplantation. *Transpl Int*. 2015;28:10–21.
73. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: executive summary. *Circulation*. 2019;139:e1046–e1081.
74. Alshayeb MM, Josephson MA, Sprague SM. CKD—mineral and bone disorder management in kidney transplant recipients. *Am J Med Sci*. 2013;345:310–325.
75. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Case Res*. 2010;62:1515–1526.
76. Brunova J, Kratochvilova S, Stepankova J, et al. Osteoporosis therapy with denosumab in organ transplant recipients. *Front Endocrinol*. 2018;9:162.
77. Early C, Stuckey L, Tischer S. Osteoporosis in the adult solid organ transplant population: underlying mechanisms and available treatment options. *Osteoporos Int*. 2016;27(4):1425–1440.
78. Jagadeesh D, Woda BA, Draper J, Evens AM. Posttransplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. *Curr Treat Options Oncol*. 2012;13:122–136.
79. Nourse JP, Jones K, Gandhi MK. Epstein-Barr virus-related post-transplant lymphoproliferative disorders: pathogenetic insights for targeted therapy. *Am J Transplant*. 2011;11:888–895.
80. Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. *Drugs*. 2007;67:1167–1198.
81. Parker A, Bowles K, Bradley JA, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients—BCSH and BTS Guidelines. *Br J Haematol*. 2010;149:693–705.
82. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med*. 2007;357:2601–2614.
83. American Society of Health-System Pharmacists. ASHP therapeutic guidelines on antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*.

1999;56:1839–1888.
84. Wolfe CR, Ison MG. Donor-derived infections: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13547.
85. Reese PP, Abt PL, Blumberg EA, et al. Twelve-month outcomes after transplant of hepatitis c-infected kidneys into uninfected recipients. *Ann Intern Med*. 2018;169:273–281.
86. Liapakis A, Formica RN, Levitsky J. Solid organ transplantation of viral hepatitis C positive donor organs into viral hepatitis C negative recipients. *Curr Opin Organ Transplant*. 2018;23:257–263.
87. Muller E. Transplantation in resource-limited setting: using HIV-positive donors for HIV-positive patients. *Clin Nephrol*. 2015;83(7):39–41.
88. Gordon SM, LaRosa SP, Kalmadi S, et al. Should prophylaxis for *Pneumocystis carinii* pneumonia in solid organ transplant recipients ever be discontinued? *Clin Infect Dis*. 1999;28:240–246.
89. Fishman JA, Gans H. AST Infectious Diseases Community of Practice. *Pneumocystis jiroveci* in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13587.
90. Silveira FP, Kusne S. AST Infectious Diseases Community of Practice. Candida infections in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:220–227.
91. Winston DJ, Limave AP, Pelletier S, et al. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. *Am J Transplant*. 2014;14(12):2758–2764.
92. Evans JDW, Morris PJ, Knight SR. Antifungal prophylaxis in liver transplantation: a systematic review and network meta-analysis. *Am J Transplant*. 2014;14:2765–2776.
93. Cholongitas E, Goulis J, Akriviadis E, et al. Hepatitis B immunologlobulin and/or nucleos(t)ide analogues for prophylaxis against hepatitis b virus recurrence after liver transplantation: a systematic review. *Liver Transpl*. 2011;17:1176–1190.
94. Gallegos-Orozco JF, Yosephy A, Noble B, et al. Natural history of post-liver transplantation hepatitis C: a review of factors that may influence its course. *Transplantation*. 2009;15:1872–1881.
95. Marino Z, Londoño MC, Forns X. Hepatitis C treatment for patients post liver transplant. *Curr Opin Organ Transplant*. 2015;20:251–258.
96. Coilly A, Roche B, Duclos-Vallée JC, Samuel D. Optimal therapy in hepatitis C virus liver transplant patients with direct acting antivirals. *Liver Int*. 2015;35 Suppl 1:44–50.
97. Griffiths P, Baraniak I, Reeves M. The pathogenesis of human cytomegalovirus. *J Pathol*. 2015;235:288–297.

98. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*. 2018;102:900–931.
99. Einsele H, Mielke S, Grigoleit GU. Diagnosis and treatment of cytomegalovirus 2013. *Curr Opin Hematol*. 2014;21:470–475.
100. Hodson EM, Craig JC, Strippoli GF, Webster AC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev*. 2013;(2):CD003774.
101. Kaul DR, Stoelben S, Cober E, et al. First report of successful treatment of multidrug-resistant cytomegalovirus disease with the novel anti-CMV compound AIC246. *Am J Transplant*. 2011;11:1079–1084.
102. Stoelben S, Arns W, Renders L, et al. Preemptive treatment of cytomegalovirus infection in kidney transplant recipients with letermovir: results of a Phase 2a study. *Transpl Int*. 2014;27(1):77–86.
103. Chou S. Approach to drug-resistant cytomegalovirus in transplant recipients. *Curr Opin Infect Dis*. 2015;28:293–299.
104. Asberg A, Humar A, Rollag H, et al; VICTOR Study Group. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus in solid organ transplant recipients: the victor trial. *Am J Transplant*. 2007;7:2106–2113.
105. Brown F, Banken L, Saywell K, Arum I. Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. *Clin Pharmacokinet*. 1999;37:167–176.
106. Gabardi S, Asipenko N, Fleming J, et al. Evaluation of low versus high-dose valganciclovir for prevention of cytomegalovirus disease in high-risk renal transplant recipients. *Transplantation*. 2015;99:1499–1505.
107. Biron KK. Antiviral drugs for cytomegalovirus diseases. *Antiviral Res*. 2006;71:154–163.
108. Fiddian P, Sabin CA, Griffiths PD. Valacyclovir provides optimum acyclovir exposure for prevention of cytomegalovirus and related outcomes after organ transplantation. *J Infect Dis*. 2002;186 Suppl 1:S110–S115.
109. Helou GE, Razonable RR. Letermovir for the prevention of cytomegalovirus infection and disease in transplant recipients: an evidence-based review. *Infect Drug Resist*. 2019;12:1481–1491.
110. de Sandes-Freitas TV, Antero Pinheiro PM, de Mattos Brito ML, Girão CM, Fernandes Campos E, de Matos Esmeraldo R. The impact of everolimus in reducing cytomegalovirus events in kidney transplant recipients on steroid-avoidance strategy: 3-year follow-up of a randomized clinical trial. *Transpl Int*. 2018;31(12):1345–1356.
111. Cristelli MP, Esmeraldo RM, Pinto CM, et al. The influence of mTOR inhibitors on the incidence of CMV infection in high-risk donor positive-recipient negative (D+/R−) kidney transplant recipients. *Transpl Infect Dis*. 2018; 20(4):e12907.

112. Sheng L, Jun S, Jianfeng L, Lianghui G. The effect of sirolimus-based immunosuppression vs. conventional prophylaxis therapy on cytomegalovirus infection after liver transplantation. *Clin Transplant*. 2015;29(6):555–559.
113. Tedesco-Silva H, Felipe C, Ferreira A, et al. Reduced incidence of cytomegalovirus infection in kidney transplant recipients receiving everolimus and reduced tacrolimus doses. *Am J Transplant*. 2015;15(10):2655–2664.
114. Randhawa P, Brennan DC. BK virus infection in transplant recipients: an overview and update. *Am J Transplant*. 2006;6:2000–2005.
115. KDIGO. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9 Suppl 3:S44–S46.
116. Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA. Treatment of polyomavirus infection in kidney transplant recipients: a systemic review. *Transplantation*. 2010;89:1057–1070.
117. Dall A, Hariharan S. BK virus nephritis after renal transplantation. *Clin J Am Soc Nephrol*. 2008;3:S68–S75.

SECTION 7

Nutrition Issues

Section Editors: R. Rebecca Couris and Susan L. Mayhew

35

Basics of Nutrition and Patient Assessment

Margaret K. Murphy, Leigh Furman, and Kathleen M. Gura

CORE PRINCIPLES		CHAPTER CASES
1	A complete nutritional assessment of the patient is imperative before specialized nutrition is initiated. Parameters to be considered are nutrition and weight history, physical examination, anthropometric and biochemical measurements, and malnutrition risk.	**Case 35-1 (Question 1)**
2	The nutritional status of a patient can be assessed using the subjective global assessment (SGA) technique, which has been found to be highly predictive of outcome, because the SGA correlates strongly with other subjective and objective measures of nutrition.	**Case 35-1 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
3	Patients who cannot meet their nutritional needs by consuming food orally should be considered for specialized nutritional support, which is the provision of parenteral or enteral nutrients.	**Case 35-1 (Question 2)**
4	Protein and calorie goals are assessed on the basis of the disease status and body weight of the patient.	**Case 35-1 (Question 3)**
5	Nutritional support regimens should be tailored on the basis of the requirements, response, and tolerance of the patient. Patients with inflammatory bowel disease are particularly at risk for developing vitamin and other micronutrient deficiencies, and, therefore, supplementation is warranted.	**Case 35-1 (Question 4)**
6	The fluid needs of a patient are determined by the following steps: (a) need to correct fluid imbalances, (b) maintenance of fluid requirements, and (c) replacement of ongoing fluid losses.	**Case 35-1 (Question 5)**

CORE PRINCIPLES		CHAPTER CASES
7	Continued success of a nutritional support regimen can be accomplished by appropriate nutritional assessment after the initiation of therapy. The parameters such as patient weight trends, nitrogen balance, and prealbumin are considered when determining the need to adjust therapy.	**Case 35-1 (Question 6)**
8	Overfeeding should be avoided in patients, and a gradual and conservative approach to instituting nutritional support should be used to prevent potential metabolic abnormalities.	**Case 35-1 (Question 7)**

INTRODUCTION

Diet and nutritional status are fundamental for good health. Adequate and appropriate nutrition is essential for growth and development, consisting of a complex system of macronutrients, vitamins, minerals, and fluids. When an imbalance exists between the supply and the demand for the sources of energy and nutrients by the body, a nutritional disorder may result. Many chronic diseases such as cancer and coronary artery disease have dietary associations. Clinicians must be aware of the importance of proper nutrition in disease prevention and the interrelationships of the biochemical roles of nutrients and their impact on deficiency states and disease processes. Years of research and clinical experience have led to the creation of various screening tools, assessment techniques, and guidelines to aid practitioners in their quest to delay

or prevent patients from developing dangerous sequelae associated with deviations from optimal nutrition.[1] This chapter reviews the basic concepts of nutrition and how diet can influence the management of disease.

NUTRITION BASICS

Adequate levels of energy sources and essential nutrients are critical for retaining the structural and biochemical integrity of the human body. Energy is provided in the diet by macronutrients such as carbohydrates, proteins, and lipids. Essential nutrients, none of which offer any caloric value, are supplied to the body in the form of water, electrolytes, vitamins, and minerals.

Macronutrients

Humans need to consume food to sustain life. The unique structure and function of our cellular architecture allow human beings to convert the chemical free energy contained within the diet into high-energy, biologically active compounds. This transformation of food energy into forms of viable free energy through cellular respiration is an extremely inefficient process. Close examination of the distribution of food energy within the human body reveals that ~50% is lost as heat, 45% is available to the body in the form of adenosine triphosphate, and the remaining 5% is thermodynamically required for the conversion to heat because the entropy of the final products is greater than that of the initial substrates. Ultimately, all of the energy derived from food is expended in the form of external work or heat.

In nutritional contexts, the energy available from food is expressed in terms of calorie. A calorie is technically defined by the amount of heat required to raise the temperature of 1 g of water by 33.08 °F (1 °C). This unit, however, is too small from a dietary perspective. A food calorie (sometimes written as *Calorie* with a large *C*, although

this convention is not strictly followed) is equivalent to 1000 calories or 1 kilocalorie (kcal). One food calorie is also equal to 4.184 kilojoules.[2] It is not uncommon for a single kilocalorie to be referred to as a calorie when communicating the energy content of food. This ambiguity must be understood by practicing clinicians to communicate properly not only with colleagues but also with patients and the general public who may not have an appreciation for this subtlety and thus remain confused when reading calories on nutrition labels while seeing kilocalories in textbooks, scientific publications, patient records, and the Internet.

CARBOHYDRATES

Carbohydrates, also known as saccharides, are organic compounds that consist of carbon, hydrogen, and oxygen. There are four main types of carbohydrates: monosaccharides, disaccharides, oligosaccharides, and polysaccharides. Carbohydrates may be classified as either simple (monosaccharides and disaccharides) or complex (oligosaccharides and polysaccharides), yet the exact delineation of these categories is often not clear. Although carbohydrates serve as a common source of energy for living organisms, these compounds also function as structural components and building blocks for complex genetic molecules.

Monosaccharides (eg, glucose) are the simplest carbohydrates and cannot be hydrolyzed into smaller saccharide molecules. They are the major sources of fuel for metabolism, with glucose serving as a nearly universal and accessible reservoir of calories. Disaccharides (eg, sucrose) consist of two monosaccharides joined by a glycosidic bond. In the context of food science, monosaccharides and disaccharides are commonly referred to as *sugars*. Natural sources of monosaccharides and disaccharides include fruits and vegetables, but these compounds are also found in commercially manufactured products such as high-fructose corn syrup.

Oligosaccharides are short chains of monosaccharides typically composed of 3 to 10 molecules linked through glycosidic bonds.

These molecules are typically found connected to proteins or lipids functioning as chemical markers for cellular recognition. Their important role in the classification of blood groups is an example. Polymeric carbohydrate structures are referred to as *polysaccharides*, and function either as storage forms of energy, such as glycogen in animals or starch in plants, or as a structural component, such as cellulose in plants. Dietary polysaccharides must be broken down into their constituent monosaccharides in the digestive tract before absorption can occur.

Dietary carbohydrates are composed of ~60% polysaccharides, mainly starch, and disaccharides such as sucrose and lactose, which represent 30% and 10%, respectively. All carbohydrates provide 4 kcal of energy/gram. Although the exact amount of dietary carbohydrates sufficient for good health is not known, a mixed-fuel diet in which carbohydrates constitute 45% to 65% of the total energy intake is considered as an acceptable distribution range.[3]

PROTEIN

Polypeptides are linear chains of amino acids. These polypeptides can twist and fold alone or in groups into three-dimensional structures, generating a biochemical compound known as protein. Proteins are crucial to all living organisms, playing important and diverse roles in the structure, function, and regulation of the body's systems. Many proteins function as enzymes, which serve as catalysts to biochemical reactions and are important for metabolism. Proteins such as actin and myosin play a role in muscle contraction and movement. Some proteins stabilize blood by giving it the appropriate viscosity and osmolarity, whereas others participate in cell signaling and immune responses.

Protein is the second largest store of energy in the body after adipose tissue.[4] Although protein differs from the other two primary dietary energy sources because of its inclusion of nitrogen, the amino acid residues from proteins can be converted to glucose via gluconeogenesis to supply a continuous source of glucose for the body after the depletion of glycogen. Similar to carbohydrates, each

gram of protein supplies 4 kcal of energy. The loss of >30% of body protein, however, can compromise muscle strength, affect respiratory function, and negatively influence the immune system, all of which ultimately lead to organ dysfunction and death. It should be noted that protein and energy requirements of the body are intimately connected. During the times of infection or injury, metabolic rates rise, and body protein is suddenly oxidized into amino acids and mobilized for fuel utilization. In most instances, the injuries that patients experience are minimal and self-limiting; however, patients with chronic illnesses or those with complicating factors that result in a long-term hypermetabolic state can subsequently experience a dangerous loss of body nitrogen.

LIPIDS

Lipids comprise a broad spectrum of molecular species ranging from hydrophobic triglycerides and sterol esters to hydrophilic phospholipids and cardiolipins, as well as dietary cholesterol and phytosterols. Depending on their structure and composition at room temperature, they may be either solid or liquid. *Lipids* is used to refer to both liquid and solid fats, as well as other related substances. The term *oil* is used for any substance that does not mix with water and has a greasy feel, regardless of its chemical structure. Biologic lipids function as a form of energy storage, serve as the structural components of cell membranes, and participate as messengers in the vital process of cellular signaling.

In a nutritional context, fats that exist as liquids at room temperature are typically called *oils*, whereas fats that remain solid at room temperature are labeled as *fats*. Although the term lipid is often used synonymously for fat, fats are actually a subgroup of lipids also known as triglycerides. Triglycerides are synthesized by chemically combining glycerol with three fatty acid molecules. These fatty acids are generally nonbranched hydrocarbons containing an even number of carbon atoms ranging from 4 to 26 carbons. Adipose tissue is composed of fatty acids in varying lengths.

An unsaturated fat is a fatty acid that includes at least one double bond within the fatty acid chain, whereas a saturated fat is one that contains no double bonds. Unsaturated fatty acids result in less energy after the oxidation process of cellular metabolism compared with an equivalent amount of saturated fatty acids. Commercial manufacturers of processed food favor saturated fats because they are less vulnerable to rancidity (lipid peroxidation) and remain solid at room temperature. Foods containing unsaturated fats include avocado, nuts, and vegetable oils such as canola and olive oils. Meat products contain both saturated and unsaturated fats.

Importantly, each gram of fat yields 9 kcal of energy, twice that of either carbohydrate or protein. Approximately 35% to 40% of the total daily calories consumed by the average person are lipids. Higher fat diets can lead to more rapid weight gain, a positive attribute if the individual is malnourished or underweight, but a negative attribute if the individual is trying to achieve weight loss.[5] Triglycerides make up by far the largest proportion of dietary lipids consumed by humans. Fats play an essential role in maintaining the integrity of the hair and skin, insulating body organs against shock, and maintaining body temperature.

Although humans possess the biologic pathways to synthesize lipids, two polyunsaturated fatty acids must be obtained from the diet to prevent essential fatty acid (EFA) deficiency. Currently, there are only two identified EFAs for humans, α-linolenic acid (an ω-3 fatty acid) and linoleic acid (an ω-6 fatty acid). Fatty acids derived from these EFAs, such as arachidonic acid (ARA, derived from linoleic acid) and docosahexaenoic acid (DHA, derived from α-linoleic acid), are important constituents of membrane lipids. Recent evidence suggests that along with eicosapentaenoic acid (EPA, derived from α-linolenic acid) that DHA and ARA should also be considered EFAs. These particular fatty acids are important in growth and neurodevelopment and are precursors of critically important metabolic products. These include inflammatory mediators (eicosanoids such as prostaglandins, leukotrienes, and thromboxanes), gene regulators, substances that assist in the resolution of an inflammatory response (eicosanoids such as

protectins, resolvins, and lipoxins), and substances that regulate overall lipid metabolism.[6] In addition to these properties, specific fatty acids are also important for membrane fluidity, membrane and intracellular cell signals, and modulation of apoptotic pathways.

Essential Nutrients—Water

Water plays a critical role in nearly every biologic function necessary for life. The total body water in an adult male without fluid and electrolyte disorders is ~50% to 60% of the lean body weight.[7] Infants and children possess a much higher fractional water content, which then decreases progressively with age. Individuals with a greater percentage of body fat, such as females or obese patients, also tend to have less water for a given weight.

The total aqueous volume in the body can be divided into the intracellular and extracellular compartments. Because the intracellular fluid is the site of major metabolic activity, homeostatic mechanisms are therefore in constant execution to provide an environment of optimal ionic strength. The primary function of the extracellular fluid is to serve as a conduit between cells and between organs. Substantial ionic alterations within extracellular fluid can occur without a clinically significant impact on body function. This extracellular compartment can be further divided into three fractions: the interstitial volume, plasma volume, and transcellular water volume. Interstitial fluid flows around cells, allowing the total surface area of a cell to serve as an area of exchange. Plasma is the route for rapid transit within the body. Transcellular water is the smallest component of extracellular fluid and is the portion of total body water that is found within epithelial-lined spaces. Transcellular water includes the luminal fluid of the gastrointestinal (GI) tract, the fluids of the central nervous system, and the fluid in the eye, as well as the lubricating fluids at serous surfaces.

The basal requirement of water for a given individual is dependent on the sensible (urinary) and insensible losses of water. Urine osmolality and the total amount of solute excreted from the body

dictate the volume of water comprising urine. Fever can promote dehydration by increasing one's basal metabolic rate (BMR) in addition to raising the vapor pressure of expired air and sweat, resulting in higher respiratory and skin water losses, respectively. In the absence of fever and sweating, water loss through the skin is relatively fixed; however, urinary water excretion can vary greatly.

Essential Nutrients—Micronutrients

ELECTROLYTES

An electrolyte is a substance that, when dissolved in the body's fluids, dissociates into electrically charged ions. Electrolytes include sodium, potassium, chloride, magnesium, phosphorus, calcium, and bicarbonate. A subtle and complex balance of electrolytes exists between the intracellular and extracellular space. The precise maintenance of these electrolyte gradients is critical because such gradients regulate hydration and acid–base balance and ultimately have an impact on nerve and muscle function. Sodium, chloride, and bicarbonate are the main solutes in the extracellular fluid, whereas potassium, magnesium, phosphate, and proteins are the dominant solutes inside the cell.

Water can freely travel across the membrane of a cell, whereas the cell membrane itself is only selectively permeable to solutes. Osmotically active solutes are those that cannot cross the cell membrane and thereby exert an osmotic pressure that determines the distribution of water between fluid compartments. Electrolyte balance is traditionally maintained by the oral intake of substances containing electrolytes. Fruits and vegetables, milk, and sports drinks are replete with electrolytes. In oral rehydration therapy, electrolyte drinks containing sodium and potassium salts replenish the water and electrolyte levels in the body after dehydration caused by exercise, diarrhea, vomiting, intoxication, or starvation. The kidneys, in concert with hormones, such as antidiuretic hormone, aldosterone, and parathyroid hormone help to maintain electrolyte homeostasis within the body.

VITAMINS

Vitamins are organic compounds that cannot be biologically synthesized in sufficient quantities by humans and yet remain a vital requirement to sustain life. The biochemical functions of vitamins are diverse. Some vitamins assist in the regulation of electrolyte metabolism, whereas others participate in the control of cell and tissue growth and differentiation. Most vitamins function as cofactors, which are molecules that bind to enzymes to promote their catalytic activities.

Vitamins are classified by their biologic and chemical activity. Vitamins are designated as either water soluble or fat soluble. There are four fat-soluble vitamins (A, D, E, and K) and nine water-soluble vitamins (eight B vitamins and vitamin C) in humans. Water-soluble vitamins are used by the body quite rapidly, and amounts in excess are readily excreted from the body in urine. The fat-soluble vitamins are absorbed by the body using processes that closely parallel the absorption of lipids. Fat-soluble vitamins are more likely to lead to toxicity, or hypervitaminosis. Fat-soluble vitamin regulation is also of particular significance in cystic fibrosis.

Vitamins are procured through the diet or supplements. The body can manufacture only three vitamins from nondietary sources: vitamins D and K, and the B vitamin, biotin. Critically ill patients experiencing metabolic stress possess vitamin needs that may increase dramatically. Many disease states such as inflammatory bowel disease, liver and renal disease, intestinal failure, cancer, and acquired immunodeficiency syndrome–associated wasting can also result in a higher demand for vitamins. A parenteral formulation of multivitamins combining both fat- and water-soluble vitamins into an aqueous solution designed for incorporation into intravenous infusions is available for these classes of patients.

TRACE ELEMENTS

Appropriate intake levels of certain dietary minerals are required in small amounts to maintain optimal health. These dietary minerals are known as *trace elements* or *ultratrace elements*. Iron, zinc, copper,

manganese, and fluoride are classified as trace elements. These minerals are required in amounts between 1 and 100 mg/day by adults. Ultratrace elements, or those dietary minerals, that are required in quantities <1 mg/day, include arsenic, boron, chromium, iodine, selenium, silicon, nickel, and vanadium.

Most trace elements act as catalysts in enzyme systems and some, such as copper, are important in energy metabolism. Iron, as a component of hemoglobin, plays a vital role in oxygen transport within the body. Consuming a well-balanced diet is the recommended method for satisfying these micronutrient requirements. Many trace elements are naturally present in foods; however, some are added to foods to prevent nutrient deficiencies, such as fortifying salt with iodine to prevent development of hypothyroidism and goiter. When dietary intake is insufficient to meet the daily nutrient requirements of an individual or when chronic or acute deficiencies develop from pathology and injury, dietary supplements remain a viable option.

MALNUTRITION

Malnutrition may occur when there is any disruption of nutritional status, including disorders resulting from overfeeding, underfeeding, or through impaired nutrient metabolism. Clinically, malnutrition results in subcellular, cellular, or organ function changes that may increase risk of morbidity and mortality.[8,9]

Overnutrition results from excess intake of calories. Obesity has become a significant national health issue. From 1999 to 2000 through 2017 to 2018, the prevalence of obesity in U.S. adults increased from 30.5% to 42.4%.[10] More commonly, malnutrition refers to undernutrition. Undernutrition is the lack of calories, protein, or other nutrients necessary for tissue maintenance and repair. Undernutrition results from inadequate intake, increased requirements, impaired absorption, altered transport, or altered utilization of nutrients.[11] Inflammation, which promotes breakdown of

skeletal muscle, has become recognized as an important underlying factor for the development of malnutrition.[12,13]

An International Guideline Committee has proposed three categories for adult malnutrition diagnoses in the clinical setting[12]:

- Starvation-related malnutrition, which involves chronic starvation without inflammation, an example of which is seen in anorexia nervosa
- Chronic disease-related malnutrition, in which mild-to-moderate inflammation is present, examples of which are seen in patients with cancer or organ failure
- Acute disease- or injury-related malnutrition, in which acute and severe inflammation is present, examples of which are seen in patients suffering major infections, traumas, or burns

Risk of severe malnutrition increases if one of these categories concurrently exists with another, for example, a chronically malnourished patient who suffers an acute trauma.[13]

Patients in starvation or semistarvation states slowly adapt to inadequate nutrient intake. In this scenario, endogenous fat stores are used for energy and a slow loss of muscle proteins ensues. Nevertheless, energy and protein stores are not unlimited, and death occurs in previously normal-weight individuals after about 60 to 70 days of starvation.[14,15]

An incidence of malnutrition as high as 30% to 50% has been reported among hospitalized patients.[13] In hospitalized patients, the risk of acute malnutrition development is greater because nutrient intake is often inadequate, nutrient stores can be depleted, or the patients may experience concurrent injury or stress (infection, major surgery). The presence of acute stress or injury increases energy requirements to repair tissues. Breakdown of skeletal muscle to release amino acids for energy production by conversion to glucose occurs if exogenous energy is not provided to stressed patients. Even patients who were well nourished before the stressful event may quickly become at risk for this type of iatrogenic malnutrition. Usually, such acute malnutrition resolves once the illness or injury

improves and normal nutrient intake is resumed. The most common type of nutritional deficiency in hospitalized patients is protein-calorie malnutrition, which includes depletion of both tissue energy stores and body proteins. Complications develop more frequently for hospitalized patients who are malnourished as a result of organ wasting and functional impairments. These complications may include weakness, decreased wound healing, altered hepatic metabolism of drugs, increased respiratory failure, decreased cardiac contractility, and infections such as pneumonia and abscesses. Complications often increase the length of hospital stay and costs of care.[8,16–18]

No single parameter is definitive for the diagnosis of adult malnutrition; however, the presence of two or more of the following criteria is recommended for diagnosis[10]:

- Insufficient energy intake
- Weight loss
- Loss of muscle mass
- Loss of subcutaneous fat
- Fluid accumulation that may mask weight loss
- Diminished functional status (eg, hand grip strength)

On the other extreme of undernutrition lies obesity, an unhealthy accumulation of fat mass, defined as a body mass index (BMI) >30 kg/m^2. Obesity is a global pandemic that is also associated with increased morbidity and mortality with diminished quality and length of life while dramatically increasing individual, national, and global health costs.[19] It is important to emphasize that many obese individuals may often present with deficits of their nutrition status.[20] Sarcopenia (ie, sarcopenic obesity) is associated with adverse effects, putting obese persons at higher risk of complications when ill.[21] Owing to the lack of routine nutrition screening and assessment, the significance of undernutrition in sick obese individuals is often underdiagnosed.[22]

Defining Malnutrition

There is a wide variety of tools to identify nutrition risk factors. Ideally, these tests should be both reliable and valid while still providing rapid results in a cost-effective manner. In contrast, nutrition assessment permits the clinician to obtain more information and perform a nutrition-focused examination to ascertain if a nutrition derangement exists and to what severity.

Although a patient's weight is often used to determine nutritional status, there are limitations depending on how that value is obtained. It is best assessed in context with a patient's height. Because adults tend to overestimate their height and underestimate their weight, it is preferred that actual measurements are obtained. When estimating body fat, the usual body weight is more helpful than using normal reported values such as those contained in insurance tables.[23] Similarly, in children, body weight is more useful than is height in determining nutrient intake as well as body fat. Trends in weight changes are used in assessing nutritional status, although changes in fluid status may falsely influence these values. Likewise, in an obese patient, a loss in lean body mass may be undetected in the presence of excess body fat. Typically, a significant weight loss is defined as a 5% loss in 1 month, 7.5% loss in 3 months, or 10% in 6 months.[24] Whenever weight loss exceeds these amounts, it is termed as severe weight loss.

NUTRITION SCREENING AND ASSESSMENT

The nutrition status of an individual is a determinant of body composition and functional status. Aberrant states negatively affect patients' outcomes, increasing morbidity/mortality, time spent in the hospital, and readmission rates as well as costs, while decreasing quality of life.[9] Screening and assessment are different processes that encompass related variables to identify nutrition problems.[25] There is a wide variety of tests to identify nutrition risk factors.

Ideally, these tools should be both reliable and valid, yet be cost-effective while providing rapid results. In contrast, nutrition assessment allows the clinician to obtain more information and perform a nutrition-focused examination to determine whether a nutrition malfunction exists and to categorize its severity.

Nutrition Screening

Within 24 hours of hospital admission, the Joint Commission (http://www.jointcommission.org) requires patients to be screened to determine whether they are malnourished or at risk for developing malnutrition. The nutrition screening process identifies needs for further nutritional intervention or monitoring based on nutritional risk. The information obtained in the screening process depends on the patient population, the health care setting, and institutional specific policies. A number of screening tools have been described in the literature with varying reliability, specificity, and sensitivity. In some instances, the parameters included in nutrition screening may be more applicable in the outpatient setting rather than in the inpatient areas.[1,26]

The nutrition status of an individual is a determinant of body composition and functional status. Deficient states negatively affect patient outcomes, increasing morbidity/mortality, time spent in the hospital, and readmission rates as well as costs, while decreasing quality of life.[9] Therefore, screening for risk factors associated with deficiencies and, when indicated, assessing an individual's nutritional status should be part of the evaluation of a patient. Deficiencies in the nutrition status (ie, undernutrition) are still the most prevalent conditions in both the hospital and outpatient settings in the world, with rates ranging from 20% to 80%, based on the group of patients evaluated or the method used to provide the diagnosis.[27]

Patient Assessment

Nutritional assessment of a patient incorporates a collection of past medical data, analysis of body composition, evaluation of physiologic function, and complete physical examination. Proper patient assessment should include the examination of multiple factors and should not rely on any one parameter. This assessment serves to identify the presence and severity of malnutrition or the risk of developing malnutrition. A complete patient assessment performed by a trained practitioner can help determine the goals of therapy and specify the need for specialized nutritional support. Goals of therapy may be maintenance of existing nutritional status, repletion of fat and lean body mass, and prevention of complications associated with malnutrition.

NUTRITION HISTORY

A nutrition history is crucial to an effective nutritional assessment. Practitioners may gain valuable information by interviewing the patient or the patient's family and by reviewing the medical record to identify factors that can contribute to malnutrition or increase the risk of developing malnutrition.

Multiple factors can contribute to the development of malnutrition, including the patient's underlying disease states, past medical history, and socioeconomic circumstances. Medications can adversely affect nutritional status by decreasing the synthesis of nutrients, minimizing food intake through alteration of appetite and taste, changing the absorption or metabolism of nutrients, or increasing nutrient requirements. A complete evaluation of present and past body weight fluctuations contributes significantly to an appropriate nutrition history.

The components of a nutrition history are summarized in **Table 35-1**, some of which are expanded subsequently.

Table 35-1
Components of a Nutrition History

Medical history
Chronic illnesses

Surgical history
Psychosocial history
Socioeconomic status
History of gastrointestinal problems (nausea, vomiting, or diarrhea)
Diet history, including diets for weight gain or loss
Food preferences and intolerances
Medications
Weight history
Increase or decrease
Intentional or unintentional
Time period for weight change
Functional capacity

WEIGHT HISTORY

Weight history and influences are important in evaluating nutritional status. Weight loss is a sign of negative energy and negative protein balance, and is often associated with poor outcome in hospitalized patients.[26,28] A patient's current weight often is compared with a standard for ideal body weight (IBW). Percentage of IBW[26] is determined as shown in Eq. 35-1:

$$\%\ \text{IBW} = \text{Current weight}\ (100)/\text{IBW} \qquad \textbf{(Eq. 35-1)}$$

The primary limitation of this method of assessing weight is that the patient's weight is compared with a population standard rather than using the individual as the reference point. For example, a patient who is significantly overweight but has lost large amounts of weight may still be more than 100% of IBW and therefore not considered at risk for developing malnutrition. A more patient-specific method of evaluating weight is to compare current weight with the patient's usual weight. This can be determined using Eq. 35-2:

$$\% \text{ Usual body weight} = \text{Current weight } (100) / \text{Usual body weight} \quad \textbf{(Eq. 35-2)}$$

Using this method, the obese patient who has lost weight may be determined to be <90% of usual weight and therefore nutritionally at risk. It is also important to assess over what period the change has occurred. Involuntary weight loss is considered severe if loss exceeds 5% of usual weight within 1 month, or 10% of usual weight within 6 months. A nonvolitional weight loss of >10% is considered significant for malnutrition.[29] Patterns of weight loss must be evaluated to determine whether the loss is stabilizing or continual, the latter being a more serious concern. Weight gain after a significant weight loss may be considered a positive sign.

BODY WEIGHT AND BODY MASS INDEX

BMI is used to estimate adiposity in adults. Both height and weight are needed to calculate this value. The formula is weight (kg) ÷ height (m^2). **Table 35-2** shows how BMI can be used to define underweight, normal, or obese individuals. However, it is not a perfect tool. In trained athletes, BMI tends to overestimate body fat, whereas it underestimates body fat in elderly patients because of a loss of lean body mass.

Table 35-2
Interpretation of Nutritional Status Using the Body Mass Index (BMI)

Nutritional Status	BMI Measure (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25–29.9
Obese	30–39.9
Severe obesity	>39.9

Source: NHLBI obesity education initiative expert panel on the identification, evaluation, and treatment of overweight and obesity in adults. NIH Publication No.

98-4083. National Institutes of Health; 1998.

PHYSICAL EXAMINATION

Nutritional deficiencies may be identified on physical examination and may require further evaluation. Physical examination may include measurement of subcutaneous fat and skeletal muscle mass. Assessment of fat stores provides information about fat loss or gain and assumes fat is gained or lost proportionally throughout the entire body. The subcutaneous compartment contains ~50% of body fat. Muscle and fat wasting (often noticed in the temporal area), loss of subcutaneous fat and muscle in the shoulders, and loss of subcutaneous fat in the interosseous and palmar areas of the hands are readily identifiable. Other physical parameters that may be less obvious are assessment of hair for color changes and sparseness; skin for turgor, pigmentation, and dermatitis; mouth for glossitis, gingivitis, cheilosis, and color of the tongue; nails for friability and lines; and abdomen for signs of ascites or enlarged liver. In addition, the patient's fluid status must also be evaluated as a part of the physical examination.

Assessment of body composition

Body composition is used to describe the percentages of bone, fat, muscle, and water in human bodies.[30] Two people of the same sex and body weight may look completely different because they have a different body composition. This is because muscle mass takes up less space within the body than does fat mass; thus, body composition, as well as weight, determines leanness. The methods used to measure body composition differ in their ease of determination, cost, accuracy, use of radiation, and utility for estimating body fat or other body compartments relevant to nutritional status (eg, bone density). The most commonly used techniques are discussed here.

ANTHROPOMETRICS

Anthropometric measurements accurately reflect total body fat and skeletal muscle mass when used for the long-term comparisons of large, nutritionally stable populations. The most widely used anthropometric measurements to assess body composition are the triceps skinfold (TSF) and the mid-upper arm circumference. Reference standards are used to compare against values obtained in the examination.[31,32] Skeletal muscle mass or somatic protein mass can be estimated by measuring mid-arm circumference (MAC) and then calculating arm muscle circumference as given subsequently.

Skinfold thickness

Measurements of multiple skinfold thicknesses are frequently used because it is noninvasive, inexpensive, and easy to perform. In comparison to other methods, however, skinfold thickness measurements often are less accurate in comparison to measurements of weight or height, especially in obese individuals.[33] The TSF measurement reflects body fat. TSF and subscapular skinfold thickness measurements are used to assess subcutaneous fat, allowing associated estimations of total body fat. However, this measurement may over- or underestimate individual fat mass by ~10%.[34] Skinfold thickness measurements may be more useful in the long-term monitoring of nutritional therapy in individuals who are malnourished, have diseases that are associated with changes in body composition, or are obese. When performed on acutely ill or hospitalized patients, however, these measurements are of little value.

Mid-arm muscle circumference

The mid-upper arm cross-sectional area reflects lean body mass. The mid-arm muscle circumference (MAMC) can be calculated from the TSF and the MAC as follows:

$$\mathrm{MAMC} = \mathrm{MAC} - (3.1416 \times \mathrm{TSF}) \qquad \textbf{(Eq. 35-3)}$$

The measured values for TSF and MAC and the calculated MAMC are compared with reference values. Values <5th percentile for age are consistent with acute malnutrition, and values >90th percentile are consistent with obesity.[35]

Limitations

Changes experienced during acute illness and stress may result in errors of interpretation of subcutaneous fat and weight assessments, and peripheral edema can result in inflated values for MAC and skinfold thickness.[26,28]

Other methods of determining body composition

Owing to the aforementioned limitations, most research studies seeking a measure of body composition will use one of the more precise measures such as air-displacement plethysmography, hydrostatic weighing, or isotope dilution.

Hydrodensitometry

Underwater weighing is one of the oldest methods for determining body density; it has been largely replaced by dual-energy x-ray absorptiometry (DEXA). Body density is estimated from the weight of the individual in air and water, using appropriate correction factors for temperature, air in the respiratory tract, and constants for the densities of fat-free tissue and fat mass.[36]

Isotope Dilution

Body composition may be determined using stable isotope dilutions. The volume of a body compartment is determined by calculating the ratio of the dose of a tracer to its concentration in the body compartment after a defined equilibration period has elapsed. For example, total body water can be estimated using stable isotopes of deuterium ($2H_2O$) or oxygen ($H_2(18)O$).[37] The fat-free mass of the body can then be calculated based on the premise that the hydration of lean tissue is constant. Errors may occur when hydrogen isotopes

are used as they exchange with nonaqueous hydrogen, resulting in overestimation of total body water by 5% to 10%. Owing to its expense and the need for special analytic equipment, isotope dilution is not often used in clinical practice.

Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) uses an electrical current to measure the fat and fat-free mass.[38] The lean tissues of the body contain dissolved electrolytes and conduct electrical current, whereas body fat and bone are relatively poor conductors. BIA measures total body water from which an estimate of fat-free mass is calculated. BIA is used because it is noninvasive, portable, and inexpensive. Errors in measurement can occur if the electrodes are placed in the wrong location.[39] BIA is also influenced by gender, age, disease state, and amount of body fat.[40]

Air-Displacement Plethysmography

Air-displacement plethysmography is a method for determining body volume and, indirectly, fat mass. Using the same whole-body measurement principle as underwater weighing, air-displacement plethysmography uses a device that measures a subject's mass and volume, from which the whole-body density is calculated. The individual sits inside the device, and computerized pressure sensors determine the amount of air displaced by the subject's body, and body fat and lean muscle mass are then calculated.[41] In comparison to hydrostatic weighing or isotope dilutions, the accuracy of air-displacement plethysmography is very good.

Dual-Energy X-ray Absorptiometry

DEXA estimates fat-free mass, body fat, and bone mineral density using the differential absorption of x-ray or photon beams of two levels of intensity. It relies on the concept that the intensity of an x-ray or a photon beam is altered by the thickness, density, and chemical composition of an object in its path.[42] The technique is

limited because estimates of fat mass become less accurate as the individual's trunk thickness increases, and it appears more accurate at a group level, compared with the individual level.[43]

Other Methods

Other parameters such as hand grip and forearm dynamometry may be used to assess skeletal muscle function, which relates changes in body composition to body function.[1,26,28] Another nutritional assessment method, subjective global assessment (SGA), combines objective parameters and physiologic function.[44] This easy-to-use tool for diagnosing malnutrition is based on a history of weight change, dietary intake, presence of significant GI symptoms, functional capacity, and physical examination to assess edema and the loss of subcutaneous fat and muscle. Using the SGA system, patients are rated as well nourished, moderately malnourished, or severely malnourished.

Biochemical Assessment

No single test or group of tests can be recommended as a routine or reliable indicator of protein status. It is a combination of measures (ie, anthropometric, biochemical, dietary, and clinical findings) that results in a more complete picture of protein status. Within the human body, protein is viewed as a two-compartment model, visceral and somatic proteins. Skeletal muscles are composed of somatic proteins, accounting for ~75% of total body protein. Visceral proteins account for the remaining 25% of total body protein, which are found in the internal organs and serum.

Visceral protein stores are often evaluated as part of a nutritional assessment. The most commonly used serum protein markers are albumin, prealbumin, transferrin, and retinol-binding protein.[45] These proteins are produced within the liver, and often reflect hepatic synthetic capability. The serum concentration of visceral proteins decreases when hepatic insufficiency develops or when intake of substrates is inadequate for synthesis of proteins. Serum protein

concentrations are altered during acute stress or inflammatory states and chronic starvation. During injury or stress, inflammatory cytokines are released and substrates are shunted away from the synthesis of visceral proteins to synthesize other acute-phase proteins such as C-reactive protein (CRP), haptoglobin, fibrinogen, and others.[46]

ALBUMIN

Albumin is the classic visceral protein and is the most widely used prognostic indicator of nutritional status. This complex, high-molecular-weight protein is produced by the liver. Because it is a negative acute-phase protein, albumin is not a sensitive marker, and levels decrease in the presence of sepsis or inflammation. Because of its long serum half-life (18–20 days) and a fractional replacement rate of 10% per day, in the absence of stress, an improvement in serum albumin level due to nutritional repletion is generally observed within 2 weeks. There are other limitations to using serum albumin as an indicator of nutritional status. Serum concentrations of <3 g/dL correlate with poor outcomes and an increased length of stay in hospitalized patients.[47] Albumin serves as a carrier protein for fatty acids, hormones, minerals, and drugs, and is necessary for maintaining oncotic pressure. Albumin has a large body pool of 3 to 5 g/kg, and 30% to 40% is localized to the intravascular space. The normal hepatic rate of albumin synthesis is 150 to 250 mg/kg/day. Because of its long half-life, a decrease in serum albumin concentrations is generally not observed until after several weeks of inadequate nitrogen intake. Serum albumin concentrations decrease rapidly in response to stress (which causes albumin to shift from the intravascular to the extravascular space), burns, nephrotic syndrome, protein-losing enteropathy, overhydration, and decreased synthesis with liver disease.[28,46] If exogenous albumin is administered, then the serum albumin level loses its predictive value. Similarly, certain states of impaired synthesis (eg, hepatic dysfunction) or major albumin loss (eg, protein-losing enteropathy, nephrotic syndrome) may make it difficult to interpret.

PREALBUMIN

A more useful measure of nutritional status is prealbumin (transthyretin). In comparison to albumin, prealbumin is more sensitive to changes in energy and protein intake. This visceral protein has a small body pool (10 mg/kg) and serves as a carrier for retinol-binding protein and functions in thyroxine transport. Its shorter serum half-life of 2 to 3 days allows for measurable changes within 1 week of a dietary modification. Normal serum prealbumin concentrations are 15 to 40 mg/dL. False elevations in prealbumin levels can occur in renal failure and corticosteroid use. Similar to albumin, prealbumin is a negative acute-phase protein and will decrease in periods of inflammation. A CRP level can be obtained to assess the extent of inflammation and assist in the interpretation of visceral protein status.

TRANSFERRIN

Transferrin is a less commonly used visceral protein marker. This is a β-globulin involved in the transport of iron. Normal serum concentrations of transferrin are 250 to 300 mg/dL, and it has a half-life of 8 to 10 days. Similar to albumin, serum levels of transferrin are affected by nutritional factors and iron metabolism. Serum transferrin levels, as with albumin and prealbumin, are inversely correlated with the risk of morbidity and mortality in hospitalized patients. Serum transferrin levels also respond to iron status. High serum transferrin levels are found in patients with iron deficiency. Low levels are found in those with iron overload. Thus, a patient with coexisting protein malnutrition and iron deficiency may have a higher serum transferrin level than one with a similar degree of protein malnutrition but with normal iron status.[48]

RETINOL-BINDING PROTEIN AND OTHER MARKERS OF NUTRITIONAL STATUS

In comparison to other visceral proteins, retinol-binding protein has the shortest half-life, 12 hours; normal serum concentrations are 2.5 to 7.5 mg/dL. However, because serum concentrations of retinol-

binding protein change rapidly in response to alterations in nutrient intake, monitoring it has limited use in clinical practice. The visceral proteins commonly used for nutritional assessment are summarized in **Table 35-3**.

Table 35-3
Visceral Proteins for Nutritional Assessment

Visceral Protein	Half-Life (days)	Normal Serum Concentration
Albumin	18–21	3.5–5 g/dL
Transferrin	8–10	250–300 mg/dL
Transthyretin (prealbumin)	2–3	15–40 mg/dL
Retinol-binding protein	0.5	2.5–7.5 mg/dL

Other proteins, such as fibronectin and somatomedin-C (insulin-like growth factor-1), are also used as markers of nutritional status. Fibronectin is a glycoprotein found in blood, lymph, and many cell surfaces. Somatomedin-C is important in regulating growth. Both fibronectin and somatomedin-C have half-lives of <1 day and respond to fasting and refeeding. Urinary measurement of 3-methylhistidine, a by-product of muscle metabolism that is excreted unchanged, has been used to estimate skeletal muscle mass. Although these markers have potential use in nutritional assessment, they are used primarily as research tools and are not readily available for routine clinical use.[28]

The interpretation of serum protein concentrations in hospitalized patients may be difficult because other factors more important than hepatic synthesis rate can alter serum concentrations. These factors may include renal, hepatic, or cardiac dysfunction, hydration status, and metabolic stress. Visceral proteins, as with any nutritional assessment parameter, must be used in conjunction with other parameters and comprehensive consideration of the patient's clinical status. Practitioners should evaluate markers of inflammation and stress, such as CRP, in conjunction with visceral protein markers periodically to ensure that an accurate assessment is made.

Classification of Malnutrition

Malnutrition is categorized through a variety of descriptive terms, each with varying characteristics. Three classic categories include marasmus, kwashiorkor, and mixed protein-calorie malnutrition. A chronic deprivation of energy (calories), or partial starvation, leads to marasmus, which means a “dying away state.” For patients with marasmus, physical examination reveals severe cachexia with loss of both fat and muscle mass; however, visceral protein production is preserved, and serum levels may remain at or near the normal range. Patients with chronic wasting diseases such as cancer or anorexia are likely to present with marasmus malnutrition.

Classic kwashiorkor malnutrition results from diets devoid of adequate protein, but with adequate caloric intake. Kwashiorkor-like malnutrition in hospitalized patients often refers to patients who are extremely catabolic from their medical complication (eg, sepsis) or injury (eg, trauma, thermal injury). Carbohydrate metabolism involves endogenous production of insulin, which in turn prevents lipolysis and promotes the movement of amino acids into muscle. To meet increased protein demands, protein can be mobilized from internal organs and circulating visceral proteins. Consequently, an individual with kwashiorkor-like malnutrition may have adequate fat and muscle mass but may demonstrate depleted serum proteins.

Hospitalized patients commonly exhibit components of both marasmus and kwashiorkor-like malnutrition, and are classified as having mixed protein-calorie malnutrition. This mixed condition occurs when an acute injury or stress compounds chronic starvation or semistarvation, resulting in wasting of fat and muscle mass, as well as depletion of serum proteins.

Estimation of Energy Expenditure

Estimating energy expenditure constitutes an important aspect of patient evaluation. The most common approach used to determine energy requirements is based on body weight in kilograms. Energy

requirements are standardized and are determined by the metabolic condition of the patient.

Many predictive equations for estimating expenditure have been described in the literature.[49,50] The traditional method of assessing energy expenditure is the basal energy expenditure (BEE): the amount of energy (kilocalories) needed to support basic metabolic functions in a state of complete rest, shortly after awakening, and after a 12-hour fast. BEE is most commonly calculated using the Harris–Benedict equations (see **Table 35-4**). Alternatively, BEE can be estimated at 20 to 25 kcal/kg/day. Utilizing either method is supported by the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN).

Table 35-4
Estimation of Energy Expenditure

Basal Energy Expenditure	
Harris–Benedict equations BEE_{male} (kcal/day) = 66.47 + 13.75 W + 5.0 H − 6.76 A BEE_{female} (kcal/day) = 655.10 + 9.56 W + 1.85 H − 4.68 A Or 20–25 kcal/kg/day	
Energy Requirements	
Hospitalized patient, mild stress	20–25 kcal/kg/day
Moderate stress, malnourished	25–30 kcal/kg/day
Severe stress, critically ill	30–35 kcal/kg/day

A, age in years; BEE, basal energy expenditure; H, height in centimeters; kcal, kilocalories; W, weight in kilograms.

BMR is the energy expended in the postabsorptive state, ~2 hours after a meal. BMR is ~10% greater than is BEE. Calculations of BEE or BMR do not include additional energy required as a result of stress or activity. The Harris–Benedict equations can be modified to include stress and physical activity factors, or these variables are estimated at 20 to 35 kcal/kg/day for moderate-to-severe stress (Table 35-4).

Indirect calorimetry determines energy expenditure using a machine known as a *metabolic cart* that measures the patient's breathing or respiratory gas exchange. The cart measures oxygen consumption and carbon dioxide production when standard testing conditions are maintained. The amount of oxygen consumed and carbon dioxide produced for carbohydrate, fat, and protein is constant and known. Energy expenditure, including that caused by stress, is measured for a defined time, and the information is then subjected to a series of equations to extrapolate the estimated 24-hour energy expenditure.[28,51] This is the measured energy expenditure (MEE). Because the measurement is usually conducted while the patient is at rest, activity is not included in MEE.

Indirect calorimetry is available to many clinicians and is considered the gold standard for energy expenditure determination. Its usefulness is particularly valuable in the energy assessment of critically ill or obese patients. In 2016, the SCCM and the ASPEN published guidelines for the provision and assessment of nutritional support therapy for the adult critically ill patient.[52] Based on expert consensus, the guidelines suggest that determination of nutritional risk be performed on all patients in the intensive care unit (ICU) for whom volitional intake is anticipated to be insufficient. High-risk patients would likely benefit from early enteral nutritional therapy. In addition, the guidelines suggest that the nutritional assessment should include evaluation of comorbid conditions, function of the GI tract, and risk of aspiration. Traditional nutrition indicators or surrogate markers should likely not be used to assess nutritional status in critically ill patients because they have not been validated in the critically ill patient population.

Estimation of Protein Goals

Estimation of protein needs is necessary in nutritional assessment. Protein needs are calculated based on body weight, degree of stress, and disease state. The initial estimation is often made with a degree of subjectivity and clinical judgment, with adjustments made

based on patient response. The United States–recommended dietary allowance is 0.8 g of protein/kg/day. Well-nourished, hospitalized patients with minimal stress need 1 to 1.2 g of protein/kg/day to maintain lean body mass. The requirement for protein intake may be as high as 2 g/kg/day for a patient in a hypermetabolic, hypercatabolic state secondary to trauma or burns. In addition, protein provision may need to be adjusted and reduced in patients with renal or hepatic dysfunction as a result of altered metabolism. Guidelines for protein needs are summarized in **Table 35-5**.

Table 35-5
Estimation of Protein Requirements

U.S.-recommended dietary allowance	0.8 g/kg/day
Hospitalized patient, minor stress	1–1.2 g/kg/day
Moderate stress	1.2–1.5 g/kg/day
Severe stress	1.5–2 g/kg/day

NITROGEN BALANCE

Nutritional status as reflected by protein stores is traditionally assessed by calculating nitrogen balance, a measure of nitrogen losses in relationship to nitrogen intake. The amount of protein in the diet is measured in comparison to the nitrogen losses in the urine and feces using the following formula:

$$\text{Nitrogen balance} = \text{nitrogen intake} - \text{nitrogen losses}$$
$$\text{Nitrogen intake} = \text{Protein intake (gram/day)}/6.25$$
$$\text{Nitrogen losses} = \text{Urine urea nitrogen (UUN; gram/day)} + 4^{\star}$$

UUN is determined from a 24-hour urine collection.

*4 g is a "correction factor" to account for miscellaneous nitrogen losses.

(Eq. 35-4)

A negative value occurs with burns, fevers, serious injuries, wasting diseases, and during periods of fasting. This means

that the amount of nitrogen excreted from the body exceeds the amount of nitrogen (in the form of protein) ingested. Conversely, a positive value is often found during periods of growth, tissue repair, or in pregnancy. This means that the intake of nitrogen into the body is greater than the loss of nitrogen from the body, so there is an increase in the total body pool of protein. In periods of growth, a nitrogen balance of +2 to +4 is considered average. As with other measurements of nutritional status, it also has limitations. It is difficult to accurately assess actual protein intake in an orally fed patient. It is easier to determine in patients receiving specialized nutrition support, such as enteral or parenteral nutrition, where intake is more tightly controlled.

SPECIAL CONDITIONS THAT IMPACT NUTRITIONAL REQUIREMENTS

In most instances, individuals who have conditions that increase their metabolic rate will also have increased nutritional requirements (**Table 35-6**). Similarly, there are situations that can negatively impact nutrient intake such as the ability to obtain food, secondary impaired mobility/declining health, or poverty. Other conditions affecting digestion (ie, acid blockade, cystic fibrosis, pancreatitis) or nutrient absorption (ie, celiac disease, Crohn disease, intestinal failure), metabolism (ie, corticosteroid use), and excretion (ie, diarrhea) may also influence overall nutritional needs. Table 35-6 provides examples of situations that can negatively affect nutrient utilization.

Table 35-6

Examples of Conditions That Impact Nutrient Requirements

Increase Nutrient Requirements			
Burns	Cystic fibrosis	Infection	Surgery
Cancer	Healing wounds	Lactation	Trauma
Chronic lung disease	Hyperthyroidism	Pregnancy	
Decrease Nutrient Utilization			
Alcohol abuse	Cholestasis	Glycosuria	Pancreatic insufficiency
Bacterial overgrowth	Cystic fibrosis	Intestinal failure	Protein-losing enteropathy
Celiac disease	Diarrhea	Irritable bowel disease	Radiation enteritis

Assessing Growth

The growth of children is typically trended on age- and gender-appropriate growth curves. Growth charts consist of a series of percentile curves that illustrate the distribution of selected body measurements in U.S. children. Pediatric growth charts have been used by pediatricians, nurses, and parents to track the growth of infants, children, and adolescents in the United States and internationally since 1977.[53] Currently, the Centers for Disease Control and Prevention (CDC) recommends that World Health Organization (WHO) growth standards be used to monitor growth for infants and children ages 0 to 2 years in the United States; for children age 2 years and older, the CDC growth charts should be used. The CDC clinical growth charts have the grids scaled to metric units with English units as a secondary scale. The charts are available for boys and girls. Table 35-6 summarizes the available charts. Infants (birth to 24 months) are measured for length, and the sex-appropriate length-for-age or weight-for-length charts for infants, birth to 36 months, are used to plot the measurements. At age 24 months and older, if children can stand unassisted and follow directions, stature should be measured and plotted on the stature-for-age chart for children (2–20 years). If unable to stand unassisted, length can continue to be used in place of stature for children between 24 and 36 months. In 2000, the CDC issued a revised version of the 1977 growth charts.[54]

Adults are compared against standard height–weight tables. In 1943, the Metropolitan Life Insurance Company introduced their standard tables for males and females. The tables were later revised in 1983. They were called “desirable” weights, which would indicate those persons with the lowest mortality rates. However, the phrase “ideal weight” has become associated with these tables, even though the word “ideal” was not specifically published with the tables. To compensate for the differences between body shapes and skeletal muscle mass, “frame size” was used. In theory, elbow width or wrist width correlates fairly well with muscle and bone mass. There are several limitations to using these tables.[55] The tables were designed

for adults ages 25 to 59 years, and height must be determined while the individual wears 1-inch (2.54 cm) heel shoes. Furthermore, these tables are not suitable for children or older individuals.

Micronutrients

Micronutrients are the electrolytes, vitamins, and trace minerals needed for metabolism. A complete assessment will include identification of risks for deficiencies or toxicities with micronutrients based on the patient's specific nutritional status and concurrent disease processes. These nutrients are available enterally and parenterally from various manufacturers as either single entities or in combinations. It is important to be aware of the specific products available in each institution to avoid providing inadequate or excessive amounts of various micronutrients.

SIGNIFICANCE

Patients who cannot meet their nutritional needs by consuming enough food orally should be considered for an alternative nutrition mechanism. Specialized nutritional support is the provision of parenteral or enteral nutrients, which are specifically formulated or delivered to maintain or restore nutritional status.[56] For those who cannot eat by mouth but have a functional GI tract, the first line of nutritional intervention to be considered should be the enteral route using an appropriate access device (see Chapter 37, Adult Enteral Nutrition, and Chapter 38, Adult Parenteral Nutrition). To mimic the normal physiologic state when possible, the GI tract should be used for providing nutrients. Enteral nutrients may be more beneficial and are generally less costly than those provided by the parenteral route.[57] Enteral nutrients stimulate the intestine, thus maintaining the mucosal barrier structure and function. This has been associated with decreased infectious morbidity in critically ill patients compared with those receiving nutrients parenterally.[57–61] Parenteral nutrition is therefore reserved for patients whose GI tracts are not functional or

cannot be accessed, or who do not absorb enough nutrients to maintain adequate nutritional status.[46]

CASE 35-1

QUESTION 1: C.W. is a 46-year-old male admitted to the hospital with GI distress. C.W. states that he has been struggling with abdominal pain, diarrhea, and nausea for some time now. Upon further evaluation, C.W. admits that he has attempted to see a specialist; however, challenges with his work schedule and busy family life have delayed this. C.W. shares that his initial symptoms presented 12 months ago, and the reason he is here today is because of blood in his stool. Upon further examination, C.W. appears to have wasting of subcutaneous fat in his face and muscle in his arms. He reports weighing 331 pounds (150.14 kg) before symptom initiation, he was excited because he noticed he was losing weight, and this was a contributing factor to ignoring the GI upset he experienced. However, his weight loss was not initiated by lifestyle changes or pharmacotherapy. Over the past 2 months, C.W. has lost an additional 22 pounds (9.98 kg), today weighing 209 pounds (94.80 kg) with a height of 69 inches (175.26 cm). His past medical history is significant for gastroesophageal reflux disease, hypertension, and obesity. C.W. states that his eating habits have not changed, but he does have to skip meals often because of nausea.

Admission laboratory values are as follows:

Sodium, 135 mEq/L
Potassium, 4.0 mEq/L
Chloride, 100 mEq/L
Bicarbonate, 25 mEq/L
Blood urea nitrogen, 4 mg/dL
Creatinine, 0.6 mg/dL
Glucose, 87 mg/dL
Calcium, 8.2 mg/dL
Magnesium, 1.7 mg/dL
Phosphorus, 2.8 mg/dL
Total protein, 6.0 g/dL
Albumin, 3.5 g/dL
Prealbumin, 14 mg/dL
CRP, 3 mg/L

His white blood cell count is 14,300/μL. Based on history and physical findings, the medical team performs a complete workup for inflammatory bowel disease and identifies ulcerative colitis with an active bleeding ulcer.

What is his current nutritional status?

PATIENT ASSESSMENT: MALE WITH ULCERATIVE COLITIS

To develop an accurate nutritional assessment of any patient, it is important to elicit a thorough history and conduct an appropriate physical examination. Although history and physical examination are of utmost importance, laboratory studies are also integral components to the assessment of C.W.'s nutritional status. C.W.'s nutrition history indicates that he is at times unable to eat because of nausea, and the ulcerative colitis diagnosis raises the question of nutrient malabsorption. Most striking about C.W.'s history is his weight loss of 22 pounds (9.98 kg) in 2 months. He is now 63% of his usual weight (see Eq. 35-2). Another way of analyzing this is that he has lost 33% of his original weight, which is characterized as severe weight loss. The physical findings of cachectic appearance, subcutaneous fat wasting in his face and arms, are significant. No anthropometric measurements are available. C.W.'s visceral proteins are also in low to normal ranges, indicating both short-term (prealbumin) and long-term (albumin) malnutrition. Consideration of these factors leads one to conclude that C.W. is severely malnourished. This assessment can be further validated using other tools such as the SGA.[44] It is often challenging to identify malnutrition and significant weight loss in patients who are presently obese. Although C.W. is obese on presentation, it is vital to consider the patient's history when assessing nutritional status because changes from baseline are influential in interpretation.

Because nutritional assessment can often be difficult, a clinician may choose to use the SGA to appropriately categorize their patients. Application of the SGA technique classifies patients into three areas: class A (the well-nourished patient), with <5% weight loss or >5% total weight loss but recent gains and improvements in appetite; class B (moderately malnourished), identified by those patients with 5% to 10% weight loss without recent stabilization or gain, poor dietary intake, and mild loss of subcutaneous tissue; and

class C (severely malnourished), with an ongoing weight loss of >10% with severe subcutaneous tissue loss and muscle wasting, often with edema. The utility of the SGA is its simplicity for implementation and strong correlation with other subjective and objective measures of nutrition.

Clinicians place patients into one of the three categories on the basis of their subjective rating of two broad factors: history and physical examination. There are four elements to the history: (a) weight loss in the 6 months before the examination, expressed as a proportionate loss from previous weight, (b) dietary intake in relation to the patient's usual pattern, (c) presence of significant GI symptoms, and (d) functional capacity or energy of the patient, ranging from full capacity to bedridden. Applying these four elements to C.W., one first finds that C.W. is reporting a 33% weight loss during the past 12 months. It is also important to recognize the pattern of weight loss. Inquiring about a patient regarding recent weight loss (in conjunction with the weight change in 6 months), often in the past 2 weeks, can help establish a pattern of chronic weight loss. In C.W.'s case, he reports increasing weight loss in the past 2 months, which confirms a progression. It is also recommended that clinicians explore weight history by asking for the patient's maximal weight at specific times, such as 1 year ago, 6 months ago, 1 month ago, and at the present time. Confirmation of weight history can be conducted by having the patient discuss their change in clothing size or how their clothes fit.

With respect to the second element regarding dietary intake, C.W. says he has to skip meals due to nausea. Using the SGA, patients are classified as having either normal or abnormal intake in the weeks to months before the examination. In this case, C.W. is experiencing abnormal intake; however, one can also ask C.W. certain questions such as "How has the amount of food you have consumed over the past several weeks to months changed?" or "Are there certain kinds of foods that you no longer can eat?" and "Give me an example of a typical meal" to establish eating patterns. It is also important to determine why a patient is eating less—intentional reduction or unintentional reduction. C.W. has communicated that

while initially the weight loss was positive because of his past medical history of obesity, he has not had any intention of wanting to lose weight or initiating lifestyle changes to do so. His change in consumption is related to his chronic pathology of underlying inflammatory bowel disease.

In terms of the third element of the history, significant GI symptoms are those that have persisted on virtually a daily basis for a period >2 weeks. Given the presentation of C.W. to the hospital with his history of 12 months of abdominal pain, diarrhea, nausea, and, ultimately, blood in stool, it is highly likely that he satisfies the definition for possessing significant GI symptoms.

The final element of C.W.'s history, functional capacity, is one that should be explored further, yet it is not likely to have an impact on the final nutritional assessment given the prior objective findings of the patient. Patients who cannot eat may feel weak and tired—many times to the point of which they are bedridden. Observation of the activity levels of patients, their overall mood, skeletal muscle function, and their respiratory movements can all provide clues to the clinician regarding functional impairment. C.W. did not mention systemic symptoms; however, he is at risk for functional impairment and has experienced physical changes in the loss of fat and muscle tissue.

Having completed the history component of the SGA, the clinician moves to the second component of the SGA or the physical. This section of the SGA essentially asks the clinician to look for physical signs of malnutrition such as loss of subcutaneous fat in the triceps and chest region, muscle wasting in areas such as the quadriceps and deltoids, presence of ankle or sacral edema, and, finally, any presence of ascites. For each of the traits, the clinician should consider the severity, if anything is present. In the case of C.W., there is definite muscle wasting. Given the history and physical components of the SGA, C.W. would be classified as severely malnourished (class C) because there are obvious signs of malnutrition such as subcutaneous tissue loss and muscle wasting in the presence of a clear and convincing pattern of ongoing weight loss >10%.

Case 35-1, Question 2: Is C.W. a candidate for specialized nutritional support therapy?

The fundamental goal of specialized nutritional support therapy is to meet the energy requirements of metabolic processes, to support the hypermetabolism associated with critical illness, and to minimize protein catabolism. Ulcerative colitis is classified as an inflammatory bowel disease that is associated with nutritional insult. Nutritional abnormalities can arise in patients with ulcerative colitis from malabsorption, decreased food intake, medications, and intestinal losses. Disease location along the GI tract, symptomatology, and dietary restrictions all contribute to the development of protein-energy malnutrition with specific nutritional deficiencies. C.W. is admitted to the hospital for tests to evaluate his GI concerns and is found to have ulcerative colitis due to weight loss and associated symptoms. The subjective and objective evidence points to a nonfunctioning GI tract. C.W. may require parenteral nutritional therapy until enteral therapy can be established because of the current state of the active bleeding ulcer and the new diagnosis of ulcerative colitis (see Chapter 38, Adult Parenteral Nutrition). With his malnourished state, continued inadequate nutrition in the hospital will result in further deterioration of his nutritional status.

Goals of Therapy

Case 35-1, Question 3: What are C.W.'s calorie and protein goals?

Nutritional support begins with an estimation of the patient's caloric requirements.[49,50] Accurate determination of caloric needs is essential to obtain the full benefits of nutritional therapy and aids in preventing the problems associated with underfeeding as well as overfeeding. The Harris–Benedict equation is one of the most commonly used methods for estimating caloric needs or BEE; however, there is still controversy regarding the best method to

accurately estimate the caloric needs of a patient. In critically ill obese patients, it is recommended to utilize the Penn State University predictive equation. This equation requires data from a patient's hospitalizations including temperature and ventilation rate. In the event this data is unavailable, in hospitalized obese patients, the equation that may be utilized is the Mifflin–St Jeor equation utilizing actual body weight. Equations are included in Table 35-4. The most common approach is based on body weight in kilograms. The energy requirements are standardized and are determined by the metabolic condition of the patient. C.W.'s initial calorie goals are to meet his current energy expenditure needed for basal metabolism and activity of ambulating. C.W. would fall into the category of "moderate stress, malnourished," requiring 25 to 30 kcal/kg/day. For this calculation, C.W.'s actual weight of 209.43 pounds (95 kg) should be used because his metabolism and current energy expenditure reflect this decrease in body mass. Using usual weight or IBW in patients who have severe weight loss may result in overfeeding. For C.W., the caloric goal should be from 2375 to 2850 kcal/day.

Protein is the building block of life. Once hepatic glycogen stores are depleted, muscle protein is degraded to provide three-carbon backbones for hepatic gluconeogenesis. Initially, protein catabolism is resistant to the administration of exogenous amino acids, and it can sometimes take weeks until a patient is found to be in a state of positive nitrogen balance. In addition to protein catabolism, exogenous protein is required for wound healing and to replace protein lost in wounds and fistulae. Protein goals are estimated based on weight, degree of stress, and disease state. The goal is to minimize the loss of lean body mass, and, as a general rule, this requires anywhere from 1.0 to 1.5 g/kg/day of protein depending on the degree of illness and injury. Because C.W. has not had surgery and his stress is minimal, his protein goal should be based on the desire to maintain his current protein status. Using the guidelines provided in Table 35-5, C.W.'s protein dose is 1.2 to 1.5 g/kg/day, or 114 to 143 g/day. As with energy expenditure, calculations of protein needs are only estimates; the patient's clinical course should be

monitored, and the protein dose should be adjusted accordingly. It is important to note that in obese patients, utilizing actual body weight is supported by ASPEN. If IBW is preferred, the conversions and dosing should be adjusted. For example, the ASPEN guidelines for nutritional management of obese patients suggest the use of 2 to 2.5 g/kg protein requirements with IBW. If C.W. requires surgery, his energy or calorie goals should be reassessed to include an additional stress factor.[62]

Micronutrients

Case 35-1, Question 4: What vitamin and mineral deficiencies would you expect to find in C.W.? What options are available to the clinician to address them?

The therapeutic effects of specialized nutritional support accrue through the combined provision of macronutrients and micronutrients. These elements support vital cellular and organ functions, immunity, tissue repair, protein synthesis, and capacity of skeletal, cardiac, and respiratory muscles. As with any medical therapy, a nutritional support regimen should be adjusted based on the requirements, response, and tolerance of the patient. Patients who have inflammatory bowel disease are particularly at risk for developing altered levels of vitamins and other micronutrients. The etiology of these micronutrient losses is multifactorial and encompasses decreased oral intake, increased losses secondary to diarrhea, and malabsorption. In particular, deficiencies in vitamin D, folate, vitamin B_{12}, calcium, magnesium, and zinc are common to this patient population.

Given the prevalence of these deficiencies, C.W. should be prescribed a daily multivitamin and mineral supplement. If it is determined that C.W. has significant fat malabsorption, a water-miscible fat-soluble vitamin formulation can be considered. There is an increased incidence of osteoporosis in patients with ulcerative colitis (with or without corticosteroid use), and, therefore, C.W.

should be assessed to ensure that his calcium and vitamin D intake is normal. Recommended daily oral calcium requirements are from 800 to 1500 mg/day, but increase from 1500 to 2000 mg/day when replacement is needed for a deficiency. C.W. should be consuming a daily amount of 400 international units (IU) of vitamin D orally; however, if serum 25-hydroxyvitamin D levels are subtherapeutic, greater amounts will be required and also doses based on the specific disease progression and functionality of C.W.'s GI tract.

Medications such as methotrexate (a folate antagonist) and sulfasalazine (which blocks folate absorption) can be used to treat inflammatory bowel disease and, therefore, increase folate requirements for patients. Daily folate supplementation at a dose of 1 mg orally can be beneficial to C.W. if he is prescribed either of these medications.

Magnesium deficiency can be a concern in patients with increased intestinal losses, as is the case with many individuals who have inflammatory bowel disease. When considering enteral magnesium supplementation, the change in pH along the GI tract, GI transit time, and fat content of a meal can all affect magnesium absorption. Large doses of enteral magnesium can result in diarrhea; therefore, administering smaller doses throughout the day can lead to improved tolerance and therapeutic efficacy. Choosing a magnesium supplement that can deliver 150 mg of elemental magnesium and dosing it four times a day is the recommended oral replacement regimen for patients.

Patients with inflammatory bowel disease can experience excessive stool losses resulting in a zinc deficiency. C.W. should receive an oral zinc supplement that delivers 50 mg of elemental zinc daily.

Maintenance Fluids

Case 35-1, Question 5: What is C.W.'s daily fluid requirements while he receives specialized nutritional support?

When determining the fluid needs of a patient, the clinician should consider the following steps: (a) correction of fluid imbalances, (b) maintenance fluid requirements, and (c) replacement of ongoing fluid losses.

The extended periods of diarrhea, vomiting, or both that occur with inflammatory bowel disease may lead to dehydration. Dehydration results in a loss of body weight, decreased urine output, dry mouth, and progressive thirst. Hypotension, tachycardia, and poor skin turgor are all clinical signs of dehydration. Apathy, stupor, coma, and death will follow if fluid replacement is not undertaken. Fluid deficits should be estimated from the clinical appearance of the patient, recent weight loss, and serum sodium and blood urea nitrogen concentrations, and replaced by giving half the estimated deficit intravenously over the course of 8 hours. After 8 hours, a new assessment of fluid status should be made, and half of the new estimated deficit should be replaced during the next 8 hours. This process should be repeated until normal hydration is achieved (see Chapter 27, Fluid and Electrolyte Disorders).

Maintenance fluid is that volume of daily fluid intake that replaces the insensible losses and at the same time allows excretion of the daily production of excess solute load in a volume of urine that is of an osmolarity similar to that of plasma. Maintenance fluid needs can be estimated using several methods. The simplest method uses 30 to 35 mL/kg/day as the basis. Another method is to provide 1500 mL for the first 20 kg of body weight plus an additional 20 mL/kg for actual weight beyond the initial 20 kg. Both methods provide estimates of fluid needs for basic maintenance. C.W.'s fluid needs are estimated as follows:

$$\begin{aligned} \text{mL/day} &= 1500\ \text{mL} + ([20\ \text{mL/kg}]\,[95\ \text{kg} - 20\ \text{kg}]) \\ &= 1500\ \text{mL} + (20\ \text{mL/kg})\,(75\ \text{kg}) \\ &= 1500\ \text{mL} + 1500\ \text{mL} \\ &= 3000\ \text{mL} \end{aligned} \quad \text{(Eq. 35-5)}$$

If C.W. experiences vomiting, nasogastric tube output, diarrhea, or other significant fluid losses, additional fluid must be provided. Some losses are measurable and can be directly replaced milliliter for milliliter on a regular basis. Others, however, are not measurable and can only be estimated. The electrolyte composition of the lost fluid is an important consideration for the clinician and dictates the ultimate choice of the replacement fluid.

Evaluating Specialized Nutritional Support Effectiveness

Case 35-1, Question 6: What parameters should be examined to determine the effectiveness of C.W.'s nutritional support regimen?

Implementing a successful nutritional support regimen begins with proper nutritional assessment of the patient. Nutritional goals that identify macronutrient, micronutrient, and fluid requirements are then established. Follow-up support and monitoring of the patient once nutritional support has been instituted is important to maintain the integrity and efficacy of the therapy.

To minimize the risk of refeeding syndrome in C.W. (a metabolic and electrolyte disturbance that occurs as a result of supplying nutrition to patients who are severely malnourished), all electrolyte abnormalities must be corrected before any nutrition is initiated. Because C.W.'s electrolytes are within normal ranges, no adjustments are necessary. Nutrition should then be implemented slowly, and vitamins administered routinely. Electrolytes, including phosphorus, potassium, magnesium, and glucose, should be monitored at least daily during the first week. Although electrolyte and mineral abnormalities may not be avoided, careful recognition of and close monitoring for refeeding syndrome will prevent serious complications.[63,64]

Although it can sometimes be difficult to obtain a reliable weight for a patient, weight can be an important parameter to help assess

not only fluid balance but also the long-term appropriateness of caloric intake. Most patients should gain or lose no >1 kg/week when receiving nutritional support (assuming normal fluid status). However, clinicians must be aware of the impact that fluids have on the weight of a patient. Large intake or loss of fluids can influence weight measurements and mask the trends of body mass. Having C.W.'s record of daily weights, in addition to fluid intake and output, and monitoring trends can serve as one, but not the only, key in determining the effectiveness of his regimen.

Nitrogen balance is another parameter that can help determine the degree of catabolism and protein requirements in a patient. Nitrogen balance is the difference between nitrogen intake and nitrogen excretion. It is estimated by the nitrogen intake along with collecting a 24-hour UUN sample from the patient. Positive nitrogen balance is a reasonable goal during nutritional support therapy for recovery of a patient, but may also require increasing caloric loads on a periodic basis. If a nitrogen balance study is ordered for C.W., increasing protein intake should be considered if results indicate a negative nitrogen balance; however, a negative nitrogen balance may be unavoidable during high-stress states, regardless of the amount of nutrients provided.

Although evaluating calcium is important in determining electrolyte needs, it is critical to remember that calcium is influenced by a number of factors, one of which is serum albumin. The mechanism driving this relationship is calcium binding to albumin, which is therefore reflected in serum levels when albumin is low. Low calcium in the setting of low albumin, however, is not indicative of ionized calcium levels because of this relationship. It is for this reason that calculating a corrected calcium should be performed for all patients in this scenario. The equation is as given:

$$\text{Corrected calcium} = \text{serum calcium} + 0.8\,(4.0 - \text{serum albumin}) \quad \textbf{(Eq. 35-6)}$$

Utilizing this equation, 4.0 refers to a normal average serum albumin and allows for the normalization of this value. The corrected

calcium for C.W. is 8.6 mg/dL, which meets the criteria for borderline hypocalcemia postcorrection calculation.

Finally, prealbumin levels for C.W. should also be monitored once a week as a marker for short-term gross adequacy of calorie and protein intake. A lack of prealbumin increase is an indicator of poor patient outcomes. With adequate feeding, prealbumin can increase >4 mg/dL/week. It should be noted that in the case of C.W., who is suffering from ulcerative colitis and may likely be receiving either oral or parenteral corticosteroids as treatment, administration of corticosteroids can falsely elevate prealbumin levels, making C.W. appear to be at a lower nutritional risk.

Case 35-1, Question 7: Members of the medical team are anxious to have C.W. gain weight and are concerned by his malnourished appearance. Therefore, there is a desire to increase the calories provided to C.W. What potential complications could result from overfeeding C.W.?

Overfeeding should be avoided in all patients including obese persons because of a number of potential complications, especially those with respiratory concerns.[65] Although restoration and maintenance of body cell mass is the goal of nutritional support therapy, a gradual and conservative approach yields fewer metabolic abnormalities. Supplying an abundance of calories to a patient in need of nutritional support increases the metabolic rate, which in turn places greater demands for cardiopulmonary effort and oxygenation. Overfeeding with carbohydrates is particularly detrimental because of the amount of carbon dioxide produced relative to the amount of oxygen consumed. This results in carbon dioxide retention that may lead to acid–base disturbances. Hyperglycemia is also a common metabolic abnormality secondary to excessive carbohydrate administration that can lead to osmotic diuresis and immune dysfunction.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of Jeff F. Binkley, the author of the previous version of this chapter.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

da Silva JSV, Seres DS, Sabino K, et al. ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutr Clin Pract*. 2020;35(2):178–195. (62)

Garvey WT, Garber AJ, Mechanick JI, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Consensus Conference on Obesity: building an evidence base for comprehensive action. *Endocr Pract*. 2014;20(9):956–976. (19)

McClave SA, Taylor BE, Martindale RG, et al. Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *J Parenter Enteral Nutr.* 2016;40(2):159–211. (52)

Mueller C, Compher C, Ellen DM, et al. A.S.P.E.N. Clinical guidelines: nutrition screening, assessment, and intervention in adults. *J Parenter Enteral Nutr.* 2011;35:16–24. (1)

Key Websites

American Society for Parenteral and Enteral Nutrition. http://www.nutritioncare.org

USDA Food and Nutrition Information Center. https://www.nal.usda.gov/legacy/fnic

COMPLETE REFERENCES CHAPTER 35 BASICS OF NUTRITION AND PATIENT ASSESSMENT

1. Mueller C, Compher C, Ellen DM, et al. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. *J Parenter Enteral Nutr*. 2011;35:16–24.
2. Ames SR. The joule—unit of energy. *J Am Diet Assoc*. 1970;57:415–416.
3. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. National Academy Press; 2005.
4. Cahill GF Jr. Starvation in man. *N Engl J Med*. 1970;282:668–675.
5. Posner BM, Cupples LA, Franz MM, Gagnon DR. Diet and heart disease risk factors in adult American men and women: the Framingham Offspring-Spouse nutrition studies. *Int J Epidemiol*. 1993;22:1014–1025.
6. Lee S, Gura KM, Kim S, Arsenault DA, Bistrian BR, Puder M. Current clinical applications of omega-6 and omega-3 fatty acids. *Nutr Clin Pract*. 2006;21(4):323–341.
7. Carroll HJ, Oh MS. *Water, Electrolyte, and Acid-base Metabolism: Diagnosis and Management*. JB Lippincott; 1989.
8. Grant JP. Nutritional screening and assessment in clinical practice. *Nutr Clin Pract*. 1986;1:3.
9. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr*. 2003;22(3):235–239.
10. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. *NCHS Data Brief*. 2020;(360):1–8.
11. White JV, Guenter P, Jensen G, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr*. 2012;36(3):275–283.
12. Jensen GL. Inflammation as the key interface of the medical and nutrition universes: a provocative examination of the future of clinical nutrition and medicine. *JPEN J Parenter Enteral Nutr*. 2006;30(5):453–463.
13. Jensen GL, Compher C, Sullivan DH, Mullin GE. Recognizing malnutrition in adults: definitions and characteristics, screening, assessment, and team approach. *JPEN J Parenter Enteral Nutr*. 2013;37(6):802–807.
14. Leiter LA, Marliss EB. Survival during fasting may depend on fat as well as protein stores. *JAMA*. 1982;248:2306–2307.
15. Keys A, Brozek J, Henschel A, et al. *The Biology of Human Starvation*. University of Minnesota Press; 1950.
16. Robinson G, Goldstein M, Levine G. Impact of nutritional status on DRG length of stay. *JPEN J Parenter Enteral Nutr*. 1987;11:49–51.
17. Reilly JJ Jr, Hull SF, Albert N, Waller A, Bringardener S. Economic impact of malnutrition: a model system for hospitalized patients. *JPEN J Parenter*

Enteral Nutr. 1988;12:371–376.
18. Detsky AS, Smalley PS, Chang J. The rational clinical examination. Is this patient malnourished? *JAMA*. 1994;271:54–58.
19. Garvey WT, Garber AJ, Mechanick JI, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Consensus Conference on Obesity: building an evidence base for comprehensive action. *Endocr Pract*. 2014;20(9):956–976.
20. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9(7):629–635.
21. Prado CM, Maia YL, Ormsbee M, Sawyer MB, Baracos VE. Assessment of nutritional status in cancer—the relationship between body composition and pharmacokinetics. *Anticancer Agents Med Chem*. 2013;13(8):1197–1203.
22. Conde WL, Monteiro CA. Nutrition transition and double burden of undernutrition and excess of weight in Brazil. *Am J Clin Nutr*. 2014;100(6):1617S–1622S.
23. Rolland-Cachera MF, Péneau S. Assessment of growth: variations according to references and growth parameters used. *Am J Clin Nutr*. 2011;94(6 suppl):1794S–1798S.
24. Soeters PB, Schols AM. Advances in understanding and assessing malnutrition. *Curr Opin Clin Nutr Metab Care.* 2009;12(5):487–494.
25. Charney P. Nutrition screening vs nutrition assessment: how do they differ? *Nutr Clin Pract*. 2008;23(4):366–372.
26. Jensen GL, Hsiao PY. Nutrition screening and assessment. In: Mueller CM, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. 2nd ed. American Society for Parenteral and Enteral Nutrition; 2012:155.
27. Correia MI. Nutrition screening vs nutrition assessment: what's the difference? *Nutr Clin Pract*. 2018;33(1):62–72.
28. Charney P. Nutrition assessment in the 1990s: where are we now? *Nutr Clin Pract*. 1995;10:131–139.
29. Definitions of terms used in A.S.P.E.N. guidelines and standards. A.S.P.E.N. board of directors. *Nutr Clin Pract*. 1995;10:1–3.
30. Heymsfield SB, Shen W, Wang Z, et al. Evaluation of total and regional adiposity. In: Bray GA, Bouchard C, eds. *Handbook of Obesity.* Marcel Dekker; 2004.
31. Thuluvath PJ, Triger DR. How valid are our reference standards of nutrition? *Nutrition*. 1995;11(6):731–733.
32. Fryar CD, Gu Q, Ogden C, Flegal KM. Anthropometric reference data for children and adults; United States, 2011–2014. In: Vital and health statistics. Series 3, Data from the National Health and Nutrition Examination Survey no. 39; DHHS publication no. (PHS) 2016–1604. Accessed October 26, 2020. https://stacks.cdc.gov/view/cdc/40572

33. Watts K, Naylor LH, Davis EA, et al. Do skinfolds accurately assess changes in body fat in obese children and adolescents? *Med Sci Sports Exerc.* 2006;38:439–444.
34. Wong WW, Stuff JE, Butte NF, et al. Estimating body fat in African American and white adolescent girls: a comparison of skinfold-thickness equations with a 4-compartment criterion model. *Am J Clin Nutr.* 2000;72:348–354.
35. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr.* 1981;34:2540–2545.
36. Siri WE. Body composition from fluid spaces and density: analysis of methods. In: Brozek J, Henschel A, eds. *Techniques for Measuring Body Composition*. National Academy of Sciences; 1961:233.
37. Schoeller DA, van Santen E, Peterson DW, et al. Total body water measurement in humans with 18O and 2H labeled water. *Am J Clin Nutr.* 1980;33:2686–2693.
38. Lukaski HC, Johnson PE, Bolonchuk WW, Lykken GI. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. *Am J Clin Nutr.* 1985;41:810–817.
39. Kyle UG, Earthman CP, Pichard C, Coss-Bu JA. Body composition during growth in children: limitations and perspectives of bioelectrical impedance analysis. *Eur J Clin Nutr.* 2015;69:1298–1305.
40. Lee SY, Gallagher D. Assessment methods in human body composition. *Curr Opin Clin Nutr Metab Care.* 2008;11:566–572.
41. Fields DA, Higgins PB, Radley D. Air-displacement plethysmography: here to stay. *Curr Opin Clin Nutr Metab Care.* 2005;8:624–629.
42. Lukaski HC. Soft tissue composition and bone mineral status: evaluation by dual-energy X-ray absorptiometry. *J Nutr.* 1993;123:438–443.
43. Silva DR, Ribeiro AS, Pavão FH, et al. Validity of the methods to assess body fat in children and adolescents using multi-compartment models as the reference method: a systematic review. *Rev Assoc Med Bras (1992).* 2013;59:475–486.
44. Detsky AS, McLaughlin JR, Baker J, et al. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr*. 1987;11:8–13.
45. Sergi G, Coin A, Enzi G, et al. Role of visceral proteins in detecting malnutrition in the elderly. *Eur J Clin Nutr.* 2006;60(2):203–209.
46. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation [published correction appears in *N Engl J Med.* 1999;340:1376]. *N Engl J Med*. 1999;340:448–454.
47. Vanek VW. The use of serum albumin as a prognostic or nutritional marker and the pros and cons of IV albumin therapy. *Nutr Clin Pract*. 1998;13:110–122.
48. Delpeuch F, Cornu A, Chevalier P. The effect of iron-deficiency anaemia on two indices of nutritional status, prealbumin and transferrin. *Br J Nutr.*

1980;43(2):375–379.
49. Garrel DR, Jobin N, de Jonge LH. Should we still use the Harris and Benedict equations? *Nutr Clin Pract*. 1996;11:99–103.
50. Wooley JA, Frankenfield D. Energy. In: Mueller CM, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. 2nd ed. American Society for Parenteral and Enteral Nutrition; 2012:22.
51. Russell MK, Andrews MR, Brewer CK, et al. Standards for specialized nutrition support: adult hospitalized patients. *Nutr Clin Pract*. 2002;17:384–391.
52. McClave SA, Taylor BE, Martindale RG, et al. Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159–211.
53. de Onis M. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ.* 2007;85(9):660–667.
54. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics.* 2002;109(1):45–60.
55. Himes JH, Bouchard C. Do the new Metropolitan Life Insurance weight-height tables correctly assess body frame and body fat relationships? *Am J Public Health.* 1985;75(9):1076–1079.
56. Lipman TO. Grains or veins: is enteral nutrition really better than parenteral nutrition? A look at the evidence. *JPEN J Parenter Enteral Nutr*. 1998;22:167–182.
57. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr*. 2001;74:534–542.
58. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. *Gut*. 1996;39:833–835.
59. Hernandez G, Velasco N, Wainstein C, et al. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. *J Crit Care*. 1999;14:73–77.
60. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg*. 1992;215:503–511.
61. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. *Ann Surg*. 1992;216:172–183.
62. Choban P, Dickerson R, Malone A, Worthington P, Compher C, American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. clinical guidelines: nutrition support of hospitalized adult patients with obesity. *JPEN J parenter Enteral Nutr*. 2013;37(6):714–744.
63. da Silva JSV, Seres DS, Sabino K, et al. ASPEN consensus recommendations for refeeding syndrome. *Nutr Clin Pract*. 2020;35(2):178–

195.
64. Brooks MJ, Melnik G. The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. *Pharmacotherapy*. 1995;15:713–726.
65. Kumpf VJ, Gervasio J. Complications of parenteral nutrition. In: Mueller CM, ed. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. 2nd ed. American Society for Parenteral and Enteral Nutrition; 2012:284.

36

Obesity

Kaelen C. Dunican and Aimee Dawson

CORE PRINCIPLES		CHAPTER CASES
1	Body mass index (BMI) should be measured at each patient encounter, and patients should be assessed for overweight, obesity, and the presence of obesity-related conditions.	**Case 36-1 (Questions 1, 3)**
2	The medication profile of patients with increased body weight should be evaluated for drugs associated with weight gain, and alternative agents that are weight neutral or associated with weight loss should be considered.	**Case 36-1 (Question 1)**
3	Obesity is a chronic disease, and therapeutic interventions must be long term. It is common for patients to regain weight after discontinuation of lifestyle or pharmacologic therapy.	**Case 36-1 (Questions 2, 7, 9)**

CORE PRINCIPLES		CHAPTER CASES
4	An appropriate weight loss goal for most patients is 5% to 10% of baseline body weight; goals may be more aggressive depending on the presence of obesity-related conditions.	**Case 36-1 (Question 4)**
5	Management and treatment of overweight and obesity should include lifestyle therapy (a combination of diet and increased physical activity along with behavioral modifications).	**Case 36-1 (Questions 4, 5)**
6	In addition to lifestyle therapy, medication to treat obesity should be considered for patients with a BMI >30 kg/m^2 without risk factors or >27 kg/m^2 with an obesity-related condition.	**Case 36-1 (Questions 4, 6, 7)**
7	Short-term weight loss drugs are unlikely to be clinically useful and should not be recommended.	**Case 36-1 (Question 6)**
8	Medication for chronic weight management includes orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, or semaglutide.	**Case 36-1 (Question 7)**
9	The use of dietary supplements for weight loss is not supported by clinical literature, and generally should be avoided because of safety concerns and lack of regulation.	**Case 36-1 (Question 8)**

CORE PRINCIPLES		CHAPTER CASES
10	Medical devices are available for the treatment of overweight and obesity, and may be considered for some patients.	**Case 36-1 (Question 10)**
11	Bariatric surgery may be considered for patients with BMI ≥40 kg/m^2, or BMI ≥35 kg/m^2 with one or more obesity-related conditions, or BMI ≥30 kg/m^2 and type 2 diabetes with inadequate glycemic control.	**Case 36-1 (Question 11)**
12	Alteration of gastrointestinal tract and stomach size after bariatric surgery can alter drug pharmacokinetics, cause nutrition deficiencies, and place patients at risk for adverse events associated with some medications.	**Case 36-1 (Question 11)**

INTRODUCTION

Obesity is a chronic disease characterized by excess body fat accumulation that may impair health.[1,2] The prevalence of obesity has become an epidemic. It is recognized by the World Health Organization (WHO) and the U.S. Federal Government as a growing problem that burdens health care organizations and the economy.[1,2] More than one-third of the worldwide population is overweight.[3] More than two-thirds of the U.S. adult population is overweight, with more than one-third considered obese.[4] Analyses estimate the medical expenses associated with obesity in the United States as $149.4 billion.[5]

DEFINITIONS

Overweight and obesity are defined by body mass index (BMI), a measure of weight in relation to height. BMI is calculated as weight (in kilograms) divided by height (in meters) squared. Normal weight is defined as BMI of 18.5 to 24.9 kg/m^2, overweight is defined as BMI of 25 to 29.9 kg/m^2, and obesity is defined as BMI ≥30 kg/m^2 (**Table 36-1**).[6] Obesity is further divided into class I (BMI 30–34.9 kg/m^2), class II (BMI 35–39.9 kg/m^2), and class III (BMI ≥40 kg/m^2).[6] Class III obesity is also referred to as *very severe obesity*, and was formerly known as extreme or morbid obesity.[6] Lower BMI cutoffs, including overweight beginning with a BMI ≥23 kg/m^2 are recommended for some ethnicities including South Asian, Southeast Asian, and East Asian adults.[6] Obesity is a chronic metabolic disorder that is determined by multiple biologic and environmental factors, an obesogenic lifestyle, and a genetic predisposition. The increase in the prevalence of obesity and negative health outcomes are major public health problems throughout the world.[1]

Table 36-1
Body Mass Index and Guidelines for Weight Classes

Weight Status	BMI[a]	Obesity Class
Underweight	<18.5	
Normal	18.5-24.9	
Overweight	25-29.9	
Obesity	30-34.9	(I)
Severe obesity	35-39.9	(II)
Very severe obesity	≥40	

BMI, body mass index.

[a]Metric conversion formula using kilograms and meters: body mass index (BMI), weight in kg/height in m^2. Nonmetric conversion formula using pounds and inches: BMI, weight in pounds/height in inches^2 × 703.

Source: Reprinted from Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(suppl 3):1–203. © 2016 Elsevier. With permission.

BMI is widely accepted as the standard to classify weight. However, a major limitation of BMI is that it does not consider body composition. According to BMI, a person may be classified as "overweight" if their muscle mass is great enough to significantly contribute to total weight. On the other hand, a patient may be considered "normal weight" while having excess fat accumulation and decreased muscle mass. The use of BMI to assess body fat and risk of morbidity and mortality is particularly problematic in certain ethnic groups because BMI does not account for differences in distribution of body fat.[6] For example, research suggests that in the Asian population, BMI underestimates body fat.[6] BMI should always be used in conjunction with clinical evaluation and judgment, particularly with those with increased muscle mass (athletes) or decreased muscle mass (sarcopenia).[6] Another limitation of BMI is that it does not consider the location of fat in the body.

Fat distribution in the abdominal region has been linked to many of the metabolic consequences of obesity.[7] Measurement of waist circumference (WC) is used to assess for increased abdominal fat accumulation and to determine health risk. WC measurements >40 inches (102 cm) in males and 35 inches (88 cm) in females are associated with increased risk of metabolic diseases.[7] Increased WC has been shown to predict obesity-related diseases such as diabetes, hypertension, dyslipidemia, and cardiovascular disease.[7–9] The waist-to-hip ratio (WHR) also provides an assessment of regional fat distribution. A WHR >1 in males and >0.8 in females indicates high intra-abdominal fat. Some research suggests that WHR is superior to both WC and BMI in determining obesity-related cardiometabolic risk.[6] Independent of BMI classification, higher WC is correlated with increased mortality.[10] Therefore, measurement of WC and the WHR are useful in identifying individuals who are normal weight or overweight with health risks owing to increased abdominal fat accumulation.

EPIDEMIOLOGY

Obesity is a major public health concern worldwide, and is a leading cause of numerous medical conditions (eg, cardiovascular disease, hypertension, dyslipidemia, diabetes, sleep apnea) and premature death[6] (**Table 36-2**). According to the WHO, there were ~1.9 billion overweight and 650 million obese adults globally in 2016.[1] In the United States, the prevalence of obesity has been examined as part of the National Health and Nutrition Examination Survey (NHANES). The NHANES data from 2017 to 2018 indicates that the prevalence of obesity and severe obesity among U.S. adults was 39.8% and 9.2%, respectively.[4] Data from 2017 to 2018 shows 73.6% of U.S. adults are overweight or obese.[11] Adult obesity usually results from steady weight gain starting in the mid-20s to between ages 40 and 59 years, when the prevalence of obesity peaks.[4] Severe obesity is more common in females, and the prevalence of obesity is highest among non-Hispanic Black females.[4] The prevalence of obesity and severe obesity among adults has continued to increase from 1999 through 2018.[4]

Table 36-2
Obesity-Related Health Conditions

Cardiovascular	**Dermatologic**
Cardiovascular disease[a]	Striae distensae (stretch marks)
Hypertension[a]	Skin tags
Heart failure	Acanthosis nigricans
Coronary artery disease	Intertrigo
Stroke	**Gastrointestinal**
Pulmonary	Gallstones
Obstructive sleep apnea[a]	GERD[a]
Asthma/reactive airway disease[a]	**Psychological**
Metabolic	Eating disorders

Cardiovascular	**Dermatologic**
Metabolic syndrome[a]	Depression[a]
Dyslipidemia[a]	Social stigma
Prediabetes[a]	
Type 2 diabetes mellitus[a]	**Gynecologic and Obstetric Complications**
Cancer	Gestational diabetes
Esophageal	Preeclampsia
Colon	Female infertility[a]
Liver	PCOS[a]
Prostate	**Musculoskeletal**
Uterine	Osteoarthritis[a]
Breast	**Other**
Ovarian	NAFLD[a]
Gallbladder	Impotence
Kidney	Male hypogonadism[a]
Cervix	Urinary stress incontinence[a]

GERD, gastroesophageal reflux disease; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome.

[a]Health conditions cited in the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines that should be considered in determining secondary and tertiary prevention.

Sources: Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract.* 2016;22 Suppl 3:1–203. doi:10.4158/EP161365.GL; Malnick SD, Knobler H. The medical complications of obesity. *QJM.* 2006;99:565–579. doi:10.1093/qjmed/hcl085.

Obesity is also a significant problem among children and adolescents, with alarmingly high prevalence rates. Overweight and obesity in children and adolescents (ages 2–19 years) are based on the Centers for Disease Control and Prevention (CDC) growth charts; overweight is defined as BMI in the 85th to 95th percentile, and obese is defined as BMI >95th percentile.[6] The WHO estimates

that 38 million children age younger than 5 years and >340 million children and adolescents ages 5 to 19 years have overweight or obesity worldwide.[1] The U.S. NHANES data from 2015 to 2016 reported that 35.1% of children and adolescents (ages 2–19 years) had either overweight or obesity including 18.5% with obesity and 5.6% with severe obesity.[12] Asian youth show the lowest prevalence followed by non-Hispanic White youth, non-Hispanic Black, and Hispanic youth. Mexican American youths show the highest prevalence, with 29.2% in boys and 24.3% in girls.[12] This prevalence rate has remained alarmingly high; childhood obesity must be addressed because of the health consequences the child takes on into adulthood. Childhood and adolescent obesity shows an increased risk for adult overweight and obesity.[13] Also, studies have shown that overweight and obesity in childhood and adolescence are correlated with an increased risk of adult diabetes, hypertension, ischemic heart disease and stroke physical morbidity, and premature mortality.[14]

ETIOLOGY AND PATHOPHYSIOLOGY

Simply stated, obesity results from an imbalance of energy intake and energy expenditure. Body fat accumulation will occur when an individual consumes more calories than are burned. However, this simple principle becomes increasingly complex when considering the effects of hormonal and neural signals that control the body's energy homeostasis.[15] This explains why simple calorie counting in relation to physical activity or calorie expenditure is not always an easy or successful method for reducing weight; the body has in place counterregulatory systems that limit the degree of a calculated weight loss.[15,16]

The exact cause of obesity is difficult to identify and is likely a mixture of genetic, neurohormonal, environmental, and behavioral factors. Investigators have tried to understand the origin of this disease by studying the influences of society, culture, socioeconomic

status, medical conditions, medications that stimulate appetite, parental weight, and hereditary traits on dietary habits and physical activity.[17] Each potential cause of obesity continues to be investigated as a possible target for treatment and prevention. It has been concluded that there are physiologic and metabolic differences in persons with a history of obesity compared to those who were never obese. These physiologic differences and the body's adaptations to weight loss are suggested to cause the weight loss plateaus and relapses commonly seen in persons with obesity after a period of weight loss. This speaks to the importance of treating obesity as a chronic disease that requires lifelong monitoring and long-term treatment strategies.

Genetic Features

There is a clear link between genetics and obesity, both in childhood and adulthood, shown mostly through twin and adoption studies.[18–23] One study by Wardle et al demonstrated a heritability estimate of 77% for BMI and 76% for WC.[20] Genetic studies have identified genes that may be associated with weight.[18,30] There is also evidence that body fat distribution is controlled by genetic factors with WHR showing heritability of up to 60%.[24]

HYPOTHALAMUS DYSREGULATION

The hypothalamus plays a key role in body weight regulation by controlling appetite and energy expenditure.[25] This occurs particularly in the arcuate nucleus within the hypothalamus. The hypothalamus is sensitive to a variety of facilitatory and inhibitory neurotransmitters and polypeptide neurohormones from the brain and gastrointestinal (GI) tract.[15,25] The hypothalamus receives input from peripheral satiety sites (eg, gastric and pancreatic peptides released secondary to food passing through the GI tract), from leptin that is produced by fat cells, and from the catecholamine neurotransmitter system in the brain.[26,27]

NEUROPEPTIDE AND LEPTIN DYSREGULATION

Leptin

Leptin is a protein synthesized by adipocytes, gastric chief cells, skeletal muscle, and other organs. It acts on receptors of the hypothalamus as an afferent satiety signal in the brain to regulate body fat mass.[26,28] Leptin reduces food intake, decreases serum glucose and insulin levels, increases metabolic rate, and reduces body fat mass and weight.[29,30] Serum leptin levels are highly correlated with BMI and body fat; leptin secretion has a circadian rhythm and an oscillatory pattern similar to that of other hormones.[26,29]

Although rare, it is estimated that 1% to 5% of children with severe obesity may have a genetic mutation that causes a leptin deficiency.[31] Without the inhibitory signaling of leptin, patients can experience imbalances in their energy homeostasis, neuroendocrine pathways, and autonomic nervous systems leading to obesity. Leptin deficiency–related obesity as well as certain types of lipodystrophy can be successfully treated with exogenous leptin.[29,30] In contrast to leptin deficiency, leptin resistance is much more common. Many patients with obesity have been shown to have high levels of leptin, but experience leptin resistance.[28,29] A potential mechanism for leptin resistance may be reduced leptin receptor protein expression found in the skeletal muscle of patients with obesity.[32] The body's failure to respond to leptin signaling results in a net positive energy imbalance similar to that seen in leptin deficiencies. Utilizing exogenous leptin, or leptin-like products, has been unsuccessful in clinical settings for most patients with obesity, likely owing to leptin resistance.[28–30] In addition, it has been demonstrated that elevated baseline serum leptin levels are associated with inability to maintain weight loss.[33]

Neuropeptides and neurohormones

Appetite is regulated in part via a feedback loop of orexigenic neuropeptides—neuropeptide Y (NPY) and agouti-related peptide (AgRP) that signal hunger and anorexigenic neuropeptides (pro-opiomelanocortin [POMC])—which, in turn, signal satiety within the

hypothalamus.[30,34] Neurons expressing the *POMC* gene release melanocyte-stimulating hormones (MSHs).[30,34] These hormones can stimulate melanocortin-3 receptors (MC3R) and melanocortin-4 receptors (MC4R) to suppress food intake.[27,30,35]

Several other neurohormonal signals and peptides play a role in appetite regulation. Ghrelin is a hormone that is released from the stomach before meals and acts to increase appetite via stimulation of NPY and AgRP.[34,35] There is a negative correlation between ghrelin levels and BMI, in which patients with obesity have increased ghrelin, and levels remain elevated even after weight loss.[35] Peptide tyrosine tyrosine (peptide YY or PYY) and pancreatic polypeptide (PP) are chemically related to NPY, but work as appetite suppressants.[35,36] Both NPY receptor antagonists and PYY have been investigated as potential anti-obesity drugs, and research is ongoing.[37] Amylin is a pancreatic hormone that is released in response to eating and has an anorectic effect.[35] Administration of amylin has been shown to result in reduced food intake and weight loss.[38] Glucagon-like peptide (GLP)-1 is secreted from the gut in response to food intake and works to reduce food intake, suppress GLP secretion, and delay gastric emptying.[35] Cholecystokinin (CCK) is a hormone that is released from the small intestines in response to food intake and works to suppress further food intake.[35]

NEUROTRANSMITTER DYSREGULATION (SEROTONIN, DOPAMINE, NOREPINEPHRINE)

POMC and AgRP neurons are responsive to central neurotransmitters (including serotonin, NPY, γ-aminobutyric acid [GABA], and melanocortin) to control appetite.[25] Serotonin has an inhibitory effect on appetite, and is responsible for satiety or the feeling of fullness after food intake.[39] Agents that block postsynaptic serotonin activity (eg, clozapine, mirtazapine, and atypical antipsychotics) can stimulate appetite and may cause weight gain.[40] Research has correlated similarities between drug addiction and food addiction, through the body's neuroadaptations in the dopamine reward system.[41] Studies have shown that people with obesity may

have impairments in dopaminergic pathways that may lead to overeating.[42] Dopamine-augmenting agents such as amphetamines were once used for the treatment of obesity, but produced tolerance, dependence, and withdrawal reactions. Conversely, dopamine receptor antagonists such as chlorpromazine and clozapine may cause dysphoria, and are often associated with weight gain. Obesity has been linked to the activation of the sympathetic nervous system (SNS).[43] This increase in the SNS response is thought to be mediated by both norepinephrine and leptin.[44] The increase in SNS activity is thought to be the primary mechanism of obesity-related hypertension.[43,45]

Medical Conditions and Medications

Although less common, certain medical conditions may cause overweight and obesity.[46] Genetic syndromes may be the primary cause of obesity such as Prader–Willi, Bardet–Biedl, Cohen, Alström, and Froehlich syndromes. Other primary causes of obesity include monogenic disorders such as MC4R mutation, leptin deficiency, and POMC deficiency.[28,29,47] Setmelanotide (Imcivree™), a novel MC4R agonist, was approved in 2020 for patients with obesity caused by proprotein subtilisin/kexin type 1 (PCSKI) deficiency, POMC deficiency, and leptin receptor deficiency.[47,48] Setmelanotide is administered as a subcutaneous injection once daily.[47] Secondary causes of obesity include neurologic issues such as brain injury, brain tumors, and hypothalamic injury.[46] Endocrine disorders may also be a secondary cause of overweight and obesity such as polycystic ovarian syndrome, Cushing syndrome, and growth hormone deficiency.[46] Hypothyroidism is often cited as a secondary cause of obesity because elevated thyroid-stimulating hormone (TSH) is correlated with obesity.[49] But the relationship between hypothyroidism and obesity is complex; because leptin and melanocortin influence the release of TSH, causality has yet to be established.[49,50] Psychological causes of obesity include eating disorders and depression when associated with overeating or

binging. Several medications are also associated with weight gain. These include antipsychotics, steroids, insulin, sulfonylureas, thiazolidinediones, some antidepressants, and some anticonvulsants.[46,51–53] When treating overweight and obesity, if medications associated with weight gain are identified, substitution with possible alternatives should be considered. **Table 36-3** provides a list of medications that may cause weight gain, along with potential alternatives.

Table 36-3
Common Drugs and Their Effect on Weight

	Associated With Weight Gain	Associated With Less Weight Gain or Weight Neutral	Associated With Weight Loss
Antidepressants	TCAs (particularly amitriptyline), citalopram, escitalopram, sertraline, paroxetine, mirtazapine	Fluoxetine, duloxetine, venlafaxine	Bupropion
Antipsychotics	Clozapine, olanzapine, paliperidone, quetiapine, risperidone, haloperidol	Aripiprazole, amisulpride, asenapine, brexpiprazole, lurasidone, ziprasidone	
Neurologic	Valproic acid, gabapentin, pregabalin, carbamazepine, vigabatrin, lithium	Lamotrigine	Topiramate, zonisamide, felbamate
Glucose lowering	Insulin, sulfonylureas (especially glyburide), meglitinides, thiazolidinediones	DPP-4 inhibitors	GLP-1 agonists, metformin, pramlintide, SGLT-2 inhibitors, α-glucosidase inhibitors
Antihypertensives	β-Adrenergic blockers (especially propranolol), α-adrenergic blockers (prazosin, terazosin)	ACEIs, ARBs, CCBs, doxazosin	
Contraceptives	Depot medroxyprogesterone	Barrier methods, oral contraceptives	
Antihistamines	First generation	Second generation	
Anti-inflammatory	Corticosteroids	NSAIDs, DMARDs	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DMARD, disease-modifying antirheumatic drug; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SGLT-2, sodium glucose–linked transporter-2; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Sources: Alonso-Pedrero L, Bes-Rastrollo M, Marti A. Effects of antidepressant and antipsychotic use on weight gain: a systematic review. *Obes Rev.* 2019;20(12): 1680–1690; Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva VA. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. *Neuropsychiatr Dis Treat.* 2017;13:2231–2241; Domecq JP, Prutsky G, Leppin A, et al. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2015;100:363–370; Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med.* 2017;376(3):254–266; Meyer JM, Ng-Mak DS, Chuang C-C, Rajagopalan K, Loebel A. Weight changes before and after lurasidone treatment: a real-world

analysis using electronic health records. *Ann Gen Psychiatry.* 2017;16:36; Uguz F, Sahingoz M, Gungor B, Aksoy F, Askin R. Weight gain and associated factors in patients using newer antidepressant drugs. Gen Hosp Psychiatry. 2015;37(1):46-48. doi: 10.1016/j.genhosppsych.2014.10.011; Weiss C, Weiller E, Baker RA, et al. The effects of brexpiprazole and aripiprazole on body weight as monotherapy in patients with schizophrenia and as adjunctive treatment in patients with major depressive disorder: an analysis of short-term and long-term studies. *Int Clin Psychopharmacol.* 2018;33(5):255–260.

Environmental Influences, Behavioral Factors, and Other Considerations

Despite the known genetic influences predisposing certain individuals to obesity, environmental influences play a role by providing exposure to a lifestyle promoting energy imbalance that may influence epigenetic factors. Modern society provides an overabundance of inexpensive, readily accessible calorie-dense food. Decreased energy expenditure owing to a sedentary lifestyle has become common, further exacerbating an obesogenic lifestyle.[30] A review of twin and adoption studies by Silventoinen et al clearly demonstrated that environmental factors affect BMI variation in childhood, but the effect of common environment disappears in adolescence.[19] These results portray a stronger influence of genetics in the incidence of obesity in adulthood.

Several association studies link short-term sleep duration and metabolic changes such as obesity, insulin resistance, and diabetes.[54,55] Alteration of the hypothalamic regulation of appetite and energy expenditure owing to sleep loss is one possible explanation. Sleep loss has also been shown to be associated with low leptin levels and high ghrelin levels; both factors contribute to signaling of energy deficit and hunger, which may contribute to overeating and obesity.[56]

Research has begun to investigate the role of gut microbiota in body composition. Data suggest that interventions that negatively impact the biodiversity of the gut microbiota such as cesarean delivery, elevated maternal prepregnancy BMI, and early antibiotic use may increase the risk of obesity.[57] A large cohort trial found that

the repeated use of broad-spectrum antibiotics during the first 2 years of life has been associated with early childhood obesity.[58]

CASE 36-1

QUESTION 1: S.B. is a 48-year-old female with a past medical history (PMH) of hypertension, sleep apnea, osteoarthritis, and depression. Her height is 66 inches (168 cm), current weight is 200 pounds (91 kg), and WC is 38 inches (96 cm). She presents to her primary physician for a routine physical examination. She notes dissatisfaction with her weight and states that she has been overweight since she was a child. She reports having tried multiple diets during the past 30 years, but has had little success with weight loss and always regains any weight she manages to lose. S.B. expresses a desire to attempt more intensive therapy for weight loss. Her current medications include hydrochlorothiazide 12.5 mg, acetaminophen 1000 mg prn, and paroxetine 20 mg. Her blood pressure is controlled at 128/78 mm Hg and her sleep apnea is managed with a continuous positive airway pressure (CPAP).

How is obesity defined and assessed in a patient such as S.B.? What factors (including medications) may be contributing to her obesity?

CLINICAL FEATURES

Initial Assessment

Current guidelines recommend that weight status should be assessed in all patients.[6] Initial assessment involves a physical exam and patient interview to classify the presence of overweight or obesity and any obesity-related comorbidities. The preferred method to classify overweight or obesity is to measure the BMI. Measurement of WC will also aid in determining risk of obesity comorbidities. However, measurement of WC in patients with BMI >35 kg/m^2 is not necessary because it will likely be elevated and will provide no additional risk information.[6,9] BMI, WC, and obesity-related comorbidities are used to determine the need to initiate treatment. S.B.'s BMI is 32.2 (91 kg/[1.68 m^2]), which is in obesity class I. Her WC >35 inches (>88 cm) indicating abdominal obesity

that puts her at additional risk for increased morbidity and mortality. S.B. also has hypertension, sleep apnea, and osteoarthritis, which are likely related to obesity and will need to be considered in her overall care plan.

During the patient interview, information should be obtained regarding the patient's eating habits and physical activity. It is important to establish baseline data so that response to changes in diet and exercise is noted throughout treatment. Successful weight loss involves a change in energy balance through reduced caloric intake or increased energy expenditure. In S.B.'s case, it will be beneficial to evaluate her current diet and physical activities to determine the most appropriate lifestyle recommendations. It is also important to evaluate a patient's "weight loss readiness" or self-motivation before initiation of therapy. A patient's motivation to lose weight is a significant predictor of success or failure in the weight management program. S.B.'s desire and willingness to make significant lifestyle changes to achieve this should be evaluated.

Patients should also be screened for medical conditions or medications that can increase the risk of obesity, and these underlying factors should be corrected before recommending treatment. S.B.'s PMH does not indicate any overt medical causes of obesity, but it would be appropriate to rule out whether she is overeating because of her depression and to check thyroid function to rule out hypothyroidism. Even though causality between obesity and thyroid dysfunction has yet to be firmly established, hypothyroidism is a common condition in females and may be associated with weight gain or inability to lose weight. S.B. is currently taking paroxetine for depression, which has been associated with weight gain.[53] S.B.'s prescriber may want to consider switching to fluoxetine, which is the selective serotonin reuptake inhibitor (SSRI) that is associated with the least amount of weight gain, or bupropion, which is associated with weight loss (**Table 36-3**).[51,53]

Course and Prognosis

Case 36-1, Question 2: S.B. states that she has struggled with her weight her whole life. She has progressively gained ~(4.4 pounds [2 kg])/year since her 20s. What is the typical course and prognosis of obesity?

Obesity is a chronic disease that often begins in childhood or adolescence, and is often characterized by a slow and steady increase in body weight during adult life. Most patients with obesity battle with weight loss and regain throughout their entire lives. The biologic response to weight loss favors regain with increased ghrelin and reductions in GLP-1, CCK, leptin, and PYY resulting in increased hunger.[46,59] Maintaining weight loss is key to long-term management of obesity. S.B. should be assured that her struggle is common and that she will need to commit to long-term lifestyle changes to manage her obesity.

Medical Complications

Case 36-1, Question 3: S.B. understands that she already has hypertension, sleep apnea, and osteoarthritis, which are comorbidities that are related to her obesity and increase her risk of morbidity and mortality. She is also at risk for experiencing additional obesity-associated medical comorbidities if she does not lose or continues to gain weight. What are the other common medical conditions associated with obesity?

Obesity is associated with an increased risk of morbidity and mortality. Obesity is linked to many significant health conditions such as type 2 diabetes mellitus; respiratory conditions; gallbladder disease; cancers; osteoarthritis; cardiac disease (hypertension, stroke, congestive heart failure, and coronary heart disease); dyslipidemia; and GI, hepatic, and gynecologic and obstetric complications (**Table 36-2**).[6,60] Weight loss helps control diseases associated with obesity, and may even help prevent development of these diseases. In S.B.'s case, weight loss could help her decrease or eliminate medications needed to control her hypertension, alleviate pain associated with osteoarthritis, decrease symptoms of

sleep apnea, and reduce her BMI and WC, thereby improving her morbidity and mortality risk.

ASSESSMENT AND TREATMENT

CASE 36-1, QUESTION 4: S.B. reports that she is highly motivated to lose weight. What are appropriate goals for S.B.'s weight loss? What should the initial treatment plan include?

The ultimate goal in the management of overweight or obesity is to prevent or improve obesity-related complications.[6] Weight loss goals should be individualized based on the patient and presence of obesity-related complications. Health benefits have been shown with >5% sustained weight loss.[6] Most health conditions including diabetes, hypertension, and dyslipidemia will improve with weight loss goals of 5% to 15%.[6] Higher goals of 10% to 40% may be necessary to demonstrate improvement for steatohepatitis.[6] Setting appropriate achievable weight loss goals is important to success; unrealistic expectations for more dramatic weight loss may lead to disappointment and ultimately cause patients to stop any efforts.

Obesity is a chronic disease that requires lifelong effort for successful treatment.[6,46] Treatment may involve a multidisciplinary approach including the expertise of a general practitioner, dietician or nutrition specialist, pharmacist, psychiatrist, or surgeon depending on the specific needs of the individual. The general goals of weight loss and management are to prevent or improve obesity-related complications, prevent further weight gain, reduce body weight, and maintain weight loss over a long period.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines recommend implementing a strategy of primary, secondary, and tertiary prevention for overweight and obesity.[6] To determine the appropriate phase, BMI must be evaluated and then patients with a BMI ≥25 (overweight or obese) must be screened for the following obesity-

related complications: metabolic syndrome, prediabetes, type 2 diabetes, dyslipidemia, hypertension, cardiovascular disease, nonalcoholic fatty liver disease, polycystic ovary syndrome, female infertility, male hypogonadism, obstructive sleep apnea, asthma or reactive airway disease, osteoarthritis, urinary stress incontinence, gastroesophageal reflux disease, and depression.[6]

- Primary prevention: For patients with a BMI <25 (normal weight), the recommended therapy is to prevent patients from developing overweight and obesity through a healthy lifestyle.[6]
- Secondary prevention: For patients with BMI 25 to 29.9 (overweight) with no obesity-related complications; the recommended therapy is to implement lifestyle therapy. For patients with a BMI ≥30 (obesity) with no complications; the recommended therapy begins with lifestyle therapy, and if lifestyle therapy fails, pharmacotherapy should be considered.[6]
- Tertiary prevention: For patients with a BMI ≥25 and one or more obesity-related complications, the recommended therapy begins with lifestyle therapy. For patients with BMI ≥27, if lifestyle therapy fails, pharmacotherapy should be considered. For patients with a BMI ≥27 and at least one severe complication, the recommended therapy includes both lifestyle therapy and pharmacotherapy. Bariatric surgery may be considered for patients with BMI ≥35.[6]

S.B. is a candidate for tertiary prevention based on her BMI and presence of obesity-related complications. An appropriate weight loss goal for S.B. is 5% to 15% (10–30 pounds [4.55–13.65 kg]) because of her hypertension. Based on her BMI and obesity-related complications, S.B. is a candidate to initiate lifestyle therapy. The initial treatment plan should include a reduced-calorie diet, increased physical activity, and behavioral modifications.[6]

Lifestyle Therapy

Case 36-1, Question 5: S.B. reports that she has never received dietary counseling from a medical professional, and has always dieted on her own by

restricting fat intake. Although she has not attempted to lose weight recently, S.B. expresses the desire to try a program for weight loss and start an exercise regimen. What types of nonpharmacologic therapies are available for weight reduction and relapse prevention?

Comprehensive lifestyle interventions including a calorie-restricted diet, increased physical activity, and behavioral modifications are the foundation of weight-loss therapy.

DIET

Diets for weight loss promote caloric restriction. Caloric recommendations for females seeking to lose weight are 1200 to 1500 kcal/day and 1500 to 1800 kcal/day for males; alternatively, a deficit of 500 to 750 kcal/day is associated with weight loss.[61] Because of the high demand by consumers, there are numerous types of weight loss programs, diets, and products that may or may not be effective for each individual patient. A variety of dietary interventions have been proved successful in weight loss including low-fat diets, higher protein diets, low-carbohydrate diets, restricted carbohydrate diets, meal replacement and liquid diets, and dietary patterns such as the Mediterranean diet.[6] Research suggests that clinically meaningful weight loss is achieved through adherence to a nutritious reduced- calorie diet regardless of the composition of dietary macronutrients.[62–65] The most effective diet is one that the patient can be in compliance with long term.[62–65]

EXERCISE

Increased physical activity will contribute to the negative energy balance that is required for weight loss. Increased physical activity is essential in preventing weight gain. Overweight children and adults should have at least 30 minutes of moderate-intensity physical exercise daily (with a gradual increment of increasing exercise by several minutes each day up to 30 minutes/day). It has been shown that moderate exercise (eg, 4 kcal/g/week) can improve physiologic variables.[63,66]

BEHAVIOR THERAPY

Behavioral interventions are an essential component of lifestyle therapy that should enhance dietary and physical recommendations. Several behavioral therapies have been proved helpful in weight loss therapy ranging from simple goal setting to more intense cognitive restructuring. Guidelines recommend that patients include one or more of the following behavioral interventions: self-monitoring food intake, physical activity, and weight monitoring; goal setting, educational sessions centering on obesity, nutrition, and exercise; support meetings or group sessions; stimulus control; stress reduction; psychological evaluation; cognitive restructuring; motivational interviewing; and behavioral contracting.[6] Early weight loss is correlated with long-term success; if, after 1 month of lifestyle interventions, patients are unable to achieve 2.5% of their baseline weight, behavioral interventions should be intensified.[6]

Overall, a combination of a reduced-calorie diet and increased physical activity with support of behavioral interventions are most effective for reducing and maintaining weight loss. Given that obesity is a chronic condition, S.B. must select a comprehensive lifestyle intervention that is most appealing and feasible to her so that she will be able to be in compliance with it in the long term.

CASE 36-1, QUESTION 6: S.B. returns to her physician for follow-up 6 months later. She has managed to lose 15 pounds (7 kg) and is at a weight of 185 pounds (84 kg). Based on her BMI of 29.8 kg/m^2, her weight is classified as overweight. This weight loss has improved her mood and symptoms of osteoarthritis. Unfortunately, her hypertension has worsened, and is uncontrolled at 148/86 mm Hg despite additional therapy. Her current medication profile includes bupropion XL 150 mg, hydrochlorothiazide 25 mg, lisinopril 10 mg, and acetaminophen as needed. Although she has achieved her personal goal with 7.7% weight loss and is now considered overweight and not obese, S.B. is disappointed that her weight loss has plateaued. She still wants to lose additional weight. She asks the physician about short-term anti-obesity medications that can help accelerate her weight loss. Would a short-term agent be appropriate for S.B.? What are the mechanisms of action, efficacy, and potential adverse effects of the short-term anti-obesity medications?

Pharmacologic Therapy

As previously stated, a comprehensive lifestyle intervention is the foundation of weight loss management. Although weight loss is achievable for most patients, it is difficult to sustain, and weight regain is common.[6] Medication should be considered for patients with a BMI ≥30 kg/m^2 without risk factors or BMI ≥27 kg/m^2 with an obesity-related comorbid medical condition (**Table 36-2**).[6] Medications should not be considered a replacement for diet, behavioral modification, and exercise, but rather as adjunctive therapy. Currently, marketed anti-obesity drugs include short- and long-term therapies.[6,67–75]

S.B. is a candidate for pharmacotherapy even though her BMI is currently considered overweight at 29.8 kg/m^2, her obesity-related comorbidities of hypertension and sleep apnea qualify her for medication therapy. The most appropriate medication for S.B. must be based on her current medication profile and her comorbid health conditions.

SHORT-TERM THERAPY

Obesity is a chronic disease state; therefore, the clinical usefulness of short-term therapy is unlikely to have a meaningful impact. The Food and Drug Administration (FDA) has approved several weight-loss drugs for short-term use defined as <12 weeks including phentermine, diethylpropion, phendimetrazine, and benzphetamine. All are sympathomimetic agents that function as appetite suppressants.[6,76] Of these drugs, phentermine is the most commonly prescribed and is frequently used off-label for long-term therapy.[77,78]

Phentermine is approved for adjunctive therapy in patients older than age 16 years, at a dosage of 18.75 to 37.5 mg taken 2 hours after breakfast. Dosing may also be divided into 18.75 mg taken twice per day or 8 mg taken three times per day.[67,79] The most common adverse effects associated with phentermine therapy are insomnia, dry mouth, dizziness, and palpitations.[67,76] Phentermine has also been associated with cardiovascular effects, including case reports of pulmonary hypertension. It is contraindicated in patients

with cardiovascular disease, uncontrolled hypertension, and hyperthyroidism.[67,80] Phentermine is classified as a controlled substance (schedule IV drug) owing to concerns of abuse; however, this concern has been questioned in the literature.[67,78]

Diethylpropion, phendimetrazine, and benzphetamine exhibit appetite-suppressive actions similar to that of phentermine, but are less widely prescribed.[76] They also share adverse effects and contraindications similar to that of phentermine.[68–70] These agents are also reported to have an abuse potential. Diethylpropion is classified as a schedule IV drug, and benzphetamine and phendimetrazine are classified as schedule III drugs.[68–70] Based on their approval for short-term use, adverse effects, and abuse potential, none of these agents should be recommended for weight loss therapy.

S.B.'s physician should not prescribe short-term weight loss medications to S.B. Short-term agents for obesity may increase S.B.'s blood pressure and interfere with her sleep. Also, short-term agents will not provide the necessary long-term treatment for S.B.'s chronic condition.

CASE 36-1, QUESTION 7: S.B. now understands that her obesity is a chronic condition and inquires about long-term medications for weight loss. What agents are available for the long-term treatment of obesity? (See **Table 36-4**.)

Table 36-4
Medications for the Treatment of Obesity

Generic Name	Trade Name	Dosing
Orlistat	Xenical®	Age >12: 120 mg PO tid
	Alli®	Age >18: 60 mg PO tid
Phentermine/topiramate	Qsymia®	Age >12: 3.75/23 mg PO QAM × 14 days; then 7.5/46 mg QAM for 12 weeks, then evaluate weight loss, <3%, dose may be titrated to 11.25/69 mg QAM × 14 days, then 15/92 mg QAM

Generic Name	Trade Name	Dosing
Naltrexone/bupropion	Contrave®	Age >18: 8/90 mg PO QAM × 1 week, then 8/90 mg bid ×1 week, then 16/180 mg QAM and 8/90 mg QPM, then 16/180 mg bid
Liraglutide	Saxenda®	Age >18: 0.6 mg SC daily × 1 week, increase dose by 0.6 mg weekly until therapeutic dose of 3 mg daily
Semaglutide	Wegovy®	Age >18: 0.25 mg SC weekly × 4 weeks then 0.5 mg weekly × 3 weeks, then 1 mg × 3 weeks, 1.7 mg × 3 weeks, then 2.4 mg weekly
Phentermine hydrochloride[a]	Adipex-P®, Lomaira™	Age >16: 8 mg tid; 30–37.5 mg QAM

bid, two times a day; OTC, over the counter; PO, by mouth; QAM, every morning; QPM, every evening; SC, subcutaneously; tid, three times a day.

[a]Not recommended for routine or long-term use.

LONG-TERM THERAPY

Orlistat (Xenical®, Alli®)

Orlistat is FDA approved for long-term obesity management as an adjunct to lifestyle modification.[71] Orlistat 120 mg was originally marketed under the trade name Xenical®. Then, in February 2007, the FDA approved the over-the-counter (OTC) marketing of orlistat, under the trade name Alli®, at a 60-mg dose.[81] Orlistat works to reduce dietary fat absorption by inhibiting GI (stomach and pancreatic) lipase activity.[71,76,82] Gastric and pancreatic lipase are enzymes that play a pivotal role in the digestion of dietary fat (triglycerides). By inhibiting these lipase enzymes, orlistat prevents the hydrolysis and absorption of triglycerides.[71,81] This results in the excretion of ~30% of ingested fat in the feces.[71,76] Orlistat does not exert appetite suppressant effects, has no central nervous system (CNS) effects, and has no systemic absorption.[82] The therapeutic activity of orlistat takes place in the stomach and small intestine, and effects are seen as soon as 24 to 48 hours after dosing.[82]

Orlistat is administered three times per day during or up to 1 hour after meals containing fat.[71] If a meal does not contain fat, the dose may be skipped. In a meta-analysis, orlistat was shown to produce average weight loss of 5.73 pounds (2.6 kg) greater than placebo.[83] In addition, a 4-year prospective, double-blind, randomized study, XENDOS, found that orlistat plus lifestyle changes was associated with a 37.3% risk reduction of type 2 diabetes in >3300 high-risk obese patients.[84] Use of orlistat has also been associated with improvements in blood pressure, as well as improvement in metabolic parameters such as fasting serum lipid profiles and C-reactive protein.[84–86]

The most common adverse effects associated with orlistat include GI problems (loose stools, oily spotting, flatus with discharge, fecal urgency, fatty or oily stools, increased defecation, fecal incontinence, bloating, and cramping).[71] Side effects usually develop early in treatment and persist for 1 to 4 weeks, but occasionally last longer than 6 months.[71] Because GI adverse effects are worse with a high-fat diet, orlistat may enhance dietary compliance with a low-fat diet, further potentiating weight loss. In addition, bothersome side effects have been associated with nonadherence, causing variability in patient outcomes. Rare cases of oxalate-induced acute kidney injury and liver injury have been reported with use of orlistat.[87,88] Pancreatitis and cholelithiasis have also been reported; therefore, patients should be monitored for both.[71] Orlistat is contraindicated in patients with chronic malabsorption syndrome, cholestasis, and pregnancy.[71]

Orlistat may reduce the absorption of fat-soluble vitamins (A, D, E, and K), and patients should take a multivitamin supplement that contains these vitamins.[71] The supplement should be separated by at least 2 hours before or after the administration of orlistat, such as at bedtime. Patients using warfarin should be closely monitored, because the reduced absorption of vitamin K may potentiate the bleeding effects of warfarin. Orlistat may also reduce the absorption of levothyroxine and lipophilic drugs including amiodarone, cyclosporine, lamotrigine, and valproic acid.[71,89]

Phentermine/topiramate extended release (Qsymia®)

Phentermine/topiramate extended release (ER) is a combination drug approved by the FDA for long-term obesity management as an adjunct to lifestyle modification.[72] Phentermine is a sympathomimetic agent that functions as an appetite suppressant by increasing the concentration of norepinephrine in the central nervous system.[72] Topiramate is an antiepileptic agent also approved for the treatment of migraines, which acts as an agonist at $GABA_A$ receptors and as an antagonist at non-*N*-methyl-d-aspartic acid (NMDA) glutamate receptors.[76] The mechanism by which weight loss occurs with topiramate is unclear, but may be related to a direct action on adipose tissue.[90]

Therapy is initiated at a dose of phentermine 3.75 mg/topiramate 23 mg daily for 14 days, after which the dose is increased to phentermine 7.5 mg/topiramate 46 mg daily.[72] If the patient has not experienced ≥3% weight loss after 12 weeks of therapy at the maintenance dose, the drug should either be discontinued or the dose escalated to phentermine 15 mg/topiramate 92 mg daily. After an additional 12 weeks of therapy, if the patient has not experienced ≥5% weight loss, the drug should be discontinued via taper to avoid precipitating a seizure.[72]

The efficacy of phentermine/topiramate ER has been demonstrated in two phase 3 clinical trials and one expansion trial: CONQUER, EQUIP, and SEQUEL (an extension of the CONQUER trial).[90–92] Phentermine/topiramate ER 7.5/46 mg was shown to produce average weight loss of 7.8% of initial body weight after 1 year and 9.3% after 2 years.[90,91] Phentermine/topiramate ER 15/92 mg was shown to produce average weight loss of 9.8% of initial body weight after 1 year and 10.5% after 2 years.[90,91] Use of phentermine/topiramate ER has also been associated with improvements in cardiometabolic parameters including decreased blood pressure, reductions in triglycerides and low-density lipoprotein (LDL) cholesterol, and improvements in high-density lipoprotein (HDL) cholesterol.[91,92] Patients taking

phentermine/topiramate ER at doses ≥7.5/46 mg also showed reduced progression to type 2 diabetes.[92]

The most common adverse effects associated with phentermine/topiramate ER include paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.[72] Cognitive effects and mood and sleep disturbances have also been observed.[72] Topiramate inhibits carbonic anhydrase activity that may lead to calcium phosphate kidney stones and interaction with other carbonic anhydrase inhibitors such as zonisamide, acetazolamide, or methazaolamide.[72] Increases in heart rate have been observed; thus, heart rate should be monitored, particularly in patients with preexisting cardiac or cerebrovascular disease.[72] Topiramate has been associated with birth defects, specifically oral clefts when taken during the first trimester, which led the FDA to approve phentermine/topiramate ER with a risk evaluation and mitigation strategy (REMS).[93] This REMS is designed to inform practitioners and patients about the risk of birth defects, the importance of contraceptive use, and the need to immediately discontinue the drug if the patient becomes pregnant.[93] Phentermine/topiramate ER is contraindicated in pregnancy and in patients with glaucoma, hyperthyroidism, monoamine oxidase inhibitor (MAOI) use within the past 14 days, and hypersensitivity to sympathomimetic amines.[72]

Naltrexone/bupropion (Contrave®)

Naltrexone/bupropion is a combination drug that is approved by the FDA for long-term obesity management as an adjunct to lifestyle modification.[73] Bupropion, an antidepressant that inhibits dopamine and norepinephrine reuptake, has a known side effect of weight loss when used for the treatment of depression and smoking cessation.[73,76] This weight loss effect is thought to be the result of appetite suppression induced by the stimulation of POMC neurons in the hypothalamus.[94] Naltrexone, an opioid receptor antagonist, is believed to enhance this appetite suppression by blocking opioid receptors on these same POMC neurons.[94] Naltrexone/bupropion is available as combination 8/90 mg tablets. Patients initiate treatment

at a dose of one tablet every morning. This dose is titrated up over the course of 4 weeks to a dose of two tablets twice daily, for a total daily dose of 32/360 mg.[73] If the patient has not experienced ≥5% weight loss after 12 weeks of therapy at the maintenance dose, the drug should be discontinued.[73]

The efficacy of naltrexone/bupropion has been demonstrated in four 1-year, placebo-controlled, phase 3 clinical trials: Contrave Obesity Research (COR)-I, COR-II, COR-Behavior Modification (BMOD), and COR-Diabetes.[95–98] Naltrexone/bupropion 32/360 mg was shown to produce average weight loss of 6.1% to 6.4% of initial body weight.[95,96] When coupled with intensive behavior modification, patients taking naltrexone/bupropion 32/360 mg experienced an average weight loss of 9.3% of initial body weight.[97] Use of naltrexone/bupropion has also been associated with improvements in cardiometabolic parameters, including hemoglobin A_{1c} (HbA_{1c}) reduction.[95–98]

The most common adverse effects associated with naltrexone/bupropion include nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea.[73] Angle-closure glaucoma and hepatitis are potentially serious adverse effects.[73] Contrave® has a black box warning for suicidal thoughts and behavior, although increased rates have not been seen in phase 3 clinical trials.[73,95,96] Bupropion is an inhibitor of cytochrome P-450 (CYP) 2D6; caution should be used when coadministering naltrexone/bupropion with drugs metabolized by this enzyme.[73] Bupropion may reduce the seizure threshold; therefore, it should be avoided in patients with seizure disorders.[73] To minimize the risk of seizure, patients should be instructed to adhere to the dosing schedule, particularly during the titration period; also, patients should not take naltrexone/bupropion with high-fat meals because this will increase the absorption.[73] Naltrexone/bupropion is contraindicated in patients with seizures or who are at increased risk such as patients with anorexia or bulimia or who are undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or anticonvulsant medication.[73] Blood pressure and heart rate may

increase with naltrexone/bupropion; thus, both parameters should be monitored, particularly in patients with underlying cardiac or cerebrovascular disease.[73] Naltrexone/bupropion is contraindicated in patients with uncontrolled hypertension.[73] Naltrexone/bupropion is also contraindicated in pregnancy, chronic use of opioids, use of MAOIs within the past 14 days, and in patients currently taking other bupropion-containing products.[73] Angle-closure glaucoma and hepatitis are also potentially serious adverse effects.

Liraglutide (Saxenda®) and semaglutide (Wegovy®)

Liraglutide and semaglutide are GLP-1 receptor agonists that are FDA approved for long-term obesity management as an adjunct to lifestyle modification.[74,75] Activation of the GLP receptor in the central nervous system promotes feelings of satiety, thereby reducing food intake and resulting in weight loss.[74,75] Both liraglutide and semaglutide are administered via subcutaneous injection. When used for obesity, the dose of liraglutide is titrated to 3 mg daily, and the dose of semaglutide is titrated to 2.4 mg weekly.[74,75] Both agents are also approved for the treatment of type 2 diabetes at lower doses. Liraglutide labeling specifies that if the patient has not experienced ≥4% weight loss by 16 weeks after initiating therapy, the drug should be discontinued.[74] Semaglutide labeling does not specify when to determine treatment failure; however, based on general treatment guidelines for other agents, it may be appropriate to discontinue semaglutide if the patient has not experienced 5% weight loss after 12 weeks at the 2.4 mg dose.

The efficacy of liraglutide for weight loss has been demonstrated in three phase 3 pivotal clinical trials: satiety and clinical adiposity—liraglutide evidence (SCALE) Maintenance, SCALE Obesity and Pre-Diabetes, and SCALE Diabetes.[99–101] The results of the SCALE Maintenance and SCALE Diabetes trials indicate that by the end of 56 weeks of treatment, liraglutide produces an average weight loss of 4% to 6.1% greater than placebo.[99,101] Use of liraglutide has also been associated with significant improvements in HbA_{1c}, fasting plasma glucose, and fasting insulin.[99–101]

Semaglutide is associated with placebo-subtracted weight loss ranging from 9.6% to 12.4% based on the findings from the four 68-week semaglutide treatment effect in people with obesity (STEP) trials.[102–105] The STEP trials also demonstrated improvement in total and LDL cholesterol, HbA_{1c}, fasting plasma glucose, and systolic blood pressure.[102–105] The most common adverse effects associated with both liraglutide and semaglutide include nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, abdominal pain, and injection-site reactions. Liraglutide also reports decreased appetite and increased lipase; semaglutide reports gastroesophageal reflux disease, abdominal distension, and eructation. To reduce the incidence of GI side effects, the dose of both agents is titrated. Liraglutide is initiated at a dose of 0.6 mg daily and titrated up to the effective dose of 3 mg daily over a 5-week period.[74] Semaglutide is initiated at a dose of 0.25 mg weekly and titrated to 2.4 mg over a 17-week period.[75] Suicidal ideation was also reported in trials; patients taking these agents should be monitored for depression, changes in mood, or suicidal thoughts.[74,75] Increases in heart rate were also observed during clinical trials; therefore, it is recommended to monitor heart rate while taking liraglutide or semaglutide.[74,75] Both agents have also been associated with an increased risk of acute pancreatitis and cholelithiasis.[74,75] Semaglutide has also been associated with exacerbations of diabetic retinopathy; therefore, patients with a history of diabetic retinopathy should be monitored.[75] Acute kidney injury has also been associated with semaglutide; therefore, renal function should be monitored when initiating or increasing the dose.[75] Both semaglutide and liraglutide have black box warnings pertaining to thyroid C-cell tumors including medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN 2).[74,75] Therefore, both are contraindicated in patients with a personal or family history of MTC, or MEN 2.[74,75] Both are also contraindicated in pregnancy.

Lorcaserin

Lorcaserin, a selective serotonin 2C (5-hydroxytryptamine [5-HT_{2C}]) receptor agonist, was approved for long-term obesity management in 2012, but was withdrawn from the market in February 2020 owing to safety concerns. Data from a large-scale trial found increased risk of several types of cancer including pancreatic, colorectal, and lung. The risk was increased with longer duration of use.[106]

Investigational Agents

Several agents approved for the treatment of type 2 diabetes have been shown to cause weight loss and are currently being investigated for the treatment of obesity.[48] These include GLP-1 agonists, sodium-glucose-linked transporter-2 (SGLT2) inhibitors, amylin mimetics, and metformin.[48] Trials with the newer, oral formulation of semaglutide for diabetes have also demonstrated weight loss.[48] A clinical trial investigating the weight loss potential of the combination dapagliflozin (an SGLT2 inhibitor) and metformin for patients with diabetes and obesity is currently under way.[48]

Numerous other agents have shown promise as weight loss pharmacotherapy with a few progressing into phase III trials. A combination therapy of bupropion and zonisamide ER has been shown to produce weight loss.[37] Much like naltrexone/bupropion, this combination drug works through a dual mechanism: bupropion stimulates POMC neurons in the hypothalamus, and zonisamide acts synergistically by suppressing an appetite-stimulating neural pathway.[37] Cetilistat is a lipase enzyme inhibitor, which acts similarly to orlistat, with a more tolerable side effect profile.[107] Tauroursodeoxycholic acid has also been proposed as a weight loss agent; it is thought to induce weight loss by increasing sensitivity to leptin, which then suppresses appetite.[37] Other potential targets for investigation as weight loss therapy include a cannabinoid type-1 receptor antagonist, leptin analogs, and anti-obesity vaccines that target ghrelin, somatostatin, and adenovirus 36.[37]

The most appropriate pharmacotherapeutic option for weight loss depends on patient-specific parameters including other disease

states, concomitant medication use, adverse effects, patient preference, and cost. Given S.B.'s PMH of uncontrolled hypertension, S.B. should avoid naltrexone/bupropion; this agent would also duplicate her current antidepressant (bupropion). Guidelines recommend topiramate/phentermine, orlistat, and liraglutide as preferred agents for patients with hypertension[6]; all three options would be safe for S.B. to use. S.B. and her health care team should choose the most appropriate agent based on her personal preference including her lifestyle. Considerations for orlistat include the many GI side effects, restricted fat intake, and multiple daily doses; considerations for semaglutide and liraglutide include the subcutaneous route of administration as well as GI side effects. In addition, weight loss expectations should be considered; semaglutide is associated with the greatest amount of weight loss followed by phentermine/topiramate ER and then liraglutide.

CASE 36-1, QUESTION 8: S.B. began therapy with phentermine/topiramate because of greater weight loss expectations with this agent, but was unable to tolerate the mental "fogginess" associated with the topiramate. After 2 weeks of therapy, her regimen was changed to orlistat 120 mg, and she lost an additional 17.6 pounds (8 kg) in 6 months. After 6 months, S.B.'s weight loss began to taper, and she regained 4.4 pounds (2 kg). It has been 1 year since her first weight loss visit, and her total net loss is 28.2 pounds (13 kg). S.B.'s current weight is 172 pounds (78 kg), and her BMI is down to 27.6 kg/m^2, but she is disappointed that she has regained weight and inquires about dietary supplements for weight loss. How would you advise S.B. with regard to dietary supplements?

Numerous dietary supplements are marketed for weight loss (**Table 36-5**). Reliable evidence of efficacy for these agents is limited, and safety data are lacking. Clinical data do not support the use of these agents, and S.B. should be advised not to use dietary supplement for weight loss.

Table 36-5
Dietary Supplements for Weight Loss

Supplement	Proposed Mechanism	Clinical Data	Adverse Effects and Safety Concerns
Chitosan	A cellulose-type polysaccharide, reported to bind dietary fat and prevent absorption	Meta-analysis (14 trials) demonstrated average placebo-subtracted weight loss of 3.74 pounds (1.7 kg); average weight loss 1.76 pounds (0.8 kg) in trials lasting >4 weeks	GI effects common (constipation, diarrhea, flatulence, bloating, nausea, heartburn) Avoid in patients with a shellfish allergy.
Caffeine	Increased thermogenesis by inhibiting the breakdown of cAMP	Several clinical trials demonstrate short-term weight loss when used in combination with ephedra (no longer available).	Common adverse effects: insomnia, irritability, tachycardia, anxiety
Green tea	Polyphenols and caffeine act synergistically to decrease fat absorption, reduce lipogenesis, and cause thermogenesis.	Several clinical trials demonstrate potential weight loss of up to 4.40 pounds (2 kg)	See caffeine Reports of hepatotoxicity
Guarana (Brazilian cocoa, *Paullinia cupana*)	See caffeine (seed contains 2.5%–7% caffeine.)	See caffeine	See caffeine
Yerba mate, *Ilex paraguariensis*)	See caffeine	See caffeine	See caffeine Hot drinks may increase risk of esophageal cancer.
Citrus aurantium (bitter orange, Seville orange, sour orange)	Contains synephrine (structurally similar to epinephrine)	No evidence of efficacy when used alone; limited data suggest minimal weight loss when used in combination with caffeine and St. John's wort (<2.20 pounds [1 kg] weight loss).	Cardiovascular effects (increased heart rate, blood pressure) Reports of angina, increased QT interval, seizures, and ischemic colitis Potential drug interactions because of inhibition of intestinal CYP3A4
Hydroxycitric acid (garcinia, *Garcinia cambogia*)	Theorized to inhibit production of lipids	No evidence of weight loss	Reports of hepatotoxicity, rhabdomyolysis (avoid with statins) May inhibit platelet aggregation
Glucomannan (Konjac)	Fibrous polysaccharide may work similar to fiber (promote/prolong satiety).	Limited data suggest minimal weight loss (2.20–4.40 pounds [1–2 kg]).	GI adverse effects (nausea, bloating, flatulence)
Hoodia	Unknown, reported to be an appetite suppressant	No clinical trials to support use	Unknown

cAMP, cyclic adenosine monophosphate; CYP, cytochrome P-450; GI, gastrointestinal.

Reprinted with permission from Dunican KC, Jarvis C. Overweight and obesity. In: Murphy JE, Lee MW, eds. *Pharmacotherapy Self-Assessment Program*. 2014 Book 2 (Chronic Illnesses). American College of Clinical Pharmacy, 2014;2:69.

CASE 36-1, QUESTION 9: S.B.'s health insurance was changed, and she no longer is able to continue orlistat. Two years after discontinuing orlistat, SB has regained 15.4 pounds (7 kg). Her current weight is 187.2 pounds (85 kg), and her BMI is 30.1 kg/m^2. She is frustrated that she has regained weight despite compliance with comprehensive lifestyle interventions. She is questioning whether her results are usual.

S.B.'s weight regain after discontinuing orlistat is typical. Trials with a crossover design have shown that the weight loss achieved with anti-obesity agents is unlikely to be sustained after

discontinuation.[6,46] Weight regain is to be expected after discontinuing anti-obesity agents because the underlying pathology of obesity has not changed.

Medical Devices for Obesity Treatment

Case 36-1, Question 10: S.B. understands that weight regain is common after discontinuing anti-obesity medication. Although she is not ready for surgical interventions, she is interested in newly advertised medical devices. What medical devices are available for weight loss and what are the weight loss expectations of each?

Oral space-occupying devices are designed to be worn during meals to limit bite size. These devices are approved by the FDA for weight management (as opposed to weight loss); although patients can expect to avoid gaining weight, weight loss expectations are minimal. The only oral space-occupying device still being marketed is the Sensor Monitored Alimentary Restriction Therapy (SMARTbyte™).[108] This device is indicated for patients with a BMI of 27 to 35 kg/m^2.[109] Similar to a dental retainer, the device is custom fitted to the roof of the mouth and has a sensor that links to a smartphone app.[109] While wearing this device, the patient needs to take smaller bites and eat slower, leading to increased satiety with reduced portions.[109] The phone app keeps track of the patient's weight loss goals, and includes personal weekly coaching.[109] Adverse events are rare, but could include soreness in the mouth or gagging on the device or food.[109]

Plenity® is a transient, ingestible, space-occupying device that helps make a patient feel full.[110] It is FDA approved as a class II medical device and consists of capsules of cellulose and citric acid.[110] The dose is three capsules twice a day, with 16 ounces of water taken 20 to 30 minutes before meals.[110] The cellulose and citric acid swell and retain the water in the stomach, making the patient feel full.[110] This increased satiety causes the patient to ingest smaller portions of food, thus inducing weight loss.[110] The contents of

the capsules are not absorbed. Once the capsule contents are in the large intestine, the water is absorbed by the body, and the device is passed naturally.[110] In clinical trials, adverse events included diarrhea, distended abdomen, infrequent bowel movements, and flatulence, but these were similar to placebo.[110] Similar non–FDA-approved products are available, regulated as food or dietary supplements; however, they do not have the same level of effectiveness as this device. In the gelesis loss of weight (GLOW) pivotal trial, patients lost an average of 6% of initial body weight versus 4% with placebo within 6 months.[111] If a patient does not lose 3% of initial body weight within the first 8 weeks, they are likely to be a nonresponder and should consider discontinuation.[110,111]

A gastric emptying system (AspireAssist®) has been approved by the FDA for weight loss. The system involves a thin gastrostomy tube placed within the stomach that connects to a port on the patient's abdomen.[112] About 20 to 30 minutes after each main meal, patients can remove up to 30% of their stomach contents through the port using a small handheld device.[112] The reduction in caloric absorption is the main mechanism of weight loss. This device is approved for use in patients age 22 years and older with a BMI of 35 to 55.0 kg/m^2 who have failed nonsurgical weight loss therapy.[112] The pivotal aspiration therapy with adjusted lifestyle (PATHWAY) study demonstrated an 8.6% weight loss after 1 year with the AspireAssist® compared to placebo.[113] Sustained results were seen in a trial lasting 4 years.[114] Adverse events tend to be related to the initial placement procedure (pain, nausea/vomiting) or local irritation from the device. Infections at the site of the port can also occur.

Several intragastric balloon systems are approved by the FDA for patients with a BMI of 30 to 40 kg/m^2.[115] Two are liquid filled (Orbera® and ReShape™), and one is gas filled (Obalon™).[115] These balloons are swallowed (Obalon™) or inserted (Orbera/ReShape™) orally through the esophagus.[115] Once in the stomach, the balloons are filled and can be used for up to 6 months.[115] These space-occupying devices lead to weight loss by increasing satiety and limiting the portion size of food a patient can consume.[115] The FDA has updated their labeling to clarify the risks of overinflation (spontaneous

hyperinflation), acute pancreatitis, and deaths associated with the liquid-filled intragastric balloons.[115] The manufacturers of ReShape™ stopped distributing this product as of January 2019.[115]

An electrical stimulation system called the vBloc system was approved by the FDA as a treatment option for patients with class III obesity.[112] However, this device is no longer marketed as of September 2018.[108]

S.B.'s current BMI is 30.1 kg/m^2, which is below the threshold for use of AspireAssist®. However, she is a candidate for the other devices. After discussion, S.B. decided that Plenity® would be the easiest option. After an 8-week trial of Plenity®, she lost 1 kg. Based on this minimal weight loss, S.B. is considered a nonresponder and should discontinue use.

Case 36-1, Question 11: S.B. returns to her physician 3 years later. She has gained an additional 35.3 pounds (16 kg), and her BMI is now 35.8 kg/m^2. Laboratory tests provide the following results:

Blood pressure, 154/92 mm Hg
Fasting blood glucose, 162 mg/dL
A1C, 8.3%
Triglycerides (TG), 288 mg/dL
Total cholesterol, 272 mg/dL
HDL, 35 mg/dL
LDL, 179 mg/dL

S.B. requests a referral to a bariatric clinic for evaluation for surgical intervention for weight loss. Is S.B. a candidate for bariatric surgery? How could a bariatric surgical procedure affect medication administration in S.B. postoperatively?

Surgery

Surgery should be considered for individuals with BMI ≥40 kg/m^2, or BMI ≥35 kg/m^2 with one or more obesity-related conditions, or BMI ≥30 kg/m^2 and type 2 diabetes with inadequate glycemic control.[116] Bariatric surgery is not without risk; therefore, patients should be evaluated for potential complications, potential success of surgery, and their ability to adhere to surgical requirements.[116] For example,

patients must avoid tobacco use for at least 6 weeks before the procedure (optimally 1 year before), and must continue tobacco abstinence following the procedure.[116]

Bariatric surgical procedures either reduce the absorptive surface of the GI tract resulting in malabsorption or reduce the stomach volume so that the patient feels full after a smaller meal. Procedures include laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYBG), and biliopancreatic diversion (BPD) or its related procedures; all have demonstrated efficacy, although the degree of weight loss and complications may differ.[116] Caution should be used when recommending BPD or its related procedures because of the nutritional risks.[116] Laparoscopic (vs open surgical) approaches are preferred for reducing postoperative complications and hospital stay.[116] LABG is considered to be the least invasive and safest procedure, and can also be reversed if necessary.[116] Each surgery has differing rates of efficacy, with estimated mean weight reduction at 1 year as 15% to 20% for LAGB and 30% for RYBG.[116,117] As with all weight-loss strategies, weight regain can commonly occur, with estimates of regain being 5% to 10% after 10 years.[116,117]

The mortality rate from bariatric surgery is estimated to be 0.3% to 1.9%, and literature has shown that centers that perform surgeries at higher volumes have better outcomes.[116,118] Some of the complications of bariatric surgery include nausea, stomach ulceration, stenosis, anemia, nutrient deficiencies, and cholelithiasis.[116] Postsurgical precautions include careful evaluation of meal sizes and timing along with meal content, especially immediately after surgery.[116]

Patients should be aware that they will not be able to resume their normal eating habits, and they should be properly educated on lifestyle modifications for maintenance of weight loss.[116] In addition, medications and adequate intake of necessary nutrients are important considerations after surgery because absorption can be impaired. An all-liquid diet will be required starting 24 hours postsurgery, with meal progression overseen by the surgeon and/or a registered dietician.[116]

Medications may need to be crushed, administered using liquid formulation, or delivered via other dosage routes to ensure absorption for the first couple of months after surgery.[119] Medications that are delayed or ER may not be absorbed, and will likely need to be changed to immediate release formulations for adequate effects.[119] Conversely, other medications may see increases in concentration because of the reduced volume of distribution as weight loss occurs.[120] Transdermal formulations, weight-based dosing, or drugs dosed using body surface area (BSA) may need to be adjusted to account for reductions in BSA.[119,120] Medications used for obesity and its associated comorbidities (including hypertension and diabetes) will require close monitoring, dose adjustments, and potentially discontinued as weight loss occurs.[116] In addition, TSH should be monitored in patients with thyroid disorders, and dose adjustments of thyroid hormone may be required.[116] Medications such as nonsteroidal anti-inflammatory drugs, salicylates, steroids, and bisphosphonates may cause ulcerations and should likely be avoided.[116,119,120] Importantly, vitamin supplementation is necessary to prevent nutritional deficiencies postoperatively.[116] The following supplements are recommended: vitamin A, vitamin B_1, vitamin B_{12}, folic acid, vitamin D, vitamin E, vitamin K, calcium, iron, zinc, and copper.[116] Dosing may vary depending on the procedure and whether an overt deficiency is present.[116] To assist with adherence to supplementation requirements, combination products such as high-dose multivitamins with minerals should be considered.[116] Liquid, orally disintegrating, sublingual, nasal, or intramuscular (IM) formulations may be needed because of the reduced potential for absorption following surgery.[116] Patients should be assisted in selecting high-quality dietary supplements, because some unregulated commercial products have been shown to be adulterated and/or mislabeled.[116]

Although S.B. is a candidate for bariatric surgery based on her BMI of 35.4 kg/m^2 and her obesity-related conditions, she is unable to commit to the dietary restrictions. She would like to consider alternative pharmacotherapeutic options. S.B.’s fasting blood

glucose and A1c indicate that she has type 2 diabetes. Semaglutide is a once-weekly option that will lower her blood glucose and result in clinically significant weight reduction.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity.* 2013;21(5):935–943. doi:10.1002/oby.20309 (95)

Domecq JP, Prutsky G, Leppin A, et al. Drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2015;100(2):363–370. (51)

Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract.* 2016;22(suppl 3):1–203. doi:10.4158/EP161365.GL (6)

Garvey WT, Ryan DH, Look M et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo- controlled, phase 3 extension study. *Am J Clin Nutr.* 2012;95(2):297–308. (92)

Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA.* 2016;315(22):2424–2434. doi:10.1001/jama.2016.7602 (83)

Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures—2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists—executive summary. *Endocr Pract.* 2019;25(12):1346–1359. doi:10.4158/GL-2019-0406 (116)

Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med.* 2015;373(1):11–22. (100)

Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the step 4 randomized clinical trial. *JAMA*. 2021;325(14):1414–1425. doi:10.1001/jama.2021.3224 (105)

Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care.* 2004;27(1):155–161. doi:10.2337/diacare.27.1.155 (84)

Key Websites

Obesity Action Coalition. http://www.obesityaction.org/

Centers for Disease Control and Prevention. Overweight & obesity. http://www.cdc.gov/obesity/

NIH. Why obesity is a health problem. http://www.nhlbi.nih.gov/health/educational/wecan/healthy-weight-basics/obesity.htm

COMPLETE REFERENCES CHAPTER 36 OBESITY

1. World Health Organization. Obesity and overweight. Accessed January 30, 2021. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Mechanick JI, Garber AJ, Handelsman Y, Timothy Garvey W. American Association of Clinical Endocrinologists' position statement on obesity and obesity medicine. *Endocr Pract*. 2012;18:642–648. doi:10.4158/EP12160.PS
3. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism*. 2019;92:6–10. doi:10.1016/j.metabol.2018.09.005
4. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. NCHS Data Brief No. 360. Updated February 2020. Accessed January 30, 2021. https://www.cdc.gov/nchs/products/databriefs/db360.htm
5. Kim DD, Basu A. Estimating the medical care costs of obesity in the United States: systematic review, meta-analysis, and empirical analysis. *Value Health*. 2016;19(5):602–613. doi:10.1016/j.jval.2016.02.008

6. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(suppl 3):1–203. doi:10.4158/EP161365.GL
7. Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current national institutes of health guidelines. *Arch Intern Med*. 2002;162(18):2074–2079. doi:10.1001/archinte.162.18.2074
8. Canoy D, Matthijs Boekholdt S, Wareham N, et al. Body fat distribution and risk of coronary heart disease in men and women in the European prospective investigation into cancer and nutrition in Norfolk cohort: a population-based prospective study. *Circulation*. 2007;116(25):2933–2943. doi:10.1161/CIRCULATIONAHA.106.673756
9. Ko GT, Tang JS. Waist circumference and BMI cut-off based on 10-year cardiovascular risk: evidence for “Central Pre-Obesity”. *Obesity*. 2007;15(11):2832–2839. doi:10.1038/oby.2007.336
10. Cerhan JR, Moore SC, Jacobs EJ, et al. A pooled analysis of waist circumference and mortality in 650,000 adults. *Mayo Clin Proc*. 2014;89(3):335–345. doi:10.1016/j.mayocp.2013.11.011
11. Fryar CD, Cearroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats. Updated 2020. Accessed January 30, 2021. https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm
12. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA*. 2014;311(8):806–814. doi:10.1001/jama.2014.732
13. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev*. 2016;17(2):95-107. doi: 10.1111/obr.12334
14. Reilly J, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes*. 2011;35(7):891–898. doi:10.1038/ijo.2010.222
15. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med*. 2017;376(3):254–266. doi:10.1056/NEJMra1514009
16. MacLean PS, Higgins JA, Giles ED, Sherk VD, Jackman MR. The role for adipose tissue in weight regain after weight loss. *Obes Rev*. 2015;16(suppl 1):45–54. doi:10.1111/obr.12255
17. Wright SM, Aronne LJ. Causes of obesity. *Abdom Imaging*. 2012;37(5):730–732. doi:10.1007/s00261-012-9862-x
18. Yang W, Kelly T, He J. Genetic epidemiology of obesity. *Epidemiol Rev*. 2007;29:49–61. doi:10.1093/epirev/mxm004

19. Silventoinen K, Rokholm B, Kaprio J, Sørensen TIA. The genetic and environmental influences on childhood obesity: a systematic review of twin and adoption studies. *Int J Obes (Lond)*. 2010;34(1):29–40. doi:10.1038/ijo.2009.177
20. Wardle J, Carnell S, Ma Haworth C, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr*. 2008;87(2):398–404. doi:10.1093/ajcn/87.2.398
21. Bouchard C. Childhood obesity: are genetic differences involved? *Am J Clin Nutr*. 2009;89(5):1494S–1501S. doi:10.3945/ajcn.2009.27113C
22. Segal N, Feng R, McGuire SA, Allison DB, Miller S. Genetic and environmental contributions to body mass index: comparative analysis of monozygotic twins, dizygotic twins and same-age unrelated siblings. *Int J Obes (Lond)*. 2009;33(1):37–41. doi:10.1038/ijo.2008.228
23. Ortega-Alonso A, Sipilä S, Kujala UM, Kaprio J, Rantanen T. Genetic influences on adult body mass index followed over 29 years and their effects on late-life mobility: a study of twin sisters. *J Epidemiol Community Health*. 2009;63(8):651–658. doi:10.1136/jech.2008.080622
24. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. *Am J Clin Nutr*. 2002;76(3):653–658. doi:10.1093/ajcn/76.3.653
25. Schneeberger M, Gomis R, Claret M. Hypothalamic and brainstem neuronal circuits controlling homeostatic energy balance. *J Endocrinol*. 2014;220(2):T25–T46.
26. Gurevich-Panigrahi T, Panigrahi S, Wiechec E, Los M. Obesity: pathophysiology and clinical management. *Curr Med Chem*. 2009;16(4):506–521. doi:10.2174/092986709787315568
27. Valassi E, Scacchi M, Cavagnini F. Neuroendocrine control of food intake. *Nutr Metab Cardiovasc Dis*. 2008;18(2):158–168. doi:10.1016/j.numecd.2007.06.004
28. Friedman JM. Leptin and the endocrine control of energy balance. *Nat Metab*. 2019;1(8):754–764. doi:10.1038/s42255-019-0095-y
29. Friedman JM. Leptin and the regulation of body weight. *Keio J Med*. 2011;60(1):1–9. doi:10.2302/kjm.60.1
30. van der Klaauw AA, Farooqi IS. The hunger genes: pathways to obesity. *Cell*. 2015;161(1):119–132. doi:10.1016/j.cell.2015.03.008
31. Kohlsdorf K, Nunziata A, Funcke J-B, et al. Early childhood BMI trajectories in monogenic obesity due to leptin, leptin receptor, and melanocortin 4 receptor deficiency. *Int J Obes (Lond)*. 2018;42(9):1602–1609. doi:10.1038/s41366-018-0049-6
32. Fuentes T, Ara I, Guadalupe-Grau A, et al. Leptin receptor 170 kDa (OB-R170) protein expression is reduced in obese human skeletal muscle: a potential mechanism of leptin resistance. *Exp Physiol*. 2010;95(1):160–171. doi:10.1113/expphysiol.2009.049270

33. Crujeiras AB, Goyenechea E, Abete I, et al. Weight regain after a diet-induced loss is predicted by higher baseline leptin and lower ghrelin plasma levels. *J Clin Endocrinol Metab*. 2010;95(11):5037–5044. doi:10.1210/jc.2009-2566
34. Timper K, Brüning JC. Hypothalamic circuits regulating appetite and energy homeostasis: pathways to obesity. *Dis Model Mech*. 2017;10(6):679–689. doi:10.1242/dmm.026609
35. Suzuki K, Jayasena CN, Bloom SR. Obesity and appetite control. *Exp Diabetes Res*. 2012;2012:824305. doi:10.1155/2012/824305
36. Zhang Y, Liu J, Yao J, et al. Obesity: pathophysiology and intervention. *Nutrients*. 2014;6(11):5153–5183. doi:10.3390/nu6115153
37. Srivastava G, Apovian C. Future pharmacotherapy for obesity: new anti-obesity drugs on the horizon. *Curr Obes Rep*. 2018;7(2):147–161. doi:10.1007/s13679-018-0300-4
38. Smith SR, Aronne LJ, Burns CM, Kesty NC. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care*. 2008;31(9):1816–1823. doi:10.2337/dc08-0029
39. Halford JCG, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic drugs: effects on appetite expression and use for the treatment of obesity. *Drugs*. 2007;67(1):27–55. doi:10.2165/00003495-200767010-00004
40. Jimerson DC, Wolfe BE. Neuropeptides in eating disorders. *CNS Spectr*. 2004;9(7):516–522.
41. Volkow ND, Wise RA, Baler R. The dopamine motive system: implications for drug and food addiction. *Nat Rev Neurosci*. 2017;18(12):741–752. doi:10.1038/nrn.2017.130
42. Volkow ND, Wang G-J, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci*. 2011;15(1):37–46. doi:10.1016/j.tics.2010.11.001
43. Eikelis N, Esler M. The neurobiology of human obesity. *Exp Physiol*. 2005;90(5):673–682. doi:10.1113/expphysiol.2005.031385
44. Larabee CM, Neely OC, Domingos AI. Obesity: a neuroimmunometabolic perspective. *Nat Rev Endocrinol*. 2020;16(1):30–43. doi:10.1038/s41574-019-0283-6
45. Seravalle G, Grassi G. Obesity and hypertension. *Pharmacol Res*. 2017;122:1–7. doi:10.1016/j.phrs.2017.05.013
46. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342–362.
47. U.S. Food & Drug Administration. FDA approves first treatment for weight management for people with certain rare genetic conditions. Updated November 27, 2020. Accessed on January 30, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-first-treatment-weight-management-people-certain-rare-genetic-conditions

48. Li X, Bello NT. Anorectic state of obesity medications in the United States. Are leaner times ahead? *Expert Opin Pharmacother*. 2020;21(2):167–172. doi:10.1080/14656566.2019.1692815
49. Reinehr T. Obesity and thyroid function. *Mol Cell Endocrinol*. 2010;316(2):165–171. doi:10.1016/j.mce.2009.06.005
50. Verma A, Jayaraman M, Kumar HKVS, Modi KD. Hypothyroidism and obesity. Cause or effect? *Saudi Med J*. 2008;29(8):1135–1138.
51. Domecq JP, Prutsky G, Leppin A, et al. Clinical reviews: drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2015;100(2):363–370.
52. Alonso-Pedrero L, Bes-Rastrollo M, Marti A. Effects of antidepressant and antipsychotic use on weight gain: a systematic review. *Obes Rev*. 2019;20(12):1680–1690. doi:10.1111/obr.12934
53. Uguz F, Sahingoz M, Gungor B, Aksoy F, Askin R. Weight gain and associated factors in patients using newer antidepressant drugs. *Gen Hosp Psychiatry*. 2015;37(1):46–48. doi:10.1016/j.genhosppsych.2014.10.011
54. Taheri S. The link between short sleep duration and obesity: we should recommend more sleep to prevent obesity. *Arch Dis Child*. 2006;91(11):881–884. doi:10.1136/adc.2005.093013
55. Cappuccio FP, Taggart FM, Kandala N-B, et al. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep*. 2008;31(5):619–626. doi:10.1093/sleep/31.5.619
56. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med*. 2004;1(3):e62. doi:10.1371/journal.pmed.0010062
57. Ajslev T, Andersen CS, Gamborg M, Sørensen TIA, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *Int J Obes (Lond)*. 2011;35(4):522–529. doi:10.1038/ijo.2011.27
58. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatr*. 2014;168(11):1063–1069. doi:10.1001/jamapediatrics.2014.1539
59. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365(17):1597–1604. doi:10.1056/NEJMoa1105816
60. Malnick SD, Knobler H. The medical complications of obesity. *QJM*. 2006;99(9):565–579. doi:10.1093/qjmed/hcl085
61. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American heart association task force on practice guidelines and the obesity society. *J Am Coll Cardiol*. 2014;63(25_PA):2985–3023. doi:10.1016/j.jacc.2013.11.004

62. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med*. 2009;360(9):859–873. doi:10.1056/NEJMoa0804748
63. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005;293(1):43–53. doi:10.1001/jama.293.1.43
64. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA*. 2014;312(9):923–933. doi:10.1001/jama.2014.10397
65. de Souza RJ, Bray GA, Carey VJ, et al. Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. *Am J Clin Nutr*. 2012;95(3):614–625. doi:10.3945/ajcn.111.026328
66. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA*. 2007;297(19):2081–2091. doi:10.1001/jama.297.19.2081
67. Adipex-P (phentermine hydrochloride). Prescribing information. Teva Pharmaceuticals; 2012.
68. Tenuate (diethylpropion hydrochloride). Prescribing information. Aventis Pharmaceuticals Company; 2003.
69. Didrex (benzphetamine hydrochloride). Prescribing information. Mova Pharmaceuticals; 2009.
70. Phendimetrazine Tartrate Extended-release Capsules CIII. Prescribing information. Epic Pharma; 2011.
71. Xenical (orlistat) capsules for oral use. Prescribing information. Genentech USA; 2013.
72. Qsymia (phentermine and topiramate extended-release) capsules. Prescribing information. Vivus; 2022.
73. Contrave (naltrexone HCl and bupropion HCl) extended release tablets. Prescribing information. Takeda Pharmaceuticals America; 2014.
74. Saxenda (liraglutide [rDNA origin] injection). Prescribing information. Novo Nordisk; 2014.
75. Wegovy (semaglutide injection 2.4 mg). Prescribing information. Novo Nordisk; 2021.
76. Pilitsi E, Farr OM, Polyzos SA, et al. Pharmacotherapy of obesity: available medications and drugs under investigation. *Metabolism*. 2019;92:170–192. doi:10.1016/j.metabol.2018.10.010
77. Hendricks EJ, Greenway FL, Westman EC, Gupta AK. Blood pressure and heart rate effects, weight loss and maintenance during long-term

phentermine pharmacotherapy for obesity. *Obesity*. 2011;19(12):2351–2360. doi:10.1038/oby.2011.94
78. Hendricks EJ, Srisurapanont M, Schmidt SL, et al. Addiction potential of phentermine prescribed during long-term treatment of obesity. *Int J Obes*. 2014;38(2):292–298. doi:10.1038/ijo.2013.74
79. Lomaira (phentermine hydrochloride). Prescribing information. KVK-Tech; 2016.
80. Bang W, Kim J-Y, Yu H-T, et al. Pulmonary hypertension associated with use of phentermine. *Yonsei Med J*. 2010;51(6):971–973. doi:10.3349/ymj.2010.51.6
81. Williams G. Orlistat over the counter. *BMJ*. 2007;335(7631):1163–1164. doi:10.1136/bmj.39385.347049.80
82. Bray GA, Ryan DH. Update on obesity pharmacotherapy. *Ann N Y Acad Sci*. 2014;1311(1):1–13. doi:10.1111/nyas.12328
83. Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA*. 2016;315(22):2424–2434. doi:10.1001/jama.2016.7602
84. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27(1):155–161. doi:10.2337/diacare.27.1.155
85. Yancy WS, Westman EC, McDuffie JR, et al. A randomized trial of a low-carbohydrate diet vs orlistat plus a low-fat diet for weight loss. *Arch Intern Med*. 2010;170(2):136–145. doi:10.1001/archinternmed.2009.492
86. de Castro JJ, Dias T, Chambel P, et al. A randomized double-blind study comparing the efficacy and safety of orlistat versus placebo in obese patients with mild to moderate hypercholesterolemia. *Rev Port Cardiol*. 2009;28(12):1361–1374.
87. Weir MA, Beyea MM, Gomes T, et al. Orlistat and acute kidney injury: an analysis of 953 patients. *Arch Intern Med*. 2011;171(7):702–710. doi:10.1001/archinternmed.2011.103
88. Morris M, Lane P, Lee K, Parks D. An integrated analysis of liver safety data from orlistat clinical trials. *Obes Facts*. 2012;5(4):485–494. doi:10.1159/000341589
89. Bigham S, McGuigan C, MacDonald BK. Reduced absorption of lipophilic anti-epileptic medications when used concomitantly with the anti-obesity drug orlistat. *Epilepsia*. 2006;47(12):2207. doi:10.1111/j.1528-1167.2006.00945_1.x
90. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised,

placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9774):1341–1352. doi:10.1016/S0140-6736(11)60205-5

91. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity*. 2012;20(2):330–342. doi:10.1038/oby.2011.330
92. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95(2):297–308. doi:10.3945/ajcn.111.024927
93. Qsymia® (phentermine and topiramate extended-release) capsules CIV. Risk evaluation and mitigation strategy (REMS). Accessed February 4, 2021. http://www.qsymiarems.com/
94. Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. *Obesity*. 2009;17(1):30–39.
95. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595–605. doi:10.1016/S0140-6736(10)60888-4
96. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity*. 2013;21(5):935–943. doi:10.1002/oby.20309
97. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity*. 2011;19(1):110–120. doi:10.1038/oby.2010.147
98. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care*. 2013;36(12):4022–4029. doi:10.2337/dc13-0234
99. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE maintenance randomized study. *Int J Obes (Lond)*. 2013;37(11):1443–1451.
100. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11–22.
101. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the scale diabetes randomized clinical trial. *JAMA*. 2015;314(7):687–699. doi:10.1001/jama.2015.9676
102. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989–1002. doi:10.1056/NEJMoa2032183

103. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10278):971–984. doi:10.1016/S0140-6736(21)00213-0
104. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the step 3 randomized clinical trial. *JAMA*. 2021;325(14):1403–1413. doi:10.1001/jama.2021.1831
105. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the step 4 randomized clinical trial. *JAMA*. 2021;325(14):1414–1425. doi:10.1001/jama.2021.3224
106. U.S. Food & Drug Administration. FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market. Updated February 13, 2020. Accessed February 4, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market
107. Kopelman P, Groot GdH, Rissanen A, et al. Weight loss, HbA1c reduction, and tolerability of cetilistat in a randomized, placebo-controlled phase 2 trial in obese diabetics: comparison with orlistat (Xenical). *Obesity*. 2010;18(1):108–115. doi:10.1038/oby.2009.155
108. U.S. Food & Drug Administration. Weight-loss and weight-management devices. Updated April 27, 2020. Accessed February 9, 2021. https://www.fda.gov/medical-devices/products-and-medical-procedures/weight-loss-and-weight-management-devices
109. Smartbyte by ScientificIntake. The SmartbyteTM Weight Management System. Accessed February 9, 2021. https://smartbyte-lp.tlmlive.com/
110. Plenity®. Meet Plenity - an FDA-cleared weight management tool. Updated March 24, 2022. Accessed April 1, 2022. https://get.myplenity.com/home-a
111. Greenway FL, Aronne LJ, Raben A, et al. A randomized, double-blind, placebo-controlled study of gelesis100: a novel nonsystemic oral hydrogel for weight loss. *Obesity*. 2019;27(2):205–216. doi:10.1002/oby.22347
112. U.S. Food & Drug Administration. Medical devices for weight loss and weight management: what to know. Updated July 24, 2019. Accessed February 9, 2021. https://www.fda.gov/consumers/consumer-updates/medical-devices-weight-loss-and-weight-management-what-know
113. Thompson CC, Abu Dayyeh BK, Kushner R, et al. Percutaneous gastrostomy device for the treatment of class ii and class iii obesity: results of a randomized controlled trial. *Am J Gastroenterol*. 2017;112(3):447–457. doi:10.1038/ajg.2016.500
114. Thompson CC, Abu Dayyeh BK, Kushnir V, et al. Aspiration therapy for the treatment of obesity: 4-year results of a multicenter randomized controlled

trial. *Surg Obes Relat Dis*. 2019;15(8):1348–1354. doi:10.1016/j.soard.2019.04.026

115. U.S. Food & Drug Administration. UPDATE: potential risks with liquid-filled intragastric balloons—letter to health care providers. Updated April 27, 2020. Accessed February 9, 2021. https://www.fda.gov/medical-devices/letters-health-care-providers/update-potential-risks-liquid-filled-intragastric-balloons-letter-health-care-providers-1
116. Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures—2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists—executive summary. *Endocr Pract*. 2019;25(12):1346–1359. doi:10.4158/GL-2019-0406
117. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357(8):741–752. doi:10.1056/NEJMoa066254
118. Snow V, Barry P, Fitterman N, Qaseem A, Weiss K. Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2005;142(7):525–531. doi:10.7326/0003-4819-142-7-200504050-00011
119. Miller AD, Smith KM. Medication and nutrient administration considerations after bariatric surgery. *Am J Health Syst Pharm*. 2006;63(19):1852–1857. doi:10.2146/ajhp060033
120. Bland CM, Quidley AM, Love BL, Yeager C, McMichael B, Bookstaver PB. Long-term pharmacotherapy considerations in the bariatric surgery patient. *Am J Health Syst Pharm*. 2016;73(16):1230–1242. doi:10.2146/ajhp151062

37

Adult Enteral Nutrition

Carol J. Rollins

CORE PRINCIPLES		CHAPTER CASES
1	Patients should be assessed for the appropriate timing and route for nutrition support.	**Case 37-1 (Questions 1, 2)**
2	The type of tube placement and site of formula delivery are determined by several factors.	**Case 37-2 (Question 1)**
3	Formula selection is based on nutrient requirements, fluid restrictions, and the extent of impaired digestion and absorption.	**Case 37-2 (Questions 2–5)**
4	The administration regimen for feeding is influenced by the feeding route, formula selected, and duration of feeding.	**Case 37-2 (Questions 6–8)**

CORE PRINCIPLES		CHAPTER CASES
5	Although the preferred route for nutrition intervention in critical illness is enteral, the ideal formula composition remains unresolved.	**Case 37-3 (Questions 1–4)**
6	Macronutrient content should be considered when selecting an enteral formula for patients with diabetes.	**Case 37-4 (Question 1)**
7	Appropriate monitoring is essential to recognize and prevent complications associated with enteral nutrition.	**Case 37-4 (Question 2)**
8	Medication administration through a feeding tube requires selection of appropriate dosage forms and proper preparation.	**Case 37-4 (Question 3)**
9	Feeding tube occlusion is a common problem influenced by medication-related and non–medication-related factors.	**Case 37-4 (Question 4)**
10	Patients must meet strict criteria for Medicare coverage of home enteral nutrition.	**Case 37-5 (Questions 1, 2)**
11	Diarrhea in patients receiving enteral nutrition is multifactorial, including both tube-feeding-related and non–tube-feeding-related causes.	**Case 37-6 (Question 1)**

INTRODUCTION

Enteral nutrition (EN) refers to nutrition provided via the gastrointestinal (GI) tract. However, as commonly used, the term *enteral nutrition* (EN) is synonymous with delivery of nutrients into the GI tract by tube (eg, nasogastric [NG] or jejunostomy feeding). Tube feeding allows continued use of the GI tract when one or more steps in the normal process of obtaining nutrients from oral intake are disrupted. **Table 37-1** lists functional anatomic units of the GI tract along with major steps occurring in preparing nutrients for absorption and examples of conditions potentially impairing each region. Chewing or swallowing may be completely disrupted, but some digestive and absorptive function must remain for tube feeding to be a viable option.

Table 37-1
Functional Units of the Gastrointestinal Tract

Functional Unit	Major Steps	Conditions/Diseases Disrupting Function
Mouth and oropharynx	Chew and lubricate food; swallow; taste	Amyotrophic lateral sclerosis, muscular dystrophy, severe RA, CVA, end-stage Parkinson disease, paralysis, coma. Anorexia caused by other disease: cardiac or cancer cachexia, renal failure and uremia, liver failure, neurologic disease
Esophagus	Transport food to the stomach	Esophageal ulcer, cancer, obstruction, or fistula; esophagectomy; CVA
Stomach	Hold food for mixing and grinding; add acid and enzymes; release chyme to small bowel; osmoregulation	Severe gastritis or ulceration, gastroparesis, gastric outlet obstruction, gastric cancer, severe gastroesophageal reflux
Duodenum	Osmoregulation; neutralize stomach acid	Severe duodenal ulcer or fistula; cancer: gastric or pancreatic; surgical resection or bypass of the duodenum: Whipple-type procedures

Functional Unit	Major Steps	Conditions/Diseases Disrupting Function
Small bowel: jejunum and ileum	Digestion; absorption	Enterocutaneous fistula, severe enteric infection, malnutrition, malabsorption, Crohn disease, celiac disease, ileus, and dysmotility syndrome
Pancreas	Secretion of digestive enzymes	Pancreatitis, pancreatic cancer, pancreatic injury, pancreatic fistula
Colon	Absorb fluid; ferment soluble fiber and unabsorbed carbohydrate; absorb water	Ulcerative colitis, Crohn disease, colon cancer, colocutaneous fistula, colovaginal fistula, diverticulitis, colitis of any etiology, colon surgery

CVA, cerebrovascular accident; RA, rheumatoid arthritis.

PATIENT SELECTION AND ROUTE OF FEEDING

CASE 37-1

Question 1: T.R., a 55-year-old female, 64 inches (162.56 cm) tall, 205.03 pounds (93 kg), was admitted to the hospital last evening with acute pancreatitis and has "nothing by mouth" (NPO) orders in her chart. A nutrition support consult was ordered. The gastroenterology service has seen her and scheduled an endoscopic retrograde cholangiopancreatography (ERCP) for tomorrow. T.R. is currently receiving intravenous (IV) 5% dextrose/0.9% sodium chloride with KCl 20 mEq/L at 150 mL/hour. She is also receiving hydromorphone via a patient-controlled analgesia (PCA) pump.

T.R. has been experiencing crampy upper right quadrant pain on and off for nearly a month and saw her primary care physician a week ago. She is allergic (rash) to erythromycin. She was told that her symptoms are consistent with gallbladder inflammation; surgery will be necessary if her symptoms continue, or the pain worsens. In addition, her doctor said blood pressure and glucose control "could use improvement," and mentioned it might be because her weight was up several pounds. She states she has been snacking more frequently

because of stress from her work. She is not a smoker; she frequently drinks one glass of wine with dinner.

Laboratory values this morning are as follows:
Sodium, 137 mEq/L
Potassium, 3.8 mEq/L
Blood urea nitrogen (BUN), 11 mg/dL
Serum creatinine (SCr), 0.8 mg/dL
Glucose, 181 mg/dL
Albumin, 3.4 g/dL
Amylase, 700 units/L (down from 1250 units/L in the emergency department [ED])
Lipase, 685 units/L (down from 1208 in the ED)
Triglycerides, 179 mg/dL
White blood cells (WBCs), 12.6×10^3/mL
Hemoglobin (Hgb), 12.4 g/dL
Hematocrit (Hct), 37.4%
C-reactive protein (CRP), 2.3 mg/dL

Does T.R. require nutritional intervention at this time? When should nutrition intervention be considered for T.R.?

Patients generally are considered at risk for nutrient depletion and associated increased morbidity and mortality when intake is <50% to 75% of requirements for 5 to 7 days acutely or when weight loss exceeds 5% or more in 1 month, 7.5% or more in 3 months, or 10% or more of preillness weight within a 6-month period.[1,2] For adequately nourished patients, specialized nutrition support is generally not warranted when support will be needed for fewer than 7 to 10 days.[3] Undernourished patients require nutritional intervention sooner. See Chapter 35, Basics of Nutrition and Patient Assessment, for further information on malnutrition. T.R. was adequately nourished before admission based on her weight for height and overall health status. She has weight gain per the clinic visit, although edema should be ruled out as a cause, and has been NPO for <24 hours. Nutrition support is not warranted at this time. However, once the ERCP has been completed, the need for nutrition intervention should be reassessed. If T.R. must remain NPO for a week or more, nutritional intervention would be warranted. Obesity does not preclude the need for nutritional intervention.

Case 37-1, Question 2: What route of nutrition intervention would be most appropriate for T.R. if she cannot restart her diet in a timely manner?

Routes of nutrition intervention may include modified oral diet, including oral supplements or altered consistency diets (eg, thickened liquids, pureed foods), EN by tube, or parenteral nutrition (PN). Tube feeding is considered the route of choice in patients with a functional GI tract in whom oral nutrient intake is contraindicated or is insufficient to meet estimated requirements.[3] Other than potential "gallstone" pancreatitis, T.R. is expected to have a functional GI tract. The ERCP and pain symptoms will help determine whether T.R. will remain NPO or have a diet started. It appears her pancreatitis is improving based on decreasing amylase and lipase values. For patients with severe acute pancreatitis, the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) Critical Care guidelines recommend initiation of EN as soon as volume resuscitation is completed.[4] For well-nourished patients such as T.R. with mild-to-moderate acute pancreatitis, which is indicated by non–intensive care unit (ICU) status, nutrition support should be considered only after 4 days if advancement of an oral diet fails.[5] Because EN may reduce the inflammatory response and decrease complications, EN is preferred over PN.[4,5]

EN may be appropriate for patients with the disorders listed in Table 37-1, depending on the extent to which normal intake, transport, digestion, and absorption of nutrients are impaired. Clinical circumstances, not specific diagnoses, should be the determining factor for initiating tube feeding. EN should be used with caution in patients with severe necrotizing or hemorrhagic pancreatitis, distal high-output (>500 mL/day) enterocutaneous fistulae, hypotension with significant inotropic support, GI ischemia, and partial bowel obstruction.[3,4] Contraindications to EN generally include diffuse peritonitis, complete bowel obstruction, severe paralytic ileus, intractable vomiting or diarrhea, severe malabsorption, severe GI bleed, inability to access the GI tract, and when aggressive

intervention is not warranted or desired. Frequent reassessment is recommended because patients may become candidates for EN as the condition improves or resolves.

FEEDING TUBE PLACEMENT AND SITE OF FORMULA DELIVERY

CASE 37-2

QUESTION 1: J.B., an 83-year-old male, was hospitalized 6 days ago after collapsing while playing with his grandchildren. He was diagnosed with ischemic stroke, and his condition has changed little since admission. J.B. is estimated to be 69 inches (175.26 cm) tall; his weight is 136.69 pounds (62 kg); clinic notes from 3 months ago show his weight at 147.71 pounds (67 kg). He appears thin, with mild wasting of arm and leg muscles. His maintenance IV drip is 5% dextrose/0.45% sodium chloride with potassium chloride (KCl) 10 mEq/L at 85 mL/hour. Laboratory evaluation today shows the following:

Sodium, 140 mEq/L
Potassium, 3.8 mEq/L
Chloride, 106 mEq/L
Glucose, 85 mg/dL
SCr, 0.9 mg/dL
Serum albumin, 3.1 g/dL

J.B. failed his swallow study today and will remain NPO for 5 weeks before a repeat swallow study, which he must pass before an oral diet is initiated. Nutrition support via tube feeding is ordered.

What is the most appropriate type of enteral access device (EAD) for J.B.?

The type of EAD (ie, feeding tube) is determined by the anticipated duration of tube feeding, disrupted region or process in the GI tract, and the risk of aspiration. **Figure 37-1** illustrates the two basic types of EAD placement—nasal versus ostomy—and the sites available for formula delivery (ie, gastric, duodenal, or jejunal). The name of the EAD usually includes both the type of tube placement and the site of formula delivery. For example, NG indicates nasal placement with

gastric delivery of formula, whereas gastrostomy indicates ostomy placement with gastric delivery of formula.

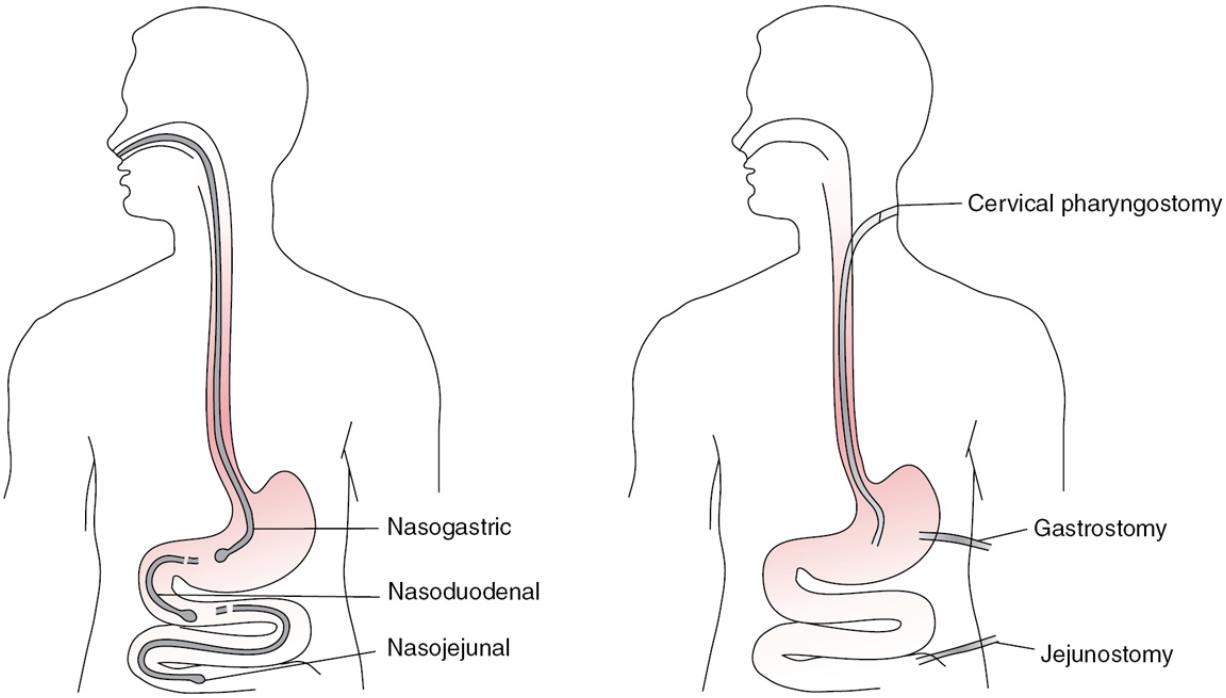


Figure 37-1 Nasoenteric and enterostomy feeding sites.

Nasal tube placement is preferred for short-term use in patients expected to resume oral feeding and without obstruction of nasal, pharyngeal, or esophageal passages. The tube is secured to the nose or cheek after placement to prevent the tube from being displaced. Radiographic confirmation of tube placement is mandatory to rule out pleural perforation and pulmonary intubation in unconscious patients, and remains the standard to ensure correct tube placement in all patients.[6]

Feeding ostomies (tube enterostomies) generally are reserved for long-term EN, interpreted as anywhere from 4 weeks to 6 months, depending on clinical circumstances and the type of tube enterostomy placed. Access for enterostomies can be achieved through open surgery, laparoscopy, or via percutaneous access. Percutaneous access is usually performed under local anesthesia or conscious sedation by endoscope (percutaneous endoscopic gastrostomy [PEG] or percutaneous endoscopic jejunostomy [PEJ])

or by radiography (percutaneous radiologic gastrostomy [PRG] or jejunostomy), including fluoroscopy, ultrasound, or computed tomography.[6] Most patients requiring long-term EN receive either a PEG or a PRG. From the clinical standpoint (ie, maintenance, feeding protocols), PEGs and PRGs are the same, and PRGs are commonly referred to as PEGs. Combined gastric and jejunal EADs (PEGJ or G-J) experience malfunctions and migration or clogging of the jejunal extension in up to 70% of patients; therefore, use is limited to selected patient situations.[6]

Major advantages of percutaneous access are shorter procedure time and lower cost; morbidity and mortality appear to be similar to surgical EADs.[6] Major complications, such as aspiration, peritonitis, hemorrhage, gastrocutaneous fistula formation, necrotizing fasciitis, gastric perforation, and migration of the tube through the gastric wall, are generally low but have been reported in up to 2.5% of patients.[6]

Formula delivery into the stomach is preferred because it is the most physiologically normal feeding site. Stimulation of normal digestive processes and hormonal responses associated with eating occur. The stomach serves as a reservoir, typically allowing tolerance of bolus, and intermittent or continuous feeding. Gastric feeding requires adequate gastric motility to prevent accumulation of formula in the stomach. Patients with gastric outlet obstruction, gastroparesis, gastric distension, or gastroesophageal reflux are poor candidates for gastric feeding.

Postpyloric feeding into the duodenum or jejunum may be appropriate when gastric dysfunction or disease is present, for early postoperative feeding when gastric emptying may be impaired or when risk of aspiration is high. Critically ill patients are at risk for aspiration and ventilator-associated pneumonia, yet evidence of reduced aspiration and improved outcomes with postpyloric feeding in any patient population remains controversial.[4,6] Moderate-quality evidence does indicate that aspiration may be reduced by 30% with postpyloric feeding versus gastric feeding; however, this has not been shown to result in reduced length of stay (LOS) or mortality.[3] Calorie and protein provision appear to be improved, and the EN goal rate achieved more quickly with postpyloric feeding compared

to gastric feeding.[7] SCCM-ASPEN Critical Care guidelines suggest postpyloric feeding for patients at high risk for aspiration, but acknowledge that gastric feeding is better than delaying EN for postpyloric tube placement.[3,4]

J.B. will require EN for at least 5 weeks, and may require longer term EN depending on repeat swallow study results. A feeding ostomy is appropriate for him based on expected minimum duration of therapy. In addition, a feeding ostomy will make discharge on EN more feasible to either home or a nursing facility. Because there does not appear to be a contraindication to feeding into the stomach, a gastrostomy is appropriate. He will likely have a PEG or PRG placed to avoid the need for surgery. However, given that J.B. has indications of malnutrition (ie, 8% weight loss, muscle wasting), he should have had a temporary EAD placed earlier in his hospitalization to provide EN. He should continue to receive EN via a temporary EAD until his feeding ostomy is placed.

FORMULA SELECTION

CASE 37-2, QUESTION 2: What factors should be considered in selecting an enteral formula for J.B.?

Enteral formula selection is based on nutrient requirements, fluid restrictions, and the extent of impaired digestion and absorption. Many enteral formulas are available, but because of similarities between products, institutional formularies are generally limited but still provide an adequate selection to meet a variety of patient needs. Categorizing formulas as listed in **Table 37-2** simplifies the formula selection process. There are three major categories of enteral formulas: (a) polymeric formulas, (b) oligomeric formulas, and (c) specialized formulas. Within each category there are other considerations such as the specific sources of carbohydrate, protein, and fat, as well as their caloric distribution in the product.

Table 37-2
Generic Groups and Subgroups of Enteral Formulas

Type of Formula	Examples from Abbott Laboratories (Abbott Park, IL)	Examples from Nestle Health Science (Vevey, Switzerland)
Polymeric Formulas[a]		
Standard Caloric Density, Standard (or High Nitrogen[b]) Content With Varied Fiber Content		
Fiber free for oral supplement or tube feeding	Ensure®	Boost®; Nutren® 1.0
Low fiber (from 1 to 9 g/1000 kcal)	Ensure®; Enlive®b	
Moderate fiber (>9–<14 g/1000 kcal)	Glucerna® 1.2 Cal[b]; Jevity® 1.0 Cal	Fibersource® HN[b]
High fiber (≥14 g/1,000 kcal)	Jevity® 1.2 Cal[b]	Nutren® 1.0 with fiber
Standard-Nitrogen Content, Fiber Free (or Low Fiber) With Varied Caloric Density		
Standard caloric density (1–1.2 kcal/mL)	Ensure®	Nutren® 1.0
Moderate density (1.5 kcal/mL) Ensure® Plus	Ensure® Plus	Boost Plus®; Isosource® 1.5 Cal[c]; Nutren® 1.5
Calorically dense (1.8–2 kcal/mL)		Nutren® 2.0
Standard Caloric Density, Fiber Free With Varied Nitrogen (Protein) Content		
Low nitrogen (6%–10% of kcal as protein)		Resource® Breeze
Standard nitrogen (11%–16% of kcal as protein)	Ensure®	Nutren® 1.0
High nitrogen (17%–20% of kcal as protein)	Osmolite® 1.2 Cal	Isosource® HN
Very high nitrogen (>20% of kcal as protein)	Promote®	Boost® High Protein; Replete®
Oligomeric Formulas		

Type of Formula	Examples from Abbott Laboratories (Abbott Park, IL)	Examples from Nestle Health Science (Vevey, Switzerland)
Polymeric Formulas[a]		
Elemental (free amino acids)		Vivonex® (RTF, T.E.N., Plus)
Peptide Based		
Standard protein		Peptamen®; Peptamen® with Prebio™
High protein	Vital® Peptide 1.5	Peptamen® 1.5
Very high protein (NPC:N <100:1; >20% calories as protein)	Pivot® 1.5	Peptamen AF®
Specialized Formulas		
Renal Failure		
Essential amino acid enriched		Renalcal®
Polymeric, low electrolyte (less than standard potassium, phosphorus, and magnesium)		
▪ Low nitrogen	Suplena®	
▪ Standard nitrogen		Novasource® Renal
▪ High nitrogen (for dialysis)	Nepro®	
Hepatic Failure (high BCAA, low AAA)		NutriHep®
Stress or Critically Ill (altered protein or fat content)		
Branched-chain enriched		Vivonex® RTF
High to very high nitrogen plus conditionally essential nutrients	Perative®, Pivot® 1.5 Cal	Impact®, Impact® Peptide 1.5
Pulmonary Disease		
Immune modulating	Oxepa®	
Standard Pulmonary (not IMP)	Pulmocare®	Nutren® Pulmonary

Type of Formula	Examples from Abbott Laboratories (Abbott Park, IL)	Examples from Nestle Health Science (Vevey, Switzerland)
Polymeric Formulas[a]		
Glucose control	Glucerna® 1.0 Cal; Glucerna® 1.2 Cal; Glucerna® 1.5 Cal	Diabetisource® AC; Glytrol®

AAAs, aromatic amino acids; BCAAs, branched-chain amino acids; IMP, immune-modulating pulmonary; NPC:N, nonprotein calorie to nitrogen ratio.

[a]All products listed in the table are lactose free.

[b]High nitrogen; 17% to 20% of calories from protein.

[c]Low fiber.

Polymeric Formulas

Polymeric formulas are designed for patients with full digestive capability and are used most often. Osmolality is decreased and palatability increased in these formulas by the use of relatively intact nutrients, including whole (ie, intact) proteins. Administration of ~1.5 to 2 L of most polymeric formulas provides 100% of dietary reference intakes (DRIs) for vitamins and minerals; thus, these formulas are considered "complete" formulas.[8] The relative cost of polymeric formulas tends to be less than that of oligomeric or specialized formulas, although prices can vary considerably based on specific nutrient content (eg, ω-3 fatty acids [ω-3FAs], antioxidants).

Oligomeric Formulas

Oligomeric formulas, also called hydrolyzed, predigested, monomeric, or chemically defined formulas, are designed for patients with reduced digestive function. Pancreatic enzyme activity is required for digestion of oligosaccharides (carbohydrates) and fats. Brush-border disaccharidase activity also is required. Minimal digestion is required, however, for the hydrolyzed protein and medium-chain triglyceride (MCT) components. These formulas can

be used for patients with pancreatic insufficiency, reduced mucosal absorption, or reduced hydrolytic capability. Although the Canadian Clinical Practice (CCP) guidelines noted that patients with GI complications, such as short-bowel syndrome and pancreatitis, may benefit from oligomeric formulas, insufficient data were available to make recommendations regarding use of such formulas.[9] Pancreatic enzyme supplementation combined with polymeric formulas may be tried before oligomeric formulas for some patients with pancreatic insufficiency (eg, cystic fibrosis, chronic pancreatitis).

Two subgroups of oligomeric formulas can be differentiated based on the protein source. Available oligomeric formulas are predominately peptide based; thus, oligomeric formulas are sometimes referred to as *peptide formulas*. However, true "elemental" formulas contain free amino acids, whereas "peptide-based" formulas contain oligopeptides plus dipeptides, tripeptides, and free amino acids from hydrolysis of protein. Amino acids require no digestion, but the sodium-dependent active transport mechanism is somewhat slow and inefficient, with only about one-third of dietary protein absorbed as free amino acids; the remaining two-thirds are absorbed as dipeptides and tripeptides.[10,11] Specific carriers for dipeptide and tripeptide absorption, located in small-bowel mucosa, do not compete with the free amino acid transport system. Peptides longer than three amino acids require further hydrolysis within the lumen of the small bowel before they are absorbed. Most peptide-based formulas contain a significant portion of peptides requiring hydrolysis before absorption. No well-designed, randomized, controlled trials have clearly delineated clinical differences in elemental (free amino acid) versus peptide-based formulas. Elemental formulas generally have the lowest fat content (≤10% of calories from fat). Peptide formulas typically contain one-fourth to one-third of calories from fat, but provide 20% to 70% of the fat as MCT to minimize the risk of malabsorption.

Oligomeric formulas are typically hypertonic owing to their partially digested nature; peptide-containing formulas are typically less hypertonic than are free amino acid products. Osmotic diarrhea can occur with hyperosmolality; however, peptide formulas may be used

for patients with diarrhea. SCCM-ASPEN Critical Care guidelines recommend consideration of a peptide formula when critically ill patients have persistent diarrhea, possible malabsorption, or diarrhea fails to respond to fiber.[4] The CCP guidelines, however, recommend considering an intact protein formula in critically ill patients with diarrhea.[9] In 2018, a systematic review comparing intact protein (polymeric formula) to peptides found no differences in mortality or infections, and for patients in ICU, no differences in LOS, diarrhea, or nutrition provided.[12] Taste and cost are disadvantages of oligomeric formulas. Bitter taste can limit intake by the oral route. The cost of oligomeric formulas tends to be considerably higher than that of polymeric formulas, although prices vary greatly depending on formula composition and institutional contract arrangements.

Specialized Formulas

Specialized formulas are designed for specific disease states or conditions; however, clinical benefits are often controversial. Formulas generally have a good theoretic basis for use, yet many lack conclusive clinical evidence of improved efficacy compared with standard formulas. Well-designed studies showing a difference in outcome between specialized and standard enteral formulas providing equal nitrogen and equal calories are limited for most types of specialized formulas. As shown in Table 37-2, there are several different types of specialized formulas; costs and evidence for use vary greatly among them.

J.B. requires EN because he cannot adequately protect his airway when swallowing. There is no evidence presented to suggest he has problems with digestion or absorption. One of the polymeric formulas on the hospital EN formulary should be selected for J.B. The choice of polymeric formula can be narrowed by several factors, including requirements for calories, protein, fluid, and fiber, as well as potential nutrient intolerances.

Case 37-2, Question 3: What are J.B.'s requirements for calories, protein, and fluid? Does he have any special nutrient requirements?

J.B.'s nutrient requirements must be assessed before proceeding in the selection of enteral formula. Based on his body mass index (BMI), 8% weight loss over 3 months, slightly elevated CRP, and mild muscle wasting, J.B. has moderate-to-severe malnutrition in the context of chronic illness. Low serum albumin is a risk factor for morbidity and mortality, but is not a reliable indicator of nutritional status.[2] J.B.'s BMI of 20 kg/m^2 is within an acceptable range based on typical U.S. standards; however, the Global Initiative on Malnutrition (GLIM) criteria include BMI <22 kg/m^2 as an indicator of malnutrition in those older than 70 years of age.[13] Weight loss most likely is caused by chronic deficiency in total energy intake, but may also be associated with sarcopenia-associated loss of muscle mass.[2,14]

Because J.B. has an actual weight less than the ideal for his height, his actual weight should be used to estimate energy and protein requirements. Use of ideal body weight (IBW) to estimate requirements for undernourished patients may result in fluid and electrolyte imbalance. Once the patient is stabilized on nutrition support, calories can be increased, if necessary, to achieve weight gain.

J.B.'s level of metabolic stress is relatively low. He has no surgical wounds, fractures or skeletal trauma, burns, or major infections, although CRP indicates mild inflammation. Caloric requirements are only slightly higher than is the resting metabolic rate (RMR), the calories needed to maintain bodily functions without activity. Although the term *calorie* is used interchangeably with kilocalorie (kcal) in nutrition literature, the large "Calorie" or kilocalorie technically is correct, and energy requirements generally are listed as kcal/day or kcal/kg body weight when specific numbers are given for a patient. See Chapter 35, Basics of Nutrition and Patient Assessment, for methods of determining nutrient requirements. An estimation of 20 to 25 kcal/kg actual weight can be used to initiate

feeding based on J.B.'s low level of metabolic stress, but higher caloric intake (25–30 kcal/kg/day) will likely be needed as mobility increases and for weight gain after he is stable. The Mifflin–St Jeor equation is a predictive equation commonly used to estimate RMR. Using this method, the RMR for J.B. is 1335 kcal/day [(10 × 62 kg) + (6.25 × 175.3 cm) − (5 × 77 years) + 5], but he needs up to 1.4 times RMR (1869 calories) to meet his total daily caloric requirement, especially if weight gain is desired.

Protein requirements for healthy elderly people are controversial, but estimated to be 1 to 1.2 g/kg/day, which is higher than the DRI of 0.8 g/kg/day.[14] J.B.'s protein needs are estimated at 1 to 1.2 g/kg actual weight per day, minimum, but slightly higher protein intake may be beneficial based on inflammation and chronic malnutrition. Renal function appears adequate for J.B. to tolerate 1.2 g/kg/day, up to 1.5 g/kg/day; however, SCr may provide a poor estimate of renal function in underweight patients owing to less-than-normal muscle mass.

Daily fluid requirements for geriatric patients can be estimated at 30 mL/kg or 1 mL/kcal ingested, with a minimum of 1500 mL daily, plus replacement of excess losses from hyperthermia, vomiting, or diarrhea.[14] Baseline requirements of 1500 mL for the first 20 kg plus 20 mL per each additional kilogram of body weight also can be used to estimate fluid requirements. J.B. does not appear to have any excess fluid losses at this time; therefore, calculation of baseline fluid requirements should provide adequate fluids.

J.B.'s estimated daily requirements are ~1240 to 1550 total calories using 20 to 25 kcal/kg but up to 1869 calories using 1.4 times RMR, a minimum of 62 to 74 g protein, and about 1860 to 2340 mL of fluid. These are estimated requirements that should be adjusted based on frequent reassessment of J.B.'s response to therapy and changes in his clinical situation. Additional calories and protein may be needed for repletion of weight and protein status.

J.B.'s apparently suboptimal nutrition before hospitalization, age, and acute illness increase his risk for vitamin deficiencies, and he may have at least some subclinical deficiencies (see Chapter 35, Basics of Nutrition and Patient Assessment). Medical, medication,

and dietary histories should be evaluated to determine nutritional risks associated with specific conditions. J.B. should receive 100% of the DRI, minimum, for vitamins and minerals daily.[8] If actual deficiencies are identified, J.B. will require higher, therapeutic doses for the specific vitamins that are deficient. For patients at risk for refeeding syndrome, consensus recommendations include supplementation of 100 mg thiamine before feeding is initiated, and, if at high risk, for 5 to 7 days during feeding.[15] A complete multivitamin product is recommended daily for 10 days in patients at risk for refeeding syndrome receiving oral nutrition or EN.

Clinical judgment suggests J.B. is at risk for refeeding syndrome. He has an 8% weight loss, his weight is below IBW, his BMI is considered at risk for malnutrition given his age, and older patients at risk for malnutrition may be at high risk for refeeding syndrome.[3,13,15] Chronic malnutrition can lead to intracellular depletion of potassium, phosphorus, and magnesium, whereas serum concentrations are maintained. When aggressive feeding by any route (oral, EN, PN) begins, refeeding syndrome may develop because these electrolytes move from the extracellular space into the cells, causing a decrease in serum concentrations, especially phosphorus, during the first few days of feeding.[15] Failure to monitor the patient and replace electrolytes as necessary can result in serious electrolyte abnormalities.

Case 37-2, Question 4: Which category of polymeric formulas would be most appropriate for J.B. based on his estimated nutritional requirements?

Polymeric formulas can be divided into several categories based on nutrient sources, caloric density, and protein content. Each category should be evaluated because formula characteristics overlap between the categories.

NUTRIENT SOURCE

Polymeric formulas can be subdivided based on lactose content. Hospitalized patients are presumed to be lactose intolerant because

of reduced disaccharidase production during fasting, malnutrition, and various GI tract diseases. In addition, most ethnic groups, except northern Europeans, have reduced lactase production in adulthood, leading to lactose intolerance. Lactose ingestion can cause bloating, flatulence, abdominal cramps, and watery diarrhea in patients with permanent or transient lactose intolerance. Lactose-free formulas are the standard for tube-fed adults. Proteins, even those derived from milk, do not contribute to lactose content because lactose is a carbohydrate. The majority of enteral formulas are also gluten-free ones to avoid GI symptoms associated with gluten intolerance or celiac disease.

CALORIC DENSITY

Caloric density influences the volume of formula needed to meet nutrient requirements. Standard caloric density is 1 to 1.2 kcal/mL. **Table 37-3** lists the general descriptions for caloric density and macronutrient quantities in enteral formulas. Increased caloric density increases formula osmolality. Gastric emptying can be reduced when osmolality exceeds 600 mOsm/kg, and this may result in feeding intolerance.[16] GI intolerance (eg, nausea, flatulence, abdominal discomfort) also can occur if the capacity of intestinal enzymes is overwhelmed by infusion of a calorically dense formula.

Table 37-3
General Descriptions of Macronutrient Quantity in Enteral Formulas

Description	Caloric Density (kcal/mL); corresponding Free Water (%)	Protein Content: % kcal as protein; typical NPC:N ratio	Fiber Content (g/1,000 kcal)
Low	<1; >85%	6%–10%; >200:1	1–9
Standard	1–1.2; 80%–85%	11%–16%; 200:1–130:1	None
Moderate	1.5; 75%–80%		>9 but <14
High	1.8–2; 65%–75%	17%–20%; 120:1–100:1	≥14
Very high	>2; ≤ 65%–75%	>20%; <100:1	

NPC:N, nonprotein calorie to nitrogen ratio.

Caloric density reflects the free-water content of EN formulas. Risk of dehydration increases with increasing caloric density; however,

standard caloric density formulas can result in fluid overload in patients with congestive heart failure, renal failure, or other fluid-sensitive conditions. Calculation of water provided by EN helps determine the volume of additional fluid needed to meet daily fluid requirements. Free-water content is generally 80% to 85% (800–850 mL/L of formula) for formulas with 1 to 1.2 kcal/mL. Table 37-3 lists free-water content associated with other caloric densities. The available history for J.B. does not suggest a need for fluid restriction; therefore, it would be reasonable to initiate feedings with a standard caloric density product (1–1.2 kcal/mL).

PROTEIN CONTENT

Protein needs increase disproportionately to caloric needs during injury and critical illness, whereas protein tolerance may limit protein provision in other conditions. To meet the need for varying ratios between calories and protein, polymeric formulas are available with a range from low- to very high-protein content. Either percentage of calories from protein or nonprotein calories to nitrogen (NPC:N) ratio can be used to define protein content. Table 37-3 lists general descriptions for protein content. High-nitrogen enteral formulas are designed for patients with an increased protein requirement without a proportional increase in caloric needs. Very high-nitrogen formulas are generally intended for critically ill patients or those with large wounds to heal, although they may be appropriate when calorie provision is to be low but protein is to be higher (ie, refeeding syndrome risk, intended weight loss). Low-nitrogen formulas are available for patients requiring protein restriction. Some low-nitrogen formulas are designed for patients with reduced renal function and can be classified as specialized formulas.

A formula with standard protein content is marginal for meeting J.B.’s protein needs. A high-nitrogen formula that meets J.B.’s calorie needs will provide protein at 1.1 to 1.2 g/kg/day, whereas a standard-nitrogen formula will provide between 0.8 and 1 g/kg/day. With J.B. at risk for refeeding syndrome, a high-nitrogen formula is the better choice initially.

Case 37-2, Question 5: Should the EN product selected for J.B. contain fiber, and, if so, what type and amount?

Fiber has potential physiologic benefits, including increased fecal bulk, decreased bowel transit time in patients susceptible to constipation, increased transit time in patients with diarrhea, reduction of serum cholesterol, and improved glycemic control in patients with diabetes. Recommended daily fiber intake for healthy Americans is 21 to 25 g for females and 30 to 38 g for males, with the lower end of these amounts for people 51 years of age or older.[17–19] Adequate intake is determined by calorie intake and fiber intake observed to protect against coronary artery disease (14 g/1000 calories). Optimal fiber intake for ill persons has not been determined. Fiber-supplemented formulas vary considerably in fiber content. There is no standardized terminology for low-fiber, moderate-fiber, and high-fiber content; however, the amounts listed in Table 37-3 can serve as a general guideline.

Enteral formulas may contain either insoluble or soluble fiber, or both types (eg, mixed fiber). Insoluble fiber is associated with changes in fecal bulk and transit time, whereas soluble fiber tends to be responsible for effects on cholesterol and glycemic control. Fructooligosaccharides (FOS) are naturally occurring sugars that are added to some enteral formulas for soluble fiber benefits. Soluble fibers and FOS are prebiotics that can be fermented to short-chain fatty acids by *Bifidobacterium* in the colon.[18,19] Short-chain fatty acids stimulate colonic blood flow, enhance fluid and electrolyte absorption, and provide a trophic effect in the colon. SCCM-ASPEN Critical Care guidelines suggest consideration for routine, prophylactic use of 10 to 20 g fermentable soluble fiber (eg, FOS, inulin) in divided doses over 24 hours to promote bowel health in “all hemodynamically stable” patients in the ICU receiving standard EN formulas.[4]

The most common fiber source for enteral formulas is soy polysaccharide, or soy fiber, which has mixed fiber effects. Although soy polysaccharide demonstrates beneficial effects in healthy

subjects and non–critically ill patients, studies do not provide clear evidence of improved bowel function in critically ill patients.[4,9,20] SCCM-ASPEN Critical Care guidelines do not recommend routine use of a mixed fiber formula to prevent diarrhea or promote bowel regularity in critically ill patients.[4] When persistent diarrhea is evident, however, the guidelines suggest that a mixed fiber formula be considered. Given available data, stable patients on long-term EN appear most likely to benefit from mixed fiber formula, and some patients on short-term EN without significant GI pathology may benefit.

The addition of fiber to enteral formulas creates some potential problems. Fiber increases viscosity and fiber-containing formulas often require a pump for administration through feeding tubes. GI symptoms from fiber can include increased gas production and abdominal discomfort.[17,19] Flatulence and bloating can limit tolerance to fiber for some patients; gradual introduction may help reduce these symptoms. Surgical and trauma patients receiving mixed fiber EN formulas have developed bowel obstruction; therefore, avoidance of fiber is recommended by the SCCM-ASPEN Critical Care guidelines when severe dysmotility or a high risk of bowel ischemia exist in critically ill patients.[4] Caution is advised for the use of fiber-containing formulas in any patient with poor GI motility and underlying GI dysfunction, and patients receiving medications that inhibit bowel motility. Inadequate fluid intake may also contribute to the risk of intestinal blockage with fiber.

J.B. does not appear to have bowel pathology precluding use of a fiber-containing formula. He will require EN for a moderate duration of time and potentially long term. It would be reasonable to provide a formula with at least moderate-fiber content. However, J.B. could experience GI symptoms from the fiber, especially if his diet has previously been of low-fiber content. If necessary, a low-fiber formula could be used initially and then transitioned to higher fiber once symptoms of bloating and gas improve.

Case 37-2, Question 6: What is an appropriate administration regimen for J.B.'s tube feeding?

The feeding route, formula selected, and anticipated duration of feeding influence the administration regimen. Patient location (eg, hospital, nursing facility, home) and cost also are considered when developing the regimen, including the rate for initiating and advancing feedings, and the administration method (ie, syringe, gravity drip, pump).

Limited scientific data exist regarding EN administration regimens; thus, expert opinion plays an important role, and different regimens can be used in various settings, all of which appear to meet the needs of the patients and personnel. The administration regimen should be adjusted as necessary for feeding intolerance. Four basic schedules for formula delivery are available: (a) continuous infusion, (b) cyclic infusion, (c) intermittent infusion, and (d) bolus delivery of formula.

Continuous Infusion

Continuous infusion provides formula at a continuous rate for 24 hours/day and can be used with any route of feeding. Intragastric continuous infusion is most commonly used for hospitalized patients, although small-bowel feeding may be more appropriate in some patients.[9] Risks of gastric distension and aspiration may decrease with continuous infusion compared with intermittent gastric infusion.[4,21,22] In addition, the slower infusion rate associated with continuous infusion may be better tolerated as judged by stool frequency and time to attain full nutrition support. However, data were considered insufficient to include a recommendation for continuous infusion versus other administration methods for critically ill patients in the CCP guidelines.[9] Feeding into the duodenum or jejunum is best initiated with continuous infusion because rapid infusion of large formula volumes into the small bowel can result in symptoms of dumping syndrome, including sweating, lightheadedness, abdominal distension, cramping, hyperperistalsis, and watery diarrhea. With time, the jejunum may adapt to larger

volumes over a shorter time, allowing cyclic or longer intermittent infusions.

Cyclic Feeding

Cyclic feeding provides formula at a continuous rate for <24 hours daily. This method is most commonly used for patients who need supplemental nutrition because of an inability to consume adequate oral nutrients, during transition to an oral diet, and for long-term home EN patients. Infusions are typically given at night for 8 to 12 hours to minimize interference with oral intake and normal activities during the day, although cycles can be as long as 20 hours. Most patients do not start on a cyclic regimen; rather, they transition from continuous feeding. Formula volume and osmolality can limit tolerance to cyclic feedings, especially jejunal feedings; transition often occurs within a couple of days for gastric feeding, but may require weeks for jejunal feeding, depending on patient tolerance and cycle time.

Intermittent and Bolus Feedings

Formula is provided in three to eight gastric feedings daily for intermittent and bolus administration. Intermittent infusion occurs for 30 to 60 minutes using a feeding container or bag, with or without an enteral pump, and bolus feedings are for about 15 minutes using gravity administration via a syringe.[3] The stomach's reservoir capacity allows administration of relatively large volumes on an intermittent or bolus schedule. This is more physiologic than continuous feeding and more convenient for patients in nursing facilities and ambulatory patients at home on EN.

INITIATION OF FEEDINGS

The regimen for initiating EN primarily depends on the site of feeding and condition of the patient's GI tract. Use of full-strength (ie, undiluted) formula is recommended for initiation of feedings.[3,21] Dilution delays delivery of adequate nutrients without significantly affecting the incidence of GI intolerance. Hypertonic formulas are diluted rapidly in the GI tract, reaching isotonicity before or shortly beyond the ligament of Treitz (distal end of the duodenum). Continuous feedings are commonly initiated at goal rate, or at 50 mL/hour with advancement by 15 mL/hour every 4 hours to reach the goal within 24 to 48 hours in non–critically ill patients.[3] For critically ill patients, those with abnormal GI function, patients without use of the GI tract for a prolonged time, those at risk for refeeding syndrome, and when calorically dense or high-osmolality formulas are used, starting at 10 to 40 mL/hour and advancing by 10 to 20 mL/hour every 8 to 12 hours may be preferable, although this is based on consensus rather than on evidence from well-designed studies.[3,15,22] Using more rapid advancement protocols does allow adequate nutrient delivery more quickly, unless intolerance requires return to lower rates of delivery. Consistently adequate nutrient delivery is also more likely with volume-based feeding protocols in which daily formula volume is ordered (rather than rate) and nurses adjust volume based on patient tolerance to achieve the daily goal volume.[3,21,23]

Hospitalized patients are typically started on continuous infusion feedings, then transition to intermittent infusions, and eventually to bolus feedings, if desired. Bolus feedings are started with 240 mL over 4 to 10 minutes (maximum rate 60 mL/minute) with a minimum of 3 hours between feedings, then advanced by 60 to 120 mL every 8 to 12 hours until the goal volume and number of feedings is achieved.[3] For intermittent feeding, volumes of 240 to 720 mL over 20 to 60 minutes four to six times per day are typical. Initiation of feedings at goal rate may be tolerated by some patients, although starting slower is appropriate for many patients. The schedule for nonhospitalized patients should allow all feedings during waking hours.

J.B. receives gastric feeds; therefore, continuous infusion, intermittent infusion, or bolus feedings could all be used. Continuous infusion most commonly is used for hospitalized patients despite no clearly established difference in tolerance compared with intermittent infusion. Full-strength formula should be used to initiate feedings. The goal volume of EN for J.B. is 1440 mL/day of a standard caloric density formula (1.06 kcal/mL, 0.44 g protein/mL, 83.5% free water), or 60 mL/hour continuous infusion. The infusion could be started at 60 mL/hour (goal rate); however, given J.B. is at risk for refeeding syndrome, it is preferable to start slower. Starting at 15 mL/hour for 12 hours and then increasing by 15 mL/hour every 12 hours would achieve the goal rate of 60 mL/hour within 48 hours. If J.B. experiences diarrhea or abdominal distension, the feeding may be held at 15 mL/hour for 24 hours, then increased by only 10 mL/hour every 12 to 24 hours as tolerated. Extra care is required to ensure he receives an adequate fluid intake until the formula is at goal rate, and that electrolytes are replaced as necessary should refeeding syndrome develop.

To prevent potentially fatal inadvertent IV infusion of non-IV products, the International Organization for Standardization (ISO) standard 80369 was developed for non–Luer-compatible connectors for small-bore liquid and gas medical device tubing, including enteral feeding connectors known as ENFit® devices.[24] Oral syringes will not fit ENFit® connectors; therefore, ENFit®-compatible syringes are required for medication administration, tube flushes, and bolus feeding via syringe when the EAD has an ENFit® connector. The type of connector should be verified because long-term EADs, such as PEGs, may have been placed before ENFit® connectors.

TRANSITION FROM CONTINUOUS TO INTERMITTENT/BOLUS FEEDING

Case 37-2, Question 7: J.B. has received EN for 5 days. He has tolerated his continuous tube feeding without problems and has not required electrolyte replacements for the past 2 days. The plan is to transfer J.B. to a skilled nursing facility (SNF) within the next 2 days. The SNF requests that J.B. be on an intermittent/bolus feeding regimen before he transfers. How should J.B. be changed from continuous infusion to intermittent or bolus feeding?

Many nursing facilities do not routinely use enteral pumps because of increased cost. Without a pump, delivery of the prescribed volume of formula at a consistent rate may not be reliable, and increased nursing time may be required to prevent tube occlusion and ensure adequate volume of formula is delivered. J.B. is currently receiving continuous infusion feedings. The transition to intermittent delivery of formula can be accomplished by various methods. An overlapping regimen of gradually decreasing the continuous infusion rate and increasing the intermittent volume can be used, but can be disruptive when a closed enteral feeding system is used in a hospital setting. For J.B., decrease the continuous rate from 60 mL/hour down to 30 mL/hour and add four intermittent feedings of 180 mL over 60 minutes every 6 hours initially. If tolerated, stop the continuous and increase intermittent feeding to 240 mL every 4 hours (six feedings daily). If tolerated, the feeding volume can be increased to 360 mL four times daily plus one 120-mL feeding, or to 380 mL four times daily. To reduce risk of contamination and waste when individual containers of formula are being used, versus large bags (1–3 L) in a closed feeding system, increments of 240 mL (full 8-ounce container), or, if necessary, 120 mL, are preferred. To keep the feeding volume in preferred increments, J.B. could receive two feedings of 360 mL and three feedings of 240 mL, no closer than every 3 hours. Based on tolerance, the feeding regimen could be changed to 480 mL four times daily during waking hours.

Another transition method is to stop continuous feedings and restart feedings with a regimen for initiating intermittent feedings. Starting volume is typically 240 mL for the first two or three feedings, and feeding intervals are often every 4 hours. Volume is increased by 60 to 120 mL every 8 to 12 hours, as tolerated, until the goal is

reached.[3] Feeding intervals can be increased once goal volume is reached. J.B. could start with 240 mL over 60 minutes every 4 hours for two feedings, then advance to 360 mL per feeding. If tolerated, the volume per feeding could increase to 480 mL to allow feedings every 6 hours. Then reduce the time between feeding to not <3 hours to fit all feedings into waking hours. Once at the regimen, the infusion time could be decreased based on tolerance. If feeding for 30 minutes is well tolerated, J.B. could be changed to bolus administration for 15 to 20 minutes.

The discharge EN prescription should include patient identifiers as required for any prescription.[21] The formula should be given in generic descriptive terms (ie, standard vs special features related to caloric density, protein content, and fiber content per 1000 kcal). The brand name may be included, but the SNF may not carry the same brand of formula. Delivery site (gastric or small bowel), the specific EAD, administration method (continuous, cyclic, intermittent, bolus), formula volume, and rate or administration time (ie, 15, 30, or 60 minutes) should be included. Total daily formula volume, and the daily calories, protein, fiber, and fluid goals should be specified. Flush orders should include the solution (ie, purified water), volume per flush and total flushes per day, frequency, and timing. Any special considerations for the feeding schedule also should be communicated (eg, J.B. does not tolerate feeding after 9 pm; raise the head of the bed to 45° for 3 hours after the last daily feeding to avoid regurgitation).

FLUID PROVISION

CASE 37-2, QUESTION 8: How much additional fluid must be included in the feeding regimen to meet J.B.'s estimated daily fluid requirements?

The free-water content of EN must be calculated to determine the volume of additional fluid that must be provided. As noted previously,

standard caloric density formulas generally contain 80% to 85% free water. The formula selected for J.B. contains 83.5% free water; therefore, at his goal volume of 1440 mL/day (six, 240 mL containers), the formula provides ~1200 mL of free water daily. Using 1860 mL daily (30 mL/kg/day × 62 kg) as J.B.'s fluid requirement (see Case 37-2, Question 5), he will need 660 mL/day in addition to the enteral formula. If J.B. had additional losses from vomiting, diarrhea, or other sources, this volume would be added to the 660 mL to determine total volume in addition to enteral formula. The additional fluid is typically provided with medications and tube irrigation (flushes). EADs should be irrigated with 30 mL of fluid every 4 hours during continuous feeding, or before and after each intermittent or bolus feeding.[3,21] The tube should be flushed with a minimum of 15 mL, although some suggest 30 mL, of water before and after medication administration through the tube, as well as with 15 mL between each medication.[3,16,21,22] Fluid also is required for diluting medications before administration through the EAD. The flush volume and/or number of flushes will need to be increased to provide J.B. with adequate fluid because 30 mL every 4 hours plus fluid for medication administration will not provide the 660 mL of fluid needed in addition to his EN. Because J.B. is receiving gastric feedings, hypotonic fluid is of less concern than in the jejunum, where the normal sodium concentration is 90 to 140 mEq/L.[25] Increasing flush volumes to between 100 and 150 mL should meet J.B.'s daily fluid requirement, depending on the amount needed for medication administration. Diluting the formula itself to increase fluid provision is not recommended because this increases the risk of error and contamination.

NUTRITION IN CRITICAL ILLNESS

Nutrition support is an important component of care in critical illness, where patients are typically in a catabolic stress state and metabolism may be altered. Multiorgan dysfunction, as well as fluid

and electrolyte imbalances, adds to the complexity of this population and confounds attempts to provide proper nutrition. The preferred route for nutrition support is generally EN, although the ideal formula composition remains unresolved. The most recently published guidelines should be consulted to determine current recommendations for formula composition, including specialized components. In addition, it is essential to review the most current summation of data from major nutrition support and/or critical care organizations to determine which populations may benefit or be harmed by specific components because guidelines may lag behind the newest data.

CASE 37-3

QUESTION 1: N.R., a 68-year-old male with a past medical history of hypertension, presents to the ED with shortness of breath, productive cough, wheezing, and fever. N.R. subsequently requires intubation and is transferred to the ICU with a diagnosis of pneumonia. His SARS-CoV-2 antibody test result for COVID-19 is negative. During the next 24 hours, his respiratory status further declines, and he is diagnosed with adult respiratory distress syndrome (ARDS). In anticipation of a prolonged course of mechanical ventilation, a feeding tube is placed into the small bowel. The chart indicates a height of 70 inches (177.80 cm) and an admission weight of 165.35 pounds (75 kg).

Laboratory evaluation today includes the following:

Sodium, 140 mEq/L
Potassium, 3.9 mEq/L
Chloride, 109 mEq/L
Carbon dioxide content, 22 mM
BUN, 18 mg/dL
SCr, 0.8 mg/dL
Glucose, 118 mg/dL
Albumin, 3.6 g/dL
Aspartate aminotransferase, 32 international units (IU)/L
Alanine aminotransferase, 37 IU/L
Alkaline phosphatase, 64 IU/L
Total bilirubin, 0.7 mg/dL
WBC, 15.3 × 10^3/mL
Hgb, 13.4 g/dL
Hct, 39.9%

Should a specialized critical care formula be used for initiation of EN in N.R.?

N.R. is critically ill, and several types of EN formulas have been developed for critically ill patients. However, the role of specialized EN formulas, and certain components in particular, remains controversial in critical illness. **Table 37-4** shows a few formulas marketed for critical illness and lists the components that are altered compared to standard polymeric formulas. Owing to the catabolic nature of critical illness, formulas are generally high protein, many with an NPC:N ratio <100:1 (ie, high or very high-protein content). Supplementation of specific amino acids, including branched-chain amino acids (BCAAs), glutamine, and arginine, in EN for critical illness remains an unsettled issue. Other formulas containing slightly lower protein content (ie, NPC:N ratio between 100:1 and 125:1) target the inflammatory element of critical illness with components designed to mitigate the inflammatory response, including altered fatty acid composition and antioxidant components. Formulas designed for critical illness are typically fiber-free ones, although a few formulas include small amounts of soluble fiber. As a whole, specialized formulas are not recommended for routine use in the ICU.

Table 37-4
Selected Enteral Formulas With Altered Protein or Fat Sources

Formula[a,b,c]	kcal/mL (mOsm/kg)	Free Water (%)	Protein g/L (% kcal)	NPC:N	Protein Source	ARG g/L[d]	GLN g/L[d]	Fat g/L (% kcal)	Fat Sources	%Fat kcal as MCT	Ratio of ω-6FA to ω-3FA[d]	Fiber g/L[d]
Impact®[c]	1.0 (375)	85	56 (22)	71:1	Sodium and calcium caseinates; L-arginine	12	–	28	Palm kernel oil; anchovy and sardine oil; high oleic sunflower oil; high oleic safflower oil	–	1.4:1	–
Impact® Peptide 1.5[c]	1.5 (510)	77	94 (25)	63:1	Hydrolyzed casein; L-arginine	18.7	–	63.6 (38)	MCT; palm kernel oil; anchovy and sardine oil	50	1.4:1	–
Oxepa®[b]	1.5 (544)	78.5	62.7 (16.7)	125:1	Sodium and calcium caseinates	–	–	93.8 (55)	Canola oil; MCT oil; marine oil; borage oil	22	1.8:1	–
Peptamen AF®[c]	1.2 (390)	81	76 (25)	75:1	Hydrolyzed whey protein	–	–	54 (38)	MCT oil; soybean oil; anchovy and sardine oil; lecithin	50	1.7:1	5.2 (FOS, inulin, guar gum)
Peptamen® Intense VHP[c]	1.0 (345)	84	92 (37)	43:1	Hydrolyzed whey protein	–	–	38 (33)	MCT; anchovy and sardine oil	NA	1.63:1	4 (FOS, inulin, guar gum)
Perative®[b]	1.3 (460)	79	66.7 (20.5)	97:1	Hydrolyzed sodium caseinate; whey protein hydrolysate; L-arginine	8	–	37.3 (25)	Canola oil; MCT; corn oil	NA	4.8:1	5 (FOS)
Pivot® 1.5 Cal[b]	1.5 (595)	75.9	93.8 (25)	75:1	Hydrolyzed sodium caseinate; whey protein hydrolysate; L-arginine	13	7.6	50.8 (30)	Structured lipid (interesterified marine oil and MCT); soy oil; canola oil	20	1.7:1	7.5 FOS
Vital AF 1.2 Cal®	1.2 (425)	81	75 (25)	75:1	Whey protein hydrolysate; hydrolyzed sodium caseinate	–	–	53.9 (39)	Structured lipid (interesterified marine oil and MCT); MCT; canola oil; soy oil	NA	0.9:1	5.1 (FOS)
Vivonex® RTF[c]	1.0 (630)	85	50 (20)	94:1	Free amino acids (29% BCAA)	5.9	–	11.6 (10)	Soybean oil; MCT	–		–

AF, advanced formula; ARG, arginine; FOS, fructooligosaccharides; GLN, glutamine; MCT, medium-chain triglycerides; NA, not available; NPC:N, nonprotein calorie to nitrogen; ω-3FA, ω-3 fatty acids; ω-6FA, ω-6 fatty acids.

[a]Changes periodically occur in nutrient sources and content; use this table as a general reference only and not for specific patient care issues.

[b]Abbott product, Abbott Laboratories, Abbott Park, IL.

[c]Nestle product, Nestle Health Science, Vevey, Switzerland.

[d]None or unknown indicated by "–."

Enhanced Branched-Chain Amino Acid Content

Standard EN formulas contain 15% to 20% of protein as BCAAs; enhanced BCAA formulas for critical care contain over 35%, and hepatic failure formulas contain 45% to 50%. High-BCAA stress/critical care formulas are not therapeutically interchangeable with hepatic formulas because of the lower than normal concentrations of aromatic amino acids (AAAs), especially phenylalanine, in hepatic formulas.

High to very high protein is currently emphasized over BCAA content for critically ill patients. A standard enteral formula is

recommended by SCCM-ASPEN Critical Care guidelines for patients in the ICU with acute or chronic liver disease.[4]

Glutamine

The proposed role of glutamine in critical illness is enhanced neutrophil function and maintenance of intestinal barrier function, thereby preventing translocation of bacteria and endotoxins from the GI tract into systemic circulation and reducing bacteremia.[26] Glutamine is considered a nonessential amino acid, because it is synthesized in sufficient quantities for its roles in transamination, as an intermediate in numerous metabolic pathways, such as gluconeogenesis and renal ammoniagenesis, as a fuel source for rapidly dividing lymphocytes and enterocytes, and in the synthesis of glutathione. However, during periods of metabolic stress, endogenous synthesis may become inadequate.

Study results are conflicting regarding effects of enteral glutamine supplementation in the critically ill population. The 2015 CCP guidelines recommend against the use of enteral glutamine in critically ill patients.[9] The exception may be patients with burns who appear to have a reduced hospital LOS and reduced mortality with enteral glutamine supplementation, although the number of patients in studies was small.[27,28] Monitoring for potential complications is essential when glutamine supplementation is used.

Protein-bound glutamine is present in all enteral formulas, but free glutamine is unstable in ready-to-use formulas. Glutamine is available as a modular supplement, which can be administered separately from the EN formula. Glutamate functions in many roles attributed to glutamine and is stable in water; therefore, it could be added to ready-to-use formulas. Additional research is needed to determine whether physiologic effects are equivalent for glutamate, protein-bound glutamine, and free glutamine.

Arginine

Arginine is a nonessential amino acid synthesized by the urea cycle during detoxification of ammonia and is normally available in sufficient quantities for growth and tissue repair. In times of metabolic stress, however, endogenous synthesis may become inadequate, making arginine conditionally essential. The postulated benefit of arginine in critical illness is related to enhanced protein synthesis, cellular growth, and immune system support. In contrast, several mechanisms that suggest potential adverse effects with arginine supplementation have been proposed, including one in which arginine is used as a substrate in the synthesis of nitric oxide (NO), a potent vasodilating agent, which may also have implications in mitochondria damage, organ dysfunction, and increased gut barrier permeability.[29] Although synthesis of NO increases during sepsis (thereby creating a negative arginine balance), the exact role of this effector molecule remains controversial. Many believe that excess NO is part of an adaptive response directed toward limiting infection, ischemia, coagulation, inflammation, and tissue injury.

Conflicting study results leave considerable uncertainty regarding use of arginine-supplemented EN in critically ill patients.[4,9,29–32] Interpretation of studies is often confounded by inclusion of other potentially immune-modulating components in the formula. As a result, clinical guidelines most often refer to “immune-modulating” formulas (IMFs) with specific references to the arginine component.

IMMUNE-MODULATING FORMULAS

Formulas included in Table 37-4 have an NPC:N ratio of 125:1 or less and contain supplemental arginine, glutamine, or nucleic acids, or a modified fat component. Such formulas are known as IMFs based on their proposed beneficial modulation of biologic responses to stress. Study formulas frequently contain varying portions of two or more potentially immune-modifying components, making it difficult to determine the effect of any given component. The subset of IMFs intended for patients with ARDS and acute lung injury (ALI) is distinct

from other IMFs, and is discussed in more detail in the section Pulmonary Disease.

The population that appears to have better outcomes with IMFs is patients undergoing major elective surgery, particularly surgery for GI malignancy. Reduced postoperative infection risk and shorter LOS, but not reduced all-cause mortality, was reported in a systematic review and meta-analysis of surgical oncology patients.[30] More than 90% of patients included in the analysis had undergone surgery for GI-related malignancy, and the majority of those in the IMF study arms (vs control arms) received a combination of arginine, nucleotides, and ω3FAs perioperatively with caloric goals of 25 to 30 kcal/kg/day. Patients who are malnourished may show greater benefit from an IMF.

SCCM-ASPEN Critical Care guidelines recommend routine use of an IMF containing arginine in postsurgical patients in the ICU requiring EN, as an option in patients with traumatic brain injury, and for consideration in patients with severe trauma.[4] The arginine dose should not exceed 15 to 30 g/day with the IMF.[4,31] Routine use is not recommended in the medical ICU. Conversely, CCP guidelines advise against use of formulas with “arginine and other nutrients” in all critically ill patients because higher quality studies indicated no effect on mortality with these formulas, and increased mortality was reported for patients with sepsis in some studies.[9] A more recent systematic review indicates no effect on overall mortality, rate of infectious complications, or hospital or ICU LOS with arginine-containing IMFs in critically ill patients.[32] Effects on reduced duration of mechanical ventilation were uncertain. Neither the CCP guidelines nor the SCCM-ASPEN Critical Care guidelines recommend use of an arginine-supplemented IMF for patients with severe sepsis.[4,9] The effects of combinations of immune-modulating components (arginine, glutamine, nucleic acids, ω-3FAs), optimal component and dose combinations, and the most beneficial timing for administration of immune-modulating components in well-defined patient populations continues to be explored.

Altered Fat Components

Stress or critical care formulas and IMFs contain different sources of fat to alter the type of fatty acids provided. Fat sources commonly include MCTs, along with predominantly canola oil, high-oleic oils, or fish oils. Absorption of MCTs is relatively independent of pancreatic enzymes and bile salts, and is carnitine independent; thus, they can be absorbed in patients experiencing malabsorption of the long-chain triglycerides. Formulas containing a relatively large percentage of fat calories as MCTs are frequently marketed for critically ill patients with malabsorption.

Canola oil and high-oleic oils have high monounsaturated fatty acid (MUFA) content. MUFAs have been popularized by reports of low cardiovascular disease in populations using olive oil; research to define the role and doses of these fatty acids in ill patients continues. Usual polyunsaturated vegetable oils (ie, corn, soy, and safflower oils) are avoided or provided in relatively small quantities in critical care formulas to limit ω-6 fatty acids (ω-6FAs), which are precursors to inflammatory, vasoconstrictive, and platelet-aggregating agents.[33,34] Small amounts of ω-6FAs are required in the diet to prevent deficiency of linoleic acid, an essential fatty acid not provided by MCT and fish oils.

Fish oils, including menhaden oil, provide fatty acids primarily from the ω-3 family, with the very long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) predominating. The proposed role of ω-3FAs in critical illness is to reduce excessive inflammatory responses, with subsequent reduction of thrombotic risks, cardiac arrhythmias, infectious complications, and, ultimately, reduce death in selected patient populations.[29] The ω-3FAs are precursors to less inflammatory and more vasodilatory eicosanoids than those from ω-6FA.[29,33,34]

Limited data are available evaluating effects of only fat modification in EN for critical illness. Although the ability of ω-3, -6, and -9FAs to modulate differences in prostaglandin, leukotriene, and thromboxane production are well known, effects in critically ill patients remain less certain.[29,35] Improved clinical outcomes for

postsurgical and critically ill patients have been associated with EN-containing ω-3FAs, usually in conjunction with other immune-modulating components, in some studies; other studies suggest data are inadequate to support routine use of fish oil.[4,9,29,32,35]

Studies suggest a minimum of 5 to 7 days of supplementation with immune-modulating components, including ω-3FAs, is necessary to see beneficial effects on postoperative outcomes.[29,33] Incorporation of ω-3FAs into cell membranes may be required to see benefits. Fat modification to provide high-ω-3FA content also has been studied in ARDS and ALI (as discussed in the section Pulmonary Disease).

The question of whether to initiate EN in N.R. with an IMF appears straightforward. The data provided for N.R. do not indicate sepsis, and he is in the medical ICU rather than in the surgical ICU. Neither SCCM-ASPEN Critical Care nor CPP guidelines recommend routine use of IMFs in patients in the medical ICU.[4,9] Because N.R. was admitted with pneumonia and now has ARDS, the more appropriate question at this time would be whether a specialized pulmonary formula would be more appropriate for his EN.

PULMONARY DISEASE

CASE 37-3, QUESTION 2: How do pulmonary formulas differ from standard polymeric formulas? If N.R. receives a specialized pulmonary formula, what nutrient modifications should the formula contain?

There are two types of EN formulas intended for patients with pulmonary conditions. Both have a moderate caloric density (1.5 kcal/mL) and the percentage of calories from fat is relatively high (40%–55%), although the types of fats differ. The premise for higher fat content is that fat metabolism produces less carbon dioxide (CO_2) than does carbohydrate metabolism, thereby reducing the work load of the lungs. Caloric intake in the older studies showing a benefit of high-fat, low-carbohydrate diets was excessive by current standards.

Excess caloric intake contributes to higher CO_2 production; thus, the early studies are of questionable relevance. In practice, preventing overfeeding is as important for control of CO_2 as high-fat, low-carbohydrate diets.[36] In addition, improved respiratory parameters with a high-fat EN product are unlikely in patients without excess CO_2 production or retention. Data from 60 malnourished, underweight patients with chronic obstructive pulmonary disease (COPD) do suggest that respiratory status in this population is more likely to benefit from a high-fat, low-carbohydrate (28% of calories) formula compared with a high-carbohydrate (60%–70% of calories) formula.[37] The percentage of calories from fat (55%) in the high-fat formula was similar to pulmonary formulas in the older studies; however, fat distribution was considerably different, reflecting that currently marketed pulmonary formulas contain 20% to 40% of fat calories as MCTs and fat sources providing higher MUFAs. During a period of high caloric intake for weight gain, pulmonary formulas may be reasonable; however, they are not warranted for routine use in most patients.

The second type of pulmonary EN formula is an immune-modulating pulmonary (IMP) formula with an anti-inflammatory lipid profile (fish oils rich in ω-3FAs, borage oil rich in γ-linolenic acids [GLAs]; reduced ω-6FA content) and antioxidants (vitamins C and E, beta carotene), which has been studied in patients with ARDS and ALI.[4,9,29,32] There is no supplemental glutamine or arginine in IMP formulas. Most studies of IMP formulas have used the specific brand Oxepa® (Abbott Laboratories, Abbott Park, IL), which contains fish oils, borage oil, antioxidants, vitamin E and C, β-carotene, taurine, and L-carnitine.[38] Interpretation of studies has often been confounded by use of a high-fat pulmonary formula as the control rather than a typical ICU EN formula. Overall, the IMP formulas appear to reduce ventilator-dependent days, and reduce mortality for patients with sepsis, ALI, or ARDS.[4,9,29,38] These formulas may reduce LOS in the ICU, but do not appear to affect infectious complications.

The SCCM-ASPEN Critical Care guidelines recommend that patients with ARDS or ALI be placed on an IMP formula, whereas

CCP guidelines have a slightly lower recommendation that such an IMP formula be considered.[4,9] However, the CCP guidelines do not reflect the more recent systematic review, indicating reduced ventilator-dependent days and lower mortality in patients with ARDS/ALI or sepsis with continuous administration of an IMP formula.[38]

N.R. was diagnosed with ARDS; therefore, an IMP formula should be considered based on the CCP and SCCM-ASPEN Critical Care guidelines.[4,9] The formula should contain fish oils to provide a high ω-3FA content, borage oil to provide GLA, and increased antioxidant vitamin content. Delayed gastric emptying is associated with high-fat diets and must be considered when evaluating possible benefits and adverse effects of high-fat EN. This applies to both IMP and routine pulmonary formulas. Abdominal distension, increased gastric residuals, nausea, and vomiting can result from delayed gastric emptying. N.R. has his feeding tube placed in the small bowel, so delayed gastric emptying is not a concern. However, the potential to overwhelm pancreatic lipase activity resulting in fat malabsorption should be considered when a high-fat load, especially long-chain triglycerides, is delivered into the small bowel. Continuous infusion is more likely to be tolerated than other, more rapid delivery methods in most patients. With continuous feeding, EN can continue at full support even if N.R. undergoes rotation to a prone position for his ARDS, although a reverse Trendelenburg position is suggested with the prone position.[39] In the reverse Trendelenburg position, the head is higher than the feet, which is equivalent to raising the head of the bed, as suggested to reduce aspiration in patients in a supine position. The cost of routine pulmonary formulas is typically slightly higher than for standard polymeric formulas, whereas IMP formulas tend to cost significantly more.

RENAL FAILURE

Case 37-3, Question 3: N.R. has been in the ICU for 10 days. His ARDS has improved; however, he now has acute kidney injury and hemodialysis will start today. Morning laboratory results include the following:

Sodium, 131 mEq/L
Potassium, 5.9 mEq/L
BUN, 85 mg/dL
SCr, 4.0 mg/dL
Glucose, 110 mg/dL on an insulin drip
Magnesium, 2.9 mg/dL
Phosphorus, 5.8 mg/dL
WBC, 9.7 × 10^3/mL
Hgb, 11.4 g/dL
Hct, 34.3%

An EN formula for renal failure is ordered. How do the nutrient components in renal formulas differ from standard polymeric EN formulas? Is a renal formula appropriate for N.R.?

Two types of EN formulas for renal disease/injury are available, balanced amino acid and essential amino acid-enriched ones. Both are calorically dense (1.8–2 kcal/mL) to limit fluid provision and contain reduced potassium, phosphorus, and magnesium content.

Balanced amino acid polymeric enteral formulas designed for renal failure or renal insufficiency are the standard for hospitalized patients with impaired renal function. These formulas are not enriched with essential amino acids. The protein content varies from high (for patients with increased nitrogen losses from dialysis) to low (typically used for patients who are nondialyzed). Many critically ill patients receiving dialysis for acute kidney injury tolerate a nonrenal formula; however, those with elevated serum potassium, phosphorus, or magnesium concentrations generally require a renal formula to control electrolyte levels. Based on his electrolytes, N.R. will require a renal formula, at least initially. A polymeric formula with high-protein content (eg, NPC:N 120:1–100:1, 17%–20% calories from protein) would be appropriate given the plan for dialysis, although a slightly lower protein formula would be acceptable as well. The choice would depend on protein provided by the formula with low potassium, phosphorus, and magnesium content on

formulary. Polymeric renal formulas meet 100% of the DRI with <2000 mL/day.

Highly specialized formulas with enriched essential amino acid content, the second type of renal formula, are based on the theory that recycling of urea nitrogen for nonessential amino acid synthesis reduces the accumulation of BUN.[36] However, clinically significant recycling of nitrogen and incorporation into nonessential amino acids does not appear to occur. Currently available essential amino acid–enriched formulas such as Renalcal® (Renalcal Nestle Health Sciences, Vevey, Switzerland, contains two-thirds essential amino acids combined with one-third nonessential amino acids) are not intended as the only source of nutrition, but may be appropriate to supplement the diet of patients with chronic renal failure for whom dialysis is not an option. Use should be limited to no more than 2 to 3 weeks, because hyperammonemia and metabolic encephalopathy have been associated with longer use. These formulas are not appropriate for patients with acute kidney injury, such as N.R., or for those receiving dialysis.

Modular Components

Case 37-3, Question 4: After several days on the renal formula (NPC:N ratio, 113:1), there are indications that N.R.'s protein intake should be higher. Serum electrolytes today include the following:

Sodium, 137 mEq/L
Potassium, 4.9 mEq/L
Phosphorus, 5.2 mg/dL
Magnesium, 2.7 mg/dL

What are the options for increasing protein provision?

N.R. is receiving a renal formula with high-protein content based on 18% of calories from protein (NPC:N ratio of 113:1). There are no very high-protein formulas with low potassium, phosphorus, and magnesium content on the market; therefore, a very high-protein formula will provide significantly more of these electrolytes than N.R.

currently receives. His current serum levels of the renally eliminated electrolytes are near the upper end of acceptable and would likely rise if the EN is changed to a nonrenal formula. Using a lower potassium concentration in the dialysis bath might keep serum potassium within an acceptable range. Addition of a phosphate binder to the medication regimen could be considered; however, the risk of tube occlusion may be increased with a phosphate binder. A better option is to provide additional protein from a modular protein component, although this can also increase the risk of tube occlusion if not administered properly.

Modular components are individual nutrient substrates, or combinations of two substrates, designed for addition to oral diets or enteral formula regimens. They provide only the macronutrient(s) without electrolytes or vitamins, and should only be used to supplement a diet or an EN, not as a sole source of nutrition. Protein modules are powders containing 3 to 5 g protein/tablespoon. Most protein modules are intact protein. Arginine and glutamine are available as individual packets to allow supplementation as a single amino acid. Glucose polymers are used to supplement calories as carbohydrate. They do not increase osmolality or alter food or formula flavor. Powdered carbohydrate modules contain 20 to 30 kcal/tablespoon, whereas liquids contain 2 kcal/mL. Protein and carbohydrate modular components typically are mixed with water and administered through the feeding tube rather than being mixed directly into the formula. Additional fat can be provided as 50% safflower oil emulsion (Microlipid®, Nestle Health Science, Vevey, Switzerland) or as MCT oil. A combination carbohydrate and fat modular product is available if both sources of calories are appropriate. A modular fiber product containing soluble fiber in the form of partially hydrolyzed guar gum is also available.

Glucose Control Formulas

CASE 37-4

Question 1: T.L., a 49-year-old female, is admitted to the hospital secondary to dehydration and for a GI workup related to a 15-pounds (6.80-kg) unintentional weight loss during the past month. She states she has been unable to eat for 8 days owing to continual nausea, although she reports no vomiting. T.L. received IV fluids in the ED and currently has 0.9% sodium chloride infusing at 125 mL/hour. Past medical history includes hypertension, hyperlipidemia, gastric reflux, and diabetes mellitus type 2. T.L. is 69 inches (175.26 cm) tall and her admit weight is 275.58 pounds (125 kg). Laboratory values from this morning show the following results:

Glucose, 245 mg/dL
BUN, 18 mg/dL, down from 35 mg/dL in the ED
SCr, 1.1 mg/dL, down from 2.3 mg/dL in the ED
Sodium, 140 mEq/L
Potassium, 4.2 mEq/L
Chloride, 105 mEq/L

Her small-bowel follow-through study indicates severely delayed gastric emptying. A feeding tube is to be placed into the small bowel for a trial of enteral feeding.

Should a "glucose control" or "diabetic" formula be used for initiating tube feedings in T.L.? How do formulas for glucose control differ from standard polymeric EN formulas?

No ideal macronutrient distribution has been identified for meals intended for patients with diabetes mellitus, and general dietary guidelines for healthy eating are considered appropriate.[40] However, specialty formulas for patients with diabetes mellitus, known as diabetic formulas, do not necessarily follow this recommendation. Diabetic formulas have caloric distributions of 33% to 40% carbohydrate, 42% to 49% fat, and 16% to 22% protein. The carbohydrate content is lower, and the fat content is higher than in most standard polymeric formulas. High MUFA sources (eg, high oleic oils, canola oil) predominate to provide >60% of fat as MUFAs. The source and type of carbohydrates in diabetic formulas vary, with a predominance of more complex and slowly digestible carbohydrates (ie, oligosaccharides, isomaltulose, fiber) with a low glycemic index. Fiber sources associated with improved glycemic control, mainly soluble fibers (ie, vegetable, gums, inulin, FOS) but also soy polysaccharide, are included in these formulas to help

minimize postprandial hyperglycemia. Fiber content ranges from 10.7 to 15.2 g/1000 calories, and the recommended fiber intake of 25 to 38 g daily generally can be achieved with <2000 kcal/day.[17]

Multiple studies comparing diabetic formulas to standard EN formulas providing equal calories and protein have been conducted. Diabetic formulas have been shown to improve fasting blood glucose, lower insulin requirements, and lower glycosylated hemoglobin concentration.[41,42] Effects on total cholesterol and triglyceride concentrations do not appear to be significant, despite their high-fat content. However, many studies have been of low methodologic quality, and most have been in ambulatory or nonacute care settings and of short duration. For hospitalized patients with hyperglycemia, no well-designed clinical trials of adequate size were found to make a recommendation regarding use of diabetic formulas in the ASPEN guidelines regarding adults with hyperglycemia.[43]

T.L. could receive either a diabetic formula or a standard formula. Glucose control may be better with a diabetic formula; however, the ASPEN guidelines found inadequate data to make a recommendation regarding use of diabetic formulas in hospitalized patients with hyperglycemia.[43] Either a diabetic or standard formula would be acceptable for T.L. based on available data. Problems with delayed gastric emptying or fat malabsorption must be weighed against possible benefits of improved glucose control with diabetic formulas. These problems are of minimal concern for T.L. because she is being fed into the small bowel and her history does not suggest fat malabsorption. Treatment goals for EN in patients with diabetes mellitus should include individualization of macronutrient composition, avoidance of excess calories, and maintenance of euglycemia.[41–43] T.L. may benefit from a treatment plan that includes gradual weight loss, and this may influence the decision of whether to use a diabetic formula or a very high-protein formula that would permit lower total calories while still providing adequate protein.

MONITORING ENTERAL NUTRITION SUPPORT

Case 37-4, Question 2: What types of complications can occur with tube feeding? What steps can be taken to prevent complications in T.L., and how should she be monitored for complications?

Appropriate monitoring of patients receiving EN is essential to recognize and prevent complications. Complications can be divided into three groups: mechanical, metabolic, and GI (**Table 37-5**).

Table 37-5
Complications of Tube Feeding

Complication	Cause/Contributing Factor	Treatment/Prevention
Mechanical Complications		
Aspiration	Deflated tracheostomy cuff	Inflate tracheostomy cuff before feeding; keep inflated 1 hour after feeding; consider small-bore feeding tube placed past the ligament of Treitz.
	Displaced feeding tube	Reinsert tube, check placement; consider hand restraints or feeding tube bridle.
	Reduced gastric emptying	Check residuals every 4–6 hours for gastric tube; raise head of bed 30–45 degrees; use lower fat formula; use prokinetic medication; use small-bowel feeding tube.
	Lack of gag reflex; coma	Place feeding tube into jejunum; keep head of bed elevated to 45 degrees; provide continuous feeding.
Nasal or pharyngeal irritation or necrosis; esophageal erosion; otitis media	Large-bore, polyvinyl chloride tube for long periods of time	Reposition tube daily, change tape; use smaller bore tube; position tube to avoid pressure on tissues; moisten mouth and nose several times daily.

Complication	Cause/Contributing Factor	Treatment/Prevention
Tube obstruction	Poorly crushed medications	Crush medications thoroughly, dissolve in water; consider using liquid medications; check compatibility of medication with tube and formula.
	Inadequate flushing after medications or thick formula	Flush tube with 50–150 mL of water after medications or thick formula and every 4–6 hours with 30 mL minimum.
	Poorly dissolved or mixed formula	Use blender to mix powdered formula (check manufacturer's mixing guidelines); use ready-to-use formula.
	Formula mixed with low-pH substance	Avoid checking gastric residuals when safe to do so; use larger diameter tubes when checking residuals; avoid administering acidic medications through small-diameter tubes; consider a nonacidic therapeutic alternative; flush with a minimum of 30 mL water before and immediately after medication administration.
Gastrointestinal Complications		
Nausea, vomiting, distension, cramping	Too rapid administration	Slow administration rate; change bolus to intermittent infusion.
	Osmolarity too high; intolerance to volume of formula	Use isotonic formula; increase the number of bolus or intermittent feedings so the volume per feeding is reduced, or change to continuous infusion; change to a more calorically dense formula if volume is the major problem (osmolarity will likely increase with higher caloric density).
	Gastric retention; poor GI motility	Place feeding tube distal to the pylorus; consider a promotility agent, such as metoclopramide; evaluate medications and change those possibly contributing to gastric dysmotility, if possible.

Complication	Cause/Contributing Factor	Treatment/Prevention
Dumping syndrome (weakness, diaphoresis, palpitations)	Hyperosmolar load bolused or infused rapidly into the small bowel	Do not bolus into the small bowel; temporarily decrease continuous infusion rate and gradually increase rate after symptoms subside; use an isotonic formula.
	Rate or volume of feeding increased too fast	Temporarily decrease continuous infusion rate or volume of intermittent or bolus feeding, and gradually increase rate after symptoms subside.
Diarrhea	Atrophy of microvilli; malabsorption related to a disease process (eg, pancreatitis, short-bowel syndrome, Crohn disease)	Use an oligomeric formula until absorption improves; use a relatively isotonic and advance slowly; use a formula low in long-chain fatty acids when fat is malabsorbed and/or consider pancreatic enzymes.
	Hypertonic formula	Change to a lower osmolarity formula.
	Dumping syndrome	See dumping syndrome entry in this table.
	Rapid advancement of formula volume	Temporarily reduce rate or volume, then advance slowly; consider enteral pump for better control of administration rate.
	Lactose intolerance	Change to lactose-free formula if previously using lactose-containing formula; evaluate lactose content of medications and supplemental foods, if patient is not strict NPO.

Complication	Cause/Contributing Factor	Treatment/Prevention
	Contaminated formula	Hang fresh formula every 4–6 hours when using an open administration system; do not add fresh formula to volume remaining in the feeding container; change the formula container and tubing daily; follow clean/aseptic technique when working with the formula or feeding tube; minimize manipulation of the feeding tube; consider changing to a closed enteral system; avoid powdered formulas requiring reconstitution.
Gastrointestinal Complications		
	Medications; antibiotics; magnesium-containing antacid; high-osmolarity liquid dosage forms	Check stool for *Clostridium difficile* and treat if present; consider probiotic agent; administer antidiarrheal if not contraindicated; consider alternative therapy such as histamine-2 blocking agent or proton-pump inhibitor; use calcium-based antacid; reduce dose or divide dose into 3–4/day, when feasible to do so; dilute medication with water before administrations; consider alternative dosage form (transdermal, IV); change to crushed tablet and use appropriate precautions to avoid tube occlusion.
Constipation	Inadequate fluid or free-water intake	Increase volume and/or frequency of tube flushes to increase fluid intake; change to a formula with lower caloric density, if possible.
	Inadequate fiber intake	Change to a formula with fiber or with a higher fiber content; administer fruit juice or bulk-forming laxative (eg, psyllium) using caution to prevent tube occlusion.
	Fecal impaction	Administer stool softener daily using caution to prevent tube occlusion if administered via the tube.

Complication	Cause/Contributing Factor	Treatment/Prevention
	Poor gastric/GI motility	Encourage ambulation; consider promotility agent.
	Medications, especially narcotics and anticholinergics	Use lowest effective dose of medication and transition to an alternative medication with fewer constipating effects, if possible.
Metabolic Complications		
Hyperglycemia, glycosuria (can lead to dehydration, coma, or death)	Stress response; diabetes mellitus	Monitor finger-stick glucose every 6 hours, use sliding scale insulin plus appropriate routine insulin (eg, insulin drip in critically ill).
	High-carbohydrate formula	Change formula.
	Drug therapy (steroids)	Monitor intake and output accurately.
Excess CO_2 production (high RQ)	High percentage of carbohydrate calories or excess calories from any source	Reduce total calories to avoid overfeeding; consider formula with higher fat calories.
Hyponatremia	Dilutional (fluid excess, SIADH); inadequate sodium intake; excess GI losses	Use full-strength formula or change to 1.5–2 kcal/mL formula; add salt to tube feeding (1 tsp–2 g Na—90 mEq); use diuretics if appropriate; replace GI losses.
Hypernatremia	Inadequate free-water intake	Use 1 kcal/mL formula; monitor intake and output accurately; temperature and weight daily; increase flush volume.
	Excess water losses (diabetes insipidus, osmotic diuresis from hyperglycemia, fever)	Correct hyperglycemia and the cause of fever or diabetes insipidus.

Complication	Cause/Contributing Factor	Treatment/Prevention
Hypokalemia	Medications (diuretics, antipseudomonal penicillins, amphotericin B)	Monitor serum potassium; give PO or IV potassium replacement PRN.
	Intracellular or extracellular shifts (insulin therapy, acidosis)	Correct underlying problem.
	Excess GI losses (NG suction, small-bowel fistula, diarrhea)	Routinely provide potassium in replacement fluid.
Hyperkalemia	Potassium-sparing medications (triamterene, amiloride, spironolactone, ACE inhibitors); potassium-containing medications (penicillin G potassium)	Monitor serum potassium; change to medications without potassium-sparing effect or without potassium salts.
	Renal failure	Monitor renal function; change to formula with lower potassium content.
Hypercoagulability	Warfarin antagonism owing to formula	Hold formula 1 hour before and after warfarin dose; monitor coagulation status; check vitamin K content and change to lower vitamin K, if appropriate (most EN formulas are not high in vitamin K).

ACE, angiotensin-converting enzyme; EN, enteral nutrition; GI, gastrointestinal; IV, intravenous; NG, nasogastric; NPO, nothing by mouth; PO, oral; PRN, as needed; RQ, respiratory quotient; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Mechanical Complications

The major mechanical complications are EAD occlusion and aspiration. Mechanical complications often can be avoided with good nursing technique and careful observation of feeding tolerance. Adequate flushing is essential to prevent EAD occlusion. Flushing with 30 mL of water every 4 hours during continuous feeding or before and after intermittent feedings is recommended.[21] Flushing must also occur before and after medication administration and after withdrawal of gastric contents. T.L.'s EAD should be flushed using these guidelines. Frequent assessment of tube placement by auscultation and location of markings on the EAD is important to prevent pulmonary aspiration of the formula secondary to displacement of the tube into the esophagus or pharynx. Tube placement should be evaluated every 4 to 6 hours with continuous feeding, or before each intermittent or bolus feeding.[3,21,22]

Withdrawal of gastric contents through a gastric tube using a syringe allows evaluation of volume in the stomach (gastric residual volume [GRV]). The reliability of GRV measurements has been questioned, and data for effectiveness as a monitor for aspiration risk are conflicting.[21,22] In combination with other parameters, such as vomiting, sedation, sepsis, and use of vasopressor agents, high GRVs may correlate with worse patient outcomes. Conversely, measurement of GRVs is associated with increased risk of EAD occlusion and reduced EN delivery because of inappropriate stopping of EN. Routine GRV measurement is no longer performed in many settings, including in ICUs; however, it may be appropriate in conjunction with other indicators of EN intolerance for some patients based on risk versus benefit.

When GRV is used, EN should not be held unless residuals are somewhere from 250 to 500 mL per CCP guidelines, or >500 mL per SCCM-ASPEN Critical Care guidelines.[4,9,21] A recent systematic review found no increase in GI complications with GRVs of 500 mL compared to that of 250 mL, but nutrient delivery was better using 500 mL GRV.[44] Jejunal feeding tube placement should be considered when GRV is consistently >500 mL. In addition, use of a

promotility agent, preferably metoclopramide (10 mg IV four times daily), should be considered when GRV is >250 mL after a second check.[4,9,21] These agents may improve feeding tolerance and formula delivery, and the risk of aspiration may be decreased, although the benefit of these agents has been questioned. If the feeding is held because of a high GRV, hourly evaluation of the GRV is recommended until the volume is <200 to 250 mL, and the feeding is restarted. The fluid withdrawn for GRV assessment may be infused through the tube back into the stomach to minimize electrolyte imbalances; however, CCP guidelines suggest either discarding GRV or feeding back up to 250 mL may be acceptable.[9] Elevating the head of the bed to 30 to 45°, with 45° preferred in patients who are critically ill, during and after feedings also is recommended to reduce the risk of aspiration.[4,9,21,22] Methylene blue or blue food coloring should not be added to the formula to evaluate reflux or aspiration of formula because of reports of mortality associated with this practice.[4,21,22] The use of glucose oxidase test strips to detect the presence of enteral formula in tracheobronchial secretions lacks sensitivity and specificity, and the results have not been shown to correlate with aspiration; thus, it is not a recommended practice.[22] The small bowel does not serve as a reservoir for residuals; therefore, GRV should not be checked through EADs placed in the postpyloric region, such as T.L.'s jejunal feeding tube.

Metabolic Complications

Major metabolic complications of EN include hyperglycemia, electrolyte abnormalities, and fluid imbalance. Although rigorous studies evaluating monitoring frequency are lacking, regular biochemical determinations similar to those used for PN are recommended to identify and correct metabolic abnormalities before severe abnormalities occur. Baseline values for serum glucose, SCr, BUN, and electrolytes should be available to guide selection of the enteral formula. The few baseline laboratory results available for T.L.

may be adequate as a baseline, but additional laboratory parameters will be necessary as part of the monitoring regimen once EN starts.

Capillary glucose measurements every 6 hours or an insulin protocol is recommended before EN starts in patients with diabetes or hyperglycemia or if hyperglycemia is anticipated. Given T.L.'s history of diabetes and a baseline glucose >200 mg/dL, diligent monitoring and treatment of her hyperglycemia is warranted even before EN starts. T.L. will require long-term glucose monitoring; however, routine glucose monitoring in patients who are not diabetic can be stopped once a stable euglycemic state is established with EN at the goal volume and infusion regimen.

A basic metabolic panel ([BMP]; serum glucose, sodium, potassium, chloride, bicarbonate, calcium, BUN, and SCr) is generally checked daily after feeding starts in critically ill patients and those at risk for electrolyte abnormalities or renal dysfunction. More stable patients may have serum glucose and electrolytes (sodium, potassium, chloride, bicarbonate) monitored rather than a BMP. During the first week of EN, whether initiated in the hospital or alternate site (SNF or at home), a BMP, phosphorus, and magnesium should be monitored a minimum of two to three times weekly in patients with weight loss; once or twice weekly may be adequate if there is no weight loss. Monitoring frequency can be reduced once tolerance to tube feeding is established and there are no metabolic abnormalities. Daily BMP for a minimum of 4 to 5 days is probably best for T.L. considering her recent dehydration. Daily phosphorus and magnesium also should be considered for a few days in T.L. because of her significant weight loss and risk of refeeding syndrome (see Chapter 38, Adult Parenteral Nutrition, for a more detailed discussion of refeeding syndrome). Despite being obese, T.L. is at risk for electrolyte abnormalities associated with refeeding syndrome.[15] Failure to monitor T.L. and replace electrolytes as necessary could result in serious electrolyte abnormalities. Once T.L.'s BMP, phosphorus, and magnesium are stable, the frequency of monitoring could be reduced to once or twice weekly. Critically ill patients generally require daily or every other day monitoring while in the ICU. For patients receiving long-

term EN, the frequency of laboratory monitoring gradually is decreased. Laboratory monitoring should be done once or twice yearly in stable patients without significant medical problems. Patients who have medical problems that can affect nutrient, electrolyte, or trace element requirements or tolerances should be monitored as appropriate to the medical condition.

Weight and fluid status are important parameters to monitor throughout EN therapy, especially in patients with unusual fluid or nutrient losses, an inability to recognize thirst, or inability to voluntarily adjust their oral fluid intake. For hospitalized patients, weight is primarily a reflection of fluid status, and total fluid can typically be adjusted by the number of times the feeding tube is flushed daily and the volume of each flush. In long-term patients, fluid is an important parameter for adequacy of caloric intake. Consistent increases or decreases from the required enteral formula volume can have significant effects on weight. For example, a weight loss of 12.5 pounds (5.67 kg) over the course of a year can be expected if the daily intake of a 1-kcal/mL formula is <120 mL required. Changing caloric density of the formula may be a potential option to help manage fluid when altering the number or volume of flushes is not adequate for fluid control. For patients with a stable fluid status, the week-to-week weight change can be used as an indicator of appropriate caloric intake. An upward trend in weight (eg, ≥3 consecutive weeks with an increase) may indicate a need for fewer calories unless weight gain is a goal. A downward trend may indicate a need to increase caloric intake, unless weight loss is desired. A plan that includes gradual weight loss is appropriate for T.L. based on her obesity.

Nursing protocols for patients receiving EN should include monitoring of respiratory status. Coughing or respiratory distress may be indications of aspiration or other developing respiratory problems. Vital signs also may provide clues to aspiration or other problems, such as dehydration, fluid overload, or infection.

In addition to monitoring for complications, routine monitoring for response to EN and changes in nutritional status is necessary for patients who are receiving EN for both short term and long term.

Chapter 35, Basic Nutrition and Patient Assessment, discusses parameters used for nutrition assessment and ongoing monitoring of nutritional status.

Gastrointestinal Complications

Assessment of GI symptoms is important for determining EN tolerance because GI complications are frequently associated with tube feeding. Abdominal distension and bloating should be evaluated at least every 8 hours while T.L. is hospitalized. Abdominal distension may be an indication of accumulating formula. Gas formation secondary to lactose intolerance or rapid increases in fiber intake, and poor gastric emptying secondary to a high-fat formula, medications, recent surgery, critical illness, or an underlying disease such as diabetes are among the conditions associated with distension. When considerable distension is present, the formula should be held temporarily, and the patient evaluated further to rule out a contraindication to EN.

Nausea, vomiting, abdominal cramping, diarrhea, and constipation are other GI symptoms monitored as indicators of EN tolerance. T.L. has some of these symptoms associated with her gastroparesis, and disease-associated symptoms should not be confused with feeding intolerance. Vomiting creates the most immediate concern because tube displacement and pulmonary aspiration can occur. Nausea and vomiting commonly occur with severe gastric distension, poor gastric emptying during gastric feeding, GI tract obstruction, or poor GI motility. The prevalence of diarrhea in patients receiving EN differs considerably depending on the definition used, but diarrhea is one of the most difficult problems for patients and caregivers to address.[21,22] Predisposing illnesses, including diabetes mellitus, GI infections, pancreatic insufficiency, and malabsorption syndromes, are more likely to cause diarrhea in patients receiving EN than does the formula itself.[3,21,22] Concurrent drug therapy is another major contributor to diarrhea in tube-fed patients; up to 25% of patients treated with antibiotics experience diarrhea.[22] T.L. has type 2

diabetes; however, at this time, diarrhea has not been reported as a problem.

Formula-related GI infections could occur from contamination of an opened can or package. Sources of contamination include the water used for reconstitution or dilution, transfer to the delivery bag, formula kept in the delivery bag for a prolonged period, and poorly cleaned feeding bags or administration sets. Water used to flush the tube can also be a source of contamination; therefore, sterile water is recommended as the flush solution for patients who are immunocompromised.[21] Closed enteral feeding systems using ready-to-hang bags of formula decrease contamination by reducing manipulation of the bag and formula, and are commonly used in the hospital setting.

Bolus feeding into the jejunum can lead to diarrhea and abdominal cramping, as well as nausea and vomiting. Because T.L. is being fed into the jejunum, she should remain on a continuous infusion protocol. Initiation of EN with a hypertonic formula, a rapid rate of infusion or a large volume, and use of formula at refrigerator temperature are other factors often cited as causing GI symptoms. Although controlled studies have not supported these factors as significant contributors to GI intolerance, subjective evidence suggests they are important. Constipation is most likely to occur with long-term tube feeding in nonambulatory patients. Inadequate fluid intake and lack of fiber may be factors associated with constipation. Diabetic EN formulas contain fiber. However, if the decision is to use a very high-protein formula rather than a diabetic formula for T.L., a fiber-containing formula would be reasonable to use based on her known history.

MEDICATIONS AND NUTRITION BY ENTERAL ACCESS DEVICE

Patients receiving EN often receive medications through the same EAD. Adverse effects caused by changes in pharmaceutical dosage forms, and alteration of medication pharmacokinetics and pharmacodynamics are among the potential problems, as is EAD occlusion.[16,45–48] Interactions related to pharmacologic or physiologic effects of medications or enteral nutrients also may occur. For this reason, oral medication administration should be considered unless a strict NPO status is required. T.L. has severe gastroparesis, a diagnosis not requiring a strict NPO status; however, the medical team is concerned that medications administered by mouth may have erratic absorption and poor efficacy because of delayed gastric emptying. Medications are ordered to be administered through T.L.'s EAD.

Case 37-4, Question 3: T.L. has been receiving EN for 5 days and has been at goal rate for 2 days. Laboratory evaluation today shows the following:

Sodium, 137 mEq/L
Potassium, 2.8 mEq/L (decreased from 3.7 mEq/L yesterday, 4.1 mEq/L the previous day, and 4.8 mEq/L when tube feeding started)
Chloride, 97 mEq/L
Calcium, 7.8 mg/dL
Magnesium, 1.3 mEq/L (decreased from 2.5 mEq/L 2 days ago)
Phosphorus, 2.5 mg/dL (decreased from 4.7 mg/dL 2 days ago)
Albumin, 2.4 g/dL

Micro-K® (10 mEq KCl/capsule) has been ordered as five capsules via feeding tube along with calcium carbonate (260-mg elemental calcium/tablet) as two tablets twice daily via feeding tube. Orders were also placed in the chart for warfarin. She was placed on a heparin drip yesterday for a newly diagnosed deep vein thrombosis (DVT) in her left leg, despite prophylactic heparin therapy since admission. Home medications are to be restarted, including enteric-coated aspirin, 81 mg daily; famotidine tablet, 20 mg twice daily; simvastatin tablet, 20 mg daily; metoprolol succinate tablet, 95 mg daily; and verapamil capsule, 240 mg daily. How should T.L.'s medications be administered when she is receiving EN?

Medication Selection

Solid dosage forms are a challenge to administer by EAD. Crushing a medication and mixing the powder in water results in an altered pharmaceutical dosage form, and this may affect its efficacy or patient tolerance. Liquid dosage forms are generally recommended for administration through an EAD, but they are not without problems, and a liquid dosage form may not always be the best choice. For example, liquid dosages may contain sorbitol, which is used as a sweetening excipient but is also an approved laxative. Liquids should be diluted at a minimum of 1:1 with water before administration to avoid coating the tube interior. High-viscosity liquids, such as suspensions, should be diluted 3:1 with water, and up to 10:1 if hyperosmolar.[16,45] Pharmaceutical syrups with a pH of ≤4 must be used with caution because immediate clumping and tackiness of formulas mixed with the syrups have been reported.[45] For medications not available in liquid form, a therapeutically equivalent medication in a liquid form can be considered. Extemporaneous preparation of a liquid also may be considered, but can increase cost significantly. Medications in a soft gelatin capsule are best avoided for administration through an EAD. If there is no alternative, the capsule can potentially be dissolved in warm water, but dissolution is slow and must be complete to avoid EAD occlusion. The safety and efficacy of simple compressed tablets are typically not affected by crushing and dissolving in water immediately before use; however, this is an off-label use of the medication.[16] The U.S. Food and Drug Administration (FDA) does not require data on EAD delivery of medications, nor the effects of enteral formula on a medication before drug approval. Simple compressed tablets can be crushed to a fine powder, then dissolved or suspended in water for administration. Powder in hard gelatin capsules can be poured into a container (eg, medicine cup, capped EAD-compatible syringe), then diluted with water, and mixed thoroughly before administration through an EAD. Failure to adequately suspend or thoroughly dissolve any of these dosage forms in water before administration can result in EAD occlusion. Dispersible tablets can be placed into a capped EAD-compatible syringe and dilutant (usually purified water) added to allow dispersion before the medication is administered from

the syringe into the EAD. Some medications appear to be particularly troublesome for administration through an EAD. Calcium salts, iron salts, lansoprazole, omeprazole, multivitamins, pentoxifylline, potassium chloride, phenytoin, protein supplements, sucralfate, and zinc salts were identified by nurses as the products most frequently contributing to EAD occlusion.[46] T.L. has both calcium and potassium ordered today.

Calcium carbonate is a simple compressed tablet that can be crushed, suspended in 30 mL of water, and administered through the EAD. Risk of occlusion from an inadequately crushed tablet may be decreased by use of calcium carbonate suspension (500-mg calcium/5 mL), if available. Administration of either crushed and suspended tablets or commercial suspension requires flushing the EAD with 15 to 30 mL of water before and after medication administration.[21] Diluting the suspension at least 1:1 with water, preferably 3:1, and flushing with 50 to 150 mL may be advisable because suspensions may otherwise coat the tube. The appropriateness of calcium supplementation should be questioned, however, because T.L.'s serum calcium concentration is within normal limits after correction for her low serum albumin concentration; an ionized calcium concentration could be considered if hypocalcemia is truly a concern. Administering any medication via the EAD may occlude the tube; therefore, administering an unneeded medication through the EAD is an unwarranted risk. For calcium, and for electrolytes in general, only oral and IV dosage forms are available, so the easiest and most cost-effective route is an oral dosage form via EAD if T.L. cannot take oral medications by mouth.

Potassium supplementation is ordered because of T.L.'s low serum potassium. Potassium should have been considered yesterday because the serum level has been decreasing since tube feeding began. The selected potassium supplement is inappropriate for administration by EAD because Micro-K® (KV Pharmaceutical for Ther-Rx Corporation., St. Louis, MO) is a slow-release product. Crushing any type of slow-release or sustained-release product destroys slow-release mechanisms, resulting in the immediate

release of several hours' worth of the medication at one time. An exaggerated therapeutic response may be seen initially, followed by a loss of response part way through the dosing interval. Deaths have occurred when sustained-release or long-acting products are crushed before administration; therefore, these dosage forms should not be crushed.[49] Instead, an immediate-release dosage form should be used, with appropriate adjustment of dose and dosing interval, or an alternate administration route (eg, IV, suppository, transdermal patch) may be available. Potassium chloride powder for solution (three packets with 15 mEq KCl/packet) or liquid (10% KCl 35 mL, 15% KCl 25 mL, or 20% KCl 15–20 mL) should be ordered rather than the slow-release product. Dividing the potassium dose into two or three smaller doses and diluting each dose with 60 mL of water may be better tolerated. Giving 50 mEq of potassium as a single dose may cause nausea, vomiting, abdominal discomfort, or diarrhea. These symptoms might be mistaken as intolerance to EN, resulting in the tube feeding being stopped temporarily. The larger fluid volume for administration also may help reduce the GI irritation associated with potassium doses.

Potassium supplementation could also be partially accomplished by changing part of the potassium ordered to potassium phosphate, which is available as a 250-mg capsule that provides 8.1 mmol of phosphate and 14.2 mEq of potassium. T.L. shows signs of refeeding syndrome, with phosphorus and magnesium slightly less than the normal range and having decreased significantly during the past 2 days.[15] Supplements should be started today so that smaller daily quantities can be used before electrolytes are critically low. This may decrease the risk of diarrhea and GI upset caused by the administration of oral phosphate or magnesium. Contents of each potassium phosphate capsule are designed to be dissolved in 75 mL of water for administration, so dissolution is not a concern. One potassium phosphate capsule twice a day plus KCl liquid to provide 20 mEq potassium is therapeutically the same potassium dose as is ordered currently. The liquid KCl dose should be separated from the potassium phosphate to minimize GI effects.

Magnesium supplementation could be accomplished with a magnesium oxide tablet (400 or 500 mg) administered two to four times daily. These are simple compressed tablets that can be crushed and suspended for administration via EAD. An alternative would be magnesium hydroxide suspension 5 mL two to four times daily. Magnesium doses are distributed through the day to reduce the risk of diarrhea. The EAD must be flushed adequately before and after each dose of electrolyte replacement. The flush volume should be a minimum of 15 mL, although 30 mL or more after the magnesium dose may be better to ensure the electrolyte preparation is out of the tube. The volume of other tube flushes can be adjusted to limit the total fluid intake to the estimated requirements. It can be difficult to provide large quantities of potassium, phosphate, and magnesium via EAD secondary to the GI intolerance they cause. Therefore, IV electrolyte replacement may be necessary if intracellular depletion is extensive and T.L. does not tolerate oral electrolyte replacement.

Famotidine is a simple compressed tablet that can be crushed. However, both the verapamil and metoprolol dosage forms ordered for T.L. contain multiple doses intended to be slowly released. The once-daily dosing schedule helps identify these two medications as slow-release products, and, for metoprolol, the succinate salt is also a clue because this is different from other dosage forms of metoprolol. Both verapamil and metoprolol should be changed to immediate-release dosage forms if T.L. cannot take them by mouth. The dose and frequency of dosing will need to be adjusted to reflect the immediate-release dosage form.

Enteric-coated tablets are designed to release medication in the small bowel because the medication is either acid labile or irritates the stomach. Protection for the medication or stomach is lost when enteric-coated tablets are crushed and delivered via EAD into the stomach, resulting in decreased efficacy of the medication or increased gastric irritation. When an irritating medication must be given by tube into the stomach, diluting the medication in at least 60 mL of water is recommended.[45] T.L. has enteric-coated aspirin ordered for administration into a jejunal EAD. The enteric coating is

designed to dissolve in the small bowel, and could be dissolved with bicarbonate solution before administration into the small bowel. However, it would be better to use a noncoated tablet for his aspirin dose. If enteric-coated beads, such as those found in several proton-pump inhibitor dosage forms, are to be administered through an EAD, use of an acidic liquid (eg, fruit juice) helps prevent the enteric coating from becoming sticky and adhering to the inside of the tube. This should only be considered for a large-bore EAD, such as a gastrostomy, or the beads will occlude the tube. Film-coated tablets may also cause problems when crushed because the coating does not crush well and becomes sticky in water; however, thinly coated products may crush and disperse in water. T.L.'s simvastatin has a film coating and may be a problem to crush and administer through her EAD.

Administering buccal or sublingual dosage forms via EAD may result in altered absorption or destruction of the medication by stomach acid. These dosage forms are not intended to be swallowed; thus, a conscious patient who is unable to swallow medications may still be able to use a buccal or sublingual product as intended. If not, therapeutically equivalent medications (eg, isosorbide dinitrate rather than sublingual nitroglycerin) or an alternate route of administration (eg, nitroglycerin ointment or transdermal system rather than sublingual nitroglycerin) should be used. A listing of medications that should not be crushed is available at http://www.ismp.org/recommendations/do-not-crush.[50] Carcinogens, teratogens, or cytotoxic agents that should not be crushed are included in the list.

Pharmacokinetic parameters can be altered when medications are administered by EAD. T.L. has a jejunal tube, and delivering medication into the jejunum could affect bioavailability, although few studies address this issue. Medications taken orally are delivered to the stomach, where dissolution typically occurs for most dosage forms and hydrolysis of some medications may occur. Delivery into the small bowel may alter these processes, thereby affecting bioavailability. For instance, recovery of digoxin from intrajejunal dosing is higher than it is with oral administration, primarily because

of reduced intragastric hydrolysis.[45] Bioavailability of medications also can be affected by the presence of enteral formula in the GI tract. Medications affected by the presence of food are expected to be affected by the presence of formula; however, meal consistency (eg, liquid enteral formula versus solid meal) may alter medication effects, as can meal composition (eg, protein content, nutrient sources).[16] Generally, it is assumed that food effects apply to EN, although studies are seldom available. For example, it is assumed that administration of tetracycline-class medications with formula present will reduce bioavailability because of interactions with divalent cations. A similar interaction is expected between ciprofloxacin and enteral formula, although some evidence suggests that a mechanism other than binding with divalent cations is responsible for reduced ciprofloxacin concentrations with enteral feeding.[45] Numerous medications have been reported to be potentially troublesome when administered with EN; several are listed in **Table 37-6**.[16,45,46] The mechanism of such troubles/interactions are often poorly understood, but can include the EAD (binding of drug with the EAD), the enteral formula (chelation or complexation of drug with formula components such as divalent cations), or drug characteristics (solubility, pH). Without a clear understanding of the mechanism of interaction, various and sometimes conflicting methods of managing the interactions may be reported. The interaction of phenytoin and warfarin with EN is described in further detail in the following paragraphs.

Table 37-6

Examples of Drugs Frequently Reported to Interact With Enteral Nutrition

Drug[a,b]	Potential Mechanism(s) of Interaction With EN	Recommendations Related to EN[c,d]

Drug[a,b]	Potential Mechanism(s) of Interaction With EN	Recommendations Related to EN[c,d]
Carbamazepine	Slow and variable GI absorption owing to solubility issues without EN; better absorption expected with food and slower gastric emptying (allows more time for dissolution). Jejunal administration may result in poorer absorption, likely related to solubility issues in the higher pH of the small intestine.	Data currently available do not support holding EN before or after drug administration. Suspension must be diluted a minimum of 1:1, although 3:1 is preferable.
Dolutegravir	Chelation or complexation with cations in EN or in water used for dilution	Dilute with mineral-free water. Hold EN for 2 hours before and after administration. Handle as a hazardous drug.

Drug[a,b]	Potential Mechanism(s) of Interaction With EN	Recommendations Related to EN[c,d]
Fluoroquinolones	Unclear if chelation or complexation with cations in EN is the primary reason for decreased drug concentrations. Interaction may not be class related, but, rather, depend upon individual drug hydrophilicity. Reduced bioavailability of ciprofloxacin and norfloxacin appears to be most significant with EN, followed by moderate reduction for levofloxacin, and slight reduction with ofloxacin. Bioavailability of gatifloxacin and moxifloxacin does not appear to be reduced in the presence of EN.	Data supporting holding of EN is limited. Holding EN for a minimum of 1 hour before and 2 hours after norfloxacin and ciprofloxacin does appear to minimize effects on bioavailability; some experts suggest holding EN for 2 hours both before and after drug administration. Data for holding EN for levofloxacin is conflicting; consider holding EN the same as for ciprofloxacin given moderate reduction in bioavailability with EN. Current data do not support holding EN for gatifloxacin or moxifloxacin. Ciprofloxacin suspension labeling states “Should not be administered through feeding or NG (nasogastric) tubes.”
Isoniazid	Isoniazid should be taken on an empty stomach (at least 1 hour before or 2 hours after a meal) to avoid decreased drug concentrations.	Limited data for EN; however, should consider holding EN for a minimum of 30 minutes before and 1 hour after drug administration. Based on limited data with other drugs, continuous tube feeding has effects on drug absorption similar to the nonfed state; thus, it may be possible to hold drug administration for a shorter time than with food to achieve the “empty stomach” effect. With bolus EN, it may be preferable to follow recommendations of no feedings for 1 hour before and 2 hours after drug administration.

Drug[a,b]	Potential Mechanism(s) of Interaction With EN	Recommendations Related to EN[c,d]
Levodopa	Protein content of formula may contribute to reduced drug efficacy/bioavailability owing to amino acid transport competition.	Hold EN for 2 hours before and after drug administration. When feasible, consider cyclic EN with formula administration overnight and drug administration during waking hours when therapeutic effects of the drug are most necessary.
Levothyroxine	Dissolution of tablets is poor. Drug may bind/adsorb to EAD. Different EAD materials (silicon, PVC, polyurethane) and drug exposure time (length and size of tube) could contribute to conflicting study results if binding/adsorption occurs.	Monitor for signs/symptoms of hypothyroidism and monitor thyroid stimulating hormone (sensitive thyrotropin test) concentration after starting or stopping EN therapy.

Drug[a,b]	Potential Mechanism(s) of Interaction With EN	Recommendations Related to EN[c,d]
Phenytoin	Drug has variable absorption because of solubility issues without EN. Proposed mechanisms of interaction: (1) pH-associated issues, which include: • dosage form issues (suspension, chewable tablets, capsule, IV formulation) • chemical form (phenytoin acid vs phenytoin sodium) • solubility (2) phenytoin binding to an EN component (3) phenytoin binding to the tubing/EAD	Data currently available do not support withholding EN around the phenytoin dose, although holding EN for an hour or more (commonly 2 hours) before and after phenytoin is still a common practice. Holding EN for 2 hours or more before and after the phenytoin dose does not reliably improve phenytoin concentrations. Suspension must be diluted a minimum of 1:1, although 3:1 is preferable. Therapeutic drug monitoring should be more frequent than without EN administration.
Voriconazole	Take on an empty stomach (at least 1 hour before or 2 hours after a meal) to reduce the risk of decreased drug concentrations. Maximum serum concentration and area under the curve are significantly reduced with high-fat meals.	Hold EN for a minimum of 1 hour before and after drug administration. Carefully weigh risk vs benefit of high-fat EN formulas such as pulmonary formulas and diabetic formulas.

Drug[a,b]	Potential Mechanism(s) of Interaction With EN	Recommendations Related to EN[c,d]
Warfarin	Several mechanisms have been proposed: (1) reversal of warfarin anticoagulation by vitamin K in EN (2) physicochemical interaction from binding or complexation of drug with a macromolecular component of EN, likely protein (3) binding/adsorption of drug to the EAD, particularly polyurethane feeding tubes	Data do not support vitamin K content of EN as a contributor to warfarin failure, or vitamin K restriction as a method to improve warfarin effect. Hold EN for at least 1 hour before and after drug administration. Limit exposure time to the EAD by diluting the drug in a small volume and administering rapidly, followed quickly by tube flushing. Monitor therapeutic response with INR when EN is started, stopped, or changed significantly.

EAD, enteral access device; EN, enteral nutrition; GI, gastrointestinal; INR international normalized ratio; IV, intravenous; PVC, polyvinylchloride.

[a]This is not an exhaustive list of drugs interacting with enteral nutrition (EN), but represents interactions more commonly reported in the literature. Caution is advised for any drug known to interact with cations such as calcium, magnesium, iron, zinc, selenium, and aluminum. Consider that effects of EN may differ from those of food, although effects with food may provide some guidance.

[b]When feasible, therapeutic alternatives should be considered. When the problematic drug is not changed, frequent monitoring for clinical signs/symptoms related to altered drug efficacy should occur when enteral nutrition (EN) is started, stopped, or changed. More frequent therapeutic drug monitoring should occur where feasible.

[c]Recommendations are in addition to the general recommendations for drug administration via enteral access device (EAD), including drug dilution and tube flushing (minimum of 15–30 mL of water before and after drug administration; 5–15 mL between drugs).

[d]When recommendations include holding enteral nutrition (EN) before or after the drug, it is imperative that EN administration directions account for the time EN is held and ensure the prescribed volume of EN is delivered. Volume-based protocols should be considered.

Phenytoin is troublesome to manage in patients receiving EN, but erratic absorption occurs without EN administration. Among the various methods suggested for managing reduced phenytoin concentrations, stopping formula delivery for 1 to 2 hours before and after the phenytoin dose has been widely used. Stopping EN around the phenytoin dose increases the risk of inadequate nutrient delivery. Stopping EN is not supported by current data.[16] Adequate dilution and flushing before and after medication administration have also been advocated to reduce loss of the medication. Both of these actions are important and may improve phenytoin delivery. No method, however, clearly prevents low phenytoin concentrations; thus, monitoring of serum concentrations is important whenever EN is started or altered. Large-scale, controlled trials are needed to determine the most appropriate method for managing the phenytoin–EN interaction. When appropriate, changing to a therapeutic alternative to phenytoin avoids the interaction; however, carbamazepine has also been reported to be a problem with EN.

Warfarin can also be problematic to manage in patients receiving their medications via an EAD, and T.L. is to start warfarin for a newly diagnosed DVT. Reversal of warfarin anticoagulation by vitamin K is an important pharmacologic interaction. Although enteral formulas do contain vitamin K, the content of most enteral formulas is about the same as that found in a mixed diet. This amount is unlikely to interfere with anticoagulation, and the consistent vitamin K dose may improve maintenance of anticoagulation. Binding of warfarin to a macular molecular component of enteral formula (eg, protein) has been proposed to explain warfarin resistance with formulas containing low vitamin K content; others suggest that binding to the feeding tube itself may occur.[16,45] Stopping formula administration for an hour before and after warfarin administration appears to prevent this type of interaction. Flushing the EAD with at least 15 mL of water before and after warfarin administration, along with use of a small volume of water for dilution and rapid administration is also advisable.[16] Unfortunately, rigorous, randomized studies to provide evidence-based guidance for the management of this potential interaction are lacking. The risks, benefits, and cost of alternative

anticoagulation therapy should be evaluated if T.L. is not achieving anticoagulation goals within the expected warfarin dosage range.

Liquid dosage forms are often hypertonic. Diarrhea is a potential problem related to physiologic effects of hypertonic medications. Diluting hypertonic medications (eg, potassium chloride) with 30 to 60 mL of water before administration is usually adequate; however, the necessary volume to achieve a desired osmolality (eg, 300 mOsm/kg) can be calculated using medication osmolality, concentration, and dose.[16] Dividing the medication dose and separating doses by about 2 hours also decrease GI effects of hypertonic medications. In addition, selection of brands and dosage forms with minimal sorbitol can reduce the risk of diarrhea. Sorbitol is a nonabsorbed sugar alcohol found in many liquid dosage forms. Cumulative sorbitol doses >5 g can cause bloating and flatulence, whereas larger doses may act as a cathartic.[45]

Enteric Access Device Occlusion

Case 37-4, Question 4: T.L.'s EAD has occluded (clogged). What are the causes of EAD occlusion and how can occlusions be managed? What can be done to avoid occluding T.L.'s EAD in the future?

The incidence of EAD occlusion is 12.5% to 40%.[6,51] Pump malfunction, lack of periodic tube flushing, formula characteristics, and tube characteristics are non–medication-related factors affecting EAD occlusion. Important EAD characteristics include the inner diameter (bore size), tube material, and the arrangement and number of delivery holes (ports) at the distal end. The most important formula characteristic appears to be the protein source. In vitro studies suggest formulas with intact protein, particularly caseinates or soy, coagulate, and clump when exposed to an acidic pH, whereas formulas with hydrolyzed protein do not.[45]

Medication-related factors influencing EAD occlusion include the administration method, dosage form, pH, and viscosity. Medications must be crushed to a fine powder, mixed with water to form a smooth

slurry, and adequately diluted before administration. Medications admixed with formula have the greatest potential for occluding EADs owing to alteration of the texture, viscosity, or physical form of the medication or formula. Therefore, medications should not be admixed directly with formula. The enteral formula infusion should be stopped, and the EAD flushed with a minimum of 15-mL water before and after medication administration and with 15 mL between each medication.[21,45,51] Contact between medications and formula within the tube lumen should be limited to decrease the risk of occlusion. Each medication should be administered separately to reduce the risk of interactions.

When an EAD occludes, it must be replaced unless patency can be restored. Frequent EAD replacement disrupts nutrient delivery and increases patient discomfort as well as the cost of care. The initial treatment for EAD occlusion is to flush the tube with warm water using a large syringe, at least 20 mL but preferably 50 mL, to avoid generation of excessive pressure that could rupture the tube. When a specific cause for occlusion can be identified (eg, a specific medication) and physiochemical characteristics of the responsible product are known (eg, solubility, pH), it may be possible to select a more appropriate flush preparation than water. In most cases, however, use of an acidic or basic flush preparation could worsen the occlusion. Acidic liquids (eg, cranberry juice, diet soda, regular soda) may perpetuate or extend the occlusion, especially when coagulated proteins are the cause.[45,51] When water fails to restore patency, activated pancreatic enzymes may be effective. A product containing multiple enzymes, buffers, and antibacterial agents in a powder form (Clog Zapper™, Halyard Health, Inc. Alpharetta, GA) is commercially available. Alternatively, one crushed uncoated pancreatic enzyme tablet and one sodium bicarbonate tablet (325 mg) can be dissolved in 5 mL of warm water just before instillation into the occluded tube.[21,45,51] Several mechanical declogging devices are also commercially available.[51] Adherence to flush protocols and proper medication administration techniques are essential to maintain patency once tube patency is restored.

Transfer to Home on Enteral Nutrition

CASE 37-5

QUESTION 1: J.B., a 77-year-old male, was admitted 2 days ago from an SNF for evaluation after he fell. He receives intermittent feedings through his PEG. The volume is 1680 mL (seven cans) daily. J.B.'s history indicates he was hospitalized ~7 weeks ago with an ischemic stroke and was discharged to an SNF (see Case 37-2, Question 1, 7). J.B.'s tube-feeding volume has increased from 1440 mL on discharge, but the formula remains the same (1.06 kcal/mL, 0.044 g protein/mL, 15 g fiber/1000 kcal polymeric formula). His weight has increased 4.41 pounds (2 kg) since hospital discharge, and his overall status has improved. Bone fractures have been ruled out, and J.B. is able to participate in physical therapy (PT). The PT consult indicates J.B. is appropriate for outpatient PT after hospital discharge. The swallow study performed this morning indicates J.B. must continue NPO for at least another 4 months when the swallow study will be repeated. J.B.'s daughter has made arrangements for him to move in with her family. She is concerned about insurance coverage for the EN therapy and states that J.B. has Medicare insurance, including a Part D prescription plan.

Will Medicare cover EN?

Based on the PT assessment, J.B. is considered appropriate for discharge home, providing he will have some supervision and assistance available. Typically, a case manager or social worker is involved in arranging appropriate discharge facilities; however, the health care professional managing nutrition support in the hospital setting should facilitate the nutrition support portion of discharge, as necessary. The pharmacist should review the medication regimen to assure it is appropriate for administration through the EAD.

Strict guidelines exist for home EN coverage. Medicare Part B (not Part D) will cover 80% of the cost if criteria are met.[52] EN must be medically necessary to "maintain weight and strength commensurate with overall health status" and there must be a functional disability of the GI tract (eg, dysphagia, swallowing disorder) that is expected to be "permanent." The formula must be delivered by feeding tube (ie, not oral supplements) and must provide most of the patient's nutritional requirements (ie, not supplemental nutrition). Approval is on an individual basis, requires a physician's written order, and

sufficient documentation must be available to support the need for EN. Calories <20 kcal/kg/day or >35 kcal/kg/day require additional documentation. The duration of therapy must be ≥90 days to meet the test of permanence. J.B.'s therapy falls within these guidelines. In addition, the formula J.B. receives is in a category that does not require him to meet additional eligibility criteria related to the formula itself. Additional documentation would be needed to justify a pump if J.B. was receiving EN via pump.

Adult enteral formulas are divided into five categories for reimbursement purposes by Medicare Part B (**Table 37-7**). Formula manufacturers typically list the Medicare category on the product label. Most polymeric formulas containing intact (whole) protein and 1 to 1.2 kcal/mL are in category I. These products do not require documentation of medical necessity for the specific formula itself, but still require documentation of the need for EN. Clear documentation of medical need for formulas in specific categories (eg, categories III and IV) is required for their higher reimbursement rates. The company selected to provide home care services should review all necessary documentation and assist with J.B.'s transition to home EN therapy.

Table 37-7
Medicare Categories for Enteral Formulas

Category and Code[a]	Description	Examples from Abbott Laboratories, Abbott Park, IL	Examples from Nestle Health Sciences, Vevey, Switzerland
Category I B4150	Semisynthetic intact protein or protein isolates (general purpose formulas)	Jevity® 1.0 Cal, Osmolite® 1.2 Cal	Boost®, Isosource® HN, Nutren® 1.0 Fiber
Category II B4152	Intact protein or protein isolates; calorically dense (≥ 1.5 kcal/mL)	Ensure® Plus HN, Jevity® 1.5 Cal	Boost® Plus, Isosource® 1.5 Cal, Nutren® 2.0, Resource® 2.0
Category III[b] B4153	Hydrolyzed protein or amino acids	Perative®, Promote®, Vital® AF 1.2 Cal®	Peptamen® 1.5, Peptamen® AF
		Documentation that may provide justification for use: dumping syndrome, uncontrolled diarrhea, evidence of malabsorption on appropriate semisynthetic formulas (eg, isotonic, low long-chain fat content, lactose free) that resolves with an oligomeric formula or documentation of the disease process causing malabsorption	
Category IV[b] B4154	Defined formula for special metabolic need (ie, disease-specific formulas)	Glucerna® 1.0, Glucerna® 1.5, Impact®, Nepro® with CARBSTEADY, Oxepa®, Pulmocare®, Suplena® with CARBSTEADY	Boost® Glucose Control, Glytrol®, Novasource® Renal, Nutren® Pulmonary, NutriHep®, Renalcal®
		Documentation that may provide justification for use: evidence of inability to meet nutritional goals with category I or II products without compromising patient safety and documentation of the specific diagnosis for which a formula is intended	
Category V[b] B4155[c]	Modular components for protein, fat, carbohydrate, and individual amino acids	*Protein*: ProMod® *Amino Acids*: ARG, GLU: Juven®	*Protein:* Beneprotein® *Amino Acids*: ARG: Arginaid® GLU: Glutasolve® *Protein and Fat*: Benecalorie® *Fat*: MCT oil®, Microlipid®
		Documentation that may provide justification for use: inability to meet specific nutrient requirements (ie, protein, carbohydrate, or fat) with a commercially available formula	

ARG, arginine; GLU, glutamine; MCT, medium-chain triglyceride.

[a]Code refers to the Health Care Procedure Code System (HCPCS) billing code used by providers billing the Center for Medicare and Medicaid.

[b]Failure to provide adequate documentation of medical necessity for the specific formula will likely result in denial of claim or payment at the lower category I rate for Medicare Part B insurance coverage.

[c]There are several other suppliers of B4155 products in addition to Abbott and Nestle products given as examples here.

CASE 37-5, QUESTION 2: J.B.'s daughter asks about using blenderized food rather than his current enteral formula to feed her father through the PEG. Can a blenderized diet be used for patients with an EAD?

Blenderized, real-food diets are viewed by some as more natural than are commercial enteral formulas. Blenderized formulas containing real foods (eg, peaches, green beans, peas, carrots, tomato) are commercially available and may be covered by insurance when documentation supports the need for such a

specialized product.[53,54] Home-prepared products are not typically covered by insurance, and nutritional balance may be compromised unless a dietitian is working with the patient/family. The Oley Foundation, an education, advocacy, and networking organization for home nutrition support, provides information on home blenderized tube feeding.[54] An adequate-size EAD is required for these products. J.B. has been tolerating his current EN; therefore, it is unlikely that he would qualify for insurance coverage of a commercial blenderized formula.

CASE 37-6

Question 1: J.N., a 27-year-old male, was admitted to the hospital 70 days ago after a motor vehicle crash. He sustained multiple traumatic injuries and exhibited multiple complications requiring several exploratory laparotomies. He has been treated for multiple infections, including pneumonia, sepsis, and wound infection. Treatment for *Clostridium difficile* diarrhea was completed 3 weeks ago, and he has not had diarrhea since then. Lysis of adhesions, closure of an enterocutaneous fistula, and placement of a feeding jejunostomy tube (J tube) were done during the last laparotomy 9 days ago. Enteral feedings were started through his J tube 4 days ago at 50 mL/hour and advanced to the goal rate of 90 mL/hour within 24 hours. The EN lactose-free and fiber-free, 460 mOsm/kg, contains 15% of calories from a 50% MCT–50% long-chain triglycerides fat mix, and provides 35 kcal/kg/day and 1.6 g protein/kg/day, which is less than his protein goal. The product is ready to use in a closed-system bag. J.N. has received PN for nutrition during most of his hospitalization, and the PN rate was decreased as EN increased. J.N. now has diarrhea, which started ~12 hours after his EN was increased to goal rate.

What is the likely cause of diarrhea? What other information related to the EN regimen would be helpful to determine whether the EN should be stopped and the PN formulation restarted?

Evaluation of Tube-Feeding Intolerance

Diarrhea develops in 12% to 32% of hospitalized patients; and in up to 80% of high-risk patients, a point preference of 12.4% has been reported.[55] In patients receiving EN, 15% to 40% develop diarrhea, which is multifactorial. Factors associated with diarrhea, but not related to EN, include medications, partial small-bowel obstruction or

fecal impaction, bile salt malabsorption, intestinal atrophy, hypoalbuminemia, malnutrition, infections such as *C. difficile*, and underlying conditions affecting the GI tract.[4,22,45,55–57] Tube-feeding–related causes of diarrhea include high-fat content, lactose content, and bacterial contamination. Formula temperature, caloric density, osmolality, formula strength, lack of fiber content, and method of delivery have been associated with diarrhea, although these factors are not shown to affect diarrhea in some studies, making a cause-and-effect relationship unclear.[56]

J.N.'s hospitalization has been unusually long and complicated. Many factors could contribute to diarrhea; however, the diarrhea coincides relatively closely with initiation and advancement of tube feeding. He may have intestinal atrophy and impaired absorptive function because of his prolonged period without GI tract stimulation. He has had multiple surgeries, including GI surgeries, and may have reduced absorptive capacity, bile salt malabsorption, dumping syndrome, or reduced pancreatic enzyme availability related to his complications and surgeries. At least theoretically, an oligomeric formula would be better absorbed if any of these conditions exist. The SCCM-ASPEN Critical Care guidelines recommend a standard formulation for those not meeting guidelines for an immune-modulating product.[4] The CCP guidelines recommend considering use of a polymeric (intact nutrient) formula, although clinical outcomes do not appear to differ between polymeric and oligomeric formulas.[9] However, studies have not evaluated patients without use of the GI tract for weeks before EN initiation. Formula selection is often determined by physician preference and the calorie, protein, and fat content of formulas on the institution's formulary. Because J.N. had been >2 months without significant use of the GI tract, he was started on an oligomeric peptide formula.

The EN formula selected for J.N. is only slightly more than isotonic. Risk of diarrhea from fat malabsorption should be minimal with the low-fat content and MCT mix. Increasing EN to goal rate within 24 hours may have contributed to diarrhea. Based on consensus rather than evidence from well-designed studies, it may have been preferable to initiate feeding for J.N. at 10 to 40 mL/hour

and advance by 10 to 20 mL every 8 to 12 hours because he was critically ill and had not used his GI tract for >2 months.[3,15,22] The jejunum adapts slowly to changes in volume or concentration, and formula volume was increased <24 hours before diarrhea started. Also, an enteral infusion pump should be used to maintain consistent flow. Changing to a lower volume should decrease stool output within 24 hours if the volume change was responsible. If J.N. does not respond to decreasing formula volume, the formula may be held for 24 hours to assess whether diarrhea decreases or stops. Diarrhea related directly to EN usually is an osmotic diarrhea that stops within 24 hours of stopping the formula. A more objective approach than stopping the formula is to measure stool osmolality. Enteral formula–induced diarrhea is associated with a large osmotic gap, whereas secretory diarrhea (eg, infectious diarrhea) is associated with a low or negative osmotic gap.

The selected oligomeric formula is ready to use and in a closed-system bag; therefore, bacterial contamination from mixing technique is not of concern. Cleanliness during formula transfer to the delivery bag, the period of time the formula is in the bag, and methods of cleaning the delivery bag may contribute to bacterial contamination of formula. J.N. is receiving formula from a closed enteral system (ie, ready-to-hang formula-filled containers), and this virtually eliminates transfer-related contamination when proper technique is used. Any addition (eg, medication, carbohydrate, fat or protein module, MCT oil) to the prefilled container before hanging can contaminate the system, and guidelines (eg, hang time, set changes) for an open enteral system then apply. Even when administered separately from the formula, modular components are a potential contributor to diarrhea because of their osmolarity and potential contamination during preparation and administration. The selected formula does not meet J.N.’s protein requirement; therefore, a modular protein is needed to supplement the enteral formula. The nutrition plan includes addition of a modular protein component; however, on review of the medication administration record, this has not been started and is ordered as separate flushes (not added to the EN container).

Medications are a major contributor to diarrhea in tube-fed patients.[3,22,55] J.N. currently receives antibiotics and has for some time. However, the prevalence of diarrhea with antibiotic therapy is difficult to determine because of failure to report stool frequency and consistency as well as lack of a clear definition of diarrhea. *C. difficile* may have relapsed after his previous treatment. Stool specimens should be sent for culture and/or *C. difficile* toxin. Evaluation of J.N.'s medications may reveal medications associated with diarrhea (eg, sorbitol-containing products, antacids, oral magnesium, potassium chloride, phosphate supplements, H_2 receptor antagonists) for which therapeutic alternatives or different routes of administration could be considered.[16,45] High-osmolality liquid medications should be diluted before administration to reduce GI side effects.[21,45]

J.N.'s GI tract should continue to be used to the extent possible. EN appears to be better than is PN for maintaining the GI tract barrier and host immunologic function.[4,9] Both the CCP and SCCM-ASPEN Critical Care guidelines recommend use of EN over PN in critically ill patients whenever feasible.[4,9] Both guidelines also recognize the need for PN at some point when EN cannot meet the patient's nutritional requirements; however, neither guideline addresses patients with long-term, chronic critical illness such as J.N. The risk of sepsis increases without enteral stimulation of the GI tract. Whether this occurs through bacterial translocation, an unproved process in humans in which enteric bacteria or endotoxin crosses the GI mucosa into mesenteric lymph nodes and portal circulation, or through another mechanism is unclear. In addition, the GI tract serves an immune function, especially with respect to immunoglobulin (Ig)A secretion. Respiratory tract infections, such as pneumonia, may increase without proper stimulation of the GI tract, owing to less effective protection from IgA. Compared with PN, EN attenuates catabolism in highly stressed patients, although initiation of feedings soon after the stressing event may be required to obtain this response. Before a decision is made to stop J.N.'s EN, all possible causes of diarrhea should be investigated. Possible benefits

of improved fluid and electrolyte balance from stopping EN should be weighed against the potential benefits of reduced infections from continued use of the GI tract. Combined EN plus PN can also be considered, especially if J.N. tolerates partial EN but cannot advance to goal rate. Full PN should be provided if EN is stopped for more than 1 or 2 days.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Boullata JI. Enteral medication for the tube-fed patient: making this route safe and effective. *Nutr Clin Pract*. 2021;36:111–132. (16)

Boullata JI, Carrera AL, Harvey L, et al. ASPEN safe practices for enteral nutrition therapy. *JPEN J Parenter Enteral Nutr.* 2017;41(1):15–103. (21)

Canadian Clinical Practice Guidelines Committee. Highlights of the 2015 Canadian Clinical Practice Guidelines. Accessed January 1, 2021. https://criticalcarenutrition.com/resources/cpgs/past-guidelines/2015. (9)

McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159–211. (4)

Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017. (2, 3, 5, 6, 11, 14, 22, 25, 33, 36, 42, 45 52)

Key Websites

Abbott Nutrition. [Provides detailed information on Abbott Nutrition products, including enteral formulas, and links to other Abbott Nutrition websites for

healthcare professions.] https://criticalcarenutrition.com/resources/cpgs/past-guidelines/2015

American Society for Parenteral and Enteral Nutrition. http://www.nutritioncare.org; http://www.nutritioncare.org/guidelines_and_clinical_resources; http://www.nutritioncare.org/Clinical_Practice_Library/ to access content for:

- American Society for Parenteral and Enteral Nutrition. Blenderized tube feeding video series. 2020. Accessed January 10, 2021. https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Enteral_Nutrition_Resources/ (53)
- Boullata JI, Carrera AL, Harvey L, et al. ASPEN safe practices for enteral nutrition therapy. *JPEN J Parenter Enteral Nutr*. 2017;41(1): 15–103. (21)
- Jensen GL, Cederholm T, Correia MI, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. *JPEN J Parenter Enteral Nutr*. 2019;43(1): 32–40. (13)
- McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159–211. (4)
- McMahon MM, Nystrom E, Braunschweig C, et al. A.S.P.E.N. clinical guidelines: nutrition support of adult patients with hyperglycemia. *Nutr Clin Pract*. 2013;37910:23–36. (43)
- White J, Guenter P, Jensen G, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *J Acad Nutr Diet*. 2012;112:730–738 [jointly published: *JPEN J Parenter Enteral Nutr*. 2012;36:275–283]. (1)

Critical Care Nutrition. Systematic Reviews. https://criticalcarenutrition.com; https://criticalcarenutrition.com/resources/cpgs/past-guidelines/2015; https://criticalcarenutrition.com/systematic-reviews; https://www.criticalcarenutrition.com/resources/pepup to access content for:

- Canadian Clinical Practice Guidelines Committee. Highlights of the 2015 Canadian Clinical Practice Guidelines. Accessed January 1, 2021. https://criticalcarenutrition.com/resources/cpgs/past-guidelines/2015 (9)
- PEP uP Tools. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2019. Accessed January 11, 2021. https://www.criticalcarenutrition.com/resources/pepu. (23)
- Systematic Reviews. 5.3 Strategies to optimize delivery and minimize risks of EN: small bowel feeding vs. gastric. In. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. Accessed January 2, 2021. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/5.3%20Small%20Bowel_2018.pd. (7)
- Systematic Reviews. 4.3 Strategies for optimizing EN and minimizing risks of EN: whole protein vs. peptides. In. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit, 2018. Accessed December 29, 2020. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.3%20Protein%20%20Peptides_2018.pd. (12)
- Systematic Reviews. 4.5 Composition of enteral nutrition: strategies for optimizing EN and minimizing risks of EN: fibre. In. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. Accessed December 28, 2020. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.5%20Fibre_2018.pd. (20)
- Systematic Reviews. 4.1c Composition of enteral nutrition: glutamine. In. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.1c%20EN%20gln_2018.pd. (28)
- Systematic Reviews. 4.1a EN composition: diets supplemented with arginine and select other nutrients. In. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018.

https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.1a%20%20Arginine_2018.pd. (32)

- Systematic Reviews. 4.1 b.(ii) Composition of enteral nutrition: fish oil supplementation. In. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit. 2018. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.1b(ii)%20Fish%20Oils%20Alone_2018.pd. (35)
- Systematic Reviews. 4.1 b.(i) Composition of enteral nutrition: fish oils, borage oils and antioxidants. In. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit. 2018. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.1b(i)%20Fish%20Oils%20Borage%20Oils%20AOXs_2018.pd. (38)
- Systematic Reviews. 5.5 Strategies to optimize the delivery of EN: use of and threshold for gastric residual volumes. In. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit. 2018. Accesse. January 3, 2021. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/5.5%20GRVs_2018.pd. (42)

Global Enteral Device Supplier Association. Stay Connected. Enteral feeding connectors. http://www.StayConnected.org/enteral-enfit (24)

Institute for Safe Medication Practices. Oral dosage forms that should not be crushed. Accessed January 8, 2021. http://www.ismp.org/recommendations/do-not-crush (50)

Nestlé Health Science. [Provides detailed information on Nestlé Nutrition products, including enteral formulas, and other nutrition information for healthcare professions.] http://www.NestleHealthScience.us

COMPLETE REFERENCES CHAPTER 37 ADULT ENTERAL NUTRITION

1. White JV, Guenter P, Jensen G, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *J Acad Nutr Diet*.

2012;112:730–738. [jointly published: *JPEN J Parenter Enteral Nutr*. 2012;36:275–283].
2. JeVenn AK, Galang M, Hipskind P, et al. Malnutrition screening and assessment. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-20.
3. Doley J, Phillips W. Overview of enteral nutrition. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-21.
4. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159–211.
5. Krueger K, McClave SA, Martindale RG. Pancreatitis. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-40.
6. Fang JC, Kinikini M. Enteral access devices. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-23.
7. Systematic Reviews. 5.3 Strategies to optimize delivery and minimize risks of EN: small bowel feeding vs. gastric. In: *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. Accessed January 2, 2021. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/5.3%20Small%20Bowel_2018.pdf
8. Food and Nutrition Board, Institute of Medicine, National Academies. Dietary Reference Intakes (DRIs): summary tables. Accessed January 3, 2021. http://www.nationalacademies.org/hmd/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx
9. Canadian Clinical Practice Guidelines Committee. Highlights of the 2015 Canadian Clinical Practice Guidelines. Accessed January 1, 2021. https://criticalcarenutrition.com/resources/cpgs/past-guidelines/2015
10. Matthews DE. Protein and amino acids. In: Ross AC, ed. *Modern Nutrition in Health and Disease*. 11th ed. Lippincott Williams & Wilkins; 2014:e-1.
11. Young LS, Kim DW. Protein. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-16.
12. Systematic Reviews. 4.3 Strategies for optimizing EN and minimizing risks of EN: whole protein vs. peptides. In: *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit, 2018. Accessed December 29, 2020. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.3%20Protein%20%20Peptides_2018.pdf

13. Jensen GL, Cederholm T, Correia MI, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. *JPEN J Parenter Enteral Nutr*. 2019;43(1):32–40.
14. Zelig R, Famularo PJ, Szeto M. Nutrition support for older adults. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-48.
15. da Silva JSV, Seres DS, Sabino K, et al. ASPEN consensus recommendations for refeeding syndrome. *Nutr Clin Pract*. 2020;35(2):178–195.
16. Boullata JI. Enteral medication for the tube-fed patient: making this route safe and effective. *Nutr Clin Pract*. 2021;36:111–132.
17. Institute of Medicine. Dietary, functional, and total fiber. In: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. The National Academies Press; 2005. Accessed January 5, 2021. http://www.nap.edu/download/10490
18. Pepe C, Rollins CJ. Functional and meal replacement foods. In: Krinsky DL, ed. *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care*. 20th ed. American Pharmacists Association; 2021:459.
19. Willis HJ. Dietary fiber. In: Ross AC, ed. *Modern Nutrition in Health and Disease*. 11th ed. Lippincott Williams & Wilkins; 2014:e-3.
20. Systematic Reviews. 4.5 Composition of enteral nutrition: strategies for optimizing EN and minimizing risks of EN: fibre. In: *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. Accessed December 28, 2020. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.5%20Fibre_2018.pdf
21. Boullata JI, Carrera AL, Harvey L, et al. ASPEN safe practices for enteral nutrition therapy. *JPEN J Parenter Enteral Nutr*. 2017;41(1):15–103.
22. Malone AM, Seres D, Lord LM. Complications of enteral nutrition. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-24.
23. PEP uP tools. *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2019. Accessed January 11, 2021. https://www.criticalcarenutrition.com/resources/pepup
24. Global Enteral Device Supplier Association. Stay Connected. Enteral feeding connectors. Accessed January 11, 2021. http://www.StayConnected.org/enteral-enfit
25. Limketkai N, Hurt RT, Palmer LB. Short bowel syndrome. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-42.

26. Coeffier M, Dechelotte P. The role of glutamine in intensive care unit patients: mechanisms of action and clinical outcome. *Nutr Rev*. 2005;63:65–69.
27. van Zanten AR, Dhaliwal R, Garrel D, Heyland DK. Enteral glutamine supplementation in critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2015;19:294.
28. Systematic Reviews. 4.1c Composition of enteral nutrition: glutamine. In: *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.1c%20EN%20gln_2018.pdf
29. McCarthy MS, Martindale RG. Immunonutrition in critical illness: what is the role? *Nutr Clin Pract*. 2018;33(3):348–358.
30. Yu K, Zeng X, Wang G, et al. Immunonutrition vs standard nutrition for cancer patients: a systematic review and meta-analysis (Part 1). *JPEN J Parenter Enteral Nutr*. 2020;44:742–767.
31. Patel JJ, Miller KR, Rosenthal C, Rosenthal MD. When is it appropriate to use arginine in critical illness? *Nutr Clin Pract*. 2016;31(4):438–444.
32. Systematic Reviews. 4.1a EN composition: diets supplemented with arginine and select other nutrients. In: *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.1a%20%20Arginine_2018.pdf
33. Hise ME, Brown JC. Lipids. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-15.
34. Jones PJH, Rideout T. Lipids, sterols, and their metabolites. In: Ross AC, ed. *Modern Nutrition in Health and Disease*. 11th ed. Lippincott Williams & Wilkins; 2014:e-4.
35. Systematic Reviews. 4.1 b.(ii) Composition of enteral nutrition: fish oil supplementation. In: *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.1b(ii)%20Fish%20Oils%20Alone_2018.pdfM
36. Roberts S, Kirsch R. Enteral formulations. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-22.
37. Cai B, Zhu Y, Ma Yi, et al. Effect of supplementing a high-fat, low-carbohydrate enteral formula in COPD patients. *Nutrition*. 2003;19:229–232.
38. Systematic Reviews. 4.1 b.(i) Composition of enteral nutrition: fish oils, borage oils and antioxidants. In: *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/4.1b(i)%20Fish%20Oils%20Borage%20Oils%20AOXs_2018.pdf

39. Behrens S, Kozeniecki M, Knapp N, Martindale RG. Nutrition support during prone positioning: an old technique reawakened by COVID-19. *Nutr Clin Pract*. 2020;36(23):105–109.
40. U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Dietary Guidelines for Americans, 2020–2025*. 9th ed. Published December 2020. Accessed January 8, 2021. https://www.dietaryguidelines.gov
41. Ojo O, Weldon SM, Thompson T, Crockett R, Wang XH. The effect of diabetes-specific enteral nutrition formula on cardiometabolic parameters in patients with type 2 diabetes: a systematic review and meta–analysis of randomised controlled trials. *Nutrients*. 2019;11(8):1905.
42. Walker R, Tucker AM, Birtcher KK. Diabetes mellitus. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-46.
43. McMahon MM, Nystrom E, Braunschweig C, et al. A.S.P.E.N. clinical guidelines: nutrition support of adult patients with hyperglycemia. *Nutr Clin Pract*. 2013;37(1):23-36.
44. Systematic Reviews. 5.5 Strategies to optimize the delivery of EN: use of and threshold for gastric residual volumes. In: *Critical Care Nutrition* [Internet]. Clinical Evaluation Research Unit; 2018. Accessed January 3, 2021. https://www.criticalcarenutrition.com/docs/systematic_reviews_2018/5.5%20GRVs_2018.pdf
45. Verdell A, Rollins CJ. Drug-nutrient interactions. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. The American Society for Parenteral and Enteral Nutrition; 2017:e-29.
46. Williams NT. Medication administration through enteral feeding tubes. *Am J Health Syst Pharm*. 2008;65:2347–2357.
47. White R, Bradnam V. *Handbook of Drug Administration via Enteral Feeding Tubes*. Pharmaceutical Press; 2007.
48. Chan LN. Drug-nutrient interactions. *JPEN J Parenter Enteral Nutr*. 2013;37(4):450–459.
49. Schier JG, Howland MA, Hoffman RS, Nelson LS. Fatality from administration of labetalol and crushed extended-release nifedipine. *Ann Pharmacother*. 2003;37:1420–1423.
50. Institute for Safe Medication Practices. Oral dosage forms that should not be crushed. Accessed January 8, 2021. https://www.ismp.org/recommendations/do-not-crush
51. Fisher C, Blalock B. Clogged feeding tubes: a clinician's thorn. Nutrition issues in gastroenterology, series #127. Practical Gastroenterology. Published March 2014. Accessed January 10, 2021. https://www.ismp.org/recommendations/do-not-crush

52. Konrad D, Mitchell R, Hendrickson E. Home nutrition support. In: Mueller C, Lord LM, Marian M, et al., eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-51.
53. American Society for Parenteral and Enteral Nutrition. Blenderized tube feeding video series. 2020. Accessed January 10, 2021. https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Enteral_Nutrition_Resources/
54. Fessler TA. *Home Tube Feeding with Blenderized Foods*. The Oley Foundation; 2019. Accessed January 10, 2021. https://oley.org/page/TFTips_LandingPage
55. Polage CR, Solnick JV, Cohen SH. Nosocomial diarrhea: evaluation and treatment of causes other than Clostridium difficile. *Clin Infect Dis*. 2012;55(7):982–989.
56. Whelan K, Schneider SM. Mechanisms, prevention, and management of diarrhea in enteral nutrition. *Curr Opin Gastroenterol*. 2011;27:152–159.
57. Pitta MR, Campos FM, Monteiro AG, Cunha AGF, Porto JD, Gomes RR. Tutorial on diarrhea and enteral nutrition: a comprehensive step-by-step approach. *JPEN J Parenter Enteral Nutr*. 2019;43:1008–1019.

38

Adult Parenteral Nutrition

Susan L. Mayhew and Richard S. Nicholas

CORE PRINCIPLES		CHAPTER CASES
1	Parenteral nutrition (PN) is indicated in patients with a nonfunctioning gastrointestinal (GI) tract. Patients should be assessed for appropriate indications of the use of PN.	**Case 38-1 (Question 1)** **Case 38-2 (Question 1)**
2	Calories, protein, fluid, electrolytes, vitamins, and minerals are based on the patient's individual needs and are determined by baseline nutritional status, medical history, clinical presentation, and intravenous (IV) access.	**Case 38-1 (Questions 1–3, 5)** **Case 38-2 (Questions 2, 4)** **Case 38-3 (Questions 1, 4, 6, 9)**

CORE PRINCIPLES		CHAPTER CASES
3	Before PN is initiated, the practitioner must be aware of potential metabolic and respiratory complications, including refeeding syndrome, increased carbon dioxide production, and hyperglycemia. Appropriate fluid, macronutrient, and micronutrient adjustments to specialized nutrition support must be implemented to avoid or diminish the expected complications.	**Case 38-1 (Question 6)** **Case 38-2 (Question 3)** **Case 38-3 (Questions 2–4)** **Case 38-4 (Question 3)**
4	PN formulations are complex IV admixtures that require strict adherence to safe compounding practices.	**Case 38-1 (Question 4)** **Case 38-2 (Questions 5–8)** **Case 38-3 (Question 8)** **Case 38-4 (Question 7)**
5	Appropriate monitoring of the patient's vital signs, body weight, temperature, serum chemistries, hematologic indices, nutrition intake, and fluid intake and output is essential to determine the success of PN therapy and to make changes in therapy.	**Case 38-2 (Question 9)** **Case 38-3 (Question 7)** **Case 38-4 (Question 1)**
6	Fluid requirements, macronutrient selections, electrolyte quantities, and vitamin and mineral alterations may be warranted in patients presenting with hepatic or renal failure, short bowel syndrome, obesity, diabetes, pancreatitis, and respiratory failure.	**Case 38-3 (Questions 2, 4–7)** **Case 38-4 (Questions 2–4)**

CORE PRINCIPLES		CHAPTER CASES
7	Practitioners should be aware of the additional complications associated with home (or long-term) delivery of PN, including hepatobiliary complications, metabolic bone disease, and catheter-related complications.	**Case 38-4 (Questions 8, 9)**
8	Advancements in the delivery of home PN (HPN) have increased patients' acceptance and empowered engagement in self-care. An understanding of the patient's fluid and nutrient needs is essential for optimal delivery of HPN, to help ensure positive outcomes and the best quality of life for the patient.	**Case 38-2 (Question 6)** **Case 38-4 (Questions 5, 6)**

INTRODUCTION

Nutritional status directly affects recovery from illness or injury. Malnutrition may stem from acute or chronic illness, injury, or starvation. Regardless of its origin, malnutrition is associated with multiple complications, including poor wound healing, infection, prolonged hospital stays, and increased mortality.[1,2] A nutritional assessment should occur for all patients admitted to a hospital or diagnosed with a chronic disease (see Chapter 35, Basics of Nutrition and Patient Assessment). For patients identified as high risk, a nutrition care plan should be initiated.

The preferred method of providing nutritional support is through the gastrointestinal (GI) tract unless there is a contraindication to oral or enteral nutrition (EN). Absolute contraindications to feeding into

the GI tract include active GI bleed, bowel trauma, intestinal obstruction, and ischemic bowel with hemodynamic instability. Other conditions such as GI infection or inflammation, malabsorption, severe acute pancreatitis, or small bowel fistulas may hinder the ability to feed into the GI tract safely. If using the GI tract is not feasible, a patient may be classified as having intestinal failure and intravenous (IV) feeding may be warranted depending on the patient's nutritional status and disease severity. Parenteral nutrition (PN) is a sterile liquid nutrition formula administered IV that generally contains a combination of protein, carbohydrate, fat, electrolytes, vitamins, and trace elements. PN may be given to neonates, infants, children, and adults and can be specifically formulated to meet individual patient needs. Some patients require PN for a short period (1–3 weeks), whereas others may require home PN (HPN) for months, years, or even a lifetime.[3]

VASCULAR ACCESS

For centuries, clinicians attempted IV feeding using crude IV cannulas and nutritional substances ranging from olive oil to cow's milk. Unfortunately, historical attempts at using the vascular system for nutritional support were fraught with challenges. Clinicians were limited by the amount of calories administered, lack of reliable IV access, and risk of infection because of the lack of sterility.[4]

The advent of central venous catheters (CVCs) in the 1960s ushered in the contemporary practice of IV feeding—PN therapy. CVCs allow the administration of concentrated nutritional admixtures that are rapidly diluted in the systemic circulation. Before the development of central catheters, peripheral catheters were used, which limited the amount of calories and nutrients that could be safely administered.[5]

Today, PN formulations are administered through peripheral or central veins. The type of venous access utilized primarily depends

on the anticipated duration of therapy and nutrient requirements of the patient.[7,8]

Peripheral Venous Access

Peripheral venous access, typically in a forearm vessel, may be used for peripheral PN (PPN) administration. PPN is used for short-term therapy, generally <7 days in patients who are not fluid restricted. Because PN formulations are hypertonic and irritating to fragile peripheral veins, low final concentrations of dextrose (<10%) and amino acids (AAs) (<5%) are necessary to maintain the osmolarity of the PPN <900 mOsm/L (normal serum osmolality 280–300 mOsm/L). The dilute nature of the PPN solutions limits the amount of deliverable calories (<1 kcal/mL) such that a large volume (~2–3 L/day) of PPN may be necessary to approach nutritional goals. The addition of lipid emulsion increases the caloric density of the PPN and may help protect the vein against irritation through dilution and by a buffering effect.[6]

Central Venous Access

Central venous access is the preferred route of administration of PN formulations for patients who have a nonfunctional GI tract, require bowel rest for >7 days, have limited peripheral venous access, or have energy and protein needs that cannot be met with peripheral nutrient formulations.[7,8] Traditionally, the CVC is percutaneously inserted into the subclavian vein and threaded through the vein so that the tip rests in the upper portion of the superior vena cava (SVC) just above the right atrium. Another technique involves the use of a peripherally inserted central catheter (PICC), which is inserted in the antecubital vein and advanced until the end of the catheter reaches the upper SVC.[7,9] The internal and external jugular veins may also be used to thread a catheter into the SVC; however, maintaining a sterile dressing on these sites is more difficult.

The SVC is an area of rapid blood flow, which quickly dilutes concentrated parenteral nutrient formulations, thereby minimizing phlebitis or thrombosis. Some patients are not the candidates for placement of catheters in the SVC and require a femoral vein insertion of the catheter with the tip in the inferior vena cava. There may be a higher risk for infection with catheters placed using this technique.[7,8] Placing catheters via the jugular vein is associated with a higher risk of infection.[49]

Differing from PPN, parenteral nutrient formulations designed for administration through central veins often contain relatively high final concentrations of dextrose (20%–35%) and AAs (5%–10%), plus lipids. The central PN (CPN) formulation typically provides a caloric density >1 kcal/mL and an osmolarity >2000 mOsm/L. CPN formulations are often termed *total PN* (TPN) because complete nutrient requirements of the patient may be achieved by this route.

COMPONENTS OF PARENTERAL NUTRIENT FORMULATIONS

PN formulations are complex mixtures containing 30 or more nutrients, including energy substrates such as carbohydrate (dextrose), protein (AAs), and fat (lipid, lipid emulsion, or intravenous fat emulsion [IVFE]), along with a variety of electrolytes, vitamins, and trace minerals. Various combinations of these components are prepared under aseptic conditions based upon individual patient needs.[10,11] The three macronutrients used in PN formulations are available in various concentrations from manufacturers. Sterile water for injection is used to dilute the macronutrients to achieve the prescribed final concentrations of dextrose, AAs, and lipids, as well as the final volume of the PN formulation.

PN formulations may be prepared in one of two ways, a dextrose–AA (2-in-1) mixture in which the lipid emulsion is administered separately as a piggybacked infusion or a total nutrient admixture

(TNA or 3-in-1) in which the dextrose, AAs, and lipids are combined in solution in the same PN bag.

Premixed PN solutions are also available commercially in different percentages of dextrose and AA preparations. Premixed PN solutions are sterile products that have a longer shelf life and are formulated to meet the standard nutrient requirements in noncritically ill patients. These formulations limit the ability to customize the final product to meet individual patient needs. However, the use of premixed formulas may be advantageous by reducing costs and the risk of bloodstream infections.[12] This may be a viable option for small institutions without a nutrition support service (**Table 38-1**).

Table 38-1
Ready to Use, Premixed Parenteral Nutrition Formulas

Product Name	Manufacturer	Formula	Volume	Comments
ProCalamine®	B. Braun Medical	Amino acids 3% Glycerin 3% Electrolytes	1000 mL	B. Braun discontinued production. Supplies depleted by May 2021
Clinimix®	Baxter	Amino acids%/dextrose% 4.25%/5% 4.25%/10% 5%/15% 5%/20% 6%/5% 8%/10% 8%/14%	1000 mL 2000 mL	Sulfite free Dual-chambered bag 6%/5% for peripheral administration 24-month shelf life
Clinimix E®	Baxter	Amino acids%/dextrose% 2.75%/5% 4.25%/5% 4.25%/10% 5%/15% 5%/20% 8%/10% 8%/14% Electrolytes with Ca	1000 mL 2000 mL	Sulfite free Dual-chambered bag 24-month shelf life
Kabiven®	Fresenius Kabi	Amino acids 3.31% Dextrose 9.8% Lipid emulsion 3.9% Electrolytes 0.7%	1026 mL 1540 mL 2053 mL 2566 mL	Specialized three-chamber bag Central TPN
Perikabiven®	Fresenius Kabi	Amino acids 2.4% Dextrose 6.8% Lipid emulsion 3.5% Electrolytes 0.5%	1440 mL 1920 mL	Specialized three-chamber bag Central or peripheral TPN

Errors have occurred in preparing and managing this complex therapy, resulting in patient harm and death. A responsibility of the pharmacist is to ensure safe, accurate, and sterile preparation of the PN formulation. Guidelines for safe practices have been developed

for situations in which inconsistent practices have the potential to cause harm. Pharmaceutical problem areas that are addressed in the Safe Practices for Parenteral Nutrition Formulations are compounding, formulas, labeling, stability, and filtering of PN formulations.[13]

PN is a costly therapy. Costs associated with PN therapy include not only the admixture itself but also the cost of obtaining venous access, human resource administration, laboratory monitoring, and treatment of complications of therapy. Because of the cost and complexity of PN therapy, its use should be scrutinized and reserved for patients who will benefit from it.

Carbohydrate

Dextrose in water is the most common carbohydrate for IV use. It is available commercially in concentrations ranging from 2.5% to 70%. Dextrose solutions are mixed with other components of the PN formulation and diluted to various final concentrations with sterile water for injection. Dextrose in its hydrated form provides 3.4 kcal/g, compared with dietary carbohydrate, which provides 4 kcal/g.

Lipid

Lipid emulsion or IVFE is the most calorically dense macronutrient for infusion and a source of essential fatty acids (FAs). For decades, soybean oil and soybean/safflower oil lipid emulsions (n-6 FAs) have been the mainstay in lipid-containing PN regimens in the United States. FAs, a component of IVFE, are classified based on carbon chain length, degree of saturation, and location of the first double bond from the ω carbon. The optimal composition of FAs within IVFE has been a focus of clinical debate because of the potential to influence immune function, inflammatory response, and liver function. This has prompted research into the development of alternative lipid formulations in which part of the n-6 polyunsaturated fatty acids (PUFAs) has been replaced by less bioactive FAs, such

as coconut oil (rich in medium-chain saturated FAs), olive oil (rich in n-9 monounsaturated FA oleic acid), or fish oil (rich in n-3 PUFA).[14-16] Emerging literature highlights benefits of these alternative lipid products as having less inflammatory properties, higher antioxidant content, and improved clinical outcomes in some patient populations.[17]

Plant-based fat emulsions contain phytosterols. When consumed orally, phytosterols are poorly absorbed; however, when administered IV, phytosterols are eliminated via the hepatobiliary system. It is thought that phytosterols are involved with cholestasis associated with chronic lipid emulsion administration. This is especially seen in pediatric populations.

Because of the bioactivity of n-6 PUFAs and liver complications associated with phytosterols, research has been conducted in the development of new lipid formulations (structured lipids). The n-6 PUFA has been reduced or replaced by less bioactive FAs, such as coconut oil (rich in medium-chain saturated FA), olive oil (rich in n-9 monounsaturated FA oleic acid), or fish oil (rich in n-3 PUFA)—challenging the traditional soybean oil and soybean/safflower oil emulsions (n-6 FA).[18] While structured IVFEs have been used for years outside the United States, the U.S. Food and Drug Administration (FDA) has approved IVFE formulations with a 4:1 combination of olive oil and soybean oil[14] and another IVFE formulation containing soybean oil, medium-chain triglycerides (MCT), olive oil, and fish oil.[14,18] Most recently, a fish oil–based fat emulsion has been approved for pediatric patients.

The traditional soybean oil IVFEs continue to be available commercially as 10% (1.1 kcal/mL), 20% (2.0 kcal/mL), and 30% (3.0 kcal/mL) concentrations. The newer IVFE products are available in 10% or 20% concentrations. While each gram of fat provides 9 kcal, the caloric density of the IVFE is increased slightly because of the glycerol within the IVFE such that each milliliter of 10% IVFE provides 1.1 kcal, and each milliliter of 20% and 30% IVFE provides 2.0 and 3.0 kcal/mL, respectively. Other components of the IVFE include glycerol to make the formulation isotonic, egg phospholipid as an emulsifier, vitamin K, and sodium hydroxide to adjust the final

pH. The 10% and 20% IVFEs may be administered concurrently (IV piggyback) alongside the dextrose/AA solutions or mixed with dextrose and AAs as a TNA formulation. The 30% IVFE is used exclusively for compounding TNA formulations that combine dextrose, AAs, and lipid in the same container.[15] **Table 38-2** summarizes available lipid products approved by the FDA.

Table 38-2
Intravenous Lipid Emulsion (IVFE)

Product Name	Percentage	Manufacturer	Composition	Fatty Acid Composition
Clinolipid®	20%	Baxter	Olive oil Soybean oil Egg phospholipid	Linoleic acid 13.8%–22.0% Oleic acid 44.3%–79.5% Palmitic acid 7.6%–19.3% Palmitoleic acid 0.0%–3.2% Linolenic acid 0.5%–4.2% Stearic acid 0.7%–5.0%
Intralipid®	10%, 20%, 30% 20% Bulk	Baxter	Soybean oil Egg phospholipid	Linoleic acid 44%–62% Oleic acid 19%–30% Palmitic acid 7%–14% Linolenic acid 4%–11% Stearic acid 1.4%–5.5%
Nutrilipid®	20%	B. Braun Medical	Soybean oil Egg phospholipid	Linoleic acid 48%–58% Oleic acid 17%–30% Palmitic acid 9%–13% Linolenic acid 4%–11% Stearic acid 2.5%–5%
Omegaven®	10%	Fresenius Kabi	Fish oil Egg phospholipid	Linoleic acid 1.5% Oleic acid 4%–11% Palmitic acid 4%–12% Palmitoleic acid 4%–10% Linolenic acid 1.1% Eicosapentaenoic acid (EPA) 13%–26% Docosahexaenoic acid (DHA) 14%–27% Myristic acid 2%–7% Arachidonic acid 0.2%–2%
SMOFlipid®	20%	Fresenius Kabi	Soybean oil MCT (coconut oil) Olive oil Fish oil Egg phospholipid	Linoleic acid 14%–25% Oleic acid 23%–35% Palmitic acid 7%–12% Linolenic acid 1.5%–3.5% Stearic acid 1.5%–4% Caprylic acid 13%–24% Capric acid 5%–15% EPA 1%–3.5% DHA 1%–3.5%

Amino Acids

Synthetic crystalline AAs serve as the source of protein and nitrogen. Nitrogen is the building block of cell structure and is used to produce enzymes, peptide hormones, and structural and serum proteins.

When oxidized for energy, protein yields 4 kcal/g. Historically, protein calories have not always been included in the calculation of energy needs for patients receiving PN formulations. Ideally, AAs are used to stimulate protein synthesis and tissue repair and are not oxidized for energy; however, the human body cannot compartmentalize energy metabolism in such a manner. Today, conventional wisdom is to include protein calories in the total calorie calculations. **Table 38-3** summarizes available nutrients and their caloric density.

Table 38-3
Caloric Density of Intravenous Nutrients

Nutrient	kcal/g	kcal/mL
Amino acids	4	
Amino acids 5%		0.2
Amino acids 10%		0.4
Dextrose	3.4	
Dextrose 10%		0.34
Dextrose 50%		1.7
Dextrose 70%		2.38
Fat	10	
Fat emulsion 10%		1.1
Fat emulsion 20%		2
Fat emulsion 30%		3
Glycerol	4.3	
Glycerol 3%		0.129
Medium-chain triglycerides	8.3	

AA concentrations of 3% to 20% are available commercially and vary slightly from one product to another in specific amounts of each AA, electrolyte content, and pH. Generally, AA products are characterized as standard mixtures or specialty mixtures. Standard AA products provide a balanced mix of essential, nonessential, and

semiessential AAs, whereas specialty AA products are modified for specific disease states.

Specialty AA mixtures are available for neonatal patients and for adult patients with hepatic encephalopathy, renal failure, or critical illness. Specialty AA formulations designed for patients with hepatic failure contain increased amounts of branched-chain amino acids (BCAAs) and decreased amounts of aromatic amino acids (AAA) compared to standard AA products. These formulations are thought to counter the imbalance between AAA and BCAA that can occur in hepatic failure. Elevations in AAA may lead to altered mental status. There is no evidence to suggest that formulations enriched with BCAA improve patient outcomes compared with standard formulas.[19–21] Formulas enriched with BCAA should be reserved for patients with hepatic encephalopathy, which is refractory to standard treatment with luminal acting antibiotics and lactulose.[19,20] Specialty AA products used in renal failure are predominantly composed of essential AAs.[22] Their use is based upon the theory that nonessential AAs can be recycled from urea and essential AAs. Indications for renal AA formulations are limited.[23] Standard AAs should be used in acute kidney injury (AKI).

Modified AA formulations are also available for critically ill patients with hypercatabolic conditions, such as trauma or thermal injury. These formulations contain increased amounts of the BCAAs (leucine, isoleucine, and valine) to address the increased skeletal muscle catabolism that can be seen in severe metabolic stress. Although these BCAA enriched products may slightly improve nitrogen balance, improved patient outcomes have not been demonstrated.[24,25] For a summary of the various AA formulas, see **Table 38-4**.

Table 38-4
Amino Acid Formulas

Description	Product Name	Available Concentrations
Standard Formulations		

Description	Product Name	Available Concentrations
Contain essential and nonessential amino acids	Aminosyn II Clinisol (sulfite free) FreAmine III Plenamine Premasol ProSol Travasol	10%, 15% 15% 3%, 8.5%, 10% 15% 10% 20% 5.5%, 8.5%, 10%
Standard Formulations with Electrolytes		
Contain essential amino acids, nonessential amino acids and electrolytes	FreAmine III	3%, 8.5%
Pediatric Formula		
Contain essential and nonessential amino acids	Aminosyn-PF Trophamine (non-DHEP)	7%, 10% 6%, 10%
Hepatic Failure Formulation		
Contain essential and nonessential amino acids with a proportion of branched-chain amino acids (leucine, isoleucine, valine)	HepatAmine (B. Braun Medical)	8%
Renal Failure Formulations		
Contain primarily essential amino acids	NephrAmine (B. Braun Medical) Aminosyn-RF (Hospira)	5.4% 5.2%
High Metabolic Stress Formulations		
Contain percentages of leucine, isoleucine, and valine, as well as all essential and nonessential amino acids	FreAmine HBC Aminosyn HBC	6.9% 7.0%

Micronutrients

Micronutrients are electrolytes, vitamins, and trace minerals needed for metabolism. These nutrients are available from various

manufacturers as either single entities or in combinations. For example, the trace element zinc is available commercially as a single trace element product or as a combination product with copper, chromium, manganese, and selenium. Likewise, electrolytes are available as either individual salts or a combination product to facilitate ease of admixing PN. Commercially available vitamins for PN formulations are generally prescribed as a combination multivitamin regimen, although some vitamins are available as single additives. It is important to be aware of the specific products available in each institution to avoid providing inadequate or excessive amounts of various micronutrients.

PARENTERAL NUTRITION

Patient Assessment: Population-Based Formulation

CASE 38-1

QUESTION 1: A.A. is a well-developed and well-nourished 70-year-old male brought to the emergency department with left-sided facial palsy and left-sided muscle weakness in his upper and lower extremities. He was admitted to the hospital 8 days ago with a diagnosis of ischemic stroke. Evaluation of swallowing with modified barium swallow showed him at an increased risk of aspiration. Enteral tube feedings were initiated, but repeated attempts of advancement of the enteral regimen were unsuccessful. A GI consult was requested. He has been receiving maintenance IV fluids containing 5% dextrose/0.45% sodium chloride with potassium chloride (KCl) 10 mEq/L infusing through a peripheral catheter at 125 mL/hour to provide hydration since admission. His weight today is 165 pounds (74.84 kg); his height is 70 inches (177.80 cm).

Nutrition laboratory panel values are as follows:

Sodium (Na), 142 mEq/L
Potassium (K), 4.1 mEq/L
Chloride (Cl), 100 mEq/L
Bicarbonate (HCO_3^-), 25 mEq/L

Blood urea nitrogen (BUN), 10 mg/dL
Creatinine, 1.0 mg/dL
Glucose, 91 mg/dL
Calcium (Ca), 9.4 mg/dL
Magnesium (Mg), 2.1 mg/dL
Phosphorus (P), 3.4 mg/dL
Total protein, 6.0 g/dL
Albumin, 3.6 g/dL
Prealbumin, 14 mg/dL
White blood cell (WBC) count, 8800/mL

After evaluation of A.A.'s nutritional status, GI function, IV fluid regimen, and other clinical findings, is PN an option for A.A.?

A.A. is a well-developed, well-nourished male before admission. Although PN support is rarely necessary for mildly stressed, well-nourished patients, A.A. has been without sustenance for 8 days and attempts at EN has been unsuccessful. A.A.'s visceral proteins (albumin and prealbumin) are in the low-normal range. Although both albumin and prealbumin have been used as nutritional markers, a low serum albumin is more reliable at indicating risk for morbidity and mortality than it is for assessing acute changes in nutritional status. The half-life of albumin is ~3 weeks, whereas the half-life for prealbumin is 2 to 3 days, making prealbumin more reflective of acute changes in nutritional status in convalescing patients. In critically ill patients, neither prealbumin nor albumin concentrations correlate with calorie and protein adequacy.[26] See Chapter 35, Basics of Nutrition and Patient Assessment, for a more detailed description of evaluation of patients with nutritional deficiencies. The principles from Chapter 35 will be applied to this and all others cases throughout this chapter.

A.A. has a peripheral IV catheter, and his peripheral access appears to be adequate. With good peripheral access, A.A. meets one of the criteria for PPN. Furthermore, he is not fluid restricted and should be able to tolerate the volume of PPN necessary to meet the majority of his nutritional needs. A common complication (up to 70% incidence) of PPN is thrombophlebitis, which generally occurs within 72 hours.[6,27] Phlebitis is usually attributed to the acidic pH or

hyperosmolarity of the PPN formulation. The osmolarity of typical peripheral parenteral feedings ranges from 600 to 900 mOsm/L compared with a normal osmolarity of 280 to 300 mOsm/L for plasma. Osmolarity of a dextrose–AA formulation can be approximated quickly by multiplying the final dextrose concentration (%) by 50 and the final AA (%) concentration by 100 (eg, final AA concentration of PPN of 3.5% × 100 = 350 mOsm/L from the AA component). Approximately 150 to 200 mOsm/L should be added to account for the contribution of electrolytes, vitamins, and trace elements. Although the concurrent administration of fat emulsions decreases osmolarity, buffers the pH, and improves peripheral vein tolerance, it does not eliminate the risk of thrombophlebitis.[28] If PPN therapy is anticipated to be >2 weeks for A.A., then central venous access should be obtained.

Case 38-1, Question 2: Based on the simplistic weight-based calculation, what is the calorie and protein goal range for A.A.?

A.A. has a minimal stress level, and his baseline electrolytes are within normal limits. A.A.'s calorie goals should meet energy expenditure needed for basal metabolism and account for mild stress associated with recovery. A.A. falls into the category of "hospitalized patient, mild stress" requiring 20 to 25 kcal/kg/day (see Table 35-3 in Chapter 35, Basics of Nutrition and Patient Assessment). For this calculation, A.A.'s actual body weight of 165 pounds (74.84 kg) is slightly higher than his ideal body weight [IBW] and should be used to calculate both energy and protein requirements. The caloric goal for A.A. is 1500 to 1875 kcal/day. Using IBW or usual body weight to calculate caloric requirements in patients who have experienced significant weight loss may result in overfeeding and should be avoided.

Protein requirements are estimated based on weight, degree of stress, and disease state. Because A.A. has had a stroke and his metabolic stress is mild, his protein goal should be based on the desire to maintain his current lean body mass. Using the guidelines

provided in Table 35-4 of Chapter 35, Basics of Nutrition and Patient Assessment, A.A. should receive a protein dose of ~1.0 g/kg/day (range 1.0–1.2 g/kg/day) or 75 g/day. As with energy expenditure, calculation of protein needs are estimates; the patient's clinical course should be monitored and the protein dose adjusted accordingly. The protein source for PN is synthetic crystalline AAs. Generally, 1 g of protein is equivalent to 1 g of AAs. A.A. will need 75 to 90 g/day of AAs.

In patients with acute and chronic kidney disease, protein intake should be adjusted to account for catabolic rate, renal function, and possible protein losses from dialysis.[29-31] AKI rarely occurs outside the critical care setting. For most critically ill patients with AKI, protein intake should fall within 1.4 to 1.6 g/kg/day.[32,33] Protein intake for patients receiving continuous renal replacement therapy should range between 1.8 and 2.5 g/kg/day.[29-31] The recommended protein intake for patients who receive maintenance hemodialysis is 1.2 g/kg/day,[34,35] whereas patients who receive chronic ambulatory peritoneal dialysis should receive 1.3 g/kg/day.[36]

CASE 38-1, QUESTION 3: What is A.A.'s daily maintenance fluid requirement?

Maintenance fluid requirements can be estimated using several methods. The simplest method uses 30 to 40 mL/kg/day (35 mL/kg/day for average adult) as the basis. Another time-tested method of estimating fluid requirements that was originally developed for the pediatric population, yet remains widely used for both adults and children, is to provide 1500 mL for the first 20 kg body weight plus an additional 20 mL/kg for actual weight beyond the initial 20 kg. Both methods provide estimates of fluid needs for basic maintenance. Additional fluid must be provided for increased losses from vomiting, nasogastric (NG) tube output, diarrhea, or large open wounds. A.A.'s fluid needs are estimated as follows:

$$\begin{aligned} \text{mL/day} &= 1500\ \text{mL} + ([20\ \text{mL/kg}][75\ \text{kg} - 20\ \text{kg}]) \quad \textbf{(Eq. 38-1)} \\ &= 1500\ \text{mL} + (20\ \text{mL/kg})\ (55\ \text{kg}) \\ &= 1500\ \text{mL} + 1100\ \text{mL} = 2600\ \text{mL} \end{aligned}$$

CASE 38-1, QUESTION 4: The institution uses a 2-in-1 system for PN and piggybacked lipids through a Y-site in the IV catheter. Based on the calorie and protein goals determined previously for A.A., what PPN regimen will you design?

A logical place to start when initiating a PPN regimen is to assess the patient's current IV fluids and compare that to the estimated daily maintenance fluid requirements (calculated for A.A. in Question 3). A.A.'s IV fluids are infusing at 125 mL/hour (3000 mL/day). Because of the aforementioned osmolality limitation of peripheral veins, PPN solutions are formulated with relatively low final concentrations of dextrose (<10%) and AAs (<5%). Therefore, a relatively large volume of PPN is required in order to approach nutrient goals. PPN solutions will be formulated for a total volume typically ranging from 2000 to 3000 mL/day depending on patient needs. While final concentrations of dextrose and AAs within PN regimens may vary slightly from patient to patient, the final concentration of dextrose for PPN will typically be 6% to 8% and AAs at 3% to 3.5%.

For A.A., a reasonable PPN regimen will be 100 mL/hour (2400 mL/day), with a final concentration of dextrose at 7% and AAs of 3.5%. Lipid emulsion will be Y-sited into the IV catheter at a dose of 250 mL of 20% lipids. This 2-in-1 regimen will provide a combined volume of 2650 mL/day (2400 mL PN + 250 mL from lipids) and will replace A.A.'s IV fluid volume. It is important to note that A.A.'s IV fluids will either need to be discontinued once the PPN starts or reduced to the minimum rate needed to keep the vein open (KVO), which is typically between 10 and 30 mL/hour. Failure to discontinue or decrease the IV fluids to KVO upon initiation of PN will pose a risk of volume overload to the patient.

Case 38-1, Question 5: Check to see if the PPN regimen for A.A. will meet the majority of his caloric and protein goals. How many total calories and grams of protein per day will the regimen above provide?

The caloric and protein goals for A.A. were previously determined to be 1500 to 1875 kcal/day and 75 to 90 g protein/day. His PPN regimen is 100 mL/hour (2400 mL/day), with a final concentration of dextrose at 7% (7 g/100 mL) and AAs of 3.5% (3.5 g/100 mL). The lipid emulsion will be Y-sited into the IV catheter at a dose of 250 mL of 20% lipids. The PPN volume (2400 mL) plus the lipid volume (250 mL) will total 2650 mL/day.

To calculate the amount of protein and dextrose provided by the 2-in-1 solution, multiply the final concentration of AAs (3.5% or 3.5 g/100 mL) and dextrose (7% or 7 g/100 mL) by the volume of the solution (exclude lipid volume since this is a 2-in-1 solution). Each gram of AA provides 4 calories. Each gram of IV dextrose will provide 3.4 cal/g.

$$
\begin{aligned}
&= 2400\ \text{mL} \times 3.5\%\ \text{AAs} \\
&= 2400\ \text{mL} \times 0.035\ \text{g/mL} \\
&= 84\ \text{g} \times 4\ \text{cal/g} \\
&= 336\ \text{calories} \\
&= 2400\ \text{mL} \times 7\%\ \text{dextrose} \\
&= 2400\ \text{mL} \times 0.7\ \text{g/mL} \\
&= 168\ \text{g} \times 3.4\ \text{cal/g} \\
&= 571\ \text{calories}
\end{aligned}
\qquad \textbf{(Eq. 38-2)}
$$

The regimen provides A.A. 250 mL of 20% lipid emulsion at a caloric density of 2 cal/mL. Therefore, 250 mL of 20% lipid emulsion will provide 500 calories from fat. The calories from fat, dextrose, and AAs are added together to determine total calories. Fat calories are added to dextrose calories (571 cal/day) and protein calories (336 cal/day) to provide a total of 1407 cal/day for A.A. (~19 cal/kg/day).

$$336 \text{ protein calories} + 571 \text{ dextrose calories} + 500 \text{ fat calories} = 1407 \text{ total calories} \quad \text{(Eq. 38-3)}$$

This regimen will provide A.A. with protein intake well within his targeted range and meet the majority of his caloric goal (>75%). If a more aggressive nutritional regimen is desired, then central venous access will need to be considered for A.A. Typically, lipids account for ~30% to 40% of total calories in PPN solutions. In A.A.'s PPN regimen, the lipids account for 35% (eg, 500 fat calories divided by 1407 total calories) of his total calories.

Case 38-1, Question 6: What are the benefits of using a mixed-fuel system, combining dextrose and fat to meet energy needs?

Providing a portion of calories as fat may reduce the metabolic consequences of excessive dextrose administration. The maximal rate of dextrose metabolism in adults is estimated at 5 to 7 mg/kg/minute, or ~7 g/kg/day. In doses >7 g/kg/day, dextrose is used inefficiently and converted to fat.[37] The conversion to fat may be associated with respiratory compromise and hepatic dysfunction.[38–40] Hyperglycemia, another complication of excessive dextrose infusion, is associated with electrolyte and acid–base disturbances, osmotic diuresis, increased risk of infections, and altered phagocyte and complement function. Furthermore, using a mixed-fuel system allows the administration of a small amount of IVFE daily to prevent essential fatty acid deficiency (EFAD). Rapid administration of IVFE has been associated with alterations in the reticuloendothelial system that are not observed with continuous administration of small doses.[18] IVFE should be infused at a rate of <0.11 g/kg/hour to prevent adverse effects, which include impaired hepatic, pulmonary, immune, and platelet function.[18] A typical daily dose of IVFE is ≤1 g/kg/day.

Administration of essential FAs as 1% to 4% of total caloric intake (eg, 250 mL of 20% lipid twice a week) is necessary to prevent EFAD. The essential FAs linoleic acid and α-linolenic acid are those

that cannot be synthesized by humans. Of these, linoleic acid appears to be the only one required by adults. Clinical symptoms of EFAD are dry, thickened, scaly skin, hair loss, poor wound healing, and thrombocytopenia, which may be observed after a few weeks to months of lipid-free parenteral feedings.[36] Biochemical evidence of EFAD, determined by a triene-to-tetraene ratio of >0.4, may be seen after 1 week of lipid-free parenteral feedings. The continuous infusion of hypertonic dextrose from the PN is associated with high circulating concentrations of insulin. Because insulin promotes lipogenesis rather than lipolysis, linoleic acid cannot be released from adipose tissue.[37]

Patient Assessment: Moderate Stress With Malnutrition

CASE 38-2

Question 1: B.B. is a 64-year-old female diagnosed with ovarian cancer 4 years ago. The cancer was treated with a combination of chemotherapy and external beam radiation therapy. Subsequently, B.B. developed chronic radiation enteritis. She was admitted to the hospital with an increasing abdominal pain with eating. She has consumed little oral intake for 7 days, and no stool output for 5 days. Questioning reveals that over the past week, she has been drinking only liquids due to nausea and vomiting, and her weight has decreased 7 pounds (3.18 kg) during that time. On physical examination, B.B. appears thin and her abdomen is distended. Vital signs are notable for a temperature of 101.30 °F (38.50 °C), heart rate of 88 beats/minute, and a blood pressure of 102/68 mm/Hg. She is 66 inches (167.64 cm) tall and weighs 110 pounds (49.90 kg). Her medical record indicates that 1 month ago, she weighed 117 pounds (53.07 kg), and 6 months ago, her weight was 124 pounds (56.25 kg). Admission laboratory values are as follows:

Na, 133 mEq/L
K, 4.5 mEq/L
Cl, 100 mEq/L
HCO_3^-, 25 mEq/L
BUN, 15 mg/dL
Creatinine, 0.6 mg/dL
Glucose, 103 mg/dL
Ca, 9.3 mg/dL

Mg, 2.2 mg/dL
P, 4.5 mg/dL
Albumin, 3.1 g/dL
WBC count, 11,800/mL
Hematocrit, 46%
Alanine aminotransferase, 31 units/L
Aspartate aminotransferase, 27 units/L
Alkaline phosphatase, 65 units/L
Total bilirubin, 0.6 mg/dL

An abdominal computed tomography (CT) scan shows bowel obstruction with a stricture distal to the obstruction and signs of chronic inflammation. B.B. is admitted with complications from chronic radiation enteritis.

After assessing B.B.'s nutritional status and other clinical data, is she a candidate for PN?

B.B. does not have a functioning GI tract and has eaten little in the past week. Patients are considered at risk for nutritional depletion when intake is <50% to 75% of requirements for 5 to 7 days or when weight loss exceeds 5% or more in 1 month, 7.5% or more in 3 months, or 10% or more of usual body weight (preillness) within a 6-month period.[41,42] B.B. falls within these categories and is considered nutritionally at risk.

Assessment of weight loss should include evaluation of hydration status, especially because B.B.'s vomiting and minimal oral intake for the past week place her at risk of dehydration. Loss of lean body mass is probably less than that reflected by the decrease in weight. In addition, B.B.'s admission serum albumin concentration is low at 3.1 g/dL. Her hydration status should be considered when evaluating this visceral protein, because B.B.'s serum albumin concentration will probably decrease further upon rehydration.

B.B. is not expected to resume oral intake soon because her radiation enteritis is being managed conservatively with bowel rest. Therefore, PN is indicated for B.B.

Case 38-2, Question 2: What type of malnutrition does B.B. have?

The origin of malnutrition may be from starvation, acute or chronic illness, or both. B.B. exhibits some loss of fat and muscle, as well as depletion of visceral proteins. She has components of both chronic and acute malnutrition. Refer to Chapter 35, Basics of Nutrition and Patient Assessment, for a more robust discussion of types of malnutrition.

Case 38-2, Question 3: Members of the medical team are anxious to have B.B. gain weight and are concerned by her malnourished appearance. What potential complications may occur from initiating an aggressive feeding regimen for B.B.?

B.B. may be at risk of refeeding syndrome because of poor oral intake and progressive weight loss over the past 6 months. Chronic malnutrition may lead to intracellular depletion of phosphorus, potassium, and magnesium that may not be evident when measuring serum electrolyte concentrations. Refeeding syndrome may occur as phosphorus, potassium, and magnesium shift from the extracellular space into the cells upon consumption of concentrated sources of calories. Carbohydrate calories are converted to glucose, which triggers the secretion of insulin, which, in turn, facilitates the uptake of glucose, water, phosphorus, and other intracellular electrolytes. This phenomenon was first reported in World War II when chronically malnourished survivors were given normal food and liquid diets. Complications coinciding with refeeding included hypertension, cardiac insufficiency, seizures, coma, and death. These complications were reported later in the 1970s and 1980s, with the introduction of PN in chronically ill, essentially starved hospitalized patients. Knowing a patient's history of weight loss and diet will help assess the risk of refeeding syndrome.

To minimize the risk of refeeding syndrome in B.B., the PN should be initiated conservatively (~50% of total dextrose calories for the first 1–2 days) and advanced to goal slowly (over 5–7 days as tolerated). Electrolyte abnormalities should be corrected before nutrition support is initiated. Because B.B.'s electrolytes are within normal range, no baseline adjustments are necessary. Close

electrolyte monitoring is warranted to avoid potentially serious electrolyte abnormalities and the cardiovascular consequences thereof. Laboratory values including phosphorus, potassium, magnesium, and glucose should be monitored at least daily for the first week. Vitamin administration should be routine. Thiamine 100 mg and folate 1 mg are commonly supplemented during the PN advancement period.[43,44] Consensus recommendations for patients at risk for refeeding syndrome include supplementation of 100 mg thiamine before feeding is initiated, and, if at high risk, continuing for 5 to 7 days during feeding.[45]

For adults, current literature supports a daily lipid dose up to 1 g/kg/day (or up to 30% of TPN calories) for soy-based lipid products, with a maximum dose of 2.5 g/kg/day. For lipid products containing other combinations of oils, the usual daily dose for adults is 1 g/kg/day, with a maximum of 2 g/kg/day. The recommended rate of infusion of lipid emulsions varies between products and should strictly follow manufacturer's recommendations. During PN therapy, it is also important to monitor serum triglyceride concentrations weekly to assess lipid tolerance, being mindful to keep triglyceride concentrations <400 mg/dL during PN therapy to decrease the risk of adverse effects.[46] Lipoprotein lipase hydrolyzes lipid particles to release FAs, which are either used for energy, metabolized by the liver, or stored in adipose tissue. In metabolically stressed patients, lipoprotein lipase activity is decreased, leading to hyperlipidemia that may result in alterations in pulmonary gas exchange, immune response, and, in rare cases, acute pancreatitis.

Case 38-2, Question 4: After rehydration with IV fluids, B.B.'s weight climbs to 113.54 pounds (51.50 kg). The initiation of PN therapy was delayed because B.B. experienced severe abdominal pain and distension and required surgery shortly after admission. An exploratory laparotomy was performed and a 25-cm ileum was resected from an area of bowel with severe disease and a stricture that was causing the obstruction. Bowel sounds are absent. She has a right port-a-cath CVC, and PN is to begin on postoperative day 1. What are the energy and protein goals for B.B.?

Energy requirements may be estimated with predictive equations, simplistic weight-based formulas (eg, 25–30 kcal/kg/day), or measured by indirect calorimetry, which is the most accurate method of assessment. The advantage that weight-based equations offer is simplicity. Over 200 predictive equations to estimate energy requirements have been published in the literature, including the Harris–Benedict equation. Using the Harris–Benedict equation for females (see Table 35-3 in Chapter 35, Basics of Nutrition and Patient Assessment) and her current weight of 113.54 pounds (51.48 kg), height of 65.98 inches (167.60 cm), and age of 64 years, B.B.'s basal energy expenditure (BEE) is 1158 kcal/day. To estimate her total energy expenditure, the BEE should be modified with an activity factor of 1.2 for being confined to bed and a stress factor of 1.1 to 1.2 for surgery. These modifications result in an estimated energy expenditure of 32% to 44% greater than her BEE, or 1528 to 1668 kcal/day. Using a target midway within this range, a goal of 1600 kcal/day is reasonable. In a similar manner, her protein goal (see Table 35-4 in Chapter 35, Basics of Nutrition and Patient Assessment) for moderate stress is estimated at 1.5 to 2.0 g/kg/day or 77 to 103 g/day of protein.

CASE 38-2, QUESTION 5: Now that calorie and protein requirements have been estimated for B.B., a goal PN regimen can be designed for her. Keep in mind that PN is initiated conservatively, particularly with patients at risk of refeeding syndrome, and advanced to the goal regimen after several days and as tolerated. To begin designing the PN formulation, the bulk macronutrients available on formulary for compounding the PN must be identified. For this case, the bulk macronutrients are 70% dextrose, 30% lipid emulsion, and 10% AAs. How will you design a TNA parenteral nutrient formulation as a single-daily PN bag for B.B. that provides 1600 kcal and 80 g of AAs with a non–protein calorie distribution of 75% carbohydrate and 25% lipid?

1. AAs calculation

$$80\ \text{g} \times 4\ \text{kcal/g} = 320\ \text{kcal} \qquad \textbf{(Eq. 38-4)}$$

$$\text{mL of 10\% AAs} = 80\ \text{g}/0.1\ \text{g/mL} = 800\ \text{mL}$$

2. Dextrose calculation

$$\begin{aligned}\text{Calories from dextrose} &= (1600 - 320)\,(0.75) = 960\ \text{g}\\ \text{of dextrose} &= 960\ \text{kcal}/3.4\ \text{kcal/g}\\ &= 282\ \text{g/mL of 70\% dextrose}\\ &= 282\ \text{g}/0.7\ \text{g/mL}\\ &= 403\ \text{mL}\end{aligned}$$

(Eq. 38-5)

3. Lipid emulsion calculation

$$\begin{aligned}\text{Calories from lipid} &= (1600 - 320)\,(0.25)\ \text{or}\ (1280 - 960)\\ &= 320\ \text{kcal/mL of 30\% lipid emulsion}\\ &= 320\ \text{kcal}/3.0\ \text{kcal/mL}\\ &= 107\ \text{mL}\end{aligned}$$

(Eq. 38-6)

4. Calculation of final volume of energy substrates

$$\begin{aligned}&800\ \text{mL of AA 10\%} +\\ &403\ \text{mL dextrose 70\%} + 107\ \text{mL lipid emulsion 30\%}\\ &= 1310\ \text{mL total volume}\end{aligned}$$

(Eq. 38-7)

B.B.'s goal of PN formulation will provide 282 g of dextrose and 32 g of lipids daily. If the PN is infused continuously over 24 hours, B.B. will receive 3.8 mg/kg/minute of dextrose and ~0.6 g/kg/day of lipids. Both dextrose and lipid doses comply with the limitations recommended in Case 38-2, Question 4. Other additives such as electrolytes, vitamins, trace elements, and sterile water are included in the parenteral nutrient formulation and increase the final volume to 1680 mL/day (~1 kcal/mL). The infusion rate for this formulation can be calculated as follows:

$$\begin{aligned}&= 1680\ \text{mL/day}/24\ \text{hours}\\ &= 70\ \text{mL/hour}\end{aligned}$$

(Eq. 38-8)

B.B.'s parenteral nutrient formulation of 1680 mL/day will not meet her maintenance fluid needs of 2130 mL/day (see Case 38-1, Question 3). She will require extra fluid to meet the remainder of her maintenance daily fluid needs. Additional hydration is generally provided through IV fluids, although volume may be supplemented by adding more sterile water for injection into the TNA.

CASE 38-2, QUESTION 6: What are the advantages and disadvantages of combining the dextrose, fat, and AAs in one TNA container?

PN formulations may be prepared in one of the following two ways: a dextrose–AA (2-in-1) mixture in which IVFE is administered separately as a piggybacked infusion or a TNA (3-in-1) in which the dextrose, AAs, and IVFE are combined in solution in the same bag.[41]

Although the use of TNAs has been widely embraced by home care providers and many institutions for convenience and cost advantages, the addition of IVFE to the traditional mixture of dextrose and AAs converts the mixture into a complex emulsion with physiologic differences that alter the stability of the product.[48] The differences between these two methods of compounding PN formulations must be considered. Specific advantages and disadvantages of each are summarized in **Table 38-5**.

Table 38-5
Advantages and Disadvantages of 2-in-1 and 3-in-1 Parenteral Nutrition

	2-in-1	3-in-1

	2-in-1	3-in-1
Advantages	▪ Improved overall stability ▪ Increased flexibility in concentrating dextrose and amino acids ▪ Allows more flexibility to add higher concentrations of electrolytes ▪ Better medication compatibility ▪ Reduced risk of bacterial growth because of high osmolarity and acidic pH ▪ Better visualization of precipitant of particulate matter. Enables the use of bacterial retention filter (0.22-µm) ▪ Lower risk of catheter occlusion if IVFE is not used daily	▪ All components are aseptically compounded by the pharmacy ▪ Simplified regimen for the patient, especially at home ▪ Less supply and equipment costs ▪ Less nursing time needed for administration ▪ Decreased preparation cost ▪ Decreased risk of contamination ▪ Inhibited bacterial growth versus separate IVFE ▪ Minimize infusion-related reactions from IVFE because of slower infusion rate ▪ May improve lipid clearance because of slower infusion rate ▪ Decreased risk of phlebitis with PPN
Disadvantages	▪ Increased administration costs and time when lipids are infused separately ▪ Increased risk of touch contamination ▪ Increased risk of phlebitis, particularly if PPN is not co-infused with IV lipid emulsion ▪ IVFE given in a piggyback manner is limited to a maximum hang time of 12 hours.	▪ Impaired visualization of particulate matter or precipitate because of opacity of IVFE admixture ▪ IVFE is less stable—more prone to lipid separation. Admixture is less stable with concentrated electrolyte additives ▪ Larger particle size of IVFE admixture. Must use 1.2-µm. Cannot use 0.22-µm bacterial retention filter. ▪ Limited compatibility with medications ▪ Containers with diethylhexyl phthalate should be avoided because this toxic material may be extracted by the lipid and may harm patients.

Source: O'Grady NP. Guidelines for the prevention of intravascular catheter-related infections, 2011. Published online 2017:80.

CASE 38-2, QUESTION 7: How stable are the TNA parenteral feeding formulations compared to 2-in-1 formulations? Why is an infusion filter necessary?

IVFE gradually deteriorates over time because of increased formation of free FAs and a resultant decrease in pH. When lipids are mixed with dextrose and AAs, this process is accelerated. IVFE consists of an interior oil phase dispersed within an external water phase. Stability of the IVFE is maintained by polar and nonpolar regions on the same fat droplet. The surface of the polar region of the fat droplet is negatively charged and repels other lipid droplets of the same charge. When the surface loses its negativity, fat droplets aggregate into larger globules and the emulsion becomes unstable and unsafe for use, risking occlusion of pulmonary vasculature. Commercially available IVFEs in the United States use an anionic egg yolk phosphatide emulsifier to stabilize the lipid droplets and maintain dispersion. Destabilization of the emulsion occurs in phases that begin with creaming and end with the coalescence of the lipid particles, or "cracking" of the emulsion. A decrease in pH and the addition of divalent cations (Mg^{2+}, Ca^{2+}) alter the electrical charge on the fat droplet surface and pose a risk to the integrity of the emulsion. Although dextrose decreases the pH, the addition of AAs provides an adequate buffer for this variable. The amount of divalent cations added to TNAs should be limited to minimize the risk of emulsion instability. Trivalent cations such as iron should never be added to a TNA parenteral nutrient formulation. PN formulations containing lipid must be assessed visually for signs of phase separation, in which the instability of the emulsion is manifested by "oiling out," indicated by a continuous layer of oil or individual fat droplets. Fat emulsion particles have an average size of 0.5 mm. A destabilized emulsion is not visibly apparent until the lipid particles are 40 to 50 mm. Fat particles as small as 5 mm may occlude pulmonary capillaries.[47,48] Therefore, the use of a 1.2-mm filter is

recommended to protect against the infusion of enlarged lipid particles.[13,48]

Using dual-chamber bags may extend the shelf life of TNAs because they allow the lipid to be physically separated from the dextrose, AAs, and other additives until it is time to administer the feeding. The use of dual-chamber PN bags has the greatest advantage for home care settings, where a 1-week supply of parenteral feedings may be prepared at a time.[47]

After preparation, TNAs should be refrigerated 39.2 °F (4.00 °C) to preserve stability. Once the bag is removed from the refrigerator, it may be warmed to room temperature and the contents mixed well before administration. Mixing is best accomplished by gently inverting the container up and down to ensure top-to-bottom transfer of the fluid. Vigorous shaking should be avoided because it introduces air, which can destabilize the emulsion.[47,48]

Case 38-2, Question 8: How does microbial growth differ between 2-in-1 and TNA (3-in-1) formulations?

Dextrose–AA PN formulations are not conducive to growth of most organisms because of the high osmolarity (>2000 mOsm/L) and acidic pH. Lipid emulsion, however, is isotonic and has a physiologic pH that provides an optimal growth medium for organisms. Combining these three substrates in a TNA provides a formulation with a microbial growth potential that is intermediate between the two.[47,48] The number of CVC manipulations correlates strongly with the incidence of catheter-related infections. From an infection control perspective, the use of a single-daily bag of PN formulation limits the number of manipulations of the CVC to one per day, thereby minimizing touch contamination. The Centers for Disease Control and Prevention guidelines allow TNA formulations to hang for up to 24 hours. However, because of concerns about the potential of lipid emulsions to support microbial growth, the suggested hang time for IVFE when administered alone in a piggyback manner with 2-in-1 PN formulations is 12 hours.[49]

Case 38-2, Question 9: How will you determine the adequacy of B.B.'s specialized nutrition support?

Routine monitoring and evaluation of nutritional status and the metabolic effects of therapy are required for patients receiving PN therapy. Nutritional goals established in the patient care plan are estimates of a patient's nutritional requirements and must be evaluated regularly to assess adequacy of therapy. Daily monitoring parameters include vital signs, body weight, temperature, serum chemistries, hematologic indices, nutrition intake, and fluid intake and output.[24]

The adequacy of nutrition therapy should be assessed weekly. This may be accomplished through measuring serum concentrations of visceral proteins (see Table 35-2 in Chapter 35, Basics of Nutrition and Patient Assessment), such as prealbumin and albumin. Because prealbumin has a half-life of only 2 to 3 days, serum concentrations of this protein should increase weekly with adequate nutrition and improving clinical status. In convalescing patients, an increase in prealbumin of 4 to 7 mg/dL/week is indicative on an anabolic response to nutritional support. Albumin has a much longer half-life of 14 to 20 days, rendering that it is less useful in reflecting an anabolic response to PN therapy.[26,50] Indirect calorimetry, if performed correctly, is the most accurate way to reassess energy expenditure.

A method to assess adequacy of protein intake is to evaluate nitrogen balance, which compares the amount of nitrogen administered to the amount of nitrogen excreted (amount "in" vs amount "out"). The nitrogen "in" is provided by the AA component of the PN formulation. Each commercially available AA formulation has a slightly different amount of nitrogen per gram of amino, so the manufacturer's product information should be consulted to obtain this value. On average, about 16% of AA is nitrogen or 1 g of nitrogen for every 6.25 g of protein. Most of the nitrogen is excreted in the urine as urea, a byproduct of protein breakdown for energy. Renal excretion of urea nitrogen increases with increasing stress. To

determine the nitrogen balance, urine must be collected for 24 hours and the amount of urine urea nitrogen (UUN) measured. Some laboratories have the capability of measuring total urine nitrogen, which measures all nitrogen entities in the urine. In addition, some nitrogen lost via skin, respiration, and stool is not measurable but is estimated to be between 2 and 4 g/day.

Achieving a positive nitrogen balance is difficult, if not impossible, in critically ill patients; therefore, the calculation may result in a negative number or zero. For convalescing patients, a nitrogen balance of >2 to 4 g is acceptable and indicates a positive nitrogen balance. A negative nitrogen balance prompts a reevaluation of the amount of protein and energy a patient is receiving. For patients with a negative nitrogen balance, it may be helpful to increase intake of both calories and protein.

As with all tests, assessment should include monitoring several parameters, including the patient's clinical status. Most important is the identification of trends that may alert clinicians to impending complications. A suggested schedule for monitoring is provided in **Table 38-6**.

Table 38-6
Routine Monitoring Parameters for Parenteral Nutrition

	Suggested Schedule for TPN Monitoring					
Parameter	**Initial**	**Daily (Critically Ill)**	**2–3× Weekly (Stable)**	**Weekly**	**Monthly (Home Health)**	**As Indicated**
Weight	X	X	X			
BUN, creatinine, glucose	X	X	X			
Na, K, Cl, HCO_3^-, Ca, P, Mg	X	X	X			
Albumin, AST, ALT, LDH, alkaline phosphatase, total bilirubin, conjugate bilirubin	X			X		X
Prealbumin	X			X		X
Triglycerides	X			X		X
RBC count, Hgb, Hct, WBC count, platelets	X			X		X

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Hct, hematocrit; Hgb, hemoglobin; LDH, lactate dehydrogenase.

CASE 38-3

Question 1: C.C., a 33-year-old male, is admitted to the hospital because of increasing shortness of breath, productive cough, wheezing, fever, abdominal pain, and vomiting. He reports consuming mainly fluids over the past week. His severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody test for COVID-19 is positive. His past medical history is significant for occasional binge ethanol abuse, asthma, pancreatitis, and type 2 diabetes. His social history is significant for 2 packs/day smoking history.

During the next 48 hours, his clinical status deteriorates requiring transfer to the intensive care unit (ICU). An NG tube is inserted to decompress the bowel. He is febrile, his WBC count has increased to 21,000/mL, and he is hypotensive, requiring large volumes of IV fluids. His respiratory distress requires endotracheal intubation and mechanical ventilation. C.C.'s clinical presentation is consistent with COVID-19 pneumonia, complicated by acute pancreatitis, and paralytic ileus. Because of C.C.'s critical condition and nonfunctional GI tract, the decision is made to begin PN. C.C. is 74 inches (187.96 cm) tall, and his usual weight is 275 pounds (124.74 kg).

What are C.C.'s energy and protein goals?

It is important to recognize that C.C. is an obese, critically ill patient. The prevalence of obesity in adults and children is steadily increasing nationwide. Clinicians can expect to see the growing numbers of patients with obesity. In 2013, the American Medical Association recognized obesity as a disease that requires medical treatment. In obese ICU patients, a nutritional assessment should be conducted to determine actual body weight, usual body weight, and IBW. Body mass index (BMI) should be calculated and obesity classified. Obesity is defined as a BMI of >30 kg/m^2 or actual body weight exceeding 120% of IBW. C.C. weighs 275 pounds (124.74 kg), which is 152% of his IBW of 180.78 pounds (82 kg) and a BMI of 35.3 as shown by Eq. 38-9. Assessment should also consider preexisting and emerging comorbidities, such as diabetes, hyperlipidemia, hypertension, and end-organ function.[51]

Guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN) support the use of high-protein hypocaloric feeding in critically ill patients with obesity in efforts to preserve lean body mass, mobilize adipose stores, and minimize metabolic complications. Obese ICU patients are more likely to experience complications and fuel utilization challenges compared to leaner

patients. ASPEN guidelines go a step further to support that if BMI is in excess of 30, goal caloric intake should not exceed 60% to 70% of target energy requirements or 11 to 14 kcal/kg actual body weight per day (or 22–25 kcal/kg IBW per day). Protein should be provided at 2.0 g/kg IBW for BMI between 30 to 40 and 2.5 g/kg IBW for BMI > 40.[24,52] In the case of C.C., his BMI is 35.3 (BMI Class II), so his energy goal is estimated at 22 kcal/kg of IBW or ~1804 kcal/day and protein goal of 2 g/kg IBW or 164 g/day.

Case 38-3, Question 2: Given the critical condition of C.C. and his diagnosis of acute pancreatitis, is the use of lipid emulsion (IVFE) contraindicated in C.C.?

Although consensus has not been reached regarding the optimal composition of lipid emulsions, recent guidelines from the Society of Critical Care Medicine (SCCM) and the ASPEN suggest that soybean oil–based lipid emulsion be withheld or limited to a dose necessary to prevent EFAD (100 g/week) during the first week of stay within an ICU.[24] It is important to note that this recommendation did not receive a consensus vote among the authors of the guidelines. The addition of n-3 FAs, eicosapentaenoic acid and docosahexaenoic acid, to lipid emulsions is recommended because of positive effects on cell membranes and inflammatory processes.[53]

Several observations have raised concern about the use of IVFE in patients with pancreatitis. Available data suggest that IVFE is a safe and efficacious form of calories for most patients with pancreatitis.[55] Although hyperlipidemia has been well described in patients with alcohol-induced pancreatitis, it is unlikely that it is primarily responsible for initiating the pancreatitis.

Acute pancreatitis associated with hypertriglyceridemia is most often seen in patients with hereditary or acquired defects in lipid metabolism (such as type I, IV, or V dyslipidemia) and in the presence of a comorbidity, such as uncontrolled diabetes or excessive alcohol use.[54] Patients with hypertriglyceridemia-associated pancreatitis often experience a more severe clinical course and higher rates of complications—warranting a lipid-free PN

formulation should parenteral feedings be necessary. Lipid emulsion should be avoided or used with caution in patients with severe hyperlipidemia, disorders of lipid metabolism, recent cardiac infarction, stroke, embolism, severe liver disease, and in critically ill patients with shock. Lipids are contraindicated in patients with any known hypersensitivity to any active ingredient with the various lipid products (eg, egg, olive, soy, fish, or peanut protein).[17]

Monitoring serum triglyceride concentrations should be part of routine management for patients with pancreatitis and those receiving parenteral nutrient formulations containing lipids. Serum triglyceride concentrations should be maintained at <400 mg/dL with a continuous infusion of lipids and <250 mg/dL when checked at least 4 hours after the infusion for patients receiving intermittent IVFE infusions.[46,55] If serum triglyceride concentrations exceed these parameters, consideration must be given to decreasing or withholding the IVFE or transitioning to an alternative lipid product.

Case 38-3, Question 3: Given C.C.'s past medical history and current clinical condition, what metabolic complication of PN therapy should be anticipated?

Hyperglycemia is the most common metabolic complication of PN therapy, especially in stressed or critically ill patients. Metabolic stress increases gluconeogenesis and glycogenolysis. This increase in endogenous glucose production coupled with the administration of hypertonic dextrose in PN formulations increases the potential for hyperglycemia.[56] C.C. is at particular risk for hyperglycemia because he is diabetic, experiencing pancreatitis, and critically ill. Stress-induced hyperglycemia may develop as a result of insulin resistance, suppressed insulin secretion, and increased gluconeogenesis and glycogenolysis.[57]

Case 38-3, Question 4: What is an appropriate initial dextrose dose in C.C.'s PN?

With a history of diabetes, coupled with acute pancreatitis, it is anticipated that C.C. will experience hyperglycemia and will need supplemental insulin when his parenteral nutrient regimen is infused. His dextrose should be limited to no >150 g during the first 24 hours of therapy and should not be increased until serum glucose concentrations are consistently <180 mg/dL. Standard practice for administering PN formulations containing hypertonic dextrose in patients with euglycemia or for those with no history of glucose intolerance is to limit the initial dextrose dose to <250 g of dextrose during the first 24 hours. Capillary blood glucose concentrations should be monitored frequently and should be consistently maintained below 180 mg/dL.[58] If C.C.'s serum glucose level consistently remains <180 mg/dL, the dextrose dose within the PN may be increased daily as tolerated and the PN formulation regimen gradually advanced over 2 to 3 days toward his energy goal.

Insulin therapy may be administered subcutaneously, IV with an insulin infusion, or directly in the PN formulation.[59,60] Regular insulin may be added to the PN formulation at a dose of 0.1 units per gram of dextrose as a reasonable starting point and should be adjusted to achieve serum glucose levels between 140 and 180 mg/dL.[62] Alternatively, a separate insulin infusion may be used for more aggressive glucose control. Capillary glucose monitoring is required during PN therapy at least every 6 hours and more frequently in patients with hyperglycemia.[60–62] An insulin administration protocol is recommended before PN starts and for the duration of therapy.

Persistent hyperglycemia may lead to glucosuria and osmotic diuresis, resulting in dehydration and electrolyte abnormalities. Hyperglycemia compromises the immune response altering chemotaxis and phagocytosis and impairing complement function, thereby increasing risk of infection. In extreme cases, hyperglycemia progresses to hyperosmolar, nonketotic acidosis and coma, a condition associated with 40% mortality.

Hyperglycemia can be minimized by limiting the goal dextrose infusion rate to <4 mg/kg/minute (20 kcal/kg/day).[63] Clinical evidence suggests that treatment of hyperglycemia and maintenance of

euglycemia may reduce morbidity and mortality, length of stay, and hospital costs.[60,61,64–66]

Furthermore, overfeeding should be avoided in all patients, especially those with respiratory concerns (ie, mechanically ventilated, chronic obstructive airway disease). Overfeeding with carbohydrates is particularly detrimental because of the amount of carbon dioxide produced relative to the amount of oxygen consumed. This may results in carbon dioxide retention, which may lead to alterations in acid–base balance. Complete oxidation of carbohydrate is demonstrated at dextrose infusions of 4 to 5 mg/kg/minute (20–25 kcal/kg/day). Dextrose infusions exceeding this rate may increase carbon dioxide production and negatively affect respiratory function and may cause respiratory distress in patients at risks.[39]

Case 38-3, Question 5: C.C.'s current laboratory values are as follows:

Na, 137 mEq/L
K, 4.5 mEq/L
Cl, 102 mEq/L
HCO_3^-, 22 mEq/L
BUN, 9 mg/dL
Creatinine, 0.8 mg/dL
Glucose, 218 mg/dL
Ca, 8.9 mg/dL
Mg, 1.9 mg/dL
P, 2.8 mg/dL
Albumin, 3.0 mg/dL

Which electrolytes should be included in C.C.'s parenteral nutrient formulation?

Once macronutrient goals are achieved and tolerance is established, the daily management of PN therapy revolves around maintaining the patient's fluid and electrolyte needs. All concurrently administered IV fluids and medications must be considered and accurate records of volume intake and output reviewed. Typical electrolytes added to PN formulations are sodium, potassium, chloride, acetate (which is metabolized to bicarbonate), magnesium,

calcium, and phosphate. Electrolyte requirements can vary widely and should be added to the PN formulation based on individual patient needs. However, patients without significant fluid and electrolyte losses, hepatic or renal dysfunction, or acid–base disturbances do well with standard maintenance doses of electrolytes. Electrolytes may be added individually or as commercially available combination products for maintenance doses. General guidelines for electrolyte requirements for parenteral feedings are included in **Table 38-7**.

Table 38-7
Recommended Adult Daily Electrolyte Requirements

Electrolyte	Amount
Sodium	80–100 mEq
Potassium	60–80 mEq
Chloride	50–100 mEq[a]
Acetate	50–100 mEq[a]
Magnesium	8–20 mEq
Calcium	10–15 mEq
Phosphorus (phosphate)	20–40 mmol

[a]As needed to maintain acid–base balance.

CASE 38-3, QUESTION 6: What doses of multiple vitamins and trace elements should C.C. receive in his parenteral nutrient formulation?

Vitamins and trace elements should be included in PN regimens and are essential for normal metabolism and effective nutrient utilization. ASPEN along with ASPEN and European Society of Parenteral and Enteral Nutrition (ESPEN) has provided consensus recommendations for daily micronutrient administration[67] (**Table 38-8**).

Table 38-8
Recommended Adult Daily Doses of Parenteral Vitamins

Vitamins	Dose
Fat-Soluble Vitamins	
A	3300–3500 IU (990–1050 µg retinol equivalents)
D	200 IU (5 µg cholecalciferol)
E	10 mg/dL α-tocopherol
K	Individual assessment
Water-Soluble Vitamins	
Thiamine (B_1)	3–6 mg
Riboflavin (B2)	3.6–5 mg
Niacin (B3)	40–47 mg
Pantothenic acid (B5)	15–17 mg
Pyridoxine (B6)	3–6 mg
Cyanocobalamin (B12)	5–6 µg
Folic acid	400–600 µg
Biotin	60 µg
Ascorbic acid (C)	110–200 mg

Source: Blaauw R, Osland E, Sriram K, et al. Parenteral provision of micronutrients to adult patients: an expert consensus paper. *JPEN J Parenter Enteral Nutr*. 2019;43(S1):S5–S23. doi:10.1002/jpen.1525.

Guidelines for daily doses of the trace elements, such as chromium, copper, manganese, and zinc, have also been developed.[67,68] In addition to these trace elements, many practitioners provide selenium on a daily basis. Recommended doses of the trace elements are listed in **Table 38-9**. As with vitamins, trace elements are available as single entities or combination products. Molybdenum and iodine are also available commercially.

Table 38-9
Recommended Daily Adult Doses of Parenteral Trace Elements

Trace Element	Dose
Chromium	10–15 µg
Copper	300–610 µg
Manganese	55–100 µg
Selenium	20–100 µg
Zinc	2.5–6.5 mg
Iron	1–1.2 mg
Molybdenum	No recommendation
Iodine	70–150 µg

Source: Blaauw R, Osland E, Sriram K, et al. Parenteral provision of micronutrients to adult patients: an expert consensus paper. *JPEN J Parenter Enteral Nutr*. 2019;43(S1):S5–S23. doi:10.1002/jpen.1525.

Case 38-3, Question 7: A comparison of C.C.'s intake and output reveals an overall negative fluid balance because a high volume of gastric fluid is being removed via the NG tube. Laboratory values at this time are the following:

Na, 138 mEq/L
K, 3.1 mEq/L
Cl, 91 mEq/L
HCO_3^-, 33 mEq/L
BUN, 28 mg/dL
Creatinine, 0.9 mg/dL
Glucose, 279 mg/dL
Ca, 7.8 mg/dL
Mg, 1.4 mg/dL
P, 1.8 mg/dL
Albumin, 2.8 g/dL

Arterial blood gas (ABG) results are pH, 7.46; PO_2, 95 mm Hg; PCO_2, 35 mm Hg; and HCO_3^-, 30 mEq/L.

What factors contribute to these metabolic abnormalities?

PN therapy may be associated with multiple metabolic complications. The most common abnormalities are hypokalemia, hypomagnesemia, hypophosphatemia, and hyperglycemia. The plan for PN therapy should include routine monitoring of these serum

chemistries to identify complications early and institute methods to manage or prevent complications.

HYPOKALEMIA

Hypokalemia, a common metabolic abnormality associated with the initiation of PN, usually occurs within the first 24 to 48 hours. Potassium moves, along with dextrose, from the extracellular to the intracellular space. Furthermore, building lean body mass (ie, anabolism) requires ~3 mEq of potassium per gram of nitrogen provided by the AAs. Administering dextrose promotes repletion of glycogen stores, which also requires potassium.[44,69]

C.C.'s decreased serum potassium concentration is compounded by metabolic alkalosis. With metabolic alkalosis, the renal excretion of potassium is increased. Additional potassium should be administered and can be provided in C.C.'s parenteral feeding or through another IV.

HYPOMAGNESEMIA

Magnesium, like potassium, is primarily an intracellular cation and is considered an anabolic electrolyte. It is common to observe decreases in magnesium serum concentrations during the administration of parenteral nutrient formulations. Synthesis of lean tissue requires 0.5 mEq of magnesium per gram of nitrogen.[44,69] Additional magnesium can be added to the PN formulation. However, when a TNA formulation is used, the amount of magnesium must stay within the guidelines for the cation content to maintain the stability of the lipid emulsion.

HYPOPHOSPHATEMIA

Hypophosphatemia occurs when phosphorus moves into the cells for the synthesis of adenosine triphosphate (ATP), an important energy carrier. Phosphorus is depleted quickly with the administration of hypertonic dextrose, especially in patients who are malnourished (see Case 38-2, Question 3, for discussion of refeeding syndrome). Phosphorus is used for ATP synthesis, primarily in the liver and

skeletal muscle. Alkalosis also decreases phosphate stores by stimulating the phosphorylation of carbohydrates. As a component of 2,3-diphosphoglycerate, found in red blood cells (RBCs), phosphorus is necessary for the disassociation of oxygen from hemoglobin.[69]

Clinical signs and symptoms of hypophosphatemia usually occur when serum concentrations fall to <1.0 mg/dL, including lethargy, muscle weakness, impaired WBC function, glucose intolerance, rhabdomyolysis, seizures, hemolytic anemia, reduced diaphragmatic contractility, and death. Moderate-to-severe, complicated hypophosphatemia can be managed by administering up to 0.625 mmol/kg of phosphate IV.[44,69–71] Although C.C.'s serum phosphorus is not <1.0 mg/dL, it is low (1.8 mg/dL), and he should receive 15 to 30 mmol of phosphate in the parenteral nutrient formulation per day. Additional supplements may be necessary to replete his phosphorus stores.[70]

METABOLIC ALKALOSIS

C.C. has evidence of a metabolic alkalosis based on his ABG results, hypochloremia, and elevated bicarbonate level. The continued loss of fluid and hydrochloric acid from the NG tube is the most probable cause of his metabolic alkalosis. Management of this type of metabolic alkalosis is to replace the fluid and chloride through another IV. Because acetate is converted to bicarbonate and can further contribute to the alkalosis, the acetate salts in the parenteral nutrient formulation can be changed to chloride salts.[69] Nevertheless, the PN formulation generally is not the primary vehicle for adjusting and supplementing electrolytes and fluids. Instead, the fluid and electrolyte balance may be adjusted with maintenance IV fluid and electrolyte supplements.

A complete metabolic panel (CMP) is typically order before PN initiation and at least weekly during PN therapy. A CMP generally includes a serum glucose, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, BUN, serum creatinine (SCr), liver function tests, albumin, and triglyceride. A basic metabolic panel

(BMP), which includes a serum glucose, sodium, potassium, chloride, bicarbonate, calcium, BUN, and SCr, is usually checked daily in critically ill patients and for those at risk of electrolyte abnormalities or renal dysfunction. More stable patients may have a BMP plus phosphorus and magnesium monitored two to three times a week rather than daily.

CASE 38-3, QUESTION 8: In response to these serum chemistries, the electrolytes in C.C.'s parenteral nutrient formulation are changed to the following per liter: NaCl, 160 mEq; KCl, 140 mEq; phosphate as K salt, 60 mmol; $MgSO_4$, 54 mEq; and calcium gluconate, 30 mEq. After analyzing the PN electrolyte content (above), what concerns to you have regarding the calcium and phosphate content of the TNA PN formulation?

Calcium and phosphate solubility is a safety concern with PN formulations. The dose of calcium ordered for C.C. is more than three times the usual maintenance dose (Table 38-7). This amount of calcium is not necessary because the observed hypocalcemia merely reflects C.C.'s low serum albumin concentration; therefore, less calcium is bound to albumin. C.C. probably does not have true hypocalcemia because his free (or ionized) calcium, which is critical for physiologic function, has not changed. If available, obtaining an ionized calcium concentration is advised. However, some laboratories do not have this test available. In this situation, a "corrected" calcium formulation may be used. For every 1 g/dL decrease in serum albumin concentration, there will be about a 0.8 mg/dL reduction in the serum calcium concentration.[72] For C.C., a serum calcium of 7.8 mg/dL will correct to a serum concentration of 8.8 mg/dL ([4.0 − 2.8 g/dL albumin][0.8] + 7.8 mg/dL calcium).

The amount of phosphate prescribed for C.C. at this time exceeds the usual recommended dose of 20 to 40 mmol/day (Table 38-8). Although C.C. has a low serum phosphorus concentration and needs additional phosphate, increasing the dosage in the parenteral nutrient formulation to 60 mmol/day may be incompatible with the calcium content, resulting in calcium phosphate precipitation.

Numerous factors affect calcium phosphate solubility, and caution is warranted when preparing PN formulations to ensure that solubility limits are not exceeded. If solubility is compromised, microprecipitates can occur and may cause diffuse pulmonary emboli, resulting in respiratory distress or death. Calcium and phosphate precipitation curves have been developed to assist practitioners in safe compounding practices. These guidelines help predict the points at which calcium phosphate precipitation is likely to occur. The solubility of calcium and phosphate must be determined based on the volume of the formulation at the time the calcium and phosphate are mixed together, not the final volume. For example, if the electrolytes including calcium and phosphate are added to 1000 mL of a dextrose–AA mixture and then 300 mL of IV fat is added, the calcium phosphate solubility is based on the 1000 mL, not the final 1300 mL volume. In addition, some AA products contain phosphate ions, and these should be considered when determining calcium phosphate solubility.[13,73]

The in vitro precipitation of calcium phosphate depends on the type of calcium salt used in compounding, concentrations of calcium and phosphate, AA concentration, temperature, pH of the formulation, and infusion time. Calcium gluconate rather than the chloride salt offers enhanced calcium phosphate solubility. In solution at equimolar concentrations, calcium chloride dissociates more than calcium gluconate, thereby increasing the yield of free calcium available for binding with phosphate. Calcium and phosphate should not be added to the PN formulation in close sequence. It is recommended to add phosphate first and calcium last, thereby taking advantage of the maximal parenteral volume. The PN formulation should be agitated periodically during preparation and inspected for precipitates.[74] Other guidelines for improving the solubility of calcium are a final AA concentration of >2.5% and a pH <6.0. An increase in the ambient temperature, such as that found in the heated isolettes within neonatal ICUs, can facilitate the precipitation of calcium phosphate. PN formulations should be infused within 24 hours after compounding if stored at room temperature; if refrigerated, it should be infused within 24

hours after rewarming. Increasing temperature and slow infusions may result in calcium phosphate precipitation in the IV catheter, even if precipitation has not occurred in the infusion container.[13]

The amount of divalent cations, calcium (20 mEq) and magnesium (30 mEq), exceeds the general guidelines for maximal amounts that can be added safely to a TNA without disrupting the stability of the lipid emulsion. A limit of 20 divalent cations per liter is a general guideline. The amount prescribed for C.C.'s regimen is excessive because it provides 50 divalent cations in 1.8 L (28 divalent cations/L) and may result in a potentially unstable admixture.

Lastly, a 1.2-mm air-eliminating filter should be used when infusing TNA PN formulations, and a 0.22-mm air-eliminating filter should be used for non–lipid-containing admixtures.[13]

Case 38-3, Question 9: As C.C. recovers and GI tract function returns, a small-bore nasojejunal enteral feeding tube is inserted. Tube feeding is considered because he cannot eat by mouth because of the endotracheal tube and mechanical ventilation. How should he be transitioned from parenteral to enteral feedings?

The EN regimen will depend on the site of feeding (eg, gastric or jejunal) and the condition of the patient's GI tract. EN should begin with a full-strength formula at a continuous infusion rate. Because C.C. has had no oral intake for over a week and is in critical condition, EN is typically started at 10 to 40 mL/hour and advanced by 10 to 20 mL/hour every 8 to 12 hours. For noncritically ill patients, continuous EN is commonly initiated at goal rate, or at 50 mL/hour with advancement by 15 mL/hour every 4 hours until goal is reached —usually within 24 to 48 hours (see Chapter 37, Adult Enteral Nutrition). Concurrently, the PN formulation should be decreased to avoid fluid overload and to keep the calorie and protein intake constant. It can be anticipated that C.C. can transition from parenteral to enteral feedings in 24 to 48 hours.

Long-Term, Chronic Parenteral Nutrition

CASE 38-4

Question 1: D.D. is a 43-year-old male with a 17-year history of Crohn disease (CD). He has had several hospital admissions over the past 2 years with exacerbations of CD. D.D. has experienced an unintentional weight loss of 12% over the past year. He is admitted to the hospital for increasing abdominal pain, nausea, and vomiting for 9 days, and no stool output. Before admission, D.D.'s condition was managed with vedolizumab 300 mg IV every 2 months and prednisone 10 mg qd. On physical examination, D.D. appears thin and his abdomen is distended. Baseline labs are as follows:

Na, 142 mEq/L
K, 4.2 mEq/L
Cl, 99 mEq/L
HCO_3^-, 15 mEq/L
BUN, 12 mg/dL
Creatinine, 0.9 mg/dL
Glucose, 114 mg/dL
Ca, 9.1 mg/dL
Mg, 1.9 mg/dL
P, 5.8 mg/dL
Albumin, 2.8 g/dL
Prealbumin, 28 g/dL

How do you interpret D.D.'s prealbumin concentration?

Although D.D.'s prealbumin concentration appears to be within the desired range, caution must be exercised with its interpretation. In the 1960s, it was shown that prednisone administration may elevate prealbumin levels.[75] Corticosteroid therapy is commonly used in patient populations likely to receive PN, such as patients with inflammatory bowel disease, cancer, and critical illness. In D.D., it is reasonable to think that his prealbumin is falsely elevated given the other indicators of his diminished nutritional status, which include chronic disease, low albumin level of 2.8 g/dL, unintentional weight loss of 12 pounds (5.44 kg) over the past year, and thin appearance.

Case 38-4, Question 2: D.D. has a prolonged hospital course complicated by intra-abdominal abscesses, poor wound healing, and necrotic bowel, requiring removal of all but 82 cm of his small intestine but leaving his ileocecal valve and colon intact. D.D. is given a diagnosis of short bowel syndrome (SBS) requiring

PN. What is the clinical significance of the presence of D.D.'s ileocecal valve and colon?

The presence of the terminal ileum and colon following small bowel resection is critical in nutritional and hydrational management as the patient may be able to tolerate a very short small intestine without TPN support. The presence of the ileocecal valve is thought to prolong intestinal transit time and serve as a barrier to bacterial reflux into the small intestine. Deficiencies of electrolytes, trace elements, and vitamins are common in CD and influenced by the presence of the terminal ileum and colon. Deficiencies are often reflective of chronic blood loss (eg, iron deficiency), chronic diarrhea (eg, magnesium, selenium, zinc deficiencies), or loss of specific absorptive sites (eg, vitamin B_{12}). There is a high prevalence of vitamin D deficiency in patients with CD.

Case 38-4, Question 3: What issues should be addressed in the nutrition and metabolic management of this patient?

SBS occurs from extensive intestinal resection that results in inadequate bowel function to support nutrient and fluid requirements. SBS becomes clinically apparent when about 75% of the small bowel is removed. Studies suggest that the average length of the small intestine may be shorter than previously thought (~11 feet), so SBS is best defined using a patient's symptoms rather than solely on remaining length of small bowel.[76] Patients with SBS frequently experience diarrhea, dehydration, and nutritional deficiencies of minerals, trace elements, and vitamins. In adults, this syndrome is commonly seen in CD, radiation enteritis, mesenteric artery infarction, adhesive obstruction, and trauma.[77] Severe malnutrition will develop without adequate nutrition support.

To maintain adequate nutritional status, D.D. will require PN until his remaining intestine begins to adapt. This adaptive period may take several weeks to months to years, with the majority of intestinal adaptation occurring within the first 2 years following massive bowel

resection. Gut adaptation is enhanced by stimulation of the enterocytes with nutrients, which is best provided by small, frequent oral meals or tube feeding.[78,79] The remaining intestine may never adapt, and SBS may necessitate lifelong PN therapy for survival.

A potential complication of SBS is hypersecretion of gastric fluids.[80-82] The volume and acid content of gastric secretions is directly proportional to the amount of bowel resected.[80–82] The patient can experience symptoms of reflux similar to a Zollinger–Ellison syndrome with epigastric pain and burning. Medications that decrease GI tract motility (antidiarrheals) and secretions (histamine type 2 [H2] blockers and proton-pump inhibitors) are frequently necessary to reduce the volume of gastric secretions and minimize the damaging effects of hypersecretion of gastric acid. These agents are also important in the management of fluid and electrolyte imbalances because of excessive GI fluid losses. Patients with extensive small bowel resection and an intact colon, such as D.D., may experience diarrhea as a result of bile salt depletion.[78,79]

Octreotide may help in decreasing diarrhea in patients with SBS. Octreotide reduces a variety of GI secretions and slows jejunal transit, but the effects are often short lasting and have not shown improved nutrient absorption.[83] It is important to be mindful that most oral medications are absorbed within the first 19.68 inches (50 cm) of the jejunum. Delayed-release medications should be avoided.

Patients with SBS are at risk for having vitamin and mineral deficiencies, especially folate, vitamin B_{12}, vitamin D, selenium, and zinc. These patients should receive supplemental vitamin B_{12} and IV parenteral or oral liquid multivitamin supplements. GI losses of trace minerals, particularly zinc and selenium, are increased in SBS, and these minerals should be supplemented.[78,79]

D.D. should be continued on PN support and will most likely need PN therapy at home to sustain his nutrient and fluid requirements. Because oral ranitidine in not an option, the treatment team orders ranitidine 150 mg to be added to D.D.’s PN formula to manage hypersecretion of gastric fluids and diarrhea. D.D.’s fluid status must be monitored and evaluated daily for clinical signs of dehydration or

fluid overload. Electrolyte abnormalities, including hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, and metabolic acidosis, should be anticipated.[79]

Case 38-4, Question 4: On hospital day 10, he presents with a fever and green, purulent fluid draining from his abdominal incision site. He is diagnosed with an enterocutaneous (EC) fistula. The fluid loss from D.D.'s fistula is about 600 mL/day. How will losses from D.D.'s fistula affect his PN?

EC fistulas are an abnormal communication between the intestine and the skin. Most EC fistulas occur 7 to 10 days following surgery and are classified by site of origin, output volume, etiology, and the number of fistulas. Fluid, electrolyte, and trace element losses from the EC fistula will vary depending on the origin of the fistula. For patients with a high-output fistula (>500 mL/day), PN may be required to meet fluid, electrolyte, and nutrient needs and to support spontaneous or surgical closure.[84] Losses must be accounted for and incorporated into the PN formulation or replaced through a separate IV fluid infusion.

Case 38-4, Question 5: D.D. has stabilized and his physician plans to discharge him home in a few days with the plan to continue PN at home. D.D. is 68 inches (172.72 cm) tall and weighs 141 pounds (63.96 kg) at discharge. How will you design an appropriate PN therapy for home infusion?

HPN has allowed patients, such as D.D., to be discharged from the hospital sooner. Candidates for home therapy must be physically and medically stable, have a strong support network in the home setting to assist with care, have an appropriate home environment, and must be educated regarding the prescribed therapy.[85]

The first step in designing an HPN regimen is to estimate the patient's energy and protein needs (see Chapter 35, Basics of Nutrition and Patient Assessment). D.D. is 10 days out from surgery, and his estimated energy requirements are 25 to 30 kcal/kg/day or ~1600 to 1920 kcal/day. Protein goals must include adequate nitrogen (protein) for wound healing and replacement for losses from

the EC fistula. A goal of 1.5 to 2.0 g/kg/day (96–127 g) is reasonable. Long-term systemic corticosteroid therapy is commonly seen in patients with CD and may cause muscle wasting. Losses of lean body mass from corticosteroids may increase AA requirements.

To simplify his nutrition and fluid regimen, all of D.D.'s fluids, including parenteral nutrients, electrolytes, vitamins, trace minerals, and water, should be provided in one TNA container per day. D.D.'s maintenance fluid needs are estimated to be 2380 mL/day (see Case 38-1, Question 5) plus an extra 600 mL/day from the EC fistula brings his total daily fluid requirement to ~3000 mL/day for his HPN regimen. While his daily doses of protein, dextrose, and fat may vary slightly from prescriber to prescriber, a typical PN regimen for D.D. will include ~100 g (96–127 g/day) providing 400 kcal, 264 g of dextrose providing 898 kcal/day, and 50 g of lipid providing 500 kcal/day plus electrolytes, vitamins, and minerals. Total caloric intake for D.D.'s PN regimen is 1798 kcal/day, which falls within his desired caloric range of 1600 to 1920 kcal/day. Initially, daily intake and output must be monitored; therapy should be adjusted based on this information and D.D.'s clinical status.

Adjustments in fluids and electrolytes may be needed. The fluids secreted by the GI tract are rich in electrolytes, including sodium, potassium, chloride, and bicarbonate. Measurement of the electrolyte content of the fistula fluid will determine those that must be replaced and in what quantities. Both fluid and electrolytes should be replaced to prevent dehydration and electrolyte and acid–base imbalances.

In addition to losses of fluids and electrolytes, the trace element zinc is lost in fluid from the small intestine. Approximately 12 mg of zinc is lost in each liter of small bowel fluid and should be replaced to prevent zinc deficiency. Furthermore, zinc may play a role in wound healing.[86] Somatostatin or a somatostatin analog may be used to manage a high-output EC fistulas (>500 mL/day). A typical regimen may be octreotide 100 μg given subcutaneously three times daily or lanreotide 30 mg intramuscularly every 10 days to decrease fistula output and enhance spontaneous closure.[84,87],

A home infusion pharmacy will be responsible for preparing D.D.'s PN formulations. Typically, a 7-day supply of PN therapy (seven bags) is prepared and delivered to the patient's home. These formulations must be refrigerated until administration; however, formulations should be warmed to room temperature and visually inspected for particulate matter before being administered. Because some additives such as multivitamins are not stable for long periods, the patient or caregiver must add these to the PN formulation just before administration.

Patients and caregivers preparing for HPN therapy must be taught how to manage home therapy. This includes assessment of fluid status, care of a CVC, infection, and the technical aspects of administering parenteral feeding formulations.[85] Preparation for HPN includes placement of a central venous access device for long-term TPN therapy.[7,8]

Case 38-4, Question 6: What other measures can be used to simplify D.D.'s PN regimen and encourage ambulation?

PN is generally administered as a 24-hour continuous infusion. However, when PN is needed long term or administered on an outpatient basis, there are advantages of transitioning from a continuous to a cyclic infusion. Cycling means that the PN formulation is infused for <24 hours per day (typically over 10–14 hours), so that there is time free from PN therapy each day. Once the patient has demonstrated stability on a continuous 24-hour PN regimen, a transition to a cyclic regimen may begin several days before hospital discharge. The cyclic PN is typically advance daily toward the goal infusion time (usually a 10- to 16-hour infusion). Advancement of the cyclic regimen is dependent on the patient's ability to tolerate the changes in fluid and nutrient intake that occur when the PN is infused over a shorter time frame each day. For example, the 24-hour PN infusion is decreased to a 20-hour infusion (eg, 8:00 pm to 4:00 pm) on cyclic PN day 1 and then the next day is decreased to a 16-hour infusion (eg, 8:00 pm to 12:00 noon), and the

next day a 12-hour infusion (eg, 8:00 pm to 8:00 am). With each incremental decrease in time, the infusion rate should be increased such that the TPN volume (previously administered in the 24-hour infusion) is infused each day. The infusion rate of the PN regimen is generally tapered up over 1 to 2 hours during PN initiation to avoid hyperglycemia and tapered down over 1 to 2 hours during PN discontinuation to avoid hypoglycemia. For example, a 16-hour cyclic PN infusion with a 1-hour taper up and down can be calculated (see Eq. 38-9) by taking the total TNA volume divided by the infusion time minus 1 hour, to estimate the goal infusion rate. The goal infusion rate is then divided by 2 to get the 1-hour taper up and down rate. For D.D.'s 3000 mL TNA, the regimen would start at 8:00 pm at 100 mL/hour for 1 hour, then at 9:00 pm the rate would increase 200 mL/hour for 14 hours. At 11:00 am the following day, the TNA rate would taper back down to 100 mL/hour and then at noon it would stop. Most infusion pumps used at home can automatically make these adjustments in the infusion rate. Eventually, the nutrient formulation can be infused for 10 to 12 hours during the night, leaving D.D. free from his PN infusion during the day.

$$\begin{aligned}\text{Cyclic PN goal infusion rate} &= \text{TNA volume}/(\text{infusion time} - 1\ \text{hour})\\ &= 3000\ \text{mL}/16\ \text{hours} - 1\ \text{hour}\\ &= 200\ \text{mL/hour}\\ \text{Cyclic PN taper up and down rate} &= \text{Goal infusion rate}/2\\ &= 200\ \text{mL/hour}/2\\ &= 100\ \text{mL/hour}\end{aligned} \quad \text{(Eq. 38-9)}$$

Vital signs, fluid intake and output, serum electrolytes, and glucose concentrations should continue to be monitored. The serum glucose concentration should be evaluated 30 minutes to 1 hour after the PN infusion is completed to be sure that hypoglycemia does not occur.

Case 38-4, Question 7: In addition to his PN formula and ranitidine 150 mg IV, D.D. is receiving hydrocortisone 100 mg IV every 8 hours, and he now needs insulin. Can these medications or any other medications be mixed with his PN formula to simplify his medication regimen?

Adding medication to PN is not advised owing to the complexity of the PN formulation and the potential for physiochemical interactions with various drug–nutrient combinations. Patients receiving PN therapy often require concomitant drug therapy. Most patients have adequate venous access or have multiple-lumen CVCs, so that mixing medications with the parenteral nutrient formulation is not necessary. However, for some patients with limited venous access, directly adding medication to the PN or co-infusing medication through the same IV tubing may be considered if stability and compatibility with the PN can be assured and there is no other reasonable medication delivery alternative. Examples of medications that may occasionally be added to PN is regular human insulin and H2-receptor antagonists. Often times, there are requests to add other medications to a PN admixture. Specific criteria for drug admixture with PN are listed as follows[88]:

1. Stability and compatibility of the drug with the specific parenteral admixture over a 24-hour period must be determined before adding the medication.
2. The medication must have appropriate pharmacokinetics and proven efficacy for continuous infusion.
3. The medication dose must have remained constant throughout the previous 24-hour period before admixture in PN.
4. There should be a stable PN infusion rate for at least 24 hours before the medication is added.
5. PN should include appropriate labeling to avoid pharmacotherapeutic problems associated with abrupt discontinuation of PN.

Case 38-4, Question 8: After receiving HPN for 4 weeks, D.D.'s liver function tests are found to be elevated. Current values are as follows:

Bilirubin, 0.8 mg/dL
Aspartate aminotransferase, 70 units/L
Alanine aminotransferase, 90 units/L
Alkaline phosphatase, 100 units/L

Could his PN be contributing to the abnormalities in liver function tests?

Elevations in liver function tests are common in children and adults receiving long-term PN therapy and may be seen as early as 2 to 3 weeks after beginning therapy.[89] The abnormalities are usually mild and transient and do not progress to significant liver dysfunction in adults. The predominant type of hepatobiliary dysfunction is steatosis (fatty liver), whereas other patients develop cholestasis or cholelithiasis (biliary obstruction). Liver-associated enzyme elevations usually resolve when PN therapy is discontinued. Although it is uncommon for PN-associated liver disease to progress to hepatic failure, it remains a feared life-threatening complication of long-term PN therapy.[40,90] ω-6 PUFAs and phytosterols in soybean oil IVFE have been thought to contribute to hepatotoxicity. Recent data suggest that IVFE containing fish oil, high in ω-3 FAs with minimal phytosterols, has a hepatoprotective effect.[91]

There are few options to prevent or manage PN-associated liver abnormalities. Some strategies include avoiding overfeeding with carbohydrate and lipid transitioning from a soybean oil to fish oil (ω-3 FAs) IVFE, and utilizing metronidazole and supplements of ursodeoxycholic acid, choline, and carnitine. In addition, transitioning the PN from a 24-hour continuous infusion to a cyclic regimen may decrease the risk of liver dysfunction for patient requiring long-term PN therapy. Patients with progressive liver disease may be the candidates for liver and small bowel transplantation.[90]

The elevations in D.D.'s liver enzymes are not of concern at this time because they are less than three times normal. However, because D.D. has been on HPN for 4 weeks and his wounds have healed, it is time to decrease his energy and protein intake to

maintenance requirements (20–25 kcal/kg/day and 0.8–1.0 g/kg/day of protein). Liver enzymes should be monitored weekly. Because he may not need lifelong PN therapy, the mild elevations are likely to resolve.

It is important to keep in mind that the liver is the primary organ involved with digestion, metabolism, and storage of nutrients. When the functional capacity of the liver is compromised (eg, cirrhosis), macronutrient intolerance and imbalances may occur. The patient may experience hyperglycemia, hypoglycemia, variations in blood lipid levels, and accumulation of AA metabolites (ammonia).

CASE 38-4, QUESTION 9: After 10 months of receiving home TPN, D.D. suffers a fall and fractures his wrist. Fracture of the wrist from a fall raises suspicions of compromised bone density. Subsequent dual-energy x-ray absorptiometry (DEXA) scan reveals a bone density T-score of −3.1. Can these results be caused by long-term PN? What are other complications of long-term parenteral therapy?

Long-term complications of PN are adverse effects associated with PN lasting >3 months. The most common complications include central catheter complications (infection or occlusion), metabolic bone disease, and hepatobiliary disease.[92]

The incidence of hepatobiliary complications associated with long-term PN ranges from 19% to 75%. These complications are variable, with patients experiencing chronic elevations in liver enzymes to advanced liver disease (fibrosis and cirrhosis). Liver disease associated with PN is termed intestinal failure–associated liver disease (IFALD). IFALD is divided into non-nutrient and nutrient-related causes. Non-nutrient causes of IFALD can include medications, biliary obstruction, bacterial overgrowth, and intrinsic liver disease. Nutrient-related IFALD can be caused by overfeeding, nutrient toxicities, and deficiencies. Nutrient toxicities associated with IFALD include manganese, aluminum, and soybean oil. Some nutrient deficiencies associated with IFALD are taurine, choline, carnitine, and essential FAs. The most common histologic finding in IFALD is steatosis followed by cholestatic stasis, fibrosis, and, finally,

cirrhosis. Hepatic steatosis is associated with both underfeeding and overfeeding, so the importance of ensuring the correct amount of calories is of utmost importance.[93]

The exact cause of metabolic bone disease in long-term PN is unknown; however, its origins appear to be multifactorial. The predominant risks factors for metabolic bone disease in D.D. include CD, the medications used to manage it (eg, corticosteroids) coupled with the use of long-term PN therapy.[93] Both osteoporosis and osteomalacia have been associated with long-term PN use. Osteoporosis is the most common form of metabolic bone disease and is because of loss of bone mass. Osteomalacia is the softening of bones and generally occurs as the result of vitamin D deficiency. A combination of both osteoporosis and osteomalacia may occur. Deficiencies in micronutrients such as calcium, magnesium, and vitamin D are risk factors. Historically, bone abnormalities were thought to be caused by aluminum toxicity. However, as aluminum has been nearly eliminated from TPNs, metabolic bone disease remains an issue. High AA concentrations and TPN cycling cause increased renal calcium excretion. Other factors include abnormalities in the handling of calcium, phosphorus, and vitamins D and K.[93]

Central catheter–related complications can vary from occlusion to central catheter–related sepsis. Both of these complications are related to CVC care and are a surrogate measure of overall catheter care.[94] Occlusion develops from fibrin and/or lipid deposits. The consequences of catheter occlusion range from diminished flow to complete occlusion, necessitating removal of the catheter. Central catheter infections are associated with the amount of times the catheter is accessed for PN administration and blood sample removal. Patients with CVC infections usually present with symptoms and signs such as pyrexia and tachycardia during PN infusion. The causes of central catheter infections are bacterial and are usually because of skin flora, *Staphylococcus epidermis* and *Staphylococcus aureus*. If CVC-related sepsis is suspected, then the CVC being used should be discontinued and peripheral and central

cultures taken, while antimicrobial therapy is started pending culture results.[94]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American Society of Health System Pharmacists. ASHP guidelines on compounding sterile preparations. *Am J Health Syst Pharm*. 2014;71(2):145–166. doi:10.2146/sp140001 (10)

McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2016;40:159–211. (24)

Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition [published correction appears in *J Parenter Enteral Nutr*. 2006;30:177]. *J Parenter Enteral Nutr*. 2004;28:S39–S70. (13)

Mueller C, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-20. (3)

Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr*. 2009;28(4):365–377. doi:10.1016/j.clnu.2009.03.015 (7)

Key Websites

American Society for Parenteral and Enteral Nutrition. https://www.nutritioncare.org/guidelines_and_clinical_resources/

Centers of Disease Control and Prevention. Overweight and obesity. https://www.cdc.gov/obesity/data/adult.html

European Society of Parenteral and Enteral Nutrition. https://www.espen.org

COMPLETE REFERENCES CHAPTER 38 ADULT PARENTERAL NUTRITION

1. Lew CCH, Yandell R, Fraser RJ, Chua AP, Chong MF, Miller M. Association between malnutrition and clinical outcomes in the intensive care unit: a systematic review. *JPEN J Parenter Enteral Nutr*. 2017;41(5):744–758. doi:10.1177/0148607115625638
2. Ruiz AJ, Buitrago G, Rodríguez N, et al. Clinical and economic outcomes associated with malnutrition in hospitalized patients. *Clin Nutr*. 2019;38(3):1310–1316. doi:10.1016/j.clnu.2018.05.016
3. Mueller C, ed. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-20.
4. Dudrick SJ. History of parenteral nutrition. *J Am Coll Nutr*. 2009;28:243–251.
5. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term parenteral nutrition with growth, development and positive nitrogen balance. *Surgery*. 1968;64:134–142.
6. Payne-James JJ, Kwahaja HT. First choice for total parenteral nutrition: the peripheral route. *JPEN J Parenter Enteral Nutr*. 1993;17:468–478.
7. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr*. 2009;28(4):365–377. doi:10.1016/j.clnu.2009.03.015
8. Kovacevich DS, Corrigan M, Ross VM, McKeever L, Hall AM, Braunschweig C. American Society for Parenteral and Enteral Nutrition guidelines for the selection and care of central venous access devices for adult home parenteral nutrition administration. *JPEN J Parenter Enteral Nutr*. 2019;43(1):15–31. doi:10.1002/jpen.1455
9. Alhimyary A, Fernandez C, Picard M, et al. Safety and efficacy of total parenteral nutrition delivered via a peripherally inserted central venous catheter. *Nutr Clin Pract*. 1996;11:199–203.
10. American Society of Health System Pharmacists. ASHP guidelines on compounding sterile preparations. *Am J Health Syst Pharm*. 2014;71(2):145–166. doi:10.2146/sp140001
11. General Chapter <797> Pharmaceutical compounding—sterile preparations. Accessed April 5, 2021. https://www.usp.org/compounding/general-chapter-797
12. Turpin RS, Canada T, Liu FX, Mercaldi CJ, Pontes-Arruda A, Wischmeyer P. Nutrition therapy cost analysis in the US: pre-mixed multi-chamber bag vs compounded parenteral nutrition. *Appl Health Econ Health Policy*. 2011;9(5):281–292. doi:10.2165/11594980-000000000-00000

13. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition [published correction appears in *JPEN J Parenter Enteral Nutr*. 2006;30:177]. *JPEN J Parenter Enteral Nutr*. 2004;28:S39–S70.
14. Vanek VW, Seidner DL, Allen P, et al. A.S.P.E.N. position paper: clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract*. 2012;27:150–192.
15. Goulet O, Antébi H, Wolf C, et al. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2010;34:485–495.
16. Reimund JM, Rahmi G, Escalin G, et al. Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. *Aliment Pharmacol Ther*. 2005;21:445–454.
17. Raman M, Almutairdi A, Mulesa L, Alberda C, Beattie C, Gramlich L. Parenteral nutrition and lipids. *Nutrients*. 2017;9(4):388. doi:10.3390/nu9040388
18. Seidner DL, Mascioli EA, Istfan NW, et al. Effects of long-chain triglyceride emulsions on reticuloendothelial system function in humans. *JPEN J Parenter Enteral Nutr*. 1989;13:614–619.
19. Marchesini G, Bianchi G, Rossi B, Brizi M, Melchionda N. Nutritional treatment with branched chain amino acids in advanced liver cirrhosis. *J Gastroenterol*. 2000;35(suppl 12):7–12.
20. Fabbri A, Magrini N, Bianchi G, Zoli M, Marchesini G. Overview of randomized clinical trials of oral branched-chain amino acid treatment in chronic hepatic encephalopathy. *JPEN J Parenter Enteral Nutr*. 1996;20:159–164.
21. Skeie B, Kvetan V, Gil KM, Rothkopf MM, Newsholme EA, Askanazi J. Branch-chain amino acids: their metabolism and clinical utility. *Crit Care Med*. 1990;18:549–571.
22. Kearns LR, Phillips MC, Ness-Abramof R, Apovian CM. Update on parenteral amino acids. *Nutr Clin Pract*. 2001;16:219–225.
23. Brown RO, Compher C. A.S.P.E.N. clinical guideline: nutrition support in adult acute and chronic renal failure. *JPEN J Parenter Enteral Nutr*. 2010;34(4):366–377.
24. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2016;40:159–211.
25. Melnick G. Value of specialty intravenous amino acids solutions. *Am J Health Syst Pharm*. 1996;53:671–674.
26. Davis CJ, Sowa D, Keim KS, Kinnare K, Peterson S. The use of prealbumin and C-reactive protein for monitoring nutrition support in adult patients

receiving enteral nutrition in an urban medical center. *JPEN J Parenter Enteral Nutr*. 2012;36(2):197–204. doi:10.1177/0148607111413896

27. Bayer-Berger M, Chioléro R, Freeman J, Hirschi B. Incidence of phlebitis in peripheral parenteral nutrition: effect of the different nutrient solutions. *Clin Nutr*. 1989;8:181–186.
28. Daly JM, Masser E, Hansen L, Canham JE. Peripheral vein infusion of dextrose/amino acid solutions ± 20% fat emulsion. *JPEN J Parenter Enteral Nutr*. 1985;9:296–299.
29. Neyra R, Chen KY, Sun M, Shyr Y, Hakim RM, Ikizler TA. Increased resting energy expenditure in patients with end-stage renal disease. *JPEN J Parenter Enteral Nutr*. 2003;27:36–42.
30. Scheinkestel CD, Adams F, Mahony L, et al. Impact of increasing parenteral protein loads on amino acid levels and balance in critically ill anuric patients on continuous renal replacement therapy. *Nutrition*. 2003;19:733–740.
31. Scheinkestel CD, Kar L, Marshall K, et al. Prospective randomized trial to assess caloric and protein needs of critically ill, anuric, ventilated patients requiring continuous renal replacement therapy. *Nutrition*. 2003;19:909–916.
32. Krenitsky J, Rosner MH. Nutrition support with patients with acute kidney injury. Nutrition Issue in Gastroenterology, Series #96. Practical Gastroenterology; June 2011:28–42. https://www.ficomputing.net/pdf/June11/KrenitksyJuneArticle.pdf
33. Fiaccadori E, Maggiore U, Rotelli C, et al. Effects of different energy intakes on nitrogen balance in patients with acute renal failure: a pilot study. *Nephrol Dial Transplant*. 2005;20:1976–1980.
34. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis*. 2020;76(3):S1–S107. doi:10.1053/j.ajkd.2020.05.006
35. Cano N, Fiaccadori E, Tesinsky P, et al. ESPEN guidelines on enteral nutrition: adult renal failure. *Clin Nutr*. 2006;25:295–310.
36. Blumenkrantz MJ, Kopple JD, Moran JK, Coburn JW. Metabolic balance studies and dietary protein requirements in patients undergoing continuous ambulatory peritoneal dialysis. *Kidney Int*. 1982;21:849–861.
37. Driscoll DF. Clinical issues regarding the use of total nutrient admixtures. *DICP*. 1990;24:296–303.
38. Wolfe RR. Glucose metabolism in burn injury: a review. *J Burn Care Rehabil*. 1985;6:408–418.
39. Delafosse B, Bouffard Y, Viale JP, Annat G, Bertrand O, Motin J. Respiratory changes induced by parenteral nutrition in postoperative patients undergoing inspiratory pressure support ventilation. *Anesthesiology*. 1987;66:393–396.
40. Quigley EM, Marsh MN, Shaffer JL, Markin RS. Hepatobiliary complications of total parenteral nutrition. *Gastroenterology*. 1993;104:286–301.
41. White JV, Guenter P, Jensen G, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral

Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr*. 2012;36(3):275–283. doi:10.1177/0148607112440285

42. JeVenn AK, Galang M, Hipskind P, et al. Malnutrition screening and assessment. In: Mueller C, Lord LM, Marian M, et al, eds. *The ASPEN Adult Nutrition Support Core Curriculum*. 3rd ed. American Society for Parenteral and Enteral Nutrition; 2017:e-20.
43. Solomon SM, Kirby DK. The refeeding syndrome: a review. *JPEN J Parenter Enteral Nutr*. 1990;14:90–97.
44. Brooks MJ, Melnik G. The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. *Pharmacotherapy*. 1995;15:713–726.
45. da Silva JSV, Seres DS, Sabino K, et al. ASPEN consensus recommendations for refeeding syndrome. *Nutr Clin Pract*. 2020;35(2):178–195. doi:10.1002/ncp.10474
46. Sacks GS, Mouser JF. Is IV lipid emulsion safe in patients with hypertriglyceridemia? *Nutr Clin Pract*. 1997;12:120–123.
47. Patel R. Parenteral nutrition formulations. In: Mueller CM, Lord LM, Marian M, et al, eds. *The ASPEN Adult Nutrition Support Core Curriculum*. American Society for Parenteral and Enteral Nutrition; 2017.
48. Slattery E, Rumore MM, Douglas JS, Seres DS. 3-in-1 vs 2-in-1 parenteral nutrition in adults: a review. *Nutr Clin Pract*. 2014;29(5):631–635. doi:10.1177/0884533614533611
49. O'Grady NP. Guidelines for the prevention of intravascular catheter-related infections, 2011. Published online 2017:80. https://www.cdc.gov/infectioncontrol/pdf/guidelines/bsi-guidelines-H.pdf
50. D'Erasmo E, Pisani D, Ragno A, Romagnoli S, Spagna G, Acca M. Serum albumin level at admission: mortality and clinical outcome in geriatric patients. *Am J Med Sci*. 1997;314:17–20.
51. Choban P, Dickerson R, Malone A, Worthington P, Compher C. A.S.P.E.N. clinical guidelines: nutrition support of hospitalized adult patients with obesity. *JPEN J Parenter Enteral Nutr*. 2013;37(6):714–744. doi:10.1177/0148607113499374
52. Choban PS, Dickerson RN. Morbid obesity and nutrition support: is bigger different? *Nutr Clin Pract*. 2005;11:300–311.
53. Singer P, Berger MM, van den Berghe G, et al. ESPEN guidelines on parenteral nutrition: intensive care. *Clin Nutr*. 2009;28:387–400.
54. de Pretis N, Amodio A, Frulloni L. Hypertriglyceridemic pancreatitis: epidemiology, pathophysiology and clinical management. *United European Gastroenterol J*. 2018;6(5):649–655. doi:10.1177/2050640618755002
55. Arvanitakis M, Ockenga J, Bezmarevic M, et al. ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. *Clin Nutr*. 2020;39(3):612–631. doi:10.1016/j.clnu.2020.01.004

56. Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med*. 1995;98:75–84.
57. Lewis KS, Kane-Gill SL, Bobek MB, Dasta JF. Intensive insulin therapy for critically ill patients. *Ann Pharmacother*. 2004;38:1243–1251.
58. McMahon MM, Nystrom E, Braunschweig C, et al. ASPEN clinical guideline: nutrition support of adult patients with hyperglycemia. *JPEN J Parenter Enteral Nutr*. 2013;37(1):23–36.
59. McMahon MM. Management of hyperglycemia in hospitalized patients receiving parenteral nutrition. *Nutr Clin Pract*. 1997;12:35–38.
60. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
61. Montori VM, Bistrian BR, McMohan MM. Hyperglycemia in acutely ill patients. *JAMA*. 2002;288:2167–2169.
62. Gosmanov AR, Umpierrez GE. Medical nutrition therapy in hospitalized patients with diabetes. *Curr Diab Rep*. 2012;12(1):93–100. doi:10.1007/s11892-011-0236-5
63. Rosemarin DK, Wardlaw GM, Mirtallo J. Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. *Nutr Clin Pract*. 1996;11:151–156.
64. van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med*. 2003;31:359–366.
65. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal would infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg*. 1999;67:352–360.
66. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg*. 1997;63:356–361.
67. Blaauw R, Osland E, Sriram K, et al. Parenteral provision of micronutrients to adult patients: an expert consensus paper. *JPEN J Parenter Enteral Nutr*. 2019;43(S1):S5–S23. doi:10.1002/jpen.1525
68. Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2004;28:S54.
69. Baumgartner TG. Enteral and parenteral electrolyte therapeutics. *Nutr Clin Pract*. 2001;16:226–235.
70. Brown KA, Dickerson RN, Morgan LM, Alexander KH, Minard G, Brown RO. A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. *JPEN J Parenter Enteral Nutr*. 2006;30:209–214.
71. Rosen GH, Boullata JI, O'Rangers EA, Enow NB, Shin B. Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. *Crit Care Med*. 1995;23:1204–1210.

72. Lau AH, How PP fluid and electrolyte disorders. In: Zeind CS, Carvalho MG, eds. *Applied Therapeutics: The Clinical Use of Drugs*. 11th ed. Wolters Kluwer Health; 2018:568.
73. Knowles JB, Cusson G, Smith M, Sitrin MD. Pulmonary deposition of calcium phosphate crystals as a complication of home parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1989;13:209–213.
74. McKinnon BT. FDA safety alert: hazards of precipitation associated with parenteral nutrition [published correction appears in *Nutr Clin Pract*. 1996;11:120]. *Nutr Clin Pract*. 1996;11:59–65.
75. Oppenheimer JH, Werner SC. Effect of prednisone on thyroxine-binding proteins. *J Clin Endocrinol Metab*. 1966;26:715–721.
76. Gondolesi G, Ramisch D, Padin J, et al. What is the normal small bowel length in humans? First donor-based cohort analysis. *Am J Transplant*. 2012;12:S49–S54.
77. Dabney A, Thompson J, DiBaise J, Sudan D, McBride C. Short bowel syndrome after trauma. *Am J Surg*. 2004;188:792–795.
78. Bernard DK, Shaw MJ. Principles of nutrition therapy for short-bowel syndrome. *Nutr Clin Pract*. 1993;8:153–162.
79. Palmer LB, Janas R, Sprang M. Gastrointestinal disease. In: Mueller CM, Lord LM, Marian M, eds. *The ASPEN Adult Nutrition Support Core Curriculum*. American Society for Parenteral and Enteral Nutrition; 2017.
80. Osborne MP, Sizer JS, Frederick MD, Zamcheck N. Massive bowel resection and gastric hypersecretion: its mechanism and a plan for clinical study and management. *Am J Surg*. 1967;114:393–397.
81. Frederick PL, Sizer JS, Osborne MP. Relation of massive bowel resection to gastric secretion. *N Engl J Med*. 1965;272:509–514.
82. Osborne MP, Frederick PL, Sizer JS, Blair D, Cole P, Thum W. Mechanism of gastric hypersecretion following massive intestinal resection. Clinical and experimental observations. *Ann Surg*. 1966;164:622–634.
83. Ladefofed K, Christensen KC, Hegnhøj J, Jarnum S. Effect of a long-acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. *Gut*. 1989;30:943–949.
84. Kumpf VJ, de Aguilar-Nascimento JE, Diaz-Pizarro Graf JI, et al. ASPEN-FELANPE clinical guidelines. *JPEN J Parenter Enteral Nutr*. 2017;41(1):104–112.
85. Konrad D, Mitchell R, Hendrickson E. Home nutrition support. In: Mueller CM, Lord LM, Marian M, eds. *The ASPEN Adult Nutrition Support Core Curriculum*. American Society for Parenteral and Enteral Nutrition; 2017.
86. Malone AM. Supplemental zinc in wound healing: is it beneficial? *Nutr Clin Pract*. 2000;15:253–256.
87. Stevens P, Burden S, Delicata R, Carlson G, Lal S. Somatostatin analogues for treatment of enterocutaneous fistula. *Cochrane Database Syst Rev*. 2019;2019(6). doi:10.1002/14651858.CD010489.pub2

88. Driscoll DF, Baptista RJ, Mitrano FP, Mascioli EA, Blackburn GL, Bistrian BR. Parenteral nutrient admixtures as drug vehicles. Theory and practice in the critical care setting. *Ann Pharmacother*. 1991;25:276–283.
89. Hwang TL, Lue MC, Chen LL. Early use of cyclic TPN prevents further deterioration of liver functions for the TPN patients with impaired liver function. *Hepatogastroenterology*. 2000;47(35):1347–1350.
90. Buchman A. Total parenteral nutrition-associated liver disease. *JPEN J Parenter Enteral Nutr*. 2002;26(5 suppl):S43–S48.
91. Park HW, Lee NM, Kim JH, Kim KS, Kim SN. Parenteral fish oil–containing lipid emulsions may reverse parenteral nutrition–associated cholestasis in neonates: a systematic review and meta-analysis. *J Nutr*. 2015;145:277–283.
92. Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. *Aliment Pharmacol Ther*. 2013;37:587–603.
93. Hamilton C, Seidner DL. Metabolic bone disease and parenteral nutrition. *Curr Gastroenterol Rep*. 2004;6:335–341.
94. Sutton CD, Garcea G, Pollard C, Berry DP, Dennison AR. The introduction of a nutrition clinical nurse specialist results in a reduction in the rate of catheter sepsis. *Clin Nutr*. 2005;24:220–223.

SECTION 8

Dermatologic Disorders

Section Editor: Katie Kiser

39

Dermatotherapy and Drug-Induced Skin Disorders

Daniel R. Malcom and Lynn Z. Fuller

CORE PRINCIPLES		CHAPTER CASES
1	Accurate assessment of dermatologic conditions is primarily based on the appearance and location of the skin lesion, plus age, sex, symptoms, and current and past medical and family histories.	**Case 39-1 (Question 1), Figure 39-1, Tables 39-1–39-3**
2	The selection of topical corticosteroid is based on the nature of the lesion (wet vs dry), the concentration of the corticosteroid, the nature of the vehicle, the corticosteroid potency, the location of the lesion, and the thickness of the epidermis.	**Case 39-2 (Question 1, 2), Figure 39-1, Tables 39-1–39-5**
3	Topical corticosteroids can cause a	**Case 39-3 (Question 1–3), Tables 39-4–39-6**

	variety of adverse effects and adverse reactions that may require adjustment of therapy, including changing products or discontinuing their use.	
4	Dry skin (xerosis) is a common condition that may occur alone or with a variety of dermatologic disorders and requires appropriate treatment depending on geographic location.	**Case 39-4 (Question 1)**
5	Atopic dermatitis is a common dermatologic condition characterized by eczematous lesions, dry skin, and intense pruritus. It is primarily treated with topical corticosteroids and emollients.	**Case 39-5 (Question 1–5), Tables 39-1, 39-3, 39-4, 39-7**
6	Allergic contact dermatitis is one of the most common dermatologic conditions seen by pharmacists. Treatment consists of removal of the antigen and use of topical or systemic corticosteroids.	**Case 39-6 (Question 1), Case 39-7 (Question 1), Tables 39-1, 39-3, 39-4, 39-7**
7	Medications are a common cause of a variety of dermatologic disorders. Timing relative to medication ingestion and principles of dermatologic assessment are important to identify potential life-threatening adverse reactions.	**Case 39-8 (Question 1), Table 39-5**

INTRODUCTION

Anatomy and Physiology of the Skin

The skin is the largest organ in the body and constitutes, on average, nearly one-fifths of a person's body weight. **Figure 39-1** shows a cross section of the anatomy of human skin. Physiologically, the major function of skin is to protect the underlying structures from trauma, temperature variations, mechanical penetrations, moisture, humidity, radiation, and invasion of microorganisms. There are three layers of skin: epidermis, dermis, and subcutaneous tissue.[1–5]

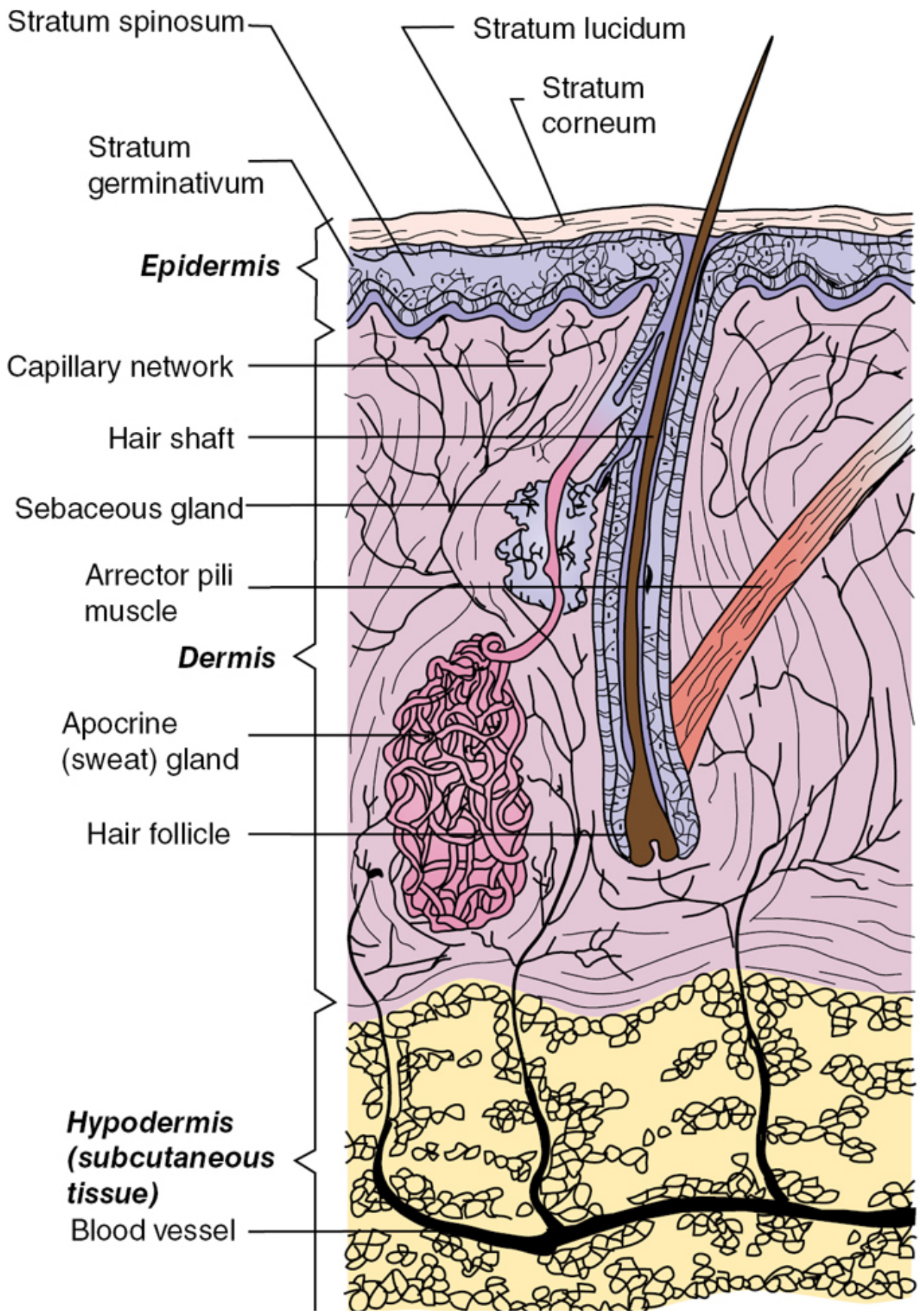

Stratum spinosum
Stratum lucidum
Stratum corneum
Stratum germinativum
Epidermis
Capillary network
Hair shaft
Sebaceous gland
Arrector pili muscle
Dermis
Apocrine (sweat) gland
Hair follicle
Hypodermis (subcutaneous tissue)
Blood vessel

Figure 39-1 Cross section of the anatomy of human skin.

EPIDERMIS

The major function of the epidermis is to serve as a barrier. The *stratum corneum*, which is the outermost layer of the epidermis, provides the greatest resistance to the percutaneous absorption of chemicals and drugs. It behaves as a semipermeable membrane through which drugs are absorbed by passive diffusion. Skin hydration and damage to the stratum corneum can enhance drug absorption. Skin diseases affecting only the epidermis typically heal without scarring.[1–5]

DERMIS

The dermis is composed of collagen fibers and provides capillary, lymphatic, and nerve supply to the skin. The dermis contains large amounts of water, thus serving as a water storage organ as well. Importantly, all but the most superficial injuries to the dermis generally result in scarring as the wound heals.[1–5]

Drugs passing through the epidermis penetrate directly into the dermis and may be absorbed into the general circulation through the capillary network. Only small amounts of topically applied drugs enter the dermis via the sweat glands or the pilosebaceous units.

SUBCUTANEOUS LAYER

The subcutaneous layer supports the dermis and epidermis and serves as a fat storage area. This layer helps regulate temperature and provides nutritional support and cushioning to the outer skin layers.[1–5]

DERMATOLOGIC DRUG DELIVERY SYSTEMS

Dermatologic formulations are available in a variety of forms: solutions, suspensions or shake lotions, powders, lotions, emulsions, gels, creams, ointments, and aerosols. Each dermatologic delivery vehicle has specific characteristics and uses based on the type, relative acuteness, and location of the lesion.

Selection of a Delivery System

Dermatologic vehicles should be matched to the type of lesion for which they will be used. Acute lesions (ie, immediately following presentation, often weeping or oozing) require aqueous vehicles until the lesions become dry. Subacute lesions (ie, after initial healing has started and crusting has occurred) also benefit from aqueous vehicles, but for shorter periods before switching to creams or gels. Chronic lesions usually require ointments because of their dry, lichenified characteristics.

Solutions

Solutions provide evaporative cooling and vasoconstriction, with resultant mild antipruritic effects. Aqueous solutions are most useful for acutely inflamed, oozing lesions and are often applied as wet dressings. The most commonly used solutions are normal saline (0.9% NaCl) and aluminum acetate 5% solution (Burow solution) diluted 1:10 to 1:40.

The most important component of a solution is water. Although active or inert substances may be added to solutions, the cleansing, drying, and cooling effect of water provides the major therapeutic benefit. Some products (eg, Burow solution) also have *astringent* properties that alter the skin surface and interstitial spaces to cause contraction and wrinkling. Water penetration is reduced to minimize edema, inflammation, and exudation.[6]

Powders

Powders can be medicated or nonmedicated, although even nonmedicated powders can have therapeutic benefit. They are drying and cooling, absorbing moisture and creating more surface area for evaporation. They are used mainly in intertriginous areas where skin touches the skin (eg, groin, under the breasts, or in skin folds) to decrease friction and irritation. Powders are useful in the treatment of chafing, tinea pedis (athlete's foot), tinea cruris (jock itch), and diaper dermatitis (diaper rash). Contrary to what may be thought given their drying effect, powders should not be applied to oozing lesions because they tend to cake into hard granules, making them difficult and painful to remove and promoting maceration. The most commonly used powder is talc.

Lotions

Lotions are suspensions or solutions of powder in a water vehicle. They are usually cooling and drying, but may provide some lubrication, depending on the formulation. Lotions are used to treat superficial dermatoses, especially if there is slight oozing. They are useful if large or intertriginous areas are affected, and they are especially advantageous in the treatment of conditions characterized by significant inflammation and tenderness.[6]

Liquid Emulsions

Liquid emulsions can be divided into two classes: *oil-in-water* (o/w) and *water-in-oil* (w/o) emulsions. Creams are generally oil-in-water emulsions, whereas ointments are water-in-oil emulsions. The indications for liquid oil-in-water emulsions (eg, Keri Lotion, Cetaphil) are similar to those for lotions and creams, except that this dosage form provides greater occlusion and is more useful in conditions in which dry skin predominates. Liquid water-in-oil emulsions (eg, Nivea, Eucerin, or Lubriderm) have similar indications to ointments, except that they can be applied more easily than ointments. Water-in-oil emulsions are most useful in conditions in which dry skin

predominates; application to hairy or intertriginous areas should be avoided.[7]

Gels

Gels are a form of ointment (semisolid emulsion) that contain propylene glycol (a drying agent) and carboxypolymethylene (a thickening agent). They are clear, nongreasy, nonstaining, nonocclusive, and quick drying. They are thixotropic (ie, become thinner with rubbing and may sting on application). Gels are most useful when applied to hairy areas or other areas such as the face or scalp, where it is considered cosmetically unacceptable to have the residue of a vehicle remain on the skin. Because of their ingredients, gels tend to be more drying.

Creams

Creams are the most commonly used vehicle in dermatology. Most are oil-in-water emulsions and are intended to be rubbed in well until they vanish. Because creams are drying and do not provide much occlusiveness, they are most often recommended for subacute lesions and occasionally for chronic lesions without significant lichenification.

Ointments

Ointments are made of inert bases such as petrolatum or may consist of droplets of water suspended in a continuous phase of oleaginous material (ie, water-in-oil emulsions such as Aquaphor® or Polysorb®). Ointments are most useful on chronic lesions, relieving dryness, brittleness, and protecting fissures owing to their occlusive properties. They should not be used on acutely inflamed lesions. Ointments should not be applied to intertriginous, burns, or hairy areas because they tend to trap heat and promote maceration. Ointments are greasy and may be cosmetically unacceptable.

Aerosols

Aerosols are the most expensive and inefficient way to apply dermatologic medications. Their only advantage over other dosage forms is that they do not require direct mechanical contact with the skin and may be useful if application causes intolerable pain for the patient. If an aerosol is used, it should be shaken well before use, and the patient should be cautioned not to spray the product around the face where it could get into the eyes or nose or be inhaled. Generally, aerosols should be sprayed from approximately 6 inches (15.24 cm) above the skin in bursts of 1 to 3 seconds. Aerosols are also useful for application to hairy areas if a special application nozzle is used. Aerosols have a drying effect and should not be used for a long period. Because aerosols contain a propellant, patients may have reactions to this dosage form.

PATIENT ASSESSMENT

CASE 39-1

QUESTION 1: C.B., a 23-year-old, 145.50 pounds (66-kg) female, with rashes.
What types of questions should C.B. be asked to help determine the appropriate diagnosis and treatment?

The diagnosis of dermatologic conditions can be simplified by considering six primary factors: appearance (what the lesions look like, pattern of the lesions); location or distribution of the lesions on the body; symptoms, both local and systemic; history of the present condition as well as related conditions; age of the patient; and biologic sex. Direct observation of the skin lesion, plus C.B.'s responses to questions about these factors, will allow an appropriate diagnosis and treatment plan.

Appearance (Morphology)

Table 39-1 provides a listing of common dermatologic lesions, their respective definitions, and some well-known clinical examples. Lesions may also be classified as either primary (first appearing on the skin) or secondary (developing from primary lesions). Early and accurate recognition of lesions can be critical to achieving optimal therapeutic outcomes.

Table 39-1
Dermatologic Lesions, Definitions, and Clinical Examples

Name	Definition	Examples
Primary Lesions		
Macule	Nonpalpable, flat, change in color, <0.39 inches (1 cm)	Freckles, flat moles
Patch	Nonpalpable, flat, change in color, >0.39 inches (1 cm)	Vitiligo, “café au lait” spots, chloasma
Papule	Palpable, solid mass, may have change in color, <0.39 inches (1 cm)	Verrucae, noninflammatory acne (comedone), raised nevus
Nodule	Palpable, solid mass, most often below the plane of the skin, 0.39–0.78 inches (1–2 cm)	Erythema nodosum, severe acne
Tumor	Palpable, solid mass, >0.78 inches (2 cm), most often above and below the plane of the skin	Neoplasms
Plaque	Flat, elevated, superficial papule with surface area greater than height, >0.39 inches (1 cm)	Psoriasis, seborrheic keratosis
Wheal	Superficial area of cutaneous edema, fluid not confined to cavity	Urticaria (hives), insect bite
Vesicle	Palpable, fluid-filled cavity, <0.39 inches (1 cm), filled with serous fluid (blister)	Herpes simplex, herpes zoster, contact dermatitis
Bulla	Palpable, fluid-filled cavity, >0.39 inches (1 cm), filled with serous fluid (blister)	Pemphigus vulgaris, second-degree burn

Name	Definition	Examples
Pustule	Similar to vesicle, but filled with purulent fluid	Acne, impetigo, folliculitis
Special Primary Lesions		
Comedone	Plugged opening of sebaceous gland	Acne, blackhead, whitehead
Cyst	Palpable lesion filled with semiliquid material or fluid	Sebaceous cyst
Abscess	Accumulation of purulent material in dermis or subcutaneous layers of skin; purulent material not visible on surface of skin	
Furuncle	Inflammatory nodule involving a hair follicle, following an episode of folliculitis	Small boil
Carbuncle	A coalescence of several furuncles	Large boil
Secondary Lesions		
Erosion	Loss of part or all the epidermis	Ecthyma
Ulcer	Loss of epidermis and dermis	Stasis ulcer
Fissure	Linear crack from epidermis into dermis	Tinea pedis
Excoriation	Self-induced linear, traumatized area caused by intense scratching	Atopic dermatitis, extreme pruritus
Atrophy	Thinning of skin with loss of dermal tissue	Striae
Crusts	Dried residue of pus, serum, or blood from a wound, pustule, or vesicle	Impetigo, scabs
Lichenification	Thickening of epidermis, accentuated skin markings, usually induced by scratching or chronic inflammation	Atopic dermatitis, allergic contact dermatitis

Many lesions present in a particular distribution or pattern. Poison ivy lesions are commonly distributed linearly. Herpetic lesions are so typical that the term “herpetiform” is used for lesions caused by other conditions that have a herpes-like distribution. The specific size of the lesion is also important in assessing a patient’s condition. Dermatologic terms related to lesion distribution or pattern are shown in **Table 39-2**. The lesion’s consistency (firm vs soft), borders, and color are also important diagnostic considerations.

Table 39-2

Descriptive Dermatologic Terms

Term	Characteristics	Examples
Annular	Ring-shaped	Tinea
Acneiform	Acne-like	Acne vulgaris
Arcuate	Shaped like an arc	Syphilis
Circinate	Circular	Tinea
Confluent	Lesions run together	Psoriasis, tinea
Discrete	Lesions remain separate	Psoriasis, tinea
Eczematous	General term for dry, red flaky, or lichenified skin without clear border	Chronic allergic contact dermatitis, atopic dermatitis
Geographic	Shaped like islands or continents; map-like	Generalized psoriasis
Grouped	Lesions clustered together	Herpes
Herpetiform	Appears like herpes simplex	Herpes simplex
Intertrigo	Irritant dermatitis in skin folds	Diaper dermatitis
Iris	Looks like a bull's-eye, lesion within a lesion, target lesion	Erythema multiforme
Keratotic	Horny thickening	Psoriasis, corn, callus
Linear	Shaped in lines	Poison ivy
Multiform	More than one type or shape of lesion	Erythema multiforme
Papulosquamous	Papules with desquamation	Psoriasis
Serpiginous	Snake-like lesions	Cutaneous larva migrans
Zosteriform	Appears like herpes zoster	Herpes zoster

Location

Certain lesions or conditions usually occur in specific body locations, usually because of physiologic reasons. **Table 39-3** provides a list of anatomic sites with common dermatoses occurring in those locations. For example, diseases of the sebaceous glands (eg, acne,

seborrheic dermatitis, rosacea) occur only in sites with high concentrations of sebaceous glands, such as the scalp, head, neck, chest, and umbilicus. Atopic dermatitis shows a predilection for the flexor surfaces of the body (ie, antecubital and popliteal fossae).

Table 39-3
Common Skin Diseases by Body Location

Location	Skin Diseases
Scalp	Seborrheic dermatitis, dandruff
Face	Acne, rosacea, seborrheic dermatitis, perioral dermatitis, impetigo, herpes simplex, atopic dermatitis
Ears	Seborrheic dermatitis
Chest or abdomen	Tinea versicolor, tinea corporis, pityriasis rosea, acne, herpes zoster
Back	Tinea versicolor, tinea corporis, pityriasis rosea
Genital area	Tinea cruris, scabies, pediculosis, condyloma acuminate (venereal warts)
Extremities	Atopic dermatitis (cubital and popliteal fossa)
Hands	Tinea manuum, scabies, primary irritant contact dermatitis, warts
Feet	Tinea pedis, contact dermatitis, onychomycosis
Generalized or localized	Primary irritant or contact dermatitis, photodermatitis

Symptoms

Most skin conditions have only localized symptoms with the most common symptom being pruritus. Occasionally, localized burning or pain is the predominant symptom.

History

Although a diagnosis may often be made from morphology, location, and symptoms, the patient history provides useful diagnostic and therapeutic information. Similar to the historical information obtained

for any acute medical problem, the following questions should always be asked:

1. When and how did the problem start?
2. How has it progressed or changed since its onset? How have the lesions changed in size, color, appearance, or severity?
3. What is the patient's past and current medical history? What other symptoms might indicate that this is a dermatologic manifestation of a systemic disease?
4. What are the patient's other symptoms?
5. What kind of allergies does the patient have?
6. What makes the condition worse or better?
7. What events or happenings have occurred with the onset or worsening of the condition (eg, increased stress, exposure to new products, recent travel, and changes in climate)?
8. What have you used to treat the condition, and how have the treatments worked?
9. How did the patient use any previous therapy, and for how long did they use it?

Age

Certain conditions occur predominantly among certain age groups, such as acne in neonates and adolescents, seborrheic dermatitis in neonates and those ages 11 to 12 years, rosacea in those older than 30 years, and atopic dermatitis primarily in children younger than 6 years. In fact, atopic dermatitis begins and ends before age 6 years in 95% of patients. It is equally important to realize that many conditions, such as primary irritant and allergic contact dermatitis, occur independent of age. In addition, the skin of children and patients older than 65 years is more penetrable, thus more responsive and more susceptible to adverse effects from therapy with topical agents. Topical therapeutic agent potency and delivery systems must be carefully evaluated before usage.

Sex

Although most dermatologic conditions occur in both sexes, sometimes frequency and severity are sex-dependent. Rosacea occurs more frequently in females but is often more serious in males.

TOPICAL CORTICOSTEROIDS

Table 39-4 lists the most common topical corticosteroid preparations by their degree of potency according to the Stoughton–Cornell classification system. When equal amounts of a corticosteroid are incorporated into ointments, gels, creams, and lotion bases, the gel and ointment preparations are generally more active than creams and lotions.[8–12] However, with the increased use of optimized vehicles, that rule is not as true as in the past. The addition of certain substances enhances penetration and potency. Using these principles, pharmaceutical manufacturers have increasingly developed optimized vehicles that maximize diffusion of individual corticosteroids into the stratum corneum. Unfortunately, these optimized bases may be labeled as ointments, creams, or gels. Therefore, for new products, the only reliable way to ascertain potency is to consult the manufacturer's literature for its Stoughton–Cornell classification. Increasing the concentration of a corticosteroid in a preparation also increases its potency, but not in a linear fashion.

Table 39-4
Selected Topical Corticosteroid Preparations by Stoughton–Cornell Classification of Potency

Corticosteroid	Example Brand Name(s)	Vehicle
1 (Most Potent) No >2 Weeks' Use		
Betamethasone dipropionate, augmented	Diprolene 0.05%	Gel, lotion, ointment (optimized)

Corticosteroid	Example Brand Name(s)	Vehicle
Clobetasol propionate	Temovate 0.05%	Cream, gel, ointment, solution (scalp)
Fluocinonide	Vanos 0.1%	Cream
Halobetasol propionate	Ultravate 0.05%	Cream, lotion, ointment
2		
Betamethasone dipropionate, augmented	Diprolene AF 0.05%	Cream
Betamethasone dipropionate	Diprosone 0.05%	Ointment
Diflorasone diacetate	Florone, ApexiCon 0.05%	Ointment
Fluocinonide	Lidex 0.05%	Cream, gel, ointment, solution
Halobetasol propionate	Bryhali® 0.01%	Lotion
Mometasone furoate[a]	Elocon 0.1%	Ointment
3		
Betamethasone dipropionate	Diprosone 0.05%	Cream, hydrophilic ointment
Betamethasone valerate	Valisone 0.1%	Ointment
Diflorasone diacetate	Florone 0.05%	Cream
Fluocinonide	Lidex-E 0.05%	Cream aqueous emollient
Triamcinolone acetonide	Aristocort HP, Kenalog, Triderm 0.05%	Cream, ointment
4		
Betamethasone dipropionate	Sernivo 0.05%	Spray
Fluocinolone acetonide	Synalar 0.025%	Ointment
Hydrocortisone valerate[a]	Westcort 0.2%	Ointment
Mometasone furoate[a]	Elocon 0.1%	Cream
Triamcinolone acetonide	Kenalog, Triderm 0.1%	Cream, ointment
5		

Corticosteroid	Example Brand Name(s)	Vehicle
Betamethasone dipropionate	Diprosone 0.05%	Lotion
Betamethasone valerate	Beta-Val, Valisone 0.1%	Cream
Fluocinolone acetonide	Synalar 0.025%	Cream
Hydrocortisone butyrate[a]	Locoid 0.1%	Cream, ointment, solution
Hydrocortisone valerate[a]	Westcort 0.2%	Cream
Triamcinolone acetonide	Kenalog 0.25%	Ointment
6		
Betamethasone valerate	Valisone 0.1%	Lotion
Desonide[a]	Desowen 0.05%	Cream
Fluocinolone acetonide	Synalar 0.01%	Cream, solution
Triamcinolone acetonide	Kenalog 0.025%	Cream, lotion
7 (Least Potent)		
Hydrocortisone[a] (base, ≥2%)	Hytone, Nutracort 2.5%	Cream, ointment
Hydrocortisone[a] (base, <2%)	Cortaid, Cortizone 1%	Cream, gel, ointment
Hydrocortisone[a] acetate	MiCort™ HC 2.5%	Cream

[a]Nonfluorinated corticosteroid.

Indications

A topical corticosteroid is often the drug of choice for many inflammatory and pruritic eruptions. In addition, topical corticosteroids are useful with hyperplastic and infiltrative disorders. The following conditions generally respond well to topical corticosteroids: allergic contact dermatitis, atopic dermatitis, psoriasis, and seborrheic dermatitis.

Contraindications

The following conditions (predominantly infectious etiologies) are worsened by topical corticosteroids: acne vulgaris, ulcers, scabies, warts, molluscum contagiosum, fungal infections, and viral infections.

CASE 39-2

QUESTION 1: A.J. is a 54-year-old male who has suffered intermittently from plaque psoriasis for almost 20 years. Most lesions have been coin-sized in various locations (mostly elbows and knees). Normally, gentle removal of the scales and application of 1% hydrocortisone ointment has been effective over several weeks during which it disappears. He has averaged less than a lesion a year. He saw a dermatologist once 18 years ago. Six weeks ago, a much larger hand-sized lesion developed on his elbow. The usual treatment has been ineffective.

What are the relevant biopharmaceutic considerations for selecting a topical corticosteroid for A.J.?

Topical corticosteroids are classified into potency categories (see Table 39-4). The relative potency assigned to a topical corticosteroid is determined by the ability of the preparation to penetrate the skin after release from the vehicle, the intrinsic activity of the corticosteroid at the receptor, and the rate of clearance from the receptor.[10] Activity of corticosteroids may be enhanced by the use of a more occlusive vehicle, the addition of penetration-enhancing substances (eg, petrolatum, propylene glycol), and pharmacologic structure modifications of the steroid molecule itself. For example, hydrocortisone has been modified at the structural level in several ways to alter its activity. The addition of a fluorine atom at the 6, 9, and 21 positions protects the steroid ring from metabolic conversion, resulting in more potent activity. The addition of a double bond between the first and second carbon atoms slows metabolism, increasing duration of action. The introduction of an acetonide bond or lipophilic ester groups increases skin penetration. Many newer topical corticosteroids have incorporated one or more of these molecular changes, resulting in increased-potency agents and a growing armamentarium of agents.[8–12]

Topical corticosteroids penetrate the stratum corneum by passive diffusion, which varies considerably, depending on thickness of the stratum corneum over the part of the body to which the preparation is applied. When a standard hydrocortisone preparation was applied to various parts of the body, absorption was found to be 0.14% on the plantar surface of the foot, 1% on the forearm, 4% on the scalp, 7% on the forehead, 13% on the cheeks, and 36% on the scrotum. Because penetration is high in the groin, axillae, and face, lower-potency nonfluorinated topical preparations such as hydrocortisone 0.5% to 1% should be used on these areas.[8–12] In areas where penetration is poor, owing to thicker stratum corneum, such as the elbows, knees, palms, or soles, higher-potency preparations should be used.[8–12]

The stratum corneum acts as a reservoir, precluding the need for more than twice daily application. In low-potency preparations, this reservoir effect persists for several days, and with the most potent preparations under occlusion, the effects may persist for up to 14 days.[8–12] The clinical implication of this reservoir effect on chronic conditions is a cumulative effect with repeated application of topical corticosteroids. As a result, the number of applications per day can be reduced, and less potent preparations can be used after the acute inflammatory process has been brought under control. It also allows less frequent administration to maintain remission.

For A.J., a high-potency cream (class 2 or 3 as listed by Stoughton–Cornell classification of corticosteroid potency in Table 39-4) should be used because the thicker stratum corneum over the elbow, the presence of scales, and a raised plaque decreases penetration.

Case 39-2, Question 2: Given A.J.'s larger lesion and the failure of his usual therapy, should occlusive therapy be used? What complications could develop from occlusion? How should the use of occlusion be explained to A.J.?

Occlusion

Occlusion increases the hydration of the skin and resultant absorption of corticosteroid preparations, thus producing a heightened therapeutic effect. Generally, occlusion can be accomplished by the following: (a) selecting an ointment-based corticosteroid, (b) applying a nonmedicated ointment base over a corticosteroid preparation (gel, cream, lotion, or aerosol), 30 minutes after applying the corticosteroid, or (c) by enveloping the medicated area with plastic (eg, plastic wrap, gloves, or plastic suit). Occlusion is best used for chronic lesions that are thick and scaly, in which drug absorption is impaired, such as psoriasis. Increasing the hydration of the skin (with a shower or bath) also increases the effects of medications immediately applied after the bath or shower. An appropriate recommendation for A.J. would be fluocinonide ointment 0.05% applied twice daily to only the psoriatic plaques.[4],[6],[8–12] For other conditions, for example, atopic dermatitis, several hours of occlusion are all that are necessary to increase potency, these relatively short periods of occlusion can be clinically useful. Occlusion can be uncomfortable and can lead to sweat retention and an increased risk of bacterial and fungal infections. To reduce these problems and the chances of systemic adverse effects, occlusion should not be maintained for more than 12 hours in a 24-hour period. Occlusion should not be used for acute lesions, which already have increased absorptive capability and need the vasoconstrictive effects of cooling first.

The powerful occlusive properties of cloth and disposable diapers tend to be underappreciated. Therefore, only lower-potency nonfluorinated topical corticosteroids such as hydrocortisone valerate or mometasone should be used in the diaper area for no more than 24 to 48 hours in the rare instances of severe diaper dermatitis not responding to conservative treatment. Use of topical corticosteroids to enhance the effectiveness of antifungals to treat diaper dermatitis complicated by fungal infection is only theoretic and does not enhance the efficacy of anticandidal antifungals. However, use of topical corticosteroids does increase the risk of potentially irreversible disfiguring local adverse effects, including scarring.

Adverse Drug Effects

Although relatively infrequent, both localized (ie, at the application site) and systemic adverse effects (from percutaneous absorption) can be caused by topical corticosteroids. The risks for adverse reactions are influenced by the potency of preparation used, frequency of application, duration of use, anatomic site of application, and individual patient factors. Any of the previously discussed factors that increase potency, such as inflammation and occlusion, increase the chances of adverse effects.[8]

CASE 39-3

QUESTION 1: K.L. is a 54-year-old male, recently diagnosed with mild Parkinson disease, who presents with a severe case of seborrheic dermatitis involving the ears, scalp line, forehead, and nasal labial folds. The areas are quite inflamed and red with yellow greasy scales. K.L. is upset with the way it looks. Because suppressing the cause of the disease, the yeast, *Malassezia furfur*, will take some time, it is decided to initially use a topical corticosteroid to reduce the redness and improve K.L.'s appearance.

What would be an appropriate choice of topical corticosteroid for K.L.?

The biggest concern for K.L. is the potential for epidermal and dermal atrophy (thinning of the skin), telangiectasia (small red or purple clusters of dilated capillaries), localized fine hair growth, bruising, hypopigmentation, and striae. These local complications can result from repeated application of topical corticosteroids.[11] Epidermal changes consisting of a reduction in cell size may begin within several days of therapy and are generally reversible after the therapy is stopped.[9] Exposed areas (face) and thin-skinned areas (groin) are most vulnerable to dermal and epidermal atrophy.

Dermal atrophy generally takes several weeks to occur and can be reversed in some cases, depending on how long the patient has used the corticosteroid, and on individual host factors such as skin age. Dermal atrophy can be reversible within 2 months after stopping the corticosteroid.[11]

Telangiectasia, which occurs most often on the face, neck, groin, and upper chest, may not be reversible after stopping corticosteroid therapy. Striae, which occur most commonly in the cubital and popliteal fossa, groin, axillary, and inner thigh areas, are usually permanent.[11] Fine hair growth may be particularly bothersome to female patients using corticosteroid preparations on the face. This problem is generally reversible after stopping therapy. Hypopigmentation, predominantly a problem of dark-skinned patients, is generally reversible after therapy is discontinued.[11]

Especially in thin-skinned areas such as the face, fluorinated corticosteroids are more likely to cause these localized reactions because of their increased potency than are nonfluorinated corticosteroids. Therefore, whenever possible, only nonfluorinated topical corticosteroids should be used in thin-skinned areas for the shortest possible time. Because the use of corticosteroids is expected to last less than a week, the risk of developing local complications is minimal with a nonfluorinated product.

Because the lesions are on the face, a nonfluorinated corticosteroid such as hydrocortisone valerate or mometasone should be used to minimize the potential for adverse effects in this thin-skinned area. Although there is minimal oozing and weeping, his sensitivity to appearance would indicate a cream might be more appropriate.

Case 39-3, Question 2: K.L. calls the next day and presents with a burning sensation lasting for about 30 minutes after each application. He wants to know whether potentially is this an allergic reaction?

Because of the time course of the burning sensation in K.L. (starting the first day and lasting only 30 minutes), it is doubtful that he is allergic to this product and the cream is likely the cause. To remedy this situation, K.L. should continue to apply the cream and if the burning sensation continues for the next 24 hours to call again. Creams applied to inflamed areas can cause burning initially. Because the inflammation lessens, the burning generally subsides. If

the burning persists, an ointment can be substituted for the cream. If the reaction continues with a new product, an allergy workup may be necessary and patch testing could be considered.

Cortisol is endogenously secreted by the adrenal gland and is essential to life. As a result, allergic reactions to topical corticosteroid preparations are rare. When allergic symptoms do occur, they are generally not caused by the corticosteroid, but rather the preservatives (eg, paraben) or other ingredients in the formulation or the base (eg, lanolin). Allergic sensitization can occur within 2 weeks of therapy, but may be difficult to diagnose because the corticosteroid can modify the allergic reaction.[13] One should suspect an allergic reaction if lesions change appearance after starting therapy, if healing does not occur within the expected time, or if the condition improves and then abruptly gets worse. In atopic dermatitis, most case reports of allergic reactions (dryness, itching, burning, or irritation) to topical corticosteroids are nonspecific reactions.[13] The use of creams or gels may cause excessive dryness, burning, and irritation, and switching to an ointment can alleviate those symptoms.

ACNE

Case 39-3, Question 3: After several weeks of continuous corticosteroid and adjuvant therapy, K.L.'s seborrheic dermatitis has disappeared, but he has developed four pustules and two closed comedones on his forehead and multiple pustules on his nasal labial folds. What problems from the use of topical corticosteroid therapy on the face or around the eyes does this represent?

The face is particularly vulnerable to corticosteroid adverse effects because of enhanced skin penetration.[11] Acne, acne rosacea, and perioral dermatitis can develop after several weeks to months of application. Corticosteroid-induced conditions can generally be distinguished from naturally occurring disorders because lesions are uniform at the same level of development throughout the affected area and are present only in areas treated with the corticosteroid.

Generally, steroid acne and perioral dermatitis resolve after discontinuing the drug. Although not specifically relevant to K.L.'s case, application of corticosteroid preparations (particularly the potent preparations) to areas around the eye can lead to increased intraocular pressure, glaucoma, cataracts, increased risk of ocular mycotic infections, and exacerbation of preexisting herpes simplex infections.[11]

Because K.L.'s original disorder was also treated with topical selenium sulfide shampoo to the face and the scalp to suppress the cause of his seborrheic dermatitis, the corticosteroid can be discontinued.

ADRENAL AXIS SUPPRESSION AND RISK OF INFECTION

Systemic adrenal axis suppression from topically applied corticosteroids appears to be more of a theoretic risk than a practical one in adults, except when the highest-potency preparations are used,[14] or other risk factors are present (**Table 39-5**). Although suppression has been reported with use of mild to moderately potent agents, these cases can be attributed to excessive use or to application of corticosteroids over large areas of the body for prolonged periods under occlusion. If suppression does occur, it reverses within 2 to 4 weeks after application is stopped. Patients using more than 45 g/week of a high-potency corticosteroid are at risk for adrenal axis suppression.[14] Therefore, the use of preparations such as clobetasol should be limited to no more than 45 g/week for 2 weeks or less. In addition, these preparations should not be used under occlusion and should be reserved for dermatoses that are unresponsive to less potent preparations.

Table 39-5
Risk Factors for Systemic Adverse Effects from Topical Corticosteroids

Duration of Application
Prolonged application (more than 3–4 weeks)
Potency of Corticosteroid

Weak or moderately strong, 100 g/week without occlusion
Very potent, >45 g/week without occlusion
Application Location
Thin stratum corneum results in easier penetration (eyelids, forehead, cheeks, armpits, groin, and genitals)
Age of Patient
Very young children and elderly people have very thin epidermis
Manner of Application
Occlusion
Presence of penetration-enhancing substances (propylene glycol, salicylic acid, urea)
General Factors
Compromised liver function
Uremia

Because young children absorb corticosteroids to a greater extent than adults, they have a greater risk of developing adrenal axis suppression and other systemic adverse effects.[14] To reduce this risk, low-potency topical preparations should be used in children, and their use should be limited to short periods. Patients whose corticosteroid clearance is impaired (eg, liver failure) should also use hydrocortisone and be monitored closely for signs of systemic toxicity.[11]

The risk of developing an Addisonian crisis during surgery or at other times of stress secondary to adrenal suppression from topical steroids is extremely low. Patients who have used potent topical corticosteroids over large areas of their bodies (>30%) or those who have used occlusion are at greater risk (see previous discussion) and are often given systemic hydrocortisone prophylactically before surgery.[14]

PROPER APPLICATION OF TOPICAL CORTICOSTEROIDS

Because overuse of topical corticosteroids leads to local and/or systemic effects and underuse results in suboptimal treatment, the

amount of corticosteroid required to treat certain anatomic areas of the body has long been an issue of debate and discussion.[15],[16] To prevent overuse in clinical practice, patients are typically given subjective instructions to apply topical products “sparingly” or “in a thin layer or coat” and is left up to the patient or caregiver’s interpretation.

The fingertip unit (FTU) was devised as a means of standardizing the way practitioners and pharmacists alike thought about how to prescribe topical corticosteroids and counsel patients on appropriate use. One FTU is defined as the amount of ointment (or other semisolid topical formulation) squeezed from a tube with a 5-mm diameter nozzle (standard in manufacturing), applied from the first distal skin crease to the tip of the index finger of an adult.[17–19] This amount is roughly equivalent to 500 mg of medication. The FTU can serve as a helpful starting point for how much product is used. Because lesions rarely conform to the exact anatomic areas in **Table 39-6**, adjustments need to be made based on the specific area involved. For example, in an adult with atopic dermatitis on the cubital fossa of both arms, the table does not provide that exact measurement. Because one FTU covers both sides of a hand and the cubital fossa is approximately hand-sized, the patient should be instructed to apply 0.5 FTU to each cubital fossa once or twice daily depending on the specific preparation. Although use of the FTU concept is not a panacea, it does provide a more objective benchmark to help patients more consistently apply the correct amount of product and avoid overuse. Use of the FTU concept must be accompanied by counseling and reinforcement based on the individual medication received, size and location of the lesion, and the desired goals of therapy. In addition, the FTU concept can be used to determine the amount to be dispensed to cover a treatment period.

Table 39-6
Fingertip Unit Charts for Adults and Children

Fingertip Unit Measures for Use in Adults				
Area of body			FTU per dose	
Face and neck			2.5	
Torso and abdomen (front of trunk)			7	
Back and buttocks (back of trunk)			7	
One arm (front and back)			3	
One hand			1	
One leg (front and back)			6	
One foot			2	
Adult Fingertip Unit Measures for Use in Children (by Age of Child)				
	3–6 months	1–2 years	3–5 years	6–10 years
Face and neck	1	1.5	1.5	2
Arm and hand	1	1.5	1	2.5
Leg and foot	1.5	2	3	4.5
Trunk (front)	1	2	3	3.5
Trunk (back including buttocks)	1.5	3	3.5	5

From Berth-Jones J. Topical therapy. In: Burns DA, Breathnach SM, Cox N, et al, eds. *Rook's Textbook of Dermatology*. 8th ed. Blackwell Scientific; 2010. © 2010 Blackwell Publishing Ltd. Reprinted by permission of John Wiley & Sons, Inc.

Summary of Principles of Topical Corticosteroid Therapy

The following principles are used to guide the choice of agent and application technique (Tables 39-4 and 39-6):

- Because of the reservoir effect of the stratum corneum, topical corticosteroids should be applied no more than twice daily. Increasing the application from twice daily to four times daily does not produce superior responses, is more expensive, and may lead to increased frequency of topical and systemic adverse effects.[9]
- Preparations should be rubbed thoroughly and, when possible, applied while the skin contains optimal moisture (eg, after bathing and drying off).[6] Hydration of the skin increases percutaneous absorption and the resultant therapeutic effect of topical corticosteroids.
- Appropriate-strength preparations should be used to control the condition. For maintenance, most dermatologic conditions requiring topical corticosteroids can be managed with medium- or low-potency corticosteroid preparations (ie, 1% hydrocortisone or a

low-strength fluorinated corticosteroid such as triamcinolone acetonide 0.025%).[9,10]

- Occluded areas and certain, thin-skinned areas of the body, such as the face and flexures, are more prone to the development of adverse effects.[8,10] If corticosteroids must be used on the face flexures or other thin-skinned areas, hydrocortisone or other nonfluorinated topical corticosteroids should be used to reduce the probability of adverse effects. These nonfluorinated corticosteroid products are highlighted in Table 39-4.
- Children, elderly patients, and patients with liver failure are at risk for systemic corticosteroid toxicities. In addition, patients who use the highest-potency preparations for longer than 2 weeks are susceptible to percutaneous absorption and systemic toxicity, including Addison syndrome upon sudden discontinuation.[8–13]
- With chronic conditions such as atopic eczema or allergic contact dermatitis, it is best to discontinue therapy gradually. This reduces the potential for rebound flares of topical lesions.[6]

Xerosis

CASE 39-4

Question 1: C.R., a 64-year-old female, requests something for dry skin on her shoulders and back. She has had this problem for a number of years. It is generally not a problem in the summer, with most symptoms troubling her in the winter. She denies any visible rash. When asked what makes it better, she tells you bathing provides some temporary relief. She has no other medical conditions and only takes an occasional aspirin for "arthritis."

How would you advise C.R. to manage this condition?

C.R.'s represent a common problem of the elderly, xerosis (dry skin). The seasonal cycle described is frequently called "winter itch." Most cases of dry skin are caused by dehydration of the stratum corneum.[7,20] Many factors can dry out the outer layers of the skin, such as decreased indoor humidity during cold temperatures because of increased use of central heating and or living in a low

humidity climate, such as in Arizona. Given the fact that bathing (moisture) provides temporary relief points to xerosis as the most likely cause.[7],[20] The location of the itching, the lack of a visible rash, the relief with bathing, and no chronic diseases rule out most other causes of xerosis (eg, atopic dermatitis, diabetes mellitus). However, given her age and sex, hypothyroidism remains a possibility.

Atopic Dermatitis

CASE 39-5

Question 1: P.K., a 17-year-old boy, presents to a dermatology clinic with 5% of his body covered with a pruritic, eczematous rash. There is extensive involvement of popliteal and cubital fossae bilaterally. There is evidence of excoriation with cosmetic disfigurement in the cubital fossae, and on his cheeks, with a history or frequent bouts of impetigo. P.K.'s mother and aunt have asthma. One sister (L.K.), age 15, has seasonal allergic rhinitis and eczema. His father and younger brother, age 11, appear to have no atopic manifestations. A rash was first noted 1 month after birth. The cheeks of the face were the only area affected, and the rash continued with varying degrees of severity until age 2 years, when it spontaneously resolved. A similar rash reappeared at age 12 years, was diagnosed as atopic dermatitis, and has not disappeared since that time. P.K. experienced seasonal allergic rhinitis beginning at age 6 years. He has had a difficult time trying to follow provided nondrug recommendations for eczema. He has used over-the-counter topical hydrocortisone cream to treat flare-ups during the years.

On physical examination, P.K. is a well-nourished, well-developed, adolescent boy with no abnormal physical findings other than marked allergic shiners, pale boggy nasal mucosa, and Dennie–Morgan folds noted near the eyes, plus extensive skin lesions. Oozing, crusted, excoriated areas caused by scratching, with erythematous, eczematous, lichenified eruptions, are on his face and the flexor aspects of both arms and legs. There is some evidence of a secondary bacterial infection in both cubital fossae and on portions of the left leg. The presenting history, symptoms, and signs are characteristics of atopic dermatitis (eczema).

What are the characteristics of atopic dermatitis, and what is the significance of P.K.'s family and medical history as it relates to this disorder?

Atopic dermatitis, a form of eczema, can be acute or subacute, but is more commonly a chronic pruritic inflammation of the epidermis

and dermis. Approximately two-thirds of the patients have a personal or family history of allergic rhinitis, eczema, or asthma. Sixty percent of patients are affected within the first year of life, 30% by 5 years of age, with the remaining 10% experiencing atopic dermatitis between 6 and 20 years of age. Atopic dermatitis in infants may be a prelude to the development of other atopic disorders later in life (eg, allergic rhinitis or asthma). Presence of these disorders many times is the key to differential diagnosis. About 80% of patients with atopic dermatitis have a type I (immunoglobulin E [IgE]–mediated) hypersensitivity reaction occurring because of the release of vasoactive substances from both mast cells and basophils that have been sensitized by the interaction of the antigen with IgE. An allergy workup is rarely helpful in determining the allergen. The disorder affects 0.5% to 1% of the general population, although its prevalence in children is 5% to 10%. In infants and young children, dermatitis often occurs on the face and sternal area of the chest. In older children and adults, it tends to localize to the flexural areas, especially the cubital and popliteal fossae with the neck and face involved in more severe cases.[21]

Pruritus is the hallmark of atopic dermatitis. Atopic dermatitis has been described as “the itch that rashes, rather than the rash that itches.” In other words, the itching precedes the rash. The constant scratching leads to a vicious cycle of itch-scratch-rash-itch, with bacterial colonization and infections intertwined. Chronically, untreated atopic dermatitis leads to lichenification of the affected areas. Wool, detergents, soaps, a change in room temperature, and mental or physical stress can precipitate itching. Patients tend to have dry skin (xerosis) all over the body. This is attributable to a reduced water-binding capacity and a higher transdermal water loss. Xerosis is worsened during periods of low humidity, such as winter in northern latitudes. Treating the xerosis can prevent or control the disease in mild or episodic cases.[21,22]

P.K.’s family and medical history are classic for atopic dermatitis. His family history is significant for asthma, allergic rhinitis, and atopic dermatitis. He had his initial outbreak at the age of 1 month and then experienced seasonal allergic rhinitis after his dermatitis went into

remission. His skin examination reveals findings of both acute and chronic atopic dermatitis, with typical lesion location and description.

Product Selection

Case 39-5, Question 2: P.K. received a prescription for halcinonide 0.25% cream, 30 g, to be applied at bedtime to nonfacial areas and mometasone furoate cream 0.1%, 30 g, twice daily to the facial lesions. Based on pertinent biopharmaceutic considerations, why is this treatment appropriate for P.K.?

P.K.'s regimen includes two topical corticosteroids, one higher-potency agent (halcinonide) to apply to nonfacial lesions and one lower-potency agent (mometasone furoate) for use on the face. This is appropriate owing to the desire to limit the potential for adverse effects from the use of high-potency topical corticosteroids on the face. Results from P.K.'s treatment regimen should include more frequent (twice daily) application or a more potent preparation to control inflamed lesions, which the prescriptions reflect. Once any weeping is stopped, a less potent preparation in the ointment form should be used for maintenance and the number of applications may be reduced. Because of the reservoir effect, control can be maintained in many cases with intermittent regimens such as once daily, every other day, or every third day use of topical corticosteroids. In addition, intermittent regimens can involve alternating corticosteroids and agents such as topical pimecrolimus or tacrolimus to maintain control and minimize adverse effects of either agent.

Because the calcineurin inhibitors are as effective as mid-potency topical corticosteroids without causing atrophy, telangiectasias, or striae, many dermatologists would use either tacrolimus or pimecrolimus on the face in preference to mometasone.[22]

Topical Antibiotics With Corticosteroids

Case 39-5, Question 3: P.K.'s atopic dermatitis presentation is complicated with areas of erythematous, honey-colored, crusted lesions on his arm, and leg. Can a corticosteroid and an antibiotic preparation be used together? What are the risks associated with topical antibiotics?

It is determined that P.K. has impetigo superimposed on his atopic dermatitis. Because impetigo can be treated with topical antibiotics such as mupirocin, combination therapy with a corticosteroid–antibiotic preparation would appear to be a logical choice. Although mupirocin may be an appropriate alternative for some topical dermatologic infections, the current over-the-counter topical antibiotics (bacitracin, neomycin, and polymyxin) are ineffective for most dermatologic infections and are indicated only for the prophylaxis of skin infections. In addition, because staphylococcal toxins act as superantigens, eliciting the production of IgE, thus worsening the atopic dermatitis, almost all clinicians treat atopic dermatitis-associated impetigo with oral antibiotics such as dicloxacillin, macrolides, or cephalexin, in combination with topical corticosteroids for the atopic dermatitis.[22] Oral antibiotics reduce the bacterial counts faster and have a lower incidence of recurrent impetigo compared with topical agents. In areas in which community methicillin-resistant *Staphylococcus aureus* rates are high, more effective antibiotic therapy might be indicated as an alternative. P.K. would most likely benefit from a treatment course of an oral antibiotic plus a topical corticosteroid preparation.

P.K. is prone to repeated infections and atopic dermatitis flares because his skin is colonized with staphylococci. Many dermatologists upon clearance of the impetigo would initiate dilute bleach baths. These consist of 5- to 10-minute baths twice a week, made by adding 120 cc (1/2 cup) of household bleach (6%) to a full bathtub (~40 gallons) to create a 0.005% solution. Because of the variety of tub sizes, the amount of bleach should be adjusted to the size of the bathtub and the amount of water in the tub.[23]

Pruritus

Case 39-5, Question 4: As stated in Case 39-5, Question 1, one of P.K.'s problems is pruritus. What could you recommend for relief of pruritus?

As previously noted, pruritus (itching) is the most common cutaneous symptom in atopic dermatitis.[21] Scratching, which can damage or fatigue receptor nerve endings, is the most common method of relieving pruritus. Topically applied local anesthetics or antihistamines could also be effective in dulling the sensation. However, this approach is often disappointing, probably because the intact epidermis poorly absorbs the salt forms of these drugs. In addition, low concentrations are used in many over-the-counter preparations. If adequate concentrations of local anesthetics are used (lidocaine 3%–4%), pruritus or pain may be reduced for up to 45 minutes. These agents are most useful for relieving pruritus or pain for short periods (eg, when trying to go to sleep at night).[21] A serious drawback to the use of topical benzocaine and antihistamine preparations is their propensity to induce allergic contact dermatitis.[24]

P.K. could also try cold water or ice cubes, which effectively relieve pruritus via vasoconstriction, as do products containing aluminum acetate (Burow solution), tannic acid, or calamine. A cool bath may be useful for the relief of pruritus from dermatologic lesions if they are widespread.

Moisturizing mixtures such as Eucerin, Nivea, Lubriderm, or even simply mineral or baby oil are useful in the treatment of pruritus caused by dry skin in patients with atopic dermatitis. Bathing should be restricted to avoid washing away normal body oils, the drying effect of water, the irritant effect of alkaline soaps, and the trauma of toweling.[6]

Topical corticosteroid applications can be very effective if dermatologic lesions exist. They reduce inflammation, which helps soothe the affected area.

Systemic antihistamines are effective antipruritic agents, although their major beneficial effect may be attributable to sedation. The newer, nonsedating antihistamines are notably ineffective at relieving

itch, with the exception of cetirizine.[25] There is disagreement over which antihistamine or antiserotonin agents are most effective for treatment of pruritus.[21,25,26] Oral hydroxyzine is a commonly used antihistamine; doses of 10 to 25 mg three to four times a day are commonly used. Oral cyproheptadine is another option. There is little evidence that antihistamines are effective in treating non–histamine-mediated pruritus, except that their inherent sedative effect may be somewhat beneficial in all pruritic conditions. Doxepin, a tricyclic antidepressant with potent H_1-blocking properties, is valuable as a second-line antihistamine topically or systemically if others fail.[27] Because P.K.'s pruritus is worse at night, as is typical with atopic dermatitis, the use of any of the three H_1-blockers mentioned at bedtime would be appropriate.[22]

Self-Care Recommendations for Atopic Dermatitis

Case 39-5, Question 5: In addition to prescriptions for topical corticosteroids, a systemic antibiotic (cephalexin 500 mg four times daily for 10 days), and an oral antihistamine (hydroxyzine 25 mg, one to two tablets by mouth at bedtime as needed), what self-care interventions should be suggested for P.K.?

The general goals of therapy for atopic dermatitis are to decrease pruritus, suppress inflammation, and moisturize the skin. The self-care recommendations shown in **Table 39-7** are useful adjuncts and mainstays for use between disease flares for patients such as P.K. with atopic dermatitis or any other irritant dermatitis. Often careful attention to nonpharmacologic measures can markedly reduce the incidence of disease flare. Because even nonlesional skin in patients with atopic dermatitis has reduced moisture, the use of emollients should include all skin surfaces.[28]

Table 39-7
Self-Care Recommendations for Patients With Atopic Dermatitis

or Other Irritant Dermatoses

- Clothing should be soft and light. Cotton or corduroy is preferred. Wools and coarse, heavy synthetics should be avoided.
- Heat should be avoided because it often makes eczema worse. The environment should be well ventilated, cool, and low in humidity (30%–50%). Rapid changes in ambient temperature should be avoided.
- Bathing should be kept to a minimum (no longer than 5 minutes), and the patient should use a nonirritating soap (eg, Basis soap). A colloid bath or the use of appropriate amounts of bath oil may be useful.
- The skin should be kept moist with frequent applications of emollients (eg, Lubriderm, Nivea, Aquaphor®, Eucerin, or petrolatum).
- Primary irritants such as paints, cleansers, solvents, and chemical sprays should be avoided.

Reprinted by permission from Springer: Lio PA. Non-pharmacologic therapies for atopic dermatitis. *Curr Allergy Asthma Rep*. 2013;13(5):528–538. © 2013 Springer Science Business Media New York.

P.K. should be warned to avoid people with active herpes simplex infections because severe disseminated infections can occur.

Tachyphylaxis and Calcineurin Inhibitors

Clinicians commonly misdiagnose tachyphylaxis because of corticosteroids. Failure of topical corticosteroids to clear difficult atopic dermatitis after an initial improvement may give the false impression of tachyphylaxis, when the actual problem is a primary failure of the treatment.[29] This could be caused by either inappropriate application technique by the patient or the choice of a product with inadequate potency. Tachyphylaxis can occur within 1 week of therapy, but generally takes several weeks to a month to occur.[29] To treat this problem, patients should discontinue the corticosteroid for a week and restart at an appropriate dose. Alternatively, patients may be switched to topical tacrolimus or pimecrolimus.

Topical tacrolimus or pimecrolimus is an effective alternative to moderate-potency topical corticosteroids and is safe for use in children.[22,23,27] In addition to inhibitory effect on cytokine production,

calcineurin inhibitors result in decreased immunologic response to antigens. Transient burning, erythema, and pruritus are the most common adverse effects. Neither pimecrolimus nor tacrolimus causes skin atrophy, making them attractive alternatives for patients with lesions on the face and the neck. Issues regarding the long-term safety of these products have led the US Food and Drug Administration to place a boxed warning in the manufacturer's literature regarding a potential increased cancer risk.[22]

ALLERGIC CONTACT DERMATITIS: POISON IVY, POISON OAK, OR POISON SUMAC

Contact dermatitis is an inflammation of the skin that occurs when a substance comes in direct contact with the epidermal surface. The most common form is irritant contact dermatitis caused by solvents or other chemicals that irritate the skin resulting in red, painful lesions, for example, dish pan hands or diaper dermatitis. Allergic contact dermatitis is a type IV delayed hypersensitivity reaction controlled by allergen-specific T cells. The resulting dermatitis is pruritic and many times vesicular in nature.[1–6]

Poison ivy (*Rhus*) dermatitis is a major cause of allergic contact dermatitis in the United States, exceeding all other causes combined. Other allergens include latex, leather, nickel, and laundry detergents. It is estimated that 50% to 95% of the population is sensitive to the plants to some degree. The severity of the condition varies from mild discomfort to an extremely painful, debilitating condition. *Rhus* dermatitis is caused by sensitization to an allergic substance in the leaves, stems, and roots of poison ivy, poison oak, and poison sumac plants. All three plants contain the same sensitizing oleoresin, urushiol oil, which contains pentadecacatechol, the actual sensitizing agent. Therefore, the dermatitis caused by the three different plants is identical.

Direct contact with the plant is unnecessary for the rash to occur. Highly sensitive persons may develop severe dermatitis merely from exposure to *Rhus* oleoresin carried by pollen or by smoke from burning leaves. This can be especially important in patients presenting with respiratory or dermatologic signs and symptoms but no memory or report of direct exposure to the resin. The oleoresin may remain active for months on clothing, shoes, tools, and sporting equipment. Once the toxic substance is exposed to the skin, it can be spread by the hands to other areas of the body (eg, genitals or eyes) or to people who may come into close contact with the exposed person. Although washing with soap and water may not prevent the dermatitis, even if it is done within 15 minutes of exposure, it will prevent spread of the oleoresin to other parts of the body.

Sensitive individuals should be instructed to avoid contact with the offending plant. If contact is inevitable, every effort should be made to shield exposed areas of the skin with appropriate clothing.

Exposed individuals should bathe or shower as soon as they come in from outdoors and should wash their clothes. Nonprescription topical cleansers (Tecnu, Zanfel, Mean Green Hand Scrub) claim to remove urushiol oil embedded in the skin through the action of microfine scrubbing beads and surfactants, thus possibly preventing the rash or limiting spread. They are applied to exposed areas of the skin, followed by vigorous scrubbing, and rinsed off after application.

After an initial incubation period of 5 to 21 days, a patient would be expected to react to the oleoresin in 12 to 48 hours after re-exposure. A mild exposure to these plants in a sensitized person results in a typical erythematous, vesicular, linear, and sometimes, oozing rash after 2 to 3 days; complete clearing occurs in 1 to 3 weeks.

If a large area is exposed, lesions appear within 6 to 12 hours and may appear blistered and eroded; in some cases, ulcers may appear. Healing occurs more slowly, often requiring 2 to 3 weeks for complete resolution. It is important to determine the areas of the body that are affected. If the eyes, genital areas, mouth, respiratory

tract, or >15% of the body is affected, the patient should receive a course of systemic corticosteroids. See Case 39-7 below.

Treatment

CASE 39-6

Question 1: K.P., a 27-year-old female, has recently returned from an outing in the woods. She now has vesicular eruptions that appear in a linear pattern on one arm and hand. She believes that she has had a poison oak reaction and requests therapy.

What should be recommended at this point? What should be recommended if the condition becomes more severe?

Weeping lesions should be treated with aqueous vehicles (eg, Burow solution or saline). Lesions that are not wet or weeping should be treated with calamine lotion applied two to four times daily. The zinc oxide in calamine lotion may act as a mild astringent, although some people find this preparation to be unacceptable because of its pink color, which can stain clothes. Alternatively, a topical corticosteroid appropriate for the body part affected could be used. If K.P.'s poison oak reaction becomes more severe, additional treatment with prednisone 1 mg/kg/day for at least 2 or 3 weeks will be required; such therapy should be tapered slowly over 1 to 2 weeks to prevent recurrence of the lesions.

SYSTEMIC THERAPY

Relapse

CASE 39-7

Question 1: Z.T., a 19-year-old male, has just returned from a fishing trip and now has an erythematous, linear, dry eruption on his leg and arm, and a generalized eruption on his hands and face. He has been in areas that have dense poison ivy growth, and he may have burned some in the campfire. Z.T. has washed himself and his clothes thoroughly. Z.T.'s physician prescribed oral prednisone for his rash. He was instructed to take 80 mg/day for 14 days and to

decrease the dose by 5 mg/day each day thereafter. Calamine lotion (three times daily to affected areas) also was prescribed. After 12 days, Z.T. reports that the lesions seem to be getting worse. The lesions had cleared after 8 days of treatment, and he began rapidly tapering the prednisone at that time.

Why is he experiencing a relapse?

Two weeks is the minimum course of treatment when systemic corticosteroids are used for severe cases of poison ivy, poison oak, or poison sumac. The oleoresin remains fixed in the skin, and if the systemic corticosteroid is withdrawn too soon, the lesions return. This is probably the most common reason for treatment failure with systemic corticosteroids. Alternatively, systemic corticosteroids can be discontinued before 2 weeks of treatment and a moderate-potency topical corticosteroid preparation can be started 24 hours before discontinuation of systemic corticosteroids and continued for 7 to 10 days to prevent relapse.

DRUG ERUPTIONS

Clinically recognizable adverse drug reactions are manifested on the skin more often than any other organ or organ system.[30–33] An estimated 1% to 5% of hospitalized patients experience a drug eruption.[31]

Acneiform Eruptions

Acneiform eruptions appear very much like common acne. They may be distinguished from acne by their sudden occurrence, the absence of comedones, uniform appearance (ie, all at the same stage of development), and the fact that they may occur on any part of the body. Cysts and scarring are rarely associated with drug-induced acne. Eruptions can also occur during any period of the patient's life; thus, drug-induced acne should be suspected when the lesions appear in persons outside the typical age bracket for acne. Drugs

implicated include adrenocorticotropic hormone, anabolic steroids, azathioprine, danazol, glucocorticoids, iodides, bromides, lithium, gefitinib, erlotinib. lapatinib, and oral contraceptives. For patients with acne vulgaris, these drugs may worsen existing lesions (see Chapter 40, Acne).

Allergic Contact Dermatitis

Topical administration of a sensitizing agent produces localized papulovesicular lesions. These lesions are limited only to areas that are exposed to the topical product. Neomycin, bacitracin, and many fragrances are well-known topical sensitizers, as well as metals like nickel and cobalt.[34–37] Systemic administration of a drug to a patient previously sensitized to the drug by topical application can provoke widespread dermatitis. Implicated systemically or topically administered drugs that reactivate allergic contact dermatitis include procaine or benzocaine, radiographic contrast media or iodine, and streptomycin and gentamicin, among others.

Erythema Multiforme

As the name implies, erythema multiforme (EM) eruptions take on a varied spectrum of morphologic forms, ranging from the mildest with tiny maculovesicular lesions to more severe forms such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with extensive bullous lesions and routine involvement of mucous membranes. Although all forms have been reported to have oral lesions, they are much more severe in SJS and TEN, in which genital, nasal, and ocular mucosae can also be involved. Target lesions are usually present in all forms of the disorder, which characteristically are erythematous, iris-shaped papules, and vesiculobullous lesions typically involving the extremities, especially the palms and soles in EM and the torso in SJS and TEN. The lesions take on the appearance of a circular target with a bull's-eye in the middle, thus the term "target lesion." Questions have recently

been raised about the shared pathologic nature of these forms of EM.[38] EM in its mildest forms, EM minor and EM major, is more common in children and young adults, and is self-limited in nature with only transient hypopigmentation or hyperpigmentation as complications. Sometimes malaise, a low-grade fever, and itching or burning may accompany this type of eruption. Etiologic factors associated with EM include drugs, mycoplasma and herpes infections, radiation therapy, foods, and sometimes neoplasms. Allopurinol, barbiturates, phenothiazine, and sulfonamides are the drugs most often implicated in EM eruptions.

Stevens–Johnson Syndrome

SJS is one of the most common types of severe drug eruptions. The syndrome is usually a moderate mucocutaneous and systemic reaction. Blisters and atypical target lesions involve <10% of the body surface area (BSA), with some epidermal detachment, which can cause scarring in some cases. Besides drugs, this syndrome has been associated with infections, pregnancy, foods, deep radiographic therapy, and neoplasms. Mortality is estimated to be in the range of 5% to 18%. The duration of the syndrome is usually 4 to 6 weeks. The long-acting sulfonamides are most often implicated. Allopurinol, carbamazepine, fluoroquinolones, hydantoin, phenylbutazone, piroxicam, and other sulfa derivatives such as sulfonylureas are also possible causative agents.

Toxic Epidermal Necrolysis

TEN is a severe, life-threatening mucocutaneous and systemic reaction that has the same pathophysiology as SJS, only differing in the amount of BSA involved (>30% of BSA vs <10% with SJS). TEN may be preceded by a prodrome characterized by malaise, lethargy, fever, and occasionally throat or mucous membrane soreness. Epidermal changes follow and consist of erythema and massive bullae formations that easily rupture and peel, giving the skin a

scalded appearance. Mortality in TEN patients is roughly 30%, often within 8 days after bullae appear. The usual cause of death is infection complicated by massive fluid and electrolyte loss, similar to patients with extensive burns. In addition to drugs, certain bacterial infections and foods are believed to cause this type of eruption. Most causes of TEN in children are because of infection (eg, *S. aureus*). A higher incidence of this type of drug eruption appears to occur in HIV-positive patients. Similar to SJS, drugs most frequently implicated include allopurinol, aminopenicillins, carbamazepine, hydantoin, phenylbutazone, piroxicam, and sulfa drugs.

Urticaria

Urticarial eruptions are immediate hypersensitivity reactions (IgE-mediated) and usually appear as sharply circumscribed (raised), edematous, and erythematous lesions (wheals) with an abrupt onset.

In most cases, individual lesions disappear within 24 hours. These are replaced with new lesions elsewhere until the offending allergen is cleared from the body. Urticarial lesions are associated with an intense itching, stinging, or prickling sensation. Commonly called *hives*, urticarial eruptions are frequently associated with certain drugs, foods, psychic upsets, and serum sickness. The most frequently implicated drugs with this type of reaction are aspirin, penicillin, and blood products. Patients who exhibit urticaria attributable to a drug are at increased risk of anaphylaxis if re-exposed to the same medication in the future.

CASE 39-8

Question 1: D.Z., a 42-year-old male with a chronic seizure disorder and long-standing anxiety, was recently given a prescription for penicillin V 250 mg four times daily for a group A, α-hemolytic streptococcal-positive pharyngitis. Chronic medications include carbamazepine 200 mg three times daily and clonazepam 2 mg two times daily. One week later, D.Z. presents with urticarial lesions on his chest and arms.

Is this a typical time of onset for a drug-induced dermatologic reaction? How should the drug eruption in D.Z. be managed?

Although most drug eruptions occur within 1 to 2 weeks after starting therapy, it may take 3 to 4 weeks after an initial exposure to a medication for the reaction to occur. Repeated exposure to the same offending agent can reduce the time of onset of the reaction to a few days or even within hours of ingestion. Because D.Z. has been taking clonazepam and carbamazepine chronically and penicillin for only 8 days, the temporal relationship would logically lead to the conclusion that penicillin is a highly probable cause. Almost all cases of urticaria are associated with extensive eosinophilia; however, it is not specific for any particular antigen. However, before labeling penicillin as the cause of his drug eruption, a thorough history to rule out other common nondrug causes should be taken.

For D.Z., a different antibiotic (macrolide) should be substituted for penicillin (to complete the 10-day course of therapy). The individual lesions should begin to clear in 24 hours of eruption (if the penicillin is the cause of the urticaria). If the urticaria does not begin to clear in a few days, another cause should be investigated.

Treatment is primarily supportive, and use of an oral antihistamine (eg, diphenhydramine 25–50 mg four times daily) for several days would be recommended. If the reaction is severe, a 1- to 2-week course of prednisone 40 to 60 mg/day will control most symptoms within 48 hours.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Arndt KA, Hsu JH. *Manual of Dermatologic Therapies: With Essentials of Diagnosis*. 8th ed. Lippincott Williams & Wilkins; 2014. (6)

Eichenfeld LF, Tom WL, Chamlin SL, et al. Guidelines of care for the diagnosis and management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014;70:338–351. (21)

Eichenfeld LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2, management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71:116. (22)

Fitzpatrick TB, Goldsmith LA, Wolff K, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. McGraw-Hill; 2012. (4)

Lee NP, Arriola ER. Topical corticosteroids: back to basics. *West J Med*. 1999;171:351–353. (10)

James WD, Berger TG, Elston DM, et al, *eds*. *Andrews' Diseases of the Skin: Clinical Dermatology*. 11th ed. WB Saunders; 2015. (2)

Tadicherla S, Ross K, Shenefelt PD, Fenske NA. Topical corticosteroids in dermatology. *J Drugs Dermatol.* 2009;8:1093–1105. (13)

Key Websites

American Academy of Dermatology. Atopic Dermatitis Clinical Guidelines. https://www.aad.org/member/clinical-quality/guidelines/atopic-dermatitis

National Eczema Association. https://nationaleczema.org/

COMPLETE REFERENCES CHAPTER 39 DERMATOTHERAPY AND DRUG-INDUCED SKIN DISORDERS

1. Hall BJ, Hall JC, eds. *Sauer's Manual of Skin Diseases*. 10th ed. Lippincott Williams & Wilkins; 2010.
2. James WD, Berger TG, Elston DM, eds. *Andrews' Diseases of the Skin: Clinical Dermatology*. 12th ed. WB Saunders; 2015.
3. Burns DA, Breathnach S, Cox N, Griffiths C, eds. *Rook's Textbook of Dermatology*. 8th ed. Blackwell Scientific; 2010.
4. Fitzpatrick TB, Goldsmith LA, Wolff K, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. McGraw-Hill; 2012.
5. Habif TP, ed. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 6th ed. St. Mosby; 2015.
6. Arndt KA, Hsu JHS, eds. *Manual of Dermatologic Therapies: With Essentials of Diagnosis*. 8th ed. Lippincott Williams & Wilkins; 2014.

7. Berger TG, Shive M, Harper GM. Pruritus in the older patient: a clinical review. *JAMA*. 2013;310:2443–2450.
8. Morley KW, Dinulos JG. Update on topical glucocorticoid use in children. *Curr Opin Pediatr*. 2012;24:121–128.
9. Lee NP, Arriola ER. Topical corticosteroids: back to basics. *West J Med*. 1999;171:351–353.
10. Giannotti B, Pimpinelli N. Topical corticosteroids. Which drug and when? *Drugs* 1992;44:65–71.
11. Fisher D. Adverse effects of topical corticosteroid use [published correction appears in *West J Med*. 1995;162:476]. *West J Med*. 1995;162:123–126.
12. Tadicherla S, Ross K, Shenefelt PD, Fenske NA. Topical corticosteroids in dermatology. *J Drugs Dermatol*. 2009;8:1093–1105.
13. Butani L. Corticosteroid-induced hypersensitivity reactions. *Ann Allergy Asthma Immunol*. 2002;89:439–445.
14. Levin C, Maibach HI. Topical corticosteroid-induced adrenocortical insufficiency: clinical implications. *Am J Clin Dermatol*. 2002;3:141–147.
15. Bewley A, Dermatology Working Group. Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. *Br J Dermatol*. 2008;158:917–920.
16. Nelson AA, Miller AD, Fleischer AB, Balkrishnan R, Feldman SR. How much of a topical agent should be prescribed for children of different sizes? *J Dermatolog Treat*. 2006;17:224–228.
17. Long CC, Finlay AY. The finger-tip unit—a new practical measure. *Clin Exp Dermatol*. 1991;16:444–447.
18. Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. *Br J Dermatol*. 1998;138:293–296.
19. Kalavala M, Mills CM, Long CC, Finlay AY. The fingertip unit: a practical guide to topical therapy in children. *J Dermatolog Treat*. 2007;18:319–320.
20. White-Chu EF, Reddy M. Dry skin in the elderly: complexities of a common problem. *Clin Dermatol*. 2011;29:37–42.
21. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1, diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70:338–351.
22. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2, management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71:116–132.
23. Tollefson MM, Brucker AL. Atopic dermatitis: skin-directed management. *Pediatrics*. 2014;134:e1735–e1744.
24. Prystowsky SD, Allen AM, Smith RW, Nonomura JH, Odom RB, Akers WA. Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine: relationships between age, sex, history of exposure, and

reactivity to standard patch tests and use tests in a general population. *Arch Dermatol*. 1979;115:959–962.
25. Dimson S, Nanayakkara C. Do oral antihistamines stop the itch of atopic dermatitis? *Arch Dis Child*. 2003;88:832–835.
26. Herman SM, Vender RB. Antihistamines in the treatment of dermatitis. *J Cutan Med Surg*. 2003;7:467–473.
27. Gupta MA, Guptat AK. The use of antidepressant drugs in dermatology. *J Eur Acad Dermatol Venereol*. 2001;15:512–518.
28. Lio PA. Non-pharmacologic therapies for atopic dermatitis. *Curr Allergy Asthma Rep*. 2013;13:528–538.
29. Miller JJ, Roling D, Margolis D, Guzzo C. Failure to demonstrate therapeutic tachyphylaxis to topically applied steroids in patients with psoriasis. *J Am Acad Dermatol*. 1999;41:546–549.
30. Fiszenson-Albala F, Auzerie V, Mahe E, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol*. 2003;149:1018–1022.
31. [No authors listed]. Cutaneous drug reaction case reports: from the world literature. *Am J Clin Dermatol*. 2003;2(4):267–274.
32. Ahmed AM, Pritchard S, Reichenberg J. A review of cutaneous drug eruptions. *Clin Geriatr Med*. 2013;29:527–545.
33. Song JE, Sidbury R. An update on pediatric cutaneous drug eruptions. *Clin Dermatol*. 2014;32:516–523.
34. Kimura M, Kawada A. Contact sensitivity induced by neomycin with cross-sensitivity to other aminoglycoside antibiotics. *Contact Dermatitis*. 1998;39: 148–150.
35. Yung MW, Rajendra T. Delayed hypersensitivity reaction to topical aminoglycosides in patients undergoing middle ear surgery. *Clin Otolaryngol Allied Sci*. 2002;27:365–368.
36. Heine A. Diphenhydramine: a forgotten allergen? *Contact Dermatitis*. 1996;35: 311–312.
37. Nassau S, Fonacier L. Allergic contact dermatitis. *Med Clin North Am*. 2020;104:61–76.
38. Williams PM, Conklin RJ. Erythema multiforme: a review and contrast from Stevens-Johnson syndrome/toxic epidermal necrolysis. *Dent Clin North Am*. 2005;49:67–76.

40

Acne

Jamie J. Cavanaugh and Kelly A. Mullican

CORE PRINCIPLES		CHAPTER CASES
1	Acne is a condition in which the pilosebaceous units of the skin become plugged and distended, presenting as comedones, papules, pustules, or nodules.	**Case 40-1 (Question 1, 2)** **Case 40-3 (Question 1)** **Case 40-4 (Question 1)** **Case 40-5 (Question 1)**
2	Drug therapies work by reducing sebum production, normalizing keratinization in the pilosebaceous units, reducing *Propionibacterium acnes*, or reducing inflammation.	**Case 40-1 (Question 1, 2)** **Case 40-3 (Question 1)** **Case 40-4 (Question 1)** **Case 40-5 (Question 1)**
3	Patients must be counseled that pharmacotherapy works best to prevent future lesions, not to resolve current	**Case 40-1 (Question 2)** **Case 40-2 (Question 1)**

	ones. Therefore, topical therapies should be applied regularly to the entire acne-prone area(s), not just to lesions. Full treatment effect takes weeks to months for most treatment options.	**Case 40-3 (Question 1, 2)** **Case 40-4 (Question 2)**
4	Appropriate choice of topical vehicle ensures efficacy and tolerability of topical therapy. Gels should be used in patients with normal to oily skin. Lotions and creams should be reserved for those with drier skin types.	**Case 40-1 (Question 3)**
5	Topical retinoids are first-line monotherapy for comedonal acne. They are also key components of combination therapies in maculopustular acne and preferred agents to continue for maintenance therapy once acne is under control. If comedonal acne cannot be controlled with topical retinoids alone, then salicylic acid or azelaic acid may be used as adjunctive therapy.	**Case 40-1 (Question 2, 3)** **Case 40-2 (Question 1)** **Table 40-1**
6	Initial treatment for maculopustular acne is a topical retinoid in combination with topical or oral antibiotics. If treatment with topical antibiotics is selected, the regimen should also include topical benzoyl peroxide to reduce the development of antibiotic resistance. Antibiotic duration should be limited to the period needed to obtain control of acne; then the retinoid, with or without benzoyl peroxide, should be continued as maintenance therapy.	**Case 40-3 (Question 1, 2), Table 40-1**

7	Antiandrogenic therapies, such as combined oral contraceptives or spironolactone, are useful alternative treatment options for maculopustular acne in nonpregnant females.	**Case 40-4 (Question 1, 2), Table 40-1**
8	Oral isotretinoin monotherapy should be used to treat nodular acne. Isotretinoin is extremely effective and can induce a lengthy remission of acne, but the adverse effect profile and the need for laboratory monitoring preclude use in comedonal or maculopustular acne. The iPLEDGE risk management program controls isotretinoin distribution to prevent accidental prescription of this severe teratogen to pregnant females.	**Case 40-5 (Question 1, 2), Table 40-1**

INTRODUCTION

Acne prevalence is estimated to be 40 to 50 million individuals within the United States, and impacts 85% of adolescents in the United States. Acne often begins when sebaceous gland activity increases in puberty and can persist into adulthood.[1]

PATHOPHYSIOLOGY

Four primary mechanisms are responsible for acne: increased sebum production, hyperkeratinization, colonization of *Propionibacterium acnes* (*P. acnes*), and release of inflammatory

mediators to the skin. Acne begins with the overproduction of sebum, often secondary to an increase in androgen levels.[2]

CLINICAL PRESENTATION

Acne presents as comedones or inflammatory papules, pustules, or nodules, and generally appears in areas with the highest density of pilosebaceous units including the face, neck, upper chest, shoulders, and back. There is limited evidence to suggest that factors such as sunlight or diet are risk factors for worsening acne. However, family history, increased body mass index, and stress have been found to potentially contribute to worsening acne symptoms.[2]

DIAGNOSIS

The differential diagnosis of acneiform eruptions includes acne vulgaris, rosacea, bacterial folliculitis, drug-induced acne, and perioral dermatitis.[3] Detailed discussions of severe acne variants, such as acne conglobata and acne fulminans, are beyond the scope of this chapter.

Initial treatment should be selected based on patient-specific factors including the presence of comedonal (**Fig. 40-1**), maculopustular (**Fig. 40-2**), and nodular acne (**Fig. 40-3**), which are used to guide treatment decisions. Although there are no standard grading systems for acne severity, clinicians may choose to adopt an acne severity scale to assist in their assessment of therapy response.[4,5]

Figure 40-1 Comedonal acne. (Reprinted with permission from Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Lippincott Williams & Wilkins; 2003: Figure 1-12.)

Figure 40-2 Maculopapular acne. (Reprinted with permission from White AJ. *The Washington Manual of Pediatrics*. 2nd ed. Wolters Kluwer; 2016:Figure 15-13A.)

Figure 40-3 Nodular acne. (Reprinted with permission from Jensen S. *Nursing Health Assessment: A Best Practice Approach*. 2nd ed. Wolters Kluwer; 2015:273.)

OVERVIEW OF THERAPY

Treatment is individualized and depends on the clinical presentation of the patient. The goals of treatment are to relieve discomfort, improve skin appearance, prevent scarring, and minimize the psychosocial impact of the condition.

Treatment is largely preventive because little can be done for existing lesions. Slow improvement over the course of weeks to months is expected for all treatments. Therefore, treatment regimens should not be modified more often than every 6 to 8 weeks. It is important to counsel patients that inflammatory acne may result in scarring or hyperpigmentation, which may take several months to

resolve and delay patient recognition of acne improvement.[6] Patients should be counseled on the basic pathophysiology of acne, proper drug administration or application technique, delay in onset of therapeutic effect, potential adverse effects of any recommended therapy, and steps to take if adverse effects occur. Clinical practice guidelines are available. **Table 40-1** outlines a general approach to the treatment of acne.[4–6]

Table 40-1
Treatment Selection by Acne Type

Type	Treatment Options
Comedonal acne	Topical retinoid, azelaic acid *or* Salicylic acid
Maculopapular acne	Topical retinoid + topical antimicrobial (antibiotic or benzoyl peroxide) *or* Topical retinoid + oral antibiotic + benzoyl peroxide *or* (additional options for female patients) Combination oral contraceptive Androgen receptor antagonist
Nodular acne	Isotretinoin

Nonpharmacologic Therapy

Nonpharmacologic therapy plays a minimal role in the management of acne. There is insufficient evidence to suggest washing as either an exacerbating factor or a treatment option. To minimize scarring, patients must resist squeezing or picking at acne lesions. Oil-based cosmetics should be avoided. Oil-free moisturizers formulated for facial skin can improve the penetration and tolerability of many topical acne drugs by improving the skin's hydration, especially in patients with sensitive skin.[1] Drugs known to cause acne, such as corticosteroids, androgens, and anabolic steroids, should be avoided when possible.[3]

Dermatologists may use procedures such as surgical comedone extraction, chemical peels, and microdermabrasion as adjunct therapy to improve cosmetic appearance. Current guidelines prefer drug therapy to light and laser therapies because there are less stringent clinical testing for devices compared to medications, a concern about long-term effects of therapies aimed at sebaceous gland function, and inadequate postmarketing clinical evidence for light and laser therapies.[4,5] Acne scarring may be treated with various microsurgical techniques such as dermabrasion, laser therapy, chemical peels, and tissue augmentation.[7]

Pharmacotherapy

Available drug therapies exhibit one or more of the following mechanisms: normalizing follicular keratinization (retinoids, benzoyl peroxide, azelaic acid, isotretinoin), decreasing sebum production (isotretinoin, hormonal therapies), suppressing *P. acnes* (antibiotics, benzoyl peroxide, azelaic acid, isotretinoin), and reducing inflammation (antibiotics, retinoids, isotretinoin).

COMEDONAL ACNE

Pharmacotherapy

Topical therapies are the most appropriate first-line treatment for comedonal acne. Options include retinoids, azelaic acid, and salicylic acid.

TOPICAL RETINOIDS AND RETINOID ACID DERIVATIVES

Retinoids, analogs of vitamin A, normalize keratinization by decreasing horny cell cohesiveness and stimulating epidermal cell turnover. These actions combine to unplug follicles and prevent microcomedo formation. Retinoids reduce inflammation by inhibiting

the production of inflammatory mediators. Topical retinoids have no antibacterial properties.[8]

As the most potent comedolytic agents, topical retinoids are preferred therapy in comedonal acne.[4,5] They are also a core component of combination therapies for maculopapular/pustule acne and a first-line treatment to maintain remission of acne once it is controlled. Tretinoin, all-*trans*-retinoic acid, is the naturally occurring form of vitamin A acid and is a first-generation topical retinoid. It is generally well tolerated, although it can cause retinoid dermatitis leading to further hyperpigmentation if used too aggressively in patients with darker skin types. Starting at a low dose or using creams over gels can minimize the risk of worsening hyperpigmentation.[9] If hyperpigmentation is a concern, adapalene, a retinoid acid derivative, is preferred. It is generally well tolerated and, in addition to decreasing risk for hyperpigmentation, has a greater anti-inflammatory effect than has tretinoin. In addition, adapalene 0.1% gel is available over the counter (OTC), making it easily accessible and a good option for patients who may be concerned with cost. Tazarotene is a second-generation topical retinoid that has demonstrated efficacy, but may be less tolerable compared to adapalene.[4]

Topical retinoids and adapalene should be applied once daily at bedtime. Tretinoin specifically may be subject to degradation in ultraviolet light. Common adverse effects of this class include skin irritation, peeling, erythema, and dryness. Irritation may be correlated to drug concentration and vehicle selected. Patients should be counseled to apply daily sunscreen and gentle moisturizing cream while using these agents.[4] Patients should be aware that acne might initially worsen during treatment because pustular flares can occur.

AZELAIC ACID

Azelaic acid is a dicarboxylic acid that works to normalize keratinization and indirectly reduces inflammation through suppression of *P. acnes*.[10,11] Formulations in the 20% strength are indicated for the treatment of acne, whereas the 15% gel is indicated

for rosacea. Although azelaic acid hits several of the pathways leading to acne formation, the evidence for use is not as robust as are other topical agents.[8] It is applied twice daily to the skin and may be an option for patients who are unable to tolerate other topical therapies.

SALICYLIC ACID

Topical salicylic acid works as a concentration-dependent keratolytic agent. Studies have demonstrated that topical salicylic acid is less effective than either topical retinoids or benzoyl peroxide. Thus, it is commonly reserved for patients with comedonal acne who cannot tolerate other comedolytic therapies or as augmentation to other therapies. It is typically applied twice daily and is not effective when used only as needed. Patients should be cautioned not to regularly apply over large body surfaces owing to increased risk of percutaneous absorption, which can lead to systemic salicylate toxicity.[11]

CASE 40-1

QUESTION 1: L.Y. is a 15-year-old female who presents to the pharmacy asking for the best way to treat her "zits." She notes that she developed acne earlier this year around the same time that she joined the track team. Upon examination, you can see that her skin is dark brown and slightly oily. She has several closed comedones on her nose and chin and open comedones dispersed across her forehead covered by makeup. She has been scrubbing her face with exfoliating gloves and mild soap several times per day.

What factors could be contributing to her acne?

Increased sweat encountered while running track can lead to favorable conditions for the colonization of *P. acnes*. Frequent washing of her face may lead to increased sebum production. The exfoliation of her skin may lead to disruption of the skin barrier and bacterial colonization. Finally, it is important to ask L.Y. whether her makeup is oil based, because oil-based products can be comedogenic.

Case 40-1, Question 2: What are the treatment options for L.Y.'s acne?

Adapalene gel is the preferred first-line treatment agent for comedonal acne. It is available OTC, is well tolerated, and has a lower risk of hyperpigmentation compared to retinoids. Start adapalene every other night for 2 weeks, then increase to nightly. She should be instructed to wash her face with a mild cleanser in the evening, wait 30 minutes, and then apply adapalene. In the morning, she should wash her face again. If she experiences excessive skin dryness or peeling occurs, she may wash the adapalene off after several hours instead of waiting until morning. It is important to let L.Y. know that adapalene should be used as scheduled (daily for most patients) and not as needed to be effective. Effectiveness should be evaluated several weeks after initiation.

Case 40-1, Question 3: What vehicle would you recommend for L.Y.?

L.Y. has slightly oily skin. Therefore, using a gel is the vehicle of choice because it has more drying effects compared to lotions and creams. If she experiences excessive dryness or peeling, she can switch to adapalene cream. The cream, however, is not available OTC.

CASE 40-2

Question 1: M.G. is a 27-year-old female who presents to the dermatology clinic with open and closed comedones spread across her cheeks and forehead. She was recently prescribed adapalene 0.1% cream, which she has been applying daily for the past 6 months without much success. She is currently using a mild soap to wash her face twice daily. She is not sure what else she can do to manage her acne.

What would you recommend?

Although topical retinoids are first-line treatment for comedonal acne, some patients require additional agents to achieve satisfactory results. M.G. should be instructed to continue adapalene and initiate

salicylic acid wash daily. This wash should be used on her entire face, not just areas with active breakouts, twice daily. It is important to remind her that it may take several weeks before she sees an effect.

MACULOPAPULAR ACNE

Pharmacotherapy

BENZOYL PEROXIDE

Benzoyl peroxide is an effective agent for patients with maculopapular acne. It works through antimicrobial, anti-inflammatory, and keratolytic effects. It is important to note that there is no reported resistance of *P. acnes* to benzoyl peroxide. Benzoyl peroxide is available OTC and by prescription in a variety of dosage forms. Benzoyl peroxide inactivates some formulations of tretinoin. Therefore, if benzoyl peroxide is added on to tretinoin, patients should be instructed to apply them at different times (morning and evening, respectively).[4],[11] Benzoyl peroxide is usually applied to the affected area once or twice daily. The most common adverse effects of benzoyl peroxide include contact dermatitis (≤2.5%), erythema, peeling, and skin drying.[11] Those who develop contact dermatitis should be instructed to stop using benzoyl peroxide. Patients should be counseled that benzoyl peroxide can bleach hair and dyed fabrics.

ANTIBIOTICS

Although *P. acnes* is part of the skin's normal flora, under the conditions leading to acne it can transform comedones into inflammatory pustules or papules. Although antibiotics do not resolve existing lesions, they can prevent future lesions by decreasing both *P. acnes* colonization and inflammation through antioxidant properties and, in turn, reduced leukocyte recruitment.[12] Owing to this multifactorial mechanism of action, clinical efficacy does not

correlate with reductions in bacterial load, and successful antibiotic courses do not necessarily eradicate *P. acnes*.[13]

Topical antibiotics

Topically applied antibiotics avoid systemic exposure and achieve high follicular concentrations. They can augment topical retinoids when initiating therapy for comedonal and papular acne with inflammatory lesions, or they can be added to regimens for patients failing monotherapy. Topical antibiotics should be used with benzoyl peroxide to limit bacterial resistance.[8] Clindamycin is the preferred topical antibiotic, and is available in fixed combination with benzoyl peroxide, which may aid adherence and reduce the risk of bacterial resistance.[4]

Topical antibiotics should be applied once or twice daily for 3 months. Local irritation, including stinging, are the most common adverse effects. The local adverse effects of topical antibiotics occur less frequently when compared to other topical therapies for acne.[11]

Oral antibiotics

Oral antibiotics are preferred in combination with benzoyl peroxide and a topical retinoid in the treatment of moderate-to-severe inflammatory acne. In addition, they are also used as a step-up therapy when topical antibiotic regimens have failed to suppress acne or in cases where lesions are widespread or difficult to reach. Oral antibiotics should not be used as monotherapy. Most oral antibiotics are given twice daily for 3 months, followed by continuation of a topical retinoid for maintenance therapy. Minocycline and doxycycline have both been found to be efficacious and are guideline recommended. Tetracyclines should not be prescribed for children younger than age 9 years owing to the potential risk of impairment in bone growth and discoloration of forming teeth. Pregnant females must avoid tetracyclines because of bone growth effects on the fetus. Trimethoprim/sulfamethoxazole is also effective, but has a less favorable adverse effect profile when compared to doxycycline and minocycline. It is reserved for

situations when tetracyclines are contraindicated. In patients who are unable to take the abovementioned oral antibiotics (including pregnant patients), erythromycin may be another option despite association with higher rates of resistance.[4,13]

Antibiotic resistance

Antibiotic resistance of *P. acnes* is increasing, and correlates with prescribing patterns. Erythromycin has the highest rate of resistance. Resistance to tetracyclines is less common, and is increasing at a slower rate than is resistance to other antibiotics. In an effort to minimize resistance, guidelines emphasize that antibiotics should be reserved for acne of at least maculopapular subtype. Antibiotics should be used in combination with drugs exerting additional mechanisms of action, ideally topical retinoids and benzoyl peroxide, rather than used as monotherapy. Antibiotic use should be limited to the shortest effective duration to obtain acne control. Antibiotics should not be used for maintenance of control (rather, retinoids should be continued for maintenance).[4,5,8,13] Dual antibiotic use is inappropriate because it increases the risk of bacterial resistance without offering therapeutic benefit, because bacterial eradication is not a therapeutic goal.

CASE 40-3

Question 1: R.P. is an 18-year-old male who has had acne since his early teens. He started out with comedonal acne alone, but now has a number of inflammatory pustules across his forehead and nose. R.P. was prescribed tretinoin 0.1% gel in the past, but he stopped this because of skin irritation and dryness. He has been using adapalene 0.1% cream and salicylic acid washes daily, without success.

What changes to R.P.'s medication regimen do you recommend?

Because he presents with pustules, R.P. can stop his salicylic acid wash, continue adapalene, and should start on a topical antimicrobial agent such as a topical clindamycin with benzoyl peroxide. The topical antibiotic should be continued for 3 months and

then R.P. may transition to adapalene and benzoyl peroxide or a trial of adapalene monotherapy.

Case 40-3, Question 2: R.P. returns to the pharmacy and reports that his acne therapy is "not working." He saw his dermatologist and has been using clindamycin lotion 1% every morning, adapalene cream 0.1% every night, and benzoyl peroxide lotion 4% daily for 12 weeks. Upon examination, you notice that he continues to have maculopapular acne in addition to a few nodules. What changes do you recommend to his treatment regimen?

Given that R.P. has now progressed to maculopapular acne mixed with nodules, he should stop his topical antibiotic and start an oral antibiotic, such as doxycycline. If he is able to tolerate doxycycline, he should continue this medication for 6 to 8 weeks, at which point changes should be made if there is no improvement. If the response is adequate, R.P. should try to stop doxycycline after a total treatment course of 3 months. Topical adapalene and benzoyl peroxide should be continued during doxycycline therapy and then continued after the antibiotic course to maintain treatment benefit. If R.P. were to experience a treatment relapse after successful use of an oral antibiotic, another course of the same antibiotic should be used. Switching antibiotics offers no therapeutic benefit, and can promote multidrug resistance.[4,5]

HORMONAL THERAPIES

Hormonal therapies with antiandrogenic effects, such as androgen receptor antagonists and combination oral contraceptives, are the only treatments besides oral isotretinoin to attack acne by reducing sebum production. Hormonal therapies may be helpful even in patients with normal serum androgen levels because hypersensitivity to androgens can occur at the follicular level with normal circulating androgen levels. These treatments are good options for females with acne who are not pregnant and desire contraception or have polycystic ovary syndrome or other hyperandrogenic conditions or symptoms. Systemic effects of hormonal therapy generally preclude their use in male patients. Response to hormonal therapies can take

3 to 6 months because their mechanism of action, reducing sebum production, is an early step in the cascade of acne pathology.[14]

Androgen receptor antagonists

Spironolactone at doses of 25 to 100 mg/day reduces acne because it is an androgen receptor antagonist and inhibits 5-α reductase. Tolerability and serum potassium should be monitored every 3 weeks until maximum tolerated dose or 100 mg/day is achieved, titrating in 25-mg increments. Spironolactone is generally well tolerated, although gynecomastia, menstrual irregularities, hypotension, and hyperkalemia are possible. Spironolactone should not be initiated in patients with baseline hypotension or hyperkalemia. Female patients should use contraception because of the potential for antiandrogen exposure to impair the sexual development of male fetuses. Spironolactone should be used with caution in male patients given the risk of gynecomastia and, possibly, lower efficacy when compared to female patients.[14]

Combination oral contraceptives

When considering initiation of combination oral contraceptives in patients with acne, it is important to review the risk of treatment versus benefit for acne. Potential long-term risks associated with use include increased risk of venous thromboembolic events, myocardial infarction, and the potential increased risk of breast cancer.[4],[14]

Estrogen, usually administered as ethinyl estradiol in a combination oral contraceptive, improves acne in females by reducing ovarian androgen production and by increasing sex hormone–binding globulin concentrations in the serum, thereby lowering free testosterone levels. Currently, there are four combination oral contraceptives approved by the U.S. Food and Drug Administration (FDA) for the treatment of acne: ethinyl estradiol/norgestimate, ethinyl estradiol/norethindrone, ethinyl estradiol/drospirenone, ethinyl estradiol/drospirenone/levomefolate. Comparative trials have not yet clearly established clinically significant superiority of one product over another.[14] In individual

patients, products containing progestins with androgenic effects (eg, norgestrel, levonorgestrel) may override the effect of ethinyl estradiol and worsen acne. Conversely, patients already on a combination oral contraceptive may improve when switched to a formulation with a less androgenic progestin (norgestimate, desogestrel).[15] Other estrogen-containing contraceptives (transdermal patches, vaginal rings) may have similar beneficial effects to combination oral contraceptives, but studies have not been conducted.

CASE 40-4

QUESTION 1: M.J. is a 24-year-old female who presents to the clinic with maculopapular acne. She is currently using adapalene gel 0.1% nightly. She reports that her acne typically worsens 1 week before her menstrual cycle starts and improves once menses begins. Her last menses began 1 week ago, and she is not interested in pregnancy within the next few years.

What factors may make hormonal therapy a good treatment option for M.J.?

M.J. is female, not currently pregnant, not interested in pregnancy in the near future, and has noted fluctuations in her acne severity that correlate with her menstrual cycle are all factors that may make hormonal therapy a good treatment option.

CASE 40-4, QUESTION 2: M.J. is prescribed a combination oral contraceptive, ethinyl estradiol/norethindrone. Should she continue adapalene?

Because the onset of hormonal therapy is delayed, M.J. should be counseled to continue using her current treatment for at least 3 months after starting a combination oral contraceptive. At that time, if she has seen adequate improvement in acne symptoms, she may try hormonal therapy as an acne monotherapy.

NODULAR ACNE

Pharmacotherapy

ORAL ISOTRETINOIN

Oral isotretinoin is the only agent effective for the treatment of nodular acne. It exhibits all four of the mechanisms of action currently used to attack acne, making it a uniquely effective monotherapy. In most cases, one or two 5-month-long courses of therapy will induce a remission lasting for several months or even years after the drug is stopped. Although this medication is very effective in the suppression of acne, it is not utilized in more mild cases of acne because of its adverse effect profile. It should be reserved as a last-line therapy for patients with nodular acne and variants of acne that are prone to scarring.[16]

For the first month of treatment, isotretinoin should be dosed 0.5 mg/kg/day split into two doses administered with food. If tolerated, the dose should be increased to a target dose of 1 mg/kg/day. For best results and minimal risk of relapse, treatment should be continued until a cumulative dose of ~120 mg/kg is reached, usually in about 5 months. Higher dosages are associated with an increased risk of adverse effects.[16]

Isotretinoin is severely teratogenic, and has a risk of severe psychiatric adverse effects.[17],[18] An FDA-mandated Risk Evaluation Mitigation Strategy (REMS) strict risk management program called iPLEDGE regulates the prescription and distribution of isotretinoin in the United States. The iPLEDGE program system verifies that all criteria, including the requirements for pregnancy testing and two methods of contraception for female patients, have been met by the prescriber, patient, and pharmacy before granting the pharmacy authorization to fill and dispense isotretinoin.[17]

In addition to following the guidelines in the iPLEDGE program, patients should have baseline labs including fasting lipid panel and liver function tests. A fasting lipid panel should be rechecked at 4 and 8 weeks after initiating isotretinoin therapy because 20% of patients develop significant triglyceride elevations, and patients may require intervention to prevent pancreatitis. If pancreatitis develops, isotretinoin must be discontinued. Liver function tests and blood

counts only need to be redrawn during therapy if symptoms suggestive of hepatitis or blood dyscrasias appear.[4,19,20]

In addition to its teratogenic effects, oral isotretinoin can also cause numerous dermatologic effects including dryness, erythema, peeling, and photosensitivity.[4,16,20] To minimize this, patients should be instructed to use daily moisturizers, sunscreen, and protective clothing. Patients should avoid waxing, dermabrasions, and any other dermatologic procedures during and up to 6 months after the completion of treatment. Isotretinoin may cause hair dryness, hair thinning, and nail fragility.

CASE 40-5

Question 1: K.S. is a 24-year-old female who first noticed acne when she was 10 years old. As a teen, she used topical benzoyl peroxide, topical adapalene, and systemic doxycycline with limited success. Two years ago, she was diagnosed with polycystic ovary syndrome and began taking norgestimate/ethinyl estradiol along with her maintenance adapalene treatment, after which her acne improved, but was not eradicated. Ten months ago, she also began taking minocycline 100 mg orally twice daily. After a few months, she experienced significant improvement, but she has not been able to stop antibiotics because of recurrent flare-ups. She now has at least a dozen nodules widely distributed among multiple papules and pustules on her face and back.

What pharmacologic therapy would you recommend for K.S.?

The most effective medication for K.S. will be oral isotretinoin at an initial dose of 0.5 mg/kg/day in two divided doses. Before starting, baseline labs must be obtained and all iPLEDGE guidelines followed. The isotretinoin dose should be increased to 1 mg/kg/day in two divided doses after 1 month. The options for contraception should be discussed with K.S. and two methods selected. If her adherence is good with norgestimate/ethinyl estradiol, it may be continued as a primary form of contraception. K.S. should stop taking minocycline when isotretinoin therapy begins because isotretinoin is effective monotherapy, and coadministration of isotretinoin and tetracyclines increases the risk of intracranial hypertension.[21] Adapalene is also unnecessary once isotretinoin

begins. Her acne should significantly improve within the first month of therapy and gradually resolve by the third or fourth month. A second course of isotretinoin therapy is usually not necessary.

Case 40-5, Question 2: After 3 weeks of therapy, K.S. states she has dry eyes, dry skin, and cracks with bleeding at the corners of her mouth. How do you recommend managing these adverse effects?

K.S. should use artificial tears to relieve the discomfort of her dry eyes; if she is still uncomfortable after several days, she can also apply lubricating ophthalmic ointment at bedtime. She should liberally apply moisturizer to dry skin, particularly after bathing (see Chapter 39, Dermatotherapy and Drug-Induced Skin Disorders). Frequent application of a lip balm or emollient, ideally one containing sunscreen, will treat cheilitis. If the symptoms become intolerable, a small reduction in the isotretinoin dose (eg, reduction of 10–20 mg/day) usually decreases the intensity of skin and mucous membrane reactions. Drug discontinuation is rarely necessary.[16]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key Reference

Zaenglen AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74:945–973. (4)

Key Websites

American Academy of Dermatology. Clinical guidelines. https://www.aad.org/education/clinical-guidelines
iPLEDGE Program. https://www.ipledgeprogram.com/

COMPLETE REFERENCES CHAPTER 40 ACNE

1. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol.* 2013; 168:474–485.
2. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet*. 2012;379:361–372.
3. Archer CB, Cohen SN, Baron SE, British Association of Dermatologists and Royal College of General Practitioners. Guidance on the diagnosis and clinical management of acne. *Clin Exp Dermatol*. 2012;37(suppl 1):1–6.
4. Zaenglen AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74:945–973.
5. European Dermatology Forum. S3-guideline for the treatment of acne. Updated 2016. Accessed October 9, 2020. https://www.edf.one/dam/jcr:549b31dd-90dc-4122-b73a-baa73523e765/Acne_2016_GL.pdf
6. Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131(S3):S163–S168.
7. Bhargava S, Cunha PR, Lee J, Kroumpouzos G. Acne scarring management: systematic review and evaluation of the evidence. *Am J Clin Dermatol*. 2018;19(4):459–477.
8. Gamble R, Dunn J, Dawson A, et al. Topical antimicrobial treatment of acne vulgaris: an evidence-based review. *Am J Clin Dermatol*. 2012;13(3):141–152.
9. Davis EC, Callender VD. Postinflammatory hyperpigmentation. *J Clin Aesthet Dermatol*. 2010;3(7):20–31.
10. Thiboutot D. Versatility of azelaic acid 15% gel in treatment of inflammatory acne vulgaris. *J Drugs Dermatol*. 2008;7:13–16.
11. Akhavan A, Bershad S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. *Am J Clin Dermatol*. 2003;4:473–492.
12. Burkhart CN, Burkhart CG. Microbiology's principle of biofilms as a major factor in the pathogenesis of acne vulgaris. *Int J Dermatol*. 2003;42:925–927.
13. Walsh TR, Efthimiou J, Dréno B. Systematic review of antibiotic resistance in acne: an increasing topical and oral threat. *Lancet Infect Dis*. 2016;16:e22–e32.

14. Bettoli V, Zauli S, Virgili A. Is hormonal treatment still an option in acne today? *Br J Dermatol*. 2015;172(1):37–46.
15. Katsambas AD, Dessinioti C. Hormonal therapy for acne: why not as first line therapy? Facts and controversies. *Clin Dermatol*. 2010;28:17–23.
16. Layton A. The use of isotretinoin in acne. *Dermatoendocrinol*. 2009;1(3):162–169.
17. iPLEDGE. iPLEDGE: committed to pregnancy prevention. Accessed October 9, 2020. https://ipledgeprogram.com/#Main
18. Huang Y, Cheng Y. Isotretinoin treatment for acne and risk of depression: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;76(6):1068–1076.
19. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory monitoring during isotretinoin therapy for acne: a systematic review and meta-analysis. *JAMA Dermatol*. 2016;152(1):35–44.
20. Vallerand IA, Lewinson RT, Farris MS, et al. Efficacy and adverse events of oral isotretinoin for acne: a systematic review. *Br J Dermatol*. 2018;178:76–85.
21. Tan HH. Antibacterial therapy for acne: a guide to selection and use of systemic agents. *Am J Clin Dermatol*. 2003;4:307–314.

41

Psoriasis

Rachel C. Long and Kelly A. Mullican

CORE PRINCIPLES		CHAPTER CASES
1	Psoriasis is a chronic, proliferative skin disease that is characterized by well-delineated, thickened erythematous skin plaques and is both topical and systemic in nature. Disease severity is classified based on effected body surface area (BSA) and recalcitrant disease.	**Case 41-1 (Question 1, 3)**
2	Precipitating factors for psoriasis include cold weather, anxiety and stress, viral or bacterial infections, epidermal trauma, or drugs.	**Case 41-1 (Question 2)**
3	Topical corticosteroids are first-line treatment for mild psoriasis given their prompt relief, convenience, and anti-	**Case 41-1 (Question 4)**

	inflammatory, immunosuppressant, and antipruritic properties.	
4	Alternative topical treatments for mild psoriasis—coal tar, anthralin, calcipotriene, calcitriol, and tazarotene—and phototherapy are not as convenient as topical corticosteroids but have well-established efficacy for initial management.	**Case 41-1 (Question 5)**
5	Treatment goals for severe psoriasis include both safe and effective resolution of the disease and long-term maintenance using agents to induce immunosuppressive or remittive cellular changes.	**Case 41-2 (Question 1)**
6	Use of immunosuppressive agents can be limited as a result of adverse effects, monitoring requirements, or toxicity. There is also a lack of evidence to support that they modify the long-term disease process. Immunomodulatory therapy, including T-cell agents and tumor necrosis factor-α (TNF-α) inhibitors and monoclonal antibodies, is thought to target the immune-mediated mechanism of psoriasis.	**Case 41-3 (Question 1, 2)**

INTRODUCTION

Definition and Epidemiology

Psoriasis is a chronic, proliferative skin disease that affects ~3% of the population in the United States and an estimated 125 million patients worldwide.[1,2] Plaque psoriasis is the most prevalent psoriasis variant, accounting for >80% of cases. It is characterized by well-delineated, thickened erythematous epidermis or dermal plaques covered with a distinctive silvery scale. Genetics plays a role in its development and certain environmental factors can exacerbate this disease. Although psoriasis can manifest at any age, a bimodal age distribution exists at ages 18 to 39 and 50 to 69 years.[1,3]

Pathogenesis

Psoriatic plaques are defined by epidermal hyperplasia, leukocyte infiltration, and changes in dermal microvasculature. Differentiation and activation of immune-mediated response systems are disrupted in psoriasis, resulting in an increase in the number of proliferating keratinocytes. This is accompanied by shortened time required for these cells to cast off into the epidermal layer (3–4 days rather than the usual 28–30 days) resulting clinically as diffuse scaling. T cells contribute to this keratinocyte hyperproliferation through the secretion of various growth factors.[4,5] In addition, T cells will release cytokines resulting in further inflammation, the recruitment of additional T cells, and, ultimately, the development of psoriatic lesions in susceptible persons.[4,5]

Prognosis

Similar to those with diabetes, cancer, or heart disease, patients with psoriasis experience a reduced quality of life related to an impairment of social, psychological, and physical functioning.[6–8] Although psoriasis is a treatable disease, there is no known cure. Shared decision-making is imperative, and patient preference should play a primary role in determining treatment because of the potentially awkward and messy topical treatments or systemic medications that have significant adverse effects. The goal of

therapy should be to achieve complete clearing of psoriatic lesions or a satisfactory improvement for the individual patient.

Clinical Presentation

A thorough medical history may reveal a cause of exacerbations of psoriatic lesions. Most patients report that hot weather, sunlight, and humidity help clear psoriasis, whereas cold weather has an adverse effect on its course. Anxiety or psychological stress is believed to contribute adversely. Viral or bacterial infections may precipitate the onset or flare-up of psoriasis. Trauma to the skin (ie, cuts, burns, abrasions, etc) can elicit the development of lesions.

Plaque psoriasis typically presents as sharply demarcated, erythematous, scaly patches or plaques, which are often symmetrical. The most commonly affected areas include the trunk, scalp, gluteal folds, elbows, and knees; however, plaque psoriasis can occur anywhere on the body including nail beds. Over 50% of patients experience pruritus.[9] The development of psoriatic lesions at the site of epidermal trauma is known as the *Koebner phenomenon*. Scratch marks, sunburn, or surgical wounds may heal, leaving psoriatic lesions in their place. The scales can be silvery or white in appearance. If the scale is lifted from the plaque, bleeding points can occur, called the *Auspitz sign*. In addition to skin manifestations, nail beds may show punctate pitting, profuse collections of keratotic material, yellow-brown discoloration (“oil spot”), or onycholysis (nail plate separation) in ~50% of patients.[10]

Although most patients (90%) have plaque psoriasis (also known as psoriasis vulgaris), several other presentations exist and can sometimes coexist in a person at any single time.[11] The most severe form of the disease is *erythrodermic psoriasis*, a condition of acute inflammatory erythema and scales involving >90% of the body surface area (BSA). *Pustular psoriasis* is generally localized to the palms and soles, but there is also a generalized version. Both generalized pustular psoriasis and erythrodermic psoriasis can be accompanied by systemic symptoms (eg, hyperthermia, tachycardia,

edema, dehydration, shortness of breath) and can have life-threatening consequences (ie, hypovolemia, electrolyte imbalance, septicemia) if not promptly treated.[12] Lesions of *guttate psoriasis* are small, fine, erythematous scales, usually found on the trunk, arms, or legs, classically after β-hemolytic streptococcal pharyngitis. *Flexural* or *inverse psoriasis* is shiny and red, and typically lacks scales and looks more like intertrigo.[13] Psoriatic arthritis is a seronegative inflammatory arthritis that occurs in ~25% of all patients with psoriasis, with combined features of both rheumatoid arthritis and the seronegative spondyloarthropathies.[9,13]

CASE 41-1

Question 1: M.M., a 35-year-old male, presents with several thick, well-defined erythematous areas on both his elbows and knees that have silvery scales on them. He states he has itching in these areas, and that the areas bleed when he removes the scales. M.M. states that he has had these lesions for some time; however, he has used over-the-counter hydrocortisone and some of his friend's triamcinolone 0.025% cream for the itching. He feels that the lesions have gotten worse since he went on vacation in the Dominican Republic, when he had to take chloroquine for malaria prophylaxis and got "a pretty bad sunburn." On physical examination, M.M. also has a few scattered, circumscribed, erythematous, scaly plaques on the flexural surfaces of both arms and legs and a dense scale on his forehead and scalp. Approximately 4% of his BSA is estimated to be affected with psoriasis. The rest of M.M.'s physical examination and laboratory results are within normal limits.

What classic signs and symptoms suggestive of psoriasis are demonstrated by M.M.?

M.M. presents with many classic signs of psoriasis, including symmetric, distinctive, chronic, and erythematous plaques covered with silvery scales on the extensor surfaces of the elbows and knees as well as the flexural surface of his arms and legs. He also shows scalp involvement, but does not appear to have plaques on his trunk or nail or systemic involvement. He exhibits the Auspitz sign and evidence of the Koebner phenomenon because his lesions worsened after skin trauma from the sunburn. His report of pruritus is consistent with the presentation in 50% of patients.

Drug-Induced Psoriasis

A number of drugs have been reported to exacerbate preexisting psoriasis, induce psoriatic lesions on apparently normal skin in patients with psoriasis, or precipitate psoriasis in persons with or without a family history of psoriasis (**Table 41-1**).[14] Antimalarial agents, such as chloroquine, may have an adverse effect on the course of psoriasis and can cause exfoliative erythroderma.[15] Hydroxychloroquine, however, has not shared this association (except for one case report) and is preferred over chloroquine in patients with psoriasis who need prophylactic treatment for malaria.[15]

Table 41-1
Drugs Reported to Induce Psoriasis

Anesthetics	**Procaine**
Antimicrobial agents	Amoxicillin, ampicillin, imiquimod, penicillins, sulfonamides, terbinafine, tetracyclines, vancomycin, voriconazole
Anti-inflammatory drugs	Corticosteroids (after withdrawal), NSAIDs (indomethacin, salicylates), mesalamine
Antimalarial agents	Chloroquine, hydroxychloroquine
Cardiovascular drugs	Acetazolamide, amiodarone, angiotensin-converting enzyme inhibitors (enalapril, lisinopril), β-blockers (atenolol, metoprolol, propranolol, timolol), calcium channel blockers (dihydropyridines, diltiazem, verapamil), clonidine, digoxin, gemfibrozil, quinidine
H_2-antagonists	Cimetidine, ranitidine
Hormones	Oxandrolone, progesterone
Opioid analgesics	Morphine
Psychotropics and neurologic agents	Lithium carbonate, venlafaxine, fluoxetine, carbamazepine, olanzapine, gabapentin, oxcarbazepine, tiagabine, valproic acid, zaleplon
Miscellaneous	Potassium iodide, mercury, α-interferon, β-interferons, GM-CSF

GM-CSF, granulocyte-macrophage colony-stimulating factor; NSAIDs, nonsteroidal anti-inflammatory drugs.

Source: Kim GK, Del Rosso JQ. Drug-provoked psoriasis: is it drug induced or drug aggravated? *J Clin Aesthet Dermatol*. 2010;3:32–38; Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. *Int J Dermatol*. 2010;49:1351; Facts & Comparisons eAnswers. Accessed September 19, 2020. https://fco.factsandcomparisons.com/lco/action/home

Lithium also can precipitate psoriasis and contribute to resistance to treatment through its effects on cell kinetics (increase in circulating neutrophils, accelerated neutrophil turnover, increased epidermal cell proliferation), which may require more intensive treatment options for psoriasis.[16]

β-Blockers and some nonsteroidal anti-inflammatory drugs (NSAIDs) can precipitate a psoriasiform state.[16] Because both lithium and propranolol inhibit cyclic adenosine monophosphate (cAMP), cyclic nucleosides may play a role in the onset and clinical course of psoriasis.

When compared with other NSAIDs, indomethacin may selectively inhibit cyclooxygenase more than that by the lipoxygenase pathways of arachidonic acid metabolism. As a result, indomethacin may have a more significant adverse psoriatic effect than that of other NSAIDs.[16]

Flare-ups of pustular psoriasis also can be precipitated by withdrawal from systemic corticosteroids or withdrawal from high-potency topical corticosteroids that are applied under occlusion to large areas.[17] Because of this problem, systemic corticosteroids are not routinely used to treat psoriasis.

Case 41-1, Question 2: What are the factors that can precipitate or aggravate psoriasis? What are the potential causes of M.M.'s psoriatic exacerbation?

Chloroquine for malaria prophylaxis, a Caribbean sunburn, and triamcinolone tachyphylaxis probably all contributed to the exacerbation of M.M.'s psoriasis.

Classification of Psoriasis

Psoriasis Area and Severity Index (PASI) is the most commonly used validated scoring index in clinical trials. This scoring system quantifies the severity (ie, induration, erythema, desquamation) and extent of psoriasis lesions.[17],[18] Scores for PASI range from 0 to 72. PASI response rates indicate the percent decrease in PASI score compared to baseline. For example, PASI 75 represents a ≥75% decrease in PASI score at 3 months from baseline and is the most prominent marker to assess systemic agent efficacy.[19]

In the clinical setting, disease severity is usually categorized based on BSA and recalcitrant disease. Mild disease is defined as <5% BSA without face, genital, hand, or foot involvement in which topical therapies alone may be used to assist with clearance. Moderate disease applies to patients with ≥5 to <10% BSA involvement or those who may require escalation of therapy to phototherapy or nonbiologic systemic agents. Severe disease generally applies to patients with >10% BSA affected or those who require escalation to biologic therapies.[18],[19] Clinicians can determine the approximate BSA involvement by having a patient hold open their hand. The area from the patient's wrist to thumb and finger is ~1% of the patient's BSA. Each "hand-sized" area affected by plaques is added to come up with the total BSA affected. In general, the head can represent up to 9% of the BSA, the front and back of the torso represent up to18% BSA each, as well as each leg (including the buttocks) representing up to 18% each.

Case 41-1, Question 3: How would you classify M.M.'s psoriasis?

M.M. would be classified as having mild psoriasis and is a candidate for topical therapy because <5% of his BSA is currently affected by psoriasis.

TREATMENT OF MILD-TO-MODERATE PSORIASIS

Topical therapies are the cornerstone of psoriasis treatment and are considered first line for mild disease (**Table 41-2**). As a patient's disease progresses or becomes more recalcitrant, other treatment modalities may need to be added to obtain control. Consideration for the addition of agents is often based on disease severity, cost, and convenience (**Table 41-3**). Nonpharmacologic treatment is also very important. Nonpharmacologic treatment options range from spa therapy to support groups.

Table 41-2
Topical Agents for the Treatment of Psoriasis (Mild to Moderate; ≤5% Body Surface Area Involvement)

Treatment Modality	Advantages	Disadvantages
Emollients	Basic adjunct for all treatments; safe, inexpensive, reduce scaling, itching, and related discomfort	Provide minimal relief alone
Keratolytics (salicylic acid, urea, α-hydroxy acids [ie, glycolic and lactic acids])	Reduce hyperkeratosis; enable other topical modalities to better penetrate; inexpensive	Provide minimal relief individually; nonspecific; salicylism (tinnitus, nausea, vomiting) with salicylic acid if applied extensively

Treatment Modality	Advantages	Disadvantages
Topical corticosteroids	Rapid response; control inflammation and itching; best for intertriginous areas and face; convenient, not messy; mainstay topical treatment modality for psoriasis	Temporary relief; less effective with continued use (tachyphylaxis occurs); withdrawal can produce flare-ups; atrophy, telangiectasia, and striae with continued use after skin returns to normalized state; expensive; adrenal suppression possible
Coal tar	Particularly effective for “flaky” scalp lesions; newer preparations are more cosmetically appealing; efficacy enhanced in combination with UVB	Effective only for mild psoriasis or scalp psoriasis; inconvenient with difficult application; stains clothing and bedding, not skin; strong smelling; folliculitis and contact allergy (bronchospasm in atopic patients with asthma after inhalation of vapor); carcinogenicity in animals
Anthralin	Effective for widespread, refractory plaques; produces long remissions; short, concentrated programs preferred; enhanced efficacy in combination with UVB	Purple-brown staining (skin, clothing, and bath fixtures); irritating to normal skin and flexures; careful application is required; can precipitate generalized psoriasis
Vitamin D analogs	As effective as topical corticosteroids, although slower onset, without long-term corticosteroid adverse effects; convenient, well tolerated	Slow onset; expensive; potential effects on bone metabolism (hypercalcemia); irritant dermatitis on face and intertriginous areas; contraindicated during pregnancy

Treatment Modality	Advantages	Disadvantages
Tazarotene	Extended response; convenient (applied once daily, in gel formulation); maintenance therapy; effective on scalp and face; used in combination with topical corticosteroids	Slow onset; local irritation and pruritus; teratogenic (adequate contraception is required)
UVB	Effective as maintenance therapy; eliminates problems of topical corticosteroids	Office-based therapy (except NB-UVB); sunburn (exacerbates psoriasis); photoaging; skin cancers
PUVA	80% efficacy; "suntan" effect is cosmetically desirable	Time consuming; expensive, office-based therapy (restrictive); sunburn (exacerbates psoriasis); photoaging; both nonmelanoma skin cancer and melanoma; contraindicated during pregnancy and lactation

NB-UVB, narrowband ultraviolet B; PUVA, psoralens plus ultraviolet A light; UVB, ultraviolet B.

Table 41-3
Agents for the Treatment of Moderate-to-Severe Psoriasis (>5% Body Surface Area Involvement)

Treatment Modality	Advantages	Disadvantages

Treatment Modality	Advantages	Disadvantages
Acitretin	Less hepatotoxic than is methotrexate	Not as effective as other systemic agents; efficacy enhanced if given with PUVA or UVB (ie, RePUVA or ReUVB); teratogenic (contraception required); contraindicated with liver or renal dysfunction, drug or alcohol abuse, hypertriglyceridemia, hypervitaminosis A
Methotrexate	Effective for both skin lesions and arthritis, as well as psoriatic nail disease	Hepatotoxicity; bone marrow toxicity; folic acid protects against stomatitis (but not against hepatic or pulmonary toxicity); drug interactions; contraindicated during pregnancy and lactation, drug or alcohol abuse; use with caution during acute infections
Cyclosporine	Used in patients with extensive disease who are unresponsive to other agents; however, given changing pathophysiology and increasing experience at lower dosages, increasing role in rotational therapy to induce remissions	Toxicities and short-lived remissions; renal impairment; suppressive therapy (relapse occurs when discontinued); increased risk of skin cancer, lymphomas, and solid tumors; phototoxic; contraindicated during pregnancy and lactation, and with hypertension, hyperuricemia, hyperkalemia, acute infections

Treatment Modality	Advantages	Disadvantages
Immunomodulators (etanercept, infliximab, adalimumab, certolizumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, risankizumab)	Specific, targeted therapy; effective for both moderate- to-severe skin lesions and arthritis; maintains remission	Expensive; parenteral therapy (often administered in an office-based practice); long-term safety unknown; increased risk of serious infections

PUVA, psoralens plus ultraviolet A light; RePUVA, retinoid-psoralens plus ultraviolet A light; ReUVB, retinoid-psoralens plus ultraviolet B light; UVB, ultraviolet B.

Nonpharmacologic Modalities

Psoriasis is often more emotionally or psychologically disturbing than is often recognized. It may cause reluctance in patients to participate in sports and other outdoor activities that may expose their skin to sunlight. Many patients alter their lifestyles or use nontraditional medications and modalities, often in desperation. Psychological encouragement and support should be part of every treatment plan.[20]

Topical Corticosteroids

Topical corticosteroids are the mainstay of treatment for localized or mild disease. This class exerts its effects through anti-inflammatory, antimitotic, immunosuppressant, and antipruritic properties.[21–23] Topical corticosteroids are classified based on their vasoconstrictive effects with class ranges from I (ultrahigh potency) to VII (low potency). Because psoriasis is generally a relatively corticosteroid-resistant disease, more potent corticosteroids are frequently required (see Table 39-8 in Chapter 39, Dermatotherapy and Drug-Induced Skin Disorders, for a listing of topical corticosteroids by potency).

Selection of strength and vehicle should be based on location of the affected area and patient preference. For the trunk and extremities, high-to-moderate potency (classes II–V) should be used. For plaques that are thicker or harder to treat, consider escalating to ultrahigh-potency corticosteroid (class I). For facial, axillary, inframammary, or groin, low-potency corticosteroids are recommended because these areas are thinner and more prone to adverse effects of topical corticosteroids. Foams or solutions should be used for scalp involvement. Although ointments are more effective than creams, treatment with this vehicle is often not preferred by patients because of its greasiness.[24]

Although multiple treatment regimens exist, a proactive management strategy is one that is commonly used. This strategy encourages patients to apply topical corticosteroids twice daily until the affected areas are almost clear or quiescent. Patients are then instructed to decrease steroid frequency to only twice weekly (eg, weekends only) with the use of a maintenance steroid-sparing agent (eg, vitamin D analog, calcineurin inhibitor) for the remaining days of the week. If a new flare occurs, patients may repeat this process. Studies have shown that classes I to III topical corticosteroids can safely be used up to 4 weeks with minimal risk for skin atrophy. However, continuous use past 4 weeks should be discouraged.[24] Keratolytic agents, such as salicylic acid, can be used with topical steroids to help penetration and potentially increase efficacy.

Intertriginous and chronically treated areas are at the highest risk for some of the common adverse effects including skin atrophy, telangiectasia (also known as spider veins), striae, folliculitis, and purpura. Occasionally, topical corticosteroids can cause a reversible suppression of the hypothalamic–pituitary–adrenal (HPA) axis, as indicated by a decrease in the morning plasma cortisol level.[25] The risk of HPA axis suppression is highest in children and those applying classes I to III corticosteroids to >20% BSA or therapies applied longer than 4 weeks.[24]

Case 41-1, Question 4: What topical corticosteroid therapy is appropriate for M.M.?

A short course of a potent topical corticosteroid is appropriate for this flare-up of erythematous plaque psoriasis in M.M. This will help reduce inflammation, redness, and irritation before initiation of a steroid-sparing agent or more appropriate chronic topical treatment. Topical corticosteroids should be applied twice daily until the affected areas are almost clear or quiescent (no more than 4 weeks). A thin layer of steroid should be applied to each affected area and rubbed in completely. For his scalp involvement, the best formulations to use include solutions, foams, shampoos, oils, gels, or sprays. M.M. can use a betamethasone foam topical steroid for up to 2 weeks on his scalp. The foam should be applied to dry hair. The foam should not be dispensed directly into the hands because it will melt on touching the warm skin. Instead, it should be dispensed on a cool clean surface (ie, a small plate). M.M. should use his fingers to apply a thin layer over the affected area and rub in completely. M.M. should then make sure to wash his hands as soon as he is done.

Alternative Topical Treatments

Effective alternative topical therapies available for patients with localized, mild psoriasis include topical calcineurin inhibitors, vitamin D analogs, coal tar, anthralin, and tazarotene. Although these agents are available in various formulations, ointments are generally favored because they help moisturize the plaques (in contrast to creams, which dry the plaques further).[23] Tachyphylaxis does not occur with chronic use of any of these alternative agents.

TOPICAL CALCINEURIN INHIBITORS

Topical calcineurin inhibitors exert their effects through the inhibition of calcineurin, thus inhibiting T-cell activation and synthesis of several key pro-inflammatory cytokines. Available topical calcineurin inhibitors, tacrolimus and pimecrolimus, are commonly applied to areas where the skin is not as thick (eg, facial and intertriginous areas) and used as steroid-sparing agents for prolonged use (ie, >4

weeks). These agents are applied twice daily for up to 8 weeks.[24] After resolution of symptoms and the initial 8 weeks of treatment, patients can use the topical calcineurin inhibitors as proactive treatment as previously mentioned. The calcineurin inhibitors may be applied twice weekly on areas that are clinically quiescent but often involved in flare-ups. Adverse effects of this class include burning and pruritis, which can improve with continued application and by treating with topical corticosteroid before transitioning to this class.[24],[26]

TOPICAL VITAMIN D ANALOGS

This class exerts their effects through binding to vitamin D receptors, thus inhibiting keratinocyte proliferation and enhancing differentiation. Calcipotriene and calcitriol are the two most commonly used. Although calcipotriene comes in several different formulations, calcitriol is only available as an ointment. In the same vehicle, these agents have comparable efficacies. They should be applied twice daily (while avoiding the face, eyes, and lips) with peak effects occurring between 6 and 8 weeks of initiation.[22],[27],[28] Topical vitamin D analogs in combination with betamethasone dipropionate can be used in the treatment of mild-to-moderate nail disease.[29] However, use is not recommended for severe nail disease because of poor penetration.[30]

The most common side effects include burning, pruritis, edema, peeling, dryness, and erythema, which improve or disappear with continued use. In patients who experience these adverse effects, short-term treatment with topical corticosteroids may be added.[24] Systemic side effects including hypercalcemia and parathyroid suppression are extremely rare. However, patients applying >30% BSA, calcipotriene doses exceeding 100 g/week, or those with underlying renal disease are at highest risk.[31] Patients on concurrent phototherapy should be instructed to apply topical vitamin D analogs after phototherapy treatment because ultraviolet A (UVA) can decrease its efficacy, and the topical vitamin D analog, if applied too

thick, can block UVB rays. Combination with salicylic acid should also be avoided because it can inactivate calcipotriene.

TAZAROTENE

Tazarotene is a topical synthetic retinoid that is rapidly converted to its biologically active metabolite, tazarotenic acid.[23],[32] By interacting with the predominant retinoid receptors on the skin surface regulating gene transcription, retinoic acids normalize abnormal keratinocyte differentiation, reduce hyperproliferation, and decrease inflammation associated with psoriasis.[32] Tazarotene can be applied once daily and used for 8 to 12 weeks for the treatment of mild-to-moderate disease. It has been found to be particularly effective in nail disease.[33],[34] Clinical trials have found efficacy similar to that of fluocinonide cream and calcipotriene 0.005% ointment.[35],[36] However, as with calcipotriene, tazarotene works slowly.

Commonly reported adverse effects include burning, erythema, and pruritis. This is more prominent in those using higher concentrations. Risk for this can be mitigated by utilizing creams, lower concentrations, combining with a moisturizer, alternative day dosing or short contact dosing (eg, 30–60 minutes) or combining with topical corticosteroids.[24] Because oral retinoids are known teratogens, tazarotene is a category X drug and is contraindicated during pregnancy. Females should be warned of the potential risk and the need to use adequate contraception while using these preparations.[32],[37]

ANTHRALIN

Anthralin, a hydroxyanthrone derivative, has a proposed mechanism of inhibiting T-lymphocyte activation and promoting keratinocyte differentiation.[23],[38] It is effective for treatment of widespread, discrete psoriatic plaques, but its use has declined in recent years because of the availability of more cosmetically appealing preparations. When used, anthralin is started at 0.1% once daily and increased as tolerated. Clearance can appear within 3 weeks, and patients are then transitioned to maintenance dosing of one to two times per

week. The primary disadvantages of anthralin are its irritant nature and property of staining skin and clothing. Plastic gloves should be used, as well as old bed linen and clothing for sleep. If possible, because of irritant properties, contact with face, eyes, mucous membranes, and non–psoriatic skin should be avoided. To minimize the risk of irritant properties, short contact up to no more than 2 hours per day is recommended. Anthralin also can precipitate generalized psoriasis if applied to unstable psoriasis (ie, plaque transformation to pustular form).

COAL TAR

Crude coal tar is a complex mixture of thousands of hydrocarbon compounds.[23],[39] It affects psoriasis through its antiproliferative and anti-inflammatory effects.[39] Tar preparations of 2% to 10% are processed as creams, ointments, lotions, gels, oils, shampoos, and coal tar solution. Newer purified preparations, using refined coal tar, are less messy and more cosmetically acceptable, but perhaps not as effective.[39] Tar may be helpful for patients with mild-to-moderate disease. The potential severity of adverse drug effects from topical tar products is less than that from anthralin and much less than that from topical corticosteroids. Because tar, in every form, is messy, stains the skin, has an odor, and is low potency compared with anthralin, it has been relegated to second-line therapy for most patients, despite its moderate price and newer, more cosmetically appealing formulations.[25],[40] Tar preparations generally are used once or twice daily, and a bedtime application (as a shampoo or cream overnight) is particularly useful in psoriasis of the scalp. Patients should be warned about the staining properties of tar on clothing and bedding. Other adverse effects include photosensitivity, acneiform eruptions, folliculitis, and irritation dermatitis. Owing to the irritant properties of coal tar, care should be taken to avoid use on the face, flexures, and genitalia and with inflammatory psoriasis. Although not proved in human studies, the potential carcinogenicity of coal tar remains controversial because of the results of animal and occupational studies.[41],[42]

Case 41-1, Question 5: M.M.'s acute psoriasis flare-up has responded well to a short course of topical corticosteroid, and his plaques have now cleared. What maintenance therapies are available for M.M.?

M.M. can apply a steroid-sparing agent, such as a vitamin D analog in combination with the topical corticosteroid that may help with steroid rebound. M.M. should be instructed to decrease his topical corticosteroid frequency to weekend applications only. All other days of the week, he can apply calcipotriene or calcitriol twice daily.

TREATMENT OF MODERATE-TO-SEVERE PSORIASIS

Treatment modalities for moderate-to-severe disease include phototherapy, systemic nonbiologics, and biologic agents. Topical agents can continue to be used as an adjunct to systemic therapy but is not recommended as monotherapy in this population. Biologics have been the focus of research and development for the treatment of psoriasis most recently. Owing to superior efficacy, biologics are recommended as first line over systemic nonbiologics or phototherapy in patients with severe disease as well as in patients with psoriatic arthritis (Table 41-3).

Phototherapy

Although many patients may achieve disease control with topical therapies alone, one in six patients will progress to moderate or severe disease and require alternative treatment modalities.[43] Systemic nonbiologic and biologic agents, although effective for moderate-to-severe disease, come at a higher cost and risk for numerous adverse effects, including immunosuppression. Phototherapy with UV light has a long history of use in the treatment

of psoriasis and other skin disorders. In addition to its use in moderate-to-severe disease, phototherapy may also be considered for patients with mild disease refractory to topical therapies or as an adjunct to biologic or systemic regimens. Although there is no first-line phototherapy modality, selection should be individualized considering factors such as percentage of BSA affected, lifestyle, and treatment expenses. Phototherapy is available as psoralen plus ultraviolet A (PUVA), narrowband ultraviolet B (NB-UVB), and broadband ultraviolet B (BB-UVB).

Before initiating phototherapy, it is important to assess the patient for any personal or family history of skin cancer. Phototherapy, regardless of type, carries an increased risk of cutaneous malignancy. All patients should also be evaluated for their Fitzpatrick skin type (ie, ease of sunburn and inherent skin color) and have their medication list reviewed for identification of any photosensitizing agents (eg, thiazides, tetracyclines). Together, this can assist in determining the appropriate initial treatment dose and reduce risk of treatment-related adverse effects. Once an initial dose has been determined, doses will be titrated up at a rate of 5% to 10% with each treatment until the minimum erythema dose at 24 hours has been reached or the patient has reached their maximum phototherapy dose.[43] Patients should be evaluated throughout their treatment to determine the degree of treatment response and treatment-related adverse effects. Erythema lasting >48 hours or adverse effects, such as itching, stinging, or burning, are all indications for reducing a patient's dose to the last dose without such adverse effects. Phototherapy is administered at a frequency of two to three times per week with time with psoriasis clearance typically occurring at 8 to 12 weeks. Patients who miss doses of phototherapy may be required to restart at lower doses and titrate back up accordingly depending on the number of treatments missed. Once a patient's psoriatic lesions have cleared, patients may have their doses tapered or indefinitely continued as maintenance therapy. Patients who choose to taper may decrease treatment to twice weekly for 4 weeks, followed by once-weekly treatment for the second month. The maintenance dosage is held constant during the

taper. For patients who prefer indefinite maintenance therapy, treatment is administered every 1 to 2 weeks, with a maintenance dosage that is ~25% lower than is the original maintenance dose.[43]

Efforts must be made to minimize the potential risk of long-term effects of phototherapy. Development of cataracts is a recognized long-term effect of prolonged exposure, and therefore use of protective goggles is required to reduce the risk for ocular toxicity. Owing to the potential increased risk of genital cancer identified in BB-UVB studies, it is recommended that patients undergoing phototherapy wear underwear to reduce this risk. In addition, owing to the concern for risk of cutaneous malignancies (highest risk with oral PUVA), patients should apply sunscreen (SPF 50 or higher) to facial area (if not effected) when undergoing phototherapy treatments. They should also be encouraged to minimize exposure to the sun and to wear protective barriers when going out in the sun.

PSORALEN PLUS ULTRAVIOLET A

PUVA combines psoralens with UVA light in the 320- to 400-nm spectrum. The psoralens (methoxsalen, 8-methoxypsoralen [8-MOP], and trioxsalen) are a group of photoactive compounds that, on absorption of UV light, are both antiproliferative and immunomodulatory. Without UVA, psoralens are not active. PUVA has greater immunomodulatory effects on the skin than has UVB. Use of PUVA for scalp or nail involvement is limited because of inadequate exposure.[44]

The most widely used psoralen, 8-MOP, is taken ~1.5 hours before exposure to UVA light.[45] 8-MOP can be administered topically (as a solution), in bathwater, or orally. Topical PUVA is unique in that it has been shown to be particularly effective in the treatment of palmoplantar pustular psoriasis. Oral PUVA, although more effective than is NB-UVB, tends to be the least tolerated. Oral PUVA is contraindicated in patients age younger than 10 years, pregnant or nursing mothers, and those with a personal history of melanoma, lupus erythematosus, or xeroderma pigmentosum. Oral PUVA should be used in caution in patients ages 10 to 18 years, those with

a personal history of dysplastic nevi, nonmelanoma skin cancer, photosensitivity, and exposure to ionizing radiation or arsenic or immunosuppressive medications (eg, methotrexate, cyclosporine). Despite studies demonstrating its superiority to UVB therapies, fewer centers are offering PUVA because of its side effect profile, treatment requirements (eg, bath PUVA), and variable insurance coverage for treatments.[43]

NARROWBAND ULTRAVIOLET B

Narrowband ultraviolet B (NB-UVB) refers to wavelengths ranging from 311 to 313 nm. This is the range widely used for the treatment of generalized plaque psoriasis. Comparative studies conducted between PUVA and NB-UVB have shown that although there was no statistically significant difference at 3 months, PUVA resulted in quicker clearance with less treatment exposures compared to NB-UVB. However, oral PUVA is not well tolerated and comes with numerous adverse effects, as previously mentioned. Thus, given its superior short- and long-term safety, ease of use, and lower cost, NB-UVB has been the preferred phototherapy treatment for plaque psoriasis.[46–48] In addition, NB-UVB is preferred over BB-UVB, given its increased efficacy, quicker response to treatment, and lower rates of adverse effects.[48–50] NB-UVB is also favored in the treatment of guttate psoriasis.

One of the most common reasons for a patient's declining phototherapy has been the need for frequent trips to the clinic for therapies to be administered. Now, for patients who are unwilling or unable to come for in-office treatments, home NB-UVB is an option. Studies have found no difference in treatment outcome or treatment-related adverse effects when comparing in-office to home NB-UVB therapy. Studies also found significantly lower treatment burden and higher satisfaction rates among patients receiving home NB-UVB treatments.

BROADBAND ULTRAVIOLET B

UVB light, unlike UVA light, is effective without additional sensitizers (ie, psoralens). BB-UVB emits wavelengths ranging from 270 to 390 nm. Given the greater spectrum of radiation exposure, BB-UVB has a higher risk for sunburn and any theoretical form of sun-related damage. Although effective, comparison studies have found BB-UVB to be less effective than are oral PUVA and NB-UVB for the treatment of plaque psoriasis. It is also less effective than is topical PUVA for the treatment of palmoplantar psoriasis.[43]

CASE 41-2

QUESTION 1: G.L., a 42-year-old male with a several-year history of psoriasis (localized), presents with diffuse, erythematous plaque-like lesions now extending over 8% of his body. The areas have become inflamed, and application of his maintenance topical medication (anthralin) causes pain and irritation. He expresses frustration with the messiness of the current topical regimen. He has reinstituted topical corticosteroids, which helped the redness and itching. However, he is concerned with long-term effects of chronic steroid use and is interested in trying something else to treat his psoriasis. He is free of cardiovascular, renal, or hepatic disease and takes no systemic medications. He is self-employed as a business consultant.

Which therapy would be most appropriate for G.L.'s psoriasis?

G.L. has moderate disease given that affected BSA is 5% to 10%. Given that treatment has not been successful with topical agents alone, the next step in therapy is the addition of phototherapy. Although PUVA is highly effective, side effect profile and variable insurance coverage limit its use. Therefore, NB-UVB may be the best option for him (either in-office or home use). It is important that G.L. be counseled on the cutaneous risk of adverse effects (both short- and long-term ones) associated with phototherapy use. He should also be counseled to apply topical therapies after phototherapy treatments. Initial NB-UVB dose should be based on his skin type and adjusted by 5% to 10% with each treatment until minimum erythema dose at 24 hours has been reached or the patient has reached their maximum phototherapy dose. Doses should be reduced if the patient experiences adverse effects or erythema 48 hours after treatment.

NONBIOLOGIC SYSTEMIC THERAPY

Acitretin

Acitretin is a second-generation systemic retinoid that exhibits antipsoriatic effects by its ability to modulate epidermal differentiation and immunologic function in addition to an anti-inflammatory action.[51] It is less beneficial in psoriasis compared to other systemic therapies, although there are no head-to-head studies. The side effect profile and onset of action (3–6 months) limit its utility for psoriasis, especially with newer medications on the market. However, because it does not have immunosuppressive properties, it can be beneficial in patients on highly active antiretroviral therapy.[52] Combination therapy with phototherapy is more beneficial than is acitretin alone because of the ability to decrease duration and frequency of therapy, lessen cumulative dose of phototherapy, and limit long-term adverse effects.[52],[53] Most patients require maintenance or intermittent therapy to prevent relapses.[54] Response to acitretin should be assessed at 4-week intervals, with dose titrations to reach therapeutic effect with minimal adverse events.[55]

Numerous other adverse effects are associated with acitretin use, including hypervitaminosis A syndrome (ie, dry skin, skin thinning and fragility, chapped lips, dry nasal mucosa, skin peeling, alopecia, and nail dystrophy), retinoid rash, extraspinal tendon and ligament calcification and bone changes in children, hyperlipidemia with elevated levels of serum triglycerides and cholesterol, and liver enzyme alteration and hepatitis.[56] Many patients find the adverse effects of the retinoids intolerable and discontinue treatment. Topical corticosteroids can reduce some of the cutaneous retinoid adverse effects.

Acitretin is teratogenic and accumulates in fatty tissues, where it is slowly released into the bloodstream for up to 1 year after final administration.[51] Therefore, strict contraception during treatment and for 2 to 3 years afterward is recommended in females of childbearing age.[52],[57] Patients also need to be advised not to donate blood while taking acitretin and up to 1 year after the end of treatment.[51]

Methotrexate

Methotrexate, a folic acid analog, at doses <25 mg/week, decreases the proliferation of lymphoid cells. It is believed that methotrexate exhibits its clinical benefit in psoriasis through its immunosuppressive effects.[58],[59] Methotrexate is usually given orally, although a parenteral preparation is available for subcutaneous administration. Methotrexate is initially dosed at 10 to 15 mg once weekly and titrated every 4 weeks as needed to a maximum dose of 25 mg/week.[52] In patients with renal impairment or who are at risk for hematologic toxicities, some clinicians may choose to initiate therapy with a 5-mg test dose with repeat complete blood count (CBC) checked 7 days after the dose. In those with minor gastrointestinal intolerances, methotrexate tablets may be given as three doses at 12-hour intervals weekly, or the patient may be switched to the solution for subcutaneous administration. It is recommended to supplement with folate to help minimize potential adverse effects with therapy.

Randomized clinical trials were not required for drug approval at the time methotrexate was approved for plaque psoriasis. However, methotrexate has been compared in studies with biologic agents and placebo. Based on the direct comparison studies, methotrexate was not found to be as effective as infliximab, adalimumab, etanercept, ustekinumab, and NB-UVB.[52],[60–63] Some studies have demonstrated additional benefit of methotrexate in combination with tumor necrosis factor-α (TNF-α) inhibitors compared to TNF-α monotherapy.[64],[65]

Common adverse events include fatigue, nausea, anorexia, and stomatitis, which tend to occur shortly after administering the methotrexate dose.[66],[67] These side effects may be lessened with folate supplementation, subcutaneous administration, dose splitting, taking tablet with food, or by administering at bedtime. Given the immunosuppressive effects of methotrexate, patients should receive hepatitis B and C screening at baseline as well as tuberculosis testing. Patients who are positive for latent or active tuberculosis must complete treatment before initiating methotrexate. It is also

recommended that tuberculosis screenings be repeated annually in high-risk patients.

Additional adverse effects include pneumonitis (rare), myelosuppression, and hepatotoxicity. The risk of hematologic and hepatic adverse effects is determined by patent characteristics and risk factors.[52] Hematologic toxicities are more common in patients with renal insufficiency, drug interactions, advanced age, and increased alcohol intake. As previously mentioned, initial test doses should be considered in these patients. CBC should be monitored at baseline and regularly thereafter (every 3–6 months).

Hepatotoxicity with methotrexate is more common in psoriasis than in rheumatoid arthritis. Patients with diabetes, obesity, and hyperlipidemia are at increased risk because these risk factors can contribute to nonalcoholic fatty liver disease as well as chronic liver disease (such as hepatitis B or hepatitis C). Additional risk factors include higher than moderate alcohol intake and abnormal liver function tests.[52],[66] Patients initiated on methotrexate should complete a baseline noninvasive blood serology to assess fibrosis and a liver function test. Liver function tests should then be repeated every 3 to 6 months. Given that high cumulative doses are at an increased risk for hepatotoxicity, it is recommended that patients reaching cumulative doses ≥3.5 g receive a gastroenterology consult and/or vibration controlled transient elastography annually or as otherwise recommended by the gastroenterologist.[52]

Methotrexate is contraindicated in pregnancy because of fetal abnormalities. It is recommended that both females and males wait 3 months after discontinuing therapy before trying to conceive. The use of methotrexate is also contraindicated in patients with cirrhosis, thrombocytopenia, leukopenia, or anemia, and in nursing mothers. Relative contraindications to treatment with methotrexate include decreased renal function, significant abnormalities in liver function (ie, fibrosis, cirrhosis, hepatitis), infectious disease, alcohol abuse, and patient unreliability.[52]

Cyclosporine

In psoriasis, cyclosporine primarily acts by inhibition of calcineurin, which is necessary for interleukin-2 (IL-2) production that amplifies helper T cells and cytotoxic lymphocytes. Cyclosporine also inhibits TNF-α and interferon-α_2.[68] Owing to potential toxicity, long-term use of cyclosporine for psoriasis is not recommended. However, it does play a role in patients who are seeking rapid improvement in recalcitrant disease, those with acute flares, and erythroderma.[69] Many patients relapse 2 to 4 months after the discontinuation of cyclosporine therapy if not started on other treatment. It is recommended to slowly taper off cyclosporine rather than abruptly discontinue.[52]

The most common side effects of cyclosporine in psoriasis include renal dysfunction and hypertension. Nephrotoxicity is usually reversible, but if treatment extends beyond 2 years, the risk of fibrosis and irreversible damage increases. Serum creatinine should be routinely monitored. Hypertension is more common in elderly patients and often resolves after discontinuation of cyclosporine. Frequent blood pressure monitoring is recommended, and if patients have two separate abnormal values, the dose of cyclosporine should be decreased or patients can be treated with additional antihypertensive therapy, particularly calcium channel blockers.[52] Other common side effects include headache, musculoskeletal pain, and paresthesia.

Patients should not receive concurrent UVB or PUVA treatment during cyclosporine therapy because of an increased risk of nonmelanoma skin cancers.[52],[69]

Phosphodiesterase 4 inhibitors

Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, reduces immune responses by increasing intracellular cAMP in T cells. This results in decreased expression of cytokines and other pro-inflammatory mediators but increased expression of anti-inflammatory mediators.[70] Mesenchymal cells, which express PDE4, are found in keratinocytes within the dermis, smooth muscle, and vascular endothelium.[71]

The most common adverse effects with apremilast include gastrointestinal (ie, diarrhea and nausea) and headache. Other adverse effects include upper respiratory infections and rebound psoriasis in 0.3% of patients after discontinuation of therapy. Apremilast is metabolized via the cytochrome P 450 3A4 (CYP 3A4) pathway, and therefore should be evaluated for any drug–drug interactions before starting therapy.[52,72]

Biologic Systemic Therapy

Biologic agents used in the treatment of psoriasis include TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors. All biologics used in the treatment of psoriasis are available as subcutaneous injections, with the exception of infliximab. Common adverse effects associated with biologics include injection site reaction and increased risk for infections. Before starting biologic therapies, patients must receive tuberculosis and hepatitis (both B and C serologies) screening. Patients who are positive for latent or active tuberculosis must receive and complete treatment before starting biologic therapies. Tuberculosis screenings should be repeated annually in high-risk patients. Patients may be instructed to hold their biologic doses in cases of complicated infections or in other cases as determined by a treating dermatologist. Patients who require treatments to be held may restart their biologic therapy once infection symptoms have fully resolved and the antibiotic course has been completed. Loading doses may need to be repeated in patients with active flares and/or more than three to four half-lives have passed since their previous dose. Caution should be used in patients with concomitant human immunodeficiency virus (HIV). Biologics may be initiated in those without a recent history of opportunistic infections.[26,73]

Patients requiring moderate- to high-risk surgical procedures may have their biologic treatment held on a case-by-case basis based on individual risk factors and comorbidities. If a decision is made to stop biologic therapy before surgery, the agent can be discontinued three

to four half-lives before and until 1 to 2 weeks after surgery pending there are no postoperative complications.[73]

In cases where biologic agents require discontinuation, repeat loading doses may be required on restarting the agent if more than three to four half-lives have passed since previous dosing. A small percentage of patients may be unable to recapture previous treatment responses when retreated after discontinuation of the agent. If an agent needs to be switched, either for clinical reasons or owing to a change in insurance coverage, the agent may be switched with a different biologic agent with the possibility of improved efficacy and/or tolerability. It is important to stress that not all switches may result in improved efficacy. At this time, there are no specific guideline recommendations for switching between biologics.[73]

TUMOR NECROSIS FACTOR-α INHIBITORS: ETANERCEPT, INFLIXIMAB, ADALIMUMAB, CERTOLIZUMAB

TNF inhibitors inhibit TNF-α, which then decreases the downstream inflammatory effects central to psoriasis. There are four different agents in this class indicated for the treatment of psoriasis: etanercept, infliximab, adalimumab, and certolizumab. Although there are no head-to-head trials, infliximab is thought to be the most efficacious, followed by certolizumab and adalimumab (similar efficacies) and etanercept.[26],[74]

Despite its efficacy, use of infliximab is limited because of the need for intravenous administration, whereas other agents in this class can be self-administered subcutaneously. An additional concern with infliximab use is antibody development, particularly in those with prolonged time between injections, which can decrease its efficacy and increase risk of infusion reactions. Risk of antibody development can be decreased by not prolonging the dosing interval and the concomitant use of methotrexate with infliximab. In addition, studies have shown that use of acetaminophen, hydroxyzine, ranitidine, and methylprednisolone before infliximab infusion may prolong drug survival.[73] Compared to lower weight patients, patients who are

overweight or obese may be less likely to respond to this class and will frequently require shortened dosing intervals to achieve satisfactory response. Infliximab is often recommended for these patients because of its weight-based dosing.

Patients started on TNF inhibitors typically achieve a response within 8 to 10 weeks for infliximab and 12 to 16 weeks for the remainder of the class. In patients who do not see effects with approved TNF inhibitor dosing (eg, adalimumab 40 mg every 2 weeks) dosing frequency should be shortened (eg, adalimumab 40 mg every 10 days) rather than increasing dose administered per injection. Partial responders to TNF inhibitors may also consider adding on adjunct therapies such as phototherapy or topical agents.

The most commonly reported adverse effects for this class include headache, nausea, injection site reactions, and increased risk of infections. Less frequently reported adverse effects include multiple sclerosis, hepatotoxicity (primarily infliximab), exacerbation or new-onset heart failure, and cytopenia. Relative contraindications to treatment include preexisting multiple sclerosis, New York Heart Class III to IV, untreated hepatitis B, and history of lymphoreticular malignancy. For patients who are pregnant or trying to conceive, certolizumab is preferred.[73]

INTERLEUKIN-12/23 INHIBITORS

Ustekinumab is the only approved IL-12/23 inhibitor and is used in the treatment of both psoriasis and psoriatic arthritis. It works to suppress IL-12/23–mediated inflammation. Ustekinumab is administered subcutaneously every 12 weeks (**Table 41-4**). Treatment effect is seen after 12 weeks of continued therapy. For patients with partial response, treatment frequency can be decreased to every 8 weeks or the dose may be increased from 45 to 90 mg.[73] When compared to other agents, post hoc analysis of six major trials found that ustekinumab is less efficacious compared with secukinumab 300 mg.[75]

Table 41-4
Systemic Agents and Dosing for the Treatment of Moderate-to-Severe Psoriasis

Drug Class	Medication	Dosing
TNF inhibitor	Adalimumab	Plaque psoriasis: Initial, 80 mg SUBQ once Maintenance: 40 mg every 2 weeks PsA: 40 mg SUBQ every other week
	Certolizumab	Plaque psoriasis and PsA: Initial, 400 mg SUBQ at weeks 0, 2, and 4 Maintenance: 200 mg every 2 weeks or 400 mg every 4 weeks
	Etanercept	Plaque psoriasis: Initial, 50 mg SUBQ twice weekly for 3 months[a] Maintenance: 50 mg once weekly PsA: 50 mg once weekly
	Infliximab	Plaque psoriasis and PsA: Initial, 5 mg/kg IV at weeks 0, 2, and 6 Maintenance: 5 mg/kg every 8 weeks and every 8 weeks thereafter
IL-12/23 inhibitor	Ustekinumab	Plaque psoriasis: ▪ Weight of ≤100 kg: 45 mg IV or SUBQ at weeks 0 and 4, then every 12 weeks ▪ Weight of >100 kg: 90 mg IV or SUBQ at weeks 0 and 4, then every 12 weeks PsA: 45 mg IV or SUBQ at weeks 0 and 4, then every 12 weeks
IL-17 inhibitors	Secukinumab	Plaque psoriasis: Initial, 300 mg SUBQ once weekly at weeks 0, 1, 2, 3, and 4 Maintenance: 300 mg SUBQ every 4 weeks[b] PsA: Initial, 150 mg SUBQ at weeks 0, 1, 2, 3, and 4[a] Maintenance: 150 mg SUBQ every 4 weeks
	Ixekizumab	Plaque psoriasis and PsA: Initial, 160 mg SUBQ once, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12 Maintenance: 80 mg SUBQ every 4 weeks

Drug Class	Medication	Dosing
	Brodalumab	Plaque psoriasis: Initial, 210 mg SUBQ at weeks 0, 1, and 2 Maintenance: 210 mg SUBQ every 2 weeks[c]
IL-23 inhibitors	Guselkumab	Plaque psoriasis and PsA: Initial, 100 mg SUBQ at weeks 0 and 4 Maintenance:100 mg SUBQ every 8 weeks
	Tildrakizumab	Plaque psoriasis: Initial, 100 mg SUBQ at weeks 0 and 4 Maintenance: 100 mg SUBQ every 12 weeks thereafter
	Risankizumab	Plaque psoriasis: Initial, two consecutive SUBQ injections (75 mg each) for a total dose of 150 mg at weeks 0 and 4 Maintenance: 75 mg SUBQ every 12 weeks thereafter
Retinoid-like compound	Acitretin	Plaque psoriasis: 25–50 mg by mouth daily with main meal
Antimetabolite	Methotrexate	Plaque psoriasis and PsA: 10–25 mg PO/SUBQ given once weekly; adjust dose gradually to optimal response (≤25 mg/week recommended) 5-mg test dose may be considered for those at increased risk for hematologic toxicities
Calcineurin inhibitor	Cyclosporine	Plaque psoriasis: 2.5 mg/kg/day by mouth in two divided doses; increase by 0.5 mg/kg/day with maximum dose of 5 mg/kg/day
Phosphodiesterase-4 enzyme inhibitor	Apremilast	Plaque psoriasis: Initial, 10 mg by mouth in the morning on day 1. Day 2: 10 mg twice daily; day 3: 10 mg in the morning and 20 mg in the evening; day 4: 20 mg twice daily; day 5: 20 mg in the morning and 30 mg in the evening Maintenance: 30 mg twice daily starting on day 6

IV, intravenous; PO, by mouth; PsA: psoriatic arthritis; SUBQ: subcutaneous.

[a]Can skip initial dosing and start with maintenance.

[b]May consider decreasing to 150 mg per dose in select patients.

[c]Consider discontinuing if an adequate response is not achieved after 12 to 16 weeks.

Sources: HUMIRA Injection. Package insert. AbbVie Inc; 2020. CIMZIA®. Prescribing information. UCB, Inc.; 2020. Enbrel. Prescribing information. Amgen Inc.; 2020. Remicade. Prescribing information. Janssen Biotech, Inc.; 2020. Stelara. Prescribing information. Janssen Biotech, Inc.; 2020. Cosentyx. Prescribing information. Novartis Pharmaceuticals Corporation; 2020. Taltz. Prescribing information. Eli Lilly and Company; 2020. Siliq. Prescribing information. Bausch Health Companies Inc; 2020. Tremfya. Prescribing information. Janssen Biotech, Inc.; 2020. Ilumya. Prescribing information. Merck & Co., Inc.; 2020. SKYRIZI. Package insert. AbbVie Inc; 2020. Soriatane. Prescribing information. Stiefel Laboratories Inc; 2018. Methotrexate. Prescribing information. Sun Pharmaceutical Industries, Inc.; 2020. Cyclosporine Prescribing information. Mayne Pharma, Inc; 2019. Otezla. Prescribing information. Amgen, Inc; 2020.

INTERLEUKIN-17 INHIBITORS

IL-17 inhibitors work via targeting the IL-17 ligand (secukinumab and ixekizumab) or receptor (brodalumab). They are approved for the treatment of both psoriasis and psoriatic arthritis. Given their similar mechanisms of action, they are considered to have comparable efficacy.[73] As a class, response should be seen within 12 weeks of use. Clinical trials comparing IL-17 inhibitors to ustekinumab have demonstrated higher efficacy with IL-17 inhibitors.[76–80] In addition, secukinumab and ixekizumab have also demonstrated improved efficacy when compared to etanercept.[80],[81] For patients with partial response, an increase in dose or addition of adjunct therapy (eg, phototherapy, topical agents, etc.) may be considered. This class has an acceptable safety profile, with no increased risk of serious infections or malignancies. Increased risk of mucocutaneous candidiasis and inflammatory bowel disease exacerbations has been reported. Rare cases of suicidal ideations and completions have been seen with brodalumab, and thus a boxed warning has been placed for this agent.[82]

INTERLEUKIN-23 INHIBITORS

IL-23 inhibitors work by binding to the p19 unit of IL-23. Available agents include guselkumab, tildrakizumab, and risankizumab. These agents are the most convenient in terms of dosing frequency (Table 41-4). Although individual short- and long-term efficacies vary, the majority of effects can be seen within 12 weeks of use. Patients with partial response should consider the addition of adjunct therapy (eg, phototherapy, topical agents). Clinical head-to-head trials have demonstrated superior efficacy with IL-23 inhibitors compared to both etanercept and adalimumab.[83],[84] Risankizumab has also demonstrated improved efficacy compared to ustekinumab.[85] The most commonly reported adverse reactions include injection site reaction and upper respiratory infections.

Primary and secondary treatment failure

Primary treatment failure is the initial nonresponse to treatment. For patients with failure to respond to TNF inhibitors, another agent in this class may be tried (although efficacy within the class may continue to be reduced).

Secondary failure occurs in patients who initially have treatment response but lose efficacy over time. Secondary failure may be attributed to the presence of antidrug antibodies. Concomitant use of methotrexate with biologic agents has been shown to decrease risk of antibody formation and thereby increase the duration of use for the biologic agent.[73]

CASE 41-3

QUESTION 1: R.T. is a 46-year-old male aerospace technician with psoriasis. His skin disease has once again become active, despite nightly betamethasone dipropionate administration. Patient does report spending a lot of time traveling because of his job. Active psoriatic lesions are noted on trunk and arms and cover 8% of his body.

What therapy would be most appropriate?

Given that the patient has 8% of BSA affected, this would be classified as moderate disease. He is not having an adequate response to topical treatment. Given disease severity, the next recommendation is to consider phototherapy or nonbiologic systemic agents. Phototherapy may not be feasible given the patient's job travel requirements. Therefore, nonbiologic systemic agents may be considered. Given the side effect profile and onset of action, consider avoiding acitretin and instead of starting methotrexate or apremilast. Apremilast may be the best option because of decreased laboratory monitoring compared to methotrexate. Apremilast is gradually titrated for 5 days up to a maintenance dose of 30 mg twice daily to minimize adverse effects. R.T. should be counseled on potential side effects such as diarrhea, nausea, headache, and weight loss. Before starting therapy, it is important to discuss risk of new or worsening depression with apremilast and when to seek medical attention.

Case 41-3, Question 2: R.T. presents to the office concerned about his new psoriasis flare. Although previously controlled for several years with apremilast and topical therapies, his plaques have now spread to over 10% of his body, and he has also been noticing psoriatic nail changes. What option does he have now to assist with treatment of his psoriasis?

Given the extent of his psoriasis and lack of control with apremilast, biologic agents should now be considered. First-line systemic therapy would be an IL-12/IL-23 (ustekinumab) or IL-23 inhibitor (guselkumab, risankizumab, tildrakizumab) because of superior efficacy in clinical trials when compared to TNF-α inhibitors. Tildrakizumab must be administered in-office, and therefore may not be as convenient as the other self-administered options. Ustekinumab and guselkumab have shown efficacy in nail psoriasis as well as in plaque psoriasis.[86,87] Before starting therapy, R.T. should be assessed for tuberculosis as well as have a CBC and comprehensive metabolic panel to assess for any active infection. R.T. should be assessed 12 weeks after continuous therapy to determine response to the chosen therapy.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Armstrong A, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis. *JAMA*. 2020;323(*19*):1945–1960. (26)

Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol*. 2021;84(*2*):432–470. doi:10.1016/j.jaad.2020.07.087 (24)

Elmets CA, Lim HW, Stoff B, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. *J Am Acad Dermatol*. 2019;81(*3*):775–804. (43)

Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology—National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol*. 2020;82:1445–1486. (52)

Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80:1029–1072. (73)

Naldi L. Scoring and monitoring the severity of psoriasis. What is the preferred method? What is the ideal method? Is PASI passé? Facts and controversies. *Clin Dermatol.* 2010;28:67–72. (17)

Pariser DM, Bagel J, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on disease severity. *Arch Dermatol.* 2007;143:239–242. (19)

Key Websites

National Psoriasis Foundation. http://www.psoriasis.org

COMPLETE REFERENCES CHAPTER 41 PSORIASIS

1. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(2):205–212. doi:10.1111/jdv.13854
2. World Health Organization. Global report on psoriasis. 2016. Accessed September 25, 2020. https://apps.who.int/iris/handle/10665/204417
3. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol*. 2014;70(3):512–516. doi:10.1016/j.jaad.2013.11.013
4. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349:2014–2022.
5. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005;366:1367–1374.
6. Kimball AB, Guerin A, Latremouille-Viau D, et al. Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. *Am J Med*. 2010;123:350–357.
7. Schmitt J, Ford DE. Understanding the relationship between objective disease severity, psoriatic symptoms, illness-related stress, health-related quality of life and depressive symptoms in patients with psoriasis—a structural equations modeling approach. *Gen Hosp Psychiatry*. 2007;29:134–140.
8. Parisi R, Rutter M, Lunt M, et al. Psoriasis and the risk of major cardiovascular events: cohort study using the clinical practice research datalink. *J Invest Dermatol*. 2015;135:2189–2197.
9. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005;64(suppl 2):ii14–ii17.
10. Jiaravuthisan MM, Sasseville D, Vender RB, Murphy F, Muhn CY. Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy. *J Am Acad Dermatol*. 2007;57:1–27.
11. Boehncke WH, Schn MP. Psoriasis. *Lancet.* 2015;386(9997):983–994. doi:10.1016/S0140-6736(14)61909-7
12. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol*. 2006;55:829–835.
13. Grifiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet.* 2007;370:263–271.

14. Kim GK, Del Rosso JQ. Drug-provoked psoriasis: is it drug induced or drug aggravated? *J Clin Aesthet Dermatol*. 2010;3:32–38.
15. Sorbara S, Cozzani E, Rebora A, Parodi A. Hydroxychloroquine in psoriasis: is it really harmful? *Acta Derm Venereol*. 2006;86:450–451.
16. Dika E, Varotti C, Bardazzi F, Maibach HI. Drug-induced psoriasis: an evidence-based overview and the introduction of psoriatic drug eruption probability score. *Cutan Ocul Toxicol*. 2006;25:1–11.
17. Naldi L. Scoring and monitoring the severity of psoriasis. What is the preferred method? What is the ideal method? Is PASI passé? Facts and controversies. *Clin Dermatol*. 2010;28:67–72.
18. Her M, Kavanaugh A. A review of disease activity measures for psoriatic arthritis: what is the best approach. *Expert Rev Clin Immunol*. 2014;10:1241–1254.
19. Pariser DM, Bagel J, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on disease severity. *Arch Dermatol*. 2007;143:239–242.
20. Magin P, Adams J, Heading G, Pond D, Smith W. The psychological sequelae of psoriasis: results of a qualitative study. *Psychol Health Med*. 2009;14:150–161.
21. Menter A, Griffiths CE. Current and future management of psoriasis. *Lancet.* 2007;370:272–284.
22. Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: a systematic review. *Br J Dermatol*. 2002;146:351–364.
23. van de Kerkof PC. An update on topical therapies for mild-moderate psoriasis. *Dermatol Clin*. 2015;33:73–77.
24. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol*. 2021;84(2):432–470. doi:10.1016/j.jaad.2020.07.087
25. Laws PM, Young HS. Topical treatment of psoriasis. *Expert Opin Pharmacother*. 2010;11:1999–2009.
26. Armstrong A, Read C. Pathophysiology, clinical presentation, and treatment of Psoriasis. *JAMA.* 2020;323(19):1945–1960.
27. Thielen AM, Laffitte E. Topical treatments for psoriasis in 2009 [in French]. *Rev Med Suisse*. 2009;5:876–881.
28. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60:643–659.
29. Rigopoulos D, Gregoriou S, Daniel Iii CR, et al. Treatment of nail psoriasis with a two-compound formulation of calcipotriol plus betamethasone dipropionate ointment. *Dermatology.* 2009;218(4):338–341.
30. Haneke E. Nail psoriasis: clinical features, pathogenesis, differential diagnoses, and management. *Psoriasis (Auckl)*. 2017;7:51–63.

31. Scott LJ, Dunn CJ, Goa KL. Calcipotriol ointment. A review of its use in the management of psoriasis. *Am J Clin Dermatol*. 2001;2(2):95–120.
32. Talpur R, Cox K, Duvic M. Efficacy and safety of topical tazarotene: a review. *Expert Opin Drug Metab Toxicol*. 2009;5:195–210.
33. Rigopoulos D, Gregorious S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs. clobetasol propionate 0.05% cream: a double-blind study. *Acta Derm Venereol*. 2007;87:167–168.
34. Scher RK, Stiller M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. *Cutis.* 2001;68(5):355–358.
35. Lebwohl M, Ast E, Callen JP, et al. Once-daily tazarotene gel versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. *J Am Acad Dermatol*. 1998;38(5 Pt 1):705–711.
36. Kaur I, Dogra S, Jain R, Kumar B. Comparative study of calcipotriol (0.005%) ointment and tazarotene (0.05% and 0.1%) gel in the treatment of stable plaque psoriasis. *Indian J Dermatol Venereol Leprol*. 2008;74(5):471–474.
37. Dando TM, Wellington K. Topical tazarotene: a review of its use in the treatment of plaque psoriasis. *Am J Clin Dermatol*. 2005;6:255–272.
38. McGill A, Frank A, Emmett N, Turnbull DM, Birch-Machin MA, Reynolds NJ. The anti-psoriatic drug anthralin accumulates in keratinocyte mitochondria, dissipates mitochondrial membrane potential, and induces apoptosis through a pathway dependent on respiratory competent mitochondria. *FASEB J*. 2005;19(8):1012–1014
39. Roelofzen JH, Aben KKH, van der Valk PGM, van Houtum JLM, van de Kerkhof PCM, Kiemeney LALM. Coal tar in dermatology. *J Dermatolog Treat*. 2007;18:329–334.
40. Brouda I, Edison B, Van Cott A, Green BA. Tolerability and cosmetic acceptability of liquor carbonis distillate (coal tar) solution 15% as topical therapy for plaque psoriasis. *Cutis.* 2010;85:214–220.
41. Roelofzen JH, Aben KK, Oldenhof UT, et al. No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. *J Invest Dermatol*. 2010;130(4):953–961.
42. Roelofzen JHJ, Aben KKH, Van de Kerkhof PCM, Van der Valk PGM, Kiemeney L. Dermatological exposure to coal tar and bladder cancer risk: a case- control study. *Urol Oncol*. 2015;33(1):20.e19–20.e22.
43. Elmets CA, Lim HW, Stoff B, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. *J Am Acad Dermatol*. 2019;81(3):775–804.
44. Stern RS. Psoralen and ultraviolet a light therapy for psoriasis. *N Engl J Med*. 2007;357:682–690.
45. Sezer E, Erbil AH, Kurumlu Z, Tas¸tan HB, Etikan I. Comparison of the efficacy of local narrowband ultraviolet B (NB-UVB) phototherapy versus

psoralen plus ultraviolet A (PUVA) paint for palmoplantar psoriasis. *J Dermatol*. 2007;34:435–440.

46. Chen X, Yang M, Cheng Y, Liu GJ, Zhang M. Narrow-band ultraviolet B phototherapy versus broad-band ultraviolet B or psoralen-ultraviolet A photochemotherapy for psoriasis. *Cochrane Database Syst Rev*. 2013; (10):1465–1858.
47. Archier E, Devaux S, Castela E, et al. Efficacy of psoralen UV-A therapy vs. narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*. 2012;26(suppl 3):11–21.
48. Almutawa F, Alnomair N, Wang Y, Hamzavi I, Lim HW. Systematic review of UV-based therapy for psoriasis. *Am J Clin Dermatol*. 2013;14(2):87–109.
49. Coven TR, Burack LH, Gilleaudeau R, Keogh M, Ozawa M, Krueger JG. Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. *Arch Dermatol*. 1997;133(12):1514–1522.
50. Walters IB, Burack LH, Coven TR, Gilleaudeau P, Krueger JG. Suberythemogenic narrow-band UVB is markedly more effective than conventional UVB in treatment of psoriasis vulgaris. *J Am Acad Dermatol*. 1999;40(6 Pt 1):893–900.
51. Ormerod AD, Campalani E, Goodfield MJD, BAD Clinical Standards Unit. British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. *Br J Dermatol*. 2010;162:952–963.
52. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol*. 2020;82:1445–1486.
53. Lebwohl M, Drake L, Menter A, et al. Consensus conference: acitretin in combination with UVB or PUVA in the treatment of psoriasis. *J Am Acad Dermatol*. 2001;45(4):544–553.
54. Lee CS, Li K. A review of acitretin for the treatment of psoriasis. *Expert Opin Drug Saf*. 2009;8:769–779.
55. Carretero G, Ribera M, Belinchón I, et al. Guidelines for the use of acitretin in psoriasis. *Actas Dermosifiliogr*. 2013;104:598–616.
56. Chroni E, Monastirli A, Tsambaos D. Neuromuscular adverse effects associated with systemic retinoid dermatotherapy: monitoring and treatment algorithm for clinicians. *Drug Saf*. 2010;33:25–34.
57. Soriatane. Prescribing information. Stiefel Laboratories ; 2018.
58. Jeffes EW III, McCullough JL, Pittelkow MR, et al. Methotrexate therapy of psoriasis: differential sensitivity of proliferating lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of methotrexate. *J Invest Dermatol*. 1995;104(2):183–188.
59. Saporito FC, Menter MA. Methotrexate and psoriasis in the era of new biologic agents. *J Am Acad Dermatol*. 2004;50(2):301–309.

60. Sbidian E, Chaimani A, Garcia-Doval I, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev*. 2017;12:1465–1858.
61. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol*. 2011;165(5):1109–1117.
62. Saurat J-H, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2008;158(3):558–566.
63. Gelfand JM, Wan J, Duffin KC, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. *Arch Dermatol*. 2012;148(4):487–494.
64. Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2012;167(3):649–657.
65. Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI. Combined use of systemic agents for psoriasis: a systematic review. *JAMA Dermatol*. 2014;150(11):1213–1220.
66. Ford AR, Siegel M, Bagel J, et al. Dietary recommendations for adults with psoriasis or psoriatic arthritis from the medical board of the National Psoriasis Foundation: a systematic review. *JAMA Dermatol*. 2018;154(8):934–950.
67. Belzunegui J, Intxausti JJ, De Dios JR, et al. Absence of pulmonary fibrosis in patients with psoriatic arthritis treated with weekly low-dose methotrexate. *Clin Exp Rheumatol*. 2001;19(6):727–730.
68. Haider AS, Lowes MA, Suárez-Fariñas M, et al. Identification of cellular path ways of “type 1,” Th17 T cells, and TNF– and inducible nitric oxide synthase-producing dendritic cells in autoimmune inflammation through pharmacogenomic study of cyclosporine A in psoriasis. *J Immunol.* 2008;180:1913–1920.
69. Maza A, Montaudié H, Sbidian E, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. *J Eur Acad Dermatol Venereol*. 2011;25(suppl 2):19–27.
70. Schafer PH, Parton A, Capone L, et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cell Signal*. 2014;26:2016–2029.
71. Hansen RB, Kavanaugh A. Novel treatments with small molecules in psoriatic arthritis. *Curr Rheumatol Rep*. 2014;16:1–7.

72. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2014;73(1):37–49.
73. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80:1029–1072.
74. Puig L, López A, Vilarrasa E, García I. Efficacy of biologics in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials with different time points. *J Eur Acad Dermatol Venereol*. 2014;28(12):1633–1653.
75. Bagel, J, Blauvelt A, Nia J, et al. Secukinumab maintains superiority over ustekinumab in clearing skin and improving quality of life in patients with moderate to severe plaque psoriasis: 52-week results from a double-blind phase 3b trial. *J Eur Acad Dermatol Venereol*. 2020;35(1):135–142. doi:10.1111/jdv.16558
76. Blauvelt A, Reich K, Tsai T-F, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. *J Am Acad Dermatol*. 2017;76(1):60–69.e69.
77. Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24 week results from IXORA-S, a phase III study. *Br J Dermatol*. 2017;177(4):1014–1023.
78. Papp KA, Gordon KB, Langley RG, et al. Impact of previous biologic use on the efficacy and safety of brodalumab and ustekinumab in patients with moderate-to-severe plaque psoriasis: integrated analysis of the randomized controlled trials AMAGINE-2 and AMAGINE-3. *Br J Dermatol*. 2018;179(2):320–328.
79. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373(14):1318–1328.
80. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis — results of two phase 3 trials. *N Engl J Med*. 2014;371(4):326–338.
81. Griffiths CEM, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet.* 2015;386(9993):541–551.
82. Siliq ® (brodalumab). Package insert. Bausch Health US; June 2020.
83. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo-

and active comparator–controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418–431.

84. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet.* 2017;390(10091):276–288.
85. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 2018;392(10148):650–661.
86. Rich P, Bourcier M, Sofen H, et al. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. *Br J Dermatol*. 2014;170(2):398–407.
87. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405–417.

42

Photosensitivity, Photoaging, and Burn Injuries

Molly E. Howard

CORE PRINCIPLES		CHAPTER CASES
PHOTOSENSITIVITY		
1	Ultraviolet radiation (UVR) exposure has been linked to many adverse effects, including malignant melanoma.	**Case 42-1 (Question 1, 2)**
2	Photoprotection encompasses all methods of UVR blocking, including sunscreens, protective clothing, and sunglasses. Sunscreens are widely used to prevent sunburn and reduce the incidence of premature aging and carcinogenesis, although clothing and avoiding direct sunlight offer greater protection.	**Case 42-1 (Question 3–8)**

3	UVA has been found to cause many of the same effects on the skins as UVB, including immunologic, degenerative, and neoplastic changes of skin.	**Case 42-2 (Question 1–3)**
4	Sunburn is a self-limiting condition, which is generally managed with symptomatic treatment including oral analgesics, topical analgesics, and topical anesthetics. Treatment beyond self-management is necessary if the sunburn is accompanied by constitutional symptoms, involves second- or third-degree burns, or is infected.	**Case 42-3 (Question 1)**
5	Phototoxicity and photoallergy are often drug- or chemical-induced reactions to UVR exposure and account for up to 8% of adverse drug reactions.	**Case 42-4 (Question 1–3)**
PHOTOAGING		
1	Photodamaged skin is characterized as being wrinkled, yellowed, and sagging.	**Case 42-5 (Question 1)**
2	Topical retinoid therapy is most effective for patients ages 50 to 70 years with moderate-to-severe photoaging and for prophylactic use in patients undergoing the initial changes of photoaging.	**Case 42-5 (Question 2–5)**
BURN INJURIES		
1	Most burn injuries are minor and can be managed in ambulatory settings.	**Case 42-6 (Question 1)**
2	Major second- or third-degree burns	**Case 42-6 (Question 1)**

	should be immediately triaged to a health system with a multidisciplinary team that can adequately manage all potential complications.	
3	Synthetic dressings and skin substitutes have expanded the options and the desired outcomes for recovery.	**Case 42-6 (Question 2)**

INTRODUCTION

Incidence, Prevalence, and Epidemiology of Ultraviolet Radiation Exposure

Changing lifestyles have considerably increased human exposure to sunlight, including more outdoor recreational activities, more emphasis on tanning, longer life spans, seasonal population shifts to the Sunbelt, and an emphasis on improving vitamin D deficiency. Epidemiologic evidence clearly implicates sunlight as a causative factor in many skin diseases, and public attitudes toward tanning and sun exposure have slowly begun to change. Skin cancer is the most common of all cancers and yet also one of the most preventable. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), which together account for more than half of all malignancies in the United States, are linked closely to exposure to ultraviolet radiation (UVR).[1] Melanoma incidence rates have increased annually from 2003 to 2016, with an average increase of around 78,000 diagnoses each year during that time period.[2] Without intervention, the annual cost of treating newly diagnosed melanomas is projected to triple by 2030, but the Centers for Disease Control and Prevention (CDC) estimates that a comprehensive national skin cancer prevention program could potentially avert 230,000 melanoma cases.[3] In July 2014, the acting surgeon general delivered “The Surgeon General’s Call to Action to Prevent Skin Cancer.” The purpose of the call was

to unite various sectors of the nation to address skin cancer as a major public health problem, increase awareness of skin cancer, and call for action to reduce risk.[4] Although melanoma diagnosis has continued to increase since 2014, mortality rates have decreased by ~5% per year, with approval of new treatments for advanced disease.[2]

Sunburn, photoaging, immunologic changes in the skin, cataracts, photodermatoses, phototoxicity, and photoallergy are other commonly encountered photosensitivity reactions that occur after UVR exposure. Phototoxicity and photoallergy are often drug- or chemical- induced reactions to UVR exposure and account for up to 8% of adverse drug reactions.[5] The appropriate use of sunscreens or other photoprotective behaviors can help mitigate the incidence of the adverse effects of UVR. Despite this fact, sunscreen use remains low, with recent survey-based estimates showing that fewer than 15% of males and 30% of females use sunscreen on both the face and the exposed skin as recommended. Forty-two percent of males reported never using sunscreen at all.[6]

Etiology

ULTRAVIOLET RADIATION SPECTRUM

UVR, the primary inducer of photosensitivity reactions in humans, is divided into ranges according to the effects of four primary wavelengths: UVA1 (ultraviolet A1) (340–400 nm), UVA2 (320–340 nm), UVB (290–320 nm), and UVC (200–290 nm) (**Fig. 42-1**; **Table 42-1**). UVA, with a wavelength of 320 to 400 nm, is closest in wavelength to visible light.[7] UVA is considerably less likely than a comparable dose of UVB to cause a similar degree of erythema.[8,9] However, UVA penetrates into the dermal layer and may cause harmful effects not caused by UVB.[6] About 10 to 100 times more UVA reaches the earth's surface than UVB. Consequently, UVA may contribute up to 15% of the erythemal response at midday.[7,10] UVB is the most erythemogenic and melanogenic of the three UVR bands.[7,11] Up to 90% of UVB is blocked by the earth's stratospheric

ozone layer, and it is absorbed completely by the epidermal layer of the skin.[12],[13] In addition, UVB radiation can alter the immune system,[13] thereby increasing the incidence of certain cancers, including skin cancers. The only known beneficial effect of UVR in humans is exposure to small amounts of UVB, most commonly through sunlight, which converts 7-dehydrocholesterol to cholecalciferol (vitamin D_3). Vitamin D enhances calcium homeostasis and has direct and indirect effects on cells involved with bone remodeling. As a result, vitamin D can decrease the risk of rickets in childhood and fractures and osteomalacia in adults.[14]

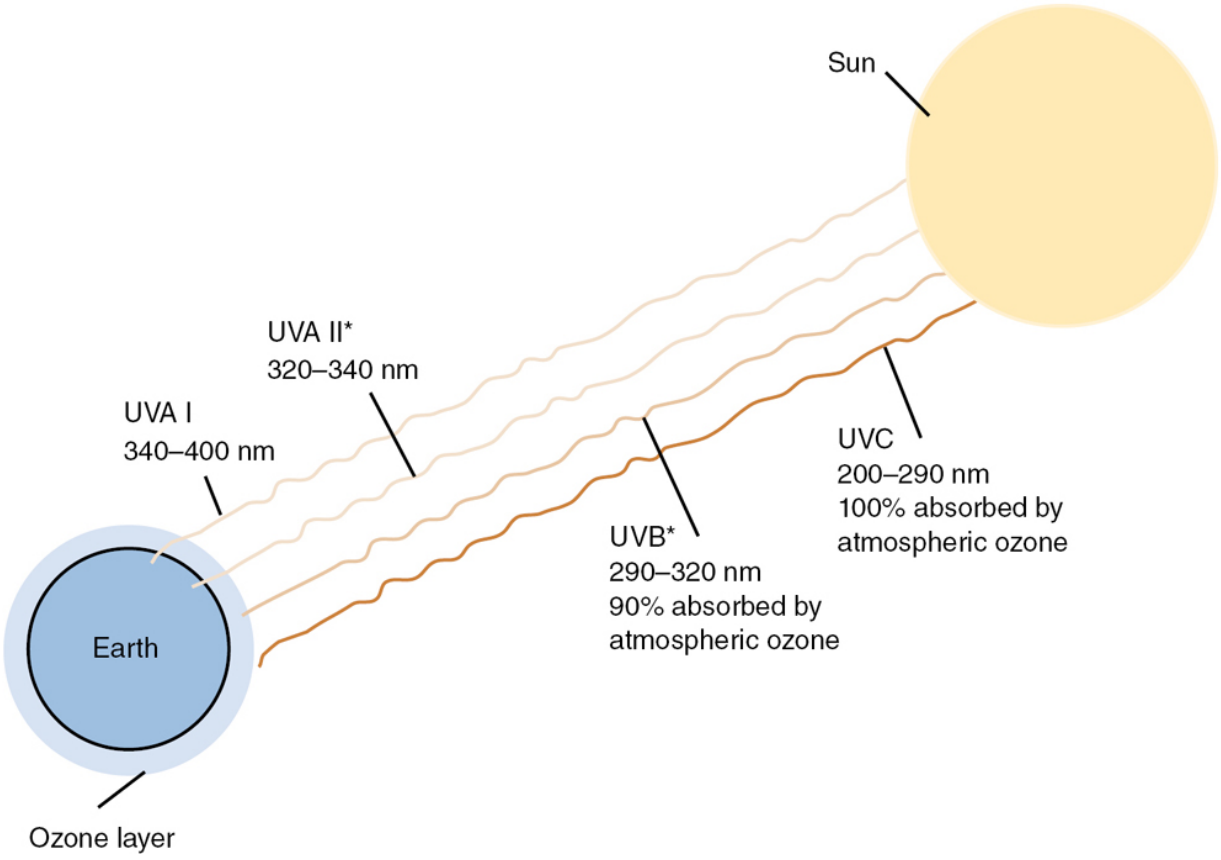


Figure 42-1 Ultraviolet radiation (UVR) spectrum. *Erythrogenic and melanogenic bands of UVR.

Table 42-1
Types of Ultraviolet Radiation and Characteristics

Radiation	Wavelength (nm)	Characteristics
UVA1 (long UVA; long-wave radiation)	340–400	Not absorbed by the ozone layer Passes through glass Produces some tanning, photoaging, and skin cancers Lower carcinogenic potential than UVA2, but harmful over long-term exposure Levels remain relatively constant throughout the day
UVA2 (short UVA)	320–340	Similar characteristics to UVA1, but greater carcinogenic potential with erythema production similar to UVB
UVB (sunburn range of radiation)	290–320	Partially absorbed by the ozone layer before reaching earth Does not pass through glass Causes erythema, sunburn, tanning, wrinkling, photoaging, skin cancers Daily and seasonal variation, with highest intensity at noon

UVA, ultraviolet A; UVB, ultraviolet B.

The UVC wavelengths are absorbed completely by the earth's stratospheric ozone layer. Artificial sources of UVC have been used in the sterilization and preservation of food and in minimizing bacterial growth in laboratories and hospital operating rooms by germicidal lamps, which can cause erythema or cataracts if mishandled.[7,11]

ENVIRONMENTAL EFFECTS ON ULTRAVIOLET RADIATION

Ozone and chlorofluorocarbons

The amount of UVR that reaches the earth's surface is influenced by many factors. Concern has been focused on the implications of depletion of the ozone layer caused by man-made pollutants, such as chlorofluorocarbons (CFCs), nitrous oxide, and other greenhouse gases (GHGs).[10,15] As GHGs contribute to ozone depletion, and because UVA is only slightly filtered by the ozone layer, any

decrease in the ozone layer would result in a disproportionate increase in UVB reaching the earth.

Time of day, cloud cover, and surface reflection

The time of day influences the amount of UVR reaching the earth's surface, with 75% of total daily UVR being received between 9 am and 3 pm. In general, whenever someone's shadow is shorter than his or her height, care should be taken; the shorter the shadow, the more likely a sunburn will occur. Cloud cover can decrease UV intensity and infrared radiation, but this can increase the risk of UVR overexposure, because less infrared radiation will be absorbed and turned into heat, resulting in less warning of overexposure to UVR. Reflection of UVR by substances (eg, sand, water, snow) is also important, with both sand and water reflecting significant amounts of harmful rays. Seasonal changes, geographic latitude, and altitude also influence the amount of UVR reaching the earth's surface.

Ultraviolet index

The UV Index/Global UV Index (http://www.epa.gov/sunwise/uvindex.html), developed by the Environmental Protection Agency (EPA), the National Weather Service, and the CDC, is a public health education service that is calculated on a next-day basis for every ZIP code across the United States and worldwide.[16] This index, with a scale ranging from 1 (low exposure) to 11+ (extremely high exposure), forecasts the probable intensity of skin-damaging UVR expected to reach the surface during the noon hour when the sun is highest in the sky. Theoretically, the UV Index can range from 0 (eg, during the night) to 15 or 16 (in the tropics at high elevations under clear skies). The higher the UV Index, the greater the dose received of skin- and eye-damaging UVR and the less time it takes before skin damage occurs.

The amount of UVR exposure needed to damage an individual's skin is affected by the elevation of the sun in the sky, the amount of ozone in the stratosphere, and the amount of clouds present. Clear skies transmit 100% of UVR to the earth's surface, with scattered

clouds transmitting 89%, broken clouds 73%, and overcast clouds 32%. The darker an individual's skin tone, the longer (or the more UVR) it takes to cause erythema.

Pathophysiology

ERYTHEMA, SUNBURN, AND TANNING

Erythema and oxygen free radicals

Excessive exposure of the epidermal and dermal layers of the skin to UVR can result in an inflammatory erythematous reaction. Excess UVA and UVB cause the release of vasodilatory mediators (eg, histamine, prostaglandins, cytokines), resulting in increased blood flow, erythema, tissue exudates, swelling, increased sensation of warmth, and a characteristic sunburn.[7],[11] Severe UVR exposure, primarily UVB, can cause blister formation, desquamation, fever, chills, weakness, and shock. UVA-induced changes in the dermis are characterized by greater damage to the vasculature and dense cellular infiltrates that penetrate to deeper levels of the skin.[11] The dermis also may be damaged when endogenous components of the skin absorb UVR energy and subsequently interact with oxygen to form tissue-damaging oxygen free radicals.[12]

Immediate pigment darkening and delayed tanning

Tanning is an adaptive mechanism of the skin to UVR. Tanning occurs by two different mechanisms: immediate pigment darkening (Meirowsky phenomenon) and delayed tanning. The primary cell involved in tanning is the melanocyte, which produces the radiation-absorbing protein melanin.[7],[10] Immediate pigment darkening begins during the actual exposure to UVA and certain bands of visible light,[7],[10] and the oxidation of existing melanin in the epidermis transiently turns the skin grayish brown. The degree of immediate pigment darkening depends on the duration and intensity of exposure, the extent of previous tanning (or amount of preexisting melanin), and the skin type of the individual.[6] Immediate pigment darkening is not protective against UVB erythema.[10]

PHOTOCARCINOGENESIS

Squamous cell and basal cell carcinoma

The association between skin cancer in humans and UVR exposure is based primarily on clinical and epidemiologic evidence. Nonmelanoma skin cancers, such as SCC and BCC, occur most commonly on areas that are maximally exposed to sunlight (eg, the face, neck, arms, back of the forearms, hands).[7] The prevalence of nonmelanoma skin cancers is inversely related to geographic distance from the equator and to the melanin content of the skin, with SCC more strongly linked than BCC to UVR.[7],[17] Persons of skin types most sensitive to sunlight, as well as persons working outdoors, have higher incidences of nonmelanoma skin cancers.[6] A family history of SCC and BCC increases the risk at least twofold, depending on the histology, number of lesions, and degree of invasiveness.[18]

Cutaneous malignant melanoma

The development of cutaneous malignant melanoma (CMM) may also be linked to UVR exposure, specifically exposures that induce sunburn. A history of five or more severe sunburns during adolescence may more than doubles the risk of CMM.[17] Similar to nonmelanoma skin cancers, CMM demonstrates an inverse relationship to geographic distance from the equator and melanin content of the skin.[7] Unlike nonmelanoma skin cancers, however, CMM does not demonstrate a clear relationship to the cumulative dose of UVR, and it occurs on areas of the body exposed to the sun intermittently (eg, on the back in males and the lower legs in females). In addition, it occurs most commonly in the middle-aged population and in individuals who work indoors, as well as in those whose sun exposure is limited to weekends and vacations.[17] A family history of melanoma is a strong risk factor, as 8% to 12% of melanoma patients display a familial propensity for the disease.[19]

PHOTOEFFECTS ON THE EYE

Exposure to UVR can cause many types of ocular adverse effects, including cataracts, conjunctival degeneration and proliferation, and SCC of the cornea and conjunctiva.[20] Age-related opacification of the ocular lens, or senescent cataracts, has been attributed to a lifetime of exposure to sunlight. The incidence of cataracts increases steadily after age 50 years, reaching nearly 30% in individuals older than 74 years.[21] UVB is absorbed by the cornea and lens, which slowly results in protein oxidation and precipitation within the lens. UVA penetrates the ocular lens and can cause cumulative damage to deeper structures of the eye. Decreased transmittance and increased scattering of light by the opacified lens eventually result in blurred vision, rings or halos around lights, changes in color perception, and blindness.[20] In advanced cases, the only treatment is surgical removal of the cataract.

High exposure of the eye to UVR can cause conjunctivitis or photokeratitis, a painful inflammation of the cornea. Photokeratitis usually begins 30 minutes to 24 hours after the exposure, and time to onset depends on the intensity of the exposure.[22] Because the corneal epithelium has a great regenerative capacity, photokeratitis tends to be transient, with regression in 24 to 48 hours. Treatment consists of cool, wet compresses, and mild anti-inflammatory analgesics, such as ibuprofen, aspirin, or naproxen sodium.

PHOTOTOXICITY AND PHOTOALLERGY

The most common type of drug-induced photosensitivity reaction is phototoxicity, which is an immediate or delayed inflammatory reaction. When the offending agent is deposited on the skin surface, it is thought to act as a chromophore, absorbing UVR. When the chromophore reaches a sufficient concentration in or on the skin, and when the skin is exposed to the appropriate wavelength of UVR, energy is emitted and transferred to the surrounding molecules, which damages the adjacent tissue to cause a phototoxic reaction. The wavelength of radiation necessary to produce such a reaction depends on the absorption spectrum of the offending agent.[23–25]

Photoallergy results from a similar mechanism to phototoxicity, except that the immune system is involved. Most commonly, it is caused by polycyclic photosensitizers that react with UVA to form antigenic macromolecules, evoking a delayed hypersensitivity response. In photoallergic photosensitivity reactions, the suspected medication or chemical agent is altered in the presence of UVR to become antigenic or to become a hapten (ie, an incomplete antigen), which can combine with a tissue antigen. These antigen–antibody or immune-mediated processes differentiate photoallergic from phototoxic reactions. Photoallergic reactions do not occur on first exposure to the medication, but as with other allergic reactions, they require prior or prolonged exposure (sensitization period) to the offending agent.[23,24] Once sensitization has occurred, subsequent exposure to even small amounts of the offending product will produce a photoallergic reaction.

Photoprotection

Photoprotection encompasses all methods of UVR blocking, including sunscreens, protective clothing, and sunglasses. Sunscreens are widely used to prevent sunburn and reduce the incidence of premature aging and carcinogenesis,[26–28] although clothing and avoiding direct sunlight offer greater protection. Sunburn preventive agents are those active ingredients that absorb >95% of UVB radiation and have the potential to prevent sunburn. Suntanning agents are those with active ingredients that absorb 85% to 95% of UVB radiation, thereby allowing suntanning without significant sunburn in the average individual. Chemical sunscreens include both aforementioned designations. Opaque sunblocks, or physical sunscreens, are those active ingredients that reflect or scatter all UVA, UVB, and visible light, thereby preventing or minimizing sunburn and suntanning.[29] The original formulations were developed to protect against the effects of UVB radiation before adverse effects of UVA were recognized. Because UVA plays a significant role in many of the adverse effects associated with UVR

exposure, broad-spectrum sunscreen products with absorption spectra in the UVA range have become commercially available, in combination with UVB absorbers. These broad-spectrum products provide additional benefit for patients with photosensitivity reactions caused by wavelengths not covered by single-ingredient sunscreens. **Table 42-2** lists the available sunscreen chemicals that have been judged to be both safe and effective.

Table 42-2
Sunscreens and UVR Absorption

Sunscreen	Absorption	UV Coverage
Anthranilates		
Meradimate (menthyl anthranilate)	260–380	Broad spectrum
Benzophenones		
Dioxybenzone	250–390	Broad spectrum
Oxybenzone (benzophenone-3)	270–350	Broad spectrum
Sulisobenzone (Eusolex 4360)	260–375	Broad spectrum
Cinnamates		
Cinoxate (diethanolamine *p*-methoxycinnamate)	280–310	UVB
Octocrylene	250–360	Broad spectrum
Octinoxate (octyl methoxycinnamate, Parsol® MCX)	290–320	UVB
Dibenzoylmethanes		
Avobenzone (butyl methoxydibenzoylmethane, Parsol® 1789 [DSM Nutritional Products, Lexington, MA])	320–400	UVA
Aminobenzoic Acid and Ester Derivatives		
Para-aminobenzoic acid (PABA)	260–313	UVB
Padimate O (octyl dimethyl PABA)	290–315	UVB
Salicylates		

Sunscreen	Absorption	UV Coverage
Homosalate	295–315	UVB
Octisalate (octyl salicylate)	280–320	UVB
Trolamine salicylate	260–320	UVB
Camphor Derivatives		
Ecamsule (terephthalylidene dicamphor sulfonic acid; Mexoryl)	290–400	Broad spectrum
Others		
Ensulizole (phenylbenzimidazole sulfonic acid)	290–340	Broad spectrum
Physical Sunscreens		
Titanium dioxide	290–700	Broad spectrum
Zinc oxide	290–700	Broad spectrum

UVA, ultraviolet A; UVB, ultraviolet B; UVR, ultraviolet radiation.

There is a clear association between UV exposure and the development of BCC and SCC,[30] and limiting UV exposure by starting sunscreen use during childhood is key to reduce the lifetime risk of nonmelanoma skin cancers.

Clinical Application of Photosensitivity

SKIN TYPES

CASE 42-1

QUESTION 1: R.J., a 26-year-old female, and her husband J.J., 28 years old, are spending a week in August vacationing on the Outer Banks of North Carolina with their two children, P.J., a 6-month-old girl, and L.J., an 18-month-old boy. They have plans for time at the beach, bicycling, and sailing. They come to your pharmacy to inquire about sunscreens for the trip. Mother R.J. has a light brown complexion with brown hair and brown eyes, and father J.J. has fair complexion with blonde hair and blue eyes. On first exposure to the sun with about an hour

of intense midday sunlight, J.J. almost always develops a deep red, painful sunburn, with only minimal subsequent tanning. He freckles easily when exposed to sunlight and remembers being severely sunburned on several occasions as a child. When R.J. is first exposed to the sun in the summer, she usually develops mild erythema, followed by moderate tanning. She cannot recall being severely sunburned as a child but does recall becoming moderately tanned each summer as a child and adolescent. R.J. is employed as a receptionist for an accounting firm, and J.J. is a lawyer for a local law firm. Both spend considerable amounts of time participating in outdoor activities.

Using subjective and objective data in this history, what are the skin types of R.J. and J.J. to guide you to a recommendation of a sunscreen product?

One of the most important pieces of information to include in the patient history is the patient's skin type.[31] Patients can be classified into six sun-reactive skin types based on their response to initial sun exposure, skin color, tendency to sunburn, ability to tan, and personal history of sunburn (**Table 42-3**). Father J.J.'s fair complexion, propensity to sunburn, and minimal tanning classify him as skin type II. Mother R.J.'s light brown complexion, minimal sunburn reaction, and moderate tanning classify her as skin type IV.

Table 42-3
Suggested SPF for Various Skin Types

Complexion	Skin Type	Skin Characteristics
Very fair	I	Always burns easily; never tans
Fair	II	Always burns easily; tans minimally
Light	III	Burns moderately; tans gradually
Medium	IV	Burns minimally; always tans well
Dark	V	Rarely burns; tans profusely
Very dark	VI	Never burns; deeply pigmented

SPF, sun protection factor.

Hair and eye colors also provide an indication to skin reactiveness to sunlight. People who have blonde, red, or light brown hair or blue or green eyes tend to have greater skin reactivity to sunlight than people with dark-colored hair or eyes. A history of severe sunburn

also can be associated with skin reactivity to sunlight, although self-reported patient histories of sunburn or tanning may not be consistently reliable and personal interviews may be a better indicator. Father J.J.'s propensity to freckle and his history of severe sunburns as a child may give an indication as to his skin's sun reactiveness. Other important information to consider in the patient before recommending a certain product is medication history, history of sun-reactive dermatoses, history of allergies (particularly contact hypersensitivities to cosmetics or other topical agents), and the intended activities during sunscreen use.

RISK FACTORS

CASE 42-1, QUESTION 2: R.J. and J.J. exhibit several risk factors that place them at risk for the long-term adverse effects of UVR. What are the risk factors for these long-term adverse effects of UVR?

The long-term effects of UVR include photocarcinogenesis and premature aging of the skin (photoaging). The associated risks for the development of these long-term effects are directly related to the congenital pigmentation of an individual (which includes skin type and hair and eye color) and intensity, duration, and frequency of exposure to UVR. With skin type II, father J.J. is at high risk for carcinogenesis and photoaging, whereas mother R.J., with skin type IV, may be at a lower risk. Excessive sun exposure, especially during early childhood, increases the risk of nonmelanoma and melanoma skin cancers. During the first 18 years of life, the average child receives three times the dose of UVB of the average adult; consequently, most sun exposure occurs during childhood.[32–34] A history of frequent sunburn or intermittent high-intensity exposures to UVR may be associated with the occurrence of malignant melanoma, whereas large cumulative doses of UVR during a lifetime may contribute to the incidence of nonmelanoma skin cancers. J.J.'s history of several severe sunburns as a child may more than double his risk of CMM.[34,35] Cumulative doses of UVR received

unintentionally from working outdoors or from participating in outdoor recreational activities also can contribute significantly to the risk of photocarcinogenesis and photoaging.[8] A large number of moles, congenital moles >1.5 cm wide, and abnormal moles also appear to be a risk factor for malignant melanoma.[17] Risk for skin cancer is increased among the first-degree relatives of patients with skin cancer[35] because frequent sunburns, suboptimal sunscreen use, and high rates of tanning bed use are common among children with a personal or family history of skin cancer.[36]

Photoprotection

Sun Protection Factor

Case 42-1, Question 3: Before deciding on the exact product for R.J., J.J., and their children, R.J. and J.J. want to know how to differentiate among products and how to interpret the sun protection factor (SPF) of a product. What type of sunscreen would be the best choice for them?

The effectiveness of a sunscreen formulation is based on its SPF and its substantivity.[37] SPF is a measure of how much solar energy (UVR) is required to produce sunburn on protected skin (ie, in the presence of sunscreen) relative to the amount of solar energy required to produce sunburn on unprotected skin. As the SPF value increases, sunburn protection increases. It is defined as the ratio of the minimal dose of UVR required to produce an erythemal response in sunscreen-protected skin compared with unprotected skin.[26] The SPF is based on tests of volunteers with skin types I to III, using either natural sunlight or a solar simulator that generates both UVB and UVA.[26],[37] Because the SPF can be influenced by the composition, chemical properties, emollient properties, and pH of the vehicle, sunscreen formulations must be evaluated on an individual basis.[37] The concept of an SPF is commonly misunderstood and is also influenced by a variety of factors, including the amount applied to the skin, the time of initial application before UVR exposure, the frequency of application, and environmental factors, such as

photodegradation during UVR exposure; therefore, the SPF achieved during actual use can be significantly less than indicated on the label.[38–42] Consumers have been shown to routinely apply only one-fourth to one-half thickness of the layer of sunscreen used to determine the SPF before marketing.[43–46]

A popular misconception is that SPF relates to time of solar exposure. For example, many people believe that if they normally get sunburn in 1 hour, then an SPF 15 sunscreen allows them to stay in the sun for 15 hours (ie, 15 times longer) without getting sunburn. This is untrue because SPF is not directly related to time of solar exposure, but to the amount of solar exposure. Although solar energy amount is related to solar exposure time, other factors have an impact on the amount of solar energy, including time of day, geographic location, and cloud cover.

In February 2019, the Food and Drug Administration (FDA) issued a proposed rule to update the regulatory requirements for sunscreen products and ensure safety and efficacy.[47] The update is necessary because sunscreen products are used much more extensively and frequently than when the FDA made initial safety determinations on sunscreens.[47] Additional information is needed relating to chronic use, including systemic absorption, as there is a growing body of evidence that sunscreen products may be more systemically absorbed than initially thought.[48],[49] This rule would put into effect final monograph regulations for over-the-counter (OTC) sunscreen products as required by the Sunscreen Innovation Act, which provided a new process for the FDA review of the efficacy and safety of nonprescription sunscreen active ingredients in 2014.[50] An OTC monograph establishes conditions under which certain OTC drugs may be marketed without approved new drug applications, because they are generally recognized as safe and effective (GRASE) and not misbranded. The FDA has noted that changed conditions because the final rule “Sunscreen Products for Over the Counter Human Use”[51] in 1999 reflects a need for additional data on products to confirm that the products are GRASE.

The proposal identifies that of the 16 currently marketed active ingredients, zinc oxide and titanium dioxide were identified as

GRASE, because sufficient evidence currently exists regarding safety and efficacy of these ingredients. Para-aminobenzoic acid (PABA) and trolamine salicylate were not GRASE owing to safety concerns, specifically risk of allergic and photoallergic skin reactions and cross-sensitization with structurally similar compounds with PABA and the potential for adverse effects from the anticoagulation effects of salicylic acid and salicylate toxicity associated with trolamine salicylate use. The remaining 12 ingredients were identified as having insufficient data for GRASE determination, with the FDA requesting additional data to make that determination. The proposal identifies the following dosage forms as GRASE: lotions, creams, gels, oils, butters, pastes, ointments, and sticks. Sunscreens combined with insect repellents are not identified as GRASE.

The proposal requires sunscreens with an SPF value of 15 or higher to also provide broad-spectrum protection that, for the broad-spectrum products, as SPF increases, the magnitude of protection against UVA radiation also increases. Additional aspects of the proposal include raising the maximum proposed SPF value on sunscreen labels from SPF 50+ to SPF 60+, requiring new labeling that assists customers in more easily identifying key information and clarifies the FDA's expectations for testing and record keeping by entities that conduct sunscreen testing. The FDA sought public comment on the proposed rule in early 2019, but the final rule has not yet been enacted. A more detailed history related to the OTC sunscreen drug review and the FDA's regulation of OTC sunscreen drug products can be found within the proposed rule document in the Federal Register.[47],[52],[53]

Evaluation of Sunscreens

Substantivity is a measure of the sunscreen formulation's effectiveness. The substantivity of a sunscreen formulation is its ability to be absorbed by, or adhere to, the skin while swimming or perspiring. The substantivity of a product largely depends on the vehicle, as well as the active ingredient.[54] The affinity of a sunscreen

to the keratinaceous layer of the stratum corneum is directly related to the keratin or vehicle partition coefficient. The saturation of the active agent in keratin depends on the drug's lipophilicity, whereas its substantivity is independent of its lipophilicity. Sunscreen compounds with a high solubility in the product's vehicle penetrate the skin most easily. Classically, vehicles such as water-in-oil emulsions or ointments tend to have a higher degree of substantivity. Some of the newer products have improved substantivity with the addition of a polymer, such as polyacrylamide, to the formulation. Table 42-2 shows the 17 ingredients that act as sunscreens currently approved in the United States, along with their absorption spectrum.

CHEMICAL ORGANIC SUNSCREENS

Chemical organic sunscreens are compounds capable of absorbing UVR, thereby protecting the skin structures from the adverse effects of the selective wavelengths absorbed.[26] After application to the skin, these aromatic compounds convert the high UVR energy into harmless longer wave radiation, which may or may not be perceived as warmth.[26] Chemical organic sunscreens are usually nonopaque because they do not absorb the wavelengths of visible light.

Ultraviolet B filters

Aminobenzoates

Commonly used in the past and the first widely used UV filter, PABA absorbs UVR in the UVB range from 260 to 313 nm, with maximal absorption around 290 nm; its molar absorptivity is considered to be high.[37] PABA readily penetrates and binds to the stratum corneum, and, after several days of application, it may remain in the skin and provide protection even after water exposure, making it an ideal candidate for water-resistant sunscreens.[37] Its major disadvantage is the potential to cause contact or photocontact dermatitis, which has been reported to happen in ~4% of the population.[55] Responsible for more sensitivity reactions than any other sunscreen,[40] PABA can also cause cross-sensitivity reactions with benzocaine, thiazides, sulfonamides, paraphenylenediamine (a common ingredient in hair

dyes), and other PABA derivatives. These sensitivity reactions are why PABA was not identified as GRASE in the 2019 FDA's proposed rule discussed previously. The use of PABA in commercial sunscreens has decreased to the point where many of the newer sunscreens are promoted as being PABA free.

The PABA esters include octyl dimethyl PABA (Padimate O) and glyceryl PABA. These esters are incorporated easily into formulations, demonstrate good substantivity, and do not discolor clothing. Their absorption spectra are similar to those of PABA (Table 42-2). With a maximal absorption of 311 nm, Padimate O has the lowest likelihood of any PABA ester to cause cross-sensitivity reactions or contact and photocontact dermatitis.[56]

Cinnamates

Octinoxate (octyl methoxycinnamate), which has high molar absorptivity and a maximal absorption of 305 nm, is the most commonly used cinnamate and most potent UVB filter.[57] Cinnamates are related chemically to balsam of Peru, balsam of Tolu, coca leaves, cinnamic acid, cinnamic aldehyde, and cinnamic oil, ingredients that are used in perfumes, topical medications, cosmetics, and flavorings.[58] These agents do not bind well to the stratum corneum, leading to poor substantivity. Cinnamate-based sunscreens tend to be comedogenic because the vehicle may contain other occlusive ingredients that are added to improve the substantivity. Cinnamates are often used in combination with benzophenones, appear to be nonstaining, and rarely cause contact dermatitis.[57]

Salicylates

Salicylates are weak UVB absorbers often found in PABA-free products. Topical salicylates are considered among the safest sunscreens, even though they must be used in high concentrations to meet the SPF requirement.[59] Salicylates have low molar absorptivities, are incorporated easily into formulations, and are used to boost the SPF of combination products, particularly oxybenzone

and avobenzone.[60] Octisalate and homosalate are water insoluble, which leads to high substantivity. Sensitization to the salicylates is rare[59]; however, it has been reported with the use of octisalate.[61]

Octocrylene

Octocrylene has an absorption profile similar to the salicylates and cinnamates, with a peak absorption at 307 nm. It has low irritation potential and low substantivity; however, it has become increasingly popular because of its ability to photostabilize avobenzone.[62]

Ultraviolet A filters

Benzophenones

Benzophenones, such as oxybenzone and dioxybenzone, are UVB-absorbing sunscreens that have absorption spectra extending into the UVA range.[63] Benzophenones are also found in shampoos, soaps, hair sprays and dyes, paints, varnishes, and lacquers. The maximal absorption for each is about 290 nm, but both are limited because of poor substantivity and sensitization.[63] Photocontact dermatitis with oxybenzone and contact dermatitis with dioxybenzone occur commonly, with the latter usually occurring as a contact urticaria.[64] Systemic absorption has also been noted with oxybenzone, and it can be detected in the urine and bloodstream.[65]

Anthranilates

Anthranilates, such as Meradimate (L'oreal Usa Products, Inc., New York, NY, menthyl anthranilate), are weak UVB-absorbing sunscreens with an absorption spectrum extending into the UVA range. As with the salicylates, they have low molar absorptivity, with a maximal absorption of ~336 nm.[37] Meradimate has a low risk of sensitization and a desirable absorption spectrum, especially when it is used in combination with other sunscreens to give broad-spectrum protection.

Dibenzoylmethanes

As a prototype of the dibenzoylmethane class, avobenzone (butyl methoxydibenzoylmethane) has high molar absorptivity and absorption spectra exclusively in the UVA range, with maximal absorption of ~360 nm.[66] It is commonly formulated with UVB sunscreens to broaden UVR coverage. Avobenzone loses ~35% of its absorption capacity about 15 minutes after UVR exposure, because of the photoinstability of the compound, thereby reducing its UVA protection efficacy.[67] One molecule of avobenzone can absorb UVA radiation only once, making it inactive from that time forward as opposed to zinc oxide or titanium dioxide, which can reflect UVA radiation over and over again with minimal decay. All of the avobenzone applied to the skin is virtually rendered inactive after 5 hours of UVA exposure. Avobenzone is also not compatible with octinoxate, the most powerful UVB filter.[68] Photostability of avobenzone can be increased with the use of UV absorbers, as well as non-UV filters. Neutrogena has marketed this technology under the name of Helioplex, which initially stabilized avobenzone using oxybenzone and diethylhexyl 2,6-naphthalate (DEHN) but has now broadened to include additional technologies and ingredients.

Ecamsule

Ecamsule is a camphor derivative that protects against short UVA rays and is photostable and water resistant and has low systemic absorption.[69] The FDA has only approved ecamsule for use in certain formulations, with the FDA determining that more research was needed to evaluate the safety and efficacy of the ingredient in other concentrations.[50] Ecamsule provides protection within the short UVA range (320–340 nm), filling the gap between octocrylene and avobenzone capabilities (210–290 and 340–400 nm, respectively). Adverse events associated with its use are infrequent and include acne, dermatitis, xerosis, eczema, erythema, pruritus, skin discomfort, and sunburn.

INORGANIC SUNSCREENS

Inorganic sunscreens are opaque formulations made of particulate insoluble compounds, incorporated into a vehicle, which have been thought to scatter and absorb UV rays. However, recent evidence indicates that they protect primarily through absorption.[70] Both the size of the particles and thickness of the film determine the degree of protection.[71] Currently, there are only two inorganic sunscreens approved by the FDA: titanium dioxide and zinc oxide.[71],[72] Other inorganic sunscreens include magnesium oxide, red veterinarian petrolatum, iron oxides, kaolin, ichthammol, and talc. Iron oxides and talc continue to be found in commercially available sunscreen products and cosmetics, whereas kaolin and ichthammol may be found in products such as cleansers, moisturizers, and ointments. These compounds are often used in conjunction with chemical sunscreens to formulate products of higher SPF and as single-ingredient products. When used alone, they are usually placed in an ointment base designed specifically for vulnerable parts of the body, such as the nose, cheeks, lips, ears, and shoulders.[29] Inorganic sunscreens are important in individuals who are unusually sensitive to UVA and visible light, such as those with vitiligo, a skin condition with amelanotic lesions (white patches) surrounded by areas of normally pigmented skin. Appropriately colored formulations can be used to camouflage and protect these vulnerable amelanotic lesions.[29] Inorganic sunscreen agents are preferred for persons who need absolute UVR and visible light protection (eg, young children, persons with skin types I–IV who receive constant exposure, and persons with drug photosensitivity reactions, xeroderma pigmentosa, lupus erythematosus, and other photosensitive skin reactions).[29]

Despite some advantages, inorganic sunscreens are not widely accepted because they are visible to others, messy, and occlusive when applied to the skin. They have a higher substantivity, but may melt in the heat of the sun, limiting their protection to a few hours. Physical sunscreen products tend to be so occlusive that they may cause or worsen acne or obstruct sweat glands.[29] Substantial effort has been made to improve the shortcomings of these products by reducing the particle size to improve the cosmetic appearance. This has created a growing trend toward incorporating nanoparticles of

titanium dioxide and zinc oxide, which have been shown to have superior UV protection while maintaining cosmetic elegance. Concern about toxicity of these agents has been raised because of the potential for increased skin penetration and interaction with lower portions of the epidermis; however, this has been disproved in both in vivo and in vitro studies.[73-77] No current regulation in the United States exists regarding the testing and labeling of nanosized titanium or zinc oxides.

Antioxidants

The addition of botanical antioxidants and vitamins C and E to a broad-spectrum sunscreen may further decrease UV-induced damage compared with sunscreen alone because of neutralization of free radicals.[72,78] Antioxidants have received increased attention for use as photoprotective agents, particularly because of the observation that vitamin C levels in the skin can be severely depleted after UVR exposure.[79] Vitamins C and E, either taken orally (po) or applied topically (incorporated into a commercially available sunscreen product), may provide additive protection against both UVA- and UVB-induced photodamage.[79,80] Topically applied antioxidants do not have adequate diffusion into the epidermal layer, however, and are susceptible to chemical instability.[60] If recommended, they should only be used in conjunction with adequate sunscreen. Commercially available products can be found with combinations of antioxidants and broad-spectrum sunscreens, specifically those formulated for facial use.

Given their plans for the week of vacation and amount of UV exposure likely, R.J. and J.J. should consider a broad-spectrum product with high substantivity and a high degree of water resistance to offer the best protection. The next section further discusses appropriate choices relating to SPF.

CROSS-SENSITIVITY

Case 42-1, Question 4: According to your assessment of mother R.J. and father J.J., you determine that they have type IV skin and type II skin, respectively. On further inquiry, you learn that R.J. has no medication allergies; however, she has a history of contact dermatitis on her scalp and around her hairline on several occasions after dyeing her hair and using certain shampoos. As a teenager, J.J. suffered from frequent sinus infections and often was treated with trimethoprim–sulfamethoxazole (TMP-SMX) because of an allergy to penicillin. He remembers developing a severe sunburn after minimal exposure to the sun while taking the sulfa-containing antibiotic. He recently has been started on hydrochlorothiazide (HCTZ) 12.5 mg po daily, for hypertension. What considerations are important in recommending sunscreens for R.J. and J.J.?

The first consideration for recommending an appropriate sunscreen to R.J. and J.J. is their skin type. R.J. has skin type IV, suggesting that a sunscreen with an SPF of at least 15 would provide adequate protection for her (Table 42-3). J.J. has skin type II, suggesting that a sunscreen with an SPF of 30 to 50 would be required to provide adequate protection for him. Furthermore, the history of contact dermatitis and photosensitivity reaction exhibited by R.J. and J.J., respectively, is important when recommending use of a sunscreen.[81] The contact dermatitis that R.J. experienced from hair dyes and shampoos may have been caused by paraphenylenediamine, an ingredient of hair dyes,[82] or a benzophenone, which sometimes is included in products such as hair dyes and shampoos.[63]

Because cross-reactivity between paraphenylenediamine and PABA or its derivatives is possible, a sunscreen for R.J. that does not contain PABA or a benzophenone should be recommended. Cinnamates and anthranilates rarely cause contact dermatoses, which would be ideal for R.J.

Because both contain sulfa moieties, the photosensitivity reaction that J.J. experienced while taking TMP-SMX may indicate that he might be susceptible to a cross-sensitivity reaction with PABA or its derivatives. This reaction to TMP-SMX also indicates that J.J. may be susceptible to a photosensitivity reaction with HCTZ. If a photosensitivity reaction is likely, it is advisable to recommend an SPF of 30 or more. Because drug-induced photosensitivity reactions

are caused by UVA, a PABA-free, broad-spectrum sunscreen that absorbs UVA as well as UVB would be necessary to provide J.J. with adequate protection. Broad-spectrum chemical sunscreens commonly contain a benzophenone and a cinnamate. A broad-spectrum sunscreen containing both of these chemical classes would be an acceptable broad-spectrum product. Alternatively, because Padimate O is the least likely of the PABA ester derivatives to cause photocontact dermatitis,[56] a broad-spectrum combination product that contains Padimate O could be recommended for J.J. If the photosensitivity reaction is caused by visible light, it would also be necessary to recommend an inorganic physical sunscreen to block all sunlight or complete avoidance of the sun.[41] With all of these issues considered, it may be preferable to recommend an alternative antihypertensive medication for J.J. that would not place him at risk for a photosensitivity reaction.

PHOTOPROTECTION FOR CHILDREN

Case 42-1, Question 5: What photoprotective measures should be provided for 6-month-old daughter P.J. and 18-month-old son L.J.?

Sun protection during childhood is very important, considering that most of a person's lifetime of sun exposure occurs in childhood and that the harmful effects of UVR are cumulative.[83] However, infants and toddlers are at increased risk of overexposure to topical sunscreen products because of an increased body surface area (BSA) to body weight ratio compared to adults and a lower ability to metabolize absorbed drug.[84],[85] It is, therefore, recommended that sunscreen should not be used for children younger than 6 months of age.[86] Daughter P.J. needs to be kept out of direct sunlight and, when outside, must be protected with proper clothing and shading.[86–90]

L.J. should be protected with a PABA-free, inorganic UV filter sunscreen, such as zinc oxide with an SPF of at least 15. Inorganic UV filters are preferred for children between the age of 6 months and

2 years because of the lack of systemic absorption.[84,85] Regular use of a sunscreen with an SPF of at least 15 for the first 18 years of life can reduce the lifetime incidence of nonmelanoma skin cancers by about three-fourths.[90] If son L.J. is in the sun during 6 hours of maximal exposure (ie, 10 am–4 pm), or otherwise for an extended period, he should wear protective clothing, covering as much of his body as possible.[89] Tightly woven clothing, long sleeves, and pants protect the skin from almost all UVR, whereas loosely woven clothing or wet T-shirts can allow up to 30% of UVR to pass through to the skin. Although not complete, water is thought to reduce UVR scattering, thus decreasing its transmission. An average-weight cotton T-shirt provides only an SPF of 7 or 8.[89]

The transmission of UVR through a fabric is measured using a spectrophotometer or spectroradiometer. The ultraviolet protection factor (UPF), rather than SPF, has been recommended as a measure of the sun-protective properties of fabrics.[91,92] It is calculated using a formula based on UV transmission through the fabric and the erythema responsible for human skin. For example, if a fabric has a UPF of 20, then only one-twentieth of the UVR at the surface of the fabric actually passes through it. Certain synthetic fabrics have UPF values that exceed 500, making them vastly superior to sunscreens.[89] **Table 42-4** compares the UPF with the amount of effective UVR transmitted and absorbed.

Table 42-4

Volume of Sunscreen Needed for Adequate Protection

Body Part	Recommended Minimum Amount of Sunscreen
Head	½ teaspoon
Neck	
Arms	
Anterior torso	1 teaspoon
Posterior torso	
Legs (each)	

No woven fabric provides complete coverage because the holes between the threads permit UVR transmission. A baseball cap shields little more than the upper central forehead. Broad-brimmed hats can protect the ears, neck, nose, and cheeks, but may provide inadequate protection against SCC of the head or neck.[93] The use of an UV-absorbing ingredient for fabric softeners (eg, bisoctrizole, Tinosorb M, BASF) is promoted to reduce transmission of excessive UVA and UVB radiation through fabrics to the skin, through absorption of UVR without impairing whiteness. This chemical absorption process has a high affinity for cotton fibers at various washing temperatures. Available as a laundry additive (eg, Sun Guard, Phoenix Brands), it works by binding to laundered fibers, and through accumulation, it increases the UV protection up to UPF 30 through up to 20 wash-and-rinse cycles.[94],[95]

Product selection

Inorganic physical sunscreens, such as zinc oxide or titanium dioxide, are generally recommended in children. However, if these options are not preferable or available, a broad-spectrum lotion of SPF 15 or higher can be utilized. A lotion is preferred for total body application versus an alcoholic lotion or gel because alcoholic preparations can cause stinging, burning, and irritation of the skin and eyes. Physical sunscreens are available in bright colors and are recommended for selected body areas, such as the nose, cheeks, and shoulders. PABA and its derivatives are considered potentially harmful to a child's tender skin. For adolescents with acne vulgaris, the use of an oil-free, noncomedogenic sunscreen formulation and a lip balm that contains a sunscreen of at least SPF 15 (eg, Blistex or ChapStick Sunblock [SPF 30]) would be appropriate.

Application

Case 42-1, Question 6: What instructions should you provide mother R.J. and father J.J. on how to apply the sunscreen that you have chosen for each of their family members?

Because R.J. and J.J. are planning to be active on the beach, sunscreens that are water resistant are recommended. Before complete application of the sunscreen to the body, because of the risk of cross-sensitivity reactions, patients can perform a patch test by applying a small quantity of the sunscreen to the inner aspect of the forearm and covering with a small bandage overnight.

Education on the appropriate volume of sunscreen to apply is vital. Most persons apply 20% to 60% of the required amount of sunscreen needed to achieve the SPF of their product.[39,42-45] Because of this, a method has been developed to determine an approximate volume of sunscreen product needed for adequate protection.[96] This rule states that you should use more than half a teaspoon on each of your head and neck area and arms and more than a teaspoonful on each of your anterior and posterior torso and your legs. This application size was determined based on the dose used in FDA sunscreen testing (**Table 42-5**).

Table 42-5
Relative Ultraviolet Protection Factor (UPF) of Fabrics by Ultraviolet Ray (UVR) Transmission and Absorption

UVR Absorbed (%)	UPF	Protection Category
90.0	10	Moderate protection
95.0	20	High protection
96.7	30	Very high protection
97.5	40	Extremely high protection
>98.0	50	Maximal protection

Studies of sunscreen application techniques have demonstrated inadequate application at all body sites.[43-45,97] The worst protected areas were the ears and top of the feet, and the back was poorly protected if sunscreen was self-applied. Patients should be reminded to apply sunscreen on those often-forgotten areas, such as the hands, cheeks, neck, ears, and dorsum of the feet. It is best to follow package directions, reapplying the sunscreen every 1 to 2 hours or

after sweating, swimming, or toweling off. There is evidence that early reapplication within 20 to 30 minutes be able to partly compensate for initial underapplication.[38,98-100]

Case 42-1, Question 7: Would father J.J. gain additional benefit from a product with an SPF >50?

Sunscreen formulations with SPF as high as 50 can be made using combinations of chemical and physical sunscreen agents.[7] Individuals who are extremely sensitive to the sun may benefit from formulations with higher SPF, but the average fair-skinned person gains adequate protection for sunbathing or for average daily exposure from a product with an SPF of 30.[39]

Protection from sunburn increases with higher SPF; however, it is important to remind J.J. that this protection does not correlate to the extent of skin damage from UVA rays. Studies have shown some benefit to higher SPF ratings.[101,102] However, in the FDA amendment that went into effect in 2012, SPF ratings were limited to a maximum of 50+ because of the lack of evidence for greater efficacy at higher SPF ratings.[103] Increasing this to a maximum of 60+ is included in the 2019 FDA's proposed rule, with increased evidence of additional benefit from higher SPF ratings.[47] J.J. should also be reminded that the SPF is only accurate if he correctly applies the sunscreen in the adequate amount.

PROTECTIVE EYEWEAR

Case 42-1, Question 8: What appropriate protective eyewear would you recommend for R.J. and J.J.'s family while they are on vacation?

R.J. and J.J. should wear sunglasses when outdoors to decrease their lifelong exposure to solar radiation and while at the beach to prevent high exposure of UVR and possible photokeratitis or conjunctivitis. Many manufacturers of sunglasses label their products according to three categories: cosmetic, general purpose, and

special purpose. Cosmetic sunglasses block at least 70% of UVB, at least 20% of UVA, and <60% of visible light and are appropriate for casual wear when high exposure to UVR is unlikely. General-purpose sunglasses block at least 95% of UVB, at least 60% of UVA, and 60% to 92% of visible light and are appropriate for most activities in sunny environments.[104] Special-purpose sunglasses block at least 99% of UVB, at least 60% of UVA, and at least 97% of visible light and are appropriate for very bright environments, such as ski slopes or tropical beaches.[104] Special- or general-purpose sunglasses are appropriate recommendations for R.J., J.J., and their children to wear while on vacation.

Tanning booths

CASE 42-2

Question 1: B.P., a 32-year-old female, is preparing for a business trip to Cancun. She is seeking advice about the use of a tanning bed to stimulate melanin for the prevention of sunburn while on her trip. B.P. has skin type III and light brown hair and green eyes. She recently heard, however, that a tan produced by artificial sunlight may not protect against sunburn and may even cause skin cancer.

What advice will you offer her?

Most tanning beds, booths, or salons use an artificial light source that emits about 95% UVA with minimal (ie, 1%–5%) UVB.[105],[106] It was originally thought that UVA is much less likely to produce photoaging and photocarcinogenic changes of the skin than UVB; however, UVA has now been found to cause many of the same effects on the skin as UVB, including immunologic, degenerative, and neoplastic changes, as well as damage to DNA and the formation of reactive oxygen species (ROS).[107] UVA also contributes to cataract formation and the activation of herpetic lesions.[21] The high doses of UVA received during a tanning session, as well as increasing cumulative UVA doses over time, raise great concern about the long-term effects of UVA.[108] In addition, UVA may augment

the photocarcinogenic effect of UVB,[67] and extensive evidence indicates a relationship between indoor tanning and melanoma.[109] Reduction of indoor tanning has been a national public health focus, including being a Healthy People 2020 goal, as part of the U.S. Department of Health and Human Services Office of Disease Prevention and Health Promotion program.[110],[111] In an attempt to combat the epidemic of use in young people, the FDA reclassified UV lamps to be class II medical devices in 2014 and include a box warning, indicating that they should not be used by minors ages 18 years or younger.[112] Although this act placed more regulation on tanning booths, concern has been raised that regulating tanning equipment as medical devices implies that they offer a therapeutic benefit and is not commensurate with other products that are known carcinogens with very little to no offered benefit.[113]

With a skin type III, B.P. may be able gradually to achieve a moderate tan with minimal burning, thus providing some protection from UVR because of increased melanization of the skin. This UVA-induced tan, however, may not be as protective as a tan achieved under normal sunlight conditions because UVA does not thicken the stratum corneum.[114] An artificially produced tan plus subsequent sun exposure has not been found to provide any net reduction in long-term damage to the skin when compared with the same amount of tan obtained by sunbathing alone.[114] For these reasons, B.P. should not use the tanning booth to obtain a protective tan, and she should use appropriate photoprotective measures during her trip.

Case 42-2, Question 2: What precautions would you recommend if she decides to visit a tanning salon?

If B.P. decides to artificially tan despite your recommendation, she should undertake some precautions. The FDA has recommended exposure schedules for first-time users based on skin type, which determines a person's minimal erythemal dose (MED) of UVR. The MED is determined by the amount of UV exposure necessary to produce any visible reddening of the skin 24 hours after exposure.

This policy suggests that exposure be limited to no >0.75 MED three times the first week, followed by a gradual increase to maintenance doses of a maximum of 4.0 MED delivered weekly or biweekly.[115] It is important to remember that MED is specific to an individual and, therefore, will be different depending on his or her skin type. Correlating the FDA's policy into time limits for an individual is, therefore, dependent on skin type as well as the amount of UV exposure provided by the tanning apparatus the individual will use. To minimize cataract development, B.P. should always wear protective eyewear that absorbs all UVA, UVB, and visible light up to 500 nm; simply closing her eyes or wearing regular sunglasses provides no protective effect against eye damage.

SUNLESS TANNING PRODUCTS

Case 42-2, Question 3: B.P. decides to accept your recommendations to avoid tanning beds; however, she would still like to have a tan before going to Cancun. Will the use of sunless tanning agents confer any photoprotection for B.P. against sunburn?

Sunless tanner is a commercial term that denotes a product that provides a tanned appearance without exposure to the sun or other sources of UVR. One commonly used ingredient in these products is dihydroxyacetone (DHA), a color additive that darkens the skin to orange brown by reacting with amino acids in the stratum corneum. The term *bronzer* is used to describe a variety of products intended to achieve a temporary tanned appearance. For example, among the products marketed as bronzers are tinted moisturizers and brush-on powders. These produce a temporary effect, similar to other types of makeup, and wash off over time. Some products are marketed with other ingredients in addition to DHA to provide a tanned appearance. Generally, neither sunless tanners nor bronzers provide any protective activity to UV exposure by themselves, unless specifically listed with an SPF rating.[116]

Treatment of sunburn

CASE 42-3

QUESTION 1: G.B., a 31-year-old male with skin type IV, returned a few hours ago from an afternoon of activity in the sun. His shoulders, back, neck, and arms are bright red and are beginning to feel hot, stretched, and painful. G.B. has been otherwise healthy, has no significant medical history, and has no known allergies to medications.

What treatment recommendations would you give G.B. for his sunburn?

Sunburn is a self-limiting condition, and treatment is usually symptomatic.[117] Suggested treatments that G.B. can try for his first-degree burn are oral (eg, naproxen or ibuprofen) or topical (eg, camphor, menthol) analgesics, topical anti-inflammatory agents (eg, hydrocortisone cream or aloe vera gel), cooling compresses (tap water, saline, or aluminum acetate solution [Burow solution]) applied to the skin, or cool protectant baths (eg, colloidal oatmeal). Nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen or ibuprofen, may be preferred over acetaminophen because of blockade of the inflammatory prostaglandin-mediated sunburn process; however, although offering symptomatic relief, corticosteroids, NSAIDs, antioxidants, antihistamines, or emollients offer only mild improvement at decreasing the time to recovery.[117]

Topical anesthetics, such as benzocaine or lidocaine, provide only transient analgesia for up to 15 to 45 minutes. These topical agents should not be used in large quantities or applied more than three or four times a day. In addition, they should not be used on raw, blistered, or abraded skin. Benzocaine has minimal systemic toxicities but is commonly associated with contact sensitization.[118] In contrast, lidocaine is associated with a low incidence of contact sensitization.[119] Topical corticosteroids have been shown to provide minimal clinical benefit when applied after UV exposure.[120] If G.B. wants to try a topical agent, application or administration is recommended when the pain is particularly bothersome, such as at bedtime. Oral antihistamines may help control pruritus associated with sunburn, as well as aid with sleep, if taken at bedtime; however,

no definitive studies have shown benefit in reducing symptoms or benefit of one agent over another.

Treatment beyond self-management is generally unnecessary unless the sunburn is extensive with constitutional symptoms (ie, fever, chills, nausea, vomiting), involves second- or third-degree burns (particularly if on the eyes or genitalia), or becomes infected. In such cases, referral of the patient to his or her health care provider is indicated as a short course (ie, up to 3 days), or an oral corticosteroid may need to be given (eg, 1 mg/kg of prednisone or equivalent, given once daily).

Clinical Application of Phototoxicity or Photoallergy

Phototoxic photosensitivity reactions are dose dependent and occur in almost any person who takes or applies an adequate amount of the offending agent. The dose necessary to produce such a reaction varies from person to person and depends on factors such as complexion, hair and eye color, usual ability to tan, and the type and amount of UVR exposure. Phototoxic photosensitivity reactions are not immunologically mediated or true allergic reactions; they can occur on first exposure to the agent and generally show no cross-sensitivity to chemically related agents.

A phototoxic reaction usually has a rapid onset, often within several hours after UVR exposure, and presents as an exaggerated or intensified sunburn with erythema, pain, and prickling or burning. Blistering, desquamation, and hyperpigmentation can occur in severe cases.[23],[24] Symptoms generally peak 24 to 48 hours after the initial exposure and are usually limited to the areas of UVR-exposed skin. Because phototoxicity reactions do not involve the immune system, prior exposure to the photosensitizer is unnecessary for this reaction to occur. Common drug classes known to be phototoxic include fluoroquinolone, tetracycline, and sulfonamide antibiotics, diuretics, sulfonylureas, and nonsteroidal anti-inflammatory agents.

Clinically, photoallergy differs from phototoxicity in that it produces an intensely pruritic, eczematous form of dermatitis.[24] The rash is preceded by pruritus and may subside within an hour. In 5% to 10% of cases, persistent hypersensitivity to light occurs, even after the offending chemical has been eliminated.[23] Photoallergic reactions are not dose related, and eruptions can also be caused by chemically related agents via cross-sensitivity or cross-allergenicity. As a type of delayed hypersensitivity reaction, time is required to develop an immune response, and the onset of a photoallergic reaction is often delayed for 1 to 3 days. These reactions can present as macular, bullous, or purpuric lesions. Acute urticaria can occur within minutes after UVR exposure. Recovery is slower than from a phototoxic reaction, and it can persist after the offending product has been removed. These reactions may present with erythema and possible edema secondary to the inflammation, but are most commonly found to be eczematous, characterized by erythema; pruritus (possible severe); and papules or vesicles or both, with weeping, oozing, and crusting. Scaling, lichenification, and pigmentation may occur later.

CASE 42-4

QUESTION 1: D.L., a 16-year-old, blond-haired, blue-eyed teenager with skin type II, presents with a severe sunburn. He states that he started a new summer job 2 days ago with typical sun exposure. He is surprised at the severity of this sunburn, which is worse than normal for the same amount of sun exposure.

What further information do you need to know before making treatment recommendations?

Because D.L. is reporting symptoms that differ from previous sun exposures, further questions should be asked regarding the history of the current scenario. Information that may be important from the history of the condition includes the temporal relationship between sun exposure and onset of symptoms; the nature and duration of symptoms; recent ingestion or topical application of medications; possible exposure to photosensitizers, chemical irritants, or plants

that can cause allergic contact dermatitis (eg, poison ivy); and the potential for arthropod bites. Information that may be important from the physical examination includes the distribution and morphology of the reaction, as well as areas of the body spared of the reaction.

A drug-induced photosensitivity reaction most commonly appears as a sunburn of greater severity than would normally be expected or as a rash in areas exposed to the sun or tanning apparatus. These reactions can be secondary to oral medications; however, it is important to remember that chemicals with photosensitization potential are found in cosmetics, shampoos, moisturizing lotions, hair dyes or tints, soaps, and other topically applied medications and agents.

Drug-induced photosensitivity reactions can be subdivided into phototoxic and photoallergic reactions. The same medication or agent may produce both phototoxic and photoallergic reactions, and it may at times be difficult to differentiate clinically between the two types of reactions.

CASE 42-4, QUESTION 2: On further questioning, you discover that D.L. first experienced painful erythema of the extensor surface of his hands and forearms, the anterior aspect of his neck, and parts of his face within hours of starting his new job at an outdoor garden and greenhouse. Besides painful erythema, the symptoms also included an immediate prickling and burning sensation. The symptoms continued to worsen until the following morning, about 24 hours after initial exposure to the sun. D.L. does not recall po ingesting or topically applying any medication or other preparation to his skin, nor does he recall exposure to any chemical irritants, or poison ivy or oak. The morphology of the skin lesions is that of an exaggerated sunburn. The skin lesions are patchy in distribution, with greater density on his forearms and hands than on his neck and face. The posterior aspect of his neck and covered areas of his body was spared completely. What are some possible causes of his exaggerated sunburn reaction?

The most likely explanation for D.L.'s exaggerated sunburn reaction is *phototoxicity,* secondary to contact with psoralen-like chemicals from the plants at his job at the outdoor garden and greenhouse. Photoallergy is another possible cause of D.L.'s symptoms. Although much less common than phototoxicity,

photoallergy requires prior or prolonged exposure to the photosensitizing compound.

Presumably, D.L. came into contact with psoralen-containing plants and simultaneous exposure to sunlight. With an unusual distribution of lesions on his hands, forearms, neck, and face and the lack of lesions on areas not contacted by the plants or sunlight, the temporal relationship between the exposure and onset of symptoms places phototoxicity higher in the differential diagnosis. D.L. is unlikely to have a photoallergic reaction because of the lack of a delayed temporal relationship between the onset of symptoms and combined exposure to a psoralen-containing plant and sunlight. Unlike phototoxicity reactions, photoallergic reactions can spread to areas that have not been exposed to sunlight; however, D.L.'s lesions were limited to areas of skin exposed to sunlight.

CASE 42-4, QUESTION 3: What nonprescription remedies might you recommend for D.L. at this time?

General recommendations for the management of phototoxicity and photoallergy reactions are focused on the removal of exposure to the potential photosensitizer and reduced exposure to the sun. Patients should be counseled not to take any medications, po or topically, without first consulting with their health care provider to minimize exposure to other photosensitizers. D.L. should try wearing long-sleeved shirts, pants, and gloves when working to limit exposure to plant photosensitizers. He may also try applying a broad-spectrum sunscreen to protect his skin from UVB and UVA radiation. If these measures do not prevent further photosensitivity reactions, D.L. should consider a different type of employment. His presenting symptoms should be managed in a manner similar to that for an exaggerated sunburn.

PHOTOAGING

Incidence, Prevalence, and Epidemiology

Photoaging, or premature aging of the skin, involves skin changes that differ from those associated with normal chronologic aging.[121],[122] Aside from advancing age, risk factors that have been associated with photoaging include fair skin, male gender, high sun exposure, and smoking.[123],[124] Because recognizing photoaging and photodamage may prevent the progression or development of skin cancer, it is important that they are recognized as real medical problems, not just cosmetic or aesthetic concerns.

Etiology

Normal aging of the skin involves fine wrinkling of the skin, atrophy of the dermis, and a decrease in the amount of subcutaneous adipose tissue, all of which lead to a state of hypocellularity of the skin.[122] Photoaging involves a chronic inflammatory state induced by long-term exposure to UVA radiation from ROS, leading to a hypermetabolic state of the skin.[125] Photodamaged skin is characterized histologically by an accumulation of excessive quantities of thickened, degenerated elastic connective tissue fibers (elastosis).[122]

Photodamaged skin is characterized as being wrinkled, yellowed, and sagging. Mildly affected skin becomes irregularly pigmented, rough, and dry, with mild wrinkles. Moderately affected skin becomes deeply wrinkled, sagging, thickened, and leathery, with vascular lesions.[122] Largely irreversible, severely affected skin can become deeply furrowed and permanently (and irregularly) pigmented and may manifest premalignant and malignant lesions.[122] Areas of the body most commonly affected are the face, back of the neck, back of the arms and hands, the V-line of the neck of females, and balding areas of the head of males.

Clinical Application of Photoaging

CASE 42-5

QUESTION 1: P.B. is a 38-year-old female who has enjoyed many outdoor activities over the years. She lives in a moderate climate, with hot, sunny summers and cold winters. She feels that she appears older than other females of her age because of wrinkling and color changes of her skin. Her facial color is somewhat yellowish in appearance, and the fine wrinkles at the corners of her eyes and mouth have become more obvious. She has noticed the formation of small brown spots mottling parts of her face, hands, and forearms. P.B. has skin type III, a clear complexion, and skin that is sensitive to soaps, heavy cosmetics, and perfumes.

What nonprescription recommendations can you provide P.B. for treatment of her photoaged skin?

Many nonprescription agents known as cosmeceuticals, products marketed as cosmetics that contain biologically active ingredients, are targeted at reducing visible signs of aged skin. These products include α-hydroxy acids, retinol, ascorbic acid, hyaluronic acid, and lipoic acid. One particular product class widely used is α-hydroxy acids and polyhydroxy acids. In normal concentrations (5%–17%), they are included in many products to lessen the appearance of damage; however, in high concentrations, they are used as facial skin peels because of their keratolytic properties. They have been shown in studies to reduce skin roughness and sallowness; however, minimal impact was seen on wrinkles.[122],[126] Topical ascorbic acid and lipoic acid have also been shown to improve skin texture and wrinkles,[127-129] whereas a coenzyme Q_{10} derivative (idebenone) may reduce skin roughness and fine lines while increasing skin hydration.[130] In patients who choose to use these products, it should be strongly recommended that they wear at least SPF 15 to 30 because they allow for greater absorption of UVR. These agents are not regulated by the FDA and, therefore, do not have substantial evidence supporting their effectiveness and can be very costly. Emphasis should be placed on protection from the sun, using photoprotective strategies previously discussed.

CASE 42-5, QUESTION 2: Are there any prescription products that you would recommend to P.B. to discuss with her physician?

There are several topical retinoids currently available that are derivatives of vitamin A and are effective for the signs of photoaging (see Chapter 41, Psoriasis). Tretinoin (all-trans-retinoic acid) is available as a cream or gel, and tazarotene is available as a cream, foam, and a gel; they are the only two topical retinoids FDA approved for the treatment of photoaging. Although not approved by FDA for photoaging, adapalene is also utilized off label, especially in those with more sensitive skin. A 2018 randomized controlled trial showed adapalene 0.3% gel to have comparable efficacy to tretinoin 0.5% cream for cutaneous photoaging.[131] In 2016, adapalene 0.1% gel (Differin) became the first retinoid approved for OTC use for acne. These agents are effective in partially reversing some of the clinical and histologic changes of photoaging by lessening fine wrinkles, mottled pigmentation, and the tactile roughness associated with photoaged skin through mechanisms such as inhibition of metalloproteinase expression.[132-135] Additional benefits of retinoid therapy include the formation of new dermal collagen and vessels, reduction in the number and melanization of freckles, resorption of degenerated connective tissue fibers, and treatment of premalignant and malignant skin lesions.[136] In one of the initial trials, all subjects treated (100%) demonstrated global improvement in the signs of photoaging, with 53% showing moderate changes and the remainder having at least slight improvement. Of the clinical parameters assessed, the most impressive improvements were found with facial skin sallowness, with respondents developing a healthy, rosy glow.[133] These agents are more potent than the retinoids found in OTC products such as retinyl esters, retinol, and retinaldehyde and, therefore, produce more profound results.

Case 42-5, Question 3: Would P.B. be an appropriate candidate for therapy with a topical retinoid product (eg, tretinoin)?

Topical retinoid therapy is most effective for patients ages 50 to 70 years with moderate-to-severe photoaging and for prophylactic use

in patients undergoing the initial changes of photoaging.[132] Recently, P.B. has noticed some of the skin changes consistent with early photoaging and would be a good candidate for prophylactic therapy with topical tretinoin. Treatment may improve her sallow skin color and lessen the mottling on her face and forearms and fine wrinkles at the corners of her eyes and mouth, as well as prevent worsening of the photoaging process that she is experiencing.

Case 42-5, Question 4: P.B.'s physician calls you asking for dosing recommendations for tretinoin. What advice do you provide?

Because both the beneficial and adverse effects of topical retinoid therapy are dose dependent, the underlying goal is to provide the maximal benefit by using the highest concentration that causes minimal skin irritation. Considering P.B.'s skin sensitivity to soaps, cosmetics, and perfumes, her skin is likely to be irritated easily by topical therapy; therefore, it would be best to initiate therapy with the lowest strength (eg, tretinoin 0.025% cream or tazarotene 0.05% cream). These agents are usually applied every night at bedtime, but in some instances, they are applied initially on an every-other-night basis until the skin accommodates to the irritant effects. The likelihood of irritation depends on the type of vehicle more than the concentration of the agent.[136] The cream or the microsphere gel formulations cause the least skin irritation and would be preferred for initiating therapy for P.B. The microsphere gel formulation is preferred for patients with persistent acne or for those with focal actinic lesions. Younger patients often prefer the gel because it leaves no residue and is compatible with most cosmetics. The solution and gel may be better tolerated in older patients with oily, thick, pigmented skin.

Case 42-5, Question 5: You are now dispensing tretinoin cream 0.025% to P.B. What patient counseling should P.B. be given?

Before applying the cream to her face at bedtime, P.B. should wash her face gently, using her fingertips and mild soap, then pat her skin dry with a towel. If gentle washing with her fingers does not remove the dry, peeling skin, a washcloth can be used gently on the face. The treated stratum corneum is fragile, and erosions could occur if P.B. is not careful when washing. After waiting about 15 minutes, she should apply a pea-sized amount of cream to her forehead and spread the cream evenly over her entire face. Care should be exercised while applying the cream to the areas adjacent to the eyes and mouth because tretinoin can cause irritation and burning of mucous membranes.

Skin irritation can be expected to start in the first 3 to 5 days of therapy and, hopefully, will subside in 1 to 3 months. Irritation can manifest as erythema, peeling, burning, and stinging. If P.B. experiences excessive irritation, she can reinitiate the regimen on a slower timeline by applying the cream on an every-other-night or every-third-night basis for the first 2 weeks to reduce skin irritation, or she can also apply a topical corticosteroid product such as hydrocortisone 1% cream. Once she begins to tolerate the therapy, her frequency of applications and strength of cream should be titrated to cause mild scaling with only occasional mild erythema. A thicker film of cream can be applied to photodamaged areas. After 9 to 12 months of therapy, she can begin maintenance therapy, which consists of application two or three nights a week indefinitely.

Because these agents can dry the skin, P.B. should be counseled to use moisturizers during the day to help decrease the dryness and irritation of the skin. Nighttime application of moisturizers should be discouraged when topical tretinoin is being used because the moisturizers can cause a pH incompatibility with the cream and possibly dilute the concentration of tretinoin. With a thinning of the stratum corneum, P.B.’s skin may be more susceptible to the effects of UVR. For this reason, as well as to prevent further actinic damage, P.B. should begin prophylactic daytime application of a sunscreen. Considering her skin type (III) and early photoaging changes, a sunscreen with an SPF of at least 30 would be appropriate. P.B. should be counseled not to become discouraged by

any apparent lack of response; her skin damage is mild, her response to therapy will be gradual, and part of the goal of therapy is to prevent further damage. Her wrinkles may actually appear to worsen early in therapy owing to an initial buildup of the stratum corneum. P.B. should avoid facial saunas and irritating soaps and cosmetics. Retinoids are recognized as being teratogenic, and although risk is more highly associated with oral forms more commonly used for acne, the use of these should generally be avoided in any patients who are pregnant or those planning to become pregnant.[137]

BURN INJURIES

Incidence, Prevalence, and Epidemiology

Approximately 489,000 Americans are treated for burns annually.[138] With the development of multidisciplinary burn centers and a better understanding of the pathophysiology of the burn wound, survival of patients with second- and third-degree burns has improved by five to six times during the past three decades.[139] The majority of burn patients admitted to the hospital are males, with a mean age of 32 years. The two most commonly reported etiologies are fire/flame and scalds, accounting for almost 8 of 10 burn admissions. Seventy-three percent of the burn injuries, with known place of occurrence, occurred in the home.[140]

Burn injuries range from relatively minor, superficial injuries to severe, extensive skin loss resulting from contact with hot solids and liquids, steam, chemical agents, electricity, or other physical agents, such as UVR or infrared radiation. Teenagers and adults between the age of 17 and 30 years are most commonly involved in accidents with flammable liquids, but the mortality associated with clothing ignition continues to decrease as a result of the use of flame-retardant forms of fabric in clothing. Both income and income

disparity by country are associated with higher rates of burn-related deaths.[139]

Complications such as fluid and electrolyte imbalances, metabolic derangements, respiratory failure, sepsis, scarring, and functional impairment are the primary causes of hospitalization for these cases. Most burns, however, are minor and can be managed in an ambulatory environment, provided the burned patient is evaluated carefully, the severity of the burn is assessed accurately, and proper and continuous follow-up care is ensured.

Etiology

ZONES OF INJURY

The skin functions as a protective barrier of the underlying organ systems from trauma, temperature variations, harmful penetrations, moisture, humidity, radiation, and invasion by microorganisms (see Fig. 39-1 in Chapter 39, Dermatotherapy and Drug-Induced Skin Disorders). It is also involved with carbohydrate, protein, fat, and vitamin D metabolism; produces secretions that lubricate the skin; is involved with the immune response; and provides the body with the sense of touch.

Burn wounds caused by thermal injury can be described by varying zones of injury.[141] The most peripheral area of injury is the *zone of hyperemia.* The tissue in this area is characterized by inflammatory changes with minimal tissue damage. The *zone of stasis* is the next area of injury, extending inward from the zone of hyperemia. This area involves ischemic, damaged tissue, with blood vessels only partially thrombosed. The damaged endothelial linings of blood vessels within this zone of injury may trigger further thrombosis, resulting in further ischemia, cell death, and deepening of the burn wound. This process of further injury can occur 24 to 48 hours after the initial injury. Drying of the burn wound or infection can cause deepening of the burn wound by preventing reestablishment of circulation to injured tissue. The central-most area, or the *zone of coagulation,* is characterized by thrombotic vessels and necrotic

tissue. This area absorbs the most thermal energy, resulting in the greatest tissue damage. Minor burns may involve only the most peripheral zones of injury, whereas severe burns encompass all three zones of injury.

EXTENT OF INJURY

Rule of nines

Total body surface area (TBSA) is used to assess the size of burns of the skin. The burned surface area is calculated as a percentage of TBSA to determine burn size. Burn severity is proportional to the percent of TBSA involvement and depth of the wound. The percent of TBSA for adults can be estimated by using the "rule of nines," in which each arm constitutes 9% of the TBSA, the head 9%, each leg 18%, the front and back of the torso 18% each, and the genitalia 1%.[142] For children younger than 10 years, the percent TBSA must be adjusted because their bodies have different proportions. Variations of the Lund and Browder chart have been used for this purpose.[143] At birth, the infant's head constitutes about 19% of the TBSA. For each additional year of age, the head decreases by about 1%, and the BSA of the legs increases by about 1% of the patient's TBSA, so a quick estimation of the size of a burn can be made.

Classification of wounds

Burn wounds are also classified according to the depth of tissue damage. Determining the depth of the burn wound can be difficult during the first 24 to 48 hours because of the presence of edema and continued tissue ischemia and infection, both of which can cause deepening of the wound. In addition, the depth of destruction can vary within the same burn, and skin surface characteristics may not match underlying tissue damage, making assessment of the burn wound difficult.[141]

First-Degree Burns (Superficial-Thickness Burn)

First-degree burns result from injury to the superficial cells of the epidermis; a common example is a mild sunburn. The burned skin does not form blisters, but it does become erythematous and mildly painful. This superficial-thickness burn heals within 3 to 4 days without scarring.

Second-Degree Burns (Partial-Thickness to Superficial Burn)

Second-degree burns may be superficial or deep, depending on the depth of dermal involvement. Superficial second-degree burns involve the epidermis and the upper layer of the dermis. The burn surface is often erythematous, blistered, weeping, painful, and very sensitive to stimuli. The erythema blanches with pressure, and the hair follicles, sweat, and sebaceous glands are spared. Superficial second-degree burns heal spontaneously within 3 weeks with little, if any, scarring. Deep second-degree burns involve the deeper elements of the dermis and may be difficult to distinguish from third-degree burns. The burn surface is pale, feels indurated or boggy, and does not blanch with pressure. This wound is less painful than more superficial wounds; some areas may be insensitive to stimuli. Healing occurs slowly over the course of about 35 days with eschar formation and possible severe scarring and permanent loss of hair follicles and sweat and sebaceous glands.

Third-Degree Burns (Partial-Thickness to Deep Burn)

Third-degree burns entail complete destruction of the full thickness of the skin, including all skin elements. The wound may appear pearly white, gray, or brown and is dry and inelastic. Pain is sensed only when deep pressure is applied. If the wound is small, healing over the course of several months can occur by epithelial migration from the margins of the injury, with scar and contracture formation. Third-degree burns are repaired by excision and grafting, or excision and primary closure to prevent contractures of the skin.[144]

Fourth-Degree Burns (Full-Thickness Burn)

Fourth-degree burns are similar to third-degree burns, except that devitalized tissue extends into the subcutaneous tissue, fascia, and bone. These burns are blackened in appearance; they are dry and generally painless because of destruction of nerve endings and are at high risk for infection.

COMPLICATIONS OF SEVERE BURN WOUNDS

Fluid loss

In severe burns, release of vasoactive mediators and capillary injury cause sequestration of large amounts of body fluid, plasma, and electrolytes in extravascular compartments, resulting in edema both locally and throughout the entire body. This redistribution of fluid, along with the loss of large amounts of fluid, electrolytes, and protein into the open wound, can cause shock, organ failure, and death if not adequately replaced.[145]

Infection

The most important threat to survival of the fully resuscitated patient is infection, with burn wound sepsis and pneumonia being the leading causes of death.[145] Impairment of the local mechanical defenses of the skin and respiratory tract and loss of circulation to the burn wound margins contribute to increased infection risk. Devitalized tissue and tissue exudates provide an ideal environment for the proliferation of bacteria. Colonization of gram-positive bacteria occurs if topical antimicrobial therapy is not initiated promptly, and gram-negative bacteria may predominate by the fifth day after injury.[145] Systemic antibiotics are of limited benefit in full-thickness burns and are used only to treat infections documented by wound biopsy.[146] Topical antimicrobials, local wound care, and strict infection control practices are the mainstays of controlling burn wound infections. Devitalized tissue initiates and perpetuates a sepsis-like state in the absence of an identifiable focus of infection.[145] For this reason, as well as for infection control, early excision of devitalized tissue and closure of the burn wound by skin grafting or substitutes have been adopted by many burn centers.

Inhalation injury

Burn injuries complicated by inhalation injury are associated with greatly increased mortality rates. Injury to the tracheobronchial mucosa is caused by inhalation of smoke or flames and may result in bronchospasm, ulceration of the mucous membranes, damage to cell membranes, edema, and impairment of bacterial ciliary clearance. The early symptoms of pulmonary injury (hoarseness, dyspnea, tachypnea, and wheezing) may not be evident for 24 to 48 hours, so patients with suspected inhalation injury (ie, facial burns or entrapment in a closed space) must be examined carefully. The diagnosis is established by bronchoscopy, and management may include endotracheal intubation and mechanical ventilation. Maintenance of the patient's fluid status is essential. Corticosteroids do not influence survival rates and should not be routinely administered to patients with inhalation injury. They can also increase morbidity and mortality associated with burns and inhalation injury by increasing the risk of infection.[145]

Clinical Management of Minor Burns

TRIAGE

CASE 42-6

Question 1: S.T., a 17-year-old, nonobese boy, has just burned the calf of his right leg on the muffler of his motorcycle. Immediately after being burned, S.T. was able to rinse his leg with cool water from a garden hose. The burn on his leg is about twice the size of the palm of his hand and appears erythematous and weeping. He sustained no other injury, but now he is in considerable pain. S.T. has no significant medical history.

Should S.T. be referred to a health care provider, or can he safely self-treat his burn? What patient information is necessary to consider in making this decision?

Before recommending treatment for a patient with a minor burn, it is important to accurately assess the patient to determine whether he or she can self-treat safely or whether referral or hospitalization is

necessary. The location and severity of the burn, the patient's age and state of health, and the cause of the burn injury all must be considered.

American Burn Association treatment categories

Three treatment categories for burn injuries are recommended by the American Burn Association: major burn injuries; moderate, uncomplicated burn injuries; and minor burn injuries.[147]

- *Major burn injuries* are second-degree burns with >25% TBSA involvement in adults (20% in children); all third-degree burns with 10% TBSA involvement; all burns involving the hands, face, eyes, ears, feet, and perineum that may result in functional or cosmetic impairment; high-voltage electrical injury; and burns complicated by inhalation injury, major trauma, or poor-risk patients (elderly patients and those with debilitating disease).
- *Moderate, uncomplicated burns* are second-degree burns with 15% to 25% TBSA involvement in adults (10%–20% in children); third-degree burns with 2% to 10% TBSA involvement; and burns not involving risk to areas of specialized function, such as the eyes, ears, face, hands, feet, or perineum.
- *Minor burn injuries* include second-degree burns with <15% TBSA involvement in adults (10% in children), third-degree burns with <2% TBSA, and burns not involving functional or cosmetic risk to areas of specialized function.

Patients with minor burn injuries may be treated on an outpatient basis if no other trauma is present; if circumferential burns of the neck, trunk, arms, or legs are not present; and if the patient is able to comply with therapy. After initial evaluation by a health care provider, patients may self-treat a second- or third-degree burn only if <1% BSA is involved.

Major or moderate, uncomplicated burns necessitate hospital admission, and surgical referral is recommended for patients of all ages who have deep second- or third-degree burns covering 3% of

the TBSA. Specific criteria exist to determine need for patient transfer to a burn center.[148]

Age- and disease-related recommendations

Children younger than 2 years and elderly patients with a burn injury should be referred for evaluation because these patients may not tolerate any trauma associated with the burn. Burn patients with any other medical condition, such as diabetes mellitus, cardiovascular disease, immunodeficiency disorders (eg, human immunodeficiency virus [HIV]–associated disease, patients receiving cancer chemotherapy), renal disease, obesity, or alcoholism, may be more susceptible to complications from the burn and may have compromised wound healing.

ETIOLOGY

The etiology of a burn should always be considered because this may provide some insight into the burn presentation and its management. Electrical burns can appear to be superficial because external injury may occur at only the entrance and exit sites of the current. These burns, however, can cause extensive damage to underlying nerve and muscle tissue that is not initially evident. Except for very minor electrical burns, these patients should be referred for further evaluation. S.T. has sustained a superficial second-degree burn over about 2% of his TBSA. Even though the burn wound on his leg was caused by thermal injury and is relatively minor, S.T. should be referred for further evaluation and treatment because it covers over 1% of his TBSA and is on his leg.

TREATMENT

Case 42-6, Question 2: How should S.T.'s burn be treated? What treatment alternatives may be used for S.T.? What immunization should S.T. be questioned about?

Goals of treatment and immediate care

Treatment goals for first- and second-degree burns are to relieve the pain associated with the burn, prevent desiccation and deepening of the wound and infection, and provide a protective environment for healing. Immediate care of the wound should be application of cold, wet compresses, or immersion in cool water.

S.T. may have prevented extension of the burn to deeper layers of tissue and alleviated some of his pain from the burn by immediately irrigating the wound with cool water. Next, the area should be cleansed with a mild hypoallergenic soap (eg, Basis, Purpose) and water. The sterile, nonadherent, fine-mesh gauze dressing impregnated with hydrophilic petrolatum (eg, Xeroflo, Kendall; 3% bismuth tribromophenate) should be placed over the wound. This type of dressing offers bacteriostatic activity and prevents the gauze from adhering to the wound and allows the burn exudate to flow freely through the dressing, thus preventing maceration.

A second layer of absorbent gauze should be placed over the petrolatum gauze, and a supportive layer of rolled gauze can be used to keep the dressing in place. The outer layer must not be too constricting, and the dressing should be replaced every 48 hours after recleaning the area and inspecting for signs of infection. If S.T.'s wound continues to weep, it may be beneficial to soak his wound or apply a towel saturated with water, normal saline, or Burow solution (diluted 1:20 or 1:40) for 15 to 30 minutes at least four times daily (see Chapter 39, Dermatotherapy and Drug-Induced Skin Disorders). The use of butter, grease, or similar home remedies should be avoided in the treatment of burns because these measures tend to retain the thermal energy sustained in the burn and may increase the area of thermal injury. Because burn patients are susceptible to secondary tetanus infections, S.T. should receive a tetanus toxoid booster if he has not been immunized within the previous 10 years.

Skin substitutes and synthetic dressings

Advances in the development of skin substitutes are being used to achieve the elusive goal of finding a skin replacement to mimic completely the interaction and functions of dermis and epidermis. Although this goal has yet to be achieved, a growing number of synthetic and biologic products are available that can serve important roles in caring for burn patients.[148] Examples of some of the current modalities include human cadaver skin allografts, xenografts from porcine skin, and allodermal grafts.

Semisynthetic or Biosynthetic Dressings

Biosynthetic dressings can be used to facilitate healing while reducing the number of dressing changes. They are composed of semipermeable membranes, allowing the draining of exudate, but allowing blood or sera to clot and adhere to the dressing while epithelialization occurs. Examples of these dressings include Biobrane® (Smith & Nephew, Andover, MA), AWBAT® (Aubrey, TX) and AWBAT® Plus (Aubrey, TX), and Suprathel® (Wound Source, Atlantic Beach, FL).[149],[150]

For superficial- to partial-thickness burns, numerous agents are available OTC. DuoDerm® (ConvaTec, Bridgewater Township, NJ) is a hydrocolloid dressing, whereas OpSite (Smith & Nephew, Andover, MA) and Tegaderm (3M, St. Paul, MN) are elastomeric polyurethane films. Comfeel® (Coloplast, Minneapolis, MN) is a semipermeable polyurethane film coated with a flexible, cross-linked adhesive mass containing sodium carboxymethyl cellulose (NaCMC) as the principal absorbent and gel-forming agent.

Hyaluronic Acid

Produced by fibroblasts, this group of dermal matrices has a demonstrated positive impact on scar-free fetal wound healing and is also used commercially as a dermal filler. It can be obtained from *Streptococcus* fermentation or extracted from rooster combs. It is available as a scaffold for keratinocytes (Laserskin), an acellular dermal matrix (Hyalomatrix, Anika, Bedford, MA), and as a cellular dermal matrix (Hyalograft-3D).[151]

Alternatives in treating S.T.'s second-degree burn include the use of synthetic dressings and topical antimicrobial agents. Synthetic dressings serve as skin substitutes that are applied to fresh, clean, and moist burns. They are trimmed to about the size of the burn and left in place until the burn is healed or the dressing separates from the wound spontaneously. Indicated for superficial second-degree burns, biosynthetic dressings keep the wound warm and moist, allowing for a faster rate of healing. These dressings offer a significantly lower rate of infection, less frequent dressing changes, with less pain and electrolyte and albumin loss.

Tissue-Engineered Biologic Dressings

Tissue-engineered biologic dressings (eg, Dermagraft, Organogenesis; OASIS Wound Matrix, Smith & Nephew) have been used in the treatment of burns, chronic ulcers, surgical wounds, and other desquamating dermatologic conditions.[152,153] Using an appropriate biologically active matrix to accelerate wound healing and achieving skin reconstruction is well established. Cellular components migrate to the wound from preexisting cell populations in adjacent tissue. Both circulating marrow-derived stem cells and preexisting organ-specific stem cells can contribute to tissue regeneration.[152]

Topical antimicrobial agents

Silver Sulfadiazine

Silver sulfadiazine 1% cream (Silvadene, generic; Aquacel® Ag [hydrofiber dressing with silver]; ConvaTec) is the usual agent of choice because it has broad-spectrum gram-positive and gram-negative antibacterial activity, provides reasonable eschar penetration, and is easy and painless to apply and wash off. The cream is a 1% suspension of silver sulfadiazine in a water-miscible base. As a consequence of poor water solubility, the active agent shows only limited diffusion into the eschar. Silver sulfadiazine cream is most effective when applied to burn wounds immediately after thermal injury to prevent bacterial colonization of the burn

wound surface as a prelude to intraeschar proliferation. This agent has the advantages of being painless when applied to the wound and being free from acid–base and electrolyte disturbances. The limitations of silver sulfadiazine cream include the potential for allergic reactions owing to its sulfadiazine moiety, silver staining of the treated burn wound, hyperosmolality, methemoglobinemia, and hemolysis as a result of a congenital lack of glucose-6-phosphate dehydrogenase.[154] Leukopenia, previously considered to be an adverse drug event associated with use of silver sulfadiazine, occurs when using other topical agents during burn care.[154] An evidence-based review of use of silver sulfadiazine in burns suggested that whereas there is evidence of antibacterial activity, no direct evidence is seen of improved healing or reduced infection compared with normal dressings.[155] In partial-thickness burns, the use of Aquacel Ag offers less treatment to reepithelialize burns 100% with less pain, as compared with silver sulfadiazine.[156] This agent should not be applied around the eyes or mouth in patients with hypersensitivity to sulfonamides or in pregnant or breastfeeding females.

Mafenide Acetate

Mafenide acetate (Sulfamylon®, UDL Labaratories, Rockford, IL) is an 11.1% cream formulation of mafenide acetate in a water-dispersible base, or a 5% powder for topical solution. An investigation in a pediatric burn population demonstrated the effectiveness of a 2.5% solution, without a change in the incidence of bacteremia or wound infection, and without experiencing adverse drug events.[157] As a water-soluble agent, mafenide diffuses freely to establish an effective antibacterial concentration throughout the eschar and at the interface of viable–nonviable tissue, where bacteria characteristically proliferate before invasion. Because of this characteristic, mafenide is the best agent for use if the patient to be treated has heavily contaminated burn wounds, if treatment is delayed for several days after the burn occurred, or if a dense bacterial population already exists on and within the eschar. Adverse effects include hypersensitivity reactions in 7% of patients (usually

responsive to antihistamines), pain or discomfort for 20 to 30 minutes when applied to partial-thickness burns (seldom a cause for discontinuation), and inhibition of carbonic anhydrase. The inhibition of carbonic anhydrase can produce both an early bicarbonate diuresis and an accentuation of postburn hyperventilation. The resulting overall reduction of serum bicarbonate levels renders such patients liable to a rapid shift from an alkalotic to an acidotic state. If acidosis should develop during use of mafenide, the frequency of application should be reduced to once daily, or it should be omitted for 24 to 48 hours, with buffering used as necessary and with efforts made to improve pulmonary function.

Either topical silver sulfadiazine or mafenide should be applied in a one-eighth-inch (0.31 cm) layer to the entire burn wound with a sterile gloved hand immediately after initial debridement and wound care. Twelve hours later, to ensure continuous topical treatment, a one-eighth-inch (0.31 cm) coat of cream should be reapplied to those areas of the burn wound from which it has been abraded by clothing. The topical cream should be cleansed gently once each day from all of the burn wound, and the wound should be inspected. Daily debridement should be carried out to a point of bleeding or pain without the use of general anesthesia. After debridement, the wound should be covered again by the topical cream.

In S.T.'s case, silver sulfadiazine cream could be chosen to treat his burn on an outpatient basis if an assessment determines that he is at particular risk of infection. The cream would be applied in a thin layer over the wound and covered with absorbent gauze and wrapped with rolled gauze. The dressing must be changed twice daily to maintain an application of cream that is biologically active. Topical bacitracin and the combination of polymyxin B and bacitracin are transparent formulations that also can be used, but, because of limited efficacy, may be desirable for use only on small, second-degree burns on the face.

Oral analgesics and topical protectants

S.T.'s burn pain can be treated with oral OTC analgesics, acetaminophen, naproxen, or ibuprofen. If these analgesics do not provide adequate relief, an oral opioid such as tramadol, codeine/acetaminophen, or hydrocodone/acetaminophen may be of additional benefit in extreme circumstances.[158] Topical protectants, such as allantoin, calamine, white petrolatum, or zinc oxide, are safe and effective in treating first-degree and minor second-degree burns. These agents protect the burn from mechanical irritation caused by friction and rubbing and prevent drying of the stratum corneum.

Postwound care

Postwound care is an essential part of total burn management to ensure adequate follow-up subsequent to wound healing, including psychological support. Good burn care that helps to alleviate physical discomfort, pain, and scarring and that promotes good wound healing will also provide psychological benefits for the patient. Healed wounds should be moisturized on a regular basis. Pruritus can be a major problem after burn injury. To reduce itching, moisturizers can be applied, and oral antihistamines may be necessary.[159] Protection from the sun will help prevent further thermal damage or pigmentation changes to the affected area. Patients in this population should avoid the sun after a burn injury whenever possible, with use of a sunscreen with an SPF of at least 50 recommended.[160] If surface changes occur (eg, skin becomes hypertrophic, or blisters or new wounds appear), the patient should be advised to return for evaluation.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Bylaite M, Grigaitiene J, Lapinskaite GS. Photodermatoses: classification, evaluation and management. *Br J Dermatol.* 2009;161(*suppl 3*):61–68. (5)

Department of Health and Human Services. *The Surgeon General's Call to Action to Prevent Skin Cancer*. U.S. Department of Health and Human Services, Office of the Surgeon General; 2014. Accessed October 10, 2020. https://www.hhs.gov/surgeongeneral/reports-and-publications/skin-cancer/index.html (4)

Federal Register. Sunscreen drug products for over-the-counter human use: a proposed rule by the Food and Drug Administration on 2/26/2019. Federal Register 84 FR 6204. Accessed October 20, 2020. https://www.federalregister.gov/d/2019-03019 (47)

Federal Register. Sunscreen drug products for over-the-counter human use; final monograph: a rule by the Food and Drug Administration on 5/21/1999. Federal Register 54 FR 27666. Accessed October 20, 2020. https://www.federalregister.gov/d/99-12853 (51)

Moyal DD, Fourtanier AM. Broad-spectrum sunscreens provide better protection from solar ultraviolet-simulated radiation and natural sunlight-induced immunosuppression in human beings. *J Am Acad Dermatol.* 2008;58(*5, suppl 2*):S149–S154. (26)

Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancers. *J Am Acad Dermatol.* 2008;58(*5, suppl 2*):S129–S132. (1)

Spanholtz TA, Theodorou P, Amini P, Spilker G. Severe burn injuries: acute and long-term treatment. *Dtsch Arztebl Int.* 2009;106(*38*):607–613. (145)

U.S. Congress Senate. Health, education, labor, and pensions. 2014. Sunscreen Innovation Act. 113th Congress. S2141. (50)

Wang SQ, Balagula Y, Osterwalder U. Photoprotection: a review of the current and future technologies. *Dermatol Ther.* 2010;23(*1*):31–47. (9)

Key Websites

American Academy of Dermatology, Sun safety. https://www.aad.org/public/everyday-care/sun-protection

What Can I Do to Reduce My Risk? Skin cancer prevention. http://www.cdc.gov/cancer/skin/basic_info/prevention.htm

Skin Cancer Organization. http://www.skincancer.org/

COMPLETE REFERENCES CHAPTER 42 PHOTOSENSITIVITY, PHOTOAGING, AND BURN INJURIES

1. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. *J Am Acad Dermatol*. 2008;58(5, suppl 2):S129–S132.
2. Centers for Disease Control and Prevention. Melanoma incidence and mortality, United States-2012–2016. U.S. Cancer Statistics data brief, no 9. 2019. Accessed October 10, 2020. https://www.cdc.gov/cancer/uscs/pdf/USCS-DataBrief-No9-July2019-h.pdf
3. Centers for Disease Control and Prevention. Vital signs: melanoma incidence and mortality trends and projections-United States, 1982–2030. *MMWR Morb Mortal Wkly Rep*. 2015;64:1–6.
4. Department of Health and Human Services. *The Surgeon General's Call to Action to Prevent Skin Cancer*. U.S. Department of Health and Human Services, Office of the Surgeon General; 2014. Accessed October 1, 2020. https://www.hhs.gov/surgeongeneral/reports-and-publications/skin-cancer/index.html
5. Bylaite M, Grigaitiene J, Lapinskaite GS. Photodermatoses: classification, evaluation and management. *Br J Dermatol*. 2009;161(suppl 3):61–68.
6. Holman DM, Berkowitz Z, Guy GP Jr, Hawkins NA, Saraiya M, Watson M. Patterns of sunscreen use on the face and other exposed skin among US adults. *J Am Acad Dermatol*. 2015;73(1):83–92.
7. Harmful effects of ultraviolet radiation. Council on scientific affairs. *JAMA.* 1989;262(3):380–384.
8. Mahmoud BH, Ruvolo E, Hexsel CL, et al. Impact of long-wavelength UVA and visible light on melanocompetent skin. *J Invest Dermatol*. 2010;130(8):2092–2097.
9. Wang SQ, Balagula Y, Osterwalder U. Photoprotection: a review of the current and future technologies. *Dermatol Ther*. 2010;23(1):31–47.
10. Consensus Development Panel. National Institutes of Health summary of the consensus development conference on sunlight, ultraviolet radiation, and the skin. *J Am Acad Dermatol*. 1991;24(4):608–612.
11. Diffey BL. Human exposure to solar ultraviolet radiation. *J Cosmet Dermatol*. 2002;1(3):124–130.
12. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer—the role of sunlight. *Adv Exp Med Biol*. 2008;624:89–103.
13. Murphy GM. Ultraviolet radiation and immunosuppression. *Br J Dermatol*. 2009;161(suppl 3):90–95.

14. Ashwell M, Stone EM, Stolte H, et al. UK Food Standards Agency Workshop Report: an investigation of the relative contributions of diet and sunlight to vitamin D status. *Br J Nutr*. 2010;104(4):603–611.
15. Norval M, Cullen AP, de Gruijl FR, et al. The effects on human health from stratospheric ozone depletion and its interactions with climate change. *Photochem Photobiol Sci*. 2007;6(3):232–251.
16. United States Environmental Protection Agency. SunWise Program. October 10, 2020. http://www.epa.gov/sunwise/uviresources.html
17. Lee TK, MacArthur AC, Gallagher RP, Elwood MJ. Occupational physical activity and risk of malignant melanoma: the Western Canada Melanoma Study. *Melanoma Res*. 2009;19(4):260–266.
18. Hemminski K, Zhang H, Czene K. Familial invasive and in situ squamous cell carcinoma of the skin. *Br J Cancer*. 2003;88(9):1375–1380.
19. High WA, Robinson WA. Genetic mutations involved in melanoma: a summary of our current understanding. *Adv Dermatol*. 2007;23:61–79.
20. Norval M, Lucas RM, Cullen AP, et al. The human health effects of ozone depletion and interactions with climate change. *Photochem Photobiol Sci*. 2011;10:199–225.
21. Sacca SC, Bolognesi C, Battistella A, Bagnis A, Izzotti A. Gene-environment interactions in ocular diseases. *Mutat Res*. 2009;667(1/2):98–117.
22. Bosnar D. Sunshine on holidays—eye risks. *Coll Antropol*. 2007;31(suppl 1):49–52.
23. Elkeeb D, Elkeeb L, Maibach H. Photosensitivity: a current biological overview. *Cutan Ocul Toxicol*. 2012;31(4):263–272.
24. Dawe RS, Ibbotson SH. Drug-induced photosensitivity. *Dermatol Clin*. 2014;32(3):363–368.
25. Onoue S, Seto Y, Gandy G, Yamada S. Drug-induced phototoxicity; an early in vitro identification of phototoxic potential of new drug entities in drug discovery and development. *Curr Drug Saf*. 2009;4(2):123–136.
26. Moyal DD, Fourtanier AM. Broad-spectrum sunscreens provide better protection from solar ultraviolet-simulated radiation and natural sunlight-induced immunosuppression in human beings. *J Am Acad Dermatol*. 2008;58(5, suppl 2):S149–S154.
27. Darlington S, Williams G, Neale R, Frost C, Green A. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. *Arch Dermatol*. 2003;139(4):451–455.
28. Hawk JLM. Cutaneous photoprotection [editorial]. *Arch Dermatol*. 2003;139(4):527–530.
29. Jain SK, Jain NK. Multiparticulate carriers for sun-screening agents. *Int J Cosmet Sci*. 2010;32(2):89–98.
30. Kütting B, Drexler H. UV-induced skin cancer at workplace and evidence-based prevention. *Int Arch Occup Environ Health*. 2010;83(8):843–854.

31. Roberts WE. Skin type classification systems old and new. *Dermatol Clin*. 2009;27(4):529–533, viii.
32. Rass K, Reichrath J. UV damage and DNA repair in malignant melanoma and nonmelanoma skin cancer. *Adv Exp Med Biol*. 2008;624:162–178.
33. Gallagher RP, Rivers JK, Lee TK, Bajdik CD, McLean DI, Coldman AJ. Broad-spectrum sunscreen use and the development of new nevi in white children: a randomized controlled trial. *JAMA.* 2000;283(22):2955–2960.
34. Harrison SL, Saunders V, Nowak M. Baseline survey of sun-protection knowledge, practices and policy in early childhood settings in Queensland, Australia. *Health Educ Res*. 2007;22(2):261–271.
35. Geller AC, Emmons K, Brooks DR, et al. Skin cancer prevention and detection practices among siblings of patients with melanoma. *J Am Acad Dermatol*. 2003;49(4):631–638.
36. Geller AC, Brooks DR, Colditz GA, Koh HK, Frazier L. Sun protection practices among offspring of women with personal or family history of skin cancer. *Pediatrics.* 2006;117(4):e688–e694.
37. Garoli D, Pelizzo MG, Bernardini B, Nicolosi P, Alaibac M. Sunscreen tests: correspondence between in vitro data and values reported by the manufacturers. *J Dermatol Sci*. 2008;52(3):193–204.
38. Diffey BL. When should sunscreen be reapplied? *J Am Acad Dermatol*. 2001;45(6):882–885.
39. Autier P, Boniol M, Severi G, Doré JF, European Organization for Research and Treatment of Cancer Melanoma Co-operative Group. Quantity of sunscreen used by European students. *Br J Dermatol*. 2001;144(2):288–291.
40. Teichmann A, Pissavini M, Ferrero L, et al. Investigation of the homogeneity of the distribution of sunscreen formulations on the human skin: characterization and comparison of two different methods. *J Biomed Opt*. 2006;11(6):064005-1–064005-8.
41. Kong BY, Sheu SL, Kundu RV. Assessment of consumer knowledge of new sunscreen labels. *JAMA Dermatol*. 2015;151(9):1028–1030.
42. Wright MW, Wright ST, Wagner RF. Mechanisms of sunscreen failure. *J Am Acad Dermatol*. 2001;44(5):781–784.
43. Diaz A, Neale RE, Kimlin MG, Jones L, Janda M. The children and sunscreen study: a crossover trial investigating children's sunscreen application thickness and the influence of age and dispenser type. *Arch Dermatol*. 2012;148:606–612.
44. Petersen B, Datta P, Philipsen PA, Wulf HC. Sunscreen use and failures—on site observations on a sun-holiday. *Photochem Photobiol Sci*. 2013;12:190–196.
45. Petersen B, Wulf H. Application of sunscreen-theory and reality. *Photodermatol Photoimmunol Photomed*. 2014;30:96–101.
46. Faurschou A, Wulf HC. The relation between sun protection factor and amount of sunscreen applied in vivo. *Br J Dermatol*. 2007;156(4):716–719.

47. Federal Register. Sunscreen drug products for over-the-counter human use: a proposed rule by the Food and Drug Administration on 2/26/2019. Federal Register 84 FR 6204. Accessed October 20, 2020. https://www.federalregister.gov/d/2019-03019
48. Matta MK, Zusterzeel R, Pilli NR, et al. Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: a randomized clinical trial. *JAMA.* 2019;321(21):2082–2091.
49. Matta MK, Florian J, Zusterzeel R, et al. Effect of sunscreen application on plasma concentration of sunscreen active ingredients: a randomized clinical trial. *JAMA.* 2020;323(3):256–267.
50. US Congress Senate. Health, education, labor, and pensions. 2014. Sunscreen Innovation Act. 113th Congress. S2141.
51. Federal Register. Sunscreen drug products for over-the-counter human use; final monograph: a rule by the Food and Drug Administration on 5/21/1999. Federal Register 54 FR 27666. Accessed October 20, 2020. https://www.federalregister.gov/d/99-12853
52. U.S. Food and Drug Administration. Regulatory Policy Information: Sunscreen Innovation Act. Accessed October 20, 2020. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/regulatory-policy-information-sunscreen-innovation-act
53. U.S. Food and Drug Administration. Questions and Answers: FDA posts deemed final order and proposed order for over-the-counter sunscreen. Accessed May 20, 2022. https://www.fda.gov/drugs/understanding-over-counter-medicines/questions-and-answers-fda-posts-deemed-final-order-and-proposed-order-over-counter-sunscreen
54. Poh Agin P. Water resistance and extended wear sunscreens. *Dermatol Clin*. 2006;24(1):75–79.
55. Lowe NJ. An overview of ultraviolet radiation, sunscreens, and photo-induced dermatoses. *Dermatol Clin*. 2006;24(1):9–17.
56. Shaw T, Simpson B, Wilson B, Oostman H, Rainey D, Storrs F. True photoallergy to sunscreens is rare despite popular belief. *Dermatitis.* 2010;21(4):185–198.
57. Pentinga SE, Kuik DJ, Bruynzeel DP, Rustemeyer T. Do “cinnamon-sensitive” patients react to cinnamate UV filters? *Contact Dermatitis.* 2009;60(4):210–213.
58. Avenel-Audran M. Sunscreen products: finding the allergen. *Eur J Dermatol*. 2010;20(2):161–166.
59. Singh M, Beck MH. Octyl salicylate: a new contact sensitivity. *Contact Dermatitis.* 2007;56(1):48.
60. Kullavanijaya P, Lim HW. Photoprotection. *J Am Acad Dermatol*. 2005;52(6):937–958.
61. Shaw DW. Allergic contact dermatitis from octisalate and cis-3-hexenyl salicylate. *Dermatitis*. 2006;17(3):152–155.

62. Nash JF. Human safety and efficacy of ultraviolet filters and sunscreen products. *Dermatol Clin*. 2006;24(1):35–51.
63. Schram SE, Glesne LA, Warshaw EM. Allergic contact cheilitis from benzophenone-3 in lip balm and fragrance/flavorings. *Dermatitis.* 2007;18(4):221–224.
64. Deleo VA. Photocontact dermatitis. *Dermatol Ther*. 2004;17(4):279–288.
65. Janjua NR, Mogensen B, Andersson A-N, et al. Systemic absorption of the sunscreens benzophenone-3, octyl-methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans. *J Invest Dermatol*. 2004;123(1):57–61.
66. Wang SQ, Stanfield JW, Osterwalder U. In vitro assessments of UVA protection by popular sunscreens available in the United States. *J Am Acad Dermatol*. 2008;59(6):934–942.
67. Chang NB, Feng R, Gao Z, Gao W. Skin cancer incidence is highly associated with ultraviolet-B radiation history. *Int J Hyg Environ Health*. 2010;8(5, suppl 2):S129–S132.
68. Chatelain E, Gabard B. Photostabilization of butyl methoxydibenzoylmethane (Avobenzone) and ethyl-hexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S), a new UV broadband filter. *Photochem Photobiol*. 2001;74(3):401–406.
69. Fourtanier A, Moyal D, Seité S. Sunscreens containing the broad-spectrum UVA absorber, Mexoryl SX, prevent the cutaneous detrimental effects of UV exposure: a review of clinical study results. *Photodermatol Photoimmunol Photomed*. 2008;24(4):164–174.
70. Cole C, Shyr T, Ou-Yang H. Metal oxide sunscreens protect by absorption, not by reflection or scattering. *Photodermatol Photoimmunol Photomed*. 2016;32:5–10.
71. Nohynek GJ, Lademann J, Ribaud C, Roberts MS. Grey goo on the skin? Nanotechnology, cosmetic and sunscreen safety. *Crit Rev Toxicol*. 2007;37(3):251–277.
72. Matsui MS, Hsia A, Miller JD, et al. Non-sunscreen photoprotection: antioxidants add value to a sunscreen. *J Investig Dermatol Symp Proc*. 2009;14(1):56–59.
73. Sadrieh N, Wokovich AM, Gopee NV, et al. Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano- and submicron-size TiO_2 particles. *Toxicol Sci*. 2010;115(1):156–166.
74. Mohammed YH, Holmes A, Haridass IN, et al. Support for the safe use of zinc oxide nanoparticle sunscreens: lack of skin penetration or cellular toxicity after repeated application in volunteers. *J Invest Dermatol.* 2019;139:308–315.
75. Mohammed YH, Haridass IN, Grice JE, Benson HAE, Roberts MS. Bathing does not facilitate human skin penetration or adverse cellular effects of

nanoparticulate zinc oxide sunscreens after topical application. *J Invest Dermatol*. 2020; 140:1656–1659.

76. Coelho SG, Patri AK, Wokovich AM, McNeil SE, Howard PC, Miller SA. Repetitive application of sunscreen containing titanium dioxide nanoparticles on human skin. *JAMA Dermatol*. 2016;152:470–472.
77. Schilling K, Bradford B, Castelli D, et al. Human safety review of “nano” titanium dioxide and zinc oxide. *Photochem Photobiol Sci*. 2010;9(4):495–509.
78. Chen L, Hu JY, Wang SQ. The role of antioxidants in photoprotection: a critical review. *J Am Acad Dermatol*. 2012;67(5):1013–1024.
79. Burke KE. Interaction of vitamins C and E as better cosmeceuticals. *Dermatol Ther*. 2007;20(5):314–321.
80. Murray JC, Burch JA, Streilein RD, Iannacchione MA, Hall RP, Pinnell SR. A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation. *J Am Acad Dermatol*. 2008;59(3):418–425.
81. Scheuer E, Warshaw E. Sunscreen allergy: a review of epidemiology, clinical characteristics, and responsible allergens. *Dermatitis.* 2006;17(1):3–11.
82. McFadden JP, Yeo L, White JL. Clinical and experimental aspects of allergic contact dermatitis to para-phenylenediamine. *Clin Dermatol*. 2011;29(3):316–324.
83. Bauer J, Büttner P, Wiecker TS, Luther H, Garbe C. Effect of sunscreen and clothing on the number of melanocytic nevi in 1,812 German children attending day care. *Am J Epidemiol*. 2005;161(7):620–627.
84. Jansen R, Osterwalder U, Wang SQ, Burnett M, Lim HW. Photoprotection: part II. Sunscreen: development, efficacy, and controversies. *J Am Acad Dermatol*. 2013;69:867.e1–e14.
85. Julian E, Palestro AM, Thomas JA. Pediatric sunscreen and sun safety guidelines. *Clin Pediatr*. 2015;54(12):1133–1140. doi:10.1177/0009922815591889
86. U.S. Food and Drug Administration. Should you put sunscreen on infants? Not usually. Updated July 6, 2016. Accessed September 29, 2020. https://www.fda.gov/consumers/consumer-updates/should-you-put-sunscreen-infants-not-usually
87. Hexsel CL, Bangert SD, Hebert AA, Lim HW. Current sunscreen issues: 2007 Food and Drug Administration sunscreen labelling recommendations and combination sunscreen/insect repellent products. *J Am Acad Dermatol*. 2008;59(2):316–323.
88. Berneburg M, Surber C. Children and sun protection. *Br J Dermatol*. 2009;161(suppl 3):33–39.
89. Ghazi S, Couteau C, Coiffard LJM. What level of protection can be obtained using sun protective clothing? Determining effectiveness using an in vitro method. *Int J Pharm*. 2010;397(1/2):144–146.

90. Dadlani C, Orlow SJ. Planning for a brighter future: a review of sun protection and barriers to behavioral change in children and adolescents. *Dermatol Online J*. 2008;14(9):1.
91. Van den Keybus C, Laperre J, Roelandts R. Protection from visible light by commonly used textiles is not predicted by ultraviolet protection. *J Am Acad Dermatol*. 2006;5(1)4:86–93.
92. Sarkar AK. An evaluation of UV protection imparted by cotton fabrics dyed with natural colorant. *BMC Dermatol*. 2004;4(1):15.
93. Gambichler T, Altmeyer P, Hoffmann K. Role of clothes in sun protection. *Recent Results Cancer Res*. 2002;160:15–25.
94. Edlich RF, Cox MJ, Becker DG, et al. Revolutionary advances in sun-protective clothing—an essential step in eliminating skin cancer in our world. *J Long Term Eff Med Implants*. 2004;14(2):95–106.
95. Schleyer V, Weber O, Yazdi A, et al. Prevention of polymorphic light eruption with a sunscreen of very high protection level against UVB and UVA radiation under standardized photodiagnostic conditions. *Acta Derm Venereol*. 2008;88(6):555–560.
96. Schneider J. The teaspoon rule of applying sunscreen. *Arch Dermatol*. 2002;138(6):838–839.
97. Lademann J, Schanzer S, Richter H, et al. Sunscreen application at the beach. *J Cosmet Dermatol*. 2004;3(2):62–68.
98. Pruim B, Green A. Photobiological aspects of sunscreen re-application. *Australas J Dermatol*. 1999;40:14–18.
99. De Villa D, Nagatomi ARdS, Paese K, Guterres S, Cestari TF. Reapplication improves the amount of sunscreen, not its regularity, under real life conditions. *Photochem Photobiol*. 2011;87:457–460.
100. Pruim B, Wright L, Green A. Do people who apply sunscreens, re-apply them? *Australas J Dermatol*. 1999;40:79–82.
101. Russak JE, Chen T, Appa Y, Rigel DS. A comparison of sunburn protection of high-sun protection factor (SPF) sunscreens: SPF 85 sunscreen is significantly more protective than SPF 50. *J Am Acad Dermatol*. 2010;62(2):348–349.
102. Kohli I, Nicholson CL, Williams JD, et al. Greater efficacy of SPF 100+ sunscreen compared with SPF 50+ in sunburn prevention during 5 consecutive days of sunlight exposure: a randomized, double-blind clinical trial. *J Am Acad Dermatol*. 2020;82:869–877.
103. Department of Health and Human Services: Food and Drug Administration. Sunscreen drug products for over-the-counter human use; final rules and proposed rules. *Fed Regist*. 2011;76(117):35620–35665. Accessed October 1, 2020.
104. Sliney DH. Photoprotection of the eye UV radiation and sunglasses. *J Photochem Photobiol*. 2001;64(2/3):166–175.

105. Gerber B, Mathys P, Moser M, Bressoud D, Braun-Fahrländer C. Ultraviolet emission spectra of sunbeds. *Photochem Photobiol*. 2002;76(6):664–668.
106. Culley CA, Mayer JA, Eckhardt L, et al. Compliance with federal and state legislation by indoor tanning facilities in San Diego. *J Am Acad Dermatol*. 2001;44(1):53–60.
107. Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol*. 2002;138(11):1462–1470.
108. Levine JA, Sorace M, Spencer J, Siegel DM. The indoor UV tanning industry: a review of skin cancer risk, health benefit claims, and regulation. *J Am Acad Dermatol*. 2005;53(6):1038–1044.
109. Lazovich D, Vogel RI, Berwick M, Weinstock MA, Anderson KE, Warshaw EM. Indoor tanning and risk of melanoma: a case-control study in a highly exposed population. *Cancer Epidemiol Biomarkers Prev*. 2010;19(6):1557–1568.
110. Centers for Disease Control and Prevention. 2019 National Youth Risk Behavior Survey. Accessed May 19, 2022. https://www.cdc.gov/healthyyouth/data/yrbs/yrbs_data_summary_and_trends.htm
111. Centers for Disease Control and Prevention. Healthy People 2020. Accessed October 22, 2020. https://www.cdc.gov/nchs/healthy_people/hp2020.htm
112. General and plastic surgery devices: reclassification of ultraviolet lamps for tanning, henceforth to be known as sunlamp products and ultraviolet lamps intended for use in sunlamp products. US Food and Drug Administration. Final Order. *Federal Register*. 2014;79(105):31205–31214.
113. Mays D, Kraemer J. FDA regulation of indoor tanning devices and opportunities for skin cancer prevention. *JAMA*. 2015;313(24):2423–2424.
114. Poorsattar SP, Hornung RL. UV light abuse and high-risk tanning behavior among undergraduate college students. *J Am Acad Dermatol*. 2007;56(3):375–379.
115. U.S. Food and Drug Administration. Quality control guide for sunlamp products: (FDA 88-8234). 1988. Accessed October 24, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-control-guide-sunlamp-products-fda-88-8234
116. U.S. Food and Drug Administration. Sunless tanners & bronzers. Accessed October 24, 2020. http://www.fda.gov/Cosmetics/ProductsIngredients/Products/ucm134064.htm
117. Han A, Maibach HI. Management of acute sunburn. *Am J Clin Dermatol*. 2004;5(1):39–47.
118. Warshaw EM, Schram SE, Belsito DV, et al. Patch-test reactions to topical anesthetics: retrospective analysis of cross-sectional data, 2001 to 2004. *Dermatitis*. 2008;19(2):81–85.
119. Zug KA, Warshaw EM, Fowler JF, et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. *Dermatitis*.

2009;20(33):149–160.
120. Faurschou A, Wulf HC. Topical corticosteroids in the treatment of acute sunburn: a randomized, double-blind clinical trial. *Arch Dermatol*. 2008;144(5):620–624.
121. Farage MA, Miller KW, Berardesca E, Maibach HI. Clinical implications of aging skin: cutaneous disorders in the elderly. *Am J Clin Dermatol*. 2009;10(2):73–86.
122. Antoniou C, Kosmadaki MG, Stratigos AJ, Katsambas AD. Photoaging: prevention and topical treatments. *Am J Clin Dermatol*. 2010;11(2):95–102.
123. Kann L, Kinchen S, Shanklin SL, et al. Youth risk behavior surveillance—United States, 2013. *MMWR Surveill Summ*. 2014;63(suppl 4):1–168.
124. Green AC, Hughes MCB, McBride P, Fourtanier A. Factors associated with premature skin aging (photoaging) before the age of 55: a population-based study. *Dermatology.* 2011;222(1):74–80.
125. Burke KE, Wei H. Synergistic damage by UVA radiation and pollutants. *Toxicol Ind Health*. 2009;25(4/5):219–224.
126. Green BA, Yu RJ, Van Scott EJ. Clinical and cosmeceutical uses of hydroxyacids. *Clin Dermatol*. 2009;27(5):495–501.
127. Fitzpatrick RE, Rostan EF. Double blind, half face study comparing topical vitamin C and vehicle for rejuvenation of photodamage. *Dermatol Surg*. 2002;28:231–236.
128. Humbert PG, Haftek M, Creidi P, et al. Topical ascorbic acid on photoaged skin: clinical, topographical and ultrastructural evaluation: double-blind study vs. placebo. *Exp Dermatol*. 2003;12:237–244.
129. Beitner H. Randomized placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% alpha-lipoic acid related to photoageing of facial skin. *Br J Dermatol*. 2003;149:841–849.
130. Ghosh DK, Murthy UV. Antiaging benefits of a topical formulation containing coenzyme Q10: results of two clinical studies. *J Cosmet Dermatol*. 2002;28:231–236.
131. Bagatin E, de Sa Goncalves H, Sato M, Costa Almeida LM, Miot HA. Comparable efficacy of adapalene 0.3% gel and tretinoin 0.05% cream as treatment for cutaneous photoaging. *Eur J Dermatol.* 2018;28(3):343–350.
132. Jurzak M, Latocha M, Gojniczek K, Kapral M, Garncarczyk A, Pierzchala E. Influence of retinoids on skin fibroblasts metabolism in vitro. *Acta Pol Pharm*. 2008;65(1):85–91.
133. Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. *Clin Interv Aging*. 2006;1(4):327–348.
134. Talpur R, Cox K, Duvic M. Efficacy and safety of topical tazarotene: a review. *Expert Opin Drug Metab Toxicol*. 2009;5(2):195–210.
135. Ogden S, Samuel M, Griffiths CEM. A review of tazarotene in the treatment of photodamaged skin. *Clin Interv Aging*. 2008;3(1):71–76.

136. Leyden JJ, Grossman R, Nighland M. Cumulative irritation potential of topical retinoid formulations. *J Drugs Dermatol*. 2008;7(8, suppl):S14–S18.
137. Panchaud A, Csajka C, Merlob P, et al. Pregnancy outcome following exposure to topical retinoids: a multicenter prospective study. *J Clin Pharmacol*. 2012;52(12):1844–1851.
138. National Hospital Ambulatory Medical Care Survey: 2017 emergency department summary tables. Accessed October 20, 2020. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2017_ed_web_tables-508.pdf
139. Peck M, Pressman MA. The correlation between burn mortality rates from fire and flame and economic status of countries. *Burns*. 2013;39:1054–1059.
140. National burn repository report: report of data from 2009 -2018. Version 14.0. American Burn Association; Accessed May 19, 2022. https://ameriburn.org/quality-care/2020-bisr/
141. Evers LH, Bhavsar D, Mailänder P. The biology of burn injury. *Exp Dermatol*. 2010;19:777–783.
142. Knaysi GA, Crikelair GF, Cosman B. The role of nines: its history and accuracy. *Plast Reconstr Surg*. 1968;41:560–563.
143. Yu C-Y, Lin C-H, Yang Y-H. Human body surface area database and estimation formula. *Burns.* 2010;36:616–629.
144. Richards WT, Vergara E, Dalaly DG, Coady-Fariborzian L, Mozingo DW. Acute surgical management of hand burns. *J Hand Surg Am*. 2014;39(10):2075–2085.
145. Spanholtz TA, Theodorou P, Amini P, Spilker G. Severe burn injuries: acute and long-term treatment. *Dtsch Arztebl Int*. 2009;106(38):607–613.
146. Barajas-Nava LA, López-Alcalde J, Figuls MRi, Solà I, Cosp XB. Antibiotic prophylaxis for preventing burn wound infection. *Cochrane Database Syst Rev*. 2013;(6):CD008738.
147. Gibran NS. American Burn Association Consensus Statements. *J Burn Care Res*. 2013;34:361–385.
148. Kagan RJ, Peck MD, Ahrenholz DH, et al. Surgical management of the burn wound and use of skin substitutes: an expert panel white paper. *J Burn Care Res*. 2013;34(2):e60–e79.
149. Jeschke MG, Shahrokhi S, Finnerty C, Branski LK, Dibildox M, The ABA Organization & Delivery of Burn Care Committee. Wound coverage technologies in burn care: established techniques. *J Burn Care Res*. 2018;39(3):313–318. doi:10.1097/BCR.0b013e3182920d29
150. Austin RE, Merchant N, Shahrokhi S, Jeschke MG. A comparison of Biobrane™ and cadaveric allograft for temporizing the acute burn wound: cost and procedural time. *Burns.* 2015;41(4):749–753.
151. Voigt J, Driver VR. Hyaluronic acid derivatives and their healing effect on burns, epithelial surgical wounds, and chronic wounds: a systematic review

and meta-analysis of randomized controlled trials. *Wound Repair Regen*. 2012;20(3):317–331.
152. Lu G, Huang S. Bioengineered skin substitutes: key elements and novel design for biomedical applications. *Int Wound J*. 2013;10(4):365–371.
153. Mogos¸anu GD, Grumezescu AM. Natural and synthetic polymers for wounds and burns dressing. *Int J Pharm*. 2014;463(2):127–136.
154. Fuller FW. The side effects of silver sulfadiazine. *J Burn Care Res*. 2009;30(3):464–470.
155. Hussain S, Ferguson C. Best evidence topic report. Silver sulphadiazine cream in burns. *Emerg Med J*. 2006;23(12):929–932.
156. Yarboro DD. A comparative study of the dressings silver sulfadiazine and Aquacel Ag in the management of superficial partial-thickness burns. *Adv Skin Wound Care*. 2013;26(6):259–262.
157. Ibrahim A, Fagan S, Keaney T, et al. A simple cost-saving measure: 2.5% mafenide acetate solution. *J Burn Care Res*. 2014;35(4):349–353.
158. de Castro RJ, Leal PC, Sakata RK. Pain management in burn patients. *Braz J Anesthesiol*. 2013;63:149–153.
159. Zachariah JR, Rao AL, Prabha R, Gupta AK, Paul MK, Lamba S. Post burn pruritus—a review of current treatment options. *Burns.* 2012;38(5):621–629.
160. Bronfenbrener R. Simplifying sun safety: a guide to the new FDA sunscreen monograph. *Cutis.* 2014;93(4):E17–E19.

SECTION 9

Rheumatic and Musculoskeletal Diseases

Section Editor: Kamala M. Nola

43

Osteoarthritis

Dominick P. Trombetta and Christopher M. Herndon

CORE PRINCIPLES		CHAPTER CASES
1	Osteoarthritis (OA) is a chronic, progressive condition, primarily affecting females, that causes loss of articular cartilage in the hands, knees, hips, and cervical and lumbar spine. OA causes significant pain and functional disability and increases costs to our health care systems.	**Case 43-1 (Question 1)**
2	The evolving role of cytokines and the resultant imbalance between cartilage maintenance and destruction contribute to the pathophysiology of OA. There are no current disease-mitigating therapies.	**Case 43-1 (Questions 2, 3), Figure 43-1**
3	The typical presentation includes stiffness and pain unilaterally in one or more joints lasting <30 minutes after a	**Case 43-1 (Questions 1, 2)**

	period of immobility. This causes significant limitations in activities of daily living (ADLs) and overall quality of life.	
4	Conservative treatment strategies include weight loss, self-management, aerobic exercise, strength training, and physical and occupational therapies to best maintain optimal functional status.	**Case 43-1 (Question 4)**
5	Initial trials of routine dosing of acetaminophen, topical agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular glucocorticoid injections represent initial pharmacologic interventions of OA.	**Case 43-1 (Questions 5, 6)** **Case 43-2 (Questions 1–4), Tables 43-1–43-3, Figure 43-2**
6	Intra-articular hyaluronan, tramadol, and duloxetine may be considered in those patients with insufficient relief of symptoms and worsening function after initial pharmacologic strategies have been attempted.	**Case 43-2 (Questions 1–6)**
7	A consistent and systematic approach to the management of chronic pain caused by OA can help identify patients with limitations in ADLs and prevent further disability. Then, the effectiveness of current therapies can be more appropriately evaluated, and the treatment plan can be updated.	**Case 43-1 (Questions 5, 7)** **Case 43-2 (Questions 1–6)** **Case 43-3 (Questions 1, 2)**

INTRODUCTION

Osteoarthritis (OA) is a chronic, progressive disorder characterized by changes to articular cartilage and bone primarily in the hands, knees, hips, and spine. The prevalence of OA was described between 2008 and 2014 as one out of seven adults, or ~32.5 million people in the United States.[1,2] Results from another study from 2013 to 2015 revealed that 59% (32.2 million people) age younger than 65 years had arthritis.[3] Females seem to carry the larger burden of the disease versus males (age-adjusted prevalence of 23.5% and 18.1%, respectively). The importance of these findings suggests that OA is not just a disease of the elderly but a chronic medical condition affecting those still working. Another study collaborated similar findings, describing 14 million people who had symptomatic OA, including 2 million people younger than age 45 and 6 million people ages 45 to 64 years.[4] Also, the ethnic minority population that was significantly younger than the White population has reported symptomatic knee OA, and this number is expected to increase.

Adults with OA may also have chronic conditions such as coronary disease, diabetes, or obesity. These conditions are known to be associated with lower levels of physical activity. Improving physical activities and reducing barriers may be particularly beneficial in these patient populations.[3]

ETIOLOGY

OA has been previously described as disease of cartilage that has undergone significant wear and tear. It is now known to be a more complex and dynamic process. Primary OA cannot be traced to any identifiable cause. In secondary OA, a known etiology or cause has been determined. We know that OA affects not only articular cartilage but also periarticular muscles, subchondral bone and ligaments, synovial membranes, and the entire joint capsule. The interplay of cellular, biochemical, and mechanical processes underlies the disease. Various risk factors have been identified and can be classified as modifiable and nonmodifiable. Modifiable risk

factors of OA include obesity and joint trauma. Increased body weight has been correlated with increased risk of OA of the knee, but not of the hip. Excess weight contributes to the biomechanical forces and stresses on the knee joints. The cascade of increased pain leading to decreased function and further worsening of obesity can be a difficult cycle to break. Weight loss and moderate amounts of activity improve symptoms of OA of the knee and improve overall health. Regular exercise and physical activity do not increase the risk of OA in normal joints and are necessary to maintain cartilage. Nonmodifiable risk factors are advancing age, sex, genetics, race, and joint location. Typically, the development of symptomatic OA occurs with increased age predominantly in the weight-bearing joints, although many females are affected by localized inflammation of the proximal and distal interphalangeal joints known as Bouchard and Heberden nodes, respectively.[5] The consequences of the biochemical and mechanical changes are articular cartilage that is less functional with structural abnormalities of cartilage, joint capsule, and subchondral bone (**Fig. 43-1**).[5]

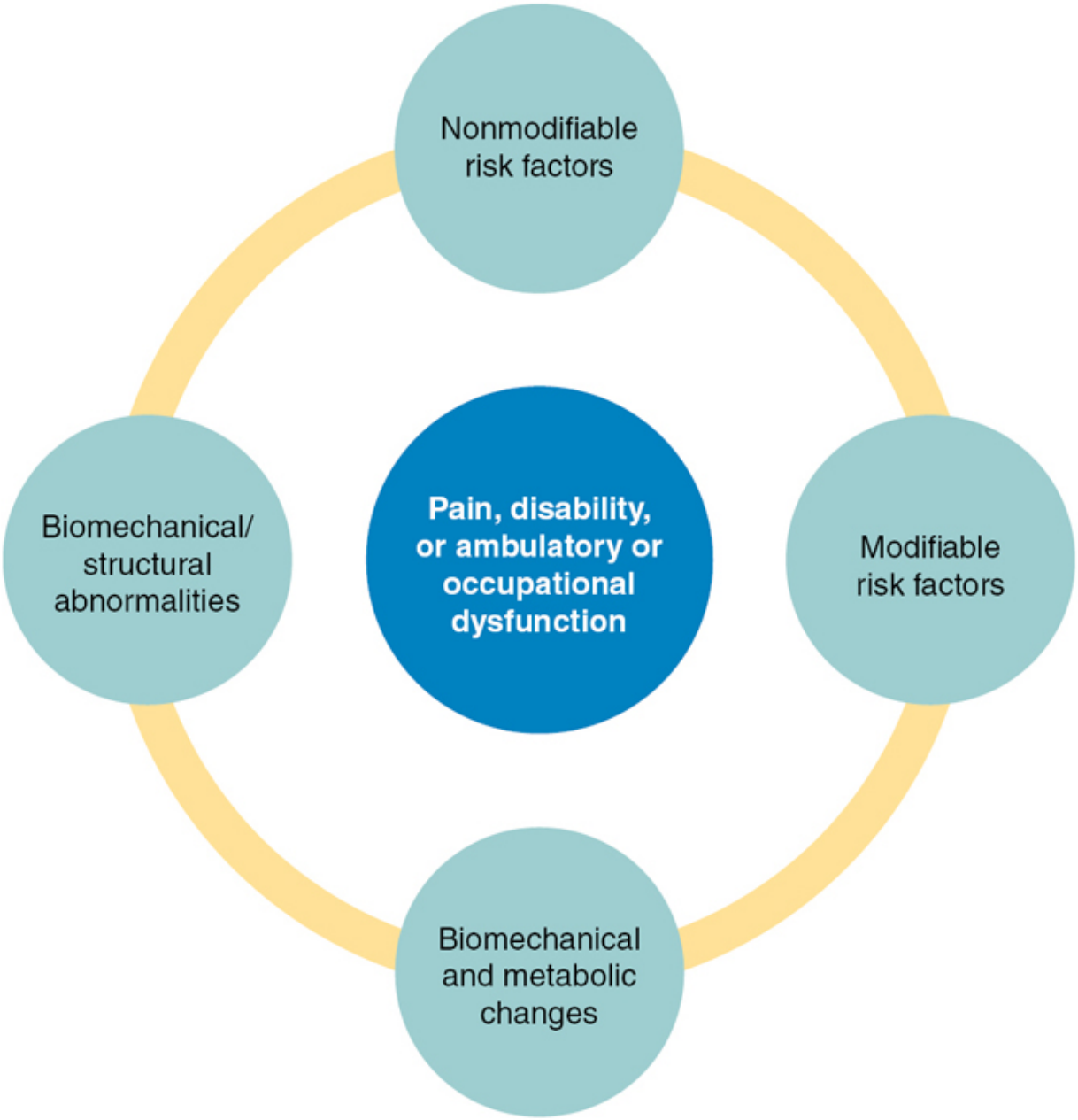


Figure 43-1 Schematic representation of the convergence of modifiable and nonmodifiable risk factors and morphologic changes associated with osteoarthritis. (Used with permission of McGraw Hill LLC from Felson DT, Neogi T. Osteoarthritis. In: Jameson JL, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 20th ed. McGraw-Hill; 2018, permission conveyed through Copyright Clearance Center, Inc.)

PATHOGENESIS

In the early stages of OA, changes that appear to begin the complex abnormalities seen in the joint capsule, subchondral bone and ligaments, periarticular muscles, and synovial membranes occur.[5] Initial insult to the articular cartilage can result from repetitive damage with time. Either repetitive or traumatic injury to articular surfaces initiates the cascade, leading to the release of inflammatory cytokines (tumor necrosis factor [TNF], interleukin [IL-1]), nitric oxide, and enzymes that break down the extracellular matrix. The breakdown of the extracellular matrix results in cartilage that is less elastic, more vulnerable, and less able to support joint loads and stiffening of subchondral bone. The cartilage is less able to support forces, with diminished efficacy for providing joint lubrication and weight distribution across the joint. In early OA, chondrocytes attempt to repair joint damage by forming osteophytes, which try to stabilize the joint or alter the biochemical properties of cartilage. The formation of osteophytes may provide an increased surface area over which to distribute the forces across the joint. Cyst formation likely arises via synovial fluid pressure exerted on the fissures or other structural defects in subchondral bone.[5]

Early in the disease process, the water content of the cartilage is increased. However, this less viscous cartilage is structurally weaker than is normal cartilage. With disease progression, the proteoglycan concentrations diminish with shorter glycosaminoglycan side chains, resulting in decreases of net aggregate proteins. Eventually, the initial water swelling of the cartilage is replaced by cartilage with a reduced propensity to allow the bone to distribute the force and slide on bone.[5] Distinct alterations in cartilage matrix metabolism favor catabolism. Chondrocytes are unable to maintain the production of essential macromolecules necessary for healthy cartilage. However, the syntheses of those enzymes that break down the matrix are increased by the same chondrocytes. The enzymes that degrade proteoglycans and collagen are called aggrecanases and collagenases, respectively. The control of these enzymes is

complicated by enzymatic activation of latent proteins and inactivation by proteinase inhibitors. Ultimately, the imbalance between cartilage maintenance and degradation leads to erosion and eventual cartilage destruction.[5]

OVERVIEW OF DRUG THERAPY

The current treatment of OA is to provide analgesia, allowing performance of activities of daily living (ADLs), participation in exercise programs facilitating weight loss for obese or overweight individuals, recommend appropriate self-managed programs, and Tai chi. There are no disease-mitigating strategies that have demonstrated acceptable safety and efficacy in the treatment of OA. Current practice guidelines largely recommend or conditionally recommend topical nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line treatment alternatives for OA of the hand and knee.[6,7] Acetaminophen is still conditionally recommended for those patients unable to tolerate topical or systemic NSAIDs. Although topical therapies include capsaicin creams, capsaicin gels, capsaicin liquids, capsaicin lotions, capsaicin topical patches, lidocaine topical patches, lidocaine topical creams, ointments, and gels, diclofenac topical gel, diclofenac topical patch, and diclofenac topical solution should each be evaluated individually based on its harm-to-benefit profile and supporting efficacy data. In patients presenting with effusions of the knee, aspiration of the affected joint and intra-articular (IA) injections of corticosteroids may be therapeutic once infectious etiologies have been ruled out.[7] The initial treatment for OA pain and stiffness is acetaminophen given on a routine basis for a 2- to 3-week trial in doses typically <4 g/day or <3 g/day in patients older than age 65 years, unless clinically contraindicated. Acetaminophen offers a considerable degree of safety over NSAIDs for mild-to-moderate OA disease. Unintentional liver injury may result from overuse of acetaminophen above recommended doses, in combination with over-the-counter (OTC) acetaminophen-containing

products, or the opioid–acetaminophen products available by prescription. A trial of a selective or nonselective NSAID would be a reasonable consideration in patients with inadequate response to acetaminophen or presenting with pain and inflammation. A careful risk and benefit analysis must be individualized for each patient starting an NSAID. Adverse events of gastrointestinal (GI) bleeding, diminishing renal function, liver toxicity, and cardiovascular risk of the specific medication considered need to be carefully assessed and a plan for therapeutic monitoring implemented. In addition, consideration of drug–drug interactions or drug–disease interactions is also warranted. In patients with inadequate relief in symptoms and worsening functions, there are few alternatives outside of surgical interventions. IA injections of hyaluronic acid derivatives are no longer recommended in the treatment of hip OA.[7] Tramadol may represent a useful option for many patients unless precluded because of seizures or opioid use disorder, or drug–drug interaction potential. There are currently no recommendations for the use of oral glucocorticoids in the treatment of OA. Glucosamine and chondroitin can be discussed with those patients interested in holistic therapies for hand OA; however, they are not recommended for OA of the knee or hip.[6,7] Recently, a small, randomized control trial suggests curcuma longa, a Chinese herbal medicine with pleiotropic properties, was of benefit for knee pain.[8] The chronic use of oral or transdermal opioids or opioid/acetaminophen combinations for pain management should be discouraged because of the limited evidence demonstrating benefit and the high potential for adverse drug reactions.

CLINICAL MANIFESTATIONS

Clinical Presentation of Osteoarthritis

CASE 43-1

Question 1: R.T., a 64-year-old nonsmoking female, presents to her primary care physician reporting pain and stiffness in her right knee. The pain is usually worse in the morning and lasts for about 15 to 20 minutes and then subsides throughout the day. She reports some increased difficulty taking care of her grandchildren while her daughter is working. Her medical history is significant for hypothyroidism, hypertension, and hyperlipidemia. Social history is negative for tobacco and alcohol use. R.T. currently takes amlodipine 5 mg daily, levothyroxine 88 µg daily, and atorvastatin 20 mg daily. On physical examination, there is a varus misalignment of the knees. The right knee has no swelling or synovial effusions, and crepitus is noted on examination of passive motion. A radiograph shows right knee joint space narrowing with osteophyte formation at the joint margins.

Laboratory values and vital signs obtained at this visit include the following:

Blood pressure (BP), 130/78 mm Hg
Heart rate (HR), 80 beats/minute
Height, 64 inches (162.56 cm)
Weight, 205 pounds (92.99 kg)
Body mass index (BMI), 35.2 kg/m^2
Sodium, 140 mEq/L
Potassium, 4.5 mEq/L
Blood urea nitrogen (BUN), 10 mg/dL
Creatinine, 0.9 mg/dL
Estimated glomerular filtration rate (eGFR), 63 mL/minute
Thyrotropin (or thyroid-stimulating hormone [TSH]), 3.08 mIU/mL
White blood cells (WBCs), 5 × 10^3/µL
Red blood cells (RBCs), 4.7 × 10^6/µL
Hemoglobin, 12.7 g/dL
Hematocrit, 38.2%
Uric acid, 5 mg/dL
C-reactive protein (CRP), 0.9 mg/dL
Erythrocyte sedimentation rate (ESR), 18 mm/hour
Anticyclic citrullinated peptide (CCP) antibodies, negative
Total cholesterol, 160 mg/dL
High-density lipoprotein (HDL), 45 mg/dL

What signs and symptoms suggestive of OA are present in R.T.?

R.T. presents with unilateral right knee pain that is worse in the morning and subsides throughout the day. The OA diagnosis can be made by a good history and physical examination. Laboratory studies are not needed to confirm the diagnosis of OA, but a normal ESR rules out inflammatory conditions such as gout or septic

arthritis. Radiographs demonstrate joint space narrowing that is consistent with OA. However, radiographs do not reliably assess disease severity.

Case 43-1, Question 2: How do the subjective and objective findings of OA correlate with disease pathogenesis in R.T.?

The characteristic joint space narrowing as seen on radiograph without joint destruction is characteristic of OA. Osteophyte formation and bone rubbing against bone are most likely responsible for the pain, stiffness, and crepitus demonstrated on physical examination. Crepitus is an audible “crackling” sound that can be heard with passive or active movement of the joint. Instead of the opposing joint surfaces gliding past each other, the movement of the joint now creates the characteristic crunching or crackling sounds. In addition, the varus misalignment contributes to the stress on the knee joint and some of the functional impairments that R.T. reported to her primary care physician. A varus misalignment is described as the patient in a standing position with his/her knees appearing further apart (bow-legged), and valgus is when the knees are closer together. Both of these deformities can affect a patient’s functioning and quality of life.

The clinical presentation of OA is usually unilateral pain and stiffness of the knee, hip, or cervical or lumbar spine; the distal interphalangeal joints generally are not painful. More often than not, OA tends to affect more than one joint. There are some distribution associations described between knee and hand OA and knee and hip OA. Elbows, wrists, and shoulders tend not to be affected by OA. Patients usually present to their primary care provider reporting increased pain or stiffness lasting <30 minutes, usually in the morning or after periods of prolonged immobility. They usually will report decreases in their ADL, functional status, and overall health-related quality of life. Typically, household activities such as kneeling, stair climbing, and walking tend to be limited. The associated

decrease in activities, range of motion, and overall physical activity contribute to muscle weakness and unsteadiness.

Problems with sleep and depression can occur, compromising attempts to lose weight, increase activity, and participate in physical or occupational therapy or in Tai chi. Joint involvement can be characterized by swelling, easily recognized in the fingers and knees. Joints usually are tender when examined during active motion or application of pressure. Bursitis, tendonitis, muscle spasms, and torn meniscus can cause limitations in range of motion and need to be ruled out. Synovial effusions can be chronic but can also present during times of disease exacerbations. The patellar tap test or the wave test can elucidate joint effusions. Patients with advanced disease may present with not only the expected loss of cartilage but also deformities in surrounding bone and soft tissue, affecting the ligaments. Joint misalignment is common and contributes to joint unsteadiness. Fingers of patients with the characteristic Bouchard and Heberden nodes are misaligned. Muscle atrophy is demonstrated by simply measuring the circumference of the quadriceps muscles. The use of radiographs is usually not necessary for the diagnosis of OA, but rather is used to rule out conditions such as avascular necrosis, Paget disease of the bone, rheumatoid arthritis, or gouty arthropathies. However, radiographs can be useful to establish disease severity or monitor for disease progression. The clinical features described on radiographs that are characteristic of OA are joint space narrowing, osteophytes at the joint margins, and sclerosis of subchondral bone. As demonstrated in Case 43-1, Question 1, R.T.’s knee radiograph revealed joint space narrowing with osteophyte formation.

An ultrasound can be useful in detecting or confirming joint effusion, popliteal cysts, or other erosive inflammatory conditions. Laboratory assessments are usually unnecessary because the ESR and CRP are typically within reference ranges. Serum uric acid can help differentiate between similar inflammatory presentations. Synovial fluid aspiration is appropriate if septic or inflammatory arthritis is suspected. In the patient with OA, the WBC count is <2000 μL, synovial fluid is clear, and crystals are absent. There are

no relevant biomarkers of bone or cartilage remodeling that are used in the routine care of patients with OA. Magnetic resonance imaging (MRI) scans represent an exciting area of research for assessing cartilage, synovium, and bone, but are not routinely used in the diagnosis of OA.

Case 43-1, Question 3: Cytokines are involved in the pathophysiology of OA. Is it possible to modulate these cytokines and thereby slow or delay the disease process to benefit R.T. before her condition worsens?

The role of IL-1 and TNF in rheumatoid arthritis pathogenesis represented exciting discoveries that have led to highly effective disease remissions. However, in OA, the role of these cytokines in upregulating matrix metalloproteinase (MMP) and the exact mechanism that they play in the disease process have not been clearly elucidated and have not resulted in any effective disease-mitigating therapies.[7]

TREATMENT OF OSTEOARTHRITIS

Case 43-1, Question 4: What nonpharmacologic therapies should be recommended for R.T.?

Nonpharmacologic Management

Nonpharmacologic modalities are a primary strategy for OA treatment. As previously discussed, there are no interventions that effectively attenuate the disease process. Pharmacologic strategies have significant untoward effects and modest efficacy in the management of OA pain and disability. Patients typically have difficulty adhering to self-management, aerobic, or strength-training programs. Many times, nonpharmacologic strategies are not even

attempted until pharmacologic interventions have failed or side effects necessitate discontinuation of the offending agent.

Optimal pain management requires an individualized approach that supports increased functional status, and the social, economic, and emotional impacts of OA.[9] Shared decision-making helps determine the influences of culture, religion, preferences, and values. A general approach would include patient education and consideration of different strategies such as physical activities, orthotic devices, psychological and social interventions, good sleep maintenance, and weight management. Physical activities would include general exercise, aerobic and resistance training, Tai chi, yoga, Qigong, and whole-body vibration. Additional interventions such as acupuncture, balneotherapy, thermotherapy, manual therapy/joint stabilization, ultrasound/radiotherapy/diathermy, and cognitive-behavioral therapy have been highly effective for many people.[9] Patients can be referred to the Arthritis Foundation website (http://arthritis.org) for local resources or programs specific to their communities.

R.T. should be encouraged to lose weight and participate in either self-management or a structured exercise program that includes aerobic and strength-training exercises. In addition, R.T. should be encouraged to participate in mind–body activities such as Tai chi classes. Weight loss should be the primary goal in obese patients with OA of the knee. Exercise improves muscle strength and helps prevent falls. The use of knee bracing may offer some degree of support in patients with misalignments of the knee joints. See **Table 43-1** for recommendations for nonpharmacologic and pharmcologic treatments by osteoarthritis sites.

Table 43-1

Recommendations for Nonpharmacologic and Pharmacologic Treatments by Osteoarthritis Site

Site	Nonpharmacologic Recommendations	Pharmacologic Recommendations
Hand	Evaluate ability to perform ADLs.	Acetaminophen

	Instruct in joint protection techniques. Self-efficacy and self-management programs First CMC orthosis Provide assistance hand devices, as needed, to help patients perform ADLs. Instruct in use of thermal/cooling agents for relief of pain and stiffness. Cognitive-behavioral therapy Acupuncture ®Kinesio Taping Paraffin	Topical/oral NSAIDs, including trolamine salicylate and COX-2 selective inhibitors (patients 75 years or older should use topical NSAIDs) Intra-articular corticosteroids Tramadol Duloxetine Chondroitin
Knee	*Participate in aerobic and/or resistance land-based exercise*. *Participate in aquatic exercise*. *Lose weight (if overweight*). Participate in self-management programs ± psychosocial interventions: Weight loss Tai chi Walking aids such as a cane Tibiofemoral brace Cognitive-behavioral therapy Acupuncture ®Kinesio Taping Balance training Consider patellofemoral brace. Yoga Consider radiofrequency ablation. Use thermal agents/cooling and manual therapy in combination with PT-supervised exercise.	Acetaminophen Topical capsaicin Topical/oral NSAIDs Patients 75 years or older should use topical NSAIDs. Patients with h/o upper GI ulcer should use COX-2 selective inhibitor or nonselective NSAID + PPI. Patients with upper GI bleed ≤1 year ago should use COX-2 selective inhibitor + PPI. Tramadol Intra-articular corticosteroid injections Duloxetine
Hip	*Participate in cardiovascular and/or resistance land-*	Acetaminophen Oral NSAIDs

	based exercise. *Participate in aquatic exercise*. Participate in self-management programs ± psychosocial interventions: Weight loss Tai chi Cognitive-behavioral therapy Acupuncture Balance training Walking aids such as a cane Use thermal/cooling agents and manual therapy in combination with PT-supervised exercise. Receive walking aids, as needed.	Tramadol Duloxetine Intra-articular corticosteroid injections (imaging guided)

ADL, activities of daily living; CMC, carpometacarpal; COX-2, cyclooxygenase-2 inhibitor; GI, gastrointestinal; h/o, history of; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor; PT, physical therapy.

Source: Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2020;72(2):149–162. © 2020 American College of Rheumatology. Reprinted by permission of John Wiley & Sons, Inc.

CASE 43-1, QUESTION 5: What is the initial pharmacologic treatment recommendation for R.T.?

Pharmacologic Management

A trial of acetaminophen 1000 mg orally (PO) three to four times a day should be attempted for 2 to 3 weeks. More aggressive medications are usually reserved for those patients who have failed acetaminophen. Medications such as NSAIDs can increase BP, cause GI ulceration, inhibit renal prostaglandins that are vasodilatory and, therefore, diminish renal function, and potentially increase cardiovascular risks. Given R.T.'s past medical history of peptic ulcer

disease and lack of knee inflammation on physical examination, the initial trial of acetaminophen is warranted.

ACETAMINOPHEN

Acetaminophen is conditionally recommended by the American College of Rheumatology (ACR) in those patients with a contraindication to systemic NSAIDs.[7] The role of acetaminophen in the treatment of hand, knee, and hip OA has been downgraded as single-agent therapy because of uncertain clinical benefits. Chronic acetaminophen use in patients who consume more than three alcoholic drinks per day can increase risk of GI bleeding and elevations of liver enzymes.[10] A 12-week randomized, controlled trial reported in 2007 that extended-release acetaminophen 3900 mg/day was safe, well tolerated, and more effective than was 1950 mg/day in patients with hip and knee OA.[11]

Case 43-1, Question 6: What is the role of topical agents in the treatment plan for R.T.?

TOPICAL THERAPY

Numerous prescription and nonprescription topical analgesics are available, containing capsaicin, diclofenac, lidocaine, or methyl salicylate. The ACR, European League Against Rheumatism (EULAR), and the Osteoarthritis Research Society International (OARSI) practice guidelines recommend topical NSAID therapy as a first-line therapy for knee OA.[7,9,12] Topical capsaicin cream is applied to the hands or knees three to four times daily. If used, R.T. should be counseled regarding proper application, initial burning and sensitivity reactions, and expectations of benefits that may take up to a few weeks. There are no systemic effects or drug interactions with topical capsaicin cream.[13]

Currently, three topical diclofenac products are commercially available in the United States, including a 1% gel, a 1.5% and 2% solution, and a 1.3% patch.[14] Diclofenac topical gel 1% has recently made the move to being available OTC. Topical diclofenac 1% gel,

alone or in combination with oral acetaminophen, represents another therapeutic option. Topical diclofenac 1% gel is indicated in the treatment of OA of the upper extremities such as the hands, elbows, and wrists, and the lower extremities such as ankles, feet, and knees. The gel is applied according to “dosing cards” in either 2- or 4-g measurements. The dose for the upper extremities is 2 g four times a day and 4 g four times daily for the lower extremities.

Diclofenac topical solution 1.5% and 2% w/w in dimethyl sulfoxide, USP (DMSO) 45.5% w/v represent another treatment option for the signs and symptoms of OA of the knee. In two 12-week, randomized, placebo-controlled trials, oral and topical diclofenac solution was equivocal for the outcome measures of pain and physical function.[15,16] Patients receiving the topical solution reported minor skin irritation, but fewer GI symptoms and abnormal liver function tests than did those patients receiving oral diclofenac.

The diclofenac 1.3% patch, although available, is indicated only for the treatment of acute pain due to musculoskeletal sprains and strains.

Case 43-1, Question 7: What monitoring parameters would be appropriate for R.T.?

Although improved tolerability and decreased toxicity profiles appear promising for topical NSAIDs, the warnings about typical NSAID-related adverse effects are similar for oral and topical agents.[17] Data are lacking for true upper GI bleed or cardiovascular event risk with topical versus oral administration. Outside of short-term efficacy trials, the risk of systemic complications with chronic therapy has not been investigated. In addition, limited comparative efficacy data exist comparing topical diclofenac with other oral NSAIDs or topical capsaicin. Oral and topical NSAIDs should not be used concomitantly unless potential benefit greatly outweighs the risk, following reports of increased incidence of rectal bleeding and abnormal laboratory findings when used together.[14] The combination of acetaminophen and topical diclofenac may be therapeutic for

some patients while avoiding other combinations with a higher degree of untoward effects. This combination, however, has yet to be evaluated in the rigor of randomized trials. In a 2010 systematic review, oral and topical NSAIDs were noted to have similar rates for discontinuation because of a high incidence of topical reactions with the latter.[18] It is unclear whether these skin reactions are caused by the type of formulation, vehicle, or other ingredients in the preparation.

R.T. does not have a history of liver disease or hepatitis C, so a short trial of acetaminophen does not require any monitoring for medication safety. However, it would be important to ask her to keep a daily pain log and complete a comfort assessment, besides a functional status questionnaire on her next visit. These tools are freely available online from multiple sources. This will engage the patient in her own care as well as provide the clinician with information regarding baseline data, medication efficacy, and the impact of medication on functional impairment. In addition, limitations or improvements in ADLs and instrumental activities of daily living (IADLs) can provide useful information in helping the clinician determine whether any changes in the plan of care need to occur.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND OTHER PHARMACOLOGIC TREATMENT

CASE 43-2

QUESTION 1: S.L., a 67-year-old female, presents to her primary care physician with increased pain and stiffness in her left knee. S.L. reports her left knee as "weak," and she has difficulty getting out of bed in the morning and after sitting on the recliner for some time. She has tried acetaminophen 1000 mg four times daily for 1 month without adequate relief. She also takes metoprolol succinate 50 mg daily, lisinopril 20 mg daily, and famotidine 10 mg twice daily. Her medical history includes hypertension, osteopenia, depression, gastroesophageal reflux disease, OA, and a right knee replacement 2 years ago. Her recent laboratory values and vital signs include the following:

BP, 135/80 mm Hg
HR, 76 beats/minute
Height, 66 inches (167.64 cm)

Weight, 190 pounds (86.18 kg)
BMI, 30.7 kg/m^2
Sodium, 145 mEq/L
Potassium, 4.8 mEq/L
BUN, 16 mg/dL
Creatinine, 1.2 mg/dL
eGFR, 48 mL/minute
WBC, 4.5 × 10^3/mL
RBC, 4.2 × 10^6/μL
Hemoglobin, 12.1 g/dL
Hematocrit, 36.6%

What medication do you recommend to provide adequate pain relief for S.L.?

In this patient who has failed an adequate trial of acetaminophen, therapeutic options include celecoxib, a nonselective NSAID, tramadol, or an opioid analgesic. There are no data to suggest that any particular NSAID is more effective than another.[19] S.L. does not have any known history of coronary heart disease or peptic ulcer disease. On the basis of the risk factors identified in **Table 43-2**, S.L. has one risk factor of age, placing her at moderate risk for GI ulceration. Data suggest that appropriate treatment of *Helicobacter pylori*, if present, reduces the risk of GI ulceration in patients taking NSAIDs chronically.[20] Therefore, if the decision is made to recommend a nonselective NSAID, then famotidine would need to be discontinued because of a lack of protection against gastric ulcers, and a proton-pump inhibitor (PPI) such as omeprazole should be initiated to prevent upper GI bleeding. Either option would represent a reasonable therapeutic recommendation.

Table 43-2
Recommendations for Nonsteroidal Anti-inflammatory Drug Selection Based on Gastrointestinal and Cardiovascular Risks

Risk Category	Low GI Risk	Moderate GI Risk	High GI Risk
	0 risk factors	1–2 risk factors	Multiple risk factors, history of previous ulcer events, or continued use of corticosteroids or anticoagulants
Low CV risk	NSAID alone	NSAID + PPI/ misoprostol	Alternative therapy or COX-2 + PPI/ misoprostol
High CV risk (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/ misoprostol	Alternative therapy recommended

COX-2, cyclooxygenase-2; CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

Adapted with permission from Lanza FL, Chan FK, Quigley EM, et al. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104(3):728–738. © 2009 The American College of Gastroenterology.

For those patients with insufficient pain relief from acetaminophen or topical agents, an oral NSAID should be considered. As with any decision regarding pharmacotherapy, the safety and efficacy of the chosen therapy needs to be evaluated in the context of a patient's specific case. The historical perspective and the knowledge of increased cardiovascular risk versus GI safety with cyclooxygenase (COX)-2 agents have had a tremendous impact on the use of these agents in clinical practice. Currently available NSAIDs have comparatively unique characteristics in terms of their ability to inhibit COX-1 (constitutive) and COX-2 (inducible). See **Table 43-3** for selectivity of COX-2 inhibition.

Table 43-3

Relative Selectivity of Cyclooxygenase Inhibitors

5- to 50-fold COX-2 Preferential	<5-fold COX-2 Preferential	COX-1 Preferential
Etodolac Meloxicam Celecoxib	Diclofenac Sulindac Meclofenamate Piroxicam Diflunisal	Fenoprofen Ibuprofen Tolmetin Naproxen Aspirin Indomethacin Ketoprofen Flurbiprofen Ketorolac

Based on log IC_{80} inhibition ratios COX-2 inhibitor/COX-1.

COX, cyclooxygenase.

Source: Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A*. 1999;96(13):7563–7568.

Patients at increased risk for cardiovascular disease include those with unstable angina, a history of myocardial infarction (MI), coronary artery bypass surgery, ischemic stroke, or a high Framingham risk score.[21] Some clinicians have recommended the addition of low-dose aspirin 81 mg to attenuate the increased risk of cardiovascular disease; however, this practice has not been the primary focus of vigorous clinical trials. The addition of aspirin can potentially increase the risk of GI ulceration and compromise cardioprotection.[22] In addition, randomized controlled studies have not clearly demonstrated the efficacy and safety of this approach.[21,23] See **Figure 43-2** for overview of pharmacologic therapy treatment for the treatment of osteoarthritis.

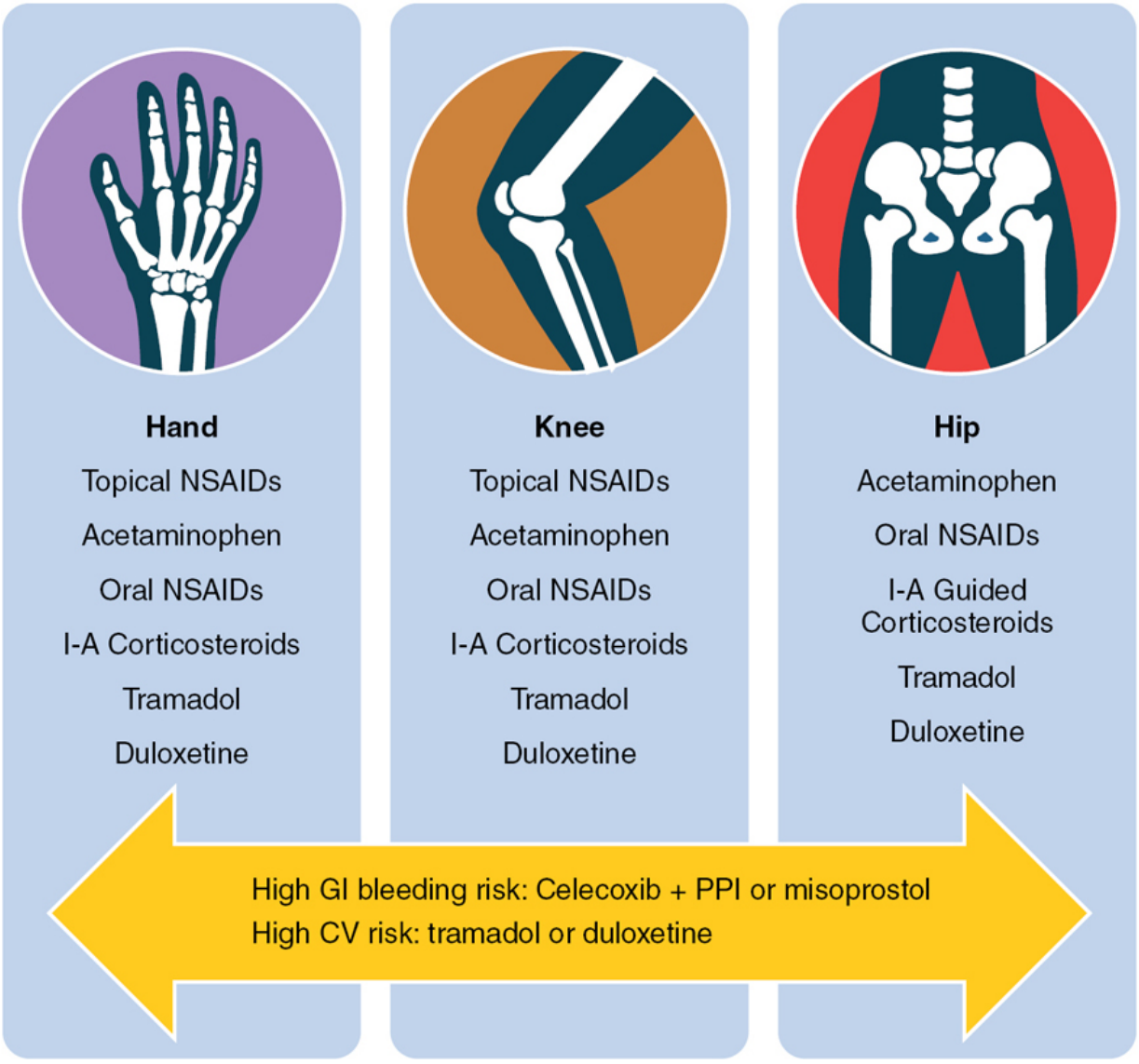


Figure 43-2 Overview of pharmacologic therapy for the treatment of osteoarthritis.

CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor. (Adapted from Kloppenburg M, Kroon FPB, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis*. 2019;78(1):16–24; Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 ACR/AF guidelines for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2020;72(2):149–162. doi:10.1002/acr.24131; Geenen R, Overman CL, Christensen R, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. *Ann Rheum Dis*. 2018;77(6):797–807. doi:10.1136/annrheumdis-2017-212662; Centers for Disease Control and Prevention. Arthritis. https://www.cdc.gov/arthritis/communications/infographics/images/large/30Million-

With-OA.jpg; Mayo Foundation for Education and Research. Osteoarthritis of the hip. https://www.mayoclinic.org/diseases-conditions/osteoarthritis/symptoms-causes/syc-20351925#dialogId49052409.)

All NSAIDs, including naproxen, carry the increased risk of cardiovascular events such as stroke or MI.[24] Cardiovascular safety of the nonselective NSAIDs naproxen and ibuprofen were prospectively compared to celecoxib in a randomized study of 24,081 patients. Celecoxib did not separate statistically from either naproxen or ibuprofen in the primary outcome measure of any cardiovascular event meeting the Antiplatelet Trialists Collaborative Criteria (APTC). However, celecoxib did exhibit statistically lower rates of clinically significant GI events than did naproxen (P = .01) or ibuprofen (P = .002).[25] In summary, for patients with low cardiovascular risk and moderate to higher risk of GI bleeding, a recommendation can be made for once-daily celecoxib or NSAID plus PPI or misoprostol. There is agreement that all NSAIDs may increase the risk of cardiovascular disease in those with or without risk factors. In the past, naproxen had been recommended in those patients, but the data have not been completely conclusive. In a non-Western population, Kang et al had found that all NSAIDs increase the risk of cardiovascular events and bleeding after MI, but meloxicam and celecoxib less so.[26] Until more data are available, physical modalities such as ice or heat or tramadol may be considered for patients at high risk for cardiovascular disease.

Case 43-2, Question 2: What monitoring parameters would be appropriate for this pharmacologic treatment recommendation for S.L.?

Many clinicians recommend checking a basic metabolic panel and complete blood count with differential 2 to 4 weeks after starting NSAIDs in older patients. Depending on the initial laboratory results, testing can occur every 3 to 4 months, thereafter for the next year. The risk of GI adverse events decreases after 1 month, but is always present, especially as age advances. Liver function should be checked regularly during the first year of treatment and periodically thereafter. Patients with significant comorbidities may need more

stringent follow-up and monitoring. Analgesic efficacy is best evaluated using a consistent systematic assessment approach. If S.L. is to remain on chronic NSAID therapy, then monitoring her liver and renal function every 3 months for the first year would be reasonable.

CASE 43-2, QUESTION 3: One week later after starting naproxen 500 mg twice daily, S.L. has been adherent to therapy and had a basic metabolic panel completed before this office visit. S.L. reported a decrease in pain since she had been started on naproxen. Laboratory values and vital signs obtained at this visit include the following:

BP, 135/78 mm Hg
HR, 88 beats/minute
Height, 66 inches (167.64 cm)
Weight, 194 pounds (87.99 kg)
BMI, 30.7 kg/m^2
Sodium, 135 mEq/L
Potassium, 5.5 mEq/L
BUN, 40 mg/dL
Creatinine, 2.2 mg/dL
RBC, 4.7 × 10^6/μL
Hemoglobin, 10.3 g/dL
Hematocrit, 33.8%

What changes, if any, need to be made with her OA therapy?

GI ulceration and bleeding are important considerations that require vigilance and concern with NSAID therapy in OA. The options to mitigate upper GI bleeding in patients taking NSAIDs are to add a PPI, use a COX-2 selective agent, or add misoprostol. A meta-analysis based on epidemiologic studies illustrates the safety of celecoxib with regard to risk of GI ulceration and bleeding. In addition, NSAIDs with long half-lives and slow-release formulations were found to demonstrate higher risks for GI events. Higher relative risk (RR) for GI bleeding (>5) was associated with naproxen, indomethacin, ketoprofen, ketorolac, and piroxicam, whereas a lower RR (<5) was found for ibuprofen, diclofenac, celecoxib, meloxicam, rofecoxib, and aceclofenac.[27] NSAIDs can also be associated with

abnormal liver function tests. Although possible with most NSAIDs, diclofenac has been associated with greater risk.[28]

In the week that has passed, there has been an increase in potassium, serum creatinine, and BUN. COX-2 preferential and nonselective inhibitors have the same potential to cause adverse renal effects. Naproxen should be discontinued, and additional monitoring should be ordered to ensure that laboratory values return to baseline. The drop in hemoglobin may also be concerning, and appropriate follow-up with either endoscopy or stool occult blood testing should be considered. High clinical suspicion of upper GI bleed would need to be accompanied by patient reports of coffee-ground emesis, black or tarry stools, abdominal cramping, and fatigue. Evaluation and treatment of possible upper GI perforation or ulceration secondary to NSAID therapy would necessitate endoscopic examination. Endoscopic assessment is necessary to determine the lesion size and location. Pharmacologic therapy with an intravenous (IV) PPI for 72 hours is recommended before initiating oral maintenance therapy for 12 weeks. Famotidine therapy would be discontinued if the patient had been initiated on maintenance therapy with a PPI.

TRAMADOL AND OPIOIDS

CASE 43-2, QUESTION 4: S.L. has seen commercials on television advertising "knee injections." What are the available therapeutic options?

In many patients with contraindications or subtherapeutic response to acetaminophen, NSAIDs, or COX-2 inhibitors, a trial of tramadol should be considered. Therapeutic alternatives for analgesia are now limited to opioids or tramadol for S.L. Tramadol is a centrally acting analgesic that binds to the μ-opioid receptor and also inhibits the uptake of norepinephrine and serotonin.[29] The ACR recommends tramadol in those patients who have failed or have contraindications to NSAIDs.[7] Tramadol should not be used in patients with a history of seizures or receiving medications with

serotonergic activity and requires dose adjustment with diminished renal function.[29] A trial of tramadol should be based on the shared decision-making trial with emphasis on safety, tolerability, and impact on functional status. Opioids or opioid/acetaminophen combinations are generally not recommended for the treatment of chronic OA knee pain.

The risks of opioid medication use include the side effects such as constipation, confusion, hallucinations, respiratory depression, tolerance, and addiction. A recent Cochrane Review evaluated the use of oral and transdermal non-tramadol opioids in the treatment of OA of the hip and knee.[30] Although the findings did conclude that opioids are effective, their modest benefits are outweighed by their side effect profiles and should thus be avoided. Randomized, placebo-controlled studies have pointed to the efficacy and tolerability of transdermal buprenorphine with or without concurrent acetaminophen in the treatment of hip or knee OA, although long-term safety cannot be concluded at this time.[31,32]

DULOXETINE

Duloxetine, a serotonin and norepinephrine reuptake inhibitor, has been approved for the treatment of chronic musculoskeletal pain, in addition to several other indications.[33] In a 13-week randomized, double-blind, placebo-controlled trial involving 231 patients, duloxetine demonstrated statistically significant reductions in osteoarthritic pain of the knee.[34] The magnitude of difference in average pain between duloxetine and placebo in the reported mean end points and the mean change from baseline was modest, yet the tolerability and adverse effect profile of this medication are preferable to other potential treatment modalities. S.L. should be initiated on duloxetine for treatment of OA-related pain, and she should be counseled on the risk of transient headaches, nausea, and, less frequently, diarrhea. The initial dose of duloxetine in the treatment of OA of the knee is 30 mg once daily for 1 week, and then, if tolerated, titrated to 60 mg once daily. Liver transaminases are also recommended for periodic monitoring. Specific education

regarding expected treatment results should also be provided because the onset of analgesia with duloxetine may be delayed following initiation. Given her concurrent diagnosis of depression, her mood should be reassessed frequently during the transition.

Intra-articular Therapy

Ultimately, many patients fail oral or topical therapies; and IA injections represent the last conservative efforts before surgical intervention for OA of the knee. Aspiration of synovial fluid and injections of glucocorticoids or viscosupplementation of hyaluronic acid are strategies that have been offered to patients with severe knee OA. Injections of triamcinolone or methylprednisolone with lidocaine 1% have been shown to be effective for ~4 to 8 weeks. Typically, IA glucocorticoids are given no more frequently than every 3 months. Side effects include a paradoxical localized inflammatory reaction.[35]

The role of IA hyaluronic acid injections in the treatment of knee and hip OA is controversial. There is agreement that hyaluronic injections are recommended against in hip OA.[7] Less clear is their use in symptomatic knee OA and the conditional recommendation against use in the 2019 guidelines. The evidence for benefit in knee OA had been reported in earlier trials; however, these trials had been subject to substantial bias. Shared patient decision-making of the benefits and risks of therapy should allow for more informed treatment strategies.

Case 43-2, Question 5: Two years have passed, and S.L. has now failed all conservative strategies including IA injections into her knee. After discussing all of her options with her physician, S.L. is referred to an orthopedic surgeon for elective left total knee replacement. She is awaiting discharge from the acute care hospital, pending transfer to a short-term rehabilitation facility to facilitate her return to home, and resumption of her previous level of function. S.L.'s current medications are metoprolol succinate 50 mg daily, lisinopril 20 mg daily, enoxaparin 30 mg subcutaneously twice daily, oxycodone controlled release (CR) 10 mg every 12 hours, senna/docusate one tablet twice daily, and oxycodone/acetaminophen 5 mg/325 mg one tablet every 4 hours as needed

for moderate pain and two tablets every 4 hours as needed for severe pain. S.L. asks you, as the counseling pharmacist, why she still needs "shots in the belly." What do you tell S.L.?

The American College of Chest Physicians (ACCP)'s highest level of evidence for elective knee arthroplasty recommends low-molecular-weight heparin, fondaparinux, dabigatran, apixaban, rivaroxaban, or warfarin (international normalized ratio [INR] goal of 2.5) for patients in whom a risk of significant bleeding does not exist. A minimal duration of therapy is for 10 days after surgery and up to 35 days for some patients.[36] It is important to educate S.L. about this information; providing the reason for enoxaparin is to prevent blood clots in her legs or lungs. In cases in which the creatinine clearance is <30 mL/minute, the appropriate dosage of enoxaparin would be 30 mg subcutaneously once daily.[37]

Case 43-2, Question 6: How long will S.L. need oxycodone CR and oxycodone/acetaminophen therapy?

Most patients return to their home environments, and the use of as-needed dosing of immediate-acting opioid/acetaminophen combinations may be necessary for the completion of the short-term rehabilitation process. However, the long-term use of opioids in the treatment of chronic pain should be discouraged.

Comorbid Conditions in the Elderly

CASE 43-3

Question 1: L.P. is a 76-year-old female who was recently admitted to the hospital for elective right total hip replacement. She had failed all previous conservative interventions. Her medical history is significant for type 2 diabetes, hypertension, dyslipidemia, OA left knee and right hip, a right knee replacement 2 years ago, coronary artery disease, and history of MI 1 year ago. Medications include metformin 850 mg twice daily, lisinopril 20 mg daily, atorvastatin 40 mg daily, metoprolol succinate 100 mg daily, rivaroxaban 10 mg once daily with dinner, aspirin 81 mg once daily, celecoxib 200 mg once daily, and

oxycodone/acetaminophen 5 mg/325 mg one tablet every 4 hours as needed for right hip pain.

What are L.P.'s risks associated with COX-2 inhibitor use?

The risks associated with nonselective NSAID or COX-2 inhibitor use in older adults with comorbid coronary artery disease include increased BP, heart failure, and worse cardiovascular outcomes. In addition, diminished renal function and GI bleeding risks are relevant and require careful follow-up and monitoring. The lowest effective nonselective NSAID or COX-2 inhibitor dose for the shortest duration would possibly be recommended in situations where continued therapy is clinically indicated.

Case 43-3, Question 2: What clinically significant drug-drug interactions may be present involving L.P.'s deep venous thrombosis prophylaxis after her hip replacement surgery?

Caution is encouraged when combining medications to rivaroxaban that may increase the risk of bleeding.[38] In this case, L.P. requires aspirin for cardiovascular protection after the MI. In addition, celecoxib was added for pain management following hip replacement surgery. The addition of antiplatelet agents and NSAIDs to oral anticoagulant therapy increases the risk of bleeding. A careful evaluation of the risks and benefits of combination therapy would suggest discontinuation of the COX-2 inhibitor.

Dietary Supplements

Dietary supplements offer patients an alternative to prescription medications. Some patients often either fail multiple prescription drugs or have intolerable side effects. Others confuse dietary supplements with natural products and consider them safer than traditional medications. In the case of OA, the role of glucosamine, chondroitin, and the combination products has represented such an alternative for many patients. As with any OTC dietary supplement, the vigor of product consistency and standardization are not equal to

U.S. Food and Drug Administration (FDA) requirements for legend drugs. Researchers have found in evaluating the use of glucosamine, chondroitin, and the combinations in OA of the knee that they were all ineffective in reducing pain. The ACR recommends against the use of glucosamine or glucosamine/chondroitin combination products in OA of the knee or hip. However, in OA of the hand, the ACR suggests consideration on a patient-to-patient basis as a low-risk intervention.[7] More recently, a small, randomized placebo-controlled trial of 70 patients followed over 12 weeks were given 1000 mg of curcuma longa daily to determine the benefits in symptomatic knee OA and effusion synovitis.[8] The trial data showed modest-to-moderate improvements in pain. Larger studies would be needed before generalizing the results for larger populations.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Kloppenburg M, Kroon FPB, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis.* 2019;78(*1*):16–24. (6)

Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 ACR/AF guidelines for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* 2020;72(*2*):149–162. doi:10.1002/acr.24131 (7)

Geenen R, Overman CL, Christensen R, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. *Ann Rheum Dis*. 2018;77(*6*):797–807. doi:10.1136/annrheumdis-2017-212662 (9)

Bannuri RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr Cartil.* 2019;27:1578–1589. (12)

Key Website

Centers for Disease Control and Prevention. Osteoarthritis. https://www.cdc.gov/arthritis/basics/osteoarthritis.htm (1)

COMPLETE REFERENCES CHAPTER 43 OSTEOARTHRITIS

1. Centers for Disease Control and Prevention. Osteoarthritis. Accessed September 28, 2020. https://www.cdc.gov/arthritis/basics/osteoarthritis.htm
2. US Bone and Joint Initiative. The burden of musculoskeletal diseases in the United States (BMUS). Accessed September 8, 2020. https://www.boneandjointburden.org/fourth-edition/iiib10/osteoarthritis
3. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitations—United States, 2013–2015. *MMWR Morb Mort Wkly Rep*. 2017;66:246–253. Accessed September 8, 2020. doi:10.15585/mmwr.mm6609e1
4. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. *Arthritis Car Res*. 2016;68(12):1743–1750.
5. Felson DT, Neogi T. Osteoarthritis. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 20th ed. McGraw-Hill; Accessed September 29, 2020. https://accesspharmacy-mhmedical-com.wilkes.idm.oclc.org/content.aspx?bookid=2129&sectionid=192286042
6. Kloppenburg M, Kroon FPB, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis.* 2019;78(1):16–24.
7. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 ACR/AF guidelines for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2020;72(2):149–162. doi:10.1002/acr.24131
8. Wang ZW, Jones G, Winzenberg T, et al. Effectiveness of curcuma longa extract for the treatment of symptoms and effusion-synovitis of knee osteoarthritis. *Ann Intern Med*. 2020;173(11):861–869. doi:10.7326/M20-0990
9. Geenen R, Overman CL, Christensen R, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. *Ann Rheum Dis*. 2018;77(6):797–807. doi:10.1136/annrheumdis-2017-212662

10. Draganov P, Durrence H, Cox C, Reuben A. Alcohol-acetaminophen syndrome. Even moderate social drinkers are at risk. *Postgrad Med*. 2000;107:189–195.
11. Altman RD, Zinsenheim JR, Temple AR, Schweinle JE. Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomized, double-blind, placebo-controlled study. *Osteoarthr Cartil*. 2007;15:454–461.
12. Bannuri RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr. Cartil*. 2019;27:1578–1589.
13. Capsaicin. Drug facts and comparisons eFacts (online). Accessed September 21, 2020. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5550055?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3DCapsaicin%26t%3Dname%26va%3DCapsaicin%26nq%3Dtrue#coi-nested-0
14. Diclofenac Topical Gel. Drug facts and comparisons eFacts (online). Accessed September 21, 2020. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5550043?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Ddiclofenac%26t%3Dname%26va%3Ddiclofenac%26nq%3Dtrue
15. Simon LS, Grierson LM, Naseer Z, Bookman AAM, Shainhouse ZJ. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. *Pain*. 2009;143:238–245.
16. Tugwell PS, Wells GA, Zev Shainhouse J. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *J Rheumatol*. 2004;31:2002–2012.
17. Stanos S. Osteoarthritis guidelines: a progressive role for topical NSAIDs. *J Am Osteopath Assoc*. 2013;113:123–127.
18. Makris UE, Kohler MJ, Fraenkel L. Adverse effects of topical nonsteroidal antiinflammatory drugs in older adults with osteoarthritis: a systematic literature review. *J Rheumatol*. 2010;37:1236–1243.
19. Lohmander LS, Roos EM. Clinical update: treating osteoarthritis. *Lancet*. 2007;370:2082–2084.
20. Lanza FL, Chan FKL, Quigley EMM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104:728–738.
21. Barthelemy O, Limbourg T, Collet JP. Impact of non-steroidal anti-inflammatory drugs (NSAIDs) on cardiovascular outcomes in patients with stable atherothrombosis or multiple risk factors. *Int J Cardiol*. 2013;163:266–271.

22. Bennett JS, Daugherty A, Herrington D, Greenland P, Roberts H, Taubert KA. The use of nonsteroidal anti-inflammatory drugs (NSAIDs): a science advisory from the American Heart Association. *Circulation*. 2005;111:1713–1716.
23. Solomon DH. Selective cyclooxygenase 2 inhibitors and cardiovascular events. *Arthritis Rheum*. 2005;52:1968–1978.
24. Naproxen oral. Drug facts and comparisons eFacts (online). Accessed September 24, 2020. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5549220?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dnaproxen%26t%3Dname%26va%3Dnaproxen%26nq%3Dtrue#warning-nested-0
25. Nissen SE. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375:2519–2525. doi:10.1056/NEJMoa1611593
26. Kang DO, An H, Park GU, et al. Cardiovascular and bleeding risks associated with nonsteroidal anti-inflammatory drugs after MI. *J Am Coll Cardiol*. 2020;5(76):518–529.
27. Masso Gonzalez EL, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum*. 2010;62:1592–1601.
28. Diclofenac oral. Drug facts and comparison eFacts (online). Accessed September 28, 2020. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5549203?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Ddiclofenac%26t%3Dname%26va%3Ddiclofenac%26nq%3Dtrue#adr-nested-0-0
29. Tramadol oral. Drug facts and comparisons eFacts (online). Accessed September 28, 2020. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5549161?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dtramadol%26t%3Dname%26va%3Dtramadol%26nq%3Dtrue#pha
30. Nuesch E, Kasteler R, Husni E, Welch V, Rutjes AWS, Jüni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*. 2009;17(9):CD003115.
31. Conaghan PG, O'Brien CM, Wilson M, Schofield JP. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomised trial. *Osteoarthr Cartil*. 2011;19:930–938.
32. Munera C, Drehobl M, Sessler NE, Landau C. A randomized, placebo-controlled, double-blinded, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis. *J Opioid Manag*. 2010;6:193–202.

33. Duloxetine Hydrochloride Oral. Drugs facts and comparisons eFacts (online). Accessed September 28, 2020. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5549306?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dduloxetine%26t%3Dname%26va%3Dduloxetine%26nq%3Dtrue
34. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain*. 2009;146:253–260.
35. Bellamy N, Hari R, Rutjes AWS, Fischer R, Silletta MG, Reichenbach S, da Costa BR. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2006:CD005328.
36. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2, suppl):e278s–e325s. Accessed July 25, 2017. http://www.sciencedirect.com/science/article/pii/S0012369212601263?via%3Dihub. doi:10.1378/chest.11-2404
37. Barras MA, Duffull SB, Atherton JJ, Green B. Individualized dosing of enoxaparin for subjects with renal impairment is superior to conventional dosing at achieving therapeutic concentrations. *Ther Drug Monit*. 2010;32:482–488.
38. Davidson BL, Verheijen S, Lensing AWA, et al. Bleeding risk of patients with acute venous thromboembolism taking nonsteroidal anti-inflammatory drugs or aspirin. *JAMA Intern Med*. 2014;174(6):947–953.

44

Rheumatoid Arthritis

Janet S. Cho and Ying Wang

CORE PRINCIPLES		CHAPTER CASES
1	Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by potentially deforming polyarthritis and a wide spectrum of extra-articular manifestations. Diagnosis of RA is based on joint involvement, serology, acute-phase reactants, and symptom duration.	**Case 44-1 (Questions 1, 2)**
2	Treatments for RA include nonpharmacologic (heat or cold therapy, range-of-motion [ROM] exercises, physical therapy, and occupational therapy) and pharmacologic options (nonsteroidal anti-inflammatory drugs [NSAIDs], synthetic [conventional and targeted] and biologic disease-modifying antirheumatic drugs [DMARDs], and	**Case 44-1 (Questions 3–5)** **Case 44-2 (Question 1)** **Case 44-3 (Questions 1–3)**

	corticosteroids). NSAIDs are for symptom management only and must be used cautiously, if at all, because of serious health risks, including gastrointestinal complications and thromboembolic cardiovascular events.	
3	Owing to the destructive nature of the disease, DMARDs should be initiated as soon as possible once diagnosis has been established. Methotrexate is the most common selection because of efficacy, safety, rapid onset, and cost-effectiveness. Other traditional DMARDs and combinations of traditional DMARDs may be selected based on disease severity, the presence of poor prognostic indicators, and patient preferences. Regardless of the DMARD chosen, all require diligent monitoring.	**Case 44-3 (Questions 4–7)** **Case 44-4 (Questions 1–7)** **Case 44-5 (Questions 1–4)**
4	Patients with RA who experience an inadequate response to traditional DMARD monotherapy or intolerable adverse effects should consider the addition of or switching to a biologic DMARD or targeted synthetic DMARD. Diligent monitoring is also critical with biologic and targeted synthetic agents owing to the risk of serious adverse effects such as infections and lymphoma.	**Case 44-5 (Questions 5–7)** **Case 44-6 (Question 1)** **Case 44-7 (Questions 1, 2)**
5	Corticosteroids, when used judiciously at the lowest effective doses and for limited duration, are very effective at	**Case 44-8 (Questions 1, 2)**

	quickly controlling inflammation while awaiting onset of DMARD therapy. Although systemic corticosteroids can be prescribed for short-term flares of RA disease activity, intra-articular corticosteroid injections are very effective at managing flares that are limited to a few joints and are not associated with the adverse effects of systemic therapy.	
6	Juvenile idiopathic arthritis (JIA) describes an assortment of arthritis conditions affecting children and adolescents. Symptoms of JIA, such as joint inflammation and ROM limitation, are present before age 16 years. As in RA, the diagnosis of JIA is based on clinical manifestations, and all infectious, traumatic, and other etiologies must be ruled out.	**Case 44-9 (Questions 1, 2)**
7	Many nonpharmacologic treatment options are also available to supplement JIA pharmacologic therapy, including healthy age-appropriate diet, exercise, massage, and physical and occupational therapies.	**Case 44-9 (Question 3)**
8	Pharmacologic treatment options for JIA include NSAIDs, synthetic DMARDs, biologic DMARDs, Janus Kinase (JAK) inhibitors, corticosteroids, and cyclosporine A.	**Case 44-9 (Questions 4, 5)** **Case 44-10 (Question 1)** **Case 44-11 (Questions 1, 2)**

INTRODUCTION

Arthritis refers to more than 100 different joint diseases causing swelling, pain, and damage to joints and connective tissue.[1] Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis and is characterized by potentially deforming polyarthritis and a wide spectrum of extra-articular manifestations resulting from abnormal systemic immune response. It has an estimated worldwide prevalence of 0.24%, although rates vary between geographic regions.[2,3] In the United States alone, RA afflicts 1.3 million adults, occurring approximately two to three times more often in females than in males.[3,4] RA most commonly affects females between ages 30 to 60 years.[1] RA-associated morbidity, mortality, and disability will rise in future years, especially as the United States' baby boomer generation ages.[4]

ETIOLOGY

The exact etiology of RA is unknown, but like many autoimmune diseases, it involves an interplay of multiple factors including genetic susceptibility, environmental influences, and effects of advancing age on somatic changes in the musculoskeletal and immune systems.[3] The onset of RA likely starts years before clinical symptoms develop with activation of specific genes, resulting in innate immunity activity leading the cascade of events.[3] It is suspected that genetics contribute 50% to 60% of the risk of developing RA. The genes with the strongest implication include the *HLA-DRB1* gene of the major histocompatibility complex (MHC) and chromosome 1's *PTPN22* gene. Cigarette smoking increases the production of rheumatoid factor (RF) and anti–cyclic citrullinated peptide antibody (anti-CCP), clinical markers associated with RA, and has been shown to double the risk of developing RA.[5,6] Female sex hormones may also play a role in RA development. In females,

peak incidence occurs at the fifth decade, a time when many enter menopause or perimenopause. Estrogen is known to stimulate the immune system; pregnant patients often experience a remission of RA symptoms, and females who take oral contraceptives appear to be somewhat protected against the development of RA.[2,5] Diets rich in fish, olive oil, and other omega-3 fatty acid sources are associated with a lower risk of developing RA.[5]

PATHOPHYSIOLOGY

Pharmacologic therapy for RA targets components of the inflammatory cascade, which lead to persistent inflammation of the synovial lining and ultimately cause joint destruction.[7] This normally thin membrane proliferates and transforms into the synovial pannus. The pannus, a highly erosive enzyme-laden inflammatory exudate, invades articular cartilage (leading to narrowing of joint spaces), erodes bone (resulting in osteoporosis), and destroys periarticular structures (ligaments, tendons), resulting in joint deformities (**Fig. 44-1**).[7,8]

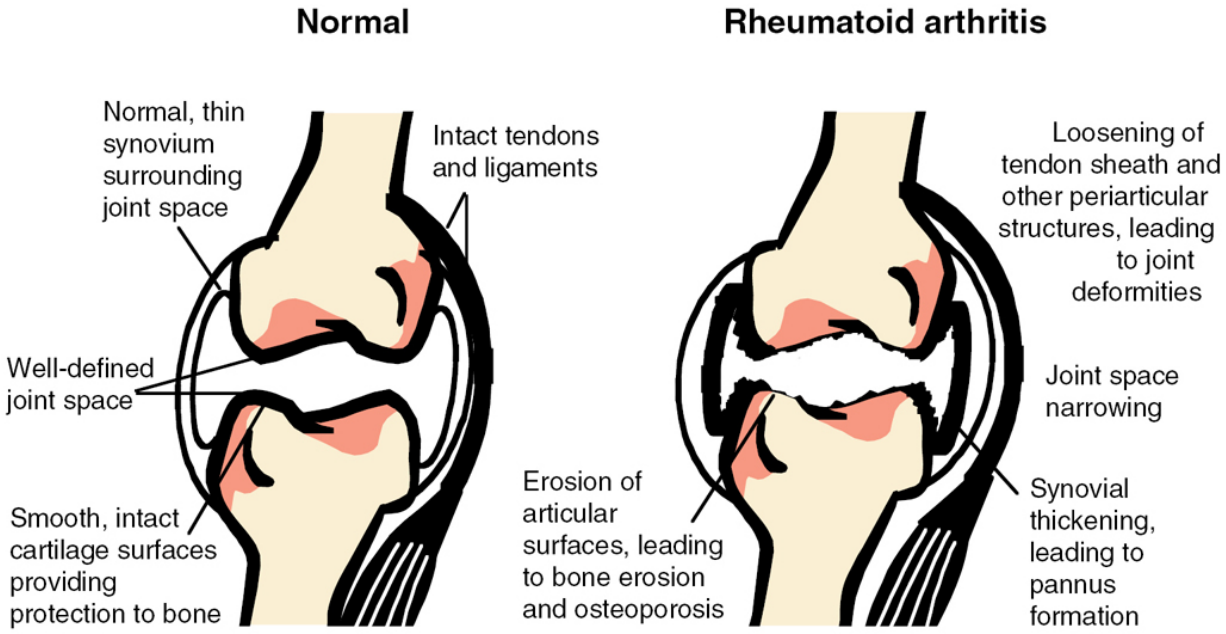
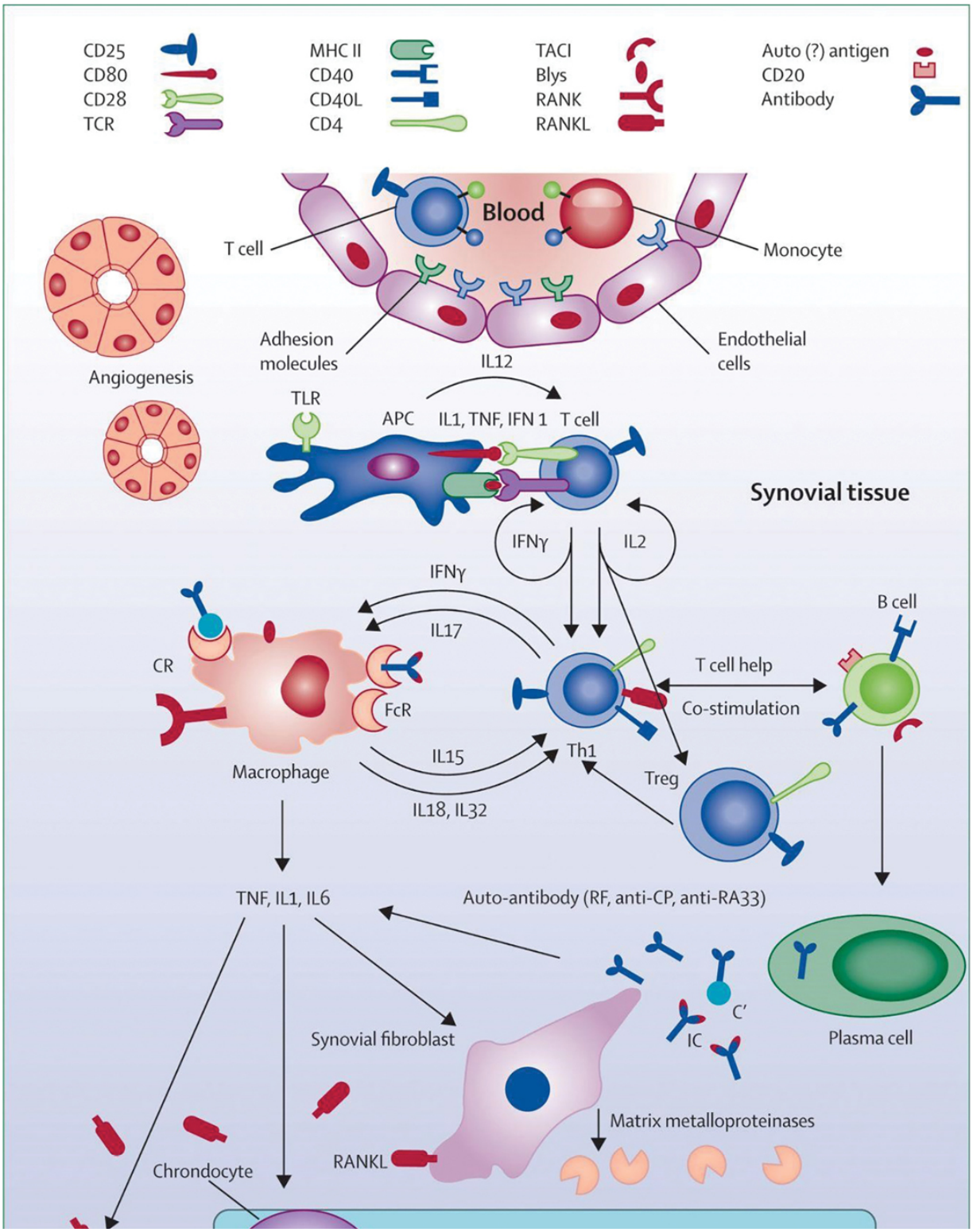


Figure 44-1 Overview of joint changes in rheumatoid arthritis.

Under normal circumstances, the body can distinguish between self (ie, proteins found within the body) and nonself (ie, foreign substances such as bacteria and viruses). On occasion, immune cells (T or B lymphocytes) can react to a self-protein while developing in the thymus or bone marrow. These developing cells are usually killed or inactivated before release from their place of formation; sometimes, however, a self-targeted immune cell can escape destruction and become activated years later to initiate an autoimmune response. When the activation source (ie, the self-targeted immune cell) reaches the joint, complex cell–cell interactions take place, leading to the pathology associated with RA.

The initiating interaction for an autoimmune response takes place between antigen-presenting cells (APCs), which display complexes of class II MHC molecules, and CD4-lineage T-cell lymphocytes (**Fig. 44-2**). In addition, B cells can become activated, leading to antibody formation (including RF and anti-CCP), pro-inflammatory cytokine production, and accumulation of polymorphonuclear leukocytes that release cytotoxins and other substances destructive to the synovium and joint structures. B cells also act as APCs, leading to T-cell activation and acceleration of the inflammatory process.[7,8] T-cell activation requires two signals: (1) an antigen-specific signal occurring when a class II MHC antigen molecule on an APC binds to a T-cell receptor and (2) binding of CD39 on the T cell to either CD80 or CD86 on the APC. T-cell activation leads to activation of macrophages and secretion of cytokines, polypeptides that serve as important mediators of inflammation, and cytotoxins, which can directly destroy cells and tissues. Pro-inflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α, stimulate both synovial fibroblasts and chondrocytes in neighboring articular cartilage to secrete enzymes that cause degradation of proteoglycan and collagen tissues. In healthy individuals, the inflammatory process is regulated by balancing the ratios of pro-inflammatory cytokines (eg, IL-1, IL-6, and TNF-α) with anti-inflammatory cytokines—for example, IL-1 receptor antagonist (IL-1Ra), IL-4, IL-

10, and IL-11. In the synovium of patients with RA, however, this balance is heavily weighted toward the pro-inflammatory cytokines, which results in sustained inflammation and tissue destruction.



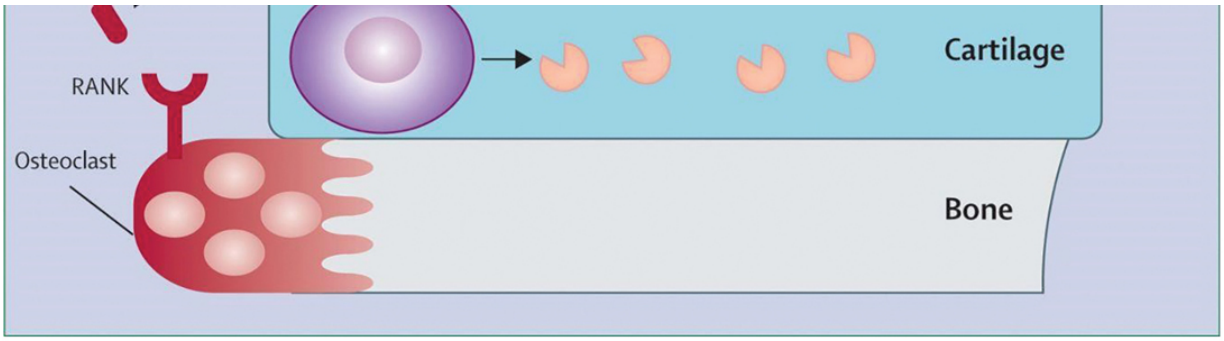


Figure 44-2 Current views on pathogenesis of rheumatoid arthritis. Arrows show some of many interactions in rheumatoid arthritis pathogenesis. Schematic depiction of events presumably occurring in synovial membrane, as well as articular cartilage and subchondral bone, which are surrounded by aggressive rheumatoid synovitis. Blys, B lymphocyte stimulator; C', complement; CP, citrullinated peptide; CR, complement receptor; FcR, receptor for the Fc portion of IgG; IC, immune complex; IFN, interferon; IFN1, type 1 interferon; IL, interleukin; RF, rheumatoid factor; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand interactor; TCR, T-cell receptor; Th1, T-helper 1 cell; TLR, toll-like receptor; Treg, regulatory T cell. (Reprinted from Smolen JS, Aletaha D, Koeller M, et al. New therapies for treatment of rheumatoid arthritis. *Lancet*. 2007;370(9602):1861–1874. © 2007 Elsevier. With permission.)

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) system are also involved in the pathogenesis of RA. JAKs are intracellular tyrosine kinases that bind and transmit signals from type 1 and type 2 cytokine receptors that eventually lead to cell formation, growth, and differentiation, and immune cell function. A variety of growth factors and cytokines (not including the TNF or IL-1 families) bind with type 1 and type 2 cytokine receptors, resulting in the phosphorylation of JAKs which activates STATs to translocate to the nucleus and modulate gene transcription. The JAK–STAT pathway facilitates cell signaling and plays a key role in immune-mediated inflammatory response.[9,10]

Clinical Presentation, Diagnosis, and Disease Course

CASE 44-1

Question 1: T.W., an otherwise healthy 42-year-old, 132.27-pound (60-kg) female, has been experiencing morning stiffness that persists for several hours, fatigue, and generalized muscle and joint pain for the past 4 months. In addition, she reports that her eyes seem red most of the time and are unusually dry. Her symptoms have been much worse during the past month and a half, causing her to limit her physical activities. She also can no longer wear her wedding ring because of swelling in her hand. Physical examination reveals bilaterally symmetrical swelling, tenderness, and warmth of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hands and the metatarsophalangeal (MTP) joints of the feet.

Pertinent laboratory findings include the following:

Erythrocyte sedimentation rate (ESR), 52 mm/hour (reference range: males 0–15 mm/hour, females 0–20 mm/hour)[11]
C-reactive protein (CRP), 2.1 mg/dL (reference range: 0–0.5 mg/dL)
Hemoglobin, 10.6 g/dL
Hematocrit, 33%
Platelets, 480,000/μL
Albumin, 3.8 g/dL
Serum iron, 40 μg/dL
Total iron-binding capacity, 275 mg/dL
Positive anti-CCP at 82 units (reference range: <20 units/mL)
Positive RF performed by latex fixation method in a dilution of 1:320 (reference range: <1:80)

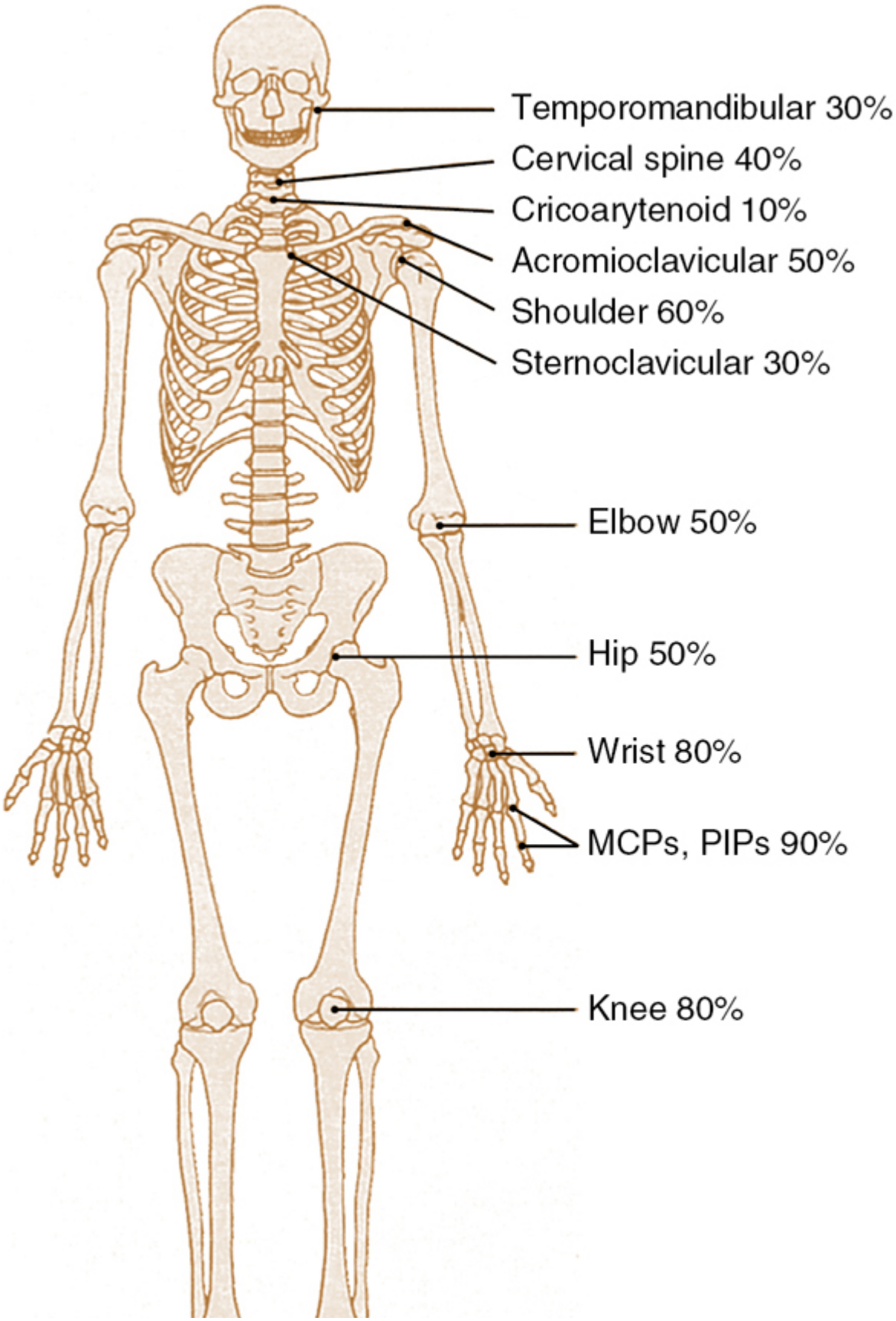
Tests for antinuclear antibodies (ANAs) and tuberculin sensitivity are negative. Her uric acid level is normal. Radiographic films of the hands and feet show soft tissue swelling, narrowing of joint spaces, and marginal erosions of the second and third MCP and PIP joints bilaterally with no evidence of calcification. Other routine laboratory data and physical findings are normal.

What signs and symptoms of RA are manifested by T.W.?

More than 50% of RA cases, like that seen in T.W., will have slow onset of symptoms over weeks to months, although up to 15% of patients experience acute-onset RA, with rapid development of symptoms over several days. Onset of symptoms may be either articular or systemic, including nonspecific symptoms such as

fatigue, weakness, muscle pains, weight loss, and low-grade fever. Joint involvement is characterized by soft tissue swelling and warmth, decreased range of motion (ROM), and sometimes muscle atrophy around affected joints. The most common symptoms include pain and stiffness in multiple joints. Classically, as illustrated by T.W., the presentation is symmetrical involving wrists, PIP joints, and MCP joints, although asymmetrical joint involvement also occurs with symmetry developing later in the disease course. The peripheral joints of the hands, wrists, and feet are usually involved first. Reflective of joint inflammation, patients usually experience prolonged morning stiffness on awakening lasting at least 30 to 45 minutes, but it can be present all day with decreasing intensity after arising.[12,13] Morning stiffness lasting for >1 hour rarely occurs in other diseases outside of RA.[14]

Ultimately, any or all of the diarthrodial joints (elbows, knees, shoulders, ankles, hips, temporomandibular joints, sternoclavicular joints, and glenohumeral joints) can be involved (**Fig. 44-3**). Progressive disease is characterized by irreversible joint deformities, such as ulnar deviation of the fingers (**Fig. 44-4**), boutonniere deformities (hyperextension of the distal interphalangeal [DIP] joint and flexion of the PIP joint), or swan neck deformities (hyperextension of the PIP joint and flexion of the DIP joint) (**Fig. 44-5**). Similar irreversible deformities can also involve the feet. Patients with more aggressive disease (multiple joint involvement, positive RF) have a greater than 70% probability of developing joint damage or erosions within 2 years of disease onset.[15]


Temporomandibular 30%
Cervical spine 40%
Cricoarytenoid 10%
Acromioclavicular 50%
Shoulder 60%
Sternoclavicular 30%
Elbow 50%
Hip 50%
Wrist 80%
MCPs, PIPs 90%
Knee 80%

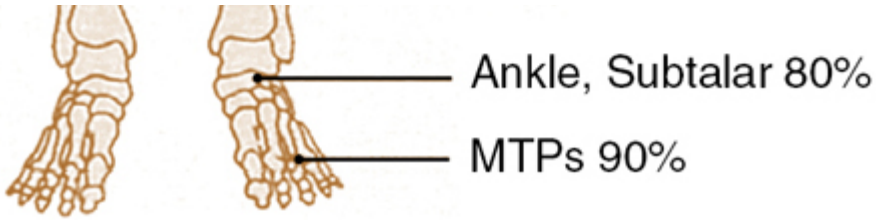


Figure 44-3 Frequency of involvement of different joint sites in established rheumatoid arthritis. MCPs, metacarpophalangeal joints; MTPs, metatarsophalangeal joints; PIPs, proximal interphalangeal joints.

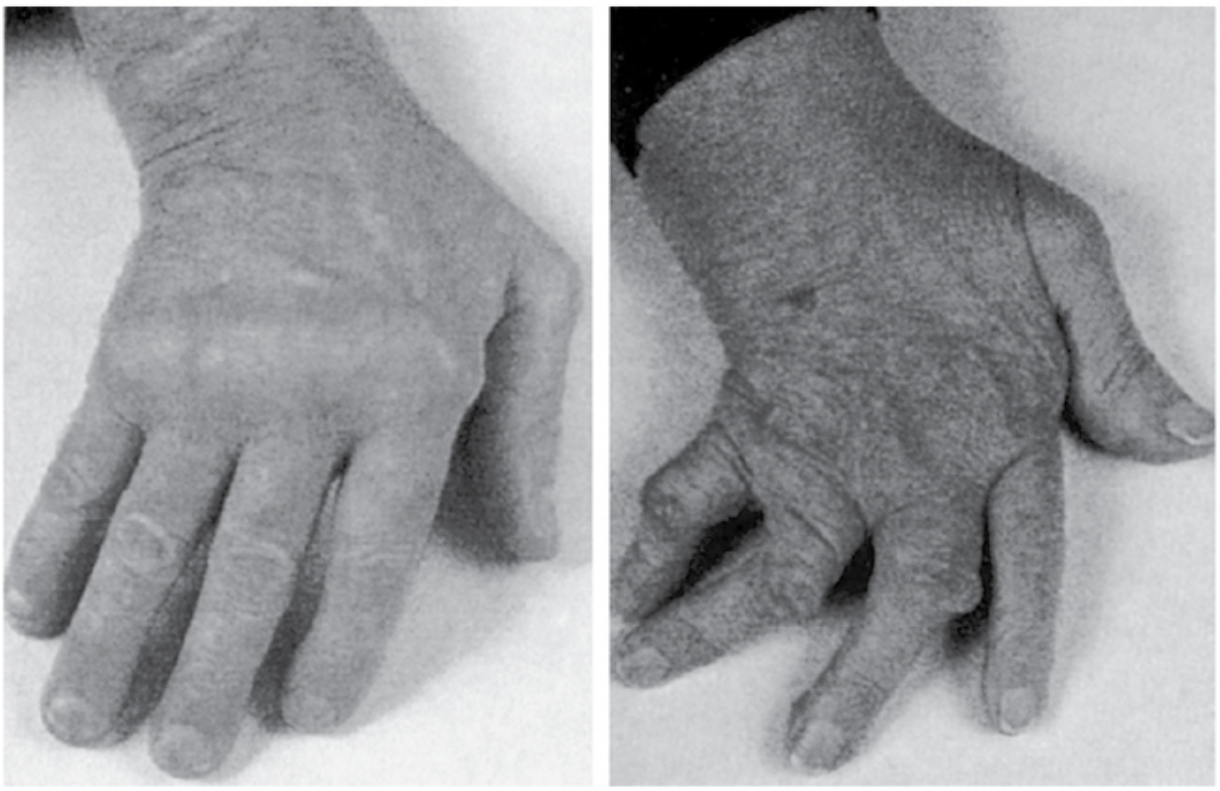


Figure 44-4 Ulnar deviation and metacarpophalangeal synovitis (left). This may progress to more marked lateral deviation with subluxation of the extensor tendons (right finger; right).

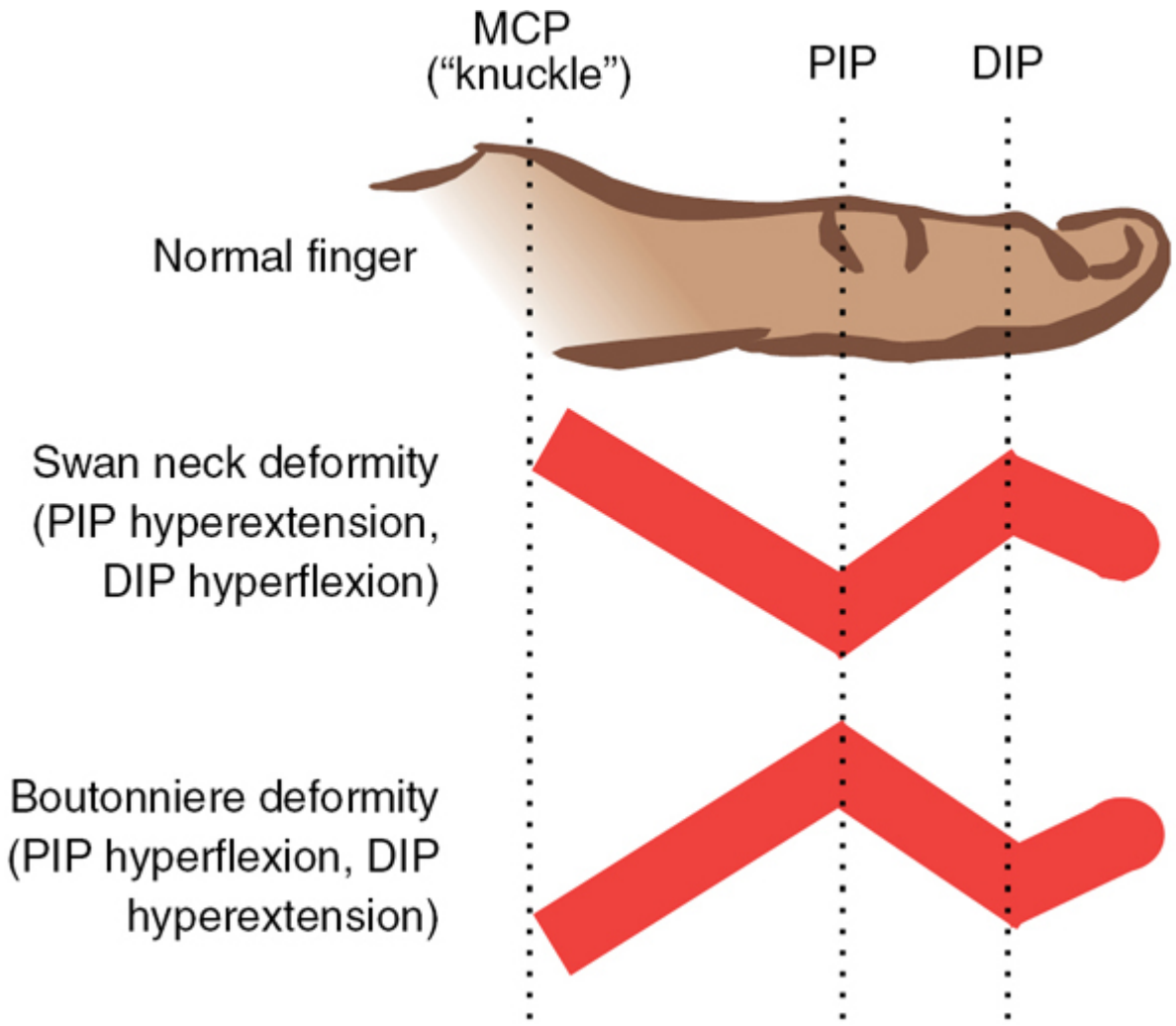


Figure 44-5 Characteristic finger deformities in rheumatoid arthritis. DIP, distal interphalangeal joint; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.

CASE 44-1, QUESTION 2: Which laboratory values in T.W. could be used to monitor her RA disease progression?

In 2010, the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) developed new classification criteria for RA. In comparison to criteria previously outlined in 1987, the intent of the new classification was to identify patients early in disease development so that therapeutic intervention can be initiated as soon as possible, ultimately decreasing disease progression and improving clinical outcomes.[16]

Diagnosis of RA is based on multiple clinical criteria. Individuals presenting with clinical synovitis (swelling) not explained by other differential diagnoses such as systemic lupus erythematosus, psoriatic arthritis, or gout, among others, should be tested for RA. RA criteria in the new classification system include quantifying joint involvement (higher scoring for small joints compared to large joints such as shoulders, elbows, hips, knees, and ankles) and symptom duration of 6 weeks or more. Other diagnostic criteria include the presence of autoantibodies (RF and/or anti-citrullinated peptide) and elevated acute-phase reactants (ESR or CRP).[13,16–18] Using a score-based algorithm based on these four categories, a summative score of 6 or more out of a total possible score of 10 suggests RA.[16]

Individually, each of the laboratory findings is characteristic for chronic systemic inflammatory disease with no test being specific for RA, although RF) and anti-CCP are more definitive than ESR or CRP.[11] Specifically, autoimmune diseases are frequently characterized by autoantibodies, with 50% to 80% of RA individuals having RF, anti-CCP, or both.[13,17,18]

RF, an IgM, or IgG autoantibody, abnormally reacts with the Fc portion of IgG to form an immune complex. It is found in 75% to 80% of patients with RA. It may also present in up to 5% of healthy individuals and in patients with diseases other than RA, including almost any condition associated with either immune complex formation or with hypergammaglobulinemia (eg, chronic infections, lymphoproliferative and hepatic diseases, systemic lupus erythematosus, and Sjogren syndrome). An RF titer of at least 1:160 is considered a positive test, and most patients with RA, such as T.W., typically have titers of at least 1:320.[11,19] Overall, RF is neither sensitive nor specific enough to independently diagnose RA, but it is found in the majority of patients and a higher titer early in disease generally correlates with increased disease severity and progression.[20]

Citrulline, a nonstandard amino acid, is also established as a key component of RA antigenicity and is more specific for RA than RF. Citrullinated proteins and anti-CCP antibodies are abundant in inflamed RA synovium. Anti-CCP antibodies can be detected in 50%

to 60% of patients with early RA, and the specificity of anti-CCP is very high at 90% to 95%.[11] Anti-CCP is present as early as 1.5 to 9 years before symptom presentation, suggesting a pathogenic role for these antibodies in RA.[21,22] A positive anti-CCP also correlates with an increased likelihood of a more erosive course of RA than either a negative anti-CCP or a positive RF. In summary, a positive anti-CCP antibody test is highly specific for RA, predictive of the development of RA, is a marker for an erosive disease course, and in combination with positive RF also correlates with 99.5% specificity for RA, making the likelihood of T.W. not having RA very minimal.[11,23]

The nonspecific markers for inflammation include ESR and CRP, but unfortunately, these acute-phase responses are also not disease-specific. T.W.'s hematologic findings are consistent with a mild anemia of chronic inflammation. Although her serum iron concentration is decreased, her normal iron-binding capacity makes a diagnosis of iron deficiency anemia unlikely. Her anemia probably results from a failure of iron release from the reticuloendothelial tissues and would not be expected to respond to iron therapy. The mild thrombocytosis is additional evidence of a systemic inflammatory response. The laboratory manifestations of inflammation should improve with effective drug therapy and, along with many of the clinical features of RA, are useful parameters for monitoring disease activity and response to therapy.

Finally, the negative test result for ANA rules out systemic lupus erythematosus in T.W. The ANA, however, can be positive in 10% to 70% of patients with RA.[16]

EXTRA-ARTICULAR MANIFESTATIONS AND COMPLICATIONS

The classic RA presentation involves joint findings; however, RA is a systemic disease reflected by accompanying extra-articular and organ system manifestations that, chronically, can occur in up to

46% of patients. These manifestations are also associated with higher disease activity,[24] and those with systemic involvement have higher mortality rates than those without, suggesting that early treatment may lower both the risk and severity of RA complications.[24,25]

Rheumatoid nodules occur in 15% to 20% of patients and are typically found on extensor surfaces, pressure points, and tendons. Pleuropulmonary manifestations include pulmonary nodules, fibrosis, and pleuritis; interstitial pneumonitis and arteritis of the pulmonary vasculature, although rare, can be potentially life-threatening. Vasculitis occurs infrequently, is more common in patients with long-standing and often severe disease. Complications include skin ulceration, peripheral neuropathy, and arteritis of organs.[12]

Some extra-articular manifestations occur as syndromes. Sjögren syndrome includes dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia), and connective tissue disease. T.W.'s eye symptoms may be an extra-articular manifestation of her RA. Felty syndrome is characterized by chronic arthritis, splenomegaly, and neutropenia; thrombocytopenia, anemia, and lymphadenopathy may also be present.[12]

Individuals with RA have a median life expectancy that is 3 to 10 years shorter than non-RA populations, with lower life expectancy associated with more severe disease.[5,26] The excess mortality has been attributed primarily to accelerated cardiovascular disease, responsible for one-third to one-half of deaths among adults compared with one-fourth to one-fifth of deaths among adults without RA. RA is associated with a twofold to threefold increased rate of myocardial infarction (MI), as well as lower MI survival. Management of cardiovascular risk includes annual cardiovascular risk evaluations for all patients, multiplying risk scores by 1.5 for patients with more than one marker of severe disease activity, use of statins and cardiovascular medications known to reduce cardiovascular risk, caution when prescribing nonsteroidal anti-inflammatory drugs (NSAIDs) owing to associated cardiovascular risk, and smoking cessation.[27] Lowering RA disease activity is also important to reduce

cardiovascular risk. Finally, pericarditis and myocarditis, although rare, may also occur.

Treatment

The treatment goals of RA are to maximize functional status through maintenance or improvement of symptoms (eg, joint pain and swelling), preserve joint function, and prevent deformity to ultimately improve quality of life and delay disability. Treatment to achieve low disease activity or remission (absence of disease activity) involves a combination of interventions. Early initiation of pharmacologic therapy starting at the point of diagnosis is critical to quality RA care.[28–30] Other supportive interventions include rest, exercise and physical therapy, occupational therapy, and emotional support. All patients with chronic diseases, such as RA, regardless of socially determined backgrounds should have equal access to treatment options in order to achieve optimal health outcomes.

Case 44-1, Question 3: What nonpharmacologic therapy should be included in the management of T.W.'s RA?

A balance of rest and physical activity can reduce inflammation and fatigue while improving muscle strengthening and flexibility. Restful and adequate sleep are particularly important in chronic, fatigue-inducing diseases such as RA. Therefore, T.W. should rest often especially when experiencing acute inflammation, but daytime rest periods should be limited to 30 to 60 minutes each as prolonged rest can also induce rapid losses in strength and endurance. Splinting of joints is typically prescribed throughout the day and night during periods of active inflammation, then only at night for several weeks after cessation of inflammation.[31]

Passive ROM exercises should be prescribed for T.W. because they minimize muscle atrophy and flexion contractures and maintain joint function without increasing inflammation or radiographic progression of the disease.[31,32] Regular low-impact aerobic

exercises, such as cycling, swimming, or walking, enhance muscle function and joint function.[33] Overall, physical and occupational therapies can provide valuable assistance to patients with compromised activities of daily living to maximize the potential for self-sufficiency. Some orthoses—medical devices secured to any part of a patient's body designed to support, immobilize, align, correct, or prevent deformity, or improve functioning—can reduce pain and inflammation or improve joint function in targeted joints for patients with RA.[34]

Finally, emotional support should be provided to all patients including T.W. As with all chronic debilitating diseases, the potential loss of independence, self-esteem, and employment, as well as altered interpersonal relationships with friends and family, can result in a twofold to threefold increase in depression.[35,36]

The expertise of different health care disciplines (eg, physical therapists, social workers, health educators, psychiatrists, clinical psychologists, podiatrists, vocational rehabilitation therapists, and pharmacists) should be consulted depending on T.W.'s needs. Pharmacists can monitor RA drug therapy for therapeutic and adverse effects under collaborative practice agreements with other practitioners and can counsel patients on proper medication use and clarify expectations.[37]

Cold treatments can be useful for acute pain and reduce inflammation; however, heat treatments can exacerbate pain and swelling and should be avoided during periods of active joint inflammation.[38]

Although symptoms of RA may be controlled by conservative management, more aggressive therapy is needed to prevent disease progression and disability. NSAIDs are often used to provide anti-inflammatory and analgesic effects. However, they do not prevent or slow joint destruction as compared to the disease-modifying antirheumatic drugs (DMARDs) and should be reserved for rapid symptomatic relief while awaiting DMARD onset of action. DMARDs alter long-term disease courses. As such, they are the mainstay of pharmacologic care and should be initiated in all patients as soon as they are diagnosed with RA.[28–30] Specific choice of treatment is

individualized based on joint function, degree of disease activity, patient age, sex, occupation, comorbidities, drug cost and coverage, prior therapies used, and patient preference. The two classes of DMARDs are synthetic compounds (sDMARDs) and biologic agents (bDMARDs). With the introduction of JAK inhibitors, EULAR has further subdivided sDMARDs into the conventional sDMARDs (csDMARDs) and targeted sDMARD (tsDMARD).[28,30]

The csDMARDs (eg, hydroxychloroquine [HCQ], sulfasalazine [SSZ], methotrexate [MTX], and leflunomide [LEF]) have demonstrated the ability to slow disease progression. These agents, alone or in combination, are considered as initial therapy for most patients and in the absence of any contraindications. MTX is the treatment of choice because of its strong efficacy and favorable safety profile. The tsDMARDs (eg, tofacitinib [TOF], baricitinib [BARI], and upadacitinib [UPA]) are considered for those with moderate-to-severe disease who have failed treatment with or are intolerant to TNF blockers.[39–41]

The bDMARDs target the physiologic pro-inflammatory and joint-damaging effects of inflammatory mediators, including TNF-α, IL-6, T cells, and B cells. Agents in this class include the TNF-α inhibitors (adalimumab [ADA], certolizumab pegol [CZP], etanercept [ETA], golimumab [GLM], and infliximab [IFX]), anti–B-cell therapy (rituximab [RXB]), IL-6 receptor antagonists (tocilizumab [TCZ] and sarilumab [SAR]), and the T-cell modulator (abatacept [ABT]). The bDMARDs are typically reserved for patients who fail to achieve an adequate response with csDMARD monotherapy.[30]

Corticosteroids are potent anti-inflammatory agents that slow the progression of joint damage in RA. However, long-term systemic use should be avoided because of serious adverse effects associated with chronic therapy. Short-term oral therapy may be reserved as bridge therapy in early RA with moderate-to-high disease activity while awaiting the onset of DMARD activity, brief periods of active disease, or with therapy failure.[30] Local intra-articular injections may be used for isolated joints experiencing disease flares.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

CASE 44-1, QUESTION 4: T.W. will be treated with a DMARD and concurrent NSAID therapy initially to rapidly control inflammation and swelling. What is the role of NSAIDs in the treatment of T.W.'s RA and which is the NSAID of choice?

NSAIDs have a long history of use in RA treatment. They are effective for providing short-term pain and inflammation control but do not alter disease course.[42] In addition, NSAIDs are associated with side effects related to cyclooxygenase (COX) inhibition such as gastrointestinal (GI) intolerance, nephrotoxicity, and increased risk of bleeding and cardiovascular events. The cardiovascular risk associated with some agents is particularly concerning because patients with RA are at higher cardiovascular mortality risk. Therefore, given both the safety profile and the lack of long-term disease-modifying efficacy, NSAID use should be reserved only as an adjunct to DMARD therapy.[42,43]

CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

With rare exception, every patient should receive csDMARD therapy soon after diagnosis to minimize loss of joint integrity, function, and risk of cardiovascular disease related to RA.[28,30] Although csDMARDs have the potential to cause serious toxicity, they can substantially reduce joint inflammation, reduce or prevent joint damage, maintain joint function and integrity, allow patients to remain productive, and ultimately reduce health care costs.[28–30] The onset of action of most csDMARDs is slow over 3 to 6 months; however, SSZ, MTX, and LEF can be beneficial within 1 to 2 months.[42] Several factors must be considered when selecting a csDMARD, including convenience of administration, monitoring requirements, medication and monitoring costs, time to therapeutic onset, and risk of severe adverse reactions.

MTX, a folate antimetabolite with immunomodulatory and anti-inflammatory properties, remains the mainstay first-line DMARD for

DMARD-naive patients with moderate-to-high disease activity because of its relatively rapid onset of action and excellent history of efficacy and safety.[28,30] LEF and SSZ are recommended if a contraindication to MTX is present, or if intolerance to MTX occurs. The primary metabolite of LEF, A77 1726 (M1), is responsible for nearly all of its pharmacologic activity. Although the exact mechanism of M1 is not completely understood, it is known that M1 inhibits dihydro-orotate dehydrogenase, an enzyme in cell mitochondria responsible for catalyzing an important step in de novo pyrimidine synthesis. SSZ appears to induce anti-inflammatory effects through one of its active metabolites, mesalamine, which is believed to inhibit both COX and lipooxygenase. HCQ may be considered for DMARD-naive patients with low disease activity, followed by SSZ, MTX, and LEF.[30] The mechanism of the anti-inflammatory effect of HCQ may be attributable to inhibition of migration of neutrophils and eosinophils, histamine and serotonin blockade, or inhibition of prostaglandin synthesis. Older csDMARDs such as azathioprine, cyclosporine, minocycline, and gold are no longer recommended because of the superior risk–benefit ratio of other csDMARDs, bDMARDs, and tsDMARDs.[29]

TARGETED SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Tofacitinib, baricitinib, and upadacitinib are Janus kinase (JAK) inhibitors, targeted molecules involved with inhibition of signal transduction pathways and are mechanistically different from the csDMARDs. These agents inhibit JAK enzymes that stimulate inflammatory cytokines; therefore, inhibition modulates leukocyte function and immune response. Because of increased safety concerns, they are only indicated for individuals with moderate-to-high disease activity who have had an inadequate response or intolerance to one or more TNF blockers.[30,39–41]

BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

In general, the bDMARDs are reserved for patients who have failed to respond to one or more csDMARDs alone or in combination. The ACR and EULAR guidelines recommend the use of bDMARDs in patients with moderate or high disease activity who are not at target taking maximally tolerated doses of MTX.[28,30] Since the late 1990s, more biologic agents have been approved for RA treatment. The earliest biologic agents targeted pro-inflammatory cytokines, such as TNF-α and IL-1, which play key roles in the immunopathogenesis of RA.[44] These cytokines are abundant in rheumatoid synovial tissues and fluid. Most cytokines can independently induce expression of the others, and IL-1 is capable of upregulating its own expression.[45] Excessive macrophage-produced cytokines (eg, TNF-α, IL-1, IL-6, and IL-8) correlate closely with RA disease activity and severity. Most importantly, RA improves when the physiologic action of TNF-α or several different ILs are suppressed. Newer agents have been developed to target additional key processes in RA, including T-cell costimulation, the depletion of $CD20^+$ B cells, and the inhibition of IL-6.[43]

The pro-inflammatory cytokine TNF-α is produced by activated macrophages and T cells in RA-affected joints. It also plays a role in keeping infections localized by increasing platelet activation and adhesion, resulting in local blood vessel occlusion and containment of infection. This action of TNF-α is responsible for its tumor necrosis properties, thus leading to the name. TNF-α exerts its physiologic effects by binding to two different cell-surface receptors known as p55 (ie, 55 kDa) and p75 (ie, 75 kDa) on inflammatory cells.[44] These receptors, with portions extending from within the cell cytoplasm to the cell exterior, are capable of binding TNF-α to the domains extending above the cell surface. Soluble forms of these receptors can be found in the serum and synovial fluid and seem to play a role in regulating TNF-α.

Two approaches have targeted the action of TNF-α: (1) the use of soluble TNF receptors with high TNF-binding affinity (ie, etanercept) and (2) antibodies against TNF-α (ie, infliximab, adalimumab, golimumab, and certolizumab pegol).[43] Etanercept is a recombinant TNF-receptor Fc fusion protein with the extracellular portion of two

p75 receptors fused to the Fc portion of human immunoglobulin G1 (IgG1).[46,47] Infliximab is a chimeric IgG monoclonal antibody directed against TNF-α, and adalimumab is a genetically engineered human IgG1 monoclonal antibody.[48,49] Certolizumab pegol is a polyethylene glycolated (PEG) Fab fragment of a humanized anti-TNF monoclonal antibody. Golimumab is a fully human anti-TNF-a IgG1 monoclonal antibody that targets and neutralizes both soluble and membrane-bound forms of TNF-α.[50,51] All five TNF-α inhibitors render TNF biologically unavailable and are highly effective in reducing RA disease activity. Currently, there is no conclusive evidence from well-controlled comparative trials that any one TNF-α inhibitor is superior to another with regard to efficacy and safety.[52] Comparative efficacy and safety will be discussed further in the section “Pharmacologic Treatment.” TNF-α inhibitor selection may be driven by cost, insurance coverage, provider preference, and patient-specific factors.

There are also four non-TNF biologic agents recommended for patients with RA who are not at target taking at least one csDMARD, which include abatacept, rituximab, tocilizumab, and sarilumab.[30] These agents possess a novel mechanism of action targeting T cells, B cells, or IL-6. Abatacept, tocilizumab, and sarilumab may be considered first-line biologic DMARDs along with the TNF-α inhibitors. However, rituximab should only be considered as a first-line bDMARD in the presence of certain contraindications (ie, recent history of lymphoma, latent tuberculosis [LTB] with contraindications to treatment, or history of demyelinating disease) to the other bDMARDs.[28] There is also one final bDMARD, anakinra, which is seldom used because of lack of comparative efficacy. Anakinra is a recombinant human interleukin-1 (IL-1) receptor antagonist, which inhibits the binding of cytokines IL-1a and IL-1b to their receptor.[43] Anakinra has not shown comparable efficacy against other bDMARDs in meta-analyses and is infrequently used, although some individuals may still respond to this agent.[28,29] Anakinra is no longer recommended in the ACR guidelines owing to lack of any new data as well as infrequent use in RA.[29]

Abatacept is a selective costimulation modulator that inhibits T-cell activation.[53] For T cells to be fully activated, a CD80/CD86:CD28 costimulatory signal is required.[54] This costimulation is blocked by cytotoxic T-lymphocyte–associated antigen 4. Abatacept is a soluble fusion protein consisting of extracellular cytotoxic T-lymphocyte–associated antigen 4 attached to the Fc portion of IgG1, which inhibits T-cell activation by preventing the binding of CD80 and CD86 ligands on the surface of APCs to the CD28 receptor on the T cell.[54]

Rituximab is a chimeric monoclonal antibody that binds to the CD20 antigen on the surface of pre-B cells and mature B cells, resulting in the depletion of B cells from peripheral blood, lymph nodes, and bone marrow.[55] Stem cells, pro-B cells, and antibody-producing plasma cells do not express CD20 and are not affected by RXB. The exact role of B cells in RA pathogenesis is not known. However, studies have shown that B cells may contribute to the autoimmune and inflammatory processes by producing RF, acting as APCs, activating T cells, and producing pro-inflammatory cytokines.[55] Owing to its chimeric composition, RXB must be administered with MTX to reduce the risk of human anti-chimeric antibody (HACA) formation.[56,57] Inhibition of T-cell activation and depletion of pro-inflammatory B cells result in significant reductions in RA-related inflammation and joint destruction.

Tocilizumab and sarilumab are humanized anti–IL-6 receptor antibodies. The pleiotropic pro-inflammatory cytokine IL-6 is produced by a variety of cell types including lymphocytes, monocytes, and fibroblasts and is involved in multiple immunologic processes, including T-cell activation and B-cell proliferation.[58,59] When bound to the soluble IL-6 receptor, IL-6 activates chemokine production and upregulates the expression of adhesion molecules. This leads to the recruitment of leukocytes at inflammatory sites, thus implicating IL-6 as an important factor in RA.[60,61] High levels of IL-6 have been found in the serum and joints of patients with RA. Additionally, IL-6 has been shown to induce the proliferation of osteoclasts, which may be a component of the bone degradation seen in RA.[60,61] TCZ and SAR are humanized, monoclonal antibodies that can bind to both membranous and soluble IL-6

receptors. This blockade prevents the interaction of IL-6 with the IL-6 receptor, thus interrupting the inflammatory pathways that contribute to the disease processes in RA.[60,61]

Owing to their immunosuppressive nature, all bDMARDs and tsDMARDs should be avoided in patients with serious infections until the infection has been controlled. All carry boxed warnings for serious infections. Although these infections occurred primarily among patients with significant risk factors for infection (eg, poorly controlled diabetes, concurrent corticosteroid use, or concomitant csDMARD therapy), these agents should not be given to patients with active infection, and cautiously given to patients with a history of recurring infections or medical conditions predisposing them to infection.[62] It is recommended that all patients be screened for latent tuberculosis infection (LTBI) prior to initiation of a bDMARD or tsDMARD. If LTBI is identified, patients should receive at least 1 month of treatment prior to starting a bDMARD or tsDMARD. Patients with active TB should complete treatment prior to initiation of a bDMARD or tsDMARD. Patients should be monitored for active TB during treatment.[29]

It is recommended that patients receive the following vaccinations prior to the initiation of csDMARD, tsDMARD, or bDMARD therapy: pneumococcal, influenza, hepatitis B, human papillomavirus, COVID-19, and herpes zoster. However, if not completed prior to the initiation of therapy, these vaccinations may be given following the initiation of csDMARDs, tsDMARDs, or bDMARDs. Live vaccines should not be administered in patients receiving bDMARDs or tsDMARDs.[29]

CORTICOSTEROIDS

Corticosteroids can be used as needed at disease onset while awaiting response to DMARD therapy and intermittently during disease flare-ups or following failure of optimized treatment to control symptoms of pain and swelling. Corticosteroids have a long history of use in RA because of their potent anti-inflammatory and immunosuppressive effects and have been shown to enhance the

clinical, functional, and structural efficacy of baseline csDMARD or combination csDMARD and bDMARD therapies.[28] Corticosteroids administered orally at low dosages or through local injections are effective in rapidly reducing disease activity and relieving RA symptoms.

Corticosteroids are particularly beneficial when patients are awaiting the onset of DMARD action (known as “bridge therapy”) or during flares of active RA involving a small number of joints.[30,63] Oral corticosteroids seem to slow the rate of disease progression and have been shown to reduce radiographic changes for 1 to 2 years.[38,63,64] Use of corticosteroids in combination with DMARD therapy appears to improve clinical outcomes (signs and symptoms, functionality, radiologic damage) for patients with RA above the benefit of a DMARD used alone.[38,63,64] In addition, newer modified-release corticosteroids targeting nocturnal increases in inflammatory mediators, IL-6 and cortisol, have demonstrated a reduction in morning stiffness compared with older, standard immediate release agents.[65–67] Long-term use of corticosteroids, however, is associated with many serious adverse effects (eg, osteoporosis, weight gain, diabetes, cataract formation, adrenal suppression, hypertension, infections, and impaired wound healing).[68] As a result, oral corticosteroid dosing should be limited to daily doses of ≤10 mg of prednisone (or equivalent) and should be administered for as short a time as possible.[30] Frequent corticosteroid injections for an extended period have the potential to accelerate bone and cartilage deterioration; therefore, the same joint should not be injected more than once every 3 months.[68]

CLINICAL USE OF DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

DMARD treatment should be started as soon as possible following RA diagnosis with a treatment goal of low disease activity or remission. MTX remains the gold standard because of high response rate, mild side effect profile, low cost, and long sustained efficacy not just as monotherapy but also in combination with glucocorticoids,

other csDMARDs, bDMARDs, and tsDMARDs.[28–30] Furthermore, MTX therapy is associated with a reduction in cardiovascular morbidity and mortality in patients with RA, important given the strong association between RA and cardiovascular disease.[27] Optimization of MTX therapy also involves appropriate dose titration, adequate trial duration, and folate supplementation.

In the setting of moderate or high disease activity unresponsive to csDMARD monotherapy, ACR guidelines conditionally recommend the addition of bDMARD or tsDMARD over csDMARD combination therapy.[30] Combination csDMARD therapy may be considered based on patient preference as an alternative for patients who fail to reach treatment goals on a single csDMARD. Similarly, EULAR recommends when failure to achieve RA treatment target with the first csDMARD, in the setting of poor prognostic features (ie, functional limitation, extra-articular disease, positive RF or anti-CCP, and bony erosions), a bDMARD or tsDMARD should be added to the RA treatment regimen.[28] However in the absence of poor prognostic features, EULAR recommends the patient trial another csDMARD(s) (ie, LEF, SSZ, and/or MTX as mono- or combination therapy).

ACR and EULAR give no preference to any bDMARD or tsDMARD over another, except in certain clinical scenarios. Non-TNF inhibitor bDMARD or tsDMARD are conditionally recommended for patients with New York Heart Association (NYHA) class III or IV heart failure.[28–30] Rituximab may be considered as a first-line bDMARD in patients having certain contraindications to other bDMARDs such as recent lymphoma, because this agent is not associated with malignancy.[69–71] It is preferred that the bDMARDs be used in combination with either MTX or other csDMARDs rather than as monotherapy.[30] However, if a patient truly cannot be treated with csDMARDs, consideration may be given to monotherapy with etanercept, adalimumab, certolizumab pegol, abatacept, tocilizumab, or sarilumab.

If a patient has an inadequate response to the initial bDMARD or tsDMARD trial, switching to another from a different class is warranted. There is no preferred step-up bDMARD or tsDMARD and choice is dependent on patient-specific factors. Although the ACR

and EULAR guidelines do not currently provide recommendations for choosing between a bDMARD versus a tsDMARD (JAK inhibitors), recent safety data requiring a boxed warning in the prescribing information for tsDMARDs may favor the use of TNF inhibitors before tsDMARDs. Ultimately, shared decision-making is advised between a patient and their prescriber after reviewing the benefits and risks of JAK inhibitors, particularly in patients who cannot use or continue to use TNF inhibitors.[39–41]

QUANTIFYING RESPONSE TO DRUG THERAPY

RA low disease activity or remission is the highest aim of therapy and has become more realistic as medications capable of halting or slowing disease progression are now widely available and commonly used in clinical practice. Therefore, it is critical for all patients to have equal access to the medications available. The ACR and EULAR consider patients with RA in clinical trials to have achieved remission if either of the following occurs: (a) tender joint count, swollen joint count (of 28 joints), CRP in mg/dL, and patient global assessment scores (scale of 0–10) are all <1 (per Boolean-based definition) or (b) Simplified Disease Activity Index (SDAI) is ≤3.3.[38] If disease remission is unattainable, then minimizing disease activity to provide pain relief, maintain activities of daily living, maximize quality of life, and slow joint damage become primary targets.

In active disease, successful implementation of the treat to target approach requires reevaluation of pharmacologic therapy every 1 to 3 months. Therapy adjustment no later than 3 months into the treatment course is warranted because if there is no improvement by this time then it is unlikely that continuing the same course will achieve satisfactory results. Once treatment targets have been achieved, monitoring may occur less frequently. In patients with good response, glucocorticoids should be the first medications tapered and withdrawn, and if remission is sustained, then tapering and discontinuing DMARD therapy (all types) may be considered.[30] This is a conditional ACR recommendation; although the quality of evidence supporting this recommendation is low in terms of the risk

of disease exacerbation/recurrence, the long-term risk and cost of continuing therapy that is potentially unnecessary makes this a valid consideration.

Evaluating treatment response using validated clinical assessment tools yields a more accurate assessment of disease activity and improves the likelihood of attaining disease remission through modifications of drug therapy.[72,73] ACR has defined response criteria; however, these are designed for clinical research and may not be practical for clinical practice.[74] Although there is no single tool adopted as the standard of practice in the clinical setting, there are various other validated assessment tools that are advantageous for objectively evaluating disease activity and tracking disease progression.

- Disease Activity Score in 28 joints
- Simplified Disease Activity Index
- Clinical Disease Activity Index
- RA Disease Activity Index
- Patient Activity Scale (PAS) or PASII
- Routine Assessment Patient Index Data

These tools use various combinations of 28-tender joint count, acute-phase reactant measures, pain and function assessments, and patient and physician global assessments of disease activity to determine disease activity. For example, the Clinical Disease Activity Index (CDAI) and the SDAI scores are determined through a simple sum of swollen joint count, tender joint count, patient global disease activity, and evaluator global disease activity (both measured by a visual analog scale). However, the SDAI includes CRP in the summation, whereas the CDAI does not.[75] It is important to note that all of these tools have distinctly defined threshold scores corresponding to high disease activity, moderate disease activity, low disease activity, and remission, although there is little agreement among the tools in terms of classifying a patient's RA activity level. Choice of tool is typically practice-specific.

The scoring tools listed above should be used in conjunction with radiographic evaluation to determine RA course and treatment strategy. Conventional radiography was previously considered the gold standard, but imaging via computed tomography, ultrasound, and magnetic resonance imaging is now available and may offer some benefit in improved resolution compared with standard radiograph technology.[76] Radiographic changes occur in more than half of patients categorized in remission and tracking these can help clinicians objectively evaluate arthritis-related joint damage.[77]

Pharmacologic Treatment

NONSTEROIDAL ANTI-INFLAMMATORY DRUG THERAPY

T.W.'s clinical presentation clearly warrants DMARD therapy (see Case 44-3, Question 4, and Clinical Use of Disease-Modifying Antirheumatic Drugs section). The purpose of NSAID therapy, which has no disease-modifying activity, is to provide rapid pain relief and reduction of joint inflammation primarily as bridge therapy while awaiting the onset of DMARD activity, which could take weeks to months.[43] In general, there is no NSAID of choice for the treatment of RA.[15,78] There is no significant difference among the NSAIDs in efficacy, and it is difficult to predict a given patient's response to a particular agent. The selection of an NSAID is based primarily on patient preference, convenience, cost, and safety.[43,79] A 1- to 2-week trial of any NSAID at a moderate-to-high dose on a scheduled basis (ie, not as needed) is the best method of determining anti-inflammatory efficacy. The analgesic and antipyretic effects are relatively prompt in onset.

NSAIDs have important differentiating properties, and individualizing selection based on these characteristics is warranted in all patients such as T.W.[78] For example, several NSAIDs increase the risk of MI, with diclofenac, meloxicam, and indomethacin showing the highest risk of thrombosis, although celecoxib and ibuprofen at high doses also carry relatively high cardiovascular risk. Naproxen appears to have the best cardiovascular safety profile.[80,81]

Longer-acting NSAIDs such as piroxicam and ketorolac have been associated with a higher frequency of peptic ulcer disease and GI bleeding and should be avoided. Other NSAIDs, depending on their COX-2 selectivity, have varying GI toxicity profiles with naproxen conferring moderate risk and ibuprofen lower risk.[82,83] The selective COX-2 inhibitor celecoxib, at least with short-term use, is associated with a 20% lower risk of GI bleeding than traditional NSAIDs.[84] Because this agent does not interfere with COX-1—the isozyme responsible for production of the stomach's mucous lining and for reduced acid secretion—in theory COX-2 inhibitors reduce inflammation as effectively as nonselective NSAIDs while reducing the risk of GI toxicity. However, concurrent daily low-dose aspirin use appears to negate any benefit of COX-2 inhibitor therapy on lowering ulcer risk.[85]

Indomethacin penetrates the blood–brain barrier better than any other NSAID, achieving levels in the cerebrospinal fluid of up to 50% of serum levels. As a result, the incidence of central nervous system side effects of indomethacin such as dizziness often precludes the use of optimal anti-inflammatory doses, particularly in the elderly.[86]

A low-cost NSAID (eg, naproxen and ibuprofen) with a good safety profile is a good choice for T.W. because she is relatively young and does not have any concomitant illnesses. If convenience of administration is a more important consideration, a longer-acting NSAID (eg, naproxen) would be preferable. If the first agent chosen is ineffective or not well tolerated, other NSAIDs can be tried to identify the optimal one for this patient.

Case 44-1, Question 5: Naproxen 500 mg twice daily has been prescribed for T.W. If T.W. were to experience dyspepsia during therapy, should she be given antiulcer prophylaxis or a COX-2 selective NSAID at this time? What is the correlation between dyspepsia and gastroduodenal mucosal injury? What instructions regarding NSAID therapy should be provided to T.W., especially with regard to GI problems?

Patients should be informed that NSAID therapy is being prescribed to provide relief of pain and inflammation associated with

RA, but that it will not slow or stop the progression of the disease. It should be explained that the latter can only be accomplished by DMARD therapy. Patients should also understand that moderate-to-high daily doses of NSAIDs are required for anti-inflammatory activity, as opposed to analgesic and antipyretic effects which can be achieved with single and low doses.

About 5% to 15% of patients with RA discontinue NSAID therapy because of dyspepsia, and about 1.3% of patients taking NSAIDs for RA experience a serious GI complication. As expected, the rate is somewhat lower for patients using NSAIDs for osteoarthritis (0.7%) because these patients generally use analgesics only on an as-needed basis. Serious NSAID-induced GI complications account for >100,000 hospitalizations annually in the United States and ~16,500 NSAID-related deaths each year.[83,87] Although these figures warrant concern, most patients who experience NSAID-induced dyspepsia suffer only superficial and self-limiting injury. Nevertheless, prevention of NSAID-induced GI bleeding should be an important focus, particularly in high-risk patients.

Patients should be taught to recognize the signs and symptoms of GI bleeding (eg, nausea, vomiting, anorexia, and gastric pain) including melena (described to the patient as “dark, tarry stool”) and emesis of coagulated blood (described to the patient as “coughing or vomiting up what seems to be coffee grounds”). It should be emphasized that GI bleeding can occur without gastric pain. The patient should be instructed to contact their health care provider immediately for further instructions if any of these signs or symptoms occur.

Gastroduodenal mucosal damage induced by NSAIDs primarily results from inhibition of COX-1 in the mucosal lining.[87] This inhibition of COX-1 decreases bicarbonate secretion, mucosal blood flow, formation of protective mucus, proliferation of gastric epithelium, and the ability of the mucosa to resist injury. Topical damage to the GI mucosa can occur from NSAIDs, but direct injury plays a smaller role than COX-1 inhibition.

Dyspepsia can be managed by ingesting the NSAID with meals or a large glass of water; however, these measures usually are

ineffective in preventing GI ulcers. In addition, dyspepsia correlates poorly with endoscopically confirmed mucosal injury.[87–89] Histamine type 2 (H_2) receptor antagonists (eg, ranitidine, famotidine) significantly reduce dyspepsia among NSAID users; however, NSAID users with RA who take an H_2-receptor antagonist as needed might have a higher risk of developing serious GI complications compared with those who do not take these medications (odds ratio, 2.14; 95% confidence interval, 1.06–4.32).[90] The suppression of dyspepsia symptoms can give a false sense of security to the patient and physician, leading to higher doses of NSAIDs and increased risk of major gastropathy. Also, routine use of H_2-receptor antagonists is associated with tachyphylaxis.[91] Therefore, H_2-receptor antagonists are not recommended for routine use in asymptomatic patients receiving NSAIDs. Proton-pump inhibitors (PPIs; eg, lansoprazole, omeprazole) relieve dyspepsia better than H_2-receptor antagonists and prevent the development of NSAID-induced gastroduodenal ulcers.[90,92] They are safe and effective for the treatment of NSAID-induced dyspepsia and should be considered if symptoms develop in T.W.

Effective prevention options for reducing the risk of NSAID-induced ulcers and related complications include a PPI, double the dose of H_2-receptor antagonists, and misoprostol. PPIs are the most efficacious and best tolerated co-therapies with NSAIDs to reduce the risk of peptic ulcers and ulcer complications. Double doses of H_2-receptor antagonists have demonstrated a reduction in NSAID-induced endoscopic peptic ulcers; however, no study has demonstrated that double-dose H_2-receptor antagonists prevent ulcer complications and PPIs remain significantly more effective. Misoprostol, a prostaglandin E_1 analog, is most effective when given at the full dose of 200 μg four times daily; however, intolerable GI upset, particularly diarrhea and abdominal cramping, frequently leads to discontinuation of therapy at this dose. Lower doses are usually prescribed (200 μg two or three times daily) with better

tolerance but lower efficacy. Sucralfate or antacids are not effective in preventing NSAID-related GI injury.[92]

Routine concomitant antiulcer prophylactic therapy is not warranted for all patients taking NSAIDs; rather the risk for GI ulcer development must be assessed to determine the need for preventive measures. Established risk factors for NSAID-induced GI bleeding include advanced age (>65 years), history of ulcers and/or upper GI bleeding, concurrent use of antiplatelets, anticoagulants, corticosteroids and/or selective serotonin reuptake inhibitors, high-dose NSAID therapy, cigarette smoking, and/or alcohol consumption. Patients can be grouped into high, moderate, or low risk of NSAID-induced GI toxicity based on these risk factors. High-risk patients (>2 risk factors) should avoid NSAID therapy or take a COX-2 inhibitor instead along with either a PPI or a misoprostol. Moderate-risk patients (one or two risk factors) should take a PPI or misoprostol with an NSAID; naproxen is the preferred NSAID for high–cardiovascular-risk patients. Low-risk patients (no risk factors) do not need concurrent GI protective therapy and should receive a relatively less GI toxic NSAID at the lowest effective dose.[92] Without risk factors other than NSAID use, T.W. does not need concurrent ulcer prophylaxis or a COX-2–selective NSAID at this time, although a less toxic agent such as naproxen or ibuprofen should be chosen.

CASE 44-2

Question 1: R.Z. is a 28-year-old female who is planning a pregnancy and is concerned about the possible effects of NSAIDs on her baby.

What are the risks to the fetus with uninterrupted consumption of NSAIDs? What are maternal- and lactation-related effects of these medications?

Although NSAIDs, including aspirin, are not teratogenic, they must be used cautiously in females who are pregnant and who plan to breastfeed infants.[93] Fetal effects of NSAIDs include possible premature ductus arteriosus closure, increased cutaneous and intracranial bleeding, transient renal impairment, and a reduction in urine output. High doses of aspirin (>3 g/day) and NSAIDs can

inhibit uterine contractions, resulting in prolonged labor. The use of NSAIDs can also increase peripartum blood loss and anemia. Aspirin and nonaspirin NSAIDs should be used sparingly and at the lowest effective doses during pregnancy and discontinued at least 6 to 8 weeks before delivery to minimize adverse fetal and maternal effects.

Aspirin generally should be avoided for females who plan to nurse their baby because salicylate serum concentrations in breast-fed neonates raise concerns about the potential for metabolic acidosis, bleeding, and Reye syndrome. Nonaspirin NSAIDs are generally compatible with breast-feeding, with the best evidence supporting the use of ibuprofen, indomethacin, and naproxen.[94,95]

CASE 44-3

Question 1: T.Z., a 68-year-old male with heart failure previously managed with furosemide 40 mg/day, digoxin 0.125 mg/day, metoprolol 50 mg twice daily, and lisinopril 40 mg/day, returns for a prescription refill of ibuprofen 600 mg three times daily, which he takes for his RA. During the past 2 weeks, he has noted increased leg swelling, a weight gain of several pounds, exacerbated shortness of breath, and easy fatigability.

Why might these signs and symptoms be associated with ibuprofen use?

Mild fluid retention occurs in ~5% of NSAID users, and NSAID-induced kidney disease occurs in <1% of patients.[94,95] NSAID therapy should be avoided, if possible, in patients with preexisting heart failure, kidney disease, or cirrhosis.[96] If a patient with these conditions requires NSAID therapy, or patients are taking angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, serum creatinine should be checked soon after NSAID initiation. Inhibition of COX by NSAIDs within the kidney reduces prostaglandin concentrations and unopposed vasoconstriction. Consequently, urine output declines, serum blood urea nitrogen and serum creatinine levels rise, and fluid is retained. In addition, ibuprofen at higher doses is associated with an increased risk of MI, a concern for T.Z. because of his risk of thrombotic cardiovascular events.[80] The provider of T.Z.'s cardiovascular care should be

informed of his symptoms of fluid overload, and an alternative to NSAID therapy should be pursued.

Case 44-3, Question 2: If NSAID therapy is discontinued, what analgesic or anti-inflammatory alternatives are there for T.Z.? What other renal syndromes are associated with NSAID use?

Although celecoxib has been associated with a slightly lower risk of death and heart failure exacerbation when compared with traditional NSAIDs, it is not a reasonable initial option for T.Z. because celecoxib is also associated with an increased risk of MI and it may contribute to worsening of heart failure.[97]

NSAIDs should be used at their lowest effective doses for minimal periods for T.Z. High-dose NSAIDs should be avoided owing to increased MI risk. Although acetaminophen is not an anti-inflammatory agent, it can provide analgesic relief. Intra-articular corticosteroid injections can be useful if inflamed joints are limited in number, or a short course of oral corticosteroids can provide rapid control of inflammation while reducing the need for longer courses of NSAID therapy. If T.Z. is not yet being treated with a DMARD, initiation should be considered immediately because disease-modifying therapy can eventually preclude T.Z.'s need for an NSAID. If an NSAID or short course of systemic corticosteroid is used, close monitoring of renal function and fluid retention status is warranted.

In addition to acute renal failure, NSAIDs can induce various adverse renal effects (eg, nephrotic syndrome, interstitial nephritis, hyponatremia, abnormalities of water metabolism, and hyperkalemia).[98] The nephrotic syndrome, unlike NSAID-induced acute renal failure, can appear anytime (ie, from days to years) after initiation of therapy and can resolve as quickly as 1 month, or as long as 1 year, after discontinuation of the NSAID. Hematuria, pyuria, and proteinuria without prior renal disease differentiates nephrotic syndrome from other NSAID-induced renal problems. Histologically, NSAID-induced nephrotic syndrome is characterized by interstitial lymphocytic infiltrates, vacuolar degeneration of

proximal and distal tubules, and fusion of epithelial foot processes of glomeruli.

Prostaglandin-mediated inhibition of active chloride transport, regulation of medullary blood flow within the kidney, and antagonism of antidiuretic hormone can be suppressed by NSAIDs. As a result, urine is maximally concentrated, free water clearance is limited, and water retention that is disproportionate to sodium retention can occur. The resulting hyponatremia can be severe and could be potentiated by thiazide diuretics.[98] Local prostaglandin synthesis can also stimulate renin production within the kidney. NSAID therapy can critically attenuate this regulatory mechanism in some situations, resulting in reduced aldosterone-mediated potassium excretion and hyperkalemia.

Although the mechanism is poorly understood, some NSAIDs have been associated with sustained mean arterial pressure increases of 5 to 6 mm Hg,[99,100] presumably the result of COX-2 inhibition and sodium and water retention. Several studies suggest that only patients taking antihypertensive medications experienced NSAID-induced mean arterial pressure elevations, but it is now clear that even normotensive individuals can experience elevations in blood pressure from NSAID use.

Case 44-3, Question 3: How frequently should T.Z.'s renal and liver function be evaluated during his NSAID therapy?

Patients at high risk for NSAID-induced renal disease, like T.Z. (see Case 44-3, Questions 1 and 2), should have their serum creatinine levels checked regularly (eg, weekly) for several weeks after initiation of NSAID therapy because renal insufficiency more commonly occurs early in the course of therapy rather than later.[101] NSAID-induced nephrotic syndrome and allergic interstitial nephritis occur, on average, about 6.6 months and 15 days after NSAID initiation, respectively.[98]

In most cases, liver function testing (LFT) is unnecessary.[101] Although NSAIDs can elevate liver enzymes, severe hepatotoxicity is

rare. Abnormal LFTs without clinical symptoms have no impact on patient outcome and have not been associated with severe hepatotoxicity. Patients who seem to be at the greatest risk for hepatotoxicity are those with established or suspected intrinsic liver disease and those taking diclofenac. These patients should have LFTs performed no later than 8 weeks after initiation of therapy because liver toxicity manifests early in therapy, if at all.

CASE 44-3, QUESTION 4: T.Z. was diagnosed with RA 18 months ago, shortly after symptoms began to manifest. He exhibits no features of a poor prognosis and has low disease activity. Which traditional DMARD (csDMARD) therapies are most appropriate for him?

TRADITIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

According to ACR and EULAR, every patient with RA should receive DMARD therapy. Guidelines for DMARD selection were discussed previously (see Treatment section). Monotherapy with MTX is considered the preferred initial treatment for most patients with RA. A high and rapid response rate for all levels of RA severity, relatively low cost and toxicity, and radiographic evidence of slowing joint erosion (which is most rapid during the first several years of active disease) are reasons why MTX is preferred.[30] Other csDMARDs to consider are HCQ, SSZ, and LEF. Although most DMARDs are associated with potentially serious adverse effects, these generally are reversible and seldom lead to serious complications if the patient is monitored appropriately.

Safety and efficacy data, which reflect several years of DMARD therapy combined with biologic agents, have been excellent, and the combination is now commonly prescribed for patients who fail MTX monotherapy (see Case 44-5, Questions 9–11).[30] Combination DMARD therapy is indicated for more severe or more advanced patients with RA (see Case 44-5, Question 8).

Hydroxychloroquine dosing

Case 44-3, Question 5: Although MTX is considered the initial DMARD of choice for newly diagnosed RA with moderate-to-high disease activity, because T.Z. has low disease activity with no poor prognostic factors, treatment was initiated with HCQ. What dosages would be appropriate, and when should clinical improvement be expected?

Although the manufacturer's literature recommends an initial HCQ adult dose of 200 to 400 mg/day, dosages for HCQ should not exceed 5 mg/kg/day based on actual body weight.[102–104] About two-thirds of patients who tolerate HCQ respond favorably. Benefits usually are apparent within 2 to 4 months of therapy, but it can vary between 1 and 6 months. About 37% of patients discontinued HCQ within a year and 54% within 2 years, primarily owing to lack of efficacy.[101]

Risk of Retinopathy

Case 44-3, Question 6: When being counseled regarding HCQ, T.Z. was told that the drug can cause vision problems. How great is the risk of retinopathy from HCQ when used for the treatment of RA? What monitoring parameters are appropriate?

HCQ is usually well tolerated. The most serious toxicity, retinal damage and subsequent visual impairment, is rare.[30,101,103,104] With daily HCQ doses ≤5 mg/kg based on actual body weight, the risk of retinopathy is <2% from HCQ use of up to 10 years. Risk factors for retinopathy include high daily doses relative to body weight and cumulative doses, reduced renal function, concomitant use of tamoxifen (retinotoxic drug), and retinal disease. Patients should be instructed to stop therapy immediately and undergo an ophthalmologic evaluation if they are experiencing symptoms of HCQ-related retinopathy (eg, difficulty seeing faces or entire words, glare intolerance, poor night vision, and loss of peripheral vision).[102–104] The fully developed lesion of antimalarial retinopathy is seen on ophthalmoscopy as a pigmentary disturbance with a characteristic bull's-eye appearance in the macular region. The 4-amino-quinolines

bind to melanin, and as a result, concentrate in the uveal tract and retinal pigment epithelium. The retinopathy can be progressive even after discontinuation of the drug.

A baseline eye examination is recommended within the first few months of starting HCQ therapy, then annually after 5 years of treatment.[103–105] More frequent testing is recommended for patients with high-risk factors (noted above). Early changes of HCQ retinopathy are now detectable with optical coherence tomography (OCT), and early intervention with discontinuing HCQ may avoid serious visual loss.

Sulfasalazine

Case 44-3, Question 7: If SSZ were chosen as initial therapy for T.Z. instead of HCQ, when should therapeutic effects become apparent, and what adverse effects might be anticipated?

SSZ may be considered for treatment in patients with low disease activity before methotrexate and leflunomide. The onset of SSZ effect is generally more rapid than that of HCQ, usually providing benefits within 2 to 3 months.[105] Overall, SSZ adverse effects are relatively mild, although SSZ is considered to be slightly more toxic than HCQ. Adverse effects include nausea, abdominal discomfort, heartburn, dizziness, headaches, skin rashes, and, rarely, hematologic effects such as leukopenia (1%–3%) or thrombocytopenia. A complete blood count (CBC) is recommended every 2 to 4 weeks for the first 3 months of therapy, then every 3 months thereafter. Leukopenia, agranulocytosis, or hepatitis are rare, but serious side effects of SSZ usually manifest within the first 2 to 3 months of therapy. To minimize GI-related adverse effects, SSZ is initiated at 500 mg/day or 1 g/day, and the dosage is increased at weekly intervals by 500 mg until a dose of 1000 mg two or three times daily is reached.

CASE 44-4

Question 1: S.S., a 41-year-old Asian female diagnosed with RA, presents with inflammation in both hands (MCP and PIP joints), wrists, elbows, shoulders, knees, hips, ankles, and MTP joints. Objective test results include radiographic evidence of joint erosion in both hands and elbows, positive RF (dilution of 1:1280), positive anti-CCP at 102 units, and ESR of 78 mm/hour. Her SDAI score is 30. When she initially developed symptoms a year ago, she self-treated with ibuprofen 800 mg three times daily; however, pain and inflammation have progressively worsened. ROM testing reveals deficits in wrist flexion and extension (20° bilaterally for both motions; normal, 90° and 70°, respectively), elbow flexion (90° bilaterally with flexion contracture; normal, 160°), shoulder abduction (70° right, 90° left; normal, 180°), and plantar flexion of both ankles (20° bilaterally; normal, 45°). Three firm, pea-sized, nontender movable subcutaneous nodules are found on both elbows at the ulnar border, two on the right and one on the left. A decision is made to treat S.S. with MTX.

Why is MTX a good selection for her?

Methotrexate

MTX is recommended as initial DMARD therapy for all patients with RA.[30] S.S. has many indicators of severe disease (eg, an SDAI score indicating high disease activity, multiple joint involvement, extra-articular manifestations [ie, subcutaneous nodules], radiographic evidence of erosions, elevated ESR, positive anti-CCP, positive RF with a high titer of 1:1280 [high titers correlate with greater disease severity]). MTX is ideal because it has a rapid onset (usually 1–2 months before a plateau of effectiveness), a high efficacy rate at managing symptoms and slowing disease progression, low toxicity, and a long history of successful use.[30]

Dosing

Case 44-4, Question 2: How should MTX be dosed and administered to S.S.?

In general, MTX is administered orally at an initial dose of 7.5 to 10 mg once a week. The dose can also be divided over 24 hours for patients who are unable to tolerate adverse effects.[79] MTX dose should be titrated to at least 15 mg/week by week 4 to 6 of therapy

for increased efficacy. If inadequate response is seen at this time, then (a) the dose can be increased to the 20 to 30 mg/week based on tolerability, (b) the dose can be administered as a subcutaneous or IM injection to address concerns of adverse effects with higher doses, (c) the same dose can be continued for a longer time, or (d) another DMARD can be added to MTX or MTX can be substituted.[106,107]

Adverse Effects

CASE 44-4, QUESTION 3: What subjective and objective data should be evaluated for evidence of MTX adverse effects in S.S.?

S.S. should be monitored for nausea and other GI distress, malaise, dizziness, mucositis, and mild alopecia, which are commonly encountered adverse effects associated with low-dose MTX therapy.[101] More serious, but less common, adverse effects include myelosuppression, pneumonitis, and hepatic fibrosis and cirrhosis. A CBC, LFTs, and a serum creatinine concentration should be obtained for her at baseline, every 2 to 4 weeks for the first 3 months, every 8 to 12 weeks during months 3 to 6, and then every 12 weeks thereafter during MTX therapy. Renal dysfunction can result in accumulation of MTX and higher risk of myelosuppression. Interstitial pneumonitis, occurring in <1% of patients, has no known risk factors for development, although it may be more common in patients with a history of lung disease.[105] In addition, interstitial pneumonitis can occur at any time during therapy and at any MTX dosage. A baseline chest radiograph is recommended within the year before MTX initiation. If the patient is found to have preexisting lung disease, MTX treatment should be reconsidered because further pulmonary damage could be devastating to the patient. S.S. also should be monitored carefully for cough, dyspnea on exertion, and shortness of breath at each clinic visit.

MTX-induced liver disease is rare, but increased age, long duration of therapy, obesity, diabetes mellitus, ethanol consumption,

and a history of hepatitis B or C increase the risk of hepatotoxicity.[106] MTX should be prescribed with great caution, if at all, in patients with preexisting liver disease. The serum concentrations of liver enzymes commonly are modestly increased after administration for 1 to 2 days. However, MTX should be withheld if liver enzymes increase to three times the baseline value or if the liver enzyme serum concentrations remain elevated for sustained periods during therapy. Patients taking MTX should avoid alcohol and be instructed to report symptoms of jaundice or dark urine to their primary-care provider. Routine liver biopsies to monitor for MTX-induced hepatotoxicity are unnecessary (see Case 44-4, Question 4).

Liver Biopsy and Methotrexate

Case 44-4, Question 4: The following laboratory test results were obtained for S.S. before starting MTX:

Alanine transaminase (ALT), 28 IU/L
Aspartate aminotransferase (AST), 30 IU/L
Alkaline phosphatase, 100 IU/L
Albumin, 4.5 g/dL
Total bilirubin, 0.8 mg/dL

Should a baseline liver biopsy be performed before S.S. starts MTX?

Liver biopsy is only recommended at baseline for MTX patients who have a history of heavy alcohol consumption, persistently elevated liver function tests (defined as elevations above the upper limit of normal [ULN] in AST for five of nine tests within a 12-month period [or 6 of 12 if tests are performed every month] or a reduction in serum albumin below normal range), or chronic hepatitis B or C. During therapy, patients with persistently elevated liver functions tests or serum albumin below normal range should have a repeat liver biopsy. Otherwise, routine liver biopsy is unnecessary and not cost-effective.[106] Diligent LFT has proven to be highly effective at preventing liver injury.[108] When initiating or escalating methotrexate dosing, ALT with or without AST, creatinine and CBC should be

checked every 4 to 6 weeks until stable dosing is achieved, then testing should be repeated every 1 to 3 months thereafter along with screening for adverse effects and hepatotoxicity risk factors at every visit.

Because S.S.'s LFTs are normal and there is not a history of liver disease noted, there is no reason to consider a baseline liver biopsy.

Methotrexate and Folate or Folinic Acid

Case 44-4, Question 5: When should folate (or folinic acid) be administered to reduce the risk of MTX-related toxicity in S.S.?

Folate supplementation appears to reduce the incidence of several MTX-related adverse effects, including GI disturbances, mucositis (mouth or GI ulcerations), and LFT elevations.[108] The current consensus and evidence-based recommendation is at least 5 mg folic acid weekly. Although daily doses of folic acid as low as 1 mg are associated with protection against liver toxicity, GI disturbances are best prevented at doses above 5 mg weekly. Although folinic acid has also proven to be effective at lowering GI and hepatotoxicity, doses above 5 mg/week are associated with worsening of arthritis symptoms, consistent with the fact that MTX is a folate antagonist, and folinic acid supplementation could adversely impact efficacy.[105,108]

Methotrexate-Related Pulmonary Disorders

Case 44-4, Question 6: S.S. is treated with MTX 7.5 mg and with folic acid 7 mg orally once a week. Nine weeks later, she returns to the clinic with subjective and objective improvement in morning stiffness, fatigability, and joint tenderness and swelling. However, she has noted increased shortness of breath and dyspnea in the past week. Why might these symptoms be related to MTX?

Pneumonitis, a rare complication of MTX therapy, is characterized by a nonproductive cough, malaise, and fever, progressing to severe dyspnea.[109] Risk factors include older age (>60 years), previous use of DMARDs, low albumin, and diabetes. Recognition of this unusual reaction is important to ensure that MTX is discontinued before the pneumonitis progresses to respiratory failure. After discontinuation of MTX, pulmonary function improves. Corticosteroids can accelerate improvement in pulmonary symptoms associated with pneumonitis. S.S.'s dyspnea and shortness of breath might be related to MTX. If appropriate tests rule out other causes for her pulmonary symptoms, MTX-induced pulmonary toxicity should be considered and MTX treatment discontinued.

Methotrexate Interactions

Case 44-4, Question 7: What major MTX drug interactions need to be discussed with S.S. by her providers?

NSAIDs increase MTX serum concentrations and increase the risk of toxicity.[106] MTX doses should be adjusted cautiously if S.S. is taking NSAIDs concurrently to manage her RA pain. Trimethoprim, frequently used as part of the treatment for urinary tract infections, can increase the risk of MTX-induced bone marrow suppression. The concurrent use of MTX and LEF has been associated with major liver damage, including fatalities; as a result, this combination should be avoided. Because MTX is protein bound and renally excreted, other drugs (eg, salicylates, probenecid, penicillin, and ciprofloxacin) also might interact with MTX.

Leflunomide: place in therapy

CASE 44-5

Question 1: B.W. is a 36-year-old female who has severe, progressive RA and is unable to tolerate MTX therapy.

Would LEF be a reasonable consideration for her?

LEF, an oral csDMARD, seems to be similar in efficacy to MTX with regard to ACR-20, radiographic response, and work productivity.[29] The onset of benefit (as early as 4 weeks) and the percentage of patients who discontinue LEF therapy because of either lack of efficacy or toxicity are similar for LEF, MTX, and SSZ. The preferred initial csDMARD is MTX because of a long history of safety and efficacy, but LEF is a reasonable consideration as a replacement for MTX-intolerant patients, along with bDMARDs.

CASE 44-5, QUESTION 2: How should therapy with LEF be initiated in B.W. and how would you monitor B.W. for adverse effects?

Dosing and Monitoring

The active metabolite of LEF, A77 1726 (M1), is responsible for virtually all the pharmacologic activity of LEF.[106] The serum half-life of the M1 metabolite is ~2 weeks. As a result, LEF may be initiated with a loading dose of 100 mg orally once daily for 3 days to reduce time to steady state, followed by 20 mg once daily. If this dose is not tolerated, the dose should be reduced to 10 mg once daily.

Monitoring for Adverse Effects

Diarrhea (20%–30%), rash (10%), alopecia (10%–17%), and reversible liver enzyme elevations more than three times the ULN (2%–4%) are common adverse effects of LEF.[106] Routine laboratory testing includes a baseline ALT followed by monthly ALT testing for several months. When it is evident that ALT results are stable and within normal limits, testing can be performed less often according to the clinician's judgment. Because of the risk of liver toxicity and the need for activation by the liver to the M1 active metabolite, LEF is not recommended in patients with preexisting liver disease, including hepatitis B or C.

Potential hepatotoxicity is the greatest concern with LEF; however, the rate of LEF-induced liver enzyme elevation is not significantly different from MTX. Guidelines for managing potential hepatotoxicity include dosage reduction from 20 to 10 mg/day if ALT increases more than two times the ULN.[106] If ALT elevations remain steady between two and three times the ULN and treatment continuation is desired, a liver biopsy is recommended. If ALT elevations are persistently more than three times the ULN despite dosage reduction and cholestyramine administration to enhance elimination (see Case 44-5, Question 3), then the drug should be discontinued, and another course of cholestyramine elimination therapy should be given.

Enhancement of Elimination With Cholestyramine

Case 44-5, Question 3: After 2 months of therapy, B.W. does not respond to LEF and the treatment was discontinued, especially because she is beginning to consider starting a family. What precautions must be taken when discontinuing LEF? What are possible alternative treatments?

LEF is contraindicated in pregnancy because it greatly increases the risk of fetal death or teratogenicity in animals receiving as little as 1% of human equivalent doses.[106] After discontinuation of therapy, however, up to 2 years may be needed to elapse before plasma M1 metabolite levels of LEF are undetectable. As a result, cholestyramine is recommended for all females who discontinue LEF and who are hoping to become pregnant. After stopping the medication, cholestyramine 8 g three times daily is administered for 11 days (may be nonconsecutive). Plasma levels of the M1 metabolite are reduced by 40% to 65% in 24 to 48 hours and should become undetectable (<0.02 mg/L) at the end of therapy. B.W.'s blood should be evaluated at least 14 days apart to verify the absence of the metabolite. If plasma M1 levels remain >0.02 mg/L, more cholestyramine should be administered. Cholestyramine also can be used to enhance the elimination of LEF in patients who

experience hepatotoxicity or who overdose with this drug. Activated charcoal also can reduce plasma M1 levels by 50% after 48 hours and can be an effective alternative to cholestyramine when LEF overdosages need to be managed.

Both HCQ and SSZ appear to be safe in pregnancy, whereas MTX is not recommended in pregnancy because of the risk for embryo-fetal harm. However, because of B.W.'s high disease activity with poor prognostic factors, a bDMARD may be considered.

Traditional disease-modifying antirheumatic drug combination therapy

Case 44-5, Question 4: Is there evidence to support the early and safe use of csDMARDs in combination for B.W.?

Because most patients with RA develop joint erosions within the first 2 years of disease, the initiation of disease-modifying agents early in the course of therapy, and using them in combination, has been associated with improved patient outcomes. The rationale for combination therapy is based on the premise that a combination of drugs might improve outcomes because of different pharmacologic mechanisms of action or different sites of actions. A combination of drugs also may allow the use of lower doses of individual drugs, thereby reducing the risk of toxicity while maintaining or possibly increasing efficacy. However, the use of csDMARD combinations may increase patient burden of adhering to multiple medications.

Current ACR guidelines conditionally recommend bDMARD or tsDMARD over csDMARD combination therapy in patients with moderate-to-high RA disease activity. Combination csDMARD therapy may be considered based on patient preference as an alternative for patients who fail to reach treatment goals on a single csDMARD.[30]

In summary, every patient with RA, including B.W., should receive csDMARD therapy at or shortly after diagnosis, with MTX monotherapy as preferred initial treatment. Patients who experience

loss of efficacy or intolerable adverse effects from MTX can add one or two csDMARDs, or add or substitute a bDMARD or tsDMARD, which will be discussed in ensuing sections.

Biologic DMARD drug therapy

Case 44-5, Question 5: After 6 months of treatment with csDMARDs (LEF after intolerance to MTX), B.W.'s response is inadequate, her RA remains highly active, and she has signs of early joint damage. B.W.'s physician would like to try a TNF-α inhibitor. Is a TNF-α inhibitor an appropriate treatment option for B.W.?

According to the EULAR guidelines, bDMARDs or tsDMARDs should be considered for patients with moderate-to-high disease activity with poor prognostic factors, who do not reach treatment targets with the first csDMARD strategy (MTX alone or in combination with another csDMARD) within 6 months or without poor prognostic factors, who fail a second csDMARD strategy.[28] For patients not at treatment target with csDMARD monotherapy, the ACR guidelines conditionally recommend the addition of bDMARD or tsDMARD over csDMARD combination therapy.[30]

Given that B.W. has tried two different csDMARDs and continues to have highly active RA with poor prognostic factors, it is time to consider a bDMARD or tsDMARD. Out of the bDMARDs, TNF-α inhibitors have been available on the market for longer and thus have more robust long-term safety data, which may influence prescribers' confidence in these agents. A TNF-α inhibitor would be an appropriate choice in therapy for B.W. Her csDMARD therapy should be continued with the selected TNF-α inhibitor.

Case 44-5, Question 6: Which TNF-α inhibitor should be started in patient B.W.?

There are five TNF-α inhibitors available for the treatment of RA including etanercept, adalimumab, infliximab, certolizumab pegol,

and golimumab. Although there are multiple studies describing the efficacy and safety of these agents, there is no consensus on the preferred initial TNF-α inhibitor. The use of each of these medications as well as comparisons between them will be explored here.

TNF-α inhibitors: place in therapy and dosing

Etanercept (ETA) was the first biologic response modifier to be approved by the U.S. Food and Drug Administration (FDA) for reducing the signs and symptoms of moderate-to-severe active RA, either alone or in combination with MTX.[47] ETA is a soluble TNF receptor that competitively binds two TNF molecules, rendering both molecules inactive. It is self-administered once weekly by subcutaneous injection at a dose of 50 or 25 mg twice weekly.[47] ETA provides rapid and significant improvement in subjective and objective measures of RA, either alone or in combination with MTX.[46,110] The addition of ETA to MTX therapy has shown greater clinical efficacy when compared with MTX monotherapy.[111] ETA alone has also been shown to be superior to MTX as monotherapy in the reduction of RA symptoms and disease activity.[112,113] ETA has demonstrated decreased radiographic progression of RA as well as long-term safety and efficacy.[114,115] Etanercept is a reasonable choice for B.W. and should be used in combination with MTX for best results.

Adalimumab (ADA) is a genetically engineered, fully humanized IgG1 monoclonal antibody that has been shown to inhibit the structural damage of RA while reducing clinical signs and symptoms. The recommended dose is 40 mg administered by subcutaneous injection every other week. It is recommended to give ADA in combination with MTX.[48] Patients who cannot or choose not to take MTX may benefit from weekly dosing or 80 mg every other week.[48] When ADA 40 mg every other week was added to the treatment regimen of patients with RA receiving stable MTX doses, significantly more ADA-treated patients (67%) achieved an ACR-20 response than those receiving only MTX (14.5%, $P < .001$) after 24 weeks.[116]

Combination therapy with ADA and MTX was shown to be superior to either MTX or ADA monotherapy for RA symptoms and disease progression.[117] In radiographic data reflecting 1 or 2 years of treatment, ADA has been shown to slow the progression of joint damage. Data also support the long-term efficacy and safety of ADA.[118] ADA would also be an appropriate choice for B.W. and would require less frequent injections than ETA.

Infliximab (IFX) is a chimeric (mouse–human) IgG antibody directed against TNF. Specifically, IFX is approved in combination with MTX for the treatment of moderate-to-severe active RA. The recommended dose is 3 mg/kg via intravenous infusion at weeks 0, 2, and 6, then every 8 weeks thereafter. Some patients may benefit from an increase in dose up to 10 mg/kg or a decrease in treatment interval to as often as every 4 weeks.[49] IFX should be given with MTX therapy to prevent the formation of antibodies to infliximab. In a randomized, double-blind, multicenter, placebo-controlled trial of patients with active RA who failed to respond adequately to at least 12.5 mg/week of MTX, IFX 3 or 10 mg/kg or placebo was administered every 4 or 8 weeks along with MTX therapy. The signs and symptoms of RA were improved in the IFX groups versus MTX alone. This study was unblinded after 1 year because of radiographic evidence of disease modification in patients receiving IFX. Analysis of radiographic results after 2 years demonstrated that IFX significantly protected against joint erosion.[119] IFX would also be an appropriate bDMARD for B.W., particularly if she prefers less frequent intravenous infusions to self-administration of subcutaneous injections. Patient preferences are an important factor to consider when choosing between the anti-TNF agents.

Certolizumab pegol (CZP) consists of a Fab attached to a 40-kDa PEG moiety. The attachment to the PEG moiety increases the half-life of CZP to ~2 weeks, which allows dosing every 2 to 4 weeks.[120] The recommended dosing regimen is 400 mg initially and at weeks 2 and 4 followed by 200 mg every other week or 400 mg every 4 weeks by subcutaneous injection.[121] CZP's unique structure lacks an Fc region, so it may not induce complement- or antibody-dependent cell-mediated cytotoxicity, which has been observed in vitro with

adalimumab, etanercept, and infliximab.[122] The efficacy of CZP has been demonstrated in patients with moderate-to-severe active RA in combination with MTX and as monotherapy.[123–125] In a randomized, double-blind, placebo-controlled study in 619 patients with active RA, significantly more patients met ACR response rates with CZP plus MTX than patients treated with placebo plus MTX ($P < .001$).[124] Physical function, as evidenced by the mean change in the Health Assessment Questionnaire (HAQ) disability index (DI) score, DAS28 remission, and radiographic progression of RA were all improved in the CZP plus MTX group.[124] CZP has shown sustained efficacy and safety over 5 years in patients with active RA.[126]

To date, CZP is the only anti-TNF that has been studied specifically in pregnancy and lactation. Because of CZP's Fc region being replaced by PEG, it was considered to be less likely to cross the placenta while the large molecular size of CZP would limit transfer into breast milk. The CRIB study demonstrated no to minimal CZP drug transfer from mother to infant and no to minimal drug transfer into breast milk from the CRADLE study (Industry sponsored).[127,128] Thus, CZP is strongly recommended by ACR for use before conception, during pregnancy, and breast-feeding in 2020.[129] Patient B.W. would also be a candidate for CZP and CZP may be preferred if she still is family planning.

Golimumab (GLM) is a human IgG1 monoclonal antibody specific for human TNF-α. GLM binds to both the soluble and the transmembrane bioactive forms of human TNF. This binding prevents the binding of TNF-α to its receptors, thus inhibiting the biologic activity of TNF-α.[51] GLM shares common characteristics with both adalimumab and infliximab. Similar to adalimumab, GLM is a fully humanized bivalent immunoglobulin monoclonal antibody.[130] GLM is made up of light and heavy chains, which are identical to infliximab, but whereas infliximab is derived from both mice and humans, GLM is completely humanized. GLM is approved for the treatment of moderate-to-severe active RA in combination with MTX.[51] It can be administered by subcutaneous injection or intravenous infusion. The subcutaneous injection is a 50-mg injection dosed monthly.[51] The dose of the intravenous infusion is 2 mg/kg

over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.[131] Clinical trials have demonstrated GLM efficacy in patients with no previous MTX use and in patients with an inadequate response to MTX or a TNF-α inhibitor.[132–134] A randomized, placebo-controlled trial conducted in 444 patients examined the efficacy of GLM in patients with active RA despite concomitant MTX use.[135] Significantly more patients in the combined GLM plus MTX group achieved an ACR-20 response compared with the MTX plus placebo group (55.6% vs 33.1%, respectively, $P < .001$), and these results were sustained at 52 weeks.[135] In another study assessing the long-term safety and efficacy of GLM in patients with RA who discontinued previous TNF-α inhibitors, GLM treatment resulted in sustained efficacy and safety.[135] Given this information, GLM would also be an appropriate treatment option for B.W., and she would have the option of choosing between intravenous or subcutaneous dosing.

There are currently no definitive guidelines recommending one TNF-α inhibitor over another. Direct head-to-head comparisons between the anti-TNF agents are lacking; therefore, prescribers must depend on surveillance data, systematic reviews, and meta-analyses to make clinical decisions regarding comparative efficacy and safety.

Case 44-5, Question 7: What side effects will need to be monitored when starting B.W. on adalimumab?

TNF-α inhibitors: side effects and monitoring

The greatest concern with adalimumab therapy is the risk of immunosuppression and subsequent serious infections, including sepsis. TNF-α is a key mediator of inflammation and plays a major role in immune system regulation. Postmarketing reports of infections, such as TB, mycobacterial infections, fungal infections, and hepatitis B virus reactivation, further reinforce the strong recommendation against the initiation of adalimumab therapy in patients with sepsis or any chronic or localized active infection.[47] Mycobacterium tuberculosis testing and hepatitis B serologies should be undertaken before initiation of anti-TNF therapy. Therapy

should be postponed for patients identified as having active TB until appropriate antituberculosis therapy has been completed.[29] Patients being treated for latent TB infection may start anti-TNF therapy after the first month of latent TB treatment. Clinicians also must be cautious when prescribing adalimumab (or any bDMARD) to patients with a history of recurring infection or with underlying illnesses that predispose them to infection. B.W. should receive a TB test, hepatitis B serologies, and be warned of the potential adverse effects of adalimumab, particularly the risk of immunosuppression and subsequent infection. Any sign of infection must be reported to her health care provider.

TNF-α has been implicated in the pathophysiology of heart failure, and increased serum levels of TNF-α seem to be associated with worsening heart failure.[136] Proposed mechanisms contributing to the onset or worsening of heart failure include accelerated left ventricular remodeling, negative inotropic effects, and increased apoptosis of myocytes and endothelial cells. Clinical trials with anti-TNF therapy (which have included etanercept and infliximab) have shown an association between TNF-α and worsening heart failure; some have also shown increased cardiovascular risk.[136] As a result, anti-TNF therapy is not recommended for patients with RA with moderate-to-severe (NYHA class III and IV) heart failure. Anti-TNF therapy can be used with caution in patients with mild (NYHA class I and II) heart failure, but patients should be closely monitored for cardiac decompensation.[28]

Included in the labeling for all anti-TNF bDMARDs is a warning for increased risk of lymphoma and other malignancies. An increased incidence of lymphoma has been observed among patients with RA receiving any of the available anti-TNF agents; however, causation has not been established because both RA and MTX are associated with an increased rate of lymphoma. Additionally, the FDA has issued a warning following reports of hepatosplenic T-cell lymphoma, a rare cancer of the white blood cells, in patients being treated with TNF blockers, AZA, or mercaptopurine.[137] The majority of these cases were found in adolescents and young adults with Crohn disease or ulcerative colitis. Incidence was also more common in

patients on a combination of immunosuppressive agents. Although it is difficult to measure the added risk associated with anti-TNF agents, caution and monitoring is advised.[137] Other adverse effects, in order of decreasing frequency, include headache, rhinitis, dizziness, pharyngitis, cough, asthenia, abdominal pain, and rash.

With anti-TNF therapies, there have been rare reports of new onset or worsening demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.[48] Patients should be screened for preexisting central nervous system and peripheral demyelinating conditions prior to initiating anti-TNF therapy.

CASE 44-6

Question 1: S.K., a 71-year-old female, was diagnosed with RA ~15 years ago. Her initial drug therapy included MTX, followed by the addition of SSZ and HCQ, which seemed to keep her RA in near-remission for 5 years. She then changed to etanercept in combination with MTX with good results until 1 year ago. In response to declining disease control, infliximab was substituted for etanercept with excellent results. Then last month, she experienced a flare in RA activity. At that time, her CRP was 5.1 mg/dL, ESR was 90 mm/hour, and anti-CCP was positive at 112 units. She also experienced morning stiffness lasting several hours and multiple joints with swelling (*N* = 26) and tenderness (*N* = 38). Of note, S.K. has a history of treated skin melanoma 2 years ago.

What are the reasonable treatment options for S.K. at this stage of her disease?

Non-TNF biologic DMARDs

Clinical studies have consistently demonstrated that bDMARDs improve the signs and symptoms of RA as well as slow the progression of structural damage. TNF-α inhibitors have long been considered first-line bDMARDs given the availability of long-term data and clinical experience compared to the non-TNF bDMARDs. However, ongoing registry and trial data suggest that the safety profiles of the non-TNF bDMARDs, abatacept, rituximab, tocilizumab, and sarilumab, are consistent with clinical trial results.[28] Some trials have shown superiority of some of these agents over

TNF-α inhibitors. TNF-α inhibitors also fail to produce an ACR-20 response in ~30% of patients, which is known as primary failure. Even more patients experience acquired resistance to treatment, known as secondary failure, which is defined as a loss of response with time and is illustrated by S.K.[138] Many patients who lose responsiveness to an initial trial of anti-TNF therapy can be successfully treated with an alternative anti-TNF agent.[139] However, studies have also shown that response rates with sequential anti-TNF therapy may be lower, and the reasons for initial anti-TNF failure (inefficacy or adverse effects) may be recurrent.[139,140] The ACR guideline conditionally recommends switching to a bDMARD or tsDMARD of a different class when not at target. Therefore, it is important to consider alternative options for the treatment of patients like S.K. with anti-TNF treatment failure.[139,140]

Abatacept (inhibitor of T-cell activation), rituximab (selectively depletes $CD20^+$ on B cells), tocilizumab, and sarilumab (anti–IL-6 receptor antibodies) have demonstrated excellent efficacy in patients with inadequate response to csDMARDs (eg, MTX) as well as to anti-TNF therapy.[28,30] Owing to their differing mechanisms of action, each of these agents possesses unique qualities with regard to efficacy and safety. (Detailed dosing information for the bDMARDs can be found in **Table 44-1**.)

Table 44-1
Biologic Disease-Modifying Antirheumatic Drug Dosing Information

Generic (Brand)	Mechanism of Action	Dosage Range	Administration Schedule	Routes of Administration	Can Be Self-Administered?
Infliximab (Remicade®)	TNF-α inhibitor	3 mg/kg[a]	Weeks 0, 2, and 6 and then every 8 weeks	IV	No
Etanercept (Enbrel®)	TNF-α inhibitor	50 mg	Weekly	SC	Yes
Adalimumab (Humira®)	TNF-α inhibitor	40 mg	Every 14 days	SC	Yes
Certolizumab pegol (Cimzia®)	TNF-α inhibitor	Initial: 400 mg SC on weeks 0, 2, 4 Subsequent: 200 mg every 2 weeks or 400 mg every 4 weeks	Weeks 0, 2, and 4 and then every 2 or 4 weeks	SC	Yes
Golimumab (Simponi®)	TNF-α inhibitor	50 mg	Every month	SC	Yes
Golimumab (Simponi Aria®)	TNF-α inhibitor	2 mg/kg infusion over 30 minutes	Weeks 0 and 4, then every 8 weeks	IV	No
Abatacept (Orencia®)	Costimulation modulator, T-cell activation inhibitor	Weight based: <60 kg, 500 mg 60–100 kg, 750 mg >100 kg, 1000 mg	Weeks 0, 2, and 4 and then every 4 weeks	IV	No
		Or			
		125 mg	Once weekly (may be initiated with or without IV loading dose)	SC	Yes
Rituximab (Rituxan®)	CD20+ B-cell inhibitor	1000 mg IV infusion: Initial: 50 mg/hour, may increase every 30 minutes to a maximum rate of 400 mg/hour Subsequent: 100 mg/hour, may increase every 30 minutes to maximum rate of 400 mg/hour[b]	Repeat in 14 days to complete course. Repeat course every 24 weeks or based on clinical response, but not sooner than every 16 weeks	IV	No
Tocilizumab (Actemra®)	IL-6 inhibitor	Initial: 4 mg/kg every 4 weeks Subsequent: Titrate to 8 mg/kg based on clinical response Max.: 800 mg/dose (8 mg/kg)	Every 4 weeks	IV	No
		Or			
		Weight-based SC dosing: <100 kg, 162 mg every other week, followed by an increase to every week based on clinic response ≥100 kg, 162 mg every week	Every 14 days or weekly	SC	Yes
Sarilumab (Kevzara®)	IL-6 inhibitor	200 mg	Every 14 days	SC	Yes

IL, interleukin; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor.

[a]For incomplete response, may increase dose to 10 mg/kg or decrease dosing interval to every 4 weeks.

[b]Premedicate with corticosteroid, acetaminophen, and an antihistamine before each dose.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

Abatacept

Abatacept (ABT) is a selective costimulation inhibitor of T-cell activation indicated for the treatment of moderate-to-severe active RA.[53] ABT may be prescribed as monotherapy or in combination with csDMARDs. It can be administered intravenously or subcutaneously. ABT intravenous dosing is based on body weight (500 mg for patients 132.27 pounds [<60 kg], 750 mg for patients 132.27–220.46 pounds [60–100 kg], and 1000 mg for patients >220.46 pounds [>100 kg]) and should be infused over 30 minutes at weeks 0, 2, and 4, and then every 4 weeks thereafter.[53] The dose for the subcutaneous injection is 125 mg weekly. The efficacy and safety profiles have been shown to be comparable between the two preparations.[141]

Abatacept has demonstrated efficacy in patients with an inadequate response to MTX as well as in patients with an inadequate response or adverse reactions to TNF-α inhibitors.[53] In a study comparing ABT plus MTX to placebo plus MTX, significantly more patients in the ABT plus MTX group attained ACR-20 response when compared with the placebo plus MTX group (73.1% vs 39.7%, respectively, $P < .001$) and had significant slowing of structural damage progression compared to the patients treated with placebo at 12-month follow-up.[54] ABT efficacy was maintained in the 5-year open-label extension of this trial.[142] Efficacy and safety data from 7 years of ABT therapy indicate that ABT maintains sustained improvements in disease activity and ACR-70 scores during this period, with no change in safety profile.[143] ABT has also demonstrated efficacy in patients with an inadequate response to one or more TNF-α inhibitors, such as S.K.[144,145]

Finally, ABT has also been compared head-to-head with the TNF-α inhibitor adalimumab. In a 2-year study in patients with RA with an inadequate response to MTX, ABT and ADA were found to be similar in both efficacy and safety. Overall, patients experienced similar improvement in clinical markers of disease control and progression.

Although rates of adverse events in both groups were similar, there were more discontinuations because of adverse events in the ADA group (9.5%) compared to the ABT group (3.8%) (95% CI −9.5 to −1.9).[146]

The side effects of greatest concern with ABT include serious infections such as pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis. Infections are significantly more common when ABT is combined with anti-TNF therapy; thus, this combination is not recommended.[53] Malignancies have also been associated with ABT, and patients with chronic obstructive pulmonary disease are noted to suffer from more respiratory-related and nonrespiratory-related adverse effects than patients with chronic obstructive pulmonary disease treated with placebo.[53]

Rituximab

Rituximab (RXB) is a chimeric monoclonal antibody that binds to the antigen CD20 on B cells. It is approved in combination with MTX for the treatment of moderate-to-severe active RA in patients who have had an inadequate response to one or more TNF antagonist medications.[55] However, according to the EULAR guidelines, rituximab may be considered as a first-line bDMARD in patients with contraindications to other bDMARDs, such as recent history of lymphoproliferative disorder, which RXB is indicated for, latent TB with contraindications to chemoprophylaxis, living in TB-endemic areas or a previous history of demyelinating disease.[28] RXB is administered as two 1000-mg IV infusions separated by 2 weeks, then every 6 months as needed.[55] RXB must be diluted to a final concentration of 1 to 4 mg/mL with either 0.9% sodium chloride or 5% dextrose in water. To reduce the incidence and severity of infusion-related adverse effects, premedication with IV methylprednisolone 100 mg, or its equivalent, 30 minutes before each infusion is strongly recommended; other premedications (eg, acetaminophen and antihistamine) may also be beneficial. Antihypertensive medications should be discontinued 12 hours

before RXB administration to avoid transient hypotension, which has been reported during RXB infusions. RXB must be given with MTX for maximal efficacy based on clinical trials and to help reduce the risk of developing HACA, which occurs in ~9% of patients receiving RXB. It is recommended that subsequent courses of RXB be given every 24 weeks. The dosing interval may be decreased on the basis of clinical evaluation, but must be no less than every 16 weeks.[55]

Rituximab has been shown to be effective in patients who have responded inadequately to MTX therapy as well as in patients who have responded inadequately to anti-TNF medications.[147] The REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab in RA) trial evaluated the use of RXB plus MTX versus placebo plus MTX in 499 patients with active, long-standing RA who responded inadequately to one or more anti-TNF medications, such as S.K.[148] At 24-week follow-up, significantly more patients in the RXB group demonstrated an ACR-20 response than those in the placebo group (51% vs 18%, respectively). And in a 56-week follow-up report of the REFLEX trial, RXB significantly inhibited radiographic progression of joint damage.[149] In the 2-year extension of this trial, RXB showed significant and sustained inhibition of joint damage. These findings support the efficacy and appropriateness of RXB for patients with RA, such as S.K., who are refractory to anti-TNF therapy.

Serious and fatal infusion reactions can be caused by RXB. Severe reactions typically occur with the first infusion; thus, careful monitoring is warranted, and premedication with methylprednisolone 100 mg or its equivalent is recommended 30 minutes prior to each infusion. RXB should be discontinued if a serious reaction occurs. Severe mucocutaneous reactions and progressive multifocal leukoencephalopathy (PML) may also occur in patients receiving RXB. Finally, hepatitis B (HBV) reactivation may occur in patients receiving RXB. Therefore, all patients should be screened for HBV infection prior to initiation. The most common adverse reactions in patients with RA receiving RXB include upper respiratory tract infections, nasopharyngitis, urinary tract infections, and bronchitis.[55] RXB has not been associated with any increase in malignancy;

therefore, it is preferred over anti-TNF agents in patients with a recent history of cancer.[28]

Because S.K. failed two TNF-α inhibitors because of inefficacy, either ABT or RXB would be an appropriate choice. Given S.K.'s history of skin melanoma 2 years ago, RXB would be the preferred agent over ABT in this patient.

CASE 44-7

Question 1: Q.O. is a 55-year-old female with highly active RA for the past year who cannot tolerate MTX therapy. Her provider would like to start a bDMARD as monotherapy.

Which medication would be best?

Tocilizumab

Tocilizumab is a humanized anti–IL-6 receptor antibody indicated for the treatment of adult patients with moderate-to-severe active RA, who have had an inadequate response to one or more csDMARDs.[58] TCZ may be administered intravenously or subcutaneously. For the intravenous infusion, the recommended dosage is 4 mg/kg, infused IV every 4 weeks with an increase to 8 mg/kg as needed based on clinical response. The dosing for the subcutaneous formulation is 162 mg per injection either weekly or every other week depending on patient weight and response.[58] The safety and efficacy of the intravenous and subcutaneous formulations have been studied and appear to be comparable. However, an increase in injection-site reactions in the subcutaneous TCZ group has been seen.[150] TCZ should not be initiated in patients with an absolute neutrophil count <2000 cells/μL, platelet count <100,000 platelets/μL, or in patients who have an ALT or AST value >1.5 times the ULN.[58] TCZ treatment should be interrupted if a patient experiences a serious infection; therapy may be resumed once the infection is controlled.[58]

TCZ has demonstrated efficacy in the treatment of RA as monotherapy, in combination with csDMARDs, and in patients who are refractory to anti-TNF medications.[151,152] In a systematic review of eight randomized controlled trials (RCTs), TCZ at a dose of 8

mg/kg in combination with MTX was shown to statistically significantly decrease disease activity and improve physical function when compared to MTX plus placebo.[153] TCZ has also shown decreased radiographic progression of RA compared to csDMARDs.[151,154] In the RADIATE trial, patients with an inadequate response to one or more TNF-α inhibitors were randomly assigned to receive 8 or 4 mg/kg of TCZ or placebo every 4 weeks for 24 weeks.[152] An ACR-20 response was achieved at 24 weeks by 50.0%, 30.4%, and 10.1% of patients in the TCZ 8 mg/kg, 4 mg/kg, and placebo arms, respectively ($P < .001$).[152] Given this information, TCZ would also be a reasonable option for patients who have failed one or more TNF inhibitors, like S.K. from Case 44-6.

According to the ACR and EULAR treatment guidelines, the standard of care indicates that patients should maintain MTX or csDMARD therapy when a bDMARD is added.[28,30] However, for up to 40% of patients, MTX therapy is discontinued because of intolerance or patient preference and as many as one-third of patients may be taking bDMARDs as monotherapy.[155] Three of the TNF inhibitors (etanercept, adalimumab, and certolizumab pegol) and three of the non-TNF bDMARDs (abatacept, tocilizumab, and sarilumab) are approved as monotherapy. In a study comparing ADA and TCZ monotherapy in patients who were either intolerant to MTX or MTX was not an appropriate treatment option, patients in the TCZ group were found to have significantly greater improvement in DAS28 as well as most clinical endpoints when compared to the ADA group.[155] Therefore, TCZ is a reasonable therapeutic option for Q.O. as monotherapy for RA and has demonstrated superiority over at least one anti-TNF agent.[152,154]

When starting TCZ, Q.O. should be monitored for potential side effects. The most serious side effects associated with TCZ therapy include severe infections, GI perforation, and laboratory abnormalities. As with the TNF-α inhibitors, TCZ has a boxed warning for increased risk of developing serious infections, especially those caused by opportunistic pathogens. The risk for infection is increased when TCZ is taken in combination with other immunosuppressant agents (eg, MTX and corticosteroids). As with

the anti-TNF agents, a TB skin test result and chest radiograph must be obtained before initiating treatment. In clinical studies, the overall rate of fatal serious infections was low at 0.13/100 patient-years.[58]

TCZ has also been associated with a number of blood chemistry changes, including neutropenia, thrombocytopenia, elevated LFTs, and lipid changes. Increases in lipids (total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides) have been shown in clinical trials. Increase in lipids may be caused in part by the decrease in inflammatory activity with TCZ use. Lipid elevations respond to lipid-lowering agents. Although clinical trials do not indicate an increase in cardiovascular risk, further studies are necessary to assess the effects of TCZ on cardiovascular risk factors.[156,157]

Sarilumab

Similar to TCZ, sarilumab is also a humanized IL-6 receptor antagonist that binds to soluble and membrane-bound IL-6 receptors to inhibit IL-6 signaling. It is approved as monotherapy or in combination with csDMARDs for the treatment of moderate-to-severe active RA in adults who have had an inadequate response or intolerance to one or more DMARDs.[59] Unlike TCZ, SAR is only administered subcutaneously with a recommended dosage of 200 mg every 2 weeks. SAR should not be initiated in patients with an absolute neutrophil count <2000 cells/μL, platelet count <150,000 platelets/μL, or in patients who have an ALT or AST value >1.5 times the ULN.[59] SAR could be another option for Q.O. if they are amenable to subcutaneous medication administration.

Three different phase III RCTs demonstrated that sarilumab improves signs and symptoms of RA, physical functioning, and radiographic progression for a wide range of patient subpopulations.[158] The efficacy of sarilumab has been demonstrated to be similar to TCZ, but SAR may be more effective in patients with RA who are anti-citrullinated protein antibody (ACPA)-positive, whereas studies for TCZ have not identified a relationship between ACPA and achievement of target endpoints. However, there were

also fewer ACPA-negative patients enrolled in the SAR studies, so the data may not be as reliable. Both SAR and TCZ studies have similar findings that IL-6 receptor inhibition had a greater effect in patients with high baseline CRP.[158]

A long-term safety study that included data from eight clinical trials found the overall incidence rates of adverse events were similar between combination SAR and csDMARD therapy and SAR monotherapy.[159] The monotherapy group reported neutropenia, injection-site erythema, and nasopharyngitis as the most common adverse effects, whereas the combination group reported neutropenia, injection-site erythema, and upper respiratory tract infections most frequently. Overall, the results of the study showed consistent safety findings of phase III trials and of IL-6 signaling inhibition. The same monitoring parameters for TCZ should apply to SAR; however, when comparing the data available thus far, SAR may have a slightly more favorable safety profile over TCZ.[159]

Targeted synthetic DMARDs: Janus kinase inhibitors

Tofacitinib, baricitinib, and upadacitinib are the three JAK inhibitors currently available in the United States for the treatment of RA. Although all three JAK inhibitors inhibit JAK1, tofacitinib also selectively inhibits JAK2 and JAK3, and baricitinib inhibits JAK2.[10,39–41] However, the importance of the specific JAK enzyme inhibition in relation to treatment effectiveness is yet to be fully understood. These tsDMARDs offer patients with RA a targeted oral treatment and an alternative route of administration compared to bDMARDs. In 2021, the FDA issued updated boxed warnings for all three JAK inhibitors, which includes the risk of major adverse cardiovascular events (MACEs), malignancies, thrombosis, and mortality. Because of these added warnings, the three JAK inhibitors are now indicated for the treatment of RA in patients with an inadequate or intolerant response to one or more TNF inhibitors.

Case 44-7, Question 2: Two years later, Q.O. remains not at target with moderate disease activity after failing adalimumab and tocilizumab. Would a

tsDMARD be an appropriate treatment option for Q.O.?

Tofacitinib

Tofacitinib (TOF) is the first JAK inhibitor FDA approved for the treatment of RA. TOF may be dosed as TOF 5 mg orally twice daily or TOF XR 11 mg orally once daily, with or without food. The TOF XR extended-release tablets should not be cut, crushed, or chewed. For patients with moderate and severe renal impairment or moderate hepatic impairment, a dose adjustment to TOF 5 mg once daily is recommended. TOF should not be initiated in patients with an absolute lymphocyte count <500 cells/μL, absolute neutrophil count <1000 cells/μL, or hemoglobin levels <9 g/dL.[39]

TOF was studied in six different trials and demonstrated improvement in signs and symptoms of moderate-to-severe RA. In the TOF Study RA-V, patients with RA and an inadequate response to TNF inhibitors were evaluated in a phase 3, double-blind, parallel-group study comparing TOF 5 mg twice daily plus MTX versus placebo plus MTX. The ACR20 response at 3 months was 41.7% in the TOF arm compared to 24% in placebo. TOF demonstrated a significant time to onset of ACR20 response at week 2 and achieved greater DAS28 rates and greater improvements in HAQ-DI compared to placebo.[160] TOF may be considered as a treatment option for Q.O. who has already failed a TNF inhibitor and non-TNF bDMARD.

Baricitinib

Baricitinib (BARI) is the second FDA-approved JAK inhibitor for RA. BARI is dosed 2 mg orally once daily and can be administered with or without food. Dose adjustment to BARI 1 mg once daily is recommended for moderate renal impairment (noted as estimated glomerular filtration rate [GFR] between 30 and 60 mL/minute/1.73 m^2). It is not recommended in severe renal impairment or severe hepatic impairment. BARI should not be initiated in patients with an absolute lymphocyte count <500 cells/μL, absolute neutrophil count <1000 cells/μL, or hemoglobin levels <8 g/dL.[40]

Two confirmatory studies demonstrated efficacy and safety of BARI for the treatment of RA. The RA-BEACON trial studied patients with RA and previous inadequate response or intolerance to one or more TNF inhibitors with or without other bDMARDs. In the phase 3, randomized, double-blind, placebo-controlled study, patients with RA were treated with BARI 4 mg daily, BARI 2 mg daily or placebo in addition to the current concomitant csDMARD therapy. The ACR20 response and DAS28-CRP at week 12 was higher in BARI treatment groups compared to placebo. ACR20 was achieved in 49% versus 27% for BARI 2 mg arm and placebo arm, respectively.[161] BARI is an alternative JAK inhibitor that may be considered for Q.O.'s RA.

Upadacitinib

Upadacitinib (UPA) is the most recently approved JAK inhibitor for RA and dosed 15 mg orally once daily, with or without food. Because of the extended-release formulation, it should not be cut, crushed, or chewed. It is not recommended to be used in patients with severe hepatic impairment. UPA should not be initiated in patients with an absolute lymphocyte count <500 cells/μL, absolute neutrophil count <1000 cells/μL, or hemoglobin levels <8 g/dL.[41]

UPA had five phase 3 studies to show efficacy and safety of UPA 15 mg daily for the treatment of moderate-to-severely active RA. The SELECT-BEYOND study evaluated patients with active RA and experienced inadequate response or intolerance to bDMARDs. Patients were randomized to receive UPA 15 mg, UPA 30 mg or placebo in addition to established csDMARDs. At week 12, ACR20 was 65% versus 28% for UPA 15 mg group and placebo, respectively ($P < .0001$). Additionally, DAS28-CRP was achieved in more patients in the UPA treatment groups.[162] Lastly, Q.O. may also consider UPA for the treatment of her RA after failure of two bDMARDs.

JAK inhibitors: side effects and monitoring

JAK inhibitors have several boxed warnings that should be reviewed and discussed with the patient prior to initiating therapy. In 2021, the

FDA issued the addition of increased risk for MACE, malignancies, thrombosis, and mortality for all three JAK inhibitors after results from the TOF postmarketing safety study. The ORAL Surveillance study examined TOF versus TNF-α inhibitors for the treatment of RA in patients 50 years and older with at least one additional cardiovascular risk factor. The incidences of MACE and malignancy were higher with TOF versus TNF inhibitor, with a hazard ratio 1.33 (95% CI, 0.91–1.95) for MACE and 1.48 (95% CI, 1.04–2.09) for malignancies.[163] Despite the study only including TOF, because of a similar mechanism of action between the three JAK inhibitors indicated for the treatment of RA, the FDA required all three medications to have prescribing information updates.

Prescribers should consider risk stratification prior to starting JAK inhibitor therapy for the treatment of RA after inadequate response or intolerance to TNF inhibitor. A previous history of MACE, thrombosis, and cancer as well as general risk factors including age older than 65 years and smoking should be first identified. Risk may be further evaluated for the presence of additional risk factors specific for thrombosis (severe obesity, varicose veins, hormones) and MACE (hypertension, dyslipidemia, and diabetes).[164] The type and number of risk factors present may facilitate the risk versus benefit discussion with the patient and ultimately the decision to initiate a JAK inhibitor or not.

As with the bDMARDs, JAK inhibitors have a boxed warning for increased risk of serious infections.[165] JAK inhibitors are not recommended to be used in combination with other JAK inhibitors, bDMARDs, or strong immunosuppressants. Patients should be screened for active and latent TB prior to initiating therapy.

Other serious side effects associated with JAK inhibitors include GI perforation and laboratory abnormalities. JAK inhibitors have been associated with lymphopenia, neutropenia, anemia, elevated LFTs, and lipid changes. Baseline labs as well as routine laboratory monitoring should be performed to ensure continued safe use of JAK inhibitors.[166]

Prior to initiating a JAK inhibitor for Q.O., the physician should stratify Q.O.’s risk for serious adverse events associated with JAK

inhibitors, review the risk versus benefits of treatment, and use shared decision-making with the patient. If the risk is low and the patient is agreeable, any of the three JAK inhibitors may be considered.

CORTICOSTEROIDS

CASE 44-8

QUESTION 1: W.M., a 57-year-old male, has progressive RA that has not been responsive to SSZ. He is having difficulty working a full day and is seeking an alternative medication. After a discussion of therapeutic options, W.M. is willing to start MTX.

Would it be appropriate to initiate corticosteroids concurrently? And if so, at what dose?

Despite the potential for serious adverse effects with long-term therapy, the judicious use of low-dose corticosteroids represents an important component of treatment during the course of unremitting disease. In addition, low-dose corticosteroids may offer some disease-modifying properties, although this is controversial because of the long-term negative effects of corticosteroid use.[67] The benefit of low-dose glucocorticoid therapy is favorable as long as the course of therapy is short.[30] Considering that W.M.'s RA is sufficiently active to compromise his ability to earn an income, MTX is a much better DMARD selection. Regardless, concurrent initiation of a DMARD and an intermediate-acting corticosteroid (eg, prednisone in a daily or divided dose of 5–10 mg) is justified.[167] A Cochrane review showed that corticosteroid doses equivalent to ≤15 mg of prednisolone were superior to placebo and NSAIDs for joint tenderness and pain in RA.[168] In large cohort studies, prednisone doses >7.5 mg/day have been associated with a greater than twofold increased risk of cardiovascular events (MI, stroke, and heart failure), as well as the risk of developing hypertension with long-term use (at least 6–12 months).[169,170] Therefore, the lowest effective corticosteroid dose is preferred for the shortest duration of time

possible.[30] The onset of action of corticosteroids is relatively rapid, and their immediate benefits will allow W.M. to maintain his current employment and continue taking care of responsibilities at home. The corticosteroid dose can be decreased gradually and eventually discontinued as W.M. begins to respond to MTX therapy. An important goal of low-dose corticosteroid treatment is to provide bridge therapy until the DMARD therapy becomes effective, in hopes of then being able to taper and discontinue the corticosteroid.

CASE 44-8, QUESTION 2: Would intra-articular corticosteroid injections be a safe and effective treatment option for W.M.?

Intra-articular corticosteroids

Intra-articular corticosteroid injections are safe and effective for pain relief in patients with RA. This strategy is most sensible when flaring occurs in one or a few joints.[171] Systemic side effects are minimal when compared with oral corticosteroid therapy. Although the onset of action is virtually immediate, effects are often short-lived. W.M. could benefit from the use of intermittent intra-articular corticosteroid injections for the treatment of RA flares.

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic arthritic conditions of unknown etiology, occurring before 16 years of age. It is one of the most common chronic diseases in the pediatric population worldwide and the most common chronic rheumatic disorder in childhood. In the United States, the incidence is estimated at more than 14 patients per 100,000 and the prevalence at 96 patients per 100,000.[172] JIA affects all races with a peak age of onset between 2 and 4 years. However, new cases are seen throughout childhood and often continue into adulthood, causing significant morbidity and physical disability.[173–178]

Clinical Presentation and Classification

By definition, symptoms of JIA (joint inflammation involving swelling, pain, limited ROM, warmth, and erythema) present before the age of 16 and must last for at least 6 weeks in at least one joint.[179] Morning stiffness and its duration is also a clear clinical symptom of JIA.

As with adult RA, JIA begins with synovial inflammation. Because children often cannot articulate, morning stiffness and joint pain may manifest as increased irritability, guarding of involved joints, or refusal to walk. Fatigue and low-grade fever, anorexia, weight loss, and failure to grow are other symptoms. Patients with JIA are categorized as having one of the following seven types of disease as established by the International League of Associations for Rheumatology (ILAR):[180]

1. Systemic
2. Oligoarthritis
3. Polyarthritis RF+
4. Polyarthritis RF−
5. Psoriatic
6. Enthesitis-related
7. Undifferentiated (patients who do not fulfill the criteria of other JIA subsets)

The most common type of JIA is oligoarthritis, which comprises about 50% of all JIA cases. This type of JIA typically presents before the age of 6 years, with most cases afflicting girls. Patients with oligoarthritis present with four or fewer affected joints, most commonly in the knee. Those who do not progress beyond four joints are categorized with persistent oligoarthritis, but 50% may eventually develop arthritis in additional joints after 6 months of disease, requiring a change in disease classification to extended oligoarthritis.[174,180]

JIA is classified as polyarthritis when the disease involves five or more joints during the first 6 months of the disease with few or no

systemic manifestations of the disease.180 Polyarthritis may be RF+ or RF− and accounts for up to 40% of all JIA disease, the majority of which is RF−.[181] Both types affect girls more often than boys. Disease onset is typically seen at age 8 or older and most often in adolescents. RF+ polyarthritis presents very similarly to adult-onset RA, involving aggressive, erosive, and symmetric joint inflammation, which may lead to general growth retardation, as well as fatigue, morning stiffness, and elevated inflammatory markers.[173,174]

Psoriatic JIA accounts for a small number of all JIA cases (about 1%) and is diagnosed if chronic arthritis and psoriasis are both evident. Children may also be diagnosed with psoriatic JIA if any two of the following are present: dactylitis (finger or toe inflammation), onycholysis, nail pitting, or family history of psoriasis.[173,180]

Enthesitis-related JIA is manifested as inflammation of the enthesis (the site of attachment of tendon to bone) along with arthritis, typically in the lower limbs, in boys older than 6 years old. Children with enthesitis-related JIA have at least two of the following in addition to arthritis or enthesitis: inflammatory lumbosacral or sacroiliac joint pain, HLA-B27 positivity, symptomatic anterior uveitis, or a family history of enthesitis-related JIA or ankylosing spondylitis (first-degree relative).[180,182]

CASE 44-9

QUESTION 1: J.R., a 4-year-old girl, is brought to the hospital for high fever and arthritis. Several weeks before admission, J.R. had a daily fever ranging from 103°F (39.44 °C) to 106°F (41.11 °C). One week before admission, her knees became painful and swollen. J.R. is listless and irritable during her physical examination, and her rectal temperature measures 102.4°F (39.11 °C). She refuses to walk. The right hip is tender, and the right wrist and both knees are warm, red, and swollen. Minimal generalized lymphadenopathy and splenomegaly are present. The Westergren ESR is 82 mm/hour, the white blood cell count is 37,000 cells/μL with a mild left shift, and hematocrit is 33%. Cultures of the throat, urine, stool, and blood are negative. MD global assessment is 4. An intermediate-strength purified-protein derivative, antistreptolysin-O titer, ANA titer, and RF titer are normal, as are radiographs of the chest and involved joints. An electrocardiogram reveals only tachycardia. After withholding aspirin, an evanescent rash becomes apparent in conjunction with fever spikes.

What signs and symptoms of JIA does J.R. manifest?

The last category is systemic JIA, which is distinguished from other forms of the disease by the presence of hallmark systemic features including rash, lymphadenopathy, hepatomegaly or splenomegaly, serositis, and cyclical high-spiking fever. J.R. exhibits these distinguishing symptoms and, in addition, she experiences joint pain in her knees, with other commonly affected joints including the wrists and ankles. The pain often worsens when fever is elevated but may not be clinically evident at disease onset. Systemic JIA occurs equally in girls and boys, and although it makes up only 5-15% of all patients with JIA, it causes the highest mortality and morbidity of all JIA categories. Children presenting with this subtype of JIA may also have macrophage activation syndrome (MAS), which is characterized by fevers, increased ferritin, liver enzyme and triglyceride levels, cytopenias, and low fibrinogen.[177]

Prognosis

Case 44-9, Question 2: What is the expected prognosis for J.R.?

Features of poor prognosis for patients with JIA include:[176–177]

- Arthritis that involves the ankle, wrist, hip, or sacroiliac joint
- Involvement of temporomandibular joint (TMJ)
- Enthesitis
- Significant or prolonged elevation of ESR or other inflammatory markers
- Radiographic damage indicating erosive disease
- Delay in JIA diagnosis

Disease remission is qualified by lack of active arthritis in joints, absence of systemic symptoms (rash, fever, lymphadenopathy, etc.), symptomatic uveitis not present, normal ESR or CRP, and no disease activity measured on a physician's global assessment scale.

Although only 5% of patients achieve true remission, sustained periods of good control are becoming more common with treatment advances, and up to 35% to 50% of patients achieve clinical remission on medication therapy. Despite improvements in care, complete remission is still uncommon, and up to one-third of patients with JIA do experience long-term disability and decreased quality of life. Preservation of joint function is least promising in children with RF+ polyarthritis.[183–185] Although J.R. is exhibiting some poor prognostic indicators (hip and wrist involvement, elevated ESR), it is unclear whether these are long-term manifestations. Normal ANA and RF titers and the absence of radiographic damage are favorable for J.R.

Treatment

The goals of JIA treatment are to minimize joint inflammation and its destructive effects, control pain, preserve or restore ROM, facilitate an acceptable quality of life, and achieve long-term disease remission. Choice of medication therapy requires consideration of the type of JIA, current treatment, degree of disease progression, level of disease activity, and prognosis.[175–178]

NONPHARMACOLOGIC THERAPY

In addition to treatment with medication, many patients with JIA can benefit from nonpharmacologic efforts to help preserve joint flexibility, maintain ROM, and prevent disability in adulthood. Patients with JIA are often less physically active and more easily fatigued than their disease-free peers, and they may meet developmental milestones later than children of the same age.[186] Children with JIA are also more prone to decreased bone mineral density than their peers.

Case 44-9, Question 3: J.R.'s parents understand the need for medication therapy but also want to encourage lifestyle interventions as a way to promote health and combat disease complications. What recommendation can the physician give to J.R. and her family once her acute symptoms are stabilized?

A healthy, balanced, and age-appropriate diet should be recommended.[175] Heat and cold therapy, massage, and regular physical activity can all help reach disease treatment goals of minimizing joint inflammation, controlling pain, and improving quality of life. Regular physical activities, including muscle-strengthening, ROM activities, stretching, and endurance training, are safe and do not worsen arthritis. Weight-bearing exercise can help prevent bone loss, but it should be avoided when joints are acutely inflamed. At these times, low-impact sports such as swimming or bicycling can be enjoyed. Physical therapy and occupational therapy can also help pediatric patients hone gross and fine motor skills, balance, and coordination.[186,187] Once J.R.'s status improves, she should be encouraged to participate in regular exercise and organized therapy sessions to improve exercise capacity and preserve joint functioning.

PHARMACOLOGIC THERAPY AND TREATMENT CONSIDERATIONS

Whereas ILAR differentiates JIA into seven disease types, the 2019 and 2021 ACR guidelines classify treatment recommendations based on the clinical presentation of JIA and into the following eight treatment groups: (1) polyarthritis, (2) sacroiliitis, (3) enthesitis, (4) oligoarthritis, (5) TMJ, (6) systemic JIA without MAS, (7) systemic JIA with MAS, and (8) uveitis.[175–178]

(1) JIA and Active Polyarthritis

Patients with JIA and active polyarthritis should have MTX considered as first-line therapy. The role of NSAIDs was recommended as an adjunct therapy and is not appropriate for monotherapy as DMARD therapy is considered a cornerstone to slow disease progression. For specific DMARD selection, MTX is preferred over LEF and SSZ. Based on the presence of risk factors for more severe disease, refractory disease (positive anti-CCP, RF+, or presence of joint damage), and moderate-to-high disease activity, a bDMARD may be initiated or added to current DMARD therapy. The bDMARD therapy options include anti-TNF agents

(adalimumab, etanercept, infliximab, and golimumab) or non-TNF agents (abatacept and tocilizumab). Rituximab is considered the last-line bDMARD agent. In the setting of low disease activity, therapy can be escalated to include intra-articular glucocorticoid injection(s), increasing the DMARD, or bDMARD dose.[176]

Because the ACR 2019 JIA guidelines focused on polyarthritis, tofacitinib was FDA approved in 2020 for the treatment of polyarticular course JIA in patients 2 years and older who have failed or had an intolerance to one or more anti-TNF therapy.[39] Tofacitinib may be considered an alternative treatment option.

(2) JIA and Sacroiliitis

Patients with active sacroiliac arthritis may include individuals from any of the JIA disease categories, but the treatment group must be defined by both clinical and imaging evidence of the disease. NSAIDs are strongly recommended with step-up therapy to include the addition of a TNF-α inhibitor. MTX monotherapy is not recommended; however, it may be used as an adjunct therapy in some cases. Alternatively, SSZ may be considered for patients with contraindications to TNF-α inhibitors or failed multiple TNF-α inhibitors.[176]

(3) JIA and Enthesitis

Patients with active enthesitis may also include patients from any of the JIA disease categories. NSAIDs are strongly recommended as the first-line treatment. ACR conditionally recommends anti-TNF therapy over csDMARD (MTX or SSZ) in patients with active enthesitis despite treatment with NSAIDs. For patients with contraindications to TNF-α inhibitors or concomitant active peripheral polyarthritis, a trial of MTX or SSZ may be appropriate.[176]

Since the ACR 2019 JIA guidelines focused on enthesitis, secukinumab was FDA approved in 2021 for the treatment of active enthesitis-related arthritis (ERA) in patients 4 years and older and juvenile psoriatic arthritis (JPsA) in patients 2 years and older.[188] Secukinumab may be considered an alternative treatment option.

(4) JIA and Active Oligoarthritis

The history of arthritis of four or fewer joints treatment group includes ILAR disease-classified patients with extended oligoarthritis, RF− polyarthritis, RF+ polyarthritis, psoriatic arthritis, ERA, and undifferentiated arthritis, all have had no more than four affected joints in their disease course. Scheduled NSAIDs may be considered for initial therapy (now conditionally recommended); however, the use of intra-articular glucocorticoid injections is strongly recommended as part of initial treatment in JIA with active oligoarthritis. Step-up therapy includes csDMARD, followed by a bDMARD in those with poor response.[177] NSAIDs may be used as adjunctive therapy for any patient with JIA; however, the use as monotherapy should be limited to a short time frame due to limited efficacy and risks of drug side effects. Triamcinolone hexacetonide is the intra-articular glucocorticoid of choice and can provide clinical improvement for a minimum of 4 months; step-up to csDMARD therapy may be warranted if symptoms are not controlled within this period.[189,190] Among the csDMARDs, MTX is conditionally preferred over LEF, SSZ, and HCQ, and MTX may be initiated in those who fail initial therapy with NSAIDs and intra-articular injections or in those who have high disease activity and poor prognosis. Finally, in those who still lack response after a trial of NSAIDs, intra-articular glucocorticoid injections and at least one csDMARD, a bDMARD may be initiated. Based on the 2021 ACR guidelines, there is no preferred bDMARD of choice and may include anti-TNF agents (adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol) or non-TNF inhibitors (abatacept and tocilizumab).

(5) Temporomandibular Joint Arthritis (TMJ)

JIA of the TMJ may develop without symptoms leading to a delay in diagnosis and treatment. Early evaluation and treatment are important to avoid dentofacial deformity, impairment in joint function, and poor quality of life.[191] Active TMJ arthritis therapy follows a similar treatment algorithm to JIA with oligoarthritis, with the exception that treatment should be promptly initiated and rapidly escalated to csDMARD (MTX over LEF) followed by bDMARD after an incomplete response to NSAIDs and/or intra-articular

glucocorticoids. Intra-articular glucocorticoids are less favored in patients with TMJ owing to TMJ-related side effects including heterotopic ossification and impaired bone growth.[177]

(6, 7) Systemic JIA (sJIA) with/without MAS and Systemic JIA with MAS

Systemic JIA is subdivided into two treatment categories based on the presence or absence of MAS. In those without MAS, biologic DMARDs (IL-1 and IL-6 inhibitors) are recommended as initial monotherapy. NSAIDs can also be used as monotherapy initially, but treatment should be escalated if a rapid and complete response does not occur.[177]

About 10% of pediatric patients with JIA develop MAS, a life-threatening complication characterized by fever, pancytopenia, liver insufficiency, and coagulopathy, among others, and if hospitalized, it is associated with a 6% mortality rate.[192] For those with MAS, initial treatment with IL-1 and IL-6 inhibitors is also recommended with the addition of glucocorticoids. Some patients will also require calcineurin inhibitors added to the treatment regimen to control MAS.

(8) JIA-Associated Uveitis

JIA-associated uveitis is the most common extra-articular manifestation and, if left untreated, may lead to sight-threatening complications.[178,193] Thus, routine screenings and prompt treatment are vital. Patients who are at high risk for developing uveitis include those with oligoarthritis, polyarthritis (RF−), psoriatic arthritis or undifferentiated JIA with positive ANA, JIA disease onset at age under 7 years old, and JIA disease duration of ≤4 years. These patients are recommended to have ophthalmic screening every 3 months. Initial treatment for chronic anterior uveitis begins with topical glucocorticoids, such as prednisolone acetate 1% drops for short-term control. If disease activity persists, systemic treatment with MTX and a monoclonal antibody anti-TNF biologic (adalimumab or infliximab) is recommended over MTX monotherapy.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Case 44-9, Question 4: Are NSAIDs an appropriate choice for initial drug therapy for the treatment of systemic JIA in patient J.R.?

NSAID therapy may be considered a first-line treatment for polyarthritis, sacroiliitis, enthesitis, oligoarthritis, TMJ, and systemic JIA without MAS, but was left out of the treatment guidelines for systemic JIA with MAS and uveitis. In the case of systemic JIA without MAS, as with patient J.R., NSAIDs may be considered as monotherapy; however, therapy should be quickly stepped up with continued disease activity.[177] NSAIDs can be useful in systemic JIA without MAS as they target joint inflammation as well as febrile episodes.[174,194] These medications work to control pain, fever, and inflammation by inhibiting prostaglandin synthesis and are usually fairly well tolerated by children. Analgesic effects usually occur first, and with continued use anti-inflammatory effects of NSAIDs will begin within a few weeks.

Many of the traditional NSAIDs as well as celecoxib have been used to treat JIA. The most commonly prescribed NSAIDs for JIA are naproxen and ibuprofen. Naproxen is approved for the treatment of JIA in children and adolescents at a dose of 10-15 mg/kg/day in two divided doses and is advantageous in school-age children because of the convenient dosing interval and availability in liquid or tablet formulations.[194] Ibuprofen is recommended at a dose of 30 to 40 mg/kg/day given in three or four divided doses. Ibuprofen is also available in tablet and liquid formulations.[195]

In most cases, at least two different NSAIDs should be tried before ruling out this group of medications owing to lack of efficacy or tolerability.[196] Failure to respond to an NSAID in a particular chemical class does not rule out the efficacy of others in the same class. As with adults, it is not possible to predict a pediatric patient's response to any one NSAID.

Given that J.R. has systemic JIA without MAS, a brief course of NSAIDs and/or initiating an IL-1 or IL-6 inhibitor would be the appropriate first-line agents for J.R.[177] For choice of NSAID, either ibuprofen or naproxen would be reasonable. Ibuprofen is available

over-the-counter in liquid and chewable forms, which is an important consideration for a 4-year-old. Naproxen is also available in an oral liquid suspension by prescription and can also be considered as initial therapy.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Case 44-9, Question 5: J.R., who weighs 33 pounds (14.97 kg), was prescribed Naproxen 125 mg/5mL oral suspension at a dose of 75 mg bid. Her parents have given her the medication twice daily as directed for the past 2 weeks, but she continues to have disease activity with persistent fever. What should the next step in therapy be for J.R.?

Biologic Agents

There are several FDA-approved biologic agents available to treat forms of JIA: etanercept, adalimumab, abatacept, tocilizumab, tofacitinib, and secukinumab for JIA, and canakinumab and tocilizumab for systemic JIA. There are other bDMARDs that are not FDA approved for the treatment of JIA but are recommended in the ACR guidelines, including anakinra, rilonacept, rituximab, and the TNF-α inhibitors as a class.[176–178] Although the TNF-α inhibitors have demonstrated excellent efficacy in the treatment of adult RA as well as polyarticular JIA, they have not shown similar efficacy in the treatment of systemic JIA. The exact pathophysiology of systemic JIA remains unclear, but the pro-inflammatory cytokines IL-1 and IL-6 have been identified as targets of pharmacotherapy.[177,197–199] Thus, IL-1 inhibitors anakinra, canakinumab, and rilonacept as well as IL-6 inhibitor, tocilizumab, have demonstrated efficacy in the treatment of systemic JIA, and their use is addressed in the ACR treatment guidelines.[177]

IL-1 inhibitors, anakinra and canakinumab, are recommended for the treatment of systemic JIA, whereas rilonacept's place in therapy remains unclear. Anakinra blocks the action of IL-1α and IL-1β by inhibiting IL-1 binding to the interleukin-1 type receptor (IL-1R1). Although anakinra has shown suboptimal efficacy in the treatment of

adult RA, patients with systemic JIA have responded well to anakinra treatment. Case reports of good response to anakinra in patients who were refractory to other treatments for systemic JIA led to increased use of anakinra in patients with systemic JIA.[197,200,201] In a small randomized, controlled trial in patients with systemic JIA, 8 out of 12 patients in the anakinra group achieved the primary outcome (30% improvement in clinical status, resolution of fever, and 50% decrease or normalization of both CRP and ESR) versus 1 out of 12 patients in the control group. Furthermore, 10 of the patients in the control group were switched to anakinra after 1 month, and nine of these patients also responded to anakinra treatment.[201] Although anakinra is not FDA approved for systemic JIA, the dose that has been used in clinical trials is 1-2 mg/kg subcutaneously daily, with a maximum daily dose of 100 mg.[201] As with all of the bDMARDs, patients should be monitored for increased risk of infection when taking anakinra. Anakinra would be an appropriate treatment for J.R.

Canakinumab is a human monoclonal antibody, which binds IL-1β and blocks its interaction with IL-1 receptors. It is FDA approved for the treatment of systemic JIA in patients 2 years and older at a dose of 4 mg/kg subcutaneously every 4 weeks for patients with a body weight of ≥16.53 pounds (7.5 kg) (maximum dose 300 mg).[202] In a randomized, placebo-controlled trial evaluating canakinumab for the treatment of systemic JIA, 84% of subjects experienced a 30% clinical response in the canakinumab group compared to only 10% in the placebo group ($p < 0.001$) 15 days after one dose of canakinumab.[203] In another trial in patients receiving open-label canakinumab for 32 weeks, there was a significantly lower risk of flares in the canakinumab patients, and the average glucocorticoid dose was reduced in the canakinumab group.[203] Canakinumab, like other bDMARDs, has been associated with an increased risk of infections. It has also been associated with MAS. This association may be attributed to the severity of the disease in patients treated with canakinumab, and a causal relationship has not been established.[202–204] Canakinumab would also be an appropriate treatment option for J.R. The monthly dosing may be preferred over the daily dosing required with anakinra.

Rilonacept is an interleukin-1 inhibitor that binds IL-1β as well as IL-1α and IL-1 receptor antagonists with lesser affinity.[205] Although rilonacept has demonstrated efficacy for the treatment of systemic JIA, its place in therapy remains unclear.[206] It should not be used as first-line therapy, and its use was not included in the updated ACR guidelines for systemic JIA.[177]

Tocilizumab is a monoclonal antibody against the IL-6 receptor. It is recommended for patients with systemic JIA with active systemic disease and FDA approved for patients 2 years and older.[60,177] The TCZ dose for systemic JIA is 12 mg/kg for weight <66.14 pounds (<30 kg) or 8 mg/kg for weight ≥66.14 pounds (≥30 kg) given intravenously every 2 weeks.[60,207] Alternatively, TCZ subcutaneous dosing is 162 mg every 2 weeks for weight <66.14 pounds (<30 kg) or 162 mg every week for weight ≥66.14 pounds (>30 kg).[60] In a randomized trial of tocilizumab for systemic JIA, 71% of children who received TCZ experienced a 70% improvement in clinic status, compared to 8% of patients who received placebo.[208] Like canakinumab, there has been an association between TCZ and MAS. However, per ACR guidelines, IL-1 and IL-6 inhibitors may be recommended for the treatment of systemic JIA with MAS.[177,197]

Patient J.R. has tried an NSAID, but she continues to have active systemic RA. Anakinra, canakinumab, and tocilizumab would all be appropriate treatment options for J.R. Canakinumab has the most convenient dosing regimen of these three options and may be the best option for J.R.

CASE 44-10

Question 1: Seven-year-old C.E. has polyarthritis that consistently has not responded to NSAID or MTX therapy. Given the many potential side effects, C.E.'s parents are concerned about her taking steroids and refuse to let their daughter take them. They are worried about permanent joint damage and wish to try a biologic agent in hopes of finally suppressing disease activity. They have heard that biologic drugs are "safer than steroids."

Which agents are available to treat JIA in C.E.?

There are several FDA-approved biologic agents available to treat polyarticular JIA: etanercept, adalimumab, abatacept, tocilizumab, and tofacitinib. Secukinumab was most recently FDA-approved bDMARD for ERA and JPsA but would not be an appropriate choice for C.E.

Etanercept is a recombinant TNF-receptor Fc fusion protein indicated for patients 2 years of age or older with polyarticular JIA. ETA is recommended for patients with oligoarticular or polyarticular JIA, who continue to have active polyarticular JIA despite 3 months of treatment with MTX at the maximum tolerated dosage.[176] The recommended dose is 0.8 mg/kg (maximum 50 mg) subcutaneously weekly.[48] The safety of etanercept in children is comparable to adults, with the exception of significantly more abdominal pain (17% of patients with JIA vs. 5% of adult patients with RA) and vomiting (14.5% of patients with JIA vs. <3% of adult patients with RA). Patients with JIA should be up-to-date on their immunizations before initiation of etanercept therapy. Safety and efficacy data reflecting up to 10 years of treatment support the long-term use of etanercept for JIA.[209]

Adalimumab is a human monoclonal TNF-α antibody approved for use in patients age 2 years and older with moderately to severely active polyarticular JIA.[49] It is a weight-based dose—10 mg for patients 22.05 to <33.06 pounds (10 to <15 kg), 20 mg for patients 33.06 to <66.14 pounds (15 to <30 kg), 40 mg for patients ≥66.14 pounds (≥30 kg)—given as a subcutaneous injection every other week.[49] In a study involving 171 patients on adalimumab monotherapy and in combination with MTX, children taking combination therapy showed better disease improvement than patients on adalimumab monotherapy.[49] Concomitant NSAIDs or other analgesic agents may also be continued during adalimumab use.

Abatacept is an injectable biologic agent that inhibits T-cell activation. It is FDA approved for the treatment of moderate-to-severe active polyarticular JIA. Patients 6 years and older weighing <165.35 pounds (75 kg) receive a dose of 10 mg/kg via IV infusion for 30 minutes, whereas patients weighing 165.35 pounds (75 kg) or

more should receive the adult intravenous regimen, with a maximum dose of 1,000 mg.[55] All patients receive IV doses at 2 and 4 weeks after the first infusion and then every 4 weeks thereafter.[55] Alternatively, patients 2 years and older may administer weekly subcutaneous weight-based dosing without an IV loading dose—50 mg for patients 22.05 to <55.12 pounds (10 to <25 kg), 87.5 mg for patients 55.12 to <110.23 pounds (25 to <50 kg), 125 mg for patients >110.23 pounds (>50 kg). Unlike TNF-α agents, abatacept does not have an immediate onset and seems to exert its effect best after repeated doses over the course of several months.[196]

Tocilizumab, an IL-6 receptor blocker monoclonal antibody, is also indicated in patients 2 years and older with active polyarticular JIA. The dose differs from systemic JIA and may be 8 mg/kg for weight ≥66.14 pounds (≥30 kg) or 12 mg/kg for weight <66.14 pounds (<30 kg) given intravenously every 4 weeks.[60] The alternative subcutaneous dosing is 162 mg every 3 weeks for weight <66.14 pounds (<30 kg) or 162 mg every 2 weeks for weight >66.14 pounds (>30 kg).[60,176]

Tofacitinib is a targeted synthetic DMARD that inhibits JAK. It is FDA approved for active polyarticular course JIA in patients 2 years who have failed or had an intolerance to one or more anti-TNF. It is administered orally twice daily, dosed based on weight—3.2 mg for weight 22.05 to <44.09 pounds (10 to <20 kg), 4 mg for weight 44.09 to <88.18 pounds (20 to <40 kg), 5 mg for weight >88.18 pounds (>40 kg)—and available as a 5-mg tablet or oral solution.[39] Tofacitinib offers a different route of administration compared to biologic therapies.[176]

Other biologic agents, including the other TNF-α inhibitors, are not FDA approved for JIA but have been studied. Available data from clinical trials suggest that all of these treatments may be safe and effective for JIA, with no evidence of significant risk for serious adverse reactions. Owing to their mechanisms of action, all biologic agents share the side effect of lowered infection resistance, and patients must be monitored for signs of infection during treatment.

Of all FDA-approved bDMARDs, C.E. is a candidate for etanercept, adalimumab, abatacept, or tocilizumab therapy.

Tofacitinib is not indicated as C.E. has not tried an anti-TNF yet. Given that abatacept does not have an immediate onset, etanercept or adalimumab may be preferred. Adalimumab with its biweekly dosing schedule may be preferred compared to weekly dosing with etanercept. C.E. will also be able to continue her concurrent NSAID and MTX therapies during adalimumab treatment because it is possible she will experience enhanced clinical improvement on combination therapy versus adalimumab alone.

Conventional Synthetic Disease-Modifying Antirheumatic Drugs

Early csDMARD therapy should be considered for patients with a history of arthritis of four or fewer joints (eg, persistent oligoarthritis) as well as patients with a history of arthritis of five or more joints (eg, extended oligoarthritis and polyarthritis).[176–177,210]

CASE 44-11

Question 1: T.T. presents to rheumatology clinic on referral from her primary care provider. She is 9 years old and has been whining at home of her shoes hurting her feet and not being able to run with her classmates at school. On physical examination, it is noted she has multiple swollen, erythematous joints (tarsometatarsal and metatarsocuneiform joints bilaterally on the feet, knees bilaterally). Her CBC values are all normal, her ESR is normal, and her RF is negative. In addition to NSAID and steroid therapy, the rheumatologist would like to start a DMARD agent.

What DMARD options are available to treat T.T.'s JIA?

Patients with JIA and active polyarthritis should be considered for csDMARD as part of initial therapy. MTX is the csDMARD of choice for polyarthritic JIA.[208] The recommended dose of MTX for JIA treatment is 10 mg/m^2 orally or subcutaneously each week.[176] Food reduces the bioavailability of MTX, so MTX should be administered on an empty stomach. Radiologic evidence of improvement or slowing of joint damage has been demonstrated in patients with JIA who responded to MTX therapy during a 2-year period.[211] Other csDMARD options for JIA include leflunomide, sulfasalazine, or hydroxychloroquine. MTX is favored over these alternate

csDMARDs, and leflunomide is the preferred second-line csDMARD.[176]

Case 44-11 Question 2: What is the expected response to MTX treatment for T.T.?

Children tolerate MTX therapy well and generally experience few serious or troublesome adverse effects (eg, transient liver enzyme elevations, nausea, vomiting, and oral ulcerations).[212] These adverse effects are reduced with daily folic acid therapy (1 mg) or weekly folinic acid (the day after MTX dosing). CBC, renal function, and liver toxicity monitoring in JIA are the same as the guidelines recommended for MTX therapy in adult RA.[175] The combination therapy of MTX and other csDMARDs has not been fully evaluated in pediatric patients.

If complete disease remission is achieved, discontinuation of MTX may be attempted. The optimal time to discontinue MTX therapy remains unknown; however, it probably should not be stopped sooner than 1 year after disease remission, with slower withdrawal in patients at high risk for relapse.[212,213] Young age at diagnosis (<4.5 years) and oligoarthritis that progresses to polyarthritis seem to be the greatest risk factors for relapse.[213,214]

Systemic and Intra-articular Corticosteroid Therapy

Despite the potential for serious adverse effects associated with high-dose or long-term therapy, the use of low-dose corticosteroids is sometimes necessary to control disease flares or provide therapeutic relief during initiation or dose adjustment of DMARDs with slow onsets of action. Bridge therapy with systemic glucocorticoids may be considered as adjunctive therapy for JIA with active polyarthritis during initiation or escalation of therapy in patients with moderate or high disease activity, but not recommended in patients with low disease activity. They are also recommended as adjunctive therapy for JIA with active sacroiliitis or enthesitis during initiation or escalation of therapy in patients with high disease

activity, limited mobility, and/or significant symptoms. For patients with systemic JIA with MAS, systemic corticosteroids may be considered as part of the initial treatment. Once the patient's disease activity is inactive, the corticosteroid should be tapered and discontinued. For patients with JIA-associated uveitis, systemic corticosteroids may be used in order to taper topical corticosteroid treatment. Systemic corticosteroids are not preferred for oligoarthritis, TMJ arthritis, or systemic JIA without MAS.

It is preferable that patients take the lowest effective corticosteroid dose for the shortest duration possible to avoid long-term side effects. Common side effects of steroids include GI upset and damage to the GI mucosa, mood changes including depression or hyperactivity, and increases in blood pressure and blood sugar.[195] Corticosteroids may also cause impaired skin healing, osteoporosis (especially with long-term use), and vision problems such as cataracts and glaucoma. Oral corticosteroids are typically dosed once daily in the morning to best mimic physiologic cortisol release and minimize suppression of the hypothalamic–pituitary–adrenal axis.

Intra-articular corticosteroid therapy seems to be highly effective in some forms of JIA. They are strongly recommended for initial treatment of JIA with oligoarthritis as monotherapy or in combination with scheduled NSAIDs. Triamcinolone hexacetonide is the preferred agent but is not readily available in the United States. Alternatively, triamcinolone acetonide may be used. Intra-articular corticosteroids are also recommended for TMJ arthritis for initial therapy as monotherapy or in combination with scheduled NSAIDs. There is no preferred agent to use for TMJ arthritis. Side effects include local lipoatrophy or articular calcification, both of which do not present many issues clinically (**Table 44-2**).

Table 44-2
Classes of Commonly used Medications for JIA Treatment

Drug	Mechanism of Action	Therapeutic Options	Adverse Event
Nonbiologic DMARDs			
MTX	■ MTX is a structural analog of folic acid that inhibits dihydrofolate reductase and DNA synthesis. ■ Acts in different pathway: cytokine production, arachidonic acid metabolism, and cell apoptosis	■ Polyarticular JIA ■ Oligoarticular JIA ■ JIA-related uveitis refractory to topical treatment ■ sJIA with predominant joint inflammation and without active systemic symptoms ■ Psoriatic JIA	■ Nausea ■ Oral ulceration ■ Infections (herpes zoster) ■ Severe complications in <1% of cases include ■ Cirrhosis ■ Pneumonitis ■ Leukopenia ■ Thrombocytopenia ■ Anemia
LEF	■ Inhibition of T-cell proliferation by blocking pyrimidine synthesis	■ Patients with polyarticular JIA who cannot tolerate MTX ■ Used rarely in pediatric patients because of its teratogenicity and long half-life	■ Diarrhea ■ Rashes ■ Cytopenia ■ Abnormal liver function test ■ Teratogenicity
SSZ	■ Immune-suppressive effect not fully established	■ ERA with moderate activity, but not in other types of JIA	■ Gastrointestinal toxicity ■ Sulfonamide allergy ■ Neuropsychiatric complications (headache, anxiety) ■ Pancytopenia ■ Pneumonitis ■ Myelosuppression ■ Hypogammaglobulinemia

Biologic DMARDs			
TNF inhibitors			
Adalimumab	■ Subcutaneous recombinant human IgG1κ monoclonal antibody ■ Neutralizes TNF-α by binding with soluble and membrane-bound TNF	■ JIA patients with resistance or intolerance to MTX ■ Polyarticular JIA ■ JIA with uveitis ■ ERA refractory to SSZ ■ Psoriatic JIA	■ Risk of reactivation of latent infections such as tuberculosis, and new infections caused by viruses, fungi, or bacteria ■ Rare reports of ■ Lymphoma ■ Demyelinating central nervous system disorders ■ Cardiac failure
Infliximab	■ Intravenous chimeric monoclonal antibody against TNF-α ■ Binding with soluble and transmembrane TNF-α, that mediates complement and antibody-dependent cytotoxicity of expressed TNF-α cells (macrophages and monocytes)	■ Polyarticular JIA where there has been the use of MTX for at least 3 months with poor response ■ Uveitis ■ Psoriatic JIA	■ Opportunistic infections: herpes, tuberculosis, pseudomonas pneumonia, reactivation of hepatitis B, fungal infection
Etanercept	■ Fusion protein consisting of the extracellular domain of the human p75 TNF-α receptor ■ Linked to the Fc region of human IgG1, binds and inhibits soluble TNF-α	■ Polyarticular JIA with resistance or intolerance to MTX ■ ERA ■ Psoriatic JIA	■ Central nervous system events (headache, neuritis) ■ Varicella infections ■ Rare ■ Malignancy
IL-1 inhibitors			
Anakinra	■ Recombinant IL-1 receptor antagonist binds to IL-1 receptors (IL-1r1) ■ Inhibits the binding of IL-1α and IL-1β	■ Refractory sJIA with persistent systemic symptoms ■ MAS	■ Vomiting, nausea, diarrhea ■ Headache ■ Abdominal pain ■ Upper respiratory and urinary tract infections ■ Neutropenia
Canakinumab	■ Human monoclonal antibody ■ Selectively blocks IL-1β	■ sJIA patients with continued disease activity after treatment with GC monotherapy and MTX or LEF, anakinra, or tocilizumab	■ Thrombocytopenia ■ Neutropenia ■ Upper respiratory tract infection ■ Cough ■ Abdominal pain ■ Gastroenteritis, vomiting, diarrhea ■ Pyrexia ■ Very rare ■ Pneumococcal sepsis
Rilonacept	■ Fusion protein between the Fc portion of IgG and the IL-1 receptor ■ Blocks the interaction of IL-1 with cell surface receptors preventing IL-1 signaling	■ Active sJIA	■ Infections ■ Developed elevations in liver transaminases ■ High cholesterol or triglycerides ■ Abdominal pain ■ Gastroenteritis, nausea, diarrhea
T-cell inhibitors			
Abatacept	■ Inhibitor of naive T-cell activation ■ Soluble fusion protein of CTLA-4 with the Fc portion of IgG that binds to CD80/CD86 and blockades signal following MHC peptide: TCR engagement necessary for T-cell activation	■ Severe sJIA ■ Polyarticular JIA patients with inadequate response to MTX and TNF blockers	■ Bacterial and opportunistic infections ■ Rare ■ Acute lymphoblastic leukemia

IL-6 inhibitors			
Tocilizumab	■ Humanized monoclonal antibody against the IL-6 ubiquitous receptor (IL-6R) ■ Block IL-6 signaling pathway by binding to cell surface and soluble IL-6R	■ sJIA ■ Polyarticular JIA with resistance and continued disease activity after treatment with MTX and TNF blockers	■ Headache ■ Upper respiratory tract infections (>10%) ■ Varicella, herpes zoster ■ Neutropenia ■ Elevation of aminotransferases
Anti-B-cells therapy			
Rituximab	■ Chimeric monoclonal antibody against B cells with mouse variable and human constant regions ■ Binds CD20 on the surface of B cells forming a cap that allow NK cells to destroy B cells ■ Leads to B-cell death and removal from circulation	■ JIA refractory to anti-TNF agents and standard immunosuppressive therapy	■ Infusion reactions (headache, throat irritation, rash, itchiness, pyrexia) in one-third of patients ■ Bacterial infections ■ Hepatitis B reactivation ■ Rare ■ Cardiac arrest ■ Cytokine release syndrome ■ Vultifocal leukoencephalopathy ■ Pulmonary toxicity
Janus kinase (JAK) inhibitors			
Tofacitinib	■ Inhibit JAK1 and JAK3 ■ Interrupt the JAK-STAT signaling pathway, which is responsible for the transmission of extracellular multiple pro-inflammatory cytokines, including IL-6, into the nucleus, leading to changes in DNA transcriptome	■ Refractory polyarticular JIA ■ sJIA refractory to other therapy	■ Diarrhea ■ Headache ■ High blood pressure ■ Upper respiratory tract infections ■ Varicella zoster virus reactivation ■ Cytomegalovirus infection ■ Pulmonary embolism ■ Rare ■ Lymphoma or other malignancies
IL-17A inhibitor			
Secukinumab	■ Human monoclonal antibody that inhibits IL-17A ■ Blocks the release of pro-inflammatory cytokines and chemokines	■ Active JPsA ■ Active ERA	■ Nasopharyngitis ■ Diarrhea ■ Upper respiratory tract infections ■ Inflammatory bowel disease warning
Other medications			
Glucocorticoids (GC)	■ Binding to glucocorticoid receptors inhibits calcium and sodium cycle across plasma membranes, reducing activation and proliferation of immune cells ■ Posttranscriptional destabilization of messenger RNA resulting in reduced production of pro-inflammatory cytokines including IL-1 and IL-6	■ √ Systemic steroids for: ■ sJIA with serious organ involvement (including pericarditis and myocarditis) ■ Patients with features indicative of MAS ■ High disease activity in oligo- and polyarticular JIA ■ Intra-articular steroids for oligo- and polyarticular JIA	■ Infections ■ Myopathy ■ Neuropsychiatric symptoms ■ Osteoporosis ■ Obesity ■ Insulin resistance ■ Cushing syndrome ■ Gastric ulcer ■ Cataract ■ Glaucoma
Cyclosporine A	■ A fungal cyclic polypeptide ■ Binds to the cellular protein cyclophilin, resulting in inhibition of the enzyme calcineurin ■ Specifically and reversibly inhibits CD4+ immunocompetent lymphocytes in the G0-G1 phase of the cell cycle ■ Then inhibits IL-2 production and release by T helpers	■ sJIA with indication of MAS	■ Nausea ■ Headache ■ Renal complications ■ Neuronal complications (paresthesia) ■ Hepatotoxicity

DMARDs, disease-modifying antirheumatic drugs; ERA, enthesitis-related arthritis; GC, glucocorticoids; IL, interleukin; JPsA, juvenile psoriatic arthritis; LEF, leflunomide; MAS, macrophage activation syndrome; MTX, methotrexate; NK,

natural killer; sJIA, systemic JIA; SSZ, sulfasalazine; TCR, T-cell receptor; TNF, tumor necrosis factor.

Source: Adapted from Zaripova LN, Midgley A, Christmas SE, et al. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. *Pediatr Rheumatol Online J*. 2021;19(1):135. Provided by the Springer Nature SharedIt content-sharing initiative.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62(9):2569–2581. (16)

Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):703–716. (178)

Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2021;73(7):924–939. (30)

Onel, KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: recommendations for nonpharmacologic therapies, medication monitoring, immunizations, and imaging. *Arthritis Care Res (Hoboken).* 2022;74(4): 505–520. (175) full reference pending

Onel, KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken).* 2022;74(4):521–537. (177) full reference pending

Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile

idiopathic arthritis: therapeutic approaches for nonsystemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):717–734. (176)

Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol.* 2016;68(1):1–26. (29)

Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685–699. (28)

Key Websites

The American College of Rheumatology. Rheumatology image bank. http://images.rheumatology.org/

Arthritis Foundation. What is arthritis? http://www.arthritis.org/about-arthritis/understanding-arthritis/ (1)

COMPLETE REFERENCES OF CHAPTER 44 RHEUMATOID ARTHRITIS

1. Arthritis Foundation. What is arthritis? Accessed June 30, 2021. http://www.arthritis.org/about-arthritis/understanding-arthritis/
2. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955–2007. *Arthritis Rheum*. 2010;62(6):1576–1582.
3. Firestein G. Etiology and pathogenesis of rheumatoid arthritis. In: Kelley W, ed. *Kelley's Textbook of Rheumatology*. 9th ed. Saunders/Elsevier; 2013:1059–1108.
4. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008;58(1):15–25.
5. Tobón GJ, Youinou P, Saraux A, et al. The environment, geo-epidemiology, and autoimmune disease: rheumatoid arthritis. *Autoimmun Rev*. 2010;9(5):A288–A292.
6. Carlens C, Hergens MP, Grunewald J, et al. Smoking, use of moist snuff, and risk of chronic inflammatory diseases. *Am J Respir Crit Care Med*. 2010;181(11):1217–1222.

7. Hale L. Pathology of rheumatoid arthritis and associated disorders. In: Koopman WJ, Moreland LW, ed. *Arthritis and Allied Conditions: A Textbook of Rheumatology*. 15th ed. Lippincott Williams & Wilkins; 2005:1117.
8. Carter RH. B cells in health and disease. *Mayo Clin Proc*. 2006;81(3):377–384.
9. Choy EH. Clinical significance of Janus Kinase inhibitor selectivity [published correction appears in *Rheumatology (Oxford)*. 2019 Jun 1;58(6):1122]. *Rheumatology (Oxford)*. 2019;58(6):953–962.
10. Harigai M, Honda S. Selectivity of Janus kinase inhibitors in rheumatoid arthritis and other immune-mediated inflammatory diseases: is expectation the root of all headache? *Drugs*. 2020;80(12):1183–1201.
11. Lee M. *Rheumatic Diseases. Basic Skills in Interpreting Laboratory Data*. 5th ed. American Society of Health-System Pharmacists; 2013.
12. Sweeney SE, Harris ED, Firestein GS. Clinical features of rheumatoid arthritis. In: Firestein G, ed. *Kelley's Textbook of Rheumatology*. 9th ed. Sanders/Elsevier; 2013:1109–1136.
13. Wasserman AM. Diagnosis and management of rheumatoid arthritis. *Am Fam Physician*. 2011;84(11):1245–1252.
14. Edworthy SM. Morning stiffness: sharpening an old saw? *J Rheumatol*. 1999;26(5):1015–1017.
15. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum*. 2002;46(2):328–346.
16. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569–2581.
17. Balsa A, Cabezón A, Orozco G, et al. Influence of HLA DRB1 alleles in the susceptibility of rheumatoid arthritis and the regulation of antibodies against citrullinated proteins and rheumatoid factor. *Arthritis Res Ther*. 2010;12(2):R62.
18. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010;376(9746):1094–1108.
19. Andrade F, Darrah E, Rosen A. Autoantibodies in rheumatoid arthritis. In: Firestein G, ed. *Kelley's Textbook of Rheumatology*. 9th ed. Saunders/Elsevier; 2013:804–817.
20. Jansen LM, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BA. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. *Ann Rheum Dis*. 2001;60(10):924–927.
21. Wild N, Karl J, Grunert VP, et al. Diagnosis of rheumatoid arthritis: multivariate analysis of biomarkers. *Biomarkers*. 2008;13(1):88–105.
22. Rantapää-Dahlqvist S, de Jong BA, Berglin E, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum.* 2003;48(10):2741–2749.

23. Sun J, Zhang Y, Liu L, Liu G. Diagnostic accuracy of combined tests of anti cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis: a meta-analysis. *Clin Exp Rheumatol*. 2014;32(1):11–21.
24. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis*. 2003;62(8):722–727.
25. Turesson C, Jacobsson LT. Epidemiology of extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol*. 2004;33(2):65–72.
26. Gerli R, Sherer Y, Bocci EB, Vaudo G, Moscatelli S, Shoenfeld Y. Precocious atherosclerosis in rheumatoid arthritis: role of traditional and disease-related cardiovascular risk factors. *Ann N Y Acad Sci*. 2007;1108:372–381.
27. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis*. 2017;76(1):17–28.
28. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685–699.
29. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68(1):1–26.
30. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2021;73(7):924–939.
31. Vliet Vlieland TP. Non-drug care for RA—is the era of evidence-based practice approaching? *Rheumatology (Oxford)*. 2007;46(9):1397–1404.
32. Häkkinen A, Sokka T, Kotaniemi A, Hannonen P. A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. *Arthritis Rheum*. 2001;44(3):515–522.
33. Van Den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM. Dynamic exercise therapy for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2000;(2):CD000322.
34. Egan M, Brosseau L, Farmer M, et al. Splints/orthoses in the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev*. 2003;(1):CD004018.
35. Rogers MP, Liang MH, Partridge AJ. Psychological care of adults with rheumatoid arthritis. *Ann Intern Med*. 1982;96(3):344–348.
36. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med*. 2002;64(1):52–60.
37. Astin JA, Beckner W, Soeken K, Hochberg MC, Berman B. Psychological interventions for rheumatoid arthritis: a meta-analysis of randomized

controlled trials. *Arthritis Rheum*. 2002;47(3):291–302.
38. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum*. 2011;63(3):573–586.
39. Xeljanz (tofacitinib citrate). Package insert. Pfizer Labs; 2022.
40. Olumiant (baricitinib). Package insert. Eli Lilly and Company; 2021.
41. Rinvoq (upadacitinib). Package insert. AbbVie Inc; 2022.
42. O'Dell J. Treatment of rheumatoid arthritis. In: Firestein G, Ed. *Kelley's Textbook of Rheumatology*. 9th ed. Saunders/Elsevier; 2013:1137–1160.
43. TheMedicalLetter.org. Drugs for rheumatoid arthritis. *Treat Guidel Med Lett*. 2012;10(117):37–44.
44. Jenkins JK, Hardy KJ. Biological modifier therapy for the treatment of rheumatoid arthritis. *Am J Med Sci*. 2002;323(4):197–205.
45. Moreland LW, Morgan EE, Adamson TC 3rd, et al. T cell receptor peptide vaccination in rheumatoid arthritis: a placebo-controlled trial using a combination of Vbeta3, Vbeta14, and Vbeta17 peptides. *Arthritis Rheum*. 1998;41(11):1919–1929.
46. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med*. 1999;130(6):478–486.
47. Enbrel (etanercept). Package insert. Amgen? Immunex; 2021.
48. Humira (adalimumab). Package insert. AbbVie Inc; 2021.
49. Remicade (infliximab). Package insert. Janssen Biotech, Inc; 2021.
50. Nurmohamed MT. Newer biological agents in the treatment of rheumatoid arthritis: do the benefits outweigh the risks? *Drugs*. 2009;69(15):2035–2043.
51. Simponi (golimumab). Package insert. Janssen Biotech, Inc; 2019.
52. Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *Can Med Assoc J*. 2009;181(11):787–796.
53. Orencia (abatacept). Package insert. Bristol Meyer Squibb; 2021.
54. Kremer JM, Genant HK, Moreland LW, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum*. 2008;58(4):953–963.
55. Rituxan (rituximab). Package insert. Biogen and Genentech; 2021.
56. Genovese MC, Rubbert-Roth A, Smolen JS, et al. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. *J Rheumatol*. 2013;40(6):768–780.
57. van Vollenhoven RF, Emery P, Bingham CO 3rd, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J Rheumatol*. 2010;37(3):558–567.
58. Actemra (tocilizumab). Package insert. Genentech; 2022.

59. Kevzara (sarilumab). Package insert. Regeneron Sanofi Genzyme; 2018.
60. Lipsky PE. Interleukin-6 and rheumatic diseases. *Arthritis Res Ther*. 2006;8(suppl 2):S4.
61. Nakahara H, Nishimoto N. Anti-interleukin-6 receptor antibody therapy in rheumatic diseases. *Endocr Metab Immune Disord Drug Targets*. 2006;6(4):373–381.
62. Singh JA, Cameron C, Noorbaloochi S, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet*. 2015;386(9990):258–265.
63. Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2010;69(6):1010–1014.
64. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2007(1):CD006356.
65. Buttgereit F, Mehta D, Kirwan J, et al. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). *Ann Rheum Dis*. 2013;72(2):204–210.
66. Buttgereit F, Doering G, Schaeffler A, et al. Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann Rheum Dis*. 2010;69(7):1275–1280.
67. Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet*. 2008;371(9608):205–214.
68. Saag KG. Resolved: low-dose glucocorticoids are neither safe nor effective for the long-term treatment of rheumatoid arthritis. *Arthritis Rheum*. 2001;45(5):468–471.
69. Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2011;70(6):909–920.
70. Slimani S, Lukas C, Combe B, Morel J. Rituximab in rheumatoid arthritis and the risk of malignancies: report from a French cohort. *Joint Bone Spine*. 2011;78(5):484–487.
71. Parida JR, Misra DP, Wakhlu A, Agarwal V. Is non-biological treatment of rheumatoid arthritis as good as biologics? *World J Orthop*. 2015;6(2):278–283.
72. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(5):625–639.

73. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Probability of continued low disease activity in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Ann Rheum Dis*. 2008;67(2):266–269.
74. Daul P, Grisanti J. Monitoring response to therapy in rheumatoid-arthritis—perspectives from the clinic. *Bull NYU Hosp Jt Dis*. 2009;67(2):236–242.
75. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol*. 2005;23(5, suppl 39):S100–S108.
76. Hicks A, Adams H, Szczepanski J. Medical imaging and radiographic analysis of the rheumatoid patient. *Clin Podiatr Med Surg*. 2010;27(2):209–218.
77. Cohen G, Gossec L, Dougados M, et al. Radiological damage in patients with rheumatoid arthritis on sustained remission. *Ann Rheum Dis*. 2007;66(3):358–363.
78. Koopman WJ Moreland LW. NSAIDs for RA. In: Koopman WJ, Moreland LW, eds. *Arthritis and Allied Conditions: A Textbook of Rheumatology*. 15th ed. Lippincott Williams & Wilkins; 2005.
79. TheMedicalLetter.org. Drugs for rheumatoid arthritis. *Treat Guidel Med Lett*. 2009;7(81):37–46.
80. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296(13):1633–1644.
81. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769–779.
82. Massó Gonzàlez EL, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum*. 2010;62(6):1592–1601.
83. Bidaut-Russell M, Gabriel SE. Adverse gastrointestinal effects of NSAIDs: consequences and costs. *Best Pract Res Clin Gastroenterol*. 2001;15(5):739–753.
84. García Rodríguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. *Gastroenterology*. 2007;132(2):498–506.
85. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA*. 2000;284(10):1247–1255.
86. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs—differences and similarities. *N Engl J Med*. 1991;324(24):1716–1725.

87. Wolfe MM, Lichtenstein DR, Singh G.et al. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340(24):1 888–1899.
88. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med*. 1996;156(14):1530–1536.
89. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol Suppl*. 1999;56:18–24.
90. TheMedicalLetter.org. Treatment of peptic ulcers and GERD. *Treat Guidel Med Lett*. 2008;6(72):55–60.
91. Graham DY, Agrawal NM, Campbell DR, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active and placebo-controlled study of misoprostol vs lansoprazole. *Arch Intern Med*. 2002;162(2):169–175.
92. Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104(3):728–738.
93. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med*. 2000;160(5):610–619.
94. Dunn MJ, Simonson M, Davidson EW, Scharschmidt LA, Sedor JR. Nonsteroidal anti-inflammatory drugs and renal function. *J Clin Pharmacol*. 1988;28(6):524–529.
95. Rossat J, Maillard M, Nussberger J, Brunner HR, Burnier M. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt-depleted subjects. *Clin Pharmacol Ther*. 1999;66(1):76–84.
96. Risser A, Donovan D, Heintzman J, Page T. NSAID prescribing precautions. *Am Fam Physician*. 2009;80(12):1371–1378.
97. Hudson M, Richard H, Pilote L, et al. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. *BMJ*. 2005;330(7504):1370.
98. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1984;310(9):563–572.
99. Chou R, Helfand M, Peterson K, Dana T, Roberts C. *Comparative Effectiveness and Safety of Analgesics for Osteoarthritis*. Agency for Healthcare Research and Quality (US); 2006.
100. Johnson AG. NSAIDs and increased blood pressure. What is the clinical significance? *Drug Saf*. 1997;17(5):277–289.
101. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. *Arthritis Rheum*. 1996;39(5):723–731.
102. Plaquenil (hydroxychloroquine). Package insert. Sanofi-Aventis; 2015.

103. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). *Ophthalmology*. 2016;123(6):1386–1394.
104. Rosenbaum JT, Costenbader KH, Desmarais J, et al. American College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and American Academy of Ophthalmology 2020 joint statement on hydroxychloroquine use with respect to retinal toxicity. *Arthritis Rheumatol*. 2021;73(6):908–911.
105. TheMedicalLetter.org. Drugs for rheumatoid arthritis. *Treat Guidel Med Lett*. 2014;56(1458):6.
106. Micromedex Healthcare Series [Internet database]. Thomson Micromedex. Updated periodically.
107. Bianchi G, Caporali R, Todoerti M, Mattana P. Methotrexate and rheumatoid arthritis: current evidence regarding subcutaneous versus oral routes of administration. *Adv Ther*. 2016;33(3):369–378. doi:10.1007/s12325-016-0295-8
108. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rhuem Dis*. 2009;68(7):1086–1093.
109. Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. *Eur Respir J*. 2000;15(2):373–381.
110. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med*. 1999;340(4):253–259.
111. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet*. 2008;372(9636):375–382.
112. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med*. 2000;343(22):1586–1593.
113. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum*. 2002;46(6):1443–1450.
114. Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of safety and effectiveness of etanercept in Japanese patients with rheumatoid arthritis. *Mod Rheumatol*. 2011;21(4):343–351.

115. Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases (May 2003). *Ann Rheum Dis*. 2003;62(suppl 2):ii2–ii9.
116. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*. 2003;48(1):35–45.
117. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum*. 2006;54(1):26–37.
118. Hetland ML, Christensen IJ, Tarp U, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum*. 2010;62(1):22–32.
119. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet*. 1999;354(9194):1932–1939.
120. Mease PJ. Certolizumab pegol in the treatment of rheumatoid arthritis: a comprehensive review of its clinical efficacy and safety. *Rheumatology (Oxford)*. 2011;50(2):261–270.
121. Cimzia (certolizumab pegol). Package insert. UCB, Inc; 2019.
122. Nesbitt A, Fossati G, Bergin M, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor alpha agents. *Inflamm Bowel Dis*. 2007;13(11):1323–1332.
123. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis*. 2009;68(6):805–811.
124. Smolen J, Landewé RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis*. 2009;68(6):797–804.
125. Strand V, Mease P, Burmester GR, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Res Ther*. 2009;11(6):R170.
126. Keystone E, Landewé R, van Vollenhoven R, et al. Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the

treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. *Ann Rheum Dis*. 2014;73(12):2094–2100.

127. Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann Rheum Dis*. 2018;77(2):228–233.
128. Clowse ME, Förger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. *Ann Rheum Dis*. 2017;76(11):1890–1896.
129. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol*. 2020;72(4):529–556.
130. McCluggage LK, Scholtz JM. Golimumab: a tumor necrosis factor alpha inhibitor for the treatment of rheumatoid arthritis. *Ann Pharmacother*. 2010;44(1):135–144.
131. Simponi Aria (golimumab). Package insert. Janssen Biotech; 2016.
132. Emery P, Fleischmann R, van der Heijde D, et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum*. 2011;63(5):1200–1210.
133. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum*. 2008;58(4):964–975.
134. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet*. 2009;374(9685):210–221.
135. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis*. 2009;68(6):789–796.
136. Danila MI, Patkar NM, Curtis JR, Saag KG, Teng GG. Biologics and heart failure in rheumatoid arthritis: are we any wiser? *Curr Opin Rheumatol*. 2008;20(3):327–333.
137. FDA Drug Safety Communication: UPDATE on Tumor Necrosis Factor (TNF) blockers and risk for pediatric malignancy. 2011. Accessed May 2022. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-update-tumor-necrosis-factor-tnf-blockers-and-risk-pediatric
138. Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. *Arthritis Res Ther*. 2009;11(suppl 1):S1.

139. Lloyd S, Bujkiewicz S, Wailoo AJ, Sutton AJ, Scott D. The effectiveness of anti-TNF-alpha therapies when used sequentially in rheumatoid arthritis patients: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2010;49(12):2313–2321.
140. Hyrich KL, Lunt M, Watson KD, et al. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum*. 2007;56(1):13–20.
141. Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum*. 2011;63(10):2854–2864.
142. Kremer JM, Peterfy C, Russell AS, et al. Long term safety, efficacy, and inhibition of structural damage progression over 5 years of treatment with abatacept in patients with rheumatoid arthritis in the abatacept in inadequate responders to methotrexate trial. *J Rheumatol*. 2014;41(6):1077–1087.
143. Westhovens R, Kremer JM, Emery P, et al. Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study. *Clin Exp Rheumatol*. 2014;32(4):553–562.
144. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med*. 2005;353(11):1114–1123.
145. Schiff M, Pritchard C, Huffstutter JE, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. *Ann Rheum Dis*. 2009;68(11):1708–1714.
146. Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis*. 2014;73(1):86–94.
147. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med*. 2004;350(25):2572–2581.
148. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum*. 2006;54(9):2793–2806.
149. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. *Ann Rheum Dis*. 2009;68(2):216–221.

150. Burmester GR, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis*. 2014;73(1):69–74.
151. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum*. 2008;58(10):2968–2980.
152. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis*. 2008;67(11):1516–1523.
153. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis: a Cochrane systematic review. *J Rheumatol*. 2011;38(1):10–20.
154. Hashimoto J, Garnero P, van der Heijde D, et al. Humanized anti-interleukin-6-receptor antibody (tocilizumab) monotherapy is more effective in slowing radiographic progression in patients with rheumatoid arthritis at high baseline risk for structural damage evaluated with levels of biomarkers, radiography, and BMI: data from the SAMURAI study. *Mod Rheumatol*. 2011;21(1):10–15.
155. Gabay C Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet*. 2013;381(9877):1541–1550.
156. Schiff MH, Kremer JM, Jahreis A, et al. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther*. 2011;13(5):R141.
157. Kume K, Amano K, Yamada S, Hatta K, Ohta H, Kuwaba N. Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial. *J Rheumatol*. 2011;38(10):2169–2171.
158. Genovese MC, Fleischmann R, Kivitz A, et al. Efficacy and safety of sarilumab in combination with csDMARDs or as monotherapy in subpopulations of patients with moderately to severely active rheumatoid arthritis in three phase III randomized, controlled studies. *Arthritis Res Ther*. 2020;22(1):139.
159. Fleischmann R, Genovese MC, Lin Y, et al. Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years' follow-up. *Rheumatology (Oxford)*. 2020;59(2):292–302.
160. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381(9865):451–460.

161. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243–1252.
162. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet*. 2018;391(10139):2513–2524.
163. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med*. 2022;386(4):316–326.
164. Kragstrup TW, Glintborg B, Svensson AL, et al. Waiting for JAK inhibitor safety data. *RMD Open*. 2022;8(1):e002236.
165. Alves C, Penedones A, Mendes D, Marques F. The risk of infections associated with JAK inhibitors in rheumatoid arthritis. *J Clin Rheumatology*. 2022;28(2):e407–e414.
166. Nash P, Kerschbaumer A, Dörner T, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis*. 2021;80(1):71–87.
167. Haraoui B. Assessment and management of rheumatoid arthritis. *J Rheumatol Suppl*. 2009;82:2–10.
168. Gotzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2004(3):CD000189.
169. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med*. 2004;141(10):764–770.
170. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2008;47(1):72–75.
171. Weiss MM. Corticosteroids in rheumatoid arthritis. Semin *Arthritis Rheum*. 1989;19(1):9–21.
172. McCurdy D, Parsa MF. Updates in juvenile idiopathic arthritis. *Adv Pediatr*. 2021;68:143–170.
173. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2011;377(9783):2138–2149.
174. Dannecker GE, Quartier P. Juvenile idiopathic arthritis: classification, clinical presentation and current treatments. *Horm Res*. 2009;72(suppl 1):4–12.
175. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the treatment of juvenile idiopathic arthritis: recommendations for nonpharmacologic therapies, medication monitoring, immunizations, and imaging. *Arthritis Care Res (Hoboken)*. 2022;74(4):505–520.
176. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the treatment of juvenile

idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):717–734.

177. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*. 2022;74(4):521–537.
178. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):703–716.
179. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res (Hoboken)*. 2011;63(4):465–482.
180. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390–392.
181. Martini A, Lovell DJ. Juvenile idiopathic arthritis: state of the art and future perspectives. *Ann Rheum Dis*. 2010;69(7):1260–1263.
182. Aggarwal A, Misra DP. Enthesitis-related arthritis. *Clin Rheumatol*. 2015;34(11):1839–1846.
183. Shenoi S, Wallace CA. Remission in juvenile idiopathic arthritis: current facts. *Curr Rheumatol Rep*. 2010;12(2):80–86.
184. Jiang K, Frank M, Chen Y, Osban J, Jarvis JN. Genomic characterization of remission in juvenile idiopathic arthritis. *Arthritis Res Ther*. 2013;15(4):R100.
185. Fantini F, Gerloni V, Gattinara M, Cimaz R, Arnoldi C, Lupi E. Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. *J Rheumatol*. 2003;30(3):579–584.
186. Long AR, Rouster-Stevens KA. The role of exercise therapy in the management of juvenile idiopathic arthritis. *Curr Opin Rheumatol*. 2010;22(2): 213–217.
187. Houghton K. Physical activity, physical fitness, and exercise therapy in children with juvenile idiopathic arthritis. *Phys Sportsmed*. 2012;40(3):77–82.
188. Cosentyx (secukinumab) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021
189. Zulian F, Martini G, Gobber D, Plebani M, Zacchello F, Manners. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. *Rheumatology (Oxford)*. 2004;43(10):1288–1291.

190. Zulian F, Martini G, Gobber D, Agosto C, Gigante C, Zacchello F. Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2003;42(10):1254–1259.
191. Patel K, Gerber B, Bailey K, Saeed NR. Juvenile idiopathic arthritis of the temporomandibular joint - no longer the forgotten joint. *Br J Oral Maxillofac Surg*. 2022;60(3):247–256.
192. Martini A, Lovell DJ, Albani S, et al. Juvenile idiopathic arthritis. *Nat Rev Dis Primers*. 2022;8(1):5.
193. Barisic Kutija M, Peric S, Knezevic J, Juratovac Z, Vukojevic N. Complication and prognosis of juvenile idiopathic arthritis associated uveitis in the era of modern immunomodulatory treatment. *Psychiatr Danub*. 2019;31(Suppl 1):44–49.
194. Goldmuntz EA, White PH. Juvenile idiopathic arthritis: a review for the pediatrician. *Pediatr Rev*. 2006;27(4):e24–e32.
195. Elsevier Inc. Clinical pharmacology [database online]. 2022. Accessed April 14, 2022. www.https://www.clinicalkey.com/pharmacology/
196. Klein A, Horneff G. Treatment strategies for juvenile idiopathic arthritis. *Expert Opin Pharmacother*. 2009;10(18):3049–3060.
197. Beukelman T. Treatment advances in systemic juvenile idiopathic arthritis. *F1000Prime Rep*. 2014;6:21.
198. Pignatti P, Vivarelli M, Meazza C, Rizzolo MG, Martini A, De Benedetti F. Abnormal regulation of interleukin 6 in systemic juvenile idiopathic arthritis. *J Rheumatol*. 2001;28(7):1670–1676.
199. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med*. 2005;201(9):1479–1486.
200. Giancane G, Minoia F, Davì S, et al. IL-1 inhibition in systemic juvenile idiopathic arthritis. *Front Pharmacol*. 2016;7:467.
201. Quartier P, Allantaz F, Cimaz R, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis*. 2011;70(5):747–754.
202. Ilaris (canakinumab). Package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.
203. Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med*. 2012;367(25):2396–2406.
204. Grom AA. Canakinumab for the treatment of systemic juvenile idiopathic arthritis. *Expert Rev Clin Immunol*. 2014;10(11):1427–1435.
205. Arcalyst (rilonacept). Package insert. London: Kiniksa Pharmaceuticals (UK), Ltd.; 2021.

206. Lovell DJ, Giannini EH, Reiff AO, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. *Arthritis Rheum*. 2013;65(9):2486–2496.
207. De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med*. 2012;367(25):2385–2395.
208. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. *JAMA*. 2005;294(13):1671–1684.
209. Lovell DJ, Reiff A, Jones OY, et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2006;54(6):1987–1994.
210. Woo P, Southwood TR, Prieur AM, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. *Arthritis Rheum*. 2000;43(8):1849–1857.
211. Ravelli A, Viola S, Ramenghi B, Beluffi G, Zonta LA, Martini A. Radiologic progression in patients with juvenile chronic arthritis treated with methotrexate.*J Pediatr*. 1998;133(2):262–265.
212. Wallace CA. The use of methotrexate in childhood rheumatic diseases. *Arthritis Rheum*. 1998;41(3):381–391.
213. Cassidy JT. Outcomes research in the therapeutic use of methotrexate in children with chronic peripheral arthritis. *J Pediatr*. 1998;133(2):179–180.
214. Gottlieb BS, Keenan GF, Lu T, Ilowite NT. Discontinuation of methotrexate treatment in juvenile rheumatoid arthritis. *Pediatrics*. 1997;100(6):994–997.

45

Gout and Hyperuricemia

Troy Lynn Lewis and Kimmy Nguyen

CORE PRINCIPLES		CHAPTER CASES
1	Gout is a disease that causes acute joint inflammation and pain secondary to the deposition of monosodium urate (MSU) crystals within the synovial fluid and lining. Clinically, acute gout presents as monoarticular inflammation in 90% of patients with the first metatarsophalangeal joint (great toe) typically affected; this is called podagra. Patients presenting with acute gout may or may not have hyperuricemia.	**Case 45-1 (Question 1)**
2	A definitive diagnosis of gout can be made if MSU crystals are present in a synovial fluid sample. However, the presence of hyperuricemia, clinical features, and imaging studies may be	**Case 45-2 (Questions 1–3)**

	useful if examination of synovial fluid is not possible.	
3	The primary goal of treating acute gout attacks is the relief of pain and inflammation. It is not necessary to lower the serum uric acid (SUA) immediately.	**Case 45-2 (Question 3), Table 45-2**
4	Acute episodes of gout are primarily treated with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids.	**Case 45-2 (Questions 4, 5) Case 45-3 (Question 1), Table 45-2**
5	Low-dose oral colchicine is as effective as and safer than traditional high-dose regimens, which are dosed to toxicity (diarrhea); avoid potential colchicine drug–drug interactions.	**Case 45-2 (Questions 4, 5) Case 45-3 (Questions 1, 5), Table 45-3**
6	Nonpharmacologic therapy for acute and chronic gout includes limiting daily alcoholic beverages, purine-rich meats, and fructose-containing beverages/foods. Specifically, beer and, to a smaller extent, spirits are associated with increased gout attacks; wine is less likely to be a risk factor. Increasing low-fat dairy protein has a favorable effect on SUA.	**Case 45-1 (Questions 3) Case 45-2 (Question 6) Case 45-1 (Question 2), Table 45-2**
7	Recent evidence has shown starting urate-lowering therapy (ULT) during a flare did not significantly worsen the flare, and guidelines now recommend initiating ULT during the flare, as opposed to after the flare has resolved.	**Case 45-3 (Questions 2, 3), Table 45-2**

	ULT should be initiated in patients with >1 subcutaneous tophi, frequent gout flares (>2 per year), and radiographic damage. Additionally, for patients experiencing their first flare and chronic kidney disease (CKD) stage >3, SUA >9 mg/dL, or urolithiasis, ULT may be initiated.	
8	Patients should be evaluated for drug-induced hyperuricemia before treatment.	**Case 45-3 (Question 3), Table 45-1**
9	The goal of ULT is to lower the SUA to <6 mg/dL. If this goal is achieved, most patients can be "cured" of acute gout attacks.	**Case 45-3 (Questions 3–5), Table 45-2**
10	The preferred first-line treatment of gout and hyperuricemia is xanthine oxidase (XO) inhibitors. Monitor for drug–drug interactions. Note that treatment of asymptomatic hyperuricemia with ULT is not recommended.	**Case 45-3 (Questions 4, 5) Case 45-4 (Question 1), Tables 45-2, 45-4**
11	Initiation of ULT can precipitate acute gout attacks, so prophylaxis with colchicine, NSAIDs, or prednisone/prednisolone is recommended, and the choice of specific anti-inflammatory prophylaxis should be based on patient factors. Prophylaxis should be continued for 3 to 6 months and continued as needed if the patient continues to experience flares.	**Case 45-3 (Question 5), Table 45-2**

INTRODUCTION

Gout is a form of arthritis characterized by recurrent episodes of acute joint pain and inflammation caused by the deposition of monosodium urate (MSU) crystals in joints and soft tissue. MSU crystals form as a result of elevated urate concentrations, and deposition in the urinary tract can cause urolithiasis and urinary obstruction.[1] Patients with gout may undergo asymptomatic periods or experience acute arthritis (gout flares) or chronic inflammation (gouty arthritis).[2] Hallmark characteristics of gout include the presence of tophi, which are hard nodules of MSU crystals that have been deposited in soft tissues. Tophi are most commonly found in the toes, fingers, and elbows. Although gout is often associated with hyperuricemia (defined as a serum urate level of ≥6.8 mg/dL),[3] elevated serum uric acid (SUA) does not always result in gout.[4] In a retrospective review of two studies on gout, 14% of patients presenting with acute symptoms had a normal SUA concentration <6 mg/dL, and 32% had an SUA concentration <8 mg/dL.[5] Another retrospective analysis that examined the cumulative incidence of gout using baseline SUA levels found that only about half of participants with SUA ≥10 mg/dL developed gout over 15 years.[6] Therefore, gout should be considered a clinical diagnosis, whereas hyperuricemia relies solely on an elevated laboratory value. These two terms are not synonymous and are not interchangeable.

Uric Acid Disposition

Uric acid is the end product of purine metabolism and serves no biologic function. Unlike animals, humans lack the enzyme uricase, which degrades uric acid into more soluble products for excretion. As a result, uric acid does not undergo metabolism, and the majority is renally excreted. Up to one-third of the daily uric acid produced is eliminated through the gastrointestinal (GI) tract.[7] Therefore, increased SUA concentrations arise from an increase in uric acid

production, a decrease in uric acid renal excretion, or a combination of the two.

OVERPRODUCTION

Overproduction of uric acid accounts for ~10% of gout cases[7] and can result from excessive de novo purine synthesis, which is primarily associated with rare genetic enzyme mutation defects, some neoplastic diseases, aggressive cytotoxic chemotherapy (causing tumor lysis syndrome), and certain myeloproliferative disorders. Overproduction of uric acid can also be the result of excessive dietary intake of purines from meat, seafood, high-fructose corn syrup (eg, soft drinks), beer, and other alcoholic beverages.[8–10] Interestingly, results from a meta-analysis suggest that dietary modifications yield minimal effect on SUA levels.[11] However, counseling and education on limiting purine and alcohol intake remain recommendations for gout management.

UNDEREXCRETION

A defect in the renal clearance of uric acid is the main cause of hyperuricemia and gout in about 90% of patients. Uric acid is filtered in the renal glomerulus and is almost completely (98%–100%) reabsorbed in the proximal tubule. Uric acid is then secreted distal to the proximal tubular reabsorption site, and most is reabsorbed again.[4] In healthy patients, homeostasis between reabsorption and secretion of urate is maintained. However, many factors (eg, renal impairment, certain drugs, excessive alcohol intake, metabolic syndrome, hypertension [HTN], coronary heart disease [CHD]) can cause this balance to fail, resulting in excess serum concentrations of uric acid and tissue deposition.[7,12]

ACUTE GOUT

Epidemiology

Global incidence and prevalence of gout vary, but higher prevalence has been observed in developed countries. Gout generally presents during middle age, and increasing age carries a strong association with a higher risk of hyperuricemia. Hyperuricemia increases the risk of gout in both males and females, but males are at an increased risk of elevated SUA levels.[13] Females have a lower prevalence of gout at all ages, whereas males experience a steady increase in gout risk with age. However, the risk of gout increases in females after menopause, and this is attributed to the uricosuric action of estrogen.[14,15]

Clinical Features

CASE 45-1

Question 1: M.D. is an obese 60-year-old female who has been referred to a medication management clinic by her primary care physician. She states that her past medical history includes HTN, type 2 diabetes, hyperlipidemia, and gout. M.D. states she was diagnosed with gout 3 months ago when she had a painful and swollen right big toe. When asked about that episode, M.D. related the following story: "One morning I just woke up and my big toe was swollen, red, and very painful. I couldn't even put weight on it. I had gone to my husband's 50th high school reunion the night before, and it was fine then because we danced all night. I did have a little too much to drink, though, so I thought maybe I had stubbed my toe without realizing it and broke it."

What signs and symptoms did M.D. exhibit that are typical of acute gout?

M.D.'s symptoms of severe, acute pain and an obviously inflamed joint are consistent with the usual presentation of gout. In addition, M.D.'s age is consistent with the epidemiologic data that are commonly associated with gout.

PAIN

The pain of gout rapidly reaches its maximum <24 hours of onset and is usually accompanied by erythema.[16] It is often so severe that patients cannot even tolerate a sheet lying on top of the affected area.

NUMBER AND TYPE OF JOINTS

M.D.'s report of a very painful big toe is typical. Approximately 90% of initial acute attacks are monoarticular, affecting a single joint. The first metatarsophalangeal joint (the great toe) is the most commonly affected joint, a condition referred to as podagra. The ankle and foot are also commonly affected joints.

Although initial gout attacks are primarily monoarticular, persistent hyperuricemia can lead to recurrent flares causing a polyarticular presentation overtime. Joints of the upper limbs can be affected. Generally, these recurrent attacks are more frequent and of longer duration than initial attacks.

Atypical presentations of gout can also occur. Elderly patients may initially present with polyarticular involvement. Multiple joints in the hands can be affected, which may be mistaken for rheumatoid arthritis or osteoarthritis in this population. This is more commonly seen in elderly females.[3,4]

NOCTURNAL OCCURRENCE

The onset of pain in M.D. during the night is typical of gout. The risk of gout attacks occurring during the night and through the early morning is approximately three times higher than during the daytime. Potential biologic mechanisms for this phenomenon include lower body temperature in the early morning, relative nocturnal arterial dehydration, or the nocturnal decrease in cortisol levels.[17]

PHYSICAL STRESS

Gout attacks also seem to be more common during episodes of increased physical activity. The acute episode of toe pain experienced by M.D. after a night of dancing is consistent with the appearance of gout after increased physical exercise or physical trauma.[18]

Risk Factors

CASE 45-1, QUESTION 2: What findings in M.D. place her at risk for gout?

The diagnoses of HTN, type 2 diabetes, hyperlipidemia, and obesity in M.D. have been associated with an increased risk of gout and hyperuricemia.

Common modifiable risk factors include alcohol consumption, the use of urate-elevating drugs, obesity, and diet. Certain conditions such as insulin resistance and other metabolic syndromes, chronic kidney disease (CKD), history of urolithiasis, CHD, organ transplant, and lead exposure are also associated with an increased risk of hyperuricemia and gout.[3,19]

URATE-ELEVATING MEDICATIONS

The consumption of urate-elevating medications is a potentially modifiable risk factor. Medications can increase blood uric acid levels through various mechanisms such as increased production, increased renal reabsorption, decreased excretion, decreased renal secretion, and decrease renal filtration. Medications that increase uric acid levels are highlighted in **Table 45-1**. Patients' medication lists should be surveyed for medications that can increase uric acid levels. A risk versus benefits assessment should be completed to determine if the offending medication can be discontinued and/or substituted with alternatives when possible. However, discontinuation of an offending medication may not always be possible. Patients taking these medications should be educated on the importance of maintaining adequate hydration. Regardless, routine monitoring of uric acid levels is recommended.[4,20]

Table 45-1
Urate-Elevating Medications

Angiotensin-converting enzyme inhibitors
Aspirin (low dose)
Cyclosporine
Diuretics
Ethambutol
Fructose

Niacin
Non-losartan angiotensin II–receptor blockers
Pyrazinamide
Ritonavir
Tacrolimus
Testosterone

Sources: Dalbeth N, Merriman TR, Stamp LK. Gout. *Lancet*. 2016;388(10055): 2039–2052; Salem CB, Slim R, Fathallah N, Hmouda H. Drug-induced hyperuricaemia and gout. *Rheumatology.* 2017;56(5):679–688.

DIETARY RISK FACTORS

Dietary factors may serve as triggers for flares. The risk of gout is increased with an increased intake of dietary purines from organ meats and seafood, as well as high-fructose corn syrup from soft drink and sugary beverages. Patients should be counseled to limit intake.[3,4,16,19]

OBESITY

Obesity has been associated with a higher risk of incident gout as observed in a large observational cohort study. In addition, the risk of recurrent gout flares was higher with an increase in body mass index (BMI) and lower with a decrease in BMI when compared with patients without a change in weight.[21]

Case 45-1, Question 3: During the medication management clinic visit, M.D. mentions that her doctor said her gout attack could have been caused by drinking too much beer, and she asks you whether this is really true. What do you tell her?

ETHANOL CONSUMPTION

Overindulgence in alcohol has been linked to acute gout attacks. Alcohol intake was examined in a prospective cohort of males with new diagnoses of gout from the Health Professionals Follow-Up Study and found that the risk of gout is 2.5-fold in patients who drink two or more beers per day.[22] Ethanol-induced gout or hyperuricemia has been attributed to several mechanisms. M.D.'s episode of

overindulgence in beer, possible dehydration from vigorous exercise, and lactic acidemia from muscle energy expenditure made the diagnosis of an acute gout attack the most likely cause of her toe pain and inflammation.

CORONARY HEART DISEASE AND IMPAIRED GLUCOSE UTILIZATION

Hyperuricemia is noted to be an independent risk factor for CHD, although it is unlikely to be a primary cause of the disease. Several observational studies have shown a link between hyperuricemia and an increase in CHD (eg, HTN, stroke, heart failure, and ischemic heart disease).[23–26] Researchers continue to study the causality and note that despite the apparent strong relationship, the subject remains controversial. Impaired glucose utilization also has a relationship with hyperuricemia. Because of these close linkages, patients who present with gout and/or hyperuricemia should be monitored closely for the development of CHD and diabetes.

RENAL DYSFUNCTION

CKD is an independent risk factor for gout. Uric acid is primarily excreted through the kidneys. Uric acid excretion is decreased in patients with renal dysfunction owing to decreased glomerular filtration, and, as a consequence, hyperuricemia occurs increasing the risk of gout.[27] Appropriate monitoring of renal function in M.D. by obtaining blood urea nitrogen (BUN), serum creatinine (SCr), and electrolytes is important for evaluating her risk factors as well as determining drug doses for treating gout.

ORGAN TRANSPLANT

The prevalence of gout is higher in renal transplant recipients. This can be because of impaired renal uric acid excretion because of poor graft function, proximal tubular dysfunction, and medication therapy such as diuretics for edema, as well as steroids and cyclosporine for immunosuppression.[28]

LEAD INTOXICATION

Both toxic and low levels of lead exposure are associated with hyperuricemia. In a large observational cohort study, blood lead levels considered acceptable by national standards were associated with a significantly increased risk of hyperuricemia and gout.[29]

Diagnosis

CASE 45-2

QUESTION 1: E.J. is a 52-year-old male school bus driver who reports to the emergency department with extreme pain in his right elbow. He reports playing several games of basketball yesterday followed by a few beers with friends. He awoke in the early hours of the morning with a sore, stiff elbow, which he self-medicated with acetaminophen before returning to sleep. However, the pain worsened, and he sought medical attention when he experienced difficulty moving the joint and was unable to apply pressure to the area. Pertinent medical history includes recently diagnosed HTN and obesity. His primary care provider prescribed hydrochlorothiazide 25 mg once daily 1 month ago. He is not on any other medications. He denies any known drug or food allergies and has not had any side effects from his antihypertensive medication. During that visit, he also received recommendations on lifestyle changes, including routine physical activity and a Mediterranean diet. On physical examination, the right elbow is tender, erythematous, and warm to the touch with moderate swelling. Vital signs are within normal limits.

What objective data would be of value in diagnosing E.J.'s elbow pain and inflammation?

CLASSIFICATION AND DIAGNOSTIC CRITERIA

The American College of Rheumatology (ACR) first suggested classification criteria for gout in 1977, which, until recently, have been commonly used for diagnosis.[30] However, the ACR released a statement in 2015 that elaborated on the distinction between classification and diagnostic criteria. Although classification criteria are used to ensure a well-defined set of patients for research studies, diagnostic criteria are a set of signs, symptoms, and tests that are needed to guide care. In collaboration with the European League Against Rheumatism (EULAR), the ACR created a set of

classification criteria in 2015.[31] Because of challenges related to creating a set of diagnostic criteria that consistently captures all presentations of a rheumatic condition, the ACR no longer funds or endorses diagnostic criteria.[32] In contrast, the EULAR published criteria for diagnosis in 2018.[16]

EULAR recommends a three-step approach to diagnose gout. The first step involves identifying MSU crystals in synovial fluid if feasible. If this is not possible, hyperuricemia and associated clinical features of gout are used to make a clinical diagnosis in step two. If the diagnosis remains uncertain and identifying MSU crystals is not possible, imaging is used to look for evidence of crystal deposition in step three.

JOINT FLUID ASPIRATION

A definitive diagnosis of gout is established through identification of MSU crystals in the affected joint by examining aspirated synovial fluid. However, the absence of MSU crystals in the synovial fluid does not rule out the diagnosis of gout. Although joint fluid aspiration is considered the gold standard for the diagnosis of acute gout, it is rarely done in clinical practice. If synovial fluid is aspirated from an inflamed joint, it should also be analyzed for bacteria, and a white blood cell (WBC) count should be obtained to aid in differential diagnosis. In gouty arthritis, the WBC count is likely to range from 5000 to 50,000/L, whereas a WBC > 50,000/L is suggestive of septic arthritis.[4] E.J.'s physician should consider fluid joint aspiration as a diagnostic measure.

LABORATORY TESTS

Because uric acid primarily is excreted renally, and renal impairment is a risk factor for gout, the serum concentrations of E.J.'s BUN and SCr should be measured along with an SUA concentration, especially in light of his recently initiated hydrochlorothiazide and new diagnosis of HTN. Although infection, in particular *septic arthritis*, could also present as sudden onset of joint pain and inflammation, it is not likely in this case. An elevated systemic WBC

count may be consistent with infection or gout. If joint infection is of genuine concern, synovial fluid aspiration could differentiate between infection and gout.

RADIOGRAPHY

Radiographic findings of the affected joint are nonspecific and generally characterized by asymmetric soft tissue swelling overlying the involved joint. When gout has been long-standing, bony changes can be noticed on a radiograph, along with calcium deposition and increased density in the areas of soft tissue swelling.[33,34] Ultrasound and computed tomography are also used for diagnosis with the latter showing early changes compared to traditional radiography. A radiograph of E.J.'s elbow may be obtained to detect tophi that may not be visible on clinical examination, but this is recommended if crystal identification is not possible and clinical diagnosis is uncertain.

PSEUDOGOUT

Deposition of microcrystals (ie, calcium pyrophosphate, calcium oxalate, calcium hydroxyapatite) into joints can cause acute or chronic arthritis in a manner similar to that caused by MSU deposition.[35] The role of these microcrystals in causing acute synovitis has been greater than previously expected because improved crystallographic technology (eg, electron microscopy, radiograph diffraction) can differentiate these diagnoses from that of acute gout. Crystal-induced diseases tend to occur in older patients as a result of prior joint disease, especially osteoarthritis, predisposing them to crystal deposition and acute episodes of joint inflammation. Older adults are also more prone to microcrystal-induced arthritis because these crystals generally accumulate for a long period and must attain a sufficient concentration and size before they precipitate into the synovial fluid and cause inflammation.[36]

CASE 45-2, QUESTION 2: Laboratory tests were ordered for E.J., and the results are as follows:

SUA, 10.1 mg/dL
BUN, 10 mg/dL
SCr, 1.0 mg/dL
WBC count, 10.2 × 10^3/μL

No MSU crystals were identified in aspirated synovial joint fluid. A radiograph of his elbow shows soft tissue swelling with no evidence of tophi. Does E.J. have gout?

Although E.J.'s clinical presentation is suggestive of gout, the absence of MSU crystals and lack of tophi through imaging studies do not support the diagnosis. E.J. appears to have hyperuricemia but not gout.

Management Guidelines

With the advances in urate-lowering medications on the market, gout is one of few rheumatologic diseases that can be treated successfully and even "cure" patients from debilitating attacks.[37] However, despite the availability of adequate and inexpensive pharmacologic interventions, gaps in care still exist including low medication adherence and dose escalation failure, inhibiting patients from achieving uric acid goals.[38] When compared to other common chronic medical conditions, gout was identified as the condition with the lowest adherence.[39] Although the prevalence of gout has increased, there has been no increase in urate-lowering therapy (ULT) utilization in recent years.[40] Because these common practices are contrary to current scientific data, the ACR Guidelines for Management of Gout were developed to provide evidence-based recommendations for treatment.[41,42] Since publication in 2012, numerous clinical trials have been completed necessitating an update published in 2020.[19] Other European guidelines include EULAR and British Society of Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) Guidelines for the Management of Gout.[33,34] A comparison of recommendations from these guidelines is found in **Table 45-2**. It is important to note that the guidelines mentioned were published in various years, and it can

be expected that the most up-to-date clinical trials are included in the most recently published guidelines.

Table 45-2

Comparison of American College of Rheumatology, European League Against Rheumatism, and British Society for Rheumatology/British Health Professionals Guidelines for Gout

2020 ACR Guideline for the Management of Gout[19]	2016 EULAR Evidence-Based Recommendations for the Management of Gout[43]	2017 BSR/BHPR Guidelines for Management of Gout[44]
Treatment of Acute Gout		
Treat an acute flare using oral colchicine, NSAIDs, or glucocorticoids (oral, intra-articular, or intramuscular) as soon as possible. Treatment selection should be driven by patient factors such as comorbidities, access, and past experiences as part of shared decision-making. Using topical ice as an adjuvant treatment is conditionally recommended.	Treat as soon as possible with colchicine, NSAIDs, oral corticosteroids, or articular aspiration and injection of corticosteroids. Medication choice should be based on the presence of contraindications, the patient's previous experience, time of initiation after flare onset, and the number and type of joint(s) involved.	Treat as soon as possible with NSAIDs or colchicine. Treatment selection should be determined by individual patient's preference and by renal function and comorbidities. Affected joints should be rested, elevated, and exposed to a cool environment.
NSAID dosing and duration should be guided by the severity of the flare.	NSAIDs should be utilized with proton-pump inhibitors if appropriate.	NSAIDs are effective at maximum doses; should be co-prescribed with a gastro-protective agent.

2020 ACR Guideline for the Management of Gout[19]	2016 EULAR Evidence-Based Recommendations for the Management of Gout[43]	2017 BSR/BHPR Guidelines for Management of Gout[44]
FDA-approved dosing of colchicine should be followed: 1.2 mg immediately followed by 0.6 mg an hour later, with ongoing anti-inflammatory therapy until the flare resolves.	Colchicine should be used within 12 hours of flare onset at a loading dose of 1 mg, followed 1 hour later by 0.5 mg on day 1.	Use colchicine at doses of 0.5 mg two to four times daily.
Injectable therapy is appropriate in certain circumstances to achieve pain relief as quickly as possible.	Oral corticosteroids at a dose of 30–35 mg/day of equivalent prednisolone for 3–5 days are recommended.	A short course of oral corticosteroids or a single injection of an intramuscular corticosteroid is an alternative in patients who are unable to tolerate NSAIDs or colchicine.
Treatment of Hyperuricemia to Prevent Recurrent Gout		
ULT is strongly recommended in patients with >1 subcutaneous tophi, frequent gout flares (>2 per year), and radiographic damage. ULT is conditionally recommended in patients experiencing their first flare and CKD stage >3, serum urate >9 mg/dL, or urolithiasis.	ULT is indicated in patients with recurrent flares, tophi, urate arthropathy, or renal stones. ULT is recommended close to the time of first diagnosis in patients older than 40 years or with a very high SUA level (>8.0 mg/dL; 480 mmol/L) and/or comorbidities (renal impairment, hypertension, ischemic heart disease, heart failure).	ULT is recommended in patients with recurring attacks (52 attacks in 12 months), tophi, chronic gouty arthritis, joint damage, renal impairment (eGFR < 60 mL/minute), a history of urolithiasis, diuretic therapy use, and primary gout starting at a young age.

2020 ACR Guideline for the Management of Gout[19]	2016 EULAR Evidence-Based Recommendations for the Management of Gout[43]	2017 BSR/BHPR Guidelines for Management of Gout[44]
A treat-to-target strategy is recommended with dose titration and subsequent dosing guided by SUA values to achieve an SUA target of <6 mg/dL. ULT should be started during the gout flare.	SUA goal is <6 mg/dL (360 mmol/L); SUA goal <5 mg/dL (300 mmol/L) is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout.	Plasma urate goal is <300 mmol/L (<5 mg/dL). Therapy should be delayed until inflammation has resolved.
Allopurinol at a dose <100 mg/day is recommended over all ULTs, including patients with CKD stage >3.	Allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required until target is reached. In patients with renal impairment, the allopurinol maximum dose should be adjusted based on creatinine clearance.	Allopurinol is the recommended first-line ULT, starting at 50–100 mg daily and increased in 100-mg increments approximately every 4 weeks until the SUA target has been achieved (maximum dose 900 mg). In patients with renal impairment, smaller increments (50 mg) should be used, and the maximum dose should be lower.

2020 ACR Guideline for the Management of Gout[19]	2016 EULAR Evidence-Based Recommendations for the Management of Gout[43]	2017 BSR/BHPR Guidelines for Management of Gout[44]
Febuxostat (<40 mg/day) is recommended as an alternative for patients who are not at SUA target and/or have continued frequent gout flares (>2 flares/year) or nonresolving subcutaneous tophi. It is recommended to switch to an alternative ALT for patients who are taking febuxostat with a history of CVD or a new CV event.	If the SUA target cannot be reached, allopurinol should be switched to febuxostat. Febuxostat is also indicated if allopurinol cannot be tolerated.	Febuxostat can be used as an alternative XOI if allopurinol is not tolerated or if renal impairment prevents sufficient doses to achieve target SUA levels. The recommended dosing for Febuxostat is 80 mg daily, increased after 4 weeks to 120 mg daily, to achieve therapeutic target.
The use of probenecid is conditionally recommended as an alternative agent starting at a low dose (500 mg once or twice daily) with dose titrations.	If the SUA target cannot be achieved at renally adjusted allopurinol doses, the patient should be switched to a uricosuric or combined with a uricosuric. Probenecid or benzbromarone can be alternatives to allopurinol if patients cannot tolerate allopurinol.	Uricosurics can be used in patients who are resistant to, or intolerant to XOI. Preferred uricosurics include sulfinpyrazone (200–800 mg/day) or probenecid (500–2000 mg/ day) in patients with normal or mildly impaired renal function, or benzbromarone (50–200 mg/day) in patients with mild-to-moderate renal insufficiency.

2020 ACR Guideline for the Management of Gout[19]	2016 EULAR Evidence-Based Recommendations for the Management of Gout[43]	2017 BSR/BHPR Guidelines for Management of Gout[44]
Concomitant anti-inflammatory prophylaxis with colchicine, NSAIDs, or prednisone/prednisolone is recommended. The choice of specific anti-inflammatory prophylaxis should be based on patient factors. Prophylaxis should be continued for 3–6 months and continued as needed if the patient continues to experience flares.	Prophylaxis is recommended during the first 6 months of ULT with colchicine, 0.5–1 mg/day and reduced in patients with renal impairment. If colchicine is not tolerated or is contraindicated, low-dose NSAIDs should be considered.	Colchicine 500 mg once or twice daily should be considered as prophylaxis and continued for up to 6 months. In patients who cannot tolerate colchicine, a low-dose NSAID or coxib, with gastroprotection, can be used as an alternative.
Adjunctive Therapy to Prevent Recurrent Gout		
Recommend limiting alcohol intake, purine intake, and high-fructose corn syrup. Weight loss is recommended for overweight/obese patients.	Patients should receive lifestyle education, including weight loss if appropriate, avoidance of alcohol (eg, beer and spirits), sugar-sweetened drinks, heavy meals, and excessive intake of meat and seafood; low-fat dairy products should be encouraged. Regular exercise should be advised.	In overweight patients, dietary modification to achieve a gradual reduction in body weight is encouraged. Patients should be educated on a well-balanced diet low in fat and added sugars, and high in vegetables and fiber; sugar-sweetened soft drinks containing fructose and excessive intake of alcoholic drinks and high purine foods should be avoided; skimmed milk and/or low-fat yogurt, soybeans and vegetable sources of protein, and cherries in the diet should be encouraged.

2020 ACR Guideline for the Management of Gout[19]	2016 EULAR Evidence-Based Recommendations for the Management of Gout[43]	2017 BSR/BHPR Guidelines for Management of Gout[44]
	Patients should be screened for associated comorbidities and CV risk factors, including renal impairment, CVD, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidemia, HTN, diabetes, and smoking, and managed as an integral part of the management of gout.	CV risk factors and comorbid conditions such as cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, obesity, and renal disease should be screened at least annually and managed appropriately.

CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease, eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; HTN, hypertension; NSAID, nonsteroidal anti-inflammatory drug; SUA, serum uric acid; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor.

Treatment of Acute Gout

GOALS OF THERAPY

Case 45-2, Question 3: What is the primary goal in the treatment of E.J.'s acute gout attack?

The primary goal in the treatment of an acute attack of gout for E.J. is to relieve his pain and inflammation. Treatment within 24 hours of symptom onset is recommended to rapidly improve patient symptoms. The immediate goal of therapy should not be aimed at decreasing the SUA concentration with ULT. Gout sufferers are most

likely to have been hyperuricemic for several months or years, and it is not necessary to treat the hyperuricemia immediately. Furthermore, a decrease in the SUA concentration at this time might mobilize urate stores and precipitate yet another acute gout attack. However, if the patient is already receiving ULT, it is not necessary to discontinue therapy during an acute attack.[19,43,44]

DRUG THERAPY OVERVIEW

Case 45-2, Question 4: What are the pharmacologic options for the treatment of E.J.'s acute pain?

Acute gouty arthritis can be effectively treated in most instances by using monotherapy with one of the following: nonsteroidal anti-inflammatory drug (NSAID), colchicine, or corticosteroids (oral, intra-articular, or intramuscular).[19,43,44] Each therapy has been proven efficacious when compared to placebo; however, to date, there are limited head-to-head comparisons between agents. As part of shared decision-making, treatment should be based on patient preference, previous response or experience with an agent, and patient-specific factors (eg, comorbidities, current medications, renal or hepatic impairment). Switching to an alternative agent or add-on therapy may be considered in refractory cases. Combination therapy is recommended in severe cases, especially those involving multiple joints. Treatment should be continued until the patient is asymptomatic (usually 7–10 days).

Nonsteroidal anti-inflammatory drugs

NSAIDs are the preferred first-line therapy for the treatment of acute gout according to the ACR, EULAR, and BSR/BHPR guidelines because of their effectiveness and tolerability.[19,43,44] Although only a few NSAIDs (ie, naproxen, indomethacin, sulindac) are U.S. Food and Drug Administration (FDA) approved for the treatment of pain associated with acute gout attacks, most have been studied, and experts consider them equally efficacious.[19,43] The choice of NSAID

should be determined based on patient-specific factors, and dosing should be consistent with the FDA-approved recommendations for the treatment of acute pain and/or acute gout. GI bleeding or ulceration and inhibition of platelet aggregation are two of the most common serious adverse effects of nonselective NSAIDs. Both compound the risk of bleeding when given concomitantly with anticoagulants (eg, warfarin). Among the nonselective NSAIDs, ibuprofen is the least likely to cause GI adverse effects and is perhaps the safest nonselective NSAID for use in patients at risk for GI bleeding, whereas piroxicam is the worst offenders.[45]

The selective cyclooxygenase-2 (COX-2) inhibitor NSAIDs are another option in patients at risk for GI bleeding or when taking chronic anticoagulants because they do not inhibit platelets at normal doses. Published data to support efficacy in acute gouty arthritis exist for etoricoxib and lumiracoxib (withdrawn in most countries because of hepatotoxicity), but these drugs are not available in the United States. Despite limited evidence for use, celecoxib and meloxicam are available in the United States with FDA-approved indications for the treatment of acute gout. A Cochrane systematic review compared nonselective NSAIDs to COX-2 inhibitors for the treatment of acute gout pain and found no significant differences in efficacy. However, the review demonstrated increased cardiovascular risk and GI adverse effects with nonselective NSAID use.[46]

The potential adverse cardiovascular effects of NSAIDs are of concern. Cardiovascular risk associated with NSAID therapy has been known for some time (eg, myocardial infarction, stroke); however, newer literature highlights the significance of this risk. Two separate cohort trials indicate an increased risk of cardiovascular morbidity and mortality in patients using NSAIDs after an acute myocardial infarction. This risk was increased in patients receiving antithrombotic therapy and was observed even with short-term use (0–3 days).[47] In patients with a history of myocardial infarction, proceed with caution when considering NSAID use. NSAIDs can also aggravate HTN, cause renal failure, inhibit diuretic-induced increases in renal sodium excretion, and decrease the hypotensive

effect of diuretics and other antihypertensive drugs.[47–52] Patients with CHD and renal insufficiency can be treated for a short duration with nonselective NSAIDs, albeit with much caution. The nonselective NSAIDs are safe for patients with stable, controlled HTN when given for only a few days and with close monitoring of blood pressure.

Colchicine

Colchicine has been successfully used to treat acute gout for more than 2000 years despite little published research supporting its efficacy.[53] By inhibiting microtubule polymerization, it decreases the action of inflammatory mediators such as cytokines and chemokines. Traditionally, colchicine has been dosed as one or two 0.5- to 0.6-mg tablets initially followed by 0.5 to 0.6 mg hourly or every other hour, until joint pain was relieved or GI effects (ie, diarrhea, nausea, vomiting) intervened. To minimize these significant adverse effects, BSR/BHPR guidelines,[44] recommend lower doses of 0.5 mg twice to four times daily. The AGREE trial,[54] multicenter, randomized, double-blind, placebo-controlled study, compared a lower-dose regimen (1.2 mg to start followed by 0.6 mg in 1 hour) with the traditional dosing and found significantly fewer adverse effects with the lower-dose regimen and similar efficacy. A 2014 systematic review, combining the AGREE trial with a separate randomized trial, found similar results.[55] Although colchicine has been marketed in the United States since 1961, it was never approved by the FDA as safe and effective. The AGREE trial was the basis of the FDA approval of a new registered colchicine product in the United States. The FDA granted brand exclusivity to this product after this, causing the cost to increase and the use of colchicine to decrease.[56] A generic form was eventually approved for use in 2015, increasing affordability.[57] The approved dosage is 1.2 mg to start followed by 0.6 mg in 1 hour for the treatment of acute gout and 0.6 mg once to twice daily for gout prophylaxis with a maximal dose of 1.2 mg/day for chronic dosing,[58] which is also consistent with the ACR recommendations.[19]

Colchicine should be used cautiously in patients with creatinine clearance (CrCl) <30 mL/minute and with hepatic impairment.[19,58]

Common adverse effects include nausea, vomiting, and diarrhea. Colchicine has a number of significant drug interactions that inhibit either cytochrome P-450 (CYP) 3A4 or P-glycoprotein (P-gp).[58,59] A thorough medication history is essential to assure safe prescribing. Some common medications that interact with colchicine include digoxin, fibric acids, statins, non-dihydropyridine calcium channel blockers, erythromycin, and antifungals. A table detailing significant colchicine drug interactions can be found in **Table 45-3**.

Table 45-3
Colchicine Drug Interaction

Interacting Drugs	Description
Conivaptan	May increase the serum concentration of CYP3A4 substrates. *Avoid combination.*
Cyanocobalamin	Colchicine may decrease the serum concentration of cyanocobalamin. *Monitor therapy.*
CYP3A4 inhibitors (moderate)	May increase the serum concentration of colchicine. Management: Reduce colchicine dose as directed when using with a moderate CYP3A4 inhibitor, and increase monitoring for colchicine-related iconicity. Use extra caution in patients with impaired renal and/or hepatic function. *Consider therapy modification.*
CYP3A4 inhibitors (strong)	May increase the serum concentration of colchicine. Management: Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a strong CYP3A4 inhibitor. In those with normal renal and hepatic function, reduce colchicine dose as directed. *Consider therapy modification.*
Digoxin	May increase the serum concentration of colchicine. *Monitor therapy.*
Fibric acid derivatives	May enhance the myopathic (rhabdomyolysis) effect of colchicine. *Monitor therapy.*

Interacting Drugs	Description
Fosamprenavir	May increase the serum concentration of colchicine. Management: Colchicine is contraindicated in patients with impaired renal or hepatic function who are receiving ritonavir-boosted fosamprenavir. In those with normal renal and hepatic function, reduce colchicine dose as directed. *Consider therapy modification.*
Grapefruit juice	Grapefruit juice may increase the serum concentration of colchicine. *Avoid combination*.
HMG-CoA reductase inhibitors	Colchicine may enhance the myopathic (rhabdomyolysis) effect of HMG-CoA reductase inhibitors. Colchicine may increase the serum concentration of HMG-CoA reductase inhibitors. *Consider therapy modification.*
Mifepristone	May increase the serum concentration of CYP3A4 substrates. Management: Minimize doses of CYP3A4 substrates and monitor for increased concentrations/toxicity during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pinacide, quinidine, sirolimus, and tacrolimus. *Consider therapy modification.*
Multivitamins/fluoride (with ADE)	Colchicine may decrease the serum concentration of multivitamins/fluoride (with ADE). Specifically, colchicine may decrease absorption of cyanocobalamin (vitamin B_{12}). *Monitor therapy.*
Multivitamins/minerals (with ADEK, folate, iron)	Colchicine may decrease the serum concentration of multivitamins/minerals (with ADEK, folate, iron). Specifically, colchicine may decrease the serum concentration of cyanocobalamin. *Monitor therapy.*
Multivitamins/minerals (with AE, no iron)	Colchicine may decrease the serum concentration of multivitamins/minerals (with AE, no iron). Specifically, colchicine may decrease absorption of cyanocobalamin (vitamin B_{12}). *Monitor therapy.*

Interacting Drugs	Description
P-gp/ABCBI inducers	May decrease the serum concentration of P-gp/ABCBI substrates. P-gp inducers may also further limit the distribution of P-gp substrates to specific cells/tissues/organs where P-gp is present in large amounts (eg, brain, T lymphocytes, testes). *Monitor therapy.*
P-gp/ABCBI inhibitors	May increase the serum concentration of colchicine. Colchicine distribution into certain tissues (eg, brain) may also be increased. Management: Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a P-gp inhibitor. In those with normal renal and hepatic function, reduce colchicine dose as directed. *Consider therapy modification.*
Stiripentol	May increase the serum concentration of CYP3A4 substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided because of the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Consider therapy modification.*
Tacrolimus (systemic)	May increase the serum concentration of colchicine. *Monitor therapy.*
Tipranavir	May increase the serum concentration of colchicine. Management: Colchicine should not be used with tipranavir in patients with impaired renal or hepatic function. In those with normal renal and hepatic function, reduced colchicine doses (as directed) are required if used with tipranavir. *Consider therapy modification.*

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

Corticosteroids

Corticosteroids were previously considered to be second-line therapy because of the potential for adverse effects and adrenal

suppression when used long-term along with the risk of rebound pain when abruptly discontinued.[60] However, adverse effects (eg, osteoporosis, myopathy, peptic ulcer disease, central nervous system effects, HTN, predisposition to infections) are not likely with short courses of treatment for gout attacks. Glucose intolerance may occur with short-term therapy. Overall, corticosteroids are highly effective, rapid-acting anti-inflammatory agents with a favorable risk versus benefit profile.

Corticosteroid recommendations, including route of administration, depend on disease severity, number of joints involved, renal function, comorbidities, and patient preference. For example, corticosteroids may be particularly useful for elderly patients or those with renal disease or heart disease who cannot tolerate NSAIDs. Corticosteroids are recommended for the treatment of acute gout flares by the ACR,[19] EULAR,[43] and BSR/BHPR[44] guidelines.

Analgesics

When a patient requires more pain control, a dose or two of nonopioid or opioid analgesics can be a reasonable adjunctive therapy to blunt the pain of acute gouty arthritis while awaiting the apparent benefits of NSAIDs, colchicine, or corticosteroids. Most patients, however, generally experience benefits from NSAIDs, colchicine, and corticosteroids soon after a dose is administered.

Other agents

Alternative regimens include the use of adrenocorticotropic hormone (ACTH) and interleukin-1 (IL-1) inhibitors. The mechanism of action for ACTH in gout is not fully known, and more large-scale studies are needed before these agents should be considered for gout.[61] The ACR guidelines do not recommend the use of ACTH drugs, such as corticotropin, over first-line therapies.[19] For patients who cannot tolerate oral therapy (NPO), intramuscular, intravenous, or intra-articular corticosteroids remain preferred over ACTH and IL-1 agents.

IL-1 agents (eg, anakinra, rilonacept, canakinumab) have not been approved by the FDA for the treatment of acute gout. A systematic review comparing canakinumab to intramuscular triamcinolone indicated that canakinumab was more effective in pain reduction during an acute flare; however, it had significantly higher serious and nonserious adverse effects.[62,63] The EULAR guidelines recommend consideration of IL-1 blockers in patients with frequent flares who have contraindications to colchicine, NSAIDs, and corticosteroids.[43] As with the ACTH medications, the cost of IL-1 agents may prohibit use.

CHOICE OF AGENT

Case 45-2, Question 5: What therapeutic intervention would be most appropriate for E.J. at this time?

An NSAID would be an appropriate first-line therapy for the acute treatment of gout in E.J. because his renal function is normal. Assuming his blood pressure is adequately controlled, a short course of ibuprofen 800 mg now and every 8 hours until resolution of symptoms (usually 7–10 days) is appropriate. The ibuprofen should be prescribed on a scheduled basis rather than "as needed" to reduce inflammation and prevent breakthrough pain. The dose of 2400 mg/day does not exceed the maximum recommended dose of 3200 mg/day.

NONPHARMACOLOGIC INTERVENTIONS

Case 45-2, Question 6: What adjunctive therapies would be beneficial for E.J.?

The use of ice, reduction of alcohol consumption, and minor diet modification may be effective and can be considered for E.J.

Ice

The benefit of ice application to the affected joint in acute gouty arthritis should not be overlooked. Evidence from a systematic review indicates the application of ice to an affected joint for 30 minutes four times daily for 1 week reduced the pain of a gout attack when used in conjunction with oral steroids or colchicine.[64] In addition, a Cochrane systematic review of a randomized controlled trial showed that gouty attack pain was significantly improved from baseline, when topical ice therapy was added as an adjunct to standard treatments.[65] The use of ice as an adjuvant treatment during flares is recommended by both the ACR[19] and BSR/BHPR[44] guidelines.

Alcohol consumption

Excessive alcohol intake is known to be a risk factor for acute gout episodes. Beer was believed to be more problematic for gout than other alcoholic beverages because of its high purine content. The Health Professionals Follow-Up study[26] examined a cohort of patients with new diagnoses of gout over a 12-year time frame and found that when beer, spirits, and wine intake were examined, the greatest risk was with beer with a significant, but less, risk with spirits. Interestingly, wine, even more than two drinks/day, was not associated with an increased risk of gout. A smaller, independent study found that the quantity of alcohol consumed in the 24 hours before an acute attack is more important than the type of beverage consumed.[66] The current ACR,[19] EULAR,[43] and BSR/BHPR[44] guidelines recommend limiting and/or avoiding alcohol in all patients with gout regardless of disease activity.

Diet modification

Diet has a twofold effect on the epidemiology of gout. First, obese patients are at a greater risk of developing elevated SUA levels, and gout might, in part, be related to insulin resistance of obesity.[8] In a prospective, longitudinal study of male health professionals, weight gain was strongly associated with an increased risk of gout, and weight loss was associated with a decreased risk.[67]

Second, much of the uric acid produced daily comes from metabolism of food. The excessive dietary intake of purine-rich foods, without a concomitant increase in urinary excretion, can lead to elevated SUA concentrations.[8,68] However, the type of protein and purine-rich foods that are detrimental, as well as the true impact of these foods on the incidence of increased SUA and gout episodes are controversial issues because of the quality of evidence available.[11,69] Despite the lack of strong evidence, it is reasonable for clinicians to recommend patients limit certain foods (eg, organ meats, beef, lamb, pork shellfish, and products containing high-fructose corn syrup). Interestingly, low-fat or nonfat dairy products and coffee consumption have been associated with a decreased incidence of gout.[8,11] E.J. should be encouraged to limit or avoid purine-rich meats and fructose-containing beverages/foods and encouraged to increase consumption of low-fat dairy products.

CASE 45-3

Question 1: V.D. is a 72-year-old female who was brought to the emergency department with shortness of breath and dizziness. On arrival, she is noted to have new-onset atrial fibrillation with a heart rate of 130 beats/minute and 2+ peripheral edema bilaterally to her knees. The latter is likely secondary to exacerbation of congestive heart failure caused by her rapid ventricular rate. In addition to administering diltiazem to control her heart rate, V.D. is given 40 mg of intravenous (IV) furosemide every 12 hours for three doses. The following day, she reports severe pain in her left great toe, and it is noted on examination to be erythematous and swollen. V.D.'s CrCl is 70 mL/minute, her SUA concentration is 7.5 mg/dL, and her blood pressure is 160/96 mm Hg.

What therapeutic option would be appropriate for V.D.?

The combination of V.D.'s advanced age, acute exacerbation of heart failure, and renal dysfunction is patient-specific parameters that are relative contraindications or precautions for the use of NSAIDs for the treatment of acute gout. Therefore, alternative treatments should be considered. Colchicine is the next drug to consider, but because she is now receiving diltiazem (a moderate CYP3A4 inhibitor), the dose of colchicine would need to be reduced. Because V.D.'s pain is monoarticular, intra-articular or oral

corticosteroids could be administered, but the latter would need to be tapered over the course of 10 to 21 days to avoid rebound gout symptoms. It is decided to give V.D. 1.2 mg of colchicine for one dose only, which is appropriate to avoid the diltiazem drug interaction.[59]

HYPERURICEMIA

Chronic Gout

Case 45-3, Question 2: V.D. is ready to be discharged 3 days later. Her toe is no longer inflamed, and her pain is gone. Should ULT be prescribed at discharge to prevent another gout attack?

ULT should be initiated in patients with >1 subcutaneous tophi, frequent gout flares (>2 per year), and radiographic damage.[19] Additionally, for patients experiencing their first flare and CKD stage >3, SUA >9 mg/dL, or urolithiasis, ULT may be initiated. If these indications are absent, ULT should not be prescribed. Long-term ULT should not be started for V.D. at this time because the criteria for therapy (see ACR, EULAR, and BSR/BHPR guidelines in Table 45-2)[19,43,44] are not met, and initiation of ULT during an acute episode can mobilize urate from tissues, worsening the problem.

DRUG-INDUCED HYPERURICEMIA

A patient's complete medication list should be reviewed to rule out drug-induced hyperuricemia before adding a medication to decrease SUA concentration. Common medications known to increase SUA can be found in Table 45-1. Perhaps, the only treatment needed would be to discontinue the offending agent. As mentioned, when discussing gout risk factors, the benefits versus the risks must be evaluated before discontinuing the offending agent.

GOAL OF URATE-LOWERING THERAPY

CASE 45-3, QUESTION 3: V.D. experienced another episode of acute gout 2 months later, which was treated successfully with colchicine. She is now on chronic warfarin to prevent stroke secondary to her atrial fibrillation and remains on diltiazem for heart rate control. Her blood pressure is 130/70 mm Hg, renal function is stable with a CrCl of 70 mL/minute, and SUA is 7.2 mg/dL. Would it be appropriate to initiate ULT at this time? If so, when would you initiate treatment?

The general goals for lowering SUA concentrations are the elimination of acute gout attacks and the mobilization of urate crystals from soft tissue. According to the ACR[19] and EULAR guidelines,[43] it is recommended to maintain SUA levels at a target <6 mg/dL for patients taking ULT. In addition, the EULAR[43] guidelines recommend a stricter goal of <5 mg/dL for patients with severe gout, which is defined as tophi, chronic arthropathy, and frequent attacks, until crystal dissolution. The EULAR guidelines state that they recommend these stricter goals for severe patients because of the fact that crystal dissolution is dependent on SUA levels. The BSR/BHPR[44] guidelines also recommend a more stringent goal of 5 mg/dL.

STARTING URATE-LOWERING THERAPY

The BSR/BHP[44] guidelines recommended to wait until the resolution of an acute attack and inflammation before starting ULT because of the risk of worsening the flare. However, based on recent evidence[70,71] that has shown starting ULT during a flare did not significantly worsen the flare, as well as evidence showing a decrease in time required to reach the target SUA,[72] the ACR[19] guidelines now recommend initiating ULT during the flare, as opposed to after the flare has resolved.

V.D. fits the criteria for initiating ULT (two attacks in <1 year); however, this should be preceded by a consideration of whether drug-induced hyperuricemia could be a contributing factor. V.D.'s initial episode of gout after aggressive diuresis with IV furosemide

was likely the cause of her first gout attack, but she is not currently on any drugs that cause hyperuricemia.

DRUG THERAPY OF HYPERURICEMIA

Xanthine oxidase inhibitors

Allopurinol

Clinical practice guidelines recommend allopurinol as a first-line agent for gout prevention.[19,43,44] It inhibits the production of uric acid and thereby decreases SUA concentrations. A 2014 systematic review of two clinical trials, with methodological limitations, shows that when compared to placebo allopurinol was superior at achieving target SUA concentrations, but failed to significantly reduce the frequency of acute gout attacks.[73] The ability of allopurinol to lower SUA concentrations is dose related. An allopurinol dose of 300 mg/day is typical maintenance dose, despite evidence to support that more than 50% of patients are unable to achieve target SUA at this dose or lower.[74,75]

The recommended initial dose of allopurinol is 50 to 100 mg once daily and then increased in 50- to 100-mg/day increments every 2 to 4 weeks until the SUA concentration is at target <6 mg/dL or until patient intolerance.[19,43,44] Starting at a low dose and titrating slowly hypothetically can reduce the risk for improved tolerance in renal impairment and hypersensitivity reactions. Allopurinol use has been associated with a rare (2%) but potentially life-threatening hypersensitivity reactions referred to as allopurinol hypersensitivity syndrome (AHS).[3] Symptoms may include erythematous rash, fever, hepatitis, eosinophilia, leukocytosis, and renal failure.[3,76] Symptoms usually begin within the first 8 weeks of therapy.[4] AHS does not have a cure; if a hypersensitivity reaction occurs, the medication should be stopped immediately and supportive measures must be taken.[76] Patients who recover should avoid future use of allopurinol. Although allopurinol desensitization can be attempted in patients with mild reactions, the risks are unknown with reactions that are more serious.[3] Risk factors for AHS include the presence of HLA-B*5801 genotype, renal impairment, and concomitant diuretic use, female

sex, and age. The relationship between allopurinol dose and AHS is unclear as studies[76,77] are contradictory to prove the association.[3,4,76] Regardless, lower initial doses are still recommended by the guidelines.

Allopurinol has several drug–drug interactions that can alter therapy and may warrant dose adjustment. Significant allopurinol drug interactions can be found in **Table 45-4**.

Table 45-4
Allopurinol Drug Interactions

Precipitant Drug	Object Drug		Description
Allopurinol	Ampicillin, amoxicillin	↑	The rate of skin reaction appears much higher with allopurinol coadministration than with either drug alone. *Monitor therapy.*
Allopurinol	Azathioprine	↑	Increase in active metabolites of azathioprine. Reduce azathioprine dose to one-third to one-quarter of the usual dose and monitor closely. *Consider therapy modification.*
Allopurinol	Carbamazepine	↑	Increase serum concentrations. *Monitor therapy.*
Allopurinol	Cyclophosphamide	↑	Myelosuppressive effects of cyclophosphamide may be enhanced increasing the risk of bone marrow suppression. *Monitor therapy.*
Allopurinol	Pegloticase	↑	Adverse effects/toxicity of pegloticase is enhanced with increased risk of anaphylaxis and infusion reactions. *Avoid combination.*
Allopurinol	Theophylline and derivatives	↑	Increased plasma theophylline levels and possible toxicity. *Monitor therapy.*
Allopurinol	Warfarin	↑	Enhanced anticoagulation effects; dose reductions in warfarin will likely be needed; monitor anticoagulation effects (eg, INR) with dose adjustments of allopurinol. *Consider therapy modification.*
ACE inhibitors	Allopurinol	↑	There is possibly a higher risk of hypersensitivity reaction to allopurinol when these agents are coadministered. *Monitor therapy.*
Loop and thiazide diuretics	Allopurinol	↑	Coadministration may increase serum concentrations and the incidence of hypersensitivity reactions to allopurinol. *Monitor therapy.*

↑, object drug increased; ↓, object drug decreased; INR, international normalized ratio.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

Febuxostat

Febuxostat, a nonpurine xanthine oxidase (XO) inhibitor, was approved by the FDA in February 2009 for chronic management of hyperuricemia in patients with gout.[79] Febuxostat is more selective

than allopurinol for XO and does not inhibit other enzymes involved in purine and pyrimidine metabolism. A 2012 Cochrane systematic review, with methodological limitations, evaluated six trials comparing febuxostat to allopurinol for clinical SUA-lowering effect and found febuxostat more effective than allopurinol 300 mg in achieving SUA of <6 mg/dL. An important consideration in evaluating the evidence is that although the studies allowed upward titration of febuxostat to achieve maximal SUA lowering, the allopurinol dosage was not titrated to >300 mg daily.[80] Because the urate-lowering effect with allopurinol is known to be dose related and some patients have required up to 900 mg/day to achieve a SUA <6 mg/dL, these results may not have allowed for an adequate comparison of efficacy between the two drugs. The same review revealed that compared to standard doses of allopurinol, higher doses of febuxostat, 120 and 240 mg daily, increased the risk of gout flares; however, long-term follow-up studies did not detect an increased risk of flares. The FDA-approved dose in the United States is 80 mg daily; however, doses of up to 240 mg daily are approved in other countries.

In addition, adverse effects were shown to be minor and similar between both drugs in comparative studies with increases in liver function tests, nausea, diarrhea, arthralgias, and rash being the most common adverse effects with >1% incidence.[74,79,81,82] However, a major concern with febuxostat was recently revealed in 2018 during the Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout (CARES) Trial, a doubled-blind, randomized, multicenter trial.[83] Results from the CARES Trial demonstrated an increase in all-cause mortality and cardiovascular mortality compared to allopurinol in patients with gout and coexisting cardiovascular conditions. These findings resulted in updated FDA labeling with a black box warning in February 2019. The warning advises on the increased risk for cardiovascular death with the drug. The warning also states that febuxostat use should only be used by patients who do not respond to or cannot tolerate allopurinol.[79] The 2020 ACR guidelines[19] recommend switching to an alternative for patients who are taking febuxostat with a history of cardiovascular disease or a

new cardiovascular event after considering the most recent data and label changes.

The starting dose of febuxostat is 40 mg once daily with a recommended dose increase to 80 mg once daily if SUA concentration is not <6 mg/dL by 2 weeks of therapy. It does not require dose adjustments for CrCl > 30 mL/minute, and the labeling provides no recommendations for use in patients with more severe renal impairment.[79] Febuxostat is a substrate of urate transporter 1 (URAT1). Significant febuxostat drug interactions can be found in **Table 45-5**.[84]

Table 45-5
Febuxostat Drug Interactions

Precipitant Drug	Object Drug		Description
Febuxostat	Didanosine	↑	Systemic exposures of didanosine are increased during coadministration. *Avoid combination.*
Febuxostat	Pegloticase	↑	Adverse effects/toxicity of pegloticase is enhanced with increased risk of anaphylaxis and infusion reactions. *Avoid combination.*
Febuxostat	Xanthine oxidase substrate drugs (eg, azathioprine, mercaptopurine, theophylline); exception: dyphylline	↑	Febuxostat is a xanthine oxidase inhibitor. Inhibition of xanthine oxidase by febuxostat may cause increased plasma concentration of these drugs, leading to toxicity. *Monitor therapy.*

↑, object drug increased; ↓, object drug decreased.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

CHOICE OF AGENT

Case 45-3, Question 4: Because an XO inhibitor is first-line therapy to lower SUA concentration, which product should be chosen for V.D.?

Although febuxostat is clearly efficacious in lowering SUA concentrations, allopurinol is also effective when the dose is appropriately titrated to response and goal SUA concentration. Guidelines recommend allopurinol as first-line therapy.[19,43,44] In addition, V.D. also has an extensive cardiovascular history consistent with heart failure and atrial fibrillation. Given recent evidence and labeled warnings,[78,83] febuxostat should only be used by patients

who do not respond to or cannot tolerate allopurinol. V.D. does not have any contraindications to allopurinol therapy. She is on chronic warfarin, which may interact with allopurinol.[79] This warrants monitoring her international normalized ratio (INR) after allopurinol therapy is initiated and with any allopurinol dosage adjustments.

Uricosuric agents

Probenecid and lesinurad are the only uricosuric agents available in the United States. Clinical practice guidelines recommend uricosurics as add-on therapy for patients who experience a partial response to XO inhibitors.[19] Uricosurics may also be considered in patients who are intolerant of XO inhibitors because of intolerability, contraindications, or significant drug interactions.[43] Overall, high fluid intake to maintain urine flow of at least 2 L/day also minimizes renal stone formation when using a uricosuric. This gradual approach to the initiation of ULT also decreases the likelihood of precipitating an acute attack of gout.

Probenecid is well absorbed orally, and plasma concentrations peak within 2 to 4 hours. Its biologic half-life is 6 to 12 hours, and its active metabolites extend the duration of action. The usual initial dose of probenecid (250 mg twice daily for the first week of therapy) can be increased to 500 mg twice a day. If necessary, the dose can be increased further to 2 to 3 g/day. Therapy should begin with small doses because the excretion of large amounts of uric acid increases the risk of urate stone formation in the kidney. Probenecid should not be administered to patients with impaired renal function or urolithiasis.

Probenecid inhibits secretion of penicillins into the renal tubule, and thereby prolongs the serum half-life of penicillin and increases penicillin serum concentrations. Probenecid can also compete with salicylates for renal tubular transport, but its interactions with salicylates involve several mechanisms.[85] Low-dose aspirin for cardioprotection is unlikely to interfere with probenecid therapy. Interestingly, high-dose aspirin (eg, >1 g) has uricosuric activity of its own.[86]

In 2015, lesinurad, a uricosuric that works as an URAT1 inhibitor, was approved as ULT in gout. However, lesinurad is only indicated in combination with an XO inhibitor because of the risk of increased renal toxicity when taken monotherapy.[87] Randomized controlled trials found that lesinurad in combination with XO inhibitors lowered SUA levels more than XO inhibitors alone.[88,89] Major cardiovascular events have been noted with lesinurad, although a causal relationship is unclear. Of note, lesinurad was discontinued by the manufacturer in late 2018 because of business reasons and not related to any efficacy, safety, or clinical concerns.[90]

Recombinant urate oxidase drugs (uricase)

Uricase, an enzyme endogenous in many animal species other than humans, converts uric acid to allantoin, which is much more soluble than uric acid and, therefore, more readily excreted into urine. Recently, two recombinant urate oxidase drugs have been developed for the treatment of hyperuricemia and gout. However, the high incidence of serious adverse reactions (23%–24%) as well as cost prohibit routine use. Rather, they should be considered as alternatives when all other ULTs have failed.[91]

Rasburicase

Rasburicase is a recombinant uricase drug that was initially approved by the FDA for the management of hyperuricemia in children who are receiving cytotoxic chemotherapy likely to result in tumor lysis syndrome and later received approval for the same indication in adults. Rasburicase does not currently carry an indication for gout. A comparative short-term study in patients with renal impairment found rasburicase was significantly more effective than allopurinol in lowering SUA concentrations at the end of 7 days of therapy.[92]

Rasburicase is administered as a short IV infusion of 0.2 mg/kg daily for up to 5 days.[93] Although lower-quality studies show significant reductions in SUA, rasburicase is not indicated for the treatment of hyperuricemia in patients with gout because of its short

half-life and immunogenicity.[94] Until further studies confirm safety and longer-term efficacy in nonchemotherapy-related hyperuricemia, rasburicase should be reserved for patients with hyperuricemia who are at risk for tumor lysis syndrome.

Pegloticase

Pegloticase, another recombinant uricase drug, has been shown to be effective in reducing SUA concentrations in patients who were refractory to conventional treatment. In clinical trials, pegloticase demonstrated lower SUA levels, decreased frequency of flares, reduction in tophi, and improved quality of life.[95–97] Pegloticase is administered IV for two hours as a dose of 8 mg every 2 weeks.[98] It has a significant risk of anaphylaxis and infusion site reactions, so each dose must be preceded by prophylaxis with an antihistamine and corticosteroid.[98] It is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, and the usual gout flare prophylaxis is recommended for the first 6 months after initiation. Finally, pegloticase antibodies occurred in the majority of patients studied, and this can ameliorate the SUA-lowering effects by decreasing the half-life of pegloticase. The full implication of this remains unknown.

However, pegloticase is not recommended as first-line therapy given significant warnings and precautions, high cost, and the need for twice monthly infusions.[19] Instead, pegloticase is reserved for patients with refractory disease, especially those in whom use of XO inhibitors, uricosurics, and other interventions have failed to lower SUA to target levels and who have frequent gout flares or persistent subcutaneous tophi.

Other agents

Some medications (eg, ascorbic acid, antihypertensive agents, and fenofibrates) used to treat conditions commonly seen in conjunction with gout have been proven to have uricosuric properties. However, current available data on these agents have significant limitations, and uric acid lowering is oftentimes minimal. It is also important to

note that to date no trials evaluating their effectiveness on clinically relevant outcomes (eg, gout attacks) have been published. If future randomized trials show promise, some patients with hyperuricemia might be better managed by selecting drugs to manage comorbid conditions rather than requiring the use of the more traditional ULT.

Ascorbic Acid

Vitamin C has a urate-lowering effect that is believed to be mediated by competition with urate for renal tubular reabsorption.[99] A meta-analysis found that vitamin C supplementation lowered SUA levels in patients without gout.[100] A prospective cohort study found an association between vitamin C and a lower risk of gout.[101] However, there is a lack of high-quality evidence to support routine use for the prevention of gout attacks.[102,103]

Antihypertensive Agents

In cases where gout occurs in patients using loop or thiazide diuretics, losartan or calcium channel blockers should be considered as substitutions for antihypertensive control. A large epidemiologic study found a lower relative risk of gout incident in patients on calcium channel blockers or losartan.[104] Based on several studies, losartan appears to be the only ARB that consistently demonstrates a reduction in SUA levels, and this does not seem to be a class effect.[105,106] Other antihypertensive agents (eg, β-blockers, diuretics, angiotensin-converting enzyme inhibitors, and non-losartan angiotensin II–receptor blockers) were also studied and were found to have increased risk of gout. In patients with hyperuricemia and HTN, losartan and calcium channel blockers may be a viable option depending on individual patient variables.

Fenofibrate

Fenofibrates have been shown to decrease SUA concentrations by increasing renal urate excretion.[107] In addition to therapeutic lifestyle changes, fibrates (ie, gemfibrozil, fenofibrate) are commonly used for

the treatment of hypertriglyceridemia. However, the use of fenofibrate remains controversial. Although fenofibrate is a reasonable option for patients with hyperlipidemia,[43,44] the 2020 ACR guidelines recommend against adding or switching to fenofibrates based on an inadequate risk versus benefit ratio.[19] However, the selection of a medication to manage hyperlipidemia should also involve other clinical variables.[108,109]

FLARE PROPHYLAXIS

Case 45-3, Question 5: V.D. is started on allopurinol 100 mg orally once daily for initial ULT. Her SUA concentration will be checked, and her allopurinol will be increased by 50 to 100 mg/day in 2 to 4 weeks if needed until she reaches the goal of ≤6 mg/dL. What other drug therapy should also be considered when starting ULT?

Paradoxically, initiation of ULT can precipitate acute gout attacks. Guidelines recommend prophylaxis with anti-inflammatory agents for all patients when ULT is initiated.[19,43,44] Prophylactic medication include colchicine, NSAIDs, or prednisone/prednisolone is recommended. The choice of agent should be based on patient-specific factors.[19] Upon initiation of ULT, anti-inflammatory therapy should be continued for at least 3 to 6 months and continued as needed if the patient continues to experience flares. V.D. would be a candidate for flare prophylaxis. As stated above, V.D.'s advanced age, acute exacerbation of heart failure, and renal dysfunction are patient-specific parameters that are relative contraindications or precautions for the use of long-term NSAID therapy for flare prophylaxis. Colchicine would be a reasonable option because it is considered first line and she tolerated colchicine during acute attacks. The colchicine dose for flare prophylaxis is 0.6 mg once or twice daily for 6 weeks. V.D. should be monitored for adverse drug reactions.

MONITORING AND FOLLOW-UP

In addition to monitoring for subjective and objective evidence of drug-related adverse effects, SUA concentrations should be monitored monthly until at goal, then every 6 to 12 months, thereafter. The optimal duration of ULT is unclear. Patients with mild gout may go years without experiencing repeat attacks after discontinuation of ULT. Lower SUA concentrations during treatment correlate with a longer interval between acute attacks or before tophi reappear. The majority of patients on long-term ULT are likely to experience recurrent acute attacks, tophi, or both if treatment is stopped.[110] Data suggest that patients with average SUA levels <7.0 mg/dL for at least 5 years can discontinue ULT and remain symptom-free for a prolonged period. The decision when to discontinue ULT should be made based primarily on patient preference after a shared-informed discussion.

Asymptomatic Hyperuricemia

CASE 45-4

QUESTION 1: T.K. is a 50-year-old male who presents to his primary care provider for an annual wellness check. His physical examination is unremarkable, and his laboratory evaluations are all within normal limits except for an SUA concentration of 9.7 mg/dL. He denies any problems.

Should his hyperuricemia be treated?

Individuals with high SUA concentrations are more likely to develop acute gouty arthritis than individuals with normal SUA levels. A large percentage of patients with hyperuricemia never experience an acute gout attack.[3] Therefore, it is not recommended to treat asymptomatic hyperuricemia with uric acid–lowering medications to prevent acute gout flares. If a gout attack occurs, it can be quickly and easily treated.

The key issue in the treatment of hyperuricemia concerns the effect of uric acid on renal function. Data suggest that hyperuricemia may play a role in the progression of CKD.[111] More recent prospective cohorts have shown that hyperuricemia may cause renal

failure.[112] Despite this, the consensus remains against treating hyperuricemia with pharmacologic therapy.

PHARMACIST'S ROLE

Pharmacists have an important role in the treatment and management of gout. As noted several times in this chapter, there are significant drug–drug interactions associated with the majority of agents used to treat both acute and chronic gout. A 2008 retrospective cohort study showed that 28% of patients did not meet with a provider prior to initiation of ULT, and 56% of patients were nonadherent with ULT.[113] Additionally, adherence rates in gout vary from 20% to 70%.[114] Patient education about the roles of medication, including the importance of adherence and how to monitor for and manage adverse drug reactions in the treatment of gout, is an essential part of therapy. In cases where a provider visit did not occur prior to starting ULT, a pharmacist could serve as a resource for education and counseling. Pharmacists are equipped with the knowledge and skills to identify drug–drug interactions, monitor and encourage medication adherence, and provide general counseling on gout and lifestyle recommendations. Open communication with the patient's other health care professionals has the potential to improve gout management.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* 2005;52:283. (69)

Dalbeth N, Merriman TR, Stamp LK. Gout. *Lancet.* 2016 Oct 22;388(*10055*): 2039–2052. (4)

FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Rheumatol 2020*; 72:879. (19)

Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology (Oxford) 2017*; 56:e1. (44)

Neogi T. Clinical practice. Gout. *N Engl J Med.* 2011;364(*5*):443. (3)

Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis 2017*;76: 29–42. (43)

Seth R, Kydd ASR, Buchbinder R, Bombardier C, Edwards CJ. Allopurinol for chronic gout. *Cochrane Database Syst Rev*. 2014;2014(10):CD006077. DOI: 10.1002/14651858.CD006077.pub3. (73)

Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. *Cochrane Database Syst Rev*. 2012;11(11):CD008653. DOI: 10.1002/14651858.CD008653.pub2. (80)

Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum.* 2010;62:1060. (54)

van Durme CMPG, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewé RBM. Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database Syst Rev*. 2014;16(9):CD010120. DOI: 10.1002/14651858.CD010120.pub2. (46)

van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. *Cochrane Database Syst Rev*. 2014;15(8):CD006190. DOI: 10.1002/14651858.CD006190.pub2. (55)

White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med.* 2018;310: 1200–1210. (83)

COMPLETE REFERENCES CHAPTER 45 GOUT AND HYPERURICEMIA

1. Terkeltaub R, Bushinsky DA, Becker MA. Recent developments in our understanding of the renal basis of hyperuricemia and the development of novel antihyperuricemic therapeutics. *Arthritis Res Ther*. 2006;8(Suppl 1):S4.

2. Bursill D, Taylor WJ, Terkeltaub R, et al. Gout, hyperuricaemia and crystal-associated disease network (G-CAN) consensus statement regarding labels and definitions of disease states of gout. *Ann Rheum Dis*. 2019;78(11):1592–1600. doi:10.1136/annrheumdis-2019-215933
3. Neogi T. Clinical practice. Gout. *N Engl J Med*. 2011;364(5):443–452.
4. Dalbeth N, Merriman TR, Stamp LK. Gout. *Lancet*. 2016;388(10055):2039–2052.
5. Schlesinger N, Norquist JM, Watson DJ. Serum urate during acute gout. *J Rheumatol*. 2009;36:1287–1289.
6. Dalbeth N, Phipps-Green A, Frampton C, Neogi T, Taylor WJ, Merriman TR. Relationship between serum urate concentration and clinically evident incident gout: an individual participant data analysis. *Ann Rheum Dis*. 2018;77(7):1048–1052. doi:10.1136/annrheumdis-2017-212288
7. Lee SJ, Terkeltaub RA. New developments in clinically relevant mechanisms and treatment of hyperuricemia. *Curr Rheumatol Rep*. 2006;8:224–230.
8. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med*. 2004;350:1093–1103.
9. Beyl RN Jr, Hughes L, Morgan S. Update on importance of diet in gout. *Am J Med*. 2016;129(11):1153–1158.
10. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ*. 2008;336:309–312.
11. Major TJ, Topless RK, Dalbeth N, Merriman TR. Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts. *BMJ*. 2018;363:k3951.
12. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. *Arthritis Res Ther*. 2006;8(Supp1):S2.
13. MacFarlane LA, Kim SC. Gout: a review of nonmodifiable and modifiable risk factors. *Rheum Dis Clin North Am*. 2014;40(4):581–604.
14. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol*. 2015;11(11):649–662.
15. Hak AE, Curhan GC, Grodstein F, Choi HK. Menopause, postmenopausal hormone use and risk of incident gout. *Ann Rheum Dis*. 2010;69(7):1305–1309.
16. Richette P, Doherty M, Pascual E, et al. 2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout. *Ann Rheum Dis*. 2020;79(1):31–38.
17. Choi HK, Niu J, Neogi T, Chen CA, Chaisson C, Hunter D, Zhang Y. Nocturnal risk of gout attacks. *Arthritis Rheumatol*. 2015;67:555–562.
18. Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot? *J Foot Ankle Res*. 2011;4:13.

19. FitzGerald JD, Dalbeth N, Mikuls T, et al. American College of Rheumatology guideline for the management of gout. *Arthritis Rheumatol*. 2020;72:879–895.
20. Salem CB, Slim R, Fathallah N, Hmouda H. Drug-induced hyperuricaemia and gout. *Rheumatology*. 2017;56(5):679–688.
21. Nguyen UD, Zhang Y, Louie-Gao Q, et al. Obesity paradox in recurrent attacks of gout in observational studies: clarification and remedy. *Arthritis Care Res (Hoboken)*. 2017;69:561–566.
22. Choi HK, Atkinson K, Karlson EW, Willett W, Curha G. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet*. 2004;363:1277–1281.
23. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359:1811–1821.
24. Bellomo G. The relationship between uric acid, allopurinol, cardiovascular events, and kidney disease progression: a step forward. *Am J Kidney Dis*. 2015;65(4):525–527.
25. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation*. 2007;116:894–900.
26. Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med*. 2010;170:1358–1364.
27. Wang W, Bhole VM, Krishnan E. Chronic kidney disease as a risk factor for incident gout among men and women: retrospective cohort study using data from the Framingham Heart Study. *BMJ Open*. 2015;5(4):e006843.
28. Clive DM. Renal transplant-associated hyperuricemia and gout. *J Am Soc Nephrol*. 2000;11(5):974–979.
29. Krishnan E, Lingala B, Bhalla V. Low-level lead exposure and the prevalence of gout. *Ann Intern Med*. 2012;157(4):233–241.
30. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum*. 1977;20:895–900.
31. Neogi T, Jansen TLTA, Dalbeth N, et al. Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2015;74(10):1789–1798.
32. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria? *Arthritis Care Res (Hoboken)*. 2015;67(7):891–897.
33. Cardenosa G, Deluca SA. Radiographic features of gout. *Am Fam Physician*. 1990;4:539.
34. Parathithasan N, Lee WK, Pianta M, Oon S, Perera W. Gouty arthropathy: review of clinico-pathologic and imaging features. *J Med Imaging Radiat Oncol*. 2016;60(1):9–20. doi:10.1111/1754-9485.12356
35. Schumacher HP, Chen LX. Gout and other crystal-associated arthropathies. In: *Harrison's Principles of Internal Medicine*, 19th ed. McGraw-Hill; 2012:Chap 365.

36. Finch W. Acute crystal-induced arthritis: gout and a whole lot more. *Postgrad Med*. 1989;85:273.
37. Wortmann RL. The management of gout: it should be crystal clear. *J Rheumatol*. 2006;33:1921–1922.
38. Rashid N, Coburn BW, Wu YL, et al. Modifiable factors associated with allopurinol adherence and outcomes among patients with gout in an integrated healthcare system. *J Rheumatol*. 2015;42:504–512.
39. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*. 2008;28:437–443.
40. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nation-wide population study. *Ann Rheum Dis*. 2015;74:661–667.
41. Khanna D, FitzGerald JD, Khanna PP, et al. American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res*. 2012;64(10):1431–1446.
42. Khanna D, FitzGerald JD, Khanna PP, et al. American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res*. 2012;64(10):1447–1461.
43. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76:29–42.
44. Hui M, Carr A, Cameron S, et al. The British society for rheumatology guideline for the management of gout. *Rheumatology (Oxford)*. 2017;56:e1–e20.
45. Gonzalez ELM, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum*. 2010;62(6):1592–1601.
46. van Durme CMPG, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewé RBM. Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database Syst Rev*. 2014;16(9):CD010120. doi:10.1002/14651858.CD010120.pub2
47. Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. *JAMA*. 2015;313(8):805–814.
48. Brater DC. Analysis of the effect of indomethacin on the response to furosemide in man: effect of dose of furosemide. *J Pharmacol Exp Ther*. 1979;210:386–390.
49. Frölich JC, Hollifield JW, Dormois JC, Frölich BL, Seyberth H, Michelakis AM, Oates JA. Suppression of plasma renin activity by indomethacin in man.

Circ Res. 1976;39:447–452.
50. Oates JA. Antagonism of antihypertensive drug therapy by nonsteroidal anti-inflammatory drugs. *Hypertension*. 1988;11(Suppl U):II-4–II-6.
51. Pavlicevic I, Kuzmanic´ M, Rumboldt M, Rumboldt Z. Interaction between antihypertensives and NSAIDs in primary care: a controlled trial. *Can J Clin Pharmacol*. 2008;15(3):e372–e382.
52. Sherve K, Gerard CJ, Neher JO, St Anna L. Cardiovascular effects of NSAIDs. *Am Fam Physician*. 2014;90(4):online. https://www.aafp.org/pubs/afp/issues/2014/0815/od2.html
53. Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum*. 2009;38:411–419.
54. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, doubleblind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum*. 2010;62:1060–1068.
55. van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. *Cochrane Database Syst Rev*. 2014;15(8):CD006190. doi:10.1002/14651858.CD006190.pub2
56. Kesselheim AS. Reductions in use of colchicine after FDA enforcement of market exclusivity in a commercially insured population. *J Gen Intern Med*. 2015;30(11):1633–1638.
57. Gallegos A. Court allows generic colchicine to enter market [from the Internet]. *MDEdge Rheumotology*. 2015. Accessed October 7, 2020. https://www.mdedge.com/rheumatology/article/96726/rheumatology/court-allows-generic-colchicine-enter-market
58. Colcrys. Prescribing information. Takeda Pharmaceuticals America, Inc; 2012.
59. Colchicine. Drug facts & comparisons. *Facts & Comparisons eAnswers [Database on the Internet]*. Wolters Kluwer Health; 2020. Accessed October 7, 2020. http://online.factsandcomparisons.com
60. Cronstein BN, Terkeltaub R. The inflammatory process of gout and its treatment. *Arthritis Res Ther*. 2006;8(Suppl 1):S3.
61. Daoussis D, Bogdanos DP, Dimitroulas T, Sakkas L, Andonopoulos AP. Adrenocorticotropic hormone: an effective “natural” biologic therapy for acute gout? *Rheumatol Int*. 2020;40(12):1941–1947. doi:10.1007/s00296-020-04659-5
62. Sivera F, Wechalekar MD, Andrés M, Buchbinder R, Carmona L. Interleukin-1 inhibitors for acute gout. *Cochrane Database Syst Rev*. 2014;1(9):CD009993. doi:10.1002/14651858.CD009993.pub2
63. Schlesinger N, Alten RE, Bardin T, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two

randomised, multicentre, active-controlled, double-blind trials and their initial extensions. *Ann Rheum Dis*. 2012;71:1839–1848

64. Schlesinger N, Detry MA, Holland BK, et al. Local ice therapy during bouts of acute gouty arthritis. *J Rheumatol*. 2002;29(2):331–334.
65. Moi JHY, Sriranganathan MK, Falzon L, Edwards CJ, van der Heijde DM, Buchbind R. Lifestyle interventions for the treatment of gout: a summary of 2 Cochrane systematic reviews. *J Rheumatol*. 2014;92(Suppl):26–32.
66. Zhang Y, Woods R, Chaisson CE, et al. Alcohol consumption as a trigger of recurrent gout attacks. *Am J Med*. 2006;119:800.e13–800.e18.
67. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. *Arch Int Med*. 2005;165(7):742–748.
68. Fam AG. Gout, diet, and the insulin resistance syndrome. *J Rheumatol*. 2002;29:1350–1355.
69. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2005;52:283–289.
70. Hill EM, Sky K, Sit M, Collamer A, Higgs J. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. *J Clin Rheumatol*. 2015;21:120–125.
71. Taylor TH, Mecchella JN, Larson RJ, Kerin KD, Mackenzie TA. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *Am J Med*. 2012;125:1126–1134.e7.
72. Feng X, Li Y, Gao W. Significance of the initiation time of urate-lowering therapy in gout patients: a retrospective research. *Joint Bone Spine*. 2015;82:428–431.
73. Seth R, Kydd ASR, Buchbinder R, Bombardier C, Edwards CJ. Allopurinol for chronic gout. *Cochrane Database Syst Rev*. 2014;2014(10):CD006077. doi:10.1002/14651858.CD006077.pub3
74. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther*. 2010;12:R63.
75. Reinders MK, Haagsma C, Jansen TLTA, van Roon EN, Delsing J, van de Laar MAFJ, Brouwers JRBJ. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. *Ann Rheum Dis*. 2009;68:892–897.
76. Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome. *Arthritis Rheum*. 2012;64(8):2529–2536.
77. Stamp LK, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic

gout, including those with renal impairment. *Arthritis Rheum*. 2011;63(2):412–421.
78. Allopurinol. Drug Facts & Comparisons. Facts & Comparisons eAnswers [database on the Internet]. Wolters Kluwer Health; 2020. Accessed October 9, 2020. http://online.factsandcomparisons.com
79. Uloric. Package insert. Takeda Pharmaceuticals America; 2019.
80. Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. *Cochrane Database Syst Rev*. 2012;11(11):CD008653. doi:10.1002/14651858.CD008653.pub2
81. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008;59:1540–1548.
82. Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. *J Rheumatol*. 2009;36:1273–1282.
83. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;310:1200–1210.
84. Febuxostat. Drug Facts & Comparisons. Facts & Comparisons eAnswers [database on the Internet]. Wolters Kluwer Health; 2020. Accessed October 9, 2020. http://online.factsandcomparisons.com
85. Yue TF, Dayton PG, Gutman AB. Mutual suppression of the uricosuric effects of sulfinpyrazone and salicylate: a study in interactions between drugs. *J Clin Invest*. 1963;42:1330–1339.
86. Reyes AJ. Cardiovascular drugs and serum uric acid. *Cardiovasc Drugs Ther*. 2003;17:397–414.
87. Zurampic. Prescribing information. AstraZeneca; 2015. Accessed October 1, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207988lbl.pdf
88. Dalbeth N, Jones G, Terkeltaub R, et al. Lesinurad, a selective uric acid reabsorption inhibitor, in combination with febuxostat in patients with tophaceous gout: findings of a phase III clinical trial. *Arthritis Rheumatol*. 2017;69(9):1903–1913.
89. Saag KG, Fitz-Patrick D, Kopicko J, et al. Lesinurad combined with allopurinol: a randomized, double-blind, placebo-controlled study in gout patients with an inadequate response to standard-of-care allopurinol (a US-based study). *Arthritis Rheumatol*. 2017;69(1):203–212. doi:10.1002/art.39840. Erratum in: *Arthritis Rheumatol*. 2018;70(8):1318.
90. Hale C. Ironwood abandons deal with AstraZeneca for lesinurad, once hoped to be a gout blockbuster. Fierce Biotech [Internet]. 2018 Aug 6. https://www.fiercebiotech.com/biotech/ironwood-abandons-lesinurad-deal-astrazeneca-once-hoped-to-be-a-gout-blockbuster

91. Sundy JS, Baraf HSB, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA*. 2011;306(7):711–720.
92. De Angelis S, Noce A, Di Renzo L, et al. Is rasburicase an effective alternative to allopurinol for management of hyperuricemia in renal failure patients? A double blind-randomized study. *Eur Rev Med Pharmacol Sci*. 2007;11:179–184.
93. Elitek. Prescribing information. Sanofi-Aventis U.S. LLC; 2010. Accessed October 1, 2020. https://products.sanofi.us/elitek/elitek.pdf
94. Richette P, Brière C, Hoenen-Clavert V, Loeuille D, Bardin T. Rasburicase for tophaceous gout not treatable with allopurinol: an exploratory study. *J Rheumatol*. 2007;34:2093–2098.
95. Baraf HS, Becker MA, Gutierrez-Urena SR, et al. Tophus burden reduction with pegloticase: results from phase 3 randomized trials and open-label extension in patients with chronic gout refractory to conventional therapy. *Arthritis Res Ther*. 2013;15:R137.
96. Strand V, Khanna D, Singh JA, Forsythe A, Edwards NL. Improved health-related quality of life and physical function in patients with refractory chronic gout following treatment with pegloticase: evidence from phase III randomized controlled trials. *J Rheumatol*. 2012;39:1450–1457.
97. Becker MA, Baraf HSB, Yood RA, et al. Long-term safety of pegloticase in chronic gout refractory to conventional treatment. *Ann Rheum Dis*. 2013;72:1469–1474.
98. Krystexxa. Prescribing information. Savient Pharmaceuticals; 2010. Accessed October 1, 2020. http://www.crealtapharma.info/pdfs/krystexxa/KRYSTEXXA_Prescribing_Information.pdf
99. Daskalopoulou SS, Tzovaras V, Mikhailidis DP, Elisaf M. Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricaemia. *Curr Pharm Des*. 2005;11:4161–4175.
100. Juraschek SP, Miller ER, Gelber AC. Effect of oral vitamin C supplementation on serum uric acid: a meta-analysis of randomized controlled trials. *Arthritis Care Res*. 2011;63:1295–1306.
101. Choi HK, Gao X, Curhan G. Vitamin C intake and the risk of gout in men: a prospective study. *Arch Intern Med*. 2009;169(5):502–507.
102. Andrés M, Sivera F, Falzon L, Buchbinder R, Carmona L. Dietary supplements for chronic gout. *Cochrane Database Syst Rev*. 2014;7(10):CD010156.
103. Stamp LK, O'Donnell JL, Frampton C, Drake JM, Zhang M, Chapman PT. Clinically insignificant effect of supplemental vitamin C on serum urate in patients with gout: a pilot randomized controlled trial. *Arthritis Rheum*. 2013;65(6):1636–1642.

104. Choi HK, Soriano LC, Zhang Y, García Rodríguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ*. 2012;344:d8190.
105. Wolff ML, Cruz JL, Vanderman AJ, Brown JN. The effect of angiotensin II receptor blockers on hyperuricemia. *Ther Adv Chronic Dis*. 2015;6(6):339–346.
106. Sutton Burke EM, Kelly TC, Shoales LA, Nagel AK. Angiotensin receptor blockers effect on serum uric acid—a class effect? *J Pharm Pract*. 2019;33(6):874–881. doi:10.1177/0897190019866315
107. Derosa G, Maffioli P, Sahebkar A. Plasma uric acid concentrations are reduced by fenofibrate: a systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacol Res*. 2015;102:63–70.
108. Feher MD, Hepburn AL, Hogarth MB, Ball SG, Kaye SA. Fenofibrate enhances urate reduction in men treated with allopurinol for hyperuricaemia and gout. *Rheumatology (Oxford)*. 2003;42:321–325.
109. Ka T, Inokuchi T, Tsutsumi Z, Takahashi S, Moriwaki Y, Yamamoto T. Effects of a fenofibrate/losartan combination on the plasma concentration and urinary excretion of purine bases. *Int J Clin Pharmacol Ther*. 2006;44:22–26.
110. Perex-Ruiz F, Atxotegi J, Hernando I, Calabozo M, Nolla JM. Using serum urate levels to determine the period free of gouty symptoms after withdrawal of long-term urate-lowering therapy: a prospective study. *Arthritis Rheum*. 2006;55(5):786–790.
111. Mallat SG, Kattar SA, Tanios BY, Jurjus A. Hyperuricemia, hypertension, and chronic kidney disease: an emerging association. *Curr Hypertens Rep*. 2016;18(10):74.
112. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease? A systematic review and metaanalysis based on observational cohort studies. *BMC Nephrol*. 2014;15:122.
113. Harrold LR, Andrade SE, Briesacher BA, et al. Adherence with urate-lowering therapies for the treatment of gout. *Arthritis Res Ther*. 2009;11(2):R46.
114. de Achaval S, Suarez-Almazor ME. Improving treatment adherence in patients with rheumatologic disease. *J Musculoskelet Med*. 2010;27(10):1691476.

46

Connective Tissue Disorders

Steven S. Kheloussi, Julie L. Olenak, and Jonathan D. Ference

CORE PRINCIPLES		CHAPTER CASES
1	Systemic sclerosis (SSc) can be classified into localized and diffuse forms, with the major differentiation point being the dermatologic areas affected.	**Case 46-1 (Question 1)**
2	Ninety-five percent of patients affected by SSc also have signs and symptoms consistent with Raynaud phenomenon, which may be treated with nifedipine, prazosin, losartan, or phosphodiesterase-5 inhibitors.	**Case 46-1 (Question 2)**
3	SSc may involve dermatologic, pulmonary, gastrointestinal (GI), cardiac, and renal manifestations. Although treatment options exist for individual	**Case 46-1 (Questions 2, 3)**

	complications, no therapies exist to target the underlying disease.	
4	Many authorities believe polymyalgia rheumatica and temporal arteritis are manifestations of the same underlying process occurring at different times during the clinical course. However, they each have characteristic symptoms and are treated differently.	**Case 46-2 (Questions 1, 2), Table 46-4**
5	Reactive arthritis is secondary to certain genitourinary, GI, or respiratory infections. Patients with the *HLA-B27* gene are more susceptible to developing spondyloarthritis.	**Case 46-3 (Question 1), Table 46-5**
6	Nonsteroidal anti-inflammatories are appropriate initial therapy for reactive arthritis to control pain and inflammation.	**Case 46-3 (Question 2)**
7	Patients with documented active infections, and their partners when caused by a sexually transmitted disease, should be offered antibiotics. However, efficacy of prolonged antibiotics as a treatment of reactive arthritis is conflicting.	**Case 46-4 (Question 1)**
8	In severe or prolonged cases of reactive arthritis, corticosteroids, disease-modifying antirheumatic drugs, and biologicals may be considered.	**Case 46-4 (Question 2)**
9	Polymyositis and dermatomyositis should initially be treated with high-dose	**Case 46-5 (Questions 1, 2)**

corticosteroids. Immunosuppressive agents are recommended if the disease is not controlled with corticosteroids alone, if the response is positive but corticosteroid-sparing effects are desired, or if the condition presents initially with extramuscular complications.

INTRODUCTION

Connective tissue diseases (CTDs) are a complex group of conditions that are inflammatory in nature and are related to dysfunction of the immune system. It often takes years to properly diagnose CTDs, given heterogeneous patient presentations, nonspecific symptoms, complex etiologies, and overlapping syndromes.[1,2] Patients may present with findings consistent with more than one CTD, and symptoms generally do not all appear simultaneously. It has been reported that as many as half of patients who have a diagnosed CTD had been identified as having undifferentiated CTD.[3] Mixed CTD is an overlap of autoimmune disease features that can include myositis, scleroderma, and lupus.[1,3] Beyond the select CTDs covered in this chapter, the reader is also referred to Chapter 33 (Systemic Lupus Erythematosus).

Systemic Sclerosis (Scleroderma)

Systemic sclerosis (SSc), or systemic scleroderma, is a CTD associated with autoimmunity characterized by excessive extracellular matrix deposition and vascular injury to the skin and other visceral organs.[4] SSc can be classified into distinct clinical subsets based on the patterns of skin and internal organ involvement, autoantibody production, and patient survival.[4] The

most common subsets include limited cutaneous (~60% of patients) and diffuse cutaneous (~35% of patients).[4] Overlap syndrome occurs in up to 20% of patients and is the term used to define SSc features that are common in one or more of the other CTDs.[5] The limited cutaneous subset is diagnosed when skin thickening is limited to areas distal to the elbows and knees. Another form of the disease, localized scleroderma, presents with no systemic involvement and is usually benign and self-limiting.[6] This section will focus on SSc.

The prevalence of SSc is estimated at 276 cases/million adults in the United States.[7] More females than males suffer from SSc (female-to-male ratio, 3:1), although it appears the ratio is higher in younger patients (ages 15–44 years) compared to those older than age 45 years.[7] Onset of SSc generally begins in adults between ages 40 and 50 years.[8] African American patients are twice as likely as non–African American patients to have diffuse disease.[7,9] Additional risk factors for development of SSc are shown in **Table 46-1**.

Table 46-1

Risk Factors for the Development of Systemic Sclerosis

Female sex
Age (onset typically between 40 and 50 years)
African American race
Environmental exposure to silica dust (eg, coal miners)
Chemotherapeutic agents (gemcitabine, taxanes)
Presence of a connective tissue growth factor polymorphism

Sources: Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103):1685–1699; Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum*. 2008; 37:223–235; Zhong L, Pope M, Shen Y, Hernandez JJ, Wu L. Prevalence and incidence of systemic sclerosis: a systematic review and meta-analysis. *Int J Rheum Dis*. 2019;22(12):2096–2107; Laing TJ, Gillespie BW, Toth MB, et al. Racial differences in scleroderma among women in Michigan. *Arthritis Rheum.* 1997;40:734–742; Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med*. 2009;360(19):1989–2003.

The underlying pathophysiologic changes that lead to systemic scleroderma remain unknown, but many believe that it results from a lymphocyte-mediated autoimmune reaction with endothelial cells, activated immune cells, and fibroblasts playing a key role in the process.[10,11] T-cell and B-cell abnormalities cause the production of autoantibodies that are seen in over 95% of patients.[11,12]

CASE 46-1

QUESTION 1: F.G. is a 47-year-old African American female with recently diagnosed diffuse cutaneous scleroderma. She presents with pain, tingling, and tricolor discoloration in her fingers. F.G. reports that she was previously diagnosed with Raynaud phenomenon and has experienced these symptoms for the previous 2 years, but they have recently worsened. Additionally, she presents with skin thickening and pruritus extending from the hands to the shoulders. It is determined upon testing that F.G.'s antinuclear antibodies are elevated, specifically anti-centromere and anti-topoisomerase I. She has a 32-year pack smoking history but has no other pertinent past medical history and does not take any medications. She also notes that she has recently gone through a divorce and has been smoking more because of the stress.

Which symptoms of SSc is F.G. experiencing that support a diagnosis of diffuse SSc?

The presentation of SSc is heterogeneous; however, several key clinical signs aid in pinpointing this condition. Diagnostic criteria for SSc rely on a scoring system that takes into account the presence and location of sclerosis (proximal or distal to the metacarpophalangeal joint), fingertip lesions, telangiectasia, abnormal nailfold capillaries, pulmonary involvement, Raynaud phenomenon, and SSc-specific autoantibodies.[10] Autoantibodies specific to SSc, including anti- centromere, anti-topoisomerase I, and anti-RNA polymerase III, are helpful in the diagnosis and differentiation of classification of the disease, but alone offer limited predictive and prognostic value.[13,14]

The major differentiation point between diffuse and localized scleroderma includes the dermatologic areas affected. Individuals, like F.G., who experience dermatologic involvement proximal to the elbows and knees are considered to have diffuse disease, whereas

those with localized SSc have distal involvement only.[4] Historically, the CREST acronym (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia) was used to describe limited cutaneous SSc, although this has recently fallen out of favor because these symptoms may be present in different subtypes of the disease.[15]

Case 46-1, Question 2: What are possible complications of Raynaud phenomenon and an appropriate treatment approach for this patient?

Raynaud phenomenon is the most universal sign of SSc, occurring in more than 95% of patients.[12] Patients may experience moderate-to-severe discoloration of affected areas, including fingers and toes, secondary to cold exposure or emotional stress.[4] Tricolor discoloration, such as that experienced by F.G., may occur, resulting in white, red, or blue phalanges or digits secondary to paroxysmal ischemia, stasis, and reactive hyperperfusion, respectively.[4,13] Vascular and tissue complications may occur and can result in digital pitting, digital ulceration, and autoamputation.[4,13] Efforts should be made to identify causative factors and reduce exposure. In F.G.'s case, stress reduction techniques and smoking cessation should be advised.

Pharmacologic therapy can also be considered for the treatment of Raynaud phenomenon. Clinical practice guidelines exist, which may assist in determining treatment for SSc complications, including Raynaud phenomenon.[16] Compared with placebo, nifedipine and prazosin modestly reduced the severity and frequency of Raynaud ischemic attacks.[17,18] When losartan was compared with low-dose nifedipine in a nonblinded, randomized, controlled trial, losartan users experienced a decrease in severity and frequency of Raynaud symptoms in a 12-week period.[19] This should not be considered as definitive evidence that losartan is superior as the lack of blinding may have resulted in an overestimation of losartan's benefit. Phosphodiesterase-5-inhibitors, including sildenafil and tadalafil, appear to be modestly effective as add-on therapy, but may also be

considered as monotherapy in patients who do not tolerate first-line therapy with a calcium channel blocker.[16,20–22] Notably, botulinum toxin was not found to increase blood flow to the hands of patients with scleroderma-related Raynaud phenomenon in one small double-blind, randomized, controlled trial.[23] In this case, F.G. is a candidate for standard first-line therapy with low-dose nifedipine, and a phosphodiesterase-5-inhibitor, such as sildenafil, may be considered if nifedipine monotherapy is ineffective.

Case 46-1, Question 3: Beyond Raynaud phenomenon, which complications of SSc is F.G. at risk for developing? What is an evidence-based treatment approach for each?

Those affected by diffuse SSc are more likely to develop organ complications compared to patients with localized disease, including an increased risk of skin, pulmonary, gastrointestinal (GI), cardiac, and renal complications.[13,24] Treatment complications are managed individually, as there are no available therapies to treat SSc.

Pulmonary disease, including pulmonary arterial hypertension and interstitial lung disease, occurs in up to 80% of individuals with SSc and represents the most common cause of death in patients with SSc.[4,5] Those with diffuse SSc tend to develop pulmonary disease sooner than those with limited skin involvement.[24] Interstitial lung disease is more prevalent in the diffuse SSc population, whereas pulmonary arterial hypertension is more common in patients with localized disease.[4]

Treatment for interstitial lung disease includes the respiratory tyrosine kinase inhibitor, nintedanib, which is approved for use in SSc-associated interstitial lung disease based on its demonstrated ability to slow the worsening of lung function in this population.[25] Tocilizumab, an interleukin-6 receptor antagonist, has also been shown to preserve lung function in SSc-associated interstitial lung disease and received approval for this indication in 2021.[26] Phase 2 data for pirfenidone, an antifibrotic agent, has shown promise, though this agent has not yet been approved for use for this

indication in the United States.[27] Additionally, cyclophosphamide, an antineoplastic agent, may be considered as it has been shown to improve forced vital capacity in these patients; however, it does not improve mortality.[28] In a single-center, retrospective study, mycophenolate mofetil showed promise for SSc-associated interstitial lung disease by leading to similar outcomes as cyclophosphamide.[29]

For patients who develop pulmonary hypertension, treatment with endothelin receptor antagonists (bosentan, macitentan, ambrisentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil), or riociguat may be considered as they have all been shown to improve functional capacity.[16] Less data support the prostanoids, iloprost and treprostinil, although these agents may still be considered. Although epoprostenol is effective, given that it must be administered through a permanent indwelling central venous catheter, it should be reserved for more severe, treatment-resistant disease.[16]

Digital ulceration may occur as a complication of prolonged ischemia in Raynaud phenomenon. Guideline-recommended therapies available for use in the United States include phosphodiesterase-5 inhibitors (sildenafil and tadalafil) and bosentan.[16] Sildenafil and tadalafil have both been shown to reduce healing time, whereas tadalafil and bosentan have been shown to reduce new digital ulcer formation.[16] Atorvastatin 40 mg daily has also been shown to reduce the number of new digital ulcers in patients with Raynaud phenomenon and SSc over a 4-month period.[30]

GI complications tend to be common in patients with SSc and may include reflux, diarrhea, constipation, dysphagia, bloating, and early satiety.[5,24] These sequelae may be managed similarly to non-SSc patients who present with these disorders, despite limited evidence. This includes proton pump inhibitors, histamine-2 receptor antagonists, and the prokinetic agent, metoclopramide.[5,16] Weight loss and malnutrition can lead to morbidity in patients with SSc, and parenteral or enteral nutrition should be considered to ameliorate these conditions.[5]

Finally, in diffuse disease, extensive skin involvement may require treatment. Methotrexate may be effective for improving skin symptoms and is recommended by guidelines.[16] Despite a variety of uses for methotrexate, it lacks efficacy on other organ manifestations of SSc. Cyclophosphamide, mycophenolate mofetil, and rituximab have also been shown to improve dermatologic symptoms.[5,31,32] Tocilizumab was found to be ineffective for improving skin involvement.[26]

Polymyalgia Rheumatica and Temporal Arteritis (Giant Cell Arteritis)

Polymyalgia rheumatica (PMR) and temporal arteritis, also known as giant cell arteritis (GCA), are closely related clinical syndromes that many authorities believe to be different phases of the same underlying disease process. PMR is two to three times more common than GCA. However, about 27% to 53% of persons with GCA also have PMR, and 18% to 26% of those with PMR also have GCA.[33] Inflammation is the hallmark of both conditions. PMR is characterized by aching and morning stiffness in the cervical region and shoulder and pelvic girdles and may result in disability.[34] Inflammation as a result of GCA most commonly involves the temporal artery, but arteries in other parts of the body can also be affected.[35] Despite certain similarities, PMR and GCA have distinct symptoms, corticosteroid requirements for treatment, and prognoses.

The incidence of PMR and GCA increases in patients after age 50 years and peaks in those ages 70 to 80 years.[34] GCA can lead to blindness if not diagnosed and treated in a timely manner. Likewise, patients with PMR are at an increased risk of peripheral arterial disease. The primary risk factor for both conditions is age, and both occur more frequently in females than in males. The incidence of PMR is 5.9/10,000/year in the United States, with an overall prevalence of about 740/100,000.[36] The incidence of GCA is 0.17

new cases annually per 1000 persons older than age 50 years with a prevalence of 2/1000 persons.[37]

Although the exact pathogeneses of PMR and GCA are yet to be determined, they are both thought to arise from an autoimmune or inflammatory dysfunction involving similar cellular immune responses from T cells, antigen-presenting cells, macrophage-derived inflammatory cytokines, genetic human leukocyte antigen molecules, and macrophages.[34,38]

CASE 46-2

Question 1: D.C. is an 85-year-old White male presenting to the emergency department with new-onset morning aching pain and stiffness in his shoulders and upper arms. He states his symptoms developed 3 weeks ago and have progressed to the point where his pain and limited range of motion are keeping him from performing activities of daily living. D.C. denies headaches or vision disturbances, but reports overall malaise, fatigue, and anorexia. He has a past medical history significant for hyperlipidemia, type-2 diabetes mellitus, and hypertension. He has been taking his current medications for the past 2 years, which are adequately controlling his hyperlipidemia, diabetes, and hypertension. His current medications include simvastatin 40 mg daily, metformin 1000 mg twice daily, lisinopril/hydrochlorothiazide 40/25 mg daily, and aspirin 81 mg daily. His physical examination was negative for decreased muscle strength. Limited range of shoulder and upper arm motion is noted along with tenderness of these areas on palpation. Routine baseline laboratory values are within normal limits, with an erythrocyte sedimentation rate (ESR) of 75 mm/hour. D.C. was admitted to a general medical ward with a diagnosis of PMR and was started on prednisone.

What signs and symptoms present in this case differentiate PMR from GCA?

No conclusive laboratory test for PMR or GCA exists, and nonspecific clinical features and the absence of physical signs often complicate diagnosis. Appropriate diagnosis requires a thorough history and physical examination. Distinguishing between the two disorders is of importance, as GCA can lead to blindness and requires higher doses of treatment medications. The typical onset of PMR is acute in nature. However, as is the case with D.C., most who present for a medical evaluation describe their symptoms as occurring for 1 month or longer.[35] D.C. is also exhibiting symptoms

associated with PMR, which include aching pain and morning stiffness in the shoulders and upper arms, hips and thighs, or neck and torso. The shoulders are affected in 95% of cases. New-onset GCA often manifests as a new headache or a headache that is described as different from previous headaches and has been occurring for 2 to 3 months. Constitutional symptoms such as fatigue, anorexia, and weight loss in an older patient often accompany headaches seen in GCA.[33] The absence of headache in D.C. further supports the diagnosis of PMR. Common findings associated with both conditions are presented in **Table 46-2**.[35] An elevated ESR is a common diagnostic finding for both PMR and GCA.[35] At least three different sets of diagnostic criteria are in use for PMR.[39] Patients with suspected GCA should be referred to a specialist for diagnostic work-up where clinical diagnosis is often confirmed by imaging or histology.[40] The 2020 British Society for Rheumatology guidelines recommend patients with suspected GCA should have a confirmatory diagnostic test. This test could be either a temporal artery biopsy or an ultrasound of the temporal and axillary arteries, or both.[41]

Table 46-2

Common Findings Associated With Polymyalgia Rheumatica and Giant Cell Arteritis

Polymyalgia Rheumatica	Giant Cell Arteritis
Age ≥ 50 years	Age ≥ 50 years
ESR > 50 mm/hour	ESR > 50 mm/hour
Anemia (mild, normochromic, normocytic)	Anemia
Aching, pain, and morning stiffness in the shoulders and upper arms, hips and thighs, or neck and torso	Headache: temporal with temporal artery involvement or occipital with occipital artery involvement
Symptoms of systemic inflammation	Visual symptoms or jaw claudication
	Fever, weight loss, depression, fatigue
	Arthralgias

ESR, erythrocyte sedimentation rate.

Source: Adapted with permission from Unwin B, Williams CM, Gilliland W. Polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician*. 2006;74(9):1547-1554. Copyright © 2006 by the American Academy of Family Physicians.

Case 46-2, Question 2: What is the preferred initial treatment approach for PMR in D.C.? What are the difference(s) in this approach as compared with those for GCA?

Owing to its anti-inflammatory properties, corticosteroids are considered first-line therapy for either PMR or GCA. Early visual loss may occur in up to 20% of GCA patients and rarely improves once present. Therefore, initiation of corticosteroid treatment should not be delayed pending temporal artery biopsy results.[33] When PMR and GCA occur simultaneously, higher corticosteroid doses (indicated for the treatment of GCA) are required to prevent significant complications. For the treatment of PMR, European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) guidelines recommend the use of corticosteroids (equivalent to prednisone 12.5–25 mg daily) in place of nonsteroidal anti-inflammatory drugs, except for short-term use for analgesia.[39] Clinicians should consider initiating treatment with the minimum effective corticosteroid dose. A higher dose may be preferred if the patient is at elevated risk of relapse and minimal risk of adverse events, whereas a lower dose may be preferred if the patient has comorbidities (eg, diabetes, osteoporosis, or glaucoma) and risk factors for corticosteroid-related adverse events. Beginning low-dose prednisone (owing to his diabetes) may improve D.C.'s PMR symptoms within days, but optimal results could take several weeks to achieve, and most patients can expect to receive therapy for 1 to 2 years. Treatment should be tailored to patient symptoms and inflammatory markers should be followed. Attempts to taper the dose to avoid long-term adverse drug events (eg, osteoporosis, hypothalamus–pituitary–adrenal axis suppression) should be made once acute relief has been achieved. Initially, the dose should be reduced to the equivalent of prednisone 10 mg daily within 4 to 8

weeks.[39] If the patient relapses, the dose should be increased back to the pre-relapse dose. Once remission is achieved, the corticosteroid dose should be tapered by 1 mg every 4 weeks. Addition of methotrexate to corticosteroid therapy may be considered in patients with comorbid conditions, those requiring prolonged treatment, and those who do not respond to therapy.[35]

GCA is a medical emergency requiring immediate treatment. As opposed to PMR, treatment for uncomplicated (no jaw or tongue claudication or visual changes) GCA should begin with high-dose corticosteroids, equivalent to prednisolone 40 to 60 mg/day.[41] Complicated GCA (evolving visual loss or history of amaurosis fugax) should be treated with intravenous methylprednisolone 250 mg to 1 g/day for 3 days, followed by oral prednisolone 60 mg/day.[41] A corticosteroid taper can be initiated after 4 weeks of treatment, resolution of symptoms, and normalization of ESR/C-reactive protein. High-quality evidence comparing different corticosteroid taper schedules is not available. Clinical practice guidelines provide examples of different schedules.[41] Use of immunosuppressants as adjunctive therapy may be recommenced in patients with refractory or relapsing GCA, and in patients with or at an increased risk of corticosteroid-related side effects.[41] In such cases, tocilizumab 162 mg/week is recommended and methotrexate, at a minimum dose of 15 mg/week, may be considered as an alternative.[40]

All patients on long-term corticosteroids should be offered calcium (1200 mg/day) and vitamin D (800 international units/day) for the prevention of osteoporosis and be monitored for other complications of corticosteroid therapy. Patients at risk for gastritis should receive prophylactic protection with a proton pump inhibitor.

Patients being treated for PMR or GCA should be monitored closely for response to treatment and disease progression. It is recommended that the first follow-up visit should take place 1 to 3 weeks after the start of corticosteroids.[38] Subsequent visits should occur at 6 weeks as well as 3, 6, 9, and 12 months, or on an as-needed basis if relapses or adverse events occur. At each visit, patients should be assessed for specific symptom improvement, and routine blood work should include ESR, C-reactive protein, a

complete blood count, and a comprehensive metabolic panel. Bone mineral density testing every 2 years may be considered in patients receiving long-term corticosteroids.

Reactive Arthritis

Reactive arthritis is defined as peripheral arthritis often accompanied by one or more extra-articular manifestations that appear after certain genitourinary (GU), GI, or respiratory infections. **Table 46-3** lists bacterial pathogens associated with the development of reactive arthritis.[42–44] In addition, it shares features with other forms of spondyloarthropathies, which is the grouping it falls under. The term "Reiter syndrome" was previously used to describe the unique combination of arthritis, urethritis, and conjunctivitis.[42] The majority of the patients do not present with all three symptoms in the triad.[42,45] The presentation of arthritis is usually a large joint monoarthritis or oligoarthritis in the lower extremities and/or enthesitis, which is an inflammation of the site where the tendon or ligament attaches to the bone.[42] Typically, reactive arthritis would occur 1 to 6 weeks after the infection.[42] The clinical course of reactive arthritis is variable and usually runs a self-limited course of 3 to 12 months.[43] Although mortality from reactive arthritis is not common, it may result from rare cardiac complications. Approximately 20% of patients may continue to have chronic, destructive, and disabling arthritis or enthesitis and some may progress to ankylosing spondylitis.[43,45]

Table 46-3
Examples of Bacterial Pathogens Associated With the Development of Reactive Arthritis

Gastrointestinal
Salmonella enteritidis and *typhimurium*
Shigella flexneri
Yersinia enterocolitica and *pseudotuberculosis*
Campylobacter jejuni

Escherichia coli
Clostridium difficile
Genitourinary
Chlamydia trachomatis
Neisseria gonorrhoeae
Respiratory
Chlamydia pneumonia
Group A streptococcus

Sources*:* Reactive arthritis. In: *DynaMed [Internet]*. EBSCO Information Services; 1995. Record number T1116312. Updated November 30, 2018. Accessed September 2, 2020. http://www.dynamed.com. Registration and login required; Garcia-Kutzback A, Chacon-Suchite J, Garcia-Ferrer H, Iraheta I. Reactive arthritis: update 2018. *Clin Rheumatol*. 2018:869–874; Schmitt S. Reactive arthritis. *Infect Dis Clin N Am.* 2017:31(2):265–277.

The annual incidence of reactive arthritis in the United States varies between 3.5 and 5/100,000/year.[42] Reactive arthritis most frequently occurs in patients between 20 and 40 years old, but it can occur at any age. In general, it occurs more frequently in males than in females following GU infection. Following bowel infections, the prevalence is equal.[42]

Reactive arthritis is considered a sterile inflammatory response to a remote infection. Genetics has been identified as a likely risk factor, playing a role in the pathogenesis of spondyloarthropathies. Between 30% and 50% of patients are surface antigen *HLA-B27* positive, which presents antigenic peptides to T cells.[44] Some sources present this as high as 80% among families.[43] These patients are susceptible to a more severe and prolonged disease.[42,43,45]

Onset of symptoms typically occurs 1 to 6 weeks after infection and may present in an insidious or acute manner. Patients usually present with joint pain and stiffness, myalgia, and low back pain that is worse with rest. Initial symptoms of the infection may no longer be present.[43] **Table 46-4** describes the clinical manifestations of reactive arthritis. It may present as arthritic in nature or as dysfunctions of the ocular, skin, GU, mucocutaneous lesions, or cardiac systems.

Urethritis, cystitis, prostatitis, mild dysuria, and a mucopurulent urethra are the most common symptoms that occur in males. Females may have dysuria, vaginal discharge, and purulent cervicitis or vaginitis. Arthritic symptoms are usually asymmetrical, involving the lower extremities, and are associated with the appearance of a "sausage finger" digit.[43–45]

Table 46-4
Clinical Signs of Reactive Arthritis

Musculoskeletal System
Arthritis affecting one to four joints of typically large, lower limb
Entheses
Low back pain (sacroiliitis)
Skin/Mucosal Manifestations
Keratoderma blennorrhagica on soles and/or palms
Mucosal ulcers
Circinate balanitis on penile gland
Genitourinary
Cervicitis
Urethritis
Ocular Manifestations
Conjunctivitis
Uveitis

Sources: Reactive arthritis. In: *DynaMed [Internet]*. EBSCO Information Services. 1995. Record number T1116312. Updated November 30, 2018. Accessed September 2, 2020. http://www.dynamed.com. Registration and login required; Schmitt S. Reactive arthritis. *Infect Dis Clin N Am*. 2017:31(2):265–277; Garcia-Kutzback A, Chacon-Suchite J, Garcia-Ferrer H, Iraheta I. Reactive arthritis: update 2018. *Clin Rheumatol*. 2018:869–874.

CASE 46-3

Question 1: E.O. is a 47-year-old male who had a stool sample–confirmed GI infection with *Salmonella Typhimurium enteritidis*. E.O. was able to manage the infection at home. Approximately 2 weeks after the diarrhea, fever, and abdominal cramps subsided, E.O. presented with two swollen, stiff, and erythemic joints (ie, right knee and left ankle). He also is experiencing tendonitis presenting as heel pain. He has no significant medical or family history and takes a multivitamin tablet daily.

Based on the history of symptoms present in this case, what supports a diagnosis of reactive arthritis?

E.O. had an infection known to be associated with reactive arthritis. Symptoms also began within a few weeks of the infection. Lower limb joints are most frequently impacted in reactive arthritis. Additionally, tendonitis is an example of endothesis. The asymmetric presentation of joint pain and swelling is typical.[43–45]

Case 46-3, Question 2: What is an appropriate initial treatment strategy for E.O.?

First-line therapy with a nonsteroidal anti-inflammatory drug would be appropriate for symptom relief. Nonsteroidal drugs offer analgesic and anti-inflammatory properties. For example, naproxen 500 mg twice daily could be initiated.[42–44]

CASE 46-4

Question 1: C.S. is a 27-year-old female who was diagnosed with *Chlamydia trachomatis* and was properly treated with antibiotics. One month later, she presented with a new painful right knee effusion; a left "sausage finger"; cervicitis; vaginal discharge; and red, irritated eyes. The effusion was drained, and no bacteria or crystals were identified. She has no cardiac or dermatologic abnormalities on physical exam. She reports no current medical conditions and a family history of a father with psoriatic arthritis. She was started on ibuprofen 800 mg three times daily and has been taking it for 6 weeks. She presents for a follow-up and reports that all of her symptoms are gone except the joint pain. She rates her pain as a 6 out of 10 and indicates that her joint pain is interfering with her activities of daily living. She has tested positive for the *HLA-B27* gene, her rheumatoid factor was negative, and her ESR was elevated at 35 mm/hour.

The laboratory confirmed that her test was now negative for *Chlamydia trachomatis*.

What additional therapies may be recommended for C.S.?

C.S. developed reactive arthritis following her chlamydia infection. It is important to confirm that any sexual partners were also treated for chlamydia at the time of her diagnosis. She is presenting with the classic triad of symptoms, including arthritis, urethritis, and conjunctivitis.[42,43] C.S. is still experiencing an active inflammatory response as evidenced by the elevated sedimentation rate. A family history of psoriatic arthritis, which is also classified as a spondyloarthropathy, and testing positive for the *HLA-B27* gene are risk factors for severe or chronic reactive arthritis.[42]

Because C.S. is still experiencing pain in her joints, an intra-articular corticosteroid injection may be considered if one joint is predominantly causing her pain or oral corticosteroids if more joints are affected. Joint pain is typically present in a limited number of joints (ie, one to six joints), and some experts prefer to use injections to avoid systemic adverse effects. However, oral corticosteroids may be helpful for the treatment of pain and swelling.[44] An example oral corticosteroid dose would be 20 to 40 mg of prednisone daily.[42] Reactive arthritis will spontaneously resolve in approximately half of cases, even without treatment.[42,43,46] Physical therapy and ice modalities may be an integral part of management to improve mobility and strength and to prevent stiffness and deformities if needed.[42,46]

Case 46-4, Question 2: What additional treatment options are available if C.S. does not respond to corticosteroid therapy or develops chronic reactive arthritis?

For those who suffer from a persistence of acute reactive arthritis, a disease-modifying antirheumatic drug (DMARD) may be used. One example is sulfasalazine, which is well tolerated and possibly effective at a dose of 1 g twice or three times daily.[42] Consideration may be given to start a nonbiologic DMARD therapy earlier in the

course of the disease if a patient is refractory to first- and second-line treatments, has a recurrence of reactive arthritis, or is *HLA-B27* positive.[42] Given its use in other rheumatologic conditions, methotrexate has been used by some as a nonbiologic DMARD despite a lack of strong evidence. Aggressive and unremitting reactive arthritis may be treated with immunosuppressants if it is confirmed the initial infection is cleared.[46] In severe cases, where patients fail to achieve adequate relief with prior therapies, antitumor necrosis factor-α treatment may be considered.[47] Tumor necrosis factor has been found to be elevated in synovial samples of patients with reactive arthritis.[42,47] Additional large-scale studies are needed to evaluate the role of these agents for routine use because most current evidence is based on case reports and small studies.[46,47]

Prolonged antibiotic use is not known to improve symptoms once the initial infection is cleared with the possible exception of chronic reactive arthritis, defined by a duration of >6 months, from an active chlamydia infection. It was noted that heterogeneity of studies potentially limits results. A small, randomized trial of 42 patients who took a 6-month course of antibiotics in chlamydia-induced reactive arthritis, including rifampin combined with doxycycline or azithromycin, improved symptoms in 63% of treated patients compared to 20% of placebo-treated patients.[42,43,48,49] GI side effects are frequently reported with prolonged antibiotic use.[42,43,48,49] Most cases of chronic reactive arthritis resolve within 1 year.[42,43]

Polymyositis and Dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are idiopathic autoimmune and inflammatory disorders of unknown etiology involving a number of voluntary skeletal muscles simultaneously. PM and DM are characterized by the presence of inflammatory myopathies. In addition, DM involves specific skin manifestations, whereas PM does not.[50,51] Dermatomyositis is also associated with an increased risk of malignancies. Twenty-five percent of patients diagnosed with DM will develop a malignancy in the future, typically

within 5 years. For PM, the risk is lower with between 10% and 15% developing a malignancy within 5 years.[50] A patient may also have a preexisting malignancy they are unaware of and when diagnosed with DM should have age-appropriate screenings (eg, mammogram, colonoscopy, pelvic exams, prostate tests, imaging of chest).[51]

In addition to maintaining functions of daily activities and improving quality of life, therapy is aimed at reducing the risk of respiratory failure, renal failure, and cardiomyopathy as potential complications of either disorder.[50] A proportion of patients will meet the diagnostic criteria for other CTDs. This overlap syndrome with myositis and other CTDs (eg, systemic lupus erythematosus, scleroderma, rheumatoid arthritis) is thought to occur in about 20% of adult patients.[50]

Polymyositis typically presents in older adults over age 50 years and is rarely seen in children. Dermatomyositis exhibits a bimodal distribution and affects middle-aged adults (ages 30–50), as well as a peak in children age 7. These disorders occur in females more than males (~2:1).[51] Additionally, unlike other myopathies PM has not been associated with any specific antibodies. Ruling out other conditions is important as PM has become a diagnosis of exclusion.[52] The estimated prevalence of idiopathic inflammatory myopathies is between 50 and 100 cases/million.[50] Of those diagnosed with myositis, DM occurs in about 35% to 50% of cases and PM in ~30% to 45%.[50]

There is no clear cause of either disorder, and both are thought to involve immune-mediated processes triggered by viruses, cancer, other autoimmune CTDs, environmental factors (ultraviolet radiation in DM), or drugs in genetically susceptible individuals.[50] Dermatomyositis is thought to be a complement-mediated microangiopathy in which inflammatory infiltrates arise owing to ischemic phenomena. In patients with PM, muscle fibers may be damaged by T-cell mediated immune response. Infectious agents implicated as causative factors include coxsackievirus, group A *Streptococcus*, influenza virus, retroviruses, cytomegalovirus, parvovirus, and Epstein-Barr virus.[50]

Symptom onset for both PM and DM are insidious, and patients initially report muscle weakness of the trunk, shoulders, hips, upper arms, thighs, neck, and pharynx. These patients usually report increasing difficulties in everyday tasks requiring the use of proximal muscles, such as getting up from a chair, climbing stairs, stepping onto a curb, and combing hair. Frequent falls, fatigue, malaise, weight loss, shortness of breath, and low-grade fever are also often present. Classification of PM and DM can be accomplished by assessing the presence or absence of certain characteristics unique to the condition. Specifically, they are largely separated by the involvement of cutaneous changes and calcinosis in DM.[50,51] Specific manifestations seen in DM are described in **Table 46-5**.[53] The recently published EULAR/ACR classification criteria are helpful in using uniform definitions in clinical trials and looking at the probability of an idiopathic inflammatory myopathy.[54] Specific autoantibodies are helpful for diagnosing DM but have not been identified for PM.[52]

Table 46-5

Cutaneous Manifestations of Dermatomyositis

Pathognomonic Skin Lesions of Dermatomyositis
1. Gottron papules: papules having a violaceous hue overlying the dorsal lateral aspect of interphalangeal and/or metacarpophalangeal joints. When fully formed, these papules become slightly depressed at the center, which can assume a white, anthropic appearance. Associated telangiectasia can be present
2. Gottron signs: symmetric macular violaceous erythema with or without edema overlying the dorsal aspect of the interphalangeal/metacarpophalangeal joints, olecranon processes, patellae, and medial malleoli
Highly Characteristic Skin Lesions of Dermatomyositis
1. Periorbital violaceous (heliotrope) erythema with or without associated edema of the eyelids and periorbital tissue
2. Grossly visible periungual telangiectasia with or without dystrophic cuticles
3. Symmetric macular violaceous erythema overlying the dorsal aspect of the hands and fingers (where it can track the extensor tendon sheaths), extensor aspects of the arms and forearms, deltoids, posterior shoulders, and neck (the shawl sign), V-area of anterior neck and upper chest, central aspect of the face and forehead

Compatible Skin Lesions of Dermatomyositis

1. Poikiloderma vasculare atrophicans (poikilodermatomyositis) circumscribed violaceous erythema with associated telangiectasia, hypopigmentation, hyperpigmentation, and superficial atrophy most commonly found over the posterior shoulders, back, buttocks, and V-area of the anterior neck and chest
2. Calcinosis cutis

Reprinted from Iaccarino L, Ghirardello A, Bettio S, et al. The clinical features, diagnosis, and classification of dermatomyositis. *J Autoimmun*. 2014;48–49:123. Copyright © 2014 Elsevier. With permission.

CASE 46-5

Question 1: C.F. is a 55-year-old female who presents with a diagnosis of PM. Other CTDs and myopathies have been ruled out. She has no dermatologic abnormalities or other organ involvement. Her primary symptoms include fatigue and moderate symmetric muscle weakness. Activities she finds particularly difficult include rising from a seated position, climbing stairs, and performing activities that require her arms to be raised.

What is a first-line pharmacotherapeutic option to recommend that may provide C.F. with symptom relief?

The initial and long-term goals of therapy are to improve muscle weakness, thereby improving the activities of daily living. The clinical course of both PM and DM varies in severity from mild to more severe progressive disease. Those with mild forms of the disease usually have a rapid response to therapy, whereas those with more severe or slowly progressive forms of the disease are more likely to not respond to treatment. This is a marker for a poor prognosis.

An appropriate first-line therapy is a corticosteroid at a dose of up to 80 mg of prednisone or the equivalent for 2 to 4 weeks.[50] Weight-based dosing of 1 mg/kg may be considered.[52,55] A slow taper is recommended to avoid a flare of PM symptoms. An example taper could include reducing the dose by 10 mg every 2 weeks until 30 mg/day is achieved; then by 5 mg every 2 weeks until 20 mg/day is achieved; finally, by 2.5 mg every 2 weeks until the prednisone is discontinued.[50] Alternatively, taper approaches may involve a switch to alternate day dosing during the taper or a 10% reduction in dose every 2 weeks.

Depending on her response to the corticosteroids and the taper, C.F. may be offered methotrexate, azathioprine, or mycophenolate mofetil, as recommended immunosuppressants and corticosteroid-sparing agents if the disease is not controlled with corticosteroids alone, is rapidly progressive, or presents with extramuscular involvement. Intravenous immune globulin can be given over 2 to 5 days, depending on the dose, for severe or refractory cases. In severe cases, it may be preferred to begin with intravenous corticosteroid therapy with methylprednisolone 1000 mg for 3 to 5 days. If the complication of interstitial lung disease is present in patients with PM or DM, mycophenolate mofetil or tacrolimus may be considered as well as intravenous cyclophosphamide or rituximab, for which there is emerging data.[50,52,55,56] Ongoing trials will evaluate the potential use of other immune-modulating therapies.[52,55]

Case 46-5, Question 2: What preventive health measures may be offered to C.F. to augment her pharmacotherapeutic treatment regimen?

Supportive therapies such as physiotherapy, rest, and moist heat applications to the affected areas can improve muscle stiffness. If oral lesions are present, irrigation of these lesions with warm saline solution is helpful. Preventive health measures for those experiencing either disorder include cancer screenings, osteoporosis prevention, a review of immunization records, minimizing aspiration risk in patients with esophageal dysmotility, and physical therapy or customized exercise in patients with muscle weakness.[51,55] Patients with DM should routinely use sunscreen. Although there have been previous concerns to not further damage muscle, appropriate exercises including passive range of motion exercises and aerobic and resistance exercises have shown benefit.[55] Female patients placed on teratogenic immunosuppressants should discuss contraception, when appropriate.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Baig S, Paik JJ. Inflammatory muscle disease—an update. *Best Pract Res Clin Rheumatol*. 2020;34(1):101484. (52)

Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of polymyalgia rheumatica. *Rheumatology (Oxford)*. 2010;49(1):186–190. (38)

Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103):1685–1699. (5)

Garcia-Kutzback A, Chacon-Suchite J, Garcia-Ferrer H, Iraheta I. Reactive arthritis: update 2018. *Clin Rheumatol*. 2018:869–874. (44)

Glaubitz S, Zeng R, Schmidt J. New insights into the treatment of myositis. *Ther Adv Musculoskel Dis*. 2020; 12:1–14. (55)

Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. *Am Fam Physician*. 2008;78(8):961–968. (4)

Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76(8):1327–1339. (16)

Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis*. 2017;76(12):1955–1964. (54)

Mackie SL, Dejaco C, Appenzeller S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. *Rheumatology (Oxford)*. 2020;59(3):e1–e23. (41)

Sticherling M. Systemic sclerosis—the dermatological perspective. *J Dtsch Dermatol Ges*. 2019;17(7):716–728. (13)

Unwin B, Williams CM, Gilliland W. Polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician*. 2006;74(9):1547–1554. (35)

Wendling D, Prati C, Chouk M, Verhoeven F. Reactive arthritis: treatment challenges and future perspectives. *Curr Rheumatol Rep*. 2020;22(7):29. (46)

Key Websites

American College of Rheumatology. Patient Fact Sheet: Reactive Arthritis. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Reactive-Arthritis

American College of Rheumatology. Patient Fact Sheet: Inflammatory Myopathies. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Inflammatory-Myopathies

The Myositis Association. http://www.myositis.org/

COMPLETE REFERENCES FOR CHAPTER 46 CONNECTIVE TISSUE DISORDERS

1. Pepmueller PH. Undifferentiated connective tissue disease, mixed connective tissue disease, and overlap syndromes in rheumatology. *Mo Med*. 2016;113(2):136–140.
2. Jog NR, James JA. Biomarkers in connective tissue diseases. *J Allergy Clin Immunol*. 2017;140(6):1473–1483.
3. Mosca M, Tani C, Vagnani S, Carli L, Bombardieri S. The diagnosis and classification of undifferentiated connective tissue diseases. *J Autoimmun*. 2014;48:50–52.
4. Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. *Am Fam Physician*. 2008;78(8):961–968.
5. Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103):1685–1699.
6. Careta MF, Romiti R. Localized scleroderma: clinical spectrum and therapeutic update. *An Bras Dermatol*. 2015;90(1):62–73.
7. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum*. 2008;37:223–235.
8. Zhong L, Pope M, Shen Y, Hernandez JJ, Wu L. Prevalence and incidence of systemic sclerosis: a systematic review and meta-analysis. *Int J Rheum Dis*. 2019;22(12):2096–2107.
9. Laing TJ, Gillespie BW, Toth MB, et al. Racial differences in scleroderma among women in Michigan. *Arthritis Rheum*. 1997;40:734–742.
10. van Caam A, Vonk M, van den Hoogen F, van Lent P, van der Kraan P. Unraveling SSc pathophysiology; the myofibroblast. *Front Immunol*. 2018;9:2452.
11. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med*. 2004;140(1):37–50.

12. Cutolo M, Soldano S, Smith V. Pathophysiology of systemic sclerosis: current understanding and new insights. *Expert Rev Clin Immunol*. 2019;15(7):753–764.
13. Sticherling M. Systemic sclerosis—the dermatological perspective. *J Dtsch Dermatol Ges*. 2019;17(7):716–728.
14. Cutolo M, Sulli A, Pizzorni C, Paolino S, Smith V. Systemic sclerosis: markers and targeted treatments. *Acta Reumatol Port*. 2016;41(1):18–25.
15. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med*. 2009;360(19):1989–2003.
16. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76(8):1327–1339.
17. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)*. 2005;44:145–150.
18. Pope J, Fenlon D, Thompson A, et al. Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev*. 2000;1998(2):CD000956.
19. Dziadzio M, Denton CP, Smith R, et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum*. 1999;42:2646–2655.
20. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Ann Rheum Dis*. 2013;72(10):1696–1699.
21. Roustit M, Giai J, Gaget O, et al. On-demand sildenafil as a treatment for Raynaud phenomenon: a series of n-of-1 trials. *Ann Intern Med*. 2018;169(10):694–703.
22. Wigley FM, Flavahan NA. Raynaud's phenomenon. *N Engl J Med*. 2016;375(6):556–565.
23. Bello RJ, Cooney CM, Melamed E, et al. The therapeutic efficacy of botulinum toxin in treating scleroderma-associated Raynaud's phenomenon: a randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol*. 2017;69(8):1661–1669.
24. Jaeger VK, Wirz EG, Allanore Y, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. *PLoS One*. 2016;11(10):e0163894.
25. Distler O, Highland KB, Gahlemann M, et al. *N Engl J Med*. 2019;380(26):2518–2528.
26. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963–974.

27. Maher TM, Corte TJ, Fischer A, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebocontrolled, phase 2 trial. *Lancet Respir Med*. 2020;8(2):147–157.
28. Barnes H, Holland AE, Westall GP, Goh NS, Glaspole IN. Cyclophosphamide for connective tissue disease-associated interstitial lung disease. *Cochrane Database Syst Rev*. 2018;1(1):CD010908.
29. Shenoy PD, Bavaliya M, Sashidharan S, Nalianda K, Sreenath S. Cyclophosphamide versus mycophenolate mofetil in scleroderma interstitial lung disease (SSc-ILD) as induction therapy: a single-centre, retrospective analysis. *Arthritis Res Ther*. 2016;18(1):123.
30. Abou-Raya A, Abou-Raya S, Helmii M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. *J Rheumatol*. 2008;35:1801–1808.
31. Namas R, Tashkin DP, Furst DE, et al. Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post hoc analyses from two randomized placebo-controlled trials. *Arthritis Care Res (Hoboken)*. 2018;70(3):439–444.
32. Tang R, Yu J, Shi Y, et al. Safety and efficacy of rituximab in systemic sclerosis: a systematic review and meta-analysis. *Int Immunopharmacol*. 2020;83:106389.
33. Caylor TL, Perkins A. Recognition and management of polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician*. 2013;88(10):676–684.
34. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med*. 2002;347:261–271.
35. Unwin B, Williams CM, Gilliland W. Polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician*. 2006;74(9):1547–1554.
36. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. 2008;58(1):26–35.
37. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med*. 1995;123(3):192–194.
38. Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of polymyalgia rheumatica. *Rheumatology (Oxford)*. 2010;49(1):186–190.
39. Dejaco C, Singh YP, Perel P, et al. 2015 recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis*. 2015;74(10):1799–1807.
40. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. 2020;79(1):19–30.

41. Mackie SL, Dejaco C, Appenzeller S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. *Rheumatology (Oxford)*. 2020;59(3):e1–e23.
42. Reactive arthritis. In: *DynaMed [Internet]*. EBSCO Information Services; 1995. Record number T1116312. Updated November 30 2018. Cited September 2, 2020. Accessed September 28, 2020. http://www.dynamed.com. Registration and login required.
43. Schmitt S. Reactive arthritis. *Infect Dis Clin North Am*. 2017;31(2):265–277.
44. Garcia-Kutzback A, Chacon-Suchite J, Garcia-Ferrer H, Iraheta I. Reactive arthritis: update 2018. *Clin Rheumatol*. 2018;37(4):869–874.
45. Cheeti A, Chakraborty RK, Ramphul K. Reactive arthritis (Reiter syndrome). In: *StatPearls [Internet]*. StatPearls Publishing; 2020.
46. Wendling D, Prati C, Chouk M, Verhoeven F. Reactive arthritis: treatment challenges and future perspectives. *Curr Rheumatol Rep*. 2020;22(7):29.
47. Zeng H, Luo B, Zhang Y, Xie Z, Ye Z. Treatment of reactive arthritis with biological agents: a review. *Biosci Rep*. 2020;40(2):BSR20191927.
48. Carter JD, Espinoza LR, Inman RD, et al. Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial. *Arthritis Rheum*. 2010;62(5):1298–1307.
49. Barber C, Kim J, Inman RD, Esdaile JM, James MT. Antibiotics for treatment of reactive arthritis: a systemic review and meta-analysis. *J Rheumatol*. 2013;40:916–928.
50. Idiopathic inflammatory myopathy. In: *DynaMed [Internet]*. EBSCO Information Services; 1995. Updated November 30, 2018. Accessed September 2, 2020. http://www.dynamed.com. Registration and login required.
51. Dermatomyositis. In: *DynaMed [Internet]*. EBSCO Information Services; 1995. Updated November 30, 2018. Accessed September 2, 2020. http://www.dynamed.com. Registration and login required.
52. Baig S, Paik JJ. Inflammatory muscle disease—an update. *Best Pract Res Clin Rheumatol*. 2020;34(1):101484.
53. Iaccarino L, Ghiradello A, Bettio S, et al. The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun*. 2014;48:122–127.
54. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis*. 2017;76(12):1955–1964.
55. Glaubitz S, Zeng R, Schmidt J. New insights into the treatment of myositis. *Ther Adv Musculoskel Dis*. 2020;12:1–14.
56. Dalakas M. Inflammatory muscle diseases. *N Engl J Med*. 2015;372:1734–1747.

SECTION 10

Women's Health

Section Editor: Trisha LaPointe

47

Contraception

Shareen El-Ibiary

CORE PRINCIPLES		CHAPTER CASES
1	Contraceptive choice is based on several factors that include preferred formulation, hormone content, effectiveness, side effect profile, cost, accessibility, past medical history, medication use, privacy of use, prevention of sexually transmitted infections (STIs), and return to fertility time.	**Case 47-1 (Question 1)**
2	Combined hormonal contraceptive (CHC) agents are a combination of estrogen and progestin. They are available in a variety of formulations that include a combination of estrogen and progestin (oral tablet, vaginal ring, and transdermal patch). CHCs may be classified by estrogen content into high	**Case 47-1 (Questions 3–5, 7), Table 47-3**

	dose (50 µg of ethinyl estradiol), low dose (30–35 µg of ethinyl estradiol), and very low dose (10–25 µg of ethinyl estradiol), and can vary in cycle length (eg, 21, 24, or 84 days of active hormone). Combined oral contraceptives (COCs) can be further classified by hormone content into monophasic, biphasic, triphasic, and quadriphasic.	
3	CHCs have benefits, aside from pregnancy prevention, that include treatment of acne, hirsutism, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), and endometrial cancer; menstrual cycle regulation and bleeding; endometriosis, and prevention of ovarian cancer and functional ovarian cysts.	**Case 47-2 (Questions 1–3)**
4	Breakthrough bleeding, nausea, acne, and weight gain are among the most commonly reported side effects in females taking hormonal contraceptives. Risks and side effects may be linked to estrogenic, progestogenic, or androgenic properties of hormonal contraceptives.	**Case 47-2 (Questions 4–8) Case 47-3 (Question 1), Table 47-4**
5	There are risks associated with CHCs and contraindications for use in some females. Estrogen-containing contraceptives should be avoided in females who are age 35 years or older	**Case 47-1 (Question 2)**

	and smoke >15 cigarettes/day and who have uncontrolled hypertension, history of gallbladder disease, stroke, migraines with aura, cardiovascular disease, and history of thromboembolic events.	
6	Progestin-only contraceptives are alternative agents for females with contraindications to CHCs. Progestin-only contraceptives vary in formulations that include oral tablet, depot and subcutaneous injection, and subdermal implant. Common side effects include weight gain, acne, mood changes, and irregular menses.	**Case 47-3 (Questions 2–6)**
7	Effectiveness of hormonal contraceptives is in part based on proper use and counseling. Patients need to understand how to use the contraceptive, what to do for mishaps (eg, missed dose, vaginal ring falls out, transdermal patch falls off), and when to use a backup method. Directions for missed doses of progestin-only contraceptives vary from those for COCs.	**Case 47-1 (Questions 6, 7) Case 47-3 (Questions 2–6)**
8	Concomitant use of certain drugs may increase or decrease the levels of hormonal contraceptive agents. In particular, antibiotics and hepatic inducers may decrease the effectiveness of CHCs. Progestin-only contraceptives or nonhormonal contraceptives including backup	**Case 47-1 (Question 8), Table 47-5**

	methods may be alternatives in these cases.	
9	Intrauterine devices (IUDs) or intrauterine systems (IUSs) are available in two formulations (copper IUD and levonorgestrel IUS) and are best for long-term pregnancy prevention. To avoid the risk of pelvic inflammatory disease, the products should be used in females involved in a monogamous relationship.	**Case 47-3 (Question 7)**
10	Some nonhormonal contraceptives include diaphragms, condoms, and spermicides. Male and female condoms are the only contraceptive products that also provide protection against STIs.	**Case 47-4 (Questions 1, 2)**
11	Timing is a key for emergency contraception (EC) to be effective. It is best taken as soon as possible after unprotected sexual intercourse but may be effective up to 120 hours after coitus. EC can be in the form of high-dose progestin pills, high-dose estrogen and progestin pills (known as the Yuzpe method), selective progesterone receptor modulator (SPRM), or copper IUD.	**Case 47-4 (Question 3)**
12	Medical abortion generally consists of mifepristone or methotrexate (to stop development of the pregnancy), or both, in combination with misoprostol (to	**Case 47-4 (Question 4)**

induce uterine contractions and expel the pregnancy).

INTRODUCTION

Contraception is currently an issue worldwide. Preventing unintended pregnancy is an important goal of contraceptive use, particularly in countries where population control is a goal. Economic implications play a role as well. Data from 2008 to 2011 show that an estimated 45% of pregnancies in the United States were unintended, and of these, 42% resulted in abortions.[1] Proper use and understanding of contraceptives is important for preventing unintended pregnancies.

HORMONAL CONTRACEPTION BACKGROUND AND PHARMACOLOGY

Hormonal contraceptives include combinations of estrogens and progestins known as *combination hormonal contraceptives (CHCs)* or *progestin-only contraceptives*. Estrogens prevent the development of the dominant follicle by suppressing follicle-stimulating hormone (FSH) secretion and stabilize the endometrial lining to minimize breakthrough bleeding (see Chapter 50, Disorders Related to the Menstrual Cycle, for more information about the menstrual cycle).[2] Progestins (synthetic progesterone) prevent ovulation by suppressing luteinizing hormone (LH) secretion. They may work in combination with estrogen in CHCs, such as combined oral contraceptives (COCs), the contraceptive patch, and the contraceptive ring, or alone in formulations such as a progestin-only pill (POP), depot intramuscular (IM) or subcutaneous injection, subdermal implant, and as part of intrauterine systems (IUSs).

Progestin-only contraceptives hamper the transport of sperm through the cervical canal by thickening cervical mucus and causing alterations in the endometrial lining (so that it is not favorable for implantation) and in the fallopian tubes (affecting ovum transport).

COMBINATION HORMONAL CONTRACEPTIVES

Patient Evaluation

CASE 47-1

Question 1: S.F., a healthy 33-year-old female, presents to the clinic stating she is getting married soon and would like birth control pills as a method of contraception. She does not have children but would like to start a family in a year or two. Her past medical history is noncontributory other than occasional headaches for which she takes ibuprofen 200 mg by mouth (PO) as needed.

Vital signs: weight, 128 pounds (58.06 kg); height, 64 inches (162.56 cm)
Blood pressure, 122/72 mm Hg
Heart rate, 85 beats/minute
Temperature, 98.6 °F (37 °C)
Social history: smokes one pack/day, denies alcohol
Family history: sister gestational diabetes, mother hypertension, father unknown

Which factors are important in the selection of a contraceptive agent for S.F.?

There are several factors that affect selection of a contraceptive. Among them is effectiveness in preventing pregnancy. It is important to determine the importance of pregnancy prevention for S.F. and choose a method based on this information. For example, patients taking teratogenic medications or those with underlying medical conditions in which pregnancy may not be desired will require a highly effective birth control method or multiple methods. Others may not desire a pregnancy, but, for a variety of reasons, an unintended pregnancy may be more acceptable.

The effectiveness of contraceptive methods depends on the mechanism of action, availability (eg, prescription required), patients' concurrent medications, past medical history, and acceptability (eg, side effects, ease of use, adherence, cost, and religious and social beliefs). Any or all of these factors can account for the discrepancy between the lowest failure rate observed for 1 year in clinical trials (perfect-use failure rate) and the actual failure rate in users (typical-use failure rate) and should be taken into account when selecting a method of contraception (**Table 47-1**).[2] Return to fertility time is also an important factor to consider. Some contraceptive methods allow a patient to conceive shortly after discontinuation, whereas others may delay fertility longer. S.F. indicated that she would like to have children in the near future. Given her age of 33 (fertility starts to decrease after age 32) and desire for future pregnancy, it would be best to select a product with a faster return to fertility.[3] However, other factors to consider when selecting a contraceptive agent for S.F. include contraindications and risks for her that may indicate one method over another. A combined hormonal contraceptive (CHC) is used commonly in females and may be appropriate for S.F. once all factors are considered.

Table 47-1

Percentage of Females Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: United States

Method	% of Females Experiencing an Unintended Pregnancy Within the First Year of Use		% of Females Continuing Use at 1 Year[c]	Relative Cost[k]
	Typical Use[a]	Perfect Use[b]		
Chance[d]	85	85	—	
Fertility awareness–based methods	15	—	47	None
Standard Days Method®[e]	12	5	—	
TwoDay Method®[e]	14	4	—	
Ovulation method[e]	23	3	—	
Symptothermal[e]	2	0.4	—	
Withdrawal	22	4	46	
Spermicides[f]	21	16	42	$–$$
Barrier methods				
Sponge			36	$$
Parous female	27	20	—	
Nulliparous female	14	9	—	
Diaphragm[g]	12	6	57	$$$
Condom[h]				$
Female (FC2™)	21	5	41	
Male	13	2	43	
Hormonal contraceptives				
Injectable MPA	4	0.2	56	$$$[l]
Pill				
Progestin only	7	0.3	67	$$–$$$
Combined	7	0.3	67	$$–$$$
Transdermal patch (Xulane®)	7	0.3	67	$$–$$$
Vaginal ring (NuvaRing®, Eluryng®)	7	0.3	67	$$–$$$
IUD/IUS	—	—	—	$$$$[l]
Copper	0.8	0.6	78	
Levonorgestrel	0.1–0.2	0.1–0.2	80	
Female sterilization	0.5	0.5	100	$$$$[m]
Male sterilization	0.15	0.10	100	$$$$[m]
Emergency contraceptive pills				$$$
Treatment initiated within 72 hours of unprotected intercourse reduces the risk of pregnancy by at least 75%.[i]				
Lactational amenorrhea method				None
LAM is a highly effective, temporary method of contraception.[j]				

IUD, intrauterine device; IUS, intrauterine system; LAM, lactational amenorrhea method; MPA, medroxyprogesterone acetate.

[a]Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides, withdrawal, fertility awareness–based methods, the diaphragm, the male condom, the oral contraceptive pill, and Depo-Provera® are taken from the 1995 National Survey of Family Growth corrected for underreporting of abortion; see the source for the derivation of estimates for the other methods.

[b]Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for

any other reason. See the table source for the derivation of estimates for the other methods.

[c]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

[d]The percentages becoming pregnant in the first year are based on data from populations in which contraception is not used and from females who cease using contraception to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentages who would become pregnant within 1 year among females now relying on reversible methods of contraception if they abandoned contraception altogether.

[e]The ovulation method and the TwoDay Method® are based on evaluation of cervical mucus. The Standard Days Method® avoids intercourse on cycle days 8 through 19. The symptothermal method is a double-check method based on evaluation of cervical mucus to determine the first fertile day and evaluation of cervical mucus and temperature to determine the last fertile day.

[f]Foams, creams, gels, vaginal suppositories, and vaginal film.

[g]With spermicidal cream or jelly.

[h]Without spermicides.

[i]ella® (ulipristal acetated) is labeled for 120 hours after unprotected intercourse. Plan B One-Step®, Next Choice One Dose®, MyWay®, Take Action®, Aftera®, EContra® Ez, EContra One-Step®, Fallback Solo™, My Choice®, New Day®, Opcicon One-Step®, and React® are levonorgestrel products specifically marketed for emergency contraception. The labeling for these products says to take the pill within 72 hours of unprotected intercourse. Research has shown that all of the brands listed here are effective when used within 120 hours of unprotected sex.

[j]However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breast-feeding is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

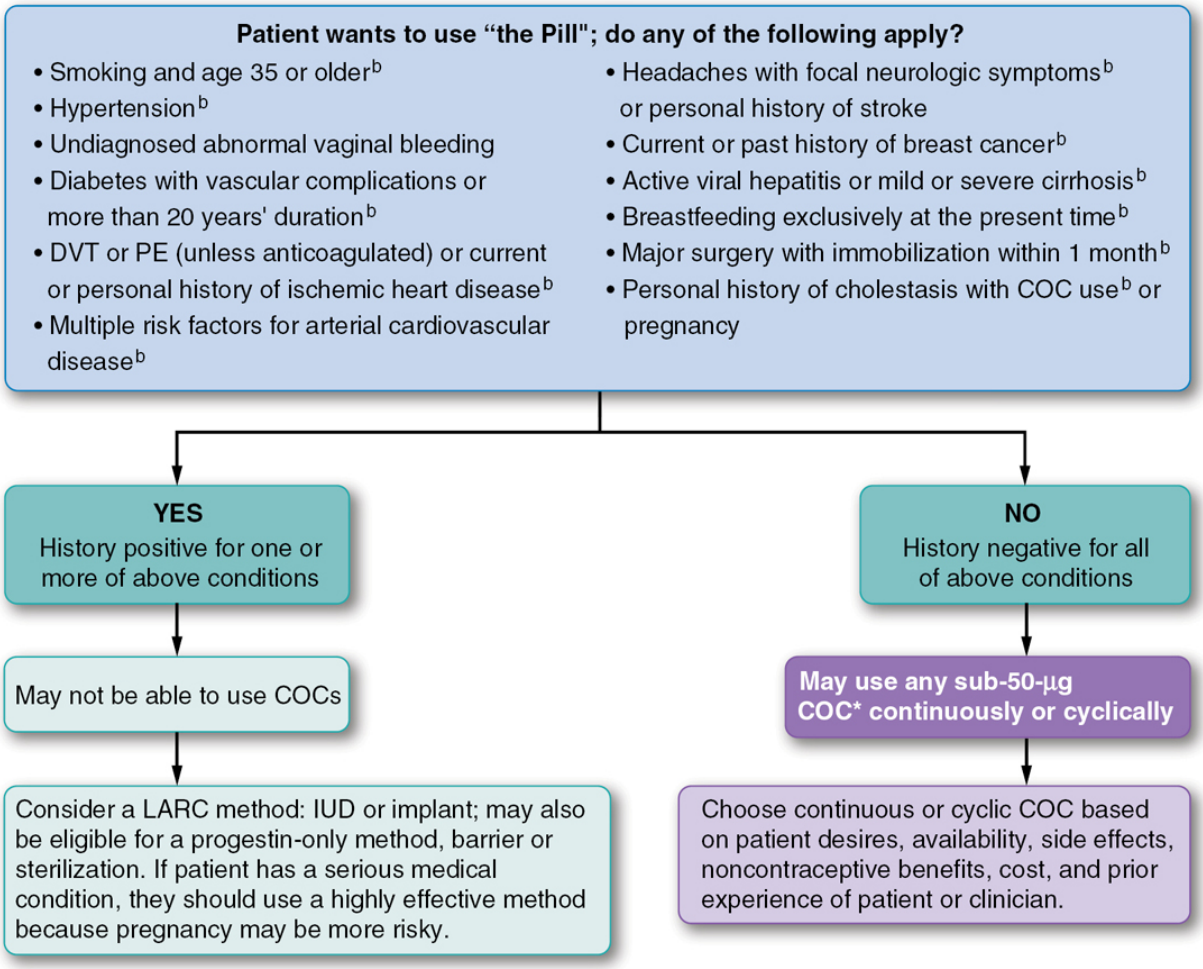
[k]$ up to $10/item, $$ up to $50/unit, $$$ up to $80/unit, $$$$ more than $80/unit. (These are approximate costs and may vary based on location of purchase and patient insurance.)

[l]Administration or clinic costs not included. Initial cost of product reported but over time similar to $$ cost (eg, injectable MPA 150 mg/mL suspension one syringe ~$100, but works for 3 months, making its monthly cost similar to combined oral contraceptives (COCs) or progestin-only pill (POPs), which range from $20 to $45/pack generic, and copper IUD and levonorgestrel IUS may cost more initially but will work for up to 10 and 5 years, respectively).

[m]Initial cost for procedure but over time may be more cost-effective than are other products used frequently (eg, monthly contraceptives, condoms, or spermicides).

Source: Hatcher RA, Kowal D, Nelson AL, et al. *Contraceptive Technology*. 21st ed. Ayers Publishing Company, Inc; 2018:100, Table 3–2; includes additional information from www.goodrx.com; http://americanpregnancy.org/preventing-pregnancy/diaphragm/; https://www.plannedparenthood.org/learn/birth-control/cervical-cap

Choosing a Pill



• The World Health Organization and the Food and Drug Administration both recommend using the lowest dose pill that is effective. All combined pills with less than 50 μg of estrogen are considered "low dose" and are effective and safe.

• There are no studies demonstrating a decreased risk for deep vein thrombosis (DVT) in females on 20-μg pills. Data on higher dose pills have demonstrated that the less the estrogen dose, the lower the risk for DVT.

• All COCs lower free testosterone. Class labeling in Canada for all combined pills states that use of pills may improve acne.

• To minimize discontinuation due to spotting and breakthrough bleeding, warn females in advance, reassure that spotting and breakthrough bleeding become better over time.

[a]The package insert for females on Yasmin® and Yaz® states [Berlex-2001]: "Yasmin is different from other birth control pills because it contains the progestin drospirenone. Drospirenone may increase potassium. Therefore, you should not take Yasmin if you have kidney, liver or adrenal disease, because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Yasmin is right for you, and during the first month that you take Yasmin, you should have a blood test to check your potassium level: NSAIDs (ibuprofen [Motrin®, Advil®], naproxen [Naprosyn®, Aleve®, and others] when taken long-term and daily for treatment of arthritis or other problems]; potassium-sparing diuretics (spironolactone and others); potassium supplementation; ACE inhibitors (Capoten®, Vasotec®, Zestril®, and others); Angiotensin-II receptor antagonists (Cozaar®, Diovan®, Avapro®, and others); heparin."

[b]These are conditions that receive a US MEC:3 or MEC:4 (based on Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep* 2016;65(No. RR-3):1–104, Category 3—A condition in which theoretical or proven risks usually outweigh the benefit of contraceptive method use, Category 4—A condition that represents an unacceptable health risk if contraceptive method is used).

Figure 47-1 Choosing a pill. ACE, angiotensin-converting enzyme; COC, combined oral contraceptive; IUD, intrauterine device; NSAIDs, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism. (Adapted from Hatcher RA, Zieman M, Lathrop E, Haddad L, Allen AZ. *Managing Contraception 2019–2020*. 15th ed. Bridging the Gap Foundation; 2019. Figure 24.1. Reprinted with permission from ManagingContraception.com)

Contraindications to Combined Hormonal Contraceptive Use

Case 47-1, Question 2: Are CHCs an appropriate form of contraception for S.F.? What contraindications to CHC therapy must be considered?

To determine whether any contraindications or precautions exist, the clinician should first obtain baseline health information from S.F. such as past medical history, social history, and family history (**Fig. 47-1**).[4] The World Health Organization (WHO) has developed medical eligibility criteria to identify appropriate contraception for patients with specific conditions. In 2010, the U.S. Centers for Disease Control and Prevention (CDC) adopted those guidelines for recommendations in the United States and updated them in 2016 (see http://who.int/reproductivehealth/publications/family_planning/MEC-5/en/) for the WHO Medical Eligibility Criteria and CDC link.[5,6] Most data regarding contraindications are based on COCs, but the conclusions are applied to all CHCs (eg, vaginal ring and transdermal patch).

CIGARETTE SMOKING AND USE OF COMBINED HORMONAL CONTRACEPTIVES

S.F. should be strongly encouraged to stop smoking (see Chapter 91, Tobacco Use and Dependence). Females who are age 35 years or older and smoke ≥15 cigarettes per day should not use CHCs as

a method of contraception. Although S.F. is not yet 35, she is smoking one pack per day (20 cigarettes). In her case, many clinicians would not prescribe CHCs. Although S.F. currently does not have any medical problems that would preclude her from using CHCs, she should be informed that CHCs should not be prescribed for her in 2 years if she continues to smoke. In addition, S.F. should be informed that smoking may decrease fertility and has adverse effects on birth outcomes, which is important given her plans to start a family in the near future.

CARDIOVASCULAR DISEASE

An increased risk of cardiovascular death in females who use COCs has been reported in multiple studies.[7–19] One study reported that in females who do not smoke or use COCs, the risk of cardiovascular death is 0.59/100,000 females younger than age 35 years and 3.18/100,000 females at least age 35 years. Among nonsmokers, using COCs increased the risk to 0.65/100,000 and 6.21/100,000 in females younger than age 35 years or at least age 35 years, respectively. For COC users who smoke, the risk is 3.3/100,000 in females younger than age 35 years and 29.4/100,000 in females at least age 35 years.[10] The increase in mortality is concentrated in smokers age 35 years and older.

Several studies have focused on the effect of COCs on serum lipoprotein concentrations because of the association between lipoproteins and atherosclerotic cardiovascular disease.[11–13] High levels of total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL) cholesterol serum concentrations are associated with the risk of developing atherosclerotic circulatory diseases, whereas high-density lipoprotein (HDL) cholesterol has an inverse relationship. Apolipoprotein levels also affect atherosclerotic risk (eg, elevations in apolipoprotein increase risk).

Patients taking COCs may be more likely to experience a myocardial infarction (MI) than do nonusers.[14] The risk is higher with higher doses of estrogen and especially if the patient is a smoker or

has hypertension. It is not clear whether certain types of progestin are more likely to cause MI than do others.[8,15] COC users may also be at a slightly higher risk of stroke, but some data are conflicting.[14,16] Those at highest risk of stroke are smokers, patients with hypertension, and patients older than 35 years.

S.F. and her fiancé should understand that the risk of adverse cardiovascular effects may be increased with CHC use, but the absolute risk is still very low no matter which product is used. S.F.'s cigarette smoking, however, is a much more significant risk factor for MI in combination with a CHC product.

MIGRAINES AND STROKE

Ischemic stroke is more likely to occur in CHC users with a history of migraines and is thought to be caused by the estrogen component. The risk is further elevated in females who have migraines with aura up to sixfold in one study or among those who smoke.[2,17,18] One study did not indicate a higher risk of ischemic stroke in females experiencing migraines without aura; however, females experiencing migraines without aura should use CHCs with caution or avoid use if they smoke and are at least age 35 years.[6,18,19] Clinical experience indicates that females who have increasing migraine attacks with CHCs are not likely to improve when the product is changed to one with a different hormone balance. Headaches or migraines may start with initiation of CHCs (see Case 47-2, Question 6); however, if a patient experiences a migraine with aura while taking CHCs, she should discontinue the product and switch to a nonestrogen method.[17–19] Evidence does not show an increased stroke risk with progestin-only contraceptives, and these agents may be used in females with risk factors for stroke.[19]

S.F. does have a history of occasional headaches, but does not have a history of migraines with aura. Therefore, she is still a candidate for CHCs but should be informed of the increased risk of stroke from cigarette smoking.

THROMBOEMBOLIC EVENTS

CHCs contribute to thromboembolic events by several mechanisms. Estrogens increase coagulability and thereby increase the possibility of clot formation. Although they have been shown to significantly increase some clotting factors, other studies have shown no changes or decreases in prothrombotic factors.[11,13] Long-term COC use is associated with an increased platelet count and increased platelet aggregation similar to that seen late in pregnancy; this is generally thought to be caused by the estrogen component. Other data show increased thrombosis rates in users of third-generation progestins (desogestrel and gestodene [not available in the United States]), suggesting that progestin may also have a role in thromboembolism risk.[20]

The baseline risk of venous thromboembolism (VTE) in females is low, at 5 to 10 cases/10,000 person-years, but increases to 8 to 10 cases with COC use.[21] The best studies looking at thromboembolism in COC users found that most users have a two- to sixfold increased risk of having superficial or deep venous thrombosis or pulmonary embolism (PE).[20] Patients requiring emergency major surgery while taking COCs are more prone to VTE than are nonusers. The risk of venous thrombosis does not seem to be associated with duration of COC use or past COC use. A greater risk is associated with ethinyl estradiol (EE) doses >35 µg.[20]

Females with a mutation in clotting factor V (also called factor V Leiden) or a deficiency in protein C, protein S, or antithrombin are more likely to experience a VTE with COCs than do females without a hereditary prothrombotic defect.[22] Females with factor V Leiden using COCs have a 30-fold increase in VTE compared with females without the mutation.[22]

The minimal risk of thrombosis associated with CHCs in the general population does not justify the cost of routine screening for deficiencies and mutations in the coagulation system; however, if a patient has a family history of thrombosis, then measurement of antithrombin III, protein C, activated protein C resistance ratio, protein S, anticardiolipin antibodies, prothrombin G mutation, factor V Leiden, and homocysteine levels should be considered.[4]

Whether third- or fourth-generation progestins (desogestrel, dienogest, drospirenone, or gestodene) are associated with a higher risk of VTE relative to other progestins is controversial.[20,21] It was believed that the risk of thrombosis with third-generation progestins would be lower than that with other progestins because they have more beneficial effects on HDL. A recent meta-analysis, however, reported that COCs containing <50 µg of EE in combination with desogestrel, dienogest, or drospirenone had an increased VTE risk of 1.5 to 2 times that of products containing levonorgestrel, but noted that the difference was not statistically significant for dienogest and that COCs containing norgestimate did not show an increased risk.[21] The finding was similar when the analysis was limited to monophasic products containing 30 µg of EE and the respective progestins, indicating that progestins may have a role in clot development, although their role is not well understood.[21] Of note, in April 2012, the U.S. Food and Drug Administration (FDA) published a safety communication regarding a possible increased risk of thrombosis with drospirenone-containing products.[23] Although the risk may be increased, the overall rate of thrombosis is still low. All patients using CHCs should be counseled about the VTE warning signs (**Table 47-2**).[4]

Table 47-2
CHC Early Danger Signs: ACHES

Signals	Possible Problem
Abdominal pain (severe)	Gallbladder disease, hepatic adenoma, blood clot, pancreatitis
Chest pain (severe), shortness of breath, or coughing up blood	Blood clot in lungs or myocardial infarction
Headaches (severe)	Stroke, hypertension, or migraine headache
Eye problems: blurred vision, flashing lights, or blindness	Stroke, hypertension, or temporary vascular problem
Severe leg pain (calf or thigh)	Blood clot in legs

CHC, combined hormonal contraceptive.

From Hatcher RA, Kowal D, Nelson AL, et al. *Contraceptive Technology*. 21st ed. Ayers Publishing Company, Inc; 2018. Reprinted with permission from Managing Contraception LLC.

S.F. does not have a history of clotting disorders or previous clots. Therefore, she is still a candidate for CHCs. Her smoking status, however, puts her at higher risk for VTE. If she experiences a VTE while taking CHCs, a progestin-only method or nonhormonal contraceptive method should be recommended and the CHC discontinued.

HYPERTENSION

CHCs appear to increase blood pressure. Small studies have found systolic blood pressure to increase by about 8 mm Hg and diastolic blood pressure to increase by 6 mm Hg in normotensive or mildly hypertensive females.[24] Other studies have shown differing results on whether females with hypertension who use COCs are more likely to suffer an MI than do nonusers.[5,25] A small study of adolescent females showed similar systolic and diastolic blood pressures in users versus nonusers.[26]

The underlying mechanisms for CHC-induced hypertension may be sodium and water retention and increased renin activity.[27,28] Hypertension secondary to COCs may develop slowly during 3 to 36 months and may not decline for 3 to 6 months after COC discontinuation.[29] Females with controlled hypertension may attempt a trial of CHCs with blood pressure monitoring; however, progestin-only contraceptives have not been shown to increase blood pressure and may be preferable for females with uncontrolled hypertension.[24]

S.F.'s blood pressure is not elevated at 122/72 mm Hg. Therefore, she is still a candidate for CHCs. If her blood pressure were >140/90 mm Hg, a nonhormonal method or a progestin-only contraceptive would be a preferred form of contraception.

HEPATOTOXICITY

COCs have been associated with benign liver tumors, hepatic adenomas, and liver cancer.[2,30] The risk of liver cancer is low, and

COCs are thought to cause only a modest increase in risk.[30,31] A European study found a small, statistically significant increase in the risk of liver cancer in females without cirrhosis and without hepatitis B or C, with an increased the risk of liver cancer by 1 case/1.5 million woman-years.[31] A meta-analysis of observational studies concluded that oral contraceptives (OCs) were not positively associated with liver cancer risk.[32] S.F. should be reassured that it is very unlikely for her to develop benign or malignant liver tumors associated with COC use.

DIABETES

Generally, low-dose COCs do not alter glucose tolerance.[13,33] Females with a history of gestational diabetes such as S.F.'s sister and those with a strong family history of diabetes in parents or siblings are at greater risk for COC-induced glucose intolerance.[24] COCs have complex effects on carbohydrate metabolism. Progestins decrease and estrogens increase the number of insulin receptors on the cell membrane. Progestins also may alter insulin receptor affinity. The different progestins in CHCs have different propensities to induce glucose intolerance. Desogestrel seems to have the best glucose values compared with other progestins, but insulin results are not consistent.[33]

For females with diabetes, the WHO recommends avoiding COCs and depot medroxyprogesterone acetate (DMPA) if they have been diabetic for >20 years or they have end-organ damage such as retinopathy, neuropathy, or nephropathy.[5]

S.F.'s sister having a history of gestational diabetes does not preclude S.F. from using a CHC at this time. Preferably, S.F. should start on a low-dose CHC.

GALLBLADDER DISEASE

The incidence of gallstones has been reported to increase with COC use; however, conflicting data exist. Estrogens and progestins may contribute to bile stasis and gallstones by reducing cholesterol clearance and altering bile acid composition.[34] The incidence of

gallbladder disease has been reported to increase during the first year of use, but then to decline steadily to a rate lower than that of control females.[35] Conversely, a meta-analysis study concluded that it is unlikely that COCs cause gallbladder disease.[36]

Females who are obese, young, or long-term users of COCs may be the most likely to develop gallstones. At this time, this is not a concern for S.F. in starting COCs.

Combined Oral Contraceptives

Case 47-1, Question 3: S.F. has decided to quit smoking. Based on her past medical history, she is a candidate for CHCs and indicates she wants to start a COC. Which COC should be selected for her?

Selecting a COC for S.F. can be confusing because of the multitude of products available, the lack of studies directly comparing products, and health insurance medication formulary restrictions. The failure rate of COCs ranges from 0.3% with perfect use to 7% with typical use (see Table 47-1).[2]

The COCs are available in varying strengths of estrogens and progestins. **Table 47-3**[37,38] lists the brand-name and generic COCs in the United States. Almost all COCs available in the United States contain the synthetic estrogen, EE. Doses of EE generally range from 10 to 50 µg, with 10- to 25-µg formulations considered very low dose; 30- to 35-µg formulations, low dose; and 50-µg formulations, high dose. Mestranol, another estrogen available in the United States and used internationally, is an inactive prodrug that is hepatically metabolized to EE. Mestranol 50 µg has approximately the same activity as EE 35 µg.[2] Estradiol valerate is a third estrogen available in one oral formulation. The formulation of estradiol valerate 2 to 3 mg with 2 to 3 mg of dienogest was compared against EE 20 µg with levonorgestrel 100 µg in clinical trials.[39,40]

Table 47-3
Oral Contraceptives and Relative Progestin, Endometrial, and

Androgen Activities

Combination Oral Contraceptives: Estimated Relative Progestin/Endometrial/Androgen Activity[30]						
Ingredients		**Example Trade Names**	**Progestin Activity**	**Endometrial Activity**	**Androgen Activity**	**Unique Properties**
Monophasic	Desogestrel 0.15 mg/ethinyl estradiol 30 µg	Apri®, Cyred®, Cyred EQ®, Emoquette®, Enskyce®, Isibloom®, Juleber™, Kalliga®, Reclipsen™	High	Intermediate	Low	
	Drospirenone 3 mg/ethinyl estradiol 20 µg	Beyaz®,[a] Gianvi®, Jasmiel™, Loryna™, Lo-Zumandimine™, Nikki™, Rajani™,[a] Yaz®			None	Antimineralocorticoid properties, FDA-approved use for treatment of acne and PMDD, only 4 days of placebos Beyaz® and Rajani™ provide folate supplementation, 24 active pills and 4 days of 0.451 mg of levomefolate calcium instead of placebos.
	Drospirenone 3 mg/ethinyl estradiol 30 µg	Ocella®, Safyral®,[a] Syeda®, Tydemy®,[a] Yasmin-28®, Zarah®, Zumandimine™				Antimineralocorticoid properties Safyral® and Tydemy® provide folate supplementation, 21 active pills, and 7 days of 0.451 mg of levomefolate calcium instead of placebos.
	Ethynodiol diacetate 1 mg/ethinyl estradiol 35 µg	Kelnor® 1/35, Zovia® 1/35E	High	Low	Low	
	Ethynodiol diacetate 1 mg/ethinyl estradiol 50 µg	Kelnor® 1/50		Intermediate		
	Levonorgestrel 0.1 mg/ethinyl estradiol 20 µg	Afirmelle®, Aubra®, Aubra EQ®, Aviane®, Balcoltra®,[b] Delyla®, FaLessa®,[a] Falmina®, Larissia®, Lessina®, Lutera®, Orsythia®, Sronyx®, Vienva®	Low	Low		Balcoltra® contains 21 active pills and 7 pills that contain ferrous bisglycinate 36.5 mg.
	Levonorgestrel 0.15 mg/ethinyl estradiol 30 µg (28 days)	Altavera™, Ayuna™, Chateal®, Chateal EQ®, Kurvelo™, Levora® 0.15/30, Lillow®, Marlissa®, Portia-28®	Intermediate	Intermediate	Intermediate	
	Levonorgestrel 0.15 mg/ethinyl estradiol 30 µg (91 days)	Jolessa®, Quasense®, Setlakin™		Low		Jolessa®, Quasense®, and Setlakin™ contain 84 active pills and 7 placebo pills.
	Levonorgestrel 0.09 mg/ethinyl estradiol 20 µg (1-year continuous formulation available in packs of 28 active pills)	Amethyst®	Intermediate/high		Intermediate/high	Amethyst® is a 1-year continuous formulation available in packs of 28 active pills.

	Norethindrone 0.4 mg/ ethinyl estradiol 35 µg	Balziva®, Briellyn®, Philith™, Vyfemla™, Wymzya Fe™,[b]	Low	Intermediate	Low	Wymzyax Fe™ is a chewable formulation and contains 7 pills of 75-mg ferrous fumarate instead of placebos.
	Norethindrone 0.5 mg/ ethinyl estradiol 35 µg	Necon® 0.5/35, Nortrel® 0.5/35, Wera®		Low		
	Norethindrone 0.8 mg/ ethinyl estradiol 25 µg	Generess Fe®,[b] Kaitlib Fe™,[b] Layolis Fe®[b]		Intermediate		Generess Fe®, Kaitlib Fe™, and Layolis Fe® are chewable tablets and contain 24 active pills and 4 pills of 75 mg ferrous fumarate instead of placebos.
	Norethindrone 1 mg/ ethinyl estradiol 35 µg	Alyacen® 1/35, Cyclafem® 1/35, Dasetta® 1/35, Nortrel® 1/35, Ortho-Novum® 1/35, Pirmella® 1/35	Intermediate		Intermediate	
	Norethindrone 1 mg/ mestranol 50 µg	N/A[c]				
	Norethindrone acetate 1 mg/ ethinyl estradiol 20 µg	Aurovela 1/20®, Aurovela 24 Fe®,[b] Blisovi Fe®,[b] Blisovi 24 Fe®,[b] Charlotte 24 Fe®,[b] Hailey Fe®,[b] Hailey 24 Fe®,[b] Junel 1/20®, Junel Fe® 1/20,[b] Junel Fe® 24,[b] Larin 1/20®, Larin 24 FE®,[b] Larin Fe® 1/20,[b] Loestrin 1/20®, Loestrin Fe® 1/20,[b] Melodetta 24 Fe™,[b] Mibelas 24 Fe™,[b] Microgestin 1/20®, Microgestin Fe® 1/20,[b] Minastrin 24 Fe®,[b] Tarina Fe® 1/20,[b] Tarina Fe® 1/20 EQ,[b] Tania 24 Fe®[b]	Intermediate/ high	Low	Intermediate/ high	"Fe" or "FE" contains 75-mg ferrous fumarate instead of placebos, and Aurovela 24 Fe®, Blisovi 24 Fe®, Charlotte 24 Fe®, Hailey 24 Fe®, Junel Fe® 24, Larin Fe® 24, Melodetta 24 Fe™, Mibelas 24 Fe™, and Minastrin 24 FE® have 24 active tablets; and Charlotte 24 Fe®, Melodetta 24 Fe™, Mibelas 24 Fe™, and Minastrin 24 FE® are also chewable tablets.
	Norethindrone acetate 1.5 mg/ethinyl estradiol 30 µg	Aurovela 1.5/30®, Aurovela 1.5/30 Fe®,[b] Blisovi 1.5/30 FE®,[b] Hailey 1.5/30®, Hailey 1.5/30 Fe®,[b] Junel 1.5/30®, Junel FE® 1.5/30,[b] Larin 1.5/30®, Larin FE® 1.5/30,[b] Loestrin 1.5/30®, Loestrin FE® 1.5/30,[b] Microgestin 1.5/30®, Microgestin FE® 1.5/30[b]				"Fe" contains 75-mg ferrous fumarate instead of placebos.

	Norgestimate 0.25 mg/ethinyl estradiol 35 µg	Estarylla™, Femynor®, Mili™, Mono-Linyah™, Previfem®, Sprintec®, VyLibra®	Low	Intermediate	Low	
	Norgestrel 0.3 mg/ethinyl estradiol 30 µg	Cryselle®, Elinest™, Low-Ogestrel®	Intermediate		Intermediate	
	Norgestrel 0.5 mg/ethinyl estradiol 50 µg	Ogestrel®	High	High	High	
Biphasic	Desogestrel/ethinyl estradiol 0.15–20/0–10 mg-µg	Azurette®, Bekyree, Kariva®, Mircette®, Pimtrea®, Simliya®, Viorele®, Volnea®		Intermediate	Low	Only 2 days of placebos, other 5 days contain EE 10 µg.
	Levonorgestrel/ethinyl estradiol 0.1–20/0–10 mg-µg	Amethia® Lo, Camrese® Lo, LoJaimiess®, LoSeasonique®	Intermediate/high	Low	Intermediate/high	Amethia® Lo, Camrese® Lo, LoJaimiess®, and LoSeasonique® contain 84 active pills and 7 pills of EE 10 µg instead of placebos.
	Levonorgestrel/ethinyl estradiol 0.15–30/0–10 mg-µg	Amethia®, Ashlyna®, Camrese®, Daysee®, Jaimiess®, Seasonique®, Simpesse®				Amethia®, Ashlyna®, Camrese®, Daysee®, Jaimiess®, Seasonique®, and Simpesse® contain 84 active pills and 7 pills of EE 10 µg.
	Norethindrone/ethinyl estradiol 0.5–35/1–35 mg-µg	Necon® 10/11c	Intermediate	Intermediate	Low	
	Norethindrone/ethinyl estradiol 1–10/0–10 mg-µg	Lo Loestrin Fe®[b]	Intermediate/high	Low	Intermediate/high	24 active pills, 2 pills of EE 10 µg, and 2 pills of 75 mg ferrous furmarate instead of placebos
Triphasic	Norgestimate/ethinyl estradiol 0.18–25/0.215–25/0.25–25 mg-µg	Ortho Tri-Cyclen Lo®, Tri-Lo-Estarylla®, Tri-Lo-Marzia®, Tri-Lo-Mili™, Tri-Lo-Sprintec®, Tri- Lo-VyLibra®	Low	Intermediate	Low	
	Levonorgestrel/ethinyl estradiol 0.05–30/0.075–40/0.125–30 mg-µg	Enpresse® 28, Levonest®, Trivora®				
	Norgestimate/ethinyl estradiol 0.18–35/0.215–35/0.25–35 mg-µg	Tri-Estarylla®, Tri-Femynor®, Tri-Mili™, Tri-Previfem®, Tri-Linyah®, Tri-Sprintec®, Tri-VyLibra®				FDA-approved use for treatment of acne
	Norethindrone/ethinyl estradiol 0.5–35/1–35/0.5–35 mg-µg	Aranelle®, Leena®		Low		
	Norethindrone/ethinyl estradiol 0.5–35/0.75–35/1–35 mg-µg	Alyacen 7/7/7®, Cyclafem 7/7/7®, Dasetta 7/7/7®, Nortrel 7/7/7®, Ortho-Novum 7/7/7®, Pirmella 7/7/7®	Intermediate	Intermediate		

	Norethindrone acetate/ethinyl estradiol 1–20/1–30/1–35 mg-μg	Estrostep Fe®,[b] Tilia Fe®,[b] Tri-Legest Fe®[b]	Intermediate/high	Low	Intermediate/high	Estrophasic (estrogen content changes), FDA-approved use for treatment of acne, "Fe" contains 75-mg ferrous fumarate instead of placebos.
	Desogestrel/ethinyl estradiol 0.1–25/0.125–25/0.15–25 mg-μg	Caziant®, Velivet®	Intermediate	Intermediate	Low	
4-phasic	Dienogest/estradiol valerate 0–3/2–2/3–2/0–1 mg-mg	Natazia®	High			Has 2 placebo pills, 2 pills with 3 mg of estradiol valerate only, 5 pills with 2 mg of dienogest and 2 mg of estradiol valerate, 17 pills with 3 mg of dienogest and 2 mg of estradiol valerate and 2 pills of 1-mg estradiol valerate Has FDA approval for use to treat heavy menstrual bleeding without organic pathology
	Levonorgestrel/ethinyl estradiol 0.15–20/0.15–25/0.15–30/0–10 mg-μg	Quartette™, Fayosim®, Rivelsa®	Intermediate/high	Low	Intermediate/high	Has 91 pills; 42 contain 0.15 mg of levonorgestrel with 20 μg of ethinyl estradiol, 21 pills contain 0.15 mg of levonorgestrel with 25 μg of ethinyl estradiol, 21 pills contain 0.15 mg of Levonorgestrel with 30 μg of ethinyl estradiol, and 7 pills contain 10 μg of ethinyl estradiol
Progestin-only pills	Norethindrone 0.35 mg	Camila®, Deblitane®, Errin®, Heather®, Incassia™, Jencycla®, Lyza®, Nora-BE®, Norlyda, Norlyroc™, Ortho Micronor®, Sharobel™, Tulana®	Low	Low	Low	No placebos, 28 days of active pills
	Drospirenone 4 mg	Slynd®	Not available	Not available	Not available	24 days of active pills, 4 days of placebo

FDA, U.S. Food and Drug Administration; PMDD, premenstrual dysphoric disorder.

[a]Also contains levomefolate.

[b]Also contains iron.

[c]Discontinued in the United States.

Source: Adapted from Facts & Comparisons eAnswers. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5546102?cesid=7LkpmpMeW2i&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Doral%252520contraceptives%26t%3Dname%26va%3Doral%252520contraceptives%26nq%3Dtrue#general-dosing-nested-6-0; Dickey RP. *Managing Contraceptive Pill Patients*. 15th ed. Essential Medical Information Systems; 2014; Slynd. Package insert. Exeltis USA, Inc; June 2019.

The COCs also contain one of the following progestins: ethynodiol diacetate, desogestrel, dienogest, drospirenone, levonorgestrel, norethindrone, norethindrone acetate, norgestimate, and norgestrel (a mixture of dextronorgestrel and levonorgestrel; dextronorgestrel appears to be progestationally inert compared with levonorgestrel).[2] Progestins differ significantly in their progestational potency and in the extent of their metabolism to estrogenic substances. Progestins have both estrogenic and antiestrogenic effects. Because the progestins have a chemical structure similar to that of testosterone, they also have varying degrees of androgenic activity (Table 47-3).[38] Minor structural changes in all of the progestins may lead to significant changes in their progestational, estrogenic, antiestrogenic, and androgenic activities, which may affect patients differently (**Table 47-4**).[2] Drospirenone is a unique progestin because it has antiandrogenic and antimineralocorticoid properties. Drospirenone is chemically similar to the potassium-sparing diuretic spironolactone, and, therefore, may increase potassium levels. Drospirenone should be used with caution in patients using medications that can increase potassium levels (eg, high-dose nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, heparin, potassium-sparing diuretics, aldosterone antagonists, and angiotensin II blockers).[37]

Table 47-4
Estrogenic, Progestogenic, and Combined Effects of Oral Contraceptive Pills

Achieving Proper Hormonal Balance in an Oral Contraceptive			
Estrogen		Progestin	
Excess	**Deficiency**	**Excess**	**Deficiency**
Nausea, bloating	Absence of withdrawal bleeding	Acne[a]	Amenorrhea
Cervical mucorrhea, polyposis	Atrophic vaginitis	Breast regression Depression	Dysmenorrhea
Melasma	Early- or mid-cycle breakthrough bleeding	Hair loss[a]	Hypermenorrhea
Hypertension	Hypomenorrhea	Hirsutism[a]	Late breakthrough bleeding
Migraine headache	Increased spotting	Hypomenorrhea	
Breast fullness or tenderness	Vasomotor symptoms	Increased appetite	
Edema		Monilial vaginitis	
Urinary tract infection		Oily scalp[a]	
Uterine enlargement		Tiredness, fatigue	
Uterine fibroid growth		Weight gain	

[a]Result of androgenic activity of progestins.

Source: Adapted from Facts & Comparisons eAnswers. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5546102?cesid=7LkpmpMeW2i&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Doral%252520contraceptives%26t%3Dname%26va%3Doral%252520contraceptives%26nq%3Dtrue#general-dosing-nested-6-0; Dickey RP. *Managing Contraceptive Pill Patients*. 15th ed. Essential Medical Information Systems; 2014.

Because no COC has been shown to be superior to the others, any COC with <50 µg of EE can be used for patients who are COC candidates.[41] The information in Figure 47-1 may be used to select an initial COC for most patients and to change formulations when side effects necessitate an alternative choice.[4,5] Concerns of decreased COC effectiveness in obese and overweight females has been debated; however, there are no contraindications for COC use.[24] Various reviews of literature found conflicting and lower quality studies addressing the issue.[42,43] Most studies reviewed did not include females with body mass indexes (BMIs) of >35 kg/m^2.[44] Pharmacokinetic studies have also provided conflicting data, with some showing a longer time to steady state in obesity and others showing no difference. It has been suggested that continuous OC use or using formulations with higher doses of EE (30–35 µg) may be more effective in females with obesity.[24] If S.F. were heavier, a COC with a higher dose of EE (eg, 35 µg) or perhaps a continuous-use OC could be a better option. Any pill containing <50 µg EE, however, can be used for S.F. because she is healthy and without medical complications or active medications.

LENGTH OF ACTIVE HORMONE: 21, 24, OR 28 DAY

The COCs are available in a variety of cycle lengths. The most common is the 28-day pack that contains 21 days of active pills (pills that contain estrogen and progestin) followed by 7 days of placebo pills. Some newer products contain 24 days of active pills followed by 4 days of placebo. CHCs with 4 days of placebo may shorten menses and minimize the hormonal withdrawal side effects (eg, headaches, mood changes) that some females experience during the placebo week.[45] It is also possible that efficacy is improved; however, this has not been proved in clinical trials.

The 21-day pill packs contain only the active pills. Most patients are instructed to take one pill daily for 21 days and then take nothing for 1 week. Many clinicians prefer the use of 28-day pill packs to minimize confusion; the patient takes one pill daily regardless of whether it is an active or a placebo pill. After taking the last pill of a 28-day pack, the patient should begin a new pack the next day. However, when continuous ovarian suppression is indicated to treat estrogen-dependent disorders such as endometriosis, the 21-day cycle products are preferred to facilitate taking active pills continuously. Alternatively, the placebo pills could be removed from 28-day cycle packs. S.F. will not be taking COCs continuously, so a 24- or 28-day pack is recommended.

MULTIPHASIC ORAL CONTRACEPTIVES

Case 47-1, Question 4: Should S.F. start a monophasic or multiphasic COC? What are the advantages and disadvantages of the monophasic versus multiphasic COC?

COCs have varying amounts of hormones in the active pills, which can be divided into phases that include monophasic, biphasic, triphasic, or quadriphasic (see Table 47-3).

Monophasic COCs contain the same dose of estrogen and progestin in each active pill throughout the pill pack, whereas multiphasic COCs have varying amounts of hormones. Because of metabolic and physiologic effects related to the progestin component of COCs, multiphasic products were initially formulated to contain less progestin overall. Some products, however, are now marketed with varying amounts of estrogen to reduce the overall exposure to estrogen or to minimize estrogen withdrawal side effects (eg, norethindrone/EE [Tri-Legest 21® and Tri-Legest® Fe 28]).

A biphasic formulation usually contains a certain amount of progestin and estrogen for the first half of the cycle, then a different amount for the second half, and then a week of placebos. Triphasic formulations have a different amount of hormones for each of the 3

weeks of active pills. No studies, however, show a superiority of one triphasic over another or compared with monophasics. The reduced progestin content is desirable for females with progestin-associated side effects (eg, increased appetite, acne, weight gain) or females with cardiovascular disease or metabolic abnormalities.[2] Females with side effects related to progestin deficiency (eg, late-cycle bleeding) or conditions necessitating progestin dominance (eg, benign breast disease) may do better with monophasics. Recently, a quadriphasic COC (Natazia®) became available, and it contains four different amounts of hormones throughout the pill pack.[39] Advantages of the product remain to be seen, but it may help decrease hormone withdrawal side effects and intermenstrual bleeding.

One drawback associated with triphasic and quadriphasic COC use is the confusion caused by the different-colored pills in each of the three different phases, making the missed-dose instructions more complicated. Monophasics are preferred for females who will be taking COCs continuously (ie, skipping the placebo pills) because of the same weekly hormone content.

Other unique formulations include Mircette® (see Table 47-3 for generic names), which is classified more appropriately as monophasic because the hormone content is consistent throughout the 21-day cycle similar to other monophasic formulations, but sometimes referred to as *biphasic* because it does not contain 7 days of placebos. It provides a unique regimen containing 21 days of 0.15 mg of desogestrel plus 20 µg of EE, then only 2 days of placebo, followed by 5 days of 10 µg of EE alone.[46] The patient does not need to take the missed 10-µg EE doses or use a backup method when those specific pills are missed. Adding low-dose estrogen for 5 days during the typical placebo week helps minimize breakthrough bleeding with this product and may be useful for patients who have estrogen-deficiency symptoms such as headaches during the hormone-free week. Because S.F. has not been on a CHC before and does not have a history of side effects associated with COCs, she may be started on any of the COC formulations.

EXTENDED CYCLE

Case 47-1, Question 5: S.F. has heard that she can skip the placebos from her pill pack to have fewer menses each year. She is interested in this approach. Is this a reasonable option for S.F.?

Continuous- or extended-cycle COC regimens (ie, skipping the placebo pills and taking no break between pill packs, thus having no menses) are often prescribed in females with underlying conditions including anemia, dysmenorrhea (less cramps with fewer menstrual cycles), menorrhagia (heavy menstrual bleeding), and endometriosis (to decrease hormone fluctuations that affect endometrial tissues).[4] In addition, for convenience and lifestyle reasons, many females prefer to take COCs continuously to minimize the number of menstrual periods. Regardless of the reason, any patient who is a candidate for CHCs can use them continuously.

Any CHC (eg, pill, patch, vaginal ring) may be used continuously; however, from the COCs, monophasic pills are recommended because of the consistent hormone content throughout the cycle. Any duration of continuous pill use is acceptable, but many providers recommend that patients take the active pills for 3 to 4 months (3–4 pill packs) and then stop COCs for 2 to 7 days. Alternatively, providers may prescribe COCs that are specifically packaged for continuous use (eg, Amethyst®, Camrese® Lo; see others in Table 47-3). Patients should be informed that continuous COC use usually results in more breakthrough bleeding or spotting than do traditional COC dosing regimens, with up to 41% of females experiencing some form of irregular bleeding in the first few months of the 1-year regimen.[47]

Concerns raised with extended-use regimens include harmful effects on the endometrium; however, one study showed no harmful changes to the endometrium with extended cycles.[48] Long-term side effects of the extended regimens are still being studied. If breakthrough bleeding continues beyond 6 months of continuous COC use, a pelvic examination may be considered. If S.F. is willing

to tolerate more irregular bleeding during the first 6 months of continuous COC use, then the extended-cycle regimen may work for her.

Patient Instructions

Case 47-1, Question 6: What instructions should be given to S.F. about her COC?

WHEN TO START ORAL CONTRACEPTIVES

S.F. should start the first cycle of COCs according to the manufacturer's package instructions or according to one of the following recommendations[2]:

1. Quick start: Take the first COC tablet as soon as possible regardless of cycle day.[49]
2. Day 1 start: Take the first tablet in the COC pack on the first day of menses.
3. Sunday start: Take the first tablet in the COC pack on the first Sunday after the beginning of menstruation. If menses begins on Sunday, start that day.

The quick start method is not described in COC package inserts; however, this method is used by family planning providers.[6,49] The method can minimize the confusion that many patients have about when to start their first pack and can increase adherence. Also, the quick start method provides contraceptive protection sooner and would, therefore, likely lower the risk of unintended pregnancy. More research on and awareness about this method are needed for it to be used routinely by all health care providers.

WHEN TO USE A BACKUP METHOD OF CONTRACEPTION

Some clinicians recommend that a patient use an alternative method of contraception for the entire first COC cycle. Others, including the 2016 CDC Selected Practice Recommendations for Contraceptive

Use, suggest that alternative methods of contraception are unnecessary if the COC is started on or before the fifth day of the menstrual cycle.[50] Most COC package inserts, with the exception of Natazia® (estradiol valerate/dienogest), state that a backup method of contraception (eg, male or female condoms, spermicides, diaphragms) is not necessary if patients use the day 1 start method.[3] If patients use the Sunday start or quick start method, backup contraception should be used for the first week of the COC cycle. A backup method is also recommended when doses are missed, as described in the following section. S.F. has decided to use the quick start method, so she will need to use another method of contraception for her first week of COC use.

COMBINED ORAL CONTRACEPTIVE ADMINISTRATION AND MISSED-DOSE INSTRUCTIONS

S.F. should take her COC at the same time each day. Nausea may be prevented or alleviated by taking the dose at bedtime or with food. The best time to take COCs depends on the patient. The optimal time for S.F. is the time when she will have the fewest problems in remembering to take her pill each day.

If a patient forgets to take one pill, she must take it as soon as she remembers and refer to the patient instructions in the package insert for further information.[2] Some unique formulations such as estradiol valerate/dienogest (Natazia®) have more specific recommendations based on the cycle day missed. If she is taking Natazia® (Bayer Healthcare Pharmaceutical Inc., Whippany, NJ)., she should be referred to the package insert for information (see http://www.natazia.com), because the advice varies from that listed subsequently.

For the majority of COCs, most manufacturers recommend that if she forgets to take one pill, she should take two pills on the day she remembers (eg, if she forgets her pill on Monday, she should take two pills on Tuesday). Then she should take the remaining pills as usual. A backup method of contraception is not necessary. If she misses two pills in a row in week 1 or 2 of her pack, she must take

two pills on the day she remembers and two pills the next day. She should use an alternative method of contraception for 7 days after missing the pills and may consider emergency contraception (EC).

If a patient misses two pills in a row during the third week (for day 1 starters), she must discard the rest of the pack, start a new pack on that same day, and use an alternative contraceptive method for 7 days. For a Sunday starter, she should keep taking one pill every day until Sunday, and then start a new pack on Sunday. She must use an alternative method of contraception for 7 days after missing the pills and may consider EC. She may miss her menstrual period this month.

If a patient misses three or more pills in a row during the first 3 weeks (for a day 1 starter), she must discard the rest of her pack, start a new pack that same day, and use an alternative method of contraception for 7 days; Sunday starters should keep taking one pill every day until Sunday, start a new pack on Sunday, and use an alternative method of contraception for 7 days after missing the pills, and they may consider EC. Females may not have a menstrual period this month. If two pills are missed from a low-dose COC (less than EE 30 μg), some references suggest following the instructions as if three pills were missed.[2] Other references and organizations may cite different recommendations. The recommendations described here are recommended by manufacturers.

CONTRACEPTIVE PATCH AND RING

CASE 47-1, QUESTION 7: S.F. returns to the clinic 3 months later and is very concerned about getting pregnant because she has trouble remembering to take her pill each day. She wants an effective contraceptive method but is wondering whether other dosage formulations are available. She also indicates concern about high doses of estrogen because she has heard that such doses can lead to blood clots. She wants the lowest possible dose. What do you tell her?

Contraceptive Patch

The contraceptive patch has an estimated failure rate of 0.3% with perfect use and 7% with typical use (see Table 47-1). There are two contraceptive patches approved by the FDA, Xulane® (Mylan Pharmaceuticals, Morgantown, WV) and Twirla® (Agile Therapeutics, Princeton, NJ). The first contraceptive patch was originally marketed as Ortho Evra® and is now known as Xulane®. It delivers 150 µg of norelgestromin and 35 µg of EE daily into the systemic circulation.[51] Twirla® was approved in 2020. It delivers 120 µg of levonorgestrel and 30 µg of EE daily.[52] Both patches are thin and beige, Xulane® is a 1.75-inch square with rounded corners, whereas Twirla® is a 28 cm^2 circular patch.

For both products, one patch is applied each week for 3 consecutive weeks for a total of three patches used, followed by 1 week with no patch. The day of the week the patch is applied is called the *patch change day*. Then this cycle is repeated. Menses should begin during the patch-free week. If a patient wants to avoid menses, the patch-free week may be skipped by applying a new patch on week 4 for an extended-use regimen.

A contraceptive patch may be worn on the buttock, abdomen, upper torso, or upper outer arm.[51,52] The patch should not be applied to the breasts to prevent direct administration of estradiol to the breast tissue. To minimize irritation from the adhesive, S.F. should rotate the patch application sites and not apply the patch to the same location within each month. When applying the patch, S.F. should select the application site and be sure it is clean and dry. She should press firmly on the patch for 10 seconds and trace her finger around the edge of the patch to be sure it adheres securely to the skin. The patch should stay attached during usual activities, including exercising, swimming, and bathing, although prolonged exposure to water could cause detachment. Patch adherence should be checked after prolonged water exposure. If the patch falls off and is off <24 hours, she should reapply it or apply a new one as soon as possible, and her patch change day will stay the same. No backup contraception is needed. If the patch is off for >24 hours, she should

start a new cycle of patches, and she will have a new patch change day.[51,52] She should use backup contraception for 1 week.

The patch may be started using the quick, Sunday, or day 1 start method, and the recommendations for backup contraception are the same as described earlier with CHCs.[51,52] If S.F. forgets to start the first patch of a new cycle, she should apply it as soon as she remembers. This day will become her new patch change day, and she should use backup contraception for 1 week. If she forgets to change the patch for 1 or 2 days during week 2 or 3, she should apply a new patch as soon as she remembers. This becomes her new patch change day. No backup contraception is needed. If she forgets to wear the patch for >2 days, she should start a new cycle as soon as she remembers. She will need to use backup contraception for 1 week and will have a new patch change day.

The effectiveness of the patches are reduced in patients weighing >198.42 pounds (90 kg) and should not be used alone for prevention of pregnancy in these females.[51,52] S.F. does not weigh >198.42 pounds (90 kg), which does not preclude her from using this method.

The most common side effects reported with the patch are breast tenderness, headache, application site reaction, and nausea. Most risks and benefits with the contraceptive patch are thought to be similar to that with COCs. One notable difference is the rate of VTE. A small pharmacokinetic trial found that overall monthly serum levels of EE are significantly higher in patch (EE/norelgestromin) users compared with vaginal ring (EE/etonorgestrel) or COC users.[53] With the patch, the peak levels of estrogen are lower, but the steady-state concentrations are higher. It has been noted that the EE/norelgestromin patch provides 60% more EE than does an oral 35-μg tablet.[51] This raised concern that the patch may have a higher incidence of VTE than do the other methods; however, it is controversial. A systematic review had conflicting results, with two studies finding a doubling of VTE risk in patch users compared with COC users, one with an elevated risk that did not meet statistical significance, and four with no difference in risk.[54] The EE/levonorgestrel patch has a lower amount of EE and theoretically may have a lower risk of VTE, although more data are needed for

confirmation. Future studies may find that there are other differences in certain risks or benefits between the patch and the pill. Given the controversy surrounding VTE with the transdermal patch, this may not be the most appropriate method for S.F. based on her concerns of VTE associated with COC use.

Contraceptive Ring

There are contraceptive vaginal rings available, NuvaRing® (Merck, Whitehouse Station, NJ) and Annovera™ (TherapeuticsMD, Boca Raton, FL). NuvaRing® and EluRyng® (Amneal Pharmaceuticals, Bridgewater, NJ) delivers 120 µg of etonogestrel and 15 µg of EE and Annovera™ delivers about 150 µg of segesterone acetate and 13 µg of EE daily through the vaginal mucosa.[37,55,56] The failure rate of a contraceptive ring is 0.3% with perfect use and 7% with typical use (Table 47-1).[2] NuvaRing®, EluRyng®, and Annovera™ are inserted vaginally and kept in place for 3 weeks in a row. After 3 weeks, the ring is removed for 1 week, and then a new ring is inserted (see https://www.nuvaring.com/ and https://www.annovera.com/pi.pdf). For extended use, the ring-free week may be skipped by inserting a new ring on week 4. Each NuvaRing® and EluRyng® is formulated for 3 weeks of use, and then discarded; after a 7-day ring-free interval, a new ring is used. Annovera™ is formulated to work for 21 days, with a 7-day ring-free interval and can be used again for a total of 13 cycles. It is not discarded after use unless the patient has used the ring for 13 cycles.

The ring may be placed anywhere in the vagina, so S.F. does not need to worry about its exact position.[55,56] To insert the ring, she should compress it so that the opposite sides of the ring are touching, and gently insert it into the vagina.

If she feels discomfort with the ring, it has probably not been inserted into the vagina far enough. Most females do not feel the ring once it is in place. To remove the ring, S.F. should grasp the ring between two fingers or hook one finger inside the ring and pull it out. Menses will usually begin within 3 days of removing the ring. If the

ring slips out, it should be rinsed with lukewarm water and reinserted. If the NuvaRing® or EluRyng® is out for <3 hours or the Annovera™ is out <2 hours, backup contraception is not needed. If the NuvaRing® or EluRyng® is out for >3 hours or the Annovera™ is out for >2 hours continuously or 2 hours cumulatively over the 21 days, backup contraception should be used for 1 week. According to the manufacturers, if the NuvaRing® has been left in the vagina for >3 weeks but no more than 4 weeks, S.F. should remove it, wait 1 week, then reinsert a new ring. The NuvaRing® is formulated to contain ~35 days of medication, but should not be promoted for use beyond 21 days.[55] If it has been in place for >4 weeks, she should remove it, confirm that she is not pregnant, reinsert a new one, and use backup contraception for 1 week. If the Annovera® ring is left in place >3 weeks, it should be removed for 7 days and then reinserted for 21 days resuming the 21-day/7-day ring-free interval as before (assuming the product has not been used for >12 cycles).[56]

Both contraceptive vaginal rings should be inserted anytime during the first 5 days of the menstrual cycle or inserted using the quick start method.[2,55,56] Backup contraception should be used for the first week with the NuvaRing® and EluRyng®. When changing from the COC, S.F. should insert the ring within 7 days of the last active pill and no backup contraception is needed.

The rings are believed to have the same contraindications and precautions as that of COCs. The most common side effects with the ring are vaginal infections, irritation, and discharge; headache; weight gain; dysmenorrhea; and nausea. Unlike the patch, the ring has not been shown to have reduced efficacy in obese females.[55,56] There are conflicting data regarding increased risk of VTE with the contraceptive ring. The ring provides the least amount of EE exposure when compared with other CHCs.[53] However, despite the lower levels of EE provided, one study has shown an increased risk of VTE with the use of the contraceptive vaginal ring when compared with levonorgestrel-containing contraceptives, although two others showed no increased risk.[54] Although one study indicated a possible increase in VTE with the vaginal ring, the FDA has not required any labeling changes or communicated any safety issues with the

vaginal rings. Given the good adherence rates and lower EE levels, the vaginal ring may be appropriate for S.F. if she is comfortable with the dosage form.

Case 47-1, Question 8: S.F. returns to the clinic 2 months later for a sore throat. She indicates that she is using the NuvaRing®.

Current vitals at clinic: weight, 132 pounds (59.87 kg); height, 64 inches (162.56 cm)
Blood pressure, 125/78 mm Hg
Heart rate, 97 beats/minute
Respiratory rate, 16 breaths/minute
Temperature, 101.1 °F (38.39 °C)
Physical examination: head, eyes, ear, nose, and throat: tonsils 2+, bright red, soft palate erythematous
Laboratory test results: rapid streptococcal antigen test, positive

S.F.'s primary care physician prescribes Augmentin® 875 mg/125 mg (amoxicillin/clavulanate) twice daily PO for 10 days. Could this medication affect her contraception? What advice should be provided to S.F.? What other drug interactions are of concern with CHCs?

Drug Interactions

A variety of drugs may alter the levels of CHCs and in turn affect their efficacy (**Table 47-5**).[6,57] Currently, most data available regarding drug interactions are with COCs. However, as a precaution, the potential drug–drug interactions observed with COCs are also applied to the other CHC dosage formulations (eg, vaginal ring and transdermal patch).

Table 47-5
Common Combined Oral Contraceptive Drug[a] Interactions

Drugs That Increase Effect of CHCs or Side Effects of CHCs	Drugs/Herbals That Decrease the Effect of CHCs	Drugs That May Decrease the Effect of CHCs (Controversial)	Metabolism or Clearance Altered by CHCs (Levels of Drug Listed May Either Increase or Decrease Depending on Patient)
Acetaminophen	Amprenavir	Amoxicillin	Acetaminophen
Ascorbic acid	Aprepitant	Ampicillin	Amprenavir
Atazanavir	Barbiturates	Ciprofloxacin	Antidepressants, tricyclic
Atorvastatin	Bexarotene	Clarithromycin	Benzodiazepines
Ginseng	Bosentan	Colesevelam	β-Blockers
Indinavir	Carbamazepine	Doxycycline	Caffeine
Red clover[b]	Darunavir	Erythromycin	Clofibric acid
Rosuvastatin	Efavirenz	Fluconazole	Corticosteroids
Tranexamic acid	Felbamate	Itraconazole	Cyclosporine
Voriconazole	Griseofulvin	Ketoconazole	Lamotrigine
	Isotretinoin	Metronidazole	Levothyroxine
	Lopinavir	Minocycline	Morphine
	Modafinil	Penicillins	Paclitaxel
	Mycophenolate mofetil	Phenylbutazone	Salicylic acid
	Nelfinavir	Ofloxacin	Selegiline
	Nevirapine	Tetracyclines	Tacrine
	Oxcarbazepine	Topiramate	Tacrolimus
	Phenobarbital		Theophyllines
	Phenytoin/Fosphenytoin		Tizanidine
	Pioglitazone		Valproic acid
	Primidone		Voriconazole
	Red clover[b]		Warfarin[c]
	Rifamycins		
	Ritonavir		
	Rufinamide		
	Saquinavir		
	St. John's wort		
	Tipranavir		

CHC, combined hormonal contraceptive.

[a]Drug list is not an all-inclusive one. Some drug interactions that are not cited in this table may exist.

[b]Indicates that drug may have variable effect on CHC either increasing or decreasing effect.

[c]May decrease anticoagulant effect of warfarin, not warfarin drug levels.

Reprinted with permission from O'Connell MB, Smith JA, eds. *Women's Health Across the Lifespan: A Pharmacotherapeutic Approach*. 2nd ed. McGraw-Hill; 2019, electronic text. © 2019 McGraw Hill LLC.

ANTIBACTERIALS

The antibacterials rifampin and griseofulvin are known to cause contraceptive failure, because these products increase the

metabolism of estrogen. For other antibacterials, the possible interaction is more complicated.

EE is conjugated in the liver, excreted in the bile, hydrolyzed by intestinal bacteria, and reabsorbed as active drug.[58] Antibacterials, by reducing the population of intestinal bacteria, interrupt the enterohepatic circulation of the estrogen, resulting in a decreased concentration of circulating estrogen. Theoretically, any antimicrobial with significant effects on intestinal bacterial flora could affect COC efficacy. Numerous reports of changes in bleeding patterns and contraceptive failure have been documented.[58] Cases of pregnancy in COC users taking antibiotics have been reported.[58–60] About 30 case reports of contraceptive failure with concomitant COC and antibiotic use have been published.[58] The antibacterials in the case reports include rifampin, ampicillin, penicillin G, tetracycline, and minocycline. In addition, surveys conducted on patients in clinics have revealed about 20 other cases of COC failure.[58] A major limitation of survey data is that they rely on patient reporting, which is often unreliable. A systematic review of 29 studies concluded that the probability of a clinically significant drug interaction between COCs and antibacterials is low and the CDC US Medical Eligibility Criteria does not recommend a need for alternative birth control methods while taking broad-spectrum antibiotics that do not affect hepatic enzymes.[6,60–62]

Numerous factors may affect the likelihood of an interaction: the hormonal content of the COC relative to the patient's requirements, the dosage and duration of use of the interacting drug, variation in the patient's response to bacterial flora alteration, and the fertility of the couple.[58] The number and complexity of these variables make prediction of outcome in a specific patient exceedingly difficult. Even if a drug produces a several-fold increase in unintended pregnancies in females taking COCs, the likelihood of pregnancy in a given patient still will be low. For patients who require long-term, low-dose tetracycline use for acne therapy (eg, tetracycline 250 mg PO daily), it is unlikely to interfere with COC efficacy.[61,62] Alternatively, topical antibacterials often can control acne and are viable alternatives to oral medications.

A practical approach to managing patients taking COCs and antibacterials is to educate them about the available data. To be conservative, S.F. should be advised to use backup contraception while taking the amoxicillin/clavulanate and to continue the backup method until her next menses occurs, although this is controversial and the CDC Medical Eligibility Criteria does not call for it.[6] For other antibiotics that affect hepatic enzymes such as rifampin, isoniazid, and griseofulvin, backup contraception should be used while taking the medication and for 4 weeks after discontinuation of the antibiotics.[6]

HEPATIC ENZYME INDUCTION

EE is a substrate of cytochrome P-450 3A4 (CYP3A4), so drugs that induce CYP3A4 activity may decrease COC efficacy. In earlier years, COC efficacy was not decreased significantly by other drugs because of their high hormone content. Because the estrogen and progestin concentrations of COCs have gradually been decreasing, reports of menstrual irregularities (eg, spotting) and unintended pregnancies attributable to drug interactions have been increasing.

Anticonvulsants such as carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, and topiramate are CYP3A4 inducers and are known to cause increased metabolism of COCs (see Chapter 60, Seizure Disorders).[63,64] Some studies have shown that another inducer of COC metabolism is St. John's wort.[65] Although drugs can influence COC efficacy, COCs also can affect the activity of other drugs. For example, COCs have been reported to decrease serum levels of lamotrigine and can affect seizure control; increased levels of lamotrigine have also been reported after COC discontinuation.[63,64] Other drugs may increase the hormone levels of COCs (see Table 47-5), increasing the risk of COC side effects (see Table 47-4).

Unlike many drug classes that are carefully dosed to maintain a therapeutic range of monitored blood levels, contraceptive estrogen and progestin blood levels are obtained only in clinical drug studies. Therefore, patients are managed by monitoring side effects and by

changes in menstrual patterns. Some prescribers suggest using a 50-µg EE COC in patients taking interacting drugs, although others might recommend using an alternative method of contraception if drug interactions are an issue.

Noncontraceptive Benefits of Combined Hormonal Contraceptives

ACNE

CASE 47-2

Question 1: D.S., a 20-year-old patient, presents to her primary care physician for a yearly pelvic examination and reports moderate acne flares. She has tried a variety of treatments without resolution and is currently using only topical medications. She heard birth control pills can help acne, especially if it occurs right before her period. She also reports fatigue most days of the month and mood changes, cravings, cramps, and bloating near the time of her period.

Vitals: weight, 118 pounds (53.52 kg); height, 63 inches (160.02 cm)
Blood pressure, 118/75 mm Hg
Heart rate, 86 beats/minute
Respiratory rate, 13 breaths/minute
Temperature, 98.6 °F (37 °C)
Past medical history: acne (since age 16)
Social history: denies tobacco and alcohol use, not sexually active
Family history: older sister cervical dysplasia grade 2 (age 26), maternal grandmother breast (at age 61) and ovarian cancer (at age 68)
Allergies: no known drug allergies
Current medications: benzoyl peroxide 5% cream, apply topically twice daily
Benzoyl peroxide 2.5% wash, wash affected area twice daily
Retin-A Micro® 0.1%, apply topically twice a week as tolerated
Multivitamin with iron PO daily
Past medications: doxycycline 100 mg PO twice daily for acne, stopped because of vaginal yeast infections
Physical examination: unremarkable with the exception of moderate facial acne
Laboratory test results: white blood cells, 6.0 × 10^3/µL
Red blood cells, 3.9 × 10^6/µL
Hemoglobin, 10.8 g/dL
Hematocrit, 32%
Mean cell volume, 79 µL

Mean corpuscular hemoglobin concentration, 31 g/dL
Red blood cell diameter width, 15%

What effect, if any, would CHCs have on her acne? Does D.S. qualify for CHC treatment of acne, and, if so, which COC would you recommend for D.S.?

Depending on the patient, a CHC may cause acne to appear, disappear, or significantly improve.[3] D.S. is interested in COCs. Four COC products, including their generic brands (norethindrone acetate/EE [Tri-Legest® 21 and Tri-Legest® Fe 28], norgestimate/EE [Ortho Tri-Cyclen® (discontinued, but generics available)], and drospirenone/EE [YAZ®, Beyaz®]) are U.S. Food and Drug Administration (FDA) approved for the treatment of moderate acne vulgaris in females at least 15 years old (at least 14 years old for Beyaz® and YAZ®), who have no known contraindications to CHCs, reached menarche, desire contraception, and have failed topical acne treatments (Tri-Legest® 21, Tri-Legest® Fe 28, and Ortho Tri-Cyclen®). Most CHCs, however, improve acne mainly as a result of the estrogen component. Higher doses of estrogen may decrease acne by suppressing the activity of sebaceous glands, decreasing the production of androgens, and increasing the synthesis of sex hormone–binding globulin (SHBG). The SHBG binds androgens and thereby diminishes their effects.[66] Progestins with higher androgenic activity may be more likely to increase acne because they stimulate sebaceous glands to produce more sebum. Both desogestrel- and norgestimate-containing OCs are less androgenic, whereas drospirenone has antiandrogenic properties, thereby decreasing acne associated with androgenic activity.[67] D.S. is 20 years old, has reached menarche, and has not responded to different acne treatments, and she therefore is a candidate for COC therapy. Her acne appears to be hormonally mediated, particularly because it appears around the time of her menses. It is likely that D.S.'s acne should improve with COC use, particularly if she uses a formulation with higher estrogenic activity and low androgenic activity (eg, Beyaz®, Safyral®, YAZ®, Yasmin®, Tri-Sprintec®, Tri-Sprintec Lo®, Mircette®, Tri-Legest 21®; see Table 47-3 for others).

MENSTRUAL CYCLE BENEFITS

Case 47-2, Question 2: D.S. has iron deficiency anemia, likely attributed to heavy menses. Will a COC help reduce her menstrual bleeding or menstrual cramps?

COCs help regulate menstrual cycles and reduce monthly blood loss.[25] This may reflect the progressive thinning of the endometrium of COC users and the lack of irregular bleeding. Bleeding may be decreased the most by COCs that have a high ratio of progestin to estrogen because endometrial thinning is maximized.[38] The formulation of EE/dienogest (Natazia™) has FDA labeling for the treatment of menstrual bleeding.[39] Some COCs have iron pills instead of placebos, often denoted with "Fe" in the name (eg, Tri-Legest® Fe 28, Femcon® Fe, Loestrin® Fe, Lo Loestrin® Fe; see Table 47-3 for others). Others have folic acid (eg, Beyaz®, Safyral®, see Table 47-3 for others), but D.S. would likely benefit more from the formulations with iron. Another option would be to have D.S. take COCs continuously so she has fewer menses.

Dysmenorrhea, or painful menstruation, may be of unknown origin or may be attributable to endometriosis or uterine fibroids. Data suggest menstrual pain might decrease by 60% after the initiation of a COC.[2] A COC with decreased estrogenic and increased progestational activity may be the best at relieving dysmenorrhea (see Chapter 50, Disorders Related to the Menstrual Cycle).

PREMENSTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDER

Case 47-2, Question 3: D.S. also reports PMS symptoms such as bloating and mood changes. What treatment approaches are appropriate? What other noncontraceptive benefits do CHCs have?

Premenstrual syndrome (PMS) is a cyclic occurrence of one or more symptoms before the onset of menses. Most females report at

least one PMS symptom, which includes irritability, bloating, and depressed mood.[68] Premenstrual dysphoric disorder (PMDD) is a more severe form of PMS and has diagnostic criteria by the American Psychiatric Association. Premenstrual tension has been reported to be reduced in COC users, and other premenstrual symptoms seem to improve as well. Nevertheless, the effect of COCs on PMS symptoms is inconsistent and unpredictable, probably because PMS symptoms are neither consistent nor predictable.[69]

There may be augmentation of depression and mood swings by the progestational component, although the probability of this effect is low with a low-dose product (see Chapter 50, Disorders Related to the Menstrual Cycle, for further discussion of PMS). Some patients may also notice depressed mood during the hormone-free period, in which case a continuous-use COC may be helpful.

Two products, drospirenone/EE (YAZ®, Beyaz® and their generics), have the FDA-approved indication for treatment of symptoms of PMDD. Drospirenone/EE has been studied most extensively in patients with PMDD.[69] D.S. may try any CHC to help with her PMS symptoms; however, because YAZ® and Beyaz® have more data to show that they are effective for PMDD and acne, one of them may be the preferred initial product for her. In addition, both products are 24-day formulations, which may help minimize her menstrual bleeding and help her iron deficiency anemia.

ENDOMETRIAL CANCER

Clinical data suggest that COCs protect against endometrial cancer. This effect continues for 20 years after the last pill.[69] The protection is directly related to duration of use and may persist for many years after discontinuation of the COC.[3] A meta-analysis of 11 studies showed a 56%, 67%, and 72% reduction in endometrial cancer risk after 4, 8, and 12 years of COC use, respectively.[70] Another prospective study found risk reductions in endometrial cancer strengthened with longer use.[71]

OVARIAN CANCER AND FUNCTIONAL OVARIAN CYSTS

The risk of developing functional ovarian cysts is decreased, preexisting cysts are more rapidly resolved, and surgery rates for ovarian masses are reduced in females taking COCs.[72,73] This is likely attributable to reducing ovulation, suppressing androgen production, or increasing progesterone levels.

Each year of COC use decreases the relative risk of developing ovarian cancer by 7% to 9%.[73] The risk reduction continues to be seen in females using COCs for >15 years and persists after discontinuation.[69] D.S. should be reassured that COC use may decrease her risk of ovarian cancer given that she has a positive family history.

Combined Hormonal Contraceptive Risks and Adverse Effects

Some patients may not be candidates for CHCs because of the risks and adverse effects associated with their use. Other patients may experience minor side effects with CHCs that may be managed by changing to a CHC with different types or doses of estrogen or progestin. All patients should be counseled on the most serious side effects, which include PE or VTE, hepatotoxicity, or visual disturbances (could be a sign of retinal and corneal changes in the eye) and stroke. A helpful acronym to remember when counseling is "ACHES" (see Table 47-2),[2] which can be used to increase a patient's awareness of serious potential adverse effects that warrant immediate medical attention.

Other less severe adverse effects are listed in Table 47-4.[38] Most side effects resolve within 3 months of use. If a patient experiences adverse effects other than those described in "ACHES" (Table 47-2), she should be encouraged to continue the CHC for at least 3 months before switching to a different contraceptive.

BREAKTHROUGH BLEEDING, SPOTTING, AND AMENORRHEA

Case 47-2, Question 4: D.S. comes to the family planning clinic after taking EE 20/30/35 µg/norethindrone acetate1 mg (Tri-Legest Fe®) for 2 months. She had been started on Tri-Legest® to help with her acne. She feels her acne has improved, but reports irregular menstrual bleeding during her last two menstrual cycles, which occurs around the fifth pill of the pack and requires a pad. What action should be taken to correct D.S.'s bleeding pattern?

Intermenstrual bleeding is a bleeding that occurs at times other than the regular menses timing. Intermenstrual bleeding that requires a pad or tampon is designated breakthrough bleeding, whereas a lesser amount of intermenstrual bleeding is called spotting. Intermenstrual bleeding is experienced by many females in the first months of starting COCs (30%–50%).[2] Intermenstrual bleeding may also occur if a patient is not adherent to her COCs or taking medications that decrease COC effectiveness (Table 47-5).

Most clinicians will recommend that patients continue the same COC for at least 3 months if breakthrough bleeding or spotting is the only problem, because this complication usually resolves within 3 months.[2] Early-cycle intermenstrual bleeding, which usually starts before the 14th day of the menstrual cycle (or never ceases completely after menses), is usually caused by insufficient estrogen. Late-cycle intermenstrual bleeding, occurring after day 14, is usually attributable to insufficient progestational support of the endometrium. Another cause of intermenstrual bleeding is drug interactions (see Case 47-1, Question 8, for more information about drug interactions).

The balance between estrogen and progestin components in COCs determines its endometrial activity and, therefore, the likelihood of intermenstrual bleeding problems. It may be helpful to envision the estrogen component as the basic building blocks or "bricks" of the endometrium and the progestational component providing the mortar that holds the bricks together. The estrogenic activity of the progestin component increases the number of bricks, whereas its antiestrogenic activity decreases their numbers. If there are not enough bricks or mortar or if they are present in the wrong

proportions, the wall will crumble, and bleeding will occur (Table 47-3).

If D.S.'s intermenstrual bleeding continues early in her cycle after 3 months, another COC with the same progestin activity, more endometrial activity, and low androgen activity should be prescribed. Drospirenone 3 mg/EE 30 µg (eg, Ocella®, Safyral®, Syeda®, Tydemy®, Yasmin®, Zarah®, Zumandimine™) or Drospirenone 3 mg/EE 20 µg (eg, Beyaz®, Gianvi®, Jasmiel™, Loryna™, Lo-Zumandimine™, Nikki™, Rajani™, Yaz®) would be a good choice because endometrial activity would be increased and endometrial activity would be maintained with no androgenic activity (Table 47-3). For D.S., products with low or no androgenic activity should be selected because of her acne.

Intermenstrual bleeding may also be the sign of other health conditions such as cervical or uterine cancer. If a patient presents with intermenstrual bleeding and has not had a recent pelvic examination, a health care provider may perform an examination to rule out other possible causes of intermenstrual bleeding. D.S. recently had a normal pelvic examination 2 months ago. Given the timing of when she began her COCs, it is likely her intermenstrual bleeding is caused by her COCs.

Some patients experience amenorrhea (no menstrual bleeding) with CHCs. If this occurs, pregnancy should first be ruled out. If the patient is not pregnant and amenorrhea is acceptable to the patient, then the CHC need not be changed. But this does make it difficult for the patient to recognize whether she may become pregnant in the future.

CASE 47-2, QUESTION 5: During the same visit, D.S. states she is gaining weight and feels "bloated on and off" since starting the new birth control pill. What might be happening, and how should the clinician respond?

WEIGHT GAIN

Weight gain associated with CHC use is another common concern for females. A Cochrane review of three trials concluded that

available evidence was insufficient to determine an association between COCs and weight gain and also stated that no large effect was seen.[74] If weight gain is a concern, a low-dose estrogen and low-dose progestin products should be considered. Cyclic weight gain is generally caused by the mineralocorticoid effects of EE-stimulating aldosterone receptors to retain sodium, causing water retention and bloating. Too much progestin may cause an increased appetite and noncyclic weight gain. Drospirenone with antimineralocorticoid properties opposes EE effects, resulting in less water retention and weight gain, and increases in appetite may not be as apparent. The clinician should explain that weight gain is a potential side effect associated with COC use and is likely related to the estrogen component. It is reasonable to consider an alternative COC because she is having breakthrough bleeding and weight gain. A possible choice for D.S. is drosperinone 3 mg/EE 30 µg, which may help decrease the cyclic weight gain and still help control her acne. In addition, drospirenone 3 mg/EE 30 µg has the same progestational activity and higher endometrial activity to address D.S.'s previous breakthrough bleeding and has nonandrogenic activity that will likely help her acne.

NAUSEA

Case 47-2, Question 6: D.S. continues to have intermenstrual bleeding early in her cycle after 3 months of use along with feeling bloated and is placed on a new COC. Five days after starting drospirenone 3 mg/EE 30 µg, D.S. calls with reports of nausea. What counseling should the clinician provide to D.S.?

Nausea from COCs can generally be attributed to the estrogen component. To help alleviate nausea, D.S. can take her pill at bedtime rather than in the morning. Another alternative may be to take it with food or to try another COC with a lower estrogen strength. Yasmin® has a higher amount of EE as compared with the start of Tri-Legest Fe® (30 vs 20 µg of EE), which may be causing nausea to D.S. She should be advised that nausea generally resolves within 3 months of use.

HEADACHE

Case 47-2, Question 7: Three months later, D.S. returns to the clinic for follow-up and states that she has daily headaches during her placebo week but not when she is taking active pills. How should she be managed?

Headache is common in females taking CHCs or COCs, as is the case with D.S. Females may notice headaches while taking active pills, which may be related to sensitivity of estrogen. Others may experience headaches during the placebo week as a result of the withdrawal of estrogen.[2] Females with migraines may find that their headaches either improve or worsen when CHCs are initiated.

Mild headaches may improve with time, or if the patient is changed to a pill with less estrogen or progestin. Headaches that occur during the placebo week can be managed by trying desogestrel 0.15 mg/EE 10 to 20 µg (eg, Azurette®, Bekyree®, Kariva®, Pimtrea®, Mircette®, Simliya®, Viorele®, Volnea®), which minimizes the estrogen withdrawal by having only 2 days of placebos, or by taking CHCs continuously (ie, skipping placebo pills or the hormone-free week). Patients with severe headaches should discontinue CHCs and should be evaluated by their health care provider (see section on Contraindications). D.S. is experiencing headaches during the placebo week, indicating withdrawal of estrogen as the cause. Skipping the placebo pills and using an extended-cycle regimen may help decrease D.S.'s headaches.

BREAST CANCER, CERVICAL DYSPLASIA, AND CERVICAL CANCER

Case 47-2, Question 8: The medical history and physical examination of D.S. return negative findings for breast and cervical diseases, except for a history of breast cancer in her maternal grandmother and a history of cervical dysplasia in her sister. D.S. asks, "How COC use will affect her risk of breast cancer and cervical cancer?"

There are conflicting data regarding the association of COC use and breast cancer. The reported overall lifetime risk of breast cancer in American females is 12% to 13%.[75] Mørch et al cited several studies, including their own, that indicate a possible link between COC use and breast cancer showing an increased risk of breast cancer that increased with longer duration of use.[76] The study noted that absolute risk increases were small, whereas another study found the increased risk of breast cancer disappeared after 5 years of stopping contraception.[76,77] Other studies suggest that COC use does not increase breast cancer risk even with long-term use (eg, 10 years).[78,79] In addition, other studies concluded that breast cancer rates in high-risk females with *BRCA* 1 and 2 mutations or strong family history of breast cancer did not increase with COC use.[71,80,81]

COCs would not be expected to increase the risk of breast cancer in D.S. She should be instructed to perform monthly breast self-examinations and to return annually for a physical examination by her primary care physician.

With regard to D.S.'s concern of cervical cancer, it is important to educate D.S. about the incidence of cervical cancer and its relation to COC use. The American Cancer Society estimates that >14,100 cases of invasive cervical cancer will be diagnosed in 2022 and more than 4280 females will die of it.[82]

Females at highest risk for cancer are those whose test results are positive for certain subtypes of human papillomavirus (HPV), who have certain sexual behaviors, who are immunosuppressed, or who smoke.[2] Sexual behaviors associated with cervical cancer include beginning sexual activity at a young age, having multiple male sexual partners, and having a male sexual partner who has had multiple partners. Females at low risk for cancer are those who have two or fewer partners, whose partners use condoms, and who do not smoke.

Pooled data on cervical cancer risk from eight case–control studies found that OC users whose test results were positive for HPV were more likely to develop cervical cancer.[83] Females who had ever used OCs and those who had used OCs for >5 years were 1.5 and 3.4 times, respectively, more likely to develop cervical cancer.

This is consistent with other studies that suggest that OC users have an increased risk of developing cervical cancer, although one study suggests that the risk disappears 10 years after discontinuation of COCs.[76]

Epidemiologic comparisons of the prevalence of cervical cancer in OC users versus nonusers often are difficult to interpret because yearly medical examinations and regular Papanicolaou (Pap) smears of COC users result in early detection and treatment of precancerous lesions. Three vaccines for HPV are available and recommended for females ages 9 to 26 years. Because D.S. is 20 years old, she may be a candidate for the HPV vaccine (see Chapter 64, Vaccinations). D.S. may use COCs, should be encouraged to have regular Pap smears, and should be counseled on the behaviors that put her at risk for cervical cancer and the risks and benefits of the HPV vaccine.

USE DURING PREGNANCY AND BREAST-FEEDING

CASE 47-3

QUESTION 1: P.K., a 35-year-old female, comes to clinic stating that she recently took a home pregnancy test that reported a positive result. Her last menstrual period (LMP) was 9 weeks ago. She would like to confirm the results and discuss the effects of her current medications on the fetus.

Vitals: weight, 143 pounds (64.86 kg); height, 66 inches (167.64 cm)
Blood pressure, 128/82 mm Hg
Heart rate, 97 beats/minute
Respiratory rate, 16 breaths/minute
Temperature, 98.6 °F (37 °C)
Past medical history: history of abnormal menses, initiated on COC therapy to help regulate
Medications: desogestrel 0.15 mg/EE 30 µg (Reclipsen™)
Laboratory test results: blood test, qualitative human chorionic gonadotropin >25 mIU/mL

P.K. was started on desogestrel 0.15 mg/EE 30 µg (Reclipsen™) extended regimen 3 months ago because of a history of abnormal menstrual periods. Unknowingly, she became pregnant in the first month, continued her COC for two cycles, and is now 8 weeks pregnant.

What can you tell P.K. about the possible effects of CHC use on the fetus?

Although older, poorly designed studies found an association between COC use and cardiac or limb anomalies, newer data suggest that CHC use does not substantially increase the risk of anomalies over that expected in other uneventful pregnancies.[3]

Although a CHC should not be started in a patient who might possibly be pregnant, P.K. should be instructed to stop using her COC and be reassured that the risks to her fetus from the use of a low-dose CHC during the first trimester are likely minimal, while also informing her that no drug is without risk and that she should follow up with her obstetrician.

Case 47-3, Question 2: P.K. plans to breast-feed her infant and begin some type of contraception after her discharge from the hospital. Her past experience with condoms and concurrent spermicidal foams or gels resulted in itching and burning. She indicates she would like a contraceptive that would be suitable for long-term use while breast-feeding. What contraceptives are best for her while she is breast-feeding?

P.K. may use CHCs 4 to 6 weeks after delivery depending on her risk factors for VTE, even if she is breast-feeding, although it is preferable for her to use a progestin-only method (oral tablets, injectable, or subdermal implant).[6,24] In females with VTE risk factors, waiting at least 6 weeks before starting any estrogen-containing contraceptive regardless of breast-feeding status is recommended. By this time, the increased risk of thrombosis that occurs during pregnancy should be reduced to baseline. For non-breast-feeding females, a progestin-only contraceptive may be used immediately postpartum and for breast-feeding females, after the onset of lactogenesis, generally, in the first 48 to 72 hours postpartum.[24] COCs have been reported to decrease milk quantity and quality, although data are sparse.[24] Therefore, many providers suggest avoiding CHCs in females who are exclusively breast-feeding. If P.K. is planning to breast-feed, a progestin-only contraceptive is probably

best, which will inhibit ovulation, thicken the cervical mucus, and suppress endometrial growth, making them effective contraceptives.

PROGESTIN-ONLY CONTRACEPTIVES

Progestin-Only Pill

ADVANTAGES

CASE 47-3, QUESTION 3: What advantages and disadvantages of the POP should you discuss with P.K.?

There are two types of POPs available, norethindrone known as the *minipill* (Camila®, Deblitane®, Errin®, Heather®, Incassia™, Jencycla™, Lyza®, Nora-BE®, Norlyroc™, Ortho Micronor®, Sharobel™, Tulana™) and drospirenone (Slynd®). Slynd® (Exeltis USA, Inc., Florham Park, NJ) is a relatively new POP.

Norethindrone and drospirenone are devoid of some of the nuisance side effects (see Table 47-4) caused by estrogen (eg, headaches, chloasma).[2] More importantly, estrogen-mediated hypertension and clotting factor changes will be avoided with norethindrone; however, clotting is still a concern with drospirenone. Possible bone loss and hyperkalemia need monitoring with drospirenone.[84] Confusion with pill taking is minimized with norethindrone because there is no placebo week and all 28 tablets in each pack are the same. Therefore, the missed-dose directions are the same whenever any tablet is missed. Drospirenone has 24 active and 4 inactive tablets. Females may choose them because they are not estrogen containing and fertility returns rapidly after discontinuation.[2]

Theoretically, progestin use in the early postpartum period may decrease milk production because milk production is triggered by the decline in progesterone that occurs after delivery. However, no data have consistently shown this to be a problem in postpartum

females.[24] Once breast-feeding has been established, progestins have not been shown to interfere with the quantity or quality of milk produced by a nursing mother. Thus, a contraceptive method that is nonhormonal or only contains progestin is preferred for a patient who plans to breast-feed her infant.

DISADVANTAGES

Norethindrone with a failure rate of 0.3% to 7% and drospirenone with a 4% failure rate (in clinical trials) are similar in effectiveness to the COCs in preventing pregnancies (see Table 47-1).[2] Minipills (norethindrone), however, must be taken even more regularly than are COCs, and, therefore, are not used often in females who are not breast-feeding (see section on Patient Instructions). Some females on minipills ovulate regularly, and some shift back and forth between ovulatory and anovulatory (no ovulation occurring) menstrual cycles. Females who consistently have menses on the minipill may be ovulating and should consider using a backup contraception or changing to a different method.

Irregular menses, decreased duration, and amount of menstrual flow, spotting, or amenorrhea commonly occur in females taking the minipill.[2] Because of this, patients often are concerned that they may be pregnant. Females who are exclusively breast-feeding will usually have amenorrhea. The high incidence of irregular menses associated with the minipill may mask underlying disease such as uterine fibroids or uterine cancer causing irregular bleeding. Other side effects reported with minipills include headaches, breast tenderness, mood changes, and nausea.

Minipills should be avoided if there is a personal history of breast cancer or unexplained vaginal bleeding. Caution should be exercised when using minipills in females with hepatic disease, multiple risk factors for cardiovascular diseases, ischemic heart disease, a current deep venous thrombosis or PE, or complicated diabetes (eg, diabetes with nephropathy, neuropathy, retinopathy), or those taking medications that may interact with COCs such as hepatic inducers that include St. John's wort and bosentan (Table 47-5).[85,86]

PATIENT INSTRUCTIONS FOR THE PROGESTIN-ONLY PILL

CASE 47-3, QUESTION 4: What instructions should P.K. receive regarding the use of a POP?

P.K. may begin taking the minipill or drospirenone on the first day of her menses.[2] Because she is breast-feeding and recently postpartum, she is less likely to have a menses. She could begin taking norethindrone immediately postpartum if she were not breast-feeding. Because she is breast-feeding, it is recommended that she wait until lactogenesis occurs about 48 to 72 hours postpartum.[24] Drospirenone does not enter breast milk and is not thought to affect lactation. It does carry a risk of thromboembolism, and, therefore, it may be best to wait 4 to 6 weeks postpartum based on the patient's VTE risk factors.[84] If at 6 weeks' postpartum, P.K. started a POP on the first day of her menses, a backup contraception is not needed with the day 1 start. Alternatively, P.K. can use the quick start method, starting any day of her cycle and using a backup method for 48 hours with norethindrone and 7 days with drospirenone.[2,84]

P.K. should be instructed to take the POP at the exact same time each day. If she is more than 3 hours late taking a norethindrone tablet, she should take the tablet as soon as she remembers and should use backup contraception for 48 hours.[85] This is quite different from the directions for COCs, so this point should be stressed with patients. If one active drospirenone tablet is missed, another should be taken as soon as possible, and she should finish the pill pack. If two active tablets are missed, she should take the last missed tablet as soon as possible and continue to take one tablet a day as instructed while using an additional backup method for 7 days.[84]

Injectable Medroxyprogesterone Acetate

Progestin-only contraceptives are available in two different injectable formulations of medroxyprogesterone acetate (MPA). Depo-Provera®

(Pharmacia & Upjohn Co., Pfizer Inc, New York, NY) is given as a 150-mg IM injection in the deltoid or gluteus maximus every 11 to 13 weeks.[2,87] More recently, Depo-subQ provera 104® (Pharmacia & Upjohn Co., Pfizer Inc, New York, NY) was approved. This product also contains MPA; however, it is given subcutaneously as a 104-mg dose every 12 to 14 weeks.[87] Package inserts instruct the patient to begin the injectable MPA methods in the first 5 days of her menses and then no backup is required; however, P.K. may also begin any other time and use backup for 1 week.[2,87]

CASE 47-3, QUESTION 5: P.K. decided to receive injectable MPA. She is now lactating and returns to the gynecology clinic for her second IM injection of MPA. She was given her first injection 3 months ago, immediately postpartum. She is experiencing prolonged intermenstrual bleeding and a 3- to 5-pound (1.36- to 2.27-kg) weight gain. Is this to be expected? What are the advantages and disadvantages of injectable MPA? How are the side effects managed?

ADVANTAGES

Injectable MPA is a reasonable contraceptive choice for P.K. because she is breast-feeding and indicated that she needed a long-term contraceptive. Among its benefits are a low failure rate of 0.3% to 4% (see Table 47-1), ease of use, lack of estrogenic side effects, decreased dysmenorrhea and monthly blood loss, and a reduced risk of endometrial cancer.[2,24] Other noncontraceptive benefits may include a reduction in seizure frequency in patients with epilepsy and a possible reduction in ovarian cancer.[3,24] Furthermore, contraceptive effectiveness is not reduced by the concurrent use of anticonvulsants or certain antibacterials as seen with COCs.[5,6] Depo-subQ provera 104® is also indicated for pain caused by endometriosis.[88]

DISADVANTAGES

Patients with breast cancer should not use injectable MPA owing to concerns that breast cancers are hormonally sensitive and the prognosis may worsen for some females.[5,6] Injectable MPA should be used with caution in females with unexplained vaginal bleeding

(MPA may cause irregular bleeding and may mask conditions resulting in vaginal bleeding such as cervical or uterine cancer), multiple risk factors for cardiovascular diseases, ischemic heart disease or multiple risk factors for cerebrovascular disease, or a current VTE or PE (for medical eligibility, see https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm?s_cid=rr6503a1_w).[6] Because clotting factors have not been shown to be clinically affected by injectable MPA, some experts disagree with the manufacturer's labeling for the injectable MPA products, which lists a history of prior thromboembolism as a contraindication.[4–6,87,88] Some clinicians also begin injectable MPA immediately postpartum rather than waiting 6 weeks postpartum, as directed by the package insert.[6]

Estrogen production declines in females using injectable MPA, so P.K. should be told that injectable MPA may decrease bone mineral density (BMD).[87] Loss of BMD may be of particular concern in adolescent patients. Numerous studies have found that females receiving injectable MPA have lower BMD compared with nonusers.[89] Although there have been reports of stress fractures in injectable MPA users, no studies to date have documented an increased rate of hip or vertebral fractures in injectable MPA users.[90] Also, BMD has been shown to recover after discontinuation of the injections.[3] The manufacturer of both products recommends that patients do not use injectable MPA >2 years unless they are unwilling or unable to use other methods.[87]

P.K. must understand that injectable MPA frequently causes irregular bleeding or spotting during the first few months or more of use because estrogen is insufficient to maintain the endometrium. After 1 and 2 years of Depo-Provera® use, 55% and 68% of females experience amenorrhea, respectively.[87] With Depo-subQ provera 104®, 56.5% of patients experienced amenorrhea after 1 year.[88] In addition, during the postpartum period, irregular bleeding may occur as well. Although not harmful, amenorrhea leads to discontinuation of injectable MPA in 13% of patients.[87] All patients beginning injectable MPA should be informed that during the first year of use they might have menstrual changes. If unusually heavy or

continuous bleeding occurs, P.K. should be evaluated. P.K. should be counseled and reassured that her intermenstrual bleeding probably will resolve in the next few months. If the bleeding is bothersome, a 4- to 21-day course of oral estrogen (eg, conjugated estrogen 0.625–2.5 mg/day) or a COC with 20 µg of EE will minimize or eliminate the bleeding.[7] However, the bleeding may recur after discontinuation of the estrogen. Low-dose estrogen may be continued if bleeding recurs.

Weight gain is another concern with injectable MPA. The mean weight gain after 1 year of therapy with injectable MPA was about 5 pounds (2.27 kg) in two-thirds of users.[87] Depo-Provera® users typically gain a total of about 8 pounds (3.63 kg) in 2 years, nearly 14 pounds (6.35 kg) in 4 years, and 16.5 pounds (7.48 kg) in 6 years. Depo-subQ provera® users gain a little less weight, 3.5 pounds (1.58 kg) in the first year of use and 7.5 pounds (3.40 kg) after 2 years.[88] Other side effects include mood changes, hair loss, and headaches. P.K. should be counseled on the weight gain associated with injectable MPA. P.K. has already reported an increase in weight since she gave birth 3 months ago, which may be caused by injectable MPA, or possibly her weight is fluctuating because of her recent delivery.

The long return to fertility time is another disadvantage of injectable MPA. After the last injection of 150 mg of MPA, median time to conception has been reported to be by 9 to 10 months, which has been reported similarly for the 104-mg dose.[2,88] It is recommended to discontinue MPA about 12 to 18 months before the desire of pregnancy. Because P.K. is 35 years old, she should be counseled on the return to fertility time with injectable MPA use in case she desired to have children in the near future. She has indicated that she is not interested in having any more children; however, the long return to fertility time with injectable MPA should be explained to all females, especially those older than age 35 years.

Subdermal Implant

Case 47-3, Question 6: P.K. returns to the clinic 7 months postpartum for her third MPA injection. She started menstruating today after missing two appointments; she is now 1 month late for her MPA dose. She states that her busy family life and work schedule make it difficult to attend appointments. She also does not like the weight gain and the prolonged intermenstrual bleeding that has occurred during the past few months. She read that an implant is available, and she would like to know whether this might be a better option for her. What information should you give P.K.?

The contraceptive implant (Nexplanon®) contains 68 mg of etonogestrel in a single, thin, radiopaque, rod.[91] The rod is inserted subdermally in the upper inner arm using a needle and a local anesthetic. Once inserted, the implant is effective for up to 3 years. Nexplanon® (Organon Global Inc., Jersey City, NJ) should be inserted during the first 5 days of menses, and no backup contraception is required. A small incision is required to remove the implant. The etonogestrel implant has the same mechanism of action as injectable MPA. The radiopaque property of Nexplanon® is preferred for ease of removal.

ADVANTAGES

The contraceptive implant is a relatively newer product, so information on its protection against cancers or effects on other diseases such as cardiovascular disease is limited. Females using the implant reported amenorrhea, decreased menstrual cramping, and less anemia than did nonusers.[2] Also, decreases in BMD have not been shown with this product. Fertility returns quickly after the removal of the implant, and this will be a benefit to P.K. if she decides to have another child, given her age.

DISADVANTAGES

As with the injectables, irregular bleeding is likely and is the most common cause of discontinuation. Side effects reported with the implant are headaches, mood changes, and acne. Nexplanon® is not recommended for patients on medications that induce hepatic enzymes (eg, anticonvulsants) because they may decrease

contraceptive efficacy. Weight gain is also common, with users gaining 2.8 pounds (1.27 kg) after 1 year and 3.7 pounds (1.68 kg) after 2 years.[91] So P.K. may still experience weight gain with this product. The implant is not recommended for patients with a current VTE; however, it may be used in patients with a personal or family history of VTE.[5,6] The effectiveness of the implant has not been that well studied in females who are 130% of their ideal body weight, which could be an issue for overweight or obese females.[91]

INTRAUTERINE DEVICE AND INTRAUTERINE SYSTEM

Case 47-3, Question 7: P.K. is concerned about weight gain and is not interested in a subdermal implant. What other long-term, reversible contraceptive methods might work for her? Is P.K. a candidate for an intrauterine device (IUD) or IUS, and, if so, what information would you provide her?

Background and Mechanism of Action

Despite concerns (increased risk of pelvic inflammatory disease [PID], tubal scarring, and infertility) with early IUDs, also known as intrauterine contraceptives (IUCs), the current devices offer a safe and effective method of contraception.[2] Currently, there are four products on the market that include the ParaGard T 380A® (copper) IUD (CooperSurgical, Trumbull, CT) and the Mirena® (Bayer Healthcare Pharmaceuticals Inc., Whippany, NJ), Skyla® (Bayer Healthcare Pharmaceuticals Inc., Whippany, NJ), Kyleena® (Bayer Healthcare Pharmaceuticals Inc., Whippany, NJ), and Liletta® (Odyssea Pharma, SPRL, Belgium, distributed by Allergan USA, Inc., Irvine, CA) (levonorgestrel) IUSs. Although the IUDs and IUSs available today are a safe and effective method of contraception, they are still not as popular in the United States (1%–6% of females

are users) as they are worldwide (12% of married females of reproductive age are users).[92,93]

The copper IUD has a polyethylene body that is wound with copper wire. Once inserted, the copper IUD may be left in place for 10 years.[94] The Mirena®, Skyla®, Kyleena®, and Liletta® IUSs also have polyethylene bodies, with levonorgestrel reservoirs in the vertical stem of the T that provide levonorgestrel daily. Mirena® is effective in preventing pregnancy for up to 7 years and helps with heavy periods for up to 5 years. Kyleena® is effective for 5 years, whereas Liletta® is effective for 6 years. Mirena® and Kyleena® provide 20 and 17.5 µg of levonorgestrel daily, respectively.[95,96] Liletta® provides 20 µg of levonorgestrel daily and progressively declines to about 8.6 µg/day after 6 years.[97] Skyla® is slightly smaller in size and provides 14 µg of levonorgestrel daily after 24 days and is effective for up to 3 years.[98]

Failure rate of the copper IUD is 0.6% to 0.8% for the first year compared with 0.1% to 0.4% for the levonorgestrel IUS (Table 47-1). Both IUDs and IUSs are inserted by a health care provider in the office. The procedure usually takes only a few minutes and does not require sedation. Many providers will recommend that patients take a dose of an NSAID before the insertion visit.

Possible mechanisms of action for copper IUDs include prevention of fertilization and implantation and the copper interfering with sperm transport, viability, or number.[94] The levonorgestrel IUS is believed to work by thickening the cervical mucus, preventing sperm from entering the uterus, altering the endometrial lining, preventing ovulation, and altering sperm activity.[92]

Advantages

Both the copper IUD and the levonorgestrel IUS are very effective, reversible, long-term methods that are easy to comply with.[2] The copper IUD is a particularly beneficial option for females who desire a nonhormonal method of contraception. The levonorgestrel IUS has

the advantages of reducing menstrual bleeding and cramping as a result of the progestin.

Although the initial cost of inserting an IUD or IUS is high (around $500 for the device plus insertion costs), there are no ongoing monthly costs to P.K. as there are with other methods. Therefore, the IUD or IUS becomes more cost-effective when used for >1 year.

Disadvantages

Menstrual changes are the most common side effect of IUDs and IUSs.[2] Copper IUD users are more likely to have heavier menstrual bleeding and cramping. Levonorgestrel users should expect to have irregular bleeding and spotting during the first 3 months after insertion. After 3 months, however, levonorgestrel IUS users report lighter menses and reduced cramping.

Both IUDs and IUSs are contraindicated in females with certain anatomic abnormalities of the uterus (eg, distortion of the uterus, cervical stenosis, or cervical lacerations), unexplained vaginal bleeding, cervical cancer, and PID or other active genital infections. They should be used with caution in females who are immunosuppressed (for medical eligibility, see https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm?s_cid=rr6503a1_w) and may be used in females at high risk for human immunodeficiency virus (HIV) (https://www.cdc.gov/mmwr/volumes/69/wr/mm6914a3.htm?s_cid=mm6914a3_w#T1_down).[6,98] The levonorgestrel IUSs should be used with caution in females with a current VTE or PE. Although the serum levels of levonorgestrel are low, the manufacturers currently do not recommend that females with active or past breast cancer use the device.

It has been reported that the greatest risk of PID occurs shortly after insertion; however, more recent studies also show that there is a low risk of getting PID and no risk at initial insertion.[2,99,100] To aid in infection prevention, all patients should be tested for gonorrhea and chlamydia before IUD or IUS insertion and evaluated for risk factors

of contracting sexually transmitted infections (STIs; eg, multiple partners, unprotected intercourse). Females whose test results are positive for an STI should consider an alternative form of contraception until the infection has resolved. Alternatively, once treatment is provided, an IUD or IUS may be initiated and the patient counseled on ways to prevent STIs.[5,6]

If an IUD or IUS user becomes pregnant, the likelihood that the pregnancy is ectopic is higher (ie, the ratio of ectopic to uterine pregnancies is higher in IUD or IUS users).[94,95] Common problems with IUD use include excessive uterine bleeding, spotting, or pain. The device may be removed as a result of these issues. Spontaneous expulsion of the copper IUD occurs in about 3% to 10% and 3% to 6% of females within the first year with the IUS.[2] Rarely, an IUD or IUS may become embedded in the endometrium or partially or totally perforate the uterine wall. P.K. should be instructed to look for the warning signs of a possible complication with IUD or IUS use, such as abdominal pain or abnormal vaginal discharge.

OTHER NONHORMONAL CONTRACEPTION

CASE 47-4

QUESTION 1: C.J. is a 22-year-old HIV-positive female presenting to the clinic for routine checkup and DMPA injection. She is currently using DMPA IM injection every 12 weeks and taking Atripla™ (efavirenz 600 mg/tenofovir 300 mg/emtricitabine 200 mg) 1 tablet PO daily.

Vitals today: height, 66 inches (167.64 cm); weight, 116 pounds (52.62 kg)
Blood pressure, 124/81 mm Hg
Heart rate, 89 beats/minute
Respiratory rate, 12 breaths/minute
Temperature, 96.8 °F (36 °C)
Laboratory test results: CD4, 581
HIV-1 RNA, <75 copies/mL (undetectable)

C.J. wants to make sure she does not get pregnant and is recommended to use a barrier method in addition to DMPA. C.J. mentions that she is concerned about STIs and, more specifically, transmission of HIV.

What barrier methods are available, and which one is best to recommend for C.J.?

Diaphragm and Cervical Cap

The diaphragm is a soft latex or silicone rubber cap with a metal spring reinforcing the rim.[2] The device is inserted vaginally and placed over the cervical os to mechanically block access of sperm to the cervix. The diaphragm is held in place by the spring tension of the rim, vaginal muscle tone, and the pubic bone.

A cervical cap marketed as FemCap™ (FemCap Inc., Del Mar, CA) is made of silicone.[101] The FemCap™ is kept in place by suction formed between the cervix and the device. Because all of these devices do not fit tightly enough to be a complete barrier to sperm, spermicidal gel must be applied to each device before it is inserted.

The first-year failure rate with diaphragms is 16% to 17% (Table 47-1).[2] C.J. should be counseled that diaphragms are less effective than are other available methods. Because breast-feeding offers some protection against pregnancy, breast-feeding females may be the best candidates for the diaphragm. Failure rates of cervical caps range about 14% in nulliparous females and 29% in parous females.[2]

TYPES AND FITTING

Diaphragms must be properly fitted to be effective. They are available in different sizes (50–95 mm in diameter) and different styles of construction of the circular rim. The goal of fitting a diaphragm is to select the largest rim size that is comfortable for the patient.[2] A diaphragm that is too small may become dislodged during intercourse because vaginal depth increases during sexual arousal. Conversely, a diaphragm that is too large may cause vaginal pressure, abdominal pain or cramping, vaginal ulceration, or recurrent urinary tract infections. Proper size is estimated during

bimanual examination, and several diaphragm sizes may need to be tried by the health care provider to find the right size for the patient. Caya® (HPSRx Enterprises, Salem, VA) is a marketed diaphragm that is contoured with one size and made of silicone and nylon spring that allows it to be used with varying vaginal and cervical sizes (see https://www.caya.us.com/).[2,102] Contraindications for use include <6 weeks postpartum, if a diaphragm sized <60 mm or >85 mm was previously used, or the patient has severe pelvic floor or uterine prolapse; it should also not be used with a silicone-based lubricant.[102] If C.J. gains or loses 10 (4.54) to 20 pounds (9.07 kg), has a pregnancy, or has abdominal or pelvic surgery, depending on the diaphragm used, it may need to be refitted.

The FemCap™ is shaped like a sailor's hat[102] (see http://www.femcap.com/). It is available in three sizes, and size selection depends on the patient's pregnancy history; the 22-mm FemCap™ is for patients who have never been pregnant, the 26-mm one is for females who have miscarried or had a cesarean section, and the 30-mm size is for females who have vaginally delivered a full-term infant.

C.J. would likely be able to tolerate the diaphragm or cervical cap. Fitting will depend on the device that she selects. These barrier methods, however, do not protect against STIs, which is important to C.J. when selecting her barrier method, and therefore, are not the best choice.

PATIENT INSTRUCTIONS, ADVANTAGES, AND DISADVANTAGES

The diaphragm and cervical cap offer pregnancy prevention without the use of hormones, and females only need to use the devices when they are sexually active.[2,101] All of these devices are available only by prescription, should not be used during menstruation, may be difficult to insert and remove for some patients, and are not as effective as the hormonal methods or IUD. All devices should be inspected for holes or puckering (small areas of wrinkle) before use.

The diaphragm should not remain in the vagina for >24 hours.[4,102] Toxic shock syndrome (TSS) has been associated with diaphragm use, and females should be alert to its symptoms, which include fever, diarrhea, vomiting, muscle aches, and a sunburn-like rash. Allergic reactions to the latex or spermicides also have been reported.

The diaphragm should always be inserted before intercourse; it can be inserted as long as 6 hours before intercourse, if desired.[2] The diaphragm should not be removed for at least 6 hours after intercourse. One teaspoon of spermicidal gel should be placed into the dome of the diaphragm before insertion or the Caya contraceptive gel® if using Caya®.[102] If intercourse is repeated, a new application of spermicide should be inserted vaginally without removal of the diaphragm.

To use the FemCap™, first apply about one-fourth teaspoon of spermicide inside the bowl and one-half teaspoon on the other side that will face the vagina (between the brim and the dome).[101] Insert the FemCap™ with the long brim side first and the dome side up. Push until the cap is in contact with the cervix. More spermicide should be applied if intercourse is repeated. The FemCap™ should be inserted at least 15 minutes before sexual arousal and can be left in for up to 48 hours. The FemCap™ must be left in place for a minimum of 6 hours after intercourse.

Both devices should be washed with mild soap and water, rinsed and dried, and stored in the accompanying container. Oil-based products also may decompose the latex of a diaphragm and should not be used. These devices should be replaced every year or sooner if there are signs of wear or holes.

Vaginal Sponge

The vaginal sponge is another barrier method. The sponge contains a polyurethane foam and 1 g of nonoxynol-9 (spermicide). The sponge is inserted into the vagina and placed against the cervix. It may be worn up to 24 hours. After intercourse, the sponge should

remain in place for 6 hours. The sponge works in three ways: It acts as a spermicide, is a mechanical barrier, and absorbs semen. The failure rate reported is 14% for nulliparous females and 27% for parous females (see Table 47-1).[2] Irritation or ulceration of the cervix and vaginal mucosa may occur. If the sponge is not removed within 24 hours or if particles remain after removal, TSS could be an issue. Because the sponge may cause irritation and does not provide protection against STIs, it may not be best for C.J.

Male Condoms

Male condoms are an effective method of contraception when used properly. The failure rate with condoms is 2% to 13% (see Table 47-1).[2] Many different brands of condoms are available in the United States. The brands differ in size, shape, color, material, and the presence or absence of lubricants or spermicide. The chief noncontraceptive benefit of latex condoms is the prevention of STIs (including gonorrhea, chlamydia, and HIV), and they can be used for vaginal, anal, or oral sex.[5] Condoms are readily available without a prescription and do not cause systemic side effects such as the hormonal methods. However, some report that condoms reduce sensitivity and spontaneity. The most commonly used and least expensive male condom is made of latex.[2] Male condoms made of polyurethane and lambskin are recommended for males or females allergic to latex. Polyurethane condoms are more expensive and sometimes break more easily than do latex condoms, but they also conduct heat better than do latex condoms.[103] Lambskin condoms also conduct heat well, but do not offer the same protection against STIs as latex and polyurethane. Lambskin condoms are not recommended for those who are concerned about STIs.[103]

Because the pre-ejaculatory secretions may contain sperm, the male condom should be applied before vaginal contact.[2] When using a male condom, the male or his partner should hold the tip of the condom and unroll it down to the base of the erect penis.[5,103] Most practitioners recommend lubricated condoms with reservoir ends to

prevent breakage and collect the ejaculate. Oil-based lubricants can degrade male latex condoms and should be avoided. Oil-based lubricants, however, may be used with polyurethane or lambskin condoms. Condoms should be used only once by their expiration date and stored in a cool, dry place, away from prolonged periods of heat or light.

Latex condoms would be best for C.J. and her partner to prevent the transmission of STIs.

Female Condoms

The female condom is less effective, with a 21% failure rate (Table 47-1)[2] (see http://www.fc2.us.com/).[104] The FC2™ (FC2, Miami, FL) is made of a nitrile sheath or pouch and polyurethane ring at the closed end of the pouch. It consists of a smaller, circular, inner ring (which secures the device around the cervix like a diaphragm) and a larger ring around the opening of the condom.

The inner ring should be compressed and inserted vaginally as far as it will go, and the larger ring remains outside of the vagina, protecting the external genitalia. Female condoms should also be inserted before sexual contact; they may be inserted up to 8 hours before intercourse. The FC2™ contains a silicone-based lubricant inside of the condom but additional lubricant may be used. Oil-based or water-based lubricants can be used with both female condoms. Just like male condoms, they should be used by their expiration date, not reused, and stored in a cool, dry place, away from heat or light.

Disadvantages of female condoms include cost, squeaking noise during use, and insertion difficulty.[2] Condoms may also break, although this is less likely with the female condom. Male and female condoms should not be used together because this may increase the risk of breakage.

An advantage for C.J. to use the female condom is that she has control of her own protection and does not need to rely on her

partner to make sure they are both protected. The female condom is a good alternative for C.J.

Vaginal Spermicides

Case 47-4, Question 2: C.J. would like to use a spermicide along with condoms. What options does she have and how effective are spermicides when used alone? What dosage form should C.J. use? How should she be instructed to use a vaginal spermicide? What side effects can be anticipated?

Vaginal spermicides currently are available as gels (jellies), suppositories, foams, and films.[2,103] Most of these products use a nonionic surfactant, nonoxynol-9, as the spermicide. First-year failure rates with these dosage forms range from 18% to 29% (Table 47-1). Most vaginal spermicides are available over the counter (OTC), a new prescription vaginal gel is available, Phexxi®. It does not contain nonoxynol-9 and instead is lactic acid 1.8%, citric acid 1%, and potassium bitartrate 0.4%.[105]

The different characteristics of the products can help guide C.J. when selecting a dosage form. Regardless of the dosage form, a new dose of spermicide should be applied before each act of intercourse.

Spermicides may cause genital irritation and, in some patients, lead to ulceration. Likely for this reason, spermicides have been shown to increase the transmission of STIs, including HIV, gonorrhea, and chlamydia. Cystitis and pyelonephritis have been reported with Phexxi®, and use in females with a history of recurrent urinary tract infection (UTI) or urinary tract abnormalities should be avoided.[105] Spermicides may not be the best choice for C.J. and her partner to prevent the risk of STI transmission.

EMERGENCY CONTRACEPTION

Case 47-4, Question 3: C.J. presents to a pharmacy 4 months later and says she missed her MPA injection last month. She had intercourse 4 nights ago using a condom and is worried she might become pregnant. She wants to know whether she should use the "morning-after pill." What do you tell C.J. about EC options? Is C.J. a candidate for EC?

EC, also referred to as the morning-after pill, is postcoital contraception useful for females who did not use a contraceptive (eg, forgot, were assaulted) or whose method failed (eg, broken condom, missed pill). EC is available in a few methods, which include oral pills or an IUD.

Emergency Contraceptive Pills

Emergency contraceptive pills (ECPs) are available in a variety of formulations known as *progestin-only*, *Yuzpe*, and *selective progesterone receptor modulators (SPRMs)*.

Currently, the one-dose progestin-only (levonorgestrel 1.5 mg) ECPs are available OTC to all ages.[106] The one tablet should be taken within 72 hours of unprotected intercourse, according to the package labeling. Studies, however, have shown that progestin-only ECPs are still effective if taken up to 120 hours (5 days) after unprotected sex.[107,108] Progestin-only ECPs reduce the risk of pregnancy by a few potential mechanisms: preventing ovulation, preventing fertilization, or preventing implantation.[2] They reduce the average risk of pregnancy by 89% after a single act of intercourse when taken within 72 hours. ECPs are most effective when taken as soon as possible after intercourse; therefore, treatment should not be delayed. Progestin-only ECPs may not be as effective in females with a BMI of ≥26 and should be recommended to use an alternative ECP, but treatment should not be denied due to BMI.[106] The most common side effects with ECPs are nausea and vomiting.[2] C.J. should be instructed that if she vomits within 1 hour of taking ECPs, the dose should be repeated. C.J.'s menses may come early or late, but she should take a pregnancy test if her menses does not come

within 3 weeks of taking ECPs. This may further be complicated if C.J. gets her next scheduled dose of injectable MPA.

As an alternative to progestin-only ECPs, regular COCs may be used as long as they contain levonorgestrel or norgestrel as the progestin. This is known as the Yuzpe method, which consists of high-dose progestin and high-dose estrogen. There are no marketed formulations of this method. Depending on the brand of COCs used, a differing number of pills are taken within 120 hours of unprotected intercourse as two separate doses 12 hours apart (see Table 47-1 footnote).[2] Compared with progestin-only ECPs, the Yuzpe method is associated with higher incidence of nausea and vomiting, and patients may wish to take an antiemetic before each dose.[107] Because progestin-only ECPs are widely available, easy to use, and more effective and have limited side effects, COCs are being used less often for EC.

Ulipristal acetate (ella®) is classified as an oral SPRM.[109] The 30-mg oral tablet should be taken within 120 hours of unprotected intercourse.[109] It is available by prescription only. Its mechanism of action is somewhat different from that of progestin-only ECPs. It has progesterone receptor antagonist and agonist effects; however, its main mechanism is through receptor antagonism at the uterus, cervix, hypothalamus, and ovaries, thus preventing ovulation even after the LH surge, which progestin-only ECPs may not do.[109] The only other SPRM on the market is mifepristone (RU-486), known for medical abortion use. Concerns were raised about the mechanism of ulipristal disrupting an existing pregnancy and leading to abortion. Current pregnancy exposure data do not suggest an increase in miscarriage. Ulipristal has not been shown to be as effective in females with a BMI of >30 and may be ineffective in females with a BMI of ≥35, but treatment should not be denied because of BMI.[106,109] It is recommended that those females use an alternative emergency contraceptive method.[106,109] Headache, dysmenorrhea, nausea, and abdominal pain were the most reported side effects in clinical trials.[109] If vomiting occurs within 3 hours of taking the dose, a repeat dose is recommended.[109]

In C.J.'s case, progestin-only ECPs are the better choice because she is taking medications that interact with COCs. She is within the window of 120 hours postcoitus, making OTC progestin-only ECPs an option. Ulipristal is another option and labeled for use 120 hours postcoitus, but would require a prescription and may delay C.J. from receiving timely EC.

Intrauterine Devices for Emergency Contraception

The copper-T IUD is also an effective method of EC when inserted within 5 days of unprotected sex.[2,107] There is no evidence that the progestin IUD is effective. An IUD must be inserted by a health care provider and as such may not be used regularly for EC. The biggest advantage of using an IUD for EC is that it provides continued contraception for the patient. In addition, it is effective in females regardless of their BMI. An IUD may be an option for C.J. if she would like to switch from MPA to an IUD. Updated CDC recommendations state there is no restriction for IUD use in HIV-positive females.[110] Having to see a provider for an IUD, however, is less convenient and makes ECPs the better choice for accessibility and timing.

MEDICAL ABORTION

Case 47-4, Question 4: C.J. presents to the clinic 4 weeks later stating that she missed her period and is concerned she may be pregnant. Her human chorionic gonadotropin test result is positive, confirming pregnancy. C.J. considers terminating the pregnancy, stating she is not ready to have a child and is concerned about the antiretroviral medication effects on the baby. What options are there for medical abortion?

It is estimated that about one-half of pregnancies are unintended, so it is important for these females to have safe options.[1] C.J. should

be counseled extensively about her options, including keeping the baby, adoption, and medical or surgical abortion. Compared with surgical abortion, medical abortion does not require a surgical procedure, so it is less likely to cause infection and is less costly.[2] Thus, some females feel more in control when choosing this option. However, some patients may not prefer medical abortion because it usually requires more medical visits and follow-up, has a slightly lower success rate (94%–97%; failures will need a surgical procedure), and involves more bleeding and cramping that usually lasts for 2 weeks.

There are many variations in how medical abortions are carried out, but the general treatment remains the same.[2] C.J. would first obtain baseline laboratory tests, including blood type and hemoglobin. She would be given either methotrexate, mifepristone, or both the same day to stop development of the pregnancy. In the United States mifepristone, a progesterone receptor blocker, is more commonly used. Misoprostol is given to induce uterine contractions and expel the pregnancy and can be administered alone or in combination with other medications.

An example regimen for a gestational age of ≤70 days (WHO also states <12 weeks), C.J. would be given mifepristone 200 mg orally on day 1, then a total of misoprostol 800 µg vaginally (6–48 hours after the mifepristone dose), buccally or sublingually (24–48 hours after the mifepristone dose).[2,111] For misoprostol-only regimens, a dose of 800 µg sublingually every 3 hours for two to three doses or every 3 to 12 hours vaginally or buccally for two to three doses.[2] Vaginal administration is considered most effective.[111] The WHO also lists a dose of misoprostol 400 µg instead of 800 µg for the misoprostol-only regimen.[111]

If using methotrexate, 50 mg/m^2 is given IM on day 1 followed by misoprostol 800 µg vaginally 3 to 7 days later.[2] Side effects may include nausea, vomiting, diarrhea, cramping, and vaginal bleeding (heavier than a menses). A repeat dose of misoprostol may be given if bleeding does not occur in 24 hours or abortion has not occurred by follow-up visit in 7 days. With either method, patients should follow up with their health care provider on about day 15 to make

sure the abortion is complete. If complete miscarriage has not occurred, another method may be used, such as aspiration, to remove all pregnancy tissues.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

ACOG Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. *Obstet Gynecol.* 2010;115:206–218. (69)

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 152: emergency contraception. *Obstet Gynecol.* 2015;126(3): e1–e11. (107)

ACOG Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin No. 206: use of hormonal contraception in women with coexisting medical conditions [published corrections appeared in *Obstet Gynecol*. 2019;133(6):1288]. *Obstet Gynecol.* 2019;133(2):e128–e150. (24)

Dickey RP. *Managing Contraceptive Pill Patients*. 15th ed. Essential Medical Information Systems; 2014. (38)

Hatcher RA. *Contraceptive Technology*. 21st ed. Ayers Publishing Company; 2018. (2)

Hatcher RA, Zieman M, Lathrop E, Haddad L, Allen AZ. *Managing Contraception for Your Pocket 2019–2020*. Bridging the Gap Foundation; 2019. (4)

Key Websites

Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep*. 2016;65(No. RR-3):1–104. Accessed September 19, 2020. https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm?s_cid=rr6503a1_w (6)

Guttmacher Institute. Facts on contraceptive use in the United States. Published April 2020. Accessed October 7, 2020. https://www.guttmacher.org/fact-

sheet/contraceptive-use-united-states (92)
International Consortium for Emergency Contraception. http://www.cecinfo.org/
Planned Parenthood Federation of America. http://www.plannedparenthood.org/

COMPLETE REFERENCES CHAPTER 47 CONTRACEPTION

1. Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008–2011. *N Engl J Med*. 2016;374(9):843–852. doi:10.1056/NEJMsa1506575
2. Hatcher RA. *Contraceptive Technology*. 21st ed. Ayers Publishing Company; 2018.
3. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and The Practice Committee of the American Society for Reproductive Medicine. Female age-related fertility decline. *Fertil Steril*. 2014;101:633–634.
4. Hatcher RA, Zieman M, Lathrop E, Haddad L, Allen AZ. *Managing Contraception for Your Pocket 2019–2020*. Bridging the Gap Foundation; 2019.
5. A WHO Family Planning Cornerstone. *Medical Eligibility Criteria for Contraceptive Use*. 5th ed. World Health Organization; 2015. Accessed September 19, 2020. http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/
6. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep*. 2016;65(No. RR-3):1–104. Accessed September 19, 2020. https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm?s_cid=rr6503a1_w
7. Baillargeon JP, McClish DK, Essah PA, Nestler JE. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab*. 2005;90(7):3863–3870.
8. Tanis BC, van den Bosch MAAJ, Kemmeren JM, et al. Oral contraceptives and the risk of myocardial infarction. *N Engl J Med*. 2001;345(25):1787–1793.
9. Khader YS, Rice J, John L, Abueita O. Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. *Contraception*. 2003;68(1):11–17.
10. Schwingl PJ, Ory HW, Visness CM. Estimates of the risk of cardiovascular death attributable to low-dose oral contraceptives in the United States. *Am J Obstet Gynecol*. 1999;180(1, pt 1):241–249.

11. Endrikat J, Klipping C, Cronin M, et al. An open label, comparative study of the effects of a dose-reduced oral contraceptive containing 20 microg ethinyl estradiol and 100 microg levonorgestrel on hemostatic, lipids, and carbohydrate metabolism variables. *Contraception*. 2002;65(3):215–221.
12. Merki-Feld GS, Rosselli M, Dubey RK, Jäger AW, Keller PJ. Long-term effects of combined oral contraceptives on markers of endothelial function and lipids in healthy premenopausal women. *Contraception*. 2002;65(3):231–236.
13. Knopp RH, Broyles FE, Cheung M, Moore K, Marcovina S, Chandler WL. Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception*. 2001;63(1):1–11.
14. ESHRE Capri Workshop Group. Hormones and cardiovascular health in women. *Hum Reprod Update*. 2006;12(5):483–497.
15. Dunn N, Thorogood M, Faragher B, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. *BMJ*. 1999;318(7198):1579–1583.
16. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA*. 2000;284(1):72–78.
17. Curtis KM, Mohllajee AP, Peterson HB. Use of combined oral contraceptives among women with migraine and nonmigrainous headaches: a systematic review. *Contraception*. 2006;73(2):189–194.
18. Champaloux SW, Tepper NK, Monsour M, et al. Use of combined hormonal contraceptives among women with migraines and risk of ischemic stroke. *Am J Obstet Gynecol*. 2017;216(5):489.e1–489.e7. doi:10.1016/j.ajog.2016.12.019
19. Harris M, Kaneshiro B. An evidence-based approach to hormonal contraception and headaches. *Contraception*. 2009;80(5):417–421.
20. Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. *Arch Intern Med*. 2004;164(18):1965–1976.
21. Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. *Int J Gynaecol Obstet*. 2018;141(3):287–294. doi:10.1002/ijgo.12455
22. Mohllajee AP, Curtis KM, Martins SL, Peterson HB. Does use of hormonal contraceptives among women with thrombogenic mutations increase their risk of venous thromboembolism? A systematic review. *Contraception*. 2006;73(2):166–178.
23. U.S. Food & Drug Administration. FDA drug safety communication: updated information about the risk of blood clots in women taking birth control pills containing drospirenone. April 10, 2012. Current content as of February 13, 2018. Accessed September 22, 2020. https://www.fda.gov/drugs/drug-safety-

and-availability/fda-drug-safety-communication-updated-information-about-risk-blood-clots-women-taking-birth-control
24. ACOG Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin No. 206: use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol*. 2019;133(2):e128–e150.
25. Petitti DB. Clinical practice. Combination estrogen progestin oral contraceptives. *N Engl J Med*. 2003;349(15):1443–1450.
26. Paulus D, Saint-Remy A, Jeanjean M. Oral contraception and cardiovascular risk factors during adolescence. *Contraception*. 2000;62(3):113–116.
27. Fisch IR, Frank J. Oral contraceptives and blood pressure. *JAMA*. 1977;237(23):2499–2503.
28. Tapla HR, Johnson CE, Strong CG. Effect of oral contraceptive therapy on the renin angiotensin system in normotensive and hypertensive women. *Obstet Gynecol*. 1973;41(5):643–649.
29. Chasan-Taber L, Chasan-Taber L, Willett WC, et al. Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation*. 1996;94(3):483–489.
30. Combined oral contraceptives and liver cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer*. 1989;43(2):254–259.
31. Macdonald GA. Hepatocellular carcinoma. *Curr Opin Gastroenterol*. 1999;15(3):253–259.
32. An N. Oral contraceptives use and liver cancer risk: a dose-response meta-analysis of observational studies. *Medicine (Baltimore)*. 2015;94(43):e1619. doi:10.1097/MD.0000000000001619
33. Lopez LM, Grimes DA, Schulz KF. Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. *Cochrane Database Syst Rev*. 2009;(4):CD006133.
34. Grodstein F, Colditz GA, Hunter DJ, Manson JE, Willett WC, Stampfer MJ. A prospective study of symptomatic gallstones in women: relation with oral contraceptives and other risk factors. *Obstet Gynecol*. 1994;84(2):207–214.
35. Oral contraceptives and gallbladder disease. Royal College of General Practitioners' oral contraception study. *Lancet*. 1982;2(8305):957–959.
36. Wang S, Wang Y, Xu J, Chen Y. Is the oral contraceptive or hormone replacement therapy a risk factor for cholelithiasis: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96(14):e6556. doi:10.1097/MD.0000000000006556
37. Oral Contraceptives and Relative Progestin, Endometrial, and Androgen Activities. Facts and Comparisons eAnswers. Wolters Kluwer NV; 2020
38. Dickey RP. *Managing Contraceptive Pill Patients*. 15th ed. Essential Medical Information Systems; 2014.
39. Natazia. Package insert. Bayer HealthCare Pharmaceuticals; August 2015.

40. Ahrendt HJ, Makalov D, Parke S, Mellinger U, Mansour D. Bleeding pattern and cycle control with an estradiol-based oral contraceptive: a seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel. *Contraception*. 2009;80(5):436–444.
41. Moreau C, Trussell J, Gilbert F, Bajos N, Bouyer J. Oral contraceptive tolerance: does the type of pill matter? *Obstet Gynecol*. 2007;109(6):1277–1285.
42. Lopez LM, Bernholc A, Chen M, et al. Hormonal contraceptives for contraception in overweight or obese women. *Cochrane Database Syst Rev*. 2016;(8):CD008452. doi:10.1002/14651858.CD008452.pub4
43. Dragoman MV, Simmons KB, Paulen ME, Curtis KM. Combined hormonal contraceptive (CHC) use among obese women and contraceptive effectiveness: a systematic review. *Contraception*. 2017;95(2):117–129. doi:10.1016/j.contraception.2016.10.010
44. Simmons KB, Edelman AB. Hormonal contraception and obesity. *Fertil Steril*. 2016;106(6):1282–1288. doi:10.1016/j.fertnstert.2016.07.1094
45. Mishell DR Jr. Rationale for decreasing the number of days of the hormone-free interval with use of low-dose oral contraceptive formulations. *Contraception*. 2005;71(4):304–305.
46. Mircette. Package insert. Teva Pharmaceuticals; August 2017.
47. Amethyst. Package insert. Teva Pharmaceuticals; December 2017.
48. Anderson FD, Hait J, Hsiu J, Thompson-Graves AL, Wilborn WH, Williams RF. Endometrial microstructure after long-term use of a 91-day extended-cycle oral contraceptive regimen. *Contraception*. 2005;71(1):55–59.
49. Westhoff C, Heartwell S, Edwards S, et al. Initiation of oral contraceptives using a quick start compared with a conventional start: a randomized controlled trial. *Obstet Gynecol*. 2007;109(6):1270–1276.
50. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. *MMWR Recomm Rep.* 2016;65(No. RR-4):1–66.
51. Xulane. Package insert. Mylan Pharmaceuticals Inc.; April 2020.
52. Twirla. Package insert. Corium International, Inc.; February 2020.
53. van den Heuvel MW, van Bragt AJM, Mohammed Alnabawy AK, Kaptein MCJ. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception*. 2005;72(3):168–174.
54. Tepper NK, Dragoman MV, Gaffield ME, Curtis KM. Nonoral combined hormonal contraceptives and thromboembolism: a systematic review. *Contraception*. 2017;95(2):130–139. doi:10.1016/j.contraception.2016.10.005
55. NuvaRing. Package insert. Organon; January 2020.
56. Annovera. Package insert. TherapeuticsMD, Inc.; January 2020.

57. O'Connell MB, Smith J, eds. *Women's Health Across the Lifespan: A Pharmacotherapeutic Approach*. McGraw-Hill; 2019.
58. Dickinson BD, Altman RD, Nielsen NH, Sterling ML; The Council on Scientific Affairs, American Medical Association. Council on scientific affairs, American Medical Association. Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol*. 2001;98(5, pt 1):853–860.
59. Sparrow MJ. Pregnancies in reliable pill takers. *N Z Med J*. 1989;102(879):575–577.
60. Helms SE, Bredle DL, Zajic J, Jatjoura D, Brodell RT, Krishnarao I. Oral contraceptive failure rates and oral antibiotics. *J Am Acad Dermatol*. 1997;36(5, pt 1):705–710.
61. Archer JS, Archer DF. Oral contraceptive efficacy and antibiotic interaction: a myth debunked. *J Am Acad Dermatol*. 2002;46(6):917–923.
62. Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between non-rifamycin antibiotics and hormonal contraception: a systematic review. *Am J Obstet Gynecol*. 2018;218(1):88–97.e14. doi:10.1016/j.ajog.2017.07.003
63. Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking anticonvulsant therapy. *Contraception*. 2011;83(1):16–29.
64. Camrese Lo. Package insert. Teva Pharmaceuticals USA Inc.; October 2011.
65. Berry-Bibee EN, Kim MJ, Tepper NK, Riley HE, Curtis KM. Co-administration of St. John's wort and hormonal contraceptives: a systematic review. *Contraception*. 2016;94(6):668–677. doi:10.1016/j.contraception.2016.07.010
66. De Leo V, Musacchio MC, Cappelli V, Piomboni P, Morgante G. Hormonal contraceptives: pharmacology tailored to women's health. *Hum Reprod Update*. 2016;22(5):634–646. doi:10.1093/humupd/dmw016
67. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. *Cochrane Database Syst Rev*. 2012;(7):CD004425. doi:10.1002/14651858.CD004425.pub6
68. Yonkers KA, O'Brien PM, Eriksson E. Premenstrual syndrome. *Lancet*. 2008;371(9619):1200–1210. doi:10.1016/S0140-6736(08)60527-9
69. ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. *Obstet Gynecol*. 2010;115(1):206–218.
70. Schlesselman JJ. Risk of endometrial cancer in relation to use of combined oral contraceptives. A practitioner's guide to meta-analysis. *Hum Reprod*. 1997;12(9):1851–1863.
71. Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers. *JAMA Oncol*. 2018;4(4):516–521. doi:10.1001/jamaoncol.2017.4942
72. Susannel G, Ming EE, Devesa SS, Hartge P, Whittemore AS. Declining ovarian cancer rates in U.S. women in relation to parity and oral

contraceptive use. *Epidemiology*. 2000;11(2):102–105.
73. Siskind V, Green A, Bain C, Purdie D. Beyond ovulation: oral contraceptives and epithelial ovarian cancer. *Epidemiology*. 2000;11(2):106–110.
74. Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. *Cochrane Database Syst Rev*. 2014;(1):CD003987. doi:10.1002/14651858.CD003987.pub5
75. National Cancer Institute Fact Sheet. Probability of breast cancer in American Women. Accessed September 28, 2020. http://www.cancer.gov/cancertopics/factsheet/Detection/probability-breast-cancer
76. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med*. 2017;377(23):2228–2239. doi:10.1056/NEJMoa1700732
77. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. *Am J Obstet Gynecol*. 2017;216(6):580.e1–580.e9. doi:10.1016/j.ajog.2017.02.002
78. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med*. 2002;346(26):2025–2032.
79. Kahlenborn C, Modugno F, Potter DM, Severs WB. Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. *Mayo Clin Proc*. 2006;81(10):1290–1302.
80. Milne RL, Knight JA, John EM, et al. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):350–356.
81. Silvera SA, Miller AB, Rohan TE. Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: prospective cohort study. *Cancer Causes Control*. 2005;16(9):1059–1063.
82. American Cancer Society. Key statistics for cervical cancer. Accessed September 28, 2020. https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html
83. Moreno V, Xavier Bosch F, Nubia Muñoz N, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet*. 2002;359(9312):1085–1092.
84. American Cancer Society. Key statistics for cervical cancer. Accessed July 6, 2022. https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html#:~:text=The%20American%20Cancer%20Society%27s%20estimates,will%20die%20from%20cervical%20cancer
85. Micronor. Package insert. Janssen Ortho, LLC; June 2014.
86. Roby CA, Anderson GD, Kantor E, Dryer DA, Burstein AH. St John's wort: effect of CYP3A4 activity. *Clin Pharmacol Ther*. 2000;67(5):451–457.
87. Depo-Provera. Package insert. Pharmacia & Upjohn; January 2015.

88. Depo-subQ provera. Package insert. Pharmacia & Upjohn; January 2015.
89. Shaarawy M, El-Mallah SY, Seoudi S, Hassan M, Abdel Mohsen I. Effects of the long-term use of depot medroxyprogesterone acetate as hormonal contraceptive on bone mineral density and biochemical markers of bone remodeling. *Contraception*. 2006;74(4):297–302.
90. Erkkola R, Landgren BM. Role of progestins in contraception. *Acta Obstet Gynecol Scand*. 2005;84(3):207–216.
91. Nexplanon. Package insert. Merck &Co.; September 2020.
92. Guttmacher Institute. Facts on contraceptive use in the United States. Published April 2020. Accessed October 7, 2020. https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states
93. Mosher WD, Jones J. Use of contraception in the United States: 1982–2008. *Vital Health Stat 23*. 2010;29:1–44.
94. ParaGard. Package insert. Cooper Surgical Inc.; February 2020.
95. Mirena. Package insert. Bayer HealthCare Pharmaceuticals; August 2021.
96. Kyleena. Package insert. Bayer HealthCare Pharmaceuticals; July 2021.
97. Liletta. Package insert. Allergan; October 2019.
98. Skyla. Package insert. Bayer HealthCare Pharmaceuticals; March 2018.
99. Turok DK, Eisenberg DL, Teal SB, Keder LM, Creinin MD. A prospective assessment of pelvic infection risk following same-day sexually transmitted infection testing and levonorgestrel intrauterine system placement. *Am J Obstet Gynecol*. 2016;215(5):599.e1–599.e6. doi:10.1016/j.ajog.2016.05.017
100. Sufrin CB, Postlethwaite D, Armstrong MA, Merchant M, Wendt JM, Steinauer JE. Neisseria gonorrhea and chlamydia trachomatis screening at intrauterine device insertion and pelvic inflammatory disease. *Obstet Gynecol*. 2012;120(6):1314–1321. doi:10.1097/aog.0b013e318273364c
101. FemCap. Accessed October 3, 2020. https://femcap.com/new/
102. Caya. Accessed October 3, 2020. https://www.caya.us.com/
103. Krinsky DL. *Handbook of Nonprescription Drugs: An Interactive Approach to Self-care*. 19th ed. American Pharmacists Association; 2018.
104. FC2 Female Condom. Accessed October 3, 2020. https://fc2.us.com
105. Phexxi. Package insert. Evofem; May 2010.
106. Trussell J, Raymond EG, Hu H. Emergency contraception: a last chance to prevent unintended pregnancy. Published January 2019. Accessed September 19, 2020. https://www.researchgate.net/publication/242730608
107. American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 152: emergency contraception. *Obstet Gynecol*. 2015;126(3):e1–e11.
108. Rodrigues I, Grou F, Joly J. Effectiveness of emergency contraceptive pills between 72 and 120 hours after unprotected sexual intercourse. *Am J Obstet Gynecol*. 2001;184(4):531–537.
109. Ella. Package insert. Afaxys Inc.; March 2015.

110. Tepper NK, Curtis KM, Cox S, Whiteman MK. Update to U.S. medical eligibility criteria for contraceptive use, 2016: updated recommendations for the use of contraception among women at high risk for HIV infection. *MMWR Morb Mortal Wkly Rep.* 2020;69:405–410. doi:10.15585/mmwr.mm6914a3external icon
111. World Health Organization. *Medical Management of Abortion*. World Health Organization; 2018.

48

Infertility

Erin C. Raney

CORE PRINCIPLES		CHAPTER CASES
1	Infertility is the inability to conceive after 12 months of unprotected intercourse. A major predictor of infertility is the age of the female. Additional risk factors for both males and females include lifestyle factors, such as tobacco use and obesity, as well as primary and secondary causes of hypogonadism.	**Case 48-1 (Questions 1–3, 6) Case 48-2 (Questions 1, 2)**
2	The evaluation of infertility in females incorporates data from physical examination and laboratory assessments of pituitary and ovarian function. In males, the semen analysis and laboratory assessments of hormone levels provide key information related to gonadal function.	**Case 48-1 (Questions 3–6) Case 48-2 (Questions 1, 2), Figure 48-1, Table 48-2**
		Case 48-1 (Questions

3	Unexplained infertility is diagnosed after a thorough evaluation of both male and female reveals no identifiable cause. Treatment is empiric and often combines ovarian stimulation (OS) with intrauterine insemination (IUI) or in vitro fertilization (IVF).	**7–10)**
4	Clomiphene citrate (CC) is a selective estrogen receptor modulator that is considered a first-line agent for OS in patients with unexplained fertility. Aromatase inhibitors are under investigation as alternative oral agents.	**Case 48-1 (Questions 8–10)**
5	IVF is the most commonly used assisted reproductive technology (ART) or procedure that involves manipulation of oocytes and sperm. Medications are used to stimulate multiple follicles for oocyte retrieval and to optimize implantation after embryo transfer.	**Case 48-2 (Questions 3–9), Table 48-4**
6	OS with gonadotropins is accomplished with follicle-stimulating hormone (FSH) either alone or in combination with luteinizing hormone (LH). A gonadotropin-releasing hormone (GnRH) agonist or antagonist is administered to prevent interruption of the cycle by endogenous hormones. Human chorionic gonadotropin (hCG) is injected in a single dose to finalize follicular development for oocyte retrieval.	**Case 48-2 (Questions 4–7), Tables 48-3, 48-5–48-7, Figure 48-3**

7	A rare but serious complication of OS is ovarian hyperstimulation syndrome (OHSS). The risk is minimized by monitoring the development of follicles carefully with sequential transvaginal ultrasounds and serum estradiol levels.	**Case 48-2 (Questions 5, 7)**
8	Multiple gestation pregnancies are associated with maternal and neonatal risks, including preterm birth and extended neonatal intensive care. These risks are considered when determining embryo transfer and cryopreservation plans.	**Case 48-2 (Question 9)**
9	The diagnosis and treatment of infertility affects the couple emotionally, financially, and socially. Psychosocial support is an important aspect of care from the early phases of evaluation and diagnosis through all stages of treatment.	**Case 48-2 (Question 10), Table 48-8**

INTRODUCTION

Infertility is defined as the inability to conceive after 1 year of regular, unprotected intercourse.[1] The definition is based upon the observation that roughly 85% of couples with normal fertility will achieve pregnancy within 1 year.[2] Data from the National Survey of Family Growth (NSFG) in 2015 to 2017 revealed that 8.8% of females age 15 to 49 years were infertile and 12.7% had used infertility services.[3] Many factors affect infertility rates, but advancing maternal age appears to be a prominent influence.[4] The physiologic factors of reproductive aging are amplified by a trend toward delayed

childbearing in the United States. The mean maternal age at first birth is now ~28 years old, owing to more females delaying pregnancy until their 30s or 40s.[5]

The complex physical, psychological, and social implications have led to a national focus on infertility as a public health priority.[6] Treatment plans vary widely depending on the contributions of both female and male factors. An individualized approach is necessary to balance the risks and benefits of the various therapeutic options and maximize clinical outcomes.

PATHOPHYSIOLOGY AND DIAGNOSIS

CASE 48-1

Question 1: T.R. is a 32-year-old female who presents to her gynecologist with concerns that she and her husband, age 37, have not conceived despite having unprotected intercourse on average two to three times per week for the past 14 months. Her prior contraceptive method was a combined oral contraceptive, which she used for 12 years and discontinued 2 years ago. At that time, the couple used male condoms until 14 months ago, when they stopped using contraception altogether.

What is the recommended initial approach to this couple's concern?

Evaluation of infertility generally begins after a couple has attempted to conceive for at least 12 months without success. Evaluation after just 6 months of unsuccessful conception is recommended in females older than 35 years or in those with a history of conditions associated with infertility, such as amenorrhea, endometriosis, or pelvic inflammatory disease. Females older than 40 years may receive more immediate evaluation and treatment.[7]

This couple has failed to conceive after 14 months of regular, unprotected intercourse, which supports an evaluation of both partners at this time. The diagnostic process first involves a thorough assessment of medical conditions, lifestyle parameters, and medication exposures. This is followed by complete physical

examinations and laboratory assessments with other diagnostic procedures as warranted.

General Risk Factors

Case 48-1, Question 2: Additional information is obtained about the couple's social history. T.R. works as a bank teller, and her husband is a financial planner. Neither T.R. nor her husband smoke tobacco or use illicit substances. Both drink one to two cups of caffeinated coffee each day and drink alcohol socially, an average of one to three drinks each on weekends. What lifestyle factors may contribute to infertility in this couple?

Lifestyle factors such as tobacco or illicit drug use and caffeine intake are known contributors to infertility. In addition to the negative effects on fetal development during pregnancy, tobacco use can worsen ovulatory function. It also induces chromosomal changes that alter sperm function.[8] Caffeine intake should be limited to <200 mg/day. Although a link between alcohol use and infertility is not definitive, complete abstinence from alcohol is recommended once pregnancy is confirmed. The use of illicit substances such as marijuana impairs fertility and decreases the success of fertility treatments. Occupational and environmental exposures to pesticides, heavy metals, and toxins such as organic solvents used in dry cleaning and printing are additional contributors.[9]

The couple's lack of tobacco or illicit drug use eliminates these as potential contributors, and their occupations do not fit known high-risk exposure profiles. T.R. should be counseled on moderating caffeine and alcohol intake. Assessment of other causes of infertility is warranted.

Female Factor Infertility

OVULATORY DYSFUNCTION

Case 48-1, Question 3: T.R.'s medical history is significant for exercise-induced asthma diagnosed at age 10. Her medications include an albuterol inhaler used as needed for shortness of breath. She is 65 inches (165.10 cm) tall and weighs 140 pounds (63.50 kg). Her reproductive history reveals menarche at age 13, no prior pregnancies, and regular menstrual cycles ~25 to 26 days in length since discontinuing the oral contraceptive. She reports the menstrual bleeding phase to be 4 to 5 days in length and does not have excessive bleeding. A physical examination is performed along with a pelvic examination with no notable abnormalities. What information does this provide about possible female factors associated with infertility?

An important focus when evaluating the causes of infertility is ovulatory function, which is associated with up to 40% of female factor infertility.[2] A thorough reproductive history should document age of menarche, menstrual cycle patterns, premenstrual symptoms, and previous pregnancies. A history of regular menstrual cycles of 21 to 35 days with premenstrual symptoms or dysmenorrhea is considered consistent with ovulatory cycles.[2]

Ovarian function is regulated through complex feedback mechanisms within the hypothalamic–pituitary–ovarian axis (see Chapter 50, Disorders Related to the Menstrual Cycle, Fig. 50-1). This involves the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland, and estrogen and progesterone from the ovaries. **Table 48-1** provides an overview of abbreviations commonly associated with diagnosis and management of infertility for use throughout the chapter.

Table 48-1
Common Abbreviations Associated With Infertility Diagnosis and Treatment

ART	Assisted reproductive technology
CC	Clomiphene citrate
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin

HSG	Hysterosalpingogram
hMG	Human menopausal gonadotropin
IUI	Intrauterine insemination
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilization
LH	Luteinizing hormone
OHSS	Ovarian hyperstimulation syndrome
OI	Ovulation induction
OS	Ovarian stimulation

Conditions such as thyroid dysfunction, hyperprolactinemia, and polycystic ovary syndrome (PCOS) can disrupt these feedback mechanisms and induce anovulation. Signs may be evident upon physical examination, including an enlarged thyroid (thyroid dysfunction), abnormal discharge from the breast (hyperprolactinemia), or signs of hyperandrogenism (PCOS). Obesity is another feature associated with PCOS. Conversely, extremely low body weight and excessive exercise may negatively impact ovulatory function at the hypothalamic level. Weight gain improves menstrual regulation in females with anovulation associated with low body fat. Primary ovarian failure can result from exposure to chemotherapy agents or radiation treatments as well as ovarian surgery. As previously discussed, the aging process itself is characterized by diminished ovarian follicular reserve.[2,7]

T.R.'s reproductive history is consistent with regular menstrual cycles that are likely ovulatory. It would be helpful to identify whether she reports any symptoms of premenstrual syndrome or dysmenorrhea, which are associated with ovulatory cycles. Her physical examination is unremarkable, and her medical history does not reveal any conditions associated with anovulation. Her weight is not likely a factor because her body mass index of ~23 kg/m^2 is in the normal range. She has no known history of exposure to chemotherapy or ovarian surgery that could directly impact ovarian function. The only parameter consistent with female factor infertility

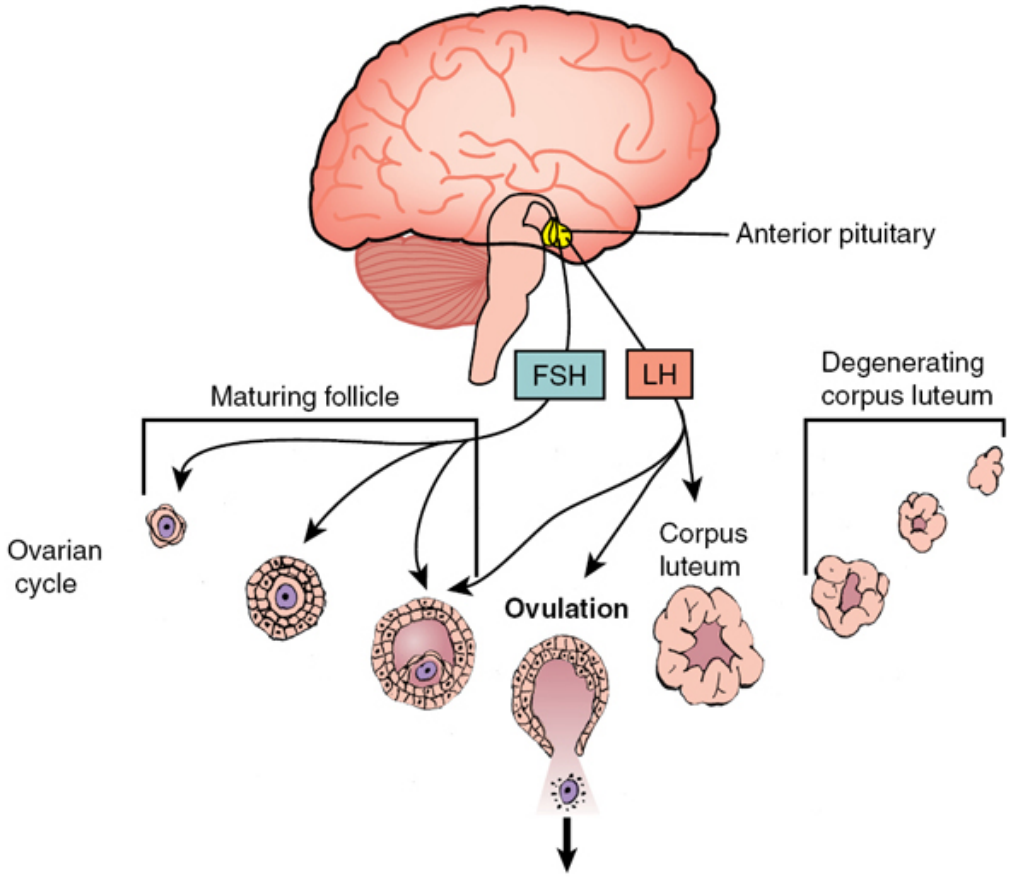
is T.R.'s age. At 32 years old, she may be experiencing an initial age-related decline in ovarian function consistent with infertility.

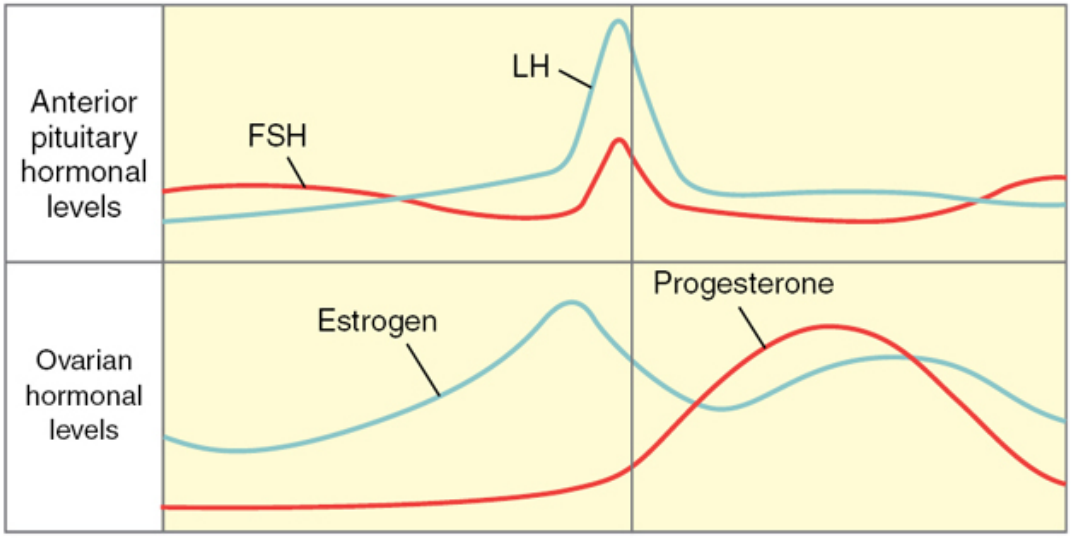
Case 48-1, Question 4: T.R. reports using a home ovulation test kit for the last two menstrual cycles that both yielded positive results. She is referred for a series of laboratory tests with the following findings:

Thyroid-stimulating hormone, 3.2 mIU/L
Prolactin, 8.4 ng/mL
Cycle day 3 FSH, 4 mIU/mL
Cycle day 3 estradiol, 38 pg/mL

What additional information about her ovulatory function can be determined from these results?

Several methods are available to further define ovulatory function. Although basal body temperature monitoring can indicate ovulation, the accuracy of this method is complicated by daily temperature fluctuations, inconsistent measurement technique, and illness. It has largely been replaced by the use of home ovulation test kits that detect urinary LH. The patient initiates daily urine tests during the follicular phase, with the initial testing day determined by the length and regularity of her menstrual cycle (**Fig. 48-1**). A positive test documents the LH surge, signaling that ovulation will occur in an average of 24 hours.[2] Home ovulation test kits that detect changes in cervical mucus or saliva samples are not typically used for diagnostic purposes. They are useful, however, for patients who are timing intercourse during their most fertile period around ovulation.[10] A serum progesterone concentration measured in the mid-luteal phase >3 ng/mL is considered consistent with an ovulatory cycle.[2]





Uterine phases	Menstrual	Proliferative	Secretory	Menstrual
Ovarian phases	Follicular		Luteal	Follicular

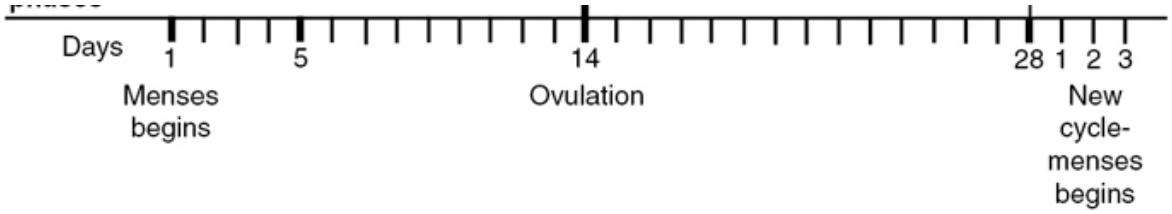


Figure 48-1 The menstrual cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

In patients who are anovulatory, additional laboratory assessments of thyroid function and prolactin levels document potential secondary causes.[2] Elevated testosterone levels may correspond with physical signs of hyperandrogenism and PCOS. The treatment of PCOS is discussed elsewhere (see Chapter 50, Disorders Related to the Menstrual Cycle).

Assessment of ovarian reserve may be performed in females older than 35 years to help guide fertility treatment choices. There are multiple methods that can be used. One involves the measurement of basal levels of serum FSH with or without estradiol between days 2 and 5 of the menstrual cycle, with day 1 being the first day of menses. Because the number of ovarian follicles declines with age, pituitary release of FSH increases. Therefore, an FSH level >10 IU/L suggests diminished ovarian function. A serum estradiol level above the typical level of 60 to 80 pg/mL is also associated with a poor prognosis for success with infertility treatments. A measurement of serum antimullerian hormone <1 ng/mL may also indicate diminished ovarian reserve.[7]

Direct visualization of the ovaries through a transvaginal ultrasound may be used in conjunction with hormone testing. The antral follicles, or those 2 to 10 mm in diameter, are responsive to FSH in the early follicular phase and decline in number with age. An antral follicle count <5 to 7 is considered low and may predict poor ovarian response to various infertility treatments.[7]

The laboratory assessment of T.R. provides additional data regarding her ovarian function. Ovulatory cycles are supported by the positive urinary LH surge with the home test kit as well as the normal (nonelevated) day 3 FSH and estradiol levels. Her normal

thyroid-stimulating hormone and prolactin levels indicate a low probability of secondary causes of anovulation. Because T.R. is younger than 35 and there are no other indicators of ovulatory dysfunction, additional testing of ovarian reserve may not be necessary. The initial findings of T.R.'s infertility assessment show that ovulatory dysfunction is not likely to be a contributor.

STRUCTURAL FACTORS

CASE 48-1, QUESTION 5: Because T.R. has normal ovulatory function, further causes of female factor infertility will be investigated. What testing is recommended to rule out structural causes of infertility?

Structural abnormalities in the uterine cavity or uterine (fallopian) tubes are associated with female factor infertility. These may develop in utero or result from scar tissue or lesions secondary to conditions such as endometriosis. In some cases of endometriosis, surgical interventions improve fertility outcomes, but this is highly dependent on the severity and location of the lesions.[11] Further discussion of the diagnosis and treatment of endometriosis is provided elsewhere (see Chapter 50, Disorders Related to the Menstrual Cycle). Pelvic inflammatory disease from sexually transmitted infections such as chlamydia or gonorrhea is a risk factor for tubal infertility. Impaired cervical mucus production and quality are additional structural factors that can impact sperm motility and the fertilization process.[2]

The use of invasive procedures to explore structural causes of female infertility is dictated by the reproductive history and findings of the physical examination and laboratory tests. Abnormalities of the ovaries, uterus, and uterine tubes are evaluated through various procedures. Transvaginal ultrasonography utilizes vaginal insertion of an ultrasound probe to visualize ovarian structure and developing follicles. A hysterosalpingogram (HSG) is performed to confirm normal uterine tube structure. During this process, dye is injected into the uterus through a catheter and visualized on x-ray to determine any blockages or malformations. Hysteroscopy and

laparoscopy are more invasive procedures that allow for direct visualization of the uterus or pelvic anatomy. These are typically reserved for further examination of abnormalities detected by initial testing.[2,7]

In the evaluation of this couple, it is important to verify T.R.'s sexual history and any possible exposures to sexually transmitted infections. An HSG can determine whether she has patent fallopian tubes and provide basic information about the shape of her uterine cavity. If there are abnormal findings, further hysteroscopic or laparoscopic procedures can be performed. A laparoscopy would fully evaluate any peritoneal adhesions from undetected endometriosis, but her medical history does not warrant this invasive procedure at this time.

Male Factor Infertility

Case 48-1, Question 6: The results of the HSG are normal, so the infertility assessment turns now to the evaluation of T.R.'s husband. He is healthy with no chronic medical conditions or medication use. He denies symptoms of low libido or signs of erectile or ejaculatory dysfunction during intercourse. A complete physical examination, including the genitalia, reveals normal findings. His semen analysis yields the following results:

Semen volume, 5 mL
Sperm number, 400×10^6
Sperm concentration, 112×10^6/mL
Sperm total motility, 65%
Sperm progressive motility, 61%
Sperm vitality, 80%
Sperm morphology, 30%
A second semen analysis confirms these results.

What conclusions about the cause of infertility can be made from these findings?

Infertility is associated with male factors in ~40% to 50% of couples.[7] Male factor infertility is often an outcome of impaired sperm production or function, which can originate from a variety of causes. Impaired sperm production associated with hypogonadism may

result from testicular trauma, cryptorchidism, radiation, or antiandrogen medications.[12,13] Varicoceles, or dilated scrotal veins, affect testicular function in up to 40% of males with infertility. The resulting abnormal venous perfusion and elevated testicular temperature impair spermatogenesis.[14] Genetic conditions may disrupt androgen synthesis or cause defects in the LH or FSH receptor. Azoospermia, or no presence of sperm in the ejaculate, is also apparent in certain genetic disorders, such as Klinefelter syndrome. Pituitary tumors can reduce FSH and LH secretion and impair sperm production. Sperm transport defects result from erectile dysfunction, retrograde ejaculation, or obstruction of the vas deferens or epididymis. Medications such as antidepressants or antihypertensives can worsen libido and ejaculatory function.[12,13]

A complete physical examination of the male is performed to identify signs of androgen deficiency, such as small testicular size or an abnormal pattern of male hair growth. However, the primary evaluation tool for male infertility is the semen analysis. Home test kits for male infertility that utilize a semen sample are not recommended for diagnostic purposes because a positive result merely confirms that the sperm count is above a predetermined level. There is no quantification of the number of sperm or evaluation of sperm quality, so it does not rule out sperm abnormalities. A detailed semen analysis of two samples on different occasions is recommended.[12] The World Health Organization publishes reference values for semen characteristics (**Table 48-2**).[15] Results lower than these cutoff values are not definitive for male factor infertility but do suggest the need to confirm the findings with a second semen analysis.[12]

Table 48-2
Semen Analysis: Lower Reference Limits for Selected Parameters

Parameter	Lower Reference Limit
Semen volume (mL)	1.5
Total sperm number (10^6/ejaculate)	39

Parameter	Lower Reference Limit
Sperm concentration (10^6/mL)	15
Total motility (progressive + nonprogressive, %)	40
Progressive motility (%)	32
Vitality (live spermatozoa, %)	58
Sperm morphology (normal forms, %)	4

Source: World Health Organization, Department of Reproductive Health and Research. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. World Health Organization Press; 2010:224.

Abnormal findings on the semen analysis may be suggestive of the underlying cause of infertility. Low semen volume suggests structural causes of ejaculatory dysfunction. Additional hormone testing, including FSH, testosterone, and prolactin levels, may be necessary to distinguish factors associated with a low sperm count or motility. Low FSH and testosterone are consistent with hypogonadotropic hypogonadism.[12,13]

T.R.'s husband's medical history does not support an identifiable cause of altered sperm production or function. He does not report any signs of sexual dysfunction or take medications that may negatively affect libido or erectile or ejaculatory function. All components of the semen analysis are above the lower limit defined by the World Health Organization. His normal physical examination and medical history do not provide an identifiable male cause of infertility. In this case, the extensive testing of both T.R. and her husband has revealed no obvious contributor to infertility.

TREATMENT APPROACHES

Case 48-1, Question 7: The couple completes their evaluation and is diagnosed with unexplained infertility. What is the initial approach to treatment?

The diagnosis of unexplained infertility, or no identifiable cause after evaluation, accounts for up to 30% of cases.[16] The treatment approach is empiric but typically incorporates medications to stimulate ovulation, often in conjunction with intrauterine insemination (IUI) or other infertility procedures, which are discussed later in this chapter.

Regardless of the treatment approach, all couples pursuing pregnancy are encouraged to avoid tobacco, alcohol, and illicit substances and to limit caffeine intake. The female partner should take a daily supplement containing 400 µg of folic acid to reduce the risk of neural tube defects once pregnancy occurs. Any chronic medications must be evaluated for potential safety issues during pregnancy and discontinued or switched to a safer alternative. Patients are encouraged to achieve and maintain a normal weight.[9] Recommendations pertinent to T.R. include discontinuation of alcohol use, limited caffeine intake, and initiation of a daily multivitamin with 400 µg of folic acid. T.R. should also confirm plans for monitoring her asthma symptoms during pregnancy. Albuterol use during pregnancy will be continued, but the frequency of use will be monitored carefully.[17]

Ovulation Induction and Ovarian Stimulation

Ovulation induction (OI) is utilized in patients who are not ovulating to promote an ovulatory cycle. This method may be accompanied by timed natural intercourse or the use of insemination procedures to achieve pregnancy. Ovarian stimulation (OS) incorporates many of the same medications but is appropriate for patients who are already having ovulatory cycles but are still experiencing infertility. In addition, OS is appropriate for infertility procedures in which the development of multiple ovarian follicles is desirable (Case 48-2).[16] The general approach to medication use with both strategies is described subsequently.

Anovulatory females with adequate ovarian reserve and no other treatable cause are the candidates for OI. This process is designed

to mimic the hormonal patterns of the normal menstrual cycle. FSH guides the initial recruitment and development of ovarian follicles early in the menstrual cycle. This is followed by development of a dominant follicle and increased estradiol levels. The elevated estrogen triggers the LH surge and the release of the ovum mid-cycle for fertilization (see Fig. 48-1). The goal of OI is the development of a single dominant follicle.[18]

The choice of medications for OI is dictated by hypothalamic–pituitary–ovarian function. With adequate hypothalamic function, an oral regimen of CC, which exhibits estrogen agonist and antagonist activity, is often utilized first line. Clomiphene citrate (CC) inhibits estrogen binding in the hypothalamus to stimulate the release of GnRH and pituitary gonadotropins and induce ovarian follicular development. Oral aromatase inhibitors are not approved by the U.S. Food and Drug Administration (FDA) for OI but increase the release of GnRH and pituitary gonadotropins.[19]

If hypothalamic or pituitary dysfunction is detected or if oral regimens are not successful, injectable gonadotropins are administered. The most common gonadotropin regimens use FSH administered either alone or in combination with LH, depending on whether the patient has hypogonadotropic or eugonadotropic hypogonadism (**Table 48-3**).[18,20] Injections are initiated at low daily doses until a dominant follicle has matured. Ovulation is then triggered with an injection of human chorionic gonadotropin (hCG) to simulate the LH surge that naturally occurs mid-cycle. This is timed with natural intercourse or other infertility procedures to achieve pregnancy.[18]

Table 48-3
Gonadotropins for Ovulation Induction/Superovulation

Ingredient	Product Name	Strength/Dosage Form	Route of Administration
hMG (menotropins)	Menopur®	Powder for reconstitution: 75 IU FSH activity and 75 IU LH activity/vial	SC
Recombinant FSH (follitropin alfa)	Gonal-f® multi-dose	Powder for reconstitution: 450 or 1050 IU FSH activity/vial	SC
	Gonal-f® RFF 75 IU	Powder for reconstitution: 75 IU FSH activity/vial	SC
	Gonal-f® RFF Redi-ject	Solution: 300, 450, or 900 IU FSH/pen	SC
Recombinant FSH (follitropin beta)			
	Follistim® AQ cartridge for Follistim Pen	Solution: 300, 600, or 900 IU FSH/cartridge	SC
Urinary hCG	Chorionic gonadotropin (generic)	Powder for reconstitution: 10,000 IU LH activity/vial	IM
	Pregnyl®	Powder for reconstitution: 10,000 IU LH activity/vial	IM
	Novarel®	Powder for reconstitution: 5000 or 10,000 IU LH activity/vial	IM
Recombinant chorionic gonadotropin alfa	Ovidrel®	Prefilled syringe: 250-µg r-hCG/0.5 mL	SC

FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; IM, intramuscular; LH, luteinizing hormone; r-hCG, recombinant human chorionic gonadotropin; SC, subcutaneous.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

The oral and injectable medications used for OI are also incorporated into regimens for OS. They are administered in doses and schedules intended to develop multiple ovarian follicles, rather than one dominant follicle. This results in a greater number of oocytes available for fertilization. Because T.R. has ovulatory cycles, but has unexplained infertility, OS is the treatment approach considered most appropriate.

CASE 48-1, QUESTION 8: What medication regimen is recommended for T.R.'s unexplained infertility?

There are multiple methods for ovulation stimulation that utilize oral or injectable medications. CC is a common initial choice because of the convenience and low cost of an oral regimen and the widespread experience with its use.

CLOMIPHENE CITRATE

The competitive binding of CC to estrogen receptors in the hypothalamus stimulates the release of GnRH. This promotes

gonadotropin release from the anterior pituitary, leading to follicular development, increased estradiol production, and ovulation. As previously described, the mechanism of action of CC requires an intact hypothalamic–pituitary–ovarian axis.[16] The typical initial dosing regimen for CC is 50 mg once daily for 5 days starting between days 2 and 5 of the menstrual cycle. Ovulation usually occurs 5 to 10 days after the fifth dose is taken. If ovulation is documented but pregnancy does not occur, the same dose of CC is used in future cycles. If ovulation does not occur, then the dose is increased to 100 mg/day.[19,20]

OS for unexplained infertility with CC is recommended in combination with IUI, because this improves pregnancy and live birth rates over CC either alone or no intervention.[16] IUI introduces a processed semen sample directly to the uterus via a catheter placed through the cervix. The procedure is timed with ovulation to maximize sperm exposure for fertilization. This is accomplished by using a urinary ovulation home test kit to identify the natural LH surge or injecting hCG to trigger ovulation and planning the IUI 24 to 36 hours later. Owing to the nature of the procedure, patients with bilateral obstruction of the fallopian tubes are not the candidates for IUI.[16]

T.R.'s evaluation shows no evidence of hypothalamic or pituitary dysfunction, so she is an appropriate candidate for CC. Once her next cycle begins, she should initiate a 5-day regimen of CC 50 mg once daily starting on the fifth day of menstrual bleeding, with plans for an IUI following documentation of ovulation.

Case 48-1, Question 9: T.R. begins a regimen of CC and experiences hot flashes and nausea but chooses to complete the 5-day course. What is the likely cause of her symptoms?

Vasomotor symptoms are a common cause during a short treatment course of CC, occurring in ~10% of users. Additional side effects include headache, breast tenderness, irritability, mood swings, and nausea. Although visual disturbances are reported in

<2% of patients, symptoms such as blurred vision or light sensitivity should be reported and evaluated to prevent serious complications.[19,20] All medications for OS can result in multiple gestation pregnancies. CC for unexplained infertility is associated with multiple gestation in up to 12.5% of pregnancies.[16]

In this case, T.R. is experiencing side effects commonly associated with CC. They are not treatment limiting, and she is not reporting a change in vision that would require further evaluation. She can safely proceed with treatment by monitoring for an LH surge using a home ovulation test kit and undergoing IUI.

CASE 48-1, QUESTION 10: The pregnancy test after the first cycle of CC and IUI is negative. What other options are available for this couple?

Multiple treatment cycles with the combination of CC and IUI are commonly pursued. The aromatase inhibitor letrozole is also a suitable alternative to combine with IUI.

AROMATASE INHIBITORS

The aromatase inhibitor letrozole is supported as an oral alternative to CC, although it is not FDA labeled for this purpose. Aromatase is an enzyme that converts androstenedione to estrone and testosterone to estradiol. Aromatase inhibitors reduce systemic estrogen levels by blocking this conversion in the ovary, resulting in increased gonadotropin secretion and follicular development. The higher concentration of androgens that remains in the ovary increases follicular sensitivity to FSH and further facilitates development.[16]

The recommended administration schedule is letrozole 2.5 or 5 mg once daily for 5 days beginning on cycle days 3 to 5. Pregnancy rates with letrozole appear to be similar to that of CC.[16] Adverse effects experienced with aromatase inhibitors resemble those of CC and include vasomotor symptoms, nausea, and fatigue.[20]

T.R.'s vasomotor symptoms are well-documented with CC. Although the aromatase inhibitors are another oral option, similar

adverse effects may occur. If three to four cycles of OS plus IUI with oral agents are not successful, in vitro fertilization (IVF) is the appropriate next step.[16]

Assisted Reproductive Technology

OVERVIEW AND INDICATIONS

There are a variety of procedures to address infertility factors specific to each couple. Insemination processes are categorized separately from those using assisted reproductive technology (ART), or the manipulation of oocytes and embryos (**Table 48-4**).[21] The Centers for Disease Control and Prevention monitors ART in the United States through the National ART Surveillance System. The use of ART is trending upward, with the number of cycles increasing from just over 122,000 in 2003 to >260,000 in 2016.[22]

Table 48-4
Description of Select Infertility Procedures

Classification	Procedure	Description
Insemination	Intrauterine, intracervical	Delivery of a prepared semen sample to the intended site (cervix, uterus) during ovulation
Assisted reproductive technology	Assisted hatching	Mechanical or chemical separation of the blastocyst from the zona pellucida (membrane surrounding the oocyte) during embryonic development in vitro
	Cryopreservation	Freezing and storage of biologic material (gametes, zygotes, embryos, blastocysts) for future ART cycles
	Gamete intrafallopian transfer	Laparoscopic transfer of the unfertilized oocytes and sperm to the fallopian tube for fertilization
	In vitro fertilization—embryo transfer	Transfer of one or more embryos resulting from in vitro fertilization into the uterus through the cervix

Classification	Procedure	Description
	Intracytoplasmic sperm injection	In vitro injection of the sperm into the oocyte
	Preimplantation genetic testing	Examination of oocytes or embryos for specific genetic abnormalities
	Zygote intrafallopian transfer	Laparoscopic transfer of the fertilized oocyte (zygote) into the fallopian tube

ART, assisted reproductive technology.

Source: Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. *Hum Reprod*. 2017;32(9):1786–1801.

The primary ART is IVF, which involves retrieval of oocytes after OS, fertilization in vitro, and transfer of the embryo(s) directly to the uterus through the cervix, bypassing the uterine tubes (**Fig. 48-2**; Table 48-4).[21] Intracytoplasmic sperm injection (ICSI), or the injection of sperm directly into the oocyte during the fertilization process, accompanies IVF if severe sperm dysfunction is evident. A variety of ancillary procedures can be used based upon each couple's history and clinical presentation, including genetic screening and cryopreservation of embryos. ART also allows couples to use donor sperm and/or oocytes to overcome severe sperm or ovarian dysfunction that cannot be addressed through other methods. The option of using donor oocytes uniquely targets infertility due to diminished ovarian reserve.

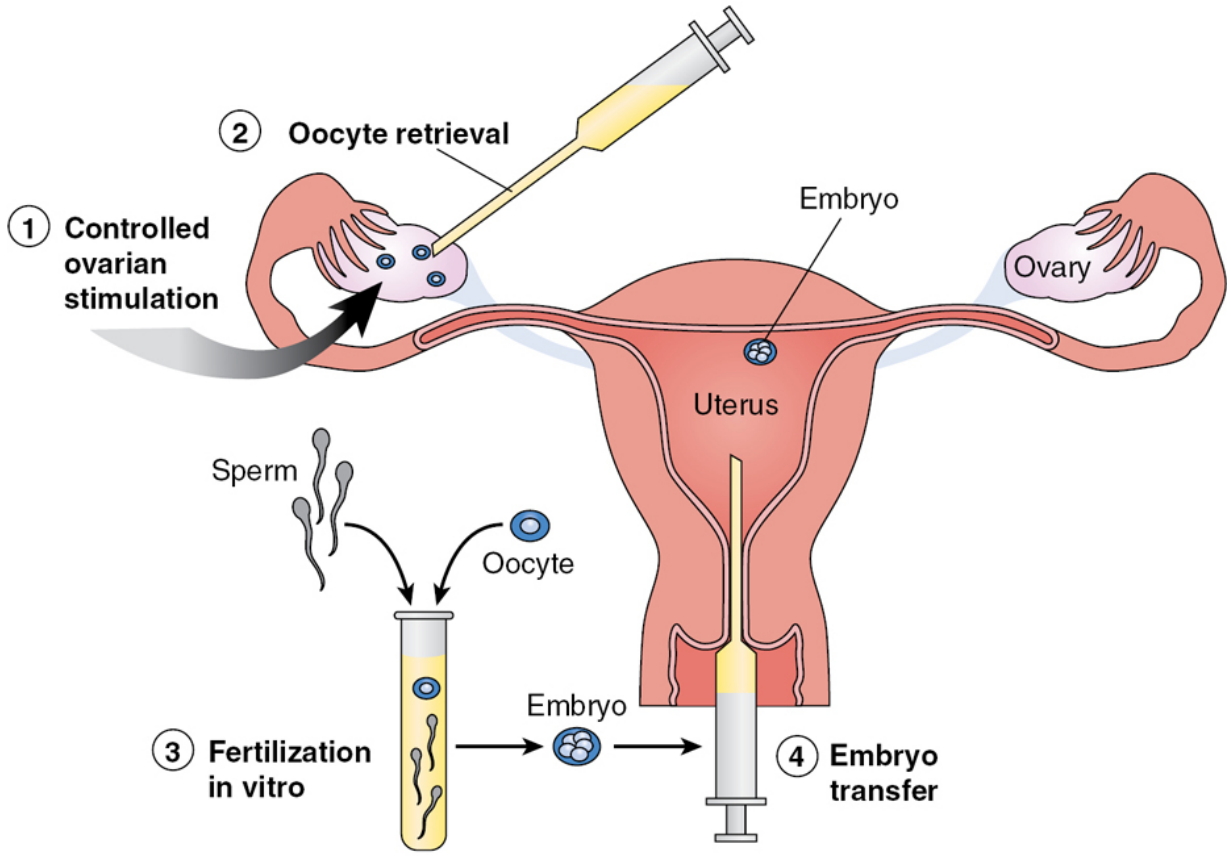


Figure 48-2 In vitro fertilization process.

CASE 48-2

QUESTION 1: F.J., a 39-year-old female, and her 42-year-old husband are a recently married couple undergoing a comprehensive infertility evaluation after 6 months without conceiving. F.J.'s medical history is positive for seasonal allergic rhinitis, dysmenorrhea, and a history of chlamydia at age 21. Her current screen for sexually transmitted infections is negative. F.J.'s reproductive history reveals menarche at age 11, no prior pregnancies, and regular menstrual cycles ~30 days in length. Her body mass index is 21 kg/m^2. There are no abnormal findings on her physical examination. Her FSH and estradiol levels on cycle day 3 are 7 mIU/mL and 46 pg/mL, respectively. An antral follicle count reveals nine follicles. Her HSG shows complete occlusion of the left uterine tube and partial occlusion of the right uterine tube.

What findings support female factor infertility?

This couple is undergoing evaluation of infertility after only 6 months without conceiving because of F.J.'s advanced age (older

than 35) and history of chlamydia, which places her at increased risk of complications from pelvic inflammatory disease. The occlusion of her uterine tubes is most likely from the chlamydial infection at age 21. Laparoscopy would be necessary to rule out any additional causes such as endometriosis. Further hysteroscopic procedures are warranted to define the location and type of obstruction and to determine whether surgical repair is feasible.[23] Her regular menstrual cycle length and history of dysmenorrhea are supportive of an ovulatory menstrual cycle, and her FSH and estradiol levels as well as antral follicle count show adequate ovarian reserve. She is within the normal weight range and has normal findings upon physical examination. However, further laboratory testing may be warranted to confirm normal thyroid and pituitary function and rule out findings associated with PCOS.

CASE 48-2, QUESTION 2: F.J.'s husband has normal findings upon physical examination. His semen analysis yields the following results:

Semen volume, 3 mL
Sperm number, 41 × 10^6
Sperm concentration, 18 × 10^6/mL
Sperm total motility, 35%
Sperm progressive motility, 30%
Sperm vitality, 60%
Sperm morphology, 2%

A repeat analysis produces similar results. Additional laboratory findings include:

Testosterone, 650 ng/dL
FSH, 4 mIU/mL
Prolactin, 14.2 ng/mL

What is the significance of these findings for male factor infertility and the choice of ART for this couple?

The semen analysis is significant for sperm motility and morphology values below the lower reference limit defined by the World Health Organization. The semen volume, sperm number, and vitality measurements are just above the lower reference limit (see

Table 48-2).[15] Interventions to improve sperm parameters typically target the underlying cause if possible, such as treatment of hyperprolactinemia or supplementation with testosterone. In some cases, sperm production can be stimulated through the use of gonadotropins or CC. The use of CC is FDA labeled for use in females only, and there is no consensus on the optimal dosage regimen.[24] Given this patient's normal serum testosterone and FSH, CC or gonadotropins are not the recommended therapies. His prolactin is normal as well, ruling out this potential secondary cause. In this case, there is no identifiable cause of the abnormal parameters, so it is deemed idiopathic, without a known etiology.

Antioxidants such as vitamin C, vitamin E, folic acid, zinc, selenium, and L-carnitine are reported to counteract negative effects from oxidative stress on sperm. Some small studies have demonstrated improvement in sperm motility, concentration, and morphology.[25] F.J.'s husband may choose to take a daily antioxidant supplement as they move forward with other treatment modalities.

Insemination procedures are one approach to address abnormal findings on semen analysis. Bypassing the cervix and placing the sperm closer to the fallopian tubes near the time of ovulation can overcome lower sperm counts and motility issues. In regard to this couple, however, F.J. does not have patent uterine tubes and would not be a candidate for IUI. An ART procedure will be necessary to address both female and male infertility factors.

IVF is more appropriate than gamete intrafallopian transfer and zygote intrafallopian transfer due to F.J.'s tubal findings. Although surgical repair of the obstructed uterine tubes may be possible in some cases, many couples choose to bypass this option and pursue ART, especially when there are additional male factors.[23] F.J. will need a surgical evaluation to confirm whether this is recommended before proceeding to ART. F.J. is ovulatory with adequate ovarian reserve, so the use of donor oocytes is not required. Her husband's abnormal sperm parameters can be addressed through ICSI, with the option of using donor sperm in the future, if necessary.

IN VITRO FERTILIZATION

The basic steps in an IVF protocol include OS, oocyte retrieval, fertilization, embryo culture, and embryo transfer. Medications are primarily used during three main stages of IVF: OS, oocyte retrieval, and luteal phase support (**Table 48-5**). Treatment protocols vary widely in the medications used, dosing regimens, and timing of administration.[26] A sample IVF protocol representing F.J.'s experience is provided in **Figure 48-3**.

Table 48-5

Role of Medications in an In Vitro Fertilization Cycle

IVF Stage	Medications[a]	Role
Stage 1: ovarian stimulation	Oral contraceptives	Control the onset of menses and the start of controlled ovarian stimulation
	GnRH agonists or GnRH antagonists	Prevent a premature LH surge or disruption of controlled ovarian stimulation
	Gonadotropins (FSH or FSH plus LH)	Stimulate development of multiple ovarian follicles for oocyte retrieval
Stage 2: oocyte retrieval	hCG	Induce final follicular maturation to prepare for oocyte retrieval
Stage 3: luteal phase support	Progesterone	Maintain the endometrium for embryo transfer and implantation

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

[a]This list reflects the medications most commonly used during each stage. Alternate regimens vary widely by specialist.

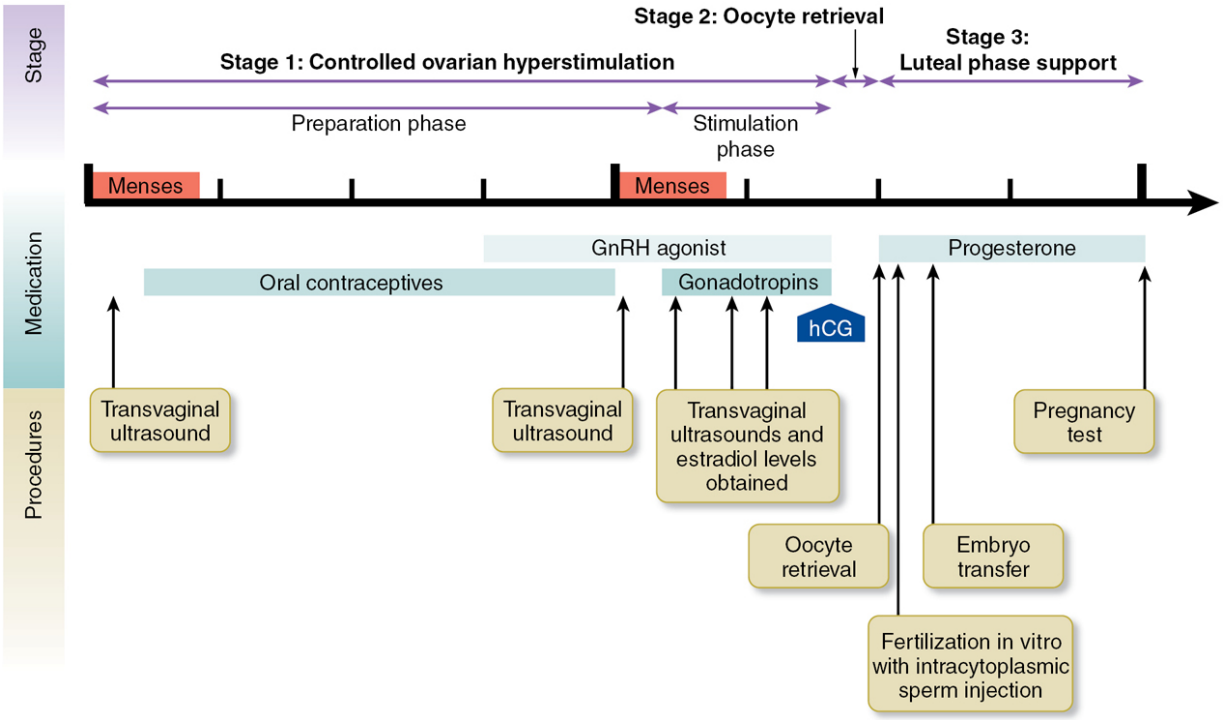


Figure 48-3 Sample in vitro fertilization protocol (Case 48-2). GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin.

CASE 48-2, QUESTION 3: After the completed evaluation, the couple chooses to undergo IVF with ICSI. What medication regimen is recommended to initiate the IVF protocol?

Stage 1: ovarian stimulation

The purpose of OS for IVF is the development of multiple follicles for oocyte retrieval. Although oocyte retrieval and fertilization can be performed during a normal ovulatory cycle without stimulation, it is more common and many times necessary to use this process.

Oral Contraceptives

OS for IVF is designed to manipulate follicular development for oocyte retrieval at the most optimal stage of maturation. Many protocols start with the administration of oral contraceptives control the timing of the onset of the next menses in order to plan for

initiating the OS regimen.[26,27] This is particularly pertinent in females who have irregular or long menstrual cycles but may be used in those with regular menstrual cycles.

Gonadotropin-Releasing Hormone Analogs

Once the OS process begins, it can be interrupted by an endogenous surge of LH that triggers ovulation prematurely and threatens the success of the cycle. Most protocols use medications to limit the influence of any endogenous hormone levels as the cycle progresses. GnRH agonists have been used for this purpose for several decades. Administration of a GnRH agonist initially increases pituitary gonadotropin release, often referred to as a "flare." Continued daily administration leads to receptor downregulation and reduced pituitary secretion of LH and FSH, allowing for direct administration of the gonadotropins by injection.[27]

IVF regimens in the United States have traditionally either subcutaneous leuprolide or intranasal nafarelin (**Table 48-6**).[20] The leuprolide formulation is often dosed in "units" using an insulin syringe to permit measurement of small volumes. Daily doses of 10 to 20 "units" correspond with 0.5 to 1 mg using the 1-mg/0.2-mL product. Intranasal nafarelin has been studied in doses of 200 to 400 µg twice daily.[26]

Table 48-6
Gonadotropin-Releasing Hormone Analogs for In Vitro Fertilization

Analog	Product Name	Strength/Dosage Form	Route of Administration
GnRH agonist	Nafarelin acetate (Synarel®)	2 mg/mL solution (200 µg/spray)	Intranasal
	Leuprolide acetate	1-mg/0.2-mL kit	SC
GnRH antagonist	Cetrorelix acetate[a] (Cetrotide®)	0.25-mg kit	SC
	Ganirelix acetate[a]	250-µg/0.5-mL syringe	SC

GnRH, gonadotropin-releasing hormone; SC, subcutaneous.

[a]FDA labeled for use with assisted reproductive technology procedures.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

Treatment protocols are identified by the timing of GnRH agonist administration. In a traditional “long” protocol, a GnRH agonist is initiated during the follicular or luteal phase of the preceding menstrual cycle. Once gonadotropins are initiated, the GnRH agonist is continued at half the daily dose until ovulation is stimulated. If an oral contraceptive is used for pretreatment, the GnRH agonist is often initiated within the last week of the contraceptive regimen. In a “short” protocol, a GnRH agonist is administered in conjunction with the gonadotropins for the stimulation cycle. When used in this manner, the flare, or initial increase in gonadotropin production, aids in the initial recruitment and development of follicles. Many other variations of the long and short protocols that adjust the length of GnRH agonist use, dose, and timing of discontinuation are utilized, with wide variability among clinics.[26,27]

Alternatively, the immediate suppression of gonadotropin secretion using GnRH antagonists such as cetrorelix and ganirelix allows for a shorter duration of administration and improved convenience and is associated with a lower risk for ovarian hyperstimulation syndrome (OHSS) (see Table 48-6).[27,28] The GnRH antagonists are administered after the gonadotropin-induced follicular development is established, as either a higher dose single injection or a lower dose daily injection that is continued until ovulation is triggered.[27] Ganirelix is administered as a daily 250-μg subcutaneous injection, and cetrorelix is either a daily subcutaneous injection of 0.25 mg or a single 3-mg dose.[20] The timing of initiation is either “fixed” on a particular day of stimulation or “flexible” based on follicular development.[27] Available data suggest that there is no difference in pregnancy and live birth rates between GnRH agonist and antagonist protocols.[27,28]

In this case example, a protocol using a GnRH agonist is chosen for F.J. For the preparation phase, an injectable (such as leuprolide) or intranasal (nafarelin) product can be used. The administration of GnRH analogs in the long protocol is associated with hot flashes, headaches, and sleep disturbances due to hypoestrogenic effects. Local reactions at the injection site and nasal and throat irritation are adverse effects expected with the subcutaneous and intranasal

routes of administration, respectively.[20] However, the symptoms and duration of her seasonal allergic rhinitis should be clarified because the absorption of the intranasal product can be affected by sneezing, congestion, and the use of other intranasal medications. After discussion, F.J. agrees to administer leuprolide injections. Once she experiences her next menses, she will begin 21 days of an oral contraceptive. On day 16 of this regimen, she will initiate leuprolide 1 mg once daily as a subcutaneous injection in conjunction with the oral contraceptives. A calendar will be provided to help her track the daily doses.

Gonadotropins

Case 48-2, Question 4: F.J. completes the oral contraceptive regimen and starts her menses. A baseline ultrasound rules out ovarian cysts and confirms ovarian suppression. She continues daily injections of leuprolide at a dose of 0.5 mg once daily (half the initial dose) upon initiation of gonadotropins for follicular development. What is the recommended gonadotropin regimen for F.J.?

The exogenous administration of FSH either alone or in combination with LH is intended to mimic the natural process of follicular recruitment and maturation. Gonadotropins are available from urinary and recombinant methods (see Table 48-3).[20] Human menopausal gonadotropin (hMG) was the first gonadotropin used in the United States as early as the 1950s. The product is extracted from urine of postmenopausal females and standardized to contain 75 IU each of FSH and LH activity. Both LH and hCG are present in the preparation and contribute to the LH activity. The development of the recombinant FSH products (follitropin alfa and follitropin beta) further expanded treatment options in the late 1990s. Although they have unique chemical structures, they result in clinically similar effects.[27]

Dosage regimens for the gonadotropins are intended to promote multiple follicles for oocyte retrieval and vary widely among clinics. A common starting dose in fixed-dose protocols is 150 to 225 IU daily,

with further dose adjustments made based on the status of the developing follicles. Treatment may continue for 7 to 12 days, although longer courses may be necessary depending on follicular response. If subsequent cycles are needed, the initial treatment doses are chosen based on the stimulation achieved in the first cycle. Lower or higher gonadotropin doses may be recommended for patients predicted to be high or low responders, respectively.[27,28] F.J. is undergoing her first cycle of IVF and has no signs of hypothalamic or pituitary dysfunction, so she can receive FSH either alone or in combination with LH. The two recombinant FSH formulations are available in pen injection devices that avoid the need for reconstitution and reduce the complexity of the injection (see Table 48-3).[20] Patient education should focus on product-specific instructions for storage, preparation for injection, and the correct subcutaneous injection technique. All products have patient-friendly video demonstrations or handouts available on the Internet to facilitate this process. (For helpful training videos and patient handouts that describe the dose preparation and injection technique, see https://www.ferringfertility.com/wp-content/themes/fercor/pdf/IVF-Explained_011817.pdf, and https://www.ferringfertility.com/our-fertility-offerings/.) The patient should be instructed to anticipate possible injection-site reactions as well as psychological symptoms of irritability, mood swings, and depression, which may increase during this phase.[26,27]

After consideration of these issues, a recombinant FSH product is chosen for F.J. because of the convenience of the pen device. She will begin a dose of 225 IU of recombinant follitropin alfa injected subcutaneously once daily.

Case 48-2, Question 5: F.J. begins daily subcutaneous injections of follitropin alfa in addition to her leuprolide injections. What medication monitoring should be provided at this time?

The goal of gonadotropin therapy is to guide the development of multiple follicles for oocyte retrieval without increasing the risk for

OHSS, a rare but serious complication of OS. In its most severe form, this syndrome is characterized by increased systemic vascular permeability that can result in ovarian rupture, thromboembolism, renal failure, and acute respiratory distress syndrome. The risk for this condition correlates most directly with the development of multiple ovarian follicles. Additional risk factors appear to include younger age, low body weight, and history of PCOS or ovulation disorder. Routine monitoring of ovarian follicular development allows the clinician to maximize efficacy and reduce the risk for overstimulation.[29]

Typical monitoring includes vaginal ultrasounds with or without serum estradiol measurements performed every 1 to 3 days during the OS phase. The monitoring frequency increases as the follicular development advances, and the gonadotropin doses may be reduced or increased depending on the number and size of the follicles. If hyperresponse is evident, the cycle may be canceled before oocyte retrieval.[28,29]

Once F.J. initiates therapy, she is scheduled for vaginal ultrasound measurements every other day. This increases to daily monitoring on day 7 of the combination of leuprolide and follitropin alfa because the number and size of the follicles continue to increase.

Stage 2: oocyte retrieval

Chorionic Gonadotropin

Case 48-2, Question 6: F.J. presents for her daily monitoring on day 10, and it is determined that she is ready for oocyte retrieval. What medication regimen is recommended at this time?

Chorionic gonadotropin is administered in preparation for oocyte retrieval to simulate the effect of the physiologic LH surge on final oocyte maturation. The oocyte retrieval must be carefully timed to coincide with the completion of the oocyte maturation process, just before ovulation. Many clinics schedule oocyte retrieval between 34 and 36 hours after chorionic gonadotropin is injected.

Chorionic gonadotropin is available from urinary or recombinant sources. The urinary hCG product is administered as a single intramuscular injection of 5000 to 10,000 IU.[20] The dose of the recombinant product is 250 µg injected subcutaneously.[20] A single dose of a GnRH agonist is an alternate method of triggering LH release in IVF protocols that incorporate a GnRH antagonist.[27]

F.J. is instructed to inject a single 250-µg dose of recombinant chorionic gonadotropin subcutaneously. She will discontinue leuprolide and follitropin alfa at this time.

Ovarian Hyperstimulation Syndrome

Case 48-2, Question 7: F.J. undergoes a transvaginal oocyte-retrieval procedure 36 hours after the administration of recombinant chorionic gonadotropin, and there are nine oocytes available for fertilization. What additional counseling is recommended for F.J. after the oocyte retrieval?

As previously described, OHSS is a rare complication associated with OS. If symptoms develop, it is typically within 1 to 2 weeks after oocyte retrieval. It is generally categorized as mild, moderate, or severe and can occur early (within 10 days after oocyte retrieval) or late (after 10 days, often associated with a pregnancy). The clinical signs of OHSS are thought to result from increased capillary permeability owing to high levels of vascular endothelial growth factor. A mild presentation of OHSS consists primarily of gastrointestinal symptoms (abdominal pain, nausea, diarrhea, bloating) or weight gain, especially abdominal distension. A patient experiencing these symptoms will be instructed to avoid physical activity, maintain oral fluid intake, and monitor daily weights and urine output. More intensive outpatient monitoring of liver and renal function, electrolytes, and hematologic parameters may be necessary. If the condition progresses, the patient may require hospitalization for the treatment of severe outcomes, such as thromboembolism, renal failure, pulmonary distress, or ovarian rupture.[29,30]

There were no initial indications of hyperstimulation during F.J.'s OS regimen, so she will be instructed to monitor for signs of OHSS during the 2 weeks after oocyte retrieval. She should notify her physician if she experiences gastrointestinal symptoms or weight gain, even if the symptoms are mild. This will facilitate early monitoring to maximize safety during the remainder of the IVF process.

Stage 3: luteal phase support

Progesterone

CASE 48-2, QUESTION 8: After the oocyte retrieval, F.J. is in need of a regimen for luteal phase support. Which agent should be selected?

Supplemental progesterone is administered immediately after oocyte retrieval to provide additional "luteal phase support" during IVF. The luteal phase of the menstrual cycle (see Fig. 48-1) is dominated by progesterone released by the corpus luteum that prepares the endometrium for implantation of the fertilized ovum. The disruption of follicles during the oocyte-retrieval process delays the production of progesterone, necessitating supplementation. In addition, cycles that utilize a GnRH agonist may be complicated by residual inhibition of pituitary LH secretion and progesterone production into the luteal phase. The use of hCG, GnRH agonists, and estradiol for luteal phase support has been investigated; however, progesterone is the most common.[31]

Progesterone is available in oral, vaginal, or injectable formulations (**Table 48-7**).[20] Intramuscular injection of progesterone in oil in a daily dose of 50 mg was the first method used for supplementation and continues to be widely used. However, alternatives to progesterone in oil have been sought because of frequent reports of rash and discomfort at the injection site.[27,31]

Table 48-7
Commercially Available Progesterone Products Used in

Assisted Reproductive Technology

Product Name	Strength/Dosage Form	Route of Administration
Crinone®	8% vaginal gel[a]	Vaginal
Endometrin®	100-mg vaginal insert[a]	Vaginal
FIRST®-Progesterone VGS	100-, 200-mg vaginal suppository (compounding kit)	Vaginal
Progesterone®	50 mg/mL (oil)	Intramuscular
Prometrium®/micronized progesterone	100-, 200-mg capsule	Oral

[a]FDA labeled for luteal phase support.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

Vaginal progesterone preparations have gained popularity for luteal phase support owing to ease of administration and avoidance of injection-site reactions. The 8% progesterone vaginal gel and the 100-mg vaginal insert are the only commercially available FDA-labeled preparations for use in ART procedures. The gel is administered as one 90-mg applicator once or twice daily. The dose of the vaginal insert is 100 mg either twice a day (every 12 hours) or three times a day (every 8 hours).[20,28,31] Patient education should focus on the correct technique for intravaginal administration. Both products utilize a disposable applicator to facilitate correct placement. (Detailed patient instructions are provided by both manufacturers: https://www.ferringfertility.com/products/endometrin/; https://www.allergan.com/assets/pdf/crinone_pi.) The vaginal preparations may cause local irritation and vaginal discharge, although the vaginal gel is generally associated with less discharge than the inserts or suppositories. Clinical studies suggest no difference in pregnancy rates between vaginal and intramuscular formulations, so clinician and patient preferences often dictate the selection.[27,31]

Oral formulations are not recommended for the purpose of luteal phase support with ART because of lower absorption and reduced

pregnancy rates.[28,31] Compounded formulations are widely available, including oral micronized progesterone and progesterone vaginal suppositories, gels, and creams. In some cases, patients are instructed to insert oral progesterone formulations intravaginally.

Because the efficacy of the parenteral and vaginal formulations is similar, F.J. chooses the vaginal route. She is most comfortable with 8% progesterone vaginal gel applied once daily and is given instructions regarding the appropriate administration technique. Progesterone is initiated after oocyte retrieval until a pregnancy test is performed and may be continued until at least 8- to 10-week gestation, depending on the type of cycle protocol.[31]

Embryo Transfer

Case 48-2, Question 9: The IVF process using ICSI yields four cleavage-stage embryos. What considerations are necessary for embryo transfer?

After fertilization, the timing of the embryo transfer into the uterus depends on the stage of development. Cleavage-stage embryos are transferred 2 to 3 days postfertilization, whereas embryos in the blastocyst stage are transferred at day 5 or 6.[32] The number of embryos placed during this process must balance the risks of a multiple gestation pregnancy with the likelihood of successful implantation.

Multiple gestation pregnancies are associated with increased maternal and neonatal morbidity. The mother is at risk for complications such as premature labor, pregnancy-induced hypertension, and gestational diabetes. Preterm labor occurs in ~15% of single gestation pregnancies compared with 75% of triplet pregnancies. The neonates are more likely to experience fetal growth restriction and require intensive care for pulmonary, gastrointestinal, and neurologic complications.[33] Additional stressors include the financial and psychosocial implications of raising children with complex medical needs that may persist beyond infancy.[33]

F.J. is 39 years old experiencing her first cycle of IVF. The American Society for Reproductive Medicine (ASRM) has developed embryo transfer recommendations to limit high-order multiple pregnancies (three or more implanted embryos). Based on her age, if the embryos are judged to have good-quality morphology, no more than three cleavage-stage or two blastocysts should be transferred according to the ASRM guidelines.[32] A pregnancy test will be performed 9 to 12 days after the embryo transfer to determine the outcome of the cycle.

Long-term considerations

Alternate Protocols

Case 48-2, Question 10: After careful consideration, the couple decides to transfer two cleavage-stage embryos and reserve two for cryopreservation. Unfortunately, the embryo transfer procedure is unsuccessful, and the couple plans to pursue a second procedure. What considerations are necessary for future cycles?

Determining an action plan for subsequent procedures requires a thorough evaluation of the response to therapy during the first cycle. If OS is repeated for oocyte retrieval, hormone levels, follicular development, fertilization rates, and the numbers of viable embryos are all considered to determine whether dosage adjustments or alternate medication protocols are necessary. The European Society of Human Reproduction and Embryology suggests specific OS protocols for patients exhibiting low, normal, or high response in previous procedures.[28]

In this case, F.J. experienced adequate follicular development for oocyte retrieval without signs of OHSS. The fertilization procedure was successful, and two embryos were cryopreserved for future procedures. The couple can choose to avoid another stimulation process for oocyte removal and move to frozen embryo transfer. Medications remain important for the frozen embryo transfer process, which can occur in a natural cycle or a cycle induced

through the use of estrogen and progesterone, with or without GnRH agonists.[34]

Psychosocial Issues

The financial impact of ART is substantial. The ASRM cites the average cost of an IVF cycle in the United States to be between $10,000 and $15,000.[35] Costs vary widely between clinics, and many offer financial counseling and payment packages to facilitate treatment. In addition, the psychological stress of the diagnosis and treatment of infertility must be considered at all stages. For couples who undergo successive ART procedures, repeated failures are commonly accompanied by feelings of grief and frustration, and psychological distress is often the reason for discontinuing treatments. Levels of emotional distress, including symptoms of depression and anxiety, can increase with each unsuccessful cycle. This response appears to remit immediately with a successful pregnancy, but in those who continue to be unsuccessful, symptoms can still be significant even months posttreatment.[36]

This couple should be offered individual counseling and social support that extends beyond the initial pretreatment consultation to promote positive outcomes.[36] There are several patient-focused resources for informational fact sheets and videos, highlighting the financial, medical, and psychosocial issues of infertility (**Table 48-8**).

Table 48-8
Patient-Focused Infertility Resources

Sponsor	Website
Path2Parenthood	http://www.path2parenthood.org/
American Society of Reproductive Medicine	http://www.reproductivefacts.org/
Centers for Disease Control and Prevention	http://www.cdc.gov/art/patientresources/preparing.html
Resolve: The National Infertility Association	http://www.resolve.org/

Sponsor	Website
Society for Assisted Reproductive Technology	http://www.sart.org/

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 781. Infertility workup for the women's health specialist. *Obstet Gynecol.* 2019;133(6):e377–e384. (7)

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 762. Prepregnancy counseling. *Obstet Gynecol.* 2019;133(6): e78–e89. (9)

Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. *2016 Assisted Reproductive Technology National Summary Report*. U.S. Dept of Health and Human Services; 2018. (22)

European Society of Human Reproduction and Embryology. Guideline: ovarian stimulation for IVF/ICSI. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI. (28)

Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male. *Fertil Steril*. 2015;103(3): e18–e25. (12)

Practice Committee of the American Society for Reproductive Medicine. Optimizing natural fertility: a committee opinion. *Fertil Steril*. 2017;107(1): 52–58. (10)

Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril*. 2015;103(6):e44–e50. (2)

Practice Committee of the American Society for Reproductive Medicine. Evidence-based treatments for couples with unexplained infertility: a guideline. *Fertil Steril*. 2019;113(2):305–322. (16)

Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertil Steril*. 2016;106(7):1634–1647. (29)

Practice Committee of the American Society for Reproductive Medicine. Use of exogenous gonadotropins for ovulation induction in anovulatory women: a committee opinion. *Fertil Steril*. 2020;113(1):66–70. (18)

Racca A, Drakopoulos P, Raquel Neves A, Polyzos NP. Current therapeutic options for controlled ovarian stimulation in assisted reproductive technology. *Drugs*. 2020;80:973–994. (26)

World Health Organization, Department of Reproductive Health and Research. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. World Health Organization Press; 2010:224. (15)

Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. *Hum Reprod*. 2017;32(9):1786–1801. (21)

Key Websites

American Society for Reproductive Medicine. http://www.asrm.org/

Society for Assisted Reproductive Technology. http://www.sart.org/

COMPLETE REFERENCES CHAPTER 48 INFERTILITY

1. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril*. 2020;113(3):533–535.
2. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril*. 2015;103(6):e44–e50.
3. National Center for Health Statistics. Key statistics from the National Survey of Family Growth. Accessed October 5, 2020. https://www.cdc.gov/nchs/nsfg/index.htm
4. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and the Practice Committee of the American Society of Reproductive Medicine. Female age-related fertility decline. Committee Opinion No. 589. *Fertil Steril*. 2014;101(3):633–634.
5. Martinez GM, Daniels K, Febo-Vasquez I. Fertility of men and women aged 15–44 in the United States: National Survey of Family Growth 2011–2015. *Natl Health Stat Report*. 2018;(113):1–17.

6. Macaluso M, Wright-Schnapp TJ, Chandra A, et al. A public health focus on infertility prevention, detection, and management. *Fertil Steril*. 2010;93(1):16.e1–16.e10.
7. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 781. Infertility workup for the women's health specialist. *Obstet Gynecol*. 2019;133(6):e377–e384.
8. Practice Committee of the American Society for Reproductive Medicine. Smoking and infertility: a committee opinion. *Fertil Steril*. 2018;110(4):611–618.
9. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 762. Prepregnancy counseling. *Obstet Gynecol*. 2019;133(6):e78–e89.
10. Practice Committee of the American Society for Reproductive Medicine. Optimizing natural fertility: a committee opinion. *Fertil Steril*. 2017;107(1):52–58.
11. Goldberg JM, Falcone T, Diamond MP. Current controversies in tubal disease, endometriosis, and pelvic adhesion. *Fertil Steril*. 2019;112(3):417–425.
12. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male. *Fertil Steril*. 2015;103(3):e18–e25.
13. McGriff SC, Lo EM, Hotaling JM, Pastuszak AW. Optimal endocrine evaluation and treatment of male infertility. *Urol Clin North Am*. 2020;47:139–146.
14. Practice Committee of the American Society for Reproductive Medicine. Report on varicocele and infertility: a committee opinion. *Fertil Steril*. 2014;102(6):1556–1560.
15. World Health Organization, Department of Reproductive Health and Research. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. World Health Organization Press; 2010.
16. Practice Committee of the American Society for Reproductive Medicine. Evidence-based treatments for couples with unexplained infertility: a guideline. *Fertil Steril*. 2019;113(2):305–322.
17. Namazy JA, Chambers C, Schatz M. Safety of therapeutic options for treating asthma in pregnancy. *Expert Opin Drug Saf.* 2014;13(12):1613–1621.
18. Practice Committee of the American Society for Reproductive Medicine. Use of exogenous gonadotropins for ovulation induction in anovulatory women: a committee opinion. *Fertil Steril*. 2020;113(1):66–70.
19. Von Hofe J, Bates GW. Ovulation induction. *Obstet Gynecol Clin North Am*. 2015;42:27–37.
20. Gonadotropins for Ovulation Induction/Superovulation. Facts & Comparisons eAnswers. Wolters Kluwer NV; 2022.

21. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. *Hum Reprod*. 2017;32(9):1786–1801.
22. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2016 Assisted Reproductive Technology National Summary Report. U.S. Dept of Health and Human Services; 2018.
23. Practice Committee of the American Society for Reproductive Medicine. Role of tubal surgery in the era of assisted reproductive technology: a committee opinion. *Fertil Steril*. 2015;103(6):e37–e43.
24. Chebab M, Madaka A, Trussell JC. On-label and off-label drugs used in the treatment of male infertility. *Fertil Steril*. 2015;103(3):595–604.
25. Ahmadi A, Bashiri R, Ghadiri-Anari A, Nadjarzadeh A. Antioxidant supplements and semen parameters: an evidence based review. *Int J Reprod Biomed*. 2016;14(12):729–736.
26. Society for Assisted Reproductive Technology. ART: step by step guide. Accessed October 5, 2020. http://www.sart.org/patients/a-patients-guide-to-assisted-reproductive-technology/general-information/art-step-by-step-guide/
27. Racca A, Drakopoulos P, Raquel Neves A, Polyzos NP. Current therapeutic options for controlled ovarian stimulation in assisted reproductive technology. *Drugs*. 2020;80:973–994.
28. European Society of Human Reproduction and Embryology. Guideline: ovarian stimulation for IVF/ICSI. Accessed October 5, 2020. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI
29. Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertil Steril*. 2016;106(7):1634–1647.
30. Humaidan P, Nelson SM, Devroey P, et al. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. *Hum Reprod*. 2016;31(9):1997–2004.
31. Labarta E, Rodriguez C. Progesterone used in assisted reproductive technology. *Best Pract Res Clin Obstet Gynaecol*. 2020;69:74–84. doi:10.1016/j.bpobgyn.2020.05.005
32. Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Criteria for number of embryos to transfer. *Fertil Steril*. 2013;99(1):44–46.
33. Practice Committee of the American Society for Reproductive Medicine. Multiple gestation associated with infertility: an American Society for Reproductive Medicine Practice Committee opinion. *Fertil Steril*. 2012;97(4):825–834.
34. Wong KM, Mastenbroek S, Repping S. Cryopreservation of human embryos and its contribution to in vitro fertilization success rates. *Fertil Steril*. 2014;102(1):19–26.

35. Society for Assisted Reproductive Technology. Frequently asked questions. Accessed October 2, 2020. http://www.sart.org/SART_Frequent_Questions/
36. Stanhiser J, Steiner AZ. Psychosocial aspects of fertility and assisted reproductive technology. *Obstet Gynecol Clin North Am*. 2018;45:563–574.

49

Obstetric Drug Therapy

Trisha LaPointe

CORE PRINCIPLES		CHAPTER CASES
1	The timing and quality of prenatal care can influence an infant's health and survival. Early comprehensive care can promote healthier pregnancies through early detection of risk factors, disease-state management, and encouragement of healthy behaviors.	**Case 49-1 (Questions 1–3)**
2	Important physiologic changes occur in almost all maternal organs during pregnancy to support the growth and development of the fetus.	**Case 49-1 (Question 4)**
3	Drug use during pregnancy presents a significant challenge to clinicians because of the potential adverse effect on the embryo, fetus, and newborn. A thorough assessment, including	**Case 49-1 (Question 5)**

	knowledge of the teratogenic potential of the drug, the critical period of exposure, and magnitude of risk, must be compared with the background risk.	
4	Gastrointestinal (GI) disturbances such as nausea and vomiting and gastric reflux that occur during pregnancy are common. Treatments include intravenous (IV) hydration, pyridoxine (vitamin B_6), antihistamines, and antiemetics for nausea and vomiting. Calcium carbonate, H_2-receptor antagonists, and proton-pump inhibitors may be used for reflux.	**Case 49-1 (Questions 6–10)**
5	Urinary tract infections can frequently occur during pregnancy and can easily be treated with nitrofurantoin, cephalexin, or penicillin if cultures are sensitive.	**Case 49-1 (Question 11)**
6	Diabetes mellitus is the most common maternal medical complication during pregnancy. Tight glycemic control can minimize neonatal and fetal morbidity and mortality associated with diabetic embryopathy.	**Case 49-2 (Questions 1–4) Case 49-3 (Questions 1, 2) Case 49-4 (Questions 1–4)**
7	Patients with pregnancy-associated hypertension can be grouped into the following categories: chronic hypertension, preeclampsia–eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension.	**Case 49-5 (Questions 1–13)**

8	The induction of labor involves the artificial stimulation of uterine contractions that lead to labor and delivery.	**Case 49-6 (Questions 1–5)**
9	Premature birth is the leading cause of neonatal mortality (infant death age <1 month). Tocolytic therapy to stop contractions, corticosteroids for fetal lung maturity, and antibiotics for preterm premature rupture of membranes can help prolong the pregnancy.	**Case 49-7 (Questions 1–7)**
10	Infectious complications, including bacterial vaginosis and urinary tract infections, can lead to preterm labor. Chorioamnionitis, an infection of the chorion and amnion usually diagnosed during labor with elevations in temperature, should be treated with IV antibiotics until delivery. Patients infected with the human immunodeficiency virus (HIV) should receive IV zidovudine and continue their antiretroviral regimens during labor.	**Case 49-7 (Questions 8–11) Case 49-8 (Questions 1, 2)**
11	Obstetric postpartum hemorrhage is one of the top three causes of maternal mortality in the United States. Pharmacologic therapy for uterine atony includes oxytocin, methylergonovine, carboprost, misoprostol, and dinoprostone.	**Case 49-8 (Questions 3, 4)**
12	Alloimmunization occurs when a patient who is Rh D negative becomes	**Case 49-9 (Questions 1–5)**

	immunized after exposure to fetal erythrocytes that carry the D antigen. Rh_o(D) immune globulin should be given to all patients who are Rh D negative at 28 weeks' gestation.	

LACTATION AND DRUGS IN BREAST MILK

1	Breast milk is recognized as the optimal source of nutrition for infants, with documented benefits not only to infants but also to mothers, families, and societies, and breast-feeding should be encouraged if possible.	**Case 49-10 (Questions 1, 2) Case 49-11 (Question 1)**
2	Most drugs are excreted in breast milk. The pharmacologic and adverse effects on the infant will be determined by the extent of oral bioavailability, distribution, metabolism, and rate of elimination. A milk-to-plasma ratio can be used to estimate the drug concentration in milk. The relative infant dose (RID) can be calculated to estimate the infant's exposure based on the volume of milk ingested.	**Case 49-8 (Question 2) Case 49-12 (Question 1) Case 49-13 (Question 1)**

INTRODUCTION

Parity and *gravida* are terms used to describe a pregnant person. Parity is the number of deliveries after 20 weeks' gestation. Parity is independent of the number of fetuses delivered (live or stillborn, single fetus, or twins) or the method of delivery. *Gravida* refers to the number of pregnancies a person has had regardless of the outcome.

For example, a person who is currently pregnant and has previously delivered one set of twins and had two spontaneous abortions is described as a gravida 4, para 1 (G4, P1).

Trimesters of Pregnancy

The average pregnancy is ~40 weeks when calculated from the first day of the last menstrual period (LMP). Pregnancy is typically divided into three trimesters, ~13 to 14 weeks each.[1] The first trimester includes the critical period of organogenesis, the time in which most of the vital organs are developing, which occurs between weeks 5 and 10. The time between the end of the 20th week of gestation and the end of the 28th day after birth is considered the perinatal period.

Delivery

Depending on the gestational age at the time of delivery, the result can be an abortion, preterm, term, or postterm birth. An abortion is a delivery before 20 weeks' gestation. A term infant is a fetus delivered between 37 and 42 weeks' gestation. A preterm birth is one occurring between 20 and 37 weeks' gestation, and a postterm (postmaturity) birth occurs after the beginning of 42 weeks' gestation. Parturition refers to labor, and the puerperium is the 6 to 8 weeks after delivery.

Preconceptional Care

CASE 49-1

QUESTION 1: S.C. is a 29-year-old, G1, P1 female who is interested in becoming pregnant. Her past medical history is significant for hypothyroidism. She currently is taking levothyroxine 88 µg orally (PO) daily.

How would you provide appropriate counseling to S.C. with regard to preconceptional care?

It is estimated that 3.6 million live births were registered in the United States in 2020, with an estimated 77.7% of patients beginning prenatal care in the first trimester. This can be contributed to several statewide initiatives to increase education and access to prenatal care.[2] Although much improved, prenatal care is still not easily accessible to all patients. Early comprehensive care can promote healthier pregnancies through early detection of risk factors, disease-state management, and encouragement of healthy behaviors, and will help ensure normal fetal organogenesis. Appropriate preconception counseling and treatment of patients with preexisting high-risk medical conditions, such as diabetes, hypertension, and epilepsy, can greatly improve pregnancy outcomes. In 2019, the mortality rate in the United States (from birth through the first year of life) for infants of patients beginning prenatal care in the first trimester was 5.58/1000 live births.[3]

S.C. should see her primary care provider for regular physical examinations and evaluation of her thyroid function before becoming pregnant. Her first prenatal visit should generally occur by 8 weeks' gestational age when she becomes pregnant.[4]

Vitamins and Mineral Supplementation

Case 49-1, Question 2: S.C. asks you to recommend vitamin and mineral supplementation. When should she begin taking these vitamins and minerals?

A balanced diet that provides S.C. with multiple B vitamins, oil-soluble vitamins (A, E, D, and K), folic acid, and minerals (iron, calcium, phosphorus, magnesium, iodine, zinc) should be encouraged. S.C. should be started on a prenatal multivitamin if she has not yet started taking one. Prenatal vitamins should be taken months before conception to ensure that proper nutritional requirements are met during critical periods of organogenesis and fetal growth.

IRON REQUIREMENTS

Iron requirements increase during pregnancy because of maternal blood volume expansion, fetal needs, placenta and cord needs, and blood loss at the time of delivery.[5] Maternal iron deficiency can cause anemia during infancy, spontaneous abortion, premature delivery, and delivery of a low-birth-weight infant, and is associated with low neonatal iron stores.[5,6]

A female needs about 18 to 21 mg of iron/day during pregnancy; the body compensates by increasing iron absorption from the gastrointestinal (GI) tract by about 15% to 50%.[5] The average diet of patients in the United States does not meet these requirements because only about 6 mg of iron is absorbed from 1000 kcal of food. In addition, some patients may already have inadequate body stores of iron before pregnancy. For these reasons, the Centers for Disease Control and Prevention recommends screening for iron deficiency in pregnancy in addition to universal iron supplementation except when genetic conditions such as hemochromatosis are present.[7] Prenatal vitamins usually contain 30 to 60 mg of elemental iron. Patients with iron deficiency anemia should be given 60 to 120 mg of elemental iron daily. Iron deficiency anemia during pregnancy generally is associated with a hemoglobin and hematocrit <11 mg/dL and <33%, respectively, during the first and third trimesters or <10.5 mg/dL and <32%, respectively, during the second trimester. The classic morphologic changes observed in the erythrocytes in iron deficiency outside of pregnancy, hypochromia, and microcytosis are not prominent in pregnant patients. Serum ferritin, however, is low, which has the highest sensitivity and specificity for diagnosing iron deficiency.[6] S.C.'s hemoglobin and hematocrit should be assessed now and again at 26 to 28 weeks' gestation. If her hemoglobin and hematocrit are normal, the amount of iron in her prenatal vitamin should be sufficient.

FOLATE REQUIREMENTS

Folic acid is essential in the synthesis of DNA and RNA. Pregnant patients who take 0.4 to 0.8 mg of folic acid daily during the first trimester of pregnancy are significantly less likely to have a child with

neural tube defects (NTDs), such as spina bifida and anencephaly.[8,9] NTD can lead to stillbirth, neonatal death, or serious disabilities. Approximately 4000 pregnancies in the United States are affected by NTD each year.[9]

NTDs develop within the first month of pregnancy at a time when many patients are unaware of their pregnancy.[9,10] In 1992, the U.S. Public Health Service recommended that all patients with childbearing potential should consume 0.4 mg/day of folic acid to reduce the risk of an NTD-affected pregnancy.[11]

It may be difficult to meet the recommended daily allowance (RDA) for folic acid because foods contain only a small amount of this vitamin; overcooking and high-fiber diets also can reduce the amount of available folic acid from food. Most prenatal vitamins contain 0.8 to 1 mg of folic acid.

Folic acid supplementation is especially important in patients with a history of infants born with NTD. Patients who have had an NTD-affected pregnancy should receive genetic counseling because they have a 2% to 3% risk of having another such outcome. Patients with previous NTD-affected pregnancies who plan another pregnancy should take 4 mg/day of folic acid at least 1 month before conception and through the first 3 months of pregnancy.[11]

Patients who require 4 mg/day of folic acid should be prescribed folic acid tablets as an addition to combination prenatal multivitamins (which contain folic acid), rather than just increasing the number of multivitamin tablets. When several fixed-combination multivitamin tablets are taken daily, the patient could be exposed to a potentially teratogenic dose of vitamin A. High doses of folic acid do not prevent NTD better than 0.4 mg/day in patients without a previous history of NTD-affected pregnancies and may complicate the diagnosis of a vitamin B_{12} deficiency.[9]

S.C. should be counseled about the risks of NTD, and given she has no history of NTD, she should receive adequate folic acid during the remainder of her pregnancy from a daily prenatal vitamin.

CALCIUM REQUIREMENTS

Calcium is needed during pregnancy for adequate mineralization of the fetal skeleton and teeth, especially during the third trimester when teeth are formed and skeletal growth is greatest. The RDA for calcium during pregnancy is 1000 mg/day for females ages 19 years and older, and 1300 mg/day for teenagers younger than age 19 years.[12] Large maternal stores can provide calcium if dietary intake is inadequate; however, depleting maternal stores may put S.C. at risk for osteoporosis later in life. Foods rich in calcium (eg, milk, cheese, yogurt, legumes, nuts, dried fruits) or calcium supplements can be used to meet the calcium RDA.

Commercially Available Home Pregnancy Tests

Case 49-1, Question 3: S.C. starts prenatal vitamins that contain iron and folic acid immediately. Two months have passed, and now S.C. believes that she may be pregnant because per period is a couple of weeks late. She requests your assistance in selecting an over-the-counter commercially available home pregnancy test. How do these home pregnancy tests work and how should S.C. be counseled?

Commercially available home pregnancy tests are enzyme immunoassays with monoclonal or polyclonal antibodies that bind to human chorionic gonadotropin (hCG) in the urine.[13] hCG is detected in the maternal circulation and urine ~8 to 10 days after conception.[14] Concentrations in the urine closely parallel those in the maternal blood. The hCG serum concentrations increase rapidly, doubling every 2 days. Peak concentrations are achieved at 60 to 70 days of pregnancy. Thereafter, hCG concentrations decline and reach a low by ~120 days, at which point concentrations are maintained for the remainder of the pregnancy.[14]

hCG is composed of an α- and a β-subunit. The α-subunit is identical to the α-subunit of other pituitary hormones (eg, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone); however, the β-subunit is specific to hCG. Pregnancy tests specific for this β-subunit are useful diagnostic tests for

confirming pregnancy.[1] They can provide accurate results within 1 to 2 weeks of ovulation.[1,13] Several kits are available. The tests can be performed privately and quickly and are easily interpreted. The results are obtained rapidly—within 1 and 5 minutes—and are highly accurate when performed at the start of the first missed menstrual period. Although home pregnancy tests are reportedly 98% to 100% accurate when used correctly, consumer studies have documented accuracy rates as low as 50% to 75% if product directions are not precisely followed.[13] Many home pregnancy tests include a second test, which should be repeated at a specified time after the first negative test result.

S.C. should purchase a product containing two tests and follow the instructions carefully. If the first test result is negative, S.C. should repeat the test in 1 week if she has not started menstruating. False-negative results occur when testing is done before the first day of a missed period or if the urine is not at room temperature.[13] False-negative results can also occur with an ectopic (outside the uterus) pregnancy or in patients with ovarian cysts and in those receiving menotropins or chorionic gonadotropin.[13] False-positive pregnancy test results are rare but can occur with serum testing if the person has circulating heterophilic antibodies directed against the animal-derived antigen used in pregnancy tests. These antibodies will not interfere with urine assays, however, because they are not present in urine.[15]

S.C.'s home pregnancy test result is positive. Because she is pregnant, she should be counseled on the possible fetal effects of any medications or herbal products she may be taking and advised to see her primary care provider as soon as possible.

Pregnancy-Induced Pharmacokinetic Changes

Case 49-1, Question 4: S.C. is now 6 weeks pregnant. She is concerned about any possible changes that might occur with her medications (levothyroxine 88 µg PO daily, prenatal vitamins). What pregnancy-induced pharmacokinetic changes that will affect her medication use might occur?

Important physiologic changes occur in almost all maternal organs during pregnancy to support the growth and development of the fetus. These physiologic changes affect the cardiovascular, respiratory, and GI systems; plasma volume, renal function, and hepatic enzymes can alter the absorption, distribution, metabolism, and elimination of drugs.[16] Alterations in the pharmacokinetics of drugs are influenced mainly by two factors: (a) maternal physiologic changes and (b) the effects of the placental–fetal compartment.[17]

ABSORPTION

Pregnancy-induced changes affecting drug absorption are (a) a decrease in intestinal motility owing to smooth muscle relaxation by progesterone, resulting in a 30% to 50% increase in gastric and intestinal emptying times; (b) a 40% decrease in gastric acidity, which increases gastric pH; and (c) altered bioavailability or absorption attributable to increased incidence of nausea and vomiting. Bioavailability may be increased for acid-labile drugs and decreased for drugs that require an acid medium for stability. Prolonged gastric and intestinal emptying times may decrease the maximum concentration (C_{max}) of a drug and the time to reach C_{max}, whereas the increased intestinal transit time may increase the area under the curve (AUC) and bioavailability of a drug. In contrast, pregnancy-induced vomiting may decrease the amount of drug ingested; it is therefore better to schedule medications during the evening when the incidence of nausea and vomiting is lower, or to use the rectal route for drug administration. In summary, the effect of pregnancy on drug absorption is variable and depends greatly on the physicochemical properties of the drug.[17] Increased blood flow to the maternal skin, which helps dissipate fetal heat production, may also increase the absorption of a topically (transdermal) administered medication.[16]

DISTRIBUTION

Changes in protein binding and increased plasma volume can theoretically increase the apparent volume of distribution (V_d) of

drugs during pregnancy. Plasma volume increases by 6 to 8 weeks' gestation and continues to expand to 40% to 50% above pregnancy volumes by 32 to 34 weeks' gestation.[16,17] Plasma volume expands even more with multiple gestations. The total body water (TBW) increases by 8 L; 40% of this increase can be attributable to the patient and 60% to the fetal–placental unit. This increase in TBW necessitates larger loading doses of water-soluble drugs (eg, aminoglycosides) because of the increase in V_d. A decrease in the C_{max} would be expected.

Plasma albumin concentrations decrease during pregnancy, mostly because of dilution by the increased plasma volume.[16,17] Albumin concentrations may also be decreased as a result of decreased synthesis or increased catabolism.[16] In addition, increased concentrations of steroid and placental hormones may decrease protein-binding sites for drugs.[18] These changes in protein binding generally result in decreased protein binding, increased free fraction (f_u) of drugs, and increased clearance of drugs when clearance is dependent on f_u (eg, valproic acid, carbamazepine).[18] When both f_u and intrinsic clearance are increased as is the case with increased cytochrome P450 (CYP) enzyme activity, both the total and free concentrations are decreased (eg, phenytoin, phenobarbital).[19] Total protein and α_1-acid glycoprotein concentrations remain fairly unchanged.

METABOLISM

Protein binding, activity of hepatic enzymes, and liver blood flow determine the hepatic clearance of drugs. Increases in estrogen and progesterone during pregnancy affect the hepatic metabolism by stimulating or decreasing different hepatic enzymes of the CYP system.[20] CYP3A4 and CYP2D6 activities are increased during pregnancy, which results in increased metabolism of certain drugs such as phenytoin.[17,20] On the other hand, CYP1A2, xanthine oxidase, and *N*-acetyltransferase activities are decreased, resulting in reduced hepatic elimination of drugs such as theophylline and

caffeine.[19,21] The clearance of caffeine can be decreased by 70%.[21] Hepatic blood flow as a percentage of the cardiac output is decreased; however, the absolute rate (in liters/minute) remains unchanged.[16] The activity of nonhepatic enzymes (eg, plasma cholinesterase) is also decreased.[19] The extent of the effect on drug therapy of these hepatic physiologic changes during pregnancy is difficult to quantify.

ELIMINATION

The glomerular filtration rate (GFR) begins to rise in the first half of the first trimester and increases by 50% by the beginning of the second trimester.[19] Renal blood flow also increases by 25% to 50% early during gestation. As a result, renal drug excretion (eg, β-lactams, enoxaparin, digoxin) can increase.[17] This increase in GFR necessitates dosage adjustments up to 20% to 65% for renally excreted drugs throughout pregnancy to maintain therapeutic concentrations.[20] The increased cardiac output and regional blood flow (eg, renal blood flow) primarily are caused by increased stroke volume and increased heart rate, which can increase drug distribution and drug excretion.

During pregnancy, the serum creatinine (SCr) concentration is lower because of the increased GFR, resulting in normal SCr values of 0.3 to 0.7 mg/dL in the first and second trimesters.[20] A normal value for SCr in nonpregnant adults is 0.6 to 1.2 mg/dL.[22] Similar changes occur with serum urea nitrogen and uric acid (UA) concentrations. These differences have important implications when assessing renal function during pregnancy. An SCr indicative of normal renal function in a nonpregnant female may be indicative of renal insufficiency in a person who is pregnant in their third trimester.

PLACENTAL–FETAL COMPARTMENT EFFECT

Maternal and fetal drug concentrations are dependent on the amount of drug that crosses the placenta, the extent of metabolism by the placenta, and fetal distribution and elimination of drug (**Fig. 49-1**).[17,20] Diffusion across the placenta is the main mechanism of drug

transfer; nonionized lipophilic substances are more readily transferred, whereas less lipid-soluble (eg, ionized) substances less readily cross the placenta.[17] Highly protein-bound or large-molecular-weight drugs (eg, heparin and insulin) do not cross the placenta. Both the immature fetal liver and placenta can metabolize drugs. Fetal drug accumulation can be problematic secondary to limited metabolic enzymatic activity along with the concern that approximately half of the blood flow from the umbilical vein bypasses the fetal liver and goes to the cardiac and cerebral circulations.[17] Another mechanism that can also lead to prolonged effects of drugs in the fetal compartment is ion trapping. This phenomenon occurs because the fetal plasma pH is more acidic than is the maternal plasma, causing weak bases (eg, usually nonionized and lipophilic substances) to diffuse across the placental barrier and become ionized in the more acidic fetal blood. The net effect is movement of drugs from the maternal to the fetal compartment. This equilibrium between the maternal and fetal compartments becomes important when therapeutic fetal drug concentrations are desired (eg, digoxin therapy for intrauterine fetal arrhythmias). Drugs are eliminated by the fetus primarily through diffusion back to the maternal compartment. As the fetal kidney matures, metabolites of drugs are excreted into the amniotic fluid.[17]

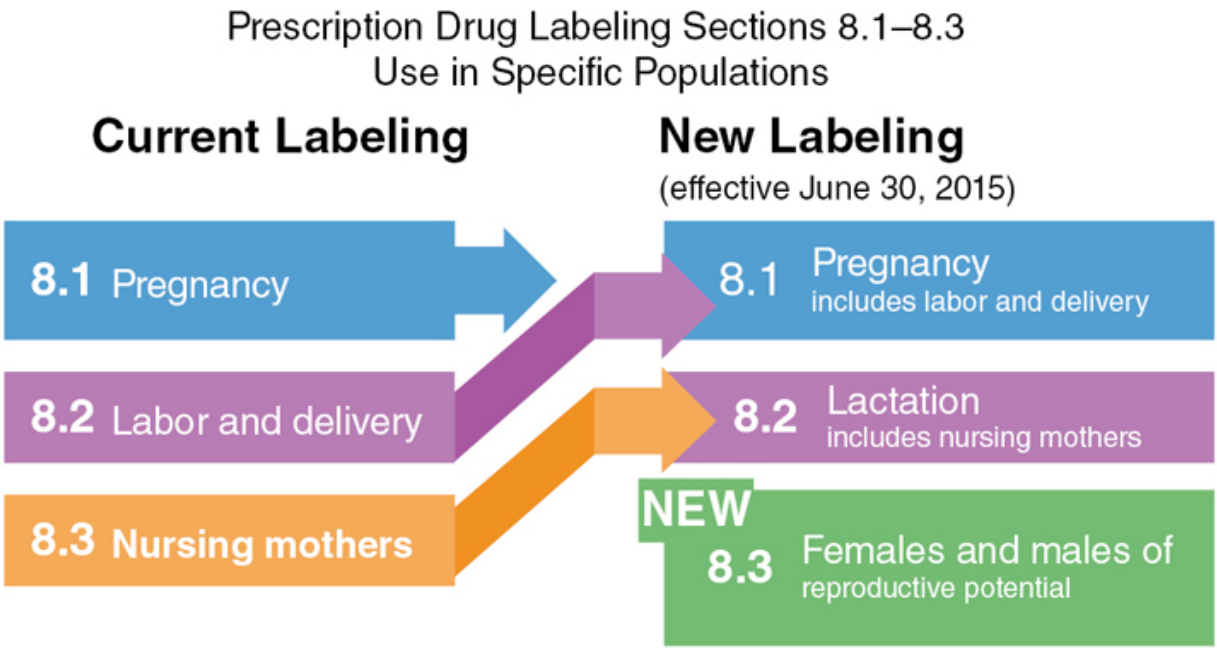


Figure 49-1 U.S. Food and Drug Administration (FDA) labeling. (From U.S. Food and Drug Administration. Pregnancy and lactation labeling (drugs) final rule. http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm.)

S.C.'s thyroid function should be checked regularly to assess the need for an increase in her levothyroxine dosage. During S.C.'s pregnancy, an increase in the V_d of thyroid hormones in the vascular, hepatic, and fetal–placental units, an increase in thyroxine-binding globulin resulting from a rise in estrogen, and an increase in placental transport and maternal metabolism of thyroxine will occur.[22] Most patients with hypothyroidism who are taking oral thyroid hormones before pregnancy, similar to S.C., will require an increase in their dosage by about 30% to 50% throughout their pregnancy and then will need decreased dose adjustments postpartum.[22]

TERATOGENICITY

Prevalence of Congenital Malformations

Case 49-1, Question 5: S.C. is currently 8 weeks pregnant and has become increasingly concerned about her medication use during pregnancy and the risk of birth defects. How should S.C. be counseled regarding the teratogenicity potential of levothyroxine use during pregnancy?

The largest concern with medication use during pregnancy is the risk of congenital malformations, defined as "structural abnormalities of prenatal origin that are present at birth and that seriously interfere with viability or physical well-being."[23] Congenital anomalies or birth defects are estimated to occur in 120,000 babies born per year.[10] Some drug-induced defects relate to changes in functions or conditions that are not structural abnormalities (eg, mental retardation, central nervous system [CNS] depression, deafness, tumors, or biochemical changes).[24] The broader term *congenital anomalies* includes the four major manifestations of abnormal fetal development—growth alterations, functional deficits, structural malformations, and fetal death.[25]

The background incidence of birth defects in the general population must be taken into consideration when interpreting the risk of drug-induced birth defects. The prevalence of major congenital malformations discovered at or shortly after birth in the general population is ~3%.[25] This number has been derived from large epidemiologic studies completed during the past several decades and depends on how terms are defined (eg, major vs minor congenital malformations), the thoroughness with which the infant is examined, and how long the exposed person is followed up after birth.[25] The collection of malformation data is a complicated task subject to numerous errors and biases. Some studies examined only "significant anomalies," others "major malformations," whereas still others reported only "live births" or "single births" or "birth weights >500 g." Stillbirths and spontaneous abortions, both often associated with congenital malformations, were excluded from epidemiologic data. Neurodevelopmental delays and growth retardation also are potential long-term effects that will not be diagnosed in the immediate postpartum period. The prevalence of congenital

anomalies is likely >3% if minor anomalies and long-term adverse effects are considered.

Despite the significant impact of drug-induced birth defects, it is difficult and unethical to conduct randomized controlled trials to assess the risk of fetal exposure to drugs in humans. Much of the data available are derived from epidemiologic studies, anecdotal experiences in humans, and animal studies. Because birth defects are species specific and influenced by many factors including genetic predisposition, the data must be carefully interpreted and the results not overgeneralized.

Causes of Malformations

CLASSIFICATION

Causes of congenital malformations are generally classified into one of five categories: (a) monogenic origin, (b) chromosomal abnormalities, (c) multifactorial inheritance, (d) environmental factors, and (e) unknown.[25] Single gene- and chromosomal-related defects account for ~25% of all congenital malformations in live-born infants (monogenetic, 7.5%–20%; chromosomal, 5%–6%).[24–26] *Multifactorial inheritance* refers to defects that are polygenic in origin; it has an environmental component. One surveillance program estimated that this interaction between genetic and environmental factors causes 23% of defects.[26] Congenital dislocation of the hip is an example of a defect in this category: The depths of the acetabular socket and joint laxity are genetically determined, and a frank breech malposition is one of the environmental factors.[27] In most cases, however, the environmental factors in multifactorial inheritance are unknown.

Environmental factors account for ~10% of malformations.[28] These include maternal conditions, mechanical effects, chemicals and drugs, and certain infectious agents. Maternal diseases associated with malformations include diabetes, phenylketonuria, virilizing tumors, and maternal hyperthermia. About 9% (range, 6.6%–13.0%) of infants of patients with diabetes develop major congenital defects,

primarily consisting of cardiovascular, neural tube, and skeletal malformations.[29] Mechanical effects, such as intrauterine compression and abnormal cord constriction, may result in fetal deformations.[28,29]

Probably, the best known of the teratogenic viruses is rubella, which can cause a fetal rubella syndrome consisting of cataracts, heart disease, and deafness.[30] In utero exposure to rubella in the first trimester can cause defects in up to 85% of fetuses. Cytomegalovirus infection occurs in 0.5% to 1.5% of newborns in the United States, resulting in deafness and mental retardation in 5% to 10% of these infants.[24] Characteristics of cytomegalic inclusion disease, the syndrome produced by cytomegalovirus, include intrauterine growth restriction (IUGR), microcephaly, and, at times, chorioretinitis, seizures, blindness, and optic atrophy. Herpes simplex 1 and 2 and varicella are also associated with malformations.[28]

The protozoan generally accepted as a teratogen is *Toxoplasma gondii*, which may be present in cat litter.[24] Most infants infected with *T. gondii* show no symptoms and develop normally. When toxicity does occur, the anomalies may consist of hepatosplenomegaly, icterus, maculopapular rash, chorioretinitis, cerebral calcifications, and hydrocephalus or microcephalous.[31] Because of the possible presence of *T. gondii* in cat litter, individuals should avoid cleaning or touching cat litter while pregnant. *Treponema pallidum* (syphilis) can cross the placenta and cause congenital syphilis as well as other defects, such as hydrocephaly, chorioretinitis, and optic atrophy.[30] In utero exposure to syphilis after the fourth month of pregnancy is associated with higher risk.

The final category, defects of unknown cause, comprises the greatest percentage of congenital malformations, accounting for about 60% to 65% of the total.[26]

Medication Use in Pregnancy and Teratogenicity

The term *teratogen* is used to denote an agent that has the potential under certain exposure conditions to produce abnormal development in the fetus.[25] Many patients have the general perception that use of any medication during a pregnancy can harm the developing fetus.[22] This thought may lead to consideration of terminating wanted pregnancies or withholding necessary drug therapy during the course of the pregnancy. The extent to which a drug will affect the development of the fetus depends on the physical and chemical properties of the drug as well as the dose, duration, route, and timing of exposure and the genetic composition and biologic susceptibility of the patient and fetus.[32,33] Numerous drugs have been associated with congenital anomalies, but only in a few cases has a consensus been reached that a specific agent is teratogenic. **Table 49-1**[34–36] lists those agents generally considered or suspected to be proven human teratogens. However, not all these teratogens will cause developmental toxicity with every exposure.

Table 49-1
Drugs With Suspected or Proven Teratogenic Effects in Humans

Alcohol	Growth restriction, mental retardation, midfacial hypoplasia, renal and cardiac defects
Androgens (testosterone)	Masculinization of female fetus
Angiotensin converting enzyme inhibitors and angiotensin receptor blockers	Pulmonary hypoplasia, hypocalvaria, oligohydramnios, fetal kidney anuria, and neonatal renal failure
Antithyroid drugs	Fetal and neonatal goiter with iodine use; small risk of aplasia cutis with methimazole
β-Blockers	IUGR and decrease in placental weight in β-blockers with intrinsic sympathomimetic activity if used in second and third trimesters
Carbamazepine	NTDs, minor craniofacial defects, fingernail hypoplasia
Cigarette smoking	IUGR, functional and behavioral deficits
Cocaine	Bowel atresias; heart, limbs, face, and genitourinary tract malformations; microcephaly;

	cerebral infarctions; growth restriction
Corticosteroids (systemic)	Oral cleft lip and palates if used during organogenesis
Cyclophosphamide	Craniofacial, eye, and limb defects; IUGR; neurobehavioral deficits
Diethylstilbestrol	Vaginal carcinoma and other genitourinary defects
Lamotrigine	Oral cleft lip and cleft palate[33]
Lithium	Ebstein anomaly
Methotrexate	CNS and limb malformations
Misoprostol	Möbius sequence (high doses) and spontaneous abortions
Nonsteroidal anti-inflammatory drugs	Constriction of the ductus arteriosus, oral clefts, cardiac defects, and possible spontaneous abortion
Paroxetine	Cardiovascular defects[34]
Phenytoin	Fetal hydantoin syndrome, growth retardation, CNS deficits
Streptomycin and kanamycin	Hearing loss, eighth cranial nerve damage; no ototoxicity reported with gentamicin, tobramycin, amikacin
Systemic retinoids (isotretinoin and etretinate)	CNS, craniofacial, cardiovascular defects
Tetracycline	Permanent discoloration of deciduous teeth
Thalidomide	Limb and skeletal shortening defects, internal organ defects
Topiramate	Cleft lip and cleft palate[35]
Trimethoprim	NTDs and cardiac defects
Vaccines (live)	Live attenuated vaccines can potentially cause fetal infection
Valproic acid	NTDs, developmental delay, and deficits
Vitamin A	Microtia, anotia, thymic aplasia, cardiovascular defects (high dose)
Warfarin	Fetal warfarin syndrome with nasal hypoplasia, stippled epiphyses, and skeletal and CNS defects

Teratogenic effects include the four major manifestations of abnormal fetal development, which include growth alterations, functional deficits, structural malformations, and fetal death.

Only drugs that are teratogenic when used at clinically recommended doses are listed. List is not an all-inclusive one.

CNS, central nervous system; IUGR, intrauterine growth restriction; NTDs, neural tube defects.

Sources: Briggs G, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 11th ed. Lippincott Williams & Wilkins; 2017; Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med.* 1998;338:1128–1137.

Because every pregnancy has the risk of an abnormal outcome regardless of drug exposure, the objective of evaluating data on drug exposure during pregnancy is to ascertain whether a particular drug increases the risk of developmental toxicity in the fetus beyond the background rate. The following basic principles of teratogenicity should be applied when assessing the potential for teratogenicity of drugs.

CRITICAL STAGE OF EXPOSURE

After fertilization, the development of the embryo and fetus is divided into three main stages: pre-embryonic period, embryonic period, and fetal period.[28] In the first 2 weeks after fertilization or the pre-embryonic period (0–14 days), little is known about the effects of drugs on human development. Exposure to a teratogenic agent during this period usually produces an “all or none” effect on the ovum[31]: The ovum either dies from exposure to a lethal dose of a teratogenic drug or regenerates completely after exposure to a sublethal dose. Some animal studies have suggested, however, that exposure to some drugs during the preimplantation stage can halt growth and development before implantation.[36] Although the damage can be repaired, intrauterine growth may be retarded in the offspring.

During the embryonic period (14–56 days after fertilization), when organogenesis occurs, the embryo is most susceptible to the effects of teratogens or other chemicals.[25,31] Exposure during this sensitive period may produce major morphologic changes (**Fig. 49-2**). These

stages of development differ significantly from that of other species, and knowledge of these stages is essential for the interpretation of the relationship between congenital malformations and drugs. For example, if a specific drug exposure occurs after the time of organ development, then a structural defect in that organ is less likely to be caused by that specific drug.

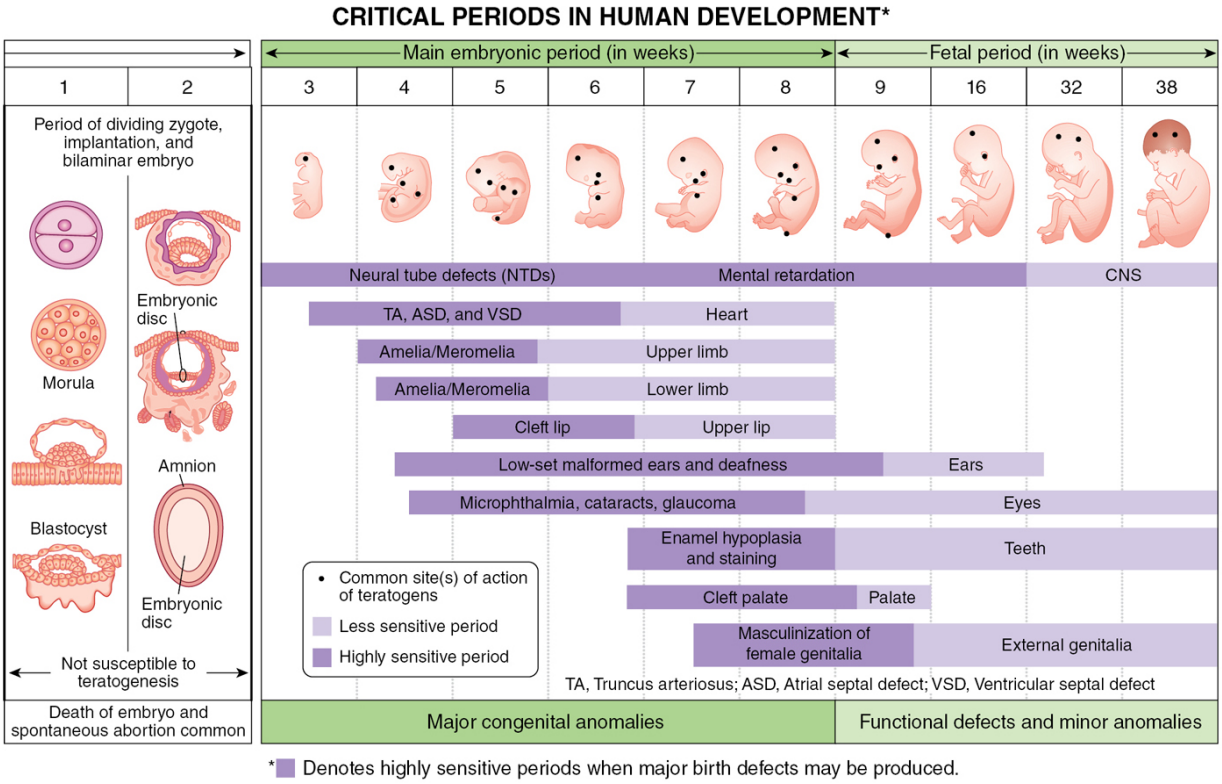


Figure 49-2 Critical stages of human development. (Adapted from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*. 7th ed. Saunders; 2003. © 2003 Elsevier. With permission.)

The fetal period (57 days to term) includes most of the stages of histogenesis and functional maturation, although the latter continues for some time after birth.[28] Minor structural changes are still possible during histogenesis, but anomalies are more likely to involve growth and functional aspects such as mental development and reproduction.

DOSE–RESPONSE CURVE

All teratogens follow a toxicologic dose–response curve.[25] These teratogens have a threshold dose below which adverse effects will not occur. The threshold dose is the dosage in which the incidence of structural malformations, rate of fetal death, growth restriction, and functional deficits do not exceed the background rate in the general population.[25] Conversely, developmental toxicity may occur when the fetus is exposed to doses above the maximum or threshold dose. There may be an increase in the severity and incidence of malformations when the fetus is exposed to increasingly higher dosages. For example, the risk of major congenital malformations, including NTD and minor anomalies, is increased statistically in patients taking valproic acid dosages >1000 mg/day during the first trimester.[37]

EXTRAPOLATION FROM ANIMAL STUDIES

In the absence of human trials, data derived from animal studies are used to assess the level of risk of developmental toxicity in humans. Most newly marketed drugs often have to rely on preclinical data to develop an estimation of teratogenic risk based on animal studies until human data become available.[38] The dose used in experimental animal data is expressed as multiples of the human dose using plasma or serum AUC or dose per unit based on body surface area.[39] The drug appears to have a low risk of teratogenicity if the toxic dose in animals (based on AUC or milligram per square meter comparison) is >10 times the anticipated human dose.[40] Risk assessment using animal data is more complicated than just considering the dosage alone. Other major factors, including the effects of metabolism and active metabolites, species differentiation, route of administration, and type of defects, must be considered.[25]

GENETIC VARIABILITY

The most potent teratogenic agent will not produce malformations with every exposure.[25] The teratogenic potential of some drugs is influenced by the genotype of both the patient and fetus. Although

the effects of known teratogens can be predictable in the general population, the possibility of individual assessment is difficult. The same dose of a teratogenic agent exposed at the same gestational window will produce variable outcomes in different people. Genetic variability can confer differences in cell sensitivities, placental transport, drug metabolism, enzyme composition, and receptor binding, which may affect how much active drug will reach fetal tissues.[41] One study showed an increased susceptibility to the teratogenic effect of phenytoin, most likely caused by elevated levels of oxidative metabolites (epoxides). These epoxides are normally eliminated from the systemic circulation by enzymes called *microsomal epoxide hydrolase*. Patients who are homozygous for the recessive allele produce low levels of epoxide hydrolase, which may expose the fetus to higher levels of epoxides. These fetuses may be at a higher risk for fetal hydantoin syndrome.[42]

PLACENTAL TRANSFER OF DRUGS

At one time, the placenta was thought to present a barrier to the passage of drugs and noxious chemicals to the fetus. It is now known, however, that most medications cross the placenta to the fetus and, in general, what the patient consumes also is consumed by the fetus. Although the placenta acts as a biologic membrane, it initially is composed of four layers effectively separating two distinct individuals.[41] These layers are (a) the endothelial lining of the fetal vessels, (b) the connective tissue in the core of the villus, (c) the cytotrophoblast layer, and (d) the covering syncytium. During gestation, the placenta's surface area increases while its thickness decreases from ~25 mm during the first trimester to 2 to 6 mm at term. Both processes tend to favor the transfer of chemicals to the fetus.

Drugs, nutrients, and other substances cross the placenta by five mechanisms: (a) simple diffusion (eg, most drugs), (b) facilitated diffusion (eg, glucose), (c) active transport (eg, some vitamins, amino acids), (d) pinocytosis (eg, immune antibodies), and (e)

breaks between cells (eg, erythrocytes).[39,41,42] The latter two mechanisms are of no practical importance in the transfer of drugs.

Several factors influence the rate of drug transfer across the placenta, including molecular weight (MW), lipid solubility, ionization, protein binding, uterine and umbilical blood flow, and maternal diseases.[39] Drugs with MWs of <600 cross easily, whereas those of >1000 (eg, heparin) cross with difficulty or not at all. Because most drugs have MWs of <600, it is safe to assume that most drugs reaching the patient's circulatory system also will reach the fetus. As with other biologic membranes, lipid-soluble substances are transferred rapidly, with the rate of entry primarily governed by the lipid solubility of the nonionized molecule. Conversely, those molecules that are ionized at physiologic pH (eg, the cholinergic quaternary amines) cross slowly, whereas weak acids and bases with dissociation constant (pK_a) values between 4.3 and 8.5 are transferred rapidly to the fetus. The penetration of highly protein-bound drugs also is inhibited; only the free, unbound drugs cross the placenta.[38,39,41]

Uterine blood flow, a major factor in determining the rate of drug transfer, increases throughout gestation. Several variables can affect uterine blood flow and the rate of drug transfer, including maternal blood pressure (BP), cord compression, and drug therapy. Maternal hypotension reduces uterine blood flow and the rate at which substances are delivered to the membrane. Cord compression reduces the blood flow on the fetal side of the membrane. The use of drugs with α-adrenergic property (eg, epinephrine) may constrict uterine vessels and thereby reduce blood flow.[27] Maternal diseases, such as pregnancy-induced hypertension, erythroblastosis, and diabetes, change the permeability of the placenta and may reduce or increase transfer.[36]

Food and Drug Administration Risk Factors

In 1979, the U.S. Food and Drug Administration (FDA) introduced a system of rating pregnancy risks associated with pharmacologic

agents. This system categorizes all drugs approved after 1983 into one of five pregnancy risk categories, A, B, C, D, and X. It establishes the level of risks to the fetus based on available animal and human data and recommends the degree of caution that should be undertaken with each drug.[38,40–42] This system had many limitations. Effective in June 2015, the FDA introduced a pregnancy labeling and category system to include narrative text to provide more clinical management advice that includes consideration of both animal and human data (see Fig. 49-1).[43] The structured narratives include the following sections for each drug: (a) pregnancy (including considerations during labor and delivery), (b) lactation (includes nursing patient considerations), and (c) females and males of reproductive potential.[43] For specific information on the FDA pregnancy labeling,[43] visit http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm.

The former FDA pregnancy classification structure states that levothyroxine is a pregnancy category A drug but does not give any further specific information. The updated FDA-structured narrative states, "Levothyroxine (T_4) is compatible with all stages of pregnancy. Untreated or undertreated maternal hypothyroidism is associated with low birth weight secondary to medically indicated preterm delivery, preeclampsia or placental abruption, and with lower neuropsychological development of their offspring."[38] S.C. should be counseled that levothyroxine can safely be used during all trimesters of pregnancy including the period of organogenesis, which she is currently in at 8 weeks' gestation. She should not discontinue her levothyroxine. Thyroxine insufficiency has been shown to impair fetal and neonatal development. Levothyroxine therapy has not been observed to increase the risk of congenital malformations beyond the reported background risk of 3%.[38]

MANAGEMENT OF CONDITIONS IN PREGNANCY

Nausea and Vomiting

Case 49-1, Question 6: S.C. is now 10 weeks pregnant and reports nausea throughout the day, with emesis occurring two to three times daily. She is able to tolerate at least two meals a day and oral liquids. She reports very little weight gain since she became pregnant. Her current weight is 158.73 pounds (72 kg). S.C. states that certain smells such as fish, eggs, and beans cause her to gag. How long is her nausea and vomiting likely to last?

According to the American College of Obstetricians and Gynecology (ACOG), nausea and vomiting during pregnancy (NVP) is a common condition occurring in ~70% to 85% of pregnancies, during weeks 5 to 12 of gestation.[44] For most patients, NVP is a self-limiting condition that usually resolves after the first trimester with no long-term detrimental effect on the fetus.[47] About 91% of cases will resolve by 20 weeks of gestation.[45] The effects of NVP can have an impact on a person's daily activities, work productivity, and quality of life. Studies estimate that $130 million/year is spent on the hospitalization for severe NVP.[46] The cause of NVP is unknown, but is most likely multifactorial including hormonal, psychological, and neurologic factors. Changes in hormonal levels of estrogen, progesterone, and hCG have been implicated as a possible cause of NVP. Mild-to-moderate NVP has been associated with lower rates of miscarriage, preterm delivery, and stillbirth.[47]

NONPHARMACOLOGIC MANAGEMENT OF NAUSEA AND VOMITING

Case 49-1, Question 7: What nonpharmacologic approaches should S.C. try for her nausea and vomiting?

Most mild forms of NVP can be managed with psychological support and lifestyle and dietary changes. Advising S.C. to eat smaller frequent meals consisting of a low-fat, bland, and dry diet (eg, bananas, crackers, rice, toast), to avoid spicy and highly aromatic foods, and to take prenatal vitamins with iron at night may alleviate some of the symptoms. Meals high in protein are more likely to alleviate NVP than do carbohydrate-laden or fatty meals. Rest and avoidance of the sensory stimuli occurring from foods, and lotions that may contribute to the effects of NVP can also be helpful.[47] Advise S.C. to avoid the foods (ie, fish, beans, eggs, spaghetti sauce) that specifically trigger her gag reflex, which may induce emesis.

PHARMACOLOGIC MANAGEMENT OF NAUSEA AND VOMITING

Case 49-1, Question 8: S.C. has tried crackers and avoiding the foods that trigger her gag reflex but does not respond to nonpharmacologic treatment of her nausea and vomiting. What pharmacologic agent would be appropriate for her?

Antiemetics are indicated for the treatment of moderate-to-severe nausea and vomiting that fails to respond to nonpharmacologic interventions or when the nausea or vomiting threatens the patient's metabolic or nutritional status (eg, hyperemesis gravidarum). Traditionally, medications for NVP have been avoided during the first trimester because of fear of the possible teratogenic effects. Most antiemetic therapies (eg, antihistamines, multivitamins, phenothiazines) can be taken during pregnancy safely. **Table 49-2**[3,8,46,48–50] shows the most common antiemetics used during pregnancy. The goal of antiemetic therapy is to choose an effective medication to improve a person's quality of life by maintaining her nutrition and hydration needs, while ensuring fetal safety.

Table 49-2
Common Antiemetics Used for Nausea and Vomiting During

Pregnancy

Drug	Dose	Comments
Vitamin B_6 (pyridoxine)	10–25 mg PO tid	First-line therapy[45] Documented safety in pregnancy
Vitamin B_6 (pyridoxine)—doxylamine combination	Pyridoxine 10–25 mg PO tid–qid Doxylamine 12.5 mg PO tid–qid Doxylamine 10 mg/ Pyridoxine 10 mg PO qhs, max four tablets/day	First-line therapy Available OTC Well-documented safety in pregnancy through large meta-analysis[53] RX only
Antihistamines		
Diphenhydramine Meclizine Hydroxyzine Dimenhydrinate	25–50 mg PO every 8 hours 25 mg PO every 6 hours 25–50 mg PO every 4–6 hours 50–100 mg PO every 4–6 hours	First-line therapy Antihistamines have not been shown to be teratogenic.[49,54]
Phenothiazines		
Promethazine Prochlorperazine	12.5–25 mg PO, PR every 6 hours 5–10 mg PO every 6–8 hours	Second line of therapy Available as suppositories Also suppositories and buccal tablets Usually, add phenothiazine or metoclopramide to therapy if antihistamines fail.[45,50] Can cause EPS
Dopamine Antagonists		
Metoclopramide	10 mg PO every 6 hours	Usually, add phenothiazine or metoclopramide to therapy if antihistamines fail.[45,50] Avoid treatment >12 weeks' duration, risk of tardive dyskinesia Can cause EPS

Drug	Dose	Comments
Droperidol	1.25–2.5 mg IV/IM or continuous infusion 1 mg/hour for treatment of hyperemesis gravidarum[49]	Boxed warning regarding torsades de pointes, may need ECG during administration Continuous infusion of droperidol requires concomitant diphenhydramine 50 mg IV every 6 hours.
5-HT_3 Receptor Antagonists		
Ondansetron	4–8 mg IV/PO every 6–8 hours	Available as ODT tablets Does not cause sedation Studies suggest low risk in pregnancy.[38,55]
Glucocorticoids		
Methylprednisolone	16 mg PO every 8 hours × 3 days, then taper over 2 weeks	For refractory cases, last line of therapy Avoid use before 10th week of gestation, associated with oral cleft and palate.[38,45]
Ginger extract	125–250 mg PO every 6 hours	Available OTC as food supplement

ECG, electrocardiogram; EPS, extrapyramidal symptoms; IM, intramuscular; IV, intravenous; ODT, oral disintegrating tablet; OTC, over-the-counter; PO, by mouth; PR, per rectum; qid, four times a day; qhs, daily at bedtime; tid, three times a day.

Sources: Briggs G, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 11th ed. Lippincott Williams & Wilkins; 2017; Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med.* 2010;363:1544–1550; McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology*. 1994;50:27–37; Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. *Am J Perinatol.* 1997;14:119–124.

The prescription delayed-release formulation, recently approved by the FDA, of 10 mg doxylamine with 10 mg of pyridoxine (vitamin B_6) called Diclegis® can be considered first-line therapy for the treatment of NVP. Several randomized controlled trials have

demonstrated its effectiveness in reducing NVP. Because of its safety and efficacy profile, doxylamine and pyridoxine are still considered first-line therapy and are available in combination as prescription or separately as over-the-counter products.[48,51–53]

Other antihistamine H_1 receptor blockers (eg, diphenhydramine, hydroxyzine, meclizine, dimenhydrinate) have been studied for NVP. The safety of antihistamines was supported in a meta-analysis including >200,000 first-trimester exposures, which did not find an increase in teratogenic risk.[54] Sedation is the main side effect that limits the use of this class of antiemetics.

Phenothiazines or metoclopramide is usually prescribed if antihistamines fail.[49,50] Phenothiazines (eg, promethazine, prochlorperazine) are generally considered safe for both the patient and fetus if used occasionally in low doses. A recent randomized trial compared IV metoclopramide versus IV promethazine in the treatment of hyperemesis gravidarum and found that both agents have similar efficacy. However, metoclopramide caused less drowsiness and dizziness.[49] Metoclopramide, a dopaminergic antagonist with prokinetic abilities, can control vomiting and gastric reflux associated with pregnancy. Oral metoclopramide can be added to an antihistamine (eg, hydroxyzine) or a regimen of doxylamine and pyridoxine.[49,50] A large cohort study of 3458 females exposed to metoclopramide in the first trimester failed to show an increase in congenital malformations. Metoclopramide issued a black box warning concerning the risk of rare incidences of tardive dyskinesia.[49,50] Risk of tardive dyskinesia increases with a longer duration of treatment and total cumulative doses; thus, length of therapy beyond 12 weeks should be avoided.[49,50]

The use of ondansetron, a 5-hydroxytryptamine type 3 antagonist, during pregnancy has increased owing to more experiences with its use. It is increasingly used for NVP and hyperemesis owing to ease of administration with oral disintegrating tablets and tolerability with minimal sedating side effects or poor fetal outcomes.[46,55] Methylprednisolone is an option for refractory cases; however, its

use during the first trimester is associated with a small but significant risk of fetal oral clefts.

Alternative therapies (eg, vitamin B_6, ginger root, acupuncture, acupressure) have improved NVP in a small number of patients.[38,45] S.C. may be started on doxylamine 10 mg and pyridoxine 10 mg two tablets PO at bedtime. S.C. may increase to two additional tablets in the afternoon if needed to a maximum of four tablets per day because of its safety and efficacy profile. Drug selection for S.C. mostly depends on the tolerability of adverse effects. If S.C. continues to have significant nausea and emesis on these antiemetics and fails to tolerate any oral liquids or solids, she should be advised to return to the clinic for evaluation and possibly be admitted for IV hydration and IV antiemetic therapy.

Case 49-1, Question 9: S.C. returns to the clinic a few weeks later at 12 weeks' gestation stating that she has lost about 8.82 pounds (4 kg) in the past 3 weeks, has been unable to tolerate any liquids or medication for 2 weeks, and feels dehydrated and dizzy. S.C. is referred for admission to the hospital. What recommendations should be given to S.C. to help control her nausea and vomiting?

Severe NVP can persist in <1% of pregnancies, leading to a condition called *hyperemesis gravidarum,* which can lead to detrimental effects on the patient and fetus. Weight loss of >5% of prepregnancy weight, ketonuria, and electrolyte abnormalities are associated with this condition. Treatment of hyperemesis gravidarum often requires hospitalization for parenteral fluid administration, electrolyte replacement, vitamin supplementation, and antiemetic therapy.[47] Metabolic acidosis, ketosis, hypovolemia, electrolyte disturbances, and weight loss may ensue if patients are not treated.[47] Reductions in lower esophageal pressure, gastric peristalsis, and gastric emptying may worsen nausea and vomiting.

In addition to ondansetron, used for NVP as mentioned earlier, droperidol, an intravenous (IV) dopamine antagonist, has been used extensively for many years in the treatment of hyperemesis and the prevention and treatment of postoperative nausea and vomiting.[38]

Although the FDA has mandated electrocardiographic monitoring for concern about the risk of prolonged QTc interval, large meta-analysis studies have failed to show an increased risk of arrhythmias when using droperidol at the low doses used for nausea and vomiting.[45] Limited experience with droperidol use in hyperemesis gravidarum has been documented in a small controlled trial.[51] Human and animal data suggest that droperidol carries a low risk of teratogenicity to the fetus.[38,49,50]

S.C. should be hydrated with IV fluids with electrolyte replacement therapy and multivitamins including pyridoxine. If hydration with multivitamins does not quell her nausea, IV ondansetron 4 to 8 mg every 4 to 6 hours should be given. IV droperidol therapy should be considered if ondansetron does not work. She should also be evaluated for other causes of nausea and vomiting if her symptoms persist (eg, gastroenteritis, cholecystitis, pancreatitis, hepatitis, peptic ulcer disease, pyelonephritis, and fatty liver of pregnancy).[47] Enteral nutrition may be needed in the treatment of hyperemesis gravidarum if S.C. cannot tolerate oral liquid and solid intake despite continuous IV antiemetics and hydration. Total parenteral nutrition should be reserved after multiple antiemetic regimens and enteral therapies have failed because of the substantial risks of catheter sepsis (25%) and thromboembolic clots.[45,46,49]

REFLUX ESOPHAGITIS

Case 49-1 Question 10: S.C. is now 30 weeks pregnant and no longer reports nausea or vomiting. However, now she has heartburn that worsens when she lies down. What causes reflux esophagitis in pregnancy, and how should S.C. manage this problem?

Reflux esophagitis or heartburn is a normal occurrence in pregnancy affecting approximately two-thirds of patients. The enlarging uterus increases intra-abdominal pressure, and estrogen and progesterone relax the esophageal sphincter. These two factors cause the reflux of stomach acid into the lower esophagus, producing symptoms of substernal burning worsened by eating, lying

down, or bending over. Lifestyle and dietary modifications, such as eating smaller meals, avoiding late meals close to bedtime, and elevation of the head of the bed, should be tried first. Avoidance of salicylates, caffeine, alcohol, and nicotine are encouraged to reduce the symptoms of reflux and fetal exposure to these harmful substances.

If these modifications are not successful, S.C. should try a calcium carbonate antacid. Animal studies have not shown antacids to have teratogenic effects.[38] Sodium bicarbonate can cause metabolic alkalosis and fluid overload and should be avoided. Despite evidence of fetal toxicity with aluminum, available data suggest that usual doses of aluminum-containing medications are not harmful to the fetus of a pregnant person with normal renal function. Sucralfate, which contains aluminum, appears to be safe in pregnancy. The American College of Gastroenterology has classified sucralfate as a medication with benefits that outweigh the risks when used in pregnant patients.[38]

H_2-receptor antagonists can be used safely during pregnancy because most studies in animals and humans have not found fetal harm with cimetidine, ranitidine, famotidine, or nizatidine.[38] If H_2-receptor antagonists fail to control symptoms, proton-pump inhibitors (PPIs) should be used as the next treatment option. Recent studies have shown that PPI use during the first trimester and throughout pregnancy is not associated with a significant increase in the risk of congenital anomalies. These studies suggest that PPIs can be safely used at any gestational age.[56,57]

URINARY TRACT INFECTIONS

Pathogenesis

CASE 49-1, QUESTION 11: S.C. is now 31 weeks pregnant, and a routine urine dip finding was positive for leukocyte esterase and nitrates. Her urine was sent

for urinalysis at her most recent prenatal visit and the result was positive for 10^5 colony-forming units (CFUs) of *Escherichia coli*. She does not report frequency and urgency when urinating and denies any fevers. Her temperature is currently 98.9 °F (37.17 °C). She denies any allergies to medications. What are the risks of having a urinary tract infection (UTI) during pregnancy, and how should S.C. be treated?

UTIs are one of the most common complications of pregnancy owing to hormonal and mechanical changes that increase the likelihood of bacteriuria. During pregnancy, increases in progesterone cause relaxation of ureteral smooth muscle, promoting urinary stasis. The enlarging gravid uterus can also mechanically compress the ureters, which may lead to urinary retention. Approximately 90% of pregnant patients may exhibit ureteral dilation or hydronephrosis, which can decrease bladder tone and ureteral tone. These physiologic changes, along with increases in the GFR, urine alkalization, and glucosuria, help promote bacterial growth.

Asymptomatic Bacteriuria and Acute Cystitis

UTIs during pregnancy can present as either asymptomatic bacteriuria (ASB) or acute cystitis. ASB is defined as the presence of significant bacteria, $>10^5$ CFU of bacteria, obtained by two consecutive clean-catch samples in the absence of any urinary symptoms.[58] In contrast, acute cystitis involves an infection of the bladder and manifests with signs and symptoms of frequency, urgency, dysuria, and hematuria without fever or evidence of systemic illness along with significant presence of bacteria of at least 10^5 CFU. Counts of $<10^5$ CFU with two or more organisms likely represent contamination and not true bacteriuria.

ASB is estimated to occur in 2.5% to 15% of pregnant patients, with about 80,000 to 400,000 cases occurring each year in the United States.[58,59] If ASBs are left untreated, they can lead to complications such as pyelonephritis, low-birth-weight infants, and premature delivery.[60] During pregnancy, treatment of ASB reduces the risk of developing pyelonephritis dramatically down from 20% to

35% to only 1% to 4%.[60] The U.S. Preventive Services Task Force recommends screening for ASB with a urine culture for all pregnant patients between 12 and 16 weeks of gestation or at the first prenatal visit if it occurs later.[61] The ACOG further recommends repeating a urine culture during the third trimester.[62]

Risk factors for ASB during pregnancy include diabetes, sickle cell disease, immunosuppression, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome, urinary tract anatomic anomalies, and spinal cord injuries.[63] The primary sources of organisms that cause bacteriuria originate from existing vaginal and perineal flora and migrate up the urethra to cause ASB and cystitis; they include *E. coli* (most common pathogen isolated), *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter* species, *Enterococcus, Staphylococcus saprophyticus*, and group B β-hemolytic *Streptococcus.*[63] Commonly used antibiotics include penicillins, cephalosporins, and nitrofurantoin. Antibiotic selection should be guided by antimicrobial susceptibility testing. For coverage of the most common organism, *E. coli,* oral nitrofurantoin, or cephalexin is often used. *E. coli* resistance to amoxicillin and trimethoprim–sulfamethoxazole has been increasing.[63,64] The antibiotic chosen should produce adequate concentration in the urine, have a low resistance rate, and be safe to use during pregnancy. A 7-day regimen of antibiotics should be used whenever possible.[63,64] A recent World Health Organization (WHO) multicenter, randomized, noninferiority trial found that a 7-day regimen with nitrofurantoin was more effective than a 1-day regimen was in treating pregnant patients with ASB, with bacteriologic cure rates of 86.2% and 75.7%, respectively.[64] Optimal antibiotics and duration of therapy have not been clearly identified and must be individualized for each patient based on cultures and sensitivity results.[60,63] For S.C., who likely has ASB, a 7-day course of nitrofurantoin is reasonable. At this gestation age of 31 weeks, nitrofurantoin can still be used safely. There is a small risk of hemolytic anemia in newborns when nitrofurantoin is used close to delivery.[38]

DIABETES MELLITUS

Diabetes mellitus is the most common maternal medical complication during pregnancy. Diabetes during pregnancy can be detected before or during pregnancy and can be separated into two groups: (a) *pregestational diabetes,* which includes patients who have been diagnosed before pregnancy with either diabetes type 1 or diabetes type 2, or (b) *gestational diabetes mellitus* (GDM), defined as carbohydrate intolerance first detected during pregnancy.[65]

More prevalent than pregestational diabetes, GDM accounts for >90% of diabetes cases during pregnancy and affects ~6% to 7% of live births each year.[66] It is estimated that 50% of patients with GDM will go on to develop type 2 diabetes 22 to 28 years postpregnancy.[67,68]

Pregestational diabetes accounts for the remaining 10% of cases. In the United States, >8 million patients have pregestational diabetes, affecting about 1% of live births each year.[71] Most patients with pregestational diabetes have type 2 diabetes characterized by peripheral insulin resistance and relative insulin deficiency.[69] The incidence of type 2 pregestational diabetes has been rapidly rising in the past decade, most likely because of the increasing prevalence of obesity. In contrast to type 2 diabetes, type 1 diabetes is characterized by complete insulin deficiency resulting from autoimmune destruction of pancreatic β cells.[69] Less than 0.5% of all pregnancies in the United States are complicated by type 1 diabetes.[70]

Fluctuating glucose levels during the first trimester may be the first signs of pregnancy for patients with pregestational diabetes owing to increased insulin resistance and reduced sensitivity to insulin action. Placental hormones (eg, human placental lactogen, progesterone, prolactin [PRL], placental growth hormone, and cortisol) are thought to be responsible for the increase in insulin resistance during pregnancy. The ACOG classifies diabetes in pregnancy according to the White classification, modified to include gestational diabetes

according to glycemic control. The White classification relies on age at onset, duration of diabetes, and presence of vascular complications for patient classification (**Table 49-3**).

Table 49-3
Modified White Classification of Diabetes During Pregnancy

Class of Diabetes	Age of Onset	Duration	Vascular Complications	Treatment of Choice During Pregnancy
Class A1	First diagnosed during pregnancy	During pregnancy	None	Diet, exercise
Class A2	First diagnosed during pregnancy	During pregnancy	None	Diet, exercise plus oral hypoglycemics or insulin
Class B	Older than 20 years	<10 years	None	Insulin therapy
Class C	Between 10 and 19 years	>10 years, <19 years	None	Insulin therapy
Class D	Younger than 10 years	>20 years	Background retinopathy Hypertension Microalbuminuria	Insulin therapy
Class F	At any age	Any duration	Nephropathy Macroalbuminuria (>500 mg/day)	Insulin therapy
Class H	At any age	Any duration	Arteriosclerotic heart disease	Insulin therapy
Class R	At any age	Any duration	Proliferative retinopathy Vitreous hemorrhage	Insulin therapy
Class T	At any age	Any duration	Renal transplantation	Insulin therapy

Sources: Cunningham FG, Leveno KJ, Bloom SL, et al. Diabetes. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill; 2014; White P. Classification of obstetric diabetes. *Am J Obstet Gynecol.* 1978;130:228–230.

Preexisting Diabetes Mellitus

FETAL AND INFANT RISKS

CASE 49-2

Question 1: K.H., a 27-year-old, 132.28-pound (60-kg) female known to have type 1 diabetes since age 12, has married recently and wishes to have children. She has been conscientious in her diabetes care and self-monitors her blood glucose concentrations two to three times a day (fasting and before meals). During the past month, her fasting blood glucose concentrations have ranged from 90 to 140 mg/dL. Today, her fasting blood glucose and glycated hemoglobin (HbA_{1c}) laboratory results are 134 mg/dL and 7.8%, respectively. Her BP is 145/94 mm Hg, renal function is normal, SCr is 0.8 mg/dL, and she does not have proteinuria. K.H. reports tingling and pain in her toes. Her current medications include lisinopril 5 mg PO daily, insulin glargine (Lantus®) 16 units

subcutaneously (SC) every day at bedtime with an insulin lispro (Humalog®) sliding scale of 2 to 10 units before each meal. She reports eating only two meals a day and no snacks in between.

How will diabetes affect the health of the offspring?

Perinatal mortality for infants of patients with diabetes has declined dramatically with strict maternal metabolic control, improved fetal surveillance, and neonatal intensive care.[71] Fetal and neonatal mortality rates are ~2% to 4%, and the risk of spontaneous abortion in patients with well-controlled type 1 diabetes is equal to that of patients without diabetes.[72] The incidence of stillbirth is greatest after 36 weeks' gestation in patients with poor glycemic control, fetal macrosomia (see subsequent discussion), maternal vascular disease, ketoacidosis, or preeclampsia.[65]

The leading cause of perinatal mortality is major congenital anomalies that occur in 9% to 14% of infants born to patients with diabetes. The major malformations observed include NTDs and other anomalies involving the cardiac, renal, and GI systems, and, rarely, caudal regression syndrome.[66] Many congenital anomalies occur during organogenesis, before the seventh week of gestation, when patients are often unaware that they are pregnant.[73] A direct correlation exists between higher HbA_{1c} levels and increased frequency of anomalies.[73] Patients with elevated HbA_{1c} values during the time of conception have a significantly higher incidence of infants with anomalies compared with patients with HbA_{1c} closer to the normal range of 4.0% to 5.6%.[74] The risk of fetal anomalies increases dramatically to ~20% to 25% when HbA_{1c} levels are near 10%.[73] HbA_{1c} levels >12% are associated with the same risk of anomalies as infants exposed to known teratogens such as thalidomide, isotretinoin, or alcohol during organogenesis.

Macrosomia, defined as birth weight >8.82 pounds (4 kg), is thought to be caused in part by fetal hyperglycemia and hyperinsulinemia.[65] Fetal hyperglycemia occurs when glucose crosses the placenta and subsequently stimulates fetal pancreatic β cells to release excessive insulin. Hyperinsulinemia promotes

excessive fetal growth in adipose tissue, causing disproportional fat concentration around the shoulders and chest and doubling the risks of trauma (eg, shoulder dystocia) during vaginal delivery.

Infants of patients with diabetes also are at increased risk for prolonged hypoglycemia after delivery, respiratory distress syndrome (RDS), hypocalcemia, polycythemia, and hyperbilirubinemia during the neonatal period.[66]

K.H. should be informed that stringent preconception glycemic control is essential for preventing early pregnancy loss and congenital malformations in the infant.[71] Tight glucose control, especially in the months before pregnancy and early in the first trimester, will maximize her chance of having a healthy baby. She should be educated before pregnancy about healthy practices she can institute now to improve a successful pregnancy outcome.

MATERNAL RISKS

CASE 49-2, QUESTION 2: K.H. wants to know what health risks she might incur from becoming pregnant and what measures could minimize these risks?

A prepregnancy assessment, including a history and physical examination, is necessary to determine the risks of or contraindications to pregnancy for K.H. She should be evaluated for ischemic heart disease, neuropathies, or retinopathy, and her renal status must be assessed.[71] Pregnancy can exacerbate the vascular complications of diabetes. For instance, diabetic retinopathy can worsen if strict glycemic control is implemented quickly in pregnant patients with proliferative retinopathy; progression to end-stage renal disease can occur in patients with mild-to-moderate renal insufficiency (eg, SCr >1.5 mg/dL or proteinuria >3 g/24 hours).[66,69] The presence of gastroparesis should be noted because it will make controlling her glucose more difficult.[71]

Controlling K.H.'s diabetes before she becomes pregnant may benefit her hypertension and neuropathies and will minimize

maternal and fetal problems. Good metabolic control of her diabetes can minimize progression of her diabetes.[73]

PRECONCEPTION MANAGEMENT

CASE 49-2, QUESTION 3: What prepregnancy interventions relative to her general health and diabetes should K.H. undertake before she attempts to become pregnant?

Pregestational care for K.H. should ideally begin 6 months before conception.[71] Recommendations for patients with diabetes who want to conceive include suggesting birth control methods until stringent glycemic control can be achieved, consulting a dietitian to develop a patient-specific nutritional diet to attain healthy weight targets, and implementing a self-monitoring blood glucose regimen.[71] Good glycemic control (HbA_{1c} levels close to normal) should be achieved months before conception to minimize risks of major congenital anomalies. K.H.'s current regimen may not achieve euglycemia (see Chapter 53, Diabetes Mellitus). Her insulin therapy should be titrated to reduce her average blood glucose range from 90 to 120 mg/dL, targeting an HbA_{1c} of <6.5% without frequent episodes of hypoglycemia.[71,74] In addition, K.H. should be started on prenatal vitamins containing at least 400 µg of folic acid.

Her BP of 145/94 mm Hg is high and should be decreased to a diastolic BP of about 80 mm Hg to minimize risks for preeclampsia (see Case 49-5, Question 6) or exacerbation of her disorder. Many patients with pregestational diabetes, such as K.H., are likely on an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker for hypertension treatment or for renal protective effects. Before pregnancy and during preconception planning, K.H. should be switched to another antihypertensive (eg, methyldopa, labetalol, or calcium channel blockers) because recent studies have observed possible increased rates of congenital cardiac malformation associated with the use of ACEIs in the first trimester.[75] Further confirmatory studies are needed to define the risk of using

ACEIs during the first trimester. However, use of ACEIs is absolutely contraindicated during the second and third trimesters of pregnancy.[38,75]

CASE 49-2, QUESTION 4: After lowering her BP to 125/80 mm Hg with labetalol 200 mg PO twice daily and her HbA_{1c} to 7.3%, K.H. discontinues her oral contraceptive and returns to the clinic 5 months later and is noted to be about 4 weeks' pregnant. How should her diabetes be managed at this time?

TYPE 1 DIABETES TREATMENT IN PREGNANCY

Goals of therapy

The overall goal of treatment of K.H.'s diabetes is to reduce the maternal and fetal morbidity and mortality associated with diabetes. Treatment of diabetes (see Chapter 53, Diabetes Mellitus) should include dietary management, appropriate maternal weight gain, insulin therapy to normalize glycemic control, and exercise.

Dietary management

The goals of dietary management for diabetes during pregnancy are directed at ensuring fetal growth and development, appropriate maternal weight gain, and normalizing maternal glucose concentrations. Patients often benefit from individualized diets developed by a dietitian. Neonatal macrosomia has been associated with high postprandial glucose levels; therefore, a reduction in postprandial hyperglycemia is an important goal.

Blood glucose and glycated hemoglobin monitoring

K.H. should begin to self-monitor her blood sugars more intensively at fasting, before meals, 1 hour postprandially, at bedtime, when she feels symptomatic hypoglycemia, and at 3:00 AM to rule out dawn phenomenon versus Somogyi effect.[76] The goal of therapy is to maintain fasting glucose levels <90 mg/dL, premeal values of <100 mg/dL, and 1-hour postprandial levels of 100 to 120 mg/dL.[66,69] Tight glycemic control without incidence of hypoglycemic episodes,

targeting HbA_{1c} levels in the normal range, is the goal. Adjusting therapy based on postprandial glucose levels (as opposed to preprandial levels) can lower HbA_{1c} levels and decrease the risk of macrosomia, neonatal hypoglycemia, and cesarean delivery. HbA_{1c} levels can be drawn at each trimester to reveal the glycemic control during the previous 3 months.[68,69]

Insulin therapy

Insulin analogs (eg, lispro, aspart, glargine) are genetically engineered by recombinant DNA technology and usually differ by a few amino acids from human insulin. Concerns about insulin analog use during pregnancy include placental drug transfer and antibody formation.[77] The use of lispro (Humalog®) and aspart (Novolog®) insulin during pregnancy is supported by several studies that found minimal passage across the placenta, an absence of antibody formation, and no adverse maternal or fetal effects. Although the rapid onset of insulin lispro and aspart can increase adherence and patient satisfaction, it also may increase the incidence of hypoglycemia. Insulin glargine (Lantus®), a long-acting insulin analog, allows for once-daily dosing and produces a peakless basal level of insulin. Only case reports have examined the safety and efficacy of insulin glargine during pregnancy.[38] Glargine is usually reserved for patients with very brittle and sensitive insulin-dependent type 1 diabetes. Neutral protamine Hagedorn (NPH) insulin is usually used twice daily during pregnancy in lieu of insulin glargine as a basal insulin because it helps control fasting blood sugars better than does a peakless basal insulin. Newer insulin analogs such as insulin detemir (Levemir®) and insulin glulisine (Apidra®) have not yet been adequately studied during pregnancy and should not be used until further studies clarify their teratogenicity risk.[39]

Glycemic control is most difficult to establish during the first trimester of pregnancy because of the effect on blood sugars of maternal fluctuating hormones.[66,69] K.H.'s insulin regimen should be optimized by changing from insulin glargine to NPH insulin (with a 1:1 ratio) to help better control her fasting blood sugars and

instituting a standard insulin lispro dosage before meals based on her carbohydrate intake. Sliding scale insulin therapy is rarely used during pregnancy.[66,69] Insulin dosages commonly need to be monitored more strictly (every 2–4 days until glycemic control is achieved) during the first trimester and adjusted usually upward every 2 to 3 weeks during pregnancy.

TYPE 2 DIABETES TREATMENT IN PREGNANCY

Insulin therapy

CASE 49-3

Question 1: V.W. is a 36-year-old G3, P0 with class B diabetes at 15 weeks' gestation with a history of two spontaneous miscarriages occurring last year. She was diagnosed with diabetes 5 years ago during a routine physical examination. She is morbidly obese with a body mass index (BMI) of 49 kg/m^2, height of 65 inches (165.10 cm), and weight of 295 pounds (133.81 kg). She recently found out that she was pregnant and has not had any prenatal care. Her current medications include metformin 1000 mg PO twice daily and glipizide 5 mg PO daily. She states she has been noncompliant with checking her blood sugars, maintaining a diabetic diet, and taking her medication. Her last HbA_{1c}, which was 8.3%, was 2 months ago.

Which medication and treatments should V.W. be started on?

Insulin is the hypoglycemic agent of choice during pregnancy because it does not cross the placenta and has an established safety record for both patient and fetus. The goal with insulin therapy is to imitate the glucose levels of a healthy pregnant person. Rapid glycemic control is of utmost importance during this critical period of organogenesis when vital organs are developing.[73]

Insulin requirements may vary, depending on the trimester. The first trimester is characterized by unstable diabetes, followed by a stable period.[65] During the first trimester, glucose and gluconeogenic substances in the blood are taken up by the fetus, which can lead to a decrease in maternal insulin requirements and increased episodes of hypoglycemia. On average, insulin dosages range from 0.7 to 0.8 units/kg/day in the first trimester.[66,69] If nausea and vomiting occur

during this time, glycemic control may be unstable and should be monitored closely. At about 24 weeks' gestation, insulin requirements begin to increase from 0.8 to 1 unit/kg/day, and insulin doses may need to be adjusted every 5 to 10 days.[66,69] These needs continue to increase during the third trimester from 0.9 to 1.2 units/kg/day, which may be twice as much as the prepregnancy dose, in part because of the placental hormones (ie, lactogen, PRL, estrogen, and progesterone), which antagonize the action of insulin. Weight-based dosing may not accurately assess the insulin requirements in all pregnant patients, especially in the obese population. Insulin regimens must be individualized for each patient, taking into consideration their educational level, compliance, and schedule constraints. Dosage adjustments must take into account the level of activity, meal plan, and other factors (eg, steroid use, stress, infections) that may affect glucose control. Some patients may be admitted into the hospital in the first trimester to (a) rapidly gain glucose control, (b) accurately assess their insulin requirements, and (c) institute an individualized insulin regimen under careful monitoring of blood sugars.[65]

An insulin regimen with three to four daily injections is most successful at maintaining adequate glucose control. Biosynthetic human insulin (eg, regular and NPH insulin) is the usual treatment of choice in pregestational diabetes mellitus because of its chemical, biologic, and immunologic equivalency to pancreatic human insulin.[38] These insulins have the most established safety profile during pregnancy, but they require more stringent timing of meals during the day.[38]

V.W. should be switched from her oral hypoglycemic agents to insulin therapy with biosynthetic human regular insulin and NPH insulin. Metformin and glipizide should be discontinued. The total daily insulin dosage can be calculated by taking into account V.W.'s gestational age and actual body weight. Her total daily dose equals 0.8 units/kg × 295.42 pounds (134 kg), or 107 units daily. Using three injections per day, her dosage would be 47 units of NPH insulin plus 24 units of regular insulin SC 30 minutes before breakfast, 18 units of regular insulin SC 30 minutes before dinner, and 18 units SC of

NPH insulin at bedtime. V.W.'s treatment plan needs to include dietary management; appropriate counseling on maternal weight gain during pregnancy given her morbid obesity; instructions on how to draw up, mix, and inject her insulin therapy to normalize glycemic control; and moderate exercise and walking 20 to 30 minutes after each meal. She should be taught to inject SC only in the abdomen area where insulin is best absorbed during pregnancy. V.W. should also be given a glucometer and taught how to self-monitor her blood sugars four times daily, at fasting and 1 hour postprandially (after the last bite of food from each meal) to target fasting blood glucose levels <90 mg/dL and 1-hour postprandial levels <120 mg/dL.

Oral hypoglycemic use in type 2 diabetes during pregnancy

Although oral hypoglycemic agents are used commonly to treat type 2 diabetes in nonpregnant patients, they are rarely used as monotherapy during pregnancy. A switch to insulin therapy is recommended before conception, if possible, or at the time the pregnancy is confirmed because many patients have inadequate control with oral hypoglycemic agents.[66–69] If insulin is not started before conception, patients should be strongly counseled to stay on oral hypoglycemics to adequately control blood glucose until insulin therapy can be implemented. Often, patients will discontinue oral hypoglycemics from fear of taking any medication in pregnancy, resulting in hyperglycemia during the critical period of organogenesis.

The ACOG recommends that the use of oral hypoglycemics for the treatment of type 2 diabetes during pregnancy be individualized until more safety and efficacy data become available.[66–71] There is limited experience with oral hypoglycemic use in type 2 diabetes during pregnancy. Metformin, a biguanide, has been used during pregnancy for hyperinsulinemic insulin resistance or in the treatment of infertility in patients with polycystic ovarian syndrome (see Chapter 50, Disorders Related to the Menstrual Cycle). Patients taking metformin should be switched to insulin therapy unless specific circumstances (eg, high insulin requirements during the second or third trimester)

warrant its use.[77]. Studies have shown that the sulfonylureas are inferior to both insulin and metformin and increase risk of neonatal hypoglycemia.[74]

Case 49-3, Question 2: Should an oral hypoglycemic be added to V.W.'s insulin regimen?

V.W. should remain on insulin therapy with three injections daily. Her insulin regimen should be adjusted every 2 to 3 days until glycemic control is achieved and targeted blood glucose levels are reached without significant hypoglycemia episodes. Metformin should only be added if V.W.'s total daily insulin requirement exceeds 250 to 300 units. If metformin is added, insulin dosages should be decreased to at least half the amount in anticipation of increased insulin sensitivity.

Gestational Diabetes Mellitus

DIAGNOSTIC CRITERIA

CASE 49-4

Question 1: J.B. is a 22-year-old Asian female in the 24th week of her first pregnancy. She is 62 inches (157.48 cm), 165.35 pounds (75 kg; prepregnancy weight), and her BMI is 30 kg/m^2. At her regular prenatal visit, her obstetrician recommends an oral glucose screening test for GDM. Her HbA_{1c} was 5.8%. Although her mother has diabetes, J.B. has had no glucosuria during pregnancy.

Is J.B. at risk for GDM?

GDM is defined as carbohydrate intolerance that develops or is recognized during pregnancy regardless of severity, necessity for treatment, time of onset, or persistence after pregnancy.[78] GDM occurs in about 7% (range, 1%–14%), and the prevalence varies with the population and methods of detection.[78] Complications noted in the offspring of affected patients include macrosomia,

hypocalcemia, hypoglycemia, polycythemia, and jaundice. Patients with GDM are more likely to experience pregnancy-induced hypertensive disorders or require a cesarean delivery. They also are at risk for type 2 diabetes later, and their children have an increased risk for obesity and diabetes later in life.

Risk factors for GDM include age older than 25 years, obesity (BMI ≥25 kg/m^2), family history of diabetes, previous delivery of an infant weighing >8.82 pounds (4 kg), a history of stillbirth, a history of glucose intolerance, or current glycosuria.[78] African Americans, Hispanic, Asian, Native American, and Pacific Islander females also are at increased risk for GDM.[66,78]

J.B. is at risk for GDM because she is Asian and obese, and she has a family history of diabetes. Her HbA_{1c} at 26 weeks' gestation was normal and ruled her out for overt diabetes. J.B. should undergo the standard screening for gestational diabetes with a 50-g, 1-hour glucose challenge. It is not essential for J.B. to fast before this test. The diagnosis of GDM is important to the patient and the fetus because of the increased risks of fetal hyperinsulinemia and macrosomia.

GESTATIONAL DIABETES MELLITUS TREATMENT

Case 49-4, Question 2: J.B. is screened with a 50-g, 1-hour glucose challenge resulting at 161 mg/dL. Because her screening test was elevated, a diagnostic 3-hour oral glucose tolerance test (OGTT) was given to her the next day, which required her to be fasting. The results of the 3-hour OGTT showed a fasting plasma glucose of 96 mg/dL, a 1-hour glucose of 183 mg/dL, 2-hour glucose of 140 mg/dL, and 3-hour glucose of 126 mg/dL. These results confirm that J.B. has GDM. How should she be managed?

J.B. requires extensive education about a gestational diabetes diet, use of a glucometer, the signs and symptoms of hyperglycemia and hypoglycemia, and treatment of low blood glucose. She should start to monitor her blood glucose four times daily, at fasting and 1 hour after the end of each meal. She should return to the clinic in 1

week for an assessment of her blood sugars to evaluate the need for medication therapy (insulin vs glyburide treatment).

It is suggested that 60% to 85% of patients with GDM can control their glucose with dietary modifications and regular exercise; however, management with medications (insulin vs oral hypoglycemics) should be initiated if dietary management fails to maintain fasting plasma blood glucose concentrations at ≤95 mg/dL or to achieve a 1-hour postprandial plasma concentration of <140 mg/dL.[74] **Figure 49-3** outlines recommendations for screening and diagnosis of gestational diabetes.

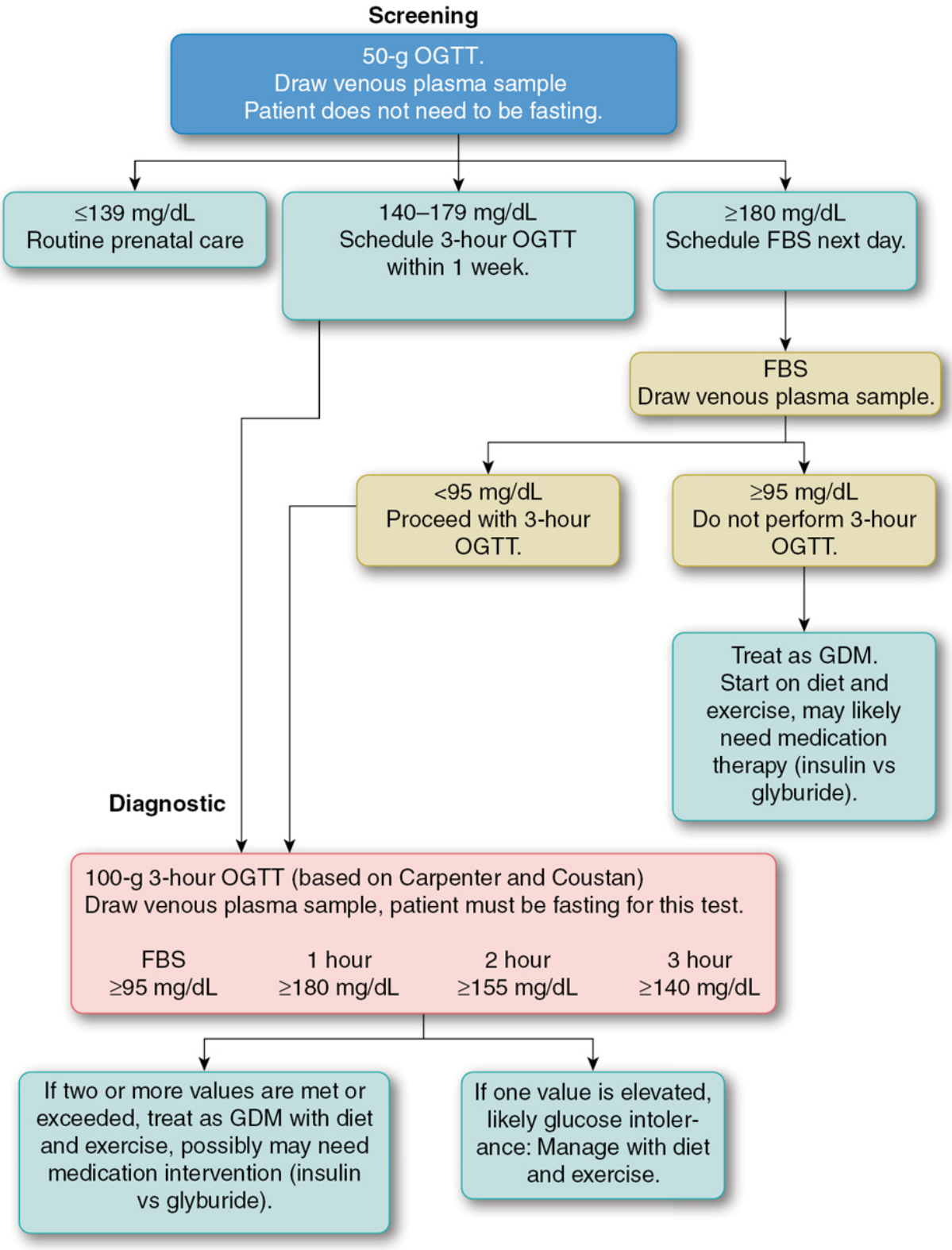


Figure 49-3 Recommendations for screening and diagnosis of gestational diabetes. FBG, fasting blood glucose; GDM, gestational

diabetes mellitus; OGTT, oral glucose tolerance test. (Sources: Cunningham FG, Leveno KJ, Bloom SL, et al. Diabetes Mellitus. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill, 2014:1125-1146; White P. Classification of obstetric diabetes. *Am J Obstet Gynecol.* 1978;130(2):228–230.)

Case 49-4, Question 3: J.B. returns to the clinic at 30 weeks' gestation with glucometer and logbook for a blood glucose assessment. She has been compliant with her diabetic diet and blood sugar monitoring for the past 4 weeks. She has been able to control her blood sugars with diet and moderate walking after meals. However, she has noticed that her fasting blood glucose has risen in the past week to an average of 98 mg/dL and her dinner postprandial values are averaging 139 mg/dL. How should J.B. be managed at this time?

Treatment of GDM with insulin therapy is implemented similar to the treatment for pregestational diabetes. An optimal insulin regimen for GDM has not been determined. Similar dosing with a weight-based, split-mixed multidose regimen is used. The insulin regimen must be tailored specifically to the needs of the person to successfully achieve target blood glucose levels.

More recently, the Metformin in Gestational Diabetes trial examined whether metformin treatment could provide outcomes equivalent to that of insulin treatment. Patients with GDM at 20 to 33 weeks' gestation were randomly assigned to open-label treatment with metformin (titrated up to 2500 mg with the option to add supplemental insulin if glycemic control was not achieved) or to insulin treatment alone.[79] The two groups achieved similar primary outcomes (composite score of neonatal morbidities), but 46% of the group allocated to metformin required supplemental insulin therapy. Those requiring supplemental insulin were more obese and had higher elevations of glycemic values at presentation. The results indicate that metformin can be used during pregnancy for GDM, but will less likely be successful as monotherapy in patients with higher glucose levels.[79] Metformin is usually reserved for patients with high insulin requirements (>300 units daily) in the second and third

trimesters.[38] More randomized trials are needed to further determine and to better understand the role of oral hypoglycemic agents in pregnancy.

Other oral hypoglycemics, such as the sulfonylureas, have inferior data and increase risk of adverse effects.[74]

J.B. is a good candidate for insulin therapy because she is at >30 weeks' gestation and has a fasting blood sugar level <110 mg/dL. Doses should be increased or decreased to achieve glycemic control.

RISK OF DEVELOPING DIABETES MELLITUS

CASE 49-4, QUESTION 4: Why is J.B. at risk for developing diabetes mellitus after delivery?

Glucose tolerance normalizes after delivery for most patients. Patients with GDM, however, have a 15% to 50% chance of developing nongestational diabetes within 5 to 16 years.[72] The highest risk is in patients who are obese or were diagnosed before 24 weeks' gestation or who had marked hyperglycemia during or soon after pregnancy. The risk of developing GDM in a future pregnancy is estimated to be 50%.[66,78]

J.B. should try to minimize the potential for development of insulin resistance by exercising and maintaining a normal weight. She should also have her glucose checked with a 2-hour OGTT at her postpartum appointment 6 weeks after delivery and then at least every 1 to 3 years with screening of either fasting blood sugar or HbA_{1c}. In addition, J.B. should be instructed about the importance of using an effective birth control method to prevent unplanned pregnancies. She also needs to schedule regular appointments with her primary care clinician.

HYPERTENSION AND PREECLAMPSIA

Chronic Hypertension

CLINICAL PRESENTATION

CASE 49-5

Question 1: T.D., a 37-year-old G1, P0, Black female with obesity was diagnosed with stage 1 hypertension several months before her pregnancy (BP, 135–145 mm Hg systolic and 90–95 mm Hg diastolic). She had no cardiovascular risk factors (ie, smoking, diabetes mellitus, dyslipidemias) and was prescribed a trial of lifestyle modification (ie, weight loss and exercise). When she initiated prenatal care at 16 weeks' gestation, her BP ranged from 130 to 135 mm Hg systolic pressure and 82 to 85 mm Hg diastolic pressure. Her BP today at 28 weeks is 142/90 mm Hg. Her serum chemistry values are creatinine (SCr) at 0.6 mg/dL and UA at 4 mg/dL. A random urinalysis did not demonstrate proteinuria. Ultrasound confirms an adequately growing fetus at 28 weeks' gestation.

What type of hypertension does T.D. have? What is the likelihood T.D. has preeclampsia?

Hypertensive disease occurs in 5% to 8% of all pregnancies and is a major cause of maternal and perinatal morbidity and mortality.[80] From 15% to 24% of maternal deaths in developed countries are attributed to hypertensive disorders in pregnancy.[81,82] *Hypertension in pregnancy* is defined as a systolic BP of at least 140 mm Hg or a diastolic BP of at least 90 mm Hg on two separate occasions at least 6 hours apart.

Patients with pregnancy-associated hypertension can be grouped into the following categories: chronic hypertension, preeclampsia–eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension.[80] After delivery, *gestational hypertension* is ultimately delineated as either (a) transient hypertension of pregnancy if preeclampsia is absent during delivery and BP normalizes by 12 weeks postpartum or (b) chronic hypertension if BP remains elevated.[80]

Chronic hypertension is defined as hypertension diagnosed before conception or before the 20th week of gestation, or hypertension persisting beyond 12 weeks postpartum.[80] Hypertension noted after

the 20th week of gestation might be difficult to classify, particularly if a patient has had inadequate prenatal care without appropriate BP monitoring.

Patients with chronic hypertension, similar to T.D., commonly have a normal BP during the first half of pregnancy because of the physiologic decline of BP during the second trimester.[83] BP usually returns to the prepregnancy level by the third trimester. T.D.'s diastolic pressure decreased from the prepregnancy levels of 90 to 95 mm Hg to 86 to 90 mm Hg during the second trimester. It is normal for T.D.'s BP to increase during the third trimester. These changes in BP make it difficult to differentiate chronic hypertension from preeclampsia during the second half of pregnancy in patients with late prenatal care or inadequate BP monitoring. It is also difficult to diagnose preeclampsia superimposed on existing hypertension using BP measurements alone. A sharp increase in T.D.'s pressure of >30 mm Hg systolic or >15 mm Hg diastolic could be consistent with preeclampsia. Without coexisting proteinuria (≥0.3 g/24 hours or ≥1+ in a random urine sample) or evidence of renal dysfunction, a diagnosis of preeclampsia would be a reach.[83] T.D. has no proteinuria, and a normal SCr and serum UA. T.D. has chronic hypertension, but it is unlikely that T.D. has preeclampsia at this time.

RISK FACTORS FOR PREECLAMPSIA

Case 49-5, Question 2: What risk factors does T.D. have for developing preeclampsia?

Preeclampsia is a pregnancy-specific condition usually occurring after 20 weeks' gestation and consisting of hypertension with proteinuria.[83] Preeclampsia can affect multiple organ systems (eg, kidney, liver, hematologic, CNS). The signs and symptoms are often unpredictable and can be mistaken for other disorders. Because edema is so common in normal pregnancy and is not specific, it is no longer used as a criterion for the diagnosis of preeclampsia.

Preeclampsia is a consequence of progressive placental and maternal endothelial cell dysfunction, increased platelet aggregation, and loss of arterial vasoregulation. A variant of preeclampsia is hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome. HELLP can also be life-threatening and may not always present with proteinuria and increases in BP.[84]

When patients with preeclampsia exhibit seizures, the term *eclampsia* is used. Patients with preeclampsia may unpredictably progress rapidly from mild-to-severe preeclampsia and to eclampsia within days or even hours. Eclampsia is a potentially preventable complication of preeclampsia. About 20% of patients who experience eclampsia have a diastolic BP <90 mm Hg or no proteinuria.[85]

The term *gestational hypertension* is used when BP is increased during pregnancy or is increased in the first 24 hours postpartum in a patient without signs or symptoms of preeclampsia and without preexisting hypertension.[80] Patients with gestational hypertension are at high risk for recurrence during subsequent pregnancies.

Preeclampsia occurs most commonly during the first pregnancy (two-thirds of cases). Obesity and increasing maternal age are risk factors.[86] Chronic diseases that increase the risk of preeclampsia include diabetes mellitus or insulin resistance and renal disease. Pregnancy-associated risk factors include multifetal gestations, UTI, certain fetal chromosomal anomalies, and hydatidiform moles. A family history of a sister or mother with preeclampsia significantly increases the risk of developing preeclampsia. Patients with previous preeclampsia are at high risk for recurrence in subsequent pregnancies, particularly if it developed before 30 weeks' gestation.[86,87] In addition to her age and obesity, chronic hypertension is the most significant aspect of T.D.'s medical history, which confers a 25% risk of developing superimposed preeclampsia.[87]

Monitoring

Case 49-5, Question 3: What subjective and objective data should be monitored in T.D. for the development of preeclampsia?

T.D. should have her BP monitored frequently. If protein is detected in a random urinalysis, then a 24-hour urine collection for protein and creatinine can be repeated to determine accurately the degree of proteinuria and severity of disease.[80] Periodic ultrasounds should be obtained to assess fetal growth because IUGR is common in pregnant patients with chronic hypertension. T.D. should be taught to recognize and immediately report all signs and symptoms of preeclampsia, such as nondependent edema (ie, swelling of face or hands), headaches, and visual disturbances. The latter two are signs of severe preeclampsia and may indicate impending eclampsia. Upper abdominal pain also can be a sign of severe preeclampsia, indicating hepatic subcapsular hemorrhage.[86] Because T.D. has chronic hypertension, worsening of hypertension alone may not be a reliable sign of superimposed preeclampsia. Proteinuria is the best indicator of superimposed preeclampsia in a pregnant patient with chronic hypertension and no renal disease.[85]

Antihypertensive drug therapy

Case 49-5, Question 4: Should T.D.'s chronic hypertension be treated with antihypertensive drugs to prevent preeclampsia?

The goal of antihypertensive therapy for patients with chronic hypertension during pregnancy is to minimize the risks to the patient of an elevated BP without compromising placental perfusion.[84] The value of treating pregnant patients with chronic antihypertension drugs remains an area of ongoing debate. A sustained diastolic BP of >100 mm Hg may cause maternal vascular damage, especially if the diastolic pressure is >105 to 110 mm Hg.[86] Morbidity is unlikely with a diastolic BP of <100 mm Hg. Therefore, many clinicians recommend treatment with antihypertensive drugs to lower diastolic pressures of >100 to 110 mm Hg.[80] Treatment of a diastolic BP of

<100 mm Hg should be reserved for patients with chronic hypertension and target-organ damage (eg, left ventricular hypertrophy) or underlying renal disease because antihypertensive drugs can decrease placental blood flow, which might increase fetal growth restriction.[88,89] Treatment of mild-to-moderate hypertension is associated with a decrease in the risk of developing severe hypertension by ~50%, but the overall risk of developing preeclampsia is unchanged.[90] Furthermore, there is no evidence of a reduction in the risk of stillbirth, fetal growth restriction, or preterm birth if patients with chronic hypertension with systolic BP of 140 to 169 mm Hg or diastolic BP of 90 to 109 mm Hg are given antihypertensive therapy.[90] Moreover, patients treated with antihypertensive therapy were more likely to experience adverse drug effects compared with those who received placebo or were untreated. Antihypertensive therapy, however, is required to reduce the risk of cardiovascular morbidity such as heart or renal failure and acute risk of stroke in pregnant patients with severe hypertension (diastolic >110 mm Hg).

T.D. has normal renal function and her BP is <100 mm Hg; she does not need antihypertensive drug treatment at this time. If T.D. had been on drug therapy before conception, some experts would have her continue it during the pregnancy.[80,85,88] In such cases, however, the doses of the antihypertensive agents often need to be lowered or discontinued altogether to prevent hypotension because the maternal BP naturally decreases during the second trimester. Perinatal outcomes in patients with untreated chronic hypertension who do not progress to preeclampsia are similar to those of the general obstetric population.[85] Although chronic hypertension is a major risk factor for preeclampsia, treating T.D.'s uncomplicated mild chronic hypertension is unlikely to prevent the development of preeclampsia.

Methyldopa

Case 49-5, Question 5: When T.D. returns to the clinic 2 weeks later at 30 weeks' gestation, her BP ranged from 160 to 165 mm Hg systolic pressure and 85 to 92 mm Hg diastolic pressure. Which medication should T.D. be started on?

Methyldopa, a centrally acting α-agonist that decreases sympathetic outflow to decrease BP, is the most commonly used antihypertensive agent for chronic treatment of hypertension in pregnancy in the United States. The usual starting dose of 750 to 1000 mg/day, to be administered in three to four daily divided doses, can be increased to 2 or 3 g/day if needed. Higher doses may be needed to control BP in pregnancy.[91]

Methyldopa, classified as category B for fetal risk, has the longest and best safety record of all antihypertensive agents during pregnancy. Despite its common use, few adverse effects have been reported in neonates exposed to methyldopa in utero. In addition, no congenital anomalies are associated with methyldopa.[38]

Dizziness and sedation, accompanied by a loss of energy, are among the most common adverse effects reported by pregnant patients.[91] Generally, these adverse effects occur early in therapy and tend to subside, but may recur with an increased dosage. Problems with postural hypotension usually do not occur in pregnant patients.[91] Patients should be monitored for methyldopa-induced liver damage.[87] Other drugs used to treat hypertension in pregnancy include labetalol and calcium channel blockers. A review of drug therapies for the treatment of chronic hypertension in pregnancy is listed in **Table 49-4**.[92–97]

Table 49-4
Drugs for Treatment of Chronic Hypertension in Pregnancy and Lactation

Drug	Dose	Comments

Drug	Dose	Comments
Methyldopa	750–1000 mg/day start twice a day, increase up to 2–3 g/day, divided in three to four doses if needed[99]	Longest safety record in pregnancy. Considered a first-line drug.[88] Dizziness, sedation, and lack of energy are common symptoms, which tend to resolve. Can cause liver toxicity. Low breast milk concentrations, so considered safe in breast-feeding
Labetalol	200–400 mg/day start, increase to up to 2400 mg/day, divided into two or sometimes three doses	Combined α- and β-receptor antagonist properties. Considered a first-line drug.[88] Increasingly preferred to methyldopa owing to fewer side effects. Neonatal effects could include bradycardia and hypotension. Low concentration in breast milk and generally considered safe in breast-feeding[92]
Other β-blockers	Various	Atenolol, in particular, associated with decreased placental weight and IUGR.[94,95] IUGR thought to be related to β-blocker–induced increased vascular resistance in patient and fetus. Atenolol, acebutolol, metoprolol, nadolol, and sotalol can have high milk-to-plasma ratios and accumulate in breast milk, creating potential risk for neonatal blockade.[96,97] Propanolol found in only small amounts in breast milk and generally considered safe, but infants should be monitored for hypotension, bradycardia, and blood glucose changes.
Nifedipine, long-acting	30 mg/day start, increase to up to 120 mg/day, once daily	Limited pregnancy data on nifedipine or other calcium channel blockers such as verapamil, diltiazem, and amlodipine. Concentrations of nifedipine in breast milk are low and considered compatible with breast-feeding[107,108]

Drug	Dose	Comments
Diuretics	Various	Not first-line agents, although probably safe.[88] Concern regarding potential interference with normal blood volume expansion in pregnancy. Avoid if preeclampsia or IUGR already present. Concentration low in breast milk, but may decrease milk production
ACEI or ARB	Contraindicated	Contraindicated in pregnancy in all trimesters. Fetal renal failure when used after first trimester, resulting in oligohydramnios, limb contractures, pulmonary hypoplasia, skull hypoplasia, and irreversible neonatal renal failure.[38] Increased risk of major birth defects with first-trimester ACEI exposure.[75] Minimal amounts of captopril and enalapril in breast milk and both considered compatible with breast-feeding.[229] Minimal amounts of benazepril in breast milk

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IUGR, intrauterine growth restriction.

T.D. should be started on methyldopa 500 mg PO three times daily. If T.D. cannot tolerate the side effects, she can be switched to labetalol 200 mg PO twice daily. The only antihypertensive drugs absolutely contraindicated during pregnancy are ACEI and angiotensin II receptor blockers because of the association with fetal and newborn morbidity and mortality.[88]

Mild Preeclampsia

Case 49-5, Question 6: T.D. returns to her obstetrician 1 week later at 31 weeks' gestation with mild hand and leg edema. She has 1+ proteinuria by dipstick, and her BP is 155/102 mm Hg. An ultrasound finding demonstrates fetal growth restriction. Laboratory results are as follows:

SCr, 0.9 mg/dL
Serum UA, 6.0 mg/dL
Aspartate aminotransferase (AST), 25 units/L
Alanine aminotransferase (ALT), 16 units/L
Platelets, 230,000/μL

She is currently on labetalol 200 mg PO twice daily and has been compliant with her medications.

What signs and laboratory evidence are consistent with preeclampsia in T.D.? Does she have mild or severe preeclampsia?

ETIOLOGY AND PATHOGENESIS

The causes of preeclampsia currently remain unknown. Although the pathogenesis begins early in pregnancy, the disease is not clinically evident until the latter half of the pregnancy and persists until the fetus is delivered.[98] Incomplete physiologic placental vascular bed changes and endothelial cell dysfunction are integral to the pathogenesis of preeclampsia.

Placental ischemia

Early in a normal pregnancy, the trophoblastic migration and invasion of the uterine spiral arteries result in physiologic changes within the placental vascular bed that facilitate maximal intervillous blood flow. The physiologic changes within these spiral arteries are responsible for creating a fixed low-resistance arteriolar circuit, which increases blood supply to the growing fetus. In preeclampsia, these physiologic changes do not occur completely, resulting in decreased perfusion and, consequently, placental ischemia.[98,99]

Endothelial damage

An intact vascular endothelium assists in preserving the integrity of vasculature, mediating immune and inflammatory responses, preventing intravascular coagulation, and modulating the contractility of the underlying smooth muscle cells.[99]

In normal pregnancy, prostacyclin is increased 8 to 10 times, creating an increased ratio of prostacyclin to thromboxane A_2.[98] The biologic dominance of prostacyclin along with nitric oxide plays an important role in maintaining vasodilation throughout pregnancy. Prostacyclin may be responsible for vascular refractoriness to angiotensin II in normal pregnancy. In preeclampsia, the ratio of prostacyclin to thromboxane A_2 is reversed. Thromboxane A_2 is

biologically dominant during preeclampsia, leading to increased vascular sensitivity to angiotensin II and norepinephrine.[98] The increased release of thromboxane A_2 is believed to be caused by endothelial cell dysfunction. The end result is vasospasm, which further increases endothelial cell dysfunction and increases BP.[98] Reduced activity of nitric oxide synthase and decreased nitric oxide–dependent or nitric oxide–independent endothelium-derived relaxing factors are believed to increase the vasoconstrictive potential of pressures such as angiotensin II.[80]

Endothelial cell dysfunction in pregnancy is thought to be caused by oxidative stress. Intermittent hypoxic and reperfusion injury that occurs as a consequence of decreased placental perfusion may increase oxidative stress.[98,99] Endothelial damage eventually leads to disruption of the vascular lining, which causes leaking capillary membranes, allowing fluid to leak into the interstitium.[99] In severe preeclampsia, this results in hypovolemia, hemoconcentration, and, consequently, an increase in hematocrit. The loss of plasma volume, vasospasm, and microthrombi decrease perfusion of the kidney, CNS, liver, and other organs. The loss of intravascular proteins in the urine secondary to renal damage, and through damaged epithelia, decreases plasma oncotic pressure and leads to a rapid onset of nondependent edema. The imbalance of endogenous procoagulants and anticoagulants produces platelet consumption and results in thrombocytopenia and coagulation defects.[99]

T.D.’s diastolic BP is now higher than it was before her pregnancy and has increased by 12 mm Hg in the past 3 weeks. Although an increase in BP by itself is not diagnostic of preeclampsia, the new finding of proteinuria confirms the diagnosis. Other evidence for preeclampsia includes the elevated serum UA concentration, which is a sensitive marker for preeclampsia, and elevated SCr.[86] T.D. denies headaches, visual disturbances, and abdominal pain, which are symptoms of severe preeclampsia. The transaminases and platelet count are normal; therefore, she does not have HELLP syndrome at this time. T.D.’s clinical presentation is consistent with mild preeclampsia; however, a 24-hour urine collection should be

obtained to measure protein excretion, quantify the urine output, and further rule out severe preeclampsia.

TREATMENT OF PREECLAMPSIA

General principles

Case 49-5, Question 7: T.D. is admitted to the hospital. The 24-hour urine protein is 500 mg/24 hours. Although fetal growth is restricted, all other fetal testing is reassuring. After 24 hours, her BP decreased to 140/95 mm Hg. Her platelet counts remained stable and >200/mL, and transaminases were normal. No other signs and symptoms of preeclampsia were noted. How should T.D.'s mild preeclampsia be managed?

The delivery of the fetus is the only cure for preeclampsia and would be the best treatment option for T.D. if she were at >37 weeks' gestation. T.D. has mild disease, however, and is not close to term. Her delivery should be postponed because premature delivery increases neonatal morbidity and mortality. T.D.'s fetus is somewhat growth restricted, which is common in patients with chronic hypertension, with or without superimposed preeclampsia. If T.D.'s fetus is severely growth restricted or if subsequent fetal biophysical testing is abnormal, premature delivery would be indicated.[80] Because neither of these is evident in the present circumstances, T.D. should continue her pregnancy under very close medical supervision. It has been suggested that continued hospitalization is appropriate for patients with preterm onset of mild preeclampsia, such as T.D.[80] This would allow for rapid intervention in case of rapid progression of disease or associated complications. Probably, a role exists for outpatient monitoring of select patients with very frequent maternal and fetal monitoring, and rehospitalization for worsening disease.[80]

T.D. is also a candidate for administration of glucocorticoids for fetal lung maturation (see Case 49-7, Question 7). Bed rest in the lateral decubitus position is usually suggested and may help reduce BP and promote diuresis by decreasing vasoconstriction and improving renal and uteroplacental perfusion.

T.D. should have her BP measured regularly each day. Liver transaminases, platelets, and creatinine should be measured periodically and whenever her clinical status changes. She also should be assessed for symptoms of severe preeclampsia (eg, headaches, visual disturbances, epigastric or right upper quadrant pain). Fetal surveillance is indicated.[80] One approach is to perform a modified biophysical profile, a test performed to ensure fetal well-being using ultrasonography measuring fetal breathing, tone, movement, and amniotic fluid volume with an assessment in fetal heart rate, twice a week and whenever maternal clinical status changes, and an ultrasound for fetal growth every 3 to 4 weeks.

Severe Preeclampsia

CLINICAL PRESENTATION

Case 49-5, Question 8: T.D.'s BP for about 2 weeks ranged from 140 to 150 mm Hg systolic and 90 to 100 mm Hg diastolic with bed rest. Her proteinuria remained stable at 1+ to 2+ by dipstick. During the past 2 days, T.D.'s BP started to increase again, and today her BP is 160/112 mm Hg and her urine dipstick is 3+. She reports headaches, dizziness, and visual disturbances and has significant edema in her face, hands, legs, and ankles. T.D. is transferred to the Labor and Delivery Unit for delivery. Pertinent laboratory results are as follows:

SCr, 1.3 mg/dL
UA, 6.7 mg/dL
AST, 30 units/L
ALT, 16 units/L
Total bilirubin, 1 mg/dL
Platelets, 95,000/mL
Hematocrit, 38%
Hemoglobin, 13 g/dL
Random urine protein, 4+

Estimated fetal weight by ultrasound is 1700 g, which is between the 10th and 25th percentile for a gestational age of 34 weeks. What signs, symptoms, and laboratory evidence of severe preeclampsia support this diagnosis in T.D., and what complications may occur?

T.D. has developed severe preeclampsia.[84] Her systolic and diastolic BP are >160 and 112 mm Hg, respectively. She has >3+ protein in a random urine sample, and her SCr is elevated. She reports headaches and visual disturbances. T.D. is also thrombocytopenic because her platelet count is 95,000/mL. Although her liver transaminases are currently normal, she may be developing HELLP syndrome, a variant of severe preeclampsia associated with a high incidence of maternal and perinatal morbidity and mortality. Therefore, her laboratory values should continue to be monitored even as delivery is being planned.

COMPLICATIONS

T.D. is at risk for cerebral hemorrhage, cerebral edema, encephalopathy, coagulopathies, pulmonary edema, liver failure, renal failure, and eclamptic seizures.[85,86] Severe preeclampsia is dangerous not only to T.D. but also to her fetus because uteroplacental perfusion is compromised. T.D. requires drug treatments to both lower her BP and prevent eclampsia, as well as for the delivery.

ACUTE TREATMENT OF SEVERE HYPERTENSION

Case 49-5, Question 9: How should T.D.'s severe hypertension be treated?

The goal of antihypertensive therapy in T.D. is to prevent cerebral complications (eg, encephalopathy, hemorrhage).[85] Although it is important to reduce the maternal BP, it must be accomplished gradually while the fetus is in utero because a sudden large drop in maternal BP could result in the reduction of uteroplacental perfusion.[86] Because of the potential for fetal bradycardia during or after acute treatment of maternal hypertension, continuous fetal heart rate monitoring should be considered.

Hydralazine

Hydralazine, a direct arterial smooth muscle dilator, has in the past been the drug of choice for the acute treatment of severe hypertension in pregnancy.[85,91] This drug induces a baroreceptor-mediated tachycardia and increases cardiac output, which increases uterine blood flow because the BP is lowered.[86]

The onset of antihypertensive effect for hydralazine ranges from 10 to 20 minutes, and duration of action ranges from 3 to 6 hours after an IV dose.[86,100] Therefore, doses of hydralazine should not be repeated more frequently than every 20 to 30 minutes to prevent drug accumulation.[91] Nausea, vomiting, tachycardia, flushing, headache, and tremors could occur. Some of these hydralazine-induced adverse effects mimic symptoms associated with severe preeclampsia and imminent eclampsia, making it difficult for a clinician to differentiate between drug-associated and disease-related problems.[91] Fetal hydralazine serum concentrations are reportedly the same as or higher than maternal serum concentrations, but drug-associated fetal abnormalities have not been reported.[38]

Labetalol

Labetalol is also a commonly used drug to treat severe hypertension during pregnancy. It should be administered IV in increasing doses of 20, 40, and 80 mg every 10 minutes to a cumulative dose of 300 mg or until the diastolic pressure is <100 mm Hg.[101] The onset of action is within 5 minutes, and its effect peaks in 10 to 20 minutes with a duration of action ranging from 45 minutes to 6 hours.

IV labetalol is as effective as IV hydralazine in lowering BP in patients with hypertension during pregnancy, but has fewer reported adverse effects.[91–102] In a meta-analysis of β-blocker trials for the treatment of hypertension in pregnancy, labetalol was associated with less maternal hypotension, fewer cesarean deliveries, and no increase in perinatal mortality.[102] Labetalol also does not appear to decrease uteroplacental blood flow even with a decrease in maternal BP.[91] Labetalol reduces cerebral perfusion pressure, which occurs in up to 43% of patients with severe preeclampsia, without negatively

affecting cerebral blood flow.[103] Decreased cerebral perfusion pressure may prevent progression to eclampsia. However, it should be avoided in patients with asthma and decompensated heart failure.[104,105] Labetalol has also been associated with higher rates of neonatal bradycardia and hypotension than has hydralazine, but not higher rates of neonatal intensive care admission.[106,107]

Nifedipine

Nifedipine has been used in doses of 10 mg for acute treatment of severe hypertension during pregnancy because it can be given PO.[91] Nifedipine is effective in decreasing BP without reducing uteroplacental blood flow or decreasing fetal heart rate. Short-acting nifedipine capsules are no longer recommended for the treatment of acute hypertensive urgency, however, because of the risk of stroke or myocardial infarction, and it was never FDA approved for this indication. Immediate-release nifedipine continues to be used to treat hypertension in pregnancy, however, because this unique patient population may not be at high risk for ischemic events secondary to atherosclerotic disease.[88] Calcium gluconate or calcium chloride should be available for IV administration in the event of sudden hypotension. Caution should be used when giving nifedipine to patients concomitantly treated with magnesium sulfate because these drugs have synergistic effects, causing hypotension and neuromuscular blockade.[106]

Several studies comparing immediate-release oral nifedipine with IV labetalol in hypertensive emergencies of pregnancy have found them to be equally effective in lowering BP.[107,108] Nifedipine lowers BP to <160 mm Hg systolic and <100 mm Hg diastolic earlier than labetalol does,[107] but it increases cardiac index[108] (see Chapter 16, Hypertensive Crises). The use of sustained-release nifedipine capsules as an alternative is associated with a delay in BP control to 45 to 90 minutes, which is probably not acceptable.[100]

Hydralazine 5 mg IV for 1 to 2 minutes should be administered to T.D. and repeated in doses of 5 to 10 mg every 20 to 30 minutes to a cumulative dose of 20 mg.[85] T.D. should have repeated

measurements of her BP at 15-minute intervals. Because intervillous blood flow depends on maternal perfusion pressure, the goal is to decrease the diastolic pressure to not <90 mm Hg.[85,100] Lowering the maternal BP excessively may decrease uteroplacental perfusion and compromise the fetus. A hypotensive overshoot can be observed with hydralazine, particularly in the setting of volume depletion, which is typical of preeclampsia.[100] If one or two doses of hydralazine are not effective in lowering T.D.'s diastolic to <100 mm Hg, labetalol 20 mg IV every 10 to 15 minutes can be given.

Eclampsia

MAGNESIUM SULFATE PROPHYLAXIS

Case 49-5, Question 10: T.D. will undergo an induction of labor for her severe preeclampsia. Which medication should be given to T.D. to prevent seizures?

The precise mechanism of anticonvulsant action of magnesium for the prevention and treatment of eclamptic seizures is unknown. The anticonvulsant activity may be partly mediated through blockade of an excitatory amino acid receptor, *N*-methyl-D-aspartate.[106] Seizures are thought to be caused by decreased cerebral blood flow because of vasospasm. Magnesium sulfate is a potent cerebral vasodilator and increases the synthesis of prostacyclin, an endothelial vasodilator. It also causes a dose-dependent decrease in systemic vascular resistance, which may explain its transient hypotensive effect. Magnesium may also protect against oxidative injury to endothelial cells.[106]

Although termination of the pregnancy is the definitive treatment for severe preeclampsia, the intrapartum and immediate postpartum periods are also the periods of greatest risk for eclampsia.[84] Although the incidence of eclampsia is extremely low, maternal morbidity and mortality are high.[109] In the United States, it has been the usual practice to treat all patients with preeclampsia with

magnesium sulfate during labor and for 12 to 24 hours postpartum.[80,85] In the United Kingdom, however, it is common to reserve magnesium sulfate therapy for severe preeclampsia.[110] The evidence for magnesium sulfate preventing the progression of disease in patients with mild preeclampsia had been largely anecdotal in the past. In a large international study of >10,000 females, published in 2002, magnesium sulfate clearly decreased the risk of eclampsia in females with preeclampsia by 58% compared with placebo.[110] An observational study of nearly 2500 females with mild preeclampsia (BP of 140/90 mm Hg and 1+ protein) found an incidence of eclampsia of about 1% without the use of seizure prophylaxis.[111]

In a prospective, randomized study, magnesium sulfate was superior to phenytoin for the prevention of eclampsia in hypertensive pregnant patients.[109] In addition, magnesium sulfate was more effective than was nimodipine for seizure prophylaxis in patients with severe preeclampsia.[112,113]

A regimen of magnesium sulfate 4 to 6 g IV as a loading dose followed by a continuous infusion of 2 g/hour is the most commonly used regimen in the United States.[114] Lower dosages (eg, 1 g/hour) have been associated with treatment failures.[115] IV loading doses of 6 g followed by continuous infusions of 2 g/hour maintain therapeutically effective magnesium serum concentrations between 4 and 8 mg/dL.[114] Because magnesium is excreted by the kidneys and will accumulate in cases of renal dysfunction, the continuous infusion rate must be lowered with oliguria or an elevated SCr.

Because of the potential for infusion errors and significant patient morbidity and even mortality with accidental overdoses of magnesium sulfate, the Institute of Medicine has identified magnesium sulfate as a high-risk medication.[115] All infusions of magnesium sulfate must be given through a controlled pump designed to protect against free flow. If such an infusion pump is not available, the intramuscular (IM) route of administration should be used. Dispensing premixed IV bags from the central pharmacy with a standardized concentration of magnesium sulfate and limiting the total grams of magnesium sulfate in each dispensed IV bag also can

help guard against inadvertent overdose. Dispensing the loading dose in a separate small bag (eg, 4 g in 100 mL) from the maintenance bag (eg, 20 g in 200 mL) also may be helpful.[116]

Magnesium sulfate should be given to T.D. to prevent eclamptic seizures during labor.[80] T.D. should be loaded with magnesium sulfate 4 g IV given for 30 minutes and then started on a continuous infusion of 2 g/hour.

MONITORING MAGNESIUM SULFATE THERAPY

Case 49-5, Question 11: T.D. has been given magnesium sulfate 4 g IV for 30 minutes and was then started on a continuous infusion of 2 g/hour. What subjective and objective data should be monitored during treatment of T.D. with magnesium?

Deep tendon reflexes (patellar reflex), respiratory rate, and urine output should be monitored periodically during treatment with magnesium sulfate.[109] The loss of patellar reflexes, the first sign of magnesium toxicity, generally occurs at serum concentrations of 8 to 12 mg/dL. The respiratory rate should be monitored hourly and should be >12 breaths/minute. Respiratory arrest can occur with serum concentrations >13 mg/dL. Urine output should be carefully monitored and should be at least 100 mL every 4 hours (or 25 mL/hour).[109] Magnesium serum concentrations are not routinely measured unless renal dysfunction is evident with oliguria or elevated SCr because magnesium is almost entirely excreted by the kidney.[106,109] Hypocalcemia and hypocalcemic tetany also can occur secondary to elevated magnesium and can be reversed by calcium gluconate 1 g (10 mL of a 10% solution) slow IV push for 3 minutes. Neuromuscular depression can occur in infants whose mothers received magnesium sulfate.[38] Parenteral magnesium sulfate is safe and rarely causes maternal or neonatal toxicity when administered properly but requires stringent, built-in system safeguards to avoid unintended dosing errors.[116]

Case 49-5, Question 12: How long should magnesium sulfate be continued in T.D.?

Depending on the severity of preeclampsia, magnesium sulfate therapy usually is continued for 24 hours after delivery, which should be the same for T.D.[117] Patients with severe preeclampsia or preeclampsia superimposed on chronic hypertension are at greater risk for disease exacerbation when magnesium sulfate is discontinued too soon.

TREATMENT OF ECLAMPSIA

Case 49-5, Question 13: T.D. delivers vaginally and her magnesium infusion was discontinued by mistake 3 hours postpartum. T.D. experiences an eclamptic seizure 4 hours later when her nurses discover that the magnesium is disconnected. What is appropriate drug therapy for eclampsia?

Lorazepam, diazepam, phenytoin, and magnesium sulfate have all been used to treat eclampsia. The use of magnesium sulfate to treat these seizures results in less maternal morbidity and mortality and less neonatal morbidity.[109,118] Generally, higher serum concentrations of magnesium sulfate are needed to treat than to prevent eclamptic seizures. However, the same therapeutic range guides both prophylaxis and treatment.[119] Seizures unresponsive to magnesium sulfate treatment should prompt an evaluation for other cerebrovascular events (eg, cerebral hemorrhage or infarction).[114] Lorazepam 2 to 4 mg slow IV push stat should be given for seizure cessation. T.D. should be reloaded with magnesium sulfate and continued on a magnesium infusion for 24 to 48 hours.

DRUG THERAPY MANAGEMENT IN LABOR AND DELIVERY

Induction of Labor

MECHANISMS OF TERM LABOR

In pregnancy, many hormones and peptides, including progesterone, prostacyclin, relaxin, nitric oxide, and parathyroid hormone–related peptide, inhibit uterine smooth muscle contractility. Labor at term occurs because the myometrium is released from its quiescent state.[120] For example, as progesterone concentrations decrease near term gestation, estrogen may stimulate uterine contractility.

Uterine activity is divided into four phases: quiescence (phase 0), activation (phase 1), stimulation (phase 2), and involution (phase 3). Each of these phases is stimulated or inhibited by several factors.[120] During activation, uterotropins such as estrogen, and, possibly others, stimulate a complex series of uterine changes (eg, increased myometrial prostaglandin and oxytocin receptors and myometrial gap junctions), which are important for the coordination of contractions. These changes help prime the myometrium and cervix for stimulation by the uterotonins oxytocin and prostaglandins E_2 and F_2a. The cervix softens, shortens, and dilates, a process referred to as *cervical ripening.* Uterine stimulation is responsible for the change in myometrial activity from irregular to regular contractions. During phase 3, involution of the uterus occurs after delivery and is mediated mostly by oxytocin.[120]

The exact stimulus of the biochemical scheme leading to labor in humans is unknown. The fetus may help facilitate this process by affecting placental steroid production through mechanical distension of the uterus and by activating the fetal hypothalamic–pituitary–adrenal axis. Ultimately, these lead to increased production of oxytocin and prostaglandins by the fetoplacental unit.

Labor is divided into three stages. Weak, irregular, rhythmic contractions (Braxton–Hicks contractions or “false labor”) may happen for weeks before the onset of true labor. The first stage begins with the start of regular uterine contractions and ends with complete cervical dilation. Stage 1 is divided further into the latent phase, active phase, and deceleration phase. During the latent

phase, the cervix effaces (thins) but dilates minimally. The contractions become progressively stronger and longer, better coordinated, and more frequent. The duration of the latent phase is the most varied and unpredictable of all aspects of labor and can continue intermittently for days. During the active phase, contractions are strong and regular, occurring every 2 to 3 minutes. The cervix dilates from 3 to 4 cm to full dilation, usually 10 cm. The second stage starts with complete cervical dilation and ends with the delivery of the fetus. The third stage of labor is the time between the delivery of the fetus and the delivery of the placenta.

INDICATIONS, CONTRAINDICATIONS, AND REQUIREMENTS

CASE 49-6

QUESTION 1: J.T., a 28-year-old primigravida, is admitted to the labor and delivery suite for labor induction. She is at 42 weeks' gestation by dates and ultrasound and has a normal obstetric examination. Cervical examination reveals an unfavorable cervix for labor induction; Bishop score is 4.

What are the indications and contraindications for labor induction in J.T.?

The induction of labor involves the artificial stimulation of uterine contractions that lead to labor and delivery. Induction of labor is indicated when the benefits to either the patient or fetus outweigh those of continuing the pregnancy. Examples may include preeclampsia, chorioamnionitis (infection of the fetal membranes, see Case 49-7, Question 11), fetal demise, significant fetal growth restriction, maternal medical problems, and postterm pregnancy.[121] Postterm pregnancy (≥42 weeks' gestation), as in J.T.'s case, is one of the most common indications for induction of labor.[121] Contraindications to labor induction are similar to those for spontaneous labor and vaginal delivery and include, but are not limited to, active genital herpes infection, placenta previa (placenta implanted over the internal cervical opening), prior classic uterine incision, transverse fetal lie (lying longitudinally across the uterus), and prolapsed umbilical cord. Maternal complications that are

associated with induction include increased rates of chorioamnionitis and uterine atony (loss of tone in uterine musculature; see Case 49-8, Question 4) resulting in hemorrhage, as well as a twofold to threefold increased risk of cesarean delivery, particularly in patients who are primigravida.[122]

A complete assessment of both patient and fetus should be performed before inducing labor.[121,123] Gestational age must be assessed accurately before the induction of labor to avoid the inadvertent delivery of a preterm fetus.[121,122] When delivery is necessary before 34 weeks' gestation with intact membranes or before 32 weeks' gestation with ruptured membranes, antenatal corticosteroids should be administered (see Case 49-7, Question 7).[123,124]

The degree of cervical ripeness and readiness for induction of labor should be assessed.[121,125] Success of labor induction is directly related to the favorability of the cervix.[126,127] The Bishop method of evaluating cervical ripeness assigns a score based on the station of the fetal head relative to the maternal ischial spines and the extent of cervical dilation, effacement (thinning of the cervix), consistency, and position.[122,125] Bishop scores of >8 are associated with rates of vaginal delivery similar to those after spontaneous labor.[121] Conversely, Bishop scores of ≤4, as documented in J.T., are associated with a high likelihood of failed induction and cesarean delivery. As a result, significant research has been directed toward methods of improving the Bishop score and cervix ripeness before stimulation of uterine contractions. However, patients with low Bishop scores who undergo cervical ripening before induction of labor still have higher rates of cesarean delivery compared with spontaneous labor.[126] Nevertheless, cervical ripening appears to have some benefits in decreasing time to delivery, shortening labor, and successfully improving Bishop score.[121]

Cervical ripening can be accomplished pharmacologically or mechanically. Pharmacologic methods include the administration of prostaglandins (E_2 and E_1) or low-dose oxytocin. Mechanical methods include membrane sweeping (or membrane stripping), and

intracervical balloons.[121,123,125] Osmotic or hygroscopic dilators (eg, Dilapan®, Lamicel®) work by absorbing cervical mucus and gradually swelling, thereby dilating the cervical canal.[122,125] In the setting of a favorable Bishop score, labor induction is accomplished most commonly by amniotomy (artificial rupture of the fetal membranes) and oxytocin administration.[121,122]

CASE 49-6, QUESTION 2: What pharmacologic agents can be used for cervical ripening in J.T.?

Although labor induction is medically indicated in J.T. to decrease the risk of an adverse fetal outcome with continuing a postterm pregnancy, such as macrosomia, asphyxia, meconium aspiration, and intrauterine infection, her cervix is unfavorable for induction, and she is a candidate for cervix ripening.

CERVICAL RIPENING

Misoprostol (Cytotec®)

Prostaglandins induce cervical ripening and enhance myometrial sensitivity to oxytocin by promoting the breakdown of collagen and increasing the submucosal hyaluronic acid and water content.[121,122,125] Misoprostol is a prostaglandin E_1 analog approved for use in the prevention of nonsteroidal anti-inflammatory drug–induced peptic ulcer disease. It also has been used for cervical ripening and the induction of labor in patients despite the lack of approval by the FDA for these latter indications.[128,129] In two large meta-analyses, misoprostol was more effective for cervical ripening and labor induction than for either placebo or treatment with dinoprostone (prostaglandin E_2).[128,129] In comparison, intravaginal misoprostol produced labor more often during cervical ripening and resulted in a reduced rate of cesarean deliveries, shorter delivery times, and a greater incidence of vaginal delivery within 24 hours but had a higher incidence of uterine contraction abnormalities than either dinoprostone vaginal insert or dinoprostone endocervical gel.[128–132] Uterine tachysystole, excessively frequent uterine

contractions, without fetal heart rate abnormalities was more common with misoprostol use. Maternal and neonatal outcomes were similar in both groups. The need for oxytocin is decreased significantly in patients treated with misoprostol compared with patients treated with dinoprostone.[131]

Oral misoprostol has also been studied for cervical ripening, but comparisons of vaginal and oral misoprostol are complicated by wide variations in dose and dose interval.[132] A meta-analysis of available studies concluded that the only consistent finding was a reduction in low 5-minute Apgar scores with oral misoprostol but no difference in neonatal intensive care unit admissions. When comparing all studies with a wide range of doses, oral misoprostol resulted in similar rates of vaginal delivery not achieved in 24 hours, uterine tachysystole with fetal heart rate changes, and cesarean delivery compared with vaginal misoprostol.[122]

Misoprostol 25 μg (one-fourth of an unscored 100-μg tablet) is inserted into the posterior vaginal fornix and repeated as needed every 3 to 6 hours.[130,131] Higher doses of 50 μg are associated with increased uterine contractile abnormalities.[128,132] Continuous fetal heart rate and uterine monitoring is recommended throughout the administration of misoprostol.[133] If oxytocin is indicated after cervical ripening, administration should be delayed at least 4 hours from the last dose of misoprostol.[121]

Misoprostol should not be used in patients with previous uterine scars because of the risk of uterine rupture.[121,130,132] Although misoprostol is a known teratogen in the first trimester of pregnancy, particularly if used in an unsuccessful attempt at medical abortion, there are no such reports with exposure beyond the first trimester.[38,130] Misoprostol's low cost and ease of administration are advantages compared with dinoprostone, and there is extensive clinical experience with this agent; however, its lack of FDA approval for cervical ripening and induction of labor is a disadvantage. Clinical trials of a controlled-release misoprostol vaginal insert are currently ongoing.[133]

Prostaglandin E2 (dinoprostone)

There are two FDA-approved forms of dinoprostone available for cervical ripening. Up to half of the patients treated with dinoprostone experience labor and deliver within 24 hours, some without oxytocin.[134,135] Dinoprostone cervical gel (Prepidil Gel®) contains dinoprostone 0.5 mg per 3-g syringe (2.5 mL gel) and is administered endocervically. The dinoprostone cervical gel must be refrigerated, and dinoprostone vaginal inserts must remain frozen until administration. Dinoprostone slow-release insert (Cervidil®) contains dinoprostone 10 mg and is inserted vaginally.[136] Postterm patients with unfavorable cervices who receive dinoprostone have shorter durations of labor, and require lower doses of oxytocin, compared with placebo or no therapy.[125,134,135,137] A large meta-analysis that included >10,000 patients found that the use of vaginal prostaglandin E_2 compared with no treatment or placebo was associated with increased rates of vaginal delivery within 24 hours, increased rates of cervix ripening, reduced need for oxytocin augmentation, and no difference in cesarean section. However, the risk of uterine tachysystole with fetal heart rate changes was increased.[138]

Both dinoprostone products are effective for cervical ripening, leading to successful induction of labor.[125,134,135,137] The two dinoprostone formulations differ in dosing and application.[139,140] The dinoprostone 10-mg vaginal insert slowly releases dinoprostone 0.3 mg/hour for a 12-hour period.[136] The insert is contained within a knitted pouch attached to a long tape. Advantages of the vaginal insert include that it is easier for the clinician to place and less uncomfortable for the patient. In addition, the insert can be removed with the onset of active labor or the development of uterine tachysystole with concurrent fetal heart rate tracing abnormalities. It should be removed within 12 hours of placement or after active labor develops, the membranes rupture, or there is evidence of tachysystole with fetal heart rate changes.[140] If dinoprostone cervical gel is used, the dose can be repeated in 6 to 12 hours if there is an inadequate change in the cervix and only minimal uterine activity, but

no more than three total doses are recommended.[140] The manufacturer of Prepidil® recommends a delay in initiation of oxytocin of 6 to 12 hours once the gel has been placed compared with a shorter delay of only 30 to 60 minutes after the vaginal insert has been removed. An initial period of uterine and fetal monitoring of up to 2 hours should occur after placement of the intracervical gel, with continued monitoring thereafter if regular uterine contractions develop and persist.[121]

The most serious side effect associated with dinoprostone administration is uterine hyperstimulation with or without an abnormal fetal heart rate tracing. The incidence of uterine hyperstimulation associated with the use of dinoprostone intravaginal insert is about 5%; the rate of occurrence for dinoprostone endocervical gel is about 1%.[121] Uterine hyperstimulation occurs more frequently if the Bishop score is >4 before administration of dinoprostone and can occur up to 9.5 hours after placement of the intravaginal insert.[121,140] Use of the vaginal insert requires continuous monitoring of fetal heart rate and uterine activity for as long as the insert is in place and for at least 15 minutes after its removal because of possible uterine hyperstimulation anytime during its administration.[137] Most episodes of uterine hyperstimulation with the use of the vaginal insert occur during active labor and resolve within a few minutes of the removal of the insert.[135] Uterine contraction abnormalities may be avoided if the insert is promptly removed at the onset of labor.[128] Both dinoprostone formulations are associated with fever, nausea, vomiting, and diarrhea, and neither is associated with adverse neonatal outcomes.[121,136,139]

For J.T., misoprostol 25 µg should be administered intravaginally every 3 to 6 hours for cervical ripening. Misoprostol is the most cost-effective option for cervical ripening.

OXYTOCIN

Mechanism of action

Case 49-6, Question 3: Twelve hours after administration of two 25-μg doses of misoprostol, J.T.'s cervix has responded and her Bishop score is now 9, but she has not developed a consistent pattern of uterine contractions. What drug therapy should be initiated at this point?

Synthetic oxytocin should be administered to J.T. to stimulate uterine contractions for accomplishing delivery. Oxytocin increases the frequency, force, and duration of uterine contractions.[141] The uterine response to oxytocin increases throughout pregnancy beginning at ~20 weeks' gestation and increases considerably at 30 weeks' gestation.[142] Oxytocin is indicated for both the induction and augmentation of labor. A prolonged latent phase or dystocia (difficult labor) caused by uterine hypocontractility in the active phase of labor is the indication for augmentation with oxytocin.[142]

Dosing and administration

Case 49-6, Question 4: How should oxytocin be administered to J.T.?

Oxytocin should be administered by continuous IV infusion using a controlled infusion device. The goal of oxytocin administration is to induce uterine contractions that dilate the cervix and aid in the descent of the fetus while avoiding uterine hyperstimulation and fetal distress.[141] There are two opposing views about oxytocin administration for the induction or augmentation of labor. One view is that oxytocin infusions should mimic physiologic doses in the range of 2 to 6 mU/minute, with the goal being vaginal delivery with as little uterine hyperstimulation and fetal distress as possible.[121] The other view is that oxytocin should be used in pharmacologic doses to cause strong uterine contractions, with the goals being shortened labor, timely correction of dysfunctional labor, decreased cesarean deliveries, and reduced maternal morbidity.[121]

Oxytocin plasma concentrations increase linearly with increasing doses, and steady state is reached within 20 to 40 minutes. However, oxytocin serum concentrations correlate poorly with uterine

activity.[143] Factors that may affect response to oxytocin include parity, gestational age, and cervical dilation.[143]

Despite many randomized controlled trials and much experience with oxytocin, the optimal starting doses, dosage increments, dosing intervals, and maximal doses are different in the various protocols.[141,142,144] Starting doses range from 0.5 to 6 mU/minute, and dose increment intervals range from 15 to 60 minutes.[121] Waiting for 30 to 40 minutes between each dosage rate increase allows time to assess the response at steady state. Most low-dose protocols usually start oxytocin 1 to 2 mU/minute and increase the rate of infusion by 1 to 2 mU/minute every 30 to 40 minutes.[141,145] High-dose protocols start oxytocin at 3 to 6 mU/minute with incremental increases of 3 to 6 mU/minute every 20 to 40 minutes. The maximal dose of oxytocin has not been established.[121] The ACOG recommends that obstetrics departments of hospitals develop guidelines for the consistent preparation and administration of oxytocin.[121]

Oxytocin protocols using higher doses or shorter dose adjustment intervals (15–20 minutes) for augmentation of labor generally result in fewer cesarean deliveries for labor dystocia, which is an abnormally slow progress of labor.[145–147] The incidence of uterine hyperstimulation during labor induction is higher with high-dose protocols (initial dose of 6 mU/minute with incremental increases of 6 mU/minute), however, when compared with shorter dosing adjustment intervals of 20 minutes or with longer dose adjustment intervals of 40 minutes.[147] Patients undergoing labor induction with high-dose oxytocin have a higher incidence of uterine stimulation and cesarean deliveries for fetal distress, but a reduced incidence of failed inductions and neonatal sepsis compared with patients treated with low-dose oxytocin.[147] In general, lower maximal doses are needed for augmentation of labor than for induction of labor.[144,148]

J.T. should be started on an infusion of oxytocin 10 units diluted in 1000 mL of an isotonic solution (concentration 10 mU/mL) at 1 mU/minute. She should have continuous uterine and fetal heart rate monitoring throughout the infusion to detect abnormal uterine contraction patterns or fetal heart rate patterns. The goal is to

establish a pattern of three to five uterine contractions of 60 to 90 seconds' duration per 10-minute period.[146] The oxytocin infusion should be increased by 1 to 2 mU/minute every 30 to 40 minutes as needed for inadequate progression of labor (cervical dilation rate of <1 cm/hour).[121,149] Fluid intake and urine output should be assessed hourly.

Adverse effects

Case 49-6, Question 5: What are the adverse effects and complications of oxytocin for which J.T. should be monitored?

Uterine hyperstimulation, usually associated with excessive maternal dosing or increased myometrial sensitivity to oxytocin, may result in uterine rupture, vaginal and cervical lacerations, precipitous delivery, abruptio placentae, emergency cesarean delivery for fetal distress, and postpartum hemorrhage secondary to uterine atony. In general, neonatal outcomes associated with oxytocin use do not differ from those achieved by spontaneous labor.[146] Although oxytocin has only weak antidiuretic properties, water intoxication resulting in seizures, coma, and death has been reported.[121] Oxytocin is structurally and functionally related to vasopressin, also known as antidiuretic hormone. Administration of high concentrations of >40 mU/minute and for long periods is associated with hyponatremia, which can lead to lethargy, drowsiness, generalized seizures, and potentially irreversible neurologic injury. IV bolus administration may cause paradoxical relaxation of vascular smooth muscle, leading to hypotension and tachycardia. J.T. should be monitored for uterine hyperstimulation with fetal heart rate deceleration because it is the most common adverse effect of oxytocin.[121,142]

Preterm Labor

Preterm delivery occurred in 12.8% of births in the United States in 2006, representing a 20% increase since 1990.[3] Approximately 55% of singleton preterm births follow spontaneous preterm labor, and ~8% follow preterm premature rupture of the chorioamniotic membranes.[150] Premature birth is the leading cause of neonatal mortality (infant death <1 month of age), resulting in ~70% of deaths.[150,151] Prematurity is the second leading cause of infant mortality at younger than 1 year of age, and resulted in 17% of such deaths in 2006.[8] However, the more inclusive classification of mortality as being "preterm related" was linked to 36.1% of all infant deaths in 2006.[8]

ETIOLOGY

Spontaneous preterm labor is a heterogeneous syndrome, and several known pathways can lead to preterm birth. These pathways include excessive uterine distension, decidual hemorrhage, activation of the maternal and fetal hypothalamic–pituitary system, and intrauterine infection leading to inflammation. These pathways ultimately lead to a final common response with production of uterine and cervical proteases and uterotonins, which result in progressive cervical ripening and dilation; weakening of the chorioamniotic membranes, which leads to rupture; and uterine contractions. Ultimately, delivery of the infant occurs. Infection, if present, triggers an inflammatory response that results in the release of cytokines, prostaglandins, and proteases, which stimulate uterine activity, induce cervix softening and dilation, and weaken the chorioamniotic membranes.[152] Variations in maternal and fetal genes coding for cytokines have been implicated in the apparent genetic predisposition to preterm birth found in some families and racial groups.[153] Thrombin is another uterotonic agent, which can cause uterine contractions, and has been implicated in causing preterm labor associated with vaginal bleeding caused by placental abruption.[154] Studies have shown a relationship between increasing maternal corticotropin-releasing hormone (CRH) and delivery timing.[155] Maternal and fetal stress can activate the hypothalamic–

pituitary system and result in the rapid increase in maternal CRH before premature birth. Infection can also activate the fetal hypothalamic–pituitary system, increasing CRH, cortisol, and, ultimately, prostaglandins.[152,154] Despite some progress in recent years, much remains unknown about the etiology of preterm birth, and little is known about how preterm birth can be prevented.

CLINICAL PRESENTATION AND EVALUATION

CASE 49-7

QUESTION 1: B.B., a 17-year-old White female, G2, P1, and at 29 weeks' gestation, is admitted to the obstetric unit with backache, cramps, and uterine contractions. She has no symptoms of preterm premature rupture of the membranes (PPROM). She had a previous preterm birth at 32 weeks' gestation. Cervicovaginal secretion findings are positive for fetal fibronectin. A pelvic examination reveals that her cervix is 2 cm dilated and 80% effaced, which is increased from 1 cm at her prenatal visit last week. Cervical culture results for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* from her previous visit are negative. Vaginal wet-mount preparations are also negative for bacterial vaginosis (BV) and *Trichomonas vaginalis.* Vital signs, urinalysis, and complete blood count with differential are normal. Uterine contractions and fetal heart rate are being monitored. Ultrasound reveals a fetus of 30 weeks' gestation size with an estimated weight of 1200 g.

What signs, symptoms, and laboratory evidence support a diagnosis of preterm labor?

B.B. has backache and uterine contractions, which are symptoms of preterm labor. Most patients with preterm contractions are not in labor, however, which results in frequent overdiagnosis. In addition, contractions during preterm labor are frequently not painful, are not detected by the person, and thus are not a sensitive marker for preterm labor. Fibronectin, a protein that serves as an adhesive between the fetal membranes and decidua, normally disappears from the cervical secretions after the first half of pregnancy, reappearing only at term as labor approaches.[156] A negative fibronectin test result can exclude imminent preterm delivery in a patient at risk for preterm delivery, between 24 and 34 weeks'

gestation with intact amniotic membranes, and with cervical dilatation of <3 cm.[157] Because of fibronectin's high negative predictive value of >95% for delivery in the next 1 to 2 weeks, it can be used to avoid overdiagnosis of preterm labor. Although fibronectin testing will yield false-positive results in the presence of blood, vaginal bleeding itself is independently associated with preterm birth. B.B. has the criteria necessary to establish a firm diagnosis of preterm labor. Not only is her fibronectin test result positive but she has persistent contractions with a documented change in cervix dilatation.

RISK FACTORS

CASE 49-7, QUESTION 2: What risk factors does B.B. have for spontaneous preterm labor?

B.B. has several risk factors for preterm delivery. The strongest predictor of preterm birth is prior preterm birth. She has a twofold or higher increased risk of preterm delivery because of one previous preterm delivery.[156] If this pregnancy also ends prematurely, her risk for a third preterm birth in her next pregnancy will be sixfold higher than that in the normal population.[156] Recurrence risk rises as the gestational age of the prior preterm birth decreases, especially for deliveries at <32 weeks. Her young age may also be a risk factor. A maternal age younger than 18 or older than 35 years is associated with spontaneous preterm birth, although it is difficult to separate age from the confounding factors associated with age.[156] Her race likely does not contribute to her risk. Black race is an independent risk factor for both preterm labor and lower neonatal birth weight. Other risk factors include low maternal weight before pregnancy, smoking, second- or third-trimester bleeding, multiple gestation, and uterine anomalies, which B.B. does not have.[120,156] Studies of cervix length by transvaginal ultrasound imaging have demonstrated that shorter lengths are associated with greater risk for preterm delivery; however, the positive predictive value varies widely.[156,157] Maternal

infections, such as untreated UTIs and pneumonia, are associated with preterm delivery. In addition, genital organisms such as *Gardnerella vaginalis*, *C. trachomatis*, *N. gonorrhoeae*, *Ureaplasma urealyticum*, and *T. vaginalis*, are also associated with preterm births.[141] Although it is important to identify patients at risk for spontaneous preterm delivery, only half of all preterm deliveries occur in patients with known risk factors.[156]

TOCOLYSIS

Goals of therapy

Treatment of spontaneous preterm labor primarily has been directed at slowing or stopping contractions (tocolysis), which are the obvious, although likely late, sign of impending preterm birth. It has been presumed that if successful, this should prevent or delay preterm birth. Few placebo-controlled trials have been conducted of agents used to diminish contractions (tocolytics), and most data suggest delay of delivery by at most 1 to 2 days.[158] This might be because of the heterogeneous causes of spontaneous preterm birth and because tocolytic agents may not arrest the underlying process that led to contractions. Most studies have been unable to demonstrate a clear benefit of tocolysis on neonatal morbidity and mortality. Instead, they have evaluated surrogate end points, such as pregnancy prolongation or number of preterm births before various cutoff points.[159] The value of prolonging pregnancy will vary by gestational age, and might be substantial if time is gained to administer glucocorticoids to improve fetal lung maturation and decrease the risk of intraventricular hemorrhage (see Case 49-7, Question 7). All patients at risk for preterm birth within 7 days and between 24 and 34 weeks' gestation should be considered for glucocorticoid therapy.[124,159,160] Delay of delivery can also allow transport to a facility best equipped to care for both patient and premature newborn.

Case 49-7, Question 3: What are the goals of tocolysis for B.B.?

Numerous factors affect the decision to treat preterm labor with a tocolytic agent. Fetal factors precluding tocolysis include nonreassuring fetal monitoring, significant IUGR, and lethal congenital anomalies. Maternal factors include evidence of chorioamnionitis, other significant maternal infections or illness, preeclampsia, and advanced labor.[156] Tocolysis is less likely to be effective in patients with cervical dilation of >3 cm and is usually unsuccessful if the patient is in advanced labor (cervical dilation >5 cm).[156] Because the etiology of preterm labor is multifactorial, B.B. should be evaluated thoroughly and periodically for potential causes of preterm labor and treated appropriately when diagnosed. For example, UTIs are associated with preterm labor, and they should be diagnosed and treated if present.[156] In addition, some would also perform amniocentesis to exclude subclinical chorioamnionitis as a cause of preterm labor before initiating or continuing tocolysis, and to evaluate lung maturity at later gestational ages.[160] B.B. has no evidence of overt infection or other complications, and has no contraindications to tocolysis. Prolonging gestation, even for a few days, would be beneficial because B.B. is only at 29 weeks' gestation.

Case 49-7, Question 4: How should B.B.'s preterm labor be managed? Which tocolytic agent should be used?

TOCOLYTIC AGENTS

Magnesium sulfate

Magnesium sulfate is the most frequently used parenteral tocolytic agent in the United States and is also prescribed for the prevention and treatment of eclampsia. Magnesium sulfate relaxes uterine smooth muscle at maternal serum levels of 5 to 8 mg/dL.[156] The mechanism by which it exerts this effect is not understood completely, but involves inhibition of myosin light-chain kinase activity by competition with intracellular calcium, reducing myometrial contractility.[159]

Despite its widespread use, the evidence for magnesium's efficacy in prolonging gestation is inadequate. In two published, randomized, placebo-controlled trials, no benefit in mean prolongation of pregnancy or mean neonatal birth weight was demonstrated. In meta-analyses of both placebo-controlled trials of magnesium for tocolysis compared with other active drugs, no prolongation of pregnancy was seen with magnesium.[158,161] Several small randomized controlled studies have directly compared magnesium with parenteral β-adrenergic agonists, mostly ritodrine.[158] Three of the four showed no differences in birth outcomes. One of the four suggested prolonged pregnancy with magnesium added to ritodrine compared with ritodrine alone. Studies on the efficacy of β-adrenergic agonists (mostly ritodrine) versus placebo have been mixed, but on balance suggest delay of delivery for 48 hours, but not for 7 days. Therefore, because most trials comparing magnesium with β-adrenergic agonists did not show differences, it has been presumed that magnesium is equally effective. Magnesium is better tolerated than are the β-adrenergic agonists, with fewer maternal side effects.[158] Magnesium is contraindicated in patients with myasthenia gravis and must be used with caution in renal failure.

β-Adrenergic agonists

β-Adrenergic agonists are not the first-line choice for preterm labor because of high costs and the significant potential for maternal adverse effects described subsequently.[156,158] Both ritodrine, the only medication approved by the FDA for the treatment of preterm labor, and terbutaline bind to β_2-adrenergic receptors in uterine smooth muscle and ultimately inhibit smooth muscle cell contractility. Results of randomized controlled trials of ritodrine have been mixed; however, a meta-analysis that included 1320 patients treated with β-agonists demonstrated fewer births at 48 hours but no change in number of births at 7 days. No benefit on neonatal morbidity or mortality was seen; however, the studies are limited by sample size.[162,163] The continued use of β-agonists can result in the

development of tachyphylaxis to its effects on the myometrium and may in part explain treatment failures with these drugs.[156,163]

Terbutaline is available for IV, SC, and PO administration. One dose of terbutaline 0.25 mg SC is often administered to patients with mild contractions and cervical dilation <2 cm. IV β-sympathomimetics are used in cases with more severe and frequent contractions and cervical dilation >2 cm. However, because of potential adverse maternal side effects such as increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia, the FDA issued a black box warning in 2011 against the use of injectable terbutaline beyond 48 to 72 hours. The FDA also recommended against any use of oral terbutaline for preterm labor owing to both lack of efficacy and the potential for significant maternal side effects.

β-Adrenergic Adverse Effects

β-Adrenergic agonists are not selective for myometrial β_2-adrenergic receptors at pharmacologic doses, and this accounts for their high incidence of adverse effects.[164] Maternal adverse effects such as pulmonary edema, palpitations, tachycardia, myocardial ischemia, hyperglycemia, hypokalemia, and hepatotoxicity result in discontinuation of therapy in up to 10% of patients.[156] Pulmonary edema can occur and, if not recognized promptly, can lead to acute respiratory distress syndrome (ARDS) and death.[156] β-Sympathomimetics should not be used in patients with underlying cardiac disease or arrhythmias, hypertension, diabetes mellitus, severe anemia, or thyrotoxicosis.[156] In addition, these drugs should be avoided if there are signs of chorioamnionitis such as maternal leukocytosis, fetal tachycardia, or maternal fever.[155]

The most commonly reported fetal or neonatal adverse effects associated with β-agonist therapy include tachycardia, hypotension, hypoglycemia, and hypocalcemia, especially if the drug is being administered within hours of delivery.[156,164] Maternal hyperglycemia causing fetal hyperglycemia and hyperinsulinemia can lead to neonatal hypoglycemia if not properly monitored postnatally. Fetal

tachycardia rarely leads to fetal myocardial ischemia or hypertrophy.[164] In summary, although β-sympathomimetic drugs have been used commonly in the past, they are now used much less frequently because of side effect profiles and safety concerns.[156]

Indomethacin

Prostaglandins F_{2a} and especially E_2 are important regulators of myometrial contractility and cervical ripening.[120] Prostaglandin synthesis requires cyclooxygenase (COX), also known as prostaglandin synthetase, to convert arachidonic acid to prostaglandin G_2. COX inhibitors such as indomethacin decrease prostaglandin production, which decreases contractions and inhibits cervical change. As with other tocolytics, these drugs have not been adequately studied in multiple randomized controlled trials. A review of available randomized trials of indomethacin compared with placebo found significant reductions in patients delivering at <37 weeks' gestation, an increase in gestational age at delivery, and a trend toward fewer deliveries at 48 hours and 7 days.[165] In three of eight trials comparing COX inhibitors with other tocolytics, a reduction in both delivery before 37 weeks' gestation and maternal drug reactions was noted. Also, seen in these studies was a trend toward a reduction in delivery within 48 hours.[165] Indomethacin is well tolerated, and GI upset can be mitigated by antacids when it occurs. However, the available studies are inadequately powered to evaluate neonatal safety and outcomes.[165,166]

Although well tolerated by the patient, concerns exist about the fetal and neonatal effects of prostaglandin synthetase inhibition. Indomethacin crosses the placenta rapidly, and fetal levels rapidly approach maternal levels.[164,166] Because indomethacin can decrease fetal urine output leading to oligohydramnios, the amniotic fluid index should be followed and indomethacin discontinued if it falls <5 cm (normal range, 5–25 cm). Oligohydramnios generally resolves within 48 to 72 hours of the discontinuation of indomethacin. The fetal ductus arteriosus, which is critical to allow blood from the right ventricle to bypass the fluid-filled lungs, constricts in 25% to 50% of

fetuses exposed to indomethacin in utero, but generally is reversible.[156] Permanent closure of the ductus arteriosus, however, can lead to fetal right heart failure and even intrauterine demise. The risk of neonatal adverse effects is increased with drug exposure of >48 hours, as well as use after 32 weeks' gestation when premature closure of the ductus occurs more frequently.[156] An increased risk of maternal postpartum hemorrhage has also been reported with indomethacin use but did not reach significance in a meta-analysis.[165] Indomethacin should not be used in the presence of oligohydramnios or suspected fetal renal or cardiac anomaly (see Chapter 105, Neonatal Therapy).

More serious fetal and neonatal effects have been reported in some retrospective and observational studies, including neonatal necrotizing enterocolitis, intraventricular hemorrhage, and renal failure.[166–168] It is difficult, however, to discern whether these complications are causally related to indomethacin or to the use of the drug in cases of refractory preterm labor caused by subclinical intra-amniotic infection.[166,169] An analysis of the risks and benefits of indomethacin suggested its continued use as second-line treatment for preterm labor between 24 and 32 weeks' gestation in patients with contraindications to other tocolytics.[166] Typical dosing regimens include a loading dose of 50 to 100 mg either rectally or PO followed by a maintenance dose of 25 mg PO every 4 to 6 hours for 24 to 48 hours.[167]

Calcium channel blockers

The calcium channel blockers nifedipine and nicardipine inhibit preterm contractions by decreasing calcium influx into uterine smooth muscle and inhibiting myometrial contractions. No placebo-controlled trials have been performed with nifedipine, the most commonly used calcium channel blocker. A meta-analysis of 12 randomized trials including a total of 1029 patients found that calcium channel blockers were superior to other tocolytics (mostly β-mimetics) in reducing preterm births within 7 days and before 34 weeks' gestation.[169] A more recent study of 192 patients comparing

nifedipine with magnesium sulfate for preterm labor found no differences in delivery in 48 hours, gestational age at delivery, or deliveries before 32 or 37 weeks' gestation.[170] Maternal side effects were significantly fewer in patients receiving calcium channel blockers compared with other tocolytics.[169–171]

Maternal side effects can include tachycardia, headache, flushing, dizziness, nausea, and hypotension in the patient with hypovolemia.[164] Nifedipine does not adversely affect uteroplacental blood flow or fetal circulation. Concurrent use with magnesium should be avoided because the combination may potentiate neuromuscular blockade.[106,160,164] The starting dose is usually 10 mg PO with repeated doses of 10 mg every 15 to 20 minutes for persistent contractions, up to a maximum of 40 mg in the first hour.[172-175] Depending on the tocolytic effect, nifedipine is then maintained at 10 to 20 mg PO every 4 to 6 hours.[172] Overall, nifedipine appears to be an attractive alternative for short-term tocolysis because the drug is usually well tolerated.[176]

B.B. should be started on a magnesium sulfate 6-g IV loading dose for 30 minutes followed by 2 g/hour continuous IV infusion through a controlled infusion pump. The hourly rate of magnesium administration for B.B. may be increased until she has one or fewer contractions per 10 minutes or a maximum of 4 g/hour is attained. B.B.'s deep tendon reflexes, respiratory rate, and urine output should be monitored regularly. Close monitoring of fluid balance is important because fluid overload has been associated with pulmonary edema and the drug is renally excreted.[172]

Magnesium serum concentrations are commonly evaluated every 6 to 12 hours in an effort to minimize adverse effects.[177] The patellar reflex disappears with magnesium serum concentrations between 9 and 10 mg/dL, and as long as deep tendon reflexes are present, many practitioners will not measure concentrations. To prevent inadvertent overdoses, a controlled infusion device should always be used to deliver magnesium as a continuous infusion. Hypocalcemia and tetany can occur with hypermagnesemia. Neuromuscular blockade and respiratory arrest develop with magnesium serum concentrations of 15 to 17 mg/dL, and cardiac arrest develops with

greater concentrations. The toxic effects of magnesium can be rapidly reversed with 1 g of parenteral calcium gluconate, which should be readily available when patients are receiving magnesium infusion.[164]

The most common side effects of magnesium loading doses are transient hypotension, flushing, a sense of warmth, headache, dizziness, lethargy, nystagmus, and dry mouth.[156,172] Other adverse effects reported with magnesium are hypothermia, paralytic ileus, and pulmonary edema, which may occur in 1% to 2% of patients treated with magnesium sulfate.[172] Pulmonary edema occurs less frequently with magnesium sulfate than with parenteral β-sympathomimetics but is more commonly encountered with prolonged infusions, multifetal pregnancy, and the use of multiple tocolytics.[164] Treatment consists of discontinuing magnesium sulfate and administration of the diuretic furosemide.

Fetal magnesium serum concentrations are similar to maternal concentrations.[172] The most common neonatal adverse effects are hypotonia and sleepiness. Hypotonia may continue for 3 or 4 days in the neonate because of decreased renal elimination of magnesium.[178–181] Rarely, assisted mechanical ventilation for neuromuscular depression may be needed.[172]

DURATION OF TOCOLYSIS

Acute therapy

Case 49-7, Question 5: B.B. has been maintained on magnesium sulfate continuous IV infusion for ~48 hours. The dose was increased to 3 g/hour shortly after the start of the infusion. B.B. has had no contractions for the past 24 hours. How long does she need to be treated? Should she be weaned off magnesium sulfate?

B.B.'s contractions have completely stopped for 24 hours. Some protocols maintain magnesium sulfate for 12 to 24 hours after successful tocolysis, or for the time it takes to complete the course of corticosteroids. The weaning of magnesium sulfate is unnecessary,

and simple discontinuation of the magnesium infusion is an easier and less costly option.[176,182]

Chronic maintenance therapy

Case 49-7, Question 6: B.B. heard that preterm labor can return once stopped and asks whether she should stay on medication. Should B.B. be started on chronic maintenance tocolytic therapy?

Maintenance tocolysis has been used in an attempt to prevent recurrence of preterm labor and prolong gestation in patients in whom preterm labor was terminated successfully with parenteral tocolytics. β-Adrenergics and oral calcium channel blockers have been evaluated for maintenance therapy.[183] Results of meta-analysis of trials comparing placebo or no treatment with oral β-adrenergics for maintenance therapy after acute preterm labor showed no benefit in delay of delivery, births at <34 or 37 weeks' gestation, or neonatal complications.[184] Moreover, increases in maternal adverse effects occurred, primarily tachycardia, hypotension, and palpitations. Lastly, inadequate data exist to support the use of calcium channel blockers as maintenance therapy.[160] B.B. should not be started on chronic maintenance tocolysis because there is not compelling evidence that continued suppression of contractions after acute tocolysis reduces the rate of preterm birth or neonatal morbidities.[155,159]

ANTENATAL GLUCOCORTICOID ADMINISTRATION

Case 49-7, Question 7: Given B.B. is in preterm labor at 29 weeks' gestation, what medication can be given to help facilitate fetal lung maturation?

B.B. should be given betamethasone 12 mg IM now and a second dose 24 hours later to facilitate fetal lung maturation by increasing production of fetal lung surfactant, thereby reducing the incidence and severity of RDS.[124] Antenatal corticosteroid administration (betamethasone and dexamethasone) also decreases the incidence

of intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death.[124] The greatest reduction in RDS occurs when delivery can be delayed 24 hours up to 7 days after starting treatment. Repeated weekly corticosteroid courses should not be given because of the association with decreased birth weight and head circumference, hypothalamic–pituitary–adrenal axis suppression, deleterious effects on cerebral myelination and lung growth, and neonatal death (particularly in neonates born to patients who received three or more courses).[125,185] However, a randomized clinical trial has now demonstrated a significant reduction in neonatal respiratory morbidity and composite neonatal morbidity when patients with preterm labor and intact membranes who had received an initial course of steroids at <30 weeks' gestation were treated again with a single rescue course of steroids (betamethasone 12 mg IM × two doses, 24 hours apart) if >2 weeks had passed and the gestational age was <33 weeks.[186] This rescue course was administered if there was judged to be a recurrent risk of preterm birth. Although long-term outcome data are not yet available, the ACOG now recommends consideration of a single rescue course of steroids under these specific circumstances.[125]

The National Institutes of Health (NIH) Consensus Panel and the ACOG recommend a course of antenatal betamethasone or dexamethasone (dexamethasone 4 mg IM × every 12 hours, for four doses) for all patients in preterm labor between 24 and 34 weeks' gestation.[124,125] Betamethasone, however, might be the preferred agent because fewer IM injections are needed and because in meta-analysis it was associated with a greater reduction in RDS compared with dexamethasone.[185] That conclusion, however, is not based on direct comparison of betamethasone with dexamethasone and should be interpreted with caution. One study, although limited by its retrospective nature, also suggested an advantage of betamethasone over dexamethasone in the reduction of periventricular leukomalacia, a finding associated with later risks for cerebral palsy.[187] In cases of PPROM, the NIH Consensus Panel recommends that corticosteroids may be given up to 32 weeks' gestation in the absence of chorioamnionitis.[124,125] Recent meta-

analysis supports the efficacy of corticosteroids in the reduction of neonatal death, RDS, duration of ventilator use, and intraventricular hemorrhage in infants born after ruptured membranes.[185] Patients at >32 weeks' gestation can be considered for amniotic fluid testing for the presence of phosphatidylglycerol or a lecithin-to-sphingomyelin ratio of >2 because these are indicators of fetal lung maturation.[185] Corticosteroids are not recommended for use in pregnant patients who are at >34 weeks' gestation unless there is an indication of fetal lung immaturity (see Chapter 105, Neonatal Therapy).

Infectious Complications During Pregnancy and Labor

Case 49-7, Question 8: Preterm labor is often associated with an infectious etiology or source. Does B.B. need to be started on any antibiotic therapy because she is in preterm labor?

PRETERM PREMATURE RUPTURE OF MEMBRANES

Increasing evidence associates preterm labor with intra-amniotic infections.[152,186] Of preterm births, 20% to 40% may be caused by an infectious or inflammatory process.[156] Intrauterine infection is associated with ~80% of early preterm deliveries.[154] Most of the bacteria found in amniotic fluid and the placenta are believed to have ascended from the vagina.[156] It has been suggested that the microbes responsible for preterm birth are already present in the endometrium before conception or early in the pregnancy, causing a chronic, subclinical infection weeks to months before eventually causing PPROM or labor.[154,156]

When PPROM has occurred, spontaneous labor and delivery occur, on average, within 7 days, although longer intervals from PPROM to delivery occur with earlier gestational ages.[187] The use of a short course of antibiotics has been shown to prolong the period between PPROM and delivery (the latency period) and decrease neonatal morbidity.[187] In the largest and best-designed trial of

antibiotic treatment of PPROM, patients between 24 and 32 weeks' gestation treated with ampicillin and erythromycin had both prolonged pregnancies and lower rates of chorioamnionitis.[188] Their newborns experienced decreased mortality, as well as decreased morbidity including RDS and necrotizing enterocolitis. These effects were not owing to tocolytics or corticosteroids because these were exclusionary factors. These results were confirmed by the results of a large meta-analysis including >6000 patients, although information on the best choice of antibiotics was less clear.[189,190] Therefore, patients with PPROM benefit from antibiotic therapy with a broad-spectrum regimen, and IV ampicillin plus erythromycin for 48 hours followed by 5 days of oral amoxicillin plus erythromycin for a total of 7 days' treatment is a reasonable choice.[191]

B.B. should not be started on any PPROM antibiotic regimen because her membranes are not ruptured. Antibiotics have not been proved to prevent premature births in the setting of acute preterm labor.[158] There is currently no role for antibiotic use to prolong pregnancy or reduce neonatal morbidity in preterm labor with intact membranes, and it may be associated with long-term harm.[158,192] There may be a role for treatment of BV antenatally to reduce the risk of preterm birth in patients with a past history of spontaneous preterm birth.

BACTERIAL VAGINOSIS

Some, but not all, studies have demonstrated that screening and treating asymptomatic patients who are at high risk for preterm delivery for BV may reduce the risk of preterm birth.[158,160] A polymicrobial overgrowth of mostly anaerobic bacteria, BV, is one of the most common genital infections in pregnancy, and it is associated with an increased risk of preterm delivery.[193] Treatment of patients with BV who had a prior preterm delivery with oral metronidazole in combination with erythromycin decreased the risk of recurrent preterm delivery in one randomized clinical trial, but there was no difference for patients without a history of recurrent preterm birth.[194,195] In addition, a meta-analysis including 622

patients with prior preterm birth found no reduction in the risk of preterm birth before 37 weeks' gestation after treatment of BV with antibiotics, but did find a reduction in PPROM. In addition, in patients with BV who were treated with oral antibiotics before 20 weeks' gestation, there was a reduction in preterm birth at <37 weeks.[195] B.B. does not have BV; therefore, treatment with metronidazole is unnecessary.

GROUP B STREPTOCOCCUS INTRAPARTUM PROPHYLAXIS

Antibiotics should be given to patients if delivery is anticipated resulting either from preterm labor with intact membranes or after PPROM to prevent group B streptococcal (GBS) infection in the newborn. Other broad-spectrum antibiotic therapy to prevent preterm delivery should not be given routinely to patients in preterm labor with intact membranes.

Approximately 10% to 30% of pregnant patients are colonized with GBS or *Streptococcus agalactiae* in the vagina or rectum, and 1% to 2% of neonates born to colonized patients experience early-onset invasive GBS disease in the absence of IV intrapartum antibiotic prophylaxis.[196] One-fourth of all cases of neonatal GBS infections occur in preterm newborns. B.B.'s fetus, therefore, is at risk for invasive GBS infection from vertical transmission (patient to infant) of bacteria during labor or delivery. The mortality rate for GBS is reported to be between 5% and 20%. Fortunately, the incidence of GBS has declined to a rate of 0.34 to 0.37 cases per 1000 live births in recent years owing to prevention efforts.[196] During pregnancy, GBS infection can cause maternal UTI, amnionitis, endometritis, and wound infection. Antibiotics given to the patient during preterm labor and delivery help prevent neonatal GBS disease, which may lead to sepsis, pneumonia, and meningitis. In the past decade, the routine administration of intrapartum antibiotic prophylaxis to certain subsets of pregnant patients has led to a 70% reduction in the overall incidence of GBS disease.[196] The decision to treat patients with intrapartum antibiotics has been based on either a positive vaginal and rectal GBS culture result routinely obtained at 35 to 37 weeks'

gestation or one or more of the following risk factors without culture screening: (a) previous infant with invasive GBS disease; (b) GBS bacteriuria during any trimester of the current pregnancy; and (c) unknown GBS status at onset of labor and any of the following—delivery at <37 weeks' gestation, amniotic membrane rupture at ≥18 hours, or intrapartum temperature of ≥100.4 °F (38 °C).[196]

Vaginal and rectal GBS cultures should be obtained from B.B., and she should be given a loading dose of penicillin G injection 5 million units, followed by 2.5 to 3.0 million units IV every 4 hours until delivery, while awaiting success of tocolysis and culture results. The Centers for Disease Control and Prevention guidelines recommend that the benchmark for optimal prophylaxis should be antibiotics given at least ≥4 hours before delivery. Penicillin G is preferred over ampicillin because it has a narrower spectrum of antimicrobial activity. If B.B. had a severe allergy to penicillin, sensitivities to clindamycin and erythromycin should be requested at the time of culture in the event GBS is found because of increasing resistance to these drugs. If the isolate is susceptible to both clindamycin and erythromycin, then clindamycin 900 mg IV every 8 hours should be used until delivery. Erythromycin is no longer recommended as an option for treatment because it is often associated with inducible resistance to clindamycin. If the isolate is not susceptible to both clindamycin and erythromycin or if sensitivities are not available, patients who are allergic to penicillin and at high risk for anaphylaxis should receive vancomycin 1 g IV every 12 hours until delivery. Patients who are allergic to penicillin but at low risk for anaphylaxis should receive cefazolin 2 g IV initially, then 1 g IV every 8 hours until delivery.[192,193] Because B.B. is only at 29 weeks' gestation and in preterm labor, she has not yet had her GBS culture obtained, which normally occurs at 35 to 37 weeks. Until the results of her rapid testing for GBS culture returns, she should receive penicillin G 3 million units IV every 4 hours until delivery to prevent perinatal GBS infection.

Case 49-7, Question 9: B.B.'s culture results are negative for GBS growth. She is still at high risk for imminent delivery. Should penicillin G administration

be discontinued?

Penicillin should be discontinued at this time. Vaginal and rectal cultures need not be repeated if B.B. delivers within the next 4 weeks. If tocolysis is successful and delivery is delayed for >4 weeks, obtaining cultures and starting penicillin G preemptively should be repeated at that time. Intrapartum prophylaxis is effective only if antibiotics can be given immediately before and during delivery.

Case 49-7, Question 10: B.B.'s contractions are gone, and her cervical examination remains unchanged for 48 hours. She is able to be discharged home undelivered but is counseled to stay on bed rest for the duration of the pregnancy. B.B. has a significant history of a prior preterm delivery at 32 weeks' gestation. What medication should be recommended to B.B. now and in her next pregnancy, to decrease her risk and prevent another preterm delivery from occurring?

Recent studies have shown that progesterone supplementation can help reduce preterm births, but should only be used in patients who have had a prior documented history of a spontaneous preterm birth before 37 weeks' gestation.[197] The optimal progesterone product is not known (vaginal suppositories, oral capsules, or IM injectables). Progesterone should be offered to patients such as B.B. who have had a prior history of spontaneous preterm delivery.[198] A recent randomized, double-blinded, placebo-controlled trial found a significant reduction in the rate of preterm deliveries in these high-risk patients with a prior documented history of preterm delivery with the use of 17-α hydroxyprogesterone (17-OHP).[199] The rate of preterm delivery in the treatment group was 6.3% versus 54.9% in the placebo group.[199] 17-OHP is given as an IM injection prepared as 250 mg/mL once weekly. Therapy should be initiated at 16 to 20 weeks' gestation and continued until 37 weeks' gestation.[199] 17-OHP is widely available from compounding pharmacies, and, most recently, a commercially marketed FDA-approved drug called Makena® has been released into the market.[200] Although B.B. is

already 29 weeks pregnant, she should be started on 17-OHP therapy at 250 mg/mL injected IM once weekly until 37 weeks. She should be counseled that progesterone should be started earlier at 16 weeks in her next pregnancies. The compounded 17-OHP is more affordable, cost-effective, and equally as effective as the marketed Makena® product.[200]

Case 49-7, Question 11: B.B. returns to labor and delivery at 36 5/7 weeks' gestation with spontaneous rupture of the membranes and is found to be 4 cm dilated and 80% effaced. Her vital signs currently are a BP of 106/79 mm Hg, heart rate of 80 beats/minute, and respiratory rate of 12 breaths/minute with 99% oxygenation on room air. Intrapartum fetal monitoring shows a reassuring reactive fetal heart rate with variability. After being in labor for about 16 hours, her temperature spikes up to 101.1 °F (38.39 °C). What are the risks of an elevated fever during labor, and how should B.B. be treated?

Chorioamnionitis

Chorioamnionitis is an infection of the amniotic fluid, membranes, and placenta occurring before, during, or immediately after birth.[194] Intra-amniotic infections occur in ~1% to 5% of term pregnancies and may complicate up to 15% of cases of preterm labor.[204] Maternal fevers are usually the most common clinical presentation in many patients. Diagnosis is based on the presence of fever, defined as ≥100.4 °F (38 °C) measured twice at least 4 hours apart, or a temperature of 101 °F (38.33 °C) measured once. Patients may also present with maternal tachycardia (>100 beats/minute), fetal tachycardia (160 beats/minute), uterine tenderness, foul odor from amniotic fluid, and maternal leukocytosis.[194,195] The exclusion of other sources of infection such as UTI, viral illness, abscesses, and drug-induced fever (ie, epidural, misoprostol) must be made. Common organisms ascending from vaginal flora causing polymicrobial intra-amniotic infections include genital mycoplasmas such as *U. urealyticum* and *Mycoplasma hominis,* anaerobes including *G. vaginalis,* enteric gram-negative bacilli, and GBS.[195,196]

The two most prominent risk factors of intra-amniotic infections are the number of digital examinations and duration of labor.[194]

Maternal complications from intra-amniotic infections include bacteremia, suboptimal uterine contractility, and risk of postpartum hemorrhage.[195] Increases in rates of neonatal sepsis, pneumonia, meningitis, and mortality have been shown in infants whose mothers had chorioamnionitis.[198] Furthermore, inflammation, intrapartum fever, and infection increase the risk of long-term neurodevelopmental delay and cerebral palsy in these neonates.[201] The risk of cerebral palsy is at least twofold to fourfold higher in infants who were exposed to intra-amniotic infection in utero.[201]

Early administration of broad-spectrum antibiotics immediately after the diagnosis of chorioamnionitis has been shown to have both maternal and neonatal benefit versus postpartum antibiotic administration. A common regimen implemented is ampicillin 2 g IV every 6 hours in addition to gentamicin dosed to a target peak of 8 µg/mL and trough of 1 µg/mL.[195] Standard dosing of gentamicin every 8 hours is preferred over once-daily dosing to prevent elevated fetal serum peak levels, although no adverse effects of high-dose therapy were noted.[202] Clindamycin 900 mg IV every 8 hours may be added to the regimen to cover anaerobic organisms. If fevers persist for >24 hours on triple antibiotics with ampicillin, gentamicin, and clindamycin, metronidazole can be substituted for clindamycin to help broaden anaerobic coverage.[195] Other options for antibiotic coverage include extended-spectrum penicillins (ie, piperacillin–tazobactam, ampicillin–sulbactam) or second-generation cephalosporins (ie, cefoxitin and cefotetan).[195] Intrapartum antibiotics administered about 1 hour after infusion produce adequate bactericidal concentrations in the fetus and placental membranes.

With a fever of 101.1 °F (38.39 °C), B.B. meets criteria for a clinical diagnosis of chorioamnionitis. However, she does not exhibit any other symptoms of systemic infection such as tachycardia, uterine tenderness, or fetal tachycardia, which is quite common. Gentamicin and ampicillin should be started promptly after diagnosis to decrease the risk of neonatal sepsis and to avoid possible neurodevelopment sequelae. In addition, clindamycin can be added

to cover anaerobic organisms. B.B.'s risk factors for chorioamnionitis include multiple digital examinations, preterm labor, spontaneous labor, and long duration of labor. Antibiotics should be continued until B.B. is afebrile for at least 24 to 48 hours or until delivery. Ultimately, immediate antibiotic administration and delivery of the offending source is paramount to ensure fetal health and safety.

Human Immunodeficiency Virus in Labor and Breast-feeding

CASE 49-8

Question 1: S.L. is a 23-year-old G1, P0 at 38 weeks' gestation and is positive for HIV. She is presenting to labor and delivery with spontaneous rupture of membranes and is having regular contractions every 5 minutes. Her last HIV RNA levels were undetectable, and her CD4 count was 400 cells/mL. Her current combination antiretroviral therapy (cART) consists of zidovudine (AZT), lamivudine, and atazanavir/ritonavir, which was started 2 years ago.

What are the risks of HIV perinatal transmission in S.L., and what medications must be started while she is in labor?

Current recommendations state that all HIV-infected pregnant patients should receive intrapartum AZT if the HIV RNA level is >1000 copies/mL, and their infants should receive neonatal AZT immediately after delivery for 6 weeks with a consideration for a 4-week treatment plan if the patient has been maintained on a cART regimen throughout the pregnancy.[203] Many factors must be taken into consideration, including cost, ease of administration for compliance, individual antiretroviral therapy (ART) resistance patterns, and risks of side effects with the possibility of teratogenicity.[204] Generally, if a patient on cART becomes pregnant, she should continue on therapy throughout the pregnancy, including the first trimester.[203] Patients who did not require cART before becoming pregnant should start cART prophylaxis after the first trimester but not later than 28 weeks of gestation.[203] cART is more effective in preventing perinatal HIV transmission if it is started

earlier, before 28 weeks' gestation versus 36 weeks' gestation.[203] All patients infected with HIV should be counseled and offered cART during pregnancy to prevent perinatal transmission regardless of HIV RNA levels.[203] Avoid the use of stavudine and didanosine entry and fusion inhibitors in patients of childbearing age and during the first trimester, if possible, owing to issues of toxicity and teratogenicity.[203] Efavirenz in the updated guidelines can be continued to be used if the patient was on an efavirenz-based regimen. A fetal ultrasound is recommended. Further studies are needed to help identify the effectiveness and safety of other cART regimens. Cesarean section delivery is highly recommended.[203]

S.L. should continue on her ART (AZT, lamivudine, and atazanavir/ritonavir) during labor without missing any doses. Prophylactic neonatal AZT should be administered to the infant at a dose of 4 mg/kg (actual weight) PO every 12 hours, within 6 to 12 hours of birth, for a total duration of 6 weeks.[203]

Case 49-8, Question 2: Should S.L. breast-feed her infant if her HIV RNA levels are undetectable and her CD4 counts are 400 cells/μL?

Although S.L. is currently on effective cART to suppress her HIV RNA levels and maintain her CD4 levels, she should not breast-feed. Breast-feeding is not recommended for HIV-infected patients in the United States because of safer and affordable alternatives such as formula. Prophylactic cART in the infant and patient does not entirely eliminate the risk of perinatal transmission through breast milk.[203]

POSTPARTUM HEMORRHAGE

Prevention

Case 49-8, Question 3: S.L. successfully has a normal spontaneous vaginal delivery with an estimated blood loss of 400 mL. Which medications should be

given to S.L. routinely after delivery?

Oxytocin is administered routinely after the delivery of the placenta to promote uterine contraction and vasoconstriction. Meta-analysis of randomized clinical trials demonstrates that the use of oxytocin preventively in the third stage of labor reduces the risk of hemorrhage and need for medical therapy for uterine atony.[205] Uterine atony, the condition in which the uterus fails to contract after delivery of the placenta, is the most common cause of postpartum hemorrhage.[206] Risks factors for uterine atony include induction and augmentation of labor, prolonged labor, an overdistended uterus such as with twins or polyhydramnios, and previous postpartum hemorrhage.[206] Oxytocin 10 to 20 units IM or diluted in 0.5 to 1 L of parenteral fluid and given as an IV infusion of 200 mU/minute until the uterus is firmly contracted reduces the risk of postpartum hemorrhage secondary to uterine atony.[207] Oxytocin should never be administered undiluted as a bolus dose because it can cause severe hypotension and cardiac dysrhythmias.[207]

MISOPROSTOL

Misoprostol 400 to 600 µg can be administered PO in the third stage of labor to prevent postpartum hemorrhage.[208,209] In a comparison of 600 µg of oral misoprostol with parenteral oxytocin for prevention of postpartum hemorrhage, oxytocin was marginally but statistically more effective and had fewer side effects.[210] Misoprostol also can be administered rectally. Rectal administration is associated with a lower incidence of fever and shivering, which is common with misoprostol administered PO during the third stage of labor.[210] The rectal route of administration also is associated with lower maximal serum concentrations and lower time to maximal concentrations than when the drug is administered PO. Although not as effective as oxytocin in preventing postpartum hemorrhage, misoprostol, which is inexpensive, stable at room temperature, and not administered parenterally, may be preferred in settings of meager resources for the management of the third stage of labor.

S.L. should receive an infusion of oxytocin 20 units in 1 L of lactated Ringer solution at 125 mL/hour.

Treatment

Case 49-8, Question 4: Within a few hours of delivering, S.L. has visible vaginal bleeding. She has a distended uterus, and the hemorrhage is attributed to uterine atony. Uterine massage, which is standard treatment, does not control the bleeding. What other pharmacologic options are available to treat her postpartum hemorrhage in addition to the infusion of more oxytocin at this time?

ERGOT ALKALOIDS

If the postpartum hemorrhaging does not respond to oxytocin administration, ergonovine maleate (Ergotrate®) and its semisynthetic derivative, methylergonovine maleate (Methergine®), can be used because of their potent uterotonic effects. IM administration is associated with less frequent adverse effects (nausea, vomiting, hypertension, headache, chest pain, dizziness, tinnitus, diaphoresis) than is the IV route.[207] Ergot alkaloids should be avoided in patients with hypertension and eclampsia because of the potential for arrhythmias, seizures, cerebrovascular accidents, and, rarely, myocardial infarction. The dose of both drugs is 0.2 mg administered IM every 2 hours as needed. This may be followed by 0.2 to 0.4 mg administered PO two to four times daily for 2 to 7 days to promote involution of the uterus (**Table 49-5**).[207]

Table 49-5
Uterotonic Medications Used for Postpartum Obstetric Hemorrhage

Drug	Dose	Comments
Oxytocin (Pitocin®)	40 IU in 1 L NS or lactated Ringer solution 10 IU IM if no IV site available	Do not give as undiluted IV bolus, can cause hypotension.

Drug	Dose	Comments
Methylergonovine maleate (Methergine®)	0.2 mg IM every 2–4 hours	Contraindicated in hypertensive patients
Carboprost tromethamine (Hemabate®)	0.25 mg IM every 15–90 minutes, not to exceed eight doses	Caution in use with patients with asthma, can cause bronchoconstriction
Misoprostol (Cytotec®)	1000 μg PR given once	Can also be given orally or sublingually, but PR is preferred route

IM, intramuscular; IV, intravenous; NS, normal saline; PR, per rectum.

Source: Used with permission of McGraw Hill LLC from Cunningham FG, Leveno KJ, Bloom SL, et al. Obstetrical hemorrhage. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill, 2014:780–828; permission conveyed through Copyright Clearance Center, Inc.

15-METHYL PROSTAGLANDIN F2A (CARBOPROST TROMETHAMINE)

Bleeding caused by uterine atony that is unresponsive to oxytocin can be treated with 15-methyl prostaglandin $F_{2\alpha}$-tromethamine, also known as carboprost tromethamine (Hemabate®).[206] Carboprost tromethamine, as with naturally occurring prostaglandins, stimulates uterine contraction and decreases postpartum hemorrhage; it is more potent and has a longer duration of effect than its parent compound, prostaglandin $F_{2\alpha}$.

Carboprost tromethamine is approved for IM use, but it has been also administered through direct myometrial injection.[207,211] Intramyometrial administration has been associated with severe hypotension and pulmonary edema.[212] An initial dose of 0.25 mg IM is given followed by 0.25 mg every 15 to 90 minutes.[207,211] The total cumulative dose should not exceed 2 mg (eight doses maximum).[211] Carboprost tromethamine is effective in treating 60% to 85% of patients with uterine atony who have failed standard treatment.[207] Improvement in bleeding typically occurs after one to two injections.

The most common adverse effects of carboprost tromethamine are GI, including nausea, vomiting, and diarrhea. Flushing and fever

also occur frequently. Many of the adverse effects are related to the contractile effect of this drug on smooth muscle.[211] Hypertension, although rare, typically occurs in patients with preexisting hypertension or preeclampsia. The potent vasoconstricting and bronchoconstricting properties of carboprost can cause uterine rupture, as well as pulmonary and cardiac problems. Carboprost must be used with caution in patients with asthma and is relatively contraindicated in the presence of pulmonary, cardiac, renal, or hepatic disease.[206,211]

MISOPROSTOL

Several case series and small randomized trials have reported that misoprostol might be useful in the treatment of postpartum hemorrhage caused by uterine atony. The available data are very limited, however, and large randomized trials are needed to clarify the efficacy of misoprostol compared with standard therapies, as well as the optimal dose and route of administration.[213] A recent double-blind, randomized, placebo-controlled clinical trial was performed to clarify the role of misoprostol in the treatment of postpartum hemorrhage.[214] Treatment was either 800 µg of sublingual misoprostol or 40 IU of oxytocin in 1 L of IV fluid given for 15 minutes. Resolution of active bleeding occurred within 20 minutes in 89% to 90% of patients in each study arm, demonstrating no advantage to misoprostol over standard IV therapy with oxytocin. Furthermore, patients who received misoprostol had significantly more shivering and fever >104 °F (40 °C). In areas with meager resources, misoprostol may offer advantages (low cost, prolonged stability, and oral formulation), but the role of misoprostol as an adjunctive therapy when oxytocin is already available remains uncertain.[207]

S.L. does not have any contraindications (ie, asthma or hypertension) to any of the postpartum hemorrhage medications. She should be given oxytocin 40 IU in 1 L of lactated Ringer solution given for 15 minutes. Methylergonovine maleate 0.2 mg IM and misoprostol 1000 µg rectally can be given in succession after

oxytocin if bleeding does not subside. Lastly, carboprost tromethamine 0.25 mg IM is an option if those medications fail to control bleeding.

PREVENTION OF RH D ALLOIMMUNIZATION

Maternal–Fetal Rh Incompatibility

CASE 49-9

Question 1: G.G., a 34-year-old primigravida, had her ABO blood group and Rh status determined during her initial prenatal visit. She is found to be type O, Rh negative. Her husband is type O, Rh positive.

What are the risks associated with Rh incompatibility that could affect G.G.'s fetus?

Blood group incompatibility between a pregnant patient and her fetus can result in alloimmunization of the patient and hemolytic anemia in the fetus. When a person is exposed during pregnancy, labor, or delivery to an antigen found on the fetus's red blood cells (RBCs; ie, AB, Rh complex) that is not found on her own RBCs, she forms antibodies against the fetus's antigen. This is referred to as *alloimmunization.* These antibodies, particularly immunoglobulin (Ig) G antibodies, cross the placenta and can interact with the fetal RBC antigens. The pregnancy in which the alloimmunization has occurred usually results in an unaffected child. The risk is carried on in subsequent pregnancies when maternal antibodies from a tiny amount of blood (<0.1 mL) can cross from the patient to the child, which can result in the destruction of RBCs and lead to hemolytic disease of the newborn (HDN). Most serious cases of HDN are caused by Rh alloimmunization involving the D antigen. The other four alleles of the Rh gene complex code for the antigens C, c, E, and e. They are also serious, but less common, causes of alloimmunization.[215]

A patient who is Rh D negative becomes immunized after exposure to fetal erythrocytes that carry the D antigen. The likelihood of having an offspring who is Rh D positive is determined by whether a father who is Rh D positive is homozygous or heterozygous for the D antigen. If the father is homozygous for the D antigen, all of his offspring will be D positive (Rh positive). If he is heterozygous for the D antigen, then there is a 50% chance that his offspring will be Rh positive.

Pregnant patients can produce detectable IgG antibodies to Rh antigens within 6 weeks to 6 months.[216] These antibodies can cross the placenta during subsequent pregnancies and destroy fetal Rh D–positive RBCs. Of patients who are Rh D negative and who do not receive Rh_o(D) immune globulin during pregnancy, 17% will become alloimmunized during a term pregnancy, with most cases occurring at the time of delivery.[217]

The severity of Rh-associated HDN or erythroblastosis fetalis depends on the concentration of maternal antibodies. The placental transfer of large amounts of antibody can cause substantial RBC destruction. This initially results in anemia and hyperbilirubinemia with compensatory extramedullary erythropoiesis (eg, liver, spleen). In severe hemolytic diseases, the fetus might develop hepatosplenomegaly, portal hypertension, edema, ascites, and hepatic and cardiac failure. The clinical presentation of profound anemia, anasarca, hepatosplenomegaly, cardiac failure, and circulatory collapse is termed *hydrops fetalis.*[216]

The severity of Rh-associated HDN generally worsens with each pregnancy in the patient who is alloimmunized if her fetus is Rh positive. Thus, it is important to discuss the consequences of alloimmunization with any person who is known to be alloimmunized and wishes to have more children in the future.[217]

Rh_o(D) Immunoglobulin

Case 49-9, Question 2: What interventions should be undertaken to prevent G.G. from becoming alloimmunized?

ANTEPARTUM PROPHYLAXIS

G.G. should have antibody screens at the beginning of each pregnancy and postpartum. Although the American Association of Blood Banks recommends that an antepartum screen should also be obtained at 28 weeks' gestation, the cost-effectiveness of such screening has not been studied, and it is estimated that sensitization before 28 weeks occurs at a rate of <0.18%. Therefore, the ACOG has suggested that the decision to obtain a third-trimester antibody screen should be dictated by individual circumstances.[217] As pregnancy progresses, both the incidence and the degree of fetomaternal hemorrhage increase. Administrating Rh_o(D) immune globulin to G.G. before or shortly after exposure to fetal Rh D–positive RBCs will prevent her from becoming alloimmunized. Giving Rh_o(D) immune globulin at 28 weeks' gestation has been shown to decrease the antepartum sensitization rate from ~2% to 0.1%.[217] One mechanism by which Rh_o(D) immune globulin might prevent sensitization is by suppression of the primary immune response to the D antigen.[216] The anti-D immune globulin binds the D antigen, and this complex is filtered by the spleen and lymph nodes, whereby it inhibits D antigen–specific B cells from proliferating.

POSTPARTUM PROPHYLAXIS

A second dose of Rh_o(D) immune globulin should be repeated within 72 hours of delivery. A larger dose is needed if a large transplacental bleed occurs at the time of delivery (0.4% of cases). Therefore, all patients who are Rho(D) negative and who deliver a newborn who is Rho(D) positive should be tested to detect fetal RBCs in maternal blood (eg, Kleihauer–Betke test) to calculate the correct dose of Rh_o(D) immune globulin. If a person at risk for sensitization has not been given Rh_o(D) immune globulin within 72 hours, she should still be treated as soon as possible because it has been demonstrated that protection can be seen in some individuals up to 13 days after exposure to Rh-positive RBCs.[217]

ADVERSE EFFECTS OF $RH_o(D)$ IMMUNE GLOBULIN

The plasma from which immune globulin is obtained is tested for viral infections, and the manufacturing process used to produce $Rh_o(D)$ immune globulin inactivates viruses such as HIV, hepatitis B virus, and hepatitis C virus.[218] Adverse reactions associated with the use of anti-D immune globulin are rare. Pain and swelling at the injection site and rash are the most common adverse reactions. Hypersensitivity reactions such as anaphylaxis, although rare, can occur owing to a small amount of IgA in the product. $Rh_o(D)$ immune globulin (RhoGAM) is a latex- and thimerosal-free (contains no mercury) drug.[218]

Prophylaxis for First- and Second-Trimester Events and Procedures

CASE 49-9, QUESTION 3: G.G. will undergo amniocentesis at 16 weeks' gestation. Will she need a dose of $Rh_o(D)$ at that time?

$Rh_o(D)$ immune globulin should be given after all clinical events (eg, spontaneous abortion) or procedures (eg, abortion, amniocentesis, fetal blood sampling, or chorionic villus sampling) in which fetomaternal hemorrhage is a risk in an Rh-incompatible pregnancy.[218] Although little evidence supports the need for prophylaxis in the early first trimester, adverse effects are rare and potential benefits are thought by most experts to outweigh the risks.[217,218] Although a 50-µg dose (MICRhoGAM) is available for first-trimester use (eg, chorionic villus sampling or abortion), many hospitals do not stock this dose and so a 300-µg standard dose is often given.

LENGTH OF PROTECTION

Case 49-9, Question 4: G.G. had an amniocentesis at 16 weeks for which she received Rh_o(D) immune globulin 300 µg IM. Will she need another dose at 28 weeks' gestation? How long will this dose protect G.G. against alloimmunization?

G.G. will still need a dose of 300 µg repeated at 28 weeks' gestation and within 72 hours postpartum if her infant is Rh_o(D) positive. The half-life of Rh_o(D) immune globulin is ~23 to 26 days.[218] Without a large fetomaternal hemorrhage, a standard dose of 300 µg will protect against alloimmunization for up to 12 weeks. If >12 weeks have lapsed between receipt of anti-D immune globulin and delivery, many practitioners recommend administering another antepartum dose.[217,218]

Failure of Immunoprophylaxis

Case 49-9, Question 5: What are the most common reasons for Rh_o(D) alloimmunization during pregnancy?

The most common reasons for Rh D alloimmunization are (a) failure to give a dose of anti-D immune globulin at 28 weeks' gestation, (b) failure to give Rh_o(D) immune globulin in a timely manner postpartum to patients who have delivered an Rh_o(D)-positive or untyped fetus, and (c) failure to recognize clinical procedures and situations that increase maternal risk for alloimmunization (ie, amniocentesis, abortions).[216,217]

Thus, G.G. should be told that with proper prophylaxis with anti-D immune globulin, there is little chance for her to become alloimmunized. She need not worry about her present pregnancy or future pregnancies.

LACTATION

Lactation is controlled primarily by PRL, but the entire process is under the intricate control of several hormones. Breast tissue maturation during pregnancy is influenced by many factors, including estrogen, progesterone, PRL, insulin, growth hormone, cortisol, thyroxine, and human placental lactogen.[219] PRL concentrations gradually increase during pregnancy, but high estrogen and progesterone concentrations inhibit milk secretion by blocking PRL's effect on the breast epithelium.[219,220] It is the dramatic decrease in progesterone that triggers lactogenesis or milk secretion for the first 3 days after delivery. Infant suckling at the breast is necessary to maintain an adequate milk supply beyond postpartum day 3 or 4. Nipple stimulation transmits sensory impulses to the hypothalamus to initiate PRL release from the anterior pituitary and oxytocin from the posterior pituitary. PRL stimulates the production and secretion of breast milk, and oxytocin stimulates the contraction of the myoepithelial cells in the breast alveoli and ducts so that milk can be ejected from the breast (milk letdown). Oxytocin also can be secreted through other sensory pathways, which is why patients can release milk on hearing, smelling, or even thinking about their infants. PRL, however, is released only in response to nipple stimulation.

PRL synthesis and release depend on the inhibition of hypothalamic PRL inhibitory factor (PIF) secretion. PRL secretion is regulated primarily by dopamine-releasing neurons. Activating the dopamine receptors on the PRL-secreting cells of the anterior pituitary inhibits the release of PRL. PIF is believed to be closely associated with dopamine.[219,220]

Although PRL controls the volume of milk produced, once lactation is established, milk production is regulated by infant demand. Lactation eventually ceases if milk is not removed from the breast. Absence of suckling stops milk letdown and restores the normal production of PIF. Decreased blood flow to the breast reduces oxytocin delivery to the myoepithelium. Consequently, milk secretion stops within a few days.[219,220]

Stimulation

NONPHARMACOLOGIC MEASURES

CASE 49-10

QUESTION 1: C.C., a 22-year-old female, vaginally delivered her first child, a healthy term infant. C.C. plans to breast-feed and was educated about breast-feeding during obstetric visits and prenatal classes. After giving birth, C.C. tried to breast-feed in the delivery room with great difficulty. Afterward, she became extremely apprehensive and continued to have trouble breast-feeding.

What can be done to encourage C.C. and help her with lactation?

The most effective stimulus for lactation is suckling. Many patients nurse in the delivery room after uncomplicated vaginal deliveries because nursing increases maternal–infant bonding and helps establish good milk production. If a patient does not nurse immediately after delivery, she should be encouraged to do so as soon as she is physically able. C.C. did try to nurse after delivery, but experienced problems that may have been related to her emotional or physical state, or to the physical state of her infant. The nursing staff should encourage and support C.C. emotionally to help her relax, be comfortable, and relieve her anxiety about breast-feeding. Health care personnel also should emphasize appropriate feeding techniques and proper positioning for breast-feeding. Allowing C.C.'s infant to sleep in her room, rather than in the nursery, may help C.C. develop a breast-feeding routine.

Most new patients who have difficulty breast-feeding initially respond to the emotional and educational support of a good obstetric nursing staff. Few require pharmaceutical intervention.

ENHANCEMENT OF MILK PRODUCTION

CASE 49-10, QUESTION 2: C.C. was successful in establishing breast-feeding. Despite good technique and adequate nutrition, however, she had trouble maintaining adequate milk production after about 2 to 3 weeks and was forced

to supplement her infant with formula. How can C.C.'s milk production be enhanced?

Although not an FDA-approved indication, metoclopramide can be used to stimulate lactation in patients with decreased or inadequate milk production.[38,221–223] Metoclopramide, a dopamine antagonist, increases PRL secretion. This is particularly useful in patients whose infants do not breast-feed effectively (eg, preterm infants).[224] Metoclopramide 10 mg PO three times daily for 1 to 2 weeks has been shown to help restore milk production.[38,221–223] Improvement in lactation occurs within 2 to 5 days of starting therapy and persists after discontinuing metoclopramide.

The estimated total daily dose of metoclopramide ingested by the nursing infant of a patient on 30 mg/day is 1 to 45 µg/kg/day.[38] This is below the maximal recommended infant daily dose of 0.5 mg/kg/day. Maternal doses of 30 mg/day do not alter PRL, thyroid-stimulating hormone, or free thyroxin serum concentrations in breast-fed infants.[224] The only adverse effect reported in nursing infants has been intestinal gas.[38,225] The short-term use of metoclopramide for reestablishing lactation appears to be safe, even in preterm infants.[38,221]

Recent randomized control trials have examined the effects of metoclopramide on breast milk volume and duration in patients with recent preterm deliveries and found that breast-feeding outcomes were poor despite medication treatment and lactation support.[225,226] In this special population, patients likely need lactation support through various resources addressing nutritional, medical, and psychosocial interventions.

Suppression

CASE 49-11

Question 1: After delivery of a nonviable fetus at 24 weeks' gestation, J.G., a 26-year-old G2, P2, informs her obstetrician that she wishes to suppress her lactation.

What methods are available to suppress lactation?

Suppression of lactation is indicated for patients who do not want to breast-feed, patients who have delivered a stillborn infant, and those who have had an abortion. Both drugs and nonpharmacologic methods have been used. In 1988, the FDA, however, recommended against drug-induced suppression of lactation.[227] The only drug therapy that the FDA recommends in patients who are not breast-feeding is analgesic for the relief of breast pain. Bromocriptine was approved for the postpartum suppression of lactation; however, the FDA rescinded its approval for that indication because of cardiovascular complications (eg, stroke, myocardial infarction) associated with its use.[220]

If breast stimulation is avoided (with or without the use of a breast binder), breast milk production will continue, leading to engorgement and distension of breast alveoli. This leads to the termination of lactation after several days. Approximately 40% of patients using this method experience breast discomfort and pain; 30% experience milk leakage from their nipples.[227,228] Ice packs may be applied to the breasts for comfort, and a mild analgesic may be used if necessary.

DRUG EXCRETION IN HUMAN MILK

Breast milk is recognized as the optimal source of nutrition for infants, with documented benefits not only to infants but also to mothers, families, and societies.[229] Evidence indicates that breast-feeding decreases the incidence or severity of many infectious processes (eg, otitis media, respiratory infections, UTIs) in infants. In children and adults who were breast-fed, the risk of developing certain medical illnesses also may decrease (eg, obesity, inflammatory bowel disease, celiac disease, childhood leukemia).[230] Breast-feeding may also positively influence cognitive and intellectual development in children and young adults.[231] Numerous benefits to the mother also have been identified, such as decreased

postpartum blood loss, more rapid uterine involution, earlier return to prepregnancy weight, and decreased risks of breast cancer, ovarian cancer, and osteoporosis.[229]

The perception that nursing should be discontinued while the patient is medicated persists, although only a finite number of drugs are absolutely contraindicated during lactation.[95] Unlike the use of drugs during pregnancy, drug excretion in breast milk can be approximated to a certain extent. Actual measurements of drug concentrations in milk and clinical observations in breast-fed infants have been published for selected drugs.

Pharmacokinetics

Different pharmacokinetic models of drug excretion in milk have been described.[232] A two-compartment open model presents the maternal fluids as one compartment and breast milk as the other. After ingestion, the drug gets absorbed into the maternal compartment, with a proportion of drug passing into breast milk and the remaining portion distributed in, and eliminated from, the maternal system. Drugs reaching breast milk will ultimately leave this compartment either by diffusing back into maternal fluids or through milk production and nursing.[233] A more popular model describes drug excretion in milk using a three-compartment model that incorporates the pharmacokinetics of the patient, mammary tissues, and infant.[234] The overall risk to the infant depends on the amount of drug bioavailable to the patient, the amount reaching breast milk, and the actual amount of drug ingested and bioavailable to the nursing infant.

Transfer of Drugs From Plasma to Milk

Transfer of drugs from maternal plasma to milk is generally through passive diffusion.[232] Low-molecular-weight, water-soluble substances diffuse through small, water-filled pores, whereas lipid-soluble compounds pass through lipid membranes.[233] Many factors

affect the excretion of drugs in breast milk, and they should be carefully assessed before making a recommendation. The extent of drug passage into breast milk is often expressed quantitatively as the milk-to-plasma (M/P) ratio. This ratio should not be used as the sole determinant of whether a drug is safe for use during breast-feeding (see the section on Estimating Infant Exposure).

Several parameters affect drug excretion into breast milk (**Table 49-6**). The pK_a of a drug partially determines how much drug can reach the milk, because only the nonionized portion of free drug is transferred. Human milk, with an average pH of 7.1, is slightly more acidic than is plasma. In general, drugs that are weak acids (eg, penicillin) tend to have a higher concentration in plasma than in milk (M/P <1). Conversely, the concentration of weak bases (eg, erythromycin) in milk is more likely to be higher or to reach an equilibrium with that measured in plasma (M/P ≥1).[38,219,232] Once in the milk, the proportion of the ionized weak base rises in the relatively acidic solution, and thus drug trapping occurs. Drug reabsorption has been found for some agents, and the prevention of passage back into the plasma by trapping may be clinically important. Lipid solubility also is determined to a large extent by the degree of ionization because drugs with relatively high lipid solubility exist in the nonionized form. Diffusion through lipid membranes is probably the most important pathway for drug transfer. Although pH, pK_a, and lipid solubility are important elements, other factors may significantly modify predictions based solely on these chemical characteristics. Two of these other factors are protein binding and MW.[38,232] Drugs with high MWs such as insulin (MW >6000) are less likely to transfer into breast milk, whereas those <300 transfer more readily.[38] Highly protein-bound drugs such as glyburide (99% protein bound) are less likely to be transferred into breast milk, although infants should still be monitored for signs of hypoglycemia.

Table 49-6
Factors Affecting the Fate of Drugs in Milk and the Nursing Infant

Maternal Parameters
▪ Drug dosage and duration of therapy ▪ Route and frequency of administration ▪ Metabolism ▪ Renal clearance ▪ Blood flow to the breasts ▪ Milk pH ▪ Milk composition
Drug Parameters
▪ Oral bioavailability (to patient and infant) ▪ Molecular weight ▪ pK_a ▪ Lipid solubility ▪ Protein binding
Infant Parameters
▪ Age of the infant ▪ Feeding pattern ▪ Amount of breast milk consumed ▪ Drug absorption, distribution, metabolism, elimination

pK_a, dissociation constant.

Sources: Anderson PO. Drugs and breast milk. *Pediatrics*. 1995;95:957; Dillon AE, Wagner CL, Wiest D, Newman RB. Drug therapy in the nursing mother. *Obstet Gynecol Clin North Am.* 1997;24:675–696; Begg EJ, Duffull SB, Hackett LP, Ilett KF. Studying drugs in human milk: time to unify the approach. *J Hum Lact*. 2002;18:323–332; Bennett PN, ed. *Drugs and Human Lactation*. 2nd ed. Elsevier; 1996; Hale TW. *Medications and Mothers' Milk*. 16th ed. Pharmasoft Medical Publishing; 2014.

Drug transfer also is influenced by the yield of milk, which is related to blood flow and PRL secretion.[232] Lactation is associated with a high blood flow to the breasts, but little is known about this flow during or between feedings. The milk yield (volume) differs slightly depending on the duration of lactation and the time of day. A diurnal pattern has been observed, with highest yields at 6:00 AM and lowest yields at 6:00 PM or 10:00 PM. The mean composition of mature human milk is ~87% aqueous solution, 3.5% lipids, 8%

carbohydrate (83% of which is lactose), 0.9% protein, and 0.2% nitrogen.[232] The proportions of these components may vary widely from person to person and even within the same person. For example, hind milk (breast milk that is expressed last and contains more fat) contains fourfold to fivefold the fat content of foremilk (breast milk that is expressed first and is high in water content, water-soluble vitamins, carbohydrates, and protein), whereas colostrum (first milk, secreted late in pregnancy and in the first few days after delivery) contains little fat. Fat content also has exhibited a diurnal variation.

After a drug reaches the milk, it equilibrates between the aqueous and lipid phases. The nature of this equilibration can modify how much drug actually reaches the infant. Infant feeding patterns differ significantly from one baby to another. The time spent suckling at each breast, and the volume of milk taken in, also determine the amount of drug ingested, especially if the drug has partitioned into one phase more so than into the other. Once the infant ingests the drug via breast milk, the pharmacologic and adverse effects on the infant will be determined by the extent of oral bioavailability, distribution, metabolism, and rate of elimination. These pharmacokinetic parameters differ, depending on the infant's age and whether he or she was born prematurely or at term.

CASE 49-12

Question 1: H.P. is a 25-year-old G3, P3 who recently was diagnosed with a distal deep vein thrombosis (DVT) in her lower left extremity confirmed by a Doppler ultrasound at 5 weeks' gestation. She has a significant history of having multiple DVTs in her prior pregnancies, and her thrombophilia workup result was negative. During her pregnancy, she was on therapeutic low-molecular-weight heparin (LMWH) 80 mg (weight, 167.55 pounds [76 kg]) SC every 12 hours. Her dosage was increased to 100 mg SC every 12 hours after subsequent anti-factor Xa levels were subtherapeutic. Her LMWH was discontinued 24 hours before she received an epidural for labor pain. After delivery, H.P. is restarted on LMWH and then changed to warfarin on day 5. H.P. also is breast-feeding.

Do either of these drugs present a risk to the nursing infant?

Heparin does not cross into breast milk (see the section on Drug Excretion in Human Milk) because of its high MW (~12,000) and is therefore safe in breast-feeding. Warfarin is a weakly acidic drug (pK_a 5.05) that is highly ionized at physiologic pH (>99%) in maternal serum.[232] It also is highly protein bound (97%).[38] These pharmacokinetic parameters make warfarin very unlikely to transfer into breast milk. Case reports in lactating patients confirm that warfarin is not detected in breast milk or infant plasma.[38] The American Academy of Pediatrics (AAP) considers warfarin compatible with breast-feeding,[92] and it is widely considered to be safe in breast-feeding.[92,235] There are no studies to guide duration of anticoagulation in patients who have had a DVT associated with pregnancy. However, most recommend anticoagulation for at least 6 weeks postpartum, with total duration of anticoagulation of a minimum of 6 months after the thromboembolic event.[235] H.P. can safely breast-feed her infant while she is on LMWH and warfarin.

Estimating Infant Exposure

The actual amount an infant will ingest is difficult to determine owing to varying maternal, drug, and infant parameters. Available data generally are from single or small numbers of case reports or pharmacokinetic studies involving a few patient–infant pairs. An M/P ratio is sometimes used alone as the basis for a recommendation, but this should be avoided because its accuracy can be affected by many factors such as the time of sampling after maternal ingestion (peak vs steady state), dose, length of therapy, route of administration, and milk composition.[232] A RID is sometimes reported in resources or literature, which is expressed as a percentage of the maternal dose.[232] Generally, a RID of <10% is interpreted as an acceptable level. This must be interpreted with caution, however, taking into account other variables such as the age and health of the infant and the safety profile of the drug. It is also important to note that these are estimated values, often based on data collected from one or only a few individuals. However, applying these equations

using measurements specific to a person and her infant is not clinically practical. Compared with the M/P ratio, experts believe that the RID is a better estimate of infant exposure.

Sampling during maternal peak drug concentration attempts to approximate the highest amount of drug that can reach the infant. This assumption is inherently flawed because peak drug concentration in the patient does not necessarily equate with peak drug concentration in milk at that same point in time.[232,236] The amount of drug an infant actually receives also depends on the volume of milk ingested. Even if a drug has a high M/P ratio, the actual amount received by the infant could be low if only a small volume of milk was consumed. Therefore, an M/P ratio describes the likelihood of drug excretion into breast milk, but it does not indicate the level of infant exposure. In general, drugs with lower M/P ratios (<1) are preferred over those with higher M/P ratios (>1) during breast-feeding, but other parameters such as maternal condition and therapeutic efficacy should be considered.

Infant exposure to a drug via ingestion of breast milk can be estimated for some drugs. The M/P ratio is used to estimate the drug concentration in milk (Eq. 49-1) and the dose the infant may ingest (Eq. 49-2).[232,236,237] The variables required to calculate Eq. 49-1 can be located in the published literature, but only for some drugs. The actual volume of milk ingested by the infant is difficult to estimate, but the average consumption is ~150 mL/kg/day. The estimated infant dose can then be used to calculate a RID, which is expressed as a percentage of the maternal dose.[236]

$$\text{Drug concentration in milk} = \text{Maternal plasma drug concentration} \times \text{M/P} \quad \textbf{(Eq. 49-1)}$$

$$\text{Infant dose (mg/kg/day)} = \text{Drug concentration in milk} \times \text{milk volume (mL/kg/day)} \quad \textbf{(Eq. 49-2)}$$

$$\text{RID \%} = \text{Infant dose (mg/kg/day)/maternal dose (mg/kg/day)} \times 100 \quad \textbf{(Eq. 49-3)}$$

The maternal dose is 50 mg/200.62 pounds (91 kg) = 0.55 mg/kg/day. The infant dose is calculated to be 80 ng/mL (1 µg/1000 ng) (1 mg/1000 µg) (150 mL/kg/day), which equals 0.012 mg/kg/day. The RID equals the actual infant dose (0.012 mg/kg/day) divided by the actual maternal dose (0.55 mg/kg/day) × 100, which equals 2.18%. Therefore, the exposure likely does not represent a risk. K.J. can continue to take hydrochlorothiazide while breast-feeding. The AAP classifies hydrochlorothiazide as compatible with breast-feeding.[38,92]

CASE 49-13

QUESTION 1: K.J., a breast-feeding, 200.62-pound (91-kg) person, is taking hydrochlorothiazide 50 mg PO daily. The drug has a long elimination half-life of about 12 hours. Peak milk levels of the drug occur 5 to 10 hours after a dose. In a recent study, the drug was excreted into milk with a mean concentration of 80 ng/mL.

Based only on dose, does this drug represent a significant risk to K.J.'s nursing infant?

Reducing Risk of Exposure

If pharmacologic treatment is medically necessary for a nursing patient, every attempt should be made to minimize infant exposure to the drug. Methods of reducing risks have been proposed.[229,232,234] **Table 49-7** summarizes critical factors that should be considered. Except for drugs that are contraindicated during lactation, the decision to continue or discontinue nursing while receiving medication is ultimately the patient's. Therefore, patient education is an integral component in this decision-making process. The patients should be informed of the potential risks, or lack thereof, associated with a drug. They also should be made aware that certain risks may be minimized by altering feeding pattern and drug administration

time and by carefully monitoring the infant for early signs of adverse effects.

Table 49-7
Reducing Risk of Infant Exposure to Drugs in Breast Milk

A drug should be used only if medically necessary, and treatment cannot be delayed until the infant is ready to be weaned.
Drug Selection
Consider whether the drug can be safely given directly to the infant.
Select a drug that passes poorly into breast milk with the lowest predicted M/P ratio, and a RID <10%.
Avoid long-acting formulations (eg, sustained release).
Consider possible routes of administration that can reduce drug excretion into milk.
Determine length of therapy and if possible avoid long-term use.
Feeding Pattern
Avoid nursing during times of peak drug concentration.
If possible, plan breast-feeding before administration of the next dose.
Other Considerations
Always observe the infant for unusual signs (eg, sedation, irritability, rash, decreased appetite, failure to thrive).
Discontinue breast-feeding during the course of therapy if the risks to the fetus outweigh the benefits of nursing.
Provide adequate patient education to increase understanding of risk factors.

M/P, milk-to-plasma ratio; RID, relative infant dose.

Sources: Anderson PO. Drugs and breast milk. *Pediatrics*. 1995;95:957; Begg EJ, Duffull SB, Hackett LP, Ilett KF. Studying drugs in human milk: time to unify the approach. *J Hum Lact.* 2002;18:323–332; Howard CR, Lawrence RA. Drugs and breastfeeding. *Clin Perinatol.* 1999;26:447–478.

Resources for Drugs and Lactation

Comprehensive sources reviewing drug use in lactation are available to assist clinicians in weighing the potential risks versus benefits of patients using medications while breast-feeding. **Table 49-8** lists

some medications that are contraindicated during lactation. The AAP Committee on Drugs periodically reviews the transfer of drugs and other chemicals into human milk and publishes their findings.[92] The Committee identifies drugs that should be avoided during breast-feeding, drugs that should be used with caution, drugs whose effects on infants are unknown but of concern, and those considered usually compatible with breast-feeding. This rigorous review is an ongoing process, and new guidelines are published every few years; therefore, the reader should locate the latest AAP recommendations available. In addition to the AAP guidelines, several other references also offer comprehensive information and recommendations on drug use in lactation.[38,92,234]

Table 49-8
Drugs Considered Contraindicated During Lactation

Drug or Drug Class	Effects on Nursing Infants
Amphetamines[a]	Accumulate in breast milk and may cause irritability and poor sleep patterns
Antineoplastics	Potential for immune suppression; cytotoxic effects of drugs on dividing cells in infants unknown[2]
Cocaine[a]	Excreted in milk; contraindicated because of CNS stimulation and intoxication
Ergotamine	Potential for suppressing lactation; vomiting, diarrhea, and convulsions have been reported.[92] Considered contraindicated by some clinicians. AAP recommends using with caution.
Heroin[a]	Possible addiction if sufficient amounts ingested
Immunosuppressants	Potential for immune suppression
Lithium	Milk and serum concentrations average 40% of maternal serum levels. Potential for toxicity exists. Considered contraindicated by some clinicians. AAP recommends using with caution.
LSD[a]	Probably excreted in milk
Marijuana[a]	Excreted in milk

Drug or Drug Class	Effects on Nursing Infants
Misoprostol	Excretion in milk has not been studied but contraindicated because of potential for severe diarrhea in infant.
Phencyclidine[a]	Potent hallucinogenic properties
Phenidone	Massive scrotal hematoma and wound oozing after herniotomy in one infant; contraindicated
Requiring Temporary Cessation of Breast-feeding	
Radiopharmaceuticals	Halt breast-feeding temporarily to allow clearance of radioactivity from milk. Suggested times for individual agents are as follows: copper-64 (^{64}Cu) 50 hours; gallium-67 (^{67}Ga) 2 weeks; indium-111 (^{111}In) 20 hours; iodine-123 (^{123}I) 36 hours; iodine-125 (^{125}I) 12 days; iodine-131 (^{131}I) 2–14 days; radioactive sodium 96 hours; technetium-99m (^{99m}Tc) 15 hours–3 days; ($^{99m}TcO_4$) (^{99m}Tc macroaggregates) 15 hours–3 days

This list is not an all-inclusive one. Selected drugs are listed by drug class and not by individual names.

AAP, American Academy of Pediatrics; CNS, central nervous system; LSD, lysergic acid diethylamide.

[a]All drugs of abuse are contraindicated during lactation.

Sources: Briggs G, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 11th ed. Lippincott Williams & Wilkins; 2017; Sachs HC, American Academy of Pediatrics Committee on Drugs. Transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics*. 2013;132(3);e796–e809; Hale TW. *Medications and Mothers' Milk*. 16th ed. Pharmasoft Medical Publishing; 2014.

Most drugs are excreted into breast milk to some extent; the reader is referred to specialty sources for an in-depth review of the drug in question. The best sources for information regarding drugs in lactation are (a) *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* by Briggs et al[38] and (b) TOXNET, an online lactation database (LactMed) sponsored by the NIH, accessible at https://www.nlm.nih.gov/toxnet/index.html and click on LactMed. These two databases are peer reviewed and contain referenced sources. Categories assigned to these drugs may change because new data become available for specific drugs.

ACKNOWLEDGMENT

The author acknowledges Kimey D. Ung, Jennifer McNulty, and Gerald G. Briggs, BPharm, for their contributions to this chapter in earlier editions.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

MEDICATION USE IN PREGNANCY AND LACTATION

Key References

Briggs G, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 11th ed. Lippincott Williams & Wilkins; 2017. (38)

Ito S. Drug therapy for breast-feeding women [published correction appears in *N Engl J Med*. 2000;343:1348]. *N Engl J Med*. 2000;343:118–126. (95)

Key Websites

American Congress of Obstetrics and Gynecology. www.acog.org

Motherisk. www.motherisk.org

National Library of Medicine: Drugs and Lactation Database. https://www.nlm.nih.gov/toxnet/index.html

Organization of Teratology Specialists (OTIS). https://mothertobaby.org/about-otis/

Perinatology. www.perinatalogy.com/index.html

REPROTOX (Reproductive Toxicology). www.reprotox.org

GENERAL INFORMATION

Key References

ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 475: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol.* 2011;117*(2, pt 1)*:422–424. (124)

ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Chronic hypertension in pregnancy. ACOG Committee on Practice Bulletins. *Obstet Gynecol.* 2001;98*(1, suppl)*:177–185. (83)

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage. *Obstet Gynecol.* 2006;108:1039–1047. (206)

American College of Obstetricians and Gynecologists. Use of progesterone to prevent preterm births. ACOG Committee Opinion No. 419 (Replaces No. 291, November 2003). *Obstet Gynecol.* 2008;112:963–965. (197)

Bates SM, Greer I, Middledorp S, et al. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2016;149(*2*):315–352. (235)

Loebstein R, Koren G. Clinical relevance of therapeutic drug monitoring during pregnancy. *Ther Drug Monit.* 2002;24:15–22. (16)

Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med.* 2010;363:1544–1550. (46)

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. Accessed December 30, 2021. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Perinatal_GL.pdf (203)

COMPLETE REFERENCES CHAPTER 49 OBSTETRIC DRUG THERAPY

1. Cunningham FG, Leveno KJ, Bloom SL, et al. Prenatal care. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill; 2014:167.

Osterman MK, Hamilton B, Martin JA, Driscoll AK, Valenzuela CP. Births:
2. final data for 2020. *Natl Vital Stat Rep*. 2022;70(17):1–50.
3. Ely D, Driscoll A. Infant mortality statistics from the 2021 period linked birth/infant death data set. *Natl Vital Stat Rep*. 2021;70(14):1.
4. Gregory K, Niebyl J, Johnson TRB. Preconception and prenatal care: part of the continuum. In: Gabbe SG, Niebyl JR, Galan JL, et al, eds. *Obstetrics: Normal and Problem Pregnancies*. 6th ed. Churchill Livingstone; 2012:101.
5. Cunningham FG, Leveno KJ, Bloom SL, et al. Hematological disorders. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill; 2014:1101.
6. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 95: anemia in pregnancy. *Obstet Gynecol*. 2008;112:201–207.
7. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep*. 1998;47(RR-3):1.
8. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med*. 1992;327:1832–1835.
9. Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Recomm Rep*. 1992;41(RR-14):1–7.
10. Centers for Disease Control and Prevention. Updated estimates of neural tube defects prevented by mandatory folic acid fortification in the United States 1995–2011. *Morb Mortal Wkly Rep*. 2015;64(1):1–5.
11. Centers for Disease Control and Prevention. CDC Grand rounds: additional opportunities to prevent neural tube defects with folic acid fortification. *Morb Mortal Wkly Rep*. 2010;59(31):980–984.
12. Food and Nutrition Board of the Institute of Medicine. Dietary reference intakes for calcium and vitamin D. November 2010. Accessed June 22, 2011. https://www.aafp.org/dam/brand/aafp/pubs/afp/issues/2011/0601/p1352.pdf
13. Newton G. Home testing medical equipment. In: Krinsky DL, Ferreri SP, Hemstreet BA, et al, eds. *Handbook of Nonprescription Drugs*. 18th ed. American Pharmaceutical Association; 2014.
14. Committee on Gynecologic Practice, The American College of Obstetricians and Gynecologists. ACOG. Committee opinion: number 278, November 2002. Avoiding inappropriate clinical decisions based on false-positive human chorionic gonadotropin test results. *Obstet Gynecol*. 2002;100(5, pt 1):1057–1059.
15. Frederiksen MC. Physiologic changes in pregnancy and their effect on drug disposition. *Semin Perinatol*. 2001;25:120–123.
16. Loebstein R, Koren G. Clinical relevance of therapeutic drug monitoring during pregnancy. *Ther Drug Monit*. 2002;24:15–22.

17. Little BB. Pharmacokinetics during pregnancy: evidence-based maternal dose formulation. *Obstet Gynecol*. 1999;93(5, Pt 2):858–868.
18. McAuley JW, Anderson GD. Treatment of epilepsy in women of reproductive age: pharmacokinetic considerations. *Clin Pharmacokinet*. 2002;41:559–579.
19. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. *Clin Pharmacokinet*. 2005;44:989–1008.
20. Harris RZ, Benet LZ, Schwartz JB. Gender effects in pharmacokinetics and pharmacodynamics. *Drugs*. 1995;50:222–239.
21. Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. *Clin Pharmacokinet*. 1997;33:328–343.
22. Abalovich M, Amino N, Barbour LA, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2007;92(8, suppl):S1–S47.
23. Kalter H, Warkany J. Medical progress. Congenital malformations: etiologic factors and their role in prevention (first of two parts). *N Engl J Med*. 1983;308:424–431.
24. Schardein JL. *Chemically Induced Birth Defects*. 3rd ed. Marcel Dekker; 2000.
25. National Research Council. *Scientific Frontiers in Developmental Toxicology and Risk Assessment*. National Academy Press; 2000.
26. Carter CO. Genetics of common single malformations. *Br Med Bull*. 1976;32:21–26.
27. O'Rahilly RR, Muller F. *Human Embryology & Teratology*. 3rd ed. Wiley-Liss; 2001.
28. Beckman DA, Brent RL. Mechanism of known environmental teratogens: drugs and chemicals. *Clin Perinatol*. 1986;13:649–687.
29. Seaver LH, Hoyme HE. Teratology in pediatric practice. *Pediatr Clin North Am*. 1992;39:111–134.
30. Shepard TH. Teratogenicity of therapeutic agents. *Curr Probl Pediatr*. 1979;10:1–42.
31. Koren G, Bologa M, Long D, Feldman Y, Shear NH. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *Am J Obstet Gynecol*. 1989;160(5, Pt 1):1190–1194.
32. ACOG educational bulletin. Teratology. Number 236, April 1997 (replaces no. 233, February 1997). American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*. 1997;57:319–326.
33. U.S. Food & Drug Administration. Postmarket drug safety information for patients and providers. 2006. Accessed June 16, 2011. https://www.fda.gov/drugs/drug-safety-and-availability/postmarket-drug-safety-information-patients-and-providers
34. U.S. Food & Drug Administration. Public health advisory: paroxetine. 2005. Accessed June 14, 2011. https://www.fda.gov/drugs/drug-safety-and-

availability/fda-drug-safety-communication-selective-serotonin-reuptake-inhibitor-ssri-antidepressant-use-during
35. U.S. Food & Drug Administration. FDA: risk of oral birth defects in children born to mothers taking topiramate. 2011. Accessed June 14, 2011. https://wwwfda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-risk-oral-clefts-children-born-mothers-taking-topamax-topiramate
36. Fabro S, McLachlan JA, Dames NM. Chemical exposure of embryos during the preimplantation stages of pregnancy: mortality rate and intrauterine development. *Am J Obstet Gynecol*. 1984;148:929–938.
37. Koren G, Nava-Ocampo AA, Moretti ME, Sussman R, Nulman I. Major malformations with valproic acid. *Can Fam Physician*. 2006;52:441–442, 444, 447.
38. Briggs G, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 11th ed. Lippincott Williams & Wilkins; 2017.
39. Scialli AR, Buelke-Sam JL, Chambers CD, et al. Communicating risks during pregnancy: a workshop on the use of data from animal developmental toxicity studies in pregnancy labels for drugs. *Birth Defects Res A Clin Mol Teratol*. 2004;70:7–12.
40. Buehler BA, Bick D, Delimont D. Prenatal prediction of risk of the fetal hydantoin syndrome. *N Engl J Med*. 1993;329:1660–1661.
41. Nishimura H, Tanimura T. *Clinical Aspects of the Teratogenicity of Drugs.* Elsevier; 1976.
42. Polin RA, Fox W, eds. *Fetal and Neonatal Physiology*. 2nd ed. WB Saunders; 1998.
43. U.S. Food & Drug Administration. Pregnancy and lactation labeling (drugs) final rule. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
44. Practice Bulletin Summary 153: nausea and vomiting of pregnancy. *Obstet Gynecol*. 2015;126(3):687–688.
45. Badell ML, Ramim SM, Smith JA. Treatment options for nausea and vomiting during pregnancy. *Pharmacotherapy*. 2006;26:1273–1287.
46. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med*. 2010;363:1544–1550.
47. Nelson-Piercy C. Treatment of nausea and vomiting in pregnancy. When should it be treated and what can be safely taken? *Drug Saf*. 1998;19:155–164.
48. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology*. 1994;50:27–37.
49. Nageotte MP, Briggs GG, Towers CV, Asrat T. Droperidol and diphenhydramine in the management of hyperemesis gravidarum. *Am J*

Obstet Gynecol. 1996;174:1801–1805.
50. Tan PC, Khine PP, Vallikkannu N, Omar SZ. Promethazine compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. *Obstet Gynecol*. 2010;115:975–981.
51. Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). *Am J Obstet Gynecol*. 2002;186(5, suppl):S256–S261.
52. Herrell H. Nausea and vomiting of pregnancy. *Am Fam Physician*. 2014;89(12):965–970.
53. Koren G, Clark S, Hankins GD, et al. Effectiveness of delayed release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trail. *Am J Obstet Gynecol*. 2010;203:571.e1–7.
54. Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. *Am J Perinatol*. 1997;14:119–124.
55. Passternak B, Svanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med*. 2013;368:814–823.
56. Gill S, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. *Am J Gastroenterol*. 2009;104:1541–1545.
57. Pasrernak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med*. 2010;363:2114–2123.
58. Lumbiganon P, Laopaiboon M, Thinkhamrop J. Screening and treating asymptomatic bacteriuria in pregnancy. *Curr Opin Obstet Gynecol*. 2010;22:95–99.
59. Mignini L, Carroli G, Abalos E, et al. Accuracy of diagnostic tests to detect asymptomatic bacteriuria during pregnancy. *Obstet Gynecol*. 2009;113(2, Pt 1):346–352.
60. Mittal P, Wing DA. Urinary tract infections in pregnancy. *Clin Perinatol*. 2005;32:749–764.
61. Lin K, Kevin Fajardo; U.S. Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med*. 2008;149:W20–W24.
62. ACOG educational bulletin. Antimicrobial therapy for obstetric patients. Number 245, March 1998 (replaces no. 117, June 1988). American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*. 1998;61:299–308.
63. Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2010;(9):CD007855.

64. Lumbiganon P, Villar J, Laopaiboon M, et al. One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: a randomized controlled trial. *Obstet Gynecol*. 2009;113(2 Pt 1):339–405.
65. Cunningham FG, Leveno KJ, Bloom SL, et al. Diabetes. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill; 2014.
66. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 60, March 2005. Pregestational diabetes mellitus. *Obstet Gynecol*. 2005;105:675–685.
67. Committee on Obstetric Practice. ACOG Committee Opinion No. 435: postpartum screening for abnormal glucose tolerance in women who had gestational diabetes mellitus. *Obstet Gynecol*. 2009;113:1419–1421.
68. The American College of Obstetricians and Gynecologist. Practice Bulletin: gestational diabetes mellitus number 137. *Obstet Gynecol*. 2013;122(2):406–416.
69. England LJ, Dietz PM, Njoroge T, et al. Preventing type 2 diabetes: public health implications for women with a history of gestational diabetes mellitus. *Am J Obstet Gynecol*. 2009;200:365.e1–e8.
70. Garner P. Type I diabetes mellitus and pregnancy. *Lancet*. 1995;346:157–161.
71. Kitzmiller JL, Wallerstein R, Correa A, Kwan S. Preconception care for women with diabetes and prevention of major congenital malformations. *Birth Defects Res A Clin Mol Teratol*. 2010;88:791–803.
72. Pregnancy outcomes in the diabetes control and complications trial. *Am J Obstet Gynecol*. 1996;174:1343–1353.
73. Greene MF, Hare JW, Cloherty JP, Benacerraf BR, Soeldner JS. First-trimester hemoglobin A1 and risk for major malformation and spontaneous abortion in diabetic pregnancy. *Teratology*. 1989;39:225–231.
74. American Diabetes Association. Management of diabetes in pregnancy. Sec 12. In Standards of Medical Care in Diabetes 2016. *Diabetes Care*. 2016;39(suppl 1):s94–s98.
75. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med*. 2006;354:2443–2451.
76. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med*. 1995;333:1237–1241.
77. Homko CJ, Reece EA. Insulins and oral hypoglycemic agents in pregnancy. *J Matern Fetal Neonatal Med*. 2006;19:679–686.
78. American College of Obstetricians and Gynecology Committee on Practice Bulletins-Obstetricians. ACOG Practice Bulletin. Clinical management guidelines for obstetricians and gynecologist. Number 30, September 2001

(replaces Technical Bulletin Number 200, December 1994). *Obstet Gynecol*. 2001;98:525–538.

79. Rowan JA, Hague WM, Gao W, et al. Metformin versus insulin for the treatment of gestational diabetes [published correction appears in *N Engl J Med.* 2008;359:106]. *N Engl J Med*. 2008;358:2003–2015.
80. Working Group on High Blood Pressure in Pregnancy. Report of the National High Blood Pressure Education Program. *Am J Obstet Gynecol*. 2000;183:S1–S22.
81. Wildman K, Bouvier-Colle MH; MOMS Group. Maternal mortality as an indicator of obstetric care in Europe. *Br J Obstet Gynecol*. 2004;111:164–169.
82. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance—United States, 1991–1999. *MMWR Surveill Summ*. 2003;52:1–8.
83. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Chronic hypertension in pregnancy. ACOG Committee on Practice Bulletins. *Obstet Gynecol*. 2001;98(1, suppl):177–185.
84. ACOG Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol*. 2002;99:159–167.
85. Sibai BM. Treatment of hypertension in pregnant women. *N Engl J Med*. 1996;335:257–265.
86. Markahm K, Funai EF. Pregnancy-related hypertension. In: Creasy RK, Reskin R, Iams JD, Lockwood CJ, Moore TR, Greene M, eds. *Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice*. 7th ed. Saunders; 2014:756.
87. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet*. 2005;365:785–799.
88. James P, Oparil S, Carter BL, et al. 2014 Evidence based guidelines for the management of high blood pressure in adults: the JNC 8 report. *JAMA.* 2014;311(5):507–520.
89. von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet*. 2000;355:87–92.
90. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev*. 2007;(1):CD002252.
91. Kyle PM, Redman CW. Comparative risk-benefit assessment of drugs used in the management of hypertension in pregnancy. *Drug Saf*. 1992;7:223–234.
92. American Academy of Pediatrics Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics*. 2013;132(3):e796–e809.

93. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *BMJ*. 1990;301:587–589.
94. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens*. 1999;12:541–547.
95. Ito S. Drug therapy for breast-feeding women [published correction appears in *N Engl J Med*. 2000;343:1348]. *N Engl J Med*. 2000;343:118–126.
96. Shannon ME, Malecha SE, Cha AJ. Beta blockers and lactation: an update. *J Hum Lact*. 2000;16:240–245.
97. Shannon ME, Malecha SE, Cha AJ. Calcium channel antagonists and lactation: an update. *J Hum Lact*. 2000;16:60–64.
98. Dekker GA, Sibai BM. Etiology and pathogenesis of preeclampsia: current concepts. *Am J Obstet Gynecol*. 1998;179:1359–1375.
99. Patrick T, Roberts JM. Current concepts in preeclampsia. *MCN Am J Matern Child Nurs*. 1999;24:193–200.
100. Vidaeff AC, Carroll MA, Ramin SM. Acute hypertensive emergencies in pregnancy. *Crit Care Med*. 2005;33(10, suppl):S307–S312.
101. Mabie WC. Management of acute severe hypertension and encephalopathy. *Clin Obstet Gynecol*. 1999;42:519–531.
102. Magee LA, Elran E, Bull SB, Logan A, Koren G. Risks and benefits of beta-receptor blockers for pregnancy hypertension: overview of the randomized trials. *Eur J Obstet Gynecol Reprod Biol*. 2000;88:15–26.
103. Belfort MA, Tooke-Miller C, Allen JC Jr, Dizon-Townson D, Varner MA. Labetalol decreases cerebral perfusion pressure without negatively affecting cerebral blood flow in hypertensive gravidas. *Hypertens Pregnancy*. 2002;21:185–197.
104. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ*. 2003;327:955–960.
105. Vigil-De Gracia P, Lasso M, Ruiz E, et al. Severe hypertension in pregnancy: hydralazine or labetalol. A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2006;128:157–162.
106. Idama TO, Lindow SW. Magnesium sulphate: a review of clinical pharmacology applied to obstetrics. *Br J Obstet Gynaecol*. 1998;105:260–268.
107. Vermillion ST, Scardo JA, Newman RB, Chauhan SP. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol*. 1999;181:858–861.
108. Scardo JA, Vermillion ST, Newman RB, Chauhan SP, Hogg BB. A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. *Am J Obstet Gynecol*. 1999;181:862–866.

109. Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med*. 1995;333:201–205.
110. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet*. 2002;359:1877–1890.
111. Alexander JM, McIntire DD, Leveno KJ, Cunningham FG. Selective magnesium sulfate prophylaxis for the prevention of eclampsia in women with gestational hypertension. *Obstet Gynecol*. 2006;108:826–832.
112. Belfort MA, Anthony J, Saade GR, Allen JC Jr; Nimodipine Study Group. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. *N Engl J Med*. 2003;348:304–311.
113. World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011. http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf
114. Sibai BM, Lipshitz J, Anderson GD, Dilts PV Jr. Reassessment of intravenous $MgSO^4$ therapy in preeclampsia-eclampsia. *Obstet Gynecol*. 1981;57:199–202.
115. Kohn LT, Corrigan J, Donaldson M. *To Err Is Human: Building a Safer Health System*. Institute of Medicine and the National Academy Press; 1999.
116. Simpson KR, Knox GE. Obstetrical accidents involving intravenous magnesium sulfate: recommendations to promote patient safety. *MCN Am J Matern Child Nurs*. 2004;29:161–169.
117. Isler CM, Barrilleaux PS, Rinehart BK, Magann EF, Martin JN Jr. Postpartum seizure prophylaxis: using maternal clinical parameters to guide therapy. *Obstet Gynecol*. 2003;101:66–69.
118. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial [published correction appears in *Lancet*. 1995;346:258]. *Lancet*. 1995;345:1455–1463.
119. Witlin AG. Prevention and treatment of eclamptic convulsions. *Clin Obstet Gynecol*. 1999;42:507–518.
120. Norwitz ER, Robinson JN, Challis JR. The control of labor. *N Engl J Med*. 1999;341:660–666.
121. ACOG Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 107. Induction of labor. *Obstet Gynecol*. 2009;114(2 Pt 1):386–397.
122. Cunningham FG, Leveno KJ, Bloom SL, et al. Induction and augmentation of labor. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill; 2014:523.
123. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. *JAMA*. 1995;273:413–418.
124. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 475: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*.

2011;117(2 Pt 1):422–424.
125. Riskin-Mashiah S, Wilkins I. Cervical ripening. *Obstet Gynecol Clin North Am*. 1999;26:243–257.
126. Vrouenraets FP, Roumen FJ, Dehing CJ, van den Akker ES, Aarts MJ, Scheve EJ. Bishop score and risk of cesarean delivery after induction of labor in nulliparous women. *Obstet Gynecol*. 2005;105:690–697.
127. Vahratian A, Zhang J, Troendle JF, Sciscione AC, Hoffman MK. Labor progression and risk of cesarean delivery in electively induced nulliparas. *Obstet Gynecol*. 2005;105:698–704.
128. Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction: a meta-analysis. *Obstet Gynecol*. 1997;89:633–642.
129. Hofmeyr GJ, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database Syst Rev*. 2010; (10):CD000941.
130. Wing DA. A benefit-risk assessment of misoprostol for cervical ripening and labour induction. *Drug Saf*. 2002;25:665–676.
131. Sanchez-Ramos L, Peterson DE, Delke I, Gaudier FL, Kaunitz AM. Labor induction with prostaglandin E1 misoprostol compared with dinoprostone vaginal insert: a randomized trial. *Obstet Gynecol*. 1998;91:401–405.
132. Blanchette HA, Nayak S, Erasmus S. Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E^1) with those of dinoprostone (prostaglandin E^2) for cervical ripening and induction of labor in a community hospital. *Am J Obstet Gynecol*. 1999;180(6, Pt 1):1551–1559.
133. Wing DA, Ham D, Paul RH. A comparison of orally administered misoprostol with vaginally administered misoprostol for cervical ripening and labor induction. *Am J Obstet Gynecol*. 1999;180:1155–1160.
134. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. *Cochrane Database Syst Rev*. 2006;(2):CD001338.
135. Rayburn WF. Prostaglandin E^2 gel for cervical ripening and induction of labor: a critical analysis. *Am J Obstet Gynecol*. 1989;160:529–534.
136. Witter FR, Rocco LE, Johnson TR. A randomized trial of prostaglandin E^2 in a controlled-release vaginal pessary for cervical ripening at term. *Am J Obstet Gynecol*. 1992;166:830–834.
137. Wing DA, Miller H, Parker L, et al. Misoprostol vaginal insert for successful labor induction: a randomized controlled trial. *Obstet Gynecol*. 2011;117:533–541.
138. Rayburn WF, Wapner RJ, Barss VA, et al. An intravaginal controlled-release prostaglandin E^2 pessary for cervical ripening and initiation of labor at term. *Obstet Gynecol*. 1992;79:374–379.
139. Cervidil. Package insert. Forrest Pharmaceuticals; 1997.
140. Prepidil Gel. Package insert. Pharmacia & Upjohn Company; 1999.

141. Battista LR, Wing DA. Abnormal labor and induction of labor. In: Gabbe SG, Niebyl JR, Galan JL, et al, eds. *Obstetrics: Normal and Problem Pregnancies*. 5th ed. Churchill Livingstone; 2007:322.
142. Kelly AJ, Fairclough A, Kavanagh J, Kelly AJ. Vaginal prostaglandin (PGE^2 and PGF^{2a}) for induction of labour at term. *Cochrane Database Syst Rev*. 2009;(4):CD003101.
143. ACOG practice patterns. Management of postterm pregnancy. Number 6, October 1997. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*. 1998;60:86–91.
144. Dudley DJ. Oxytocin: use and abuse, science and art. *Clin Obstet Gynecol*. 1997;40:516–524.
145. Perry RL, Satin AJ, Barth WH, Valtier S, Cody JT, Hankins GD. The pharmacokinetics of oxytocin as they apply to labor induction. *Am J Obstet Gynecol*. 1996;174:1590–1593.
146. Shyken JM, Petrie RH. The use of oxytocin. *Clin Perinatol*. 1995;22:907–931.
147. Satin AJ, Leveno KJ, Sherman ML, McIntire D. High-dose oxytocin: 20- versus 40-minute dosage interval. *Obstet Gynecol*. 1994;83:234–238.
148. Satin AJ, Leveno KJ, Sherman ML, Brewster DS, Cunningham FG. High- versus low-dose oxytocin for labor stimulation. *Obstet Gynecol*. 1992;80:111–116.
149. Xenakis EM, Langer O, Piper JM, Conway D, Berkus MD. Low-dose versus high-dose oxytocin augmentation of labor—a randomized trial. *Am J Obstet Gynecol*. 1995;173:1874–1878.
150. Ananth CV, Joseph KS, Oyelese Y, Demissie K, Vintzileos AM. Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. *Obstet Gynecol*. 2005;105(5, Pt 1):1084–1091.
151. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995–1997 rates for whites, Hispanics, and blacks. *Pediatrics*. 2003;111:e61–e66.
152. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med*. 2000;342:1500–1507.
153. Esplin MS. Preterm birth: a review of genetic factors and future directions for genetic study. *Obstet Gynecol Surv*. 2006;61:800–806.
154. Bujimschi C, Norman C. Pathogenesis of spontaneous preterm labor. In: Creasy RK, Reskin R, Iams JD, Lockwood CJ, Moore TR, Greene M, eds. *Creasy and Resnik's Maternal-Fetal Medicine Principles and Practice*. 7th ed. WB Saunders; 2014:599.
155. Smith R. Parturition. *N Engl J Med*. 2007;356:271–283.
156. Iams JD, Creasy PK, Resnik JD, Lookwood TR. Preterm labor and birth. In: Creasy RK, Reskin R, Iams JD, Lockwood CJ, Moore TR, Greene M, eds. *Creasy and Resnik's Maternal-Fetal Medicine*. 7th ed. Saunders; 2014:624.

157. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 31. Assessment of risk factors for preterm birth. Clinical management guidelines for obstetrician-gynecologists. Number 31, October 2001. *Obstet Gynecol*. 2001;98:709–716.
158. Berkman ND, Thorpe JM Jr, Lohr KN, et al. Tocolytic treatment for the management of preterm labor: a review of the evidence. *Am J Obstet Gynecol*. 2003;188:1648–1659.
159. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med*. 2007;357:477–487.
160. ACOG Committee on Practice Bulletins. American College of Obstetricians and Gynecologist. ACOG Practice Bulletin No 43. Management of preterm labor. *Obstet Gynecol*. 2003;101(5, Pt 1):1039.
161. Crowther CA, Brown J, McKinlay CJ, Middleton P. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev*. 2002;(4):CD001060.
162. Canadian Preterm Labor Investigators Group. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. The Canadian Preterm Labor Investigators Group. *N Engl J Med*. 1992;327:308–312.
163. Anotayanonth S, Subhedar NV, Garner P, Neilson JP, Harigopal S. Betamimetics for inhibiting preterm labour. *Cochrane Database Syst Rev*. 2004;(4):CD004352.
164. Goldenberg RL. The management of preterm labor. *Obstet Gynecol*. 2002;100(5, Pt 1):1020–1037.
165. King J, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database Syst Rev*. 2005;(2):CD001992.
166. Macones GA, Marder SJ, Clothier B, Stamilio DM. The controversy surrounding indomethacin for tocolysis. *Am J Obstet Gynecol*. 2001;184:264–272.
167. Iannucci TA, Besinger RE, Fisher SG, Gianopoulos JG, Tomich PG. Effect of dual tocolysis on the incidence of severe intraventricular hemorrhage among extremely low-birth-weight infants. *Am J Obstet Gynecol*. 1996;175(4, Pt 1):1043–1046.
168. Norton ME, Merrill J, Cooper BA, Kuller JA, Clyman RI. Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med*. 1993;329:1602–1607.
169. Loe SM, Sanchez-Ramos L, Kaunitz AM. Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. *Obstet Gynecol*. 2005;106:173–179.
170. King JF, Flenady VJ, Papatsonis DN, Dekker GA, Carbonne B. Calcium channel blockers for inhibiting preterm labour. *Cochrane Database Syst Rev*. 2003;(1):CD002255.
171. Lyell DJ, Pullen K, Campbell L, et al. Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labor: a randomized controlled trial.

Obstet Gynecol. 2007;110:61–67.
172. Cunningham FG, Leveno KJ, Bloom SL, et al. Preterm birth. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill; 2014.
173. Glock JL, Morales WJ. Efficacy and safety of nifedipine versus magnesium sulfate in the management of preterm labor: a randomized study. *Am J Obstet Gynecol*. 1993;169:960–964.
174. Carr DB, Clark AL, Kernek K, Spinnato JA. Maintenance oral nifedipine for preterm labor: a randomized clinical trial. *Am J Obstet Gynecol*. 1999;181:822–827.
175. Gaunekar NN, Crowther CA. Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour. *Cochrane Database Syst Rev*. 2004;(3):CD004071.
176. Papatsonis DN, Van Geijn HP, Adèr HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. *Obstet Gynecol*. 1997;90:230–234.
177. Lewis DF. Magnesium sulfate: the first-line tocolytic. *Obstet Gynecol Clin North Am*. 2005;32:485–500.
178. Crowther CA, Hiller JE, Doyle LW, et al. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA*. 2003;290:2669–2676.
179. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics*. 1995;95:263–269.
180. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med*. 2008;359:895–905.
181. American College of Obstetricians and Gynecologists Committee on Obstetric Practice; Society for Maternal-Fetal Medicine. Committee Opinion No. 455: magnesium sulfate before anticipated preterm birth for neuroprotection. *Obstet Gynecol*. 2010;115:669–671.
182. Lewis DF, Bergstedt S, Edwards MS, et al. Successful magnesium sulfate tocolysis: is “weaning” the drug necessary? *Am J Obstet Gynecol*. 1997;177:742–745.
183. Thornton JG. Maintenance tocolysis. *Br J Obstet Gynecol*. 2005;112(suppl 1):118–121.
184. Dodd JM, Crowther CA, Middleton P. Oral betamimetics for maintenance therapy 5 after threatened preterm labour. *Cochrane Database Syst Rev*. 2006;(1):CD003927.
185. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2006;(3):CD004454.
186. Garite TJ, Kurtzman J, Maurel K, Clark R; Obstetrix Collaborative Research Network. Impact of a “rescue course” of antenatal corticosteroids: a

multicenter randomized placebo-controlled trial. *Am J Obstet Gynecol*. 2009;200:248.e1–e9.

187. Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med*. 2000;342:534–540.
188. Goldenberg RL, Rouse DJ. Prevention of premature birth. *N Engl J Med*. 1998;339:313–320.
189. Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *JAMA*. 1997;278:989–995.
190. Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of membranes. *Cochrane Database Syst Rev*. 2010;(8):CD001058.
191. ACOG Committee Opinion No. 445: antibiotics for preterm labor. *Obstet Gynecol*. 2009;114:1159–1160.
192. Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *N Engl J Med*. 1995;333:1732–1736.
193. McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev*. 2007;(1):CD000262.
194. Newton ER. Chorioamnionitis and intraamniotic infection. *Clin Obstet Gynecol*. 1993;36:795–808.
195. Edwards RK. Chorioamnionitis and labor. *Obstet Gynecol Clin North Am*. 2005;32:287–296.
196. Sperling RS, Newton E, Gibbs RS. Intraamniotic infection in low-birth-weight infants. *J Infect Dis*. 1988;157:113–117.
197. Society for Maternal Fetal Medicine Publications Committee. ACOG Committee Opinion No. 419 (Replaces No. 291, November 2003). Use of progesterone to prevent preterm births. *Obstet Gynecol*. 2008;112:963–965.
198. Gibbs RS, Duff P. Progress in pathogenesis and management of clinical intraamniotic infection. *Am J Obstet Gynecol*. 1991;164(5 Pt 1):1317–1326.
199. Meis P, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate [published correction appears in *N Engl J Med*. 2003;349:1299]. *N Engl J Med*. 2003;348:2379–2385.
200. Armstrong J. Unintended consequences—the cost of preventing preterm births after FDA approval of a branded version of 17OHP. *N Engl J Med*. 2011;384:1689–1691.
201. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. *JAMA*. 2000;284:1417–1424.
202. Locksmith GJ, Chin A, Vu T, Shattuck KE, Hankins GD. High compared with standard gentamicin dosing for chorioamnionitis: a comparison of maternal

and fetal serum drug levels. *Obstet Gynecol*. 2005;105:473–479.
203. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. Accessed December 30, 2021. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Perinatal_GL.pdf
204. Sturt AS, Dokubo EK, Sint TT. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. *Cochrane Database Syst Rev*. 2010;(3):CD008440.
205. Elbourne DR, Prendiville WJ, Carroli G, Wood J, McDonald S. Prophylactic use of oxytocin in the third stage of labour. *Cochrane Database Syst Rev*. 2001;(4):CD001808.
206. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage. *Obstet Gynecol*. 2006;108:1039–1047.
207. Cunningham FG, Leveno KJ, Bloom SL, et al. Obstetrical hemorrhage. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams Obstetrics*. 24th ed. McGraw-Hill; 2014:780.
208. Khan RU, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. *Obstet Gynecol*. 2003;101(5, Pt 1):968–974.
209. Caliskan E, Dilbaz B, Meydanli MM, Oztürk N, Narin MA, Haberal A. Oral misoprostol for the third stage of labor: a randomized controlled trial. *Obstet Gynecol*. 2003;101(5 Pt 1):921–928.
210. Gülmezoglu AM, Villar J, Ngoc NT, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet*. 2001;358:689–695.
211. Hemabate. Package insert. Pharmacia & Upjohn Company; 1999.
212. O'Brien WF. The role of prostaglandins in labor and delivery. *Clin Perinatol*. 1995;22:973–984.
213. Blum J, Alfirevic Z, Walraven G, Weeks A, Winikoff B. Treatment of postpartum hemorrhage with misoprostol. *Int J Gynaecol Obstet*. 2007;99(suppl 2):S202–S205.
214. Blum J, Winikoff B, Raghavan S, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet*. 2010;375:217–223.
215. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 75: management of alloimmunization. *Obstet Gynecol*. 2006;108:457–464.

216. Moise KJ Jr. Management of rhesus alloimmunization in pregnancy. *Obstet Gynecol*. 2008;112:164–176.
217. American College of Obstetrics and Gynecology. ACOG Practice Bulletin. Prevention of Rh D alloimmunization. Number 4, May 1999 (replaces educational bulletin Number 147, October 1990). Clinical management guidelines for obstetrician-gynecologists. *Int J Gynaecol Obstet*. 1999;66:63–70.
218. Rhogam Ultra-Filtered Plus. Package insert. Ortho Clinical Diagnostics; 2017.
219. Lawrence RA, Lawrence RM. Anatomy of the breast. In: Lawrence RA, Lawrence RM, eds. *Breastfeeding: A Guide for the Medical Professional*. 8th ed. Mosby-Year Book; 2016:34.
220. Neville MC, Walsh CT. Effects of drugs on milk secretion and composition. In: Bennett PN, ed. *Drugs and Human Lactation*. 2nd ed. Elsevier Science; 1996:15.
221. Ehrenkranz RA, Ackerman BA. Metoclopramide effect on faltering milk production by mothers of premature infants. *Pediatrics*. 1986;78:614–620.
222. Gupta AP, Gupta PK. Metoclopramide as a lactogogue. *Clin Pediatr (Phila)*. 1985;24:269–272.
223. Kauppila A, Kivinen S, Ylikorkala O. A dose response relation between improved lactation and metoclopramide. *Lancet*. 1981;1:1175–1177.
224. Kauppila A, Anunti P, Kivinen S, Koivisto M, Ruokonen A. Metoclopramide and breast feeding: efficacy and anterior pituitary responses of the mother and the child. *Eur J Obstet Gynecol Reprod Biol*. 1985;19:19–22.
225. Fife S, Gill P, Hopkins M, Angello C, Boswell S, Nelson KM. Metoclopramide to augment lactation, does it work? A randomized trial. *J Matern Fetal Neonatal Med*. 2011;24(11):1317–1320.
226. Hansen WF, McAndrew S, Harris K, Zimmerman MB. Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol*. 2005;105:383–389.
227. Spitz AM, Lee NC, Peterson HB. Treatment for lactation suppression: little progress in one hundred years. *Am J Obstet Gynecol*. 1998;179(6, Pt 1):1485–1490.
228. Lawrence RA. Breastfeeding and medical disease. *Med Clin North Am*. 1989;73:583–603.
229. Gartner LM, Morton J, Lawrence RA, et al. Breastfeeding and the use of human milk. *Pediatrics*. 2005;115:496–506.
230. Zembo CT. Breastfeeding. *Obstet Gynecol Clin North Am*. 2002;29:51–76.
231. Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM. The association between duration of breastfeeding and adult intelligence [published correction appears in *JAMA.* 2002;287:2946]. *JAMA*. 2002;287:2365–2371.
232. Breitzka RL, Sandritter TL, Hatzopoulos FK. Principles of drug transfer into breast milk and drug disposition in the nursing infant. *J Hum Lact*.

1997;13:155–158.
233. Anderson PO. Drugs and breast milk. *Pediatrics*. 1995;95:957.
234. Dillon AE, Wagner CL, Wiest D, Newman RB. Drug therapy in the nursing mother. *Obstet Gynecol Clin North Am*. 1997;24:675–696.
235. Bates SM Greer I, Middledorp S, et al. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2016;149(2):315–352.
236. Begg EJ, Duffull SB, Hackett LP, Ilett KF. Studying drugs in human milk: time to unify the approach. *J Hum Lact*. 2002;18:323–332.
237. Bennett PN, ed. *Drugs and Human Lactation*. 2nd ed. Elsevier; 1996.

50

Disorders Related to the Menstrual Cycle

Laura M. Borgelt and Karen M. Gunning

CORE PRINCIPLES		CHAPTER CASES
1	A normal menstrual cycle involves the hypothalamus, anterior pituitary gland, ovaries, and endometrial lining of the uterus to create hormonal release. This process results in follicle development, ovulation, and either pregnancy or menstruation every 28 days (average) during reproductive life.	
2	Polycystic ovary syndrome (PCOS) is a heterogeneous disorder that presents with signs and symptoms of hyperandrogenism (eg, acne, hirsutism) or ovulatory dysfunction.	**Case 50-1 (Question 1)**
3	Long-term complications of PCOS may	**Case 50-1 (Question 2)**

	include impaired glucose tolerance, diabetes, metabolic syndrome, infertility, endometrial cancer, and obstructive sleep apnea.	
4	Treatment for PCOS involves nonpharmacologic and pharmacologic management. Pharmacologic management targets the pathophysiologic aspects of the syndrome and individual goals of treatment. Oral contraceptives are preferred when contraception is desired; letrozole is warranted when pregnancy is desired.	**Case 50-1 (Questions 3–7)**
5	Dysmenorrhea, or painful cramping that occurs with the onset and first days of menstruation, can be categorized as either primary (without underlying uterine pathology) or secondary as a result of uterine pathology, including endometriosis, uterine polyps, or fibroids; complications of intrauterine contraceptive device use; or pelvic inflammatory disease. A careful history can distinguish most cases of primary dysmenorrhea from secondary dysmenorrhea, which should always be investigated further to identify its underlying etiology.	**Case 50-2 (Questions 1, 2)**
6	Dysmenorrhea is the single largest cause of lost productivity and school absence among adolescent females. Health care providers can play a	**Case 50-2 (Questions 3–8)**

	significant role in patient education and the development of rational evidence-based nonpharmacologic and pharmacologic therapy plans that include nonsteroidal anti-inflammatory drugs (NSAIDs) and/or hormonal contraceptives to decrease symptoms and improve functionality.	
7	Endometriosis is defined as the presence of functional endometrial tissue occurring outside the uterine cavity. It is the most common cause of secondary dysmenorrhea in young females and can result in chronic pelvic pain, infertility, and dyspareunia. A significant delay in diagnosis of endometriosis is common, and recognition of the potential for a diagnosis of endometriosis, through a careful history and physical, is important to start appropriate care.	**Case 50-3 (Question 1)**
8	Pain control in endometriosis is directed at suppression of endometrial implants that respond to estrogen with bleeding, resulting in subsequent inflammation and pain. Pharmacologic therapy is directed at reducing inflammation (via use of NSAIDs) and reduction in estrogen through use of hormonal contraception) or by use of gonadotropin-releasing hormone (GnRH) agonists or antagonists. A treatment plan should take into account	**Case 50-3 (Questions 2–4)** **Case 50-4 (Question 1)** **Case 50-5 (Question 1)**

	cost, ease of use of therapy, adverse effects, and the patient's desire for future fertility.	
9	Endometriosis treatment plans that include GnRH agonists or antagonists may also require the use of "add-back" therapy. Add-back therapy is the addition of progestins with or without estrogens to decrease drug-related menopausal side effects, including hot flashes, vaginal dryness, and decreases in bone density.	**Case 50-4 (Question 1)**
10	More than 200 premenstrual symptoms have been described as occurring during the days before menstruation. It is not until the symptoms have a decidedly negative influence on the physical, psychological, or social function of a female that premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) exists. Both PMS and PMDD have physical and/or behavioral symptoms that occur in the luteal phase with resolution within a few days of menstruation, lasting across at least two menstrual cycles, and disrupt normal activities. PMDD is a more severe form of PMS with prominent symptoms of anger, irritability, and internal tension.	**Case 50-5 (Questions 1, 3)**
11	Mind–body approaches and chasteberry have been studied as nonprescription	**Case 50-5 (Question 2)**

	options and have shown some benefit in PMS.	
12	Treatment for PMS and PMDD includes lifestyle modifications, psychological interventions, selective serotonin reuptake inhibitors (SSRIs), oral contraceptives, and GnRH agonists. Because serotonin is critical in the pathogenesis of these disorders, SSRIs have become the treatment of choice for PMDD and severe PMS.	**Case 50-5 (Question 4)**

INTRODUCTION

The average 28-day menstrual cycle is controlled by feedback biologic mechanisms involving the hypothalamus, anterior pituitary gland, ovaries, and endometrial lining of the uterus.[1] The hypothalamus synthesizes gonadotropin-releasing hormone (GnRH) and secretes the hormone in a pulse-like manner with varying frequencies throughout the menstrual cycle (typically every 60–90 minutes). GnRH stimulates the anterior pituitary to produce and release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH is important for stimulating growth of ovarian follicles and LH is critical for ovulation and sex steroid production. FSH and LH act on the ovaries to produce estrogen and progesterone. Estrogen in turn acts on the hypothalamus and anterior pituitary, in a negative feedback manner, to stop FSH and LH secretion (**Fig. 50-1**).

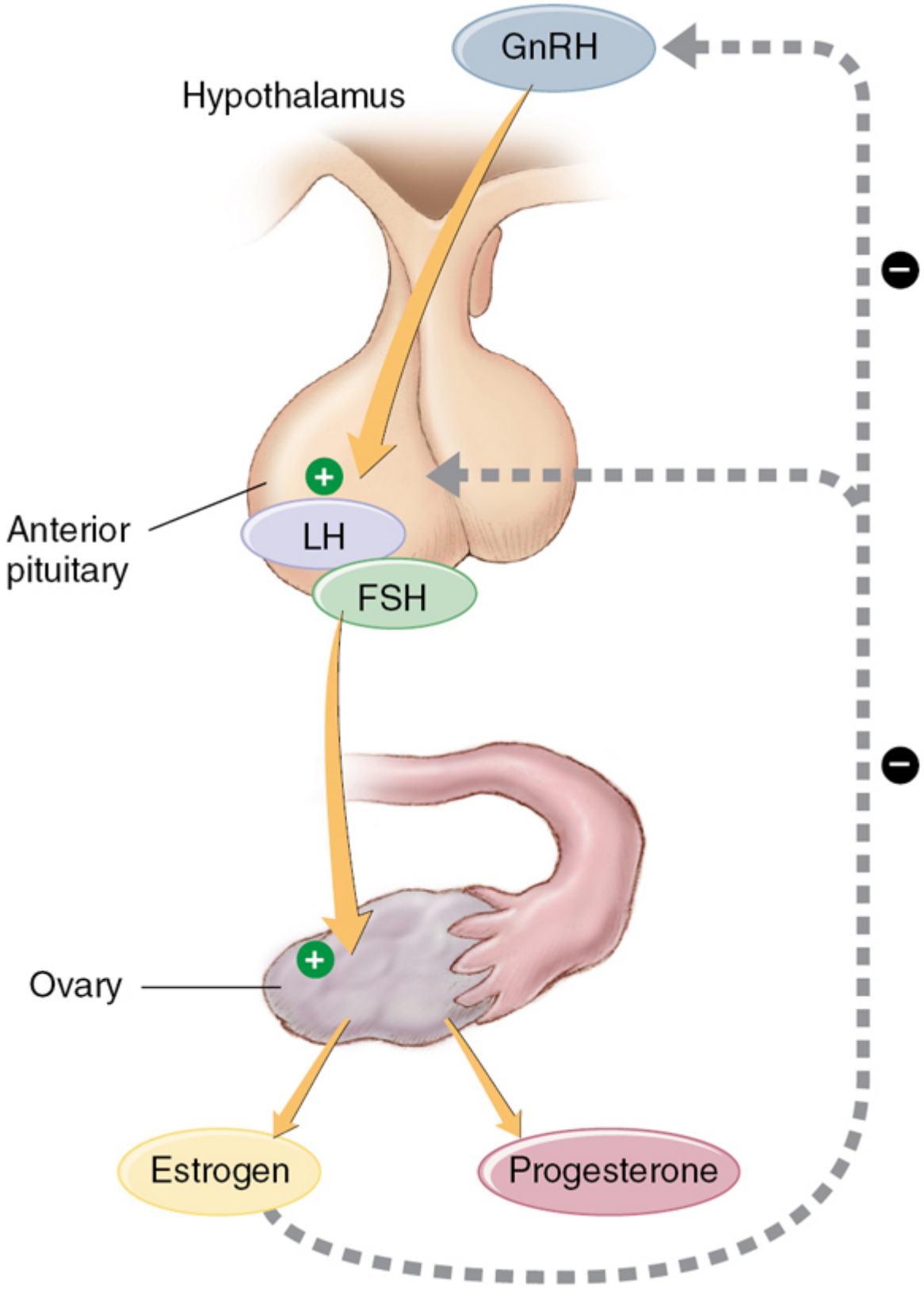
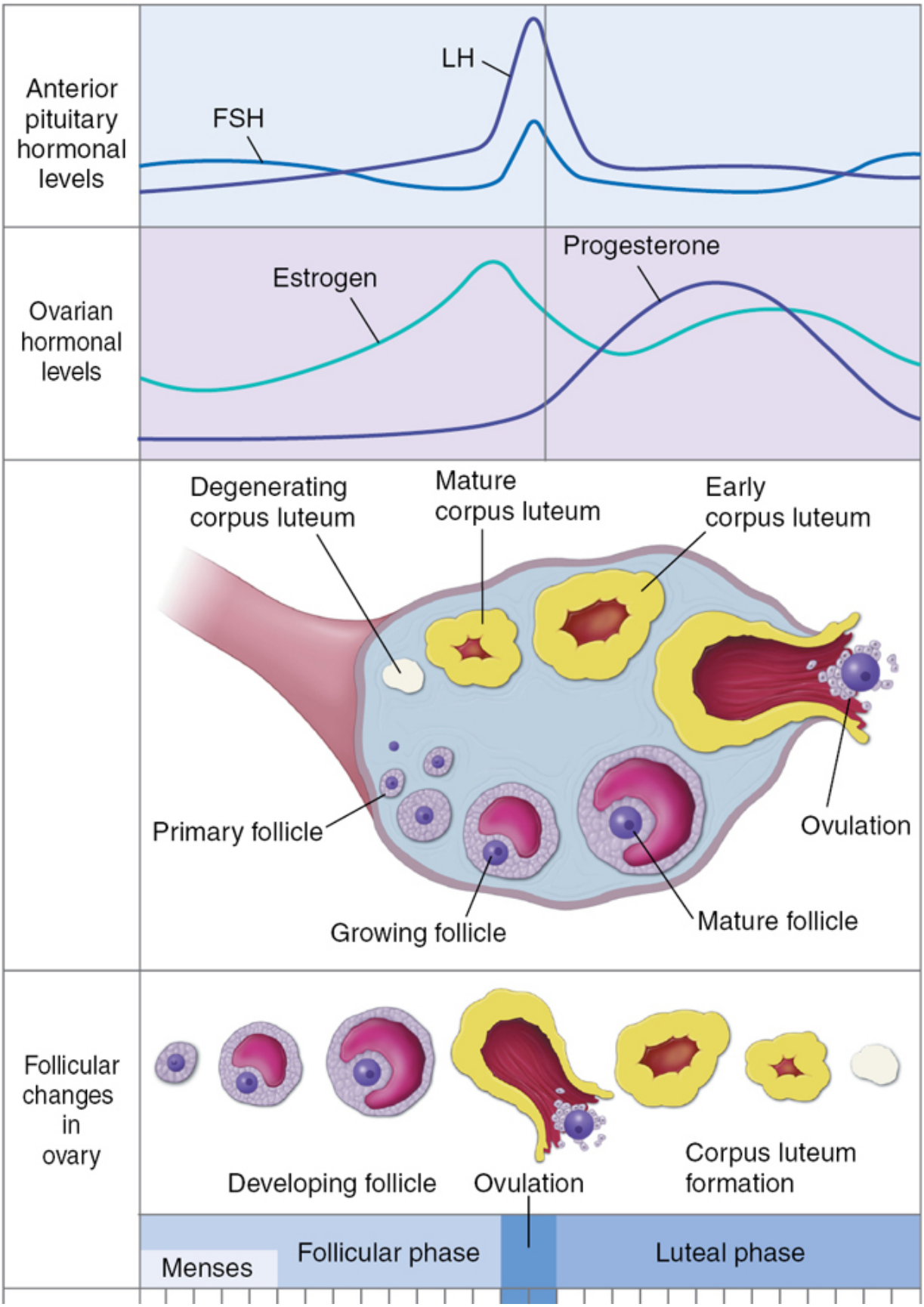

GnRH
Hypothalamus
Anterior pituitary
LH
FSH
Ovary
Estrogen
Progesterone

Figure 50-1 Menstrual cycle physiology. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone. (Adapted with permission from Premkumar K. *The Massage Connection: Anatomy and Physiology*. Lippincott Williams & Wilkins; 2004.)

The menstrual cycle can be divided into three phases: the follicular phase, ovulation, and the luteal phase (**Fig. 50-2**).[1] The day bleeding begins is referred to as the first day (or day 1) of the menstrual cycle. Bleeding usually occurs from days 1 to 5 of the cycle, although may be longer in some patients. The follicular phase begins at the onset of menstruation and lasts ~10 to 14 days (see Fig. 50-2). At the beginning of this phase, several follicles begin to develop within the ovary. In the second half of the follicular phase, most of the developing follicles atrophy, whereas the dominant follicle develops further and produces estrogen in increasing amounts. Elevated estradiol levels during the ovulatory phase lead to a surge in LH and FSH. The LH surge is responsible for final-stage growth and maturation of the follicle, ovulation, and the formation of the corpus luteum. Ovulation usually occurs 14 days before the last day of the cycle and is followed by the luteal phase. The luteal phase is 13 to 15 days in duration and is the least variable part of the human reproductive cycle.[1] During this progesterone-dominant phase, the corpus luteum produces progesterone and estrogen. Progesterone prepares the endometrium for the implantation of a fertilized ovum. If implantation does not occur, corpus luteum regression causes a decrease in the levels of estrogen and progesterone. When these hormone levels decrease, the endometrium cannot be maintained and is sloughed off (menstrual phase). Using the average 28-day cycle as an example, day 28 is the last day of the cycle and is the day before bleeding begins again for the next menstrual cycle.


Anterior pituitary hormonal levels
LH
FSH
Ovarian hormonal levels
Estrogen
Progesterone
Degenerating corpus luteum
Mature corpus luteum
Early corpus luteum
Primary follicle
Ovulation
Growing follicle
Mature follicle
Follicular changes in ovary
Developing follicle
Ovulation
Corpus luteum formation
Menses
Follicular phase
Luteal phase

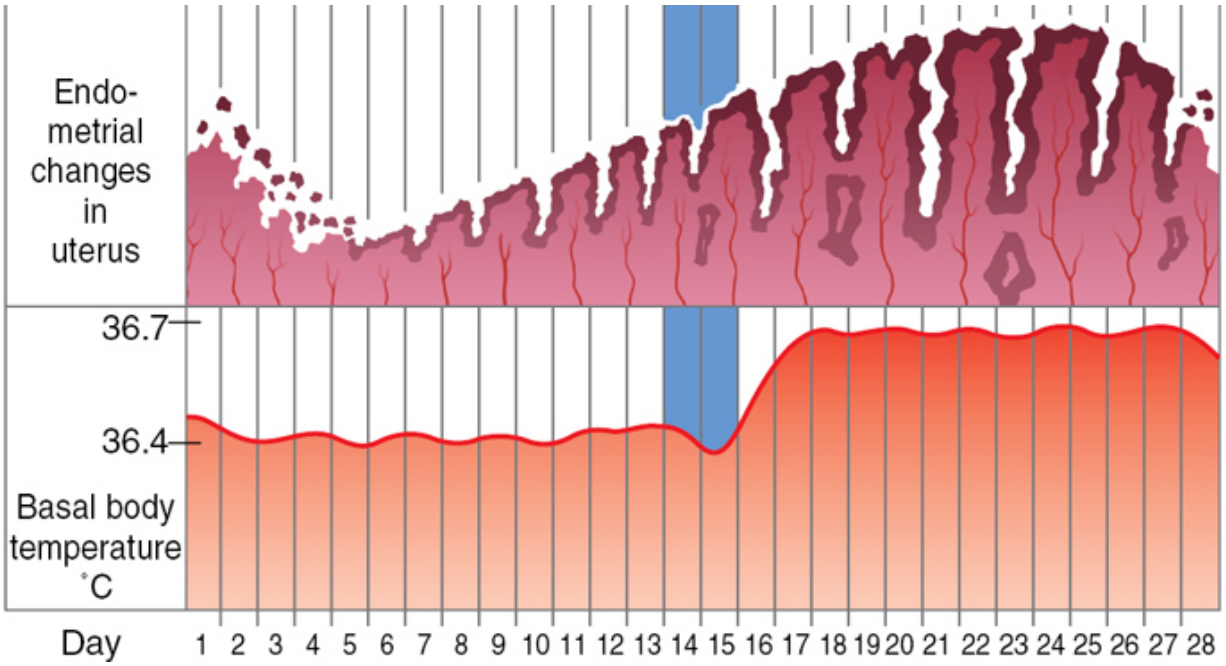


Figure 50-2 The menstrual cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Adapted with permission from Premkumar K. *The Massage Connection: Anatomy and Physiology.* Lippincott Williams & Wilkins; 2004.)

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) affects ~6% to 21%, or ~1 in 10, patients of reproductive age, making it the leading cause of anovulatory infertility and the most common endocrine abnormality for this age group.[2,3] This syndrome, or constellation of symptoms, was first described in 1935 by Stein and Leventhal when they reported infertility and amenorrhea in seven patients with enlarged cystic ovaries.[4] Excessive male-pattern hair growth and obesity were added later to the description of this syndrome.[5] PCOS also has been referred to as Stein–Leventhal syndrome, polycystic ovary, polycystic ovarian disease, hyperandrogenic chronic anovulatory syndrome, metabolic reproductive syndrome, and functional ovarian hyperandrogenism. The name polycystic ovary syndrome has been most widely accepted because “syndrome” best describes the

heterogeneous nature of this disorder. However, there have been recommendations to change the name because it focuses on the polycystic ovarian morphology, which is not necessary for diagnosis.[6] It has been suggested that the name should include the complex metabolic, reproductive, hypothalamic, pituitary, ovarian, and adrenal interactions of the syndrome.

Diagnostic Criteria

The diagnosis of PCOS is complicated by patients presenting with varying signs and symptoms of PCOS and because precise and uniform criteria for diagnosis have not been firmly established. Three major diagnostic criteria for PCOS have been proposed by different organizations.

The initial diagnostic criteria were developed in 1990 during an expert conference sponsored by the U.S. National Institutes of Health and U.S. National Institute of Child Health and Human Development. The panel concluded that the major criteria for PCOS should include (in order of importance): (a) hyperandrogenism (clinical signs of hyperandrogenism such as hirsutism) or hyperandrogenemia (biochemical signs of hyperandrogenism such as elevated testosterone levels), (b) oligo-ovulation (infrequent or irregular ovulation with fewer than nine menses per year), and (c) exclusion of other known disorders such as hyperprolactinemia, thyroid abnormalities, and congenital adrenal hyperplasia.[7] The second set of criteria was proposed at an expert conference in Rotterdam sponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine in 2003.[8] They concluded that the presence of two of these three features, after exclusion of related disorders, confirmed diagnosis of PCOS: (a) oligo-ovulation or anovulation, (b) clinical or biochemical signs of hyperandrogenism, or (c) polycystic ovaries. Recent guidelines suggest that one of four phenotypes should be used with a diagnosis of PCOS; however, clinical implications of using these phenotypes are unclear (**Table 50-1**). The

third set of criteria was developed by a task force of the Androgen Excess Society in 2006 with a complete report including phenotyping in 2009.[9,10] These criteria include hyperandrogenism (hirsutism or hyperandrogenemia), ovarian dysfunction (oligo-ovulation or polycystic ovaries), and exclusion of other androgen excess or related disorders. Recent practice guidelines support the Rotterdam criteria for diagnosing PCOS and specifically indicate that serum anti-müllerian hormone (AMH) levels should not yet be used as an alternative for the detection of polycystic ovary morphology or as a single test for the diagnosis of PCOS.[11]

Table 50-1
Phenotypes of Polycystic Ovarian Syndrome Based on Rotterdam Criteria

Phenotype	Androgen Excess	Ovulatory Dysfunction	PCOM on Ultrasound
A	X	X	X
B	X	X	
C	X		X
D		X	X

PCOM, polycystic ovary morphology.

Criteria for diagnosis of PCOS in adolescence can be difficult to assess because of typical changes during puberty and is different than those used for older patients of reproductive age.[11,12] Specific criteria to improve diagnostic accuracy and avoid overdiagnosis include irregular menstrual cycles; hyperandrogenism defined as hirsutism, severe acne and/or biochemical hyperandrogenism confirmed using validated high-quality assays; and exclusion of other disorders that mimic PCOS. Pelvic ultrasound is not recommended for diagnosis of PCOS within 8 years postmenarche because of the high incidence of multifollicular ovaries in this life stage and AMH levels are not recommended for PCOS diagnosis. In recent

guidance, irregular menstrual cycles in this population were more clearly defined according to years postmenarche.[12] Irregular menstrual cycles in adolescents are defined as <21 or >45 days if 1–3 years postmenarche, <21 or >35 days or <8 cycles per year if more than 3 years postmenarche, and >90 days for any one cycle if more than 1 year postmenarche. Irregular menstrual cycles within the first year postmenarche are considered part of the normal pubertal transition. Adolescents who have features of PCOS but do not meet diagnostic criteria may be considered “at risk” for PCOS and reassessment is advised at or before full reproductive maturity (ie, 3 years postmenarche for menstrual irregularity or 8 years postmenarche for pelvic ultrasound). Adolescents with PCOS should be screened for anxiety and depression and assessment of eating disorders warrants consideration.

Clinical Characteristics

Common clinical signs of hyperandrogenism in PCOS include hirsutism, acne, and alopecia. Hirsutism, the most common of these characteristics, occurs in 70% to 80% of patients with PCOS.[13] However, ethnic variations in the presentation and manifestations of PCOS can be seen and should be considered. Examples include a higher body mass index (BMI) in Caucasian females; more severe hirsutism in Middle Eastern, Hispanic, and Mediterranean females; increased central adiposity, insulin resistance, diabetes, metabolic risks, and acanthosis nigricans in Southeast Asians and Indigenous Australians; lower BMI and milder hirsutism in East Asians; and higher BMI and metabolic features in Africans.[11]

Hirsutism is defined as an excess of thickly pigmented body hair in a male-pattern distribution and is commonly found on the upper lip, lower abdomen, and around the nipples. Patients seeking treatment for hirsutism may be evaluated for PCOS. Acne affects over 40% of patients with PCOS compared with ~20% in the general population.[14] The prevalence of alopecia, or female-pattern hair loss, occurs in

20% to 30% of patients with PCOS, typically in the third decade of life.[15]

Ovulatory dysfunction in PCOS is typically described as oligo-ovulation or anovulation, presenting clinically as a female with irregular, infrequent, or absent menstrual bleeding. A majority of patients with PCOS and oligo-ovulation have menstrual dysfunction, usually oligomenorrhea or amenorrhea. The menstrual disturbances usually begin in the peripubertal years; however, menstrual cycles in patients with PCOS become more regular as they approach menopause.

Obesity (defined as a body mass index [BMI] ≥30 kg/m^2) is likely not a cause of PCOS, but it occurs in 50% to 80% of patients with PCOS and in nearly three times more patients with PCOS than those without PCOS.[16,17] Central or abdominal obesity is the typical pattern. Central obesity is a risk factor for the development of diabetes and heart disease and, when present in a female with PCOS, worsens the clinical features (eg, insulin resistance) of the syndrome. Therefore, lifestyle modification with appropriate diet and exercise is a cornerstone of therapy for many patients with PCOS.

Pathophysiology

The pathophysiology of PCOS is complex. The primary abnormalities underlying PCOS include functional ovarian hyperandrogenism because of inappropriate gonadotropin secretion that can be aggravated by insulin-resistant hyperinsulinism.[18] **Figure 50-3** displays the closely integrated relationship between these mechanisms in the development of PCOS.

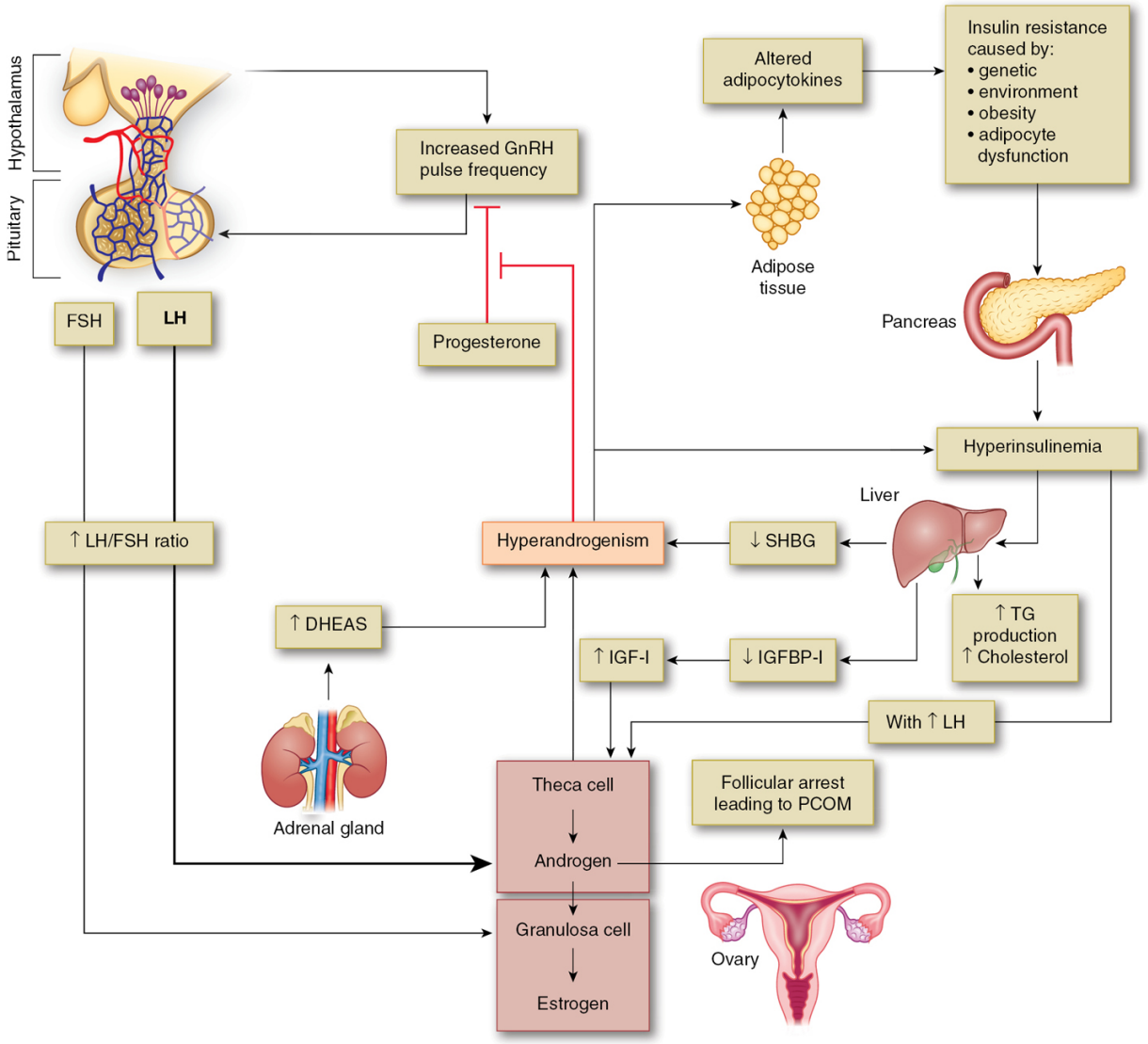


Figure 50-3 Pathophysiology of PCOS. DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-stimulating hormone; IGF-1, insulin-like growth factor 1; IGFBP, insulin-like growth factor–binding protein; LH, luteinizing hormone; PCOM, polycystic ovarian morphology; SHBG, sex hormone–binding globulin; TG, triglycerides. (Source: Yau TT, Ng NY, Cheung LP, et al. Polycystic ovary syndrome: a common reproductive syndrome with long-term metabolic consequences. *Hong Kong Med J*. 2017;23(6):622–634.)

Data to support a genetic basis for PCOS have accumulated, and genome-wide association studies have identified 19 risk gene loci in

the neuroendocrine, metabolic, and reproductive pathways of PCOS.[19–22] Additional analyses suggest a causal link between PCOS and variants associated with other aspects of the syndrome such as BMI, fasting insulin, menopause timing, depression, and male-pattern baldness.[23] Daughters born to mothers with PCOS have a fivefold higher risk for inheriting PCOS.[24,25] However, known genetic risk alleles account for <10% of PCOS heritability; therefore, other etiologic factors also have to be considered.[11]

GONADOTROPIN SECRETION

In PCOS, there is an increased frequency of GnRH stimulation, leading to an increase in LH pulse frequency and amplitude, while FSH secretion remains normal or low. The development of a dominant follicle does not occur because LH secretion occurs too early in the menstrual cycle. Therefore, a female is left with several immature follicles and usually will not ovulate. It is not clear whether the abnormal pulse frequency of GnRH is a result of genetic association or neuroendocrine mechanisms.[26] A female with this abnormality does not enter the luteal phase of her menstrual cycle, leaving estrogen unopposed. Unopposed estrogen leads to endometrial hyperplasia and increases the risk for endometrial cancer. Increased LH stimulation also leads to increased steroidogenesis in the ovary, leading to excess androgen production. Amenorrheic patients have high AMH serum concentrations and higher antral follicle counts compared with both oligomenorrheic patients and regularly cycling patients with PCOS.[27] Additionally, concentrations of AMH tend to remain persistently elevated over time in patients with PCOS.

EXCESS ANDROGEN PRODUCTION

Androgen production occurs in the theca cell of the ovary to facilitate follicular growth and estradiol synthesis in the granulosa cell. In patients with PCOS, hypersecretion of LH and insulin increases the production of androgens, causing abnormal sex steroid synthesis, hyperandrogenism, and hyperandrogenemia. The dysregulation in

steroid synthesis and metabolism is believed to result primarily from a dysfunction of the cytochrome P-450 (CYP) genes involved in steroidogenesis and especially activities that are required to form androstenedione.[28] Androstenedione is then converted to testosterone or is aromatized by the aromatase enzyme to form estrone. Theca cells in patients with PCOS are more efficient than normal theca cells at the conversion to testosterone.[18] Also, a similar steroid pathway occurs in the adrenal cortex, and, when hyperandrogenism or hyperinsulinemic state exist, androgen production is further enhanced.[18]

Elevated androgen levels are seen in most patients with PCOS, mostly as increased free testosterone concentrations. Calculated free testosterone, free androgen index, or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS.[11] High-quality assays such as liquid chromatography–mass spectrometry and extraction/chromatography immunoassays should be used for the most accurate assessment of total or free testosterone.[11] Clinical assessment is the primary tool for assessment of excess androgen.

INSULIN

Patients with PCOS generally exhibit an increased risk of insulin resistance, yet the cellular and molecular mechanisms for insulin resistance are different than those seen with obesity and type 2 diabetes.[18] Insulin resistance is associated with reproductive and metabolic abnormalities in patients with PCOS and can occur in both obese and nonobese patients. There are several mechanisms by which this occurs. One proposed mechanism is a postbinding defect in insulin-receptor signaling.[18,29] The insulin resistance in PCOS has been shown to be a selective, tissue-specific process where insulin sensitivity is increased in the ovarian androgenic pathway (causing hyperandrogenism), but insulin resistance is seen in other tissues involved with carbohydrate metabolism, specifically in the fat and muscle. Hyperinsulinemia results because of the compensatory increase in insulin secretion secondary to insulin resistance.

Insulin has both direct and indirect roles in PCOS. In the ovary, insulin acts alone or synergistically with LH to increase androgen production in theca cells. In the liver, insulin inhibits the synthesis of sex hormone–binding globulin (SHBG), a key protein that binds to testosterone, and thus increases the free fraction of androgens available for biologic activity. Therefore, hyperinsulinemia is a major contributor to both hyperandrogenism and hyperandrogenemia in PCOS. Treatments targeted to improve insulin resistance in patients with PCOS have shown improvements in ovulatory function, hirsutism, androgen levels, and metabolic profiles.[29] Indirectly, insulin may enhance the amplitude of LH pulses, further exacerbating the gonadotropin secretion defect in PCOS.[29]

CASE 50-1

Question 1: B.F. is a 21-year-old female with mild hair growth above her upper lip, mild acne, and a history of irregular menstrual periods. Since age 12, she has had six to nine periods per year at intervals that vary from 30 to 70 days. When she does have a period, she considers them to be "normal" without pain or excessive bleeding. Her irregular periods were not bothersome until recently when she became sexually active and worries about becoming pregnant. She uses condoms for birth control. She reports no other medical conditions. B.F. is 67 inches (170.18 cm) tall and weighs 180 pounds (81.65 kg; BMI 28.2 kg/m^2). Her vital signs today are as follows: blood pressure (BP) 116/80 mm Hg, heart rate (HR) 68 beats/minute, temperature 98.6 °F (37 °C), and respiratory rate (RR) 18 breaths/minute. Her physical examination is normal, with the exception of noted excessive facial hair and mild acne. She takes a multivitamin daily and acetaminophen as needed for headaches. She has no known medication allergies.

What signs and symptoms does B.F. have that are consistent with PCOS?

B.F. exhibits several signs and symptoms that would indicate the presence of PCOS. According to the Rotterdam criteria, her history of abnormal menstrual periods (oligomenorrhea) and clinical signs of hyperandrogenism, including hirsutism and acne, would indicate PCOS with phenotype B. B.F. is overweight, which is common in patients with PCOS but is not considered a criterion for diagnosis. Before a diagnosis of PCOS is made, laboratory testing to exclude

other related causes of her symptoms would have to be performed. Studies may include prolactin, thyroid-stimulating hormone, testosterone, and 17-hydroxyprogesterone concentrations to rule out hyperprolactinemia, hypothyroidism, virilizing tumor, and congenital adrenal hyperplasia, respectively. PCOS is primarily diagnosed by clinical assessment; therefore, these tests assist only in confirming or excluding a diagnosis. Although an assessment of polycystic ovarian morphology (PCOM) is not necessary for diagnosis in this case, if it needed to be done, a transvaginal ultrasound should be performed and the threshold for PCOM is a follicle number per ovary of ≥20 and/or an ovarian volume ≥10 mL on either ovary, ensuring no corpora lutea, cysts, or dominant follicles are present.[11]

Long-Term Complications

Case 50-1, Question 2: B.F. has a mother with diabetes and hypertension and a father with type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia. Her significant laboratory values include the following:

Fasting glucose, 102 mg/dL
Low-density lipoprotein (LDL), 150 mg/dL
High-density lipoprotein (HDL), 52 mg/dL
Triglycerides, 130 mg/dL
Total cholesterol, 228 mg/dL

What risk does B.F. have for experiencing long-term complications from PCOS?

B.F. has an increased risk for experiencing impaired glucose tolerance, diabetes, and metabolic syndrome, especially considering her family history. Furthermore, the diagnosis of PCOS places her at possible increased risk for sleep apnea and endometrial cancer.

IMPAIRED GLUCOSE TOLERANCE AND DIABETES

Studies have shown that patients with PCOS have a higher prevalence of impaired glucose tolerance, gestational diabetes, diabetes, and insulin resistance compared with patients without the

syndrome.[11,30,31] The risk of diabetes is higher when patients with PCOS are overweight or obese.[31] Therefore, screening and diagnosis of these conditions is important for patients with PCOS. B.F. is overweight and her mildly elevated fasting glucose and overweight suggest that she may be at increased risk for impaired glucose tolerance.

Glycemic status should be assessed at baseline in all patients with PCOS and every 1 to 3 years thereafter based on the presence of other diabetes risk factors.[11] An oral glucose tolerance test (OGTT), fasting plasma glucose (FPG), or HbA_{1c} should be performed to assess glycemic status with OGTT recommended in high-risk patients with PCOS (including a BMI >25 kg/m^2 or in Asians >23 kg/m^2, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of T2DM, hypertension or high-risk ethnicity).[11] Measurement of insulin or insulin resistance is not recommended at this time.

METABOLIC SYNDROME AND CARDIOVASCULAR RISK

Approximately one-third to one-half of patients with PCOS have metabolic syndrome.[32] Using a joint statement by the International Diabetes Federation; the American Heart Association; the National Heart, Lung and Blood Institute; the World Heart Federation; the International Association for the Study of Obesity; and the International Atherosclerosis Society, metabolic syndrome is present when a patient exhibits any three of these symptoms: increased waist circumference, with ethnic-specific waist circumference cut-points; triglycerides ≥150 mg/dL or treatment for elevated triglycerides; HDL cholesterol <40 mg/dL in males or <50 mg/dL in females, or treatment for low HDL; systolic blood pressure ≥130, diastolic blood pressure ≥85, or treatment for hypertension; or FPG ≥100 mg/dL or previously diagnosed type 2 diabetes.[33] For waist circumference in the U.S. population, >35 inches (88.9 cm) for females and >40 inches (101.6 cm) for males is the common cut-off. It is believed that insulin resistance and hyperandrogenism are contributing factors to metabolic syndrome in patients with PCOS.[34]

Common cardiometabolic features in patients with PCOS include low HDL, high triglycerides, increased BMI and waist circumference, high blood pressure, elevated fasting glucose, and presence of markers for early atherosclerosis (eg, increased C-reactive protein concentrations, increased carotid intima-media thickness).[35] These create increased risk for cardiovascular disease (CVD) and T2DM, especially among those with phenotype A and B.[35,36] Data have shown increased risk of incident MI (HR 1.38, 95% CI 1.11–1.72), angina (HR 1.60, 95% CI 1.32–1.94), and revascularization (HR 1.50, 95% CI 1.08–2.07), in young patients with PCOS compared to those without PCOS.[37]

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is cessation of breathing that occurs during sleep. It can disrupt sleep and cause daytime fatigue. Patients may not be aware that they are having the symptoms of OSA, which include snoring and a gasping or snorting when breathing resumes. Studies indicate that the prevalence of OSA in PCOS is higher than expected and cannot be explained by obesity alone.[38] OSA appears to be a prevalent and important determinant of insulin resistance, glucose intolerance, and type 2 diabetes in PCOS.[39] This can be treated with continuous positive airway pressure (CPAP), which may help metabolic dysfunction.

ENDOMETRIAL HYPERPLASIA AND CANCER

Chronic anovulation in patients with PCOS results in an endometrium that is exposed to the prolonged effects of estrogen unopposed by progesterone. Therefore, PCOS is a risk factor for endometrial hyperplasia. Patients with PCOS have a two- to sixfold increased risk of endometrial cancer, but absolute risk remains low.[11] In one study, patients with PCOS were at significantly increased risk for endometrial cancer compared to controls (OR: 2.8, 95% CI: 1.3–5.9; P = .008) and that risk increased further when patients older than 54 years were excluded from analysis (OR: 4.1, 95% CI: 2.4–6.8; P < .001).[40] Optimal prevention for endometrial hyperplasia and

endometrial cancer is not known, but clinicians could endorse combined oral contraceptives (COCs) or progestin therapy in those with cycles longer than 90 days.[11]

Treatment Goals

Case 50-1, Question 3: B.F. worries about becoming pregnant when she does not have regular periods. She also has mild hair growth above her upper lip, which is somewhat bothersome. Given these concerns, what are the treatment goals for B.F.?

The primary goals for B.F. are to prevent pregnancy and address her hirsutism. Additionally, treatment goals in B.F. would include maintaining a normal endometrium, blocking the actions of androgens at target tissues, reducing insulin resistance and hyperinsulinemia, reducing weight, and preventing long-term complications. Other goals of treatment in patients with PCOS may include correcting anovulation or oligo-ovulation and improving fertility.

Therapy goals should encompass both long-term and short-term objectives because the response to nonpharmacologic and pharmacologic therapy is slow, often requiring 3 to 9 months. Addressing long-term goals can minimize the risk for future complications, and specifying short-term goals can improve motivation and adherence to therapy.

NONPHARMACOLOGIC TREATMENT

Case 50-1, Question 4: B.F. has indicated that she would like to lose weight. B.F. does not smoke, drinks one to two beers on weekends, and exercises by walking 20 minutes twice weekly. What nonpharmacologic method(s) would be most effective?

Dietary changes have been significantly related to decreased insulin resistance and body composition in patients with PCOS.[41]

The DASH diet was shown to be more effective in improving insulin sensitivity in PCOS, and calorie-restricted diets may be optimal for weight loss. Achievable goals such as 5% to 10% weight loss over 6 months in those with excess weight can have significant clinical improvements.[11] Lifestyle intervention (preferably including diet, exercise, and behavioral strategies) should be recommended in those with PCOS and excess weight, for reductions in weight, central obesity, and insulin resistance. A 5% to 10% weight loss in B.F. would be 9 to 18 pounds (4.08–8.16 kg) and may be achieved through a combination of calorie-restricted, healthy diet, and exercise. Weight reduction should be considered first-line therapy in all patients with PCOS who are overweight or obese, and this should be recommended for B.F.

EXERCISE

Exercise is a key component in the attainment and maintenance of weight loss. To prevent weight gain and maintain health, adults should exercise a minimum of 150 minutes per week of moderate-intensity physical activity or 75 minutes per week of vigorous intensities (or an equivalent combination of both), including muscle strengthening activities on 2 nonconsecutive days per week.[11] Adolescents should exercise at least 60 minutes per day with moderate-to-vigorous intensity physical activity with bone and muscle strengthening muscle at least three times weekly. For modest weight loss, preventing weight gain, and greater health benefits, a minimum of 250 minutes per week of moderate-intensity activities or 150 minutes per week of vigorous intensity (or an equivalent combination of both) with muscle strengthening on 2 nonconsecutive days per week is recommended. B.F. should increase her exercise to at least 150 minutes per week of moderate intensity for at least 3 days of the week. If she is going to continue walking as her exercise, she should walk at a brisk pace. Titrating her time to a goal of exercising 30 minutes daily will help her lose weight.

Pharmacologic Treatment

Case 50-1, Question 5: B.F. would like to improve her menstrual irregularity and be sure that she will not get pregnant. If possible, she would also like to minimize her hirsutism and acne. What options would be appropriate to recommend for B.F.?

Several different pharmacologic options could be recommended to B.F. (**Table 50-2**). Consideration of her personal characteristics, preferences, and values is important in recommending pharmacologic treatment. A COC will address her concerns about irregular menstruation, hyperandrogenism, and pregnancy prevention. An insulin sensitizer would improve her menstrual irregularity and possibly reduce her hirsutism and acne, but it does not address her desire to prevent pregnancy. An antiandrogen, such as spironolactone, would address only hyperandrogenism, and other agents would have to be used concurrently to address pregnancy prevention and the other hormonal and metabolic alterations in PCOS.

Table 50-2
Selected Treatment Options for Polycystic Ovarian Syndrome

Drug Class (Example)	Purpose of Therapy	Mechanism of Action	Effective Dose	Side Effects
Combined oral contraceptive (estrogen and progestin)	Menstrual cyclicity, hirsutism, acne	Suppresses LH (and FSH) and thus ovarian androgen production; increases sex hormone–binding globulin, which decreases free testosterone	One tablet orally daily for 21 (or 24) days, then 7-day (or 4-day) pill-free interval	Breast tenderness, breakthrough bleeding, mood swings, libido changes
Progestins (medroxyprogesterone)	Menstrual cyclicity	Creates withdrawal bleeding by transforming proliferative endometrium into secretory endometrium	5–10 mg orally daily for 10–14 days every 1–2 months	Breakthrough bleeding, spotting, mood swings
Biguanide (metformin)	Impaired glucose tolerance, type 2 diabetes	Decreases hepatic glucose production, secondarily reducing insulin levels; may have direct effects on steroidogenesis	1500 mg orally daily in divided doses (up to 2550 mg/day)	Gastrointestinal problems, diarrhea, abdominal pain
Antiandrogen (spironolactone)	Hirsutism, acne	Inhibits androgens from binding to androgen receptor	50–100 mg orally twice daily	Hyperkalemia, polymenorrhea, headache, fatigue
Aromatase inhibitor (letrozole)	Ovulation induction	Inhibits androgen-to-estrogen conversion to directly affect hypothalamic–pituitary–ovarian function and increase FSH secretion and ovarian follicle development	2.5 mg orally daily for 5 days; may increase to 7.5 mg	Nausea, headaches
Antiestrogen (clomiphene citrate)	Ovulation induction	Increases GnRH secretion, which induces rise in FSH and LH	50 mg orally daily for 5 days; may increase to 150 mg	Vasomotor symptoms, gastrointestinal problems

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

COMBINED ORAL CONTRACEPTIVES

Estrogen–progestin combination therapy with a COC is the treatment of choice for patients seeking regularity in menstrual cycles and relief from hyperandrogenic symptoms (see Chapter 47, Contraception, for a list of possible therapies). The estrogen component suppresses LH, resulting in a reduction of androgen production, and increases hepatic production of SHBG, thereby reducing free testosterone. The progestins in various COCs possess variable androgenic effects, so the choice of the COC may be considered to minimize androgenic exposure.

COCs therapy in PCOS should be initiated with a formulation that contains a low dose or very low dose of estrogen (20–30 μg of ethinylestradiol or equivalent) and a progestin informed by general population guidelines.[11] For B.F., a COC containing ethinylestradiol and desogestrel would prevent pregnancy, improve menstrual cycle regularity, and reduce her signs of hyperandrogenism (hirsutism and

acne). If B.F. desired monthly cycles, she could take the typical 21/7 regimen (21 days active pill, 7 days inactive pill) or a 24/4 regimen (24 days active pill, 4 days inactive pill). Although not specifically evaluated in patients with PCOS, a monophasic regimen may also be prescribed using extended cycles of 84 or even 365 days. Extended regimens reduce the number of cycles per year while providing contraception. Regardless of the COC selected, one of the long-term benefits is that her risk for endometrial cancer would be reduced by 30% to 50%, even up to two decades after discontinuation.[42] She should continue therapy for as long as she desires contraception and minimization of the androgenic effects of PCOS. Higher doses of ethinylestradiol (30–35 μg) may be needed for better suppression of ovarian androgens and management of hyperandrogenic features. Although transdermal or vaginal ring preparations are potential options, they have not been well studied in PCOS.

CASE 50-1, QUESTION 6: Two months later, B.F. reports she is experiencing mood swings and weight gain on her ethinylestradiol/desogestrel oral contraceptive. She is debating if she wants to continue with the COC and would like to explore other treatment possibilities. What other therapy options may be beneficial for B.F. if she considers this COC to be intolerable?

AGENTS FOR INSULIN RESISTANCE

Improving insulin sensitivity with insulin-sensitizing agents is associated with a decrease in circulating androgen levels, improved ovulation rate, and improved glucose tolerance. Metformin and glucagon-like peptide-1 (GLP-1) agonists appear to be the most promising agents for patients with PCOS. Thiazolidinediones have been evaluated, but they are not recommended in patients with PCOS who do not have diabetes because of limited clinical data, potential weight gain, and a possible association with cardiovascular adverse events.

Metformin

Metformin inhibits hepatic glucose output, providing lower insulin concentrations and reducing androgen production in the ovary. Metformin in addition to lifestyle could be recommended in patients with PCOS, especially those with BMI ≥25 kg/m^2 for the treatment of weight, hormonal, and metabolic outcomes.[11] Metformin has minimal effectiveness for hirsutism or acne. Metformin can be used in combination with COCs if desired goals are not being achieved.

The most commonly used and most effective dose of metformin in PCOS is 500 mg orally three times daily (tid). It should be titrated slowly to this effective dose; doses up to 2000 or 2550 mg daily may be necessary for individual circumstances. The gastrointestinal (GI) side effects of diarrhea, nausea, vomiting, and abdominal bloating are usually transient and dose related and can be minimized by taking with food instead. Renal function should be evaluated at least annually in patients using metformin because it is contraindicated in those with estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2 and is not recommended in patients with eGFR between 30 and 45 mL/minute/1.73 m^2.

Glucagon-like peptide-1 agonists

Although not specifically approved for PCOS, GLP-1 agonists such as exenatide and liraglutide have been evaluated in patients with PCOS. A meta-analysis showed that GLP-1 receptor agonists were significantly more effective than metformin in improving several key parameters in these patients.[43] Specifically, compared with metformin, GLP-1 receptor agonists were more effective in improving insulin sensitivity (standard mean difference [SMD] −0.40, 95% confidence interval [CI] −0.74 to −0.06, *P* = .02) and reducing BMI (SMD −1.02, 95% CI −1.85 to −0.19, *P* = .02) and abdominal girth (SMD −0.45, 95% CI −0.89 to −0.00, *P* = .05). GLP-1 receptor agonists were associated with a higher incidence of nausea and headache than metformin. GLP-1 agonists, with or without metformin, offer a unique opportunity to expand the treatment options available to patients with PCOS.

AGENTS FOR HIRSUTISM

Although frequently used, antiandrogens do not have FDA-approved uses for the treatment of female hirsutism or acne in the United States. Spironolactone is commonly prescribed to patients for hirsutism. Finasteride has been used for female hirsutism, but its lack of specificity for type I 5α-reductase in the pilosebaceous unit and toxicity may make this a suboptimal treatment choice. Flutamide is effective for hirsutism, but it is not used because of hepatotoxicity. These three agents have improved efficacy over placebo but are similar to each other.[44] Eflornithine hydrochloride has been approved for topical use in treating facial hirsutism but has not been well studied in patients with PCOS. Electrolysis and laser treatments may be acceptable physical approaches to hair removal for patients with PCOS.

Spironolactone

Spironolactone acts by competitively inhibiting dihydrotestosterone (DHT) from interacting with its androgen receptor. This causes a decrease in the activity of ovarian-produced testosterone. Treatment with 100 mg or rarely 200 mg of spironolactone for 6 to 9 months is very effective in reducing hair growth.[45] Spironolactone may be associated with possible teratogenicity (feminization of the male fetus), so it is prudent to advise patients to avoid pregnancy for at least 4 months after the discontinuation of spironolactone. It is recommended that spironolactone be used with a COC to avoid teratogenicity as well as the side effect of polymenorrhea (more frequent menses) when used as monotherapy. Spironolactone in combination with a COC would also improve hormonal and metabolic manifestations of PCOS as well. Serum potassium and renal function should be monitored because this aldosterone antagonist can cause hyperkalemia. Furthermore, spironolactone should not be used with a COC containing drospirenone because of potential risk for hyperkalemia.

Finasteride

Finasteride is a type II 5α-reductase inhibitor, which decreases the conversion of testosterone to DHT. Compared with spironolactone, finasteride is as effective in patients with hirsutism.[44] The dose of 5 to 7.5 mg orally daily typically takes 6 months for clinical improvement. It is critical to avoid pregnancy while taking this drug owing to the potential teratogenic effect of abnormal genitalia in the male fetus. Finasteride should not be touched or handled by patients who are or may be pregnant. This danger limits the usefulness of finasteride in patients with PCOS because most are of childbearing age or desire pregnancy.

B.F. should be encouraged to continue her COC for at least 3 months as most COC side effects resolve within 3 months of use. If B.F. decides that the side effects from the COC are intolerable, an appropriate recommendation for B.F. would be spironolactone 50 mg orally daily. She should continue this therapy for as long as she desires the benefits of this therapy, but it will not provide contraception. B.F. should ensure proper contraception is used while taking spironolactone to avoid teratogenicity.

CASE 50-1, QUESTION 7: B.F. successfully used oral contraceptives for 7 years. After getting married 2 years ago, B.F. and her husband have decided to have children. She lost 30 pounds (13.61 kg) with diet and exercise when she got married and has been able to maintain that weight loss. They have been trying to get pregnant for the last 18 months. The reason for infertility has been identified as oligo-ovulation associated with PCOS. What treatments for ovulation induction should be used in B.F. and why?

Anovulation or oligo-ovulation in patients with PCOS is usually first treated with diet, exercise, and weight reduction. Weight loss improves pregnancy rates and reduces miscarriage rates in patients with PCOS. B.F. has been successful at losing weight and now must consider agents for ovulation induction.

AGENTS FOR OVULATION INDUCTION

Letrozole

Although not approved by the FDA for this purpose, letrozole should be considered first-line treatment for ovulation induction in patients with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy, and live birth rates.[11,46] It is a highly selective aromatase inhibitor, preventing androgen-to-estrogen conversion and improving ovulation rates.[47] It appears beneficial over clomiphene citrate for ovulation rates and live birth rates likely because it does not block estrogen receptors in both central and peripheral target tissues, and normal central feedback mechanisms remain intact.[48,49] Although similar risk for twin gestation, another potential benefit for the use of letrozole is a lower risk of high-order multiple births compared to clomiphene citrate.[46,48]

The initial dose of letrozole is 2.5 mg once daily for 5 days, starting on day 3, 4, or 5 following menses or progestin-induced bleed, and the dose may be increased to 5 mg/day for 5 days in subsequent cycles if ovulation does not occur. The maximum dose is 7.5 mg/day, and letrozole has been used for up to five cycles.[46] If letrozole alone does not provide an adequate response, patients who received the combination of letrozole and CC had a statistically higher ovulation rate compared with those who received letrozole alone.[47]

Clomiphene citrate

Clomiphene citrate induces ovulation via an antiestrogenic effect on the hypothalamus. GnRH secretion is increased, which increases LH and FSH production. The increase in FSH concentrations causes appropriate follicle development and estrogen secretion, which produces a positive feedback on the hypothalamic–pituitary system to create an LH surge for ovulation. This often results in adverse events related to vasomotor symptoms and mood swings.

The usual initial dose of clomiphene citrate is 50 mg orally daily for 5 days, started on day 5 after a spontaneous or progestin-induced menses. The clinician must determine if ovulation occurs with each cycle through laboratory testing, ultrasound monitoring, or both. If ovulation does not occur, the dose can be increased by 50 mg orally daily up to 150 mg orally daily; however, doses >100 mg orally daily

for 5 days are not recommended. A repeat cycle can be administered as early as 30 days after the previous cycle as long as pregnancy has not occurred. If conception does not occur, patients can use clomiphene for three to four cycles before considering another regimen. Long-term cyclic therapy is not recommended beyond a total of six cycles because of potential ovarian cancer risk. For patients who do not respond to letrozole, clomiphene, or the combination, the recommended second-line intervention is either exogenous gonadotropins or laparoscopic ovarian surgery.[46] In vitro fertilization would be considered third-line therapy.[11]

Patients with PCOS exhibit unique clinical features and have individual concerns that should be addressed when making treatment recommendations. Assessment should include gathering relevant medical information, such as menstrual history, signs and symptoms of hyperandrogenism, time course of symptoms, weight history, previous agents tried, and family history. If PCOS is suspected, laboratory assessments should be performed to rule out any other related disorders. Once a diagnosis has been made with the appropriate phenotype identified, a recommendation about treatment must consider the patient's priorities and motivation. For B.F., letrozole would likely be the pharmacologic agent of choice. Ovulation induction and live birth occur in ~48% and 27% of patients with PCOS, respectively, using letrozole.[48] The initial dose would be 2.5 mg orally once daily for 5 days, started on day 3 after a spontaneous or progestin-induced menses. If nonresponse occurs, the dose may be increased by 2.5 mg and up to a maximum of 7.5 mg daily for 5 days on following cycles. Although side effects (eg, fatigue, dizziness) can occur, the benefit of this therapy outweighs the risk for B.F. Appropriate follow-up for B.F. should include quality-of-life measures, laboratory monitoring when necessary, and medication adherence monitoring. Providers should be educators, facilitators, and empathetic listeners to help patients with PCOS become informed and actively engaged in their therapy plan.

DYSMENORRHEA

Dysmenorrhea, or painful cramping that occurs with the onset and first days of menstruation, can be categorized as either primary (without underlying uterine pathology) or secondary (owing to underlying uterine pathology). Secondary dysmenorrhea can result from uterine conditions, including endometriosis, uterine polyps, or fibroids; complications of intrauterine device (IUD) use; or pelvic inflammatory disease.

Up to 90% of adolescents report some pain with menstruation, and up to 15% experience pain that is sufficiently severe and disabling to interfere with activities of daily life.[50] Dysmenorrhea is the single largest cause of lost productivity and school absence among adolescent girls. It most commonly begins within 1 to 2 years after the onset of menses, and up to 91% of adult patients report some pain with menses, of which up to 28% experience severe pain and/or limitation of activity.[51]

Clinical Characteristics

CASE 50-2

QUESTION 1: A.B., a 15-year-old female, presents at the pharmacy with her father with severe cramping pain associated with her menstrual cycles. The pain predictably begins with the onset of menses and has been occurring for the past 4 years but is now limiting A.B.'s ability to play sports. A.B. states that she experienced her first menstrual period at age 11. The pain usually is "like a fist, clenching and relaxing," and it starts in the pelvic area, and radiates to her lower back. She reports no headache, but usually has diarrhea and some nausea, without vomiting. Her symptoms are most severe during the first 12 to 24 hours of her menses, then subside during the next few days. She usually takes two acetaminophen 325-mg tablets when her pain begins and then one tablet every 4 to 6 hours, as needed, with little relief. She has taken no other medications for her symptoms, has no known allergies to medications, and is not taking any other medications. She has no other medical problems. Her social history is significant for occasional social use of nicotine vapes. A recent physical examination was within normal limits.

Which of A.B.'s symptoms are consistent with primary dysmenorrhea?

No specific diagnostic criteria exist for primary dysmenorrhea. Typically, the diagnosis is one of exclusion and is based on response to known effective therapy. If patients do not respond to therapy, an investigation of pelvic pathology and secondary dysmenorrhea should occur.[52] A.B.'s symptoms that are typical of primary dysmenorrhea include cramping pain in the suprapubic area, which may radiate into the back and thighs, nausea, and diarrhea. Some patients also experience vomiting, fatigue, headache, lightheadedness, flushing, loss of appetite, irritability, nervousness, and insomnia.[52] Symptom severity seems to correlate with patients who have early menarche (onset of menses before age 12) and those with increased duration and quantity of menstrual flow.[50] Risk factors for dysmenorrhea include age younger than 20 years, depression or anxiety, perceived high life or work stress, nulliparity, menorrhagia, and smoking.[50,51]

Primary dysmenorrhea occurs only with ovulatory cycles, which typically begin after the first year following menarche. Dysmenorrhea occurring several years after menarche is most likely secondary dysmenorrhea. Because A.B.'s pain began within 1 year of menarche and her physical examination is normal, a treatment trial can be initiated without further investigation into the secondary causes of dysmenorrhea. The typical pattern of dysmenorrhea is to have pain beginning up to 12 hours before menses, increasing in severity for up to 24 hours, and continuing with reduced intensity for 24 to 72 hours.[52] A.B.'s description of pain, as a cramping–relaxing cycle, as well as the timing of the onset of pain in relation to her menses is typical for dysmenorrhea. Likely, her symptoms will decrease with age, after the onset of sexual activity, and after childbirth.[50]

Pathophysiology

Case 50-2, Question 2: What underlying pathophysiology explains A.B.'s symptoms and guides us to rational pharmacotherapy?

In the normal menstrual cycle, prostaglandins are released by the endometrium in the late luteal phase inducing contraction of the uterine smooth muscle and subsequent sloughing of the endometrium, leading to menstrual flow and the beginning of the follicular phase of the next cycle. Patients with primary dysmenorrhea appear to have increased prostaglandin secretion, inducing more intense uterine contractions, leading to decreased uterine blood flow and uterine hypoxia, which results in cramping and pain that are the hallmarks of dysmenorrhea.[52] The decreasing levels of progesterone in the late luteal phase trigger the release of arachidonic acid from cell membranes, ultimately resulting in the production of prostaglandins and leukotrienes.[50,52]

The importance of prostaglandin secretion in the pathology of primary dysmenorrhea is confirmed by studies of the exogenous administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and PGE_2, each of which produce pain and uterine contractions similar to those observed in patients with primary dysmenorrhea.[53] These prostaglandins, with potent platelet disaggregation and vasodilatory properties, also induce nausea, vomiting, and diarrhea. Thus, A.B.'s pain, nausea, and diarrhea may be caused by elevated prostaglandin levels. This also explains the rationale for the effectiveness of the two main treatments for primary dysmenorrhea: nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis, and hormonal contraceptives, which minimize the progesterone increase typically seen in the luteal phase.

Nearly 85% to 90% of patients initially thought to have primary dysmenorrhea respond to NSAIDs with or without oral contraceptive therapy. The remaining patients deserve further investigation into potential causes of secondary dysmenorrhea.

Treatment

NONPHARMACOLOGIC TREATMENT

Case 50-2, Question 3: What nonpharmacologic therapies may be effective for the treatment of A.B.'s symptoms of primary dysmenorrhea?

A.B. should be educated about the causes of primary dysmenorrhea, its associated symptoms, and the rationale behind nonpharmacologic and pharmacologic treatment options. Nonpharmacologic therapies that may have benefit in the relief of A.B.'s symptoms include aerobic exercise, yoga, heat therapy, and tobacco cessation.

Exercise, particularly aerobic exercise, has been correlated with decreased menstrual pain and pain intensity in observational and randomized studies, and is, in all patients, associated with positive general health benefits.[54] In addition, yoga has demonstrated benefit in the reduction of pain and pain intensity in patients with dysmenorrhea.[55] The benefit may be because of improved pelvic blood flow and decreased ischemia or increased release of β-endorphins. Application of local heat to the lower abdomen has been studied in three well-designed clinical trials.[56–58] Heat plus ibuprofen (400 mg orally tid) demonstrated a reduction in the time to pain relief compared with an unheated patch plus ibuprofen in two controlled studies.[56–58] With few adverse effects, heat, in the form of a heating pad or heated patch or wrap device, and exercise (aerobic or yoga) represent reasonable and safe suggestions for patients with dysmenorrhea.

Patients should be advised and assisted in efforts to discontinue tobacco use as there is an association with increased risk and severity of dysmenorrhea in patients who smoke.[50] There is no solid evidence to recommend any specific dietary supplements or vitamins to alleviate menstrual pain.[59]

A.B.'s treatment plan should be based on her specific symptoms, response to previous therapy, and any adverse effects of therapy. The regimen of acetaminophen that A.B. is currently using is not providing relief owing to its relative lack of effect on prostaglandin

activity. For A.B., discussion of the nonpharmacologic therapies, particularly continuous low-level heat applied at onset of symptoms, exercise/yoga, and smoking cessation, provide low-risk, potentially beneficial, and low-cost suggestions for pain relief, in addition to drug therapy. A.B. should be informed that continuous heat therapy via heat "wraps" or hot water bottle or heating pad should not be used while sleeping.

CASE 50-2, QUESTION 4: A.B. states that her pain is decreased about 50% with the use of a heating pad and heat wraps, but she finds them bulky and hard to use when she is not at home. She asks about the use of Midol™. What would be effective over-the-counter (OTC) pharmacologic options for A.B.?

Although nonpharmacologic therapy with heat, exercise, and smoking cessation may have benefit, often the use of pharmacologic therapies is required to further improve functionality.

OVER-THE-COUNTER PHARMACOLOGIC THERAPY

OTC pharmacologic therapy for primary dysmenorrhea is focused on reducing prostaglandin activity. Anti-inflammatory drugs act by directly inhibiting prostaglandin synthesis. NSAIDs provide relief from the symptoms of primary dysmenorrhea for most patients (see Case 50-2, Question 5, for further information). Naproxen (as the sodium salt) and ibuprofen are approved without a prescription for the treatment of primary dysmenorrhea. Acetaminophen is of limited efficacy in the treatment of dysmenorrhea when compared with NSAIDs or hormonal contraception.

Other therapies, including OTC products marketed for dysmenorrhea and other menstrual disorders (eg, Pamprin, Midol) are combination products that may include weak muscle relaxants (such as pyrilamine, pamabrom), diuretics (caffeine), and acetaminophen, all of which have limited efficacy for the specific treatment of dysmenorrhea. Because they do not address the underlying pathophysiology of primary dysmenorrhea, OTC combination products, narcotic analgesics, and acetaminophen do not have a role in the treatment of primary dysmenorrhea, and

combination products, in particular, may have excessive adverse effects with minimal benefit.

Adolescents with dysmenorrhea frequently use OTC medications to treat primary dysmenorrhea, usually without consultation from a health care professional.[60] This lack of professional advice results in the use of lower doses that may not be as effective to treat symptoms. Many patients choose ineffective combination medications and/or acetaminophen, indicating patients would benefit from pharmacist advice regarding OTC treatments of dysmenorrhea.[60] Ibuprofen 200 to 400 mg orally up to three times daily is a reasonable initial plan for A.B.'s dysmenorrhea.

Prescription pharmacologic agents: nonsteroidal anti-inflammatory drugs

Case 50-2, Question 5: A.B. has tried ibuprofen 400 mg tid starting at onset of her cramping symptoms but has not had optimal relief. A.B. presents to her family physician for an evaluation. What prescription medications could be recommended for A.B.'s dysmenorrhea?

The NSAIDs are effective for treatment of dysmenorrhea, but in some cases, OTC doses are not adequate and prescription-strength NSAIDs or hormonal contraceptives may be required for improved relief. Hormonal contraceptives reduce the amount of endometrial proliferation and, as a result, decrease the amount of prostaglandins secreted. By inhibiting ovulation, hormonal contraceptives eliminate the cyclic changes in progesterone that induce prostaglandin release. Choice of therapy depends on the need for contraception, concomitant medical conditions, and preference of the patient. Treatment efficacy can be monitored by evaluating pain relief, improved functionality, reduced absenteeism, and relief of other symptoms (eg, diarrhea, nausea) associated with dysmenorrhea. Prescription-strength NSAIDs should be tried for two to three cycles before switching to other agents.

Initial selection of NSAID therapy should be based on effectiveness, incidence of adverse effects, cost, patient history of previous benefit, and availability. In a Cochrane review, 80 trials of NSAIDs for treatment of primary dysmenorrhea were reviewed to assess for any differences in efficacy or safety among the different NSAIDs.[61] When compared with placebo, NSAIDs were significantly more effective (OR, 4.50; 95% CI, 3.85–5.27). When compared with acetaminophen, NSAIDs were, as expected, significantly better at reducing symptoms (OR, 1.90; 95% CI, 1.05–3.44). In limited head-to-head trials comparing NSAIDs, no significant differences in efficacy were seen, with the exception of aspirin being slightly less effective than other NSAIDs when directly compared. Adverse effects seen in these trials were generally mild GI (nausea, upset stomach) and neurologic (sleepiness, dizziness, headache) symptoms.

Some data suggest that an oral loading dose of naproxen sodium (550 mg) might improve pain control in dysmenorrhea.[50] Loading doses generally are twice the regular dose. If A.B. experienced adverse effects with the higher loading dose, an alternative strategy is to initiate dosing 24 hours before menses is expected to start, based on the calendar if the patient has predictable cycles, or based on the start of premenstrual-syndrome–type symptoms. This prophylactic dosing may be helpful, especially for patients who have severe dysmenorrhea with absenteeism and decreased work or school productivity.[61] Although no specific evidence supports the use of scheduled NSAID dosing regimens, avoiding as needed (PRN) dosing may provide consistent serum levels to maintain reduced prostaglandin levels. As the duration of therapy is typically limited to 2 or 3 days, risk of adverse effects is outweighed by the potential benefit of loading doses, prophylactic dosing, and scheduled versus PRN therapy.

The next step for A.B. could include initiating naproxen sodium 550 mg orally at the beginning of menses, followed by 275 mg every 8 hours thereafter for the 2 to 3 days she experiences cramping.

Adverse Effects

Case 50-2, Question 6: What adverse effects might A.B. experience from her NSAID?

All NSAIDs have a similar adverse effect profile. Nausea, vomiting, indigestion, anorexia, diarrhea, constipation, abdominal pain, melena, and bloating are common GI symptoms.

Careful attention should be given to previous trials of NSAIDs for dysmenorrhea and other conditions, because patients may respond favorably to one NSAID over another. If a 2- or 3-month trial at appropriate doses of one NSAID is unsuccessful for A.B., another agent from a different chemical class may be tried. Because dysmenorrhea is most prevalent in younger patients who tend to be healthy, the risk of adverse events may be lower than would be expected in an older population.

Contraindications

Case 50-2, Question 7: What medical history information is important to collect to avoid serious adverse effects with NSAIDs?

A.B. should be questioned about medication allergies and any prior history of ulceration or GI bleeding; a history of cardiovascular and renal disease, although uncommon in young patients, should be elicited before prescribing therapy. A thorough medication history, including OTC agents and dietary supplements, is important. Particular attention should be paid to any potential therapeutic duplications (eg, prescription and OTC NSAIDs), drug–drug (eg, warfarin), and drug–disease (hypertension) interactions.

Patients who are allergic to aspirin or have a history of allergic reaction to any NSAID should not use NSAIDs. A.B. has not had a previous allergic reaction to NSAID or aspirin; she is not taking any medications that may interact and does not have any history of

medical problems that would prevent her from a trial of NSAID therapy.

Hormonal contraception

Oral Contraceptives

Case 50-2, Question 8: After 6 months of treatment, A.B. has some relief from her pain, nausea, and diarrhea with the naproxen sodium, but is unhappy with the amount of time that she is spending at home because of menstrual cramps. She is asking about other treatment options for further pain relief. What other options are available for A.B.?

As mentioned previously, hormonal contraceptives may be an option for A.B. if prescription NSAIDs are not adequate for her symptoms. Oral contraceptives (OCs) suppress ovulation, decrease menstrual fluid volume, and decrease prostaglandin production and uterine cramping.[50,52] OCs alone, or in combination with an NSAID, are appropriate as first-line treatment in patients with or without a need for contraception.[50,52] OCs relieve dysmenorrhea symptoms in 50% to 80% of patients within 3 to 6 months after beginning hormone therapy.[62] A Cochrane review of OCs and primary dysmenorrhea found OCs containing <35 µg of ethinylestradiol to be effective at reducing pain but failed to demonstrate a significant difference between various 35-µg ethinylestradiol OC formulations.[62] Selection of an OC should be based on factors presented in Chapter 47, Contraception. A continuous versus cyclic regimen of administration may result in a reduction in days in pain.[63] This reduction may not be sustained over time, as a randomized controlled trial evaluated the use of continuous dosing of OCs compared to the traditional 21 active days, 7 placebo days regimen, with an initial benefit in favor of decreased pain in the continuous dosing group at 1 and 3 months that was lost after 6 months of use.[64]

Adverse effects and contraindications associated with OC use must be considered (see Chapter 47, Contraception). Although serious complications from OC use are uncommon in young, healthy

patients, breakthrough bleeding and spotting, nausea, and breast tenderness may occur, especially early in treatment. A.B. may choose to add an OC to her naproxen sodium, with potentially improved pain relief compared with either agent alone. Pain that does not respond to either course of therapy, investigation for causes of secondary dysmenorrhea would be appropriate.

Other Hormonal Contraceptive Agents

Other hormonal contraceptive agents that suppress ovulation have also been used in the treatment of primary dysmenorrhea, although none have undergone rigorous trials for this indication.[50] The levonorgestrel intrauterine system (IUS) is associated with amenorrhea and a reduction in dysmenorrhea over time, unlike the copper IUD, which may result in increased pain, cramping, and blood loss. Three years after insertion, fewer patients with a levonorgestrel IUS reported menstrual pain (60% baseline, 29% after 3 years), with 47% of patients with amenorrhea.[65] In patients with primary dysmenorrhea who desire long-term contraception or who have contraindications to estrogen, the levonorgestrel IUS would be a reasonable option.

Medroxyprogesterone depot injection is another hormonal contraceptive agent that has been used to treat primary dysmenorrhea. Negative effects of medroxyprogesterone injections on bone density and body weight should be balanced with potential benefit when considering this option (see Chapter 47, Contraception). Progestin contraception implants represent another option, without the effect on bone density or weight.[50,52] Given that A.B.'s past history does not include any absolute contraindications to COCs and her dysmenorrhea symptoms have not been well-controlled with prescription NSAIDs, she is a candidate for combined hormonal contraception. A trial of COCs would be an appropriate plan for better control of her dysmenorrhea. She should be counseled that hormonal contraceptives may require 3 or more months to provide maximal relief of symptoms. The goals of therapy, namely, reduction in pain and associated symptoms, as well as

improvement in functionality, should be explained to A.B. and reviewed at each contact.

ENDOMETRIOSIS

Endometriosis is a chronic inflammatory disorder characterized by the presence of functional endometrial tissue occurring outside the uterus. It is the most common cause of secondary dysmenorrhea in young patients and can result in chronic pelvic pain, infertility, and dyspareunia.[52,66] The ovaries are commonly the site of endometriosis, which can also be found in the pelvic peritoneum, cervix, vagina, vulva, rectosigmoid colon, and appendix.

Less common sites of implantation of endometrial tissue include the umbilicus, scar tissue resulting from surgery, kidneys, lungs, and even arms and legs.[66] Endometriosis is present in up to 47% of patients with infertility. Overall, it is difficult to determine the prevalence of endometriosis, because many patients do not experience symptoms or seek treatment, and formal diagnostic criteria currently require visual identification of endometrial tissue during surgery. In patients who have laparotomies for any reason, endometriosis is identified in 5% to 15%. This increases to 33% in patients with chronic pelvic pain.[67] In contrast to primary dysmenorrhea, endometriosis usually occurs in patients who have been menstruating for some time; with pain occurring anytime throughout the cycle. Endometriosis symptoms are rarely seen in patients near the menarche, after menopause, or in amenorrheic patients. The average age at diagnosis is 28 years, and even, before diagnosis, patients with endometriosis have higher health care costs and utilization, particularly emergency room utilization, than age-matched controls.[66,68]

Diagnostic Criteria

Diagnosis of endometriosis is difficult, with a delay in diagnosis in the range of 8 to 12 years from initial symptom presentation.[69] Endometriosis, interstitial cystitis, irritable bowel syndrome, and pelvic adhesions represent the four most common causes of chronic pelvic pain (defined as pain not associated with the menses, severe in nature, resulting in functional disability, and lasting at least 6 months).[67,69] The delay in diagnosis is the unfortunate consequence of the lack of diagnostic biomarkers and its similarities to other conditions. There are at least two international and five national guidelines for the diagnosis and treatment of endometriosis, and they are inconsistent in many of their recommendations for diagnosis.[70] The physical examination is often normal, although the most common physical finding is a fixed retroverted uterus, with scarring and tenderness. A definitive diagnosis is only possible with visualization of endometriosis on laparoscopy, although this is not considered as absolutely necessary today as it has been in the past.[69] Although no diagnostic criteria currently exist, endometriosis can be staged at the time of laparoscopy according to the Revised American Fertility Society Classification of Endometriosis.[70,71] The stages are classified as minimal (stage I), mild (stage II), moderate (stage III), and severe (stage IV), as determined by an accumulated point total, with points based on the location of the endometrial lesions, the size of the lesions, the presence and extent of the adhesions, and the degree of obliteration of the posterior cul-de-sac. The classification system is designed to document the location and extent of endometriosis and does not predict infertility, aid in treatment selection or outcomes, or predict recurrence of the disease. Making diagnosis and prognosis even more challenging is that reported severity of pelvic pain and level of functional disability are not correlated to the stage of endometriosis.[66,67]

Pathophysiology

Although the first description of endometriosis was made in the 1860s, the precise etiology of endometriosis remains a mystery.

Several theories exist regarding the origins of endometriosis, and the exact etiology is probably a complex interplay between physical and individual patient-specific immunologic factors.[66,67]

The most commonly cited theory is that of retrograde menstruation or the flow of menstrual fluid, endometrial cells, and other debris backward through the uterine (fallopian) tubes, resulting in implantation in the peritoneal cavity. Once endometrial cells reach the peritoneum, stimulated angiogenesis (potentially by estrogen, among other factors) appears to be a determinant of the development and growth of lesions.[66,72] Also at this point, the lesion stimulates an immune response, triggering the activation of macrophages, as well as cytokine and growth factor release. Peritoneal lesions may contribute to more distant disease by spread via hematogenous or lymphatic routes, or even by movement owing to iatrogenic causes, such as cesarean section and other forms of gynecologic surgery. Although the retrograde menstruation theory makes scientific sense, it has been discovered that retrograde menstruation occurs in nearly all patients who are menstruating (90%), and not all patients have endometriosis. This suggests that an additional factor, such as genetic susceptibility or altered immunity, or altered hormone receptor functioning such as progesterone resistance, must be present for the pathogenesis of endometriosis in certain patients.[72]

Another theory for the etiology of endometriosis is the coelomic metaplasia theory. This theory rests on the belief that the coelomic epithelium, the fetal originator tissue for the reproductive tract, retains its ability to differentiate into multiple cell types.[66,67] The trigger for differentiation is thought to be, in part, estrogen or environmental factors. This theory would explain the presence of endometriosis in prepubertal girls, in females born without a uterus, and in the rare cases of endometriosis seen in males. Genetics also plays a role in the development of endometriosis. For first-degree relatives of females with severe endometriosis, there is a six times higher rate of developing endometriosis when compared with females who do not have affected relatives. These patients also have more severe disease and disease that appears earlier in life.[69]

More than 15 different gene and gene-product abnormalities have been documented in patients with endometriosis, although currently no genetic tests or any biomarker tests are predictive or used clinically for the diagnosis of endometriosis.[67,70]

Once endometrial tissue becomes implanted, hormones are necessary for their continued growth. As with intrauterine endometrium, the implants of endometriosis possess estrogen, progesterone, and androgen receptors. The endometrial implants may, however, respond differently to hormonal stimulation than normal endometrium. In general, estrogens stimulate the implants, whereas androgens or lack of estrogen results in implant atrophy. Because of their complex hormonal effects, progestins have variable effects on the implants.[73] In addition, lesions also show high levels of estrogen biosynthesis, owing to abnormally increased aromatase activity, with a concomitant decrease in the inactivation of estrogen, resulting in high intralesional estrogen concentrations.[73] The responsiveness of endometrial implants to ovarian hormones plays a role in the pathology of endometriosis. Withdrawal of estrogen and progesterone causes the endometrial implants to bleed, leading to an inflammatory response in the adjacent tissues. Repetitive cycles of bleeding and inflammation lead to the development of scar tissue and adhesions between adjacent peritoneal tissues. On laparoscopy, these areas of involvement appear as multiple hemorrhagic foci composed of endometrial epithelium, stroma, and glands. Ovarian endometriosis usually involves the formation of endometriomas, blood-filled cysts (“chocolate cysts”) ranging in size from microscopic to 10 cm. Nodules may form on uterosacral ligaments. Fibrosis usually is present with the endometrial implants, and extensive adhesions may form between pelvic structures.

Clinical Characteristics

CASE 50-3

QUESTION 1: N.H. is a 35-year-old female who has been married for 6 years and is currently using COCs pills taken 21 days per month to prevent pregnancy. She and her spouse have been contemplating the timing of a pregnancy but have not yet attempted to become pregnant. She presents to her gynecologist to discuss preconceptual planning and reports that she has been having severe lower abdominal cramps, associated with her menses, occurring on day 1 and lasting until day 4 or 5. This has been occurring for the past 4 years after many years of pain-free cycles when she was using a levonorgestrel intrauterine device for contraception and has recently been increasing in severity. The pain is slightly relieved by ibuprofen 400 mg orally tid, and during the past 6 months, she has had to work from home at least 1 to 2 days per month owing to pain that has been increasing in frequency. On further questioning, she also reports mild-to-moderate pain that occurs randomly in her cycle, associated with low-back pain, constipation with painful defecation, and pain with intercourse. Her menstrual history reveals menarche at age 10 with regular cycles every 26 to 27 days and heavy menses for 6 to 7 days. She reports discussing her symptoms with her mother, who described similar symptoms during her childbearing years.

N.H. is 67 inches (170.18 cm) and weighs 145 pounds (65.77 kg). She does not smoke and does not drink alcohol. She plays recreation league basketball and softball but does not have a regular exercise regimen. She usually eats five servings of fruits or vegetables per day, but does not like to drink milk. She is concerned about her heart because her father had a cardiac stent placed at age 40, and she has been told she has high cholesterol.

Her physical examination is normal, with the exception of tenderness on palpation of the posterior fornix, and a fixed retroverted uterus. A pregnancy test, and tests for gonorrhea and chlamydia, HIV and hepatitis C, are negative, and a Pap smear is within normal limits.

What subjective and objective data in N.H.'s presentation are compatible with a diagnosis of endometriosis?

A patient presenting with endometriosis may have signs and symptoms that are difficult, initially, to distinguish from primary dysmenorrhea (**Table 50-3**).[66,67] N.H.'s symptoms of lower abdominal cramps accompanying her menses are often mistaken for primary dysmenorrhea when other history details are not evaluated in total. Another key detail is emergence of increased symptoms after stopping her IUD and starting a cyclic regimen of combined hormonal contraceptive pills. N.H.'s age and her nulliparity are consistent with the characteristics of patients with endometriosis. Although endometriosis has been diagnosed in patients of all ages, it

most commonly occurs in patients in their late 20s and early 30s who have delayed pregnancy or who have infrequent pregnancies. On average, patients with endometriosis have seen seven physicians for their symptoms prior to being diagnosed with endometriosis.[67]

Table 50-3
Primary Versus Secondary Dysmenorrhea

Characteristic	Primary Dysmenorrhea	Secondary Dysmenorrhea
Onset	Around menarche	Any age (while menstruating)
Timing in menstrual cycle	Worse on day 1, lasts 24–48 hours	Increases in severity, may last days
Change over time	Stable, predictable	Increasing pain with increasing age
Symptoms	Low-back pain, premenstrual syndrome, nausea, bloating	Low-back pain, dyspareunia, diarrhea or constipation, dysuria, infertility
Signs	Normal pelvic examination	Fixed retroverted uterus, tenderness, but may be completely normal

Adapted with permission from Reddish S. Dysmenorrhea. *Aust Fam Physician*. 2006;35(11):842–849.

N.H.'s menstrual pattern of short cycle length with prolonged flow is characteristic of patients with endometriosis. Risk factors for endometriosis are related to exposure to estrogen (ie, early menarche and late menopause) and shorter menstrual cycle length (<28 days) with longer duration of menstrual flow (≥6 days), as well as having a mother or sister with endometriosis, as may be true with N.H.'s mother.[74] Patients who have four or more pregnancies lasting more than 6 months have a 50% lower risk of being diagnosed with endometriosis, and there is a decrease in risk of endometriosis that is parallel to duration of time spent in breast-feeding.[74] Regular physical exercise appears to be protective.[67]

N.H.'s chief problems center on her progressive pelvic pain occurring throughout the cycle, with worsening during menses,

constipation, and pain with intercourse (dyspareunia). Patients who report deep pain during intercourse may have a fixed, retroverted uterus (as N.H. does) or endometriosis located in the posterior fornix of the vagina or along the uterosacral ligaments.[66,69] This pain may persist for several hours after intercourse. Other symptoms such as the constipation and painful defecation N.H. is experiencing are associated with endometriosis and may (but not always) depend on the organs affected by the location of the endometrial tissue (**Table 50-4**).[67] Depression also is a common symptom in patients with endometriosis, particularly those with chronic pelvic pain, and may express as sadness, somatic symptoms, and inability to work or carry on activities of normal living.[69]

Table 50-4

Location of Endometriosis and Associated Symptoms

Sites	Symptoms
Pelvic	
Cervix	Abnormal uterine bleeding
Ovaries	Dysmenorrhea
Peritoneum	Dyspareunia
Rectovaginal septum	Infertility
Uterosacral ligaments	Pelvic pain
Intestinal	
Abdominal scars	Intestinal obstruction
Sigmoid colon	Midabdominal pain
Small intestines	Nausea
	Painful defecation
	Rectal bleeding
Urinary Tract	
Bladder	Cyclic flank pain
Ureter	Hematuria
	Hydronephrosis

Sites	Symptoms
	Hydroureter

Source: American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 114: management of endometriosis. *Obstet Gynecol.* 2010;116:223–236.

Although it is unclear yet whether infertility will be a problem in N.H., endometriosis occurs in up to 47% of patients with infertility.[66] The cause of endometriosis-associated infertility is not clear, but is probably caused by a combination of factors, which may include physical distortion of the pelvic architecture, inflammatory factors (including prostanoids, cytokines, and growth factors that may interfere with normal reproductive processes), impaired folliculogenesis (follicle development), or defects in fertilization or implantation.[66] Treatment for endometriosis, in inducing a "pseudomenopause," results in impaired fertility while the disease is actively being treated.

N.H.'s limited physical findings are not uncommon in patients with endometriosis; physical findings, other than visualization of endometrial tissue during exploratory surgery, may not be present, and outward physical findings may have no correlation with the stage of endometriosis determined with surgery. Many symptoms and physical findings of endometriosis can be associated with other gynecologic conditions or diseases (particularly irritable bowel syndrome), and, if the patient is not responsive to empiric therapy, laparoscopy is indicated to confirm the diagnosis. N.H.'s negative pregnancy, HIV, hepatitis c, chlamydia, and gonorrhea tests, as well as her normal Pap smear, are reassuring. Although many biomarkers have been and are being studied, none have demonstrated sufficient sensitivity and specificity to be clinically useful.[70]

Treatment

CASE 50-3, QUESTION 2: N.H.'s pain is uncontrolled after trials of three different NSAIDs (ibuprofen, naproxen, and meloxicam) and she would like relief to improve her functionality at work and home. Given the potential mechanisms behind the pathophysiology of endometriosis, what therapeutic approaches are appropriate for the treatment of endometriosis in N.H.?

Therapy for endometriosis should be individualized and consider N.H.'s desire for future fertility, severity of symptoms, extent of disease, and potential for infertility. This should be done with the knowledge that a high likelihood exists of recurrence and a lack of good prognostic indicators for future severity. The goals of treatment are to relieve symptoms and, if desired, to preserve or improve fertility. Options currently available to treat endometriosis include definitive and conservative surgery, hormonal therapy with estrogen–progestin combinations used continuously or progestins, including IUDs alone, danazol, aromatase inhibitors, GnRH agonists, GnRH antagonists, and expectant management. Pharmacologic treatment of endometriosis is based on manipulation of this hormonal response: danazol, GnRH agonists, GnRH antagonists, progestins, aromatase inhibitors, and estrogen–progestin combination all result in endometrial tissue atrophy. No treatment has been shown to provide 100% protection against recurrence when discontinued; even surgical removal of the uterus and ovaries is associated with recurrence rates of up to 10%.[66] Two international and five national guidelines for treatment are available, and they are generally limited by the poor quality and limited depth of evidence for most treatments; and there are significant differences in the recommendations in the various guidelines, with little homogeneity.[70,75]

PAIN MANAGEMENT: PHARMACOLOGIC THERAPY

Nonsteroidal anti-inflammatory drugs

NSAIDs, particularly those available as OTC products, are often the first medications that patients try for relief of pain from endometriosis, often before they are officially diagnosed. NSAIDs

may provide some relief of mild symptoms, particularly in patients with endometriosis who have pain associated with the menses (see Dysmenorrhea section) and are an appropriate first choice for patients with mild symptoms who do not desire contraception. They should not be the only therapy offered to patients with confirmed endometriosis, as evidence supporting their benefit for endometriosis pain is limited.[76] Clinicians should be aware of and consider the potential for endometriosis in patients with noncyclic pain, including pain that does not respond to an appropriate trial of an NSAID. N.H. has tried three different NSAIDs with limited relief; a higher dose or trial of another NSAID is not an appropriate strategy at this time. Additional treatment should be considered.

Combined hormonal contraceptives

For patients who do not receive pain relief from a trial of an NSAID, a reasonable next step for those patients desiring contraception is the use of combined hormonal contraceptives (pill, patch, ring). They may be used alone or in combination with NSAIDs. Combined contraceptives improve symptoms of endometriosis by inhibiting ovulation, decreasing hormone levels, reducing menstrual flow, potentially to the point of amenorrhea. These mechanisms contribute to atrophy of endometrial implants. When used, the most appropriate regimen is continuous dosing, so that there is not a “placebo week” that allows for growth of endometrial implants.[77] A Cochrane review found that the pain reduction seen with OCs (≤35 μg of ethinylestradiol) is similar to a GnRH analog (goserelin).[76] After surgery, continuous regimens appear to provide better pain symptom control than cyclic regimens.[78]

Progestins

Similar to OCs, injectable, oral, implantable, and IUD progestins reduce symptoms of endometriosis by inhibiting ovulation, reducing hormone levels, and inducing endometrial atrophy. They may be particularly useful if estrogen use is contraindicated. Regimens used include oral medroxyprogesterone, depot medroxyprogesterone (see

Case 50-3, Question 4), etonogestrel implants, or levonorgestrel IUDs. Several studies have evaluated the use of the levonorgestrel IUDs as a means of providing consistent progestin dosing. Levonorgestrel IUDs have the advantage of providing longer-term contraception than other available progestin-only contraceptives. A meta-analysis evaluated the efficacy of levonorgestrel IUD 52 mg as postoperative maintenance therapy for endometriosis, compared to danazol, GnRH agonists, and OCs, and found pain relief comparable to GnRH agonists, and decreased recurrence similar to OCs and danazol, with improved patient satisfaction compared to OCs.[79] A 3-year direct comparison of the levonorgestrel IUS versus depot medroxyprogesterone was conducted in patients with moderate-to-severe endometriosis for medical control of symptoms after conservative surgery.[80] Although symptoms were improved with both regimens, more IUS patients remained adherent to the regimen, and at 3 years, bone density was increased in the IUS group and decreased in the depot group.

Gonadotropin-releasing hormone agonists

GnRH agonists induce a pseudomenopausal state, resulting in the relief of endometriosis symptoms. Because the GnRH agonists have a longer half-life than endogenous GnRH, their binding to GnRH receptors in the pituitary results in downregulation of the hypothalamic–pituitary–ovarian axis, decreasing release of FSH and LH, leading to low estrogen levels and amenorrhea.[73] GnRH agonists are available in a variety of dosage forms, outlined in **Table 50-5**. When compared in clinical trials, GnRH agonists have efficacy that is similar to OCs, progestins, and danazol, but their increased cost and adverse effect profile (including menopausal-type symptoms and decreased bone density) make them second-line agents, after OCs and progestins.[81,82] In addition, because they initially cause an increase in release of FSH and LH, they can provoke an initial worsening of symptoms, followed by improvement of symptoms as the GnRH receptors become desensitized, resulting in complete suppression of estradiol.

Table 50-5
Gonadotropin-Releasing Hormone Agonists and Antagonist

GnRH Analog (Brand Name)	Strength	Dosage Form	Dosage Regimen
Nafarelin (Synarel®) (agonist)	2 mg/mL delivers 200 µg/spray	Intranasal	200–800 µg bid
Leuprolide (Lupron®) (agonist)	3.75 mg, 11.25 mg	IM depot	3.75 mg/month or 11.25 mg every 3 months
Goserelin (Zoladex®) (agonist)	3.6 mg, 10.8 mg	SC implant	3.6 mg implant every month or 10 8 mg implant every 3 months
Elagolix (Orilissa®) (antagonist)	150 mg, 200 mg	Oral tablet	150 mg once daily for up to 24 months 200 mg twice daily for up to 6 months

Bid, twice daily; GnRH, gonadotropin-releasing hormone; IM, intramuscular; SC, subcutaneous.

Gonadotropin-releasing hormone antagonists

GnRH antagonists (eg, elagolix) work similarly to GnRH agonists with a few key differences. The antagonists immediately block and result in complete suppression of the GnRH receptor, which is rapid and dose dependent. This means that they do not result in an initial exacerbation of symptoms as can be seen with the GnRH agonists. Because the blockade of GnRH receptors is dose dependent, there is a hope this may balance efficacy directed at endometriosis pain reduction, while trying to reduce the menopausal-like adverse effects of blocking GnRH receptors.[82] In placebo-controlled clinical trials, higher doses are more effective at reducing endometriosis pain and are associated with adverse effects similar to GnRH agonists, requiring add-back therapy to minimize menopausal-like adverse effects.[81]

Aromatase inhibitors

Aromatase, the enzyme responsible for the synthesis of estrogens, is required for the conversion of androstenedione and testosterone to estrone and estradiol.[83] Although aromatase inhibitor (AI), OCs, progestins, and GnRH agonists/antagonists all decrease serum levels of estrogen, only AIs decrease secretion and production of estrogen by endometrial tissue itself. Anastrozole and letrozole are type II AIs, binding reversibly to the enzyme to produce a beneficial effect on endometriosis symptoms.[83] Although AIs effectively

decrease estrogen conversion in the periphery, addition of an agent to reduce ovarian estrogen levels is also necessary in premenopausal patients; hence, most of the studies in this population have included double therapy with AIs and OCs or GnRH agonist.[83]

Further research is needed to determine the role of AIs in the treatment of endometriosis, because currently they do not have an FDA indication for the treatment of endometriosis. Their use should be reserved at this time for those patients with severe endometriosis who have failed other therapies.[83]

Danazol

Danazol, an androgenic drug derived from 17-ethinyl testosterone, also induces a pseudomenopausal state by increasing androgen levels and decreasing estrogen levels. It inhibits the enzymes involved in ovarian steroidogenesis and increases the metabolic clearance of estradiol. By creating a hypoestrogenic, hypoprogestogenic state, danazol causes anovulation, amenorrhea, and atrophy of endometrial implants. Although effective at decreasing pelvic pain, danazol is poorly tolerated because of its significant side effects, which include weight gain, voice changes, edema, acne, hot flashes, vaginal dryness, hirsutism, liver disease, and increased cholesterol; these occur in up to 85% of patients who are treated.[66] Because of safety concerns, use should be limited to 6 months at a time and should only be initiated in patients after all other therapy options have failed.

PAIN MANAGEMENT: NONPHARMACOLOGIC THERAPY

Definitive surgery

Definitive surgery, referring to total abdominal hysterectomy, bilateral salpingo-oophorectomy, and removal of all visible endometriosis, theoretically should eliminate the risk of recurrence of the disease. These procedures are not an option for the many patients with endometriosis who desire pregnancy in the future. They are invasive surgeries, reserved for those patients whose pain is unresponsive to

other therapies or to conservative surgery. Furthermore, removal of all endometriosis is difficult, and recurring pain is not uncommon. Sinaii et al surveyed patients with endometriosis regarding treatments and benefits, and found that, of the 1160 patients surveyed, 12% had had definitive surgery, with 40% reporting the surgery was successful, 33% reporting partial benefit, 5.6% reporting no benefit, and 6% of patients reported increased pain and symptoms after surgery.[84]

Conservative surgery

In contrast to definitive surgery, conservative surgery (involving ablation and removal of implants, and lysis of adhesions) preserves fertility and is commonly conducted during the initial diagnostic laparoscopy. In the Sinaii et al survey, 70% of patients had undergone laparoscopy with removal of lesions, with 30% considering the procedure a success, 50% reporting partial benefit, 15% with no difference in symptoms, and 10% reporting increased symptoms.[84] On average, patients reported having three surgical procedures.[84] Drug treatment is used after conservative surgery, as it is not possible to remove all lesions, many of which are difficult to visualize.

Clinical trials in endometriosis have not singled out one treatment as the treatment of choice for all patients, with most investigations demonstrating equivalence of the studied therapies. An NSAID and combined hormonal contraception (eg, N.H.'s contraceptive vaginal ring) are the drugs of choice for initial management, owing to their safety profile, and, in this case, the contraceptive agent's dual utility in preventing conception. As a next step, progestins, GnRH agonists/antagonists, and AIs are options. Because of adverse effects and poor tolerability, danazol should be reserved as an agent of last choice. If N.H. were uninterested in having children in the future, surgical sterilization would be an option. Conservative surgery, including removal of endometriomas and adhesions and ablation of visible lesions is not curative, but a combination of conservative surgery, followed by postoperative drug therapy

directed at endometriosis, has been shown to prolong the duration of pain relief and decrease recurrence after surgery.[85]

Case 50-3, Question 3: N.H. has not had a problem in the past tolerating a variety of contraceptive products but does have some problems with daily medication adherence and would like to avoid giving herself injections if possible. How does this information assist in the selection of therapy for her endometriosis?

N.H. is a smoker, with poor calcium intake and some cardiovascular risk factors (family history, high cholesterol), who would rather avoid self-injectable medication and has trouble with daily medication taking. Danazol, with its ability to increase cardiovascular risk factors and extensive side effects, is not a good option. Although some GnRH analogs are available as nasal sprays or injectable implants, the significant risk of decreased bone density and menopause-like adverse effects place them as a second-line option. Progestins, particularly the long-acting progestins, either in the form of the medroxyprogesterone acetate 3-month depot or subcutaneous injection or the levonorgestrel IUS make these appropriate first-line options for N.H., although the risk of diminished bone density with depot formulations remains an issue. An alternative option that would not provide contraceptive benefits would be the GnRH antagonists (elagolix) as they are available as oral tablets. More significant adverse effects with this medication class would point to the use of the progestins initially, reserving the GnRH antagonists until additional therapy is needed.

Case 50-3, Question 4: N.H. would like to start the levonorgestrel IUS, but her insurance company will not pay for it to be used in the treatment of endometriosis because of its lack of FDA indication. She decides to start depot medroxyprogesterone acetate (DMPA). What information can you provide her regarding use and the benefits and risks of treatment?

DMPA is available in two dosage forms: 150 mg to be given intramuscularly (IM) every 3 months and a 104-mg formulation given

subcutaneously (SC) every 3 months. Product choice may be based on insurance coverage or the potential for the patient to self-administer (the SC product is more patient-friendly). Because N.H. does not want to self-inject, either choice, administered by her provider's office, or a pharmacist if law allows, would be an appropriate option. Although the DMPA does provide the contraception N.H. desires, she should be informed that it may take longer than usual (up to 1 year) to become pregnant after discontinuation. More than 80% of patients treated with progestins will experience partial or complete pain relief.[73] Although devoid of the menopause-like adverse effects of other medications used to treat endometriosis, DMPA is associated with weight gain (which may be significant in some patients), bloating, and irregular periods or bleeding for several months, with most users eventually experiencing amenorrhea. To reduce bone density loss, which is significant but less than with GnRH agonists, N.H. should be advised to ensure her daily intake by diet or supplementation of calcium is at least 1000 mg/day, and at least 400 to 600 international units of vitamin D per day, receive smoking cessation counseling and pharmacotherapy as appropriate, and start a regular weight-bearing exercise regimen. She should be monitored for pain relief, weight gain, amenorrhea or bleeding changes, and adherence to the quarterly injections. If N.H. desires conception, significant planning is required, and she may require a different therapy for her endometriosis as she regains fertility.

GONADOTROPIN-RELEASING HORMONE AGONISTS/ANTAGONISTS AND ADD-BACK THERAPY

CASE 50-4

QUESTION 1: M.F., a 24-year-old single female with a history of moderate-to-severe endometriosis, has been treated with some benefit with NSAIDs (three different NSAIDs at appropriate doses), COCs, and the levonorgestrel IUS. She has no desire for conception and is looking for pain relief. She has also had two conservative laparoscopic surgical procedures, each of which was successful, with pain relief lasting 6 months to 1 year. She recently had her "last ever" (by

her description) surgical procedure and is looking to extend the improvement she has seen previously after surgery. She does not mind injections but has had trouble with adherence in the past.

What options are available for the treatment of M.F.'s pain?

M.F. has tried numerous pharmacologic and surgical treatments (NSAIDs, combined oral contraception, and progestin-only contraception) for endometriosis with limited benefit. Given that she does not desire pregnancy at this time, GnRH analogs, GnRH antagonists, aromatase inhibitors, and danazol are other options. Leuprolide, nafarelin, and goserelin are GnRH analogs (agonists) typically used for the treatment of endometriosis (see Table 50-5). Although GnRH analogs have not been shown to produce better results than the therapies M.F. has already used, they may provide her with pain relief as they represent a different mechanism of action. Choice of GnRH agonist is driven by patient choice of administration method (nasal twice daily [bid] with nafarelin, monthly SC implant with goserelin, or IM injection either once monthly or once every 3 months with leuprolide). In M.F.'s case, the once every 3 months dosing with leuprolide would be most desirable for her, eliminating the need for daily administration. Efficacy is similar for all the GnRH agonists. Before use of these agents, pregnancy, undiagnosed vaginal bleeding, and breast-feeding should be ruled out. Because M.F. does not desire conception, and use of the GnRH agonists is contraindicated in pregnancy, she should be counseled regarding choices of nonhormonal contraceptive agents.

Usual therapy duration is 6 months, although a small pilot study suggested long-term treatment (up to 10 years) with estrogen add-back therapy is without major adverse effects, with continued efficacy.[86] Add-back therapy is based on the concept of an estrogen threshold hypothesis, formulated by Barbieri,[87] which states that there is a critical amount of estrogen that exacerbates endometriosis and below that level the presence of estrogen serves to decrease adverse effects but does not have an adverse effect on the disease itself.[87] Add-back therapy should be initiated at the beginning of

GnRH agonist therapy to try to reduce the occurrence of all hypoestrogenic adverse effects.[86]

Estrogen-containing OCs contain a dose of estrogen that is above the threshold, and they should not be used for add-back therapy. Doses of estrogen equivalent to 0.625 mg of conjugated equine estrogen have been studied in combination with either medroxyprogesterone 2.5 mg daily or norethindrone 5 mg daily. No studies have demonstrated superior efficacy or safety of one regimen over another. Patients using add-back therapy should consume in diet or supplements a total of 1000 mg of calcium daily and have vitamin D levels in the normal range.

Therapy beyond 3 to 6 months requires the use of add-back therapy to reduce the risk of hypoestrogenic complications. Monitoring for efficacy includes monitoring for amenorrhea, decreases in pain and dyspareunia, and quality of life. After discontinuation of GnRH agonists, menses and ovarian function return to normal in 6 to 12 weeks, although benefits may be maintained for another 6 to 12 months.[67]

GnRH antagonists represent a newer option with a similar yet distinct mechanism of action compared to GnRH agonists for the second-line treatment of endometriosis pain in patients who are not desiring conception. Elagolix is an oral GnRH antagonist approved for treatment of endometriosis-related pain. Although lower doses may reduce adverse effects because of a dose-dependent effect on estrogen suppression, higher doses that more completely suppress estrogen may be needed for symptom control and may also require add-back therapy as with GnRH agonists to reduce adverse effects including detrimental effects on bone.

Adverse effects

Adverse effects should be discussed in detail with M.F. because they differ significantly from the other therapies she has tried. Adverse effects are related to the induction of the pseudomenopausal state. Nearly all patients experience hot flashes; vaginal dryness and insomnia also are common. GnRH agonists/antagonists do not affect

SHBG or testosterone levels, so the androgenic side effects of danazol, including changes in lipid profiles, are not experienced with these agents.[66] Significant bone loss can occur with GnRH agonists and high doses of GnRH antagonists, necessitating adequate calcium and vitamin D intake, and estrogen add-back therapy to decrease loss.

A reduction in bone density is a significant concern with GnRH agonists, even at 3 months after the onset of therapy, and is particularly concerning because these agents are being used in young patients, many of whom have not reached their peak bone mass.

Monitoring for decreases in bone density should be accomplished via dual-energy x-ray absorptiometry scan every 24 months if GnRH therapy is continued. M.F. should also be counseled regarding adequate calcium and vitamin D intake, smoking cessation, and a regimen of weight-bearing exercise.

Based on insurance coverage and patient preference, M.F. should initiate a GnRH agonist or antagonist therapy, with add back if GnRH agonist therapy is used. A 6-month trial followed by an evaluation of symptom control is reasonable. If a GnRH antagonist is used and a higher dose is required, the patient should be evaluated for the need for add-back therapy.

PREMENSTRUAL SYNDROME AND PREMENSTRUAL DYSPHORIC DISORDER

Premenstrual disorders affect up to 12% of patients.[88] The premenstrual syndrome (PMS) and the more severe variant premenstrual dysphoric disorder (PMDD) are characterized by the presence of behavioral and/or physical symptoms that interfere with a female's life and occur repetitively in the second half of the menstrual cycle and typically resolve within the first few days of menses. More than 200 premenstrual symptoms have been

described, including positive symptoms such as increased energy, libido, and ability to relax, as well as negative symptoms such as abdominal distension, fatigue, headaches, and crying spells. It is not until the symptoms have a decidedly negative influence on the physical, psychological, or social function of a female that PMS or PMDD occurs.

The symptoms of PMS and PMDD experienced by patients can vary widely. The most common affective or behavioral symptom of PMS is mood swings. Other frequent nonphysical behavioral symptoms include irritability, anxiety/tension, sad or depressed mood, increased appetite/food cravings, sensitivity to rejection, and diminished interest in activities.[89] The most common physical manifestations of PMS are abdominal bloating and an extreme sense of fatigue. Other common symptoms include breast tenderness, headaches, hot flashes, and dizziness.[89]

Diagnosis

No specific physical findings or laboratory tests can be used to make a diagnosis of PMS. Several different organizations have attempted to provide diagnostic criteria for PMS and PMDD; their criteria are inconsistent and disparate. The International Society for Premenstrual Disorders (ISPMD) published a consensus statement in 2011 that defined core premenstrual disorders as typical, pure or reference disorders associated with spontaneous ovulatory menstrual cycles, and variant premenstrual disorders that are separate from core premenstrual disorders and exist where more complex features are present (eg, symptoms result from underlying disorder or exogenous progesterone administration).[90] Core premenstrual features (somatic and psychological symptoms) must occur during all or part of the 2-week premenstrual phase and resolve during or shorting after menstruation. A symptom-free interval between the end of menstruation and the time of ovulation must occur. This cyclic pattern must also occur in most (typically two out of three) menstrual cycles. Lastly, the severity of symptoms must

(a) affect normal daily functioning; (b) interfere with work, school performance, or interpersonal relationships; or (c) cause significant distress. Core premenstrual disorders is an umbrella term for PMS and PMDD.

The American Psychiatric Association has developed criteria for PMDD.[91] The criteria for PMDD focus on the mood and mental health symptoms, leading to a higher level of dysfunction compared with PMS. These criteria require prospective documentation of physical and behavioral symptoms (using diaries) being present for most of the preceding year; five or more symptoms present during the week prior to menses, resolving within a few days after menses starts; and PMDD may be superimposed on other psychiatric disorders, provided it is not merely an exacerbation of those disorders. One or more of the following symptoms must be present: mood swings, sudden sadness, or increased sensitivity to rejection; anger, irritability; sense of hopelessness, depressed mood, or self-critical thoughts; and tension, anxiety, or feeling on edge. Additionally, one or more of the following symptoms must be present to reach a total of five symptoms overall: difficulty concentrating; change in appetite, food cravings, or overeating; diminished interest in usual activities; easy fatigability or decreased energy; feeling overwhelmed or out of control; breast tenderness, bloating, weight gain, or joint/muscles aches; and sleeping too much or not sleeping enough. Symptoms must have been present in most menstrual cycles that occurred the previous year, and the symptoms must be associated with significant distress or interference with usual activities (eg, work, school, social life).

Although criteria for PMS and PMDD are different, they share three essential characteristics: (a) symptoms must occur in the luteal phase and resolve within a few days of menstruation, (b) symptoms are documented for at least two menstrual cycles and are not better explained by other physical or psychological conditions, and (c) symptoms are sufficiently severe to disrupt normal activities. Auditable standards for diagnosis and treatment of premenstrual disorders have been created to prioritize recommendations in clinical care.[92]

The role of genetic factors in the predisposition to PMS and PMDD is an area of active exploration. Some studies suggest that patients with mothers reporting PMS are more likely to develop PMS than those with unaffected mothers (70% vs 37%, respectively).[93,94] One article found that traumatic events, such as physical threat, childhood sexual abuse, and severe accidents, increased the risk of developing PMDD.[95]

Pathophysiology

The wide range of symptoms exhibited in patients with PMS or PMDD can be explained by multiple possible mechanisms, probably a result of interactions between sex steroids and central neurotransmitters.[96] Alterations in neurotransmitters, primarily reductions in serotonin and decreases in central γ-aminobutyric acid (GABA) mediated inhibition, triggered by normal hormonal fluctuations of the menstrual cycle appear to be the most probable factors for the development of PMS or PMDD. These potential mechanisms provide a rational basis for the symptoms that appear in PMS and PMDD, but also support the therapeutic benefits of treatments that increase serotonin or GABA levels. Patients with PMS typically have normal concentrations of serum estrogen and progesterone, but they may have an abnormal response to normal hormonal changes. Many treatments have limited and variable efficacy, which reinforces the argument that PMS or PMDD is a result of multiple factors.

CASE 50-5

Question 1: M.P., a 30-year-old female, presents with significant mood changes that occur the week before her menstrual cycle. She experiences increased irritability and anxiety as well as breast tenderness and abdominal bloating. These symptoms usually subside the first or second day after her menses begin. For 2 to 3 weeks after her menstrual period, M.P. is her "normal, usual self" until the symptoms begin again just before her next menstruation. She has had these symptoms every month for the past several years. She states that she is very uncomfortable when these symptoms occur. Although

she is able to work most of the time, she typically avoids going out with her friends when she has these symptoms. Her menstrual cycles are regular, occurring every 28 to 30 days with a light flow lasting 3 to 4 days.

Pelvic, cardiovascular, and neurologic examinations are normal, and all laboratory assessments are within normal limits. Her serum pregnancy test was negative, and she is not sexually active. She has no significant past medical history, and she does not take any medications.

What symptoms does M.P. have that are consistent with a diagnosis of PMS?

M.P. has affective symptoms that include irritability and anxiety, and somatic symptoms include breast tenderness and abdominal bloating. These symptoms occur during the luteal phase of the menstrual cycle, resolve within 4 days of menses, and do not recur until after day 12 of her cycle. M.P.'s symptoms appear to be affecting her social activities. She states that these symptoms have been present for years and that they occur every month, although she has not prospectively recorded this information. M.P. does not meet the criteria for PMDD because her symptoms are not severe or markedly impairing her ability to participate in daily activities.

Treatment: Premenstrual Syndrome

Case 50-5, Question 2: M.P. asks about nonprescription therapy. Which agents, if any, are appropriate for M.P.?

The management of premenstrual disorders has been outlined by the ISPMD.[92,97] Treatment may be aimed at symptoms, especially if one particular symptom is dominant. Mind–body approaches may be helpful for mild symptoms. Vitamins and minerals that have been studied but have demonstrated minimal benefit include calcium, magnesium, and pyridoxine. The use of vitamin B_6, high doses of calcium supplements, or other vitamins are not recommended in any guidelines given the low-quality evidence and the potential for harm. Chaste tree or chasteberry may be helpful for PMS, but its role in PMDD is unclear. Acetaminophen and NSAIDs may be beneficial for the physical symptoms of PMS, but diuretics found in various OTC

products (eg, ammonium chloride, caffeine, pamabrom) have limited data and unproven efficacy. Given the high placebo response rate in PMS, only agents with clinically proven efficacy should be used.

MIND–BODY APPROACHES

Evidence regarding mind–body approaches for PMS is somewhat limited. Because these modalities are risk-free and are generally accepted as components of a healthy lifestyle, they are favored in the treatment of PMS. Mind–body approaches that have demonstrated benefit in PMS include relaxation response, cognitive-behavioral therapy, yoga, aerobic exercise, and light therapy. Exercise may be especially helpful for physical symptoms.[98]

CHASTE TREE OR CHASTEBERRY

Chasteberry (Vitex agnus-castus or VAC) is the fruit of the chaste tree, a small shrublike tree native to Central Asia and the Mediterranean region. Liquid or solid extracts from the dried ripe chasteberry are used to make chasteberry capsules and tablets. The mechanism of action of chasteberry relative to PMS is unclear, but several trials have reported its beneficial effects. A systematic review found chasteberry to be more effective than placebo and well-tolerated.[99] A randomized, double-blind, placebo-controlled trial of 170 patients taking chasteberry extract 20 mg daily for three menstrual cycles showed a treatment response rate of 52% compared with 24% for placebo ($P < .001$).[100] Individual symptoms of irritability, mood alteration, anger, headache, and breast fullness were reduced. Bloating was not significantly altered compared with placebo. The incidence of side effects was low, but long-term safety is unknown. A prospective, randomized, placebo-controlled study in 67 Chinese patients showed that one VAC tablet daily containing 40 mg of herbal drug produced an 85% efficacy rate compared with a 56% efficacy rate for placebo on symptom scores after three treatment cycles.[101] Studies comparing chasteberry with fluoxetine in PMDD have conflicting results and do not support its use in PMDD.[99] In general, data indicate that chasteberry 20 to 40 mg may be

effective for PMS, but should probably not be used as routine treatment for either PMS or PMDD.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND DIURETICS

NSAIDs have been used to relieve the physical symptoms (eg, headache, joint pain) of PMS, but do not improve the mood symptoms. Regimens have included taking naproxen or mefenamic acid during the luteal phase and stopping therapy after menses begin. Diuretics commonly found in OTC products, such as ammonium chloride, caffeine, and pamabrom, are not effective.

Although several OTC options are available to M.P. and trials including chasteberry have shown some positive findings, the evidence is not compelling because of methodologic limitations and lack of substantial efficacy. Mind–body approaches, such as yoga and relaxation, are part of a healthy lifestyle and could be recommended to M.P. because M.P. is having mood symptoms (ie, anxiety); NSAIDs would not be an effective recommendation.

CASE 50-5, QUESTION 3: M.P. has been eating well and exercising four to five times per week, including two sessions of yoga. She also has been taking naproxen sodium 220 mg orally bid without significant reduction of her symptoms. Her physician requests that she keep a daily dairy for two consecutive cycles to document her symptoms. What information should be included in this tool?

M.P. should keep a daily diary for two consecutive menstrual cycles to demonstrate a temporal relationship between her symptoms during the luteal phase and to document the severity of these symptoms (**Table 50-6**). In addition, she should indicate the presence of menstrual flow, weight, and daily basal body temperature readings to help determine when ovulation occurs. The diary establishes a baseline for each patient and documents the most troublesome symptoms. Once therapy is selected for these symptoms, the diary can aid in assessing patient response.

Table 50-6

Menstrual Cycle Daily Diary Chart

Month 1

Grading Severity of Symptoms:
1 = Mild; general awareness of discomfort but does not interfere with daily activities
2 = Moderate; interferes with activities but not disabling
3 = Severe; symptoms disabling, unable to meet daily social, family, or work obligations
* = Menstrual bleeding
Blank = no symptoms

Each Day
1. List the major symptoms (mood, physical, emotional, behavioral) that you experience during your menstrual cycle
2. Grade the severity of the symptom if present (1–3)
3. Record daily weight
4. Record basal body temperature, which helps determine ovulation date
5. Check the days of the cycle when menstrual flow occurs

Day of month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Day of menstrual cycle	18	19	20	21	22	23	24	25	26	27	28	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Menses												*	*	*	*															
Breast tenderness and pain				1	1	1	1	1	1	1	1																				
Sadness or depression				1	2	3	3	3	3	3	3	2	1																		
Fatigue				3	3	3	3	3	3	3	3	2	1																		
Irritability					2	2	3	3	3	3	3																				
Inability to concentrate							2	2	3	3	3																				
Daily weight (lb)	130	130	130	130	130	130	130	130	130	130	130	131	131	131	130	130	130	130	130	130	129	129	129	128	128	129	128	128	128	128	128
Basal body temperature (°)	98.0	98.2	98.0	98.2	98.0	98.0	98.2	97.8	98.0	97.8	97.6					97.8	97.8	97.6	97.8	97.6	97.8	97.8	97.6	97.4	98.4	98.0	98.4	98.6	98.0	98.2	98.0

Month 2

Day of month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Day of menstrual cycle	21	22	23	24	25	26	27	28	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
Menses									*	*	*	*																			
Breast tenderness and pain				1	1	1	1	1	1		1																				
Sadness/ depression		1	2	3	3	3	3	3	2	2	1																				
Fatigue		2	2	3	3	3	3	3	2	1																					
Irritability	1	2	2	2	3	3	3	3	3	2	2	1																			
Inability to concentrate			1	1	2	2	3	3																							
Daily weight (lb)	128	128	128	128	128	128	128	129	129	129	128	128	128	128	128	128	128	128	128	128	128	128	128	128	128	129	128	128	128	128	
Basal body temperature (°)	98.0	98.2	98.4	98.0	98.2	97.8	98.0	97.4					97.6	97.6	97.8	97.8	97.6	97.8	97.6	97.6	97.6	97.2	97.2	97.0	98.4	98.6	98.0	98.2	98.2	98.0	

Treatment: Premenstrual Dysphoric Disorder

Case 50-5, Question 4: M.P. returns to clinic with the diary presented in Table 50-6. The physician determines that M.P. has PMDD. What evidence supports this diagnosis and what should be recommended to M.P. for treatment?

M.P. meets the criteria for PMDD as evidenced by her symptoms during the one week before her menstrual cycle (luteal phase). Specifically, she has at least five symptoms required for the

diagnosis of PMDD: sadness or depression (core symptom), fatigue, irritability, inability to concentrate, breast tenderness, and bloating. She rated several of those symptoms as severe, which indicates the symptoms are disabling and she is unable to meet her daily obligations. There is no reason to suspect any other disorder based on her history. PMDD seems to be the most likely diagnosis for M.P.

Therapy options at this time include lifestyle modifications, psychosocial interventions such as cognitive-behavioral therapy, and pharmacologic therapy. Psychotropic drugs targeted to her most severe symptoms may include selective serotonin reuptake inhibitors (SSRIs), serotonergic tricyclic antidepressants, and anxiolytics. OCs have also been approved for PMDD and could be considered.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Serotonin is critical in the pathogenesis of PMDD, and for that reason, SSRIs have become the treatment of choice for PMDD and severe PMS (**Table 50-7**).[92] SSRIs have demonstrated efficacy in reducing irritability, depressed mood, dysphoria, psychosocial function, and the physical symptoms of PMDD, including bloating, breast tenderness, and appetite changes. Fluoxetine, sertraline, and paroxetine controlled release each have an approved indication for PMDD.

Table 50-7

Selective Serotonin Reuptake Inhibitors for the Management of Premenstrual Syndrome or Premenstrual Dysphoric Disorder

Drug (Brand Name)	Daily Dosing Regimen (mg)	Intermittent Dosing Regimen (mg)[a]
Citalopram (Celexa)	5–30	10–30
Escitalopram (Lexapro)	10–20	10–20
Fluoxetine (Prozac or Sarafem[b])	20–60	20 or 90 weekly
Paroxetine controlled release (Paxil CR)[b]	12.5–25	12.5–25

Drug (Brand Name)	Daily Dosing Regimen (mg)	Intermittent Dosing Regimen (mg)[a]
Sertraline (Zoloft)[b]	50–150	100

[a]Day 14 until the onset of menses.

[b]Medication has FDA-approved indication for premenstrual dysphoric disorder.

The onset of SSRI effect in patients with PMDD or severe PMS is much more rapid than when these agents are used for treatment of major depression or anxiety disorders. Patients may experience symptom relief or resolution within the first days of treatment versus 4 to 8 weeks for other psychological disorders. Several different dosing strategies have been employed, including continuous dosing (once daily), intermittent dosing (last 2 weeks of menstrual cycle or luteal phase), and semi-intermittent dosing (continuous administration throughout the cycle with increased doses during luteal phase).[102] Continuous dosing would be reasonable for patients with concurrent mood or anxiety disorders or those who may have difficulty remembering the timing of the intermittent dosing. Intermittent dosing should be considered for patients with regular menstrual cycles who are able to adhere to the regimen, an absence of symptoms during the follicular phase, concerns about long-term effects (eg, sexual dysfunction) or cost of daily therapy, and few side effects at treatment initiation. Studies evaluating these dosing strategies have reported equal efficacy for continuous or intermittent strategies; treatment should be individualized based on patient history, willingness to adhere to therapy, and drug response. A beneficial effect can be expected with the first SSRI use. If the response is suboptimal, the dose can be increased in the next cycle. The most common side effects of SSRIs include nausea, headache, insomnia, and decreased libido.

In a systematic review of 31 randomized controlled trials including fluoxetine, paroxetine, sertraline, escitalopram, and citalopram, SSRIs reduced overall self-rated symptoms significantly more effectively than placebo (end scores for moderate-dose SSRIs: SMD −0.65, 95% CI −0.46 to −0.84, nine studies, 1276 patients).[102]

Withdrawals because of adverse effects were significantly more likely in the SSRI group (moderate dose: OR 2.55, 95% CI 1.84–3.53, 15 studies, 2447 patients) with side effects being dose dependent and most commonly reported as nausea (NNH = 7), asthenia or decreased energy (NNH = 9), somnolence (NNH = 13), fatigue (NNH = 14), decreased libido (NNH = 14), and sweating (NNH = 14). Overall quality of the evidence was considered to be low-to-moderate with poor reporting of methods as the prominent weakness, but it was concluded that SSRIs are effective in reducing PMS symptoms whether taken in the luteal phase only or continuously.

COMBINATION ORAL CONTRACEPTIVES

A treatment approach with COCs allows for suppression of the hypothalamic–pituitary–ovarian axis to minimize cyclic changes in gonadal steroids and may be preferred over SSRIs if/when contraception is a high priority.[92] Two low-dose COC formulations containing 20 μg ethinylestradiol and 3 mg drospirenone (an antimineralocorticoid spironolactone analog) with a 4-day hormone-free interval have been approved for the treatment of emotional and physical symptoms of PMDD. Studies using this agent have shown efficacy for reduced mood, physical, and behavioral symptoms of PMDD, including a 48% improved response with this agent compared with a 36% response using placebo (P = .015).[103] Side effects occurring in at least 10% of patients treated with this medication included intermenstrual bleeding, headache, nausea, breast pain, and upper respiratory infection. Another COC approved for PMDD contains 20 μg of ethinylestradiol, 3 mg of drospirenone, and 0.451 mg of levomefolate calcium. In a systematic review of five randomized controlled trials comparing COCs containing drospirenone to placebo or other COCs for effect on premenstrual symptoms, the authors concluded that drospirenone 3 mg plus ethinylestradiol 20 μg may help treat PMDD better than placebo.[104] They were unable to determine if this combination would help patients with less severe symptoms or would be more effective than

other COCs. For patients desiring contraception, these particular agents have only been evaluated for efficacy in PMDD when used for up to three cycles and may be best for mild-to-moderate symptoms because COCs could worsen PMS/PMDD symptoms in some cases.[92]

GONADOTROPIN-RELEASING HORMONE AGONISTS

Treatment with GnRH agonists has been used for the physical and psychological symptoms of PMS. Their use may be considered when PMS symptoms are severe or life threatening and not responsive to SSRI therapy.[92] These agents are not typically used for long periods of time, however, because of vasomotor symptoms and the potential for negative long-term effects on bone. They also have to be administered by injection or nasal spray which may affect adherence. This treatment is reserved for patients with very severe PMDD who do not respond to other treatments.

M.P. has PMDD and does not need contraception. Mood symptoms predominate and are impairing her functionality. An SSRI should be started in either a continuous or intermittent manner. M.P. appears to be a good candidate for intermittent therapy because she can adhere to the regimen and does not have a concurrent depression or anxiety disorder. An appropriate initial treatment regimen is fluoxetine 20 mg orally daily for the last 2 weeks of the menstrual cycle. Her response rate should be assessed after two to three cycles of treatment.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Falcone T, Flyckt R. Clinical management of endometriosis. *Obstet Gynecol*. 2018;131:557–571. (66)

Ferries-Rowe E, Corey E, Archer J. Primary dysmenorrhea: diagnosis and therapy. *Obstet Gynecol*. 2020;136:1047–1058. (50)

Hoeger KM, Dokras A, Piltonen T. Update on PCOS: consequences, challenges, and guiding treatment. *J Clin Endocrinol Metab*. 2021;106:e1071–e1083. (16)

Ismaili E, Walsh S, O'Brien PMS, et al. Fourth consensus of the International Society for Premenstrual Disorders (ISPMD): auditable standards for diagnosis and management of premenstrual disorder. *Arch Womens Ment Health.* 2016;19:953–958. (92)

Marjoribanks J, Ayeleke R, Farquhar C, Proctor M. Nonsteroidal anti- inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*. 2015;2015(7):CD001751. doi:10.1002/14651858.CD001751.pub3 (61)

Pena AS, Witchel SF, Hoeger KM, et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. *BMC Med.* 2020;18:72. (12)

Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod.* 2018;33:1602–1618. (11)

Key Websites

Androgen Excess and PCOS Society. http://www.ae-society.org

International Association for Premenstrual Disorders. https://iapmd.org/

PCOS Awareness Association. https://www.pcosaa.org/

COMPLETE REFERENCES CHAPTER 50 DISORDERS RELATED TO THE MENSTRUAL CYCLE

1. Hatcher RA, Kowal D, Nelson AL, et al. *Contraceptive Technology*. 21st ed. Ardent Media; 2021.
2. Deswal R, Narwal V, Dang A, Pundir CS. The prevalence of polycystic ovary syndrome: a brief systematic review. *J Hum Reprod Sci*. 2020;13:261–271.
3. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review

and meta-analysis. *Hum Reprod*. 2016;31:2841–2855.
4. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol*. 1935;29:181–191.
5. Stein IF. Bilateral polycystic ovaries. *Am J Obstet Gynecol*. 1945;50:385–398.
6. Rosenwaks Z. Polycystic ovary syndrome, an enigmatic syndrome begging for a name change. *Fertil Steril*. 2017;108:748–749.
7. Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, eds. *Polycystic Ovary Syndrome*. Blackwell Scientific Publications; 1992:377.
8. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril*. 2004;81:19–25.
9. Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril*. 2009;91:456–488.
10. Azziz R, Carmina E, Dewailly D, et al. Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab*. 2006;91:4237–4245.
11. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod*. 2018;33:1602–1618.
12. Pena AS, Witchel SF, Hoeger KM, et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. *BMC Med*. 2020;18:72.
13. Spritzer PM, Barone CR, Oliveira FB. Hirsutism in polycystic ovary syndrome: pathophysiology and management. *Curr Pharm Des*. 2016;22:5603–5613.
14. Tehrani FR, Gandevani SB, Yarandi RB, Ghare Naz MS, Carmina E. Prevalence of acne vulgaris among women with polycystic ovary syndrome: a systemic review and meta-analysis. *Gynecol Endocrinol*. 2021;37:392–405.
15. Carmina E, Azziz R, Bergfeld W, et al. Female pattern hair loss and androgen excess: a report from the multidisciplinary androgen excess and PCOS committee. *J Clin Endocrinol Metab*. 2019;104:2875–2891.
16. Hoeger KM, Dokras A, Piltonen T. Update on PCOS: consequences, challenges, and guiding treatment. *J Clin Endocrinol Metab*. 2021;106:e1071–e1083.
17. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18:618–637.

18. Rosenfield RL. Current concepts of polycystic ovary syndrome pathogenesis. *Curr Opin Pediatr*. 2020;32:698–706.
19. Hiam D, Moreno-Asso A, Teede HJ, et al. The genetics of polycystic ovary syndrome: an overview of candidate gene systematic reviews and genome-wide association studies. *J Clin Med*. 2019;8(10):1606.
20. Dapas M, Lin FTJ, Nadkarni GN, et al. Distinct subtypes of polycystic ovary syndrome with novel genetic associations: an unsupervised, phenotypic clustering analysis. *PLoS Med*. 2020;17(6):e1003132.
21. Stener-Victorin E, Deng Q. Epigenetic inheritance of polycystic ovary syndrome—challenges and opportunities for treatment. *Nat Rev Endocrinol*. 2021;17:521–533. https://doi.org/10.1038/s41574-021-00517-x
22. Zhang Y, Ho K, Keaton JM, et al. A genome-wide association study of polycystic ovary syndrome identified from electronic health records. *J Obstet Gynecol*. 2020;223:559.e1–559.21.
23. Day F, Karaderi T, Jones MR, et al. Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. *PLoS Genet*. 2018;14(12):e1007813.
24. Stener-Victorin E, Padmanabhan V, Walters KA, et al. Animal models to understand the etiology and pathophysiology of polycystic ovary syndrome. *Endocr Rev*. 2020;41:538–576.
25. Risal S, Manti M, Lu H, et al. Prenatal androgen exposure and transgenerational susceptibility to polycystic ovary syndrome. *Nat Med*. 2019;25:1894–1904.
26. Coutinho EA, Kauffman AS. The role of the brain in the pathogenesis and physiology of polycystic ovary syndrome (PCOS*). Med Sci*. 2019;7:84.
27. Teede H, Misso M, Tassone EC, et al. Anti-Müllerian hormone in PCOS: a review informing international guidelines. *Trends Endocrinol Metab*. 2019;30:467–478.
28. Ashraf S, Nabi M, Rashid F, Amin S. Hyperandrogenism in polycystic ovarian syndrome and role of CYP gene variants: a review. *Egypt J Med Hum Genet*. 2019;20:25.
29. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev*. 2012;33:981–1030.
30. Azziz R, Carmina E, Chen Z, et al. Polycystic ovary syndrome. *Nat Rev Dis Primers*. 2016;11:16057.
31. Anagnostis P, Paparodis RD, Bosdou JK, et al. Risk of type 2 diabetes mellitus in polycystic ovary syndrome is associated with obesity: a meta-analysis of observational studies. *Endocrine*. 2021;74(2):245–253. doi:10.1007/s12020-021-02801-2
32. Chandrasekaran S, Sagili H. Metabolic syndrome in women with polycystic ovary syndrome. *Obstet Gynaecol*. 2018;20:245–252.

33. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
34. Essah PA, Wickham EP, Nestler JE. The metabolic syndrome in polycystic ovary syndrome. *Clin Obstet Gynecol*. 2007;50:205–225.
35. Osibogun O, Ogunmoroti O, Michos ED. Polycystic ovary syndrome and cardiometabolic risk: opportunities for cardiovascular disease prevention. *Trends Cardiovasc Med*. 2020;30:399–404.
36. Rizzo M, Berneis K, Hersberger M, et al Milder forms of atherogenic dyslipidemia in ovulatory versus anovulatory polycystic ovary syndrome phenotype. *Hum Reprod*. 2009;24:2286–2292.
37. Berni TR, Morgan CL, Aled Rees D. Women with polycystic ovary syndrome have an increased risk of major cardiovascular events: a population study. *J Clin Endocrinol Metab*. 2021;106(9):e3369–e3380. doi:10.1210/clinem/dgab392
38. Helvaci N, Karabulut E, Demir AU, Yildiz BO. Polycystic ovary syndrome and the risk of obstructive sleep apnea: a meta-analysis and review of the literature. *Endocr Connect*. 2017;6:437–445.
39. Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93:3878–3884.
40. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2014;20:748–758.
41. Shang Y, Zhou H, Hu M, Feng H. Effect of diet on insulin resistance in polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2020;105:3346.
42. Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers. *JAMA Oncol*. 2018;4:516–521.
43. Han Y, Li Y, He B. GLP-1 receptor agonists versus metformin in PCOS: a systematic review and meta-analysis. *Reprod Biomed Online*. 2019;39:332–342.
44. Barrionuevo P, Nabhan M, Altayar O, et al. Treatment options for hirsutism: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2018;103:1258–1264.
45. Armanini D, Lisboa KO, Mattiello S, Lhullier F. Spironolactone in the treatment of polycystic ovary syndrome. *Expert Opin Pharmacother*. 2016;17:1713.
46. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 194: polycystic ovary syndrome. *Obstet Gynecol*. 2018;131:1174.

47. Mehia RB, Summers KM, Kresowik JD, Van Voorhis BJ. A randomized controlled trial of combination of letrozole and clomiphene citrate versus letrozole alone for ovulation induction in women with polycystic ovary syndrome. *Fertil Steril*. 2018;111:571–578.
48. Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2014;371:119–129.
49. Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2018;5:CD010287.
50. Ferries-Rowe E, Corey E, Archer J. Primary dysmenorrhea: diagnosis and therapy. *Obstet Gynecol*. 2020;136:1047–1058.
51. Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. *Epidemiol Rev*. 2014;36:104–113.
52. Committee on Adolescent Health Care. ACOG Committee opinion number 760: dysmenorrhea and endometriosis in the adolescent. *Obstet Gynecol*. 2018;132:e249–e258.
53. Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. *Epidemiol Rev*. 1995;17:265–286.
54. Armour M, Ee C, Naidoo D, et al. Exercise for dysmenorrhea. *Cochrane Database Syst Rev.* 2019;9(9):CD004142.
55. Kim S. Yoga for menstrual pain in primary dysmenorrhea: a meta-analysis of randomized controlled trials. *Comp Ther Clin Pract*. 2019;36:94–99.
56. Jo J, Lee S. Heat therapy for primary dysmenorrhea: a systematic review and meta-analysis of its effects on pain relief and quality of life. *Sci Rep*. 2018;8:16252.
57. Akin MD, Weingand KW, Hengehold DA, Goodale MB, Hinkle RT, Smith RP. Continuous low level topical heat in the treatment of dysmenorrhea. *Obstet Gynecol*. 2001;97:343–349.
58. Navvabi Rigi S, Kermansaravi F, Navidian A, et al. Comparing the analgesic effect of heat patch containing iron chip and ibuprofen for primary dysmenorrhea: a randomized controlled trial. *BMC Womens Health*. 2012;12:25.
59. Pattanittum P, Kunyanone N, Brown J, et al. Dietary supplements for dysmenorrhea. *Cochrane Database Syst Rev*. 2016;3(3):CD002124.
60. Armor M, Parry K, Al-Dabbas M, et al. Self care strategies and sources of knowledge on menstruation in 12526 young women with dysmenorrhea: a systematic review and meta-analysis. *PLoS One*. 2019;14(7):e0220103.
61. Marjoribanks J, Ayeleke R, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*. 2015;2015(7):CD001751. doi:10.1002/14651858.CD001751.pub3
62. Wong CL, Farquhar C, Roberts H, Proctor M. Oral contraceptive pill for primary dysmenorrhoea. *Cochrane Database Syst Rev*. 2009;2009(4):CD002120.

63. Damm T, Lamvu G, Carrillo J, Ouyang C, Feranec J. Continuous vs cyclic combined hormonal contraceptives for the treatment of dysmenorrhea: a systematic review. *Contraception*. 2019;1:100002.
64. Dmitrovic R, Kunselman AR, Legro RS. Continuous compared with cyclic oral contraceptives for the treatment of primary dysmenorrhea: a randomized controlled trial. *Obstet Gynecol.* 2012;119:1143–1150.
65. Baldaszti E, Wimmer-Puchinger B, Löschke K. Acceptability of the long term contraceptive levonorgestrel releasing intrauterine system: a 3-year follow up study. *Contraception*. 2003;67:87–91.
66. Falcone T, Flyckt R. Clinical management of endometriosis. *Obstet Gynecol*. 2018;131:557–571.
67. Zondervan KT, Becker CM, Missmer SM. Endometriosis. *NEJM*. 2020;382:1244–1256.
68. Fuldeore M, Yang H, Du EX, Soliman AM, Wu EQ, Winkel C. Healthcare utilization and costs in women diagnosed with endometriosis before and after diagnosis: a longitudinal analysis of claims databases. *Fertil Steril*. 2015;103:163–171.
69. Agarwal S, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol*. 2019;220(4):354.e1–354.e12.
70. Hirsch M, Begum MR, Paniz E, et al. Diagnosis and management of endometriosis: a systematic review of international and national guidelines. *BJOG*. 2018;125:556–564.
71. [No authors listed]. Revised American Fertility Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril*. 1997;67:817–821.
72. Saunders PTK, Horne AW. Endometriosis: etiology, pathobiology and therapeutic prospects. *Cell*. 2021;184:2807–2824.
73. Donnez J, Dolmans MM. Endometriosis and medical therapy: from progestogens to progesterone resistance to GNRH antagonists: a review. *J Clin Med.* 2021;10:1085.
74. McLeod BS, Retzloff MG. Epidemiology of endometriosis: an assessment of risk factors. *Clin Obstet Gynecol*. 2010;53:389–396.
75. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014;29:400–412.
76. Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2014;2014(3):CD009590. doi:10.1002/14651858.CD009590.pub2
77. Jensen J, Schlaff W, Gordon K. Use of combined hormonal contraceptives for the treatment of endometriosis related pain: a systematic review of the evidence. *Fertil Steril.* 2018;110:137–151.
78. Muzil L, Di Tucci C, Achilli C, et al. Continuous versus cyclic oral contraceptives after laparoscopic excision of ovarian endometriomas: a

systematic review and metaanalysis. *Am J Obstet Gynecol*. 2016;214:203–211.
79. Song SY, Park M, Lee GW, et al. Efficacy of levonorgestrel releasing intrauterine system as a postoperative maintenance therapy of endometriosis: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2018;231:85–92.
80. Wong AY, Tang LC, Chin RK. Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomised controlled trial. *Aust N Z J Obstet Gynaecol*. 2010;50:273–279.
81. Vercellini P, Vigano P, Barbara G, et al. Elagolix for endometriosis: all the glitters is not gold. *Hum Reprod*. 2019;34:193–199.
82. Ferrero S, Barra F, Maggiore U. Current and emerging therapeutics for management of endometriosis. *Drugs*. 2018;78:995–1012.
83. Pavone ME, Bulun SE. Aromatase inhibitors for the treatment of endometriosis. *Fertil Steril*. 2012;98:1370–1379.
84. Sinaii N, Cleary SD, Younes N, Ballweg ML, Stratton P. Treatment utilization for endometriosis symptoms: a cross-sectional survey study of lifetime experience. *Fertil Steril*. 2007;87:1277–1286.
85. Nexhat C, Vang N, Tanaka P, Nezhat C. Optimal management of endometriosis and pain. *Obstet Gynecol*. 2019;134:834–839.
86. Bedaiwy M, Casper RF. Treatment with leuprolide acetate and hormonal add-back for up to 10 years in stage IV endometriosis patients with chronic pelvic pain. *Fertil Steril*. 2006;86:220–222.
87. Barbieri RL. Endometriosis and the estrogen threshold theory: relation to surgical and medical treatment. *J Reprod Med*. 1998;43:287–292.
88. Hoffmeister F, Bodden S. Premenstrual syndrome and premenstrual dysphoric disorder. *Am Fam Physician*. 2016;94:236–240.
89. Hartlage SA, Freels S, Gotman N, Yonkers K. Criteria for premenstrual dysphoric disorder: secondary analyses of relevant data sets. *Arch Gen Psychiatry*. 2012;69:300–305.
90. O'Brien PMS, Bäckström T, Brown C, et al. Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: the ISPMD Montreal consensus. *Arch Womens Ment Health*. 2011;14:13–21.
91. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. (*DSM-V*). APA; 2013.
92. Ismaili E, Walsh S, O'Brien PMS, et al. Fourth consensus of the International Society for Premenstrual Disorders (ISPMD): auditable standards for diagnosis and management of premenstrual disorder. *Arch Womens Ment Health*. 2016;19:953–958.

93. Dalton K, Dalton ME, Guthrie K. Incidence of premenstrual syndrome in twins. *BMJ*. 1987;295:1027–1028.
94. Van der Akker OB, Stein GS, Neale MC, Murray RM. Genetic and environmental variation in 2 British twin samples. *Acta Genet Med Gemellol*. 1987;36:541–548.
95. Perkonigg A, Yonkers KA, Pfister H, Lieb R, Wittchen HU. Risk factors for premenstrual dysphoric disorder in a community sample of young women: the role of traumatic events and posttraumatic stress disorder. *J Clin Psychiatry*. 2004;65:1314–1322.
96. Rapkin AJ, Akopians AL. Pathophysiology of premenstrual syndrome and premenstrual dysphoric disorder. *Menopause Int*. 2012;18:52–59.
97. Nevatte T, O'Brien PM, Bäckström T, et al. ISPMD consensus on the management of premenstrual disorders. *Arch Womens Ment Health*. 2013;16:279–291.
98. Dehnavi ZM, Jafarnejad F, Sadeghi Goghary S. The effect of 8 weeks aerobic exercise on severity of physical symptoms of premenstrual syndrome: a clinical trial study. *BMC Womens Health*. 2018;18:80.
99. Van Die MD, Burger HG, Teede HJ, Bone KM. Vitex agnus-castus extracts for female reproductive disorders: a systematic review of clinical trials. *Planta Med*. 2013;79:562–575.
100. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ*. 2001;322:134–137.
101. Ma L, Lin S, Chen R, Wang X. Treatment of moderate to severe premenstrual syndrome with Vitex agnus castus (BNO 1095) in Chinese women. *Gynecol Endocrinol*. 2010;26:612–616.
102. Marjoribanks J, Brown J, O'Brien PM, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev.* 2013;2013(6):CD001396.
103. Yonkers KA, Brown C, Pearlstein TB, Foegh M, Sampson-Landers C, Rapkin A. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. *Obstet Gynecol*. 2005;106:492–501.
104. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. *Cochrane Database Syst Rev*. 2012;2012(2):CD006586.

51

The Transition Through Menopause

Louise Parent-Stevens and Trisha LaPointe

CORE PRINCIPLES		CHAPTER CASES
1	Menopause, the natural progression of reproductive aging in females, is characterized by declining ovarian function and decreased synthesis of sex hormones.	**Case 51-1 (Question 1), Figure 51-1**
2	Management of females who experience distressing symptoms associated with menopause, including hot flushes and genitourinary atrophy, is targeted at relieving symptoms while minimizing risks.	**Case 51-1 (Questions 1–6)** **Case 51-2 (Questions 1, 2), Figure 51-2**
3	Estrogen therapy (ET), the most effective treatment for menopausal symptoms, is associated with significant	**Case 51-1 (Questions 3, 5), Table 51-1**

	risks, including thromboembolic disease (TED) and breast and endometrial cancer. Progestogens are added to systemic estrogen therapy (EPT) to provide endometrial protection in patients with an intact uterus. Females must be adequately counseled so that they can make educated decisions about treatment.	
4	Selection of appropriate hormone therapy (HT) regimens (ET or EPT), including route, dose, and duration, is necessary to optimize outcomes. Based on current knowledge, systemic HT use should be limited to the management of menopausal symptoms.	**Case 51-1 (Questions 4, 5), Table 51-2, 51-3**
5	Risk for cardiovascular disease (CVD) is not increased when HT is initiated within 10 years of menopause and before age 60 years but is increased if started after this age and time frame.	**Case 51-1 (Question 3)**
6	Nonhormonal drugs, including serotonergic antidepressants and gabapentinoids, are alternatives in females who are unable or unwilling to take HT. Although commonly used, efficacy and safety data on herbal medicines for menopausal symptoms are limited.	**Case 51-1 (Questions 2, 6)** **Case 51-2 (Question 2), Table 51-4**
7	Genitourinary syndrome of menopause (GSM) does not wane with time after	**Case 51-2 (Questions 1, 2)**

menopause; long-term use of low-dose vaginal estrogen can be recommended.

INTRODUCTION

The perimenopausal or climacteric phase in the female aging process (ie, the time between the reproductive and nonreproductive years) is distinguished by waning ovarian function and irregular menstrual cycles. Menopause, the last spontaneous episode of physiologic uterine bleeding, is identified retrospectively after 12 months of amenorrhea and typically occurs 4 to 5 years after the onset of perimenopause. In females younger than 45 years, menopause can be confirmed by two elevated follicle-stimulating hormone (FSH) levels >4 weeks apart. Postmenopause is characterized by significantly decreased hormone levels that may contribute to an increased risk of disease. While life expectancy has increased, the average age of females at menopause has remained relatively constant at 51 years.[1] Females today may spend one-third of their lives in the postmenopausal state. Approximately 35% of the female population in the United States is older than 50 years and at risk for menopause-related health issues.[2] Age at menopause is determined primarily by genetics but may be decreased by low body weight and poor health status. Cigarette smoking decreases age at menopause by 1 to 2 years.[3] Higher socioeconomic status and prior oral contraceptive use may increase the age at menopause.[3] Cytotoxic drugs and radiotherapy may induce ovarian failure, and bilateral oophorectomy results in surgically induced menopause. Onset of menopause before age 40 is termed *premature ovarian insufficiency*.

PATHOPHYSIOLOGY

Perimenopause results from an age-related acceleration in oocyte (immature female egg) degeneration and ovarian resistance to gonadotropins. The aging follicles produce less inhibin, which triggers increased production of FSH (**Fig. 51-1**).[4,5] Despite this increase in FSH levels, the declining ovary is unable to consistently produce mature follicles, resulting in frequent anovulatory cycles during the years approaching menopause. However, spontaneous ovulation can still occur, and contraception should be used if pregnancy is not desired. When all ovarian follicles have been depleted, menopause occurs. This corresponds with an increase in FSH and luteinizing hormone levels, which peak 1 to 3 years after menopause.[5]

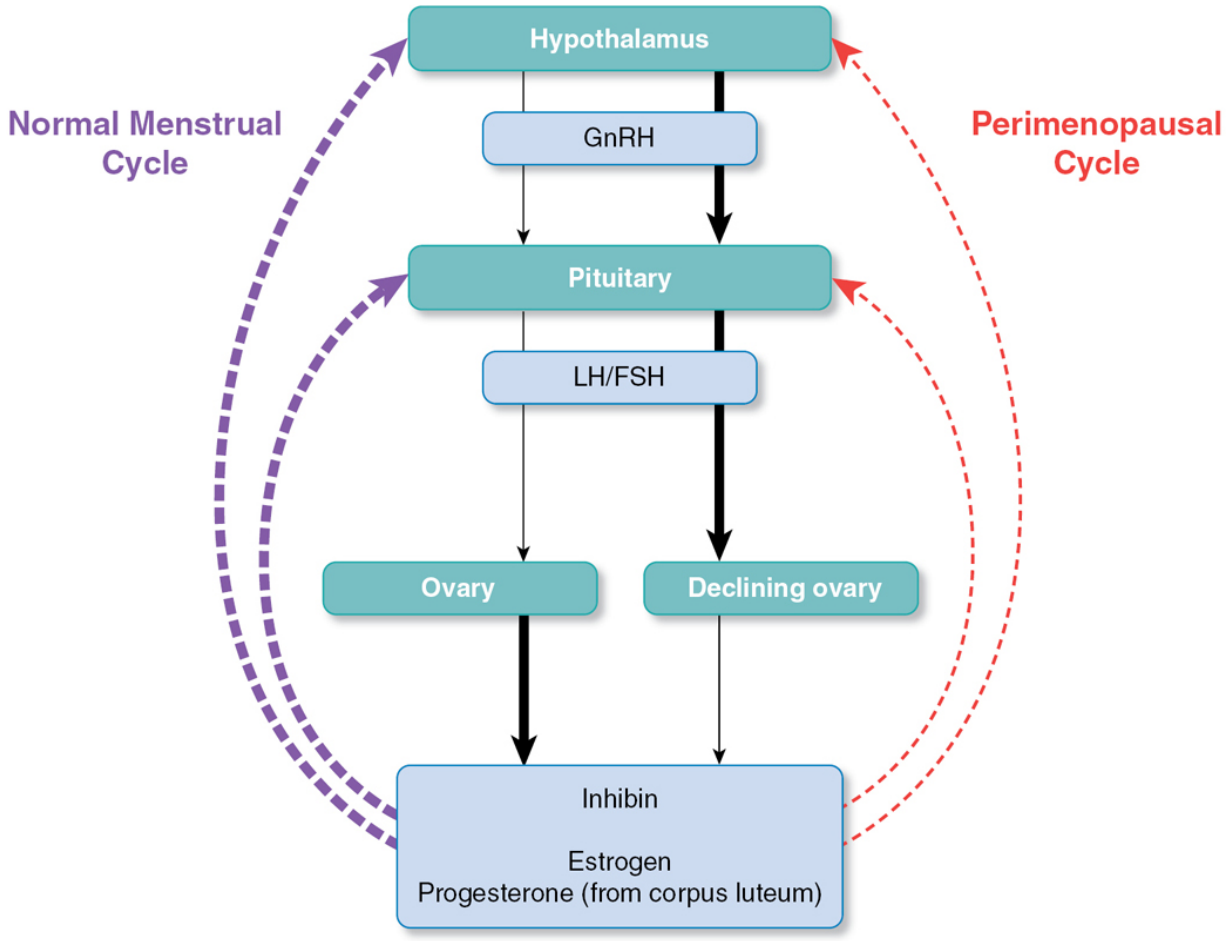


Figure 51-1 Perimenopausal changes in hypothalamus–pituitary–ovary axis. *Dashed line* indicates inhibitory effect, *solid line* stimulatory effect, and *wider line* more pronounced effect. FSH,

follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Postmenopausal estrogen production is ~10% of premenopausal levels.[6] After menopause, circulating estrogen is largely estrone, whereas the more potent estradiol is the primary estrogen during the reproductive years.[7]

Unlike the reproductive years, estrogen levels postmenopausally do not vary in a cyclic pattern. The source of postmenopausal estrogen is androstenedione, an androgen converted to estrogen by an aromatase enzyme found predominantly in fat, liver, and skin. Enzyme levels increase with age and body weight, resulting in higher estrogen levels in females with greater body fat.[7,8] As the failed ovary no longer produces progesterone, levels after menopause are roughly one-third of premenopausal levels and are derived from the adrenal gland.[7] Androgen production declines by ~50% with normal aging; however, owing to the greater drop in estrogen levels, the androgen-to-estrogen ratio increases markedly after menopause, often resulting in mild symptoms of androgenism, such as hirsutism.[7]

CLINICAL PRESENTATION

The decrease in estrogen production associated with menopause can result in clinical symptoms, such as hot flushes and genitourinary symptoms. Risk for cardiovascular disease (CVD), the leading cause of death in postmenopausal females, appears to be amplified by estrogen deficiency.[9] Postmenopausal osteoporosis may result from estrogen deficiency (see Chapter 110, Osteoporosis). Loss of estrogen has also been associated with adverse effects on cognition, neurologic functioning, well-being, and sexual health.[10] Other consequences of menopause may not yet be elucidated.

Signs and Symptoms

HOT FLUSHES

CASE 51-1

QUESTION 1: L.K., a 50-year-old female, is having sudden feelings of warmth accompanied by flushing of her skin and increased sweating for the past month. These symptoms often wake her at night. Her menses have recently been irregular (five menses in the past 12 months). Her physical examination is normal for a 50-year-old female. Her last mammogram 6 months ago was normal. She does not smoke, and her body mass index is 24 kg/m^2. She has hypertension that is controlled with hydrochlorothiazide and migraine headaches without aura, which she treats with oral sumatriptan as needed. Her family history is positive for osteoporosis but negative for CVD and breast cancer.

Which of L.K.'s current symptoms are consistent with menopause?

It appears that L.K. is having hot flushes, a vasomotor symptom (VMS) experienced by up to 80% of females during the menopause transition.[11] The onset of VMS may precede the last menstrual period, but the prevalence peaks 1 to 2 years after menopause and declines with time since menopause.[11] Frequent symptoms persist an average of 7 years; up to 30% of females may experience symptoms for >10 years.[11] Obesity and surgically induced menopause are risk factors for more frequent or severe hot flushes.[10,12] Symptoms include a feeling of warmth in the chest, neck, and facial areas that may be accompanied by visible flushing and increased sweating. Nocturnal hot flushes (night sweats) cause nighttime awakening and may lead to insomnia and sleep deprivation. Hot flushes average ~4 minutes in duration and are characteristically episodic rather than continuous but may occur hourly in females with severe symptoms.[11]

The specific etiology of hot flushes is unknown, but they are clearly associated with the declining estrogen concentrations that occur during menopause. It is postulated that the drop in estrogen leads to alterations in serotonergic and noradrenergic activity. These hormones are involved in temperature regulation; fluctuations in

levels trigger an inappropriate activation of the body's heat-release mechanisms, leading to cutaneous vasodilation and sweating seen with hot flushes.[11,13]

Cognitive and mood changes, including depression, are not uniformly associated with menopause but are reported more frequently in females during the perimenopausal period.[10,14] Genitourinary syndrome of menopause (GSM) is also associated with menopause (see Case 51-2, Question 1).[15]

Overview of Therapy

The goal of drug therapy in a symptomatic female is to relieve symptoms and improve quality of life without increasing the risk of serious adverse effects related to therapy.

TREATMENT

Case 51-1, Question 2: L.K. is seeking relief for her hot flushes but is not sure that she wants to use medications for this problem. What nonmedication therapies are appropriate for the management of L.K.'s hot flushes?

Lifestyle modifications

First-line treatment for hot flushes is lifestyle modification, including avoidance of known triggers (eg, hot beverages, alcohol, warm environments), wearing layered clothing, and the use of personal cooling devices. However, there is limited evidence for the efficacy of these interventions.[16] Weight loss in overweight females, cognitive–behavioral therapy, and clinical hypnosis may improve VMS, whereas regular exercise, yoga, and acupuncture have not demonstrated benefit.[16,17] If the patient continues to experience bothersome symptoms, drug therapy should be considered. It is noteworthy that placebo responses of 20% to 60% have been seen in clinical trials evaluating interventions for hot flushes.[16]

Black cohosh

Black cohosh (*Cimicifuga racemose*), an herbal product derived from a plant in the buttercup family, has a long tradition of use for the management of VMSs. It does not appear to have estrogenic effects but may exert a serotonergic effect.[18] Overall data do not support use; however, studies using standardized extracts have demonstrated efficacy.[19] Black cohosh is generally well tolerated, but use beyond 12 months has not been evaluated. The most common adverse effects are gastrointestinal upset and rash. There have been case reports of hepatotoxicity that cannot be directly attributed to black cohosh.[18,19]

Phytoestrogens

Phytoestrogens, including isoflavones and lignans, are plant-based substances that exhibit mild estrogenic effects. A meta-analysis of randomized, placebo-controlled trials concluded that phytoestrogens may modestly improve VMS.[20] However, further data are needed regarding optimal agent and dose. In general, isoflavones are well tolerated; the most commonly reported side effect is gastrointestinal intolerance.[19] Endometrial stimulation appears to be rare.[19] Data are limited on the safety of phytoestrogens in females with a history of estrogen-dependent disease.

L.K. does not have any estrogen-dependent diseases and, therefore, could try either black cohosh or phytoestrogens for her hot flushes if lifestyle modifications do not provide adequate benefit. She should be counseled that these products have mixed data supporting their benefits and that phytoestrogens could potentially have side effects similar to hormone therapy (HT).

Hormone therapy

Case 51-1, Question 3: L.K. returns to clinic after 2 months. She initiated lifestyle modifications and tried black cohosh but has noted worsening of her flushes, awakening multiple times at night due to night sweats, which is causing

daytime fatigue and irritability. She asks about HT to control her hot flushes. Is L.K. a candidate for hormone therapy?

HT has received a great deal of scientific and media attention during the past decades. The Women's Health Initiative (WHI), a large, prospective study of estrogen therapy (ET) and estrogen/progestogen therapy (EPT) in postmenopausal females, and several large cohort studies have provided a great deal of data, some of it conflicting, on the risks and benefits of hormone use after menopause. Before selecting a treatment option, patients should be evaluated for contraindications to HT and counseled about its possible risks and benefits (**Table 51-1**).

Table 51-1
Benefits and Risks of Postmenopausal Hormone Therapy

	Evidence	Indications/Contraindications Patient Considerations	Ref
Established Benefits[a]			
VMS	Systemic (oral or TD) ET/EPT is most effective therapy for hot flushes. There may be a dose–response relationship.	This is the primary indication for the use of systemic hormone therapy.	21,25
Osteoporosis	Numerous clinical trials support reduced risk of vertebral and hip fractures with the use of estrogen.	Provides bone protection during use of ET/EPT for menopausal symptoms.	23
Vaginal atrophy	Numerous studies show both local and systemic estrogens reverse the atrophy induced by menopause.	Localized therapy should be used for patients with only genitourinary syndrome of menopause.	15
Cardiovascular disease (CVD)	No increased risk or possible decreased risk when initiated before age 60 and within 10 years of menopause (see also established risk).	Prevention of CVD is not a primary indication for use; this information can reassure patient needing HT for menopause symptoms or replacement for females with premature ovarian failure.	24–26
Unconfirmed Benefits[b]			
All-cause mortality	Several systematic reviews noted reduced or no change in all-cause mortality in females starting HT early after menopause.	This information can be used to reassure females that timely HT use is associated with overall low risk.	26,32
Colorectal cancer	Decreased risk is seen with EPT, but not with ET.	May be secondary benefit in females using for hot flushes.	55
Recurrent UTIs and incontinence	Low-dose localized estrogen treatment can decrease the risk for recurrent UTIs and incontinence.	May be secondary benefit in females using localized therapy for vaginal atrophy.	56,57
Diabetes mellitus (DM)	Decreased incidence of new-onset diabetes in females taking EPT or ET.	This suggests that DM is not a contraindication for females who wish to use EPT/ET.	55
Cognitive effects	Some studies showed reduced risk for the development of Alzheimer dementia or cognitive deficits when HT was initiated within 5 years of menopause.	This suggests potential protective effects on cognition in females who initiate HT early after menopause.	25,58
Established Risks[a]			
Thromboembolic disease	Increased risk of DVT and PE, greatest within the first 1–2 years of use, risk with EPT possibly higher than with ET. TD estrogen has lower risk than oral estrogen.	**Absolute contraindication:** current tobacco use, history of thrombosis. **Relative contraindication:** obesity, females age 65 years and older. Therapy should be discontinued before surgery or anticipated period of immobilization.	25,32
Breast cancer	Risk increased ~25%–50% after 5 years of use, increases with continued use. Risk is higher with EPT vs ET.	**Absolute contraindication:** personal history of breast cancer. **Relative contraindication:** strong family history of breast cancer.	28–31
Cardiovascular disease	Increased risk of MI, when started >10 years after menopause or in females age 60 years or older (see also unconfirmed benefit).	**Relative contraindication:** age 60 years or older, >10 years since menopause.	24,26,32
Endometrial cancer	Risk related to dose and duration of use. Addition of adequate progestogen reduces or eliminates risk.	**Absolute contraindication:** undiagnosed postmenopausal vaginal bleeding, prior history of endometrial cancer. Rationale for the use of concomitant progestogen in patients with an intact uterus.	27
Ischemic stroke	30%–50% increased risk for ischemic stroke seen. Dose-related risk seen with both ET and EPT may be less with nonoral route. Risk higher with increasing age (because of underlying age-related risk of stroke). HT does not affect risk of hemorrhagic stroke.	**Absolute contraindication:** history of stroke or transient ischemic attacks, current tobacco use. **Relative contraindication:** obesity, uncontrolled hypertension, uncontrolled diabetes.	26,32

Gallbladder disease	~60% increased risk of cholecystitis, cholelithiasis seen with ET and EPT, less risk with nonoral route.	**Relative contraindication:** history of gallbladder disease.	55
Hypertriglyceridemia	Oral estrogen increases triglycerides. Nonoral route has less effect. EPT may have less effect than ET alone owing to attenuating effect of progestogen.	**Relative contraindication:** hypertriglyceridemia. If estrogen is to be used in female with elevated TG, select transdermal route and monitor TG levels.	59
Estrogen sensitive conditions	Systemic therapy with ET/EPT may worsen these conditions.	**Absolute contraindication:** known/suspected pregnancy **Relative contraindication:** uterine fibroids, endometriosis, porphyria	49
Unconfirmed Risks[b]			
Ovarian cancer	Increased risk seen with ET/EPT, longer durations of treatment.	**Relative contraindication:** strong family history of ovarian cancer.	60
Urinary incontinence	Systemic estrogen caused or worsened urinary incontinence, not seen with ultralow dose.	Avoid systemic estrogen in females with urinary incontinence, monitor for new onset in females taking HT.	55
Cognitive effects	Studies report worsening of dementia in females with preexisting dementia; no improvement or protection in older females taking HT.	**Absolute contraindication:** patients with evidence of dementia. Avoid use in females age 65 years or older.	21,61
Migraine headaches	HT may cause worsening of migraine headaches, nonoral estrogen and continuous progestin are preferred.	**Relative contraindication:** migraine with/without aura. Monitor for changes in HT frequency.	62

DVT, deep venous thrombosis; EPT, estrogen/progestogen therapy; ET, estrogen therapy; HA, headache; HT, hormone therapy; MI, myocardial infarction; PE, pulmonary embolism; TD, transdermally; TED, thromboembolic disease; TG, triglycerides; UTI, urinary tract infection.

[a]Well-documented benefit or risk supported by multiple clinical studies.

[b]Possible benefit or risk shown in limited clinical trials, additional data needed to confirm.

Established benefits of hormone therapy

Vasomotor Symptoms

Systemic estrogen, with or without a progestogen, is well documented to reduce the frequency and severity of hot flushes. In females with hot flushes, HT has been shown to improve quality of life.[21] During perimenopause, combined hormonal contraceptives are effective in reducing VMS as well as preventing pregnancy.[22]

Osteoporosis

Systemic HT prevents postmenopausal bone loss associated in a dose-related manner, reducing the risk of osteoporotic hip and vertebral fractures by ~25%.[23] Many estrogen products are U.S. Food and Drug Administration (FDA) approved for the prevention (but not treatment) of osteoporosis (**Table 51-2**). HT may be used for

the prevention of osteoporosis in recently menopausal females, even in the absence of menopausal symptoms, if alternate osteoporosis therapies cannot be used. Fracture protection dissipates upon discontinuation of systemic estrogen (see Chapter 110, Osteoporosis).[21] Alternative therapies should be initiated when HT is stopped in females at risk for osteoporosis.

Table 51-2
Hormones for Treatment of Vasomotor Symptoms and/or GSM

Drug (Brand Name)	Route	Initial Dosage
Estrogens, Systemic[b]		
Conjugated estrogens (Premarin®)[a] Esterified estrogen (Menest®)[a]	PO	0.3 mg
Estradiol (Estrace®)[a,c]	PO	0.5 mg
Estradiol weekly patch (Climara®)[a,c]	TD	0.025 mg/24 hour
Estradiol twice-weekly patch (Lyllana, Minivelle, Vivelle-Dot®)[a,c]	TD	0.025 mg/24 hour
Estradiol acetate vaginal ring (Femring®)[c]	HDV	0.05 mg/24-hour ring
Estradiol topical emulsion/gel/solution (Divigel®, Elestrin®, Estrogel®/Evamist®)[c]	TD	0.0125–0.75 mg (product dependent)
Progestogens (Minimum Recommended Dose to Prevent Endometrial Hyperplasia)[34]		
Medroxyprogesterone acetate (Provera®)	PO	5 mg for sequential regimen; 2.5 mg for continuous regimen
Norethindrone acetate	PO	2.5 mg for sequential regimen; 1 mg for continuous regimen
Micronized progesterone (Prometrium®)[c]	PO	200 mg for sequential regimen; 100 mg for continuous regimes
Progesterone vaginal gel (Crinone®)[c]	V	One full applicator of 4% gel every other day

Drug (Brand Name)	Route	Initial Dosage
Progesterone vaginal suppository (First® Progesterone VGS)	V	200 mg/day for 12 days
Levonorgestrel-releasing IUD (Mirena®)	IU	0.02 mg/day
Examples of Estrogen and Progestogen Combination Products		
Prempro®[a]	PO	0.3 mg CE and 1.5 mg MPA
Premphase®[a]	PO	0.625 mg CEE and 0.625 mg CEE/5 mg MPA
Climara Pro®[a,c] weekly patch	TD	0.045 mg estradiol/0.015 mg levonorgestrel/24-hour
CombiPatch®[a,c] weekly patch	TD	0.05 mg estradiol/0.014 mg norethindrone/24-hour
Low-Dose Vaginal Estrogens (Localized Effect Only)		
Conjugated equine estrogen cream (Premarin®)	LDV	0.5–2 g cream (0.3125–1.25 mg CEE) daily
Estradiol cream (Estrace®)[c]	LDV	Initial: 2–4 g cream (0.2–0.4 mg estradiol) daily
Estradiol inserts (Imvexxy®)[c]	LDV	4 µg daily
Estradiol ring (Estring®)[c]	LDV	2-mg ring (7.5 mg/day)
Estradiol tablets (Vagifem®, Yuvafem®)	LDV	One tablet (10 µg) daily

CEE, conjugated equine estrogens; HDV, high-dose vaginal estrogen, sufficient absorption to produce systemic estrogenic effect (ie, for the treatment of hot flushes); IU, intrauterine; IUD, intrauterine device; LDV, low-dose vaginal estrogen, provides localized estrogenic effect (ie, for vaginal atrophy), owing to low-dose, minimal systemic absorption; MPA, medroxyprogesterone acetate; PO, orally; TD, transdermally; V, vaginal.

[a]Approved by the U.S. Food and Drug Administration for the prevention of osteoporosis.

[b]Requires addition of progestogen in females with an intact uterus.

[c]FDA-approved bioidentical hormone.

[d]Not FDA approved in the United States, available in Canada.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

Cardiovascular Disease

Although the WHI trial was stopped early owing to evidence of increased heart disease in subjects receiving estrogen, further analysis of those data and results from other studies found no increased risk of coronary heart disease in females younger than 60 years who began therapy within 10 years of menopause. A possible reduced risk of CVD was seen in females initiating therapy before age 55 and within 2 to 3 years of menopause, whereas an increased risk was seen in females age 60 years and older who initiated HT >10 years after menopause.[24–26] In younger patients such as L.K. who initiate HT for VMS soon after the onset of menopause, the risk of CVD is not increased.

Other Possible Benefits

Less established benefits of systemic HT (see Table 51-1) include beneficial effects on diabetes mellitus and colorectal cancer.[15,21,25]

Established risks of hormone therapy

Cardiovascular Disease

As noted earlier, an increased risk of CVD has been noted in females older than 60 years who initiated HT >10 years postmenopause.[21,24,25]

Endometrial Cancer

In a patient with an intact uterus, the use of ET alone stimulates endometrial proliferation, resulting in hyperplasia and a twofold to fourfold increased risk of endometrial cancer.[25] Higher estrogen dose and longer duration of use are associated with higher risk; risk persists for several years after discontinuation of ET.[21] Addition of adequate progestogen significantly attenuates the increased risk of endometrial cancer; a progestogen should be added to ET in a patient with an intact uterus (see Case 51-1, Question 4).[21,27]

Breast Cancer

Studies demonstrate a 25% to 50% overall increased risk of invasive breast cancer with HT, with a higher risk with EPT compared to ET. Risk increases with longer duration of use and returns to baseline 5 to 10 years after HT is stopped.[28,29] There is no apparent relationship to estrogen route or dose; synthetic progestins may confer higher risk than natural agents.[30,31] A shorter interval between the onset of menopause and the initiation of HT is associated with higher risk compared with a longer interval.[28] Risk may be attenuated in females with obesity because of their baseline increased risk.[29]

Thromboembolic Disease

HT use increases the overall risk for venous thromboembolic disease (TED), including deep venous thrombosis and pulmonary embolism, approximately twofold.[21,25,32] This risk may be mediated by inhibition of hepatic synthesis of anticoagulant factors. Nonoral estrogen, which avoids the first-pass metabolic effects of oral therapy, appears to have a significantly lower risk than oral estrogen. Risk is highest within the first 2 years of treatment and decreases upon discontinuation of HT.[21,25] Observational data suggest that synthetic progesterone derivatives, but not bioidentical progesterone, further increase the risk of TED.[25] Females who are older, have a higher body mass index, or have a prothrombotic mutation are at additional risk. HT should be avoided in females with a history of or at high risk for TED.[21,25]

Other Possible Risks

Other risks of systemic HT include potential adverse effects on cognition and urinary tract function, an increased risk of stroke, and the development of ovarian cancer and gallbladder disease (see Table 51-1).[25]

Recommendations

Current guidelines on systemic HT recommend use only in females with moderate-to-severe hot flushes (**Fig. 51-2**).[21,25] For females with

premature ovarian failure, HT is recommended until the typical age of natural menopause to avoid early manifestations of estrogen deficiency.[33]

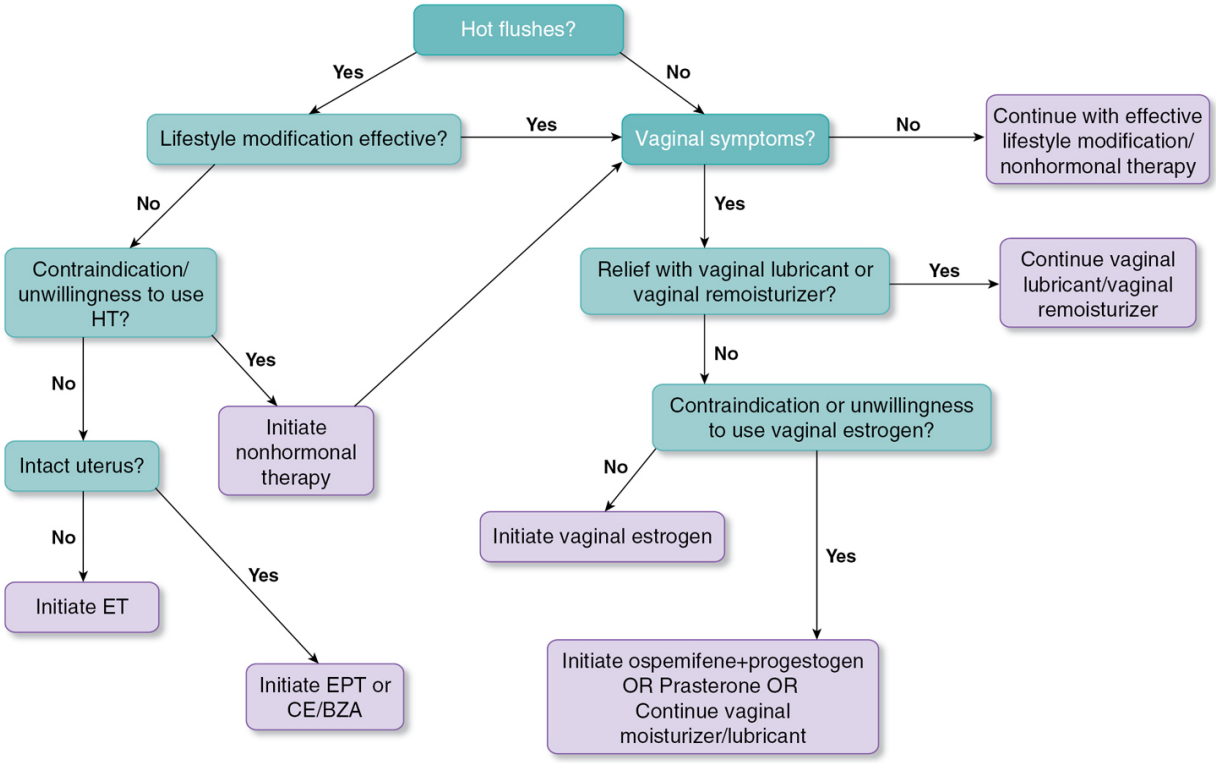


Figure 51-2 Algorithm for the management of symptomatic menopausal females. EPT, estrogen/progestogen therapy; ET, estrogen therapy; HT, hormone therapy.

As L.K. continues to experience severe hot flushes that are affecting her quality of life, as she is recently postmenopausal, and as she has no absolute contraindications to estrogen (see Table 51-1), a trial of HT is appropriate.

CASE 51-1, QUESTION 4: What is an appropriate HT regimen for the management of L.K.'s hot flushes?

SELECTION OF THERAPY

Estrogens

Multiple hormonal products are currently available for the management of VMS (Table 51-2). Oral and nonoral estrogens appear to be equally efficacious in treating VMS. Because it is associated with lower risk, nonoral estrogen is preferred in females at risk for TED, hypertension, migraine headaches, hypertriglyceridemia, or gallbladder disease.[21,25]

Current recommendations are to initiate estrogen at a low dose (eg, 0.3 mg of conjugated estrogens [CEs] or 0.025 mg of transdermal estradiol). If symptoms persist after 2 to 3 weeks of therapy, the dose of estrogen can be increased to the next available dosage strength for the product being used. Although better tolerated, ultralow-dose transdermal estradiol products (0.014 mg/24 hours) may have slower onset and lower efficacy than traditional doses.[34]

Bioidentical hormones

Bioidentical HT (BHT) is defined as having the same chemical structure as the hormones produced by the human reproductive system and includes estradiol, estrone, progesterone, and testosterone. Studies of commercially available BHT products demonstrate an efficacy and risk profile similar to synthetic hormones. Females desiring to use bioidentical products should be prescribed commercially available products (see Table 51-2); extemporaneously compounded BHT does not carry FDA-approved warnings and may be of inadequate quality.[35]

Progestogens

In patients with an intact uterus, such as L.K., a progestogen must be added to the regimen to minimize the risk of endometrial cancer (**Table 51-3**). Currently, there is no indication for the addition of a progestogen in patients without a uterus. Synthetic progestogens may be more effective at reducing risk than natural progestogens, and combined continuous regimens appear to provide better endometrial protection than sequential regimens (Table 51-3).[27,30] Although not FDA approved for this indication, progesterone vaginal

gel and progestogen-releasing intrauterine systems protect against endometrial hyperplasia from ET.[30,36]

Table 51-3
ET/EPT Regimens and Expected Vaginal Bleeding Patterns

Estrogen/Progestogen Dosing	Typical Bleeding Pattern
Combined Systemic Regimens (EPT) for Patient With Intact Uterus	
Sequential Regimens	
Estrogen: daily ***PLUS*** Progestogen: days 10–25 or 14–25 of each 28-day cycle (minimum of 10 days)	1–2 days after progestogen dosing ended[a], ~80% experience regular withdrawal bleeding throughout treatment[c] that persists throughout therapy, ~10% experience spotting[d]
Estrogen: daily ***PLUS*** Progestogen: daily for 3–5 days/week	~40% experience irregular bleeding/spotting
Continuous Regimen	
Estrogen: daily ***PLUS*** Progestogen: daily	~40% have irregular bleeding/ spotting for first 6–12 months[b] ~80% become amenorrheic within 12 months
Systemic Estrogen-only Regimens (ET) for Patients Without Uterus	
Continuous Regimen	
Estrogen (PO or TD): daily	None None

EPT, estrogen/progestogen therapy; ET, estrogen therapy; TD, transdermally.

[a]Bleeding earlier than 11 days after beginning of the progestogen suggests need for endometrial evaluation.

[b]Bleeding >6 months after initiation of therapy requires endometrial evaluation.

[c]Withdrawal bleeding is vaginal bleeding for multiple days (usually <10 days) that resembles menstrual period and requires use of a tampon or sanitary pad.

[d]Spotting is light bleeding that lasts <1 day.

Sources: Archer DF, Pickar JH, Bottiglioni F. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. Menopause Study Group. *Obstet Gynecol*. 1994;83(5 Pt 1):686–692; Furness S, Roberts H, Marjoribanks J, Lethaby

A, Hickey M, Farquhar C. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev.* 2009;(2):CD000402; Kroft J, Klostermann NR, Moody JR, Taerk E, Wolfman W. A novel regimen of combination transdermal estrogen and intermittent vaginally administered progesterone for relief of menopausal symptoms. *Gynecol Endocrinol.* 2010;26(12):902–908.

EPT may result in resumption of uterine bleeding. The pattern and frequency of bleeding depend on the EPT regimen used (Table 51-3).[37] Lower doses of estrogen are associated with a lower risk of bleeding.[38] Bleeding is a common reason for regimen discontinuation; patient preference regarding bleeding patterns should be considered when selecting an EPT regimen.[39]

Progestogen monotherapy appears to be similar to estrogen in relieving the symptoms of VMS. Effective regimens include megestrol acetate 20 mg/day orally, micronized progesterone 300 mg/day orally, and medroxyprogesterone acetate (MPA) 10 mg/day orally.[21] Adverse effects of progestogens include vaginal bleeding, fluid retention, increased appetite, breast tenderness, acne, hirsutism, headaches, mood swings, fatigue, and depression. In the absence of ET, progestogens do not appear to increase the risk of TED.[40] However, data on long-term safety, especially in regard to breast cancer, are lacking. Progestogen monotherapy for the treatment of hot flushes is generally reserved for females with contraindications to estrogen use.

DURATION OF HORMONE THERAPY

As some risks of HT increase with longer use, use beyond 5 years has generally not been recommended. However, many females continue to have VMS beyond this time frame; a thorough risk-versus-benefit review is needed to determine the appropriate duration for each female.[41] Because hot flushes are self-limiting, it can be difficult to assess whether symptom relief is related to the treatment or natural resolution of symptoms. Six to 12 months after hot flushes are fully treated, discontinuation of EPT should be attempted. There are no specific guidelines for withdrawing therapy; typical taper regimens involve decreasing the daily estrogen dose to

the next available dosage strength or increasing the dosing interval. If symptoms recur during the taper, therapy can be resumed at the lowest effective dose and another taper can be attempted in 6 months.[42,43]

ADVERSE EFFECTS

Case 51-1, Question 5: To minimize the risks of TED, L.K. is prescribed a combined estrogen/progestogen patch. How should she be counseled about possible side effects of EPT?

In addition to being counseled about the serious risks of EPT, L.K. should be advised regarding nuisance side effects from HT. Most common are resumption of vaginal bleeding and breast tenderness.[44] Nausea, weight gain, edema, headache, premenstrual syndrome–like symptoms, and increased vaginal discharge have also been reported.[45] Skin irritation may occur with the use of transdermal products. Frequently, these side effects diminish with time or may respond to a change in dosage or product. Although ET and EPT have not been shown to consistently induce or worsen hypertension, patients with hypertension, such as L.K., should be monitored for increases in blood pressure.[45,46]

TISSUE-SELECTIVE ESTROGEN COMPLEX

The tissue-selective estrogen complex (TSEC) of CE and the selective estrogen receptor modulator (SERM), bazedoxifene (BZA), is FDA approved for the treatment of VMS and the prevention of osteoporosis in postmenopausal patients with an intact uterus. The estrogen component reduces VMS and prevents bone loss, whereas the estrogen-antagonistic properties of BZA in the breast and uterus mitigate the effects of estrogen on these tissues, eliminating the need for concurrent progestogen. Clinical trials have demonstrated that CE/BZA produces fewer bleeding events and breast symptoms than the traditional combination of CE/MPA and may improve

symptoms of vaginal atrophy.[44,47] This agent is an alternative for females who do not tolerate EPT because of adverse effects.

NONHORMONAL AGENTS

Case 51-1, Question 6: L.K. returns 3 months later. Her hot flushes and night sweats resolved with EPT, but she experienced worsening of her migraine headaches, so she discontinued HT. Her hot flushes recurred soon thereafter. What alternative therapies are available for the management of L.K.'s symptoms?

Nonhormonal regimens, recommended for females with preexisting hormone-dependent cancers or females unwilling or unable to take HT, are modestly effective in reducing hot flush frequency and severity.[48] Serotonergic antidepressants may exert this effect, regulating neurotransmitter levels in the thermoregulatory area of the hypothalamus (**Table 51-4**).[49] In clinical trials, relief of VMSs with serotonergic antidepressants was seen at lower doses and with a more rapid onset than is seen for their antidepressant effects.[16] Venlafaxine and paroxetine, the most studied agents for VMSs, are considered the drugs of choice; paroxetine mesylate, at a dose of 7.5 mg, is FDA approved for this indication. Other selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors are considered the second-line agents.[16] Dosing should be initiated at the lowest effective dose (Table 51-4); this can be increased after 2 to 3 weeks if the patient has an inadequate response. To avoid withdrawal symptoms, patients should be advised not to discontinue therapy abruptly. Commonly seen side effects of nonhormonal agents are listed in Table 51-4. Paroxetine and fluoxetine are strong inhibitors of CYP2D6 and should be avoided in females taking tamoxifen because formation of its active metabolite may be reduced.[16]

Table 51-4
Nonhormonal Agents for the Management of Vasomotor Symptoms

Drug	Recommended Dosage	Common Adverse Reactions Reported
Serotonergic Antidepressants: SSRIs		
Citalopram (Celexa®) Escitalopram (Lexapro®) Fluoxetine Paroxetine hydrochloride (Paxil™, Paxil CR™) Paroxetine mesylate[a] (Brisdelle®)	10–20 mg 10–20 mg 10–20 mg 10–20 mg 12.5–25 mg (CR) 7.5 mg	Dizziness, drowsiness, headache, insomnia, diarrhea, sexual dysfunction, dry mouth, nausea
Serotonergic Antidepressants: SNRIs		
Desvenlafaxine (Pristiq®)	50–150 mg	Dizziness, drowsiness, insomnia, dry mouth, sexual dysfunction, nausea, constipation, possible increase in blood pressure at higher doses
Venlafaxine (Effexor®, Effexor® XR)	37.5–75 mg 37.5–150 mg XR	
Gabapentinoids		
Gabapentin (Neurontin®)	900–2400 mg	Somnolence, fatigue, dizziness, nausea
Pregabalin (Lyrica®)	150–300 mg	Dizziness, sleepiness, weight gain, coordination/cognitive difficulty
Antihypertensive Agents		
Clonidine	PO: 0.05–0.15 mg TD: 0.1 mg/24 hour	Headache, dry mouth, drowsiness Skin reaction/itching (patch only), risk of rebound hypertension if stopped abruptly

HTN, hypertension; PO, orally; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TD, transdermally.

[a]FDA approved for the management of vasomotor symptoms.

Sources: Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. *Menopause*. 2015;22(11):1155–1172; Shan D, Zou L, Liu X, Shen Y, Cai Y, Zhang J. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor

symptoms: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020;222(6):564–579.e12; Biglia N, Bounous VE, De Seta F, Lello S, Nappi RE, Paoletti AM. Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update. *Ecancermedicalscience*. 2019;13:909.

The antiepileptic drug gabapentin has been shown in multiple studies to decrease VMS through an unidentified mechanism. The therapeutic effect occurs at a dose of 900 mg/day with an onset within 4 weeks of starting treatment. To minimize side effects, dosing should be initiated at 300 mg daily and titrated up in 300-mg/day increments as tolerated. Although one study showed benefit with 2400 mg/day, the optimal dose of gabapentin for hot flushes is unknown.[50,51]

Paroxetine mesylate 7.5 mg daily can be tried in L.K. If her symptoms are not improved after 2 to 3 weeks, an alternate serotonergic agent can be tried with dose titration as needed.

Genitourinary Syndrome of Menopause

SIGNS AND SYMPTOMS

CASE 51-2

QUESTION 1: B.L., a 64-year-old female, presents with persistent vaginal dryness and irritation as well as pain associated with intercourse. She has tried vaginal lubricants, which help with intercourse-related pain but do not relieve her daily vaginal symptoms.

She experienced menopause at age 50, which was accompanied by moderate hot flushes for 2 to 3 years that have since resolved without intervention. She denies symptoms of urinary incontinence.

What is causing B.L.'s condition?

B.L. appears to be experiencing symptoms of GSM. Estrogen is the dominant hormone of the vagina and lower urinary tract. With the postmenopausal loss of estrogen production, the vagina decreases in size and loses its rugal pattern; the mucosa becomes pale, thin, and dry; and vaginal blood flow decreases. A decrease in *Lactobacillus* production of lactic acid leads to an increase in vaginal

pH to 5.0 or greater (compared with a premenopausal pH of 3.5–4.5).[15] These changes make the vagina more susceptible to infection from bacterial colonization and localized trauma secondary to intercourse. In the urinary tract, loss of estrogen is associated with changes to the bladder and pelvic floor.[52] Unlike hot flushes, GSM does not abate with time since menopause.

Symptoms of GSM include vaginal dryness, itching, pain, and dyspareunia (painful coitus) and recurrent urinary tract infections and stress or urge incontinence. In the United States, almost half of postmenopausal females experience symptoms of GSM; however, few report these symptoms to their health care provider.[15,52]

Case 51-2, Question 2: What would be an appropriate regimen for B.L. to decrease her vaginal symptoms?

TREATMENT

Nonhormonal treatment

Vaginal moisturizers, which are the first-line treatment, adhere to the vaginal mucosa and improve vaginal symptoms but do not reverse atrophy. Patients report symptom relief within 3 months of continuous treatment.[15] Personal lubricants can be used for dyspareunia related to GSM. Silicone and iso-osmolar water-based products are preferred to oil-based products to minimize adverse effects.[15,45] Nonhormonal treatments used for VMSs do not improve GSM symptoms.

Ospemifene (Osphena®) is an orally active vaginal tissue–specific estrogen agonist/antagonist. Ospemifene, 60 mg once daily by mouth, has shown significant improvement in dyspareunia and vaginal atrophy. Although ospemifene does not contain estrogen, it does have estrogen agonist effects, and postmenopausal females with an intact uterus should be considered for concomitant progestin therapy. Use in females with preexisting breast cancer has not been adequately studied. The most common side effect is hot flushes.[15,45]

Dehydroepiandrosterone (DHEA) (prasterone, Intrarosa®) is an FDA-approved vaginal insert for the treatment of dyspareunia in

postmenopausal females. Prasterone, an adrenal steroid metabolized to estrogen and androgen in the vaginal mucosa, has been shown to reduce symptoms of GSM. Prasterone does not induce endometrial proliferation. The most common side effects are vaginal discharge and abnormal Pap smear.[45,53] No data exist on its use in females with a history of estrogen-dependent cancer.

Localized estrogen treatment

ET reverses vaginal epithelial thinning, decreases the vaginal pH, and improves the symptoms of vaginal atrophy. For vaginal symptoms alone, low-dose vaginal estrogen is the preferred treatment. The available products (see Table 51-2) appear to be equivalent in restoring vaginal cytology and pH and in relieving symptoms of vaginal dryness, pruritus, and dyspareunia; product selection should be based on patient preference. Vaginal creams and tablets are initiated with once-daily dosing; after symptoms have resolved, the patient should be switched to maintenance dosing of once- or twice-weekly administration. The low-dose vaginal ring releases a constant dose of estrogen for 90 days.[15]

The most common adverse effects of vaginal estrogens are vaginal discharge and bleeding, vulvovaginal candidiasis, and breast tenderness. Based on limited studies, the risk of endometrial hyperplasia from low-dose vaginal estrogen is small, and the addition of a progestogen is generally considered unnecessary. In the absence of vaginal bleeding, endometrial surveillance is not needed during low-dose vaginal ET.[45] Low-dose vaginal estrogen does not appear to increase the risk for TED, CVD, or breast cancer.[15]

For females with a history of estrogen-dependent cancer, vaginal ET can be considered for the management of GSM unresponsive to nonhormonal treatments, provided that the patient is informed of the risks and benefits.[45,54]

Because B.L. has not had relief with non-HT, localized ET such as estradiol cream applied vaginally once daily is appropriate. After her

symptoms have resolved, the dose can be decreased to a maintenance regimen of twice-weekly administration.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Biglia N, Bounous VE, De Seta F, Lello S, Nappi RE, Paoletti AM. Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update. *Ecancermedicalscience.* 2019;13:909.

Cobin RH, Goodman NF; AACE Reproductive Endocrinology Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause- 2017 update [published correction appears in *Endocr Pract*. 2017;23(12):1488]. *Endocr Pract*. 2017;23(7):869–880 (25)

European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, Webber L, Davies M, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod.* 2016;31(5):926–937. (33)

Moore TR, Franks RB, Fox C. Review of efficacy of complementary and alternative medicine treatments for menopausal symptoms. *J Midwifery Womens Health*. 2017;62(3):286–297. (19)

Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. *Menopause.* 2015;22(11):1155–1172. (16)

Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med*. 2020;382(5):446–455. (41)

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728–753. (21)

The North American Menopause Society. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020;27(9):976–992. (15)

Key Websites

European Menopause and Andropause Society. http://www.emas-online.org/home
International Menopause Society. https://www.imsociety.org/
National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ng23
The North American Menopause Society. http://www.menopause.org

COMPLETE REFERENCES CHAPTER 51 THE TRANSITION THROUGH MENOPAUSE

1. Peacock K, Ketvertis KM. Menopause. In: *StatPearls*. StatPearls Publishing; 2020.
2. United States Census Bureau. Accessed October 5, 2020. https://data.census.gov/cedsci/table?q=percentage%20women%2050%20years%20or%20oler&tid=ACSST1Y2019.S0101&hidePreview=false
3. Gold EB, Crawford SL, Avis NE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. *Am J Epidemiol*. 2013;178(1):70–83.
4. Hale GE, Robertson DM, Burger HG. The perimenopausal woman: endocrinology and management. *J Steroid Biochem Mol Biol*. 2014;142:121–131.
5. Hall JE. Endocrinology of the menopause. *Endocrinol Metab Clin North Am*. 2015;44(3):485–496.
6. Rothman MS, Carlson NE, Xu M, et al. Reexamination of testosterone, dihydrotestosterone, estradiol and estrone levels across the menstrual cycle and in postmenopausal women measured by liquid chromatography-tandem mass spectrometry. *Steroids*. 2011;76(1–2):177–182.
7. Sundheimer LW, Nathan L. Menopause & postmenopause. In: DeCherney AH, Nathan L, Laufer N, Roman AS. eds. *CURRENT Diagnosis & Treatment: Obstetrics & Gynecology*. 12th ed. McGraw-Hill. Accessed September 30, 2020. https://accessmedicine.mhmedical.com/content.aspx?bookid=2559&sectionid=206968293
8. Liedtke S, Schmidt ME, Vrieling A, et al. Postmenopausal sex hormones in relation to body fat distribution. *Obesity (Silver Spring)*. 2012;20(5):1088–1095.
9. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular

outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol*. 2016;1(7):767–776.
10. Kingsberg SA, Larkin LC, Liu JH. Clinical effects of early or surgical menopause. *Obstet Gynecol*. 2020;135(4):853–868.
11. Avis NE, Crawford SL, Green R. Vasomotor symptoms across the menopause transition: differences among women. *Obstet Gynecol Clin North Am*. 2018;45(4):629–640.
12. Anderson DJ, Chung HF, Seib CA, et al. Obesity, smoking, and risk of vasomotor menopausal symptoms: a pooled analysis of eight cohort studies. *Am J Obstet Gynecol*. 2020;222(5):478.e1–478.e17.
13. Rapkin AJ. Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. *Am J Obstet Gynecol*. 2007;196(2):97–106.
14. Natari RB, Clavarino AM, McGuire TM, Dingle KD, Hollingworth SA. The bidirectional relationship between vasomotor symptoms and depression across the menopausal transition: a systematic review of longitudinal studies. *Menopause*. 2018;25(1):109–120.
15. The North American Menopause Society. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020;27(9):976–992.
16. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. *Menopause*. 2015;22(11):1155–1172.
17. Johnson A, Roberts L, Elkins G. Complementary and alternative medicine for menopause. *J Evid Based Integr Med*. 2019;24:2515690X19829380.
18. Drewe J, Bucher KA, Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. *Springerplus*. 2015;4:65.
19. Moore TR, Franks RB, Fox C. Review of efficacy of complementary and alternative medicine treatments for menopausal symptoms. *J Midwifery Womens Health*. 2017;62(3):286–297.
20. Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. *JAMA*. 2016;315(23):2554–2563.
21. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728–753.
22. Voedisch AJ, Ariel D. Perimenopausal contraception. *Curr Opin Obstet Gynecol.* 2020;32(6):399–407. doi:10.1097/GCO.0000000000000667
23. Barrionuevo P, Kapoor E, Asi N, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *J Clin Endocrinol Metab*. 2019;104(5):1623–1630.

24. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the women's health initiative randomized trials. *JAMA*. 2017;318(10):927–938.
25. Cobin RH, Goodman NF; AACE Reproductive Endocrinology Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause-2017 update [published correction appears in *Endocr Pract*. 2017;23(12):1488]. *Endocr Pract*. 2017;23(7):869–880.
26. Nudy M, Chinchilli VM, Foy AJ. A systematic review and meta-regression analysis to examine the "timing hypothesis" of hormone replacement therapy on mortality, coronary heart disease, and stroke. *Int J Cardiol Heart Vasc*. 2019;22:123–131.
27. Tempfer CB, Hilal Z, Kern P, Juhasz-Boess I, Rezniczek GA. Menopausal hormone therapy and risk of endometrial cancer: a systematic review. *Cancers (Basel)*. 2020;12(8):2195.
28. D'Alonzo M, Bounous VE, Villa M, Biglia N. Current evidence of the oncological benefit-risk profile of hormone replacement therapy. *Medicina (Kaunas)*. 2019;55(9):573.
29. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet*. 2019;394(10204):1159–1168.
30. Davey DA. Menopausal hormone therapy: a better and safer future. *Climacteric*. 2018;21(5):454–461.
31. Stute P, Wildt L, Neulen J. The impact of micronized progesterone on breast cancer risk: a systematic review. *Climacteric*. 2018;21(2):111–122.
32. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev*. 2015;(3):CD002229.
33. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI; Webber L, Davies M, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod*. 2016;31(5):926–937.
34. Mattsson LÅ, Ipsen HE, Granqvist CJ, Kokot-Kierepa M; Study Group. Ultra-low-dose estradiol and norethisterone acetate: bleeding patterns and other outcomes over 52 weeks of therapy. *Climacteric*. 2015;18(3):419–425.
35. Stanczyk FZ, Niu C, Azen C, Mirkin S, Amadio JM. Determination of estradiol and progesterone content in capsules and creams from compounding pharmacies. *Menopause*. 2019;26(9):966–971.
36. Depypere H, Inki P. The levonorgestrel-releasing intrauterine system for endometrial protection during estrogen replacement therapy: a clinical review. *Climacteric*. 2015;18(4):470–482.

37. Archer DF, Pickar JH, Bottiglioni F. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. Menopause Study Group. *Obstet Gynecol*. 1994;83(5 Pt 1):686–692.
38. Gompel A. Progesterone, progestins and the endometrium in perimenopause and in menopausal hormone therapy. *Climacteric*. 2018;21(4):321–325.
39. Pickar JH, Archer DF, Goldstein SR, Kagan R, Bernick B, Mirkin S. Uterine bleeding with hormone therapies in menopausal women: a systematic review. *Climacteric*. 2020;23(6):550–558.
40. Prior JC. Progesterone for treatment of symptomatic menopausal women. *Climacteric*. 2018;21(4):358–365.
41. Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med*. 2020;382(5):446–455.
42. Lindh-Astrand L, Bixo M, Hirschberg AL, Sundström-Poromaa I, Hammar M. A randomized controlled study of taper-down or abrupt discontinuation of hormone therapy in women treated for vasomotor symptoms. *Menopause*. 2010;17(1):72–79.
43. Haskell SG, Bean-Mayberry B, Gordon K. Discontinuing postmenopausal hormone therapy: an observational study of tapering versus quitting cold turkey: is there a difference in recurrence of menopausal symptoms? *Menopause*. 2009;16(3):494–499.
44. Kim SE, Lee DY, Choi D. Tissue-selective estrogen complex for women who experience breast discomfort or vaginal bleeding when on hormone therapy. *Menopause*. 2019;26(4):383–386.
45. Kagan R, Kellogg-Spadt S, Parish SJ. Practical treatment considerations in the management of genitourinary syndrome of menopause. *Drugs Aging*. 2019;36(10):897–908.
46. Casanova G, Bossardi Ramos R, Ziegelmann P, Spritzer PM. Effects of low-dose versus placebo or conventional-dose postmenopausal hormone therapy on variables related to cardiovascular risk: a systematic review and meta-analyses of randomized clinical trials. *J Clin Endocrinol Metab*. 2015;100(3):1028–1037.
47. Pinkerton JV. Tissue-selective estrogen complex for menopausal hormone therapy. *Clin Obstet Gynecol*. 2018;61(3):463–469.
48. Marsden J, Marsh M, Rigg A; British Menopause Society. British Menopause Society consensus statement on the management of estrogen deficiency symptoms, arthralgia and menopause diagnosis in women treated for early breast cancer. *Post Reprod Health*. 2019;25(1):21–32.
49. Krause MS, Nakajima ST. Hormonal and nonhormonal treatment of vasomotor symptoms. *Obstet Gynecol Clin North Am*. 2015;42(1):163–179.
50. Mintziori G, Lambrinoudaki I, Goulis DG, et al. EMAS position statement: non-hormonal management of menopausal vasomotor symptoms. *Maturitas*. 2015;81(3):410–413.

51. Shan D, Zou L, Liu X, Shen Y, Cai Y, Zhang J. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020;222(6):564–579.e12.
52. Angelou K, Grigoriadis T, Diakosavvas M, Zacharakis D, Athanasiou S. The genitourinary syndrome of menopause: an overview of the recent data. *Cureus*. 2020;12(4):e7586.
53. Holton M, Thorne C, Goldstein AT. An overview of dehydroepiandrosterone (EM-760) as a treatment option for genitourinary syndrome of menopause. *Expert Opin Pharmacother*. 2020;21(4):409–415.
54. Rees M, Angioli R, Coleman RL, et al. European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis. *Maturitas*. 2020;134:56–61.
55. U.S. Preventive Services Task Force; Grossman DC, Curry SJ, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: U.S. Preventive Services Task Force recommendation statement. *JAMA*. 2017;318(22):2224–2233.
56. Biehl C, Plotsker O, Mirkin S. A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. *Menopause*. 2019;26(4):431–453.
57. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obstet Gynecol*. 2014;124(6):1147–1156.
58. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(11):3975–4011.
59. Anagnostis P, Bitzer J, Cano A, et al. Menopause symptom management in women with dyslipidemias: an EMAS clinical guide. *Maturitas*. 2020;135:82–88.
60. Shi LF, Wu Y, Li CY. Hormone therapy and risk of ovarian cancer in postmenopausal women: a systematic review and meta-analysis. *Menopause*. 2016;23(4):417–424.
61. Wu M, Li M, Yuan J, et al. Postmenopausal hormone therapy and Alzheimer's disease, dementia, and Parkinson's disease: a systematic review and time-response meta-analysis. *Pharmacol Res*. 2020;155:104693.
62. MacGregor EA. Perimenopausal migraine in women with vasomotor symptoms. *Maturitas*. 2012;71(1):79–82.

SECTION 11

Endocrine Disorders

Section Editors: Jennifer D. Goldman and David Schnee

52

Thyroid Disorders

Eric F. Schneider and Kamaria K. Brown

CORE PRINCIPLES		CHAPTER CASES
1	Thyroid function tests are essential to confirm the presence of thyroid disorders but can be altered by acute and chronic illness and certain drugs. Thyrotropin (TSH) is the most accurate indicator of euthyroidism.	**Case 52-1 (Questions 1, 2) Case 52-2 (Question 1) Case 52-3 (Question 1) Case 52-4 (Question 1) Case 52-5 (Question 5) Case 52-22 (Question 1) Case 52-23 (Question 1), Tables 52-1, 52-7, Figures 52-1, 52-2**
2	Thyroid hormone deficiency can cause a goiter and hypothyroid symptoms (eg, weight gain, constipation, cold intolerance), including myxedema coma, heart failure, and hyperlipidemia. The most common cause of hypothyroidism is Hashimoto thyroiditis.	**Case 52-5 (Question 1) Case 52-8 (Question 2) Case 52-9 (Question 1) Case 52-10 (Questions 1, 2) Case 52-11 (Question 1) Case 52-12 (Question 1) Case 52-17 (Question 1), Tables 52-2, 52-3**

3	Generic or branded L-thyroxine (levothyroxine) is the preparation of choice for optimal correction of hypothyroidism. Triiodothyronine (T_3) containing preparations are not necessary because thyroxine (T_4) is converted to T_3.	**Case 52-5 (Question 2) Case 52-6 (Question 1) Case 52-9 (Question 2), Tables 52-4, 52-8**
4	The signs and symptoms of hypothyroidism can be corrected by the administration of L-thyroxine on an empty stomach at average oral replacement dosages of 1.6 µg/kg/day or intravenously. Dosing is altered by weight, comorbidities, and drug interactions.	**Case 52-5 (Questions 3–5) Case 52-7 (Question 1) Case 52-8 (Question 1) Case 52-9 (Question 2) Case 52-10 (Question 3), Tables 52-4, 52-8, 52-9**
5	The signs and symptoms of hyperthyroidism mimic those of adrenergic excess (eg, tachycardia, tremors, thyroid storm), but symptoms in the elderly may be absent ("apathetic"). Graves disease, a common cause of hyperthyroidism, can be complicated by ophthalmopathy.	**Case 52-20 (Questions 1, 2) Case 52-13 (Question 1) Case 52-18 (Questions 1, 2) Case 52-19 (Questions 1, 2), Tables 52-5, 52-6**
6	Management of hyperthyroidism includes antithyroid drugs (ATDs), iodides, radioactive iodine, and surgery. β-Blockers can provide symptomatic relief of hyperthyroid symptoms.	**Case 52-13 (Questions 2–8) Case 52-14 (Question 1) Case 52-16 (Questions 1, 2) Case 52-17 (Question 1) Case 52-19 (Question 2), Table 52-10**
7	Of the thioamides, methimazole (MMI) is preferable to propylthiouracil (PTU)	**Case 52-13 (Questions 4–7, 9, 10)**

	except during the first trimester of pregnancy and during thyroid storm. Thioamide toxicity includes gastrointestinal symptoms, rash, agranulocytosis, and hepatitis.	**Case 52-15 (Question 1)**
8	Both hypothyroidism and hyperthyroidism can alter metabolism of coadministered medications (eg, warfarin).	**Case 52-20 (Questions 2)**
9	The management of subclinical hypothyroidism and hyperthyroidism should be individualized.	**Case 52-11 (Question 1) Case 52-21 (Question 1)**
10	Certain drugs (eg, amiodarone, interferon, lithium, tyrosine kinase inhibitors) can cause thyroid disorders.	**Case 52-22 (Question 1) Case 52-23 (Question 1), Tables 52-2, 52-5**

INTRODUCTION

Thyroid disease, including hypothyroidism, hyperthyroidism, and nodular disease, are common, affecting 5% to 15% of the general population. Females are affected three to four times more than males.[1,2] Triiodothyronine (T_3) and thyroxine (T_4) are the two biologically active thyroid hormones produced by the thyroid gland. The hypothalamic thyrotropin-releasing hormone (TRH) stimulates release of thyrotropin (thyroid-stimulating hormone [TSH]) from the pituitary in response to low circulating levels of thyroid hormone. TSH in turn promotes hormone synthesis and release by increasing thyroid activity. High-circulating thyroid hormone levels block further production by inhibiting TSH release (negative feedback). As the serum concentrations of thyroid hormone decrease, the

hypothalamic– pituitary centers again become responsive by releasing TRH and TSH (**Fig. 52-1**).

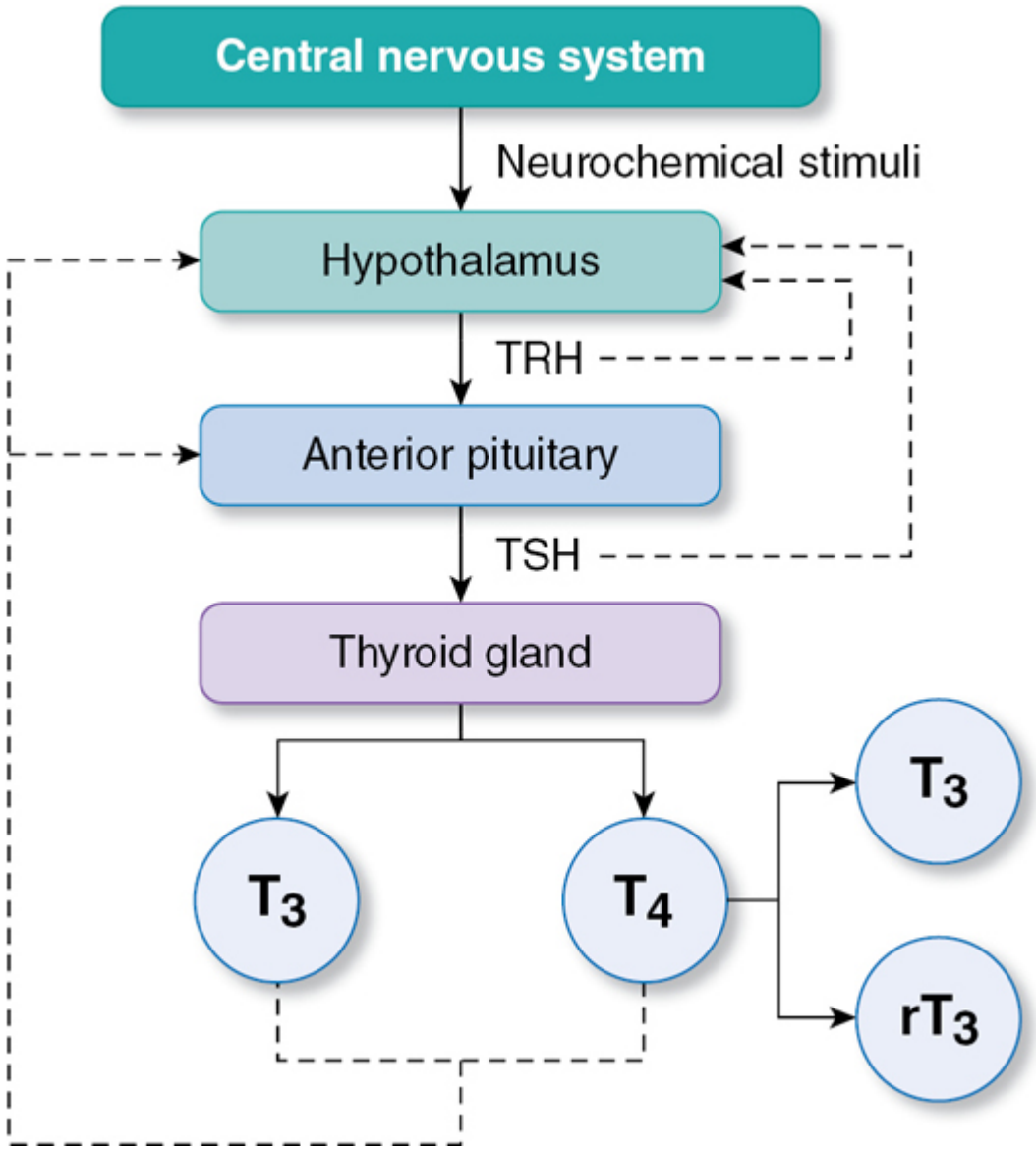


Figure 52-1 Regulation of thyroid hormone secretion. Release of thyroid hormones is controlled by the hypothalamic–pituitary–thyroid axis. Dashed lines represent negative feedback, rT_3, reverse triiodothyronine (inactive); T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone or thyrotropin.

T_3 is four times more potent than T_4, the major circulating hormone secreted by the thyroid. About 80% of the total daily T_3 production results from the peripheral deiodination of T_4 to T_3. Approximately 35% to 40% of secreted T_4 is converted peripherally to T_3; another 45% of secreted T_4 undergoes peripheral conversion to inactive reverse T_3 (rT_3). Certain drugs and diseases can modify the conversion rate of T_4 to T_3 and reduce the serum T_3 levels (**Table 52-1**[3,4]; see Case 52-1, Question 2).

Table 52-1
Factors That Can Significantly Alter Thyroid Function Tests in Patients Who Are Euthyroid

Factors	Drugs/Situations
Elevated TBG Binding Capacity	
Elevated TT_4	Estrogens,[3,4] tamoxifen,[71] raloxifene[70]
Elevated TT_3	Oral contraceptives[23]
Normal TSH	Heroin[69]
Normal FT_4I, FT_4	Methadone maintenance[69]
Normal FT_3I, FT_3	Genetic elevation in TBG
	Clofibrate
	Active hepatitis[47,48]
Decreased TBG Binding Capacity/Displacement T4 From Binding Sites	
Decreased TT_4	Androgens[23]
Decreased TT_3	Salicylates,[23,61,62] salsalate[62]
Normal TSH	High-dose furosemide
Normal FT_4I, FT_4	Decreased TBG synthesis-cirrhosis/hepatic failure
Normal FT_3I, FT_3	Nephrotic syndrome[23,47,48]
	Danazol[23,47,48]
	Glucocorticoids[23,47,48,73]
Decreased Peripheral T4 → T3 Conversion	

Factors	Drugs/Situations
Decreased TT_3	PTU
Normal TT_4	Propranolol[193]
Normal FT_4I, FT_4	Glucocorticoids[23,73,280]
Normal TSH	
Decreased Pituitary and Peripheral T4 → T3	
Decreased TT_3	Iodinated contrast media (eg, ipodate)[281-285]
Elevated TT_4	Amiodarone[5,14,19]
Elevated TSH (transient)	Nonthyroidal illness[53,55,286]
Elevated FT_4I	
Elevated T4 Clearance by Enzyme Induction/Elevated Fecal Loss[a]	
Decreased TT_4	Phenytoin[63,64]
Decreased FT_4I	Phenobarbital[63]
Normal or Decreased FT_4	Carbamazepine[63–68]
Normal or Decreased TT_3	Cholestyramine, colestipol[105]
Normal or elevated TSH	Rifampin[63]
	Bexarotene[22]
Decreased TSH Secretion	
	Dopamine,[23,47,48] dobutamine[287]
	Levodopa,[23] cabergoline[288]
	Glucocorticoids[23,49,73]
	Bromocriptine,[23] Pramipexole,[72,73] Ropinirole[72,73]
	Octreotide[50]
	Metformin[74,75]
	Bexarotene[12]
Elevated TSH Secretion	
	Metoclopramide[23,47]
	Domperidone[23,47]

FT_3, free triiodothyronine; FT_3I, free triiodothyronine index; FT_4, free thyroxine; FT_4I, free thyroxine index; PTU, propylthiouracil; T_3, triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone; TT_3, total triiodothyronine; TT_4, total thyroxine.

[a]Can also cause hypothyroidism in patients receiving L-thyroxine therapy.

T_4 exists in the circulation as 0.1% free (active) and 99.9% protein-bound (inactive), primarily to thyroxine-binding globulin (TBG) with a long half-life ($t_{1/2}$) of 7 days. T_3 is bound to plasma proteins (99.8%), with about 0.2% free and has a threefold greater metabolic potency and a shorter $t_{1/2}$ of 1.5 days.[2]

Hypothyroidism is a clinical syndrome that results from a deficiency of thyroid hormone. The prevalence of hypothyroidism is 1.4% to 2% in females and 0.1% to 0.2% in males and is increased to 6% of females and 2.5% of males in persons older than 60 years.[1] Hypothyroidism can be caused by either primary (thyroid gland) or, less commonly, by secondary (hypothalamic–pituitary) malfunction.

Hashimoto thyroiditis, an autoimmune disorder, is the most common cause of primary hypothyroidism and appears to have a strong genetic predisposition. The pathogenesis of Hashimoto thyroiditis results from an impaired immune surveillance, causing dysfunction of normal suppressor T lymphocytes and excessive production of thyroid antibodies by plasma cells (differentiated B lymphocytes). The destruction of thyroid cells by circulating thyroid antibodies produces an underlying defect or block in the intrathyroidal, organobinding of iodide. The typical presentation is hypothyroidism and goiter (thyroid gland enlargement), but patients can present with hypothyroidism and no goiter, with euthyroidism and goiter, or rarely (<5%) with hyperthyroidism (hashitoxicosis).

Other common causes of hypothyroidism, including drug-induced, are presented in **Table 52-2**.[5–27]

Table 52-2
Causes of Hypothyroidism

Primary Hypothyroidism (Dysfunction of the Gland)[136,289,290]

Autoimmune thyroiditis (Hashimoto thyroiditis)
Idiopathic atrophy
Iatrogenic destruction of thyroid (surgery, radioactive iodine therapy, x-ray therapy)
Iodine deficiency
Dyshormonogenesis: defect in hormone synthesis, transport, or action
Thyroiditis (subacute, postpartum, silent, destructive)
Congenital hypothyroidism (thyroid aplasia/hypoplasia, defective hormone synthesis)
Secondary Hypothyroidism[134,289,290]
Deficiency of TSH because of pituitary dysfunction (Sheehan syndrome)
Deficiency of TRH because of hypothalamic dysfunction
Drug-Induced
Aminoglutethimide[23]
Amiodarone[5,14,19]
Bexarotene[12,22]
Ethionamide[20]
Iodides and iodide-containing preparations[18]
Rifampin[24]
Tyrosine kinase inhibitors (eg, imatinib, sunitinib, sorafenib)[10,11,16,21]
Interleukin[13,25]
Interferon-α [8,9,17,26]
Lithium[6,7,15]
Thiocyanates, phenylbutazone, sulfonylureas[23]

TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

Sources: Vaidya B, Anthony S, Bilous M, et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab*. 2007;92:203; McDermott MT. Hypothyroidism. *Ann Intern Med*. 2020;173(*1*):ITC1–ITC16. doi:10.7326/AITC202007070; Vaidya B, Pearce SH. Management of hypothyroidism in adults. *BMJ*. 2008;337:a801. doi:10.1136/bmj.a801.

The clinical presentation, physical findings, and laboratory abnormalities of overt hypothyroidism are summarized in **Table 52-3**. Myxedema coma is a rarely occurring, often fatal medical emergency resulting from long-standing, uncorrected hypothyroidism (see Case 52-9). Patients with myxedema coma can present with hypothermia, confusion, coma, carbon dioxide retention, hypoglycemia, hyponatremia, and ileus. Hypothyroid symptoms increase with the severity of the hypothyroidism, except in older patients who often present with minimal or atypical symptoms. Patients with subclinical hypothyroidism might have few or no symptoms. Laboratory findings that are diagnostic for overt hypothyroidism include elevated TSH and low free thyroxine (FT_4) levels; for subclinical or early hypothyroidism, the findings are an elevated TSH and normal FT_4 levels. Despite the prevalence of asymptomatic subclinical disease, there is no universally agreed upon strategy for screening for thyroid disorders. Recommendations range from screening all adults over age 35 every 5 years (American Thyroid Association) to insufficient evidence for or against screening any specific population of patients (U.S. Preventive Task Force).[28–30]

Table 52-3

Clinical and Laboratory Findings of Primary Hypothyroidism

Symptoms	Physical Findings	Laboratory
General: weakness, tiredness, lethargy, fatigue	Thin and brittle nails	Decreased TT_4
Cold intolerance	Thinning of skin	Decreased FT_4I
Headache	Pallor	Decreased FT_4
Loss of taste/smell	Puffiness of face, eyelids	Decreased TT_3
Deafness	Yellowing of skin	Decreased FT_3I
Hoarseness	Thinning of outer eyebrows	Elevated TSH

Symptoms	Physical Findings	Laboratory
No sweating	Thickening of tongue	Positive antibodies (in Hashimoto)
Modest weight gain	Peripheral edema	Elevated cholesterol
Elevated cholesterol Muscle cramps, aches, pains	Pleural/peritoneal/pericardial effusions	Elevated CPK
Dyspnea	Decreased DTRs	Decreased Na
Slow speech	“Myxedema heart”	Elevated LDH
Constipation	Bradycardia (Decreased HR)	Elevated AST
Menorrhagia	Hypertension	Decreased Hct/Hgb
Galactorrhea	Goiter (primary hypothyroidism)	

AST, aspartate aminotransferase; CPK, creatinine phosphokinase; DTRs, deep tendon reflexes; Hct, hematocrit; Hgb, hemoglobin; HR, heart rate; LDH, lactate dehydrogenase; FT_3I, free triiodothyronine index; FT_4, free thyroxine; FT_4I, free thyroxine index; Na, sodium; TSH, thyroid-stimulating hormone; TT_3, total triiodothyronine; TT_4, total thyroxine.

Sources: Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Practice Guideline. *Endocr Pract.* 2012;18(6):988–1028. doi:10.4158/EP12280.GL; Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. *Thyroid*. 2014;24(*12*): 1670–1751. doi:10.1089/thy.2014.0028; McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab.* 2001;86:4585–4590; McDermott MT. Hypothyroidism. *Ann Intern Med*. 2020;173(*1*):ITC1–ITC16. doi:10.7326/AITC202007070; Vaidya B, Pearce SH. Management of hypothyroidism in adults. *BMJ*. 2008;337:a801. doi:10.1136/bmj.a801.

L-Thyroxine, at an oral replacement dosage of 1.6 μg/kg/day administered on an empty stomach, is the preferred thyroid replacement preparation.[31,32] Several brand name and less costly generic preparations are interchangeable in most patients. Older patients, those with severe hypothyroidism, and those with cardiac

disease may require minute T_4 doses initially to avoid cardiac toxicity (**Table 52-4**); complete reversal of hypothyroidism might not be indicated or possible. In myxedema coma (see Case 52-9, Question 2), an intravenous (IV) L-thyroxine loading dose is necessary to reduce the high mortality rate. In subclinical hypothyroidism (see Case 52-11), T_4 replacement therapy is beneficial in those with TSH >10 milli-international units (IU)/mL (normal, 0.40–4.5 μIU/).

Table 52-4
Treatment of Hypothyroidism

Patient Type/Complications	Dose (L-Thyroxine)	Comment
Uncomplicated adult	1.6 μg/kg/day; 100–125 μg/day average replacement dose; usual increment 25 μg q6–8 wk	*Onset of action:* 2–3 weeks; *max effect:* 4–6 weeks. Reversal of skin and hair changes may take several months. An FT_4 and TSH should be checked 6–8 weeks after initiation of therapy because T_4 has a half-life of 7 days, and three to four half-lives are needed to achieve steady state. Levels obtained before steady state can be very misleading. Because 80% is bioavailable, adjust IV doses downward. Small changes can be made by varying dose schedule (eg, 150 μg daily except Sunday).
Elderly	50 μg/day	Initiate T_4 cautiously. Elderly may require less than younger patients. Sensitive to small dose changes. Patients older than 60 years may require ≤50 μg/day.
Cardiovascular disease (angina, CAD)	Start with 12.5–25 μg/day. Elevated by 12.5–25 μg/day q2–6 wk as tolerated	These patients are very sensitive to cardiovascular effects of T_4. Even subtherapeutic doses can precipitate severe angina, MI, or death. Replace thyroid deficit slowly, cautiously, and sometimes even suboptimally.

Patient Type/Complications	Dose (L-Thyroxine)	Comment
Long-standing hypothyroidism (>1 year)	Dose slowly. Start with 25 μg/day; elevated by 25 μg/day q4–6 wk as tolerated	Sensitive to cardiovascular effects of T_4. Steady state may be delayed because of Decreased clearance of T_4.[a] Correct replacement dose is a compromise between prevention of myxedema and avoidance of cardiac toxicity.
Pregnancy	Most will require 45% elevation in dose to ensure euthyroidism	Evaluate TSH, TT_4, and FT_4I. *Goal:* Normal TSH and TT_4/FT_4I in upper normal range to prevent fetal hypothyroidism. TSH should be no higher than 2.5 μIU/mL during the first trimester and 3.0 μIU/mL in the second and third trimesters.
Pediatric (0–3 months)	10–15 μg/kg/day	Hypothyroid infants can exhibit skin mottling, lethargy, hoarseness, poor feeding, delayed development, constipation, large tongue, neonatal jaundice, piglike facies, choking, respiratory difficulties, and delayed skeletal maturation (epiphyseal dysgenesis). The serum T_4 should be increased rapidly to minimize impaired cognitive function. In the healthy term infant, 37.5–50 μg/day of T_4 is appropriate. Dose decreases with age (Table 52-9).

CAD, coronary artery disease; FT_4, free thyroxine; FT_4I, free thyroxine index; IV, intravenous; MI, myocardial infarction; q, every; T_4, thyroxine; TSH, thyroid-stimulating hormone; TT_4, total thyroxine.

[a]In patients with severe myxedema, steady state may require ≥6 months. In patients who are clinically euthyroid but have Elevated TT_4 and FTI, use TT_3 and TSH as guide to dose adjustments.

Sources: Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Practice Guideline. *Endocr Pract*. 2012;18(6):988–1028. doi:10.4158/EP12280.GL; Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement.

Thyroid. 2014;24(*12*):1670–1751. doi:10.1089/thy.2014.0028; Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis*. 2010;5:17. doi:10.1186/1750-1172-5-17; McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab*. 2001;86:4585–4590; McDermott MT. Hypothyroidism. *Ann Intern Med*. 2020;173(*1*):ITC1–ITC16. doi:10.7326/AITC202007070; Vaidya B, Pearce SH. Management of hypothyroidism in adults. *BMJ*. 2008;337:a801. doi:10.1136/bmj.a801.

The goal of therapy is to reverse the signs and symptoms of hypothyroidism and normalize the TSH and FT_4 levels without causing iatrogenic thyrotoxicosis.[32] Some improvement of hypothyroid symptoms is often evident within 2 to 3 weeks of starting T_4 therapy, before steady state is reached. Overreplacement of T_4 (ie, suppressed serum concentrations of TSH) is associated with osteoporosis and cardiac toxicity. The optimal T_4 replacement dosage must be administered for ~6 to 8 weeks to achieve steady-state levels. The list of medications that interfere with T_4 absorption is extensive (eg, iron, aluminum-containing products, some calcium preparations, cholesterol resin, phosphate binders, sucralfate, and bile acid sequestrants).[32] These agents should be separated by at least 4 hours from concomitant T_4 administration.[32]

Hyperthyroidism or thyrotoxicosis is the hypermetabolic syndrome that occurs from excessive thyroid hormone production. Hyperthyroidism affects about 1.3% of the U.S. population (0.5% clinical disease and 0.7% subclinical hyperthyroidism).[1] The condition is more prevalent in females and White patients and increases with age.[1]

The classic symptoms of hyperthyroidism are summarized in **Table 52-5**. The typical symptoms are often absent in the older patient, producing a masked or “apathetic” picture. Because of the atypical presentation in the older patient, occult hyperthyroidism always must be considered, especially in patients with new or worsening cardiac findings (eg, atrial fibrillation). Untreated hyperthyroidism can progress to thyroid storm, a life-threatening form of hyperthyroidism characterized by exaggerated symptoms of thyrotoxicosis and the acute onset of high fever. The diagnosis of

hyperthyroidism is confirmed by high serum concentrations of FT_4 and free T_3 (FT_3) or an undetectable TSH level. Positive thyroid antibodies confirm an autoimmune origin for the hyperthyroidism (eg, Graves disease).[33]

Table 52-5
Clinical and Laboratory Findings of Hyperthyroidism

Symptoms
Heat intolerance
Weight loss common, or weight gain caused by Elevated appetite
Palpitations
Pedal edema
Diarrhea/frequent bowel movements
Amenorrhea/light menses
Tremor
Weakness, fatigue
Nervousness, irritability, insomnia
Physical Findings
Hair loss
Proptosis, lid lag, lid retraction, stare, chemosis, conjunctivitis, periorbital edema, loss of extraocular movements
Diffusely enlarged goiter, bruits, thrills
Wide pulse pressure
Pretibial myxedema
Plummer nails[a]
Flushed, moist skin
Palmar erythema
Brisk DTRs
Laboratory Findings
Elevated TT_4
Elevated TT_3

Elevated FT_4I/FT_4
Elevated FT_3I/FT_3
Suppressed TSH
TSI present
TgAb present
TPOAb present
RAIU >50%
Decreased cholesterol
Elevated alkaline phosphatase
Elevated calcium
Elevated AST

AST, aspartate aminotransferase; DTRs, deep tendon reflexes; FT_3, free triiodothyronine; FT_3I, free triiodothyronine index; FT_4, free thyroxine; FT_4I, free thyroxine index; RAIU, radioactive iodine uptake; TgAb, thyroglobulin autoantibodies; TPOAb, thyroid peroxidase antibody; TSI, thyroid-stimulating immunoglobulin; TSH, thyroid-stimulating hormone; TT_3, total triiodothyronine; TT_4, total thyroxine.

[a]The fingernail separates from its matrix, but only one or two nails are generally affected.

Sources: Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum. *Thyroid*. 2017;27(3):315–389. doi:10.1089/thy.2016.0457; Smith TJ, Hegedus L. Graves' disease. *N Engl J Med*. 2016;375(*16*):1552–1565. doi:10.1056/NEJMra1510030; Brent GA. Graves' disease. *N Engl J Med*. 2008;358:2594–2605; Nayak B, Burman K. Thyrotoxicosis and thyroid storm. *Endocrinol Metab Clin North Am*. 2006;35:663–686; Iagaru A, McDougall IR. Treatment of thyrotoxicosis. *J Nucl Med*. 2007;48:379; Takasu N, Seki H. Plummer's nails (onycholysis) in a thyroid-stimulation-blocking antibody (TSBAb)-positive patient with hypothyroidism. *Intern Med*. 2018;57(*20*):3055–3056. doi:10.2169/internalmedicine.0809-18.

Graves disease, an autoimmune disease, is the most common cause of hyperthyroidism. Characteristics include diffuse goiter, ophthalmopathy (exophthalmos), dermopathy (pretibial myxedema), and acropachy (thickening of fingers or toes). The production of excessive thyroid hormone is attributed to a circulating immunoglobulin G or thyroid receptor antibody (TRAb), which has a

TSH-like ability to stimulate hormone synthesis. The abnormal production of TRAb differentiated B lymphocytes results from a deficiency of suppressor T-cell lymphocytes. Other causes of hyperthyroidism, including iatrogenic, are outlined in **Table 52-6**.[5,13,14,17,19,23,26,34–38]

Table 52-6
Causes of Hyperthyroidism

Graves disease (toxic diffuse goiter); may be caused by polymorphisms in the TSH receptor
Toxic uninodular goiter (Plummer disease)
Toxic multinodular goiter
Nodular goiter with hyperthyroidism caused by exogenous iodine (Jod-Basedow)
Iatrogenic thyrotoxicosis (prescription of excessive thyroid hormone dosage)
Factitious hyperthyroidism (exogenous thyroid excess through self-administration)
Tumors (thyroid adenoma, follicular carcinoma, thyrotropin-secreting tumor of the pituitary, and hydatidiform mole with secretion of a thyroid-stimulating substance)
Drug-induced (iodides,[37] amiodarone,[5,14,19] interleukin,[13,23] interferon-α,[17,26] lithium[34,35])

Sources: Peeters RP, van der Deure WM, Visser TJ. Genetic variation in thyroid hormone pathway genes: polymorphisms in the TSH receptor and the iodothyronine deiodinases. *Eur J Endocrinol*. 2006;155:655–662; Cappelli C, Rotondi M, Pirola I, et al. TSH-lowering effect of metformin in type 2 diabetic patients: differences between euthyroid, untreated hypothyroid, and euthyroid on L-T4 therapy patients. *Diabetes Care.* 2009;32(*9*):1589–1590. doi:10.2337/dc09-0273; Iagaru A, McDougall IR. Treatment of thyrotoxicosis. *J Nucl Med*. 2007;48:379–389; Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011;17(*3*):456–520; Kravets I. Hyperthyroidism: diagnosis and treatment. *Am Fam Physician*. 2016;93(*5*):363–370.

Both Graves disease and Hashimoto thyroiditis share similar clinical features and can exist in the same gland: positive antibody titers, goiter with lymphocytic infiltration of the gland, familial

tendency, and predilection for females. Thyrotoxicosis can precede the onset of Hashimoto hypothyroidism, and the end result of Graves hyperthyroidism is often hypothyroidism.[39]

Effective treatment options for hyperthyroidism include thioamide antithyroid drugs (ATDs), radioiodine, and surgery. Therapy selection is influenced by the etiology of the hyperthyroidism, size of the goiter, presence of eye complications (ophthalmopathy), coexisting conditions (eg, angina, pregnancy), patient age, patient preference, and physician preference. Radioactive iodine (RAI) is preferred in older patients, those with coexisting cardiac disease, ophthalmopathy, and a toxic multinodular goiter, whereas surgery is appropriate if obstructive symptoms are present or concomitant malignancy is suspected. Pregnant patients can be managed with ATDs or surgery in the second trimester; RAI is absolutely contraindicated.[40,41]

The ATDs (eg, methimazole, propylthiouracil) primarily prevent hormone synthesis but do not affect existing stores of thyroid hormone. Therefore, hyperthyroid symptoms will continue for 4 to 6 weeks after beginning ATD therapy and initial treatment with β-blockers or iodides is often required for symptomatic relief. Methimazole (MMI), given once daily, is considered the ATD of choice versus propylthiouracil (PTU), which requires two to three times daily dosing and has been associated with severe and fatal hepatitis. PTU should be reserved for use during pregnancy, in thyroid storm, and in those experiencing adverse reactions to methimazole (other than agranulocytosis or hepatitis). The onset of action of PTU is more rapid than MMI in thyroid storm because PTU can also inhibit the peripheral conversion of T_4 to T_3. PTU is also preferred during the first trimester of pregnancy because congenital defects have been reported with MMI. Although both drugs are secreted in breast milk, no adverse effects have been reported in the exposed infants. The duration of treatment is empiric, and ATDs typically are prescribed for 12 to 18 months in hopes of long-term spontaneous remission once the drug is discontinued.[42] Although ATDs maintain euthyroidism, they do not change the natural course

of the disease and the likelihood of spontaneous remission once treatment is discontinued is about 60%. Major adverse effects from ATDs include skin rash, gastrointestinal (GI) symptoms (eg, nausea, upset stomach, and metallic taste), agranulocytosis, and hepatitis. Cross-sensitivity between the ATDs is not complete, and the alternative drug can be used if rash or GI symptoms do not resolve. This is not true for agranulocytosis and hepatitis where the alternative agent is not recommended.[43]

Nodular goiters, both multinodular and uninodular, are common thyroid problems that occur in 4% to 5% of the adult population. The nodular goiter is usually found on routine physical examination in patients who are asymptomatic and euthyroid. A *cold nodule* is a "hypofunctioning" area of the thyroid that fails to collect radioiodine. *Hot nodule* is a term used to describe a "hyperfunctioning" or iodine-concentrating area of the thyroid. The hyperfunctioning autonomous nodule typically suppresses activity in the remainder of the gland, but it need not produce clinical or chemical evidence of hyperthyroidism and may remain unchanged for years. Some nodules may develop into toxic goiters, causing overt symptoms of toxicosis. Most hot nodules are benign; malignancies are rarely reported.[44,45] Treatment options include surgery, RAI, or thyroid replacement therapy if hypothyroid. All goitrogens should be removed if possible. L-Thyroxine suppression therapy is no longer recommended because the dangers from supraphysiologic dosages of T_4 (eg, osteoporosis and the potential for cardiac arrhythmias) outweigh the benefits. Nontoxic multinodular goiter is a common finding in about 5% of the population.[44,45] In low-risk patients, long-standing asymptomatic nodules that have not exhibited recent growth are likely to be benign and can be followed or excised surgically for cosmetic reasons. If the patient develops symptoms (swallowing or respiratory difficulty), surgery is the treatment of choice. Observation with close follow-up is the preferred treatment option for most benign multinodular goiters.[44,45]

Malignancy must be considered if there is recent growth in a "cold" single or dominant nodule, a firm nodule clinically suspicious for

cancer on a physical examination, a history of thyroid irradiation, or a strong family history of medullary thyroid carcinoma. Most cold nodules turn out to be benign adenomas rather than cancers. The incidence of malignancy in a cold nodule varies between 10% and 20%.[44] A fine-needle aspiration (FNA) of the thyroid nodule can document an underlying malignancy. Surgery is indicated if malignancy is suspected or if any obstructive or respiratory symptoms are present. After a total thyroidectomy for thyroid cancer, RAI ablation is usually given to remove any remaining thyroid tissue. A yearly evaluation for detection of recurrence of some thyroid cancers requires the patient to be off T_4 for 4 to 6 weeks so that a repeat radioactive uptake and scan can be completed. An elevated TSH level is also necessary to allow thyroglobulin levels, a tumor marker, to rise if any malignant tissue is present.[44,46]

THYROID TESTS

The principal laboratory tests recommended in the initial evaluation of thyroid disorders are the TSH and the FT_4 levels.[47,48] Testing for thyroid disorders, whether it be for diagnosis in symptomatic patients or screening at risk populations, should begin with assessment of TSH. Where TSH is abnormal, assessment of free T_4 should occur to confirm the presence of clinical or subclinical disease.[28] Other tests are available to further evaluate function of the thyroid gland as well as thyroid disease etiology. The presence of thyroid antibodies indicates an autoimmune thyroid etiology. Adjuncts to the previous tests include the total T_3 (TT_3), free T_3 (FT_3) or FT_3 index (FT_3I), and TRAb (**Table 52-7**).[49] The relationship between laboratory tests and thyroid disorders is summarized in **Figure 52-2**.

Table 52-7
Common Thyroid Function Tests

Tests	Measures	Normal[a]	Assay Interference	Comments
Hypothalamic–Pituitary–Thyroid Axis				
TSH	Pituitary TSH level	0.40–4.5 μIU/mL	Dopamine, glucocorticoids, metoclopramide, thyroid hormone, amiodarone, metformin (Table 52-1), biotin	Most sensitive index for hyperthyroidism, hypothyroidism, and replacement therapy
Circulating Hormone Levels				
FT_4	Direct measurement of free thyroxine	0.8–1.8 ng/dL (10–23 pmol/L)	No interference by alterations in TBG, biotin may interfere with assay	Most accurate determination of FT_4 levels; might be higher than normal in patients on thyroxine replacement
T_3RU (THBR)	Measures the uptake of T_3 by TBG	22%–35%	Biotin	Indirect and reciprocal estimate of the available binding sites on TBG
FT_4I	Calculated free thyroxine index $TT_4 \times T_3RU$	1.4–3.8	Nonthyroidal illness (see Case 52-1, Question 2)	Estimates direct FT_4 measurement; compensates for alterations in TBG
TT_4	Total free and bound T_4	4.8–10.4 μg/dL (62–134 nmol/L)	Alterations in TBG (Table 52-1), biotin	Specific and sensitive test if no alterations in TBG
TT_3	Total free and bound T_3	76–181 ng/dL (1.2–2.8nmol/L)	Alterations in TBG levels; T_4 to T_3 (Table 52-1). Nonthyroidal illness (see Case 52-1, Question 2), biotin	Useful in detecting early, relapsing, and T_3 toxicosis; not useful in evaluation of hypothyroidism
FT_3	Direct measurement of free T_3	2.3–4.2 pg/mL (3.5–6.5 pmol/L)	No interference by alterations in TBG, biotin may interfere with assay	Most accurate determination of FT_4 levels; might be lower than normal in patients on thyroxine replacement
FT_3I	Calculated free T_3 index	80–180	Nonthyroidal illness (see Case 52-1, Question 2)	Estimates direct FT_3 measurement; compensates for alterations in TBG
Autoimmunity				
TgAb	Thyroglobulin autoantibodies	<1 IU/mL	Nonthyroidal autoimmune disorders	Present in autoimmune thyroid disease; undetectable during remission
TPOAb	Thyroid peroxidase antibodies	<9 IU/mL	Nonthyroidal autoimmune disorders	More sensitive of the two antibodies; titers detectable even after remission
TSI	Thyroid-stimulating antibody	<140%		Confirms Graves disease; detects risk of neonatal Graves
TRAb	Thyroid receptor antibody	<2.0 IU/L		Confirms Graves disease; detects risk of neonatal Graves

FT_3, free triiodothyronine; FT_3I, free triiodothyronine index; FT_4, free thyroxine; FT_4I, free thyroxine index; T_3, triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; TgAb, thyroglobulin autoantibodies; TPOAb, thyroid peroxidase antibodies; TSI, thyroid receptor–stimulating or thyroid-stimulating antibodies; TRAb, thyroid receptor antibody; TSH, thyroid-stimulating hormone; TT_3, total triiodothyronine; TT_4, total thyroxine; T_3RU, triiodothyronine resin uptake; THBR, thyroid hormone–binding ratio.

[a]At Quest Diagnostic Laboratories.[49]

Sources: Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Practice Guideline. *Endocr Pract*. 2012;18(6):988–1028. doi:10.4158/EP12280.GL; Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. *Thyroid*. 2014;24(*12*):1670–1751. doi:10.1089/thy.2014.0028; Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association

for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(*3*):315–389. doi:10.1089/thy.2016.0457; Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011;17(*3*):456–520; Quest Diagnostics Incorporated. Quest diagnostics: test directory. Accessed September 7, 2020. https://testdirectory.questdiagnostics.com/test/home.

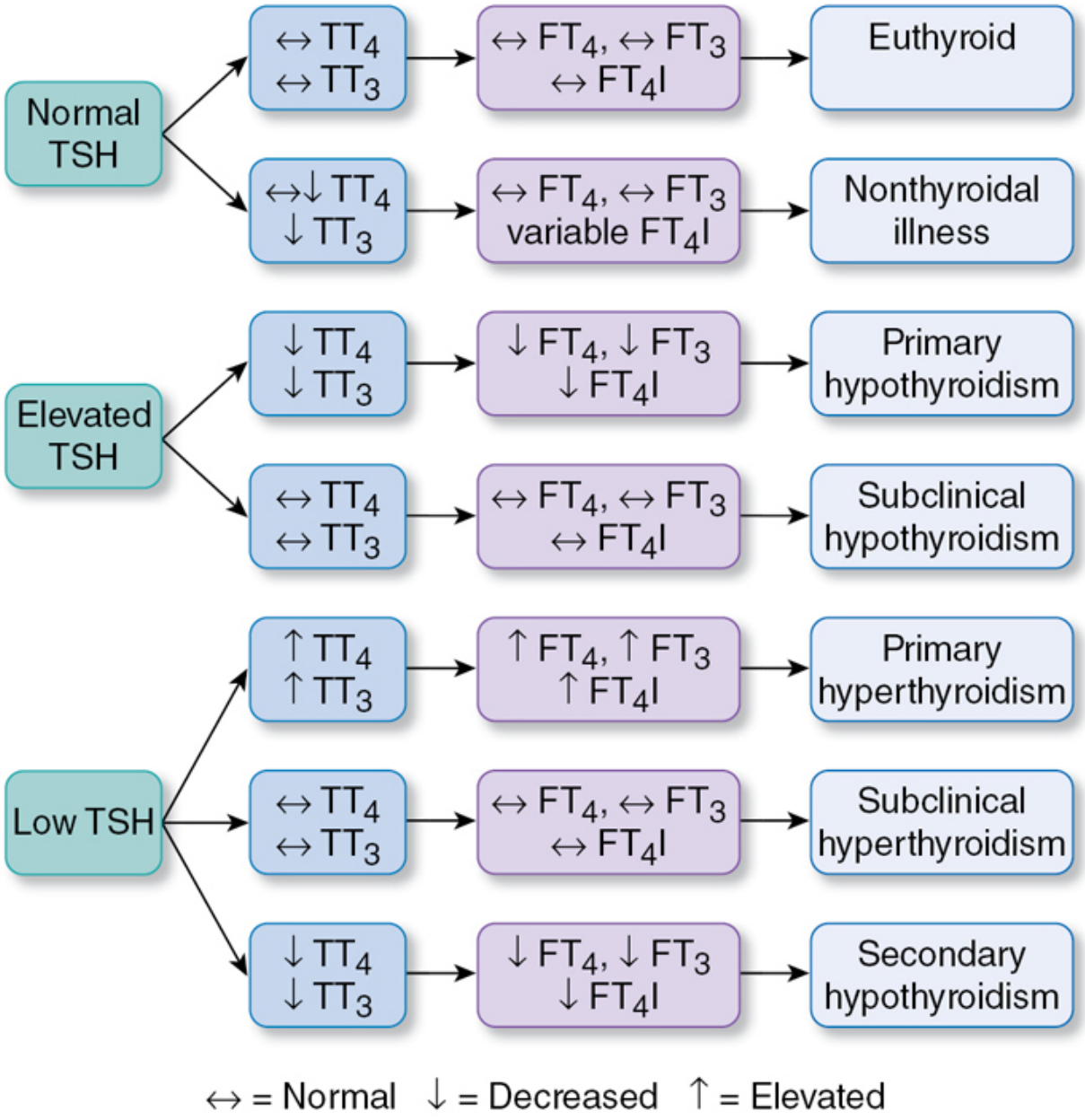


Figure 52-2 Evaluation of thyroid function tests. FT_3, free triiodothyronine; FT_4, free thyroxine; FT_4I, free thyroxine index; TSH,

thyrotropin; TT_3, total triiodothyronine; TT_4, total thyroxine.

Hypothalamic–Pituitary–Thyroid Axis

THYROID-STIMULATING HORMONE

The serum TSH, also known as thyrotropin, is the most sensitive test to evaluate thyroid function.[47,48,50] TSH, secreted by the pituitary, is elevated in early or subclinical hypothyroidism (when thyroid hormone levels appear normal) and when thyroid hormone replacement therapy is inadequate. TSH can be abnormal even if the FT_4 remains within the normal range because the TSH is specific for each person's physiologic set point. Polymorphisms in the TSH receptor contribute to this interindividual variability.[36] Consequently, low-normal free hormone levels can stimulate the pituitary to synthesize increased amounts of TSH. TSH cannot differentiate between primary hypothyroidism (thyroid failure), which is characterized by elevated TSH levels and secondary (pituitary or hypothalamus failure) hypothyroidism where TSH levels may be low or normal. The TSH assay can quantitate the upper and lower limits of normal so that a suppressed TSH level is highly suggestive of hyperthyroidism or exogenous thyroid overreplacement. Of note, TSH is not entirely specific for thyroid disease because abnormal levels are observed in patients who are euthyroid with nonthyroidal illnesses and in patients receiving drugs that can interfere with TSH secretion (see Table 52-1). TSH secretion is increased at bedtime and is affected by lack of sleep and exercise.[51] TSH secretion is suppressed physiologically by dopamine that antagonizes the stimulatory effects of TRH. Therefore, both dopaminergic agonists and antagonists can alter TSH secretion (see Case 52-4). Whether the upper limits of normal for TSH should be lowered to 2.5 μIU/mL is controversial.[36,48,51]

Free and Total Serum Hormone Levels

FREE THYROXINE, FREE THYROXINE INDEX, FREE TRIIODOTHYRONINE, AND FREE TRIIODOTHYRONINE INDEX

The free thyroxine (FT_4) and free triiodothyronine (FT_3) are the most reliable tests for the evaluation of hormone concentrations, especially when thyroid hormone–binding abnormalities exist.[28,33] The FT_3 is most useful in hyperthyroidism but can be normal or low in hypothyroidism. If a direct measure of the free hormone levels is not available, the estimated free hormone indices (FT_4I, FT_3I) can provide comparable information. However, these indices do not correct for changes observed in patients with "euthyroid sick" nonthyroidal illnesses in whom TBG binding affinity is altered. In these circumstances, the FT_4 and FT_3 are preferable.[28,33]

TOTAL THYROXINE AND TOTAL TRIIODOTHYRONINE

The total thyroxine (TT_4) and total triiodothyronine (TT_3) measure both free and bound (total) serum T_4 and T_3. Because the bound fraction is the major fraction measured, situations that change the hormone's affinity for TBG or the TBG level will influence the results. For example, falsely elevated levels of TT_4 and TT_3 are common in the euthyroid pregnant female (see Case 52-3). In addition, the TT_3 is often low in older patients and in many acute and chronic nonthyroidal illnesses because the peripheral conversion of T_4 to T_3 is decreased (see Case 52-1, Question 2, and Case 52-2). Therefore, careful interpretation of these tests is necessary in situations that alter thyroid hormone binding, TBG levels, or T_4 to T_3 conversion (Table 52-1). The TT_3 (and FT_3) is particularly helpful in detecting early relapse of Graves disease and in confirming the diagnosis of hyperthyroidism despite normal TT_4 levels. Conversely, TT_3 and FT_3 are not good indicators of hypothyroidism because T_3 levels can be normal. Measurement of only the total hormone levels is less reliable than either the free or estimated free hormone levels when alterations in thyroid-binding globulin or nonthyroidal illnesses exist.[28,33]

Thyroid Gland Function

RADIOACTIVE IODINE UPTAKE

The radioactive iodine uptake (RAIU), a measure of iodine utilization by the gland, is an indirect measure of hormone synthesis. It is elevated in hyperthyroidism and in early hypothyroidism when the failing gland is trying to increase hormone synthesis. A low or undetectable RAIU occurs in hypothyroidism, thyrotoxicosis factitia, and subacute thyroiditis. Typically, RAIU is used to calculate the dose of RAI therapy for treatment of Graves disease and to determine the activity of one or several nodules in a gland. The RAIU is not necessary to diagnose classic Graves disease or hypothyroidism.[30,31,48]

A tracer dose of iodine-123 (^{123}I) is administered, and the radioactivity of the gland is measured at 5 and 24 hours after ingestion. It is necessary to measure both the 5- and 24-hour RAIU so that patients with rapid turnover of iodine will not be missed. In some patients who are hyperthyroid, the 5-hour uptake is elevated, but the 24-hour uptake can fall to normal or subnormal levels. The normal range of the RAIU (Table 52-7) is affected by any condition that alters iodine intake. Iodine depletion caused by rigorous diuretic therapy or an iodine-deficient diet increases uptake because of replenishment of depleted total iodide pools. Conversely, dilution of ^{123}I with exogenous iodide sources (eg, contrast dyes) decreases RAIU.[52]

IMAGING STUDIES

Thyroid scan

A scan of the gland is performed simultaneously with the RAIU or after ingestion of technetium (^{99m}Tc) pertechnetate. The scan provides information concerning gland size and shape and identifies hypermetabolic (“hot”) and hypometabolic (“cold”) areas. The possibility of carcinoma must be considered if cold areas are present. A scan is often obtained in the evaluation of a patient with nodular thyroid disease.[30,31,42]

Thyroid ultrasound

A thyroid ultrasound can provide information about gland size and number of clinically palpable or nonpalpable nodules or cysts in the thyroid gland.[31]

Autoimmunity

THYROID PEROXIDASE AND ANTITHYROGLOBULIN ANTIBODIES

Thyroid peroxidase antibodies (TPOAb) and thyroglobulin autoantibodies (TgAb) to the thyroid gland indicate an autoimmune process.[47,48] About 50% to 90% of patients with Graves disease and nearly 100% of patients with Hashimoto thyroiditis have positive antibodies to both thyroid antigens.[48] Positive antibodies alone do not indicate thyroid disease because 5% to 10% of asymptomatic patients, as well as patients with other nonthyroidal autoimmune disorders, have positive antibodies.[48]

Clinically, the TPOAb is more specific than TgAb in assessing disease activity. Although both antibodies are elevated during acute flares of the disease, lower titers of TPOAb remain positive during quiescent periods of the disease, while TgAb levels revert to negative.[47,48]

THYROID RECEPTOR–STIMULATING ANTIBODIES OR THYROID-STIMULATING IMMUNOGLOBULIN

Thyroid receptor–stimulating antibodies (TRAb) or thyroid-stimulating immunoglobulin (TSI) are IgG immunoglobulins that are present in virtually all patients with Graves disease.[47,48] Like TSH, these immunoglobulins can stimulate the thyroid gland to produce thyroid hormones. In addition to aiding in the diagnosis of hyperthyroidism, TRAb titers are useful in predicting remission when discontinuing antithyroid drugs.[48] High titers of TSI are useful in diagnosing otherwise asymptomatic Graves disease (ie, ophthalmopathy), in predicting the risk of relapse of Graves disease after discontinuing medication, and in predicting the risk of neonatal hyperthyroidism in

utero through transplacental passage of TSI from the pregnant mother.[30,33] Otherwise, TSI measurement is expensive and offers no additional information in the patient with a typical Graves disease presentation.

Clinical Application and Interpretation

EUTHYROIDISM AND NONTHYROIDAL ILLNESS SYNDROME

CASE 52-1

Question 1: R.K., an obese 42-year-old female, is admitted to the hospital because of increasing fatigue, sluggishness, shortness of breath (SOB), and pitting edema of the legs during the past 3 weeks. Bilateral pleural effusions found on her chest radiograph indicate a worsening of her heart failure with reduced ejection fraction (HFrEF). Her other medical problems include cirrhosis of the liver, type 2 diabetes, and chronic bronchitis, for which she takes glipizide 10 mg every day and an iodine-containing herbal supplement three times a day (tid).

Pertinent physical findings include a palpable but normal-size thyroid, bibasilar rales, cardiomegaly, hepatomegaly, 4+ pitting edema, and normal deep tendon reflexes (DTRs). A diagnosis of worsening HFrEF secondary to hypothyroidism is suspected based on the following laboratory findings:

Cholesterol, 385 mg/dL
RAIU at 24 hours, 13% (normal, 5–35*)
Scan, normal-size gland with homogenous uptake
TT_4, 1.4 µg/dL (normal, 4.8–10.4)
TT_3, 22 ng/dL (normal, 62–134)
TSH, 4 µIU/mL (normal, 0.40–4.5 µIU/mL)
FT_4, 1.0 ng/dL (normal, 0.8–1.8)
TPOAb, 3 IU/mL (normal, <9)
TgAb, 0.3 IU/mL (normal, <1)

Based on her clinical and laboratory findings, what is R.K.'s thyroid status?

*Please note that the normal values used in this chapter are those reported by Quest Diagnostics. Normal values at other locations may differ based on assay method used.

Although low-output failure can be a presenting sign of hypothyroidism, the normal TSH and FT_4 indicates that R.K. is euthyroid, despite the confusing results of her other thyroid function tests. The depressed RAIU is consistent with her history of iodide ingestion and dilution of the ^{131}I. The low TT_4 and TT_3 may be explained by her cirrhosis and nonthyroidal illness syndrome (see Case 52-1, Question 1). The negative thyroid antibodies, the normal scan, and normal DTRs further substantiate the diagnosis of euthyroidism.

CASE 52-1, QUESTION 2: What is the significance of R.K.'s TT_4, FT_4I, and TT_3 values?

R.K.'s thyroid function test results are consistent with the nonthyroidal illness syndrome. Abnormal thyroid function tests are commonly found in patients who are euthyroid with various serious systemic diseases including starvation, infections, sepsis, acute psychiatric disorders, human immunodeficiency virus (HIV) infection, myocardial infarction (MI), bone marrow transplantation, and severe chronic cardiac, pulmonary, renal, hepatic, and neoplastic diseases.[23,47,48,53–58]

This "euthyroid sick" syndrome occurs in around 45% of chronically ill or hospitalized patients and must be recognized. In general, the more sick the patient, the greater the degree of abnormal thyroid function findings, even though the patient has no thyroid disease.[55]

The most common finding is a low TT_3 (eg, 15–20 ng/dL) and high inactive reverse T_3 levels (rT_3). Other typical changes include a normal or low TT_4 and a suppressed or normal TSH level. A borderline high TSH may occur as patients recover from nonthyroidal illness.[59] In more serious illness, the TT_4, FT_4I, and FT_3 are often low. Free hormone levels (eg, FT_4, FT_3) are often normal or slightly low. However, these inconsistent findings fuel the controversy over whether thyroid hormone therapy is beneficial or detrimental. These

findings are believed to be explained by a central hypothyroidism caused by reduction in hypothalamic TRH because of increased hypothalamic T_3, increased peripheral metabolism of T_3, or by a reduction in serum thyroid hormone–binding proteins.[54] Impaired protein synthesis of thyroid-binding prealbumin (TBPA) and an increase in the proportion of a lower-binding-capacity form of TBG might account for the lower bound hormone levels, but the concomitant increase in the free hormone concentrations would maintain a euthyroid state. Furthermore, circulating substances that inhibit the binding of T_4 and T_3 to the serum-binding proteins might also be present.

Less common changes include a modestly elevated TT_4 and FT_4I in patients with acute viral hepatitis, psychiatric disorders, renal failure, and advanced HIV infection. The TT_3 is usually normal but can be low in critically ill patients. Modest elevations in hormonal binding affinity and increased synthesis of TBG explain these findings.[54]

Several studies have shown a strong inverse correlation between mortality and total serum T_4, T_3, and rT_3 levels.[55–57] Of 86 hospitalized, intensive care patients, 84% of those with a serum T_4 of <3 μg/dL died, whereas 85% of those with a serum T_4 of >5 μg/dL survived.[56] In 331 patients with acute MI, rT_3 levels >0.41 nmol/L were significantly associated with a greater risk of death at 1 year.[57] During recovery, TSH levels increase and hormone levels start to normalize. Therefore, a favorable outcome is associated with reversal of the hormone indices.

Thyroid experts are divided about whether nonthyroidal illness should be treated, and few randomized studies are available to guide therapeutic decisions.[53–58] The few available studies found no survival benefits or favorable clinical outcomes from hormone therapy, although cardiac hemodynamics improved. The benefits of hormone replacement are unproven and might be detrimental. In one trial, the mortality of patients with acute renal failure treated with T_4 was 43% versus 13% in the control group.[58] Other small trials have

shown thyroid hormones to be well-tolerated and safe.[60] Opponents argue that T_4 therapy, by inhibiting TSH, may interfere with normal thyroid recovery and is preferentially converted to inactive rT3.[59,60] Conversely, proponents argue that there may be cardiovascular benefits and there is no clear evidence that therapy is toxic.[59]

In summary, T_4 and T_3 measurements are not helpful in the diagnosis of thyroid dysfunction in patients with significant nonthyroidal illness. A normal or near-normal TSH is necessary to establish euthyroidism in sick patients with nonthyroidal illness. The available data are not supportive of starting thyroid hormone treatment. The abnormal laboratory findings should reverse with correction of R.K.'s nonthyroidal illness. To confirm euthyroidism, the slightly elevated TSH should be repeated once R.K.'s medical condition improves.[54]

Drug Interference With Thyroid Hormone Concentrations

CASE 52-2

Question 1: J.R., a 45-year-old male, describes symptoms of fatigue, dry skin, and constipation. His other medical problems include alcoholism for 10 years, cirrhosis, generalized tonic-clonic seizures treated with phenytoin (Dilantin®) 300 mg/day and phenobarbital 90 mg at night, and rheumatoid arthritis for which he takes celecoxib 200 mg twice daily.

The results of his thyroid function tests are as follows:

TT_4, 4.2 µg/dL (normal, 4.8–10.4)
FT_4, 0.6 ng/dL (normal, 0.8–1.8)
TSH, 2.5 µIU/mL (normal, 0.40–4.5)

How should these laboratory findings be interpreted? What factors are responsible for the observed changes?

Despite symptoms that could be consistent with hypothyroidism (eg, fatigue, dry skin, constipation) and findings of low serum hormone values, J.R. is euthyroid, as evidenced by the normal TSH

level. Secondary hypothyroidism is unlikely at this age without a history of central nervous system (CNS) trauma or tumor. Some nonthyroidal factors could account for J.R.'s low TT_4 and FT_4 values.[23] Anti-inflammatory doses of salicylates >2 g/day and salicylate derivatives can displace T_4 from both TBG and TBPA, causing these abnormal findings.[23,61,62] Elevation in free T_4 levels and suppression of TSH below normal occur transiently (ie, no longer than first 3 weeks of administration) but normalize with chronic administration. Cirrhosis, stress, severe infections, and hereditary factors can also decrease TBG and TBPA synthesis to produce similar TT_4 findings. A medication history for drugs such as androgens or glucocorticoids that can lower TBG levels, and therefore TT_4 levels, should be elicited (Table 52-1).[23]

Enzyme inducers, such as rifampin and anticonvulsants (phenytoin, phenobarbital, valproic acid, carbamazepine), can alter serum thyroid hormone levels.[23,63–68] A 40% to 60% reduction in total T_4 serum concentrations results from an increase in the metabolism of T_4 and from hormone displacement in patients receiving chronic anticonvulsant therapy. Serum T_3 levels are normal or slightly decreased. In addition, therapeutic levels of phenytoin and carbamazepine interfere with the FT_4 assay, causing a 20% to 40% lower FT_4 than would be expected in persons who are euthyroid.[64] TSH levels remain normal and patients are euthyroid; however, those who previously required T_4 therapy may need a dosage increase to maintain euthyroidism.[67,68] Valproic acid is reported to have similar but less potent effects on thyroid function.[63,65] Phenobarbital can increase T_4 uptake by the liver and increase the fecal excretion of T_4. Serum binding of thyroid hormones is unaffected by phenobarbital.[23]

In summary, J.R. is taking several drugs that can further compromise the already low serum T_4 levels resulting from his liver disease. FT_4 remains subnormal in persons who are euthyroid

receiving phenytoin. For J.R., the normal TSH confirms euthyroidism and no thyroid replacement is warranted.

CASE 52-3

QUESTION 1: S.T., a 23-year-old, sexually active female whose only medication is birth control pills, comes to the clinic with symptoms of extreme nervousness, diaphoresis, and scanty menstrual periods. Although she appears healthy, the possibility of hyperthyroidism is considered based on the following laboratory values:

TT_4, 16 µg/dL (normal, 4.8–10.4)
FT_4, 1.2 ng/dL (normal, 0.8–1.8)
TSH, 1.2 µIU/mL (normal, 0.40–4.5)

Based on this information, what would be a reasonable assessment of S.T.'s thyroid status?

The normal FT_4 and TSH confirm that S.T. is not hyperthyroid. The elevated TT_4 is consistent with increased TBG levels observed in patients with acute hepatitis; in pregnancy; and in persons taking estrogens, estrogen-containing contraceptives, tamoxifen, raloxifene, heroin, or methadone.[3,4,23,69–71] Because TBG and therefore bound T_4 levels are increased by estrogens in S.T., total serum T_4 measurements are falsely elevated but free thyroxine levels remain normal. In patients requiring L-thyroxine, the use of estrogens can increase requirements of hormone replacement because the increased pituitary secretion of TSH cannot increase thyroid production needed to offset the increased binding of T_4.[3] Thyroid function tests should return to normal within 4 weeks after estrogen-containing contraceptives are discontinued.

CASE 52-4

QUESTION 1: J.P., a 55-year-old female, reports 3 months of progressive tremors, dizziness, and ataxia. Two months ago, she had a silent MI complicated by malignant ventricular ectopy that was responsive only to amiodarone therapy. Her other medical problems include Parkinsonism, type 2 diabetes, and diabetic gastroparesis. Her current medications include

amiodarone, insulin glargine, metformin, metoclopramide, pramipexole and levodopa/carbidopa. Physical examination of the thyroid was unremarkable. Thyroid function tests yielded the following results:

TT_4, 14.5 µg/dL (normal, 4.8–10.4)
FT_4, 2.3 ng/dL (normal, 0.8–1.8)
TSH, 3.8 µIU/mL (normal, 0.40–4.5)
TT_3, 40 ng/dL (normal, 62–134)
TPOAb, 4 IU/mL (normal, <9)

How should J.P.'s laboratory values be interpreted?

Although the symptoms of tremors, dizziness, and weight loss are suggestive of hyperthyroidism, the low TT_3, negative antibodies, normal TSH, and normal thyroid examination make this diagnosis unlikely. Her drug therapy could also explain her laboratory findings.

The drugs J.P. is taking—pramipexole, levodopa, metformin, and metoclopramide—may add to the diagnostic confusion. Although these drugs do not affect the actual circulating hormone levels, they affect the dopaminergic system that controls both TSH and TRH secretion.[23,50,72] Infusions of dopamine and dobutamine can decrease both TSH secretion and the TSH response to TRH in patients who are euthyroid and hypothyroid.[23,50,73] Therefore, dopamine agonists such as pramipexole, cabergoline, and levodopa can blunt the normal TSH response.[23,50,72,73] In addition, metformin after 1 year of therapy can cause significant TSH suppression without changes in free thyroxine levels by as yet an unknown mechanism of action.[74,75] Conversely, dopamine antagonists such as metoclopramide or domperidone can elevate TSH levels.[23,50] Fortunately, the alterations in TSH caused by these agents are usually not substantial enough to completely obscure the true thyroid abnormality; however, doses of thyroid drugs should be adjusted to maintain patients in a euthyroid state. See Table 52-2 and Cases 52-23 and 52-24 for more information about drug effects on thyroid function.

J.P.'s thyroid tests present a confusing picture; however, the presence of a TSH within the normal range indicates euthyroidism.

J.P. should be continued on her current regimen with follow-up monitoring of thyroid tests.

HYPOTHYROIDISM

Clinical Presentation

CASE 52-5

Question 1: M.W., a 2.20-pound (70-kg), 23-year-old voice student, thinks that her neck has become "fatter" over the past 3 to 4 months. She has gained 22.05 pounds (10 kg), feels mentally sluggish, tires easily, and finds that she can no longer hit high notes. Physical examination reveals puffy facies, yellowish skin, delayed DTRs, and a firm, enlarged thyroid gland. Laboratory data include the following results:

FT_4, 0.6 ng/dL (normal, 0.8–1.8)
TSH, 60 μIU/mL (normal, 0.40–4.5)
TPOAb, 136 IU/mL units (normal, <9)

What is M.W.'s thyroid status based on her clinical and laboratory findings?

M.W. presents with many of the clinical features of hypothyroidism as presented in Table 52-3. These include weight gain, mental sluggishness, easy fatigability, lowering of the voice pitch, puffy facies, yellowish tint of the skin, delayed DTRs, and enlarged thyroid.[76] The diagnosis of hypothyroidism is confirmed by her laboratory findings of a low FT_4, an elevated TSH value, and positive TPOAb.

A firm goiter, thyroid antibodies, and clinical symptoms of hypothyroidism strongly suggest Hashimoto thyroiditis.[28] She has no history of prior antithyroid drug use, surgery, or RAI treatment, which are common causes of iatrogenic hypothyroidism. She is also not taking any goitrogens or drugs known to cause hypothyroidism (Table 52-2).

Treatment With Thyroid Hormones

THYROID HORMONE PRODUCTS

CASE 52-5, QUESTION 2: What thyroid preparation should be used to treat M.W.'s hypothyroidism? Are differences, advantages, or disadvantages significant among the various generic and brand name formulations of thyroid hormones?

The principal goals of thyroid hormone therapy are to attain and maintain a euthyroid state. Thyroid preparations (**Table 52-8**)[31,77–79] are synthetic (L-thyroxine, L-triiodothyronine) or natural (desiccated thyroid). The latter comes from animal tissues.

Table 52-8
Thyroid Preparations

Drug/Dosage Forms	Composition	Dosage Equivalent	Comments
Thyroid USP (Armour®) *Tab:* 15, 30, 60, 90, 120, 180, 240, and 300 mg	Desiccated hog, beef, or sheep thyroid gland	60–100 µg[a]	Unpredictable T_4:T_3 ratio; supraphysiologic elevations in T_3 levels might produce toxic symptoms; Armour brand preferred
L-Thyroxine (Levoxyl®, Levothroid®, Synthroid®, Unithroid®, various) *Tab:* 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 µg. *Inj:* 200 and 500 µg	Synthetic T_4	60 µg[a]	Stable, predictable potency; well-absorbed; more potent than desiccated thyroid. When changing from >2 gr desiccated thyroid to L-T_4, a lower dosage of L-T_4 might be needed to avoid toxicity. Weight should be considered in dosing (1.6 µg/kg/day). L-T_4 absorption can be impaired by iron, aluminum-containing products (eg, antacids, sucralfate), Kayexalate, calcium preparations, proton-pump inhibitors, cholesterol resin and phosphate binders, raloxifene, soy, bran, coffee, fiber enriched foods. L-T_4 metabolism increased by anticonvulsants, rifampin, imatinib, bexarotene, and pregnancy
Triiodothyronine (Cytomel®) *Tab:* 5, 25, and 50 µg *Inj:* 10 µg/mL (Triostat®)	Synthetic T_3	25–37.5 µg	Complete absorption; requires multiple daily dosing; toxicity similar to all T_3-containing products; see desiccated thyroid comments

Inj, injection; L-T_4, L-thyroxine; T_3, triiodothyronine; T_4, thyroxine; Tab, tablet; USP, United States Pharmacopeia.

[a]Historically, 60 mg (1 g) of desiccated thyroid = 60 µg of T_4.[79] This conversion was determined with older TSH assays, without direct measurement of FT_4 and has been challenged. The conversion is now typically reported as equivalent to 80 µg,[77] 88 µg,[78] or 100 µg,[32] of T_4 per 60 mg of desiccated thyroid. The T_3 component of desiccated thyroid is an additional factor to consider when converting from one to the other and an exact equivalent dose has not been determined.

Desiccated thyroid

Desiccated thyroid is obtained from dried powdered pork thyroid glands that have had connective tissue and fat removed. Today, starting patients on desiccated thyroid is not justified. The United States Pharmacopeia (USP) requires thyroid content to be 90% to 110% of the labeled 38 µg T_4 and 9 µg T_3 for each 65 mg of the desiccated compound.[80] Advocates of desiccated thyroid use cite the inclusion of metabolically active components (eg, diiodothyronine) and the inclusion of both T_4 and T_3 in the preparation. However, the 4.2:1 ratio of T_4:T_3 is lower than the human 14:1 ratio, potentially resulting in toxic amounts of T_3.[32] The lack of conclusive and long-term evidence combined with the potential for toxicity makes routine use of desiccated thyroid products unwarranted.[32] Clinicians should be aware that some patients may oppose the use of animal-derived products on religious or social grounds.

Allergic reactions to the animal protein are another concern. In addition, desiccated thyroid suffers from two problems inherent to all T_3-containing preparations. Because T_3 is absorbed more rapidly than T_4, supraphysiologic elevations in plasma T_3 levels occur after oral ingestion, which can produce mild thyrotoxic symptoms in some patients. FT_4 levels are low during T_3 administration and, if misinterpreted, can result in the erroneous administration of more hormone. These problems with T_3 are easily missed unless T_3 levels are routinely monitored. Because significant amounts of T_4 are converted to T_3 peripherally, oral administration of T_3 offers no advantage and is not usually needed[32,81,82] (see Triiodothyronine section).

Patients maintained on desiccated thyroid should be encouraged to change to L-thyroxine (T_4). Although 65 mg (1 g) of desiccated thyroid is theoretically equal in potency to 75 to 100 µg of T_4,[79] this equivalency may not hold true if the desiccated thyroid preparation is less active than its labeled content. The patient's weight also should be considered when switching therapy (see Case 52-5, Question 3).

L-Thyroxine (Levothyroxine)

L-Thyroxine, also known as levothyroxine, is the thyroid replacement of choice.[28,32,83] Its advantages include stability, uniform potency, relatively low cost, and lack of allergenic foreign protein content. The mean absorption of a commonly used branded preparation is 81%.[84] Absorption is optimal on an empty stomach.[85] Current guidelines recommend taking L-thyroxine either 60 minutes before breakfast or 3 to 4 hours after the evening meal for consistent absorption.[28,32] Several medications can also impair L-thyroxine absorption.

Concerns about generic and branded L-thyroxine tablet stability and potency, bioavailability, and product interchangeability have caused confusion in the management of thyroid disorders. Several Food and Drug Administration (FDA)–approved brand and generic formulations exist. Raising concerns about the methodology the FDA used to determine bioequivalence, the American Thyroid Association, the Endocrine Society, and the American Association of Clinical Endocrinologists issued joint position statements expressing their displeasure with the FDA's conclusions of interchangeability.[87] Although this issue remains controversial, the preponderance of the evidence supports the FDA ratings and suggests that these preparations are likely to be interchangeable in the majority of patients.[28,32,87–90] Current guidelines recommend maintaining therapy with products of a consistent manufacturer, particularly in high-risk, frail, or elderly patients in whom fluctuations are most critical.[32] In the event of a L-thyroxine manufacturer change, TSH should be monitored when the patient achieves steady state on the new product.[86]

Triiodothyronine

T_3 (Cytomel®) is not recommended for routine thyroid hormone replacement because of the problems identified earlier with T_3 administration (see Desiccated Thyroid section). Although T_3 is well-absorbed, it has a relatively short half-life (1.5 days), necessitating multiple daily dosing to ensure a uniform response. Proposed

advantages of T_3 include beneficial effects on weight and lipids; however, more studies are required to establish whether a clinical benefit exists.[32] Further, a longer-acting form of T_3 would be needed to make this a practical therapeutic option. Other disadvantages include higher expense and a greater potential for cardiotoxicity.[32] Its primary use is for patients who require short-term hormone replacement therapy and rarely in those in whom T_4 conversion to T_3 might be impaired. Proponents favoring thyroid treatment of the "euthyroid sick" syndrome identify T_3 as the hormone replacement of choice. T_3 therapy should be monitored using the TSH and TT_3 or FT_3 levels.

Several randomized studies now conclude that routine replacement with combination T_4 and small dosages of T_3 offer no consistent advantage to T_4 alone. However, there is evidence of improved cognitive performance and mood changes in some patients, and some trials indicate a patient preference in favor of the T_4/T_3 combination.[32,81,82] One proposed explanation for why some people report a cognitive benefit relates to polymorphism in deiodinase enzymes that convert T_4 to T_3 resulting in local tissue hypothyroidism and potentially leading to decreased brain concentrations of T_3.[91] The short half-life of T_3 and the need for multiple doses per day to prevent symptoms of toxicity further complicates the potential use in combination with T_4. Until high-quality, long-term controlled trials exist to prove if a specific subset of patients with hypothyroidism would benefit from combination therapy, the standard of care remains long-term treatment with L-thyroxine.[32]

L-THYROXINE

Dosage and administration

CASE 52-5, QUESTION 3: What would you recommend as appropriate starting and maintenance dosages of T_4 for M.W.?

The maintenance dosage for M.W. can be estimated from her weight. Average replacement doses of 1.6 μg/kg/day (eg, 100–125 μg) are sufficient in most patients to normalize the TSH.[32] L-Thyroxine dosages that suppress TSH levels to below normal or undetectable levels (subclinical hyperthyroidism) should be avoided to prevent osteoporosis and cardiac toxicity.[83,92–96] Excessive L-thyroxine can cause tachycardia, atrial arrhythmias, impaired ventricular relaxation, reduced exercise performance, and increased risk of cardiac mortality.[92] These considerations are especially important in older patients who might require less T_4 than their younger counterparts and who are particularly sensitive to minute changes in T_4 doses (see Table 52-4). As patients age, the dosage should be evaluated yearly and, if necessary, decreased to maintain a normal TSH level.[97]

How rapidly T_4 replacement can proceed depends on the likelihood of invoking cardiac toxicity in susceptible patients. Minute doses of T_4 (eg, <75 μg) can increase heart rate, stroke volume, oxygen consumption, and cardiac workload before euthyroidism occurs. One double-blind study compared the clinical outcome between starting full replacement doses versus gradual 25-μg incremental doses in relatively young hypothyroid subjects with asymptomatic cardiac disease and concluded that those receiving full doses normalized thyroid function tests more rapidly (4 weeks) and without any toxicity.[98] Because M.W. has no identifiable risk factors (see Case 52-10, Question 3) for cardiotoxicity that require careful dosage titration (eg, old age, cardiac disease, long duration of hypothyroidism), she can be started on an estimated full replacement dose of 125 μg daily of L-thyroxine (70 kg × 1.6 μg/kg/day = 112 μg).[28,32] An alternative conservative approach would be to start with 100 μg/day, check the FT_4 or FT_4I and TSH tests after 6 to 8 weeks of therapy, and if the TSH is still elevated without any symptoms of toxicity, increase the dosage to 112 μg/day. The appropriate replacement dose will produce a TSH of 1 to 2 μIU/mL, normalize FT_4 or FT_4I levels, and reverse clinical symptoms of

hypothyroidism. Generally, doses should not be adjusted more frequently than once a month and should not exceed increments of 12.5 to 25 µg/day. Even in the absence of overt coronary disease, patients older than 50 to 60 years should be started on a lower dose of L-thyroxine (50 µg/day) and titrated.[28]

L-Thyroxine bioavailability is improved when it is taken on an empty stomach and at night.[83,85,99,100] Simultaneous coadministration of T_4 with soy proteins, coffee, or high-fiber diets (eg, oat bran, soybean) should be avoided because T_4's absorption can be impaired.[101–103] Estrogen therapy can increase T_4 requirements by increasing TBG to increase T_4 binding.[3] Cholestyramine, colestipol, iron sulfate, antacids, sucralfate, calcium preparations, particularly the carbonate salt, and raloxifene can impair thyroid absorption if these medications are administered at the same time.[83,104–111] Cholesterol-lowering agents (eg, HMG-CoA reductase inhibitors, bile acid sequestrants) and phosphate binders are also reported to interfere with thyroid absorption.[107,112] Aluminum-containing products (ie, antacids, sucralfate) should also be avoided because separating the administration from T_4 does not consistently correct this interaction.[108,109] Data are conflicting as to whether proton-pump inhibitors (eg, omeprazole) reduce T_4 absorption; therefore, addition or deletion of a proton-pump inhibitor warrants additional monitoring.[113,114]

Monitoring therapy

CASE 52-5, QUESTION 4: Ten days after starting L-thyroxine therapy, M.W. continues to experience of tiredness, fatigue, and difficulty singing despite excellent adherence. Thyroid function tests show a TT_4 of 4 µg/dL (normal, 4.8–10.4), an FT_4 of 0.5 ng/dL (normal, 0.8–1.8), and a TSH of 40 µIU/mL (normal, 0.40–4.5). What therapeutic options are available? How should M.W.'s thyroid function tests be interpreted?

Clinical improvement in the signs and symptoms of hypothyroidism and normalization of laboratory parameters are appropriate therapeutic end points. If the replacement dose is sufficient, some correction of her symptoms should occur after 2 to 3 weeks, but maximal effects will not be evident for 4 to 6 weeks. Typically, improvement of anemia and hair and skin changes is delayed and requires several months of treatment before resolution.[74,79]

In patients with severe myxedema, a transiently elevated T_4 level might occur at 6 weeks because the metabolic clearance of T_4 is decreased by the hypometabolic state associated with hypothyroidism.

FT_4 or FT_4I and TSH should be checked about 6 to 8 weeks after the initiation of therapy because T_4 has a half-life of 7 days, and three to four half-lives are needed to reach steady-state levels. Levels obtained before this time (as in M.W.) may be misleading and should be interpreted cautiously. No change in her L-thyroxine dosage should be attempted at this time.

CASE 52-5, QUESTION 5: Eight weeks later, on a routine follow-up visit, M.W. still feels tired and not back to her normal self. She denies any symptoms of hyperthyroidism. Her thyroid function tests show a TT_4 of 14 µg/dL (normal, 4.8–10.4), a TT_3 of 100 ng/dL (normal, 62–134), FT_4 of 1.9 ng/dL (normal, 0.8–1.8), and a TSH of 3.5 µIU/mL (normal, 0.40–4.5). How should M.W.'s thyroid function tests be interpreted? What changes, if any, should be recommended in her therapeutic regimen?

Patients treated with L-thyroxine may develop an elevated TT_4 concentration and FT_4 without overt clinical signs of hyperthyroidism.[115,116] Despite these elevated levels, patients are euthyroid, as evidenced by a normal TSH. Because T_3 is not being released from the nonfunctioning thyroid gland, a higher concentration of T_4 is necessary to increase the amount of T_3 obtained from peripheral conversion. Jonklaas et al reported that the mean FT_4 was significantly higher (1.34 ng/dL) in patients receiving

L-thyroxine postoperatively compared to their euthyroid levels before thyroidectomy (FT_4, 1.06 ng/dL).[116] T_3 levels on L-thyroxine replacement were also comparable after surgery to pre-surgery levels. However, lower T_3 levels were noted only in those in whom TSH levels were >4.5 μIU/mL, indicating that low T_3 levels are likely a result of suboptimal L-thyroxine replacement. Thus, the TSH appears to be the best indicator of euthyroidism in patients treated with L-thyroxine.

Another possibility is that the elevated thyroid levels may only be an artifact of the laboratory collection time. Before any changes in her dosing regimen are made, M.W. should be asked about the time she takes the drug and its relationship to the time of her blood drawn. Random sampling of FT_4 and TSH levels can be significantly different when compared with trough levels.[117,118] In one study, the FT_4 level was 12% higher, and the TSH level 19% lower when obtained from random samples compared with trough samples.[118] Transient elevations in FT_4 levels were detected for 9 hours after ingestion of the oral L-thyroxine.

The symptoms of fatigue that M.W. is experiencing are likely not because of her hypothyroidism. Patients may continue to have symptoms of hypothyroidism despite normalization of the TSH value.[32] Although some have suggested that the goal TSH be titrated to 1 to 2 μIU/mL or lower for replacement therapy to improve well-being, this is controversial. One study found that changes in T_4 dosing to achieve TSH concentrations of 2 to 4.8 μIU/mL, 0.3 to 1.9 μIU/mL, or <0.3 μIU/mL in patients who are hypothyroid did not result in improvements in well-being, psychological, or hypothyroid symptoms, or quality of life.[119] Data justifying the safety of higher T_4 replacement doses found that achievement of a low but detectable TSH level (0.04–0.4 μIU/mL) was not associated with an increased risk of cardiovascular disease or fractures compared to those with suppressed (<0.03 μIU/mL) or elevated (>4 μIU/mL) TSH levels.[120]

In conclusion, if an elevated TT_4 and FT_4 are noted without any symptoms of thyrotoxicosis (as in M.W.), the dosage should not be

decreased; rather, a trough FT_4 and TSH level should be obtained to eliminate excessive dosing or any laboratory artifacts. Alternatively, obtaining a level at least 9 hours after L-thyroxine administration also seems appropriate. Repeat values should be in the normal range if the dosing is correct. An excessively suppressed TSH confirms a dosage that is too high. In M.W., the lack of hyperthyroid symptoms suggests euthyroidism, and no changes in her therapeutic regimen should be attempted until trough levels are available. Evaluation for other causes of fatigue should be explored.

TRIIODOTHYRONINE

CASE 52-6

Question 1: C.B., a 65-year-old female, is currently experiencing fatigue and vague muscle aches and pains that she attributes to insufficient thyroid medication. On physical examination, the thyroid gland is palpable but not enlarged and DTRs are 2 plus and brisk. Her dose of T_3 was increased from 25 µg tid to 50 µg tid about 2 weeks ago based on the results of a recent FT_4 of 0.5 ng/dL (normal, 0.8–1.8). She denies taking any other medications.

Is C.B.'s thyroid hormone replacement appropriate?

As noted previously, T_3 is not the drug of choice for thyroid replacement. The use of L-thyroxine would simplify her dosing regimen and facilitate monitoring.

The low FT_4 did not justify increasing C.B.'s T_3 dose. Because she is receiving T_3, the FT_4, which is a measure of free T_4, will always be low and will never reach normal levels. In fact, her vague symptoms may be related to hyperthyroidism because she is receiving the equivalent of ~450 µg of L-thyroxine daily (based on a pharmacodynamic study showing an equivalent T_3 :T_4 ratio of 1:3).[121] TSH and FT_3 levels are most useful in monitoring patients receiving T_3 therapy. A TSH level should be obtained to evaluate her thyroid function. A suppressed TSH and an elevated FT_3 would indicate hyperthyroidism. It is important to remember that in an older patient,

hyperthyroidism might not always produce symptoms because of an "apathetic" sympathetic system.

L-thyroxine should be initiated cautiously in older patients to avoid exacerbating any preexisting arteriosclerotic heart disease that might be masked by the hypothyroidism (see Case 52-10, Questions 2 and 3). In general, older patients require smaller replacement dosages (approximately ≤1.6 μg/kg/day of T_4) than their younger counterparts.[97,122,123] Dosages of <50 μg/day of T_4 are common in patients older than 60 years. However, this lower T_4 dosage is not universal for all older subjects.[123] The reason that older patients need lower dosages is unclear, but it has been suggested that the lower requirements result from an age-related decrease in T_4 degradation rates. Because dosage requirements change with age, patients should be reassessed annually to determine whether the original dosage prescribed is still appropriate.[97,124]

In C.B., who had been on T_3 without any evidence of cardiac toxicity, a less cautious approach in changing to T_4 can be attempted. An empiric L-thyroxine dosage of 68 μg/day (40 kg × 1.6 μg/kg/day) is an approximate dosing end point for C.B. The T_3 should be discontinued and T_4 should be initiated in a dose of 50 μg/day; this dosage can be adjusted as needed based on C.B.'s symptoms and thyroid function tests. After T_3 therapy is discontinued, its effects will disappear over 3 to 5 days. In contrast, T_4 levels rise slowly over 4 to 5 days, so no overlap in T_3 administration is necessary to prevent hypothyroidism.

Parenteral dosing

CASE 52-7

QUESTION 1: G.F., a 70-year-old male with long-standing hypothyroidism, has been receiving L-thyroxine 100 μg/day. Currently, he is in the hospital with a stroke and paralysis that prohibits him from swallowing oral medications. His last thyroid function tests were normal.

What is a reasonable method of administering thyroid hormone to G.F.?

Because L-thyroxine has a half-life of 7 days, administration can be delayed for up to 1 week (assuming G.F. can resume oral intake at that time). However, if parenteral administration is required, L-thyroxine is available as an intramuscular (IM) or IV injection. The IV route is preferred because IM absorption may be slow and unpredictable, particularly if the circulation is compromised. Because the oral absorption of T_4 is ~80%,[84] parenteral doses should be decreased. Once IV L-thyroxine replacement is successful, maintenance with a once-weekly IM injection can be continued if oral ingestion is not feasible.[125]

HYPOTHYROIDISM IN PREGNANCY

CASE 52-8

QUESTION 1: P.K. is a 35-year-old female with Hashimoto thyroiditis who is 6 weeks' pregnant. Laboratory test results showed TT_4 5 µg/dL (first trimester normal, 6.4–15.2) and FT_4 0.7 ng/dL (first trimester normal, 0.9–2.0). She takes her medications in the morning, which include L-thyroxine 100 µg/day and a prenatal vitamin enriched with iron and calcium.

What dosing adjustments are required because of P.K.'s pregnancy?

Inadequately treated or undiagnosed maternal hypothyroidism can be detrimental to the mother and the developing fetus.[126,127] Miscarriage, spontaneous abortion, hypertension, preeclampsia, and higher rates of cesarean sections and stillbirths have been reported with maternal hypothyroidism.[128] Congenital defects, congenital hypothyroidism (see Case 52-8, Question 2), abnormal fetal development, and impaired cognitive development in the newborn have been attributed to maternal hypothyroidism.[129] Measurement of TPOAb is recommended in patients with recurrent miscarriage because of an association with elevated levels and miscarriage after the first trimester.[48] The IQ scores of children born to mothers with undiagnosed hypothyroidism during pregnancy averaged 7 points

lower than children born to euthyroid mothers.[126] A delay in both mental and motor development has been observed in children ages 1 to 2 years old who were born to mothers with hypothyroxinemia but normal TSH levels during the first trimester of pregnancy.[127] Children born to mothers with untreated hypothyroidism are also more likely to have learning and attention deficit disorders and are at a higher risk of being born with unilateral spastic cerebral palsy.[130,131] Data such as these have led to the conclusion that normal maternal thyroid function is essential during early fetal development. However, a 2018 cohort study showed that children born to mothers with TSH and T_4 abnormalities in the first trimester had no clinically important impairment in educational achievement.[132] Fetal thyroid hormone production begins by the end of the first trimester, with the fetus relying on maternal thyroid hormones until that time. Transfer of maternal thyroid hormones is under the control of the placenta.[133] There is a small risk of congenital hypothyroidism if maternal antibodies from Hashimoto thyroiditis cross the fetal circulation. The infant's cord blood should be assayed at birth to ensure that TSH is normal and that the child is euthyroid.

The majority of females with primary hypothyroidism will require a 30% to 50% increase in the prepregnancy T_4 dosage to maintain euthyroidism during the first trimester of pregnancy.[41,133–135] The only evidence of increased T_4 demands is an elevated TSH level (eg, subclinical hypothyroidism) that occurs between weeks 5 (but can be as early as 3) and 16 of gestation. Often, no clinical symptoms of hypothyroidism are evident and the FT_4 and the index are normal. Because of the adverse consequences associated with maternal hypothyroidism, it is reasonable to evaluate TSH in all pregnant females[136] as well as empirically increase the prepregnancy T_4 dosage by 30% (extra two pills/week) as soon as pregnancy is confirmed.[135] Because there is a physiologic decrease in TSH during pregnancy caused by the TSH-like activity of human chorionic gonadotropin (HCG), the upper limit of the normal TSH range should be adjusted for pregnancy.[128,133] Where possible, population-based trimester-specific TSH reference ranges should be used. In the

absence of available data, first trimester lower and upper reference ranges can be reduced by 0.4 and 0.5 μIU/mL, respectively beginning weeks 7 to 12.[128] Reference ranges gradually return toward normal, nonpregnant ranges in the second and third trimesters. For a treatment goal, the lower half of the trimester-specific reference range (or <2.5 μIU/mL if reference range is unavailable) should be used.[128]

Physiologic explanations for the increase in thyroid hormone requirements include the twofold increase in TBPA caused by high estrogen levels, increased volume of distribution of thyroid hormones, and maternal transport of T_4.[41,133] Rising HCG concentrations result in increased production of thyroid hormones.[133] Changes in serum proteins cause direct immunoassay of FT_4 to yield incorrect results. A newer assay has been shown to produce reliable trimester-specific reference ranges for FT_4; however, these assays are not universally available.[40] In the absence of trimester-specific reference ranges for FT_4, the FT_4 index or TT_4 should be used to evaluate thyroxine production.[28,128] It is important to recognize that coadministration of iron- and calcium-containing prenatal vitamins reduces T_4 absorption (see Case 52-5, Question 3) and that these drug interactions may affect dosage requirements. When prenatal vitamins with iron and calcium were separated by 4 hours from T_4 administration, only 31% of females required an increase in T_4 dose.[137] Females should be followed closely during pregnancy with monthly monitoring during the first half of pregnancy and at least once between gestation weeks 26 and 32. If necessary, the T_4 dosage should be adjusted to maintain a TSH in pregnancy-adjusted ranges and an ultrafiltrate measured FT_4, FT_4I, or TT_4 in the upper limits of normal based on adjusted normal ranges. When the TT_4 is used, reference ranges should be increased by 50%.[28,40] Combination therapy with T_4 and T_3 or desiccated thyroid should not be given to pregnant females or those planning pregnancy.[28,31,128]

P.K.'s low TT_4 and FT_4 are concerning. The TT_4 should be much higher because of pregnancy-associated increases in TBG. The TSH

level should be obtained, and the daily dosage of T_4 should be increased to 125 µg after eliminating the possibility of patient nonadherence and drug interactions. Ingestion of the prenatal vitamins with iron and calcium should be separated by at least 4 hours from T_4. P.K. could also be instructed to take the T_4 at night for better absorption.[85] The TSH should be repeated in 6 weeks, and the dosage should be adjusted as needed to keep the TSH in the range as above. After delivery, the dosage should be reduced to prepregnancy levels and the FT_4 and TSH rechecked to ensure euthyroidism.

CONGENITAL HYPOTHYROIDISM

Case 52-8, Question 2: P.K. delivered a healthy baby, T.K., at term without difficulty. T.K.'s postpartum screening serum T_4 level was 5 µg/dL (normal, 4.8–10.4), and TSH was 35 µIU/mL (normal, 0.40–4.5). At home, T.K. became lethargic, had a weak cry, sucked poorly, and failed to thrive. Assess the situation (including a treatment plan and prognosis). How is mental development affected?

T.K.'s symptoms are suggestive of congenital hypothyroidism, although in most infants the clinical signs and symptoms are so subtle and nonspecific that they are easily missed until the child is several months old. The early clinical findings include prolonged jaundice, skin mottling (cutis marmorata), lethargy, poor feeding, constipation, hypothermia, hoarse cry, large fontanels, distended abdomen, hypotonia, slow reflexes, and piglike facies.[138] Respiratory difficulties, delayed skeletal maturation, and choking (but not palpable goiter) may be present. These infants are also at risk for additional congenital defects or complications.[138] Mass neonatal screening programs have been successful in detecting congenital hypothyroidism within the first few weeks of life before clinical manifestations are apparent and before irreversible changes occur.[138]

The postpartum low serum T_4 concentration and elevated TSH level (>20 μIU/mL) in T.K. are of concern and should be verified. Transient hypothyroidism can result from intrauterine exposure to ATDs or excess iodides, or from transplacental passage of TRAb from the mother. Thyroid function tests often normalize without treatment in 3 to 6 months as the TRAb is cleared by the infant.[138] The diagnosis of hypothyroidism should be confirmed by a low serum T_4, a low FT_4, and an elevated TSH concentration during the next few weeks. Serum T_3 concentrations are often in the normal range and are not helpful. Normal serum T_4 concentrations are higher in the first few weeks of life and gradually return to normal by 2 to 4 months of life. The FT_4I may also be elevated. Because of these confusing changes, thyroid serum levels should be compared with the normal range for the approximate postnatal age.

Thyroid hormones play a critical role in normal growth and development, particularly of the CNS, during the first 3 years of life. If untreated, dwarfism and irreversible mental retardation occur. T.K.'s normal mental (IQ) and physical development will be determined by the age at which treatment is started, the initial dosage of T_4, the serum T_4 level attained during therapy, the adequacy with which treatment is maintained, and the cause and severity of the initial deficiency.[139–145] There is an inverse relationship between the amount of time to reach a euthyroid state and the likelihood of impaired neurologic development.[138]

Sodium L-thyroxine is the preparation of choice for replacement.[138] T_4 tablets can be crushed and mixed with breast milk or formula; suspensions are not stable and should not be used. T_4 tablets should not be mixed with soy-based formulas because decreased absorption and longer time to reach a TSH <10 μIU/mL may occur. If a soy-based formula is required, the dosage of T_4 should be administered halfway between feeds.[138] T_3 is less desirable because its short half-life causes a greater fluctuation in plasma levels (Table 52-8). The initial replacement dose of T_4 should raise the serum T_4

as rapidly as possible to minimize the consequences of hypothyroidism on cognitive function. A delay in starting therapy of even a few days has resulted in a poorer IQ outcome.[140,141,145] A minimum T_4 dosage of 10 to 15 µg/kg/day is recommended to raise the serum T_4 to >10 µg/dL (129 nmol/L) by 7 days.[139] However, some suggest that higher than previously recommended dosages of 12 to 17 µg/kg/day might be more effective, but concern about negative neurologic outcomes exists.[138,140,141] In the full-term healthy infant, full initial replacement T_4 doses are appropriate.[138,146] In these infants, reduced doses of T_4 (~25%–33% of the recommended dose) can be started and increased gradually by similar increments until the therapeutic dose is achieved. The recommended replacement dose decreases with age and is shown in **Tables** 52-4 and **52-9**.[147]

Table 52-9
T_4 Recommended Replacement Dose

Age	Daily µg/kg/day T_4
Newborn–3 months	10–15
3–6 months	8–10
6–12 months	6–8
1–5 years	5–6
6–12 years	4–5
>12 years	2–3
Adolescent/post puberty	Adult dose (1.6)

T_4, thyroxine.

Sources: Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. *Thyroid*. 2014;24(*12*):1670–1751. doi:10.1089/thy.2014.0028; Lexicomp. Levothyroxine: Lexi-Drugs. 2021. Updated September 4, 2021. Accessed April 9, 2021. http://online.lexi.com/.

Mental development and attainment of normal growth are not severely impaired if adequate T_4 treatment is initiated before 3 months of age to achieve a T_4 level >10 µg/dL (129 nmol/L).[138–141,143]

Children with the most severe congenital hypothyroidism had IQs lower than their siblings.[141] Young adults 20 years after congenital hypothyroidism showed impaired motor and intellectual outcomes after suboptimal T_4 (<7.8 μg/kg/day) therapy compared to sibling controls.[143] However, those receiving optimal therapy still had some memory, attention, and behavior deficits.[148] Newborns starting L-thyroxine during the first 4 to 6 weeks of life have mean IQs similar to controls. The IQ drops if treatment is delayed until 6 weeks and 3 months (mean IQ, 95), or until 3 and 6 months (mean IQ, 75). When treatment is delayed until 6 months to 1 year of age, normal mental development is impaired despite subsequent treatment. Higher IQs also were found in children who received T_4 dosages >10 μg/kg/day and achieved a mean T_4 level >14 μg/dL (181 nmol/L) in the first month of therapy.[138,140,141,145,149] Neurologic deficits were also more likely to occur in infants whose thyroid replacement was delayed or inadequate (T_4 <8 μg/dL [103 nmol/L] within 30 days of therapy and or had delayed TSH normalization [18–24 months]). Additional risk factors for low IQs and poor motor and speech skills despite adequate therapy include clinical signs of hypothyroidism during fetal life, T_4 <2 μg/dL at birth, thyroid aplasia, and retarded bone age.[138,139,141]

The goal of therapy is a T_4 in the upper normal range (eg, 10–18 μg/dL) and/or an FT_4 of 2 to 5 ng/dL during the first 2 weeks of therapy, and then a lower target thereafter: a T_4 of 10 to 16 μg/dL (and/or an FT_4 of 1.6–2.2 ng/dL). IQs are improved if TSH levels are normalized within the first month of therapy, but no later than 3 months.[140,141,145,149] Thyroid function tests should be routinely monitored 2 to 4 weeks after starting therapy, then every 1 to 2 months during the first 6 months of life, every 3 to 4 months until age 3, and finally, every 6 to 12 months until growth is complete.[138] Although TSH suppression is the most reliable index of adequate replacement in older children, normalization of the TSH should not be used as the sole monitoring parameter in infants because the TSH may lag behind correction of the T_4 and/or FT_4 levels.

Overtreatment should be avoided to prevent brain dysfunction, acceleration of bone age, and craniosynostosis (premature closure of the cranial sutures).[138,146] Normal growth and development should also be a treatment goal. Other clinical end points include an improvement in activity level, skin color, temperature, facial appearance, and reversal of other symptoms and signs of hypothyroidism. The child will require lifelong replacement therapy.

Myxedema Coma

CLINICAL PRESENTATION

CASE 52-9

Question 1: R.B., a 65-year-old, agitated female arrived at the emergency department with chest pain unrelieved by nitroglycerin (NTG). Her medical problems include alcoholic cardiomyopathy, angina, and hypothyroidism. Although she has been advised repeatedly to take her T_4 regularly, she continues to take it sporadically. An FT_4 drawn 4 months ago was 0.5 ng/dL (normal, 0.7–1.9). Haloperidol 2 mg IM and morphine sulfate 10 mg IM were given for the agitation. After the injection, the nurse noticed mental depression, lethargy, and shallow breathing. R.B.'s oral temperature was 94.1 °F (34.5 °C), and she exhibited chills and shakes.

What is your assessment of R.B.'s subjective and objective data?

R.B. has several symptoms consistent with myxedema coma.[150] The classic features are hypothermia, delayed DTRs, and an altered sensorium that ranges from stupor to coma. Other predominant features include hypoxia, carbon dioxide retention, severe hypoglycemia, hyponatremia, and paranoid psychosis.[150] Typical physical findings (see Table 52-3) include a puffy face and eyelids, a yellowish discoloration of the skin, and loss of the lateral eyebrows. Pleural and pericardial effusions and cardiomegaly may be present. Because myxedema coma frequently occurs in older females, it is often difficult to distinguish the signs and symptoms from dementia or other disease states, as illustrated by R.B. Precipitating factors include cold weather or hypothermia, stress (eg, surgery, infection,

trauma); coexisting disease states such as MI, diabetes, hypoglycemia, or fluid and electrolyte abnormalities (especially hyponatremia); and medications such as sedatives, narcotic analgesics, antidepressants, and other respiratory depressants and diuretics.[150–152]

Haloperidol and morphine might be responsible for what appears to be impending myxedema coma in R.B. In patients with severe myxedema, respiratory depressants (anesthetics, narcotic analgesics, sedative hypnotics) alone or in combination with the hypothermic effects of the phenothiazines can aggravate the preexisting hypothermia and carbon dioxide retention to precipitate myxedema coma.[150,151] Tranquilizers such as haloperidol should not be given; small doses of less depressive sedative hypnotics such as the benzodiazepines should be used only when necessary. Patients with myxedema are also inherently sensitive to the respiratory depressant effects of narcotic analgesics, especially morphine. A dose as small as 10 mg may induce coma in a patient who are hypothyroid or cause death in a patient who is already comatose.[150–152] If morphine is required, the dose should be decreased to one-third to one-half the usual analgesic dose and the respiratory rate should be monitored closely.

TREATMENT

CASE 52-9, QUESTION 2: What would be a reasonable therapeutic plan for the management of R.B.'s myxedema coma?

Emergency treatment, usually in the intensive care unit, of myxedema coma is directed toward thyroid replacement, maintenance of vital functions, and elimination of precipitating factors. Despite immediate and aggressive therapy with large replacement doses of thyroid, mortality rates of 60% to 70% are common.[150]

Whether T_4 or T_3 is the drug of choice in myxedema coma is controversial because no comparative trials have been conducted.

Although T_3 is potentially more cardiotoxic, it has been recommended because its more rapid onset might reverse coma faster and the peripheral conversion from T_4 to the biologically active T_3 might be inhibited in severe systemic disease.[151–155] T_4 alone, T_3 alone, and a combination of the two have all been used successfully to treat myxedema coma.[150,152,156] However, L-thyroxine is generally regarded as the hormone of choice because of greater clinical experience with T_4 than with T_3. Also, mortality has occurred despite the higher T_3 levels achieved after T_3 administration.[152] T_3 might be considered after failure of T_4 or if concomitant systemic illness (eg, heart failure) is likely to impair conversion of T_4 to T_3.[150] Supraphysiologic elevations in T_3 levels occur only after oral administration but are not seen after IV T_3 infusion. Factors associated with a higher mortality 1 month after therapy include older age, cardiac complications, and T_4 replacement ≥500 μg/day or T_3 replacement >75 μg/day.[151,152] If T_3 is used, it should be administered concurrently with T_4 and not as monotherapy to avoid the need for high doses associated with increased mortality.[32]

L-Thyroxine 200 to 400 μg should be given IV initially in patients younger than 55 years without cardiac disease to saturate empty TBG sites and raise the serum T_4 level to 6 to 7 μg/dL.[32,150,156] A maintenance dose of 1.2 μg/kg/day IV or 1.6 μg/kg/day orally should follow the initial dose. The initial dose can be adjusted based on the patient's weight and other restrictive factors (eg, age, cardiac disease). The initial T_4 dosage for R.B. should be 200 μg/day to avoid worsening her angina. If the proper dosage is given, consciousness, restoration of vital signs, and decreased TSH levels should occur within 24 hours. If T_3 is to be coadministered, the dose is 5 to 20 μg IV, followed by a maintenance dose of 2.5 to 10 μg every 8 hours.[32] Dosage of 10 μg every 4 hours for the first 24 hours and then 10 μg every 6 hours for a few days until oral therapy can be started.[150]

Maintenance doses should be titrated to the patient's clinical response. Because myxedema can impair oral absorption, the IV route is preferred to ensure adequate drug concentrations. Oral administration is permitted once GI function returns to normal.[150,156]

Supportive measures include assisted ventilation, glucose for hypoglycemia, restriction of fluids for hyponatremia, and the use of blood or plasma expanders to prevent circulatory collapse and to maintain blood pressure. The use of blankets to treat R.B.'s hypothermia is not advised because vasodilation will occur and further compromise the cardiovascular components of shock. Although steroids have not been shown to be clearly beneficial in primary myxedema, they may be lifesaving in patients with hypopituitarism masquerading as myxedema coma. Because it is difficult to distinguish between primary and secondary myxedema, hydrocortisone 50 to 100 mg every 6 hours should be given empirically, beginning before the first dose of thyroid hormones.[32,150]

Appropriate measures should be taken to relieve R.B.'s chest pain while ruling out the possibility of an MI. The use of a narcotic antagonist such as naloxone may be beneficial in this instance because it can reverse the effects of the morphine. Naloxone can also arouse comatose patients intoxicated with alcohol.

Hypothyroidism With Cardiac Disease

CLINICAL PRESENTATION

CASE 52-10

Question 1: E.B., a 45-year-old female, is admitted with chest pain, SOB, dyspnea on exertion, and orthopnea suggestive of heart failure. Significant past medical history reveals exertional angina and Graves disease, treated with RAI ablation 10 years ago. Testing and physical examination reveal cardiomegaly, diastolic hypertension, obesity, facial edema and puffiness, delayed DTRs, and nonpitting pretibial edema. Pertinent laboratory findings include the following results:

FT_4, 0.2 ng/dL (normal, 0.8–1.8)
TSH, 100 μIU/mL (normal, 0.40–4.5)

Brain natriuretic peptide, 550 pg/mL (normal, <100 pg/mL)

A chest radiograph reveals cardiomegaly and pericardial effusions, and an electrocardiogram (ECG) shows bradycardia and flattened T waves with ST depression. Left ventricular ejection fraction was 25% on echocardiography. Furosemide, nitrates, metoprolol, and lisinopril are started. E.B.'s symptoms improve, but her cardiac abnormalities are not reversed.

Why do these clinical findings suggest hypothyroidism?

E.B.'s abnormal thyroid function tests, symptoms, physical findings, and history of RAI therapy are consistent with severe hypothyroidism. "Myxedema heart" can be confused with HFrEF because the signs and symptoms are similar: cardiomegaly, dyspnea, edema, pericardial effusions, elevated brain natriuretic peptide (BNP) and abnormal ECG.[150,157] Therefore, hypothyroidism should be ruled out as a reversible cause in all patients with new or worsening symptoms of cardiovascular disease (eg, angina, arrhythmia).

TREATMENT

Case 52-10, Question 2: What might be the effect of hypothyroidism on the cardiac treatment and status of E.B.?

If E.B.'s cardiac abnormalities are caused by hypothyroidism, adequate doses of T_4 will restore the heart size, normalize the diastolic blood pressure, reverse the ECG findings, and normalize the serum enzyme elevations within 2 to 4 weeks.

Angina or premature beats can develop or worsen with the institution of T_4 therapy, so doses should be titrated carefully (see Case 52-10, Question 3).[158–160] Nitrates may precipitate hypotension and/or syncope in patients who are hypothyroid because these patients have a low circulating blood volume and their response to vasodilation can be exaggerated. Furthermore, if β-blockers are required, the cardioselective β-blockers are preferred. The non–cardioselective β-blockers have produced coronary spasm by

exacerbating the compensatory increase in norepinephrine levels and α-adrenergic tone found in hypothyroidism.[159–161]

Case 52-10, Question 3: How aggressively should thyroid hormone therapy be initiated in a patient like E.B. who has angina? What is the hormone replacement of choice in patients with cardiac disease?

Patients with long-standing hypothyroidism, arteriosclerotic cardiac disease, or advanced age tend to be extremely sensitive to the cardiac effects of thyroid hormone. Initiation of normal or even subtherapeutic doses might produce severe angina, MI, supra- and ventricular premature beats, cardiac failure, or sudden death and underscore the need to replace thyroid cautiously, and sometimes suboptimally, to avoid cardiac toxicity.[158–161] The angina and cardiac status should be controlled before initiating T_4 therapy. In the patient with poorly controlled angina, cardiac catheterization is warranted to assess the coronary artery status before starting hormone therapy.

For E.B., 12.5 to 25 μg daily of T_4 should be initiated cautiously and increased as tolerated by similar increments of T_4 every 4 to 6 weeks until a therapeutic dosage is reached. The rapidity with which the increments can proceed is determined by how well each increased dose is tolerated. If cardiac toxicity occurs, therapy should be stopped immediately. Once symptoms resolve, therapy can be restarted using smaller dosage increments and longer intervals between dosage adjustments. If cardiac symptoms recur, further T_4 therapy should be stopped pending cardiac evaluation. In patients with severe cardiac sensitivity, complete euthyroidism may be difficult to achieve; however, revascularization procedures (coronary artery stenting or bypass grafting) may allow full T_4 replacement therapy.[32] E.B.'s clinical status and ECG should be monitored closely during the titration period. T_4 should be discontinued or decreased at the first sign of cardiac deterioration. It is not necessary to monitor thyroid function tests (eg, TSH or FT_4) during the titration period because the results will remain abnormal until adequate replacement

is achieved. Thyroid function tests should be obtained once maximally tolerated or estimated euthyroid dosages are achieved.

Subclinical Hypothyroidism

CASE 52-11

Question 1: M.P., a healthy 53-year-old female, comes in for her regular checkup. She denies any symptoms of hypothyroidism and feels well. She has no other medical problems, takes no medications, and has no known allergies. Her physical examination is within normal limits. Routine screening laboratory tests are normal except for an FT_4 of 1.2 ng/dL (normal, 0.8–1.8) and a TSH of 8 μIU/mL (normal, 0.40–4.5).

Does M.P. require thyroid treatment, based on her clinical presentation and laboratory findings?

M.P.'s free thyroid levels are normal, but her TSH level is elevated, indicating subclinical hypothyroidism (SH). The prevalence of SH ranges from 4% to 10% and increases to 26% in the elderly population, particularly females.[94,95] It is unclear whether SH represents the early stages of thyroid failure. The estimated risk of developing overt hypothyroidism after 10 years in untreated patients by Kaplan–Meier curves was 0% for a TSH level of 4 to 6 μIU/mL, 42.8% for a TSH level of 6 to 12 μIU/mL, and 76.9% for a TSH level >12 μIU/mL. This risk increased in patients with positive thyroid antibodies.[162] Because the most common clinical scenarios involve asymptomatic patients with TSH levels <10 μIU/mL, negative thyroid antibodies, and no history of prior thyroid disease, routine thyroid screening has been recommended, particularly in elderly females.[95]

Mild symptoms of hypothyroidism, including psychiatric and cognitive abnormalities, are found in ~30% of patients with SH, but the average TSH level usually exceeds 11 μIU/mL. Cardiac dysfunction, including impaired left ventricular diastolic function at rest, systolic dysfunction with exercise, atherosclerosis, heart failure, and MI has been reported.[92,95,163–165] Data showing an increased risk of coronary artery disease (CAD) are conflicting and influenced by

the severity of SH, study design, and length of follow-up. A meta-analysis noted a 1.6 times increased risk of CAD,[166] a cross-sectional analysis noted an odds ratio of 2.2 only in those with TSH levels of ≥10 μIU/mL, whereas a 20-year longitudinal analysis found a significant risk (hazard ratio [HR] of 1.7) regardless of the degree of TSH elevation.[167] However, a large prospective cohort study found no significant association with atherosclerotic disease or cardiac mortality but observed an increase in all-cause mortality at 10 years of follow-up.[168] Compelling data reported from 11 large prospective cohorts with a median follow-up of 2.5 to 20 years involving 3450 subjects with SH found an increased risk of CAD (HR 1.89) and mortality (HR 1.5) but not total mortality only in those with TSH level >10 μIU/mL after adjustment for traditional cardiovascular factors. No increased CAD or CAD mortality was noted with more minimal TSH elevations.[169]

Other atypical and nonspecific signs and symptoms reflecting dysfunction of any part of the body may occur, primarily in the elderly. Failure to thrive, mental confusion, weight loss with poor appetite, incontinence, depression, inability to walk, carpal tunnel syndrome, deafness, ileus, anemia, hypercholesterolemia, and hyponatremia have been reported.[94,95,163–165]

Treatment of SH with T_4 is controversial because study results are conflicting. Potential benefits of treatment include (a) preventing progression to hypothyroidism, (b) improving the lipid profile and reducing cardiac risks, and (c) reversing symptoms of hypothyroidism. Patients with higher TSH levels (eg, >10 μIU/mL), a history of previously diagnosed thyroid disease, elevated lipid levels, or evidence of positive thyroid antibodies gained the most benefit from L-thyroxine therapy.[92,95,162,165,170] L-thyroxine significantly reduced total cholesterol by 7.9 to 15.8 mg/dL and low-density cholesterol concentrations by 10 mg/dL; serum high-density lipoprotein (HDL) cholesterol and triglyceride concentrations remain unchanged.[95,164,165,170] Improvement of elevated intraocular pressures, memory, mood, somatic symptoms, and diastolic dysfunction has also been reported after T_4 replacement.[162,164,165,170]

Conversely, a meta-analysis published in 2018 indicated that treatment of SH does not improve general quality of life or thyroid symptoms.[171] Recent guidelines suggest that T_4 therapy should be reserved for females who are attempting pregnancy, patients with TSH levels >20 μIU/mL, and in those with severe symptoms despite normal thyroxine levels.[172]

Treatment of older patients requires an assessment of the risks versus benefits of therapy. Thyroid therapy carries the risk of unmasking underlying cardiac disease in older patients. Nevertheless, thyroid replacement appears reasonable in asymptomatic patients with TSH levels >10 μIU/mL and especially those with symptoms of mild hypothyroidism, dyslipidemia, laboratory abnormalities, or end-organ alterations.[94,95,162,164,170] Patients with mild SH (TSH 6–10 μIU/mL) may benefit from therapy with L-thyroxine 25–75 μg/day when there is evidence of cardiovascular risk (eg, diastolic dysfunction, risk of atherosclerotic disease, diabetes) or clinical indicators suggestive of hypothyroidism (eg, goiter, antibodies).[95] There is no evidence supporting the treatment of mild subclinical disease in patients older than 80 years.[95] Conversely, patients with asymptomatic SH and a TSH level <10 μIU/mL do not warrant immediate therapy, but close follow-up is recommended.

Because M.P. is asymptomatic and has a TSH level <10 μIU/mL, it is reasonable to delay therapy and recheck the TSH in a few months.

Secondary Hypothyroidism

CASE 52-12

QUESTION 1: J.R. is a 65-year-old female who is currently experiencing fatigue, cold intolerance, dry skin, and weight gain for the past several months. Her thyroid examination and DTRs are within normal limits. Her TSH level was 0.5 μIU/mL (normal, 0.40–4.5). She denies taking any other medications. J.R. is started empirically on a 3-month trial of L-thyroxine.

How should the TSH level be interpreted? Is T_4 therapy indicated, based on her presenting findings?

Despite symptoms that could be consistent with hypothyroidism (eg, fatigue, cold intolerance, dry skin, weight gain), the normal TSH level implies that J.P. is euthyroid. However, because a diagnosis of hypopituitarism (ie, TSH level could be normal or low) cannot be ruled out, a FT_4 level should be obtained. A low FT_4 would increase the likelihood of hypopituitarism and the presence of secondary hypothyroidism. Some argue that hypopituitarism is underdiagnosed and would advocate adding FT_4 to the primary screening tests.[173]

If the FT_4 level is normal, indicating euthyroidism, then hypopituitarism is unlikely and L-thyroxine therapy is not indicated. A randomized, double-blind, placebo-controlled crossover trial found that T_4 supplementation in patients with hypothyroid symptoms and normal thyroid function tests was not more effective than placebo in improving cognitive function or psychological well-being despite changes in the TSH and FT_4 levels.[174,175]

HYPERTHYROIDISM

Clinical Presentation

CASE 52-13

QUESTION 1: C.R., a 47-year-old female, has a 3-month history of intermittent heat intolerance, sweats, tremor, and severe muscle weakness, which has limited her ability to climb stairs. Her weight has increased because of increased appetite. She is also bothered by the pounding of her heart and some minor difficulty in swallowing. There is a family history of thyroid disease, but she denies taking any thyroid medications or any history of radiation to her neck. C.R. previously received iodide drops with symptomatic improvement, but her disease recurred despite its continued administration. Her other medical problems include type 2 diabetes controlled by diet, and osteoarthritis treated

with acetaminophen 650 mg PO q6h. She has a history of noncompliance with her clinic visits.

Physical examination reveals a thin, flushed, hyperkinetic, nervous female. Blood pressure (BP) is 180/90 mm Hg; pulse is 130 beats/minute, irregularly irregular; respiratory rate is 30 breaths/minute; and temperature is 99.5 °F (37.5 °C). Other pertinent findings include a lid lag with stare, proptosis with tearing, decreased visual acuity, a diffusely enlarged thyroid gland without nodules, a bruit in the left lobe of the thyroid, positive jugular venous distension (JVD), bibasilar rales, warm moist skin with multiple bruises, new-onset atrial fibrillation (AF), slight diarrhea, hepatomegaly, acropachy, 2+ pitting edema, a fine tremor, proximal muscle weakness, and irregular scant menses.

Laboratory data include the following:

FT_4, 2.9 ng/dL (normal, 0.8–1.8)
TSH, <0.5 μIU/mL (normal, 0.40–4.5)
RAIU at 24 hours, 80% (normal, 5%–35%)
International normalized ratio (INR) 4.8 (normal, 1; therapeutic, 2–3)
TRAb, 2.3 IU/L (normal, <2)
Fasting blood glucose, 350 mg/dL

What do you make of these subjective and objective data?

C.R. presents with many of the clinical and laboratory features[176] associated with an increased metabolic state resulting from excessive thyroid hormones (Table 52-5). Her ocular symptoms are consistent with Graves disease and include lid lag (lid falls behind the movement of the eye and a narrow white rim of sclera becomes visible between the upper lid and cornea, producing a “staring” appearance), ophthalmopathy (protrusion of the eyeball), and decreased visual acuity. The thyroid bruit, palpitations, exertional dyspnea, heart failure signs (JVD, bibasilar rales, edema, hepatomegaly), diarrhea, irregular scant menses, nervousness, tremor, muscle weakness, increased perspiration, and flushing of the skin are consistent with a hypermetabolic state.[176,177] Although sinus tachycardia is the most common arrhythmia in hyperthyroidism, new-onset AF is the presenting symptom in 5% to 20% of patients with hyperthyroidism, particularly in those older than 70 years.[178] Together with C.R.’s symptoms, a diagnosis of Graves disease is confirmed by an elevated FT_4 level, an undetectable TSH level, an

increased RAIU, positive TRAb, and a diffusely enlarged goiter (Table 52-6 lists the causes of hyperthyroidism).

Iodides

Case 52-13, Question 2: Why were the iodide drops initially effective in improving C.R.'s symptoms and later ineffective? When are iodides indicated? What is their mechanism of action?

Iodides have several effects: They inhibit thyroid hormone release, they block iodotyrosine and iodothyronine synthesis by blocking organification, and they decrease the vascularity of the thyroid gland.[179] However, large doses may accentuate hyperthyroidism because they provide a significant increase in available substrate for hormone synthesis (see Case 52-23).[37,179]

The inhibitory effect of exogenous iodides on the intrathyroidal organification of iodides is known as the Wolff–Chaikoff effect. This is an inherent autoregulatory function of the normal gland to prevent excessive hormone synthesis in the event of a large iodide load. The Wolff–Chaikoff effect occurs when intrathyroidal concentrations of iodides reach a critical level, and this is not overcome by TSH stimulation. However, as illustrated by C.R., the gland can "escape" from this block even with continued iodide use. The gland escapes by decreasing iodide transport or by leaking iodide. Both mechanisms decrease the critical intrathyroidal iodide level, thereby decreasing the block to organification.[18,37,179] This effect is illustrated in C.R. Therefore, iodides should not be used as primary therapy for Graves disease.

The most important pharmacologic effect of iodides is their ability to promptly inhibit thyroid hormone release when dosages of 6 mg/day are given.[18,179] The mechanism is unknown, but it is not related to the Wolff–Chaikoff effect, which may take several weeks to manifest. Unlike the Wolff–Chaikoff effect, this effect can be overcome partially by an increase in TSH secretion. Thus, the normal gland can escape in 7 to 14 days because inhibition of

thyroid hormone release stimulates a reflex increase in TSH secretion. Because patients with hyperthyroidism experience an improvement in symptoms within 2 to 7 days of initiation of therapy, inhibition of hormone release must be the predominant mechanism of action for the iodides. This rapid onset is the reason iodides are used in the treatment of thyroid storm and as an ameliorative measure while awaiting the onset of the therapeutic effects of ATDs or RAI.[180]

Large doses of iodides are also used 2 weeks before thyroid surgery to increase the firmness of the thyroid gland by decreasing its size, vascularity, and friability. Iodides facilitate a smoother, less complicated surgery and reduce the risk of postoperative complications by inducing a euthyroid state.[179]

Stable iodine can be administered orally either as an unpleasant-tasting Lugol solution (5% iodine and 10% potassium iodide), containing 8 mg/drop of iodide, or as the more palatable saturated solution of potassium iodide (SSKI), containing 50 mg/drop of iodide. The minimum effective daily dose is 6 mg,[179] although larger doses (eg, 5–10 drops qid of SSKI) are often administered.

The advantages of iodide therapy are that it is simple, inexpensive, and relatively nontoxic and involves no glandular destruction. Disadvantages include "escape," accentuation of thyrotoxicosis, allergic reactions, relapse after discontinuation of treatment, and subsequent interference with RAI if used before therapy.[18,33,179]

Treatment Modalities

Case 52-13, Question 3: What are the advantages and disadvantages of the different treatment modalities available for C.R.?

The three major treatment modalities for Graves-related hyperthyroidism are the ATDs, RAI, and surgery (**Table 52-10**).[176] In most cases, any of these three modalities can be used, and there is controversy as to which is the most effective therapy. Often the final

decision is empiric, depending on the clinician's available resources and the patient's desires. A review of treatment guidelines published by the major endocrine organizations found that RAI is the most common treatment, while surgery is the least common.[181] Patients who are older and those with cardiac disease, concomitant ophthalmopathy, and hyperthyroidism caused by a toxic multinodular goiter are treated best with RAI.[33] Surgery is the preferred therapy for pregnant females who are drug-intolerant, when obstructive symptoms are present, or if malignancy is suspected.[33,128]

Table 52-10
Treatment for Hyperthyroidism

Modality	Drug/Dosage	Mechanism of Action	Toxicity	Indication
Primary Treatment				
Antithyroid Drugs				
Methimazole (Tapazole®) 5–10 mg tablet; rectal suppositories can be made[189]	30–40 mg PO daily or in two divided doses (*max:* 60 mg/day) for 6–8 weeks or until euthyroid, then maintenance of 5–10 mg/day PO × 12–18 months	Blocks organification of hormone synthesis, does not block conversion of T_4 to T_3	Skin rashes, GI symptoms, arthralgias, cholestatic jaundice, agranulocytosis, aplasia cutis, and embryopathy syndrome in pregnancy (MMI only)	DOC in adults/children except in thyroid storm and first trimester of pregnancy (see PTU). Once-daily dosing can improve adherence.
PTU 50 mg tablet; rectal formulation can be made[187,188]	100–200 mg PO q6–8h (*max:* 1200 mg/day) for 6–8 weeks or until euthyroid; then maintenance of 50–150 mg daily PO × 12–18 months	Similar to methimazole, and blocks peripheral conversion of T_4 to T_3 (PTU only)	Hepatitis, some fatal. Similar to MMI	DOC in thyroid storm, first trimester of pregnancy
Surgery				
	Preoperative preparation with iodides, ATDs, or β-blockers before surgery; see specific operative agent	Near-total thyroidectomy	Hypothyroidism, cosmetic scarring, hypoparathyroidism, risks of surgery, and anesthesia, vocal cord damage	Obstruction, choking, malignancy, pregnancy in second trimester, contraindication to RAI or ATDs
RAI				
	^{131}I radioactive isotope; 80–100 μCi/g thyroid tissue. Average dose, ≈10 mCi; pretreatment with corticosteroids indicated in patients with ophthalmopathy	Destruction of the gland	Hypothyroidism; worsening of ophthalmopathy; fear of radiation-induced leukemia; genetic damage; malignancy; rarely, radiation sickness	Adults, older patients who are poor surgical risks or have cardiac disease; patients with a history of prior thyroid surgery; contraindications to ATD usage; increasingly used in kids

Adjuncts to Primary Usage				
Iodides				
Lugol solution 8 mg/drop (5% iodine, 10% potassium iodide; saturated [SSKI] 50 mg/drop)	5–10 drops tid PO for 10–14 days before surgery; minimum effective dose 6 mg/day	Decreased vascularity of gland and Elevated firmness; blocks release of thyroid hormone	Hypersensitivity reactions, skin rashes, mucous membrane ulcers, anaphylaxis, metallic taste, rhinorrhea, parotid, and submaxillary swelling; fetal goiters and death	Preoperative preparation before surgery; thyroid storm, provides symptomatic relief of symptoms. *Do not use before RAI or chronically during pregnancy*
β-*Blockers*				
Propranolol or equivalent β-blocker. *Avoid* those with ISA	Propranolol 10–40 mg PO q6h or PRN to control HR <100 beats/minute; IV 0.5–1 mg slowly	Blocks effects of thyroid hormone peripherally, no effect on underlying disease; blocks T_4 to T_3 conversion	Related to β-blockade; bradycardia, HF, blocks hyperglycemic response to hypoglycemia, bronchospasm, CNS symptoms at high doses; fetal bradycardia	Symptomatic relief while awaiting onset of ATDs, RAI; preoperative preparation for surgery; thyroid storm
Calcium Channel Blockers				
	Diltiazem 120 mg PO tid–qid or verapamil 80–120 mg PO tid–qid PRN to control HR <100 beats/minute	Blocks effects of thyroid hormone peripherally, no effect on underlying disease	Bradycardia, peripheral edema, HF, headache, flushing, hypotension, dizziness	Alternative for symptomatic relief of hyperthyroid symptoms in patients who cannot tolerate β-blockers
Corticosteroids				
	Prednisone or equivalent corticosteroids 50–140 mg PO daily in divided doses; IV hydrocortisone 50–100 mg q6h or equivalent for thyroid storm	Decreased TSI, suppression of inflammatory process; blocks T_4 to T_3 conversion	Complications of steroid therapy	Ophthalmopathy, thyroid storm (use IV steroid), pretibial myxedema, pretreatment before RAI therapy in patients with ophthalmopathy

CNS, central nervous system; DOC, drug of choice; GI, gastrointestinal; HF, congestive heart failure; HR, heart rate; ISA, intrinsic sympathomimetic activity; IV, intravenous; mCi, millicurie; MMI, methimazole; PO, orally (by mouth); PRN, as needed; PTU, propylthiouracil; q, every; qid, four times a day; RAI, radioactive iodine; SSKI, saturated solution of potassium iodide; T_3, triiodothyronine; T_4, thyroxine; tid, three times a day; TSI, thyroid receptor–stimulating or thyroid-stimulating immunoglobulin; µCi, microcurie.

Sources: Ross DS, Burch HB, *Cooper DS, et al. 2016* American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26(10):1343–1421. doi:10.1089/thy.2016.0229; Burch HB, Cooper DS. Management of Graves disease: a review. *JAMA*. 2015;314(*23*):2544–2554. doi:10.1001/jama.2015.16535; Smith TJ, Hegedus L. Graves' disease. *N Engl J Med*. 2016;375(*16*):1552–1565. doi:10.1056/NEJMra1510030; Brent GA. Graves' disease. *N Engl J Med*. 2008;358:2594–2605; Cooper DS. Antithyroid drugs. *N Engl J Med*. 2005;352:905–917; Boostrom S, Richards ML. Total thyroidectomy is the preferred treatment for patients with Graves' disease and a thyroid nodule. *Otolaryngol Head Neck Surg*. 2007;136:278–281; Hoffmann R. Thyroidectomy in Graves' disease: subtotal, near total or total? *Orbit*. 2009;28(*4*):241–244. doi:10.1080/01676830903104595; Nayak B, Burman K. Thyrotoxicosis and thyroid storm. *Endocrinol Metab Clin North Am*. 2006;35:663–686; Iagaru A, McDougall IR. Treatment of thyrotoxicosis. *J Nucl Med*. 2007;48:379–389; Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis:

management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011;17(*3*):456–520; Wiersinga WM. Management of Graves' ophthalmopathy. *Nat Clin Pract Endocrinol Metab*. 2007;3:396–404.

ANTITHYROID DRUGS

The ATDs are the preferred treatment for children, pregnant females, and young adults with uncomplicated Graves disease.[176,182,183] This is the only treatment that leaves the thyroid gland intact and does not carry the added risk of permanent hypothyroidism often associated with RAI or surgery.

Because the thyrotoxicosis of Graves disease might be self-limiting, ATDs are used to control the symptoms until spontaneous remission occurs. Thioamides should also be given before treatment with RAI or surgery to deplete the gland of stored thyroid hormone, which prevents subsequent thyroid storm. Although hyperthyroidism from toxic nodules will also respond to ATDs, more definitive therapy (surgery or RAI) is needed because these conditions do not undergo spontaneous remission.[33,44]

Disadvantages of ATD therapy include the numerous tablets required, patient adherence, possible drug toxicity, the long duration of treatment, and the low remission rates after discontinuation of therapy (see Case 52-14).

The use of ATDs in C.R. has several potential drawbacks. Her relatively large gland and severe disease make the prognosis for spontaneous remission somewhat less favorable. A delay in the onset of ATD effect may be expected if intraglandular stores of thyroid have been increased by her prior iodide therapy. Furthermore, her nonadherence and difficulty swallowing may necessitate another means of treatment. Thioamides may also be prepared for administration by the rectal routes.[184–186]

SURGERY

Surgery is considered the treatment of choice[176,187–189] when (a) malignancy is suspected; (b) esophageal obstruction, evidenced by difficulty swallowing, is present; (c) respiratory difficulties are

present; (d) contraindications to the use of ATDs (eg, allergy) or RAI (eg, pregnancy) exist; (e) a large goiter that regresses poorly on RAI or ATD therapy is present; or (f) it is the patient's preference. Some argue that surgery is underused in the treatment of Graves disease, especially with Graves disease complicated by ophthalmopathy.[187,190] In a prospective, randomized trial comparing the three treatment modalities, surgery produced euthyroidism more quickly and was associated with a lower relapse rate than either RAI or ATDs.[188] A meta-analysis of 35 studies encompassing 7241 patients with Graves disease found that thyroidectomy was successful in 92% of patients with a low recurrence (7.2%) of hyperthyroidism.[191] If C.R.'s minor difficulty in swallowing persists because of poor regression of goiter size with drug therapy, then surgery is a reasonable alternative. If surgery is contemplated, C.R. must be brought to surgery in a euthyroid state to prevent rapid postoperative rises in T_4 levels and subsequent thyroid storm (see Case 52-19, Question 1). A total or near-total rather than a subtotal thyroidectomy is the procedure of choice when performed by an experienced surgeon.[187,189,191] Although subtotal thyroidectomy theoretically avoids the predictable risk of hypothyroidism from total thyroidectomy, the likelihood of recurrent hyperthyroidism increases in proportion to the amount of residual thyroid tissue remaining.[187,188] Recurrent thyrotoxicosis following a subtotal thyroidectomy should be treated with RAI because the incidence of surgical complications increases with a second surgery.[33]

Patients should be in a euthyroid state at the time of surgery to avoid precipitation of thyroid storm and morbidity. Generally, iodides (see Case 52-13, Question 2), ATDs, or propranolol can be used.[33,179,192] The combination of iodides and propranolol is more effective than either used alone.[193] Propranolol used alone has been associated with thyroid crisis postoperatively and may be less effective than iodides in decreasing gland friability and vascularity.[193]

Surgical complication rates are low when the procedure is performed by a competent surgeon and when the patient is adequately prepared for surgery. Postoperative complications

include hypoparathyroidism, adhesions, laryngeal nerve damage, bleeding, infection, and poor wound healing.[189,190,194] Complications are also higher if a total rather than a subtotal thyroidectomy is performed, but there is a lower risk of recurrent hyperthyroidism. Development of hypothyroidism, especially SH, is greatest during the first year after surgery, with an insidious rise in incidence over the next 10 years. Permanent hypothyroidism following surgery is inversely related to the amount of remnant thyroid tissue left behind and varies widely (rates ranging from below 10% to as high as 80% are reported).[195] Thyroid function tests should be monitored annually after surgery. When total thyroidectomy is performed, postoperative L-thyroxine should be initiated at a dose of 1.6 μg/kg/day.[33] Inadvertent parathyroidectomy can result in life-threatening hypocalcemia. Patients receiving total thyroidectomy should have postoperative measurement of serum calcium and/or intact parathyroid hormone concentrations.[33,190]

The disadvantages of surgery are expense, hospitalization, hypothyroidism, the small risk of postoperative complications, and the patient's fear of surgery.[187,188,191]

RADIOACTIVE IODINE

RAI, the most common treatment modality in the United States, is the preferred treatment for (a) debilitated, cardiac, or older patients who are poor surgical candidates; (b) patients who fail to respond to drug therapy or who experience adverse drug reactions; and (c) patients who develop recurrent hyperthyroidism after surgery.[176,181,188,196]

Pregnancy is an absolute contraindication to RAI therapy. Previously, the use of RAI was restricted to adults older than an arbitrary age of 20 to 35 years because it was feared that RAI could result in genetic damage or neoplasia. However, its use in adolescents is increasing after more than 50 years of clinical experience with RAI showing that it is safe and effective.[196–199] There is no reported evidence of genetic damage after ^{131}I ingestion and the dose of radiation to the gonads is <3 rads, which is comparable

to other radiographic diagnostic tests (eg, barium enemas).[200] The incidence of leukemia or malignancy is no higher in recipients of ^{131}I than in patients who are thyrotoxic treated with drugs or surgery.[197,201] In a retrospective review of 98 adolescents followed for 36 years after receiving ^{131}I, no cancers of the thyroid or leukemia were reported.[199] One interesting finding is that patients receiving RAI should be warned that they can set off radiation detectors at airport screening terminals for up to 12 weeks after RAI and that they should carry documentation of their treatment.[202,203]

RAI is painless, effective, economical, and quick, but unsubstantiated fears about radiation and malignancy, as well as the high incidence of hypothyroidism, may deter its use.[33,204,205] RAI could be used safely in this nonpregnant young patient. However, C.R.'s prior use of iodides will dilute the ^{131}I pool. Thus, it will be impossible to achieve therapeutic thyroid concentrations of RAI for as long as 3 to 6 months.

Treatment With Antithyroid Drugs

PROPYLTHIOURACIL VERSUS METHIMAZOLE

Case 52-13, Question 4: C.R. is started on MMI 15 mg twice daily after baseline FT_4 and TSH levels have been obtained. Three weeks later, she angrily states that the medication is not working because her symptoms are worse; however, she reluctantly admits to missing doses because of difficulty swallowing, nausea, vomiting, diarrhea, fatigue, a cough, and a sore throat. What are the advantages of using either PTU or MMI in the treatment of hyperthyroidism?

Both ATDs are effective in treating hyperthyroidism. The antithyroid effectiveness of the ATDs primarily depends on their ability to block the organification of iodides, thereby inhibiting thyroid hormone synthesis.[182,183] Thyroid autoantibody synthesis may also be suppressed. In most hyperthyroid adults and children, MMI should be considered the ATD of choice because of increasing reports of hepatitis, some fatal, from PTU.[50] PTU should be reserved

for use in thyroid storm, during the first trimester of pregnancy because of rare teratogenicity from MMI, and in those allergic to MMI (except agranulocytosis and hepatitis) who are not candidates for RAI or surgery.[44,206]

Dosing and administration

Methimazole is effective when administered initially as a single-dose compared with the multiple-dose regimen required with PTU to achieve a euthyroid state.[182,183] Although a single-dose regimen of PTU has been tried acutely, it is most effective when given in divided doses. Compared to PTU, MMI is also less hepatotoxic, less expensive, requires daily ingestion of fewer numbers of tablets, and is not associated with a bitter tablet taste.[50,183] However, PTU is preferred in thyroid storm because, unlike MMI, it also blocks the peripheral conversion of T_4 to T_3.[192] Within 24 to 48 hours after PTU administration, a 25% to 40% reduction in peripheral T_3 production is seen, which contributes to PTU's rapid onset. A significantly greater fall in T_3 concentration and the T_3:T_4 ratio can be demonstrated in patients who are hyperthyroid treated acutely with PTU and iodine than with MMI and iodides. Lastly, PTU is preferred over MMI during the first trimester of pregnancy (see Case 52-15).[40]

Monitoring therapy

Case 52-13, Question 5: What additional objective baseline data should be obtained to monitor both the efficacy and toxicity of ATDs?

Before ATDs are administered, a baseline FT_4 and TSH should be obtained. A baseline white blood cell (WBC) count with differential can also help differentiate the leukopenia associated with hyperthyroidism from drug-induced leukopenia and/or agranulocytosis (see Case 52-13, Question 10). Baseline liver function tests can assist in the evaluation of ATD-induced hepatotoxicity (see Case 52-13, Question 9). A repeat FT_4 and TSH

should be obtained after 4 to 6 weeks on therapy and 4 to 6 weeks after any change in the dosing regimen. Once the patient is euthyroid on maintenance dosages, thyroid function tests can be obtained every 3 to 6 months.

Duration of therapy

Case 52-13, Question 6: How long should C.R. be continued on ATD treatment?

Traditionally, ATD therapy is continued for 1 to 2 years despite the lack of data regarding the optimal treatment period.[176,182,183] The goal of treatment is to control the symptoms of Graves disease until spontaneous remission occurs. Graves disease remits spontaneously in about 30% to 50% of patients but relapse is high.[207] Because it is unknown when or if remission will occur, it is understandable why the optimal duration of therapy is unclear. Short-term therapy (ie, <6 months) has been advocated to save time and money and improve adherence because earlier studies suggested remission rates comparable to a longer course of therapy. However, short-term therapy is not recommended because longer follow-ups of patients receiving short-term therapy have noted poorer remission rates.[182,183]

Most data support a 12- to 18-month course of treatment to achieve remission rates of ~60%.[182,183] Two prospective randomized trials found that extending treatment from 6 to 18 months was beneficial but that 42 months of therapy was not significantly better than 18 months.[208] A retrospective study of 211 patients determined that therapy for more than 24 months independently predicted long-term remission.[209] A 2017 meta-analysis also concluded that long-term ATD treatment is safe and effective in adults.[210] However, one retrospective study of patients treated for >12 months observed remission rates of only 17.5%.[211] These conflicting results underscore the fact that determining the optimal treatment period is confounded by the large variability that exists with regard to

spontaneous remission. Nevertheless, treatment periods of 1 to 2 years are justifiable in adherent patients. Therapy can be reinstituted if hyperthyroidism reappears shortly after therapy is discontinued. Methimazole can also be continued indefinitely if there are no side effects and treatment with either RAI or surgery is not desired. In C.R., this goal might not be achievable, given her history of nonadherence.

PRECAUTIONS

CASE 52-13, QUESTION 7: Can ATD therapy affect any of C.R.'s preexisting medical conditions?

Thyrotoxicosis can activate or intensify diabetes, primarily by increasing the basal hepatic glucose production and the metabolism of insulin.[212] Therefore, effective therapy with ATDs may restore control of C.R.'s type 2 diabetes.

C.R.'s arthritis should not be affected, although ATDs have been associated with the development of systemic lupus erythematosus (SLE), lupus-like syndromes, and vasculitis.[182,213] These adverse drug reactions are rare; the incidence is <0.1%. Lupus-like syndromes include skin ulcers, splenomegaly, migratory polyarthritis, pleuritis and pericarditis, periarteritis, and renal abnormalities.[33,213] Serologic abnormalities may also occur with these connective tissue disorders and include hyperglobulinemia, positive SLE preparations, and positive antinuclear antibodies. Recovery occurs with adequate steroid therapy and withdrawal of the ATD. Because cross-reaction between MMI and PTU is likely to occur, patients exhibiting these reactions should be treated with surgery or RAI. C.R.'s treatment should be monitored with this lupus-like adverse effect in mind, but the occurrence of this syndrome is so uncommon that a trouble-free course of therapy can be anticipated.[213]

ADJUNCTIVE THERAPY

CASE 52-13, QUESTION 8: What adjunctive therapy might help alleviate some of C.R.'s symptoms while awaiting the onset of the ATD's effects?

****

Iodides (see Case 13, Question 2), β-adrenergic blocking agents without intrinsic sympathomimetic activity, or calcium channel blockers can be used acutely to ameliorate some of C.R.'s symptoms.[193,214] Because iodides were previously ineffective in C.R., a β-blocker should be tried.

β-Adrenergic blocking agents rapidly decrease the nervousness, palpitations, fatigue, weight loss, diaphoresis, heat intolerance, and tremor associated with thyrotoxicosis, probably because many of the signs and symptoms mimic sympathetic overactivity.[176,193] An increase in the number of β-adrenergic receptors rather than an elevation in catecholamine levels is probably responsible for this overactivity. Because the underlying disease process and thyroid hormone levels are not affected significantly by β-blockers, patients generally remain mildly symptomatic and fail to gain weight. For this reason, they should not be used as the sole treatment for thyrotoxicosis.

All β-blockers without intrinsic sympathetic activity (eg, atenolol, metoprolol, propranolol) are effective in alleviating the hyperthyroid symptoms, but propranolol and nadolol are the only β-blockers that may inhibit peripheral conversion of T_4 to T_3 at high doses.[33] Thyroid function tests are generally not affected except for a mild decrease in the T_3 level.

In summary, β-blockers are (a) effective adjuncts in the management of thyroid storm, (b) useful to prepare patients for surgery, and (c) useful in the short-term management of thyrotoxicosis during pregnancy.[33,187,192] Surprisingly, propranolol also improves many of the neuromuscular manifestations of hyperthyroidism, including thyrotoxic periodic paralysis. Current guidelines recommend elderly patients, those with concomitant heart disease, and those with a resting heart rate over 90 beats/minute receive adjunctive therapy with β-blockers.[33,215]

Diltiazem or verapamil are effective alternatives when β-blockers are contraindicated.[214] Diltiazem 120 mg tid or qid can be tried. The dihydropyridine calcium channel blockers are unlikely to be effective.

Because of C.R.'s history of diabetes, the effects of β-adrenergic blocking drugs in patients with diabetes must be considered (see Chapter 53, Diabetes Mellitus). If β-blockers are instituted, a cardioselective β-blocker would be a better choice for patients on therapy that can cause hypoglycemia because of lower risk of hypoglycemia unawareness.[216] The appropriate dosage should be based on clinical and objective improvement of hyperthyroid symptoms, such as a reduction in heart rate. Metoprolol 25 to 50 mg bid can be started initially, and the dosage titrated to maintain the heart rate at <90 beats/minute. Otherwise, diltiazem, verapamil, or a retrial of iodides is warranted.[193,214,215]

ADVERSE EFFECTS

Case 52-13, Question 9: A pruritic area over the pretibial aspects of both legs, as well as several maculopapular erythematous patches and abdominal tenderness, were noticed during C.R.'s physical examination. Do these reactions require the discontinuation of her PTU?

Antithyroid drug rash

Although C.R. may be experiencing a drug rash from PTU, pretibial myxedema or the dermopathy of Graves disease may also be possibilities because of the location of the pruritic area. About 4% of patients with Graves disease who exhibit infiltrative exophthalmos also have dermatologic changes.[177] The skin is thickened, erythematous, and nonpitting because of mucopolysaccharide infiltration and accentuation of hair follicles. Pruritus or pain may be present. Treatment includes topical corticosteroids, control of the Graves disease, and reassurance.[177]

Thioamides can produce a maculopapular pruritic rash in 5% to 6% of treated patients.[183] The rash can occur at any time but is more common early in therapy. If the rash is mild, drug therapy can be

continued while the patient's symptoms are treated with an antihistamine and a topical steroid; such rashes generally subside spontaneously. Alternatively, another ATD can be substituted because cross-sensitivity to this side effect is uncommon. Antithyroid drugs should be stopped if the rash is urticarial in nature or associated with systemic manifestations (eg, fever, arthralgias).

Hepatitis

C.R.'s symptoms of nausea, vomiting, diarrhea, fatigue, and abdominal tenderness require further evaluation. Her symptoms could be consistent with mild GI side effects from her PTU therapy, impending thyroid storm from nonadherence (see Case 52-19, Question 1) or more seriously, PTU-induced hepatitis. PTU has been associated with 0.1% severe hepatotoxicity, leading to liver transplants and fatalities primarily in children.[44,206,217,218] Although usually hepatocellular in nature, cholestasis, hepatic necrosis, and fulminant hepatic failures have been reported.[183,219,220] Transient elevations in transaminases occur in ~30% of asymptomatic patients within the first 2 months of PTU therapy and may not require drug discontinuation.[219] Liver enzymes usually normalize within 3 months of reducing the PTU to maintenance dosages despite drug continuation. However, PTU should be stopped immediately in patients with clinical symptoms of hepatitis to ensure complete recovery. The mechanism of PTU-induced hepatotoxicity appears to be autoimmune because circulating autoantibodies and in-vitro peripheral lymphocyte sensitization to PTU have been detected.[220] Overt hepatitis typically occurs during the first 2 months of PTU therapy and is not dose-related. In contrast, MMI rarely produces a cholestatic jaundice picture that might be more common in older patients and in those receiving higher dosages (ie, >40 mg/day).[221] In patients with ATD-induced hepatitis, changing to the alternative ATD is not recommended because fatalities have been reported on rechallenge. In such patients, either radioactive therapy or surgery should be used.[177]

In C.R., PTU should be stopped while awaiting results of thyroid function tests, transaminases, and bilirubin. Routine monitoring of liver function tests is not recommended during ATD therapy because patients can be asymptomatic. However, routine monitoring might be reasonable in patients with a history of liver disease and risk factors for hepatitis (eg, alcohol use). All patients receiving ATDs should be questioned closely during the first 2 months of therapy for symptoms of hepatitis, and hepatic function tests should be obtained if appropriate.

Agranulocytosis

Case 52-13, Question 10: What is your assessment of C.R.'s symptoms of sore throat and cough?

C.R.'s symptoms should not be dismissed casually because they might indicate PTU-induced agranulocytosis. Agranulocytosis (<500/mm^3 of neutrophils) is the most severe adverse hematologic reaction associated with the ATDs and should be considered strongly in C.R.[183,222] An accurate history should be obtained from C.R. The clinician should be particularly alert for a temperature of 101 °F (38.33 °C) for 2 or more days, malaise, or other flu-like findings that appeared temporally with her sore throat. If subjective or objective data are consistent with agranulocytosis, the PTU should be discontinued immediately until the results of a repeat WBC count with a differential are obtained. Traditionally, routine serial determinations of WBC counts are not recommended for monitoring the development of agranulocytosis because the onset is so abrupt. Instead, patients should be instructed to immediately report rash, fever, sore throat, or any flu-like symptoms. However, one study suggested that weekly monitoring of the WBC count with a differential during the first 3 months of antithyroid therapy might identify asymptomatic patients with agranulocytosis before infection occurs.[222]

The prevalence of agranulocytosis is about 0.5% but ranges from 0.5% to 6%.[183,222] The risk factors for agranulocytosis are unknown. There is no predilection for either gender, and the reaction may be idiosyncratic or dose-related. Some reports suggest that patients older than 40 years and those taking high dosages of MMI (eg, >40 mg/day) might be more susceptible than those on any dosage of PTU. Although controversial, patients receiving low dosages of MMI (eg, <40 mg/day) might be at less risk than those receiving high or conventional dosages of PTU.[183,222]

Agranulocytosis typically develops within the first 3 months of treatment, although it can occur at any time and as late as 12 months after starting ATD therapy.[183] A delayed reaction is more common with MMI therapy than with PTU. In 55 patients who developed agranulocytosis while taking ATDs, the duration of PTU therapy (17.7 ± 9.7 days) was significantly shorter than for MMI therapy (36.9 ± 14.5 days).[222] The mechanism of ATD-induced agranulocytosis is unknown. Both allergic (idiosyncratic) and toxic-type (dose-related) reactions have been suggested. An autoimmune reaction with circulating antineutrophil antibodies and lymphocyte sensitization to antithyroid drugs has been demonstrated.[223] Death usually results from overwhelming infection.

If agranulocytosis is diagnosed, the drug should be discontinued, the patient monitored for signs of infection, and antibiotics instituted if necessary. Granulocyte colony-stimulating factors may shorten the recovery period.[183,224] If the patient recovers, granulocytes begin to reappear in the periphery within a few days to 3 weeks; a normal granulocyte count occurs shortly thereafter.[222,224]

Although some cases of granulocytopenia have resolved with substitution or continuation of ATDs, the risks of drug rechallenge clearly outweigh the benefits, and other treatments should be instituted. Changing to an alternative ATD should also be avoided because of possible cross-sensitivity between these agents.[183]

In summary, all patients receiving ATD therapy should be well educated regarding the signs and symptoms of agranulocytosis. If these symptoms develop, they should be advised to contact their physician or pharmacist. If they cannot reach their own physician,

patients should inform the emergency physician that they are taking ATDs, and a WBC count with differential should be obtained. Routine monitoring of a WBC and differential is not recommended until further studies justify that it is indicated and cost-effective.

REMISSION RATES WITH THIOAMIDES

CASE 52-14

QUESTION 1: B.D., a 30-year-old female, has been maintained on MMI 5 mg daily for >2 years. Her MMI has been discontinued twice in the past, and each time her hyperthyroidism recurred. She refuses either surgery or RAI therapy. Although she is clinically euthyroid on MMI, her gland is larger than her usual size and has never decreased with therapy. Recent laboratory tests showed an FT_4 of 1 ng/dL (normal, 0.8–1.8) and a TSH level of 6.5 μIU/mL (normal, 0.40–4.5).

What is responsible for the enlarging gland? What subjective or objective data in B.D. would influence her remission rate and justify a longer course of ATD therapy? Would the addition of T_4 be helpful?

The high TSH level suggests that TSH stimulation caused by excessive suppression of hormone synthesis by MMI is contributing to the enlarging thyroid gland.[225] The easiest solution to this problem is to decrease the maintenance dose of MMI to 2.5 mg daily to normalize the TSH value and minimize gland stimulation.

Long-term remission rates achieved with the ATDs are disappointing. Remission rates within 6 years after discontinuing therapy average 50% (range, 14%–75%),[182,183,208,211,226] although relapse rates are as high as 80%. The rate of permanent remission is usually <25% if the follow-up period is long enough.[182,183,227] Why some patients remain in remission while others relapse once ATDs are discontinued is unclear, although patients who remain euthyroid for >10 to 15 years after discontinuing therapy probably do so because of disease progression to Hashimoto thyroiditis rather than as a direct result of treatment.[176] In other words, the natural course of Graves hyperthyroidism might be eventual hypothyroidism regardless of the treatment modality used. Several factors have a

limited role in predicting relapse and remission and have been used to guide therapy.

A longer duration of ATD treatment (see Case 52-13, Question 6) improves the remission rate by changing the basic underlying abnormality of Graves disease.[182,208,211,226] Numerous studies show that titers of antithyroid receptor (TSI) and antimicrosomal antibodies fall during ATD therapy but are unchanged during therapy with placebo or β-blockers.[182,183,208,228] Patients with low or undetectable TSI titers at the end of 12 to 24 months of ATD therapy had a 45% chance of remission compared to <10% chance of remission for those with higher titers within 1 to 5 years after completing therapy.[227–230] The best response was obtained in those with smaller goiters, less severe disease, and nonsmokers. A higher ATD dose did not improve the remission rate but resulted in more toxicity, including agranulocytosis, arthralgias, dermatitis, gastritis, and hepatotoxicity.[182,226,227]

Certain clinical features have been associated with a greater chance of disease remission and might help clinicians identify patients who deserve a longer ATD trial before changing to RAI or surgery. These clinical features include smaller goiter, mild symptoms of short duration, a reduction in goiter size during treatment, nonsmokers, absence of ophthalmopathy, and undetectable or low TSI levels.[183,227,228] Smokers should be advised to discontinue smoking to increase the chance of remission (see Chapter 91, Tobacco Use and Dependence).[231]

In a preliminary study, the addition of L-thyroxine to maintenance doses of ATDs for 1 year, followed by an additional year of L-thyroxine alone, significantly reduced the risk of relapse after stopping ATDs.[230] Those receiving the T_4–MMI combination experienced significant reductions in TSH receptor antibody titers compared to those taking MMI alone. At 3 years, the combination-treated patients had a lower rate of recurrence after stopping therapy (1.7%) than those receiving MMI alone (recurrence rate, 34.7%). Unfortunately, several prospective studies evaluating the addition of T_4 to ATDs have not validated these initial favorable

results.[227,229,232,233] Support for this therapeutic approach has waned, and the addition of T_4 to existing ATD therapy is not recommended.

B.D.'s large goiter reduces her chance of remission with longer therapy.[234] Although ATD therapy can be continued indefinitely if well-tolerated, surgery or RAI therapy should seriously be considered for B.D., who already has received MMI for >2 years. Alternative therapy is especially crucial if she plans to become pregnant within the next few years (see Case 52-15).

Hyperthyroidism in Pregnancy

CASE 52-15

Question 1: N.N., a 32-year-old female who is 3 months pregnant, is referred for management of her Graves disease.

What are the therapeutic ramifications of managing thyrotoxicosis during pregnancy?

Hyperthyroidism develops in ~0.2% of pregnant females and often precedes conception.[129] Symptoms of thyrotoxicosis are typically ameliorated during the second and third trimesters and exacerbated early in the postpartum period. Treatment is crucial to prevent damage to the fetus and to maintain the pregnancy. RAI, chronic iodide therapy, and iodine-containing compounds are contraindicated during pregnancy because they will cross the placenta to produce fetal goiter and athyreosis.[235–237] If rapid control of hyperthyroid symptoms is required, short-term use (<1–4 weeks) of propranolol is safe.[41,129,134] Iodide use in pregnancy should be limited to transient preoperative use prior to thyroidectomy or in the management of thyroid storm.[41,238]

Either surgery or ATD is the treatment of choice for pregnant patients who are hyperthyroid. Surgery is safe during the second trimester with adequate preoperative preparation. PTU is preferable during the first trimester (through week 16) because of rare reports of teratogenicity from MMI.[128,239] Females taking MMI should be

switched to PTU at a dose of 1:20 as soon as possible after confirmation of pregnancy.[128] Both ATDs are equally efficacious,[240] demonstrate similar placental crossing properties,[241] and produce similar thyroid hormone concentrations in fetal umbilical cord blood samples.[242] Methimazole has been associated with anecdotal reports of congenital scalp defects (eg, aplasia cutis) and an embryopathy syndrome (esophageal and choanal atresia).[243–246] However, the risks of reversible aplasia cutis were not greater in females receiving MMI (eg, 2.7%) compared to PTU (eg, 3%) or hyperthyroid controls (eg, 6%).[240,243,244] Therefore, MMI can be considered throughout pregnancy if there is intolerance or nonadherence to PTU[235,236,240] (see Chapter 49, Obstetric Drug Therapy).

Fetal hypothyroidism and goiter can develop when large doses of ATDs are administered to the mother, even if the mother is still hyperthyroid.[235,236] Therefore, to avoid goiter and suppression of the fetal thyroid gland, which begins to function at about 12 to 14 weeks of gestation, the lowest effective ATD dose should be given. Normal FT_4 levels occur in >90% of neonates when maternal FT_4 is maintained in the upper third of the normal range (1.5–1.9 ng/L).[41,238] Conversely, over 30% of neonates exhibit a low FT_4 when maternal levels are maintained in the lower two-thirds of the normal range.[41] Complete control of maternal hyperthyroidism increases the risk of fetal hypothyroidism. Current guidelines recommend maintaining the T_4/FT_4 at or just above the upper limit of the normal range and monitoring every four weeks.[128] Start PTU (eg, maximum of 300 mg/day in three divided doses) or MMI if after gestational week 16 (eg, maximum of 20–30 mg given once daily) until control is achieved, then taper to the lowest effective dose. Consideration can be given to changing PTU to MMI after the first trimester; however, there is risk of over/under-treating the condition and lack of evidence supporting the change.[128] In many patients, remission of Graves disease occurs during pregnancy and some patients can discontinue ATDs in the second half of pregnancy.[235] Measurement of TRAb levels between weeks 18 and 22 of gestation can be useful, because disappearance of TRAb is an indication that ATD therapy my no

longer be necessary. If TRAb remains elevated in the second trimester, it should be measured again near term, between weeks 30 and 34. Presence of sustained high TRAb concentrations (>5 IU/L or three times the upper limit of normal) indicate the need for neonatal monitoring. The neonate will clear the ATD faster than antibodies passed through the placenta, resulting in neonatal hyperthyroidism.[128]

Although transient fetal or neonatal hypothyroidism does not appear to be a major threat to the baby, it is advisable to maintain the mother in a mildly hyperthyroid state.[235,236] Mild maternal hyperthyroidism appears to be well-tolerated, but maternal hypothyroidism is poorly tolerated by both the mother and the fetus (see Case 52-8, Question 1). T_4 levels should be maintained at or just above the upper limit of the normal range to decrease the risk of fetal hypothyroidism.[128] The goal of therapy is a measurable, but suppressed maternal TSH level (0.1–0.4 μIU/mL) because complete correction of maternal hyperthyroidism increases the risk of fetal hypothyroidism.[33,133]

Both ATDs can be safely used in the lactating mother if the maximal dose of MMI does not exceed 10 to 20 mg daily or less preferably, if PTU does not exceed 200 mg/day (up to 750 mg/day in one report).[247,248] Iodides are secreted in breast milk, and transient SH may occur in breastfed infants; therefore, they should be used with caution in breast feeding females (see Chapter 49 Obstetric Drug Therapy).[249,250]

Treatment With Radioactive Iodine

PRETREATMENT

CASE 52-16

Question 1: B.J., a 35-year-old female, has newly diagnosed Graves disease complicated by HFrEF and angina. After a few days of treatment with MMI 30 mg daily and Lugol solution, 5 drops/day, B.J. received RAI therapy. Six months later, she is still symptomatic.

What is the influence of B.J.'s pretreatment therapy on the efficacy of her RAI therapy?

Older or debilitated patients with severe hyperthyroidism and/or concomitant cardiac disease should receive antithyroid pretreatment before RAI therapy to deplete stored thyroid hormone and minimize post-RAI hyperthyroidism (occurring in the first 10 days after ^{131}I administration) and thyroid storm caused by leakage of hormones from the damaged thyroid gland.[183,192,205] Other patients who are hyperthyroid can receive RAI safely without pre-therapy.

Lugol solution or other iodides should not be given before RAI because iodides decrease the gland's uptake of RAI and its effectiveness. This effect of iodides persists for several weeks. Iodides can be given after RAI treatment if needed to rapidly control symptoms of hyperthyroidism.[33,42]

Prior to RAI, ATDs achieve a euthyroid state, but pretreatment may lower the cure rate and increase the need for subsequent RAI.[183,196,251] A meta-analysis of 14 trials found that use of ATDs (PTU, MMI, carbimazole [not available in the United States]) before and after RAI was associated with an increased risk of treatment failure (relative risk of 1.28; 95% CI, 1.07–1.52) and a 32% reduced risk of hypothyroidism regardless of the ATD used.[196] To facilitate optimal uptake and retention of 131RAI by the gland, ATDs should be stopped at least 2 to 3 days, before RAI administration.[251–253] If necessary, ATDs can be restarted 3 to 7 days after RAI administration without impairing its efficacy. β-Adrenergic blocking agents can be used before, during, and after RAI therapy without interfering with its uptake.

B.J. remains symptomatic because MMI and iodides decreased RAI's efficacy. Propranolol should be given to B.J. before RAI therapy to relieve hyperthyroid symptoms because only a short course of ATD was given. Iodides might be preferable to propranolol following RAI therapy if B.J.'s HFrEF worsens. For subsequent RAI doses, MMI pretreatment should be stopped 2 to 3 days before RAI, thereby allowing a shorter duration of hyperthyroidism.

ONSET OF EFFECTS

CASE 52-16, QUESTION 2: B.J. still is symptomatic 2 weeks after a second dose of RAI. When can she expect to experience the therapeutic effects of RAI therapy? What educational precautions about radiation safety should B.J. receive?

Although some benefits from RAI therapy are evident within 1 month, a period of 6 to 18 weeks is generally required for maximal effects.[176,196,205] Euthyroidism or, more commonly, hypothyroidism occurs in ~85% to 95% of patients treated with a single nonablative dose of RAI; the remaining 5% to 15% become euthyroid or hypothyroid after two or more doses.[42] This slow onset is a disadvantage, but symptomatic control can be obtained quickly by administration of a β-adrenergic blocking agent or iodides starting 1 to 14 days after the ^{131}I dose. Iodides are less preferable if a second dose of RAI is necessary. Antithyroid drugs can also be given, although their therapeutic effects are delayed for 3 to 4 weeks.

Most patients become hypothyroid 2 to 3 months after receiving RAI; however, some require longer. For this reason, at least 6 months should elapse before a second dose of RAI is administered, unless the patient remains severely thyrotoxic.[33,42] It is inadvisable to give a second dose before the major effects of the first dose have become apparent. Although the use of iodides before RAI in B.J. may have decreased the amount of ^{131}I retained by her thyroid, it still is advisable to wait at least 6 months before a second dose is given.

Safety precautions to reduce radiation exposure to family members and members of the public are not universal and vary across the United States depending on the dose of RAI administered.[196] B.J. should avoid close contact (eg, 6 feet) with children for 5 days, with pregnant females for 10 days, and intimate contact with body fluids for 5 days. B.J. should avoid airplane travels, public transportation, and work if contact with others during these activities last more than 2 hours. Other recommendations include sole use of bathroom facilities; sitting while urinating to avoid splashing, and to flush the toilet twice with the lid down.[196,254]

IATROGENIC HYPOTHYROIDISM

CASE 52-17

QUESTION 1: S.D., a 54-year-old female, returns to the thyroid clinic after being lost to follow-up for 6 months. She initially received RAI 3 years ago but required a repeat dose of RAI one year ago. She has no other medical problems and is not taking any medications. She is a mildly obese, puffy-faced female wearing several layers of clothing who reports of fatigue and lack of energy. Her reflexes are delayed, and her skin is cool and dry.

What is a likely explanation for her symptoms?

S.D.'s clinical presentation and history are compatible with hypothyroidism secondary to RAI therapy. An FT_4 and a TSH level would confirm this diagnosis. Iatrogenic hypothyroidism is the major complication of RAI therapy, although transient hypothyroidism can occur in the first 3 to 6 weeks after therapy.[176] The incidence of iatrogenic myxedema is often reported as 7% to 8%, but it increases at a constant rate of 2.5% per year. The reported prevalence of this complication ranges from 26% to 70% after 1 to 14 years.[205]

The best predictor of eventual hypothyroidism is the total dose of RAI administered. Prevention of iatrogenic hypothyroidism is directed toward calculation of a dose that will produce neither recurrent hyperthyroidism nor hypothyroidism. Unfortunately, when lower doses of RAI were used to avoid hypothyroidism, the cure rate was reduced but the incidence of hypothyroidism was unaffected.[255] Thus, the appearance of iatrogenic hypothyroidism may be inevitable with time. However, hypothyroidism is managed easily and is an acceptable therapeutic end point. Because hypothyroidism after RAI therapy is latent and often insidious, patients should be informed of this and monitored closely at monthly intervals for subsequent hypothyroidism. Awareness of a transient hypothyroidism soon after RAI therapy should minimize the institution of unnecessary hormone replacement.

Ophthalmopathy

CLINICAL PRESENTATION

CASE 52-18

QUESTION 1: H.R., a 50-year-old male, first developed "large eyes with stare," weakness, diaphoresis, and thyroid enlargement when he was diagnosed with Graves disease. RAI therapy caused some worsening of his eye symptoms. Although he is clinically euthyroid, physical examination reveals severe bilateral conjunctival edema and injection, proptosis of the right eye, incomplete lid closure, and decreased visual acuity. He reports of photophobia, tearing, and extreme irritation, which is worse after smoking cigarettes. His other medical problems include type 2 diabetes treated with metformin and pioglitazone.

What is the association of H.R.'s ocular changes with Graves disease?

H.R. presents with symptoms consistent with the infiltrative ophthalmopathy of Graves disease.[256–258] The eye signs of Graves disease are the most striking abnormality of this disorder. Rarely, ophthalmopathy can occur without any evidence of hyperthyroidism. Fortunately, severe ophthalmopathy occurs in only 3% to 5% of patients, whereas 25% to 50% have some eye findings. Eye disease is more severe in older patients and in males than females. Smokers often have higher levels of TSI and more severe ophthalmopathy.[231,257,259]

It is unknown why the eye and its muscles are attacked in Graves disease but is likely related to the presence of TSH receptor antibodies along with other immunoglobulins that activate both thyrotropin and insulin-like growth factor 1 (IGF-1) receptors on orbital fibroblasts.[258,260,261] Histologic examination reveals lymphocytic infiltration, increased mucopolysaccharides, fat (because of increased adipogenesis and glycosaminoglycans), and water in all retrobulbar tissue. Ocular symptoms include edema, chemosis, excessive lacrimation, photophobia, corneal protrusion (proptosis), scarring, ulceration, extraocular muscle paralysis with loss of eye movements, and blindness from retinal and optic nerve damage.[177]

The eye involvement can occur at any time and is usually bilateral. The ocular symptoms usually subside or remain stable once the

patient is euthyroid; however, some cases will progress if patients become hypothyroid and are left untreated following RAI treatment (see Question 2).[215] Pioglitazone has been associated with a 1- to 2-mm increase in eye protrusion by stimulating adipogenesis and increasing retrobulbar fat production.[262] Although eye changes were more common in people with a history of thyroid disorders, the overall incidence of eye changes associated with pioglitazone is unknown.[262]

MANAGEMENT OF EYE SYMPTOMS

CASE 52-18, QUESTION 2: Was previous treatment of H.R.'s hyperthyroidism appropriate? How should his current ocular symptoms be managed?

The optimal treatment of hyperthyroidism and its effect on the course of ophthalmopathy remain controversial.[256,257,263] ATDs might improve eye symptoms through an immunosuppressive mechanism of action and control of the hyperthyroidism or exert a neutral effect.[256] Many clinicians believe that RAI ablation or surgical removal is preferable because it removes the antigen source and prevents progression of the ophthalmopathy.[187,256] However, several studies have confirmed development or worsening of eye symptoms immediately after RAI therapy.[259,263] Concomitant use of 0.4 to 0.5 mg/kg of prednisone begun 1 to 3 days post-RAI continued for 1 month and tapered over 2 months may be used in patients with mild active eye disease to prevent progression of eye symptoms.[33,259] Lower-dose, shorter-duration prednisone therapy (0.2 mg/kg/day for 6 weeks) may be as effective as conventionally used doses.[264] Patients with active moderate-to-severe or sight threatening ophthalmopathy at the time of treatment should be treated with surgery or ATDs instead of RAI.[33,215] Regardless of the treatment used, control of the hyperthyroidism often improves most eye findings, except for proptosis.

In H.R., prednisone 40 to 60 mg/day should have been started after his RAI treatment and continued for 2 to 3 months until the eye

symptoms improved. Because the pathophysiology of the ophthalmopathy is unclear, treatment is limited to symptomatic and empiric measures once the patient is euthyroid.[256,257] H.R. should also be encouraged to stop smoking to prevent progression of the ophthalmopathy.[231] His pioglitazone should be discontinued, in case this is contributing to his ophthalmopathy. Although it is too late for steroids to mitigate RAI-induced worsening of ophthalmopathy, there is evidence that corticosteroids reduce orbital inflammation and congestion and are useful in the management of the disease.[177,265] H.R. could be considered for a course of corticosteroids; however, this must be weighed against the potential for worsening his glycemic control (see Chapter 53, Diabetes Mellitus).

Because periorbital edema and chemosis are worse in the morning after being in the horizontal position, elevating the head of the bed, diuretics, and restricting salt intake may be helpful. Protective glasses can relieve photophobia and external irritation. Topical corticosteroid drops are effective in decreasing local irritation, but they should be used cautiously because they increase the risk of infection. Ocular irritants such as smoke and dust should be avoided. Bothersome symptoms (eg, dry eye, redness, tearing) caused by eyelid retraction can be relieved by artificial tears and lubricants.[256] Incomplete lid closure predisposes to corneal scarring and ulceration, so lubricant eye drops should be applied several times daily and at night to keep the bulbs moist. Taping the eyelids shut at night prevents drying and scarring. Lateral surgical closure of the lids (tarsorrhaphy) may be required to improve lid closure.[177]

With severe and progressive ophthalmopathy, an aggressive approach is necessary. Systemic corticosteroids can produce either dramatic or marginal results in the emergency treatment of progressive exophthalmos associated with decreasing visual acuity. Prednisone at dosages of 35 to 80 mg/day is often effective, although dosages as high as 100 to 140 mg/day may be necessary.[256,257] Pain, irritation, tearing, and other subjective symptoms often respond within 24 hours of administration. Therapy for about 3 months is necessary to improve eye muscle and optic nerve function disturbances. Initial large doses should be tapered

rapidly once the desired response is obtained to minimize adverse effects. Subconjunctival and retrobulbar injections of steroids are not as effective.

Orbital x-ray therapy also relieves congestive and inflammatory symptoms.[256] The combination of orbital irradiation and systemic steroids may be required to achieve maximal benefits. Plasmapheresis and immunosuppressive agents, such as cyclophosphamide, azathioprine, cyclosporine, and methotrexate, combined with steroids have also been used with limited success. Similarly, the plasma B cell–depleting agent rituximab has resulted in improvement in eye disease.[266] Clinical trials with an IGF-I receptor inhibitor, teprotumumab, administered every 3 weeks for 21 weeks resulted in significant improvement in the clinical activity score used to assess severity of ophthalmopathy as well as the degree of proptosis.[261,267] Future investigations are focusing on anti-TNF and anti-interleukin receptor antibodies agents that may neutralize some of the inflammatory reactions in the eye.[256,258]

When the previous measures and thyroid ablation fail to arrest the progression of visual loss and exophthalmos, then surgical orbital decompression should be considered.[176]

Thyroid Storm

CLINICAL PRESENTATION

CASE 52-19

Question 1: H.L., a 48-year-old female, is admitted to the hospital with a 3-week history of fatigue, weakness, dyspnea on exertion, SOB, palpitations, and inability to keep food and liquids down. One year before admission, she began noticing a preference for cold weather and an increase in nervousness and emotional lability. After her husband died a few days ago, she experienced increased nausea and vomiting, irritability, insomnia, tremor, and a 104 °F (40 °C) fever, which she attributed to an upper respiratory tract infection. She denies taking any current medications. Her laboratory data obtained on admission included an FT_4 of 4.65 ng/dL (normal, 0.8–1.8) and an undetectable TSH level.

What is your assessment of H.L.'s subjective and objective data?

The presentation is consistent with thyroid storm, a life-threatening medical emergency that might have been precipitated by the stress associated with the death of her husband. The clinical manifestations of thyroid storm[192] include the acute onset of high fever, tachycardia, and tachypnea, and involvement of the following organ systems: cardiovascular (tachycardia, pulmonary edema, hypertension, shock), CNS (tremor, emotional lability, confusion, psychosis, apathy, stupor, coma), and GI (diarrhea, abdominal pain, nausea and vomiting, liver enlargement, jaundice, nonspecific elevations of bilirubin and prothrombin time).

Thyroid storm develops in about 2% to 8% of patients who are hyperthyroid. The pathogenesis of thyroid storm is not well understood, but the condition can be described as an "exaggerated" or decompensated form of thyrotoxicosis. The term *decompensated* implies failure of body systems to adequately resist the effects of thyrotoxicosis. It is not attributed solely to the release of massive quantities of hormones, which can occur after surgery or RAI therapy. Catecholamines also play an important role; the increased quantities of thyroid hormone in conjunction with increased sympathetic and adrenal output contribute to many of the manifestations of thyroid storm. Although thyroid hormones exert an independent effect, many of the symptoms of hyperthyroidism are ameliorated by catecholamine-blocking agents such as β-blockers and calcium channel blockers (eg, diltiazem, verapamil).[180,268]

TREATMENT

Case 52-19, Question 2: What treatment plan (including route of administration) should be initiated promptly in H.L.?

Intensive, continuous, and immediate treatment can significantly reduce the mortality of thyroid storm. Mortality rates in thyroid storm are high, ranging between 20% and 30%.[192] Treatment of thyroid

storm should be directed against four major areas discussed in the following sections.[192]

Decrease in synthesis and release of hormones

High dosages of ATDs, preferably PTU 500 to 1000 mg/day or MMI 60 to 80 mg/day, should be given orally in four divided doses. If H.L. cannot take oral doses, a rectal formulation of PTU (better bioavailability with enema than suppository) or MMI, which is as effective as the oral route, can be administered.[33,184] No commercial parenteral preparation is available for either drug, limiting their use by the IV route. PTU is the ATD of choice because it acts more rapidly than MMI by blocking the peripheral conversion of T_4 to T_3, a dominant source of the hormone.[180]

Iodides, which rapidly block further release of intraglandular stores of T_4, should be given at least 1 hour after ATD administration. Given in this way, the substrate for hormone synthesis is not increased, and the therapeutic effect of ATD is not blocked. The addition of iodides (eg, Lugol solution 15–30 drops/day orally in divided doses) to the ATDs ameliorates symptoms rapidly and may restore T_4 concentrations to near-normal levels in 4 to 5 days.[180,215]

Lithium interferes with production of T_3 and T_4 and may decrease release of thyroid hormones from the thyroid gland and can be used in doses of 300 mg every 6 to 8 hours in patients where iodine administration is not possible.[180] Lithium is a narrow therapeutic index drug, and its use must be weighed against the risk of toxicity in a patient who is already critically ill. Cholestyramine 4 g orally (PO) qid may assist in lowering hormone levels by interfering with enterohepatic recirculation of thyroid hormones, but should be administered apart from other agents to prevent inhibiting their absorption.[180,269] Other effective modalities include plasmapheresis, charcoal hemoperfusion, and plasma exchange.[180,192]

Reversal of the peripheral effects of hormones and catecholamines

β-Adrenergic blocking drugs are the preferred agents to decrease the tachycardia, agitation, tremulousness, and other symptoms of excessive adrenergic stimulation seen in thyroid storm. Propranolol is the β-blocker of choice because its clinical efficacy in storm is well documented and it inhibits the peripheral conversion of T_4 to T_3.[192,193] If rapid effects are necessary, propranolol 1 mg by slow IV push can be given every 5 minutes to lower the heart rate to ~90 beats/minute. A 5- to 10-mg/hour IV infusion can maintain the desired heart rate. IV esmolol 50 to 100 µg/kg/minute can also be given. If perfusion is maintained, oral β-blockers (eg, propranolol, 40 mg every 6 hours; atenolol, 50–100 mg bid; metoprolol, 50–100 mg daily; nadolol, 40–80 mg daily), titrated to response, can also be given.[180,215]

Supportive treatment of vital functions

This may include sedation, oxygen, IV glucose, vitamins, treatment of infections with antibiotics, rehydration, and treatment of hyperpyrexia with cooling blankets, sponge baths, and the judicious use of antipyretics.[180,192] Because hypoadrenalism is often suspected, hydrocortisone should be given empirically IV with a 300-mg loading dose followed by 100 mg every 8 hours.[33] Because pharmacologic doses of steroids offer a beneficial effect in storm by acutely depressing serum T_3 levels and inhibiting conversion of T_4 to T_3, their routine use is recommended.[180,215]

Elimination of precipitating causes of storm

Precipitating causes of thyroid storm include infection (most common), trauma, inadequate preparation before thyroidectomy, surgical operations, stress, diabetic ketoacidosis, pregnancy, emboli, discontinuation or withdrawal of antithyroid medications, drug therapy, and RAI therapy.[192]

T_3 Thyrotoxicosis: Clinical Presentation

CASE 52-20

QUESTION 1: S.K., a 48-year-old female, is admitted to the hospital for a possible MI. Her symptoms include chest pain that is unrelieved by NTG, increasing SOB with exercise, nervousness, palpitations, muscle weakness, weight loss despite an increased appetite, and epistaxis; she also bruises easily. She has a history of deep venous thrombosis treated with warfarin 5 mg/day; her last INR was 2.8 (normal, 1; therapeutic, 2–3). She has angina, treated with NTG 0.4 mg, and HF, treated with lisinopril 20 mg/day.

Pertinent physical findings include a BP of 180/90 mm Hg, a pulse of 110 beats/minute, hyperreflexia, lid lag, and a diffusely enlarged thyroid gland that is about four times normal (about 100 g).

Laboratory data include the following results:

TT_4, 6 µg/dL (normal, 4.8–10.4)
FT_4, 2 ng/dL (normal, 0.8–1.8)
TSH, <0.01 µIU/mL (normal, 0.40–4.5)
TPOAb, 35 IU/mL (normal, <9)
TRAb, 3.2 IU/L (normal, <2)
Alkaline phosphatase, 200 units/L
Total bilirubin, 1.1 mg/dL
An RAI scan shows a diffusely enlarged gland, three to four times the normal size.

What subjective and objective data are suggestive of hyperthyroidism in S.K.?

S.K.'s laboratory findings of positive TRAb and TPOAb with elevated thyroid hormone levels verify an autoimmune hyperthyroid state. However, the serum FT_4 is elevated only slightly and is disproportionately low relative to the severity of her symptoms, the undetectable TSH level, and her other laboratory findings. The low-normal TT_4 could be explained by displacement of T_4 from TBG by aspirin (see Case 52-2). The possibility of a variant type of hyperthyroidism known as T_3 toxicosis should be considered. The clinical features include signs and symptoms of thyrotoxicosis, normal or borderline high FT_4, an undetectable TSH level, and elevated T_3 levels. The latter occurs through preferential secretion and peripheral conversion of T_4 to T_3. A T_3 level should be obtained to establish the diagnosis.[270]

Asymptomatic elevations of T_3 levels often precede elevation of T_4 levels and the development of overt hyperthyroidism. T_3 toxicosis probably represents an early stage of classic T_4 toxicosis and is useful for early diagnosis or as an early indicator of relapse after discontinuation of ATD therapy.

Together with S.K.'s symptoms, laboratory results support a diagnosis of Graves disease. Her cardiac status and other medical problems are aggravated by the hyperthyroidism.

Effects on Clotting and Warfarin Metabolism

Case 52-20, Question 2: What factors contribute to S.K.'s hypoprothrombinemia? What effect could this have on her subsequent drug treatment?

The easy bruising and bleeding observed in S.K. are most likely related to an exaggerated response to warfarin. This may be related to a decrease in the hepatic metabolism of warfarin (secondary to hepatic congestion), but it is more likely that S.K.'s findings are because of the combined effects of hyperthyroidism and warfarin on vitamin K–dependent clotting factors.

Warfarin metabolism and the metabolism of vitamin K–dependent clotting factors can be altered by thyroid status.[14] Net circulating levels of vitamin K–dependent clotting factors are generally not altered in patients who are hyperthyroid because both the synthesis and catabolism of these clotting factors are increased. However, an enhanced anticoagulant response occurs when the warfarin-induced decrease in clotting factor synthesis is combined with the hyperthyroidism-induced increase in clotting factor catabolism.[14,271] This may explain S.K.'s elevated INR, bruising, and history of epistaxis.

The opposite occurs in hypothyroidism, in which a decrease in both the metabolism and synthesis of clotting factors occurs. In patients who are hypothyroid, the response to oral anticoagulants is

delayed because the clotting factors are eliminated more slowly.[14,271] Therefore, patients who are hyperthyroid need less warfarin, whereas patients who are hypothyroid require more warfarin to achieve the same anticoagulant response. The anticoagulant response to warfarin should be monitored carefully in patients with thyroid abnormalities, and the dosage adjusted as the thyroid status changes.

Subclinical Hyperthyroidism

CASE 52-21

Question 1: J.C. is a 68-year-old male who is found to have a TSH level of 0.15 μIU/mL (normal, 0.40–4.5) with normal FT_4 and FT_3 hormone levels on routine blood tests. He is otherwise healthy and denies any symptoms of thyroid dysfunction. On physical examination, his thyroid gland is normal. He denies any family history of thyroid disease and is taking no medications.

How should these tests be interpreted? How should J.C. be managed?

J.C.'s laboratory findings of a suppressed TSH value below the limits of normal and normal free thyroid hormone levels are consistent with subclinical hyperthyroidism (SHyper)[94–96] Other unlikely causes of a suppressed TSH in J.C. include medications (eg, metformin, bexarotene, glucocorticoids) (Table 52-1), pituitary hypothyroidism, and nonthyroidal illness (see Case 52-1, Questions 1 and 2).[12,74] Because of age-dependent decline in TSH secretion, a low TSH may also be a normal finding in healthy elderly patients.[272]

The dangers of SHyper are similar to those of overt hyperthyroidism and include cardiac findings (eg, atrial and ventricular premature beats, AF, left ventricular hypertrophy, diastolic dysfunction), loss of bone mass, higher fracture rates, especially in postmenopausal females, and if present, subtle symptoms of hyperthyroidism.[92–96] In elderly patients, hyperthyroid symptoms, even if overtly hyperthyroid, may be "apathetic" unapparent because of impaired sympathetic nervous system responsiveness.[272] A significant relationship between AF and degree of SHyper is clear,

whereas an association with increased atherosclerotic heart disease or mortality is weak.[168] The relative risk of AF in SHyper may be as high as 5.2 and increased by older age, male gender, higher FT_4 levels, and degree of TSH suppression. In two cohorts followed for 10 to 13 years, the relative risk of AF ranged from 1.6 to 3.1, depending on the degree of TSH suppression.[168,273] The likelihood a patient with endogenous SHyper will progress to overt hyperthyroidism is not clear. Patients may spontaneously revert to euthyroidism, progress to hyperthyroidism, or continue with SHyper. Individuals with undetectable TSH concentrations appear most likely to progress, and overall the rate of progression to overt disease is 1% to 5% annually.[95] A study of 2024 patients with 7-year follow-up of SHyper importantly found 36% reverted back to normal within 7 years, especially those with TSH levels between 0.1 and 0.4 μIU/mL.[274]

The management of subclinical hyperthyroidism is controversial, especially in asymptomatic patients because of limited treatment outcomes evidence.[94–96] Current guidelines recommend treatment of subclinical hyperthyroidism (TSH levels <0.1 μIU/mL) in patients older than 65 years, postmenopausal female not taking antiresorptive therapy (see Chapter 110, Osteoporosis), and those with cardiac disease and osteoporosis.[33,94,95] For patients with TSH levels of 0.1 to 0.45 μIU/mL, treatment of patients older than 65 years and those with cardiovascular disease or hyperthyroid symptoms can be considered.[33,215] A 2010 review recommends RAI or ATD therapy only if the TSH level is <0.1 μIU/mL in postmenopausal females, in those age 60 years and older, and in patients with a history of heart disease, osteoporosis, or hyperthyroid symptoms.[96] For patients with TSH levels of 0.1 to 0.4 μIU/mL, treatment can be considered if they are in the aforementioned groups; otherwise, therapy is not recommended because TSH normalization may occur.[95,215]

In J.C., his thyroid function tests should be repeated. An RAIU and scan should be obtained to detect any hyperactive areas or nodules that might be responsible for the suppressed TSH. Because J.C. is

generally healthy, treatment can be considered if there are concerns about cardiac disease or bone loss; otherwise, no therapy is also reasonable based on the available evidence. Close monitoring of thyroid function tests is recommended every 6 months to a year. If hyperthyroid symptoms or changes in cardiac or bone function occur, then RAI therapy is recommended.

DRUG-INDUCED THYROID DISEASE

Lithium

CASE 52-22

QUESTION 1: D.A., a 56-year-old male, reports of sluggishness, cold intolerance, fatigue, and a "rundown" feeling, which doctors attribute to the depressive phase of his bipolar affective illness. He previously had been well controlled with sertraline 100 mg/day, but lithium carbonate 900 mg/day was added 4 months ago because of unreasonable mirthfulness and uncontrollable gift-buying tendencies. Physical examination reveals a puffy face and a large goiter.

What is a reasonable assessment of these subjective and objective data?

Thyroid function tests (ie, TSH, FT_4) and a thyroid ultrasound should be obtained to evaluate the possibility of lithium- and possibly sertraline-induced hypothyroidism and goiter.[6,7,15,275] If the TSH is elevated, T_4 should be initiated and lithium continued if necessary. Although the incidence of goiter and hypothyroidism in the manic-depressive population is unknown, the 10% incidence of baseline elevated TSH appears higher than in the general population.

The exact mechanism of lithium's antithyroid effect on the gland is unclear, although it is highly concentrated by the gland. Like the iodides, chronic lithium therapy inhibits the release of thyroid hormone from the gland. The fall in serum T_4 and T_3 hormone levels

leads to a compensatory and transient increase in serum TSH levels until a new steady state is achieved.[6,7,15]

Elevated TSH levels are reported in ~19% of patients on chronic lithium therapy.[15] Typically, the serum thyroid hormone levels decrease and the TSH levels increase during the first few months of treatment, returning to pretreatment levels after 1 year.[15] Normalization of the TSH level is less likely to occur in patients with preexisting positive thyroid antibodies before lithium therapy.[6,15] Induction of thyroid antibodies and increases in baseline antibody titers also occur after chronic lithium therapy. Because abnormal thyroid function tests can be transient, a longer period of observation is justified before starting thyroid therapy in patients with SH.

Overt hypothyroidism appears in a small percentage of the population after 5 months to 2 years of therapy; one 15-year study found an incidence of 1.5% but an 8.4 relative risk in females with antibody positivity compared to negative subjects.[6,7,15] Lithium-induced goiter with or without hypothyroidism is common after weeks to months of therapy. Although incidences of <6% have been reported, higher rates of 40% to 60% are observed if the goiter is diagnosed using more specific imaging techniques (eg, ultrasound).[6,7,15] A direct goitrogenic effect of lithium on inducing cell proliferation might explain the occurrence of euthyroid goiter. The goiters respond to discontinuation of lithium or to suppression with thyroid hormone despite continuation of lithium therapy.[7,15] Surgical removal of the goiter is required if there are local obstructive symptoms. In D.A.'s case, sertraline could be exerting an additive or synergistic antithyroid effect with lithium because antithyroid effects have also been associated with this drug.[275]

Most patients with lithium-induced thyroid abnormalities are females older than 50 years, have a prior history of compromised thyroid function (eg, Hashimoto thyroiditis), positive thyroid antibodies before lithium therapy, or a strong family history of thyroid disease.[6,7,15] Therefore, baseline thyroid function tests (ie, FT_4, TSH), antibodies, and thyroid ultrasound should be obtained before starting lithium therapy, and levels should be checked annually thereafter or

more frequently if clinically indicated. Patients should also be questioned about a positive history or family history for thyroid disease and the concurrent use of other, potentially goitrogenic medications (eg, tricyclic antidepressants, iodides, iodinated expectorants/herbals).

Iodides and Amiodarone

CASE 52-23

QUESTION 1: C.Y., a 54-year-old male with chronic AF presents with a 6-month history of weakness, fatigue, tremor, heat intolerance, and increased palpitations, previously controlled for the last 2 years on amiodarone 200 mg/day. Physical examination reveals a 50-g multinodular gland, which C.Y. says has "been there forever." He denies any family history of thyroid disease or ingestion of any thyroid medication. His current symptoms began after a magnetic resonance imaging (MRI) procedure with iodinated radiocontrast media.

What might be responsible for C.Y.'s hyperthyroid symptoms?

The iodine load from the MRI or the amiodarone could be responsible for C.Y.'s hyperthyroid symptoms.[33,179,276] Iodine-induced hyperthyroidism, or Jod-Basedow phenomenon, was first described in the 1800s when patients residing in iodide-deficient areas became toxic when given adequate iodide supplementation.[277] Both T_3 toxicosis and classic T_4 toxicosis have been reported following iodide ingestion or injection of iodinated contrast media.[277]

Although it is presumed that both iodide deficiency and a multinodular goiter, as in C.Y., are required to invoke the Jod-Basedow phenomenon, iodine-induced disease has been reported in patients residing in iodide-sufficient areas as well as in patients who are euthyroid with normal glands and no apparent risk factors (eg, family history).[37,179] Iodine-induced hyperthyroidism is rare in iodine-sufficient populations and generally subclinical and self-limiting when it does occur.[33] In the event iodine-induced hyperthyroidism persists, it can be managed with ATDs.[215]

Amiodarone can cause hypo- or hyperthyroidism in susceptible patients because of its high iodine content.[33,179,276] Patients beginning therapy with amiodarone should have thyroid testing before treatment is begun, within the first three months, and then at 3- to 6-month intervals thereafter.[33] Twelve milligrams (37%) of free iodine is released per 400-mg dose of amiodarone. Patients with multinodular goiters who lose the ability to turn off iodide organification from increased iodide loads (Wolff–Chaikoff effect) are most likely to develop iodide-induced thyrotoxicosis. Conversely, patients with positive antibodies or with underlying Hashimoto thyroiditis who cannot escape from the Wolff–Chaikoff block are most likely to develop hypothyroidism.[5]

Amiodarone-induced hypothyroidism may occur at any time during therapy and does not appear to be related to the cumulative dose. A low-normal or low FT_4 and a persistently elevated TSH (see Case 52-4) are consistent with amiodarone-induced hypothyroidism, which occurs in up to 14% of long-term users.[278] The hypothyroidism responds readily to T_4 therapy, even if the amiodarone is continued.[5,19,276] Amiodarone-induced hypothyroidism typically resolves after stopping the drug but resolution may be delayed because of its long half-life.[5,276]

In contrast, amiodarone-induced thyrotoxicosis, which occurs in up to 6% of long-term users in iodine-sufficient areas (with a higher prevalence in areas of iodine deficiency).[33] Elevated hormone levels, an undetectable TSH level, and clinical symptoms consistent with hyperthyroidism are the best indicators of amiodarone-induced thyrotoxicosis.

Amiodarone-induced hyperthyroidism can be classified as either type I or type II.[33,276] Type I occurs in patients with underlying thyroid disease (eg, multinodular goiter, Graves disease, autonomous nodules) and is related to the iodine load. The formation of large amounts of preformed hormone from the massive iodine load produces a protracted course of hyperthyroidism, which is challenging to manage. Type II amiodarone-induced hyperthyroidism is because of an inflammatory destructive thyroiditis, with excessive

release of thyroid hormone into the systemic circulation.[33] This occurs most often in patients with normal thyroid glands. Unique laboratory findings include a low RAIU and elevated interleukin-6 levels.[5,276]

The management of amiodarone-induced thyrotoxicosis is complicated because it is not always possible to identify the type of hyperthyroidism and a mixture of the two types can occur. Stopping amiodarone alone does not immediately improve the hyperthyroidism because of the drug's long half-life (22–55 days) and its sequestration in fat. RAI ablation is rarely effective because the high iodine load from amiodarone will suppress RAI uptake.[276] Methimazole is the treatment of choice for type I hyperthyroidism.[5,14,179,276] In patients with type II hyperthyroidism, corticosteroids are the most appropriate choice.[33] In the case of hemodynamic instability or poor clinical improvement, ATD therapy can be added to corticosteroid therapy.[33] A total thyroidectomy can rapidly control the thyrotoxicosis, permitting continued therapy with amiodarone if necessary; however, in a case series of 34 patients there was a 9% mortality rate with an overall complication rate of 29%.[279] Changing amiodarone to dronedarone, which is devoid of iodine and lacks the undesirable thyroid effects, should be strongly considered in C.Y.[276]

Large doses of iodides should be avoided in patients with nontoxic multinodular goiters who are predisposed to thyrotoxicosis (see Case 52-4 and Case 52-13, Question 2).

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid.* 2017;27(*3*):315–389. doi:10.1089/thy.2016.0457 (128)

Bach-Huynh TG, Nayak B, Loh J, Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. *J Clin Endocrinol Metab*. 2009;94:3905–3912. doi:10.1210/jc.2009-0860 (100)

Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ.* 2019;365: l2006. (172)

Burch HB, Cooper DS. Management of Graves disease: a review. *JAMA.* 2015;314(*23*):2544–2554. doi:10.1001/jama.2015.16535 (42)

Cohen-Lehman J, Dahl P, Danzi S, Klein I. Effects of amiodarone therapy on thyroid function. *Nat Rev Endocrinol*. 2010;6:34–41. (276)

Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19(*11*):1167–1214. doi:10.1089/thy.2009.0110 (44)

Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract.* 2012;18(*6*):988–1028. doi:10.4158/EP12280.GL (28)

Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. *Best Pract Res Clin Endocrinol Metab*. 2009;23:793–800. (73)

Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. *Thyroid.* 2014;24(*12*):1670–1751. doi:10.1089/thy.2014.0028 (32)

Ross DS. Radioiodine therapy for hyperthyroidism. *N Engl J Med*. 2011;364: 542–550. (196)

Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid.* 2016;26(*10*):1343–1421. doi:10.1089/thy.2016.0229 (33)

Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid.* 2011;21(*10*):1081–1125. doi:10.1089/thy.2011.0087 (38)

Key Websites

American Thyroid Association. ATA patient information (includes patient education brochures, frequently asked questions, and patient resources). http://www.thyroid.org/thyroid-information/

American Thyroid Association. The professional community (includes updated clinical practice guidelines, online education center, and laboratory information). http://www.thyroid.org/professionals/

Graves' Disease & Thyroid Foundation. http://www.gdatf.org/

COMPLETE REFERENCES CHAPTER 52 THYROID DISORDERS

1. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87(2):489–499. doi:10.1210/jcem.87.2.8182
2. Colucci P, Yue CS, Ducharme M, Benvenga S. A review of the pharmacokinetics of levothyroxine for the treatment of hypothyroidism. *Eur Endocrinol*. 2013;9(1):40–47. doi:10.17925/EE.2013.09.01.40
3. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med*. 2001;344:1743–1749.
4. Marqusee E, Braverman LE, Lawrence JE, Carroll JS, Seely EW. The effect of droloxifene and estrogen on thyroid function in postmenopausal women. *J Clin Endocrinol Metab*. 2000;85:4407–4410.
5. Basaria S, Cooper DS. Amiodarone and the thyroid. *Am J Med*. 2005;118:706–714.
6. Bocchetta A, Cocco F, Velluzzi F, et al. Fifteen-year follow-up of thyroid function in lithium patients. *J Endocrinol Invest*. 2007;30:363–366.
7. Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. *Clin Pract Epidemiol Ment Health*. 2006;2:23.
8. Carella C, Mazziotti G, Morisco F, et al. Long-term outcome of interferon-alpha-induced thyroid autoimmunity and prognostic influence of thyroid autoantibody pattern at the end of treatment. *J Clin Endocrinol Metab*. 2001;86:1925–1929.
9. Dalgard O, Bjøro K, Hellum K, et al. Thyroid dysfunction during treatment of chronic hepatitis C with interferon alpha: no association with either interferon dosage or efficacy of therapy. *J Intern Med*. 2002;251:400–406.
10. de Groot JWB, Zonnenberg BA, Plukker JTM, van Der Graaf WTA, Links TP. Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin Pharmacol Ther*. 2005;78:433–438.

11. Desai J, Yassa L, Marqusee E, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med*. 2006;145:660–664.
12. Golden WM, Weber KB, Hernandez TL, Sherman SI, Woodmansee WW, Haugen BR. Single-dose rexinoid rapidly and specifically suppresses serum thyrotropin in normal subject. *J Clin Endocrinol Metab*. 2007;92:124–130.
13. Krouse RS, Royal RE, Heywood G, et al. Thyroid dysfunction in 281 patients with metastatic melanoma or renal carcinoma treated with interleukin-2 alone. *J Immunother Emphasis Tumor Immunol*. 1995;18:272–278.
14. Kurnik D, Loebstein R, Farfel Z, Ezra D, Halkin H, Olchovsky D. Complex drug–drug–disease interactions between amiodarone, warfarin, and the thyroid gland. *Medicine*. 2004;83:107–113.
15. Lazarus JH. Lithium and thyroid. *Best Pract Res Clin Endocrinol Metab*. 2009;23:723–733.
16. Lodish MB, Stratakis CA. Endocrine side effects of broad-acting kinase inhibitors. *Endocr Relat Cancer*. 2010;17(3):R233–R244. doi:10.1677/ERC-10-0082
17. Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. *Hepatology*. 2006;43:661–672.
18. Markou K, Georgopoulos N, Kyriazopoulou V, Vagenakis AG. Iodine-induced hypothyroidism. *Thyroid*. 2001;11:501–510.
19. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. *Endocr Rev*. 2001;22:240–254.
20. McDonnell ME, Braverman LE, Bernardo J. Hypothyroidism due to ethionamide. *N Engl J Med*. 2005;352:2757–2759.
21. Rini BI, Tamaskar I, Shaheen P, et al. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst*. 2007;99:81–83.
22. Smit JWA, Stokkel MPM, Pereira AM, Romijn JA, Visser TJ. Bexarotene-induced hypothyroidism: bexarotene stimulates the peripheral metabolism of thyroid hormones. *J Clin Endocrinol Metab*. 2007;92:2496–2499.
23. Surks MI, Sievert R. Drugs and thyroid function. *N Engl J Med*. 1995;333:1688–1694.
24. Takasu N, Kinjou Y, Kouki T, Takara M, Ohshiro Y, Komiya I. Rifampin-induced hypothyroidism. *J Endocrinol Invest*. 2006;29:645–649.
25. Weijl NI, Van der Harst D, Brand A, et al. Hypothyroidism during immunotherapy with interleukin-2 is associated with antithyroid antibodies and response to treatment. *J Clin Oncol*. 1993;11:1376–1383.
26. Wong V, Fu AX-L, George J, Cheung NW. Thyrotoxicosis induced by alpha-interferon therapy in chronic viral hepatitis. *Clin Endocrinol*. 2002;56:793–798.

27. Takasu N, Seki H. Plummer's nails (onycholysis) in a Thyroid-Stimulation-Blocking Antibody (TSBAb)-positive patient with hypothyroidism. *Intern Med*. 2018;57(20):3055–3056. doi:10.2169/internalmedicine.0809-18
28. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18(6):988–1028. doi:10.4158/EP12280.GL
29. LeFevre ML, U.S. Preventive Services Task Force. Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;162(9):641–650. doi:10.7326/M15-0483
30. Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Intern Med*. 2000;160(11):1573–1575. doi:10.1001/archinte.160.11.1573
31. Vasileiou M, Gilbert J, Fishburn S, Boelaert K, Guideline C. Thyroid disease assessment and management: summary of NICE guidance. *BMJ*. 2020;368:m41. doi:10.1136/bmj.m41
32. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. *Thyroid*. 2014;24(12):1670–1751. doi:10.1089/thy.2014.0028
33. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26(10):1343–1421. doi:10.1089/thy.2016.0229
34. Barclay ML, Brownlie BE, Turner JG, Wells JE. Lithium associated thyrotoxicosis: a report of 14 cases, with statistical analysis of incidence. *Clin Endocrinol*. 1994;40:759–764.
35. Dang AH, Hershman JM. Lithium-associated thyroiditis. *Endocr Pract*. 2002;8:232–236.
36. Peeters RP, van der Deure WM, Visser TJ. Genetic variation in thyroid hormone pathway genes; polymorphisms in the TSH receptor and the iodothyronine deiodinases. *Eur J Endocrinol*. 2006;155:655–662.
37. Roti E, Uberti ED. Iodine excess and hyperthyroidism. *Thyroid*. 2001;11:493–500.
38. Kravets I. Hyperthyroidism: diagnosis and treatment. *Am Fam Physician*. 2016;93(5):363–370.
39. Umar H, Muallima N, Adam JM, Sanusi H. Hashimoto's thyroiditis following Graves' disease. *Acta Med Indones*. 2010;42(1):31–35.
40. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*. 2011;21(10):1081–1125. doi:10.1089/thy.2011.0087

41. Abalovich M, Amino N, Barbour LA, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2007;92(8 suppl):S1–S47.
42. Burch HB, Cooper DS. Management of Graves disease: a review. *JAMA*. 2015;314(23):2544–2554. doi:10.1001/jama.2015.16535
43. Marino M, Vitti P, Chiovato L. Chapter 82- Graves' Disease. In: Jameson JL, De Groot LJ, de Kretser DM, et al, eds. *Endocrinology: Adult and Pediatric (Seventh Edition)*. W.B. Saunders; 2016:1437–1464.e8.
44. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Practice Guideline. *Thyroid*. 2009;19(11):1167–1214. doi:10.1089/thy.2009.0110
45. The ATAGT. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2006;16:109–142.
46. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26(1):1–133. doi:10.1089/thy.2015.0020
47. Demers LM, Spencer CA. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid*. 2003;13:3–126.
48. Esfandiari NH, Papaleontiou M. Biochemical testing in thyroid disorders. *Endocrinol Metab Clin North Am*. 2017;46(3):631–648. doi:10.1016/j.ecl.2017.04.002
49. Quest Diagnostics Incorporated. Quest diagnostics: test directory. Accessed September 7, 2020. https://testdirectory.questdiagnostics.com/test/home
50. Ross DS. Serum thyroid-stimulating hormone measurement for assessment of thyroid function and disease. *Endocrinol Metab Clin North Am*. 2001;30:245–264.
51. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. *J Clin Endocrinol Metab*. 2005;90:5489–5496.
52. Kim PD, Tran HD. I-123 *Uptake*. StatPearls; 2022.
53. deGroot LJ. Non-thyroidal illness syndrome is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence, should be treated with appropriate replacement therapies. *Crit Care Clin*. 2006;22:57–86.
54. Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome, an update. *J Endocrinol*. 2010;205:1–13.
55. Plikat K, Langgartner J, Buettner R, et al. Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. *Metabolism*. 2007;56:239–244.

56. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. *JAMA*. 1981; 245:43–45.
57. Friberg L, Drvota V, Bjelak AH, Eggertsen G, Ahnve S. Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. *Am J Med*. 2001;111:699–703.
58. Acker CG, Flick R, Shapiro R, et al. Thyroid hormone in the treatment of post-transplant acute tubular necrosis (ATN). *Am J Transplant*. 2002;2:57–61.
59. DeGroot LJ. The non-thyroidal illness syndrome. In: Feingold KR, Anawalt B, Boyce A, et al, eds. *Endotext*. MDText.com; 2000.
60. Lechan RM. The dilemma of the nonthyroidal illness syndrome. *Acta Biomed*. 2008;79(3):165–171.
61. Wang R, Nelson JC, Wilcox RB. Salsalate administration: a potential pharmacological model of the sick euthyroid syndrome. *J Clin Endocrinol Metab*. 1998;83:3095–3099.
62. McDonnell RJ. Abnormal thyroid function test results in patients taking salsalate. *JAMA*. 1992;267:1242–1243.
63. Curran PG, Degroot LJ. The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. *Endocr Rev*. 1991;12:135–150.
64. Surks MI, DeFesi CR. Normal serum free thyroid hormone concentrations in patients treated with phenytoin or carbamazepine: a paradox resolved. *JAMA*. 1996;275:1495–1498.
65. Isojärvi JI, Turkka J, Pakarinen AJ, Kotila M, Rättyä J, Myllylä VV. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. *Epilepsia*. 2001;42:930–934.
66. Tiihonen M, Liewendahl K, Waltimo O, Ojala M, Välimäki M. Thyroid status of patients receiving long-term anticonvulsant therapy assessed by peripheral parameters: a placebo-controlled thyroxine therapy trial. *Epilepsia*. 1995;36:1118–1125.
67. Blackshear JL, Schultz AL, Napier JS, Stuart DD. Thyroxine replacement requirements in hypothyroid patients receiving phenytoin. *Ann Intern Med*. 1983;99:341–342.
68. De Luca F, Arrigo T, Pandullo E, Siracusano MF, Benvenga S, Trimarchi F. Changes in thyroid function tests induced by 2 month carbamazepine treatment in L-thyroxine-substituted hypothyroid children. *Eur J Paediatr*. 1986;145:77–79.
69. English TN, Ruxton D, Eastman CJ. Abnormalities in thyroid function associated with chronic therapy with methadone. *Clin Chem*. 1988;34:2202–2204.
70. Hsu SHJ, Cheng WC, Jang MW, Tsai KS. Effects of long-term use of raloxifene, a selective estrogen receptor modulator, on thyroid function test profiles. *Clin Chem*. 2001;10:1865–1867.

71. Kostoglour-Athanassiou I, Ntalles K, Markopoulos C, Athanassiou P, Gogas J, Proukakis C. Thyroid function in postmenopausal women with breast cancer on tamoxifen. *Eur J Gynaecol Oncol*. 1998;19:150–154.
72. Samuels ER, Hou RH, Langley RW, Szabadi E, Bradshaw CM. Comparison of pramipexole and modafinil on arousal, autonomic, and endocrine functions in healthy volunteers. *J Psychopharmacol*. 2006;20(6):756–770. doi:10.1177/0269881106060770
73. Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. *Best Pract Res Clin Endocrinol Metab*. 2009;23:793–800.
74. Vigersky RA, Filmore-Nassar A, Glass AR. Thyrotropin suppression by metformin. *J Clin Endocrinol Metab*. 2006;91:225–227.
75. Cappelli C, Rotondi M, Pirola I, et al. TSH-lowering effect of metformin in type 2 diabetic patients: differences between euthyroid, untreated hypothyroid, and euthyroid on L-T4 therapy patients. *Diabetes Care*. 2009;32(9):1589–1590. doi:10.2337/dc09-0273
76. Roberts CGP, Ladenson PW. Hypothyroidism. *Lancet*. 2004;363:793–803.
77. Brent GA, Koenig RJ. Thyroid and anti-thyroid drugs. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. The McGraw-Hill; 2011:1129–1162.
78. Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. *J Clin Endocrinol Metab*. 2013;98(5):1982–1990. doi:10.1210/jc.2012-4107
79. Sawin CT, Hershman JM, Fernandez-Garcia R, Ghazvinian S, Ganda OP, Azukizawa M. A comparison of thyroxine and desiccated thyroid in patients with primary hypothyroidism. *Metabolism*. 1978;27:1518–1525.
80. USP. Thyroid tablets. United States Pharmacopeia. Accessed September 28, 2020. https://online.uspnf.com/uspnf/document/1_GUID-286B4BB6-CF94-4650-B937-FDF8C74D5568_1_en-US?source=Search%20Results&highlight=thyroid
81. Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L. Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab*. 2006;91:2592–2599.
82. Escobar-Morreale HF, Botella-Carretero JI, del Rey FE, de Escobar GM. Review: treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J Clin Endocrinol Metab*. 2005;90:4946–4954.
83. Wiersinga WM. Thyroid hormone replacement therapy. *Horm Res*. 2001;56(suppl 1):74–81.
84. Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH. Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. *N Engl J Med*. 1987;316:764–770.

85. Bolk N, Visser TJ, Kalsbeek A, van Domburg RT, Berghout A. Effects of evening vs morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients. *Clin Endocrinol (Oxf)*. 2007;66:43–48.
86. American Thyroid Association, Endocrine Society, American Association of Clinical Endocrinologists. Joint statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. *Thyroid*. 2004;14:486.
87. Toft A. Which thyroxine? *Thyroid*. 2005;15:124–126.
88. Gibaldi M. Bioequivalence of thyroid preparations: the final word? *AAPS J*. 2005;7:E59–E60.
89. Bolton S. Bioequivalence studies for levothyroxine. *AAPS J*. 2005;7:E47–E53.
90. Klein I, Danzi S. Evaluation of the therapeutic efficacy of different levothyroxine preparations in the treatment of human thyroid disease. *Thyroid*. 2003;13:1127–1132.
91. Bianco AC, Kim BS. Pathophysiological relevance of deiodinase polymorphism. *Curr Opin Endocrinol Diabetes Obes*. 2018;25(5):341–346. doi:10.1097/MED.0000000000000428
92. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. *Recent Prog Horm Res*. 2004;59:31–50.
93. Murphy E, Williams GR. The thyroid and the skeleton. *Clin Endocrinol*. 2004;61:285–298.
94. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004;291:228–238.
95. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*. 2008;29:76–131.
96. Mitchell AL, Pearce SHS. How should we treat patients with low serum thyrotropin concentrations? *Clin Endocrinol (Oxf)*. 2010;72:292–296.
97. Sawin CT, Herman T, Molitch ME, London MH, Kramer SM. Aging and the thyroid: decreased requirement for thyroid hormone in older hypothyroid patients. *Am J Med*. 1983;75:206–209.
98. Annemieke R, Linn-Rasker SP, van Domburg RT, Tijssen JP, Berghout A. The starting dose of levothyroxine in primary hypothyroidism treatment: a prospective, randomized, double-blind trial. *Arch Intern Med*. 2005;165:1714–1720.
99. Benvenga S, Bartolone L, Squadrito S, Lo Giudice F, Trimarchi F. Delayed intestinal absorption of levothyroxine. *Thyroid*. 1995;5:249–253.
100. Bach-Huynh TG, Nayak B, Loh J, Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. *J Clin Endocrinol Metab*. 2009;94(10):3905–3912. doi:10.1210/jc.2009-0860
101. Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult

hypothyroid patients. *J Clin Endocrinol Metab*. 1996;80:857–859.
102. Bell DS, Ovalle F. Use of soy protein supplement and resultant need for increased dose of levothyroxine. *Endocr Pract*. 2001;7:193–194.
103. Benvenga S, Bartolone L, Pappalardo MA, et al. Altered intestinal absorption of L-thyroxine caused by coffee. *Thyroid*. 2008;18(3):293–301. doi:10.1089/thy.2007.0222
104. Siraj ES, Gupta MK, Sethu S, Reddy K. Raloxifene causing malabsorption of levothyroxine. *Arch Intern Med*. 2003;163:1367–1370.
105. Harmon SM, Seifert CF. Levothyroxine-cholestyramine interaction reemphasized. *Ann Intern Med*. 1991;115:658–659.
106. Campbell NRC, Hasinoff BB, Stalts H, Rao B, Wong NC. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med*. 1992;117:1010–1013.
107. Demke DM. Drug interaction between thyroxine and lovastatin. *N Engl J Med*. 1989;321:1341–1342.
108. Sperber AD, Liel Y. Evidence for interference with the intestinal absorption of levothyroxine sodium by aluminum hydroxide. *Arch Intern Med*. 1992;152:183–184.
109. Havrankova J, Lahaie R. Levothyroxine binding by sucralfate. *Ann Intern Med*. 1992;117:445–446.
110. Singh N, Singh PN, Hershman JM. Effect of calcium carbonate on the absorption of levothyroxine. *JAMA*. 2000;283:2822–2825.
111. Singh N, Weisler SL, Hershman JM. The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. *Thyroid*. 2001;11:967–971.
112. Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. Effect of phosphate binders upon TSH and L-thyroxine dose in patients on thyroid replacement. *Int Urol Nephrol*. 2007;39:599–602.
113. Centanni M, Gargano L, Canettieri G, et al. Thyroxine in goiter, helicobacter pylori infection, and chronic gastritis. *N Engl J Med*. 2006;354:1787–1795.
114. Dietrich JW, Gieselbrecht K, Holl RW, Boehm BO. Absorption kinetics of levothyroxine is not altered by proton-pump inhibitor therapy. *Horm Metab Res*. 2006;38:57–59.
115. Grund FM, Niewoehner CB. Hyperthyroxinemia in patients receiving thyroid replacement therapy. *Arch Intern Med*. 1989;149:921–924.
116. Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. *JAMA*. 2008;299(7):769–777. doi:10.1001/jama.299.7.769
117. Dong BJ, Hauck WW, Gambertoglio JG, et al. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA*. 1997;277:1205–1213.
118. Ain KB, Pucino F, Shiver TM, Banks SM. Thyroid hormone levels affected by time of blood sampling in thyroxine-treated patients. *Thyroid*. 1993;3:81–85.

119. Walsh JP, Ward LC, Burke V, et al. Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. *J Clin Endocrinol Metab*. 2006;91:2624–2630.
120. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab*. 2010;95(1):186–193. doi:10.1210/jc.2009-1625
121. Celi FS, Zemskova M, Linderman JD, et al. The pharmacodynamic equivalence of levothyroxine and liothyronine: a randomized, double blind, cross-over study in thyroidectomized patients. *Clin Endocrinol (Oxf)*. 2010;72(5):709–715. doi:10.1111/j.1365-2265.2009.03700.x
122. Davis FB, LaMantia RS, Spaulding SW, Wehmann RE, Davis PJ. Estimation of a physiologic replacement dose of levothyroxine in elderly patients with hypothyroidism. *Arch Intern Med*. 1984;144:1752–1754.
123. Kabadi UM. Variability of L-thyroxine replacement dose in elderly patients with primary hypothyroidism. *J Fam Pract*. 1987;24:473–477.
124. Cunningham JJ, Barzel US. Lean body mass is a predictor of the daily requirement for thyroid hormone in older men and women. *J Am Geriatr Soc*. 1984;32(3):204–207. doi:10.1111/j.1532-5415.1984.tb02003.x
125. Grebe SKG, Cooke RR, Ford HC, et al. Treatment of hypothyroidism with once weekly thyroxine. *J Clin Endocrinol Metab*. 1997;82:870–875.
126. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341:549–555.
127. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol*. 2003;59:282–288.
128. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(3):315–389. doi:10.1089/thy.2016.0457
129. Korevaar TIM, Tiemeier H, Peeters RP. Clinical associations of maternal thyroid function with foetal brain development: epidemiological interpretation and overview of available evidence. *Clin Endocrinol (Oxf)*. 2018;89(2):129–138. doi:10.1111/cen.13724
130. Komendova I, Spitalnikova S. Intellectual performance of children of mothers with an untreated thyroid disorder in the first trimester of pregnancy. *Endokrynol Pol*. 2018;69(3):241–245. doi:10.5603/EP.a2018.0025
131. Petersen TG, Andersen AN, Uldall P, et al. Maternal thyroid disorder in pregnancy and risk of cerebral palsy in the child: a population-based cohort study. *BMC Pediatr*. 2018;18(1):181. doi:10.1186/s12887-018-1152-5

132. Nelson SM, Haig C, McConnachie A, et al. Maternal thyroid function and child educational attainment: prospective cohort study. *BMJ*. 2018;360:k452. doi:10.1136/bmj.k452
133. Galofre JC, Davies TF. Autoimmune thyroid disease in pregnancy: a review. *J Womens Health (Larchmt)*. 2009;18(11):1847–1856. doi:10.1089/jwh.2008.1234
134. Mandel SJ, Larsen PR, Seely EW, Brent GA. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *N Engl J Med*. 1990;323:91–96.
135. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med*. 2004;351:241–249.
136. Vaidya B, Anthony S, Bilous M, et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab*. 2007;92:203–207.
137. Chopra IJ, Baber K. Treatment of primary hypothyroidism during pregnancy: is there an increase in thyroxine dose requirement in pregnancy? *Metabolism*. 2003;52:122–128.
138. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis*. 2010;5:17. doi:10.1186/1750-1172-5-17
139. Rovet JF. In search of the optimal therapy for congenital hypothyroidism. *J Pediatr*. 2004;144:698–700.
140. Salerno M, Militerni R, Bravaccio C, et al. Effect of different starting doses of levothyroxine on growth and intellectual outcome at four years of age in congenital hypothyroidism. *Thyroid*. 2002;12:45–52.
141. Bongers-Schokking JJ, de Muinck Keizer-Schrama SMPF. Influence of timing and dose of thyroid hormone replacement on mental, psychomotor, and behavioral development in children with congenital hypothyroidism. *J Pediatr*. 2005;147:768–774.
142. Rovet JF. Children with congenital hypothyroidism and their siblings: do they really differ? *Pediatrics*. 2005;115:e52–e57.
143. Oerbeck B, Sundet K, Kase BF, Heyerdahl S. Congenital hypothyroidism: influence of disease severity and L-thyroxine treatment on intellectual, motor, and school-associated outcomes in young adults. *Pediatrics*. 2003;112:923–930.
144. Simoneau-Roy J, Marti S, Deal C, Huot C, Robaey P, Van Vliet G. Cognition and behavior at school entry in children with congenital hypothyroidism treated early with high-dose levothyroxine. *J Pediatr*. 2004;144:747–752.
145. Heyerdahl S, Oerbeck B. Congenital hypothyroidism: developmental outcome in relation to levothyroxine treatment variables. *Thyroid*. 2003;13:1029–1038.
146. American Academy of Pediatrics, Rose SR, Section on Endocrinology and Committee on Genetics, American Thyroid Association, et al. Update of

newborn screening and therapy for congenital hypothyroidism. *Pediatrics*. 2006;117(6):2290–2303. doi:10.1542/peds.2006-0915

147. Lexicomp. Levothyroxine: Lexi-drugs. 2021. Updated September 4, 2021. Accessed April 9, 2021. http://online.lexi.com/
148. Oerbeck B, Sundet K, Kase B, Heyerdahl S. Congenital hypothyroidism: no adverse effects of high dose thyroxine treatment on adult memory, attention, and behaviour. *Arch Dis Child*. 2005;90:132–137.
149. Selva KA, Mandel SH, Rien L, et al. Initial treatment dose of L-thyroxine in congenital hypothyroidism. *J Pediatr*. 2002;141:786–792.
150. Wartoksky L. Myxedema coma. *Endocrinol Metab Clin North Am*. 2006;35:687–698.
151. Yamamoto T, Fukuyama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. *Thyroid*. 1999;9:1167–1174.
152. Hylander B, Rosenqvist U. Treatment of myxoedema coma: factors associated with fatal outcome. *Acta Endocrinol (Copenh)*. 1985;108:65–71.
153. MacKerrow SD, Osborn LA, Levy H, Eaton RP, Economou P. Myxedema-associated cardiogenic shock treated with intravenous triiodothyronine. *Ann Intern Med*. 1992;117:1014–1015.
154. Pereira VG, Haron ES, Lima-Neto N, Medeiros-Neto GA. Management of myxedema coma: report on three successfully treated cases with nasogastric or intravenous administration of triiodothyronine. *J Endocrinol Invest*. 1982;5:331–334.
155. Ladenson PW, Goldenheim PD, Ridgway EC. Rapid pituitary and peripheral tissue responses to intravenous L-triiodothyronine in hypothyroidism. *J Clin Endocrinol Metab*. 1983;56:1252–1259.
156. Ariot S, Debussche X, Lalau JD, et al. Myxoedema coma: response of thyroid hormones with oral and intravenous high-dose L-thyroxine treatment. *Intensive Care Med*. 1991;17:16–18.
157. Madan N, Tiwari N, Stampfer M, Schubart U. Hypothyroid heart: myxoedema as a cause of reversible dilated cardiomyopathy. *BMJ Case Rep*. 2015;2015. doi:10.1136/bcr-2015-212045
158. Kohno A, Hara Y. Severe myocardial ischemia following hormone replacement in two cases of hypothyroidism with normal coronary arteriogram. *Endocr J*. 2001;48:565–572.
159. Fadeyev VV, Sytch J, Kalashnikov V, Rojtman A, Syrkin A, Melnichenko G. Levothyroxine replacement therapy in patients with subclinical hypothyroidism and coronary artery disease. *Endocr Pract*. 2006;12:5–17.
160. Levine D. Compromise therapy in the patient with angina pectoris and hypothyroidism. *Am J Med*. 1980;69:411–418.
161. Myerowitz PD. Diagnosis and management of the hypothyroid patient with chest pain. *J Thorac Cardiovasc Surg*. 1983;86:57–60.

162. Huber G, Staub J-J, Meier C, et al. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab*. 2002;87:3221–3226.
163. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab*. 2001;86:4585–4590.
164. Kong WM, Sheikh MH, Lumb PJ, et al. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med*. 2002;112:348–354.
165. Meier C, Staub JJ, Roth CB, et al. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). *J Clin Endocrinol Metab*. 2001;86:4860–4866.
166. Rodondi N, Aujesky D, Vittinghoff E, Cornuz J, Bauer DC. Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. *Am J Med*. 2006;119:541–551.
167. Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med*. 2005;165:2467–2472.
168. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. 2006;295:1033–1041.
169. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304(12):1365–1374. doi:10.1001/jama.2010.1361
170. Danese MD, Ladenson PW, Meinert CL, Powe NR. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab*. 2000;85:2993–3001.
171. Feller M, Snel M, Moutzouri E, et al. Association of Thyroid Hormone Therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. *JAMA*. 2018;320(13):1349–1359. doi:10.1001/jama.2018.13770
172. Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ*. 2019;365: l2006.
173. Wardle CA, Fraser WD, Squire CR. Pitfalls in the use of thyrotropin concentration as a first-line thyroid-function test. *Lancet*. 2001;357:1013–1014.
174. Pollock MA, Sturrock A, Marshall K, et al. Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. *BMJ*. 2001;323:891–895.

175. Weetman AP. Thyroxine treatment in biochemically euthyroid but clinically hypothyroid individuals. *Clin Endocrinol*. 2002;57:25–27.
176. Brent GA. Graves' disease. *N Engl J Med*. 2008;358:2594–2605.
177. Smith TJ, Hegedus L. Graves' disease. *N Engl J Med*. 2016;375(16):1552–1565. doi:10.1056/NEJMra1510030
178. Shimizu T, Koide S, Noh JY, Sugino K, Ito K, Nakazawa H. Hyperthyroidism and the management of atrial fibrillation. *Thyroid*. 2002;12:489–493.
179. Burgi H. Iodine excess. *Best Pract Res Clin Endocrinol Metab*. 2010;24:107–117.
180. Chiha M, Samarasinghe S, Kabaker AS. Thyroid storm: an updated review. *J Intensive Care Med*. 2015;30(3):131–140. doi:10.1177/0885066613498053
181. Arbelle JE, Porath A. Practice guidelines for the detection and management of thyroid dysfunction: a comparative review of the recommendations. *Clin Endocrinol*. 1999;51:11–18.
182. Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. *Cochrane Database Syst Rev*. 2010:CD003420.
183. Cooper DS. Antithyroid drugs. *N Engl J Med*. 2005;352:905–917.
184. Jongjaroenprasert W, Akarawut W, Chantasart D, Chailurkit L, Rajatanavin R. Rectal administration of propylthiouracil in hyperthyroid patients: comparison of suspension enema and suppository form. *Thyroid*. 2002;12:627–631.
185. Yeung SCJ, Go R, Balasubramanyam A. Rectal administration of iodide and propylthiouracil in the treatment of thyroid storm. *Thyroid*. 1995;5:403–405.
186. Nabil N, Miner DJ, Amatruda JM. Methimazole: an alternative route of administration. *J Clin Endocrinol Metab*. 1982;54:180–181.
187. Alsanea O, Clark OH. Treatment of Graves' disease: the advantages of surgery. *Endocrinol Metab Clin North Am*. 2000;29:321–337.
188. Torring O, Tallstedt L, Wallin G, et al. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine: a prospective, randomized study. *J Clin Endocrinol Metab*. 1996;81:2986–2993.
189. Boostrom S, Richards ML. Total thyroidectomy is the preferred treatment for patients with Graves' disease and a thyroid nodule. *Otolaryngol Head Neck Surg*. 2007;136:278–281.
190. Hoffmann R. Thyroidectomy in Graves' disease: subtotal, near total or total? *Orbit*. 2009;28(4):241–244. doi:10.1080/01676830903104595
191. Palit TK, Miller CC 3rd, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: a meta-analysis. *J Surg Res*. 2000;90:161–165.
192. Nayak B, Burman K. Thyrotoxicosis and thyroid storm. *Endocrinol Metab Clin North Am*. 2006;35:663–686.
193. Geffner DL, Hershman JM. Beta-adrenergic blockade for the treatment of hyperthyroidism. *Am J Med*. 1992;93:61–68.

Gaujoux S, Leenhardt L, Trésallet C, et al. Extensive thyroidectomy in
194. Graves' disease. *J Am Coll Surg*. 2006;202:868–873.
195. Hollander JM, Davies TF. Chapter 12 - Graves' Disease. In: Wondisford FE, Radovick S, eds. Clinical Management of Thyroid Disease. W.B. Saunders; 2009:153–189.
196. Ross DS. Radioiodine therapy for hyperthyroidism. *N Engl J Med*. 2011;364:542–550.
197. Ron E, Doody MM, Becker DV, et al. Cancer mortality following treatment for adult hyperthyroidism: Cooperative Thyrotoxicosis Therapy Follow-up Study Group. *JAMA*. 1998;280:347–355.
198. Rivkees SA. The management of hyperthyroidism in children with emphasis on the use of radioactive iodine. *Pediatr Endocrinol Rev*. 2003;1(suppl 2):212–221.
199. Read CH, Tansey MJ, Menda Y. A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' patients. *J Clin Endocrinol Metab*. 2004;89:4229–4233.
200. Robertson J, Gorman CA. Gonadal radiation dose and its genetic significance in radioiodine therapy of hyperthyroidism. *J Nucl Med*. 1976;17:826–835.
201. Holm LE. Thyroid cancer after exposure to radioactive 131I. *Acta Oncol*. 2006;45:1037–1040.
202. Zuckier L, Stabin M, Garetano G, Monetti M, Lanka V. Sensitivity of personal homeland security radiation detectors to medical radionuclides and implications for counseling of nuclear medicine patients. Paper presented at: RSNA 2004, 90th Scientific Assembly and Annual Meeting; November 28–December 3, 2004; Chicago IL.
203. Gangopadhyay KK, Sundram F, De P. Triggering radiation alarms after radioiodine treatment. *BMJ*. 2006;333:293–294.
204. Diana T, Brown RS, Bossowski A, et al. Clinical relevance of thyroid-stimulating autoantibodies in pediatric graves' disease-a multicenter study. *J Clin Endocrinol Metab*. 2014;99(5):1648–1655. doi:10.1210/jc.2013-4026
205. Iagaru A, McDougall IR. Treatment of thyrotoxicosis. *J Nucl Med*. 2007;48:379–389.
206. Hardee JT, Barnett AL, Thannoun A, Eghtesad B, Wheeler D, Jamal MM. Propylthiouracil-induced hepatotoxicity. Case reports. *West J Med*. 1996;165(3):144–147.
207. McIver B, Morris JC. The pathogenesis of Graves' disease. *Endocrinol Metab Clin North Am*. 1998;27:73–89.
208. Maugendre D, Gatel A, Campion L, et al. Antithyroid drugs and Graves' disease: prospective randomized assessment of long-term treatment. *Clin Endocrinol*. 1999;50:127–132.
209. Anagnostis P, Adamidou F, Polyzos SA, et al. Predictors of long-term remission in patients with Graves' disease: a single center experience.

Endocrine. 2013;44(2):448–453. doi:10.1007/s12020-013-9895-0

210. Azizi F, Malboosbaf R. Long-term antithyroid drug treatment: a systematic review and meta-analysis. *Thyroid*. 2017;27(10):1223–1231. doi:10.1089/thy.2016.0652
211. Bolanos F, González-Ortiz M, Durón H, Sánchez C. Remission of Graves' hyperthyroidism treated with methimazole. *Rev Invest Clin*. 2002;54:307–310.
212. Nijs HG, Radder JK, Frölich M, Krans HM. Increased insulin action and clearance in hyperthyroid newly diagnosed IDDM patient: restoration to normal with antithyroid treatment. *Diabetes Care*. 1989;12:319–324.
213. Aloush V, Litinsky I, Caspi D, Elkayam O. Propylthiouracil-induced autoimmune syndromes: two distinct clinical presentations with different course and management. *Semin Arthritis Rheum*. 2006;36:4–9.
214. Milner MR, Gelman KM, Phillips RA, Fuster V, Davies TF, Goldman ME. Double-blind crossover trial of diltiazem versus propranolol in the management of thyrotoxic symptoms. *Pharmacotherapy*. 1990;10:100–106.
215. Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011;17(3):456–520.
216. White JR, Campbell RK. Dangerous and common drug interactions in patients with diabetes mellitus. *Endocrinol Metab Clin North Am*. 2000;29(4):789–802. doi:10.1016/s0889-8529(05)70164-x
217. Rivkees SA, Mattison DR. Ending propylthiouracil-induced liver failure in children. *N Engl J Med*. 2009;360(15):1574–1575. doi:10.1056/NEJMc0809750
218. Bahn RS, Burch HS, Cooper DS, et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid*. 2009;19(7):673–674. doi:10.1089/thy.2009.0169
219. Liaw Y, Huang MJ, Fan KD, Li KL, Wu SS, Chen TJ. Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism: a cohort study. *Ann Intern Med*. 1993;118:424–428.
220. Williams KV, Nayak S, Becker D, Reyes J, Burmeister LA. Fifty years of experience with propylthiouracil-associated hepatotoxicity: what have we learned? *J Clin Endocrinol Metab*. 1997;82:1727–1733.
221. Woeber KA. Methimazole-induced hepatotoxicity. *Endocr Pract*. 2002;8:222–224.
222. Tajiri J, Noguchi S, Murakami T, Murakami N. Antithyroid drug-induced agranulocytosis: the usefulness of routine white blood cell count monitoring. *Arch Intern Med*. 1990;150:621–624.
223. Wall JR, Fang SL, Kuroki T, Ingbar SH, Braverman LE. In vitro immunoreactivity to propylthiouracil, methimazole, and carbimazole in

patients with Graves' disease: a possible cause of antithyroid drug-induced agranulocytosis. *J Clin Endocrinol Metab*. 1984;58:868–872.

224. Jakucs J, Pocsay G. Successful treatment of methimazole-induced severe aplastic anemia with recombinant human granulocyte colony-stimulating factor and high-dosage steroids. *J Endocrinol Invest*. 2006;29:74–77.
225. Yildirim Simsir I, Cetinkalp S, Kabalak T. Review of factors contributing to nodular goiter and thyroid carcinoma. *Med Princ Pract*. 2020;29(1):1–5. doi:10.1159/000503575
226. Allannic H, Fauchet R, Orgiazzi J, et al. Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. *J Clin Endocrinol Metab*. 1990;70:675–679.
227. Orgiazzi J, Madec AM. Reduction of the risk of relapse after withdrawal of medical therapy for Graves' disease. *Thyroid*. 2002;12:849–853.
228. Vitti P, Rago T, Chiovato L, et al. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. *Thyroid*. 1997;3:369–375.
229. Glinoer D, de Nayer P, Bex M, Belgian Collaborative Study Group on Graves' Disease. Effects of L-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves' hyperthyroidism treated with antithyroid drugs: a double-blind prospective randomized study. *Eur J Endocrinol*. 2001;144:475–483.
230. Hashizume K, Ichikawa K, Sakurai A, et al. Administration of thyroxine in treated Graves' disease: effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. *N Engl J Med*. 1991;324:947–953.
231. Vestergaard P. Smoking and thyroid disorders—a meta-analysis. *Eur J Endocrinol*. 2002;146:153–161.
232. Hoermann R, Quadbeck B, Roggenbuck U, et al. Relapse of Graves' disease after successful outcome of antithyroid drug therapy: results of a prospective randomized study on the use of levothyroxine. *Thyroid*. 2002;12:1119–1128.
233. McIver B, Rae P, Beckett G, Wilkinson E, Gold A, Toft A. Lack of effect of thyroxine in patients with Graves' hyperthyroidism who are treated with an antithyroid drug. *N Engl J Med*. 1996;334:220–224.
234. Azizi F, Amouzegar A, Tohidi M, et al. Increased remission rates after long-term methimazole therapy in patients with Graves' disease: results of a randomized clinical trial. *Thyroid*. 2019;29(9):1192–1200. doi:10.1089/thy.2019.0180
235. Mestman JH. Hyperthyroidism in pregnancy. *Best Pract Res Clin Endocrinol Metab*. 2004;18:267–288.
236. Atkins P, Cohen SB, Phillips BJ. Drug therapy for hyperthyroidism in pregnancy: safety issues for mother and fetus. *Drug Saf*. 2000;23:229–244.
237. Bulletin AP. Thyroid disease in pregnancy. *Obstet Gynecol*. 2002;100:387–396.

238. Fitzpatrick DL, Russell MA. Diagnosis and management of thyroid disease in pregnancy. *Obstet Gynecol Clin North Am*. 2010;37(2):173–193. doi:10.1016/j.ogc.2010.02.007
239. Clementi M, Di Gianantonio E, Cassina M, et al. Treatment of hyperthyroidism in pregnancy and birth defects. *J Clin Endocrinol Metab*. 2010;95(11):E337–E341. doi:10.1210/jc.2010-0652
240. Wing DA, Millar LK, Koonings PP, Montoro MN, Mestman JH. A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol*. 1994;170:90–95.
241. Mortimer RH, Cannell GR, Addison RS, Johnson LP, Roberts MS, Bernus I. Methimazole and propylthiouracil equally cross the perfused human term placental lobule. *J Clin Endocrinol Metab*. 1997;82:3099–3102.
242. Momotani N, Noh JY, Ishikawa N, Ito K. Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism. *J Clin Endocrinol Metab*. 1997;82:3633–3636.
243. Momotani N, Ito K, Hamada N, Ban Y, Nishikawa Y, Mimura T. Maternal hyperthyroidism and congenital malformation in the offspring. *Clin Endocrinol*. 1984;20:695–700.
244. Van Dijke CP, Heydendael RJ, De Kleine MJ. Methimazole, carbimazole, and congenital skin defects. *Ann Intern Med*. 1987;106:60–61.
245. Momotani N, Noh J, Oyanagi H, Ishikawa N, Ito K. Antithyroid drug therapy for Graves' disease during pregnancy: optimal regimen for fetal thyroid status. *N Engl J Med*. 1986;315:24–28.
246. Wolf D, Foulds N, Daya H. Antenatal carbimazole and choanal atresia: a new embryopathy. *Arch Otolaryngol Head Neck Surg*. 2006;132:1009–1011.
247. Momotani N, Yamashita R, Makino F, Noh JY, Ishikawa N, Ito K. Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol*. 2000;53:177–181.
248. Azizi F, Khoshniat M, Bahrainian M, Hedayati M. Thyroid function and intellectual development of infants nursed by mothers taking methimazole. *J Clin Endocrinol Metab*. 2000;85:3233–3238.
249. Hamada K, Mizokami T, Maruta T, et al. Thyroid function of infants breastfed by mothers with Graves disease treated with inorganic iodine: a study of 100 cases. *J Endocr Soc*. 2021;5(2):bvaa187. doi:10.1210/jendso/bvaa187
250. Hamada K, Mizokami T, Maruta T, et al. Effects of inorganic iodine therapy administered to lactating mothers with Graves disease on infant thyroid function. *J Endocr Soc*. 2017;1(10):1293–1300. doi:10.1210/js.2017-00297
251. Kubota S, Ohye H, Yano G, et al. Two-day thionamide withdrawal prior to radioiodine uptake sufficiently increases uptake and does not exacerbate hyperthyroidism compared to 7 day withdrawal in Graves' disease. *Endocr J*. 2006;53:603–607.
252. Imseis RE, Vanmiddlesworth L, Massie JD, Bush AJ, Vanmiddlesworth NR. Pretreatment with propylthiouracil but not methimazole reduces the

therapeutic efficacy of iodine-131 in hyperthyroidism. *J Clin Endocrinol Metab*. 1998;83:685–687.

253. Braga M, Walpert N, Burch HB, Solomon BL, Cooper DS. The effect of methimazole on cure rates after radioiodine treatment for Graves' hyperthyroidism: a randomized clinical trial. *Thyroid*. 2002;12:135–139.
254. Meier DA, Brill DR, Becker DV, et al. Procedure guideline for therapy of thyroid disease with (131)iodine. *J Nucl Med*. 2002;43(6):856–861.
255. Mumtaz M, Lin LS, Hui KC, Mohd Khir AS. Radioiodine I-131 for the therapy of Graves' disease. *Malays J Med Sci*. 2009;16(1):25–33.
256. Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. *Endocr Rev*. 2000;21:168–199.
257. Wiersinga WM. Management of Graves' ophthalmopathy. *Nat Clin Pract Endocrinol Metab*. 2007;3:396–404.
258. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010;362(8):726–738. doi:10.1056/NEJMra0905750
259. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med*. 1998;338:73–78.
260. Smith TJ. Teprotumumab in thyroid-associated ophthalmopathy: rationale for therapeutic insulin-like growth factor-I receptor inhibition. *J Neuroophthalmol*. 2020;40(1):74–83. doi:10.1097/WNO.0000000000000890
261. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748–1761. doi:10.1056/NEJMoa1614949
262. Dorkhan M, Lantz M, Frid A, Groop L, Hallengren B. Treatment with a thiazolidinedione increases eye protrusion in a subgroup of patients with type 2 diabetes. *Clin Endocrinol (Oxf)*. 2006;65:35–39.
263. Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G, Pinchera A. Relationship between Graves' ophthalmopathy and type of treatment of Graves' hyperthyroidism. *Thyroid*. 1992;2:171–178.
264. Lai A, Sassi L, Compri E, et al. Lower dose prednisone prevents radioiodine-associated exacerbation of initially mild or absent graves' orbitopathy: a retrospective cohort study. *J Clin Endocrinol Metab*. 2010;95(3):1333–1337. doi:10.1210/jc.2009-2130
265. Tu X, Dong Y, Zhang H, Su Q. Corticosteroids for Graves' ophthalmopathy: systematic review and meta-analysis. *Biomed Res Int.* 2018;2018:4845894. doi:10.1155/2018/4845894
266. Salvi M, Vannucchi G, Campi I, Beck-Peccoz P. Rituximab in the treatment of thyroid eye disease: science fiction? *Orbit*. 2009;28(4):251–255.
267. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341–352. doi:10.1056/NEJMoa1910434

268. Carroll R, Matfin G. Endocrine and metabolic emergencies: thyroid storm. *Ther Adv Endocrinol Metab*. 2010;1(3):139–145. doi:10.1177/2042018810382481
269. Tsai WC, Pei D, Wang T-F, et al. The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. *Clin Endocrinol*. 2005;62:521–524.
270. Mittra ES, Niederkohr RD, Rodriguez C, El-Maghraby T, McDougall IR. Uncommon causes of thyrotoxicosis. *J Nucl Med*. 2008;49(2):265–278. doi:10.2967/jnumed.107.041202
271. Loeliger EA, Van der Esch B, Mattern MJ, Hemker HC. The biological disappearance rate of prothrombin, factors VII, IX and X from plasma in hypothyroidism, hyperthyroidism, and during fever. *Thromb Diath Haemorrh*. 1964;10:267–277.
272. Ajish TP, Jayakumar RV. Geriatric thyroidology: an update. *Indian J Endocrinol Metab*. 2012;16(4):542–547. doi:10.4103/2230-8210.98006
273. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med*. 1994;331:1249–1252.
274. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): the natural history of endogenous subclinical hyperthyroidism. *J Clin Endocrinol Metab*. 2011;96(1):E1–E8. doi:10.1210/jc.2010-0854
275. McCowen KC, Garber JR, Spark R. Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N Engl J Med*. 1997;337:1010–1011.
276. Cohen-Lehman J, Dahl P, Danzi S, Klein I. Effects of amiodarone therapy on thyroid function. *Nat Rev Endocrinol*. 2010;6(1):34–41. doi:10.1038/nrendo.2009.225
277. Fradkin JE, Wolff J. Iodide-induced thyrotoxicosis. *Medicine (Baltimore)*. 1983;62(1):1–20. doi:10.1097/00005792-198301000-00001
278. Zhong B, Wang Y, Zhang G, Wang Z. Environmental iodine content, female sex and age are associated with new-onset amiodarone-induced hypothyroidism: a systematic review and meta-analysis of adverse reactions of amiodarone on the thyroid. *Cardiology*. 2016;134(3):366–371. doi:10.1159/000444578
279. Houghton SG, Farley DR, Brennan MD, van Heerden JA, Thompson GB, Grant CS. Surgical management of amiodarone-associated thyrotoxicosis: Mayo Clinic experience. *World J Surg*. 2004;28(11):1083–1087. doi:10.1007/s00268-004-7599-6
280. Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. *JAMA*. 1990;263:1529–1532.

281. Fontanilla JC, Schneider AB, Sarne DH. The use of oral radiographic contrast agents in the management of hyperthyroidism. *Thyroid*. 2001;22:561–567.
282. Wu SY, Shyh TP, Chopra IJ, Solomon DH, Huang HW, Chu PC. Comparison sodium ipodate (oragrafin) and propylthiouracil in early treatment of hyperthyroidism. *J Clin Endocrinol Metab*. 1982;54:630–634.
283. Bal CS, Kumar A, Chandra P. Effect of iopanoic acid on radioiodine therapy of hyperthyroidism: long-term outcome of a randomized controlled trial. *J Clin Endocrinol Metab*. 2005;90:6536–6540.
284. Roti E, Gardini E, Minelli R, Bianconi L, Braverman LE. Sodium ipodate and methimazole in the long-term treatment of hyperthyroid Graves' disease. *Metabolism*. 1993;42:403–408.
285. Martino E, Balzano S, Bartalena L, et al. Therapy of Graves' disease with sodium ipodate is associated with a high recurrence rate of hyperthyroidism. *J Endocrinol Invest*. 1991;14:847–851.
286. Fliers E, Alkemade A, Wiersinga WM. The hypothalamic-pituitary-thyroid axis in critical illness. *Best Pract Res Clin Endocrinol Metab*. 2001;15:453–464.
287. Lee E, Chen P, Rao H, Lee J, Burmeister LA. Effect of acute high dose dobutamine administration on serum thyrotrophin (TSH). *Clin Endocrinol*. 1999;50:486–492.
288. Keogh MA, Wittert GA. Effect of cabergoline on thyroid function in hyperprolactinaemia. *Clin Endocrinol*. 2002;57:699.
289. McDermott MT. Hypothyroidism. *Ann Intern Med*. 2020;173(1):ITC1–ITC16. doi:10.7326/AITC202007070
290. Vaidya B, Pearce SH. Management of hypothyroidism in adults. *BMJ*. 2008;337:a801. doi:10.1136/bmj.a801

53

Diabetes Mellitus

Jennifer D. Goldman, Nikhil A. Sangave, and David Schnee

CORE PRINCIPLES		CHAPTER CASES
1	A glycated hemoglobin (A_{1c}) level can be used to diagnose diabetes, in addition to a fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT). Each test must be confirmed on a subsequent day.	**Case 53-1 (Questions 1, 2) Case 53-2 (Question 1) Case 53-11 (Question 1) Case 53-17 (Question 1)**
2	The primary metabolic goals for diabetes are an A_{1c} <7%, a systolic blood pressure <140 mm Hg, and statin therapy for most patients older than age 40. Management of cholesterol should include a statin drug, and management of hypertension should include an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.	**Case 53-2 (Question 2) Case 53-11 (Question 2)**
3	Glycemic treatment goals should be	**Case 53-2 (Question 2) Case 53-4**

	individualized. For patients with a short duration of diabetes, long life expectancy, and no significant vascular disease, more stringent goals can be considered, if it can be achieved without increasing hypoglycemia. For patients with existing vascular disease, other significant macrovascular or microvascular disease, a history of hypoglycemia, or limited life expectancy, or for those with long-standing diabetes who have difficulty lowering their A_{1c}, a less stringent A_{1c} goal should be considered.	**(Question 2) Case 53-11 (Question 2) Case 53-17 (Question 3) Case 53-18 (Question 3)**
4	Medical nutrition therapy (MNT) and physical activity are cornerstones to the treatment of diabetes.	**Case 53-2 (Questions 11, 12) Case 53-11 (Question 3) Case 53-17 (Question 4) Case 53-18 (Question 4)**
5	Self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM) should be performed by all patients with type 1 diabetes and most patients with type 2 diabetes, particularly those on antidiabetic therapy that can cause hypoglycemia or those engaged in self-management. The key to SMBG is to educate patients on how to respond to their blood glucose (BG) levels.	**Case 53-2 (Questions 9–11, 17) Case 53-4 (Questions 1, 5, 7) Case 53-8 (Question 2) Case 53-11 (Question 6) Case 53-21 (Question 1) Case 53-22 (Question 1)**
6	The avoidance of hyperglycemic and hypoglycemic emergencies is critical. Basal-bolus insulin regimens should be	**Case 53-2 (Questions 3-8, 13-16) Case 53-3 (Question 1) Case 53-4 (Question 3, 4, 6)**

	used for patients with type 1 diabetes. These can be administered either by multiple daily injections or by an insulin pump. Basal-bolus insulin regimens are also effective for patients with type 2 diabetes who no longer are able to achieve A_{1c} goals with noninsulin therapies.	**Case 53-5 (Question 1) Case 53-6 (Question 1) Case 53-8 (Questions 1, 3) Case 53-9 (Question 1) Case 53-10 (Questions 1-5) Case 53-13 (Question 5) Case 53-17 (Question 2)**
7	Metformin is the first-line therapy for type 2 diabetes unless a patient has a contraindication to its use or is unable to tolerate this agent. It should be added at diagnosis along with lifestyle changes.	**Case 53-11 (Questions 3–5)**
8	After monotherapy, a second antidiabetic agent should be added to the regimen. Factors to consider include the patient's current comorbidities (history of atherosclerotic cardiovascular disease [ASCVD], chronic kidney disease [CKD], congestive heart failure [CHF], or obesity), A_{1c} goal, the amount of reduction in A_{1c} required, the patient's kidney and liver function, medication side effects, risk of hypoglycemia and cost of therapy.	**Case 53-11 (Questions 7, 8) Case 53-12 (Question 1) Case 53-13 (Questions 1-3, 7) Case 53-14 (Question 1) Case 53-15 (Questions 1, 2) Case 53-16 (Question 1) Case 53-17 (Question 5)**
9	In type 2 diabetes, insulin therapy should be considered any time there are symptoms of hyperglycemia, evidence of catabolism, when A_{1c} is >10% or evidence of high BG levels >300 mg/dL.	**Case 53-11 (Question 7) Case 53-12 (Question 1) Case 53-13 (Question 4)**
10	Owing to concerns about the effects of hypoglycemia and new trials indicating a	**Case 53-7 (Question 1)**

	lack of benefit of very tight glucose control in acutely ill patients, the current-recommended goal BG in hospitalized patients is 140 to 180 mg/dL.	
11	Although acute hyperglycemic crises can occur in patients with diabetes, most morbidity and mortality occur over the course of years and can be classified as either microvascular (nephropathy, neuropathy, and retinopathy) or macrovascular (coronary heart disease [CHD], stroke, and peripheral vascular disease).	**Case 53-18 (Questions 1, 2, 5) Case 53-19 (Questions 1–3) Case 53-20 (Questions 1)**
12	Aspirin therapy may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding.	**Case 53-18 (Question 6)**
13	The incidence and severity of microvascular complications has a strong correlation with long-term glycemic control as measured by A_{1c}. Macrovascular complications are influenced by glycemic control but are more dependent on multiple etiologic factors including dyslipidemia, hypertension, and smoking.	**Case 53-11 (Question 2)**

INTRODUCTION

An estimated 34.2 million people, just over 1 in 10, or 13% of the U.S. population, currently have diabetes. This total includes 7.3 million adults who are not yet diagnosed.[1] Prediabetes can be found in 88 million American adults, ~1 in 3. In 2018, there were 1.5 million new cases in adults diagnosed.[1] New cases diagnosed in adults decreased between 2008 and 2018, but new diagnosed cases of type 1 and type 2 have increased among youth in the United States. Racial and ethnic minorities continue to develop type 2 diabetes at higher rates.[1] Globally, the prevalence of diabetes in 2019 is 9.3% (463 million people) and expected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[2] The incidence of type 2 diabetes is epidemic. This is directly related to obesity, decreased physical activity levels, and also the fact that people with diabetes are living longer.[1] Additional individual factors include a genetic predisposition for increased insulin resistance and progressive β-cell failure. Clinical studies have affirmed that type 2 diabetes can be delayed or prevented in patients with prediabetes when significant lifestyle changes are implemented with or without medications.[3]

DEFINITION, CLASSIFICATION, AND EPIDEMIOLOGY

Diabetes is a chronic condition caused by an absolute lack of insulin or a relative lack of insulin as a result of impaired insulin secretion and action. Its hallmark clinical characteristics are symptomatic glucose intolerance resulting in hyperglycemia and alterations in lipid and protein metabolism. In the long term, these metabolic abnormalities contribute to the development of complications such as cardiovascular disease (CVD), retinopathy, nephropathy, and neuropathy and a higher risk of cancer.[4–7]

Genetically, etiologically, and clinically, diabetes is a heterogeneous group of disorders. Nevertheless, most cases of diabetes mellitus (DM) can be assigned to type 1 or type 2 diabetes

(**Table 53-1**). The term gestational diabetes mellitus (GDM) is used to describe glucose intolerance that has its onset during pregnancy. Glucose intolerance that cannot be ascribed to causes consistent with these three classifications includes specific genetic defects in β-cell function or insulin action (usually genetically defective insulin receptors); diseases of the exocrine pancreas; endocrinopathies; drug- or chemical-induced; infections; and other genetic syndromes. Early glucose intolerance or "prediabetes" is identified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), and they are considered risk factors for the future development of diabetes and are associated with obesity, hypertriglyceridemia, and/or low high-density lipoprotein (HDL) cholesterol and hypertension.[4,5]

Table 53-1
Type 1 and Type 2 Diabetes

Characteristics	Type 1	Type 2
Other names	Previously, type I; insulin-dependent diabetes mellitus (IDDM); juvenile-onset diabetes mellitus	Previously, type II; non–insulin-dependent diabetes mellitus (NIDDM); adult-onset diabetes mellitus
Percentage of diabetic population	5%–10%	90%
Age at onset	Usually <30 years; peaks at 12–14 years; rare before 6 months; some adults develop type 1 during the fifth decade.	Usually >40 years, but increasing prevalence among obese children
Pancreatic function	Usually none, although some residual C-peptide can sometimes be detected at diagnosis, especially in adults	Insulin present in low, "normal," or high amounts
Pathogenesis	Associated with certain HLA types; presence of islet cell antibodies suggests autoimmune process.	Defect in insulin secretion; tissue resistance to insulin; ↑ hepatic glucose output

Characteristics	Type 1	Type 2
Family history	Generally not strong	Strong
Obesity	Uncommon	Common (60%–90%)
History of ketoacidosis	Often present	Rare, except in circumstances of unusual stress (eg, infection)
Clinical presentation	Moderate-to-severe symptoms that generally progress relatively rapidly (days to weeks): polyuria, polydipsia, fatigue, weight loss, ketoacidosis	Mild polyuria, fatigue; often diagnosed on routine physical or dental examination
Treatment	MNT	MNT
	Physical activity	Physical activity
	Insulin Amylin mimetic (pramlintide)	Antidiabetic agents (biguanides, glinides, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, incretin mimetics/analogs, DPP-4 inhibitors, SGLT-2 inhibitors)
	Insulin	Insulin
Amylin mimetic (pramlintide)		Amylin mimetic (pramlintide)

DPP-4, dipeptidyl peptidase-4; HLA, human leukocyte antigen; MNT, medical nutrition therapy; SGLT2, sodium–glucose transporter 2.

Approximately 5% to 10% of the diagnosed diabetic population has type 1 diabetes, which usually results from autoimmune destruction of the pancreatic β cells. At clinical presentation, these patients have little or no pancreatic reserve, have a tendency to develop ketoacidosis, and require exogenous insulin to sustain life. The incidence of autoimmune-mediated type 1 diabetes peaks during childhood and adolescence, but it can occur at any age. A minority of patients diagnosed with type 1 diabetes, mostly of African or Asian ancestry, can have no evidence of autoimmunity; the etiology is, therefore, unknown. In these individuals, the rate of pancreatic destruction seems to occur more slowly, leading to a later onset and less acute presentation.[4]

Most people with diabetes have type 2 diabetes, a heterogeneous disorder that is characterized by obesity, β-cell dysfunction, resistance to insulin action, and increased hepatic glucose production. Both the incidence and prevalence of diabetes increase dramatically with age, obesity, and lack of physical activity.[4] In the United States, the percentage of patients with diagnosed or undiagnosed diabetes in those ages 18 to 44 years is 4.1%. This increases to 26.8% in those 65 and older.[1] The prevalence of type 2 diabetes also differs among adult ethnic populations. Relative to non-Hispanic Whites (7.9%), the prevalence of diagnosed diabetes is higher in Asian Americans (11.3%), Hispanics (13.7%), African Americans (11.7%), and American Indians and Alaskan Natives (14.7%).[1] Diabetes is a serious condition that places people at risk for greater morbidity and mortality relative to the nondiabetic population. Diabetes is the seventh leading cause of death in the United States, although deaths attributed to diabetes and its complications are likely to be underreported. Compared with the general population, the mortality rate for people with diabetes is about twice that for people without diabetes.[1]

Medical management of people with diabetes is costly. In 2017, the total cost of diabetes in the United States was estimated to be $327.2 billion, with 1 of 4 health care dollars being spent on people with diabetes.[8] The average health care expenditures for people with diabetes were ~2.3 times higher than those for individuals without diabetes. The majority (56%) of all health care expenditures attributed to diabetes are used by people ages 65 years and older. Hospital inpatient costs, nursing facility resources, home care, physician visits, and medications (not just diabetes agents) made up the majority of these expenditures. Because many expenditures are related to the treatment of long-term complications, considerable effort has been directed toward early diagnosis and metabolic control of patients with diabetes.[8]

CARBOHYDRATE METABOLISM

An understanding of the signs and symptoms associated with diabetes is based on a knowledge of glucose metabolism and the metabolic effects of insulin in nondiabetic subjects and in subjects with diabetes during the fed (postprandial) and fasting (postabsorptive) states.[9] Homeostatic mechanisms maintain plasma glucose concentrations between 55 and 140 mg/dL. A minimum concentration of 40 to 60 mg/dL is required to provide adequate fuel for the central nervous system, which uses glucose as its primary energy source and is independent of insulin for glucose utilization. When BG concentrations exceed the reabsorptive capacity of the proximal tubule in the kidneys (~180 mg/dL), glucose spills into the urine (glucosuria), resulting in a loss of calories and water. Muscle and fat, which use glucose as a major source of energy, require insulin for glucose uptake. If glucose is unavailable, these tissues are able to use other substrates such as amino acids and fatty acids for fuel.[9]

Postprandial Glucose and Lipid Metabolism in the Nondiabetic Individual

After food is ingested, BG concentrations rise and stimulate insulin release. Insulin is the key to efficient glucose utilization. It promotes the uptake of glucose, fatty acids, and amino acids, and their conversion to storage forms in most tissues. Insulin also inhibits hepatic glucose production by suppressing glucagon and its effects. In muscle, insulin promotes the uptake of glucose and its storage as glycogen. It also stimulates the uptake of amino acids and their conversion to protein. In adipose tissue, glucose is converted to free fatty acids and stored as triglycerides. Insulin also prevents a breakdown of these triglycerides to free fatty acids, a form that may be transported to other tissues for utilization. The liver does not require insulin for glucose transport, but insulin facilitates the conversion of glucose to glycogen and free fatty acids.[9,10]

Free fatty acids are esterified to triglycerides, which are transported by very-low-density lipoproteins (VLDLs) to adipose and

muscle tissue. Normal insulin signaling suppresses VLDL secretion by reducing the production of fatty acids in the liver.[10] Once secreted by the liver, VLDL is acted on primarily by hepatic lipase in the liver and by lipoprotein lipase on endothelial cells.[10] Acting through apolipoprotein (apo) CII on the surface of the VLDL particle, these lipases remove free fatty acids from the lipoprotein and convert VLDL to intermediate-density lipoprotein (IDL) and then IDL to low-density lipoprotein (LDL). Insulin plays a role in stimulating apoCII expression, which partly explains the hypertriglyceridemia that occurs in type 2 diabetes.[10]

Fasting Glucose Metabolism in the Nondiabetic Individual

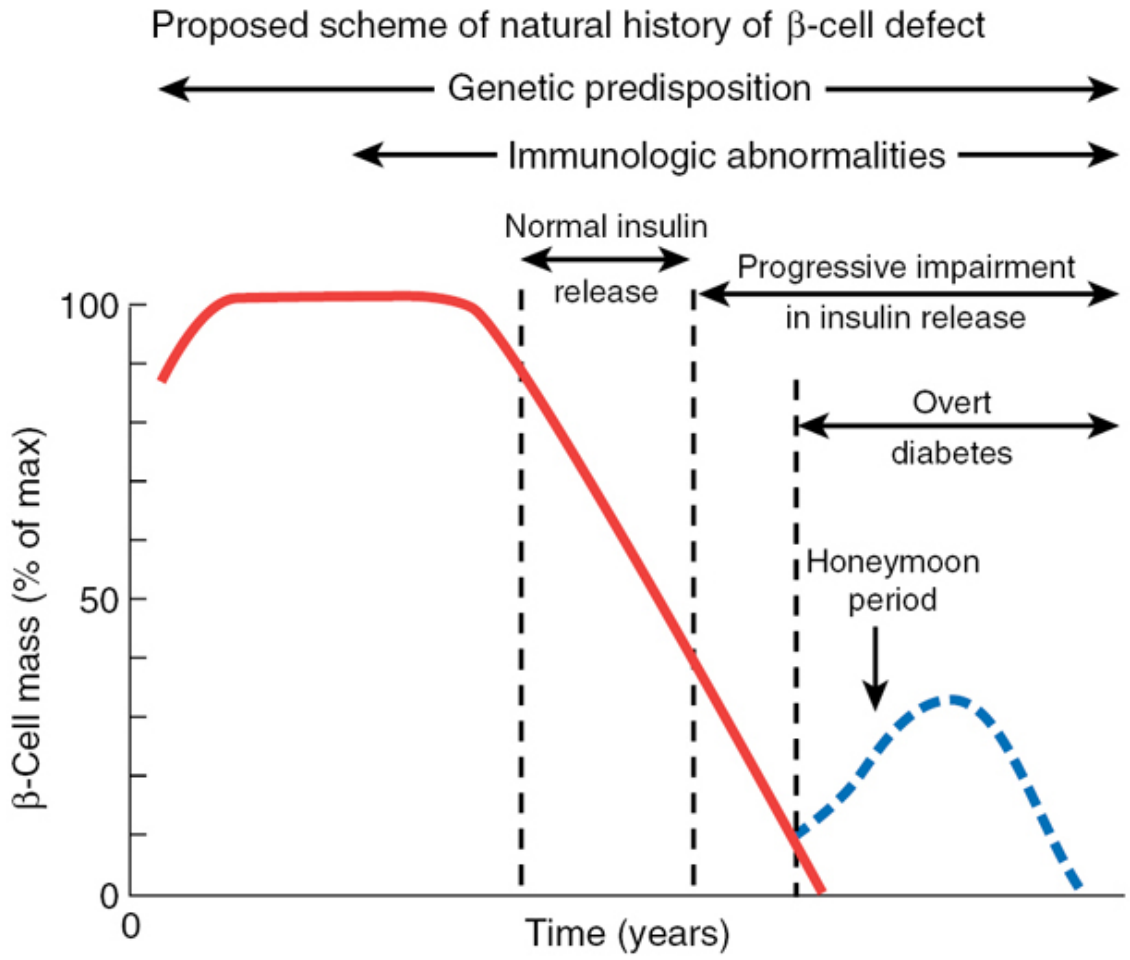
As BG concentrations drop toward normal during the fasting state, insulin release is inhibited. Simultaneously, a number of counterregulatory hormones that oppose the effect of insulin and promote an increase in blood sugar are released (eg, glucagon, epinephrine, growth hormone, and cortisol). As a result, several processes maintain a minimum BG concentration for the central nervous system. Glycogen in the liver is broken down into glucose (glycogenolysis). Amino acids are transported from muscle to liver, where they are converted to glucose through gluconeogenesis. Uptake of glucose by insulin-dependent tissues is diminished to conserve glucose for the brain. Finally, triglycerides are broken down into free fatty acids, which are used as alternative fuel sources.[9,10]

TYPE 1 DIABETES

Pathogenesis

The loss of insulin secretion in type 1 DM results from autoimmune destruction of the insulin-producing β cells in the pancreas, which is thought to be triggered by environmental factors, such as viruses or

toxins, in genetically susceptible individuals.[4,11] This form of diabetes is associated closely with histocompatibility antigens (human leukocyte antigen [HLA]-DR3 or HLA-DR4) and the presence of circulating antibodies, including insulin autoantibodies, glutamic acid decarboxylase (GAD65) autoantibodies, islet cell autoantibodies (ICAs), and autoantibodies to tyrosine phosphatases (eg, ICA 512). The capacity of normal pancreatic β cells to secrete insulin far exceeds the normal amounts needed to control carbohydrate, fat, and protein metabolism. As a result, the clinical onset of type 1 diabetes is preceded by an extensive asymptomatic period during which β cells are destroyed (**Fig. 53-1**). β-cell destruction may occur rapidly but is more likely to take place over a period of weeks, months, or even years. The earliest detectable abnormality in insulin secretion is a progressive reduction of immediate or first-phase plasma insulin response. However, this initial impairment has few detrimental effects on overall glucose homeostasis, and plasma glucose concentrations remain normal. Most affected individuals have circulating antibodies to islet cells or to their own insulin at this stage of the disease. These represent markers of an ongoing autoimmune process that culminates in type 1 diabetes. Fasting hyperglycemia occurs when the β-cell mass is reduced by 80% to 90%. One or more of these autoantibodies is usually present in 85% to 90% of individuals at this point. Initially, only postprandial hyperglycemia occurs, but as insulin secretion becomes further compromised, progressive fasting hyperglycemia is seen. Within 8 to 10 years of clinical presentation, β-cell loss is complete and insulin deficiency is absolute.[4,11]



Timing of trigger in relation to immunologic abnormalities is unknown. Note that overt diabetes is not apparent until insulin secretory reserves are <10%–20% of normal.

Figure 53-1 Pathogenesis of type 1 diabetes. In an individual with a genetic predisposition, an event (such as a virus or toxin) triggers autoimmune destruction of the pancreatic β cells, probably during a period of several years. When the number of β cells diminishes to ~250,000, the pancreas is unable to secrete sufficient insulin, and intolerance to glucose ensues. At this point, a stressful event, such as a viral infection, can produce acute symptoms of hyperglycemia and ketoacidosis. Once the acute event has passed, the pancreas temporarily recovers, leading to a remission (honeymoon period). Continued destruction of the β cell ultimately leads to an insulin-dependent state.

Clinical Presentation

Although the onset of type 1 diabetes seems to be abrupt, evidence now exists for an extended preclinical period that can precede obvious symptoms by several years. Because insulin secretion becomes compromised, progressive fasting hyperglycemia occurs. Glucosuria, which occurs when BG levels exceed the renal threshold, results in an osmotic diuresis, producing the classic symptoms of polyuria with compensatory polydipsia. If symptoms are untreated, weight loss occurs because glucose calories are lost in the urine, and body fat and protein stores are broken down owing to increased rates of lipolysis and proteolysis. Muscle begins to metabolize its own glycogen stores and fatty acids for fuel, and the liver begins to metabolize free fatty acids that are released in response to epinephrine and low insulin concentrations. An absolute lack of insulin may cause excessive mobilization of free fatty acids to the liver, where they are metabolized to ketones. This can result in ketonemia, ketonuria, and, ultimately, ketoacidosis. Patients present with fatigue, significant weight loss, polyuria, and polydipsia. A significant elevation in A_{1c} confirms weeks or months of preceding hyperglycemia.

Because glucose provides an excellent medium for microorganisms, patients may present also with recurrent respiratory, vaginal, and other infections. Patients also may experience blurred vision secondary to osmotically induced changes in the lens of the eye. Treatment with insulin is essential to prevent severe dehydration, ketoacidosis, and death.[4,7,11]

Honeymoon Period

Within days or weeks of the initial diagnosis and implementing treatment, many patients with type 1 diabetes experience an apparent remission, which is reflected by decreased BG concentrations and markedly decreased insulin requirements. This is called the *honeymoon period* because it may last for only a few weeks to months. Once hyperglycemia, metabolic acidosis, and ketosis resolve, endogenous insulin secretion recovers temporarily

(Fig. 53-1). Although the honeymoon period may last for up to a year, increasing exogenous insulin requirements are inevitable and should be anticipated. During this time, patients should be maintained on insulin even if the dose is very low because interrupted treatment is associated with a greater incidence of resistance and allergy to insulin.[12]

TYPE 2 DIABETES

Pathogenesis

Type 2 diabetes is characterized by impaired insulin secretion and resistance to insulin action. In the presence of insulin resistance, glucose utilization by tissues is impaired, hepatic glucose and free fatty acid production is increased, and excess glucose accumulates in the circulation. This hyperglycemia stimulates the pancreas to produce more insulin in an attempt to overcome insulin resistance. The simultaneous elevation of both glucose and insulin levels is strongly suggestive of insulin resistance. Genetic predisposition may play a role in the development of type 2 diabetes. People with type 2 diabetes have a stronger family history of diabetes than do those with type 1. There is no association with HLA types, however, and circulating ICAs are absent.[13,14] People with type 2 diabetes also exhibit varying degrees of tissue resistance to insulin, impaired insulin secretion, and increased basal hepatic glucose production. Finally, environmental factors such as obesity and a sedentary lifestyle also contribute to the development of insulin resistance.

Despite being the most common form of diabetes, the exact pathogenesis of type 2 is less well understood. Basal insulin levels are typically normal or elevated at diagnosis. First- or early-phase insulin release in response to glucose often is reduced, and pulsatile insulin secretion is absent, resulting in postprandial hyperglycemia. The effects of other insulinotropic substances such as incretin hormones, which contribute to meal-stimulated insulin release, are

also altered.[15] With time, β cells lose their ability to respond to elevated glucose concentrations, leading to increased loss of glucose control. In patients with severe hyperglycemia, the amount of insulin secreted in response to glucose is diminished, and insulin resistance is worsened (glucose toxicity).

Most individuals with type 2 exhibit decreased tissue responsiveness to insulin.[13] Excess weight or hyperglycemia may contribute to hyperinsulinemia, which in time may lead to a decrease in or downregulation of the number of insulin receptors on the surface of target tissues and organs. Evidence suggests that decreased peripheral glucose uptake and utilization in muscle is the primary site of insulin resistance and results in prolonged postprandial hyperglycemia. Resistance may be secondary to decreased numbers of insulin receptors on the cell surface, decreased affinity of receptors for insulin, or defects in insulin signaling and action that follows receptor binding. Defects in insulin signaling and action are referred to as *postreceptor* or *postbinding defects* and are likely to be the primary sites of insulin resistance.

Patients with type 2 diabetes also exhibit increased hepatic glucose production (glycogenolysis and gluconeogenesis) reflected by an elevated fasting plasma or BG concentration.[13] As noted, hepatic glucose production is the primary source of glucose in the fasting state. In patients with type 2 diabetes, altered hepatic glucose production may also contribute to or cause postprandial hyperglycemia. Glucagon, produced by the α-cells in the pancreatic islets and secreted in response to low BG, stimulates hepatic glucose production.[16] Its production is inhibited by insulin. Glucagon response to carbohydrate ingestion is altered in patients with type 2 diabetes who have a defective or absent early insulin response secondary to β-cell dysfunction or failure. For patients with type 2 diabetes, untreated fasting and postprandial hyperglycemia caused by decreased glucose uptake and increased hepatic glucose production, hyperinsulinemia, and insulin resistance lead to a vicious cycle that inflicts ongoing damage to tissues and organs. Type 2 diabetes is a multifactorial disease and eight core defects were first described and called the *Ominous Octet*.[17] These eight defects

include (1) decreased insulin secretion, (2) decreased incretin effect, (3) increased lipolysis, (4) increased glucose reabsorption, (5) decreased glucose uptake, (6) neurotransmitter dysfunction, (7) increased hepatic glucose production, and (8) increased glucagon secretion.[17] The Ominous Octet was followed by the "Egregious Eleven," which further expanded on these eight pathophysiologic defects and added three more: (9) systemic low-grade inflammation, (10) changes in gut microbiota, and (11) reduction in amylin production.[18] Various drug therapies impact one or multiple of these defects.

Patients with type 2 diabetes are often subclassified based on weight. Obese individuals account for >80% of patients with type 2 diabetes.[13] Patients with type 2 diabetes who are not obese often have increased body fat distributed in the abdominal area. Nonobese individuals account for about 10% of the type 2 population. Typically, they develop a mild form of diabetes during childhood, adolescence, or as young adults (usually before age 25), and their insulin levels are low in response to a glucose challenge. Included in this group are patients who have maturity-onset diabetes of the young (MODY).[4,13] MODY is associated with a strong family history that suggests an autosomal dominant transmission. The underlying defect is heterogeneous, and multiple abnormalities at loci on different chromosomes have been discovered. More common defects include those for hepatic transcription factors and glucokinase (the "glucose sensor" in β cells). Patients with MODY may present with moderate-to-severe symptoms with or without ketosis. Unlike type 1 diabetes, however, the disease generally is mild and controlled with diet, oral agents, or low doses of insulin. With the increasing prevalence of obesity and type 2 diabetes in children and adolescents, it is important to distinguish between a youth with type 2 diabetes and one who really has autoimmune type 1 diabetes and is also obese.[19]

Type 2 diabetes is associated with a variety of comorbid disorders, including dyslipidemia, hypertension, and premature atherosclerosis (**Fig. 53-2**). Currently termed the *metabolic syndrome*, this triad of clinical findings (hypertension, elevated fasting glucose, and

dyslipidemia) is proposed to derive from insulin resistance itself and the resulting compensatory hyperinsulinemia.[20] The labeling of this triad as a separate “syndrome” remains the subject of considerable debate, partly because it appears to have little diagnostic utility beyond its component parts.[21] Metabolic syndrome is common in the United States. Utilizing the National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2013, it was estimated that nearly 35% of all adults and 50% of those older than age 60 have metabolic syndrome.[22] Metabolic syndrome is highly correlated with cardiovascular (CV) events.[23] Not all individuals with the metabolic syndrome progress to IGT or diabetes, but those who do may be genetically predisposed to β-cell dysfunction. **Figure 53-3** depicts the typical dyslipidemia pattern seen in diabetes and how insulin resistance affects normal lipoprotein metabolism.[20,21]

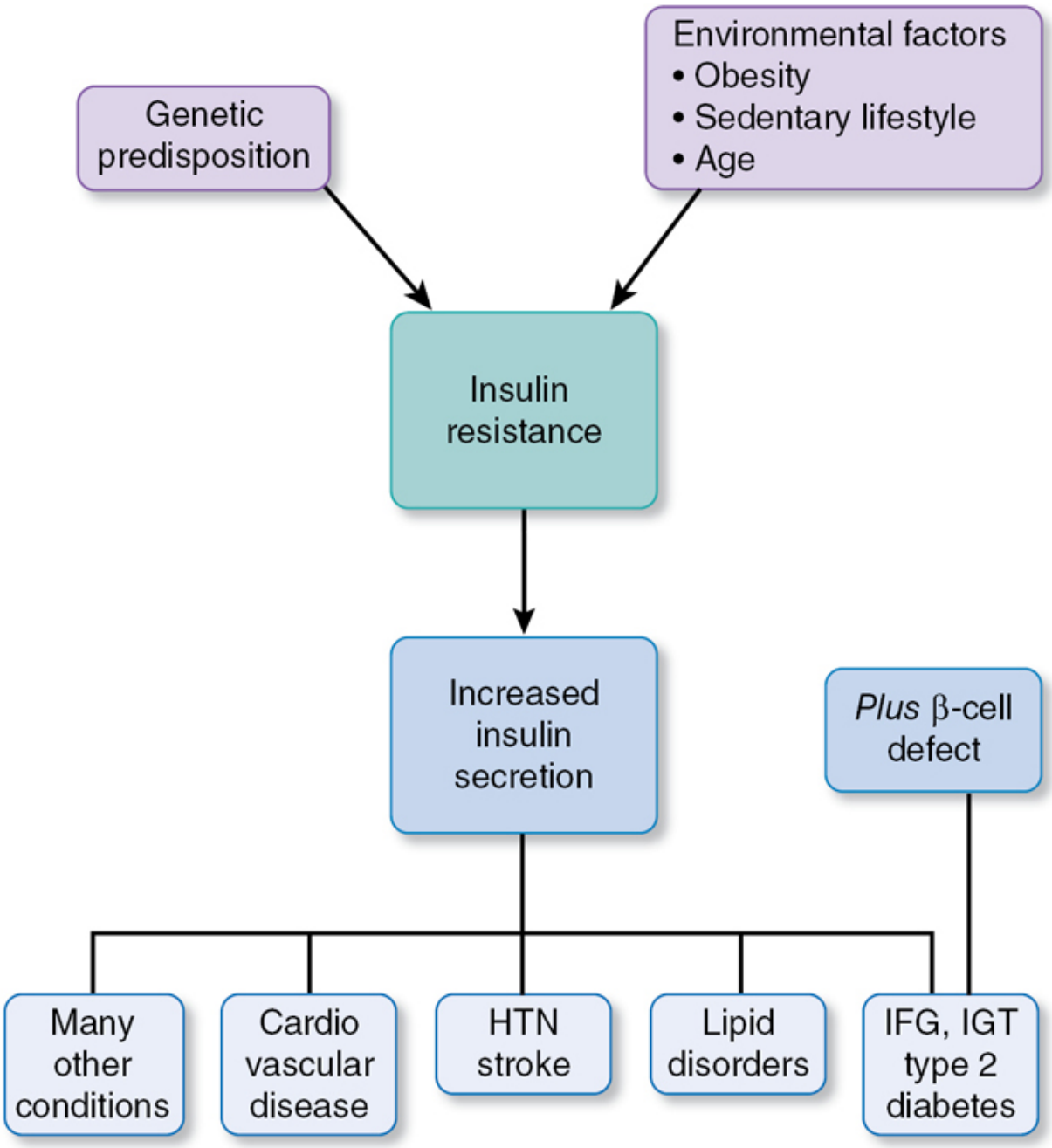


Figure 53-2 Metabolic syndrome. Genetic and environmental factors (visceral obesity, sedentary lifestyle, and aging) predispose some individuals to insulin resistance. To overcome the resistance, the pancreas secretes more insulin, leading to hyperinsulinemia. People with insulin resistance and hyperinsulinemia commonly develop a cluster of medical problems and biochemical abnormalities: cardiovascular disease, hypertension, dyslipidemia, hyperuricemia, and type 2 diabetes mellitus. Only those individuals

who are further genetically predisposed to β-cell failure go on to develop IGT, IFG, and type 2 diabetes. Many people with type 2 diabetes already have evidence of cardiovascular disease at the time of diabetes diagnosis. The cause-and-effect relationship between insulin resistance or hyperinsulinemia and these clinical conditions has not been clarified. See text for expanded discussion. HTN, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

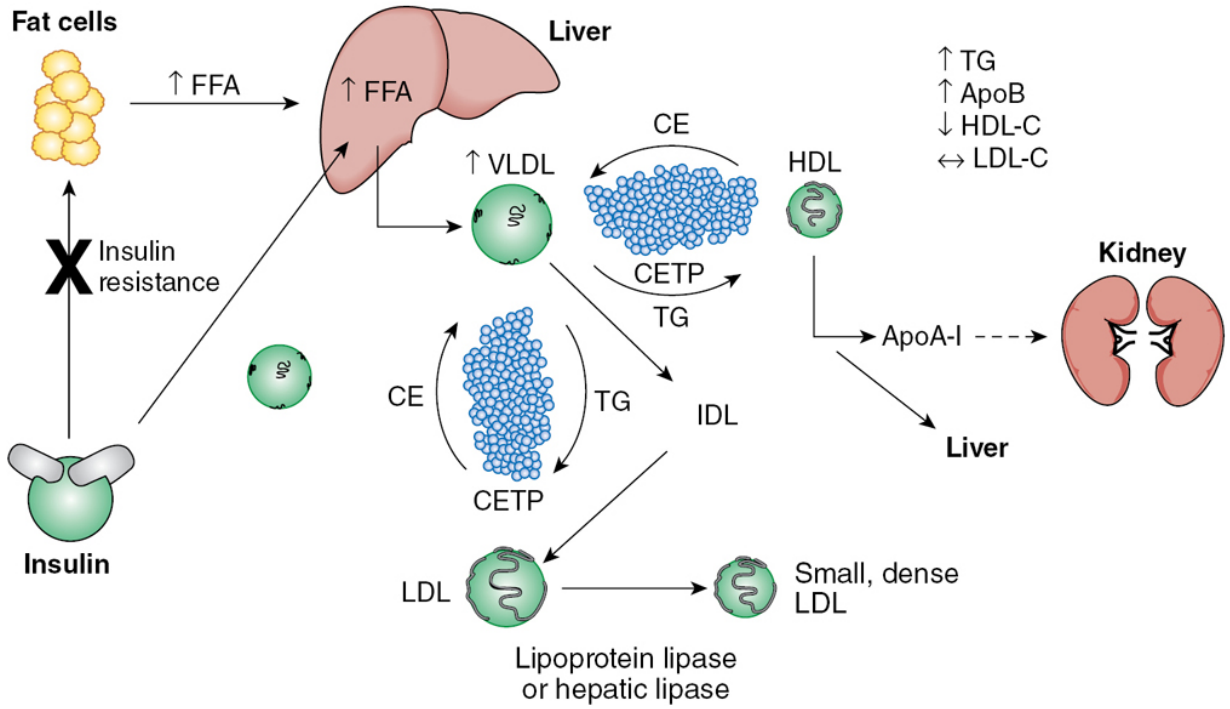


Figure 53-3 Changes in lipoprotein metabolism are a direct consequence of insulin resistance and are present before the onset of overt diabetes. Apo, apolipoprotein; CE, cholesteryl esters; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; VLDL, very-low-density lipoprotein.

Clinical Presentation

Type 2 diabetes is typically diagnosed incidentally during a routine physical examination or when the patient seeks other medical attention. Because symptoms are mild in their onset, patients will rarely report symptoms of fatigue, polyuria, and polydipsia, but may admit to them during clinical examination. Because these patients have sufficient insulin concentrations to prevent lipolysis, there is usually no history of ketosis except in situations of unusual stress (eg, infections and trauma). Weight loss is therefore uncommon because relatively high endogenous insulin levels promote lipogenesis. Macrovascular disease is typically evident at diagnosis. Microvascular complications at diagnosis suggest the presence of undiagnosed or subclinical diabetes for 7 to 10 years. Because patients with type 2 diabetes retain some pancreatic reserve at the time of diagnosis, they generally can be treated with MNT, physical activity, and noninsulin antidiabetic medications for several years. Nevertheless, many eventually require insulin for control of their symptoms.[24]

Screening

The American Diabetes Association (ADA) advises that adults without risk factors should be screened starting at age 45.[4] Repeat testing should take place every 3 years if results are normal or yearly if they have prediabetes. Adults may be tested at a younger age and more frequently if they are overweight (body mass index [BMI] ≥25 or 23 kg/m^2 in Asian Americans) and have one or more of the risk factors listed in **Table 53-2**. An FPG or A_{1c} is preferred over the OGTT to test for diabetes, because they are much less cumbersome, although all are equally appropriate for diagnosis. Asymptomatic children who are age 10 or who experience the onset of puberty before age 10 should be screened for type 2 diabetes if they are overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) for age and sex and have one or more risk factors listed in Table 53-2.[4]

Table 53-2
Risk Factors for Type 2 Diabetes Mellitus

Adults	Children[a]
Overweight (≥25 kg/m^2 or (≥23 kg/m^2 in Asian Americans))	Overweight (BMI >85th percentile for age and sex; or weight >120% of ideal for height)
Family history of diabetes (first-degree relative)	Family history of diabetes (first- or second-degree relative)
Physical inactivity	
Ethnic predisposition[b]	Ethnic predisposition[b]
Previous IFG, IGT, or A_{1c} ≥5.7%	
History of PCOS, GDM, or macrosomia	Maternal history of diabetes (including GDM)
Clinical conditions associated with insulin resistance (eg, severe obesity and acanthosis nigricans)	Signs of insulin resistance (eg, acanthosis nigricans)
Hypertension (≥140/90 mm Hg or on antihypertensive therapy)	Conditions associated with insulin resistance (eg, hypertension, dyslipidemia, or PCOS)
Dyslipidemia	
HDL-C <35 mg/dL (0.90 mmol/L)	
Triglyceride >250 mg/dL (2.82 mmol/L)	
Cardiovascular disease	

A_{1c}, glycated hemoglobin; BMI, body mass index; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PCOS, polycystic ovarian syndrome.

[a]Children are younger than age 18 years.

[b]Ethnic predisposition includes individuals of African American, Latino, Native American, Asian, or Pacific Islander descent.

Source: American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S15–S33. doi:10.2337/dc21-S002.

GESTATIONAL DIABETES MELLITUS

GDM affects about 7% of all pregnancies and is defined as "any carbohydrate intolerance with onset or first recognition during pregnancy."[4,25] The onset of diabetes during pregnancy and its duration affects the prognosis for a good obstetric and perinatal outcome (see Chapter 49, Obstetric Drug Therapy).

Diagnostic Criteria

The categories for normal diabetic plasma glucose levels, increased risk for diabetes, and diabetic plasma glucose levels for FPG, A_{1c}, and the OGTT are listed in **Table 53-3**.[26] The Expert Committee of the ADA has established the diagnostic criteria for diabetes for nonpregnant individuals of any age. For these individuals, a diagnosis of diabetes can be made when one of the following is present[4]:

Table 53-3
Diagnostic Criteria for Prediabetes and Diabetes

	FPG (in mg/dL [mmol/L])	A_{1c}	OGTT (in mg/dL [mmol/L])
Normal	<100 (5.6)	≤5.6%	<140 (7.8)
Prediabetes (ie, IFG, IGT)	100–125 (5.6–6.9)	≥5.7%–6.4%	140–199 (7.8–11.0)
Diabetes (nonpregnant adult)	≥126 (7.0)	≥6.5%	≥200 (11.1)

Equivalent venous whole-blood glucose concentrations are ~12%–15% lower. Arterial samples are higher than venous samples postprandially because glucose has not yet been removed from peripheral tissues. Capillary whole-blood samples contain a mixture of arterial and venous blood. Fasting levels are equivalent to whole-blood venous samples.

A_{1c}, glycated hemoglobin; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

Sources: American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S73–S84. doi:10.2337/dc21-S006.

1. An A_{1c} of ≥6.5%: The test must be performed in a laboratory (not with a point-of-care test). It should be performed using a method

certified by the National Glycohemoglobin Standardization Program.

2. An FPG of ≥126 mg/dL: *Fasting* means no caloric intake for at least 8 hours.
3. Classic signs and symptoms of diabetes (polyuria, polydipsia, ketonuria, and unexplained weight loss) combined with a random plasma glucose of ≥200 mg/dL.
4. After a standard OGTT (75 g of glucose for an adult or 1.75 g/kg for a child), the venous plasma glucose concentration is ≥200 mg/dL at 2 hours.[4]

The diagnosis must be confirmed by repeating the test, preferably the same test in the absence of unequivocal hyperglycemia. If two different tests are performed (eg, FPG and A_{1c}), and both are above the diagnostic threshold, then diabetes is confirmed. If only one test's value is above the diagnostic cut point, the test that is above the diagnostic cut point should be repeated. The diagnosis is made based on the results of the confirmed test.[4]

At times, it may be difficult to classify patients as having type 1 or type 2 DM. Type 1 is more likely when a patient is younger than age 30 years, lean, and has an elevated FPG and signs and symptoms of diabetes. The presence of moderate ketonuria with hyperglycemia in an otherwise unstressed patient also strongly supports a diagnosis of type 1 diabetes. Absence of ketonuria, however, is not of diagnostic value. The presence of autoantibodies to insulin or islet cell components may also indicate the need for eventual insulin therapy.[4,27] Relatively, lean older adults believed to have type 2 diabetes because they are initially responsive to oral agents or low doses of insulin may be subsequently diagnosed with type 1 diabetes. In addition, clinicians are beginning to observe more cases of type 2 diabetes in obese children and adolescents.[4,25] Individuals with A_{1c}, FPG, or OGTT values that are intermediate between normal and those considered diagnostic of diabetes are considered to have prediabetes. The terms IFG and IGT should not be used interchangeably because each results from somewhat different

physiologic processes. It is important to interpret the categories listed in Table 53-3 as a continuum of increased risk for diabetes, rather than focus on the absolute cutoff points for prediabetes or diabetes.

Many factors can impair glucose tolerance or increase plasma glucose. These must be excluded before a definitive diagnosis is made. For example, an individual who has not fasted for a minimum of 8 hours may have an elevated FPG. Patients who are tested for glucose tolerance during, or very soon after, an acute illness (eg, a myocardial infarction [MI]) or who are on corticosteroids (eg, prednisone and dexamethasone) may be misdiagnosed because of the presence of high concentrations of counterregulatory hormones that increase glucose concentrations. Glucose tolerance often returns to normal in these individuals.[28]

LONG-TERM COMPLICATIONS

Although acute hyperglycemic crises can occur in patients with diabetes, the long-term sequelae of diabetes account for most of the morbidity and mortality in the diabetic population. Complications are typically designated as microvascular or macrovascular in nature. Glucose toxicity contributes most to the development and progression of microvascular complications (retinopathy, nephropathy, and neuropathy) owing to the particular susceptibility of these cell systems to elevated glucose.[7] Diabetes is the leading cause of new cases of adult blindness and kidney failure in the United States.[1] About 60% to 70% of people with diabetes also have some manifestation of peripheral or autonomic neuropathy. Severe peripheral neuropathy coupled with abnormalities in immune function likely contributes to the high rate of lower extremity amputations among patients with diabetes.[1,7] Finally, poor glucose control promotes the development of dental and oral complications and increases the risk of complications during pregnancy for both mother and fetus.[25,29] Macrovascular complications are multifactorial in their

etiology and less dependent on hyperglycemia. DM itself is a well-known risk factor for macrovascular disease (peripheral vascular disease, CVD, and stroke). Despite a significant decline in all diabetes-related complications over the course of time, patients with diabetes have an eight times greater risk of acute MI and a 6.7 times greater risk of stroke when looking at the data for the 2010 time point.[30] An assessment of patients enrolled in the Framingham Heart Study showed that those with diabetes are at a three times greater risk of CVD-related mortality than are those without diabetes.[31] Thus, although tight glycemic control (A_{1c} <7.0%) will dramatically reduce the risk of microvascular disease, its relationship to macrovascular disease is still under intense debate.

RELATIONSHIP OF GLYCEMIC CONTROL TO MICROVASCULAR AND MACROVASCULAR DISEASE

Although epidemiologic studies have shown a general relationship between glucose control and CV events, recent randomized trials have failed to confirm a benefit of tight glucose control compared with standard control, which highlights the multifactorial nature of macrovascular disease.[32] However, the clear relationship between microvascular events and glycemic control is well established from randomized, clinical trials. The Diabetes Control and Complications Trial (DCCT), which included patients with T1DM, and the open-label follow-up trial, DCCT-EDIC (Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications), established the benefits of intensive glycemic control on microvascular end points.[33,34] In the DCCT, intensive treatment (A_{1c} 7.1% vs 9.0%) reduced the risk of clinically meaningful retinopathy, nephropathy, and neuropathy by ~60%. The Epidemiology of Diabetes Interventions and Complications (EDIC) study was followed as an open-label extension of the DCCT cohorts. Patients originally

assigned to the intensive treatment group were shown to have a persistently lower incidence of microvascular complications even after the glucose control reached parity between the two study groups after the end of the randomized portion of the trial.[34,35] The EDIC study also showed a significant reduction in CV complications among patients previously assigned to the intensive therapy DCCT arm.[36] See **Table 53-4** for the glycemic goals of intensive insulin therapy (herein called *physiologic* or *basal-bolus therapy*). This persistence of the microvascular benefits of glycemic control has also been demonstrated in patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) (see Case 53-11, Question 2).[37]

Table 53-4
Goals of Physiologic (Basal-Bolus) Insulin Therapy

Monitoring Parameter	Adults (mg/dL)	School Age (6–12 years) (mg/dL)	Adolescents and Young Adults (13–29 years) (mg/dL)	Pregnancy (mg/dL)
Premeals	80–130	90–130	90–130	60–99
2-Hour postprandial plasma glucose	<180	Not routinely recommended	Not routinely recommended	100–129
Bedtime/overnight (2:00–4:00 AM) plasma glucose	>70	90–150	90–150	60–99
A_{1C}[a]	<7.0%[b]	<7.5%[c]	<7.5%[c]	<6%
Urine ketones[d]	Absent to rare	Absent to rare	Absent to rare	Rare

See Case 53-2, Question 2, and Case 53-4, Question 2, for discussion. Basal-bolus insulin therapy is a complete therapeutic program of diabetes management and requires a team approach.

[a]A_{1c}, glycated hemoglobin, referenced to a nondiabetic range of 4% to 6% using a Diabetes Control and Complications Trial (DCCT)-based assay.

[b]Acceptable values should be individualized to levels that are attainable without creating undue risk for hypoglycemia. These results are similar to the results achieved in the DCCT trial. The American Diabetes Association recommends consideration for a lower goal (eg, <6%) in individuals with a short duration of diabetes, long life expectancy, and no significant cardiovascular disease. Less stringent goals may be appropriate for patients with hypoglycemic unawareness, history of severe hypoglycemia, counterregulatory insufficiency, advanced microvascular or macrovascular complications, or other complicating features (Table 53-10).

[c]A lower goal (<7%) is reasonable if it can be achieved without creating excessive risk of hypoglycemia.

[d]Does not apply to patients with type 2 diabetes.

Sources: American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S73–S84. doi:10.2337/dc21-S006. American Diabetes Association. 13. *Children and adolescents: Standards of Medical Care in Diabetes—2021. Diabetes Care*. 2021;44(suppl 1):S180–S199. doi:10.2337/dc21-S013; 25. American Diabetes Association. 14. Management of diabetes in pregnancy: *Standards of Medical Care in Diabetes—2021. Diabetes Care*. 2021;44(suppl 1):S200–S210.doi:10.2337/dc21-S014

The relationship between glycemic control and macrovascular disease has always been less clear. Evidence of early atherosclerosis in patients with type 1 diabetes in whom dyslipidemia and hypertension are typically absent argues strongly for a role of hyperglycemia itself in the development or progression of macrovascular disease.[38] The UKPDS trial was the first to report the benefit of tight BG control on CV complications in type 2 diabetes.[39] Although the microvascular benefits were clear, the 21% relative risk reduction for fatal and nonfatal MI and sudden cardiac death failed to reach statistical significance (P = .052). However, in a planned 10-year follow-up of patients enrolled in the trial, a significant 15% reduction was seen in the risk of MI (P = .01).[37] A similar finding for macrovascular benefit was reported in a 17-year follow-up of the DCCT-EDIC study.[36] Thus, although glycemic control benefited macrovascular disease, it took more than a decade to see the benefit. Reducing macrovascular risk in patients with diabetes thus takes a more comprehensive approach than does just glycemic control. In a trial of multiple risk factor control in type 2 diabetes, the STENO-2 trial found a significant 53% reduction in macrovascular events, with modest control of hypertension, dyslipidemia, and glycemia simultaneously.[40] Control of all major CVD risk factors is highlighted by the ADA for its importance in reducing macrovascular disease risk.[5] See **Table 53-5** for the metabolic goals for adults with diabetes.[41,42]

Table 53-5
American Diabetes Association Metabolic Goals for Adults With

Diabetes Mellitus

Glycemic goals	
A_{1c}	<7.0% (normal, 4%–6%)[a]
Preprandial plasma glucose	80–130 mg/dL (3.9–7.2 mmol/L)[b]
Postprandial plasma glucose	<180 mg/dL (<10.0 mmol/L)[c]
Blood pressure	<140/90 mm Hg (Refer to Chapter 9, Essential Hypertension.)
Lipids	Refer to Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease.

Goals must be individualized to the patient. See Case 53-2, Question 2, for a broader discussion.[64]

A_{1c}, glycated hemoglobin.

[a]More stringent goals (ie, <6%) can be considered for select individuals. The American Association of Clinical Endocrinologists/American College of Endocrinology recommends an A_{1c} goal of ≤6.5%.[64]

[b]The American Association of Clinical Endocrinologists recommends a fasting blood glucose goal of <110 mg/dL (6.1 mmol/L).[64]

[c]The American Association of Clinical Endocrinologists/American College of Endocrinology recommends a goal of <140 mg/L (7.8 mmol/L).[100,101]

Source: American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S73–S84. doi:10.2337/dc21-S006.

Three trials published in 2008 and 2009 have raised new questions about tight glycemic control in patients with type 2 diabetes. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a higher rate of mortality was seen in the intensive treatment arm, which achieved an A_{1c} of 6.4% compared with the standard arm, which achieved 7.5%.[43] The ACCORD study was a National Heart, Lung, and Blood Institute study of >10,000 patients with type 2 diabetes with known heart disease or multiple CV risk factors. The intensively treated group had an excess of 3 deaths per 1000 participants per year compared with the standard group during

an average of 4 years on treatment (257 vs 203 deaths). The higher mortality rate was not attributable to a specific drug therapy or to severe hypoglycemia.[44] A second trial, the Action in Diabetes and Vascular Disease a Controlled Evaluation (ADVANCE), was an even larger study of >11,000 patients, which had findings different from that of ACCORD. In ADVANCE, there was an insignificant trend for reduced CV mortality and reduced overall mortality with tight glycemic control (A_{1c} of 6.3% compared with 7.0%).[45] Lastly, in the smaller Veterans Affairs Diabetes Trial (VADT), nearly 2000 patients were studied and found to have an insignificant 12% relative risk reduction in macrovascular end points but a 7% relative increase in overall mortality (95 vs 102 deaths). Neither finding was statistically significant.[46] After the ~10-year follow-up to the VADT trial, the study found one fewer CV event/116 person-years without a reduction in mortality. The intensive arm of this study had a mean A_{1c} of 6.9%, not <6.5%.[47]

In the face of these new data, the ADA, along with the American Heart Association (AHA) and the American College of Cardiology (ACC), issued a position statement in 2009.[48] Although acknowledging the findings of the ACCORD trial, the persistent trend for reductions in macrovascular events in all three trials was found to be reassuring. The position of the committee (which continues to be the official position of the ADA in the 2015 guidelines) is that although intensive glycemic control did not improve macrovascular outcomes, a goal of <7% is still reasonable based on microvascular benefits and a clear lack of harm across the trials of intensive versus standard glycemic control.[41] However, the ADA does acknowledge that there is room to individualize the A_{1c} goal and that achieving an A_{1c} of <7% has limited macrovascular benefit compared with A_{1c} values of 7% to 8%. Patients with type 2 diabetes and CVD or multiple risk factors for CVD should discuss their treatment goals with their providers. In these patients, a less intensive goal may be appropriate, particularly for patients who have difficulty achieving the goal of <7%.[41]

PREVENTION OF TYPE 1 AND TYPE 2 DIABETES MELLITUS

Because the clinical symptoms of type 1 DM are the overt expression of an insidious pathogenic process that begins years earlier, investigators are focusing attention on strategies that alter the natural history of the disease (Fig. 53-1). First-degree relatives of individuals with type 1 DM have an increased risk of developing diabetes and can be identified by the presence of immune markers that may herald the disease by many years.[11] This has led to attempts at immune intervention at the prediabetes stage (primary prevention) or after the development of islet antibodies (secondary prevention). Most immunotherapy trials are tertiary prevention after diagnosis of type 1 diabetes. Results have not been extraordinary, but will be areas of future study. For primary prevention, vaccines, and secondary prevention, immunomodulatory agents will continue to be an area of research.[49] The Diabetes Prevention Program Research Group studied a diverse group of 3234 individuals at high risk for developing diabetes to determine whether lifestyle interventions or metformin (850 mg by mouth [PO] twice a day [bid]) would prevent or delay the onset of type 2 diabetes.[50] After 3 years, the incidence of diabetes was reduced by 58% and 31% in the intensive lifestyle and metformin groups, respectively, compared with the control group. Diabetes incidence during 10 years of follow-up was persistently lower in the groups originally treated with lifestyle (34% reduction) and metformin (18% reduction) interventions compared with the control group.[51] Other studies have confirmed the value of lifestyle intervention and other drugs (acarbose, orlistat, and various thiazolidinediones [TZDs]) in the prevention of type 2 diabetes, but the strongest evidence is with metformin.[3] Lifelong medication therapy, however, is not without its own risks and complications. Current recommendations regarding the treatment for individuals with prediabetes include lifestyle modification (5%–10% weight loss and 150 minutes/week of moderately intense physical

activity).[52] Metformin, although less effective than are lifestyle changes, can be considered for very high-risk individuals.[53]

CASE 53-1

QUESTION 1: R.P. is a 43-year-old African American female visiting a primary care clinic to obtain a routine physical examination for her new job. Her past medical history is significant for GDM. She was told during her two pregnancies (last child born 3 years ago) that she had "borderline diabetes," which resolved each time after giving birth. Her family history is significant for type 2 diabetes (mother, maternal grandmother, and older first cousin), hypertension, and CVD. She denies tobacco or alcohol use. She states that she tries to walk 15 minutes twice a week. Physical examination is significant for moderate central obesity (64 inches [162.56 cm]; 160 pounds [72.57 kg]; BMI, 30.2 kg/m^2, and blood pressure [BP] 145/85 mm Hg). R.P. denies any symptoms of polyphagia, polyuria, or lethargy. On checking her electronic medical record, she has documented hypertension and an FPG value of 119 mg/dL, measured 2 months prior.

What features of R.P.'s history and examination are consistent with an increased risk of developing type 2 diabetes?

The features of R.P.'s history that are consistent with an increased risk of developing type 2 diabetes include her age, ethnicity, weight, family history of diabetes, history of GDM, and a documented IFG. In addition, type 2 diabetes is also often associated with other disorders such as hypertension. The fact that R.P. has hypertension that is not well controlled and has a family history of hypertension and CVD may indicate that she is predisposed to insulin resistance, further putting her at risk for developing type 2 diabetes.

CASE 53-1, QUESTION 2: The physician orders an A_{1c} for R.P., which comes back at 6.1%. How should R.P. be managed at this time?

Both the A_{1c} and FPG values are in the prediabetes range. R.P. should be educated about her risk of developing type 2 diabetes. Working with her health care providers, R.P. should be encouraged and educated on how to institute lifestyle modifications (MNT and physical activity) that will help her lose weight, improve her CV

health, and decrease her risk of developing type 2 diabetes. A weight loss goal of 5% to 10% during the next 6 to 12 months should be recommended, and she should increase her level of moderate physical activity to at least 150 minutes/week. Her hypertension should be managed. At this time, the use of pharmacologic agents (ie, metformin) to prevent the development of type 2 diabetes is not recommended.

TREATMENT

There are three major components to the treatment of diabetes: diet, drugs (insulin and antidiabetic agents [oral and injectable]), and exercise. Each of these components interacts with the others to the extent that no assessment and modification of one can be made without knowledge of the other two.

Medical Nutrition Therapy

PRINCIPLES

MNT plays a crucial role in the therapy for all individuals with diabetes.[52,54] Unfortunately, patient acceptance and adherence to diet and meal planning are often poor, but revised evidence-based recommendations that are more flexible than are the previous approaches offer new opportunities to increase the effectiveness of nutrition therapy.

Nutrition therapy is designed to help patients achieve appropriate metabolic and physiologic goals (eg, glucose, lipids, BP, proteinuria, and weight), select healthy foods, and take into consideration personal and cultural preferences. Appropriate levels and types of physical activity to achieve a healthier status are incorporated into the nutrition plan.[52,55-57]

NUTRITION THERAPY AND TYPE 1 DIABETES MELLITUS

For patients with type 1 diabetes taking fixed doses of insulin, a meal plan is designed to provide adequate carbohydrates timed to match the peak action of exogenously administered mealtime insulin. Regularly scheduled meals and snacks should contain consistent carbohydrate amounts, which are required to prevent hypoglycemic reactions. Fortunately, newer insulins and insulin regimens provide much more flexibility in the amount and timing of food intake. Patients who are taught to count carbohydrates can inject rapid- or short-acting insulin doses designed to match their anticipated intake. Integration of food intake, physical activity, and insulin dose is critical and discussed extensively in the cases that follow.[52,55-57]

NUTRITION THERAPY AND TYPE 2 DIABETES MELLITUS

For patients with type 2 diabetes, meal plans emphasize normalizing plasma glucose and lipid levels as well as maintaining a normal BP to prevent or mitigate CV morbidity. Although weight loss reduces insulin resistance and improves glycemic control, traditional dietary strategies incorporating hypocaloric diets have not been effective in achieving long-term weight loss. A sustainable weight loss can be achieved within structured programs that emphasize lifestyle changes, physical activity, and food intake that modestly reduces caloric and fat intake.[52,55-57]

SPECIFIC NUTRITION COMPONENTS

MNT is an integral and critical component of diabetes care. For a more extensive discussion of the principles underlying nutrition therapy, the reader is directed to other sources. A few key principles are briefly noted subsequently because they are common sources of misunderstanding.[52,55-57]

Carbohydrates and artificial sweeteners

Carbohydrates include sugar (sucrose), starch, and fiber, and are liberally incorporated into the diet of a person with diabetes. In fact, the amount of dietary carbohydrate is the main determinant of insulin demand and is commonly used to determine the premeal insulin

dose. Furthermore, patients using fixed doses of insulin or antihyperglycemic medications (eg, sulfonylureas) must eat meals containing consistent amounts of carbohydrates to avoid hypoglycemia. Because isocaloric amounts of sucrose and starch produce the same degree of glycemia, sucrose can be substituted for a portion of the total carbohydrate intake and should be incorporated into an otherwise healthful diet.

Whole grains, fruits, and vegetables high in fiber are recommended for people with diabetes because they are for the general population. There is no evidence that larger amounts produce a differential metabolic benefit with regard to plasma glucose and lipid levels. Nonnutritive sweeteners (saccharin, aspartame, neotame, acesulfame potassium, and sucralose) and sugar alcohols have been rigorously tested by the U.S. Food and Drug Administration (FDA) for safety in people with diabetes and are safe at approved daily intakes. Fructose and the reduced-calorie sweeteners called *sugar alcohols* produce lower postprandial glucose responses than do sucrose, glucose, and starch. When sugar alcohols (eg, sorbitol, mannitol, lactitol, xylitol, and maltitol) are consumed, it is recommended to subtract half of their grams from the total carbohydrate amount because their effect on BG is less. Patients should be advised that when these sweeteners are used in foods labeled “dietetic” or “sugar free,” they still add to the carbohydrate content and provide substantial calories (2 cal/g). Furthermore, excessive intake of sorbitol-sweetened foods (eg, 30–50 g/day) can induce an osmotic diarrhea, and excessive amounts of fructose can increase total and low-density lipoprotein cholesterol (LDL-C).[58]

Counting carbohydrates

When patients are taught to estimate the grams of carbohydrate in a meal, they are given the following guideline: One carbohydrate serving—1 starch or 1 fruit or 1 cup milk—15 g carbohydrate. Patients vary with regard to their insulin-to-carbohydrate ratio

throughout time and throughout the day; however, a typical starting point is 1 unit/15 g carbohydrate.[52,55-57]

Fat

CVD is a major cause of morbidity and mortality in patients with diabetes. Therefore, saturated fats should be limited to <7% of calories. The intake of *trans* fat should also be minimized. The recommended cholesterol intake is <200 mg/day for patients with diabetes. Two or more servings/week of fish to provide *n*-3 polyunsaturated fatty acids and ω-3 fatty acids are advised.[52,55-57]

Protein

Data are insufficient to support special dietary protein recommendations for persons with diabetes if kidney function is normal. Generally, 15% to 20% of the daily caloric intake comes from animal and vegetable protein sources in the U.S. diet. This amount may be liberalized in pregnant and lactating females or in elderly people. With the onset of nephropathy, a lower protein intake of 0.8 to 1.0 g/kg/day is considered sufficiently restrictive. For patients in later stages of nephropathy, reduction of protein intake to 0.8 g/kg/day is recommended. High-protein diets are not recommended as a long-term method for weight loss, because the effects on kidney function are not known.[52,55-57]

Sodium

The ADA recommends a reduced sodium intake of <2300 mg/day in normotensive and hypertensive individuals. For patients with diabetes and symptomatic heart failure (HF), sodium should be further restricted to <2000 mg/day to help reduce symptoms. For all other patients, the ADA has no particular restrictions on sodium intake but recommends individualizing amounts based on the patient's sensitivity to salt and concurrent conditions such as hypertension or nephropathy.[55-57]

Alcohol

The ADA's recommendation for alcohol is consistent with general recommendations of no more than two alcoholic drinks/day for males or one drink/day for females. A drink is equivalent to 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of distilled spirits (each contains about 15 g of carbohydrate). Nevertheless, its caloric contribution must be considered (1 alcoholic beverage = 2 fat exchanges), and it should always be taken with food to minimize its hypoglycemic effect. In people with diabetes, light-to-moderate alcohol intake (one to two drinks/day) is associated with a decreased risk of CVD. A note of caution: Evening consumption of alcohol may increase the risk of nocturnal and fasting hypoglycemia, particularly in people with type 1 diabetes.[52,55-57,59,60]

PHYSICAL ACTIVITY

Physical activity is a key factor in the treatment of diabetes, particularly in type 2 diabetes, because obesity and inactivity contribute to the development of glucose intolerance in genetically predisposed individuals. Regular exercise reduces cholesterol levels, raises high-density lipoprotein cholesterol (HDL-C), lowers BP, augments weight reduction diets, reduces the dose requirements or need for insulin or antihyperglycemic agents, enhances insulin sensitivity, and improves psychological well-being by reducing stress. Exercise increases glucose utilization, which is provided initially from the breakdown of muscle glycogen and, subsequently, from hepatic glycogenolysis and gluconeogenesis. These effects are mediated through norepinephrine, epinephrine, growth hormone, cortisol, and glucagon, along with the suppression of insulin secretion. In patients using insulin, hyperglycemia, normoglycemia, or hypoglycemia can occur secondary to exercise depending on the degree of control, recent administration of rapid-acting insulin, and food intake. Exercise in patients taking insulin must be tempered by increased food intake, potential delay in insulin administration, decreased doses of insulin, or a combination of these actions to minimize hypoglycemia.[61]

In patients with type 2 diabetes, plasma glucose concentrations usually decrease in response to exercise, but symptomatic hypoglycemia is uncommon. The vascular benefits of exercise are particularly helpful in patients with diabetes given their predisposition to CVD. In general, exercise that produces moderate exertion (increase in heart rate of 20%–40% from resting baseline) is recommended with a starting goal of 150 minutes/week. The eventual goal is for patients to be able to achieve 50% to 70% of their age-adjusted maximal heart rate.[59]

Resistance exercise has been shown to improve insulin sensitivity. Therefore, in the absence of any contraindications, people with type 2 diabetes are encouraged to perform resistance training three times per week. Patients with conditions that may preclude certain types of physical activity (eg, coronary artery disease, uncontrolled hypertension, severe autonomic neuropathy, severe peripheral neuropathy or history of foot lesions, and advanced retinopathy in which retinal detachment may occur) should be carefully evaluated before starting an exercise regimen.[62]

Pharmacologic Treatment

Insulin, along with diet, is crucial to the survival of individuals with type 1 diabetes and plays a major role in the therapy for people with type 2 diabetes when their symptoms cannot be controlled with diet or noninsulin antidiabetic agents. Insulin also is used for people with type 2 diabetes during periods of intercurrent illness or stress (eg, surgery and pregnancy). The use of other antidiabetic agents is primarily reserved for the treatment of patients with type 2 diabetes. The ADA recommends a patient-centered approach to the use of pharmacologic agents. Comorbidities of patients should be considered when choosing drug therapy. These include the presence of atherosclerotic cardiovascular disease (ASCVD) or who are at high risk, established chronic kidney disease (CKD) and congestive heart failure. Additional considerations include the risk of hypoglycemia, the impact on weight, the risk of side effects, cost,

and patient preferences.[63] The clinical use of these agents and the complications associated with their use are discussed later in this chapter.

Overall Goals of Therapy

The overall goal of diabetes management is to prevent acute and chronic complications. Periodic assessments of A_{1c} coupled with regular measurement of fasting, preprandial, and postprandial glucose levels should be used to assess therapy. The following overall goals of therapy are agreed on by most endocrinologists:

1. Landmark randomized, prospective trials of various interventional therapies in patients with both type 1 and type 2 diabetes have clearly demonstrated that reductions in hyperglycemia significantly decrease microvascular complications. In both the UKPDS and the DCCT follow-up studies, significant reductions in macrovascular complications were also observed. Recent trials of specific agents have also shown a reduction in major adverse CV events (MACE) and a reduction in CKD and hospitalizations and deaths owing to HF. Target BG goals may need to be adjusted for patients with frequent, severe hypoglycemia or hypoglycemia unawareness (see Case 53-8, Questions 1–3, and Case 53-9), or with CVD. In addition, established renal insufficiency, proliferative retinopathy, severe neuropathy, and other advanced complications are not likely to be improved by tight glucose control. See Table 53-5 for the ADA glycemic goals.[64] The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology established glycemic goals as well (Table 53-5).[14,63] The ADA guidelines will be discussed throughout this chapter.
2. Try to keep patients free of symptoms associated with hyperglycemia (polyuria, polydipsia, weight loss, fatigue, recurrent infection, and ketoacidosis) or hypoglycemia (hunger, anxiety, palpitations, and sweatiness).

3. Maintain normal growth and development in children. Intensive therapy is not recommended across any age group with a goal A_{1c} of <7.5%. Goals can be individualized, targeting <7% if it can be done so safely with minimum hypoglycemia (see Case 53-4, Questions 2 and 3).
4. Eliminate or minimize all other CV risk factors (obesity, hypertension, tobacco use, and hyperlipidemia; see Table 53-5 for glycemic and BP goals).
5. Try to integrate the patient into the health care team through intensive education. The patient's knowledge and understanding of this disease can favorably influence its outcomes (see Table 53-14).

Methods of Monitoring Glycemic Control

In addition to monitoring signs and symptoms associated with hyperglycemia, hypoglycemia, and the long-term complications of diabetes, an ongoing assessment of metabolic control is an integral component of diabetes management. Ideally, SMBG results combined with laboratory measures of acute and chronic glycemia can be used to evaluate and adjust therapy.[14,63] SMBG and A_{1c} levels continue to be the two primary methods used to access glycemic control. Continuous glucose monitoring (CGM) of interstitial fluid is also available for people with diabetes. CGM is currently recommended for consideration, along with SMBG, for patients with type 1 diabetes and patients with type 2 diabetes utilizing insulin, especially those with hypoglycemic unawareness.[63]

KETONE TESTING

Ketone testing is recommended for patients with gestational and type 1 diabetes. Urine ketones (acetoacetic acid) should be evaluated when glucose concentrations consistently exceed 300 mg/dL or during acute illness.[14] There are several commercially available meters available that either test both BG and ketones or blood ketones alone. Persistently high glucose concentrations of this

magnitude signal insulin deficiency that can, in turn, lead to lipolysis and ketoacidosis. A positive test may indicate impending or established ketoacidosis and demands a more extensive diagnostic workup. Testing also is recommended during pregnancy and if the patient has symptoms of ketoacidosis. Although there are generally no ketones in the urine, they may be present in people who are on extremely low-caloric diets and in the first morning sample of females who are pregnant. Also, see discussions of sick day management and ketoacidosis in other sections of this chapter (Cases 53-7 and 53-13).

PLASMA GLUCOSE

FPG concentrations are commonly used to assess glycemic control in the fasting state because this is when glucose concentrations are most reproducible. FPG concentrations generally reflect glucose derived from hepatic glucose production because this is the primary source of glucose in the postabsorptive state. The FPG is the most frequent test performed by patients when self-monitoring. Postprandial glucose concentrations (1–2 hours after the start of the meal) also are used to assess glycemic control when fasting glucose concentrations are within normal limits or when there is a need to assess the effects of food or drugs (eg, rapid-acting insulins and glinides) on meal-related glycemia. In individuals without diabetes, glucose concentrations generally return to <140 mg/dL within 2 hours of a meal. One- to 2-hour postprandial concentrations primarily reflect the efficiency of insulin-mediated glucose uptake by peripheral tissue.

Because glucose concentrations are affected by various factors (eg, meals, medications, and stress), single time point measurements cannot be used to assess a patient's overall control. Most laboratories measure plasma glucose concentrations rather than whole blood because these values are not subject to changes in the hematocrit. The majority of glucose monitors report plasma-referenced glucose concentrations. Whole BG concentrations are

~10% to 15% lower than are plasma glucose concentrations because glucose is not distributed into red blood cells (RBCs).[14]

SELF-MONITORING OF BLOOD GLUCOSE

SMBG has made euglycemia, both preprandially and postprandially, an achievable goal. Patients and their health care providers can use SMBG and/or CGM to assess directly the effects of drug dose changes, meals, exercise, and illness on BG concentrations. With improved technology, decreasing costs, and increased coverage by health plans, either SMBG or CGM is an option for all patients with diabetes. However, SMBG and CGM remain expensive for patients without health insurance; and when using SMBG, insurance carriers will often limit how often a patient can check their BG levels. Furthermore, to achieve maximal benefit from SMBG, both the clinician and patient must be motivated and willing to spend the time required to interpret the data and modify therapy to improve glycemic control. Selection and use of SMBG testing materials are discussed in Case 53-2, Questions 9 and 10. Patients in whom SMBG and/or CGM is particularly valuable include the following[14,63]:

- *Patients with type 1 diabetes*: Frequent BG measurements help the patient correlate meals, exercise, and insulin dose with BG concentrations. This instant feedback gives the patient an increased sense of control and motivation, leading to improved glucose control.
- *Pregnant patients*: Infant morbidity and mortality are associated with the mother's overall glucose control. Using SMBG and/or CGM, the mother with diabetes who achieves normoglycemia before conception and throughout pregnancy improves her chances of delivering a live, healthy infant.
- *Patients having difficulty recognizing hypoglycemia*: With time, patients with diabetes can develop a sluggish counterregulatory response to hypoglycemia, whereby hypoglycemic symptoms are blunted or even absent. This is often referred to as *hypoglycemic unawareness*. Routine SMBG and/or CGM to detect asymptomatic hypoglycemia is essential in these individuals. In addition, acute

anxiety attacks or signs and symptoms associated with a rapidly falling BG concentration may mimic a true hypoglycemic reaction. This can be evaluated easily by measuring a finger stick BG concentration.

- *Patients who are using physiologic (eg, basal-bolus) insulin therapy*: Individuals who are on multiple daily doses of insulin or those using an insulin pump should perform SMBG and/or CGM to evaluate the effectiveness of their insulin regimens and meal plans and to check for hypoglycemic or hyperglycemic reactions (see Case 53-2, Question 10). Knowledge of preprandial, postprandial, bedtime, and nocturnal (eg, 2:00 AM) BG concentrations is essential in determining basal and preprandial insulin requirements.
- *Patients with type 2 diabetes who are on therapy that can cause hypoglycemia*: Individuals taking glinides, a sulfonylurea, or insulin therapy should know how to perform SMBG and/or CGM to detect hypoglycemia when experiencing symptoms consistent with hypoglycemia.
- *Patients with type 2 diabetes who are engaged in self-management of their diabetes*: Even individuals using noninsulin therapies can benefit from SMBG to evaluate the impact of food, exercise, and antidiabetic medications on their BG.

CONTINUOUS GLUCOSE MONITORING

As with SMBG, CGM provides real-time information on glucose concentrations. However, the difference is that the CMG system automatically detects glucose concentrations (subcutaneous [SC] interstitial fluid glucose concentrations) on a continual basis. CGM systems use electrochemical sensors that are inserted into the skin. Sensor probe length varies as does the duration that the sensor can remain in the skin up to 14 days depending on the sensor. The sensors transmit a signal to a receiver (wired or wireless), which records and displays the data every 1 to 5 minutes. The sensors require a warmup or initialization period and may have calibration requirements. Calibration is performed by using a BG monitor.

Interstitial glucose levels lag behind plasma or BG levels by 8 to 18 minutes, depending on the glucose rate of change.[14] Therefore, if a person's glucose is low, or trending downward, SMBG is required. Some CGM systems have alarms that can go off at certain high and low glucose thresholds. The ability to detect hypoglycemia during the night with these alarms has been a very attractive reason for using CGM. Another key feature is the ability to follow trends and rates of change in BG levels. Any acute treatment changes still require SMBG. Small, short-term studies have demonstrated modest improvements in A_{1c} (0.3%–0.6% reductions) in adults and children with type 1 diabetes.[65] Just as for SMBG with a glucose meter, use of CGM requires a person to actively assess and react to their readings for this self-management tool to have an impact on A_{1c}. The ambulatory glucose profile (AGP) is created from all available CGMs and provides data on time in range, percentage above and below range, and variability.[66] Pharmacists in clinical practice can integrate CGM into their clinical services utilizing both professional and personal use monitors. This can facilitate the drug therapy management and aid in collaborative data interpretation, documentation, and billing.[67]

GLYCATED HEMOGLOBIN

The glycated hemoglobin, or A_{1c}, has become the gold standard for measuring chronic glycemia and is the clinical marker for predicting long-term complications, particularly microvascular complications. A_{1c} is most commonly measured because it comprises the majority of A_{1c} and is the least affected by recent fluctuations in BG. A_{1c} measures the percentage of hemoglobin A that has been irreversibly glycated at the *N*-terminal amino group of the β-chain; the plasma glucose level and the life span of an RBC (~120 days) determine its value. Thus, A_{1c} is an indicator of glycemic control during the preceding 2 to 3 months. In patients without diabetes, A_{1c} comprises ~4% to 6% of the total hemoglobin. Values may be three times this level in patients with diabetes.[63,68]

The following formula was developed to convert an A_{1c} into an average glucose: $28.7 \times A_{1c} - 46.7$ = eAG (estimated average glucose). A formula that approximates (not exact) this very closely and is much easier to use in practice is $(A_{1c} - 2) \times 30$. The ADA now recommends reporting an eAG (units, mg/dL or mmol/L) along with the A_{1c}. An eAG calculator is available on their website to do this conversion (https://professional.diabetes.org/diapro/glucose_calc). The correlation between A_{1c} and eAG is shown in the following table with 95% confidence intervals (CIs) in parentheses.[4,63,69,70]

A_{1c} (%)	Estimated Average Plasma Glucose (mg/dL)
5	97 (76–120)
6	126 (100–152)
7	154 (123–185)
8	183 (147–217)
9	212 (170–249)
10	240 (193–282)
11	269 (217–314)
12	298 (240–347)

Hemoglobinopathies, such as sickle cell trait or chemically modified derivatives of hemoglobin as seen in uremia, in which hemoglobin becomes carbamylated, or acetylated hemoglobin with high-dose aspirin, can affect A_{1c} values (increase or decrease depending on the assay), resulting in inaccurate indications of glycemic control. Alterations in RBC survival or turnover, seen in hemolytic anemia and acute blood loss, can falsely lower the A_{1c}. Also, a recent blood transfusion or use of intravenous (IV) iron therapy or erythropoietin-stimulating agents in patients with CKD can falsely lower A_{1c} values. A glycated serum protein (fructosamine) should be considered for these patients. Antioxidants such as vitamins C and E also may interfere with the glycosylation process.[71]

A_{1c} can be measured without any special patient preparation (eg, fasting), and generally is not subject to acute changes in insulin dosing, exercise, or diet. A_{1c} values can be used as an adjunct to assess overall glycemic control in patients with diabetes or to diagnose diabetes and prediabetes.[63] Normalization can indicate whether euglycemia has been achieved. However, A_{1c} does not replace the day-to-day monitoring of BG concentrations, which is essential for evaluating acute changes in BG concentrations. These values are needed to adjust the meal plan or medication doses. Sometimes, an A_{1c} is used to verify clinical impressions related to glucose control and patient adherence. It should be measured quarterly in patients who do not meet treatment goals and at least semiannually in stable patients who are meeting treatment goals.[72]

GLYCATED SERUM PROTEIN, GLYCATED SERUM ALBUMIN, AND FRUCTOSAMINE

Assays for glycated serum proteins reflect the extent of glycosylation of a variety of serum proteins, including glycated serum albumin.[63] The fructosamine assay is one of the most widely used methods to measure glycated proteins (normal, 2–2.8 mmol/L). Because the half-life of albumin is ~14 to 20 days, fructosamine provides an indication of glycemic control during a shorter time frame (1–2 weeks) than does the A_{1c}. The ADA does not consider measurement of fructosamine equivalent to that of A_{1c}, although it correlates well with this value. Fructosamine levels may be useful as an adjunct to A_{1c} in determining whether a patient is improving or worsening in the short term (eg, a patient on insulin therapy undergoing multiple dosage adjustments; for females with type 2 diabetes during pregnancy or gestational diabetes) or in patients with conditions such as hemolytic anemia in whom the A_{1c} test is inaccurate.[73,74]

INSULIN

Insulin is a hormone secreted from the pancreatic β cell in response to glucose and other stimulants (eg, amino acids, free fatty acids, gastric hormones, parasympathetic stimulation, and β-adrenergic stimulation).[73] The hormone is made up of two polypeptide chains (a 21-amino acid A chain and a 30-amino acid B chain), which are connected by two disulfide bonds. Proinsulin, the precursor of insulin, is a single-chain 86-amino acid polypeptide that is processed in the Golgi apparatus of β cells and then packaged into granules.[75–80] In the storage granule, the connecting or C-peptide is cleaved from proinsulin to produce equimolar amounts of insulin and C-peptide. Insulin and C-peptide are cosecreted; thus, measurable C-peptide levels indicate the presence of endogenously produced insulin and functioning β cells. Insulin is crucial to the survival of individuals with type 1 diabetes, whose β cells have been destroyed. It also plays a major role in the therapy for many individuals with type 2 diabetes in combination with antidiabetic agents. Insulin also is used in patients with type 2 diabetes during pregnancy or periods of illness or stress (eg, surgery).

Commercially available insulin products differ in their physical and chemical properties as well as in the pharmacokinetics of their action. Prior issues with immunogenicity have been eliminated through modern manufacturing processes and the cessation of use of animal-derived insulin products. Consequently, immunologically mediated sequelae, such as lipodystrophy, hypersensitivity, and insulin resistance caused by “blocking” antibodies, are extremely rare.

Pharmacokinetics: Absorption, Distribution, and Elimination

The route of administration for insulin is primarily via SC injection. Regular insulin, a solution, can be administered by any parenteral route: IV, intramuscular (IM), or SC, and all injectable rapid-acting insulins may be administered by either SC injection or IV infusion.[81] Afrezza® (insulin human) is the only insulin currently available as a

powder for inhalation.[82] Other routes for insulin administration have been studied, including dermal, nasal, buccal, and oral; however, these formulations are not currently approved for use in the United States.

After SC injection, insulin is absorbed directly into the bloodstream, bypassing the lymphatic system. The rate-limiting step of insulin activity after SC administration is the absorption of insulin from the injection site, which depends on a multitude of factors such as type of insulin administered, injection site utilized, and patient technique. Variations in SC absorption can occur, primarily related to changes in blood flow around the injection site.[73]

Endogenous insulin is secreted directly into the portal circulation and is primarily cleared by the liver in nondiabetic individuals (60%), with the kidneys removing only 35% to 40% of it.[83] Exogenous insulin is degraded at both renal and extrarenal (liver and muscle) sites. Degradation also takes place at the cellular level after internalization of the insulin–receptor complex. In contrast to endogenously secreted insulin, up to 60% of exogenous insulin is cleared from the systemic circulation by the kidneys, with the liver accounting for only 30% to 40% of its clearance. Insulin is filtered by glomerular capillaries, but >99% is reabsorbed by the proximal tubules. The insulin is then degraded in glomerular capillary cells and postglomerular peritubular cells.[74,84] See Case 53-6 for changes in insulin requirement in renal dysfunction.

Pharmacodynamics

Clinically, the most important differences among insulin products relate to their onset, peak, and duration of action (not the actual insulin levels, which is pharmacokinetics). Current insulin products can be categorized as rapid-acting, short-acting, intermediate-acting, long-acting, and ultralong-acting insulin. Products available in the United States are listed in **Table 53-6**, and the onset of action, peak effect, and durations of action of each insulin category are listed in **Table 53-7**. However, these data are derived primarily from studies

in normal, healthy volunteers in the fasting state or in well-controlled patients with diabetes stabilized in a metabolic ward. In reality, intersubject and intrasubject variations in response to insulin can be substantial because an individual pattern of response to insulin can be affected by numerous factors (eg, the formation of insulin hexamers, the presence of insulin-binding antibodies, dose, exercise, site of injection, massage of the injection site, ambient temperature, and interactions between insulins that have been mixed together; see **Table 53-8** and Case 53-2, Question 14).[62] Nevertheless, knowledge of when one might expect the various insulins to exert their effects is absolutely essential to the rational adjustment of insulin dosages.

Table 53-6
Insulins Available in the United States

Type/Duration of Action	Brand Name	Manufacturer
Ultrarapid Acting		
Insulin aspart	Fiasp®	Novo Nordisk
Insulin lispro-aabc	Lyumjev®	Eli Lilly
Rapid Acting		
Insulin lispro	Humalog® Insulin lispro	Eli Lilly
	Admelog®	Sanofi Aventis
Insulin aspart	NovoLog®	Novo Nordisk
Insulin glulisine	Apidra®	Sanofi Aventis
Short Acting		
Regular	Humulin® R[a]	Eli Lilly
	Novolin® R	Novo Nordisk
Intermediate Acting		
NPH (isophane insulin suspension)	Humulin® N	Eli Lilly
	Novolin® N	Novo Nordisk

Type/Duration of Action	Brand Name	Manufacturer
Long Acting		
Insulin glargine	Lantus®	Sanofi Aventis
	Toujeo® (U-300)	Sanofi Aventis
	Semglee®	Viatris
	Basaglar®	Eli Lilly
Insulin detemir	Levemir®	Novo Nordisk
Insulin degludec	Tresiba® (U-100 and U-200)	Novo Nordisk
Premixed Insulins		
NPH/regular (70%/30%)	Humulin® 70/30	Eli Lilly
	Novolin® 70/30	Novo Nordisk
Insulin aspart protamine suspension/insulin aspart (70%/30%)	NovoLog® Mix 70/30™	Novo Nordisk
Insulin lispro protamine suspension/insulin lispro (75%/25%)	Humalog® Mix 75/25™	Eli Lilly
Insulin lispro protamine suspension/insulin lispro (50%/50%)	Humalog® Mix 50/50™	Eli Lilly
Inhaled Insulin		
Regular insulin	Afrezza®	MannKind

Insulin is made through recombinant DNA technology. Only regular and neutral protamine Hagedorn (NPH) are human insulin. All other insulins are human insulin analogs. All insulins available in the United States have a concentration of 100 units/mL (U-100), except as noted.

[a]A U-500 concentration is available for use in rare circumstances in patients with severe insulin resistance requiring very large insulin doses.

Sources: Fiasp. Package insert. Novo Nordisk; January 2020; Lyumjev. Package insert.Eli Lilly and Company; June 2020; Humalog. Package insert. Eli Lilly and Company; November 2019; Insulin lispro. Package insert. Eli Lilly and Company; February 2020; Admelog. Package insert. Sanofi-Aventis U.S. LLC; November 2019; Novolog. Package insert. Novo Nordisk; December 2019; Apidra. Package insert. Sanofi-Aventis U.S. LLC; November 2019; Humulin R. Package insert. Eli Lilly and Company; November 2019; Novolin R Package insert. Novo Nordisk;

November 2019; Humulin N. Package. insert. Eli Lilly and Company; November 2019; Novolin N Package insert. Novo Nordisk; November 2019; Lantus. Package insert. Sanofi-Aventis U.S. LLC; November 2019; Toujeo. Package insert. Sanofi-Aventis U.S.LLC; November 2019; Semglee. Package insert. Mylan; July 2021; Basaglar. Package insert. Eli Lilly and Company; July 2021; Levemir. Package insert. Novo Nordisk; March 2020; Tresiba. Package insert. Novo Nordisk; November 2019; Humulin 70/30. Package insert. Eli Lilly and Company; November 2019; Novolin 70/30. Package insert. Novo Nordisk; April 2021; Novolog 70/30. Package insert. Novo Nordisk; November 2019; Humalog 75/25. Package insert. Eli Lilly and Company; November 2019; Humalog 50/50. Package insert. Eli Lilly and Company; November 2019; Afrezza. Package insert. Mannkind. February 2020.

Table 53-7
Insulin Pharmacodynamics

Insulin	Onset (Hours)	Peak (Hours)	Duration (Hours)	Appearance
Ultrarapid/rapid-acting (insulin aspart, glulisine, lispro, lispro-aabc)	5–15 minutes	30–90 minutes	<5	Clear
Regular	0.5–1	2–4	5–7	Clear
NPH	2–4	4–12	12–18	Cloudy
Insulin glargine U-100	1.5	No pronounced peak	20–24	Clear[a]
Insulin glargine U-300	6	None	24	Clear[a]
Insulin detemir	0.8–2	Relatively flat	5.7–23.2	Clear[a]
Insulin degludec	1	None	42	Clear
Insulin inhalation regular	≤15 minutes	1	3–5	

The onset, peak, and duration of insulin activity may vary considerably from times listed in this table. See text and Table 53-8.

NPH, neutral protamine Hagedorn.

[a]Should not be mixed with other insulins. Some patients require twice-daily dosing.

Sources: Fiasp. Package insert. Novo Nordisk; January 2020; Novolog. Package insert. Novo Nordisk; December 2019; Apidra. Package insert. Sanofi-Aventis U.S. LLC; November 2019; Humalog. Package insert. Eli Lilly and Company; November 2019; Lyumjev. Package insert. Eli Lilly and Company; June 2020; Humulin R. Package insert. Eli Lilly and Company; November 2019; Novolin R Package insert. Novo Nordisk; November 2019; Humulin N. Package. insert. Eli Lilly and Company; November 2019; Published online November 2019; Novolin N Package insert. Novo Nordisk; November 2019; Lantus. Package insert. Sanofi-Aventis U.S. LLC; November 2019.

Table 53-8
Factors Altering Onset and Duration of Insulin Action

Factor	Comments

Factor	Comments	
Route of administration	Onset of action more rapid and duration of action shorter for IV > IM > SC	
	Intrapulmonary insulin has onset and duration comparable to SC rapid-acting insulins.	
Factors altering clearance		
Renal function	Renal failure lowers insulin clearance; may prolong and intensify action of exogenous and endogenous insulin.[366]	
Insulin antibodies	IgG antibodies bind insulin as it is absorbed and release it slowly, thereby delaying or prolonging its effect.	
Thyroid function	Hyperthyroidism increases clearance, but also increases insulin action, making control difficult; patients stabilize as they become euthyroid.	
Factors altering SC absorption	Factors that raise SC blood flow ↑ absorption rates of regular insulin; effect on intermediate- and long-acting insulins are minimal.	
Site of injection	Rate of absorption is fastest from the abdomen, intermediate from the arm, and slowest from the thigh. Less variation is observed in patients with type 2 diabetes; less variation is observed with current rapid-acting and long-acting insulins.	
	Site	*Half-life absorption (minutes)*
	Abdomen	87 ± 12
	Arm	141 ± 23
	Hip	153 ± 28
	Thigh	164 ± 15
Exercise of injected area	Strenuous exercise of an injected area within 1 hour of injection can increase absorption rate; rate of absorption of regular insulin is increased, but little effect on intermediate-acting insulin.	
Ambient temperature	Heat (eg, hot weather, hot bath, and sauna) increases absorption rate; cold has opposite effect.	
Local massage	Massaging injected area for 30 minutes substantially increases absorption rate of regular insulin as well as longer-acting insulins.	
Smoking	Controversial; vasoconstriction may decrease absorption rate.	

Factor	Comments
Jet injectors	Insulin absorption is more rapid, probably secondary to increases in surface area for absorption.
Lipohypertrophy	Insulin absorption is delayed from lipohypertrophic sites.
Insulin preparation	More soluble forms of insulin are absorbed more rapidly and have shorter durations of action (see Table 53-7 and text); human insulin may have shorter action than does animal insulin.
Insulin mixtures	The short-acting properties of rapid-acting insulins may be blunted if mixed with NPH insulin (see Case 53-2, Question 15).
Insulin concentration	More dilute solutions (eg, U-40, U-10) are absorbed more rapidly than are the more concentrated forms (U-100, U-500).
Insulin dose	Lower doses are absorbed more rapidly and have a shorter duration of action than do larger doses.

IgG, immunoglobulin G; IM, intramuscular; IV, intravenous; NPH, neutral protamine Hagedorn; SC, subcutaneous.

Sources: Binder C, Brange J. Insulin chemistry and pharmacokinetics. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 5th ed. Appleton & Lange; 1997:481; Koivisto VA, Felig P. Alterations in insulin absorption and in blood glucose control associated with varying insulin injection sites in diabetic patients. *Ann Intern Med*. 1980;92(1):59–61. doi:10.7326/0003-4819-92-1-5; DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA*. 2003;289(17):2254–2264. doi:10.1001/jama.289.17.2254; Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care*. 2002;25(3):593–598. doi:10.2337/diacare.25.3.593; Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. *Mayo Clin Proc*. 2016;91(9):1231-1255. https://www.mayoclinicproceedings.org/article/S0025-6196(16)30321-4/fulltext; Gradel AKJ, Porsgaard T, Lykkesfeldt J, et al. Factors Affecting the Absorption of Subcutaneously Administered Insulin: Effect on Variability. *J Diabetes Res*. 2018;2018:1205121. Published 2018 Jul 4. doi:10.1155/2018/1205121

BASAL INSULIN

Basal insulin is required for all patients with type 1 DM and some patients with type 2 DM. The primary purpose of basal insulin is to suppress hepatic glucose production and maintain normal glucose levels in the fasting state and in between meals.[62] There are multiple

basal insulin products available including neutral protamine Hagedorn (NPH) insulin, insulin glargine (U-100 and U-300), insulin detemir, and insulin degludec (U-100 and U-200), which all differ based on the onset and duration of action. If used appropriately, all basal insulins can adequately manage a patient's fasting and in-between-meal glucose levels. However, the newer basal insulin analogs (insulin detemir, glargine, and degludec) have displayed an added benefit over NPH insulin with a longer duration of action with a more constant plasma concentration. It is these features that minimize the likelihood of hypoglycemia.[85] NPH insulin may be used once daily; however, often twice-daily dosing is required to achieve appropriate glucose control. Insulin detemir and glargine have demonstrated a decreased risk of nocturnal hypoglycemia in some patients, and may also be dosed once daily. Insulin detemir and insulin glargine U-100 are typically dosed once daily; however, because insulin detemir's duration is dose dependent and insulin glargine's duration of action averages between 18 and 24 hours, patients may require twice-daily dosing for these agents.[86–90] The newer, even longer-acting basal insulins (glargine U-300 and degludec U-100 and U-200) provide the patient with the convenience of once-daily dosing, and have a decreased risk of hypoglycemia compared to the other basal insulin options for patients with both type 1 and 2 diabetes.[91] A consideration, however, that must be made when choosing any insulin product is the out-of-pocket cost to the patient. Although the cost of all insulin products has risen significantly in recent years, follow-on products (specifically for insulin glargine U-100) have been approved by the FDA (Basaglar® and Semglee®), which provide the patient with a similar effect at a potentially lower cost to the patient.[92]

BOLUS/MEALTIME INSULIN

Similar to basal insulin, bolus/mealtime insulin is required for use in all patients with type 1 DM and for some patients with type 2 DM. There are many bolus/mealtime insulins available, which are classified as short-acting (regular insulin), rapid-acting (insulin

aspart, lispro, glulisine), ultrarapid-acting (insulin lispro-aabc (brand name Lyumjev®), faster-acting insulin aspart (brand name Fiasp®), and inhaled human insulin (brand name Afrezza®), all of which differ based on their onset and duration of action. Of all the bolus/mealtime insulin products, regular insulin has the longest onset and duration of action compared to the newer rapid-acting insulins, which have both a faster onset and shorter duration of action. Because they can be injected shortly before eating (0–15 minutes), all rapid-acting insulins provide patients greater flexibility in lifestyle compared to using regular insulin, and are available in vials and various insulin pens. Rapid-acting insulins also lower postprandial BG levels and can decrease the risk of late postprandial and nocturnal hypoglycemia compared with regular insulin formulations.[75,93] Insulin aspart is the only rapid-acting insulin available as brand name only. Recently, insulin lispro has become available both as a generic product (marketed by Eli Lilly) and a follow-on product (marketed under the name Admelog®) providing this particular rapid-acting insulin at a decreased cost to patients.[94–96] The ultrarapid-acting insulins may provide a benefit in some patients because they have been shown to potentially improve postprandial glucose control over the rapid-acting insulins.[81] Lastly, insulin human powder for inhalation (Afrezza®) is indicated for postprandial coverage in patients with type 1 or type 2 diabetes with a pharmacodynamic profile similar to that of rapid-acting insulin.[97] Inhaled insulin offers a patient the unique ability to administer mealtime insulin without the need to inject, and may also decrease the risk of hypoglycemia in some patients.[98] Insulin human powder for inhalation is available as prefilled inhalers containing 4, 8, or 12 units of rapid-acting insulin to be used at the beginning of a meal. It is contraindicated for use in patients with chronic lung disease such as asthma and chronic obstructive lung disease as well as current smokers. Because all mealtime insulins are comparable in efficacy for postprandial BG reduction, cost and patient preference must be taken into consideration when choosing the optimal product.

U-500 CONCENTRATED REGULAR INSULIN

Regular insulin U-500 (500 units/mL) is a concentrated insulin that is indicated for SC use in insulin-resistant patients requiring >200 units of insulin per day. Because this product is five times more potent than the 100 units/mL formulation, its usefulness is that a large insulin dose may be administered in a smaller volume. Its onset of action is ~30 minutes and peaks similar to regular insulin U-100. Regular insulin U-500, however, has a longer duration of action (up to 24 hours) compared to the U-100 formulation and is therefore recommended to be administered between two and three times daily.[99] A U-500 syringe is required to draw up and administer a dose with this product to avoid dosing errors. The manufacturer of U-500 regular insulin has incorporated multiple differences in packaging between regular insulin U-100 and U-500 to decrease the risk of dispensing errors. Specifically, the regular insulin U-500 vial contains 20 mL compared to the U-100 vial, which contains only 10 mL. The U-500 insulin vial is also marked with a band of diagonal brown stripes to distinguish it from the U-100 vial, which contains no stripes.[4] The U-500 insulin pen (Humulin® R U-500 KwikPen®) approved by the FDA in 2016 may help eliminate many of these issues.

PREMIXED INSULIN

Products that contain premixed NPH and regular insulin in a fixed ratio of 70:30 are available from Lilly (Indianapolis, Indiana) as Humulin® 70/30 and from Novo Nordisk (Bagsværd, Denmark) as Novolin® 70/30. Additional premixed formulations are available in which both insulin lispro and insulin aspart have been cocrystallized with protamine to create an intermediate-acting insulin similar to NPH. Humalog® Mix 75/25™ and Humalog® Mix 50/50™ (Lilly) are products with lispro protamine and insulin lispro in a fixed ratio of 75:25 and 50:50, respectively. NovoLog® Mix 70/30™ (Novo Nordisk) is aspart protamine and insulin aspart in a fixed ratio of 70:30. These premixed insulins are useful for patients who have difficulty measuring and mixing insulins and are dosed twice daily. These insulins are compatible when mixed together and retain their

individual pharmacodynamic profiles. Each of these mixed insulin combinations is available as both vials and insulin pens, with the exception of Novolin® 70/30, which is available in insulin vials only (see Table 53-19 later in this chapter and Case 53-2, Question 15).

TREATMENT OF TYPE 1 DIABETES: CLINICAL USE OF INSULIN

Clinical Presentation of Type 1 Diabetes

CASE 53-2

Question 1: A.H., a slender, 18-year-old female who was recently discharged from the hospital for severe dehydration and mild ketoacidosis, is referred to the Diabetes Clinic from the University Student Health Service (no records available). A fasting and a random plasma glucose ordered subsequently were 190 and 250 mg/dL. Approximately 4 weeks before she was hospitalized, A.H. had moved across the country to attend college—her first time away from home. In retrospect, she remembers that she had symptoms of polydipsia, nocturia (six times a night), fatigue, and a 12-pounds (5.44-kg) weight loss during this period, which she attributed to the anxiety associated with her move away from home and adjustment to her new environment. Her medical history is remarkable for recurrent upper respiratory infections and three cases of vaginal moniliasis in the past 6 months. Her family history is negative for diabetes, and she takes no medications.

Physical examination is within normal limits. She weighs 110.23 pounds (50 kg) and is 64 inches (162.56 cm) tall. Laboratory results are as follows: FPG, 280 mg/dL; A_{1c}, 14%; and trace urine ketones as measured by Keto-Diastix®.

On the basis of her history and laboratory findings, the presumptive diagnosis is type 1 diabetes.

Which findings are consistent with this diagnosis in A.H.?

A.H. meets several of the diagnostic criteria for diabetes. She has classic symptoms of type 1 diabetes (polyuria, polydipsia, weight loss, fatigue, and recurrent infections), a random plasma glucose >200 mg/dL, and an FPG >126 mg/dL on at least two occasions as well as an A_{1c} >6.5%[4] (Tables 53-1 and 53-3). Features of A.H.'s

history that are consistent with type 1 diabetes, in particular, include the relatively acute onset of symptoms in association with a major life event (moving away from home), ketones in the urine, negative family history, and a relatively young age at onset.[33,34]

Treatment Goals

Case 53-2, Question 2: A.H. will be started on insulin therapy on this visit. What are the goals of therapy? Will normoglycemia prevent the development or progression of long-term complications?

The goal of diabetes management is the prevention of acute and chronic complications. The results of the DCCT and DCCT-EDIC studies convincingly demonstrated that lowering BG concentrations through intensive insulin therapy in persons with type 1 diabetes slows or prevents the development of microvascular complications.[26] The ADA recommends an A_{1c} goal of <7% for most patients, and an individual goal as close to normal as possible (<6.5%) if it can be achieved without significant hypoglycemia. For children and adolescents, the ADA recommends an A_{1c} goal of <7.5%, and an individualized goal of <7% if achievable without significant hypoglycemia.[100,101]

It is important to understand that physiologic or basal-bolus insulin therapy involves a *complete* program of diabetes management that includes a balanced meal plan, physical activity, frequent SMBG, and insulin adjustments based on these factors (Table 53-4).

In summary, A.H. is a patient newly diagnosed with type 1 diabetes who has not yet developed any signs or symptoms of long-term complications. Therefore, she is an ideal candidate for basal-bolus insulin therapy, and if she is willing and motivated, normoglycemia with rare hypoglycemic episodes is a reasonable long-term goal. This goal should be achieved gradually over the course of several months with insulin therapy, diet, education, and strong clinical support. A desirable goal is an A_{1c} value as close to

the normal range as possible with minimal episodes of hypoglycemia.

Basal-Bolus (Physiologic) Insulin Therapy

Case 53-2, Question 3: What methods of insulin administration are available to achieve optimal glucose control?

A physiologic insulin regimen is designed to mimic normal insulin secretion as closely as possible. Problems with insulin delivery include factors that affect the SC absorption of insulin (Table 53-8).[102] Before the development of the rapid-acting insulin analogs and basal insulins, previous insulins lacked pharmacodynamic profiles that allowed one to closely simulate normal pancreatic release of the hormone. In the nondiabetic individual, the pancreas secretes boluses of insulin in response to food. Between meals and throughout the night, the pancreas secretes small amounts of insulin that are sufficient to suppress lipolysis and hepatic glucose output (basal insulin). Clinicians now have more tools to mimic this basal-bolus model. Two methods have been used to achieve this pattern of insulin release: (a) insulin pump therapy (previously referred to as continuous SC infusion of insulin) and (b) basal-bolus insulin regimens consisting of once- or twice-daily doses of basal insulin coupled with premeal doses of rapid-acting insulin (see Case 53-2, Questions 3–5).

CONTINUOUS SUBCUTANEOUS INSULIN INJECTION

The use of continuous subcutaneous insulin infusion (CSII), commonly known as *insulin pumps*, is currently the most precise way to mimic normal insulin secretion. This consists of a battery-operated pump and a device that can program the pump to deliver predetermined amounts of rapid-acting insulin (ie, lispro, aspart, or glulisine) from a reservoir to an SC inserted catheter or needle.[89,90] One systematic review found that insulin pump therapy had a

modest A_{1c} reduction (−0.30% [95% CI, −0.58 to −0.02]) and reduction in severe hypoglycemia rates in children and adults (ADA section 7). In addition, older patients with type 1 diabetes may confer benefit from CSII. It has also shown to be beneficial in pediatric patients with type 1 diabetes in reducing diabetic ketoacidosis (DKA), neuropathy, and retinopathy. These systems are designed to deliver preset levels of insulin throughout the day to mimic basal insulin secretion, and can also be programmed to deliver meal-related boluses as needed. Most patients using an insulin pump use a rapid-acting insulin, rather than regular insulin. For meal coverage, the rapid-acting insulin can be given 0 to 15 minutes before eating. The delivery of the bolus can be adjusted based on the carbohydrate content of the meal.

If CSII delivery is interrupted, check for rise in glucose and urine ketones after 2 to 3 hours. CSII may also lead to lipohypertrophy and, in some instances, lipoatrophy. Most patients with diabetes discontinue CSII because of high costs, poor glycemic control, or discomfort from the device physically and emotionally (ie, depression and anxiety).

The preferred meal-planning approach for patients using an insulin pump is carbohydrate counting. The insulin-to-carbohydrate ratio, or how much carbohydrate is covered by 1 unit of insulin, must be determined. One method is to use the “500 rule.” The number 500 (or 450 for regular insulin) is divided by the total daily dose (TDD) of insulin the patient is using to determine the insulin-to-carbohydrate ratio (see Case 53-2, Question 11). Insulin pumps are capable of delivering many basal insulin rates. The basal insulin infusion rate may be adjusted depending on the situation. Many patients find it advantageous to decrease the basal rate during the middle of the night when nocturnal hypoglycemia is most likely to occur. The basal rate also may be increased before awakening to avoid hyperglycemia secondary to the “dawn phenomenon” or adjusted when physically active adjustments that are not possible when using SC basal insulin injections.

Several new CSII devices that allow a patient to manage their diabetes have emerged. One such device attaches on the skin like a patch and releases a set amount of insulin throughout the day while mealtime insulin can be released in 2-unit increments as needed. Features of the current pump models include bolus dose calculators based on preset carbohydrate-to-insulin ratios and correction factors, carbohydrate counts for selected foods, and an "insulin-on-board" feature, which helps avoid excessive dosing of insulin by indicating how much insulin from a previously administered dose should still be acting. Sensor-augmented pumps have effectively suspended insulin when glucose was low or predicted to go low in 30 minutes. One study showed that nocturnal hypoglycemia was significantly reduced with these types of systems Automation to Simulate Pancreatic Insulin REsponse (ASPIRE). Many of these systems have been FDA approved, and the most recent ones have been shown to effectively administer insulin if BG is either high or low, only requiring the patient to record meals and exercise. This has been called the *hybrid closed-loop approach* and is one step closer to a truly automated process for diabetes management.

Most insurance plans provide coverage for insulin pumps for patients with type 1 diabetes and for some patients with type 2 diabetes. Factors to consider when choosing a pump include safety features, durability, ability of the manufacturer to provide service, availability of training, clinically desirable features, CGM compatibility, and cosmetic attractiveness for the user.[90,103,104] The ADA website (www.diabetes.org) contains helpful information about insulin pumps for patients under the section on Living with Diabetes.

MULTIPLE DAILY INJECTIONS

CASE 53-2, QUESTION 4: How can insulin be administered to A.H. to model physiologic release of insulin from the pancreas?

There are a variety of insulin regimens that are intended to mimic the natural release of insulin from the pancreas.[105–107] Examples of

these are displayed and illustrated in **Figure 53-4**. A TDD of insulin is estimated empirically (eg, 0.3–0.5 units/kg/day for patients with type 1 diabetes) or according to guidelines listed in **Table 53-9**. The TDD of insulin then is split into several doses. In general, the basal dose comprises ~40% to 50% of the TDD, and the other bolus doses comprise the remaining 50%. If a patient eats three meals a day, the bolus dose would then be divided by three to calculate the number of units of bolus insulin required to cover each meal.

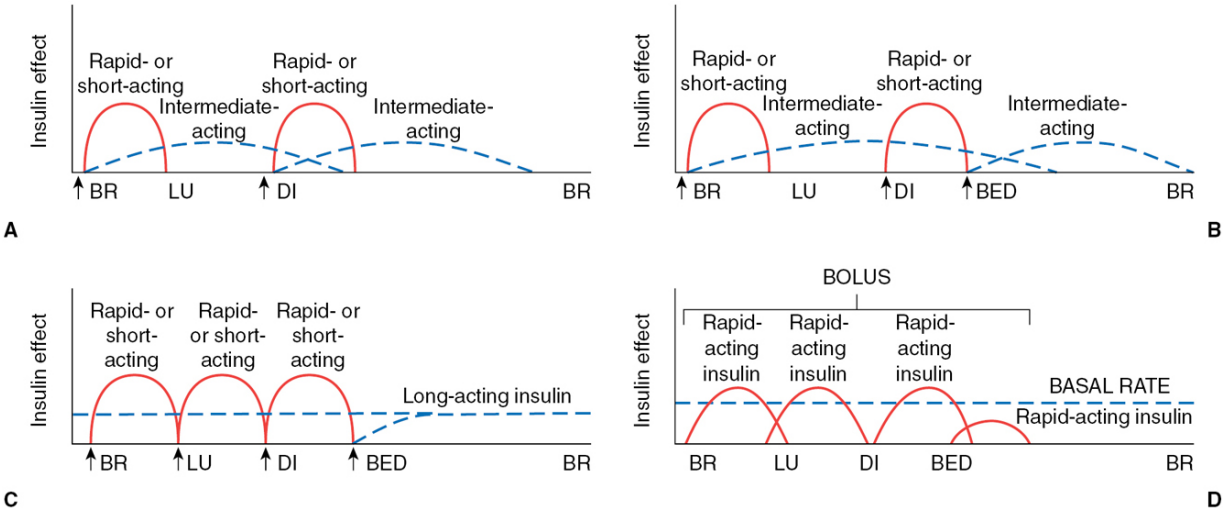


Figure 53-4 Theoretic insulin effect provided by various insulin regimens. A, Two daily injections of rapid-acting (insulin aspart, glulisine, or lispro), short-acting (regular), and intermediate-acting insulin (neutral protamine Hagedorn [NPH]). B, Morning injection of rapid-acting or short-acting insulin and intermediate-acting insulin, a predinner injection of rapid-acting or short-acting insulin, and a bedtime injection of intermediate-acting insulin. Suggested for patients with early morning hypoglycemia, and also those who have early morning hyperglycemia (owing to rebound phenomenon from hypoglycemia). C, Premeal injections of rapid-acting or short-acting insulin and long-acting (eg, insulin glargine or detemir) or intermediate-acting insulin (NPH) at bedtime. D, Continuous subcutaneous insulin infusion, showing an example with bolus given for a bedtime snack. BR, breakfast; Bed, bedtime; DI, dinner; LU, lunch. Arrows indicate time of insulin injection (<15 minutes before

meals for rapid-acting insulin and 30 minutes before meals for short-acting insulin).

Table 53-9
Empiric Insulin Doses

Estimating Total Daily Insulin Requirements	
These are initial doses only; they must be adjusted using SMBG results. Patients may be particularly resistant to insulin if their blood glucose concentrations are high (glucose toxicity); once glucose concentrations begin to drop, insulin requirements often decrease precipitously. The weight used is actual body weight. Insulin dose requirements can change dramatically with time depending on circumstances (eg, a growth spurt, modest weight gain or loss, changes in physical activity, stress, or illness).	
Type 1 diabetes	
Initial dose	0.3–0.5 units/kg
Honeymoon phase	0.2–0.5 units/kg
With ketosis, during illness, during growth	1.0–1.5 units/kg
Type 2 diabetes	
With insulin resistance	0.7–1.5 units/kg
Estimating Basal Insulin Requirements	
These are empiric doses only and should be adjusted using appropriate SMBG results (fasting or premeal). Basal requirements vary throughout the day, often increasing during the early morning hours. The basal requirement also is influenced by the presence of endogenous insulin, the degree of insulin resistance, and body weight. Basal requirements are ~50% of total daily insulin needs. Thus, basal insulin dose is ~50% of TDD. A conservative approach is to reduce the calculated 50% basal dose by 20% to avoid hypoglycemia.[63]	
Estimating Premeal Insulin Requirements	
The premeal insulin requirements are ~50% of the TDD, usually divided equally into three doses initially, taken with each meal (ie, breakfast, lunch, and dinner), and then each premeal dose is individually adjusted based on BG readings. The “500 rule” estimates the number of grams of carbohydrate that will be covered by 1 unit of rapid-acting insulin. The rule is modified to the “450 rule” if using regular insulin.	
500/TDD of insulin—number of grams covered	
Example: For a patient using 50 units/day, 500/50 = 10. Therefore, 10 g of	

carbohydrate would be covered by 1 unit of insulin lispro, glulisine, or aspart. This equation works very well for patients with type 1 diabetes in estimating their premeal insulin requirements. Because patients with type 2 diabetes have insulin resistance, the rule may underestimate their insulin requirements.
Determining the "Correction Factor"
Supplemental doses of rapid-acting insulin are administered to acutely lower glucose concentrations that exceed the target glucose concentration. These doses must be individualized for each patient and again are based on the degree of sensitivity to insulin action. For example, if the premeal blood glucose target is 120 mg/dL and the patient's value is 190 mg/dL, additional units of rapid-acting insulin could be added to the premeal dose. The correction factor determines how far the blood glucose drops per unit of insulin given and is known as the "1700 rule." For regular insulin, the rule is modified to the "1500 rule." The equation is as follows:
1700/TDD = point drop in blood glucose per unit of insulin
Example: If a patient uses 28 units/day of insulin, their correction factor (or insulin sensitivity) would be 1700/28 = 60 mg/dL. Therefore, the patient can expect a 60-mg/dL drop for every unit of rapid-acting insulin administered. Patients with a higher sensitivity factor have lower insulin requirements. Individuals with a lower sensitivity factor (higher insulin requirements) typically achieve a smaller reduction in blood glucose per unit of insulin

SMBG, self-monitored blood glucose; TDD, total daily dose.

Sources: DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA*. 2003;289(17):2254–2264. doi:10.1001/jama.289.17.2254; Walsh J, Roberts R. *Pumping Insulin: Everything You Need for Success on a Smart Insulin Pump*. 4th ed. Torrey Pines Press; 2006; Walsh J, Roberts R, Bailey T, Varma CB. *Using Insulin: Everything You Need for Success With Insulin*. Torrey Pine Press; 2003.

A regimen much less commonly used in patients with type 1 diabetes involves injecting a mixture of intermediate-acting and regular or rapid-acting insulin twice daily, before breakfast and before dinner (Fig. 53-4A). The morning dose of regular or rapid-acting insulin is intended to cover the increase in BG due to the breakfast meal; the morning dose of NPH covers the noon meal and provides basal insulin throughout the day; the evening dose of regular or rapid-acting insulin covers the evening meal; and the evening dose of NPH provides basal insulin levels during the night and covers any evening snack that is ingested. Because NPH is an intermediate-acting insulin and has a peak effect, it does not provide

true basal insulin coverage. When NPH is injected in the morning, the patient must eat lunch on time because of this peak effect; otherwise, he/she will experience hypoglycemia. Also, when NPH is taken with mealtime insulin before dinner, the patient is at risk for nocturnal hypoglycemia from the peak effect of the evening dose of NPH. The advantage of using a rapid-acting insulin (eg, insulin lispro, insulin aspart, or insulin glulisine) instead of regular insulin in this regimen is to facilitate the patient being able to take insulin doses immediately before a meal. However, the peak effect of the NPH component in this combined dose still presents the same problems. Although this type of regimen may decrease the overall total number of injections per day, it does not mimic physiologic insulin release.

Figure 53-4B depicts a variation of this method. It is the same except that the evening dose of NPH is given as a third injection at bedtime. This shifts the time of peak effect from ~2:00 to 3:00 AM to ~7:00 AM. By administering NPH at bedtime, nocturnal hypoglycemia is reduced, and peak insulin activity occurs when the patient is more likely to be awake and ingesting food. This method may be useful for patients in whom nocturnal hypoglycemia and fasting hyperglycemia are particularly troublesome; however, this regimen also does not mimic physiologic insulin release.

The regimen that most closely mimics physiologic insulin release besides the use of an insulin pump is the use of a once-daily basal insulin such as insulin glargine, detemir, or degludec to provide basal insulin levels throughout the day, along with doses of a rapid-acting insulin (preferred) or regular insulin before meals (Fig. 53-4C depicts the long-acting insulin given at bedtime, but it may alternatively be given in the morning). When smaller doses are used, twice-daily insulin detemir and possibly U-100 insulin glargine will be required for 24-hour coverage.[108,109] Insulins U-100 and U-200 degludec and U-300 glargine will last 24 hours with once-daily dosing. This method theoretically provides insulin similar to the insulin pump: constant basal levels plus small boluses for meals and snacks. In doing so, it offers some of the same advantages of the pump in that it permits

some degree of flexibility in the patient's lifestyle. For example, if a patient with diabetes chooses to skip a meal, they omit a premeal bolus; if the patient chooses to eat a larger meal than usual, they increase the premeal bolus. Similar dose adjustments can be made to accommodate snacks, exercise patterns, and acute illnesses. Alternatives to this regimen are depicted in Table 53-4, where the long-acting insulin is replaced with intermediate-acting insulin for basal coverage and or the rapid-acting insulin is replaced with short-acting insulin for bolus coverage. These options, however, are not preferred because they do not as closely mimic normal physiologic insulin release.

CASE 53-2, QUESTION 5: Should A.H. use an insulin pump or multiple daily insulin injections?

Indications for basal-bolus insulin therapy are listed in **Table 53-10**. Patients with type 1 diabetes should be placed on a basal-bolus insulin regimen. A.H. is an ideal candidate to strive for an A_{1c} goal of <6.5%. She is newly diagnosed, has not yet developed the long-term complications of diabetes, and should derive the benefits of normoglycemia. Assuming A.H. will be able to manage a basal-bolus insulin regimen, individualized target BG levels that strive for the best level of glucose control possible without placing her at undue risk for hypoglycemia should be prescribed. She must be willing to test her BG concentrations four or more times daily or utilize a continuous BG monitor and inject herself four or more times daily or learn about the use and care of an insulin pump. She also must be willing to keep detailed BG and food records and participate in an extensive education program that enables her to adjust her insulin doses based on BG concentrations, physical activity, and the carbohydrate content of her snacks and meals.

Table 53-10
Basal-Bolus (Physiologic) Insulin Therapy: Indications and Precautions

Patient Selection Criteria
Type 1 diabetes, otherwise healthy patients (age >7 years) who are highly motivated, engaged in diabetes self-management, and are able to adhere to a complex insulin regimen. Must be willing to test blood glucose concentrations multiple times daily and inject four doses of insulin daily, on average
Females with diabetes who plan to conceive
Pregnant patients with diabetes (preexisting)
Patients poorly controlled on conventional therapy, 2–3 injections daily (includes patients with type 2 diabetes)
Technical ability to test blood glucose concentrations
Intellectual ability to interpret blood glucose concentrations and adjust insulin doses appropriately
Access to trained and skilled medical staff to direct treatment program and provide close supervision
Avoid or Use Cautiously in Patients Who Are Predisposed to Severe Hypoglycemic Reactions or in Whom Such Reactions Could Be Fatal
Patients with counterregulatory insufficiency
β-Adrenergic blocker therapy
Autonomic insufficiency
Adrenal or pituitary insufficiency
Patients with coronary or cerebral vascular disease
(*Note:* Counterregulatory hormones released in response to hypoglycemia may have adverse effects in these individuals.)
Unreliable, nonadherent individuals, including those who abuse alcohol or drugs and those with psychiatric disorders

Transition to an insulin pump is facilitated by patients being able to attain these skills using multiple daily SC insulin injections before insulin pump initiation. The ADA recommends that the use of insulin pumps be limited to highly motivated individuals under the guidance of a health care team trained and knowledgeable in their use. Pumps offer the patient the ability to use multiple basal rates during the 24-hour period and assist with the calculation of bolus and correction insulin doses. Most studies have shown that pump therapy provides

equivalent and sometimes better glycemic control than does intensive management with multiple injections.[102,110]

Insulin pumps are particularly useful in patients with frequent, unpredictable hypoglycemia, or marked dawn phenomena (see Case 53-3). Others have described the methods by which insulin doses are established and altered in patients using the insulin pump.[111] Because A.H. has just been diagnosed, she should be initiated on a basal-bolus SC insulin therapy. Once she has acquired these skills, she may be considered for pump therapy.

Clinical Use of Insulin

INITIATING INSULIN THERAPY

CASE 53-2, QUESTION 6: How should multiple daily insulin injections be initiated in A.H.?

A conservative TDD of insulin is estimated empirically or according to guidelines similar to those listed in Table 53-9 in newly diagnosed patients and will differ in patients with type 1 and type 2 diabetes. Many weight-based empiric dose calculations have been proposed, as listed in Table 53-9, for patients with both type 1 and type 2 diabetes; however, these regimens are mostly beneficial for patients with type 1 diabetes because these patients are completely insulin deficient. For patients with type 2 diabetes, initial basal insulin doses that are weight based or a starting dose of ~10 units daily are appropriate options based on patient-specific information. Insulin doses would then be adjusted based on home blood glucose (HBG) levels.[76,111]

For a basal-bolus insulin regimen, insulin glargine, insulin detemir, or insulin degludec could ideally be used as the basal insulin with bolus doses of a rapid- or short-acting insulin (insulin lispro, insulin aspart, or insulin glulisine) given at mealtime. During the initial visit, A.H. needs to learn how to inject her insulin (see Case 53-2, Question 8), how to test her BG (**Table 53-11**), how and when to test

for ketones (either urine or blood), and how to recognize and treat hypoglycemia (**Table 53-12**). She also needs to understand the importance of meal planning and the relationship between carbohydrate intake and insulin action (**Table 53-13**). It is very important not to overwhelm A.H. with information on the first visit. One should be particularly sensitive to the psychological impact of this diagnosis on A.H., address her major concerns, and provide only the information that is absolutely essential before the next visit. Between visits, she should be assessed and provided information on an as-needed basis by phone. **Table 53-14** lists important areas of patient education.

Table 53-11

Self-Monitored Blood Glucose Testing: Areas of Patient Education

When and How Often to Test
Technique
How and when to calibrate the glucose monitor
Review all “buttons” and their purposes. Identify battery type. Review cleaning procedures, if applicable.
Preparation
1. Calibrate monitor/set code for batch of test strips, if required. 2. Insert test strip to turn machine on (some meters require user to turn machine on). 3. Prepare all materials: tissue, strip, and lancet. 4. Remember to close the lid of the strip container immediately. Strips exposed to air and moisture deteriorate rapidly. 5. Wash hands with warm water. *Dry thoroughly.* A wet finger causes blood to spread rather than form a drop. Milk the finger from the base to ensure an adequate flow of blood. 6. Lance the tip of the finger. Avoid the pads of the finger where nerve endings are concentrated. 7. Hold the finger *below* the heart with the lanced area pointing toward the floor. 8. Once a sufficient amount of blood is available, *quickly* apply blood to designated area of the test strip. Depending on the strip type, the blood sample is placed in an area on the surface of the strip, or it is applied to the side of the strip where it is taken up by capillary action.

Record Results in a Log Book and Bring to All Clinician Visits. Include relevant information regarding diet or exercise.
How to Use Results to Achieve Glycemic Targets; Educate Patients on What to Do With Their Blood Glucose Readings (eg, adjust their insulin dose; modify their carbohydrate content).

Table 53-12
Hypoglycemia

Definition
Level 1: Blood glucose concentration <70 mg/dL, but <54 mg/dL: Patient may or may not be symptomatic (tremors, palpitations, sweating, intense hunger); patients are able to self-treat.
Level 2: Blood glucose <54 mg/dL: Patient is generally symptomatic; patient may be neuroglycopenic (experience autonomic symptoms: headache, mood changes, decreased attention, drowsiness). Patients may require assistance in treating.
Level 3: No designated blood glucose: Severe hypoglycemia associated with altered mental status and physical function; patient may become unconscious, unresponsive, or have convulsions. Patients require assistance for appropriate treatment.
Common Signs and Symptoms of Hypoglycemia
Blurred vision, sweaty palms, generalized sweating, tremulousness, hunger, confusion, anxiety, circumoral tingling, and numbness. Patients vary with regard to their symptoms. Behavior can be confused with alcohol inebriation. Patients become combative and use poor judgment.
Nocturnal hypoglycemia: nightmares, restless sleep, profuse sweating, morning headache, morning “hangover.” Not all patients have symptoms during nocturnal hypoglycemia.
Clinical Considerations
Irregular eating patterns
↑ Physical exercise
Gastroparesis (delayed gastric emptying)
Defective counterregulatory responses
Excessive dose of insulin or insulin secretagogues (sulfonylureas, glinides)
Alcohol ingestion
Drugs

Treatment	
Ingest 10–20 g of rapidly absorbed carbohydrate. Repeat in 15–20 minutes if glucose concentration remains <70 mg/dL or if patient is symptomatic. Follow with complex carbohydrate/protein snack if mealtime is not imminent.	
The following are examples of food sources that provide 15 g of carbohydrate:	
Orange, grapefruit, or apple juice; regular, non-diet soda	1/2 cup
Fat-free milk	1 cup
Grape juice, cranberry juice cocktail	1/3 cup
Sugar	1 tbsp or 3 cubes
Lifesavers	5–6 pieces
Glucose tablets	3–4 tablets
If patient is unconscious, the following measures should be initiated:	
Glucagon 1 mg intranasal, SC, IM, or IV (generally administered IM in outpatient setting; mean response time, 6.5 minutes)	
Glucose 25 g IV (dextrose 50%, 50 mL; mean response time, 4 minutes)	

IM, intramuscular; IV, intravenous; SC, subcutaneous.

Source: American Diabetes Association. 6. Glycemic targets. *Diabetes Care*. 2015;38(suppl1):S33–S40. doi:10.2337/dc15-S009.

Table 53-13
Interpreting Self-Monitored Blood Glucose Concentrations

Test Time	Target Insulin Dose	Target Meal/Snack
Prebreakfast (fasting)	Predinner/bedtime intermediate-acting or basal insulin	Dinner or bedtime snack
Prelunch	Prebreakfast regular or rapid-acting insulin	Breakfast or midmorning snack
Predinner	Prebreakfast intermediate-acting insulin or prelunch regular or rapid-acting insulin	Lunch or midafternoon snack
Bedtime	Predinner regular or rapid-acting insulin	Dinner
2-hour postprandial	Premeal regular or rapid-acting insulin	Preceding meal or snack

Test Time	Target Insulin Dose	Target Meal/Snack
2:00–3:00 AM or later	Predinner intermediate-acting insulin or basal insulin if given in AM	Dinner or bedtime snack

Considerations: (a) Assumes a regular meal pattern. For patients who travel, have odd working or sleeping hours, or have irregular meal patterns, these guidelines may not apply. (b) Assumes administration of regular insulin 30 to 60 minutes before meals or rapid-acting insulin 0 to 15 minutes before meals and a normal pattern of insulin response (see Table 53-8 for factors that can alter insulin absorption and response). (c) If prebreakfast concentrations are high, rule out reactive hyperglycemia (Somogyi reaction or posthypoglycemic hyperglycemia). Consider contribution of dawn phenomenon as well. Whenever blood glucose concentrations are high, consider reactive hyperglycemia (excessive insulin doses). (d) Consider accuracy of reported test results: (i) Do they correlate with the glycated hemoglobin (A_{1c}) and patient's signs and symptoms? (ii) What is the patient's medication adherence? Could results be fabricated? (iii) Is the patient's technique appropriate? Check timing, adequate blood sample, machine, strips, and calibration (Table 53-11). (iv) Are insulin kinetics altered? (v) What is the carbohydrate content, quality, and regularity of meals?

Table 53-14
Areas of Patient Education

Diabetes: Pathogenesis and the complications
Hyperglycemia: Signs and symptoms
Ketoacidosis: Signs and symptoms (Tables 53-22 and 53-23)
Hypoglycemia: Signs, symptoms, and appropriate treatment (Table 53-12)
Exercise: Effect on blood glucose concentrations and insulin dose (Table 53-19)
Diet: See text. Emphasis placed on carbohydrate counting because the carbohydrate is responsible for 90% of the rise in blood glucose after a meal
Insulins
Injection technique
Types of insulin
Time of action profiles (onset, peak, and duration)
Storage
Stability (look for crystallization and precipitation with NPH insulin)
Therapeutic goals: A_{1c}, fasting, preprandial, and postprandial blood glucose

levels, cholesterol, triglyceride, blood pressure (refer to Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease; and Chapter 9, Essential Hypertension)
SMBG testing: Table 53-13
Interpretation of SMBG testing results
Foot care: Inspect feet daily; wear well-fitted shoes; avoid self-care of ingrown toenails, corns, or athlete's foot; see a podiatrist.
Sick day management: Table 53-20
Cardiovascular risk factors: Tobacco use, high blood pressure, obesity, elevated cholesterol
Importance of annual ophthalmologic examinations; tests for microalbuminuria; keeping up to date with immunizations

A_{1C}, glycated hemoglobin; NPH, neutral protamine Hagedorn; SMBG, self-monitored blood glucose.

A reasonable first approach for A.H. is to provide a TDD of 24 units of insulin (~0.5 units/kg). Because 50% of the daily dose should be given as basal insulin and the remainder given as rapid-acting insulin divided into three doses, A.H. would take the following: 12 units of basal insulin (either insulin glargine or insulin degludec) once daily (morning or bedtime) with 4 units of rapid-acting insulin (insulin aspart or lispro) given ~5 to 10 minutes before each meal.[111] Alternatively, if insulin detemir is used, the dose would generally be split twice daily (6 units bid) because the duration of action of insulin detemir is typically <24 hours when given at such a small dose. Caveat: As A.H.'s glucose concentration returns to normal; glucose toxicity will recede, and she may require less insulin.

SELECTING AN INSULIN DELIVERY DEVICE

CASE 53-2, QUESTION 7: What kind of insulin delivery device should be prescribed for A.H.?

Insulin delivery is achieved utilizing syringes, prefilled insulin delivery devices (pens), or through oral inhalation. Insulin syringes are plastic, disposable syringes with needles that are extremely fine

(typically 30–31 gauge), sharp, and well lubricated to ease insertion. Pen needles and syringes have been improved so that insulin injections are relatively painless if proper technique is used. The lengths of needles are 15/64 inch (6 mm), 5/16 inch (8 mm), or ½ inch (12.7 mm).[112] Research has shown that there is no medical reason why a patient would require use of a needle longer than 4 to 6 mm for insulin administration because skin thickness does not vary between different demographics. Previous thoughts that larger or obese patients require longer needle length for proper insulin administration have been disproven. Manufacturers produce 1-, 0.5-, and 0.3-mL syringes for U-100 insulin. For patients such as A.H., using fewer than 30 units of insulin per injection, the 0.3-mL syringe is preferred for ease of reading the dose markings on the syringe. Insulin syringes are available in 1-unit increments or 0.5-unit increments. One-half-unit increments are useful for pediatric patients and for patients who count carbohydrates because mealtime insulin doses can be rounded to the 0.5 unit.[112,113]

Insulin pen devices are also available for injecting insulin. Pen devices may increase dosing accuracy and are often preferred because they make insulin administration much easier, especially for patients who need to take their insulin doses away from home.[114–116] The pens are particularly useful for patients with (a) regimens consisting of multiple daily doses of rapid- or short-acting insulin before meals and snacks (such as A.H.), (b) a fear of needles, (c) impaired visual or dexterity problems, (d) hectic work schedules or lifestyle, or (e) a need to train alternative individuals who administer insulin (eg, school nurses or siblings). In addition, studies have shown that use of insulin pen devices versus vial and syringe insulin administration may result in fewer discontinuations of insulin therapy and improve overall adherence to an insulin regimen.[117]

Pens eliminate the need to draw insulin up in a syringe because the insulin dose is dialed up on the device. Pen devices are available as a disposable prefilled pen or a durable pen in which an insulin cartridge is replaced. Most typically used are the prefilled pens that contain a built-in, single-use insulin cartridge. Most U-100 formulations contain 300 units of insulin, whereas concentrated

insulins will contain more units in each device. Pen devices are available to dose insulin in 1-unit (most) and 0.5-unit increments. Pen needles are available in 29-, 30-, 31-, and 32-gauge needles and 5/32 inch (4 mm), 3/16 inch (5 mm), 1/4 inch (6 mm), 5/16 inch (8 mm) lengths, and ½ inch (12.7 mm), but there is no medical rationale to use needles longer than 6 mm. Patients are advised to use a new disposable needle for each injection. Unfortunately, limited health insurance coverage and higher copays may deter pen use.[112]

For insulin delivery using an insulin pump, see Case 53-2, Questions 3 and 5.

If she elected to use a syringe, a 0.3-mL U-100 insulin syringe with a short needle length should be prescribed for A.H. Subjectively, patients can "feel" the difference between different brands, or they may prefer the "ease of bubble removal," physical characteristics, or packaging of one syringe over another. If she elected to use an insulin pen, a prefilled pen for insulin glargine and insulin aspart or insulin lispro are available. The shortest possible needle length (4 mm for pen needles and 6 mm for syringes) should be prescribed for A.H.

MEASURING AND INJECTING INSULIN

Injection

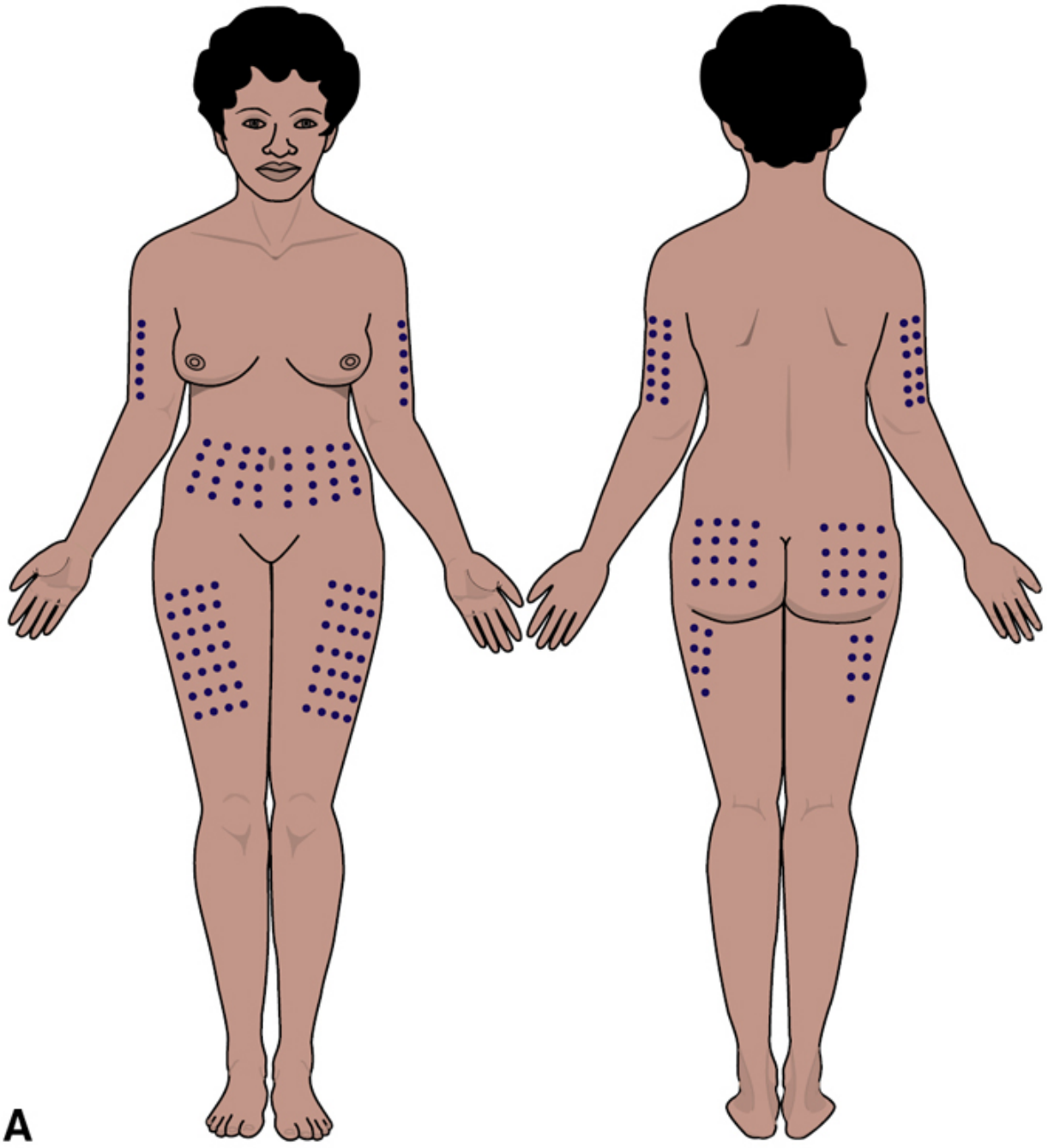
Case 53-2, Question 8: How should A.H. be instructed to administer her insulin injections?

A.H. should prepare an area for injection. Alcohol swabs may be used to clean the rubber stopper of the insulin vial (or pen device). To inject the insulin SC, A.H. should be instructed to firmly pinch up the area to be injected (this creates a firm surface for the injection) and to quickly insert the needle perpendicularly (90° angle) into the center of this area. Note, however, that pinching is only necessary when A.H. is using a syringe that is ≥6 mm.[112] The syringe should be held toward the middle or back of the barrel, like a pencil. Anxious

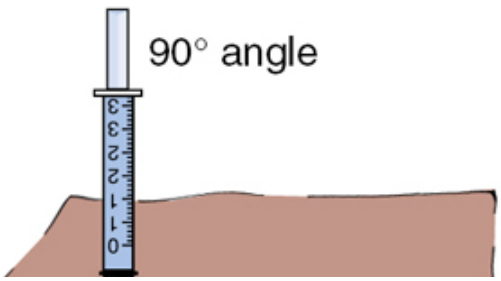
patients have a tendency to “choke” the hub of the syringe, and this prevents proper needle insertion. A 45° angle of injection may be used for infants and very thin individuals who have little SC fat, especially in the thigh area.[112] The site should not be massaged, because this may accelerate the absorption and onset of action of insulin (Table 53-8). When using an insulin pen, the needle should be embedded within the skin for about 5 to 10 seconds after depressing the dosing knob to ensure full delivery of the insulin dose.[112,118]

Rotating injection sites

The primary sites used for injecting insulin are the lateral thigh, abdomen (avoid the 2-inch radius around the navel), and upper arm (**Fig. 53-5**). The ADA and American Association of Diabetes Educators (AADE) recommend that insulin injections be rotated within the same anatomic region to decrease the chances of variability in insulin absorption.[82] The abdominal area is often the most recommended site of administration because this site has the most predictable absorption and is least affected by exercise.[119] Alternatively, A.H. can be instructed to rotate her morning injection within one region (eg, the abdomen) and her evening injection in another anatomic region. This minimizes the variables that can alter her response to insulin.



A



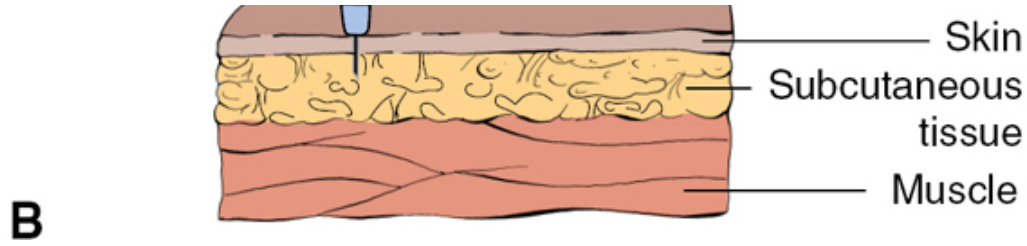


Figure 53-5 Selecting insulin injection sites. A, Areas of the body most suitable for insulin injections. The actual point of injection should be varied each time within a chosen body area. Give injections at least 1 inch apart. Patients should consult with their provider or diabetes educator about which area is most appropriate for use. B, The site where insulin should be injected. Insulin is injected into the subcutaneous tissue (between the skin and the muscle layer). If the skin is pinched up and the needle is pushed all the way in, the needle will reach the proper space under the skin. (A, LifeART image © 2011. Lippincott Williams & Wilkins. All rights reserved; B, Adapted with permission from Springhouse. *Lippincott's Visual Encyclopedia of Clinical Skills*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009.)

Rotating injection sites is recommended to avoid the lipodystrophic effect of insulin (lipohypertrophy and lipoatrophy); however, because insulin has been purified, these complications are less common.[82,112] Nevertheless, repetitive use of the same site of injection may still result in lipohypertrophy, and it does toughen the skin, making needle penetration more difficult. Furthermore, insulin absorption from lipohypertrophic sites can be slowed.[112]

Agitation

A.H. does not need to agitate insulin glargine or aspart because these are clear insulins. For NPH insulin, which is a suspension, or a combination/mixed insulin, the vial or pen must be gently agitated before use. The vial should be rolled between the palms of the hands to minimize foaming. A pen device is inverted back and forth to mix the insulin. Agitation is only required for insulin suspensions (ie, insulin mixtures).

Measurement

First, A.H. should make sure her hands and the injection site are clean. She should withdraw the plunger to the level of insulin she intends to inject (eg, 12 units for her insulin glargine dose), then she should insert the needle into the vial, and inject the air to prevent creation of a vacuum within the vial. The vial then should be inverted with the syringe inserted, and 12 units of insulin glargine should be withdrawn. The bevel of the needle should be well below the surface of the insulin to avoid withdrawing air or bubbles into the syringe. Insulin glargine must not be mixed in the same syringe with her rapid-acting insulin, and it should be injected into a different site if it is injected at the same time as her glargine dose.[14]

The barrel of the syringe should be held at eye level to check for air bubbles and to allow accurate placement of the plunger tip at the 12-unit mark. If bubbles are present, they should be removed by tapping the syringe gently to coax the bubbles to the top of the barrel, where they can be injected back into the insulin vial. To remove air bubbles in an insulin pen, prime the pen with 2 units of insulin before each use (repeat until an insulin drop appears at tip of pen needle). Also, remove and discard the pen needle from the device in between uses to prevent air bubbles from accumulating.

CASE 53-2, QUESTION 9: How should A.H. be educated to self-monitor her BG? What types of self-monitoring BG tests are available, and what are the major differences among them? How accurate are results obtained from home BG testing? Should she begin CGM at the same time?

SELF-MONITORING OF BLOOD GLUCOSE

The ADA recommends that most individuals with diabetes should attempt to attain and achieve normoglycemia as safely as possible. SMBG is a tool to allow patients to safely achieve these goals. For patients with type 1 diabetes, this can be achieved by the routine use of SMBG. SMBG is also important in (a) pregnancy complicated by diabetes, (b) patients with unstable diabetes, (c) patients with a propensity for severe ketosis or hypoglycemia, (d) patients prone to

hypoglycemia who may not experience the usual warning symptoms, and (e) patients using an insulin pump. The technology in this area is changing rapidly, with new monitors with advanced features being introduced yearly.[14]

All monitors use test strips and are self-timing, requiring no patient action after the blood is placed on the strip. Several factors should be taken into account when evaluating a monitor and its appropriateness for an individual. The primary considerations are ease of use, accuracy relative to a reference standard, reliability, insurance coverage, and cost.[14]

Most monitors no longer require coding for the test strips, which simplifies the process for patients. Convenience factors include meter size, volume of blood required for testing, site to obtain sample (eg, finger vs alternative site such as forearm), capacity of the meter to store BG values (memory) and data such as comments, required testing time, ability to download BG values, general availability of strips, ability to turn off audible signals, audible readings and instructions for visually impaired, and availability of technical support. Some devices are less reliable for use in anemic patients (eg, patients undergoing renal transplant), and all function most reliably within certain temperature ranges (usually 60–95 °F [15.56–35 °C]) and humidity (generally <90%) conditions. Strips are sensitive to light, moisture, and temperature extremes and must be stored and handled with care. In recent years, CGMs have also become more readily available to the public, and offer a more convenient option for testing glucose levels compared to a traditional home BG monitor.

Patient education regarding any testing procedures, and, if needed, the importance of logging results in a diary, and test times is critical. Ultimately, A.H. should be taught how and when to check her BG levels to optimize her insulin regimen (**Table 53-15**).

Table 53-15
Guidelines for Dosing Insulin

Basic Insulin Doses

First, adjust the basic insulin dose (ie, the dose that the patient will be instructed to take daily).

Only adjust insulin doses if a *pattern* of response is observed under stable diet and exercise circumstances. That is, the same response to insulin is observed for ≥3 days, particularly for the basal insulin dose. It is important to verify the stability of diet and exercise. Consider adjusting these variables as well.

Unless all levels are >200 mg/dL, try to adjust one component of insulin therapy at a time.

Start with the insulin component affecting the FBG concentration. This glucose level often is the most difficult to control, and often affects all other glucose concentrations measured throughout the day. The basal insulin dose is often what is adjusted to control the FBG. However, if the dinner insulin dose (of rapid-acting or short-acting insulin) is not adequate, this can result in hyperglycemia that can persist into the morning. The basal dose is typically adjusted by 2–4 units, no sooner than every 3–4 days.

Prandial/mealtime insulin dose:

- For patients eating a set amount of carbohydrate at meals: typically adjust the basic insulin dose by 1–2 units at a time. The amount given is based on the individual patient's response to insulin. This can be determined by looking at the patient's TDD using the "500 rule" (see the following, and Table 53-9).
- For patients using the insulin-to-carbohydrate method (ie, 1 unit rapid-acting or short-acting insulin for every *x* g of carbohydrate), adjust the "ratio" based in the patient's response to insulin (eg, 1:8, 1:10, 1:12, 1:15, 1:18, 1:20).

General Principles

Assume that diet and physical activity are stable. Set a reasonable goal initially. This may mean the upper limits of the acceptable concentrations may be high initially (eg, <200 mg/dL). Move toward a more ideal goal slowly.

Supplementary Insulin Doses (with rapid-acting or short-acting insulin)

Once the basic dose of prandial insulin has been established, supplemental doses of rapid- or short-acting insulin can be prescribed to correct *preprandial* hyperglycemia. For example, if the goal is 140 mg/dL and the glucose value is 190 mg/dL, administer one additional unit. Supplemental doses also can be used when the patient is ill (Table 53-15).

Algorithms for correction doses are based on the patient's sensitivity to insulin using the "1500 or 1700 rule" (Table 53-9).

If premeal glucose concentrations are <70 mg/dL, the dose of aspart, glulisine, lispro, or regular insulin administered before the meal is ↓ by 1–2 units; insulin administration is delayed until just before the meal; the meal should include an extra 15 g of glucose if the value is <50 mg/dL.

If supplemental doses before a given meal are required for ≥3 days, the basic insulin dose should be adjusted appropriately. For example, if a patient taking lispro before meals requires an extra 2 units before lunch for ≥3 days, 2 units should be added to the prebreakfast dose, or the insulin-to-carbohydrate ratio at breakfast should be adjusted (eg, if patient was using a 1:15 ratio, a 1:12 ratio could be used). Rapid-acting insulin doses should be adjusted no more frequently than every 2–3 days.
Anticipatory Insulin Doses (With Rapid-Acting or Short-Acting Insulin)
The basic insulin dose is ↑ or ↓ based on the anticipated effects of diet or physical activity.
↑ Aspart/glulisine/lispro or regular insulin by 1 unit for each additional 15 g of carbohydrate ingested (eg, holiday meal) or ↓ the usual dose by 1–2 units if the meal is smaller than usual (Table 53-9).
See Table 53-19 for the recommended insulin adjustments for exercise.

FBG, fasting blood glucose; TDD, total daily dose.

Used properly, available monitors provide accurate results that can be used by patients to manage their diabetes. Problems with a monitor can be detected by performing a quality control test. **Table 53-16** lists factors that can affect results of SMBG test results. Any time SMBG values are inconsistent with the patient's symptoms or A_{1c} values, sources of error should be evaluated. A.H.'s technique should be reviewed periodically because clinical decisions are often based on the patient's BG testing record.

Table 53-16
Factors That Can Alter Self-Monitored Blood Glucose Test Results: Troubleshooting

Glucose monitor not coded for batch of test strips[a]
An inadequate amount of blood applied to test strip[b]
Improper storage of test strips (temperature and humidity)[a]
Dirty glucose monitor[a]
Low battery[a]
Test performed outside of altitude, temperature, and humidity operating conditions[a]

Low[c] or high[b] hematocrit
Dehydration[b]
Hyperosmolar, nonketotic state[b]
Lipemia[a]
Interfering substances
Nonglucose sugars (eg, maltose, xylose, galactose) in meters using GDH-PQQ test strips[118]
Large amounts of acetaminophen[c]
Large amounts of ascorbic acid or salicylates (rare)[b]

GDH-PQQ, glucose dehydrogenase pyrroloquinoline quinone.

[a]Effect unpredictable.

[b]Values tend to be lower.

[c]Values tend to be higher.

Source: Heinemann L. Quality of glucose measurement with blood glucose meters at the point-of-care: relevance of interfering factors. *Diabetes Technol Ther*. 2010;12:847–857.

Because A.H. is just starting insulin therapy and SMBG, it would be reasonable to hold off on considering CGM until she becomes comfortable with these skills. Then, she and her practitioner could assess whether CGM would be useful.

TESTING FREQUENCY

Case 53-2, Question 10: How often should A.H. test her BG concentrations?

Although the exact frequency and timing of BG tests should be dictated by individualized patient goals, most patients with type 1 diabetes using an intensive basal-bolus insulin regimen should perform SMBG multiple times per day. This may include before meals and snacks, bedtime, 2 hours postprandially, and before exercise, when the patient suspects hypoglycemia, after treatment of hypoglycemia, or when the patient is performing a critical task such as driving.[14]

Because A.H. is being initiated on insulin therapy with the goal of normoglycemia, she should ideally self-monitor her BG four times/day (before meals and at bedtime) for 2 weeks until the pattern of blood sugar fluctuation can be assessed and adjustments to her insulin regimen can be made. Motivated patients may continue this degree of monitoring, but it may be reduced to twice daily for patients on long-term insulin who have achieved glycemic control. Varying the time of day in which testing is performed will allow the clinician and patient to make informed decisions on how to make adjustments. For those patients who are not using an intensive insulin regimen, such as patients with type 2 diabetes using insulin, there is insufficient evidence as to how often a patient should check their BG because of the decreased risk of hypoglycemia.[120,121] There is also insufficient evidence regarding the overall benefit of checking BG levels in patients with type 2 diabetes not using insulin therapy.[122] Instead, patients along with their providers should determine the appropriate frequency and timing to check BG levels to best optimize drug therapy and decrease the risk of hypoglycemia.[41]

The objective of ongoing, frequent BG testing is to determine whether normoglycemia is being achieved, assess effectiveness of drug therapy as well as the impact of meals, food, illness, or exercise on BG levels. Typical times to check BG may include before meals and snacks, 2 hours postprandial, at bedtime, and, occasionally, at 2:00 to 3:00 AM. However, it can be challenging for patients to adhere to such a rigorous regimen. A.H. should set her alarm for 3:00 AM two or three times/week and test her BG. BG concentrations measured before meals allow patients and clinicians to determine whether the rapid-acting insulin dose is appropriate for the amount of carbohydrate consumed; FPG levels are used to determine whether the basal insulin dose is adequate; and the 2:00 to 3:00 AM BG level is used to identify if the patient is experiencing nocturnal hypoglycemia. For example, the BG measured before dinner reflects the action of A.H.'s prelunch insulin aspart dose on food she has eaten for lunch, as well as hepatic glucose production between

meals. Increasingly, patients who use carbohydrate counting with rapid-acting insulins test 2-hour postprandial levels when initiating therapy to enhance proper dosage adjustment (Table 53-13).

The importance of frequent BG testing in patients newly diagnosed with type 1 diabetes cannot be overemphasized. When BG is tested less frequently than four times daily, it becomes difficult to adjust insulin doses based on infrequent readings or to assess patterns in glucose levels (ie, pattern management). If patients refuse to test four times daily, they should be encouraged to test four times daily on representative days of the week or to test at different times of the day each day so that a weekly profile can be developed. A.H. also should be encouraged to test her BG concentration any time she is feeling unusual, if she is experiencing hypoglycemic symptoms, or to evaluate the effect of unusual circumstances on her BG concentration (eg, increased physical exercise, a large holiday meal, final examinations, or a family crisis).[14] If a patient is unable or unwilling to check BG at these varying times, a CGM, which measures interstitial glucose levels, may be recommended. Monitors that either measure and display glucose levels continuously or ones that measure glucose levels continuously are available; however, they only display glucose values when swiped by a reader or smartphone.[123–126] Use of a CGM would allow the patient the ability to determine their glucose values easily at any point throughout the day. CGMs require more initial training and education; however, when used appropriately, they may be a useful tool to both decrease A_{1c} levels and the overall incidence of hypoglycemia.[63]

USING BLOOD GLUCOSE TEST RESULTS TO EVALUATE INSULIN DOSES

Case 53-2, Question 11: A.H. was instructed to inject herself with 12 units of insulin glargine each evening and to give 4 units of insulin aspart just before each meal. She was asked to test her BG four times daily (before meals and at bedtime), to record her results and other unusual events or symptoms during the day, and to bring her BG logbook to the clinic. A.H. was also instructed to track her food and record the number of carbohydrates she ingested at each

meal. The initial goal of therapy is to lower her BG to eliminate symptoms of hyperglycemia. The ultimate goal is to achieve an A_{1c} level of <7%, fasting glucose of 80 to 130 mg/dL, and postprandial values of <180 mg/dL.[72] One week later, trends in her BG concentrations were as follows:

Time	Glucose Concentration (mg/dL)
7:00 AM	160–200
Noon	220–260
5:00 PM	130–180
11:00 PM	140–180

Occasional 3:00 AM tests averaged 160 mg/dL, and A.H.'s urine is negative for ketones. She eats approximately four carbohydrate servings for breakfast (60 g) and two to four carbohydrate servings for lunch and dinner (30–60 g). Subjectively, A.H. feels a bit better, and her weight has stabilized, but she still urinates two to three times nightly. How would you interpret these results, and how should A.H.'s insulin doses be altered?

Values from SMBG appropriately form the basis for insulin adjustments. Ultimately, the goal is to move motivated patients toward being able to recognize their own glucose trends and make insulin adjustments accordingly based on recommendations between the patient and provider.[103] Before using A.H.'s BG results to adjust her insulin dose, it is important to observe and reassess her testing technique. One also should determine whether there were any unusual circumstances in her life such as acute illness, diet changes or excursions, drug therapy changes, or exercise patterns during the past week that may have affected her response to insulin. Once these have been ruled out as confounding factors, one can begin making adjustments in A.H.'s insulin dose, realizing that fine-tuning will be impossible until a consistent diet and exercise pattern have been instituted.

Several principles must be kept in mind whenever BG tests are used to adjust a patient's basic insulin dose (**Table 53-17**). Because many factors can alter a patient's response to insulin, it is important to review BG concentration *trends* measured for a minimum of 3

days to adjust the patient's standing insulin dose (ie, the dose the patient will use every day). The only exception to this rule is the use of supplemental insulin doses to correct exceptionally high glucose concentrations after A.H. has acquired sophisticated insulin adjustment skills (see Case 53-2, Question 16). SMBG results should always be evaluated in conjunction with A_{1c} values.

Table 53-17
Factors That Can Alter Blood Glucose Control

Diet
Insufficient calories (eg, alcoholism, eating disorders, anorexia, nausea, and vomiting)
Overeating (eg, during the holidays)
Irregularly spaced, skipped, or delayed meals
Dietary content (eg, fiber, carbohydrate content)
Physical Activity
See Table 53-19
Stress
Infection
Surgery/trauma
Psychological
Drugs
Certain medications can increase or decrease blood glucose levels. It is important to assess for potential effects on the blood glucose when starting new medications.
Hormonal Changes
Menstruation: Glucose concentrations may increase premenstrually and return to normal after menses.
Pregnancy
Puberty: hyperglycemia probably related to high growth hormone levels
Gastroparesis
Delays gastric emptying time. Peak insulin action and meal-related glucose excursions may become mismatched.

Altered Insulin Pharmacokinetics
See Table 53-8
Insulin Injection Technique
Measuring
Timing
Technique
Inactive Insulin
Outdated insulin
Improperly stored insulin (heat or cold)
Crystallized insulin

The daily dose of insulin glargine is inadequately controlling A.H.'s FPG and should be increased by 2 to 4 units. A more conservative approach would be to increase the dose to 14 units each evening (or a designated time of day that she will be able to do consistently) and further titrate as needed.[26] She is achieving some response from her lunchtime dose of insulin aspart, but there is room for improvement in her meal insulin coverage overall. The BG concentration of 160 mg/dL at 3:00 AM indicates that rebound hyperglycemia is an unlikely cause of her high fasting levels (see Case 53-2, Question 13, and Case 53-3). As an initial step toward control, A.H.'s daily dose of insulin glargine should be increased in an attempt to control her fasting hyperglycemia. However, this approach does not address A.H.'s elevated prelunch values. Her intake of carbohydrates also varies from meal to meal. Thus, a more appropriate method would be to calculate the insulin-to-carbohydrate ratio for A.H. and allow her to determine her premeal aspart dose based on the amounts of carbohydrates she will ingest at each meal. A typical starting point for the insulin-to-carbohydrate ratio is 1 unit to every 15 g of carbohydrate ingested. To calculate her insulin-to-carbohydrate ratio, the "500 rule" is used: Divide the number 500 by her TDD of insulin (14 units of insulin glargine plus 12 units of insulin aspart for meal coverage: total of 26 units):

$$500/26 = 19 \text{ g of carbohydrate covered by 1 unit of insulin} \quad \text{(Eq. 53-1)}$$

Because most single servings of carbohydrate contain 15 g, A.H. decides to start with a ratio of 1 unit for every 15 g or single serving of carbohydrates she consumes at each meal. If A.H. were using regular insulin for meal coverage, she could use the "450 rule": 450 divided by the total daily insulin dose yields grams of carbohydrate covered by 1 unit of insulin.

To evaluate the accuracy of her insulin-to-carbohydrate ratio, A.H. will need to check her BG values 2 hours after each meal (postprandial) to assess the appropriateness of her ratio. She agrees to test her BG level eight times/day and return in 2 weeks.

CASE 53-2, QUESTION 12: A.H. is getting more comfortable with carbohydrate counting and adjusting her insulin doses accordingly. A review of her food diary reveals that for the most part, she is able to determine the appropriate serving sizes for 15 g of carbohydrate. She admits to difficulty determining carbohydrate amounts when eating out. As a result, A.H. notices that her preprandial BG concentrations exceed her goal of 80 to 130 mg/dL on occasion.[127] Sometimes they are as high as 200 mg/dL. Evaluate A.H.'s BG trends. How should occasional preprandial glucose concentrations that exceed the desired goal of 80 to 130 mg/dL be managed?

Once the basal insulin dose and insulin-to-carbohydrate insulin dose have been established, one can begin to teach A.H. how to use a correction factor to adjust her dose of insulin when preprandial BG concentrations fall above or below the range of BG concentrations that have been established as her goal of therapy (80–130 mg/dL per the ADA; Table 53-15).

A correction insulin dose is used to compensate for unusually high BG concentrations (high-sugar correction). To reemphasize, this assumes there are no unusual changes in the patient's overall diet or exercise patterns (**Table 53-18** explains the effects of exercise on BG). Many clinicians favor rapid-acting insulin versus regular insulin because of their shorter duration of action, and patients do not have

to worry about residual effects 3 to 4 hours after its injection. This is particularly valuable when correctional doses of insulin are needed at bedtime.

Table 53-18
Exercise in Patients With Diabetes

1. Test blood glucose before, during, and after exercise.
2. For moderate exercise (eg, bicycling or jogging for 30–45 minutes), ↓ the preceding dose of regular or rapid-acting insulin by ~30%–50%. If glucose concentration is normal or low before exercise, supplement the diet with a snack containing 10–15 g of carbohydrate.
3. To avoid ↑ absorption of regular insulin by exercise, inject into the abdomen or exercise 30–60 minutes after injection. Avoid exercise when rapid-acting insulin is peaking.
4. Individuals with low glycogen stores may be predisposed to the hypoglycemic effects of exercise. Examples include alcoholics, fasted individuals, or patients on extremely hypocaloric (<800 calories), low-carbohydrate (<10 g/day) diets.
5. Patients taking insulin are more susceptible to hypoglycemia than are those taking oral insulin secretagogues (sulfonylureas, glinides). Patients with type 2 diabetes treated with diet are unlikely to develop hypoglycemia.
6. Watch for postexercise hypoglycemia. Individuals who have been exercising during the day will likely need to ↑ their carbohydrate intake and should test their blood glucose during the night to detect nocturnal hypoglycemia. Hypoglycemia can occur 8–15 hours after exercise.
7. If the glucose concentration is >240–300 mg/dL, the patient should not exercise. This indicates severe insulin deficiency. These patients are predisposed to hyperglycemia secondary to exercise.
8. Patients with severe proliferative retinopathy or retinal hemorrhage should avoid jarring exercise or exercise that involves moving the head below the waist.

The patient's sensitivity to insulin, as reflected by his/her TDD on a unit per kilogram basis, is a major determinant of any algorithm developed. A general approach is to give an additional 1 to 2 units of supplemental rapid-acting insulin for each 30- to 50-mg/dL elevation above the target level.[93] An alternative method of estimating the drop in a person's BG per unit of regular insulin is the "1500 Rule."[110] The derived value is referred to as the *sensitivity factor*: The rule was modified to the "1800 rule" for use with rapid-acting insulin (insulin

lispro, aspart, or glulisine). Because these insulins tend to drop the BG level faster and farther, 1500 turns out to be too aggressive. Others have recommended other numerators such as 1600, 1700, 2000, and 2200.[128] For this case, the "1700 rule" will be used. The calculation for A.H. would be as follows:

$$1700/24 = 70\ \mathrm{mg/dL} \qquad \textbf{(Eq. 53-2)}$$

Thus, 1 unit of insulin aspart for A.H. will drop her BG level by about 70 mg/dL. People with a lower sensitivity factor (higher insulin requirements) typically achieve a smaller reduction in BG per unit of insulin compared with those with a higher sensitivity factor (lower insulin requirement). Thus, an algorithm of 1 unit of insulin aspart for every 70-mg/dL excursion above her goal of 120 mg/dL is a reasonable place to begin. If this dose of insulin is insufficient, one can decrease the BG excursion required per unit of insulin dose (eg, 50 mg/dL). Correctional insulin doses also are used for sick day management (see Case 53-5). The following is an example of a high-sugar correction algorithm for A.H.:

Glucose Concentration (mg/dL)	Insulin Aspart
<80	1 unit less
80–120	Usual dose
120–190	1 unit extra
191–260	2 units extra
261–330[a]	3 units extra
331–400[a]	4 units extra

[a]Check urine or blood ketone levels. If ketones are positive and blood glucose (BG) concentrations remain >300 mg/dL for ≥12 hours, call the physician for directions.

EVALUATING FASTING HYPERGLYCEMIA

CASE 53-2, QUESTION 13: A.H. returns after 1 month. She is currently using 14 units of insulin glargine each evening, 1 unit of insulin aspart for each 15 g of carbohydrate ingested at mealtime, and a high-sugar correction factor of 1 unit

of insulin aspart for every 70 mg/dL above 130 mg/dL. Presuming that her diet is consistent, her SMBG results are as follows:

Time	Glucose Concentration (mg/dL)
7:00 AM	140–180
Noon	120–150
5:00 PM	90–130
11:00 PM	90–120
3:00 AM	60–90

Overall, A.H. feels her diabetes is in good control. Her energy level has returned to normal, and her nocturia has diminished, but she occasionally gets up one or two times nightly to urinate. A.H. has also noticed that nightmares or "sweats" sometimes awaken her. When this occurs, she generally has something to eat because she is "famished." She is able to get back to sleep but wakes up the next morning with a "splitting headache" and a "hungover" feeling. A.H.'s weight remains the same, and she has begun to develop some consistency in her dietary patterns with the help of a dietitian. She has been consistently correcting her prelunch and predinner insulin doses by adding or subtracting 2 units from her premeal insulin doses based on her premeal BG values. The A_{1c} from her last visit is 7.3%. Evaluate A.H.'s BG values. What are the possible causes of A.H.'s fasting hyperglycemia?

When evaluating morning hyperglycemia, several causes must be considered:

- An insufficient basal dose of insulin. If the basal dose is insufficient, hepatic glucose output during the fasting state will be excessive, thereby producing hyperglycemia
- Insufficient dinner coverage with insulin aspart, resulting in hyperglycemia that persists into the morning. This can be distinguished from insufficient basal insulin by assessing glucose control at bedtime
- Reactive hyperglycemia in response to a nocturnal hypoglycemic episode (Somogyi effect or rebound hyperglycemia)
- Excessive bedtime snacking
- The dawn phenomenon (see Case 53-3)

The presence of normoglycemia at bedtime, low BG concentrations at 3:00 AM, and symptoms of nocturnal hypoglycemia (nightmares, sweating, hunger, and morning headache) in A.H. are consistent with a rebound hyperglycemic reaction in the morning (ie, posthypoglycemic hyperglycemia, also referred to as the Somogyi effect).[104,129,130]

Theoretically, this effect occurs after any episode of severe hypoglycemia and is secondary to an excessive increase in glucose production by the liver that is activated by insulin counterregulatory hormones such as cortisol, glucagon, epinephrine, and growth hormone. The waning effects of the basal insulin dose can also be a cause of fasting hyperglycemia because insulin is needed to suppress hepatic glucose output during the fasting state; however, this is not likely in A.H.'s case. Asymptomatic nocturnal hypoglycemia can occur in patients taking more than necessary doses of insulin in the evening, and may potentially cause rebound hyperglycemia in the morning. By correcting the nocturnal hypoglycemia, normalization of A.H.'s fasting hyperglycemia also may be achieved. Thus, a decrease in the daily dose of insulin glargine is warranted. A.H. should continue to monitor her BG concentrations at 3:00 AM to determine whether her BG levels return to normal.

Caveat: If A.H. were using NPH bid to supply her basal insulin, one option would be to shift the evening injection of NPH from before dinner to bedtime. This preferred method effectively shifts the peak action of NPH to the early morning, when she is awake, and decreases the risk of nocturnal hypoglycemia.[131,132] This peak action also corresponds to the dawn phenomenon (see Case 53-3) and the breakfast meal.

Another option if a patient is using NPH and experiencing nocturnal hypoglycemia is to change from NPH to either insulin glargine or insulin detemir because these insulins are associated with less nocturnal hypoglycemia.[133] When switching from NPH insulin to insulin detemir, a one-to-one dose conversion may be used, although higher doses of detemir may be required. In one

crossover study of patients with type 1 diabetes, the average detemir basal dose was approximately double that of the NPH basal dose.[134] However, when switching from NPH insulin to insulin glargine, a one-to-one dose conversion is utilized only when a patient is using NPH insulin once daily. If a patient is taking NPH insulin twice daily, then the total daily insulin dose should be decreased by 20% when switching to insulin glargine. In this case of AH, the daily dose of NPH should be decreased by 20% to determine the insulin glargine dose, to err on the conservative side.[86,88] Alternatively, switching to an even longer-acting basal insulin such as glargine U-300 (brand name Toujeo®) or degludec (either U-100 or U-200) (brand name Tresiba®) would be an option to decrease a patient's overall risk of nocturnal hypoglycemia. Both U-300 insulin glargine and insulin degludec (both U-100 and U-200) have been shown to decrease the overall risk of hypoglycemia compared to use of NPH, detemir, or glargine U-100 insulin.[135] When switching a patient to insulin degludec from another basal insulin, patients should begin using insulin degludec at the same unit dose as their total daily long or intermediate-acting insulin.[109] When switching to insulin glargine U-300, patients currently using their basal insulin once daily should be converted at the same unit dose as their total daily long or intermediate-acting insulin dose. Patients currently using their intermediate or long-acting basal insulin twice daily should begin glargine U-300 at 80% of their total daily basal insulin dose.

Although A.H.'s prelunch BG values are above her goal, this may be attributable to the fasting BG being elevated and then continuing to be elevated midmorning, like a domino effect. It is important to first correct fasting hyperglycemia and generally correct one BG concentration at a time.

MIXING INSULINS

Case 53-2, Question 14: If A.H. were to use NPH as basal insulin, how should she be instructed to measure and withdraw this insulin mixture?

Although mixing two insulins in the same syringe has become less common with use of basal-bolus therapy (because insulin degludec, glargine, and detemir cannot be mixed) and the use of rapid-acting insulin pen devices, the procedure used to mix and withdraw NPH and mealtime insulin (regular or rapid-acting insulin) is basically the same as that described in Case 53-2, Question 8. The major difference is that an adequate volume of air must be injected into the NPH vial before the regular or insulin aspart is measured and withdrawn. Also, the mealtime clear insulin is measured and withdrawn into the insulin syringe *first* to avoid contamination of the vial of regular, aspart, lispro, or glulisine insulin with NPH. For example, contamination with NPH ultimately alters the NPH to regular insulin ratio that is administered. When patients withdraw NPH insulin first, the vial of regular insulin eventually becomes cloudy. In contrast, contamination of the NPH insulin with regular insulin is insignificant because the protamine contained in NPH can bind the regular insulin (see Case 53-2, Question 15). The procedure A.H. should use to mix her insulins is described in the section on Premeal Hyperglycemia, using her morning dose as an example.

- After dispersing the NPH insulin suspension, inject 14 units of air into the NPH vial and withdraw the needle.
- Inject 7 units of air into the insulin aspart vial and withdraw the 7 units of insulin, as described in Case 53-2, Question 8.
- Insert the needle into the NPH vial and pull the plunger down to the 21-unit mark (14 units of NPH plus 7 units of insulin aspart).

STABILITY OF MIXED INSULINS

CASE 53-2, QUESTION 15: Will mixing NPH with a rapid-acting insulin or regular insulin blunt the rapid action of the mealtime insulins? How stable are other insulin mixtures?

Regular insulin and all of the rapid-acting insulin analogs (aspart, lispro, and glulisine) may be mixed with NPH. In general, it is recommended to mix the insulins just before administration. See

Table 53-19 for details on compatibility and stability of insulin mixtures. However, with the increased use of longer-acting basal insulins and the use of insulin pen devices, mixing of insulins in the same syringe has become a less common practice.

Table 53-19
Compatibility of Insulin Mixtures

Mixture	Proportion	Comments
Regular + NPH	Any proportion	The pharmacodynamic profiles of regular and NPH insulin are unchanged when premixed and stored in vials or syringes for up to 3 months.
Regular + normal saline	Any proportion	Use within 2–3 hours of preparation.
Regular + insulin diluting solution	Any proportion	Stable indefinitely
Rapid-acting insulin + NPH	Any proportion	The absorption rate and peak action of the rapid-acting insulins are blunted; total bioavailability is unaltered. Rapid-acting insulin and NPH should be mixed just before use (within 15 minutes).
Insulin glargine and detemir	Do not mix with other insulins	Pharmacodynamics could be modified.

NPH, neutral protamine Hagedorn.

Sources: Humulin R. Package insert. Eli Lilly and Company; November 2019; Humulin N. Package. insert. Eli Lilly and Company; November 2019; Humalog. Package insert. Eli Lilly and Company; November 2019; Lantus. Package insert. Sanofi-Aventis U.S. LLC; November 2019; Levemir. Package insert. Novo Nordisk; March 2020.

Case 53-2, Question 16: After reducing the dose of insulin glargine to 14 units each evening, A.H.'s FPG is now 110 to 125 mg/dL. However, her noon BG concentrations remain in the 120- to 150-mg/dL range. Are there any other changes that you would recommend making at this time?

PREMEAL HYPERGLYCEMIA

When evaluating midmorning hyperglycemia, it is important to remember that the FPG concentration can contribute up to 50% of this plasma glucose excursion. Therefore, a key to the control of midmorning hyperglycemia may be to normalize the fasting glucose concentration. However, for A.H., the reduction in the insulin glargine has now corrected the reactive fasting hyperglycemia.

Hyperglycemia before a meal can be a result of several factors. The following are possible explanations for A.H.'s midmorning hyperglycemia:

- An insufficient dose of insulin aspart before breakfast: For A.H., this means that her insulin-to-carbohydrate ratio needs to be adjusted.
- Excessive carbohydrate ingestion at breakfast or inaccurate (under) counting of the carbohydrates ingested: Patients having difficulty accurately counting their carbohydrates should meet with a dietitian or diabetes educator for education; this is often necessary periodically throughout their lives as a refresher, just like many other skills require.
- Poor synchrony between meal intake and insulin action: This could be caused by the administration of rapid-acting insulin too long before or after the meal (eg, ≥30 minutes). If regular insulin is used, this could be caused by administering regular insulin just before or after meals.
- An insufficient dose of evening insulin glargine to suppress hepatic glucose production (glycogenolysis and gluconeogenesis) during the fasting state or the dawn phenomenon (see Case 53-3): In A.H.'s case, however, her fasting blood glucose (FBG) values are on target, so this is not likely.

The following interventions may be considered:

- Adjust her insulin-to-carbohydrate ratio to increase her insulin aspart dose at breakfast: The ratio should be changed to 1 unit of aspart for every 10 or 12 g (which are typical ratios used) of carbohydrate for the breakfast meal. This assumes a patient is technically able to use a different "ratio" at different mealtimes.

- Alter the carbohydrate content of the meals: This may include decreasing the amount of carbohydrate in the breakfast meal, changing the type of carbohydrate ingested, or adding fiber to that meal to minimize glucose excursions.
- Adjust the high-sugar correction factor if the glucose excursions appear to be caused by reduced insulin sensitivity in the morning: For example, the high-sugar correction can be adjusted to give 1 unit of aspart for every 50 mg/dL above 130 mg/dL.

PREPRANDIAL HYPOGLYCEMIA

CASE 53-2, QUESTION 17: A.H. is now taking insulin glargine 12 units each night and using an insulin-to-carbohydrate ratio of 1:15 (1 unit of insulin aspart for every 15 g of carbohydrate) at lunch and dinner and 1:12 at breakfast. She is continuing with the same high-sugar premeal correction of 1 unit of insulin aspart for every 70 mg/dL more than her premeal BG target of 120 mg/dL. Two weeks later, she brings in her BG records.

Time	Glucose Concentration (mg/dL)
7:00 AM	110–120
Noon	90–115
5:00 PM	60–110
11:00 PM	80–110
3:00 AM	110–120

A.H. feels that she is now “back to normal.” She has no signs or symptoms of hyperglycemia, and her weight has remained stable. Occasionally, she becomes hypoglycemic before dinner, but this most often occurs when her dinner is delayed because of a hectic work schedule. Evaluate A.H.’s BG trends. What could be the cause of her predinner hypoglycemia, and how could she be managed?

A.H.’s BG concentrations indicate that her basic insulin regimen is generally adequate to achieve the overall goal of preprandial BG concentrations of <80 to 130 mg/dL.

The hypoglycemia that A.H. is experiencing before dinner could be caused by insufficient carbohydrate intake at lunch (inaccurate carbohydrate counting), increased activity during the day, or an excessive dose of insulin aspart (insulin-to-carbohydrate ratio is too high). Thus, the problem could be resolved by augmenting A.H.'s lunch meal, adjusting the lunch insulin-to-carbohydrate ratio to 1 unit of insulin aspart for every 18 (or 20) g of carbohydrate, or adding a midafternoon snack.

CASE 53-3

QUESTION 1: R.D., a 37-year-old male, has had type 1 diabetes since age 14. During the past 2 years, he has been very well controlled on the following insulin regimen: insulin glargine 20 units each morning with insulin lispro 3 to 4 units depending on carbohydrate intake before meals. On this regimen, his BG concentrations for the past 2 weeks have been as follows:

Time	Glucose Concentration (mg/dL)
7:00 AM	140–170
Noon	100–120
5:00 PM	100–130
11:00 PM	115–140
3:00 AM	100–120

What are the likely causes of R.D.'s fasting hyperglycemia?

DAWN PHENOMENON

As discussed in Case 53-2, Question 13, fasting hyperglycemia may be the result of insufficient doses of insulin in the evening and, possibly, reactive hyperglycemia. In R.D.'s case, the dawn phenomenon also must be considered.[89] The *dawn phenomenon* is a rise in the BG concentration that occurs between 4:00 and 8:00 AM after a physiologic nadir in the BG concentration that occurs between midnight and 3:00 AM. This 30- to 40-mg/dL increase in the morning BG concentration cannot be attributed to increases in

counterregulatory hormones secondary to an antecedent hypoglycemic event, but it may be secondary to rising growth hormone levels. This phenomenon is inconsistently observed in individuals with type 1 and type 2 diabetes as well as nondiabetic individuals; furthermore, it is inconsistently present from one day to the next.[136]

R.D.'s normal 3:00 AM BG concentration indicates that posthypoglycemic hyperglycemia is an unlikely cause of his fasting hyperglycemia. Thus, the modest increase in his BG concentration between 3:00 and 8:00 AM may be attributed to the waning effects of insulin or the dawn phenomenon. In both cases, an increase in R.D.'s daily dose of insulin glargine would be indicated. Another option would be to switch R.D. to an insulin pump. He has demonstrated a desire and the ability for intensive management with multiple daily injections, frequent SMBG, record-keeping skills, the ability to make appropriate insulin dose adjustments, and accurate carbohydrate counting. The advantage to using a pump is the ability to program an increase in the basal infusion rate in the early morning hours (eg, beginning around 2:00–3:00 AM and continuing until 7:00–9:00 AM).

Type 1 Diabetes in Children

DIAGNOSIS AND CLINICAL PRESENTATION

CASE 53-4

QUESTION 1: J.C., a 7-year-old, 66.14-pound (30-kg; 95th percentile), 50-inch (127-cm) tall (90th percentile) girl, was brought to the emergency department by her parents because of nausea, vomiting, and a persistent stomach pain secondary to the flu. For the past week, J.C. had flulike symptoms, resulting in a 6-pound (2.72-kg) weight loss. Initial laboratory values revealed a BG of 600 mg/dL, serum pH of 6.8 with bicarbonate level of 13 mEq/L, plasma ketone level of 5.2 mmol/L, and positive ketonuria. J.C. was diagnosed with DKA secondary to new-onset type 1 diabetes. In retrospect and on further questioning, J.C.'s parents realized that she probably had symptoms as early as 4 weeks before her hospitalization. While on a driving vacation, she drank large quantities of

juice and had to stop hourly to urinate. She began experiencing enuresis, which her parents attributed to her increased fluid intake.

What signs and symptoms are consistent with the diagnosis of type 1 diabetes in a child?

The diagnosis of type 1 diabetes in children is generally straightforward. Presenting symptoms include a several-week history of polyuria, polydipsia, polyphagia, and weight loss, with hyperglycemia, glucosuria, ketonemia, and ketonuria. J.C.'s presentation is typical for a child newly diagnosed with diabetes who is brought in for medical attention because of severe symptoms related to the flu. An acute viral illness can trigger autoimmune destruction of the pancreas and abdominal pain, which may masquerade as gastroenteritis. Abdominal pain is a common presenting symptom of DKA.[19] J.C.'s weight loss probably represents fluid and caloric loss secondary to uncontrolled diabetes as well as decreased caloric intake from the flu. The symptoms of polyuria are less obvious in an infant and are frequently missed until metabolic derangement has occurred. Unlike J.C., infants frequently present with severe dehydration and metabolic acidosis despite a negative history of diarrhea or significant vomiting.

GOALS OF THERAPY

CASE 53-4, QUESTION 2: What are the goals of therapy for J.C.? Do the results of the DCCT apply to children such as J.C.? Are there age-specific goals?

Current ADA guidelines recommend an A_{1c} goal of <7.5% for all pediatric groups and adolescents (<19 years old) such as J.C. with DM. Individualization of goals, however, is still encouraged.[19,137–139]

Additional targets should also be kept in mind, including (a) to achieve normal growth and development, (b) to facilitate positive psychosocial adjustment to diabetes, and (c) to prevent acute and chronic complications. Attainment of these goals requires a tremendous amount of support and education for the parents, and can best be provided by a multidisciplinary team of professionals,

including a pediatric endocrinologist, nurse educator, pharmacist, dietitian, and mental health professional.[140]

Growth serves as an important clinical indication of overall general health and well-being in children with diabetes. Height and weight should be measured at each visit and plotted on standard growth grids. If, at the time of diagnosis, a child has fallen behind in height or weight, prompt and appropriate treatment should quickly return the child to the appropriate percentile and pattern of growth. An overweight child should be encouraged to achieve a more appropriate percentile of weight gradually, over the course of several months.[141]

Although recommendations for glycemic control are based on data from studies mostly in adult patients with diabetes, achieving the same near normalization of BG levels in children and adolescents is recommended. However, special consideration must be given to the unique risks and consequences of hypoglycemia in young children. A cohort of adolescents included in the DCCT was analyzed separately.[142] Similar to the adults in the DCCT, adolescents had sustained benefits from intensive management with little further progression to proliferative retinopathy 4 years after the DCCT was terminated.[41] Thus, J.C.'s pediatrician must strive for the best glucose control that she, her family circumstances, and currently available treatment regimens will permit.

The risk of hypoglycemia is of great concern in children younger than 6 years of age because they can have a form of hypoglycemic unawareness that results partly from their reduced capacity to communicate symptoms of hypoglycemia, but may be contributed to by less-developed counterregulatory mechanisms.[137] In addition, food intake and physical activity are unpredictable in this age group. These factors must be taken into consideration when determining an A_{1c} goal in this patient population where the long-term benefits of achieving a lower A_{1c} need to be weighed against the risk of hypoglycemia.[41,137,143] Per the ADA recommendations, the ultimate goal is to achieve the best A_{1c} possible without experiencing symptoms of hypoglycemia. The management of diabetes in children

ages 6 to 12 years, such as J.C., is particularly challenging because many children require insulin with lunch or at other times when they are away from home. Administration of insulin at school demands flexibility and close communication between the parents, the health care team, and school personnel (Table 53-4).[41,137,143] The greatest amount of evidence-based data exists for adolescents with diabetes (13–19 years). As mentioned, teenagers included in the DCCT achieved a mean A_{1c} level of 8.06% in an era before the availability of rapid-acting or basal insulins. As stated previously, an A_{1c} goal of <7.5% is recommended in this age group.[137]

INSULIN THERAPY

CASE 53-4, QUESTION 3: How should J.C. be started on insulin? Is the use of an insulin pump appropriate in children such as J.C.?

Generally, rapid-acting and basal insulin analogs are used in children to reduce the risk of hypoglycemia. Insulin requirements are generally based on body weight, age, and pubertal status. Newly diagnosed children with type 1 diabetes usually require an initial TDD of ~0.5 to 1.0 unit/kg.[76,77] The small insulin requirements of infants and toddlers may be delivered by using diluted insulin (eg, 10 units/mL, U-10; or 50 units/mL, U-50)[144] to measure doses in <1-unit increments. Diluents are available for insulin aspart and lispro. Insulin syringes and pens that deliver insulin in 0.5-unit increments are also very useful in pediatric patients. Most children are treated with basal-bolus regimens. These regimens have demonstrated lower FBG levels with less nocturnal hypoglycemia versus regimens using NPH in children and adolescents.[137,145]

Basal-bolus insulin regimens combined with carbohydrate counting are attractive regimens for middle and high school students. Because children often have erratic eating habits, rapid-acting insulins are advantageous over regular insulin because they can be injected directly before or immediately after a meal, accounting for the portion of the meal a child actually consumed. J.C. should be

started on approximately a TDD of 15 units (ie, 0.5 units/kg/day), such as 3 units of rapid-acting insulin before meals and 7 units of insulin glargine at bedtime.[137] In some patients, insulin glargine may not last a full 24 hours; in this case, the dose of insulin glargine should be divided and given twice daily, and then each adjusted based on the BG patterns.[146] Alternatively, insulin glargine U-300 glargine may be beneficial in this situation and is indicated for use in children ages 6 years and older.[135] Insulin degludec would last 24 hours; however, it is not an option for J.C. because it is not FDA approved for use in children at this time.[147,148]

When J.C. and her caregivers become skilled with carbohydrate counting, insulin kinetics, dosing insulin based on her carbohydrate intake, and diabetes management, the use of an insulin pump may be considered. The insulin pump therapy in the pediatric population is increasing rapidly because it provides increased flexibility with meal timing and has been shown to improve glycemic control and quality of life.[147] Young children (not just adolescents) are now recommended for consideration of insulin pump therapy.[149] Family and adult support both at home and school is critical for successful pump use until the child is able to manage his/her diabetes independently.

INJECTION SITES

Case 53-4, Question 4: Where should J.C. administer her insulin? Are the recommended sites of injection different for children? Does the age of the child play a factor?

For infants with abundant SC tissue, injection sites are usually plentiful. For some toddlers who have lost their "baby fat," locating an appropriate site for injection can be difficult. Injecting insulin into the abdomen of children with minimal SC abdominal fat or in very young children may not be advisable. Rotation of injection sites among arms, thighs, and the upper outer quadrant of the buttock or hip area, as well as the abdominal area in older children, may be

beneficial. To achieve consistent absorption, insulin injections can be patterned, for example, using the arms for the morning injection and the thighs for the evening injection. Children and teens should be cautioned to not consistently inject their insulin into a single area, which may be more convenient for them.[150] Fatty deposits and scar tissue can develop secondary to insulin action at the local tissue level. Insulin absorption from these hypertrophied areas is generally poor and unpredictable, resulting in variability in glycemic control. Insulin pen devices are very helpful for use in children because they are easy to use, have the option for an even smaller needle size, and are less intimidating (see Case 53-2, Question 7).[137]

BLOOD GLUCOSE MONITORING

Case 53-4, Question 5: How often should J.C. monitor her BG?

The eventual goal for children with diabetes is self-management, with insulin dosing decisions based on interpretation of BG results. Self-management skills and basal-bolus insulin regimens rely on frequent SMBG. For children with type 1 diabetes, four or more BG tests per day are generally necessary. Many home BG meters allow for alternative site testing, which may also decrease the discomfort of finger sticks. Enthusiasm for frequent BG testing tends to wane with duration of diabetes. However, families who are instructed on managing diabetes on the basis of test results are better motivated to persevere with SMBG. CGM may also be considered as a more convenient method to assess glucose control particularly to detect nocturnal hypoglycemia. If using a conventional home BG monitor, J.C. should test her BG before each meal and at bedtime, at a minimum. Additional tests should be performed whenever J.C. experiences hypoglycemia, ketonuria, or when she becomes acutely ill.

HONEYMOON PERIOD

Case 53-4, Question 6: During the next 2 months, J.C.'s insulin requirements decreased to a TDD of 10 units (~0.3 unit/kg). Has her diabetes gone into remission?

Approximately 20% to 30% of individuals with type 1 diabetes go into a remission phase (honeymoon period) within days to weeks of their diagnosis.[137,151] During this phase, which can last for weeks to months, insulin requirements can fall well below the usual initial dose of 0.5 to 1.0 units/kg/day, and C-peptide can be detected, indicating a return of pancreatic function. A child may require minimal to no basal insulin replacement, and mealtime replacement requirements may need to be reduced. As illustrated by J.C., this presents clinically as markedly decreased insulin requirements to maintain normoglycemia. J.C. should continue to perform SMBG and closely monitor for rising BG concentrations, as β-cell destruction continues during the honeymoon phase, and she will eventually return to higher insulin requirements.

Case 53-4, Question 7: J.C.'s parents contacted the clinic to report that J.C. is having nightmares and is awakening in the middle of the night reporting symptoms of a headache and stomach pain. However, these symptoms resolve by noon the following day. Her current insulin regimen is insulin aspart 2 units before meals and 3 units of insulin glargine twice daily (at breakfast and bedtime). Could J.C. be experiencing nocturnal hypoglycemia? How do the symptoms of hypoglycemia differ in a child compared with an adult? How can the risk of hypoglycemia be minimized for J.C.?

HYPOGLYCEMIA

J.C.'s parents are appropriately worried. Hypoglycemia is a serious and often life-threatening complication of diabetes management in children, and the risk of hypoglycemia increases with attempts to maintain meticulous control of BG levels.[152] It was previously thought that pediatric patients may be at risk for cognitive impairment following severe episodes of hypoglycemia; however, current literature does not support this finding. Common causes of hypoglycemia include changes in carbohydrate intake, late or

skipped meals or snacks, exercise or unusual activity, and administration of excessive insulin. Young children may not be able to identify or express symptoms of hypoglycemia, caretakers must observe the child closely and identify symptoms or behaviors associated with a falling BG. Symptoms of hypoglycemia may include crankiness, sudden crying, restless sleep, or nightmares as seen in J.C.

- Hypoglycemia is more frequent in children with lower A_{1c} values, a prior history of severe hypoglycemia, larger insulin doses, and younger children.[153] Nocturnal hypoglycemia is reported in 14% to 47% of children with type 1 diabetes and is thought to be related to impaired counterregulatory response to hypoglycemia during sleep.[137] Bedtime BG levels are poor predictors of nocturnal hypoglycemia. J.C.'s parents should be instructed to test her BG at 2:00 AM closely for the next few nights, and then continue to check at least twice weekly. In children, insulin glargine can exhibit a small peak effect during the initial 3 to 5 hours after administration, increasing the risk for nocturnal hypoglycemia.[143,144,154] If this is the case, the insulin glargine dose should be moved to dinnertime or in the morning. If this does not correct the nocturnal hypoglycemia, then the dose should be reduced. Use of insulin glargine is associated with less nocturnal hypoglycemia (and asymptomatic nocturnal hypoglycemia) compared with NPH insulin in children and adolescents.[155] Insulin glargine U-300 may also be a consideration for J.C. Because U-300 insulin glargine has a longer duration of action, it may be beneficial in this situation. One study comparing the use of insulin glargine U-100 to U-300 evaluated the overall risk of hypoglycemia in children ages 6 and older. The results displayed a similar percentage of severe hypoglycemia in both groups; however, the overall number of events was smaller in the insulin glargine U-300 group. This may indicate a clinical benefit of using U-300 insulin glargine versus U-100 glargine in this patient population.[155] A bedtime snack may also be needed. Treatment of hypoglycemia is addressed in Case 53-8, Question 3.

SICK DAY MANAGEMENT

CASE 53-5

QUESTION 1: G.M., a 32-year-old female with type 1 diabetes, has been well controlled on a basal-bolus regimen (four injections daily) for the past 6 months. However, 2 days ago, she began to exhibit signs and symptoms consistent with the flu. This has made her nauseated, and now she has begun to vomit; consequently, her food intake has been minimal.

Because R.D. is not eating at this time, should she discontinue her insulin?

Insulin requirements always increase in the presence of an infection or acute illness, even if food intake is diminished. Patients with type 1 diabetes, such as G.M., commonly decrease or eliminate insulin doses under these circumstances, and it is in just this setting that ketoacidosis may occur.

Therefore, G.M. should be instructed to maintain her usual dose of insulin and test her BG and urine ketones every 3 to 4 hours. If BG concentrations are above the usual range, extra doses of her rapid-acting insulin should be administered according to a prescribed algorithm based on her body's sensitivity to insulin (eg, 1 unit for each 50 mg/dL above her BG target). People with type 1 diabetes should be instructed to test for ketones if their BG concentration is 300 mg/dL or higher. G.M. should call her physician if her BG concentration remains >240 mg/dL after three corrective insulin doses; if she has moderate-to-large amounts of ketones in her urine or blood (if using a meter that can measure these); if she has been vomiting or having diarrhea for >6 hours; or if she begins to experience signs and symptoms related to ketoacidosis (polyuria, polydipsia, dehydration, ketonuria, and a fruity breath [see Case 53-10]). G.M. also should attempt to maintain her fluid, mineral, and carbohydrate intake with easily digested food and fluids (**Table 53-20**).[156]

Table 53-20
Sick Day Management

1. Continue taking your basic dose of insulin *even* if you are not eating well or have nausea or vomiting.
2. Test your blood glucose more frequently: every 3–4 hours.
3. If indicated, give yourself extra doses (high-sugar correction) of lispro, aspart, glulisine, or regular insulin: for example, 1–2 units for every 30–50 mg/dL over an agreed-on target glucose concentration (eg, 150 mg/dL). Correction doses must be individualized based on the patient's sensitivity to insulin (Table 53-9).
4. Begin testing your ketones (urine or blood) if you have type 1 diabetes. If you have type 2 diabetes, begin testing especially when glucose readings exceed 300 mg/dL.
5. Try to drink plenty of fluids (½ cup/hour for adults) and maintain your caloric intake (50 g carbohydrate every 4 hours). Foods such as gelatin, noncarbonated soft drinks, crackers, soup, and soda may be used.
6. Call a physician if your blood glucose concentration remains >300 mg/dL, or your urine ketones remain high after two or three supplemental doses of insulin, or your blood glucose level remains >240 mg/dL for more than 24 hours.

Source: Centers for Disease Control and Prevention. Managing sick days. Published March 31, 2020. https://www.cdc.gov/diabetes/managing/flu-sick-days.html

INSULIN REQUIREMENTS IN RENAL FAILURE

CASE 53-6

QUESTION 1: M.B., a 32-year-old female, has had type 1 diabetes for 15 years. During the past 2 years, a gradual deterioration of her renal function—as reflected by increased proteinuria, serum creatinine (SCr), and blood urea nitrogen (BUN) values, and reduced glomerular filtration rate (GFR)—has been observed.

What are the anticipated effects of decreased renal function on M.B.'s insulin requirements?

The effects of renal failure on insulin requirements are complex, and under various circumstances, insulin requirements may increase or decrease. The kidney is the most important site of extrahepatic insulin metabolism and excretion. In nondiabetic individuals, the liver extracts ~60% of insulin secreted endogenously before it reaches the peripheral circulation.[83,157] Because exogenous insulin is delivered directly to the periphery, the kidneys play a more important

role in its elimination. Insulin is filtered by the glomerulus and reabsorbed in the proximal tubules, where it is destroyed enzymatically. The kidney also clears insulin from the peritubular circulation.[158] At that site, insulin can enhance the reabsorption of sodium, which may account for the edema occasionally observed after the initiation of insulin therapy in some individuals.

Diminished renal function can be accompanied by decreased clearance of endogenous and exogenous insulin, resulting in increased plasma concentrations of insulin. Therefore, M.B.'s insulin requirements may diminish as her renal disease progresses. Patients with moderate degrees of renal failure (GFR >22.5 mL/minute) remove 39% of insulin from arterial plasma, similar to normal subjects. In contrast, patients with severe renal insufficiency (GFR <6 mL/minute) have a marked reduction in insulin removal from arterial plasma (9%).[8] Decreased insulin clearance in conjunction with nausea and decreased food intake associated with uremia can lead to hypoglycemia in such individuals. In some patients with diabetes, particularly those with residual endogenous insulin secretion (eg, type 2 diabetes), glucose tolerance may normalize as renal function diminishes, eliminating the need for insulin. In contrast, severe uremia is associated with glucose intolerance. This seems to be related to tissue resistance to insulin secondary to an unknown factor that can be removed by dialysis.

As M.B.'s renal function worsens, a reduction in her insulin requirements should be anticipated.

MANAGEMENT OF THE HOSPITALIZED PATIENT

CASE 53-7

QUESTION 1: A.G., a 55-year-old, 132.28-pound (60-kg) female with a 35-year history of type 1 diabetes, was admitted to the critical care unit for an abdominal hysterectomy. Before admission, she was well controlled on 24 units of insulin glargine at bedtime and premeal doses of insulin aspart.

How should A.G.'s diabetes be managed while in the critical care unit?

In 2017, nearly 23 million inpatient hospital days were attributed to diabetes management.[8] Approximately 30% of the nearly $237 billion dollars spent annually on diabetes direct medical costs is related to inpatient care; nearly half is spent on inpatient care.[159] A clear, linear relationship exists between hyperglycemia and adverse clinical outcomes in the hospitalized patient.[159–161] However, this relationship exists regardless of a baseline diagnosis of diabetes at the time of admission, and iatrogenic hyperglycemia in the hospital does not have the same relationship morbidity that spontaneous hyperglycemia does.[162–165] These observations have raised important questions about the relationship between hyperglycemia and morbidity in the hospitalized patient.

Complex responses to acute illness including excess secretion of catecholamines and cortisol result in peripheral insulin resistance and so-called stress hyperglycemia. This makes it difficult to discern whether glycemia is a marker or a mediator of adverse outcomes in the acutely ill patient. Accordingly, historic practice had been to only aim for BG concentrations that prevent glucosuria (<200 mg/dL) and the subsequent risk of dehydration in the hospitalized patient. However, beginning in 2001, a series of randomized trials tested glycemic control in critically ill patients. Significant changes have subsequently been made to practice recommendations for both the critically and the noncritically ill hospitalized patient.

Although several trials beginning in the 1990s tested intensive insulin regimens in patients with acute MI, they were small, placebo-controlled studies and reached different conclusions that proved difficult to rectify.[166] In 2001, the first of the van den Berghe trials tested two different levels of glycemic control in a relatively large number of patients in surgical intensive care unit (ICU) with hyperglycemia with or without known diabetes.[166] A liberal glucose control strategy (reduction only if BG rose above 215 mg/dL) was compared with normalization of BG (80–110 mg/dL). Overall, normalization of BG significantly reduced ICU mortality from 8.0% to 4.5%.[167] However, the same researchers were unable to replicate their findings in a subsequent, similarly designed study in patients in the medical ICU with substantially higher baseline mortality rates.[168]

Although a substudy showed that an ICU stay of ≥3 days was predictive of benefit from tight control, a subsequent and much larger trial not only failed to confirm that finding but also found increased mortality from a blood sugar of 80 to 110 mg/dL compared with 140 to 180 mg/dL (27.5%, 829 of 3010 vs 24.9%, 751 of 3012).[166] The incidence of severe hypoglycemia (<40 mg/dL) in the different study groups assigned to tight control was between 7% and 18% and did not explain the different findings between studies. However, several important differences between these trials, which helped to inform current guidelines, should be noted.

The 2001 van den Berghe trial used parenteral nutrition in all patients and allowed for higher glucose values (insulin started if blood sugar exceeded 215 mg/dL) to occur in the conventional glycemia arm.[167] It is therefore possible that the aggressive insulin therapy in the tight control group helped blunt the excessive glucotoxicity that may have been occurring from the parenteral nutrition. In the second van den Berghe trial as in the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) study, parenteral nutrition was rarely used, and initiation of insulin therapy in the conventional arms began at blood sugar values >180 mg/dL.[166–168] In addition, in NICE-SUGAR, a more aggressive target of <180 mg/dL was used rather than 180 to 200 mg/dL as in the two van den Berghe studies.[169,170] **Table 53-21** summarizes these three trials assessing the level of glucose control in critically ill patients.

Table 53-21
Summary Data of Three Major Trials of Intensive Versus Conventional Glycemic Control With Insulin in Critically Ill Patients

Trial	*N*	Glucose Target (mg/dL)		Glucose Achieved (mg/dL)		Primary Outcome	End Point	OR (95% CI)
		Intensive	Conventional	Intensive	Conventional			
Van den Berghe et al[166]	1548	80–110	180–200	103	153	ICU mortality	4.6% vs 8%	0.58 (0.38–0.78)
Van den Berghe et al[167]	1200	80–110	180–200	111	153	Hospital mortality	37.3% vs 40.0%	0.94 (0.84–1.06)
NICE-SUGAR[168]	6104	81–108	<180	115	145	90-day mortality	27.5% vs 24.9%	1.14 (1.02–1.28)

CI, confidence interval; OR, odds ratio.

Overall, numerous individual studies as well as meta-analyses have reached different conclusions regarding whether tight control of BG is superior to conventional control in the hospitalized, acutely ill patient.[171–173]

Although existing randomized trials of glycemic control have been performed in critical care settings, the ADA guideline included non-ICU settings. To make recommendations for patients in the non-ICU setting, ADA relied on case series and retrospective analyses, which will ultimately need to be subjected to randomized, prospective trials.[171–174] In the meantime, recommendations for both critically ill and noncritically ill hospitalized patients are the same: Initiate insulin therapy to treat persistent hyperglycemia (glucose levels ≥180 mg/dL) with a goal range of 140 to 180 mg/dL. A tighter goal of 110 to 140 mg/dL, however, may be beneficial in specific subgroups of patients, such as critically ill postsurgical patients or those patients undergoing cardiac surgery, if these levels are able to be achieved without significant hypoglycemia.[175] Admitted patients with severe comorbidities may benefit from even less stringent glucose control by maintaining BG levels between 180 and 250 mg/dL.[175]

For perioperative insulin needs, A.G. should receive her usual basal insulin dose (insulin glargine 24 units) on the night before surgery. If the basal insulin is normally administered in the morning, the usual dose can still be given for patients with type 1 diabetes; for those with type 2 diabetes, 78% to 80% of the basal insulin is administered the morning of surgery.[176]

Correction doses of rapid-acting insulin can be administered the morning of surgery if the BG is >180 mg/dL.[175] If a current A_{1c} is not available, it can be measured to assess the patient's glycemic control before admission.[176] Most insulin infusion protocols include the use of IV regular insulin and maintenance IV fluids, either 5% dextrose in water (D5W) or D5W with 0.45% normal saline (0.45% NaCl). For a patient requiring fluid restriction, 10% dextrose in water (D10W) may be used.[41] The adjustment algorithms are used by nursing to change the rate of infusion (in units/hour) depending on

the BG level. Most often, the insulin infusion is prepared in a solution of 1 unit/1 mL of normal saline (eg, 100 units of regular insulin in 100 mL of 0.9% NaCl). A dedicated IV line is used for the insulin infusion to avoid iatrogenic hypoglycemia. The insulin infusion is connected to the maintenance IV containing dextrose (can be Y-connected). Because insulin binds to plastic, the insulin solution should be flushed through the IV tubing before the line is connected to the patient. An IV dextrose infusion is maintained while a patient is on an insulin infusion. Most patients need 5 to 10 g of glucose per hour (or D5W or D5W/0.45% NaCl at 100–200 mL/hour). Additional maintenance fluids (and electrolytes) can be administered via a different port or line. Some protocols include an initial bolus dose of insulin. The initial insulin infusion rate is primarily based on current BG level and BMI; other factors such as body weight, current daily insulin requirements, and renal function should be taken into consideration. An initial rate of 1 unit/hour is common (can range from 0.5 units/hour to ≥2 units/hour). The choice of initial infusion rate is not critical but should be based on patient history. A rate of 0.5 units/hour is appropriate for a patient who has never previously received insulin, whereas 2 units/hour would be appropriate for a patient with known insulin-dependent diabetes. Adjustments in the insulin infusion rate are determined by BG levels every 60 minutes until the BG is stable and close to the target. Then, the frequency of BG testing may be reduced to every 2 to 3 hours. Algorithms should consider both the current and previous BG level, the rate of change of the BG level, and the current infusion rate.[177]

Insulin infusion should be started at least 2 to 3 hours before the surgery to titrate to the desired level of glucose control.

Thus, A.G.'s usual SC insulin regimen should be discontinued, and she should be initiated on an insulin infusion that is adjusted according to an algorithm. Throughout the perioperative period, she should receive a minimum of 100 g of glucose daily to prevent starvation ketosis.

Assessment of interfering substances with point-of-care BG testing is particularly important for hospitalized patients. Some immunoglobulins and dialysates contain nonglucose sugars

(including maltose, xylose, and galactose), which can interfere with glucose measurements with glucose dehydrogenase pyrroloquinoline quinone test strips (will falsely elevate the reading, Table 53-16). BG concentrations should only be performed by the laboratory in these patients.[41]

Adverse Effects of Insulin

HYPOGLYCEMIA

CASE 53-8

Question 1: G.O., a 42-year-old, slightly overweight (71 inches [180.34 cm], 200 pounds [90.72 kg], BMI 27.9 kg/m^2) male, has had a history of type 1 DM for 17 years. G.O.'s medical care was sporadic until 1 year ago when he referred himself to a diabetes clinic because he was beginning to experience pain and numbness in his feet. At that time, he was poorly controlled on a single daily dose of a premixed NPH and regular insulin mixture (Humulin® 70/30), 45 units. He had not been testing his BG concentrations, and his A_{1c} was 13%.

On physical examination, G.O. was found to have an elevated BP (160/94 mm Hg), background retinopathy, and decreased pedal pulses bilaterally. He had decreased sensation to vibration and monofilament testing in both feet. G.O. also reports of impotence and "shooting pains" in both legs. A spot collection for microalbuminuria was 450 mg of albumin/g creatinine (normal, <30 mg/g creatinine).[41]

G.O. was transitioned to a basal-bolus insulin regimen. His physician gave him a premeal BG target of 80 to 130 mg/dL.[178] For the past several months, he has been treated with the following regimen: 14 to 18 units of insulin glulisine before breakfast; 14 to 18 units of insulin glulisine before lunch; 16 to 18 units of insulin glulisine before dinner; and 40 units of insulin glargine at bedtime. If his BG level is high after lunch, he takes additional glulisine (~2 hours after eating). If his BG is high at bedtime (eg, >150 mg/dL), he takes additional insulin glulisine (7–10 units) because his physician told him that his BG level needed to be lowered significantly. BG concentrations have been as follows:

Time	Glucose Concentration (mg/dL)
7:00 AM	60–320
Noon	140–280
5:00 PM	40–300

In the past year, G.O.'s A_{1c} has decreased to 7.1%. Currently, he has approximately five hypoglycemic episodes per week, primarily in the late afternoon and early morning hours. These are characterized by intense hunger, sweating, palpitations, and (according to his wife) a short temper. He has found that he can avoid nocturnal hypoglycemia (night sweats, nightmares, and headaches) by eating a large bedtime snack. During the past 3 months, he has gained 15 pounds (6.80 kg).

Are G.O.'s signs and symptoms consistent with mild, moderate, or severe hypoglycemia? What are the causes?

G.O.'s case illustrates one of the major hazards of aggressive BG targets and intensive insulin therapy: hypoglycemia. Hypoglycemia is a fact of life for patients with type 1 diabetes, virtually all of whom experience a hypoglycemic episode at one time or another. Nocturnal hypoglycemia is of particular concern. A syndrome called *dead-in-bed* has been described for patients with type 1 diabetes, who experience repeated hypoglycemia and have an underlying CV pathology, and die in their sleep.[179]

Hypoglycemia is a BG concentration <70 mg/dL, and its occurrence is potentially fatal if not promptly recognized and treated. However, the exact level at which patients experience symptoms is difficult to define and will vary from patient to patient. Clinical hypoglycemia is associated with typical autonomic (neurogenic) and neuroglycopenic symptoms relieved by the administration of a quickly absorbed carbohydrate.

Pathophysiology

Normal brain function depends on glucose, the exclusive fuel for cerebral metabolism. Because the brain is unable to synthesize or store glucose, it must be provided with a constant exogenous quantity via the brain's blood supply. As BG concentrations fall, a series of physiologic responses occur to restore glucose levels. These responses create symptoms warning a patient to take corrective action by consuming carbohydrates. If these counterregulatory responses fail to alert the patient and BG concentrations fall below a critical level, cognitive function becomes impaired, and confusion and coma may ensue.

In people without diabetes, the peripheral responses to hypoglycemia are so efficient that clinically important hypoglycemia probably never occurs. As glucose levels fall between 50 and 60 mg/dL, a series of neuroendocrine events occur, raising the plasma glucose concentration back toward normal by increasing hepatic glucose output. The major hormone responsible for producing acute recovery from insulin-induced hypoglycemia is glucagon; however, epinephrine alone also can produce near-normal recovery. Rising levels of adrenergic and cholinergic hormones generate warning symptoms of hypoglycemia. When hypoglycemia is prolonged, growth hormone and cortisone play a greater role in producing recovery.

Patients with type 1 diabetes who maintain insulin depots throughout the day are predisposed to severe hypoglycemic reactions because deficiencies in the normal feedback system occur with time. Glucagon secretion becomes deficient within the first 2 to 5 years of diagnosis, and by 10 years or longer, epinephrine secretion may become impaired. The latter defect leads to asymptomatic hypoglycemia or hypoglycemic unawareness (see Case 53-9).

Certain circumstances predispose patients with type 1 diabetes to severe hypoglycemia. These include (a) a defective counterregulatory hormonal response to hypoglycemia (see Case 53-9), which may be further diminished with frequent hypoglycemia, (b) medications such as β-blockers that diminish early warning signs of impending hypoglycemia, (c) intensive insulin therapy that can alter secretion of counterregulatory hormones, (d) skipped meals or inadequate carbohydrate intake relative to the insulin dose, (e) physical activity, and (f) excessive alcohol intake (Table 53-12).

Symptoms

The signs and symptoms associated with hypoglycemia vary in intensity according to the presence of cognitive deficits and the patient's ability to self-treat the reaction. They vary substantially from

one patient to another. Symptoms are conventionally divided into two categories: neurogenic (or autonomic) and neuroglycopenic.[63,179]

Autonomic symptoms include sweating, intense hunger, palpitations, tremor, tingling, and anxiety. Epinephrine is thought to mediate many of the neurogenic responses to hypoglycemia.

Neuroglycopenic symptoms resulting from neuronal fuel deprivation (glucose) include difficulty concentrating, lethargy, confusion, agitation, weakness, and, possibly, slurred speech, dizziness, and fainting. Profound behavioral changes, seizures, and coma are more severe manifestations of neuroglycopenia. Prolonged, severe neuroglycopenia may ultimately result in death if gone untreated. The ADA categorizes hypoglycemia based on levels of severity, which are listed along with symptoms as follows:

- Level 1 hypoglycemia: Defined by a glucose level <70 mg/dL but >54 mg/dL. Symptoms include tremor, palpitations, sweating, and intense hunger. Diminished cerebral function is not present, and patients are capable of self-treating.
- Level 2 hypoglycemia: Defined by a glucose level <54 mg/dL. Neuroglycopenic and autonomic symptoms may occur, including headache, mood changes, irritability, decreased attention, and drowsiness. Patients may require assistance in treating themselves because of the presence of impaired judgment or weakness. Symptoms are more severe, usually last longer, and often require a second dose of a simple carbohydrate. If patients do not experience symptoms in this level, then they likely have hypoglycemia unawareness.
- Level 3 hypoglycemia: Symptoms of severe hypoglycemia include an altered physical function and mental status. Patients may potentially become unresponsive, unconscious, or convulse. These reactions require assistance from another individual for appropriate treatment. Approximately 10% of patients treated with insulin experience at least one severe, disabling episode of hypoglycemia per year that requires emergency treatment.[33]

G.O. is experiencing level 2 hypoglycemia, which he is able to self-treat. This is likely caused by G.O. receiving too much insulin resulting in “stacking” (giving rapid- or short-acting insulin injections too close together, so that the doses “stack” on top of the other) with his rapid-acting insulin.

INSULIN STACKING

CASE 53-8, QUESTION 2: Evaluate G.O.’s overall control. What signs and symptoms in G.O. are consistent with insulin stacking? How should he be managed?

The following is a list of signs and symptoms indicating that G.O. is receiving too much rapid-acting insulin:

- A total daily insulin dose of more than 1 unit/kg: This dose is unusually high for a patient with type 1 diabetes, who should not be resistant to the action of insulin.
- Weight gain in the past several months: This is secondary to the anabolic effects of insulin and G.O.’s increased carbohydrate intake to match his high insulin doses for treatment of hypoglycemia.
- Frequent hypoglycemic reactions
- High glycemic variability (ie, BG concentrations that fluctuate wildly between hypoglycemia and hyperglycemia): In G.O.’s case, high BG concentrations may represent reactive hyperglycemia or overtreatment of hypoglycemic episodes. His low BG level may represent excessive rapid-acting insulin at bedtime and insulin stacking of his rapid-acting insulin after lunch. At lunchtime, he is administering a high-sugar correction dose of insulin glulisine too soon; his mealtime glulisine is still likely at a peak action and working to lower his prandial BG. By administering additional glulisine soon after the meal, the two insulin doses are adding up, or stacking, causing hypoglycemia.

- Near-normal A_{1c} levels: Such levels indicate mean BG concentrations that must be within the normal range even though the patient has recorded numerous high BG concentrations. Patients treated with intensive insulin therapy in the DCCT experienced hypoglycemic episodes three times more often than did patients treated with standard insulin therapy.[180] A_{1c} levels were ~7.2%.

G.O. should be managed by discontinuing his high-sugar corrections at bedtime and after lunch. He should check his BG premeal, 1 to 2 hours after meals, and at bedtime to obtain a better picture of his glucose patterns and insulin requirements. He should avoid the large bedtime snack because one should not have to add food just to avoid hypoglycemia (ie, the insulin regimen should be adjusted). He should also begin testing his BG at 2:00 or 3:00 AM to assess whether he is still experiencing nocturnal hypoglycemia after stopping the bedtime insulin glulisine. It will be important that he records the actual dose he administers before each meal and brings the record to the clinic so that his insulin doses can be fine-tuned. Next, if he is capable, an algorithm for adjusting his preprandial insulin glulisine doses should be provided to minimize hypoglycemic and hyperglycemic reactions (see Case 53-2, Question 12); eventually, he can transition to counting carbohydrates (see Case 53-2, Questions 11 and 12).

TREATMENT OF HYPOGLYCEMIA

CASE 53-8, QUESTION 3: How should G.O.'s hypoglycemic episodes be managed?

As G.O. illustrates, many patients with diabetes are frightened of hypoglycemia and have a tendency to over-treat their reactions with, for example, large quantities of juice or regular soda. This should be discouraged because overcorrection together with glucose

generated by counterregulatory hormones ultimately results in hyperglycemia.

The key to successful management of hypoglycemia is recognition and prevention. Because early warning symptoms of hypoglycemia vary from person to person, it is important that G.O. learns to recognize and pay attention to his earliest warning symptoms and treat early. Patients generally can recall prodromal symptoms after recovery from a severe hypoglycemic reaction if they have not developed hypoglycemic unawareness (see Case 53-9). As a caveat, occasionally patients “feel” hypoglycemic after their BG concentrations have been normalized from very high levels with intensive insulin therapy, owing to the amount of BG change. Encourage patients to test their BG level any time they “feel unusual” to verify a low BG concentration before treatment. G.O. should treat his symptoms only if he is truly hypoglycemic.

A second component of prevention is determining its cause and taking preventive or corrective action. This entails assessment of his diet (did he skip or delay a meal or change its content?), exercise pattern, time of insulin administration, insulin dose, and accuracy of carbohydrate counting, and dose administered. If hypoglycemic reactions consistently occur at a certain time of day, he should determine whether this corresponds with a mealtime dose of his rapid-acting insulin and reduce that insulin dose by 1 to 2 units. If his FPG is running low, his insulin glargine dose can be reduced.

If a reaction occurs, G.O. should be instructed to treat it as follows (Table 53-12).

Management of level 1 and level 2 hypoglycemia

Most hypoglycemic reactions are managed readily with the equivalent of 10 to 20 g of glucose (see Table 53-12 for examples of carbohydrate sources containing 15 g of glucose). If the blood concentration remains low after 15 minutes, the patient should ingest another 10 to 20 g of carbohydrate. This quick-acting source of glucose should be followed by a small complex carbohydrate or protein snack (eg, milk or peanut butter sandwich) to provide a

continual source of glucose if a meal is not scheduled within the next 1 to 2 hours. An easy rule of thumb that can be used by patients is “15-15-15”: 15 g of glucose followed by a second 15 g if the patient is still symptomatic after 15 minutes.

Glucose tablets are available and have the added benefit of being premeasured to prevent overtreatment of hypoglycemia. Glucose gels, liquid, or small tubes of cake frosting are useful for children or patients who become uncooperative and combative when hypoglycemic.

Management of level 3 hypoglycemia

As previously stated, patients experiencing level 3 hypoglycemia will have an altered mental and/or physical functioning and will require the assistance of another person to treat their hypoglycemia. In this case, treatment with oral glucose is not an appropriate option owing to the risk of choking, and, instead, treatment of hypoglycemia in this case will require the administration of glucagon. There are multiple, commercially available glucagon-containing products, which deliver glucagon via SC, IM, IV (under medical supervision), or nasal routes.

Originally, glucagon was only available in an emergency kit, which included a powder that required reconstitution before use where parents, spouses, or other close contacts should be taught how to mix, draw up, and administer glucagon during emergency situations.

The dose of glucagon recommended to treat severe hypoglycemia for a pediatric patient <55.12 pounds (25 kg) or of unknown weight younger than 6 years old is 0.5 mg (0.5 mL).

Pediatric patients weighing ≥55.12 pounds (25 kg) or children older than 6 years of unknown weight should receive 1 mg (1 mL), which is the same dose for adult patients. The dose should be administered either IM or SC into the upper arm, thigh, or buttocks.[181]

Glucagon is now also available in prefilled syringes, autoinjecting devices, and nasal spray for more convenient administration. Glucagon prefilled syringes and autoinjecting devices (brand name GVOKE®) are indicated for use in patients age older than 2 years

and do not require reconstitution. These products easily deliver either 0.5 or 1 mg of glucagon to patients experiencing severe hypoglycemia. The recommended dose for adults and patients 12 years and older is 1 mg, whereas the dosing for patients 2 to 12 years old is weight based (children <99.20 pounds [45 kg] should receive 0.5 mg, and children >99.20 pounds [45 kg] should receive 1 mg). The dose should be administered SC into the lower abdomen, outer thigh, or outer upper arm.[182]

Glucagon powder (brand name Baqsimi®) is available in a single-use device that administers 3 mg of glucagon powder nasally and is recommended for use in patients ages 4 years and older to treat severe hypoglycemia. The recommended dose for all patients is 3 mg delivered as one actuation into one nostril. Patients do not need to inhale the powder; it is absorbed following actuation of the device.[63]

Patients who are administered glucagon should be positioned so that their face is turned toward the floor to prevent aspiration in the event of vomiting. As soon as the patient awakens (10–25 minutes), he/she should be fed. Because glucagon is recommended to treat severe hypoglycemia in patients who cannot treat their symptoms independently, family members, friends, and coworkers should be educated on the proper use of the prescribed glucagon device. This should include where the device is stored so that it can be easily obtained and administered during an emergency.[41]

Intravenous Glucose

If glucagon is unavailable, the patient should be taken to the hospital's emergency department, where he/she can be treated with IV glucose (~10–25 g administered as 20–50 mL of 50% dextrose for 1–3 minutes) in preference to glucagon. After the bolus injection of glucose, IV glucose (5–10 g/hour) should be continued until the patient has gained consciousness and is able to eat.

HYPOGLYCEMIC UNAWARENESS

CASE 53-9

QUESTION 1: M.M., a 35-year-old, 165.35-pound (75-kg), unemployed male, has had type 1 diabetes since the age of 3. As a consequence of diabetes, he has developed proliferative retinopathy and progressive diabetic nephropathy (current SCr, 2.2 mg/dL). M.M. has an erratic lifestyle. Because he does not work, he often stays out late at night and sleeps late into the morning. His insulin is injected whenever he awakens, and his meals are irregularly spaced. Each time he comes to the clinic, he brings with him a complete log of glucose concentrations that range from 80 to 140 mg/dL. He has two to three severe hypoglycemic reactions a month that require trips to the emergency department for treatment with IV glucose. On several occasions, his BG concentration has been 30 mg/dL, and he states he may feel weak, but otherwise feels "not too bad." M.M.'s last A_{1c} was 10%. He says that he adheres to the following insulin regimen: 18 units NPH/11 units regular insulin before breakfast, 10 units regular insulin before lunch and dinner, and 14 units NPH at bedtime.

At this visit, M.M. comes with his girlfriend. He has a large gash on his nose that occurred 3 days ago when he lost consciousness at ~1:30 PM while pushing his stalled car. He was unable to eat lunch at the usual hour because he had problems with his car.

Assess M.M.'s hypoglycemic reactions and BG control.

Should his current insulin regimen be continued? How should he be managed?

M.M. illustrates a patient with type 1 diabetes who has defective glucose counterregulation and, as a result, is unable to counteract a hypoglycemic reaction effectively. He also is an example of a patient who should not have aggressive BG targets because he does not feel the symptoms of low blood sugar and has already developed end-stage organ damage (proliferative retinopathy and nephropathy). Neither is likely to be reversed with improved glycemic control. In fact, proliferative retinopathy may actually worsen with intensive insulin therapy initially.[33] In the DCCT study, severe hypoglycemic reactions were three times more common among patients treated with intensive insulin therapy, and nocturnal hypoglycemia accounted for 41% of the total hypoglycemic episodes.[179] In patients with defective counterregulation, the risk of severe hypoglycemia may be 25 times higher than that in patients with adequate counterregulatory mechanisms treated with intensive

insulin therapy.[183] M.M. is at great risk for death secondary to hypoglycemia.

M.M.'s lifestyle is erratic, he eats irregularly, and his reported BG concentrations (80–140 mg/dL) do not correspond to his elevated A_{1c} value. This may indicate that M.M.'s technique is incorrect or that he simply fills in the log with fictitious numbers before he comes to the clinic. Irregular entries in different colored inks and bloodstains usually indicate authentic records.

As noted, the primary hormones that are secreted in response to a low BG concentration are glucagon and epinephrine. In patients who have had type 1 diabetes for >2 to 5 years, a deficiency in glucagon secretion is a relatively consistent finding, and these patients must rely on epinephrine to reverse low BG concentrations.[179] Unfortunately, ~40% of patients with long-standing type 1 diabetes (8–15 years) have defective epinephrine secretion as well, and this may be related to the development of autonomic neuropathy. Patients whose diabetes is tightly controlled also have reduced counterregulatory hormone responses to hypoglycemia. As illustrated by M.M., patients with defective epinephrine secretory responses also lose the warning signs and symptoms of hypoglycemia. These patients are said to have hypoglycemia unawareness because they have no awareness of BG concentrations <50 mg/dL. In these individuals, loss of consciousness, seizures, or irrational behavior may be the first objective sign of exceedingly low BG concentrations. The glycemic threshold for symptoms also is lowered in patients on intensive insulin therapy whose glucose concentrations have been lowered to normal or near-normal levels.[184] Consequently, their hypoglycemic reactions may go unnoticed and untreated until they lose consciousness. M.M. should be managed as follows:

- Because his waking, sleeping, and eating patterns are highly irregular, M.M. should be treated with an insulin regimen that addresses his lifestyle. For example, he could be switched to a basal-bolus insulin regimen, in which he can give himself a rapid-acting insulin just before he actually intends to eat. A dose of

insulin degludec could be given before his first meal to supply a basal level of insulin between meals. Because M.M. has an inconsistent sleep pattern, he may be administering his basal insulin dose at varying times. This would not be a concern if MM was using degludec because of its extremely long half-life. In addition, when switching to insulin degludec, M.M. should be provided this insulin in a pen formulation if cost is not a concern, so as to avoid any dosing errors from drawing insulin into a syringe based on M.M.'s current symptoms of visual impairment.

- Because M.M. has no warning symptoms of hypoglycemia, the importance of regular SMBG should be emphasized. When BG testing was reviewed with M.M., it was discovered that his eyesight was so poor that he was unable to distinguish between the right and wrong sides of the glucose test strip. Furthermore, because he had lost his depth of field, he was unable to apply the drop of blood into the test strip. To address this situation, M.M.'s girlfriend was taught how to perform BG testing. Also, a glucose monitor that requires a very small blood sample and beeps with an adequate blood sample would be beneficial for him. Alternatively, a CGM may be an excellent option for MM to more easily obtain glucose values versus using a traditional finger stick home BG monitor.
- M.M.'s girlfriend also was taught how to recognize and treat symptoms of hypoglycemia and how to administer glucagon. Often, patients ignore early warning symptoms and progress to a point that they lose the judgment needed to treat the condition. If M.M. has not yet become combative, a quick-acting carbohydrate source should be offered. If he has lost consciousness, glucagon should be administered.

All of these maneuvers diminished the frequency of M.M.'s severe hypoglycemic reactions. On the whole, his BG concentrations were maintained <180 mg/dL, and he remained relatively free of hyperglycemic symptoms. M.M.'s A_{1c} using a basal-bolus insulin regimen was 8.0%.

DIABETIC KETOACIDOSIS

CASE 53-10

QUESTION 1: J.L., a 40-year-old, 132.27-pound (60-kg) female with an 8-year history of type 1 diabetes, is moderately well controlled on 24 units of insulin glargine plus premeal doses of insulin lispro. Her family brings her to the emergency department, where she reports abdominal tenderness, nausea, and vomiting. According to her family, J.L. was well until 2 days ago when she awoke with nausea, vomiting, diarrhea, and chills. Because she has been unable to eat, she has omitted her usual morning dose of insulin for the past 2 days. Her gastrointestinal (GI) symptoms progressed, and she was brought to the emergency department when she became lethargic.

Physical examination reveals an ill-appearing female who is lethargic but responsive. Her temperature is 98.60 °F (37 °C). Skin turgor is poor, mucous membranes are dry, and her eyeballs are shrunken and soft. J.L.'s lungs are clear, but respirations are deep, and her breath has a fruity odor. Cardiac examination is within normal limits.

In the supine position, J.L.'s pulse rate is 115 beats/minute, and her BP is 105/60 mm Hg. In the upright position, her pulse increased to 140 beats/minute, and her BP dropped to 85/40 mm Hg. There is mild, diffuse tenderness over her abdomen.

Laboratory results on admission disclosed the following:

BG, 450 mg/dL
Sodium (Na), 150 mEq/L
Potassium (K), 5.4 mEq/L
Chloride (Cl), 106 mEq/L
HCO_3, 10 mEq/L
SCr, 2.0 mg/dL
Hemoglobin, 15.7 g/dL
Hematocrit, 49%

White blood cell count, 15,000/μL with 3% bands (normal, 3%–5%), 70% polymorphonuclear neutrophils (normal, 54%–62%), and 27% lymphocytes (normal, 25%–33%)

Serum ketones, moderate at 1:10 dilution (normal, negative)
The urinalysis showed the following:
Glucose, 2+ (normal, 0)
Moderate ketones (normal, 0)
pH, 5.5 (normal, 4.6–8)
Specific gravity, 1.029 (normal, 1.020–1.025)
No white blood cells, RBCs, bacteria, or casts

Arterial blood gas results were as follows:
pH, 7.05 (normal, 7.36–7.44)
Pco_2, 20 mm Hg (normal, 35–45)
Po_2, 120 mm Hg (normal, 90–100)

What supports the diagnosis of DKA in J.L.?

The fact that J.L. has type 1 diabetes puts her at risk for developing ketoacidosis. About 80% of DKA cases occur in patients older than age 18 years with about one-third of those occurring in patients older than age 45 years.[185] In DKA, an absolute or relative insulin deficiency promotes lipolysis and metabolism of free fatty acids to β-hydroxybutyrate, acetoacetic acid, and acetone in the liver. Excess glucagon enhances gluconeogenesis and impairs peripheral ketone utilization. Physiologic stress contributes to the development of DKA by stimulating the release of insulin counterregulatory hormones including glucagon, catecholamines, glucocorticoids, and growth hormone. Common stress factors include infection, pregnancy, pancreatitis, trauma, hyperthyroidism, and acute MI.

J.L. presented with symptoms of nausea, vomiting, diarrhea, and chills; and these are suggestive of an acute viral gastroenteritis. Patients such as J.L. commonly discontinue their insulin in this setting, which can rapidly precipitate the development of DKA (see Case 53-5). **Table 53-22** lists patient education points with regard to DKA.

Table 53-22
Diabetic Ketoacidosis: Patient Education

Definition: DKA occurs when the body has insufficient insulin.

Questions to Ask

1. Has insulin use been discontinued or a dose skipped for any reason?
2. If an insulin pump is being used, is the tubing clogged or twisted? Has the catheter become dislodged?
3. Has the insulin being used lost its activity? Is the bottle of rapid-acting/regular or basal insulin cloudy? Does the bottle of NPH look frosty?

4. Have insulin requirements increased owing to illness or other forms of stress (infection, pregnancy, pancreatitis, trauma, hyperthyroidism, or MI)?
What to Look for
1. Signs and symptoms of hyperglycemia: thirst, excessive urination, fatigue, blurred vision, consistently elevated blood glucose concentrations (>300 mg/dL) 2. Signs of acidosis: fruity breath odor, deep and difficult breathing 3. Signs of dehydration: dry mouth, warm, dry skin, fatigue 4. Others: stomach pain, nausea, vomiting, loss of appetite
What to Do
1. Review “sick day management” (Table 53-20). 2. Test blood glucose ≥four times daily. 3. Test urine for ketones when blood glucose concentration is >300 mg/dL. 4. Drink plenty of fluids (water, clear soups). 5. Continue taking insulin dose. 6. Contact physician immediately.

DKA, diabetic ketoacidosis; MI, myocardial infarction; NPH, neutral protamine Hagedorn.

As illustrated by J.L., patients with DKA present with moderate- to-high serum glucose concentrations secondary to decreased peripheral utilization and increased hepatic production (**Table 53-23**). This increases serum osmolality, which initially shifts fluid from the intracellular to the extracellular space. When serum glucose concentrations exceed the renal threshold for reabsorption of about 200 mg/dL, glucose “spills” over into the urine and causes an osmotic diuresis that depletes the total body water and electrolytes. J.L. also has lost fluid and electrolytes from vomiting and diarrhea. Eventually, as losses exceed input, the patient becomes dehydrated (dry mucous membranes; dry skin; soft, shrunken eyeballs; increased hematocrit), and intravascular volume becomes depleted (orthostatic BP and pulse changes).

Table 53-23

Common Laboratory Abnormalities in Diabetic Ketoacidosis

Glucose	250 mg/dL

Glucose	250 mg/dL
Serum osmolarity	Variable, can be >320 mOsm/kg in presence of coma
Sodium	Low, normal, or high[a]
Potassium	Normal or high
Ketones	Present in urine and blood
pH	Mild: 7.25–7.30
	Moderate: 7.00–7.24
	Severe: <7.00
Bicarbonate	Mild: 15–18 mEq/L
	Moderate: 10 to <15 mEq/L
	Severe: <10 mEq/L
WBC count	15,000–40,000 cells/mL even without evidence of infection

WBC, white blood cell.

[a]Total body sodium is always low.

The finding of hyperkalemia in J.L. is also common in DKA because insulin contributes to the intracellular shift of potassium.[186] The relative deficiency of insulin in DKA results in an extracellular shift of potassium that is worsened by the acidosis that often develops.[185] A finding of hypokalemia in DKA (<3.3 mg/dL) is uncommon and is a marker of more severe disease. In the patient with hypokalemia, the combination of the extracellular shift of potassium and polyuria has led to excessive depletion of total body potassium. Care must be used in these patients to replace potassium via IV before beginning insulin therapy, which will cause further hypokalemia as potassium shifts back into cells.[185,187]

Evidence of excessive ketone production in J.L. includes ketonuria, ketonemia, and the characteristic fruity odor of acetone on the breath. Elevated levels of these organic acids increase the anion gap and decrease the pH and carbonate levels. The respiratory rate is increased to compensate for the metabolic acidosis, leading to hypercapnia.[184]

Treatment

Case 53-10, Question 2: How should J.L. be treated?

Treatment of patients with DKA is aimed at expansion of intravascular and extravascular volume, replacement of electrolyte losses, and cessation of ketone production (**Table 53-24**).

Table 53-24
Management of Diabetic Ketoacidosis

Fluid Administration
Start IV fluids using normal saline (0.9% NaCl) unless patient has cardiac compromise.
Rate is 15–20 mL/kg body weight or 1–1.5 L during first hour.
Then, if corrected sodium is normal or elevated, use 0.45% NaCl at a rate of 4–14 mL/kg/hour (250–500 mL/hour). Use 0.9% NaCl if corrected sodium is low.
Once serum glucose reaches 200 mg/dL, change to 5% dextrose with 0.45% NaCl at 150–250 mL/hour.
Insulin
Continuous IV infusion of regular insulin is preferred. Use IM route only if infusion is not available.
Bolus dose: 0.1 units/kg IV
Maintenance dose: 0.1 units/kg/h our IV
If blood glucose level has not decreased by 50–75 mg/dL after 1 hour, double infusion rate.
Once blood glucose reaches 200 mg/dL, reduce infusion rate to 0.05–0.1 units/kg/hour and change fluid to 5% dextrose with 0.45% NaCl (do not stop insulin infusion).
When SC insulin can be initiated, administer dose 1–2 hours before discontinuing IV infusion.
For uncomplicated DKA, SC rapid-acting insulin can be considered. A bolus dose of 0.2 units/kg followed by 0.1 units/kg every hour *or* an initial dose of 0.3 units/kg followed by 0.2 units/kg every 2 hours until the blood glucose reaches <250 mg/dL; then the SC insulin dose is decreased by half (to either 0.05 or 0.1 units/kg every 1–2 hours).

Potassium
Establish adequate renal function (urine output ~50 mL/hour). If K is <3.3 mEq/L, hold insulin and give 20–40 mEq/hour until K >3.3 mEq/L. If K is >5.5 mEq/L, do not give K and check serum K every 2 hours. If K is >3.3 but <5.3 mEq/L, give 20–30 mEq in each liter of IV fluid to maintain K between 4 and 5 mEq/L.
Phosphate
Initiate if level <1 mg/dL, or in patients with cardiac dysfunction, anemia, or respiratory depression. Use potassium phosphate salt, 20–30 mEq added to replacement fluid. Rarely needed
Bicarbonate
Replacement is controversial and may be dangerous.
For adults with pH <6.9, 100 mmol of sodium bicarbonate may be added to 400 mL of sterile water with 20 mEq of KCl; infuse for 2 hours (200 mL/hour). For adults with pH of 6. 9–7.0, 50 mmol of sodium bicarbonate diluted in 200 mL of sterile water with 10 mEq of KCl; infuse for 1 hour (200 mL/hour). No bicarbonate is necessary if pH >7.0.

DKA, diabetic ketoacidosis; IM, intramuscular; IV, intravenous; SC, subcutaneous.

Source: Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1335–1343. doi:10.2337/dc09-9032

FLUIDS

Rapid correction of fluid loss is most crucial. The usual fluid deficit is difficult to estimate in the absence of overt hypernatremia but approximates 5% to 10% of body weight in most patients depending on the severity of the DKA. In the absence of cardiac compromise, hypernatremia, or significant renal dysfunction, isotonic saline (0.9% NaCl) should be used.[185]

J.L. has evidence of significant dehydration and intravascular volume depletion. Based on body weight, if the patient has the typical 5% to 10% weight loss, it will indicate that ~3 to 6 L of fluid will be needed to fully replete (10% of 132.27 pounds [60 kg]—13.23-pound [6-kg] loss and 1 L—2.20 pounds [1 kg]). It is recommended that fluids be replaced at the rate of 15 to 20 mL/kg/hour during the first hour (~1–1.5 L in the average adult). The subsequent choice for fluid replacement depends on the patient's state of hydration, serum electrolyte levels, and urinary output. If the

corrected sodium is normal or elevated, 0.45% NaCl infused at a rate of 4 to 14 mL/kg/hour is appropriate. If the corrected serum sodium is low, 0.9% NaCl is preferred.[185] When serum glucose concentrations approach 200 mg/dL, solutions should be changed to D5W/0.45% NaCl. Glucose is added to allow the continuation of insulin therapy without causing hypoglycemia (see Case 53-10, Question 5).[185]

SODIUM

Total body sodium usually is depleted by 7 to 10 mEq/kg of body weight in patients with DKA. In assessing serum sodium in these patients, it is important to remember that falsely low values (ie, pseudohyponatremia) may be the result of hyperglycemia and hypertriglyceridemia. A corrected sodium value can be estimated by adding 1.6 mEq/L to the observed sodium value for every 100 mg/dL glucose in excess of 100 mg/dL. Sodium is replaced adequately with normal saline, which has a sodium concentration of 154 mEq/L.[185,187]

POTASSIUM

Potassium balance is altered markedly in patients with DKA because of combined urinary and GI losses. Invariably, total body potassium is at least partly depleted; however, the serum potassium concentration may be high, normal, or low, depending on the degree of acidosis and volume contraction and severity of insulin deficiency. Usual potassium deficits in this situation average 3 to 5 mEq/kg of body weight, although they may be as high as 10 mEq/kg.[185]

Thus, J.L. needs ~200 to 350 mEq of potassium to replenish her body stores, assuming her normal weight is 154.32 pounds (70 kg). To prevent hypokalemia, potassium replacement should be started after her serum potassium concentrations decrease to <5.3 mEq/L (assuming an adequate urine output of 50 mL/hour). The addition of 20 to 30 mEq/L is usually sufficient to maintain the serum potassium at >4 mEq/L. In cases when serum potassium is low at presentation (<3.3 mEq/L), potassium replacement should be initiated with fluid therapy, and insulin therapy delayed until the potassium level is >3.3

mEq/L to avoid severe hypokalemia and the risk of cardiac arrhythmias and diaphragmatic weakness. In these cases, initial IV solutions should contain 20 to 30 mEq/L of potassium chloride.

PHOSPHATE

Phosphate is lost as the result of increased tissue catabolism, impaired cellular uptake, and enhanced renal excretion. As with other electrolytes, serum levels initially may seem normal, even though body stores are depleted. However, replacement can result in hypocalcemia, and the use of phosphate in DKA has resulted in no clinical benefit to patients.[185] Severe hypophosphatemia (<1.0 mg/dL) can cause cardiac and skeletal muscle weakness as well as respiratory depression. To avoid this, phosphate can be carefully replaced in patients with cardiac dysfunction or respiratory depression when phosphate concentrations are <1.0 mg/dL. Potassium phosphate can be added to the replacement fluids in amounts of 20 to 30 mEq/L.

INSULIN

Case 53-10, Question 3: What is an appropriate insulin dose and route of administration for J.L.?

Insulin therapy is the key to DKA management because it is what stops the production of ketones. Because insulin allows glucose metabolism to resume, the counterregulatory signals for ketone production are turned off. Unless the episode of DKA is mild (pH 7.25–7.30) and uncomplicated, regular insulin by continuous infusion is the treatment of choice. Once hypokalemia (K^+ <3.3 mEq/L) is excluded or treated, an IV bolus of regular insulin at 0.1 units/kg followed by a continuous infusion at a dose of 0.1 units/kg/hour should be administered. This should decrease the plasma glucose by at least 10% in the first hour. If there is not at least a 10% reduction in the first hour, then a second bolus of 0.15 units/kg should be administered. Once the plasma glucose reaches 200

mg/dL, the insulin infusion can be decreased to 0.05 units/kg/hour. Alternatively, insulin can be switched to SC at a dose of 0.1 units/kg every 2 hours. Regardless of the route of insulin therapy, serum glucose should be maintained at <200 mg/dL.[185] At this point, the fluid should be changed to D5W with 0.45% NaCl. Thereafter, the rate of insulin administration and the rate of infusion of D5W with 0.45% NaCl are adjusted to maintain the glucose value at around 200 mg/dL until the ketosis is resolved.[185] Resolution of ketosis is marked by a serum bicarbonate level of at least 15 mEq/L, a venous pH >7.3, and a calculated anion gap of ≤12 mEq/L. Once any two of those three findings are present, the patient can be converted to a longer-acting SC regimen.

For mild DKA (serum bicarbonate ≥15 mEq/L, anion gap <15), SC rapid-acting insulin has been used with no differences in patient outcomes. The advantage is that patients can be treated in a non-ICU setting, thus reducing hospital costs. The dosing for rapid-acting insulin is included in Table 53-24.

SODIUM BICARBONATE

Case 53-10, Question 4: J.L. was treated with fluids, electrolytes, and insulin, as discussed in previous questions. Laboratory and clinical data 4 hours after therapy are as follows:

pH, 7.1
BG, 400 mg/dL
K, 3.8 mEq/L
SCr, 3.1 mg/dL
Serum ketones, strongly positive at a 1:40 dilution

Her BP was 120/70 mm Hg with no orthostatic changes. Urine output for the past 3 hours has been 500 mL. Because serum ketones have increased, should J.L. receive more insulin? Should she receive bicarbonate therapy?

The assumption that ketosis is worse in J.L. is incorrect. In DKA, low levels of insulin and elevated glucagon levels promote the metabolism of free fatty acids in the liver to acetoacetate and β-hydroxybutyrate. The standard nitroprusside reaction test for ketones

measures only acetoacetate, even though β-hydroxybutyrate is the more important ketone. The conversion of acetoacetic acid to β-hydroxybutyrate is coupled closely with the reduced nicotinamide adenine dinucleotide hydrogen:nicotinamide adenine dinucleotide (NADH:NAD) ratio. If this ratio is high (as in the presence of alcohol), so much β-hydroxybutyrate may be formed that acetoacetate is virtually undetectable; thus, the absence of ketones in the serum does not rule out ketoacidosis.

Conversely, treatment with insulin begins to suppress lipolysis and fatty acid oxidation; NAD is regenerated, shifting the reaction back in favor of acetoacetate.[184] Thus, even though there seem to be higher concentrations of ketones in the serum, J.L.'s declining BG concentration, improved bicarbonate concentrations, and improved acid–base and CV responses indicate that she is responding appropriately. Therefore, no change in the insulin dose is indicated. It is important to emphasize that the glucose concentrations normalize before ketones (4–6 hours vs 6–12 hours) because the latter are metabolized more slowly. For this reason, it is important to continue insulin to maintain suppression of lipolysis until plasma and urine ketones have cleared.

The use of bicarbonate in patients with DKA has been controversial.[185] Most investigators discourage its routine use, reserving it for patients with severe acidemia (pH <6.9) or those in clinical shock. Coma is correlated most closely with BG concentrations (>700 mg/dL) and hyperosmolality (calculated osmolality >340 mOsm/kg).[188] In a small randomized, prospective study, bicarbonate did not affect recovery in patients with severe DKA (arterial pH, 6.9–7.14).[189] Thus, even though J.L.'s acidosis seemed severe on admission (pH, 7.05; bicarbonate, 10 mEq/L; Kussmaul respirations [deep, frequent respirations resulting in blowing off of CO_2]), bicarbonate was not administered. It is apparent that with fluid and insulin therapy alone, her acidosis is beginning to improve.

Case 53-10, Question 5: What is the expected course of DKA in J.L.?

After 3 L of fluid and a constant insulin infusion of 6 units/hour for 3 hours, J.L.'s glucose concentration had dropped to 400 mg/dL and she had no orthostatic BP changes, reflecting recovery from her volume-depleted status. Potassium (40 mEq/L) was added to her fluids, which were administered at a reduced rate of 300 mL/hour.

Three hours later, the glucose concentration had dropped to 350 mg/dL, and her pH had increased to 7.21 with an anion gap of 24 mEq/L. The serum potassium remained low-normal at 3.4 mEq/L, and serum sodium increased to 151 mEq/L. In view of these changes, the IV infusion fluid was changed to half-normal saline with 5% dextrose to which 40 mEq/L of potassium was added. The rate was slowed to 250 mL/hour, and the insulin infusion was continued at 6 units/hour.

Four hours later (10 hours after admission), the BG was 205 mg/dL, and the serum potassium was 3.5 mEq/dL. The IV fluids were changed to 5% dextrose with 40 mEq/L of potassium chloride, administered at a rate of 250 mL/hour, and the regular insulin infusion was decreased from 6 to 3 units/hour. J.L. continued to improve during the next 12 hours, and she began taking full oral liquids by the second hospital day. At that time, her IV infusion rate was decreased to 200 mL/hour, but her insulin infusion was continued.

Approximately 24 hours after admission, J.L.'s BG concentration was 175 mg/dL, potassium was 4.6 mEq/L, sodium was 144 mEq/L, and the anion gap had closed down to 16 mEq/L. There were no ketones in the plasma. The urine contained 1% glucose and moderate amounts of ketones. IV fluids were discontinued, and a rapid-acting insulin was administered SC 1 hour before the insulin infusion was discontinued. J.L. continued to receive rapid-acting insulin SC every 4 hours according to a sliding scale (see Case 53-2, Question 12). Thirty-six hours after admission, J.L. was given her usual dose of insulin glargine and insulin lispro and was sent home for follow-up in the clinic.

TREATMENT OF TYPE 2 DIABETES: ANTIDIABETIC AGENTS

Type 2 diabetes must be managed in the context of metabolic syndrome. At the time of diagnosis, many people with type 2 diabetes already have evidence of macrovascular and microvascular disease. Every effort to lower glucose concentrations toward normal values and to control BP and lipids is important to delay the onset or slow the progression of these complications, improve the overall quality of the patient's life, and save the health care system millions of dollars in hospitalization costs to treat these complications. MNT, physical activity, and SMBG are cornerstones in the treatment of people with type 2 diabetes. Unfortunately, these measures alone are usually not successful in achieving control for the majority of patients, and drug therapy is eventually required. Because these patients also often require a number of medications to treat related conditions (eg, hypertension, dyslipidemia, CVD, and depression) and may also be medicating themselves with over-the-counter drugs, herbal products, and nutritional supplements, the aim of therapy for type 2 diabetes should be the simplest and safest regimen that provides the best glycemic control possible.

Tables 53-25 and **53-26** summarize the comparative pharmacology, pharmacokinetics, and dosing of the noninsulin antidiabetic drugs. The clinical use of these agents in specific situations is illustrated in cases presented later in this chapter.

Table 53-25
Comparative Pharmacology of Antidiabetic Agents

Agent/Generic Name (Brand Name)/Mechanism	FDA Indications	A_{1c} Efficacy[a]	Adverse Effects	Comments
Insulin replaces or augments endogenous insulin	Monotherapy; combined with any oral agent	↓ A_{1c}b ↓FPGb ↓ PPGb ↓ TG	Hypoglycemia, weight gain, lipodystrophy, local skin	Offers flexible dosing to match lifestyle and glucose concentrations. Rapid onset. Safe in pregnancy, renal failure, and liver dysfunction. Drug of choice when patients do not respond to other antidiabetic agents.
Insulin-Augmenting Agents				
Nonsulfonylurea secretagogues (glinides) Repaglinide (Prandin) Nateglinide (Starlix) Stimulates insulin secretion	Monotherapy; combined with metformin or TZD	Monotherapy: ↓ A_{1c} ~1% (repaglinide) ↓ A_{1c} ~0.5% (nateglinide) Combination: additional 1% ↓ A_{1c}	Hypoglycemia, weight gain	Take only with meals. If a meal is skipped, skip a dose. Flexible dosing with lifestyle. Safe in renal and liver failure. Rapid onset. Useful to lower PPG
Sulfonylureas Various; see Table 53-26. Stimulates insulin secretion. May decrease hepatic glucose output and enhance peripheral glucose utilization	Monotherapy; combined with metformin; combined with insulin (glimepiride)	Monotherapy: ↓ A_{1c} ~1% Combination: additional 1% ↓ in A_{1c}	Hypoglycemia, especially long-acting agents; weight gain (5–10 pounds [2.26–4.54 kg]); rash, hepatotoxicity, alcohol intolerance, and hyponatremia are rare.	Very effective agents. Some can be dosed once daily. Rapid onset of effect (1 week)

Incretin-Based Therapies				
Glucagon-like peptide-1 receptor agonists/incretin mimetic Exenatide (Byetta®) Extended-release exenatide (Bydureon®) Lixisenatide (Adlyxin®) Liraglutide (Victoza®) Dulaglutide (Trulicity®) Semaglutide (Ozempic®) Semaglutide oral (Rybelsus®) Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Monotherapy combined with metformin, SFU, or TZD; combined with metformin + SFU; combined with metformin + TZD Can be used in combination with basal insulin	Monotherapy: ↓ A_{1c} 0.8%–0.9% Combination: additional 1% ↓ in A_{1c}	GI: nausea, vomiting, diarrhea; hypoglycemia (with SFUs); weight loss; reports of acute pancreatitis; URTIs	Weight loss Exenatide: take in the 60 minutes before morning and evening meals or before two main meals of the day (≥6 hours apart). Liraglutide, extended-release exenatide, lixisenatide, dulaglutide, semaglutide: Do not use if there is personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2. Do not use in patients with gastroparesis or severe GI disease. Administered by SC injection; pen device in use does not need to be refrigerated. Rare cases of pancreatitis
DPP-4 inhibitors Sitagliptin (Januvia®) Saxagliptin (Onglyza®) Linagliptin (Tradjenta®) Alogliptin (Nesina®) Stimulates insulin secretion and reduces postprandial glucagon levels	Monotherapy; combined with metformin, SFU, or TZD; insulin (sitagliptin, linagliptin, and saxagliptin)	Monotherapy: ↓ A_{1c} 0.5%–0.8% Combination: ↓ A_{1c} 0.5%–0.9%	Headache, nasopharyngitis, hypoglycemia (with SFU), rash (rare)	Dosed once daily. Taken with or without food. No weight gain or nausea. Need to adjust sitagliptin, saxagliptin, and alogliptin dose in renal dysfunction. Reduce dose of SFU when combined. Rare reports of pancreatitis. Saxagliptin and alogliptin may increase the risk of exacerbating HF.
Amylin Receptor Agonists				
Amylin mimetic Pramlintide (Symlin®) Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Type 1: Adjunct to mealtime insulin Type 2: Adjunct to mealtime insulin; ± SFU and metformin	T1: ↓ A_{1c} 0.33% T2: ↓ A1C 0.40%	GI: nausea, decreased appetite, headache; hypoglycemia; weight loss (mild)	Take only immediately before meals; administered by SC injection. Do not use in patients with gastroparesis. Reduce dose of mealtime insulin by 50% to avoid hypoglycemia when starting therapy.
Insulin Sensitizers				
Biguanides Metformin (Glucophage®) ↓ Hepatic glucose output; ↑ peripheral glucose uptake	Monotherapy; combined with SFU or TZD; or with insulin	Monotherapy: ↓ A_{1c} ~1% Combination: additional 1% ↓ in A_{1c}	GI: nausea, cramping, diarrhea; lactic acidosis (rare)	Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain; weight loss possible. Mild reduction in cholesterol. Do not use in patients with renal or severe hepatic dysfunction.
Thiazolidinediones Rosiglitazone (Avandia®) Pioglitazone (Actos®) Enhances insulin action in periphery; increases glucose utilization by muscle and fat tissue; decreases hepatic glucose output	Monotherapy; combined with SFU, TZD, or insulin; combined with SFU + TZD	Monotherapy: ↓ A_{1c} ~1% Combination: additional 1% ↓ in A_{1c}	Mild anemia; fluid retention and edema, weight gain, macular edema, fractures (in females)	Can cause or exacerbate HF; do not use in patients with symptomatic HF or class III or IV HF. Rosiglitazone may increase risk of MI. Increased risk of distal fractures in older females. Pioglitazone may increase risk of bladder cancer when used for >1 year. Slight reduction in TG with pioglitazone; slight increase in LDL-C with rosiglitazone. LFTs must be measured at baseline and periodically thereafter. Slow onset (2–4 weeks)

Glucose Reabsorption Inhibitors				
Sodium–glucose cotransporter type 2 inhibitors Canagliflozin (Invokana®) Dapagliflozin (Farxiga®) Empagliflozin (Jardiance®) Ertugliflozin (Steglatro®) Selectively and reversibly bind to SGLT-2 preventing reabsorption of glucose leading to the excretion of glucose in the urine	May be used as second- or third-line agent or first line in patients who cannot tolerate metformin	↓A_{1c} 0.7%–1.0% ↓FPG ↓PPG May cause weight loss	Genital mycotic infections Urinary tract infections ↓GFR in patients with renal failure	Low risk of hypoglycemia. Dose adjustments may be necessary in patients with renal impairment. SGLT-2 inhibitors not recommended in patients with eGFR <30
Delayers of Carbohydrate Absorption				
α-Glucosidase inhibitors Acarbose (Precose®) Miglitol (Glyset®) Slow absorption of complex carbohydrates	Monotherapy; combined with SFUs, metformin, or insulin	Monotherapy: ↓ A_{1c} ~0.5% Combination: additional ~0.5% ↓ A_{1c}	GI: flatulence, diarrhea. Elevations in LFTs seen in doses >50 mg tid of acarbose	Useful for PPG control (↓ PPG 25–50 mg/dL) LFTs should be monitored every 3 months during the first year of therapy and periodically thereafter. Because miglitol is not metabolized, monitoring of LFTs is not required. Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain. If used in combination with hypoglycemic agents, advise patients to treat hypoglycemia with glucose tablets because absorption is not inhibited as with sucrose. Avoid use in patients with GI disorders (IBD, Crohn disease, intestinal obstruction).
Bile acid sequestrant Colesevelam (Welchol®)	Combined with metformin, SFU, or insulin	↓ A_{1c} 0.3%–0.4%	Constipation, dyspepsia, and nausea; ↑ TG	Added benefit of ↓ LDL-C (by 12%–16%). Administer certain drugs 4 hours before. Take with a meal and liquid.
Enhancers of Dopaminergic Tone				
Bromocriptine (Cycloset®)	Monotherapy; combined with SFU or metformin in patients with type 2 diabetes	Monotherapy ↓ A_{1c} 0.1%; Combo: ↓ A_{1c} 0.5%	Hypotension, dizziness, syncope, nausea, somnolence, headache, exacerbation of psychotic disorders	Very limited role as a therapeutic agent

Theoretically, unlimited glucose lowering with insulin therapy.

A_{1c}, glycated hemoglobin; DPP-4, dipeptidyl peptidase-4; FDA, U.S. Food and Drug Administration; FPG, fasting plasma glucose; GI, gastrointestinal; HF, heart failure; IBD, irritable bowel disease; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; MI, myocardial infarction; PPG, postprandial glucose; SC, subcutaneously; SFU, sulfonylureas; SGLT2, sodium–glucose transporter 2; TG, triglycerides; tid, three times a day; T1, type 1 diabetes; T2, type 2 diabetes; TZD, thiazolidinediones.

[a]Comparative effectiveness data provided for sulfonylureas (SFUs), glinides, thiazolidinediones (TZDs), and α-glucosidase inhibitors.[325]

Source: American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020*;43(suppl 1):S98–S110. doi:10.2337/dc20-S009

Table 53-26
Antidiabetic Pharmacokinetic Data

Drug (Brand Name), Available Tablet Strengths (mg)	Typical Dosing Regimen (mg)	Usual Minimum and Maximum TDD/How Divided	Mean Half-Life	Approximate Duration of Activity	Bioavailability, Metabolism, and Excretion	Comments
α-Glucosidase Inhibitors						
Acarbose (Precose®) 25, 50, 100 mg	25–100 mg with first bite of each meal Begin with 25 mg; ↑ by 25 mg/meal every 4–8 weeks	Minimum: 25 mg tid Maximum dose is 50 mg tid if ≤60 kg; 100 mg tid if >60 kg	2 hours	Affects absorption of complex carbohydrates in a single meal	*F* = 0.5%–1.7%; extensively metabolized by GI amylases to inactive products; 50% excreted unchanged in the feces	Titrate doses slowly to avoid GI effects.
Miglitol (Glyset®) 25, 50, 100 mg	25–100 mg with first bite of each meal Begin with 25 mg; ↑ by 25 mg/meal every 4–8 weeks	Minimum: 25 mg tid Maximum: 100 mg tid	2 hours	Affects absorption of complex carbohydrates in a single meal	Dose of 25 mg is completely absorbed; dose of 100 mg 50%–70% absorbed; elimination by renal excretion as unchanged drug	
Biguanides						
Metformin (-Glucophage®) 500, 850, 1000 mg; 500 mg/mL liquid	Begin with 500 mg daily or bid; ↑ by 500 mg daily every 1–2 weeks	0.5–2.5 g bid or tid	Plasma, 6.2 hours Whole blood, 17.6 hours	6–12 hours	*F* = 50%–60%; excreted unchanged in urine	Take with food. Avoid in patients with renal dysfunction or those who could be predisposed to lactic acidosis (eg, alcoholism, severe HF, severe respiratory disorders, liver failure).
Metformin extended-release (Glucophage® XR) 500, 750, 1000 mg	500–1000 mg daily with evening meal; ↑ by 500 mg every 1–2 weeks	1500–2000 mg daily	As for metformin, but active drug is released slowly.	24 hours	As for metformin	As for metformin
Nonsulfonylurea Insulin Secretagogues (Glinides)						
Repaglinide (Prandin®) 0.5, 1, 2 mg	If A_{1c} is <8% or if this is first drug, begin with 0.5 mg with each meal. For others, begin with 1–2 mg/meal.	0.5–4 mg with each meal (16 mg/day) tid or qid	1 hour	C_{max} is at 1 hour; duration is ~2–3 hours	*F* = 56%; 92% metabolized to inactive products by the liver; 8% excreted as metabolites unchanged in the urine	Take only with meals. Skip dose if meal is skipped. Maximum dose per meal is 4 mg.
Nateglinide (Starlix®) 60, 120 mg	120 mg tid 1–30 minutes before meals; 60 mg tid for patients with near-normal A_{1c} at initiation	60 or 120 mg tid	1.5 hours	Onset, 20 minutes; peak, 1 hour; duration, 2–4 hours	*F* = 73%; metabolized to inactive products (predominantly) that are excreted in the urine (83%) and feces (10%)	Skip dose if meal is skipped.

First-Generation Sulfonylureas						
Acetohexamide (Dymelor®) 250, 500 mg	250 or 500 mg daily; ↑ by 250 mg daily every 1–2 weeks	0. 25–1.5 g daily or bid	5 hours (active metabolite)	12–18 hours	Activity of metabolite greater than that of parent drug. Metabolite excreted, in part, by kidney	Caution in elderly and patients with renal disease; Significant uricosuric effects
Chlorpropamide (Diabinese®) 100, 250 mg	100 or 250 mg daily; ↑ by 100 or 250 mg every 1–2 weeks	0.1–0.5 g daily	≥35 hours	24–72 hours	Inactive and weakly active metabolites; 20% excreted unchanged; varies widely	Caution in elderly and patients with renal impairment. Highest frequency of side effects relative to other sulfonylureas
Tolazamide (Tolinase®) 100, 250, 500 mg	100–250 mg daily; ↑ by 100 or 250 mg every 1–2 weeks	0.2–1 g daily or bid	7 hours (4–25)	12–24 hours	Some metabolites with moderate activity excreted via kidney	Active metabolites may accumulate in renal failure.
Tolbutamide (Orinase®) 250, 500 mg	250 mg bid before meals; ↑ by 250 mg daily every 1–2 weeks	0.5–3 g bid or tid	7 hours	6–12 hours	Metabolized to compounds with negligible activity	No special precautions. Shortest-acting sulfonylurea
Second-Generation Sulfonylureas						
Glimepiride (Amaryl®) 1, 2, 4 mg	1–2 mg daily initially; usual maintenance dose is 1–4 mg.	1–8 mg daily	9 hours	24 hours	*F* = 100% completely metabolized by liver. Principal metabolite is slightly active (30% of parent compound). Excreted by the urine (60%) and feces (40%)	Probably safe in patients with renal failure, but low initial doses recommended for older patients and those with renal insufficiency. Incidence of hypoglycemia may be lower than with other long-acting sulfonylureas.
Glipizide (Glucotrol®) 5, 10 mg	2.5 mg daily in the elderly, 5 mg daily in others; ↑ by 2.5 or 5 mg every 1–2 weeks	2.5–40 mg daily or bid[a]	2–4 hours	12–24 hours	Metabolized to inactive compounds	No special precautions. Daily dose >15 mg should be divided. Dose 30 minutes before meals.
Glipizide extended-release (Glucotrol® XL) 5 mg	5 mg daily; ↑ by 5 mg every 1–2 weeks	5–20 mg daily	4–13 hours	24 hours	Same as glipizide	Use with caution in patients with preexisting GI narrowing owing to possible obstruction.
Glyburide (Diabeta®, Micronase®) 1.25, 2.5, 5 mg	1.25 mg daily in the elderly, 2.5 mg daily in others; ↑ by 1.25 or 2.5 mg every 1–2 weeks	1.25–20 mg daily or bid	4–13 hours	12–24 hours	Metabolized to inactive or weakly inactive compounds; 50% excreted in urine and 50% in feces.	Caution in elderly patients with renal failure and others predisposed to hypoglycemia. Daily doses >10 mg should be divided.

Micronized glyburide (Glynase® PresTab®) 1.5, 3 mg	1.5 mg daily; ↑ by 1.5 mg every 1–2 weeks	1.0–12 mg daily	4 hours	24 hours	Metabolized to inactive or weakly inactive compounds; 50% excreted in urine and 50% in feces.	Daily doses >6 mg should be divided. ↑ Bioavailability relative to original formulation. Resulted in reduced dose
Thiazolidinediones						
Rosiglitazone (Avandia™) 2, 4, 8 mg	4 mg daily; ↑ to 8 mg daily (or 4 mg bid)	4–8 mg daily in single or divided doses	3–4 hours	Onset and duration poorly correlated with half-life because of mechanism of action. Onset at 3 weeks; max at ≥4 weeks Offset likely to be similar	F = 99%; extensively metabolized in liver into inactive metabolites; excreted two-thirds in urine and one-third in feces.	Food has no effect on absorption. Bid dosing may have greater A_{1c} lowering effect. No dose adjustments required in renal failure. Avoid in patients with liver disease and heart failure.
Pioglitazone (Actos®) 15, 30, 45 mg	15–30 mg daily; ↑ to 45 mg daily. If used with insulin, ↓ insulin dose by 10%–25% once FPG <120 mg/dL	15–45 mg daily	3–7 hours (16–24 hours for all metabolites)	Same as previous	Extensively metabolized in liver; 15%–30% excreted in urine, remainder eliminated in the feces	Food delays absorption, but is not clinically significant. No dose adjustments required in renal disease. Avoid in patients with liver disease and heart failure.
Glucagon-Like Peptide-1 Receptor Agonists/Incretin Mimetics						
Exenatide (Byetta®)	5 μg SC bid; ↑ to 10 μg SC bid after 1 month	5–10 μg bid	2.4 hours	C_{max} is at 2.1 hours; duration 10 hours	Glomerular filtration	Take in the 60 minutes before morning and evening meal. Nausea usually subsides with time.
Exenatide ER (Bydureon®)	2 mg SC once weekly	2 mg once weekly	10 weeks	Initial C_{max} is at 2 weeks, second peak is at 6–7 weeks	Glomerular filtration	Take daily without regard to meals. Nausea usually subsides with time.
Liraglutide (Victoza®)	0.6 mg daily for 1 week; ↑ to 1.2 mg daily	0.6–1.8 mg daily	13 hours	24 hours; C_{max} is 8–12 hours after dosing	Metabolized as other large proteins	Take daily without regard to meals. Nausea usually subsides with time.
Lixisenatide	10 μg daily for 2 weeks; ↑ to 20 mg once daily on day 15	10–20 μg daily	~3 hours	C_{max} is 1–3.5 hours after dosing.	Eliminated through glomerular filtration and proteolytic degradation	Take once daily 1 hour before the first meal of the day.
Dulaglutide (Trulicity®)	0.75 mg SC once weekly; can ↑ to 1.5 mg once weekly	0.75–1.5 mg weekly	Approximately 5 days	C_{max} is at 48 hours.	Degraded into amino acids by protein catabolism	Take daily without regard to meals. Nausea usually subsides with time.

Semaglutide (Ozempic®)	0.25 mg weekly for 1 week; ↑ to 0.5 mg daily, can ↑ to 1.0 mg	0.25–1.0 mg weekly	~7 days	C_{max} ~1–3 days	*F* = 87% Metabolism following proteolytic cleavage of peptide backbone and β-oxidation of fatty acid side chain ~3% excreted unchanged in urine	Administer weekly without regard to meals.
Semaglutide (Rybelsus®)	3 mg daily for 30 days; ↑ to 7 mg daily, can ↑ to 14 mg	3–14 mg daily	Approximately 7 days	~1 hour	*F* = 0.4%–1% Metabolism following proteolytic cleavage of peptide backbone and β-oxidation of fatty acid side chain ~3% excreted unchanged in urine.	Take 30 minutes before any food, beverage, or oral medication with plain water only (no more than 4 oz).
DPP-4 Inhibitors						
Sitagliptin (Januvia®)	100 mg daily CrCl ≥30 to <50 mL/minute: 50 mg daily CrCl <30 mL/minute: 25 mg daily	100 mg daily	12.4 hours	24 hours	*F* = 87%; 79% excreted unchanged in urine.	Requires dose adjustment in renal insufficiency
Saxagliptin (Onglyza®)	5 mg daily CrCl ≤50 mL/minute: 2.5 mg daily	2.5–5 mg daily	2.5 hours (3.1 hours for active metabolite)	24 hours	Metabolized by CYP 3A4/5. Excreted by renal and hepatic pathways	Active metabolite is half as potent. Reduce dose to 2.5 mg with strong CYP 3A4/5 inhibitors.
Linagliptin (Tradjenta®)	5 mg daily	5 mg daily	12 hours	24 hours	*F* = 30%; 90% excreted unchanged (80% enterohepatic system, 5% urine). Small fraction metabolized to inactive metabolite.	No dose adjustment needed in liver or renal disease.
Alogliptin (Nesina®)	25 mg daily CrCl 30–59 mL/minute: 12.5 mg daily CrCl <30 mL/minute: 6.25 mg daily	25 mg daily	21 hours	24 hours	*F* = 100%, 76% excreted unchanged and 13% eliminated in feces. Small fraction metabolized to inactive metabolite	Requires dose adjustment in renal insufficiency.
Amylin Mimetics						
Pramlintide (Symlin®)	Type 1 DM: 15 μg SC before major meals; ↑ by 15-μg increments after minimum of 3 days.	Type 1: 15–60 μg before major meals	48 minutes	C_{max} is 20 minutes	*F* = 30%–40%; metabolized by kidneys	Reduce mealtime insulin dose by 50%. Titrate dose if no significant nausea.

	Type 2 DM: 60 µg SC before major meals; ↑ to 120 µg after 3–7 days.	Type 2: 60 or 120 µg before major meals				
Sodium–Glucose Transporter 2 Inhibitors						
Canagliflozin (Invokana®)	100 mg by mouth before first meal	May increase to 300 mg daily	10.6 hours		*F* = ~65% *Metabolism:* Primarily UGT1A9 and UGT2B4. ~7% *Metabolism* through CYP3A4	
Dapagliflozin (Farxiga®)	5 mg by mouth daily before first meal	May increase to 10 mg daily	12.9 hours		*F* = 78% *Metabolism:* Primarily (UGT) isoenzyme 1A9	
Empagliflozin (Jardiance®)	10 mg by mouth daily before first meal	May increase to 25 mg daily	12.4 hours		*Metabolism:* Primarily through glucuronidation by UGT2B7, UGT1A3, UGT1A8, UGT1A9	
Ertugliflozin (Steglatro™)	5 mg by mouth every morning with or without food	May increase to 15 mg	16.6 hours		*Metabolism*: O-glucuronidation by UGT1A9, UGT 2B7	
Bile Acid Sequestrants						
Colesevelam (Welchol®)	6 tablets once daily or 3 tablets bid (625-mg tablets)	3.75 g	N/A	N/A	Drug is not absorbed systemically and not metabolized.	Take with food and liquid. Do not use if history of bowel obstruction, TG >500 mg/dL, or history of pancreatitis from ↑ TG.
Enhancers of Dopaminergic Tone						
Bromocriptine (Cycloset®), 0.8 mg	1.6–4.8 mg once daily in the morning; Begin with 0.8 mg daily and increase by 1 tablet each week until max tolerated dose	1.6–4.8 mg daily	6 hours		*F* = 65%–95% Metabolized extensively by CYP3A4; 93% undergoes first-pass metabolism Excreted primarily in bile; 2%–6% in urine	Take with food to reduce GI side effects. Food increases AUC. Highly protein bound.

A_{1c}, glycated hemoglobin; bid, two times a day; C_{max}, maximal concentration; CrCl, creatinine clearance; CYP, cytochrome P-450; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; F, bioavailability; FPG, fasting plasma glucose; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HF, heart failure; N/A, not available; qid, four times a day; SC, subcutaneously; TG, triglycerides; tid, three times a day.

Biguanides

Metformin belongs to the biguanide class of oral antidiabetic agents. It has been available in the United States since 1995 and became

generically available in 2002; Currently, both the immediate-release and the extended-release (ER) formulations are available generically.[26,189] Metformin is recommended by both the AACE and ADA guidelines as the first-line agent for patients with prediabetes or type 2 diabetes.

MECHANISM OF ACTION

The biguanides are described more accurately as antihyperglycemic agents. Although they lower BG concentrations in people with type 2 diabetes, they do not cause hypoglycemia in nondiabetic individuals or individuals with diabetes when used as monotherapy. Partly because of this lack of hypoglycemia, metformin is recommended by the ADA to reduce the risk of developing diabetes in patients at high risk (IGT and IFG) because of its strong evidence base and long-term safety. Metformin is considered first-line therapy for diabetes because it has been considered safe, cost-effective, and it was the first agent with outcome data showing a reduction in all-cause mortality and vascular complications independent of glycemic control.[189] Metformin primarily lowers FPG concentrations by decreasing hepatic gluconeogenesis, increasing insulin-stimulated glucose uptake by skeletal muscle and adipose tissue by increasing insulin sensitivity, and also decreasing intestinal absorption of glucose.[190]

Metformin modestly lowers total cholesterol and triglycerides and may maintain or improve HDL-C levels.[190] The observed effects on lipid metabolism as well as others on clotting factors, platelet function, and vascular function may impart some of metformin's favorable effects on CVD and outcomes (see Case 53-11, Question 3). A key advantage with metformin is that weight loss rather than weight gain is more likely to occur with its use (mean weight loss of 1.10–8.38 pounds [0.5–3.8 kg] can occur in adults receiving metformin immediate-release tablets as monotherapy and negligible weight loss occurs with ER tablets).[190]

PHARMACOKINETICS

Approximately 50% to 60% of metformin is absorbed from the small intestine, and peak plasma concentrations are achieved at ~2.5 hours.[190] Approximately 10% of an oral dose is excreted in the feces, and about 90% of a dose is excreted through an active tubular process in the kidneys. The rate and extent of absorption are both decreased by food. Metformin has a plasma half-life of 6.2 hours in patients with normal renal function and a whole-blood half-life of 17.6 hours.[190] It is not bound to plasma proteins.

ADVERSE EFFECTS

Gastrointestinal effects

Transient side effects include diarrhea and other GI disturbances such as nausea, abdominal discomfort, metallic taste, flatulence, and anorexia.[191] Relative to placebo, diarrhea is the most common GI complaint with immediate-release tablets (53.2% metformin vs 11.7% placebo-treated patients) which decreases to ~9.6% in patients taking ER tablets. Symptoms can be further minimized by taking metformin with food and slowly titrating the dose. To enhance adherence to therapy, patients should be informed of the possibility of GI side effects that will likely subside with continued use and instructed to discuss any suspected side effects with their provider before discontinuing therapy (see Case 53-11, Question 4). Patients should not crush or chew metformin tablets and should be counseled regarding the appearance of a ghost tablet that may be noticeable in the stool when taking the ER tablets. Metformin is also available as a liquid formulation for patients who have difficulty swallowing large tablets.[192]

Lactic acidosis

Much of the perceived risk of lactic acidosis secondary to metformin use is based on historic data for phenformin, a biguanide that was withdrawn from the market in 1977.[193] The risk of lactic acidosis secondary to metformin is 10 to 20 times lower than that with phenformin. Unlike phenformin, metformin is not metabolized, does not inhibit peripheral glucose oxidation, and does not enhance

peripheral lactate production.[193,194] However, it may decrease the conversion of lactate to glucose (decreased gluconeogenesis) and increase lactate production in the gut and liver.[186] Metformin has rarely been associated with lactic acidosis. The few patients in whom this event has been reported had renal, liver, or cardiorespiratory contraindications to the use of biguanides. A Cochrane review including 347 studies compared the risk of lactic acidosis among patients taking metformin, placebo, or other nonbiguanide therapies. The review found no difference between groups in either lactate levels or in the development of lactic acidosis.[190] Despite the rarity of lactic acidosis with metformin therapy, patients should be warned to bring the following symptoms of lactic acidosis to the attention of their physician: weakness; malaise; myalgias; abdominal distress; and heavy, labored breathing.

CONTRAINDICATIONS AND PRECAUTIONS

Patients with renal impairment, liver disease, or other states predisposing them to hypoxia, acute or chronic metabolic acidosis, DKA, or a history of lactic acidosis should be excluded from therapy.[195] Metformin can accumulate in patients whose renal function is impaired, thereby increasing their risk for lactic acidosis. For this reason, metformin carries a black box warning. The FDA changed the metformin label restrictions from contraindicated at SCr level >1.5 mg/dL in males and >1.4 mg/dL in females to contraindicated at an estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2, and not recommended to initiate metformin at eGFR <45 mL/minute/1.73 m^2 (see Dosage and Clinical Use; see Case 53-16, Question 2, for a detailed discussion).[190] Because even a temporary reduction in renal function could cause lactic acidosis in patients taking metformin, the manufacturer recommends withholding it after some radiologic procedures (see the section on Drug Interactions). Other predisposing factors for lactic acidosis include the following: excessive alcohol ingestion, dehydration, surgery, decompensated congestive HF, hepatic failure, shock, or sepsis. Because aging is associated with reduced renal function,

metformin should be titrated to the minimal effective dose, and renal function should be monitored regularly. An eGFR or creatinine clearance (CrCl) should be measured in patients older than age 80 years to ensure adequate renal function before metformin use because these patients are more susceptible to experiencing lactic acidosis.[196]

DRUG INTERACTIONS

- Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while taking metformin. Metformin should be avoided in patients who are alcoholics.
- Vitamin B_{12} absorption may be decreased in patients taking metformin. Each 1 g/day increment dose of metformin significantly increases the odds of vitamin B_{12} deficiency, as well as taking metformin therapy for more than 3 years.
- Dofetilide should not be administered in patients taking metformin because of the competition for common renal tubular transport systems, which may result in an increase in the plasma concentrations of either drug.
- Topiramate should be avoided in patients on metformin because topiramate may increase the risk of developing metabolic acidosis via inhibition of carbonic anhydrase.
- Parenteral contrast studies (eg, pyelography or angiography) that use iodinated materials may pose—although minimal—a risk for acute kidney injury and lactic acidosis when combined with metformin. It is recommended that metformin be stopped at the time of or before administration of iodinated IV contrast only in patients with an eGFR <60 mL/minute/1.73 m^2, or in patients with a history of liver disease, alcoholism, or HF. After 48 hours, eGFR should be reevaluated, and metformin should be restarted if renal function is stable.[189]

EFFICACY

As monotherapy, metformin can be expected to reduce the A_{1c} by 1.3% to 2.0% and the FPG by 50 to 70 mg/dL[197] Research suggests that certain genetic variations may impact patient response to metformin therapy. Patients exhibiting reduced function polymorphisms of organic cation transporter (OCT) 1, which is involved in the hepatic uptake of metformin, may be less responsive to metformin therapy.[26,41]

DOSAGE AND CLINICAL USE

Metformin is the first line of therapy for type 2 diabetes.[64] The ADA recommends its initiation as monotherapy in combination with lifestyle interventions (eg, MNT, physical activity, weight loss education, and lifestyle education) on diagnosis. To minimize GI side effects, metformin should be initiated at 500 mg twice a day or 850 mg once a day, to be taken with food, followed by weekly increases in 500-mg increments or 850-mg increases every 2 weeks (see Case 53-11, Question 4). Metformin is dosed bid to three times daily (tid; 500–1000 mg/dose; maximal dose 2550 mg/day or 850 mg PO tid), unless an ER preparation is prescribed. Using the ER formulation as initial therapy may decrease GI side effects. It should still be initiated at 500 mg daily and titrated similarly. It can, however, be dosed once a day, usually with the evening meal. Clinicians should obtain an SCr/eGFR (using the Modification of Diet in Renal Disease equation) and hepatic function tests at baseline and then annually. The AACE recommends that metformin dose reduction should be considered in patients with an eGFR <45 mL/minute/1.73 m^2, and the TDD should not exceed 1000 mg/day. Renal function should be closely monitored in these patients every 3 months. Metformin should be discontinued in patients with an eGFR <30 mL/minute/1.73 m^2 or in patients with additional risk factors such as hypotension, hypoxia, sepsis, or an increased risk of acute kidney injury (eg, use of radiocontrast dye in patients with an eGFR <60 mL/minute/1.73 m^2.[26] Metformin should not be used in patients older than age 80 years unless a CrCl/eGFR demonstrates normal renal function.[198,199] Patients are good candidates for treatment if the CrCl is >60 mL/minute (or eGFR >60

mL/minute/1.73 m^2). For patients unable to achieve goals of therapy with metformin alone within 3 months of initiating therapy, addition of insulin or another agent should be considered (also see Case 53-13).

Nonsulfonylurea Insulin Secretagogues (Glinides)

Repaglinide (Prandin®) and nateglinide (Starlix®) are nonsulfonylurea insulin secretagogues (ie, they stimulate insulin secretion). They belong to a class of agents referred to as meglitinides and are often called *glinides*. Repaglinide was approved by the FDA in December 1997, and nateglinide was approved in December 2000 (Table 53-25).

MECHANISM OF ACTION

These agents close the adenosine triphosphate (ATP)-sensitive potassium channels in the β cell, which leads to cell membrane depolarization, an influx of calcium, and secretion of insulin. The release of insulin depends on the glucose level and decreases at low concentrations of glucose.[198] Unlike the sulfonylureas, they have a rapid onset and shorter duration of action, so they are given meals to enhance postprandial glucose utilization.

PHARMACOKINETICS

Repaglinide has a bioavailability of 56% and is rapidly absorbed and excreted.[199] Its maximal serum concentration (C_{max}) occurs at ~1 hour, and its half-life is 1 hour. Repaglinide is highly (>98%) protein bound (volume of distribution, 31 L). It is completely metabolized (via cytochrome P-450 [CYP] 3A4 and 2C8) by the liver to inactive products, with 90% excreted in the feces and 8% excreted in urine. Nateglinide has a bioavailability of 73%.[198,199] It is rapidly absorbed, with a C_{max} occurring within 1 hour of dosing and a half-life of 1.5 hours. Nateglinide is metabolized (CYP2C9, 70%; CYP3A4, 30%) to

less potent compounds, which are 75% excreted in the urine and 10% in the feces. Sixteen percent is excreted unchanged in the urine. It is highly (98%) protein bound, primarily to albumin, and, to a lesser extent, to α_1-acid glycoprotein.

ADVERSE EFFECTS

Mild hypoglycemia may occur, particularly if patients delay or forget to eat after the dose. A weight gain of 1.98 to 6.61 pounds (0.9–3 kg) compared with baseline has been observed.[200] Rare side effects include elevated hepatic enzymes and hypersensitivity reactions. There has been at least one case report of repaglinide-induced hepatic toxicity.[198]

CONTRAINDICATIONS AND PRECAUTIONS

Because a functioning pancreas is required, these agents should not be used in people with type 1 diabetes. They should be used with caution in patients with liver dysfunction. They are contraindicated for use in patients with DKA. Repaglinide clearance is reduced in patients with severe renal insufficiency, but may still be used safely at a reduced dose.[199] The clearance of nateglinide is not affected in patients with moderate-to-severe renal insufficiency.[201]

DRUG INTERACTIONS

Clinically relevant drug interactions include those that occur when these drugs are taken in combination with other glucose-lowering agents or drugs known to induce or inhibit their metabolism.[198] Therefore, BG levels should be closely monitored when either drug is taken in combination with other agents known to lower BG or affect their metabolism. Repaglinide is metabolized by CYP2C8 and 3A4.[199] Studies have shown that repaglinide has no pharmacokinetic effects on digoxin or warfarin. Gemfibrozil should be avoided in combination with repaglinide owing to the risk of hypoglycemia. The combination of gemfibrozil and itraconazole synergistically inhibits repaglinide metabolism and should be avoided. Concomitant use of clopidogrel may result in increased serum concentrations of

repaglinide; therefore, dose reduction of repaglinide may be required. Cyclosporine inhibits the metabolism of repaglinide, causing increased serum concentrations of repaglinide; therefore, a dose reduction may be required. Nateglinide is metabolized largely by CYP2C9 (70%) and to a lesser extent by 3A4 (30%).[201] When evaluated in clinical studies, there were no clinically relevant interactions with nateglinide and glyburide, metformin, digoxin, diclofenac, or warfarin. Concomitant use of oral systemic azole antifungals should be used cautiously because of the potential for increased hypoglycemic effects. Fibric acid derivatives including fenofibrate, clofibrate, and gemfibrozil may increase the effects of nateglinide. Concomitant use of either repaglinide or nateglinide with rifampin may lower their efficacy.[202]

EFFICACY

The efficacy of repaglinide is comparable to that of metformin and the sulfonylureas.[198] When used as monotherapy, the mean decrease in FPG, postprandial glucose, and the A_{1c} values were 61 mg/dL, 104 mg/dL, and 1.7%, respectively, compared with placebo (−31.0 mg/dL, −47.6 mg/dL, and −0.6% compared with baseline).[199] Nateglinide as monotherapy results in a mean decrease in FPG and A_{1c} of 13.6 mg/dL and 0.7%, respectively, compared with placebo (−4.5 mg/dL and −0.5% compared with baseline).[198,199] In comparison with metformin monotherapy, both drugs produce a similar or slightly smaller reduction in A_{1c}.

DOSAGE AND CLINICAL USE

Repaglinide and nateglinide are approved to treat people with type 2 diabetes as monotherapy or in combination with metformin or a TZD.[198,199] Because they have the same mechanism of action as do the sulfonylureas, combining these agents does not produce any additional benefit. The agents are usually added to therapy for patients with postprandial hyperglycemia, particularly nateglinide. When repaglinide is used as the initial treatment in patients who are naive to oral antidiabetic therapy or in patients with A_{1c} values <8%,

the recommended starting dose is 0.5 mg 15 to 30 minutes before eating up to four times a day. When used in patients who have failed sulfonylureas or in those with A_{1c} values >8%, the initial dose is 1 to 2 mg with each meal up to four times a day. Doses can be titrated weekly at a rate of 1 mg/meal to a maximum of 4 mg/dose or 16 mg/day. Repaglinide should be initiated at a 0.5-mg dose in patients with severe renal dysfunction and should be titrated cautiously in patients with liver dysfunction. The recommended starting dose of nateglinide is 120 mg tid 0 to 30 minutes before meals. For patients close to their A_{1c} goal, a dose of 60 mg tid may be used. Doses should be omitted if a meal is skipped and added if an extra meal is ingested (repaglinide only). There are no dosage adjustments required for nateglinide in patients with renal or hepatic insufficiency.[73,203] Owing to the frequent dosing, risk of hypoglycemia, and weight gain, these medications are not routinely recommended by the ADA or AACE guidelines as first-line management.

Sulfonylureas

Until metformin and other antidiabetic agents became available in the United States, sulfonylureas were the first-line pharmacologic treatment for people with type 2 diabetes who had failed diet and exercise therapy. Six sulfonylureas are available in the United States. The three first-generation sulfonylureas (chlorpropamide, tolazamide, and tolbutamide) are considered equally effective despite differences in their pharmacokinetic properties and adverse effect profiles (see the following discussion and Tables 53-25 and 53-26); however, owing to the increased risk of hypoglycemia, these agents have fallen out of favor and are not discussed in detail.

Glipizide and glyburide, two second-generation sulfonylureas, were first introduced into the United States in May 1984. Glimepiride was approved for use in 1995. Despite being more potent than the first-generation sulfonylureas, these second-generation sulfonylureas are clinically equivalent to the first-generation sulfonylureas, however, they have a decreased risk of adverse

effects. Their duration of activity allows for once- or twice-daily dosing.

MECHANISM OF ACTION

Sulfonylureas stimulate the release of insulin from pancreatic β cells and enhance β-cell sensitivity to glucose. A specific sulfonylurea receptor closely linked to the ATP-sensitive potassium ion channel exists on the β cell. Sulfonylureas inhibit this potassium ion channel, thus blocking the efflux of potassium and lowering the membrane potential to cause depolarization. The voltage-dependent calcium channels then open, increasing intracellular calcium concentration. The increased intracellular concentration of calcium ultimately stimulates preformed insulin secretion. In addition, sulfonylureas can normalize hepatic glucose production and enhance peripheral glucose disposal.[204]

PHARMACOKINETICS

The duration of hypoglycemic activity is related to the half-life of these compounds only in very general terms and may correlate poorly in some cases.[205–207] All sulfonylureas are highly protein bound (90%–100%), mainly to albumin. Binding characteristics, however, vary among individual sulfonylureas. Food does not impair the extent of drug absorption but may delay the time to peak levels of some agents. The relationship between sulfonylurea doses and their BG-lowering effect remains unclear. Studies of glyburide and glipizide suggest that these agents may operate within a narrow range of plasma concentrations that may be achieved with low (10 mg/day) doses.[207] The maximal recommended daily doses of 40 mg for glipizide and 20 mg for glyburide may therefore not be more effective and may decrease β-cell function.[204]

Glipizide is an intermediate-acting second-generation agent with a half-life of 2 to 4 hours, but with a duration of action of 12 to 24 hours. Patients receiving <20 mg/day may require only once-daily dosing. Food delays its rate of absorption, but not its bioavailability. Glipizide should be taken 30 minutes before meals. The onset of

action occurs in 90 minutes, and the maximum decrease in serum glucose occurs within 2 to 3 hours. Glipizide is extensively metabolized by the liver to inactive products that are eliminated primarily by the kidney.[208] An ER formulation of glipizide also is available.

Glyburide is a longer-acting second-generation agent similar to glipizide. The half-life is ~1.5 to 4 hours after single-dose studies and up to 13.7 hours when chronically administered.[209] Nevertheless, as with glipizide, the duration of action can last for up to 24 hours in many patients, allowing for once-daily dosing with small-to-intermediate doses (<15 mg). Food does not delay the rate or extent of absorption. The onset of action is 2 hours, and the maximum decrease in serum glucose occurs within 3 to 4 hours. Glyburide is metabolized completely by the liver to two weakly active metabolites, half of which are excreted in the urine and feces. A micronized formulation is available (eg, Glynase® PresTab®), but it is not bioequivalent to the conventionally formulated tablets. Thus, patients switched between the conventional form and the micronized product must be carefully monitored and the dose titrated again.

Glimepiride is a long-acting second-generation sulfonylurea. Its half-life is 9 hours and its duration of action is 24 hours, allowing for once-daily dosing.[210] The administration of glimepiride with food slightly decreases the area under the plasma concentration–time curve (AUC) and slightly increases the time to peak concentration. Its peak effect on plasma glucose concentrations is observed 2 to 3 hours after each dose. Glimepiride is completely metabolized by the liver, and its principal metabolite has 30% of the activity of the parent drug. Metabolites are excreted in feces and urine. Interestingly, research suggests that the sulfonylureas may close ATP-sensitive potassium channels in cardiac tissue, similar to their action at the β cell. In the heart, this effect could prevent vasodilation during an ischemic episode (ie, ischemic preconditioning).[89]

ADVERSE EFFECTS

The primary side effects of the sulfonylureas are hypoglycemia (particularly for those that are long acting, see Case 53-16, Question 2, and Case 53-18, Question 6) and weight gain (~4.41 pounds [2 kg]).[211] Other adverse effects attributed to the sulfonylureas generally are so infrequent and mild that <2% of patients discontinue these agents because of them. In general, the type, incidence, and severity of reported side effects are similar for all the sulfonylureas. An important exception is chlorpropamide, which has several unique adverse effects (see following discussion). Adverse reactions to the sulfonylureas include GI symptoms (nausea, fullness, and bloating that can be relieved if taken with meals), rare blood dyscrasias, allergic dermatologic reactions and photosensitivity, hepatotoxicity, and hyponatremia (also see Case 53-16).[204]

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications and precautions to the use of sulfonylureas include the following:

1. Type 1 diabetes
2. Pregnancy or breast-feeding, because these agents (except glyburide) can cross the placental barrier and can be excreted into breast milk
3. Documented hypersensitivity to sulfonylureas
4. Severe hepatic or renal dysfunction
5. Severe, acute intercurrent illness (eg, infection, MI), surgery, or other stress that can unduly affect BG control, in which case insulin therapy should be used
6. Glucose-6-phosphate-dehydrogenase (G6PD) deficiency: Patients with this deficiency may be at risk for hemolytic anemia if they take chlorpropamide; consider using a nonsulfonylurea medication as an alternative.

DRUG INTERACTIONS

Drug interactions with sulfonylureas have a pharmacodynamic or pharmacokinetic basis. Pharmacodynamic interactions are

discussed later in this chapter in sections addressing Drug-Induced Hypoglycemia and Drug-Induced Hyperglycemia. Most of the reported pharmacokinetic drug interactions with the sulfonylureas involve chlorpropamide and tolbutamide. Because most of the clinically significant interactions occur with drugs that alter liver metabolism or urinary excretion, possible interactions with all of the sulfonylureas must be anticipated, even though the outcomes may be quite different. Glipizide and glyburide also differ from the first-generation agents in that they are highly bound to albumin at nonionic rather than at ionic sites.[201] On this basis, these agents are unlikely to interact with other highly protein-bound drugs, such as phenylbutazone, salicylates, or certain sulfonamide antibiotics that have been reported to enhance the effects of the first-generation sulfonylureas. These highly protein-bound drugs, however, seem to interact with the sulfonylureas by altering their hepatic metabolism as well. Therefore, glipizide and glyburide should be used cautiously with drugs reported to interact with first-generation sulfonylureas. Sulfonylureas are CYP2C9 substrates; therefore, coadministration with a medication that is an inhibitor or inducer of CYP2C9 will increase or decrease levels of sulfonylurea medications, respectively.[212]

EFFICACY

As with metformin, the sulfonylureas decrease the A_{1c} by 1.5% to 1.7% and the FPG by 50% to 70%. With time and increased duration of type 2 diabetes, the pancreas may respond less to a sulfonylurea. Whether sulfonylureas actually contribute to β-cell dysfunction and decline remains to be clearly determined.[62]

DOSAGE AND CLINICAL USE

The sulfonylureas are effective, inexpensive, and easy to titrate. Sulfonylureas may be used as add-on therapy to patients unable to achieve BG goals on metformin monotherapy, especially when cost may be a burden to the patient.[90] In the United States, second-generation sulfonylureas are preferred owing to their more tolerable

adverse event profile. Similar to the other antidiabetic agents discussed, sulfonylureas may also be considered as monotherapy in patients with contraindications to metformin. The doses of the sulfonylureas are displayed in **Table 53-26**. As a general rule, patients should be started with low doses and titrated upward every 1 to 2 weeks until the desired goal is achieved. Exceeding maximal doses will most likely potentiate increased adverse drug reaction (ADR) without an increase in efficacy (see Case 53-18, Questions 5 and 6).

Thiazolidinediones

MECHANISM OF ACTION

The two available TZDs in the United States, rosiglitazone and pioglitazone, are often referred to as *insulin sensitizers*. The proposed mechanism of action for TZDs involves the medication binding to and activating a nuclear receptor (peroxisome proliferator-activated receptor-γ [PPAR-γ]), which is expressed in many insulin-sensitive tissues, including adipose, skeletal muscle, and liver tissue.[213] PPAR-γ regulates transcription of the genes that influence glucose and lipid metabolism. PPAR-γ stimulation increases the transcription of GLUT-4, a glucose transporter that stimulates glucose uptake[213] and insulin sensitivity.

Pioglitazone also activates PPAR-α, which inhibits the transcription of tumor necrosis factor-α-induced vascular cell adhesion molecule (VCAM-1).[214] This dual effect results in increased HDL and lowered triglycerides. PPAR-α stimulation may also have anti-inflammatory effects.[90,203]

TZDs either directly or indirectly sensitize adipose tissue to insulin action.[90,203] The effects may include stimulating apoptosis of large adipocytes, increasing the number of small adipose cells, and promoting fatty acid uptake and storage in adipose tissue. The subsequent reduction in free circulating fatty acids may spare other insulin-sensitive tissues (eg, liver, skeletal muscle, and β cells) from the effects of lipotoxicity. TZDs also lower expression of tumor

necrosis factor-α, a cytokine produced by adipose tissue that may contribute to insulin resistance and fatty acid release.[203] Other adipokines are likely involved, including adiponectin, resistin, and leptin.[90,190] TZD interaction with adipocytes may be their primary mechanism of action in sensitizing other tissues to insulin action. As with metformin, TZDs have been shown to directly stimulate the 5' adenosine monophosphate-activated protein kinase (AMPK) pathway in liver and adipose tissue, resulting in a lowering of glucose and free fatty acids.[90,203]

Other favorable effects of TZDs that may be beneficial in patients with type 2 diabetes and metabolic syndrome include inhibition of vascular smooth muscle cell proliferation, improved endothelial function, decreased microalbumin excretion, and enhanced fibrinolysis.[215] Despite these improved surrogate markers, the data regarding TZDs and vascular risk are mixed and controversial. In 2009, the FDA added language to the label for rosiglitazone indicating an increased risk of angina and MI. The FDA and GlaxoSmithKline instituted a risk evaluation and management strategy (REMS) to restrict the distribution and prescribing of rosiglitazone. The REMS status was however changed in 2014 to allow for the prescribing and filling of prescriptions of rosiglitazone.

PHARMACOKINETICS

Rosiglitazone is completely absorbed, with peak plasma concentrations reached in ~1 hour.[213] Pioglitazone has a bioavailability of 83%, with peak plasma concentrations reached within 2 hours.[215] Food delays the time to peak concentration, but does not alter the extent of absorption of either drug. Both TZDs are extensively (>99%) protein bound, primarily to albumin. The plasma elimination half-life of rosiglitazone is 3 to 4 hours.[213] Pioglitazone has a serum half-life of 3 to 7 hours, and its metabolites have a serum half-life of 16 to 24 hours.[215] Rosiglitazone is extensively metabolized in the liver by CYP2C8 and to a much lesser extent by 2C9. Its conjugated metabolites are considerably less potent than is the parent drug, and are excreted two-thirds in urine and one-third in

feces.[90,213] Pioglitazone is hepatically metabolized, mainly by CYP2C8 and 3A4, and to a lesser degree by CYP1A1, to three active metabolites; however, the main metabolites found in serum are M-III and M-IV. Approximately 15% to 30% of the dose is recovered in the urine as metabolites, with the remainder excreted either into the bile as unchanged drug or into the feces as metabolites.[213,215]

Because the action of the TZDs relies on gene transcription and protein production, the onset and duration of action are unrelated to the plasma half-life. The onset of their effect occurs in 1 to 2 weeks, although maximal effects are not usually seen before 8 to 12 weeks. No dose adjustment is necessary in patients with renal impairment. There is no dose adjustment needed for hepatic impairment with pioglitazone; however, rosiglitazone should be avoided in patients with moderate-to-severe hepatic impairment.[216–218]

ADVERSE EFFECTS

Hepatotoxicity

Liver failure has been very rarely reported with either rosiglitazone or pioglitazone, although causality in most cases remains uncertain.[219] For both drugs, monitoring of liver function tests (LFTs) is recommended at baseline, and then periodically thereafter (see section on Contraindications and Precautions). One study suggests that LFTs should be ordered before therapy, every 1 month for the first year, and periodically thereafter for both pioglitazone and rosiglitazone.[90,203]

Hematologic effects

TZD therapy may result in small decreases in hemoglobin and hematocrit and, infrequently, anemia.[90] These effects may be attributable to dilutional effects (see subsequent text).

Weight gain

Dose-related weight gain (4.41–6.61 pounds [2–3 kg] for every 1% decrease in A_{1c}) has been seen with rosiglitazone and pioglitazone.[90,203] Weight gain is likely caused by fluid retention or fat accumulation. The weight gain seems to be associated with an increase in peripheral adipose tissue along with a reduction in visceral adiposity.[90]

Vascular and cardiovascular effects

Increases in plasma volume and peripheral edema (4%–6%), possibly caused by increased endothelial cell permeability, occur with the TZDs.[213,215] The incidence of peripheral edema is greatly increased when TZDs are used in combination with insulin.

The FDA added black box warnings to rosiglitazone and pioglitazone based on the association of their use with an increased risk of developing or exacerbating HF in patients with type 2 diabetes.[220] TZDs are contraindicated for use in patients with New York Heart Association (NYHA) class III or IV HF and are not recommended in patients with acute or systemic HF. TZDs should be used with caution in patients with preexisting edema, which may increase the risk of developing new-onset HF or exacerbating preexisting HF (see Case 53-15).

CV outcomes evaluating the risk of MI and stroke have been studied with TZDs. Pioglitazone for 3 years with type 2 DM and a history of MI, stroke, or percutaneous coronary intervention (PCI) may reduce the risk of all-cause mortality, nonfatal MI, and stroke.[220-223] Pioglitazone does not appear to increase the risk of MI or mortality.[224] In the RECORD trial, rosiglitazone did not have an overall impact on CV morbidity or mortality.[225–227] Meta-analysis and retrospective observational studies have, however, suggested that rosiglitazone is associated with risk of MI,[227] but not for overall CV or all-cause mortality.[62] Rosiglitazone has also been shown to increase LDL levels.[213,215]

Other effects

Hypersensitivity reactions including rash, pruritus, urticaria, angioedema, anaphylactic reaction, and Stevens–Johnson syndrome have been rarely reported with rosiglitazone.[213,215,228] Macular edema has been rarely reported with TZDs.[229] Patients experiencing changes or worsening in vision should be referred to an ophthalmologist for follow-up. In some cases, macular edema improved or resolved after discontinuation of TZD therapy.[230]

Pioglitazone has been associated with an increased risk of bladder cancer compared to the general population, and is contraindicated in patients with bladder cancer.[230] In patients with previous history of bladder cancer, the need for use of pioglitazone for glycemic control must outweigh the potential recurrence of bladder cancer.[230] The FDA has released a safety communication warning that the use of pioglitazone for >1 year may increase the risk of bladder cancer.[230] Recently analyzed 10-year findings show no statistically significant increase in bladder cancer, but a risk as previously identified cannot be ruled out. This meta-analysis identified a possible increased risk of pancreatic and prostate cancer. Monitoring for causal effect of cancers should be continued.[231–234]

An increased risk of distal limb bone fractures (eg, forearm, hand, wrist, foot, and ankle) and bone loss have been observed in females receiving TZDs.[233,234] Males may also be at increased fracture risk, but the evidence is not as strong.[235] The mechanism is thought to be reduced osteoblast differentiation as a result of increased adipogenesis in the bone marrow.[213] The potential for fractures in older female patients and patients on chronic steroids should be carefully considered before using a TZD.

CONTRAINDICATIONS AND PRECAUTIONS

- *Type 1 diabetes:* Because insulin is required for their action, TZDs should not be used in people with type 1 diabetes.
- *Patients with type 2 diabetes using insulin:* TZDs should be used with caution because of the increased risk of developing edema.
- *Preexisting hepatic disease:* Pioglitazone and rosiglitazone should not be used in patients whose alanine aminotransferase (ALT) is

>2.5 times normal. TZDs should be discontinued if the ALT is more than three times normal, if serum bilirubin levels begin to rise, or if the patient reports of any symptoms that could be attributed to hepatitis (eg, fatigue, nausea, vomiting, abdominal pain, and dark urine).

- *Symptomatic or severe (NYHA classes III and IV) HF*: See previous discussion.
- *Myocardial ischemia* (rosiglitazone only): See previous discussion.
- *Premenopausal anovulatory females:* TZDs may cause resumption of ovulation and menstruation in females with polycystic ovarian syndrome, placing these patients at risk for an unwanted pregnancy.
- *History of hypersensitivity to TZDs*
- *Patients with osteoporosis or at risk for bone fractures* (eg, chronic steroid use)
- *Drugs metabolized by CYP3A4:* See the section on Drug Interactions for further details.
- *Patients with a current or previous history of bladder cancer: Such patients should not use TZDs.*
- *Macular edema:* Patients should receive regular eye examinations to evaluate acute visual changes.

DRUG INTERACTIONS

Coadministration of a TZD with other antidiabetic medications or insulin does not alter the pharmacokinetics of either drug, but may increase the patient's risk for hypoglycemia. Pioglitazone induces CYP3A4 and may, therefore, decrease the effectiveness of other drugs metabolized by this enzyme, such as estrogens, cyclosporine, tacrolimus, and β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. Ketoconazole may significantly inhibit the metabolism of pioglitazone.[215] Patients taking oral contraceptives or estrogen-replacement therapy should be informed of the possible risk of decreased effectiveness of estrogen therapy. Rosiglitazone does not seem to inhibit any of the major CYP enzymes.[236] Rifampin

decreases the AUC for both rosiglitazone and pioglitazone, although the clinical significance of this interaction is unknown. Pioglitazone is a substrate of CYP2C8; therefore, interactions may occur when administered with drugs that inhibit or induce CYP2C8.[213] The maximum dose of pioglitazone is 15 mg once a day if given with a strong CYP2C8 inhibitor.[236] Gemfibrozil significantly increases the AUC of both drugs. For patients receiving both a TZD and a gemfibrozil, a dose reduction of the TZD may be warranted.[90,203]

EFFICACY

The effects of TZDs on A_{1c} and FPG are intermediate between those of acarbose and the sulfonylureas or metformin.[213,215] When combined with other antidiabetic agents in a patient with poorly controlled type 2 diabetes, one can expect to see an augmented effect on the A_{1c} (0.9%–1.3% decrease with a sulfonylurea, 0.8%–1.0% decrease with metformin, and 0.7%–1.0% decrease with insulin).[237] When added to the therapy for a patient with type 2 diabetes taking insulin, rosiglitazone and pioglitazone can enhance glycemic control (~0.6% lower with pioglitazone) while decreasing insulin requirements; however, weight gain (>6.61 pounds [3 kg]) and increased edema will likely occur.[90,213,215] Individuals who are minimally responsive or unresponsive to TZD therapy may include those who are not obese and have lower levels of endogenous insulin.

Other potential benefits of the TZDs are their favorable, but variable, effects on lipids.[213] Pioglitazone and, to a lesser extent, rosiglitazone may decrease triglycerides. Both drugs may increase HDL-C levels by 10%. Rosiglitazone has been observed to increase LDL-C by 8% to 16%, whereas pioglitazone may not affect LDL-C. As noted, TZD therapy has been associated with weight gain, and this may be substantial when used in combination with sulfonylureas or insulin.

DOSAGE AND CLINICAL USE

Patients who are unable to take or have failed metformin or sulfonylurea monotherapy or who have not responded to dipeptidyl peptidase-4 (DPP-IV) inhibitor or sodium–glucose transporter 2 (SGLT-2) inhibitor therapy may be candidates for TZDs. TZDs are also a cost-effective therapy for patients with financial insecurity and can be used in patients unwilling to inject. For monotherapy or combination therapy with a sulfonylurea, metformin, or insulin, the starting dose for pioglitazone is 15 or 30 mg once daily with or without food. The dose can be titrated up to a maximum of 45 mg/day.[215] The starting dose for rosiglitazone is 4 mg given once daily or in divided doses. The dose may be increased after 8 to 12 weeks if adequate response is not seen. The maximum daily dose is 8 mg.[238]

α-Glucosidase Inhibitors

MECHANISM OF ACTION

The α-glucosidase inhibitors, acarbose[239] and miglitol,[238] reversibly inhibit glucosidases present in the brush border of the mucosa of the small intestine. These enzymes break down complex polysaccharides and disaccharides into glucose and other absorbable monosaccharides. Enzyme inhibition delays carbohydrate digestion and subsequent glucose absorption. Postprandial BG concentrations are therefore lowered when these agents are taken with a meal containing complex carbohydrates.

PHARMACOKINETICS

Acarbose is minimally absorbed from the GI tract, with an oral bioavailability of the parent drug of <2.0%.[239] It is extensively metabolized by GI amylases to inactive metabolites. The peak plasma concentration occurs in ~1 hour, and the elimination half-life for acarbose is 2 hours, although there may be a longer terminal half-life. Unlike acarbose, miglitol is absorbed. Absorption of miglitol is saturable at higher doses (>25 mg), and peak concentration occurs in 2 to 3 hours.[238,239] The drug is primarily distributed in

extracellular fluids and is not metabolized. After a 25-mg dose, 95% of the drug is excreted unchanged by the kidneys within 24 hours.

ADVERSE EFFECTS

Flatulence, diarrhea, and abdominal pain are the most frequently reported adverse effects of α-glucosidase inhibitors.[240] In placebo-controlled trials of acarbose, these ADRs were experienced by 74%, 31%, and 19% of subjects, respectively. GI side effects are attributable to fermentation of unabsorbed carbohydrate in the small intestine, and can be minimized by slowly titrating the dose of either agent. GI discomfort usually improves with continued therapy because induction of the α-glucosidase enzymes occurs in the distal jejunum and terminal ileum.

In studies using doses of acarbose 300 mg/day or more, a transient increase in serum hepatic transaminases was reported.[238,239] The manufacturer recommends monitoring hepatic transaminases every 3 months for the first year of therapy and periodically thereafter. If an elevation of serum transaminases occurs, the dose should be decreased or discontinued if elevations persist. Because miglitol is not metabolized, it does not seem to affect hepatic function.

CONTRAINDICATIONS AND PRECAUTIONS

Acarbose and miglitol are contraindicated with known hypersensitivity to the medications.[238,239] Both medications are contraindicated in patients with DKA, and acarbose is contraindicated in patients with cirrhosis.

Gastrointestinal conditions

Because of their profound GI effects (flatulence and diarrhea), acarbose and miglitol are contraindicated in patients with malabsorption, inflammatory bowel disease, colonic ulceration or other marked disorders of digestion or absorption, or with intestinal obstruction.[238,239]

Renal impairment

Acarbose has not been studied in patients with severe renal impairment (SCr >2.0 mg/dL) and should not be used in these patients.[209] There is little information with regard to safety of the use of miglitol in patients with a CrCl <25 mL/minute; therefore, its use is contraindicated in these patients.[238–240]

DRUG INTERACTIONS

Patients who use acarbose or miglitol in combination with other antidiabetic agents may experience hypoglycemia. These reactions should be treated with dextrose because acarbose may limit the availability of the disaccharide sucrose (table sugar). Because acarbose and miglitol delay carbohydrate passage through the bowel, they could influence the absorption kinetics of concomitantly administered drugs. Conversely, because their own absorption may be diminished by digestive enzyme preparations and charcoal, they should not be taken concomitantly with these agents.[239] The bioavailability of digoxin can be reduced, and may require dose adjustment. Miglitol decreases the bioavailability of ranitidine and propranolol by 60% and 40%, respectively.[238,239]

EFFICACY

By delaying the absorption of glucose after ingestion of complex carbohydrates and disaccharides, the α-glucosidase inhibitors can lower postprandial plasma glucose concentrations in patients with type 2 diabetes by 25 to 50 mg/dL.[238,239] FPG concentrations remain unchanged or are slightly lowered (20–30 mg/dL), but this effect may be related to decreased glucose toxicity, which improves insulin secretion and action. Mean A_{1c} values decline by 0.3% to 0.7%. Acarbose and miglitol have no effect on weight or lipid profiles.[238,239]

DOSAGE AND CLINICAL USE

Because of limited effects on A_{1c} and their side effect profile, α-glucosidase inhibitors are used infrequently and, when used, are usually given as add-on therapy in patients who have failed

monotherapy or combination therapy with other oral antidiabetic agents. The recommended initial dose of either drug is up to 25 mg tid, taken at the start of each meal.[15] The dosage of acarbose can be gradually increased (eg, 25 mg/meal) every 4 to 8 weeks to a maximum of 50 mg tid for individuals weighing ≤132.28 pounds (60 kg), or 100 mg tid for individuals weighing >132.28 pounds (60 kg). The dose for miglitol is titrated up after 4 to 8 weeks to a dose of 50 to 100 mg tid if needed, regardless of a patient's weight. A maximal response is observed at 6 months.

Incretin-Based Therapies

Incretins are insulinotropic hormones secreted from specialized neuroendocrine cells in the small intestinal mucosa in response to carbohydrate ingestion and absorption.[241] The two hormones accounting for most incretin effects are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). GIP and GLP-1 stimulate pancreatic β cells in a glucose-dependent manner, contributing to the early-phase insulin response. GLP-1 also inhibits pancreatic α-cells, thus reducing glucagon secretion and hepatic glucose production. Incretin action is efficient, but short lived. As they enter the blood vessels, incretins undergo rapid metabolism via proteolytic cleavage by DPP-4 to inactive metabolites. Thus, only small amounts are needed to exert their effects on glucose metabolism.

Glucagon-Like Peptide-1 Agonists (Mimetics/Analogs)

The available glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the United States include exenatide, ER exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide (both oral and injectable). The formulations available are a once-daily injection (liraglutide), twice-daily injection (exenatide), once-weekly injections (ER exenatide, dulaglutide, and semaglutide) and once-daily oral tablet

(semaglutide). Albiglutide was previously available; however, it was removed from the market because of limited prescribing and poor market share as of August 2017. The ADA recommends GLP-1 agonists as first-line injectable therapy in patients with type 2 diabetes, especially in scenarios where hypoglycemia, ASCVD, or weight loss is seen. AACE recommends that GLP-1 agonists be used after patients on metformin therapy do not receive glycemic goals or if they cannot tolerate metformin. Liraglutide has been studied as an adjunct to insulin therapy in patients with type 1 diabetes to minimize weight gain, but is not currently recommended for routine use in this patient population.[242]

MECHANISM OF ACTION

GLP-1 mimetics and analogs have stability in the presence of DPP-4, resulting in a longer duration of action than does endogenous GLP-1. These agents augment early- or first-phase insulin response in response to elevated glucose concentrations (ie, glucose dependent), moderate glucagon secretion, and decrease hepatic glucose production without impairing the normal glucagon response to hypoglycemia. They slow gastric emptying, thereby reducing the rate at which glucose is absorbed. In addition, they suppress appetite, which may contribute to the prevention of weight gain and the weight loss (3.31–11.02 pounds [1.5–5 kg]) observed in patients. A promising action of these agents is their potential to increase β-cell mass and preservation, which has been shown in animal models.

PHARMACOKINETICS

After SC injection, exenatide reaches peak plasma concentrations in 2.1 hours.[243] The median peak plasma level for lixisenatide is achieved between 1 and 3.5 hours (lixisenatide PI). The injection site (abdomen, thigh, or upper arm) does not significantly alter pharmacokinetics. Both exenatide formulations and lixisenatide are eliminated predominantly by glomerular filtration with subsequent proteolytic degradation. The mean terminal half-life of exenatide is 2.4 hours, with levels measurable up to 10 hours, thus allowing for

twice-daily dosing. The mean terminal half-life for lixisenatide is 3.5 hours. The metabolism and elimination are dose independent. ER exenatide is released from microspheres over ~10 weeks after administration. After discontinuation of therapy, minimal detectable concentrations can be seen in ~10 weeks.[244]

Absorption of liraglutide is delayed owing to its self-association in heptameric aggregates within the injection depot that are too large to cross the capillary membranes.[244,245] On disassociation of the heptamers at the absorption site, liraglutide is absorbed. This delayed absorption is the primary reason for its prolonged action. Liraglutide is highly protein bound (>98%), with a half-life of 13 hours, allowing for once-daily dosing.[244,245] Metabolism of liraglutide occurs endogenously in a manner similar to that of large proteins, and there is no specific organ as its route of elimination.[246]

Dulaglutide achieves maximum plasma concentration in about 48 hours, and steady state occurs between 2 and 4 weeks with once-weekly administration. There is no statistically significant difference of exposure to dulaglutide between the site of administration in the abdomen, upper arm, or thigh. Metabolism occurs through general protein catabolism pathways into its component amino acids. The elimination half-life is ~5 days.[247]

The SC once-weekly semaglutide formulation reaches maximum concentration 1 to 3 days after the first dose and is highly protein bound. The medication reaches steady state after 4 to 5 weeks of once-weekly administration. Both semaglutide oral and SC formulations are also metabolized after proteolytic cleavage, but β-oxidation is also required to break down the fatty acid sidechain. Semaglutide has a half-life of 1 week, and will stay in circulation for ~5 weeks after the last dose. The formulation of semaglutide to salcaprozate sodium allows the polypeptide chain to be absorbed more readily in the stomach while minimizing degradation from the acidic environment.

ADVERSE EFFECTS

GI side effects are common and dose dependent, particularly nausea, vomiting, and diarrhea. Rates vary between agents, with exenatide ER appearing to have the lowest rates in placebo-controlled trials.[242,243,245,246,248] These side effects may be lessened by starting patients on lower doses for daily injections, ensuring correct timing and administration of the drug, and titrating the dose slowly. Other reported side effects have included decreased appetite and injection site reactions. Hypoglycemic risk can be increased in patients who are also taking an oral insulin secretagogues (eg, sulfonylurea) or insulin.[242,243,245,246,248]

These agents have been rarely related to hypersensitivity reactions, acute pancreatitis, and reduced renal function. Patients should be educated about symptoms of acute pancreatitis, including severe abdominal pain accompanied by vomiting, and instructed to report to their practitioner immediately. Patients in whom acute pancreatitis is confirmed with no other probable cause should not be rechallenged with GLP-1 agonists.[242,243,245,246,248,249]

The development of antibodies against these agents is well established. In general, the presence of antibodies does not appear to significantly affect the A_{1c} reduction seen with GLP-1 agonists, although some patients with high antibody titers may experience reduced efficacy.[242,243,245,246,248] Patients who demonstrate adherence to therapy, yet experience no change or worsening in glycemic control, should discontinue therapy and be switched to alternative agents.

CONTRAINDICATIONS AND PRECAUTIONS

GLP-1 agonists are contraindicated in patients with known hypersensitivity. They should not be used in patients with a history of pancreatitis.[243,250] They are not recommended for use in patients with severe GI disease. Exenatide should not be used in severe renal impairment (CrCl <30 mL/minute) or end-stage renal failure, or in those requiring hemodialysis.[246,248] There is limited clinical experience using dulaglutide in patients with end-stage renal disease (ESRD) and should be used with caution in these patients. If these

patients experience GI adverse effects, renal function should be closely monitored.[242,243,245,246,248]

GLP-1 agonists are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) because of risks in rodents. A causal relationship in humans has not been established.[242,243,245,246,248] Currently, the FDA has required black box warnings on each of the GLP-1 agonists for MTC, MEN 2, and thyroid cancer, as well as a REMS program for each medication.

DRUG INTERACTIONS

GLP-1 agonists may increase the risk of hypoglycemia when used with sulfonylureas or insulin. Because of their mechanism of action, they may reduce the rate and extent of absorption of orally administered drugs.[242] They should, therefore, be used with caution in patients taking medications that require rapid GI absorption and are dose dependent on threshold concentrations for efficacy, such as antibiotics and oral contraceptives. The manufacturers of twice-daily exenatide recommend that patients take the affected medications at least 1 hour before exenatide administration.[242,243] There have been case reports of an increased international normalized ratio, sometimes associated with bleeding, in patients taking exenatide and warfarin. Patients should be closely monitored, with dose adjustments to warfarin therapy made as needed.[242,243,246,251–254]

EFFICACY

In clinical trials, maximal doses of GLP-1 agonists combined with a sulfonylurea, metformin, a TZD, or sulfonylurea plus metformin therapy reduced FBG between by 5 and 41 mg/dL, 2-hour postprandial BG by 60 to 70 mg/dL. In patients with type 2 diabetes, A_{1c} was reduced by 0.7% to 1.9%, and body weight was reduced from 3.08 to 11.02 pounds (1.4–5 kg).[255]

CARDIOVASCULAR BENEFIT

The ADA guidelines recommend that patients with high ASCVD risk be placed on GLP-1 agonists (or SGLT-2 inhibitors) if extra glycemic control is needed past metformin. Four GLP-1 agonists on the market have shown to improve MACE: liraglutide, dulaglutide, semaglutide, and semaglutide oral. Liraglutide was shown to decrease MACE by 13%, CV death by 22%, and all-cause mortality by 15%.[256,257] SC semaglutide and dulaglutide were found to reduce MACE by 26% and 12%, respectively.[258] Oral semaglutide showed a 21% reduction in MACE and other statistically significant findings with all-cause mortality and hospitalization due to HF.[255–258] With this abundance of positive data, liraglutide, dulaglutide, and semaglutide have been FDA approved to reduce the risk of MACE in adults with type 2 DM and established CVD.[259]

RENAL BENEFIT

GLP-1 agonists are recommended in the ADA guidelines for patients with underlying renal insufficiency second only to SGLT-2 inhibitors. Comprehensive and well-powered renal studies with GLP-1 agonists have yet to be conducted; however, renal function has been monitored as secondary end points in CV trials. The urine albumin–creatinine ratio (UACR) favored lixisenatide (24% vs 34% placebo group, P = .004); however, there were similar median UACR at baseline and at follow-up.[255] Liraglutide was found to have a decrease in composite microvascular outcomes and a decrease in nephropathic events by 16% and 22%, respectively.[256] Semaglutide was observed to decrease new or worsening nephropathy by 36%.[257] Dulaglutide decreased renal outcomes by 15%.[257] Uniquely, patients on dulaglutide 1.5 and 0.75 mg were compared to patients on insulin glargine and were found to have higher eGFRs after 1 year, but no significantly different reduction in UACR.

DOSAGE AND CLINICAL USE

Exenatide (not the ER formulation) is approved for use as monotherapy, whereas the other GLP-1 agonists are not recommended as monotherapy per the manufacturers. GLP-1

agonists are indicated as add-on agents in patients with type 2 diabetes who have been unable to reach target goals on monotherapy with metformin or in combination therapy. Although not indicated for weight loss, these agents may be helpful in patients with type 2 diabetes who are obese and struggling with obesity. Exenatide has been studied in patients with type 2 diabetes already on insulin glargine; exenatide lowered the A_{1c} by 1.7% and patients required lower doses of insulin glargine compared with the placebo group.[242,243,245,246,248]

The starting dose of exenatide is 5 µg injected SC into the abdomen, thigh, or arm twice daily in the 60 minutes before morning and evening meals. Patients who experience severe GI side effects may try injecting just before meals initially, and then move from 30 to 60 minutes before meals. If a patient tolerates the 5-µg dose, then it can be titrated after 1 month of therapy to the maximal dose of 10 µg SC twice daily. The dose of ER exenatide is 2 mg given SC once weekly without regard to meals at any time of the day. The starting dose of liraglutide is 0.6 mg injected SC into the abdomen, thigh, or arm once daily for 1 week, and then it may be increased to 1.2 mg SC daily. If the A_{1c} goal is not achieved with a 1.2-mg dose, the dose can be further increased to 1.8 mg daily. The starting dose of dulaglutide is 0.75 mg injected SC into the abdomen, thigh, or upper arm once weekly given at any time of the day, and may be increased to 1.5 mg once weekly if adequate glycemic control is not achieved.[242,243,245,246,248]

When any of these agents are added to the treatment regimen of a patient who is also taking a sulfonylurea or glinide, the insulin secretagogue dose may need to be lowered (by about half) to reduce the risk of hypoglycemia. If used in combination with basal insulin, the insulin dose may need to be decreased.[250,254,260–262]

Dipeptidyl Peptidase-4 Inhibitors

Currently, four DPP-4 inhibitors are available in the United States: sitagliptin, saxagliptin, linagliptin, and alogliptin.[263]

MECHANISM OF ACTION

The DPP-4 inhibitors inhibit the degradation of GIP and GLP-1 on entering the GI vasculature, thus increasing the effects of these endogenous incretins on first-phase insulin secretion and glucagon inhibition.[260] They are all competitive inhibitors of DPP-4. Sitagliptin, at a 100-mg dose, reduces DPP-4 activity by 80% for up to 24 hours,[261] whereas saxagliptin, at a 2.5-mg dose, reduces DPP-4 activity by 50% for up to 24 hours.[262] Alogliptin, at a dose of at least 25 mg, has been shown to reduce DPP-4 activity by >80% at a dose of at least 25 mg for at least 24 hours.[250] Linagliptin, at the standard dose of 5 mg, has been shown to reduce DPP-4 activity by >80% for up to 24 hours.[264] In contrast to GLP agonists, which increase GLP-1 levels by 6- to 10-fold,[254] these agents not only modestly increase GLP-1 levels (two- to threefold) but also increase GIP levels. As a result, DPP-4 inhibitors have minimal to no effect on satiety and delaying gastric emptying.

PHARMACOKINETICS

Sitagliptin is rapidly absorbed, with an absolute bioavailability of 87%.[265] Absorption is unaffected by food. Peak plasma concentrations occur in 1 to 4 hours, and its terminal half-life is 12.4 hours. Only 38% of sitagliptin is plasma protein bound. Eighty-seven percent of the parent drug is excreted unchanged in the urine, primarily by active renal tubular secretion, and may involve P-glycoprotein (P-gp) and human organic anion transporter (OAT) 3. Metabolism by CYP3A4, and to a much lesser extent, CYP2C8, plays a minimal role in the excretion of metabolites in the feces.[260]

Saxagliptin is well absorbed, with a bioavailability estimated to be 75%.[266] Although food increases absorption by 27%, it can be administered with or without food. Peak plasma concentrations occur at 2 hours for saxagliptin and at 4 hours for the active metabolite. Saxagliptin is metabolized by CYP3A4/5 to a major metabolite that is one-half as potent.[265] Protein binding of saxagliptin and its active metabolite is negligible. The mean plasma terminal half-lives of saxagliptin and its active metabolite are 2.5 and 3.1 hours,

respectively. Saxagliptin is excreted primarily by the kidneys, with 25% excreted unchanged in the urine, and 36% of the active metabolite found in urine. Approximately 22% of drug and metabolite are excreted in feces.[250]

Linagliptin is well absorbed and has a bioavailability of 30%. A high-fat meal can decrease the absorption by 15%; however, this is not clinically significant. Therefore, linagliptin may be administered with or without food. Peak plasma concentrations occur at ~1.5 hours after a dose of 5 mg. Linagliptin has a long terminal half-life (>100 hours) because of the biphasic decline in plasma concentrations, which is related to the binding of DPP-4. Approximately 90% of linagliptin is excreted unchanged in the urine, and a small percentage is metabolized to an inactive metabolite.[262]

Alogliptin is well absorbed and has a bioavailability of 100%. A high-fat meal results in no significant change in absorption; therefore, it may be administered with or without food. Alogliptin is 20% plasma protein bound, with 60% to 71% of the dose excreted unchanged in urine and 13% excreted in the feces. Limited metabolism occurs via CYP2D6 and CYP3A4. The terminal half-life of alogliptin is ~21 hours after the administration of a 25-mg dose.[263]

ADVERSE EFFECTS

Because these agents differ significantly in chemical structure from one another, some adverse events may be unique to the individual agent, and may not be indicative of a class-wide effect.[254,262] The most commonly reported side effects with sitagliptin and alogliptin include nasopharyngitis, upper respiratory tract infection, hypoglycemia, and headache.[260,261] Saxagliptin can cause these same adverse effects, as well as urinary tract infection, whereas linagliptin adverse effects can include hypoglycemia, nasopharyngitis, diarrhea, and cough.[267] It is possible that DPP-4 inhibitors may have an effect on the immune system, because lymphocytes express DPP-4. These medications have been suggested to increase risk of pancreatitis; however, studies have shown this risk to be low.[268,269] DPP-IV inhibitors pose relatively low

risk for hypoglycemia, and are recommended for patients with a compelling need to reduce hypoglycemic episodes per ADA and AACE guidelines.

CONTRAINDICATIONS AND PRECAUTIONS

All DPP-4 inhibitors should be avoided in patients with a history of serious hypersensitivity reaction to the drug. The FDA released an alert in regard to saxagliptin and alogliptin in April 2016. These medications were found to increase the risk of HF, especially in patients with heart or kidney disease.[254]

DRUG INTERACTIONS

Sitagliptin is not significantly protein bound.[254,264] It also does not inhibit CYP isoenzymes or induce CYP3A4; therefore, it is not expected to interact with other drugs that are metabolized by these pathways. Patients taking digoxin, a substrate of P-gp–like sitagliptin, should be monitored for any signs or symptoms of digoxin toxicity, because a slight increase in the AUC (11%) and C_{max} (18%) has been observed.[260]

Saxagliptin does have significant drug interactions because it is metabolized by CYP3A4/5.[261] Therefore, if used with strong inhibitors of these enzymes (eg, ketoconazole, itraconazole, clarithromycin, telithromycin, and protease inhibitors such as indinavir), the dose of saxagliptin is reduced to 2.5 mg daily.

Linagliptin is a weak-to-moderate inhibitor of CYP3A4 and a P-gp substrate, and inhibits P-gp–mediated transport of digoxin at high concentrations.[262] Medications that are strong inducers of CYP3A4 or P-gp, such as rifampin, decrease linagliptin to levels that are subtherapeutic and ineffective; therefore, if treatment with those medications is necessary, an alternative to linagliptin should be used.

Alogliptin is not significantly protein bound, and metabolism through the cytochrome P450 pathway is negligible; therefore, there are no significant drug interactions with alogliptin.[254]

EFFICACY

In monotherapy clinical trials versus placebo, sitagliptin lowers fasting glucose by 12 mg/dL and A_{1c} by 0.5% to 0.6% compared with baseline (0.6%–0.8% compared with placebo)[260]; saxagliptin is comparable, with A_{1c} lowering by 0.5% (0.6% vs placebo) and FPG by 15 mg/dL.[254,260,264] In addition, both agents reduce 2-hour postprandial glucose by ~45 mg/dL.[261] When used as add-on combination therapy, A_{1c} lowering is greater (0.7%–0.9%). Linagliptin, as monotherapy in clinical trials versus placebo, decreased fasting glucose by 13 mg/dL from baseline and A_{1c} by 0.4%.[262] Alogliptin, as monotherapy in clinical trials versus placebo, decreased fasting glucose by 16 mg/dL and A_{1c} by 0.6%.[264] Unlike the GLP-1 mimetics and analogs, DPP-4 inhibitors do not significantly affect body weight, appetite, or satiety, and are considered weight neutral.[268–271] As is the case for the GLP-1 mimetics and analogs, further studies are needed to more clearly determine the effects of DDP-4 inhibitors on long-term preservation of β-cell function.

CARDIOVASCULAR BENEFIT

Several clinical studies were conducted to determine the impact of DPP-IV inhibitors on CV health. When compared with placebo saxagliptin, alogliptin, sitagliptin, and linagliptin had no statistically significant difference in reduction of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina,[272] Linagliptin was also compared to glimepiride, a sulfonylurea, and was found to be noninferior for MACE.[269]

RENAL BENEFIT

Limited data exist with DPP-IV inhibitors and long-term renal impact. Post hoc analyses were conducted on CV trials involving saxagliptin, alogliptin, and sitagliptin. Saxagliptin was shown to have reduced development and progression of microalbuminuria[268,270]; however, alogliptin and sitagliptin demonstrated no significant differences in

renal outcomes between groups.[254] In the CV trial for linagliptin, renal findings were recorded as secondary outcomes. No differences were found between linagliptin and placebo.

DOSAGE AND CLINICAL USE

DPP-4 inhibitors are mainly used as add-on therapy in combination with other agents. However, all are approved for use as monotherapy. Sitagliptin may be initiated at 100 mg taken once daily with or without food.[260] Renal function should be assessed before initiation of this agent. In patients with moderate renal insufficiency (CrCl 30–50 mL/minute), the dose for sitagliptin should be reduced to 50 mg once daily, and in severe renal insufficiency (CrCl <30 mL/minute) or for those in end-stage renal failure requiring dialysis, the sitagliptin dose is 25 mg once daily. Sitagliptin may be administered without regard to the timing of hemodialysis. Only sitagliptin should be used in patients on peritoneal dialysis.

Saxagliptin is dosed at 2.5 to 5 mg once daily with or without food.[261] Renal function should be assessed before initiation of this agent. In patients with moderate or severe renal impairment or ESRD with a CrCl < 50 mL/minute, the recommended dose is 2.5 mg daily. If patients are taking strong CYP3A4/5 inhibitors, the dose of saxagliptin should be 2.5 mg daily. In patients on hemodialysis, the dose is 2.5 mg daily to be administered after hemodialysis.

Linagliptin is dosed at 5 mg once daily with or without food. No dose adjustment is necessary for patients with renal impairment; however, patients with a CrCl <30 mL/minute may be more prone to hypoglycemia; therefore, dosing adjustments of concomitant antidiabetic medications and frequent monitoring may be necessary.[262]

Alogliptin is dosed at 25 mg once daily with or without food. Renal function should be assessed before initiation of this medication. In patients with moderate renal impairment with a CrCl of 30 to 60 mL/minute, the recommended dose is 12.5 mg once daily. In patients with severe renal impairment (CrCl <30 mL/minute) or ESRD, the dose is 6.25 mg once daily. Patients on hemodialysis should be

given 6.25 mg once daily, and it may be administered without regard to the timing of dialysis.[273]

When any of these agents are added on for a patient also on a sulfonylurea or glinide, the insulin secretagogue dose may need to be lowered (by about half) to reduce the risk of hypoglycemia. Similarly, when sitagliptin is added on for a patient already on insulin therapy, the dose(s) of insulin may need to be lowered initially and then readjusted depending on the response to sitagliptin.

Amylin Receptor Agonists (Amylinomimetics)

MECHANISM OF ACTION

Amylin is a hormone found in the β cells where it is comanufactured, stored, and released with insulin in response to food intake.[274] Its actions seem to be centrally mediated and include slowing gastric emptying, suppressing glucagon secretion, and modulating the regulation of appetite. Amylin is absent in patients with type 1 diabetes. In patients with type 2 diabetes, its concentrations are altered to mirror those of insulin at different points in the progression of the disease. Pramlintide, a synthetic amylin analog, is available in the United States for the adjunctive treatment of patients with both type 1 and type 2 diabetes who use mealtime insulin.

PHARMACOKINETICS

The absolute bioavailability of SC injected pramlintide is 30% to 40%.[274] SC injection into the abdomen and thigh allows for more predictable absorption and distribution than when administered into the arm. Approximately 40% of the drug is unbound in plasma. The half-life is about 48 minutes, and time to maximum concentration is ~20 minutes. Pramlintide is metabolized by the kidneys to an active metabolite with a half-life similar to the parent drug.

ADVERSE EFFECTS

GI symptoms—including mild-to-moderate nausea (28%–48%), vomiting (8%–11%), and anorexia (9%–17%)—are the most

frequently reported adverse reactions associated with therapy.[274] GI symptoms are usually transient, subsiding after 4 to 8 weeks of treatment or with dose reduction and slow dose escalation. Hypoglycemia can occur in up to 16.8% of patients with type 1 diabetes receiving pramlintide and insulin therapy, and in 8.2% of patients with type 2 diabetes receiving pramlintide and insulin.

CONTRAINDICATIONS AND PRECAUTIONS

Pramlintide is contraindicated in patients with known cresol hypersensitivity, hypoglycemic unawareness, and gastroparesis.[274] Severe hypoglycemia can occur when it is used in combination with insulin and medications that can slow gastric emptying. Amylin mimetics are not recommended for use in patients with poor adherence to insulin regimen or in patients who have difficulty taking BG levels routinely. This agent should also be avoided in patients with an A_{1c} >9%. Drugs that can alter glucose metabolism when administered with pramlintide, and therefore cause hypoglycemia, include oral antidiabetics, fibrates, fluoxetine, salicylates, and angiotensin-converting enzyme inhibitors (ACEIs), and should be used with caution if administered concomitantly. Pramlintide has a black box warning for severe hypoglycemia, which can occur within 3 hours of an injection of pramlintide. Caution individuals while driving, those who operate heavy machinery, and those who engage in other high-risk activities because of potential serious injuries that may result during a hypoglycemic episode.

DRUG INTERACTIONS

As noted, severe hypoglycemia can occur in patients who are concurrently taking an oral hypoglycemic agent (eg, sulfonylurea) or insulin (see following section on Dosage and Clinical Use).[274] Because pramlintide can delay the absorption of medications that are administered concomitantly, medications that require rapid onset for effectiveness, such as antibiotics, oral contraceptives, and analgesics, should be administered at least 2 hours after or 1 hour before the pramlintide injection.

EFFICACY

In clinical studies of patients with type 2 diabetes with doses up to 150 µg/day for 52 weeks, pramlintide combined with insulin decreased A_{1c} by 0.3% and weight by 5.66 pounds (2.57 kg).[72] Clinical studies of patients with type 1 diabetes taking insulin in combination with pramlintide or placebo demonstrated A_{1c} reductions of 0.2% to 0.4% and weight loss of 0.88 to 2.87 pounds (0.4–1.3 kg).[274]

DOSAGE AND CLINICAL USE

In clinical practice, pramlintide is considered an add-on agent primarily for patients with type 1 diabetes who have failed to achieve target BG goals on insulin therapy alone. Its practical use is more limited to obese patients with type 2 diabetes who have failed to achieve target BG levels with a regimen that includes a sulfonylurea or insulin. Pramlintide is available in a pen device (SymlinPen®). It cannot be mixed with any type of insulin. The pens (60 pen-injector for 15-, 30-, 45-, or 60-µg doses and 120 pen-injector for 60- and 120-µg doses) in use may be stored at room temperature (86 °F [30 °C]) for up to 30 days.[274]

For patients with type 1 diabetes, the initial dose is 15 µg, and for patients with type 2 diabetes, the initial dose is 60 µg. Pramlintide is injected SC into the abdomen or thigh immediately before every major meal. A major meal is one that contains ≥30 g of carbohydrate or ≥250 kcal. If a meal is skipped, the pramlintide dose should be skipped. When initiating pramlintide therapy, the dose of premeal insulins must be reduced by at least 50%. Patients should be closely followed up and instructed to intensively monitor and record BG (fasting, preprandial, and postprandial) levels and any hypoglycemic episodes until control has stabilized. Pramlintide is titrated based on achieving optimal glucose control with minimal side effects (eg, nausea). The dose can be increased when no clinically significant nausea has occurred for 3 to 7 days. For patients with type 1 diabetes, doses may be increased in 15-µg increments up to a

maximum meal dose of 60 µg. For patients with type 2 diabetes, the dose may be increased to 120 µg before every major meal.[275–277]

Sodium–Glucose Transporter 2 Inhibitors

SGLT-2 inhibitors reduce BG by decreasing tubular reabsorption of glucose in the kidney, thereby increasing the excretion of urinary glucose.[275–277] These agents are highly selective, reversible inhibitors of SGLT-2. Currently, there are four agents in this class: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, which are available as individual agents or in combination with various other antidiabetic agents.[278] Because their mechanism of action is independent of insulin resistance or β-cell function, these medications can be used in combination with all antidiabetic agent classes, including insulin, for the treatment of type 2 DM in addition to diet and exercise. These agents have added benefits of weight loss, increase in HDL, and decrease in BP; however, they are associated with an increased risk of genital and urinary infections.[279–285] SGLT-2 inhibitors have become a preferred agent in patients with CKD and HF.[62] Per the ADA guidelines, these versatile agents are also recommended as a treatment option for patients with ASCVD, high ASCVD risk, hypoglycemic risk, or with a need to reduce weight. In addition, they are a preferred first choice for patients with CKD and HF.[286] SGLT-2 inhibitors have been studied in patients with type 1 diabetes with positive effects on glycemic control; however, these agents increased the risk of DKA significantly, and are therefore not recommended for this patient population.[275]

PHARMACOKINETICS

Canagliflozin has a bioavailability of 65%, and peak plasma concentrations occur within 1 to 2 hours of the dose being administered.[276] There was no effect on absorption when administered with a high-fat meal; therefore, canagliflozin may be administered with or without food. Canagliflozin is 99% protein bound, primarily to albumin. This agent is metabolized primarily by

glucuronidation by UGT1A9 and UGT2B4 to two inactive metabolites. Approximately 7% is metabolized by CYP3A4. Approximately 33% of a dose is excreted in the urine as metabolites, and <1% is excreted as unchanged canagliflozin in the urine. The terminal half-life is 10.6 hours for a 100-mg dose and 13.1 hours for a 300-mg dose.

Dapagliflozin has a bioavailability of 78% after the administration of a 10-mg dose.[277] The C_{max} occurs at ~2 hours under fasting state. Taking dapagliflozin with a high-fat meal decreases the C_{max} by up to 50%; however, this change is not clinically significant. Therefore, it may be administered with or without food. Dapagliflozin is ~91% protein bound, and is metabolized primarily by the UGT1A9 pathway and to a small extent by CYP 3A4 to yield inactive metabolites. This agent and the inactive metabolites are excreted 75% in the urine and 21% in the feces, with 15% being excreted as unchanged drug. The terminal half-life is ~12.9 hours following a single-dose administration.

Empagliflozin reached peak plasma concentrations at 1.5 hours postoral administration.[275] Plasma concentrations then declined in a biphasic manner, with a rapid distribution phase and a slower terminal phase. The C_{max} decreased by 37% after administration with a high-fat meal; however, this was determined to be clinically insignificant. Therefore, empagliflozin may be administered with or without food. Empagliflozin is 86.2% bound to plasma proteins, and the agent is primarily metabolized by glucuronidation by UGT3B7, UGT1A3, UGT1A8, and UGT1A9. No major metabolites were detected in plasma. Approximately 41.2% of the drug was eliminated in feces (unchanged parent drug), whereas 54.4% was eliminated in urine (half is unchanged parent drug). The terminal half-life is ~12.4 hours.

ADVERSE EFFECTS

In clinical trials, SGLT-2 inhibitors commonly reported adverse effects that include female genital mycotic infections, increased urination, and urinary tract infections[287]; with an overall incidence of

4% to 6%.[275–277,288] Another common adverse effect associated with SGLT-2 inhibitors includes nasopharyngitis.[275–277]

CONTRAINDICATIONS AND PRECAUTIONS

All SGLT-2 agents are contraindicated in patients with hypersensitivity reactions to the agents and in patients with severe renal impairment, ESRD, and dialysis.[278] Although these agents have proven benefit in patients with CKD, they are not recommended in patients with severe renal impairment and would place these patients at increased risk for renal adverse effects. Renal function should be assessed before the initiation of these agents and periodically during treatment. BP should be assessed in patients before initiation with these agents, and hypovolemia should be corrected because of the potential of these agents to lower BP, especially in patients already taking antihypertensive medications. Hypoglycemia may occur when SGLT-2 agents are used in combination with insulin and secretagogues; therefore, the doses of the concomitant agents may need to be decreased. Renal function may be impaired with use of these agents; therefore, renal function monitoring should occur during therapy. Serum concentrations of LDL may be increased with SGLT-2 therapy, which may require medication therapy, and serum LDL concentrations should be monitored. In clinical trials, dapagliflozin has shown an increase in bladder cancer cases as compared to placebo; therefore, patients with previous history of bladder cancer should not take dapagliflozin.[289]

In May 2015, the FDA released a Drug Safety Communication warning that SGLT-2 agents may cause ketoacidosis and that patients should be warned to seek medical attention if they experience signs and symptoms of ketoacidosis including confusion, fatigue, difficulty breathing, abdominal pain, nausea, or vomiting.[290] The cases were not typical of DKA cases, because blood sugars were not highly elevated. In some of the cases, DKA may have been triggered by major illness. The FDA will monitor the safety of these

agents and determine whether prescribing information changes are warranted.

As of 2015, the FDA strengthened a precaution regarding canagliflozin as evidence surrounding low bone mineral density and increased risk of bone fractures emerged. Conversely, the FDA rescinded a precaution involving canagliflozin and increased risk of foot amputations in 2020.[275]

DRUG INTERACTIONS

Canagliflozin weakly inhibits CYP2B6, CYP2C8, CYP2C9, and CYP3A4, is a weak inhibitor of P-gp, and is a substrate of drug transporters P-gp and multidrug resistance–associated protein 2 (MRP2).[276] Rifampin decreases the efficacy of canagliflozin; therefore, the dose of canagliflozin may need to be increased. When administered concomitantly with digoxin, there was an increase in the AUC (20%) and C_{max} (36%) of digoxin; therefore, digoxin should be monitored appropriately.

Dapagliflozin does not inhibit CYP enzymes and is a weak substrate of the P-gp active transporter. The dapagliflozin metabolite is a substrate for the OAT3 active transporter; however, it did not inhibit P-gp, OCT2, OAT1, or OAT3 active transporters with any clinical significance. Therefore, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these enzymes. Coadministration of dapagliflozin with rifampin, a nonselective inducer of UGT1A9, may cause a decrease in dapagliflozin serum concentrations, which may lead to a decrease in dapagliflozin efficacy.[277]

Empagliflozin does not induce or inhibit CYP450 enzymes or UGT1A1; therefore, it is not expected to have interactions with concomitantly administered medications that are substrates of the CYP450 pathway or UGT1A1.[276]

EFFICACY

Canagliflozin monotherapy versus placebo decreased A_{1c} by 0.77% to 1.03%, decreased FPG by 27 to 35 mg/dL, and decreased body

weight by 2.8% to 3.9%.[276] In a clinical trial comparing dapagliflozin monotherapy to placebo, A_{1c} was decreased by 0.8% to 0.9% and FPG was decreased by 24.1 to 28.8 mg/dL.[277] Empagliflozin monotherapy, in a clinical trial compared to placebo, decreased A_{1c} by 0.7% to 0.8%, decreased FPG by 19 to 25 mg/dL, and decreased body weight by 2.8% to 3.2%.[279]

CARDIOVASCULAR EFFECTS

Several SGLT-2 inhibitors have shown significant reductions in CV events when compared with placebo. Empagliflozin showed a 32% reduction in all-cause mortality and a 38% reduction in CV death.[277] As a result, the FDA approved empagliflozin for another indication: prevention of death from CVD in adults with type 2 diabetes and existing CVD.[281] Canagliflozin demonstrated a 14% reduction in MACE,[283] and dapagliflozin showed a 17% reduction in CV death or hospitalization for HF as a composite end point[291] when compared with placebo. Ertugliflozin has not demonstrated a statistically significant reduction in CV death, MI, or stroke.[280]

HEART FAILURE EFFECTS

The current body of evidence suggests that SGLT-2 inhibitors have significant benefit in patients with heart failure with reduced ejection fraction (HFrEF). Empagliflozin showed a 25% reduction in the composite end point of HF hospitalization and CV death regardless of type 2 diabetes status and a 30% reduction in HF hospitalization.[285] The study involving dapagliflozin indicated a 26% reduction in worsening HF or CV mortality and a 25% reduction in CV death and HF hospitalization.[281] This data prompted the FDA to give dapagliflozin a new indication for patients with HFrEF. Canagliflozin was found to have a 22% composite reduction in HF hospitalization and CV death and an overall 33% reduction in HF hospitalization.[291] Ertugliflozin was also found to reduce the risk of HF-related hospitalizations with a number needed to treat (NNT) of ~29 patients.[292] In 2021, empagliflozin was found to significantly reduce the risk of the composite CV death or hospitalization for HF in

adults, with or without diabetes, in patients with HF with preserved ejection fraction (HFpEF).[279] Dapagliflozin is currently still being studied for patients with HFpEF.

RENAL EFFECTS

SGLT-2 inhibitors operate within the kidney, and were thus postulated to affect the nephropathic nature of type 2 diabetes. Empagliflozin was shown to have a 39% reduction in development of nephropathy when compared with placebo.[282] The trials investigating the renal outcomes involving canagliflozin and dapagliflozin were both stopped early because of overwhelmingly positive effects. Canagliflozin demonstrated a 30% reduction in the composite end point of ESRD, a doubling of SCr, or death from renal or CV causes.[284] Dapagliflozin showed a 39% reduction in the risk of declining kidney function, onset of ESRD, or death from renal failure even in patients without diabetes.[291] As of 2021, dapagliflozin was given an added indication for patients with CKD (with or without diabetes) to help reduce the risk of kidney function decline, kidney failure, CV death, and hospitalization due to HF. A secondary end point of ertugliflozin in the CV trial—a sustained 40% in eGFR, dialysis/transplant, or renal death—was 34% lower in the ertugliflozin group than when compared with placebo.[293]

DOSAGE AND CLINICAL USE

The SGLT2 agents are indicated for use in patients with type 2 DM as an adjunct to diet and exercise as monotherapy or concomitantly with other antidiabetic agents. The initial dose of canagliflozin is 100 mg once daily taken before the first meal of the day, and can be increased to 300 mg once daily in patients who need additional glycemic control and have an eGFR >60 mL/minute/1.73 m^2.[275] In patients with an eGFR of 30 to 60 mL/minute/1.73 m^2, the dose is limited to 100 mg once daily, and should be discontinued in patients with an eGFR <30 mL/minute/1.73 m^2.[276] Dapagliflozin should be initiated at a dose of 5 mg once daily in the morning, with or without food, and the dose may be increased in patients who need additional

glycemic control.[277] Monitor renal function before initiation, and do not use in patients with an eGFR <30 mL/minute/1.73 m^2. Empagliflozin should be initiated at a dose of 10 mg once daily in the morning, with or without food, and may be increased to 25 mg once daily.[277] Empagliflozin is not recommended for use to improve glycemic control in adults with type 2 diabetes with an eGFR <30 mL/minute/1.73 m^2.[288] Ertugliflozin should be initiated at 5 mg once daily and increased to 15 mg if tolerated and extra glycemic control is needed. Continued use is not recommended in patients with an eGFR between 30 and 45 mL/minute/1.73 m^2. Use is not recommended in patients with an eGFR <30 mL/minute/1.73 m^2.[294]

Other Agents

COLESEVELAM

In January 2008, the FDA approved a new indication for colesevelam (Welchol®), a bile acid sequestrant, to be used as add-on therapy in type 2 diabetes as an adjunct to diet and exercise.[294–297] The mechanism by which colesevelam reduces glucose is not known. It is a hydrophilic, water-insoluble polymer that is not absorbed. Therefore, its distribution is limited to the GI tract.[295–297] The primary side effects of colesevelam are GI (constipation, nausea, and dyspepsia). The following are contraindications for use of colesevelam:

- Patients with triglyceride levels of >500 mg/dL
- Patients with a history of bowel obstruction
- Patients with a history of pancreatitis caused by hypertriglyceridemia
- Patients with type 1 diabetes or for the treatment of DKA

Because of its constipating effects, it should not be used in patients with gastroparesis, other GI motility disorders, or in those who have had major GI tract surgery and may be at risk for bowel obstruction. The tablets are large and can cause dysphagia or esophageal obstruction; therefore, it should be used with caution in

patients with dysphagia or swallowing disorders. It should be used with caution in patients with triglycerides in excess of 300 mg/dL because bile acid sequestrants can cause concentrations of serum triglycerides to increase.[294]

Drug interactions are an important consideration for colesevelam because it reduces GI absorption of some drugs. Drugs with a known interaction with colesevelam (eg, phenytoin, warfarin, levothyroxine, and oral contraceptives) should be administered at least 4 hours before colesevelam. The bioavailability of glimepiride, glyburide, and glipizide may be affected by concomitant administration of colesevelam; therefore, these medications should be administered 4 hours before colesevelam.[298]

A_{1c} reductions associated with colesevelam are 0.3% to 0.4% compared with baseline (0.5% vs placebo). Colesevelam also reduces LDL-C by 12% to 16% when used in combination with metformin or a sulfonylurea, respectively.[294–297] Bile acid sequestrants can increase triglycerides by 5% to 22% in patients with type 2 diabetes, depending on which antidiabetic medications are given concomitantly.[294] Colesevelam is approved for use as combination therapy with metformin, a sulfonylurea, and insulin.[299] It has not been studied as monotherapy or in combination with DPP-4 inhibitors. It can provide an added benefit in patients with dyslipidemia. The dose is six (625 mg) tablets once daily or three tablets twice daily taken with a meal and liquid. Alternatively, a 3.75-g packet (powder for oral suspension) once daily or 1.875-g packet twice daily may be used by dissolving each dose in 4 to 8 ounces of water, fruit juice, or diet soda, and administering with a meal. Since its approval, its use for treatment of type 2 diabetes remains quite limited.

BROMOCRIPTINE

Bromocriptine mesylate, an ergot derivative, is a dopamine-2 receptor agonist that is a quick-release formulation.[293] It was FDA approved in May 2009 for use in type 2 diabetes. Bromocriptine has been available since 1978 and was once widely used for Parkinson

disease. The mechanism by which bromocriptine improves glycemic control is not known. A normal circadian peak in the central dopaminergic tone occurs in the early morning, and has been linked to induction of normal insulin sensitivity and glucose metabolism.[299] It is theorized that taking bromocriptine in the morning will increase central dopaminergic tone and reset the normal circadian rhythm to that of leaner people. The recommended dose of bromocriptine in diabetes is initiation with 0.8 mg daily, increasing by one tablet weekly until the maximum tolerated dose of 1.6 to 4.8 mg is reached. Bromocriptine is administered once daily within 2 hours of waking in the morning.[299] It should be taken with food to help reduce GI side effects such as nausea. Its effect on A_{1c} lowering is very mild: As monotherapy, A_{1c} is lowered by 0.1% compared with baseline (0.4% vs placebo), and as add-on therapy to a sulfonylurea or metformin, A_{1c} is reduced by 0.5%.[299] Common side effects include hypotension, dizziness, syncope, nausea, somnolence, headache, and exacerbation of psychotic disorders. Bromocriptine is contraindicated in patients with known hypersensitivity to ergot-related drugs, patients with syncopal migraine, and females who are nursing.[299] Bromocriptine is highly protein bound, and when given concomitantly with other drugs that are highly protein bound, such as sulfonamides, salicylates, and probenecid, the unbound fraction of these other drugs may increase, altering their risk of adverse effects or their effectiveness. Bromocriptine is metabolized by CYP3A4; therefore, caution should be used when administering concomitant drugs that are CYP3A4 substrates, inducers, or inhibitors. Neuroleptic agents with dopamine receptor agonist properties, such as olanzapine, clozapine, and ziprasidone, may reduce the effectiveness of both bromocriptine and the other drugs; therefore, concomitant use is not recommended. Given the minor A_{1c} lowering, bromocriptine quick release has a very limited role as a therapeutic agent.[63]

TREATMENT OF PATIENTS WITH TYPE 2 DIABETES

Clinical Presentation

CASE 53-11

QUESTION 1: L.H. is a 45-year-old, overweight, Mexican American female with central obesity (height, 65 inches [165.10 cm]; weight, 165 pounds [74.84 kg]; and BMI, 27.5 kg/m^2). Three months ago, she was referred to the diabetes clinic when her gynecologist, who had been treating her for recurrent monilial infections, noted glucosuria on routine urinalysis. Subsequently, on two separate occasions, she was found to have an FPG of 150 and 167 mg/dL; A_{1c} was also checked, and it was 8.2%. L.H. denies any symptoms of polyphagia or polyuria, although lately she has been more thirsty than usual. She does report symptoms of lethargy and takes afternoon naps when she can.

L.H.'s other medical problems include hypertension, which is well controlled on lisinopril 20 mg/day, and recurrent monilial infections, which are treated with fluconazole. She has given birth to four children (birth weights, 7 [3.18], 8.5 [3.69], 10 [4.54], and 11 pounds [4.99 kg]), and was told during her last pregnancy that she had "borderline diabetes." She currently works as a loan officer in a local bank and spends her weekends "catching up on her sleep" and reading. L.H. has been smoking one pack of cigarettes per day for 20 years and drinks an occasional glass of wine. She drinks at least two regular sodas daily and has a "large" glass of orange juice every morning. Her physical activity consists of routine walking during the day (eg, to her car). Her family history is significant for a sister, aunt, and grandmother with type 2 diabetes; all have "weight problems." L.H.'s mother is alive and well at age 77; her father died of a heart attack at age 47.

On presentation, fasting laboratory assessment reveals glucose of 147 mg/dL, triglycerides of 400 mg/dL, and an A_{1c} of 8.3% (normal, <5.7%).[26] All other values (including the complete blood count, electrolytes, LFTs, and renal function tests) are within normal limits. L.H. is given the diagnosis of type 2 diabetes.

What features in L.H.'s history and physical examination are consistent with this diagnosis?

The features of L.H.'s history that are consistent with type 2 diabetes include an FPG concentration of ≥126 mg/dL on more than

one occasion, an A_{1c} of ≥6.5%, high BMI with central obesity, age older than 40, physical inactivity, family history of diabetes, and Mexican American descent. L.H. also has delivered large babies, which suggests that she may have had undiagnosed gestational diabetes, a condition that places females at high risk for subsequently developing type 2 diabetes. Diagnosis on routine examination and mild signs and symptoms of hyperglycemia (including increased thirst and lethargy), recurrent monilial infections, hypertriglyceridemia, and indications of CVD (hypertension) also are typical in patients with type 2 diabetes (see section on Type 2 Diabetes and Table 53-1).

Treatment Goals

Case 53-11, Question 2: What should the goals of therapy be for L.H. and other patients with type 2 diabetes? Which biochemical indices should be monitored?

The beginning of this chapter discussed general goals of therapy for all people with diabetes, which include eliminating acute symptoms of hyperglycemia, avoiding hypoglycemia, reducing CV risk factors, and preventing or slowing the progression of both microvascular and macrovascular diabetic complications. The ADA recommends that otherwise healthy patients with type 2 diabetes strive to achieve the same biochemical goals as those recommended for people with type 1 diabetes (Tables 53-4 and 53-5).[62] When determining treatment goals for L.H. and others with type 2 diabetes, the same individual characteristics should be considered as for type 1 diabetes, such as the patient's capacity to understand and carry out the treatment regimen and the patient's risk for severe hypoglycemia. Given the data from the ACCORD, ADVANCE, and VADT trials, patients with type 2 diabetes and CVD or multiple CVD risk factors should be carefully assessed when determining their glycemic goals. For example, less aggressive A_{1c} goals should be considered for patients with advanced age (and short life

expectancy), longer duration of diabetes (>10 years), advanced microvascular complications, comorbid conditions such as significant cerebrovascular or coronary artery disease (because of the serious consequences related to hypoglycemia) or patients with long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple antihyperglycemic agents including insulin.[39,47,300] Therefore, glycemic goals for patients with type 2 diabetes must be individualized. Emphasis should be placed on assessment of *all* CV risk factors, including hypertension, tobacco use, dyslipidemia, and family history.

As presented earlier in the section on Relationship of Glycemic Control to Microvascular and Macrovascular Disease, the UKPDS was a landmark study in patients with type 2 diabetes that conclusively demonstrated that improved BG control reduces the risk of developing retinopathy, nephropathy, and, potentially, neuropathy.[37] The 10-year follow-up study demonstrated that these outcomes persist even though the conventional group achieved similar glycemic control with time; an overall relative risk reduction in microvascular complications (24%) in the sulfonylurea- or insulin-treated group compared with patients who initially received conventional therapy was seen.[301–303] The exciting finding was that reductions in macrovascular complications emerged with time, with significant reductions in MI (15%) and death of any cause (13%) in patients initially intensively treated with sulfonylurea or insulin. Metformin appeared to be of particular benefit, with even greater reductions in MI and death of any cause (33% and 27%, respectively).

An additional finding of the UKPDS was that aggressive control of BP also significantly reduced microvascular complications, stroke, diabetes-related deaths, HF, and vision loss; during the 10-year follow-up study, these benefits diminished with time as the BP difference between the two groups was lost (ie, BP increased in the tight control group and decreased in the conventional group).[5] These findings emphasize the significance of maintaining BP control to reduce the risk of long-term complications.

Because L.H. is relatively young and has no symptoms of microvascular disease or neuropathy, every effort should be made to normalize her glucose concentrations to prevent these complications from occurring. Furthermore, a lipid panel should be ordered, and steps should be taken to achieve normal LDL-C, HDL-C, and triglyceride levels. Regardless of her current LDL level, L.H. should be initiated on at least a moderate-intensity statin therapy for CV risk reduction based on her age (between 40 and 75 years old).[5] A high-intensity statin would alternatively be recommended in patients considered to be at a higher CV risk (patients with multiple ASCVD risk factors or age 50–70 years) regardless of initial LDL cholesterol levels.[26] Often, triglyceride levels improve as BG concentrations decline and the metabolic response to insulin improves. (Management of dyslipidemia is addressed more fully later in this chapter.)

Biochemical indices that should be followed to monitor L.H.'s response to therapy include fasting, postprandial, and preprandial BG concentrations; A_{1c} values; and fasting triglyceride levels, as well as LDL-C and HDL-C concentrations. Based on ADA guidelines, initial metabolic goals for L.H. should be an A_{1c} value of <7%, an FPG of 80 to 130 mg/dL, and postprandial glucose concentrations <180 mg/dL.[26]

Treatment

LIFESTYLE INTERVENTIONS AND INITIAL THERAPY WITH METFORMIN

CASE 53-11, QUESTION 3: How should L.H. be managed initially?

Initial therapy for type 2 diabetes is aimed at lifestyle changes that will minimize insulin resistance and risk of CVD. In L.H.'s case and in the case of other overweight (BMI, 25.0–29.9 kg/m^2) or obese (BMI ≥30.0 kg/m^2) individuals with type 2 diabetes, this includes a lower calorie, low-fat, low-cholesterol diet; regular exercise; smoking

cessation (see Chapter 91, Tobacco Use and Dependence); and aggressive management of dyslipidemia and hypertension. Because central obesity is associated with increased insulin resistance, L.H. should be strongly encouraged to decrease her caloric intake, start exercising, and lose weight. Simple changes in her diet (such as cutting out juice and regular soda) and physical activity level can have a large impact on her glucose control. SMBG monitoring should be encouraged, and education that addresses the serious nature of DM and its long-term consequences also should begin. This is discussed in the previous sections on Medical Nutrition Therapy and Physical Activity, under Treatment (see also Table 53-14).

Initial pharmacologic therapy with metformin

The ADA recommends that most patients diagnosed with type 2 diabetes begin therapy with lifestyle modifications, including those mentioned earlier. In addition, most patients should begin monotherapy with metformin upon diagnosis. If metformin is contraindicated or poorly tolerated, an alternative agent approved for monotherapy may be used.[300] In the case that L.H. could not tolerate metformin, it may be beneficial to select an SGLT-2 inhibitor or a GLP-1 agonist to help reduce A_{1c} and help with comorbidities such as obesity. The selection of alternative agents is discussed later in this chapter. Although the UKPDS demonstrated that intensive therapy with sulfonylureas, metformin, and insulin reduces glucose with equal effectiveness (TZDs, DPP-IV inhibitors, SGLT-2 inhibitors, and GLP-1 agonists were not studied), metformin is favored as a first-choice agent in type 2 diabetes, particularly in overweight patients. This is because metformin lowers BG by decreasing hepatic glucose output and insulin resistance (indirectly) without causing weight gain or hypoglycemia. Metformin also has beneficial effects on plasma lipid concentrations, as well owing to a reduction in LDL and fatty acids.[37]

Another reason for metformin being a first choice for initial therapy is not only its proven benefit to reduce risk of microvascular complications but also macrovascular disease and mortality.[298]

Furthermore, in an observational study of patients with type 2 diabetes, and established coronary artery disease, cerebrovascular disease, or peripheral arterial disease, metformin use was associated with a significant reduction in all-cause mortality (22%) after only 2 years of follow-up.[304] Metformin is also emerging as a therapy that may reduce cancer risk, possibly attributable to its activation of AMPK, which can suppress tumor formation. Data so far have been in animal models and observational studies in humans.[305]

A drawback to immediate-release metformin is that it requires multiple daily dosing, and its dose also must be titrated to minimize GI effects. After the dose is established, it is possible to use a long-acting product that can be dosed once daily. Alternatively, ER metformin may be initiated at a dose of 500 mg daily and titrated upward as tolerated. The ER formulation may be preferred in many patients owing to the overall decreased risk of GI adverse effects associated with this formulation. One study revealed that any GI ADR was decreased by ~15% and diarrhea was reduced by ~10% after switching to ER formulation.[306] Renal function tests should be evaluated before the drug is initiated. L.H. does not have any contraindications (renal or hepatic dysfunction, cardiorespiratory disease, or binge alcohol use) to the use of metformin that could predispose her to its most significant side effect, lactic acidosis (see Case 53-16, Question 2). Because L.H. exhibits the typical features of insulin resistance syndrome and has no contraindications for its use, she should be started on metformin. For the purposes of this case, the ADA guidelines will be followed. However, it is important to note that the AACE guidelines suggest a more aggressive A_{1c} goal (<6.5%), and because L.H.'s current A_{1c} is between 7.5 and 9.0%, her case would merit dual therapy to delay progression disease (AACE). One trial found that dual therapy with metformin and DPP-IV inhibitor extended the time to treatment failure and therapy intensification.[307] Her A_{1c} goal, per the ADA guidelines, of <7% will require an additional 1.3% lowering in her A_{1c}, which can likely be achieved with metformin. However, any changes in her lifestyle will

further help lower her A_{1c}. L.H. should be instructed to initiate metformin at a dose of 500 mg twice daily with food.

Titrating metformin doses

Case 53-11, Question 4: L.H. is started on metformin 500 mg bid with food and instructed to increase her dosage to 500 mg every morning and 1000 mg every evening after 1 week. Three days after starting metformin, she phones the clinic reporting nausea and diarrhea. She admits to taking her doses on an empty stomach. How should L.H.'s symptoms be addressed?

GI disturbances such as diarrhea, bloating, anorexia, abdominal discomfort, nausea, and metallic taste often dissipate with time, and can be minimized by initiating metformin in a single 500- or 850-mg dose at breakfast or with the patient's largest meal of the day. Consistently taking metformin with food significantly minimizes the GI side effects. The dosage should be slowly increased (eg, 500 mg/day every 2 weeks) until the appropriate clinical effect is achieved or the patient is taking the maximal dose (1000 mg bid or 850 mg tid). Therefore, L.H.'s metformin dose should be reduced to 500 mg daily with her largest meal, and she should be titrated more slowly during a period of several weeks. Metformin is typically dosed two to three times daily (the long-acting formulation is dosed once daily with dinner). Twice-daily dosing for adherence purposes is preferred if a patient can tolerate a 1000-mg dose or once daily with the ER formulation. If she continues to experience GI symptoms, an alternative approach is to switch her to the ER formulation; small studies have demonstrated improved tolerability with the ER tablets versus the immediate-release dosage form.[308] A drawback to these tablets is their large size. Also, patients may report that metformin has a fishy odor,[309] which seems to be more apparent with certain generic formulations. If this is significant enough to cause a patient to stop taking it, the ER formulation can be tried, which may be more tolerable. One generic company offers blackberry-scented

metformin, which may also be a beneficial option if odor is an issue for patients.[310]

Monitoring metformin therapy

Case 53-11, Question 5: How should metformin therapy be monitored in L.H.?

As is standard with other agents, L.H. should be encouraged to perform SMBG (see Case 53-11, Question 6) and have an A_{1c} test drawn quarterly until she achieves consistent values <7%. Additional evidence of the therapeutic benefits of metformin may include an improved lipid profile and some weight loss. Initially, it is important to monitor GI problems, and although lactic acidosis is unlikely, L.H. should be warned to bring to the attention of her physician any sudden symptoms of shortness of breath, weakness, and malaise. A baseline SCr, eGFR, LFTs, and complete blood count should be obtained for L.H. and repeated yearly. Metformin can reduce vitamin B_{12} absorption, and it is associated with reductions in vitamin B_{12} levels (19% after 4 years of use in one study) and actual deficiency.[311,312] Therefore, monitoring of vitamin B_{12} levels every 2 to 3 years should be considered with long-term use.

SELF-MONITORING OF BLOOD GLUCOSE IN TYPE 2 DIABETES

Case 53-11, Question 6: L.H. is interested in learning how to perform BG testing. What are the advantages and disadvantages of SMBG tests? When and how often should L.H. be instructed to test her BG concentrations?

SMBG is an important self-management tool for patients such as L.H. to assess the efficacy of therapy and guide adjustments in nutrition, exercise, and medications. Disadvantages include cost of testing, inadequate understanding by both health care providers and patients regarding the benefits and proper use of SMBG results,

patient psychological and minor physical discomfort associated with obtaining a blood sample, and the inconvenience of testing. However, with the current advances in meter technology and proper patient education, most of these potential barriers can be overcome.

The ADA states that SMBG may be a useful guide for patients with type 2 diabetes treated with MNT or noninsulin therapies, although there is insufficient evidence to determine optimal frequency of testing and demonstrate cost-effectiveness for these patients. Although one meta-analysis of SMBG effects in patients with type 2 diabetes not on insulin concluded the overall effect on A_{1c} was a 0.4% reduction, others failed to show a benefit.[312] SMBG studies in patients with type 2 diabetes are often limited in that multiple interventions, such as education, diet, and medication adjustments, were used. However, a primary reason studies fail to show a benefit is that patients are not taught what to do with their BG numbers (ie, how to respond to a low BG reading); the BG values are solely used by the providers to make adjustments to their therapy.[313]

SMBG should be considered for most patients with type 2 diabetes, particularly those who are learning to adjust their carbohydrate intake and portion sizes and want to measure how well medications and lifestyle changes are working to improve their glucose control. Although not always cost-effective, testing four times daily before meals and at bedtime for 1 week is useful, so that the patient can observe his/her glucose profiles and determine the effect various types of food and physical activity can have on BG levels. Later, once the desired A_{1c} has been achieved, BG can be tested less frequently. Testing times should vary throughout the day so that fasting, postprandial, and bedtime values can be assessed. As emphasized by the ADA, intensive patient education regarding testing technique and interpretation are vital to the cost-effective use of this monitoring tool. The patient must learn how to respond to his/her glucose profile and institute lifestyle changes that can have a favorable effect.

Clinical Use of Antidiabetic Agents

CASE 53-11, QUESTION 7: L.H. was quite motivated to improve her glucose control because her grandmother "lost a leg" to diabetes and her aunt is undergoing dialysis because "her kidneys have failed." She is taking metformin 1000 mg PO bid and tolerating it reasonably well (she occasionally gets some stomach discomfort, but states she is fine with it). She is proud that she remembers to take the metformin every day as instructed. She met with a dietitian who suggested an 1800-calorie diet and 45-minute walks three times weekly. After 3 months, L.H. lost 6 pounds (2.72 kg). L.H. stopped drinking regular sodas and juices, but eats bread or two large tortillas at each meal. She admits to eating only small amounts of "greens" and vegetables. She has not been able to implement her walks three times weekly; more often, she only walks once a week. Although her FPG fell to 130 mg/dL, a majority of her postprandial BG levels were >180 mg/dL. Her A_{1c} is 7.4%, and fasting triglyceride levels are now 260 mg/dL. How should her therapy be adjusted? What factors should be considered when deciding on the next steps for pharmacologic therapy?

L.H.'s A_{1c} has improved by 0.9%. However, she has not fully instituted lifestyle interventions. Although she has cut out juices and regular sodas, she can still further improve her diet and lower her postprandial BG (to <180 mg/dL) by reducing her carbohydrate intake, switching to whole-grain breads, and increasing her vegetable intake. She also can increase her physical activity to at least three times weekly. Although the A_{1c} is not <7%, a reasonable approach would be to continue metformin at 1000 mg PO bid and reinforce lifestyle changes at this point before modifying her pharmacologic therapy.

The amount of A_{1c} lowering in response to adding an antidiabetic agent appears to depend on the baseline glycemic level. A meta-regression analysis of 61 clinical trials evaluated the efficacy of five classes of oral agents (sulfonylureas, glinides, metformin, TZDs, and α-glucosidase inhibitors).[314] Significant correlations were found between the baseline A_{1c} and FPG, and their mean decreases as a result of these agents. Greater reductions in A_{1c} and FPG were observed in groups with higher baseline levels. In addition, a meta-analysis of oral agents found that every 1% higher baseline A_{1c} level predicted a 0.5% greater reduction in the A_{1c} after 6 months of

therapy.[314] Overall, on initiation of noninsulin monotherapy, the A_{1c} will typically lower by ~1% to 1.25%.[315] One meta-analysis revealed that, on average, A_{1c} was lowered an additional (approximately) 1.2% in patients on long-acting GLP-1 agonists, 1.0% in patients on short-acting GLP-1 agonists, and 0.8% in patients on DPP-IV inhibitors[316] when combined with metformin. Another meta-analysis indicated that after 52 weeks in combination with metformin, SGLT-2 inhibitors may help lower A_{1c} an additional 0.11%.

If L.H. is not able to reach an A_{1c} of <7% with lifestyle interventions, the next step for her would be to add a second antidiabetic agent. Selecting an antidiabetic agent to treat type 2 diabetes has become more complex because new agents with unique mechanisms of action have been introduced into the market. Several considerations should be taken into account when choosing initial oral therapy for patients with type 2 diabetes. As with all therapeutic decisions, clinicians should also blend their knowledge of the drug (eg, its efficacy, safety, hypoglycemic risk, weight gain, other side effects, route of administration, and cost/hospital formulary) with the unique characteristics of the patient (eg, level of glycemic control, organ function, other concurrent diseases and medications, ability to adhere to complex medication regimens, and health insurance coverage) when making a choice of drug products.[42] The current A_{1c} level and reduction required to reach the A_{1c} goal is a key consideration.

Table 53-25 compares and contrasts the efficacy, advantages, and disadvantages of antidiabetic agents used to treat patients with type 2 diabetes, and can be used to help select drugs for a specific patient. The ADA guidelines provide recommendations on subsequent medications (after metformin) to select based on patient comorbidities, socioeconomic barriers, and other complications.

The AACE guidelines recommend consideration of initiating insulin therapy (most often basal insulin) if the A_{1c} is >9% with symptoms of hyperglycemia.[26] The ADA guidelines recommend choosing based on patient's level of hyperglycemia and if they are symptomatic.[62,64] It

is an option for dual therapy in all patients, especially if A_{1c} >9%, but should be strongly considered with an A_{1c} >10%.[63,306] Practitioners should attempt to avoid unnecessarily complex therapy that may confuse the patient, increase drug costs, and complicate the clinician's ability to assess each medication's contribution to the overall therapeutic outcome.

The ADA recommends initial therapy with lifestyle changes and metformin monotherapy. Early combination therapy can be used in some patients at treatment initiation to extend the time to treatment failure.[26] If the patient cannot tolerate metformin, other agents recommended for diabetes management may be used. These agents include sulfonylureas, TZDs, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and insulin. Selection of appropriate agents is discussed later in this chapter. If after 3 months of monotherapy the patient has not achieved their glycemic targets, a second agent may be added. If the patient still has not achieved their glycemic targets after 3 months of dual therapy, a third agent may be added. If glycemic targets still have not been reached after 3 months of triple therapy, different drug classes should be tried and a basal-bolus insulin approach may be considered.[26]

SELECTING AN ALTERNATIVE TO METFORMIN AS MONOTHERAPY

CASE 53-11, QUESTION 8: Which other antidiabetic agents could be considered for L.H. as monotherapy if she cannot tolerate metformin therapy?

Although the ADA recommends the use of metformin, in combination with lifestyle modification, as first-line therapy, other antidiabetic agents are approved for use as monotherapy as well. L.H. is a typical overweight patient with type 2 diabetes with early evidence of CVD (hypertension), but with no evidence of microvascular complications. Her liver, renal, and GI functions are normal. Patients such as L.H. have varying degrees of β-cell dysfunction and tissue resistance to insulin. In these individuals,

pulsatile insulin secretion and first-phase insulin release are absent, and the pancreas is “blind” or unresponsive to high glucose concentrations (glucotoxicity). Because target tissues are less responsive to insulin, hepatic glucose output typically is increased, and higher concentrations of insulin may be needed for peripheral glucose utilization. Insulin causes more weight gain and hypoglycemia than do the other antidiabetic agents, and is usually reserved for combination therapy unless the initial A_{1c} at diagnosis is very elevated (>10%) or ketonuria is present.[317]

Often, acarbose is eliminated from consideration because slow titration is required to minimize GI effects; anecdotally, however, people of Mexican American origin, such as L.H., seem less susceptible to flatulence and diarrhea. Also, because acarbose has less dramatic effects on the FPG (20–30 mg/dL decrease) and A_{1c} (0.5%–1.0% decrease) than have the other agents, biochemical goals are less likely to be achieved in patients whose A_{1c} is 8.5% or higher.

Pioglitazone also can be used as monotherapy, and, similar to metformin, will not cause hypoglycemia, but weight gain and edema are likely. On the positive side, the TZDs have been shown to have better “glycemic durability” compared with metformin and the sulfonylureas. In a double-blind, randomized, controlled trial of 4360 patients with type 2 diabetes, time to monotherapy failure, defined as FPG >180 mg/dL, was assessed for rosiglitazone, metformin, and glyburide (A Diabetes Outcome Progression Trial [ADOPT]).[318] Patients were treated for a median of 4 years. The Kaplan–Meier analysis showed that the cumulative incidence of failure at 5 years was 15% for rosiglitazone, 21% for metformin, and 34% for glyburide ($P < .0001$). The suggested explanation for the favorable rosiglitazone results was that it slowed the rate of β-cell function decline. On the negative side, TZDs are associated with many adverse effects, including an increased risk in bone fractures and HF.[213,215] TZDs are associated with an approximately twofold increased risk of HF and thus are contraindicated in NYHA classes III to IV HF.[317] In the long-term ADOPT trial, rosiglitazone was

associated with a mean weight gain of 10.58 pounds (4.8 kg), whereas weight decreased by 6.39 pounds (2.9 kg) in the metformin group; glyburide-treated patients had a mean weight gain of 3.53 pounds (1.6 kg) during the first year, and then remained stable.[26,42] The TZDs also have been found to reduce bone density and increase fracture risk. Given the adverse effects associated with TZDs, and the availability of other agents, their use has fallen out of favor.

Sitagliptin, saxagliptin, and exenatide, which are approved for monotherapy, are often reserved for combination therapy. However, DPP-4 inhibitors may be useful as monotherapy for patients in whom the use of other oral agents is precluded (such as renal dysfunction with metformin or severe HF with pioglitazone). Of note, saxagliptin and alogliptin are not recommended in patients with HF. GLP-1RAs may be particularly useful in obese patients.[42] It should be noted that AACE recommends GLP-1RAs as first line if metformin cannot be used initially.[319,320]

For several years, sulfonylureas were used successfully to treat patients with type 2 diabetes. Although these agents lower A_{1c} significantly as monotherapy (~1%–1.5%), there are still several issues with this class of medications such as hypoglycemia, weight gain, diminished durability, and poor lipid profile. Although the use of these agents has fallen out of favor because of these effects, they are still often utilized when cost is a concern for a patient (Table 53-26).

Several products that combine two oral agents into one medication are available. Although many of these products are approved as first-line therapy, consider reserving them for use in patients who are already established on two agents or whose medication regimens must be simplified to enhance adherence or decrease cost. Based on this discussion, metformin is favored as initial therapy in L.H.

CASE 53-12

Question 1: N.H. is a 46-year-old, obese (BMI 33 kg/m^2) male with a history of type 2 diabetes, and hyperlipidemia. He presents with fatigue and nocturia. N.H.

used to smoke two packs of cigarettes per day for 15 years, but he quit after his diabetes diagnosis. He has a strong family history of CHD. At diagnosis 3 months ago, an elevated A_{1c} was documented (7.6%), confirming the diagnosis of type 2 diabetes. Test reports of liver and renal functions are within normal limits. Current medications include lisinopril and atorvastatin. N.H. started metformin, but stopped taking it because of GI symptoms (loose stools); he refuses to try this medication again.

What is a reasonable next monotherapy option for N.H.?

Unfortunately, N.H. did not tolerate metformin. Although this is less common if patients take metformin with food, the dose is titrated slowly or are switched to the ER formulation, some do not overcome the GI adverse effects. N.H. is refusing to even consider a retrial. An A_{1c} goal of <7% may be appropriate for N.H., although given his young age and long life expectancy, a target of <6.5% would be appropriate. Therefore, the A_{1c} lowering required to get to the goal is only 0.6% to 1.1%.

With a BMI of 33 kg/m^2, hypertension, and dyslipidemia, N.H. has many components of the metabolic syndrome and insulin resistance (see section on Pathogenesis). Sulfonylureas or insulin would not be an optimal next choice of drug for N.H. because they do not exert a favorable effect on plasma lipids and are generally associated with weight gain and hypoglycemia. Although the A_{1c} is elevated, it still does not merit insulin therapy. However, it must be acknowledged that some sulfonylureas remain the least expensive oral antidiabetic agents, and this may be an important factor in the initial selection of therapy for some patients. Acarbose as monotherapy is not likely to attain near-normal plasma glucose concentrations. Pioglitazone improves peripheral target tissue responses to insulin and lipid profiles; however, because N.H. is obese, it would be prudent to avoid pioglitazone because of weight gain (see Case 53-11, Question 8, and Case 53-15). A GLP-1 agonist, DPP-4 inhibitor, or an SGLT-2 inhibitor are reasonable options for N.H. because they are not associated with weight gain (GLP-1 agonists and SGLT-2 inhibitors may even promote weight loss).

DPP-IV inhibitors may be used in the case of N.H. if he is reluctant to inject; however, these agents usually are weight neutral and modestly decrease A_{1c}. Sitagliptin 100 mg may be started once daily to help achieve glycemic goals and to avoid hypoglycemia. Another oral option may include an SGLT-2 inhibitor, such as empagliflozin 25 mg daily, which has weight loss benefit, renal and CV protection, and a low risk of hypoglycemia.

For N.H., initiation of a GLP-1RA, such as liraglutide, may be the most beneficial option for weight loss. A GLP-1RA, along with lifestyle changes, can help N.H. achieve the A_{1c} goal and would be a good option for N.H. if he is willing to use an injectable medication. If liraglutide is used, it should be initiated at a dose of 0.6 mg once daily for 1 week and then increased to the therapeutic dose of 1.2 mg once daily thereafter. Some patients may require further titration to 1.8 mg once daily to reach their glycemic goals. N.H. should be counseled about the likelihood of GI side effects, which should subside over time, as well as the rare risk of pancreatitis (and to stop taking and notify his provider if he has persistent severe abdominal pain that may radiate to the back and vomiting) and severe allergic reactions. Once-weekly GLP-1RAs, such as semaglutide, dulaglutide, and exenatide ER, would also be appropriate options and potentially improve adherence (see section on GLP-1RAs for specific dosing recommendations). Before choosing a specific GLP to be initiated in any patient, one must consider patient preference in terms of cost and dosing.

N.H. was successful in reducing his A_{1c} to 6.4% through a combination of lifestyle modifications and liraglutide. He was able to lose 10 pounds (4.54 kg) with walking and reduction in fatty food.

N.H. quit smoking 3 months ago. Smoking has been shown to increase the risk of IFG and type 2 diabetes.[321] The mechanism for this is thought to be related to increased insulin resistance and oxidative stress and reduced insulin secretion. Smoking also increases the risk of microvascular and macrovascular disease in people with diabetes.[322] Therefore, N.H. should be congratulated on his cessation, and continued abstinence should be encouraged

through follow-up visits (see Chapter 91, Tobacco Use and Dependence). If needed, pharmacologic intervention for the treatment of smoking cessation could be recommended.

Failure of Antidiabetic Monotherapy

PATHOGENESIS

CASE 53-13

QUESTION 1: Q.R. is a 68-year-old, 61 inches (154.94 cm), 165-pound (74.84 kg; BMI, 31.2 kg/m^2) female with an 8-year history of type 2 diabetes who has been treated with diet, exercise, and metformin. According to clinic records, she was well controlled initially (A_{1c} 6.7%–7.2%) for the first 5 years. When her glycemic control worsened (FPG, 130–160 mg/dL; A_{1c}, 7.5%–8.5%), her metformin dose was increased from an initial dose of 500 mg bid to her current dose of 1000 mg bid. Recent chart notes indicate that Q.R.'s chief complaints have included loss of appetite and fatigue. Her current A_{1c} is 8.4%. Other medical problems include hypertension managed with hydrochlorothiazide 25 mg daily and mild peripheral neuropathy managed with acetaminophen 500 mg bid. Her eGFR is 70 mL/minute.

At this clinic visit, Q.R., who is well known to you, seems particularly listless and flat in her affect. Her BG records, which are typically meticulous, are incomplete. Morning fasting BG values consistently exceed 200 mg/dL and range from 202 to 340 mg/dL. While taking her history, you discover that her husband passed away last year and that one of her adult children has recently been diagnosed with a terminal illness.

What factors may be contributing to Q.R.'s poor glucose control?

Several factors may be contributing to Q.R.'s deteriorating BG control and apparent lack of responsiveness to maximal dose of metformin during the past year (as evidenced by her elevated BG and A_{1c}, listlessness, and lack of appetite). Monotherapy failure (also called secondary failure) is characterized by progressively poor glucose control that occurs after a period of good response (months to years). The cause of failure may be related to progressive pancreatic failure; poor adherence to diet, exercise, or medications; and exogenous diabetogenic factors such as increased weight,

illness, or drugs that induce hyperglycemia (eg, atypical antipsychotics or glucocorticoids).

Type 2 diabetes is a progressive condition, which is most likely to require combination drug therapy. The UKPDS confirmed that monotherapy failure represents a natural progression of type 2 diabetes. In this study, only 16% and 19% of the subjects achieved an FPG <108 mg/dL and A_{1c} <7%, respectively, after 3 years of dietary therapy alone.[322] By 9 years, only 9% were able to maintain their glycemic goals using just diet therapy. The investigators also found monotherapy failure occurred at the same rate regardless of the initial treatment selected: glyburide, chlorpropamide, metformin, or insulin. In all the monotherapy treatment groups, patients required additional therapies over the course of the study duration.[317] At 3 years, fewer than 55% of patients randomly assigned to single-pharmacologic therapy could maintain an A_{1c} <7%, and by 9 years this dropped to about 25% of patients. In the ADOPT study, patients were able to maintain A_{1c} levels <7% using monotherapy for 60, 45, and 33 months with rosiglitazone, metformin, and glyburide, respectively.[323] The reason for glycemic deterioration is likely owing to the natural progression of type 2 diabetes in which β-cell function declines with increased duration of disease.

Q.R.'s deteriorating control on a therapeutic dose of metformin after 5 years of reasonable response is consistent with the natural progression of type 2 diabetes. However, the stress and depression arising from her life situation have no doubt contributed to her poor control. The latter may have led to a change in her usual adherence to diet, exercise, and medications, and should resolve with time and appropriate management. Females with type 2 diabetes are at increased risk for depression. Evidence exists for a bidirectional association between diabetes and depression in females.[324] Although hyperglycemia has been attributed to hydrochlorothiazide, the dose prescribed for Q.R. has few adverse metabolic effects.

MANAGING MONOTHERAPY FAILURE

Case 53-13, Question 2: How should Q.R. be managed? What is an appropriate antidiabetic agent to add?

Q.R. is exhibiting symptoms of depression (eg, listlessness and flat affect). Her depression likely started after her husband's death. Every effort must be made to address Q.R.'s depression because it is unlikely that she will be able to effectively implement more aggressive treatment of her diabetes until her situation is improved. Resources that may be used include her family, a therapist, and a social worker.

Treatment of monotherapy failure includes identifying and correcting any diabetogenic factors and altering her drug therapy. When failure to any oral agent occurs, one should always add another agent rather than switch to another, unless adverse effects are intolerable, or contraindications warrant the discontinuation of the drug. This is supported by a study that evaluated the effect of metformin alone in a population of patients who had failed oral sulfonylureas and the effect of metformin plus the sulfonylureas. Substitution of metformin for glyburide did not produce any significant change in glycemic control, but the addition of metformin to glyburide therapy substantially improved glucose concentrations.[325] Many combinations of antidiabetic agents can be used. The key is that they should have different mechanisms of action. For example, it is not reasonable to combine a sulfonylurea with a glinide (ie, repaglinide and nateglinide) because they are both insulin secretagogues. Options for Q.R. include adding one of the following to metformin (in no particular order): insulin secretagogue (sulfonylurea or glinide), acarbose, TZD (pioglitazone), DPP-4 inhibitor (sitagliptin, linagliptin, alogliptin, or saxagliptin), SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin), or a GLP-1 agonist (exenatide, exenatide ER, liraglutide, lixisenatide, dulaglutide, or semaglutide or semaglutide oral).

Table 53-25 summarizes the FDA-approved combination therapy indications. Insulin therapy may be considered at this time; however, because Q.R.'s A_{1c} can be lowered to <7% with an additional

noninsulin agent, two noninsulin antidiabetic agents should be utilized first. In addition, the ADA recommends that if an injectable agent is necessary for treatment, a GLP-1 agonist should be initiated first, before insulin. In summary, patients such as Q.R. who are unresponsive to the maximally effective dose of metformin should be initiated on combination, noninsulin therapy.

When agents from different antidiabetic classes are combined, their effects are additive. With the availability of many antidiabetic agents, there is no one best combination therapy for A_{1c} lowering. As discussed, the choice of therapy should take into account the patient's organ function, the amount of A_{1c} lowering required to reach an individual's goal, comorbidities (ie, HF, CKD, ASCVD), possible adverse effects of a particular drug or drug combination, cost, hypoglycemia risk, and patient preference.

A mixed-treatment comparison meta-analysis evaluated the efficacy of second-line antidiabetic therapy added to patients on stable doses of metformin.[256] The risk of weight gain and hypoglycemia was also determined. A total of 27 randomized controlled trials were included in the analysis, with a mean study duration of 32 weeks. The different agents had similar A1C reductions. TZDs, sulfonylurias, and glinides had more weight gain, and sulfonylureas had more hypoglycemia. In addition, the change in A_{1c} depending on the baseline level of A_{1c} was evaluated and found, as previously discussed (see Case 53-11, Question 7), to be greater when the baseline A_{1c} was ≥8%.

Q.R. is not opposed to injections, but would rather take oral medications to manage her diabetes. Because she is postmenopausal, avoid a TZD owing to the concerns of increased risk of fractures. Sulfonylureas are a cheaper option; however, it may contribute to weight gain. Given the significant GI side effects associated with the α-glucosidase inhibitors, their use is often avoided all together. The DPP-4 inhibitors may be an option; however, they may have only moderate A_{1c} lowering capacity. SGLT-2 inhibitors are an excellent option for this patient because they can help further reduce A_{1c} and help with Q.R.'s comorbidities (obesity).

Combination Antidiabetic Therapy

Case 53-13, Question 3: Q.R. is started on empagliflozin 25 mg/day and continued on metformin 1000 mg bid. This improved her FPG and A_{1c} modestly for ~12 months (FPG, 120–150 mg/dL; currently A_{1c}, 7.6%). She has heard about a new, injectable class of diabetes medications that cause weight loss. Is she a candidate for this new class of medication?

It quickly becomes apparent that Q.R. is referring to the GLP-1 agonists, (exenatide, exenatide ER, liraglutide, lixisenatide, dulaglutide, semaglutide, and semaglutide oral); only semaglutide is on her health plan's formulary. Q.R. states that she has no history of thyroid cancer or pancreatitis.

When the A_{1c} is above goal despite the use of a combination of two agents, practitioners often add a third agent before considering insulin. Although this is tempting, depending on a patient's current level of glycemic control, this practice only delays insulin therapy, which is likely to be required to achieve A_{1c} goals. However, because Q.R. is close to an A_{1c} level of <7%, it is reasonable to try a third, noninsulin antidiabetic agent.

Semaglutide has been studied as monotherapy and also in combination with metformin and basal insulin. These studies have indicated that semaglutide 0.5 or 1.0 mg once weekly in combination with metformin may help lower A_{1c} by 1.0% to 1.5% (Ozempic® powder inhaler [PI]). Thus, for Q.R., the addition of semaglutide could result in an A_{1c} of <7%. If Q.R. were on a sulfonylurea, there may be a heightened risk of hypoglycemia when used in combination with semaglutide. Therefore, if this combination is used, the dose of the sulfonylurea on initiation of semaglutide may need to be lowered to minimize the risk of hypoglycemia. Adjustments can be made based on the patient's glycemic response to liraglutide accordingly.

Q.R. should be started on semaglutide 0.25 mg SC once weekly for 4 weeks, independent of meals. After 4 weeks, Q.R. should increase the dose to 0.5 mg SC once weekly if tolerated. She can further increase the dose to 1.0 mg if further glycemic control is

needed. Q.R. should be counseled about nausea and diarrhea, which are the most frequent side effects. Her A_{1c} should be reevaluated after 3 months of being on at least the 0.5 mg dose. An advantage of semaglutide is the potential for weight loss and CV benefit. One multicentered, randomized controlled trial, compared semaglutide to placebo and showed a significant 26% reduction in time to first occurrence of death from CV causes, nonfatal MI, nonfatal stroke. In addition, mean body weight was found to be significantly decreased by 6.39 pounds (2.9 kg) and 10.80 pounds (4.9 kg) for the 0.5 and 1.0 mg semaglutide groups, respectively.[256]

Q.R. should be counseled about the rare risk of pancreatitis. Also, if she finds that nausea is significant enough to reduce her fluid intake, she should contact her provider. There have been postmarketing reports of altered renal function and renal failure with semaglutide, which are likely owing to dehydration from reduced fluid intake because of GI side effects (ie, nausea, vomiting, and diarrhea). Semaglutide was also found to increase the absolute risk of worsening diabetic retinopathy. Q.R. should have an annual ophthalmic examination.

A small proportion of patients will form anti-semaglutide antibodies. Antibody formation did not equate with reduced efficacy of liraglutide when examining mean A_{1c} levels between antibody-positive and antibody-negative patients. It is important to note that any of the available GLP-1RAs are options for Q.R. for initial GLP-1RA therapy. Discussions should be regarding adherence, efficacy, side effects, and cost.

Combination Antidiabetic With Insulin Therapy

Case 53-13, Question 4: If Q.R.'s therapy failed and she required insulin based on continuously elevated A_{1c} levels, why would it be reasonable to use insulin in combination with other antidiabetic agents? How should it be combined with other agents? Is this combination more effective than is insulin alone?

Most patients with type 2 diabetes eventually require insulin. The combined use of insulin with a variety of oral agents has been extensively evaluated, but the studies differ in their interventions. In some studies, single doses of an intermediate- or a long-acting insulin or once- or twice-daily doses of premixed insulin are added to a single or combination of oral antidiabetic agents in poorly controlled patients. The primary outcomes that have been evaluated include measures of glycemic control (eg, A_{1c}, FPG) and the extent to which insulin doses have been decreased. DeWitt and Hirsch published a comprehensive review of these studies, and readers are referred to this article for this evidence.[104] The combined use of insulin and oral agents can be considered based on the AACE algorithm, particularly when the A_{1c} is higher than ~9%.

Before starting insulin, it is important to review the BG profile:

- Fasting hyperglycemia, which may improve or persist throughout the day: This is the more typical glucose profile for patients with type 2 diabetes, in whom addition of basal insulin at nighttime would be the most appropriate next step.
- Fasting BG is at target, with daytime hyperglycemia: This is less common for people with type 2 diabetes, in whom addition of prandial insulin would be an appropriate next step for therapy (see Case 53-13, Question 5).

In Q.R.'s case, it makes the most sense to add a single dose of basal insulin to metformin, empagliflozin, and semaglutide. Advantages attributed to adding insulin to an oral agent as the next step after failure, as opposed to using insulin alone, include the following[104]:

- Lower insulin dosages can be used, and this minimizes weight gain and hypoglycemia.
- Simpler, single-dose insulin regimens are possible (vs monotherapy with insulin).
- Lowering the fasting glucose concentrations improves glucose control throughout the day because glucose excursions related to

meals are layered over lower values. Furthermore, lower glucose values improve β-cell responsiveness to glucose and enhance tissue responsiveness to insulin action.

However, lowering glucose concentrations is the first priority, not attempting to use lower insulin doses. Q.R. should be started on 10 units or 0.1 to 0.2 units/kg of NPH, or basal insulin glargine, detemir or degludec. This dose is based on empiric use of insulin in a variety of studies (0.1–0.2 units/kg)[326] and a conservative estimate for basal insulin of ~0.5 units/hour (Q.R. weighs 155 pounds [70.31 kg]). The dose also takes into account the possibility that Q.R. is secreting some basal insulin of her own. The basal dose should be titrated upward based on the FPG for 3 consecutive days. A common titration method used is the "treat-to-target" schedule.[103,327]

FPG (mg/dL)	Adjustment of Basal Insulin Dose (Units)
≥180	8
160–180	6
140–159	4
120–139	2
100–119	1
80–99	Maintain dose.
60–79	−2
<60	−4 or more

Alternatively, the basal insulin dose can be increased by 2 units every 3 days until the FPG is in a target range (80–130 mg/dL); if the FPG is >140 to 180 mg/dL, larger increments can be used (eg, by 4 units every 3 days).[326] If hypoglycemia occurs or the FPG is <80 mg/dL, the dose should be reduced by at least 4 units, or by 10% if the dose is >60 units. Of note, if U-300 glargine and U-100 and U-200 degludec are used, doses should not be titrated sooner than every 3 to 5 days. If there is no improvement in glycemic control after 3 months, prandial insulin or a GLP-1RA (if not already being used) should be added to the patient's regimen (see Case 53-13,

Questions 5 and 6). In the setting of insulin resistance, such as with type 2 diabetes, continuing metformin therapy should be a priority if possible.

Overbasalization may occur with basal insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose >~0.5 units/kg, high bedtime–morning or postprandial–preprandial glucose differential (eg, bedtime–morning glucose differential ≥50 mg/dL), hypoglycemia (aware or unaware), and high variability in BG measurements.[62,328]

Insulin Monotherapy in Patients With Type 2 Diabetes

INSULIN REGIMENS

Case 53-13, Question 5: Q.R. was initiated on insulin glargine and titrated to 25 units at bedtime. In combination with empagliflozin 25 mg/day, semaglutide 1.0 mg once weekly, and metformin 1000 mg bid, her fasting glucose levels fell to the 110s and 120s on most occasions; her A_{1c} dropped to as low as 6.9%. However, after 1 year, she began to note a gradual rise in glucose concentrations throughout the day. This resulted in a further increase in her bedtime insulin glargine to 40 units (0.57 units/kg). Currently, her morning BG levels are 120 to 140 mg/dL, and BG levels before or after meals range between 170 and 200 mg/dL. A recent A_{1c} value was 8.5%. For the past 6 months, Q.R. has noted increasing fatigue, bouts of blurred vision, and polyuria. How should she be managed now?

The next step in managing Q.R.'s diabetes is to institute prandial insulin therapy, which is needed as indicated by her daytime hyperglycemia. Like patients with type 1 diabetes, those with long-standing type 2 disease may require prandial insulin before meals to minimize postprandial excursions. Insulin lispro has been shown to decrease postprandial glucose concentrations to a greater extent than has regular insulin (30% lower at 1 hour and 53% lower at 2 hours) and was associated with a lower rate of hypoglycemia, particularly between midnight and 6:00 AM (36%). However, A_{1c}

levels were not significantly different after 6 months.[329] A similar response with insulin aspart, glulisine, and lispro-aabc would be expected.

Because Q.R. is on insulin glargine, the most appropriate next step is to add prandial insulin using a rapid-acting insulin. Initiation of basal-bolus insulin regimens are discussed in detail in the section on Type 1 Diabetes Insulin Therapy (see Case 53-2, Questions 4–6). An easy way to introduce prandial insulin is to initially add only one mealtime dose. The premeal BG levels that are associated with the most hyperglycemia are targeted. For example, if the prelunch BG levels are elevated, a prandial dose at breakfast is added; or if the bedtime BG levels are mainly elevated (owing to large dinners), a prandial dose at dinner is added. Once a patient adjusts to this, prandial insulin is added to the other meals. Patients with type 2 diabetes may require large insulin TDDs (>1 unit/kg) to reach A_{1c} targets <7%. Although not technically insulin monotherapy, metformin, empagliflozin, and semaglutide can be continued to assist in reducing insulin resistance and minimizing weight gain with insulin.

PREMIXED INSULINS

CASE 53-13, QUESTION 6: Q.R. has difficulty adhering to a basal-bolus insulin regimen. She is currently taking insulin glargine 38 units at nighttime and ~7 units of insulin aspart before each meal (she follows a high-sugar correction scale). What options are available for Q.R.?

Because people with type 2 diabetes retain some pancreatic function, it often is possible to achieve an acceptable level of control with twice-daily doses of intermediate-acting insulin in combination with rapid- or short-acting insulins, which are available as premixed insulins. These are referred to as *split-mixed insulin regimens*. Although convenient, they do limit flexibility in dosing, and thus A_{1c} lowering ability without increasing hypoglycemia risk. In the United States, fixed mixtures of NPH and regular insulin in a 70:30 ratio and

a 50:50 ratio are available (see Table 53-6). Commercial combinations of the rapid-acting insulins plus an intermediate-acting insulin also are available as Humalog® Mix 75/25™ (a mixture of insulin lispro plus lispro protamine suspension), Humalog® Mix 50/50™ (a mixture of insulin lispro plus lispro protamine suspension), and NovoLog® Mix 70/30™ (a mixture of insulin aspart plus aspart protamine suspension). These fixed mixtures are also available in prefilled syringes, which can add to their flexibility and convenience for administration.

The Treating to Target in Type 2 Diabetes (4-T) study assessed the efficacy of a basal insulin (detemir), prandial insulin (insulin aspart), and biphasic insulin (NovoLog® Mix 70/30™) regimen added to patients on metformin and a sulfonylurea.[330] After 3 years, a biphasic-based insulin regimen was found to be less effective in achieving an A_{1C} goal of <6.5% compared with prandial and basal insulin regimens (31.9%, 44.7%, and 43.2%, respectively). Despite the findings of this large multicenter study, use of twice-daily, premixed insulin remains a common insulin therapy for patients with type 2 diabetes.

Q.R. is currently receiving a TDD of insulin of 59 units, or 0.84 units/kg/day. To convert her to a premixed insulin, one could begin with a conservative TDD of 0.5 to 0.6 units/kg/day, split equally before breakfast and dinner. An older method of two-thirds in the morning and one-third in the evening is used less commonly now. When starting an insulin-naive patient with type 2 diabetes on premixed insulin, doses of 5 to 6 units twice daily (administered before breakfast and dinner) are often used, with the doses being titrated before breakfast (to affect prelunch and predinner glucose levels) and before dinner (to affect the bedtime and fasting glucose levels).[103,331]

If the premixed insulin does not achieve adequate glycemic control, an option is to mix the short- or rapid-acting insulin with NPH in the same syringe. By doing this, each insulin dose can be individually adjusted. A disadvantage to this is the chance for patients to make errors in measuring and mixing insulin, especially in

the elderly when they may have vision and/or dexterity issues. Alternatively, a prandial dose of rapid-acting insulin (ie, a third injection) can be added at lunch; the breakfast dose of premixed insulin should be decreased as well.[104] Another option is to add a third dose of the premixed insulin at lunch (so premix insulin tid); however, the lunchtime dose is smaller than are the breakfast and dinner doses. An initial premixed insulin lunchtime dose of 2 to 6 units, or 10% of the current TDD of premixed insulin, can be started.[332]

Q.R. should be started on a rapid-acting premixed insulin twice daily, because this has the convenience of being administered right before eating (within 15 minutes). A dose of 20 units SC bid represents a conservative starting dose. She should monitor her fasting and predinner BG levels, at a minimum, to further adjust her insulin doses.

Adding Antidiabetic Agents to a Basal Insulin Therapy–Based Regimen

CASE 53-14

Question 1: M.A., a 62-year-old female, has had type 2 diabetes for 11 years. She is currently taking metformin 1000 mg PO bid and insulin glargine 47 units at bedtime. Her A_{1c} is 8.2%. She tries to follow a meal plan that a dietitian developed for her, but her BMI remains 31 kg/m^2. Her physical activity is limited because of an arthritic knee, for which she plans to have knee replacement surgery in the future. Other medical problems include hypertension (hydrochlorothiazide 25 mg daily and benazepril 40 mg daily) and dyslipidemia (atorvastatin 40 mg daily), which are both well controlled.

Can any antidiabetic agents be added to her current therapy?

The TZDs have been well studied in patients with type 2 diabetes who are already taking insulin. In a meta-analysis, pioglitazone lowered A_{1c} by 0.58% when added to insulin therapy; unfortunately, it was associated with weight gain (6.61 pounds [3 kg]) and increased peripheral edema, and, therefore, should be avoided.[237]

A GLP-1 agonist would be a logical agent to consider adding for obese patients. Any GLP-1RA would be a good option. The agents should be chosen based on cost, effectiveness, and adherence. For example, exenatide may be the only GLP-1RA on formulary, or perhaps M.A. has trouble remembering to take once-weekly medications, such as dulaglutide, and as such would be more successful with once-daily liraglutide. Alternatively, an SGLT-2 inhibitor can be utilized because it also promotes weight loss. If additional glycemic control is needed after either is initiated, then the ADA guidelines support using the other agent.[62] Adding a DPP-4 inhibitor would be another option and would be weight neutral. Sitagliptin is FDA approved for use with insulin; however, the A_{1c} lowering may be less than that with a GLP-1 agonist.

Therefore, addition of liraglutide may be a reasonable approach in M.A. Her A_{1c} can reach her target goal of <7%, with potential for weight loss and lower insulin glargine requirements. Liraglutide should be initiated at a dose of 0.6 mg injected SC once daily for 1 week, after which the dose should be increased to 1.2 mg once daily. Some patients may require further titration to a maximum dose of 1.8 mg once daily to reach their glycemic targets. Another option would be to use a fixed ratio combination insulin/GLP-1RA such as liraglutide/degludec U-100, which provides a maximum daily degludec insulin dose of 50 units, and liraglutide 1.8 mg or lixisenatide/glargine U-100, which provides a maximum glargine insulin dose of 60 units and lixisenatide 20 µg.

Uses of Antidiabetic Agents in Special Situations

HYPOGLYCEMIA

CASE 53-15

QUESTION 1: C.A. is a 73-year-old female who has had a 20-year history of type 2 diabetes and a 5-year history of mild renal dysfunction (SCr, 1.2 mg/dL; eGFR, 47 mL/minute/1.73 m^2; BUN, 22 mg/dL). Her son, who lives with her, quickly called 9-1-1 when he noticed his mother appearing lethargic and sleepy,

with her eyes closed, as she was sitting on the couch. He assumed she was having a "low sugar reaction." When the paramedics arrived, her BG concentration was 46 mg/dL. C.A. was able to be aroused, and indicated she could drink something, so 4 ounces of orange juice was administered. After 10 minutes, her BG level was 80 mg/dL, so she was given another 4 ounces of juice. According to her son, C.A.'s diabetes has been well controlled for the past several months with glyburide 10 mg bid and metformin 850 mg tid. For the past 3 days, C.A. has been eating less and vomiting on association, with the "flu."

What was the likely cause of her hypoglycemic episode? Were there any predisposing factors?

C.A. is likely experiencing a hypoglycemic episode secondary to glyburide. Hypoglycemia is the most common and potentially severe adverse effect of the sulfonylureas, especially in the elderly population. The incidence and severity of this effect increase with the duration of action and potency of the agents.

Most sulfonylurea-induced hypoglycemia occurs in patients who are predisposed to hypoglycemia in some way, and C.A. is no exception. She is an elderly female with renal impairment who was on relatively high doses of an agent, a portion of which is excreted unchanged in the urine. Even in the face of decreased carbohydrate intake (reduced appetite and vomiting), she continued to take her usual dose of glyburide. Even though the stress of illness most often raises glucose levels, the decreased food intake resulted in glyburide causing hypoglycemia. Because glyburide has a long duration of action, hypoglycemia may last for several hours.

C.A. and her son should be educated about treatment of hypoglycemia. It is likely that her son did not need to call 9-1-1, and he could have treated the hypoglycemia. Glucagon (Glucagon emergency kit, GVOKE® or Baqsimi®) should not be used to treat hypoglycemia caused by a sulfonylurea, BECAUSE glucagon can cause a paradoxic fall in the glucose levels.[333]

RENAL DYSFUNCTION

CASE 53-15, QUESTION 2: C.A. has mild renal insufficiency (eGFR, 47 mL/minute/1.73 m^2 and is taking the maximal dose of metformin. How should

age and kidney function be taken into account with metformin use? Which agents should be avoided? Which agents could be used?

Sulfonylurea compounds that are metabolized to active products that depend on the kidney for elimination (eg, acetohexamide, chlorpropamide glyburide, and tolazamide) should be avoided in the elderly and in patients with decreased renal function. Sulfonylureas that are completely metabolized to inactive or weakly active products may be used (ie, glipizide, glimepiride, or tolbutamide). Although glyburide is unlikely to accumulate in patients with a CrCl >30 mL/minute, it should not be used in C.A. because it caused a severe hypoglycemic reaction.[334] C.A. should be instructed to eat regularly because skipped meals may result in recurrent hypoglycemia. Discontinuing the sulfonylurea and adding an agent with a lower incidence of hypoglycemia should be considered.

Although metformin rarely is associated with lactic acidosis, the manufacturer and the FDA have taken extreme measures to prevent its improper use because another biguanide, phenformin, which induced this life-threatening condition, was removed from the market in 1977.[335] The estimated rate of phenformin-induced lactic acidosis was 0.25 to 4 cases per 1000 users versus 5 to 9 cases per 100,000 users for metformin. A group of clinicians from the FDA summarized 47 confirmed cases of metformin-related lactic acidosis (lactate levels ≥5 mmol/L) that had been reported to the FDA between May 1995 and June 1996.[321] Unfortunately, the condition continues to be resistant to treatment; the mortality rate was 43%. Importantly, 43 of the 47 cases (91%) had concurrent conditions that predisposed them to lactic acidosis. These included cardiac disease (64%), decreased renal function (28%), and chronic pulmonary disease (6%). Several patients (17%) were older than age 80 years and may have had decreased renal function despite normal SCr concentrations. Interestingly, 38% of the patients had HF, and those who died were more likely to be under treatment with digoxin and furosemide. The mean daily dose of metformin was well within the therapeutic range and was not higher in the group that succumbed (1259 ± 648 mg in the group that died and 1349 ± 598 mg in the group that survived).

Metformin should be initiated with care in patients older than age 80 years because of the potential for a low GFR, even when SCr is normal.[190] Because C.A. has moderate renal dysfunction (GFR <60 mL/minute, but >40 mL/minute), her dose of metformin should be decreased to 500 mg bid to minimize the potential for accumulation.

The TZDs are primarily metabolized by the liver, and are not contraindicated in patients with mild renal failure. The use of pioglitazone, beginning with low doses, could be considered, as can acarbose, which is poorly absorbed from the GI tract. The DPP-4 inhibitors could also be used, but their doses may require adjustment depending on the degree of renal dysfunction (except for linagliptin).

SGLT-2 inhibitors can be beneficial in this patient population. C.A. has an eGFR of 47 mL/minute/1.73 m^2, and thus meets the renal cutoff for this class of medications. Empagliflozin, dapagliflozin, and canagliflozin all demonstrated reduction in CKD progression in CV outcome trials.[279,281,283] Dapagliflozin and canagliflozin were tested in separate trials, and were both found to significantly reduce the sustained decline of eGFR in patients with CKD.[282,284]

GLP-1 agonists are recommended in patients with CKD if SGLT-2 inhibitors are not tolerated. Exenatide can be used in patients with CrCl >30 mL/minute, and the dose does not need to be adjusted. Liraglutide should be used with caution in renal insufficiency, but does not require dose adjustment. No changes were seen in renal status, and no renal dose adjustments are necessary when using injectable dulaglutide, lixisenatide, semaglutide, or oral semaglutide. None of these agents cause hypoglycemia when used as monotherapy.

HEPATIC DYSFUNCTION

CASE 53-16

QUESTION 1: B.R., a 60-year-old male with cirrhosis of the liver, is found to have type 2 diabetes. Glipizide 10 mg/day is initiated.

How will B.R.'s liver function affect the disposition of glipizide and his response to this agent?

Most noninsulin antidiabetic agents should be avoided in patients with severe liver disease, and insulin therapy—either basal-bolus or mixed insulin regimens—is often the safest option. Because hepatic metabolism is the primary route of elimination for most sulfonylureas, including glipizide, patients with hepatic disease should be expected to have an exaggerated response to those drugs metabolized to fewer active products. Liver disease can be a separate predisposing factor for severe, prolonged hypoglycemia because glycogenolysis and gluconeogenesis are impaired; thus, sulfonylureas should be avoided in patients with cirrhosis. If they are used, shorter-acting agents are preferred, and small initial doses should be used. For B.R., glipizide could be initiated at a dose no greater than 2.5 mg/day and increased if needed by 2.5-mg increments at no less than weekly intervals. Other options are low doses of repaglinide (0.5 mg) or nateglinide (60 mg) with meals because they are very short acting. Other options for which severe liver disease is not a specific contraindication include GLP-1RAs, DPP-4 inhibitors, and SGLT-2 inhibitors, although generally these drug classes should be avoided in Child–Pugh class C staging.[336]

CASE 53-17

Question 1: J.M. is a frail, 82-year-old, unresponsive male who is brought to the emergency department. According to J.M.'s family, he has become increasingly confused, dizzy, and lethargic, with a recent weight loss of 10 pounds (4.54 kg). J.M. lives by himself and has been generally healthy, with the exception of mild-to-moderate chronic obstructive pulmonary disease and arthritis.

Fasting serum chemistry reveals the following:

Na, 128 mEq/L
Glucose, 798 mg/dL
Serum osmolality, 374 mOsm/L (normal, 280–295 mOsm/kg H_2O)
Blood pH, 7.5
HCO_3, 22

His serum testing returns a negative finding for ketones. On physical examination, J.M. has poor skin turgor and dry mucous membranes and is responsive only to deep pain. His BP is 90/60 mm Hg with a pulse of 96 beats/minute. He has rales at the left lower base of his lung, and a chest

radiograph confirms pneumonia. Despite aggressive fluid replacement, J.M.'s BG remains consistently >250 mg/dL and his A_{1c} is 11%. J.M. presents with very high glucose concentrations but has no history of DM.

What special factors contribute to a late and atypical presentation of diabetes in the elderly?

Diabetes in the Elderly

CLINICAL PRESENTATION

Diabetes in the elderly commonly is underdiagnosed and undertreated because it often presents atypically.[337,338] Classic symptoms associated with DM may be masked by other illnesses, entirely absent, or explained away by the normal aging process. For example, polyuria is minimized by higher renal thresholds for glucose, or it may be confounded by urinary incontinence or "prostate problems." Thirst is commonly blunted in elderly persons, increasing their risk of dehydration and electrolyte imbalance. Hunger can be altered by medications or depression. Fatigue often is discounted as "part of getting old," and weight loss, although sometimes profound, may be so gradual that it goes unnoticed for months to years. (See **Table 53-27** for a comparison of presenting symptoms for DM in elderly patients compared with younger patients.)

Table 53-27

Presentation of Diabetes Mellitus in Elderly Patients Compared With Younger Patients

Metabolic Abnormality	Symptoms in Young Patients	Symptoms in Elderly Patients
Serum osmolality	Polydipsia	Dehydration, confusion, delirium
Glucosuria	Polyuria	Incontinence
Catabolic state owing to insulin deficiency	Polyphagia	Weight loss, anorexia

HYPEROSMOLAR HYPERGLYCEMIC STATE

CASE 53-17, QUESTION 2: J.M. is diagnosed with hyperosmolar hyperglycemic state (HHS). Why are the elderly predisposed to this condition, and what signs and symptoms are consistent with this diagnosis?

HHS is a condition characterized by extremely elevated plasma glucose concentrations (>600 mg/mL) and high serum osmolality (>320 mOsm/L) without ketoacidosis. Because patients with type 2 diabetes have some residual insulin production, they are usually protected against excessive lipolysis and ketone production. Patients with type 2 diabetes may exhibit HHS in later stages of diabetes as loss of β cells becomes advanced and residual insulin production continues to drop.[185] Measurements of serum ketones and blood pH differentiate this condition from DKA (see Case 53-10). The condition occurs when urinary fluid and electrolyte losses secondary to glucosuria are inadequately replaced by oral fluid intake.[185]

HHS primarily occurs in the elderly because several factors predispose this population to hypodipsia. These include an inability to recognize thirst,[339] an inability to ask for fluids (eg, dementia, sedation, and intubation), and an inability to get fluids on demand (eg, physical disabilities or restraints). Infections or other acute illnesses (eg, MI, GI bleeding, or pancreatitis) that exacerbate diabetes can interact with the hyperosmolar diuresis and hypodipsia to produce severe dehydration and hyperglycemia. Drugs that increase plasma glucose concentrations (eg, glucocorticoids), increase diuresis, or decrease mentation also can contribute to this unfortunate situation.

J.M. presents with several symptoms of HHS dehydration, including osmolality >320 mOsm/L, plasma glucose >600 mg/dL, pH >7.3, elevated bicarbonate, decreased skin turgor, hypotension, and the absence of serum ketones. His pneumonia was probably the precipitating factor. Treatment involves rapid IV hydration. Fluid replacement is provided in the same manner as with DKA. See Case 53-10, Question 2, and Table 53-24 for details.[185] Insulin infusion is

given simultaneously. The initiation and rate adjustments are the same as with DKA, except that the plasma glucose cutoff to reduce the insulin infusion rate is 300 mg/dL (not 200 mg/dL as with DKA; see Case 53-10, Question 3, and Table 53-24 for details). Rehydration and insulin administration corrected J.M.'s metabolic imbalance, allowing his diabetes control to be addressed.

GOALS OF THERAPY

Case 53-17, Question 3: What are the goals of therapy for J.M.?

It is widely recognized that strict glycemic control is associated with an increased incidence of hypoglycemia.[33] In the elderly patient with age-related autonomic dysfunction and CVD, hypoglycemia may present without the usual premonitory symptoms and can result in severe adverse effects such as angina, seizures, stroke, or MI. Therefore, the general tendency when treating elderly patients with diabetes is to aim for slightly less aggressive glycemic goals. Thus, an FBG target of between 90 and 150 mg/dL with bedtime glucose values between 100 and 180 mg/dL and an A_{1c} goal of close to 8%, while avoiding hypoglycemia, is appropriate in this frail patient.[340]

DIET AND EXERCISE

Nutrition

Case 53-17, Question 4: How should diet and exercise recommendations be modified for elderly patients with diabetes such as J.M.?

The ADA recommends individualized MNT for all patients with DM. The Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean diets have been shown to be effective for glycemic control and lowering CVD risk.[54,56,57]

Because most elderly patients have type 2 diabetes, nutrition and exercise programs are the initial steps in therapy. Older people with

diabetes, especially those in a long-term care facility, have a tendency to be underweight rather than overweight.[54,56,57] Therefore, caution should be used when considering a weight loss diet because this could cause malnutrition or dehydration. For obese individuals, a modest weight loss of 5% to 7% may be indicated.[340] However, an involuntary weight gain or loss of >10 pounds (4.54 kg) or 10% of body weight in <6 months should be carefully assessed.[54,56,57]

Several factors can adversely affect proper nutrition in the elderly. They include an impaired ability to shop for and prepare food, limited finances, an age-related decline in taste perceptions, and coexisting illnesses. Ill-fitting dentures, difficulty in chewing and swallowing, and lack of companionship during meals also can contribute to malnutrition as well.

High-fiber diets may lower BG and improve plasma lipids. However, high-fiber diets in frail, elderly patients, particularly those who are bedridden, should be used cautiously because they can be constipating and result in fecal impaction. Ambulatory patients, on the other hand, generally benefit from increased dietary fiber. Because many elderly patients are malnourished, a daily multivitamin preparation containing the recommended daily allowance of each vitamin should be prescribed.[54,56,57]

Exercise

Exercise in the elderly provides all the benefits derived by younger individuals. It increases well-being and glucose stability and may decrease propensity for falls. Exercise also improves BP, lipid profile, hypercoagulability, and bone density. Physical activity is necessary to minimize any lean body mass loss that can occur with caloric restriction. For patients with arthritis, aquatic exercise may be substituted. Before such an exercise program is initiated, careful evaluation is mandatory to avoid myocardial ischemia or the acceleration of retinopathy.

SELECTING AN ANTIDIABETIC AGENT IN THE ELDERLY

CASE 53-17, QUESTION 5: Why is it important to institute drug therapy to treat J.M.'s diabetes? What considerations should be made in selecting an initial treatment regimen?

As in all patients with DM, poor glycemic control increases the risk of long-term complications. Although it is tempting to minimize the importance of glycemic control because these complications take so long to develop, patients such as J.M. may have had unrecognized hyperglycemia for many years before clinical diagnosis. Thus, many have already begun to develop complications. Furthermore, as life expectancy increases, one can expect that these individuals will live long enough to experience morbidity related to diabetes if they are not treated. Therefore, pharmacologic treatment should be considered in J.M.

The general approach to treating an elderly patient with type 2 diabetes is basically the same as that described in Case 53-11, Questions 3, 7, and 8. The initial choice of an antidiabetic agent should be based on the severity of hyperglycemia. Other considerations include body weight, coexisting diseases, and cost of the agent. Patients with IFG (FPG >100, but <126 mg/dL) should be treated with diet and exercise tailored to their individual capabilities. For patients with type 2 diabetes, pioglitazone, SGLT-2 inhibitors, GLP-1 agonists, or DPP-4 inhibitors are all appropriate options as they minimize the risk of hypoglycemia. Sulfonylurea-induced hypoglycemia is a concern in elderly patients. However, if inability to adhere to the multiple daily regimens is problematic, a short-acting sulfonylurea is an appropriate alternative agent. In J.M.'s case, metformin should probably be used in caution because he has chronic obstructive pulmonary disease increasing the risk of hypoxia. Also, he is older than age 80 years and requires an assessment of his eGFR, which is likely diminished. If the eGFR is <30, SGLT-2 inhibitors would not be recommended. GLP-1 agonists are not recommended in patients with a history of pancreatitis or thyroid medullary neoplasia. The favorable effect metformin has on weight is irrelevant in J.M. Thus, although the efficacy of metformin is

comparable to that of sulfonylureas, it is not the agent of first choice for elderly patients such as J.M.[341,342] Patients with an FPG >300 mg/dL and no overt stress should be considered insulin deficient and started on basal insulin therapy.

HYPERTENSION

CASE 53-18

QUESTION 1: L.S. is a 53-year-old, obese male with an 8-year history of type 2 diabetes. His current problems include a BP of 155/103 mm Hg (documented on two occasions), blurry vision, and impotence, which he now admits has troubled him for the past few years. Physical examination reveals decreased pedal pulses bilaterally, loss of sensation to monofilament testing, and evidence of an amputated toe on the right foot. His laboratory values are as follows:

FPG, 170 mg/dL
A_{1c}, 7.8%
Total cholesterol, 240 mg/dL
Triglycerides, 160 mg/dL

L.S. has normal electrolyte values and albuminuria (180 mg/g creatinine). His only medication is metformin 500 mg PO bid. Describe the pathogenesis of hypertension in patients such as L.S.

Why is it so important to treat his hypertension?

Seventy-five percent of adults with diabetes report having a BP of ≥130/80 mm Hg or use medications for hypertension.[343] Hypertension in type 1 diabetes is usually of renal parenchymal origin and occurs 1 to 2 years after the onset of nephropathy as indicated by albuminuria (see Case 53-19, Question 2).[26] The relationship between type 2 diabetes and hypertension is more complex and not as closely correlated to nephropathy. In type 2 diabetes, hypertension is often part of the metabolic syndrome and may be present for years before diabetes is actually detectable.

Patients with diabetes and hypertension have an increased risk for experiencing microvascular complications such as retinopathy and nephropathy. They are also at a twofold increased risk for having CVD.[26] A 5 mm Hg reduction in mean diastolic BP can produce a

37% reduction in microvascular complications, and a 10 mm Hg reduction in mean systolic BP had previously been found to reduce the risk of MI by 11% and death related to diabetes by 15%.[26,301,302] However, because lower BP targets are tested, the benefits are becoming less clear. In the ACCORD BP study, the intensive control arm (achieved systolic BP of 119 mm Hg) did not reduce total CV events (nonfatal MI, nonfatal stroke, or death from CV causes) compared with standard therapy (achieved systolic BP of <133 mm Hg).[9] However, microvascular benefits were observed, as was a statistically significant reduction in stroke. Therefore, the existing ADA BP goal of <140/90 mm Hg is reasonable, and lower goals should not be targeted in practice unless it can be done without adverse effects.[26]

Treatment includes weight management, exercise, sodium restriction (<1500 mg/day), smoking cessation, and antihypertensive therapy. L.S. should be started on an ACEI. ACEIs have traditionally been available as less expensive generics, although angiotensin receptor II blockers (ARBs) are also available and appropriate. Both these agents are recommended in patients with diabetes with concurrent albuminuria and hypertension. Many patients require two or three medications to achieve the target BP goal of <140/90 mm Hg.[26]

NEPHROPATHY

CASE 53-18, QUESTION 2: What is the significance of the presence of albumin in L.S.'s urine? How should it be managed?

Diabetes is the leading cause of ESRD, and it accounted for 44% of new cases of renal failure in 2005.[26,343] Diabetic nephropathy is characterized by nephrotic syndrome and azotemia. It is a major cause of death in patients with type 1 diabetes and is an increasing source of morbidity in individuals with type 2 diabetes.[344] Thickening of the glomerular capillary basement membranes is the hallmark of diabetic nephropathy.[345] Diffuse deposition of basement membrane–

like material expands the mesangium. This process narrows the capillary lumina, impedes blood flow, and thereby reduces the filtering surface area in the glomerulus. Hyperglycemia causes intraglomerular hypertension and renal hyperfiltration. Hyperfiltration is followed by albuminuria with minimal glomerulosclerosis, which still is potentially reversible. If left untreated, overt proteinuria occurs, and the patient usually progresses to nephrotic syndrome. Progression of diabetic renal disease can be accelerated in the presence of hypertension, proteinuria, and diabetic retinopathy. Lipid abnormalities also may contribute to the progression of glomerulosclerosis. Management includes early detection through screening for albuminuria, tight glucose control, use of ACEIs and ARBs for patients with albuminuria (to slow progression), aggressive management of hypertension that includes an ACEI or ARB as first-line therapy,[26] aggressive management of dyslipidemia, and smoking cessation. A thorough discussion on the management of diabetic nephropathy and ESRD is presented in Chapter 28, Chronic Kidney Disease, and of hypertension in people with diabetes, in Chapter 9, Essential Hypertension.

Screening for and confirmation of albuminuria

The preferred method of screening for albuminuria is the measurement of the albumin-to-creatinine ratio in a random spot collection (preferably the first-void or morning sample). Albuminuria is defined as a urinary albumin excretion of ≥30 μg/mg of creatinine (or mg albumin/g creatinine) during a spot collection.[26] Because of day-to-day variability in albumin excretion, two of three urine samples collected in a 3- to 6-month period need to be abnormal before a designation is made. Annual screening should be performed in patients with type 1 diabetes with a duration of at least 5 years and in patients with type 2 diabetes from the time of diagnosis. More frequent screening is indicated if hypertension, any increase in SCr, or retinopathy develops. Urine albumin concentrations can be falsely elevated over true baseline values by

exercise within 24 hours, fever, infection, uncontrolled diabetes, uncontrolled hypertension, and HF.

On the basis of established criteria, L.S. has albuminuria (180 mg albumin/g creatinine). Management includes tight BG control, and an ACEI or ARB should be started (L.S. should already be receiving one of these agents to treat his hypertension as noted). After initiation of therapy, continued periodic monitoring of the albuminuria is recommended to assess the response to therapy and progression of the disease.[26] Serum potassium and creatinine levels should be followed up as well.

CARDIOVASCULAR DISEASE

CASE 53-18, QUESTION 3: L.S. is treated with lisinopril 20 mg/day, which controls his BP and improves his albuminuria. His dose of metformin is titrated to 1000 mg bid. Recent laboratory values include an FPG of 130 mg/dL, A_{1c} of 6.0%, triglyceride level of 170 mg/dL, total cholesterol of 204 mg/dL, LDL-C of 135 mg/dL, and HDL-C of 35 mg/dL. How does the risk of heart disease for patients such as L.S. compare with that for persons without diabetes? What is the pathogenesis of CHD in persons with diabetes?

CHD is the leading cause of premature death in the type 2 population and accounts for 50% of the deaths in people with diabetes. Relative to nondiabetic individuals, those with diabetes are two to three times more likely to develop CHD, and their risk of death after an MI also is two to three times higher than that of their nondiabetic counterparts. Females with diabetes, regardless of their age or menopausal status, have an equal risk for CHD to that of nondiabetic males. These sobering figures point to the importance of minimizing or eliminating all other preventable risk factors for CVD in patients with diabetes (ie, tobacco use, hypertension, hypercholesterolemia, and obesity) through the prescription of exercise, diet, and utilization of medications with known CV benefit.[346]

Pathogenesis

The pathogenesis of CVD in people with diabetes is complex. The metabolic syndrome with its attendant CV risk factors, dyslipidemia, inflammation, and hemostatic abnormalities are only some of the mechanisms under study.[347,348]

The most common lipid abnormality in type 2 diabetes is hypertriglyceridemia (>150 mg/dL) with low levels of HDL-C (<40 mg/dL in males or <50 mg/dL in females), similar to the lipid profile seen in L.S. Poor control of type 1 diabetes also is associated with low levels of HDL-C and a smaller, more-dense LDL particle. These lipid abnormalities, along with a greater prevalence of hypertension, contribute to the risk factors for CVD.

In patients with diabetes, clinical trials of lipid-lowering therapy (primarily with statins) have demonstrated primary and secondary CHD prevention. Although the evidence for the reduction in "hard" CVD outcomes (eg, CHD death and nonfatal MI) is stronger in patients with diabetes who have a high baseline CVD risk (ie, known CVD or very high LDL-C levels), the overall benefits of statins in patients with diabetes at moderate or high risk for CVD are convincing. Readers are referred to the ADA Standards of Medical Care for more detailed information on the CVD clinical trials in patients with diabetes.[26]

DYSLIPIDEMIA

Case 53-18, Question 4: Should L.S. be treated with drug therapy for his dyslipidemia?

The ACC mainly recommends initiating statin therapy based on CV risk. CV risk is determined by age, comorbidities, lipid panel, and social and family history. The ACC/AHA guidelines recommend a moderate-intensity statin for patients with diabetes between the ages of 40 and 75 with LDL between 70 and 189 mg/dL with an estimated 10-year ASCVD risk <20%. A high-intensity statin is recommended for patients with diabetes between the ages of 40 and 75 with LDL between 70 and 189 mg/dL with multiple ASCVD risk factors. The

ACC/AHA further recommends that those patients with diabetes with an estimated 10-year ASCVD risk ≥20% add ezetimibe to maximally tolerated statin therapy to reduce LDL levels by ≥50%. All patients between ages 40 and 75 are recommended a high-intensity statin if they have clinical ASCVD, including CHD, MI, unstable/stable angina, stroke, TIA, or peripheral arterial disease. Patients older than age 75 years are generally recommended to be initiated on a moderate-intensity statin because of the risk of myalgias.[26]

Diet and exercise are cornerstones in the management of dyslipidemia in patients such as L.S. Weight loss is associated with improvements in insulin sensitivity and glucose control, as well as a reduction in triglycerides, total cholesterol, and LDL-C. Physical activity enhances weight loss and increases HDL-C levels. Thus, L.S.'s diet and exercise habits should be reassessed, and instruction in both should be reinforced as appropriate. Because insulin resistance may be the underlying cause of elevated lipids in these patients, efforts should be devoted to reversing insulin resistance as well. Given L.S.'s age (between 40 and 75) and risk factors, he should be prescribed at least a moderate-intensity statin therapy (simvastatin 20–40 mg, atorvastatin 10–20 mg, or rosuvastatin 5–10 mg) to decrease his CV risk.

For a detailed discussion on statin therapy and other lipid-lowering agents, see Chapter 8 (Dyslipidemias, Atherosclerosis, and Coronary Heart Disease).

RETINOPATHY

CASE 53-18, QUESTION 5: L.S. is referred to the ophthalmologist for his persistent vision problems despite improvement in his glycemic control. He is diagnosed with mild background retinopathy. Should L.S. be concerned?

Ocular disorders related to diabetes are the leading cause of new cases of legal blindness in Americans. Patients with diabetes may experience blurred vision associated with poor glycemic control, but retinopathy, senile-type cataracts, and glaucoma are the

complications that threaten sight. Diabetic retinopathy appears as early as 3 years after diagnosis and is evident in 90% of individuals with type 1 diabetes after 15 years. Comparable figures for patients with type 2 diabetes treated with insulin and for those treated with diet and oral agents are 80% and 55%, respectively. Proliferative retinopathy is less prevalent but nevertheless is present in 30% of people with type 1 diabetes and in 10% to 15% of insulin-treated patients with type 2 diabetes who have had diabetes for 15 years or longer.[349]

Patients with type 1 diabetes should have a dilated retinal examination within 5 years of diagnosis; evaluation is not necessary before 10 years of age. Patients with type 2 diabetes should have a comprehensive eye examination soon after diagnosis. The ADA recommends annual comprehensive eye examinations.[26] Less-frequent eye examinations (every 2–3 years) can be considered in patients with normal examinations based on the advice of an ophthalmologist.[349]

Current theories addressing the possible causes of this complication have been thoroughly reviewed.[349] Microvascular disease characterized by thickening of the capillary membrane may be the underlying lesion for two forms of retinopathy. The first and most common presentation is a nonproliferative retinopathy, which is characterized by microaneurysms that may progress to hard, yellow exudates, signifying chronic leakage, retinal edema, and punctate hemorrhage. This form of retinopathy may be associated with loss of central vision, but generally is associated with an excellent visual prognosis. Focal laser photocoagulation of the retina in patients with nonproliferative diabetic retinopathy and macular edema decreases the likelihood of visual loss by 50%.[26]

A second, less common presentation is proliferative retinopathy. This form is characterized by neovascularization (presumably owing to retinal hypoxia). Neovascularization ultimately leads to fibrosis, vitreous hemorrhage, and retinal detachment. Photocoagulation therapy may arrest progression and decrease the loss of vision associated with neovascularization.[349] Because hypertension, smoking, uremia, and hyperglycemia may lead to more rapid

progression of the retinopathy, every effort should be made to eliminate these risk factors for L.S.

The ACCORD study assessed the impact of intensive glycemic, BP, and lipid control on the progression of retinopathy.[350] After 4 years, the rates of progression of diabetic retinopathy were reduced with intensive glycemic control (7.3% vs 10.4% with standard therapy) and also with fenofibrate (6.5% vs 10.2% with standard therapy of just a statin alone). Somewhat surprisingly, intensive BP control did not have an effect (10.4% vs 8.8% with standard therapy). However, on closer interpretation, this finding makes sense because the BP in the standard therapy group achieved excellent control (133.5 mm Hg), so further lowering the BP (119.3 mm Hg in the intensive group) did not provide additional benefit in reducing the rate of retinopathy progression (see Case 53-19, Question 1).

Case 53-18, Question 6: Should L.S. be started on aspirin therapy?

The issue of aspirin use for primary prevention continues to be debated. The ADA recommends aspirin therapy as secondary prevention in patients with a documented history of ASCVD (eg, MI, vascular bypass procedure, peripheral vascular disease, stroke or transient ischemic attack, claudication, or angina). Primary prevention is indicated in individuals with diabetes who have a significant risk of CVD events (10-year risk >10%). Although the ADA lists several risk calculators that can be used in patients with diabetes, the UKPDS calculator can be downloaded and is relatively easy to use (http://www.dtu.ox.ac.uk/riskengine/).[351]

According to the ADA guidelines, aspirin therapy (75–162 mg/day) may be considered for primary prevention in patients with diabetes who are at increased CV risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. Recommendations for using aspirin as primary prevention include both males and females ages 50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria)

who are not at increased risk of bleeding (eg, older age, anemia, or renal disease).

In patients (with or without diabetes) older than age 70, aspirin may pose more of a risk than a benefit. Therefore, aspirin can be considered but is generally not recommended in this patient population.

AUTONOMIC NEUROPATHY: GASTROPARESIS

CASE 53-19

QUESTION 1: H.D. is a 36-year-old male with a 20-year history of type 1 diabetes. He has poor glycemic control (A_{1c}, 12%) and frequent, severe hypoglycemic reactions that "don't make sense." According to H.D., "I have insulin reactions right after I eat, but later on, my glucose concentrations are sky high." H.D. presents to the diabetes clinic with a 2-month history of nausea, postprandial fullness, early satiety, and occasional vomiting, all of which are unrelieved by antacids. H.D. also has peripheral neuropathy involving both his hands and feet and manifestations of autonomic neuropathy (impotence and orthostatic hypotension). An upper GI series was ordered to rule out peptic ulcer disease and gastroesophageal reflux disease, and a solid-meal, gastric emptying study using scintigraphy indicates the diagnosis of diabetic gastroparesis.

What is the cause of diabetic gastroparesis? How should H.D. be treated?

Autonomic neuropathy may present as gastroparesis with feelings of bloating and nausea, urinary retention, impotence in males (manifested as retrograde ejaculation or an inability to attain an erection), postural hypotension, tachycardia, and diarrhea with incontinence of stool.[352] The presence of autonomic insufficiency may have profound effects on the patient's response to vasodilating drugs and ability to counteract hypoglycemia.

Poor glycemic control with "unexplained" hypoglycemia may result from the disrupted delivery of food to the intestine; that is, glucose delivery does not correspond with prandial insulin action. As a result, the BG levels can fluctuate greatly. Many patients with diabetic gastroparesis, such as H.D., have had diabetes for many years and also have evidence of peripheral and autonomic neuropathies.

Conventional antiemetic therapy is usually not helpful in the treatment of gastroparesis. Prokinetic agents, such as metoclopramide, are considered first-line therapy.[353] Metoclopramide increases gut motility through indirect cholinergic stimulation of the gut muscle. However, symptomatic improvement does not always correlate with improved gastric emptying, which implies that the effectiveness of metoclopramide also is related to its centrally mediated antiemetic activity. A usual starting dose of metoclopramide is 10 mg orally four times daily (qid), 30 minutes before meals, and at bedtime. Patients should be monitored for tardive dyskinesia, a potentially irreversible and disfiguring condition that is characterized by involuntary movements of the tongue, face, or extremities. In 2009, the FDA added tardive dyskinesia as a black box warning for metoclopramide.[354] The risk of tardive dyskinesia increases with the duration of treatment and the total cumulative dose.

Other pharmacotherapeutic interventions include domperidone (not available in the United States), cisapride (withdrawn from the U.S. market), erythromycin, and cholinergic agonists.[353] A key component to treating H.D.'s gastroparesis is improving his glycemic control. Also, H.D. should be advised to try eating smaller, more frequent meals and to chew his food well; this of course will require adjustments to his prandial insulin therapy. Also, eating a low-fiber and low-fat diet may help with his symptoms.[353]

PERIPHERAL NEUROPATHY

CASE 53-19, QUESTION 2: Six months after institution of metoclopramide 10 mg qid and several insulin adjustments, H.D.'s GI symptoms have been alleviated, and his diabetes is now reasonably well controlled, as evidenced by elimination of hypoglycemic episodes and a recent A_{1c} of 7.5%. However, H.D. has increasing bilateral foot pain, which he describes as a burning, tingling, or prickly sensation. An examination of his feet reveals cool extremities with absent pulses, reduced vibration perception, and loss of 10-g monofilament pressure sensation. What are appropriate steps that can be taken to alleviate H.D.'s peripheral neuropathy?

Diabetic neuropathy may be a consequence of metabolic disturbances in the neurons, microangiopathy affecting the capillary supply to neurons, or an autoimmune process. It affects 60% to 70% of the diabetic population and has a broad spectrum of presentation. Clinically, it most commonly presents as a diffuse symmetric sensorimotor syndrome, as carpal tunnel syndrome, or as autonomic neuropathy (eg, tachycardia or orthostatic hypotension caused by CV autonomic neuropathy). Symptomatic diabetic peripheral neuropathy occurs in 25% of patients with diabetes. It is characterized by paresthesia and pain in the lower extremities that may be mild or severe and unrelenting, decreased sensation to monofilament testing, decreased ankle and knee jerks, and decreased nerve conduction velocity. The decreased sensation associated with peripheral neuropathy contributes to the progression of foot injuries and infections that may go unnoticed by the patient until they are severe. The management of diabetic neuropathies has been reviewed.[26,355,356] To view a video of how to perform a complete foot examination, see http://www.medscape.com/viewarticle/708703.

Pharmacologic management consists of symptomatic therapies. Painful neuropathy may respond to simple analgesics (eg, acetaminophen) or nonsteroidal anti-inflammatory drugs. The analgesic selected should be based on the patient's history of responsiveness to these agents and their duration of action and side effect profiles. Analgesics such as acetaminophen, when overused, can lead to hepatotoxicity. Avoid chronic nonsteroidal anti-inflammatory drug use owing to their renal toxicity, bleeds, and development of GI ulcers. Other pharmacologic options include tricyclic antidepressants (TCAs), duloxetine (a serotonin and norepinephrine reuptake inhibitor), gabapentin, pregabalin, and other anticonvulsants (carbamazepine, lamotrigine, topiramate, and oxcarbazepine). Only pregabalin and duloxetine have the FDA indication for the treatment of diabetic peripheral neuropathy (DPN); others are off label (ie, gabapentin). Efficacy, side effects, drug interactions, renal and hepatic function, and cost should all be considered when an agent is chosen. Often less expensive options are tried first, off label such as gabapentin or a TCA.[357-359]

Topical application of 0.075% capsaicin has been recommended for diabetic neuropathy, but may take several weeks to work. Lidocaine 5% patches have also been used. These may be helpful in patients intolerant to oral medications. These may be used in combination with oral medications. Tramadol or opiates may also be used as a second line.[357-359]

CASE 53-19, QUESTION 3: Can anything be done for H.D.'s peripheral vascular disease?

Peripheral vascular disease or peripheral arterial disease presents as diminished or absent foot pulses, intermittent claudication, skin ulcers, gangrene, or amputation. People with diabetes are 2 to 10 times more likely to experience symptoms of peripheral arterial disease than are those without diabetes, and half of all nontraumatic amputations in the United States are performed in patients with diabetes. In one study that followed type 2 patients for 7 years, 5.5% had an amputation. The prevalence of this condition increases with age, duration of diabetes, and the presence of risk factors such as hypertension or smoking.[356,360]

Signs and symptoms of peripheral arterial disease include leg pain, which is relieved by rest; cold feet; nocturnal leg pain, which is relieved by dangling the feet over the bed or walking; absent pulses; loss of hair on the foot and toes; and gangrene. Treatment of this condition includes elimination and treatment of risk factors such as smoking, dyslipidemia, hypertension, and hyperglycemia; antiplatelet therapy; exercise, which is the mainstay of therapy; and revascularization surgery.[360] H.D. should be thoroughly educated regarding proper foot care, perform daily self-foot examinations, and receive regular care by a podiatrist.[361]

DRUG-INDUCED ALTERATIONS IN GLUCOSE HOMEOSTASIS

Persons with diabetes are likely to take more drugs in their lifetime than do any other group of patients. Patients with type 2 diabetes present with a constellation of chronic conditions, including hypertension, dyslipidemia, and CVD, all of which will likely require drug therapy. Drugs to manage depression, intermittent infections, and neurologic and ophthalmologic conditions also are commonly prescribed. Because we know that the actions of drugs are complex and that for every desired effect there are several other unwanted effects, each time a drug is added to the regimen of someone with diabetes, it is important to assess the patient's situation to determine whether a potential exists for a drug–drug or drug–disease interaction or whether the benefit of the newly prescribed drug is likely to outweigh its risks. With the availability of online drug information databases to assist in the assessment of drug–drug and drug–disease interactions, a detailed listing of drugs that can exacerbate hyperglycemia and hypoglycemia is not provided. But a few case examples are illustrated here. Some medications that can have significant hyperglycemic effects include atypical antipsychotics, protease inhibitors, corticosteroids, immunosuppressants (eg, tacrolimus and cyclosporine), niacin (higher doses), gonadotropin-releasing hormone agonists (used in males for prostate cancer), and pentamidine (can also cause hypoglycemia).[362,363] Patients should be monitored closely for a medication's possible effect on the BG levels.

Drug-Induced Hyperglycemia

CORTICOSTEROIDS

CASE 53-20

Question 1: A.L., a 37-year-old obese female with systemic lupus erythematosus, has been taking 60 mg/day of prednisone for 6 months. During this period, her weight has increased by 30 pounds (13.61 kg) and she has experienced glycosuria (no ketones). Her primary provider asked her to start SMBG. She was referred to the diabetes clinic, where her predinner and bedtime BG values were found to be 140 to 160 mg/dL and FBG values were

80 to 105 mg/dL. Physical examination shows a 62 inches (157.48 cm), 150-pounds (68.04 kg), depressed female with truncal obesity and an acneiform rash. Her mother and one sister have type 2 diabetes.

How do corticosteroids contribute to DM? How should A.L. be treated?

The term *steroid diabetes* was first used to describe the hyperglycemia and glycosuria seen in patients with Cushing syndrome. Now, it is associated more commonly with exogenously administered glucocorticoids and has been a side effect of parenteral, oral, and even topical therapy. Corticosteroids are one of the most common drug groups that unmask latent diabetes or aggravate preexisting disease, and they may produce hyperglycemia and overt diabetes in individuals who are not otherwise predisposed.

Corticosteroids increase hepatic gluconeogenesis, suppress insulin secretion, and decrease tissue responsiveness to insulin.[363] The primary effect is impaired glucose disposal after meals, resulting in daytime hyperglycemia, and by morning, the glucose levels normalize. Although steroid-induced diabetes generally is mild and rarely associated with ketonemia, a wide spectrum of severity may be encountered—from asymptomatic, abnormal glucose tolerance tests to difficult-to-control, insulin-requiring disease. The onset of glucose tolerance can occur within hours to days or after months to years of chronic therapy. The effect generally is considered dose dependent and usually is reversible on discontinuation of the drug.

A.L. exhibits many symptoms that can be attributed to supraphysiologic doses of corticosteroids: truncal obesity, depression, acneiform rash, and diabetes. Mildly elevated glucose levels in obese individuals, as in A.L.'s case, sometimes can be controlled by diet but may require treatment with a short-acting insulin secretagogue or rapid-acting insulin before meals.[363] A person with diabetes whose BG is increased by the use of a glucocorticoid should modify treatment appropriately to restore glycemic control. It is important to anticipate the need to modify insulin or other antidiabetic therapy because corticosteroid doses are increased or decreased.

SYMPATHOMIMETICS

CASE 53-21

QUESTION 1: R.C., a 41-year-old male with type 1 diabetes, is well controlled on a basal-bolus insulin regimen and has been taking pseudoephedrine 30 mg qid for 7 days and Robitussin DM 10 mL qid (which contains 2.92 g of sugar/5 mL) for a cold. Recently, glucose concentrations have been higher than usual.

Can pseudoephedrine or the cough preparation be the cause of his poor glycemic control? How can sympathomimetics and cough preparations affect patients with diabetes?

Over-the-counter drug products, such as decongestants and diet aids, which contain sympathomimetics, carry warning labels that caution against their use in patients with diabetes. Standard sugar- and ethanol-containing cough preparations also carry such warning labels. However, clinically significant drug-induced glucose intolerance probably is very infrequent. It is well established that parenterally administered epinephrine increases BG concentrations secondary to increased glycogenolysis and gluconeogenesis. Other sympathomimetics generally do not have as potent an effect on BG as does epinephrine, and their use usually does not pose a practical problem in patients with diabetes. Furthermore, the effects of sympathomimetics on BP must be considered in many patients with diabetes. Therefore, antihistamines or occasional use of nasal sprays for severe congestion may be needed.

In summary, pseudoephedrine or the cough preparation may be aggravating R.C.'s glycemic control, although at these low-to-normal therapeutic doses, it is quite unlikely. The stress related to R.C.'s underlying cold is more likely to be impairing his glucose tolerance than do these low doses of sympathomimetic agents or the small amounts of sugar contained in the cough syrup.

Drug-Induced Hypoglycemia

ETHANOL

CASE 53-22

QUESTION 1: C.F., a 22-year-old female with newly diagnosed type 1 diabetes, enjoys a glass or two of wine with her evening meal.

What effect does alcohol have on a patient with diabetes, particularly one using insulin? Is alcohol contraindicated in C.F. or any person with diabetes?

Clinicians often are reluctant to permit the use of alcoholic beverages in patients with diabetes. However, barring contraindications that are similar in the nondiabetic individual and patient with diabetes alike (eg, alcoholism, hypertriglyceridemia, gastritis, pancreatitis, and pregnancy), a person with diabetes can safely enjoy a moderate alcohol intake as long as certain precautions are taken. For an in-depth discussion, the reader is referred to two comprehensive reviews of alcohol and diabetes,[364,365] parts of which are summarized in the following list:

- Drink in moderation: The ADA defines this as a daily intake of one drink for adult females and two drinks for adult males (one drink is defined as 5 ounces of wine, 12 ounces of beer, or 1.5 ounces of distilled liquor). The patient should be aware of his/her own sensitivity to the intoxicating effects of ethanol and adjust consumption downward, if needed. This is particularly important for insulin-dependent patients. When having a drink, be sure to have it with a carbohydrate-containing meal.
- Avoid drinks that contain large amounts of sugar: Instead of drinks such as liqueurs, sweet wines, and sugar-containing mixes, consider dry wines, light beers, and distilled spirits. Not only does the simple sugar content add an additional source of glucose and calories to the diet but ethanol ingested with simple sugar-containing mixers also enhances reactive hyperglycemia.
- Remember to count the calories in alcohol: Instead of (calories – [0.8] × [proof] × [ounces]); substitute 1 ounce of alcohol for two fat exchanges.
- Be aware that the symptoms of alcohol intoxication and hypoglycemia are similar: If hypoglycemia is mistaken for

intoxication by others, appropriate and potentially life-saving treatment can be delayed.

- Be aware of alcohol–sulfonylurea drug interactions: and, specifically, the alcohol-induced enzyme induction of tolbutamide metabolism and the chlorpropamide–alcohol flush reaction.

ACKNOWLEDGMENT

The authors acknowledge Lisa A. Kroon and Craig Williams for their contributions to this chapter in earlier editions.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

ACCORD Study Group; ACCORD Eye Study Group; Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes [published correction appears in *N Engl J Med*. 2011;364:190]. *N Engl J Med*. 2010;363:233–244. (268)

Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD), Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559. doi:10.1056/NEJMoa0802743 (43)

ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–2572. (45)

American Diabetes Association. 1. Strategies for improving care. *Diabetes Care*. 2015;38(suppl 1):S5–S7. doi:10.2337/dc15-S004 (26)

Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374:1677–1686. doi:10.1016/S0140-6736(09)61457-4 (51)

Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes [published corrections appear in *N Engl J Med*. 2009;361:1028; *N Engl J Med*. 2009;361:1024]. *N Engl J Med*. 2009;360:129–139. doi:10.1056/NEJMoa0808431 (46)

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group [published correction appears in *Lancet*. 1998;352:1558]. *Lancet*. 1998;352(9131):854–865. (300)

Effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. Diabetes Control and Complications Trial Research Group*. J Pediatr*. 1994;125(2):177–188. doi:10.1016/s0022-3476(94)70190-3 (141)

Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology—clinical practice guidelines for developing a diabetes mellitus comprehensive care plan —2015. *Endocr Pract*. 2015:21 (suppl 1):1–87. doi:10.4158/EP15672.GL (42)

Hayward RA, Reaven PD, Wiitala WL, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;372(23):2197–2206. doi:10.1056/NEJMoa1414266 (47)

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577–1589. doi:10.1056/NEJMoa0806470 (37)

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352(9131):837–853. (39)

Inzucchi S, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient centered approach update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140–149. doi:10.2337/dc14-2441 (111)

Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643–2653. doi:10.1056/NEJMoa052187 (36)

NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283–1297. doi:10.1056/NEJMoa0810625 (168)

Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic

treatment in the ACCORD trial. *Diabetes Care*. 2010;33:983–990. doi:10.2337/dc09-1278 (44)

Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association [published correction appears in *Diabetes Care*. 2009;32:754]. *Diabetes Care*. 2009;32: 187–192. doi:10.2337/dc08-9026 (48)

Turner R, Cull C, Holman R. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med*. 1996;124(1 Pt 2):136–145. doi:10.7326/0003-4819-124-1_part_2-199601011-00011 (322)

UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ*. 1998;317(7160):713–720. (301)

UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group [published correction appears in *BMJ*. 1999;318:29]. *BMJ*. 1998;317(7160):703–713. (302)

Key Websites

American Diabetes Association. http://www.diabetes.org

COMPLETE REFERENCES CHAPTER 53 DIABETES MELLITUS

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Published February 11, 2020. Accessed August 14, 2020. https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html
2. *IDF Diabetes Atlas*. 9th ed. 2019. Accessed August 14, 2020. https://diabetesatlas.org/en/
3. American Diabetes Association. 3. Prevention or delay of type 2 diabetes: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S34–S39. doi:10.2337/dc21-S003

4. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S15–S33. doi:10.2337/dc21-S002
5. American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S111–S134. doi:10.2337/dc20-S010
6. Renehan A, Smith U, Kirkman MS. Linking diabetes and cancer: a consensus on complexity. *Lancet*. 2010;375(9733):2201–2202. doi:10.1016/S0140-6736(10)60706-4
7. American Diabetes Association. 11. Microvascular complications and foot care: *Standards of Medical Care in Diabetes−2020*. *Diabetes Care*. 2020;43(suppl 1):S135–S151. doi:10.2337/dc20-S011
8. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*. 2018;41(5):917–928. doi:10.2337/dci18-0007
9. Shulman GI. Integrated fuel metabolism. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003:1.
10. Ginsberg HN. New perspectives on atherogenesis: role of abnormal triglyceride-rich lipoprotein metabolism. *Circulation*. 2002;106(16):2137–2142. doi:10.1161/01.CIR.0000035280.64322.31
11. Naik R. The pathophysiology and genetics of type 1 (insulin-dependent) diabetes. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003:301.
12. Zhong T, Tang R, Gong S, Li J, Li X, Zhou Z. The remission phase in type 1 diabetes: changing epidemiology, definitions, and emerging immuno-metabolic mechanisms. *Diabetes Metab Res Rev*. 2020;36(2). doi:10.1002/dmrr.3207
13. Kahn S, Porte D. The pathophysiology and genetics of type 2 diabetes mellitus. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003:331.
14. American Diabetes Association. 7. Diabetes technology: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S85–S99. doi:10.2337/dc21-S007
15. D'Alessio D. Incretins: glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003:85.
16. Amatruda J, Livingston J. Glucagon. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003:97.
17. DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773–795. doi:10.2337/db09-9028
18. Schwartz SS, Epstein S, Corkey BE, Grant SFA, Gavin JR, Aguilar RB. The time is right for a new classification system for diabetes: rationale and

implications of the β-cell–centric classification schema. *Diabetes Care*. 2016;39(2):179–186. doi:10.2337/dc15-1585

19. American Diabetes Association. 13. Children and adolescents: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S180–S199. doi:10.2337/dc21-S013
20. Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol*. 2008;28(4):629–636. doi:10.1161/ATVBAHA.107.151092
21. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2005;28(9):2289–2304. doi:10.2337/diacare.28.9.2289
22. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA*. 2015;313(19):1973–1974. doi:10.1001/jama.2015.4260
23. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1046–e1081. doi:10.1161/CIR.0000000000000624
24. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet*. 2017;389(10085):2239–2251. doi:10.1016/S0140-6736(17)30058-2
25. American Diabetes Association. 14. Management of diabetes in pregnancy: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S200–S210. doi:10.2337/dc21-S014
26. American Diabetes Association. 1. Strategies for improving care. *Diabetes Care*. 2015;38(suppl_1):S5–S7. doi:10.2337/dc15-S004
27. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet*. 2018;391(10138):2449–2462. doi:10.1016/S0140-6736(18)31320-5
28. Writing Committee, Unwin N, Shaw J, Zimmet P, Alberti KGMM. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med*. 2002;19(9):708–723. doi:10.1046/j.1464-5491.2002.00835.x
29. Ship JA. Diabetes and oral health: an overview. *J Am Dent Assoc*. 2003;134 Spec No:4S–10S. doi:10.14219/jada.archive.2003.0367
30. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. *N Engl J Med*. 2014;370(16):1514–1523. doi:10.1056/NEJMoa1310799
31. Preis SR, Hwang S-J, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation*. 2009;119(13):1728–1735. doi:10.1161/CIRCULATIONAHA.108.829176

32. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405–412. doi:10.1136/bmj.321.7258.405
33. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977–986. doi:10.1056/NEJM199309303291401
34. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342(6):381–389. doi:10.1056/NEJM200002103420603
35. Martin CL, Albers J, Herman WH, et al. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care*. 2006;29(2):340–344. doi:10.2337/diacare.29.02.06.dc05-1549
36. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353(25):2643–2653. doi:10.1056/NEJMoa052187
37. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577–1589. doi:10.1056/NEJMoa0806470
38. Retnakaran R, Zinman B. Type 1 diabetes, hyperglycaemia, and the heart. *Lancet*. 2008;371(9626):1790–1799. doi:10.1016/S0140-6736(08)60767-9
39. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837–853.
40. Gaede P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348(5):383–393. doi:10.1056/NEJMoa021778
41. American Diabetes Association. 6. Glycemic targets. *Diabetes Care*. 2015;38(suppl_1):S33–S40. doi:10.2337/dc15-S009
42. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology—clinical practice guidelines for developing a diabetes mellitus comprehensive care plan—2015. *Endocr Pract*. 2015;21(suppl 1):1–87. doi:10.4158/EP15672.GL
43. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545–2559. doi:10.1056/NEJMoa0802743
44. Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care*. 2010;33(5):983–990. doi:10.2337/dc09-1278

45. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560–2572. doi:10.1056/NEJMoa0802987
46. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes [published corrections appear in *N Engl J Med*. 2009;361:1028; *N Engl J Med*. 2009;361:1024]. *N Engl J Med*. 2009;360(2):129–139. doi:10.1056/NEJMoa0808431
47. Hayward RA, Reaven PD, Wiitala WL, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;372(23):2197–2206. doi:10.1056/NEJMoa1414266
48. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association [published correction appears in *Diabetes Care*. 2009;32:754]. *Diabetes Care*. 2009;32(1):187–192. doi:10.2337/dc08-9026
49. Dayan CM, Korah M, Tatovic D, Bundy BN, Herold KC. Changing the landscape for type 1 diabetes: the first step to prevention. *Lancet*. 2019;394(10205):1286–1296. doi:10.1016/S0140-6736(19)32127-0
50. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393–403. doi:10.1056/NEJMoa012512
51. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677–1686. doi:10.1016/S0140-6736(09)61457-4
52. American Diabetes Association. 5. Facilitating behavior change and well-being to improve health outcomes: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S53–S72. doi:10.2337/dc21-S005
53. American Diabetes Association. 5. Prevention or delay of type 2 diabetes. *Diabetes Care*. 2015;38(suppl 1):S31–S32. doi:10.2337/dc15-S008
54. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2014;37(suppl 1):S120–S143. doi:10.2337/dc14-S120
55. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care*. 2019;42(5):731–754. doi:10.2337/dci19-0014
56. Franz MJ, Bantle JP, Beebe CA, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*. 2003;26(suppl 1):S51–S61. doi:10.2337/diacare.26.2007.s51

57. Franz MJ, Warshaw H, Daly AE, Green-Pastors J, Arnold MS, Bantle J. Evolution of diabetes medical nutrition therapy. *Postgrad Med J*. 2003;79(927):30–35. doi:10.1136/pmj.79.927.30
58. Vaz EC, Porfírio GJM, Nunes HRC, Nunes-Nogueira VS. Effectiveness and safety of carbohydrate counting in the management of adult patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *Arch Endocrinol Metab*. 2018;62(3):337–345. doi:10.20945/2359-3997000000045
59. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2016;39(11):2065–2079. doi:10.2337/dc16-1728
60. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol*. 2017;5(5):377–390. doi:10.1016/S2213-8587(17)30014-1
61. American Diabetes Association. 4. Foundations of care: education, nutrition, physical activity, smoking cessation, psychosocial care, and immunization. *Diabetes Care*. 2015;38(suppl 1):S20–S30. doi:10.2337/dc15-S007
62. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S98–S110. doi:10.2337/dc20-S009
63. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S73–S84. doi:10.2337/dc21-S006
64. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm —2020 executive summary. *Endocr Pract*. 2020;26(1):107–139. doi:10.4158/CS-2019-0472
65. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593–1603. doi:10.2337/dci19-0028
66. Schumacher CA, Isaacs D, Collier I, Klinkebiel D. Use of continuous glucose monitoring to improve glycemic management: a clinician's guide. *J Am Coll Clin Pharm*. 2020;3(7):1333–1343. doi:10.1002/jac5.1295
67. Gorus F, Mathieu C, Gerlo E. How should HbA1c measurements be reported? *Diabetologia*. 2006;49(1):7–10. doi:10.1007/s00125-005-0073-7
68. Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008;31(8):1473–1478. doi:10.2337/dc08-0545
69. Ng JM, Cooke M, Bhandari S, Atkin SL, Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. *Diabetes Care*. 2010;33(11):2310–2313. doi:10.2337/dc10-0917

70. Davie SJ, Gould BJ, Yudkin JS. Effect of vitamin C on glycosylation of proteins. *Diabetes*. 1992;41(2):167–173. doi:10.2337/diab.41.2.167
71. The International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care*. 2009;32(7):1327–1334. doi:10.2337/dc09-9033
72. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. *Diabetes Care*. 2004;27(7):1761–1773. doi:10.2337/diacare.27.7.1761
73. Nolte M. Pancreatic hormones and antidiabetic drugs. In: Katzung BG, Masters S, Trevor AJ, *eds. Basic and Clinical Pharmacology*. 11th ed. Lange Medical Books/McGraw-Hill; 2009:727.
74. Binder C, Brange J. Insulin chemistry and pharmacokinetics. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 5th ed. Appleton & Lange; 1997:481.
75. Admelog. Package insert. Sanofi-Aventis U.S. LLC; November 2019.
76. Novolog. Package insert. Novo Nordisk; December 2019.
77. Humalog. Package insert. Eli Lilly and Company; November 2019.
78. Fiasp. Package insert. Novo-Nordisk; January 2020.
79. Lyumjev. Package insert. Eli Lilly and Company; June 2020.
80. Insulin Aspart Injection. Package insert. Novo Nordisk; November 2019.
81. Afrezza. Package insert. Sanofi-Aventis U.S. LLC; March 2017.
82. Gradel AKJ, Porsgaard T, Lykkesfeldt J, et al. Factors affecting the absorption of subcutaneously administered insulin: effect on variability. *J Diabetes Res*. 2018;2018:1205121.
83. Rabkin R, Ryan MP, Duckworth WC. The renal metabolism of insulin. *Diabetologia*. 1984;27(3):351–357. doi:10.1007/BF00304849
84. Burge MR, Schade DS. Insulins. *Endocrinol Metab Clin North Am*. 1997;26(3):575–598. doi:10.1016/s0889-8529(05)70268-1
85. Eledrisi M, Suleiman NN, Salameh O, et al. Twice-daily insulin glargine for patients with uncontrolled type 2 diabetes mellitus. *J Clin Transl Endocrinol*. 2019;15:35–36. doi:10.1016/j.jcte.2018.12.002
86. Lane W, Bailey TS, Gerety G, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. *JAMA*. 2017;318(1):33–44. doi:10.1001/jama.2017.7115
87. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA*. 2017;318(1):45–56. doi:10.1001/jama.2017.7117
88. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). *Diabetes Care*. 2015;38(12):2217–2225. doi:10.2337/dc15-0249

Bolli GB, Gerich JE. The dawn phenomenon—a common occurrence in both
89. non-insulin-dependent and insulin-dependent diabetes mellitus. *N Engl J Med*. 1984;310(12):746–750. doi:10.1056/NEJM198403223101203
90. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351(11):1106–1118. doi:10.1056/NEJMra041001
91. White J, Goldman J. Biosimilar and follow-on insulin: the ins, outs, and interchangeability. *J Pharm Technol*. 2019;35(1):25–35. doi:10.1177/8755122518802268
92. Garg S, Ampudia-Blasco FJ, Pfohl M. Rapid-acting insulin analogues in basal-bolus regimens in type 1 diabetes mellitus. *Endocr Pract*. 2010;16(3):486–505. doi:10.4158/EP09294.RA
93. Insulin lispro. Package insert. Eli Lilly and Company; February 2020.
94. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). *Diabetes Care*. 2017;40(7):943–950. doi:10.2337/dc16-1771
95. Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. *Diabetes Obes Metab*. 2020;22(10):1799–1807. doi:10.1111/dom.14100
96. Blevins T, Zhang Q, Frias JP, Jinnouchi H, Chang AM. Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. *Diabetes Care*. 2020;43(12):2991–2998. doi:10.2337/dc19-2550
97. Bode BW, McGill JB, Lorber DL, Gross JL, Chang P-C, Bregman DB. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. *Diabetes Care*. 2015;38(12):2266–2273. doi:10.2337/dc15-0075
98. Humulin R U500. Package insert. Eli Lilly and Company; November 2019.
99. Institute For Safe Medication Practices. As U-500 insulin safety concerns Mount, it's time to rethink safe use of strengths above U-100. Accessed August 9, 2020. https://www.ismp.org/resources/u-500-insulin-safety-concerns-mount-its-time-rethink-safe-use-strengths-above-u-100
100. Turnheim K. Basic aspects of insulin pharmacokinetics. In: Brunetti P, Waldhäusl WK, eds. *Advanced Models for the Therapy of Insulin-Dependent Diabetes*. Raven Press; 1987:91.
101. Koivisto VA, Felig P. Alterations in insulin absorption and in blood glucose control associated with varying insulin injection sites in diabetic patients. *Ann Intern Med*. 1980;92(1):59–61. doi:10.7326/0003-4819-92-1-59
102. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care*. 2002;25(3):593–598. doi:10.2337/diacare.25.3.593

103. Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med*. 2006;145(2):125–134. doi:10.7326/0003-4819-145-2-200607180-00010
104. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA*. 2003;289(17):2254–2264. doi:10.1001/jama.289.17.2254
105. Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with type 1 diabetes using meal-time insulin aspart. *Diabet Med*. 2006;23(8):879–886. doi:10.1111/j.1464-5491.2006.01913.x
106. Bott S, Tusek C, Jacobsen LV, et al. Insulin detemir under steady-state conditions: no accumulation and constant metabolic effect over time with twice daily administration in subjects with type 1 diabetes. *Diabet Med*. 2006;23(5):522–528. doi:10.1111/j.1464-5491.2006.01839.x
107. Porcellati F, Rossetti P, Busciantella NR, et al. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. *Diabetes Care*. 2007;30(10):2447–2452. doi:10.2337/dc07-0002
108. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ*. 2002;324(7339):705. doi:10.1136/bmj.324.7339.705
109. Campbell PJ, Bolli GB, Cryer PE, Gerich JE. Pathogenesis of the dawn phenomenon in patients with insulin-dependent diabetes mellitus. Accelerated glucose production and impaired glucose utilization due to nocturnal surges in growth hormone secretion. *N Engl J Med*. 1985;312(23):1473–1479. doi:10.1056/NEJM198506063122302
110. Walsh J, Roberts R, Bailey T, Varma CB. *Using Insulin: Everything You Need for Success with Insulin*. Torrey Pines Press; 2003.
111. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140–149. doi:10.2337/dc14-2441
112. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. *Mayo Clin Proc*. 2016;91(9):1231-1255. https://www.mayoclinicproceedings.org/article/S0025-6196(16)30321-4/fulltext
113. Gradel AKJ, Porsgaard T, Lykkesfeldt J, et al. Factors Affecting the Absorption of Subcutaneously Administered Insulin: Effect on Variability. *J Diabetes Res*. 2018;2018:1205121. Published 2018 Jul 4. doi:10.1155/2018/1205121
114. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Medication adherence and the associated health-economic impact among patients with type 2

diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. *Clin Ther*. 2006;28(10):1712–1725; discussion 1710–1711. doi:10.1016/j.clinthera.2006.10.004

115. Grabner M, Chu J, Raparla S, Quimbo R, Zhou S, Conoshenti J. Clinical and economic outcomes among patients with diabetes mellitus initiating insulin glargine pen versus vial. *Postgrad Med*. 2013;125(3):204–213. doi:10.3810/pgm.2013.05.2656
116. Davies MJ, Gagliardino JJ, Gray LJ, Khunti K, Mohan V, Hughes R. Real-world factors affecting adherence to insulin therapy in patients with type 1 or type 2 diabetes mellitus: a systematic review. *Diabet Med*. 2013;30(5):512–524. doi:10.1111/dme.12128
117. Kesavadev J, Saboo B, Krishna MB, Krishnan G. Evolution of insulin delivery devices: from syringes, pens, and pumps to DIY artificial pancreas. *Diabetes Ther*. 2020;11(6):1251–1269. doi:10.1007/s13300-020-00831-z
118. American Diabetes Association. Insulin administration. *Diabetes Care*. 2004;27(suppl 1):S106–S107. doi:10.2337/diacare.27.2007.S106
119. Kadiyala P, Walton S, Sathyapalan T. Insulin induced lipodystrophy. *Br J Diabetes*. 2014;14(4):131. doi:10.15277/bjdvd.2014.036
120. Young LA, Buse JB, Weaver MA, et al. Glucose self-monitoring in non–insulin-treated patients with type 2 diabetes in primary care settings: a randomized trial. *JAMA Intern Med*. 2017;177(7):920–929. doi:10.1001/jamainternmed.2017.1233
121. Farmer A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ*. 2007;335(7611):132. doi:10.1136/bmj.39247.447431.BE
122. Malanda UL, Welschen LMC, Riphagen II, Dekker JM, Nijpels G, Bot SDM. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. *Cochrane Database Syst Rev*. 2012;1:CD005060. doi:10.1002/14651858.CD005060.pub3
123. Messaaoui A, Tenoutasse S, Crenier L. Flash glucose monitoring accepted in daily life of children and adolescents with type 1 diabetes and reduction of severe hypoglycemia in real-life use. *Diabetes Technol Ther*. 2019;21(6):329–335. doi:10.1089/dia.2018.0339
124. Cowart K, Updike W, Bullers K. Systematic review of randomized controlled trials evaluating glycemic efficacy and patient satisfaction of intermittent-scanned continuous glucose monitoring in patients with diabetes. *Diabetes Technol Ther*. 2020;22(5):337–345. doi:10.1089/dia.2019.0345
125. Evans M, Welsh Z, Ells S, Seibold A. The impact of flash glucose monitoring on glycaemic control as measured by HbA1c: a meta-analysis of clinical trials and real-world observational studies. *Diabetes Ther*. 2020;11(1):83–95. doi:10.1007/s13300-019-00720-0

126. Paris I, Henry C, Pirard F, Gérard A-C, Colin IM. The new FreeStyle libre flash glucose monitoring system improves the glycaemic control in a cohort of people with type 1 diabetes followed in real-life conditions over a period of one year. *Endocrinol Diabetes Metab*. 2018;1(3):e00023. doi:10.1002/edm2.23
127. Walsh J, Roberts R. *Pumping Insulin: Everything You Need for Success with an Insulin Pump*. Torrey Pines Press; 2006.
128. Perriello G, De Feo P, Torlone E, et al. The effect of asymptomatic nocturnal hypoglycemia on glycemic control in diabetes mellitus. *N Engl J Med*. 1988;319(19):1233–1239. doi:10.1056/NEJM198811103191901
129. Fanelli CG, Pampanelli S, Porcellati F, Rossetti P, Brunetti P, Bolli GB. Administration of neutral protamine Hagedorn insulin at bedtime versus with dinner in type 1 diabetes mellitus to avoid nocturnal hypoglycemia and improve control. A randomized, controlled trial. *Ann Intern Med*. 2002;136(7):504–514. doi:10.7326/0003-4819-136-7-200204020-00007
130. Rybicka M, Krysiak R, Okopien´ B. The dawn phenomenon and the Somogyi effect—two phenomena of morning hyperglycaemia. *Endokrynol Pol*. 2011;62(3):276–284.
131. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care*. 2000;23(5):639–643. doi:10.2337/diacare.23.5.639
132. De Leeuw I, Vague P, Selam J-L, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab*. 2005;7(1):73–82. doi:10.1111/j.1463-1326.2004.00363.x
133. Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. *Diabetes Care*. 2001;24(2):296–301. doi:10.2337/diacare.24.2.296
134. Lantus. Package insert. Sanofi-Aventis U.S. LLC; November 2019.
135. Tresiba. Package insert. Novo Nordisk; November 2019.
136. Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes*. 2009;10(suppl 12):118–133. doi:10.1111/j.1399-5448.2009.00569.x
137. Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28(1):186–212. doi:10.2337/diacare.28.1.186
138. Grey M, Schreiner B, Pyle L. Development of a diabetes education program for youth with type 2 diabetes. *Diabetes Educ*. 2009;35(1):108–116. doi:10.1177/0145721708325156

139. Atkinson A, Radjenovic D. Meeting quality standards for self-management education in pediatric type 2 diabetes. *Diabetes Spectr*. 2007;20(1):40–46. doi:10.2337/diaspect.20.1.40
140. Chiang JL, Kirkman MS, Laffel LMB, Peters AL, Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care*. 2014;37(7):2034–2054. doi:10.2337/dc14-1140
141. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J Pediatr*. 1994;125(2):177–188. doi:10.1016/s0022-3476(94)70190-3
142. White NH, Cleary PA, Dahms W, et al. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr*. 2001;139(6):804–812. doi:10.1067/mpd.2001.118887
143. Siminerio LM, Albanese-O'Neill A, Chiang JL, et al. Care of young children with diabetes in the child care setting: a position statement of the American Diabetes Association. *Diabetes Care*. 2014;37(10):2834–2842. doi:10.2337/dc14-1676
144. Murphy NP, Keane SM, Ong KK, et al. Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care*. 2003;26(3):799–804. doi:10.2337/diacare.26.3.799
145. Chase HP, Dixon B, Pearson J, et al. Reduced hypoglycemic episodes and improved glycemic control in children with type 1 diabetes using insulin glargine and neutral protamine Hagedorn insulin. *J Pediatr*. 2003;143(6):737–740. doi:10.1067/S0022-3476(03)00415-3
146. Toujeo. Package insert. Sanofi-Aventis U.S. LLC; November 2019.
147. Phillip M, Battelino T, Rodriguez H, et al. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2007;30(6):1653–1662. doi:10.2337/dc07-9922
148. McMahon SK, Airey FL, Marangou DA, et al. Insulin pump therapy in children and adolescents: improvements in key parameters of diabetes management including quality of life. *Diabet Med*. 2005;22(1):92–96. doi:10.1111/j.1464-5491.2004.01359.x
149. Patton SR, Eder S, Schwab J, Sisson CM. Survey of insulin site rotation in youth with type 1 diabetes mellitus. *J Pediatr Health Care*. 2010;24(6):365–371. doi:10.1016/j.pedhc.2009.11.002

150. Kalra S, Hirsch LJ, Frid A, Deeb A, Strauss KW. Pediatric insulin injection technique: a multi-country survey and clinical practice implications. *Diabetes Ther*. 2018;9(6):2291–2302. doi:10.1007/s13300-018-0514-1
151. Asvold BO, Sand T, Hestad K, Bjørgaas MR. Cognitive function in type 1 diabetic adults with early exposure to severe hypoglycemia: a 16-year follow-up study. *Diabetes Care*. 2010;33(9):1945–1947. doi:10.2337/dc10-0621
152. Davis EA, Keating B, Byrne GC, Russell M, Jones TW. Impact of improved glycaemic control on rates of hypoglycaemia in insulin dependent diabetes mellitus. *Arch Dis Child*. 1998;78(2):111–115. doi:10.1136/adc.78.2.111
153. Jones TW, Porter P, Sherwin RS, et al. Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med*. 1998;338(23):1657–1662. doi:10.1056/NEJM199806043382303
154. Deiss D, Kordonouri O, Hartmann R, Hopfenmüller W, Lüpke K, Danne T. Treatment with insulin glargine reduces asymptomatic hypoglycemia detected by continuous subcutaneous glucose monitoring in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2007;8(3):157–162. doi:10.1111/j.1399-5448.2007.00252.x
155. Danne T, Tamborlane WV, Malievsky OA, et al. Efficacy and safety of insulin glargine 300 units/mL (Gla-300) versus insulin glargine 100 units/mL (Gla-100) in children and adolescents (6–17 years) with type 1 diabetes: results of the EDITION JUNIOR randomized controlled trial. *Diabetes Care*. 2020;43(7):1512–1519. doi:10.2337/dc19-1926
156. Centers for Disease Control and Prevention. Managing sick days. Published March 31, 2020. https://www.cdc.gov/diabetes/managing/flu-sick-days.html
157. Rubenstein AH, Spitz I. Role of the kidney in insulin metabolism and excretion. *Diabetes*. 1968;17(3):161–169. doi:10.2337/diab.17.3.161
158. Rabkin R, Simon NM, Steiner S, Colwell JA. Effect of renal disease on renal uptake and excretion of insulin in man. *N Engl J Med*. 1970;282(4):182–187. doi:10.1056/NEJM197001222820402
159. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med*. 2009;37(12):3001–3009. doi:10.1097/CCM.0b013e3181b083f7
160. Kosiborod M, Inzucchi SE, Goyal A, et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA*. 2009;301(15):1556–1564. doi:10.1001/jama.2009.496
161. Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation*. 2005;111(23):3078–3086. doi:10.1161/CIRCULATIONAHA.104.517839
162. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes

mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ*. 1997;314(7093):1512–1515. doi:10.1136/bmj.314.7093.1512

163. Malmberg K, Rydén L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J*. 2005;26(7):650–661. doi:10.1093/eurheartj/ehi199
164. Mehta SR, Yusuf S, Díaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA*. 2005;293(4):437–446. doi:10.1001/jama.293.4.437
165. Cheung NW, Wong VW, McLean M. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care*. 2006;29(4):765–770. doi:10.2337/diacare.29.04.06.dc05-1894
166. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359–1367. doi:10.1056/NEJMoa011300
167. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449–461. doi:10.1056/NEJMoa052521
168. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283–1297. doi:10.1056/NEJMoa0810625
169. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2004;164(18):2005–2011. doi:10.1001/archinte.164.18.2005
170. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA*. 2008;300(8):933–944. doi:10.1001/jama.300.8.933
171. Bruno A, Gregori D, Caropreso A, Lazzarato F, Petrinco M, Pagano E. Normal glucose values are associated with a lower risk of mortality in hospitalized patients. *Diabetes Care*. 2008;31(11):2209–2210. doi:10.2337/dc08-0672
172. McAlister FA, Majumdar SR, Blitz S, Rowe BH, Romney J, Marrie TJ. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. *Diabetes Care*. 2005;28(4):810–815. doi:10.2337/diacare.28.4.810
173. Baker EH, Janaway CH, Philips BJ, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2006;61(4):284–289. doi:10.1136/thx.2005.051029

174. Magaji V, Johnston JM. Inpatient management of hyperglycemia and diabetes. *Clin Diabetes*. 2011;29(1):3–9. doi:10.2337/diaclin.29.1.3
175. American Diabetes Association. 15. Diabetes care in the hospital: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care*. 2021;44(suppl 1):S211–S220. doi:10.2337/dc21-S015
176. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27(2):553–591. doi:10.2337/diacare.27.2.553
177. U.S. Food and Drug Administration. FDA public health notification: potentially fatal errors with GDH-PQQ* glucose monitoring technology. Published August 13, 2009. Accessed July 1, 2015. https://www.nsmedicaldevices.com/news/fda_warns_of_potentially_fatal_errors_with_gdhpqq_glucose_monitoring_technology_090813/
178. Parekh B. The mechanism of dead-in-bed syndrome and other sudden unexplained nocturnal deaths. *Curr Diabetes Rev*. 2009;5(4):210–215. doi:10.2174/157339909789804387
179. Cryer P, Gerich J. Hypoglycemia in insulin-dependent diabetes mellitus: interplay of insulin excess and compromised glucose regulation. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003:523.
180. Glucagon Emergency Kit. Package insert. Fresenius Kabi; September 2019.
181. GVOKE injection. Package insert. Xeris Pharmaceuticals, Inc.; September 2019.
182. Baqsimi glucagon powder. Package insert. Eli Lilly and Company; October 2020.
183. de Galan BE, Schouwenberg BJJW, Tack CJ, Smits P. Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. *Neth J Med*. 2006;64(8):269–279.
184. Markovitz LJ, Wiechmann RJ, Harris N, et al. Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. *Endocr Pract*. 2002;8(1):10–18. doi:10.4158/EP.8.1.10
185. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1335–1343. doi:10.2337/dc09-9032
186. Salpeter SR, Greyber E, Pasternak GA, Salpeter Posthumous EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010;(1):CD002967. doi:10.1002/14651858.CD002967.pub3
187. Ennis E, Kreisberg R. Diabetic ketoacidosis. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003:573.
188. Viallon A, Zeni F, Lafond P, et al. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? *Crit Care Med*.

1999;27(12):2690–2693. doi:10.1097/00003246-199912000-00014
189. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med*. 2002;137(1):25–33. doi:10.7326/0003-4819-137-1-200207020-00009
190. Glucophage and Glucophage XR. Package insert. Bristol-Myers Squibb Company; May 2018.
191. Christofides EA. Practical insights into improving adherence to metformin therapy in patients with type 2 diabetes. *Clin Diabetes*. 2019;37(3):234–241. doi:10.2337/cd18-0063
192. Tahrani AA, Varughese GI, Scarpello JH, Hanna FWF. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? *BMJ*. 2007;335(7618):508–512. doi:10.1136/bmj.39255.669444.AE
193. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med*. 2003;163(21):2594–2602. doi:10.1001/archinte.163.21.2594
194. Fitzgerald E, Mathieu S, Ball A. Metformin associated lactic acidosis. *BMJ*. 2009;339:b3660. doi:10.1136/bmj.b3660
195. Lazarus B, Wu A, Shin J-I, et al. Association of metformin use with risk of lactic acidosis across the range of kidney function: a community-based cohort study. *JAMA Intern Med*. 2018;178(7):903–910. doi:10.1001/jamainternmed.2018.0292
196. Lipska KJ, Flory JH, Hennessy S, Inzucchi SE. Citizen petition to the US Food and Drug Administration to change prescribing guidelines: the metformin experience. *Circulation*. 2016;134(18):1405–1408. doi:10.1161/CIRCULATIONAHA.116.023041
197. Shu Y, Sheardown SA, Brown C, et al. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *J Clin Invest*. 2007;117(5):1422–1431. doi:10.1172/JCI30558
198. Prandin. Package insert. Novo Nordisk; January 2019.
199. Starlix. Package insert. Novartis Pharmaceuticals Corporation; May 2018.
200. Nan DN, Hernández JL, Fernández-Ayala M, Carrascosa M. Acute hepatotoxicity caused by repaglinide. *Ann Intern Med*. 2004;141(10):823. doi:10.7326/0003-4819-141-10-200411160-00024
201. Scheen AJ. Drug-drug and food-drug pharmacokinetic interactions with new insulinotropic agents repaglinide and nateglinide. *Clin Pharmacokinet*. 2007;46(2):93–108. doi:10.2165/00003088-200746020-00001
202. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007;(2):CD004654. doi:10.1002/14651858.CD004654.pub2
203. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA*. 2002;287(3):360–372. doi:10.1001/jama.287.3.360
204. Groop LC. Sulfonylureas in NIDDM. *Diabetes Care*. 1992;15(6):737–754. doi:10.2337/diacare.15.6.737

205. Groop LC, Ratheiser K, Luzi L, et al. Effect of sulphonylurea on glucose-stimulated insulin secretion in healthy and non-insulin dependent diabetic subjects: a dose-response study. *Acta Diabetol*. 1991;28(2):162–168. doi:10.1007/BF00579720
206. Wåhlin-Boll E, Sartor G, Melander A, Scherstén B. Impaired effect of sulfonylurea following increased dosage. *Eur J Clin Pharmacol*. 1982;22(1):21–25. doi:10.1007/BF00606420
207. Stenman S, Melander A, Groop PH, Groop LC. What is the benefit of increasing the sulfonylurea dose? *Ann Intern Med*. 1993;118(3):169–172. doi:10.7326/0003-4819-118-3-199302010-00002
208. Jaber LA, Antal EJ, Slaughter RL, Welshman IR. Comparison of pharmacokinetics and pharmacodynamics of short-and long-term glyburide therapy in NIDDM. *Diabetes Care*. 1994;17(11):1300–1306. doi:10.2337/diacare.17.11.1300
209. Amaryl. Package insert. Sanofi-Aventis U.S. LLC; December 2018.
210. Klepzig H, Kober G, Matter C, et al. Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J*. 1999;20(6):439–446. doi:10.1053/euhj.1998.1242
211. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest*. 2001;108(8):1167–1174. doi:10.1172/JCI13505
212. Donath MY, Ehses JA, Maedler K, et al. Mechanisms of beta-cell death in type 2 diabetes. *Diabetes*. 2005;54(suppl 2):S108–S113. doi:10.2337/diabetes.54.suppl_2.s108
213. Actos. Package insert. Takeda Pharmaceuticals America; December 2017.
214. Hanefeld M. Pharmacokinetics and clinical efficacy of pioglitazone. *Int J Clin Pract Suppl*. 2001;(121):19–25.
215. Avandia. Package insert. GlaxoSmithKline LLC; February 2019.
216. Al-Salman J, Arjomand H, Kemp DG, Mittal M. Hepatocellular injury in a patient receiving rosiglitazone: a case report. *Ann Intern Med*. 2000;132(2):121. doi:10.7326/0003-4819-132-2-200001180-00006
217. Su D-H, Lai M-Y, Wu H-P. Liver failure in a patient receiving rosiglitazone therapy. *Diabet Med*. 2006;23(1):105–106. doi:10.1111/j.1464-5491.2006.01791.x
218. Farley-Hills E, Sivasankar R, Martin M. Fatal liver failure associated with pioglitazone. *BMJ*. 2004;329(7463):429. doi:10.1136/bmj.329.7463.429
219. Tice SA, Parry D. Medications that require hepatic monitoring. *Hosp Pharm*. 2001;36(4):456–464. doi:10.1177/001857870103600417
220. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a

randomised controlled trial. *Lancet*. 2005;366(9493):1279–1289. doi:10.1016/S0140-6736(05)67528-9

221. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007;298(10):1180–1188. doi:10.1001/jama.298.10.1180
222. Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. *Pharmacoepidemiol Drug Saf*. 2007;16(10):1065–1071. doi:10.1002/pds.1470
223. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*. 2010;304(4):411–418. doi:10.1001/jama.2010.920
224. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med*. 2007;357(1):28–38. doi:10.1056/NEJMoa073394
225. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007;298(10):1189–1195. doi:10.1001/jama.298.10.1189
226. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457–2471. doi:10.1056/NEJMoa072761
227. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med*. 2010;170(14):1191–1201. doi:10.1001/archinternmed.2010.207
228. Ryan EH, Han DP, Ramsay RC, et al. Diabetic macular edema associated with glitazone use. *Retina*. 2006;26(5):562–570. doi:10.1097/00006982-200605000-00011
229. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. *Arch Intern Med*. 2012;172(13):1005–1011. doi:10.1001/archinternmed.2012.1938
230. U.S. Food and Drug Administration. FDA Drug Safety Communication: ongoing safety review of actos (pioglitazone) and potential increased risk of bladder cancer after two years exposure. Published September 17, 2010. Accessed December 9, 2010. http://www.fda.gov/Drugs/DrugSafety/ucm226214.htm
231. Schwartz AV, Sellmeyer DE. Thiazolidinedione therapy gets complicated: is bone loss the price of improved insulin resistance? *Diabetes Care*. 2007;30(6):1670–1671. doi:10.2337/dc07-0554
232. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ*. 2009;180(1):32–39.

doi:10.1503/cmaj.080486
233. Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM. Thiazolidinediones and fractures in men and women. *Arch Intern Med*. 2009;169(15):1395–1402. doi:10.1001/archinternmed.2009.214
234. Aubert RE, Herrera V, Chen W, Haffner SM, Pendergrass M. Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(8):716–721. doi:10.1111/j.1463-1326.2010.01225.x
235. Ali AA, Weinstein RS, Stewart SA, Parfitt AM, Manolagas SC, Jilka RL. Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. *Endocrinology*. 2005;146(3):1226–1235. doi:10.1210/en.2004-0735
236. Scheen AJ. Pharmacokinetic interactions with thiazolidinediones. *Clin Pharmacokinet*. 2007;46(1):1–12. doi:10.2165/00003088-200746010-00001
237. Clar C, Royle P, Waugh N. Adding pioglitazone to insulin containing regimens in type 2 diabetes: systematic review and meta-analysis. *PloS One*. 2009;4(7):e6112. doi:10.1371/journal.pone.0006112
238. Precose. Package insert. Bayer Corporation; March 2015.
239. Glyset. Package insert. Pfizer/Pharmacia and Upjohn Company; October 2015.
240. Van de Laar FA, Lucassen PLBJ, Akkermans RP, Van de Lisdonk EH, Rutten GEHM, Van Weel C. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2005;(2):CD003639. doi:10.1002/14651858.CD003639.pub2
241. Dimitrios P, Michael D, Vasilios K, et al. Liraglutide as adjunct to insulin treatment in patients with type 1 diabetes: a systematic review and meta-analysis. *Curr Diabetes Rev*. 2020;16(4):313–326. doi:10.2174/1573399815666190614141918
242. Byetta. Package insert. AstraZeneca Pharmaceuticals LP; February 2020.
243. Bydureon. Package insert. AstraZeneca Pharmaceuticals LP; February 2020.
244. Vilsbøll T. Liraglutide: a once-daily GLP-1 analogue for the treatment of type 2 diabetes mellitus. *Expert Opin Investig Drugs*. 2007;16(2):231–237. doi:10.1517/13543784.16.2.231
245. Victoza. Package insert. Novo Nordisk A/S; August 2020.
246. Trulicity. Package insert. Eli Lilly and Company; February 2020.
247. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. *Diabetes Obes Metab*. 2017;19(3):336–347. doi:10.1111/dom.12824
248. Tanzeum. Package insert. GlaxoSmithKline LLC; December 2017.

249. Drab SR. Incretin-based therapies for type 2 diabetes mellitus: current status and future prospects. *Pharmacotherapy*. 2010;30(6):609–624. doi:10.1592/phco.30.6.609
250. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care*. 2009;32(1):84–90. doi:10.2337/dc08-1355
251. Frias JP, Bonora E, Nevarez Ruiz L, et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). *Diabetes Care*. 2021;44(3):765–773. doi:10.2337/dc20-1473
252. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009;32(7):1224–1230. doi:10.2337/dc08-2124
253. Marre M, Shaw J, Brändle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabet Med*. 2009;26(3):268–278. doi:10.1111/j.1464-5491.2009.02666.x
254. Januvia. Package insert. Merck & Co; August 2019.
255. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311–322. doi:10.1056/NEJMoa1603827
256. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834–1844. doi:10.1056/NEJMoa1607141
257. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121–130. doi:10.1016/S0140-6736(19)31149-3
258. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381(9):841–851. doi:10.1056/NEJMoa1901118
259. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373(23):2247–2257. doi:10.1056/NEJMoa1509225
260. Onglyza. Package insert. Bristol-Myers Squibb Company; July 2019.
261. Tradjenta. Package insert. Boehringer Ingelheim Pharmaceuticals; March 2020.
262. Nesina. Package insert. Takeda Pharmaceuticals America; July 2019.
263. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes.

Lancet. 2006;368(9548):1696–1705. doi:10.1016/S0140-6736(06)69705-5
264. Langley AK, Suffoletta TJ, Jennings HR. Dipeptidyl peptidase IV inhibitors and the incretin system in type 2 diabetes mellitus. *Pharmacotherapy*. 2007;27(8):1163–1180. doi:10.1592/phco.27.8.1163
265. Golightly LK, Drayna CC, McDermott MT. Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. *Clin Pharmacokinet*. 2012;51(8):501–514. doi:10.1007/BF03261927
266. Lajara R. The potential role of sodium glucose co-transporter 2 inhibitors in combination therapy for type 2 diabetes mellitus. *Expert Opin Pharmacother*. 2014;15(17):2565–2585. doi:10.1517/14656566.2014.968551
267. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ*. 2014;348:g2366. doi:10.1136/bmj.g2366
268. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1327–1335. doi:10.1056/NEJMoa1305889
269. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317–1326. doi:10.1056/NEJMoa1307684
270. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373(3):232–242. doi:10.1056/NEJMoa1501352
271. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019;321(1):69–79. doi:10.1001/jama.2018.18269
272. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA*. 2019;322(12):1155–1166. doi:10.1001/jama.2019.13772
273. Singh-Franco D, Robles G, Gazze D. Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. *Clin Ther*. 2007;29(4):535–562. doi:10.1016/j.clinthera.2007.04.005
274. Symlin. Package insert. AstraZeneca Pharmaceuticals LP; December 2019.
275. Invokana. Package insert. Janssen Pharmaceuticals; January 2020.
276. Farxiga. Package insert. AstraZeneca Pharmaceuticals LP; May 2020.
277. Jardiance. Package insert. Boehringer Ingelheim Pharmaceuticals; January 2020.
278. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2014;16(5):457–466. doi:10.1111/dom.12244

279. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117–2128. doi:10.1056/NEJMoa1504720
280. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-reduced trial. *Circulation*. 2021;143(4):326–336. doi:10.1161/CIRCULATIONAHA.120.051783
281. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657. doi:10.1056/NEJMoa1611925
282. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295–2306. doi:10.1056/NEJMoa1811744
283. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347–357. doi:10.1056/NEJMoa1812389
284. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436–1446. doi:10.1056/NEJMoa2024816
285. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008. doi:10.1056/NEJMoa1911303
286. Taylor SI, Blau JE, Rother KI, Beitelshees AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. *Lancet Diabetes Endocrinol*. 2019;7(12):949–958. doi:10.1016/S2213-8587(19)30154-8
287. Williams SM, Ahmed SH. 1224-P: improving compliance with SGLT2 inhibitors by reducing the risk of genital mycotic infections: the outcomes of personal hygiene advice. *Diabetes*. 2019;68(suppl 1):1224-P. doi:10.2337/db19-1224-P
288. Steglatro. Package insert. Merck & Co.; January 2020.
289. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Published 2015. https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious
290. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). September 17, 2020. Accessed June 15, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin

291. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383(15):1425–1435. doi:10.1056/NEJMoa2004967
292. Boehringer Ingelheim. Breakthrough results for Jardiance® (empagliflozin) confirm EMPEROR-Preserved as first and only successful trial for heart failure with preserved ejection fraction. Accessed July 19, 2021. https://www.boehringer-ingelheim.us/press-release/breakthrough-results-jardiance-empagliflozin-confirm-emperor-preserved-first-and-only
293. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care*. 2010;33(7):1503–1508. doi:10.2337/dc09-2009
294. Welchol. Package insert. Daiichi Sankyo Inc; July 2020.
295. Bays HE, Goldberg RB, Truitt KE, Jones MR. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. *Arch Intern Med*. 2008;168(18):1975–1983. doi:10.1001/archinte.168.18.1975
296. Goldberg RB. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med*. 2008;168(14):1531–1540. doi:10.1001/archinte.168.14.1531
297. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care*. 2008;31(8):1479–1484. doi:10.2337/dc08-0283
298. Roussel R, Travert F, Pasquet B, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. *Arch Intern Med*. 2010;170(21):1892–1899. doi:10.1001/archinternmed.2010.409
299. Cycloset. Package insert. VeroScience LLC; April 2020.
300. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group [published correction appears in *Lancet*. 1998;352:1558] *Lancet*. 1998;352(9131):854–865.
301. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ*. 1998;317(7160):713–720.
302. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group [published correction appears in *BMJ*. 1999;318:29]. *BMJ*. 1998;317(7160):703–713.
303. Holman RR, Paul SK, Bethel MA, Neil HAW, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med*.

2008;359(15):1565–1576. doi:10.1056/NEJMoa0806359
304. Saraei P, Asadi I, Kakar MA, Moradi-Kor N. The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances. *Cancer Manag Res*. 2019;11:3295–3313. doi:10.2147/CMAR.S200059
305. Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. *Curr Med Res Opin*. 2004;20(4):565–572. doi:10.1185/030079904125003278
306. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet*. 2019;394(10208):1519–1529. doi:10.1016/S0140-6736(19)32131-2
307. Feher MD, Al-Mrayat M, Brake J, Leong KS. Tolerability of prolonged-release metformin (Glucophage® SR) in individuals intolerant to standard metformin—results from four UK centres. *Br J Diabetes Vasc Dis*. 2007;7(5):225–228. doi:10.1177/14746514070070050501
308. Pelletier AL, Butler AM, Gillies RA, May JR. Metformin stinks, literally. *Ann Intern Med*. 2010;152(4):267–268. doi:10.7326/0003-4819-152-4-201002160-00023
309. Amneal upgrades generic metformin family by listening to customers. Published May 15, 2012. Accessed June 15, 2021. https://www.amneal.com/wp-content/uploads/2017/04/Metformin_Release_FINAL1-1.pdf
310. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ*. 2010;340:c2181. doi:10.1136/bmj.c2181
311. Welschen LMC, Bloemendal E, Nijpels G, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care*. 2005;28(6):1510–1517. doi:10.2337/diacare.28.6.1510
312. Clar C, Barnard K, Cummins E, Royle P, Waugh N, Aberdeen Health Technology Assessment Group. Self-monitoring of blood glucose in type 2 diabetes: systematic review. *Health Technol Assess*. 2010;14(12):1–140. doi:10.3310/hta14120
313. Bloomgarden ZT, Dodis R, Viscoli CM, Holmboe ES, Inzucchi SE. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. *Diabetes Care*. 2006;29(9):2137–2139. doi:10.2337/dc06-1120
314. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels: a systematic review and

meta-analysis. *Diabetes Care*. 2010;33(8):1859–1864. doi:10.2337/dc09-1727

315. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med*. 2007;147(6):386–399. doi:10.7326/0003-4819-147-6-200709180-00178
316. Deacon CF, Mannucci E, Ahrén B. Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes-a review and meta analysis. *Diabetes Obes Metab*. 2012;14(8):762–767. doi:10.1111/j.1463-1326.2012.01603.x
317. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355(23):2427–2443. doi:10.1056/NEJMoa066224
318. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2005;28(5):1092–1100. doi:10.2337/diacare.28.5.1092
319. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2007;298(22):2654–2664. doi:10.1001/jama.298.22.2654
320. Rafalson L, Donahue RP, Dmochowski J, Rejman K, Dorn J, Trevisan M. Cigarette smoking is associated with conversion from normoglycemia to impaired fasting glucose: the Western New York Health Study. *Ann Epidemiol*. 2009;19(6):365–371. doi:10.1016/j.annepidem.2009.01.013
321. Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. *Diabetes Care*. 1999;22(6):925–927. doi:10.2337/diacare.22.6.925
322. Turner R, Cull C, Holman R. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med*. 1996;124(1 Pt 2):136–145. doi:10.7326/0003-4819-124-1_part_2-199601011-00011
323. Pan A, Lucas M, Sun Q, et al. Bidirectional association between depression and type 2 diabetes mellitus in women. *Arch Intern Med*. 2010;170(21):1884–1891. doi:10.1001/archinternmed.2010.356
324. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA*. 2010;303(14):1410–1418. doi:10.1001/jama.2010.405
325. DeWitt DE, Dugdale DC. Using new insulin strategies in the outpatient treatment of diabetes: clinical applications. *JAMA*. 2003;289(17):2265. doi:10.1001/jama.289.17.2265

326. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26(11):3080–3086. doi:10.2337/diacare.26.11.3080
327. Anderson JH, Brunelle RL, Keohane P, et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. *Arch Intern Med*. 1997;157(11):1249–1255.
328. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;357(17):1716–1730. doi:10.1056/NEJMoa075392
329. American Diabetes Association. Efficacy of biphasic insulin aspart 70/30 in patients with T2DM not achieving glycemic targets on OADs with/without basal insulin therapy. Accessed August 10, 2020. https://professional.diabetes.org/abstract/efficacy-biphasic-insulin-aspart-7030-patients-t2dm-not-achieving-glycemic-targets-oads
330. Unnikrishnan AG, Tibaldi J, Hadley-Brown M, et al. Practical guidance on intensification of insulin therapy with BIAsp 30: a consensus statement. *Int J Clin Pract*. 2009;63(11):1571–1577. doi:10.1111/j.1742-1241.2009.02192.x
331. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in Diabetes. *Diabetes Care*. 2003;26(6):1902–1912. doi:10.2337/diacare.26.6.1902
332. Sarkar A. Pharmacological and pharmaceutical profile of gliclazide: a review. *J Appl Pharm Sci*. 2011;(09):11–19.
333. Bailey CJ. Metformin: historical overview. *Diabetologia*. 2017;60(9):1566–1576. doi:10.1007/s00125-017-4318-z
334. Gangopadhyay KK, Singh P. Consensus statement on dose modifications of antidiabetic agents in patients with hepatic impairment. *Indian J Endocrinol Metab*. 2017;21(2):341–354. doi:10.4103/ijem.IJEM_512_16
335. Gambert SR. Atypical presentation of diabetes mellitus in the elderly. *Clin Geriatr Med*. 1990;6(4):721–729.
336. Morley JE, Perry HM. The management of diabetes mellitus in older individuals. Drugs. 1991;41(4):548–565. doi:10.2165/00003495-199141040-00004
337. Silver AJ, Morley JE. Role of the opioid system in the hypodipsia associated with aging. *J Am Geriatr Soc*. 1992;40(6):556–560. doi:10.1111/j.1532-5415.1992.tb02102.x
338. American Diabetes Association. 12. Older adults: *Standards of Medical Care in Diabetes*—2021. Diabetes Care. 2021;44(suppl 1):S168–S179. doi:10.2337/dc21-S012
339. Brown AF, Mangione CM, Saliba D, Sarkisian CA, California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with

diabetes mellitus. *J Am Geriatr Soc*. 2003;51(5 suppl guidelines):S265–S280. doi:10.1046/j.1532-5415.51.5s.1.x

340. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc*. 1996;44(7):751–755. doi:10.1111/j.1532-5415.1996.tb03729.x
341. Centers for Disease Control. National Diabetes Statistics Report. Published February 14, 2020. https://www.cdc.gov/diabetes/data/statistics/statistics-report.html
342. Molitch ME, DeFronzo RA, Franz MJ, et al. Nephropathy in diabetes. *Diabetes Care*. 2004;27(suppl 1):S79–S83. doi:10.2337/diacare.27.2007.s79
343. DeFronzo RA. Diabetic nephropathy. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003:723.
344. Lteif AA, Mather KJ, Clark CM. Diabetes and heart disease an evidence-driven guide to risk factors management in diabetes. *Cardiol Rev*. 2003;11(5):262–274. doi:10.1097/01.crd.0000086892.07437.05
345. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486–2497. doi:10.1001/jama.285.19.2486
346. Young L, Chyun D. Heart disease in patients with diabetes. In: Porte D, Sherwin RS, Baron A, et al, eds. *Ellenberg & Rifkin's Diabetes Mellitus*. 6th ed. McGraw-Hill; 2003.
347. Fong DS, Aiello LP, Ferris FL, Klein R. Diabetic retinopathy. *Diabetes Care*. 2004;27(10):2540–2553. doi:10.2337/diacare.27.10.2540
348. ACCORD Study Group, ACCORD Eye Study Group, Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010;363(3):233–244. doi:10.1056/NEJMoa1001288
349. Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Circulation*. 2010;121(24):2694–2701. doi:10.1161/CIR.0b013e3181e3b133
350. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care*. 2003;26(5):1553–1579. doi:10.2337/diacare.26.5.1553
351. Kashyap P, Farrugia G. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. *Gut*. 2010;59(12):1716–1726. doi:10.1136/gut.2009.199703
352. U.S. Food and Drug Administration. Reglan (metoclopramide) tablets, ODT (Orally Disintegrating Tablets), and injection. Accessed December 19, 2010. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm170934.htm

353. Tesfaye S, Boulton AJM, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*. 2010;33(10):2285–2293. doi:10.2337/dc10-1303
354. Boulton AJM, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care*. 2005;28(4):956–962. doi:10.2337/diacare.28.4.956
355. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–173. doi:10.1016/S1474-4422(14)70251-0
356. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision: treatment of neuropathic pain. *Eur J Neurol*. 2010;17(9):1113-e88. doi:10.1111/j.1468-1331.2010.02999.x
357. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. *Pain Pract*. 2014;14(2):167–184. doi:10.1111/papr.12054
358. Lüscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. *Circulation*. 2003;108(13):1655–1661. doi:10.1161/01.CIR.0000089189.70578.E2
359. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM. Preventive foot care in people with diabetes. *Diabetes Care*. 1998;21(12):2161–2177. doi:10.2337/diacare.21.12.2161
360. Vue MH, Setter SM. Drug-induced glucose alterations part 1: drug-induced hypoglycemia. *Diabetes Spectr*. 2011;24(3):171–177. doi:10.2337/diaspect.24.3.171
361. Rehman A, Setter SM, Vue MH. Drug-induced glucose alterations part 2: drug-induced hyperglycemia. *Diabetes Spectr*. 2011;24(4):234–238. doi:10.2337/diaspect.24.4.234
362. Pietraszek A, Gregersen S, Hermansen K. Alcohol and type 2 diabetes. A review. *Nutr Metab Cardiovasc Dis*. 2010;20(5):366–375. doi:10.1016/j.numecd.2010.05.001
363. van de Wiel A. Diabetes mellitus and alcohol. *Diabetes Metab Res Rev*. 2004;20(4):263–267. doi:10.1002/dmrr.492
364. Consumer Guide 2014. Diabetes Forecast. Accessed June 23, 2021. http://archives.diabetesforecast.org/2014/Jan/consumer-guide-2014.html
365. Apidra. Package insert. Sanofi-Aventis U.S. LLC; November 2019.
366. Levemir. Package insert. Novo Nordisk Inc; November 2019.

SECTION 12

Eye Disorders

Section Editor: Susan Jacobson

54

Eye Disorders

Katherine Carey and Bridget C. Hendricks

CORE PRINCIPLES		CHAPTER CASES
GLAUCOMA		
1	There are different types of glaucoma, including open-angle glaucoma and angle-closure glaucoma. Angle-closure glaucoma is a medical emergency requiring immediate intervention. Open-angle glaucoma is a chronic condition, which can result in progressive loss of vision leading to blindness if left untreated.	**Case 54-1 (Question 1) Case 54-2 (Question 1)**
2	Treatment for open-angle glaucoma is targeted toward reducing intraocular pressure (IOP), a clinical measure of drug efficacy. Prostaglandin analogs (PGAs), β-adrenergic blockers, and α-	**Case 54-1 (Question 2-7), Figure 54-1, Table 54-1**

	adrenergic agonists are the mainstay of treatment. Treatment is not curative.	
	OCULAR AND SYSTEMIC SIDE EFFECTS OF DRUGS	
1	Many widely used medications for various conditions cause ocular side effects. The true incidence is frequently not known, making the reporting of ocular side effects of drugs an important function for any health care practitioner.	**Case 54-3 (Question 1), Table 54-3**
2	Conversely, many topically administered ocular medications may cause systemic symptoms.	**Case 54-10 (Question 1)**
	OCULAR EMERGENCIES	
1	Ocular emergencies like chemical burns, corneal trauma, corneal ulceration, acute angle closure glaucoma, and gonococcal conjunctivitis require immediate referral to the emergency department or an ophthalmologist.	**Case 54-4 (Question 1), Case 54-7 (Question 1)**
	COMMON OCULAR DISORDERS	
1	Dry eye disease (keratoconjunctivitis sicca) is a common ocular disorder involving chronically reduced tear film and inflammation of the ocular surface. There are a wide array of treatments, including tear replacement and anti-inflammatory therapies.	
2	Stye (hordeolum) is a common ocular disorder for which no viable over-the-	

	counter (OTC) treatment exists.	
3	Conjunctivitis (pinkeye) is frequently related to bacterial or viral infection, or allergy. Viral conjunctivitis is generally self-limiting. Bacterial conjunctivitis should be treated with an appropriate antimicrobial, recognizing that Gram-positive organisms are frequently the cause. A number of agents are available for the treatment of allergic conjunctivitis. Among those, decongestants (eg, tetrahydrozoline) should be used for no >72 hours, because they may mask a more serious condition or result in rebound redness.	**Case 54-5 (Question 1), Case 54-6 (Question 1)**
	CORTICOSTEROIDS	
1	Topical corticosteroids are used for a variety of ocular inflammatory conditions. The most potent topical corticosteroid is prednisolone acetate 1%.	**Case 54-8 (Question 1), Table 54-4**
2	Topical and oral corticosteroids may be associated with serious side effects, such as increases in IOP and cataracts (with long-term use).	**Case 54-8 (Questions 1,2) Case 54-9 (Question 1), Table 54-5**
	OCULAR HERPES SIMPLEX VIRUS INFECTIONS	
1	Ocular herpes is common and may be caused by herpes simplex virus or, less commonly, varicella-zoster virus. Treatment options include trifluidine, acyclovir, ganciclovir, and cidofovir.	**Case 54-12 (Question 1)**

AGE-RELATED MACULAR DEGENERATION

1	There are two forms, non-neovascular (affecting 80% of patients) and, the more serious form, neovascular (affecting 20% of patients).	**Case 54-13 (Question 1)**
2	Neovascular macular degeneration is associated with abnormal growth of blood vessels behind the retina (choroidal neovascularization) and may be treated by vascular endothelial growth factor (VEGF) inhibitors.	**Case 54-13 (Question 1)**

INTRODUCTION

The eye is a highly complex organ composed of various parts, all of which must function in integration to permit vision. A brief overview of the anatomy and physiology of the eye prefaces the presentation of specific eye disorders. Readers should consult an ophthalmology textbook for an understanding of ocular anatomy, physiology, and general ophthalmology (eg, *Vaughan and Asbury's General Ophthalmology*).[1]

OCULAR ANATOMY AND PHYSIOLOGY

The eyeball is ~1 inch wide and is housed in a cavity (ie, eye socket) formed by two bony orbits that are lined with fat, which serves to protect the eyeball. Six ocular muscles facilitate movement of the eyeball (**Fig. 54-1**).

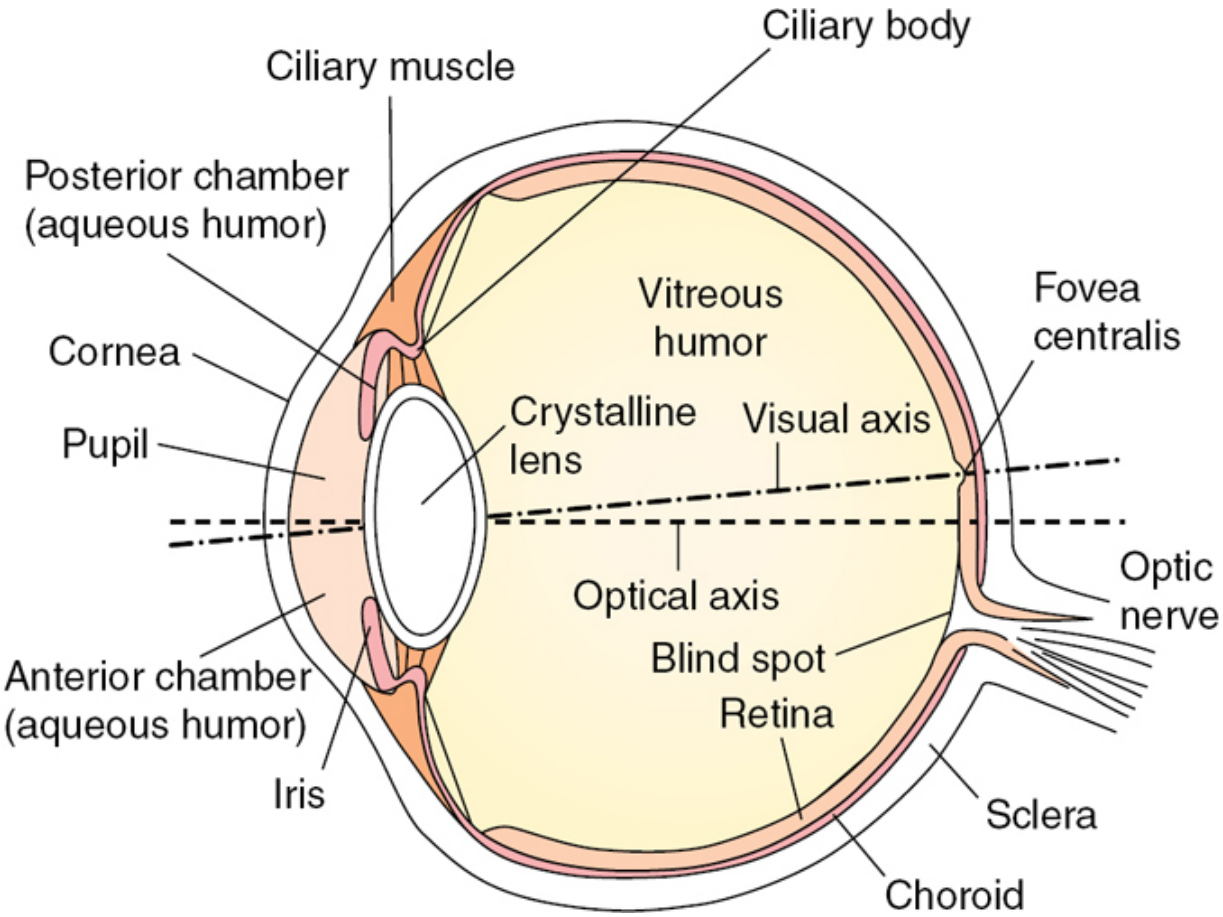


Figure 54-1 Anatomy of the human eye. (Adapted from http://commons.wikimedia.org/wiki/File:Eyesection.svg.)

The outer coat of the eye is made up of the sclera, conjunctiva, and cornea. The *sclera* is the white, dense, fibrous protective coating. The *episclera*, a thin layer of loose connective tissue, contains blood vessels that cover and nourish the sclera. The *conjunctiva* is a mucous membrane that covers the anterior portion of the eye and lines the eyelids. The *cornea* is the transparent, avascular tissue that functions as a refractive and protective window membrane through which light rays pass en route to the retina.

The corneal epithelium and endothelium are lipophilic, and the centrally located stroma is hydrophilic. These three corneal layers are particularly important because they affect drug penetration through the cornea. Ophthalmic medications, which are both fat and water soluble, are best able to penetrate through the intact cornea.

The iris, choroid, and ciliary body are known collectively as the uveal tract. The *iris* is a colored, circular membrane suspended between the cornea and the crystalline lens. It controls the amount of light that enters the eye. The *choroid*, located between the sclera and the retina, is largely made up of blood vessels, which nourish the retina. The *ciliary body* is adherent to the sclera and contains the ciliary muscle and ciliary processes. The ciliary muscle contracts and relaxes the zonular fibers, which hold the crystalline lens in place. The ciliary processes are responsible for the secretion of aqueous humor, a clear liquid that occupies the anterior chamber. The anterior chamber is bounded anteriorly by the cornea and posteriorly by the iris. The posterior chamber lies between the iris and the crystalline lens.

The inner segment of the eye contains the retina with the optic nerve. The *retina*, the light-sensitive tissue at the back of the eye, contains all of the sensory receptors for light transmission. The *optic nerve*, a bundle of more than a million nerve fibers, transmits visual impulses from the retina to the brain.

The crystalline lens, aqueous humor, and vitreous humor assist the cornea with the refraction of light. The *lens*, located behind the iris, functions to focus light onto the retina by changing its shape to accommodate near or distant vision. The innermost part of the lens (ie, the nucleus) is surrounded by the softer material of the cortex. The *aqueous humor*, the thin watery fluid that fills the anterior chamber (ie, the space between the cornea and the iris) and posterior chamber of the eye, functions to provide nourishment to the cornea and lens. Disorders involving the aqueous humor are presented in the section on glaucoma. The primary function of the *vitreous humor* (ie, the jellylike substance between the lens and the retina) is to maintain the shape of the eye and allow the transmission of light to the retina.

The eyelids and eyelashes are the outermost means of protection for the eye. The eyelids contain various sebaceous and sweat glands, which may become infected or inflamed, contributing to many ocular disorders.

The eye is innervated by both the sympathetic and parasympathetic nervous systems. Parasympathetic fibers, originating from the oculomotor nerve in the brain, innervate the ciliary muscle and sphincter pupillae muscle that constrict the pupil. As a result, parasympathomimetic (cholinergic) medications generally are associated with *miosis* (pupillary contraction), and parasympatholytic (anticholinergic) agents are associated with *mydriasis* (pupillary dilation) and *cycloplegia*. The term *cycloplegia* refers to a paralysis of the ciliary muscle and zonules (fibrous strands connecting the ciliary body to the lens) that results in decreased accommodation (adjustment of the lens curvature for various distances) and blurred vision. Tear secretion by the lacrimal glands is also a parasympathetic function.

Sympathetic fibers from the superior cervical ganglion in the spinal cord innervate the dilator pupillae muscle, the blood vessels of the ciliary body, the episclera, and the extraocular muscles. Sympathomimetics cause mydriasis without affecting accommodation.

In this chapter, we discuss glaucoma and other common ocular disorders, such as ocular infectious conditions, ocular inflammatory conditions, dry eye syndrome, age-related macular degeneration (AMD), as well as ocular and systemic side effects of drugs. The conditions discussed are all common conditions that the pharmacist may encounter in all practices of pharmacy. It is important for the pharmacist to be educated on these disorders and their associated treatment so that the pharmacist can evaluate the appropriateness of pharmacotherapy, screen for adverse effects and drug interactions, and counsel patients on their ocular medications.

GLAUCOMA

Glaucoma is the leading cause of irreversible blindness worldwide. The estimated number of suspected cases worldwide is 76 million and that number is expected to increase to 111 million in 2040. In the

United States, an estimated 3 million Americans are living with glaucoma, but only half know they have it.[2] Glaucoma is a general term used for a group of diseases that can irreversibly damage the optic nerve. The nerve damage presents as optic neuropathy with a characteristic “cupping” or excavation of the optic disc. Damage to the nerve results in corresponding visual field loss. Increased intraocular pressure (IOP) is one of the most common risk factors for the development of glaucoma. Generally, the higher the IOP, the greater the risk for developing glaucoma. However, there are forms of glaucoma that can develop in people with normal IOP. Increasing age, race (African descent), family history, thinner central corneas, and larger vertical cup-to-disc ratios are other risk factors for glaucoma.[1,3,4]

Intraocular Pressure

IOP is maintained by the balance between production of aqueous humor by the ciliary processes and the outflow of aqueous humor through the trabecular meshwork and uveoscleral outflow pathway. A test called *tonometry* can indirectly measure the IOP based on the pressure required to flatten a small area of the central cornea. Goldmann Applanation tonometry is the gold-standard method of determining IOP in a glaucoma evaluation. Generally, an IOP of 10 to 21 mm Hg is considered normal. An IOP of 22 mm Hg or greater poses an increased risk of glaucoma, although one of the less prevalent forms of glaucoma is associated with a low-to-normal IOP. IOP alone is not sufficient to rule in or rule out glaucoma. A thorough analysis of risks and comprehensive ocular health examination is necessary in order to diagnose glaucoma.[5]

Ocular Hypertension

Although elevated IOP poses a significant risk for glaucoma, it is possible to have elevated IOPs and not have glaucoma. This is referred to as *ocular hypertension*. Ocular hypertension is defined as

an IOP exceeding 21 mm Hg with normal visual fields, normal optic discs, open angles, and the absence of any ocular disease contributing to the elevation of IOP. Ocular hypertension is sometimes treated prophylactically with IOP-lowering medications, as it poses an increased risk for the development of glaucoma. Patients with normal visual fields and IOPs of 24 mm Hg or greater have a 10% likelihood of developing glaucoma in 5 years.[6,7] Patients with ocular hypertension are monitored closely, and a diagnosis of glaucoma can be applied when pathologic cupping of the optic nerve and/or a defect in the visual field is observed.[8]

Open-Angle Glaucoma

Primary open-angle glaucoma (POAG) is glaucoma in the presence of open anterior chamber angles and in the absence of other known causes of glaucomatous disease. Similar to other forms of glaucoma, it manifests by cupping (ie, excavation) of the optic disc and corresponding visual field loss. POAG occurs in ~2% of people older than 40 years in the United States. However, it can affect other age groups, including children.[1,3,4] In patients with POAG, aqueous humor outflow from the anterior chamber is continuously subnormal, primarily because of a degenerative process in the trabecular meshwork. Owing to diurnal variation, the IOP can fluctuate during the course of a day from normal to significantly high pressures.[1] The decreased outflow appears to be caused by degenerative changes in outflow channels (ie, the trabecular meshwork and Schlemm canal) and tends to worsen with the passage of time.[1] In rare cases, the outflow is normal even during a phase of elevated IOP, and the elevation appears to be the result of hypersecretion of aqueous humor.[1]

The onset of POAG is usually gradual and asymptomatic. A defect in the visual field (ie, scotoma) may be present in early glaucoma, but noticeable loss of peripheral vision is usually not seen until late in the course of the disease. Visual field defects correlate well with changes in the optic disc and help differentiate glaucoma from ocular

hypertension in patients with increased IOP. In addition, the characteristic pattern of visual field loss seen in glaucoma can help differentiate it from other nonglaucomatous forms of optic neuropathy.[9]

Angle-Closure Glaucoma

Examination of the anterior chamber angle by gonioscopy, using a corneal contact lens, a magnifying device, and a light source (eg, a slit-lamp biomicroscope), assists in differentiating between open-angle glaucoma and *angle-closure glaucoma*. Angle-closure glaucoma accounts for ~10% of all primary glaucoma cases in the United States. However, the prevalence is higher in Asian populations, in which 50% of glaucoma cases are angle closure.[10] The sole cause of the elevated IOP in angle-closure glaucoma is blockage of the anterior chamber angle, causing aqueous humor to build up in the anterior chamber, leading to an increase in IOP.[1,7]

Angle-closure glaucoma, which is a medical emergency in the acute form, usually presents as a rapid increase in IOP, blurring or sudden loss of vision, appearance of haloes around lights, and pain that is often severe. When patients are predisposed to angle-closure glaucoma, their pupils should not be dilated (eg, during an ophthalmic examination) and they should be taught the signs and symptoms of angle closure. Acute attacks can sometimes terminate without treatment, but if the IOP remains high, the optic nerve can be irreparably damaged.[1] Patients with chronic angle-closure glaucoma generally experience a gradual closure of aqueous humor outflow channels, and patients may remain asymptomatic until the glaucoma is in an advanced stage.[1] Permanent medical management of acute or chronic angle-closure glaucoma can be difficult: surgical procedures (eg, peripheral iridectomies) are typically indicated as the definitive treatment and are often used in conjunction with medical treatment.

Therapeutic Agents for Treatment of Primary Open-Angle Glaucoma

INITIAL THERAPY

The goals of medical treatment of POAG are to obtain 24-hour IOP control with minimum concentration of medications, minimum number of medications, and minimal local and systemic side effects.[8] Major drug classes for medical treatment of POAG include the following: α-agonists, β-adrenergic blockers (β-blockers), carbonic anhydrase inhibitors (CAIs), miotic agents, nitric oxide (NO) donors, prostaglandin analogs (PGAs), and rho-kinase (ROCK) inhibitors. PGAs are the most commonly prescribed first-line agents for POAG due to their increased efficacy and decreased dosage schedule. β-Adrenergic blockers are another first-line treatment option, although, in recent years, they have become more commonly used as a second-line or adjunctive treatment option. All of the ophthalmic β-blockers currently on the market are available in generic formulation, allowing for cost-effective treatment. Some of the PGAs are available as generic formulations as well, making their cost comparable to β-blockers. NO donors and ROCK inhibitors are newer agents, which can be very effective treatment options when traditional treatments have failed or are contraindicated.[11]

Prostaglandin analogs

Latanoprost (Xalatan®), travoprost (Travatan Z), bimatoprost (Lumigan®), and tafluprost (Zioptan®) are all PGAs. Latanoprost, travoprost, and tafluprost are analogs of prostaglandin $F_2\alpha$, and they lower IOP by serving as selective prostaglandin $F_2\alpha$-receptor agonists. Bimatoprost is a synthetic prostamide analog. Tafluprost is a preservative-free formulation supplied in single-use containers.[12]

The PGAs increase uveoscleral outflow of aqueous humor and thereby decrease IOP.[13] These agents are often prescribed as the

first-line agents for the treatment of POAG because they have been shown to be more effective than β-blockers, can be administered once a day, and are associated with minimal systemic adverse effects. On average, PGAs decrease IOP by 25% to 35% depending on the strength used.

Latanoprost

Latanoprost (Xalatan®) is approved for the initial treatment of POAG or ocular hypertension.[14] When administered once daily in the evening, the IOP-lowering effects of latanoprost have been shown to be superior to those of timolol 0.5% twice daily (bid).[15,16] In addition, the nocturnal control of IOP with latanoprost was superior to that with timolol. Latanoprost should be dosed only once daily in the evening because the IOP-lowering effects of latanoprost might actually be inferior when administered more frequently. Overdosing of latanoprost can in fact cause a paradoxical rise in IOP.

Systemic side effects are minimal with latanoprost, but local reactions (eg, iris pigmentation; eyelid skin darkening; periorbital fat atrophy resulting in deepening of superior lid sulcus with ptosis and enophthalmos; eyelash lengthening, thickening, pigmentation, and misdirected growth; conjunctival hyperemia; ocular irritation; and superficial punctate keratitis) are relatively common. Latanoprost can gradually increase the amount of brown pigment in the iris by increasing the melanin content in the stromal melanocytes of the iris. This pigment change occurs in 7% to 22% of patients and is most noticeable in those with green-brown, blue/gray-brown, or yellow-brown eyes.[14] The onset of increased iris pigmentation is usually noticeable within the first year of treatment and can be permanent.

Latanoprost has additive effects when administered with β-blockers (eg, timolol), CAIs (eg, dorzolamide), and α_2-adrenergic agonists (eg, brimonidine, apraclonidine). When added to existing therapy, latanoprost decreases IOP an additional 2.9 to 6.1 mm Hg. As a result, latanoprost is a good adjunctive ophthalmic agent for patients who are unable to adequately lower their IOP with single-agent therapy. The effectiveness of latanoprost when used once a

day either alone or as an adjunct to other IOP-lowering drugs and its relative tolerability makes it one of the most common, if not, treatment option for POAG and ocular hypertension.[15–20]

Travoprost

Travoprost (Travatan Z) is U.S. Food and Drug Administration (FDA) approved for the reduction of elevated IOP and ocular hypertension in patients who are intolerant or who fail to respond to other agents. Travoprost is often used as a first-line agent in clinical practice because it is more effective than timolol and at least as effective as latanoprost. In addition, it has been shown to be more effective than other PGAs in African Americans. The mean IOP reduction with travoprost in African American patients was 1.8 mm Hg greater than in non–African American patients. Travoprost, as adjunctive therapy to timolol in patients not responding adequately to timolol alone, reduced IOP an additional 6 to 7 mm Hg. The side-effect profile of travoprost is similar to that for latanoprost, including increased iris pigmentation and eyelash changes.[21–23] Local irritation may be less with travoprost because the current formulation (Travatan Z) is free of the preservative benzalkonium chloride (BAK). Rather, travoprost is preserved in the bottle with SofZia, which is a unique ionic buffer containing borate, sorbitol, propylene glycol, and zinc.

Bimatoprost

Like travoprost, bimatoprost (Lumigan®) once daily achieved lower target IOPs than did timolol bid. Iris pigmentation changed in 1.1% of patients treated with bimatoprost. In a 6-month randomized multicenter study, bimatoprost once a day lowered IOP more effectively than latanoprost once a day. Side effects were similar between treatment groups; however, conjunctiva hyperemia was more common ($P < .001$) in patients treated with bimatoprost. Overall, the side-effect profile of bimatoprost appears to be similar to that for latanoprost and travoprost.[24–26] The local side effects seen with other PGAs also appear to be relatively common with bimatoprost. In addition to treatment of glaucoma and ocular

hypertension, the FDA approved the cosmetic use of bimatoprost solution under the trade name Latisse®. Latisse® solution is applied with an applicator to the base of the upper eyelashes for the treatment of hypotrichosis (inadequate eyelashes). Eyelash lengthening, thickening, and darkening or pigmentation are seen after 8 to 16 weeks of use.[27]

Tafluprost

Tafluprost (Zioptan®) is a preservative-free product approved by FDA for the reduction of elevated IOP and ocular hypertension. Tafluprost daily in the evening is as effective as latanoprost daily in the evening and timolol 0.5% bid and has demonstrated additive efficacy when administered with timolol. Switch studies evaluating tafluprost in patients receiving BAK-containing agents demonstrated some improvement in adverse effects. As a result, tafluprost is an important option for patients with a documented hypersensitivity to BAK or other PGAs. The adverse-effect profile is similar to other PGAs.[28–32]

Xelpros (Latanoprost Ophthalmic Emulsion)

Xelpros is an ophthalmic emulsion containing latanoprost 50 µg/mL (0.005%) with potassium sorbate 0.47% is added as a preservative. Xelpros is the first formulation of latanoprost that does not contain the common preservative BAK. Dosing is once daily at night, and side effects are similar to latanoprost ophthalmic solution.[33]

β-Adrenergic blockers

Ophthalmic β-adrenergic antagonists block the β-adrenergic receptors in the ciliary epithelium of the eye and lower IOP primarily by decreasing aqueous humor production. On average, β-blockers decrease IOP by 20% to 30% depending on the strength used and the frequency of administration.[34–42]

Timolol (Timoptic®)

Timolol, a nonselective β_1- and β_2-adrenergic antagonist, is one of the most commonly prescribed glaucoma medications. Because timolol was the first ocular β-adrenergic blocker marketed, subsequently marketed ophthalmic β-blockers are usually compared with timolol for safety and effectiveness. Most β-blockers are approved for bid therapy. Therapy is usually initiated with a 0.25% solution administered as one drop bid. Concentrations or dosages exceeding one drop of timolol 0.5% bid do not produce further significant decreases in IOP.[43] In many cases, once daily with the nonselective agents is possible. Evidence suggests that β-blockers decrease aqueous production during the day but have much less effect during sleep. Therefore, dosing first thing in the morning is preferred in order to effectively blunt an early-morning pressure rise while minimizing the risk of systemic hypotension during sleep, when aqueous production is diminished. As systemic absorption occurs, a contralateral IOP-lowering effect in the untreated eye can also be observed.[44] In some cases, an escape phenomenon, or tachyphylaxis, can occur with timolol over time.

Timolol has been associated with a modest reduction of resting pulse rate (5–8 beats/minute),[44,45] worsening of heart failure, and adverse pulmonary effects (eg, dyspnea, airway obstruction, pulmonary failure).[46,47] After chronic administration in susceptible individuals, timolol can cause corneal anesthesia.[48,49] Although uveitis has been reported in patients receiving ophthalmic timolol, a cause-and-effect relationship has not been established.[50,51]

Systemic absorption after topical administration does occur, but it may not be significant in the majority of patients. Care should be taken when timolol is used in patients with sinus bradycardia, heart failure (see Chapter 14, Heart Failure), or pulmonary disease. Systemic side effects could be exaggerated in elderly patients secondary to inadvertent overdosing associated with poor administration technique (see Case 54-1, Question 3).

Timoptic XE®

Timoptic XE®, a timolol ophthalmic gel-forming solution, is administered once daily. The ophthalmic vehicle, gellan gum (Gelrite®), is a solution that forms a clear gel in the presence of monovalent or divalent cations.[52] This ion-activated gelation prolongs precorneal residence time and increases ocular bioavailability, allowing timolol to be administered once daily.[52] Timoptic XE® is comparable to timoptic solution in lowering IOP.[53]

Levobunolol (Betagan®)

Levobunolol, a nonselective β-adrenergic antagonist, is approved for either once-daily or bid administration. Levobunolol 0.5% and 1% are comparable to timolol in lowering IOP. The incidence of adverse reactions, including decreases in heart rate, is also comparable to that for timolol.[35,54]

Metipranolol (OptiPranolol®)

Another nonselective β-adrenergic blocking agent, metipranolol 0.1% to 0.6%, is comparable to timolol 0.25% to 0.5% in reducing IOP.[36,37] Like timolol, metipranolol produces corneal anesthesia, which occurs within 1 minute of instillation and returns to baseline after 10 minutes.[48] Metipranolol is associated with a greater incidence of stinging or burning on administration and has been associated with granulomatous anterior uveitis.[55,56] As a result of these side effects, the use of metipranolol is limited.

Carteolol (Ocupress®)

Carteolol, a nonselective β-adrenergic blocking agent with partial β-adrenergic agonist activity, theoretically should minimize the bronchospastic, bradycardic, and hypotensive effects associated with other ocular β-adrenergic blockers.[57] However, no clinical differences were seen when the cardiovascular and pulmonary function effects of carteolol were compared with those of timolol. Carteolol 1% and timolol 0.25% administered bid are equally effective in reducing IOP.[39–41]

Betaxolol (Betoptic®)

In contrast to other β-adrenergic blocking ophthalmic agents, betaxolol is a selective β_1-adrenergic blocker. This cardioselective property may result in less adverse effects on pulmonary function than nonselective β-adrenergic blockers in patients with reactive airway disorders. Betaxolol is slightly less effective than timolol in IOP reduction, and more patients tend to need adjunctive therapy with betaxolol.[42,58–60]

α_2-Adrenergic agonists

Apraclonidine (Iopidine®) and brimonidine (Alphagan®) are selective α_2-adrenergic agonists similar to clonidine. α_2-Adrenergic agonists decrease IOP by constriction of the afferent ciliary process vasculature, leading to decreased aqueous humor production, and also by increasing uveoscleral outflow.[61] Apraclonidine is less lipophilic than clonidine and brimonidine, does not cross the blood–brain barrier as readily, and theoretically has fewer systemic side effects (eg, hypotension, decreased pulse, dry mouth). Brimonidine is more highly selective for α_2-adrenergic receptors than clonidine or apraclonidine and, theoretically, should be associated with fewer ocular side effects.

Brimonidine is an alternative first-line agent in the treatment of POAG. It may also be used as adjunctive therapy in patients not responding to other agents. Apraclonidine 1% is indicated to control or prevent postsurgical elevations in IOP after argon laser trabeculoplasty or iridotomy. The 0.5% apraclonidine solution is indicated for short-term adjunctive therapy in patients on maximally tolerated medical therapy. Long-term IOP control should be monitored closely in patients taking α_2-adrenergic agonists because tachyphylaxis can occur. Common ocular side effects include burning, stinging, blurring, conjunctival follicles, and an allergic-like reaction consisting of hyperemia, pruritus, edema of the lid and conjunctiva, and foreign-body sensation. Topical sensitivity to α_2-adrenergic agonists is seen in ~10% to 20% of patients. These

events may result in discontinuation of treatment in ~12% of patients. Although ocular side effects are less common with brimonidine than with apraclonidine, systemic side effects (eg, dry nose and mouth, mild hypotension, decreased pulse, and lethargy) are more common with brimonidine. α_2-Adrenergic agonists should be used with caution in patients with cardiovascular disease, orthostatic hypotension, depression, and renal or hepatic dysfunction.[61,62] Brimonidine (Alphagan® P) is available with Purite as a preservative, which facilitates drug delivery into the eye, allowing use of a lower drug concentration. The substitution of Purite (in Alphagan® P) for BAK also results in decreased local irritation relative to that seen with the original BAK-containing brimonidine.[62]

The IOP reduction effects (peak and trough) of brimonidine 0.2% bid are 14% to 28%. Although the approved dosing schedule of brimonidine is three times a day (tid), brimonidine 0.2% bid lowers IOP comparably to timolol 0.5% bid, and both are slightly better than betaxolol 0.25% bid.[63,64] The IOP-lowering effect of brimonidine also may be comparable to that of latanoprost; however, conflicting efficacy and tolerability results in clinical studies may be related to differences in study design.[65] The combination of brimonidine and timolol is as equally tolerable and effective as the combination of dorzolamide and timolol.[66] The FDA-approved Combigan® ophthalmic solution combines an α_2-adrenergic agonist (brimonidine tartrate 0.2%) with a β-adrenergic blocker (timolol maleate 0.5%).

Topical carbonic anhydrase inhibitors

Carbonic anhydrase occurs in high concentrations in the ciliary processes and retina of the eye. CAIs lower IOP by decreasing bicarbonate production and, therefore, the flow of bicarbonate, sodium, and water into the posterior chamber of the eye, resulting in a 40% to 60% decrease in aqueous humor secretion.

Although CAIs have been used orally for many years in the treatment of elevated IOPs, they have been replaced by the topical ophthalmic CAIs, dorzolamide (Trusopt®) and brinzolamide (Azopt®), which are safer and better tolerated. Although topical CAIs are

acceptable options in the initial management of elevated IOPs, they are more typically used as secondary or tertiary treatment options owing to their relatively reduced efficacy and increased dosing schedule. They are also effective as adjunctive agents. Brinzolamide 1% tid reduces IOP comparably to that achieved with dorzolamide 2% tid and to betaxolol 0.5% bid, but slightly less than timolol 0.5% bid. The IOP reduction effects (peak and trough) of dorzolamide 2% tid are 16% to 25%. Brinzolamide and dorzolamide are approved for tid dosing; however, bid dosing may be adequate. Dorzolamide provides additional IOP-lowering effects when added to existing β-blocker therapy.[67,68] Typically, CAIs are dosed bid when used as adjunctive therapy and tid when used as monotherapy. An ophthalmic solution of dorzolamide hydrochloride and timolol maleate is marketed as Cosopt®, and a combination of brinzolamide and brimonidine is marketed as Simbrinza™.[69]

The combined use of topical dorzolamide and oral acetazolamide does not result in additive effects and might increase the risk of toxicity. Therefore, the concomitant use of topical and oral CAIs is not advised.[64–66]

The topical CAIs are well tolerated with few systemic side effects. The most common adverse effects reported with dorzolamide are ocular burning, stinging, discomfort and allergic reactions, bitter metallic taste, and superficial punctate keratitis. Corneal epithelial decompensation is possible. Therefore, CAIs should not be used in patients with corneal compromise. Brinzolamide causes less burning and stinging of the eyes than dorzolamide because its pH more closely resembles that of human tears. Dorzolamide and brinzolamide are sulfonamides and may cause the same types of adverse reactions attributable to sulfonamides. These drugs should not be used in patients with renal or hepatic impairment.[70–72]

Nitric oxide donors

In November 2017, the FDA approved latanoprostene bunod ophthalmic solution (Vyzulta®, 0.024%, Bausch & Lomb) for reduction of IOP in patients with open-angle glaucoma or ocular

hypertension. Latanoprostene bunod has a dual mechanism of action. The first is PGA activity (latanoprost), which increases outflow of aqueous humor through the uveoscleral pathway. The second component (butanediol mononitrate) releases NO, which induces cell relaxation in the trabecular meshwork, leading to a widening of intercellular spaces, thereby increasing outflow through the trabecular meshwork. Latanoprostene bunod is dosed once daily. Results from the LUNAR and APOLLO studies have shown that latanoprostene bunod is more effective than timolol with a 32% reduction in IOP from baseline.[73,74] The VOYAGER study compared latanoprostene bunod to latanoprost alone. Latanoprostene bunod was associated with 1.2 mm Hg of additional IOP lowering compared to latanoprost. Safety, tolerability, and side effects of latanoprostene bunod are very similar to those of latanoprost.[75]

Rho-kinase inhibitors

Netarsudil ophthalmic solution (Rhopressa®, 0.02%) is indicated for reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Netarsudil is dosed once daily. Netarsudil has three different mechanisms of action. It increases outflow through the trabecular meshwork, decreases the production of aqueous humor, and decreases episcleral venous pressure. ROCKET-1 and ROCKET-2 studies showed noninferiority of netarsudil to timolol.[76] The studies demonstrated consistent IOP reduction of about 5 mm Hg across a range of baseline IOPs. Efficacy of netarsudil was particularly notable in patients with low baseline IOPs. Common side effects include significant conjunctival hyperemia, small conjunctival hemorrhages at the limbus, and corneal verticillata (whirl-like corneal deposits that are seen in 20% of patients treated with netarsudil).

The combined netarsudil/latanoprost ophthalmic solution (Rocklatan®, 0.02%/0.005%) is indicated for reduction of IOP in patients with open-angle glaucoma or ocular hypertension. This fixed combination of netarsudil/latanoprost is dosed once daily and has a quadruple mechanism of action. The combined netarsudil/latanoprost acts on both the trabecular meshwork and the

uveoscleral outflow pathways to increase aqueous outflow. In addition, it decreases aqueous production and decreases episcleral venous pressure. This combination drug has been shown to reduce IOP by 1 to 3 mm Hg more than either netarsudil or latanoprost monotherapy. Side effects are similar to those of netarsudil and latanoprost.[77]

Pilocarpine

Pilocarpine (Isopto-Carpine®) historically was an initial treatment of choice, but with the introduction and widespread use of newer agents, and unfavorable side effects of pilocarpine (reduced vision, accommodative spasm, and brow ache), pilocarpine has fallen out of favor. Pilocarpine is now typically reserved for refractory cases. Therapy is usually begun using lower concentrations (1%), one drop four times a day (qid). It can also be used in angle-closure attacks. Pilocarpine is a direct-acting cholinergic (parasympathomimetic) that causes contraction of ciliary muscle fibers attached to the trabecular meshwork and scleral spur. This opens the trabecular meshwork to enhance aqueous humor outflow. There may also be a direct effect on the trabecular meshwork. Pilocarpine causes miosis by contraction of the iris sphincter muscle, but the miosis is not related to the decrease in IOP.

Carbachol

Carbachol (Isopto Carbachol®) is reserved as a third-line agent in patients who are unresponsive or intolerant to initial medications. In addition to having direct cholinergic effects, carbachol is more resistant to cholinesterase than pilocarpine. Added benefits include increased release of acetylcholine from parasympathetic nerve terminals and a weak anticholinesterase effect. Carbachol is administered tid.

Anticholinesterase agents

If control of IOP is not achieved with optimal use of other topical monotherapy and combination therapy agents, then anticholinesterase agents may be prescribed as a last topical therapy option. Anticholinesterase agents inhibit the enzyme cholinesterase, thereby increasing the amount of acetylcholine and its naturally occurring cholinergic effects.

Echothiophate iodide

Echothiophate iodide (Phospholine iodide®), an irreversible cholinesterase inhibitor, primarily inactivates pseudocholinesterase and secondarily inhibits true cholinesterase. Echothiophate iodide may be used if maximal doses of other agents and combination therapy are ineffective. Echothiophate iodide has a long duration of action that affords good control of IOP; however, miosis and myopia are significant side effects. Concentrations greater than 0.06% are associated with a significant increase in subjective concerns (eg, brow ache).[78]

COMBINATION THERAPY

In general, drugs with different pharmacologic actions have at least partially additive effects in lowering IOP in the treatment of glaucoma. Drugs with similar pharmacologic actions (ie, from the same pharmacologic class) should not be combined because dose-related adverse effects are more likely and the incremental increase in benefits is likely to be more modest. When considering combination IOP-lowering drugs, it is best to trial at least one of the components first. Combination therapy is rarely initiated first. Monotherapy is typically the first-line treatment, then addition of a second drug via a combination product can be trialed if the initial single drug failed to meet target pressure.[79]

Timolol and other β-adrenergic blocking drugs have additive IOP-lowering effects when used in combination with miotic agents, PGAs, α_2-agonists, and CAIs. For example, the IOP-lowering effect is greater when timolol is used in combination with pilocarpine, dorzolamide, brimonidine, and travoprost. Likewise, for example,

latanoprost has additive effects when administered with timolol, dorzolamide, and α_2-adrenergic agonists.[16–20,80–85] The trend toward the development of fixed combination products offers many advantages in the treatment of POAG. These advantages include improved adherence because of a reduction in the number of dosages and bottles, eliminating the need to instill two separate drugs 5 to 10 minutes apart to prevent a washout effect from the second medication, improving safety and tolerability by limiting the exposure to the BAK preservative, and a cost savings for the patient by potentially eliminating a copay for one of the medications. There are two β-adrenergic blocker combination products currently on the market, timolol/dorzolamide (Cosopt®) and brimonidine/timolol (Combigan®). The IOP-lowering effects of timolol/dorzolamide (Cosopt®) are comparable to or greater than those of latanoprost monotherapy.[71] Brinzolamide and brimonidine are combined and available as Simbrinza™.[69]

Predisposing Factors

CASE 54-1

Question 1: L.S., a 65-year-old African American male with brown eyes, presented for routine eye examination. Visual acuity with correction was 20/20 in the right eye and 20/25 in the left eye. Pupils were normal in both eyes. IOP via Goldmann Applanation tonometry was 26 mm Hg in the right eye and 24 mm Hg in the left eye. Anterior chamber angles were open in both eyes on gonioscopic examination. Dilated fundus examination with ophthalmoscopy revealed large cupping of the optic discs in both eyes, with thinning of the neuroretinal rim tissue, and corresponding nerve fiber bundle defects. There were no signs of cataract formation. Visual field examination revealed superior and inferior arcuate bundle defects consistent with glaucoma. L.S. related a positive family history of glaucoma and presently is being treated for systemic hypertension, chronic heart failure (CHF), chronic obstructive pulmonary disease, and asthma. His medications include the following:

Amitriptyline, 75 mg at bedtime
Chlorpheniramine, 4 mg every 6 hours as needed (PRN)
Lisinopril, 10 mg once daily
Furosemide, 40 mg bid

Nitroglycerin, 0.3 mg sublingual PRN
Fluticasone/salmeterol 250/50 µg dry powder inhaler, one inhalation bid
Albuterol 90 µg metered-dose inhaler, 1 to 2 puffs qid PRN
Tiotropium bromide inhaler, 18 µg inhaled once daily

Findings on examination indicate that L.S. has POAG. What other factors may predispose L.S. to an increased IOP?

POAG is thought to have a genetic component, and L.S. has a positive family history. The disease is more prevalent and aggressive in African Americans.[1] In addition, he is taking several medications that have been associated with increases in IOP.

ANTICHOLINERGIC DRUGS

Most reports dealing with drug-induced increases in IOP center around precipitation of angle-closure glaucoma by ophthalmic mydriatic or cycloplegic agents (anticholinergics). In patients with open-angle glaucoma, topical anticholinergics can significantly increase resistance to aqueous humor outflow and elevate IOP, while the anterior chamber remains grossly open.[6] As part of any routine ophthalmic examination, the pupils are dilated with a mydriatic or cycloplegic agent (unless otherwise contraindicated). The IOP is always measured before this procedure, so the use of these agents would not have influenced the IOP readings for L.S.

If systemic anticholinergic agents are administered in doses sufficient to cause pupillary dilation, the risk of precipitating angle-closure increases. However, it is unlikely that these agents will aggravate open-angle glaucoma unless the amount reaching the eye is sufficient to cause cycloplegia.[6] Although literature documentation of POAG exacerbation by these agents is scarce, medications with anticholinergic side effects (eg, antihistamines, benzodiazepines, disopyramide, phenothiazines, tricyclic antidepressants, tiotropium) should be considered. L.S. is receiving chlorpheniramine PRN, amitriptyline at bedtime, and tiotropium bromide once daily, but his pupil examination is normal with no evidence of mydriasis or cycloplegia. Therefore, it is highly unlikely that these medications contributed to his increased IOP.

ADRENERGIC DRUGS

Adrenergic agents, such as central nervous system stimulants, vasoconstrictors, appetite suppressants, and bronchodilators, may produce minimal pupillary dilation. These have no proven adverse influences on IOP in patients with either normal eyes or eyes with open-angle glaucoma. Consequently, the use of salmeterol and albuterol in L.S. is also an unlikely source of the increased IOP.

OTHER DRUGS

Conclusive evidence for the production of angle-closure glaucoma by vasodilators is lacking, although slight increases in IOP have been reported. The use of nitroglycerin PRN for L.S. is not a cause for concern. There have been isolated reports of other medications causing mydriasis in patients with glaucoma, including muscle relaxants (carisoprodol), monoamine oxidase inhibitors, fenfluramine, ganglionic blocking agents, salicylates, and oral contraceptives. Succinylcholine, ketamine, and caffeine have been associated with increases in IOP. Corticosteroid-induced IOP elevation has been shown in systemic, topical, and inhaled corticosteroid use. IOP elevation occurs more frequently with topical administration of corticosteroids (drops or ointment applied directly to the eye or over the skin of the eyelids) than with systemic or inhaled administration. However, studies have shown a strong association between inhaled corticosteroid and the presence of ocular hypertension in patients with family history of glaucoma. The risk increases with higher dose and more puffs. The use of fluticasone/salmeterol inhaler bid could pose a risk for increased IOP in L.S. Corticosteroid-induced IOP elevation is addressed further in Case 54-8, Question 2.

If L.S. requires administration of any other medications associated with increases in IOP, the risk of potential adverse effects can be minimized by routine follow-up, with modification of treatment PRN.

Initial Therapy

Case 54-1, Question 2: It is determined that L.S. has POAG and requires initiation of treatment with a goal of 30% reduction in IOP (18 mm Hg in the right eye, 17 mm Hg in the left eye) in order to halt the progression of glaucoma. What is the best initial therapeutic treatment for L.S.?

PGAs (or in some cases topical β-blockers) are the initial agents of choice in the treatment of POAG (**Fig. 54-2**). Their efficacy is well documented in numerous studies, and side effects are well characterized. Brimonidine (Alphagan®) and topical CAIs are alternative first-line agents. **Table 54-1** lists the common topical agents used in the treatment of POAG.

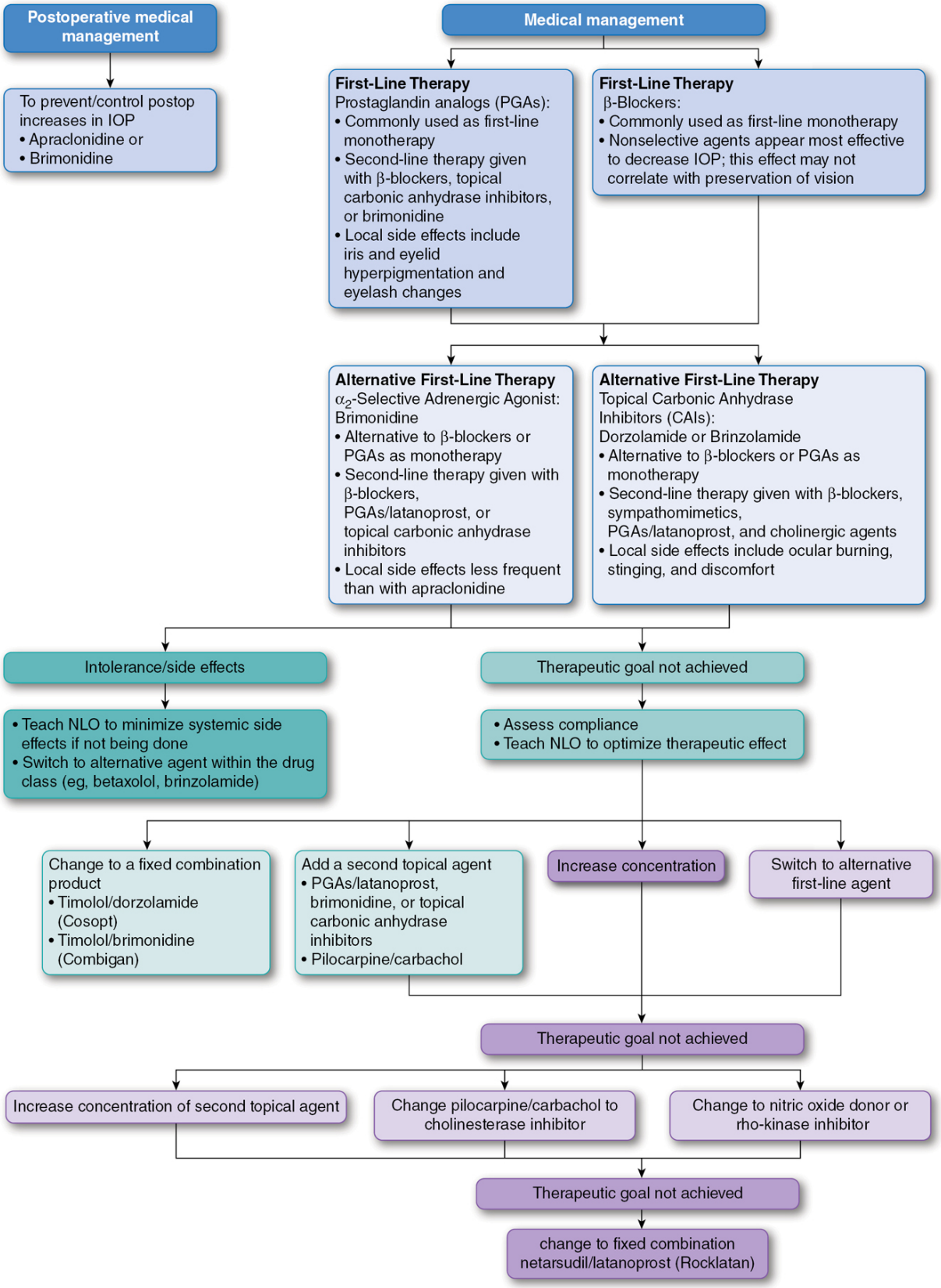

Postoperative medical management
To prevent/control postop increases in IOP
• Apraclonidine or
• Brimonidine
Medical management
First-Line Therapy
Prostaglandin analogs (PGAs):
• Commonly used as first-line monotherapy
• Second-line therapy given with β-blockers, topical carbonic anhydrase inhibitors, or brimonidine
• Local side effects include iris and eyelid hyperpigmentation and eyelash changes
First-Line Therapy
β-Blockers:
• Commonly used as first-line monotherapy
• Nonselective agents appear most effective to decrease IOP; this effect may not correlate with preservation of vision
Alternative First-Line Therapy
α2-Selective Adrenergic Agonist: Brimonidine
• Alternative to β-blockers or PGAs as monotherapy
• Second-line therapy given with β-blockers, PGAs/latanoprost, or topical carbonic anhydrase inhibitors
• Local side effects less frequent than with apraclonidine
Alternative First-Line Therapy
Topical Carbonic Anhydrase Inhibitors (CAIs):
Dorzolamide or Brinzolamide
• Alternative to β-blockers or PGAs as monotherapy
• Second-line therapy given with β-blockers, sympathomimetics, PGAs/latanoprost, and cholinergic agents
• Local side effects include ocular burning, stinging, and discomfort
Intolerance/side effects
• Teach NLO to minimize systemic side effects if not being done
• Switch to alternative agent within the drug class (eg, betaxolol, brinzolamide)
Therapeutic goal not achieved
• Assess compliance
• Teach NLO to optimize therapeutic effect
Change to a fixed combination product
• Timolol/dorzolamide (Cosopt)
• Timolol/brimonidine (Combigan)
Add a second topical agent
• PGAs/latanoprost, brimonidine, or topical carbonic anhydrase inhibitors
• Pilocarpine/carbachol
Increase concentration
Switch to alternative first-line agent
Therapeutic goal not achieved
Increase concentration of second topical agent
Change pilocarpine/carbachol to cholinesterase inhibitor
Change to nitric oxide donor or rho-kinase inhibitor
Therapeutic goal not achieved
change to fixed combination netarsudil/latanoprost (Rocklatan)

Figure 54-2 Medical management of glaucoma. IOP, intraocular pressure; NLO, nasolacrimal occlusion.

Table 54-1
Common Topical Agents Used in the Treatment of Open-Angle Glaucoma

Generic	Mechanism	Strength	Usual Dosage	Comments
Prostaglandin Analogs				
Bimatoprost (Lumigan®)	Prostamide	0.01%, 0.03%	One drop once a day at bedtime	Bid dosing may be less effective than qhs dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare but include colds and upper respiratory tract infections and headache. May be more effective than timolol and latanoprost
Latanoprost (Xalatan®)	Prostaglandin $F_{2\alpha}$ agonist	0.005%	One drop once a day at bedtime	Bid dosing may be less effective than once a day at bedtime dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare but may cause muscle, joint, back pain, headaches, migraines, and skin rash. Effective monotherapy or adjunctive therapy. Store unopened bottles in refrigerator. Opened bottles may be stored at room temperature up to 6 weeks.
Latanoprost ophthalmic emulsion (Xelpros™)	Prostaglandin $F_{2\alpha}$ agonist	0.005%	One drop once a day at bedtime	Bid dosing may be less effective than once a day at bedtime dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare but may cause muscle, joint, back pain, headaches, migraines, and skin rash. Effective monotherapy or adjunctive therapy. Store unopened bottles in refrigerator. Opened bottles may be stored at room temperature up to 6 weeks BAK-free formulation of latanoprost
Tafluprost (Zioptan®)	Prostaglandin $F_{2\alpha}$ agonist	0.0015% preservative-free dropperette	One drop once a day at bedtime	Bid dosing may be less effective than qhs dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare but include common cold, cough, headache, and urinary tract infections. Store unopened foiled pouches in refrigerator. Single-use container may be stored in the opened foil pouch for 28 days at room temperature.
Travoprost (Travatan Z®)	Prostaglandin $F_{2\alpha}$ agonist	0.004%	One drop once a day at bedtime	Bid dosing may be less effective than once a day at bedtime dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare, but may include colds and upper respiratory tract infections. Effective monotherapy or adjunctive therapy with timolol. May be more effective than timolol and latanoprost and more effective in African Americans. Does not contain benzalkonium chloride as a preservative. Contains the preservative SofZia that may be better tolerated.
β-*Adrenergic Blockers*				
Betaxolol (Betoptic [solution], Betoptic S® [suspension])	Sympatholytic	0.25% (suspension) 0.5% (solution)	One drop bid One drop bid	Shake suspension well before use. Effective with few associated ocular side effects. Bid dosage enhances compliance. Considered β-blocker of choice in patients with preexisting HF or pulmonary disease because of β_1-adrenergic specificity. Patient response may be less than that seen with timolol.
Carteolol (Ocupress®)	Sympatholytic	1%	One drop bid	Effective with few associated side effects. Bid dosage enhances compliance. Use with caution in patients with preexisting HF or pulmonary disease.

Levobunolol (Betagan®)	Sympatholytic	0.25%, 0.5%	One drop daily or bid	Effective with few associated ocular side effects. Daily and bid dosage enhances compliance. Use with caution in patients with preexisting HF or pulmonary disease.
Metipranolol (OptiPranolol®)	Sympatholytic	0.3%	One drop bid	Effective with few associated side effects. Bid dosage enhances compliance. Use with caution in patients with preexisting HF or pulmonary disease.
Timolol (Timoptic®) (Betimol®) (Istalol®)	Sympatholytic	0.25%, 0.5% 0.5% (Istalol®) 0.25%, 0.5% preservative-free (Timoptic Ocudose)	One drop bid One drop daily in the morning (Istalol®)	Effective with few associated ocular side effects. Daily and bid dosage enhances compliance. Use with caution in patients with preexisting HF or pulmonary disease. Proven long-term effectiveness, with well-defined side-effect profile
Timolol Gel-Forming Solution (Timoptic XE, Timolol GFS)	Sympatholytic	0.25%, 0.5%	One drop daily	Once-daily timolol formulation. The ophthalmic vehicle, gellan gum (Gelrite), prolongs precorneal residence time and ↑ ocular bioavailability, allowing once-daily administration.
α_2-Selective Adrenergic Agonists				
Apraclonidine (Iopidine)	Sympathomimetic	0.5%, 1%	One drop preoperatively and postoperatively or one drop bid to tid	May be used preoperatively and postoperatively for the prevention of ↑ IOP after anterior-segment laser procedures. Use of NLO minimizes systemic side effects and allows for bid dosing. Does not penetrate the blood–brain barrier, therefore negligible systemic hypotension. Local adverse effects fairly common. Tachyphylaxis may be observed.
Brimonidine (Alphagan®)	Sympathomimetic	0.15%, 0.2%	One drop bid to tid	Effective long-term monotherapy or adjunctive therapy. Use of NLO minimizes systemic side effects and allows for bid dosing. Penetrates the blood–brain barrier, therefore may cause mild systemic hypotension and lethargy. Local adverse effects less common than with apraclonidine
Brimonidine (Alphagan® P)	Sympathomimetic	0.1%, 0.15%	One drop bid to tid	Contains Purite preservative. Purite preservative and lower concentrations may improve tolerability.
Topical Carbonic Anhydrase Inhibitors				
Brinzolamide (Azopt®)	Decreased aqueous humor production	1%	One drop tid	Shake suspension well before use. Effective long-term monotherapy or adjunctive therapy. Well tolerated with few systemic side effects. Less burning and stinging compared with dorzolamide
Dorzolamide (Trusopt®)	Decreased aqueous humor production	2%	One drop tid	Effective long-term monotherapy or adjunctive therapy. Well tolerated with few systemic side effects
Nitric Oxide Donors				
Latanoprostene bunod (Vyzulta®)	Nitric oxide–donating prostaglandin $F_{2\alpha}$ analog	0.024%	One drop once a day at bedtime	Bid dosing may be less effective than once a day at bedtime dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare but may cause muscle, joint, back pain, headaches, migraines, and skin rash. Effective monotherapy or adjunctive therapy. Store unopened bottles in refrigerator. Opened bottles may be stored at room temperature up to 6 weeks.

Rho-Kinase Inhibitor				
Netarsudil (Rhopressa®)	ROCK inhibitor plus norepinephrine transporter: increase trabecular meshwork outflow, lower episcleral venous pressure, decrease aqueous production	0.02%	One drop once a day at bedtime	Significant conjunctival hyperemia, small conjunctival hemorrhages, and corneal deposits. Particularly effective in patients with low baseline IOPs.
Miotics				
Pilocarpine (Isopto® Carpine)	Parasympathomimetic	1%, 2%, 4%	One to two drops tid or qid	Long-term proven effectiveness. Little rationale for administration more frequently than every 4 hours. Side effects of miosis with decreased vision and brow ache are common sources of patient problems.
Carbachol (Isopto® Carbachol)	Parasympathomimetic	1.5%, 3%	One to two drops tid or qid	Used in patients allergic to or intolerant of other miotics. May be used as frequently as every 4 hours. Corneal penetration is enhanced by benzalkonium chloride in commercial preparations. Side effects are similar to those of pilocarpine.
Echothiophate iodide (Phospholine iodide®)	Anticholinesterase	0.125%	One drop bid	Long duration, although usually dosed bid, which enhances compliance. Available as powder plus diluent; after reconstitution, stable 30 days at room temperature, 6 months refrigerated. Side effects similar to those of pilocarpine. Increased cataract formation has been associated with its use.
Combination Products				
Brimonidine tartrate 0.2%/timolol 0.5% (Combigan)	Sympathomimetic/ sympatholytic	0.2%/0.5%	One drop bid	Combination products may improve adherence. Eliminates the 5- to 10-minute wait between instillation of drops
Brinzolamide 1%/brimonidine 0.2% (Simbrinza™)	Decreased aqueous humor production/sympathomimetic	1%/0.2%	One drop tid	Shake suspension well before use. Combination products may improve adherence. Eliminates the 5- to 10-minute wait between instillation of drops
Dorzolamide 2%/timolol 0.5% (Cosopt®)	Decreased aqueous humor production/ sympatholytic	2%/0.5% 2%/0.5% preservative free (Cosopt® PF)	One drop bid	Combination products may improve adherence. Eliminates the 5- to 10-minute wait between instillation of drops
Netarsudil/latanoprost (Rocklatan®)	Netarsudil plus latanoprost: increase trabecular meshwork and uveoscleral outflow, lower episcleral venous pressure, decrease aqueous production	0.02%/0.005%	One drop once a day at bedtime	Significant conjunctival hyperemia, small conjunctival hemorrhages, and corneal deposits. Bid dosing may be less effective than once a day at bedtime dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare but may cause muscle, joint, back pain, headaches, migraines, and skin rash. Particularly effective in patients with low baseline IOPs.

Bid, twice daily; GFS, gel-forming solution; HF, heart failure; IOP, intraocular pressure; NLO, nasolacrimal occlusion; qhs, every day at bedtime; qid, four times a day; tid, three times a day.

Timolol or other nonselective β-adrenergic blockers should not be initiated for L.S. because of his history of asthma and chronic

obstructive pulmonary disease (the indications and use of β-blockers for patients with heart failure are described in Chapter 14, Heart Failure). Betaxolol, a β_1-adrenergic blocker, is better tolerated than the nonselective β-adrenergic blocker, timolol, in patients with reactive airway disease and could be considered in cases in which topical β-blocker therapy is the only viable option.[40,58,59,86] L.S. does not have any contraindications for PGA use. Therefore, latanoprost 0.005% every day at bedtime (qhs) would be the ideal initial treatment of L.S.'s glaucoma because of its once-a-day dosing and superior efficacy. Travoprost is another PGA option that has been shown to be particularly effective in African Americans.[21] In this case, latanoprost was chosen because it was available as a cost-effective generic formulation.

Betaxolol 0.25% suspension bid could be an acceptable alternative to latanoprost if L.S. had contraindications for use of PGAs. Betaxolol is a cardioselective β_1-adrenergic blocker; nevertheless, adverse pulmonary and cardiac side effects can still occur with betaxolol. L.S. would need to be followed closely for these adverse effects. Although ocular burning and stinging have been associated more frequently with betaxolol and metipranolol than with other topical β-blockers, the 0.25% suspension is better tolerated than the 0.5% solution and is as effective.[58] Brimonidine and topical CAIs are other alternatives to latanoprost as initial therapy. Although brimonidine and topical CAIs may not exacerbate his asthma or CHF, they can cause localized side effects and brimonidine can cause systemic hypotension and lethargy.

Patient Education

Case 54-1, Question 3: Latanoprost 0.005%, one drop in both eyes qhs, is ordered for L.S. How should L.S. be instructed regarding the proper use of his latanoprost and expected therapeutic side effects?

L.S. should be instructed to hold the inverted latanoprost bottle between his thumb and middle finger and to rest that hand on his

forehead to minimize the risk of inadvertent eye injury caused by sudden unexpected movement of the hand. The index finger is left free to depress the bottom of the container, releasing one drop for the dose. With a little practice, this technique is easy to master. The lower eyelid should be drawn downward with the index finger of the opposite hand to form a pouch. The patient should look up and administer the drug into the pouch of the eye.

Patients must be encouraged to continue regular use of their medications for effective treatment of glaucoma. Chronic glaucoma is a silent disease and often not associated with symptoms; therefore, the continuation of therapy should be encouraged continuously in patients, especially when side effects to drug therapy can be encountered. Latanoprost is best administered every 24 hours in the evenings because this schedule of administration is consistent with its duration of action (see Table 54-1).

L.S. should be informed of the PGA-induced potential for hyperpigmentation of the iris, which may be permanent. He also needs to be educated on the possibility of periorbital fat atrophy, eyelid skin darkening, and increased thickness, length, and pigmentation of his eyelashes, which all may or may not be reversible. These side effects might not be as cosmetically concerning to L.S., because he has brown eyes and will be instilling latanoprost eye drops into both eyes so the effects would be symmetrical. Systemic side effects (eg, muscle, joint, and back pain; headaches; migraines; skin rash) are rare with latanoprost, but L.S. should be instructed to report any of these effects to his primary care provider.

NASOLACRIMAL OCCLUSION

Case 54-1, Question 4: How much would occlusion of the nasolacrimal ducts (punctal occlusion) by L.S. influence systemic absorption or alter the therapeutic effects of latanoprost?

Nasolacrimal, or punctal, occlusion is a technique that can decrease the amount of drug absorbed systemically.[87] Occlusion of the puncta (through the application of slight pressure with the finger to the inner corner of the eye closest to the nose for 3 to 5 minutes during and after drug instillation) can minimize systemic absorption of ophthalmic medications, decrease the incidence of side effects, and improve medication effectiveness.[87–89] When a single drop of ophthalmic timolol 0.5% was instilled into the eyes of patients at various times before cataract surgery and the nasolacrimal duct was occluded for 5 minutes, drug levels in the aqueous humor were significantly greater in patients who had their nasolacrimal ducts occluded than those who did not.[88] Nasolacrimal occlusion is effective and can maximize drug benefits and decrease systemic absorption and side effects.[81]

Alternative Therapy

Case 54-1, Question 5: Two weeks after initiation of therapy, L.S. returns to clinic for a follow-up evaluation. His IOP measures 22 mm Hg in the right eye and 21 mm Hg in the left eye. Although the latanoprost did lower the IOP in each eye, it did not reach the treatment goal (ie, target IOP). He denies nonadherence and has no intolerable side effects. How should therapy be altered? What alternative dosage forms or drugs can be used?

L.S. should be evaluated to determine whether he has been using proper technique when instilling the drops and performing nasolacrimal occlusion. If not, L.S. should be again instructed on proper technique and nasolacrimal occlusion and the importance of this technique in achieving the maximal therapeutic effect of her therapy (see Case 54-1, Question 4).

After the initiation of therapy, patients should be seen for a follow-up evaluation within about 2 weeks. If L.S. has been adherent to therapy and has been occluding his nasolacrimal ducts, a new course of action is needed because his IOP still is elevated. When the goal of therapy has not been achieved, the drug concentration of

the ophthalmic formulation can be increased, adjunctive therapy (eg, betaxolol, brimonidine, or a topical CAI) can be initiated, or an alternative first-line agent can be selected. Patients who are experiencing unstable reductions of IOP should be followed up within 3 months.[7] Stable patients are usually evaluated every 6 months.[7]

Adverse Effects

Case 54-1, Question 6: After the follow-up evaluation, dorzolamide 2% solution, one drop both eyes bid, is added to L.S.'s latanoprost therapy. This option was selected in order to avoid potential local and systemic side effects of brimonidine, as well as potential systemic side effects of betaxolol. Two weeks later, L.S. returns for a follow-up evaluation for bilateral stinging and foreign-body sensation. His IOP measures 22 mm Hg in the right eye and 21 mm Hg in the left eye. What are the possible causes of his side effects and poor response to therapy?

The exposure of dorzolamide to the outside environment may result in the aggregation of dry white granules on the tip of the dorzolamide bottle. These granules can drop into a patient's eyes when instilling the medication, leading to local side effects, such as stinging and foreign-body sensation. Such foreign bodies may cause enough discomfort to induce nonadherence, resulting in a poor response to therapy. These granules may be rinsed off the tip with sterile water. L.S. should be questioned about the presence of dry white granules on the tip of his dorzolamide bottle.[90]

These problems may also be a side effect from the medications, regardless of the granule presence. Ocular burning, stinging, and discomfort were reported in one-third of patients in dorzolamide clinical trials. L.S.'s administration technique should also be assessed to determine whether he is administering the two drugs at least 5 to 10 minutes apart so that the first drug is not washed away by the second drug. This should be a consideration when assessing his response to therapy.[43]

Case 54-1, Question 7: After further discussions with L.S., it is determined that he has not been adherent to his dorzolamide therapy because of intolerable side effects. The dorzolamide is discontinued and replaced with brimonidine (Alphagan® P) 0.1% one drop both eyes bid. What are the benefits of Alphagan® P? What patient education information should be provided to L.S. about side effects of brimonidine?

Brimonidine is a reasonable adjunctive therapy in patients who are not responding to or are having intolerable side effects from other medications. Alphagan® P is an ideal formulation for L.S. because it contains Purite preservative and is available in a lower concentration, which may decrease side effects and improve tolerability. Nevertheless, L.S. still needs to be informed about the potential for localized ocular sensitivity reactions (burning, stinging, blurring, conjunctival follicles, and an allergic-like reaction), systemic hypotension, and lethargy.

ANGLE-CLOSURE GLAUCOMA

Treatment

CASE 54-2

Question 1: D.H., a 72-year-old male, presents to the emergency department with an intensely red right eye, a "steamy" appearing cornea, haloes around lights, and extreme pain. A diagnosis of acute angle-closure glaucoma is made.
How should D.H. be managed?

D.H. should be seen immediately by an ophthalmologist because acute angle-closure glaucoma is a medical emergency. Medical treatment usually consists of pilocarpine 2% to 4%, one drop every 5 minutes for four to six administrations. It is recommended that the puncta be covered during administration to decrease the possibility of systemic absorption. Stronger miotic agents are contraindicated

because they may potentiate angle closure. Topical timolol also has been used in acute angle-closure glaucoma, commonly in combination with pilocarpine. However, drugs that decrease aqueous humor production may be ineffective in this situation because they have a decreased ability to reduce aqueous production if the ciliary body is ischemic.[7]

HYPEROSMOTIC AGENTS

Hyperosmotic agents (**Table 54-2**) act by creating an osmotic gradient between the plasma and ocular fluids.[91] Agents that are confined to the extracellular fluid space (eg, mannitol) provide a greater effect on blood osmolality at the same dosage than do agents distributed in total body water.[91] Intravenously administered drugs provide a faster, somewhat greater effect than oral agents. Palatability may be a problem with oral agents and can be improved by serving these agents over crushed ice or with lemon juice or cola flavoring.

Table 54-2
Hyperosmotic Agents

Generic	Mode of Administration	Strength	Onset	Peak	Duration	Dose (g/kg)	Ocular Penetration	Distribution
Mannitol	IV	5%, 10%, 15%, 20%	30–60 minutes	1 hour	6–8 hours	1–2	Very poor	E
Glycerin	PO	50%	10–30 minutes	30 minutes	4–5 hours	1–1.5	Poor	E
Isosorbide	PO	45%	10–30 minutes	1 hour	5 hours	1.5–2	Good	TBW

E, extracellular water; IV, intravenous; PO, orally; TBW, total body water.

Orally, 50% glycerin is the usual drug of choice and is administered in dosages of 1 to 1.5 g/kg.[92] Isosorbide is an alternative, especially in patients with diabetes because it is not metabolized to provide calories.[93] Parenterally, mannitol is the drug of choice. It is administered in doses of 1 to 2 g/kg, is not metabolized to provide calories, and may be used in patients with renal failure.[94,95]

Primary side effects of hyperosmotic agents include headache, nausea, vomiting, diuresis, and dehydration. It is important that the

patient not be allowed to drink because this will counteract the osmotic effects of these agents.

Precipitation of pulmonary edema and CHF has been reported with hyperosmotic agents, and an allergic reaction has been reported with mannitol.[96]

Acetazolamide (Diamox) 500 mg intravenously may be administered in addition to hyperosmotic agents.

OCULAR SIDE EFFECTS OF DRUGS

CASE 54-3

QUESTION 1: B.C., a 64-year-old male, has a history of hypertension managed with hydrochlorothiazide 25 mg/day. He takes amiodarone 800 mg/day for cardiac arrhythmia and chlorpheniramine 12 mg bid PRN for allergies. Four weeks ago, risperidone 1 mg bid was added to his medication regimen. He also takes sildenafil 100 mg an average of twice weekly. He reports occasional blurred vision.

Could these symptoms be related to his medications?

All the drugs that B.C. is taking have been associated with ocular side effects. Thiazide diuretics have been associated with acute myopia that may last from 24 to 48 hours.[97,98] However, hydrochlorothiazide is an unlikely cause of B.C.'s blurred vision considering its recent onset.

Amiodarone can cause keratopathy, but it is asymptomatic.[99,100] A high percentage of patients who receive this drug exhibit microdeposits within the corneal epithelium that resembles the verticillata keratopathy induced by chloroquine.[97] These corneal deposits are bilateral, dose and duration related, reversible, and unassociated with visual symptoms.

Risperidone has been associated with disturbances of accommodation and blurred vision.[101]

B.C. may be in the ~1% of the population who experiences blurred vision with chlorpheniramine. This effect has been seen in patients

receiving 12 to 14 mg/day.[97] If an antihistamine is indicated, an agent such as cetirizine would be less likely to cause such an effect. Sildenafil has been associated with change in color and light perception as well as blurred vision.[102] These effects generally subside within 4 hours of the dose.

Table 54-3[97–127] outlines some of the more common ocular side effects associated with systemic medications. Each case should be evaluated individually, and alternative therapy considered in intolerant patients.

Table 54-3
Ocular Side Effects of Systemic Medications

Drug Class	Effect(s)	Clinical Remarks
Analgesics		
Narcotics, including pentazocine	Miosis	Miosis often with morphine in normal doses: slight with other agents; effect secondary to CNS action on the pupilloconstrictor center[97]
	Tearing Irregular pupils Paresis of accommodation Diplopia	Effects associated with narcotic withdrawal[97]
Antiarrhythmics		
Amiodarone	Keratopathy	Dose and duration related; resembles chloroquine keratopathy. Corneal deposits are bilateral, reversible, and unassociated with visual symptoms. Patients taking 100–200 mg/day have only minimal deposits. Deposits occur in almost 100% of patients receiving 400 mg/day[99,100]

Drug Class	Effect(s)	Clinical Remarks
	Cataracts	Previously reported as insignificant, anterior subcapsular lens opacities have been associated with amiodarone therapy. Rarely, such opacities may progress, increasing in density and in the diffuse distribution of the deposits, ultimately covering an area somewhat larger than the undilated pupil's aperture. The mechanism for this effect is unclear, but like chlorpromazine, amiodarone is a photosensitizing agent. Given that the lens changes are limited largely to the pupillary aperture, light exposure may result in the lens changes[97–100]
	Optic neuropathy	Approximately 2% of patients experience optic neuropathy[102]
Anticholinergics		
Atropine Dicyclomine Glycopyrrolate Propantheline Scopolamine Trihexyphenidyl	Mydriasis Cycloplegia with ↓ accommodation Photophobia	Systemic and transdermal anticholinergic agents may cause mydriasis and, less frequently, cycloplegia. Mydriasis may precipitate angle-closure glaucoma. Photophobia is related to mydriasis. Accommodation for near objects[97,103]
Anticonvulsants		
Carbamazepine	Diplopia Blurred vision	Ocular adverse reactions when dosage >1–2 g/day; disappear when dosage is reduced[97]
Phenytoin	Nystagmus cataracts	Nystagmus in patients with high blood levels (>20 μg/mL); rarely occurs with other hydantoins. Cataracts may occur rarely with prolonged therapy[97,104]

Drug Class	Effect(s)	Clinical Remarks
Topiramate	Acute myopia, secondary angle-closure glaucoma	Topiramate has been associated with angle-closure glaucoma. Symptoms including ocular pain, headache, nausea, vomiting, hyperemia, visual field defects, and blindness have been reported. This process is usually bilateral, but if symptoms are recognized and the drug is stopped in a timely manner, adverse outcomes may be minimized[102]
Trimethadione	Visual glares	A prolonged glare or dazzle occurs when eyes are exposed to light. The glare is reversible, occurs at the retinal level, and is more common in adolescents and adults; rarely in young children[97]
Vigabatrin	Visual field abnormalities	Visual field abnormalities including bilateral, symmetrical, and irreversible peripheral constriction occur in up to 30% of patients. Most patients are asymptomatic, and <0.1% of patients are clinically affected[102]
Antidepressants		
Tricyclic antidepressants (TCAs)		Mydriasis is the most common ocular side effect of TCAs. Cycloplegia is rare. Reports of precipitation of angle-closure glaucoma.[97]
Anti-Infectives		
Amantadine	Corneal lesions	Diffuse, white punctate subepithelial corneal opacities have been reported, occasionally associated with superficial punctate keratitis. Onset has been 1–2 weeks after initiation of therapy with dosages of 200–400 mg/day. Resolves with drug discontinuation[105]

Drug Class	Effect(s)	Clinical Remarks
Chloroquine	Corneal deposits	Some patients using ordinary doses may develop corneal deposits in a few months. The deposits are visible with use of a biomicroscope and appear as white yellow in color, but are of no consequence[97]
	Retinopathy (macular degeneration)	Serious retinopathy when total dose >100 g. Usually develops after 1–3 years; can occur in 6 months. Visual loss may be peripheral, with progression to central vision loss and disturbance of color vision. Rarely, effects such as blurred vision are seen earlier when larger doses (500–700 mg/day) are used. Macular changes may progress after drug is discontinued. These agents concentrate in pigmented tissue[97]
Ethambutol	Retrobulbar neuritis	At dosages of 15 mg/kg/day, virtually void of ocular side effects. Such effects are rare at dosages of 25 mg/kg/day for a duration of a few months. Patients treated for prolonged periods should have routine visual examinations including visual fields. Most effects are reversible after the drug is discontinued, but optic neuritis may continue to progress for 1–2 months after the drug has been discontinued[97,102]
Gentamicin	Pseudotumor cerebri	Rare, but has been well documented with secondary papilledema and visual loss[97]

Drug Class	Effect(s)	Clinical Remarks
Linezolid	Optic neuropathy	Blurry vision progressing to optic neuropathy and blindness has been reported rarely, most often in patients taking linezolid for >28 days of therapy. Ophthalmic adverse effects were reversible upon discontinuation.[106]
Nalidixic acid	Visual sensations	Most common ocular side effect. Main feature is a brightly colored appearance of objects; occurs soon after the drug is taken. Although quinolone antibiotics are nalidixic acid derivatives, they have rarely been associated with these ocular side effects.[97]
	Visual loss	Temporary effect (30 minutes–3 days)
	Papilledema	Primarily in infants and young children and secondary to intracranial pressure; reversible on withdrawal of the drug
Sulfonamides	Myopia	Acute and reversible; most common ocular side effect[97]
	Conjunctivitis	Primarily with topical sulfathiazole, 4% incidence between 5 and 9 days of therapy[97]
	Optic neuritis	Even in low dosages. Usually reversible with complete recovery of vision[97]
	Photosensitivity	Associated with use of sulfisoxazole lid margin therapy[107,108]
Voriconazole	Altered visual perception	May be associated with higher doses or plasma concentrations[109]
	Blurred vision	
Anti-Inflammatory Agents (Also See Analgesics; Corticosteroids)		

Drug Class	Effect(s)	Clinical Remarks
Gold	Corneal Conjunctival deposits	Deposition in the conjunctiva and superficial cornea more common than in the lens or deep cornea. Incidence in cornea of 40%–80% in total doses of 1.5 g; visual acuity is unaffected. One reported case after oral therapy[97]
Indomethacin	Decreased vision	Rare; also changes in color vision have been rarely reported.[97]
Phenylbutazone	Decreased vision	Most common ocular side effect with this drug may be caused by lens hydration.[97]
	Conjunctivitis retinal hemorrhage	Occurs less often than vision. The conjunctivitis may be associated with development of Stevens–Johnson syndrome or an allergic reaction[97]
Antineoplastic Agents		
Busulfan	Cataracts	Reported with high dosages[97]
Carmustine	Arterial narrowing Nerve fiber layer infarcts Intraretinal hemorrhages	These ocular side effects are not well established. Evidence of delayed bilateral ocular toxicity developed in 2 of 50 patients treated with high-dose IV carmustine (800 mg/m^2). Symptoms of ocular toxicity became evident 4 weeks after IV treatment. Evidence of delayed ocular toxicity (mean onset 6 weeks) ipsilateral to the site of infusion developed in 7 of 10 patients treated with intra-arterial carotid doses of carmustine to a cumulative minimum of 450 mg/m^2 in two treatments[110]
Cytarabine	Keratoconjunctivitis Ocular burning Photophobia Blurred vision	Corneal toxicity and conjunctivitis have been reported with high-dose (3 g/m^2) therapy[111]

Drug Class	Effect(s)	Clinical Remarks
Doxorubicin	Conjunctivitis	May last for several days after treatment[97]
	Excessive tearing	
Erlotinib	Trichomegaly and ocular irritation	
Fluorouracil	Ocular irritation	Reversible and seldom interfere with continued therapy[97]
	Lacrimation	
Tamoxifen	Corneal opacities Decreased vision Retinopathy	Generally occurs in patients receiving >1 year of treatment when a total dose exceeding 100 g has been taken[97]
Vinca alkaloids (especially vincristine)	Extraocular muscle paresis (EMP) Ptosis	The onset of EMP or paralysis may be seen as early as 2 weeks. Dose related. Most recover fully when drug is discontinued[97]
Barbiturates		
	Miosis Mydriasis Disturbances in ocular movement Ptosis	Most significant ocular side effects occur in chronic users or in toxic states. Pupillary responses are variable; miosis seen most frequently, except in toxicity when mydriasis predominates. Nystagmus and weakness in extraocular muscles may be seen. Chronic abusers have a characteristic ptosis[95]
Bisphosphonates (Alendronate, Etidronate, Pamidronate, Risedronate)		
	Blurred vision, pain, photophobia, conjunctivitis, scleritis, uveitis	Adverse events more common with pamidronate. Scleritis and uveitis are of greatest concern. After persistent reduction in vision of sustained ocular pain, refer patient to an ophthalmologist. Ocular NSAID treatment may be of symptomatic benefit[102]
Corticosteroids		

Drug Class	Effect(s)	Clinical Remarks
	Cataracts	Posterior subcapsular cataracts have been associated with systemic corticosteroids in patients who have received >15 mg/day of prednisone or its equivalent daily for periods >1 year.[112,113] Rare reports of bilateral posterior subcapsular cataracts associated with nasal aerosol or inhalation of beclomethasone dipropionate have been received. Most patients had received therapy for >5 years, often in higher than the recommended dosage. Approximately 40% of patients were also receiving systemic corticosteroids.[114]
	↑ Intraocular pressure (IOP)	More common with topical corticosteroids than with systemic therapy. Of little consequence in patients without preexisting glaucoma. Patients with glaucoma should be monitored routinely if receiving systemic corticosteroids[97] (see Case 54-8, Question 2).
	Papilledema	Intracranial hypertension or pseudotumor cerebri from systemic corticosteroids has been well documented. The incidence appears to be greater in children than in adults; primarily associated with chronic therapy
Digitalis		

Drug Class	Effect(s)	Clinical Remarks
	Altered color vision, visual acuity	Changes in color vision. A glare phenomenon and a snowy appearance in objects have been associated primarily with digitalis intoxication. In a small number of cases, reversible reduction in visual acuity has been noted. Also associated with changes in the visual fields.[97]
	Decreased IOP	Digitalis derivatives can decrease IOP, but clinical use for glaucoma is not practical because the therapeutic systemic dose for this effect is very near the toxic dose.[97]
Diuretics		
Carbonic anhydrase inhibitors	Myopia	Acute myopia that may last from 24 to 48 hours. Probably caused by an increase in the anteroposterior diameter of the lens, which may be reversible even if drug use is continued.[97]
Thiazides	Myopia	Thiazide diuretics have been associated with acute myopia that may last from 24 to 48 hours[97,98]
Estrogens		
Clomiphene	Blurred vision Mydriasis Visual field changes Visual sensations	5%–10% experience ocular side effects. Blurred vision is the most common effect, although visual sensations such as flashing lights, distortion of images, and various colored lights (primarily silver) may occur.[97]
Immunomodulators		
Imatinib	Visual deficits	Ocular symptoms include blurred vision, conjunctivitis, dry eyes, epiphora, and periorbital edema. The latter occurs in up to 74% of treated patients.[115]

Drug Class	Effect(s)	Clinical Remarks
Interleukin-2	Visual deficits	Interleukin-2 visual complications have occurred during the first or second treatment cycle, usually within 5–6 days of initiation of therapy. Ocular symptoms included diplopia, binocular negative scotomas (isolated areas of varying size and shape in which vision is absent or depressed; these are not perceived ordinarily but would be apparent on completion of a visual field examination), and palinopsia (abnormal recurring visual imagery). In most cases, treatment was continued for the entire planned duration of therapy. Symptoms resolved after discontinuation.[116]
Phenothiazines		
Chlorpromazine	Deposits on the lens	Rare when total dose <0.5 kg. Visible after a total dose of 1 kg in most cases; incidence may increase to 90% after ≥2.5 kg. Usually, deposits do not affect vision appreciably. The cornea and conjunctiva may be affected after the lens shows pigment changes.[97]
PDE-5 inhibitors Sildenafil Tadalafil Vardenafil	Changes in color or light perception, blurred vision, conjunctival hyperemia, ocular pain, photophobia	Color vision alterations are mild to moderate. Blurred vision does not impair visual acuity. Visual alterations usually subside within 4 hours after the dose.[117–119] Ocular adverse effects are uncommon, dose dependent, and fully reversible to date. Incidence is not related to age but is related to blood concentration. Peak visual effects usually occur within 60 minutes after ingestion.[102]

Drug Class	Effect(s)	Clinical Remarks
α_1 Antagonists Prazosin Terazosin Doxazosin Alfuzosin Tamsulosin Silodosin	Blurry vision Intraoperative floppy iris syndrome	Approximately 1%–3% of patients taking second-generation α_1 antagonists (prazosin, terazosin, doxazosin, alfuzosin) have reported blurry vision. α_1 Antagonists have been associated with intraoperative floppy iris syndrome, a potential complication of cataract surgery. Patients should notify their ophthalmologist if they take α_1 antagonists currently or did so in the past.[120–125]
Retinoid		
Isotretinoin	Dry eyes, blepharoconjunctivitis optic neuropathy, vision disturbances	Approximately one-third of patients report dry or irritated eyes when taking isotretinoin. Higher doses of 1–2 mg/kg are associated with blepharoconjunctivitis (20%–43% of patients experiencing). Decreased night vision, optic neuropathy, and vision disturbances have been reported by clinical trial participants and in postmarketing surveillance.[126,127]

CNS, central nervous system; NSAID, nonsteroidal anti-inflammatory drug.

OCULAR EMERGENCIES

Chemical Burns

CASE 54-4

QUESTION 1: S.J., a 24-year-old construction worker, has splashed an unidentified chemical in his eyes and runs into a nearby pharmacy for burning in both eyes.

Should the pharmacist attempt to treat S.J. or refer him to the emergency department?

Chemical burns require immediate attention. The immediate treatment is copious irrigation using the most accessible source of water (eg, shower, faucet, drinking fountain, hose, bathtub). After at least 5 minutes of initial irrigation, S.J. should be taken immediately to the emergency department. A water-soaked towel or cloth should be kept on his eyes during transport.

Other Ocular Emergencies

When health care professionals are approached by patients with acute ocular emergencies (eg, chemical burns, corneal trauma, corneal ulcers, acute angle-closure glaucoma), patients require immediate treatment and should be referred to an ophthalmologist if the practitioner has even the slightest doubt about appropriate therapy. It is difficult to effectively evaluate the severity of ocular disorders without the benefit of a thorough ophthalmologic workup and specialized training. In situations of corneal trauma from abrasion or foreign bodies, the patient often has a gritty, scratchy feeling and can be aware of a foreign body's presence. The corneal tissue is an excellent culture medium for bacteria (eg, *Pseudomonas aeruginosa*), and therapy should be initiated as soon as possible to avoid corneal perforation and possible blindness.[1] Signs and symptoms of acute angle-closure glaucoma are reviewed in Case 54-2, Question 1.

Gonococcal conjunctivitis is an ocular emergency, and patients should be referred immediately to an ophthalmologist to minimize the potential of corneal perforation.[1] These patients, who can present with symptoms of red, tender, swollen eyelids with exophthalmos and mild pain, may be suffering from orbital cellulitis or endophthalmitis, which require immediate treatment with systemic antibiotics. Conjunctivitis of other origins (see Acute Bacterial Conjunctivitis [Pinkeye] and Allergic Conjunctivitis sections) generally is not an ocular emergency.

Any loss of vision (whether sudden, complete, or transient), flashes of light, pain, or photophobia can signify potentially damaging ocular disorders (eg, retinal artery occlusion, optic neuritis, amaurosis fugax, retinal detachment), and an ophthalmologist should evaluate the patient as soon as possible. Referral is also recommended for patients with blurred vision, pupil disorders, diplopia, nystagmus, or ocular hemorrhage.

COMMON OCULAR DISORDERS

Dry Eye Disease (Keratoconjunctivitis Sicca)

Dry eye disease is one of the most common ocular disorders. Global prevalence ranges from 5% to 50%.[128] Based on data from the National Health and Wellness Survey, 6.8% of the U.S. adult population have been diagnosed with dry eye disease. The prevalence increases with age (2.7% in those age 18–34 years vs 18.6% in those age ≥75 years or older) and is higher in females than males (8.8% vs 4.5%).[129] Dry eye disease is a multifactorial chronic disease of the corneal surface associated with persistent symptoms of foreign-body sensation, irritation, burning, redness, photosensitivity, and intermittent blurred vision. Dry eye disease is often associated with reduced or abnormal tears and inflammation of the ocular surface. Risk factors include advancing age, female sex, low humidity environments, systemic medications, and autoimmune disorders.[128] Initial therapies to relieve symptoms include warm compresses, tear replacement (ie, over-the-counter [OTC] artificial tears), reducing environmental causes, discontinuing medications that cause or worsen dry eye, and improved nutrition. Most patients require long-term use of nonprescription tear replacements, and, if these are not sufficient, other treatments are prescribed. These treatments include ophthalmic anti-inflammatory agents (eg, fluorometholone and/or cyclosporine eye drops), punctal occlusion, systemic cholinergic agents, and autologous serum tears.[130] In July

2016, the FDA approved lifitegrast (Xiidra®) ophthalmic solution) for the treatment of signs and symptoms of dry eye disease. Lifitegrast is the first medication in a new class of drugs, called lymphocyte function–associated antigen 1 (LFA-1) antagonist. Lifitegrast is preservative free, comes in unit vials, and is dosed twice daily. Side effects include transient instillation site burning, blurred vision, and unpleasant or distorted taste.[131]

Stye (Hordeolum)

Styes are infections of the hair follicles or sebaceous glands of the eyelids. They present as well-defined, painful lumps at the eyelid margin.[132] The most common infecting organism is *Staphylococcus aureus.* Most styes resolve spontaneously over days to weeks with treatment of warm compresses and massage. OTC products should not be recommended. An ophthalmologist should evaluate styes that do not respond to warm compresses within a few days.

Conjunctivitis

Conjunctivitis, a common external eye problem that involves inflammation of the conjunctiva is usually associated with symptoms of a diffusely reddened eye with purulent or serous discharge accompanied by itching, smarting, stinging, or a scratching foreign-body sensation.[133] Patients with pain, decreased vision, unequal distribution of redness, irregular pupils, or opacity should be referred immediately to an ophthalmologist because these are signs of more serious eye disease.

Conjunctivitis can be bacterial, fungal, parasitic, viral, or allergic in origin. Most cases of bacterial conjunctivitis are caused by *S. aureus, Streptococcus pneumoniae*, and *Haemophilus influenzae*, although a number of other organisms may be responsible.[134] The infection usually starts in one eye and is spread to the other by the hands. It is highly contagious, and patients should be advised to wash their hands frequently with soap and water, avoid sharing

personal items with others, and to discard multiple-dose eye drop containers if inadvertent contact with the eye occurs. Unlike bacterial conjunctivitis, corneal infections can obliterate vision rapidly; therefore, accurate diagnosis is important.

VIRAL CONJUNCTIVITIS

Viral conjunctivitis is the most common cause of infective conjunctivitis, accounting for 80% of all acute conjunctivitis.[135] Usually self-limiting, adenovirus is the reported cause in 65% to 90% of viral conjunctivitis cases. Other causes include enterovirus, herpes simplex virus, varicella-zoster virus, Epstein–Barr virus, and influenza. Adenoviral conjunctivitis is characterized by a sudden onset and, often, bilateral symptoms of watery discharge, redness, chemosis, and eyelid swelling. Topical antibiotics are not needed to treat adenovirus conjunctivitis and should be avoided owing to their own risks for adverse effects, toxicity, and cost to the patient. Symptomatic treatment may include artificial tears, topical antihistamines, and cold compresses. In severe cases involving ocular complications, topical corticosteroids may be used.

ACUTE BACTERIAL CONJUNCTIVITIS

CASE 54-5

QUESTION 1: L.T. is a 6-year-old boy with diffuse bilateral conjunctival redness that has been present for 2 days. A crusting discharge is deposited on his lashes and the corners of his eyes. His vision is normal, and his pupils are round and equal. The diagnosis of acute bacterial conjunctivitis is made, and sodium sulfacetamide 10% ophthalmic drops, two drops in both eyes every 2 hours while awake, are prescribed.

What other measures should be used? What instructions should his caregivers receive?

Treatment of acute typical bacterial conjunctivitis such as this is usually empirical. Other ophthalmic antibiotic drops or ointments, such as neomycin-polymyxin B-gramicidin combination or polymyxin B-trimethoprim (Polytrim®), are also used in these situations.

Although other antimicrobials, such as the ocular quinolones, may be used for bacterial conjunctivitis, these agents should be reserved as second-line therapies because of cost and the potential development of resistance. Proper management of this infection also includes mechanical cleaning of the eyelids and hygienic measures that prevent spreading the infection to other children. The deposits should be removed as often as possible with moist cotton swabs or cotton-tipped applicators. A mild baby shampoo can be used to moisten the applicator. Firm-adherent crusts may be softened with warm, moist compresses. Because this material is infectious, it should be disposed of in a sanitary manner. The common use of washcloths by several individuals will spread bacterial conjunctivitis.

ALLERGIC CONJUNCTIVITIS

CASE 54-6

QUESTION 1: N.V., a 10-year-old girl, has experienced redness in both eyes accompanied by "hay fever" for the past 2 months (June and July). There is no crusting on her eyelids, and her vision is normal; she rubs her eyes often because they itch.

What treatment is best for N.V.'s allergic conjunctivitis?

Allergic conjunctivitis is an immunologic inflammatory process of the eye.[133,136] Typically, it initially presents in late childhood or early adulthood as redness, tearing, itching, and foreign-body sensation. Mild disease is managed conservatively by avoiding allergens, irritants, and rubbing the eyes. Patients may use cold compresses, artificial tears, and air filtration systems for relief. For patients with moderate-to-severe disease, pharmacologic treatment is indicated. First-line treatment includes topical antihistamines, mast cell stabilizers, and dual-action agents.

Ophthalmic antihistamines relieve itching and redness and tend to provide a faster response compared to oral antihistamines, but have a limited duration of action and require more frequent dosing.[133,136] They should not be used by patients at risk for angle-closure

glaucoma. They include pheniramine maleate 0.3%/naphazoline 0.025% up to qid (a combination of antihistamine plus vasoconstrictor), epinastine 0.05% bid, and cetirizine (Zerviate®) 0.24% bid. Mast cell stabilizers include nedocromil (Alocril®) 2% bid, cromolyn 4% qid to six times daily, and lodoxamide tromethamine (Alomide®) 0.1% up to qid. These agents take about 3 to 5 days to start working but may be useful for prophylaxis or for patients who did not tolerate topical antihistamines. Dual-action agents that have both antihistamine plus mast cell–stabilizing effects have become the treatment of choice owing to their multiple symptomatic benefits. Medications in this class include ketotifen 0.025% bid, alcaftadine (Lastacaft®) 0.25% daily, bepotastine (Bepreve®) 1.5% bid, and olopatadine (Patanol®/Pataday®) 0.1% bid and 0.2% daily. Adverse effects of all the agents in this section include chemosis, headache, bloodshot eye appearance, rhinitis, nasopharyngitis, nasal congestion, bitter taste, and eye irritation, such as burning, stinging, redness, and pruritis.

Other treatments for allergic conjunctivitis include ocular decongestants, ocular nonsteroidal anti-inflammatory drugs (NSAIDs), ocular steroids, intranasal corticosteroids, oral antihistamines, and allergen immunotherapy.[133,136] Ocular decongestants (vasoconstrictors) are typically used in conjunction with antihistamines and mast cell stabilizers. They can cause rebound vasodilation with continued use, so they should be limited to short-term treatment. They should not be used in patients at risk for angle-closure glaucoma and should be used with caution in patients with cardiovascular disease, hyperthyroidism, and diabetes. Ocular NSAIDs and steroids may have a role in patients who are unresponsive to other therapies, with moderate-to-severe symptoms, or repeated exposure to allergens. Patients who wear contact lenses, have herpes simplex virus eye disease, have symptoms that do not improve with treatment, or who are experiencing vision loss, photophobia, or eye pain or discharge should be referred for evaluation with an ophthalmologist.

Corneal Ulcers

CASE 54-7

Question 1: T.S. presents with a diagnosis of bacterial corneal ulcer in the right eye and prescriptions for "fortified gentamicin" and cefazolin eye drops, which are not commercially available.

What is the rationale for this therapy, and how can the patient obtain it?

The initial choice of therapy for bacterial corneal ulcers commonly is based on a Gram stain and clinical impression of the severity of the ulcer.[137] Monotherapy with a fluoroquinolone eye drop or combination therapy with fortified topical antibiotics can be prescribed. *Fortified antibiotics* refers to preparation of a concentration that is higher than in commercially available topical antibiotics.

Commonly prescribed products include bacitracin 5000 to 10,000 units/mL, cefazolin 33 to 100 mg/mL, gentamicin or tobramycin 9.1 to 13.6 mg/mL, and vancomycin 25 to 50 mg/mL.[137] Fortified gentamicin has been prepared by adding 80 mg of parenteral gentamicin to the commercially available gentamicin ophthalmic solution. The final concentration of this solution is 13.6 mg/mL. Cefazolin ophthalmic solution is prepared by reconstituting 500-mg parenteral cefazolin with 2 mL of sterile normal saline. Two milliliters of artificial tears solution is removed from a commercially available 15-mL bottle and replaced with the 2-mL reconstituted cefazolin solution (resulting in a final cefazolin concentration of 33 mg/mL). Therapy initially can be administered as frequently as every 15 to 30 minutes with extension of intervals as the ulcer resolves.[138] The preparation of extemporaneously compounded ophthalmic products must adhere to established federal and state agency guidelines and must address quality control concerns (eg, pH, tonicity, sterility, particulate matter). The formulation of sterile products should not be undertaken without due consideration of well-established practice standards.

OPHTHALMIC CORTICOSTEROIDS

Comparison of Preparations and Clinical Use

CASE 54-8

QUESTION 1: S.S. has undergone cataract extraction from his left eye. Prednisolone acetate 1% administered qid has been prescribed.
Is prednisolone acetate an appropriate choice?

The topical ophthalmic corticosteroid preparations are described in **Table 54-4**. The salt form affects the ability of the preparation to penetrate the cornea. For example, biphasic salts penetrate the intact cornea better than water-soluble salts. The ability of a formulation to penetrate the cornea, however, does not indicate increased therapeutic effectiveness. Prednisolone acetate 1% and fluorometholone acetate 0.1% have the best anti-inflammatory effects.[139–141] The most commonly prescribed ophthalmic corticosteroid is prednisolone acetate because of its availability in generic form and generally lower cost.

Table 54-4
Ophthalmic Corticosteroids and Relative Potency

High Potency	Difluprednate 0.05% (Durezol®) Fluorometholone acetate 0.1% (Flarex®) Prednisolone acetate 1% (Pred Forte®)
Intermediate Potency	Dexamethasone alcohol 0.1% (Maxidex®) Fluorometholone 0.1% (FML) Fluorometholone 0.25% (FML Forte®) Lotreprednol 0.2% (Lotemax®) Loteprednol 0.5% (Alrex®) Prednisolone acetate 0.12% (Pred Mild®) Prednisolone sodium phosphate 1%
Low Potency	Dexamethasone phosphate 0.1% Medrysone 1% (HMS)

Topical ophthalmic corticosteroids are used for a variety of conditions associated with inflammation of the conjunctiva, cornea, and within the anterior segment of the eye. They are generally contraindicated in individuals with active ocular varicella, vaccinia, herpes simplex, and mycobacterial infections.

Adverse Effects

INCREASED INTRAOCULAR PRESSURE

Case 54-8, Question 2: S.S. continued using topical prednisolone acetate 1%, one drop in the left eye qid for 8 weeks. Before therapy, the IOPs in both eyes were 16 mm Hg, but on the last follow-up visit, his IOP was 16 mm Hg in the right eye and 26 mm Hg in the left eye. How do you assess these observations?

S.S.'s elevated IOP could be related to topical steroid therapy. In one study, the ophthalmic administration of corticosteroid preparations (**Table 54-5**) increased IOP in three genetically distinct subgroups.[112,113,142] Fluorometholone acetate increased IOP by >10 mm Hg in known steroid responders in 29.5 days (median), whereas dexamethasone did the same in 22.7 days (median).[143] In a retrospective follow-up, 13% of high-corticosteroid responders developed POAG, and 63.8% developed ocular hypertension. No low responders developed POAG, and only 2.4% developed ocular hypertension.[143] Although corticosteroid-induced increases in IOP are associated most frequently with topical ophthalmic preparations, systemic corticosteroids may cause a similar response, although the magnitude is somewhat less.[144] The risk for corticosteroid-induced ocular hypertension is higher in patients with high myopia, diabetes mellitus, or connective tissue disease (particularly rheumatoid arthritis).

Table 54-5
Intraocular Pressure Response to Topical Steroids in Random

Populations

Author	Parameter of Response	Number of Subjects	Low	Medium	High	Mean
Armaly[113]	Increase of pressure in eye medicated with 0.1% dexamethasone	80	<5 mm Hg 66%	6–15 mm Hg 29%	16 mm Hg 5%	5.5 mm Hg
Becker and Ballin[142]	Final pressure in eye medicated for 6 weeks with 0.1% betamethasone	50	<19 mm Hg 70%	20–30 mm Hg 26%	32 mm Hg 4%	17.0 mm Hg
	Time to maximal response		2 weeks	4 weeks	4 weeks	

Topical corticosteroids exert their effects by decreasing aqueous humor outflow, whereas systemic corticosteroids may increase aqueous humor production.[144] The effects on IOP apparently are unrelated to the ability of the corticosteroid to penetrate the cornea. Dexamethasone has been associated with the greatest IOP increase.[145] Fluorometholone, medrysone, rimexolone, and loteprednol have been associated with lower, although sometimes significant, increases in IOP.[146–148] The pressure response is often reversible when the offending agent is discontinued. In subjects with prolonged IOP elevation, glaucomatous field defects are more likely to develop in corticosteroid-responsive patients.[149]

CATARACTS

CASE 54-9

QUESTION 1: G.A., who had asthma, has been taking prednisone 10 mg/day for 1 year. A routine ophthalmic examination revealed early cataract formation. Why could this be related to the prednisone?

Systemic and topical ophthalmic corticosteroids have been associated with the development of cataracts. About 23% of patients treated with 10 to 16 mg/day of prednisone orally (or its equivalent dose) for 1 year or more developed posterior subcapsular cataracts (PSCs).[150,151] The estimated occurrence of PSC in patients treated with >16 mg/day of prednisone for more than a year increased to >70% during the same period. Patients receiving <10 mg/day prednisone or its equivalent are unlikely to develop PSC, although some contend that the concept of a “safe” dosage should be

abandoned because of variable patient sensitivity to this side effect.[152] As illustrated by G.A., the cataracts cause few subjective problems and little measurable decrease in visual acuity. Although systemic corticosteroids are primarily implicated, the use of topical corticosteroids has also been associated with PSC formation.[153] Patients treated with alternate-day dosing of oral corticosteroids may be at lower risk for PSC formation.[154] Any patient receiving long-term corticosteroids should receive routine ophthalmic follow-up.

SYSTEMIC SIDE EFFECTS FROM OPHTHALMIC MEDICATION

CASE 54-10

QUESTION 1: J.F., a 62-year-old female, received one drop of phenylephrine 10% in each eye to dilate the pupils. Shortly after administration, her blood pressure increased to 210/130 mm Hg for 5 minutes, and she became confused.

How common is this type of reaction in patients receiving topical phenylephrine? What other topical ophthalmic medications have been associated with systemic effects?

In 33 cases, possible adverse effects have been associated with topical phenylephrine 10%.[155] In a double-blind study, no statistically significant differences were observed in blood pressure or pulse rate between experimental and control groups when phenylephrine 10% or tropicamide (Mydriacyl®) 1% was administered to 150 patients.[156] Nevertheless, care should be taken when phenylephrine 10% is administered in patients with hypertension or cardiac abnormalities in whom systemic absorption could be hazardous. No similar reports have been associated with topical use of phenylephrine 2.5%.

In addition to the systemic effects from topical administration of cholinergic agents, epinephrine, and timolol that were previously described, topical atropine, cyclopentolate (Cyclogyl®), and

scopolamine have been associated with psychosis.[157–159] Fatalities have been associated with topical atropine,[160] ataxia has occurred with topical homatropine, and one case of unconsciousness with tropicamide was reported.[161]

Topical chloramphenicol-polymyxin-B sulfate ophthalmic ointment has been associated with bone marrow aplasia after intermittent use for 4 months.[162] A Cushingoid reaction has been reported in a 30-month-old baby girl treated with dexamethasone alcohol (Maxidex®) qid in both eyes for 14 months.[163]

The administration of ophthalmic prostaglandins and PGAs is associated with systemic side effects (see Table 54-1).

OCULAR NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

CASE 54-11

QUESTION 1: W.A. is scheduled to undergo cataract extraction with implantation of an intraocular lens. Preoperative orders include administration of flurbiprofen 0.03% to inhibit intraoperative miosis. The formulary includes only diclofenac 0.1%.

Is this a suitable alternative to flurbiprofen?

Commercially available ophthalmic NSAIDs (eg, bromfenac, diclofenac, flurbiprofen, ketorolac, and nepafenac) share a similar mechanism of action involving inhibition of prostaglandin synthesis and reduction of prostaglandin-mediated ocular effects.[164] Minor clinical differences, which probably insignificant, exist, and approved indications differ (**Table 54-6**).[165–172] These agents are generally well tolerated, but they can cause transient burning and stinging on instillation. Diclofenac is not approved for the prevention of intraoperative miosis, but various dosage regimens have been reported as effective for this use.

Table 54-6
Ocular Nonsteroidal Anti-inflammatory Drugs

Indication	Drug/Approval Status for Indication	Dosage(s)
Inhibition of intraoperative miosis	Diclofenac 0.1% (Voltaren®, U)[165]	Three reported regimens; one drop every 15–30 minutes for four doses; one drop tid for 2 preoperative days; one drop at 2 hours, 1 hour, and 15 minutes before surgery
	Flurbiprofen 0.03% (Ocufen®, A)[166]	One drop every 30 minutes for 2 hours before surgery
	Ketorolac 0.5% (Acular, U)	One drop every 15 minutes beginning 1 hour before surgery
Anti-inflammatory after cataract surgery	Bromfenac 0.09% (Xibrom™, A)	One drop bid beginning 24 hours after surgery and continuing through the 2 weeks of the postoperative period
	Diclofenac 0.1% (A)[167] Nepavanac 0.1% (Nevanac™, A)	One drop bid to qid, including 24 hours preoperative administration. One drop tid beginning 1 day before cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period
	Ketorolac 0.5% (A)[168]	One drop tid, including 24 hours preoperative administration
Prevention/treatment of cystoid macular edema	Diclofenac 0.1% (U)[169]	Two drops five times preoperatively followed by one drop three to five times daily
	Ketorolac 0.5% (U)[168,170]	One drop tid or qid, including 24 hours preoperative administration
Ocular inflammatory conditions (iritis, iridocyclitis, episcleritis)	Diclofenac 0.1% (U)	One drop qid
Seasonal allergic/vernal conjunctivitis	Bromfenac 0.1% (U)	One drop bid

Indication	Drug/Approval Status for Indication	Dosage(s)
	Diclofenac 0.1% (U)	One drop every 2 hours for 48 hours; then qid
	Ketorolac 0.5% (A)[171,172]	One drop qid

A, approved use; bid, twice daily; qid, four times a day; tid, three times a day; U, unapproved use.

OCULAR HERPES SIMPLEX VIRUS INFECTIONS

CASE 54-12

QUESTION 1: P.B., a 34-year-old male, presents with a 2-week history of a red, irritated left eye with watery discharge. Recently, vision in his left eye became blurred, and he has light sensitivity. A slit-lamp examination with rose bengal stain revealed a multibranched corneal epithelial defect. This dendritic ulcer is the hallmark of ocular herpes simplex (type 1) infection.

What is the therapy of choice for P.B.?

Ocular herpes is common and can be caused by herpes simplex virus or, less commonly, by the varicella-zoster virus (herpes zoster ophthalmicus). Herpes simplex of the eye typically affects the eyelids, conjunctiva, and cornea, and patients often present with symptoms of pain, tearing, eye redness, sensitivity to light, and irritation or a foreign-body sensation. When herpes affects the epithelium of the cornea (herpes keratitis), it generally heals without scarring. Occasionally, deeper layers of the cornea are affected (stromal keratitis), and scarring can lead to blindness. Trifluridine is the drug of choice for P.B.

Trifluridine

In vitro, the mechanism of action of trifluridine is similar to that of idoxuridine (IDU). Trifluridine also inhibits thymidylate synthase, an enzyme required for DNA synthesis.

For the treatment of ocular herpes, one drop of trifluridine 1% ophthalmic solution should be instilled into the affected eye every 2 hours while awake with a maximal daily dose of nine drops. After reepithelialization, application of trifluridine should be continued for an additional 7 days at a reduced dosage of one drop every 4 hours while awake with a minimum of five drops daily. Continuous administration for periods exceeding 21 days is not recommended because of potential ocular toxicity.

Approximately 96% of treated herpetic corneal ulcers heal within 2 weeks.[173] Therapeutic levels of trifluridine can be found in the aqueous humor after topical administration of a 1% solution, enhancing its possible effectiveness in the treatment of stromal keratitis and uveitis. Trifluridine is also effective in treating herpes simplex virus infections resistant to IDU or vidarabine.

Despite the apparent superiority of trifluridine compared with its antiviral predecessors (IDU, vidarabine), it is not without disadvantages. Trifluridine is activated by uninfected corneal cells and is incorporated into cellular as well as viral DNA. Punctate lesions in the corneal epithelium are clinical manifestations of trifluridine cytotoxicity.[174] However, these effects seem to occur less often with trifluridine than with IDU and vidarabine.

Acyclovir

Acyclovir in in vitro plaque inhibition assays has 5 to 10 times the activity of IDU and trifluridine and >100 times the activity of vidarabine against strains of type 1 and type 2 herpes simplex virus.[175] Acyclovir's apparent superiority lies in its lack of toxicity to normal host cells. In rabbits (rabbit eyes are similar to human eyes), acyclovir 3% ointment healed established herpes simplex epithelial ulcerations at a faster rate and eliminated the virus more effectively than 0.5% IDU and 3% vidarabine ointments.[176] In humans,

ulcerative corneal epithelial lesions appear to respond similarly to acyclovir and IDU.[176] In comparison with IDU, the topical application of acyclovir or trifluridine resulted in a greater proportion of subjects healing within 1 week, and neither was superior for the treatment of dendritic epithelial keratosis.[177] The dose is usually a 1-cm ribbon of ointment instilled five times a day at 4-hour intervals for 14 days or for at least 3 days after healing is completed, whichever is shorter. Detailed dosing instructions are available in product literature of specific manufacturers, and brief reviews of acyclovir and acyclovir resistance are presented in Chapter 77, Opportunistic Infections in Patients Living With HIV, and Chapter 79, Viral Infections.

Other Drugs

Ganciclovir 0.05% and 0.15% gel have been shown to be equivalent to 3% acyclovir ointment in the treatment of superficial herpes simplex keratitis.[178] Cidofovir 1% ointment administered bid was equivalent to trifluridine administered five times daily in the rabbit model.[179] Cidofovir was more efficacious than 3% penciclovir ointment administered bid or qid.[179]

AGE-RELATED MACULAR DEGENERATION

CASE 54-13

QUESTION 1: E.A., a 77-year-old female, informs you she read information from the Internet, and she thinks her symptoms of blurred vision and the need for a bright light to read are consistent with AMD.

Which of the available medicines would be best for her?

AMD is a chronic, progressive disease of the retina that primarily affects patients age 50 years or older. It is characterized by the development of drusen (yellow deposits under the retina made of lipids and proteins), atrophy of the retinal epithelium, and

neovascularization that can lead to vision impairment.[180] It is responsible for an estimated 46% of cases of severe vision loss in persons older than 40 years in the United States. Risk factors for AMD include increasing age, northern European ancestry, genetic factors, and smoking. Commonly referred to as wet AMD, ~20% of patients with AMD have a neovascular form characterized by retinal exudates and hemorrhages originating from under the retina, which increases the risk of central vision distortion, blurring, and blindness. The other form of AMD, referred to as dry, non-neovascular, or atrophic, accounts for the remaining 80% of cases. The disease may be classified as early, intermediate, or advanced (may be neovascular [wet] or non-neovascular [dry]) based on the number and size of drusen that are present and the degree of pathologic abnormality seen on the macula.

Smoking is the most important modifiable risk factor for disease progression, and all patients with AMD who smoke should receive counseling and assistance on smoking cessation.[180] Prospective, randomized controlled clinical trials have shown that in patients with intermediate or advanced AMD, antioxidant vitamins and minerals slow the progression of the disease. The supplements used in the Age-Related Eye Disease Study (AREDS2) included vitamin C 500 mg, vitamin E 400 IU, lutein/zeaxanthin 10 mg/2 mg, zinc oxide 80 or 25 mg, and cupric oxide 2 mg, dosed once daily. Although this combination has shown benefit in patients with intermediate or advanced AMD, it failed to show benefit in patients with early AMD or those with family members who have AMD. Pharmacists may recommend appropriate antioxidant vitamin and mineral supplements to patients with AMD.

Vascular endothelial growth factor (VEGF) is associated with the pathogenesis of choroidal and retinal neovascularization that occurs in patients with advanced, neovascular AMD. VEGF may stimulate neovascularization by influencing endothelial cell proliferation, vascular permeability, and ocular inflammation.[181] Inhibition of VEGF with intravitreal anti-VEGF therapy has become the standard of care for neovascular AMD. The VEGF inhibitors include off-label bevacizumab (Avastin®), ranibizumab (Lucentis®), and aflibercept

(Eylea™).[180–183] All are administered as intravitreal injections by an ophthalmologist. Bevacizumab is a full-length monoclonal antibody that binds all isoforms of VEGF. It is administered as 1.25 mg monthly for 3 months and then monthly or PRN based on ophthalmologic assessment. Ranibizumab is a recombinant, humanized immunoglobulin G1κ isotype therapeutic antibody fragment that inhibits biologic activity of all isoforms of human VEGF-A. The dose is 0.5 mg monthly then PRN based on ophthalmologic assessment. Aflibercept, the newest anti-VEGF for neovascular AMD, is a pan–VEGF-A and placental growth factor inhibitor. It is dosed 2 mg monthly for 3 months and then every 8 weeks thereafter. Clinical studies have shown the anti-VEGF agents to be approximately equal in efficacy. Intravitreal formulations of these medications have been associated with adverse effects, including endophthalmitis infection, intraocular inflammation, intraocular hemorrhage, and rhegmatogenous retinal detachment.[184]

ACKNOWLEDGMENTS

The authors and editors wish to acknowledge and thank Dr. Suellyn J. Sorensen and Dr. Steven R. Abel, authors of this chapter in previous editions of this book.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key reference and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Flaxel CJ, Adelman RA, Bailey ST, et al. Age-related macular degeneration preferred practice pattern® [published correction appears in *Ophthalmology*. 2020;127(9):1279]. *Ophthalmology*. 2020;127(1):P1–P65. doi:10.1016/j.ophtha.2019.09.024 (180)

Fraunfelder FT, Fraunfelder FW, eds. *Drug-Induced Ocular Side Effects*. 8th ed. Elsevier; 2020. (97)

Gedde SJ, Vinod K, Wright MW, et al. Primary open-angle glaucoma preferred practice pattern® guidelines. *Ophthalmology*. 2021;128(1):P71–P150. doi:10.1016/j.ophtha.2020.10.022 (7)

Glaucoma Research Foundation. Glaucoma Facts and Stats. Published May 5, 2015. Accessed November 2020. http://www.glaucoma.org/glaucoma/glaucoma-facts-and-stats.php (4)

Lin A, Rhee MK, Akpek EK, et al. Bacterial keratitis preferred practice pattern®. *Ophthalmology*. 2019;126(1):P1–P55. doi:10.1016/j.ophtha.2018 .10.018 (137)

Riordan-Eva P, Augsburger J, eds. *Vaughan and Ashbury's General Ophthalmology*. 19th ed. McGraw-Hill Professional; 2018. (1)

Varu DM, Rhee MK, Akpek EK, et al. Conjunctivitis preferred practice pattern®. *Ophthalmology*. 2019;126(1):P94–P169. doi:10.1016/j.ophtha.2018 .10.020 (133)

Key Websites

American Academy of Ophthalmology. Preferred practice guidelines. 2021. https://www.aao.org/about-preferred-practice-patterns

COMPLETE REFERENCES CHAPTER 54 EYE DISORDERS

1. Riordan-Eva P, Augsburger J, eds. *Vaughan and Ashbury's General Ophthalmology*. 19th ed. McGraw-Hill Professional; 2018.
2. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262–267. doi:10.1136/bjo.2005.081224
3. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121(11):2081–2090.
4. Glaucoma Research Foundation. Glaucoma Facts and Stats. Published May 5, 2015. Accessed December 2015. http://www.glaucoma.org/glaucoma/glaucoma-facts-and-stats.php

5. Glaucoma Research Foundation. High eye pressure and glaucoma. Published October 29, 2017. Accessed November 2020. https://www.glaucoma.org/gleams/high-eye-pressure-and-glaucoma.php
6. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:714–830.
7. Gedde SJ, Vinod K, Wright MW, et al. Primary open-angle glaucoma preferred practice pattern® guidelines. *Ophthalmology*. 2021;128(1):P71–P150. doi:10.1016/j.ophtha.2020.10.022
8. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. 2014;311(18):1901–1911. doi:10.1001/jama.2014.3192
9. Gupta PK, Asrani S, Freedman SF, El-Dairi M, Bhatti MT. Differentiating glaucomatous from non-glaucomatous optic nerve cupping by optical coherence tomography. *Open Neurol J*. 2011;5:1–7. doi:10.2174/1874205X01105010001
10. Khondkaryan A, Francis BA. Angle-closure glaucoma. American Academy of Ophthalmology. Published December 18, 2013. Accessed December 1, 2020. https://www.aao.org/munnerlyn-laser-surgery-center/angleclosure-glaucoma-19
11. Cvenkel B, Kolko M. Current medical therapy and future trends in the management of glaucoma treatment. *J Ophthalmol*. 2020;2020:6138132. doi:10.1155/2020/6138132
12. Zioptan. Prescribing information. Merck Sharp & Dohme Corp.; 2012.
13. Alexander CL, Miller SJ, Abel SR. Prostaglandin analog treatment of glaucoma and ocular hypertension. *Ann Pharmacother*. 2002;36:504–511.
14. Xalatan. Prescribing information. Pfizer, Pharmacia and Upjohn Company; 2009.
15. Camras CB, Wax MB, Ritch R, et al. Latanoprost treatment for glaucoma: effects of treating for 1 year and of switching from timolol. United States Latanoprost Study Group. *Am J Ophthalmol*. 1998;126:390–399.
16. Bucci MG; Italian Latanoprost Study Group. Intraocular pressure-lowering effects of latanoprost monotherapy versus latanoprost or pilocarpine in combination with timolol: a randomized, observer-masked multicenter study in patients with open-angle glaucoma. *J Glaucoma*. 1999;8:24–30.
17. Simmons ST, Earl ML; Alphagan/Xalatan Study Group. Three-month comparison of brimonidine and latanoprost as adjunctive therapy in glaucoma and ocular hypertension patients uncontrolled on j-blockers: tolerance and peak intraocular pressure lowering. *Ophthalmology*. 2002;109:307–315.
18. Hoyng PF, Rulo A, Greve E, Watson P, Alm A. The additive intraocular pressure-lowering effects of latanoprost in combined therapy with other ocular hypotensive agents. *Surv Ophthalmol*. 1997;41(suppl 2):S93–S98.

19. Kimal Arici M, Topalkara A, Güler C. Additive effect of latanoprost and dorzolamide in patients with elevated intraocular pressure. *Int Ophthalmol*. 1998;22:37–42.
20. Smith SL, Sine CS, Pruitt CA, Stewart WC. The use of latanoprost 0.005% once daily and its effect on intraocular pressure as primary or adjunctive therapy. *J Ocul Pharmacol Ther*. 1999;15:29–39.
21. Netland PA, Landry T, Sullivan EK, et al. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol*. 2001;132:472–484.
22. Goldberg I, Cunha-Vaz J, Jakobsen JE, et al. Comparison of topical travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma*. 2001;10:414–422.
23. Travatan. Prescribing information. Alcon Laboratories; 2004.
24. Sherwood M, Brandt J; Bimatoprost Study Groups 1 and 2. Six-month comparison of bimatoprost once-daily and twice daily with timolol twice daily in patients with elevated intraocular pressure. *Surv Ophthalmol*. 2001;45(suppl 4):S361–S368.
25. Noecker RS, Dirks MS, Choplin NT, et al. A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Am J Ophthalmol*. 2003;135:55–63.
26. Lumigan. Prescribing information. Allergan; 2010.
27. Latisse (Bimatoprost Ophthalmic Solution). Prescribing information. Allergan; 2009.
28. Uusitalo H, Pillunat LE, Ropo A; Phase III Study Investigators. Efficacy and safety of tafluprost 0.0015% versus latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study. *Acta Ophthalmol*. 2010;88:12–19.
29. Chabi A, Varma R, Tsai JC, et al. Randomized clinical trial of the efficacy and safety of preservative-free tafluprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthamol*. 2012;153:1187–1196.
30. Egorov E, Ropo A; Investigators. Adjunctive use of tafluprost with timolol provides additive effects for reduction of intraocular pressure in patients with glaucoma. *Eur J Ophthamol*. 2009;19:214–222.
31. Janulevicˇiene˙ I, Derkacˇ I, Grybauskiene L, Paulauskaite˙ R, Gromnickaite R, Kuzmiene˙ L. Effects of preservative-free tafluprost on tear film osmolarity, tolerability, and intraocular pressure in previously treated patients with open-angle glaucoma. *Clin Ophthalmol*. 2012;6:103–109.
32. Uusitalo H, Chen E, Pfeiffer N, et al. Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication. *Acta Ophthamol*. 2010;88:329–336.
33. Xelpros. Package insert. Sun Pharmaceutical Industries; 2018

34. Rakofsky SI, Melamed S, Cohen JS, et al. A comparison of the ocular hypotensive efficacy of once-daily and twice-daily levobunolol treatment. *Ophthalmology*. 1989;96:8–11.
35. Berson FG, Cohen HB, Foerster RJ, Lass JH, Novack GD, Duzman E. Levobunolol compared with timolol for the long-term control of elevated intraocular pressure. *Arch Ophthalmol*. 1985;103:379–382.
36. Battershill PE, Sorkin EM. Ocular metipranolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in glaucoma and ocular hypertension. *Drugs*. 1988;36:601–615.
37. Mills KB, Wright G. A blind randomised cross-over trial comparing metipranolol 0.3% with timolol 0.25% in open-angle glaucoma: a pilot study. *Br J Ophthalmol*. 1986;70:39–42.
38. Krieglstein GK, Novack GD, Voepel E, et al. Levobunolol and metipranolol: comparative ocular hypotensive efficacy, safety, and comfort. *Br J Ophthalmol*. 1987;71:250–253.
39. Scoville B, Mueller B, White BG, Krieglstein GK. A double-masked comparison of carteolol and timolol in ocular hypertension. *Am J Ophthalmol*. 1988;105:150–154.
40. Stewart WC, Shields MB, Allen RC, et al. A 3-month comparison of 1% and 2% carteolol and 0.5% timolol in open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 1991;229:258–261.
41. Brazier DJ, Smith SE. Ocular and cardiovascular response to topical carteolol 2% and timolol 0.5% in healthy volunteers. *Br J Ophthalmol*. 1988;72:101–103.
42. Levy NS, Boone L, Ellis E. A controlled comparison of betaxolol and timolol with long-term evaluation of safety and efficacy. *Glaucoma*. 1985;7:54–62.
43. Zimmerman TJ, Kaufman HE. Timolol: dose response and duration of action. *Arch Ophthalmol*. 1977;95:605–607.
44. Britman NA. Cardiac effects of topical timolol. *N Engl J Med*. 1979;300:566.
45. Kim JW, Smith PH. Timolol-induced bradycardia. *Anesth Analg*. 1980;59:301–303.
46. McMahon CD, Shaffer RN, Hoskins HD Jr, Hetherington J Jr. Adverse effects experienced by patients taking timolol. *Am J Ophthalmol*. 1979;88:736–738.
47. Jones FL Jr, Ekberg NL. Exacerbation of asthma by timolol. *N Engl J Med*. 1979;301:270.
48. Van Buskirk EM. Corneal anesthesia after timolol maleate therapy. *Am J Ophthalmol*. 1979;88:739–743.
49. Draeger J, Winter R. The local anaesthetic action of metipranolol versus timolol in patients with healthy eyes. In: Merte HJ, ed. *Metipranolol Pharmacology of Beta-blocking Agents and Use of Metipranolol in Ophthalmology. Contributions to the First Metipranolol Symposium, Berlin 1983*. Springer-Verlag Wien; 1983:76.

50. Akingbehin T, Villada JR. Metipranolol-associated granulomatous anterior uveitis. *Br J Ophthalmol*. 1991;75:519–523.
51. Zimmerman TJ, Baumann JD, Hetherington J Jr. Side effects of timolol. *Surv Ophthalmol*. 1983;28(suppl):243–251.
52. Rozier A, Mazuel C, Grove J, Plazonnet B. Gelrite: a novel, ion-activated, in-situ gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. *Int J Pharm*. 1989;57:163–168.
53. Shedden AH, Laurence JK, Tipping RW, et al. Multiclinic, double-masked study of 0.5% timoptic-XE (TXE) once daily versus 0.5% timoptic (TS) twice daily. *Ophthalmology*. 1993;100(suppl):111.
54. Levobunolol: a beta-adrenoreceptor antagonist effective in the long-term treatment of glaucoma. The Levobunolol Study Group. *Ophthalmology*. 1985;92:1271–1276.
55. Akingbehin T, Villada JR, Walley T. Metipranolol-induced adverse reactions: I. The rechallenge study. *Eye (Lond)*. 1992;6(Pt 3):277–279.
56. Akingbehin T, Villada JR. Metipranolol-induced adverse reactions: II. Loss of intraocular pressure control. *Eye (Lond)*. 1992;6(Pt 3):280–283.
57. Bacon PJ, Brazier DJ, Smith R, Smith SE. Cardiovascular responses to metipranolol and timolol eyedrops in healthy volunteers. *Br J Clin Pharmacol*. 1989;27:1–5.
58. Berry DP Jr, Van Buskirk EM, Shields MB. Betaxolol and timolol: a comparison of efficacy and side effects. *Arch Ophthalmol*. 1984;102:42–45.
59. Stewart RH, Kimbrough RL, Ward RL. Betaxolol vs. timolol: a six-month double-blind comparison. *Arch Ophthalmol*. 1986;104:46–48.
60. Allen RC, Hertzmark E, Walker AM, Epstein DL. A double-masked comparison of betaxolol vs. timolol in the treatment of open-angle glaucoma. *Am J Ophthalmol*. 1986;101:535–541.
61. Toris CB, Gleason ML, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humor dynamics in human eyes. *Arch Ophthalmol*. 1995;113:1514–1517.
62. Alphagan P. Prescribing information. Allergan; 2008.
63. Melamed S, David R. Ongoing clinical assessment of the safety profile and efficacy of brimonidine compared with timolol: year-three results. Brimonidine Study Group II. *Clin Ther*. 2000;22:103–111.
64. Serle JB. A comparison of the safety and efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% in subjects with elevated intraocular pressure. The Brimonidine Study Group III. *Surv Ophthalmol*. 1996;41(suppl 1):S39–S47.
65. DuBiner HB, Mroz M, Shapiro AM, Dirks MS; Brimonidine vs. Latanoprost Study Group. A comparison of the efficacy and tolerability of brimonidine and latanoprost in adults with open-angle glaucoma or ocular hypertension: a three-month, multicenter, randomized, double-masked, parallel-group trial. *Clin Ther*. 2001;23:1969–1983.

66. Sall KN, Greff LJ, Johnson-Pratt LR, et al. Dorzolamide/timolol combination verses concomitant administration of brimonidine and timolol: six-month comparison of efficacy and tolerability. *Ophthalmology*. 2003;110:615–624.
67. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. *Arch Ophthalmol*. 1995;113:1009–1016.
68. Wayman L, Larsson LI, Maus T, Alm A, Brubaker R. Comparison of dorzolamide and timolol as suppressors of aqueous humor flow in humans. *Arch Ophthalmol*. 1997;115:1368–1371.
69. Simbrinza. Prescribing information. Alcon Laboratories; 2014.
70. Azopt. Prescribing information. Alcon Laboratories; 2008.
71. Trusopt. Prescribing information. Merck & Co.; 2009.
72. Rosenberg LF, Krupin T, Tang LQ, Hong PH, Ruderman JM. Combination of systemic acetazolamide and topical dorzolamide in reducing intraocular pressure and aqueous humor formation. *Ophthalmology*. 1998;105:88–93.
73. Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965–973.
74. Medeiros FA, Martin KR, Peace J, Scassellati Sforzolini B, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250–259.
75. Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. *Br J Ophthalmol*. 2015;99(6):738–745. doi:10.1136/bjophthalmol-2014-305908
76. Serle JB, Katz LJ, McLaurin E, et al. Two phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure: rho kinase elevated IOP treatment trial 1 and 2 (ROCKET-1 and ROCKET-2). *Am J Ophthalmol*. 2018;186:116–127.
77. Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%. Prescribing information. Aerie Pharmaceuticals; 2019.
78. Harris LS. Dose-response analysis of echothiophate iodide. *Arch Ophthalmol*. 1971;86:503–505.
79. Fechtner RD, Realini T. Fixed combinations of topical glaucoma medications. *Curr Opin Ophthalmol*. 2004;15(2):132–135. doi:10.1097/00055735-200404000-00013
80. Yüksel N, Altintas¸ O, Karabas¸ L, Alp B, Cag˘lar Y. The short-term effect of adding brimonidine 0.2% to timolol treatment in patients with open-angle glaucoma. *Ophthalmologica*. 1999;213:228–233.

81. Sorensen SJ, Abel SR. Comparison of the ocular beta-blockers. *Ann Pharmacother*. 1996;30:43–54.
82. Berson FG, Epstein DL. Separate and combined effects of timolol maleate and acetazolamide in open-angle glaucoma. *Am J Ophthalmol*. 1981;92:788–791.
83. Strahlman ER, Vogel R, Tipping R, Clineschmidt CM. The use of dorzolamide and pilocarpine as adjunctive therapy to timolol in patients with elevated intraocular pressure. The Dorzolamide Additivity Study Group. *Ophthalmology*. 1996;103:1283–1293.
84. thoe Schwartzenberg GW, Buys YM. Efficacy of brimonidine 0.2% as adjunctive therapy for patients with glaucoma inadequately controlled with otherwise maximal medical therapy. *Ophthalmology*. 1999;106:1616–1620.
85. Orzalesi N, Rossetti L, Bottoli A, Fumagalli E, Fogagnolo P. The effect of latanoprost, brimonidine, and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with glaucoma or ocular hypertension. *Arch Ophthalmol*. 2003;121:453–457.
86. Van Buskirk EM, Weinreb RN, Berry DP, Lustgarten JS, Podos SM, Drake MM. Betaxolol in patients with glaucoma and asthma. *Am J Ophthalmol*. 1986;101:531–534.
87. Zimmerman TJ, Sharir M, Nardin GF, Fuqua M. Therapeutic index of pilocarpine, carbachol, and timolol with nasolacrimal occlusion. *Am J Ophthalmol*. 1992;114:1–7.
88. Ellis PP, Wu PY, Pfoff DS, Bloedow DC, Riegel MR. Effect of nasolacrimal occlusion on timolol concentrations in the aqueous humor of the human eye. *J Pharm Sci*. 1992;81:219–220.
89. Urtti A, Salminen L. Minimizing systemic absorption of topically administered ophthalmic drugs. *Surv Ophthalmol*. 1993;37:435–456.
90. Zambarakji HJ, Spencer AF, Vernon SA. An unusual side effect of dorzolamide. *Eye (Lond)*. 1997;11(Pt 3):418–419.
91. Galin MA, Davidson R, Shachter N. Ophthalmological use of osmotic therapy. *Am J Ophthalmol*. 1966;62:629–634.
92. Drance SM. Effect of oral glycerol on intraocular pressure in normal and glaucomatous eyes. *Arch Ophthalmol*. 1964;72:491–493.
93. Becker B, Kolker AE, Krupin T. Isosorbide: an oral hyperosmotic agent. *Arch Ophthalmol*. 1967;78:147–150.
94. Adams RE, Kirschner RJ, Leopold IH. Ocular hypotensive effect of intravenously administered mannitol; a preliminary report. *Arch Ophthalmol*. 1963;69:55–58.
95. D'Alena P, Ferguson W. Adverse effects after glycerol orally and mannitol parenterally. *Arch Ophthalmol*. 1966;75:201–203.
96. Spaeth GL, Spaeth EB, Spaeth PG, Lucier AC. Anaphylactic reaction to mannitol. *Arch Ophthalmol*. 1967;78:583–584.

97. Fraunfelder FT. Fraunfelder FW, eds. *Drug-induced Ocular Side Effects*. 8th ed. Elsevier; 2020.
98. Grant WM. *Toxicology of the Eye*. 2nd ed. Charles C. Thomas; 1974.
99. D'Amico DJ, Kenyon KR, Ruskin JN. Amiodarone keratopathy: drug-induced lipid storage disease. *Arch Ophthalmol*. 1981;99:257–261.
100. Kaplan LJ, Cappaert WE. Amiodarone keratopathy: correlation to dosage and duration. *Arch Ophthalmol*. 1982;100:601–602.
101. Risperidone (Risperdal). Prescribing information. Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 1997.
102. Santaella RM, Fraunfelder FW. Ocular adverse effects associated with systemic medications. *Drugs*. 2007;67:75–93.
103. Hamill MB, Suelflow JA, Smith JA. Transdermal scopolamine delivery system (TRANSDERM-V) and acute angle-closure glaucoma. *Ann Ophthalmol*. 1983;15:1011–1012.
104. Bar S, Feller N, Savir H. Presenile cataracts in phenytoin-treated epileptic patients. *Arch Ophthalmol*. 1983;101:422–425.
105. Fraunfelder FT, Meyer SM. Amantadine and corneal deposits. *Am J Ophthalmol*. 1990;110:96–97.
106. Zyvox. Prescribing information. Pfizer; 2013. Accessed May 28, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf
107. Flach A. Photosensitivity to sulfisoxazole ointment. *Arch Ophthalmol*. 1981;99:609–610.
108. Flach AJ, Peterson JS, Mathias CG. Photosensitivity to topically applied sulfisoxazole ointment: evidence for a phototoxic reaction. *Arch Ophthalmol*. 1982;100:1286–1287.
109. VFEND. Prescribing information. Pfizer Roerig Pharmaceuticals; 2003.
110. Shingleton BJ, Bienfang DC, Albert DM, Ensminger WD, Chandler WF, Greenberg HS. Ocular toxicity associated with high-dose carmustine. *Arch Ophthalmol*. 1982;100:1766–1772.
111. Hopen G, Mondino BJ, Johnson BL, Chervenick PA. Corneal toxicity with systemic cytarabine. *Am J Ophthalmol*. 1981;91:500–504.
112. Leibowitz HM, Ryan WJ Jr, Kupferman A. Comparative anti-inflammatory efficacy of topical corticosteroids with low glaucoma-inducing potential. *Arch Ophthalmol*. 1992;110:118–120.
113. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. I. The demonstration of three levels of response. *Invest Ophthalmol*. 1965;4:187–197.
114. Franufelder FT, Meyer SM. Posterior subcapsular cataracts associated with nasal or inhalation corticosteroids. *Am J Ophthalmol*. 1990;109:489–490.
115. Gleevec. Prescribing information. Novartis Pharmaceuticals Corporation; 2010.

Friedman DI, Hu EH, Sadun AA. Neuro-ophthalmic complications of
116. interleukin 2 therapy. *Arch Ophthalmol*. 1991;109:1679–1680.
117. Cialis. Prescribing information. Eli Lilly & Company; 2003.
118. Levitra. Prescribing information. Bayer Health Care; 2003.
119. Viagra. Prescribing information. Pfizer Inc.; October 2007.
120. Minipress. Prescribing information. Pfizer; 2009. Accessed May 28, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017442s033lbl.pdf
121. Hytrin. Prescribing information. Abbott; 2009. Accessed May 28, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019057s022lbl.pdf
122. Cardura. Prescribing information. Pfizer; 2009. Accessed May 28, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019668s021lbl.pdf
123. Uroxatral. Prescribing information. Sanofi-Aventis; 2008. Accessed May 28, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021287s011lbl.pdf
124. Flomax. Prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc.; 2009. Accessed May 28, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020579s026lbl.pdf
125. Rapaflo. Prescribing information. Allergan USA Inc.; 2020. Accessed May 28, 2021. https://media.allergan.com/actavis/actavis/media/allergan-pdf-documents/product-prescribing/RAPAFLO-PLR-06-2017-(003).pdf
126. Sotret. Prescribing information. Ranbaxy Laboratories Inc.; 2006. Accessed May 28, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/Sotret.pdf
127. Accutane. Prescribing information. Roche; 2002. Accessed May 28, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/18662s051lbl.pdf
128. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf.* 2017;15:334–365.
129. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. *Am J Ophthalmol.* 2017;182:90–98.
130. Marshall LL, Roach JM. Treatment of dry eye disease. *Consult Pharm*. 2016;31(2):96–106. doi:10.4140/TCP.n.2016.96
131. Xiidra. Package insert. Novartis Pharmaceuticals Corp; June 2020.
132. McAlinden C, González-Andrades M, Skiadaresi E. Hordeolum: acute abscess within an eyelid sebaceous gland. *Cleve Clin J Med*. 2016;83(5):332–334. doi:10.3949/ccjm.83a.15012

133. Varu DM, Rhee MK, Akpek EK, et al. Conjunctivitis preferred practice pattern®. *Ophthalmology*. 2019;126(1):P94–P169. doi:10.1016/j.ophtha.2018.10.020
134. Teweldemedhin M, Gebreyesus H, Atsbaha AH, Asgedom SW, Saravanan M. Bacterial profile of ocular infections: a systematic review. *BMC Ophthalmol*. 2017;17(1):212. doi:10.1186/s12886-017-0612-2
135. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment [published correction appears in *JAMA*. 2014;311(1):95. Dosage error in article text]. *JAMA*. 2013;310(16):1721–1729. doi:10.1001/jama.2013.280318
136. Dupuis P, Prokopich CL, Hynes A, Kim H. A contemporary look at allergic conjunctivitis. *Allergy Asthma Clin Immunol*. 2020;16:5. doi:10.1186/s13223-020-0403-9
137. Lin A, Rhee MK, Akpek EK, et al. Bacterial keratitis preferred practice pattern®. *Ophthalmology*. 2019;126(1):P1–P55. doi:10.1016/j.ophtha.2018.10.018
138. Çaça I, Ünlü K, Ari S, Sakalar YB. Therapeutic effect of culture and antibiogram in bacterial corneal ulcers. *Ann Ophthalmol*. 2005;37:191.
139. Leibowitz H, Kupferman A. Bioavailability and therapeutic effectiveness of topically administered corticosteroids. *Trans Am Acad Ophthalmol Otolaryngol*. 1975;79:78–88.
140. Leibowitz HM, Kupferman A. Anti-inflammatory effectiveness in the cornea of topically administered prednisolone. *Invest Ophthalmol*. 1974;13:757–763.
141. Kupferman A, Leibowitz HM. Therapeutic effectiveness of fluorometholone in inflammatory keratitis. *Arch Ophthalmol*. 1975;93:1011–1014.
142. Becker B, Ballin N. Glaucoma and corticosteroid provocative testing. *Arch Ophthalmol*. 1965;74:621–624.
143. Stewart RH, Smith JP, Rosenthal AL. Ocular pressure response to fluorometholone acetate and dexamethasone phosphate. *Curr Eye Res*. 1984;3:835–839.
144. Godel V, Feiler-Ofry V, Stein R. Systemic steroids and ocular fluid dynamics. II. Systemic versus topical steroids. *Acta Ophthalmol (Copenh)*. 1972;50:664–676.
145. Cantrill HL, Palmberg PF, Zink HA, Waltman SR, Podos SM, Becker B. Comparison of in vitro potency of corticosteroids with ability to raise intraocular pressure. *Am J Ophthalmol*. 1975;79:1012–1017.
146. Stewart RH, Kimbrough RL. Intraocular pressure response to topically administered fluorometholone. *Arch Ophthamol*. 1979;97:2139–2140.
147. Leibowitz HM, Bartlett JD, Rich R, McQuirter H, Stewart R, Assil K. Intraocular pressure-raising potential of 1.0% rimexolone in patients responding to corticosteroids. *Arch Ophthalmol*. 1996;114:933–937.
148. Dell SJ, Shulman DG, Lowry GM, Howes J. A controlled evaluation of the efficacy and safety of loteprednol etabonate in the prophylactic treatment of

seasonal allergic conjunctivitis. International Dorzolamide Study Group. *Am J Ophthalmol*. 1997;123:791–797.
149. Kitazawa Y, Horie T. The prognosis of corticosteroid-responsive individuals. *Arch Ophthalmol*. 1981;99:819–823.
150. Oglesby RB, Black RL, Von Sallmann L, Bunim JJ. Cataracts in rheumatoid arthritis patients treated with corticosteroids: description and differential diagnosis. *Arch Ophthalmol*. 1961;66:519–523.
151. Oglesby RB, Black RL, Von Sallmann L, Bunim JJ. Cataracts in patients with rheumatic diseases treated with corticosteroids: further observations. *Arch Ophthalmol*. 1961;66:625–630.
152. Skalka HW, Prchal JT. Effect of corticosteroids on cataract formation. *Arch Ophthalmol*. 1980;98:1773–1777.
153. Yablonski ME, Burde RM, Kolker AE, Becker B. Cataracts induced by topical dexamethasone in diabetics. *Arch Ophthalmol*. 1978;96:474–476.
154. Sevel D, Weinberg EG, Van Niekerk CH. Lenticular complications of long-term steroid therapy in children with asthma and eczema. *J Allergy Clin Immunol*. 1977;60:215–217.
155. Fraunfelder FT, Scafidi AF. Possible adverse effects from topical ocular 10% phenylephrine. *Am J Ophthalmol*. 1978;85:447–453.
156. Brown MM, Brown GC, Spaeth GL. Lack of side effects from topically administered 10% phenylephrine eye drops: a controlled study. *Arch Ophthalmol*. 1980;98:487–489.
157. Morton HG. Atropine intoxication: its manifestations in infants and children. *J Pediatr*. 1939;14:755–760.
158. Mark HH. Psychotogenic properties of cyclopentolate. *JAMA*. 1963;186:430–431.
159. Freund M, Merin S. Toxic effects of scopolamine eye drops. *Am J Ophthalmol*. 1970;70:637–639.
160. Hoefnagel D. Toxic effects of atropine and homatropine eye drops in children. *N Engl J Med*. 1961;264:168–171.
161. Wahl JW. Systemic reaction to tropicamide. *Arch Ophthalmol*. 1969;82:320–321.
162. Abrams SM, Degnan TJ, Vinciguerra V. Marrow aplasia following topical application of chloramphenicol eye ointment. *Arch Intern Med*. 1980;140:576–577.
163. Musson K. Cushingoid status: induced by topical steroid medication. *J Pediatr Ophthalmol Strabismus*. 1968;5:33.
164. Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. *Surv Ophthalmol*. 1992;36:259–284.
165. Goa KL, Chrisp P. Ocular diclofenac: a review of its pharmacology and clinical use in cataract surgery, and potential in other inflammatory ocular conditions. *Drugs Aging*. 1992;2:473–486.
166. Ocufen. Prescribing information. Allergan America; 1992.

167. Voltaren Ophthalmic. Prescribing information. CIBA Vision Ophthalmics; 1991.
168. Flach AJ, Lavelle CJ, Olander KW, Retzlaff JA, Sorenson LW. The effect of ketorolac tromethamine solution in reducing postoperative inflammation after cataract extraction and intraocular lens implantation. *Ophthalmology*. 1988;95:1279–1284.
169. Flach AJ, Stegman RC, Graham J, Kruger L. Prophylaxis of aphakic cystoid macular edema without corticosteroids. *Ophthalmology*. 1990;97:1253–1258.
170. Flach AJ, Jampol LM, Weinberg D, et al. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. *Am J Ophthalmol*. 1991;112:514–519.
171. Tinkelman DG, Rupp G, Kaufman H, Pugely J, Schultz N. Double-masked, paired-comparison clinical study of ketorolac tromethamine 0.5% ophthalmic solution compared with placebo eyedrops in the treatment of seasonal allergic conjunctivitis. *Surv Ophthalmol*. 1993;38(suppl):133–140.
172. Ballas Z, Blumenthal M, Tinkelman DG, Kriz R, Rupp G. Clinical evaluation of ketorolac tromethamine 0.5% ophthalmic solution for the treatment of seasonal allergic conjunctivitis. *Surv Ophthalmol*. 1993;38(suppl):141–148.
173. Pavan-Langston DR, Foster CS. Trifluorothymidine and idoxuridine therapy of ocular herpes. *Am J Ophthalmol*. 1977;84:818–825.
174. McGill J, Holt-Wilson AD, McKinnen JR, et al. Some aspects of the clinical use of trifluorothymidine in the treatment of herpetic ulceration of the cornea. *Trans Ophthalmol Soc UK*. 1974;94:342.
175. Collins P, Bauer DJ. The activity in vitro against herpes virus of 9-(2-hydroxyethoxymethyl) guanine (acycloguanosine), a new antiviral agent. *J Antimicrob Chemother*. 1979;5:431–436.
176. Pavan-Langston D, Campbell R, Lass J. Acyclic antimetabolite therapy of experimental herpes simplex keratitis. *Am J Ophthalmol*. 1978;86:618–623.
177. Coster DJ, Wilhelmus KR, Michaud R, Jones BR. A comparison of acyclovir and idoxuridine as treatment for ulcerative herpetic keratitis. *Br J Ophthalmol*. 1980;64:763–765.
178. Colin J, Hoh HB, Easty DL, et al. Ganciclovir ophthalmic gel in the treatment of herpes simplex keratitis. *Cornea*. 1997;16:393–399.
179. Kaufman HE, Varnell ED, Thompson HW. Trifluridine, cidofovir, and penciclovir in the treatment of experimental herpetic keratitis. *Arch Ophthalmol*. 1998;116:777–780.
180. Flaxel CJ, Adelman RA, Bailey ST, et al. Age-related macular degeneration preferred practice pattern® [published correction appears in *Ophthalmology*. 2020;127(9):1279]. *Ophthalmology*. 2020;127(1):P1–P65. doi:10.1016/j.ophtha.2019.09.024
181. Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. *Ann Pharmacother*. 2007;41:614–625.

182. Chapman JA, Beckey C. Pegaptanib: a novel approach to ocular neovascularization. *Ann Pharmacother*. 2006;40:1322–1326.
183. Lucentis. Prescribing information. Genentech; 2007.
184. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye (Lond)*. 2013;27(7):787–794. doi:10.1038/eye.2013.107

SECTION 13

Neurologic Disorders

Section Editors: Michele Matthews and Adrian Wong

55

Pain and Its Management

Virginia Ghafoor, Lee A. Kral, and Timothy J. Atkinson

CORE PRINCIPLES		CHAPTER CASES
1	Multimodal perioperative analgesia utilizes neuraxial (epidural or intrathecal) or regional (peripheral nerve) anesthesia in combination with systemic medications to optimize pain control. A preoperative pain assessment is important to identify history of analgesic intolerance, medication contraindications, risks and benefits of neuraxial or regional anesthesia, and the presence of preoperative pain or anxiety.	**Case 55-1 (Questions 1–3)**
2	Intravenous (IV) and oral opioids are used for acute pain management. Risk factors for respiratory depression are important in determining medication selection and dose. Naloxone is the	**Case 55-2 (Questions 1–6)**

	antidote for reversing opioid-induced respiratory depression. Opioid side effects including nausea, vomiting, and constipation require medications for preventative treatment.	
3	Nonopioid medications are the foundation of acute pain management. These medications provide synergistic effects between different classes of analgesics and lower opioid requirements for pain control. Medication options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), ketamine, IV lidocaine, and gabapentinoids. Selection of nonopioid medication depends on history of prior use, contraindications, and risk factors for adverse events.	**Case 55-2 (Question 7)**
4	Low back pain is a very common chronic pain condition. It is complex, often involving physical and emotional factors. Patients may have musculoskeletal, neuropathic, and/or central pain that needs to be assessed, as well as comorbidities.	**Case 55-3 (Questions 1, 2)**
5	Chronic pain management requires multimodal therapies, both pharmacologic and nonpharmacologic. Many factors affect analgesic selection, including comorbidities, available routes of administration, and cost.	**Case 55-3 (Questions 3–7)**

6	Neuropathic pain may be caused by injury to peripheral nerves or to the central nervous system (CNS). Neuropathic pain is treated with analgesic antidepressants and anticonvulsants. Peripheral or localized nerve pain may be treated with topical agents.	**Case 55-4 (Questions 1, 2)**
7	Older adults and patients with multiple comorbidities are at high risk for adverse effects from analgesics. Pharmacokinetic and pharmacodynamic drug interactions must be considered with the use of anticonvulsants and antidepressants.	**Case 55-4 (Questions 3, 4)**
8	Functional pain does not have a clear pathophysiology. Comorbid mental health issues and psychosocial stressors complicate chronic pain management. Analgesic antidepressants and anticonvulsants, in conjunction with cognitive-behavioral therapies (CBTs), are recommended for the management of functional pain syndromes (FPSs).	**Case 55-5 (Questions 1, 2)**
9	An open discussion on the benefits and risks of opioid therapy needs to occur frequently with patients. Opioid therapy requires effective risk assessment to avoid medication misuse, opioid use disorder, and diversion. Monitoring recommendations include the use of written opioid agreements, urine drug	**Case 55-6 (Questions 1–6)**

testing, opioid risk screening tools, and electronic prescription monitoring program records.

INTRODUCTION

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”[1] The ability to experience pain is critical for survival because it informs the body about real or potential injury (eg, touching a hot stove). The body is then able to respond to the threat and protect itself from further injury (eg, refraining from touching or removing the hand from the hot stove). Pain is a hallmark of many acute and chronic conditions. More than 80% of patients who undergo surgical procedures experience acute pain, 75% of whom report the severity as moderate, severe, or extreme.[2,3] Chronic pain affects >50 million Americans daily, with 19.6 million adults experiencing high-impact chronic pain impeding their ability to work and activities of daily living. The estimated cost to the United States for disability related to chronic pain is estimated at between $560 and $635 billion annually.[4] However, nearly all cases of chronic pain begin as acute pain stemming from surgery, trauma, or illness.[5] Back pain and osteoarthritis (OA) are among the top five chronic pain conditions associated with high health care costs, and the prevalence continues to rise with the aging U.S. population. A study of insurance utilization data for Medicare members from 2007 to 2011 found that annual costs were $327 million for OA and $218 million for back pain.[6] There are also gender, racial, and socioeconomic disparities that exist with chronic pain. Chronic pain is reported more often in females than in males and in non-Hispanic White patients compared with other races and ethnicities.[7] Chronic pain is also more common in those whose income is two times less than the level of poverty. Pain is more complex than just physiology.

It is a subjective experience, and sometimes, the severity of pain does not appear to equal the extent of tissue damage. A person's perception of pain is affected by environmental, emotional, cultural, spiritual, and cognitive factors. Unrelieved chronic pain affects not only physical well-being but also a person's psychological and social well-being and relationships with loved ones. Recent estimates showed that musculoskeletal-related conditions with low back pain, neck pain, and knee OA ranked among the top 10 noncommunicable diseases for global disability-adjusted life years (ie, years of life lost and years lived in disability).[8,9]

Factors that increase pain and suffering include sensory factors, cognitive factors, and emotional factors (**Fig. 55-1**). All are interrelated and illustrate the complex nature of chronic pain.

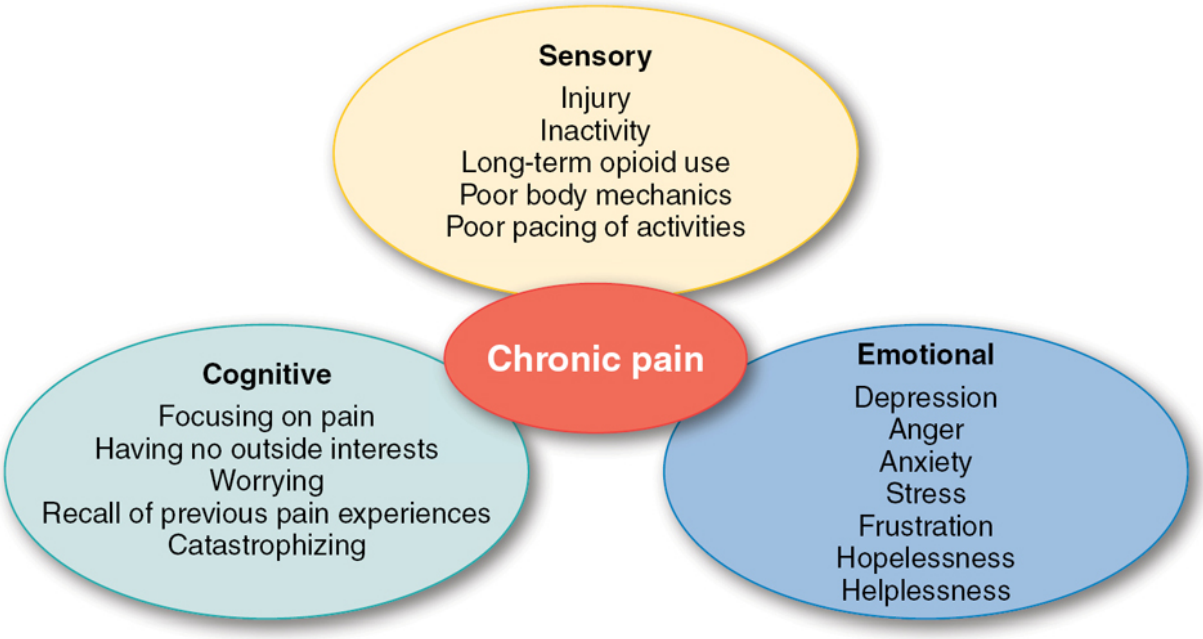


Figure 55-1 Factors affecting chronic pain.

Pathophysiology

ASCENDING PATHWAY

Nociception, or the sensation of pain, is composed of four basic processes: transduction, transmission, modulation, and perception

(**Fig. 55-2**). *Transduction* is the process by which noxious stimuli are translated into electrical signals at peripheral receptor sites (ie, free nerve endings located throughout the skin, muscle, joints, fascia, and viscera). Normal sensory stimuli do not activate the pain signal, but if the stimulus is powerful enough to surpass the threshold for innocuous activation, the receptors become *nociceptors* (ie, pain receptors). These sensory receptors target mechanical (crushing or pressure), chemical (endogenous or exogenous), or thermal (hot or cold) stimuli. Some nociceptors are polymodal, transducing more than one type of stimuli. One of these types of nociceptors is called the transient receptor potential (TRP). This family has a large number of members that are activated by the whole spectrum of thermal stimuli (very hot to very cold), as well as some mechanical and various chemical stimuli. Other receptors are “silent,” but are recruited if the stimulus is more intense or prolonged.

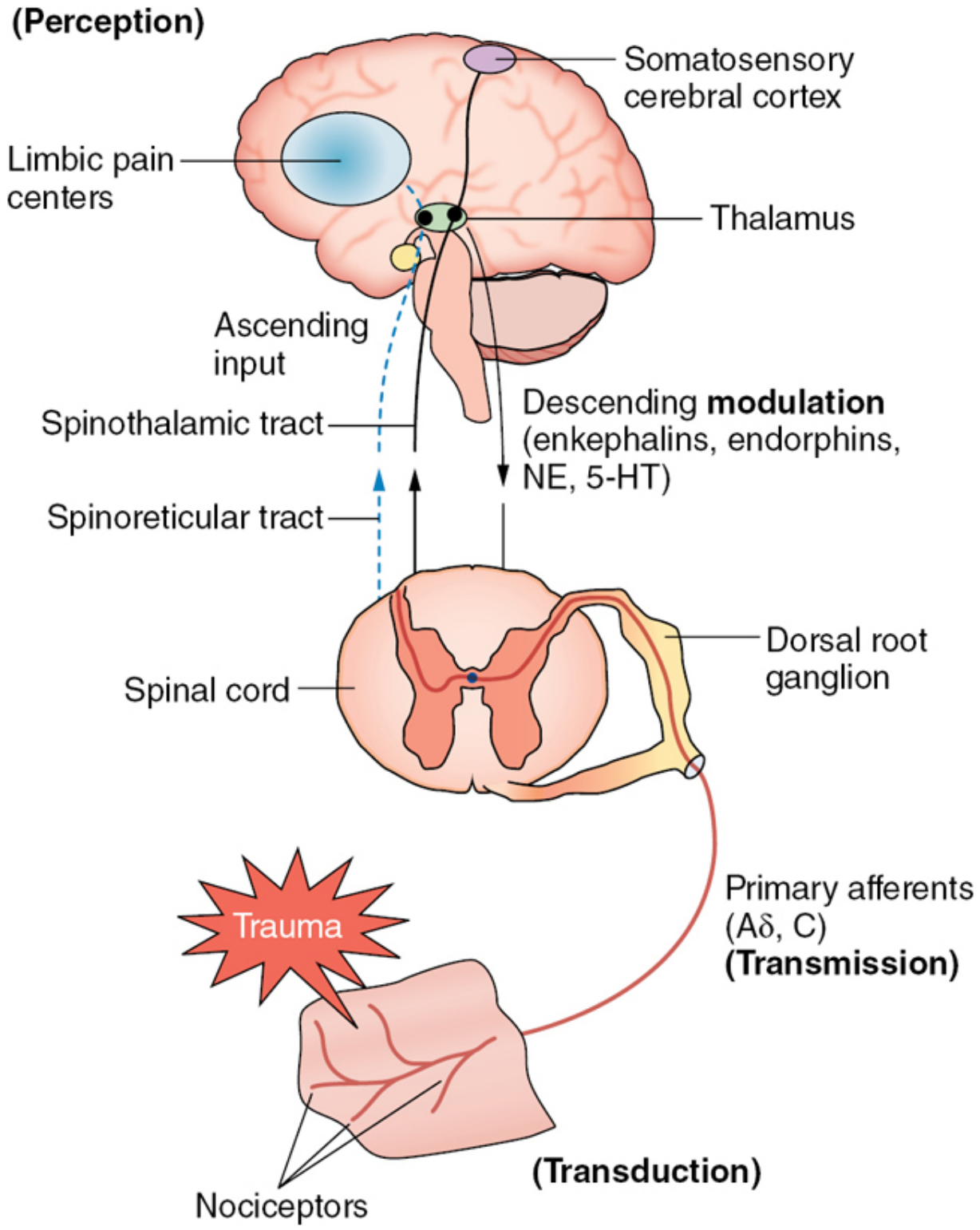


Figure 55-2 Pain pathways. 5-HT, serotonin; NE, norepinephrine.

After stimulation of nociceptors, several processes occur. Pro-inflammatory mediators, including histamine, substance P, prostaglandins, bradykinins, and serotonin, are released at the site of injury. Immune mediators are also released, including tumor necrosis factor, nerve growth factors, interleukins, and interferons. These mediators sensitize the nociceptors, lowering the pain threshold in and around the injury (peripheral sensitization). The sensitized nociceptors may fire more frequently and erratically and are stimulated by much weaker stimuli (hyperalgesia). More frequent firing is correlated with an increase in pain intensity.[10]

Transmission is the propagation of the electrical signal along primary afferent nerves, through the dorsal horn of the spinal cord to the central nervous system (CNS). Painful impulses are generated at the nociceptor, with voltage-gated sodium channels initiating the action potentials. Voltage-gated calcium channels are responsible for allowing calcium influx to the presynaptic terminal, causing neurotransmitter release. The message is then transmitted to the spinal cord via two primary afferent nerve types: myelinated A fibers and unmyelinated C fibers. The Aδ fibers are responsible for rapidly conducting impulses associated with thermal and mechanical stimuli. Transmission of signals along Aδ fibers results in sharp or stabbing sensations that alert the patient to an injury (also called “first pain”). This produces reflex signals, such as musculoskeletal withdrawal, to prevent further injury.[10]

The smaller, unmyelinated C fibers respond to mechanical, thermal, and chemical stimuli but conduct impulses at a much slower rate compared with Aδ fibers. Transmission of electrical impulses via C fibers results in pain that is dull, aching, burning, and diffuse (called “second pain”). Prolonged stimulation of C fibers causes an additive effect on the perceived intensity of second pain, called *windup.*

At the level of the dorsal horn of the spinal cord, the primary afferents cause calcium release into the presynaptic terminal. This leads to the release of excitatory amino acids (EAAs) such as glutamate into the synapse (**Fig. 55-3**). C fibers also release peptides such as substance P, neurokinins, and calcitonin gene–

related peptide (CGRP). The EAAs then stimulate the postsynaptic receptors, and the electrical signals stimulate second-order neurons in the CNS. The postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) receptors are sodium channel mediated and are responsible for the first pain mentioned previously. *N*-Methyl-D-aspartate (NMDA) receptor channels allow both sodium and calcium passage. Usually, a magnesium ion holds the channels closed; however, when there is sustained firing from the primary afferents, the magnesium ion is displaced and the NMDA receptor is activated. This sensitizes the second-order neurons that will then discharge at a higher frequency. When sensitization occurs, the firing threshold is reduced, so even slightly painful stimuli (hyperalgesia) and nonpainful stimuli (allodynia) cause sustained activation of the second-order neurons. NMDA receptor activation is linked to *windup* and *central sensitization* (ie, decreased thresholds for response or increased vigor of responses after a sensitizing event) and may contribute to the maintenance of chronic pain conditions with processes occurring both at the dorsal horn level and in the supraspinal areas. Central sensitization may occur with all types of pain when prolonged primary afferent activation causes *plasticity* (adaptation) of the pain sensory thresholds in the CNS.[11]

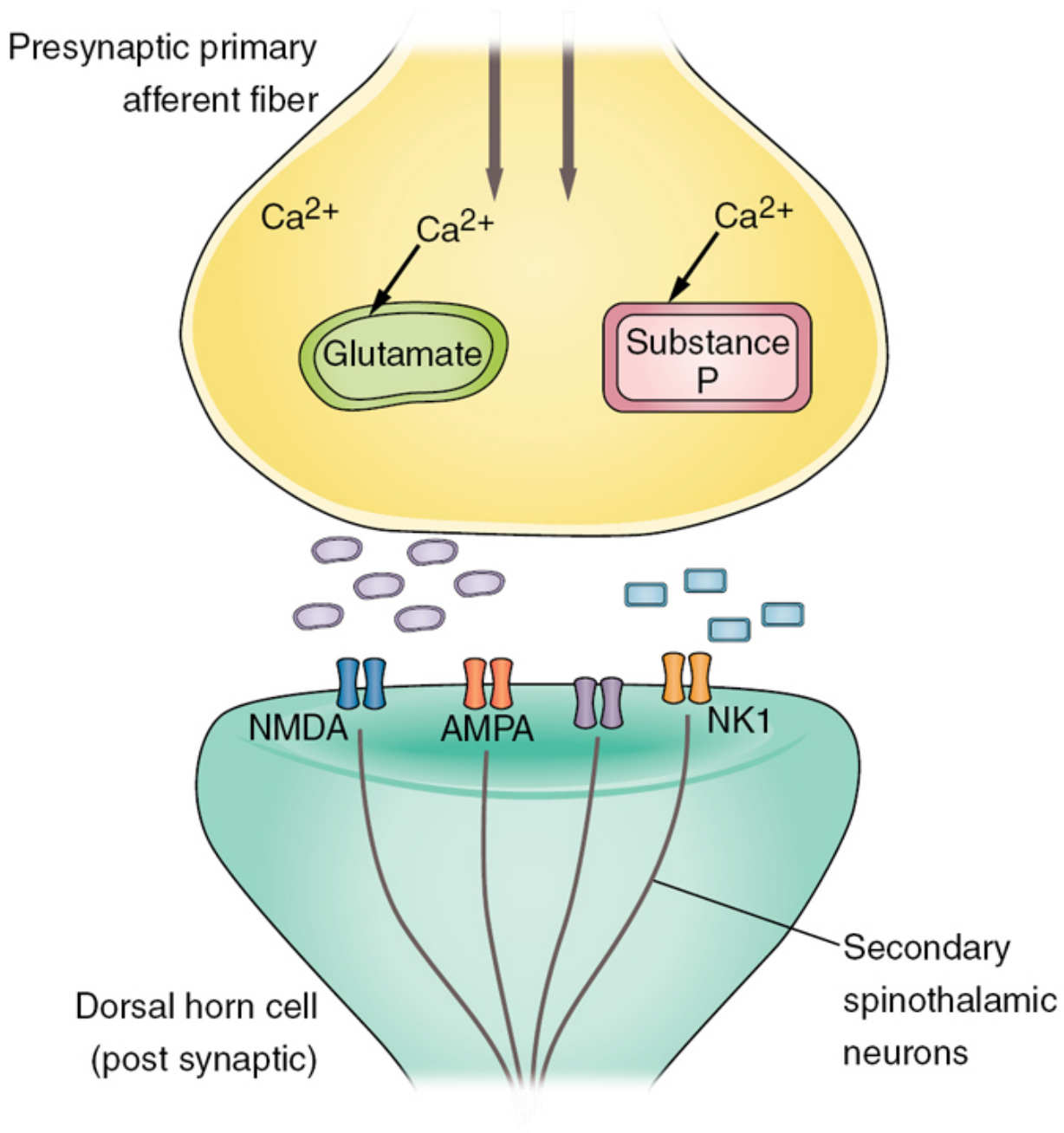


Figure 55-3 Synaptic activity at the dorsal horn. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate; NK1, neurokinin 1; NMDA, *N*-methyl-D-aspartate.

One of the predominant contributors to pain propagation at the synapse and in the CNS is the glial cell. In the periphery, these are Schwann cells and satellite cells. In the CNS, these include oligodendrocytes, astrocytes, ependymal cells, and microglia. Glial

cells account for 70% of the CNS, and under normal conditions, microglia account for 5% to 20% of glia.[12] The glial cells have historically been seen as support cells for synaptic homeostasis; however, they also have an important role in the synthesis, release, and uptake of neurotransmitters and serve as a link between the nervous system and the immune system. Nerve damage caused by trauma, infection, drugs, or toxins exposes peripheral nerve proteins, and they are seen by the immune system as “nonself,” initiating an immune reaction. Glial cells are activated, causing the release of cytokines and inflammatory mediators, thus contributing to peripheral sensitization, increasing nociceptor sensitivity, and lowering of the firing threshold. Continuous nociceptive input results in high levels of glutamate at the synapses. In the setting of chronic pain, glial cells swell (called *gliosis*), and an increase in cell-surface markers is seen. The more persistent the stimulus, the more they swell and release inflammatory mediators. This contributes to the development and maintenance of central sensitization. Glial cells and NMDA receptors may also be activated by medications, such as opioids. This is thought to contribute to opioid tolerance, dependence, addiction, and a phenomenon called *opioid-induced hyperalgesia* (OIH).[11,13]

Visceral pain is very complex. It follows somatosensory pathways and its own systems. Aδ and C fibers have been found in the heart, pleura, abdominal cavity, gallbladder, and testicles. In addition, the intestinal tract has its own neuronal system called the “brain–gut axis” that operates independently and in conjunction with the rest of the CNS.[14] Like the somatosensory pathways, peripheral and central sensitization occurs with chronic visceral pain. Activation of the autonomic nervous system may also affect visceral sensitivity and the role of emotions in modulating visceral pain. Visceral pain may be referred to areas of the somatosensory system (eg, myocardial ischemia causes left arm pain), leading to a complex presentation of pain.[7,14]

SUPRASPINAL MODULATION AND THE DESCENDING PATHWAY

Once nociceptive signals reach the CNS (typically at the spinal cord level), they ascend to the thalamus, primarily via the spinothalamic tract. From the thalamus, tertiary neurons project to many structures in the brain, including the brainstem, diencephalon (includes the thalamus), primary and secondary somatosensory cortices, and frontolimbic area. The somatosensory cortex is where the brain interprets the qualities of pain, such as location, duration, and intensity. Tertiary neurons also project to the limbic system, which is involved in the affective or emotional component of pain. *Perception* is when the sensory (physical) and affective (psychological) components of the nociceptive message are integrated into the patient's overall experience. An individual does not experience pain until the brain has processed and interpreted the electrical nociceptive signal.

A second tract, called the *spinoreticular* tract, not only ascends to the thalamus but also branches off at the brainstem to stimulate descending modulation. *Modulation* happens throughout the CNS and results in either an increase or a decrease in transmission. Neurons from the thalamus and brainstem release inhibitory neurotransmitters, such as norepinephrine (NE), serotonin (5-HT), γ-aminobutyric acid (GABA), glycine, endorphins, and enkephalins, which inhibit EAA activity in the ascending pathway. GABA is more active at the supraspinal sites, and glycine is more active at the spinal sites. The GABA-A receptor is a binding site for benzodiazepines and barbiturates, and the GABA-B receptor is a binding site for baclofen, causing muscle relaxation. Glycine has both pronociceptive and antinociceptive effects, depending on the receptor. Endogenous opioids (endorphins, enkephalins) are the most common group of inhibitory peptides, inhibiting EAA release from the presynaptic terminals and activation of the second-order neurons in the postsynaptic terminals. Opioids also enhance the descending pathway via the release of NE and 5-HT. In fact,

activation of most of the supraspinal structures results in enhancement of NE and 5-HT effects.

Diagnosis and Clinical Presentation

Pain is a symptom and a reactionary response to real or potential bodily harm, but it is not currently defined as a specific disease state. It also cannot be measured objectively. It is a symptom that relies on a patient's subjective report and any physical findings indicative of underlying pathology. Health care teams take on the task of identifying the cause of the pain using everything from noninvasive imaging such as magnetic resonance imaging to invasive testing such as electromyelograms and spinal discography.

Pain can be classified in many ways. Some conditions are classified as syndromes because the patient presents with a constellation of symptoms that cannot be attributed to any definitive diagnosis or disease process (eg, complex regional pain syndrome). Often, clinicians simply state the location and type of pain (eg, neuropathic pain in bilateral lower extremities). Cancer-related pain, whether from the disease process itself or the treatment of the disease (eg, surgery, chemotherapy, or radiation), presents very much like noncancer pain. One of the most common ways to classify pain is to describe the time course. *Acute pain* is caused by an injury or illness. It alerts an individual to the injury and initiates withdrawal from the noxious stimulus. It typically has an easily identified cause and location. The course is predictable, and the pain is expected to diminish in hours, days, or weeks as the injury heals. It may be associated with an inflammatory response, producing redness and swelling. Inadequately treated acute pain can evoke physiologic hormonal responses that alter circulation and tissue metabolism; these can also produce tachypnea, tachycardia, widening of the pulse pressure, and increased sympathetic nervous system activity. It can also cause emotional distress.

Chronic pain serves no biologic purpose. It is characterized by persistent pain that lasts beyond the length of an illness or the

healing of an injury. Sometimes, there is no apparent cause. It may be either continuous or recurrent and of sufficient duration and intensity to adversely affect a patient's well-being, level of function, and quality of life. Risk factors for developing chronic pain include individual predisposition (eg, female sex, increasing age, or a genetic predisposition), environmental factors (eg, previous painful experiences or abuse), and psychological factors (eg, anxiety, depression, or catastrophizing).[7]

Chronic pain can be further classified based on mechanism, symptoms, or location of injury. *Musculoskeletal* or *inflammatory pain* is described as constant, aching pain, often mediated by prostaglandins. It is usually caused by injury to the skeletal muscles or joints. Pain may be localized to the joints (as in rheumatoid arthritis and OA) or more regional (as with myofascial pain or muscle strain). *Neuropathic pain* is described as tingling, sharp, shooting, stabbing, burning, or other uncomfortable feelings (*dysesthesias*) such as the sensation that there are bugs crawling on the skin. Neuropathic pain may be constant (as in diabetic peripheral neuropathy [DPN]) or intermittent (as in trigeminal neuralgia). It is typically caused by injury in the nervous system or a nervous system response to persistent pain stimulus from outside the nervous system. *Visceral pain* can have a vague presentation, because the enteric and autonomic nervous systems are involved. Patients may report nausea or generalized abdominal discomfort (as in endometriosis, hepatitis, or pancreatitis). Some people report pain in the absence of physiologic tissue damage; however, their perception of the pain is very real. This is called *dysfunctional pain.* Conditions such as irritable bowel syndrome, fibromyalgia, interstitial cystitis, and some abdominal or pelvic pain fall into this category. In these conditions, pain appears to be generated by an imbalance in pronociceptive signals and antinociceptive signals in the CNS. Patients with dysfunctional pain syndromes are heavily influenced by factors that augment or diminish the CNS pathways, including stress, anxiety, depression, or illness.

Assessment

Pain is very subjective and difficult to measure in quantitative terms. It is essential to obtain a thorough history and examination, both physical and psychological. When obtaining a pain history, clinicians should gather details about the pattern, duration, location, and character of the pain and should additionally determine what makes the pain worse and what makes it better, what medications and nonpharmacologic therapies have been tried in the past, and the result of those therapies (positive or negative outcome) (**Table 55-1**).

Table 55-1
Patient Evaluation

General History
Chief reason History of present illness Past medical history Family history Social history (smoking, alcohol, illicit drugs) Current medications, including allergies or intolerances Sleep
Pain Assessment
Location Onset Duration Quality Intensity Ameliorating factors Exacerbating factors Pain rating, if possible
History of Nonpharmacologic Therapy
Interventional procedures Physical therapy Chiropractic Acupuncture TENS Aquatic therapy Yoga/Tai Chi

History of Pain Pharmacotherapy
Current and past analgesics Dose/route Duration of use Effectiveness Adverse effects
Clinical Examination
Clinician observations of patient behavior (grimacing, withdrawing, guarding) Physical examination Functional assessment

TENS, transcutaneous electrical nerve stimulation.

Pain intensity should be measured using an appropriate pain scale according to the patient's ability to communicate (**Table 55-2**, **Fig. 55-4**).[15] Single-dimensional pain scales tend to be more accurate in the acute pain setting and not as helpful for chronic pain because they only capture a "snapshot" of what the patient is feeling. Chronic pain symptoms wax and wane over time, so more useful tools are multidimensional pain scales that evaluate function, including sleep, appetite, performance of activities of daily living, work, and social interactions. Examples of multidimensional tools include the PEG (Pain intensity, Enjoyment of life, General activity) scale, McGill Pain Questionnaire, and the Brief Pain Inventory.[16–18] Ultimately, the most useful aspect of patient assessment is the information provided by the patient on how pain impacts day-to-day life, such as the number of hours they spend on their hobbies, or how well they can perform activities of daily living. Some of the most difficult patients to assess are young children and patients with cognitive, visual, or hearing impairment. These patients may have difficulty describing and communicating their pain and discomfort. There are multiple assessment tools that are designed and tested in these special populations to increase the accuracy of pain assessment. In addition to physical and functional assessments, psychological evaluations help to identify those patients who may need behavioral interventions to help them cope with their chronic pain. Because controlled substances may be used to treat chronic pain, screening

for substance use disorders is recommended (see Case 55-6, Question 4).[19]

Table 55-2
Pain Assessment Tools for Adults

Tool	Method of Administration	Advantages	Disadvantages
Visual analog scale (VAS)	Verbal, visual	Reliable; sensitive to acute changes in pain	Requires paper/pencil, mechanical skills; decreased reliability with cognitive, visual, or auditory impairment; not sensitive to long-term changes in pain
Numerical rating scales (NRS)	Verbal, visual	Reliable; good validity; detects treatment effects acutely	Decreased reliability with extremes of age; requires abstract thought, difficult to use with cognitive, visual, or auditory impairment; not sensitive to long-term changes in pain
Pain intensity [P], Enjoyment of life [E], General activity [G] (PEG)	Verbal, visual	Reliable; good validity; 3-item brief assessment; sensitive to long-term changes. Assesses function and values in addition to NRS	Does not provide specifics about reported pain. Does not assess quality of pain or affective component. Difficult to use with cognitive, visual, or auditory impairment
Verbal description scales (VDS)	Verbal, visual (4- or 5-point scales)	Reliable; good validity; preferred by older adults; preferred by some over NRS or VAS	Dependent on literacy and language; limited number of response categories, unequal intervals between anchors; not very sensitive to changes in pain
Faces pain scale	Visual	Reliable; good validity; good with poor literacy or language barrier; possibly easier than NRS or VDS	Requires abstract thinking; not specific for pain
Brief pain inventory (BPI)	Verbal, written	Reliable; intensity and interference components; sensitive to change in condition over time	Does not assess quality of pain or affective component
McGill Pain Questionnaire (MPQ)	Verbal, written (long form—30 minutes; short form—2–3 minutes)	Reliable; measures sensory and affective components; valid in older patients	Not recommended for illiterate or cognitively impaired patients

Source: Kang Y, Demiris G. Self-report pain assessment tools for cognitively intact older adults: integrative review. *Int J Older People Nurs*. 2018;13(2):1–29.

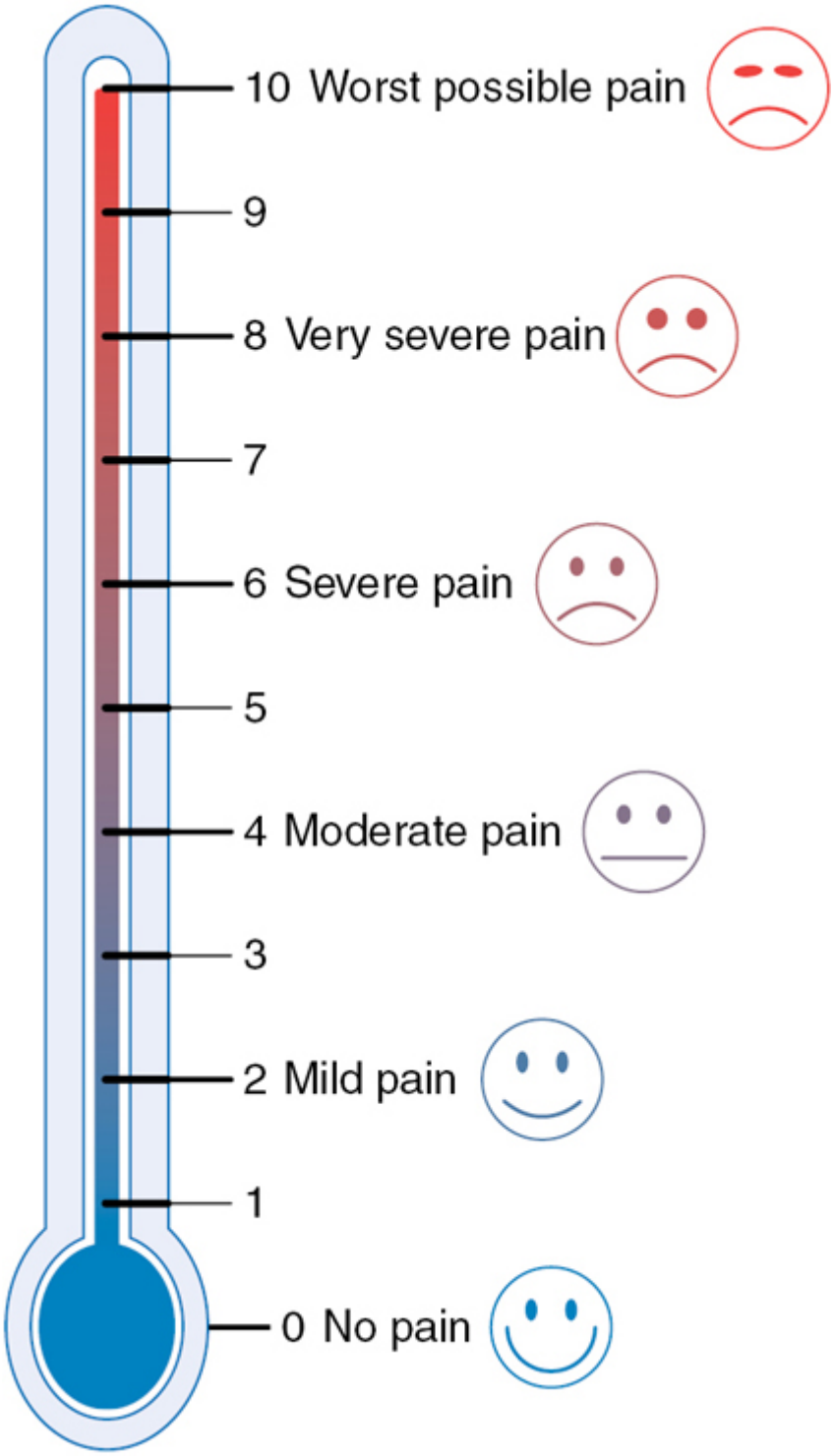


Figure 55-4 Pain assessment scale. (Adapted from Northeast Health Care Quality Foundation [NHCQF], the Medicare Quality Improvement Organization [QIO] for Maine, New Hampshire and Vermont, under contract with the Centers for Medicare & Medicaid

Services [CMS], an Agency of the U.S. Department of Health and Human Services.)

Overview of Treatment

Treatment of pain is based on guidelines whenever possible. However, the number of treatment guidelines for pain management is limited. More commonly, clinicians choose a therapy based on the type of pain (eg, neuropathic, musculoskeletal, inflammatory, visceral, and central). For all types of pain, multimodal therapy including pharmacologic, physical rehabilitation, and behavioral interventions should be combined. Interventional therapies should be considered if possible.

A treatment plan must always include evaluation of the following factors: age, comorbidities (such as renal and liver disease), route of administration (the oral route may not be suitable), concurrent medications (for duplication or drug–drug interactions), laboratory abnormalities, and financial resources.

Acute pain is usually managed very effectively with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and/or opioids, but may include adjunctive therapies as well. Pharmacotherapy for chronic pain is more complex. The first-line agents for the treatment of neuropathic pain consist of antidepressants, preferably serotonin-norepinephrine reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs). These agents enhance the descending inhibitory pain pathway. Anticonvulsants (eg, sodium-channel blockers, calcium-channel blockers, or GABA agonists) are also considered the first-line therapy for many common types of neuropathic pain. They inhibit activation of sodium and calcium channels, block release of EAAs such as glutamate, or block the postsynaptic receptors. Some anticonvulsants also enhance the inhibitory effects of GABA. If the pain is localized, topical agents may be useful (eg, capsaicin or lidocaine). Addition of an opioid may be considered if the former agents fail to provide adequate analgesia. Combination therapy has been shown to be more effective in some

cases (TCA–anticonvulsant or opioid–anticonvulsant combinations).[20] Nerve blocks and other interventional therapies may be helpful for short-term relief.[21]

Chronic musculoskeletal pain usually responds to acetaminophen, salicylates, or NSAIDs, in addition to nonpharmacologic therapies such as heat and ice or physical rehabilitation modalities. Localized pain may be amenable to topical therapies (NSAIDs, capsaicin), and trigger points (ie, taut muscle bands) may be amenable to injections. SNRIs may also be considered for this indication.[22]

Visceral pain is complex, and there are no clear treatment guidelines. Because it travels the somatosensory pathways, antidepressants that enhance inhibitory modulation are most commonly used. In addition, anticonvulsants that reduce central sensitization and hyperalgesia may be helpful.[23]

Trials of any pharmacologic therapy must be monitored for both efficacy and toxicity. Patients must have realistic expectations for any medication trial. Even the most effective analgesics are expected to achieve only about 30% to 50% improvement in chronic pain. This is why multimodal therapy is essential. NSAID therapy should be accompanied by monitoring for dyspepsia, peptic ulcers, gastrointestinal (GI) bleeding, elevated blood pressure, and declining renal function, at a minimum. Antidepressants do not usually require laboratory monitoring but are known to cause dry mouth, constipation, urinary retention, and drowsiness. Some of the anticonvulsants require laboratory monitoring for liver toxicity, electrolyte imbalance, or bone marrow abnormalities. All anticonvulsants may cause drowsiness, dizziness, and cognitive dysfunction, with short-term memory loss and word-finding difficulty. Opioids require laboratory monitoring for long-term adverse effects, such as osteoporosis, hypogonadism, and end-organ impairment, and patients must be routinely screened for sleep apnea, constipation, drowsiness, nausea, and vomiting. Drug interactions, both pharmacokinetic (eg, hepatic enzyme interactions) and pharmacodynamic (eg, additive sedation), are common with many of these agents, particularly when used in combination.

Perioperative Pain Management

More than 80% of surgical patients experience postoperative pain, and of those patients, up to 40% experience “severe” pain.[2,3] The mismanagement of postoperative pain, whether undertreatment or overtreatment, is associated with negative physiologic consequences, such as persistent postoperative pain, impaired rehabilitation, increased hospital length of stay, and adverse events related to excessive analgesic use. Multimodal treatment must be utilized throughout the perioperative continuum to effectively manage pain.

Pain management during the perioperative period can be divided into three phases: preoperative, intraoperative, and postoperative analgesia. Preoperative analgesia is treatment started 1 to 2 hours before surgery, with medications used to decrease peripheral sensitization. Intraoperative analgesia prevents the establishment of central sensitization caused by incisional injury and includes only the procedure time period. Postoperative analgesia is aimed at proactively reducing acute pain and preventing central sensitization, thereby avoiding subsequent development of chronic pain.[11]

Normally, the acute pain trajectory has a rapid decline during the first week after surgery, and most patients fully recover within a few weeks with no residual pain.[24] For 10% to 13% of patients, pain intensity will remain high throughout the postoperative course and persist for several months.[25] Although there is no single definition of a time frame for chronic pain, chronic postsurgical pain (CPP) is pain that occurs at the site of the incision or related areas of the surgery and continues beyond the time frame that it takes for most injured tissues to fully heal. The time of CPP onset is between 3 and 6 months.[26,27]

The prevalence of CPP is highest with limb amputation, thoracotomy, mastectomy, hernia repair, and cardiac surgery (**Table 55-3**).[11,27] Risk factors for CPP include history of chronic pain before surgery, gender, age, surgical site, invasiveness of surgery, unrelieved postoperative pain, and comorbid anxiety or depression.[26]

Genetic factors also account for a significant degree of interindividual variation in pain sensitivity and treatment response.[11,26]

Table 55-3
Prevalence of Chronic Postsurgical Pain

Type of Surgery	Incidence of Chronic Pain (%)	Clinical Presentation
Limb amputation	30–85	Phantom limb pain
Mastectomy	20–50	Scar pain, phantom breast pain, shoulder or arm pain, chest wall pain
Thoracotomy	60–75	Scar pain, chest wall pain
Coronary artery bypass surgery	30–50	Sternal pain, postsaphenectomy pain
Inguinal hernia repair	5–55	Scar pain, ilioinguinal nerve pain, inflammatory pain

Source: Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain pathophysiology and preventative pharmacologic considerations. *Anesthesiology*. 2018;129: 590–607; Glare P, Aubrey KR, Myles PR. Postoperative pain management and opioids: transition from acute to chronic pain after surgery. *Lancet*. 2019;393:1537–1546.

CASE 55-1

Question 1: B.B. is a 46-year-old female who sustained a shoulder injury while pulling a cart at work. She will be undergoing total shoulder arthroplasty in 2 weeks. She also has fibromyalgia and takes hydrocodone/acetaminophen 5 mg/325 mg with one to two tablets by mouth every 6 hours (usually takes eight tablets daily) as well as duloxetine 30 mg by mouth daily and pregabalin 75 mg by mouth twice daily. She smokes one pack of cigarettes daily and has "a few" glasses of wine nightly to help her pain because she does not think her current analgesic regimen is effective.

What assessment should be done with B.B. before surgery? What risk factors does she have for increased pain after surgery?

It is paramount that all patients have a thorough preoperative assessment, including review of medical comorbidities, medications, history of chronic pain, and substance abuse, as well as prior postoperative analgesic regimens and responses.[28] Pharmacists

should also ask about sleep-disordered breathing (SDB) because some patients may experience sleep apnea but are unaware of the condition. The presence of central sleep apnea or obstructive sleep apnea (OSA) is associated with a higher risk for perioperative complications. Preexisting SDB, often rated as moderate to severe, is present in 70% to 85% of patients taking long-term opioids.[29] Central sleep apnea is repetitive cessation or decrease of both airflow and ventilatory effort during sleep and is more predominant than OSA.[30] A screening tool called STOP-BANG can be utilized to assess for sleep apnea risk (**Table 55-4**).[31]

Table 55-4
Stop-Bang Questionnaire

Do you snore loudly?
Do you feel tired, fatigued, sleepy during the day?
Has anyone observed you stop breathing during sleep?
Are you being treated for high blood pressure?
BMI >35 kg/m^2
Age >50 years
Neck circumference >40 cm
Male gender
Yes to ≥3 items = high risk for OSA
Yes to <3 items = low risk of OSA

BMI, body mass index; OSA, obstructive sleep apnea.

Adapted with permission from Dr. Frances Chung and University Health Network. www.stopbang.ca.

As part of a preoperative medication assessment, pharmacists need to review medications that the patient takes at home and develop a plan to resume them after surgery. Laboratory data for renal, liver, and pulmonary function need to be reviewed to determine whether medication dose adjustment may be needed before surgery. For patients taking opioids before surgery, pharmacists should obtain prescribing data from their respective

state prescription drug monitoring program (PDMP) to determine what controlled substances the patient has been filling and ask the patient how each medication has been taken at home. Current and past substance use should be addressed in an open and nonjudgmental manner.[32]

Patients always bring their past experiences and current fears to surgery. These factors affect how they perceive and cope with acute pain after surgery (**Table 55-5**).[26] Risk factors for increased pain after surgery in B.B. include female gender, work injury, and chronic opioid therapy.[26] Functional pain syndromes (FPSs) such as fibromyalgia are associated with inefficient diffuse noxious inhibitory control (DNIC). This means that the inhibitory pathway is not effectively blocking pain transmission into the CNS, and she will likely have an exaggerated pain response to surgery. Her chronic opioid use could also complicate pain management because she will likely require higher opioid doses after surgery.[32]

Table 55-5
Risk Factors for Increased Postoperative Pain

Adverse experience with previous surgery
Preexisting pain (moderate-severe >1 month)
Psychological vulnerability
Younger age
Female
Workers' compensation
Inefficient diffuse noxious inhibitory control (DNIC)
Genetic predisposition
Use of chronic opioid therapy

Reprinted with permission from Gulur P, Nelli A. Persistent postoperative pain: mechanisms and modulators. *Curr Opin Anaesthesiol*. 2019;32(5):668–673.

Case 55-1, Question 2: What should be done to help B.B. prepare for surgery?

Clinicians should provide the patient and family with individually tailored education, including information on treatment options for the management of postoperative pain, making sure to document the plan and goals in the medical record and on paper for the patient to take home.[28] Patient-tailored education has been shown to reduce postoperative opioid consumption, preoperative anxiety, requests for sedatives, and length of stay.[28,33] Education should include changes in analgesics before surgery, reporting and assessment of pain and when to report, multimodal pharmacologic and nonpharmacologic options, as well as realistic goals for pain control.[32]

For B.B., there needs to be education about her substance use. Many surgeons require patients to stop smoking before surgery to improve healing (for smoking cessation strategies, see Chapter 91, Tobacco Use and Dependence). Given her regular intake of alcohol, tapering off this before surgery is important, because she may develop alcohol withdrawal after surgery if she continues to consume alcohol. This complicates postoperative care and prevents the use of valuable analgesics such as acetaminophen because of additive liver toxicity. Because she is getting little to no benefit from her opioid, it is recommended to discontinue hydrocodone/acetaminophen via taper over the next 2 weeks to reduce her tolerance and improve her postoperative response to opioid analgesics.[32] Some time also needs to be devoted to reducing her anxiety and educating her that she may have an exaggerated pain response. Increasing the dose of pregabalin may help with this as part of a multimodal analgesic regimen, and duloxetine could be continued.

Case 55-1, Question 3: Based on current guidelines, what anesthesia modalities may be part of a multimodal pain management approach for B.B.?

A multimodal approach to surgical pain management may include a combination of nonpharmacologic therapies, nonopioid medications, systemic analgesics, and nerve blockade through regional or neuraxial anesthesia.[34] It is important to note that there

are many different nerve blocks for the body trunk and extremities. The choice of nerve block depends on the type of surgery, location of the block, medication, and risk for complications. *Neuraxial anesthesia* is a term associated with the epidural or intrathecal route of administration. An intrathecal spinal injection is a single dose of either an opioid and/or local anesthetic administered into the cerebrospinal fluid (CSF) in the subarachnoid space near the region where pharmacologic effect in the spinal cord is needed.[35]

Intrathecal medication doses are significantly lower compared to epidural owing to the direct injection into the CSF. Analgesia with an intrathecal single injection will wear off according to the half-life of the medication used (**Table 55-6**).[36] Some anesthesiologists use a small amount of epinephrine to cause local vasoconstriction and keep the medication from dispersing rapidly through the CSF.[37] Common complications with intrathecal injections include postdural puncture headaches (ie, CSF can leak after puncture of the subarachnoid dura) and itching with opioids. More serious complications include delayed respiratory depression (with opioids), hypotension (with local anesthetics), infection, and intraspinal hematomas.

Table 55-6
Injectable Local Anesthetics

Pharmacodynamics/Kinetics								
Injectable Local Anesthetics: Pharmacokinetics								
	Distribution	**Protein Binding**	**Onset of Action**	**Time to Peak**	**Duration of Action**	**Metabolism**	**Half-life Elimination**	**Excretion**
Bupivacaine hydrochloride	Children: 2.7 ± 0.2 L/kg Infants: 3.9 ± 2 L/kg	84%–95%	Anesthesia (route and dose dependent): ■ Epidural: ≤17 minutes to spread to T6 dermatome ■ Dental injection: 2–10 minutes ■ Infiltration: Fast ■ Spinal: Within 1 minute; maximum dermatome level achieved within 15 minutes in most cases	Caudal, epidural, or peripheral nerve block 30–45 minutes	Route and dose dependent: ■ Epidural: 2–7.7 hours ■ Infiltration: 2–8 hours ■ Dental injection: ≤7 hours ■ Spinal: 1.5–2.5 hours	Hepatic; forms metabolite (pipecoloxylidine [PPX])	Age dependent: ■ Adults: 2.7 hours ■ Neonates: 8.1 hours	Urine (~6% unchanged)
Bupivacaine liposomal		95%	Rapid	Within 1 hour (initial peak); 12–36 hours (second peak)	Local: ≤72 hours Systemic: Plasma levels can persist for 96 hours after local administration and 120 hours after interscalene brachial plexus nerve block	Hepatic via conjugation; major metabolite PPX (inactive)	13–34 hours	Urine (~6% unchanged)
Chloroprocaine	Depends upon route of administration; high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain		6–12 minutes		Up to 60 minutes (patient, type of block, concentration, and method of anesthesia dependent)	Rapidly hydrolyzed by plasma enzymes to 2-chloro-4-aminobenzoic acid and β-diethylaminoethanol (80% conjugated before elimination)	In vitro. plasma: ■ Adults: 21 ± 2 seconds (males). 25 ± 1 seconds (females) ■ Neonates: 43 ± 2 seconds	Urine (minimal as unchanged drug in urine; metabolites: Chloroaminobenzoic acid and β-diethylaminoethanol primary excreted unchanged)
Lidocaine	1.5 ± 0.6 L/kg; range: 0.7–2.7 L/kg; alterable by many patient factors; decreased in CHF and liver disease; crosses blood–brain barrier	60%–80% to α-1 acid glycoprotein	Single bolus dose: 45–90 seconds		10–20 minutes	90% hepatic; active metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) can accumulate and may cause CNS toxicity	Biphasic: ■ Initial: 7–30 minutes ■ Terminal: ■ Adults: 1.5–2 hours ■ Infants, premature: 3.2 hours	Urine (<10% as unchanged drug. ~90% as metabolites)
Mepivacaine		~75%	Route and dose dependent: Range: 3–20 minutes; dental: upper jaw: 30–120 seconds; lower jaw: 1–4 minutes		Route and dose dependent: 2–2.5 hours; dental: upper jaw: 20 minutes; lower jaw: 40 minutes	Primarily hepatic via *N*-demethylation, hydroxylation, and glucuronidation	Adults: 1.9–3.2 hours Neonates: 8.7–9 hours	Urine (90%–95% as metabolites)
Prilocaine	190–260 L; crosses blood–brain barrier	40%–55% (α-1 acid glycoprotein)	Infiltration: <2 minutes Inferior alveolar nerve block: <3 minutes		Infiltration: Complete anesthesia for procedures lasting 20 minutes Inferior alveolar nerve block: ~2.5 hours	Primarily metabolized hepatically and to a lesser renally; prilocaine hydrolyzed by amidases to produce ortho-toluidine and *N*-propylalanine; these compounds may also undergo ring hydroxylation	1.6 hours	Urine (~5% as unchanged drug)
Ropivacaine	Vdc ■ Adults: Intravascular infusion: 41 ± 7 L ■ Children: Epidural infusion: 2.1–4.2 L/kg		Anesthesia (route dependent): 3–15 minutes	Dose and route depended: Caudal: ■ Children: Mean: 60 minutes (range: 12–249 minutes) ■ Infants: Median: 60 minutes (range: 15–90 minutes)	Dose and route dependent: 3–15 hours	Hepatic. Via CYP1A2 to metabolites	Adults: ■ Epidural: 5–7 hours ■ Children: ■ Epidural: Terminal phase: 4.9 hours (range: 3–6.7 hours)	Urine (86% as metabolites)
Tetracaine					1.5–3 hours	Hepatic: Detoxified by plasma esterases to aminobenzoic acid		Urine

Data from Injectable Local Anesthetics: Pharmacokinetics. Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5545932?

cesid=3mnc6mWIOHi&-searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dlocal%252520anesthetics%26t%3Dname%26va%3Dlocal%252520anesthetics%26nq%3Dtrue#phk-nested

Epidural analgesia is a pain management option for invasive abdominal surgical procedures and labor pain. The epidural space is the outmost region of the spinal canal that contains fat, epidural veins, spinal nerve roots, and connective tissue. Medication selection, concentration, and delivery mode (eg, continuous infusion, patient-controlled epidural dose) depend on the clinical indication. Morphine and hydromorphone are commonly used for surgical epidural administration in combination with a local anesthetic, such as bupivacaine or ropivacaine. Both morphine and hydromorphone are more hydrophilic compared to fentanyl, so it is difficult for them to pass through the lipophilic arachnoid meninges for penetration in the CSF once injected into the epidural space. Fentanyl is highly lipophilic and easily passes through membranes into the systemic circulation and CSF. Typically, fentanyl is combined with a local anesthetic for obstetrical labor. All epidural opioids travel cephalad to the brain via the CSF and may cause central respiratory depression. Epidural opioids also cause typical class-related adverse effects, such as itching and nausea, and cognitive effects, such as sedation or confusion, although these are centrally mediated.[38]

Local anesthetics must be monitored not only for pain coverage but also for toxicity. They most commonly cause hypotension, because sympathetic nerves are small. The more cephalad the epidural catheter tip is placed, the more likely that the sympathetic nerves serving the lungs, diaphragm, and heart will be affected. Local anesthetic systemic toxicity (LAST) can be life-threatening, causing seizures and cardiac dysrhythmias. The treatment of LAST involves rapid administration of intralipid, which will bind the local anesthetic.[39]

Regional anesthesia is commonly used for surgical procedures involving the upper trunk (chest and shoulders), upper extremities (arms and hands), and lower extremities (hip and legs).[40] Nerve blockade results from infiltration of local anesthetic around one or

more peripheral nerves to cause temporary loss of sensation in an area of the body.[41] Local anesthetics are highly lipophilic and diffuse across the plasma membrane to reversibly block voltage-gated sodium channels on the peripheral nerves. The sodium channel block interrupts the action potential and influx of sodium ions, thereby decreasing the sensory nerve conduction.[42] Advantages to peripheral nerve blockade include avoidance of general anesthesia, better management of the surgical stress response, reduction in postoperative opioid requirements, and quicker recovery from surgery.[43] The choice of local anesthetic in peripheral nerve blockade is mainly determined by desired speed of onset, block intensity, and duration of anesthesia. Plain bupivacaine or liposomal bupivacaine is more frequently used for single-injection peripheral nerve blocks.[44] Ropivacaine has largely replaced bupivacaine as the most commonly used long-acting (LA) local anesthetic in continuous peripheral nerve blocks (Table 55-6).[36] In equivalent doses, ropivacaine produces less motor blockade compared to bupivacaine but an equally effective sensory block.

The major limitation to a single-injection block is that the local anesthetic will only last a few hours. A single injection is best suited for surgical procedures in which postoperative pain is not expected to exceed 12 to 24 hours in duration; otherwise, patients are at risk for significant rebound pain.[34] Administration of local anesthetics via continuous infusion allows for a duration of analgesia significantly longer than that of a single injection. Continuous peripheral nerve blockade involves placement of an indwelling catheter in the perineural space (eg, around the peripheral nerves). The local anesthetic infusion can be delivered until the postoperative pain has subsided. The catheter may be connected to a hospital infusion pump or portable elastomeric pump for discharge to home with the patient. When comparing single-injection peripheral nerve blocks to continuous peripheral nerve blocks, continuous techniques tend to be associated with improved postoperative analgesia, improved patient satisfaction, and decreased total opioid consumption for certain surgeries.[45] The most commonly cited risks associated with peripheral nerve blocks include nerve injury, bleeding, infection,

intravascular injection, systemic local anesthetic toxicity, and injury to surrounding anatomic structures.[46]

For B.B., the anesthesia team will use regional anesthesia with an interscalene brachial plexus nerve block (ISB). The ISB is increasing in popularity with use in ~42% of patients undergoing shoulder arthroplasty in the United States.[47] Because shoulder surgery is so painful and recovery is long, B.B. will be discharged to home with a continuous infusion of ropivacaine for pain relief up to 7 days. Home care services will follow B.B. to assess the postoperative recovery and discontinue the ropivacaine infusion pump. B.B. will have her arm in a sling because her arm and hand will be numb and not functional while the nerve block is running. This form of longer term acute analgesia has been shown to reduce length of hospital stay and provide excellent pain relief.[48]

Multimodal Pain Management

CASE 55-2

Question 1: D.K. is a 35-year-old male admitted for a spine surgery. His past medical history is significant for lumbar spinal stenosis, resulting in foraminal compression of the spinal canal. Conservative therapies have failed to reduce the severity of the low back pain. Before admission for the surgery, the patient's medical history included:

Medical conditions:

Morbid obesity: height 70.86 inches (180 cm), weight 376.99 pounds (171 kg), body mass index (BMI) 51.5 kg/m^2

Type 2 diabetes, noninsulin dependent
Sleep apnea, uses continuous positive airway pressure (CPAP) at home
Degenerative joint disease of the lumbar spine
Hypertension
Medications:
Glimepiride 8 mg orally once daily
Lisinopril 20 mg orally once daily
Ibuprofen 600 mg orally once or twice daily for pain
Oxycodone/acetaminophen 5 mg/325 mg, one tablet every 4 hours as needed (prn) (reports taking four tablets every day)
Docusate/senna 100 mg/17.2 mg, two tablets orally at bedtime prn

In the postoperative anesthesia care unit (PACU), morphine 2 to 4 mg intravenous (IV) every 5 minutes is ordered for severe pain. D.K. received 8 mg of IV morphine over 30 minutes, then became very drowsy but is still reporting severe pain. The nurse is concerned about the level of sedation and does not want to give additional morphine.

Is morphine an appropriate opioid for postoperative pain control in D.K.?

After surgery is completed in the operating room, patients are transferred to the PACU for stabilization of respiratory function and pain. Most patients emerging from general anesthesia are still quite sedated when they are transferred to the PACU. When the anesthetic agents begin to wear off, it is very important to achieve rapid control of severe pain, so frequent administration of small IV opioid doses is common practice in this setting. Currently, there is not a universally accepted standard for titration of IV opioids in the PACU. Some institutions will allow the use of both IV fentanyl to gain fast pain control and morphine for a longer duration of action. Hydromorphone is an acceptable alternative to morphine for patients with renal insufficiency or intolerable side effects to morphine.

Morphine is considered the standard for IV opioid administration. The hydrophilic property of morphine delays penetration across the blood–brain barrier, so the relative time to onset is ~6 minutes after an IV dose. The concentration peak effect after an IV morphine dose is 20 minutes.[49] Major morphine metabolites include morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).[50] The M3G metabolite is inactive, but M6G crosses the blood–brain barrier and has potent analgesic activity. Therefore, the analgesic and ventilatory depressant effects of morphine and M6G may not be evident with initial high plasma morphine concentrations.[51] Adverse events may occur 40 to 60 minutes after the last IV morphine dose.[51] Patients with renal insufficiency will have M6G metabolite accumulation and be at increased risk for respiratory depression, so morphine use is not recommended in this population.[52]

Hydromorphone is a semisynthetic hydrogenated ketone analog of morphine with 10 times higher lipid solubility compared to morphine, which contributes to its rapid CNS effects.[53,54] In comparison to morphine, the potency of hydromorphone is approximately seven

times higher for the IV route and four times higher than the oral route.[54–56] The concentration peak effect after IV hydromorphone administration is between 8 and 20 minutes.[57,58] Hydromorphone is predominately metabolized through the phase II glucuronidation pathway similar to morphine producing hydromorphone-3-glucuronide (H3G) and hydromorphone-6-glucuronide (H6G). The primary metabolite, H6G, lacks analgesic activity and has not been found to contribute significantly to side effects, thus making hydromorphone the preferred opioid over morphine. H3G metabolite production is significantly less than H6G, but H3G has been shown to accumulate in animal models, leading to dose-dependent myoclonus.[54,58] In patients with renal failure, the H3G metabolite may increase side effects, including nausea, delirium, and seizures.[54,59] Therefore, low initial dosing of hydromorphone is recommended in patients with renal failure.

Fentanyl is a synthetic phenylpiperidine compound with high lipid solubility, resulting in rapid transfer across the blood–brain barrier. Compared to morphine, fentanyl is 100 to 300 times more potent owing to optimization of the molecular configuration.[60] Fentanyl is almost completely metabolized in the liver by cytochrome P450 3A4 (CYP3A4), rendering the oral route ineffective because of the first-pass effect. For acute pain, the IV route of administration is recommended owing to the rapid onset of action. Analgesic effects occur within 1 to 2 minutes after IV bolus administration and last for ~30 minutes.[61] Caution with IV bolus dosing is needed because of the risk of chest wall rigidity resulting in respiratory failure. Chest wall rigidity is related to the dose and speed of delivery that has occasionally been encountered with a 50-μg dose.[61] After an IV dose, fentanyl redistributes into muscle and adipose tissue. Removal of fentanyl from muscle and adipose tissue is slower than uptake, because both tissues act as storage sites; in muscle, this is because of its mass, and in adipose tissue, this is because of the high lipid solubility of fentanyl. After initial equilibration, the adipose tissue slowly releases fentanyl back into the plasma, resulting in a lengthy elimination half-time of 3.1 to 7.9 hours.[60] Multiple, frequent fentanyl bolus dosing will lead to accumulation as a result of its long half-

time. Fentanyl is a good option for rapid pain control during surgical procedures in the operating room, but is not the best choice for postoperative pain control in obese patients.[62]

For the management of D.K.'s pain in the PACU, the morphine order should be changed to IV hydromorphone 0.2 to 0.4 mg every 10 minutes for severe pain. Hydromorphone does not have appreciable H6G metabolite accumulation and does not distribute into adipose tissue. After D.K.'s pain is stabilized in the PACU, the interval will need to be longer between doses owing to the declining acute pain trajectory and addition of other multimodal medications that will decrease the opioid requirements. In addition to pain management, it is very important to anticipate postoperative nausea and vomiting (PONV) caused by anesthetic agents and opioids. Antiemetics are commonly used for the prevention of severe PONV (refer to Chapter 22 for management of PONV).

CASE 55-2, QUESTION 2: Is D.K. an appropriate candidate for IV patient-controlled analgesia (PCA)?

For postoperative pain management after discharge from the PACU, the oral route is preferred to IV administration unless the patient is unable to take oral medication or has severe uncontrolled pain.[28] The use of PCA provides a precise and convenient method for IV opioid administration that allows the patient to activate the dose for acute pain management. The IV PCA route is preferred to nurse-administered IV doses because the patient does not have to notify the nurse when more medication is needed, wait until it is given, and then further wait for the peak effect to occur for pain relief. Self-administration of smaller and more frequent IV opioid doses reduces the variation between the peak and trough effect of the dosing interval, thus providing better maintenance of the plasma opioid concentration.[63]

Patients who are appropriate for PCA must be able to cognitively understand how to use a dose button for opioid self-administration and who will require IV opioid for many hours.[28] The PCA dose

button is connected to an infusion pump that will allow the administration of an opioid dose when the button is pushed (ie, demand). To prevent overdosage by continual demand, all PCA devices use a lockout interval, which is the length of time after a successful patient demand during which the device will not administer another dose even if the patient pushes the button.[63] Most patients who start IV PCA are opioid naïve, meaning that their opioid use the week before surgery was <60 mg[64,65] of oral morphine or its equivalent.[64] For this reason, the starting dose for IV PCA is standardized for opioid-naïve patients (**Table 55-7**).[65]

Table 55-7

Patient-Controlled Analgesia

Dosing Parameter	Fentanyl 10 µg/mL	Hydromorphone 0.2 mg/mL	Morphine 1 mg/mL
Maximum dose	The total amount of drug over time and the maximum number of patient demand doses per hour will vary.	The total amount of drug over time and the maximum number of patient demand doses per hour will vary.	The total amount of drug over time and the maximum number of patient demand doses per hour will vary.
Loading dose	20 µg bolus	0.4 mg (400 µg) bolus	2 mg bolus
Clinician dose	20 µg bolus. One clinician bolus may be given each hour.	0.4 mg (400 µg) bolus. One clinician bolus may be given each hour.	2 mg bolus. One clinician bolus may be given each hour.
PCA dose	10 µg with a lockout time of 10 minutes	0.2 mg (200 µg) with a lockout time of 10 minutes	1 mg with a lockout time of 10 minutes
Basal dose	Not recommended for starting PCA		

PCA: patient-controlled analgesia.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

The use of a continuous opioid infusion for postoperative pain management is generally reserved for patients who are opioid tolerant. The role of the continuous infusion is to provide a steady baseline of opioid medication that mimics the dose taken before surgery. The use of IV PCA along with a continuous infusion in opioid-tolerant patients can help optimize pain control.

In this case, PCA therapy without a continuous infusion would be appropriate for D.K. based on the invasive surgery and anticipated severe postoperative pain. Before admission, D.K. reported taking 20 mg of oxycodone daily. Using the equianalgesic conversion table (**Table 55-8**), 20 mg of oral oxycodone is equivalent to 30 mg of oral morphine.[55,56] Therefore, D.K. is opioid naïve based on total daily

use of oxycodone being equivalent to <60 mg of oral morphine. Hydromorphone 0.2 mg IV with a lockout interval of 10 minutes is recommended because D.K. is at high risk for respiratory depression as he is opioid naïve, morbidly obese, and has a history of sleep apnea.[53] Because D.K. is experiencing sedation because of morphine administration in the PACU, the PCA dose should be started after he is more alert. Nonopioid analgesic medications that are not sedating should be used to provide synergistic pain management and can be used throughout the postoperative period.

Table 55-8
Opioid Conversion Calculations

Drug	Equianalgesic Dose Calculation[a]		Oral Morphine Milligram Equivalent[b]
	Use for conversion between intravenous (IV) and oral opioid		Conversion factor for oral opioid prescription data calculations. Do not use for IV conversions.
	Oral	IV	
Fentanyl	Not available	0.1 mg	0.13 (buccal or sublingual)
Hydrocodone	30 mg	Not available	1
Hydromorphone	7.5 mg	1.5 mg	4
Morphine	30 mg	10 mg	1
Oxycodone	20 mg	Not available	1.5
Oxymorphone	10 mg	1 mg	3

[a]See below for example of equianalgesic dose calculation.

[b]See below for example of calculation using oral morphine milligram equivalent (MME).

Calculation Example 1: **Equianalgesic conversion from oxycodone 5 mg to morphine IV.**

Step 1: Select the equianalgesic dose ratio that corresponds to the opioid and route that will be converted from the table above. Ratio calculations should be set up to correlate the actual dose with the equianalgesic equivalent as shown below:

"X" mg total daily dose of new opioid = equianalgesic factor of new opioid

<60 mg total daily dose of current opioid = equianalgesic factor of current opioid

Step 2: For the conversion, 20 mg of oral oxycodone is equianalgesic to 10 mg IV morphine.

"X" mg total daily dose of new opioid = 10 mg IV morphine

5 mg oral oxycodone = 20 mg oral oxycodone

Step 3: Cross multiply the ratio to determine the total daily dose of IV morphine.

(20)(X) = (10)(5)

20X = 50

X = 2.5 mg of IV morphine

When switching to a new opioid, the initial daily dose for the new opioid should be reduced by 25% to 50% to adjust for incomplete μ-receptor cross-tolerance.

Calculation Example 2: Calculate the daily MME for an acute pain discharge prescription of oxycodone 5 mg oral every 4 hours prn.

Step 1: Determine the maximum units per day of tablets that could be taken.

(1 oxycodone 5 mg tablet) (6 per day) = 6 tablets per day

Step 2: Determine the MME per day

Tablet strength × units per day × MME factor = MME per day

(5 mg) (6 per day) (1.5) = 45 MME per day

Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home; National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2016 version. Centers for Disease Control and Prevention; 2016. https://www.cdc.gov/drugoverdose/media/

Case 55-2, Question 3: What are potential risk factors for respiratory depression related to opioid therapy that need to be considered for D.K.?

Respiratory depression remains the most serious adverse event related to opioid therapy, often because of excessive amounts or frequent use of an opioid beyond what is needed to achieve pain control. There are many factors that increase the risk of opioid-induced respiratory depression with IV and oral therapy related to comorbid medical conditions. Patients with advanced age older than 65 years, renal insufficiency, history of sleep apnea, or morbid obesity are at higher risk for developing opioid-induced respiratory depression. Morbid obesity is defined as a BMI >40 kg/m^2 and presents a significant challenge for perioperative acute pain management. Patients with morbid obesity have a higher risk of respiratory depression related to OSA and altered medication clearance due physiologic changes in organ systems, including renal and liver.[62]

To prevent respiratory depression in high-risk patients, the lowest possible starting dose of an opioid should be initiated, and the use of a continuous infusion should be avoided. For all patients, avoid administration of more than one drug with sedating properties at the same time with opioids.[28] Medications including antihistamines, benzodiazepines, gabapentin, pregabalin, and skeletal muscle relaxants should be scheduled ~2 hours apart to prevent accumulation of sedating side effects.

Case 55-2, Question 4: How is naloxone administered for reversal of respiratory depression?

For hospitalized patients who experience excessive sedation and cannot be aroused with sternal stimulation, or have a significant decline in breathing, naloxone administration may be needed to reverse the opioid CNS effects. Naloxone is a nonselective competitive opioid antagonist of all pharmacologic effects on μ, δ, and κ receptors. After oral administration, naloxone is extensively metabolized in the liver (ie, >95% first-pass effect), rendering it ineffective; therefore, IV, intramuscular, or subcutaneous administration at an initial dose of 0.4 mg is required for reversal of life-threatening respiratory depression.[66] The extent and duration of naloxone reversal of opioid-induced respiratory effects is highly variable and is related to many factors, including the specific opioid used, the opioid dose, administration mode, concurrent medication, underlying disease, and pain. Therefore, naloxone administration may need to be repeated every 2 to 3 minutes or given as a continuous infusion until full recovery of respiratory function.[67]

Case 55-2, Question 5: How can opioid-induced constipation be prevented?

Owing to the distribution of μ-opioid receptors in the enteric nervous system, common side effects of opioid therapy include constipation, decreased appetite, increased reflux, nausea, and vomiting. An abundance of literature and guidelines exist endorsing

the use of stool softeners, osmotic agents, and stimulant laxatives for the prevention of opioid-induced constipation with acute pain management.[28] However, there are many shortcomings to laxative use with chronic opioid therapy. Peripherally acting μ-opioid receptor antagonists such as methylnaltrexone or naloxegol bind to receptors in the enteric nervous system and may be needed to restore functional motility with severe constipation.[68,69]

Before surgery, D.K. was taking oxycodone/acetaminophen for chronic low back pain. It is anticipated that D.K. will have opioid-induced constipation with postoperative opioid therapy. The docusate/senna dose that D.K. was taking before admission may need to be increased to two tablets twice daily for the management of increased constipation owing to more frequent opioid use for acute pain.

Case 55-2, Question 6: What oral short-acting opioid dose should D.K. be prescribed when discharged from the hospital?

As soon as D.K. can tolerate oral medication, the IV PCA dose should be discontinued and a short-acting oral opioid such as oxycodone or hydromorphone be administered prn with frequent reassessment of pain. Because D.K. is at high risk for respiratory depression, the lowest starting dose should be prescribed. Oxycodone 5 mg by mouth every 4 hours prn or hydromorphone 2 mg by mouth every 4 hours prn would be options in this case. Oral short-acting morphine is not recommended owing to concern for metabolite accumulation. LA oral formulations (ie, sustained release or extended release [ER]) and transdermal fentanyl patches should be avoided for acute pain in patients who cannot tolerate around-the-clock opioid administration for a prolonged period of time.[65]

Guidelines from the Centers for Disease Control and Prevention recommend that a short-acting oral opioid prescription of 3 days or less is sufficient for acute pain.[70] For surgical pain, there is not a consensus on the maximum quantity of oral short-acting opioid tablets for a discharge postoperative prescription. When D.K. is

ready for discharge, a prescription for a limited supply of short-acting oral opioid should be written to cover the duration of severe postoperative pain, but not exceeding 7 days. D.K. needs education on how to safely take the opioid medication because postoperative pain management is different from chronic pain management. Discharge instructions should instruct D.K. to not take oxycodone/acetaminophen for chronic pain until the postoperative opioid therapy course is discontinued. Any unused opioid from the postoperative prescription should be appropriately discarded in pharmacy disposal boxes or through drug take-back programs in the community.

Case 55-2, Question 7: What other nonopioid medications would be helpful in the management of D.K.'s postoperative pain?

Guidelines on postoperative pain management endorse the use of nonopioid medication. There is evidence that the combination of acetaminophen and NSAIDs is more effective than either drug alone in reducing pain and opioid consumption.[28] Acetaminophen is useful in treating mild-to-moderate nociceptive pain.[28] Perioperative oral acetaminophen at a dose of 975 mg on a scheduled frequency after surgery in adults with normal liver function is supported in the literature.[62] After the initial postoperative period, the dose should be reduced to 650 mg and administered on a "prn" frequency. Acetaminophen-induced hepatotoxicity, which can be life-threatening, has been associated with daily use >4000 mg/day. Over-the-counter (OTC) acetaminophen product directions and experts recommend a lower maximum of 3000 mg/day in adults when used for a longer duration exceeding 7 days. To reduce the risk of hepatotoxicity, patients who will need opioid therapy should not be prescribed combination products containing acetaminophen, such as oxycodone/acetaminophen or hydrocodone/acetaminophen. The use of IV acetaminophen has generally been reserved for patients who cannot take oral medications after surgery and cannot use NSAIDs because of increased risk of GI bleeding or renal

insufficiency. Most research indicates that there is no clear difference between IV and oral acetaminophen in reducing postoperative pain.[28,62,71,72]

Compared with acetaminophen, NSAIDs are more efficacious for reducing postoperative pain owing to their anti-inflammatory effects. Most of the oral nonselective NSAIDs are comparable in efficacy, so selection may be influenced by other factors, such as onset and duration, availability for use OTC, and adverse effects. Growing concerns related to the cardiovascular toxicity of OTC NSAIDs resulted in a PRECISION study conducted by the U.S. Food and Drug Administration (FDA) on the safety of celecoxib, ibuprofen, and naproxen.[73] A post hoc analysis of the PRECISION study randomized patients to receive celecoxib 100 to 200 mg by mouth twice daily, ibuprofen 600 to 800 mg by mouth three times daily, or naproxen 375 to 500 mg by mouth twice daily along with a proton-pump inhibitor. Patients using naproxen or ibuprofen experienced significantly higher risk of major toxicity than those using celecoxib, resulting in updated boxed warnings for cardiovascular and GI bleeding on NSAID product labels.[74] All NSAIDs are contraindicated in patients with a history of hypersensitivity, asthma, urticaria, or allergic-type reaction to aspirin or other NSAID; and are use in the setting of coronary artery bypass graft surgery.

For postoperative pain management, NSAIDs should not be used in patients with an estimated glomerular filtration rate of <60 mL/minute.[75] There remains uncertainty regarding the potential harm of NSAIDs with bone healing in patients who undergo surgery for orthopedic fractures and spinal fusion, so this decision needs to be made after discussions with the surgeon.[28,76] Refer to Chapter 43 Osteoarthritis, for more detailed information on NSAIDs.

IV ketorolac is a nonselective NSAID that is very effective in reducing postoperative pain. The recommended IV ketorolac dose for adult patients with normal renal function is 30 mg every 6 hours prn. The maximum duration for ketorolac administration is limited to 5 days to prevent adverse events related to GI bleeding with prolonged use. Ketorolac is contraindicated in advanced renal disease or patients at risk for renal failure owing to volume

depletion.[28,76] The Beers criteria recommends against using ketorolac in older adults.[77]

Gabapentin and pregabalin, also referred to as *gabapentinoids*, are neuromodulators that are helpful in reducing postoperative neuropathic pain. For patients who were not taking gabapentin or pregabalin for chronic pain before surgery, the lowest dose should be started for postoperative pain.[78] In December 2019, the FDA updated product labels warning that serious, life-threatening, and fatal respiratory depression may occur in patients using gabapentinoids. The risk may be increased with the concomitant use of opioids and other CNS depressants, conditions such as chronic obstructive pulmonary disease, and in older adult patients.[79] Caution should be used with gabapentin and pregabalin in patients with renal insufficiency as both require dose reduction based on creatinine clearance. Patients who were taking gabapentin or pregabalin for preexisting neuropathic pain before surgery should have their dose and frequency resumed as soon as possible after surgery to prevent uncontrolled chronic pain.[11]

Ketamine has been used for decades in the operating room and emergency department to induce and maintain general anesthesia during procedures. Analgesic properties of ketamine are derived from the NMDA receptor antagonist activity that prevents central sensitization of pain. Low-dose ketamine (ie, subanesthetic) is becoming increasingly popular postoperatively to improve pain control in patients with a history of chronic pain that is poorly responsive to traditional analgesic medications and to reduce subsequent risk adverse effects with acute opioid therapy. The use of low-dose ketamine is an appealing nonopioid pain control option for morbidly obese patients because it is almost devoid of respiratory depression and sedation side effects when administered in subanesthetic doses.[62] The common subanesthetic dose of ketamine for acute postoperative pain is 0.3 to 0.5 mg/kg IV bolus with or without an infusion (usually started at 0.1–0.2 mg/kg/hour) depending on the duration of analgesic response required for a patient.[80] For morbidly obese patients, ideal body weight should be used when calculating the ketamine dose.[62] Commonly reported side

effects of ketamine are nausea, vomiting, vivid dreams or hallucinations, and dissociative effects. Clinicians should consider limiting the use of ketamine in patients with poorly controlled psychiatric conditions involving psychosis, such as schizophrenia.

IV lidocaine, an amide local anesthetic and Class 1b antiarrhythmic, interacts with several receptors to prevent hypersensitization and hyperalgesia. IV lidocaine has been evaluated as part of multimodal analgesia in patients who underwent open or laparoscopic abdominal procedures. Data to support that perioperative or intraoperative IV lidocaine infusions are associated with shorter duration of ileus and reduction in postoperative opioid consumption compared to placebo are inconclusive.[81] In trials, lidocaine was typically administered as an IV bolus (100–150 mg or 1.5–2 mg/kg), followed by an infusion of 2 to 3 mg/kg/hour at the end of surgery.[81,82] IV lidocaine is generally not considered a first-line therapy for postoperative pain management with spine surgery.[83]

D.K. should have acetaminophen started at 975 mg orally scheduled every 8 hours for 2 to 3 days, then changed to 650 mg every 6 hours prn. The acetaminophen dose should be given separately from the oral opioid. Combination tablets containing opioid/acetaminophen increase the risk of acetaminophen toxicity with scheduled acetaminophen. Gabapentin is a good option for postoperative neuropathic pain. The dose and frequency of gabapentin should start low at 100 mg, then increased based on D.K.'s pain control in the absence of side effects. A low-dose ketamine infusion for 24 to 48 hours after surgery may be beneficial in reducing D.K.'s IV opioid use in the PACU and on the postsurgical unit, which could lower the risk for respiratory depression. Before D.K. is discharged, plans should be made for prescribing the oral multimodal medications for a short duration of time because moderate-to-severe postoperative pain is generally less intense after 1 to 2 weeks.

LOW BACK PAIN

Low back pain is the leading cause of disability worldwide, with a global point prevalence of 7.8%.[9] In the 2012 National Health Survey, low back pain was reported in 27.5% of U.S. adults in the past 3 months.[84] It has been reported that low back pain affects 70% to 85% of adults at some point in their lives, and 12 months after the onset of low back pain, 45% to 75% of people still have pain.[85,86] There is a bimodal distribution with peaks between the age of 25 and 29 years (2.58/1000 person-years) and between the age of 95 and 99 years (1.47/1000) without differentiation by underlying etiology.[85] There is an association between psychological factors and the occurrence of low back pain, including anxiety, depression, somatization symptoms, stress, and negative body image. Chronic low back pain patients have higher rates of emotional distress and depression (25%) compared to acute low back pain subjects (2.9%).[87] Socioeconomic risk factors include job dissatisfaction, physical work, psychologically stressful work, low educational achievement, and workers' compensation insurance.[88] Biomechanical and physical work factors such as heavy lifting, repetitive motion, and non-neutral body postures are established risks for back disorders.[86] Chronic low back pain also creates a large financial burden on the workplace. Low back pain accounts for almost $87.6 billion in total costs, the majority of which was lost wages and productivity, and patients who have been on disability for >1 year rarely return to work.[89]

Low back pain, by definition, affects the lumbosacral spine and associated muscles and nerves. It is multifactorial in nature, either nociceptive (musculoskeletal, myofascial), neuropathic (radicular pain), or has a central sensitization component.[90] In about 85% of cases, no pathophysiologic cause can be found.[86] The functional spinal unit is made up of two vertebral bodies, two zygapophyseal (facet) joints, the intervertebral disc, and the supporting ligamentous structures (**Fig. 55-5**). The facet joints of the spine form the junction where vertebral bodies meet. The joint space is maintained by cartilage and fluid in the joint. Like all weight-bearing joints of the body, the spine also develops joint space narrowing, bony hypertrophy, and deterioration of cartilage with normal use, resulting

in the musculoskeletal pain of OA. If the spine is used more, as with jobs involving heavy lifting and manual labor, the joints deteriorate faster. In addition to deterioration of the facet joint spaces, the intervertebral discs lose water content with time and may become desiccated, reducing the cushion between the vertebral bodies. These discs are fragile and can be torn or damaged and may herniate into the spinal canal foramen (Fig. 55-5). If vertebral bodies shift because of deterioration, spondylolisthesis may occur. This shift, or a herniated disc, may impinge on the spinal nerve root, or cause nerve root irritation, which can produce radicular neuropathic pain. This is sometimes referred to as *sciatica*. Shifting of the vertebral bodies may also reduce the size of the foramen where the nerves exit the spinal cord (spinal stenosis). If the vertebral bodies shift too far into the central spinal canal, pressure can be exerted on the spinal cord, which may lead to spinal cord injury and subsequent loss of sensory and motor nerve function (paralysis). If the motor nerves are affected (as with lower extremity muscle weakness, bowel or bladder incontinence), a “red flag” is present and surgery may be necessary to preserve function. **Table 55-9** lists other serious conditions that call for immediate medical or surgical attention.[91] Sometimes, low back pain is more intense than would be expected, or is much more widespread than imaging would predict. These are hallmarks of central sensitization.[90]

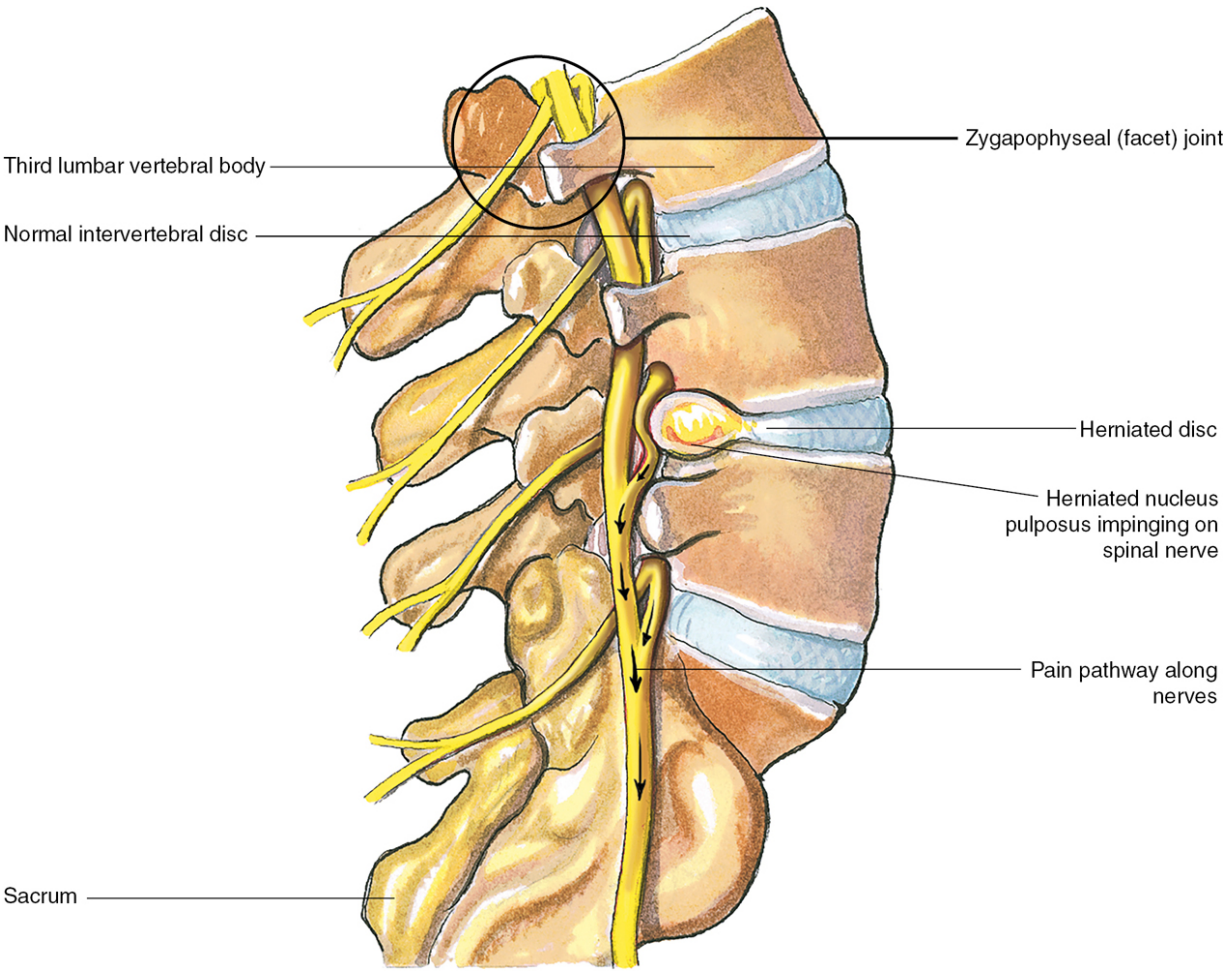


Figure 55-5 Spine anatomy and disc herniation.

Table 55-9
Red Flags for Potentially Serious Conditions That Cause Back Pain

Possible Fracture	Possible Tumor or Infection	Possible Cauda Equina Syndrome
Major trauma, such as vehicle accident or fall from height	Age <20 or >50 years	Saddle anesthesia
Minor trauma or strenuous lifting in older or potentially osteoporotic patients	History of cancer	Recent onset of bladder dysfunction (eg, urinary retention, increased frequency, overflow incontinence)

Possible Fracture	Possible Tumor or Infection	Possible Cauda Equina Syndrome
	Constitutional symptoms (recent fever, chills, unexplained weight loss)	Severe or progressive neurologic deficit in the lower extremities
	Risk factors for spinal infections: Recent bacterial infection IV drug abuse Immunosuppression	Unexpected laxity of the anal sphincter
	Pain that worsens when supine	Perianal/perineal sensory loss
	Severe nighttime pain	Major motor weakness: Quadriceps (knee extension weakness) Ankle plantar flexors, evertors, and dorsiflexors (foot drop)

IV, intravenous.

Source: VA/DoD. VA/DoD Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain. 2017.

Myofascial pain is very common in patients with chronic low back pain. Myofascial pain is localized to specific regions or muscle groups. It affects all age groups and is associated with numerous other pain conditions. It is classically associated with muscle knots called “trigger points.” A trigger point is described as a hyperirritable spot in skeletal muscle that is associated with a palpable “taut band” of muscle. Trigger points are hypothesized to evolve from excessive acetylcholine release from the motor endplate, leading to sustained muscle fiber contracture. Development of trigger points is usually associated with mechanical overuse or overload of a muscle group (as with repetitive work). It is also associated with postural problems, prolonged static positions, emotional stress (causing muscles to tense), and nutritional deficiencies (such as vitamins B_1, B_6, B_{12}, and D; iron; magnesium; and zinc) or metabolic problems, such as

thyroid disease. It is thought that low-intensity exertions related to static posture cause small muscle fibers to be continuously activated, leading to the development of trigger points.[92] Nociceptors are abundant in muscle nerves, and there are a variety of nociceptors that can be stimulated by substances such as prostaglandins, bradykinins, protons, ATP, 5-HT, and glutamate, which are released from damaged tissue. The neuropeptides, substance P and CGRP, are also found in the nociceptor terminals, which stimulate the inflammatory cascade, leading to peripheral sensitization and the clinical manifestation of muscle pain. Continuous activation of muscle nociceptors leads to the release of substance P and glutamate from the presynaptic terminal at the dorsal root ganglion. These substances activate postsynaptic AMPA and NMDA receptors, respectively, and subsequently may lead to neuroplasticity (see Fig. 55-3).

Acetaminophen has traditionally been considered the safest choice for the management of musculoskeletal pain. Its mechanism of action is not well defined, but it has analgesic activity in the CNS. It has no peripheral clinical effect on prostaglandins, so it lacks typical anti-inflammatory activity. A meta-analysis of acetaminophen versus placebo for spinal pain and OA, however, found acetaminophen to be ineffective.[92] As a result, more recent guidelines suggest that NSAIDs should be the first-line medications for the treatment of acute or chronic low back pain.[93] NSAIDs reduce pain and inflammation by inhibiting cyclooxygenases (COX-1 and COX-2) at the site of injury and along the ascending pain pathway. The NSAIDs are equally effective across the drug class, although some patients may respond to one agent better than another. They are more effective as monotherapy for acute low back pain than in combination with a muscle relaxant or an opioid. A meta-analysis showed that NSAIDs are better than placebo for back pain without neuropathic symptoms, but not for back pain with neuropathic symptoms. COX-2 selective inhibitors are as effective as traditional NSAIDs for analgesia but are better tolerated.[94] Celecoxib is the only COX-2 selective inhibitor available in the United States.

Acetaminophen is often used in combination with NSAIDs for additive analgesia.

There are several guidelines published for the management of low back pain. Oliveira et al reviewed evidence-based management guidelines from 14 different countries and 1 multinational committee that were published between 2008 and 2017.[93] **Table 55-10** presents a summary of common recommendations. All guidelines were in agreement with the use of NSAIDs as the first-line therapy for both acute and chronic low back pain.

Table 55-10
Summary of Common Recommendations for Treatment of Low Back Pain

Acute or Subacute Pain
Reassure patients that diagnosis is not serious
Advise to stay active
Prescribe medication if necessary
First line: NSAIDs
Second line: muscle relaxants
Discourage bed rest
Do not recommend supervised exercise program
Chronic Pain
Discourage use of alternative therapies (ultrasound, electrotherapy)
Short-term use of medication/manipulation
First line: NSAIDs
Second line: Duloxetine or tramadol
Supervised exercise therapy
Cognitive-behavioral therapy
Multidisciplinary treatment

NSAIDs, nonsteroidal anti-inflammatory drugs.

From Oliveira CB, Maher CG, Pinto RZ, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J*. 2018;27(11):2791–2803. https://creativecommons.org/licenses/by/4.0/

Most guidelines recommend muscle relaxants only for acute low back pain either alone or in combination with NSAIDs. Despite the fact that muscle relaxants are used commonly, there is no evidence that they are effective for chronic low back pain. Agents such as cyclobenzaprine and tizanidine, as well as benzodiazepines such as diazepam, show moderate efficacy in the short term (<2 weeks) but are associated with a higher incidence of adverse effects than placebo.[95] For chronic low back pain, second-line treatment recommendations include either tramadol for short periods or duloxetine. Tramadol has also shown modest relief with short-term use (<4 weeks).[96,97] There are several studies showing some efficacy for most LA and short-acting opioids, but they do not show any long-term functional improvement or return to work.[98–100]

A few guidelines, including those from the American College of Physicians, recommend the use of duloxetine over other antidepressants or anticonvulsants for neuropathic pain symptoms.[96] Antidepressants, specifically the TCAs, have shown modest analgesia compared with placebo, but they have not been shown to be effective for acute low back pain, nor have they shown demonstrable improvement in function.[101] Duloxetine, an SNRI, has shown efficacy and safety for the treatment of low back pain.[102] There have been a very small number of trials using the anticonvulsants topiramate and gabapentin for back pain. Anticonvulsants traditionally have been helpful for treating neuropathic pain (eg, peripheral neuropathies) but produce only small improvements for back pain with radiculopathy.[103–105]

Myofascial pain treatment is aimed at correcting precipitating behaviors, including ergonomic factors. Physical rehabilitation is essential for teaching patients appropriate stretching and strengthening exercises, as well as postural support and stabilization. Some clinicians inject the trigger point(s). There are several techniques that are all equally effective, including dry needling, saline injection, local anesthetic injection, or botulinum toxin. Several other pharmacologic therapies may be used, but none have more than anecdotal support. General approaches to pain management, including NSAIDs, muscle relaxants, antidepressants,

anticonvulsants, and opioids, may be helpful for individual patients. Vitamin D deficiency has been linked to chronic musculoskeletal pain, although this is somewhat controversial.[106,107]

CASE 55-3

Question 1: J.P. is a 48-year-old male who presents with low back and leg pain. He has had chronic low back pain for several years, which has progressively worsened during the past several months. He reports an aching pain that is localized to his lumbosacral spine with some radiation into his buttocks and hips. He also describes burning pain into his right leg all the way down to his toes. He rates his pain as 7 out of 10 on the numeric pain scale. On good days, his pain is 5 of 10. He recently did some yard work and had an acute exacerbation of his pain. He reports that this felt like 10 out of 10 on the numeric pain scale, and he was in bed for the following 2 days because of pain. He is usually able to do some chores around the house, but activity makes his pain worse. He sleeps poorly (only about 4–5 hours/night), and he does not go out or socialize very often because he is afraid that this will exacerbate his pain. He used to golf and play softball but is not able to participate in these hobbies any more as a result of pain. He smokes two packs of cigarettes daily and drinks about a six-pack of beer each week. He was previously a plumber but had to quit his job earlier this year because of health problems. He denies any lower extremity weakness and loss of bowel or bladder control. He has not found anything that really helps his pain, except rest and acetaminophen/codeine that his sister gave him. His past medical history includes hypertension, hyperlipidemia, depression, and morbid obesity. His current medications are lisinopril for hypertension, simvastatin for hyperlipidemia, carisoprodol, cyclobenzaprine prn, low-dose aspirin, and acetaminophen/ codeine. He also takes three tablets of OTC strength (200 mg/tablet) ibuprofen and three tablets of extra strength (500 mg/tablet) acetaminophen about four times daily with minimal relief of his pain. Upon physical examination, J.P. has pain with palpation along his lumbar paraspinal muscles with several trigger points noted and marked tenderness at the level of L4–L5. His reflexes are intact, and he has full strength in his lower extremities. The remainder of his physical examination is unremarkable, except that general deconditioning is noted. There are no laboratory tests or imaging studies available. He reports that his blood pressure is usually around 150/80 mm Hg with a pulse around 75 beats/minute.

What are the clinically relevant findings (or absence of findings) for J.P.'s pain assessment, and how would you characterize his pain?

The presentation and assessment of back pain can be very complex, given its multifactorial nature. Acute low back problems are defined by the Agency for Health Care Policy and Research as "activity intolerance attributable to lower back or back-related leg symptoms of <3 months' duration."[108] J.P.'s acute exacerbation would fit this definition. When J.P. has acute exacerbations of his low back pain, the numeric pain scale is an accurate assessment tool (see Table 55-2 and Fig. 55-4). His rating of 10 out of 10 indicates severe acute pain. Clinicians should also consider a patient's vital signs, which may be elevated with acute pain. If a patient is unable to communicate (eg, on a respirator), changes in vital signs may be the only indicator of discomfort.

Assessment of chronic low back pain in this patient must rely heavily on the history he provides, because there is minimal objective evidence to base the assessment on, other than his findings on physical examination or imaging studies. He indicated that his chronic pain is about 7 out of 10 on the numeric pain scale. Even though the numeric pain scale has been validated for chronic pain, it is less useful in this setting because it only gives a snapshot of the whole pain picture. A multidimensional tool, such as the Brief Pain Inventory or the McGill Pain Questionnaire, is more useful to assess chronic pain (see Table 55-2).[17,18] Physical activities, sleep, diet, and social interactions may be affected by chronic pain. J.P. notes that his pain is worse with physical activity. He reports sleeping poorly and has limited physical activity and minimal social interaction. All of these factors contribute to a patient's pain experience and must be considered (see Fig. 55-1). Assessment of chronic pain is not only more complex, but is more extensive, because the perception and response to chronic pain is widely variable. Each patient experience with pain is individualized. A psychological assessment is essential to identify comorbidities such as depression or anxiety and any history of abuse (eg, physical, verbal, sexual) or previous trauma, as well as to assess a patient's coping ability. It may be helpful to ask J.P. about his spirituality and cultural values, because these may offer unique opportunities (or barriers) to any proposed treatment plan.

If opioids are being considered, many clinicians endorse the use of a screening tool such as the Screener and Opioid Assessment of Patients with Pain-Revised (SOAPP-R) or Opioid Risk Tool (ORT) to assess for the risk of misuse.[109] J.P. drinks alcohol, smokes tobacco, and has used his sister's acetaminophen/codeine. These factors may warrant the use of a screening tool to assess his risk for opioid misuse.

J.P.'s chronic pain has been present for several years and has gradually worsened. Based on his history and current physical examination, he appears to have mechanical musculoskeletal pain. He is a former plumber, which involves bending and lifting, which puts him at risk for facet joint arthritis. He describes the aching, localized pain that is typical of arthritis, either in his spine–hip junction (sacroiliac joint) or his zygapophyseal (facet) joints, which are the most common locations for lumbosacral pain. He demonstrated localized tenderness at the L4–L5 level. This is most consistent with facet joint disease. He also has tenderness along muscles in his low back, reaching into his buttocks, which is very common, because the body attempts to accommodate structural spine abnormalities. Muscular pain may radiate into the mid-back or into the buttocks, but does not travel below the knees. J.P. does not have any motor weakness, past experiences, or comorbidities that would indicate a red flag (see Table 55-9). J.P.'s physical examination reveals radicular pain in the L5 dermatome (ie, an area of the skin supplied by nerves from a single spinal root). Unlike muscular pain, radicular pain travels from the spine past the knee into the distal extremities. J.P. describes burning and shooting pain that radiates from his spine down his right leg to his toes. These are hallmarks of neuropathic pain. J.P. appears to have both musculoskeletal/myofascial and neuropathic pain. This mixed picture is very common with back pain and adds complexity to both diagnosis and treatment plans.

Case 55-3, Question 2: What comorbidities will affect J.P.'s presentation and pain assessment?

J.P. has a concurrent diagnosis of depression, which is quite common in patients with chronic pain. The incidence of depression in chronic pain patients is two or three times higher than the general population.[110] Depression is often underrecognized in the face of pain as a presenting symptom. Many times, health care providers investigate for a functional cause of the pain, but overlook the psychosocial aspects of pain. Variables associated with depression in chronic pain are female sex, younger age, lower socioeconomic status, unmarried, Caucasian, and higher pain severity.[111] In fact, because pain severity worsens, depressive symptoms worsen, medical visits become more frequent, and health care costs increase. The relative deficiency of NE and 5-HT that occur with depression makes the pain-blocking function of the descending pain pathway less effective. As a result, J.P. may feel more pain physiologically and may also have a greater emotional response to his pain and other stressors. His depression may be contributing to his sleep disturbance and his diminished social interactions. Untreated depression may be detected with a multidimensional pain assessment tool. If identified and treated, his pain may improve concurrently with his depression. Other psychiatric comorbidities that commonly occur with chronic pain include anxiety, personality disorders, and substance use disorder.

J.P. also has a diagnosis of hypertension. Although this will not directly contribute to his pain, any acute exacerbations may cause an increase in his pulse and blood pressure. Increases in blood pressure are associated with an increased incidence of stroke. The presence of hypertension is also a factor when developing a treatment plan. He is currently taking ibuprofen for pain, and NSAIDs are known to cause fluid retention, compromise renal function, and diminish the benefits of antihypertensives (such as lisinopril). Corticosteroids, which may be used during an interventional pain procedure, may also increase blood pressure.

CASE 55-3, QUESTION 3: How can current low back pain treatment guidelines be applied to J.P.'s pharmacologic regimen?

J.P. has been using acetaminophen up to 6000 mg daily, which exceeds the recommended maximum daily dose, and acetaminophen is no longer recommended for the treatment of low back pain. He has also been using some acetaminophen/codeine that he obtained from his sister. J.P. is at risk for liver toxicity from high doses of acetaminophen. In addition, he has not found the acetaminophen to be helpful, so it should be stopped. J.P. is also taking ibuprofen, which is recommended as the first-line therapy. He is taking 2400 mg daily without benefit. His pain relief is unlikely to improve with a dose increase, but he may benefit from rotation to another NSAID with a different chemical structure. Naproxen, meloxicam, etodolac, and celecoxib are all commonly used to treat inflammatory pain, but only naproxen is inexpensive and available OTC. He does not demonstrate any muscle spasm, so a muscle relaxant is not indicated, nor is it recommended for chronic low back pain. He has radicular pain, so a trial of gabapentin may be helpful, but duloxetine would be considered the first line for neuropathic pain in either acute or chronic low back pain. He has been using the codeine-containing product and notes that this has been helpful; however, opioids, other than tramadol, are not recommended for short-term or long-term management of chronic low back pain. He should be encouraged to reduce or discontinue use of the opioid. Selective serotonin reuptake inhibitors (SSRIs) may be used to treat depression, but have very little independent analgesic effects. However, if his depression improves, a proportional improvement in his pain would be expected. Because SSRIs are better tolerated than TCAs, and TCAs have not demonstrated improvement in function in the long term, J.P. should have a trial of a generic SSRI, such as citalopram. An SNRI, particularly duloxetine, would be the preferred antidepressant therapeutic option owing to its ability to treat both his depression and pain with fewer adverse effects than TCAs.

Case 55-3, Question 4: J.P. has been taking two different muscle relaxants for his back pain. He reports that neither of these is very helpful, and he usually does not have muscle spasms but does have trigger points on physical

examination. What would you recommend with regard to continuing these drugs? Would a trial of a different muscle relaxant be appropriate?

Muscle relaxants are commonly used to treat chronic musculoskeletal pain. They are recommended for short-term use for acute low back pain (all are fairly equal). A systematic review with fair quality evidence concluded that for the treatment of musculoskeletal pain, tizanidine, orphenadrine, carisoprodol, and cyclobenzaprine were more effective than placebo. There were not sufficient data of good quality to determine whether metaxalone, methocarbamol, chlorzoxazone, baclofen, or dantrolene was better than placebo for this indication.[95,96] At this time, guidelines do not recommend chronic use of muscle relaxants for musculoskeletal pain. There is a small study that shows improvement in myofascial pain with tizanidine, but there are no data supporting continued use of carisoprodol or cyclobenzaprine.[112] These agents belong to a chemically diverse family, but all work in the CNS, either in the brain or in the spinal cord. They are categorized as either antispasmodics or antispasticity agents. The *antispasmodics* are either benzodiazepines (eg, diazepam) or nonbenzodiazepines (eg, cyclobenzaprine) and are used for muscular pain and spasms associated with peripheral musculoskeletal conditions. The *antispasticity* agents reduce spasticity associated with upper motor neuron disorders, such as multiple sclerosis (eg, tizanidine, baclofen) (**Table 55-11**). Because J.P. has not experienced any improvement in his pain with previous trials of muscle relaxants, switching to another is not likely to yield any improvement in his symptoms, although tizanidine has shown some promise.

Table 55-11
Oral Muscle Relaxants

Drug	Oral Dose	Adverse Effects	Monitoring/Comments
Antispasmodic			
Cyclobenzaprine	5 mg tid, titrate to 10 mg tid	Dry mouth, constipation, urinary retention, somnolence, confusion, blurred vision	Also available in extended-release formulation Tricyclic structure and associated adverse effects
Metaxalone	800 mg tid–qid	GI upset, nausea, vomiting, dizziness, headache, somnolence, hemolytic anemia, leucopenia, jaundice	Contraindicated in anemia, liver impairment, renal impairment Monitor liver function, CBC
Methocarbamol	1500 mg tid, or 1000 mg qid	Itching, rash, indigestion, nausea, vomiting, dizziness, headache, nystagmus, somnolence, vertigo, blurred vision, arrhythmias, hypotension, leucopenia, urine discoloration	Monitor heart rate, blood pressure
Orphenadrine citrate	100 mg bid	Syncope, nausea, vomiting, dry mouth, dizziness, blurred vision, palpitations	Monitor CBC, liver function
Chlorzoxazone	500–750 mg tid–qid	Lightheadedness, dizziness, somnolence, malaise, liver toxicity	Monitor liver function
Carisoprodol	250–350 mg tid and at bedtime	Dizziness, headache, somnolence, respiratory depression	Monitor for weakness, dizziness, confusion, misuse, or abuse
Antispastic			
Tizanidine	4 mg tid, titrate to maximum of 12 mg tid	Hypotension, somnolence, muscle weakness	Monitor blood pressure, liver function
Baclofen	10 mg tid, titrate to maximum of 20 mg qid	Somnolence, muscle weakness, ataxia	

bid, two times a day; CBC, complete blood cell count; GI, gastrointestinal; qid, four times a day; tid, three times a day.

CASE 55-3, QUESTION 5: J.P. returns after 3 months with a small improvement in his back pain. He is sleeping a bit better (6 hours/night). He is attending physical therapy sessions, although infrequently. He has been taking citalopram 20 mg by mouth daily for his depression and feels that this is somewhat helpful for his mood. He has been taking naproxen 500 mg by mouth three times a day and gabapentin 300 mg by mouth three times a day for his pain. Neither of these has provided adequate relief. Another provider gave him a prescription for oxycodone 5 mg/acetaminophen 325 mg one to two tablets every 6 hours prn. J.P. has been taking two tablets every 6 hours on a regular schedule. This helps his pain (30% improvement and he notes that the addition of the opioid has allowed him to start working part time again as a handy male); however, the relief only lasts 3 to 4 hours and then he is in pain for another 2 to 3 hours before he can take another dose. He also reports a lot of nausea with this regimen. He has heard about "pain patches" and wonders whether these might be an option for him. J.P. is getting about 30% improvement with oxycodone/acetaminophen, which is a good response for any analgesic, but the duration of relief is short, and he is having nausea after each dose. He has asked about using a pain patch. What therapy might you suggest to optimize J.P.'s analgesia? Is a pain patch a good choice?

Although opioids are not recommended for chronic low back pain, J.P. has noted an improvement in pain and function.[113] The consequences of long-term opioid therapy are significant and have resulted in recent guidelines discouraging their use. If all first- and second-line therapies have been or are currently being trialed without adequate relief, it would be reasonable to consider continuing his analgesic combination as long as evidence of improved function justifies continued use. There are several analgesic options available for patients who are unable to tolerate or ingest solid oral dosage forms (tablets and capsules). It is common for patients with feeding tubes and patients who have maxillofacial surgery to use alternative dosage forms, such as oral liquids, topicals, or transdermal products. J.P. has asked about a pain patch. It is likely that he is referring to either a fentanyl transdermal system or a buprenorphine patch. These agents offer extended delivery options, but are often not cost-effective; therefore, a pain patch may not be the best choice for J.P. Because he is able to take oral medications, it would be most reasonable to rotate to an oral opioid that offers a longer duration of action. When considering product rotation for J.P., it is important to consider drug formulation and availability, route of administration, drug interactions, adverse effects, and cost. The oxycodone/acetaminophen product that he is currently using is not providing an adequate duration of analgesia. He may need to use an ER/LA opioid to achieve sustained analgesia. There are many ER/LA opioid formulations available, including morphine (tablets, capsules), oxycodone (tablets), hydromorphone (capsules), methadone (tablets), oxymorphone (tablets), hydrocodone (capsules, tablets), buprenorphine (patch, buccal film), and fentanyl (patch). Several of these agents are formulated with abuse-deterrent technologies. Because he is getting good pain relief with oxycodone/acetaminophen, converting to an ER formulation of oxycodone seems the most logical choice. J.P. is currently taking eight 5-mg tablets of oxycodone daily (40 mg total per day). This may be directly converted to ER oxycodone 20 mg orally twice daily, with elimination of the short-acting product. If he continues to have nausea after his doses of oxycodone, he may need to rotate to

another opioid or use a nonoral route of administration, an antiemetic, or a nonopioid analgesic.

J.P. has been using several different analgesics for his pain, including an NSAID, an anticonvulsant, an antidepressant, and an opioid. These agents will offer pharmacologic activity at several points in the pain pathway (see Fig. 55-2) and offer additive analgesic effects.[114,115] However, multimodal therapy also carries the risk of additive adverse effects and possible drug interactions. For example, the anticonvulsant and the opioid may cause additive sedation. The balance between adverse effects and analgesia must be considered with any changes in drug therapy. He is also taking lisinopril. Using an NSAID concurrently with an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker may cause hyperkalemia or acute renal blood flow compromise. A nonacetylated salicylate such as salsalate or diflunisal may offer analgesia with a lower risk potential and fewer adverse effects and drug interactions. They have minimal effects on prostaglandin production.

Case 55-3, Question 6: J.P. returns 6 months later, after seeing a pain specialist and a psychologist. He is now taking gabapentin 1200 mg by mouth three times a day, meloxicam 7.5 mg by mouth once daily, amitriptyline 25 mg by mouth every night at bedtime, and oxycodone controlled-release (CR) 20 mg by mouth twice a day. How should J.P.'s therapy be monitored?

Clinicians must assess each part of J.P.'s care plan, both the positive aspects and the negative aspects. Is J.P. meeting his goals on his personal care plan? Is he getting more sleep? Is he more physically active? Is he managing his stressors better? Is his pain improved? There are several monitoring tools that may be used routinely to record long-term progress. The "5 As" of monitoring therapy are often used: analgesia, activities of daily living, adverse effects, affect, and potential aberrant drug-related behavior.[116]

In addition to monitoring for efficacy, assessing for adverse effects of his medication is critical. Gabapentin may cause sedation, dizziness, edema, and cognitive impairment of short-term memory,

concentration, and word finding. Meloxicam, an NSAID, may cause GI upset or ulceration, so he should be advised to watch for black, tarry, sticky stools or any sign of internal bleeding. He may experience easy bruising and bleeding related to the platelet inhibitory effects of NSAIDs and should have his serum creatinine and potassium checked regularly to monitor for NSAID-induced renal toxicity. His blood pressure should also be monitored regularly because this has been elevated in the past. Oxycodone may cause constipation, sedation, dry mouth, and urinary retention. If he is using the opioid regularly, he should be advised to also use a bowel regimen with a stool softener, osmotic laxative, or a motility agent. In addition, if he is using the opioid for an extended period of time, he may need to have his testosterone levels checked and bone density testing done periodically to monitor for hypogonadism and osteoporosis, which are associated with chronic opioid therapy. Amitriptyline may cause additive sedation, constipation, and urinary retention. He is unlikely to have problems with orthostatic hypotension, but this is common in older patients.

Case 55-3, Question 7: What nonpharmacologic therapies may be beneficial for J.P.'s pain?

Oliveira et al found that most guidelines recommend exercise therapy, cognitive-behavioral therapy (CBT), and short-term pharmacologic therapy.[93] Recent guidelines emphasize insufficient or mixed evidence to recommend specific therapies for radicular pain.[91,96] Epidural steroid injections, radiofrequency ablations, and, possibly, surgery may be considered in patients with persistent radicular low back pain with specific spinal pathology but are discouraged for nonspecific low back pain. Because J.P. has radicular pain into his legs and he has tried the first-line therapies, he may be a candidate for an epidural steroid injection. This will only offer temporary relief, at best, but may provide him with enough relief to participate more in physical rehabilitation. Studies show mixed results with both invasive procedures (ie, injections, laser therapies,

spinal cord stimulators) and surgery, so J.P. must be part of the decision-making process.[92,96]

In the past, patients were advised to use bed rest for acute back pain; it is now recommended that patients remain physically active. This has been shown to improve pain and function at 3 to 4 weeks compared with bed rest.[96,117] Bed rest is also not recommended for chronic back pain. J.P. still has limited physical activity and was noted to be deconditioned. Inactivity can increase muscular pain. Physical rehabilitation is a key component of management, but there is no difference in benefit among different forms of exercise, so J.P. may choose a program that best fits his interests and needs. Physical rehabilitation also may include stretching and strengthening, but these are less effective when used outside a comprehensive exercise program. Heat wraps are recommended for acute low back pain with moderate evidence, whereas other modalities such as cold packs to reduce inflammation in the acute phase of an injury have no evidence supporting their use. Spine manipulation, low back corsets, and acupuncture have shown some efficacy, but other physical modalities such as massage, ultrasound, traction, or shoe lifts have not been shown to be effective.[96] J.P. may report that he has more pain after he starts an exercise regimen, because his muscles will be reconditioned. J.P. should be encouraged and given assurances that physical activity that is at an appropriate level for his needs may cause him to hurt but will not harm him. He can also learn how to pace his activities so he does not overdo it with yard work as he has done in the past.

CBT and mindfulness-based stress reduction (MBSR) have been shown to improve back pain and functional limitations.[118] Mental health care is an essential component of multidisciplinary pain management. CBT works on a patient's perception of pain and expectations, focusing on mood, catastrophizing, negative thinking, and poor coping skills. MBSR focuses on increasing awareness and acceptance of moment-to-moment experiences, including physical discomfort and difficult emotions. After J.P.'s depression is addressed, he can work with a therapist on coping skills and how to use self-regulation and manage stressors.

NEUROPATHIC PAIN

Pain may be centrally or peripherally mediated. Peripheral sensory neuropathy usually involves injury or insult to peripheral nerves, such as postherpetic neuralgia (PHN), which affects spinal nerve dermatomes. The pain tends to be fairly localized, either regionally or along an associated dermatome. Central pain syndromes originate from injury to the CNS or alteration in central pain processing, as occurs with neuroplasticity. Central pain presents with a larger affected area, up to and including unilateral, head-to-toe pain that may be seen after a stroke. Poststroke pain is a central pain syndrome, caused by a lesion in the CNS. Sometimes, the cause of central pain syndromes cannot be identified, and even though a stroke presents with a specific lesion, it is still very difficult to treat. However, by far, the most difficult and far-reaching pain is central neuropathic pain generated in the CNS, which is called *central poststroke pain* (CPSP). CPSP has been reported in as many as 25% of stroke survivors.[119] The diagnostic criteria for CPSP are as follows: (a) pain in an area of the body corresponding to the lesion of the CNS, (b) history suggestive of stroke and onset of pain at or after stroke onset, (c) confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion, and (d) other causes of pain, such as nociceptive or peripheral neuropathic pain, that are excluded or considered highly unlikely.[119] The clinical presentation of CPSP is similar to other neuropathic pain. The onset of pain ranges from immediate to several months after stroke. It may affect a small region of the body or a large area (from head to toe). Central pain after a contralateral stroke is quite common, particularly after thalamic strokes (eg, patients with a stroke in the left side of the brain will have symptoms on the right side of the body). Because the thalamus is the brain's "relay station," any abnormal signaling may be amplified.[120] Temperature-sensory dysregulation via the spinothalamic tract is common, as well as dysesthesias and allodynia. It is described as "burning," "aching," "squeezing,"

"pricking," or "cold." These symptoms are frequently aggravated by a cold environment, psychological stress, heat, fatigue, or body movement.

There are no guidelines for the management of CPSP, and few robust studies exist but lack data related to comparative efficacy. Therapy is usually selected on a trial-and-error basis. The strongest evidence currently supports the use of lamotrigine (titrated to 400 mg/day).[121] Some data support a trial of amitriptyline (with titration from 10 up to 100 mg/day), or nortriptyline may be used as an alternative TCA in patients who do not tolerate amitriptyline.[122] SNRIs have been shown to be beneficial for other types of neuropathic pain, but not for CPSP. If pain relief is insufficient, an anticonvulsant may be used. Other anticonvulsants that have shown efficacy for both central and peripheral neuropathic pain are listed in **Table 55-12**.[123] Opioids have been studied in patients with CPSP but were not effective, and there was a high withdrawal rate.[124] Nonpharmacologic therapies for CPSP include deep brain stimulation, motor cortex stimulation, and transcranial magnetic stimulation. Physical rehabilitation (physical and occupational) is essential to help improve function, and CBT is used to help patients cope with their new circumstances and cognitive or physical limitations.

Table 55-12
Anticonvulsant and Neuromodulator Options for Treatment of Neuropathic Pain

Drug	Oral Dose[a]	Adverse Effects	Monitoring/Comments
Carbamazepine[b]	200 mg tid, titrate to maximum of 400 mg tid	Diplopia, rash, hepatitis, neutropenia, aplastic anemia, dizziness, cognitive effects, hyponatremia	Check LFTs, CBC, sodium at baseline and every 3 months during therapy, periodic serum levels
Oxcarbazepine	75 mg bid, titrate to maximum of 1200 mg bid	Rash, cognitive effects, hyponatremia, sedation, blurred vision, nausea	Check sodium every 2 weeks for 3 months, then with dose increases
Lamotrigine	25 mg daily, titrate to maximum 200 mg bid	Desquamating rash, cognitive effects	Requires very slow titration to avoid rash
Topiramate[b]	25 mg bid, titrate to maximum of 200 mg bid	Nausea, anorexia, paresthesias, metabolic acidosis, cognitive effects, nephrolithiasis	Check serum bicarbonate at baseline and every 3 months or with each dose increase
Gabapentin[b]	300 mg daily, titrate to maximum of 1200 mg tid	Somnolence, dizziness, edema, cognitive effects	Reduce dose for renal impairment or older adults
Pregabalin[b]	75 mg bid, titrate to maximum of 300 mg bid	Same as gabapentin	Same as gabapentin

bid, two times a day; CBC, complete blood cell count; ECG, electrocardiogram; LFTs, liver function tests; tid, three times a day.

[a]All oral agents are titrated up to reduce adverse effects and titrated down when discontinuing therapy.

[b]The Food and Drug Administration approved for treating pain conditions.

Herpes zoster occurs in 6.1 per 1000 Americans each year, and ~20% of these patients experience PHN.[125] Evidence-based guidelines for treating neuropathic pain have been published by several international organizations in the past several years.[20] Most studies have been conducted in PHN and DPN, because these are the most common neuropathic pain conditions. Some types of neuropathic pain (eg, spinal cord injury and human immunodeficiency virus neuropathy) have been quite resistant to pharmacologic therapy. Studies to date have shown only partial relief of neuropathic pain, regardless of pharmacologic treatment. Doses, adverse effects, and monitoring for these agents can be found in Tables 55-11 and **55-13**.

First-line treatments for neuropathic pain include antidepressants such as SNRIs and TCAs. These antidepressants demonstrate effective pain relief, even in patients without concurrent depression. TCAs are inexpensive and easily administered once daily; however, they have significant anticholinergic adverse effects, such as dry mouth and constipation that many patients do not tolerate. The secondary amine TCAs, like nortriptyline, have fewer anticholinergic adverse effects than the parent compound amitriptyline and are similarly effective. TCAs are known to cause orthostatic hypotension and urinary retention in older adult patients and may cause cardiac arrhythmias with higher doses. Venlafaxine functions as an SSRI at low doses and needs to be titrated by 37.5- or 75-mg increments each week to reach a target dose of at least 200 mg daily. At this dose, venlafaxine offers SNRI activity. However, at higher doses (>225 mg/day), increases in blood pressure and heart rate caused by increased NE activity may cause patients to stop therapy. Duloxetine has shown efficacy in treating neuropathic pain with doses of 60 to 120 mg/day.[126] Cardiac rhythm, blood pressure, and

pulse rate do not seem to be affected by duloxetine. The most common adverse effect with duloxetine is nausea on initiation and sweating. The dose of duloxetine is titrated up over 2 weeks to minimize the nausea. Duloxetine is contraindicated in patients with liver disease or those who drink alcohol, because there have been reports of liver failure with this medication.[127]

Anticonvulsants that bind to voltage-gated calcium channels are also considered the first-line therapies for C fiber–related neuropathic pain (such as DPN and PHN), allodynia, and nonpainful dysesthesias (ie, abnormal sensations). They have also been very helpful in reducing central sensitization by preventing the release of glutamate and blocking glutamate receptors. Gabapentin and pregabalin (gabapentinoids), both voltage-gated calcium-channel blockers, have shown efficacy and are FDA approved for treating neuropathic pain, including PHN and DPN.[128–130] These agents must be taken two or three times daily and may cause dizziness, somnolence, peripheral edema, and cognitive problems. The somnolence is usually managed with a slow titration, but these combined effects may be significant in older adult patients. Although neither agent has many significant pharmacokinetic drug interactions, the doses must be reduced for renal insufficiency, because they are mostly renally eliminated.

Anticonvulsants that block sodium channels, such as carbamazepine, oxcarbazepine, and lamotrigine, have been shown to be helpful for Aδ fiber–mediated pain such as trigeminal neuralgia that has sharp, shooting qualities. Carbamazepine is an older agent that requires routine monitoring of complete blood counts for blood dyscrasias, liver transaminases for possible hepatitis, and serum sodium for possible syndrome of inappropriate antidiuretic hormone–induced hyponatremia. It is also a strong CYP enzyme inducer, and there are numerous drug–drug interactions with carbamazepine. Oxcarbazepine has substantially fewer drug interactions and does not require significant laboratory monitoring because it does not form the same 10,11-epoxide metabolite as carbamazepine; however, monitoring of serum sodium for the first 3 months of therapy and periodically thereafter is required. Lamotrigine has few drug

interactions, except with valproic acid, and does not require any laboratory monitoring. It may, however, cause a desquamating rash (eg, Stevens–Johnson syndrome) if the dose is escalated too quickly. A newer agent, lacosamide, shows modest efficacy for treating DPN but is not FDA approved for treating pain.

Topical agents such as local anesthetics and capsaicin are effective for treating localized areas of neuropathic pain, such as PHN. The 5% lidocaine patch available by prescription is approved by the FDA for the treatment of PHN and is particularly helpful for treating allodynia. There is a 4% lidocaine patch available OTC for the treatment of musculoskeletal pain. The lidocaine patch is very well tolerated and easy to apply. The patch may be cut to the desired shape and minimal local anesthetic penetrates the skin, so there is no systemic toxicity with proper administration. Other topical lidocaine products are available (eg, ointments and creams), but most do not penetrate the skin deep enough to reach the affected nerve endings. Capsaicin depletes substance P in the periphery and downregulates the TRP vanilloid 1 receptors. Because it is derived from chili peppers, it causes a significant amount of burning until the substance P is depleted, and many patients do not tolerate the application of the cream several times daily to accomplish this. Capsaicin cream is available in several strengths, and there is an FDA-approved 8% patch available for medical office use that is applied for an hour under local anesthesia and can be reapplied once every 3 months.[131]

Opioid analgesics have shown moderate efficacy at best in treating neuropathic pain and are not usually considered the first-line therapy because of potential long-term effects, such as hyperalgesia, tolerance, immunosuppression, and hypogonadism with osteoporosis.[20,21] Tramadol and tapentadol, atypical opioids, have both opioid and SNRI activity and have been shown to be effective in several types of neuropathic pain. Their adverse effects are similar to those of both opioids and SNRIs, including constipation, sedation, and, possibly, seizures, which are a dose-limiting effect.[20,132]

When compared in a systematic review and meta-analysis, all of the first-line agents and most second-line agents were equally

effective, with no significant differences in safety.[20]

There are some data that show that a combination of agents, such as an opioid and a gabapentinoid, or a TCA and a gabapentinoid, may offer more analgesia than either agent alone.[114,115] This polypharmacy may offer additive analgesia because different agents act on different parts of the pain-signaling pathways. If more than one agent is used, lower doses of each may reduce adverse effects. However, polypharmacy adds complexity to regimens, which may reduce compliance and cause confusion, particularly in older adult patients.

Atypical Opioids in Neuropathic Pain

When targeting neuropathic pain, atypical opioids with their complex mechanisms may provide solutions to refractory neuropathic pain that are often unresponsive to usual care. Tramadol is a recommended treatment option for low back pain, which is considered a mixed pain state with components of both nociceptive and neuropathic pain, but it is commonly utilized to augment treatment for various neuropathic pain conditions.[96] Tramadol is considered a prodrug because the parent molecule has low affinity for μ-opioid receptors (6000 times less than morphine) but, when metabolized via CYP2D6, undergoes a significant upgrade in potency to 200 to 300 times less affinity compared to morphine. This is comparable to potency of codeine in patients who are not poor metabolizers and have a functioning CYP2D6 enzyme.[133] The NE reuptake inhibition of tramadol increases potency and utility for targeting neuropathic pain. However, tramadol also contributes significant serotonergic activity that increases risk of seizures, serotonin syndrome, and is highly susceptible to drug interactions as a substrate of CYP3A4 and CYP2D6.[134] Tapentadol was designed to overcome the deficiencies of tramadol and is FDA approved for DPN.[135] Tapentadol has minimal serotonergic activity while maintaining NE reuptake ability, avoids significant CYP metabolism, and has decreased drug interactions, which improve predictability of

patient response. In addition, tapentadol is a schedule II opioid in part because of its significantly increased potency compared to tramadol with μ-opioid receptor affinity 18 times less than morphine and, when combined with NE reuptake inhibition, results in two to three times less potency than morphine.[136]

Methadone is a unique opioid with a complex mechanism including significant potency at the μ-opioid receptor, NE reuptake inhibition, and NMDA antagonism.[137,138] Utilizing methadone is a multimechanistic approach in a single medication, but its use is often restricted to pain specialists because of significant risk for harm compared to other opioids. Factors that increase risk of treatment with methadone include significant drug interactions, QTc prolongation, and complex pharmacokinetics, resulting in drug accumulation and higher risk of overdose if not used appropriately.[139,140] The half-life of 15 to 60 hours and high lipophilicity means a tissue reservoir develops, and steady state is not reached until a patient has taken methadone for 5 to 7 days after initiation or dose adjustment.[141] These factors combined result in complicated transitions when starting or stopping methadone therapy. Methadone equianalgesic conversions are complex and variable and should be performed by a pain specialist.

Postherpetic Neuralgia

CASE 55-4

Question 1: K.J. is a 73-year-old male with a history of Hodgkin lymphoma. He is in remission after chemotherapy and radiation treatment. He is seen in consult for PHN attributable to a case of shingles during chemotherapy. The zoster episode was after his first chemotherapy cycle 2 years ago. The lesions covered an area around his right lower abdomen below the umbilicus in a 10- to 15-cm strip around the lower back and buttock. At rest, his pain is a 1 to 2 out of 10 on the numerical pain scale. At its worst, it is 7 to 8 out of 10. Pain is aggravated by light touch or any jarring motion (such as riding in a car) or rubbing of clothes on the location of the zoster. He has two areas that have greater pain, one located in the lower right aspect of his back and the other in the right lower abdominal quadrant. He describes the pain as a burning

sensation. He gets mild relief from topical aquaphilic ointment. If he stays busy, it sometimes takes his mind off the pain. He has not been sleeping well because of the pain. His past medical history includes Hodgkin lymphoma (in remission), low back pain, and benign prostatic hypertrophy (BPH). He currently takes acyclovir 400 mg by mouth once daily, alprazolam 0.25 mg by mouth every night at bedtime prn for sleep, docusate 100 mg by mouth twice daily prn for constipation, multivitamin one tablet by mouth once daily, tamsulosin 0.4 mg by mouth every night at bedtime, and zolpidem 5 mg by mouth every night at bedtime. K.J. is married, has never smoked, and denies alcohol and illicit drug use. His physical examination is unremarkable, with the exception of scarring noted from the right lower abdomen to the back. Laboratory results and vital signs obtained at this visit are the following:

Serum creatinine, 1.2 mg/dL
Electrolytes, within normal limits
Blood pressure, 137/80 mm Hg
Heart rate, 77 beats/minute
Weight, 176.37 pounds (80 kg)

Which of K.J.'s presenting symptoms are consistent with neuropathic pain and PHN?

K.J. is past the acute phase of his herpes zoster (shingles) pain, but now notices that the pain has a burning quality, localized over the region where his lesions have healed. This is quite typical for a PHN presentation. Another feature that indicates a neuropathic type of pain is his increase in pain with light touch or rubbing of his clothing (allodynia). It is a localized pain that does not radiate past the dermatomal distribution of his zoster infection. Opportunistic infections such as herpes zoster are common in patients who are immunocompromised such as K.J. when he was receiving chemotherapy.

Postherpetic Neuralgia Treatment

CASE 55-4, QUESTION 2: What factors need to be considered when choosing a medication for K.J.? Which medication is the most appropriate option for treating K.J.'s PHN pain?

The 2004 American Academy of Neurology guidelines for PHN treatment state that TCAs (eg, amitriptyline, nortriptyline, and desipramine), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN.[142] Since that time, there have been many more studies published, but there has been very little change in the approach to treating neuropathic pain. The International Association for the Study of Pain has also published guidelines on the general treatment of neuropathic pain.[20]

Ideally, patients should be treated with the most effective therapy that has the lowest risk of adverse effects. K.J. has peripheral neuropathic pain in a localized area, which is typical of PHN, so a reasonable first-line choice would be a lidocaine patch. His pain is in a 10- to 12-cm strip that covers a large surface area from his abdomen to his back. He would need to use at least two patches daily to cover this area, which is fewer than the maximal recommended dose of three patches daily, and would be an effective barrier against the pain of clothing rubbing against this location. Another localized option would be capsaicin (as either a patch or a cream). Capsaicin cream is available OTC and is substantially less expensive than lidocaine patches. Insurance plans may require a trial of capsaicin before approving the more expensive lidocaine patch. Unfortunately, many patients cannot tolerate the burning associated with capsaicin.

Another first-line option would be a TCA, which may help him sleep. However, he has BPH, and the anticholinergic effects of a TCA may cause increased urinary retention. These medications also cause orthostatic hypotension and may be a risk for K.J. if he has to get up during the night to use the bathroom (see Table 55-13). An SNRI such as duloxetine would have fewer anticholinergic adverse effects but is not FDA approved for treating PHN.

Table 55-13
Common Antidepressants for Neuropathic Pain or Functional Pain Syndromes

Drug	Oral Dose[a]	Maximum Daily Dose	Adverse Effects	Monitoring/Comments
Tricyclic Antidepressants (TCAs)				
Amitriptyline	25 mg qhs	150–300 mg	Dry mouth, constipation, urinary retention, orthostatic hypotension, somnolence	Caution in older adults
Nortriptyline	25 mg qhs	50–150 mg		
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)				
Duloxetine[b]	30 mg once daily × 1 week, then titrate to 60–120 mg	120 mg	Nausea, dry mouth, headache, diarrhea constipation, fatigue, sweating, anorexia	Contraindicated with liver disease or concurrent alcohol consumption. Monitor liver transaminases
Venlafaxine, extended release	37.5 mg once daily	225 mg	Headache, nausea, sweating, sedation, hypertension, seizures, tachycardia	Serotonergic effects <150 mg and noradrenergic effects >150 mg Monitor blood pressure and heart rate
Milnacipran[b]	12.5 mg on day 1; 12.5 mg bid on days 2 and 3, 25 mg bid on days 4–7, and 50 mg bid after day 7	100–200 mg	Nausea, headache, constipation, insomnia, hot flashes	Monitor blood pressure, heart rate

bid, two times a day; qhs, every night at bedtime.

[a]All oral agents are titrated up to reduce adverse effects and titrated down when discontinuing therapy.

[b]The Food and Drug Administration approved for treating pain conditions.

Source: Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. *Cochrane Database Syst Rev.* 2017;1:CD012188.

As new medications are considered to address PHN, the risk of polypharmacy and additive adverse effects is significant and must be considered. K.J. takes both alprazolam and zolpidem for sleep, which represents a duplication of therapy and the potential for more severe adverse events, particularly when combined with sedating medications such as gabapentinoids, TCAs, or opioids. A calcium-channel blocking anticonvulsant such as gabapentin is a possibility. The sedating effects of gabapentin may help him sleep if his last dose is given at bedtime and would not cause the urinary retention, constipation, and orthostatic hypotension associated with TCA use. Given his age, a slow dose escalation starting at 100 mg by mouth three times a day would be appropriate. Upon initiation of gabapentin, alprazolam should be tapered and discontinued. As gabapentin is titrated to a therapeutic dose, zolpidem use should be reassessed and discontinued if possible. A disproportionately higher dose of gabapentin may be utilized at night to improve sleep and pain coverage without risking daytime sedation or dizziness. The

most important aspect of monitoring for this agent would be for cognitive effects, such as short-term memory problems or difficulty with word finding.

If the abovementioned options do not provide adequate analgesia, addition of an opioid such as morphine or oxycodone may be considered owing to the potential for additive analgesia. Opioids have synergistic effects with gabapentin that result in improved analgesia and some increased risk, resulting in an FDA warning in 2019 that the combination can result in respiratory depression and should be monitored carefully.[143] Initially, a short-acting opioid should be used so that K.J. may be titrated to the optimal analgesic dose. Opioids should not be initiated if he remains on benzodiazepines because there are 4 to 10 times increased risk of overdose with combination therapy.[144,145] Tramadol is another alternative with some TCA-like activity and mild opioid effects. However, if an opioid is added, it may increase the adverse effects of the abovementioned agents, including constipation, sedation, urinary retention, and cognitive effects. Whenever an opioid is added to a medication regimen, a bowel regimen must be implemented as well. A commonly used regimen includes a stool softener such as docusate sodium 100 mg by mouth twice daily or an osmotic agent such as polyethylene glycol 17 g by mouth daily and a mild stimulant laxative such as senna 8.6 mg one to two tablets by mouth once daily.

Modifying the Neuropathic Pain Regimen

Case 55-4, Question 3: K.J. returns after 2 months stating that he could not tolerate the burning of the capsaicin cream and so discontinued use. He is currently taking gabapentin 1200 mg by mouth three times daily and tramadol 50 mg one tablet by mouth four times daily. He continues to have 5 out of 10 burning pain over his right abdomen and back. He states that he has felt drowsy and has “unclear thoughts” with the gabapentin and does not feel that it has been very effective, despite titrating this to the maximal dose of 3600 mg daily. His wife reports that he is withdrawing from friends and he does not feel as involved. He is sleeping better, however, and believes that the tramadol is somewhat helpful in “taking the edge off” his pain. Given this information, what would be an appropriate adjustment in his therapy?

Adverse cognitive effects, such as problems with memory, concentration, and word finding, are common with anticonvulsants, especially in older patients. No anticonvulsant is better than any other in this regard; however, some of the adverse effects are dose related, and patients may exhibit tolerance to some of the effects (like sedation) with time. K.J. is at the maximal recommended daily dose of gabapentin and does not feel that this has been very helpful. At this time, he may need to be tapered off the gabapentin. Sometimes, patients do not notice analgesic effects of their medications until they are discontinued. It is a good practice to titrate oral analgesics upward when starting therapy and downward when discontinuing, to avoid a marked increase in pain and withdrawal syndromes that have been reported with both antidepressants and some anticonvulsants. He could reduce his dose by 300 mg every 3 to 5 days until his pain increases or he is off the gabapentin.

A different topical agent would be the lidocaine patch. Because he and his wife are reporting some signs of depression, an antidepressant may be an option. An antidepressant was not chosen previously because of concerns about his BPH symptoms; however, an SNRI such as duloxetine may be an effective alternative to treat his depression as well as his pain, although there are no studies reporting its effectiveness for this indication. Another option may be to switch to another anticonvulsant. Pregabalin has very similar pharmacologic activity to gabapentin, so it may not offer any additional analgesia over gabapentin. Possibly, a sodium-channel blocking anticonvulsant such as oxcarbazepine could be used for a trial. However, there are minimal data supporting the sodium-channel blockers for typical C fiber–mediated pain associated with PHN.

Case 55-4, Question 4: K.J.'s doctor decides to prescribe duloxetine and a lidocaine patch and taper off the gabapentin as tolerated. When the doctor orders K.J.'s new regimen, a drug–drug interaction listed between duloxetine and tramadol is identified. What recommendations are appropriate with regard to the potential drug–drug interactions with analgesics and, in particular, with K.J.'s regimen? What changes to his regimen could be suggested?

Analgesic Drug–Drug Interactions

Antidepressants either increase the concentrations of NE or 5-HT or both. Opioids also have serotonergic effects, so it is possible to have a net excess of either of these neurotransmitters or both. The consequence of an excess of NE is CNS excitation and possible seizures. The consequence of an excess of 5-HT is a possibly life-threatening syndrome called *serotonin syndrome.* Symptoms of serotonin syndrome include muscle rigidity, hyperpyrexia, mental status changes, and possible organ failure. None of these serious adverse effects are very predictable, although they are more likely with higher doses of either agent. If opioids are used with antidepressants, the lowest effective doses should be used, and patients should be counseled to watch for mental status changes.

Pharmacodynamic interactions are more likely to occur with analgesic polypharmacy. Because several analgesics may be used together to decrease the excitatory effects of the pain signal, there is always a risk of additive sedation, dizziness, or even respiratory depression. Several pharmacokinetic drug–drug interactions may occur with analgesics as well. In K.J.'s case, his duloxetine and tramadol are both substrates of CYP2D6 and may compete with each other for this enzyme. This may alter the blood levels and clinical effects of these agents. K.J. likely needs an antidepressant for his depression symptoms, so alternatives will need to be considered.

FUNCTIONAL PAIN SYNDROMES

FPSs are a cluster of disorders for which the pathophysiologic mechanisms have not been clearly defined to explain the symptoms.[146] FPSs include medically unexplained symptoms for both GI and non-GI disorders, such as dyspepsia, irritable bowel syndrome, fibromyalgia, chronic fatigue, and interstitial cystitis. There can be overlap in the syndromes with the presentation of

chronic pain and associated psychiatric comorbidities, including depression, anxiety, and posttraumatic stress disorder.[147,148] Somatic symptoms associated with significant distress and disruption of daily life are common with FPS. Patients with FPS often have health concerns manifested by disproportionate and persistent thoughts of serious symptoms, a high level of anxiety about symptoms, and excessive time and energy devoted to health concerns.[149–151]

Fibromyalgia

Fibromyalgia is a chronic debilitating condition with the primary symptoms of chronic widespread pain and fatigue. It affects between 3 and 6 million people in the United States, with an incidence of 4.9% in females and 2.9% in males.[152] Out-of-pocket health care costs for patients with fibromyalgia are three times higher than those without fibromyalgia.[153] According to guidelines by the American College of Rheumatology, all of the following must be met for the diagnosis of fibromyalgia: (a) generalized pain in at least four or five regions of the body, (b) symptoms present for at least 3 months, (c) Widespread Pain Index (WPI) ≥ 7 and Symptom Severity Scale (SSS) score ≥5 or WPI of 4 to 6 and SSS score ≥9, and (d) the absence of exclusion of a diagnosis of fibromyalgia in the presence of other clinically important illnesses.[154] The WPI quantifies bodily pain on a 0 to 19 scale and consists of asking patients if they have tenderness or pain in any of 19 different body regions over the past week. The SSS uses a scale of 0 to 3 in three categories: fatigue, waking unrefreshed, and cognitive symptoms, to assess a patient's level of pain over the past week.[155]

Fibromyalgia was previously thought to be peripherally mediated pain related to an inflammatory or muscular disorder, but new research into the pathophysiology is uncovering mechanisms associated with central sensitization owing to neurotransmitter dysfunction. Studies have shown an imbalance in neurotransmitters in which excitatory neurotransmitters in the CNS of fibromyalgia patients are increased, including glutamate (a twofold increase) and

substance P (a threefold increase), whereas inhibitory neurotransmitters (NE and 5-HT) are decreased. Patients with fibromyalgia have an enhanced perception of pain at substantially lower threshold and at a lower frequency of stimulation than control patients.[156] Input may be from the periphery or may be triggered by a central stimulus, such as a stressor. Heightened sensitivity to lower stimulus seems to contribute to the persistent pain.[157] This can be widespread, and symptoms seem to be largely affected by an exaggerated response to personal stressors, noxious stimuli (hyperalgesia), and non-noxious sensory stimuli (allodynia).

Fibromyalgia, as an FPS, is associated with other comorbidities that need to be addressed for symptom management, even though treating these symptoms may not directly benefit the hallmark tenderness associated with the syndrome. There is a high incidence of comorbidity between fibromyalgia, chronic fatigue syndrome, depression, and irritable bowel syndrome, and some have postulated that the gut–brain axis could be the common denominator. Communication between the gut and the CNS may be through the vagus nerve, enteric nervous system, endocrine system, and/or the immune system.[158,159]

Mental health conditions, such as depression and anxiety, may be present in 25% to 65% of patients with fibromyalgia.[160] Early life experiences (eg, verbal, sexual, or physical abuse), adult stressors (eg, divorce, bereavement), lack of social support, and other social learning experiences can affect an individual's physiologic and psychological responses.[151] The changes in these responses can lead to maladaptive learned-illness behaviors and predispose to functional GI and psychiatric disorders.[161]

CASE 55-5

QUESTION 1: G.R. is a 38-year-old female who presents with chronic widespread muscle pain from her neck down past her buttocks. She also has headaches when her pain is severe. She has had this pain for several years and notes that her pain developed after a car accident in which she sustained a whiplash injury. She describes difficulty sleeping, poor concentration, and fatigue. Her pain rating is 8 out of 10 on most days. She works part time doing

some home transcription. She has not identified anything that helps her pain, and physical activity makes the pain worse, so she does not exercise. Her pain is also worse when she is stressed. She was previously told that she has fibromyalgia, and while others have told her that "it's all in her head." Her past medical history includes depression and irritable bowel syndrome. She has tried ibuprofen, cyclobenzaprine, carisoprodol, and acetaminophen in the past without relief. She is currently taking tramadol 50 mg by mouth four times daily, which provides about 20% pain relief. She is also taking sertraline for depression. G.R. is married and has three children. She smokes one pack of cigarettes daily but denies drinking alcohol or using illicit drugs. She reports that her mother and sister have fibromyalgia and depression. She reports diffuse tenderness to palpation along her paraspinal muscles bilaterally, as well as her bilateral trapezius and levator scapulae muscles and her hips bilaterally. Several tender points are elicited. Her only remarkable laboratory result is vitamin D, 24 ng/mL (normal >30 ng/mL).

What part of G.R.'s presentation supports the presence of a FPS?

G.R. likely has fibromyalgia, given her widespread pain that has been present for >3 months and was precipitated by a traumatic event (car accident). She reports sleeping poorly, fatigue, and the comorbidities of depression and irritable bowel syndrome. On physical examination, she exhibits widespread musculoskeletal tenderness, including, but not limited to, several of the identified fibromyalgia tender points, bilaterally, both above and below the waist. Her vitamin D level represents a mild deficiency.

CASE 55-5, QUESTION 2: What pharmacologic and nonpharmacologic therapies could be recommended for G.R.?

There have been several evidence-based guidelines published for the treatment of fibromyalgia. Management should take the form of a graduated approach with the aim of improving health-related quality of life and focus first on nonpharmacologic modalities.[155,162,163] Among the nonpharmacologic therapies, exercise is highly recommended, particularly given its effect on pain, physical function, and well-being. A meta-analysis evaluated different regimens of aerobic activity and found that land- and water-based aerobic exercise, at a slight to moderate intensity, two to three times a week

for at least 4 weeks resulted in improvement of depressed mood and increased health-related quality of life scores and physical fitness. This was maintained if the patient continued exercise at home.[164] Aquatic training is beneficial for improving wellness, symptoms, and fitness in adults with fibromyalgia.[165] Luciano et al found that CBT is more cost-effective than routine FDA-approved medications for adult fibromyalgia patients.[166]

Psychological therapies should be considered for patients with mood disorder or unhelpful coping strategies. CBT has been found effective at producing modest, long-term reductions in pain and disability and improving mood.[162] Bernardy et al conducted a systematic review of CBT for fibromyalgia and found that this therapy improves coping with pain and reduces depressed mood and health care–seeking behavior.[167]

Pharmacologic therapies should be considered for patients with severe pain. Because evidence indicates a CNS neurotransmitter imbalance, the most effective pharmacologic approaches have targeted these imbalances. Antidepressants have been shown to reduce pain and improve function by increasing the levels of 5-HT and NE in the CNS. Historically, TCAs (most commonly amitriptyline) have been shown to moderately improve pain, sleep, and, to a smaller extent, fatigue and health-related quality of life. Although cyclobenzaprine is indicated for muscle spasms, studies have indicated its weak TCA effects may help with sleep in patients with fibromyalgia.[162] Studies on mirtazapine at 15 to 45 mg daily found that pain was not substantially reduced with fibromyalgia.[168] Duloxetine and milnacipran are both SNRIs that are FDA approved for fibromyalgia. A comprehensive review of SNRIs in the treatment of fibromyalgia concluded that a minority of patients may experience pain relief with duloxetine or milnacipran but neither SNRI improved quality of life with fatigue reduction.[169] Hauser et al compared duloxetine, milnacipran, and pregabalin in fibromyalgia and found that duloxetine and pregabalin were better than milnacipran in improving pain and sleep.[170] Duloxetine was better for symptoms of depression, and pregabalin and milnacipran were better for fatigue. Headache and nausea were more common with duloxetine and

milnacipran, and diarrhea was more common with duloxetine. Tramadol has demonstrated only a slight improvement in pain. Evidence on the efficacy of SSRIs for improvement of pain is weak, so they are not recommended.[162]

Gabapentinoids have been shown to reduce the activity of excitatory neurotransmitters, particularly glutamate. Pregabalin is an anticonvulsant that was approved by the FDA in 2007 for treating fibromyalgia. It targets the increased levels of glutamate in the CNS by binding to the $a_2\delta$ subunit of voltage-gated calcium channels, preventing the release of glutamate from presynaptic terminals (see Fig. 55-3). This agent has been shown to improve average pain scores and patient perception of improvement but failed to show improvement in Fibromyalgia Impact Questionnaire scores.[171,172] An analysis of randomized controlled trials found that pregabalin was effective in treating fibromyalgia, and results were observed within 1 to 2 days of starting treatment.[173] Gabapentin, a similar compound, has not been formally approved for fibromyalgia but has support for its use. Some insurance companies require a trial with gabapentin before allowing use of pregabalin because of its lower cost. A recent systematic review concluded that there is insufficient evidence to support or refute observations that gabapentin reduces pain in fibromyalgia.[174]

NSAIDs, acetaminophen, and opioids are not recommended for treating fibromyalgia pain.[162,175] In fact, Goldenberg et al conducted a literature review and found no evidence from clinical trials that opioids are effective for the treatment of fibromyalgia. The studies reviewed found that patients with fibromyalgia receiving opioids had poorer outcomes than those receiving nonopioids.[176]

An appropriate first step for G.R. is to develop a multidisciplinary approach, including physical rehabilitation, CBT, and pharmacologic therapy adjustments. She is currently taking an antidepressant (sertraline), which may be helpful for her depression but is likely not very helpful for her fibromyalgia. It may be possible to switch her to an SNRI such as duloxetine or milnacipran in consultation with her mental health provider. She is currently taking tramadol with some

relief. She has not maximized her dose (maximum daily dose is 400 mg); however, she is also taking an SSRI, which may place her at a higher risk of serotonin syndrome. The risks and benefits of combining antidepressants with tramadol must be considered on a patient-by-patient basis. Because she is having trouble sleeping, she could be offered a trial of amitriptyline or pregabalin, both of which have sedating side effects (see Tables 55-12 and 55-13).[177] Pregabalin is a recommended agent and has a different mechanism of action than the medications that she has previously tried. If cost of therapy is a concern, then gabapentin could be tried instead. A vitamin D supplement should also be considered to correct her slightly low vitamin D levels. There is not strong evidence supporting vitamin D supplementation, but there is little harm in correcting her slight deficiency.

Psychological Comorbidity and Opioid Risk Management

CASE 55-6

Question 1: M.T. is a 33-year-old female with chronic abdominal pain. She first experienced recurrent episodes of abdominal pain at the age of 13 after menarche. At age 21, she was diagnosed with acute pancreatitis secondary to alcohol use. Her pain has persisted despite numerous trials of medications, including gabapentin, sertraline, tramadol, and hydrocodone/acetaminophen. She has undergone multiple diagnostic evaluations for the abdominal pain, but all have resulted in negative findings. During the past year, M.T. has had eight visits to the emergency department for severe pain where she usually receives a discharge prescription for five tablets of oxycodone/acetaminophen 5 mg/325 mg. In addition to the emergency department visits, she has been hospitalized three times in the past year for abdominal pain.

Today, M.T. is being seen in the clinic by her primary care physician for continued management of chronic abdominal pain, which she describes as "constantly aching." Over the past 2 years, M.T.'s primary care physician has been prescribing oxycodone in conjunction with an opioid agreement focused on minimizing the use of emergency department visits for pain management. M.T. believes her current management with oxycodone 5 mg by mouth every 4 hours prn for severe pain is insufficient and would like the 30-day supply limit increased from 180 to 240 tablets.

The primary care physician is concerned about M.T.'s functional status since starting opioid therapy. There has been no noticeable improvement in M.T.'s pain despite three increases in the 30-day oxycodone supply over the past 2 years. During the office visit, M.T. is emotionally labile at times and tearful when discussing her pain but is emphatic that she is not depressed. She states that she drinks one or two "highballs" (whisky and soda) about two times a week to help her relax when she is feeling "stressed out." M.T. denies smoking or illicit drug use. She is currently unemployed and seeking permanent disability because the pain interferes with her ability to work. Her physical examination is unremarkable, except for diffuse abdominal tenderness.

What is the clinical relevance of M.T.'s self-description of abdominal pain?

CLINICAL RELEVANCE OF ABDOMINAL PAIN

The prevalence of chronic abdominal pain ranges from 0.5% to 25% of the population.[111] M.T.'s self-report of pain is consistent with centrally mediated abdominal pain syndrome (CAPS).[175] CAPS is more common in females and peaks around the fourth decade of life. Patients with CAPS have high work absenteeism and health care utilization.[147,179] Key features in the diagnosis of CAPS include abdominal pain that is present for at least 6 months and is not related to GI function. Patients will often have a decrease in daily activity with time. The principal criterion differentiating CAPS from other GI disorders, such as pancreatitis or irritable bowel syndrome, is constant pain that lacks symptom relationship to food intake or defecation. Psychological disturbances are more likely when pain has persisted for a long period and manifests as symptom-related behaviors that dominate a patient's life (**Table 55-14**).[149,179]

Table 55-14

Symptom-Related Behaviors of Centrally Mediated Abdominal Pain Syndrome (CAPS)

Expressing pain of varying intensity through verbal and nonverbal methods
Urgent reporting of intense symptoms disproportionate to available clinical and laboratory data
Minimizing or denying a role for psychosocial contributors, anxiety, depression; attributing symptoms of anxiety or depression to presence of pain
Requesting diagnostic studies to validate the condition as "organic"

Focusing attention on complete relief of symptoms
Seeking health care frequently
Taking limited personal responsibility for self-management
Making requests for opioid analgesics when other treatment options have been implemented

Source: Derry S, Wiffen PJ, Häuser W, et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. *Cochrane Database Syst Rev.* 2017;3:CD012332.

From the physiologic perspective, M.T.'s abdominal pain most likely originated from a combination of peripheral and visceral components. When the pain symptoms occur frequently in conjunction with a stressor as in CAPS, the main mechanism for altered pain regulation relates to the failure to inhibit the amplification of normal regulatory afferent input from the gut to central mechanisms in the prefrontal, cingulated cortex, and limbic structures in the brain (eg, cognitive and emotions centers). This impairment in homeostatic inhibition of pain may be related to low levels of 5-HT, NE, endorphin, and other neuropeptides that mediate descending pain transmission in the CNS. Recognition of the brain–gut axis in CAPS is essential to understanding its clinical presentation, diagnosis, and therapeutic strategies.[14,146] A new condition in the spectrum of CAPS is narcotic bowel syndrome characterized by incompletely controlled abdominal pain that cannot be explained by another known or previous diagnosis in patients receiving steady or increasing doses of opioids. Abdominal pain caused by narcotic bowel syndrome is centrally mediated visceral hyperalgesia rather than GI dysmotility.[161] Narcotic bowel syndrome is often under diagnosed by clinicians and can be the underlying cause of chronic abdominal pain. Patients typically report poorly localized, moderate-to-severe constant abdominal pain despite starting opioid therapy, and the pain gets worse as the opioid dose is increased. The phenomenon of pain getting worse with escalating opioid doses is called *opioid-induced hyperalgesia*. Successful treatment must include reducing the opioid dose.[178] Clinicians need to understand that most patients with narcotic bowel syndrome might not see reduction of opioids as a logical option. M.T. believes that

opioids have been the most helpful pain treatment and fears being perceived as “drug seeking” or having a psychiatric problem. The primary care physician will need to communicate each time this conversation occurs with M.T. that despite using high-dose opioids, the benefit is incomplete and describe the value of other treatments (eg, antidepressants).

CENTRALLY MEDIATED ABDOMINAL PAIN TREATMENT

CASE 55-6, QUESTION 2: What are the current recommendations for pharmacologic treatment of CAPS? What approaches to the management of CAPS are appropriate for M.T.?

The cornerstone to pain management depends on an effective relationship between the clinician and the patient. In this case, the primary care physician needs to listen to M.T.’s concerns, ask questions like “How do you believe I can be helpful to you?” and have a conversation about realistic expectations for ordering tests, medical interventions, and medications. M.T. needs to be an active participant in the pain management plan and take responsibility for self-care.[178]

Pharmacotherapy for patients with CAPS is empirical and not based on results from well-designed clinical trials. Clinical trials have not been targeted to this diagnostic entity, so treatments are typically designed on the basis of data from other chronic pain disorders. Antidepressants, such as TCAs in low daily dosages, may be useful in treating CAPS for both pain and depression owing to their combined noradrenergic and serotonergic effects. In other chronic pain conditions, TCAs generally have been more successful than using SSRIs.[179] Medications with combined 5-HT and NE reuptake activity (eg, SNRIs such as venlafaxine and duloxetine) have recognized pain-reducing effects with visceral pain conditions and may be useful in CAPS. For patients who are refractory to usual doses of antidepressant medication, referral to psychiatry should be made for treatment with atypical antipsychotic agents such as

quetiapine. Quetiapine has been used in lower doses for treating patients with anxiety, sleep disturbance, and associated psychological comorbid symptoms.[180] To ensure treatment adherence, M.T. needs affirmation that the antidepressant is not prescribed simply to treat depression. It is important that the clinician educate the patient on the role of antidepressants in the treatment of pain. Patient education resources such as diagrams help to show the physiologic basis for treatment of pain and describe descending inhibitory pathways.[149,179]

Gabapentin and pregabalin clinical trials have established their efficacy for neuropathic pain and fibromyalgia, but benefit for visceral or central pain syndromes is not established. NSAIDs offer little benefit because their action is located in the peripheral nervous system. Long-term treatment with benzodiazepines is not recommended because of the abuse potential and tendency to interact with other medications.[149,179]

RISK OF ADDICTION

Case 55-6, Question 3: There is concern about M.T.'s use of alcohol and escalating use of opioid medication. What is the risk that M.T. will become addicted to opioids?

Opioid use behaviors are stratified based on the risk of aberrant drug use. Aberrant drug use behaviors may occur along a spectrum from those less suggestive of addiction, such as an occasional, sanctioned increase in the opioid dose by a medical provider, to those that may be more suggestive of addiction, such as concurrent illicit drug use. **Table 55-15** provides a list of risk factors for opioid misuse.[19,181,182] Important but less consistent risk factors include pain-related functional impairment, such as sleep disturbance, mental health issues, history of child sexual abuse or neglect, and legal problems. With respect to gender, females with chronic pain who report significant emotional issues were at increased risk for opioid misuse.[182,183]

Table 55-15

Risk Factors for Opioid Addiction

Concurrent abuse of alcohol or illicit drugs
Selling medication
Stealing medication
Injecting oral formulations
Multiple dose escalations or other nonadherence with therapy despite warnings
Obtaining prescription drugs from nonmedical sources
Prescription forgery
Repeated resistance to changes in therapy despite clear evidence of physical or psychological effects
Repeatedly seeking prescriptions from other prescribers or emergency departments
Selling prescription drugs
Stealing or borrowing drugs from others

Sources: Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 2. *Pain Physician*. 2017;20:S111–S133; Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. *Gastroenterology*. 2016;150(6):P1408–P1419; Clouse RE, Mayer EA, Aziz Q, et al. Functional abdominal pain syndrome. *Gastroenterology*. 2006;130:1492–1497.

M.T. has multiple behaviors in which some are more indicative of addiction such as concomitant alcohol use whereas others can be explained, given the etiology of CAPS. For example, high health care utilization for pain validation is common in patients with CAPS. Also, aggressive about the need for more opioid medication may be driven by M.T.'s perception that the current dose prescribed by her primary care physician no longer relieves her pain, implying tolerance has developed (**Table 55-16**).[182,183]

Table 55-16

Terms Related to Opioid Use

Term	Definition

Term	Definition
Misuse	Taking a prescription for a reason or at a dose or frequency other than for which it was prescribed. Use of a medication for a nonmedical use. For example, altering dosing or sharing medicines, which has harmful or potentially harmful consequences.
Abuse	Misuse with consequences involving the use of a substance to modify or control mood or state of mind in a manner that is illegal or harmful to oneself or others. Potentially harmful consequences include accidents, injuries, blackouts, legal problems, and sexual behavior that increase the risk of infectious diseases.
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
Physical dependence	A state of adaptation manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist.
Tolerance	A state of adaptation in which markedly increased drug doses are required to achieve desired effect or exposure results in diminution of one or more opioid effects over time.

Sources: Clouse RE, Mayer EA, Aziz Q, et al. Functional abdominal pain syndrome. *Gastroenterology*. 2006;130:1492–1497; Potvin S, Morin M, Cloutier C, Gendron A, Bissonnette A, Marchand S. Add-on treatment of quetiapine for fibromyalgia: a pilot, randomized, double-blind, placebo-controlled 12-week trial. *J Clin Psychopharmacol*. 2012;32:684–687.

The factor that is most concerning for addiction is M.T.'s continued use of alcohol despite previous pancreatitis and misusing it to treat anxiety. There is also a risk of increased opioid side effects, especially sedation and respiratory depression, with concurrent use of alcohol. Multiple literature reports have confirmed there is a strong association between alcohol abuse and opioid addiction.[181,182] Guidelines for chronic opioid therapy strongly recommend clinicians conduct a risk assessment before initiating opioid therapy.[70,181]

Screening tools that assess the potential risks for opioid misuse based on patient characteristics are helpful in determining eligibility for chronic opioid therapy. Patient self-report questionnaires for assessing risk of aberrant drug-related behavior include the SOAPP-R, ORT, Alcohol Use Disorder Identification Test, and Drug Abuse Screening Test.[19,181]

ASSESSMENT OF CHRONIC OPIOID THERAPY

CASE 55-6, QUESTION 4: M.T. would like to continue with opioid therapy despite the concerns of her primary care physician. Is M.T. a candidate for chronic opioid therapy?

The Centers for Disease Control and Prevention released recommendations for opioid therapy that support the establishment of a treatment plan with the patient before starting opioid therapy that includes realistic goals for pain and function along with consideration of when therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.[70] In the case of M.T., a pain agreement (eg, contract) should be established even if the goal is to eventually discontinue opioid therapy. There are multiple sources in the literature for information and guidelines on written agreements between the clinician and patient for chronic opioid therapy.

The written agreement should include goals of therapy, how opioids will be prescribed and taken, expectations for follow-up and monitoring, alternatives to therapy, expectations regarding use of concomitant therapies, and potential for tapering the regimen and discontinuing.[19] Indications for tapering and/or discontinuation of the opioid include failure to make progress toward therapeutic goals, intolerable adverse effects, or repeated or serious aberrant drug-related behaviors. Patient compliance requirements in the written agreement should include random urine drug screens for illicit substances or opioids obtained from other sources and limited

prescribing (eg, reduced quantities, biweekly prescribing) to help the patient manage use if necessary. In this case, M.T. has not made progress in meeting the goal of decreased emergency department utilization, she continues to use alcohol with her medication, and she has been resistant to trying other therapies despite the ineffectiveness of opioids in treating her pain. These behaviors would indicate M.T. is not a candidate for chronic opioid therapy.

DISCONTINUING OPIOID THERAPY

Case 55-6, Question 5: M.T. is going to be discontinued from opioids as part of the pain management plan. What methods are appropriate to safely discontinue opioid therapy in M.T.?

Guidelines strongly recommend that clinicians taper patients from chronic opioids if they have repeated aberrant drug-related behaviors, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects.[19,70] When tapering patients from long-term opioid therapy, the length of time the patient has been taking opioids needs to be considered. Approaches to opioid tapering range from a slow 10% dose reduction per week to a more rapid 25% reduction every few days. Evidence to guide specific recommendations on the rate of reduction is lacking, although the slower rate may help reduce the unpleasant symptoms of opioid withdrawal.[19]

There is insufficient evidence to guide recommendations for the use of short-acting versus LA oral opioids, or prn versus around-the-clock dosing during taper.[184] In this case, it is recommended that M.T.'s oxycodone dose be reduced slowly over 2 months in conjunction with starting psychological therapy for stress management and counseling for alcohol use. M.T. will need to be monitored for signs of withdrawal, which include anxiety, tachycardia, sweating, and other autonomic symptoms. Should withdrawal symptoms occur, they may be lessened by clonidine 0.1 to 0.2 mg by mouth twice a day.

COGNITIVE-BEHAVIORAL THERAPIES

Case 55-6, Question 6: What nonpharmacologic therapies could be offered to M.T. to help with her pain management?

Psychological counseling and CBT are key components to successful management of the patient. The psychological approach to CBT has been shown to be beneficial in the treatment of CAPS.[178] CBT typically combines stress management, problem-solving, goal setting, pacing of activities, and assertiveness into a strategy for self-management of pain. Biofeedback, meditation, guided imagery, and hypnosis can all be incorporated into a CBT plan (**Table 55-17**). The objective is to help patients acquire a sense of hopefulness and resourcefulness and develop positive coping skills.[185]

Table 55-17
Cognitive-Behavioral Therapy

Meditation—intentional self-regulation of attention using a systematic focus on particular aspects of inner and outer body experience.
Biofeedback—self-regulatory technique that teaches a patient how to exert control over the physiologic processes exacerbating pain. Biofeedback equipment conveys physiologic responses as visual or auditory signals that the patient can observe on a computer monitor. With practice, the patient learns to control and change his/her physiologic responses by manipulating the auditory or visual signals.
Guided imagery—useful method to help patients with pain to relax and achieve a sense of control and distraction. This modality involves the generation of different mental images, evoked either by oneself or with help from the practitioner.
Hypnosis—a state of heightened awareness and focused concentration that can be used to manipulate the perception of pain.

Source: Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 1. *Pain Physician*. 2017;20:S93–S109.

Complementary and alternative therapies such as spinal manipulation, massage, and acupuncture are commonly used in

patients with chronic pain, but data supporting their use in CAPS are limited. Transcutaneous electrical nerve stimulation has been studied in CAPS patients, but the results are inconclusive.[178,185]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key reference and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Chou R, Cruciani R, Fiellin D, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College of Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain*. 2014;15(*4*):321–337. (139)

Chou R, Gordon DB, de Leon-Casasola OA, et al. Guidelines on the management of postoperative pain. *J Pain*. 2016;17(*2*):131–157. (28)

Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep*. 2016;65:1–50. (70)

Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–173. (20)

Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 1. *Pain Physician.* 2017;20:S93–S109. (182)

Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 2. *Pain Physician.* 2017;20:S111–S133. (19)

Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017;76:318–328. (162)

Nijs J, Apeldoorn A, Hallegraeff H, et al. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician*. 2015;18(*3*):E333–E346. (90)

Key Websites

Centers for Disease Control and Prevention. https://www.cdc.gov/opioids/providers/prescribing/index.html

International Association for the Study of Pain. https://www.iasp-pain.org/

Institute for Safe Medication Practices. *2020-2021 ISMP Targeted Medication Safety Best Practices for Hospitals, Best Practice 15*. Accessed November 14, 2020. https://www.ismp.org/sites/default/files/attachments/2020-02/2020-2021%20TMSBP-%20FINAL_1.pdf

COMPLETE REFERENCES CHAPTER 55 PAIN AND ITS MANAGEMENT

1. Raja S, Carr D, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161(9):1976–1982.
2. Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The incidence and severity of postoperative pain following inpatient surgery. *Pain Med*. 2015;16(12):2277–2283.
3. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin*. 2014;30:149–160.
4. U.S. Department of Health and Human Services. Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. U.S. Department of Health and Human Services. Accessed November 23, 2020. https://www.hhs.gov/sites/default/files/pain-mgmt-best-practices-draft-final-report-05062019.pdf
5. Tighe P, Buckenmaier CC III, Boezaart AP, et al. Acute pain medicine in the United States: a status report. *Pain Med*. 2015;16:1806–1826.
6. Pasquale MK, Dufour R, Schaaf D, et al. Pain conditions ranked by healthcare costs for members of a national health plan. *Pain Pract*. 2014;14(2):117–131.
7. Mills S, Nicolson K, Smith B. Chronic pain: a review of its epidemiology and associated factors in population-based studies. *Br J Anaesth*. 2019;123(2):e273–e283.
8. Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage*. 2013;21:1145–1153.
9. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis of the Global Burden of Disease Study 2016. *Lancet.* 2017;390:1211–1259.

10. Fregoso G, Wang A, Tseng K, Wang J. Transition from acute to chronic pain: evaluating risk for chronic postsurgical pain. *Pain Physician*. 2019;22:479–488.
11. Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain pathophysiology and preventative pharmacologic considerations. *Anesthesiology.* 2018;129:590–607.
12. Block L. Glial dysfunction and persistent neuropathic postsurgical pain. *Scand J Pain.* 2016;10:74–81.
13. Thomas J, Mustafa S, Johnson J, Nicotra L, Hutchinson M. The relationship between opioids and immune signalling in the spinal cord. *Handb Exp Pharmacol*. 2015;227:207–238.
14. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. *Annu Rev Med*. 2011;62:381–396.
15. Kang Y, Demiris G. Self-report pain assessment tools for cognitively intact older adults: integrative review. *Int J Older People Nurs*. 2018;13(2):1–29.
16. Krebs E, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *J Gen Intern Med*. 2009;24(6):733–738.
17. Melzack R. The short-form McGill pain questionnaire. *Pain.* 1987;30:191–197.
18. Kean J, Monahan PO, Kroenke K, et al. Comparative responsiveness of the PROMIS pain interference short forms, brief pain inventory, PEG, and SF-36 bodily pain subscale. *Med Care*. 2016;54(4):414–421.
19. Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 2. *Pain Physician*. 2017;20:S111–S133.
20. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–173.
21. Dworkin RH, O'Connor AB, Kent J, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain.* 2013;154:2249–2261.
22. Kolasinski S, Neogi T, Hochberg M, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* 2020;72(2):149–162.
23. Meerveld B, Johnson A. Mechanisms of stress-induced visceral pain. *J Neurogastroenterol Motil*. 2018;24(1):7–18.
24. Althaus A, Arránz BO, Neugebauer E. Distinguishing between pain intensity and pain resolution: using acute post-surgical pain trajectories to predict chronic post-surgical pain. *Eur J Pain.* 2014;18(5):513–521.
25. Althaus A, Arránz BO, Moser KH, et al. Postoperative pain trajectories and pain chronification—an empirical typology of pain patients. *Pain Med.* 2018;19:2536–2545.

26. Gulur P, Nelli M. Persistent postoperative pain: mechanisms and modulators. *Anesthesiology.* 2019;32(75):668–673.
27. Glare P, Aubrey KR, Myles PR. Postoperative pain management and opioids: transition from acute to chronic pain after surgery. *Lancet.* 2019;393:1537–1546.
28. Chou R, Gordon DB, de Leon-Casasola OA, et al. Guidelines on the management of postoperative pain. *J Pain*. 2016;17(2):131–157.
29. Van Ryswyk E, Antic NA. Opioids and sleep-disordered breathing. *Chest.* 2016;150(4):934–944.
30. Chung F, Liao P, Yang Y, et al. Postoperative sleep-disordered breathing in patients without preoperative sleep apnea. *Anesth Analg*. 2015;120(6):1214–1224.
31. American Sleep Association. Sleep Apnea Screening Questionnaire—'Stop Bang'. Accessed November 23, 2020. https://www.sleepassociation.org/sleep-apnea/testing/stop-bang/
32. Macintyre PE, Roberts LJ, Huxtable CA. Management of opioid-tolerant patients with acute pain: approaching the challenges. *Drugs.* 2020;80:9–21.
33. Moulton LS, Evans PA, Starks I, Smith T. Pre-operative education prior to elective hip arthroplasty surgery improves postoperative outcome. *Int Orthop*. 2015;39(8):1483–1486.
34. Joshi GP, Gandhi K, Shah N, Gadsden J, Corman SL. Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. *J Clin Anesth.* 2016;35:524–529.
35. Kuttler A, Dimke T, Kern S, Helmlinger G, Stanski D, Finelli LA. Understanding pharmacokinetics using realistic computational models of fluid dynamics: biosimulation of drug distribution within the CSF space for intrathecal drugs. *J Pharmacokinet Pharmacodyn.* 2010;37:629–644.
36. Becker DE, Reed KL. Essentials of Local Anesthetic Pharmacology. *Anesth Prog*. 2006;53:98-109
37. Emelife P, Eng MR, Menard BL, et al. Adjunct medications for peripheral and neuraxial anesthesia. *Best Pract Res Clin Anaesthesiol.* 2018;32:83–99.
38. Pöpping D, Elia N, Van Aken H, et al. Impact of epidural analgesia on mortality and morbidity after surgery. Systematic review and meta-analysis of randomized controlled trials. *Ann Surg*. 2014;259:1056–1067.
39. Neal JM, Barrington MJ, Fettiplace MR, et al. The third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on local anesthetic systemic toxicity: executive summary 2017. *Reg Anesth Pain Med*. 2018;43:113–123.
40. Eng HC, Ghosh SM, Chin KJ. Practical use of local anesthetics in regional nerve blocks. *Curr Opin Anaesthesiol.* 2014;27(5):549–555.
41. Joshi GP, Schug SA, Kehlet H. Procedure-specific pain management and outcome strategies. *Best Pract Res Clin Anaesthesiol.* 2014;28:191–201.

42. Shah J, Votta-Velis EG, Borgeat A. New local anesthetics. *Best Pract Res Clin Anaesthesiol.* 2018;32:179–185.
43. Valsamis EM, Wade S, Thornhill C, Carey C, Ricketts D. A simple guide to regional anaesthesia. *Br J Hosp Med.* 2018;79(4):211–217.
44. Gabriel RA, Ilfeld B. Peripheral nerve blocks for postoperative analgesia: from traditional unencapsulated local anesthetic to liposomes, cryoneurolysis and peripheral nerve stimulation. *Best Pract Res Clin Anaesthesiol.* 2019;33:293–302.
45. Fredrickson MJ, Ball CM, Dalgleish AJ. Analgesic effectiveness of a continuous versus single-injection interscalene block for minor arthroscopic shoulder surgery. *Reg Anesth Pain Med*. 2010;35:28–33.
46. Neal JM, Barrington MJ, Brull R, et al. The second ASRA practice advisory on neurologic complications associated with regional anesthesia and pain medicine: executive summary 2015. *Reg Anesth Pain Med*. 2015;40:401–430.
47. Gabriel RA, Nagrebetsky A, Kaye AD, Dutton RP, Urman RD. The patterns of utilization of interscalene nerve blocks for total shoulder arthroplasty. *Anesth Analg*. 2016;123(3):758–761.
48. Bingham AE, Fu R, Horn JL, Abrahams MS. Continuous peripheral nerve block compared with single-injection peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. *Reg Anesth Pain Med*. 2012;37:583–594.
49. Aubrun F, Mazoit J-X, Riou B. Postoperative intravenous morphine titration. *Br J Anaesth*. 2012;108(2):193–201.
50. De Gregori S, De Gregori M, Ranzani GN, Allegri M, Minella C, Regazzi M. Morphine metabolism, transport and brain disposition. *Metab Brain Dis*. 2012;27:1–5.
51. Macintyre PE, Loadsman JA, Scott DA. Opioids, ventilation and acute pain management. *Anaesth Intensive Care*. 2011;39:545–558.
52. Kilmas R, Mikus G. Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-3-glucuronide, and morphine-6-glucuronide. *Br J Anaesth*. 2014;113(6):935–944.
53. Pourmand A, Jasani G, Shay C, Mazer-Amirshahi M. The evolving landscape of acute pain management in the era of the opioid crisis. *Curr Pain Headache Rep.* 2018;22:1–73.
54. Mazer-Amirshahi M, Motov S, Nelson LS. Hydromorphone use for acute pain: misconceptions, controversies and risks. *J Opioid Manag.* 2018;14(1):61–71.
55. *Opioid Analgesics: Approximate Equianalgesic Doses for Adults. Facts & Comparisons eAnswers*. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5545901?

cesid=7uk2iVT27MS&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dopioid%26t%3Dname%26va%3Dopioid%26nq%3Dtrue#general-dosing-nested-0

56. WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. ANNEX 6, Pharmacological Profiles and Opioid Conversion Tables. https://www.ncbi.nlm.nih.gov/books/NBK537482/
57. Murray A, Hagen N. Hydromorphone. *J Pain Symptom Manage*. 2005;29:S57–S66.
58. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician*. 2008;11:S113–S153.
59. Paramanadam G, Prommer E, Schwenke DC. Adverse effects in hospice patients with chronic kidney disease. *J Palliat Med*. 2011;14:1029–1033.
60. Peng PW, Sandler AN. A review of the use of fentanyl analgesia in the management of acute pain in adults. *Anesthesiology.* 1999;90:576–599.
61. Stanley, TH. The fentanyl story. *J Pain*. 2014;15(12):1215–1226.
62. Belcaid I, Eipe N. Perioperative pain management in morbid obesity. *Drugs.* 2019;79:1163–1175.
63. Grass JA. Patient controlled analgesia. *Anesth Analg*. 2005;101:S44–S61.
64. Institute for Safe Medication Practices. *2020–2021 ISMP Targeted Medication Safety Best Practices for Hospitals, Best Practice 15*. Accessed November 14, 2020. https://www.ismp.org/sites/default/files/attachments/2020-02/2020-2021%20TMSBP-%20FINAL_1.pdf
65. Momeni M, Crucitti M, DeKock M. Patient-Controlled Analgesia in the Management of Postoperative Pain. *Drugs 2006*;66(18):2321-2337
66. Algera MH, Kamp J, van der Schrier R, et al. Opioid-induced respiratory depression in humans: a review of pharmacokinetic-pharmacodynamic modelling of reversal. *Br J Anaesth*. 2019;122(6):e168–e179.
67. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology.* 2010;112:226–238.
68. Streicher JM, Bilsky EJ. Peripherally acting μ-opioid receptor antagonists for the treatment of opioid-related side effects: mechanism of action and clinical implications. *J Pharm Pract.* 2018; 31(6):658–669.
69. Nelson AD, Camilleri M. Opioid-induced constipation: advances and clinical guidance. *Ther Adv Chronic Dis*. 2016;7(2):121–134.
70. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep*. 2016;65:1–50.
71. Pogatzki-Zahn E, Chandrasena C, Schug SA. Nonopioid analgesics for postoperative pain management. *Curr Opin Anesthesiol*. 2014;27:513–519.
72. Hickman SR, Mathieson KM, Bradford LM, Garman CD, Gregg RW, Lukens DW. Randomized trial of oral versus intravenous acetaminophen for postoperative pain control. *Am J Health Syst Pharm*. 2018;75:367–375.

73. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375(26):2519–2529.
74. Solomon DH, Husni E, Libby PA, et al. The risk of major NSAID toxicity with Celecoxib, Ibuprofen, or Naproxen: a secondary analysis of the PRECISION trial. *Am J Med.* 2017;130:1415–1422.
75. Tawfic QA, Bellingham G. Postoperative pain management in patients with chronic kidney disease. *J Anaesthesiol Clin Pharmacol*. 2015;31(1):6–13.
76. Maslin B, Lipana L, Roth B, Kodumudi G, Vadivelu N. Safety considerations in the use of ketorolac for postoperative pain. *Curr Drug Saf*. 2017;12:67–73.
77. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694.
78. Kumar AH, Habib AS. The role of gabapentinoids in acute and chronic pain after surgery. *Curr Opin Anesthesiol*. 2019;32:629–634.
79. U.S. Food and Drug Administration. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). FDA Safety Alert. MedWatch. Published December 19, 2019. Accessed November 13, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin
80. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43:456–466.
81. Weibel S, Jelting Y, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. *Cochrane Database Syst Rev.* 2018;6(6):CD009642. doi:10.1002/14651858.CD009642.pub3
82. Bailey M, Corcorana T, Schuga S, Tonera A. Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety. *Pain.* 2018;159:1696–1704.
83. Beaussier M, Delbos A, Maurice-Szamburski A, Ecoffey C, Mercadal L. Perioperative use of intravenous lidocaine. *Drugs.* 2018;78:1229–1246.
84. Centers for Disease Control and Prevention. Severe headache or migraine, low back pain, and neck pain among adults aged 18 and over, by selected characteristics: United States, selected years 1997–2012. National Health Survey, 2012.
85. Becker A, Held H, Redaelli M, et al. Low back pain in primary care: costs of care and prediction of future health care utilization. *Spine (Phila Pa 1976).*

2010;35:1714–1720.
86. Hartvigsen J, Hancock MJ, Kongsted, et al. What low back pain is and why we need to pay attention. *Lancet.* 2018;391:2356–2367.
87. Lacey R, Belcher J, Croft P. Does life course socio-economic position influence chronic disabling pain in older adults? A general population study. *Eur J Public Health*. 2013;23:534–540.
88. Shmagel A, Foley R, Ibrahim H. Epidemiology of chronic low back pain in US adults: data from the 2009–2010 National Health and Nutrition Examination Survey. *Arthritis Care Res*. 2016;68:1688–1694.
89. Dieleman JL, Baral R, Birger M, et al. US spending on personal health care and public health, 1996–2013. *JAMA.* 2016;316(24):2627–2646.
90. Nijs J, Apeldoorn A, Hallegraeff H, et al. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician*. 2015;18(3):E333–E346.
91. Pangarkar SS, Kang DG, Sandbrink F, et al. VA/DoD clinical practice guideline: diagnosis and treatment of low back pain. *J Gen Intern Med*. 2019;34(11):2620–2629.
92. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ.* 2015;350:h1225.
93. Oliveira C, Maher C, Pinto R, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *Eur Spine J*. 2018;27:2791–2803.
94. Roelofs PD, Deyo RA, Koes BW, Scholten RJPM, van Tulder MW. Nonsteroidal anti-inflammatory drugs for low back pain: an updated Cochrane review. *Cochrane Database Syst Rev*. 2008;1:CD000396.
95. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM. Muscle relaxants for non-specific low back pain. *Cochrane Database Syst Rev*. 2003;2:CD004252.
96. Qaseem A, Wilt T, McLean R, Forciea MA. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2017;166:514–530.
97. Vorsanger GJ, Xiang J, Gana TJ, Pascual MLG, Fleming RRB. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. *J Opioid Manag*. 2008;4:87–97.
98. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain*. 2005;6:21–28.
99. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled phase III study. *Expert Opin Pharmacother*. 2010;11:1787–1804.

100. Deshpande A, Furlan A, Mailis-Gagnon A, Atlas S, Turk D. Opioids for chronic low-back pain. *Cochrane Database Syst Rev*. 2007;3:CD004959. doi:10.1002/14651858.CD004959.pub3
101. Urquhart DM, Hoving JL, Assendelft WW, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. *Cochrane Database Syst Rev*. 2008;1:CD001703.
102. Skljarevski V, Zhang S, Desaiah D, et al. Duloxetine versus placebo in patients with chronic low back pain: a 12-week fixed-dose, randomized, double-blind trial. *J Pain*. 2010;11(12):1282–1290.
103. Yildirim K, Deniz O, Gureser G, et al. Gabapentin monotherapy in patients with chronic radiculopathy: the efficacy and impact on life quality. *J Back Musculoskelet Rehabil*. 2009;22:17–20.
104. Khoromi S, Patsalides A, Parada S, Salehi V, Meegan JM, Max MB. Topiramate in chronic lumbar radicular pain. *J Pain*. 2005;6:829–836.
105. Muehlbacher M, Nickel MK, Kettler C, et al. Topiramate in treatment of patients with chronic low back pain: a randomized, double-blind, placebo-controlled study. *Clin J Pain*. 2006;22:526–531.
106. McBeth J, Pye SR, O'Neill TW, et al. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. *Ann Rheum Dis*. 2010;69:1448–1452.
107. Warner AE, Arnspiger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. *J Clin Rheumatol*. 2008;14:12–16.
108. U.S. Agency for Health Care Policy and Research. Acute low back pain problems in adults: assessment and treatment. *Clin Pract Guidel Quick Ref Guide Clin*. 1994;(14):iii–iv, 1–25.
109. Cheattle M. Risk assessment: safe opioid prescribing tools. In Kean N, ed. Opioid Prescribing and Monitoring—How to Combat Opioid Abuse and Misuse Responsibly. 1st ed. Book Suppl to Practical Pain Management. Vertical Health. September 2016.
110. Michaelides A, Zis P. Depression, anxiety and acute pain: links and management challenges, *Postgrad Med.* 2019;131(7):438–444. doi:10.1080/00325481.2019.1663705
111. Velly AM, Mohit S. Epidemiology of pain and relation to psychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;87:159–167.
112. Malanga GA, Gwynn MW, Smith R, Miller D. Tizanidine is effective in the treatment of myofascial pain syndrome. *Pain Physician*. 2002;5(4):422–432.
113. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev*. 2013;8:CD004959.
114. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised, controlled crossover trial. *Lancet.* 2009;374:1252–1261.

115. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352:1324–1334.
116. Passik S, Kirsh K, Whitcomb L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clin Ther*. 2004;26(4):552–561.
117. Hagen KB, Jamtvedt G, Hilde G, Winnem MF. The updated Cochrane review of bed rest for low back pain and sciatica. *Spine (Phila Pa 1976)*. 2005;30:542–546.
118. Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: a randomized clinical trial. *JAMA.* 2016;215(12):1240–1249.
119. Mulla S, Wang L, Kholar R, et al. Management of central poststroke pain: systematic review of randomized controlled trials. *Stroke.* 2015;46:2583–2860.
120. Kim JS. Pharmacological management of central post-stroke pain: practical guide. *CNS Drugs*. 2014;28:787–797.
121. Liampas A, Velidakis N, Georgiou T, et al. Prevalence and management challenges in central post-stroke Neuropathic pain: a systematic review and meta-analysis. *Adv Ther*. 2020;37:3278–3291.
122. Leijon G, Boivie J. Central post-stroke pain—a controlled trial of amitriptyline and carbamazepine. *Pain.* 1989;36:27–36.
123. Vranken JH, Dijkgraaf MGW, Kruis MR, van der Vegt MH, Hollmann MW, Heesen M. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain.* 2008;136:150–157.
124. Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med*. 2003;348:1223–1232.
125. Harpaz R, Leung J. The epidemiology of Herpes Zoster in the United States during the era of Varicella and Herpes Zoster vaccines: changing patterns among older adults. *Clin Infect Dis*. 2019;69(2):341–344.
126. Lunn MPT, Hughes RAC, Wiffen PJ, et al. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev*. 2014;1:CD007115.
127. Cymbalta. Package insert. Lilly; 2020.
128. Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2014;4:CD007938.
129. Arnold L, McCarberg B, Clair A, et al. Dose-response of pregabalin for diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. *Postgrad Med*. 2017;129(8):921–933.

130. Wiffen PJ, Derry S, Andrew Moore R, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia—an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2013;11:CD010567.
131. Qutenza. Package insert. Acorda Therapeutics; 2020.
132. Vinik AI, Shapiro DY, Rauschkolb C, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care*. 2014;37(8):2302–2309.
133. Raffa R, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther*. 1992;260:275–285.
134. Boyer E, Shannon M. The serotonin syndrome [published correction appears in *N Engl J Med*. 2007;356:2437]. *N Engl J Med.* 2005;352(11):1112–1120.
135. Nucynta ER (tapentadol HCl). Package insert. Published October 7, 2019. Accessed November 17, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/200533s020lbl.pdf
136. Tzschentke T, Christoph T, Kögel B, et al. (-)-(1R,2R)-3-(3-Dime-thylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride(tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther*. 2007;323:265–276.
137. Zorn K, Fudin J. Treatment of neuropathic pain: the role of unique opioid agents. *Pract Pain Manag*. 2011;11:26–33.
138. Codd E, Shank R, Schupsky J, Raffa RB. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. *J Pharmacol Exp Ther*. 1995;274:1263–1270.
139. Chou R, Cruciani R, Fiellin D, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain*. 2014;15(4):321–337.
140. Pham T, Fudin J, Raffa R. Is Levorphanol a better option than Methadone? *Pain Med*. 2015;16(9):1673–1679.
141. Fudin J, Marcoux M, Fudin JA. A mathematical model for methadone conversion examined. *Pract Pain Manag*. 2012;12(8):46–51.
142. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H, Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;63:959–965.
143. FDA Drug Safety Communication. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin and pregabalin

when used with CNS depressants or in patients with lung problems. Published December 19, 2019. Accessed March 8, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin

144. Dasgupta N, Jonsson F, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med*. 2016;17:85–98.
145. Park T, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ*. 2015;350:1–8.
146. Sperber AD, Drossman DA. Functional abdominal pain syndrome: constant or frequently recurring abdominal pain. *Am J Gastroenterol*. 2010;105:770–774.
147. Kim SE, Chang L. Overlap between functional GI disorders and other functional syndromes: what are the underlying mechanisms. *Neurogastroenterol Motil*. 2012;24:895–913.
148. Katz J, Rosenbloom, Fashier S. Chronic pain, psychopathology, and DSM-5 somatic symptom disorder. *Can J Psychiatry.* 2015;60(4):160–167.
149. Egloff N, Cámara RJA, von Känel N, Klingler N, Marti E, Ferrari M-LG. Hypersensitivity and hyperalgesia in somatoform pain disorders. *Gen Hosp Psychiatry*. 2014;36:284–290.
150. Keefer L, Mandal S. The potential role of behavioral therapies in the management of centrally mediated abdominal pain. *Neurogastroenterol Motil*. 2015;27(3):313–323.
151. Häuser W, Sarzi-Puttini P, Fitzcharles MA. Fibromyalgia syndrome: under-, over-and misdiagnosis. *Clin Exp Rheumatol.* 2019;37(suppl 116):S90–S97.
152. Lacasse A, Bourgault P, Choinière M. Fibromyalgia-related costs and loss of productivity: a substantial societal burden. *BMC Musculoskelet Disord*. 2016;17:168–176.
153. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract*. 2007;61(9):1498–1508.
154. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*. 2016;46(3):319–329.
155. Prabhakar A, Kaiser JM, Novitch MB, Cornett EM, Urman RD, Kaye AD. The role of complementary and alternative medicine treatments in fibromyalgia: a comprehensive review. *Curr Rheumatol Rep.* 2019;21:14.
156. O'Brien AT, Deitos A, Triñanes Pego Y, Fregni F, Carrillo-de-la-Peña MT. Defective endogenous pain modulation in fibromyalgia: a meta-analysis of temporal summation and conditioned pain modulation paradigms. *J Pain*. 2018;19:819–836.
157. Clauw DJ. Fibromyalgia: a clinical review. *JAMA.* 2014;311:1547–1555.

158. Neumeister MW, Neumeister EL. Fibromyalgia. *Clin Plast Surg.* 2020;47:203–213.
159. Malatji BG, Mason S, Mienie LJ, et al. The GC-MS metabolomics signature in patients with fibromyalgia syndrome directs to dysbiosis as an aspect contributing factor of FMS pathophysiology. *Metabolomics.* 2019;15(4):1–54.
160. Loge-Hagen JS, Saele A, Juhl C, Bech P, Stenager E, Mellentin AI. Prevalence of depressive disorder among patients with fibromyalgia: systematic review and meta-analysis. *J Affect Disord*. 2019;245:1098–1105.
161. Bharucha AE, Chakraborty S, Sletten CD. Common functional gastroenterologic disorders associated with abdominal pain. *Mayo Clin Proc*. 2016;91(8):1118–1132.
162. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017;76:318–328.
163. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al. Canadian Pain Society and Canadian Rheumatology Association recommendations for rational care of persons with fibromyalgia: a summary report. *J Rheumatol*. 2013;40:1388–1393.
164. Häuser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther*. 2010;12(R79):1–14.
165. Bidonde J, Busch AJ, Webber SC, et al. Aquatic exercise training for fibromyalgia. *Cochrane Database Syst Rev*. 2014;10:CD011336.
166. Luciano JV, D'Amico F, Cerdà-Lafont M, et al. Cost-utility of cognitive behavioral therapy versus U.S. Food and Drug Administration recommended drugs and usual care in the treatment of patients with fibromyalgia: an economic evaluation alongside a 6-month randomized controlled trial. *Arthritis Res Ther*. 2014;16:451–468.
167. Bernardy K, Füber N, Köllner V, Häuser W. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome—a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol*. 2010;37:1991–2005.
168. Welsch P, Bernardy K, Derry S, Moore RA, Häuser W. Mirtazapine for fibromyalgia in adults. *Cochrane Database Syst Rev.* 2018;8:CD012708. doi:10.1002/14651858.CD012708.pub2
169. Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev.* 2018;2:CD010292. doi:10.1002/14651858.CD010292.pub2
170. Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. *J Pain*. 2010;11:505–521.
171. Mease PJ, Russell IJ, Arnold LM, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with

fibromyalgia. *J Rheumatol*. 2008;35:502–514.
172. Arnold LM, Russell IJ, Diri EW, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain*. 2008;9:792–805.
173. Arnold LM, Choy E, Clauw DJ, et al. An evidence-based review of pregabalin for the treatment of fibromyalgia. *Curr Med Res Opin.* 2018;34(8):1397–1409.
174. Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. *Cochrane Database Syst Rev*. 2017;1:CD012188.
175. Derry S, Wiffen PJ, Häuser W, et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. *Cochrane Database Syst Rev*. 2017;3:CD012332.
176. Goldenberg DL, Clauw DJ, Palmer RE, Clair AG. Opioid use in fibromyalgia: a cautionary tale. *Mayo Clin Proc*. 2016;91:640–648.
177. Rush JA. 2018 Unipolar major depression in adult: choosing initial treatment. *Up To Date*. Accessed February 26, 2020. https://www.uptodate.com/contents/unipolar-major-depression-in-adults-choosing-initial-treatment
178. Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. *Gastroenterology.* 2016;150(6):P1408–P1419.
179. Clouse RE, Mayer EA, Aziz Q, et al. Functional abdominal pain syndrome. *Gastroenterology.* 2006;130:1492–1497.
180. Potvin S, Morin M, Cloutier C, Gendron A, Bissonnette A, Marchand S. Add-on treatment of quetiapine for fibromyalgia: a pilot, randomized, double-blind, placebo-controlled 12-week trial. *J Clin Psychopharmacol.* 2012;32:684–687.
181. Brady KT, McCauley JL, Back SE. Prescription opioid misuse, abuse, and treatment in the United States: an update. *Am J Psychiatry*. 2016;173(1):18–26.
182. Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 1. *Pain Physician*. 2017;20:S93–S109.
183. Volkow ND, Jones EB, Einstein EB, Wargo EM. Prevention and treatment of opioid misuse and addiction: a review. *JAMA Psychiatry*. 2019;76(2):208–216. doi:10.1001/jamapsychiatry.2018.3126
184. Pedersen L, Borchgrevink PC, Riphagen II, Fredheim OMS. Long or short-acting opioids for chronic non-malignant pain? A qualitative systematic review. *Acta Anaesthesiol Scand*. 2014;58:390–401.
185. Turk DC, Swanson KS, Tunks ER. Psychological approaches in the treatment of chronic pain patients—when pills, scalpels, and needles are not enough. *Can J Psychiatry*. 2008;53:213–223.

56

Care of the Critically Ill Adult

Philip Grgurich, Adrian Wong, and John Marshall

CORE PRINCIPLES	CHAPTER CASES
HOME MEDICATIONS IN THE INTENSIVE CARE UNIT	
1 Medications used to treat chronic conditions are often administered in the intensive care unit (ICU) as long as it does not provide harm to the patient. The decision to continue or hold medications that cause bleeding (eg, warfarin, clopidogrel), have hemodynamic effects (eg, blood pressure medication), have hypoglycemic effects (eg, diabetes medications), and/or that can potentially interact with medications administered in the ICU is made on an individual basis based on risk and benefit.	**Case 56-1 (Question 1)** **Case 56-2 (Question 1)**
PHARMACOKINETICS OVERVIEW AND DRUG SELECTION	

1	Available pharmacokinetic data are often determined in healthy subjects. Critically ill patients may have significant changes in all pharmacokinetic parameters. The clinician should be attuned to those disease states most likely to induce alterations and to develop appropriate monitoring and management strategies for specific medications.	**Case 56-3 (Questions 1–7)**
PAIN, AGITATION, AND DELIRIUM		
1	Pain, agitation, and delirium commonly occur in critically ill patients for a variety of reasons. Clinicians should vigilantly assess patients for pain and provide adequate analgesia. They should attempt to identify and address underlying conditions leading to agitation and delirium.	**Case 56-4 (Questions 1, 2)** **Case 56-5 (Question 1)** **Case 56-6 (Question 1), Table 56-1**
2	Opioids are the most commonly used analgesics in the ICU. Patient-specific characteristics and differences between hydromorphone, fentanyl, and morphine should be considered when designing the optimal analgesic regimen for a patient.	**Case 56-4 (Question 3), Table 56-2**
3	Sedative agents may be utilized in some patients who remain agitated after reversible causes of agitation are thoroughly addressed. Propofol and dexmedetomidine are recommended the first-line sedatives in most patients	**Case 56-5 (Question 2), Table 56-3**

	and should be titrated to achieve light sedation.	
4	Clinicians can reduce the incidence of delirium by minimizing patients' exposure to risk factors for delirium and by implementing early mobilization protocols.	**Case 56-6 (Question 2)**
	STRESS ULCER PROPHYLAXIS IN THE INTENSIVE CARE UNIT	
1	Stress-related mucosal damage can lead to occult gastrointestinal (GI) bleeding in high-risk critically ill patients. All ICU high-risk patients should be evaluated to determine the appropriateness of pharmacologic stress ulcer prophylaxis (SUP).	**Case 56-7 (Questions 1–3)**
	GLYCEMIC CONTROL IN THE INTENSIVE CARE UNIT	
1	Both hypoglycemia and hyperglycemia result in negative outcomes for critically ill patients. Generally, clinicians should target a blood glucose concentration of 140 to 180 mg/dL utilizing insulin to manage hyperglycemia. Ranges of 110 to 140 mg/dL may be appropriate for some patients.	**Case 56-8 (Question 1)**

INTRODUCTION

Patients who are admitted to the intensive care unit (ICU) require close monitoring, given their potential severity of illness or risk of

decompensation. Many different types of ICUs exist, which are often focused on a certain type of organ dysfunction or familiarity with certain procedures or monitoring. Often, these ICUs are quite interdisciplinary in nature, relying on the expertise of many to improve the care of the patient. Evidence-based medicine in the critical care setting is often limited, requiring the synthesis of multiple types of literature as well as clinical experience to determine medication choice, route, dosing, and monitoring.

In this chapter, foundations of medication therapy for the critically ill patient are reviewed, including considerations for continuing home medications, and medication therapies that may improve clinical outcomes, such as sedation and analgesia, stress ulcer prophylaxis (SUP), and glycemic therapies for glucose control.

HOME MEDICATIONS IN THE INTENSIVE CARE UNIT

The management of home medications in an ICU can be a very challenging aspect of care for the medical team. Medication reconciliation has become an increased priority for hospitals, and pharmacists play a vital role. One study found that 36% of patients admitted to the hospital had at least one medication error, and 85% originated from the patient's medication history.[1] Often, the ideal method of obtaining a home medication list is through information obtained in a patient interview. However, this can be difficult in an ICU because many patients are intubated, sedated, delirious, and/or unable to participate in a patient interview. Thus, other methods are required, including interviewing family or friends, calling community pharmacies, locating outside medical records, or looking at previous hospital admissions. Medication reconciliation was shown to decrease discharge medication errors from 57% to 33% on a medical unit and from 80% to 47% on a surgical unit.[2] The importance of restarting home medications in the ICU varies among

different agents and medication classes. Multiple types of adult ICUs exist in the United States, including medical, surgical, burn, and neurosurgical. This section limits discussion to surgical and nonsurgical ICUs and the role of home medications for common situations in these ICUs. In addition, transitions of care from the ICU, with the potential impact of post-intensive care syndrome (PICS) are discussed.

Patients in the ICU can be very complex by definition, and it can be difficult to ensure all important aspects of critical care are addressed daily. To enhance patient care and safety, the medical field has started to incorporate an effective tool borrowed from the airline industry: the checklist. One of the most widely used ICU checklists worldwide is FAST HUG, which stands for **F**eeding, **A**nalgesia, **S**edation, **T**hromboembolic prophylaxis, **H**ead of bed elevation, stress **U**lcer prophylaxis, and **G**lycemic control.[3] These are issues that should be addressed daily because of their impact on morbidity, mortality, and length of ICU stay. Clinical pharmacists working in an ICU have the option to use a personal checklist or other available checklists, including a modified version of FAST HUG, FASTHUG-MAIDENS. This acronym adds **M**edication reconciliation, **A**ntibiotics, **I**ndications for medications, drug **D**osing, **E**lectrolytes, **N**o drug interactions, allergies, duplications, or side effects, and **S**top dates (of medications) to FAST HUG.[4] These are checklists that could be used in any ICU; however, each pharmacist needs to find what works best for them to ensure optimal medical care for their service and patients.

CASE 56-1

QUESTION 1: S.M. is a 62-year-old male who comes to the ICU with an upper gastrointestinal (GI) bleed. He reports a 2-week history of poor oral intake and weight loss. For the past 2 days, he has had several episodes of bloody stools and presented to his local clinic today with the following vitals: 90/51 mm Hg, heart rate (HR) 110 beats/minute, and temperature 97.16 °F (36.2 °C). He is brought immediately to the emergency department (ED) where the following labs are obtained: hematocrit (Hct) 17%, white blood cell count (WBC) 8.2 × 10^9/L, international normalized ratio (INR) 5.2, Na 128 mEq/L, K 3.1 mEq/L, and

serum creatinine (SCr) 1.9 mg/dL. His current home medications are aspirin 81 mg by mouth daily, clopidogrel 75 mg by mouth daily, atorvastatin 40 mg by mouth daily, metoprolol XL 50 mg by mouth daily, lisinopril 10 mg by mouth daily, and warfarin 7.5 mg by mouth daily. The patient is immediately transfused with 2 units of red blood cells and is brought to the ICU.

Which of his home medications should be held after he is admitted to the ICU?

Nonsurgical Intensive Care Unit Patients

For the nonsurgical ICU patient, the indication for admission is a major determinant in what medications can be restarted. Often, medical ICU patients come in with hemodynamic instability, reduced left ventricular ejection fraction, and/or alterations in renal or hepatic function, which significantly alter baseline pharmacokinetics. These patients must be evaluated on a case-by-case basis to determine whether home medications should be restarted. Patients are admitted to the ICU because they need frequent monitoring and are in constant need of reevaluation. The medical team must consider that withdrawal can manifest from discontinuation of chronic home medications (eg, β-blockers, baclofen) or from discontinuation of other illicit substances (eg, heroin, cocaine, methamphetamine). Obtaining a thorough patient history may help prevent medication withdrawal; however, because of the frequent inability to obtain a medical history, the ICU team must determine whether withdrawal treatment is appropriate based on vital signs and physical examination. This section discusses home medications and how they should be addressed in common scenarios encountered in ICU patients.

Hemodynamic instability is one of the most common issues encountered in ICUs. The causes of hypotension include hypovolemia, heart failure, and infection. Knowing the patient's baseline blood pressure can help determine the seriousness of the hypotension. A drop in baseline blood pressure can result in hypoperfusion and in the development of shock. If a patient cannot maintain adequate blood pressure, vasoactive medications (eg,

epinephrine, norepinephrine, phenylephrine, vasopressin) may need to be initiated. Common indicators of lack of perfusion are monitored in the ICU, including cool skin, metabolic acidosis, change in mental status, elevated serum lactate levels, and reduced urine output. If a patient comes to the ICU with hypotension and signs of hypoperfusion, home blood pressure medications of all classes should be held until there is a resolution of the underlying cause of the hypotension and hypoperfusion. Blood pressure medications should be slowly added back at reduced doses to the patient's hospital medication regimen.

Severe cases of hypertension in the ICU must be dealt with urgently to prevent stroke and/or end-organ damage. Common causes of hypertension in the ICU are missed hemodialysis, medication nonadherence, volume overload, and pain. The differential of high blood pressure is extensive, so determining the cause will help determine the direction of treatment. Hypertensive emergencies, defined as a large elevation of systolic blood pressure (SBP >180 mm Hg) or diastolic blood pressure (DBP >120 mm Hg) along with target-organ damage, need to be treated immediately because of possible complications, including cerebral infarction, intracranial hemorrhage, aortic dissection, and renal failure.[5] Intravenous (IV) medications are often required to control blood pressure in the ED or during the early hours of ICU admission. Common medications used are esmolol, diltiazem, hydralazine, labetalol, and nicardipine. These medications work immediately and can be titrated to lower blood pressures to the desired targets. IV medications are used in the short term until chronic antihypertensives can be administered and titrated. Restarting home blood pressure medications in the ICU is important unless there is a contraindication (ie, new renal dysfunction) or the patient now has a new condition that warrants a change in medication class (ie, β-blockers and angiotensin-converting enzyme inhibitor [ACEI] for new heart failure). This topic is discussed further in Chapter 16, Hypertensive Crises.

Because renal function is often unpredictable and unstable in the ICU, many classes of medications are withheld in the ICU. Renal

function can change very quickly in the ICU, and classic indicators of renal function such as SCr, which is used in creatinine clearance equations such as Cockcroft–Gault (CG) equation and the simplified four-variable Modification of Diet in Renal Disease (MDRD) equation, are delayed in acute renal failure or falsely low in the elderly. For this reason, drugs that can be evaluated using therapeutic drug monitoring (eg, vancomycin) should be monitored frequently. Other indicators including urine output, blood pressure, and volume status should be factored into determining an appropriate dosing for medications that are eliminated through the kidney. All medications administered in the hospital setting should be monitored daily and adjusted based on renal function.

Diabetes medications can cause complications in the ICU. Metformin can cause a metabolic acidosis if given to patients with renal dysfunction and is withheld in most ICU patients. Sulfonylureas are also withheld because of the frequent changes in diet in the ICU, which can result in hypoglycemia. As a substitute to prevent hyperglycemia, most patients are converted to a short-acting sliding scale insulin regimen, which accounts for poor oral intake or the withholding of nutrition at certain points in an ICU stay. Sliding scale insulin regimens give varying doses of insulin based on a patient's most recent glucose level. Basal insulin can be considered for patients diagnosed with diabetes, who are not receiving adequate control from sliding scale insulin.

Pain and medications used to treat pain are discussed in various chapters in this textbook (see Chapter 55, Pain and Its Management, for more details). For a new ICU patient, knowing a patient's home medication pain regimen can be very helpful and often vital to good patient care. A patient on chronic opioids should be continued on a pain regimen that includes opioids unless there is a contraindication to do so. Often, the regimen must be modified to account for renal function and route of administration. For example, many of the long-acting formulations cannot be crushed and put down a feeding tube, and a patient with renal dysfunction may need a lower dose or accounting for potential active metabolite accumulations with certain opioids (eg, morphine).

The dynamic nature of the ICU can make anticoagulation a very challenging issue. Unless the patient will likely be in the ICU for a short period of time, vitamin K antagonists (eg, warfarin) or the direct oral anticoagulants (eg, apixaban, dabigatran, rivaroxaban) will often be held in the ICU to prevent complications surrounding procedures and the altered pharmacokinetics in ICU patients. A detailed patient history is essential to determine the indication for anticoagulation. This will help the medical team determine if full anticoagulation should be continued. The discussion to continue anticoagulation will be determined on a case-by-case basis after weighing the risks and benefits of anticoagulation and often discussing the issue with consult services, such as cardiology, vascular surgery, and the primary care team. If full anticoagulation is required in the ICU, unfractionated heparin (UFH) may be the best option, because it can be more readily stopped and reversed if needed, compared to other agents. Almost all patients in the ICU are at increased risk for a venous thromboembolism (VTE) because of the lack of mobility, older age (70 years or older), heart failure, respiratory failure, previous VTE, acute infection, obesity, and/or ongoing hormonal treatment. Because of increased risk for VTE, patients should be placed on anticoagulant thromboprophylaxis with low-molecular-weight heparin (LMWH) daily or two times daily (bid), low-dose unfractionated heparin (LDUH) bid or three times daily (tid), or fondaparinux unless a contraindication exists.[6]

One of the biggest complications for a pharmacist in an ICU patient is finding an ideal medication regimen for a patient who cannot take any medications by mouth or who have a feeding tube. For patients who have a feeding tube, medications can be given down the feeding tube in certain circumstances. The pharmacist must determine which home medications can be crushed or come in a solution or liquid form. Often, long-acting medications must be converted to immediate release, or the medication must be changed so it can be crushed to go down a feeding tube. The Institute for Safe Medication Practices (ISMP) has created a resource for medications that cannot be crushed: http://www.ismp.org/tools/donotcrush.pdf. Certain patients in the ICU

will be ordered to not receive anything by mouth, including medications. It should always be clarified with the medical teams whether an NPO or "nothing by mouth" order includes medications. Many circumstances allow for the patient to receive oral medications on an NPO order. If medications cannot be given by mouth or there are concerns about absorption in the GI tract, the ICU teams will request that medications be converted from oral to IV form, if possible. Although some medications have IV formulations, many do not. A clinical pharmacist can assist with dosage conversions, frequency of administration, and alternative options for medications that do not have IV equivalents.

Owing to the fact that S.M. is actively bleeding, all anticoagulant and antiplatelet medications should be held. S.M. should have his aspirin, clopidogrel, and warfarin held. In addition, because he has an elevated INR, he should receive vitamin K to reverse the effect of warfarin. Once his bleeding has stopped, the team will have to determine which medications can be restarted and at what time the medications can be restarted.

Surgical Patients

CASE 56-2

Question 1: D.H. is a 68-year-old with a past medical history (PMH) of coronary artery disease (CAD) (drug-eluting stent placed 11 months ago), diabetes, and atrial fibrillation, who will be undergoing a knee replacement procedure in 1 week. His home medications on arrival to the hospital today include aspirin 81 mg by mouth daily, clopidogrel 75 mg by mouth daily, metoprolol XL 100 mg by mouth daily, and metformin 1000 mg by mouth bid. All his labs are within normal limits on the day of arrival.

The surgery team wants your advice: what medications should be continued throughout surgery, and what medications should be stopped?

Consequences of stopping a chronic medication before, or failing to restart that medication after surgery, can be significant. For example, abrupt discontinuation of a β-blocker during the perioperative period in a patient who has been on chronic β-blocker

therapy can increase the risk of death in the intraoperative and postoperative period. The American College of Cardiology/American Heart Association (ACC/AHA) recommends continuation of β-blocker therapy in patients undergoing surgery who are on a β-blocker chronically.[7] The use of ACEIs and angiotensin-receptor blockers (ARBs) may increase the risk of hypotension after induction of anesthesia when these agents are not withheld 24 hours before surgery.[8] Stopping the ACEI before surgery, however, can result in adverse postoperative effects, such as rebound hypertension and atrial fibrillation. Therefore, the decision to continue or stop before surgery is made on an individual basis, taking into consideration the indication and the type of surgery.[7] Medications such as amiodarone, calcium-channel blockers, clonidine, digoxin, and statins should be continued. Preoperative withdrawal of a statin in a patient undergoing major vascular surgery, for example, increases the risk of myocardial infarction and cardiovascular death after surgery.[7] Diuretics are typically held the morning of surgery to minimize the risk of hypovolemia and electrolyte abnormalities.

Oral antidiabetic agents and noninsulin injectable agents are typically held the morning of surgery and not restarted until normal food intake resumes. In patients with renal dysfunction and those who may receive IV contrast media, metformin should be discontinued 24 to 48 hours before surgery to reduce the risk of perioperative lactic acidosis. For patients on insulin therapy, a portion of the morning dose of intermediate- or long-acting insulin is generally administered on the day of surgery after a check of the patient's blood glucose. Close blood glucose monitoring guides subsequent insulin doses to avoid hypoglycemia.[9]

Antiepileptics, antipsychotics, benzodiazepines, lithium, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and carbidopa/levodopa has a higher risk for withdrawal or disease decompensation than for perioperative complications. These medications should, therefore, be continued up to and including the morning of surgery.

Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit platelet aggregation and are often stopped 1 to 3 days before surgery, depending on the duration of action of the drug. Celecoxib does not affect platelet aggregation and may be continued up to and including the day of surgery. Nonselective NSAIDs and celecoxib should be held if there is a concern for impaired renal function during or after surgery.

For patients on anticoagulant or antiplatelet therapy, the risks for thromboembolism must be balanced with the risk for bleeding during and after the surgical procedure. For patients on warfarin who are at high risk for perioperative thromboembolism, bridging anticoagulation therapy with IV heparin or LMWH before surgery may be recommended, depending on the underlying indication. Warfarin may not need to be discontinued if the patient is undergoing minor surgery (eg, certain dental, dermatologic, or ophthalmic procedures). For patients who have had coronary stents recently placed, discontinuing antiplatelet therapy prematurely can significantly increase the risk of perioperative stent thrombosis and have catastrophic consequences.[10] The 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery: Executive Summary recommends that patients undergoing urgent noncardiac surgery during the first 4 to 6 weeks after receiving a bare metal stent or drug-eluding stent implantation should continue dual-antiplatelet therapy (aspirin plus P2Y12 platelet receptor inhibitor) unless the relative risk of bleeding outweighs the benefit of the prevention of stent thrombosis.[7] They also recommend that the management of perioperative antiplatelet therapy be determined by a consensus of the surgeon, anesthesiologist, cardiologist, and patient, who should weigh the relative risk of bleeding with those of prevention of stent thrombosis.

Traditionally, it was thought that patients who have been taking long-term corticosteroid therapy before surgery will experience adrenal insufficiency in the perioperative period and should receive a supplemental stress dose of hydrocortisone or methylprednisolone during and up to 2 to 3 days after surgery.[11] A review of the literature,

however, found that patients on long-term corticosteroid therapy only require continuation of their normal daily dose of corticosteroid in the perioperative period.[12] These patients are generally able to increase their endogenous adrenal function above their baseline corticosteroid dose to meet the increased demand from surgery; a supplemental stress dose of corticosteroid is not necessary. These patients can be closely monitored, and if hypotension develops, a stress dose of a corticosteroid should be administered at that time. Patients who have a known dysfunctional hypothalamic–pituitary–adrenal axis deficiency (eg, Addison disease), on the other hand, will require supplemental corticosteroid doses in the perioperative period as they cannot increase endogenous cortisol production to meet the increased demand from surgery.[12]

Patient on chronic opioids who undergo surgery often experience more severe acute pain after surgery. These patients should receive either their chronic opioid medication or a comparable dose of an IV opioid the morning of surgery to meet their daily requirements to avoid uncontrolled pain and opioid-withdrawal symptoms. The use of nonopioid analgesics or analgesic techniques (eg, acetaminophen, epidural analgesia, peripheral nerve blockade) for perioperative analgesia should be maximized in a postoperative patient.[13]

For D.H., because his stent is over 6 weeks old, his clopidogrel should be held 5 to 7 days before surgery. His warfarin should also be held 5 to 7 days before surgery and likely does not need bridging with an UFH or LMWH. His aspirin can be continued through surgery.

Transitions of Care/Post-Intensive Care Syndrome

The transition of a patient from the ICU to another clinical setting, such as the general ward, skilled nursing facility, or even home, should be seen as an opportunity to closely evaluate the appropriateness of a patient's medication therapies. This often includes not only medications that were initiated in the ICU setting

but also a patient's home medications that were held during their ICU stay. Studies have shown that antipsychotics (more details in "Pain, Agitation, and Delirium in the Intensive Care Unit" section), a class of medications that may be prescribed for the management of agitation and/or delirium in the ICU, are often continued upon transfer to the general ward and even upon hospital discharge, with rates of 26% and 21%, respectively.[14,15] The continuation of these therapies may result in this becoming an inappropriately prescribed chronic medication, along with the potential adverse chronic effects associated with antipsychotics. Midodrine, an α_1-agonist used for increasing blood pressure, has been shown to be continued at discharge in 34% of patients who were newly prescribed it in the ICU.[16] Finally, a multicenter study of medication errors focusing on transition from the ICU to a non-ICU setting found that ~45% of patients had at least one medication error present during transitions of care.[17] These studies underscore the importance of ensuring that an adequate pass-off of a therapeutic plan for medications started in the ICU is completed before transfer to another setting.

One important aspect of transitions of care is PICS, which is an increasingly studied phenomenon that occurs in patients who survive their ICU stay. This term was first described in 2012 and is associated with cognitive impairment, altered ability to participate in activities of daily living, as well as mental health impairment.[18] This may persist for months to years after ICU discharge and is estimated to occur (in various degrees) in up to 60% of ICU survivors.[19] One innovation that has attempted to mitigate the effects of PICS is interdisciplinary clinic, often including a pharmacist, which helps to support ICU survivors, which includes identifying signs and symptoms of PICS. One study of pharmacist involvement in a PICS clinic found a median number of four interventions per patient, which included medication discontinuation in 39% of patients and the identification of adverse drug events in 16% of patients.[20] Pharmacist involvement in this arena can be another method to decrease patient morbidity associated with transitions of care.

PHARMACOKINETIC ALTERATIONS IN THE INTENSIVE CARE UNIT AND MANAGEMENT STRATEGIES

Pharmacokinetics in the Critically Ill

The dynamic nature of critical illness may cause drastic changes in the pharmacokinetic profile of many medications. Before describing these changes, it is important to first consider where the majority of available pharmacokinetic data are generated.

As a medication makes its way through the discovery process, pharmacokinetic data are obtained in phase I trials and in noncritically ill patients. Phase 1 trials in humans are most commonly done in healthy subjects in highly controlled environments. When pharmacokinetic data are obtained in phase II/III trials, critically ill patients are excluded. As a result, errors may arise in assuming that patients with the disease of interest and, more importantly, critically ill patients have similar pharmacokinetic parameters. Although available pharmacokinetic data should always be consulted in formulating a therapeutic regimen, the pharmacist should be attuned to the limitations inherent in the data.

CASE 56-3

QUESTION 1: J.K. is a 67-year-old male who presents to the ICU with a 3-day history of cough and shortness of breath. J.K. is diagnosed with severe sepsis owing to pneumonia and is intubated on admission to the ICU. J.K. is started on broad-spectrum IV antibiotics, including piperacillin–tazobactam and vancomycin. After receiving 6 L of lactated ringers, J.K. remains hypotensive, and a norepinephrine infusion is initiated to maintain his mean arterial pressure >65 mm Hg. J.K. is placed on enoxaparin 40 mg subcutaneously daily and pantoprazole IV daily for deep venous thromboembolism (DVT) and SUP, respectively. On day 3 of his ICU course, J.K. develops acute kidney injury (AKI) secondary to sepsis/hypoperfusion, with his SCr rising from a baseline of 1.1 to 3.4 mg/dL. J.K. has a nasogastric (NG) tube placed for enteral nutrition. On day 6 of his ICU stay, J.K. develops a severe *Clostridioides difficile* colitis for which oral vancomycin is initiated.

What are potential abnormalities of medication absorption in J.K.?

With the exception of IV administration, all medications must undergo absorption in order to reach the systemic circulation. Bioavailability (F) is defined as the percentage of the administered dose that reaches the systemic circulation.

Gut function may be altered in J.K. for a variety of reasons, including delayed gastric emptying, ischemic bowel, inflammation, and coadministration of interacting substances. Each of these issues may lead to significant delays and/or decreases in the amount of orally/enterally administered medication absorption.

Delayed gastric emptying is a common occurrence in the ICU patient population, occurring in 40% to 60% of patients.[21] It may be caused by many factors, including postoperative ileus, trauma, head injury, sepsis, burns, or opioid use.[22] Delayed gastric emptying would be evident in J.K. if he was manifesting high gastric residual volumes or enteral feeding intolerance. Because most medications are absorbed in the small intestine, delayed emptying would most likely affect the rate of absorption, slowing the onset of action of medications in J.K.

Ischemic bowel may also cause J.K. to have alterations in his ability to absorb oral/enteral medications depending on what portion and how much of the bowel is affected. In J.K., ischemic bowel may be caused by vasopressor use and/or the presence of a shock state. Because drug absorption occurs primarily in the small bowel, impaired blood flow to this area would be more likely to decrease the extent of absorption of medications.

Acute gut inflammation may increase the absorption of certain medications in J.K. With the development of severe clostridium colitis on day 6, J.K. may experience increased oral absorption of oral vancomycin. Under normal patient conditions, oral vancomycin is not orally absorbed because of the ionization and large size of the molecule. There have been several reports of therapeutic plasma levels of vancomycin being achieved with oral treatment of severe *C. difficile* infections.[23–26] The postulated mechanism is the severe

inflammation in the colon allowing for the passage of larger, charged molecules into the bloodstream.

Orally administered medications are not the only route that may have altered absorption in the ICU. Subcutaneous absorption has also been shown to be remarkably altered in ICU patients, particularly those on vasopressor therapy. It is postulated that vasopressor treatment causes a decrease in subcutaneous tissue perfusion, resulting in impaired absorption of subcutaneously administered medications. Studies have shown that patients on LMWH therapy also receiving vasoconstrictive agents have markedly reduced peak and total anti-Xa activity when compared to other hospitalized patients.[27–30]

Case 56-3, Question 2: How should absorption issues in J.K. be managed?

Generally speaking, when there is a question of gut function in the ICU, IV formulations are preferred when available. In cases where a given medication would produce an objective response (eg, antihypertensive, hypoglycemic agents), enteral therapy may be attempted to assess patients' response. The pharmacist should be attuned to the specific pharmacodynamic response of a given medication to assess therapeutic response with oral/enteral dosing.

In the case of J.K., consideration may be given to monitoring anti-factor Xa levels for enoxaparin, while he remains on vasopressor therapy. Trough levels of <0.1 IU/mL have been associated with increased risk of the development of DVT.[29] In addition, if J.K. is deemed suitable for enteral medication therapy, his proton-pump inhibitor (PPI) therapy could be changed to a dissolvable (solu-tab) formulation, which generally is preferred to crushing and dissolving oral tablets to prevent obstructing tubes and for ease of administration. Consideration could also be given to monitoring serum vancomycin concentrations more aggressively, because J.K. may be at risk for significant vancomycin absorption given his severe *C. difficile* infection while also receiving systemic vancomycin therapy.

Case 56-3, Question 3: What are the potential changes in the distribution of a medication in J.K.?

The distribution of a medication is defined briefly as where the drug goes once it is absorbed into the bloodstream. The extent of distribution of a medication is dependent on both physiochemical drug properties and patient-specific factors. The physiochemical properties of a drug that determine how extensively it distributes to tissues include lipophilicity and protein binding, with high lipophilicity leading to extensive tissue distribution, and lower protein binding contributing to more extensive distribution. Patient-specific factors that determine the distribution of a medication include weight, volume status, and vascular permeability.

J.K. has a multitude of factors that may affect the distribution of hydrophilic (ie, low volume of distribution) medications, including the presence of sepsis and large volume of crystalloid (eg, normal saline) administration. These conditions result in decreased plasma concentrations of hydrophilic medications, leading to potentially subtherapeutic concentrations.[31]

Patients who have sepsis may possess several factors that would lead to a decreased plasma concentration of hydrophilic medications, including the presence of capillary leak (ie, third spacing), causing intravascular fluid to distribute to tissues, the administration of large volumes of IV crystalloid medications, and reduced tissue perfusion. This is particularly well-documented with antibiotic therapy in this patient population. Most infections occur in the interstitial fluid of tissues; thus, interstitial antibiotic concentrations would be most relevant to determine efficacy. Studies have shown that the interstitial fluid concentration and subcutaneous concentration of antibiotics is 5 to 10 times lower and 1 to 5 times lower, respectively, in septic patients as compared to normal controls.[32]

Septic ICU patients may also have drastic changes in plasma protein (eg, albumin) concentration because of reduced liver production and third spacing of albumin into tissue sites. Low plasma

protein will cause an increase in the unbound fraction of drug, increasing distribution to tissues. Unfortunately, this increased distribution is more than offset by the increase in fluid concentration secondary to capillary leak and volume administration of the interstitial tissues, causing low concentrations of antibiotics in interstitial fluid.

Understanding that the distribution of hydrophilic antibiotics (piperacillin/tazobactam, vancomycin) is likely increased in J.K., several strategies can be employed to offset these changes. Interventions include giving more frequent doses or continuous infusions with β-lactam therapy and using large initial doses (30–40 mg/kg/day) of vancomycin in conjunction with targeting trough levels of 15 to 20 mg/L.[32]

CASE 56-3, QUESTION 4: What are the potential alterations in metabolism in J.K.?

Drug metabolism can occur in a variety of body tissues, including the kidneys, GI tract, lung, and liver. The liver is the predominant metabolizing organ and is the focus of this section. Patients in the ICU may have alterations in hepatic enzyme activity, liver blood flow, and protein binding, all of which may influence the rate at which hepatically metabolized medications are biotransformed.

Liver metabolism is broken into two major categories, phase I and phase II metabolism, both of which transform drugs into more polar substances that are more readily excreted. Phase I metabolism refers to the cytochrome P450 (CYP) enzyme system that works through oxidation, reduction, and hydrolysis. Phase II metabolism, in contrast, adds large polar molecules to the parent compound, including glucuronidation, sulfation, and acetylation.

There may be significant factors that alter phase I metabolism in J.K., including kidney injury, inflammation, and hypothermia.

Renal dysfunction can reduce phase I metabolism through reduced hepatic cell uptake of medications and reduced biliary excretion.[33,34] The inflammatory response secondary to trauma has

shown variable effects on enzymatic activity, with reduction in CYP3A4, CYP2C19, and CYP2E1 and with increased CYP2C9 activity.

Therapeutic hypothermia has been well-documented to reduce CYP activity across all isoenzyme families. This is especially well-documented with medications commonly given to ICU patients, including neuromuscular blockers, fentanyl, phenytoin, and midazolam. It is important to consider that enzyme activity recovers during the rewarming process, necessitating close monitoring and potential dose adjustment.[29]

Hepatic blood flow (ie, perfusion) may also be altered in J.K. Reductions in hepatic blood flow because of hypotension (eg, shock) or shunting (eg, cirrhosis) may have significant effects on prolonging the half-life of medications that are dependent on liver blood flow for metabolism. These medications are defined as having a high hepatic extraction ratio ($E > 0.7$) and would include medications such as midazolam and fentanyl.[22]

Protein-binding alterations may also occur in the critically ill and may subsequently affect the metabolism of select medications. Specifically, albumin concentrations may acutely decrease, thus increasing the free fraction of medications that are normally bound. This is especially relevant for medications that have high extraction ratios, as more medication would be available for removal, causing a net reduction in drug half-life.

Case 56-3, Question 5: How should metabolism issues be managed in J.K.?

To properly manage metabolism alterations in the ICU, the pharmacist should first be aware of the patient populations who are most likely to have altered metabolic rates/pathways, including renal dysfunction, burns, therapeutic hypothermia, and decreased hepatic perfusion. In addition to identifying at-risk patients, the pharmacist should be aware of those medications that are most likely to have altered metabolism. These would include medications metabolized through the CYP system as well as those with high extraction ratios

(E > 0.7). Increased vigilance in monitoring for therapeutic effect/toxicity with these medications in at-risk patients is warranted.[22,35]

CASE 56-3, QUESTION 6: How is elimination altered in J.K.?

Elimination is the process by which a drug or its metabolites are removed from the body. Although the kidney is the main organ that eliminates medications, it is important to remember that there are other organs (liver/lung) that also may contribute to elimination.[22] In addition, there exist several therapeutic interventions that occur in the ICU that also contribute to medication elimination, including continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO).[36]

Glomerular filtration is the primary method of renal clearance of medications, and renal drug removal is usually directly proportional to glomerular filtration rate (GFR). AKI is a common comorbidity in the ICU population, occurring in 1% to 25% of patients, leading directly to reduced medication elimination.[22] Other factors may increase the GFR in ICU patients, including trauma, burns, and use of vasopressors.

Renal function assessment is critical to appropriately dose adjusting renally eliminated medications and proves to be difficult, especially in the ICU population. The SCr measurement often lags behind actual GFR, because there exist changes in creatinine production and altered tubular secretion. In addition, most estimates of renal function, including the CG equation and the MDRD equation, were validated only in patients with stable renal function.[37,38] Attempting to apply these equations to a patient with fluctuating SCr measurements will result in inaccurate estimations of renal clearance.

In addition to renal function, there exist other modalities that contribute to drug elimination in specific ICU populations, including CRRT and ECMO. Although a detailed description of these processes is beyond the scope of this chapter, the clinician should

remember that both may remove medications in clinically relevant quantities.

It is also important that the pharmacist consider not only the elimination of the parent compound but also the presence of active/toxic metabolites that require renal elimination. Examples of medications with clinically significant toxic metabolites are nitroprusside and meperidine.[39,40] Renal dysfunction may lead to accumulation of toxic metabolites, causing patient harm. Common medications given in the ICU with active metabolites are midazolam and diazepam. These active metabolites may accumulate in renal insufficiency and cause exaggerated/prolonged sedation/delirium.[41,42]

CASE 56-3, QUESTION 7: How should elimination alterations be managed in J.K.?

Estimation of renal function is critical to appropriately dosing many medications in the ICU. As discussed earlier, using the usual process of calculating renal function is often inaccurate, and typical equations (eg, CG/MDRD) should only be used in patients with stable SCr values. In patients with unstable SCr values, consideration should be given to calculating creatinine clearance using a 24-hour urine collection. Other data points should also be considered when determining an appropriate dose in critical illness and include urine output, trends in SCr, and the specific medication to be dosed. For J.K., this would mean frequent monitoring of vancomycin serum concentrations, anti-Xa monitoring for enoxaparin, and daily assessment of SCr and urine output trends. In addition, medications with active metabolites requiring renal elimination (eg, midazolam) should be avoided if possible.

Pain, Agitation, and Delirium in the Intensive Care Unit

Pain, agitation, and delirium commonly occur in critically ill patients for a variety of reasons. Invasive interventions such as intubation and mechanical ventilation, acute and preexisting disease states, and surgery are just a few of the common causes of pain in critically ill patients.[43,44] Patients may become agitated and develop delirium because of untreated or inadequately treated pain or because of many other reasons, including substance use disorder or withdrawal, adverse effects of medications, sleep deprivation, and the impact of comorbidities or severe illness.[43,44] Pain, agitation, and delirium are interrelated, and it is often difficult to differentiate these conditions based on symptoms in patients who are severely ill and often unable to communicate. They require prompt and effective interventions because they can lead to patient discomfort, heightened sympathomimetic activity, and negative patient outcomes. Clinicians should judiciously balance management of pain, agitation, and delirium in an effort to keep patients lucid, calm, interactive, free of pain, and cooperative with their care.[45]

CASE 56-4

Question 1: J.A. is a 28-year-old male who presents to the ED after a severe motor vehicle accident. He presents with hemorrhagic shock, multiple rib and leg bone fractures, and a traumatic brain injury. He is immediately intubated and taken to the operating room for control of his bleeding and initial management of his fractures. His PMH is significant for opioid use disorder and bipolar disorder. After the operation, J.A. is transferred to the surgical ICU on mechanical ventilation with multiple chest tubes in place for management of injuries he sustained in the accident.

What causes of pain does J.A. have, and what complications might they cause?

Up to 77% of patients discharged from ICUs report experiencing moderate or severe pain during their ICU stay.[46,47] This pain occurs during rest and with activity and is the most common memory patients have of their ICU stays.[48] Pain may occur because of injuries or diseases, therapeutic interventions, routine ICU care, or monitoring. Common causes of pain are listed in **Table 56-1**.

Patients consistently report pain as the most traumatic memory from their ICU stay.[49] During the ICU stay, untreated pain can result in increased energy requirements, hyperglycemia, muscle breakdown, immunosuppression, increased risk of wound infection, decreased tissue perfusion, psychological distress, and impaired sleep. Long-term complications of untreated pain include chronic pain syndromes, neuropathy, posttraumatic stress disorder, and a decreased health-related quality of life.[50] In light of the acute and long-lasting consequences of pain as well as the prevalence of untreated pain in critically ill patients, it is important to diligently assess patients and utilize appropriate analgesics when indicated.

Table 56-1
Common Causes of Pain in Critically Ill Patients

Injuries and Diseases	Interventions and Monitoring	Routine Care
Trauma	Endotracheal intubation	Turning
Burns	Endotracheal tube for mechanical ventilation	Suctioning of respiratory secretions
Pancreatitis	Chest tube placement	Physical therapy
Necrotizing fasciitis	Wound care	
Decubitus ulcers	Surgery	
Immobility	Vascular access (arterial catheter)	
Preexisting disease states (eg, cancer, chronic back pain)		

In J.A., the potential causes of pain include trauma, postoperative pain, and the presence of an endotracheal tube and chest tubes. During his ICU stay, he may experience pain from routine care, including turning, suctioning of respiratory secretions, and, eventually, physical therapy.

Case 56-4, Question 2: How should J.A. be assessed for pain in the ICU?

Because patient-reported pain assessment is the optimal way to assess pain, whenever possible, clinicians should ask patients to rate their pain on a scale from 0 to 10, with 0 representing no pain and 10 representing the worst pain imaginable. For patients who cannot communicate with caregivers because of mechanical ventilation or other limitations, clinicians should assess patients' pain scores using validated nonverbal pain assessment tools that utilize patient behaviors as indicators of pain. The two nonverbal pain assessment tools recommended in guidelines are the Behavioral Pain Scale and the Critical-Care Pain Observation Tool.[43,44] The maximum score on each tool is 12 and 8, respectively, with higher values indicating more severe pain. Pain assessment should be protocolized such that it routinely occurs throughout each day of the patient's ICU stay. Clinicians should set the goal pain level and utilize analgesics as needed to maintain patients at the goal score while considering potential adverse effects. Generally, hemodynamic parameters such as blood pressure, HR, and respiratory rate should not be used to assess pain because they can be affected by other factors and do not correlate with self-reported pain; however, changes in vital signs may be used as a cue to further assess patients.[43,44]

Case 56-4, Question 3: How should clinicians manage pain in critically ill patients like J.A.?

Opioids are the primary analgesics used in the critical care setting. Fentanyl, hydromorphone, and morphine are used most commonly, whereas methadone is mainly used for long-term pain or pain that is refractory to other opioids. Because it is very short acting, very potent, and metabolized in the plasma, remifentanil is most appropriate for pain that lasts only a short period of time in patients who are mechanically ventilated and in those with severe renal or hepatic dysfunction. Meperidine should not be used because it may cause seizures and other complications.[50] For the treatment of acute pain, opioids should be given IV because enteral administration may

be unreliable in critically ill patients because of incomplete absorption in patients with altered GI motility and intramuscular absorption can be erratic. Enteral opioids, including methadone, may be utilized when transitioning patients off of long-term analgesic infusions or treating chronic pain as patients transition to less acute levels of care. In some cases, it may be impossible to completely alleviate pain because of dose-limiting side effects, such as respiratory depression or altered mental status. In these cases, clinicians should attempt to make patients as comfortable as possible without inducing significant adverse effects.

The selection of a specific opioid relates to the pharmacokinetics and pharmacodynamics of the medications and depends on patient-specific characteristics as well as the nature of the pain the patient is experiencing. **Table 56-2** lists key considerations for choosing between available opioids. When given as a single IV bolus injection, fentanyl has a faster onset and shorter duration of action compared to hydromorphone and morphine. This makes an IV injection of fentanyl most appropriate for pain that is short-lived such as procedural pain that might be associated with placement of a chest tube or IV catheter. In fact, procedural pain is best treated preemptively through administration of a bolus agent before the procedure.[43,44] The longer duration of action of hydromorphone and morphine makes these agents better when IV bolus treatment of longer lasting pain is indicated. Alternatively, fentanyl, hydromorphone, and morphine may all be administered as continuous IV infusions in patients needing ongoing analgesia or in those with severe pain.

Table 56-2
Selected Characteristics of Opioids Used in Critically Ill Patients

	Onset	Duration (IV Bolus Dose)	Active Metabolite	Adverse Effects and Other Considerations	Equipotent IV Dose (mg)
Morphine	5–10 minutes	2–4 hours	Yes (cleared renally)	Histamine release (hypotension, bronchospasm, flushing)	10
Hydromorphone	5–15 minutes	2–4 hours	No		1.5
Fentanyl	1–2 minutes	30–60 minutes	No	Accumulates in adipose tissue with prolonged infusion	0.1

IV, intravenous.

All opioids can cause constipation, confusion, hallucinations, altered mental status, and respiratory depression when given in high doses. Clinicians should regularly monitor the bowel movements of patients receiving opioid analgesia and a bowel regimen containing both a stimulant laxative and a stool softener should be administered, if indicated. Opioids may cause a decrease in blood pressure if the patient's blood pressure is increased because of pain and in patients who are hypovolemic. Importantly, morphine is the most likely opioid to cause histamine release, which can lead to flushing, bronchospasm, and hypotension. These complications underlie the recommendation to avoid morphine in patients who are hemodynamically unstable, at risk for hypotension, or those with bronchospasm. Morphine is metabolized to an active metabolite that is cleared by the kidneys, whereas fentanyl and hydromorphone are metabolized in the liver to inactive metabolites. Thus, hydromorphone and fentanyl are preferred to morphine in patients with renal disease or injury. Another unique side effect relates to QTc prolongation resulting from methadone. Because QTc prolongation can potentially cause cardiac arrest, electrocardiograms should be regularly monitored in patients receiving methadone, especially when patients are concurrently receiving other QTc-prolonging agents. Serum concentrations of magnesium and potassium should be monitored, and these electrolytes should be repleted, as needed, to minimize arrhythmias. Because fentanyl is the most lipophilic of the most commonly used opioid analgesics, prolonged administration via IV infusion may lead to formation of a depot in adipose tissue. After cessation of the fentanyl infusion, the drug may distribute from the fat into the bloodstream and prolong the effects of drug.

In addition to opioids, clinicians may consider adjunctive analgesics in selected patients. For example, NSAIDs and acetaminophen may be considered to minimize overall opioid requirements and potentially reduce opioid-related complications. For patients experiencing neuropathic pain, enterally administered gabapentin, carbamazepine, and SNRIs can be helpful. For patients with rib fractures or those who have undergone thoracic or

abdominal surgery, thoracic epidural analgesia results in better pain control as compared to opioid monotherapy.[57] Select nonpharmacologic strategies such as music therapy and massage may help with pain in some patients.[43,44]

Because J.A. is likely to experience ongoing pain as a result of his trauma, multiple fractures, and surgery, he should be initiated on opioid analgesia. If he remains hypotensive, at risk for hemodynamic compromise, or is in renal failure, morphine should be avoided. Some centers would routinely use fentanyl or hydromorphone in most patients to minimize hemodynamic complications. It would be most appropriate to administer fentanyl as a continuous infusion, whereas hydromorphone could be given continuously or as repeated IV boluses. Because of his rib fractures, J.A. could also be considered for thoracic epidural analgesia with an opioid.

CASE 56-5

QUESTION 1: During his stay in the surgical ICU, J.A. begins to exhibit signs of agitation, including diaphoresis, tachycardia, pulling at his endotracheal tube, and even trying to strike his caregivers.

What are some causes of agitation that J.A. might be experiencing, and how should he be initially treated?

Agitation is very common in critically ill patients and can lead to adverse consequences arising from sympathomimetic effects.[51] Patient care can be complicated if agitation leads to patient removal of devices, such as endotracheal tubes or IV lines, necessary for their care. Patients may exhibit symptoms of agitation for a variety of reasons, including pain, delirium, hypoxemia, hypoglycemia, hypotension, or withdrawal from alcohol and other drugs. Given the ubiquity of pain in critically ill patients and the difficulty in assessing patients who cannot communicate, clinicians should always consider pain as a potential cause of agitation and administer analgesics when they suspect pain. In fact, current guidelines recommend analgesia-first sedation strategies that emphasize adequate use of analgesics before administration of sedative agents.[43,44] Other

general strategies to treat anxiety and agitation in critically ill patients include keeping patients as comfortable as possible, reorienting patients if they misperceive their surroundings or situations, and promoting a normal sleep–wake cycle by helping patients to stay awake during the day and minimizing barriers to sleep overnight. Whenever possible, clinicians should attempt to identify and treat the underlying cause of agitation before initiating a sedative agent. For instance, if an agitated patient is found to be hypoglycemic, the hypoglycemia should be corrected, and the patient should be reevaluated before starting a sedative. By identifying and addressing the cause of agitation, clinicians can avoid complications associated with sedative medications, such as oversedation and delirium.[43,44]

Clinicians should assess critically ill patients who are agitated using a validated sedation assessment tool.[43,44] The two most rigorously evaluated tools are the Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS). Both tools effectively discriminate the level of sedation, have high inter-rater reliability, and have been shown to correlate reasonably well with objective measures of brain function.[52–54] Score on the RASS ranges from −5 to +4, whereas the SAS score varies from 1 to 7. The lowest number of the scales indicates a patient is unarousable, whereas the highest number on the RASS and SAS corresponds to combativeness and dangerous agitation, respectively. By quantifying patients' level of sedation using one of these tools, multidisciplinary caregivers can determine the desired level of consciousness and appropriately administer medications to target this level of consciousness while avoiding excessive sedation. Generally, sedatives should be titrated to achieve light levels of sedation, which correspond to RASS scores of −1 to 0 and SAS scores of 3 to 4.[43,44] Maintaining patients at light levels of sedation instead of deeper levels of sedation, in which they are more difficult to arouse and are less interactive, has been shown to reduce duration of mechanical ventilation and ICU length of stay.[55,56] Sometimes, patients' clinical conditions may necessitate deeper levels of sedation. Some clinical situations in which deeper sedation may be appropriate include active severe alcohol withdrawal, refractory status epilepticus,

intracranial hypertension, ventilator dyssynchrony, severe acute respiratory distress syndrome, or paralysis with neuromuscular receptor blocking agents.

J.A. may be agitated because of pain from his traumatic injuries as well as metabolic disturbances or other causes. His level of consciousness should be evaluated using the RASS or the SAS. Because he is intubated, J.A. should be assessed for pain using a validated nonverbal pain assessment tool, and his pain should be treated if indicated. His vital signs should be evaluated to identify hypotension or hypoxia, and his blood glucose concentration should be measured. Abnormalities in these values should be corrected as needed. Clinicians should review J.A.'s PMH, social history, and home medication list to identify any potential that he might be experiencing withdrawal from alcohol, illicit substances, or prescribed medications that he was taking before hospital admission, such as benzodiazepines or opioids. If he is unaware of his surroundings or current condition, J.A. should be reoriented. His sleep pattern should be addressed. Finally, the patient's current medication list should be reviewed for medications, such as steroids and anticholinergic drugs, that might cause behavioral changes, and these medications should be discontinued if identified. Only after thoroughly assessing the patient for potentially reversible causes of agitation, should the health care team consider initiating a sedative medication with the goal of achieving a light level of sedation in J.A.

CASE 56-5, QUESTION 2: If J.A. requires sedation, which medication would be preferred?

Several agents, including propofol, dexmedetomidine, and benzodiazepines, can be used to treat agitation in critically ill patients. No one sedative is best for all patients. Although benzodiazepines have been widely used over time, propofol and dexmedetomidine are currently preferred in most patients because they may result in decreased ICU length of stay and duration of mechanical ventilation as compared to benzodiazepines.[43,44,57–59]

End points about the optimal sedative agent for individual patients depend on the reason for sedation and sedation goals, expected duration of sedation, pharmacology of the medication in the specific patient, and cost-effectiveness.[43,44] A summary of key clinical considerations relative to commonly used sedatives is provided in **Table 56-3**.

Table 56-3
Clinical Considerations With Sedative Agents

	Receptor-Binding Site	Onset (minutes)	Effect of Renal Failure	Effect of Hepatic Failure
Midazolam	$GABA_A$	2–5	Effect prolonged owing to accumulation of parent drug and active metabolite	Effect prolonged
Lorazepam	$GABA_A$	15–20	Accumulation of propylene glycol	Effect prolonged
Propofol	$GABA_A$, nicotinic, glycine, muscarinic	1–2	No clinically significant effect	No clinically significant effect
Dexmedetomidine	Central α-2	5–10	No clinically significant effect	Effect may be prolonged in severe hepatic failure

Propofol is a highly lipophilic sedative that binds to multiple receptors and exerts sedative, hypnotic, anxiolytic, antiemetic, and anticonvulsant properties. Because of its high lipophilicity and formulation in a 10% lipid emulsion, propofol readily crosses the blood–brain barrier and demonstrates a rapid onset of effect and quick offset after short-term use. However, patient awakening after prolonged use can be variable because of its deposition in adipose tissues.[60] Propofol can be rapidly titrated in order to achieve the desired level of sedation. It is suited for regular awakenings that are required for neurologic examinations in patients with brain injuries, and it facilitates daily awakening as part of sedative and ventilator weaning protocols.[59,61] Adverse effects of propofol include respiratory depression, hypotension resulting from vasodilation, bradycardia, hypertriglyceridemia, pancreatitis, myoclonus, and green or white discoloration of the urine.[62,63] Because of the dose-dependent suppression of respiratory drive, continuous infusions of propofol should only be administered to patients who are mechanically ventilated. Patients should be regularly monitored for hypertriglyceridemia when receiving propofol over the course of several days, and the drug should be stopped or weaned if significant hypertriglyceridemia develops. Patients with allergies to

eggs, soybeans, and sulfites may experience allergic reactions because of components of the lipid emulsion and some generic formulations.[64] In order to reduce burning and stinging associated with administration, propofol should be administered through large-bore IV lines whenever possible. Although propofol is formulated with a preservative to prevent bacterial growth, product labeling suggests the bottles and tubing should be changed every 12 hours, and line integrity should be assessed to prevent bacterial contamination. The caloric load of the lipid vehicle should be considered when evaluating nutritional needs in patients receiving propofol.

Propofol may cause a life-threatening syndrome called propofol infusion syndrome (PRIS) in about 1% of patients. PRIS is characterized by metabolic acidosis, hypertriglyceridemia, progressive hypotension, bradyarrhythmias, and cardiovascular collapse. Other complications of PRIS may include AKI, hyperkalemia, rhabdomyolysis, and liver failure.[65,66] PRIS has been observed most commonly at doses exceeding 70 μg/kg/minute and with use beyond 48 hours, but it has been reported at lower infusion rates and with shorter infusions.[67,68] Because PRIS can be difficult to distinguish from other conditions in critically ill patients and because of its high mortality rate, members of the health care team should diligently monitor patients in order to rapidly identify PRIS. When PRIS is suspected, propofol should be discontinued and patients should receive appropriate supportive care.[43,44]

Dexmedetomidine is a centrally acting α-receptor agonist that is similar to clonidine. It demonstrates greater anxiolytic and fewer sympatholytic properties as compared to clonidine. In addition to anxiolysis, dexmedetomidine also has sedative and opioid-sparing effects. It does not have anticonvulsive characteristics, induce amnesia, or cause respiratory depression.[43,44] Dexmedetomidine often allows patients to awaken more easily and better interact with caregivers as compared to propofol and benzodiazepines, but it is not appropriate for patients requiring deeper levels of sedation and those paralyzed with neuromuscular receptor antagonists.[69] Dexmedetomidine starts working within ~15 minutes after the

initiation of an infusion and reaches its peak effect at 1 hour.[70,71] Clinicians may administer a bolus to achieve faster onset, but bolus administration is associated with increased risk of hemodynamic instability, which can manifest as either hypertension or hypotension and bradycardia.[72] Additional adverse effects include nausea, atrial fibrillation, and, rarely, cardiogenic shock.[73] In the United States, dexmedetomidine is approved for use as a continuous infusion at doses up to 0.7 μg/kg/hour for a maximum of 24 hours, but clinical trials have demonstrated safety and effectiveness at doses up to 1.5 μg/kg/hour for as many as 28 days.[74–76] Doses may be titrated every 30 minutes. Patients with severe hepatic disease may require lower doses of dexmedetomidine to avoid prolonged offset of effect and excessive hemodynamic effects. Dexmedetomidine-induced hypotension and bradycardia may occur more commonly in patients who are hypovolemic or in those who have cardiovascular instability.[77] Importantly, because dexmedetomidine does not cause respiratory depression, it can be continued during and after extubation, unlike propofol.[77,78] When continuing dexmedetomidine in this manner, clinicians should be aware that it may cause loss of oropharyngeal muscle tone, resulting in airway obstruction. Consequently, patients getting dexmedetomidine without mechanical ventilation must receive continuous respiratory monitoring.

Benzodiazepines are γ-aminobutyric acid (GABA) receptor agonists that demonstrate anxiolytic, sedative, hypnotic, and anticonvulsant effects.[79] Current guidelines no longer recommend the use of benzodiazepines as the first-line sedatives in most critically ill patients, although they remain the mainstay of therapy for the management of alcohol withdrawal.[43,44] Benzodiazepines can potentiate respiratory failure and hypotension, especially when coadministered with opioids.[41] They can also cause mental status changes and are risk factors for the development of delirium.[76,80,81] Patients may occasionally experience a paradoxical reaction involving agitation and restlessness. Elderly patients are more likely to experience adverse effects, whereas patients taking benzodiazepines before hospitalization and those on them for long periods of time may demonstrate decreased sensitivity. Usually,

benzodiazepines are administered parenterally in the critical care setting, and the most commonly used agents are lorazepam and midazolam. Either lorazepam or midazolam may be given via intermittent or continuous IV infusion, but the two drugs have key differences relative to their pharmacokinetic, pharmacodynamic, and adverse effect profiles. Because it is more lipophilic, midazolam has a faster onset and shorter duration of action than lorazepam. However, because midazolam deposits in the adipose tissue, it can lead to variable and prolonged awakening when it is administered continuously over the course of several days.[82] Midazolam undergoes hepatic metabolism to an active metabolite, which is eliminated renally, whereas lorazepam is inactivated in the liver. Both agents should be used cautiously in renal and hepatic dysfunction because end-organ impairment prolongs the elimination half-life of both drugs. Lorazepam is formulated in a propylene glycol vehicle, which can accumulate at doses as low as 1 mg/kg/day and cause metabolic acidosis and AKI.[83,84] When benzodiazepines must be used, clinicians should carefully manage the dosing regimen to target the desired level of sedation at the lowest dose possible. Avoiding continuous infusions of benzodiazepines in favor of as-needed bolus doses based on symptoms of agitation may result in decreased total benzodiazepine exposure and a lower chance of benzodiazepine-related complications.

After thoroughly assessing J.A. and addressing reversible causes of agitation such as metabolic disorders and withdrawal syndromes, sedation with propofol should be considered if he remains agitated and his hemodynamics are adequate. Both propofol and dexmedetomidine are suggested the first-line sedatives according to current guidelines. However, because J.A. may require frequent awakenings for neurologic examinations, the faster offset of effect with propofol may make it more appropriate. J.A.’s blood pressure and HR should be monitored when propofol is started, and it should be titrated to a light level of sedation based on the RASS or the SAS. His triglyceride concentrations should be evaluated periodically if propofol is administered for several days, and clinicians should be

aware of the symptoms of PRIS in order to identify any potential episodes as soon as possible.

CASE 56-6

QUESTION 1: After receiving care in the ICU and remaining intubated and lightly sedated for several days, J.A.'s sedation is lightened, but he does not seem to be himself. He alternates between unresponsiveness and agitation. He is unable to tell caregivers where he is or answer simple questions.

Could J.A. be experiencing delirium?

Delirium is a symptom of acute brain dysfunction that involves the following combination of symptoms: acute change or fluctuation from baseline mental status, inattention, and disorganized thinking or altered level of consciousness.[85,86] Patients who are delirious may experience hallucinations, delusions, or hyperactivity, but these symptoms are not present in all delirious patients. In fact, three different forms of ICU delirium have been described based on the symptoms that patients demonstrate. In hyperactive delirium, patients are agitated, whereas in hypoactive delirium, they are calm or lethargic. Patients with mixed delirium fluctuate between these two subtypes.[43,44]

Delirium occurs at least once during the ICU stay in up to 80% of critically ill patients and is associated with negative patient outcomes, including increased mortality, ICU and hospital length of stay, long-term cognitive impairment, and health care costs.[87–90] Clinicians are more likely to fail to identify delirium if patients manifest hypoactive delirium rather than hyperactive delirium.[91] In order to identify patients who have delirium, current guidelines recommend that clinicians routinely assess patients several times each day using a validated delirium assessment tool.[43,44] The two recommended tools for assessing delirium are the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC).

Based on his symptoms, J.A. is likely experiencing delirium. It is clear that his mental status has changed from baseline as "he does

not seem to be himself." In addition, the fluctuation between unresponsiveness and agitation combined with the inattention and disorganized thinking he is exhibiting by not being able to answer simple questions fulfill the other criteria of delirium. Clinicians should formally evaluate J.A. for delirium using a validated tool, such as the CAM-ICU or the ICDSC.

Case 56-6, Question 2: How should clinicians work to prevent and treat delirium in critically ill patients like J.A.?

There are a variety of modifiable and nonmodifiable risk factors associated with the development of delirium in critically ill patients.[43,44] Nonmodifiable risk factors include baseline dementia, hypertension, alcoholism, and greater severity of illness.[43,44,81,92] Current evidence suggests that benzodiazepine exposure, very deep sedation, and anticholinergic medications may increase the risk that patients develop delirium. Any association between opioids and propofol and delirium is unclear because of conflicting and limited evidence, respectively.

Evidence suggests delirium may be prevented with early mobilization protocols, in which nurses, physical therapists, and other clinicians assist critically ill patients in getting out of bed and ambulating. Studies of these protocols have demonstrated that they are safe and associated with significant reductions in delirium, hospital and ICU length of stay, and duration of mechanical ventilation when used in critically ill patients.[93,94] No pharmacologic therapy has been shown to prevent delirium in heterogeneous groups of critically ill patients.[43,44]

Although haloperidol and atypical antipsychotics have been used historically to treat delirium in critically ill patients, there is an absence of high-quality published literature in broad groups of critically ill patients supporting their effectiveness. Studies suggest these agents may not affect the duration of delirium in ICU patients.[95] Consequently, current guidelines recommend not using these agents for the treatment of delirium. Evidence suggests that using

dexmedetomidine instead of a benzodiazepine for the management of agitation may result in less delirium.[74,76,96]

Delirium can be prevented in patients like J.A. through the use of early mobilization protocols and minimizing risk factors for delirium, such as benzodiazepines. No pharmacologic strategy has been demonstrated to reduce delirium.

Stress Ulcer Prophylaxis in the Intensive Care Unit

The development of stress ulcers in critically ill patients is a common complication of ICU patients. Stress ulcers from critical illness began to be recognized in the 1960s when one study found that 5% of consecutive ICU patients had massive bleeding resulting from stress ulcers.[97] Stress ulcers usually develop in the mucosal layer of the stomach after high-stress events and can result in ulceration and progression to clinically significant bleeding.[98] Historically, up to 15% of patients in the ICU will develop an overt GI bleed if not given SUP, which makes it a preventable complication of critical illness.[99] However, more data indicate that this incidence is <5%.[100] Despite there being a large volume of research in this area, there lacks a consensus on the management and prevention of stress ulcers.

Patients with serious illness or trauma can develop stress ulceration within hours of the inciting event. There are various degrees of stress ulceration, and they can develop from hours to weeks after hospital admission. Critical illness often leads to increased vasoconstriction, decreased cardiac output, and a pro-inflammatory state, which leads to splanchnic hypoperfusion.[101] The cause of stress ulceration in the ICU evolves from several factors, including gastric acid secretion, mucosal ischemia, and upper intestinal reflux. This leads to the lack of perfusion and oxygen delivery to intestinal cells, resulting in mucosal damage.

CASE 56-7

Question 1: A.K. is a 76-year-old male admitted to the medical ICU for likely sepsis from a urinary source. He was acidotic on arrival to the ED and intubated. He has a PMH of hypertension, diabetes, pulmonary embolism, several urinary tract infections, and reports drinking 10 to 12 beers/day. His home medications include atorvastatin 20 mg by mouth daily, lisinopril 20 mg by mouth daily, metoprolol XL 100 mg by mouth daily, metformin 1000 mg by mouth twice daily, and warfarin 7.5 mg by mouth daily. Labs on arrival are Na 131 mEq/L, K 3.2 mEq/L, blood urea nitrogen (BUN) 33 mg/dL, SCr 2.7 mg/dL, Hct 20%, platelet count (Plt) 47 × 10^3/μL, and INR 5.9.

What risk factors does A.K. have that would qualify him for SUP?

Several risk factors have been identified to help determine who should get SUP. One study[102] investigated 2252 ICU patients and found that there were two major risk factors for clinically important GI bleeding: (a) mechanical ventilation for >48 hours (OR 15.6) and (b) coagulopathy (OR 4.3) defined as a Plt of <50,000 mm^3, an INR of >1.5, or a partial thromboplastin time of more than two times the control value.[96] Other risk factors that have been identified include head injury, burn involving >35% of body surface area, partial hepatectomy, hepatic or renal transplantation, multiple trauma with Injury Severity Score of >16, spinal cord injury, hepatic failure, history of gastric ulceration or bleeding during year before admission, and two or more of the following: sepsis, length of ICU stay >1 week, occult bleeding for at least 6 days, and administration of high-dose corticosteroids (>250 mg/day of hydrocortisone or equivalent).[97] Most clinicians will start SUP in patients who have one or more major risk factor. However, the utility of SUP in the ICU is controversial, given inconsistent demonstration of benefit. One clinical trial comparing pantoprazole to placebo found no difference in 90-day mortality (RR 1.02, 95% CI 0.91–1.13), although pantoprazole was associated with a decreased risk of clinically important GI bleeding (RR 0.58, 95% CI 0.40–0.86).[100] The guidelines for SUP are expected to be updated in the next few years, given the recent advances in this field.[103] For patients who have multiple minor risk factors or patient groups excluded from major trials (eg, spinal cord injury, traumatic brain injury, or thermal injury), SUP is determined by the primary team on a case-by-case basis.

A.K. has a major risk factor in that he is likely to be intubated for at least 48 hours. For this reason, he should be started on SUP.

Case 56-7, Question 2: What medication could be initiated in A.K. to reduce his chance of developing a stress ulcer?

The mechanisms to pharmacologically prevent against stress ulcers are to layer the gastric lining with a protective coating, lowering the gastric pH by neutralizing gastric acid secretions, or by preventing gastric acid secretion. The three classes of medications used for SUP are histamine 2-receptor antagonists (H_2 blockers), PPIs, and protective barrier-producing medications. A fourth class of medication, prostaglandin analogs, has been used for SUP in the past, but it has not been shown to be beneficial and is not discussed in this chapter.[104]

After deciding to start SUP, the next decision to make is what agent to use. The two most commonly used classes of medications are H_2 blockers and PPIs. H_2 blockers were found to be superior to antacids and sucralfate in two different trials.[105,106] There has been an increasing amount of research comparing PPIs to H_2 blockers, but there still lacks a consensus on what agent to use based on conflicting data. One randomized trial comparing H_2 blockers to PPIs in ICU patients requiring mechanical ventilation found no difference in in-hospital mortality (RR 1.05, 95% CI 1.0–1.1; *P* = .054). However, there was a decrease in clinically important upper GI bleeding with PPI use (RR 0.73, 95% CI 0.57–0.92). One of the primary study limitations was that 20% of patients randomized to H_2 blockers received a PPI at some point during their ICU stay.[107] A cohort study of over 35,000 ICU patients showed H_2 blockers had a lower risk of GI hemorrhage compared to PPIs (6% vs 2%; adjusted OR, 2.24; 95% CI, 1.81–2.76).[108] This differed with a previous meta-analysis of 13 randomized trials showing reduced GI bleeding in the PPI prophylaxis group compared to the H_2 blocker group (1.3% vs 6.6%; OR, 0.30; 95% CI, 0.17–0.54).[109] The most recent meta-

analysis on this topic, evaluating 74 trials and over 39,000 patients, found that there was no difference between PPIs and H_2 blockers on mortality (RR 1.05, 95% CI 0.97–1.14), although PPIs may be associated with a lower rate of clinically important GI bleeding (RR 0.69, 95% CI 0.45–0.93).[110] Common agents used for SUP are provided in **Table 56-4**.

Table 56-4

Common Agents Used for Stress Ulcer Prophylaxis

Agent	Trade Name	Adult Dosing	Routes	Generic Available
Proton-Pump Inhibitors				
Dexlansoprazole[a,b]	Dexilant®	30 or 60 mg once daily	Oral	Yes
Esomeprazole[a,b]	Nexium®	20–40 mg once daily ≥1 hour before a meal	Oral, IV	Yes
Lansoprazole[a,b]	Prevacid®	15 or 30 mg once daily before a meal	Oral	Yes
Omeprazole[a,b]	Prilosec®	20 or 40 mg once daily on an empty stomach ≥1 hour before a meal	Oral, IV	Yes
Pantoprazole[a,b]	Protonix®	40 mg once daily (administer suspension 30 minutes before a meal)	Oral, IV	Yes
Rabeprazole[a,b]	Aciphex®	20–60 mg once daily (administer capsule 30 minutes before a meal; if capsule is opened and dispersed on food, administer within 15 minutes of preparation)	Oral	Yes
Histamine H_2 Antagonists				
Famotidine[a,b]	Pepcid®	20 mg twice daily (20 mg daily for CrCl <30 mL/minute)	Oral, IV	Yes
Ranitidine[a–c]	Zantac®	150 mg twice daily (150 mg once daily if CrCl <50 mL/minute)	Oral, IV	Yes
Gastric-Coating Agents				
Sucralfate[a,b]	Carafate®	1 g four times daily	Oral	Yes

CrCl, creatinine clearance; FDA, Food and Drug Administration; IV, intravenous.

[a]Off-label indication for stress ulcer prophylaxis.

[b]Able to administer oral formulation via feeding tube, dependent on formulations available.

[c]Currently not available via oral route owing to recall by FDA owing to contaminant.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

An area of debate is whether a patient who is receiving full caloric supplementation through tube feeds requires pharmacologic SUP. Enteral nutrition has been shown to increase gastric pH to >3.5 more often than H_2 blockers or PPIs.[111] Animal models have shown a protective benefit of alimentation on the gastric mucosa from stress-related damage. The practice of whether to discontinue

pharmacologic SUP if enteral nutrition has been started varies among different institutions.

CASE 56-7, QUESTION 3: Are there any adverse effects associated with placing A.K. on SUP?

Although pharmacologic SUP has shown to decrease bleeding events, it appears this does not come without risk. Gastric acid plays an important part in sterilizing the upper GI tract, and alterations of physiologic pH have shown adverse effects. The higher pH level allows increased colonization of potentially pathogenic bacteria in the GI tract.

After the implementation of SUP as a standard of care in ICUs, several studies and meta-analyses identified an increased risk of nosocomial pneumonia and *C. difficile* infections in patients receiving H_2 blockers or PPIs. The increased pH levels as a result of these medications have been proposed as a mechanism of action. Available data are conflicting on the incidence of nosocomial pneumonia among the agents that alter gastric pH. Two studies showed an increased risk for H_2 blockers compared to those who did not receive acid-suppressive therapy or sucralfate.[106,112] One meta-analysis showed no difference on the incidence of nosocomial pneumonia when comparing PPIs to H_2 blockers.[109] Data have also shown that PPIs had a higher incidence of pneumonia compared to H_2 blockers.[108] Both PPIs and H_2 blockers have been associated with an increased risk of *C. difficile* infection.[113] Most of these studies are observational and did not control for comorbidities, so there is still much debate in the critical care community.

Although sucralfate does not alter gastric pH, it can interfere with the absorption of many medications, including ciprofloxacin, phenytoin, digoxin, and levothyroxine. To help prevent this, sucralfate should be given 2 hours after these medications. Sucralfate has been shown to bind to tube feeds and cause bezoars (solid mass within GI tract) and cannot be given through duodenal or jejunostomy feeding tubes. In addition, sucralfate is an aluminum

salt, which increases the risk of aluminum toxicity (eg, altered mental status, seizure) with prolonged use in patients with renal dysfunction. There are several options of SUP for A.K. A PPI or H_2 blocker would be the best choice. Because he is intubated and does not have a feeding tube yet, an IV H_2 blocker such as famotidine (renally dosed) or IV PPI such as pantoprazole would be appropriate.

Glycemic Control in Intensive Care Unit Patients

Critically ill patients may develop hyperglycemia for a variety of reasons, including acute illness, preexisting disease states, and the effects of medications. Glycemic goals and treatments differ for patients managed in the ICU as compared to those treated in other settings, including patients receiving chronic therapy for diabetes as outpatients.

CASE 56-8

QUESTION 1: D.M. is a 74-year-old female admitted to the medical ICU for pneumonia and a chronic obstructive pulmonary disease (COPD) exacerbation. Her PMH includes hypertension, hyperlipidemia, and COPD. On the first day of her ICU stay, she decompensates and develops respiratory failure requiring intubation. Among other laboratory abnormalities, her blood glucose concentration is 212 mg/dL.

How should clinicians manage D.M.'s hyperglycemia?

A variety of biochemical mediators, such as cortisol, glucagon, catecholamines, and growth factor, may rise in critical illness and contribute to hyperglycemia by increasing glycogenolysis and decreasing gluconeogenesis.[114] In addition to the effects of critical illness, inadequately treated diabetes, adverse effects of drugs like corticosteroids, and exposure to caloric loads from nutritional regimens or dextrose used as a base for IV solutions can contribute to hyperglycemia. Although studies suggest that hyperglycemia of critical illness is associated with poor outcomes, it is not clear whether hyperglycemia leads to worsened outcomes or if it is simply

an indicator of disease severity.[115–117] In addition to the magnitude of hyperglycemia, glycemic variability has also been associated with negative outcomes.[118]

The optimal blood glucose range for critically ill patients has not been definitely established.[119] Uncontrolled hyperglycemia has the potential to cause severe effects. Single-center studies of surgical and medical ICU patients treated with intensive insulin therapy to achieve blood glucose concentrations between 80 and 110 mg/dL initially suggested improved outcomes, but these findings were not replicated in subsequent trials.[120,121] In fact, some studies suggest aggressive insulin therapy may increase mortality as compared to liberal blood glucose control typically targeting 140 to 180 mg/dL.[122–126] It has been suggested that the higher rates of hypoglycemia observed in patients receiving intensive insulin may increase mortality by leading to neurologic complications. On the basis of these findings, the American Diabetes Association recommends that insulin is administered to ICU patients when blood glucose concentrations exceed 180 mg/dL, and it is used to maintain blood glucose concentrations between 140 and 180 mg/dL. In some critically ill patients, such as postsurgical patients and those who have had cardiac surgery, targeting blood glucose ranging between 110 and 140 mg/dL may be appropriate if this practice does not result in significant hypoglycemia. Because parenteral administration of insulin achieves more rapid and reliable results than oral therapy, patients are typically managed with subcutaneous insulin or IV insulin infusions while in the ICU. Subcutaneous regimens typically include as-needed sliding scale insulin involving rapid- or short-acting formulations. Scheduled long-acting insulin may be combined with sliding scales in some patients; however, clinicians should cautiously dose insulin in order to avoid hypoglycemia. Some patients with significant insulin needs may benefit from a continuous IV infusion of regular insulin that is carefully titrated to the blood glucose goal.

Because D.M.’s blood glucose exceeds 180 mg/dL, clinicians should attempt to achieve better glycemic control. First, dextrose-containing fluids should be minimized, and any enteral nutrition she

is receiving should be evaluated. Medications, like steroids, that might increase her blood glucose concentrations should be assessed and minimized as possible. If her blood glucose remains high after these measures, it would be appropriate to initially consider sliding scale insulin with regular insulin.

INTERPROFESSIONAL CARE

Interprofessional care is a unique and critical aspect to patient care in the ICU, supported by the Society of Critical Care Medicine guidelines in 2003.[127] The role of the pharmacist in the ICU care team was most recently supported by a position paper in 2020.[128] Throughout the practice experiences that pharmacy trainees have, they may encounter multiple professions they may not have collaborated with before that experience. It is through this teamwork that the patient has optimal outcomes, given the shared expertise of each clinician. Examples of clinician roles, responsibilities, and potential learning points are detailed in **Table 56-5**.

Table 56-5
Examples of Clinician Roles, Responsibilities, and Learning Points in the ICU

Clinician	Roles and Responsibilities	Learning Points
Nurse	▪ Medication administration ▪ Patient monitoring	▪ Types of lines and tubes ▪ Technology (eg, intravenous infusion pumps)
Nutritionist	▪ Development of enteral and parenteral nutrition plans	▪ Patient nutrition goals ▪ Development of total parenteral nutrition
Pharmacist	▪ Drug information ▪ Order verification ▪ Medication safety	▪ Interpretation of published literature ▪ Development of medication guidelines

Clinician	Roles and Responsibilities	Learning Points
Physical therapist	▪ Development of mobility ▪ Rehabilitation	▪ Effect of medications on mobility
Provider[a]	▪ Diagnosis ▪ Orders (eg, imaging, labs, medications)	▪ Diagnostic procedure interpretation (eg, cardiac rhythm, imaging)
Respiratory therapist	▪ Administration of inhaled medications ▪ Management of respiratory devices (eg, mechanical ventilation)	▪ Inhaled medication logistics ▪ Mechanical ventilation settings

[a]Includes nurse practitioners, physicians, and physician assistants.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. *Am J Health Syst Pharm.* 1999;56(4):347–379. (103)

Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam J-J, Jaber S. A prospective study of pain at rest: incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients. *Anesthesiology.* 2007;107(*5*):858–860. (45)

Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825–e873. (43)

Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and

Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence- Based Clinical Practice Guidelines. *Chest.* 2012;141*(2 suppl*):7S–47S. (6)

Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest.* 2012;141(5): 1327–1336. (22)

Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. *Crit Care Clin.* 2011;27(1):19–34. (32)

COMPLETE REFERENCES CHAPTER 56 CARE OF THE CRITICALLY ILL ADULT

1. Bluml BM. Definition of medication therapy management: development of professionwide consensus. *J Am Pharm Assoc* (2003). 2005;45(5):566–572.
2. Murphy EM, Oxencis CJ, Klauck JA, Meyer DA, Zimmerman JM. Medication reconciliation at an academic medical center: implementation of a comprehensive program from admission to discharge. *Am J Health Syst Pharm*. 2009;66(23):2126–2131.
3. Vincent JL. Give your patient a fast hug (at least) once a day. *Crit Care Med*. 2005;33(6):1225–1229.
4. Mabasa VH, Malyuk DL, Weatherby E-M, Chan A. A standardized, structured approach to identifying drug-related problems in the intensive care unit: FASTHUG-MAIDENS. *Can J Hosp Pharm*. 2011;64:366–669.
5. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens*. 2013;31(10):1925–1938.
6. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):7S–47S.
7. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2014;64(22):e77–e137.

8. Rosenman DJ, McDonald FS, Ebbert JO, Erwin PJ, LaBella M, Montori VM. Clinical consequences of withholding versus administering renin-angiotensin-aldosterone system antagonists in the preoperative period. *J Hosp Med*. 2008;3(4):319–325.
9. Joshi GP, Chung F, Vann MA, et al. Society for Ambulatory Anesthesia consensus statement on perioperative blood glucose management in diabetic patients undergoing ambulatory surgery. *Anesth Analg*. 2010;111(6):1378–1387.
10. Jaffer AK. Perioperative management of warfarin and antiplatelet therapy. *Cleve Clin J Med*. 2009;76(suppl 4):S37–S44.
11. Axelrod L. Perioperative management of patients treated with glucocorticoids. *Endocrinol Metab Clin North Am*. 2003;32(2):367–383.
12. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. *Arch Surg*. 2008;143(12):1222–1226.
13. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016;17:131–157.
14. Flurie RW, Gonzales JP, Tata AL, Millstein LS, Gulati M. Hospital delirium treatment: continuation of antipsychotic therapy from the intensive care unit to discharge. *Am J Hosp Pharm*. 2015;72(23 suppl 3):S133–S139.
15. Marshall J, Herzig SJ, Howell MD, et al. Antipsychotic utilization in the intensive care unit and in transitions of care. *J Crit Care*. 2016;33:119–124.
16. Rizvi MS, Nei AM, Gajic O, Mara KC, Barreto EF. Continuation of newly initiated midodrine therapy after intensive care and hospital discharge: a single-center retrospective study. *Crit Care Med*. 2019;47(8):e648–e653.
17. Tully AP, Hammond DA, Li C, Jarrell AS, Kruer RM. Evaluation of medication errors at the transition of care from an ICU to non-ICU location. *Crit Care Med*. 2019;47(4):543–549.
18. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502–509.
19. Marra A, Pandharipande PP, Girard TD, et al. Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. *Crit Care Med*. 2018;46(9):1393–1401.
20. Stollings JL, Bloom SL, Wang L, Ely EW, Jackson JC, Sevin CM. Critical care pharmacists and medication management in an ICU recovery center. *Ann Pharmacother*. 2018;52(8):713–723.
21. Nguyen NQ, Ng MP, Chapman M, Fraser RJ, Holloway RH. The impact of admission diagnosis on gastric emptying in critically ill patients. *Crit Care*.

2007;11(1):1–10.
22. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest.* 2012;141(5):1327–1336.
23. Aradhyula S, Manian FA, Hafidh SAS, Bhutto SS, Alpert MA. Significant absorption of oral vancomycin in a patient with *Clostridium difficile* colitis and normal renal function. *South Med J*. 2006;99(5):518–520.
24. Spitzer PG, Eliopoulos GM. Systemic absorption of enteral vancomycin in a patient with pseudomembranous colitis. *Ann Intern Med*. 1984;100(4):533–534.
25. Yamazaki S, Nakamura H, Yamagata S, et al. Unexpected serum level of vancomycin after oral administration in a patient with severe colitis and renal insufficiency. *Int J Clin Pharmacol Ther*. 2009;47(11):701–706.
26. Rao S, Kupfer Y, Pagala M, Chapnick E, Tessler S. Systemic absorption of oral vancomycin in patients with *Clostridium difficile* infection. *Scand J Infect Dis*. 2011;43(5):386–388.
27. Dörffler-Melly J, de Jonge E, Pont A-C, et al. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. *Lancet.* 2002;359(9309):849–850.
28. Cheng SS, Nordenholz K, Matero D, et al. Standard subcutaneous dosing of unfractionated heparin for venous thromboembolism prophylaxis in surgical ICU patients leads to subtherapeutic factor Xa inhibition. *Intensive Care Med*. 2012;38(4):642–648.
29. Jochberger S, Mayr V, Luckner G, et al. Antifactor Xa activity in critically ill patients receiving antithrombotic prophylaxis with standard dosages of certoparin: a prospective, clinical study. *Crit Care*. 2005;9(5):R541–R548.
30. Priglinger U, Delle Karth G, Geppert A, et al. Prophylactic anticoagulation with enoxaparin: is the subcutaneous route appropriate in the critically ill? *Crit Care Med*. 2003;31:1405–1409.
31. Malinoski D, Jafari F, Ewing T, et al. Standard prophylactic enoxaparin dosing leads to inadequate anti-Xa levels and increased deep venous thrombosis rates in critically ill trauma and surgical patients. *J Trauma*. 2010;68(4):874–880.
32. Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. *Crit Care Clin*. 2011;27(1):19–34.
33. Sun H, Frassetto L, Benet LZ. Effects of renal failure on drug transport and metabolism. *Pharmacol Ther*. 2006;109(1–2):1–11.
34. Vilay AM, Churchwell MD, Mueller BA. Clinical review: drug metabolism and nonrenal clearance in acute kidney injury. *Crit Care*. 2008;12(6):1–9.
35. Šunjic´ KM, Webb AC, Šunjic´ I, Creus MP, Folse SL. Pharmacokinetic and other considerations for drug therapy during targeted temperature management. *Crit Care Med*. 2015;43(10):2228–2238.

36. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J Crit Care*. 2012;27(6):741.e9–741.e18.
37. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31–41.
38. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate [published corrections appear in *Ann Intern Med*. 2011;155(6):408]. *Ann Intern Med*. 2009;150(9):604–612.
39. Schulz V. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. *Clin Pharmacokinet*. 1984;9(3):239–251.
40. Shochet RB, Murray GB. Analytic reviews: neuropsychiatric toxicity of meperidine. *J Intensive Care Med*. 1988;3(5):246–252.
41. Shafer A. Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. *Crit Care Med*. 1998;26(5):947–956.
42. Mandelli M, Tognoni G, Garattini S. Clinical pharmacokinetics of diazepam. *Clin Pharmacokinet*. 1978;3(1):72–91.
43. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825–e873.
44. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med*. 2014;370(5):444–454.
45. Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam J-J, Jaber S. A prospective study of pain at rest: incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients. *Anesthesiology.* 2007;107(5):858–860.
46. Gélinas C. Management of pain in cardiac surgery ICU patients: have we improved over time? *Intensive Crit Care Nurs*. 2007;23(5):298–303.
47. Stein-Parbury J, McKinley S. Patients' experiences of being in an intensive care unit: a select literature review. *Am J Crit Care*. 2000;9(1):20–27.
48. Schelling G, Richter M, Roozendaal B, et al. Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. *Crit Care Med*. 2003;31(7):1971–1980.
49. Schelling G, Stoll C, Haller M, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Crit Care Med*. 1998;26(4):651–659.
50. Erstad BL, Puntillo K, Gilbert HC, et al. Pain management principles in the critically ill. *Chest.* 2009;135(4):1075–1086.
51. Fraser GL, Prato BS, Riker RR, Berthiaume D, Wilkins ML. Frequency, severity, and treatment of agitation in young versus elderly patients in the ICU. *Pharmacotherapy.* 2000;20(1):75–82.

52. Ryder-Lewis MC, Nelson KM. Reliability of the Sedation-Agitation Scale between nurses and doctors. *Intensive Crit Care Nurs*. 2008;24(4):211–217.
53. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA.* 2003;289(22):2983–2991.
54. Riker RR, Fraser GL, Simmons LE, Wilkins ML. Validating the Sedation-Agitation Scale with the Bispectral Index and Visual Analog Scale in adult ICU patients after cardiac surgery. *Intensive Care Med*. 2001;27(5):853–858.
55. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371(9607):126–134.
56. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471–1477.
57. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult [published corrections appear in *Crit Care Med*. 2002;30(3):726]. *Crit Care Med*. 2002;30(1):119–141.
58. Payen JF, Chanques G, Mantz J, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology.* 2007;106(4):687–695.
59. Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med*. 2006;34(5):1326–1332.
60. Barr J, Egan TD, Sandoval NF, et al. Propofol dosing regimens for ICU sedation based upon an integrated pharmacokinetic-pharmacodynamic model. *Anesthesiology.* 2001;95(2):324–333.
61. Tanios MA, de Wit M, Epstein SK, Devlin JW. Perceived barriers to the use of sedation protocols and daily sedation interruption: a multidisciplinary survey. *J Crit Care*. 2009;24(1):66–73.
62. Riker RR, Fraser GL. Adverse events associated with sedatives, analgesics, and other drugs that provide patient comfort in the intensive care unit. *Pharmacotherapy.* 2005;25(5, Pt 2):8S–18S.
63. Walder B, Tramèr MR, Seeck M. Seizure-like phenomena and propofol: a systematic review. *Neurology.* 2002;58(9):1327–1332.
64. Marik PE. Propofol: therapeutic indications and side-effects. *Curr Pharm Des*. 2004;10(29):3639–3649.
65. Fong JJ, Sylvia L, Ruthazer R, Schumaker G, Kcomt M, Devlin JW. Predictors of mortality in patients with suspected propofol infusion syndrome. *Crit Care Med*. 2008;36(8):2281–2287.
66. Diedrich DA, Brown DR. Analytic reviews: propofol infusion syndrome in the ICU. *J Intensive Care Med*. 2011;26(2):59–72.

67. Merz TM, Regli B, Rothen H-U, Felleiter H. Propofol infusion syndrome—a fatal case at a low infusion rate. *Anesth Analg*. 2006;103(4):1050.
68. Chukwuemeka A, Ko R, Ralph-Edwards A. Short-term low-dose propofol anaesthesia associated with severe metabolic acidosis. *Anaesth Intensive Care*. 2006;34(5):651–655.
69. Triltsch AE, Welte M, von Homeyer P, et al. Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study. *Crit Care Med*. 2002;30(5):1007–1014.
70. Szumita PM, Baroletti SA, Anger KE, Wechsler ME. Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. *Am J Health Syst Pharm*. 2007;64(1):37–44.
71. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. *Br J Anaesth*. 2002;88(5):669–675.
72. Dasta JF, Kane-Gill SL, Durtschi AJ. Comparing dexmedetomidine prescribing patterns and safety in the naturalistic setting versus published data. *Ann Pharmacother*. 2004;38(7–8):1130–1135.
73. Sichrovsky TC, Mittal S, Steinberg JS. Dexmedetomidine sedation leading to refractory cardiogenic shock. *Anesth Analg*. 2008;106(6):1784–1786.
74. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA.* 2009;301(5):489–499.
75. Shehabi Y, Ruettimann U, Adamson H, Innes R, Ickeringill M. Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. *Intensive Care Med*. 2004;30(12):2188–2196.
76. Pandharipande PP, Brenda TP, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA.* 2007;298(22):2644–2653.
77. Venn M, Newman J, Grounds M. A phase II study to evaluate the efficacy of dexmedetomidine for sedation in the medical intensive care unit. *Intensive Care Med*. 2003;29(2):201–207.
78. Martin E, Ramsay G, Mantz J, Sum-Ping ST. The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. *J Intensive Care Med*. 2003;18(1):29–41.
79. Young CC, Prielipp RC. Benzodiazepines in the intensive care unit. *Crit Care Clin*. 2001;17(4):843–862.
80. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology.* 2006;104(1):21–26.

81. Pisani MA, Murphy TE, Araujo KLB, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med*. 2009;37(1):177–183.
82. Spina SP, Ensom MH. Clinical pharmacokinetic monitoring of midazolam in critically ill patients. *Pharmacotherapy.* 2007;27(3):389–398.
83. Yaucher NE, Fish JT, Smith HW, Wells JA. Propylene glycol-associated renal toxicity from lorazepam infusion. *Pharmacotherapy.* 2003;23(9):1094–1099.
84. Yahwak JA, Riker RR, Fraser GL, Subak-Sharpe S. Determination of a lorazepam dose threshold for using the osmol gap to monitor for propylene glycol toxicity. *Pharmacotherapy.* 2008;28(8):984–991.
85. Gupta N, de Jonghe J, Schieveld J, Leonard M, Meagher D. Delirium phenomenology: what can we learn from the symptoms of delirium? *J Psychosom Res*. 2008;65(3):215–222.
86. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
87. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med*. 2004;32(4):955–962.
88. Shehabi Y, Riker RR, Bokesch PM, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med*. 2010;38(12):2311–2318.
89. Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med*. 2009;180(11):1092–1097.
90. Ely EW, Shintani AS, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA.* 2004;291(14):1753–1762.
91. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc*. 2006;54(3):479–484.
92. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med*. 2007;33(1):66–73.
93. Schweickert WD, Pholman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373(9678):1874–1882.
94. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil*. 2010;91(4):536–542.
95. Girard TD, Exline MC, Carson SS, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med*. 2018;379(26):2506–2516.
96. Jakob SM, Ruokonen E, Grounds MR, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA.* 2012;307(11):1151–1160.

97. Skillman JJ, Bushnell LS, Goldman H, Silen W. Respiratory failure, hypotension, sepsis, and jaundice. A clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. *Am J Surg*. 1969;117(4):523–530.
98. Anderberg B, Sjödahl R. Prophylaxis and management of stress ulcers. *Scand J Gastroenterol Suppl*. 1985;110:101–104.
99. Shuman RB, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: a reappraisal. *Ann Intern Med*. 1987;106(4):562–567.
100. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*. 2018;379:2199–2208.
101. Stollman N, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *J Crit Care*. 2005;20(1):35–45.
102. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med*. 1994;330(6):377–381.
103. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. *Am J Health Syst Pharm*. 1999;56(4):347–379.
104. Guth PH. Mucosal coating agents and other nonantisecretory agents. Are they cytoprotective? *Dig Dis Sci*. 1987;32(6):647–654.
105. Cook DJ, Witt LG, Cook RJ, Guyatt GH. Stress ulcer prophylaxis in the critically ill: a meta-analysis [published corrections appear in *Am J Med.* 1991;91(6):670]. *Am J Med*. 1991;91(5):519–527.
106. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med*. 1998;338(12):791–797.
107. The PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group. Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: the PEPTIC randomized clinical trial. *JAMA.* 2020;323(7):616–626.
108. MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. *JAMA Intern Med*. 2014;174(4):564–574.
109. Barkun AN, Bardou M, Pham CQD, Martel M. Proton pump inhibitors vs. histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. *Am J Gastroenterol*. 2012;107(4):507–520.

110. Wang Y, Ge L, Ye Z, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: an updated systematic review and network meta-analysis of randomized trials. *Intensive Care Med*. 2020;46(11):1987–2000. doi:10.1007/s00134-020-06209-w
111. Bonten MJ, Gaillard CA, van Tiel FH, van der Geest S, Stobberingh EE. Continuous enteral feeding counteracts preventive measures for gastric colonization in intensive care unit patients. *Crit Care Med*. 1994;22(6):939–944.
112. Eom CS, Jeon CY, Lim J-W, Cho E-G, Park SM, Lee K-S. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ.* 2011;183(3):310–319.
113. Dial S, Delaney JAC, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA.* 2005;294(23):2989–2995.
114. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin*. 2001;17(1):107–124.
115. Yendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. *J Trauma*. 2003;55(1):33–38.
116. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. *J Trauma*. 2005;58(1):47–50.
117. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med*. 2009;37(12):3001–3009.
118. Bochicchio GV, Sung J, Joshi M, et al. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients [published corrections appear in *J Trauma*. 2005;59(5):1277–1278]. *J Trauma*. 2005;58(5):921–924.
119. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P, Clinical Guidelines Committee of the American College of Physicians. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2011;154(4):260–267.
120. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359–1367.
121. van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449–461.
122. NICE-SUGAR Study Investigators; Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283–1297.
123. COIITSS Study Investigators; Annane D, Cariou A, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA.* 2010;303(4):341–348.

124. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125–139.
125. Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med*. 2009;35(10):1738–1748.
126. American Diabetes Association. 15. Diabetes care in the hospital: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care*. 2020;43(suppl 1):S193–S202.
127. Haupt MT, Bekes CE, Brilli RJ, et al. Guidelines on critical care services and personnel: recommendations based on a system of categorization of three levels of care. *Crit Care Med*. 2003;31(11):2677–2683.
128. Lat I, Paciullo C, Daley MJ, et al. Position paper on critical care pharmacy services (executive summary): 2020 update. *Crit Care Med*. 2020;48(9):1375–1382.

57

Multiple Sclerosis

Melody Ryan

CORE PRINCIPLES		CHAPTER CASES
1	Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system in which demyelination and axonal damage occur. MS can take one of several forms: relapsing-remitting, secondary-progressive, or primary-progressive are the most common forms.	**Case 57-1 (Questions 1, 5)**
2	The diagnosis of MS is based on clinical symptoms and is supported by magnetic resonance imaging (MRI) and laboratory testing (cerebrospinal fluid oligoclonal bands and immunoglobulin-G synthesis rate; evoked potential testing). In an individual patient, dissemination in space and time must be demonstrated before the diagnosis of MS is made.	**Case 57-1 (Questions 1, 5)**

3	Glucocorticoids are the agents of choice for treatment of acute MS relapses.	**Case 57-1 (Question 7)**
4	Clinically isolated syndrome (CIS) is a term used to describe a first demyelinating neurologic event before the diagnosis of MS has been made. When a patient presents with CIS and MRI abnormalities, progression to clinically definite MS is likely, and therapy with glatiramer acetate, interferon-β, or teriflunomide helps to prevent this progression.	**Case 57-1 (Questions 1, 2)**
5	The choice of drug for relapsing forms of MS is highly individualized with consideration of disease activity and medication adverse effects. The choice of treatment is often based on provider or patient preference.	**Case 57-1 (Questions 3, 5–9)** **Case 57-2 (Question 1)**
6	Adherence to MS therapy is low and a potential point for intervention.	**Case 57-1 (Question 4)**
7	Patient monitoring is necessary and specific for each MS therapy.	**Case 57-2 (Question 2)**
8	Individuals with highly active MS are usually considered for induction therapy protocols with alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, or ofatumumab.	**Case 57-2 (Question 3)**
9	Patients with MS can experience many symptoms, such as walking problems or impaired ambulation, sexual dysfunction, pain, bladder dysfunction,	**Case 57-1 (Question 10) Case 57-2 (Question 4)**

fatigue, cognitive dysfunction, spasticity, bowel dysfunction, dysphagia or dysarthria, and pseudobulbar affect. These symptoms may require both nonpharmacologic and pharmacologic therapies.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS) in which demyelination and axonal damage occur.[1] The disease has a mean age at onset of 30 years, with diagnoses typically occurring between ages 20 and 50 years.[1] Because of the young age at onset, MS has a dramatic effect on employment and, in fact, is the most common cause of disability in young adults.[2] Overall life expectancy is decreased by about 7 years compared with age- and sex-matched control subjects.[3] Cardiovascular, cerebrovascular, cancer, and infectious causes of death are the most commonly reported, similar to a control population, but occurring in higher frequencies in patients with MS.[3,4] Health-related quality of life is lower in patients with MS than in the general population, and this decrease is related to the severity of MS.[5]

MS affects ~0.1% of the U.S. population (900,000 people) and about 2.2 million people worldwide.[2,4] Females are two to three times more likely to have MS than males.[1] Many environmental and genetic factors have been associated with MS (**Table 57-1**); however, the causal nature of any of these factors has yet to be established.[1,2,6–11] Current thought is that an environmental trigger acting in a genetically susceptible individual is the probable cause of MS.[6]

Table 57-1
Factors Associated With Multiple Sclerosis

Female Sex[2]	Low Sun Exposure[1,6]
Higher latitudes of residence[6,7]	Low serum concentrations of vitamin D (25-hydroxyvitamin D)[2,6,8]
Northern European heritage[6]	High serum antibody titers to the Epstein–Barr virus nuclear antigens[6,9]
Infectious mononucleosis[2,9]	Tobacco smoking[2,10]
Childhood and adolescent obesity[11]	

MS is most frequently encountered between 40 and 60 degrees North or South latitude. Regions with a high prevalence include Western and Northern Europe, Canada, Russia, Israel, Northern United States, New Zealand, and Southeast Australia.[4,7] Additionally, relapse rates may also vary seasonally with latitude.[12] This finding has spurred many research studies and hypotheses. One hypothesis is that the development of MS is related to sunlight exposure or vitamin D.[8] Higher serum concentrations of 25-hydroxyvitamin D (the major circulating form and the one that is measured by clinical laboratory testing) are associated with reduced hazard of an MS relapse, and lower concentrations are associated with higher rates of MS diagnoses.[8] Genetically, lack of the vitamin D receptor and cytochrome P-450 (CYP) 27B1 (encodes the enzyme responsible for vitamin D activation converting 25-hydroxyvitamin D to 1,25-hydroxyl-vitamin D) is associated with impaired immune system.[11] Some investigators have found links between season of birth and development of MS, suggesting that maternal vitamin D status may be important.[13] Relapses also follow a seasonal pattern, with peaks in the early spring and troughs in the autumn in both hemispheres, further suggesting a role of vitamin D in relapses.[12]

Epstein–Barr virus (EBV) is a ubiquitous infection; however, high EBV titers and a history of infectious mononucleosis both increase risk of developing MS.[9,11] Further, there is some evidence linking the

human leukocyte antigen (HLA)-DRB1*1501 genotype to an increased risk of developing MS in patients with either EBV or infectious mononucleosis.[9] Smoking is a risk factor, with higher levels of smoking conferring greater risk.[2,10,11] There is also evidence that obesity in childhood or adolescence increases the risk of developing MS.[11]

A genetic predisposition to the development of MS is likely. First-degree relatives of people with MS have a risk of MS that is 10 to 25 times greater than the general population; the concordance rate in identical twins is 35%.[6] There are probably several genetic factors that increase the risk for MS, including HLA type and various single-nucleotide polymorphisms that control T-cell receptors, B cells, vitamin D receptors, and estrogen receptors.[8,14] A specific major histocompatibility complex (MHC) associated with MS is HLA-DRB1*1501 class II,[9] but 233 different genetic variations have been associated with MS.[15] No genetic association has been found for a particular clinical course or rate of progression.[15]

Although MS is more prevalent in Caucasian populations in the United States, there is evidence that African American patients may be more likely to have primary-progressive forms and may have a more severe disease course. The reasons for these differences are poorly understood but may have genetic, environmental, and socioeconomic bases and prevalence among African Americans may be increasing.[16–18]

MS is generally characterized as one of three main types according to the presentation and clinical course of the disease: relapsing-remitting MS, secondary-progressive MS, and primary-progressive MS. These three types of MS are distinguished by their natural histories. Relapsing-remitting MS was named for the relapses (also called exacerbations or attacks) of clinical disease activity that alternate with periods of symptom remission. Recovery during the remission periods can be complete, or the patient may continue to have some clinical deficits.[19] Between 80% and 90% of patients have relapsing-remitting MS when they are first diagnosed.[20,21] Patient registry data provide insight regarding the prognosis of those with relapsing-remitting MS. Patients diagnosed

with relapsing-remitting MS at onset have slower progression to disability than patients with primary-progressive MS; patients having complete or near-complete recovery from the first attack of MS have a longer time to disability compared with those with significant persistent deficits after the first attack.[21]

Approximately 80% of patients initially diagnosed with relapsing-remitting MS experience a secondary-progressive form in which fewer relapses occur, but disability continues to progress.[2] The cause of the conversion from relapsing-remitting MS to secondary-progressive MS is unknown, but it has been hypothesized that the change occurs when axonal loss in the CNS reaches a critical threshold.[21] The time to development of secondary-progressive MS is quite variable. The usual time to conversion is 20 to 25 years after diagnosis, with median patient age at the time of conversion of 43 years; however, it may occur much sooner.[19,21] It is not known how treatment affects this process. In one study, the number of early relapses (within 2 years of diagnosis) was associated with a shorter time to development of secondary-progressive MS.[21] Therefore, early treatment with a therapy that reduces relapses might be expected to delay the development of secondary-progressive MS.

Approximately 10% to 15% of patients have primary-progressive MS.[21] This type of MS is progressive from onset with occasional minor improvements or periods of stabilization.[19] Primary-progressive MS is more common in patients who are older than age 50 years at diagnosis.[2] Select studies have found this form to be more common in males, but others have found no association with sex.[21] Non-Hispanic Blacks have primary-progressive MS compared to other racial and ethnic groups.[17]

In the absence of treatment, patients who initially present with relapsing-remitting MS develop average Expanded Disability Status Scale (EDSS) scores of 4.0 or higher (indicating significant disability) by 7 years after diagnosis.[4] The EDSS is a scale commonly used in MS to measure the level of disability and progression of the disease.[22] Some predictors of a more progressive disease course include male gender, multisystem symptoms, incomplete recovery from the initial episode, progressive disease from the time of

diagnosis, older age at onset, and abnormal baseline magnetic resonance imaging (MRI) results.[19,21] Although patients present with different types of MS, once progression begins, all forms of progressive MS follow a similar time course for subsequent progression.[19]

A classification system is used to denote disease activity and progression over a 1-year period.[23] Patients with new, active MRI lesions or with clinical relapses within a specified time frame are classified as active, whereas those without new lesions or relapses are classified as inactive. In a similar way, patients are categorized as progressing if they have steadily increasing objectively documented neurologic dysfunction without recovery or nonprogressing. For example, a patient with relapsing-remitting MS who has had a clinical relapse in the last year, but who had full recovery, would be classified as relapsing-remitting MS-active and not progressing.[23] Because MS begins during young-to-middle adulthood, there is a large economic burden associated with the disease. MS has the fourth most expensive drug costs among commercially insured patients.[24] One study in which newly diagnosed patients were matched to healthy control subjects found that patients with MS were 3.5 times as likely to be hospitalized, twice as likely to have at least one emergency department visit, and 2.4 times as likely to have at least one visit for physical, occupational, or speech therapy during the course of a year.[25] These services are associated with a mean annual total health care cost of $62,500, and disease-modifying therapy makes up almost 70% of the total health care costs.[26] These estimates do not consider the loss of employment or loss of caregiver employment. One study found that earnings of people with MS were less than their matched counterparts, beginning 1 year before diagnosis and increasing during the diagnosis year (15% less than controls) and at 5 years after diagnosis (27% less than controls).[26]

Ten years after diagnosis, 50% to 80% of patients with MS are unemployed. Surprisingly, only 15% of unemployment is related to physical restrictions.[27] Of the factors most often cited as leading to unemployment, only decreased walking ability relates to physical

disability. The other common factors are increased age, decreased verbal fluency, and loss of memory.[27]

PATHOPHYSIOLOGY

Many aspects of the pathophysiology of MS remain unclear, although research in this area is progressing rapidly. Foremost in unresolved issues is the identity of the actual initiating factor for the autoimmune and inflammatory processes that characterize MS. Through the years, several dozen triggers have been proposed. Current thinking is that a genetically susceptible individual has an environmental factor that triggers the immune system to cause MS.[6]

There are two pathologic processes that occur during MS. The first is inflammatory. During this process, the body mounts an autoimmune attack on the myelin covering of nerve fibers of the white matter in the CNS. These areas of demyelination are visualized as plaques or lesions and are seen on brain tissue directly (eg, on autopsy) or on MRI with contrast agents (**Fig. 57-1**).[14] It is this inflammation that causes the relapses that are seen clinically, and it is the resolution of these relapses that is seen as remission.

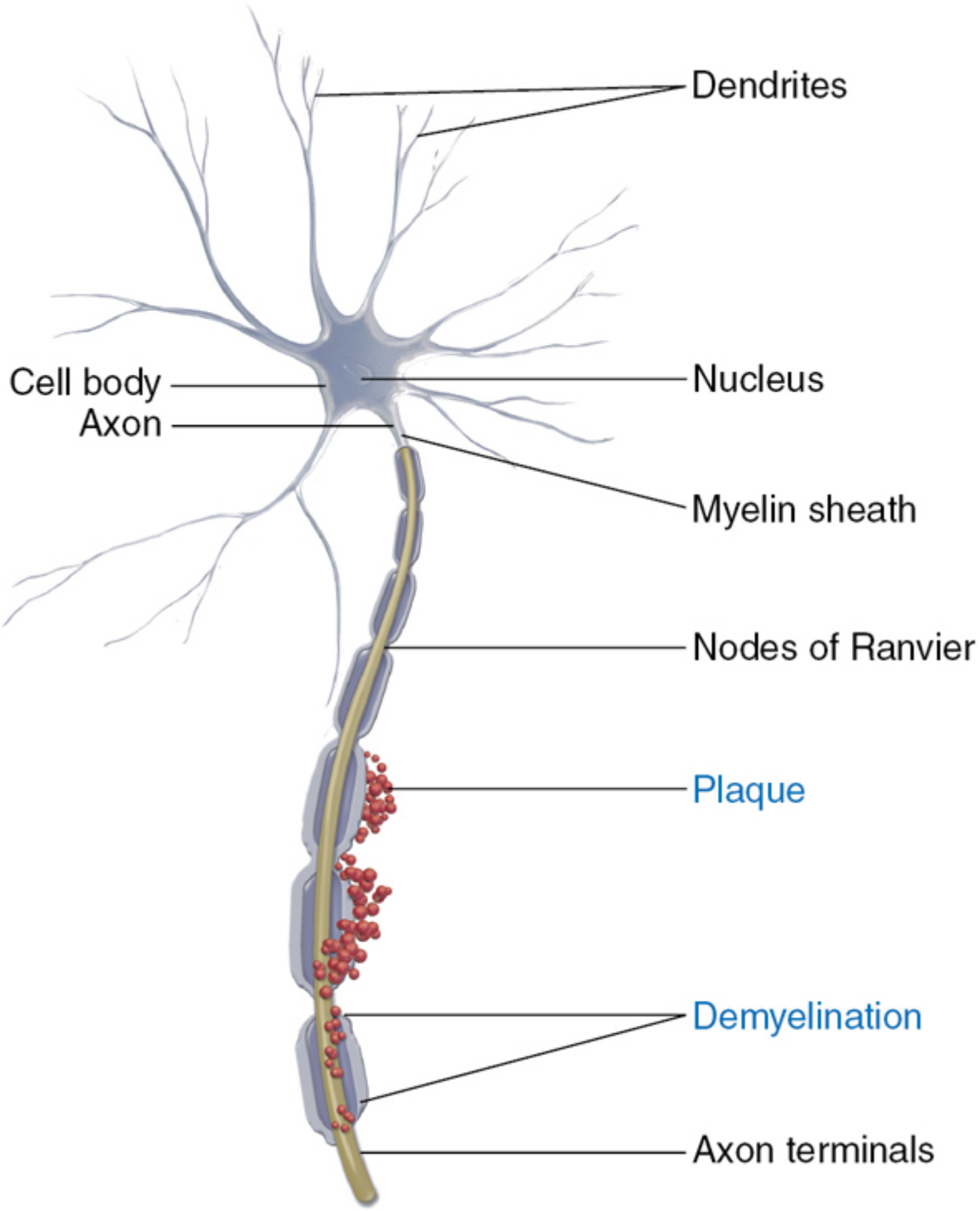


Figure 57-1 Myelin destruction in multiple sclerosis.

The second process is neurodegenerative, during which the axons of nerves in brain white matter are damaged, some irrevocably. This neurodegeneration causes a progressive disability when

transmission through the nerve cell is slowed or fails completely. It is cumulative with time and may be irreversible. It is not known whether the inflammatory or neurodegenerative process occurs first in MS or whether they are simultaneous.[14] Additionally, the pathophysiology of progressive MS likely differs substantially from relapsing forms of MS with greater axonal loss, but specific, treatable issues are elusive.[28]

Inflammation

The inflammatory cascade in MS is complex. Various types of T cells play a role early in the process.[14] The unknown antigen couples with MHC molecules.[2,6] These antigen–MHC pairs encounter antigen-presenting cells (APCs) such as dendrites, macrophages, and microglia.[9,22] T cells recognize this antigen–MHC–APC complex, become activated, and initiate the immunologic cascade.[14] Under normal circumstances, regulatory T cells (T_{reg}) monitor for and control autoimmune T-cell formation in the periphery. It has been hypothesized that T_{reg} cells malfunction in people with MS.[14] The activated T cells then retreat to the lymphatic tissues in the body, such as the spleen and lymph nodes, to expand.[14] At the appropriate time, the T cells exit the lymphatic tissues and rejoin the circulation. Sphingosine-1-phosphate (S1P), a small, circulating lipid molecule, is important in this process. For the T cells to exit the lymphatic tissues, the S1P receptor 1 must be expressed on their surface.[29] The T cells follow an S1P concentration gradient to exit the lymphatic tissues and join the circulation. The activated T cells must cross the blood–brain barrier to attack myelin in the CNS. An adhesion molecule, $\alpha_4\beta_1$-integrin (VLA4), is found on the surface of T cells.[14] When the T cells approach the blood–brain barrier, they slow and bind to the α_4-integrin and p-selectin glycoprotein ligand 1. This bonding allows the T cells to transmigrate through the endothelial cells of the blood vessel.[30]

In the perivascular space, the T cells must be reactivated by new APC.[30] Through the action of matrix metalloproteinases 2 and 9, the activated T cells invade the parenchyma of the brain.[30] Once

ensconced in the brain, the T cells begin to secrete various pro-inflammatory cytokines that further stimulate the inflammatory cascade, including stimulation of microglia.[30] The microglia produce proteolytic enzymes, lipolytic enzymes, reactive oxygen species, reactive nitrogen species, excitotoxins, and more pro-inflammatory cytokines. Activated microglia can also serve as APCs for activation of additional T cells.[30] Nitric oxide, a reactive nitrogen species, is increased during inflammation and can inhibit mitochondrial respiration, inhibit the sodium–potassium adenosine triphosphatase pump, and cause the intracellular release of calcium. The excess calcium leads to degenerative processes within the cell.[21]

Although the role of T cells is central to MS pathology, the role of B and natural killer (NK) cells is much less clear. B cells may be involved in antigen presentation, production of cytokines, and the production of the immunoglobulin found in the cerebrospinal fluid (CSF) of patients with MS.[31,32] Antibodies produced by B cells in the CSF may target myelin oligodendrocyte glycoprotein or myelin basic protein.[31] Among the subtypes of B cells, memory B cells may be the most pathogenic in MS.[32] NK cells have been postulated to have both helpful and deleterious effects.[30]

At some point, the resolution of inflammation begins. During the inflammatory cascade, myelin is broken down, and this myelin debris inhibits remyelination. The microglia use phagocytosis to clear myelin structures, axons, apoptotic cells, and myelin debris from the area of inflammation.[30] After this process, the microglia begin to produce immunomodulatory cytokines.[30] Helper T type 2 cells become more prominent and begin secreting immunomodulatory cytokines as well.[30]

Remyelination then begins; however, some evidence suggests that the ability of the body to remyelinate decreases with age.[30] Microglia produce more cytokines and some growth factors that cause oligodendrocyte progenitor cells to migrate to the area. Remyelination occurs when oligodendrocyte progenitor cells differentiate into new oligodendrocytes.[30] Sphingosine-1-phosphate receptors 1 and 5 present on oligodendrocytes appear to help with differentiation.[33] Remyelination may not be complete and, in some

cases, does not occur at all. The myelin also may be thinner and shorter than the original myelin.[30]

Neurodegeneration

Axonal injury can occur throughout the course of the disease and may even occur before any clinical symptoms.[34] Inside chronic MS lesions, there are 60% to 70% fewer axons compared with other white matter in the same patient.[34] In addition to producing myelin, oligodendrocytes support axons through the production of insulin-like growth factor type I and neuregulin; thus, axons can die without the support of the oligodendrocytes. However, axonal loss has been demonstrated at sites separate from MS lesions, particularly the thalamus.[34] Although oligodendrocytes provide trophic support for the axons, they also inhibit new growth to prevent random neurite sprouting. Three myelin-associated inhibitor factors, myelin-associated glycoprotein, Nogo-A, and oligodendrocyte myelin glycoprotein, lie in the sheath of myelin closest to the axon, where they prevent this sprouting.[34]

Microtubules are also important for neurite growth. The assembly of microtubules is controlled by collapsin-response mediator protein 2 (CRMP-2).[34] When CRMP-2 is phosphorylated, neurite growth is inhibited.[34] *Ras* homolog gene family, member A (RhoA)–guanosine triphosphate (GTP), has action on both the myelin-associated inhibitory factors and CRMP-2. The myelin-associated inhibitory factors signal RhoA–GTP to neurite retraction rather than growth.[34] It also activates Rho kinase, which phosphorylates CRMP-2.[34] Myelin normally allows saltatory, fast conduction (ie, conduction via leaps) at the nodes of Ranvier; thus, loss of myelin slows or prevents transmission of nerve impulses.[34]

In the demyelinated state, sodium channels under the myelin sheath may become functional to allow improved nerve conduction.[34] The activation of sodium channels results in sodium entry into the cell. The excess sodium activates the sodium–calcium exchanger to export sodium and import calcium, fueling the degenerative

processes within the neuron.[34] Additionally, increased numbers of glutamate-regulated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are seen in demyelinated axons. Activation of these receptors results in increased levels of intracellular sodium and calcium, further contributing to neurodegeneration.[34]

CLINICAL PRESENTATION

Because the demyelination associated with MS can occur in any part of the CNS, many different symptoms are associated with the disease. At first presentation, the most common clinical symptoms are sensory disturbances, particularly of the extremities, partial or complete visual loss, motor dysfunction of the limbs, diplopia, and gait dysfunction.[2] Two demyelinating syndromes are so distinct that they have been recognized, named, and deserve particular mention: optic neuritis and transverse myelitis. Optic neuritis is the acute demyelination of the optic nerve. Symptoms may include ocular pain, blurred vision, or changes in color perception.[35] Transverse myelitis is impairment of motor control or sensory function, or control over bladder, bowel, and sexual functions that are consistent with a lesion at a specific point in the spinal cord, but without a structural cause such as a herniated disc.[36]

As concern has developed about neurodegenerative changes that occur early in the course of MS, there has been more interest in very early treatment after the emergence of symptoms to delay or decrease the development of MS. The term clinically isolated syndrome (CIS) describes a first demyelinating neurologic event involving the optic nerve, cerebrum, cerebellum, brainstem, or spinal cord.[37] Up to 85% of people with MS may first present with CIS.[37] Of those who present with CIS, 63% will develop MS during the ensuing 20 years.[38]

Patients younger than 40 years are more likely to convert from CIS to clinically definite MS than those age 40 years or older.[39] Patients

with optic neuritis as the presenting diagnosis are less likely than those with other symptoms to develop clinically definite MS. The presence of oligoclonal bands in the CSF, low serum concentrations of vitamin D, and multiple lesions on MRI are associated with a particularly high risk of development of MS.[38,39]

Occasionally, MS-type lesions will be visible on an MRI scan performed for other reasons. If the patient has no other symptoms, this condition is known as radiologic-isolated syndrome.[40] About 30% to 50% of these patients have a clinical episode within 5 years of the detection of their MRI abnormality.[40] Younger patients, males, and those with lesions on the spinal cord were more likely to develop a CIS.[40] No treatment is suggested for patients with these findings at this time.[40]

With time and with neurodegeneration, many other symptoms can develop in people with MS. The most common symptoms are listed in **Table 57-2**.[41–48]

Table 57-2
Common Symptoms in Chronic Multiple Sclerosis

Symptom	Prevalence (%)
Sexual dysfunction[41]	40–90
Walking problems or impaired ambulation[42]	45–90
Pain[43]	30–90
Bladder dysfunction[43]	50–90
Fatigue[44]	30–80
Cognitive dysfunction[43]	40–65
Spasticity[45]	60
Bowel dysfunction[43]	50
Depression[46]	50
Dysphagia or dysarthria[47]	40
Pseudobulbar affect[48]	10

DIAGNOSIS

When patients first present for medical care with symptoms of MS, diseases as diverse as infections, cancers, vascular disease, or other inflammatory demyelinating diseases are commonly part of the differential diagnosis. Thus, the addition of MRI and other laboratory findings can help with the diagnosis. At other times, the diagnosis is not apparent until the occurrence of a second attack.[49]

Diagnostic criteria have been proposed in an effort to standardize diagnoses of MS and to promote earlier treatment. The initial criteria stated that the patient must have experienced at least two demyelination-related episodes separated by time and space (ie, at least two episodes involving distinct regions of the CNS).[1] Guidelines proposed in 2001 and revised in 2005, 2010, and 2017 allow for the use of MRI and CSF findings to fulfill these time and space criteria after an initial clinical attack.[1] In particular, the 2017 criteria also allow for the presence of oligoclonal bands in the CSF to substitute for the dissemination in time criteria.[1] Primary-progressive MS is diagnosed when there is a continuous progression of neurologic symptoms during a 1-year period with characteristic MRI and CSF findings.[1]

OVERVIEW OF TREATMENT

Although the mechanisms of action of MS pharmacotherapies are diverse, they all can be generally categorized as immunomodulating agents. To date, all therapies for MS have targeted the inflammatory response rather than the accompanying neurodegeneration features of the disease.

Treatment of Acute Relapses

Corticosteroids are used in the treatment of MS to control inflammation during acute relapses. Although most patients respond to treatment with corticosteroids, some do not. These agents have several actions that contribute to their acute anti-inflammatory effects. Corticosteroids increase the activity of T_{reg} cells, reduce the activity of T and B cells, reduce adhesion molecule production, and reduce pro-inflammatory cytokines.[50]

Treatment of Relapsing-Remitting Multiple Sclerosis

Most of the therapeutic research conducted in MS has focused on the relapsing-remitting form of the disease. This is the most common form of MS at presentation, and it has an important inflammatory aspect. The agents that are currently U.S. Food and Drug Administration (FDA)-approved for MS include alemtuzumab, anti-CD20 antibodies (eg, ocrelizumab, ofatumumab) β-interferons, cladribine, fumarates (eg, dimethyl fumarate, diroximel fumarate, monomethyl fumarate), glatiramer acetate, mitoxantrone, natalizumab, S1P-receptor modulators (eg, fingolimod, ozanimod, ponesimod, siponimod), and teriflunomide.

ALEMTUZUMAB

Alemtuzumab is a monoclonal antibody aimed at CD52. It reduces the population of circulating B and T cells. The peripheral circulating lymphocytes are undetectable within minutes of infusion.[51] These cells repopulate, but fairly slowly; B cells have a median recovery time of 8 months, $CD8^+$ T cells 20 months, and $CD4^+$ T cells 35 months. However, some patients took as long as 12 years to reach baseline levels.[51] Because of the significant lymphocyte depletion, alemtuzumab is thought to “reset” the immune system, a process called immune reconstitution therapy.[52] Alemtuzumab reduced relapses and MRI lesions compared to interferon β-1a subcutaneously, but had similar rates of disability progression; 77% of patients taking alemtuzumab were completely relapse-free at 2

years.[53] One long-term study saw benefits sustained from alemtuzumab over 5 years.[51]

ANTI-CD20 ANTIBODIES

Ocrelizumab and ofatumumab are monoclonal antibodies that target CD20-positive cells. Cells that express CD20 include B-cell precursors, mature B cells, and a subpopulation of T cells.[54] Ocrelizumab works rapidly, reducing the number of active lesions on MRI and the number of relapses by the fourth week of treatment.[55] Like alemtuzumab, ocrelizumab and ofatumumab are immune reconstitution therapies. Treatment with ocrelizumab reduced annualized relapse rates, disability progression, and number of MRI lesions compared to interferon-β.[56,57] Compared to teriflunomide, ofatumumab decreases relapses, prevents worsening disability, and decreases new or enlarging lesions on MRI.[58]

β-INTERFERONS

β-Interferons are thought to work by suppressing T-cell activity, downregulating antigen presentation by MHC class II molecules, decreasing adhesion molecules and matrix metalloproteinase 9, and increasing anti-inflammatory cytokines while decreasing pro-inflammatory cytokines.[59,60] There are two types of interferon-β (interferon β-1a and interferon β-1b) and a total of four preparations available to treat MS.[61–64] Placebo-controlled trials of each of the interferon-β agents have shown a reduced number of relapses and decreased disease progression measured on the EDSS in patients treated with interferon versus those who were given placebo.[65]

Data are available for patients who have been treated with interferon β-1b for up to 16 years. A sustained reduction in relapse rate of 40% was seen in patients who received the drug continuously, an improved response compared with those who received placebo or interferon only for a short time. Patients who received continuous interferon therapy also had slower rates of disease progression.[66,67] Eight-year follow-up data for interferon β-1a given intramuscularly did not show this sustained reduction in

relapse rate but did show that those who began treatment earlier had better long-term outcomes.[66]

CLADRIBINE

Cladribine was initially approved for hematologic malignancies, but has been repurposed as a treatment for relapsing-remitting MS. Like alemtuzumab and the anti-CD20 antibodies, it is an immune reconstitution therapy.[52] Its probable mechanism of action in MS is depletion of B and T lymphocytes.[68] Cladribine may also prevent activation of T cells.[68] Regulatory B and T cells increase fairly rapidly, but memory B cells and some T helper cells are at low levels at least 24 months after beginning treatment.[69] This extended action of cladribine has led to a pulsed dosing schedule of two doses per year for 2 years.[70] Cladribine decreased annualized relapse rate by about half compared to placebo, and almost 80% of patients treated with cladribine were relapse-free at 96 weeks.[71] Patients treated with cladribine also had fewer lesions on MRI and decreased progression of disability.[71] These improvements were sustained for at least two additional years beyond the end of the study.[72]

FUMARATES

Dimethyl fumarate and diroximel fumarate are rapidly cleaved in the intestine to form their active forms, monomethyl fumarate. All three agents, dimethyl fumarate, diroximel fumarate, and monomethyl fumarate, are now on the market for treatment of MS. Monomethyl fumarate causes a shift in cytokine production from interferon-γ and tumor necrosis factor-α to interleukin-4 and -5[73] and alterations of the subpopulations of B and T cells.[74] Dimethyl fumarate also activates the antioxidant effects of nuclear 1 factor (erythroid-related 2)-like 2 (Nrf2) transcriptional pathway that may prevent the neurodegeneration in MS by decreasing oxidative damage.[73,74] Dimethyl fumarate reduces the relapse rate by about half and new lesion development on MRI scan compared to placebo.[75]

GLATIRAMER ACETATE

Glatiramer acetate decreases type-1 helper T (T_H1) cells while increasing type-2 helper T (T_H2) cells. Additionally, it increases production of nerve growth factors.[60] The short-term and long-term efficacy of glatiramer acetate is similar to that of the interferons.[65]

MITOXANTRONE

Mitoxantrone works as a general immunomodulator. It decreases monocytes and macrophages and inhibits T and B cells.[76] Compared with placebo, mitoxantrone decreased the number of exacerbations and improved MRI in treated patients.[76]

NATALIZUMAB

Natalizumab is a humanized monoclonal IgG4 antibody. It blocks T-cell entry into the CNS by binding to $\alpha_4\beta_1$-integrin located on the lymphocyte to keep it from binding to the vascular cell adhesion molecule-1 on the endothelial cell.[77] In clinical trials, natalizumab was very effective, reducing the 1-year relapse rate by 68%, the risk of progression of disability in 2 years by 42%, and new lesions on MRI by 83%.[76]

S1P-RECEPTOR MODULATORS

Fingolimod, ozanimod, ponesimod, and siponimod are S1P-receptor modulators. They bind to the S1P receptor 1 expressed on T cells.[29] This binding causes the receptor to be internalized in the T cell, where it is unresponsive to the normal signal that causes the T cell to exit the lymphoid tissues and recirculate.[29] Without the T cells circulating, they are not activated, which disrupts the inflammatory cycle. There are different S1P receptor subtypes (1–5). Fingolimod binds to S1P receptor subtypes 1, 3, 4, and 5; ozanimod and siponimod bind to S1P receptor subtypes 1 and 5.[78,79] Fingolimod has been shown to decrease the relapse rate by about half compared with placebo as well as to reduce disability progression.[80] Ozanimod reduced active brain lesions within 6 months compared to placebo.[81] Ozanimod decreased the relapse rate and the number of new MRI lesions, but not disability progression compared to

interferon β-1a at 12 or 24 months.[82,83] Siponimod decreased new MRI lesions as quickly as 3 months compared to placebo and sustained this effect for up to 2 years.[79] Siponimod was also compared to placebo for secondary-progressive MS. It decreased disability progression at 6 months, decreased lesions in the brain, and decreased relapse rate by about half.[84]

TERIFLUNOMIDE

Teriflunomide is the active metabolite of leflunomide. It is thought to act in MS by blocking de novo pyrimidine synthesis, inhibiting B- and T-cell division, and blocking the inflammatory pathway prominent in MS.[85] It may also inhibit the pairing of T cells and APC to prevent T-cell activation. Teriflunomide reduces the annualized relapse rate by about 20% to 30% and reduces the risk of new MRI lesions by 60% to 80% compared to placebo in clinical trials.[85]

Treatment of Progressive Forms of Multiple Sclerosis

Patients with both secondary-progressive and primary-progressive MS may experience relapses. In these cases, all of the agents used for relapsing-remitting MS may be useful to reduce the number of relapses.[86] Some evidence suggests that therapies (specifically, interferon β-1a) are less effective for relapses in secondary-progressive MS than for relapsing-remitting MS.[86] This finding is consistent with the known mechanisms of action for the currently available agents, which are directed at the inflammatory processes. Siponimod has demonstrated benefit in secondary-progressive MS compared to placebo.[84] Treatment for primary-progressive MS are even more sparse, with secondary data analysis showing no effect for most drugs.[87] Ocrelizumab is the only FDA-approved medication for primary-progressive MS. It improved disability progression and decreased lesions on MRI compared to placebo at 24 weeks.[88]

Symptom Management

As disability increases, many patients with MS exhibit other associated symptoms that require targeted treatment (see **Table 57-2**).

BLADDER, BOWEL, AND SEXUAL DYSFUNCTION

Bladder, bowel, and sexual dysfunction are very common in patients with MS. Up to 90% of patients have bladder symptoms; constipation or bowel incontinence occur in ~50% of patients; and sexual dysfunction occurs in 50% to 90% of males and 40% to 80% of females.[41,43] It is also known that those patients with more bladder symptoms or sexual dysfunction have lower quality of life compared with patients without these problems.[41] The treatment approaches for these disorders in MS are similar to those used when these symptoms occur as part of a primary disorder.

IMPAIRED AMBULATION

Up to 90% of patients with MS stated that they had some limitation to their walking ability within 10 years of diagnosis.[42] Physical therapy and conditioning may be of some help for this problem.[42,89] Another approved treatment option is extended-release dalfampridine. This agent blocks potassium channels and prevents repolarization of the cell, thus prolonging action potentials and nerve impulse transmission in the demyelinated axon.

In clinical studies of extended-release dalfampridine, 57% of treated patients were unable to decrease the amount of time it took them to walk 25 feet. The 43% who did decrease their time were considered responders. On average, they improved their speed to walk 25 feet by 25% (~3 seconds faster).[42] Clinically, it may be difficult to determine which patients respond well to extended-release dalfampridine without conducting timed 25-foot walks.[42] Patients self-reported improvement when extended-release dalfampridine was compared to placebo.[42] In those patients who respond, the effect appears to be sustained for at least 2 years.[90]

Adverse effects associated with extended-release dalfampridine include urinary tract infections, insomnia, dizziness, headache, and nausea. Seizures are a less common adverse effect and are related to dose and use of immediate-release dalfampridine. Therefore, this agent is contraindicated in patients with a history of seizures.[91]

PAIN

Between 30% and 90% of patients with MS report experiencing pain.[43] Pain related to MS is of two types: non-neurogenic and neurogenic. Non-neurogenic pain is often related to paralysis, immobility, or spasticity; examples include tension-type headache, low back pain, and limb pain associated with poor mobility or postural changes.[92] Physical therapy, repositioning limbs, and typical analgesics may be effective for treatment of non-neurogenic pain.

A number of painful neurogenic conditions have been described in association with MS (**Table 57-3**).[92] Patients often describe neurogenic pain as having a burning, aching, pricking, stabbing, or smarting quality. Atypical analgesics are used for neurogenic pain. For trigeminal neuralgia, carbamazepine and oxcarbazepine are first-line treatments.[92] Baclofen, lamotrigine, gabapentin, topiramate, or nabiximols may be helpful as second-line treatments.[92] Surgical options may provide relief if drug treatments are ineffective.[92] Antiepileptic medicines and antidepressants are also commonly used for other types of neurogenic pain.

Table 57-3
Types of Neurogenic Pain Associated With Multiple Sclerosis

Trigeminal neuralgia—sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve
Lhermitte phenomenon—sudden onset, brief, electric shock-like sensation traveling rapidly down to the spine or into the arms or legs. Usually caused by flexing the neck. Sometimes occur occasionally for short periods
Tonic spasms
Burning dysesthesia of the limbs and trunk

Migraine headache

Source: Chisari CG, Sgarlata E, Arena S, D'Amico E, Toscano S, Patti F. An update on the pharmacological management of pain in patients with multiple sclerosis. *Expert Opin Pharmacother*. 2020;21:2249–2263.

FATIGUE

Often described as the most disabling symptom by patients with MS, 74% experience fatigue.[43] The reason that patients exhibit fatigue is not well understood; however, hypotheses include direct effects of cytokines, axonal loss, or cortical disorganization.[44] Conduction is impaired in demyelinated axons, and increases in temperature may further worsen conduction.[44] However, fatigue may be caused or worsened by other mechanisms such as sleep dysfunction, depression, or medication adverse effects.[43]

Nonpharmacologic approaches are often the mainstay of therapy for fatigue and may include interventions to improve sleep quality, treatment for depression when present, improvements in diet, and increased physical activity.[43,93] Cognitive behavioral therapy has been helpful for some patients.[94] Cooling therapy with jackets worn over large areas of the body has demonstrated benefit in clinical trials.[95]

The only pharmacologic therapy for fatigue with proven benefit is amantadine; however, the clinical trials for this agent have included small numbers of patients.[43] Sustained-release fampridine may be helpful in some patients.[43] Modafinil has been used in two placebo-controlled studies, but neither trial showed significant differences in response between modafinil and placebo.[43]

COGNITIVE DYSFUNCTION

Cognitive dysfunction may occur early in the course of the disease and has a negative impact on quality of life.[96] Among patients with CIS, 29% had cognitive impairment at the time of presentation. In this study, the only predictor of cognitive impairment was the number of lesions on MRI.[96] Between 40% and 70% of MS patients eventually have some cognitive dysfunction.[43] Another study

followed patients diagnosed with CIS and determined that lower levels of vitamin D and smoking in the 2 years following MS diagnosis predicted worse cognitive functioning 11 years later.[97] The most common problems are memory impairment, slowed speed of information processing, decreased mental flexibility, and impaired executive functioning.[43] Cognitive dysfunction can also limit the ability of patients with MS to understand discussion of disease and treatments.[96] Breaking down discussions into various components (eg, intended effects, adverse effects) helps with understanding.[96]

Nonpharmacologic interventions such as cognitive rehabilitation to develop the use of intact cognitive skills to compensate for areas of poor cognitive performance may be beneficial.[96] Treatment of MS with immunomodulatory drugs has shown some benefit for cognitive impairments.[97,98] In several small studies, dalfampridine treatment improved several indicators of cognitive function: processing speed, psychomotor speed, attention, alertness, planning, and fluency.[99–101] Additionally, a meta-analysis of acetylcholinesterase inhibitors and stimulants did not show cognitive benefit for patients with MS.[102] One small study of high-dose simvastatin was promising[103] and another small study of vitamin D replacement in patients with deficient serum 25-hydroxyvitamin D concentrations improved cognitive performance.[104]

SPASTICITY

Spasticity can be defined as an increased resistance of muscle to an externally imposed stretch.[45] Approximately 60% of patients with MS exhibit spasticity, which may worsen with other noxious stimuli such as a full bladder or colon, infection, or MS exacerbations.[43,45] Complications from spasticity may include pain, spasms, reduced mobility, limited range of movement, contractures, fatigue, poor quality of sleep, cardiopulmonary deconditioning, decubitus ulcers, and skin breakdown.[45]

Nonpharmacologic therapies, such as repositioning physical therapy, stretching, or splinting, may help with spasticity.[45] These efforts are usually most successful with spasticity that is localized to

one area of the body. Injection of intramuscular botulinum toxin can also be beneficial for localized spasticity.[45] Spasticity that is generalized to many areas of the body is best addressed with systemic therapy in addition to nonpharmacologic treatments. Baclofen and tizanidine are first-line therapies for spasticity. Gabapentin, benzodiazepines, and dantrolene are considered as second-line agents.[45] In severe cases, intrathecal baclofen can be delivered via infusion pump through a catheter into the intrathecal space.[45] A combination of tetrahydrocannabinol and cannabidiol oromucosal spray has shown some benefit for spasticity for patients with MS, but trials have been small.[105–107] There is no FDA-approved indication for this use in the United States.

PSYCHIATRIC DYSFUNCTION

Psychiatric problems, including depression, bipolar disorder, pseudobulbar affect (emotional lability), anxiety, and psychosis, all occur at increased rates in patients with MS compared with the general population.[46] Depression can affect up to 50% of patients with MS.[43] Several clinical trials of depression treatment have been conducted in patients with MS. In these, cognitive behavioral therapy has been shown to be effective, and fluoxetine, desipramine, paroxetine, and sertraline have been shown to have benefit in some trials.[46,108]

Pseudobulbar affect occurs in ~10% of patients with MS and involves frequent and inappropriate episodes of crying, laughing, or both, which may be unrelated to underlying mood. The exact cause of pseudobulbar affect is not known, but it may be caused by disruption of neural pathways from the brainstem and cerebellum. Serotonin, dopamine, and glutamate also appear to be important in the development of pseudobulbar affect. It is not isolated to patients with MS but may also occur in other neurologic disorders such as stroke. This disorder can be socially stigmatizing and highly disabling.[109]

When used together, dextromethorphan and quinidine have shown efficacy for pseudobulbar affect, and a combination product is

approved for this indication by the FDA. Dextromethorphan is an agonist at σ-1 receptors, suppressing release of excitatory neurotransmitters, and an antagonist at *N*-methyl-D-aspartate glutamate receptors.[109] Dextromethorphan is metabolized by CYP 2D6 to dextrorphan, which does not cross the blood–brain barrier. When a low dose of quinidine, a CYP 2D6 inhibitor, is added, dextromethorphan serum concentrations are increased 20-fold. In a 12-week study of 283 patients, a 49% improvement in inappropriate emotional episodes was demonstrated.[109]

Vitamin D

Although early clinical trials with vitamin D appeared to benefit patients with MS,[8] other studies did not find benefits.[8,110–112] A larger clinical trial is ongoing to evaluate the therapeutic potential of vitamin D supplementation in patients with MS.[113]

CASE 57-1

QUESTION 1: C.B. is a 32-year-old female of Finnish descent who presents to the neurology clinic with slurred speech and double vision. These symptoms began a week ago and have not changed. C.B. saw her primary care physician at that time, who referred her to the neurology clinic. Her past medical history is unremarkable other than a normal gestation and vaginal delivery of a female infant 3 years ago. Today, her vital signs are a blood pressure of 126/82 mm Hg, heart rate of 78 beats/minute, respirations at 20 breaths/minute, and a temperature of 99.32 °F (37.4 °C). Review of systems is negative, except as noted above. On neurologic examination, C.B. is alert and her speech is fluent, but slurred. Her cranial nerves examination reveals sixth nerve palsy, and C.B. cannot abduct the right eye on rightward gaze; her visual fields are full. Her tongue and palate are at midline and there is no facial asymmetry. Her motor examination reveals normal tone and strength; her sensory examination is intact to light touch, pinprick, vibration, and position sense. Her finger-to-nose, rapid alternating movements, heel-to-shin, and gait are all normal. On MRI, C.B. has one gadolinium-enhancing lesion in the right mid-pons. Examination of her CSF reveals the following:

Red blood cells, 0 (normal 0)
White blood cells, 0 (normal 0–5)

Protein, 24 mg/dL (normal 15–50 mg/100 mL)
Glucose, 60 mg/dL (normal 50–80 mg/100 mL)

Her CSF is positive for oligoclonal bands, and immunoglobulin G (IgG) synthesis rate is 4.3 mg/24 hours (normal <3.3 mg/24 hours). Her current medications include a multivitamin one by mouth (PO) every morning, loratadine 10 mg PO every morning, and levonorgestrel-releasing intrauterine system.

What risk factors, signs, and symptoms suggestive of MS are present in C.B.? How do her MRI and CSF findings support or refute a diagnosis of MS?

C.B. has several epidemiologic factors associated with MS (see **Table 57-1**). She is 32 years old, consistent with onset between the ages of 20 and 50 years; she is female—females are two to three times more likely to develop MS than males—and she is of northern European ancestry, which also increases her risk of MS. Her symptoms and physical examination findings are consistent with a demyelinating event in the pons area of the brainstem. On MRI, C.B. has one active (gadolinium-enhancing) lesion in this area. This finding on the MRI is abnormal, and gadolinium-enhancing lesions are found commonly in patients with MS. Her CSF examination on lumbar puncture shows the presence of oligoclonal bands and an increased rate of IgG synthesis. These findings are also consistent with a diagnosis of MS. Although the combined evidence from her history, examination, and MRI studies make the eventual diagnosis of MS likely, they do not demonstrate dissemination in space and time. The criteria for dissemination in time is met by the presence of oligoclonal bands. To show dissemination in space, another clinical event affecting another part of the body or another MRI showing lesions in a different area of the brain would be necessary.[1] At the present time, C.B. would be diagnosed as having CIS.

Case 57-1, Question 2: Should C.B. begin treatment at this time? If so, what treatment(s) would be appropriate?

Cladribine, glatiramer acetate, interferon-β preparations, ozanimod, siponimod, and teriflunomide have demonstrated reduced

development of MS if taken after the identification of CIS.[114,115] Further, there is evidence that earlier treatment with a disease-modifying regimen delays conversion to clinically definite MS compared to delaying treatment.[116–118] C.B. should be educated on the risk of developing clinically definite MS, and she should begin therapy with one of these agents. There is no evidence on which to base the choice of therapy; commonly the prescriber will have a preference based on discussion with the patient. However, the FDA does not recommend cladribine for CIS therapy based on its safety profile.[70]

CASE 57-1, QUESTION 3: C.B. is started on glatiramer acetate 20 mg subcutaneously daily. How should C.B. be counseled regarding the injection of glatiramer acetate and the potential adverse effects of this treatment? How can she help alleviate or avoid these adverse effects? What monitoring is required?

Glatiramer acetate is supplied as a single-use, prefilled syringe. In general, the recommended administration techniques are similar to those used for other subcutaneously administered products, and the important counseling points are summarized in **Table 57-4**. The administration technique is slightly different for the intramuscular injection. There are product-specific differences in dose preparation for which it is important to consult the product information. C.B. should be instructed on administration technique, and it is recommended that the first injection be self-administered under the supervision of a health care professional.

Table 57-4
Patient Counseling Points for β-Interferon and Glatiramer Acetate Products

For All Products
Use clean technique—wash hands with soap and water, clean injection site with an alcohol swab, do not touch site or needle tip to other surfaces or with fingers.
Choose an appropriate site:

For subcutaneous injection—fleshy part of upper back, arm, front of thighs, lower abdomen, fleshy area of upper hip For intramuscular injection—front of thigh, side of thigh, upper arm
Rotate between injection sites to avoid overuse of any one site.
Examine the reconstituted product for particles, cloudiness, or color changes. The products should be colorless to light yellow.
For subcutaneous injection—pinch up a fold of skin between index finger and thumb for the injection. For intramuscular injection—stretch the skin between index finger and thumb for the injection.
Insert the needle at a 90 degree angle to the skin.
Release the skin.
Steadily push down on the plunger until all the medicine is injected.
Pull needle straight out of skin and dispose of it in a hard-walled plastic container.

Sources: Betaseron (interferon beta-1b). Package insert. Bayer HealthCare Pharmaceuticals; 2020; Rebif (interferon beta-1b). Package insert. EMD Serono; 2020; Avonex (interferon beta-1a). Package insert. Biogen Inc.; 2020; Plegridy (peginterferon beta-1a). Package insert. Biogen Inc.; 2020; Copaxone (Glatiramer Acetate Injection). Package insert. Teva Neuroscience; 2019.

Glatiramer acetate is initiated at a dose of 20 mg subcutaneously daily or 40 mg three times weekly.[119] No dosage titration is required. However, for interferon-β products, a product-specific titration schedule is recommended to minimize flu-like symptoms.[61–64]

Common adverse effects of glatiramer acetate are injection site reactions and post-injection systemic reactions.[119] Injection site reactions with glatiramer acetate include hemorrhage, hypersensitivity, inflammation, mass, pain, edema, and atrophy at the injection sites. Rarely, necrosis at the injection site can develop. Lipoatrophy may be seen in up to 45% of patients with longer-term use.[119] Acute injection site reactions may be reduced by applying warm compresses or ice to the injection site before injection, warming the medication to room temperature before injection, and ensuring that the needle completely penetrates the skin during injection.[120,121] Symptoms of post-injection systemic reactions include facial flushing, chest tightness, dyspnea, palpitations, tachycardia, and anxiety.[119] Approximately 16% of patients experience this

reaction. When this reaction occurs, its onset is within seconds to minutes after injection, and it may last up to 60 minutes.[119] No specific treatment is recommended for post-injection systemic reactions to glatiramer acetate.

Adverse effects are fairly common with interferon-β; they include leukopenia (36%–86%), injection site reaction (6%–92%) and necrosis (3%–6%), flu-like symptoms (49%–57%), breakthrough menstrual bleeding (28%), and increased liver function tests (12%–27%).[61–64,122] Depression and suicide are seen in patients treated with the β-interferons; however, it is difficult to distinguish the independent contribution of interferon from any possible concomitant effects of MS itself.[123]

Flu-like reactions include the symptoms of fever, chills, myalgia, malaise, and sweating, and they occur in about half of patients who are initiated on an interferon-β.[60] Symptoms usually begin 3 to 6 hours after administration and last ~24 hours. Female patients and those with lower body mass index may have more severe flu-like symptoms.[122] Most patients find that these symptoms decrease with time, with only 10% of patients reporting flu-like symptoms after 1 year of therapy.[60] Helpful tips for patients to reduce flu-like symptoms include administering the injections at night to sleep through the time of peak symptoms, taking ibuprofen or acetaminophen before and every 4 to 6 hours as needed after the injection, and gradual titration to full dose.[122,123]

Injection site reactions vary from 92% with some subcutaneous preparations of interferon-β to 6% with the intramuscular preparation.[61–64] These symptoms are similar to those seen with glatiramer acetate except, that lipoatrophy is not seen with interferon-β. Females appear to be more likely to experience injection site reactions than males.[122] Strategies to reduce injection site reactions include injecting the drug in areas with more subcutaneous fat (abdomen or buttocks), rotating injection sites, using an auto-injection device, and icing the site after injection.[122,123]

General monitoring recommendations for both interferon-β and glatiramer acetate include observation of injection sites for infection, necrosis, and atrophy. Specifically for the β-interferons, complete

blood counts and liver function tests are monitored.[61–64] The frequency of monitoring is not specified in product literature, but a reasonable approach would be at baseline and 1 to 3 months after initiation and then every 6 to 12 months during continuation of therapy. Additionally, patients should be monitored for signs or symptoms of depression. Therefore, the specific counseling and monitoring plan needed for C.B. is instruction in self-injection technique for the subcutaneous injection and discussion of injection site reactions, including their prevention and monitoring, and post-injection systemic reactions. C.B. should also be counseled regarding the value of ongoing clinical monitoring (for efficacy, injection site reactions, and post-injection reactions) during glatiramer acetate therapy.

Case 57-1, Question 4: Six months later, C.B. returns for an appointment with her neurologist. During the discussion, she states that she is not having any problems with injection technique or adverse effects, but she reveals that she is only using the glatiramer acetate three or four times a week instead of the daily injection schedule that was prescribed. When questioned, she states, "I just don't know that it's doing anything." How might C.B.'s neurologist deal with this adherence problem?

Adherence is often poor with disease-modifying therapy for MS; over 2 to 5 years, only 60% to 76% of patients adhere to therapy.[124] Patient characteristics and other factors that have been associated with poor adherence are listed in **Table 57-5**.[124–130] In one study, self-efficacy and belief that the medicine would have benefit were strong predictors of adherence, whereas cognitive difficulties, occurrence of adverse effects, depression, more disability, and poor quality of life predicted nonadherence.[131] In another interesting study among patients who had discontinued treatment against medical advice, 42.3% were found to be using avoidance coping strategies by avoiding engaging in care or rationalizing their decision to not use treatment such as exaggerated skepticism about medication effectiveness, irrational concerns about treatment, or unrealistic optimism about the projected course of MS.[129] Adherent patients

have a lower risk of relapses, fewer emergency department visits, and fewer hospitalizations.[132,133]

Table 57-5

Patient Characteristics and Other Factors Associated With Reduced Adherence to Therapies

For All Therapies	Specific to a-Interferons or Glatiramer Acetate
Younger age	Secondary-progressive multiple sclerosis
Female sex	Cognitive impairment
Perceived lack of efficacy	Depression
Unrealistic expectations	Lifestyle or economic instability
Inpatient stay in previous year	Needle phobia
More than two relapses in previous year	Lack of family or other support
Out of pocket costs	
Mild disease course	
Adverse effects	
Inconvenience	
Avoidance coping (avoiding engaging in care, rationalizing decision to not take therapy)	

Source: Kleinman NL, Beren IA, Rajagopalan K, Brook RA. Medication adherence with disease modifying treatments for multiple sclerosis among US employees. *J Med Econ. 2010*;13:633–640; Li P, Ladage VP, Berger J, et al. Disease-modifying therapy adherence and associated factors in a national sample of Medicare patients with multiple sclerosis. *Value Health*. 2020;23:328–334; Schoor R, Bruce A, Bruce J, et al. Reasons for nonadherence and response to treatment in an adherence intervention trial for relapsing-remitting multiple sclerosis patients. *J Clin Psychol*. 2019;75:380–91; Bruce J, Bruce A, Lynch S, et al. A pilot study to improve adherence among MS patients who discontinue treatment against medical advice. *J Behav Med*. 2015; 39:276–287; Caon C, Saunders C, Smrtka J, Baxter N, Shoemaker J. Injectable disease-modifying therapy for relapsing-remitting multiple sclerosis: a review of adherence data. *J Neurosci Nurs*. 2010;42(5, suppl):S5–S9; Steinberg SC, Faris RJ, Chang CF, Chan A, Tankersley MA. Impact

of adherence to interferons in the treatment of multiple sclerosis: a non-experimental, retrospective, cohort study. *Clin Drug Investig*. 2010;30:89–100.

For C.B., it appears that she has perceived lack of efficacy for the glatiramer acetate; however, other factors associated with nonadherence should be sought and discussed with her. For an individual patient, it is impossible to know what the course of disease would be without treatment; thus, many patients believe that the medicine is not having a positive impact. Particularly for a patient with CIS who does not have ongoing symptoms, embarking on a lifelong therapy can be challenging. Additionally, there is no immediate feedback to the patient that the medication is having an effect, in contrast to some other diseases such as diabetes in which a fingerstick blood glucose measurement provides positive reinforcement.[125] Some evidence suggests that patients would prefer not to take a treatment that causes significant adverse effects until the symptoms experienced from their MS are worse than the perceived adverse effects.[134,135] Strategies that may improve adherence include establishing a good patient–health care provider relationship, patient education and periodic reinforcement, management of adverse effects, involving care partners, treating depression, and motivational interviewing/cognitive behavioral therapy.[125,129]

CASE 57-1, QUESTION 5: After re-education and frank discussion, C.B.'s adherence improves, and she does well for a year on glatiramer acetate therapy. However, a routine monitoring MRI scan shows a new gadolinium-enhancing lesion on her right optic nerve. Additionally, a new nonenhancing lesion is apparent on the MRI scan. Does this new information change her diagnosis and treatment?

With these new MRI lesions, the "separation in space and time" criteria for the diagnosis of MS have been met. Thus, C.B. now would be diagnosed with MS. Given her history, she is diagnosed with relapsing-remitting MS. To guide the clinician in choosing the most efficacious therapy, there are data from several clinical trials that directly compare first-line therapies (see **Table 57-**

6).[53,58,75,82,83,136–142] From the data available, it appears that interferon β-1a intramuscularly once weekly is less effective than the other first-line treatments. There is emerging evidence that some therapies (eg, alemtuzumab, ofatumumab, and ozanimod) are more efficacious than some older medicines.[53,58,82,83,142]

Table 57-6
Clinical Trials Directly Comparing Active Treatments

Trial	Treatments	Results
INCOMIN[136]	Interferon β-1b 250 µg subcutaneously every other day versus interferon β-1a 30 µg IM weekly	Compared with patients treated with interferon β-1a, more patients treated with interferon β-1b were relapse-free (51% vs 36%), there were fewer mean relapses (0.38% vs 0.5%), and fewer patients progressing 1 point on the EDSS (13% vs 30%) after 2 years.
EVIDENCE[137]	Interferon β-1a subcutaneously 44 µg three times weekly versus interferon β-1a 30 µg IM weekly	Compared with patients treated interferon β-1a IM, patients treated with interferon β-1a subcutaneously had fewer mean relapses (0.29% vs 0.4%) and fewer lesions on MRI after 24 weeks.
REGARD[138]	Interferon β-1a 44 µg subcutaneously three times weekly versus glatiramer acetate 20 mg subcutaneously daily	No significant differences in time to first relapse or MRI changes after 96 weeks.
BEYOND[139]	Interferon β-1b 250 µg subcutaneous every other day versus interferon β-1b 500 µg subcutaneous every other day versus glatiramer acetate 20 mg subcutaneous daily	No differences in relapse rate, EDSS progression, or MRI lesions after 2–3.5 years.

Trial	Treatments	Results
CONFIRM[77]	Dimethyl fumarate 240 mg PO twice daily versus dimethyl fumarate 240 mg PO three times daily versus glatiramer acetate 20 mg subcutaneous daily versus placebo	Compared to placebo, all active therapies reduced annualized relapse rates (0.22, 0.20, 0.29 vs 0.40), EDSS progression, and MRI lesions. No differences between dimethyl fumarate 240 mg twice daily and glatiramer for any outcome except for one type of MRI lesion after 2 years.
TENERE[140]	Teriflunomide 7 mg PO daily versus teriflunomide 14 mg PO daily versus interferon β-1a 44 µg subcutaneous three times weekly	No differences in relapse rate, treatment failure after 48 weeks.
CARE-MS I[53]	Alemtuzumab 12 mg IV daily for 5 days, then 12 mg IV daily for 3 days 12 months later versus interferon β-1a 44 µg subcutaneous three times weekly	More patients taking alemtuzumab were relapse-free (78%) at 2 years than the interferon group (59%). Fewer patients taking alemtuzumab had disease progression (8% vs 11%).
CARE-MS II[141]	Alemtuzumab 12 mg IV daily for 5 days, then 12 mg IV daily for 3 days 12 months later versus interferon β-1a 44 µg subcutaneous three times weekly	More patients taking alemtuzumab were relapse-free (65.4%) at 2 years than the interferon group (46.7%). Fewer patients taking alemtuzumab had disease progression (12.71% vs 21.13%). Fewer patients taking alemtuzumab had new MRI lesions (9% vs 23%).

Trial	Treatments	Results
ASCLEPIOS I/ASCLEPIOS II[58]	Teriflunomide 14 mg PO daily versus ofatumumab 20 mg subcutaneous days 1, 7, 14 and every 4 weeks	Annualized relapse rates were lower in the ofatumumab group (0.11) than the teriflunomide group (0.22). Patients with worsening disability was less with ofatumumab (10.9%) than teriflunomide (15%) at a mean follow-up of 1.6 years. The mean number of MRI lesions/scan was also less in the ofatumumab group.
RADIANCE[82]	Ozanimod 0.5 mg PO daily versus ozanimod 1 mg PO daily versus interferon β-1a IM 30 µg weekly	Annualized relapse rates were lower with ozanimod 0.5 mg (0.22) and 1 mg (0.17) compared to interferon (0.28). New MRI lesions were lower with both ozanimod groups. There was no difference in disability progression after 24 months.
SUNBEAM[83]	Ozanimod 0.5 mg PO daily versus ozanimod 1 mg PO daily versus interferon β-1a IM 30 µg weekly	Annualized relapse rates were lower with ozanimod 0.5 mg (0.24) and 1 mg (0.18) compared to interferon (0.35). New MRI lesions were lower with both ozanimod groups. There was no difference in functional scores or quality of life after at least 12 months of treatment.

EDSS, Expanded Disability Status Scale; IM, intramuscular; MRI, magnetic resonance imaging; PO, orally; IV, intravenous.

Case 57-1, Question 6: C.B. admits that she disliked giving herself daily injections and began therapy with dimethyl fumarate delayed-release 120 mg PO twice daily for 7 days, then 240 mg PO twice daily thereafter. What counseling should she receive regarding the adverse effects of this medication?

Dimethyl fumarate commonly causes flushing and gastrointestinal (GI) adverse effects; it has been formulated as a delayed-release product to help with these problems. Flushing occurs in about 30% to 38% of patients taking dimethyl fumarate in clinical trials.[75,143] The GI adverse effects include diarrhea 13%, nausea 11%, and upper abdominal pain 10%.[75,143] Taking doses with food helps decrease

both of these types of adverse effects. In a small study specifically examining flushing and GI effects, the incidence of flushing was much higher, up to 98% in some groups, but decreased somewhat with continued use. Each event lasted between 1 and 2 hours. Aspirin 325 mg taken 30 minutes prior to the dose decreases the incidence of flushing by about 14%. The subjects also had much higher incidences of GI effects, between 79% and 81%, falling to 53% to 61% during the second month of use. GI event onset was a median time of 2 weeks. Aspirin had no effect on GI symptoms.[73] Metoclopramide, ondansetron, domperidone, antacids, H_2-receptor antagonists, proton pump inhibitors, and antidiarrheals have been recommended to combat the GI symptoms, and antihistamines have been used for flushing but no testing of these approaches has been performed.[73] Use of diroximel fumarate may also decrease GI effects,[144] but use of monomethyl fumarate may not.[145] Lymphopenia occurs in about 2% of patients taking dimethyl fumarate; however, mean lymphocyte count decreases by about 30% in the first year of treatment and then stabilizes. Patients should have a complete blood count at baseline and then annually.[143]

C.B. should be counseled to take her doses with food. Because it is a delayed-release product, she should swallow the capsules whole. If she experiences flushing, aspirin 325 mg PO 30 minutes prior to dosing could be recommended. If she experiences GI problems, those could be treated symptomatically.[73]

Case 57-1, Question 7: C.B. continued on therapy with dimethyl fumarate. However, 1 year later, she has experienced one relapse and is currently hospitalized with another. She has been adherent to therapy. Her MRI shows several new gadolinium-enhancing lesions. What therapy should be recommended for acute treatment of C.B.'s current relapse? Would you change her maintenance therapy at this time?

Corticosteroids should be used to decrease the time to recover from acute relapses. The most commonly used regimen is 500 to 1000 mg intravenous methylprednisolone daily for 3 to 5 days with or without a subsequent regimen of tapering dose oral steroids for 1 to

3 weeks.[146] Comparison of oral and intravenous corticosteroid treatment shows that there are no major differences in clinical outcomes, and both treatments appear to be equally effective and safe.[50] A commonly recommended oral corticosteroid regimen is prednisone 1250 mg daily every other day for five doses.[146] Some investigators have attempted to use corticosteroids on a chronic basis, giving pulse doses of one or several days monthly; however, this type of regimen does not affect disability progression and should not be recommended.[147] Because C.B. is already hospitalized, she should receive methylprednisolone 1000 mg intravenously daily for 3 days. If she were an outpatient, either intravenous or oral steroid therapy could be recommended, but an oral corticosteroid regimen would be more convenient.

As MS therapies have become more effective, tolerance for relapses has decreased. No evidence of disease activity (NEDA) is a composite measure that indicates that there are (a) no new or enlarging T2-weighted lesions on MRI, (b) no new gadolinium-enhancing lesions on MRI, (c) no relapses, and (d) no progression on EDSS scores over a period of time.[148] Percentages of patients in clinical trials achieving NEDA status are between 28% and 45% over the first 2 to 3 years of therapy; however, this number may decrease over time.[148]

It appears that C.B. is failing treatment with dimethyl fumarate because she has experienced two relapses within ~1 year and has substantial new lesion formation on MRI; there are several alternatives at this point. C.B. should change to another therapy. A careful discussion of the potential risks and benefits of each possible treatment will ensure that the patient is well educated on the options and that an appropriate selection is made.

Case 57-1, Question 8: After lengthy discussion, C.B. elects to discontinue dimethyl fumarate therapy and start fingolimod 0.5 mg PO daily. How should C.B. be counseled regarding the potential benefits and adverse effects of fingolimod? What monitoring will be necessary?

In studies of fingolimod, 70.4% of patients remained relapse-free for 2 years compared with 45.6% for those treated with placebo. At 1 year, 82.6% of fingolimod-treated patients were relapse-free compared with 69.3% of those treated with interferon β-1a intramuscularly. The annualized relapse rate was 0.16/year for fingolimod, 0.40/year for placebo, and 0.33/year for interferon β-1a intramuscularly.[80] C.B. should expect good suppression of her MS with fingolimod treatment.

Because S1P receptors are not confined to lymphocytes, adverse effects of S1P receptor modulators (fingolimod, ozanimod, ponesimod, and siponimod) may affect other body organs and tissues. For example, a transient, dose-dependent reduction in heart rate can occur within 1 hour after the first fingolimod dose (bradycardia in 1.3%); first- and second-degree atrioventricular block can also occur (0.1% and 0.2%, respectively).[80,115,149–151] Patients with pre-existing sinus bradycardia or heart block without pacemakers should not be given S1P receptor modulators. Sphingosine-1-phosphate receptor modulators may cause a small increase in blood pressure over time.[115,149–151] However, foods with large amounts of tyramine (>150 mg) could cause severe hypertension when given with ozanimod because an active metabolite of ozanimod inhibits monoamine oxidase type B.[115] Ozanimod, ponesimod, and siponimod have several other drug–drug interactions that require precautions.[115,150] Patients with CYP 2C9*3/*3 genotype should not be given siponimod because of substantially elevated plasma concentrations; dose decreases are needed with other genotypes.[150] Other adverse effects of S1P receptor modulators include macular edema and a reduction in forced vital capacity.[80] Macular edema occurs in <1% of patients who receive S1P receptor modulators; however, patients with a history of uveitis or diabetes have an increased risk.[80]

Because the mechanism of action of S1P receptor modulators is to prevent lymphocytes from circulating, there is a reduction in peripheral blood lymphocytes and an increase in infections and, possibly, cancers.[80] This reduction in peripheral blood lymphocytes is reversible within 4 to 8 weeks of discontinuation of fingolimod,[149] 30

days for ozanimod,[115] 10 days for siponimod,[150] and 1 week for ponesimod.[151] Sphingosine-1-phosphate receptor modulators do not inhibit humoral immunity to infections.[80] Progressive multifocal leukoencephalopathy (PML) has been reported in patients taking fingolimod.[149] PML is caused by JC DNA polyomavirus (JCV) reactivation. JCV then causes an infection of oligodendrocytes that is often fatal or causes permanent disability.[152] Dormant JCV infection is relatively common, with 50% to 86% of adults having antibodies to JCV. When a patient is immunosuppressed, JCV may become reactivated.[152] PML is rapidly progressive and has a mortality rate of ~50%.[152] Symptoms of PML include neurobehavioral, motor, language, and cognitive changes; seizures; vision changes; hemiparesis; and tremor.[152] Notably, all of these symptoms could be mistaken for an MS relapse. Other MS medications can cause PML. A drug risk classification scheme has been proposed for PML, which places natalizumab in class I (high risk); dimethyl fumarate and fingolimod in class II (low risk); and alemtuzumab, mitoxantrone, rituximab, and teriflunomide in class III (very low or no risk).[153] Some of the newer MS agents were not in use at the time this classification scheme was proposed. Of note, PML has been reported with cladribine and ofatumumab when used in oncology.[154,155] It would seem likely that ocrelizumab, ozanimod, ponesimod, and siponimod could also be associated with PML, and the risk is listed in prescribing information for these medicines.[115,150,151,156]

Increases in liver enzymes (transaminase and bilirubin) have also been observed with S1P receptor modulator treatment.[80] Because fingolimod has a long half-life of 9 to 10 days, its pharmacologic effects will still be present for up to 2 months after therapy is discontinued.[149] Ozanimod has a half-life of 21 hours, but the half-life of its active metabolite is 11 days, and effects may remain for up to 3 months after stopping treatment.[115] Siponimod has a shorter half-life of 30 hours, and most effects have dissipated within 10 days.[150] Ponesimod's half-life is 33 hours with most effects resolving in 1 to 2 weeks.[151] Baseline testing and continued monitoring recommended with the use of S1P-receptor modulators is summarized in **Table 57-7**. These agents should be given as monotherapy, and the patient

should not have had a relapse or have been treated with corticosteroids within 30 days of starting treatment. If patients do not have an existing history of varicella zoster infection or vaccination, vaccination should be undertaken before initiating therapy.[115,149–151] Live-attenuated vaccines should not be used while receiving S1P-receptor modulators, and it is not known how effective the body's response to other vaccination is during treatment.[115,150–152,157] Rates of varicella infections are between 7 and 11/1000 patient-years.[158] C.B. should wait for 30 days after her relapse and any corticosteroid treatment before starting fingolimod. During this time, she can have baseline testing before starting treatment. She should be educated on potential adverse effects and the long-lasting pharmacologic effects of fingolimod that may persist for up to 2 months after therapy is discontinued.

Table 57-7

Baseline Testing and Monitoring Associated With S1P Receptor Modulators

Baseline
Varicella zoster immunity evaluation and vaccination, if needed
Ophthalmology evaluation for macular edema
FEV_1 or full pulmonary function testing, if patient has history of asthma or chronic obstructive pulmonary disease
Pulse and blood pressure
Complete blood count
Liver function tests
Electrocardiogram
Fingolimod Only
Dermatologic evaluation for melanomas
Siponimod Only
CYP 2C9 genotype determination
Monitoring
Ophthalmology evaluation at 4 months and as needed thereafter
Complete blood count every 6 months
Liver function tests every 6 months
Dermatologic evaluation as needed
FEV_1 as needed

For All Patients Initiating Fingolimod and Patients Initiating Ponesimod and Siponimod With Certain Cardiac History

Observe in clinical area for 6 hours after initial dose with monitoring of blood pressure and pulse and repeat electrocardiogram at 6 hours post-dose

CYP, cytochrome P_{450}; FEV_1, forced expiratory volume in 1 second.

Sources: Zeposia (ozanimod). Package insert. Celgene Corporation; 2020; Gilenya (fingolimod). Package insert. Novartis Pharma Stein AG; 2019; Mayzent (siponimod). Package insert. Novartis Pharmaceuticals Corporation; 2020; Ponvory (ponesimod). Package insert. Janssen Pharmaceutical Companies; 2021.

CASE 57-1, QUESTION 9: C.B. is appropriately started on fingolimod and does very well with visits to the neurologist every 6 months. When she is seen 2 years later, she informs her care providers that she is considering having another child. How should C.B. be counseled regarding fingolimod therapy during pregnancy?

It is well-documented that the rate of relapses for females with MS decreases during pregnancy, increases in the first 3 months after delivery, then returns to the prepregnancy rate.[159] No treatment for MS is recommended for use during pregnancy, and some therapies, such as cladribine and mitoxantrone, require pregnancy tests before each infusion. However, there are limited data regarding the exposure of fetuses to some of the treatments for MS when given during early pregnancy. No increase in spontaneous abortions or stillbirths was seen with glatiramer acetate or β-interferons.[159] However, very few of these exposures were for the full term of pregnancy. A report of 66 pregnancies in females taking fingolimod found fetal abnormalities in 7.6%. In all these cases, the exposure was in the first trimester.[159] Pregnancy is contraindicated during treatment with teriflunomide, with contraception required for both females and males.[160] Eighty-nine pregnancies (70 in females exposed to teriflunomide and 19 in partners of males exposed to teriflunomide) were reported during clinical trials. Of these, 42 healthy live births, 31 induced abortions, and 14 spontaneous abortions were reported. It should be noted that in almost all cases, teriflunomide was stopped and accelerated elimination procedures were undertaken as soon as the pregnancy was known to minimize

fetal exposure.[161] Alemtuzumab is also contraindicated during pregnancy. Females should use adequate contraceptive measures during treatment and for 4 months following treatment. Alemtuzumab can cause thyroid disorders, which, during pregnancy, can have serious adverse effects on the fetus.[162] Cladribine is contraindicated in pregnancy and lactation, and males taking cladribine should also prevent pregnancy.[70] Pregnancy should be avoided in females taking ocrelizumab and ofatumumab and for 6 months after discontinuing the drugs.[156,163]

In general, MS therapy should be discontinued before conception. In the case of C.B., she should be advised that she would need to discontinue fingolimod at least 2 months before conception and stay off the medication while pregnant. It is not known whether fingolimod is excreted into the breast milk of nursing females.[149] Because of the potential adverse effects of fingolimod on an infant's immune system, she should be advised either to not breast-feed or to abstain from taking fingolimod during nursing. Similar recommendations are in place for ozanimod and siponimod, but recommendations for length of time to avoid conception after discontinuation is different because of differences in elimination; 3 months for ozanimod, 10 days for siponimod, and 1 week for ponesimod.[115,149–151]

Case 57-1, Question 10: C.B. discontinued fingolimod, conceived ~4 months later, and delivered a healthy male child after a normal gestation and labor. She experienced a relapse of MS 2 months after delivery, discontinued nursing, and was treated with corticosteroids. Two months after the relapse and treatment, she returns to the neurology clinic for a follow-up appointment. She states that she is ready to restart fingolimod therapy at this time. She states that she is often very tired and feels that "she can't continue." However, she admits that this feeling may also be related to being a new mother. She states that her husband and daughter help significantly with care of the infant. She has noticed some jerkiness in her gait, and she states that sometimes her toes will contract toward her head involuntarily. Her neurologic examination shows spasticity in her lower extremities. What treatments would be appropriate for management of C.B.'s spasticity? How should her fatigue be addressed?

Nonpharmacologic therapy such as stretching may help with C.B.'s spasticity. Her symptoms are more generalized (involving the

lower extremities) than localized, so systemic therapy may be more beneficial than localized therapy such as splinting or botulinum toxin injections (therapies that might be considered if only her toes were involved).[43,45] Systemic therapies that may relieve spasticity include baclofen and tizanidine; because both agents appear to be equally effective, neither agent is preferred over the other for C.B.

Although fatigue is a common problem when caring for infants, C.B. also may be experiencing fatigue related to her MS. She would likely benefit from nonpharmacologic therapy such as avoiding sleep deprivation to the extent possible and concentrating her infant care during the morning hours, enlisting more assistance in the afternoon and evening. She should also be assessed for any symptoms of depression.[44]

CASE 57-2

Question 1: N.R. is a 47-year-old female who was diagnosed with relapsing-remitting MS 5 years ago. She has been taking interferon β-1b 250 μg subcutaneously every other day since diagnosis. For the first 4 years, she did very well with only one relapse. However, in the past year, she has sustained two relapses, and she feels that her treatment is not working as well as it did in the past. Her neurologist sends a blood specimen for neutralizing antibody assay with a result of 160 neutralizing units/mL (reported as high by the laboratory).

How might this result assist in the recommendation of future therapy for N.R.?

Neutralizing antibodies develop in many patients given therapy for MS, including alemtuzumab, β-interferons, natalizumab, ocrelizumab, and ofatumumab. Neutralizing antibodies are seen in up to 44% of patients given interferon-β.[60,65] Fewer patients given interferon β-1a intramuscularly once weekly develop them than those given interferon β-1a subcutaneously three times weekly or interferon β-1b subcutaneously every other day.[65] For patients with persistently high antibody titers, their relapse rates are also higher.[111] With time, neutralizing antibodies often disappear.[65]

Despite these observations, the indications for neutralizing antibody testing and the interpretation of test results are areas of

ongoing controversy. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has issued the following statements regarding neutralizing antibodies to interferon-β: (a) treatment with interferon-β is associated with the production of neutralizing antibodies; (b) it is probable that neutralizing antibodies, especially in persistently high titers, are associated with a reduction in the radiographic and clinical effectiveness of treatment; (c) it is probable that the rate of neutralizing antibody production is less with interferon β-1a compared with interferon β-1b treatment; (d) it is probable that the seroprevalence of neutralizing antibodies is affected by one or more of the following: formulation, dose, route of administration, or frequency of administration of interferon-β; and (e) there is insufficient information on the utilization of neutralizing antibody testing to provide specific recommendations regarding the indications for testing or interpretation of antibody titer results.[164]

A panel of MS and neutralizing antibody experts was convened in 2009 to develop practical recommendations. Some of their findings are as follows: (a) persistently high titers might provide sufficient guidance to suggest stopping therapy in a patient; however, with low or intermediate titers, additional information might be needed to make a decision regarding therapy continuation; (b) different interferon-β products are associated with different rates of antibody formation; chemical formulation, route of administration, and frequency of dosing appear to have an effect; and different formulations of the same molecule may result in different immunogenicity; and (c) to minimize assay variability, antibody measurements should be done in laboratories that have fulfilled the criteria for validation of neutralizing antibody assays, and interferon β-1a should be used in the assays to standardize the assays.[165] Thus, there is continued discussion about the appropriate use of neutralizing antibody assays for β-interferons.

Antibodies also form to therapies for MS other than the β-interferons. Up to 95% of patients treated with glatiramer acetate have antibodies, but they do not appear to change the efficacy of glatiramer acetate.[166] Antibodies may develop to natalizumab and

may affect treatment efficacy or increase the likelihood of natalizumab infusion reactions. Many patients who express antibodies to natalizumab do so within the first 6 months of treatment, but these antibodies often disappear with continued treatment. Antibodies to natalizumab are more likely to persist if they develop more than 6 months after treatment initiation. High antibody titers are associated with increased rates of relapse and, generally, therapy should be changed.[167] Neutralizing antibodies have been detected with alemtuzumab, but they do not appear to affect efficacy.[141] It is not known if the presence of neutralizing antibodies alters the efficacy of ocrelizumab, and ofatumumab.

N.R. has a high titer of neutralizing antibodies, and they appear to be associated with a decline in efficacy of her interferon β-1b. Therefore, it is appropriate to change therapy at this time. Because of the potential for cross-reactivity of the neutralizing antibodies to other β-interferons, a change to another β-interferon product would not be expected to provide benefit.

Case 57-2, Question 2: N.R.'s interferon β-1b therapy was discontinued, and she was started on teriflunomide 14 mg PO daily. What monitoring will be required while taking this medicine?

Elevated alanine aminotransferase (ALT), alopecia, and diarrhea were seen in 10% to 20% of patients in clinical trials and more commonly in patients treated with teriflunomide than with placebo.[161] White blood cell counts decrease by about 15% and platelets by about 10% during the first 6 weeks of teriflunomide treatment and remain low throughout the treatment. A complete blood count (CBC) is recommended at baseline.[161] Because of the immunosuppression seen, patients should be monitored for infection, and patients should not receive live virus vaccines while under the effects of teriflunomide.[161] Modest increases in blood pressure were also observed. Other required monitoring includes baseline liver enzymes and bilirubin, blood pressure, and screening for latent tuberculosis infection. The monitoring of ALT should occur monthly for the first 6

months of therapy and periodically thereafter.[161] Teriflunomide rarely causes the serious adverse effects of peripheral neuropathy, acute renal failure, hyperkalemia, and bone marrow suppression.[85] Serious adverse effects are not reported with teriflunomide, but those seen with the parent drug leflunomide are Stevens–Johnson syndrome, interstitial lung disease, and hepatotoxicity.[162] Teriflunomide has a very long half-life of ~18 days.[162] Because of this, it can take up to 3 months to achieve steady-state serum concentrations and a proportionally long time to eliminate the medicine (8–24 months). In situations requiring rapid elimination of teriflunomide (eg, serious adverse effects, desired pregnancy), accelerated elimination procedures are recommended. The recommended accelerated elimination procedures are administration of cholestyramine 8 g every 8 hours for 11 days or administration of activated charcoal powder 50 g every 12 hours for 11 days. Verification of elimination should be undertaken by two teriflunomide serum concentrations of <0.02 µg/mL taken 2 weeks apart.[162]

Prior to N.R. starting teriflunomide, her immunization status should be carefully checked, and she should be screened for tuberculosis. If necessary, her immunizations should be updated, and any infectious diseases should be completely treated before starting therapy. She should have a baseline CBC, liver enzymes, bilirubin, and blood pressure. Monthly for the first 6 months, she should have blood drawn for ALT. This would also be an opportune time to check blood pressure and screen for signs of infection.

Case 57-2, Question 3: N.R. successfully began teriflunomide and continued without adverse effects for 1 year. At her annual MRI visit, however, five new lesions were seen in her brain. She continued for another 6 months and had a follow-up MRI with three additional lesions detected. In discussion with her neurologist, she decided to change therapy. Alemtuzumab, cladribine, natalizumab, ocrelizumab, and ofatumumab are considered as therapy alternatives for N.R. How should N.R. be counseled regarding the potential adverse effects and monitoring for these agents?

Recently, there has been interest in defining highly active MS and developing treatment approaches. One definition that has been

advanced is relapsing-remitting MS that meets one of the following criteria: (a) EDSS score of 4 at 5 years after disease onset, (b) multiple relapses (two or more) with incomplete recovery in the current year, (c) more than two brain MRI studies demonstrating new lesions or increases in the size of the lesions despite treatment, and (d) no response to treatment with one or more disease-modifying therapies for at least 1 year.[168] Individuals with highly active MS are usually considered for induction therapy protocols with alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, or ofatumumab.[168–170] There is some evidence that treatment with these medicines is more beneficial if begun early in the disease course.[171–175] Autologous hematopoietic stem cell transplantation is also a consideration.[168,175]

Cladribine has significant adverse effects associated with its use. Because of its mechanism of action, lymphopenia always occurs. Additionally, neutropenia, anemia, and thrombocytopenia occur.[70] Infections, particularly herpes zoster, pyelonephritis, and fungal infections, are also a common occurrence with cladribine treatment.[70] If patients have lymphocyte counts <200 cells/μL, they require anti-herpes prophylaxis.[70] Eleven percent of patients treated with cladribine develop hypersensitivity reactions.[70] Other common adverse effects include headache and nausea. Less common, but severe concerns include development of malignancies, PML, cardiac failure, and heptatoxicity.[70] A thorough evaluation of vaccination needs is recommended prior to beginning treatment with cladribine.[70] There are several drug–drug interactions with cladribine; however, many can be managed by holding the interacting medication for several days around the cladribine dose.[70] Cladribine has a unique dosing regimen with a maximum of two courses divided into two 4- to 5-day cycles given a year apart with significant monitoring associated with each course (**Table 57-8**).[168]

Table 57-8
Monitoring Required for Cladribine Use

Baseline and Before Each Course

▪ Pregnancy test, in females ▪ Complete blood count with differential ▪ Human immunodeficiency virus screening ▪ Tuberculosis screening ▪ Hepatitis B and C ▪ Liver function tests
Baseline
▪ Varicella zoster immunity evaluation and vaccination, if needed ▪ MRI within 3 months
Ongoing
▪ Standard cancer screenings ▪ Complete blood count with differential 2 and 6 months after start of treatment in each treatment course, then periodically

Source: Mavenclad (cladribine). Package insert. EMD Serono; 2019.

Ocrelizumab has been associated with infections, particularly respiratory tract and herpes infections. Infusion reactions may include itching, rash, redness, bronchospasms, dyspnea, pharyngeal or laryngeal edema, hypotension, pyrexia, headache, fatigue, nausea, and tachycardia.[156] To prevent infusion reactions, premedication is recommended with methylprednisolone 100 mg intravenously, an antihistamine, and an antipyretic 30 minutes before the infusion is also recommended.[156] The patient should be monitored for at least an hour following the end of the infusion, although infusion reactions can occur up to 24 hours later.[156] Even with premedication, infusion reactions were seen in 34% to 40% of patients.[156] As with other B-cell depleting therapies, the patient should receive any vaccinations needed prior to start of therapy, and live-attenuated vaccines should not be administered during treatment.[156] It is important to observe all monitoring recommendations during ocrelizumab treatment (**Table 57-9**).

Table 57-9
Recommended Monitoring for Use of Alemtuzumab, Ocrelizumab, and Ofatumumab

Test	Alemtuzumab				Ocrelizumab		Ofatumumab
	Baseline	Monthly for 48 Months After Last Dose	Every 3 Months for 48 Months After Last Dose	Yearly	Baseline	Before Each Infusion	Baseline
CBC with differential	x	x					
Serum creatinine	x	x					
Urinalysis with urine cell counts	x	x					
Thyroid-stimulating hormone	x		x				
Skin examination	x			x			
Human papilloma virus	x			x			
Tuberculosis	x						
Hepatitis B virus	x				x		x
Hepatitis C virus	x						
Active infection assessment	x	x			x	x	
Quantitative serum immunoglobulins							x

Sources: Ocrevus (ocrelizumab). Package insert. Genentech, Inc.; 2020; Lemtrada (alemtuzumab). Package insert. Genzyme Corporation; 2020; Kesimpta (ofatumumab) Package insert. Novartis Pharmaceuticals Corporation; 2020.

Ofatumumab commonly causes infections.[163] Ofatumumab is self-injected subcutaneously and can cause injection reactions such as fever, headache, myalgia, chills, fatigue, erythema, swelling, itching, and pain at the injection site in 11% to 21% of patients with the first injection. The number of patients experiencing injection reactions decreased with further injections.[163] Decreases in immunoglobulin levels were seen in clinical trials, and a baseline should be established before treatment begins (**Table 57-9**).[163] As with other B-cell depleting therapies, the patient should receive any vaccinations needed prior to start of therapy and live-attenuated vaccines should not be administered during treatment.[163]

Several serious adverse effects, infusion reactions, autoimmune conditions, and malignancies associated with alemtuzumab use have caused the FDA to require a limited distribution program for this agent. Infusion reactions associated with alemtuzumab are triggered by cytokine release, may include rash, fever, headache, itching, nausea, and chills, and occur in about 90% of patients; serious reactions occurred in 3% of patients.[51,162] Patients should be

monitored for 2 hours after each infusion, but reactions may occur after that period.[162] Premedication should consist of methylprednisolone 1000 mg infused immediately before the first infusion and for the first 3 days of each treatment course. Antihistamines and acetaminophen may also be helpful premedications.[162] Autoimmune diseases have been associated with alemtuzumab therapy and may include thyroid disorders (34%), immune thrombocytopenia (2%), and antiglomerular basement membrane disease (0.3%).[51,142,162] Thyroid disorders have been seen up to 60 months after the initial treatment with alemtuzumab.[142] Of thyroid dysfunction seen, 73% is hyperthyroidism and 14% is hypothyroidism.[176] Patients receiving alemtuzumab had higher rates of some malignancies, including thyroid cancer and melanoma at a rate of 0.3% each.[142] Infections were more common in patients treated with alemtuzumab than those treated with interferon-β, including urinary tract infections (17%), herpes virus infections (16%), respiratory infections (16%), and fungal infections (12%).[51,142] Infections were more common in the first year of treatment (58.7%), then declined until year 6 (38.1%).[177] The herpes virus infections are most common in the month following the infusion and can be significantly reduced by prophylaxis.[51] The recommendation is that patients receive antiviral prophylaxis for herpetic viral infections starting on the first day of each treatment course and continuing for a minimum of 2 months following treatment or until the $CD4^+$ lymphocyte count is ≥200 cells/μL, whichever occurs later.[162] The dosing of alemtuzumab is unique for MS medicines in that it is a 12-mg/day infusion for 5 days and then an additional 12 mg/day infusion for 3 days 12 months after the first treatment course.[162] No vaccines should be administered during treatment and all should be completed at least 6 weeks prior to treatment, including varicella zoster virus vaccine, if patients have not been vaccinated and do not have a history of infection.[162] Monitoring recommendations can be found in **Table 57-9**.

Adverse effects of natalizumab include fatigue, liver dysfunction, infections, hypersensitivity reactions, and infusion-related reactions.[178] Hypersensitivity reactions are IgE-mediated and occur

within 2 hours of the start of the infusion. Patients who exhibit HLA-DRB1*13 or HLA-DRB*14 are more likely to have hypersensitivity reactions.[179] Genotyping may be helpful to identify these patients prior to natalizumab prescribing. Symptoms include urticaria, dyspnea, and vital sign changes. If these symptoms occur, the infusion should be discontinued.[178] Hypersensitivity reactions should be distinguished from infusion-related reactions. These latter reactions are nonallergic and include symptoms of headache, dizziness, fatigue, nausea, sweats, and rigors. If this type of reaction occurs, there is no need to discontinue therapy; the patient can be pretreated with histamine type 1 and 2 receptor antagonists and acetaminophen.[178]

As previously mentioned, PML is associated with natalizumab therapy. It appears that PML risk is proportional to the duration of natalizumab exposure; one case is reported per 1000 patients in those who have received 24 or more infusions.[154] Overall, reporting appears to occur at a rate of one or two per month.[154] In a 5-year observational cohort study, 0.7% of patients given natalizumab developed PML, two of whom died (4.5% fatality rate).[180] This may be because of the heightened sensitivity to clinical changes that may suggest PML and aggressive immune reconstitution with either plasma exchange or immunoabsorption if PML is diagnosed. However, this immune reconstitution can lead to immune reconstitution inflammatory syndrome (IRIS), which is itself life-threatening. IRIS usually presents as an acute worsening of MS symptoms and is treated with high-dose corticosteroids.[180] Several groups have developed recommendations for natalizumab use to reduce the risk of PML (**Table 57-10**).[153,181]

Table 57-10
Recommendations for Use of Natalizumab

Patients Who Should Not Receive Natalizumab
Immunocompromised
Active viral hepatitis
Active malignancy that requires treatment
Inability to get MRI

Have or have had progressive multifocal leukoencephalopathy
Recommendations for Use
Monotherapy with natalizumab only After failure of interferon or glatiramer acetate Therapy-free interval of 14 days after interferon or glatiramer acetate, 3 months after azathioprine, or 6 months after mitoxantrone
Baseline Testing
Clinical neurologic examination Human immunodeficiency virus testing Complete blood count Liver function tests MRI with IV contrast Anti-JC virus antibody testing
Monitoring
Neurologic examination at 3 months, 6 months, and then yearly MRI with IV contrast at 6 months and then yearly Periodic anti-JC virus antibody testing

IV, intravenous; MRI, magnetic resonance imaging.

Sources: Bartsch T, Rempe T, Leypoldt F, et al. The spectrum of progressive multifocal leukoencephalopathy: a practical approach. *Eur J Neurol*. 2019;26:566–e41; Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61:1332–1338.

Although approved for treatment of MS, mitoxantrone is no longer commonly used because of significant adverse effects, including nausea, menstrual abnormalities, alopecia, upper respiratory and urinary tract infections, neutropenia, and a temporary change to blue color in the urine and sclera.[76] Dose-related cardiotoxicity occurs with mitoxantrone use, requiring an estimation of left ventricular ejection fraction before each dose.[182] Cardiotoxicity limits the lifetime dose of mitoxantrone to 140 mg/m^2 or ~3 years of therapy. The most common cardiotoxic effects are cardiomyopathy, decreased left ventricular ejection fraction, and irreversible congestive heart failure.[182] Leukemia also occurs with mitoxantrone therapy, usually during the first few years and it may be dose-related.[182]

There is no clear best choice of therapy for N.R. Careful discussion of the potential risks and benefits of each medication should be discussed with her so that her preferences are considered. All of these therapies carry substantial adverse effects about which she will need to be informed. Additionally, she will need to enroll in the restricted distribution systems for the chosen medicine. Another area that requires consideration is that she may be at higher risk for PML or other opportunistic infections when beginning one of these medicines after taking teriflunomide. Conversely, being completely without medicine allows for return or possible "rebound" of disease activity. Possible strategies include undergoing accelerated elimination procedures for the teriflunomide and then (a) allowing for a washout period during which the patient receives no treatment, (b) providing a monthly regimen of methylprednisolone while allowing for a washout period, or (c) switching directly to another therapy without a washout period. It is not known which of these options is best for a patient.

CASE 57-2, QUESTION 4: N.R. experiences another relapse while she is considering which therapy to begin. One month after completing corticosteroid treatment for this relapse, she returns to the neurology clinic for a follow-up appointment. N.R. explains that she has been experiencing episodes of uncontrollable laughing. When these episodes first began, she thought they might be an adverse effect of the corticosteroid treatment for her relapse. However, 1 month after stopping corticosteroid treatment, she is still having these episodes. She states that the episodes are very embarrassing, often occurring at inappropriate times such as in movie theaters, at parent–teacher conferences, and in grocery stores. She is diagnosed with pseudobulbar affect. What treatment is available for pseudobulbar affect, and how should N.R. be counseled regarding this treatment?

Dextromethorphan with quinidine is effective for reducing the rate of pseudobulbar affect episodes and is FDA-approved for this indication. It is dosed one capsule (dextromethorphan 20 mg/quinidine 10 mg) orally twice daily.[183] Adverse effects related to the dextromethorphan component may include dizziness and the possibility of serotonin syndrome. Adverse effects associated with

quinidine are an immune-mediated thrombocytopenia, lupus-like syndrome, hepatotoxicity, dose-dependent QTc interval prolongation, and anticholinergic effects.[183]

There are several drug interactions associated with dextromethorphan–quinidine.[183] It is contraindicated with monoamine oxidase inhibitors, requiring a 14-day washout before starting therapy. Similarly, caution should be exercised when this therapy is used concomitantly with selective serotonin reuptake inhibitors and tricyclic antidepressants. It is contraindicated with drugs that prolong the QTc interval and are metabolized by CYP 2D6. Dextromethorphan–quinidine should be used with caution with drugs that inhibit CYP 3A4. Because quinidine inhibits CYP 2D6, dose adjustments for CYP 2D6 substrates are necessary. Quinidine also inhibits P-glycoprotein, requiring caution and perhaps dose adjustments when this treatment is used in combination with digoxin.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Claflin SB, van der Mei IAF, Taylor BV. Complementary and alternative treatments of multiple sclerosis: a review of the evidence from 2001 to 2016. *J Neurol Neurosurg Psychiatry.* 2018;89:34–41. (94)

Crabtree-Hartman E. Advanced symptom management in multiple sclerosis. *Neurol Clin.* 2018;36(1):197–218. (43)

Farez MF, Correale J, Armstrong MJ, et al. Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis. *Neurology*. 2019;93:584–894. (157)

Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation

Subcommittee of the American Academy of Neurology. *Neurology.* 2018;90:777–788. (169)

Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2018;90:789–800. (170)

Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17:162–173. (49)

Key Websites

National Multiple Sclerosis Society. http://www.nationalmssociety.org

COMPLETE REFERENCES CHAPTER 57 MULTIPLE SCLEROSIS

1. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: a review. *JAMA.* 2021;325:765–779.
2. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. *Curr Opin Neurol.* 2018;31:752–759.
3. Lunde HMB, Assmus J, Myhr KM, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. *J Neurol Neurosurg Psychiatry*. 2017;88:621–625.
4. GBD 2016 Multiple Sclerosis Collaborators. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:269–285.
5. Jongen PJ. Health-related quality of life in patients with multiple sclerosis: impact of disease-modifying drugs. *CNS Drugs.* 2017;31:585–602.
6. Tarlinton RE, Khaibullin T, Granatov E, Martynova E, Rizvanov A, Khaiboullina S. The interaction between viral and environmental risk factors in the pathogenesis of multiple sclerosis. *Int J Mol Sci*. 2019;20:303.
7. Lam T, VoPham T, Munger KL, Laden F, Hart JE. Long-term effects of latitude, ambient temperature, and ultraviolet radiation on the incidence of multiple sclerosis in two cohorts of US women. *Environ Epidemiol.* 2020;4:e105.
8. Miclea A, Bagnoud M, Chan A, Hoepner R. A brief review of the effects of vitamin D on multiple sclerosis. *Front Immunol.* 2020;11:781.

9. Jacobs BM, Giovannoni G, Cuzick J, Dobson R. Systematic review and meta-analysis of the association between Epstein-Barr virus, multiple sclerosis and other risk factors. *Mult Scler*. 2020;26(11):1281–1297
10. Nishanth K, Tariq E, Nzvere FP, Miqdad M, Cancarevic I. Role of smoking in the pathogenesis of multiple sclerosis: a review article. *Cureus.* 2020;12:e9564.
11. Belbasis L, Bellou V, Evangelou E, Tzoulaki I. Environmental factors and risk of multiple sclerosis: findings from meta-analyses and Mendelian randomization studies. *Mult Scler.* 2020;26:397–404.
12. Spelman T, Gray O, Trojano M, et al. Seasonal variation of relapse rate in multiple sclerosis is latitude dependent. *Ann Neurol*. 2014;76:880–890.
13. Ismailova K, Poudel P, Parlesak A, Frederiksen P, Heitmann BL. Vitamin D in early life and later risk of multiple sclerosis—a systematic review, meta-analysis. *PLoS One.* 2019;14:e0221645.
14. Pegoretti V, Swanson KA, Bethea JR, Probert L, Eisel ULM, Fischer R. Inflammation and oxidative stress in multiple sclerosis: consequences for therapy development. *Oxid Med Cell Longev*. 2020;2020:7191080.
15. International Multiple Sclerosis Genetics Consortium. Multiple sclerosis genomics map implicates peripheral immune cells and microglia in susceptibility. *Science.* 2019;365:eaav7118.
16. Amezcua L, McCauley JL. Race and ethnicity on MS presentation and disease course: ACTRIMS Forum 2019. *Mult Scler.* 2020;26:561–567.
17. Romanelli RJ, Huang Q, Lacy J, Hashemi L, Wong A, Smith A. Multiple sclerosis in a multi-ethnic population from Northern California: a retrospective analysis, 2010–2016. *BMC Neurol.* 2020;20:163.
18. Cipriani VP, Klein S. Clinical characteristics of multiple sclerosis in African-Americans. *Curr Neurol Neurosci Rep.* 2019;19:87.
19. Hurwitz BJ. Analysis of current multiple sclerosis registries. *Neurology*. 2011;76(suppl 1):S7–S13.
20. Scott TF, Schramke CJ. Poor recovery after the first two attacks of multiple sclerosis is associated with poor outcome five years later. *J Neurol Sci*. 2010;292:52–56.
21. Kantarci OH. Phases and phenotypes of multiple sclerosis. *Continuum.* 2019;25:636–654.
22. Inojosa H, Schriefer D, Ziemssen T. Clinical outcome measures in multiple sclerosis: a review. *Autoimmun Rev*. 2020;19(5):102512.
23. Lublin FD, Coetzee T, Cohen JA, Marrie RA, Thompson AJ. The 2013 clinical course descriptors for multiple sclerosis: a clarification. *Neurology.* 2020;94:1088–1092.
24. Express Scripts. Express scripts 2018 drug trend report. Accessed October 3, 2020. https://corporate-site-labs-prod.s3.us-east-2.amazonaws.com/2020-02/Express%20Scripts%202018%20Drug%20Trend%20Report.pdf

25. Asche CV, Singer ME, Jhaveri M, Chung H, Miller A. All-cause health care utilization and costs associated with newly diagnosed multiple sclerosis in the United States. *J Manag Care Pharm*. 2010;16:703–712.
26. Kim Y, Krause TM, Blum P, Freeman L. Disease modifying therapies continue to drive up health care cost among individuals with multiple sclerosis. *Mult Scler Relat Disord.* 2019;30:69–75.
27. Bishop M, Rumrill PD. Multiple sclerosis: etiology, symptoms, incidence and prevalence, and implications for community living and employment. *Work*. 2015;52(4):725–734.
28. Faissner S, Plemel JR, Gold R, Yong VW. Progressive multiple sclerosis: from pathophysiology to therapeutic strategies. *Nat Rev Drug Discov.* 2019;18:905–922.
29. Comi G, Hartung H-P, Bakshi R, Williams IM, Weindl H. Benefit-risk profile of sphingosine-1-phosphate receptor modulators in relapsing and secondary progressive multiple sclerosis. *Drugs.* 2017;77:1755–1768.
30. van Langelaar J, Rijvers L, Smolders J, van Luijn MM. B and T cells driving multiple sclerosis: identity, mechanisms and potential triggers. *Front Immunol*. 2020;11:760.
31. Arneth BM. Impact of B cells to the pathophysiology of multiple sclerosis. *J Neuroinflammation.* 2019;16:128.
32. Rahmanzadeh R, Weber MS, Brück W, Navardi S, Sahraian MA. B cells in multiple sclerosis therapy—a comprehensive review. *Acta Neurol Scand.* 2018;137:544–556.
33. Roggeri A, Schepers M, Tiane A, et al. Sphingosine-1-phosphate receptor modulators and oligodendroglial cells: beyond immunomodulation. *Int J Mol Sci*. 2020;21(20):7537.
34. Campbell G, Mahad DJ. Mitochondrial dysfunction and axon degeneration in progressive multiple sclerosis. *FEBS Letters.* 2018;592:1113–1121.
35. Bennett JL. Optic neuritis. *Continuum (Minneap Minn)*. 2019;25(5):1236–1264.
36. Simone CG, Emmady PD. Transverse myelitis. 2020 Dec 12. In: *StatPearls* [Internet]. StatPearls Publishing; 2021.
37. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain*. 2008;131(Pt 3):808–817.
38. Tintore M, Rovira À, Río J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain*. 2015;138:1863–1874.
39. Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: a large multicentre study. *Mult Scler J*. 2015;21:1013–1024.
40. Barboza AG, Contentti EC, Curbelo MC, et al. Radiologically isolated syndrome: from biological bases to practical management. *Neurol Sci.*

2021;42:1335–1344.
41. Li V, Haslam C, Pakzad M, Brownlee WJ, Panicker JN. A practical approach to assessing and managing sexual dysfunction in multiple sclerosis. *Pract Neurol.* 2020;20:122–32.
42. Baird JF, Sandroff BM, Motl RW. Therapies for mobility disability in persons with multiple sclerosis. *Expert Rev Neurother.* 2018;18:493–502.
43. Crabtree-Hartman E. Advanced symptom management in multiple sclerosis. *Neurol Clin*. 2018;36(1):197–218.
44. Capone F, Collorone S, Cortese R, Di Lazzaro V, Moccia M. Fatigue in multiple sclerosis: the role of thalamus. *Mult Scler*. 2020;26:6–16.
45. Maitin IB, Cruz E. Special considerations and assessment in patients with multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2018;29:473–481.
46. Murphy R, O'Donoghue S, Counihan T, et al. Neuropsychiatric syndromes of multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2017;88:691–708.
47. National Multiple Sclerosis Society. Swallowing problems. Accessed April 19, 2021. http://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Swallowing-Problems
48. Schoedel KA, Morrow SA, Sellers EM. Evaluating the safety and efficacy of dextromethorphan/quinidine in the treatment of pseudobulbar affect. *Neuropsychiatr Dis Treat.* 2014;10:1161–1174.
49. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17:162–173.
50. Lattanzi S, Cagnetti C, Danni M, Provinciali L, Silvestrini M. Oral and intravenous steroids for multiple sclerosis relapse: a systematic review and meta-analysis. *J Neurol*. 2017;264:1697–1704.
51. Zhang J, Shi S, Zhang Y, et al. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2017;11:CD010968.
52. Hermann R, Karlsson MO, Novakovic AM, Terranova N, Fluck M, Munafo A. The clinical pharmacology of cladribine tablets for the treatment of relapsing multiple sclerosis. *Clin Pharmacokinet.* 2019;58:283–297.
53. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet*. 2012;380:1819–1828.
54. Gingele S, Jacobus TL, Konen FF, et al. Ocrelizumab depletes CD20+ T cells in multiple sclerosis patients. *Cells.* 2019;8:12.
55. Barkhof F, Kappos L, Wolinsky JS, et al. Onset of clinical and MRI efficacy of ocrelizumab in relapsing multiple sclerosis. *Neurology.* 2019;93:e1778–e1786.
56. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med.* 2017;376:221–234.
57. Stahnke AM, Holt KM. Ocrelizumab: a new B-cell therapy for relapsing remitting and primary progressive multiple sclerosis. *Ann Pharmacother*.

2018;52:473–483.
58. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med.* 2020;383:546–557.
59. Hou M, Li Y, He L, et al. Effect of interferon-beta treatment on the proportion of T helper 17 cells and related cytokines in multiple sclerosis: a meta-analysis. *J Interferon Cytokine Res*. 2019;39:771–779.
60. Grabber JJ, McGraw CA, Kimbrough D, Dhib-Jalbut S. Overlapping and distinct mechanisms of action of multiple sclerosis therapies. *Clin Neurol Neurosurg*. 2010;112:583–591.
61. Betaseron (interferon beta-1b). Package insert. Bayer HealthCare Pharmaceuticals; 2020.
62. Rebif (interferon beta-1b). Package insert. EMD Serono; 2020.
63. Avonex (interferon beta-1a). Package insert. Biogen Inc.; 2020.
64. Plegridy (peginterferon beta-1a). Package insert. Biogen Inc.; 2020.
65. Melendez-Torres GJ, Armoiry X, Court R, et al. Comparative effectiveness of beta-interferons and glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network meta-analysis of trials including recommended dosages. *BMC Neurol.* 2018;18:162.
66. Freedman MS. Long-term follow-up of clinical trials of multiple sclerosis therapies. *Neurology*. 2011;76(1, suppl 1):S26–S34.
67. Reder AT, Ebers GC, Traboulsee A, et al. Cross-sectional study assessing long-term safety of interferon-B-1b for relapsing-remitting MS. *Neurology*. 2010;74:1877–1885.
68. Jacobs BM, Ammoscato F, Giovannoni G, Baker D, Schmierer K. Cladribine: mechanisms and mysteries in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2018;89:1266–1271.
69. Moser T, Schwenker K, Seiberl M, et al. Long-term peripheral immune cell profiling reveals further targets of oral cladribine in MS. *Ann Clin Transl Neurol.* 2020;7(11):2199–2212.
70. Mavenclad (cladribine). Package insert. EMD Serono; 2019.
71. Deeks ED. Cladribine tablets: a review in relapsing MS. *CNS Drugs*. 2018;32:785–796.
72. Giovannoni G, Sorensen PS, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: results from the randomized extension trial of the CLARITY study. *Mult Scler.* 2018;24:1594–1604.
73. Blair HA. Dimethyl fumarate: a review in relapsing-remitting MS. *Drugs*. 2019;79:1965–1976.
74. Hansen RH, Cow HH, Sellebjerg F, von Essen MR. Dimethyl fumarate therapy suppresses B cell responses and follicular helper T cells in relapsing-remitting multiple sclerosis. *Mult Scler.* 2019;25:1289–1297.
75. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367:1087–

1097.
76. Koffman BM, Hacker M, Gunning WT 3rd, Quinn A. Something old, new, borrowed, blue: anthracenedione agents for treatment of multiple sclerosis. *Clin Neuropharmacol*. 2016;39:102–111.
77. Shirani A, Stüve O. Natalizumab: perspectives from the bench to bedside. *Cold Spring Harb Perspect Med*. 2018;8:a029066.
78. Sørensen PS. Ozanimod: a better or just another S1P receptor modulator? *Lancet Neurol.* 2016;15:345–347.
79. Kappos L, Li DKB, Stuve O, et al. Safety and efficacy of siponimod (BAF312) in patients with relapsing-remitting multiple sclerosis. Dose-blinded, randomized extension of the phase 2 BOLD study. *JAMA Neurol.* 2016;73:1089–1098.
80. Chun J, Kihara Y, Jonnalagadda D, Blaho VA. Fingolimod: lessons learned and new opportunities for treating multiple sclerosis and other disorders. *Annu Rev Pharmacol Toxicol*. 2019;59:149–170.
81. Cohen JA, Arnold DL, Comi G, et al. Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomized, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2016;15:373–381.
82. Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a muticentre, randomized, 24-month, phase 3 trial. *Lancet Neurol.* 2019;18:1021–1033.
83. Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomized, minimum 12-month, phase 3 trial. *Lancet Neurol.* 2019;18:1009–1020.
84. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 trial. *Lancet.* 2018;391(10127):1263–1273.
85. Vermersch P, Oh J, Cascione M, et al. Teriflunomide vs injectable disease modifying therapies for relapsing forms of MS. *Mult Scler Relat Disord*. 2020;43:102158.
86. Ontaneda D. Progressive multiple sclerosis. *Continuum.* 2019;25:736–752.
87. Lorscheider J, Kuhle J, Izquierdo G, et al. Anti-inflammatory disease-modifying treatment and disability progression in primary progressive multiple sclerosis: a cohort study. *Eur J Neurol.* 2019;26:363–370.
88. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med.* 2017;376:209–220.
89. Charron S, McKay KA, Tremlett H. Physical activity and disability outcomes in multiple sclerosis: a systematic review (2011–2016). *Mult Scler Relat Disord*. 2018;20:169–177.

90. Filli L, Zömer B, Kapitza S, et al. Monitoring long-term efficacy of fampridine in gait-impaired patients with multiple sclerosis. *Neurology.* 2017;88:832–841.
91. Ampyra (dalfampridine). Package insert. Acorda Therapeutics; 2019.
92. Chisari CG, Sgarlata E, Arena S, D'Amico E, Toscano S, Patti F. An update on the pharmacological management of pain in patients with multiple sclerosis. *Expert Opin Pharmacother.* 2020;21:2249–2263.
93. Byrnes KL, Whillier S. Effects of nonpharmaceutical treatments on symptom management in adults with mild or moderate multiple sclerosis: a meta-analysis. *J Manipulative Physiol Ther.* 2019;42:514–531.
94. Claflin SB, van der Mei IAF, Taylor BV. Complementary and alternative treatments of multiple sclerosis: a review of the evidence from 2001 to 2016. *J Neurol Neurosurg Psychiatry.* 2018;89:34–41.
95. Toomey E, Coote SB. Physical rehabilitation interventions in nonambulatory people with multiple sclerosis: a systematic review. *Int J Rehab Res.* 2012;35:281–291.
96. Gromisch ES, Dhari Z. Identifying early neuropsychological indicators of cognitive involvement in multiple sclerosis. *Neuropsychiatr Dis Treat*. 2021;17:323–337.
97. Landmeyer NC, Bürkner PC, Wiendl H, et al. Disease-modifying treatments and cognition in relapsing-remitting multiple sclerosis: a meta-analysis. *Neurology.* 2020;94:e2373–e2383.
98. Comi G, Patti F, Rocca MA, et al. Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomized, multicentre study (the GOLDEN study). *J Neurol.* 2017;264:2436–2449.
99. De Giglio L, De Luca F, Gurreri F, et al. Effect of dalfampridine on information processing speed impairment in multiple sclerosis. *Neurology.* 2019;93:e733–e746.
100. Arreola-Mora C, Silva-Pereyra J, Fernández T, Paredes-Cruz M, Bertado-Cortés B, Grijalva I. Effects of 4-aminopyridine on attention and executive functions of patients with multiple sclerosis: randomized, double-blind, placebo-controlled clinical trial. Preliminary report. *Mult Scler Relat Disord.* 2019;28:117–124.
101. Broicher SD, Filli L, Geisseler O, et al. Positive effects of fampridine on cognition, fatigue and depression in patients with multiple sclerosis over 2 years. *J Neurol.* 2018;265:1016–1025.
102. Cotter J, Muhlert N, Talwar A, Granger K. Examining the effectiveness of acetylcholinesterase inhibitors and stimulant-based medications for cognitive dysfunction in multiple sclerosis: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2018;86:99–107.
103. Chan D, Binks S, Nicholas JM, et al. Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in

secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomized, placebo-controlled trial. *Lancet Neurol.* 2017;16:591–600.
104. Darwish H, Haddad R, Osman S, et al. Effect of vitamin D replacement on cognition in multiple sclerosis patients. *Sci Rep.* 2017;4:45926.
105. Carotenuto A, Iodice R, Petracca M, et al. Upper motor neuron evaluation in multiple sclerosis patients treated with Sativex®. *Acta Neurol Scand.* 2017;135:442–448.
106. Haupts M, Vila C, Jonas A, Witte K, Álvarez-Ossorio L. Influence of previous failed antispasticity therapy on the efficacy and tolerability of THC-CBD oromucosal spray for multiple sclerosis spasticity. *Eur Neurol.* 2016;756:236–243.
107. Marková J, Essner U, Akmaz B, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomized clinical trial. *Int J Neurosci.* 2019;129:119–128.
108. Nathoo N, Mackie A. Treating depression in multiple sclerosis with antidepressants: a brief review of clinical trials and exploration of clinical symptoms to guide treatment decisions. *Mult Scler Relat Disord.* 2017;18:177–180.
109. Pioro EP, Brooks BR, Cummings J, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol*. 2010;68:693–702.
110. Hupperts R, Smolders J, Vieth R, et al. Randomized trial of daily high-dose vitamin D3 in patients with RRMS receiving subcutaneous interferon β-1a. *Neurology.* 2019;93:e1907–e1916.
111. Camu W, Lehert P, Pierrot-Deseilligny C, et al. Cholecalciferol in relapsing-remitting MS: a randomized clinical trial (CHOLINE). *Neurol Neuroimmunol Neuroinflamm.* 2019;6:e597.
112. Muris AH, Smolders J, Rolf L, et al. Vitamin D status does not affect disability progression of patients with multiple sclerosis over three year follow-up. *PLoS One.* 2016;11:e0156122.
113. Bhargava P, Cassard S, Steele SU, et al. The vitamin D to ameliorate multiple sclerosis (VIDAMS) trial: study design for a multicenter, randomized, double-blind controlled trial of vitamin D in multiple sclerosis. *Contemp Clin Trials*. 2014;39:288–293.
114. Yamout B, Sahraian M, Bohlega S, et al. Consensus recommendations for the diagnosis and treatment of multiple sclerosis: 2019 revisions to the MENACTRIMS guidelines. *Mult Scler Relat Disord.* 2020;37:101459.
115. Zeposia (ozanimod). Package insert. Celgene Corporation; 2020.
116. Miller AE, Vermersch P, Kappos L, et al. Long-term outcomes with teriflunomide in patients with clinically isolated syndrome: results of the TOPIC extension study. *Mult Scler Relat Disord.* 2019;33:131–138.
117. Kappos L, Edan G, Freedman MS, et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. *Neurology.* 2016;87:978–987.

118. Comi G, De Stefano N, Freedman MS, et al. Subcutaneous interferon β-1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing frequency-blind muticentre REFLEXION study. *J Neurol Neurosurg Psychiatry.* 2017;88:285–294.
119. Copaxone (Glatiramer Acetate Injection). Package insert. Teva Neuroscience; 2019.
120. Jolly H, Simpson K, Bishop B, et al. Impact of warm compresses on local injection site reactions with self-administered glatiramer acetate. *J Neurosci Nurs*. 2008;40:232–239.
121. Galetta SL, Markowitz C. US FDA-approved disease modifying treatments for multiple sclerosis: review of adverse effect profiles. *CNS Drugs*. 2005;19:239–252.
122. Förster M, Küry P, Aktas O, et al. Managing risks with immune therapies in multiple sclerosis. *Drug Saf.* 2019;42:633–647.
123. Dumitrescu L, Constantinescu CS, Tanasescu R. Recent developments in interferon-based therapies for multiple sclerosis. *Expert Opin Biol Ther.* 2018;18:665–680.
124. Costello K, Kennedy P, Scanzillo J. Recognizing nonadherence inpatients with multiple sclerosis and maintaining treatment adherence in the long term. *Medscape J Med*. 2008;10:225.
125. Saunders C, Caon C, Smrtka J, Shoemaker J. Factors that influence adherence and strategies to maintain adherence to injected therapies for patients with multiple sclerosis. *J Neurosci Nurs*. 2010;42(5, suppl):S10–S18.
126. Patti F. Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. *Patient Prefer Adherence*. 2010;4:1–9.
127. Kleinman NL, Beren IA, Rajagopalan K, Brook RA. Medication adherence with disease modifying treatments for multiple sclerosis among US employees. *J Med Econ*. 2010;13:633–640.
128. Li P, Ladage VP, Berger J, et al. Disease-modifying therapy adherence and associated factors in a national sample of Medicare patients with multiple sclerosis. *Value Health.* 2020;23:328–334.
129. Schoor R, Bruce A, Bruce J, et al. Reasons for nonadherence and response to treatment in an adherence intervention trial for relapsing-remitting multiple sclerosis patients. *J Clin Psychol.* 2019;75:380–91.
130. Bruce J, Bruce A, Lynch S, et al. A pilot study to improve adherence among MS patients who discontinue treatment against medical advice. *J Behav Med.* 2015; 39:276–287.
131. Caon C, Saunders C, Smrtka J, Baxter N, Shoemaker J. Injectable disease-modifying therapy for relapsing-remitting multiple sclerosis: a review of adherence data. *J Neurosci Nurs*. 2010;42(5, suppl):S5–S9.
132. Steinberg SC, Faris RJ, Chang CF, Chan A, Tankersley MA. Impact of adherence to interferons in the treatment of multiple sclerosis: a non-

experimental, retrospective, cohort study. *Clin Drug Investig*. 2010;30:89–100.

133. Cohen BA, Coyle PK, Leist T, Oleen-Burkey MA, Schwartz M, Zwibel H. Therapy optimization in multiple sclerosis: a cohort study of therapy adherence and risk of relapse. *Mult Scler Relat Disord.* 2015;4:75–82.
134. Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Patient and community preferences for treatments and health states in multiple sclerosis. *Mult Scler*. 2003;9:311–319.
135. Carlin CS, Higuera L, Anderson S. Improving patient-centered care by assessing patient preference for multiple sclerosis disease-modifying agents: a state-choice experiment. *Perm J.* 2017;21:16–102.
136. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet*. 2002;359:1453–1460.
137. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: the EVIDENCE trial. *Neurology*. 2002;59:1496–1506.
138. Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol*. 2008;7:903–914.
139. O'Connor P, Filippi M, Arnason B, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study [published corrections appear in *Lancet Neurol*. 2009;8:981; *Lancet Neurol*. 2011;10:115]. *Lancet Neurol*. 2009;8:889–897.
140. Vermersch P, Czlonkowska A, Grimaldi LM, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Mult Scler*. 2014;20:705–716.
141. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet*. 2012;380:1829–1839.
142. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab more effective than interferon β-1a at five-year follow-up of CAMMS223 clinical trial. *Neurology*. 2012;78:1069–1078.
143. Tecfidera (Dimethyl Fumarate Delayed-Release Capsules). Package insert. Biogen; 2020.
144. Naismith RT, Wundes A, Ziemssen T, et al. Diroximel fumerate demonstrates an improved gastrointestinal tolerability profile compared with dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: results from

the randomized, double-blind, phase III EVOLVE-MS-2 study. *CNS Drugs.* 2020;34:185–196.
145. Wynn D, Lategan TW, Sprague TN, Rousseau FS, Fox EJ. Monomethyl fumarate has better gastrointestinal tolerability profile compared with dimethyl fumarate. *Mult Scler Relat Disord.* 2020;45:102335.
146. Repovic P. Management of multiple sclerosis relapses. *Continuum.* 2019;25:655–669.
147. Ravnborg M, Sørensen PS, Andersson M, et al. Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial [published correction appears in *Lancet Neurol*. 2010;9:759]. *Lancet Neurol*. 2010;9:672–680.
148. Mayssam EN, Eid C, Khoury SJ, Hannoun S. “No evidence of disease activity”: is it an aspirational therapeutic goal in multiple sclerosis? *Mult Scler Relat Disord*. 2020;40:101935.
149. Gilenya (fingolimod). Package insert. Novartis Pharma Stein AG; 2019.
150. Mayzent (siponimod). Package insert. Novartis Pharmaceuticals Corporation; 2020.
151. Ponvory (ponesimod). Package insert. Janssen Pharmaceutical Companies; 2021.
152. Bartsch T, Rempe T, Leypoldt F, et al. The spectrum of progressive multifocal leukoencephalopathy: a practical approach. *Eur J Neurol*. 2019;26:566–e41.
153. Berger JR. Classifying PML risk with disease modifying therapies. *Mult Scler Relat Disord.* 2017;12:59–63.
154. Raisch DW, Rafi JA, Chen C, Bennett CL. Detection of cases of progressive multifocal leukoencephalopathy associated with new biologicals and targeted cancer therapies from the FDA’s adverse event reporting system. *Expert Opin Drug Saf.* 2016;15:1003–1011.
155. Alstadhaug KB, Fykse Halstensen R, Odeh F. Progressive multifocal leukoencephalopathy in a patient with systemic mastocytosis treated with cladribine. *J Clin Virol*. 2017;88:17–20.
156. Ocrevus (ocrelizumab). Package insert. Genentech, Inc.; 2020.
157. Farez MF, Correale J, Armstrong MJ, et al. Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis. *Neurology.* 2019;93:584–594.
158. Redelman-Sidi G, Michielin O, Cervera C, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors). *Clin Microbiol Infect.* 2018;24(suppl 2):S95–S107.
159. Varyte. G, Zakarevicˇiene. J, Ramašauskaite. D, Laužikiene. D, Arlauskiene. A. Pregnancy and multiple sclerosis: an update on the disease modifying

treatment strategy and a review of pregnancy's impact on disease activity. *Medicina (Kaunas)*. 2020;56:49.

160. Aubagio (teriflunomide) Package insert. Genzyme Corporation; 2019.
161. Kieseier BC, Benamor M. Pregnancy outcomes following maternal and paternal exposure to teriflunomide during treatment for relapsing-remitting multiple sclerosis. *Neurol Ther*. 2014;3:133–8.
162. Lemtrada (alemtuzumab). Package insert. Genzyme Corporation; 2020.
163. Kesimpta (ofatumumab) Package insert. Novartis Pharmaceuticals Corporation; 2020.
164. Goodin DS, Deisenhammer F, Giovannoni G, Killestein J, Schellekens H. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology [published correction appears in *Neurology*. 2007;69:712]. *Neurology*. 2007;68:977–984.
165. Polman CH, Bertolotto A, Deisenhammer F, et al. Recommendations for clinical use of data on neutralizing antibodies to interferon-beta therapy in multiple sclerosis. *Lancet Neurol*. 2010;9:740–750.
166. Karussis D, Teitelbaum D, Sicsic C, Brenner T; AC001 Multi-center Israeli Study Group. Long-term treatment of multiple sclerosis with glatiramer acetate: natural history of the subtypes of anti-glatiramer acetate antibodies and their correlation with clinical efficacy. *J Neuroimmunol*. 2010;220:125–130.
167. Link J, Ramanujam R, Auer M, et al. Clinical practice of analysis of anti-drug antibodies against interferon beta and natalizumab in multiple sclerosis patients in Europe: a descriptive study of test results. *PLoS One*. 2017;12:e0170395.
168. Díaz C, Zarco LA, Rivera DM. Highly active multiple sclerosis: an update. *Mult Scler Relat Disord.* 2019;30:216–224.
169. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2018;90:777–788.
170. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2018;90:789–800.
171. Perumal J, Fox RJ, Balabanov R, et al. Outcomes of natalizumab treatment within 3 years of relapsing-remitting multiple sclerosis diagnosis: a prespecified 2-year interim analysis of STRIVE. *BMC Neurol.* 2019;19:116.

172. He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol.* 2020;19:307–316.
173. Harding K, Williams O, Willis M, et al. Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. *JAMA Neurol.* 2019;76:536–541.
174. Brown JWL, Coles A, Horakova D, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA.* 2019;32:175–87.
175. Bertolotto A, Martire S, Mirabile L, Capobianco M, De Gobbi M, Cilloni D. Autologous hematopoietic stem cell transplantation (AHSCT): standard of care for relapsing-remitting multiple sclerosis patients. *Neurol Ther*. 2020;9(2):197–203.
176. Pariani N, Willis M, Muller I, et al. Alemtuzumab-induced thyroid dysfunction exhibits distinctive clinical and immunological features. *J Clin Endocrinol Metab*. 2018;103:3010–3018.
177. Wray S, Havrdova E, Snydman DR, et al. Infection risk with alemtuzumab decreases over time: pooled analysis of 6-year data from the CAMMS223, CARE-MS I, and CARE-MS II studies and the CAMMS03409 extension study. *Mult Scler.* 2019;25:1605–1617.
178. Tysabri (natalizumab). Package insert. Biogen Inc.; 2020.
179. de la Hera B, Urcelay E, Brassat D, et al. Natalizumab-related anaphylactoid reactions in MS patients are associated with HLA class II alleles. *Neurol Neuroimmunol Neuroinflamm*. 2014;1:e47.
180. Foley J, Carrillo-Infante C, Smith J, et al. The 5-year Tysabri global observational program in safety (TYGRIS) study confirms the long-term safety profile of natalizumab treatment in multiple sclerosis. *Mult Scler Relat Disord.* 2020;39:101863.
181. Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61:1332–1338.
182. Novantrone (mitoxantrone injection). Package insert. EMD Serono; 2010.
183. Nuedexta (Dextromethorphan and Quinidine). Package insert. Avanir Pharmaceuticals; 2019.

58

Headache

Steven J. Crosby

CORE PRINCIPLES		CHAPTER CASES
1	Migraine, tension-type, and cluster headache are classified as primary headache disorders. Subtle differences in symptomatology and the presence of auxiliary symptoms assist in defining the headache type.	**Case 58-1 (Questions 1, 2, 3, 6)** **Case 58-2 (Questions 1, 3)** **Case 58-4 (Question 1)**
2	Virtually all patients who suffer from migraine, tension-type, and cluster headaches are candidates to receive abortive (or symptomatic) medications during an acute attack. Prophylactic treatment may be considered for all primary headache types and is driven by various factors, including headache frequency, the level of disability imparted by the headache, and response to acute treatment modalities.	**Case 58-1 (Questions 4, 7–12)** **Case 58-2 (Questions 2, 4, 5)** **Case 58-4 (Questions 2, 3)** **Case 58-5 (Questions 1, 2)**

3	Triptans are the drugs of choice as migraine-specific treatments for acute episodes. Triptans are effective in managing associated symptoms of migraine (eg, nausea, photo- and phonophobia). Differences within the class are observed on the basis of pharmacokinetics.	**Case 58-1 (Questions 5, 7, 8)** **Case 58-2 (Question 4)**
4	Evidence supports the use of propranolol, amitriptyline, or topiramate as first-line agents for migraine prophylaxis. Calcitonin gene-related peptide receptor antagonists represent alternatives for treatment failure or intolerance. The decision to initiate prophylaxis takes into account headache frequency, the impact of attacks on patient functioning, and response to acute treatments. Medical history and adverse effect profile are relevant considerations for specific drug selection.	**Case 58-1 (Question 12)** **Case 58-2 (Questions 5, 6)**
5	Overuse of symptomatic or abortive agents (including triptans and over-the-counter, combination, and opioid analgesics) can increase the intensity and chronicity of all headache types. To prevent medication overuse headache, use of these agents should be limited to <10 days/month.	**Case 58-3 (Question 1)**
6	Cluster headaches are severely painful and short-duration attacks that tend to	**Case 58-4 (Questions 1–3)**

	occur nightly during susceptible periods and then enter remission for a period of months or years. Treatments of choice for abortive treatment must be fast-acting and include subcutaneous sumatriptan, intranasal zolmitriptan, and oxygen inhalation.	
7	Tension-type headaches (previously known as tension or muscle contraction headaches) usually cause mild-to-moderate discomfort. Conventional analgesics are often appropriate for acute management. Some patients with tension-type headache may require prophylactic treatment, for which amitriptyline, mirtazapine, and venlafaxine have demonstrated efficacy.	**Case 58-5 (Questions 1, 2)**

INTRODUCTION

Epidemiology

The prevalence of migraine in the United States approximates 15%.[1] There is noted variability in the data relative to parameters of sex and age, with a higher incidence observed in females, and a decline observed with advancing age.[1] Such age- and gender-associated prevalence has been further substantiated in surveillance reviews.[2] Across ambulatory care settings, migraine accounts for 0.5% of all encounters, with a majority occurring in primary care settings, whereas emergency department (ED) visits ~3%,[1,3] being further stratified within the top 10 causes for ED encounters in the United States.[2]

Classification

There is inherent difficulty in evaluating and classifying headache, because this symptom may be attributed to physiologic, psychological, or pathologic process or may be an adverse outcome associated with medications. The completion of a comprehensive assessment of the patient is critical for adequate management. Broadly categorized, headache is defined as primary or secondary, with the latter typically being attributable to an organic cause. Primary headache is inclusive of migraine, tension headache, and trigeminal cephalalgias, of which cluster headache would be one category. Further, headache associated with physical activity, exposure to exogenous stimuli, or those evolving during the sleep cycle would be categorized as primary.[4] Secondary headache may be attributable to, but not limited to, traumatic injury, vascular or nonvascular cranial pathology, tumor formation (neurofibroma), or an infectious process.[4]

The appropriate classification ultimately speaks to the larger issue of optimal management, via either medical procedures or the initiation of medication. Secondary headache is associated with a causative component.[4] Targeting that cause becomes a principle intervention strategy.

PRIMARY HEADACHE DISORDERS

Migraine

The timeline for the evolution of migraine can often be expressed in terms of minutes. The clinical assessment process for differentiating headache type is dependent upon recognizing general characteristics of migraine and further distinguishing such characteristics from other primary headache forms. An assessment of location can be useful but is not a prime differentiator between headache types because migraine location can be unilateral or bilateral in nature. Patient assessment should include an evaluation of both pain intensity and pain quality because migraines are commonly described as moderate-to-severe pulsating pain.[4]

Migraine duration typically ranges from 4 to 72 hours and may be accompanied by auditory (phonophobia) and light (photophobia) sensitivity, as well as nausea and vomiting.[4,5] These auxiliary symptoms are mediated via the hypothalamus and the chemoreceptor trigger zone (CTZ), indicating diffuse neuroanatomic involvement. The aforementioned features have demonstrated reliable predictive value in migraine diagnosis, as defined by the POUND mnemonic (pulsating, 4- to 72-hour duration, unilateral nature, nausea or vomiting, disabling effect).[6] The presence of four out of the five criteria indicates high probability of migraine.[6]

Migraine may be preceded by a constellation of optical or sensory features, defined as an aura. The presence or absence of an aura highlights an important differentiator in migraine diagnosis. International Classification of Headache Disorders criteria indicate a disparity in the number of episodes consistent with a diagnosis of migraine without aura (eg, minimum of five episodes) versus migraine with aura (eg, minimum of two episodes).[4] This criterion is not the only parameter considered, because additional criteria pertaining to headache characteristics also need to be met for an appropriate migraine diagnosis. Auras most often affect vision, with either positive (eg, visual feature) or negative (eg, localized blindness) character.[4] Sensory effects can be characterized similarly as positive (eg, pins and needles description) or negative (eg, loss of sensation or numbness)[4] (**Table 58-1**). Aura character that extends beyond the visual and sensory, such as motor or speech irregularity, is linked more toward specialized migraine diagnoses.[4] Patients with suspected migraine should be advised to document aura timing and description because this information can be valuable for accurate diagnosis.

Table 58-1

Comparative Diagnostic Criteria for Migraine and Migraine With Aura

Criterion	Migraine	Migraine With Aura

Criterion	Migraine	Migraine With Aura
Occurrence	Minimum of five episodes	Minimum of two episodes
Duration	4–72 hours	4–72 hours
GI symptoms	Yes	Yes
Light- and/or auditory-sensitivity	Yes	Yes
Aura presence	No	Yes
Aura symptoms	None	Visual and/or sensory effects occur more frequently. Disturbances in motor function and/or speech may also occur. Motor and speech disturbance are less frequent.

Source: Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1–211. © 2018 SAGE Publications. Reprinted by permission of SAGE Publications, Inc.

Table 58-1 provides a comparison between migraine and migraine with aura diagnoses.

The location of migraine pain may be widespread because of the branching of the trigeminal nerve, which facilitates sensory effects across facial regions. Anatomically, the trigeminal nerve features branches of V1, V2, and V3.[7] Branch V1 innervates the scalp, orbital region, and meninges; V2 is directed to the top of the jaw and sinus region; and V3 innervates lower mandibular regions.[7] Additionally, patients may report pain referral to the suboccipital region because of the proximity of occipital nerves and the spinal nucleus.[7]

Cluster headache

Cluster headache is characterized within the domain of primary headache disorders. Cluster headache is primarily unilateral involving orbital and/or temporal pain, which can persist for up to 3 hours.[4] Independent of duration, such episodes may occur multiple times during the day.[4] Associated symptoms that occur with high

prevalence during cluster headache include lacrimation, rhinorrhea, miosis, ptosis, diaphoresis, and flushing.[4] Preferential incidence of cluster headache occurs in males, but there is similarity to migraine on the basis of age prevalence.

Tension-type headache

Tension-type headache is of bilateral character and, by comparison to migraine, is often associated with less intense pain without a pulsating quality. An individual's subjective description of pain quality and intensity can be useful in differentiation. Patients may use such terminology as "tightening" to characterize symptoms. The *combination* of symptoms of photophobia, phonophobia, and nausea/vomiting is not considered to be consistent with the diagnosis of tension-type headache; however, the *individual* symptoms of photo- or phonophobia may accompany tension-type headache.[4]

SECONDARY HEADACHE

Causation is the key principle underlying secondary headache. Such attributable causes include head or neck trauma, cervical vascular dysfunction, nonvascular cranial dysfunction, infection, psychiatric pathology, or substance withdrawal effects.[4] Causation becomes a critically important principle to consider in patient assessment, particularly when headache onset deviates substantially from existing prevalence and epidemiologic data.

Acute headaches

Acute headaches may be linked to subarachnoid hemorrhage, stroke, meningitis, or intracranial mass (eg, neurofibroma, abscess). It is within this clinical context that diagnostic measures of neuroimaging and lumbar puncture are more commonly implemented. Commonalities of headaches associated with such pathology are of severe quality and rapid evolution, perhaps described as the "worst headache" experienced. An increase in intracranial pressure is of particular importance, and recognition of

factors that can affect intracranial pressure becomes critical in patient assessment.

Subacute headaches

Subacute headaches may be a sign of increased intracranial pressure, intracranial mass lesion, temporal arteritis, sinusitis, or trigeminal neuralgia. Trigeminal neuralgia usually occurs after the age of 40 and is more common in females than in males. The pain usually occurs along the second or third divisions of the trigeminal (facial) nerve and lasts only moments. Trigeminal neuralgia is characterized by sudden, intense pain that recurs paroxysmally, often in response to triggers such as talking, chewing, or shaving.

The evaluation of headache pathology should incorporate the consideration of reported prevalence data, patient age, the presence of triggers or aggravating factors, the contribution of past medical history to headache origin, the patient's description and characterization of symptoms and frequency, and any record of self-care interventions employed to manage headache. Evaluating the impact of headache on daily activity and function is a similarly important consideration. A diagnosis may be confirmed on the basis of this information without the need for further laboratory or procedural measures. If objective or subjective information becomes suggestive of a clinical anomaly (eg, late-age onset of headache, suspected structural anomalies, or neural tissue pathology), a more comprehensive evaluation, inclusive of additional diagnostic measures (eg, imaging, lumbar puncture), is indicated. Imaging will be valuable in the identification of neurofibromas and potential changes in white matter.

Pathologic Basis

The pathologic picture of headache requires an understanding of vascular physiology and the functions of the trigeminovascular circuit and neuropeptides. Headache involves both peripheral and central pain processing, afferent neuronal excitability, and pain sensitivity of

cerebral arteries and venous sinuses.[4,8] The pathology has often been described within the context of interactions between vascular and neurologic systems.[5,9] Muscular tenderness similarly contributes to headache pathology.[8,10] Such an effect is more closely linked with tension headache.

The interplay between vascular and neurologic function is of considerable importance. Afferent and efferent fibers of the trigeminovascular circuitry, vasoactive neuropeptides stored within this system, and serotonin (5-HT) maintain significant pathologic importance.[5,11,12] Neuropeptides, such as substance P, neurokinin A, nitric oxide, calcitonin gene-related peptide (CGRP), and adenylate cyclase-activating peptide, are promoters of neuroinflammation and vessel dilation.[5,12] The vasodilatory potential of CGRP has been widely established, with evidence of increased synthesis during episodes of inflammation.[13] It is a process of continually promoting vasodilation. Evidence further suggests an elevation in pro-inflammatory C-reactive protein in migraine sufferers compared to controls.[14] Therapeutic interventions have focused on modulating the effects of 5-HT with recent efforts directed toward the modulation of neuropeptide function.

Drug Therapy

The primary goal of therapy is the resolution of headache symptoms, most prominently pain, and attenuating disability associated with the headache. Nonpharmacologic recommendations should similarly be paired with therapeutic options. Pharmacologic treatment options can be divided into abortive and prophylactic, the former resolving acute episodes and the latter being administered chronically to reduce the incidence of recurrent headaches. Abortive treatment may sufficiently manage tension-type headache, often negating the need for prophylactic treatment; however, this may be considered when acute treatment is ineffective, overused, or when the headache is chronic or occurring in frequent episodes. Conversely, patients with migraine and cluster headache, while requiring abortive

treatment, may commonly also require long-term prophylactic treatment.

Success in managing acute episodes can often be achieved with the use of conventional analgesics or headache-specific medications (eg, triptans, CGRP antagonists). Medication selection should be based on the patient's prior treatment experience and the level of disability imparted by the headache episode. With regard to prophylactic therapy, evidence supports the use of CGRP monoclonal antibodies, select antidepressants, anticonvulsants, and antihypertensives. The selection of such agents should be considered within the context of adverse effect profiles and the potential for utility in managing other medical conditions (eg, prescribing a β-antagonist for migraine prophylaxis in a patient with a history of hypertension).

MIGRAINE HEADACHE

Migraine is characterized by pain of a throbbing quality with moderate-to-severe intensity and the presence of associated symptoms, including nausea, vomiting, light, and/or auditory sensitivity.[4,5] Migraine can be unilateral or bilateral and can be further classified on the presence of an aura.[4] The occurrence of an aura has diagnostic relevance based on the number of episodes and can encompass a range of sensory disturbances, not solely limited to visual field effects.[4]

Pathophysiology

Vascular constriction was a prior central focus of migraine pathology, resulting in hypoperfusion and being resolved through compensatory vasodilation.[5,15] Such alterations in blood flow have been observed in neuroimaging of migraine patients.[5,16–18] There are further alterations in neuronal depolarization, termed cortical spreading depression.[5,19,20] There has been further demonstration of causality

between cortical spreading depression and the activation of trigeminovascular circuitry.[5,21] The trigeminovascular system consists of afferent fibers with a foundation in trigeminal ganglia, projecting peripherally to intracranial blood vessels and venous sinuses and to extracranial tissues.[5,21] Activation of the trigeminovascular system facilitates the release of vasodilatory-promoting neuropeptides (eg, substance P, neurokinin A, CGRP, nitric oxide), and subsequent release results in vessel dilation and inflammation.[5,12,22,23] The elevation of neuropeptides has become an increasingly important component of the pathologic process. There are noted elevations in CGRP and pituitary adenylate cyclase–activating polypeptide.[24,25] The presence of CGRP in the trigeminal system is significant, and further activity at the level of the trigeminal nucleus caudalis supports the propagation of pain impulses in various neuroanatomical regions.[26]

Migraine pathology is multifaceted and neuroanatomically diffuse, involving the brainstem trigeminal nuclei, trigeminovascular afferents, thalamus, hypothalamus, CTZ, and cortical regions. Therapeutic strategies target the dysfunction in these regions, the mediation of associated symptomatology, and the modulation of neuropeptides and serotonergic neurotransmission.

GENETICS

The genetic basis of migraine is most effectively understood within the context of familial hemiplegic migraine. This subtype has been further categorized into multiple mutation-induced forms with associated genes *CACNA1A*, *ATP1A2*, *SLC1A3*, *SLC4A4*, and *SCN1A*.[27,28]

Such genes encode α_1-subunits (*CACNA1A*, *SCN1A*) and α_2-subunits (*ATP1A2*) or are linked with glutamate-associated (SLC1A3) and sodium bicarbonate–associated (SLC4A4) transporters.[5,29]

A further genetic linkage with migraine pathology has been identified in *TRESK*, *TREK1*, and *TREK2*.[30] As the co-expression of these potassium channels is observed in trigeminovascular circuitry,

mutations at this level contribute to altered neuronal function.[30] Advances in the understanding of the genetic bases for pathology maintain importance, as such developments impart promise for novel interventional strategies.

Assessment Tools

Various patient assessment instruments used to evaluate headache impact include the Headache Impact Test (HIT-6), Migraine Disability Assessment (MIDAS), and the Migraine-Specific Quality of Life Questionnaire (MSQ). The HIT-6 uses a Likert scale and evaluates pain, social and cognitive function, and psychological impact.[31,32] A higher score on this assessment confers a greater headache impact. Rendas-Baum et al[32] confirmed validation of this instrument in the context of chronic migraine. The MIDAS is a self-administered, seven-item questionnaire, assessing headache-induced absenteeism, activity limitations, and headache frequency and intensity. This instrument has demonstrated reliability and validity.[33–35] The MSQ addresses migraine impact across patient social activity, emotional activity, and the capacity of migraine to prevent activity.[32] With established validity and reliability,[36–38] strong correlations between the MSQ and HIT-6 have been confirmed in the context of chronic migraine.[38]

MIGRAINE WITHOUT AURA

CASE 58-1

Question 1: L.P. is a 27-year-old female presenting to her primary care physician (PCP) with a "severe, throbbing headache." L.P. reports that headaches began 18 months ago, but during the past 3 months, headaches have been occurring with greater frequency, approximating one episode every 2 to 3 weeks. She further describes bilateral headache pain, occurring "without warning," and coinciding symptoms of nausea and vomiting, photophobia, and suboccipital pain. Prior episodes have been self-treated with oral acetaminophen 500 mg (2–4 tablets/ episode as needed) with variable efficacy. Her past medical history is significant for generalized anxiety disorder (GAD),

gastroesophageal reflux disease (GERD), and seasonal allergies. Current medication usage includes levonorgestrel/ethinyl estradiol 0.10/0.02 mg by mouth daily, venlafaxine XR 75 mg by mouth daily for GAD, and omeprazole 20 mg by mouth daily × 2 months for recent-onset GERD symptoms. Social history is negative for tobacco use and illicit substances. L.P. reports occasional consumption of alcohol, stated as "1 to 2 cocktails after work on Fridays." As headaches have occurred with greater frequency, she has missed time at work and this issue has prompted a visit with the PCP. Physical and neurologic examinations are unremarkable.

What subjective and objective information is consistent with a migraine diagnosis, and how do these signs/symptoms differ from tension-type headache?

Symptoms reported by L.P. are consistent with migraine. For L.P., migraine location would not be a differentiating characteristic between migraine and tension-type headache, because tension-type headache is more commonly associated with bilateral character.[39] Pain quality, described as "severe" and "throbbing," is consistent with migraine and precipitates interruptions with daily activity (eg, absenteeism from work) contrasted with tension headache that is associated with sensations of tightness or soreness.[39] Similarly, the occurrence of nausea, vomiting, and photophobia more appropriately aligns with migraine.[4] L.P.'s sex and age would be compatible with prevalence data for migraines.[1]

Case 58-1, Question 2: Which characteristics may be classified as precipitating factors, or "triggers," for migraine pathology? What are possible precipitating factors in L.P.?

Factors involved in precipitating migraine should be routinely assessed for all patients. Assessment should address factors within a patient's medical history, medication usage, social history, and environment. L.P.'s medical history is significant for GAD. Alterations in neurotrophic factors and an increase in anxiety symptoms have been demonstrated in migraine patients.[40] Such evidence imparts value to assess this aspect of L.P.'s medical history. She denies use of tobacco and illicit substances but does report the occasional use of alcohol. Although the consumption of alcohol should be

addressed, the linkage between alcohol consumption and precipitating migraines is less clear.[41,42] The potential provocation of cortical spreading depression, an electrophysiologic factor underlying migraine pathology, in association with alcohol has been suggested.[43] Although not reported by L.P., an evaluation of diet may provide useful information in determining migraine triggers. The evaluation of dietary patterns and quality has yielded disparities, reporting lower-quality dietary intake in migraine patients.[44]

Case 58-1, Question 3: Are further diagnostic and laboratory tests indicated in the case of L.P.?

The most important diagnostic evaluations of patients presenting with headache should be based on a thorough medical history and physical examination. Imaging (eg, computed tomography [CT] scans, magnetic resonance imaging [MRI]) is generally not required in the context of uncomplicated migraine.[45] The report of symptoms by L.P. is consistent with migraine and is sufficient for diagnosis. Her symptoms are not associated with a secondary cause, such as trauma or other injury to the head or neck, and her neurologic examination is unremarkable. Similarly, without reason to suspect subarachnoid hemorrhage or symptoms secondary to meningitis, lumbar puncture would not be indicated. Clinical manifestations that may warrant neurologic imaging to identify artifacts or structural anomalies include coordination deficits, localized neurologic pathology, sensory manifestations, an abnormal neurologic examination, or the presence of atypical headache characteristics.[45] Any change in headache character or headache onset with advanced age warrants consideration for neuroimaging.[6]

Case 58-1, Question 4: What are the goals of therapy for the management of headache in L.P.?

The approach to management and the treatment objectives for L.P. include resolving the acute symptoms of pain, nausea, and

photosensitivity, educating L.P. on both prescription and self-care treatment, addressing the contribution of past medical history and concurrent medication usage to headache episodes, and identifying potential triggers.

Case 58-1, Question 5: What is the most appropriate recommendation with regard to the use of acetaminophen to treat headache episodes in L.P.?

L.P. has confirmed self-treatment of headaches with acetaminophen, and in such instances, it is critical to not only evaluate each patient's potential for self-care but also determine whether self-care treatment options can effectively and safely manage the diagnosis. Reported efficacy of acetaminophen has been mixed. Trial data has provided evidence of oral acetaminophen efficacy, in combination with aspirin and caffeine, in migraine treatment.[46] Doses of 1000 mg have demonstrated efficacy and have provided improvement in associated symptoms.[47,48] However, a study evaluating the parenteral administration of acetaminophen for acute management found no significant difference in efficacy versus placebo.[49,50] Considering L.P.'s report of variable efficacy and increase in headache frequency, she is not an appropriate self-care candidate and continued, routine use of acetaminophen to manage acute episodes is not recommended.

Case 58-1, Question 6: What drug-related problems associated with the precipitation or worsening of migraine should be addressed in L.P.?

Oral contraceptives may either worsen or precipitate migraine attacks in females without a previous history of this problem.[51] Incidence may be related to estrogen dose and/or duration of oral contraceptive use.[52,53] Alternatively, migraine has been implicated as an effect of estrogen withdrawal.[52] Such patients may benefit from use of a continuous combined oral contraceptive product (eg, one with no hormone-free interval), use of low-dose estrogen

supplementation after 21 days of active contraceptives, or the use of a progestin-only oral contraceptive.[51,54,55]

The American Congress of Obstetricians and Gynecologists supports oral contraceptive use in migraine patients but recommends avoidance in patients with tobacco use, in those 35 years and older, and/or in those with the presence of neurologic signs.[56] None of these factors are present in L.P.; therefore, oral contraceptive use may be continued. The implications of oral contraceptive usage and headache should be discussed with L.P. to allow for informed decision-making.

Consultation with L.P. should address whether GAD is being optimally managed. The innervation of trigeminovascular circuitry by neurotransmitters (eg, norepinephrine, 5-HT) linked to affective pathology (eg, anxiety, depression) has been established[57] and is known to coexist with such patients reporting increased headache frequency.[58] It is prudent to address anxiety management with L.P. and to further assess her response to venlafaxine to determine whether dose adjustments or medication changes are warranted.

Case 58-1, Question 7: What strategies and medication recommendations can be used as first-line treatment for L.P.?

Treatment should be aimed at rapidly resolving symptoms and the restoration of the patient's routine activity.[59] Migraines may be managed via a "step" or "stratified" approach.[59,60] With a "step" care model, conventional analgesics are initiated first with the opportunity to progress to using more targeted therapies as necessary.[59,60] A "stratified" care model is based on the character of the migraine and will further incorporate validated assessment measures into the treatment decision.[59,60] The current treatment approach for L.P. has mimicked a "step" care model, using acetaminophen as a first-line medication.

Triptans (5-$HT_{1B/1D}$ receptor agonists)

Triptans, categorized as first (sumatriptan) and second generation (zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan), are effective and well tolerated in acute migraine management and are considered appropriate for those not responsive to conventional analgesics. Triptans can be compared on the basis of efficacy, onset, and recurrence potential. Naratriptan and frovatriptan demonstrate lower recurrence potential, whereas the remaining agents within the class yield higher efficacy and faster onset.[59] Compared with ergot derivatives, triptans exhibit greater receptor subtype specificity, targeting 5-HT_{1B} and 5-HT_{1D} receptors.[59,61] It is important to note that the specific nature of the effect differs according to receptor subtype. Constriction of the vasculature is mediated via 5-HT_{1B} interaction,[59,61,62] whereas interaction via 5-HT_{1D} antagonizes the release of neuropeptides.[59,62] Evidence supports alterations induced by triptans in the interplay between trigeminal nuclei and higher cortical regions.[63]

Sumatriptan

Sumatriptan is the prototype of the triptan class and is available in several formulations. A systematic review confirmed efficacy relative to placebo across sumatriptan doses and formulations; however, subcutaneous delivery yielded a more robust analgesic response.[64] Migraine intensity and the character of associated symptoms (eg, severity of nausea and vomiting, early-onset nausea) impact formulation selection. For patients who are nauseated and prone to vomit during an acute attack, the subcutaneous and intranasal dosage forms are preferred. Both formulations have a rapid onset of effect. Reduction in headache intensity is reported within 10 minutes after subcutaneous injection and within 15 minutes after administration of the nasal spray.[65] A proof-of-concept trial yielded a significant difference in pain reduction, compared with placebo, for a 3-mg subcutaneous sumatriptan dose. Superiority to placebo was also demonstrated for the resolution of auditory and light sensitivity effects.[66] An advancement in formulation has been realized with the development of a breath-powered intranasal powder, and a more

favorable pharmacokinetic profile with a reduction in T_{max} and an AUC increase relative to the sumatriptan oral and nasal spray formulations has been observed.[67–70] A key finding was the improved management of emergent nausea relative to oral administration.[70]

Adverse Effects

Although sumatriptan is well tolerated, there is some variability in the adverse effect profile across different formulations. Both oral and intranasal sumatriptan formulations are associated with a low incidence of systemic adverse events. Oral administration of sumatriptan has been associated with adverse effects, including dizziness, fatigue, nausea, and vomiting,[71,72] whereas intranasal administration may cause abnormal taste and nasal discomfort.[67,68] Parenteral administration is associated with bruising, redness, and discomfort at the injection site.[73] Because of the risk of vasoconstriction associated with triptan use, special attention is required for patients with cardiovascular disease or risk factors. The provocation of coronary artery spasm secondary to sumatriptan administration has been demonstrated in those with variant angina, an effect likely mediated via the 1B receptor subtype.[74] A baseline electrocardiogram is recommended for patients with potential cardiac risk prior to triptan administration and may be considered for those patients without cardiovascular risk factors experiencing chest tightness following triptan administration.[75]

Drug Interactions

Drug interaction potential associated with sumatriptan centers on the modulation of serotonergic activity, the risk of serotonin syndrome, and the potential for additive vasoconstrictive properties. A 2006 Food and Drug Administration (FDA) advisory further underscored the need for caution and consideration of risk versus benefit with the use of triptans in combination with selective serotonin-reuptake inhibitors (SSRIs) and serotonin/norepinephrine-reuptake inhibitors (SNRIs).[76]

The medication profile for L.P. includes venlafaxine, an SNRI, for the management of GAD; however, this does not exclude the possibility of using triptans to manage her migraines. The clinician should evaluate the entire regimen to ensure optimal management of all indications, and if the addition of a triptan is deemed appropriate, L.P. should be educated on the potential for interaction and the clinical implications of the combination. Because L.P. has attempted treatment with conventional analgesics, she would be a candidate for initiating sumatriptan.

Case 58-1, Question 8: During her annual physical examination, L.P. reports success in managing her migraines with sumatriptan but notes that two doses are often required for resolution of symptoms. She inquires as to whether another triptan would be more effective. How do second-generation triptans compare with sumatriptan? Is an alternative triptan appropriate for L.P.?

Second-generation triptans

Second-generation triptans include almotriptan, eletriptan, frovatriptan, rizatriptan, naratriptan, and zolmitriptan. These agents differ based on the pharmacokinetic profile and the capacity for headache recurrence.[59,77] Among the class, zolmitriptan, rizatriptan, eletriptan, and almotriptan are associated with a faster onset and higher likelihood of recurrence compared with naratriptan and frovatriptan, both of which have a slower onset of action with a lower risk of recurrence.[59,77] Comparisons of 74 randomized trials found that among the triptans, eletriptan was associated with the greatest potential of producing a pain-free state at 2 hours and at 24 hours.[78] Favorable efficacy was further observed for rizatriptan (2 hours) and zolmitriptan (24 hours).[78] Comparisons between rizatriptan and frovatriptan have yielded similar pain-free outcomes at 2 hours and have favored frovatriptan for pain-free status at 4 hours.[79] An assessment of sustained headache relief, using a 24-hour window, yielded the most substantial benefit with zolmitriptan and eletriptan.[80] These agents were also associated with minimal usage of additional "rescue" medication.[80]

Drug Interactions

Striking the balance between theoretic drug interaction risk for triptans and what is observed in clinical practice presents a challenge, especially because it relates to the risk of serotonin syndrome.[76,81,82] For L.P., potential drug interactions exist between triptans and venlafaxine (SNRI) and levonorgestrel/ethinyl estradiol (oral contraceptive). Attributed to metabolism via CYP1A2, a slight increase in frovatriptan AUC has been observed with oral contraceptive administration.[83] Prospective investigations assessing the combination of paroxetine and rizatriptan and fluoxetine and zolmitriptan found no instances of serotonin syndrome.[81] Similarly, there were no significant pharmacokinetic and pharmacodynamic alterations when assessing the combination of fluoxetine and almotriptan.[84] These studies lie in contrast to reports of symptoms of serotonin syndrome with the combination of triptans and SSRIs or SNRIs.[65] The administration of a triptan should not be excluded based on L.P.'s medication profile; however, educating her on the potential for the interaction is warranted.

Increases in rizatriptan and zolmitriptan exposure have been observed secondary to monoamine oxidase (MAO) inhibition.[82] Inhibition of CYP3A4 results in increased eletriptan[82] and almotriptan exposure.[82,85] Frovatriptan is not a substrate for CYP3A4 and represents an alternate treatment option is such instances.[86,87]

L.P. can be considered an appropriate candidate for a triptan. Although associated migraine symptoms are reported, the rapidity of onset for such symptoms (eg, nausea, vomiting) is less clear and should be a point of discussion with the patient. Such information is important for optimal formulation selection. A nonoral formulation may be recommended in the context of early-onset vomiting. Although a loss of efficacy is associated with triptan discontinuation,[88] the timeline for triptan use prior to discontinuation has spanned years.[88] Evidence for replacing one triptan with another is mixed. If treatment with one triptan results in suboptimal efficacy, an alternative triptan may be prescribed.[77] However, evidence

evaluating the impact of such change does not suggest substantial benefit.[89,90]

CASE 58-1, QUESTION 9: L.P. has noted that for some migraine episodes, nausea and vomiting has been severe, and asks about the use of dihydroergotamine (DHE) and antiemetics. What is the role of ergot alkaloids and/or antiemetics in migraine management?

ERGOT ALKALOIDS

Relative to triptans, ergot alkaloids function as receptor agonists with strong affinity at 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}.[91] In addition, these agents express activity at 5-HT_{1F} as well as α-receptors and dopaminergic receptors.[91,92] This pharmacologic profile differs from that of the triptans because the latter exhibit no affinity for dopaminergic or α-receptors.[91] Actions of ergot alkaloids are multifaceted, blocking neuropeptide release, stimulating the ventroposteromedial thalamus, and blocking transmission of afferent signals in the trigeminal circuit.[91] Although ergot alkaloids have demonstrated benefit in managing migraine,[77] the more targeted pharmacologic profile of the triptans has gained preference.

Orally inhaled DHE is a noninvasive delivery system that has demonstrated superiority to placebo across end points of pain relief and freedom from auditory sensitivity, light sensitivity, and nausea.[93,94] Associated adverse effects included product taste and nausea, 6% and 4%, respectively.[93] This delivery system is not commercially available.

Peripheral and cerebrovascular disease, renal and hepatic disease, sepsis, and cardiac disease qualify as contraindications to the use of ergot alkaloids.[91,95] Because of the potential to induce uterine contraction and distribute into breast milk, use is contraindicated during pregnancy and lactation.[91,96] In patients with a history of hypertension, it is important to determine whether blood pressure is appropriately controlled before considering the use of these agents in migraine because of the potential for peripheral arterial constriction.[97] Compared with ergotamine, DHE exerts a

more variable effect on blood pressure.[97] Despite such variability, DHE is not recommended for use in patients with an unstable cardiovascular status.

Adverse effects

Nausea is the most prominent adverse outcome with ergot alkaloids.[97] The effect is dose-related and is linked with 5-HT_2 and 5-HT_3 receptor activation.[59] Intranasal DHE and orally inhaled DHE have been associated with prolonged nasal congestion[59] and altered taste.[93] Parenteral administration has been associated with lightheadedness and leg cramping.[97]

Antiemetics

In most patients, triptans provide effective relief of migraine-associated nausea. Therefore, specific antiemetic therapy usually is not required. However, persistent nausea is more common in patients who use ergotamine for acute migraine therapy. In these patients, and in triptan-treated patients who experience incomplete nausea relief, adjunctive antiemetic therapy should be considered. Demonstrated improvement in emesis has been observed with metoclopramide and granisetron.[98] Comparable efficacy in nausea management has been noted for intravenous (IV) prochlorperazine 10 mg and IV metoclopramide 20 mg.[99] Efficacy of intravenous metoclopramide has been demonstrated at the lower end of the dosing scale (10 mg), but higher doses (20–40 mg) were not associated with improved outcomes.[100]

Case 58-1, Question 10: In addition to triptans and ergot derivatives, what other abortive agents are available for outpatient treatment of acute migraine?

CGRP receptor antagonists

Efficacy and tolerability of ubrogepant (a calcitonin gene-related peptide receptor antagonist [CGRP-RA]) has been evaluated in the ACHIEVE II clinical trial (phase 3, multicenter, randomized, double-

blind, placebo-controlled single attack study to evaluate the efficacy, safety, and tolerability of oral ubrogepant in the acute treatment of migraine). Efficacy in managing migraine pain (achievement of a pain-free state at 2 hours) for ubrogepant, compared to placebo, was confirmed for doses of 50 and 25 mg following oral administration.[101,102] The amelioration of auxiliary migraine symptoms (photo- and phonophobia, nausea) was observed with the 50-mg dose.[101] Superiority to placebo in achieving a pain-free condition at 2 hours has also been demonstrated with a dose of 100 mg.[103] Similar clinical outcomes have been observed for comparisons between rimegepant and placebo.[104–106]

Ubrogepant and rimegepant are alternatives to triptans in the management of acute migraines. There is insufficient evidence to support the complete replacement of triptans by CGRP-RAs for managing acute migraines. However, these agents should be considered for patients experiencing suboptimal triptan response (failed trials of triptans), or intolerable triptan effects. Patients that report experiencing "triptan sensations" (eg, flushing, chest tightness) are viable candidates for CGRP-RAs, if such effects do not resolve. The effect on the vasculature represents a primary advantage in the use of these agents.[106–108]

In comparison with triptans, CGRP-RAs do not exhibit potential for vasoconstrictive effects.[107,108] The lack of vasoconstriction associated with these agents supports the use in patients with cardiovascular and/or cerebrovascular disease. There is similar utility for patients with disease states exacerbated by vasospasm (eg, Raynaud).

The use of CGRP-RAs may also be considered in the context of concerns with serotonergic modulation. Although triptans are not contraindicated for patients maintained on serotonergic agents, concerns regarding augmented serotonergic effects are bypassed with the use of CGRP-RAs.

Adverse outcomes include hepatic enzyme elevations, incidences of upper respiratory tract infection,[109] and nausea.[105]

5-HT_{1F} receptor agonists

Lasmiditan is a 5-HT_{1F} receptor agonist for acute migraine management. With demonstrated selectivity for the 1F receptor subtype, coupled with limited affinity for receptor subtypes targeted by triptans, lasmiditan represents an alternative with limited vasoconstrictive action.[110,111] Doses of 100 and 200 mg have yielded efficacy in acute management relative to placebo.[111]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND COMBINATION ANALGESICS

Many nonsteroidal anti-inflammatory drugs (NSAIDs) and combination analgesics containing caffeine have been shown to be effective for the acute treatment of migraine headache.[112,113] Significant clinical benefit in double-blind, placebo-controlled trials has been shown for aspirin, ibuprofen, naproxen sodium, and combination analgesics containing acetaminophen, aspirin, and caffeine.[113,114]

Case 58-1, Question 11: L.P. reports that her migraines have been successfully managed with naratriptan 2.5 to 5 mg/episode, with most episodes resolving with the lower dose. Naratriptan was selected on the basis of a lower likelihood of recurrence. L.P. has been experiencing a severe migraine for the past few days and has been unsuccessful in treating the episode with naratriptan. She has now sought treatment at a nearby hospital and has been diagnosed with status migrainosus. What is the most appropriate approach to managing status migrainosus in L.P.?

Intractable Migraine

Status migrainosus, or intractable migraine, is characterized by an extended duration of headache, exceeding 72 hours.[4] The typical management strategy usually requires hydration and parenteral therapy with ergot derivatives, sumatriptan, or opioid analgesics.

DIHYDROERGOTAMINE

Dihydroergotamine has demonstrated efficacy in treating intractable migraine by either intermittent or continuous administration.[115]

Adjunctive antiemetics should be administered for nausea.[115,116]

SUMATRIPTAN

Sumatriptan 6 mg subcutaneously is also effective for the treatment of established migraine.[65] If the first injection does not provide relief at 1 hour, a second injection may be administered. Sumatriptan should not be administered within 24 hours of ergot alkaloids because of the potential for prolonged vasospastic reactions.

PROCHLORPERAZINE

Prochlorperazine has established efficacy in managing migraine-related nausea, with intravenous administration being effective during intractable migraine.[115,117] In randomized, controlled trials, prochlorperazine 10 mg IV was more effective than placebo, IV metoclopramide, IV ketorolac, and IV valproate for the treatment of acute migraine in the ED.[117]

CORTICOSTEROIDS

Parenteral dexamethasone may be administered in cases of intractable migraine.[115] Among a subset of patients experiencing migraine symptoms beyond 72 hours, a greater percentage of patients achieved pain-free status following parenteral dexamethasone administration, relative to placebo.[118] Lower headache recurrence has been observed in patients receiving dexamethasone after standard abortive treatment.[119]

L.P. may be treated with DHE, sumatriptan, prochlorperazine, or metoclopramide because of demonstrated efficacy and tolerability in comparison with other treatment options.[120]

Case 58-1, Question 12: During a return visit to her PCP, L.P. has reported that most migraine episodes have been successfully managed with naratriptan. Although effective, she expresses concern related to episode frequency noting that in some instances, she is using naratriptan three times weekly. Her PCP wants to prescribe propranolol. Is propranolol an appropriate option for L.P.?

Prophylactic Therapy

CRITERIA FOR USE

The relevance of initiating prophylactic therapy for migraine is not simply defined by one common feature among patients. Rather, the impact of migraine for an individual patient needs to be assessed. Targeted outcomes for prophylactic therapy include a reduction in both migraine frequency and severity, enhancing response to acute management strategies, and a general improvement in daily function.[121] Guidance on a patient's suitability for prophylactic management should also address the level of disability associated with episodes, prior experience (success or failure) with acute management modalities, potential for mitigation of adverse effects, and the pathologic complexity of a migraine (eg, basilar or hemiplegic episodes, prolonged auras).[121,122] Among panel recommendations, patients experiencing 6 or more headache days per month were deemed appropriate for prophylactic management.[123] The absolute number of episode days per month is only one parameter to evaluate. It is also important to assess the impact on a patient's daily functioning, as patients may meet criteria for prophylactic management with a lower occurrence of monthly episodes (each episode is associated with a higher level of impairment). Optimizing prophylactic treatment may likely require a 2- to 3-month window. This becomes an important consideration to convey to patients with a focus on maintaining adherence. The evaluation of evidence associated with prophylactic treatments is often challenging because of the lack of studies with comparisons between agents or with crossover design.

PROPRANOLOL

Evidence supports propranolol safety and efficacy in migraine prophylaxis.[121,122,124] Various mechanisms for efficacy may be considered, including the modulation of central catecholamines[125] and interaction with serotonin receptors.[125,126] Propranolol has also demonstrated a suppressive effect on cortical spreading depression

in animal models.[125,127] In a small study of migraine patients, propranolol decreased cerebrovascular reactivity, mediated by action on vascular tone.[128] For L.P., the prescribing of propranolol for migraine prophylaxis could be considered, as there are no contraindications that would prevent use. A limiting variable to continued use may be the adverse effect profile, including lethargy, fatigue, and sleep disruption.[121] As an alternative to propranolol, metoprolol could be considered similarly appropriate for L.P. Comparisons with aspirin[121] or propranolol[121] suggest that metoprolol would be appropriately effective. Metoprolol has been further compared with nebivolol.[129] Although similarly effective in prophylactic migraine management, better tolerability and ease of titration were associated with nebivolol.[129]

Dosing

Initial dosing for propranolol for prophylaxis of migraine headaches is 20 mg by mouth two or three times a day, with gradual weekly titration according to patient tolerability to 80 to 160 mg/day in two to four divided doses.[122] Once the daily dosage of propranolol required to control headaches is established, patient adherence may be improved by changing to a long-acting oral dosage form.

Migraine With Aura

CASE 58-2

Question 1: V.M. is a 24-year-old female who presents for a visit with her PCP and reports a 3-month history of throbbing headaches. Although V.M. has reported experiencing tension-type headaches "on and off" in the past, the character of these recent headaches has been different, accompanied by early-onset, severe nausea and vomiting, and preceded by "flashes of light" and a unilateral facial numbness. The numbness and visual flashes have typically resolved after 30 minutes with headaches developing soon after. She has taken naproxen or ibuprofen for treating recent episodes, but neither has proven effective. The MIDAS score was 11. Medical history includes hypothyroidism treated with levothyroxine 100 µg by mouth daily and a past history of tension-type headache. Her medication profile also includes use of an oral

contraceptive (norgestimate/ethinyl estradiol) for the past 5 years. She describes herself as an occasional smoker and denies a history of alcohol use or illicit substances.

Which information is consistent with the diagnosis of migraine with aura in V.M.?

Although both the “throbbing” character of the headache and associated gastrointestinal (GI) symptoms are consistent with migraine, it is the presence of both the visual (light flashes) and sensory (numbness) disturbances that correlate with the diagnosis of migraine with aura. Relevant information for confirming this diagnosis would be a minimum of two episodes, the accompaniment of an aura symptom, the duration and unilateral nature of the aura, and the evolution of the headache following the aura.[4]

Propagating glial and neuronal depolarization, characterized as cortical spreading depression, has been implicated in aura.[20,130] It is suggested that the pathologic basis for aura involves gap junction modulation at the neuronal level of the trigeminovascular circuitry.[20] Aura has been associated with migraine in approximately one-third of patients,[130] and visual phenomena are typically the most prevalent aura features.[130] It is important to note that visual effects are substantially varied and can include flashing lights, waving lines, or areas of localized blindness (scotoma).[131] A “visual snow” effect has been described in the literature.[132] Although visual phenomena are most prevalent, sensory disturbances (eg, numbness, pins, and needles sensation) may also comprise an aura.[4] In the case of V.M., the aura includes both visual and sensory disturbances, and coupled with the report of additional symptoms (eg, throbbing headache, nausea/vomiting), a diagnosis of migraine with aura is appropriate. The temporal relationship between the aura and evolution of the migraine is one of further consideration. Although V.M. reports the evolution of the migraine following the aura, there is evidence to support classical migraine symptoms occurring during the aura phase.[133]

Case 58-2, Question 2: Should the migraine that V.M. is experiencing be treated according to a stratified-care or step-care model?

In accordance with a step-care model, a conventional analgesic medication would be considered as primary therapy. A stratified-care model would focus on patient effects and characteristics of migraine. V.M. has reported self-treatment with conventional agents (eg, naproxen or ibuprofen) without adequate relief. Further considering that V.M.'s MIDAS score corresponds to "moderate" disability and the reported variance of MIDAS score with age,[33] a stratified-care model would be preferable.

Case 58-2, Question 3: V.M. has been counseled previously regarding the cardiovascular risks associated with oral contraceptives and questions whether she is at greater risk considering her migraine diagnosis. Is an oral contraceptive appropriate for V.M.?

No consistent increased risk for stroke has been found among males, females older than 45 years old, and females who have migraine without aura.[134] Among patients with a diagnosis of migraine with aura, a twofold increase in ischemic stroke risk has been reported.[135] An additional finding in this meta-analysis supported an increased risk among migraine patients using oral contraceptives.[135] The World Health Organization considers migraine with aura in females of any age an absolute contraindication to the use of combined oral contraceptives.[51] The American College of Obstetricians and Gynecologists guidelines permit the use of combined oral contraceptives in females who suffer from migraine with aura as long as they have no focal neurologic signs, do not smoke, and are younger than age 35 years.[51] V.M. describes herself as an occasional smoker, so relevant management strategies include discussing other contraceptive options and a smoking cessation plan.

Case 58-2, Question 4: What is the most appropriate recommendation for acute management of V.M.'s migraine?

Given the severity of symptoms and past treatment experience with conventional analgesics, the selection of a migraine-targeted treatment (eg, ergot alkaloid, triptan) would be preferable. Of similar importance is the presence of severe, early-onset nausea; therefore, nonoral administration is recommended. Sumatriptan and zolmitriptan are available as nonoral formulations, and either could be considered appropriate for V.M. The presence of severe nausea becomes a pivotal factor in treatment selection for V.M. Ergot agents may exacerbate the effect.

Case 58-2, Question 5: V.M. has now returned to her PCP reporting success in managing her migraines with zolmitriptan. The frequency of migraine episodes remains an issue, reporting four to five episodes monthly which have caused her to miss work. Her PCP is considering prophylactic treatment but would prefer not to prescribe propranolol. Which medication may be prescribed to prevent migraines?

AMITRIPTYLINE

Amitriptyline is an appropriate first-line therapy option for migraine prophylaxis[122,136] with such effects being independent of antidepressant activity.[137–139] Mechanistically, therapeutic effects in migraine are imparted via gamma-aminobutyric acid (GABA) receptor upregulation, adenosine modulation, and altering neuronal sensitivity to neuropeptides.[140] Additional effects on the serotonergic system provide further support for tricyclic antidepressant (TCA) benefit in migraine management. Amitriptyline treatment has been associated with significant improvement in MIDAS scores following a 45-day treatment cycle.[141] Particularly applicable to the case of V.M., there is demonstrated benefit for amitriptyline in the treatment of tension-type headache as well,[8] making it a viable option for patients with both headache forms.

Amitriptyline has been compared with propranolol, divalproate, and topiramate in various studies. A randomized trial comparing extended-release divalproate with amitriptyline yielded similar efficacy, measured by headache frequency at 6 months, while being inferior to divalproate at 3 months.[140] Two separate studies have provided comparison between amitriptyline and topiramate.[142,143] With a primary efficacy measure of monthly migraine episode rate, 100-mg doses of each proved comparable and similarly well tolerated.[142] A smaller study reported similar results; however, the combination treatment of amitriptyline and topiramate was assessed as a separate, third treatment arm.[143] Patient satisfaction among subjects taking the combination was noted to be higher relative to either monotherapy group.[143] A comparable response to propranolol has been observed in the evaluation of migraine episode severity and duration.[144] However, in the assessment of rescue medication usage, a more favorable response was noted with propranolol.[144]

Dosing

The initial dose of amitriptyline is 10 to 25 mg by mouth at bedtime. This nightly dose can be increased at weekly intervals by 10 to 25 mg until the maximal dose of 150 mg/day is reached.

Although generally tolerated, common adverse effects attributed to amitriptyline treatment have included drowsiness, anticholinergic effects, and weight increase.[140,142,143] Amitriptyline has been associated with cardiac conduction issues, and there is the potential for patients to experience palpitations and QT prolongation.[145] Patients should be routinely monitored for conduction abnormalities, and alternative treatment options should be considered for patients with cardiovascular concerns.

There is evidence to support the prescribing of other TCAs when intolerance to amitriptyline is observed.[146] The administration of nortriptyline may be considered for patients intolerant to amitriptyline. As a metabolite of amitriptyline, a more favorable adverse effect profile has been observed.[146]

TOPIRAMATE

Topiramate is considered a first-line option for migraine prophylaxis.[122,136] In addition to aforementioned comparisons with amitriptyline, prospective studies have reported similar efficacy between topiramate and sodium valproate.[147–149] Three large randomized, placebo-controlled trials have documented the efficacy of this agent for reducing the number of monthly attacks.[150] With initial dosing of 25 mg daily,[142,143,151] target doses of 100 mg daily[142] and 200 mg daily[151] have been assessed. Evidence supports dose titration to 100 mg for optimal outcomes.[149,152] Further titration to 200 mg has not demonstrated significantly better outcomes relative to 100 mg.[149,153]

Paresthesia, fatigue, weight loss, memory, and concentration deficits have been associated with topiramate therapy.[142,143,154] Research has strengthened the foundation for topiramate-associated alterations in cognition, and such potential should be addressed in consults with migraine sufferers.[155]

VALPROATE

Valproate and divalproex sodium are approved for migraine prophylaxis and are viable treatment options for prevention.[122,136] Results from a prospective trial comparing propranolol and sodium valproate in a small sample of migraine patients suggest greater favorability and a larger response rate with propranolol administration; however, the study did support efficacy of sodium valproate in treating migraines based on duration and severity.[156] Similarities in therapeutic efficacy were observed in comparison with topiramate, as therapeutic end points were not found to be significantly different across treatments.[147] One of the findings of this study was greater favorability with the adverse effect profile of topiramate.[147]

Dosing

Delayed- or extended-release formulations of divalproex sodium may be prescribed for prophylaxis with the advantage of the latter

formulation being once-daily administration. Initial dosing for the delayed-release formulation is 250 mg by mouth twice daily, whereas the extended-release formulation is 500 mg by mouth once daily.

Adverse effects associated with valproate treatment include alopecia, nausea, drowsiness, and weight gain.[148] Incidences of tremor and menstrual irregularities have also been reported.[157] Potential for hepatotoxicity and pancreatitis[158] limits utility.

GABAPENTIN

There is evidence of safety and efficacy in managing migraine patients with gabapentin. Gabapentin administration has yielded reductions in duration, frequency, and migraine severity.[159] The therapeutic benefit needs to be evaluated cautiously, as results from this study reflected greater efficacy with topiramate.[159] Gabapentin enacarbil, a gabapentin prodrug, has been evaluated in the prophylaxis of migraines in dosing levels up to 3000 mg daily but was not associated with significant therapeutic benefit relative to placebo.[160]

CANDESARTAN

Candesartan, an angiotensin II type-1 (AT_1) receptor antagonist, has demonstrated efficacy for migraine prophylaxis in a small randomized, placebo-controlled, crossover trial.[161] Outcomes of migraine frequency (number of days) and duration (number of hours) were favorable with candesartan.[161] Although dizziness was the most frequently reported adverse event associated with treatment, neither this effect nor any other adverse outcome differed significantly from placebo.[161] A 16-mg dose of candesartan was found to have comparable efficacy to a 160-mg propranolol dose in a 12-week clinical trial.[162]

TONABERSAT

As both cortical spreading depression and gap junctional modulation have been linked with migraine aura,[20,130] the inhibition of cortical spreading depression constitutes a potential approach to

treatment.[163] Comparisons with placebo have been mixed[163–165] with efficacy exclusive to migraine with aura.[163] Tonabersat is currently an investigational treatment.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Effectiveness of NSAIDs as preventive therapy is considered modest compared with the first-line agents.[122] NSAIDs may be effective as short-term therapy for menstruation-associated migraine.[122]

In selecting an alternative prophylactic medication for V.M., evidence supports use of selective β-antagonist (eg, metoprolol), amitriptyline, or topiramate. In all such instances, V.M. should be counseled with regard to dose titrations, adverse effects, and allowing for a sufficient trial duration to adequately determine efficacy.

CASE 58-2, QUESTION 6: V.M. has experienced an increase in migraine frequency. She reports 10 to 12 episodes monthly. She reports that headaches have occurred on a consistent basis for at least 5 months. Which treatment options are available for V.M.?

The PREEMPT-2 trial (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) demonstrated onabotulinumtoxin A superiority to placebo in reducing the frequency of headache days.[166] The COMPEL study (Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy Open-Label Study) has provided insight relative to onabotulinumtoxin A efficacy and tolerability for the long-term management of chronic migraine.[167] Administration yielded significant reductions in headache days per month, coupled with improvements observed in HIT-6 scores.[167] Comparable results were obtained in the REPOSE (**RE**al-life use of botulinum toxin for the symptomatic treatment of adults with chronic migraine, measuring healthcare resource utilisation, and **P**atient-reported **O**utcome**S** observed in practice) trial, a nonintervention study assessing patients for 24 months following treatment initiation. A reduction in headache days was observed from a baseline of 20.6 to 7.4.[168] In both trials, adverse effects of neck pain, eyelid ptosis, and muscle

stiffness were reported. Onabotulinumtoxin A is administered via intramuscular injection at a dose of 155 units across 31 injection sites.[169] Monoclonal antibodies are newer therapeutic alternatives in the management of chronic migraine. Four monoclonal antibodies have been FDA approved for the treatment of chronic migraine: eptinezumab, erenumab, fremanezumab, and galcanezumab. There is a slight variation in mechanism among these agents. Erenumab binds to the CGRP receptor, whereas eptinezumab, galcanezumab, and fremanezumab bind to CGRP.[170] The use of monoclonal antibodies is beneficial for patients experiencing inadequate responses to two, or more, established prophylactic treatments.[171] The use of the monoclonal antibodies should also be considered for patients experiencing intolerable adverse effects from other prophylactic treatments.

Erenumab

In a study of nearly 700 patients, two dosing levels (70 and 140 mg) of erenumab were evaluated against placebo. A significant reduction in the number of migraines relative to placebo was observed with both doses.[172] A unique aspect to this study involved the assessment of anti-erenumab antibodies in treated subjects. A larger incidence of antibody presence was noted at the lower dosing level, but a relationship between antibody presence and adverse effects could not be established.[172] Erenumab is administered via subcutaneous injection at doses of 70 and 140 mg once monthly.[173]

Eptinezumab, fremanezumab, and galcanezumab

Efficacy relative to placebo has been observed for fremanezumab in a study assessing both monthly and quarterly administration.[174] Although not statistically significant, there was a slightly better therapeutic outcome observed with monthly administration.[174] There is limited data regarding the utility of such agents for patients with prior treatment failures. The FOCUS trial (A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study With an Open-Label Period to Evaluate the Efficacy and

Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients With Inadequate Response to Prior Preventive Treatments) yielded results supporting fremanezumab efficacy for those patients with prior treatment failures.[175] Trials of galcanezumab (EVOLVE-1 [Evaluation of LY2951742 in the Prevention of Episodic Migraine], EVOLVE-2, and REGAIN [phase 3, randomized, double-blind, placebo-controlled study of LY2951742 in patients with chronic migraine]) have provided comparable results regarding efficacy versus placebo.[176–178] Efficacy with eptinezumab (PROMISE-2 [Parallel Group, Double-Blind, Randomized, Placebo Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients With Chronic Migraine]) has also been demonstrated, with a significant reduction in monthly migraine days versus placebo.[179]

Eptinezumab is administered as an intravenous infusion quarterly.[180] Galcanezumab (monthly) and fremanezumab (monthly or quarterly) are administered by subcutaneous injection. All have been associated with injection site reactions as adverse effects.[180–182] An important consideration for these agents is the eliciting of an immune response.[183,184] The recognition of these proteins by the immune system leads to the generation of neutralizing and anti-drug antibodies, with implications for diminished efficacy.[184] Evidence reflects a greater potential for eptinezumab in facilitating the immunologic response, with nearly 20% of patients developing anti-drug antibodies and 6% of patients developing neutralizing antibodies.[185] The immunologic response reported in studies with erenumab, galcanezumab, and fremanezumab has been lower. Studies with erenumab and galcanezumab have reported anti-drug antibody development in 8% and 11% of subjects and neutralizing antibody formation in 1% and 3% of subjects, respectively.[177,186,187]

Fremanezumab has demonstrated the lowest potential for the formation of anti-drug and neutralizing antibodies.[188,189]

Medication Overuse

CASE 58-3

QUESTION 1: L.D. is a 39-year-old female with a 7-year history of migraine (without aura) and tension-type headache who comes to the clinic requesting a refill of almotriptan. She reports an increase in the frequency of both her throbbing and dull, pressure sensation headaches during the past year, and lately she has had difficulty distinguishing the two types. In the past 2 months, she has had only 5 days with no headache, and she has been much less productive in her work as a magazine editor. She has reported using 4 to 5 almotriptan tablets weekly with multiple episodes also requiring naproxen sodium, which she has purchased over the counter (OTC). She has requested two refills for her almotriptan during the past 1½ months.

What is the role of medication overuse in worsening symptoms, and how should this condition be managed in L.D.?

Medication overuse is defined as the use of triptans, ergot alkaloids, opioid analgesics, or combination analgesics on 10 or more days/month (the criterion for use of simple OTC analgesics is 15 or more days/month)[136] and often occurs in migraine and tension-type headache sufferers.[190] The use of opioids and butalbital-containing products has been associated with a shorter time frame for progression to medication overuse headache. Progression has been associated with butalbital use for 5 or more days per month and with opioid use for 8 or more days per month.[191] The pathophysiology of medication overuse headache is multidimensional and is related to hypometabolism in neuroanatomic structures,[190,192] neurochemical alterations (eg, orexin-A, corticotropin-releasing factor),[193] and alterations in receptor expression and neuropeptide levels (eg, increase in CGRP).[194] There has also been an association between caffeine overuse and morphologic alterations in multiple brain regions.[195]

Chronic daily headaches often have features of both migraine and tension-type headaches.[196]

L.D. displays many of the features of medication overuse headache. She reports an increase in the frequency of headaches to a near-daily pattern, and she is no longer able to distinguish between migrainous and tension-type headaches. Laboratory tests should be ordered to assess L.D.'s renal and hepatic function, and she should

be questioned regarding the occurrence of GI discomfort, acute bleeding, or a change in her stool color.

In general, patients who receive abortive agents for headache treatment should be counseled to restrict their use of these agents to no more than twice per week.[122] The design of medication withdrawal procedures can be tapered or abrupt, with a tapered withdrawal procedure recommended for opioid, barbiturate, or benzodiazepine overuse.[196] Abrupt discontinuation can be considered suitable for triptans and nonopioid analgesics.[196] For L.D., the discussion of a discontinuation strategy would be recommended. Such an intervention has demonstrated positive outcomes in headache reduction.[197,198] Prophylaxis may be considered, and topiramate has demonstrated efficacy in this context.[196,199]

CLUSTER HEADACHE

Cluster headache is characterized by severe, unilateral pain, potentially described as a pulsating or burning sensation, often involving the orbital, temporal, or maxilla regions.[4,200] In addition to pain, cluster headache typically involves autonomic features (eg, miosis, nasal congestion, ptosis, lacrimation).[4,200]

Pathophysiology

The pathology surrounding cluster headache includes stimulation of parasympathetic outflow, disturbance at the level of the hypothalamus, and vasodilation.[201,202] Such pathology is also a function of alterations in testosterone levels,[201] melatonin,[201] and diminished response to thyrotropin-releasing hormone.[201] Further assessments of pineal functioning in the context of cluster headache have revealed anomalies in serial plasma melatonin sampling, reflected as diminished peaks.[203] The pathology further includes

angiographic changes and the interplay of parasympathetic and sympathetic function at the level of the cavernous sinus.[204]

Signs and Symptoms

CASE 58-4

Question 1: R.H. is a 31-year-old male with a 3-year history of episodic cluster headache. He has been headache-free for the past year, but today states that the headaches are returning in their characteristic fashion. He reports abrupt onset of right-sided retro-orbital pain with occasional superimposed knifelike "jabs" that increase in intensity for several minutes to a severe, unrelenting pain lasting about 90 minutes. The headache then gradually subsides. Associated symptoms include right-sided lacrimation, conjunctival injection, and rhinorrhea. He denies any premonition of ensuing headache or GI upset during the attacks. Physical examination during a cluster headache shows right eyelid droop and pupillary miosis. R.H.'s cluster periods characteristically last about 2 months and usually recur once or twice yearly. The first headache of the current episode awoke him from a short nap. R.H. expects to suffer one or two such headaches daily because this has been the usual pattern during each cluster period. Previous cluster headaches have been symptomatically treated with aspirin and codeine 30 mg. However, R.H. reports only modest relief with this treatment approach.

R.H.'s medical history is unremarkable. He does not use tobacco but admits to occasional social drinking.

What subjective and objective evidence in this case is consistent with a diagnosis of cluster headaches?

R.H.'s sex, age of onset, quality and intensity of headache pain, periodicity of headache attacks, and associated symptoms all support the diagnosis of cluster headaches.

An aura may precede a cluster headache episode; however, this effect occurs in a small percentage of patients.[200,205] The episodic timeline of cluster headache is variable, extending from weeks to months, with the potential for extended remission periods.[4] R.H.'s headache quality (severe, unrelenting pain), site (unilateral), evolution and resolution pattern (worsens over several minutes and resolves within 90 minutes), and periodicity of attacks (one or two headaches occurring daily for about 2 months followed by a period of

remission that lasts about 1 year) are all compatible with the usual character of cluster headaches.

Associated symptoms reported by R.H. during headache attacks (eg, lacrimation, rhinorrhea, conjunctival injection) and the absence of GI or neurologic disturbances are also compatible with the cluster headache diagnosis.

CASE 58-4, QUESTION 2: What abortive measures are available for symptomatic treatment of individual headaches during R.H.'s current cluster period?

Abortive Therapy

The treatments of choice for abortive treatment of cluster headaches are sumatriptan by subcutaneous injection, zolmitriptan nasal spray, and oxygen inhalation.[206,207] Among these agents, subcutaneous sumatriptan is often preferred.[208]

SUMATRIPTAN

Sumatriptan 6 mg administered subcutaneously for cluster headaches reduced severity in 74% of attacks within 15 minutes, compared with 26% of attacks treated with placebo.[208] An additional injection of 6 mg does not appear to give additional headache relief.[208] However, in patients who experience a recurrent headache after initial relief with sumatriptan, a second injection is often useful.[202] Sumatriptan should not be used more often than twice daily during cluster bouts.

OXYGEN

High-flow oxygen has demonstrated efficacy in the acute management of cluster headaches and can be used as a first-line treatment option.[209,210] Although the mechanism is not fully understood, there is evidence of inhibited neuronal activation in the trigeminovascular circuit.[211]

Advantages to oxygen treatment include a lack of adverse effects, and a lack of drug interaction potential, allowing for concurrent usage with other treatment options.[212–214] The capacity to administer oxygen treatments multiple times daily represents another advantage in the treatment of cluster headaches.

ZOLMITRIPTAN

Two controlled trials have established the effectiveness of intranasal zolmitriptan for the acute treatment of cluster headache attacks. Cluster headache relief rates were 40% and 50% with 5 mg of zolmitriptan, and 62% and 63% with 10 mg of intranasal zolmitriptan in these two studies, respectively.[207,215]

Reasonable options for the acute treatment of R.H.'s acute cluster headaches include subcutaneous sumatriptan, oxygen inhalation, and intranasal zolmitriptan. For many patients, oxygen is a less convenient therapy because the equipment is not easily portable, and the patient must sit still during the treatment.

Case 58-4, Question 3: What therapeutic agents are available for headache prophylaxis during an active cluster period? Which option is most appropriate for R.H.?

Prophylactic Therapy

Prophylaxis should be considered in the context of chronic cluster headache episodes. In a similar manner to managing migraines, it is important to monitor the use of acute treatment. Instituting prophylactic treatment limits the potential for medication overuse.

VERAPAMIL

Evidence supports verapamil efficacy in cluster headache prophylaxis[200,201,209,216,217] with daily doses in the range of 240 to 320 mg.[201,218,219] Baseline and periodic electrocardiography should be performed for those maintained on verapamil therapy.[200,201] The need

for such monitoring is a function of verapamil's electrophysiologic effects on cardiac nodal tissue.

LITHIUM CARBONATE

Where primary treatment is either ineffective or contraindicated, the use of lithium as a second-line option is supported.[209] There is evidence of direct association with several circadian genes, and there is a direct effect on the retinal-hypothalamic pineal circuitry. The latter effect plays a role in melatonin modulation and impacts sensitivity to light.[220]

Lithium serum levels associated with efficacy in cluster headache prophylaxis are usually between 0.4 and 0.8 mEq/L.[208] In addition to assessing serum levels, routine monitoring of electrolytes, hepatic, renal, and thyroid function is required.[209]

TOPIRAMATE

Topiramate has demonstrated efficacy for cluster headache prophylaxis.[209,221–225] In a study of patients with prior prophylactic treatment exposure, topiramate produced favorable outcomes, inducing remission in > 50% of treated patients.[221]

GALCANEZUMAB

Defining the role of monoclonal antibodies in the prophylaxis of cluster headaches is an area of continued investigation. Galcanezumab has been compared to placebo in the assessment of cluster episode frequency.[226] The administration of galcanezumab did yield a decrease of nearly 9 mean cluster headache episodes over 3 weeks.[226] The decrease in frequency was significant in comparison to placebo.[226] Although a larger volume of research is needed for bolstering the utility of monoclonal antibodies in the therapeutic management of cluster headache, the results support involvement of CGRP in pathogenesis.

Prompt consideration should be given to the aforementioned additional treatments if suppression of headaches during the cluster period is warranted. In general, after response to prophylactic agents

has been established and maintained for at least 2 weeks, attempts can be made to discontinue the drug. Treatment should be reinstituted if headaches recur. With consideration toward patient ease of use and efficacy, treating R.H. with verapamil or topiramate would be rational. Intolerance to such treatment options would support a trial of galcanezumab for R.H.

TENSION-TYPE HEADACHE

Prevalence of tension-type headache is variable but has been shown to be as high as 78%.[4,227,228] Females are slightly more affected by tension-type headaches than males, with a ratio of 5:4.[229] Tension-type headache is typically bilateral and is characterized by milder pain intensity and a tightening quality.[4] Nausea and vomiting are not typical of tension headache presentation but photo- or phonophobia may be present.[4]

Headache frequency is an important determinant for tension-type headache classification, expressed in terms of headache days/month.[4,227] Episodic tension headache can be either infrequent (>1 day/month) or frequent (1–14 days/month), whereas chronic tension headache is classified with a threshold of 15 headache days/month.[4,227]

Pathophysiology

The pathology of tension-type headache is theorized to be a function of both peripheral and central pain pathways, including modulation of trigeminal nociceptors and pericranial muscle strain.[230]

General Management and Abortive Therapy

CASE 58-5

QUESTION 1: K.B., a 27-year-old female financial analyst, presents to her PCP with recurring headaches that worsened when she started her current job. Before this time, she had experienced infrequent headaches, which she associated with periods of stress. The headaches would occur three to four times yearly; were of a constant, dull, or "pressing" character; and were present around the entire head. Recently, headaches of similar character have been occurring about one to two times weekly, usually toward the end of her workday. The pain usually lasts the rest of the day but varies in intensity. Occasionally, a headache is present when she wakes up in the morning. K.B. denies GI and aura symptoms associated with her headaches. She has noticed that relaxation and alcohol ingestion seem to relieve these headaches, but aspirin and acetaminophen have been ineffective. Her blood pressure is 120/74 mm Hg; her physical and neurologic examinations are normal.

What measures should be taken to relieve K.B.'s headaches? What is an appropriate goal for treatment?

K.B. appears to be suffering from frequent episodic tension-type headaches. She reports approximately four to eight headache episodes per month, and these headaches have features that are typical for tension-type headache. As in the treatment of other chronic headache disorders, a cure for recurrent tension-type headache is unlikely. K.B. should clearly understand that the goal of treatment is a reduction in the frequency and severity of headache. Drug therapy and relaxation techniques are the primary means by which tension-type headaches are treated.

ANALGESICS

Conventional analgesics, including NSAIDs, are appropriate first-line treatments for tension-type headache.[227] A meta-analysis of four controlled trials supported the effectiveness of both a combination product (acetaminophen, aspirin, and caffeine) and acetaminophen alone relative to placebo in achieving pain-free status at 2 hours postadministration for tension-type headache treatment.[231] Secondary end points included pain-free status at 1 hour, headache response at 2 hours, and level of impact on daily activity. Improvement in secondary end points was statistically significant for the combination product versus acetaminophen and placebo.[231]

An NSAID (eg, ibuprofen or naproxen) would be an appropriate recommendation for the treatment of K.B.'s tension-type headaches because of her previous inadequate responses to aspirin and acetaminophen.

Case 58-5, Question 2: K.B. was prescribed ibuprofen 400 mg by mouth every 4 to 6 hours as needed for acute relief of recurrent tension-type headaches. At her next scheduled follow-up visit, K.B. reported moderate relief with ibuprofen but with GI upset with each dose, even when taken with food. What prophylactic agents are available for continuous suppression of K.B.'s tension-type headaches?

Prophylactic Therapy

Prophylaxis is relevant in the context of both frequent, episodic tension-type headache and chronic tension headache.[227] Amitriptyline has demonstrated efficacy in managing tension-type headache.[227,232] A median daily dose of 75 mg yielded a significant improvement in headache index relative to placebo.[232] Mirtazapine and venlafaxine have both demonstrated efficacy in tension-type headache treatment relative to placebo.[233,234] Superiority for mirtazapine was demonstrated in measures of headache frequency, intensity, and duration for patients with prior treatment experience.[233]

Given K.B.'s increasing frequency of tension-type headache and her intolerance to moderate doses of ibuprofen, prophylactic treatment with amitriptyline would be appropriate. A starting dose of amitriptyline 10 mg by mouth nightly, increasing by 10 to 25 mg weekly to a maintenance dose of 50 mg/day, should be prescribed, at which time headache response can be assessed and the dose increased or decreased as necessary. If effective, amitriptyline should be continued for 3 to 4 months before gradually decreasing the dose until the drug is completely discontinued. Therapy should be reinstituted if headaches return. Mirtazapine may be initiated as a second-line option for K.B., if amitriptyline is not effective.

Interprofessional Management

Practices in the areas of spiritual meditation,[235] cognitive therapy and stress reduction,[236,237] and acupuncture[238] have been assessed in headache management. A study assessing outcome measures of headache frequency, severity, and medication use, as impacted by spiritual meditation, secular meditation (internally and externally focused), or muscle relaxation, reported a favorable impact on episode frequency induced by spiritual meditation.[235] A decrease in medication usage was similarly reflected in this cohort; however, neither pain sensitivity nor severity differed.[235] Interventions directed toward stress reduction, although deemed feasible, have not met statistical significance for changes in headache severity or frequency.[236] Although stress reduction favorably impacted MIDAS and HIT-6 assessments relative to controls, the study lacked the statistical power to confer significance.[236] Similarly, traditional acupuncture has yielded headache-associated pain relief; however, prospective trials are warranted to better elucidate the therapeutic impact of this practice.[238]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Cameron C, Kelly S, Hsieh SC, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. *Headache.* 2015;55(suppl 4):221–235. (80)

Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a

randomised, phase 3, double-blind, placebo-controlled trial. *Lancet.* 2019;394(*10200*):737–745. (105)

Deng H, Li GG, Nie H, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine—an updated systematic review and meta-analysis. *BMC Neurol.* 2020;20(*1*):57. (170)

Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med.* 2019;381(*2*):142–149. (104)

Marmura MJ, Silberstein SD. Current understanding and treatment of headache disorders. *Neurology.* 2011;76(suppl 2):S31–S36. (29)

Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache.* 2015;55:3–20. (49)

Negro A, Martelletti P. Gepants for the treatment of migraine. *Expert Opin Investig Drugs.* 2019;28(*6*):555–567. (106)

Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol.* 2017;16(*6*):425–434. (172)

Thorlund K, Mills EJ, Wu P, et al. Comparative efficacy of triptans for the abortive treatment of migraine: a multiple treatment comparison meta-analysis. *Cephalalgia.* 2014;34(*4*):258–267. (78)

Key Websites

American Academy of Neurology. https://www.aan.com/

American Headache Society. http://www.americanheadachesociety.org/

International Headache Society. http://www.ihs-headache.org/

COMPLETE REFERENCES CHAPTER 58 HEADACHE

1. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. *Headache*. 2018;58:496–505.
2. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. *Headache*. 2013;53(3):427–436.

3. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache*. 2015;55:21–34.
4. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2018;38(1):1–211.
5. Gasparini CF, Sutherland HG, Griffiths LR. Studies on the pathophysiology and genetic basis of migraine. *Curr Genomics*. 2013;14:300–315.
6. Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM. Does this patient with headache have a migraine or need neuroimaging*? JAMA*. 2006;296(10):1274–1283.
7. Lenaerts M, Couch J. Headache. In: Rosenberg RN, ed. *Atlas of Clinical Neurology*. Current Medicine Group, LLC; 2009.
8. Loder E, Rizzoli P. Tension-type headache. *BMJ*. 2008;336:88–92.
9. Tajti J, Párdutz A, Vámos E, et al. Migraine is a neuronal disease. *J Neural Transm*. 2011;118(4):511–524.
10. Ashina M. Neurobiology of chronic tension-type headache. *Cephalalgia*. 2004;24:161–172.
11. Panconesi A. Serotonin and migraine: a reconsideration of the central theory. *J Headache Pain*. 2008;9:267–276.
12. Samsam M, Rafael C, Raheleh A, Javier Y. Major neuroanatomical and neurochemical substrates involved in primary headaches. In: Flynn CE, Callaghan BR, eds. *Neuroanatomy Research Advances*. Nova Science Publishers; 2010:1–58.
13. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin gene related peptide: physiology and pathophysiology. *Physiol Rev*. 2014;94(4):1099–1142.
14. Avci AY, Lakadamyali H, Arikan S, Benli US, Kilinc M. High sensitivity C-reactive protein and cerebral white matter hyperintensities on magnetic resonance imaging in migraine patients. *J Headache Pain*. 2015;16:9.
15. Eadie MJ. The pathogenesis of migraine-17th to early-20th century understandings. *J Clin Neurosci*. 2005;12(4):383–388.
16. Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci USA*. 2001;98(8):4687–4692.
17. Borsook D, Hargreaves R. Brain imaging in migraine research. *Headache*. 2010;50(9):1523–1527.
18. Sprenger T, Borsook D. Migraine changes in the brain: neuroimaging makes its mark. *Curr Opin Neurol*. 2012;25(3):252–262.
19. Charles AC, Baca SM. Cortical spreading depression and migraine. *Nat Rev Neurol*. 2013;9:637–644.
20. Sarrouilhe D, Dejean C, Mesnil M. Involvement of gap junction channels in the pathophysiology of migraine with aura. *Front Physiol*. 2014;5(78):1–11.

21. Edvinsson L, Villalón CM, MaassenVanDenBrink A. Basic mechanisms of migraine and its acute treatment. *Pharmacol Ther*. 2012;136(3):319–333.
22. Arulmani U, Maassenvandenbrink A, Villalón CM, Saxena PR. Calcitonin gene-related peptide and its role in migraine pathophysiology. *Eur J Pharmacol*. 2004;500(1–3):315–330.
23. Moskowitz MA. Defining a pathway to discovery from bench to bedside: the trigeminovascular system and sensitization. *Headache*. 2008;48(5):688–690.
24. Amin FM, Hougaard A, Schytz HW, et al. Investigation of the pathophysiological mechanisms of migraine attacks induced by pituitary adenylate cyclase-activating polypeptide-38. *Brain*. 2014;137:779–794.
25. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol*. 2018;17:174–182.
26. Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache*. 2017;57:47–55.
27. Pelzer N, Haan J, Stam AH, et al. Clinical spectrum of hemiplegic migraine and chances of finding a pathogenic mutation. *Neurology*. 2018;90:575–582.
28. de Boer I, van den Maagdenberg AMJM, Terwindt GM. Advance in genetics of migraine. *Curr Opin Neurol*. 2019;32(3):413–421.
29. Marmura MJ, Silberstein SD. Current understanding and treatment of headache disorders. *Neurology*. 2011;76(suppl 2):S31–S36.
30. Royal P, Andres-Bilbe A, Ávalos Prado P, et al. Migraine-associated TRESK mutations increase neuronal excitability through alternative translation initiation and inhibition of TREK. *Neuron*. 2019;101(2):232–245.
31. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res*. 2003;12:963–974.
32. Rendas-Baum R, Yang M, Varon SF, Bloudek LM, DeGryse RE, Kosinski M. Validation of the Headache Impact Test (HIT-6) in patients with chronic migraine. *Health Qual Life Outcomes*. 2014;12:117.
33. Stewart WF, Lipton RB, Kolodner K. Migraine disability assessment (MIDAS) score: relation to headache frequency, pain intensity, and headache symptoms. *Headache*. 2003;43:258–265.
34. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: the Migraine Disability Assessment (MIDAS) Questionnaire. *Headache*. 2001;41:854–861.
35. Lipton RB, Stewart WF, Stone AM, Láinez MJ, Sawyer JP; Disability in Strategies of Care Study group. Stratified care vs step care strategies for migraine. *JAMA*. 2000;294:2599–2605.
36. Martin BC, Pathak DS, Sharfman MI, et al. Validity and reliability of the Migraine-Specific Quality of Life Questionnaire (MSQ version 2.1). *Headache*. 2000;40(3):204–215.
37. Cole JC, Lin P, Rupnow MF. Validation of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. *Qual Life Res*. 2007;16(7):1231–1237.

38. Rendas-Baum R, Bloudek LM, Maglinte GA, Varon SF. The psychometric properties of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ) in chronic migraine patients. *Qual Life Res*. 2013;22:1123–1133.
39. Jensen RH. Tension-type headache-the normal and most prevalent headache. *Headache*. 2018;58(2):339–345.
40. Martins LB, Duarte H, Ferreira AV, Rocha NP, Teixeira AL, Domingues RB. Migraine is associated with altered levels of neurotrophins. *Neurosci Lett*. 2015;587:6–10.
41. Panconesi A. Alcohol and migraine: trigger factor, consumption, mechanisms. A review. *J Headache Pain*. 2008;9(1):19–27.
42. Rist PM, Buring JE, Kurth T. Dietary patterns according to headache and migraine status: a cross-sectional study. *Cephalalgia*. 2015;35(9):767–775.
43. Paconesi A, Bartolozzi ML, Mugnai S, Guidi L. Alcohol as a dietary trigger of primary headaches: what triggering site could be compatible?. *Neurol Sci*. 2012;33(suppl 1):S203–S205.
44. Evans EW, Lipton RB, Peterlin BL, et al. Dietary intake patterns and diet quality in a nationally representative sample of women with and without severe headache or migraine. *Headache*. 2015;55(4):550–561.
45. Russo A, Silvestro M, Tessitore A, Tedeschi G. Functional neuroimaging biomarkers in migraine: diagnostic, prognostic and therapeutic implications. *Curr Med Chem*. 2019;26(34):6236–6252.
46. Goldstein J, Hagen M, Gold M. Results of a multicenter, double-blind, randomized, parallel-group, placebo-controlled, single-dose study comparing the fixed combination of acetaminophen, acetylsalicylic acid, and caffeine with ibuprofen for acute treatment of patients with severe migraine. *Cephalalgia*. 2014;34(13):1070–1078.
47. Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2013;2013(4):CD008040.
48. Prior MJ, Codispoti JR, Fu M. A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache. *Headache*. 2010;50(5):819–833.
49. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55:3–20.
50. Leinisch E, Evers S, Kaempfe N, et al. Evaluation of the efficacy of intravenous acetaminophen in the treatment of acute migraine attacks: a double-blind, placebo-controlled parallel group multicenter study. *Pain*. 2005;117:396–400.
51. Allais G, Castagnoli Gabellari I, De Lorenzo C, Mana O, Benedetto C. Oral contraceptives in migraine therapy. *Neurol Sci*. 2011;32(suppl 1):S135–S139.
52. Allais G, Gabellari IC, Airola G, Borgogno P, Schiapparelli P, Benedetto C. Headache induced by the use of combined oral contraceptives. *Neurol Sci*.

2009;30(suppl 1):S15–S17.
53. Loder EW, Buse DC, Golub JR. Headache as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. *Am J Obstet Gynecol*. 2005;193:636–649.
54. Merki-Feld GS, Imthurn B, Langner R, Seifert B, Gantenbein AR. Positive effects of the progestin desogestrel 75 mcg on migraine frequency and use of acute medication are sustained over a treatment period of 180 days. *J Headache Pain*. 2015;16:522.
55. Merki-Feld GS, Imthurn B, Seifert B, Merki LL, Agosti R, Gantenbein AR. Desogestrel-only contraception may reduce headache frequency and improve quality of life in women suffering from migraine. *Eur J Contracept Reprod Health Care*. 2013;18(5):394–400.
56. ACOG Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin No. 73: use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol*. 2006;107(6):1453–1472.
57. Noseda R, Kainz V, Borsook D, Burstein R. Neurochemical pathways that converge on thalamic trigeminovascular neurons: potential substrate for modulation of migraine by sleep, food intake, stress and anxiety. *PLoS One*. 2014;9(8):1–14.
58. Baldacci F, Lucchesi C, Cafalli M, et al. Migraine features in migraineurs with and without anxiety-depression symptoms: a hospital-based study. *Clin Neurol Neurosurg*. 2015;132:74–78.
59. Da Silva AN, Tepper SJ. Acute treatment of migraines. *CNS Drugs*. 2012;26(10):823–839.
60. Diamond ML, Wenzel RG, Nissan GR. Optimizing migraine therapy: evidence-based and patient-centered care. *Expert Rev Neurother*. 2006;6(6):911–919.
61. Johnston MM, Rapoport AM. Triptans for the management of migraine. *Drugs*. 2010;70(12):1505–1518.
62. Tepper SJ, Rapoport AM, Sheftell FD. Mechanisms of action of the 5-HT1B/1D receptor agonists. *Arch Neurol*. 2002;59(7):1084–1088.
63. Kröger IL, May A. Triptan-induced disruption of trigemino-cortical connectivity. *Neurology*. 2015;84(21):2124–2131.
64. Derry CJ, Derry S, Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults-overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2014;5:CD009108.
65. Loder E. Triptan therapy in migraine. *N Engl J Med*. 2010;363:63.
66. Landy S, Munjal S, Brand-Schieber E, Rapoport AM. Efficacy and safety of DFN-11 (sumatriptan injection, 3 mg) in adults with episodic migraine: a multicenter, randomized, double-blind, placebo-controlled study. *J Headache Pain*. 2018;19(1):69.
67. Tepper SJ, Cady RK, Silberstein S, et al. AVP-825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral

sumatriptan in the acute treatment of migraines (the COMPASS study): a comparative randomized clinical trial across multiple attacks. *Headache*. 2015;55:621–635.

68. Cady RK, McAllister PJ, Spierings EL, et al. A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (the TARGET study). *Headache*. 2015;55:88–100.
69. Cady R. A novel intranasal breath-powered delivery system for sumatriptan: a review of technology and clinical application of the investigational product AVP-825 in the treatment of migraine. *Expert Opin Drug Deliv*. 2015;12:1565–1577.
70. Lipton RB, McGinley JS, Shulman KJ, Silberstein SD, Wirth RJ, Buse DC. AVP-825 (Sumatriptan Nasal Powder) reduces nausea compared to sumatriptan tablets: results of the COMPASS randomized clinical trial. *Headache*. 2018;58(2):229–242.
71. Tepper SJ, Cady R, Dodick D, et al. Oral sumatriptan for the acute treatment of probable migraine: first randomized, controlled study. *Headache*. 2006;46:115–124.
72. Pini LA, Guerzoni S, Cainazzo M, Ciccarese M, Prudenzano MP, Livrea P. Comparison of tolerability and efficacy of a combination of paracetamol + caffeine and sumatriptan in the treatment of migraine attack: a randomized, double-blind, double-dummy, cross-over study. *J Headache Pain*. 2012;13:669–675.
73. Landy SH, Tepper SJ, Wein T, Schweizer E, Ramos E. An open-label trial of a sumatriptan auto-injector for migraine in patients currently treated with subcutaneous sumatriptan. *Headache*. 2013;53(1):118–125.
74. Shimizu M, Hata K, Takaoka H, et al. Sumatriptan provokes coronary artery spasm in patients with variant angina: possible involvement of serotonin 1B receptor. *Int J Cardiol*. 2007;114:188–194.
75. Stillman MJ, Tepper DE, Tepper SJ, Cho L. QT prolongation, torsade de pointes, myocardial ischemia from coronary vasospasm, and headache medications. Part 2: review of headache medications, drug-drug interactions, QTc prolongation, and other arrhythmias. *Headache*. 2013;53:217–224.
76. Evans RW. The FDA alert on serotonin syndrome with combined use of SSRIs or SNRIs and Triptans: an analysis of the 29 case reports. *MedGenMed*. 2007;9(3):48.
77. Becker WJ. Acute migraine treatment in adults. *Headache*. 2015;55:778–793.
78. Thorlund K, Mills EJ, Wu P, et al. Comparative efficacy of triptans for the abortive treatment of migraine: a multiple treatment comparison meta-analysis. *Cephalalgia*. 2014;34(4):258–267.
79. Savi L, Mogavero S, Egan CG. Efficacy and pharmacokinetic activity of frovatriptan compared to rizatriptan in patients with moderate-to-severe

migraine. *Drug Des Devel Ther*. 2014;8:983–992.
80. Cameron C, Kelly S, Hsieh SC, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. *Headache*. 2015;55(suppl 4):221–235.
81. Shapiro RE, Tepper SJ. The serotonin syndrome, triptans, and the potential for drug–drug interactions. *Headache*. 2007;47:266–269.
82. Rolan PE. Drug interactions with triptans. Which are clinically significant? *CNS Drugs*. 2012;26:949–957.
83. Buchan P, Wade A, Ward C, Oliver SD, Stewart AJ, Freestone S. Frovatriptan: a review of drug-drug interactions. *Headache*. 2002;42(suppl 2):S63–S73.
84. McEnroe JD, Fleishaker JC. Clinical pharmacokinetics of almotriptan, a serotonin 5-HT(1B/1D) receptor agonist for the treatment of migraine. *Clin Pharmacokinet*. 2005;44(3):237–246.
85. Fleishaker JC, Herman BD, Carel BJ, Azie NE. Interaction between ketoconazole and almotriptan in healthy volunteers. *J Clin Pharmacol*. 2003;43:423–427.
86. Negro A, Lionetto L, Casolla B, Lala N, Simmaco M, Martelletti P. Pharmacokinetic evaluation of frovatriptan. *Expert Opin Drug Metab Toxicol*. 2011;7(11):1449–1458.
87. Markus F, Mikko K. Frovatriptan review. *Expert Opin Pharmacother*. 2007;8(17):3029–3033.
88. Wells RE, Markowitz SY, Baron EP, et al. Identifying the factors underlying discontinuation of triptans. *Headache*. 2014;54(2):278–289.
89. Serrano D, Buse DC, Kori SH, et al. Effects of switching acute treatment on disability in migraine patients using triptans. *Headache*. 2013;53:1415–1429.
90. Buse DC, Serrano D, Reed ML, et al. Adding additional acute medications to a triptan regimen for migraine and observed changes in headache-related disability: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. 2015;55:825–839.
91. Dahlof C, Maassen VanDenBrink A. Dihydroergotamine, ergotamine, methysergide and sumatriptan-basic science in relation to migraine treatment. *Headache*. 2012;52:707–714.
92. Silberstein SD, Hargreaves RJ. The history and pharmacology of ergotamine and dihydroergotamine. In: Diener HC, ed. *Drug Treatment of Migraine and Other Frequent Headaches*. Karger Press; 2000:52–65.
93. Aurora SK, Silberstein SD, Kori SH, et al. MAP0004, orally inhaled DHE: a randomized, controlled study in the acute treatment of migraine. *Headache*. 2011;51:507–517.
94. Shrewsbury SB, Cook RO, Taylor G, Edwards C, Ramadan NM. Safety and pharmacokinetics of dihydroergotamine mesylate administered via a novel (Tempo) inhaler. *Headache*. 2007;48:355–367.

95. Tfelt-Hansen P, Saxena PR. Ergot alkaloids in the acute treatment of migraines. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*. Lippincott Williams & Wilkins; 2006:459–467.
96. Banhidy F, Acs N, Puhó E, Czeizel AE. Ergotamine treatment during pregnancy and a higher rate of low birthweight and preterm birth. *Br J Clin Pharmacol*. 2007;64:510–516.
97. Saper JR, Silberstein S. Pharmacology of dihydroergotamine and evidence for efficacy and safety in migraine. *Headache*. 2006;46(suppl 4):S171–S181.
98. Amiri H, Ghodrati N, Nikuyeh M, Shams-Vahdati S, Jalilzadeh-Binazar M. Comparison of granisetron and metoclopramide in the treatment of pain and emesis in migraine patients: a randomized controlled trial study. *Turk J Emerg Med*. 2017;17(2):61–64.
99. Friedman BW, Esses D, Solorzano C, et al. A randomized controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine. *Ann Emerg Med*. 2008;52(4):399–406.
100. Friedman BW, Mulvey L, Esses D, et al. Metoclopramide for acute migraine: a dose-finding randomized clinical trial. *Ann Emerg Med*. 2011;57(5):475–482.
101. Lipton RB, Dodick DW, Ailani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial [published correction appears in *JAMA*. 2020 Apr 7;323(13):1318]. *JAMA*. 2019;322(19):1887–1898.
102. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant, an acute treatment for migraine, improved patient-reported functional disability and satisfaction in 2 single-attack phase 3 randomized trials, ACHIEVE I and II. *Headache*. 2020;60(4):686–700.
103. Voss T, Lipton RB, Dodick DW, et al. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. *Cephalalgia*. 2016;36(9):887–898.
104. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med*. 2019;381(2):142–149.
105. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet*. 2019;394(10200):737–745.
106. Negro A, Martelletti P. Gepants for the treatment of migraine. *Expert Opin Investig Drugs*. 2019;28(6):555–567.
107. Petersen KA, Birk S, Lassen LH, et al. The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers. *Cephalalgia*. 2005;25:139–147.

108. Petersen KA, Lassen LH, Birk S, Lesko L, Olesen J. BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation. *Clin Pharmacol Ther.* 2005;77:202–213.
109. Ailani J, Lipton RB, Hutchinson S, et al. Long-term safety evaluation of ubrogepant for the acute treatment of migraine: phase 3, randomized, 52-week extension trial. *Headache*. 2020;60(1):141–152.
110. Färkkilä M, Diener HC, Géraud G, et al. Efficacy and tolerability of lasmiditan, an oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. *Lancet Neurol.* 2012;11:405–413.
111. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: a phase 3 randomized study. *Neurology*. 2018;91(24):e2222–e2232.
112. Whyte C, Tepper SJ, Evans RW, et al. Expert opinion. Rescue me: rescue medication for migraine. *Headache*. 2010;50:307–313.
113. Goldstein J, Silberstein SD, Saper JR, Ryan RE Jr, Lipton RB. Acetaminophen, aspirin, and caffeine in combination versus ibuprofen for acute migraine: results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. *Headache*. 2006;46:444–453.
114. Rabbie R, Derry S, Moore RA, McQuay HJ. et al. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2013;4:CD008039.
115. Antonaci F, Ghiotto N, Wu S, et al. Recent advances in migraine therapy. *Springerplus*. 2016 May 17;5:637.
116. Schurks M. Dihydroergotamine: role in the treatment of migraine. *Expert Opin Drug Metab Toxicol*. 2009;5:1141–1148.
117. Tanen DA, Miller S, French T, Riffenburgh RH. Intravenous sodium valproate versus prochlorperazine for the emergency department treatment of acute migraine headaches: a prospective, randomized, double-blind trial. *Ann Emerg Med*. 2003;41:847–853.
118. Friedman BW, Greenwald P, Bania TC, et al. Randomized trial of IV dexamethasone for acute migraine in the emergency department. *Neurology*. 2007;69(22):2038–2044.
119. Colman I, Friedman BW, Brown MD, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. *BMJ*. 2008;336:1359–1361.
120. Goadsby PJ, Lipton RB, Ferrari MD. Migraine-current understanding and treatment. *N Engl J Med*. 2002;346:257–270.
121. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337–1345.

122. Fenstermacher N, Levin M, Ward T. Pharmacological prevention of migraine. *BMJ*. 2011;342:583.
123. Serrano D, Lipton RB, Scher AI, et al. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. *J Headache Pain*. 2017;18:101.
124. Shamliyan TA, Choi JY, Ramakrishnan R, et al. Preventive pharmacologic treatments for episodic migraine in adults. *J Gen Intern Med*. 2013;28(9):1225–1237.
125. Wang DW, Mistry AM, Kahlig KM, Kearney JA, Xiang J, George AL Jr. Propranolol blocks cardiac and neuronal voltage-gated sodium channels. *Front Pharmacol*. 2010;1(144):1–12.
126. Casucci G, Villani V, Frediani F. Central mechanism of action of antimigraine prophylactic drugs. *Neurol Sci*. 2008;29(Suppl 1):S123–S126.
127. Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. *Ann Neurol*. 2006;59:652–661.
128. Min JH, Kwon HM, Nam H. The effect of propranolol on cerebrovascular reactivity to visual stimulation in migraine. *J Neurol Sci*. 2011;305(1–2):136–138.
129. Schellenberg R, Lichtenthal A, Wöhling H, Graf C, Brixius K. Nebivolol and metoprolol for treating migraine: an advance on β-blocker treatment? *Headache*. 2008;48:118–125.
130. Hansen JM, Baca SM, Vanvalkenburgh P, Charles A. Distinctive anatomical and physiological features of migraine aura revealed by 18 years of recording. *Brain*. 2013;136:3589–3595.
131. Hansen JM, Goadsby PJ, Charles AC. Variability of clinical features in attacks of migraine with aura. *Cephalalgia*. 2016;36(3):216–224.
132. Schankin CJ, Maniyar FH, Sprenger T, Chou DE, Eller M, Goadsby PJ. The relation between migraine, typical migraine aura and “visual snow”. *Headache*. 2014;54:957–966.
133. Hansen JM, Lipton RB, Dodick DW, et al. Migraine headache is present in the aura phase. A prospective study. *Neurology*. 2012;79:2044–2049.
134. Cole JW, Kittner SJ. Meta-analysis of results from case control and cohort studies finds that migraine is associated with approximately twice the risk of ischaemic stroke. *Evid Based Med*. 2010;15:193–194.
135. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2009;339:b3914.
136. Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. *Lancet Neurol*. 2010;9:285–298.
137. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain*.

2005;118(3):289–305.
138. Smitherman TA, Walters AB, Maizels M, Penzien DB. The use of antidepressants for headache prophylaxis. *CNS Neurosci Ther*. 2010;17(5):462–469.
139. Liang J, Liu X, Pan M, et al. Blockade of Nav1.8 currents in nociceptive trigeminal neurons contributes to anti-trigeminovascular nociceptive effect of amitriptyline. *Neurol Med*. 2014;16:308–321.
140. Kalita J, Bhoi SK, Misra UK. Amitriptyline vs divalproate in migraine prophylaxis: a randomized controlled trial. *Acta Neurol Scand*. 2013;128:65–72.
141. Moras K, Nischal H. Impact of amitriptyline on migraine disability assessment score. *J Clin Diagn Res*. 2014;8(9):KC01–KC02.
142. Dodick DW, Freitag F, Banks J, et al. Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clin Ther*. 2009;31(3):542–559.
143. Keskinbora K, Aydinli I. A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. *Clin Neurol Neurosurg*. 2008;110:979–984.
144. Israil A, Ahmed S, Rahman KM, et al. Efficacy of amitriptyline, pizotifen and propranolol in the prevention of migraine. *Mymensingh Med J*. 2013;22(1):93–100.
145. Silberstein S. Preventative migraine treatment. *Continuum (Minneap., Minn)*. 2015;21(4):973–989.
146. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci*. 2021;39(2):S1–S59.
147. Afshari D, Rafizadeh S, Rezaei M. A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. *Int J Neurosci*. 2012;122(2):60–68.
148. Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. Comparison of the effect of topiramate and sodium valproate in migraine prevention: a randomized blinded crossover study. *Headache*. 2006;46:642–648.
149. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev*. 2013;2013(6):CD010610.
150. Wenzel RG, Schwarz K, Padiyara RS. Topiramate for migraine prevention. *Pharmacotherapy*. 2006;26:375–387.
151. Silberstein SD, Hulihan J, Karim MR, et al. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. *Clin Ther*. 2006;28(7):1002–1011.

152. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. *JAMA*. 2004;291(8):965–973.
153. Diener HC, Tfelt-Hansen P, Dahlöf C, et al. Topiramate in migraine prophylaxis: results from a placebo-controlled trial with propranolol as an active control. *J Neurol*. 2004;251(8):943–950.
154. Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache*. 2009;49:1153–1162.
155. Öztürk B, Övünç Özön A, Karadas¸ Ö. Evaluation of cognitive functions in migraineurs treated with topiramate. *J Clin Neurosci*. 2019;59:89–92.
156. Dakhale GN, Sharma VS, Thakre MN, Kalikar M. Low-dose sodium valproate versus low-dose propranolol in prophylaxis of common migraine headache: a randomized, prospective, parallel, open-label study. *Indian J Pharmacol*. 2019;51(4):255–262.
157. Hesami O, Sistanizad M, Asadollahzade E, Johari MS, Beladi-Moghadam N, Mazhabdar-Ghashghai H. Comparing the effects of atorvastatin with sodium valproate (divalproex) on frequency and intensity of frequent migraine headaches: a double-blind randomized controlled study. *Clin Neuropharmacol*. 2018;41(3):94–97.
158. Gerstner T, Büsing D, Bell N, et al. Valproic acid-induced pancreatitis: 16 new cases and a review of the literature. *J Gastroenterol*. 2007;42:39–48.
159. Zain S, Khan M, Alam R, Zafar I, Ahmed S. Comparison of efficacy and safety of topiramate with gabapentin in migraine prophylaxis: randomized open label control trial. *J Pak Med Assoc*. 2013;63(1):3–7.
160. Silberstein S, Goode-Sellers S, Twomey C, Saiers J, Ascher J. Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. *Cephalalgia*. 2013;33(2):101–111.
161. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker. A randomized controlled trial. *JAMA*. 2003;289(1):65–69.
162. Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. *Cephalalgia*. 2014;34(7):523–532.
163. Hauge AW, Asghar MS, Schytz HW, Christensen K, Olesen J. Effects of tonabersat on migraine with aura: a randomized, double-blind, placebo-controlled crossover study. *Lancet Neurol*. 2009;8:718–723.
164. Dahlof CG, Hauge AW, Olesen J. Efficacy and safety of tonabersat, a gap-junction modulator, in the acute treatment of migraine: a double-blind, parallel-group, randomized study. *Cephalalgia*. 2009;29(suppl 2):7–16.
165. Goadsby PJ, Ferrari MD, Csanyi A, Olesen J, Mills JG; Tonabersat TON-01-05 Study Group. Randomized, double-blind, placebo-controlled, proof-of-

concept study of the cortical spreading depression inhibiting agent tonabersat in migraine prophylaxis. *Cephalalgia*. 2009;29(7):742–750.

166. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010;30(7):804-814.
167. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack Adams A. Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. *J Headache Pain*. 2018;19(1):13.
168. Ahmed F, Gaul C, García-Moncó JC, Sommer K, Martelletti P; REPOSE Principal Investigators. An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study. *J Headache Pain*. 2019;20(1):26.
169. Botox injection. Package insert. Allergan; July 2020.
170. Deng H, Li GG, Nie H, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine—an updated systematic review and meta-analysis. *BMC Neurol*. 2020;20(1):57.
171. Sacco S, Bendtsen L, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *J Headache Pain*. 2019;20(1):6.
172. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425–434.
173. Aimovig injection. Package insert. Amgen; April 2020.
174. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med*. 2017;377(22):2113–2122.
175. Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial [published correction appears in *Lancet*. 2019 Oct 29;]. *Lancet*. 2019;394(10203):1030–1040.
176. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91(24):e2211–e2221.
177. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial [published correction appears in *JAMA Neurol*. 2019 Jul 1;76(7):872]. *JAMA Neurol*. 2018;75(9):1080–1088.
178. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results

of the EVOLVE-2 phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38(8):1442–1454.
179. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE 2. *Neurology*. 2020;94(13):e1365–e1377.
180. VYEPTI intravenous injection. Package insert. Lundbeck Seattle BioPharmaceuticals; 2020.
181. AJOVY subcutaneous injection. Package insert. Teva Pharmaceuticals; 2018.
182. EMGALITY subcutaneous injection. Package insert. Eli Lilly; 2018.
183. Levin M, Silberstein SD, Gilbert R, et al. Basic considerations for the use of monoclonal antibodies in migraine. *Headache*. 2018;58(10):1689–1696.
184. Cohen JM, Ning X, Kessler Y, et al. Immunogenicity of biologic therapies for migraine: a review of current evidence. *J Headache Pain*. 2021;22(1):3
185. Dodick DW, Goadsby PJ, Silberstein SD, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene related peptide, for the prevention of frequent episodic migraine: a randomised, double blind, placebo controlled, exploratory phase 2 trial. *Lancet Neurol*. 2014;13(11):1100–1107.
186. Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG334 for prevention of episodic migraine: a randomised, double-blind, placebo controlled, phase 2 trial. *Lancet Neurol*. 2016;15:382–390.
187. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene related peptide, for the prevention of migraine: a phase 2 randomised, double blind, placebo controlled study. *Lancet Neurol*. 2014;13:885–892.
188. Bigal ME, Dodick DW, Rapoport AM, et al. Safety, tolerability, and efficacy of TEV48125 for preventative treatment of high frequency episodic migraine: a multicentre, randomised, double blind, placebo controlled, phase 2b study. *Lancet Neurol*. 2015;14:1081–1090.
189. Bigal ME, Edvinsson L, Rapoport AM, et al. Safety, tolerability, and efficacy of TEV for preventative treatment of chronic migraine: a multicentre, randomised, double blind, placebo controlled phase 2b study. *Lancet Neurol*. 2015;14:1091–1100.
190. Srikiatkhachorn A, le Grand SM, Supornsilpchai W, Storer RJ. Pathophysiology of medication overuse headache-an update. *Headache*. 2014;54:204–210.
191. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache*. 2008;48:1157–1168.
192. Fumal A, Laureys S, Di Clemente L, et al. Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. *Brain*. 2006;129:543–550.

193. Sarchielli P, Rainero I, Coppola F, et al. Involvement of corticotrophin-releasing factor and orexin-A in chronic migraine and medication-overuse headache: findings from cerebrospinal fluid. *Cephalalgia*. 2008;28:714–722.
194. Chatchaisak D, Srikiatkhachorn A, Maneesri-le Grand S, Govitrapong P, Chetsawang B. The role of calcitonin gene-related peptide on the increase in transient receptor potential vanilloid-1 levels in trigeminal ganglion and trigeminal nucleus caudalis activation of rat. *J Chem Neuroanat*. 2013;47:50–56.
195. Chen X, Chen Z, Dong Z, Liu M, Yu S. Morphometric changes over the whole brain in caffeine-containing combination-analgesic-overuse headache. *Mol Pain*. 2018;14:1744806918778641.
196. Evers S, Jensen R. Treament of medication overuse headache-guideline of the EFNS headache panel. *Eur J Neurol*. 2011;18:1115–1121.
197. Tassorelli C, Jensen R, Allena M, et al. A consensus protocol for the management of medication-overuse headache: evaluation in a multicentric, multinational study. *Cephalalgia*. 2014;34(9):645–655.
198. Grande RB, Aaseth K, Benth JŠ, Lundqvist C, Russell MB. Reduction in medication-overuse headache after short information. The Akershus study of chronic headache. *Eur J Neurol*. 2011;18:129–137.
199. Diener HC, Bussone G, Van Oene JC, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2007;27:814–823.
200. Nesbitt AD, Goadsby PJ. Cluster headache. *BMJ*. 2012;344:e2407.
201. May A. Cluster headache: pathogenesis, diagnosis, and management. *Lancet*. 2005;366:843–855.
202. Bussone G. Cluster headache: from treatment to pathophysiology. *Neurol Sci*. 2008;29(suppl 1):S1–S6.
203. Bruera O, Sances G, Leston J, et al. Plasma melatonin pattern in chronic and episodic headaches: evaluation during sleep and waking. *Funct Neurol*. 2008;23(2):77–81.
204. Gooriah R, Buture A, Ahmed F. Evidence-based treatments for cluster headache. *Ther Clin Risk Manag*. 2015;11:1687–1696.
205. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study in 230 patients with diagnostic implications. *Neurology*. 2002;58(3):354–361.
206. Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. *Neurology*. 2010;75:463–473.
207. Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ. Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo-controlled, double-blind crossover study. *Arch Neurol*. 2006;63:1537–1542.
208. Ashkenazi A, Schwedt T. Cluster headache: acute and prophylactic therapy. *Headache*. 2011;51:272–286.

209. May A, Leone M, Afra J, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol*. 2006;13:1066–1077.
210. Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of cluster headache: the American Headache Society evidence-based guideline. *Headache*. 2016;56:1093–1106.
211. Guo XN, Lu JJ, Ni JQ, Lu HF, Zhao HR, Chen G. The role of oxygen in cluster headache. *Med Gas Res*. 2019;9(4):229–231.
212. May A, Schwedt TJ, Magis D, Pozo-Rosich P, Evers S, Wang SJ. Cluster headache. *Nat Rev Dis Primers*. 2018;4:180–186.
213. Tepper D. Oxygen for cluster headache. *Headache*. 2017;57:1493–1494.
214. Pearson SM, Burish MJ, Shapiro RE, Yan Y, Schor LI. Effectiveness of oxygen and other acute treatments for cluster headache: results from the Cluster Headache Questionnaire, an international survey. *Headache*. 2019;59:235–249.
215. Rapoport AM, Mathew NT, Silberstein SD, et al. Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study [published correction appears in *Neurology*. 2007;69:2029]. *Neurology*. 2007;69:821–826.
216. Leone M, D'Amico D, Frediani F, et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology*. 2000;54:1382–1385.
217. Blau JN, Engel HO. Individualizing treatment with verapamil for cluster headache patients. *Headache*. 2004;44:1013–1018.
218. Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs*. 2003;63:1637–1677.
219. May A. Headaches with (ipsilateral) autonomic symptoms. *J Neurol*. 2003;250:1273–1278.
220. Moreira J, Geoffroy PA. Lithium and bipolar disorder: impacts from molecular to behavioural circadian rhythms. *Chronobiol Int*. 2016;33(4):351–373.
221. Lainez MJ, Pascual J, Pascual AM, Santonja JM, Ponz A, Salvador A. Topiramate in the prophylactic treatment of cluster headache. *Headache*. 2003;43:784–789.
222. McGeeney BE. Topiramate in the treatment of cluster headache. *Curr Pain Headache Rep*. 2003;7:135–138.
223. Forderreuther S, Mayer M, Straube A. Treatment of cluster headache with topiramate: effects and side-effects in five patients. *Cephalalgia*. 2002;22:186–189.
224. Rozen TD. Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia. *Headache*. 2001;41(suppl 1):25–33.
225. Leone M, Dodick D, Rigamonti A, et al. Topiramate in cluster headache prophylaxis: an open trial. *Cephalalgia*. 2003;23:1001–1002.

226. Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med*. 2019;381(2):132–141.
227. Bendtsen L, Evers S, Linde M, et al. EFNS guideline on the treatment of tension-type headache—report of an EFNS task force. *Eur J Neurol*. 2010;17:1318–1325.
228. Lyngberg AC, Rasmussen BK, Jørgensen T, Jensen R. Has the prevalence of migraine and tension-type headache changed over a 12-year period? A Danish population survey. *Eur J Epidemiol*. 2005;20:243–249.
229. Bendtsen L, Jensen R. Tension-type headache. *Neurol Clin*. 2009;27:525–535.
230. Fumal A, Schoenen J. Tension-type headache: current research and clinical management. *Lancet Neurol*. 2008;7:70–83.
231. Diener HC, Gold M, Hagen M. Use of a fixed combination of acetylsalicylic acid, acetaminophen and caffeine compared with acetaminophen alone in episodic tension-type headache: meta-analysis of four randomized, double-blind, placebo-controlled, crossover studies. *J Headache Pain*. 2014;15:76.
232. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA*. 2001;285:2208–2215.
233. Bendtsen L, Jensen R. Mirtazapine in effective in the prophylactic treatment of chronic tension-type headache. *Neurology*. 2004;62(10):1706–1711.
234. Zissis NP, Harmoussi S, Vlaikidis N, et al. A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. *Cephalalgia*. 2007;27(4):315–324.
235. Wachholtz AB, Malone CD, Pargament KI. Effect of different meditation types in migraine headache medication use. *Behav Med*. 2015;11:1–8.
236. Wells RE, Burch R, Paulsen RH, Wayne PM, Houle TT, Loder E. Meditation for migraines: a pilot randomized controlled trial. *Headache*. 2014;54(9):1484–1495.
237. Day MA, Thorn BE, Ward LC, et al. Mindfulness-based cognitive therapy for the treatment of headache pain: a pilot study. *Clin J Pain*. 2014;30(2):152–161.
238. Ahn CB, Lee SJ, Lee JC, Fossion JP, Sant'Ana A. A clinical pilot study comparing traditional acupuncture to combined acupuncture for treating headache, trigeminal neuralgia and retro-auricular pain in facial palsy. *J Acupunct Meridian Stud*. 2011;4(1):29–43.

59

Parkinson Disease and Other Movement Disorders

Shedrick Martin and Kimberly Tallian

CORE PRINCIPLES		CHAPTER CASES
1	Parkinson disease (PD) is a chronic, progressive movement disorder resulting from loss of dopamine from the nigrostriatal tracts in the brain and is characterized by rigidity, bradykinesia, postural disturbances, and tremor.	**Case 59-1 (Question 1, 2)**
2	Treatment for PD is aimed at restoring dopamine supply through one or a combination of the following methods: exogenous dopamine in the form of a precursor, levodopa; direct stimulation of dopamine receptors via dopamine agonists; and inhibition of metabolic pathways responsible for degradation of levodopa.	**Case 59-1 (Question 3–17)**

3	It was once thought to delay the introduction of levodopa with dopamine agonists or monoamine oxidase type B (MAO-B) inhibitors as to avoid peak-dose levodopa-induced dyskinesias as long as possible, but this therapeutic approach has changed more recently, and levodopa/carbidopa should be introduced when early PD is associated with motor symptoms that impact quality of life.	**Case 59-1 (Question 3, 4), Figure 59-1**
4	Initial therapy with levodopa-sparing agents is not associated with a lower risk of developing motor complications than with levodopa. Start with the lowest dose of levodopa to maintain functionality while balancing the development of motor complications.	**Case 59-1 (Question 4–9), Figure 59-1**
5	Advanced PD is characterized by motor fluctuations, including a gradual decline in on-time and by the development of troubling dopaminergic-induced dyskinesias. Modified carbidopa/levodopa formulations, dopamine agonists, MAO-B inhibitors, adenosine A_{2A} receptor antagonist, and catechol-*O*-methyltransferase (COMT) inhibitors can reduce motor fluctuations; amantadine can improve dyskinesias. Deep brain stimulation of the globus pallidus interna or subthalamic nucleus may benefit patients with advanced PD.	**Case 59-1 (Question 13–19), Figure 59-3**
		Case 59-2 (Question

6	Multiple dietary supplements and other investigational therapies have been studied for the management of PD.	1)
7	Comprehensive therapy for patients should include attention to many progressive complications of PD, including neuropsychiatric disturbances and autonomic dysfunction.	Case 59-3 (Question 1, 2)
	RESTLESS LEGS SYNDROME	
1	Restless legs syndrome (RLS) is a disabling sensorimotor disorder typically marked by irresistible urges to move the legs (akathisia). It is often associated with uncomfortable paresthesias or dysesthesias and often occurs in the evening or night.	Case 59-4 (Question 1)
2	Several conditions are associated with or can aggravate RLS. Periodic limb movements of sleep (PLMS) is not the same as RLS but often coexists.	Case 59-4 (Question 2)
3	Dopamine agonists are first-line treatments for RLS. They are preferred because they are longer acting than levodopa and reduce symptoms throughout the entire night. Other effective therapies include carbidopa/levodopa, gabapentin, benzodiazepines, and opiates.	Case 59-4 (Question 3)
4	A common problem with long-term use of dopaminergic agents in RLS, particularly levodopa, is an	Case 59-4 (Question 4)

	augmentation effect. This effect refers to a gradual dosage intensification that occurs in response to a progressive worsening of symptoms after an initial period of improvement. Gradual withdrawal of therapy and substitution with other agents should be performed, rather than continued dopaminergic dose escalation.	
ESSENTIAL TREMOR		
1	Essential tremor (ET) should be distinguished clinically from tremor associated with PD or other causes.	**Case 59-5 (Question 1)**
2	Treatments of choice for ET include propranolol or primidone. In refractory cases, targeted botulinum toxin A injections can be useful.	**Case 59-5 (Question 2)**

INTRODUCTION

Parkinson disease (PD) is a chronic, progressive movement disorder first described in 1817 by Dr. James Parkinson. Since that time, the term parkinsonism has come to refer to any disorder associated with two or more features of tremor, rigidity, bradykinesia, or postural instability.[1] Most cases of PD are of unknown cause and referred to as idiopathic parkinsonism; however, viral encephalitis, cerebrovascular disease, and hydrocephalus have symptoms similar to PD as part of their clinical presentation.[1] Unless otherwise stated, all references to PD in this chapter refer to the idiopathic type.

PD age of onset is variable, increasing after age 50 and peaking around age 80.[2] Both the incidence and prevalence of PD are age-

dependent, with annual incidence estimates ranging from 13.4/100,000 person-years (ages 50–59 years), 58.52/100,000 person-years (ages 60–69 years), 132.72/100,000 person-years (age 70–79 years), and an estimated prevalence of 1% of the population older than age 65 years.[3–5] The overall incidence rate of PD in females 40 years and older is 37.55/100,000 person-years (95% CI: 26.20–53.83) and 61.21/100,000 (95% CI: 43.57–85.99) in males 40 years and older.[5] Males have higher incidence rates than females (70–79 years) with 162.58/100,000 person-years compared to 93.32/100,000 person-years (P = .023).[5] Despite the availability of effective symptomatic treatments to improve both quality of life and life expectancy, no cure exists. The symptoms of PD are progressive and, within 10 to 20 years, significant immobility results for most patients.[6] More rapid rates of symptom progression and motor disability have been observed in patients of older age at disease onset.[7] PD itself does not cause death; however, patients often succumb to complications related to impaired mobility and function (eg, aspiration pneumonia, thromboembolism) and overall frailty.[6]

Etiology

The etiology of PD is poorly understood. Most evidence suggests it is multifactorial and attributable to a complex interplay between age-related changes in the nigrostriatal tract, underlying genetic risks, and/or environmental triggers. Support for this hypothesis can be found in several historic observations.[7]

The relative contributions of environment and genetics to the occurrence of PD remain controversial; rural living, pesticide exposure, and consumption of well water have consistently been associated with increased lifetime risk of PD, whereas exercise, cigarette smoking, and caffeine ingestion appear to be protective.[8,9] Additional risk factors such as mood disorders, head injury, and chronic constipation may contribute to the development of PD.[10] Most cases of PD are sporadic and may be attributed to risk factors over a lifetime. Hereditary PD is thought to be caused by one or

more mutations in 23 Parkinson (*PARK*) genes that have been associated with possible links to the development of PD. Mutations at Parkin RBR E3 ubiquitin protein ligase (PRKN), phosphatase and tensin homolog (PTEN)–induced putative kinase 1 (PINK1), DJ-1, α-synuclein (SCNA), and leucine-rich repeat kinase 2 (LRRK2) vacuolar protein sorting–associated protein 32 (VPS32), and glucocerebrosidase (GBA) show inheritable characteristics. These genes have been reported in 10% to 15% of familial inherited cases of PD, but these genes lack typical Mendelian patterns of inheritance, with occurrence in only about 5% of cases. These heritable factors do not account for the threefold increased risk of developing PD for individuals who have a first-degree relative affected with sporadic PD.[11,12] The exact linkage between genetics, environment, and clinical expression of disease remains uncertain.[13]

Pathophysiology

The salient features of PD result from a loss of dopaminergic neurons in the nigrostriatal tracts of the brain and development of abnormal intraneuronal protein aggregates called Lewy bodies that interfere with neuronal function. The nigrostriatal tracts are neuronal tracts between the substantia nigra and the striatum. They are part of the extrapyramidal system of the brain involving the basal ganglia. This area is involved with maintaining posture and muscle tone by regulating voluntary smooth muscle activity. The pigmented neurons within the basal ganglia have dopaminergic fibers, and in PD, these dopamine-producing neurons are progressively depigmented. The remaining dopaminergic-producing cells have been shown (in postmortem examination) to contain Lewy bodies.[14] Lewy body pathology appears to ascend the brain in a predictable manner in PD, which begin in the medulla oblongata in preclinical stages. These neurologic pathways may explain observations of anxiety, depression, and olfactory disturbance, which ascend to the midbrain (motor dysfunction) and spread eventually to the cortex (cognitive and behavioral changes).[15] The loss of dopamine neurons, either

from death or from dysfunction, results in loss of dopamine-mediated inhibition of acetylcholine neurons. In PD, the typical balance of dopamine and acetylcholine is lost, which results in a relative increase in cholinergic activity.

The exact pathologic sequence leading to neurodegeneration is unclear, but free radicals formed as byproducts of dopamine auto-oxidation, cell apoptosis, protein misfolding and aggregation, defective proteolysis, oxidative stress and iron metabolism, and mitochondrial dysfunction have all been implicated. The finding that a critical threshold of neuronal loss (at least 70%–80%) occurs before PD becomes clinically apparent suggests that adaptive mechanisms (eg, upregulation of dopamine synthesis or downregulation of synaptic dopamine reuptake) may somehow influence disease progression during the preclinical stages.

Clinical Presentation of Parkinson Disease

CASE 59-1

Question 1: L.M., a 55-year-old, right-handed male artist, presents to the neurology clinic reporting difficulty painting because of unsteadiness in his right hand. He also endorses a loss in the sense of smell. His medical history is significant for gout (currently requiring no treatment), constipation (ie, progressively worsened in the past 10 years), benign prostatic hypertrophy, depression, and aortic stenosis. He does not smoke but usually drinks one alcoholic beverage in the evenings. His only prescription medication is citalopram 10 mg by mouth once daily. On physical examination, L.M. is noted to be a well-developed, well-nourished male who displays a notable lack of normal changes in facial expression but speaks in a soft, monotone voice. He lacks rigidity in both of his arms or legs but is noted to have a mild resting tremor in his right hand. His gait is slow but otherwise normal with a slightly bent posture. His balance is normal with no retropulsion or loss of righting reflexes after physical threat. His genitourinary examination is remarkable only for prostatic enlargement. The remainder of his physical examination is within normal limits. Laboratory values and vital signs obtained at this visit include the following:

Blood pressure, 119/66 mm Hg
Heart rate, 71 beats/minute
Sodium, 132 mEq/L

Potassium, 4.4 mEq/L
Blood urea nitrogen, 19 mg/dL
Creatinine, 1.1 mg/dL
Thyroid-stimulating hormone, 3.65 μU/L
Vitamin B_{12}, 612 pg/mL
Folate, 5.2 ng/mL
White blood cells, 4400 cells/mL
Red blood cells, 5.9×10^6/mL
Hemoglobin, 13.8 g/dL
Hematocrit, 41%
Uric acid, 6.3 mg/dL

How is PD best diagnosed? Is neuroimaging or any other testing recommended in the diagnosis of PD? What early signs and symptoms suggestive of PD are present in L.M.? What symptoms are among the classic features seen in PD?

The diagnosis of PD remains firmly grounded in obtaining a careful history and physical examination.[14] The neurologic examination to assess motor function, along with a positive response to levodopa, is highly diagnostic. The search for biomarkers of premotor PD in blood, cerebrospinal fluid, and urine has not uncovered single, practical candidates that are sensitive and specific.[11] Likewise, although imaging techniques can visualize nigrostriatal nerve terminals of dopamine synthesis and identify presymptomatic pathology, their routine use in asymptomatic, at-risk individuals is not yet recommended. In some instances, 123I-ioflupane (123I-FP-CIT) single-photon emission computed tomography (SPECT) scanning can be considered in clinical diagnosis of patients where there is uncertainty between PD and nondegenerative parkinsonism or tremor disorders. Other associated premotor symptoms, such as constipation, hyposmia (a reduced ability to smell and detect odors), rapid eye movement (REM) sleep disorder, and softening as well as tonal changes of the voice are among the earliest symptoms to appear. Screening for these findings may prove more economically practical in identifying a high-risk population worthy of further diagnostic evaluation.[16] However, by the time patients such as L.M. present with early symptoms, some burden of neuropathologic

evidence has accumulated, and, therefore, a diagnosis can be made clinically without the need for further laboratory or radiologic testing.

The classic features of PD—tremor, limb rigidity, and bradykinesia — are easily recognized particularly in advanced stages of the disease. Limb rigidity and bradykinesia are direct consequences of dopamine loss by disinhibiting cholinergic transmission whereby dopamine loss indirectly causes tremor. It is important to note that not all classic features are required to make the diagnosis of PD. The presence of two or more features indicates clinically probable PD.[17] Tremor, which is most often the first symptom observed in younger patients, is usually unilateral on initial presentation. Frequently, the low-amplitude tremor is of a pill-rolling type involving the thumb and index finger (3–6 Hz). The tremor is present at rest, worsens under fatigue or stress, and is absent with purposeful movement or when asleep.[1] These features help distinguish it from essential tremor (ET), which usually manifests as a symmetric tremor in the hands, often accompanied by head and voice tremor.[14] Approximately 20% of patients with PD do not present with tremor.[14] Muscular rigidity, resulting from increased muscle tone, often manifests as a cogwheel or ratchet (catch-release) type of motion when an extremity is moved passively.[1] Rigidity may also be experienced as stiffness or vague aching or limb discomfort.[14] Bradykinesia refers to an overall slowness in initiating movement. Early in the disease, patients may describe this as weakness or clumsiness of a hand or leg.[14] Because the disease progresses, difficulty initiating and terminating steps results in a hurried or festinating gait; the posture becomes stooped (simian posture), and postural reflexes are impaired.[1] Symptoms that were unilateral on initial presentation progress asymmetrically and often become bilateral as well as more severe with disease progression.[1] Patients with PD may develop masked facies or a blank stare with reduced eye blinking.

Because the diagnosis of PD is clinical, misdiagnosis can occur, leading to inappropriate, ineffective, or delayed treatment. Several conditions can be mistaken for PD and are important to distinguish from PD because they respond poorly to dopaminergic medications

and are associated with worse prognosis.[14] Falls or dementia early in the disease, symmetric parkinsonism, wide-based gait, abnormal eye movements, marked orthostatic hypotension, urinary retention, or marked disability within 5 years after the onset of symptoms suggest alternative diagnoses to PD.[14] Drugs may also mimic idiopathic PD. Drugs that act as antagonists at dopaminergic D_2 receptors (eg, neuroleptics, prochlorperazine, and metoclopramide), and others such as valproate, amiodarone, lithium, carbamazepine, and phenytoin (least) may cause a state of drug-induced parkinsonism or tremor. This potential etiology should be excluded before the diagnosis of PD is established. Although generally reversible, symptoms may persist for weeks or months after discontinuation of the offending agent.[14]

L.M. initially presents with classic premotor features such as his soft, monotone voice, reduced sense of smell, and constipation in addition to the classic symptoms of PD. A noticeable unilateral resting tremor is present along with decreased manual dexterity, as evidenced by his difficulty handling a paintbrush. Handwriting abnormalities occur frequently, particularly micrographia, a symptom of bradykinesia. Because L.M. is an artist, this abnormality would be particularly troublesome. Although he has a partially stooped posture, it is difficult to attribute this entirely to the disease because postural changes commonly occur with advancing age and, on physical examination, his balance was normal. To confirm the diagnosis of PD, a therapeutic trial of medication (levodopa) should be considered. A positive response to levodopa, as evidenced by an improvement in motor function, suggests the diagnosis of PD. However, patients with the tremor-predominant form of the disease may not respond to levodopa, especially in the early stages of the disease.[14]

Staging of Parkinson Disease

Case 59-1, Question 2: What are the four stages of PD? In what stage of PD is L.M. in?

To assess the degree of disability and determine the rate of disease progression relative to treatment, various scales have been developed. The most common of these is the Hoehn and Yahr scale (**Table 59-1**) and the modified Hoehn and Yahr scale.[2] In general, patients in Hoehn and Yahr[2] stage 1 or 2 of PD have mild disease that does not interfere with activities of daily living (ADLs) or work and usually requires minimal or no treatment. In stage 3 disease, daily activities are restricted, and employment may be significantly affected unless effective treatment is initiated. According to the scale, L.M. appears to be in late stage 2, early stage 3 of the disease (early symptomatic PD).

Table 59-1
Staging of Disability in Parkinson Disease

Stage 1	Unilateral involvement only; changes in posture, walking, and facial expressions occur; minimal or no functional impairment
Stage 2	Bilateral involvement, without impairment of balance; walking problems and poor posture may be apparent
Stage 3	Evidence of postural imbalance and slowness of movement; some restriction in activities; capable of leading independent life; mild-to-moderate disability such as dressing and eating
Stage 4	Severely disabled, possibility can stand without assistance but cannot walk and stand unassisted; significantly incapacitated required help needed for activities of daily living and is unable to live alone
Stage 5	Stiffness in the legs making it impossible to stand or walk; restricted to bed or wheelchair unless aided; experience hallucinations and delusion where both motor and nonmotor symptom management are needed

Source: Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol.* 2016;15(12):1257–1272.

With advanced-stage disease (stages 3 and 4), most patients require a double- or triple-drug therapy strategy. Patients with end-stage disease (stage 5) are severely incapacitated and, because of advanced disease progression, often do not respond well to drug therapy.

Treatment of Parkinson Disease

OVERVIEW OF THERAPY

Numerous national and international guidelines exist regarding the management of motor and nonmotor symptoms of PD. These guidelines include the American Academy of Neurology (AAN) practice parameters developed in 2002 and 2006,[18,19] the United Kingdom National Institute for Health and Care Excellence (NICE) national guideline developed in 2006 and revised in July 2017,[20] the European Federation of Neurological Societies Movement Disorder Society-European Section (EFNS MDS-ES) guidelines developed in 2016,[21] and the Canadian guideline for Parkinson disease in 2019.[22]

Although most of this chapter is devoted to the drug therapy of PD, the importance of nonpharmacologic, supportive care cannot be overemphasized. Patients in early PD stages should be enrolled in rehabilitative services to improve balance and motor function. These therapies include exercise, physical and occupational therapy, yoga, and speech therapy. Additionally, dietary recommendations of increased protein and vitamin D can be beneficial at the earlier stages to increase strength and enhance well-being and mood.[20] Psychological support is often necessary in dealing with depression and other related problems. Patients who are newly diagnosed and their family members need to be educated about what to expect from the disease and the various forms of treatment available. The support of family members is vital in establishing an overall effective therapeutic plan.

Nonpharmacologic therapy should continue throughout the course of care; however, because of the progressive nature of PD, pharmacologic therapy is often necessary. Because the salient pathophysiologic feature of PD is the progressive loss of dopamine from the nigrostriatal tracts in the brain, drug therapy for the disease is aimed primarily at replenishing the supply of dopamine. This pharmacologic intervention is accomplished through one, or a combination, of the following methods: (a) administering exogenous dopamine in the form of a precursor, levodopa; (b) stimulating dopamine receptors within the striatum through the use of dopamine

agonists (eg, pramipexole, ropinirole); or (c) inhibiting the major metabolic pathways within the brain that are responsible for the degradation of levodopa and its metabolites. This latter effect is achieved by using aromatic L-amino acid decarboxylase (AAD) inhibitors (eg, carbidopa), catechol-*O*-methyltransferase (COMT) inhibitors (eg, entacapone), or monoamine oxidase type B (MAO-B) inhibitors (eg, selegiline, rasagiline). Anticholinergics are also used; however, they are solely efficacious for the cholinergic-mediated tremor, and their routine use is limited by physical side effects (eg, blurry vision, constipation) and central nervous system (CNS) adverse effects, particularly in older patients. Amantadine is also used occasionally and may provide modest benefits via both dopaminergic and nondopaminergic (inhibition of glutamate) mechanisms (**Table 59-2**). A unique agent, istradefylline, works as an adenosine A_{2A} receptor antagonist that has shown benefit as an adjunctive therapy for levodopa "off" time. Because PD progresses, additional options, such as surgery, may be appropriate for a subset of patients.

Table 59-2
Medications Used for the Treatment of Parkinson Disease

Generic (Trade) Name	Dosage Unit	Titration Schedule	Usual Daily Dose	Adverse Effects
Amantadine (Symmetrel®)	100-mg capsule and tablet Liquid: 50 mg/5 mL 68.5- and 137-mg ER capsule 129-, 193-, and 258-mg ER tablet	IR capsule, tablet, liquid: 100 mg every day; increased by 100 mg every 1–2 weeks ER capsule: 137 mg every day; increased by 137 mg every week ER tablet: 129 mg every day; increased by 129 mg every week	IR capsule, tablet, liquid: 100–400 mg ER capsule: 274 mg ER tablet: 129–322 mg	Orthostatic hypotension, insomnia, depression, hallucinations, livedo reticularis, xerostomia
Anticholinergic agents				
Benztropine (Cogentin)	0.5-, 1-, and 2-mg tablets Injection: 1 mg/mL	0.5 and 1 mg at bedtime or in two to four divided doses increased by 0.5 mg every 5–6 days	1–3 mg given every day to bid	Constipation, xerostomia, dry skin, dysphagia, confusion, memory impairment
Trihexyphenidyl (Artane)	2- and 5-mg tablets Liquid: 2 mg/5 mL	1–2 mg/day increased by 1–2 mg every 3–5 days	6–10 mg divided tid to qid	Constipation, xerostomia, dry skin, dysphagia, confusion, memory impairment
Combination agents				
Carbidopa–levodopa (IR)/entacapone (Stalevo®)	12.5-/50-/200-, 18.75-/75-/200-, 25-/100-/200-, 31.25-/125-/200-, 37.5-/150-/200-, 50-/200-/200-mg tablets	Titrate with individual dosage forms (carbidopa/levodopa and entacapone) first, then switch to combination tablet	Varies (see individual drugs)	See individual drugs; <70–100 mg daily of carbidopa component may experience nausea and vomiting
Dopamine replacement				
Carbidopa–levodopa (IR) (Sinemet®)	10-/100-, 25-/100-, and 25-/250-mg tablets	25/100 mg bid, increased by 25/100 mg weekly to effect and as tolerated	30/300 to 150/1500 mg divided tid to qid	Nausea, orthostatic hypotension, confusion, dizziness, hallucinations, dyskinesias, blepharospasm
Carbidopa–levodopa (CR) (Sinemet® CR)	25-/100- and 50-/200-mg tablets	25/100 mg bid (spaced at least 6 hours apart), increased every 3–7 days	50/200 to 500/2000 divided qid	Same as regular Sinemet®
Carbidopa–levodopa (ER) (Rytary®)	23.75-/95-, 36.25-/145-, 48.75-/195-, 61.25-/245-mg capsules	23.75/95 mg tid; may increase to 36.25/145 mg tid on day 4 and titrate to response	Variable	Same as regular Sinemet®
Carbidopa–levodopa (enteral suspension) (Duopa™)	4.63-/20-mg/mL in 100-mL cassette	Total daily dose administered over 16 hours	Variable	Same as regular Sinemet®
Carbidopa–levodopa ODT (Parcopa®)	10-/100-, 25-/100-, and 25-/250-mg tablets	25/100 tid, increased every 1–2 days; if transferring from regular levodopa <1500 mg/day, start 25/100 mg tid to qid (start 25/250 mg tid to qid if already on >1500 mg/day of regular levodopa)	25/100 to 200/2000 divided tid to qid	Same as regular Sinemet®; may occur more rapidly than with regular Sinemet®
Levodopa inhaled (Inbrija®)	42-mg capsule per inhalation	84 mg up to five times daily as needed	84–420 mg	Cough, upper respiratory tract infection, discolored sputum, hallucinations, confusion, nausea, dyskinesias
Dopamine agonists				
Bromocriptine (Parlodel®)	2.5-mg tablet, 5-mg capsule	1.25 mg bid, titrate slowly as tolerated (2.5 mg/day every 2–4 weeks)	10–40 mg divided tid; max 100 mg/day	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, muscle cramps; retroperitoneal, pleural, pericardial fibrosis; cardiac valve thickening

Pramipexole (Mirapex®, Mirapex® ER)	IR: 0.125-, 0.25-, 0.50-, 0.75-, 1-, 1.5-mg tablets ER: 0.375-, 0.75-, 1.5-, 2.25-, 3-, 3.75-, 4.5-mg tablets	IR: 0.375 mg divided tid; titrate 5 to 7 days by 0.125–0.25 mg/dose ER: 0.375 mg once daily; titrate 5–7 days by 0.75 mg/dose	Immediate release: 1.5–4.5 mg divided tid ER: 1.5–4.5 mg once daily	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, somnolence
Ropinirole (Requip, Requip XL)	0.25-, 0.5-, 1-, 2-, 3-, 4-, 5-mg tablet XL: 2-, 4-, 6-, 8-, 12-mg tablets	0.25 mg tid; titrate weekly by 0.25 mg/dose XL: 2 mg once daily; titrate weekly or longer intervals by 2 mg/day	3–24 mg divided tid XL: 3–24 mg once daily	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, somnolence
Apomorphine (Apokyn®), (Kynmobi™)	10 mg/mL injection; 10-, 15-, 20-, 25-, 30-mg sublingual film	Initial 2-mg subcutaneous test dose; begin with 2 mg; increase by 1 mg every few days Concomitant trimethobenzamide should be begun 3 days prior to initial oral dose; initial dose 10-mg	2–6 mg 10–30 mg	Orthostatic hypotension, drowsiness, yawning, injection site reactions, nausea, vomiting (administer with trimethobenzamide, not 5-hydroxytryptamine-3 [5-HT_3] antagonists)
Rotigotine (Neupro®)	1-, 2-, 3-, 4-, 6-, 8-mg/24-hour transdermal delivery system	Early stage: 2 mg/24 hour; advanced stage: 4 mg/24 hour; titrate weekly by 2 mg/24 hour; application site should be rotated daily between abdomen, thigh, hip, flank, shoulder, or upper arm and do not use same site within 14 days	Early stage: 4–6 mg/24 hour Advance stage: 4-8 mg/24 hour	Hallucinations, nausea, vomiting, anorexia, somnolence, insomnia, dizziness, hyperhidrosis, visual disturbance, peripheral edema, and application site reactions; avoid in patients with known sulfite sensitivity
Catechol-O-methyltransferase inhibitors				
Entacapone (Comtan®)	200-mg tablet	200 mg with each administration of carbidopa/levodopa, up to 1600 mg daily	600–1600 mg daily	Diarrhea, dyskinesias, abdominal pain, urine discoloration
Tolcapone (Tasmar®)	100-mg tablet	100 mg tid	300–600 mg divided tid	Diarrhea, dyskinesias, abdominal pain, urine discoloration, hepatotoxicity
Opicapone (Ongentys®)	25-, 50-mg tablets	N/A	50 mg/day	Dyskinesia, constipation, hypotension, syncope, weight decrease
Monoamine oxidase type B inhibitors				
Rasagiline (Azilect®)	0.5-, 1-mg tablets	0.5–1 mg once daily	0.5–1 mg/day	Similar to selegiline
Safinamide (Xadago™)[a]	50-, 100-mg tablets	50 mg once daily; dose may be increased after two weeks to 100 mg once daily	50–100 mg/day	Similar to selegiline
Selegiline (Eldepryl®)[b]	5-mg tablet, capsule	5 mg every morning; may increase to 5 mg bid (5 mg with breakfast and 5 mg with lunch)	5–10 mg/day	Insomnia, dizziness, nausea, vomiting, xerostomia, dyskinesias, mood changes; use caution when coadministered with sympathomimetics or serotoninergic agents (increased risk of serotonin syndrome); avoid tyramine-containing foods

Selegiline ODT (Zelapar®)	1.25-mg tablet	1.25 mg every day; avoid food or liquids for 5 minutes before and after administration; may increase to 2.5 mg every day after 6 weeks	1.25–2.5 mg every day	Insomnia, dizziness, nausea, vomiting, xerostomia, dyskinesias, mood changes; use caution when coadministered with sympathomimetics or serotoninergic agents (increased risk of serotonin syndrome); avoid tyramine-containing foods
Adenosine receptor antagonist				
Istradefylline (Nourianz®)	20-, 40-mg tablets	20 mg once daily; dose may be increased up to 40 mg once daily	20–40 mg/day	Dyskinesia, constipation, nausea, hallucinations, insomnia

[a]Approved only for use as adjunctive treatment to levodopa/carbidopa in patients experiencing "off" episodes.

[b]A transdermal formulation is also available, but not approved for use in PD.

bid, twice daily; CR, controlled release; COMT, catechol-*O*-methyltransferase; ER, extended release; IR, immediate release; MAO-B, monoamine oxidase type B; ODT, orally disintegrating tablet; qid, four times daily; tid, three times daily; XL, extended release.

Despite optimization of both pharmacologic and nonpharmacologic therapies in PD, physical disability is progressive and unavoidable. In many instances, adverse effects of the medications themselves can lead to additional problems. These include neuropsychiatric problems (eg, cognitive impairment and dementia, hallucinations and delirium, depression, agitation, anxiety), autonomic dysfunction (eg, constipation, urinary problems, sexual problems, orthostasis, thermoregulatory imbalances), falls, sleep disorders (eg, insomnia or sleep fragmentation, nightmares, restless legs syndrome [RLS]), and motor complications (eg, disabling periods of either too much [dyskinetic] or too little [akinetic] dopaminergic activity).

Treatment of Early Parkinson Disease

Case 59-1, Question 3: What factors would indicate L.M. should begin treatment for his PD?

In choosing when to treat the symptoms of PD and which therapy to use, care must be taken to approach each patient individually. Although no consensus has been reached about when to initiate

symptomatic treatment, most clinician's agree that treatment should begin when the patient begins to experience functional impairment or impact quality of life as defined by (a) threat to employment status, (b) symptoms affecting the dominant side of the body, or (c) bradykinesia or rigidity.[23,24] Individual patient preferences also should be considered. Judging by the symptoms L.M. is displaying, he would likely benefit from immediate treatment. His symptoms are unilateral but are occurring on his dominant side and are interfering with his ability to paint, thus affecting his livelihood. He is also showing signs of rigidity and bradykinesia but can otherwise live independently. An algorithm for the management of patients with early PD is presented in **Figure 59-1**. The long-term, individualized treatment plan is usually characterized by frequent dosage adjustments because of the chronic and progressive nature of the disease.

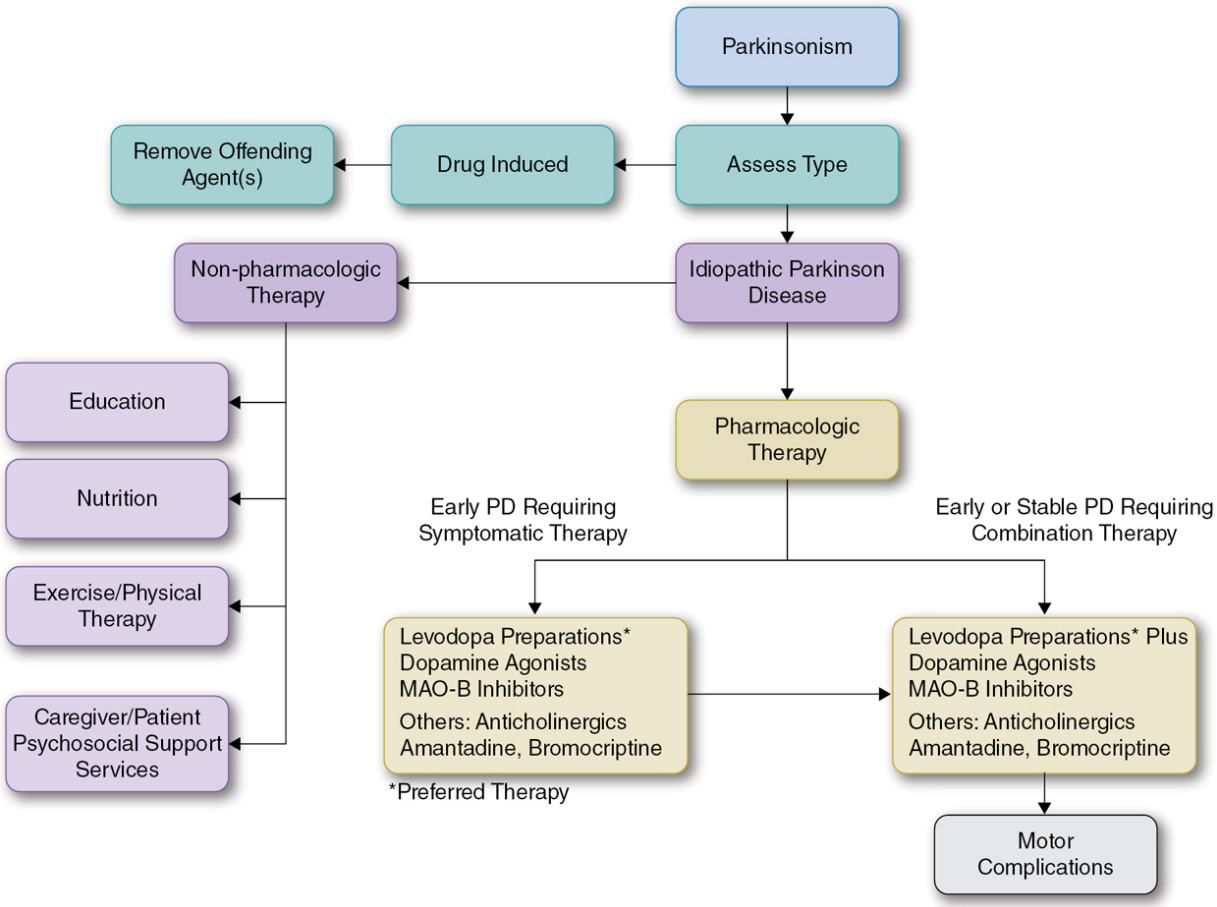


Figure 59-1 Suggested treatment algorithm for the management of early Parkinson disease. MAO, monoamine oxidase; PD, Parkinson disease.

CASE 59-1, QUESTION 4: The decision is made to begin drug therapy for L.M. Should therapy be initiated with a levodopa or levodopa-sparing therapy? What characteristics assist in selecting the initial treatment of choice for L.M.?

Despite advances in pharmacologic treatment options for PD, no therapy has been proven to be disease-modifying or neuroprotective. Therapy continues to be symptomatic, and levodopa remains the most effective antiparkinsonian agent.[20] Based on multiple guidelines, levodopa should be used first line at the lowest effective dose while balancing the long-term risks of motor fluctuations and dyskinesias.[20–22] There are two levodopa-sparing methods that may be used instead of or in combination with levodopa: dopamine agonists (ie, motor PD complications) and MAO-B inhibitors (ie, extend on-time and reduce off-time).[22] Both of these modalities have proven efficacy early in early PD.[20]

Dopamine agonists, which bind directly to dopamine receptors, do not require metabolic conversion to an active product and, therefore, act independently of degenerating dopaminergic neurons. In clinical trials comparing dopamine agonists with levodopa, ADLs and motor features are improved to a greater degree with levodopa compared with dopamine agonists.[21] Although they are not as effective as levodopa, the dopamine agonists have potential advantages. Unlike levodopa, circulating plasma amino acids do not compete with dopamine agonists for absorption and transport into the brain, which eliminate administration constraints. Dopamine agonists have a longer half-life than levodopa formulations, which reduce the need for multiple daily dosing. As a class, dopamine agonists provide adequate control of symptoms when given as monotherapy in up to 80% of patients with early-stage disease.[25]

Short- and long-term comparisons of patients with early disease started on either levodopa or dopamine agonists have varying

results. In trials extending 4 to 5 years, therapy with dopamine agonists is associated with fewer motor complications such as dyskinesias, delayed time to dyskinesias, and delayed need for initiation of dopaminergic therapy.[26–28] As opposed to levodopa as initial therapy, early trials of the dopamine agonists appear to delay the onset of dyskinesias. In a randomized, controlled trial evaluating the development of motor complications with levodopa or the dopamine agonist pramipexole, 301 untreated patients with early PD were randomly assigned to receive either pramipexole 0.5 mg three times daily or carbidopa/levodopa 25/100 mg three times daily.[28] Patients in both arms could be prescribed open-label levodopa as needed for disability during the maintenance phase of the study. After a mean follow-up of 24 months, fewer patients who are treated with pramipexole reached the primary endpoint of time to the first occurrence of wearing-off, dyskinesias, or on–off motor fluctuations (28% vs 51%; $P < .001$) than the patients initially randomly assigned to levodopa therapy. Additionally, patients in the pramipexole group were receiving lower daily doses of levodopa, theoretically conferring a reduced risk of developing motor complications. Long-term follow-up of this cohort (mean = 6 years) revealed a persistently lower rate of dopaminergic motor complications in the pramipexole-treated patients compared with those receiving levodopa (50% vs 68.4%, respectively; $P = .002$).[29]

Despite the continued increased risk of motor complications in patients started on levodopa, trials extending 10 to 15 years found no significant difference in disease severity rating or rates of disabling dyskinesias.[30,31] Patients treated initially with ropinirole were less likely to experience dyskinesias compared with those treated initially with levodopa at the end of a 5-year evaluation.[26] Patients in the ropinirole group used lower mean daily doses of levodopa (427 mg vs 753 mg) but were almost twice as likely to need open-label levodopa supplementation (66% vs 36%). Dyskinesias developed in 20% of the ropinirole-treated patients compared with 45% of the levodopa-treated patients. For ropinirole-treated patients who were able to remain on monotherapy without open-label levodopa supplementation, only 5% experienced

dyskinesia, compared with 36% of those receiving levodopa monotherapy. Although the lower incidence of dyskinesias was shown to persist in a long-term open-label follow-up of this study cohort, there was no difference in disease severity between the ropinirole-treated group and the levodopa-treated group at 10 years.[30] There may be additional trends toward better cognitive and health-related quality of life outcomes in the patients started on levodopa.[31] This result may be due in part to the fact that although dopamine agonists may delay motor complications and are not without side effects, trials have consistently shown higher rates of adverse drug reactions in patients initially started on dopamine agonists.[26,28] One open-label, randomized trial found that 28% of patients discontinued initial therapy with dopamine agonists because of side effects versus only 2% of patients initially given levodopa.[31]

MAO-B inhibitors are an alternative method of enriching dopamine supply in early disease. These agents increase nigrostriatal dopamine supply via the irreversible inhibition of MAO-B, a major enzymatic pathway responsible for the metabolism of dopamine in the brain, require the presence of dopamine for clinical effect.[32] Although MAO-B inhibitors have been shown to delay the need for dopaminergic therapy with levodopa, definitive efficacy comparisons are lacking.[32]

Early guidance from the AAN and EFNS MDS-ES supports either dopamine agonists or levodopa as initial therapy for PD; however, Canadian and NICE, and EFNS MDS-ES guidelines support the use of MAO-B inhibitors in initial therapy, whose motor symptoms affect their quality of life, levodopa should be initiated.[18–22] The long-term effectiveness of dopamine agonists and MAO-B inhibitors compared with levodopa as initial treatment for PD (PD MED) trial set out to compare and contrast levodopa versus levodopa-sparing therapies.[33] Patients assigned to monotherapy with MAO-B inhibitors or dopamine agonists were generally younger and healthier than those assigned levodopa as initial therapy. At 7-year follow-up, 72% of patients initially assigned to MAO-B inhibitors withdrew from initial therapy and changed treatment compared to 50% in the dopamine agonist group and 7% in the levodopa group ($P < .0001$). Among

those patients initiated on MOA-B inhibitors, 23% withdrew because of side effects and 17% withdrew because of lack of efficacy, and for patients initiated on dopamine agonists, 28% withdrew because of side effects and 6% withdrew because of lack of efficacy.[33] As shown in prior studies, levodopa improved function and quality of life to a greater degree; however, the primary mobility outcome did not reach the prespecified minimal difference. Mobility scores were not significantly different between MAO-B inhibitors and dopamine agonists, indicating that MAO-B inhibitors are at least as effective as dopamine agonists in early therapy of PD.[33] Additionally, at 7 years, patients on dopamine agonists were on the highest overall amount of medication. The study confirms that initial treatment with a dopamine agonist, MAO-B inhibitor, or levodopa may all be reasonable approaches.

Disease severity, degree of functional impairment, life expectancy, and age guide therapeutic drug selection in early PD. In milder disease, such as L.M., the initiation of levodopa or a levodopa-sparing therapy (either a dopamine agonist or MAO-B inhibitor) would be appropriate. Although the PD MED trial did conclude that MAO-B inhibitors are at least as effective as dopamine agonists for initial therapy, other meta-analyses show that the degree of symptomatic benefit over placebo is small in comparison with those of dopamine agonists over placebo.[34] Overall, there is a lack of comparative data between MAO-B inhibitors and dopamine agonists. Therefore, use of MAO-B inhibitors in initial therapy is often limited to young patients with more mild functional impairments. With more significant functional impairments or with limited life expectancy, use of levodopa may be warranted as the benefit (ie, symptomatic benefits) outweighs the risk (ie, relatively high risk of motor complications and side effects) compared to levodopa-sparing therapy. Additionally, levodopa may be more appropriate initial treatment in older patients as they may be more likely to experience intolerable CNS side effects from dopamine agonists as well as are less likely to develop motor complications over their lifetime.[23]

In the case of L.M., his relatively young age, mild disease, and moderate functional impairments make him a good candidate for

initial therapy with low-dose levodopa. When more advanced stages of disease are reached, L.M. will require levodopa therapy later. By initiating therapy first with a dopamine agonist, rescue levodopa therapy can likely be started at smaller doses, and the onset of motor complications that often occur with escalating doses as well as extended therapy with levodopa may be delayed.

DOPAMINE AGONISTS

CASE 59-1, QUESTION 5: L.M. is to be initiated on a dopamine agonist for L.M.'s concern that levodopa will worsen his insomnia. He discloses he has had an extensive sleep disorder worked up and gets about 5 hours of sleep each night despite trying melatonin, doxepin, and trazodone without improvement. Additionally, his neurologist feels his insomnia is related to his PD motor symptoms. Which agent should be selected?

Two generations of dopamine agonists have been used for the treatment of idiopathic PD in early-stage PD as monotherapy or as an adjunct to levodopa in patients with advanced disease. The comparative pharmacologic and pharmacokinetic properties of these agents are shown in **Table 59-3**. The first-generation dopamine agonists, which are derived from ergot alkaloids, include bromocriptine, pergolide, and cabergoline. These older agents are now rarely used because of increased risk of retroperitoneal, pleural, and pericardial fibrosis as well as a two- to fourfold increased risk for cardiac valve fibrosis when compared with nonergoline dopamine agonists and controls.[35,36] Pergolide was voluntarily withdrawn in the United States in 2007 for this reason, and although cabergoline continues to be used in Europe, it is only indicated in the United States for the treatment of hyperprolactinemia. Pramipexole, ropinirole, apomorphine, and rotigotine are second-generation nonergoline dopamine agonists. Of these agents, pramipexole and ropinirole are commonly prescribed. Apomorphine is available as an injectable and sublingual film for use as a rescue agent in the treatment of hypomobility "off" episodes in patients with PD.

Rotigotine, a once-daily transdermal formulation, was recently reintroduced into the market.

Table 59-3
Pharmacologic and Pharmacokinetic Properties of Dopamine Agonists

	Bromocriptine	Pramipexole	Ropinirole	Apomorphine	Rotigotine
Type of compound	*Ergot derivative*	*Nonergoline*	*Nonergoline*	*Nonergoline*	*Nonergoline*
Receptor specificity	D_2, D_1,[a] α_1, α_2, 5-HT	D_2, D_3, D_4, α_2	D_2, D_3, D_4	D_1, D_2, D_3, D_4, D_5, α_1, α_2, 5-HT_1, 5-HT_2	D_1, D_2, D_3, 5-HT_1
Bioavailability	7% (extensive first-pass metabolism)	Immediate release (IR): 90%; extended release (ER): 100%	55% (first-pass metabolism)	<5% orally; 100% subcutaneous	<1% (hip and abdomen), 46% (shoulder)
T_{max} (minutes)	70–100	IR: ~120; ER: 100%	IR: 60–120; ER: 6-10 hours	30–60	15–18 (hours); no characteristic peak observed
Protein binding	90%–96%	15%	40%	>99.9%	~90%
Metabolism	Hepatic via CYP3A4	Negligible (<10%)	Hepatic via CYP1A2	Auto-oxidation, glucuronidation, methylation, demethylation, and sulfation	Conjugation, dealkylation, sulfation, glucuronidation, and multiple CYP isoenzymes
Half-life (hours)	2–8	8–12	~6	0.8–3	~5–7
Elimination	Feces (~82%); urine (2%–6%)	Urine (90% unchanged)	Urine (<10% unchanged, 60% metabolites)	Urine	Urine (~71% inactive, <1% unchanged), feces (~23%)

5-HT, serotonin; NA, not applicable.

[a]Antagonist.

Dopamine agonists work by directly stimulating postsynaptic dopamine receptors within the striatum. The two families of dopamine receptors are D_1 and D_2. The D_1-like receptor family includes the D_1 and D_5 dopamine subtype receptors, and the D_2-like receptor family includes D_2, D_3, and D_4 dopamine subtype receptors. Stimulation of D_2 receptors is largely responsible for reducing rigidity and bradykinesia, whereas the precise role of the D_1 receptors remains uncertain.[37] Pramipexole and ropinirole exhibit selectivity for D_2 receptors without any significant affinity for D_1 receptors, whereas rotigotine has activity at all dopamine receptors.[38–40] Although the dopamine agonists differ slightly from each other in terms of their affinities for dopamine receptor subtypes, these agents produce similar clinical effects when used to treat PD, and no compelling

evidence favors one agent over another strictly on efficacy measures. Instead, experience with the nonergoline dopamine agonists, specifically pramipexole and ropinirole, makes them currently preferred as initial dopamine agonists. Thus, either agent would be acceptable as initial therapy in L.M. where drowsiness occurs at roughly the same incidence (ie, pramipexole 36% vs ropinirole 40%).

CASE 59-1, QUESTION 6: The decision is made to begin pramipexole in L.M. How effective is pramipexole compared to ropinirole in the initial treatment of PD?

Pramipexole

Pramipexole has been well studied as monotherapy in patients with early-stage PD and as an adjunct to levodopa therapy in advanced-stage disease.[38–40] These trials were multicenter, placebo-controlled, parallel-group studies, and parts of the Unified Parkinson's Disease Rating Scale (UPDRS) were used as the primary outcome measures, which includes improvement in ADLs (Part II) and motor function scores (Part III). Each evaluation on the UPDRS is rated on a scale of 0 (normal) to 4 (can barely perform). Lower scores on the UPDRS after treatment indicate an improvement in overall performance.

To view the UPDRS and other assessment tools for the symptoms of PD, visit http://www.movementdisorders.org/MDS/Education/Rating-Scales.htm.

The evidence for the efficacy of pramipexole in early PD comes from two large-scale, double-blind, placebo-controlled studies that included a total of 599 patients with early-stage PD (mean disease duration of 2 years).[39,40] In the first study, 264 patients were randomly assigned to receive one of four fixed doses (1.5, 3, 4.5, or 6 mg/day) or placebo.[39] The pramipexole-treated patients had a 20% reduction in their total UPDRS scores compared with baseline values, whereas no significant improvement was observed in the

placebo-treated patients. A trend toward decreased tolerability was noted because the pramipexole dosage was escalated especially in the 6 mg/day group. A second study of 335 patients titrated doses up to the maximal tolerated dose (not to exceed 4.5 mg/day) and then followed patients for a 6-month maintenance phase.[40] The mean pramipexole maintenance dosage was 3.8 mg/day. Those treated with pramipexole experienced significant improvements in both the ADL scores (22%–29%; $P < .0001$) and motor scores (25%–31%; $P < .0001$), whereas there were no significant changes in the placebo group.

Ropinirole

Similar to pramipexole, ropinirole is a synthetic nonergoline dopamine agonist. Although the drug is pharmacologically similar to pramipexole, it has some distinct pharmacokinetic properties (see Table 59-3). Unlike pramipexole, which is primarily eliminated by renal excretion, ropinirole is hepatically metabolized and undergoes significant first-pass hepatic metabolism.[41] Similar to pramipexole, ropinirole is approved for use as monotherapy in early-stage idiopathic PD and as an adjunct to levodopa therapy in patients with advanced-stage disease.

Ropinirole has not been directly compared with pramipexole in randomized, double-blind comparisons, but it appears to have comparable efficacy in indirect comparison. In several randomized, double-blind, multicenter, parallel-group studies, the efficacy and safety of ropinirole versus bromocriptine or levodopa after 6 months of treatment in patients with early PD were compared. Significant improvement was seen in UPDRS motor scores by ~20% to 30% when compared with baseline values for levodopa over ropinirole, but ropinirole was superior to bromocriptine.[42,43]

Rotigotine

Rotigotine is a nonergoline dopamine receptor agonist that is formulated in a transdermal patch delivery system designed for once-a-day application. It was voluntarily withdrawn from the U.S.

market in 2008 because of problems with crystal formation in the patches; however, the patch was reformulated and reapproved by the U.S. Food and Drug Administration (FDA) in April 2012. The original and reformulated patches have demonstrated efficacy as monotherapy in early-stage PD,[44–47] whereas only the original formulation has demonstrated efficacy as adjunctive therapy to levodopa in patients with advanced stages of PD.[48,49] It is, however, used in both situations.

A randomized, controlled trial conducted in Japanese patients with early-stage PD found that the mean improvement in UPDRS Part II and III sum scores was 8.4 in the rotigotine-treated group versus 4.1 in the placebo group (95% CI: –7.0 to –1.7*; P* = .002).[50] The average dose of rotigotine was 12.8 mg/24 hours in this study, which exceeds the highest recommended dose for early PD (6 mg/24 hours). A later 2016 study found similar results for improving motor control and ADLs.[51] Despite clear benefits in improving ADLs and motor function, there is insufficient evidence at this time to support that rotigotine prevents or delays motor fluctuations or dyskinesias.[21]

The transdermal delivery may have several advantages over traditional oral preparations, including possible increase in adherence, ease of use in patients with swallowing difficulty, and a more continuous stimulation of dopamine receptors. In theory, these benefits may translate into improved efficacy. In randomized, controlled trials comparing rotigotine to ropinirole as monotherapy or pramipexole as adjunct therapy, rotigotine has been found to be noninferior when typical clinical doses are used.[47,49]

Dosing

Case 59-1, Question 7: How are pramipexole and ropinirole dosed? What is the appropriate dose of pramipexole for L.M.?

Dopamine agonists should always be initiated at a low dosage and gradually titrated to the maximal effective dose, as tolerated. This approach minimizes adverse effects that may result in nonadherence

or discontinuation of the drug. In clinical trials, the maximal effective doses are variable and correlate with disease severity and tolerability. Studies have found no difference in efficacy or safety measures between immediate and long-acting formulations of dopamine agonists.[52] One fixed-dose study of pramipexole in early PD showed that most patients responded maximally at a dosage of 0.5 mg three times daily, although it has been shown to be effective and well tolerated in doses as high as 4.5 mg/day (divided).[38]

L.M. has normal renal function; therefore, immediate-release (IR) pramipexole should be started at an initial dosage of 0.125 mg three times daily for 5 to 7 days. His dosage may be increased weekly by 0.125 to 0.25 mg/dose as tolerated and up to the maximal effective dose, not to exceed the maximum dose of 4.5 mg/day.[38] Patients with a creatinine clearance of <50 mL/minute should be dosed less frequently than those with normal renal function.[38] Patients with a creatinine clearance of 30 to 50 mL/minute should receive a starting dose of 0.125 mg twice daily up to a maximal dose of 0.75 mg three times daily. Patients with a creatinine clearance of 15 to 30 mL/minute should receive a starting dose of 0.125 mg daily up to a maximal dose of 1.5 mg daily. Pramipexole has not been studied in patients with a creatinine clearance of <15 mL/minute or those receiving hemodialysis. A once-daily extended-release (ER) formulation of pramipexole is also available; patients can be switched overnight from IR pramipexole at the same daily dose. The use of the ER formulation is not recommended for patients with a creatinine clearance <30 mL/minute or for those receiving hemodialysis.

Ropinirole should be initiated at a dosage of 0.25 mg three times daily with gradual titration to clinical response in weekly increments of 0.25 mg/dose over the course of 4 to 6 weeks, not to exceed 24 mg/day.[41] Patients wishing to take the drug less frequently can be switched directly to an ER once-daily formulation, whereby the dose that is selected should most closely match the total daily dose of the IR formulation. No dose adjustments for ropinirole are necessary in patients with renal dysfunction and can be used in doses up to 18 mg/day in patients on hemodialysis.

Transdermal rotigotine is available in several patch strengths (see Table 59-2). For patients with early-stage PD, it is recommended to start rotigotine at 2 mg/24 hours with dose increases of 2 mg/24 hours that are adjusted no sooner than weekly based on clinical response and tolerability.[53] The maximum recommended dose in early PD is 6 mg/24 hours, whereas 8 mg/24 hours is recommended in advanced PD. Clinical trials have often used doses up to 16 mg/24 hours.[49,54] The time to reach steady-state plasma concentrations of rotigotine is ~2 to 3 days after initial patch application.[53] A multinational, open-label study demonstrated that patients with advanced PD taking pramipexole <2 mg/day or ropinirole <9 mg/day can be safely switched directly to rotigotine with no cross-titration.[55] Rotigotine is metabolized via conjugation and *N*-dealkylation, and the inactive conjugates are excreted in the urine. No adjustments are required for patients with hepatic or renal insufficiency.

Adverse effects

Case 59-1, Question 8: What are the adverse effects of pramipexole and ropinirole? How can these be managed?

Because pramipexole, ropinirole, and rotigotine are all approved for use as monotherapy in early-stage disease and as adjunctive therapy in advanced-stage disease, the adverse events of these agents have been evaluated as a function of disease stage. In studies of patients with early-stage disease, the most common side effects were nausea (28%–47%), application site reactions (39%, rotigotine only), dizziness (25%–40%), somnolence (22%–40%), insomnia (17%–19%), constipation (14%), asthenia (14%), hallucinations (9%), and leg edema (5%).[25,38–43,54,56] Administration with food may help to relieve nausea and/or vomiting. With continued use, many patients exhibit tolerance to the gastrointestinal side effects. CNS side effects were the most common reason for discontinuation of these agents with older patients, particularly susceptible to hallucinations and other CNS side effects. The

incidence of orthostatic hypotension was relatively low (1%–9%), and may, in part, reflect the exclusion of patients with underlying cardiovascular disease in several of the studies.

In advanced-stage disease, the most common adverse events of dopamine agonists were orthostatic hypotension (10%–54%), dyskinesias (26%–47%), application site reactions (46%, rotigotine only, dose-related), nausea (25%), insomnia (27%), hallucinations (11%–17%), somnolence (11%), and confusion (10%).[38,41,53,57] The most common reasons for discontinuing these agents are mental disturbances (eg, nightmares, confusion, hallucinations, insomnia), and orthostatic hypotension. Dyskinesias that are experienced when dopamine agonists are used in combination with levodopa in advanced-stage disease may require lowering the dose of levodopa or, in some cases, the dopamine agonist.

Sudden, excessive daytime somnolence, including while driving, has been reported with dopamine agonists and has resulted in accidents.[38,41,53,58] Affected patients did not always report warning signs before falling asleep and believed they were alert immediately before the event. Labeling for these drugs includes a warning that patients should be alerted to the possibility of falling asleep while engaged in daily activities. Patients should be advised to refrain from driving or other potentially dangerous activities until they have gained sufficient experience with the dopamine agonist to determine whether it will hinder their mental and motor performance. Caution should be advised when patients are taking other sedating medications or alcohol in combination with dopamine agonists. If excessive daytime somnolence does occur, patients should be advised to contact their health care practitioner.

Dopamine agonist therapy in patients with PD is associated with 2- to 3.5-fold increased odds of developing an impulse control disorder.[59] The frequency appears similar for both pramipexole and ropinirole, whereas it is less clear with rotigotine. In one study, a prevalence of 6.1% was noted for pathologic gambling in patients with PD compared with 0.25% for age- and sex-matched controls.[60] These cases may represent variations of a behavioral syndrome termed “dopamine dysregulation syndrome.”[61] Other features of the

syndrome have been reported, including punding (carrying out repetitive, purposeless motor acts), hypersexuality, walkabout (having the urge to walk great distances during on-times, often with no purpose or destination and abnormalities in time perception), compulsive buying, binge eating, drug hoarding, and social independence or isolation.[61] The syndrome appears to be more common among younger, male patients with early-onset PD as well as those having novelty-seeking personality traits, depressive symptoms, and current use of alcohol or tobacco.[59,62] Management of impulse control disorders can be challenging because it often requires modification of dopaminergic therapies, which must be carefully balanced with the accompanying risk of worsening motor function. Underlying depression, if present, should be treated and may improve impulse control. Nonpharmacologic measures (such as limiting access to money or the Internet) may be helpful. In some cases, antipsychotic drugs may be considered, but they must also be used carefully to avoid precipitating motor disability.[63]

Lastly, it should be noted that the abrupt discontinuation of dopamine agonists and levodopa may precipitate the development of a withdrawal syndrome similar to neuroleptic malignant syndrome (NMS). This NMS-like syndrome known as parkinsonism hyperreflexia syndrome can lead to symptoms of hyperthermia, muscle rigidity, hyperreflexia, mental status changes, autonomic instability (eg, tachycardia, tachypnea, and blood pressure fluctuations), and laboratory changes.[64] Patients that develop these symptoms should be restarted on therapy and gradually tapered off to reduce withdrawal symptoms. When gone untreated, withdrawal from dopamine agonist therapy may be fatal.[65]

Although L.M. is younger than age 65 years, he may be at increased risk for visual hallucinations and cognitive problems from dopamine agonist therapy. He should be monitored closely for occurrence or exacerbation of these side effects. He should also be evaluated for lightheadedness before initiation of pramipexole and counseled to report dizziness or unsteadiness because this may lead to falls. He should be reassured that if these effects are caused by pramipexole. They should subside with time and that he should not

drive or operate complex machinery until he can assess the effect of the drug on his mental status. L.M. should be counseled about the possibility of excessive and potentially unpredictable, daytime somnolence because pramipexole is introduced. L.M. does not appear to have a problem with excessive alcohol use; however, he and his family should be educated about his increased risk for impulse control disorders and advised to report any new, unusual, or uncharacteristic behaviors or increased use of alcohol.

MONOAMINE OXIDASE-B INHIBITORS

The MAO-B inhibitors are irreversible inhibitors of MAO-B, a major enzymatic pathway responsible for the metabolism of dopamine in the brain, and inhibition increases the amount of striatal dopamine.[66] The discovery that ingestion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes rapid and irreversible parkinsonism, which led to the finding that neurotoxicity associated with MPTP is not directly caused by MPTP itself but rather the oxidized product, L-methyl-4-phenylpyridinium (MPP).[8] The conversion to MPP is a two-step process mediated in part by MAO-B. Inhibition of MAO-B can inhibit the oxidative conversion of dopamine to potentially reactive peroxides. This finding has led investigators to study whether inhibition of this enzyme is neuroprotective.

Selegiline

In animals, pretreatment with selegiline (also referred to as deprenyl) protects against neuronal damage after the administration of MPTP.[32] The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study was designed to test the hypothesis that the combined use of selegiline and an antioxidant (α-tocopherol) early in the course of the disease may slow disease progression.[67] The primary outcome was the length of time that patients could be sustained without levodopa therapy (an indication of disease progression). Early treatment with selegiline 10 mg/day delayed the need to start levodopa therapy by ~9 months compared with patients

given placebo; however, long-term observation showed that the benefits of selegiline were not sustained and diminished with time. In an extension of the study, patients originally assigned to selegiline tended to reach the endpoint of disability after 1 year of observation even more quickly than did those not assigned to receive selegiline.[68] Initial selegiline treatment did not alter the development of levodopa's adverse effects such as dyskinesias and wearing-off and on–off phenomena.

Although selegiline did not prove to be neuroprotective, the finding that MAO-B inhibitors can delay the need for dopaminergic therapy by at least several months is clinically relevant and is supported by several randomized, controlled trials.[69,70] Aside from the DATATOP trial, studies of selegiline are limited by relatively small sample sizes. As a result, a large meta-analysis of MAO-B inhibitors in early PD was conducted.[34] When analyzed for selegiline, the levodopa dose necessary to control symptoms was 67 mg (14–119 mg; P = .01) lower in the selegiline arm. This analysis found that the total, motor, and ADL scores of the UPDRS were significantly improved in the selegiline arm at 3 months. A subsequent Cochrane Review found that the selegiline-treated arms scored 3.79 points better (95% CI: 2.21, 5.3) when looking at the weighted mean difference in motor UPDRS score.[32] Although oral selegiline continues to be FDA-approved only as an adjunct treatment to carbidopa/levodopa, the evidence suggests efficacy in monotherapy and is used as monotherapy in practice.

Rasagiline

Rasagiline is a second-generation, irreversible selective inhibitor of MAO-B that is FDA-approved as both monotherapy and adjunct therapy in PD. Rasagiline is otherwise differentiated from selegiline primarily in that it is a more potent inhibitor of MAO-B and does not carry the same potential for adverse effects resulting from metabolites.[71] Like selegiline, rasagiline has also been found to protect from MPTP-induced parkinsonism in animal models.[32]

Rasagiline was studied as monotherapy in early PD in a randomized, double-blind, placebo-controlled trial comparing rasagiline 1 or 2 mg daily with placebo (N = 404).[72] After 6 months of therapy, the mean adjusted change in UPDRS scores compared with placebo was improved in both the 1- and 2-mg groups (P < .001).[72] These changes are quantitatively similar to those observed with levodopa therapy. This study used a delayed-start design, wherein at the end of the initial 6 months of treatment, patients who received placebo were then switched over to receive active treatment with rasagiline. For the rasagiline-treated patients, they continued on therapy. After an additional 6 months of study, it was found that patients receiving rasagiline for all 12 months had less functional decline than patients in whom rasagiline was delayed.[73] The mean adjusted difference in total UPDRS scores at 12 months for patients receiving rasagiline 2 mg/day for all 12 months was −2.29 compared with the delayed-start rasagiline 2-mg group (P = .01). As a result, rasagiline was FDA-approved for use as monotherapy in early PD. These encouraging findings also suggested that neuroprotection might be afforded by rasagiline and prompted a larger, more definitive study.

The Attenuation of Disease Progression with Azilect given once-daily (ADIAGO) study was also a randomized, placebo-controlled trial using the delayed-start methodology but with a much larger sample size (N = 1176).[74] Patients were randomly assigned to receive rasagiline or placebo for 36 weeks, at which time rasagiline-treated subjects continued therapy, and the placebo group was switched to rasagiline. All these patients were then followed for an additional 36 weeks. To prove disease modification attributable to rasagiline with either dose, the early-start treatment group had to meet each of three hierarchic endpoints, which was based on the magnitude and rate of change of UPDRS scores during different periods of the study. At the end of the study, rasagiline failed to meet all of the prespecified endpoints, and the authors were unable to confirm any disease-modifying effects.[74]

There are no head-to-head randomized controlled trials comparing rasagiline versus selegiline. Multiple meta-analysis and smaller

studies have compared both medications, but little difference between motor symptom control and time to levodopa therapy were seen.[75–77] Existing data were compared in an industry-sponsored, indirect meta-analysis, which found a significant advantage for rasagiline monotherapy on UPDRS scores.[78] Additionally, risk for discontinuation and adverse events favored rasagiline. Rasagiline is primarily metabolized via cytochrome P450 (CYP) 1A2 and *N*-dealkylation, whereas selegiline is metabolized via CYP2B6, CYP2C9, and CYP3A4/5 to amphetamine-like metabolites (L-methamphetamine and L-amphetamine). As a result of their MAO-B inhibition, similar precautions regarding drug interactions exist. Caution should be taken when using MAO-B inhibitors with proserotonergic agents such as antidepressants, triptans, and linezolid because of the risk of serotonin syndrome. Although tyramine-challenge studies have not demonstrated any clinically significant reactions with these MAO-B inhibitors, the product labeling still contains a warning that patients should be advised to restrict tyramine intake.[79,80]

Dosing

Selegiline is available in a 5-mg capsule or tablet and as a 1.25-mg orally disintegrating tablet. It is also available in a transdermal patch, but this formulation is not approved for use in PD (approved for the treatment of major depressive disorder). The bioavailability of conventional selegiline is low, and it undergoes extensive hepatic first-pass metabolism into amphetamine-based metabolites, which may contribute to neurologic side effects.[66] The usual dosage of conventional selegiline is 10 mg/day administered as 5 mg in the morning and early afternoon. It is not given in the evening because excess stimulation from metabolites (L-methamphetamine and L-amphetamine) can cause insomnia and other psychiatric side effects.[81] The orally disintegrating tablet formulation dissolves in the mouth in contact with saliva and undergoes pregastric absorption. This formulation minimizes the effect of first-pass metabolism in comparison with conventional selegiline, which results in higher

plasma concentrations and reductions in the amphetamine-based metabolites.[66] Selegiline should be used with caution in patients with severe hepatic impairment or with creatinine clearance <30 mL/minute.

Rasagiline is available in 0.5- and 1-mg tablets. When used as monotherapy, it is initiated at 1 mg daily. When combined with levodopa, the initial dose is lowered to 0.5 mg daily and can be increased to 1 mg daily based on response. In patients with mild hepatic impairment, the dose should be reduced to 0.5 mg daily, but use should be avoided in those with moderate-to-severe hepatic impairment. Additionally, because rasagiline lacks the amphetamine-like metabolites of selegiline, it also lacks the time-specific dosing constraints.

Adverse effects

The most common adverse effects of both agents include nausea (6%–20%), dizziness (11%–14%), headache (4%–14%), and dry mouth (4%–6%).[66,80,81] CNS effects such as hallucinations, vivid dreams, and confusion also occur but at a lower rate as compared with dopamine agonists. Although the oral disintegrating tablet reduces the amphetamine-based metabolites, there are higher rates of reported side effects likely as a result of the higher plasma concentration of selegiline.[66] A large meta-analysis of MAO-B inhibitors in early PD found a higher incidence of reported side effects among the MAO-B inhibitor (all but one study used selegiline) versus non-MAO-B inhibitor groups (OR: 1.36, 1.02–1.8, P = .04).[34] However, these agents are generally considered well tolerated.[80]

LEVODOPA

Case 59-1, Question 9: L.M. initially responded well to pramipexole 1 mg three times daily for 18 months with increased ability to paint and carry out ADLs. During the past few weeks, he has noticed a gradual worsening in motor symptoms without improvement in insomnia and once again is having difficulty holding a paintbrush, getting out of a chair, and his posture is slightly more stooped. He also notes feeling tired throughout much of the day. The

neurologist wants to start levodopa at this time for his PD symptoms. What should be considered before starting levodopa?

Dopamine itself does not cross the blood–brain barrier. Levodopa, a dopamine precursor with no known pharmacologic action of its own, crosses the blood–brain barrier, where it is converted by the enzyme aromatic amino acid (dopa) decarboxylase to dopamine. Levodopa has been a mainstay of PD treatment since the 1960s. Nearly all patients will eventually require treatment with the drug regardless of their initial therapy.

Because significant amounts of levodopa are peripherally (extracerebrally) metabolized to dopamine by dopa decarboxylase, extremely high doses are necessary if administered alone. For this reason, levodopa is always coadministered with a dopa decarboxylase inhibitor. This allows the dose of levodopa to be decreased by 75%.[82] By combining levodopa with a dopa decarboxylase inhibitor that does not penetrate the blood–brain barrier, a decrease in the peripheral conversion of levodopa to dopamine can be achieved, whereas the desired conversion within the striatum remains unaffected. This combination also shortens the time needed to achieve optimal effects by several weeks because the dopa decarboxylase inhibitor substantially decreases dose-limiting levodopa-induced nausea and vomiting. The two peripheral decarboxylase inhibitors in clinical use are benserazide (unavailable in the United States) and carbidopa. A fixed combination of carbidopa and levodopa is available in ratios of 1:4 (carbidopa/levodopa 25/100) and 1:10 (carbidopa/levodopa 10/100 and 25/250). Carbidopa/levodopa is also available as an IR, orally disintegrating tablet, and ER capsule, which both may be used in early PD. In addition, controlled-release (CR), ER, and intestinal gel formulations are available and are discussed for management of motor complications.

In the case of L.M., he is now experiencing bothersome symptoms despite near-maximal dopamine agonist therapy without improvement in sleep besides. Moreover, his bothersome symptoms have progressed sufficiently to threaten his livelihood. Although the

dose of pramipexole could be increased, he may experience more daytime somnolence; thus, levodopa should be added to his regimen.

Dosing

Case 59-1, Question 10: The decision is made to begin L.M. on carbidopa/levodopa. How should it be dosed?

About 70 to 100 mg/day of carbidopa is necessary to saturate peripheral dopa decarboxylase.[82] It is usually unnecessary and more costly to administer carbidopa in higher amounts. Therapy should be initiated with IR carbidopa/levodopa 25 mg/100 mg three times a day. The IR formulation is preferred because it allows for much easier dose adjustment. In the case of L.M., the dose can then be increased by 100 mg of levodopa every day or every other day up to eight tablets (800 mg), up to the maximal effective dose, to individual requirements, or as tolerated.

Troublesome peak-dose dyskinesias may occur because of high levels of dopaminergic drug activity. If these occur, the dose or frequency may be adjusted while giving consideration to balancing the most useful dose (eg, maximizing the patient's on-time) with that which does not produce unacceptable side effects (eg, troublesome dyskinesias). Because L.M. is currently being treated with a dopamine agonist, he must be monitored closely for the development of motor complications with the addition of levodopa.

Most patients with early PD will begin therapy on levodopa 300 mg/day and will demonstrate response before reaching 1000 mg/day.[14,82] When levodopa doses exceed 750 mg/day, patients such as L.M. can be switched from the 1:4 ratio of carbidopa/levodopa to the 1:10 ratio to prevent providing excessive amounts of decarboxylase inhibitor. For example, if L.M. needed 800 mg/day of levodopa, two carbidopa/levodopa 10/100 tablets four times daily could be administered. If L.M. had not been initially treated with a dopamine agonist, some clinicians would consider

adding a dopamine agonist after the daily levodopa dose has been increased to >600 mg because dopamine agonists directly stimulate dopamine receptors, have longer half-lives, and result in a lower incidence of dyskinesias, which provides a smoother dopaminergic response.

Clinical response to levodopa therapy may be altered by modifying dietary amino acid ingestion.[82] Levodopa is actively transported across the blood–brain barrier by a large neutral amino acid transport system. This transport system also facilitates the blood-to-brain transport of amino acids such as L-leucine, L-isoleucine, L-valine, and L-phenylalanine. Levodopa and these neutral amino acids compete for transport mechanisms, and high plasma concentrations of these amino acids can decrease brain concentrations of levodopa.[83] Patients should be instructed to take IR carbidopa/levodopa 30 minutes before or 60 minutes after meals for optimal efficacy. If nausea develops and administration with food is considered, a low-protein meal should be encouraged.

Adverse effects

Case 59-1, Question 11: Since initiating carbidopa/levodopa, L.M. reports feeling restless and agitated at times, but these symptoms do not impact his sleep. He further discloses that his sleep has seemingly improved to about 7 hours per night. Could levodopa be contributing to these problems? If so, how should this be managed?

Although levodopa is the most effective agent for PD, it is associated with many undesirable side effects such as nausea, vomiting, and anorexia (50% of patients); postural hypotension (30% of patients); and cardiac arrhythmias (10% of patients).[14] In addition, mental disturbances are encountered in 15% of patients, and abnormal involuntary movements (dyskinesias) can be seen in up to 55% of patients during the first 6 months of levodopa treatment.[83]

Although more commonly encountered with dopamine agonists, psychiatric side effects are also associated with levodopa therapy

and include confusion, depression, psychosis, hypomania, vivid dreams, and insomnia (1%–9% of patients).[82] Those with underlying or preexisting psychiatric disorders and those receiving high doses of levodopa for prolonged periods are at the greatest risk.[84] Concurrent anticholinergics or amantadine therapy can exacerbate these symptoms. Advancement of the PD itself correlates with cognitive decline and greater frequency of CNS findings, possibly mediated through an underlying Lewy body pathology.[20] In some situations, it may be difficult to separate the respective drug from disease effects.

Some patients receiving levodopa experience psychomotor excitation (eg, overactivity, restlessness, agitation). Similarly, hypomania has been reported in up to 8% of patients and is characterized by grandiose thinking, flight of ideas, tangential thinking, and poor social judgment. Normal sexual activity often is restored with improved motor function; however, hypersexuality and libido are increased in about 1% of levodopa-treated patients.[85]

In general, most of the mental disturbances are dose-related and can be lessened by reducing the dose of the dopaminergic agent. In patients such as L.M. who are concurrently receiving levodopa and a dopamine agonist, the dose reduction should be attempted first with the dopamine agonist. If symptoms do not improve, a reduction in the dose of levodopa may also be warranted. These dose reductions may, however, be impractical for L.M. because a return of parkinsonian symptoms is likely, and the benefits of levodopa therapy may outweigh the risk for mental disturbances.

ANTICHOLINERGICS

Case 59-1, Question 12: What role do anticholinergic drugs play in the treatment of PD? Should L.M. receive an anticholinergic agent?

Anticholinergic drugs have been used to treat PD since the mid-1800s, when it was discovered that symptoms were reduced by the belladonna derivative hyoscine (scopolamine).[20] Currently, they are

used to specifically target tremor. Although tremor may improve with dopaminergic drugs via the restoration of balance between dopamine and acetylcholine, resolution of tremor may be incomplete. Anticholinergic drugs such as benztropine and trihexyphenidyl work by blocking the excitatory neurotransmitter acetylcholine in the striatum, which minimizes the effect of the relative increase in cholinergic sensitivity. Until the late 1960s, when amantadine and levodopa were introduced, anticholinergics were a mainstay of treatment; however, because of their undesirable side effect profile and poor efficacy relative to levodopa in treating bradykinesia and rigidity, anticholinergic agents are no longer used as first-line agents. These drugs produce both peripherally and centrally mediated adverse effects. Peripheral effects, such as dry mouth, blurred vision, constipation, and urinary retention, are common and bothersome.[24] Anticholinergic agents can increase intraocular pressure and should be avoided in patients with angle-closure glaucoma. CNS effects can include confusion, impairment of recent memory, hallucinations, and delusions.[20,24] Patients with PD are often more susceptible to these central effects because of advanced age, intercurrent illnesses, and impaired cognition.[24] Anticholinergics are usually reserved for the treatment of resting tremor early in the disease, particularly in younger patients with preserved cognitive function. Given his history and clinical presentation and based on the absence of tremor, L.M. would not be an appropriate candidate for an anticholinergic drug.

Treatment through the Progression of Parkinson Disease

LEVODOPA AND ADJUNCTIVE THERAPY

The chronic, progressive nature of PD predicts that patients will develop worsening of motor control through the later stages of the disease; thus, enhanced motor control through the use of levodopa, in conjunction with symptomatic adjunctive agents, will be necessary. Agent selection is guided by efficacy for motor symptom control,

adverse effects, and motor complication risk. Agents indicated by the AAN,[19] EFNS/MDS-ES,[21] NICE,[20] and Canadian[22] guidelines for symptomatic adjunct therapy and management of motor complications in late PD are outlined in **Figure 59-2**.

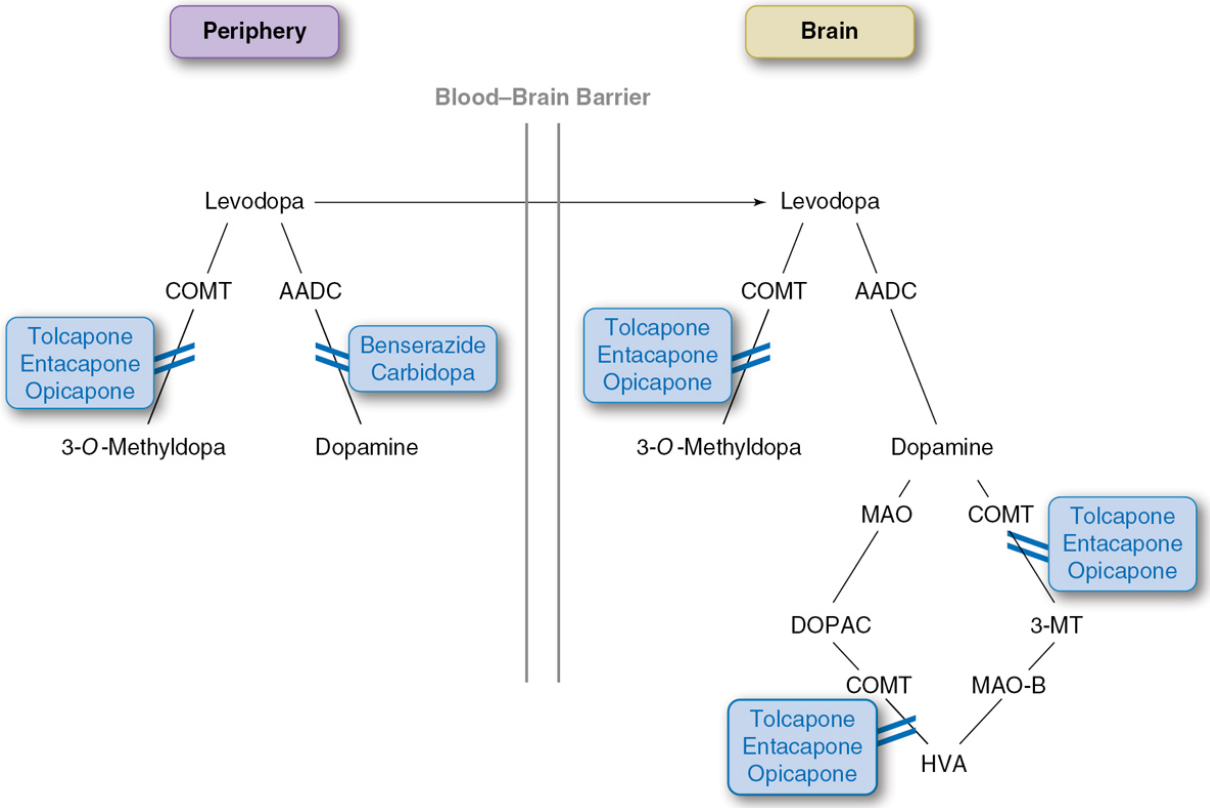


Figure 59-2 Levodopa metabolism in the human body. AADC, aromatic amino acid decarboxylase; COMT, catechol-*O*-methyltransferase; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; MAO, monoamine oxidase; 3-MT, 3-methoxytyramine.

MOTOR COMPLICATIONS

CASE 59-1, QUESTION 13: After 3 years of levodopa therapy, L.M. began to experience immobility in the mornings. Nearly every day, he has periods in which he cannot move followed by a sudden switch to a fluid-like state, which is often associated with dyskinetic activity. He continues to take carbidopa/levodopa three times daily but gains symptomatic relief for only 3 to 4 hours after a dose. Also, the response to a given dose varies and is often less

in the afternoon. At times, he becomes “frozen,” particularly when he needs to board an elevator or is required to move quickly. What are possible explanations for these alterations in clinical response?

Although variable, the initial levodopa response period may last up to 5 years. After this initial period of stability, 50% to 90% of patients receiving levodopa for 5 or more years will eventually experience motor complications.[86] Motor complications may present as periods of too much (dyskinetic) dopaminergic activity, too little (akinetic) dopaminergic activity, or in combination.

In evaluating these motor fluctuations, it is important to ascertain which effects are attributable to the disease and which are attributable to the drug. For example, levodopa-induced peak-dose dyskinesias often appear concurrently with the development of motor fluctuations.[86,87] Peak-dose dyskinesias consisting of choreiform with brief, irregular, and jerky movements are the most common form of dyskinesias that occur with chronic levodopa (and sometimes dopamine agonist) therapy. These symptoms frequently subside at the end of the dosing interval because levodopa levels fall. Their severity is related to levodopa dose, disease duration and stage, and younger age at onset.[87] If peak-dose dyskinesias occur, the following strategies should be considered: levodopa dose can be lowered, but given more frequently; consideration can be given to switching patients to IR tablets if taking modified-release formulations of carbidopa/levodopa (for ease in refining dose adjustments); agents that prolong the half-life of levodopa, but do not provide stable levodopa plasma concentrations (eg, COMT inhibitor, MAO-B inhibitor) can be added, or an antidyskinetic agent such as amantadine can be used. Variations in the rate and extent of levodopa absorption, dietary substrates (eg, large neutral amino acids) that compete with cerebral transport mechanisms, levodopa drug–drug interactions (**Table 59-4**), and competition for receptor binding by levodopa metabolites can further explain the variable responses observed to levodopa.

Table 59-4
Levodopa Drug Interactions

Drug	Interaction	Mechanism	Comments
Anticholinergics	↓ Levodopa effect	↓ Gastric emptying, thus ↑ degradation of levodopa in gut, and ↓ amount absorbed	Watch for ↓ levodopa effect when anticholinergics cause ↓ GI motility. When anticholinergic therapy is discontinued in a patient on levodopa, watch for signs of levodopa toxicity. Theoretic interaction with minor clinical significance
Ferrous sulfate	↓ Levodopa oral absorption by 50%	Formation of chelation complex	Avoid concomitant administration or separate administration by at least 2 hours.
Food	↓ Levodopa effect	Large, neutral amino acids compete with levodopa for intestinal absorption	Although levodopa is usually taken with meals to slow absorption and ↓ central emetic effect, high-protein diets should be avoided.
MAOI (eg, phenelzine, tranylcypromine)	Hypertensive crisis	Peripheral dopamine and norepinephrine	Avoid combination use; monoamine oxidase type B (MAO-B) inhibitors such as selegiline can be used, but the dose of levodopa should be reduced after 2–3 days of therapy; carbidopa might minimize hypertensive reaction to levodopa in patients receiving an MAOI.
Methyldopa	↑ or ↓ levodopa effect	Acts as central and peripheral decarboxylase inhibitor	Observe for response; may need to switch to another antihypertensive.
Metoclopramide	↓ Levodopa effect	Central dopamine blockade	Avoid combination use.
Neuroleptics (eg, butyrophenones, phenothiazines)	↓ Levodopa effect	Central blockade of dopamine neurotransmission	Avoid combination use; important interaction.
Phenytoin	↓ Levodopa effect	Mechanism unknown	Avoid combination use.
Pyridoxine (vitamin B_6)	↓ Levodopa effect	Peripheral decarboxylation of levodopa	Not observed when levodopa given with carbidopa; avoid levodopa monotherapy with vitamin B_6 supplementation.
Tricyclic antidepressants	↓ Levodopa effect	Levodopa degradation in gut because of delayed emptying	Use with caution.

GI, gastrointestinal; MAOI, monoamine oxidase inhibitor.

Two of the more common motor complications are the wearing-off effect and the on–off effect. The wearing-off effect is most predictable, which occurs in the latter part of the dosing interval after a period of relief. Because levodopa is a short-acting agent with an elimination half-life of about 1.5 hours, much of the effect from the evening dose will dissipate by morning.[82,86] For this reason, it is not surprising that L.M. is experiencing a period of immobility on arising. This symptom is alleviated in most patients shortly after taking the morning dose. Wearing-off can be improved by various means such as shortening the dosing interval or with the addition of adjunctive therapy (if not already present) with a dopamine agonist, MAO-B inhibitor, or levodopa extender such as a COMT inhibitor. The on–off effect is described as random fluctuations from mobility (often associated with dyskinesias) to the parkinsonian state, which

appears suddenly as if a switch has been turned on or off. These fluctuations can last from minutes to hours and increase in frequency and intensity with time. Despite accompanying dyskinesias, most patients prefer to be in an on rather than an off (or akinetic) state; however, for some patients, dyskinesias can be more disabling than parkinsonism.

Early in the course of disease, it is usually possible to control parkinsonian symptoms without inducing dyskinesias via medication adjustments; however, because the disease advances and the therapeutic window narrows, cycling between on-periods complicated by dyskinesia and off-periods with resulting immobility is common.[86,87] Eventually, despite adjustments in levodopa dose, many patients with advanced PD experience either mobility with severe dyskinesias or complete immobility. In most patients, this effect has no clear relationship to the timing of the dose or levodopa serum levels.[86]

The pathophysiologic basis for motor complications and dyskinesias is not entirely clear, but incomplete delivery of dopamine to central receptors is likely responsible.[86] Because the disease progresses and dopamine terminals are lost, the capacity to store dopamine presynaptically is diminished, whereby the ability to maintain relatively constant striatal dopamine concentrations is impaired.[86] As a consequence, dopamine receptors are subject to intermittent and pulsatile stimulation rather than a more physiologic tonic stimulation. Overactivity of excitatory pathways mediated by neurotransmitters such as glutamate may also be involved.[86]

CASE 59-1, QUESTION 14: What options are available to reduce the motor fluctuations experienced by L.M.?

MODIFIED-RELEASE CARBIDOPA/LEVODOPA FORMULATIONS

A more sustained delivery of levodopa than that achieved with routine oral dosing may theoretically reduce motor complications by more effectively replicating normal physiology. Three products designed to prolong carbidopa/levodopa delivery include a CR tablet,

an ER capsule, and an enteral suspension administered as a gastrointestinal infusion. The use of the enteral suspension for gastrointestinal infusion has shown reductions in off-time of 1.91 hours (P = .0018) and an increase in on-time of 1.86 hours (P = .0059) in a 12-week study of patients with severe motor fluctuations and hyper/dyskinesias.[88] As a result of its pump administration via a permanent duodenal/upper jejunal tube, this method is typically reserved as last-line therapy for use in specialized centers.

Controlled-release carbidopa/levodopa

A CR tablet formulation of carbidopa/levodopa is available, which contains 25-mg carbidopa and 100-mg levodopa or 50-mg carbidopa and 200-mg levodopa in an erodible polymer matrix that retards gastric dissolution. Although off-time should theoretically be reduced by the slower rate of plasma levodopa decline, clinical study has generally not found a sustained difference in off-time or a reduction in dyskinesias with the CR preparation compared with the IR preparation.[20,21] As a result, switching to CR carbidopa/levodopa as a primary strategy to reduce off-time or lessen dyskinesias is not recommended.[20]

A likely reason for the lack of superior effect with CR carbidopa/levodopa as compared with the IR formulation is its variable absorption. CR carbidopa/levodopa is about 30% less bioavailable than the IR formulation. Patients converted from standard carbidopa/levodopa to the CR formulation should receive a dose that will provide 10% more levodopa, and then the dose should be titrated upward to clinical response.[89] Interestingly, administration with food enhances levodopa's peak by 25%. Given that there is no obvious advantage to CR carbidopa/levodopa, L.M. should not be switched to this formulation.

Extended-release carbidopa/levodopa

The ER capsule formulation of carbidopa/levodopa contains a combination of both immediate- and ER beads designed to circumvent the pharmacokinetic concerns seen with the CR tablet

formulation. Although both formulations persist for up to 6 hours, the ER capsule provides a faster time to symptom relief, with a peak that is comparable to the IR formulation (1 hour vs up to 2 hours for CR).[90] Similar to CR, the ER formulation reduces levodopa bioavailability by ~50%.[91] As such, the manufacturer provides specific dose conversions from IR preparations. Converse to the CR preparation, high-fat and high-calorie food reduces levodopa peak and may delay absorption by 2 to 3 hours, and it is recommended that the first dose of the day be given 1 to 2 hours prior to eating. In patients with difficulty swallowing, these capsules may be opened and sprinkled on applesauce, which is an additional advantage to the CR formulation.

The ability of the ER formulation to reduce off-time was evaluated in a placebo-controlled study randomizing 393 patients to immediate or ER formulations over 22 weeks.[92] After being titrated to a stable dose during weeks 1 to 9, patients were followed for an additional 13 weeks. Compared to baseline evaluations, ER patients had a reduction in off-time by ~1 hour/day ($P < .0001$) when compared to the IR formulation. This effect was accompanied by an increase in on-time without troubling dyskinesia of ~1 hour ($P = .0002$). Notably, of patients converted per manufacturer direction, 60% of patients required a further dosage increase and 13% required a dosage decrease.[92]

Based upon this evidence, the ER formulation may improve off-time for L.M. but is unlikely to impact his dyskinesias. Therefore, it may not be appropriate to switch therapy. Taking his IR carbidopa/levodopa more frequently while avoiding substantial increases in the total daily dose, which could worsen his dyskinesias, may improve his condition. Taking his morning dose before arising from bed may help with his early-morning problems. If the symptoms that L.M. is experiencing are not improved with these changes, a number of adjunctive agents such as dopamine agonists, apomorphine rescue, amantadine, COMT inhibitors, and MAO-B inhibitors can be considered.

Inhaled levodopa

The inhaled version of levodopa (Inbrija®) was FDA-approved in 2018 for use as an on-demand rescue therapy during wearing-off periods of carbidopa/levodopa therapy.[93] Patients can introduce an additional 42 to 84 mg of levodopa up to five times daily with a maximum dose of 420 mg/day. In a randomized study, inhaled levodopa improved symptoms with a mean difference of 3.9 points on the UPDRS scale versus placebo at 30 minutes as well as leading to more patients having and maintaining an "on" response at 60 minutes (57% vs 36%).[94] Compared to apomorphine for rescue therapy, inhaled levodopa has a significantly smaller magnitude of difference in UPDRS and longer time to onset around 30 minutes. This finding may be concerning where the effects may not translate into a clinically meaningful response for some patients. In studies, a patient's time in the "off" state was not reduced in the levodopa group, which may also indicate that therapy is not adequate. Common side effects with inhaled levodopa compared with placebo in trials included cough (15% vs 2%), upper respiratory tract infection, nausea, and discolored sputum. The rate of dyskinesia was low.

DOPAMINE AGONISTS

The effectiveness of pramipexole added to levodopa therapy in advanced PD was evaluated in a multicenter, placebo-controlled study of 360 patients with a mean disease duration of 9 years.[95] Pramipexole was titrated gradually to the maximal effective dose as tolerated. At the end of a 6-month maintenance period, patients treated with pramipexole had a 22% improvement in their ADLs ($P < .0001$) and a 25% improvement in their motor scores ($P < .01$) compared with baseline values. Patients treated with pramipexole also had a 31% improvement in the mean off-time compared with a 7% improvement in the placebo-treated group ($P < .0006$). Dyskinesias and hallucinations were more common in pramipexole-treated patients and necessitated levodopa dose reduction in 76% of patients compared with 54% in the placebo group. The total daily

levodopa dose was decreased by 27% in those treated with pramipexole compared with 5% in the placebo group.

Ropinirole has been found to improve motor scores when added to levodopa therapy in patients with advanced-stage disease.[52] In a multicenter, double-blind, randomized parallel-group study, patients treated with ropinirole achieved a greater reduction in the percentage of time spent off during waking hours when compared to placebo (11.7% vs 5.1%), which was a difference of 0.4 hours. A greater number of ropinirole-treated patients achieved a significant 20% reduction in time spent off (35% vs 13%, $P = .003$). In those treated with levodopa, the levodopa dose was decreased by an average of 19%.

Long-acting dopamine agonist formulations, including ER ropinirole and rotigotine, have also shown reductions in off-time. In a study of 208 patients with PD not optimally controlled with levodopa after up to 3 years of therapy with <600 mg/day of levodopa, a prolonged-release, once-daily formulation of ropinirole was found to improve motor scores in a similar fashion to increase the levodopa dose; however, only 3% of ropinirole-treated subjects experienced dyskinesias compared with 17% of levodopa-treated patients ($P < .001$).[96] In moderate-to-advanced PD, treatment benefits were observed within 2 weeks of initiation.[97] ER ropinirole has been found to reduce off-time more than the IR preparation in advanced PD. A randomized, double-blind trial of 343 patients over 24 weeks found that compared to the IR formulation, significantly more patients given the ER formulation maintained at least a 20% reduction in off-time (adjusted OR: 1.82, 1.16–2.86, $P = .009$).[98] These results are confounded by the relatively higher doses of ER ropinirole and greater reductions in levodopa achieved by the ER formulation. Rotigotine has also been evaluated for reduction in off-time in patients with advanced PD and has been shown to significantly reduce off-time by ~2.5 hours, with benefits seen as early as the first week of therapy.[53]

Because L.M. has advanced disease and is experiencing motor fluctuations despite a treatment regimen that includes a dopamine agonist whereby further dose adjustments of the dopamine agonist

may provide little additional benefit. Any adjustments must be made with consideration of worsening his dyskinesias and the possibility of exacerbating CNS adverse effects.

Apomorphine

Apomorphine is a dopamine agonist that is approved as rescue therapy for the treatment of hypomobility or "off" episodes in patients with PD. In a randomized, double-blind, parallel-group study of 29 patients, rescue treatment with injectable apomorphine resulted in a 34% reduction in off-time, ~2 hours, compared with 0% in the placebo group (P = .02).[99] Mean UPDRS motor scores were reduced by 23.9 points (62%) in those treated with apomorphine when compared with 0.1 (1%) in those receiving placebo (P < .001). Adverse events in the apomorphine group included yawning (40%), dyskinesias (35%), drowsiness or somnolence (35%), nausea or vomiting (30%), and dizziness (20%), although only yawning was statistically different from placebo (40% vs 0%; P = .03). Additionally, a randomized, double-blind, placebo-controlled, parallel-group study compared the mean change from predose to 30 minutes postdose in the MDS-UPDRS III at 12 weeks during the maintenance phase with sublingual apomorphine for acute, intermittent treatment of "off" episodes. Apomorphine showed a least-square mean improvement of −11.1 points (95% CI: −14.0, −8.2), versus −3.5 points for the placebo group (95% CI: −6.1, −0.9). Adverse events were similar to those seen in previous studies of apomorphine except for an increase in oropharyngeal-related events reported in 31% of patients taking the sublingual formulation.[100]

Because nausea and vomiting frequently occur with both sublingual and injectable apomorphine treatment, it should be administered with an antiemetic such as trimethobenzamide. The antiemetic should be started 3 days before initiating apomorphine and continued for the first 2 months of treatment.[99,101] Apomorphine should not be used with ondansetron and other serotonin antagonists used to treat nausea because the combination may cause severe hypotension. In addition, other antiemetics, such as

prochlorperazine and metoclopramide, should not be given concurrently because these dopamine antagonists may decrease the effectiveness of apomorphine.

Doses of sublingual apomorphine range from 10 to 30 mg as needed for intermittent treatment of “off” episodes with a maximum of five doses in one day. Doses of injectable apomorphine range from 2 to 6 mg per subcutaneous injection.[99] A 2-mg test dose is recommended prior to injectable apomorphine while monitoring blood pressure. If tolerated, the recommendation is to start with a dose of 2 mg and increase the dose by 1 mg every few days if needed. Peak plasma levels are observed within 10 to 60 minutes after dosing, so the onset of therapeutic effect is rapid. The test dose and titration are time-consuming and must be done under physician supervision, and patients may require someone else to inject the drug once hypomobility has occurred. In severe cases, subcutaneous infusions have been used, but are limited to research settings and high-level clinical centers. For these reasons, apomorphine is not widely used. Given that L.M. is experiencing motor fluctuations almost daily, long-term frequent apomorphine use would not be a viable solution in his situation.

AMANTADINE

The antiviral agent, amantadine, was serendipitously found to improve PD symptoms when a patient given the drug for influenza experienced a remission in her parkinsonism.[101] Amantadine reduces all the symptoms of parkinsonian disability in about 50% of patients usually within days after starting therapy; however, early trials indicated that amantadine efficacy might be limited by the development of tachyphylaxis within 1 to 3 months.[102] Although the trials suggested reductions in dyskinesias by up to 40%, previous evaluations of amantadine for the reduction of dyskinesias have been limited by methodological concerns.

The pathophysiologic basis for the efficacy of amantadine in PD is not entirely understood. It may augment dopamine release and possibly inhibit its reuptake.[103] Anticholinergic action has also been

suggested. Excess glutamatergic activity has been implicated in the pathophysiology of dopaminergic dyskinesias. Amantadine has been found to be an antagonist at *N*-methyl-D-aspartate (NMDA) receptors and to block glutamate transmission[100] and has consistently shown ~50% reductions in dyskinesia severity and duration without adversely impacting motor performance.[104–117] Two trials have evaluated long-term efficacy of amantadine in patients with levodopa-induced dyskinesia after treatment for 6 months to 1 year. These trials assessed for change in UPDRS motor examination and motor complication subscores with amantadine washout over 3 weeks to 3 months. Those discontinuing amantadine had deterioration in levodopa-induced dyskinesia compared to the continuing group within a median time of 7 days suggesting the possibility of continued benefit despite the tachyphylaxis suggested in earlier trials.[108,109] Guidance suggests reserving consideration for amantadine use to those in whom dyskinesia is not adequately managed on other therapies.[20]

The decision to use amantadine in L.M. should be based on whether his dyskinesias are deemed more problematic than his duration of off-time. If so, amantadine should be started at 100 mg/day taken at breakfast; an additional 100-mg dose can be taken with lunch 5 to 7 days after initiation. The dose can be increased to a maximum of 300 mg/day; however, doses >200 mg/day are associated with increased adverse effects and should be used cautiously. Amantadine is renally excreted, and the dose should be reduced in patients with renal impairment.[110] If the dyskinesias that L.M. is experiencing are tolerable but the duration of off-time is more problematic, then selection of another agent such as a COMT inhibitor or MAO-B inhibitor may be more appropriate than the initiation of amantadine at this time.

Side effects of amantadine mainly involve the gastrointestinal (eg, nausea, vomiting) and CNS (eg, dizziness, confusion, insomnia, nightmares, and hallucinations). Patients receiving concomitant anticholinergic therapy may experience more prominent CNS side effects.[111] Livedo reticularis, a rose-colored mottling of the skin

usually involving the lower extremities, can occur with amantadine as early as 2 weeks after initiating therapy. The consequences of livedo reticularis are entirely cosmetic, and discontinuation of therapy is unnecessary. Ankle edema may be seen in association with livedo reticularis. Elevation of the legs, diuretic therapy, and dosage reduction often alleviate the edema.

CATECHOL-O-METHYLTRANSFERASE INHIBITORS

COMT is an enzyme widely distributed throughout the body that is responsible for the biotransformation of many catechols and hydroxylated metabolites including levodopa. When carbidopa, an inhibitor of aromatic AAD, is coadministered with levodopa, the peripheral conversion of levodopa to dopamine via this pathway is inhibited. As a consequence, the conversion of levodopa to 3-*O*-methyldopa (3-OMD) by COMT is amplified and becomes the major metabolic pathway for levodopa degradation. The metabolite 3-OMD lacks antiparkinsonian activity and may compete with levodopa for transport into the circulation and brain. By preventing its peripheral degradation, the therapeutic effect of levodopa can be extended via inhibition of COMT.

Entacapone, tolcapone, and opicapone are selective, reversible, and potent COMT inhibitors that increase the amount of levodopa available for transport across the blood–brain barrier (**Fig. 59-3**) to prolong its therapeutic effect. Use of these agents is associated with increased on-time and a decrease in the daily levodopa dose.[111,112] The pharmacologic and pharmacokinetic effects of each COMT inhibitor are compared in **Table 59-5**.[111–117] Two uncontrolled trials and one controlled evaluation of patients with motor fluctuations newly placed on entacapone compared switching patients to tolcapone versus continuing the newly started entacapone. These trials alluded to the therapeutic benefits of tolcapone compared to entacapone; however, tolcapone is associated with cases of fatal, acute fulminant liver failure. This fatal as well as acute liver failure has led to stringent liver function monitoring requirements and limited clinical use. If initiated, liver function monitoring should be performed

at baseline and every 2 to 4 weeks for the first 6 months followed periodically thereafter as clinically necessary.[112] Because of the risks for hepatotoxicity associated with tolcapone, entacapone or opicapone are the preferred COMT inhibitors and either would be a good choice for L.M. if he desires an increase in his on-time.

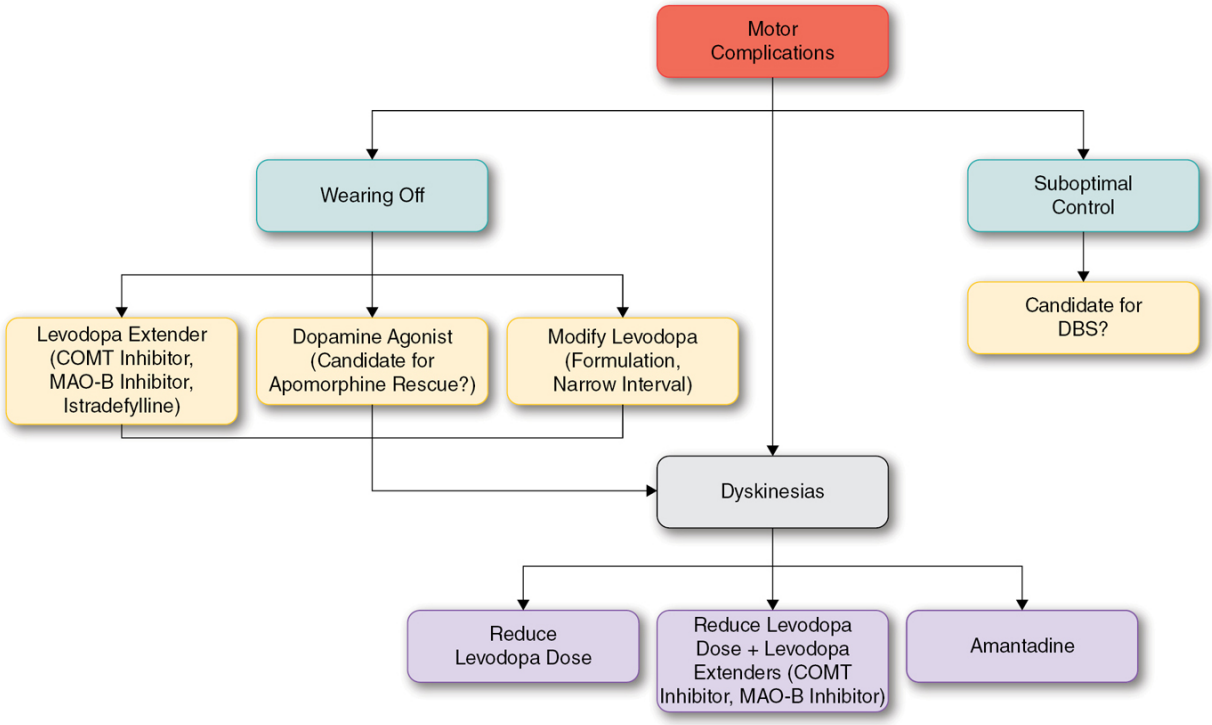


Figure 59-3 Suggested treatment algorithm for the management of motor complications in late Parkinson disease. *COMT, catechol-O-methyltransferase*; DBS, deep brain stimulation; MAO, monoamine oxidase.

Table 59-5
Pharmacologic and Pharmacokinetic Properties of Catechol-*O*-Methyltransferase Inhibitors

	Tolcapone	Entacapone	Opicapone
Bioavailability	65%	35%	Decreased by 62% following moderate fat/calorie meal
T_{max} (hours)	~2	1	2
Protein binding	>99.9%	98%	>99%
Metabolism	Glucuronidation; CYP3A4, CYP2A6; methylated by COMT	Isomerization, glucuronidation	Sulfation, glucuronidation, methylation (by COMT), reduction, and glutathione conjugation
Half-life (hours)	2–3	Biphasic; 0.4–0.7 (beta phase), 2.4 (gamma phase)	1–2
Excretion	Urine (60% metabolites, 0.5% unchanged); feces (40%)	Feces (90%); urine (10%)	Feces (22%), expired air (20%), urine (5% unchanged)
Time to reverse COMT inhibition (hours)	16–24	8	>5
Maximal COMT inhibition at 200-mg dose	>80%	65%	>84%
Increase in levodopa AUC	100%	35%	64%–94%
Increase in levodopa half-life	75%	85%	NA
Dosing method	tid, spaced 6 hours apart	With every administration of levodopa	Once daily

AUC, area under the curve; COMT, catechol-*O*-methyltransferase; CYP, cytochrome P-450; tid, three times daily.

Entacapone

Case 59-1, Question 15: Six months after adjusting the frequency of his carbidopa/levodopa dose and adding amantadine, L.M. reports that his dyskinesias are not too bothersome, but he is now having increased periods (lasting a few minutes) in which he cannot move. He is currently taking amantadine 100 mg twice daily, pramipexole 0.5 mg three times daily, and IR carbidopa/levodopa 25 mg/250 mg five times a day, but, "even on a good day," gains symptomatic relief for only about 2 to 3 hours after a dose. When should entacapone be initiated? How effective is entacapone for reducing the symptoms of PD?

Early initiation of a COMT inhibitor at the same time that levodopa is first introduced has been proposed as a way of reducing the development of levodopa-induced motor complications[115]; theoretically, this strategy should provide more stable plasma levels of levodopa and lessen pulsatile stimulation of striatal dopamine receptors normally observed with intermittent levodopa dosing. This strategy was tested in the Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) study, a multicenter,

double-blind study that randomly assigned 747 patients to initiate either carbidopa/levodopa or carbidopa/levodopa/entacapone four times daily.[115] Surprisingly, patients randomly assigned to receive carbidopa/levodopa/entacapone actually had a shorter time to onset of dyskinesia (hazard ratio: 1.29; *P* = .04) and increased dyskinesia frequency at week 134 (42% vs 32%; *P* = .02). These findings may have been confounded by an increased use of dopaminergic therapy in the entacapone group. The findings of the STRIDE-PD study do not support the early administration of entacapone in combination with levodopa to reduce the occurrence of motor complications.

The efficacy and safety of entacapone as an adjunct to levodopa therapy in the presence of motor complications was established in two pivotal multicenter, randomized, double-blind, placebo-controlled trials.[116,117] Subjects for both studies had idiopathic PD with motor fluctuations, including wearing-off phenomena, despite maximal tolerated doses of levodopa. In both trials, patients were randomly assigned to receive either entacapone 200 mg or placebo (up to 10 doses/day) with each dose of carbidopa/levodopa.[116,117] In both trials, significant improvements in off-time (~1 hour), UPDRS scores (10% improvement), and levodopa doses (reductions of ~80–100 mg/day) were consistent.

Opicapone

Opicapone is the newest selective COMT inhibitor on the market approved by FDA in 2020 for adjunctive treatment in patients with PD experiencing “off” episodes. It boasts no major benefits over entacapone except for once-daily dosing making it more attractive and still seems to be safer than tolcapone. Two double-blind, randomized, parallel-group, placebo- and active-controlled and placebo-controlled trials were conducted over 14 to 15 weeks evaluating opicapone as adjunctive to levodopa therapy. The first study compared patients taking 50 mg (*N* = 115) versus placebo (*N* = 120) and showed mean decrease in absolute off-time of −1.95 hours (*P* = .002) as well as an increase in on-time without troublesome dyskinesia by 1.84 hours (*P* = .001).[118] The second study also

evaluated patients taking 50 mg of opicapone (*N* = 147) versus placebo (*N* = 135). Similar results were seen in mean decrease in absolute off-time of 1.98 hours (*P* = .008) and increased absolute on-time without troublesome dyskinesia of 1.43 hours (*P* = .065).[119] Opicapone may have some advantages over entacapone making it a more attractive first choice of COMT inhibitor. When compared to entacapone, opicapone provides a superior response as evidence by bioavailability of coadministered levodopa associated with more pronounced, long-lasting, and sustained COMT inhibition with only daily dosing.[120] One study evaluated the efficacy of switching from entacapone to opicapone 50 mg daily (*N* = 495) for a 1-year follow-up period. Switching from opicapone to entacapone, decreased the off-time further by 39.3 minutes over 1 year as well as those that did not switch maintained their efficacy.[121]

Dosing

CASE 59-1, QUESTION 16: The decision is made to gradually discontinue pramipexole as guided by symptoms or side effects. How should entacapone be dosed, and how does entacapone compare to opicapone?

Entacapone is approved for use as adjunctive therapy to levodopa for the treatment of PD in patients experiencing wearing-off or end-of-dose deterioration. It is given as one 200 mg tablet with each carbidopa/levodopa administration, up to eight tablets/day. It is available in a combination tablet with a 1:4 ratio of IR carbidopa/levodopa that patients can be switched to once they are stabilized on individual formulations of carbidopa/levodopa and entacapone. As for opicapone, it is dosed 50 mg tablet daily at bedtime without food 1 hour before and at least 1 after administration for adjunctive therapy to levodopa for PD in patients experiencing wearing-off. For patients with moderate liver dysfunction, the dose can be reduced to 25 mg daily and avoided in severe liver impairment. Opicapone has decreased C_{max} up to 62% when administered with food and should be administered 1 hour before or

after food. If dyskinesias occur, it may be necessary to lower the levodopa dose by ~10% to 25% particularly if the patient is receiving >800 mg/day of levodopa. Although pramipexole is being discontinued in L.M., he should still be monitored for dyskinesias, especially during the first few weeks of therapy, as it may also be necessary to lower his carbidopa/levodopa dose.

Adverse Effects

CASE 59-1, QUESTION 17: What are the adverse effects of entacapone, and how should they be managed?

Most COMT inhibitor adverse effects are associated with increased levodopa exposure. For example, entacapone-induced adverse effects include dyskinesias (50%–60%), dizziness (10%–25%), nausea (15%–20%), and hallucinations (1%–14%).[116,117] To circumvent these effects, reducing the levodopa dosage by 10% to 15% is a successful strategy in about one-third of patients experiencing dyskinesias. Other adverse effects include urine discoloration (11%–40%), diarrhea (10%), and abdominal pain (6%).[116,117] Urine discoloration (brownish orange) is attributed to entacapone and its metabolites and is considered benign, but patients should be counseled regarding this effect. The most common reason for the withdrawal of entacapone from clinical studies and discontinuation of therapy was severe diarrhea (2.5%).[122] Although the results of the STRIDE-PD study indicated that patients taking the combination of carbidopa/levodopa/entacapone may be at an increased risk for cardiovascular events (eg, heart attack, stroke, and cardiovascular death) compared with those taking carbidopa/levodopa, subsequent FDA analysis has found no increased risk.[123]

MONOAMINE OXIDASE-B INHIBITORS

Selegiline

Selegiline may have a role as a symptomatic adjunct to levodopa in more advanced disease. Studies have found improvement in the wearing-off effect in 50% to 70% of patients and a reduction in as much as 30% in the total daily dose of levodopa without improvements in on-time.[124,125] This improvement has also been shown to arrive with an initial worsening of dyskinesis in 60% of treated patients, which may be counteracted with levodopa dose reductions. Selegiline has been shown to reduce off-time by 32% (2.2 hours) compared with 9% (0.6 hours; $P < .001$) for placebo in a 12-week, randomized, multicenter, parallel-group, double-blind study but was not reproducible in an identical trial.[126,127] Authors hypothesize that this conflict may be due in part to large and potentially variable placebo effects seen in PD trials. The on–off effect is less responsive to the addition of selegiline.

Rasagiline

Rasagiline has also been studied as an adjunct to levodopa in advanced disease. When added to levodopa therapy, rasagiline can improve motor fluctuations, reducing off-time by 1.4 hours and 1.8 hours (for the 0.5- and 1-mg/day groups, respectively) compared with 0.9 hours for placebo.[128] Patients treated with 0.5 mg/day and 1 mg/day of rasagiline had 0.49 hour (0.08–0.91; $P = .02$) and 0.94 hour (1.36–0.51; $P < .001$) less off-time compared with placebo. Significant improvements were reported in the UPDRS subscores for ADLs in the off-state and motor performance in the on-state as well as clinician global assessments. Dyskinesias were slightly worsened in the 1-mg/day group. As adjunctive therapy to levodopa, rasagiline appears to provide similar benefit to entacapone.[128] In the lasting effect in adjunct therapy with rasagiline given once daily (LARGO) study when compared with entacapone 200 mg administered with each levodopa dose, rasagiline 1 mg/day reduced total daily off-time in a similar manner (decrease of 21% or 1.18 hours for rasagiline and 21% or 1.2 hours for entacapone).[129] Reduction of levodopa dose may be necessary if dyskinesias occur when rasagiline is added in combination with levodopa.

Safinamide

Safinamide (Xadago™) was approved by the FDA in May 2017 as an adjunct to carbidopa/levodopa for patients experiencing "off" episodes. It is not approved as monotherapy but found to be effective in randomized controlled trials for motor complications in PD when used as adjunctive treatment with levodopa. Compared with placebo, safinamide increased mean daily "on" time without troublesome dyskinesia and improved motor function. A 24-week trial of 549 patients with PD taking oral levodopa who had "off" time ≥1.5 hours per day found that treatment with safinamide increased the mean on-time without troublesome dyskinesia by ~1.4 hours compared with 0.6 hours for placebo.[130,131] The side effect profile is similar to rasagiline (see Table 59-2). Patients should additionally be monitored for visual changes as retinal detachment and loss of photoreceptor cells were noted in animal studies. The list of contraindicated medications is extensive and should be reviewed prior to starting therapy. Safinamide has a half-life of 20 to 26 hours, reaches a steady state in 5 to 6 days, and can be taken without regard to meals. It requires hepatic dose adjustment but no renal dose adjustments. The extent of use in clinical practice and eventual place in therapy are unknown at this time.

Istradefylline

Istradefylline (Nourianz™) is a mechanistically novel agent used as an adjunct treatment to carbidopa/levodopa for patients that develop "off" episodes. It was FDA-approved in April 2019. Istradefylline is a selective adenosine receptor agonist that exerts its action via adenosine A_{2A}. Originally denied by FDA in 2008 because of lack of follow-up data, istradefylline was later approved in Japan in 2013. Thereafter, four clinical studies lasting >12 weeks and included >1100 participants evaluated istradefylline versus placebo for adjunctive therapy to carbidopa/levodopa. In a 2008 study including 196 patients, a decrease of daily awake off-time for istradefylline had a mean of −10.8 ±16.6% (95% CI: −13.46 to −7.52) from baseline compared with −4.0 ±15.7% (95% CI: −7.73 to 0.31; *P* = .007) for

placebo.[13] One study published in 2016 showed a trend toward a greater decrease in daily off-time versus placebo for both the 20 mg and 40 mg doses, but statistical significance was not reached.[132] In 2018, an analysis of a postmarketing surveillance data was conducted in Japan, in 476 patients. This study showed the drug was effective in 61.3% of patients treated with istradefylline, based on the physician's global assessment, as well as UPDRS III scores were reduced by 33.7 to 30.3 from baseline. This analysis also showed that off-time was reduced in 38.2% of patients, and off-time symptoms improved in 44.7% of patients while motor dysfunction was improved in 48.5% of patients.[133] Lastly, a meta-analysis reviewed six randomized studies and concluded that istradefylline at 20 mg/day improved UPDRS III as well as at 40 mg/day improved both off-time and UPDRS III.[134] All trials revealed that this medication is well tolerated with dyskinesia and hallucinations being the most reported adverse events.[133]

Surgical Therapies for Parkinson Disease

Case 59-1, Question 18: L.M. is now classified as Hoehn and Yahr[2] late stage 3. He is now on amantadine 100 mg twice daily, IR carbidopa/levodopa 25 mg/250 mg five times daily, and entacapone 200 mg five times daily with carbidopa/levodopa administrations. His overall control of his PD has diminished greatly in the last couple of months. His on-time averages around 6 hours/day with the majority of it accompanied by troublesome dyskinesias. Most days he needs some assistance with ADLs. His cognitive function remains well preserved, and he is not depressed. He has heard about surgical procedures that might benefit patients with PD. Is surgical therapy superior to medical therapy in patients with advanced PD?

Two types of surgical therapies have been used in patients with advanced PD who cannot be adequately controlled with medications. The first involves making an irreversible surgical lesion in a specific location in the brain (eg, posteroventral pallidotomy or stereotactic thalamotomy). The second involves surgical implantation of a device that sends electrical impulses to specific parts of the brain (eg, deep

brain stimulation [DBS]). Posteroventral pallidotomy has been shown to reduce dyskinesias on the contralateral side and may permit the use of higher dosages of levodopa for managing rigidity and bradykinesia.[135] A significant disadvantage, however, is the need to make a lesion near the optic tract, which may risk visual loss. Other possible risks of pallidotomy include weakness, paralysis, and hemorrhage that can cause stroke as well as speech difficulty. Stereotactic thalamotomy has been shown to reduce symptoms of debilitating tremor and improve rigidity in patients with PD.[136] This intervention has eliminated contralateral tremor in 80% of patients, and improvement has been sustained for up to 10 years. As with pallidotomy, a disadvantage of thalamotomy, however, is the need to make an irreversible lesion in the basal ganglia that may limit the effectiveness of newer procedures because they become available. Thus, DBS is now the preferred surgical method for treating advanced PD that cannot be adequately controlled with medications. DBS uses an implanted electrode in the brain, in either the subthalamic nucleus (STN) or the globus pallidus interna (GPi), which is connected to a subcutaneously implanted pacemaker. This implanted electrode permits the delivery of high-frequency stimulation to the desired target. Advantages of DBS include no need for an irreversible brain lesion, and it provides flexibility for altering the target site and program stimulation parameters.

The efficacy of DBS in advanced PD was shown in a two-part study of 255 patients with idiopathic PD responsive to levodopa but with persistent and disabling motor symptoms.[137] Patients were randomly assigned to DBS or best medical therapy and followed for 6 months. Patients receiving DBS gained a mean of 4.6 hours/day of on-time without troubling dyskinesias compared with 0 hours/day for best medical therapy ($P < .001$). Additionally, 71% of patients receiving DBS experienced clinically meaningful motor function improvements (≥5-point change in UPDRS motor score) compared with only 32% of patients receiving best medical therapy ($P < .001$).[137] Patients whose goal is to reduce the amount of dopaminergic agents needed for symptoms control STN is the preferred intervention. On the other hand, if there are additional

concerns for depression, cognitive decline, and/or reduced medication dyskinesias, use of GPi is then the preferred DBS intervention.[138–142]

Case 59-1, Question 19: What surgical therapy would be most appropriate for L.M.?

L.M. appears to be an ideal candidate for DBS. Candidates for DBS should have idiopathic PD and be levodopa-responsive but continue to experience motor complications or tremor despite optimal pharmacotherapeutic regimens. Ideally, DBS should be avoided in patients with preexisting cognitive or psychiatric problems owing to a slight risk of decline in cognition. No strict age limitation for DBS exists, but patients younger than age 70 years, such as L.M., appeared to recover from surgery more quickly and showed greater motor improvements. DBS of the STN consistently demonstrates a marked reduction in the need for escalating levodopa dosages compared with GPi DBS,[138–143] but data suggest other nonmotor symptoms such as visual processing speed and depression may be affected more favorably when targeting the GPi.[139]

Investigational Pharmacotherapy

CASE 59-2

Question 1: K.B. is a 61-year-old female who presents to the movement disorders clinic after referral from her family doctor for a presumptive diagnosis of PD. She is Hoehn and Yahr[2] stage 1 with slightly decreased arm swing on the left side and unilateral resting hand tremor. Her past medical history is significant for hypertension and mild renal insufficiency (serum creatinine of 1.4 mg/dL). Since her initial visit with her family physician, she has been researching information about alternative PD treatments from several PD-related websites.

Are there any dietary supplements or other investigational therapies that may benefit K.B.?

DIETARY SUPPLEMENTS

Multiple mechanisms have been implicated in the development of PD and, thus, have produced a variety of dietary supplements studied as possible alternatives or neuroprotective agents. These supplements have been hypothesized to benefit patients with PD as antioxidants by scavenging free radicals, prevention of mitochondrial dysfunction, reduction of neuronal inflammation, and modulation of neurons to slow down apoptosis as well as cell degeneration. Despite numerous studies, many supplements fall short of being viable options as effective alternative treatments. For this reason, many supplements may not provide the expected benefit, but they can be utilized in patients seeking alternative options in the context of medication intolerance.

Coenzyme Q10

A study in untreated patients with PD provided coenzyme Q_{10} (CoQ_{10}) failed to show statistical significance but met the threshold for futility. Two subsequent phase III trials of patients with early PD failed to show symptomatic or neuroprotective benefits.[143–145] In an evaluation of 600 patients with early PD, subjects were randomized to receive either 1200- or 2400-mg of CoQ_{10} daily in addition to 1200 IU of α-tocopherol. The study was terminated prematurely because of failure to meet prespecified futility endpoints and trend in adverse outcomes compared to placebo.[145]

Creatine and minocycline

Minocycline (anti-inflammatory and antiapoptotic properties) and creatine (an antioxidant and enhances mitochondrial energy production) were evaluated to determine both safety and if either slowed the progressive decline in function associated with PD. The use of both creatine and minocycline in PD was examined in a futility-design study, which patients with early PD not requiring therapy were randomly assigned to receive creatine 10 g/day, minocycline 200 mg/day, or placebo.[146] After 12 months, the mean

change in the total UPDRS could not be rejected as futile and met the criteria for further clinical testing. A long-term follow-up to this trial found that by 18 months, patients requiring symptomatic treatment did not differ, but significantly more patients on minocycline discontinued therapy prematurely (23% vs 9% of creatine and 6% of placebo patients) because of gastrointestinal discomfort within 30 to 60 days postinitiation. Given the unresolved issues surrounding the induction of antibiotic resistance with long-term use of an agent such as minocycline and concerns for tolerability, it is generally not recommended. A long-term, randomized, double-blind, placebo-controlled trial of creatine 10 g/day versus placebo in early treated PD was terminated early for futility based on an interim analysis. The trial concluded that treatment with creatine for at least 5 years does not support its use in PD.[147]

Vitamins

Multiple studies have found a relationship between vitamins and PD. Vitamins may play a role as antioxidants and affect biologic functions by regulating gene expression, which may be beneficial for the treatment of PD. The B vitamins and vitamin C have evaluated their neuroprotective benefits for PD with little evidence to support these claims.

The most comprehensive evaluation of antioxidant therapy for PD comes from the DATATOP study.[67,124,148] In this study, patients with early PD were assigned to one of four treatment regimens: α-tocopherol (vitamin E 2000 international units [IU]/day) and selegiline placebo; selegiline 10 mg/day and α-tocopherol placebo; selegiline and α-tocopherol active treatments; or dual placebos. After ~14 months of follow-up, no difference was seen between the α-tocopherol group and placebo group in time to require levodopa.[67] Thus, despite the theoretic benefit, clinical data are lacking to support the routine use of α-tocopherol, and it would not be recommended in K.B.[7]

In contrast, vitamins D and B_{12} may hold some promise in PD. A recent 2020 cohort study has shown that higher levels of B_{12} were observed in patients with PD who did not develop dementia.[149] Vitamin B_{12} cutoff of <587 ng/L was 87% sensitive and 70% specific (95% CI: 0.60–0.98) in determining patients with dementia. Patients with PD and vitamin B_{12} levels <587 ng/L were 5.4 times more likely to develop dementia with half having dementia within 5 years of PD diagnosis versus 11% in those with a vitamin B_{12} level of ≥587 ng/L ($P < .05$).[150] A study using a drug reimbursement database conducted over 29 years in 3173 individuals found 50 cases of PD. Vitamin D_3 levels were evaluated based on frozen samples collected at baseline and showed that higher levels of vitamin D_3 are related to a lower risk of developing PD, which has a potential to be neuroprotective effect in PD.[151] Additionally, a randomized, double-blind, placebo-controlled trial reviewing vitamin D_3 supplementation (1200 IU/day for 12 months) in patients with PD significantly prevented the deterioration of PD.[152]

Omega-3 fatty acids

Omega-3 fatty acids have a long history of research in neuronal health, including neuroprotective properties, anti-inflammatory activity, antiapoptotic activity, and enhanced synthesis of brain-derived neurotrophic factor (BDNF). A pilot study of 31 individuals studied the effects of omega-3 fatty acids in patients with PD and with depression leading to improvements in the Montgomery–Asberg Rating Scale for depression and Clinical Global Impression-Depression Score.[153] These same improvements were unfortunately not seen on the Beck Depression Inventory score. In patients who may already be inclined to take omega-3 fatty acid supplements, there may be some additional benefits in improving mood and depressive symptoms.

EMERGING THERAPIES

With developments in PD research and biopharmaceutical technology, new treatment targets and modalities are constantly being investigated, including new disease-modifying targets, tetrahydrocannabinol (THC), nabilone (synthetic cannabinoid), cannabidiol (CBD) treatments, and stem cell transplant.

Disease-modifying targets include transcription factors, proteins, and their mutations. Novel pharmaceutical and biologic technologies under development include small-molecule drug delivery such as with glial cell–derived neurotrophic factor, stem cell therapies, and nerve cell grafts. Phase 2 and 3 clinical trials are currently underway exploring molecular targets such as GLP-1, LRRK2, α-synuclein, and GBA, which may provide a breakthrough in the development of disease-modifying therapies in PD.[154,155]

Growing research related to the benefits of CBD in PD is emerging. Cannabidiol (Epidiolex®) was evaluated in an open-labeled, dose escalation study in 13 patients with PD to establish its safety and tolerability along with its impact on common PD symptoms. Doses were titrated from 5 mg/kg/day up to 25 mg/kg/day but subsequently reduced to a maximum dose of 20 mg/kg/day as a result of adverse events in about a third of patients.[155] The most common adverse effects reported were diarrhea (85%), somnolence (69%), fatigue (62%), transaminitis (38.5%), and weight gain (31%) as well as 23% of patients discontinuing therapy because of intolerability. Although not a primary outcome, improvements in UPDRS scores were seen in the 10 patients that completed the study along with nighttime sleep and emotional/behavioral dyscontrol scores. One meta-analysis included three studies that evaluated nabilone, CBD, and THC in patients with PD. Nabilone was noted to improve Parkinson dyskinesia, whereas CBD and THC products did not show improvement in dyskinesias, but CBD did show an improvement in daily living activities.[156]

Lastly, stem cell transplantation to replace destroyed dopaminergic neurons to treat PD is being evaluated. It has been identified that abnormalities of protein misfolding in stem cell–derived neurons from patients with PD may be reversed by manipulating genes or exposing the cells to drug-like molecules. In vivo transplantation of

the neurons from a mini-substantia niagra–like structure have resulted in early and progressive amelioration of PD in rats.[157]

Nonmotor Symptoms of Parkinson Disease

Although PD is mostly recognized for its cardinal features of motor dysfunction, nonmotor symptoms are an important part of the disease throughout all stages and are a key determinant of quality of life (**Table 59-6**).[158] More than 98% of patients with PD have at least one nonmotor symptom. The average per patient is nearly eight with the number and impact increasing with disease duration and severity.[159] Common nonmotor symptoms include autonomic dysfunction (eg, gastrointestinal disorders, orthostatic hypotension, sexual dysfunction, urinary incontinence, sialorrhea, seborrhea, and constipation), sleep disorders (eg, RLS, periodic limb movements of sleep [PLMS], excessive daytime somnolence, insomnia, REM sleep behavior disorder), fatigue, and psychiatric disorders (eg, dementia, depression, and anxiety).[159] In one longitudinal study of patients with PD, the most common nonmotor symptoms were psychiatric symptoms (68%, most commonly anxiety), fatigue (58%), leg pain (38%), insomnia (37%), urinary symptoms (35%), drooling (31%), and difficulty concentrating (31%).[159] Regular screening for these nonmotor symptoms should occur. L.M. has a history of depression treated with citalopram that could be attributable to PD, and his therapy should be periodically evaluated. The forgetfulness and decreased memory described by L.M. could be early signs of cognitive decline and warrant close observation.

Table 59-6
Nonmotor Symptom Management

Nonmotor Symptoms	Potential Interventions
Central nervous system	
Cognitive impairment/dementia	Reduce anticholinergic agents, cholinesterase inhibitor.
Fatigue	Caffeine, CNS stimulant, amantadine, encourage sleep

	hygiene or refer to specialist.
Daytime sleepiness	Encourage sleep hygiene, reduce dose of dopamine agonist, bright light therapy, exercise, refer to specialist.
Behavioral	
Psychosis	Reduce or discontinue anticholinergic agent and/or dopamine agonist. Antipsychotics (eg, quetiapine, clozapine, pimavanserin).
Impulse control disorder	Reduce or discontinue dopamine agonist. Add clozapine, quetiapine, or naltrexone.
Anxiety	Reduce dose or discontinue contributing agents, cognitive behavioral therapy, selective serotonin-reuptake inhibitors, minimize off-times.
Depression	Selective serotonin-reuptake inhibitor, newer-generation serotonin norepinephrine-reuptake inhibitor, cognitive behavioral therapy
Sleep related	
Insomnia	Reduce or discontinue activating agents. Add trazodone, melatonin, nonbenzodiazepine hypnotic. Encourage sleep hygiene, refer to specialist. Note: Avoid agents on Beer list in patients >65.
REM sleep behavior disorder	Clonazepam, melatonin
Musculoskeletal	
Falls	Referral to physical therapy and/or occupational therapy, aid with ambulation, minimize risk for bone fractures, treat osteoporosis, reduce or remove sedating agents.
Dysphagia	Referral to speech therapist, dysphagia diet, avoid anticholinergic medications, manage dry mouth.
Pain	Appropriate treatment for type of pain, minimize off-times, physical therapy, referral to pain specialist
Autonomic dysfunction	
Orthostatic hypotension	Reduce dose of α-blockers, dopamine agonist, diuretics, vasodilators, psychotropics. Encourage sodium and fluid intake, fludrocortisone, midodrine, droxidopa, pyridostigmine.
Constipation	Fiber (supplement or dietary), probiotics, hydration,

	exercise, laxatives, enema, stool softeners, new drug therapies (Amitiza®, Linzess®, Trulance®)
Overactive bladder	Behavioral therapies (eg, bladder training, fluid management, pelvic floor muscle exercises), antimuscarinic agents, mirabegron, intradetrusor injections of botulinum toxin
Sialorrhea	Local injection of botulinum toxin, atropine sublingual drop, glycopyrrolate, ipratropium sublingual spray
Rhinorrhea	Avoid food triggers, ipratropium nasal spray, anticholinergic agent.
Seborrhea	Avoid alcohol-containing skin products and hard soaps, encourage consistent skin care, refer to dermatologist.
Sexual side effects	Sildenafil, tadalafil, vardenafil

DEMENTIA

CASE 59-3

Question 1: J.D. is a 74-year-old male with advanced PD, Hoehn and Yahr[2] stage 4. During the last year, his family has noticed that he is increasingly forgetful and anxious. Twice recently, he left home alone for brief periods and called 911 because he thought someone was trying to break into the house. He also calls his daughter two or three times each day, often repeating the same questions and forgetting that he called her earlier. His wife is his primary caregiver, and he is nearly entirely reliant on her for help in performing ADLs. He scored 20 (below normal) on his most recent Mini-Mental Status Examination, and his family reports that he is no longer interested in social activities or hobbies. Neuropsychiatric testing is performed and demonstrates a significant depressive component to his dementia. Subsequent recommendations from the neuropsychiatrist are that he receives 24-hour supervision, along with participation in structured leisure activities including adult day care for several hours/week to help relieve his wife's caregiver burden.

What is the best treatment for progressive cognitive decline that J.D. is experiencing?

Approximately 48% to 80% of patients may develop dementia during their disease course at a rate of about six times greater than healthy individuals.[20,160] One longitudinal study of 136 incident cases

of PD followed for 20 years found that nearly 100% eventually exhibited dementia.[161] The prevalence of cognitive decline and dementia among patients with PD ranges from 10% to 30% and may be associated with a more rapid progression of disease-related disability.[7] Successful management of cognitive impairment in patients with PD first requires that all potentially reversible causes and underlying contributing factors be addressed. These include treating infections, dehydration, and metabolic abnormalities as well as eliminating unnecessary medications (particularly anticholinergics, sedatives, and anxiolytics) that can exacerbate dementia or delirium.

Experience with cholinesterase inhibitors for treating cognitive impairment in PD indicates marginal improvements with their use.[162–164] Two randomized, controlled trials evaluated donepezil have failed to show consistent benefit, whereas galantamine has only been evaluated in a single open-label trial.[165,166] Rivastigmine was found to provide clinically meaningful (moderate or marked improvement on the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change) benefit to significantly more patients than placebo in a large, randomized, placebo-controlled trial and has demonstrated sustained cognitive benefit for up to 48 weeks.[164,167,168] As a result, rivastigmine was FDA-approved for the management of mild-to-moderate dementia in PD and is, therefore, the drug of choice. Compared with placebo, the cholinesterase inhibitors often result in statistically significant changes on cognitive scales. Their impact on function and disposition, however, is unclear.

A cholinesterase inhibitor such as rivastigmine may be considered for patients such as J.D., although he must be monitored closely for signs of deterioration of motor function such as worsening of tremor.[165] Cholinesterase inhibitors are associated with other adverse events that may be overlooked and attributed to the PD itself, including sialorrhea, excessive lacrimation, incontinence, nausea, vomiting, and orthostasis. Perhaps more important than any medication therapy, adequate social support for J.D. should be ensured. Because he becomes further dependent on family members for assistance with ADLs, the increased needs of the

caregiver(s) should also be considered. In the case of J.D., attending adult day care several times weekly, if available, would provide a structured, supervised environment for interaction with others as well as providing a rest period for his caregiver. Dementia is a leading cause of nursing home placement for patients with PD.[165]

Although not a cholinesterase inhibitor, memantine is commonly used for the treatment of moderate-to-severe dementia. In a 24-week randomized, placebo-controlled trial, patients with dementia with Lewy body (DLB) had improvement in global clinical improvement; on the other hand, there was no significant difference from placebo in those with PD dementia (PDD).[169] A later meta-analyses revealed patients with PDD may see benefits in attention, processing speed, and executive functions with memantine use. In clinical trials, memantine has been shown to be well tolerated in patients with DLB and PDD.[170] Unfortunately, hallucinations and worsened neuropsychiatric symptoms have occasionally been reported, which has led to be cautious in this patient population.

DEPRESSION/ANXIETY

Case 59-3, Question 2: How should anxiety and depression be treated in J.D.?

Depression is often poorly recognized and inadequately treated in patients with PD.[166] This fact is likely because of the overlapping symptoms of depression and PD, which confound the identification of depression. Withdrawal, lack of motivation, flattened affect, decreased physical activity, and bradyphrenia are examples of overlapping features.[166]

Treatment of depression in patients with PD should first focus on providing adequate symptomatic treatment to restore mobility and independence as depression can be attributed to lengthy off-periods. Antiparkinsonian drugs, such as pramipexole, can be associated with mood-enhancing effects independent of their ability to reduce the time in the off-state.[166] Case reports and small trials have shown

that depression in patients with PD can be successfully treated with antidepressant drugs, including tricyclic agents (eg, amitriptyline, desipramine, nortriptyline), bupropion, and selective serotonin-reuptake inhibitors (SSRIs) (eg, citalopram and paroxetine).[166] Given the overall poor quality of clinical trials, it is difficult to know whether these desirable outcomes reflect a class effect or are unique to each individual agent. Some antidepressants may worsen symptoms in patients with PD. For example, fluoxetine can be activating and worsen agitation; nevertheless, SSRIs have been shown to worsen PD tremor in ~5% of patients.[171] With tricyclic antidepressants (TCAs), care must be taken to observe for anticholinergic side effects that may worsen PD symptoms such as impaired cognition, delayed gastric emptying (which may reduce levodopa effectiveness by increasing levodopa degradation in the gut), urinary problems, orthostatic hypotension, and increased risk of falls. Additionally, consideration should be taken for the risk of drug–drug interactions and serotonin syndrome associated with the combination of SSRIs or TCAs with concomitant MAO-B inhibitors. Electroconvulsive therapy may also be considered in refractory cases but may adversely affect cognition.

Based on his symptoms, it is reasonable to start J.D. on an antidepressant. Clinical experience suggests selecting initially an SSRI, which balances efficacy and safety. For other patients with depression, the drug of choice should be individualized based on other pragmatic factors such as cost, potential for adverse effects, and personal or family response to prior agents. Regardless of which agent or class of antidepressant selected, therapy should be started at the lowest dose and gradually titrated to effect. He should be monitored closely for side effects particularly anticholinergic symptoms from TCAs and for any adverse effects related to mobility. He should be observed carefully for changes in parkinsonian symptoms, including the development of extrapyramidal symptoms as well as any signs of psychomotor agitation. Short-term use of benzodiazepines, such as lorazepam or alprazolam, may be provided to relieve anxiety symptoms but used cautiously for a limited time because of adverse effects related to cognition and risk

of falling as well as addiction potential.[172] Generally, anxiety symptoms should improve with treatment of the underlying depression.

PSYCHOSIS

In PD, the incidence of psychotic symptoms increases with age, cognitive impairment, and disease duration.[173] Other risk factors include higher age at PD onset, high doses of dopaminergic drugs, and REM sleep behavior disorder.[174] Symptoms are often more pronounced at night (the “sundowning” effect), and hallucinations are typically visual. As with the management of cognitive impairment, it is important to eliminate or minimize any potential causative factors or polypharmacy, particularly anticholinergic medications that could be contributing to the hallucinations or delirium. In some patients, reducing the dose of levodopa improves mental function and also provides satisfactory control of motor features. If it is not possible to achieve a balance between preserving motor control and decreasing neuropsychiatric symptoms through reduction in levodopa dosage, antipsychotics may be considered.

Older antipsychotic medications, such as haloperidol, perphenazine, and chlorpromazine, block striatal dopamine D_2 receptors as well as may exacerbate parkinsonian symptoms and are not recommended. Newer atypical antipsychotics are more selective for limbic and cortical D_3, D_4, and D_5 receptors. They have minimal activity at D_2 receptors and may control symptoms without worsening parkinsonism. Of these agents, clozapine has the best evidence of efficacy in patients with PD without adversely affecting motor function and should be preferentially considered.[161] However, its use is complicated by the need for frequent monitoring of white blood cell counts because of the risk of agranulocytosis. Other newer agents, particularly quetiapine controls psychosis without worsening parkinsonism.[20,165] Both risperidone and olanzapine worsen parkinsonism and are inferior to clozapine in patients with PD.[165,175] Aripiprazole has been associated with worsening motor function in patients with PD, whereas experience with ziprasidone has yielded

mixed results.[176] A newer atypical antipsychotic, pimavanserin, was FDA-approved based on results from one randomized, placebo-controlled trial. It acts through serotonin receptors and avoids interactions with dopamine receptors responsible for the worsening of PD symptoms as seen with other antipsychotics. It is not without its own risks, including cardiovascular and paradoxical worsening of psychosis.[177]

AUTONOMIC DYSFUNCTION

Patients with PD frequently experience dysautonomia, including orthostasis, erectile dysfunction, constipation, nocturia, sensory disturbances, dysphagia, drooling, seborrhea, and thermoregulatory imbalances. Management of these symptoms is generally supportive, and appropriate medical interventions similar to those used in other geriatric patients can be used to treat these symptoms whenever encountered. In some cases, fludrocortisone or midodrine can be considered if orthostatic hypotension is severe, although these drugs have not been well studied in patients with PD specifically.[158] Other possibly effective treatments for symptoms of autonomic dysfunction include sildenafil for erectile dysfunction and polyethylene glycol for constipation.[159]

FALLS

Patients with PD and their caregivers should be counseled on the prevention of falls because they can result in serious morbidity and mortality. Generally, falls result from one of several factors, including postural instability, freezing and festination, levodopa-induced dyskinesia, symptomatic orthostatic hypotension, coexisting neurologic or other medical disorders, and environmental factors. Prevention remains the best strategy and includes environmental precautions such as proper lighting, use of handrails, removing tripping hazards, and incorporating physical and occupational therapy. Reversible causes of postural or gait instability should be addressed whenever suspected. Patients with PD are advised to

take a vitamin D supplement to reduce their risk of fracture with future falls.[20]

SLEEP DISORDERS

Sleep disorders may occur at any time during the disease course and may even precede motor symptom development.[20] Excessive daytime drowsiness is a common sleep disorder in PD, which may be treated with modafinil.[158] Other sleep disorders such as insomnia, sleep fragmentation owing to PD symptoms, RLS, and REM sleep disorder (characterized by vivid dreams that are often acted out especially if frightening) are common and a source of decreased quality of life. When sleep dysfunction can be directly attributed to PD symptoms such as akinesia, tremor, dyskinesia, or nightmares, dosage adjustment of dopaminergic medications is indicated. Proper sleep hygiene should be encouraged. Insomnia symptoms unrelated to PD symptoms are treated similar to patients without PD and can be managed supportively.

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS OF SLEEP

Clinical Presentation

CASE 59-4

QUESTION 1: J.J., a 47-year-old female, presents to her family physician reporting daytime fatigue and difficulty sleeping at night because of "jumpy legs." She reports being able to sleep only 4 to 5 hours/night because of leg restlessness and feels unrefreshed after sleep. On further questioning, she describes the sensation in her legs as being like "bugs crawling under the skin." The sensation is not painful. She explains that the symptoms worsen in the evening and at night and are partially relieved with walking. She recalls that her mother had similar symptoms. Her spouse notes that she often "kicks" him in her sleep. Review of her medical history shows an otherwise healthy postmenopausal female.

What signs and symptoms are suggestive of RLS in J.J.? What laboratory tests or diagnostic procedures should be performed in J.J. to evaluate her condition?

RLS, also known as Willis–Ekbom disease, is a disabling sensorimotor disorder with an estimated prevalence of ~3.9% to 14.3% of the adult population and generally increases by age.[178] Although most patients with mild symptoms will not require treatment, RLS can be associated with adverse health outcomes, including sleep-onset insomnia, missed or late work, anxiety, depression, marital discord, and even suicide in severe cases.

Four essential criteria have been established by the International Restless Legs Syndrome Study Group to diagnose RLS (**Table 59-7**).[179] The pathognomonic trait of RLS is an almost irresistible urge to move the legs (akathisia), often associated with uncomfortable paresthesias or dysesthesias felt deep inside the limbs. Patients describe the sensation as "creepy-crawly, tingling, pulling, or painful" deep inside the limbs or "like soda water in the veins."[180] The symptoms may occur unilaterally or bilaterally, affecting the ankle, knee, or entire lower limb. With progressive disease, symptoms can begin earlier in the day, and progressive involvement of the arms or trunk may occur. Temporary or partial relief of symptoms can be achieved with movement. If patients attempt to ignore the urge to move the legs, akathisia will progressively intensify until either they move their legs or the legs jerk involuntarily.[180] Insomnia, especially having difficulty initiating sleep, is the most common reason for a patient with RLS to seek medical attention. Symptoms usually manifest in a circadian pattern with onset or worsening during nighttime hours (usually between 6 PM and 4 AM, with peak symptoms between midnight and 4 AM). The circadian pattern persists even in patients with inverted sleep–wake cycles. As a result of their symptoms, patients with RLS become "nightwalkers," spending significant time walking, stretching, or bending the legs in an effort to relieve symptoms.

Table 59-7

Clinical Features of Restless Legs Syndrome

Essential Criteria
Urge to move legs, associated with paresthesias or dysesthesias
Relief of symptoms with movement
Onset or exacerbation of symptoms at rest
Onset or worsening of symptoms during nighttime
Supportive Clinical Features
Accompanying sleep disturbance (sleep-onset insomnia)
Periodic leg movements
Positive response to dopaminergic therapy
Positive family history of RLS
Otherwise normal physical examination

RLS, restless legs syndrome.

The symptoms described by J.J. are an example of a classic presentation of RLS. The prevalence of RLS increases with age and is twice as more common in females than males.[181] She describes “creepy-crawly” sensations that are relieved partially with walking, a core feature of RLS. Her symptoms are worse during the evening hours. J.J. reports that her mother suffered from similar symptoms. The observation of a familial tendency suggests a genetic component, and several chromosomal loci have been linked to the disease.[182] A strong family history of RLS appears to correlate with an early age of onset (<45 years), whereas presentation at a later age is associated with more neuropathy and accelerated disease progression.[180]

Most cases of RLS are considered primary or idiopathic; therefore, the diagnosis does not require elaborate laboratory tests or diagnostic procedures. Several conditions are associated with RLS and include iron deficiency, pregnancy, and end-stage renal disease. Several medications and substances are known aggravators of RLS, including medications with antidopaminergic properties, such as metoclopramide and prochlorperazine. Nicotine, caffeine, and

alcohol can aggravate RLS through their own ability to interfere with quality of sleep. Additionally, SSRIs, TCAs, and commonly used over-the-counter antihistamines, such as diphenhydramine, can trigger or worsen RLS symptoms.[182] Hypotensive akathisia, leg cramps, and other conditions such as arthritis, which can cause positional discomfort with extended periods of sitting in one position, can mimic RLS. These conditions are easily distinguished from RLS because they are usually localized to certain joints or muscles, do not have a circadian pattern, and are not associated with an uncontrollable urge to move.

With an otherwise unremarkable physical examination and medical history, specific laboratory tests that should be performed in J.J. are limited to serum ferritin and percent transferrin saturation (total iron-binding capacity [TIBC]) to rule out iron deficiency anemia. Several studies have documented a relationship between low ferritin concentrations and increased symptom severity.[183] J.J. is postmenopausal, so a pregnancy test is not necessary. Polysomnography is not usually indicated unless there is clinical suspicion for sleep apnea or if sleep remains disrupted despite treatment of RLS. When clinical suspicion from the physical examination or medical history suggests a possible peripheral nerve or radiculopathy cause, a routine neurologic panel should be obtained.[182] In end-stage renal failure, screening for uremia should be considered because this can trigger symptoms.

Case 59-4, Question 2: What is the difference between RLS and PLMS?

In addition to the presence of RLS, the symptoms reported by the spouse of J.J. are likely related to PLMS. These are also known as nocturnal myoclonus and are best described as involuntary clonic-type movements of the lower extremities while sleeping that usually involve bilateral ankle dorsiflexion, knee flexion, and hip flexion. Approximately 80% of patients with RLS also have PLMS, but PLMS can occur by itself and is also associated with significant sleep dysfunction. The diagnosis of PLMS usually requires a

polysomnogram; the universally accepted criteria for diagnosis are that there should be at least four periodic leg movements (PLMs) in a 90-second period, with contractions typically lasting 0.5 to 5 seconds and recurring every 5 to 90 seconds.[184] A PLM index (PLMI) is calculated by dividing the total number of PLMs by sleep time in hours; an index of >5 but <25 is considered mild, a PMLI of >25 and <50 is moderate, and a PLMI of >50 is severe. The diagnosis of PLM disorder can be made when patients present with insomnia, tiredness, and daytime sleepiness in the presence of a high PLMI.[185] There is considerable overlap in the treatments of PLMS and RLS. Because J.J. clearly has RLS, there is no need to perform a polysomnogram. The diagnosis of PLMS in her case is incidental and would not alter the clinical management. An exception to this would be whether her medical history revealed the possibility of sleep apnea, because there is a high association between PLMS and upper airway resistance.[186]

Treatment

Case 59-4, Question 3: The decision is made to initiate drug therapy in J.J. for the management of her symptoms. What pharmacologic therapy should be selected? What nonpharmacologic therapies should be recommended?

It is important to rule out possible reversible causes before treating RLS. Three aspects should be considered including iron deficiency (defined as ferritin <75 ng/mL or iron/TIBC ratio <20%), medications, and lifestyle changes. Iron supplements can potentially cure RLS symptoms in patients found to be iron deficient.[188,189] If J.J. is iron deficient, she should be prescribed 50 to 65 mg of elemental iron one to three times daily on an empty stomach with 200 mg of vitamin C to enhance absorption. After ruling out possible reversible causes of RLS, it is important to establish the frequency of her symptoms and to select appropriate therapy.

Several classes of medications are effective for treating RLS.[183,187–189] Dopaminergic therapies are most consistently effective

in relieving RLS symptoms, improving sleep, and reducing leg movements. High-quality evidence has found that levodopa/carbidopa improves RLS symptoms.[183,188,189] Dopamine agonists are the preferred dopaminergic class to treat RLS because they are longer acting than levodopa, which allows for more sustained efficacy and control of symptoms throughout the entire night.[183,186,187] J.J. should be started on either ropinirole (0.25 mg initially, up to 0.5–4 mg/day) or pramipexole (0.125 mg initially, up to 0.5 mg/day) because both are FDA-approved for treating RLS. Although rotigotine is approved and supported by guidelines, the transdermal formulation may limit use in the early titration phases of RLS management.[57] Several randomized, controlled clinical trials have documented efficacy of these agents in both objective and subjective ratings of improvement by patients and clinicians with either short- or long-term use.[183,187–189] Ropinirole and pramipexole do not appear to differ with regard to efficacy or adverse effects. When used for RLS, ropinirole and pramipexole should be administered 2 hours before bedtime. Adverse effects are similar to those seen with the use of these agents in PD, and patients should be counseled accordingly.

Other medications may also provide benefit in RLS. Guidelines recommend the use of pregabalin and gabapentin enacarbil.[183,187–189] A recent double-blind study over 12 weeks compared the efficacy of pregabalin, pramipexole, and placebo, demonstrating a better efficacy of pregabalin rather than dopamine agonist or placebo.[190] Efficacy varied based on drug dosages. As a result of their mechanisms of action, these agents may be helpful if J.J. had RLS involving neuropathic pain or if she could not tolerate dopaminergic therapy. Although studied, there are inconclusive data to support the use of benzodiazepines, opiates (tramadol, methadone), anticonvulsants, clonidine, iron, folate, vitamin B_{12}, magnesium, vitamin E, and botulinum toxin.[183,187–189] Opiates may be helpful in patients who experience significant pain related to RLS, but these agents have not proven to conclusively treat RLS symptoms. Opiates are also associated with an increased risk of abuse potential

and should be avoided, especially along with benzodiazepines, alcohol, and other illicit drugs.[183,187,188,190] Risks associated with the use of opiates, including respiratory depression and addiction, should be reviewed with the patient prior to initiation. Benzodiazepines and opiates should be strongly avoided in concomitant sleep apnea because of their ability to suppress respiratory drive resulting in respiratory depression including death as well as abuse potential.

In addition to pharmacologic therapy, nonpharmacologic therapies and behavioral techniques should also be recommended for J.J. Most important among these include discontinuing all RLS aggravators (ie, sleep deprivation, alcohol or tobacco use, decreased mobility) and practicing good sleep hygiene. Physical and mental activity (eg, reading, playing card games, or working on the computer) if patients are unable to sleep can reduce symptoms.[182] Counter stimuli such as massage or hot baths may also be helpful.[182]

Case 59-4, Question 4: After carefully considering the costs of therapy, J.J. and her physician choose levodopa to treat her RLS instead of a dopamine agonist. She initially responds well to the therapy. One year later, J.J. returns for follow-up. Her dose of carbidopa/levodopa has progressively increased to three 25 mg/100 mg tablets at bedtime. She describes continued worsening of her symptoms that do not seem to be relieved with increasing doses of carbidopa/levodopa. Her symptoms are now starting earlier in the evening, occur almost every night, and are now painful. How should her therapy be further adjusted?

J.J. is likely experiencing augmentation, a common problem with long-term use of dopaminergic drugs, particularly levodopa.[191] Augmentation is described as a progressive worsening of RLS symptoms after an initial improvement and is manifested by gradually intensified symptoms that occur earlier in the evening and spread to other parts of the body.[192] It is the most common side effect occurring with long-term use (>3 months) of dopaminergic agents and usually occurs 6 to 18 months after therapy is initiated.[182] Doses of dopaminergic agents are often increased in response; however, with each incremental dose increase, symptoms progress

more rapidly until they may occur continuously throughout the day.[182] Although augmentation has been clinically recognized for many years, it has not been systematically studied. The exact etiology is uncertain, but it likely relates to the finding that RLS, unlike PD, is actually a hyperdopaminergic condition with an apparent postsynaptic desensitization that overcompensates during the circadian low point of dopaminergic activity in the evening and night. Adding dopamine in the evening initially corrects the symptoms, but ultimately leads to increasing postsynaptic desensitization.

The highest risk for augmentation is with levodopa. An estimated 50% to 85% of patients on levodopa will develop augmentation, compared with only 20% to 30% with dopamine agonists.[193] The primary treatment strategy for the management of augmentation is to withdraw the dopaminergic agent and substitute this with nondopaminergic agents. Given her presentation, J.J. should have her carbidopa/levodopa discontinued. She should be counseled that her symptoms will likely rebound severely for 48 to 72 hours, but ~4 to 7 days later, her symptoms should gradually return to baseline or pretreatment state.[182]

With the discontinuation of carbidopa/levodopa in J.J., an alternative therapy should be selected. The selection of an alternative agent in cases in which the initial therapy failed or augmentation occurs must be approached on an individual basis. Although a number of agents are available to choose from, clinical experience generally guides the decision because lack of comparative trials precludes development of any formal recommendations. Because J.J. describes increasing pain with her RLS, it would be appropriate to initiate a trial of gabapentin enacarbil or pregabalin. If ineffective or not tolerated, J.J. could be prescribed an opiate to manage her pain. Hydrocodone, oxycodone, methadone, codeine, and tramadol have all been evaluated in RLS.[182] Risks associated with opiate use, including respiratory depression and addiction, should be discussed in detail with J.J. prior to initiation. Augmentation does not prevent a future reintroduction of dopaminergic therapy; in the case of J.J., a dopamine agonist could be added after an extended dopaminergic

free period if her symptoms are not completely controlled with nondopaminergic agents or if her symptoms were not painful.

ESSENTIAL TREMOR

Clinical Presentation

CASE 59-5

QUESTION 1: K.H. is a 52-year-old White female office manager who was referred to a neurologist for evaluation of bilateral tremor. She is otherwise healthy and reports not taking any regularly prescribed medications. She describes her tremor as being present mainly when she performs voluntary movements. The tremor is not noticeable during rest. She also notices that the tremor seems to disappear in the evening after drinking a couple of glasses of wine. The tremor interferes with several of her ADLs, including writing, eating, drinking from a cup, and inserting her keys into the ignition. She reports mild interference with her job function and some social embarrassment. No bradykinesia or rigidity is elicited on physical examination. A handwriting sample reveals large characters that are difficult to decipher. Family history reveals that her maternal grandmother and mother both had similar symptoms.

What signs and symptoms are consistent with ET in K.H.?

Beginning in the mid-20th century, the term ET has been consistently used to describe a kinetic tremor for which no definite cause has been established. ET is a common neurologic disorder with an estimated incidence of 616 cases/100,000 person-years and a prevalence of about 0.9% to 4.6%.[194,195] Despite its prevalence, it is underrecognized and undertreated likely because it has been traditionally viewed as a monosymptomatic disorder of little consequence. More recently, it is recognized to be complex and progressive, which has resulted in significant disability in ADLs, job performance, and social embarrassment.[194] Both the incidence and prevalence of ET increase with age. Additionally, ethnicity and family history of ET are consistently identified risk factors. These risk factors are approximately five times more common in Whites than

Blacks, and ~50% of patients report a positive family history. The latter finding suggests that genetic predisposition may play a role in ET; however, differences in intrafamilial onset and severity suggest environmental factors may also influence underlying susceptibility to the disease. Several environmental toxins have been proposed as causes of ET, including β-carboline alkaloids (eg, harmane and harmine) and lead, both of which have been found in elevated concentrations in patients with ET compared with normal control subjects.[196–198]

Because parkinsonian tremor and ET are the most common forms of tremor observed in practice, it is important to distinguish between these two because the treatments differ substantially. Tremor should first be identified as either an action (ie, kinetic, postural, and isometric) or resting tremor. The defining feature of ET is a bilateral, largely symmetrical, 5- to 10-Hz kinetic and postural tremor of the arms. The tremor can also affect the head or voice. The symptoms must be present for >5 years and must not be attributable to other causes such as tremorogenic drugs.[197] Although both kinetic and postural action tremors can be present in ET and PD, the presence of resting tremor is much more common in PD. Lack of resting tremor and absence of bradykinesia or rigidity in K.H. suggests the tremor is not parkinsonian. She describes interference of her tremor occurring with voluntary movement such as with her ADLs and drinking from a cup. Other signs and symptoms that support a diagnosis of ET include her age, family history, large and tremulous handwriting (as opposed to micrographia in PD), and improvement in tremor with alcohol consumption. **Table 59-8** summarizes the similarities and differences of ET and parkinsonian tremor.

Table 59-8
Differentiation of Essential Tremor and Parkinson Disease

Characteristic	Essential Tremor	Parkinson Disease
Kinetic tremor areas frequently involved	Neck, voice	Mouth/ tongue, jaw, leg
Hemibody (arm and leg) tremor	0	++

Kinetic tremor > resting tremor	++	+
Resting tremor > kinetic tremor	0	++
Rigidity or bradykinesia	0	++
Postural instability	0	++
Usual age of onset (years)	15–25, 45–55	55–65
Symmetry	Bilateral	Unilateral > bilateral
Family history of tremor	+++	+
Response to alcohol	+++	0
Response to rest	+++	0
Response to activity	0	+++
Response to anticholinergics	0	++
Response to levodopa	0	+++
Response to primidone	+++	0
Response to propranolol	+++	+
Handwriting analysis	Large, tremulous script	Micrographia
Voice (when affected)	Intensity fluctuations	Hypophonic

0, Not observed; +, rarely observed; ++, sometimes observed; +++, often observed.

Several medications and substances are known to cause tremor, and all patients should have thorough medication history to rule out these causes. Medications commonly implicated include corticosteroids, metoclopramide, valproate, sympathomimetics (eg, albuterol, amphetamines, pseudoephedrine), SSRIs, TCAs, theophylline, and thyroid preparations.[199,200] In addition, caffeine, tobacco, and chronic alcohol use can cause tremor that resembles ET. K.H. does not report taking any regularly prescribed medications; however, she should be questioned regarding any over-the-counter medication use as well as her alcohol use and caffeine and smoking habits.

The diagnosis of ET is based solely on clinical examination and neurologic history. Neuroimaging is not useful, and there are no available biologic markers or diagnostic tests that are specific to ET.

The evaluation of the tremor that K.H. is experiencing should include laboratory analysis to rule out possible medical conditions associated with tremor. Such conditions may include the presence of hyperthyroidism or Wilson disease (particularly in patients younger than 40 years of age).[199,200]

Treatment

Case 59-5, Question 2: What therapies are effective in treating ET? How should K.H. be treated?

Patients with ET who have a mild disability that does not cause functional impairment or social embarrassment can go without treatment. Because K.H. is experiencing tremor that is interfering with her occupation and causing social embarrassment, she should be considered for pharmacotherapy (**Table 59-9**). It is important to note that although effective treatments exist, tremor is rarely eliminated completely. Factors predicting lack of response have not been readily identified.

Table 59-9
Pharmacotherapy for Essential Tremor

Drug	Initial Dose	Usual Therapeutic Dose	Adverse Effects
β-Blockers			
Propranolol	10 mg every day to bid	120–320 mg divided every day to bid-tid; LA given once daily	Bradycardia, bronchospasm, fatigue, hypotension, lightheadedness, exercise intolerance, sexual dysfunction, depression
Atenolol	12.5–25 mg every day	50–150 mg every day	Bradycardia, fatigue, hypotension, exercise intolerance
Nadolol	40 mg every day	120–240 mg every day	Bradycardia, fatigue, hypotension, exercise intolerance
Anticonvulsants			
Gabapentin	300 mg every day in single or divided doses	1200–3600 mg divided tid	Nausea, drowsiness, dizziness, unsteadiness, weight gain, peripheral edema, potential for abuse
Pregabalin	75 mg bid	75–300 mg divided bid	Weight gain, dizziness, drowsiness, potential for abuse
Primidone	12.5 mg every day at bedtime	50–750 mg divided every day to tid	Sedation, fatigue, nausea, vomiting, malaise, ataxia, dizziness, confusion, vertigo
Topiramate	25 mg every day	150–400 mg divided bid	Appetite suppression, weight loss, paresthesias, concentration difficulties, nausea, fatigue, memory difficulties
Zonisamide	100 mg every day	225 mg divided doses	Headache, nausea, fatigue/sleepiness, diarrhea
Benzodiazepines			
Alprazolam	0.125 mg every day	0.75–3 mg divided tid	Sedation, fatigue, ataxia, dizziness, potential for misuse
Clonazepam	0.25 mg every day	0.5–2 mg divided every day to bid	Sedation, fatigue, ataxia, dizziness, impaired cognition, potential for misuse
Miscellaneous			
Botulinum toxin A	Varies by injection site: 50–100 units/arm for hand tremor; 40–400 units/neck for head tremor; 0.6–15 units/vocal cords for voice tremor; repeat no sooner than every 3 months (extend as long as possible)		Hand weakness (with wrist injection); dysphagia, hoarseness, breathiness (with neck or vocal cord injection)
Clozapine	12.5–25 mg every day	25–75 mg every day or divided every day to bid	Sedation, QT prolongation, orthostatic hypotension
Nimodipine	30 mg every day	120 mg every day	Hypotension, diarrhea, dyspepsia
Olanzapine	5 mg every day	10–20 mg every day or divided every day to bid	Weight gain, somnolence, extrapyramidal symptoms

bid, two times daily; tid, three times daily.

Propranolol, a nonselective β-adrenergic receptor blocker, or primidone, an anticonvulsant, are recommended as first-line agents to treat ET.[196,197] Propranolol is typically effective in doses of at least 120 mg/day with about 50% of patients having long-lasting benefit.[201] Long-acting propranolol is as effective as the regular-release formulation. Other β_1-selective blockers such as atenolol and metoprolol have also been studied but with mixed findings.[198,201,202] Propranolol has demonstrated greater efficacy than these β_1-selective agents, which suggests that blockade of β_2-receptors is of importance. β-Adrenergic receptor blockers with intrinsic sympathomimetic activity, such as pindolol, appear ineffective in ET.[198–202] Caution should be exercised with propranolol in patients with asthma, congestive heart failure, diabetes mellitus where signs

as well as symptoms of hypoglycemia can be masked, and atrioventricular block.

Several studies have compared propranolol and primidone in ET, and they are considered to have similar efficacy.[201–203] Primidone is metabolized to a phenobarbital-based metabolite; however, phenobarbital is inferior to primidone in treating ET.[203] Acute adverse effects of primidone include nausea, vomiting, and ataxia, which can occur in up to one-fourth of patients, often limiting its use.[201] A double-blind, comparative study showed that all doses were beneficial for ET; however, lower doses (250 mg) were as effective or better than higher dosages (750 mg).[204] Primidone should be initiated at 12.5 mg/day and administered at bedtime to reduce the occurrence of acute side effects. It can be titrated gradually as tolerated up to 750 mg/day in divided doses, although side effects become more common at doses >500 mg/day.[201]

Other agents that have demonstrated variable efficacy in ET include gabapentin, pregabalin, topiramate, zonisamide, clozapine, olanzapine, nimodipine, and benzodiazepines (specifically, alprazolam and clonazepam).[170–172] They are generally considered to be less-proven, second-line or third-line therapies. Adverse effects and potential for abuse should be considered when an agent is selected.

If oral pharmacotherapy options for ET are not beneficial, intramuscular injections of botulinum toxin A or surgical treatments can be used in selected patients.[170] Targeted botulinum toxin A injections can reduce hand, head, and voice tremor; however, they are associated with focal weakness of the adjacent areas.[169] Injections in the wrist can cause hand weakness, and dysphagia, hoarseness, and breathiness can occur with injections into the neck or vocal cords. The use of botulinum toxin injections in the United States is also limited by cost. Treatment should occur with the lowest dose, and the interval should be as long as possible between injections. DBS of the ventral intermediate nucleus of the thalamus or unilateral thalamotomy is possibly efficacious in reducing ET.[170] Greater improvement in self-reported measures of function and fewer adverse events make DBS the preferred surgical option of the

two.[170] Other therapies are being evaluated, including implantation in the caudal zona incerta (cZI) (alternative to ViM), lesional surgery (MRI-guided high-intensity focused ultrasound [MRIgFUS]) (less invasive than DBS), and perampanel.

Because K.H. is otherwise healthy, she is a good candidate for propranolol therapy. Propranolol can be initiated as needed or on a scheduled basis depending on the degree of impairment and desire of the patient. If the decision is made with K.H. to use propranolol on an as-needed basis, she should begin with one-half of a 20-mg tablet administered 30 minutes to 1 hour before the desired effect. The dose can be increased from one-half to two tablets. An example of a situation in which this may occur is whether she wants to avoid embarrassment with attending a social activity or before certain tasks requiring manual dexterity at work. Given the degree of her impairment, she is probably a better candidate for chronic suppressive therapy with propranolol. In this situation, she can be prescribed 10 mg twice daily, because it can be safely and easily uptitrated every few days to a minimally effective dose, generally not >120 to 360 mg/day in divided doses.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Ciulla M, Marinelli L, Cacciatore I, Stefano AD. Role of dietary supplements in the management of Parkinson's disease. *Biomolecules.* 2019;9(7):271. doi:10.3390/biom9070271 (151)

Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. *Eur J Neurol.* 2013;20:5–15. (24)

Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2018;33(8):1248–1266. (21)

Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, et al; European Federation of Neurological Societies; European Neurological Society; European Sleep Research Society. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. *Eur J Neurol.* 2012;19(11):1385–1396. (187)

Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med.* 2013;14(7): 675–684. (186)

Grimes D, Fitzpatrick M, Gordon J, et al. Canadian guideline for Parkinson disease. *CMAJ*. 2019;191:E989–E1004. (22)

Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2002;58:11–17. (18)

Miyasaki JM, Shannon K, Voon V, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson's disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;66:996–1002. (165)

National Collaborating Centre for Chronic Conditions. Parkinson's disease in adults. Published July 19, 2017. Accessed June 2022. https://www.nice.org.uk/guidance/ng71 (20)

Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;66:983–995. (19)

PD Med Collaborative Group, Gray R, Ives N, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase-B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomized trial. *Lancet.* 2014;384(9949): 1196–1205. (33)

Rughani A, Schwalb JM, Sidiropoulos C, et al. Congress of neurological surgeons systematic review and evidence-based guideline on subthalamic nucleus and globus pallidus internus deep brain stimulation for the treatment of patients with Parkinson's disease: executive summary. *Neurosurgery.* 2018;82(6):753–756. (138)

Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2011;77(19): 1752–1755. (201)

Zesiewicz TA, Sullivan KL, Arnulf I, et al. Practice parameter: treatment of non-motor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2010;74(11):924–931. (158)

COMPLETE REFERENCES CHAPTER 59 PARKINSON DISEASE AND OTHER MOVEMENT DISORDERS

1. Rao G, Fisch L, Srinivasan S, et al. Does this patient have Parkinson disease? *JAMA*. 2003;289:347–353.
2. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol*. 2016;15(12):1257–1272.
3. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol*. 2003;157:1015–1022.
4. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. *Mov Disord*. 2003;18:19–31.
5. Hirsch L, Jette N, Frolkis A, Steeves T, Prinsheim T. The incidence of Parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology*. 2016;46:292–300.
6. Fall PA, Saleh A, Fredrickson M, Olsson JE, Granérus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. *Mov Disord*. 2003;18:1312–1316.
7. Suchowersky O, Reich S, Perlmutter J, et al. Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66:968–975.
8. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006;5(6):525–535.
9. Sanyal J, Chakraborty DP, Sarkar B, et al. Environmental and familial risk factors of Parkinson's disease: a case-control study. *Can J Neurol Sci*. 2010;37:637–642.
10. Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol*. 2012;72(6):893–901. doi:10.1002/ana.23687
11. Morley JF, Hurtig HI. Current understanding and management of Parkinson disease: five new things. *Neurology*. 2010;75(18, suppl 1):S9–S15.

12. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. *Ageing Res Rev*. 2018;42:72–85.
13. Vance JM, Ali S, Bradley WG, Singer C, Di Monte DA. Gene-environment interactions in Parkinson's disease and other forms of parkinsonism. *Neurotoxicology*. 2010;31:598–602.
14. Nutt JG, Wooten GF. Clinical practice. Diagnosis and initial management of Parkinson's disease. *N Engl J Med*. 2005;353:1021–1027.
15. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003;24:197–211.
16. Savica R, Rocca WA, Ahlskog JE. When does Parkinson disease start? *Arch Neurol*. 2010;67:798–801.
17. Massano J, Bhatia KP. Clinical approach to Parkinson's disease: features, diagnosis, and principles of management. *Cold Spring Harb Perspect Med*. 2012;2(6):a008870.
18. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2002;58:11–17.
19. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66:983–995.
20. National Collaborating Centre for Chronic Conditions. Parkinson's disease in adults. Published July 19, 2017. Accessed June 2022. https://www.nice.org.uk/guidance/ng71
21. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248–1266.
22. Grimes D, Fitzpatrick M, Gordon J, et al. Canadian guidelines for Parkinson disease. *CMAJ.* 2019;191:E989–E1004.
23. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology*. 2001;56(11 suppl 5):S1–S88.
24. Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. *Eur J Neurol*. 2013;20:5–15.
25. Shannon KM, Bennett JP Jr, Friedman JH. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. The Pramipexole Study Group [published correction appears in *Neurology*. 1998;50:838]. *Neurology*. 1997;49:724–728.

26. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. *N Engl J Med*. 2000;342:1484–1491.
27. Holloway RG, Shoulson I, Fahn S, et al. Pramipexole vs levodopa as initial treatment for Parkinson's disease: a 4-year randomized controlled trial [published correction appears in *Arch Neurol*. 2005;62:430]. *Arch Neurol*. 2004;61:1044–1053.
28. Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson disease: a randomized controlled trial. Parkinson Study Group. *JAMA*. 2000;284:1931–1938.
29. Parkinson Study Group CALM Cohort Investigators. Long term effect of initiating pramipexole vs levodopa in early Parkinson disease. *Arch Neurol*. 2009;66:563–570.
30. Hauser RA, Rascol O, Korczyn AD, et al. Ten-year follow-up of Parkinson's disease patients randomized to initial therapy with ropinirole or levodopa. *Mov Disord*. 2007;22:2409–2417.
31. Katzenschlager R, Head J, Schrag A, et al. Parkinson's Disease Research Group of the United Kingdom. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. *Neurology*. 2008;71(7):474–480.
32. Macleod AD, Counsell CE, Ives N, Stowe R. Monoamine oxidase B inhibitors for early Parkinson's disease. *Cochrane Database Syst Rev.* 2005;2005(3):CD004898.
33. PD Med Collaborative Group, Gray R, Ives N, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomized trial. *Lancet*. 2014;384(9949):1196–1205.
34. Ives NJ, Stowe RL, Marro J, et al. Monoamine oxidase type B inhibitors in early Parkinsons's disease: meta-analysis of 17 randomised trials involving 3525 patients. *Br Med J*. 2004;329(7466):593–596.
35. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac valve regurgitation. *N Engl J Med*. 2007;356:29–38.
36. Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med*. 2007;356:39–46.
37. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev*. 2011;63(1):182–217.
38. Mirapex. Package insert. Boehringer Ingelheim Pharmaceuticals; 2015.
39. Hubble JP, Koller WC, Cutler NR, et al. Pramipexole in patients with early Parkinson's disease. *Clin Neuropharmacol*. 1995;18:338–347.

40. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson's disease. A randomized dose-ranging study. Parkinson Study Group. *JAMA*. 1997;278:125–130.
41. Requip. Package insert. GlaxoSmithKline; 2014.
42. Rascol O, Brooks DJ, Brunt ER, Korczyn AD, Poewe WH, Stocchi F. Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa controlled study. 056 Study Group. *Mov Disord*. 1998;13:39–45.
43. Korczyn AD, Brooks DJ, Brunt ER, Poewe WH, Rascol O, Stocchi F. Ropinirole versus bromocriptine in the treatment of early Parkinson's disease: a 6-month interim report of a 3-year study. 053 Study Group. *Mov Disord*. 1998;13:46–51.
44. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol*. 2003;60:1721–1728.
45. Güldenpfennig WM, Poole KH, Sommerville KW, Boroojerdi B. Safety, tolerability, and efficacy of continuous transdermal dopaminergic stimulation with rotigotine patch in early-stage idiopathic Parkinson disease. *Clin Neuropharmacol*. 2005;28:106–110.
46. Watts RL, Jankovic J, Waters C, Rajput A, Boroojerdi B, Rao J. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease [published corrections appear in *Neurology*. 2007;69:2187; *Neurology*. 2007;69:617]. *Neurology*. 2007;68:272–276.
47. Giladi N, Boroojerdi B, Korczyn AD, et al. Rotigotine transdermal patch in early Parkinson's disease: a randomized, double-blind, controlled study versus placebo and ropinirole. *Mov Disord*. 2007;22:2398–2404.
48. LeWitt PA, Lyons KE, Pahwa R; SP 650 Study Group. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. *Neurology*. 2007;68:1262–1267.
49. Poewe WH, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomized controlled trial. *Lancet Neurol*. 2007;6:513–520.
50. Nomoto M, Nomoto M, Kondo T, et al. Rotigotine Trial Group. Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Mov Disord*. 2013;28(10):1447–1450.
51. Hauser RA, Slawek J, Barone P, et al. Evaluation of rotigotine transdermal patch for the treatment of apathy and motor symptoms in Parkinson's disease. *BMC Neurol.* 2016;16:90.
52. Zhou CQ, Zhang JW, Wang M, Peng GG. Meta-analysis of the efficacy and safety of long-acting non-ergot dopamine agonists in Parkinson's disease. *J Clin Neurosci*. 2014;21(7):1094–1101.
53. Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinsons disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology*. 1997;49:162–168.

54. Elmer LW, Surmann E, Boroojerdi B, Jankovic J. Long-term safety and tolerability of rotigotine transdermal system in idiopathic Parkinson's disease: a prospective, open label extension study. *Parkinsonism Relat Disord*. 2012;18(5):488–493.
55. Chung SJ, Kim JM, Kim JW, et al. Switch from oral pramipexole or ropinirole to rotigotine transdermal system in advanced Parkinson's disease: an open-label study. *Expert Opin Pharmacother*. 2105;16(7):961–970.
56. Adler CH, Sethi KD, Hauser RA, et al. Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group. *Neurology*. 1997;49:393–399.
57. Lieberman A, Olanow CW, Sethi K, et al. A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. Ropinirole Study Group [published correction appears in *Neurology*. 1999;52:435]. *Neurology*. 1998;51:1057–1062.
58. Homann CN, Wenzel K, Suppan K, et al. Sleep attacks in patients taking dopamine agonists: review. *BMJ*. 2002;324(7352):1483–1487.
59. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*. 2010;67:589–595.
60. Avanzi M, Baratti M, Cabrini S, Uber E, Brighetti G, Bonfà F. Prevalence of pathological gambling in patients with Parkinson's disease. *Mov Disord*. 2006;21:2068–2072.
61. O'Sullivan SS, Evans AH, Lees AJ. Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management. *CNS Drugs*. 2009;23(2):157–170.
62. Evans AH, Lawrence AD, Potts J, Appel S, Lees AJ. Factors influencing susceptibility to compulsive dopaminergic drug use in Parkinson disease. *Neurology*. 2005;65:1570–1574.
63. Ceravolo R, Frosini D, Rossi C, Bonuccelli U. Spectrum of addictions in Parkinson's disease: from dopamine dysregulation syndrome to impulse control disorders. *J Neurol*. 2010;257(suppl 2):S276–S283.
64. Mizuno Y, Takubo H, Mizuta E, Kuno S. Malignant syndrome in Parkinson's disease: concept and review of the literature. *Parkinsonism Relat Disord*. 2003;9(suppl 1):S3–S9.
65. Newman EJ, Grosset DG, Kennedy PG. The parkinsonism-hyperpyrexia syndrome. *Neurocrit Care*. 2009;10(1):136–140.
66. Zelapar. Package insert. Valeant Pharmaceuticals North America LLC; 2014.
67. Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1989;321:1364–1371.
68. Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1993;328:176–183.

69. Shoulson I, Oakes D, Fahn S, et al. Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial. *Ann Neurol*. 2002;51:604–612.
70. Palhagen S, Heinonen EH, Hägglund J, et al. Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group. *Neurology*. 1998;51:520–525.
71. Knudsen GD. Selegiline and rasagiline: twins or distant cousins? *Consult Pharm*. 2011;1(4):48–51.
72. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO study. *Arch Neurol*. 2002;59:1937–1943.
73. Parkinson Study Group. A controlled, randomized, delayed start study of rasagiline in early Parkinson disease. *Arch Neurol*. 2004;61:561–566.
74. Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med*. 2009;361:1268–1278.
75. Peretz C, Segev H, Rozani V, et al. Comparison of selegiline and rasagiline therapies in Parkinson disease: a real-life study. *Clin Neuropharmacol*. 2016;39(5):227–231. doi:10.1097/WNF.0000000000000167
76. Cereda E, Cilia R, Canesi M, et al. Efficacy of rasagiline and selegiline in Parkinson's disease: a head-to-head 3-year retrospective case-control study [published correction appears in *J Neurol*. 2017 Sept;264:2051]. *J Neurol*. 2017;264(6):1254–1263. doi:10.1007/s00415-017-8523-y
77. Marconi S, Zwingers T. Comparative efficacy of selegiline versus rasagiline in the treatment of early Parkinson's disease. *Eur Rev Med Pharmacol Sci*. 2014; 18(13):1879–1882.
78. Jost WH, Friede M, Schnitker J. Indirect meta-analysis of randomized placebo-controlled clinical trials on rasagiline and selegiline in the symptomatic treatment of Parkinson's disease. *Basal Ganglia*. 2012:2:S17–S26.
79. Azilect. Package insert. Teva Neuroscience; 2014.
80. deMarcaida JA, Schwid SR, White WB. Effects of tyramine administration in Parkinson's disease patients treated with selective MAO-B inhibitor rasagiline. *Mov Disord*. 2006;21:1716–1721.
81. Eldepryl. Package insert. Aspen Pharmacare Australia Pty Ltd; 2010.
82. Sinemet. Package insert. Merck & Co; 2014.
83. Camargo SM, Vuille-dit-Bille RN, Mariotta L, et al. The molecular mechanism of intestinal levodopa absorption and its possible implications for the treatment of Parkinson's disease. *J Pharmacol Exp Ther*. 2014;351(1):114–123.
84. Riley DE, Lang AE. The spectrum of levodopa-related fluctuations in Parkinson's disease. *Neurology*. 1993;43:1459–1464.
85. Goodwin FK. Psychiatric side effects of levodopa in man. *JAMA*. 1971;218:1915–1920.

86. Thanvi B, Lo T. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgrad Med J*. 2004;80(946):452–458.
87. Marques de Sousa S, Massano J. Motor complications in Parkinson's disease: a comprehensive review of emergent management strategies. *CNS Neurol Disord Drug Targets*. 2013;12:1017–1049.
88. Duodopa. Package insert. AbbVie Corporation; 2015.
89. Sinemet CR. Package insert. Merck & Co; July 2014.
90. Hauser RA, Ellenbogen AL, Metman LV, et al. Crossover comparison of IPX066 and a standard levodopa formulation in advanced Parkinson's disease. *Mov Disord*. 2011;26:2246–2252.
91. Rytary. Package insert. Impax Laboratories; 2015.
92. Hauser RA, Hsu A, Kell S, et al. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. *Lancet Neurol*. 2013;12:346–356.
93. Inbrija (levodopa). Prescribing information. Acorda Therapeutics, Inc; September 2019.
94. LeWitt PA, Hauser RA, Pahwa R, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol*. 2019;18(2):145–154.
95. Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology*. 1997;49:162–168.
96. Watts RL, Lyons KE, Pahwa R, et al. Onset of dyskinesia with adjunct ropinirole prolonged-release or additional levodopa in early Parkinson's disease. *Mov Disord*. 2010;25:858–866.
97. Hersh BP, Earl NL, Hauser RA, Stacy M. Early treatment benefits of ropinirole prolonged release in Parkinson's disease patients with motor fluctuations. *Mov Disord*. 2010;25:927–931.
98. Stocchi F, Giorgi L, Hunter B, Schapira AH. PREPARED: comparison of prolonged and immediate release ropinirole in advanced Parkinson's disease. *Mov Disord*. 2011;26(7):1259–1265.
99. Apokyn. Package insert. US World Meds, LLC; 2014.
100. Olanow CW, Factor SA, Espay AJ, et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomized, double-blind, placebo-controlled phase 3 study. *Lancet Neurol*. 2020;19(2):135–144.
101. Schwab RS, England AC Jr, Poskanzer DC, Young RR. Amantadine in the treatment of Parkinson's disease. *JAMA*. 1969;208:1168–1170.
102. Fahn S, Isgreen WP. Long-term evaluation of amantadine and levodopa combination in parkinsonism by double-blind crossover analyses. *Neurology*. 1975;25:695–700.

103. Bailey EV, Stone TW. The mechanism of action of amantadine in Parkinsonism: a review. *Arch Int Pharmacodyn Ther*. 1975;216:246–262.
104. Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, Chase TN. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology*. 1998;50:1323–1326.
105. Metman LV, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch Neurol*. 1999;56:1383–1386.
106. Snow BJ, Macdonald L, Mcauley D, Wallis W. The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: a double-blind, placebo-controlled study. *Clin Neuropharmacol*. 2000;23:82–85.
107. Thomas A, Iacono D, Luciano AL, Armellino K, Di Iorio A, Onofrj M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004;75:141–143.
108. Ory-Magne F, Corvol JC, Azulay JP, et al. NS-Park CIC Network. Withdrawing amantadine in dyskinetic patients with Parkinson disease: the AMANDYSK trial. *Neurology*. 2014;82(4):300–307.
109. Crosby N, Deane KH, Clarke CE. Amantadine in Parkinson's disease. *Cochrane Database Syst Rev*. 2003;(1):CD003468.
110. Symmetrel. Package insert. Endo Pharmaceuticals; 2009.
111. Tasmar. Package insert. Valeant Pharmaceuticals North America, LLC; 2013.
112. Comtan. Package insert. Novartis Pharmaceuticals Corporation; 2014.
113. De Santi C, Giulianotti PC, Pietrabissa A, Mosca F, Pacifici GM. Catechol-O-methyltransferase: variation in enzyme activity and inhibition by entacapone and tolcapone. *Eur J Clin Pharmacol*. 1998;54:215–219.
114. Ongentys (opicapone). Prescribing information. Neurocrine Biosciences Inc; April 2020.
115. Stocchi F, Rascol O, Kieburtz K, et al. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study [published correction appears in *Ann Neurol*. 2010;68:412]. *Ann Neurol*. 2010;68:18–27.
116. Rinne UK, Larsen JP, Siden A, Worm-Petersen J. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. *Neurology*. 1998;51:1309–1314.
117. Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients [published correction appears in *Ann Neurol*. 1998;44:292]. *Ann Neurol*. 1997;42:747–755.
118. Ferreira JJ, Lees A, Rocha JF, et al. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomized, double-blind, controlled trial. *Lancet Neurol*. 2016;15(2):154–165.

119. Lees AJ, Ferreira J, Rascol O, et al. Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol*. 2017;74(2):197–206.
120. Rocha JF, Falcão A, Santos A, et al. Effect of opicapone and entacapone upon levodopa pharmacokinetics during three daily levodopa administrations. *Eur J Clin Pharmacol*. 2014;70(9):1059–1071.
121. Ferreira JJ, Lees AJ, Poewe W, et al. Effectiveness of opicapone and switching from entacapone in fluctuating Parkinson disease. *Neurology*. 2018;90(21):e1849–e1857.
122. Gottwald MD. Entacapone, a catechol-O-methyltransferase inhibitor for treating Parkinson's disease: review and current status. *Expert Opin Investig Drugs*. 1999;8(4):453–462.
123. U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA review found no increased cardiovascular risks with Parkinson's disease drug entacapone. 2015. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-found-no-increased-cardiovascular-risks-parkinsons-disease
124. Golbe LI. Deprenyl as symptomatic therapy in Parkinson's disease. *Clin Neuropharmacol*. 1988;11:387–400.
125. Elizam TS, Yahr MD, Moros DA, Mendoza MR, Pang S, Bodian CA. Selegiline as an adjunct to conventional levodopa therapy in Parkinson's disease. Experience with this type B monoamine oxidase inhibitor in 200 patients [published correction appears in *Arch Neurol*. 1990;47:160]. *Arch Neurol*. 1989;46:1280–1283.
126. Waters CH, Sethi KD, Hauser RA, Molho E, Bertoni JM; Zydis Selegiline Study Group. Zydis selegiline reduces off-time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. *Mov Disord*. 2004;19:426–432.
127. Ongo WG, Sethi KD, Kricorian G. Selegiline orally disintegrating tablets in patients with Parkinson disease and "Wearing Off" symptoms. *Clin Neuropharmacol*. 2007;30(5):295–300.
128. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol*. 2005;62:241–248.
129. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomized, double-blind, parallel-group trial. *Lancet*. 2005;365:947–954.
130. Borgohain R, Szasz J, Stanzione P, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord*. 2014;29(2):229–237.

131. LeWitt PA, Guttman M, Tetrud JW, et al. Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces “off” time in Parkinson’s disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). *Ann Neurol*. 2008;63(3):295–302. doi:10.1002/ana.21315
132. Pourcher E, Huot P. Adenosine 2A receptor antagonists for the treatment of motor symptoms in Parkinson’s disease [published correction appears in *Mov Disord Clin Pract*. 2016 June 01;3(3):320]. *Mov Disord Clin Pract*. 2015;2(4):331–340.
133. Takahashi M, Fujita M, Asai N, Saki M, Mori A. Safety and effectiveness of istradefylline in patients with Parkinson’s disease: interim analysis of a post-marketing surveillance study in Japan. *Expert Opin Pharmacother*. 2018;19(15):1635–1642. doi:10.1080/14656566.2018.1518433
134. Sako W, Murakami N, Motohama K, Izumi Y, Kaji R. The effect of istradefylline for Parkinson’s disease: a meta-analysis. *Sci Rep*. 2017;7(1):18018. doi:10.1038/s41598-017-18339-1
135. Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchinson W. Posteroventral medial pallidotomy in advanced Parkinson’s disease. *N Engl J Med*. 1997;337:1036–1042.
136. Jankovic J, Cardoso F, Grossman RG, Hamilton WJ. Outcome after stereotactic thalamotomy for parkinsonian, essential and other types of tremor. *Neurosurgery*. 1995;37:680–687.
137. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*. 2009;301:63–73.
138. Rughani A, Schwalb JM, Sidiropoulos C, et al. Congress of neurological surgeons systematic review and evidence-based guideline on subthalamic nucleus and globus pallidus internus deep brain stimulation for the treatment of patients with Parkinson’s disease: executive summary. *Neurosurgery*. 2018;82(6):753–756. doi:10.1093/neuros/nyy037
139. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson’s disease. *N Engl J Med*. 2010;362:2077–2091.
140. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson’s disease [published correction appears in *N Engl J Med*. 2006;355:1289]. *N Engl J Med*. 2006;355:896–908.
141. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson’s disease. *N Engl J Med*. 2003;349:1925–1934.
142. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in Parkinson’s disease: a multicentre study with 4 years follow-up. *Brain*. 2005;128(Pt 10):2240–2249.
143. Storch A, Jost WH, Vieregge P, et al. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson

disease. *Arch Neurol*. 2007;64(7):938–944.
144. The NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. *Neurology*. 2007;68:20–28.
145. The Parkinson Study Group QE3 Investigators. A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease no evidence of benefit. *JAMA Neurol*. 2014;71(5):543–552.
146. The NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. *Neurology*. 2006;66:664–671.
147. The NINDS NET-PD Investigators. Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: a randomized clinical trial. *JAMA*. 2015;313(6):584–593.
148. Parkinson Study Group. DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. *Arch Neurol*. 1989;46:1052–1060.
149. McCarter SJ, Stang C, Turcano P, et al. Higher vitamin B12 level at Parkinson's disease diagnosis is associated with lower risk of future dementia. *Parkinsonism Relat Disord*. 2020;73:19–22. doi:10.1016/j.parkreldis.2020.03.009
150. Knekt P, Kilkkinen A, Rissanen H, et al. Serum vitamin D and the risk of Parkinson's disease. *Arch Neurol*. 2010;67(7):808–811.
151. Ciulla M, Marinelli L, Cacciatore I, Stefano AD. Role of dietary supplements in the management of Parkinson's disease. *Biomolecules*. 2019;9(7):271. doi:10.3390/biom9070271
152. Suzuki M, Yoshioka M, Hashimoto M, et al. Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. *Am J Clin Nutr*. 2013;97(5):1004–1013.
153. Silva TM, Munhoz RP, Alvarez C, et al. Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. *J Affect Disord*. 2008;111(2–3):351–359.
154. McFarthing K, Buff S, Rafaloff G, Dominey T, Wyse RK, Stott SRW. Parkinson disease drug therapies in the clinical trial pipeline: 2020. *J Parkinsons Dis*. 2020;10(3):757–774. doi:10.3233/JPD-202128
155. Leehey MA, Liu Y, Hart F, et al. Safety and tolerability of cannabidiol in Parkinson disease: an open label, dose-escalation study. *Cannabis Cannabinoid Res*. 2020;5(4):326–336. doi:10.1089/can.2019.0068
156. Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. *Clin Psychopharmacol Neurosci*. 2017;15(4):301–312. doi:10.9758/cpn.2017.15.4.301
157. Zhang S, Sun P, Lin K, et al. Extracellular nanomatrix-induced self-organization of neural stem cells into miniature substantia nigra-like structures with therapeutic effects on Parkinsonian rats. *Adv Sci*. 2019;6(24):1901822.

158. Zesiewicz TA, Sullivan KL, Arnulf I, et al. Practice parameter: treatment of non-motor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74:924–931.
159. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord*. 2009;24:1641–1649.
160. Chaudhuri KR, Healy DG, Schapira AH; National Institute for Clinical Excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol*. 2006;5(3):235–245.
161. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord*. 2008;23:837–844.
162. Maidment I, Fox C, Boustani M, et al. Cholinesterase inhibitors for Parkinson's disease dementia. *Cochrane Database Syst Rev*. 2006; (1):CD004747.
163. van Laar T, De Deyn PP, Aarsland D, Barone P, Galvin JE. Effects of cholinesterase inhibitors in Parkinson's disease dementia: a review of clinical trial data. *CNS Neurosci Ther*. 2011;17(5):428–441.
164. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med*. 2004;351:2509–2518.
165. Miyasaki JM, Shannon K, Voon V, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson's disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66:996–1002.
166. Litvinenko IV, Odinak MM, Mogil'naya VI, Emelin AY. Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial). *Neurosci Behav Physiol*. 2008;38(9):937–945.
167. Poewe W, Wolters E, Emre M, et al. Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: an active treatment extension study. *Mov Disord.* 2006;21(4):456–461.
168. Schmitt FA, Aarsland D, Brønnick KS, Meng X, Tekin S, Olin JT. Evaluating rivastigmine in mild-to-moderate Parkinson's disease dementia using ADAS-cog items. *Am J Alzheimers Dis Other Demen*. 2010;25(5):407–413.
169. Emre M, Tsolaki M, Bonuccelli U, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomized, double-blind, placebo-controlled trial. *Lancet Neurol*. 2010;9(10):969–977.
170. Leroi I, Overshott R, Byrne EJ, Daniel E, Burns A. Randomized controlled trial of memantine in dementia associated with Parkinson's disease. *Mov Disord*. 2009;24(8):1217–1221.
171. Madhusoodanan S, Alexeenko L, Sanders R, Brenner R. Extrapyramidal symptoms associated with antidepressants—a review of the literature and an analysis of spontaneous reports. *Ann Clin Psychiatry*. 2010;22(3):148–156.

172. Chen JJ, Marsh L. Anxiety in Parkinson's disease: identification and management. *Ther Adv Neurol Disord*. 2014;7(1):52–59.
173. Fénelon G, Alves G. Epidemiology of psychosis in Parkinson's disease. *J Neurol Sci*. 2010;289(1–2):12–17.
174. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. A 12-year population-based study of psychosis in Parkinson disease. *Arch Neurol*. 2010;67:996–1001.
175. Rich SS, Friedman JH, Ott BR. Risperidone versus clozapine in the treatment of psychosis in six patients with Parkinson's disease and other akinetic-rigid syndromes. *J Clin Psychiatry*. 1995;56:556–559.
176. Friedman JH. Parkinson's disease psychosis 2010: a review article. *Parkinsonism Relat Disord*. 2010;16:553–560.
177. Hawkins T, Berman BD. Pimavanserin: a novel therapeutic option for Parkinson disease psychosis. *Neurol Clin Pract*. 2017;7(2):157–162.
178. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. *Sleep Med Rev*. 2012;16(4):283–295.
179. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology; a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. 2003;4:101–119.
180. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med*. 2004;164:196–202.
181. Gamaldo CE, Earley CJ. Restless legs syndrome: a clinical update. *Chest*. 2006;130:1596–1604.
182. Aurora RN, Kristo DA, Bista SR, et al. Update to the AASM clinical practice guideline: "The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses." *Sleep*. 2012;35(8):1037.
183. The Atlas Task Force. Recording and scoring leg movements. *Sleep*. 1993;16:748–759.
184. Avidan AY. Parasomnias and movement disorders of sleep. *Semin Neurol*. 2009;29:372–392.
185. Baran AS, Richert AC, Douglass AB, May W, Ansarin K. Change in periodic limb movement index during treatment of obstructive sleep apnea with continuous positive airway pressure. *Sleep*. 2003;26:717–720.
186. Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med*. 2013;14(7):675–684.
187. Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, et al; European Federation of Neurological Societies; European Neurological Society; European Sleep Research Society. European guidelines on management of

restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. *Eur J Neurol*. 2012;19(11):1385–1396.

188. Högl B, García-Borreguero D, Kohnen R, et al. Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multicenter study. *J Neurol*. 2010;257:230–237.
189. Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: treatment of restless legs syndrome in adults. Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*. 2016;87:2585–2593.
190. Hubner A, Krafft A, Gadient S, Werth E, Zimmermann R, Bassetti CL. Characteristics and determinants of restless legs syndrome in pregnancy: a prospective study. *Neurology.* 2013;80:738–742.
191. García-Borreguero D, Allen RP, Kohnen R, et al. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a world association of sleep medicine—international restless legs syndrome study group consensus conference at the Max Planck Institute. *Sleep Med*. 2007;8:520–530.
192. Trenkwalder C, Hening WA, Montagna P, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord*. 2008;23:2267–2302.
193. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord*. 2010;25:534–541.
194. Benito-León J, Bermejo-Pareja F, Louis ED; Neurological Disorders in Central Spain (NEDICES) Study Group. Incidence of essential tremor in three elderly populations of central Spain. *Neurology*. 2005;64:1721–1725.
195. Lorenz D, Poremba C, Papengut F, Schreiber S, Deuschl G. The psychosocial burden of essential tremor in an outpatient-and a community-based cohort. *Eur J Neurol*. 2011;18(7):972–979.
196. Louis ED, Zheng W, Jurewicz EC, et al. Elevation of blood beta-carboline alkaloids in essential tremor. *Neurology*. 2002;59:1940–1944.
197. Louis ED, Jurewicz EC, Applegate L, et al. Association between essential tremor and blood lead concentration. *Environ Health Perspect*. 2003;111:1707–1711.
198. Deuschl G, Bain P, Brin M. Consensus statement of the movement disorder society on tremor. Ad Hoc Scientific Committee. *Mov Disord*. 1998;13(suppl 3):2–23.
199. Hedera P, Cibulcˇík F, Davis TL. Pharmacotherapy of essential tremor. *J Cent Nerv Syst Dis*. 2013;5:43–55.

200. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. *Lancet Neurol*. 2011;10:148–161.
201. Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology*. 2011; 77(19):1752–1755.
202. Zesiewicz TA, Elble R, Louis ED, et al. Practice parameter: therapies for essential tremor. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2005;5(64):2008–2020.
203. Sasso E, Perucca E, Calzetti S. Double-blind comparison of primidone and phenobarbital in essential tremor. *Neurology*. 1988;38:808–810.
204. Serrano-Dueñas M. Use of primidone in low doses (250 mg/day) versus high doses (750 mg/day) in the management of essential tremor. Double-blind comparative study with one-year follow-up. *Parkinsonism Relat Disord*. 2003;10:29–33.

60

Seizure Disorders

Sulaiman Almohaish, Melissa Sandler, Nicole E. Omecene, and Gretchen M. Brophy

CORE PRINCIPLES		CHAPTER CASES
1	Epilepsy is a disorder characterized by spontaneously recurring seizures. Seizures can arise from a focal area of the brain (focal seizures) or arise diffusely from both brain hemispheres (primary generalized seizures).	**Case 60-1 (Question 1) Case 60-9 (Question 1)**
2	The optimal choice of antiseizure drug (ASD) treatment is based on patient-specific considerations, including seizure type (or epilepsy syndrome, if defined), age, sex, concomitant medical conditions and therapies, and ASD adverse effects. Monotherapy is preferred; polytherapy should be considered for patients with multiple seizure types and/or when monotherapy	**Case 60-1 (Question 2, 3) Case 60-3 (Question 1) Case 60-4 (Question 1) Case 60-6 (Question 1) Case 60-7 (Questions 1-6) Case 60-9 (Question 2,3)**

	(with two or three agents) fails at maximal tolerated doses.	
3	Standard ASDs, such as carbamazepine, phenytoin, and valproate, are used commonly for patients with newly diagnosed epilepsy. Newer ASDs (eg, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, zonisamide, perampanel, eslicarbazepine) are often initially approved for add-on therapy in patients with focal-onset seizures who do not respond to other ASDs. Lamotrigine, oxcarbazepine, topiramate, lacosamide, and felbamate are indicated for monotherapy.	**Case 60-1 (Question 3)** **Case 60-2 (Question 1-4)** **Case 60-6 (Question 1)**
4	Enzyme-inducing ASDs (carbamazepine, phenobarbital, phenytoin) increase the metabolism of many other drugs (eg, warfarin, contraceptive hormones). In addition, carbamazepine induces its own metabolism and its levels may decline during the first month of therapy despite excellent adherence.	**Case 60-1 (Question 5,6)** **Case 60-11 (Question 1)**
5	Serious idiosyncratic adverse effects have been associated with most standard and new ASDs and include carbamazepine-associated hematologic abnormalities; lamotrigine-associated skin rash; valproate-induced hepatotoxicity; and hypersensitivity	**Case 60-1 (Question 4)** **Case 60-2 (Question 1,3)** **Case 60-5 (Question 1)** **Case 60-7 (Questions 2, 8, 9)**

	syndrome seen with carbamazepine, phenobarbital, and phenytoin. The role of routine laboratory monitoring for the detection of these adverse effects is controversial. Patients should know the signs or symptoms that should prompt them to seek medical attention.	**Case 60-10 (Question 1, 2)** **Case 60-11 (Question 2)**
6	Unlike other ASDs, phenytoin displays capacity-limited pharmacokinetics at serum concentrations that are clinically useful for epilepsy treatment. As a consequence, phenytoin blood levels often change disproportionately to changes in dosage, and time to steady state varies significantly in individual patients based on the phenytoin concentration.	**Case 60-3 (Question 2, 3)**
7	Serum concentration monitoring can be useful for selected ASDs when there is a good correlation between concentration and therapeutic or toxic responses. However, clinical criteria (seizure control, medication tolerability) are the primary determinants of the need for dosage adjustments.	**Case 60-7 (Question 7)**
8	The occurrence of seizure clusters (acute repetitive seizures) and status epilepticus (SE; prolonged or repeated seizures without recovery of consciousness) warrants emergent ASD therapy. Acute repetitive seizures are often treated by parents or caregivers with rectal diazepam. SE is a life-	**Case 60-8 (Question 1)** **Case 60-12 (Question 1–4)**

threatening emergency and should be treated with intravenous (IV) lorazepam as initial therapy.

INTRODUCTION

Approximately 10% of the population will experience a seizure at some time in their life. Up to 30% of all seizures are provoked by central nervous system (CNS) disorders or insults (eg, meningitis, trauma, tumors, and exposure to toxins); these seizures may become recurrent and require chronic treatment with antiseizure drugs (ASDs). Reversible conditions such as alcohol withdrawal, fever, and metabolic disturbances may provoke acute, isolated seizures. These seizures, along with drug-induced seizures, are not considered to be epilepsy and usually do not require long-term ASD therapy. Approximately 1% of the general population has epilepsy.[1]

TERMINOLOGY, CLASSIFICATION, AND DIAGNOSIS OF EPILEPSIES

Classification of Seizures and Epilepsies

A seizure is the "transient occurrence of signs and/or symptoms because of abnormal excessive or synchronous neuronal activity in the brain."[2] These signs or symptoms "may include alterations of consciousness, motor, sensory, autonomic, or psychic events."[1] Epilepsy is a "disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequence of this condition."[2] By definition, epilepsy requires the occurrence of two or more seizures that are not acutely provoked by other illnesses or conditions.[3] Guidelines have recently been updated to include a

patient who has had one unprovoked seizure and has a high risk (>60%) of a second seizure to be included in the definition of a person with epilepsy.[4]

Generalized Seizures

Tonic–clonic seizures affect both cerebral hemispheres. It is usually associated with loss of consciousness. In the initial tonic phase, sudden muscle spasms begin and may be accompanied by a cry that results from air being forced through the larynx. This tonic phase is followed by a clonic phase characterized by symmetric twitching movements of the bilateral muscles. After the clonic phase, patients return to consciousness but may remain lethargic and may be confused for varying periods of time (postictal state). Urinary incontinence and tongue biting are common. Primary generalized tonic–clonic seizures affect both cerebral hemispheres from the outset. Secondary generalized tonic–clonic seizures begin as focal seizures. The aura described by some patients before a generalized tonic–clonic seizure represents an initial focal seizure that spreads to become a secondary generalized seizure. Identification of secondary generalized tonic–clonic seizures is important because some ASDs are more effective at controlling primary generalized seizures than secondary generalized seizures. In general, focal seizures are often more difficult to control with ASDs as compared to primary generalized seizures. Other types of generalized seizures include myoclonic seizures (asymmetric twitching movements of muscles), clonic seizures, tonic seizures, and atonic seizures.[3,5–7]

Nonmotor/absence seizures occur primarily in children and often remit during puberty; affected patients may exhibit a second type of seizure. Absence seizures consist of a brief loss of consciousness, usually lasting several seconds. Typical absence seizures are not accompanied by motor symptoms; automatisms, muscle twitching, myoclonic jerking, or autonomic manifestations may accompany atypical absence seizures. Other types of absence seizures include myoclonic absence and eyelid myoclonia.[3,5–8]

Patients are unaware of their surroundings and will have no recall of events during the seizure. Consciousness returns immediately when the seizure ends, and postictal confusion does not occur. Differentiation of atypical absence seizures from complex partial seizures may be difficult if only a second-hand account of the episodes is available; identification of a focal abnormality by an electroencephalogram (EEG) often is necessary to identify complex partial seizures. This distinction is important for the proper selection of an ASD.

Focal Seizures

Focal seizures without impairment of consciousness, previously called simple partial seizures, are localized in a single cerebral hemisphere or portion of a hemisphere. Consciousness is not impaired during these events. Various motor, sensory, or psychic manifestations may occur depending on the area of the brain that is affected. A single part of the body may twitch, or the patient may experience only an unusual sensory experience.[7,8]

Focal seizures with impairment of consciousness or “dyscognitive features,” previously called complex partial seizures, result from the spread of focal discharges to involve a larger area. Consciousness is impaired and patients may exhibit complex but inappropriate behavior (automatisms), such as lip smacking, picking at clothing, or aimless wandering. A period of brief postictal lethargy or confusion is common.[7,8]

Focal seizures that evolve to generalized seizures (secondary generalized seizure) include one or both types of focal seizures that evolve to generalized seizures.[7,8]

Epilepsy Syndromes

Epilepsy syndromes can be defined on the basis of seizure type as well as cause (if known), precipitating factors, age of onset, characteristic EEG patterns, severity, chronicity, family history, and

prognosis. Accurate diagnosis of epilepsy syndromes may better guide clinicians regarding the need for drug therapy, the choice of appropriate medication, and the likelihood of successful treatment.[1,5,6] Many epilepsy syndromes have been defined; a complete listing is beyond the scope of this chapter. Several are of interest with respect to pharmacotherapy. Some examples are described in **Table 60-1**.[6]

Table 60-1
Examples of Epilepsy Syndromes and Associated Pharmacotherapy

Syndrome	Seizure Patterns and Characteristics	Preferred ASD Therapy	Comments
Juvenile myoclonic epilepsy	Myoclonic seizures often precede generalized tonic–clonic seizures Sleep deprivation, photosensitivity, and excess alcohol consumption commonly precipitate seizures	Valproate Levetiracetam FDA approved as an adjunct for myoclonic seizures Lamotrigine and levetiracetam preferred in patients of childbearing potential Topiramate and zonisamide may also be effective	5%–10% of all epilepsies; 85%–90% response to valproate Lifelong therapy usually needed High relapse rate with attempts to discontinue ASD therapy
Lennox–Gastaut syndrome	Generalized, atypical absence, atonic/akinetic, myoclonic, and tonic seizures most common Often accompanied by cognitive dysfunction and mental retardation	Valproate and benzodiazepines may be effective Lamotrigine, rufinamide, topiramate, cannabidiol, and clobazam FDA-approved Felbamate may be effective, but potential hematologic toxicity limits use	Poorly responsive to ASD therapy and requires multiple agents for control Oversedation with aggressive treatment strategies may increase seizure frequency Tolerance to benzodiazepines limits their usefulness
Childhood absence epilepsy	Typical absence seizures often present in clusters Tonic–clonic seizures occur in ~40% Onset usually between ages 4 and 8 years and disappears by adolescence Significant genetic component	Ethosuximide or valproate Lamotrigine less effective	80%–90% response rate to ASD therapy Good prognosis for remission Tonic–clonic seizures may persist

ASD, antiseizure drug; FDA, U.S. Food and Drug Administration.

DIAGNOSIS

Optimal treatment of seizure disorders requires accurate classification (diagnosis) of seizure type and appropriate choice and use of medications. Seizure classification may be straightforward if an adequate history and description of the clinical seizure are available. Physicians often do not observe patients' seizures; thus,

family members, teachers, nurses, and others who have frequent direct contact with patients should learn to objectively describe and record these events. The onset, duration, and characteristics of a seizure should be described as completely as possible. Several aspects of the events surrounding a seizure may be especially significant: the patient's behavior before the seizure (eg, Did the patient report feeling ill or describe an unusual sensation?), deviation of the eyes or head to one side or localization of convulsive activity to one portion of the body, impaired consciousness, loss of continence, and the patient's behavior after the seizure (eg, Was there any postictal confusion?). In addition, it is helpful if the observer can record the length of the event and how long it took for the patient to return to baseline. A video of the event could be especially helpful. The patient and caregivers should have a seizure calendar or diary to record events. Many options exist to track seizures including online sites and smartphone applications. Those who observe a seizure should not try to label the seizure but should be encouraged to describe the event fully and objectively.

Accurate seizure diagnosis and identification of the type of epilepsy or epilepsy syndrome also depend on neurologic examination, medical history, and diagnostic techniques, such as EEG, computed tomography (CT), and magnetic resonance imaging (MRI). The EEG often is critical for identifying specific seizure types. CT scanning may help assess newly diagnosed patients, but MRI is preferred. MRI may locate brain lesions or anatomic defects that are missed by conventional radiographs or CT scans.[9]

CASE 60-1

QUESTION 1: A.R. is a 14-year-old, 88.18-pound (40-kg) female high school student. A.R. had three complex febrile seizures when she was 3 years old. According to her parents, she received phenobarbital prophylaxis "off and on," for about 6 months after her second febrile seizure. Since then, she had no reported seizures until 24 hours before admission. At that time, she had a "convulsion" shortly after arriving at school in the morning. A teacher who witnessed the episode describes her as behaving "oddly" before the seizure. She abruptly got up from her desk and began to walk clumsily toward the door;

she bumped into several desks and did not respond to the teacher's attempts to redirect her back to her seat. After ~1 minute of this behavior, she fell to the floor and experienced an apparent generalized tonic–clonic seizure that lasted ~90 seconds. During the episode, she was incontinent of urine and was described as "turning kind of blue." After this episode, A.R. was transported to the hospital.

On arrival at the hospital, A.R. appeared drowsy and confused. Laboratory studies—a complete blood count (CBC), serum glucose, electrolytes, drug and alcohol screen, and lumbar puncture—were normal. Physical examination and a complete neurologic evaluation were normal. An EEG showed diffuse slowing with focal epileptiform discharges in the left temporal area; it was interpreted as abnormal. There was no history of recent illness or injury, although A.R. had stayed up late several nights recently studying for an examination.

A second seizure occurred in the hospital. The nursing staff described an episode similar to the one that occurred at school. After recovery from each episode, A.R. had no memory of events during the seizures; she only remembered a "funny feeling" in her stomach and a "buzzing" in her head before she lost consciousness. She described having these feelings "a couple of times" in the past; she attributed them to "just getting dizzy" and had not reported them to her parents. After these previous episodes, A.R. described feeling confused and groggy for a few minutes.

What subjective and objective features of A.R.'s seizures are consistent with a diagnosis of focal impaired awareness seizures with secondary generalization?

A.R.'s clinical pattern of observed seizure activity (an apparent aura preceding her loss of consciousness), her history of apparent focal seizures not accompanied by generalized seizures, and the findings of focal abnormal activity on EEG are all concordant with this diagnosis. Postictal confusion and grogginess are common after both generalized tonic–clonic and focal seizures. Her unusual or inappropriate behavior represents a focal seizure that subsequently generalized. The clinical features, accompanied by her EEG findings, also help rule out possible atypical absence seizures, which can be confused with focal epilepsy syndromes if based on clinical presentation alone. In both syndromes, patients may briefly appear to lose contact with their surroundings and display automatisms and mild clonic movements during seizure activity. In A.R.'s case, the EEG and the generalized tonic–clonic seizures during her episodes would rule out atypical absence as a likely possibility.

TREATMENT

Early control of epileptic seizures is important because it allows normalization of patients' lives and prevents acute physical harm and long-term morbidity associated with recurrent seizures. In addition, early control of tonic–clonic seizures is associated with a reduced likelihood of seizure recurrence. Early control of epileptic seizures also correlates with successful discontinuation of ASD treatment after long-term seizure control.[10–12]

Nonpharmacologic Treatment of Epilepsy

Caregivers, teachers, and nurses should be familiar with recommendations for providing first aid to a person experiencing a seizure. These steps include the following: (a) remain with the person until they recover and time and record the seizure; (b) move any close objects away to ensure safety; (c) if unconscious, turn the person on their side, maintain a clear airway, and secure their head; (d) if available, give the person their rescue medication; (e) do not put any objects in their mouth; and (f) call emergency providers if a seizure lasts longer than 5 minutes, the person is mentally altered after the episode, or if the person develops any difficulty in breathing.[13]

Alternatives or adjuncts to pharmacotherapy may be helpful in some patients. Surgery is an extremely effective treatment in selected patients. Depending on the epilepsy syndrome and procedure performed, up to 90% of patients treated surgically may improve or become seizure-free. A study of 80 patients with medically refractory temporal lobe epilepsy randomly assigned to either surgery or continued medical treatment showed that, after 1 year, patients were more likely to be seizure-free after surgery.[14] Surgery is advocated as early therapy for some patients with specific epilepsy syndromes, such as mesial temporal sclerosis. Early surgical intervention may prevent or lessen neurologic deterioration and developmental delay.

Dietary modification may be used for patients who cannot tolerate ASDs or to treat seizures that are not completely responsive to ASDs. In most circumstances, dietary modification consists of a ketogenic diet. This low-carbohydrate, high-fat diet results in persistent ketosis, which is believed to play a major role in the therapeutic effect. Evaluation of the amount of carbohydrates patients receive from their medications while on ketogenic diets is also very important. Ketogenic diets seem to be most beneficial in children; they are also used as an adjunct to ongoing ASD treatment.[15,16]

The vagus nerve stimulator is an implantable device approved for the treatment of intractable focal seizures. This device uses electrodes attached around the left branch of the vagus nerve. The electrodes are attached to a programmable stimulator that delivers stimuli on a regular cycling basis; patients can also use “on-demand” stimulation at the onset of seizures by swiping the magnet over the subcutaneously implanted stimulator. Approximately 30% to 40% of patients who are so treated have a positive response (50% reduction in seizures).[17] The primary adverse effect of this device is hoarseness during stimulation; infrequently, this is accompanied by left vocal cord paralysis.

Responsive neurostimulation (RNS) is a newer nonpharmacologic option for treating intractable focal seizures and for patients who are not surgical candidates. This implantable device acts like a heart pacemaker as it can monitor abnormal brain activity and provide on-demand small electrical impulses to reduce seizures. One study found the risk of sudden unexpected death in epilepsy (SUDEP) was significantly reduced when using RNS.[18] It also appears to be safe with low cognitive adverse events and low risk for bleeding or infection as compared to other neurosurgical procedures.[19] However, its exact role in therapy is yet to be determined as some patients respond to treatment better than others and efficacy improves over time.

AVOIDANCE OF POTENTIAL SEIZURE PRECIPITANTS

It is impossible to generalize about environmental and lifestyle precipitants of seizure activity in persons with epilepsy. Individual patients or caregivers may identify specific circumstances such as stress, sleep deprivation, acute illness, or ingestion of excessive amounts of caffeine or alcohol, which may increase the likelihood of a recurrent seizure event. Individuals may experience an increase in the frequency and/or severity of seizures around the time of menstruation or ovulation. Patients with epilepsy should avoid activities that seem to precipitate seizures; as always, the goal is complete seizure control with as little alteration in the quality of life as possible.

Antiseizure Drug Therapy

Pharmacotherapy is the mainstay of treatment for epilepsy. Therefore, patient education regarding medications and consultation among health care professionals regarding the optimal use of ASDs are essential to quality patient care. Optimal ASD therapy completely controls seizures in approximately two-thirds of patients.[20,21] Optimization of drug therapy depends on several factors, with the choice of appropriate ASD, individualization of dosing, and adherence being the most important.

CHOICE OF ANTISEIZURE DRUG

Many ASDs have a relatively narrow spectrum of efficacy against selected seizure types; therefore, the choice of appropriate drug therapy for a specific patient depends on an accurate diagnosis of epilepsy. In addition, toxicity must be considered when selecting an ASD. Preferred drugs for specific types of seizures and common epileptic syndromes are listed in **Tables 60-2** and **60-3**. Although certain drugs are preferred, the identification of the most effective drug for a particular patient may be a process of trial and error; several medication trials may be necessary before success is achieved. It is important to keep in mind that certain ASDs can worsen seizures.[22]

Table 60-2
Antiseizure Drugs Useful for Various Seizure Types

Primary Generalized Tonic–Clonic	Secondary Generalized Tonic–Clonic	Focal—With or Without Awareness	Absence	Myoclonic, Atonic/Akinetic
Most Effective with Least Toxicity[a]				
Valproate	Carbamazepine	Carbamazepine	Ethosuximide	Valproate
Levetiracetam	Oxcarbazepine	Oxcarbazepine	Valproate	Clonazepam
Lamotrigine	Levetiracetam	Levetiracetam or brivaracetam	Lamotrigine	Rufinamide (Lennox–Gastaut syndrome)
(Oxcarbazepine)	Lamotrigine	Lamotrigine	Topiramate	Levetiracetam (juvenile myoclonic epilepsy)
Perampanel	Valproate	Valproate		Lamotrigine
	Gabapentin	Gabapentin		Clobazam (Lennox–Gastaut syndrome)
	Topiramate	Cenobamate		Topiramate
	Tiagabine Zonisamide Pregabalin Lacosamide Perampanel Eslicarbazepine	Topiramate Tiagabine Pregabalin Zonisamide Lacosamide Perampanel Eslicarbazepine		
Effective, but Often Poorly Tolerated or Cause Unacceptable Toxicity				
Phenobarbital	Phenobarbital	Clorazepate	Clonazepam	Felbamate[b]
Primidone	Primidone	Phenobarbital		
Felbamate[b]	Felbamate[b]	Primidone		
Phenytoin	Phenytoin Vigabatrin[c]	Felbamate[b] Phenytoin Vigabatrin[c]		

[a]Drugs are listed in general order of preference within each category. Recommendations by various authorities may differ. The use of phenobarbital and primidone is discouraged.

[b]Felbamate is placed on this table only to indicate the types of seizures for which it appears to be effective. Felbamate has been associated with aplastic anemia and hepatic failure; until a possible causative role is clarified, felbamate cannot be recommended for treatment of epilepsy unless all other, potentially less toxic, treatment options have been exhausted.

[c]Vigabatrin causes progressive and permanent visual field constriction that is related to total dose and duration of exposure. Vigabatrin cannot be recommended for treatment of epilepsy unless other potentially less toxic treatment options have been exhausted.

The consensus method was used to analyze expert opinion on the treatment of three epilepsy syndromes and status epilepticus (SE).[23] The experts recommended monotherapy first, followed by a second monotherapy agent if the first failed. If the second monotherapy failed, the experts were not in agreement on whether to try a third monotherapy agent or to combine two therapies. The experts

recommended epilepsy surgery evaluation after the third failed ASD for patients with symptomatic localization-related epilepsies.

To assess the evidence on efficacy, tolerability, and safety of many of the new ASDs in treating children and adults with new-onset and refractory focal and generalized epilepsies, a panel evaluated the available evidence.[24,25] They concluded that ASD choice depends on seizure and syndrome type; patient age; concomitant medications; and ASD tolerability, safety, and efficacy. The results of these two evidence-based assessments provide guidelines for the use of newer ASDs in patients with new-onset and refractory epilepsy.

THERAPEUTIC END POINTS

The individual patient's response to ASD treatment (ie, seizure frequency and severity and symptoms of toxicity) must be the major focus for therapy assessment. In general, the goal of ASD treatment is the administration of sufficient medication to completely prevent seizures without producing significant toxicity.[26] Realistically, this goal may be compromised for many patients; it may not be possible to completely prevent seizures without producing intolerable adverse effects. Thus, the therapeutic end points achieved can vary among patients; optimization of ASD therapy for a specific person depends on tailoring therapy to the patient's needs and lifestyle. It is rarely optimal to administer "standard" or "usual" doses of an ASD to a patient or to adjust doses to achieve a "therapeutic blood level" without considering the effect of the dose or serum concentration on the patient's condition and quality of life. As with many conditions requiring chronic drug therapy, patient participation in developing and evaluating a therapeutic plan is extremely important. Patients should be educated regarding the expected positive and negative effects of their ASD therapy, and they must be encouraged to communicate with their health care provider regarding their responses to prescribed ASDs.

CASE 60-1, QUESTION 2: What factors should be considered in a decision to treat A.R.'s seizures with scheduled ASD therapy?

Once a diagnosis of epilepsy is established, the decision to treat the patient with medication is based on the likelihood of recurrence. The need for ASD therapy after a single seizure is controversial. Evidence-based guidelines for adults and children generally state that the risk of recurrence is greatest within the first two years after the initial seizure occurrence and depends on etiology and EEG status.[4,27]

In A.R.'s case, the seizures experienced in the past 24 hours count as an initial unprovoked seizure. She experienced focal seizures, and some were followed by secondary generalized tonic–clonic seizures. Recurrence of seizure activity is likely to result in physical injury, social embarrassment, and interference with her participation in activities typical of a person her age. If her seizures are not controlled, she faces future limitation of her driving privileges and may face barriers to employment. A.R. also has a baseline risk of epilepsy given her history of complex febrile seizures. The potential benefits of immediate introduction of ASD therapy appear to outweigh potential associated risks.

SERUM DRUG CONCENTRATIONS

Relation to clinical response

For selected ASDs, proper use and interpretation of serum concentrations are important for optimizing treatment regimens in epilepsy.[28,29] An individual patient's clinical response to ASD treatment must be the major focus for therapy assessment. Individual patients often differ dramatically in their response to a particular serum drug concentration; therefore, therapeutic serum concentrations should be considered only as guidelines for treatment. Many patients' condition may be controlled with serum drug concentrations above or below the usual therapeutic range.[30] In these patients, dosage adjustment to get the patient "in range" is not warranted. It is better to "treat the patient, not the level."

Interestingly, a recent Cochrane Review found no evidence that measuring ASD concentrations routinely to inform dose adjustments is superior to dose adjustments based on clinical information.[31]

However, the authors do state that their review does not exclude the possibility that ASD serum concentration might be useful in special situations or in selected patients.

Indications for use

Measurement of serum drug concentrations may provide clinically useful information in the following situations:

- Uncontrolled seizures despite administration of greater-than-average doses: Serum concentrations of ASD may help distinguish drug resistance from subtherapeutic drug concentrations caused by malabsorption, nonadherence, or rapid metabolism.
- Seizure recurrence in a patient whose seizures were previously controlled: This is often owing to nonadherence to the prescribed medication regimen.
- Documentation of intoxication: In patients who exhibit signs or symptoms of dose-related ASD toxicity, documentation of the dose and serum concentration of the responsible drug is helpful.
- Assessment of patient adherence: Although monitoring ASD serum concentrations can be used to assess patient adherence to therapy, conclusions must be based on comparisons with previous steady-state serum concentrations that reflected reliable intake of a given dose of ASD.
- Documentation of desired results from a dose change or other therapeutic maneuver (eg, administration of a loading dose): When patients are receiving multiple ASDs, it is often appropriate to measure serum concentrations of all drugs after a change in the dose of one agent because changes to one drug frequently affect the pharmacokinetic disposition of other drugs.
- When precise dosage changes are required: On occasion, small changes in the dose of a drug (eg, phenytoin) can result in large changes in both the serum concentration and clinical response. In addition, cautious titration of dosage and serum concentration may be necessary to avoid intoxication. Knowledge of the serum drug

concentration before the dosage change may allow the clinician to select a more appropriate new maintenance dose.

- During pregnancy, ASDs serum concentrations often decline, and dosage adjustments may be warranted to maintain adequate seizure protection. Free (unbound) concentrations should be monitored for highly protein-bound ASDs (eg, phenytoin and valproate). ASD serum concentrations should be monitored after delivery, particularly when dosage escalations have been made during pregnancy.

Frequent, "routine" determinations of serum ASD concentrations are costly and not warranted for patients whose clinical status is stable. Clinicians may tend to focus attention on normal variability in serum concentrations rather than on the patient's clinical status; as a result, unnecessary dosage adjustments may be made to make serum concentrations fit the "normal range." A plan of action for what the clinician is going to do with the information once it is obtained should be in place before obtaining the sample. Therefore, the results of individual serum concentration determinations must be evaluated carefully to decide whether a significant, clinically meaningful change has occurred.[32]

Interpretation of serum concentrations

Several factors can alter the relationship between ASD serum concentration and the patient's response to the drug. Whenever a change in serum concentration is apparent, pharmacokinetic factors (see Table 60-3) should be considered (along with the patient's clinical status) before a decision is made to adjust the ASD dosage. Laboratory variability can cause minor fluctuations in reported ASD serum concentrations. Under the best conditions, reported values for serum concentrations may be within 10% of "true" values.[33,34] Therefore, the magnitude of any apparent change must be considered. Published therapeutic ranges may have been determined in small numbers of patients or may more accurately represent average serum concentrations at usual doses. Inappropriate sample timing can result in inconsistent and clinically

meaningless changes in ASD serum concentrations.[28] Generally, serum concentrations of ASD should not be measured until a minimum of four to five half-lives have elapsed since initiation of therapy or a dosage change. Blood samples should be obtained in the morning, before any doses of the ASD have been taken; this practice provides reproducible, postabsorptive (ie, “trough”) serum concentrations. Binding to serum proteins is significant for some ASDs (eg, phenytoin, valproate, tiagabine). Changes in protein binding can result from drug interaction, renal failure, pregnancy, or changes in nutritional status. These changes can alter the usual relationship between the measured total drug concentration (bound and unbound to plasma proteins) and the unbound (pharmacologically active) drug concentration. This change may not be apparent when only total serum concentrations are measured. Determination of serum concentrations of free (ie, unbound) ASDs is available from many commercial laboratories; these determinations are expensive, and results may not be available for several days. If significant changes in protein binding are suspected, measurement of free concentrations of ASD may provide additional information useful for adjustment of doses or interpretation of the patient’s symptoms.[23,34,35]

Table 60-3
Pharmacokinetic Properties of Antiseizure Drugs

Drug	Oral Absorption (%)	Half-Life (hours)	Time to Steady State[a]	Usual Therapeutic Serum Concentration	Plasma Protein Binding (%)	Volume of Distribution (L/kg)
Brivaracetam	NA	9	2–3 days	Not determined	<20	0.5
Cannabidiol	NA	56–61	9–10 days	Not determined	>94	NA
Carbamazepine	90–100	*Chronic:* 5–25	2–4 days	5–12 μg/mL	75 (50–90)	0.8–1.6
Cenobamate	>88	50–60	8–10 days	Not determined	60	NA
Clobazam	NA	16–42; *N*-desmethyl (active metabolite) 71–82	3–7 days	Not determined	80–90	NA
Eslicarbazepine	>90	*Normal renal function*: 13–20	4–5 days	Not determined	<40	0.8
Ethosuximide	90–100	*Pediatric:* 30 *Adult:* 60	5–10 days	40–100 μg/mL	0	0.7
Felbamate	90	12–20	3–4 days	50–110 μg/mL	24	0.7–0.8
Gabapentin	40–60; ↓ with ↑ dose	*Normal renal function:* 5–9; ↑ with ↓ renal function	*Normal renal function:* 1–1.5 days	2 μg/mL (proposed)	0	≈0.8
Lacosamide	100	13 ↑ slightly with renal impairment	2–3 days	Not determined	<15	0.6
Lamotrigine	90–100	*Monotherapy:* 24–29 *Enzyme inducers:* 15 *Enzyme inhibitors (VPA):* 59	4–9 days	4–18 μg/mL (proposed)	55	0.9–1.2
Levetiracetam	100	*Normal renal function:* 6–8; ↑ with ↓ renal function	*Normal renal function:* 1–1.5 days	Not determined	<10	≈0.7
Oxcarbazepine	100	8–13	2–3 days	Not determined	40	
Perampanel	100	*Normal hepatic function*: 105	2–3 weeks	Not determined	95	NA
Phenobarbital	90–100	2–4 days	8–16 days	15–40 μg/mL	50	0.5–0.6
Phenytoin	90–100	Varies with dose	5–30 days	10–20 μg/mL	95	0.5–0.7
Pregabalin	≥90	*Normal renal function:* 6; ↑ with ↓ renal function	24 hours	Not determined	0	0.5
Rufinamide	85	9	1–2 days	Not determined	<35	Dose dependent
Stiripentol	NA; bioavailability 30%	4–13	1–3 days	Not determined	99	NA
Tiagabine	90	*Monotherapy:* 7–9 *Enzyme inducers:* 4–7	1–2 days	Not determined	96	1.1
Topiramate	≥80	12–24	3–4 days	Not determined	10–15	0.7
Valproate	100 (≈80% with divalproex ER)	10–16	2–3 days	50–150 μg/mL	90+	0.09–0.17
Vigabatrin	80–90	8–12 (not clinically important. Irreversible enzyme inhibitor)	NA	NA	NA	NA
Zonisamide	≈80	*Monotherapy:* ≈60 *Enzyme inducers:* 27–36	2 weeks	Not determined	50–60	1.3

NA, not available; VPA, valproic acid.

[a]Based on four half-lives. This lag time should allow determination of steady-state serum concentrations within the limits of most assay sensitivities.

MONOTHERAPY VERSUS POLYTHERAPY

Evaluation of the effectiveness of polytherapy has shown little advantage for most patients. Use of a single drug at optimal tolerated serum concentrations produces excellent therapeutic results and minimal adverse effects in most patients. Addition of a second ASD significantly improves seizure control in only 10% to 20% of patients.[36,37] Reduction or elimination of existing polytherapy in patients with longstanding seizure disorders often lessens or eliminates cognitive impairment and other adverse effects; seizure control actually may improve.[36,38–41]

Most experts advocate the use of a single ASD (monotherapy) whenever possible. Successful monotherapy may require higher-than-usual ASD doses or serum concentrations greater than the upper limit of the usual therapeutic range.[42,43] Addition of a second

drug may be necessary in some patients; however, polytherapy should be reserved for patients with multiple seizure types or for patients in whom first-line ASDs have failed to control seizures when titrated to maximal tolerated doses.[23,39,42] When a new ASD is added to a patient's regimen with the goal of improving seizure control, the existing ASD regimen should be scrutinized for continued value. In some cases, a patient's ASD regimen can accumulate drugs that may be unnecessary because they were started and never re-evaluated. Continued vigilance and critical assessment of every drug in a patient's regimen is important.

Use of polytherapy creates several disadvantages that must be weighed against possible benefits. Seizure control may not significantly improve. Health care costs, for medications and for increased laboratory monitoring, may increase significantly with polytherapy. In addition, drug interactions among ASDs can complicate assessment of the patient's response and serum concentrations. Patient adherence often is worsened when multiple medications are prescribed, and adverse effects often increase.

Although ASD monotherapy is preferred whenever feasible, the recent introduction of several new ASDs has increased the use of polytherapy.[43]

DURATION OF THERAPY AND DISCONTINUATION OF ANTISEIZURE DRUGS

A diagnosis of epilepsy may not necessitate lifelong drug therapy. Several long-term studies have shown that ASD therapy may be successfully withdrawn from some patients after a seizure-free period of 2 to 5 years.[10–12] Seizures recurred in only 12% to 36% of patients who were followed for up to 23 years after ASD withdrawal. Therefore, many patients whose epilepsy is completely controlled with medication can stop therapy after a seizure-free period of at least 2 years.

Discontinuation of medications is advantageous for economic, medical, and psychosocial reasons. Costs associated with health care visits, serum concentration determinations, and the medications

themselves are eliminated or reduced. The risk of adverse effects from long-term medication use is eliminated, and patients can expect fewer lifestyle restrictions. Attempts to withdraw ASD therapy are associated with risks, however. Primary among them is the reappearance of seizure activity, which can result in SE, loss of driving privileges, employment difficulties, and/or physical injury.

Risk factors for seizure recurrence after discontinuation of ASD have been identified in observational studies; complete agreement, however, is not found among studies regarding the nature and importance of specific risk factors (**Table 60-4**). Opinions and data also differ regarding the optimal duration of the seizure-free period before discontinuation of ASD is attempted.[10,12,44,45]

Table 60-4

Risk Factors Possibly Predicting Seizure Recurrence After Antiseizure Drug Withdrawal

- <2 years seizure-free before withdrawal
- Onset of seizures after age 12
- History of atypical febrile seizures
- Family history of seizures
- 2–6 years before seizures controlled
- Large number of seizures (>30) before control or total of >100 seizures
- Focal seizures (with or without impaired awareness)
- Abnormal EEG persisting throughout treatment
- Slowing on EEG before medication withdrawal
- Organic neurologic disorder
- Moderate-to-severe mental retardation

EEG, electroencephalogram.

In nonemergency situations, ASD should be withdrawn slowly; if a patient receives multiple drugs, each drug should be withdrawn separately. Too-rapid withdrawal can result in SE. Clinical studies of ASD discontinuation usually used a 2- to 3-month withdrawal schedule for each drug. The optimal rate of withdrawal of ASD has not been identified. One study compared withdrawal of individual drugs for a 6-week and a 9-month period and found no difference in

seizure recurrence between the groups.[46] Another study compared seizure frequencies in patients withdrawn from carbamazepine rapidly (for 4 days) and in patients withdrawn more slowly (for 10 days).[47] Significantly more generalized tonic–clonic seizures occurred when carbamazepine was withdrawn rapidly; focal impaired awareness seizures, however, did not occur at a higher rate with rapid withdrawal. Therefore, withdrawal of each ASD for at least 6 weeks would seem to be a safe approach. Gradual withdrawal is recommended even for medications such as phenobarbital that have long half-lives and should theoretically be "self-tapering." In our experience, gradual reduction of medications such as phenobarbital is associated with a significantly higher success rate. If ASDs are withdrawn at an appropriate rate and seizures recur, drug treatment is usually reinstituted. In most patients, good seizure control is regained by restarting therapy. However, ~1% of patients had recurrent seizures that could not be controlled again with ASDs.[48] This uncommon, but potentially serious, the outcome should be considered when therapy withdrawal is considered.

CLINICAL ASSESSMENT AND TREATMENT OF EPILEPSY

Choice of Antiseizure Drug

CASE 60-1, QUESTION 3: Which ASDs are commonly used for A.R.'s seizure type?

Based on the subjective and objective data available, recommend a first-line ASD for A.R. and a plan for initial dosing of this medication.

Many ASDs would be appropriate choices for A.R.'s focal seizures with secondary generalized seizures (see **Table 60-2**).[37,49,50] Although valproate is effective for treating both generalized and focal

seizures,[51] it would not be a good initial choice for this patient owing to the risk of teratogenicity in a patient of childbearing age (see Other Therapeutic Considerations section).

Cenobamate, eslicarbazepine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, tiagabine, topiramate, carbamazepine, and zonisamide are effective for control of focal seizures with or without secondary generalization. Most experience with these drugs was obtained when they were used as adjunctive agents when previous ASD therapies were unsuccessful. Initial clinical trials with these medications indicate that several of them may be useful as single agents. Cenobamate, felbamate, lacosamide, lamotrigine, oxcarbazepine, carbamazepine, and topiramate have monotherapy indications. These medications appear to be safe and are usually well tolerated. The usefulness of felbamate is limited, however, owing to its potential for serious hematologic and hepatic toxicity.

Carbamazepine has several advantages that make it a reasonable first-line agent. Compared with other agents, carbamazepine is less sedating and is not associated with adverse effects such as hirsutism, acne, gingival hyperplasia, and coarsening of facial features. Although typical dosing generally requires multiple daily doses, there are extended-release formulations available to minimize the frequency of administration. In A.R.'s case, the lack of cosmetic adverse effects may be especially significant because she may be taking medication for many years. In addition, reduced sedation may be important with respect to her school performance.

Carbamazepine Therapy

INITIATION AND DOSAGE

It is recommended to screen the patients of Asian ancestry for HLA-B*15:02 allele prior starting carbamazepine therapy to avoid life-threatening adverse events such as Stevens–Johnson syndrome or toxic epidermal necrolysis. Initiation of treatment with full therapeutic maintenance doses of carbamazepine often causes excessive

adverse effects such as nausea, vomiting, diplopia, and significant sedation. Therefore, carbamazepine therapy should be gradually increased over time. Final dosing requirements are difficult to anticipate in individual patients. A reasonable starting dosage of carbamazepine for A.R. would be 100 mg twice a day; her dosage could be increased by 100 to 200 mg/day every 7 to 14 days. The titration schedule will depend on A.R.'s tolerance for the drug and the frequency of her seizures.

CASE 60-1, QUESTION 4: Carbamazepine has been associated with hematologic and hepatic toxicities. What is the incidence and significance of these toxicities? How should A.R. be monitored for them?

HEMATOLOGIC TOXICITY

Aplastic anemia and agranulocytosis have occurred in association with carbamazepine therapy.[52] Several cases have been fatal; however, most cases occurred in older patients treated for trigeminal neuralgia. Many patients were receiving other medications, and occasionally the reports were incomplete; thus, causal relationship for carbamazepine is difficult to assess.[53] Blood dyscrasias from carbamazepine seem rare (estimated prevalence <1/50,000) and have predominantly occurred in patients without epilepsy. Data in case series and clinical trials of carbamazepine therapy in patients with epilepsy do not report severe hematologic toxicity.[54,55]

Leukopenia is relatively common in patients taking carbamazepine. It is usually mild and often resolves without discontinuation of the drug.[54] Total leukocyte counts may fall to <4,000 cells/μL in some patients, but differentials and platelet and erythrocyte counts remain normal. Symptoms (eg, fever, sore throat) that might suggest early stages of agranulocytosis do not occur. Carbamazepine-associated hematologic disorders are not generally dose related.

Routine hematologic testing

Laboratory monitoring of A.R.'s hematologic status is recommended before and during carbamazepine therapy. Hematologic toxicity from carbamazepine typically occurring early in therapy monitoring does not appear to provide a benefit in the detection of aplastic anemia or agranulocytosis.[54,56] Therefore, baseline and monthly CBCs are advised for the first 3 months of therapy. Thereafter, A.R. should have a yearly CBC with differential.

HEPATOTOXICITY

Carbamazepine-related liver damage is extremely rare despite warnings in the package insert.[57,58] Hepatotoxicity from carbamazepine is believed to be idiosyncratic or immunologically based. Aggressive laboratory monitoring of liver function tests (LFTs) probably is unnecessary.[56,59]

In summary, hepatic and hematologic toxicities of carbamazepine are rare. Although potentially serious, they are best monitored clinically rather than by extensive or frequent laboratory testing. Patients, families, or caregivers should be aware that the appearance of unusual symptoms (eg, jaundice, abdominal pain, excessive bruising and bleeding, or sudden onset of severe sore throat with fever) should be reported to a health care professional. After initial monitoring, annual CBC and LFTs are appropriate unless signs or symptoms of hepatic or hematologic disorders are observed.

PHARMACOKINETICS AND AUTOINDUCTION OF METABOLISM

Case 60-1, Question 5: A.R.'s carbamazepine dosage was gradually increased over 6 weeks to 400 mg twice daily (bid) (20 mg/kg/day). Until the last dose increase, she had been experiencing one or two focal seizures weekly. She had experienced only one generalized tonic–clonic seizure since her initial presentation. One week after the increase to 20 mg/kg/day, her serum carbamazepine concentration was 9 µg/mL just before her first dose of the day. No seizures occurred for 4 weeks, and she tolerated the medication well. After 4 weeks, she again began experiencing one seizure weekly. What factor(s) might be responsible for the loss of seizure control?

Several factors may account for this change. It is important always to consider the possibility of poor medication adherence when clinical response changes unexpectedly. This should be investigated, and A.R. and her family should be educated regarding the importance of medication adherence.

The observed changes in A.R.'s seizure control may also be because of unique features of carbamazepine pharmacokinetics. Carbamazepine is a potent inducer of hepatic cytochrome P-450 3A4 (CYP3A4). As a result, carbamazepine not only induces the metabolism of other CYP3A4 substrates but also induces its own metabolism by autoinduction. Carbamazepine's half-life after single acute doses is ~35 hours; with chronic dosing, its half-life decreases to 15 to 25 hours. This increase in clearance necessitates increased carbamazepine doses, increased frequency of administration, or both. Autoinduction of carbamazepine metabolism appears to be related to the dose and serum concentration. Approximately 1 month may be required for the autoinduction process to reach steady state after initiation or an increase in carbamazepine dose.[60]

Assuming good adherence, A.R.'s carbamazepine dose should be increased to overcome the autoinduction. The drug's pharmacokinetics are generally linear with respect to acute dosage changes.[61] A 50% increase in dosage to 1200 mg/day should re-establish seizure control. Depending on A.R.'s clinical status, further increases in dosage may be necessary.

BIOEQUIVALENCE OF GENERIC CARBAMAZEPINE PRODUCTS

Case 60-1, Question 6: A.R.'s dosage was increased to 600 mg bid. Four weeks later, she was still experiencing one focal seizure weekly. A repeat trough serum carbamazepine concentration was 6.5 µg/mL. A.R. denied missing doses of medication, and a tablet count confirmed good adherence to the prescribed regimen. A.R. reports mild nausea after administration, but she denies vomiting. You discover that A.R.'s dispensing pharmacy recently begun substituting generic carbamazepine tablets for the brand product. What role, if any, might this carbamazepine product change have played in the failure of A.R.'s serum concentrations to increase as expected? What other factors might be considered in explaining this situation?

Several manufacturers make generic carbamazepine tablets. Bioavailability data supplied by the manufacturers are based on single-dose or short multiple-dose studies in healthy subjects. Therefore, it is impossible to completely predict the results of a change from the brand to generic carbamazepine product during maintenance therapy in an individual patient.[62] Variations in brand and generic products may cause some patients with epilepsy to experience changes in seizure control or drug toxicity when transitions between brand and generic products for several ASDs, a term known as generic-brittle.[63] However, two bioequivalence studies found no evidence of pharmacokinetic differences between brand and generic products of lamotrigine in patients with epilepsy.[64,65]

Data suggest that the generic carbamazepine products currently on the market may be substituted safely for the brand product. Nonetheless, in A.R.'s case, substitution of generic carbamazepine may be a possible cause for the loss of seizure control. Readjustment of her dose to gain seizure control or consistent use of one product (either brand or generic) might alleviate this problem. Furthermore, switching to an extended-release formulation offers an alternative for A.R. Many patients tolerate extended-release formulations of carbamazepine better because large fluctuations in plasma concentrations are avoided. Three extended-release forms of carbamazepine are available (Tegretol® XR, Carbatrol®, and Equetro®) and are dosed every 12 hours. Tegretol® XR compared with three and four times daily immediate-release carbamazepine dosing schedules may improve adherence.[66] An important counseling point for patients is that the empty osmotic-controlled-release oral delivery system (OROS) tablet shell from the Tegretol® XR does not dissolve as it passes through the gastrointestinal (GI) tract and may be visible in the stool. Tegretol® XR tablets should not be broken or crushed; Carbatrol® beads may be administered on food or via feeding tube.[67] Equetro® is not FDA (United States Food and Drug Administration) approved for epilepsy; it is indicated for the treatment of acute manic and mixed episodes associated with bipolar I disorder.

In conclusion, it may be impossible to identify a single cause for the unexpected change in A.R.'s seizure control. Common reasons for loss of seizure control include seizure triggers such as sleep deprivation, increased stress, acute illness, and/or medication nonadherence. Controversy remains surrounding the impact of switching between generic and brand ASD products but should be considered when assessing seizure control in patients with epilepsy.

Treatment Failure and Alternative Antiseizure Drugs

CASE 60-2

QUESTION 1: R.H., a 19-year-old, 141.09-pound (64-kg) female, has experienced focal seizures, with and without impaired awareness, and secondary generalized tonic–clonic seizures for the past 2 years. She could not tolerate treatment with phenytoin (severe gingival hyperplasia and mental "dullness") or valproate (hair loss, tremor, and a weight gain of 8 kg). In addition, neither phenytoin nor valproate was dramatically effective in reducing her seizures. She currently receives carbamazepine 600 mg three times daily (tid). For the past 3 months, while being treated with carbamazepine, she has had approximately five focal seizures without impaired awareness, three focal seizures with impaired awareness, and one generalized tonic–clonic seizure. This represents an approximate 30% reduction in her frequency of seizures. She tolerates her present dose of carbamazepine but has experienced significant drowsiness, incoordination, and mental confusion at higher doses.

What are possible therapeutic options for R.H.? Evaluate the newer ASDs and their possible usefulness for R.H.

R.H. is exhibiting an incomplete response to maximally tolerated doses of carbamazepine. An alteration in her current ASD regimen is indicated. She has not tolerated other ASDs because of adverse effects. Although valproate is effective for control of focal seizures, it is not considered an alternative in a female of childbearing age. R.H.'s CNS adverse effects (eg, persistent drowsiness) with other ASDs would make many clinicians reluctant to consider medications such as phenobarbital or primidone as either alternatives or adjunctive agents to her current carbamazepine regimen. Use of one

of the newer ASDs as adjunctive medication may be of value for R.H.

New ASDs marketed in the United States since 1993 for maintenance treatment of epilepsy include the following: cenobamate, eslicarbazepine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, tiagabine, topiramate, and zonisamide (**Table 60-5**).[68] Clinical trials for new ASDs are most often carried out in patients with focal seizures refractory to standard ASDs.[69] Most of these newer or "second-generation" ASDs were initially FDA approved as "add-on" or adjunctive treatment in patients with focal seizures with or without secondary generalization. Also, consensus is that some of these ASDs may be effective as broad-spectrum agents; for example, lamotrigine appears to be a useful treatment in absence seizures.

Table 60-5
Drugs Used for the Treatment of Seizures

ASD	Mechanism of Action	Regimen	Adverse Effects	Comments
Brivaracetam (Briviact®)	Modulates neurotransmitter release through binding to the synaptic vesicle protein SV2A	■ Initial 50 mg bid ■ May titrate based on response by increasing or decreasing 10–50 mg/day; maximum 200 mg/day ■ Children 4–16 years old: ■ If >50 kg, refer to adult dosing ■ If 20–50 kg, initial dose starts from 0.5 to 1 mg/kg/day; maximum 4 mg/kg/day ■ If 11–20 kg, initial dose 0.5 to 1.25 mg/kg/day; maximum 5 mg/kg/day	■ Sedation ■ Fatigue ■ Nystagmus ■ Irritability ■ Aggressive behavior ■ Anxiety ■ Decrease neutrophils ■ Psychosis ■ Bronchospasm	■ Dose adjustment required for patients with hepatic impairment ■ A substrate of CYP2C19, which may be impacted by genomics ■ May convert patients from levetiracetam to brivaracetam if patients cannot tolerate the psychiatric adverse effects
Cannabidiol (Epidiolex®)	Unknown	■ Initial 2.5 mg/kg bid; maximum 10 mg/kg bid ■ May ↑ by 2.5 mg/kg bid weekly	■ Somnolence ■ Sleep disorder ■ Asthenia ■ Fatigue ■ Decrease appetite ■ Diarrhea ■ Hepatotoxicity	■ May increase lamotrigine and clobazam levels ■ CYP2C19 inhibitor ■ May increase the risk for hepatotoxicity while on valproate therapy
Carbamazepine (Tegretol®, Tegretol® XR, Carbatrol®, Equetro®)	Inhibits sodium channels	■ Initial 200 mg bid (adults) or 100 mg bid (children) ■ ↑ weekly until therapeutic response or target serum concentrations ■ Usual maintenance doses 7–15 mg/kg/day in adults; 10–40 mg/kg/day in children	■ Sedation ■ Visual disturbance may limit dosage ■ Severe blood dyscrasias extremely rare ■ Mild leukopenia more common ■ Asian patients positive for HLA-B*1502 are at 10-fold higher risk for Stevens–Johnson syndrome/toxic epidermal necrolysis ■ Hepatotoxicity rare ■ May cause hyponatremia ■ Long-term use may cause osteomalacia	■ Usually, little sedation and minimal interference with cognitive function or behavior ■ Preferred by most for focal or secondary generalized seizures ■ Extended-release products may allow less frequent dosing with fewer peak serum concentration-related adverse effects. These products may also facilitate adherence
Cenobamate (Xcopri®)	Inhibits sodium channels and may increase GABA activity	■ Initial 12.5 mg/day for weeks 1–2 ■ Increase biweekly as tolerated by doubling the dose until 100 mg in week 7 then increase by 50 mg/day biweekly ■ Maximum 400 mg/day	■ QT shortening ■ Hypersomnia ■ Lethargy ■ Malaise ■ Hyperkalemia ■ Visual disturbance ■ Diplopia	■ Slow titration required to avoid hypersensitivity reactions (eg, DRESS) ■ Not approved for pediatrics ■ Avoid use in end-stage renal or liver disease ■ Consider gradual withdrawal over at least 2 weeks, and if on chronic therapy may decrease dosing over 2–6 months ■ Contraindicated in patients with familial short QT syndrome

Clobazam (Onfi®; Sympazan®)	Increases GABA activity	■ Initial 5 mg bid, then double the dose every week to the desirable effect ■ No established maximum dose ■ In older adults, start with 5 mg once daily and double the dose every week	■ Sedation ■ Lethargy ■ Drooling ■ Aggressive behavior ■ Irritability ■ Ataxia ■ Fever ■ Possible upper respiratory tract infection	■ Boxed warning for concomitant use of benzodiazepines and opioids ■ Has off-label use as an adjunctive in refractory seizures ■ Needs dose adjustment upon initiation for patients with liver disease ■ Major substrate of CYP2C19
Eslicarbazepine (Aptiom®)	Inhibits sodium channels	■ Initial 400 mg once daily ■ ↑ by 400 mg/day after one week ■ Maximum recommended dose is 1200 mg/day ■ Once-daily dosing recommended	■ Dizziness ■ Somnolence ■ Nausea ■ Headache	■ Enzyme-inducing ASDs reduce eslicarbazepine exposure; thus, higher doses may be needed ■ May reduce effectiveness of hormonal contraceptives
Ethosuximide (Zarontin®)	Inhibits calcium channel	■ Initial 20 mg/kg/day or 250 mg daily or bid ■ ↑ by 10 mg/kg/day or 250 mg/day every 2 weeks to therapeutic effect or target serum concentration	■ GI upset and sedation common with a large single dose, especially upon initiation ■ Divided doses may be necessary for tolerability ■ Leukopenia (mild, transient) in up to 7% ■ Serious hematologic toxicity extremely rare	■ Parents/patient should be educated on GI effects and sedation, but tolerance usually develops ■ Administration with food can alleviate GI upset ■ Effective for absence seizures ■ Evidence does not support precipitation of tonic–clonic seizures
Felbamate (Felbatol®)	Increases GABA activity and antagonizes NMDA receptor	■ Initial 1.2 g/day in three to four divided doses ■ For monotherapy increase by 600 mg/day every 2 weeks ■ For adjunctive therapy, increase by 1.2 mg/day every week	■ Anorexia ■ Insomnia ■ Headache ■ Dizziness ■ Somnolence ■ Increases the risk for infections ■ Serious liver damage	■ Boxed warning for aplastic anemia and acute liver failure ■ Increases phenytoin, valproic acid, phenobarbital, and carbamazepine levels; therefore, reduce the dose for these agents by 20% upon initiation of felbamate ■ Might be considered for refractory seizures
■ Fosphenytoin (Cerebyx®) ■ Phenytoin (Dilantin®, Phenytek®)	Inhibits sodium channels	■ Initiate at maintenance dose of 4–5 mg/kg/day (300–400 mg/day) ■ Titrate on basis of clinical response and target serum concentration ■ Waiting for 3–4 weeks between doses is recommended before increasing the dose because of potentially slow accumulation	■ Nystagmus ■ Ataxia ■ Sedation may limit dosage ■ Gum hyperplasia ■ Hirsutism ■ Long-term use may cause osteomalacia ■ Peripheral neuropathy, hypersensitivity with liver damage rare ■ Possible increased risk of Stevens–Johnson syndrome/toxic epidermal necrolysis in Asian patients positive for HLA-B*1502	■ Clearance and half-life change with dose ■ Small ↑ in dose (30-mg capsule) recommended as plasma concentrations exceed 7–10 μg/mL ■ Cautious use of suspension; dose measurement and potential mixing difficulties along with potential interactions with tube feeding formula ■ IM administration not recommended

				■ Potential precipitation in IV solutions ■ Fosphenytoin recommended for IM and IV use because of faster administration rate, admixture compatibility, and lower rate of injection site complications
Gabapentin (Neurontin®)	Inhibits calcium channels	■ Initial 300 mg/day with titration to 900–1800 mg/day for 1–2 weeks ■ Doses of 2400 mg/day and higher have been well tolerated ■ Owing to short half-life, tid or qid dosing recommended	■ Common with initiation of therapy ■ Sedation ■ Dizziness ■ Ataxia ■ Commonly associated with weight gain	■ Excreted unchanged by kidneys ■ No significant drug–drug interactions ■ Absorption dose dependent; fraction absorbed ↓ as size of individual dose ↑
Lacosamide (Vimpat®)	Inhibits sodium channels	■ Initiate at 50 mg bid ■ Increase weekly by 100 mg/day ■ Target doses of 200–400 mg/day ■ Maximum recommended dose is 400 mg/day	■ Dizziness ■ Ataxia ■ Diplopia ■ Headache ■ Nausea ■ May slow cardiac conduction via inhibition of the cardiac sodium channels; caution is advised in patients with second-degree AV block ■ Syncope has been reported	■ Currently only indicated for treatment of focal seizures in adults ■ IV form available; currently only approved for short-term replacement of oral therapy ■ Little evidence of significant risk of drug–drug interactions ■ Some hepatic metabolism by CYP2C19; significant renal elimination
Lamotrigine (Lamictal®)	Inhibits sodium channels	■ *When added to enzyme inducers alone:* ■ Initiate at 50 mg daily HS or 50 mg bid ■ Daily dose can be ↑ by 50–100 mg every 7–14 days ■ Usual maintenance doses of 400–500 mg/day ■ Bid dosing may be necessary with enzyme inducer co-therapy ■ *When added to valproate alone:* ■ Initiate at 25 mg qod HS ■ Daily dose can be ↑ by 25 mg every 14 days ■ Usual maintenance doses of 100–200 mg/day ■ *For patients not taking valproate or an enzyme inducer:* ■ Initiate at 25 mg once-daily HS ■ Daily dose can be ↑ by 25 mg every 14 days ■ Usual daily doses of 225–375 mg/day	■ Common with initiation of therapy; may limit speed of titration ■ Dizziness ■ Diplopia ■ Sedation ■ Ataxia ■ Blurred vision ■ Incidence of serious rash ranges from 0.8 to 8 per 1000	■ Significant ↑ in clearance of lamotrigine when coadministered with enzyme inducers ■ Significant ↓ in clearance when coadministered with valproate ■ Slow, gradual titration of dose may reduce risk of skin rash ■ Estrogen increases clearance
Levetiracetam (Keppra®, Keppra®-XR, Spritam®)	Modulates neurotransmitter release through binding to the synaptic vesicle protein SV2A	■ Initial 250–500 mg bid ■ ↑ by 500–1000 mg/day every 2 weeks ■ Usual maximal dose is 3000 mg/day ■ Doses up to 4000 mg/day have been used ■ Bid dosing recommended	■ Somnolence ■ Dizziness ■ Asthenia ■ Behavioral symptoms (agitation, emotional lability, hostility, depression, and depersonalization) reported	■ No hepatic metabolism ■ 66% excreted unchanged in urine ■ Less than 10% protein bound ■ No significant drug interactions reported
Oxcarbazepine (Trileptal, Oxtellar®)	Inhibits sodium channels	■ *Monotherapy:* ■ Initial 300 mg bid ■ ↑ weekly up to 1200 mg/day ■ Can increase to 2400 mg/day ■ *Adjunctive therapy:* ■ Initial 300 mg bid ■ ↑ weekly up to 1200 mg/day	■ Dizziness ■ Somnolence ■ Diplopia ■ Nausea ■ Ataxia ■ May cause hyponatremia; most cases asymptomatic, more common in older adults ■ A 25% cross-sensitivity for skin rash reported between oxcarbazepine and carbamazepine	■ Parent is a prodrug; the MHD is the active component ■ Readily converted to MHD via omnipresent cytosolic enzymes ■ Lacks autoinduction properties ■ In doses >1200 mg/day, may affect oral contraceptives
Perampanel (Fycompa®)	Inhibits (AMPA) glutamate receptor	■ Initial 2 mg once-daily HS (not on enzyme-inducing ASDs) ■ OR ■ 4 mg once-daily HS (on enzyme-inducing ASDs) ■ ↑ by 2 mg/day every week ■ 4–12 mg/day recommended as target dosage range ■ Once-daily dosing HS recommended	■ Dizziness ■ Gait disturbance ■ Somnolence ■ Fatigue ■ Risk of falls in older adult patients ■ Aggression ■ Hostility ■ Irritability ■ Anger ■ Homicidal ideation ■ Adverse effects may be worsened by alcohol	■ Avoidance of alcohol is recommended ■ Enzyme-inducing ASDs reduce perampanel exposure by 50%–67%; higher doses may be needed ■ Perampanel 12 mg/day may reduce effectiveness of hormonal contraceptives containing levonorgestrel ■ Boxed warning for serious or life-threatening psychiatric and behavioral adverse effects
Phenobarbital	Prolongs opening of GABA receptors	■ Initial 1 mg/kg/day; titrate to therapeutic response ■ For full dose response, wait for 2–3 weeks between doses	■ Sedation (chronic) ■ Behavior disturbances common, especially in children ■ Possibly impairs learning and intellectual performance ■ Long-term use may cause osteomalacia	■ Considered outmoded for ASD therapy in most patients ■ Adverse effects outweigh benefits ■ IV use for refractory status epilepticus
Pregabalin (Lyrica®)	Inhibits calcium channels	■ Initial 50 mg bid ■ Titrate to therapeutic response with maximal daily dose at 600 mg/day in divided doses (bid or tid)	■ Dizziness ■ Blurred vision ■ Weight gain	■ No significant interactions with other ASDs ■ Can be useful for patients with concomitant pain disorders

Primidone (Mysoline®)	Prolongs opening of GABA receptors	■ Initial 100–125 mg/day ■ Usual dose 750–1500 mg/day ■ In divided doses 3–4/day ■ Maximum 2000 mg	■ Nystagmus ■ Diplopia ■ Fatigue ■ Drowsiness ■ Emotional disturbances ■ Blood dyscrasias ■ Liver dysfunction ■ Rarely causing SJS	■ Valproate may increase its level, whereas phenytoin may decrease it ■ May decrease concentration of AntiXa anticoagulation drugs ■ Contraindicated in patients with porphyria
Rufinamide (Banzel®)	Inhibits sodium channels	■ Initial 200–400 mg/bid ■ Increase by 200–400 mg/bid every other day ■ Maximum 3200 mg bid ■ Initial dose in children is 10 mg/kg bid, and increase by the same amount every other day	■ QT shortening ■ Drowsiness ■ Headache ■ Vomiting ■ Nausea	■ No renal or hepatic dose adjustment ■ On discontinuation reduce the dose by 25% every 2 days ■ Should be taken with food ■ Contraindicated in patients with familial short QT syndrome
Stiripentol (Diacomit®)	May enhance GABA activity	■ Initial 10–15 mg/kg/day ■ May divide the amount in two to three doses ■ Titrate to a target dose of 50 mg/kg/day over 2–4 weeks ■ Maximum 3 g/day	■ Decreased appetite ■ Drowsiness ■ Agitation ■ Ataxia ■ Hypotonia ■ Tremor ■ Decreased platelet and neutrophil count	■ Used as adjunctive therapy for Dravet syndrome ■ Multiple drug interactions as it is a major substrate of CYP3A4 and moderately inhibits CYP2C19
Tiagabine (Gabitril®)	Inhibits GABA reuptake	■ Initial 4 mg/day ■ ↑ by 4 mg/day at 7 days; then ↑ daily dose by 4–8 mg every week ■ Maximal recommended dose of 32 mg/day in adolescents or 56 mg/day in adults ■ Bid to qid dosing recommended	■ Drowsiness ■ Nervousness ■ Difficulty with concentration or attention ■ Tremor ■ Nonspecific dizziness described by some patients	■ Increased clearance when given with enzyme inducers ■ Tid or qid doses probably needed ■ Potential for protein-binding displacement interactions with other highly protein-bound drugs (eg, valproate) ■ Significance of protein-binding displacement not known ■ Substrate for CYP3A4
Topiramate (Topamax®, Trokendi®, Qudexy®)	Inhibits sodium channels and activates GABA receptors, inhibits glutamate receptors	■ Initial 50 mg HS ■ ↑ daily dose by 50 mg every 7 days ■ 200–400 mg/day recommended as target dosage range ■ Larger daily doses associated with increased CNS adverse effects ■ Bid dosing recommended	■ May be dose related: ■ Sedation ■ Dizziness ■ Difficulty concentrating ■ Confusion ■ Possible weight loss ■ Weak CA inhibitor; may cause or predispose to kidney stones; CA inhibition also possibly related to paresthesias in up to 15% ■ Risk of hypohidrosis and hyperthermia especially in children ■ Rarely associated with angle-closure glaucoma	■ Approximately 70% renal elimination ■ Phenytoin and carbamazepine may reduce topiramate plasma concentrations and potentially increase dosage requirements ■ Topiramate may cause small ↑ in phenytoin plasma concentration ■ Advise patients to drink plenty of fluids ■ May affect oral contraceptives above 200 mg/day
Valproate (Depakene®, Depakote®, Depakote®-ER)	Increase activity of GABA, inhibits sodium channel	■ Initial 5–10 mg/kg/day (sprinkle caps or syrup) ■ ↑ by 5–10 mg/kg/day weekly to therapeutic effect or target serum concentration ■ Daily dosing recommended for ER product ■ Doses should be 8%–20% higher than non-ER products	■ GI upset ■ Hair loss ■ Appetite stimulation ■ Weight gain ■ Dose-related tremor and thrombocytopenia may occur ■ Serious hepatotoxicity extremely rare with monotherapy	■ Enteric-coated products or ER tablets may ↓ GI upset ■ Time to peak serum concentrations delayed for 3–8 hours with enteric coating; longer delay if given with food ■ Effective against primarily generalized tonic–clonic and absence seizures ■ Young children are generally at a higher risk for serious hepatotoxicity, but it can occur at any age ■ Monitor LFTs and platelet count
Vigabatrin (Sabril®, Vigadrone®)	Irreversibly inhibits GABA transaminase that increases GABA concentration	■ Initial 500 mg bid ■ Titrate in increments of 500 mg weekly ■ Usual dose 1500 mg bid ■ No established maximum dose in adults	■ Skin rash ■ Weight gain ■ Viral infection ■ Vomiting ■ Constipation ■ Dizziness ■ Drowsiness ■ Fatigue ■ Tremor ■ Blurred vision ■ Nystagmus ■ Vision loss	■ Boxed warning for permanent vision loss ■ Ophthalmic examination every 3–6 months is recommended ■ On discontinuation reduce by 1 g/day every week ■ Require dose adjustment in patients with renal impairment
Zonisamide (Zonegran®)	Inhibits sodium and calcium channels	■ Initial 100 mg daily ■ ↑ by 100 mg/day every 2 weeks ■ Usual maintenance doses of 200–400 mg/day ■ Maximum 600 mg/day	■ Somnolence ■ Nausea ■ Ataxia ■ Dizziness ■ Headache ■ Anorexia ■ Weight loss ■ Nephrolithiasis ■ Serious skin eruptions, oligohidrosis, and hyperthermia have also occurred	■ Broad spectrum, long half-life ■ 35% of dose is excreted unchanged in the urine ■ A substrate of CYP3A4; enzyme induction may increase clearance ■ Advise patients to drink plenty of fluids

ASD, antiseizure drugs; AV, atrioventricular; bid, twice daily; CA, carbonic anhydrase; CNS, central nervous system; CYP, cytochrome P-450; DRESS, drug reaction with eosinophilia and systemic symptoms; ER= extended release; GABA,

gamma-aminobutyric acid; GI, gastrointestinal; HS, at bedtime; IM, intramuscular; IV, intravenous; LFT, liver function test; MHD, monohydroxy derivative; NMDA, *N*-methyl-D-aspartate; qid, four times daily; qod, every other day; SJS, Stevens-Johnson syndrome; tid, three times daily.

ADVERSE EFFECTS

Common adverse effects for ASDs are described in Table 60-5. Most of them are less sedating than older medications such as phenobarbital or phenytoin. The most common adverse effects seen in the clinical trials with eslicarbazepine were ataxia, blurred and double vision, dizziness, fatigue, headache, nausea, somnolence, tremor, vertigo, and vomiting.[70]

Cenobamate is one of the newest ASDs, and therefore limited data exist for adverse effects. In clinical trials, the most common adverse effects were somnolence, dizziness, fatigue, diplopia, and headache. Serious adverse events included drug reaction with eosinophilia and systemic symptoms (DRESS) and QT shortening.[71]

Gabapentin and tiagabine have not been associated with serious adverse effects; gabapentin can cause weight gain,[72] and tiagabine can cause nonspecific dizziness relatively frequently.[73]

Common adverse effects associated with lacosamide include dizziness, headache, diplopia, nausea, and dose-dependent per rectum (PR)-prolongation. Gradual escalation to the desired dose reduces the adverse event risk.

The most serious adverse effect associated with lamotrigine is skin rash. Rashes occur in ~10% of treated patients, usually in the first 8 weeks.[74] Rashes leading to hospitalization occurred in 1 of 300 adults and 1 of 100 children. Widespread, maculopapular rashes usually appear and may progress to erythema multiforme or toxic epidermal necrolysis. Lamotrigine-related rashes may resolve rapidly when lamotrigine is discontinued. Coadministration of valproate with lamotrigine may increase the likelihood of dermatologic reactions; it is partly for this reason that more conservative dosage titration and lower maintenance doses of lamotrigine are recommended for patients receiving concomitant valproate. Higher starting doses and

more rapid dose escalation than those recommended by the manufacturer also increase the risk of skin rash.

Levetiracetam is generally well tolerated, with the most common adverse events in clinical trials being asthenia, vertigo, flu syndrome, headache, rhinitis, and somnolence. The most serious adverse effects are behavioral and are more common in patients with a history of behavioral problems.[75] Levetiracetam should be used with caution in patients with a history of suicidal ideations.

Oxcarbazepine, a keto derivative of carbamazepine, is essentially a prodrug for the monohydroxy active metabolite.[76] Oxcarbazepine probably causes less frequent, less severe adverse effects compared with carbamazepine, with the exception of hyponatremia. Hyponatremia is more common with oxcarbazepine than with carbamazepine. Baseline and periodic serum sodium monitoring is indicated during oxcarbazepine therapy. The most commonly reported adverse effects of oxcarbazepine in clinical trials include ataxia, dizziness, fatigue, nausea, somnolence, and diplopia.

Adverse effects of pregabalin are dose dependent and usually occur within the first 2 weeks of treatment.[77] Somnolence, dizziness, and ataxia are the most common. Pregabalin also appears to be associated with a dose-related weight gain.

Topiramate can cause cognitive disturbances, lethargy, and impaired mental concentration when given in large daily doses (especially in combination with other ASDs) or when the dosage is titrated too aggressively.[78] Topiramate has caused nephrolithiasis in ~1.5% of treated patients. This adverse effect is believed to be related to the inhibition of carbonic anhydrase by topiramate, with resulting increased urinary pH and decreased citrate excretion. Topiramate can also cause acute, secondary angle-closure glaucoma, which presents within the first month of therapy. Topiramate is associated with weight loss.

Zonisamide is a sulfonamide derivative and thus is contraindicated in patients allergic to sulfonamides.[79] The most commonly reported adverse events include ataxia, somnolence, agitation, and anorexia. Kidney stones have developed in 3% to 4% of patients, some of whom had a family history of nephrolithiasis.

PHARMACOKINETICS

The newer ASDs have somewhat different pharmacokinetic profiles from those of older agents. They also differ in their tendency to interact with other ASDs. Gabapentin is excreted entirely by the kidneys as unchanged drug and is not significantly bound to plasma protein. Gabapentin has a relatively short half-life and should be administered three times daily.[80]

Cenobamate is extensively metabolized by glucuronidation via UGT2B7 and by oxidation via CYP2E1, CYP2A6, and CYP2B6. With a long half-life of 50–60 hours, cenobamate can be administered once daily.[71]

Lacosamide is excreted mostly by the kidneys. Dosage reductions are warranted for patients with renal impairment (creatinine clearance <30 mL/minute). It is <15% bound to plasma protein, has a 12- to 13-hour half-life, and is administered twice daily.[81]

Lamotrigine is primarily eliminated by hepatic glucuronidation and excretion of metabolites in the urine. Other ASDs, such as carbamazepine and phenytoin, induce the hepatic metabolism of lamotrigine. When lamotrigine is coadministered with enzyme-inducing drugs, its half-life decreases from ~24 to 15 hours. Valproate inhibits lamotrigine metabolism, causing increases in half-life and serum concentrations.[82,83] Patients treated with both lamotrigine and carbamazepine may experience more nausea, drowsiness, and ataxia. It appears likely that this interaction represents a pharmacodynamic interaction between lamotrigine and carbamazepine.[84]

Levetiracetam has a short half-life and is eliminated primarily by renal mechanisms. Dosage reductions are warranted for patients with renal impairment (creatinine clearance <80 mL/minute). The drug has a low potential for interactions with other drugs.[85]

Both eslicarbazepine acetate and oxcarbazepine are prodrugs. They cause less hepatic enzyme induction than carbamazepine and may therefore be less likely to interact with other medications. Both, however, increase the metabolism of oral contraceptive hormones.[86,87] Because eslicarbazepine and oxcarbazepine have

similar mechanisms of action to that of carbamazepine, it is unlikely that either would offer significant benefits to R.H. because she has not responded to maximal tolerated doses of carbamazepine.[70,76]

Pregabalin is excreted entirely by the kidneys as unchanged drug and is not significantly bound to serum proteins. Unlike gabapentin, which requires more frequent dosing, pregabalin can be administered two or three times daily.[77]

Tiagabine has a relatively short half-life (4–7 hours). It should be administered at least twice daily.[73] Concurrently administered enzyme-inducing ASDs may reduce the half-life of tiagabine to 2 to 3 hours and necessitate use of larger daily doses and, possibly, shorter dosing intervals. Tiagabine is highly protein bound (96%), and it is displaced from protein-binding sites by valproate, salicylate, and naproxen. The clinical significance of these protein-binding interactions is unknown.

Topiramate has a half-life of ~20 hours, which allows twice-daily administration. It is only partially excreted by hepatic metabolism; ~70% of the drug is excreted unchanged by the kidneys. Topiramate is minimally protein bound (~10%–15%). When topiramate is coadministered with enzyme-inducing agents, topiramate clearance is increased. This interaction may necessitate titration to somewhat higher doses when topiramate is used with enzyme-inducing drugs.

Zonisamide has a long half-life and low protein binding. It is eliminated by both hepatic metabolism and renal excretion. The average half-life of zonisamide is 63 hours, but there is wide interpatient variation. Serum levels of zonisamide are reduced by enzyme-inducing ASDs, but clinical consequences of pharmacokinetic interactions with zonisamide are rare.[79]

On the basis of efficacy and adverse effect characteristics, cenobamate, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, or zonisamide could be considered for use as adjunctive therapy for R.H. In young, active patients such as R.H., sedation might prove to be a problem; however, it is not clear that any of these drugs predictably causes more initial or long-term sedation. The short half-lives of gabapentin and tiagabine and the associated need for R.H. to take several

doses during the day might decrease her adherence. Therefore, cenobamate, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, or zonisamide would be reasonable choices on the basis of convenience. Because the patient is not tolerating carbamazepine, it does not make sense to switch to either eslicarbazepine or oxcarbazepine.

The reason felbamate and perampanel were not discussed in the Adverse Effects and Pharmacokinetics sections above is that these authors do not believe they are good options for R.H. at this point. Perampanel has an FDA box warning (behavioral reactions). Felbamate's usefulness is seriously limited by its association with aplastic anemia and hepatic failure.

POTENTIAL THERAPIES

Other ASDs that may become available in the near future include fenfluramine, padsevonil, ganaxolone, and huperzine A.[88–90] These drugs may become useful as alternatives or adjuncts to established and newer medications in the future.

With advancing technology and knowledge about genes and brain networks, future treatment strategies should move from controlling symptoms of epilepsy with ASDs to prevention and cure. For ASD-resistant epilepsy, much research is examining the role of multidrug transporters (eg, *P*-glycoprotein) at the blood–brain barrier. These proteins may act as a defense mechanism by limiting the accumulation of ASD in the brain.[91] Although it has not yet had much of an impact on the clinical care of patients with epilepsy, pharmacogenetics of ASD therapy is continually advancing.[92]

Lamotrigine Therapy

INITIATION AND DOSAGE TITRATION

Case 60-2, Question 2: R.H. is to be started on lamotrigine as adjunctive therapy to her carbamazepine. Outline a treatment plan for initiating and monitoring therapy for R.H. What should R.H. and her family be told about this medication and how to use it?

Lamotrigine therapy should be initiated in R.H. with a slow upward dosage titration to minimize early sedative effects and reduce the likelihood of skin rash. An initial dosage of 50 mg/day given at bedtime is recommended; the daily dose can be increased by 50 mg every 1 to 2 weeks. Because R.H. is currently receiving carbamazepine, induction of liver enzymes is likely to increase her dosage requirements for lamotrigine and allow a less conservative dosage titration. A twice-daily schedule is recommended for maintenance therapy. Usual maintenance dosages of lamotrigine are ~300 to 500 mg/day. A patient's ability to tolerate this medication ultimately determines dosage limitations. Onset of adverse effects (eg, nausea, diplopia, ataxia, and dizziness) may prevent further dosage increases.

R.H. should be told that she may feel drowsy and possibly experience headache and upset stomach, but that these adverse effects usually disappear with ongoing therapy. She should contact her physician or other health care professional if severe adverse effects occur that make it difficult to take the medication; this is especially important if she exhibits a rash.

ADVERSE EFFECTS AND POSSIBLE INTERACTION WITH CARBAMAZEPINE

CASE 60-2, QUESTION 3: Two days after her dosage of lamotrigine was increased to 300 mg/day (12 weeks after beginning therapy), R.H. noticed that her vision was blurring; she also reported feeling dizzy and having difficulty maintaining her balance. Previously, she had experienced only mild, occasional nausea. She had continued to experience seizures at approximately the same frequency she had before the initiation of lamotrigine. Her physician had encouraged her to continue taking the medication and explained that it would take time to increase the dose to possibly effective levels. Her current carbamazepine serum concentration is essentially unchanged when compared with when she was taking it in monotherapy. Do these new adverse effects represent treatment failure with lamotrigine? If not, how might these new adverse effects be managed?

R.H.'s adverse effects may limit further dosage increases. Her current adverse effects might represent carbamazepine intoxication, lamotrigine adverse effects, or an interaction between these two medications. Because R.H. tolerated the same carbamazepine dose previously, carbamazepine "intoxication" seems a less likely cause. Assessing the role of lamotrigine as the only cause is difficult. Obtaining a lamotrigine serum concentration to aid in assessing her adverse effects is not likely to be helpful. A usual "therapeutic range" for lamotrigine serum concentrations has not been established. Clinical studies have failed to demonstrate a significant correlation between lamotrigine serum concentrations and either therapeutic or adverse responses.[93,94] Her symptoms may also be related to an apparent pharmacodynamic interaction between lamotrigine and carbamazepine.[84] The effects experienced by some patients taking both drugs may be relieved by reducing the carbamazepine dosage.

Levetiracetam Therapy

INITIATION AND DOSAGE TITRATION

Case 60-2, Question 4: R.H.'s carbamazepine dosage was reduced from 1800 to 1400 mg/day. After 5 days, her adverse effects persisted, and her seizure frequency appeared to be increasing. The clinician decides to abandon lamotrigine therapy and institute treatment with levetiracetam. Recommend a plan for initiating R.H.'s levetiracetam treatment. How should R.H. levetiracetam therapy be initiated?

R.H. previously tolerated and had a better therapeutic response to a higher carbamazepine dose. Therefore, the dosage of carbamazepine should be returned to 1800 mg/day before levetiracetam therapy is initiated. Little specific information is available to help determine how lamotrigine can be safely discontinued. As a general rule, rapid dose reduction or abrupt discontinuation of ASDs is not recommended in other than emergency situations. Therefore, immediate reduction of R.H.'s lamotrigine dosage to 200 mg/day would seem reasonable. This

dosage could then be reduced by 50 to 100 mg every week until lamotrigine is discontinued.

Levetiracetam treatment should be instituted immediately for R.H. because of her continuing seizures. Levetiracetam does not interact with other ASDs. Therefore, discontinuing lamotrigine during initiation of levetiracetam should not create difficulties in assessing R.H.'s response. Levetiracetam should be initiated at a dosage of 250 to 500 mg two times daily.[85] Although the manufacturer recommends initiating treatment at 500 mg twice daily, patients may better tolerate lower initial doses and more gradual titration. R.H.'s daily levetiracetam dose can be increased by 500 to 1000 mg every 2 or 3 weeks, according to her tolerance of adverse effects and her change in seizure frequency. Although the drug reaches steady state quickly, allowing at least 2 weeks for observation before dosage increases may improve patient tolerability and allow for a more thorough evaluation of therapeutic response. At present, the relationship between serum concentrations of levetiracetam and therapeutic response or symptoms of intoxication is not well defined. Therefore, R.H.'s dose should be titrated to the maximal tolerated amount required to control her seizures. In controlled trials, no clear benefits were apparent at doses >3000 mg/day.

PATIENT EDUCATION

R.H. should be informed that with levetiracetam she may experience adverse effects similar to those she had with lamotrigine. R.H.'s mood should be assessed at each visit. Much reassurance and encouragement may need to be given along with this information to help ensure that R.H. adheres to her treatment regimen. Many patients become discouraged when multiple trials of medication are necessary and adverse effects are prominent.

Given that R.H.'s seizures are still not well controlled, driving restrictions that were likely put into place earlier should be continued. R.H. should be counseled not to drive until she is seizure-free, and her driving privileges have been reinstated according to applicable

state law. This restriction can be very hard for some patients to accept because it can significantly decrease their independence.

Phenytoin Therapy

INITIATION AND DOSAGE

CASE 60-3

QUESTION 1: J.N., an 18-year-old, 194.01-pound (88-kg) male college student, was diagnosed with epilepsy. He experiences generalized tonic–clonic seizures that last 2 minutes approximately three times monthly. J.N. describes a "churning" feeling in his abdomen before his seizures; this is followed by involuntary right-sided jerking of his upper extremities. An EEG showed diffuse slowing with focal epileptiform discharges in the left temporal area; it was interpreted as abnormal. No correctable cause for his seizure disorder was identified despite a thorough workup. He has no other medical conditions and takes no routine medications. He was treated initially with carbamazepine up to 600 mg/day. He could not tolerate the medication because of nausea and diplopia despite relatively low doses. J.N.'s physician has elected to implement a therapeutic trial of phenytoin. Recommend an initial dosage.

What information should be provided to J.N. about his new medication?

Selecting a nontoxic, therapeutic dose of any ASD is difficult without having information about the drug's disposition in the individual patient (ie, prior dosages and clinical response). Although "average" dosages and resulting serum concentrations for phenytoin often are quoted, interpatient variability is significant. An initial phenytoin dosage of 400 mg/day (~4.5 mg/kg/day) would be appropriate for J.N. In most patients, phenytoin therapy is initiated at or near the anticipated maintenance dose (eg, 300 or 400 mg daily in J.N.). If tolerability problems arise, J.N.'s phenytoin dose could be reduced to 200 mg daily (or 100 mg every 12 hours) and increased by 100 mg/day at weekly intervals until 400 mg/day is reached. Recently, there has been significant interest in using patient-specific genetic information to more accurately dose certain drugs, including phenytoin, with the goals of achieving a therapeutic effect quickly and avoiding dose-related toxicity. Although certain CYP2C9

homozygous allele variants have been shown to confer "slow-metabolizer" status on patients treated with phenytoin,[95] CYP2C9 genotyping of patients is not presently a part of routine clinical practice.

PATIENT EDUCATION

J.N. should be informed that he may experience initial mild sedation from phenytoin. He should be cautioned that symptoms such as blurred or double vision, dysarthria, dizziness, or staggering may indicate that his dosage is too high; he should be instructed to notify his physician, pharmacist, or other health care professional of these symptoms. It is also a good idea to inform patients, at the beginning of therapy, that adjustments of medication dosage may be necessary before the regimen is stabilized. Although J.N. is at relatively low risk for osteomalacia given his age and sex, he should be informed that long-term use of phenytoin (as well as other ASDs; see Table 60-5) is associated with an increased risk of bone mineral loss and that this adverse effect warrants monitoring periodically.

ACCUMULATION PHARMACOKINETICS

CASE 60-3, QUESTION 2: What are the characteristics of phenytoin accumulation pharmacokinetics?

Phenytoin exhibits dose-dependent (Michaelis–Menten or capacity- limited) pharmacokinetics; therefore, the usual pharmacokinetic concepts of "clearance" and "half-life" are meaningless. The apparent half-life of phenytoin changes with the dose and serum concentration. Thus, the time required to reach a new steady state after dose alteration is difficult to predict because it depends on the dose itself and the patient's pharmacokinetic parameters, V_{max} and K_m.[33] V_{max} is a kinetic constant representing the maximal rate of phenytoin elimination from the body. K_m is the Michaelis constant, the serum concentration at which the rate of elimination is 50% of V_{max}. Values for these parameters vary widely

among patients; as a result, patterns of phenytoin accumulation and the time required to achieve steady state also vary.

Many clinicians assume that phenytoin's apparent half-life is ~24 hours, and they wait 5 to 7 days before assessing the patient's clinical response and measuring serum phenytoin concentrations. Both clinical studies[96] and model simulations[97] using observed values for K_m and V_{max} have been used to estimate time required for serum concentrations of phenytoin to reach steady state. Up to 30 days may be needed for this to occur either with doses sufficient to produce steady-state serum concentrations of 10 to 15 µg/mL or with doses of 4 mg/kg/day.[33,98] Occasionally, such a dose may exceed a patient's V_{max}; the result is extremely high serum phenytoin concentrations, with probable intoxication. It is important not to assume that steady state has been reached unless widely spaced, serial serum concentrations indicate that accumulation has ceased. Alterations in phenytoin dosage before steady state has been reached can result in significant fluctuations in serum concentrations and the patient's clinical status. Such situations occur frequently and result in unnecessary confusion and expense. As always, serum concentrations in J.N. must be interpreted in the context of his clinical response.

PHENYTOIN INTOXICATION

Case 60-3, Question 3: J.N. was started on phenytoin and is now taking 200 mg every 12 hours. One week after achieving this dose, mild lateral gaze nystagmus was noted, but J.N. had no subjective problems and was seizure-free. After 3 weeks, J.N. reported double vision and feeling "drunk" and "unsteady." Significant nystagmus was present. How should J.N.'s phenytoin dosage be altered?

J.N.'s signs and symptoms indicate phenytoin intoxication. Dosage reduction is indicated. Reducing J.N.'s dosage to 360 mg/day (accomplished using both 100- and 30-mg phenytoin capsules) would be reasonable. A larger reduction may result in a loss of seizure control. Many clinicians also would have J.N. omit 1 day's

dose of phenytoin before beginning the new maintenance dosage. This would accelerate the decline in phenytoin serum levels. After this dosage change, clinical response should be monitored closely. The new maintenance dose may still be excessive, if J.N.'s V_{max} for phenytoin is low. If this were the case, continued accumulation of drug would occur despite the dosage reduction.[33]

INTRAMUSCULAR PHENYTOIN AND FOSPHENYTOIN (PHENYTOIN PRODRUG)

CASE 60-4

QUESTION 1: S.D. is a 24-year-old male institutionalized patient with a history of focal seizures with impaired awareness and secondary generalized tonic–clonic seizures. Within the past year, his phenytoin formulation was switched from phenytoin sodium capsules to phenytoin suspension because S.D. was suspected of "cheeking" his medicines and not swallowing the capsules. He has had no seizures in the past 3 months on 275 mg/day of phenytoin suspension. S.D. has now been transferred to the acute medical unit after a 2-day history of anorexia, nausea, occasional vomiting, and abdominal pain accompanied by diarrhea. His chart now states, "nothing by mouth." IM phenytoin, 275 mg (phenytoin sodium equivalents [PEs]) per day, has been ordered.

Should IM phenytoin be used for S.D.? What is the ideal dosage regimen?

S.D. is a candidate for parenteral administration of his ASD. If placement of an IV line is not planned, then IM administration is an acceptable approach to treatment; however, the type of phenytoin product administered will need to be changed. Phenytoin, itself, should not be administered by IM injection. Injectable phenytoin is highly alkaline (pH 12) and extremely irritating to tissue. After IM injection, the drug may precipitate at the injection site because of the change in pH. As a result, phenytoin crystals form a repository or depot from which the drug is slowly absorbed.[99–101] Often injection site discomfort is noted, although severe muscle damage does not seem to occur.[101]

Fosphenytoin, a phosphate ester prodrug of phenytoin, is highly water-soluble. Its solubility allows this preparation to be administered

parenterally without the need for solubilization using propylene glycol or the adjustment of pH to nonphysiologic levels. Therefore, fosphenytoin may be administered either IM or IV with less risk of tissue damage and venous irritation than with parenteral administration of phenytoin.[102–104] (See also subsequent discussion of IV administration of phenytoin and fosphenytoin.) After administration, fosphenytoin is rapidly absorbed and converted to phenytoin by phosphatase enzymes. Ultimately, the bioavailability of phenytoin from IM fosphenytoin administration is 100%.

Fosphenytoin is available as a solution containing 50 mg PE/mL. By labeling fosphenytoin this way, no dosing adjustments are necessary when converting from phenytoin sodium to fosphenytoin or vice versa. Although the prescriber ordered 275 mg PE, S.D. may be underdosed. His oral dosage of phenytoin suspension is providing the equivalent of 300 mg/day of sodium phenytoin. Phenytoin suspension and chewable tablets contain free acid, whereas capsules contain sodium phenytoin. Therefore, phenytoin capsule products contain only 92% of the labeled content as phenytoin acid (ie, a 100-mg sodium phenytoin capsule contains only 92 mg of phenytoin acid). He should receive a 300-mg dose of fosphenytoin daily to fully replace his current dosage of phenytoin suspension.[104]

Assuming that S.D. will be given 300 mg PE of fosphenytoin daily, he will require a total of 6 mL of this injection given IM. This medication is well tolerated when given IM, and S.D.'s full daily dose can be given in a single injection without causing excessive discomfort. Some clinicians report administering IM injections of fosphenytoin as large as 20 mL in a single site without adverse consequences or serious discomfort.[105] It is also possible to divide his daily dosage into two injections given in two different sites, although many patients prefer to receive fewer injections.

ADVERSE EFFECTS

CASE 60-5

Question 1: G.R. is a 53-year-old male with focal-onset epilepsy characterized by occasional tonic–clonic seizures. He has taken phenytoin for the past 2 years. His dosage of phenytoin was recently reduced from 400 to 360 mg/day because of symptoms of ASD intoxication (mild confusion, occasional diplopia, ataxia, and lateral gaze nystagmus). After the dose reduction, his confusion and diplopia decreased significantly. The neurologic evaluation at the lower dose was within normal limits. No seizures occurred during the subsequent 8 weeks. He continued to report being mildly "unsteady" on his feet. He also exhibits mild-to-moderate gingival hyperplasia and significant halitosis.

How should phenytoin-related gingival hyperplasia be managed? Because G.R.'s seizures are apparently under complete control, is there any problem maintaining him on his current dose of phenytoin?

Gingival hyperplasia

Gum hyperplasia related to phenytoin is common and troublesome. Prevalence is estimated at 40% to 50% of treated patients.[106] Prevalence and incidence rates, however, are misleading because the occurrence and severity of hyperplasia are related to the dose and serum concentration of phenytoin.[106,107] Gingival hyperplasia is of obvious cosmetic importance. Also, as in G.R., formation of pockets of tissue leads to difficulties with oral hygiene and halitosis may result. The mechanism of phenytoin-induced gingival hyperplasia is not well understood.[106,107]

Three approaches to the treatment of existing hyperplasia[107] are (a) dosage reduction or replacement of phenytoin with an alternative ASD, if possible, which will permit partial or complete reversal of hyperplasia; (b) surgical gingivectomy, which will correct the problem temporarily, but hyperplasia eventually recurs; and (c) periodontal treatment, which will eliminate local irritants and maintains oral hygiene. Treatment for existing hyperplasia and prevention of further tissue enlargement is important. Assuming that phenytoin is producing adequate seizure control, a combination of gingivectomy and follow-up periodontal treatment may be the best approach.

Oral hygiene programs appear to reduce the degree and severity of gingival hyperplasia when they are initiated before phenytoin therapy is started.[107] Patients who are beginning phenytoin therapy

should be educated about the role of oral hygiene in diminishing this adverse effect.

Neurotoxicity

Patients chronically maintained on intoxicating doses of phenytoin appear to be at risk for developing irreversible cerebellar damage and/or peripheral neuropathy. Cerebellar degeneration, resulting in symptoms such as dysarthria, ataxic gait, intention tremor, and muscular hypotonia, is of particular concern; this complication has been observed after episodes of acute phenytoin intoxication.[108,109] Generalized seizures also can cause cerebellar degeneration secondary to hypoxia. For this reason, the relative importance of phenytoin in the development of this condition is controversial. Nevertheless, cerebellar degeneration has been reported in several patients without hypoxic seizures.[109,110]

Symptomatic phenytoin-related peripheral neuropathy is rare, although electrophysiologic evidence of impaired neuronal conduction is found in many patients.[108,111] Symptomatic patients may report paresthesia, muscle weakness, and occasional muscle wasting. Knee and ankle tendon reflexes are absent in 18% of patients on long-term phenytoin therapy; the upper limbs are rarely affected.[112] Although areflexia may be irreversible,[112] electrophysiologic abnormalities may be closely related to excessive serum phenytoin concentrations and are reversible after dosage reduction or discontinuation.[110]

In G.R., the general discomfort of mild phenytoin intoxication and the potential for producing cerebellar degeneration necessitate a therapy alteration. The phenytoin dose should be reduced to 330 mg/day because it may produce adequate seizure control without toxic symptoms. Should seizures recur at this lower dosage, it may be advisable to consider an alternative ASD.

ANTISEIZURE DRUG IMPACT ON BONE

Some ASDs have a negative impact on bone density. People with epilepsy treated with these drugs are at increased risk for bone

disorders and fractures.[113] Longer duration of ASD therapy and exposure to multiple ASDs are thought to predict bone loss. Enzyme-inducing ASDs (carbamazepine, phenytoin, and phenobarbital) have been associated with bone loss and an increased risk for fracture. Valproate, although not an enzyme inducer, is associated with decreased bone mineral density in children.[114] Less is known about the impact of newer ASDs on bone mineral metabolism.[115] Because of the length of phenytoin use, G.R. is at risk. His bone health should be further evaluated by a dual-energy x-ray absorptiometry (DEXA) scan to examine his bone mineral density. G.R. should be evaluated for other risk factors of reduced bone health (eg, immobility, poor diet, family history). Oral calcium and vitamin D supplementation should be implemented. Depending on the outcome of evaluation, a change from phenytoin to an ASD with less or no effect on bone should be considered.

NEW-ONSET SEIZURES IN OLDER ADULTS

CASE 60-6

QUESTION 1: J.R., a 74-year-old male with newly diagnosed focal seizures, is referred to the neurology clinic for evaluation and treatment. The etiology of his new-onset seizures is presumed to be a recent cerebral infarct. His seizures are focal seizures with impaired awareness (he "blacks out" and loses track of time). He has no history of secondary generalized tonic–clonic convulsions. He has had three seizures in the last 4 weeks. His last seizure resulted in a fall down a flight of stairs. His wife reports that he is more likely to have a seizure if he gets "overtired" or "stressed-out." He is also being treated for hypertension and diabetes.

What options are available for the treatment of J.R.'s epilepsy?

There are relatively few head-to-head comparative studies of ASDs in patients with epilepsy. Even fewer studies address the comparative efficacy of ASDs in older adults. Three studies, in particular, are important when discussing ASD treatment in older adults with epilepsy.

Brodie et al[116] compared lamotrigine (*n* = 102) with carbamazepine (*n* = 48) in older adults with newly diagnosed epilepsy via a double-blind, randomized, parallel study. Discontinuation rates because of adverse effects (the primary outcome) were higher for carbamazepine (42%) than for lamotrigine (18%). Using time to first seizure as a measure of efficacy, no differences were found between the two ASDs, and the authors suggested that lamotrigine is "acceptable" as initial treatment in older adults with newly diagnosed epilepsy.

Carbamazepine (600 mg/day), gabapentin (1500 mg/day), and lamotrigine (150 mg/day) were compared for efficacy and tolerability in 593 patients older than age 55 years (mean age 72 years) with newly diagnosed epilepsy.[117] Although efficacy was similar in all three groups, study termination for adverse events varied between treatment groups. Carbamazepine had the highest termination rate (31%), followed by gabapentin (21.6%), and then lamotrigine (12.1%) (*P* = .001). The authors concluded that lamotrigine and gabapentin should be considered as initial therapy for new-onset seizures in older adults with epilepsy.

Werhahn et al[118] evaluated carbamazepine (controlled-release), lamotrigine, and levetiracetam in 359 patients age 60 years and older (mean age 71.4 years) with newly diagnosed focal epilepsy via a double-blind, randomized, multicenter trial. As with the other two studies, efficacy (as measured by seizure freedom rates) did not differ between the three drugs. But retention rate at week 58 (primary outcome) was significantly higher for levetiracetam (61.5%) than for carbamazepine (45.8%) (*P* = .02). The retention rate for lamotrigine (55.6%) was close to that of levetiracetam.

These studies in older adults with new-onset epilepsy suggest that gabapentin, lamotrigine, or levetiracetam would be good choices for initial treatment of J.R.'s epilepsy. It is noteworthy that none of these ASDs are FDA approved for newly diagnosed epilepsy.

It is also important to consider drug interaction profile, dosing frequency, and drug costs when selecting ASD therapy. Generally, older adults take more medicines than younger individuals. For example, the average number of concomitant medications in the

study by Rowan et al[117] was seven. J.R. is likely to be taking other medicines for diabetes and hypertension. Gabapentin, lamotrigine, nor levetiracetam cause drug–drug interactions, although lamotrigine is influenced more so than gabapentin or levetiracetam by other medicines. Doses of gabapentin and levetiracetam must be adjusted for renal function.

ADVERSE EFFECTS

Comparative studies identified minimal differences in efficacy. Newer ASDs, however, showed better tolerability than the older ASDs. In general, older adults not only respond to ASDs at lower doses and concentrations but they also exhibit toxicity symptoms at lower doses than do younger patients. Age-related declines in renal and hepatic function may account for those observations. The pharmacokinetics of many ASDs have been studied in older adults, and a decrease in clearance is noted as compared with the young.[119] Decreased clearance of ASDs in older adults has often been cited as a reason for their increased responsiveness to these drugs.

The impact of ASDs on cognition is an important issue for all patients with epilepsy and perhaps it is an even greater issue in older adults.[120–122] As evidenced from the study by Rowan et al,[117] CNS toxicities such as dizziness, unsteady gait, and ataxia are common adverse effects of ASDs in older adults. These symptoms may increase the risk of falls, which are of particular concern in light of the potential negative effects of ASDs on bone mineral density.

J.R. and his family should be informed about the benefits and risks associated with each ASD and they should also be incorporated into the decision-making process. ASD therapy in older adults should follow the “start low and go slow” adage, and older adults should be monitored for both efficacy (via a seizure calendar) and toxicity (reporting any intolerable adverse effects).

ABSENCE SEIZURES

Choice of Medication and Initiation of Ethosuximide Therapy

CASE 60-7

Question 1: T.D., a 7-year-old, 55.12-pound (25-kg) female, is reported by her teacher to have three or four episodes of "staring" daily. Each spell lasts 5 to 10 seconds. No convulsive movements occur during the episodes, but her eyelids appear to flutter. She is fully alert afterward. T.D.'s school performance is somewhat below average, despite an intelligence quotient (IQ) of 125. An EEG shows 3-Hertz (Hz) spike-and-wave activity. T.D. is diagnosed with typical childhood absence epilepsy. Physical examination and laboratory evaluation findings are normal, and no other positive findings are present on the neurologic examination.

What drug should be prescribed for T.D., and how should therapy with this drug be initiated?

Ethosuximide, valproate, and lamotrigine are commonly used to treat absence epilepsy in the United States. Ethosuximide and valproate are considered highly effective and preferred over lamotrigine for the treatment of childhood absence epilepsy.[123] Ethosuximide is a succinimide agent that blocks T-type calcium currents in the thalamus. The drug is effective against absence seizures but is ineffective against other seizure types. Ethosuximide is generally well tolerated. Given its lack of idiosyncratic hepatic toxicity in children, it may be preferred over valproate for the treatment of childhood absence epilepsy. Valproate, a carboxylic acid derivative, has broad-spectrum activity against many focal-onset and generalized-onset seizure types. Valproate is associated with many adverse effects that may limit use in childhood absence epilepsy. In addition to ethosuximide and valproate, lamotrigine also has been recommended as an initial monotherapy agent for treatment of absence epilepsy, although it is not FDA approved for this indication[124–126] (see Tables 60-1 and 60-5).

Valproate, ethosuximide, and lamotrigine were studied in the treatment of newly diagnosed childhood absence epilepsy.[127] The primary outcome assessed freedom from treatment failure. The rates

for valproate and ethosuximide were similar and were statistically significantly higher than lamotrigine-treated patients. Moreover, attention dysfunction was significantly more common with valproate than with ethosuximide. Valproate was also more efficacious than lamotrigine for treatment of idiopathic generalized seizures (including absence) in the Standard and New Antiepileptic Drugs (SANAD) trial.[128] Because of similar rates of efficacy and potentially more favorable adverse effect profile compared with valproate, ethosuximide is considered first line as monotherapy for childhood absence epilepsy. Valproate is more likely to cause significant nausea and initial drowsiness, and it is more likely to interact with other drugs, including ASDs. Valproate usually is reserved as a second-line therapy for patients whose absence seizures do not respond to ethosuximide.[129]

Lamotrigine is considered an alternative for patients who do not respond to the first- or second-line therapies or experience intolerable adverse effects. One-third of patients may respond favorable to a trial of lamotrigine, making it an attractive option in refractory cases. Furthermore, in select patients, a trial of a combination of valproate and lamotrigine may be considered in the event inadequate control is established with monotherapy valproate.[130] Finally, clonazepam, a benzodiazepine, may be effective for control of absence seizures as add-on therapy.[131]

Therapy with this drug is limited by prominent CNS adverse effects (sedation, ataxia, and mood changes) and development of tolerance to its antiseizure effect after long-term use.[132]

A reasonable starting agent and dose for T.D. is ethosuximide 15 to 20 mg/kg/day by mouth divided twice daily. The child should be assessed for tolerability of swallowing capsules. Ethosuximide is available in 250-mg capsules and a commercially available oral solution at a concentration of 250 mg/5 mL. The oral solution may allow for ease of titration in this patient if additional seizure control is needed. With either formulation, T.D. can start at a dose of ethosuximide 250 mg by mouth twice daily. The dose can be increased by 10 mg/kg/day or 250 mg/day for T.D., every 10 to 14 days as necessary to control seizures. The average half-life of

ethosuximide in children is ~30 hours, which would require 7 days to achieve steady state in the blood. Delaying dose adjustments by 10 to 14 days allows the drug to reach steady state and additional time to assess the response to therapy after steady state is achieved.[34]

THERAPEUTIC MONITORING

Case 60-7, Question 2: What subjective or objective clinical data should be monitored in T.D. for evidence of therapeutic and adverse effects of ethosuximide?

T.D.'s seizure frequency and any adverse effects are the primary monitoring parameters. The usual target range for ethosuximide serum concentrations is 40 to 100 µg/mL; however, a clearly defined toxicity syndrome does not reliably develop when serum concentrations exceed 100 µg/mL. Although ethosuximide traditionally is administered in divided doses, its long half-life may allow for daily administration in patients who tolerate it well. Clinicians should be alert to acute adverse effects of nausea and vomiting that are associated with large single doses of ethosuximide; should these occur, divided daily doses may be necessary.[34]

Ethosuximide causes neutropenia in ~7% of patients. Rarely patients may exhibit fatal pancytopenia, even upon discontinuation of the drug. Laboratory monitoring for idiosyncratic hematologic toxicity from ethosuximide often is recommended by checking a periodic CBC.[133] These hematologic reactions, however, can occur unpredictably at any time during therapy and often are missed by routine laboratory monitoring. Patient or caregiver education regarding signs and symptoms associated with leukopenia and pancytopenia (eg, sudden onset of severe sore throat with oral lesions, easy bruising, increased bleeding tendency) may be more important than laboratory monitoring.[56]

PATIENT OR CAREGIVER EDUCATION

T.D. and her parents should be counseled on the importance of good adherence to the prescribed regimen. Rapid discontinuation of ASDs (often secondary to nonadherence) may precipitate SE. The family should also be educated on the idea that antiseizure medication controls but does not cure the seizure disorder. The family should also be informed of the expectation for response to therapy, including time to achieve stable blood levels as well as potential for dose increases. T.D.'s parents should be educated on typical adverse effects such as nausea and sedation. Tolerance to these effects usually develops, although temporary dose reductions may be necessary.

GENERALIZED TONIC–CLONIC SEIZURES ACCOMPANYING ABSENCE SEIZURES

CASE 60-7, QUESTION 3: Three months later, T.D. experiences an average of one absence seizure every 2 weeks. She is currently receiving ethosuximide 750 mg/day. Her initial drowsiness has almost disappeared, and nausea was alleviated by administering doses with food. She has, however, experienced two tonic–clonic convulsions in the past month. Both seizures were witnessed by her parents and were well described. No auras or signs of focal seizure activity were apparent, and each episode consisted of typical tonic–clonic activity lasting 1 to 2 minutes. T.D. was incontinent of urine on both occasions, and postictal confusion and drowsiness were significant. Physical examination and laboratory testing showed no abnormalities. A repeat EEG continued to show infrequent 3-Hz spike-and-wave discharges; no abnormal focal discharges were noted. What is the relationship between T.D.'s tonic–clonic seizures and ethosuximide therapy?

It is commonly believed, and often stated in the literature, that ethosuximide may precipitate or worsen tonic–clonic seizures; however, this effect has not been clearly demonstrated. As many as 50% of patients who initially present with absence seizures also experience tonic–clonic seizures.[134] Historically, another ASD (eg, phenobarbital or phenytoin) was added to ethosuximide therapy to

prevent tonic–clonic seizures.[135] However, routine use of drugs for prophylaxis of tonic–clonic seizures may increase the risk of toxicity and potentially reduce adherence with medication regimens. Sedative drugs, especially phenobarbital, actually may aggravate absence seizures in some patients.[136]

Assessment Regarding Need for Alteration in Antiseizure Drug Therapy and Choice of Alternative Antiseizure Drug

Case 60-7, Question 4: What alterations are indicated in T.D.'s drug therapy because of the appearance of generalized tonic–clonic seizures?

Drug therapy for prevention of tonic–clonic seizures is indicated. Phenytoin, carbamazepine, or valproate might be considered for use in T.D. Owing to her age and sex, many clinicians would avoid using phenytoin because of its dysmorphic and cosmetic adverse effects. Carbamazepine is widely used for secondary generalized tonic–clonic seizures and some cases of tonic–clonic seizures in children. It lacks many of the troublesome, common adverse effects associated with phenytoin. Carbamazepine, however, is not effective for control of absence seizures. Therefore, it is likely that both ethosuximide and carbamazepine would be needed by T.D. Additionally, carbamazepine may exacerbate absence seizures in children with mixed seizure disorders.[137,138] The need for polytherapy and the possible risk of seizure exacerbation make carbamazepine a less attractive treatment option for T.D.

Valproate is effective for controlling both absence and primary generalized tonic–clonic seizures.[42,50] T.D. appears to have primary generalized tonic–clonic convulsions; focal signs (eg, unilateral or single limb involvement) were not observed, and focal discharges (eg, isolated abnormal electrical activity localized to one portion of the brain) were not found on the EEG. Although neither observation completely rules out secondary generalized tonic–clonic seizures,

the likelihood seems low. Therefore, valproate may offer advantages over carbamazepine in terms of efficacy. In addition, both of T.D.'s seizure types potentially could be controlled with a single medication.

Valproate Therapy

INITIATION AND DOSAGE

Case 60-7, Question 5: T.D.'s physician elects to start valproate and discontinue ethosuximide. The goal is to control both seizure types with valproate alone. What process should be used to discontinue ethosuximide and initiate valproate?

Techniques used by clinicians to substitute one ASD for another depend largely on experience and clinical judgment. Generally, it is best to attain a potentially therapeutic dose of a new medication before attempting to discontinue the previous drug. Ethosuximide has a relatively long half-life, whereas valproate has a short half-life. Steady-state serum concentrations of valproate can be established and evaluated rapidly. Evaluation of the effect of decreases in the ethosuximide dose will take longer because of the prolonged elimination. Once a desired valproate dose or serum concentration has been achieved, the ethosuximide dose can be reduced gradually by 250 mg/day every 2 to 4 weeks.

Valproate should be initiated at a dose of 10 to 15 mg/kg/day divided twice daily. A reasonable starting dose for T.D. is 125 to 250 mg twice daily. Valproic acid syrup or capsules or divalproex sodium can be used. Divalproex often is preferred because it may cause fewer GI adverse effects than valproic acid. Syrup forms of valproate probably should be avoided unless extremely small doses are required (eg, for infants) or the patient cannot swallow capsules. Valproate syrup has an unpleasant taste, and its rapid absorption increases the likelihood of acute, dose-related adverse effects such as nausea. Lower initial valproate doses are less likely to cause acute adverse effects (eg, drowsiness and GI upset). Weekly dose increases of 5 to 10 mg/kg/day usually are well tolerated and would

be appropriate for T.D. More rapid increases may be desirable if tonic–clonic seizures occur frequently. The maximal recommended dosage of valproate is 60 mg/kg/day. Many patients, especially those receiving enzyme-inducing drugs, require higher-than-recommended doses to achieve adequate clinical effect; other patients may respond at much lower doses. Valproate can be titrated in T.D. to a target serum concentration of 50 to 100 µg/mL. Once ethosuximide is withdrawn, the valproate dose can be further adjusted on the basis of seizure frequency and adverse effects.

DOSAGE FORMS

Case 60-7, Question 6: T.D. has been taking valproic acid capsules, 250 mg tid, for 3 weeks. Ethosuximide was discontinued 2 weeks ago. At that time, a valproate serum level just before her morning dose was 68 µg/mL. She has not experienced generalized tonic–clonic seizures for 6 weeks but continues to have an absence seizure every 2 to 3 weeks. T.D. reports nausea, epigastric burning pain, and occasional vomiting lasting ~1 hour after her doses of valproate. All recent laboratory tests were within normal limits. Administration of the drug with meals is only partially helpful. What alterations can be made in T.D.'s dosing regimen to relieve these symptoms and possibly improve seizure control?

T.D. appears to be a candidate for the use of an enteric-coated valproate preparation or extended-release divalproex. Divalproex tablets are available as an enteric-coated delayed-release preparation, which causes delayed rather than extended absorption of valproate; therefore, these tablets are not a sustained-release product formulation. When patients are switched from nonenteric-coated formulations to divalproex tablets, the frequency of administration should not be decreased. Valproic acid and enteric-coated dosage forms of valproic acid or divalproex are completely absorbed so they can be interconverted at the same total daily dose of medication.[139,140] An extended-release formulation of divalproex sodium is also available that can be administered as a single daily dose. Extended-release divalproex (divalproex ER), however, is not bioequivalent to other dosage forms of valproate.[141] The

manufacturer recommends a dose increase of 8% to 20% when patients are converted to divalproex ER from other forms of valproate. T.D.'s valproic acid capsules can be replaced with an equal daily dose of divalproex tablets to attempt to alleviate the GI disturbances. Divalproex should be administered three times daily. Alternatively, T.D. could be given 1000 mg of divalproex ER once daily. T.D. should see relief from GI adverse effects within a week of the therapy change. Furthermore, if the GI upset resolves, the dose of divalproex can be increased in an effort to improve seizure control.

Capsules containing enteric-coated beads of divalproex also are available; the 125-mg capsule contents can be dispersed in food for administration to children or others who have difficulty swallowing tablets or capsules. In addition, use of the "cap" end of the capsule to measure half of the contents can approximate doses of 62.5 mg.

PHARMACOKINETICS AND SERUM CONCENTRATION MONITORING

Case 60-7, Question 7: Two weeks later, T.D. returns for follow-up. Her GI symptoms have resolved. She has been taking divalproex tablets 250 mg with breakfast and lunch and 375 mg with a bedtime snack for the past week. She has had no seizures in the past 2 weeks and no adverse effects. A valproate serum level before her morning dose today was 117 µg/mL (recall her previous valproate level of 68 µg/mL). The laboratory reports that duplicate determinations of this level agreed within 5 µg/mL. T.D. and her parents are able to correctly state the instructions and the tablet count in her prescription bottle is correct. She denies other medication use. How can this disproportionate increase in her valproate serum concentration be explained, and what is the clinical significance? Does valproate exhibit dose-dependent pharmacokinetics?

The observed changes in T.D.'s valproate serum concentrations are probably not the result of dose-dependent metabolism as is seen with phenytoin. Instead, these changes are more readily explained by the absorption characteristics of divalproex tablets. Peak serum concentrations of valproate after administration of divalproex may be

delayed for 3 to 8 hours, and administration of food may further delay absorption.[142] In addition, diurnal fluctuation in both the rate and extent of absorption of divalproex may be significant. Absorption may be reduced by approximately one-third, and peak plasma concentrations may be delayed for up to 12 hours for divalproex doses administered in the evening.[35] Twelve to 15 hours probably elapsed between the administration of T.D.'s last dose and blood sampling; therefore, the currently reported blood level may more closely approximate a peak concentration than a trough concentration. Previous blood levels, determined while she was receiving immediate-release valproic acid capsules, are more likely to have been trough concentrations. Another explanation is that T.D.'s adherence to her prescribed regimen also may have increased because of the change in dosage form and reduced adverse effects.

Other pharmacokinetic factors may have actually moderated this unusual increase in valproate concentrations. Valproate concentrations may fluctuate throughout the day in a pattern that does not reflect the timing of doses.[143] This fluctuation may be partially related to changes in serum concentrations of endogenous fatty acids that displace valproate from protein-binding sites. Valproate's hepatic clearance is restrictive (ie, valproate has a low extraction ratio, and its clearance is limited by the free fraction of drug in plasma). Therefore, when valproate is displaced from protein-binding sites, the free fraction of drug in the plasma increases and subsequently the clearance increases. As a result, free serum concentrations of valproate increase only transiently, whereas total serum concentrations decrease. Valproate also exhibits dose dependency in its binding to serum proteins. As the serum concentration approaches 70 to 80 μg/mL, binding sites on albumin molecules become saturated, and the free fraction of drug in the plasma increases.[34,139] Considering the extensive variability in serum concentrations, serum valproate concentrations may not be particularly useful to guide therapeutic decisions.[137]

The clinical significance of T.D.'s elevated valproate serum concentrations is minimal. She is not experiencing symptoms suggestive of valproate toxicity, and it is too soon after the dosage

increase to assess the effect of this change on her seizure frequency. Therefore, alteration in her drug therapy is unnecessary at present and might only confuse evaluation of her response to this drug. She should be observed for an additional 4 to 6 weeks to evaluate seizure frequency before further alterations in her dosing regimen are considered. Further increases in her dosage are not contraindicated as long as she is tolerating the medication and requires additional seizure control.

HEPATOTOXICITY

Case 60-7, Question 8: Two months later, T.D. is taking 375 mg of divalproex tid with meals. She has had no absence seizures for 5 weeks and no generalized tonic–clonic seizures for 10 weeks. Yesterday, her valproate plasma concentration was 132 μg/mL. In addition, her alanine aminotransferase (ALT) was 32 international units/mL, and her aspartate aminotransferase (AST) was 41 international units/mL. All other laboratory tests (bilirubin, alkaline phosphatase, lactate dehydrogenase, prothrombin time, and serum albumin) were normal. T.D.'s LFTs have been monitored monthly since she began taking valproate, and they were previously normal. Physical examination was negative for scleral icterus, abdominal pain, or other signs of liver disease. What is the most appropriate approach to manage elevated liver enzymes caused by valproate therapy in T.D.?

Liver damage related to valproate therapy appears to be caused by accumulation of hepatotoxic metabolites of valproate (probably 4-en-valproate) in certain patients.[144,145] These metabolites may be formed in larger quantities in patients who also receive enzyme-inducing drugs such as phenobarbital. Most cases of fatal hepatotoxicity have occurred in young (age <2 years) patients with neurologic and metabolic abnormalities who also had severe, difficult-to-control seizures and who were taking multiple ASDs.[144–149] It is important to recognize, however, that severe hepatotoxicity is not limited to this population.[150] Liver damage occurs early in therapy and symptomatically resembles fulminant hepatitis with hepatic failure. Patients may experience vomiting, drowsiness, lethargy, anorexia, edema, and jaundice, which often precede laboratory

evidence of hepatic damage. Liver biopsies in affected patients show evidence of hepatic necrosis and steatosis. Death results from hepatic failure or a Reye-like syndrome.[145,147,151]

Asymptomatic elevations in liver enzymes (such as those found in T.D.) occur commonly during the first 6 months of treatment with valproate and usually are not associated with severe or potentially fatal valproate-induced hepatotoxicity. These changes in aminotransferase usually disappear without alteration in therapy; in some cases, temporary dosage reduction is followed by normalization of laboratory tests within 4 to 6 weeks.[145,147] Without systemic symptoms or other signs of significant liver damage, it is unlikely that the laboratory abnormalities observed in T.D. represent severe liver toxicity from valproate. Because T.D. is responding well to valproate therapy, no change in therapy is warranted at this time. Laboratory testing probably can be repeated in 4 to 6 weeks. T.D. and her family should be educated regarding the possible signs and symptoms of valproate-induced liver damage and instructed to consult their physician if T.D. experiences these symptoms.

Routine liver function tests

Case 60-7, Question 9: What is the usefulness of routinely monitoring LFTs in patients receiving valproate?

Serious hepatotoxicity related to valproate therapy is extremely rare. Historically, the rate of fatal hepatotoxicity decreased significantly (despite substantial increases in the use of valproate) after the use of the drug in high-risk patients (eg, the very young) decreased and its use as monotherapy increased. Hepatotoxicity is estimated to occur in <0.002% of patients treated with valproate.[145,146,148] In children younger than age 2 years who receive ASD polytherapy, the incidence of this complication is 1 in 500 to 1 in 800. Because asymptomatic, apparently benign elevations in liver enzymes are common early in therapy with valproate and symptoms of liver damage often precede laboratory changes, frequent LFTs

during early valproate therapy are unlikely to detect serious hepatotoxicity.[56,145–147,152] Education of caregivers or patients regarding potential symptoms of hepatotoxicity, with careful observation and follow-up by health care professionals, is recommended as the most effective method to monitor for this drug-induced illness.

In patients with risk factors for hepatotoxicity (ie, very young children with associated neurologic abnormalities and those receiving polytherapy), increases in LFT values that are noted early in therapy may be clinically significant. At the onset of symptoms suggesting this condition, laboratory testing may help early detection of hepatotoxicity.

ACUTE REPETITIVE (CLUSTER) SEIZURES

Rectal Diazepam Gel

CASE 60-8

QUESTION 1: B.N., a 7-year-old, 61.73-pound (28-kg) male, has had seizures since age 3 months. He suffered anoxia at birth. His seizures usually involve initial confusion and disorientation, followed by generalized tonic–clonic convulsive activity. Despite treatment with carbamazepine at maximal tolerated doses and serum concentrations (300 mg tid; 9–11 µg/mL), he continues to have approximately two seizures monthly. Recent trials of topiramate and tiagabine as additions to his carbamazepine were unsuccessful and caused intolerable sedation and lethargy. During the past year, he has been admitted to the emergency department (ED) five times because of seizure "flurries" consisting of three to six seizures occurring during a period of 12 or fewer hours. Although he regains consciousness between these "flurry" seizures, he remains lethargic. During ED admissions, IV diazepam was administered. This was rapidly successful in terminating seizure activity. B.N.'s mother relates that she usually can identify the onset of seizure flurries; B.N.'s behavior changes, and he becomes "clingy," "whiny," and hyperactive. She also indicates that the initial seizure in a flurry differs from B.N.'s typical episodes. Before the onset of generalized seizure activity, he experiences much briefer periods of confusion.

In addition, the generalized seizures are longer and more severe (often with dramatic cyanosis) at the beginning of a "flurry."

Why is prophylactic or abortive therapy for B.N.'s seizure flurries indicated? What factors about B.N. predict successful use of such treatment, and how can it be administered?

Frequent ED visits resulting from cluster seizures are expensive and frightening for many patients and their families. B.N. continues to experience seizure flurries despite carbamazepine therapy. He responds well to IV diazepam and has a caregiver who can identify the onset of seizure clusters. His seizure clusters appear to be distinct from the other seizures that he experiences. All of these factors indicate that a trial of caregiver-administered treatment to abort these cluster episodes is likely to be helpful and should be initiated.

Rectal diazepam gel is available for home administration to patients with acute episodes of repetitive seizure activity.[153] When diazepam gel is administered rectally, peak plasma concentrations occur in ~1.5 hours,[154] and cluster seizures are often terminated within 15 minutes. Use of diazepam rectal gel is recommended only when caregivers can recognize the onset of cluster seizures, which are different from a patient's usual seizure activity. The caregivers should be trained to administer the preparation safely and to monitor the patient's response (eg, respiratory status) after administration. Caregivers should be informed that this preparation is not for as needed use with every seizure; it should be used only for identifiable cluster seizures or prolonged seizures.

B.N.'s mother should administer rectal diazepam gel at the onset of identifiable cluster seizure activity. A dose of ~0.3 mg/kg (10 mg in this patient) should be given and repeated, if necessary, within 4 to 12 hours of the first dose. B.N.'s mother should be counseled on the administration of this product and given the patient package insert, which gives complete instructions for the administration of rectal diazepam. After administration, B.N. should be monitored for at least 4 hours to ensure that no respiratory depression or other adverse effects are occurring and to assess the effect of the medication on

his seizures. The most common adverse effect seen with rectal diazepam is somnolence, occasionally accompanied by dizziness and ataxia. Respiratory depression is very uncommon.

A commercially available intranasal formulation of midazolam was approved in 2019 for use in seizure clusters.[155] Dosing and FDA approval limit the use of this formulation in children younger than age 12 years. A compounded version has been used for many years in management of cluster seizures. Some potential benefits of intranasal midazolam, regardless of formulation, over rectal diazepam may include increased social acceptability and ease of administration, improved absorption and seizure control, and less adverse effects.[156,157] Other IM, buccal, and intranasal formulations of benzodiazepines are currently being investigated for their utility in aborting cluster seizures.[158]

FEBRILE SEIZURES

Incidence and Classification

CASE 60-9

QUESTION 1: J.J., a 14-month-old female, is brought to the ED after having a generalized tonic–clonic convulsion lasting ~5 minutes. The episode occurred in association with an upper respiratory infection. On arrival in the ED, her rectal temperature was 103.1 °F (39.5 °C). She was alert at that time. All laboratory and neurologic findings, including lumbar puncture, were normal. J.J. has no history of neurologic abnormality. Her 7-year-old brother suffers from both absence and generalized tonic–clonic seizures.

What is the relationship between febrile seizures and epilepsy? How may J.J.'s convulsion be classified on the basis of the data available?

Up to 8% of children have a febrile seizure between ages 6 months and 6 years.[159,160] Simple febrile seizures occur with a fever of ≥100.4 °F (38 °C) in previously normal children younger than age 5 years. They last <15 minutes and have no focal features. The

associated seizure does not arise from CNS pathology. Complex febrile seizures show focal characteristics, lasts longer than 15 minutes, or has recurrence within 24 hours. The child may or may not have previous neurologic abnormalities. The risk of experiencing an unprovoked afebrile seizure after a febrile seizure is four times greater than in the general population. Risk factors for the development of chronic epilepsy include a family history of afebrile seizures, complex febrile seizures, and pre-existing neurologic abnormality.[159,160]

J.J.'s seizure appears to be a simple febrile seizure that developed in association with her upper respiratory tract infection. The lack of previous neurologic abnormality and normal findings on lumbar puncture and laboratory evaluation help confirm this assessment.

Treatment of Acute Seizure

Case 60-9, Question 2: How should J.J.'s febrile seizures be treated?

Because J.J. is not having a seizure at present, ASD therapy is not required. Measures to reduce her elevated temperature should be initiated; however, these measures may not reduce the risk of further seizures. Acetaminophen and tepid sponge baths usually are helpful.

If patients experience prolonged or recurrent febrile seizures, either diazepam or, less commonly, midazolam may be administered.[160–162] Rectal diazepam gel can be used for this purpose.

Prophylaxis and Choice of Antiseizure Drug

Case 60-9, Question 3: On the basis of the subjective and objective data available for J.J., is ASD therapy indicated on a long-term basis? What are the benefits and risks of ASD prophylaxis for febrile seizures?

Long-term treatment or prophylaxis with an ASD for simple febrile seizures is not recommended. Up to 54% of affected patients will have recurrent febrile seizures, and the risk of recurrence is even greater when the first episode occurs before age 13 months. Nonetheless, recurrent febrile seizures are not associated with brain damage or development of epilepsy.[159] Although administration of continuous ASD treatment may reduce the recurrence rate of febrile seizures, published guidelines recommend against this practice because of the associated adverse effects of medication use.[163]

Prophylactic administration of various fast-acting agents, given during fever episodes, has been studied as an alternative to continuous treatment for the prevention of febrile seizures. Agents in both the ASD and antipyretic drug classes have been studied in this regard, but no clinically important benefits have been found.[164–168] Thus, ASD prophylaxis for febrile seizures is probably not warranted for J.J., even though she is at risk for both development of epilepsy and recurrence of febrile seizures. Currently, evidence does not suggest that medication will reduce the likelihood of developing epilepsy. Close medical follow-up of J.J. is warranted. Her parents should be counseled to contact a physician if J.J.'s febrile seizure is accompanied by focal features or last longer than 15 minutes; or, if J.J. experiences afebrile seizures. Antipyretic medications may be administered for comfort measures during febrile illnesses, but there is no evidence to support that the administration of antipyretics reduces the occurrence of future febrile seizures.

SKIN RASH: HYPERSENSITIVITY REACTIONS TO ANTISEIZURE DRUGS

CASE 60-10

QUESTION 1: R.S., a 34-year-old male, has been taking phenytoin 200 mg bid for the past 7 weeks to control focal seizures with impaired awareness and secondary generalized tonic–clonic seizures. Seizures began ~4 months ago

after surgical evacuation of a subdural hematoma. Today, he appears at the walk-in clinic with an “itchy rash” that began 2 days ago. He describes “feeling lousy” for the past week. On examination, he is febrile (101.3 °F [38.5 °C] orally). A maculopapular, scaly, erythematous rash covers his upper extremities and torso, and the mucous membranes of his mouth appear to be mildly inflamed. Cervical lymphadenopathy is noted, and the liver is found to be enlarged and tender. R.S. also relates that his urine has become very dark in the past 2 days and that his stools are light colored.

What is the significance of R.S.’s skin rash and other signs and symptoms? Are these likely to be related to his phenytoin therapy?

Skin-related adverse reactions (eg, rash, urticarial) are relatively common (2%–3% of patients) adverse effects related to ASD therapy. Skin rash is most commonly associated with phenytoin, lamotrigine, carbamazepine, and phenobarbital. Most cases are relatively mild, but severely affected patients may exhibit Stevens–Johnson syndrome or a systemic hypersensitivity syndrome accompanied by severe hepatic damage. In R.S.’s case, signs and symptoms suggesting hepatic involvement accompany the skin rash. Fever, lymphadenopathy, and apparent inflammation of mucous membranes also suggest a hypersensitivity reaction to phenytoin with multisystem involvement and the potential for progression to Stevens–Johnson syndrome. Viral infection (eg, hepatitis, influenza, infectious mononucleosis) should be considered and ruled out as a possible cause of R.S.’s symptoms before they are attributed to phenytoin therapy.[169–172]

DRESS syndrome is a type of hypersensitivity syndrome that can occur with some drugs, including phenytoin and other ASDs, that is most commonly seen in adults. Typically, patients with this syndrome present with fever, skin rash, and lymphadenopathy during the first 2 months of ASD therapy. Hepatomegaly, splenomegaly, jaundice, or bleeding manifestations may occur. Laboratory manifestations often include leukocytosis with eosinophilia, elevated serum bilirubin, and elevated AST and ALT. When a phenytoin hypersensitivity reaction includes significant hepatotoxicity, fatality may occur in as many as 38% of affected patients.[169]

A high likelihood exists that R.S. has developed a severe reaction to phenytoin; the clinical manifestations and the timing of their appearance are typical of this reaction. Phenytoin should be discontinued immediately pending diagnostic clarification. R.S. should be hospitalized for evaluation of other possible causes of his symptoms such as viral illness and treatment. Treatment of phenytoin-related hypersensitivity and hepatotoxicity is symptomatic and supportive. Intensive therapy with corticosteroids has commonly been used, although little objective evidence exists for beneficial effects of this treatment. Potential complications of this reaction include sepsis and hepatic failure; these conditions should be treated specifically.

CASE 60-10, QUESTION 2: R.S. was hospitalized and treated with oral prednisone and topical corticosteroids. Other potential causes for his condition were ruled out, and his signs and symptoms were attributed to cutaneous and systemic phenytoin hypersensitivity. His fever resolved within 5 days; the skin rash became exfoliative but resolved without infectious complications. Laboratory parameters began to normalize after 10 days. While he was hospitalized, R.S. experienced three generalized tonic–clonic seizures that were treated acutely with administration of IV lorazepam. R.S. was afebrile at the time these episodes occurred. What information regarding the pathogenesis of phenytoin hypersensitivity and hepatotoxicity can be used to guide selection of an alternative ASD for R.S.?

Further administration of phenytoin to R.S. is contraindicated on the basis of his history of a severe hypersensitivity reaction to this drug. Although the mechanism of this reaction is not fully understood, research implicates reactive arene oxide metabolites of phenytoin (and other chemically similar ASDs) as possible causative agents for hypersensitivity reactions. Affected patients purportedly are predisposed genetically to the development of hypersensitivity, possibly because a relative deficiency of epoxide hydrolase enzymes allows the accumulation of toxic concentrations of reactive epoxide metabolites. These metabolites are believed to exert a direct cytotoxic effect and to interact with cellular macromolecules, thereby functioning as haptens that stimulate an immunologic reaction.[173,174]

Carbamazepine, phenytoin, and phenobarbital all are metabolized by similar pathways and converted to reactive arene oxides. It is hypothesized that carbamazepine-induced liver damage also may result from the effects of accumulation of reactive epoxide metabolites; these reactive metabolites differ from the 10,11-epoxide metabolite that accumulates during carbamazepine therapy. For this reason, these drugs potentially cross-react in susceptible patients. Cases of apparent cross-reactivity between phenytoin and phenobarbital or carbamazepine have been documented.[175–177] In addition, both carbamazepine and phenobarbital can produce hypersensitivity reactions similar to those seen with phenytoin. This potential for cross-reactivity should be considered when an alternative ASD is selected for R.S. An analysis of cases of ASD-related skin rashes found that the most significant nondrug predictor of skin rash was the occurrence of a rash with another ASD.[178]

Valproate has been suggested as the preferred alternative ASD for patients who have exhibited hypersensitivity reactions to phenytoin.[176] Valproate is not metabolized to arene oxides and also is chemically dissimilar to all other ASDs. Because valproate often shows good efficacy for focal seizures with impaired awareness with secondary generalization, it would seem to be a safe and potentially effective alternative ASD for R.S. Of the newer ASDs, lamotrigine should probably be avoided in R.S. because of its likelihood of causing skin rash and apparent hypersensitivity reactions. Oxcarbazepine is potentially an alternative ASD for R.S. because it is not metabolized through the arene oxide pathway. Nevertheless, 25% to 30% of patients who experience a rash in response to carbamazepine will also experience a rash with oxcarbazepine.[179] Therefore, many clinicians would avoid oxcarbazepine. Gabapentin, lacosamide, levetiracetam, pregabalin, tiagabine, topiramate, or zonisamide could be considered as alternative medications for R.S. These medications appear less likely to cause skin rash or hypersensitivity reactions.[178,180]

It is recommended that R.S. be advised to add phenytoin to his list of medication allergies.

Additional recognized genetic risk factors for ASD-related hypersensitivity reactions in specific populations are presented in Table 60-5.

OTHER THERAPEUTIC CONSIDERATIONS

Although epilepsy affects males and females equally, many health issues are of specific importance to females, such as contraceptive interactions with ASDs, teratogenicity, pharmacokinetic changes during pregnancy, breast-feeding, menstrual cycle influences on seizure activity (catamenial epilepsy), ASD impact on bone, and sexual dysfunction.[181,182] It is noteworthy that the latter two issues can also occur in males. A great need exists to educate both health care professionals and patients about the many complex issues facing females with epilepsy.[183]

For females of childbearing potential, prepregnancy planning and counseling are important, because significant ASD exposure of the fetus often occurs by the time pregnancy is known. Furthermore, some ASDs interact with contraceptive medications that can increase the risk for an unplanned pregnancy. Prepregnancy counseling also should include the importance of medication adherence to prevent seizure occurrence during pregnancy. Patients should also be informed about the risk of teratogenicity and the importance of prenatal care, including the daily supplementation of 0.4 mg of folic acid to prevent neural tube defects.

Although complete seizure control is desirable for all patients with epilepsy, adequate seizure control for a female planning to become pregnant is especially important. Falls and anoxia associated with uncontrolled generalized tonic–clonic seizures may increase the risk to the unborn baby. Monotherapy is preferred whenever possible, because the relative risk of birth defects dramatically increases with ASD polytherapy.[184,185] The ASD should be given at the lowest effective dose to reduce the possibility of birth defects.[163] Gradual

discontinuation of ASD before pregnancy may be considered if a female has been seizure-free for 2 years or longer.

Antiseizure Drug–Oral Contraceptive Interaction

CASE 60-11

Question 1: P.Z., a 26-year-old female, experiences focal seizures with impaired awareness and secondary generalized tonic–clonic seizures. She is taking phenytoin 400 mg/day and divalproex 2000 mg/day. She reports having two or three focal seizures and one generalized seizure every 3 to 4 months. Despite taking Lo/Ovral® (norgestrel 0.3 mg with ethinylestradiol 30 µg), she has just learned she is pregnant. Her last menstrual period was 6 weeks ago.

What is the relationship between P.Z.'s apparent contraceptive failure and her ASD therapy?

There have been several reports of reduced efficacy of oral contraceptives in patients receiving various ASDs.[186,187] These reports describe both breakthrough bleeding and pregnancy. Phenobarbital, phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, perampanel, and felbamate have been shown to increase the metabolism of ethinylestradiol and progestogens.[188] This effect is not associated with valproate, lamotrigine, gabapentin, tiagabine, zonisamide, levetiracetam, lacosamide, or pregabalin.[188] Topiramate in polytherapy and at high dosages (200–800 mg/day) appears to have a mild, though measurable, effect on oral contraceptive pharmacokinetics; apparent clearance of the estrogen component of combined oral contraceptives is increased in patients taking topiramate.[189] In contrast, topiramate monotherapy in lower dosages (50–200 mg/day) has a lesser impact on the pharmacokinetics of the oral contraceptive.[190]

A lack of contraceptive efficacy may present as irregular or breakthrough menstrual bleeding. Decreased efficacy is not always associated with breakthrough bleeding, however. Oral contraceptive doses can be increased to compensate for the effect of an ASD.[191] However, estrogens also may exacerbate seizures in some

females.[192] Furthermore, females older than 35 years of age and those who smoke must consider the risk of thromboembolic complications associated with higher doses of contraceptives. A second contraceptive method (eg, condoms, intrauterine devices, or spermicide) is recommended to avoid contraceptive failure.[178] Tubal ligation is also an alternative. An additional alternative that could be considered is injectable depot medroxyprogesterone acetate. Although there is a lack of clinical studies substantiating its effectiveness in patients on enzyme-inducing ASD, the pharmacokinetic characteristics of this agent suggest that its effect is not reduced by enzyme induction. Medroxyprogesterone is a high-clearance drug; its clearance is directly dependent on hepatic blood flow. Thus, enzyme induction would have little effect on the metabolism of this drug when it is administered by injection. Depot medroxyprogesterone acetate may, however, have other negative effects that would limit its choice as an alternative contraceptive in this situation.[193]

Assuming P.Z. was taking her contraceptive pills on a regular basis, it is possible that the enzyme-inducing effects of phenytoin is responsible for the reduced efficacy. Patients receiving enzyme-inducing ASD should be prospectively informed that this interaction can occur and advised concerning the use of alternative contraceptives (see Chapter 47, Contraception).

Interestingly, the estrogen component in oral contraceptives increases the clearance of lamotrigine. Lamotrigine clearance may increase twofold with concomitant use of hormonal contraceptives and decrease by 50% when the hormonal contraceptive is discontinued. Changes in lamotrigine levels associated with initiation and discontinuation of hormonal contraceptives can result in increased seizure activity in some patients and toxicity in others.[194]

Teratogenicity

Case 60-11, Question 2: What are the risks of teratogenic effects from P.Z.'s medications? What steps might be taken to minimize these risks?

P.Z.'s child is at risk of congenital malformations because of exposure to several potentially teratogenic drugs: estrogen–progestin combination oral contraceptives, valproate, and phenytoin (also see Chapter 49, Obstetric Drug Therapy).

Many ASDs have teratogenic effects.[195] Animal data regarding the teratogenic potential of the new ASDs are encouraging, but there is limited evidence in pregnant females at this time. A useful resource for clinicians is the American Epilepsy Society and the American Academy of Neurology (AAN) Practice Parameter series on management of females of childbearing potential and pregnant females with epilepsy. The series provides evidence-based recommendations in obstetric complications and change in seizure frequency; teratogenesis and perinatal outcomes, vitamin K and folic acid supplementation, and breast-feeding.[196–198] A major challenge in managing females with epilepsy in pregnancy is balancing the risk of harm to the unborn fetus with ASD exposure and/or seizure occurrence.

Assessing the risk for teratogenicity from ASDs in pregnancy is challenging, especially when multiple ASDs are used to control seizures. Several ASDs are associated with congenital malformations when administered alone. Meador et al provide data from 333 pregnancies in females with epilepsy taking an ASD monotherapy in the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study.[199] Serious adverse outcomes (major malformations and fetal death) were significantly more likely to occur with exposure to valproate (20.3%) than with carbamazepine (8.2%), phenytoin (10.7%), or lamotrigine (1%). In addition to physical malformations, ASD exposure in utero may have an adverse effect on neurodevelopment.[200] The NEAD study found that valproate-exposed children had significantly lower IQ scores at age 6 years (mean 97) compared with children exposed to carbamazepine (mean 105), phenytoin (mean 108), and lamotrigine (mean 108) monotherapy, even after controlling for the mother's IQ and seizure type.[201] As such, when possible, valproate should be avoided in females of childbearing potential.[202]

Several strategies can be used to reduce the potential adverse effects of ASDs on pregnancy outcomes. If feasible, before conception, seizure control should be optimized using the ASD of first choice for the prospective mother's seizure type or epilepsy syndrome. Monotherapy at the lowest effective dose is the goal. Maintenance of adequate folic acid stores before conception and during fetal organogenesis is also important. Folic acid supplementation can reduce the risk of congenital neural tube malformations in infants in the general population. The American College of Obstetrics and Gynecology recommends supplementation of folic acid at 4 mg/day in females who are receiving ASD that increase the risk of neural tube defects.[203] Currently, no evidence suggests that folate supplementation reduces potential teratogenic effects of ASD nor is there an established dose for patients who are taking ASDs. Nevertheless, there is no risk of harm and standard supplementation of folic acid of at least 0.4 mg/day is recommended.[198] Because about half of pregnancies are unplanned and not evident until weeks after conception, folate supplementation should be given routinely to females of childbearing age with epilepsy. It is reasonable to consider 4 mg of folic acid supplementation daily in P.Z. because she is using valproic acid.

Physiologic changes in pregnant females may affect the pharmacokinetics of ASDs.[179] Absorption can be influenced by nausea and vomiting of pregnancy. Both hepatic metabolism and renal function increase during pregnancy. The binding capacity of albumin is decreased during pregnancy, resulting in decreased protein binding for highly bound drugs. Unbound fractions of phenobarbital, phenytoin, and valproate increase with decreased concentrations of albumin.[204–206] For drugs predominately metabolized by the liver with a restrictive clearance (eg, carbamazepine and valproate), decreased protein binding without changes in intrinsic clearance should result in a decrease in total drug concentrations; unbound drug concentrations usually remain unchanged. For drugs with both increased hepatic metabolism and decreased protein binding (eg, phenytoin and phenobarbital), both

total and unbound plasma concentrations decrease, but not necessarily proportionately.

The clearance of lamotrigine increases as pregnancy progresses, presumably related to the impact of estrogen on lamotrigine metabolism.[207] This alteration in clearance changes immediately postpartum. Preliminary data suggest that oxcarbazepine concentrations may also decrease as pregnancy progresses.[208]

The effects of changes in renal function during pregnancy on ASD concentrations are not well known.[208] Renal blood flow and glomerular filtration rate increase during pregnancy. Thus, the renal clearance of drugs that are predominately excreted through the kidneys, such as gabapentin, levetiracetam, and pregabalin, may increase during pregnancy.

During pregnancy, serum levels of ASDs (including free serum levels for highly protein-bound drugs) can be monitored. In this case, a prepregnancy level would be optimal for comparison. Dosage adjustments may help to prevent the increase in seizure frequency that may occur in pregnant females with epilepsy.

For P.Z., it can be presumed that significant exposure of the fetus to any teratogenic influence of ASD has already occurred. Optimization of seizure control is now the primary concern for her. Any major alterations in P.Z.'s ASD regimen should be made cautiously to avoid precipitating seizures. P.Z. can also be referred to the antiepileptic drug (AED) pregnancy registry at Massachusetts General Hospital (1-888-233-2334 or www.aedpregnancyregistry.org). The registry collects data to provide safety recommendations for ASD use in pregnancy. The website also contains useful patient education on the subject.

VITAMIN K SUPPLEMENTATION

There is a theoretical risk that babies born to females with epilepsy who are taking an enzyme-inducing ASD are at risk of hemorrhage secondary to increased metabolism of vitamin K–dependent clotting factors. Based on available evidence, the AAN neither supports nor refutes the practice of supplementing vitamin K in females receiving

carbamazepine, phenobarbital, primidone, or phenytoin.[198] One could consider supplementing vitamin K 10 mg orally daily from 36 weeks of gestation until delivery.[209] Furthermore, all infants are recommended to receive IM vitamin K at birth to prevent hemorrhagic complications.[210]

BREAST-FEEDING

The risk of drug exposure to the breast-feeding infant should be weighed against the benefits of breast-feeding.[211] All drugs transfer into milk to some extent and several drug characteristics help predict how much will pass into the milk, including protein binding, milk/plasma (M/P), maternal plasma concentration, and so on. For the ASDs, a large intersubject variability in the M/P ratio exists, presumably owing to a difference in volume and composition of the milk. Thus, the M/P ratio is not useful for predicting infant ASD exposure. Reviews on ASD and breast-feeding are available.[212] For most first-generation ASDs (carbamazepine, phenytoin, valproic acid, and phenobarbital), breast-feeding results in negligible ASD plasma concentrations in the infants. For the newer ASDs, less data are available for breast-feeding should be done cautiously, and the infant should be monitored for excess ASD plasma concentrations and toxicity. Moreover, ASD and patient-specific factors should be extensively assessed and reviewed with the patient regarding the potential implications of breast-feeding while taking ASDs. P.Z. should be educated on the risks associated with drug transfer into the breast milk. Once she delivers, reevaluation and optimization of P.Z.'s ASD therapy should occur.

STATUS EPILEPTICUS

Characteristics and Pathophysiology

CASE 60-12

QUESTION 1: V.S., a 22-year-old, 187.40-pound (85-kg) male, was recently diagnosed as having idiopathic epilepsy with generalized tonic–clonic seizures. For the past 3 months, he has been treated with 600 mg/day of carbamazepine, which completely eliminated his seizures. His steady-state carbamazepine serum concentration was 10 µg/mL. While at his parents' home, he had two tonic–clonic seizures, each lasting 3 to 4 minutes. On arrival at the hospital (~30 minutes after the first seizure began), he was noted to be only semiconscious. His blood pressure was 197/104 mm Hg, his pulse was 124 beats/minute, respirations were 23 breaths/minute, and his body temperature was 100.4 °F (38 °C) rectally. Shortly after his arrival, another generalized tonic–clonic seizure began.

How does V.S.'s current condition meet accepted diagnostic criteria for SE? What risks are associated with SE?

SE is operationally defined as "either continuous seizures lasting at least 5 minutes or two or more discrete seizures between which there is incomplete recovery of consciousness."[213] Because V.S. has had three seizures within slightly more than 30 minutes and did not return to his baseline level of consciousness between seizures, his present condition meets this definition. V.S. is experiencing generalized convulsive SE; this is the most common type, and it is associated with the greatest risk of213systemic and neurologic damage. SE also may be characterized by nonconvulsive seizures that produce a persistent state of impaired consciousness, or by focal seizures (with or without impaired awareness). These forms of SE are associated with much lower morbidity and mortality than generalized convulsive SE.

Uncontrolled, convulsive SE can cause severe metabolic and hemodynamic alterations. V.S.'s vital signs (tachycardia, elevated blood pressure, increased respiratory rate, and elevated body temperature) are typical for a patient in SE. Prolonged, severe muscle contractions and CNS dysfunction from uncontrolled seizure discharges result in hyperthermia, cardiorespiratory collapse, myoglobinuria, renal failure, and neurologic damage. Even in the absence of convulsive muscle movements, neurologic damage can occur from excessive electrical activity and the resultant alterations in brain metabolism. When seizure activity persists longer than ~30

minutes, failure of mechanisms that regulate cerebral blood flow is more likely; this failure accompanies dramatic increases in brain metabolism and demand for glucose and oxygen. Failure to meet the metabolic demands of brain tissue results in accumulation of lactate and cell death. Peripherally, lactate accumulates, and serum glucose and electrolytes are altered. After 30 minutes of seizure activity, the body often fails to compensate for increased metabolic demands, and cardiovascular collapse can occur.[214,215] For these reasons, SE is considered a medical emergency that requires immediate treatment to prevent or lessen both systemic and neurologic damage. Mortality in adults with SE is ~20%[213]; fatal outcome is often the result of the condition that precipitated SE (eg, acute symptomatic causes, such as cardiopulmonary arrest, stroke). Long-term neurologic consequences of severe SE may include cognitive impairment, memory loss, and worsening of seizure disorders.

General Treatment Measures and Antiseizure Drug Therapy

Case 60-12, Question 2: What is a general treatment plan for V.S.'s episode of SE?

The immediate therapeutic concern in V.S. is to ensure ventilation, stabilize vital signs, and terminate current seizure activity. If possible, an airway should be placed for airway protection and if ventilatory support is needed; however, this may not be possible while he is convulsing. Objects (eg, spoons, tongue blades) should never be placed into the mouth of a patient during a seizure. If airway placement is impossible, V.S. should be positioned on his side to allow drainage of saliva and mucus from the mouth and prevent aspiration. An IV line should be established using normal saline, and blood should be obtained for serum chemistries (especially glucose and electrolytes), ASD serum concentrations, and toxicology screens. Glucose, 25 g (50 mL of 50% dextrose solution) by IV push

should be administered to correct any hypoglycemia, which may be responsible for SE.[216]

IV administration of rapid-acting anticonvulsant medication should begin as soon as possible to terminate V.S.'s seizure activity. SE becomes more resistant to treatment the longer the seizure continues; thus, treatment is more likely to stop seizures the sooner it is administered.[213] For in-hospital treatment of SE, IV medication administration is usually preferred.

Case 60-12, Question 3: Which anticonvulsants are available for IV administration? Evaluate the available drugs and recommend a drug, dosage, and regimen for initial treatment of SE in V.S.

Lorazepam, phenytoin, and fosphenytoin are the agents most commonly studied and as IV therapy in the initial treatment of SE.[213,217] Phenytoin and fosphenytoin are indicated for treatment of SE, but owing to limitations on their rates of infusion, the onset of their peak effect may be delayed. Therefore, phenytoin or fosphenytoin is usually used after initial treatment with lorazepam.

IV valproate sodium (Depacon®), phenytoin or fosphenytoin, and levetiracetam have been used. Refer to **Table 60-6** for more information regarding dosing and rate of administration. Lacosamide is also available in an IV formulation, and there are several case reports and some prospective trials of its successful use for refractory nonconvulsive SE.[218,219] IV phenobarbital is usually reserved for SE that does not respond to benzodiazepines and phenytoin.[213]

Table 60-6
Status Epilepticus Treatment

Stage	Agent and Dosing	Infusion Rate	Adverse Drug Effects/Clinical Pearls
Emergent[a]	■ Lorazepam 0.1 mg/kg (max 4 mg) IV ■ Midazolam 0.2 mg/kg (max 10 mg) IM ■ Diazepam 0.2 mg/kg PR	■ Lorazepam: 2 mg/minute	■ Chosen based on of access ■ Diazepam can be used at home by a trained family member, whereas both lorazepam and midazolam require administration by a medical professional ■ Differences in pharmacokinetics are addressed in Table 60-7
Urgent	■ Phenytoin/fosphenytoin 20 mg/kg IV ■ Levetiracetam 40–60 mg/kg IV ■ Valproate sodium 20–40 mg/kg IV	■ Phenytoin: 50 mg/minute (adults), 1 mg/kg/minute (children) ■ Fosphenytoin: 150 mg PE/minute (adults), 3 mg PE/kg/minute (children) ■ Levetiracetam: 2–5 mg/kg/minute ■ Valproate sodium: 3–6 mg/kg/minute (adults), 1.5–3 mg/kg/minute (children)	■ Fosphenytoin can be given via IM route and its IV administration rate is faster than phenytoin ■ Valproic acid might not be the best agent for patient with end-stage liver disease ■ Levetiracetam has the lowest drug interactions risk
Refractory	■ Midazolam 0.2 mg/kg IV load ■ Propofol 20 μg/kg/minute CIVI	■ Midazolam: 2 mg/minute (loading) then 0.05–2 mg/kg/hour CIVI ■ Propofol: may increase to 30–200 μg/kg/minute CIVI	■ Midazolam has an active metabolite, and its half-life can be prolonged especially in patients with renal impairment, whereas propofol has the risk to cause hypertriglyceridemia ■ Propofol at higher doses (>80 μg/kg/minute) is associated with PRIS, which is characterized by metabolic acidosis, rhabdomyolysis, and renal failure
Super-refractory	■ Pentobarbital 5–15 mg/kg load ■ Ketamine 1.5–4.5 mg/kg IV load	■ Pentobarbital: ≤50 mg/minute (load), then 0.5–5 mg/kg/hour CIVI ■ Ketamine: 0.5 mg/kg/minute (load), then 1.2–7.5 mg/kg/hour CIVI	■ Pentobarbital can cause ileus, cardiac suppression, and hypotension ■ Ketamine might trigger or worsen the condition of patients with psychiatric illness

CIVI, continuous IV infusion; IM, intramuscular; IV, intravenous; PE, phenytoin sodium equivalent; PR, per rectum; PRIS, propofol-related infusion syndrome.

[a]May repeat after 5–10 minutes and used as needed for seizures control.

Four IV regimens for generalized convulsive SE were directly compared in one randomized controlled trial.[220] The study evaluated diazepam followed by phenytoin, lorazepam alone, phenobarbital alone, and phenytoin alone. For initial IV treatment of overt generalized SE, lorazepam was more effective than phenytoin alone. Lorazepam was as effective as the other two regimens, and it was easier to use.

IV administration of either diazepam or lorazepam is usually effective for rapid termination of seizure activity in SE.[221] Owing to diazepam's higher lipid solubility, it redistributes from the CNS to peripheral tissues rapidly after administration; this results in a short duration of action (<60 minutes).[222] Lorazepam's lower lipid solubility

prevents rapid redistribution and accounts for its longer duration of action.[220] Lorazepam may be effective for up to 72 hours.[223,224] Owing to this longer duration, lorazepam is the preferred benzodiazepine for immediate treatment of SEs.[216,217]

Lorazepam 0.1 mg/kg (up to 4 mg/dose) given intravenously at 2 mg/minute would be appropriate initial therapy for V.S.[216,225] Lorazepam may cause significant venous irritation, and the manufacturer recommends dilution with an equal volume of normal saline solution or water for injection before IV administration. Lorazepam may be repeated after 5 minutes if seizures continue. The efficacy of lorazepam depends on rapid achievement of high serum and CNS concentrations. Although lorazepam can be administered IM, this route should not be used for treatment of SE because it is unlikely that it would achieve serum concentrations necessary for termination of seizure activity and there is little experience with its use for terminating SE. Midazolam given IM has been shown to quickly and effectively terminate SE when used in out-of-hospital settings. This treatment is an acceptable alternative for in-hospital use when IV access is not feasible.[226,227] The most common adverse effects after IV administration of benzodiazepines are sedation, hypotension, and respiratory arrest.[222] These adverse effects are usually short-lived and, when adequate facilities are available for assisted ventilation and administration of fluids, they usually can be managed without major risk to the patient. Respiratory depression occurs most commonly in patients who receive multiple IV medications for control of SE. Refer to **Table 60-7** for more pharmacokinetic comparisons of benzodiazepines.[228–233]

Table 60-7
Pharmacokinetic Properties of Benzodiazepines Used for Seizures

Agent	Onset (minutes)	Duration of Action	Vd (L/kg)	Metabolism	Excretion	$T_{1/2}$ (hours)
Lorazepam IV	1.6	4–6 hours	1.3	Liver to inactive metabolites	Hepatic metabolism to inactive metabolites; IV formulation with propylene glycol	12
Midazolam IM	3.3	2–6 hours	1–3	CYP3A4 to active metabolite	Renally cleared	3–5
Midazolam IN	3–10	—				2–6
Midazolam IV	1.5–2.5	30–80 minutes				3–4
Diazepam IV	1–3	15–30 minutes	0.8–1	CYP2C19 and CYP3A4 to active metabolites	Renally cleared; IV formulation with propylene glycol	48, but removed from plasma quickly and therefore short duration of action
Diazepam PR	5–10	15–30 minutes				

CYP, cytochrome P-450; IM, intramuscular; IN, intranasal; IV, intravenous; PR, per rectum.

INTRAVENOUS PHENYTOIN AND FOSPHENYTOIN

Case 60-12, Question 4: V.S. was given lorazepam 4 mg IV. Seizure activity ceased 2 minutes after the injection was completed. What drug should be administered to V.S. for prolonged control of seizures? What is the recommended dose, route, and method of administration?

Continued effective seizure control is important for patients who experience SE. After a benzodiazepine is administered for emergent therapy, an urgent control therapy agent is typically administered. The drug of choice for urgent therapy has not been established, but options include phenytoin/fosphenytoin, valproate sodium, or levetiracetam.[225] Currently, some ASD agents, such as levetiracetam and lacosamide, are being administered as an intravenous bolus over 5–10 minutes to control seizures.[234–237] Levetiracetam at doses of 2000–4500 mg showed to be safe and tolerable when administered undiluted and rapidly through the intravenous route. Other studies also showed that rapid infusion of levetiracetam has comparable efficacy to phenytoin and valproic acid when used to treat SE.[238,239]

The Established Status Epilepticus Treatment Trial (ESETT) was a double-blind, randomized controlled trial of 384 children and adults with convulsive SE that was unresponsive to an adequate dose of a benzodiazepine.[238] Patients were randomized to fosphenytoin 20 mg/kg (maximum dose: 1500 mg), levetiracetam 60 mg/kg

(maximum dose: 4500 mg), or valproate sodium 40 mg/kg (maximum dose: 3000 mg) administered IV over 10 minutes. There was no difference in the primary outcome of absence of clinically relevant seizures and improvement of consciousness at 60 minutes (45% with fosphenytoin, 47% with levetiracetam, and 46% with valproate) or any of the secondary outcomes including admission to intensive care unit, time to termination of seizure, hypotension, intubation, or death. There are many limitations to the interpretation of this trial including unconventional dosing for both phenytoin and levetiracetam and a median duration of seizure at enrollment of more than an hour. Overall, fosphenytoin, levetiracetam, and valproate sodium remain options for urgent control of SE and choice of drug should be individualized.[238]

The availability of fosphenytoin for IV administration has provided an additional option for administration of phenytoin in the treatment of SE, and in most centers, fosphenytoin is preferred over phenytoin. Use of this phenytoin prodrug allows more rapid administration of large IV loading doses of phenytoin with less risk of injection site complications. Fosphenytoin is also better tolerated than phenytoin.[227] Fosphenytoin itself is inactive; the therapeutic effect results from its conversion to phenytoin.[103,104]

In the United States, phenytoin is considered the long-acting anticonvulsant of choice for most patients with generalized convulsive SE.[217] Phenytoin causes much less sedation and respiratory depression than drugs such as phenobarbital when it is used in conjunction with IV benzodiazepines.[216] V.S.'s maintenance carbamazepine therapy was previously effective. Without obvious precipitating factors such as head trauma, CNS infection, and drug or alcohol abuse, SE, in a patient with a history of epilepsy, most commonly results from poor adherence with maintenance ASD medication. Therefore, IV fosphenytoin (the prodrug of phenytoin that has less adverse effects) is a good choice for re-establishing effective ASD therapy for V.S. Phenytoin is an acceptable alternative if fosphenytoin is unavailable.

Loading dose

Whether or not V.S. has a detectable serum concentration of carbamazepine, he should be given an IV loading dose of either fosphenytoin (20 mg/kg PE IV at 150 mg/minute) or phenytoin (20 mg/kg IV at 50 mg/minute). After administration of either of these loading doses, serum phenytoin concentrations should remain >10 µg/mL for ~24 hours; this will allow time for determination of V.S.'s serum carbamazepine concentration and estimation of an appropriate maintenance dose of oral carbamazepine once oral therapy can be restarted. In this setting, the use of IV phenytoin or fosphenytoin is a temporary measure. V.S.'s previous positive response to carbamazepine indicates that he should likely continue to receive this drug as his oral maintenance medication.

IV phenytoin can be administered by direct injection into a running IV line of normal saline but is incompatible with dextrose solutions. The rate of administration should be no faster than 50 mg/minute to minimize the risk of hypotension and acute cardiac arrhythmias. Cardiovascular status (blood pressure, electrocardiogram) should be monitored closely during administration. Hypotension or electrocardiographic abnormalities usually reverse if the administration of phenytoin is slowed or stopped temporarily. Fosphenytoin can be given by either direct IV injection or, after dilution in any suitable IV solution, by infusion at up to 150 mg PE/minute.[103] Absence of propylene glycol as a diluent renders fosphenytoin potentially less likely than phenytoin to cause cardiovascular adverse effects, but this advantage is not well supported.[240] Electrocardiographic and blood pressure monitoring is recommended when this drug is given IV. Pruritus and paresthesia, usually localized to the face and groin, are relatively common adverse effects during IV fosphenytoin administration. These sensations are not allergic reactions to the medication. Their occurrence is related to the administration rate, and they are reversible with temporary discontinuation or slowing of the injection.[103]

Maintenance Therapy

The undetectable serum carbamazepine concentration appears to confirm the role of nonadherence in this episode of SE. Because V.S. was previously well controlled on 600 mg/day, this would be a reasonable target dose. Because V.S. may not tolerate carbamazepine if restarted at the prior maintenance dose, gradually escalating up to this dose should be initiated as soon as V.S. can take oral medication. V.S. should be counseled regarding the importance of taking his medication according to directions, and any potential barriers to adherence should be addressed.

Phenobarbital may be useful for treatment of SE if the patient cannot tolerate phenytoin or when seizures continue after administration of appropriate loading doses of phenytoin. Patients who receive phenobarbital after being treated with IV benzodiazepines should be monitored closely for respiratory depression because this effect may be additive. Equipment and personnel to provide ventilatory assistance should be available.[216]

Alternative Therapies for Refractory Status Epilepticus

SE that does not respond to lorazepam and a longer-acting agent (eg, phenytoin/fosphenytoin, valproate, levetiracetam, phenobarbital, or lacosamide) is considered *refractory status epilepticus (RSE)*. Between 20% to 40% of patients with SE will progress to RSE. In such circumstances, an alternative long-acting agent from those mentioned above may be considered; and, in recent years, the use of such “third-line” agents was a common practice. Recently, it has become a more common practice to escalate therapy to the use of an anesthetic agent after the failure of second-line therapy.[217] The most commonly used anesthetic agents for RSE are midazolam and propofol; pentobarbital is also sometimes used. Significant respiratory depression is expected with these therapies; patients require intubation and mechanical ventilation. In addition,

vasopressors, such as norepinephrine, may be required to control hypotension.[241] Continuous EEG monitoring also is required to assess the anticonvulsant effect of the drug and to gauge the level of anesthesia.

Midazolam is given as a loading dose of 0.2 mg/kg IV and is followed by an IV infusion of 0.2 to 2 mg/kg/hour.[216] Many practitioners adjust the infusion rate to control electrographic seizures and/or to produce a burst-suppression EEG pattern.[242] Most protocols for anesthetic therapy of RSE recommend attempts at gradually reducing the dose of medication after 24 hours of treatment. If clinical or EEG seizure activity recurs, the dose is increased again to produce the desired EEG pattern. Patients receiving midazolam may experience tachyphylaxis and require higher doses with longer durations of treatment. Anesthetic agents may need to be continued for several days or even weeks in some patients.

Continuous IV infusions of propofol are useful for RSE, but patients should be monitored for propofol-related infusion syndrome (PRIS), which can occur with high doses.[241]

Other treatment strategies might be considered in case of super-RSE when a drug-induced coma approach fails. Ketamine is another option for RSE that has a growing interest; however, there is limited data to support its use.[243] One theory about pathophysiology of RSE is that gamma-aminobutyric acid (GABA) receptors are internalized and *N*-methyl-D-aspartate (NMDA) receptors upregulate in this state. As an NMDA antagonist, ketamine may be an option for RSE. Recommended dosing is 1 to 4 mg IV load, then 1 to 5 mg/kg/hour as an IV infusion. Ketamine does not cause hypotension but may cause emergence psychosis/hallucinations and increased salivation.

Limited evidence is available for the use of inhaled anesthetics, lidocaine infusion, electroconvulsive therapy, ketogenic diet, or surgical intervention in super-RSE.[225,244]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Betjemann JP, Lowenstein DH. Status epilepticus in adults. *Lancet Neurol*. 2015;14:615–624. (217)

Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Twelfth Eilat Conference (EILAT XII). *Epilepsy Res.* 2015;111:85–141. (90)

French JA, Pedley TA. Clinical practice. Initial management of epilepsy. *N Engl J Med*. 2008;359:166–176. (3)

Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16:48–61. (227)

Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med*. 2010;362:790–799. (127)

Harden CL, Hopp J, Ting TY. Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1229–1236. (196)

Harden CL, Meador KJ, Pennell PB, et al. Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1237–1246. (197)

Harden CL, Pennell PB, Koppel BS, et al. Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1247–1255. (198)

Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset

epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018;91(2):74–81. (68)

Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018;91(2):82–90. (69)

Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019;381(22):2103–2113. doi:10.1056/nejmoa1905795. (238)

Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2015;84:1705–1713. (4)

Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007;369:1016–1026. (128)

Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013;12:244–252. (201)

Potschka H. Transporter hypothesis of drug-resistant epilepsy: challenges for pharmacogenetic approaches. *Pharmacogenomics*. 2010;11:1427–1438. (91)

Werhahn KJ, Trinka E, Dobesberger J, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia*. 2015;56:450–459. (118)

Key Websites

AED Pregnancy Registry. http://www.aedpregnancyregistry.org/

American Epilepsy Society. http://www.aesnet.org

Epilepsy and Seizure Information for Patients and Health Professionals. http://www.epilepsy.com

Neurocritical Care Society. http://www.neurocriticalcare.org

COMPLETE REFERENCES CHAPTER 60 SEIZURE DISORDERS

1. [No authors listed]. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia*. 1993;34:592–596.
2. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*. 2005;46:470–472.
3. French JA, Pedley TA. Clinical practice. Initial management of epilepsy. *N Engl J Med*. 2008;359:166–176.
4. Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2015;84:1705–1713.
5. Dreifuss FE. Classification of epileptic seizures and the epilepsies. *Pediatr Clin North Am*. 1989;36:265–279.
6. Dreifuss FE. The epilepsies: clinical implications of the international classification. *Epilepsia*. 1990;31(Suppl 3):S3–S10.
7. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522–530. doi:10.1111/epi.13670
8. Luders HO, Kellinghans C. Classification of seizures. In: Wyllie E, Cascino GD, Gidal BE, eds. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Lippincott Williams & Wilkins; 2001:287.
9. Bronen RA, Fulbright RK, Spencer DD, et al. Refractory epilepsy: comparison of MR imaging, CT, and histopathologic findings in 117 patients. *Radiology*. 1996;201:97–105.
10. Berg AT, Shinnar S, Chadwick D. Discontinuing antiepileptic drugs. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Lippincott-Raven; 1998:1275.
11. Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years: a prospective study [published correction appears in *N Engl J Med*. 1988;319:188]. *N Engl J Med*. 1988;318:942–946.
12. Matricardi M, Brinciotti M, Benedetti P. Outcome after discontinuation of antiepileptic drug therapy in children with epilepsy. *Epilepsia*. 1989;30:582–589.
13. Epilepsy Foundation. Seizure first aid and safety. Accessed October 30, 2020. https://www.epilepsy.com/living-epilepsy/seizure-first-aid-and-safety
14. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001;345:311–318.

15. Bainbridge JL, Gidal BE, Ryan M. The ketogenic diet. Central Nervous System Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy*. 1999;19:782–786.
16. Hassan AM, Keene DL, Whiting SE, Jacob PJ, Champagne JR, Humphreys P. Ketogenic diet in the treatment of refractory epilepsy in childhood. *Pediatr Neurol*. 1999;21:548–552.
17. Tecoma ES, Iragui VJ. Vagus nerve stimulation use and effect in epilepsy: what have we learned? *Epilepsy Behav*. 2006;8:127–136.
18. Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. *Epilepsia*. 2018;59(3):555–561. doi:10.1111/epi.13998
19. Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology*. 2020;95(9):e1244–e1256. doi:10.1212/WNL.0000000000010154
20. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342:314–319.
21. Devinsky O. Patients with refractory seizures. *N Engl J Med*. 1999;340:1565–1570.
22. Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia*. 1998;39:5–17.
23. Karceski S, Morrell MJ, Carpenter D. Treatment of epilepsy in adults: expert opinion, 2005. *Epilepsy Behav*. 2005;7(Suppl 1):S1–S67.
24. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62:1252–1260.
25. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62:1261–1273.
26. Garnett WR. Antiepileptic drug treatment: outcomes and adherence. *Pharmacotherapy*. 2000;20:191S–199S.
27. Hirtz D, Berg A, Bettis D, et al. Practice parameter: treatment of the child with a first unprovoked seizure: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2003;60(2):166–175. doi:10.1212/01.wnl.0000033622.27961.b6
28. Schoenenberger RA, Tanasijevic MJ, Jha A, Bates DW. Appropriateness of antiepileptic drug level monitoring. *JAMA*. 1995;274:1622–1626.
29. Choonara IA, Rane A. Therapeutic drug monitoring of anticonvulsants: state of the art. *Clin Pharmacokinet*. 1990;18:318–328.

30. Hayes G, Kootsikas ME. Reassessing the lower end of the phenytoin therapeutic range: a review of the literature. *Ann Pharmacother*. 1993;27:1389–1392.
31. Tomson T, Dahl ML, Kimland E. Therapeutic monitoring of antiepileptic drugs for epilepsy. *Cochrane Database Syst Rev*. 2007;(1):CD002216.
32. [No authors listed]. Guidelines for therapeutic monitoring of antiepileptic drugs. Commission on Antiepileptic Drugs, International League Against Epilepsy. *Epilepsia*. 1993;34:585–587.
33. Tozer TN, Winter ME. Phenytoin. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. 3rd ed. Applied Therapeutics; 1992.
34. Levy RH, Wilensky AJ, Anderson GD. Carbamazepine, valproic acid, phenobarbital, and ethosuximide. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. 3rd ed. Applied Therapeutics; 1992.
35. Cloyd JC. Pharmacokinetic pitfalls of present antiepileptic medications. *Epilepsia*. 1991;32(Suppl 5):S53–S65.
36. Schmidt D. Reduction of two-drug therapy in intractable epilepsy. *Epilepsia*. 1983;24:368–376.
37. Smith DB, Mattson RH, Cramer JA, Collins JF, Novelly RA, Craft B. Results of a nationwide Veterans Administration Cooperative Study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia*. 1987;28(Suppl 3):S50–S58.
38. Thompson PJ, Trimble MR. Anticonvulsant drugs and cognitive functions. *Epilepsia*. 1982;23:531–544.
39. Albright P, Bruni J. Reduction of polypharmacy in epileptic patients. *Arch Neurol*. 1985;42:797–799.
40. Prevey ML, Mattson RH, Cramer JA. Improvement in cognitive functioning and mood state after conversion to valproate monotherapy. *Neurology*. 1989;39:1640–1641.
41. Mirza WU, Credeur LJ, Penry JK. Results of antiepileptic drug reduction in patients with multiple handicaps and epilepsy. *Drug Invest*. 1993;5:320–326.
42. Pellock JM. Efficacy and adverse effects of antiepileptic drugs. *Pediatr Clin North Am*. 1989;36:435–448.
43. Guberman A. Monotherapy or polytherapy for epilepsy? *Can J Neurol Sci*. 1998;25:S3–S8.
44. Beghi E, Giussani G, Grosso S, et al. Withdrawal of antiepileptic drugs: guidelines of the Italian League Against Epilepsy. *Epilepsia*. 2013;54(Suppl 7):2–12.
45. Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology*. 1994;44:601–608.
46. Tennison M, Greenwood R, Lewis D, Thorn M. Discontinuing antiepileptic drugs in children with epilepsy. A comparison of a six-week and a nine-month

taper period. *N Engl J Med*. 1994;330:1407–1410.
47. Malow BA, Blaxton TA, Stertz B, Theodore WH. Carbamazepine withdrawal: effects of taper rate on seizure frequency. *Neurology*. 1993;43:2280–2284.
48. Camfield P, Camfield C. The frequency of intractable seizures after stopping AEDs in seizure-free children with epilepsy. *Neurology*. 2005;64:973–975.
49. Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med*. 1985;313:145–151.
50. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *N Engl J Med*. 1992;327:765–771.
51. Beydoun A, Sackellares JC, Shu V. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: a double-blind, concentration-response design clinical trial. Depakote Monotherapy for Partial Seizures Study Group. *Neurology*. 1997;48:182–188.
52. Franceschi M, Ciboddo G, Truci G, Borri A, Canal N. Fatal aplastic anemia in a patient treated with carbamazepine. *Epilepsia*. 1988;29:582–583.
53. Pisciotta AV. Carbamazepine: hematological toxicity. In: Woodbury DM, Penry JK, eds. *Antiepileptic Drugs*. 2nd ed. Raven Press; 1982:533.
54. Pellock JM. Carbamazepine side effects in children and adults. *Epilepsia*. 1987;28(Suppl 3):S64–S70.
55. Holmes GL. Carbamazepine: adverse effects. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 5th ed. Lippincott Williams & Wilkins; 2002:285.
56. Camfield C, Camfield P, Smith E, Tibbles JA. Asymptomatic children with epilepsy: little benefit from screening for anticonvulsant-induced liver, blood, or renal damage. *Neurology*. 1986;36:838–841.
57. Horowitz S, Patwardhan R, Marcus E. Hepatotoxic reactions associated with carbamazepine therapy. *Epilepsia*. 1988;29:149–154.
58. Hadzic N, Portmann B, Davies ET, Mowat AP, Mieli-Vergani G. Acute liver failure induced by carbamazepine. *Arch Dis Child*. 1990;65:315–317.
59. Livingston S, Pauli LL, Berman W. Carbamazepine (Tegretol) in epilepsy: nine-year follow-up study with special emphasis on untoward reactions. *Dis Nerv Syst*. 1974;35:103–107.
60. Tomson T, Svensson JO, Hilton-Brown P. Relationship of intraindividual dose to plasma concentration of carbamazepine: indication of dose-dependent induction of metabolism. *Ther Drug Monit*. 1989;11:533–539.
61. Sanchez A, Durán JA, Serrano JS. Steady-state carbamazepine concentration-dose ratios in epileptic patients. *Clin Pharmacokinet*. 1986;11:411–414.

62. Oles KS, Gal P. Bioequivalency revisited: Epitol versus Tegretol. *Neurology*. 1993;43:2435–2436.
63. Crawford P, Feely M, Guberman A, Kramer G. Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. *Seizure*. 2006;15:165–176.
64. Ting TY, Jiang W, Lionberger R, et al. Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: a field test of the FDA bioequivalence standard. *Epilepsia*. 2015;56(9):1415–1424.
65. Privitera MD, Welty TE, Gidal BE, et al. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. *Lancet Neurol*. 2016;15(4):365–372. doi:10.1016/S1474-4422(16)00014-4
66. [No authors listed]. Double-blind crossover comparison of Tegretol-XR and Tegretol in patients with epilepsy. The Tegretol Oros Osmotic Release Delivery System Study Group. *Neurology*. 1995;45:1703–1707.
67. Riss JR, Kriel RL, Kammer NM, Judge MK, Montgomery MJ. Administration of Carbatrol to children with feeding tubes. *Pediatr Neurol*. 2002;27:193–195.
68. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy: report of the Guideline Development, Dissemination, and Implementtion Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018;91(2):74–81. doi:10.1212/WNL.0000000000005755
69. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018;91(2):82–90. doi:10.1212/WNL.0000000000005756
70. Verrotti A, Loiacono G, Rossi A, Zaccara G. Eslicarbazepine acetate: an update on efficacy and safety in epilepsy. *Epilepsy Res*. 2014;108:1–10.
71. Accessdata.fda.gov. 2020. [online] Accessed October 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212839s000lbl.pdf
72. McLean MJ, Morrell MJ, Willmore LJ, et al. Safety and tolerability of gabapentin as adjunctive therapy in a large, multicenter study. *Epilepsia*. 1999;40:965–972.
73. Leppik IE, Gram L, Deaton R, Sommerville KW, et al. Safety of tiagabine: summary of 53 trials. *Epilepsy Res*. 1999;33:235–246.
74. Guberman AH, Besag FM, Brodie MJ, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. *Epilepsia*. 1999;40:985–991.
75. Sirsi D, Safdieh JE. The safety of levetiracetam. *Expert Opin Drug Saf*. 2007;6:241–250.

76. Martinez W, Ingenito A, Blakeslee M, Barkley GL, McCague K, D'Souza J. Efficacy, safety, and tolerability of oxcarbazepine monotherapy. *Epilepsy Behav*. 2006;9:448–456.
77. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. *Ann Pharmacother*. 2005;39:2029–2037.
78. Jones MW. Topiramate—safety and tolerability. *Can J Neurol Sci*. 1998;25:S13–S15.
79. Oommen KJ, Mathews S. Zonisamide: a new antiepileptic drug. *Clin Neuropharmacol*. 1999;22:192–200.
80. Goa KL, Sorkin EM. Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. *Drugs*. 1993;46:409–427.
81. Harris JA, Murphy JA. Lacosamide: an adjunctive agent for partial-onset seizures and potential therapy for neuropathic pain. *Ann Pharmacother*. 2009;43:1809–1817.
82. Yuen AW, Land G, Weatherley BC, Peck AW. Sodium valproate acutely inhibits lamotrigine metabolism. *Br J Clin Pharmacol*. 1992;33:511–513.
83. Anderson GD, Yau MK, Gidal BE, et al. Bidirectional interaction of valproate and lamotrigine in healthy subjects. *Clin Pharmacol Ther*. 1996;60:145–156.
84. Besag FM, Berry DJ, Pool F, Newbery JE, Subel B. Carbamazepine toxicity with lamotrigine: pharmacokinetic or pharmacodynamic interaction? *Epilepsia*. 1998;39:183–187.
85. Welty TE, Gidal BE, Ficker DM, Privitera MD. Levetiracetam: a different approach to the pharmacotherapy of epilepsy. *Ann Pharmacother*. 2002;36:296–304.
86. Fattore C, Cipolla G, Gatti G, et al. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. *Epilepsia*. 1999;40:783–787.
87. Falcão A, Vaz-da-Silva M, Gama H, Nunes T, Almeida L, Soares-da-Silva P. Effect of eslicarbazepine acetate on the pharmacokinetics of a combined ethinylestradiol/levonorgestrel oral contraceptive in healthy women. *Epilepsy Res*. 2013;105:368–376.
88. Clinicaltrials.gov. A trial of two fixed doses of ZX008 (fenfluramine HCl) as an adjunctive therapy in children and young adults with Dravet syndrome [online]. 2020. Accessed October 30, 2020. https://clinicaltrials.gov/ct2/show/NCT02826863
89. Clinicaltrials.gov. A study to test the efficacy and safety of padsevonil as treatment of focal-onset seizures in adult subjects with drug-resistant epilepsy [online]. 2020. Accessed October 30, 2020. https://clinicaltrials.gov/ct2/show/NCT03739840
90. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Twelfth Eilat Conference (EILAT XII). *Epilepsy Res*. 2015;111:85–141.

91. Potschka H. Transporter hypothesis of drug-resistant epilepsy: challenges for pharmacogenetic approaches. *Pharmacogenomics*. 2010;11:1427–1438.
92. Piana C, Antunes Nde J, Della Pasqua O. Implications of pharmacogenetics for the therapeutic use of antiepileptic drugs. *Expert Opin Drug Metab Toxicol*. 2014;10:341–358.
93. Fitton A, Goa KL. Lamotrigine: an update of its pharmacology and therapeutic use in epilepsy. *Drugs*. 1995;50:691–713.
94. Kilpatrick ES, Forrest G, Brodie MJ. Concentration-effect and concentration-toxicity relations with lamotrigine: a prospective study. *Epilepsia*. 1996;37:534–538.
95. Caudle KE, Rettie AE, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. *Clin Pharmacol Ther*. 2014;96:542–548.
96. Allen JP, Ludden TM, Burrow SR, Clementi WA, Stavchansky SA. Phenytoin cumulation kinetics. *Clin Pharmacol Ther*. 1979;26:445–448.
97. Evens RP, Fraser DG, Ludden TM, Sutherland EW 3rd. Phenytoin toxicity and blood levels after a large oral dose. *Am J Hosp Pharm*. 1980;37:232–235.
98. Ludden TM, Allen JP, Schneider LW, Stavchansky SA. Rate of phenytoin accumulation in man: a simulation study. *J Pharmacokinet Biopharm*. 1978;6:399–415.
99. Kostenbauder HB, Rapp RP, McGovren JP, et al. Bioavailability and single-dose pharmacokinetics of intramuscular phenytoin. *Clin Pharmacol Ther*. 1975;18:449–456.
100. Serrano EE, Roye DB, Hammer RH, Wilder BJ. Plasma diphenylhydantoin values after oral and intramuscular administration of diphenylhydantoin. *Neurology*. 1973;23:311–317.
101. Serrano EE, Wilder BJ. Intramuscular administration of diphenylhydantoin. Histologic follow-up studies. *Arch Neurol*. 1974;31:276–278.
102. Jamerson BD, Dukes GE, Brouwer KL, Donn KH, Messenheimer JA, Powell JR. Venous irritation related to intravenous administration of phenytoin versus fosphenytoin. *Pharmacotherapy*. 1994;14:47–52.
103. Fischer JH, Patel TV, Fischer PA. Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet*. 2003;42:33–58.
104. Boucher BA. Fosphenytoin: a novel phenytoin prodrug. *Pharmacotherapy*. 1996;16:777–791.
105. Ramsay RE, Wilder BJ, Uthman BM, et al. Intramuscular fosphenytoin (Cerebyx) in patients requiring a loading dose of phenytoin. *Epilepsy Res*. 1997;28:181–187.
106. Butler RT, Kalkwarf KL, Kaldahl WB. Drug-induced gingival hyperplasia: phenytoin, cyclosporine, and nifedipine. *J Am Dent Assoc*. 1987;114:56–60.

107. Stinnett E, Rodu B, Grizzle WE. New developments in understanding phenytoin-induced gingival hyperplasia. *J Am Dent Assoc*. 1987;114:814–816.
108. Bruni J. Phenytoin and other hydantoins: adverse effects. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 5th ed. Lippincott Williams & Wilkins; 2002:605.
109. Kuruvilla T, Bharucha NE. Cerebellar atrophy after acute phenytoin intoxication. *Epilepsia*. 1997;38:500–502.
110. Rapport RL 2nd, Shaw CM. Phenytoin-related cerebellar degeneration without seizures. *Ann Neurol*. 1977;2:437–439.
111. So EL, Penry JK. Adverse effects of phenytoin on peripheral nerves and neuromuscular junction: a review. *Epilepsia*. 1981;22:467–473.
112. Lovelace RE, Horwitz SJ. Peripheral neuropathy in long-term diphenylhydantoin therapy. *Arch Neurol*. 1968;18:69–77.
113. Fraser LA, Burneo JG, Fraser JA. Enzyme-inducing antiepileptic drugs and fractures in people with epilepsy: a systematic review. *Epilepsy Res*. 2015;116:59–66.
114. Sheth RD. Bone health in pediatric epilepsy. *Epilepsy Behav*. 2004;5(Suppl 2):S30–S35.
115. Pack AM, Morrell MJ, Marcus R, et al. Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. *Ann Neurol*. 2005;57:252–257.
116. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK lamotrigine elderly study group. *Epilepsy Res*. 1999;37:81–87.
117. Rowan AJ, Ramsay RE, Collins JF, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology*. 2005;64:1868–1873.
118. Werhahn KJ, Trinka E, Dobesberger J, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia*. 2015;56:450–459.
119. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. *Clin Pharmacokinet*. 2013;52:627–645.
120. Martin RC, Griffith HR, Faught E, Gilliam F, Mackey M, Vogtle L. Cognitive functioning in community dwelling older adults with chronic partial epilepsy. *Epilepsia*. 2005;46:298–303.
121. Piazzini A, Canevini MP, Turner K, Chifari R, Canger R. Elderly people and epilepsy: cognitive function. *Epilepsia*. 2006;47(Suppl 5):82–84.
122. Bambara JK, Griffith HR, Martin RC, Faught E, Wadley VG, Marson DC. Medical decision-making abilities in older adults with chronic partial epilepsy. *Epilepsy Behav*. 2007;10:63–68.

123. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. *Epilepsia*. 2013;54(1):141–155. doi:10.1111/epi.12028
124. Coppola G, Auricchio G, Federico R, Carotenuto M, Pascotto A. Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized parallel-group study. *Epilepsia*. 2004;45:1049–1053.
125. Frank LM, Enlow T, Holmes GL, et al. Lamictal (lamotrigine) monotherapy for typical absence seizures in children. *Epilepsia*. 1999;40:973–979.
126. Beran RG, Berkovic SF, Dunagan FM, et al. Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy. *Epilepsia*. 1998;39:1329–1333.
127. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med*. 2010;362:790–799.
128. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007;369:1016–1026.
129. Mattson RH. Antiepileptic drug monotherapy in adults: selection and use in new-onset epilepsy. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 5th ed. Lippincott Williams & Wilkins; 2002:72.
130. Brodie MJ, Yuen AW. Lamotrigine substitution study: evidence for synergism with sodium valproate? 105 Study Group. *Epilepsy Res*. 1997;26(3):423–432. doi:10.1016/s0920-1211(96)01007-8
131. Mikkelsen B, Birket-Smith E, Bradt S, et al. Clonazepam in the treatment of epilepsy. A controlled clinical trial in simple absences, bilateral massive epileptic myoclonus, and atonic seizures. *Arch Neurol*. 1976;33(5):322–325. doi:10.1001/archneur.1976.00500050008002
132. Sato S, Malow BA. Benzodiazepines: clonazepam. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 4th ed. Raven Press; 1995:725.
133. Glauser TA. Succinimides: adverse effects. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 5th ed. Lippincott Williams & Wilkins; 2002:658.
134. Browne TR, Mirsky AF. Absence (petit mal) seizures. In: Browne TR, Feldman RG, eds. *Epilepsy: Diagnosis and Management*. Little Brown; 1983:61.
135. Livingston S, Torres I, Pauli LL, Rider RV. Petit mal epilepsy: results of a prolonged follow-up study of 117 patients. *JAMA*. 1965;194:227–232.
136. Penry JK, So EL. Refractoriness of absence seizures and phenobarbital. *Neurology*. 1981;31:158.
137. Snead OC 3rd, Hosey LC. Exacerbation of seizures in children by carbamazepine. *N Engl J Med*. 1985;313:916–921.

138. Shields WD, Saslow E. Myoclonic, atonic and absence seizures following institution of carbamazepine therapy in children. *Neurology*. 1983;33:1487–1489.
139. Zaccara G, Messori A, Moroni F. Clinical pharmacokinetics of valproic acid, 1988. *Clin Pharmacokinet*. 1988;15:367–389.
140. Cloyd JC, Kriel RL, Jones-Saete CM, Ong BY, Jancik JT, Remmel RP. Comparison of sprinkle versus syrup formulations of valproate for bioavailability, tolerance, and preference. *J Pediatr*. 1992;120:634–638.
141. Dutta S, Zhang Y, Selness DS, Lee LL, Williams LA, Sommerville KW. Comparison of the bioavailability of unequal doses of divalproex sodium extended-release formulation relative to the delayed-release formulation in healthy volunteers. *Epilepsy Res*. 2002;49:1–10.
142. Fischer JH, Barr AN, Paloucek FP, Dorociak JV, Spunt AL. Effect of food on the serum concentration profile of enteric-coated valproic acid. *Neurology*. 1988;38:1319–1322.
143. Bauer LA, Davis R, Wilensky A, Raisys V, Levy RH. Valproic acid clearance: unbound fraction and diurnal variation in young and elderly adults. *Clin Pharmacol Ther*. 1985;37:697–700.
144. Tennison MB, Miles MV, Pollack GM, Thorn MD, Dupuis RE. Valproate metabolites and hepatotoxicity in an epileptic population. *Epilepsia*. 1988;29:543–547.
145. Eadie MJ, Hooper WD, Dickinson RG. Valproate-associated hepatotoxicity and its biochemical mechanisms. *Med Toxicol*. 1988;3:85–106.
146. Dreifuss FE, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB. Valproic acid hepatic fatalities: a retrospective review. *Neurology*. 1987;37:379–385.
147. Dreifuss FE, Langer DH, Moline KA, Maxwell JE. Valproic acid hepatic fatalities. II. U.S. experience since 1984. *Neurology*. 1989;39:201.
148. Dreifuss FE. Valproic acid hepatic fatalities: revised table. *Neurology*. 1989;39:1558.
149. Scheffner E, König S, Rauterberg-Ruland I, Kochen W, Hofmann WJ, Unkelbach S. Fatal liver failure in 16 children with valproate therapy. *Epilepsia*. 1988;29:530–542.
150. Koenig SA, Buesing D, Longin E, et al. Valproic acid-induced hepatopathy: nine new fatalities in Germany from 1994 to 2003. *Epilepsia*. 2006;47:2027–2031.
151. Willmore LJ. Clinical manifestations of valproate hepato-toxicity. In: Levy RH, Penry JK, eds. *Idiosyncratic Reactions to Valproate: Clinical Risk Patterns and Mechanisms of Toxicity*. Raven Press; 1992:3.
152. Willmore LJ, Triggs WJ, Pellock JM. Valproate toxicity: risk-screening strategies. *J Child Neurol*. 1991;6:3.
153. Kriel RL, Cloyd JC, Pellock JM, Mitchell WG, Cereghino JJ, Rosman NP. Rectal diazepam gel for treatment of acute repetitive seizures. The North

American Diastat Study Group. *Pediatr Neurol*. 1999;20:282.
154. Cloyd JC, Lalonde RL, Beniak TE, Novack GD. A single-blind, crossover comparison of the pharmacokinetics and cognitive effects of a new diazepam rectal gel with intravenous diazepam. *Epilepsia*. 1998;39:520–526.
155. Detyniecki K, Van Ess PJ, Sequeira DJ, Wheless JW, Meng T-C, Pullman WE. Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters-a randomized, double-blind, placebo-controlled trial. *Epilepsia*. 2019;60(9):1797–1808. doi:10.1111/epi.15159
156. Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. *Pediatr Neurol*. 2006;34(5):355–359. doi:10.1016/j.pediatrneurol.2005.09.006
157. Holsti M, Dudley N, Schunk J, et al. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. *Arch Pediatr Adolesc Med*. 2010;164(8):747–753. doi:10.1001/archpediatrics.2010.130
158. Haut SR. Seizure clusters: characteristics and treatment. *Curr Opin Neurol*. 2015;28:143–150.
159. Waruiru C, Appleton R. Febrile seizures: an update. *Arch Dis Child*. 2004;89:751–756.
160. Sadleir LG, Scheffer IE. Febrile seizures. *Br Med J*. 2007;334:307–311.
161. McIntyre J, Robertson S, Norris E, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet*. 2005;366:205–210.
162. Patterson JL, Carapetian SA, Hageman JR, Kelley KR. Febrile seizures. *Pediatr Ann*. 2013;42:249–254.
163. Delgado-Escueta AV, Janz D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. *Neurology*. 1992;42(Suppl 5):149–160.
164. Fischbein CA, Berg IJ. Diazepam to prevent febrile seizures. *N Engl J Med*. 1993;329:2033.
165. Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child*. 1988;63:1189–1191.
166. Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures: effects on intelligence and on seizure recurrence [published correction appears in *N Engl J Med*. 1992;326:144]. *N Engl J Med*. 1990;322:364–369.
167. Sulzbacher S, Farwell JR, Temkin N, Lu AS, Hirtz DG. Late cognitive effects of early treatment with phenobarbital. *Clin Pediatr*. 1999;38:387–394.
168. Offringa M, Newton R. Prophylactic drug management for febrile seizures in children. *Evid Based Child Health*. 2013;8:1376–1485.
169. Smythe MA, Umstead GS. Phenytoin hepatotoxicity: a review of the literature. *DICP*. 1989;23:13–18.

170. Howard PA, Engen PL, Dunn MI. Phenytoin hypersensitivity syndrome: a case report. *DICP*. 1991;25:929–932.
171. Blaszczyk B, Lason´ W, Czuczwar SJ. Antiepileptic drugs and adverse skin reactions: an update. *Pharmacol Rep*. 2015;67:426–434.
172. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome: in vitro assessment of risk. *J Clin Invest*. 1988;82:1826–1832.
173. Pirmohamed M, Kitteringham NR, Breckenridge AM, Park BK. Detection of an autoantibody directed against human liver microsomal protein in a patient with carbamazepine hypersensitivity. *Br J Clin Pharmacol*. 1992;33:183–186.
174. Engel JN, Mellul VG, Goodman DB. Phenytoin hypersensitivity: a case of severe acute rhabdomyolysis. *Am J Med*. 1986;81:928–930.
175. Reents SB, Luginbuhl WE, Davis SM. Phenytoin-carbamazepine cross-sensitivity. *DICP*. 1989;23:235–236.
176. Ettinger AB, Moshé SL, Sinnett MJ, Canton JC, Shinnar S. Use of ethotoin in phenytoin-related hypersensitivity reactions. *J Epilepsy*. 1993;6:29–31.
177. Arif H, Buchsbaum R, Weintraub D, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology*. 2007;68:1701–1709.
178. Beran RG. Cross-reactive skin eruption with both carbamazepine and oxcarbazepine. *Epilepsia*. 1993;34:163–165.
179. Asconape JJ. Some common issues in the use of antiepileptic drugs. *Semin Neurol*. 2002;22:27–39.
180. Luef G. Female issues in epilepsy: a critical review. *Epilepsy Behav*. 2009;15:78–82.
181. Reimers A. New antiepileptic drugs and women. *Seizure*. 2014;23:585–591.
182. McGrath A, Sharpe L, Lah S, Parratt K. Pregnancy-related knowledge and information needs of women with epilepsy: a systematic review. *Epilepsy Behav*. 2014;31:246–255.
183. Kluger BM, Meador KJ. Teratogenicity of antiepileptic medications. *Semin Neurol*. 2008;28:328–335.
184. Dreifuss FE, Langer DH. Hepatic considerations in the use of antiepileptic drugs. *Epilepsia*. 1987;28(Suppl 2):S23–S29.
185. Yerby MS, Leavitt A, Erickson DM, et al. Antiepileptics and the development of congenital anomalies. *Neurology*. 1992;42(Suppl 5):132–140.
186. Mattson RH, Cramer JA, Darney PD, Naftolin F. Use of oral contraceptives by women with epilepsy. *JAMA*. 1986;256:238–240.
187. Back DJ, Grimmer SF, Orme ML, Proudlove C, Mann RD, Breckenridge AM. Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol*. 1988;25:527–532.
188. Johnston CA, Crawford PM. Anti-epileptic drugs and hormonal treatments. *Curr Treat Options Neurol*. 2014;16:288.

189. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia*. 1997;38:317–323.
190. Doose DR. Oral contraceptive-AED interactions: no effect of topiramate as monotherapy at clinically effective dosages of 200 mg or less. *Epilepsia*. 2002;43(Suppl 7):205.
191. Krauss GL, Brandt J, Campbell M, Plate C, Summerfield M. Antiepileptic medication and oral contraceptive interactions: a national survey of neurologists and obstetricians. *Neurology*. 1996;46:1534–1539.
192. Morrell MJ. Catamenial epilepsy and issues of fertility, sexuality, and reproduction. In: Wyllie E, Cascino GD, Gidal BE, eds. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Lippincott Williams & Wilkins; 2001:671.
193. O'Brien MD, Guillebaud J. Contraception for women with epilepsy. *Epilepsia*. 2006;47:1419–1422.
194. Christensen J, Petrenaite V, Atterman J, et al. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. *Epilepsia*. 2007;48:484–489.
195. Vajda FJ, O'Brien TJ, Lander CM, Graham J, Eadie MJ. The teratogenicity of the newer antiepileptic drugs—an update. *Acta Neurol Scand*. 2014;130:234–238.
196. Harden CL, Hopp J, Ting TY. Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1229–1236.
197. Harden CL, Meador KJ, Pennell PB, et al. Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1237–1246.
198. Harden CL, Pennell PB, Koppel BS, et al. Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1247–1255.
199. Meador KJ, Baker GA, Finnell RH, et al. NEAD Study Group. In utero antiepileptic drug exposure: fetal death and malformations. *Neurology*. 2006;67:407–412.
200. Meador KJ, Loring DW. Developmental effects of antiepileptic drugs and the need for improved regulations. *Neurology*. 2016;86(3):297–306.

201. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013;12:244–252.
202. Tomson T, Marson A, Boon P, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. *Epilepsia*. 2015;56(7):1006–1019.
203. ACOG educational bulletin. Seizure disorders in pregnancy. Number 231, December 1996. Committee on Educational Bulletins of the American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*. 1997;56(3):279–286.
204. Chen SS, Perucca E, Lee JN, Richens A. Serum protein binding and free concentration of phenytoin and phenobarbitone in pregnancy. *Br J Clin Pharmacol*. 1982;13:547–552.
205. Perucca E, Crema A. Plasma protein binding of drugs in pregnancy. *Clin Pharmacokinet*. 1982;7:336–352.
206. Patel IH, Levy RH. Valproic acid binding to human serum albumin and determination of free fraction in the presence of anticonvulsants and free fatty acids. *Epilepsia*. 1979;20:85–90.
207. Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology*. 2008;70(22, pt 2):2130–2136.
208. Tomson T, Battino D. Pharmacokinetics and therapeutic drug monitoring of newer antiepileptic drugs during pregnancy and the puerperium. *Clin Pharma cokinet*. 2007;46:209–219.
209. Pack AM. Therapy insight: clinical management of pregnant women with epilepsy. *Nat Clin Pract Neurol*. 2006;2:190–200.
210. American Academy of Pediatrics Vitamin K Ad Hoc Task Force: controversies concerning vitamin K and the newborn. *Pediatrics*. 1993;91(5):1001–1003.
211. [No authors listed]. American Academy of Pediatrics Committee on Drugs: the transfer of drugs and other chemicals into human milk. *Pediatrics*. 1994;93:137–150.
212. Veiby G, Bjørk M, Engelsen BA, Gilhus NE. Epilepsy and recommendations for breastfeeding. *Seizure*. 2015;28:57–65.
213. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med*. 1998;338:970–976.
214. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiologic mechanisms of brain damage from status epilepticus. *Epilepsia*. 1993;34(Suppl 1):S37–S53.
215. Lothman E. The biochemical basis and pathophysiology of status epilepticus. *Neurology*. 1990;40(Suppl 2):13–23.
216. Alldredge BK, Treiman DM, Shorvon SD. Treatment of status epilepticus. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. 2nd ed. Wolters Kluwer; 2008:1357.

217. Betjemann JP, Lowenstein DH. Status epilepticus in adults. *Lancet Neurol*. 2015;14:615–624.
218. Albers JM, Möddel G, Dittrich R, et al. Intravenous lacosamide: an effective add-on treatment of refractory status epilepticus. *Seizure*. 2011;20:428–430.
219. Kellinghaus C, Berning S, Besselmann M. Intravenous lacosamide as successful treatment for nonconvulsive status epilepticus after failure of first line therapy. *Epilepsy Behav*. 2009;14:429–431.
220. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med*. 1998;339:792–798.
221. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA*. 1983;249:1452–1454.
222. Rey E, Tréluyer JM, Pons G. Pharmacokinetic optimization of benzodiazepine therapy for acute seizures. Focus on delivery routes. *Clin Pharmacokinet*. 1999;36:409–424.
223. Levy RJ, Krall RL. Treatment of status epilepticus with lorazepam. *Arch Neurol*. 1984;41:605–611.
224. Lacey DJ, Singer WD, Horwitz SJ, Gilmore H. Lorazepam therapy of status epilepticus in children and adolescents. *J Pediatr*. 1986;108:771–774.
225. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17(1):3–23. doi:10.1007/s12028-012-9695-z
226. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012;366:591–600.
227. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16:48–61.
228. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system–mediated effects. *Ochsner J*. 2013;13(2):214–223.
229. Accessdata.fda.gov. 2020. [online] Accessed October 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018140s028lbl.pdf
230. Accessdata.fda.gov. 2020. [online] Accessed October 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208878Orig1s000lbl.pdf
231. Accessdata.fda.gov. 2020. [online] Accessed October 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211321s000lbl.pdf
232. Accessdata.fda.gov. 2020. [online] Accessed October 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/013263s094lbl.

pdf
233. Accessdata.fda.gov. 2020. [online] Accessed October 30, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020648s014lbl.pdf
234. Haller JT, Bonnin S, Radosevich J. Rapid administration of undiluted intravenous levetiracetam. *Epilepsia*. 2021;62(8):1865–1870. doi:10.1111/epi.16961
235. Davidson KE, Newell J, Alsherbini K, Krushinski J, Jones GM. Safety and efficiency of intravenous push lacosamide administration. *Neurocrit Care*. 2018;29(3):491–495. doi:10.1007/s12028-018-0560-6
236. Ramsay RE, Sabharwal V, Khan F, et al. Safety & pK of IV loading dose of lacosamide in the ICU. *Epilepsy Behav*. 2015;49:340–342. doi:10.1016/j.yebeh.2015.06.032
237. Burakgazi E, Bashir S, Doss V, Pellock J. The safety and tolerability of different intravenous administrations of levetiracetam, bolus versus infusion, in intensive care unit patients. *Clin EEG Neurosci*. 2014;45(2):89–91. doi:10.1177/1550059413496777
238. Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019;381(22):2103–2113. doi:10.1056/NEJMoa1905795
239. Lyttle MD, Rainford NEA, Gamble C, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. *The Lancet*. 2019;393(10186):2125–2134. doi:10.1016/S0140-6736(19)30724-X
240. Adams BD, Buckley NH, Kim JY, Tipps LB. Fosphenytoin may cause hemodynamically unstable bradydysrhythmias. *J Emerg Med*. 2006;30:75–79.
241. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia*. 2002;43:146–153.
242. Yaffe K, Lowenstein DH. Prognostic factors of pentobarbital therapy for refractory generalized status epilepticus. *Neurology*. 1993;43:895–900.
243. Rai S, Drislane FW. Treatment of refractory and super-refractory status epilepticus. *Neurotherapeutics*. 2018;15(3):697–712. doi:10.1007/s13311-018-0640-5
244. Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain*. 2012;135(Pt 8):2314–2328. doi:10.1093/brain/aws091

61

Acute Ischemic and Hemorrhagic Stroke

Oussayma Moukhachen and Philip Grgurich

CORE PRINCIPLES		CHAPTER CASES
1	Acute ischemic and hemorrhagic stroke are medical emergencies, requiring prompt medical attention at the first sign of symptoms. Signs and symptoms of cerebrovascular disease usually occur acutely and vary depending on the area of the brain involved. Ischemic and hemorrhagic events have similar symptoms and must be distinguished before initiating treatment.	**Case 61-1 (Question 1–3), Table 61-2**
2	Acute goals of therapy for ischemic stroke focus on early reperfusion strategies to salvage brain tissue and restoring blood flow, in addition to prevention of complications such as	**Case 61-1 (Question 4)** **Case 61-2 (Question 7),** **Figure 61-2, Table 61-2**

	venous thromboembolism, aspiration pneumonia, and hemorrhagic conversion of the ischemic stroke. The sequelae of stroke on functional status and the degree of disability are assessed using scales such as the modified Rankin Scale (mRS).	
3	Treatment of acute ischemic stroke includes the use of alteplase given via intravenous (IV) infusion. Alteplase should be started after confirming an event is ischemic and not hemorrhagic. The treatment window for use of alteplase is limited to 4.5 hours after the onset of neurologic symptoms. Indication and contraindication criteria for administration of IV alteplase must be followed to reduce the risk of intracranial hemorrhage.	**Case 61-2 (Question 1), Table 61-3**
4	Provision of appropriate reperfusion strategy (IV alteplase or endovascular thrombectomy or both), supportive care during the hospitalization, and patient rehabilitation are key to improve patient prognosis.	**Case 61-2 (Questions 2, 3, 5, 6, 8), Figure 61-1**
5	Blood pressure control before, during, and after administration of IV thrombolytics and endovascular thrombectomy is extremely important to reduce the risk of intracranial hemorrhage.	**Case 61-2 (Question 4), Table 61-4**
6	Within 14 days of an ischemic event, the	**Case 61-2 (Question 5, 7), Tables 61-5, 61-6**

	risk of recurrence of a stroke is the highest. Acutely, antiplatelet therapy is typically initiated 24 hours after IV thrombolysis. In patients who did not receive IV thrombolysis, dual antiplatelets for 21 days are currently recommended.	
7	Secondary lifelong prevention of a non-cardioembolic ischemic stroke and transient ischemic attacks involves the use of antiplatelet agents as well as controlling modifiable risk factors. Anticoagulants are indicated in high-risk patients with atrial fibrillation. Surgical interventions such as carotid endarterectomy or carotid artery angioplasty/stenting may be appropriate in select patients. Selection of a specific approach is dependent on patient comorbidities.	**Case 61-2 (Question 9), Tables 61-1, 61-5**
8	The strongest risk factor for hemorrhagic stroke because of nontraumatic intracerebral hemorrhage is uncontrolled hypertension. Intracerebral hemorrhage may also occur as a result of an anatomic abnormality in the brain or a disease process, such as a brain tumor. Bleeding disorders, including those induced by anticoagulant drugs, also predispose patients to intracerebral hemorrhage.	**Case 61-3 (Question 1)**
9	Acute treatment of intracerebral	**Case 61-3 (Question**

	hemorrhage focuses on minimizing hemorrhage expansion through careful blood pressure control and reversal of coagulopathies, when appropriate, as well as prevention and management of elevated intracranial pressure.	**2–6)**
10	Modifiable risk factors for hemorrhagic strokes include blood pressure control, smoking cessation, and avoiding excessive alcohol and cocaine use.	**Case 61-3 (Question 7)**
11	Rehabilitation after a cerebrovascular event is essential to patient recovery. Common complications encountered in rehabilitation include spasticity, depression, and neurogenic bowel or bladder. Pharmacotherapy interventions should be directed at each of these complications, with the goal of improving the patient's quality of life and ability to function independently.	**Case 61-4 (Question 1)**

INTRODUCTION

Acute ischemic stroke (AIS), transient ischemic attack (TIA), and hemorrhagic stroke result from either inadequate blood flow to the brain (ie, cerebral ischemia) with subsequent infarction of the involved portion of the central nervous system (CNS) or hemorrhages into the parenchyma or surrounding structures of the CNS and subsequent neurologic dysfunction. This group of cerebrovascular disorders is the fifth leading cause of deaths among adults in the United States.[1] Ischemic strokes constitute 87% of all

cases of cerebrovascular disorders, whereas hemorrhagic strokes account for 13%.

Transient Ischemic Attack

A transient ischemic attack (TIA) is defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia not associated with permanent cerebral infarction.[2] It used to be described as the clinical condition in which a patient experiences a temporary (lasting <24 hours) focal neurologic deficit such as slurred speech, aphasia, weakness or paralysis of a limb, or blindness. However, the original description is no longer valid because it implied that TIAs are minor and that symptoms disappeared completely, whereas recent studies and imaging techniques have shown that TIA can actually lead to brain injury and increased risk of recurrent stroke. Some would argue that the TIA term should not be even used at all.

Acute Ischemic Stroke

Acute ischemic stroke (AIS) is defined as an infarction of the CNS. Unlike TIAs, an AIS may be either symptomatic or silent.[2] Clinical signs of focal or global cerebral, spinal, or retinal dysfunction caused by a CNS infarction are the manifestation of symptomatic AIS. The infarct can affect either the anterior or posterior cerebral circulation, or both. An AIS is categorized into five subtypes depending on the cause as described by the multicenter Trial of Org 10172 in Acute Stroke Treatment (TOAST) investigators.[3] According to the TOAST classification, the five subtypes of AIS include (a) large artery atherosclerosis or large-vessel occlusion (LVO), (b) small artery atherosclerosis (also referred to as lacunar), (c) cardioembolic, (d) undetermined causes, and (e) strokes of other causes.

Intracranial Hemorrhage

Intracranial hemorrhage (ICH) involves the movement of blood from blood vessels inside the brain into the brain tissue, or parenchyma, or its surrounding structures. Clinical symptoms associated with ICH are similar to, but often more severe than, those resulting from ischemic strokes. These symptoms commonly include neurologic deficits as well as headache, vomiting, and a decreased level of consciousness. Some patients may experience other symptoms including seizures, electrocardiographic (ECG) abnormalities, and a stiff neck. Depending on the type and size of the ICH, symptoms may develop abruptly or worsen slowly over minutes to hours.

The location of the hemorrhage within the intracranial vault determines the type of ICH. ICHs occur when blood moves into the brain parenchyma, whereas other types of hemorrhages develop when blood moves into spaces around the brain tissue.

EPIDEMIOLOGY

An estimated 7 million Americans age 20 years or older reported having a stroke.[1] Each year, an estimated 795,000 individuals in the United States experience a new or recurrent stroke and ~610,000 of these are first attacks.[1] There is a higher regional incidence and prevalence of stroke and a higher stroke mortality rate in the southern part of the United States compared to the rest of the country. Younger males have a higher incidence of stroke than do females in the same age group; however, in the age group older than 75 years, females have a higher incidence. Blacks and Hispanics have an increased risk of stroke compared with Whites. The precise reasons for these differences are unclear, but genetic, geographic, dietary, and cultural factors have been considered.[1,4] In addition, the incidence of risk factors for stroke such as hypertension, diabetes, and hypercholesterolemia differs among racial groups. There is a strong relationship between the occurrence of TIA and an increased risk of subsequent cerebral infarction.[1,2] The risk of an ischemic stroke is highest in the first 30 days after a TIA, and the risk within 90

days of a TIA is 3% to 17.3%. In addition, nearly 25% of patients who experience a TIA will die within a year.[2] Risk factors for AIS/TIA are listed in **Table 61-1** and are categorized as either nonmodifiable (eg, age, race, gender) or modifiable (eg, hypertension, high cholesterol level, smoking).[5] Prevention efforts for AIS/TIA will be focused on elimination and control of the modifiable risk factors.[5,6]

Table 61-1
Risk Factors for Transient Ischemic Attack and Acute Ischemic Stroke

Modifiable	Potentially Modifiable	Nonmodifiable
Cardiovascular disease (coronary heart disease, heart failure, peripheral arterial disease) Hypertension Cigarette smoking Diabetes Asymptomatic carotid stenosis Atrial fibrillation Sickle cell disease	Metabolic syndrome Alcohol abuse (≥5 drinks daily) Hyperhomocysteinemia Drug abuse (eg, cocaine, amphetamine, methamphetamine) Hypercoagulability (eg, anticardiolipin, factor V Leiden, protein C deficiency, protein S deficiency, antithrombin III deficiency)	Age (doubling every 10 years after age 55) Race (Blacks > Hispanics > Whites) Biologic sex (males > females) Low birth weight (<2500 g) Family history of stroke (paternal > maternal)
Dyslipidemia (high total cholesterol, low HDL)	Oral contraceptive use (females 25–44 years old)	
Dietary factors (sodium intake <2300 mg/day; potassium intake <4700 mg/day)	Inflammatory processes (eg, periodontal disease, cytomegalovirus, *Helicobacter pylori* seropositive)	
Obesity Physical inactivity	Acute infection (eg, respiratory infection, urinary tract infection)	
Postmenopausal hormone therapy (females 50–74 years old)	CD40 ligand >3.71 ng/mL in females free of cardiovascular disease	

	IL-18 upper tertile	
	hs-CRP >3 mg/L in females ages 45 years and older	
	Migraine headaches	
	High Lp(a)	
	High Lp-PLA_2	
	Sleep-disordered breathing	

HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; Lp(a), lipoprotein(a); Lp-PLA_2, lipoprotein-associated phospholipase A_2.

Source: Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754–3832.

ICHs account for 10% of all strokes in North America, whereas subarachnoid hemorrhage, most commonly resulting from cerebral artery aneurysms, comprises 3% of all strokes. Hypertensive hemorrhage is the most common cause of ICH, with 46% of ICHs resulting from hypertension. A number of medications including warfarin and direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban, significantly predispose patients to ICH.

PATHOPHYSIOLOGY

Acute Ischemic Stroke

The neurologic sequelae of cerebral ischemia or infarction directly result from an embolic or thrombotic source. A clot may form in the heart, along the wall of a major blood vessel (eg, aorta, carotid, or basilar artery), or in small arteries penetrating deep into the brain. If the clot is located near the infarction, it is a *thrombus*; however, when the clot has migrated to the brain from a distant source, it is an *embolus*. Either can diminish or block blood flow to the affected area

of the brain. Disorders such as atrial fibrillation, mitral or aortic valve disease, patent foramen ovale, or coagulopathies are associated with the formation of clots that may embolize the brain. Inflammatory mechanisms also contribute to the development of ischemia, especially thrombotic lesions. Inflammation is thought to enhance the development of thrombotic lesions and result in sudden, intermittent occlusion of blood vessels. Disorders such as arteritis (Takayasu, giant cell), and Moyamoya syndrome are examples of diseases in which inflammation plays an important role in the development of brain ischemia.

Cerebral blood flow (CBF) in the normal adult brain is 30 to 70 mL/100 g of brain tissue per minute. When a thrombotic or embolic clot partially occludes a cerebral artery, causing a reduction in blood flow to <20 mL/100 g/minute, various compensatory mechanisms are activated. These include vasodilation and increased oxygen extraction. If the artery is further occluded and CBF is reduced to <12 mL/100 g/minute, the affected neurons become sufficiently anoxic to die within minutes.[7] Rapid reestablishment of blood flow to the ischemic area can delay, prevent, or limit the onset of infarction, improving the outcome of AIS.

Ischemia in the brain usually involves a core or focal region of profound ischemia that results in neuronal death. The extent of this region is dependent on the amount of brain that is perfused directly by the blood vessel that becomes occluded. There is a surrounding area of the brain that becomes marginally ischemic, with normal function being disrupted. This region of marginal ischemia is frequently called the *ischemic penumbra.* If ischemia continues, neurons in this region will die too. However, if normal blood flow is restored quickly, neurons in this area will survive. The *ischemic penumbra* is the targeted area for salvaging with our current available pharmacologic tools and endovascular interventions.[8]

Intracranial Hemorrhage

ICHs occur because of weakened intracranial blood vessels, elevated pressure inside the blood vessels, and anatomic abnormalities. Specific causes include hypertension, cerebral amyloid angiopathy, brain tumors, coagulopathies, and trauma. An anatomic derangement called arteriovenous malformations (AVMs) may also result in an ICH. An AVM is a clump of arteries and veins that are intertwined, resulting in weakened blood vessel walls. Pathophysiologic mechanisms differ depending on whether the bleeding occurs within the intracerebral space or outside the brain parenchyma in the subarachnoid, epidural, or subdural space.

Spontaneous ICH because of hypertension develops in areas of the brain where smaller blood vessels branch out from large blood vessels often at 90° angles, exposing the smaller vessels to the higher pressure of the preceding blood vessel and eventually resulting in bleeding of the smaller vessels.[9] In ICH, the movement of blood from blood vessels into the brain parenchyma causes local irritation of the brain tissue and edema. In the case of large hemorrhages and significant edema, mass effect can ultimately increase intracranial pressure (ICP), reducing blood flow to the brain and potentially causing brain tissue herniation.[10] Secondary brain injury occurs in many patients after spontaneous ICH. It is caused by a disrupted blood–brain barrier, release of inflammatory mediators, and progressive edema that may last 7 to 12 days.[11–14] In spontaneous ICH, hematoma enlargement is associated with poor outcomes. Nonmodifiable risk factors for hematoma expansion are large hematoma size and contrast extravasation on computed tomography (CT) at the time of presentation, whereas potentially modifiable risk factors include coagulopathies and ongoing uncontrolled hypertension after hospital admission.[15,16]

In subarachnoid hemorrhage, blood moves quickly into the cerebrospinal fluid (CSF), causing an acute elevation of ICP. Intracranial pressure refers to the pressure inside the intracranial vault and may be elevated because of brain tissue swelling, the development of a hematoma (collection of blood) inside the brain, or other conditions. Blood may also migrate into the intraventricular space or into the brain tissue.[17,18] Obstruction of CSF fluid

reabsorption and movement out of the brain because of the presence of blood in the brain can result in hydrocephalus, which is the buildup of CSF within the ventricles of the brain. Delayed cerebral ischemia, commonly referred to as *vasospasm* of the cerebral vasculature, may also complicate subarachnoid hemorrhage.

Epidural and subdural hematomas are other types of ICHs that occur outside the brain parenchyma. Depending on their size, epidural and subdural hematomas may significantly compress and displace brain tissue, resulting in elevated ICP and brain herniation because of mass effect. Brain herniation refers to abnormal movement of brain tissue across structures inside the skull that occurs because of elevated pressures within the intracranial vault. This squeezing of brain tissue can significantly compress CBF, consequently compromising oxygen delivery to the brain and causing brain cells to die.

CLINICAL PRESENTATION

Signs and Symptoms

Stroke and TIA can occur in the community or in the hospital. Clinical signs and symptoms of AIS and TIA must be recognized early by bystanders and/or providers to facilitate activation of stroke-specific management, the outcomes of which are time dependent. Early recognition of symptoms of AIS using the acronym BEFAST can facilitate a faster stroke chain of survival activation and provision of timely interventions.[19] The BEFAST acronym stands for *B* for balance, with the patient reporting of acute sudden loss of *b*alance or coordination; *E* for eyes, and the patient reporting blurred or unclear vision and gaze preference; *F* for *f*acial weakness or facial symmetry referred to as droop; *A* for *a*rm weakness and/or leg weakness; and, finally, *S* for *s*peech difficulty or slurring of. Given that time is important, *T* is for reminding to activate stroke system and alert.

Activation of the 9-1-1 system by patients or bystanders is recommended if stroke is suspected.

A sudden altered mental status or inability to move a limb in a hospitalized patient is also a potential sign of stroke that warrants further investigation.

Nausea and severe headache are often the most common cause of hemorrhagic stroke.

Stroke symptom severity can be rated using preferably the National Institutes of Health Stroke Scale (NIHSS).[8] The scale is available in table format online or in the current stroke guidelines. The link to the online scale can be found with this chapter's key websites. Pharmacists participating in the care of patients with stroke could complete the assessment of the stroke severity using the NIHSS as part of planning with the team to develop a pharmacist patient care process (PPCP).

Neuroimaging

The etiology of a stroke (ischemic vs hemorrhagic) is difficult to discern based solely on a physical and neurologic examination. As a result, CT or magnetic resonance imaging (MRI) is valuable in the evaluation of these patients. A noncontrast head CT is sensitive enough to assist in excluding hemorrhagic stroke and can be performed fairly rapidly in most hospitals. It is important to obtain the noncontrast head CT and its results within 20 minutes of the imaging, according to the current guidelines.[8] Computed tomography angiography (CTA) can be also added, and that would help in discerning the presence of large-vessel atherosclerosis or LVO, and stroke etiology.[20] Computed tomography-perfusion (CT-P) is also available in some institutions and can be used to quantify the ischemic core and to estimate the *ischemic penumbra*. This information can be helpful to guide the management. MRI is superior to a head CT with its tissue contrast, ability to obtain images in multiple planes, absence of artifacts caused by bone, vascular imaging capabilities, absence of ionizing radiation, and safer contrast

media. MRI also allows for a magnetic resonance angiogram to be performed, allowing visualization of the cerebrovasculature and possible identification of the precise location of the thrombus or embolus. MRI with diffusion-weighted imaging (DWI) will reveal an evolving infarct within minutes of stroke onset.

Unfortunately, MRI imaging is more difficult to perform in unstable patients, not always available in smaller hospitals or communities, and is unsafe to do in patients who have metallic implants, or pacemakers.

Obtaining more advanced imaging with CTA, CT-P, or even an MRI should not be favored over delaying therapy.[8]

GENERAL TREATMENT PRINCIPLES

Rapid recognition of stroke symptoms and immediate initiation of treatment are essential to the management of AIS or hemorrhagic stroke (**Fig. 61-1**). Appropriate pharmacotherapy of stroke requires a precise diagnosis.[8,21] It is vital to differentiate between an AIS/TIA and a hemorrhagic stroke because an inaccurate diagnosis can lead to the use of drugs that may cause severe morbidity or mortality. Interventions to prevent and treat AIS are directed at reducing risk factors, eliminating or modifying the underlying pathologic process, and reducing secondary brain damage. In hemorrhagic stroke, the emphasis of treatment is on preventing hematoma expansion, managing ICP, and providing supportive therapy to maximize neurologic function and minimize complications. Rehabilitation is a key component of long-term care for many patients, regardless of whether the stroke is ischemic or hemorrhagic.

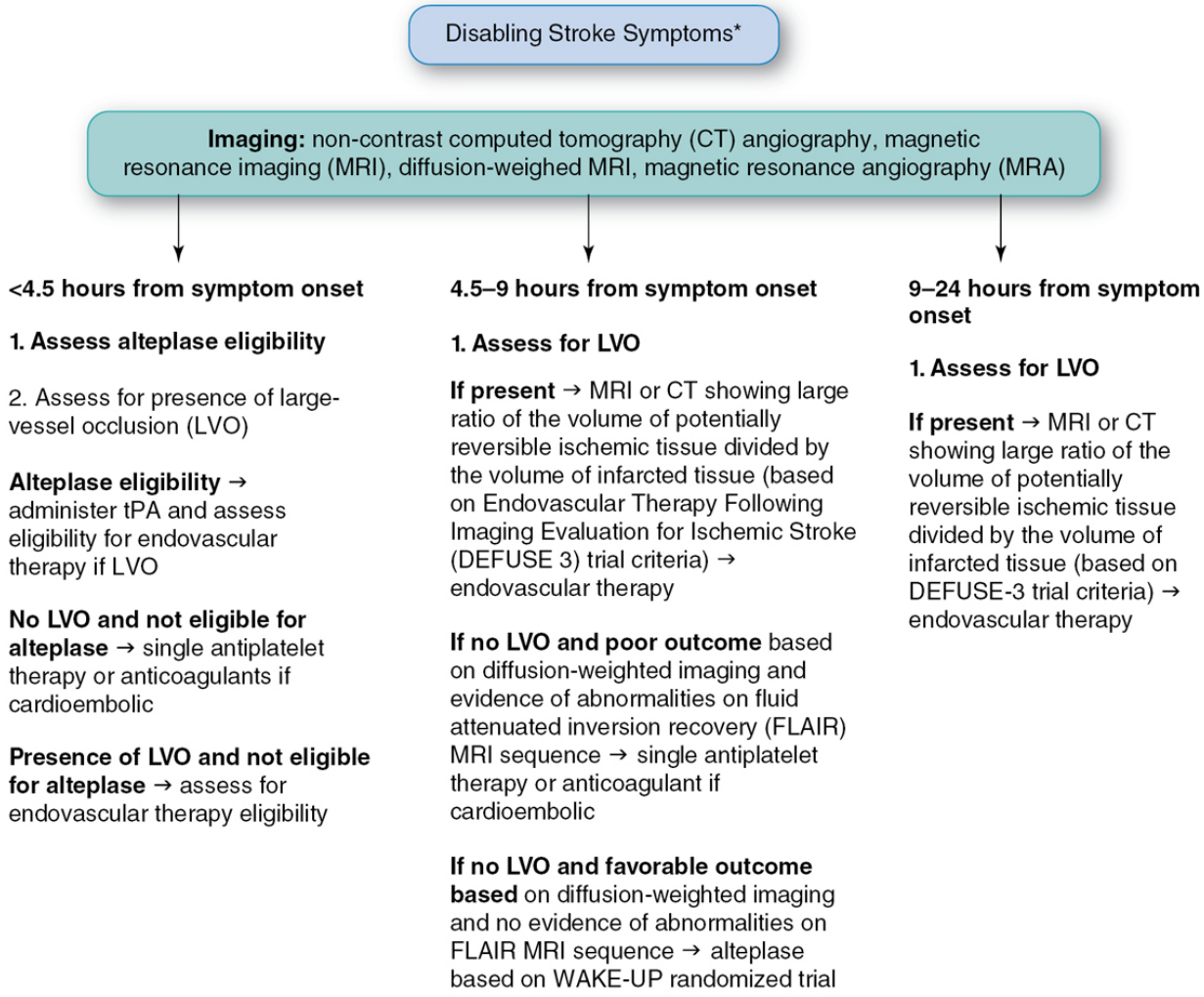


Figure 61-1 Treatment algorithm of acute ischemic stroke. (Adapted from Mendelson SJ, Prabhakaran S. Diagnosis and management of transient ischemic attack and acute ischemic stroke: a review. *JAMA*. 2021;325(11):1088–1098. doi:10.1001/jama.2020.26867.)

Any plan for *primary prevention* (ie, prevention of a first event) of TIA or AIS must address the control or reduction of risk factors (Table 61-1). The reader is referred to a detailed discussion of treatment of diseases[21] such as hypertension, diabetes, coronary artery disease, chronic kidney disease, and so on in their respective chapters (see Chapters 9, Essential Hypertension, 13, Acute

Coronary Syndrome, 28, Chronic Kidney Disease, and 53, Diabetes Mellitus).

ACUTE ISCHEMIC STROKE AND TRANSIENT ISCHEMIC ATTACK

Early Management of Acute Ischemic Stroke

CASE 61-1

QUESTION 1: P.C., a 65-year-old male (220.46 pounds [100 kg], 69 inches [175.26 cm]), is admitted through the emergency department (ED) with right-sided weakness. As per report, the patient was last seen well around 8:30 PM by his wife. Around 9:15 PM, P.C.'s son heard a bump and went upstairs to find his father on the floor. The patient had a slurred speech and had a right facial droop. At this point, 911 was called, and emergency medical services (EMS) picked up the patient and arrived at 9:45 PM at the ED of a large medical center certified for stroke. P.C. regained consciousness by the time he arrived in the ED. Both right extremities are flaccid. He is unable to speak but is capable of understanding instructions (ie, expressive aphasia). Gross ophthalmologic examination indicates right-sided neglect (inability of his eyes to track to the right or acknowledge the right side of his body). His blood pressure (BP) is 165/95 mm Hg and other vital signs are normal. Laboratory studies are all within normal limits. NIHSS score is 6.

Which signs and symptoms are consistent with AIS?

P.C. is showing typical signs of slurred speech, right facial droop, right-sided weakness and paralysis, loss of ability to speak, and right-sided neglect. His NIHSS score is 6, which categorizes his presentation as mild to moderately severe requiring acute inpatient hospitalization and rehabilitation.[22] The definition of severity of AIS according to the NIHSS score include normal severity for NIHSS score of 0 or 1; mild for a score of 1 to 4; mild to moderately severe for a score of 15 to 25, and very severe for an NIHSS score exceeding 25.

Case 61-1, Question 2: What interventions should have been initiated before arrival in the ED?

Immediate recognition of, and response to, stroke symptoms are essential to an optimal outcome. As soon as stroke symptoms are recognized, the emergency medical system should be activated. Emergency medical personnel should be trained to gather important historical information, especially when the symptoms started. This is defined as "when the patient was at their previous baseline or symptom-free state. For patients unable to provide information or who was awakened with stroke symptoms, the time of onset is defined as when the patient was last awake and symptom-free or known to be normal."[8] Use of a standardized evaluation tool such as the Cincinnati Prehospital Stroke Scale or the Los Angeles Prehospital Stroke Screen is useful in distinguishing stroke symptoms from other disorders, such as conversion disorder, hypertensive encephalopathy, hypoglycemia, complicated migraine, or seizures.[8,23]

General supportive care for respiratory and cardiovascular function should be initiated before transporting the patient to the ED. Mobile stroke units (MSUs) equipped with CT scanners and telemedicine links have shown an optimization of timely stroke treatments as opposed to regular ambulances and reinforcing the need for effective structured stroke approaches.[24] Although MSUs may not be available in all areas, professional societies and current guidelines encourage the development of stroke workflows to effectively manage patients with AIS by having a well-designed evaluation and treatment algorithm that addresses assessment and care of the patient from initial onset of symptoms through rehabilitation.[8] Patients with suspected cerebral infarction should be transported, if possible, to the closest certified primary stroke center. A certified primary stroke center would have a multidisciplinary team that would be activated and notified by the emergency personnel while a potential patient with stroke is en route.[23] If a primary stroke center is not locally available, patients can be stabilized in an acute

stroke–ready hospital. In these situations, local providers may use practice arrangements such as telemedicine with comprehensive stroke centers, which allows the provision of advanced care under the supervision of experts at a comprehensive stroke center. The organization of stroke centers and their capacity to provide care can be found in **Figure 61-2**.

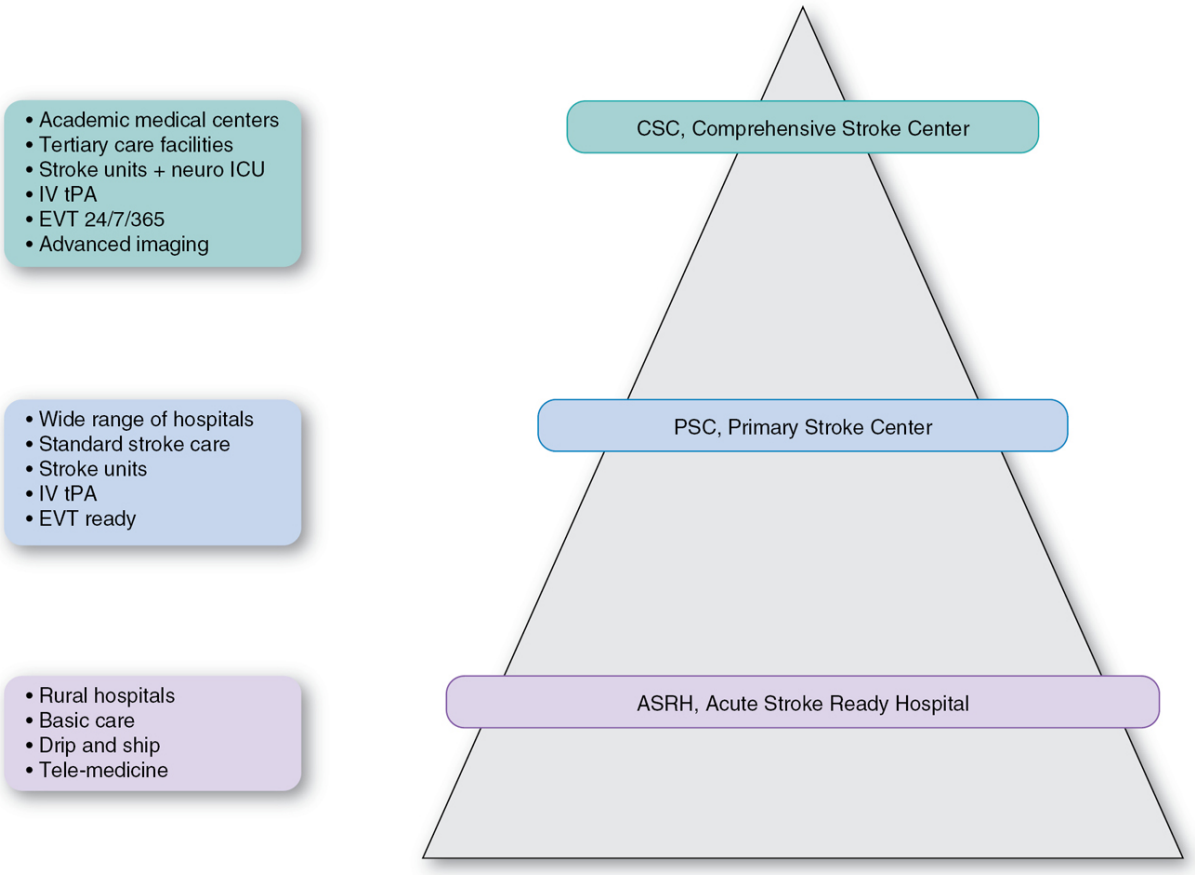


Figure 61-2 Organizations of Stroke Centers and capacity to provide acute stroke care. EVT, endovascular therapy; ICU, intensive care unit; IV tPA, intravenous tissue plasminogen, alteplase. (Source: Reprinted with permission from Herpich F, Rincon F. Management of acute ischemic stroke. *Crit Care Med*. 2020;48(11):1654–1663.)

CASE 61-1, QUESTION 3: What diagnostic tests and evaluations will be helpful in guiding P.C.'s therapy?

Basic laboratory and diagnostic tests should be quickly performed to exclude non-cerebrovascular causes of P.C.'s symptoms, such as metabolic or toxicologic derangement or infections. These tests include a routine serum chemistry profile (electrolytes, blood urea nitrogen, serum creatinine, hepatic enzymes, calcium, phosphorus, magnesium, and albumin), complete blood count, and toxicology screen. Coagulation studies, including a prothrombin time with international normalized ratio (INR) and partial thromboplastin time, should be performed to provide baseline values for potential anticoagulation or thrombolytic therapy. In addition, a thorough physical, neurologic, cardiovascular, and mental status examination should be performed. The neurologic examination will assist in the localization of the lesion in the CNS. The physical examination should include use of the NIHSS.[8] In addition to providing important information for diagnosis of his neurologic compromise, these tests will provide baseline data for ongoing assessment of P.C.'s progress and recovery.

P.C. must have a noncontrast head CT before initiation of any specific therapy for stroke. A follow-up CT or MRI is useful to determine the extent of neurologic damage resulting from the ischemic stroke.

CASE 61-1, QUESTION 4: What are the goals of therapy for AIS in P.C.?

The immediate goal is to reestablish adequate blood flow in the diseased cerebral vessels to salvage the ischemic penumbra and limit the expansion of the ischemic core. In addition, the acute goals include prevention of AIS complications such as hemorrhagic conversion, aspiration pneumonia, formation of venous thromboembolism, and brain swelling.

Longer range objectives are to prevent reocclusion, decrease the risk of a future ischemic stroke, and provide education and rehabilitation to allow return to normal functional status with minimal disability. Screening for depression and minimizing the risk of dementia are additional holistic long-term goals.[8]

The modified Rankin Scale (mRS) is the gold standard for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke.[25] It has become the most widely used clinical outcome measure for clinical trials evaluating therapy efficacy for AIS. The mRS ranges from 0 to 5, with 0 representing the absence of disability and 5 representing severe disability. A separate category of 6 is usually added for patients who expire. Functional status measured by mRS is typically assessed at discharge from the hospital and again at 90 days following discharge. The mRS score at 90 days is used as part of the standard performance outcome measure for the joint commission–certified comprehensive stroke centers in the United States.[26] Details about the mRS can be found in **Table 61-2**.

Table 61-2
Modified Rankin Score to Evaluate Functional Status Outcome After an Acute Ischemic Stroke

Label	Value	Interpretation
Independent Functional Status	0	**No symptoms**
	1	**No significant disability despite symptoms:** able to carry out all usual duties and activities
	2	**Slight disability:** unable to carry out all previous activities but able to look after own affairs unassisted
Dependent Functional Status	3	**Moderate disability:** requires some help but able to walk without assistance
	4	**Moderate severe disability:** unable to walk unassisted and unable to attend to own bodily needs without assistance
	5	**Severe disability:** bedridden, incontinent, and requiring constant nursing care and caregiver attention
Death	6	

Source: Reprinted with permission from van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap

in stroke patients. *Stroke*. 1988;19(5):604–607. Copyright © 1988 by American Heart Association.

Therapy

INTRAVENOUS THROMBOLYSIS

CASE 61-2

Question 1: R.W. is an 84-year-old right-handed female with history of macular degeneration, spondylosis of lumbar region, and benign parotid gland neoplasm status post removal who presented to the ED for acute-onset slurred speech and right hand/arm weakness. The patient was last at her normal state of health at 7:30 AM when she was talking to her husband. She then got up to go to the bathroom around 7:45 to 8:00 AM and felt dizzy and unwell. She fell in the bathroom unwitnessed. Her husband called EMS, who noted that she was not moving her right side with right-sided facial asymmetry and had abnormal, aphasic speech. At present, the patient is having difficulty with history reporting. She states she has pain on the left shoulder from a recent fall, which limits her range of motion on that side. The patient has no history of neurologic disorders including strokes, mini strokes, seizures, and dementia. She has baseline vision loss related to her macular degeneration. She has no other baseline neurologic deficits. The patient has a history of arthritis and has had recent mechanical falls; most recently, she was seen in the ED 2 weeks before presentation for a mechanical fall in which her foot got stuck on a stair and she fell. The patient does not take aspirin, clopidogrel, or any anticoagulant. Her NIHSS was scored as 8 by the neurologist and her neurologic exam is documented for the following findings:

Mental status: Awake, oriented to person, not to place or time, unable to state her correct age, confused speech, able to follow simple commands but has difficulty with multistep commands, unable to describe the cookie theft scene or name items in the stroke booklet, although this may be due to visual limitations, seems to have difficulty naming items in the exam room, responds "yes" or "no" to questions not always appropriately, able to repeat short sentences but has difficulty with longer sentences.
Cranial nerves: Pupils are reactive to light; full visual fields; extraocular movements are intact; no dysarthria; mild right facial droop.
Motor: Moving all extremities antigravity with some resistance strength with encouragement, has motor neglect affecting the right upper and lower extremity that limits her movements. Drift of the right upper extremity.
Sensory: Decreased throughout the right side, sensory neglect of the right side.

Coordination: Has difficulty following commands to participate in coordination tasks.

Noncontrast CT of the head showed no acute hemorrhage, no acute or evolving infarct, white matter disease, and chronic infarct in the right hemisphere seen on prior CT obtained 2 weeks ago. CTA showed an area of cutoff, thrombus in the inferior branch of the left middle cerebral artery (MCA). CT-P showed a small core infarct (3) and a larger area of ischemic penumbra (14).

Her vital signs in the ED: temperature 98.60 °F (37 °C), heart rate 70 beats/minute (bpm), blood pressure 148/52, relevant laboratory point-of-care test for glucose 105 mg/dL, glycated hemoglobin 6.3%, platelet count 250,000 cells/L, INR 1.2.

Is R.W. a candidate for intravenous (IV) thrombolysis?

The critical primary event in a thromboembolic stroke is the development of an acute thrombus. Prospective cerebral angiography has demonstrated an arterial occlusion corresponding to the area of acute neurologic deficit in >90% of cases.[27] Occlusion of cerebral arteries does not cause complete ischemia because collateral circulation from other arterial sources provides unstable and incomplete circulation to the ischemic region of the brain.[28] When CBF is sustained in the range of 10 to 18 mL/100 g/minute, irreversible cellular damage may occur. Blood flow must be restored quickly after the event. Experimental studies in dogs and cats have shown that when CBF is restored within 2 to 3 hours, neurologic deficits are prevented.[29,30]

Thrombolytic agents are capable of reestablishing blood flow to ischemic regions of the brain and to limit the growth of the *ischemic penumbra*. The most important factor in successful thrombolytic therapy is early treatment. Door-to-needle (DTN) time is quality performance measure of stroke centers measuring the time of presentation to the ED to the time the infusion of thrombolytics is started. Current guidelines recommend a DTN time as fast as possible (eg, ≤60 minutes) and that stroke centers monitor the time to enhance the center's performance.[8] Pharmacists' involvement in stroke teams or in the ED have been shown to play a major role in improving DTN time.[31] In addition, to ensure safety of thrombolytics, the selection of appropriate candidates for thrombolysis is extremely

important and requires the correct neurologic evaluation by a specialized team. Current guidelines include a list of indication and contraindications found in table 8 of the guidelines for IV thrombolysis compared to the prior edition that listed inclusion and exclusion citeria.[8,32] All patients who meet eligibility criteria for IV thrombolysis should be offered such therapy, and the list of eligible patients became more inclusive in the most current version of the guidelines. **Table 61-3** lists indications and contradictions for patients with AIS who could be treated with IV thrombolysis, as adapted from table 8 from the current guidelines.[8] Before the initiation of IV thrombolysis, patients with high BP should have their BP lowered carefully to systolic blood pressure (SBP) <185 and diastolic blood pressure (DBP) <110 mm Hg (refer to **Table 61-4** and the discussion later on BP control).

Table 61-3

Eligibility Criteria for IV Alteplase Use in Treatment of Acute Stroke

Indication Criteria	Contraindication Criteria (No Benefit or Harm)
▪ Age 18 years and older ▪ Clinical diagnosis of stroke with clinically meaningful neurologic deficit ▪ Within 3–4.5 hours of AIS symptom onset or patient last known well or at baseline state ▪ Wake up with stroke and unknown time of onset and have a DW-MRI lesion smaller than one-third of MCA territory with no visible signal change on FLAIR ▪ Baseline noncontrast CT with no evidence of intracranial hemorrhage	▪ Mild nondisabling stroke (NIHSS 0–5) ▪ CT signs of intracranial hemorrhage, multilobar infarction, or symptoms of subarachnoid hemorrhage ▪ Active internal bleeding ▪ History of intracranial hemorrhage ▪ Intracranial neoplasm, aneurysm, or arteriovenous malformation ▪ Ischemic stroke or serious head injury within 3 months ▪ Systolic BP >185 mm Hg, diastolic BP >110 mm Hg ▪ Glucose <50 mg/dL or >400 mg/dL if unable to normalize ▪ Infective endocarditis given increased risk of ICH

	▪ Aortic arch dissection
	▪ Active bleeding diathesis including but not limited to:
	  ▪ Current use of anticoagulant with INR >1.7
	  ▪ Use of IV aspirin
	  ▪ Current use if direct thrombin inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, ECT, TT, and factor Xa activity assay)
	  ▪ Heparin received in last 48 hours resulting in abnormally elevated aPTT or LMWH full treatment dose within the previous 24 hours
	  ▪ Platelet count <100,000/mm^3
	▪ *Pregnancy if risk outweighs benefit*
	▪ *GI or urinary tract hemorrhage within 3 weeks*

	Extended 3- to 4.5-hour window: ▪ Uncertain benefit NIHSS score >25 ▪ Taking an oral anticoagulant with INR >1.7 or any direct oral anticoagulants ▪ Imaging evidence of ischemic stroke involving more than one-third of MCA territory

AIS, acute ischemic stroke; aPTT, activated partial thromboplastin time; BP, blood pressure; CT, computed tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; ECT, ecarin clotting time; FLAIR, fluid-attenuated inversion recovery; GI, gastrointestinal; ICH, intracranial hemorrhage; INR, international randomized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TT, thrombin time.

Source: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2019;50(12):e344–e418 (full list of indications and contraindications found in Table 8).

Table 61-4
Management Guideline for Blood Pressure Treatment in Acute Ischemic Stroke

Treatment	Received Alteplase/Mechanical Thrombectomy	Did Not Receive Alteplase or Mechanical Thrombectomy
No treatment recommended	If BP is <185/110 mm Hg	If BP <220/120 mm Hg unless there is another specific medical condition
Nicardipine 5 mg/hour, titrate up by 2.5 mg/hour every 5–15 minutes (maximum 15 mg/hour) Labetalol 10–20 mg IV over 1–2 minutes, every 5 minutes may repeat to a maximum of 300 mg total, or labetalol 10 mg IV followed by continuous infusion 2–8 mg/minute Clevidipine 1–2 mg/hour, titrated by doubling the dose every 2–5 minutes until desired BP achieved (maximum 21 mg/hour)	If BP >185/110 mm Hg, goal is to lower below 185/105 mm Hg to limit risk of ICH before start of alteplase and to keep BP ≤180/105 mm Hg after alteplase for 24 hours	If systolic BP >220 mm Hg or diastolic 120–140 mm Hg
IV sodium nitroprusside 0.5 µg/kg/minute	If BP not controlled by abovementioned measures or if diastolic BP is >140 mm Hg	If not controlled or if diastolic BP >140 mm Hg

BP, blood pressure; ICH, intracranial hemorrhage; IV, intravenous.

Source: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2019;50(12):e344–e418.

Several thrombolytics (streptokinase, alteplase, tenecteplase, reteplase, and urokinase) are available. However, only alteplase trials have shown benefits and improved outcomes.[33–36]

In three studies, streptokinase was used as the thrombolytic, and all of these studies were terminated early owing to high rates of mortality and ICH associated with streptokinase.[33,34,37] The rates of ICH ranged from 6% to 17% for patients receiving streptokinase compared with 0.6% to 3% for patients receiving placebo.

The National Institute of Neurological Disorders and Stroke (NINDS) alteplase trial[35] and the European Cooperative Acute Stroke Study (ECASS) I[36] used different doses, inclusion criteria, and treatment protocols. Both trials showed the benefit of alteplase in at least some outcome parameters. In the NINDS alteplase study, patients were enrolled within 3 hours of symptom onset using strict inclusion and exclusion criteria. When enrolled, patients received either IV tissue plasminogen activator (tPA) known as alteplase 0.9 mg/kg (maximal dose, 90 mg), with 10% of the dose given as a bolus for 1 minute and the remainder infused for 60 minutes, or placebo. In this study, there were no differences in the primary outcome defined as improvement by at least 4 points on the NIHSS score or complete resolution of neurologic deficit at 24 hours in responses between the placebo group and those who received IV tPA. However, at 3 months, patients who received IV tPA were 30% more likely to have minimal or no disability, as measured by the outcome scales. There was an 11% to 13% absolute increase in the number of patients with excellent outcomes and a corresponding decrease in the number of patients with severe neurologic impairment or death at 3 months. ICH occurred more frequently among patients receiving IV tPA (6.4%) than in patients receiving placebo (0.6%). Despite the increased incidence of ICH, outcomes remained better for patients receiving tPA. For the ECASS I trial, patients were enrolled within 6 hours of the onset of symptoms.[36] The treatment protocol consisted of IV tPA 1.1 mg/kg (maximal, 100 mg) or placebo. There was no difference in the primary outcome measures of functionality at 3 months. However, with target population analysis, there was a significant difference favoring tPA. Of patients treated with tPA, 41%

had minimal or no disability compared with 29% of patients treated with placebo. A variety of secondary outcome measures favored tPA. There was no difference in 30-day mortality rates, but 19.8% of patients treated with alteplase had major parenchymal hemorrhages compared with 6.5% of patients treated with placebo.

Since NINDS and ECASS-I, three subsequent trials, the ECASS-II[38] and Alteplase Thrombolysis for Acute Non-Interventional Therapy in Ischemic stroke (ATLANTIS A and B) found largely the same effects as NINDS when therapy was initiated in the ≤3-hour time period. The ECASS-II study used a tPA dose of 0.9 mg/kg and replicated the NINDS trial[38]; however, patients were enrolled up to 6 hours after the onset of stroke symptoms. This study found no difference between tPA and placebo. Too few patients were enrolled with stroke symptoms within 3 hours to reliably evaluate the influence of this variable on outcome.

Since NINDS, several trials have also investigated the use of IV tPA up to 6 hours after stroke onset. ECASS-I, ECASS-II, and ATLANTIS A and B all enrolled patients with an extended window use of tPA. None of these trials found individually a benefit; however, a pooled analysis suggested improved outcomes.[39] Hence, the ECASS-III study was conducted to evaluate the efficacy and safety of tPA administered using the NINDS tPA dose (0.9 mg/kg up to maximum of 90 mg), but it focused on the efficacy and safety of tPA administered 3 to 4.5 hours after the onset of symptoms.[40] A significantly greater number of patients receiving tPA had favorable outcomes on the mRS global disability scale compared with placebo (odds ratio [OR] 1.34; 95% confidence interval, 1.02–1.76). Although the rate of ICH was greater with tPA, mortality and reports of adverse events were similar between the two groups. When considering the use of tPA in the 3- to 4.5-hour window, the ECASS-III criteria should be followed (Table 61-3). In a large, randomized, placebo-controlled trial, the third International Stroke Trial (IST-3), which followed the NINDS dosing scheme for tPA, where patients were enrolled within 6 hours of symptoms onset, there was a significant improvement in functional outcome in the Oxford Handicap score (OR 1.27; 95% confidence interval, 1.10–1.47). However, there were more deaths at

7 days in the tPA group. IST-3 included patients age older than 80 years in comparison to ECASS-III and a broader BP eligibility. In summary, controlled trials have shown IV tPA to be beneficial for select patients with AIS who start treatment within 4.5 hours. For indicated patients (Table 61-3), once a CT ruled out a hemorrhage, IV tPA should be started within 4.5 hours of clearly defined symptoms. There are specific criteria to select patients for tPA eligibility if they present within 3 hours of onset of symptoms versus if they present up to 4.5 hours of symptoms (see Table 61-3).

Tenecteplase, a structurally modified alteplase at three points resulting in a more fibrin-specific agent with a better pharmacokinetic profile and longer duration of action compared to tPA, has been recently evaluated as an alternative to tPA for AIS.[41–44] IV tenecteplase is administered as a bolus dose with fewer steps for preparation and reconstitution as opposed to a 60-minute infusion of tPA, providing the former with an additional logistic advantage. Tenecteplase appears to have safety similar to that of tPA, but it is unclear if it is as effective as or superior to tPA. Indeed, IV tenecteplase (0.4 mg/kg bolus), in patients presenting within 4.5 hours of symptom onset of mild stroke (NIHSS score 0–7) was found at best to achieve similar functional outcomes at 90 days as assessed with mRS with tPA with similar rates of ICH.[44] Based on these trials, current guidelines suggest tenecteplase as an alternative to tPA in patients with minor neurologic impairment and no major intracranial occlusion.[8,45] In the tenecteplase versus tPA before thrombectomy for ischemic stroke (EXTEND-IA TNK) trial, patients with LVO and who are candidates for mechanical thrombectomy, IV tenecteplase 0.25 mg/kg (maximum 25 mg) administered within 4.5 hours showed at least noninferiority to alteplase and a statistically significant better reperfusion rate of >50% pre-CT–guided thrombectomy.[46] Based on the results of EXTEND-IA TNK, the current guidelines added a recommendation to select tenecteplase over alteplase before thrombectomy in patients without contraindications to IV thrombolysis who are also eligible for mechanical thrombectomy.

Finally, in patients who are awake with stroke symptoms or have an unclear time of onset >4.5 hours from last known well or at baseline, a diffusion-weighted (DW) MRI is recommended. If lesions are present and are smaller than one-third of the MCA territory and there is no evidence of abnormalities on fluid-attenuated inversion recovery (FLAIR) MRI sequence, in the absence of LVO, IV tPA is recommended.[8] Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial was investigated. The MRI-guided thrombolysis in patients with stroke with unknown time of onset led to better functional outcome and numerically more ICHs than placebo at 90 days.[47] In this randomized clinical trial, an mRS score 0 to 1 was achieved in 53.3% of the tPA group and 41.8% of the placebo group (P = .02). The median time from last known well to symptom recognition was about 7 hours and to tPA administration slightly >10 hours. Only 20% of the patients randomized had LVO of the intracranial carotid or proximal middle cerebral arteries. In addition, a recent meta-analysis also confirmed the WAKE-UP investigators' findings by combining the results of three other published trials that investigated MRI-guided tPA administration in unclear time of onset of stroke symptoms from last known well.[48]

R.W. is considered a candidate for IV tPA, because she presented to the ED within the 3-hour window of her stroke symptom onset, her NIHSS score was 8, and there was absence of obvious contraindications according to the current guidelines, as outlined in Table 61-3. Her total IV tPA dose will be 0.9 mg/kg, with 10% of the dose administered as an IV push over 1 minute followed by the reminder of the dose infused over 60 minutes. The DTN time should be recorded in the institution database for performance measure tracking. During and after receiving tPA, the patient should be monitored for the onset of adverse reactions associated with alteplase such as orolingual angioedema and ICH. The current guidelines recommend BP checks, neurologic examination, and angioedema screenings every 15 minutes for the first 2 hours after initiating alteplase and then every 30 minutes for 6 hours followed by every hour for 16 hours.[8] Orolingual angioedema is rare, and it is thought to occur by histamine release and increase in circulating

bradykinin induced by the activation of conversion of plasminogen to plasmin. If it occurs during tPA infusion, the infusion should stop immediately, and the American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend rapid administration of methylprednisolone, diphenhydramine, and an IV histamine-2 blocker such as famotidine along with 0.3 mg intramuscular (IM) epinephrine if angioedema is not responsive to steroids. Icatibant, a selective bradykinin B_2 receptor antagonist or plasma–derived C1 esterase inhibitor are expensive alternatives that may need to be entertained if the patient fails to respond, given that tPA-mediated angioedema is most likely mediated by bradykinin. Alternatively, ecallantide, a kallikrein inhibitor that prevents the transformation of kininogen to bradykinin, may be considered as an option to target the angioedema associated with tPA.[49]

Symptomatic intracranial hemorrhage (sICH) that occurs within 24 hours of IV tPA administration is the most feared complication of IV thrombolysis. It can be treated with cryoprecipitate 10 units infused over 10 to 30 minutes, tranexamic acid 1000 mg IV over 10 minutes, or aminocaproic acid 4 to 5 g over 1 hour.[8,50,51]

CASE 61-2, QUESTION 2: What general supportive care interventions should be made for R.W.?

In addition to the general supportive therapy needed for a hospitalized patient, several issues are important to the proper management of R.W.

Assessing vital signs and ensuring stabilization of airway, breathing, and circulation is the initial part of the evaluation. Intubation and mechanical ventilation may be required to ensure adequate ventilation and to protect the airways from aspiration. Careful attention should be given to fluid and electrolyte control. Excessive hydration or inadequate sodium supplementation may result in hyponatremia, potentially causing cerebral edema. This can result in compression and displacement of brain tissue, which can disrupt cerebral perfusion. In addition, hyponatremia can produce

seizures, which increases the metabolic demand on compromised neurons. Thus, 0.9% saline or lactated Ringer are the preferred fluids in patients at risk for cerebral edema.[23]

Attention to body temperature needs to be given. Studies have shown that even small increases in temperature are associated with worse outcomes after acute stroke.[52,53] Hypothermia is neuroprotective, and a reduction in body temperature of 0.26 °F (−17.63 °C) can be beneficial in patients with stroke.[23,54] Use of antipyretics, such as acetaminophen, is advised to maintain normal or slightly subnormal body temperatures.

Another metabolic parameter that must be followed carefully is the serum glucose concentration, because hyperglycemia may adversely affect ischemic infarction outcomes. A review of multiple studies on the effects of hyperglycemia in acute stroke concluded that hyperglycemia results in poor outcomes and increased mortality.[55] If hyperglycemia is detected, appropriate insulin therapy should be initiated to keep the serum glucose concentration <140 mg/dL without causing hypoglycemia.[23]

The general daily needs of the patient should be assessed and provided on an as-needed basis. Attention should be provided to prevent deep venous thrombosis (DVT), decubitus ulcers, and delirium. Neurologic deficits will compromise the ability of many patients to adequately meet these needs, increasing the necessity for medical assistance.

ENDOVASCULAR INTERVENTIONS

CASE 61-2, QUESTION 3: What other reperfusion interventions might be considered for the acute treatment of stroke in R.W.?

A number of endovascular treatment options for ischemic stroke are available and include intra-arterial fibrinolytics, endovascular thrombectomy (EVT) with coil retrievers such as the Mechanical Emboli Removal in Cerebral Ischemia (MERCI) device or stent retrievers, combination intra-arterial thrombolytics with EVT, direct

aspiration thrombectomy, and emergency angioplasty and stenting. The most current guidelines recommend using the stent retrievers over coil retrievers.[8]

IV tPA can fail to achieve revascularization in patients with LVO such as the internal carotid artery or the MCA. R.W. has an MCA infarct (and, therefore, an LVO), and IV tPA could fail to achieve the revascularization goal; hence, R.W. should be considered for eligibility for EVT.

EVT has been evaluated alone or in combination with IV thrombolysis.

In patients with stroke secondary to occlusions in the proximal anterior intracranial circulation, EVT using a stent retriever device after receiving IV tPA significantly reduced the 90-day functional disability without increasing risk of ICH or mortality compared to IV alteplase monotherapy.[56] Similar results were also found in four other trials comparing endovascular therapy with IV thrombolytics to standard therapy with IV thrombolytics alone for documented large occlusions in the proximal anterior circulation. Intra-arterial thrombectomy reduced disability and improved outcomes.[57–60] These trials required angiographic confirmation by CT of an intracranial occlusion for eligibility, whereas earlier trials that did not require such confirmation or used older devices (MERCI® and Penumbra System®) did not find such benefit.[61–64]

The superiority of EVT combined with IV thrombolysis was shown in several randomized controlled trials.[56,58,60,65] Performing EVT within 6 hours of symptom onset doubles the rate of revascularization at 24 hours and mRS at 90 days when combined with tPA. Current guidelines recommend the combination of IV tPA in addition to EVT in patients who meet eligibility criteria for EVT. These include age 18 years or older, LVO demonstrated on CTA, Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≥6, NIHSS score ≥6, and treatment initiated (groin puncture) within 6 hours of symptom onset.[8] The ASPECTS is a 10-point scoring tool that assesses early ischemic changes in the patient's initial noncontrast head CT. Lower scores indicate a great degree of

ischemic changes, whereas a score of 10 (the highest) indicates no ischemic changes.

In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation, EVT is recommended if they meet the eligibility criteria derived from two recent landmark trials that evaluated the extension window for EVT beyond 6 hours.[66,67] Despite the possibility for extended treatment windows for EVT, these procedures are not available outside of comprehensive stroke centers. Starting the IV tPA in smaller medical centers or community hospitals remains the best approach for the moment. Telemedicine or telestroke can facilitate connecting these smaller medical or community centers with comprehensive stroke centers to coordinate the transfer of patients after completion of the IV tPA infusion. Patients eligible for IV tPA should always receive tPA even if mechanical thrombectomy is being considered.[8]

Finally, intra-arterial thrombolytic administration requires an experienced stroke center and careful selection to identify patients who would benefit. As with IV thrombolysis, intra-arterial thrombolytics should be administered, within 6 hours of onset of symptoms, in patients with occlusions of the MCA who are not candidates for IV tPA. Although intra-arterial thrombolytics can be considered when IV tPA is predicted to fail (LVO) or is contraindicated, these therapies, if available to be administered by a skillful interventional neuroradiologist, should be considered. Lack of identification of optimal dose and evidence of effectiveness in occlusions outside of the MCA limit the widespread use of intra-arterial thrombolytics. Intra-arterial thrombolytics are no longer recommended as a first-line reperfusion strategy.[8]

Unfortunately for R.W., the location of the clot was deemed by the neurologist to be too distant to recommend EVT. Otherwise, the other eligibility criteria for EVT were met.

Case 61-2, Question 4: What BP goal should be targeted in R.W.?

Caution should be exercised in the acute management of R.W.'s BP. Decreasing the BP too rapidly will compromise CBF and expand the region of ischemia and infarction, whereas hypertension may place her at a greater risk for cerebral hemorrhage, especially when a thrombolytic agent is used. However, a study comparing treated and untreated patients who were hypertensive in association with an acute stroke failed to demonstrate any difference in outcomes between the groups.[68]

For patients with an SBP >185 mm Hg or a DBP >110 mm Hg, who are otherwise candidates for IV thrombolysis, IV labetalol, continuous infusion of nicardipine, or clevidipine should be used to reduce the BP to these goals before starting alteplase.[8] The decision to select one antihypertensive agent over another depends on the hospital formulary; concomitant heart rate favoring labetalol, for example; or agent availability to quickly administer in the ED. Continuous infusion of clevidipine or nicardipine may provide a more stable BP control over labetalol IV and, therefore, may be preferred after alteplase administration for a tighter control. If BP is not controlled with nicardipine, clevidipine, or labetalol or if DBP >140 mm Hg, IV sodium nitroprusside could be considered. After administration of tPA, SBP should be kept <180/105 mm Hg to limit the risk of ICH 24 hours post IV thrombolysis. BP should be monitored every 15 minutes for 2 hours from the start of IV tPA, then every 30 minutes for 6 hours, and then every hour for 16 hours.[8]

Similarly, in patients who are candidates for mechanical thrombectomy, targeting a BP of <180/105 mm Hg is recommended for the first 24 hours post the thrombectomy based on the results of two major trials.[8,66,67] Higher BPs within the first 24 hours of successful thrombectomy increased the risk of sICH, mortality, and the need for hemicraniectomy.[69] In a recent retrospective analysis of 217 patients, the 90-day clinical outcomes, mortality, and functional status pointed out that a moderate BP target of <160/90 mm Hg was reasonable in patients who achieved successful thrombectomy and is potentially more preferred.[70]

In all other patients who are not candidates for IV thrombolysis or mechanical thrombectomy, "permissive hypertension" up to 220/120

mm Hg is recommended to maintain perfusion to the brain. This means that BP will be permitted to go up to 220/120 mm Hg without antihypertensive agents being administered. If there is a clinical deterioration in the neurologic function associated with the reduction in BP, the infusion rate of the antihypertensive agent should be slowed, or the drug discontinued. Specific BP management recommendations are outlined in Table 61-4.

After the first 24 hours of stroke onset, maintenance antihypertensive therapy can then be initiated using an oral agent, such as thiazide diuretics, calcium channel antagonists, or angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs). The reader is referred to the more detailed discussion of hypertension management in Chapter 9, Essential Hypertension.

CASE 61-2, QUESTION 5: Should anticoagulation or antiplatelet agents be used acutely in R.W.?

Several studies have evaluated the use of anticoagulants in the treatment of acute strokes. However, most of these studies are poorly designed or underpowered to determine the efficacy of these agents.

HEPARIN AND HEPARINOIDS

Three studies have evaluated the use of heparin in acute stroke.[71–73] In one double-blind study, heparin doses were adjusted to maintain the activated partial thromboplastin time (aPTT) at 1.5 to 2 times control and continued for 7 days.[71] There were no significant differences in death at 7 days, no differences in functional ability 1 year after the stroke, and a greater mortality rate at 1 year for patients treated with heparin. Another study compared aspirin, and two doses of subcutaneous heparin (5000 IU or 12,500 IU bid) for patients with AIS.[72] There was no reduction in mortality or morbidity for patients receiving either dose of heparin. Heparin use has also been studied in progressing stroke (stroke with evolving neurologic

symptoms), and no benefit was demonstrated with its use.[73] No studies have demonstrated that heparin is useful in mitigating the neurologic effects of a stroke.

Low-molecular-weight heparins (LMWHs) and heparinoids have been evaluated in several studies for acute stroke. Two doses of nadroparin were compared with placebo in one randomized, double-blind, placebo-controlled trial.[74] There were no differences in death rates or functional ability at 3 months among the three treatment arms. However, at 6 months, patients receiving high-dose nadroparin (ie, 4100 anti-Xa IU bid) had improved function. A large randomized, placebo-controlled trial of dose-adjusted danaparoid, a low-molecular-weight heparinoid, did not demonstrate improvement in patients treated with danaparoid.[75] In addition, no improvements were observed in studies of dalteparin and certoparin.[76,77]Similar to heparin, LMWHs and heparinoids are not indicated in the acute treatment of stroke.

DVT and pulmonary embolism (PE) are common complications in patients following a stroke. Intermittent compression devices such as Venodynes, which prevent pooling of blood in the lower extremities, should be applied within 24 hours of admission to the hospital unless contraindicated. The incidences of DVT and PE were reduced in most studies in which patients received heparin, LMWHs, or heparinoids.[78]

Unfractionated heparin 5000 units subcutaneously twice daily (bid) or three times daily can be initiated in R.W. for DVT prophylaxis after 24 hours of IV tPA administration once a repeat head CT ruled out ICH. Heparin is considered an inexpensive and effective option compared to LMWHs.

ANTIPLATELETS

The risk of recurrent ischemic stroke is high in the first 2 weeks after AIS or TIA. Up to 80% of recurrent strokes occur within the 14 days of the index event.[79]

Aspirin

One study evaluated early administration of aspirin in acute stroke. The Chinese Acute Stroke Trial compared 160 mg/day of aspirin administered within 48 hours of the onset of stroke symptoms with placebo.[80] Patients who received aspirin had reduced early mortality rates, but there was no difference in the primary end point of death or dependency at discharge from the hospital. Two other studies did not demonstrate benefit with aspirin.[37,72] When data from these studies are combined, a slight beneficial effect of aspirin is seen with regard to reducing the risk of early stroke recurrence. Current recommendations are for aspirin 325 mg to be administered within 24 to 48 hours of the onset of stroke symptoms, except when alteplase is administered. When alteplase is given, aspirin should be given 24 to 48 hours after alteplase administration but still within 48 to 72 hours of onset of stroke symptoms.[8] In R.W., IV tPA was used; hence, aspirin should not be administered until at least 24 hours after the end of the alteplase infusion have lapsed and once a repeat head CT ruled out hemorrhagic conversion.

Other antiplatelets

There has been limited published evidence available for the usage of other antiplatelets such as clopidogrel or dipyridamole in the acute treatment of ischemic stroke. Small pilot studies suggested some utility to these antiplatelets without providing solid evidence of a clear benefit of the well-established aspirin in AIS treatment. Platelet glycoprotein IIb/IIIa inhibitors have also been studied in acute stroke. A placebo-controlled phase 2 trial of abciximab given within 24 hours of acute stroke showed a trend toward improved functionality in patients treated with abciximab, but the study was not powered to show the significance of this outcome.[81]

Combination of antiplatelets

In the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, the investigators randomized 5170 patients in a double-blind, placebo-controlled study within 24 hours of the onset of symptoms of a minor stroke or TIA to

an initial loading dose of 300 mg clopidogrel followed by 75 mg/day for 90 days with aspirin at a dose of 75 mg/day, or to placebo plus aspirin 75 mg for 90 days. This study conducted in China found that the combination was superior to aspirin in reducing the risk of stroke in the first 90 days. The patient selection did not include major stroke or patients who received IV thrombolysis.[82] In the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, results noted from CHANCE were replicated in a more diverse ethnic background.[83] Within 12 hours of symptom onset, clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg/day, plus aspirin (at a dose of 50–325 mg/day) for 21 days, compared to the same range of doses of aspirin alone resulted in absolute risk reduction of 1.5% and 30% relative risk reduction of major ischemic events in the combination arm. The risk of hemorrhage from the antiplatelet combination was higher than from the aspirin monotherapy at 90 days. Of note, the patients included in this study had mild strokes (NIHSS <4) or high-risk TIA and were not candidates for IV thrombolysis or endovascular therapy; therefore, the safety of the combination antiplatelets post IV thrombolysis remain not well studied. Finally, the combination of ticagrelor and aspirin has been recently evaluated in the Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA [acetylsalicylic acid] for Prevention of Stroke and Death (THALES) trial.[84] Patients with mild-to-moderate acute non-cardioembolic ischemic stroke (NIHSS score of ≤5) or TIA and who were not undergoing thrombolysis or thrombectomy were randomized to within 24 hours of symptom onset to receive a 30-day regimen of either ticagrelor (180-mg loading dose followed by 90 mg bid) plus aspirin (300–325 mg on the first day followed by 75–100 mg daily) or matching placebo plus aspirin. The risk of the composite of stroke or death within 30 days was lower with the combination compared to aspirin alone. Severe bleeding was more frequent with the combination therapy.

Based on these studies, in patients with mild stroke (NIHSS <5) or TIA and not receiving IV thrombolysis or EVT, a short 21- to 30-day regimen of dual antiplatelet therapy (clopidogrel + aspirin or

ticagrelor + aspirin) initiated within 24 hours of symptom onset may be considered more beneficial than is aspirin monotherapy if the patients have no contraindications to the combination therapy. Other combinations have not been evaluated acutely and not recommended for use.

Given that R.W. received IV thrombolysis, aspirin 325 mg followed by 81 mg monotherapy is the preferred option. Aspirin is typically started after 24 to 48 hours of administration of thrombolysis after a repeat head CT confirmed absence of hemorrhagic transformation.

Ischemic Stroke Education

Case 61-2, Question 6: What information and instruction should be given to R.W. regarding future stroke symptoms?

Early treatment of acute stroke with available or investigational drugs appears to be the most important factor in determining optimal outcome. Nearly every clinical trial demonstrating some benefit of pharmacotherapy for acute stroke has shown the greatest effect for patients who are treated within a few hours of the onset of stroke symptoms. Immediate detection of stroke symptoms and initiation of treatment are imperative. The primary rate-limiting step in diagnosis and provision of medical care is early recognition of stroke symptoms. Every patient who is at increased risk for stroke should be carefully instructed to seek emergent medical attention if they experience any weakness or paralysis, speech impairment, numbness, blurred vision or sudden loss of vision, or altered level of consciousness. These symptoms should be handled with the same urgency as the symptoms of a myocardial infarction. The pharmacist should ensure that R.W. and her caregivers know the symptoms of stroke and understand what to do if they occur.

Ischemic Stroke Complications

Case 61-2, Question 7: What complications associated with stroke might R.W. experience?

Agitation, delirium, stupor, coma, cerebral edema, and increased ICP are other acute symptoms that can be associated with ischemic stroke. These symptoms correlate with the specific blood vessels that are affected, and the development of these complications in R.W. would depend on the progression of her stroke.

Seizures may occur in up to 20% of patients with stroke. Pneumonia, pulmonary edema, cardiac arrest, DVT, and arrhythmias are commonly associated with ischemic stroke and should be managed as they occur. In R.W., these may occur soon after her stroke or be related to a rapidly developing neurologic event such as further infarction, hemorrhage, or severe cerebral edema. Pneumonia or DVTs are related primarily to inactivity, and the risk of these events will increase the longer R.W. remains immobile.[85]

Patients with stroke frequently experience psychological reactions. The most common psychiatric complication is depression, occurring in 30% to 50% of patients.[86]

The severity of depression varies from mild to major depressive episodes. If the depression interferes with recovery and the rehabilitative process, it should be managed with the use of a selective serotonin reuptake inhibitor or other appropriate agents.

Ischemic Stroke Prognosis

Case 61-2, Question 8: After 4 days in the hospital, R.W.'s neurologic status is stabilized. Will further neurologic improvements be realized?

Neurologic deficits in patients with stroke are not considered stable or fixed until at least 8 to 12 months have elapsed. During this time, neurologic function may return but rarely to normal. The prognosis after ischemic stroke depends on a variety of factors including age, hypertension, coma, cardiopulmonary complications,

hypoxia, and neurogenic hyperventilation. However, infarction of the MCA is associated with a poor chance for recovery. Physical and occupational therapy techniques involving restriction of activity in the unaffected limb or limbs have proved to be effective in patients regaining lost function. Therefore, it is possible that R.W. will experience further neurologic improvement.

Secondary Prevention After Ischemic Stroke or Transient Ischemic Attack

Case 61-2, Question 9: What antiplatelet or anticoagulation therapy would be recommended for secondary stroke prevention for R.W.?

ANTIPLATELET THERAPY FOR SECONDARY PREVENTION

Because platelets play a key role in the formation of atheromatous clots, various antiplatelet drugs, such as aspirin, combination aspirin/dipyridamole, ticlopidine, clopidogrel, and cilostazol, have been studied for secondary prevention. Cilostazol is the only agent not approved by the U.S. Food and Drug Administration (FDA) for secondary prevention of ischemic strokes and TIAs arising from non-cardioembolic origin. These agents generally work by either preventing the formation of thromboxane A_2 (TXA_2) or increasing the concentration of prostacyclin. These actions seek to reestablish the proper balance between these two substances, thus preventing the adhesion and aggregation of platelets (**Table 61-5**). An ~22% relative risk reduction of stroke, myocardial infarction, or death is noted with these agents compared to placebo in patients with prior TIA or stroke.[87] Aspirin, clopidogrel, or a combination aspirin/dipyridamole is considered first-line therapy based on the current guidelines for non-cardioembolic ischemic stroke and TIA secondary prevention.[5]

Table 61-5
Drugs for Preventing Transient Ischemic Attacks and Ischemic

Stroke

Drug	Action	Dose	Adverse Effects
Aspirin	Antiplatelet	50–325 mg/day	Diarrhea, gastric ulcer, GI upset
Dipyridamole	Antiplatelet (use in combination with aspirin)	200 mg sustained release twice daily with aspirin 50 mg bid	GI upset
Ticlopidine	Antiplatelet	500 mg/day	Diarrhea, neutropenia, thrombocytopenic purpura, rash
Ticagrelor	Antiplatelet	180 mg once followed by 90 mg bid	Bleeding, bradyarrhythmias, hyperuricemia thrombocytopenia
Clopidogrel	Antiplatelet	75 mg/day	Bleeding, thrombocytopenia, neutropenia
Cilostazol	Antiplatelet	100 mg bid	Headache, peripheral edema. Contraindicated in patients with congestive heart failure
Warfarin	Anticoagulant (only in patients with cardioembolic cause of stroke/TIA)	Titrate to goal INR 2–3 for most patients 2.5–3.5 with mitral mechanical valve	Bleeding, bruising, petechiae
Rivaroxaban	Anticoagulant (only in patients with cardioembolic cause of stroke/TIA)	If CrCl >15 mL/minute, 20 mg once daily with evening meal	Bleeding
Apixaban	Anticoagulant (only in patients with cardioembolic cause of stroke/TIA)	5 mg bid If SCr ≥1.5 mg/dL, 2.5 mg bid (if age >80 years or weight ≤60 kg)	Bleeding
Edoxaban	Anticoagulant (only in patients with cardioembolic cause of stroke/TIA)	60 mg daily If CrCl 15–50 mL/minute 30 mg daily	Do not use if CrCl >95 mL/minute as there is an increased risk of ischemic stroke
Dabigatran	Anticoagulant (only in patients with cardioembolic cause of stroke/TIA)	150 mg bid If CrCL 15–30 mL/minute: 75 mg bid	GI bleed

bid, two times daily; CrCl, creatinine clearance; GI, gastrointestinal; INR, international normalized ratio; SCr, serum creatinine; TIA, transient ischemic attacks.

Aspirin

The effectiveness of aspirin for secondary prevention of non-cardioembolic ischemic stroke and TIA is supported by evidence of high quality. At least 15 randomized trials, with 7 being placebo controlled, have studied aspirin alone or in combination with other antiplatelet drugs in the prevention of vascular events.[88–93]

Patients were enrolled in these studies for as long as 5 years after experiencing a vascular event (ie, TIA, stroke, unstable angina, or myocardial infarction). Follow-up periods lasted from 1 to 6 years. The incidence of ischemic stroke or TIA ranged from 7% to 23%: the patients treated with aspirin experienced an average 22% decrease in relative risk of a stroke compared with those receiving placebo. In 10 trials that considered only patients with TIA or stroke, there was a 24% relative risk reduction in the incidence of nonfatal stroke associated with the use of aspirin. The risk reduction rate is equal for males and females.[89,94]

Dosages of aspirin used in clinical trials have ranged from 30 to 1500 mg/day. In a meta-analysis of placebo-controlled studies comparing 900 to 1500 mg/day of aspirin with similar studies of 300 to 325 mg/day, there was a 23% reduction in the risk of cerebrovascular events for patients receiving 900 to 1500 mg/day and a 24% reduction in risk for patients receiving 300 to 325 mg/day.[87] A prospective comparison of aspirin doses in 3131 patients showed a 14.7% frequency of nonfatal stroke or nonfatal myocardial infarction in patients receiving 30 mg of aspirin a day and a 15.2% frequency in patients receiving 283 mg of aspirin a day, a nonsignificant difference between these two doses.[95] The Swedish Aspirin Low-Dose Trial showed an 18% reduction in stroke in patients taking 75 mg of aspirin daily compared with placebo.[96] Helgason et al. compared the effects of 325, 650, 975, and 1300 mg of aspirin a day in patients with stroke.[97] Platelet aggregation studies were performed to determine the effects of aspirin. Eighty percent of patients had complete suppression of aggregation at a daily dose of 325 mg, an additional 5% responded at 650 mg/day, only 1% more responded at 975 mg/day, and there was no further response at 1300 mg. As aspirin doses increase, so does the risk of gastrointestinal (GI) bleeding.[98]

The recommended dose for aspirin is 50 to 325 mg/day. The goal is to use the lowest effective aspirin dosage, thereby limiting the risk of GI adverse effects. In the United States, a dose of 81 mg aspirin is usually started.

Ticlopidine

Ticlopidine is an antiplatelet agent approved only for the prevention of TIA and stroke for patients with a prior cerebral thrombotic event. By inhibiting adenosine diphosphate (ADP)-induced platelet aggregation, its activity differs from that of aspirin. Although effective in reducing the risk of stroke, its use is limited by serious hematologic and GI adverse effects.[99,100]

Clopidogrel

Clopidogrel is chemically related to ticlopidine and works by inhibiting platelet aggregation induced by ADP. A randomized, double-blind, international trial (Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events [CAPRIE]) compared clopidogrel 75 mg/day with aspirin 325 mg/day.[101] Patients enrolled in the study had a history of atherosclerotic vascular disease manifested by recent ischemic stroke, myocardial infarction, or symptomatic peripheral vascular disease. Using intention-to-treat analysis, a 5.3% risk of an event in patients receiving clopidogrel and a 5.83% risk in patients receiving aspirin were observed. This represents a statistically significant relative risk reduction of 8.7%, favoring clopidogrel. On-treatment analysis showed a relative risk reduction of 9.4%, again in favor of clopidogrel. For patients whose primary condition for entry into CAPRIE was stroke, the relative risk reduction was 7.3%; however, this difference was not statistically significant. Patients receiving clopidogrel more frequently experienced rash and diarrhea compared with those receiving aspirin. Patients receiving aspirin were more frequently affected by upper GI distress, ICH, and GI hemorrhage. Significant reductions in neutrophils occurred in 0.10% of patients on clopidogrel and in 0.17% of patients on aspirin. Some cases of thrombocytopenia purpura are reported in the literature.[102]

Clopidogrel is as effective and safe as aspirin. Clopidogrel is an alternative to aspirin in secondary prevention of stroke.[5] Polymorphisms in the hepatic enzymes involved in the metabolism and activation of clopidogrel (cytochrome P450 [CYP] 1A2, CYP3A4, CYP2C19) or within the platelet $P2Y_{12}$ receptor may affect clopidogrel's antiplatelet therapy. Similarly, drug interactions affecting the CYP2C19 can lead to decreased effectiveness of clopidogrel. Commonly prescribed proton-pump inhibitors, such as omeprazole, have been suggested to decrease the efficacy of clopidogrel. It is suggested to avoid the combination of omeprazole and clopidogrel until more solid evidence is available.[5]

Aspirin/dipyridamole

Dipyridamole inhibits phosphodiesterase and augments prostacyclin-related platelet aggregation inhibition. Four large randomized clinical trials have evaluated the secondary prevention effect of the aspirin and dipyridamole combination among patients with stroke or TIAs. Two European studies have shown benefit with a combination of aspirin and dipyridamole. In the first study, a combination of aspirin 325 mg/day and immediate-release 75 mg dipyridamole three times per day was compared with placebo.[103] Results from this study showed that the combination reduced the combined risk of stroke and death by 33% and the risk of stroke by 38%. The Second European Stroke Prevention Study enrolled patients who had experienced a previous stroke or TIA and found that aspirin combined with dipyridamole was more effective than placebo, dipyridamole alone, and aspirin alone.[104]

A sustained-release formulation of dipyridamole was used for this study. A 37% relative risk reduction was found for the combination treatment, and a 23% relative risk reduction was found for aspirin alone. The dipyridamole dose for this study was 200 mg bid, and the aspirin dose was 25 mg bid. Absolute risk reduction was ~1.5% annually. Headache occurred more frequently in patients receiving dipyridamole alone or in combination with aspirin. Bleeding complications were less frequent in patients receiving dipyridamole compared with aspirin alone. As a result of these findings, a combination product of aspirin and dipyridamole is available. The combination of sustained-release dipyridamole and aspirin is an acceptable alternative for secondary prevention of stroke when initial secondary prevention has failed.

In the 2006 open-label European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), with a mean follow-up of 3.5 years, the combination aspirin/dipyridamole was associated with an absolute risk reduction of 1% per year for the composite primary outcome of vascular mortality, nonfatal stroke, nonfatal myocardial infarction (MI), or major bleeding (13% vs 16%). Bleeding rates were similar between the two groups. Combination aspirin/dipyridamole was discontinued secondary to headaches in 8.8% of patients. Of

note, the aspirin dose ranged from 30 to 325 mg, and 83% of the patients took the extended-release formulation of dipyridamole.[105]

Clopidogrel was compared with the combination aspirin and extended-release dipyridamole in the noninferiority Prevention Regimen for Effectively Avoiding Second Strokes trial.[106] Among the patients with non-cardioembolic ischemic stroke who were followed up for a mean of 2.5 years, there was no difference in stroke rates between the two intervention arms. The risk of GI hemorrhage was higher in the aspirin plus extended dipyridamole group compared to clopidogrel (4.1% vs 3.6%). Clopidogrel was better tolerated with less bleeding and less headaches than was the combination.

Cilostazol

Cilostazol is a vasodilator and antiplatelet agent. It has action on intracellular cyclic adenosine monophosphate (AMP) and is a phosphodiesterase-3 inhibitor that is used mainly for intermittent claudication in patients with peripheral artery disease.[107] In studies conducted in Asia, cilostazol 100 mg bid was found to equally reduce the risk of vascular events compared to aspirin in non-cardioembolic stroke. However, headache, diarrhea, palpitations, dizziness, and tachycardia were more frequent with cilostazol than with aspirin, leading to more discontinuation in therapy (20% vs 12%).[108,109] Given the ventricular tachycardia risk associated with cilostazol, it is contraindicated in patients with heart failure.[107]

Aspirin combined with clopidogrel

A major study has compared clopidogrel 75 mg/day with the combination of clopidogrel 75 mg/day and aspirin 75 mg/day.[110] There was no difference in the risk of recurrent stroke or other cardiovascular outcomes between the groups, but the combination therapy group had a significant increase in life-threatening bleeding. Some individuals may be resistant to aspirin's effects on platelets.[111] Although poorly understood and studied, aspirin resistance may be related to the presence of extra platelet sources of TXA_2 and an interaction with over-the-counter nonsteroidal anti-inflammatory

drugs or high levels of circulating 11-dehydro-thromboxane B_2. Cyclooxygenase-2 expression is induced during human megakaryopoiesis and characterizes newly formed platelets.[112–114] There are no data to suggest that increasing the aspirin dose will overcome possible resistance to the antiplatelet effects of aspirin, but it is clear that an increased dose of aspirin increases the risk of major bleeding.

Warfarin and oral anticoagulants

Large, randomized trials have compared oral anticoagulants with aspirin in the secondary prevention of stroke and TIA. In one study, aspirin 30 mg/day was compared with oral anticoagulants in doses adjusted to maintain an INR between 3.0 and 4.5.[115] This study was terminated early when the mortality rate attributable to major bleeding events in the anticoagulant group was double the rate in the aspirin group. In this study, there was no difference between anticoagulants and aspirin in the frequency of stroke. A second study compared warfarin, dosed to maintain the INR between 1.4 and 2.8, and aspirin 325 mg/day.[116] Results from this study did not demonstrate a significant difference between aspirin and warfarin with regard to the prevention of stroke or major hemorrhagic events. However, minor hemorrhages were significantly more frequent among patients receiving warfarin. A third study was terminated early because of safety concerns in the warfarin arm of the study.[117] The target INR for this study was 2 to 3 in the warfarin arm compared with that in the aspirin arm. The study was stopped owing to significantly higher rates of adverse events in individuals receiving warfarin and no difference in the risk of stroke. Events including major hemorrhage, myocardial infarction, or sudden death, and overall death were increased in those receiving warfarin. Warfarin is not generally recommended for secondary prevention of non-cardioembolic stroke. In secondary prevention of cardioembolic stroke originating from atrial fibrillation, in patients with CHA_2DS_2-VAsc score ≥2 (see **Table 61-6** for the calculation of $CHAD_2S_2$-VASc score), warfarin or the are preferred first-line therapy.[118,119] The

reader is referred to Chapter 15, Cardiac Arrhythmias for further discussion of stroke prevention in atrial fibrillation. The timing of beginning oral anticoagulants is recommended between 4 and 14 days after the onset of neurologic symptoms.[8]

Table 61-6

CHA_2DS_2-VAsc Score: Secondary Stroke Prevention in Atrial Fibrillation

CHA_2DS_2-VAsc score *Add points for the following items. If score is <2, aspirin can be considered. If score is ≥2, anticoagulants (warfarin, apixaban, rivaroxaban, edoxaban) are recommended.*
Congestive heart failure = 1 point
Hypertension = 1 point
Age >75 years = 2 points Age 65–74 years = 1 point
Diabetes mellitus = 1 point
Prior stroke or TIA = 2 points
Vascular disease (eg, peripheral artery disease, myocardial infarction, aortic plaque) = 1 point
Sex category (ie, female) = 1 point

TIA, transient ischemic attack.

Source: Reprinted from January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74(1):104–132. © 2019 by the American Heart Association, Inc, the American College of Cardiology Foundation, and the Heart Rhythm Society. With permission.

Surgical Interventions for Secondary Prevention

Carotid endarterectomy (CEA) and carotid artery angioplasty and stenting (CAS) are available to prevent ischemic stroke or TIAs. These are designed to either remove the source of an embolism or improve circulation to ischemic areas of the brain.

CAROTID ENDARTERECTOMY

CEA is a common surgical procedure for correcting atheromatous lesions responsible for causing a TIA or an ischemic stroke. In this procedure, the carotid artery is surgically exposed, and the atheromatous plaque is excised. CEA combined with pharmacotherapy is considered the first-line option for patients with a high-grade (>70% angiographic stenosis) atherosclerotic carotid stenosis.[5] Other patients do not benefit as much from such procedures, and the benefit does not outweigh the risks. CEA is most effective for patients with an ulcerated lesion or a stenotic clot that occludes >70% of blood flow in the ipsilateral carotid artery and who experience symptoms of a TIA or stroke. Use of CEA in these patients may result in a 60% reduction in stroke risk during the subsequent 2 years.[120] Of six to eight patients treated with CEA, one stroke will be prevented within 2 years.[121] The use of CEA in other patient groups must be balanced with the risk of the procedure and life expectancy.[122] CEA is beneficial in patients with 50% to 69% stenosis of the carotid artery, and the procedure should be done within 2 weeks of a TIA or stroke.[5] Finally, CEA is not indicated in patients who have permanent neurologic deficits or total occlusion of the carotid artery.

Aspirin also has been used for the prevention of restenosis after CEA. During the first year after CEA, 25% of patients will redevelop a stenotic lesion, with more than half of these causing a >50% reduction in carotid blood flow.[95] Initial studies indicated that combination therapy with aspirin 325 mg/day and dipyridamole 75 mg three times a day would decrease the rate of restenosis. However, a subsequent randomized, placebo-controlled study using this regimen in post-CEA patients did not substantiate the earlier findings.[123] A combination of clopidogrel with aspirin has been shown to reduce postoperative ischemic events.[124]

CAROTID ARTERY ANGIOPLASTY AND STENTING

As an alternative to CEA, carotid artery angioplasty and stenting (CAS) can also improve blood flow through the placement of a stent

in a stenosed artery.[125] This is a less invasive procedure associated with less patient discomfort and a shorter recovery time. During this procedure, a catheter with a small, deflated balloon is placed in the stenosed artery, and the atherosclerotic lesion is pressed into the arterial wall when the balloon is inflated. A small, plastic tube stent is placed in the artery to prevent the vessel from collapsing at the site of the lesion. The initial study of this procedure was halted because of poor outcomes.[126] Subsequently, two studies have shown that CAS is not inferior to CEA.[127,128] CAS can be used in patients who are not candidates for CEA. CEA and CAS are typically recommended to be performed between 48 and 72 hours after initial AIS in eligible patients.[8] Noninvasive imaging obtained within 24 hours of AIS can help guide future CEA or CAS. After CAS, dual antiplatelet therapy with clopidogrel and aspirin is needed for 3 months, followed by a single antiplatelet agent thereafter.[129]

SPONTANEOUS INTRACEREBRAL HEMORRHAGE

Clinical Presentation and Treatment

CASE 61-3

QUESTION 1: S.P. is a 58-year-old male who was sitting at home watching television with his wife when he developed confusion, nausea, severe headache, and right arm weakness. His wife immediately calls for an ambulance; by the time the paramedics arrive, S.P. is slumped in his chair and unresponsive. Significant past medical history includes poorly controlled hypertension, atrial fibrillation, and osteoarthritis. He takes lisinopril 10 mg by mouth daily, warfarin 4 mg by mouth daily, and acetaminophen 1000 mg by mouth three times daily for these conditions. Upon presentation to the ED, his BP is 184/114 mm Hg. A CT scan shows an ICH. Key electrolyte concentrations, coagulation studies, and blood counts are within normal limits except for an INR of 4.8 and a blood glucose level of 194 mg/dL. S.P.'s neurologic symptoms and the appearance of blood on his CT scan are consistent with a diagnosis of ICH.

What risk factors for spontaneous ICH does S.P. have?

S.P.'s uncontrolled hypertension and his use of warfarin have increased his risk of ICH.[130] Specifically, use of warfarin increases the risk of ICH by two to five times depending on the degree of anticoagulation.[131,132] Patients such as S.P. who are taking warfarin before ICH and present with an INR >3 are at greater risk for developing larger hematomas, which are associated with worse outcomes, compared to those taking warfarin and presenting with a lower INR.[133,134] Patients taking oral anticoagulants are also at greater risk of death after ICH versus those not taking anticoagulants.[131] Other drugs that may increase the risk of ICH include target-specific agents such as DOACs, heparin, LMWHs, fondaparinux, and other parenteral anticoagulants; aspirin and other antiplatelet agents; selective serotonin reuptake inhibitors; and sympathomimetics, such as amphetamines, phenylpropanolamine, cocaine, and caffeine-containing medications.[135–139] Additional risk factors for nontraumatic ICH include advanced age, history of stroke, diabetes, smoking, excessive alcohol consumption, African American ethnicity, and low cholesterol levels, especially in the absence of HMG-CoA reductase inhibitor use.[140,141] Genetic predisposition does not play a role in most hemorrhagic strokes except for those caused by AVMs.

Case 61-3, Question 2: What are the key principles of therapy in patients presenting with spontaneous ICH?

Initial management of spontaneous ICH involves (a) preventing hematoma expansion and (b) preventing and managing elevated ICP.

To minimize hematoma expansion, anticoagulants should be reversed immediately in patients such as S.P. who present with drug-induced coagulopathies, and elevated BP should be carefully managed. Methods for preventing and managing elevated ICP include avoiding hypotonic fluids as well as medical and surgical

methods. Ancillary therapies including treatment of fever and avoiding hypoglycemia and hyperglycemia are also suggested. Recombinant factor VIIs have been studied in patients with ICH but have not been associated with benefits in patient-centered outcomes.[142]

Case 61-3, Question 3: What pharmacotherapy should be initiated to reverse S.P.'s anticoagulant-induced coagulopathy?

Up to 20% of patients with ICH present with a drug-induced coagulopathy, as S.P. did.[143,144] Because hematoma growth within the first 24 hours of ICH is directly associated with worse outcomes and reversal of warfarin-induced coagulopathies within 4 hours of ICH has been shown to limit hematoma expansion, it is important to reverse coagulopathies in a timely manner.[145,146] All anticoagulant and antiplatelet medications should be immediately discontinued, and agents should be administered to remove the anticoagulant medication from the body and reverse its effect.[147] Although S.P. was using warfarin for the prevention of ischemic stroke in the setting of atrial fibrillation, because of his acute ICH, the benefit of reversing the warfarin to improve neurologic outcome greatly outweighs the short-term risk of ischemic stroke resulting from anticoagulant reversal. If a patient has taken an oral anticoagulant within the past 2 hours, activated charcoal may be considered to prevent absorption; however, it is important to ensure the patient can tolerate enteral administration. Historically, fresh frozen plasma (FFP) has been used to reverse warfarin-induced coagulopathies in patients such as S.P.; however, because they have fewer complications and may be administered more rapidly, prothrombin complex concentrates (PCCs) have become the preferred agents to rapidly reverse warfarin-induced anticoagulation.[147] FFP contains all the clotting factors depleted by warfarin but can take several hours to thaw and administer and may be associated with pulmonary complications and edema because of the volume required. In contrast, PCCs may reverse the INR within minutes because they can be administered

more rapidly. Use of PCCs has been shown to more effectively limit hematoma expansion compared to FFP.[148,149] Three-factor PCCs contain factors II, IX, and X, whereas four-factor PCCs also include factor VII. Four-factor PCCs are generally preferred in the setting of ICH and coagulopathy due to warfarin or DOACs because they have all of the vitamin K–dependent clotting factors and other clotting factors overall. Because the effect of PCC and FFP is short-lived, patients with warfarin-induced coagulopathy should concomitantly receive 10 mg of IV vitamin K (phytonadione) by slow infusion.[150] INR should be checked after administration of PCC and serially thereafter to ensure it is not >1.4. It is important to note that because most PCC formulations are compounded with heparin, they may be contraindicated in patients with a recent history of heparin-induced thrombocytopenia.

DOACs are used more often nowadays to prevent stroke in patients with nonvalvular atrial fibrillation.[151–153] Similar to warfarin-induced coagulopathy, rapid reversal is indicated in patients who present with ICH after using one of these agents. If the patient was taking dabigatran, the anti-dabigatran monoclonal antibody fragment, idarucizumab, should be used for reversal. Dabigatran may also be removed through hemodialysis, although establishing vascular access may be challenging or impractical in patients with active bleeding. Rivaroxaban, apixaban, and edoxaban may be reversed with andexanet alfa or PCCs. Andexanet alfa is an inactive version of factor Xa that acts as a “decoy” and binds to the DOAC, thus preventing it from binding to factor Xa and exerting an anticoagulant effect. It was approved based on a single-arm study that demonstrated good hemostasis and reduction in anti-factor Xa activity after patients who had taken a direct-acting oral anticoagulant were given andexanet alfa; however, it was not compared to a PCC.[154] PCCs have been studied for reversal of direct-acting oral anticoagulants in a number of observational studies.[155,156] Because andexanet alfa and PCCs have not been rigorously compared to one another and because patient-centered outcomes have not been evaluated in large studies, either may be considered for reversal of coagulopathies in patients presenting with

ICH after taking DOACs.[157,158] It is important to note that both andexanet alfa and PCCs may predispose to thrombotic events, so clinicians should make a careful patient-specific decision regarding their use.

As with warfarin-induced coagulopathies, reversal agents should be administered promptly when indicated, and activated charcoal should be considered.

Other drug-induced ICHs may occur in patients receiving heparin, LMWHs, the parenteral factor Xa inhibitor fondaparinux, and antiplatelet agents such as aspirin and clopidogrel. Protamine sulfate may be used for the reversal of heparin and LMWH, whereas fondaparinux activity may be antagonized with PCCs. Limited evidence suggests that desmopressin may limit hematoma expansion in patients taking antiplatelet agents who develop ICH, but platelet infusions have not been shown to improve patient-centered outcomes.[50,159,160]

To reverse his warfarin-induced coagulopathy, current guidelines suggest that S.P. should receive a weight-based dose of a PCC product and 10 mg IV vitamin K by slow IV infusion.[50] The role of fixed doses of PCCs for vitamin K–antagonist reversal is being investigated. Studies to date indicate that fixed dosing shortens time to administration but may be associated with the need to repeat PCC administration and INR reversal failure in patients presenting with especially elevated INRs.[161]

Case 61-3, Question 4: How should S.P.'s acute hypertension be managed?

Excessive hypertension may expose patients with ICH to elevated risk of hematoma expansion, neurologic deterioration, and worse outcomes.[162,163] Lower BPs have been suggested to potentially worsen prognosis.[164] Some studies have shown that rapid BP reduction to an SBP <140 mm Hg is safe in patients with ICH presenting with hypertension.[165–168] However, more recent large trials that evaluated SBP lowering to <140 mm Hg versus maintaining an SBP between 140 and 179 mm Hg after ICH failed to show a

difference in death and severe disability, and a study in patients presenting with ICH and SBP >220 mm Hg demonstrated worse outcomes with BP management with a goal of 100 to 139 mm Hg versus 140 to 179 mm Hg.[169]

Based on these studies, SBP should be lowered to ~140 mm Hg in patients presenting with an SBP of 150 to 220 mm Hg who do not have contraindications to antihypertensive therapy. In patients presenting with an SBP >220 mm Hg, it is recommended to initiate aggressive antihypertensive therapy with an IV infusion and to carefully monitor the patient.[147] These patients may require a somewhat higher SBP goal range because their cerebral vasculature may have adapted somewhat to chronic high BPs.

Nicardipine and labetalol are the most commonly used antihypertensive agents in patients with ICH, but hydralazine, nitroprusside, or nitroglycerin may be considered depending on the clinical situation. If labetalol is used to control acute BP, it should be administered as IV boluses, potentially in combination with an IV infusion. Nicardipine is only administered as an IV infusion.

S.P.'s BP is elevated, so IV antihypertensive therapy is indicated. It would be appropriate to initiate an IV nicardipine infusion at 5 mg/hour and titrate every 5 minutes to achieve an SBP of ~140 mm Hg in S.P.

Case 61-3, Question 5: Hours after admission, S.P.'s mental status worsens, likely because of severely elevated ICPs. What therapy should S.P. receive for his elevated ICP?

Elevated ICP refers to excessive pressure inside the intracranial vault that may occur in patients with severe hemorrhagic and ischemic strokes as well as in those suffering from traumatic brain injury, brain tumors, hydrocephalus, and hepatic encephalopathy. It can lead to brain hypoxemia and cause herniation. S.P.'s worsened mental status may be consistent with elevated ICP. Other symptoms of elevated ICP include headache, vomiting, cranial nerve palsies,

and the combination of bradycardia, respiratory depression, and hypertension.

In patients with neurologic emergencies, such as S.P., hypotonic fluids such as dextrose 5% in water should be avoided in favor of isotonic fluids such as 0.9% sodium chloride (normal saline) and lactated Ringer because hypotonic fluids can exacerbate cerebral edema and worsen ICP.[148] When considering the fluids patients are receiving, it is important to evaluate both maintenance fluids and the fluids in which IV medications are diluted. In patients with elevated ICPs, IV medications should be diluted in 0.9% sodium chloride rather than dextrose 5% in water or other hypotonic fluids whenever possible.

Treatment of elevated ICP involves patient care measures, pharmacotherapy, and surgical interventions. First, the head of the bed should be elevated to at least 30° once it is clear that S.P. is not hypovolemic in order to minimize blood and fluid accumulation in the brain. Hyperventilation (increasing the patient's respiratory rate and/or the volume of air he breathes with each respiration) with a $Paco_2$ goal of <30 mm Hg may be considered for a very short time in S.P. until other interventions can be implemented. Because the low $Paco_2$ induced by hyperventilation leads to a lower CBF, this will lower ICP, but hyperventilation should not be continued long-term because reduced CBF may lead to brain hypoxia.

S.P. should receive analgesic medications, such as fentanyl. Sedatives, such as propofol, should also be administered.[148] Hyperosmolar agents, including IV hypertonic sodium chloride, hypertonic sodium acetate, or mannitol, dosed at 0.25 to 1 g/kg every 4 to 6 hours, may be considered to establish an osmotic gradient that can facilitate the movement of fluid out of the brain, thus reducing ICP.[147,170,171] The patient's osmolar gap, electrolytes, acid–base status, and renal function should be monitored closely when using these agents. Clinicians may place an ICP monitor or utilize neurologic exams to guide treatment with hyperosmolar agents. If an ICP monitor is used, hyperosmolar therapy would be indicated to maintain an ICP of <20 mm Hg, whereas if an ICP

monitor is not utilized, a worsening in neurologic exam consistent with elevated ICP would warrant therapy. If S.P. continues to exhibit elevated ICPs after hyperosmolar therapy and adequate analgesia and sedation, a continuous infusion of a neuromuscular blocking agent may be considered. One last-line measure that may be considered is the use of a barbiturate coma; however, side effects, such as hypotension, cardiac depression, and ileus, as well as limited utility complicate these strategies. Lowering a patient's body temperature (therapeutic hypothermia) to reduce ICP has been studied, although efficacy remains dubious, and so it is not considered the standard of care but may be used as a salvage therapy in carefully selected patients.[172]

In patients who develop hydrocephalus because of an ICH or another condition, a ventriculostomy may be employed. A ventriculostomy is a surgically placed drain that resides in the ventricle and is used to drain CSF. Finally, open craniotomy, or removal of a portion of the skull, in the area of edema, may be considered in highly selected situations; however, the efficacy of this approach is questionable in many patients.

Case 61-3, Question 6: What other ancillary therapies may be appropriate for S.P.?

S.P. may benefit from (a) maintenance of normothermia with antipyretics and nonpharmacologic cooling strategy if he develops a fever and (b) avoiding hypoglycemia and excessive hyperglycemia.

Although the clinical benefit of antipyretic therapy has not been clearly established in ICH, fever is associated with a worse prognosis.[173] It is recommended that S.P.'s body temperature should be monitored and antipyretics and nonpharmacologic cooling strategies may be employed to achieve normothermia.[147]

Both hypoglycemia and hyperglycemia should be avoided in hemorrhagic stroke. Hypoglycemia can directly lead to neurologic injury, whereas hyperglycemia is associated with worsened neurologic outcome after a stroke. Considering that his blood

glucose is markedly elevated, S.P. should be initiated on an insulin regimen in accordance with institutional policies.

Seizures can complicate ~16% of all strokes and may be difficult to observe because they are often nonconvulsive.[147,174] However, because studies of prophylactic antiepileptic therapy have failed to demonstrate consistent benefit and have sometimes indicated harm,[175] current guidelines do not recommend routine seizure prophylaxis.[147] Antiepileptic therapy should be initiated promptly if a patient develops seizures during or after the development of an ICH.

Case 61-3, Question 7: What secondary prevention strategies should be recommended for S.P. after he recovers from his ICH?

For S.P. and any patient who has suffered an ICH, key modifiable risk factors that should be addressed upon stabilization include maintaining BP at <130/80 mm Hg, smoking cessation, treating sleep apnea, avoiding excessive alcohol use, and abstaining from cocaine and other illicit drugs.[147,174] The optimal duration of oral anticoagulant cessation in patients with spontaneous ICH is unclear; however, these agents should be held for at least 4 weeks after the development of ICH.[147]

REHABILITATION

CASE 61-4

Question 1: Patient J.A. has had a stroke and has received appropriate acute care. He is ready to be discharged from the hospital but still has trouble walking, talking, and performing activities of daily living.

For patients who require rehabilitative care after hospital treatment of an ischemic or hemorrhagic stroke, what interventions will aid their recovery?

Patients who have suffered ischemic and hemorrhagic strokes often require long-term rehabilitation after their acute treatment.

Rehabilitation is directed at managing daily functions, enhancing existing neurologic function, and attempting to regain lost function. Considerations for daily functions include activities of daily living and bowel and bladder management through balanced pharmacologic interventions. Efforts should be made to allow patients to function independently with activities of daily living and manage the psychological effects of stroke. Enhancement of current neurologic function and minimizing depression include elimination of drugs that may compromise patients' memory and mental function. These include benzodiazepines, major tranquilizers, and sedating antiepileptic drugs.

Localized spasticity is a common complication after strokes. Spasticity affecting a single limb frequently responds to regional motor nerve blocks with botulinum toxin. Aggressive physical therapy is also essential to the management of spasticity. Systemic antispasticity agents such as diazepam, baclofen, or dantrolene sodium are not used routinely because of the risk of toxicity. They are used only when spasticity involves multiple parts of the body or is unresponsive to other therapies.

Other less common impediments to patients' recovery after stroke include decubitus ulcers, hypercalcemia, and heterotopic ossification (eg, the laying down and calcification of a bone matrix in muscle surrounding major joints). Prevention through meticulous skincare is the key to the management of pressure ulcers. Mobilizing patients as soon as possible after stroke can prevent hypercalcemia and heterotopic ossification.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Eikelboom J, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 96th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(*2, suppl*):e89s–e119s. (107)

Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329. (39)

Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(*7*):2032–2060. (147)

Mendelson SJ, Prabhakaran S. Diagnosis and management of transient ischemic attack and acute ischemic stroke: a review. *JAMA.* 2021;325(*11*):1088–1098. doi:10.1001/jama.2020.26867 (120)

Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2019;50(*12*):e344–e418. (8)

Key Websites

American Heart Association

Stroke symptoms. https://www.stroke.org/en/about-stroke/stroke-symptoms

Get with the guidelines® (GTWG) stroke. https://www.heart.org/en/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-stroke

American Stroke Association

http://www.stroke.org

National Institutes of Health

NIH Stroke Scale (NIHSS). https://www.stroke.nih.gov/resources/scale.htm

National Institute of Neurological Disorders and Stroke. http://www.ninds.nih.gov/disorders/stroke/stroke.htm

COMPLETE REFERENCES CHAPTER 61 Acute Ischemic and Hemorrhagic Stroke

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistic—2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139–e596.
2. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and The Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40(6):2276–2293.
3. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35–41.
4. Howard G, Howard VJ, Katholi C, Oli MK, Huston S. Decline in US stroke mortality: an analysis of temporal patterns by sex, race, and geographic region. *Stroke*. 2001;32(10):2213–2220.
5. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160–2236.
6. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754–3832.
7. Astrup J, Symon L, Branston NM, Lassen NA. Cortical evoked potential and extracellular K+ and H+ at critical levels of brain ischemia. *Stroke*. 1977;8(1):51–57.
8. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418.
9. Burns JD, Manno EM. Primary intracerebral hemorrhage: update on epidemiology, pathophysiology, and treatment strategies. *Compr Ther*. 2008;34(3–4):183–195.
10. Ko SB, Choi HA, Lee K. Clinical syndromes and management of intracerebral hemorrhage. *Curr Atheroscler Rep*. 2012;14(4):307–313.
11. Aksoy D, Bammer R, Mlynash M, et al. Magnetic resonance imaging profile of blood-brain barrier injury in patients with acute intracerebral hemorrhage. *J Am Heart Assoc*. 2013;2(3):e000161.
12. Venkatasubramanian C, Mlynash M, Finley-Caulfield A, et al. Natural history of perihematomal edema after intracerebral hemorrhage measured by serial

magnetic resonance imaging. *Stroke*. 2011;42(1):73–80.
13. Staykov D, Wagner I, Volbers B, et al. Natural course of perihemorrhagic edema after intracerebral hemorrhage. *Stroke*. 2011;42(9):2625–2629.
14. Li N, Liu YF, Ma L, et al. Association of molecular markers with perihematomal edema and clinical outcome in intracerebral hemorrhage. *Stroke*. 2013;44(3):658–663.
15. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. *Lancet Neurol*. 2012;11(1):101–118.
16. Barras CD, Tress BM, Christensen S, et al. Density and shape as CT predictors of intracerebral hemorrhage growth. *Stroke*. 2009;40(4):1325–1331.
17. Biesbroek JM, van der Sprenkel JW, Algra A, Rinkel GJ. Prognosis of acute subdural haematoma from intracranial aneurysm rupture. *J Neurol Neurosurg Psychiatry*. 2013;84(3):254–257.
18. Schuss P, Konczalla J, Platz J, Vatter H, Seifert V, Güresir E. Aneurysm-related subarachnoid hemorrhage and acute subdural hematoma: single-center series and systematic review. *J Neurosurg*. 2013;118(5):984–990.
19. Aroor S, Singh R, Goldstein LB. BE-FAST (Balance, Eyes, Face, Arm, Speech, Time). *Stroke*. 2017;48(2):479–481.
20. Herpich F, Rincon F. Management of acute ischemic stroke. *Critical Care Medicine*. 2020;48(11):1654–1663.
21. Mendelson SJ, Prabhakaran S. Diagnosis and management of transient ischemic attack and acute ischemic stroke: a review. *JAMA*. 2021;325(11):1088–1098.
22. Schlegel D, Kolb SJ, Luciano JM, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. *Stroke*. 2003;34(1):134–137.
23. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870–947.
24. Kunz A, Ebinger M, Geisler F, et al. Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. *Lancet Neurol*. 2016;15(10):1035–1043.
25. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604–607.
26. American Heart Association. Comprehensive stroke fact sheet: get with the guidelines stroke. Published 2018. Accessed September 2020. https://www.heart.org/-/media/files/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-stroke/stroke-fact-sheet_-comprehensive_-final_ucm_501843.pdf?la=en>

27. Solis OJ, Roberson GR, Taveras JM, Mohr J, Pessin M. Cerebral angiography in acute cerebral infarction. *Rev Interam Radiol*. 1977;2(1):19–25.
28. Symon L, Branston NM, Strong AJ, Hope TD. The concepts of thresholds of ischaemia in relation to brain structure and function. *J Clin Pathol Suppl (R Coll Pathol)*. 1977;11:149–154.
29. Sharbrough FW, Messick JM Jr, Sundt TM Jr. Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy. *Stroke*. 1973;4(4):674–683.
30. Sundt TM Jr, Grant WC, Garcia JH. Restoration of middle cerebral artery flow in experimental infarction. *J Neurosurg*. 1969;31(3):311–321.
31. Jacoby JS, Draper HM, Dumkow LE, Farooq MU, DeYoung GR, Brandt KL. Emergency medicine pharmacist impact on door-to-needle time in patients with acute ischemic stroke. *Neurohospitalist*. 2018;8(2):60–65.
32. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2016;47(2):581–641.
33. Hommel M, Cornu C, Boutitie F, Boissel JP. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med*. 1996;335(3):145–150.
34. Donnan GA, Davis SM, Chambers BR, et al. Streptokinase for acute ischemic stroke with relationship to time of administration: Australian Streptokinase (ASK) Trial Study Group. *JAMA*. 1996;276(12):961–966.
35. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581–1587.
36. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274(13):1017–1025.
37. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Multicentre Acute Stroke Trial—Italy (MAST-I) Group. *Lancet*. 1995;346(8989):1509–1514.
38. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352(9136):1245–1251.
39. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363(9411):768–774.
40. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317–1329.

41. Rønning OM, Logallo N, Thommessen B, et al. Tenecteplase versus alteplase between 3 and 4.5 hours in low national institutes of health stroke scale. *Stroke*. 2019;50(2):498–500.
42. Coutts SB, Dubuc V, Mandzia J, et al. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. *Stroke*. 2015;46(3):769–774.
43. Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol*. 2015;14(4):368–376.
44. Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol*. 2017;16(10):781–788.
45. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med*. 2012;366(12):1099–1107.
46. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med*. 2018;378(17):1573–1582.
47. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379(7):611–622.
48. Thomalla G, Boutitie F, Ma H, et al. Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. *Lancet*. 2020;396(10262):1574–1584.
49. Rathbun KM. Angioedema after thrombolysis with tissue plasminogen activator: an airway emergency. *Oxf Med Case Reports*. 2019;2019(1):omy112.
50. Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016;24(1):6–46.
51. Yaghi S, Willey JZ, Cucchiara B, et al. Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48(12):e343–e361.
52. Kammersgaard LP, Jørgensen HS, Rungby JA, et al. Admission body temperature predicts long-term mortality after acute stroke: The Copenhagen Stroke Study. *Stroke*. 2002;33(7):1759–1762.
53. Zaremba J. Hyperthermia in ischemic stroke. *Med Sci Monit*. 2004;10(6):RA148–RA153.

54. Dippel DW, van Breda EJ, van der Worp HB, et al. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke PISA, a phase II double-blind, randomized, placebo-controlled trial [ISRCTN98608690]. *BMC Cardiovasc Disord*. 2003;3:2.
55. Kagansky N, Levy S, Knobler H. The role of hyperglycemia in acute stroke. *Arch Neurol*. 2001;58(8):1209–1212.
56. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285–2295.
57. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11–20.
58. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019–1030.
59. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009–1018.
60. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372(24):2296–2306.
61. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke*. 2008;39(4):1205–1212.
62. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2013;368(10):904–913.
63. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368(10):914–923.
64. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013;368(10):893–903.
65. Pierot L, Derdeyn C. Interventionalist perspective on the new endovascular trials. *Stroke*. 2015;46(6):1440–1446.
66. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708–718.
67. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2017;378(1):11–21.
68. Brott T, Lu M, Kothari R, et al. Hypertension and its treatment in the NINDS rt-PA Stroke Trial. *Stroke*. 1998;29(8):1504–1509.
69. Anadani M, Orabi MY, Alawieh A, et al. Blood pressure and outcome after mechanical thrombectomy with successful revascularization. *Stroke*.

2019;50(9):2448–2454.
70. Goyal N, Tsivgoulis G, Pandhi A, et al. Blood pressure levels post mechanical thrombectomy and outcomes in large vessel occlusion strokes. *Neurology*. 2017;89(6):540–547.
71. Duke RJ, Bloch RF, Turpie AG, Trebilcock R, Bayer N. Intravenous heparin for the prevention of stroke progression in acute partial stable stroke. *Ann Intern Med*. 1986;105(6):825–828.
72. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet*. 1997;349(9065):1569–1581.
73. Rödén-Jüllig A, Britton M. Effectiveness of heparin treatment for progressing ischaemic stroke: before and after study. *J Intern Med*. 2000;248(4):287–291.
74. Kay R, Wong KS, Yu YL, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. *N Engl J Med*. 1995;333(24):1588–1593.
75. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *JAMA*. 1998;279(16):1265–1272.
76. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet*. 2000;355(9211):1205–1210.
77. Diener HC, Ringelstein EB, von Kummer R, et al. Treatment of acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the TOPAS trial. Therapy of Patients With Acute Stroke (TOPAS) Investigators. *Stroke*. 2001;32(1):22–29.
78. Coull BM, Williams LS, Goldstein LB, et al. Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association (a division of the American Heart Association). *Neurology*. 2002;59(1):13–22.
79. Wang Y, Johnston SC, Bath PM, et al. Acute dual antiplatelet therapy for minor ischaemic stroke or transient ischaemic attack. *BMJ*. 2019;364:1895.
80. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. *Lancet*. 1997;349(9066):1641–1649.
81. Abciximab in Ischemic Stroke Investigators. Abciximab in acute ischemic stroke. A randomized, double-blind, placebo-controlled, dose-escalation study. *Stroke*. 2000;31(3):601–609.
82. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369(1):11–19.

83. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379(3):215–225.
84. Johnston SC, Amarenco P, Denison H, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med*. 2020;383(3):207–217.
85. Langhorne P, Stott DJ, Robertson L, et al. Medical complications after stroke. *Stroke*. 2000;31(6):1223–1229.
86. Robinson RG. Treatment issues in poststroke depression. *Depress Anxiety*. 1998;8(suppl 1):85–90.
87. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71–86.
88. Iso H, Hennekens CH, Stampfer MJ, et al. Prospective study of aspirin use and risk of stroke in women. *Stroke*. 1999;30(9):1764–1771.
89. Bousser MG, Eschwege E, Haguenau M, et al. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. *Stroke*. 1983;14(1):5–14.
90. Sorensen PS, Pedersen H, Marquardsen J, et al. Acetylsalicylic acid in the prevention of stroke in patients with reversible cerebral ischemic attacks. A Danish cooperative study. *Stroke*. 1983;14(1):15–22.
91. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. Antiplatelet Trialists' Collaboration. *Br Med J (Clin Res Ed)*. 1988;296(6618):320–331.
92. High-dose acetylsalicylic acid after cerebral infarction. A Swedish Cooperative Study. *Stroke*. 1987;18(2):325–334.
93. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54(12):1044–1054.
94. Bernstein EF, Humber PB, Collins GM, Dilley RB, Devin JB, Stuart SH. Life expectancy and late stroke following carotid endarterectomy. *Ann Surg*. 1983;198(1):80–86.
95. van Gijn J, Algra A, Kappelle J, Koudstaal PJ, van Latum A. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med*. 1991;325(18):1261–1266.
96. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. The SALT Collaborative Group. *Lancet*. 1991;338(8779):1345–1349.
97. Helgason CM, Tortorice KL, Winkler SR, et al. Aspirin response and failure in cerebral infarction. *Stroke*. 1993;24(3):345–350.
98. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351(9118):1755–1762.

99. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet*. 1989;1(8649):1215–1220.
100. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med*. 1989;321(8):501–507.
101. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348(9038):1329–1339.
102. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med*. 2000;342(24):1773–1777.
103. The European Stroke Prevention Study (ESPS). Principal end-points. The ESPS Group. *Lancet*. 1987;2(8572):1351–1354.
104. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143(1–2):1–13.
105. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367(9523):1665–1673.
106. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359(12):1238–1251.
107. Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e89S–e119S.
108. Huang Y, Cheng Y, Wu J, et al. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. *Lancet Neurol*. 2008;7(6):494–499.
109. Shinohara Y, Katayama Y, Uchiyama S, et al. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol*. 2010;9(10):959–968.
110. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9431):331–337.
111. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest*. 2004;126(3 suppl):234s–264s.
112. Rocca B, Secchiero P, Ciabattoni G, et al. Cyclooxygenase-2 expression is induced during human megakaryopoiesis and characterizes newly formed

platelets. *Proc Natl Acad Sci U S A*. 2002;99(11):7634–7639.
113. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345(25):1809–1817.
114. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation*. 2002;105(14):1650–1655.
115. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. *Ann Neurol*. 1997;42(6):857–865.
116. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001;345(20):1444–1451.
117. Chimowitz MI, Kokkinos J, Strong J, et al. The warfarin-aspirin symptomatic intracranial disease study. *Neurology*. 1995;45(8):1488–1493.
118. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74(1):104–132.
119. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154(5):1121–1201.
120. Barnett HJM, Taylor DW, Haynes RB, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325(7):445–453.
121. Barnett HJM, Eliasziw M, Meldrum HE. Evidence based cardiology: prevention of ischaemic stroke. *BMJ*. 1999;318(7197):1539–1543.
122. Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation*. 1998;97(5):501–509.
123. Harker LA, Bernstein EF, Dilley RB, et al. Failure of aspirin plus dipyridamole to prevent restenosis after carotid endarterectomy. *Ann Intern Med*. 1992;116(9):731–736.
124. Bhatt DL, Kapadia SR, Bajzer CT, et al. Dual antiplatelet therapy with clopidogrel and aspirin after carotid artery stenting. *J Invasive Cardiol*. 2001;13(12):767–771.
125. White CJ. Carotid artery stenting. *J Am Coll Cardiol*. 2014;64(7):722–731.
126. Alberts MJ. Results of a multicenter prospective randomized trial of carotid artery stenting vs. carotid endarterectomy. *Stroke*. 2001;32(suppl_1):325–325.

127. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357(9270):1729–1737.
128. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351(15):1493–1501.
129. Huibers A, Halliday A, Bulbulia R, Coppi G, de Borst GJ. Antiplatelet therapy in carotid artery stenting and carotid endarterectomy in the asymptomatic carotid surgery trial-2. *Eur J Vasc Endovasc Surg*. 2016;51(3):336–342.
130. Toyoda K, Yasaka M, Uchiyama S, et al. Blood pressure levels and bleeding events during antithrombotic therapy: the Bleeding with Antithrombotic Therapy (BAT) Study. *Stroke*. 2010;41(7):1440–1444.
131. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. *Arch Intern Med*. 2004;164(8):880–884.
132. García-Rodríguez LA, Gaist D, Morton J, Cookson C, González-Pérez A. Antithrombotic drugs and risk of hemorrhagic stroke in the general population. *Neurology*. 2013;81(6):566–574.
133. Flaherty ML, Tao H, Haverbusch M, et al. Warfarin use leads to larger intracerebral hematomas. *Neurology*. 2008;71(14):1084–1089.
134. LoPresti MA, Bruce SS, Camacho E, et al. Hematoma volume as the major determinant of outcomes after intracerebral hemorrhage. *J Neurol Sci*. 2014;345(1–2):3–7.
135. Hackam DG, Mrkobrada M. Selective serotonin reuptake inhibitors and brain hemorrhage: a meta-analysis. *Neurology*. 2012;79(18):1862–1865.
136. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. *JAMA*. 1998;280(22):1930–1935.
137. Martin-Schild S, Albright KC, Hallevi H, et al. Intracerebral hemorrhage in cocaine users. *Stroke*. 2010;41(4):680–684.
138. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med*. 2000;343(25):1826–1832.
139. Lee SM, Choi NK, Lee BC, Cho KH, Yoon BW, Park BJ. Caffeine-containing medicines increase the risk of hemorrhagic stroke. *Stroke*. 2013;44(8):2139–2143.
140. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke*. 2003;34(8):2060–2065.
141. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke*. 2007;38(10):2718–2725.
142. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*.

2008;358(20):2127–2137.
143. Huhtakangas J, Tetri S, Juvela S, Saloheimo P, Bode MK, Hillbom M. Effect of increased warfarin use on warfarin-related cerebral hemorrhage: a longitudinal population-based study. *Stroke*. 2011;42(9):2431–2435.
144. Flaherty ML, Kissela B, Woo D, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology*. 2007;68(2):116–121.
145. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA*. 2015;313(8):824–836.
146. Davis SM, Broderick J, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66(8):1175–1181.
147. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(7):2032–2060.
148. Huttner HB, Schellinger PD, Hartmann M, et al. Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. *Stroke*. 2006;37(6):1465–1470.
149. Hanger HC, Geddes JA, Wilkinson TJ, Lee M, Baker AE. Warfarin-related intracerebral haemorrhage: better outcomes when reversal includes prothrombin complex concentrates. *Intern Med J*. 2013;43(3):308–316.
150. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e152S–e184S.
151. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–1151.
152. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–891.
153. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992.
154. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor xa inhibitors. *N Engl J Med*. 2019;380(14):1326–1335.
155. Majeed A, Ågren A, Holmström M, et al. Management of rivaroxaban-or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 2017;130(15):1706–1712.

156. Ross B, Miller MA, Ditch K, Tran M. Clinical experience of life-threatening dabigatran-related bleeding at a large, tertiary care, academic medical center: a case series. *J Med Toxicol*. 2014;10(2):223–228.
157. Barra ME, Das AS, Hayes BD, et al. Evaluation of andexanet alfa and four-factor prothrombin complex concentrate (4F-PCC) for reversal of rivaroxaban- and apixaban-associated intracranial hemorrhages. *J Thromb Haemost*. 2020;18(7):1637–1647.
158. Frontera JA, Bhatt P, Lalchan R, et al. Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage. *J Thromb Thrombolysis*. 2020;49(1):121–131.
159. Feldman EA, Meola G, Zyck S, et al. Retrospective assessment of desmopressin effectiveness and safety in patients with antiplatelet-associated intracranial hemorrhage. *Crit Care Med*. 2019;47(12):1759–1765.
160. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet*. 2016;387(10038):2605–2613.
161. Schwebach AA, Waybright RA, Johnson TJ. Fixed-dose four-factor prothrombin complex concentrate for vitamin K antagonist reversal: does one dose fit all? *Pharmacotherapy*. 2019;39(5):599–608.
162. Sakamoto Y, Koga M, Yamagami H, et al. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. *Stroke*. 2013;44(7):1846–1851.
163. Rodriguez-Luna D, Piñeiro S, Rubiera M, et al. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. *Eur J Neurol*. 2013;20(9):1277–1283.
164. Garg RK, Liebling SM, Maas MB, Nemeth AJ, Russell EJ, Naidech AM. Blood pressure reduction, decreased diffusion on MRI, and outcomes after intracerebral hemorrhage. *Stroke*. 2012;43(1):67–71.
165. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368(25):2355–2365.
166. Anderson CS, Huang Y, Arima H, et al. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke*. 2010;41(2):307–312.
167. Qureshi AI. Significance of lesions with decreased diffusion on MRI in patients with intracerebral hemorrhage. *Stroke*. 2012;43(1):6–7.
168. Arima H, Anderson CS, Wang JG, et al. Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute

intracerebral hemorrhage. *Hypertension*. 2010;56(5):852–858.
169. Qureshi AI, Huang W, Lobanova I, et al. Outcomes of intensive systolic blood pressure reduction in patients with intracerebral hemorrhage and excessively high initial systolic blood pressure: post hoc analysis of a randomized clinical trial. *JAMA Neurol*. 2020;77(11):1355–1365.
170. Helbok R, Kurtz P, Schmidt JM, et al. Effect of mannitol on brain metabolism and tissue oxygenation in severe haemorrhagic stroke. *J Neurol Neurosurg Psychiatry*. 2011;82(4):378–383.
171. Cook AM, Morgan Jones G, Hawryluk GWJ, et al. Guidelines for the acute treatment of cerebral edema in neurocritical care patients. *Neurocrit Care*. 2020;32(3):647–666.
172. Andrews PJD, Sinclair HL, Rodriguez A, et al. Hypothermia for intracranial hypertension after traumatic brain injury. *N Engl J Med*. 2015;373(25):2403–2412.
173. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. *Stroke*. 2008;39(11):3029–3035.
174. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association stroke council, high blood pressure research council, and the quality of care and outcomes in research interdisciplinary working group. *Stroke*. 2007;38(6):2001–2023.
175. Messé SR, Sansing LH, Cucchiara BL, Herman ST, Lyden PD, Kasner SE. Prophylactic antiepileptic drug use is associated with poor outcome following ICH. *Neurocrit Care*. 2009;11(1):38–44.

SECTION 14

Infectious Diseases

Section Editors: Dorothea Rudorf, G. Christopher Wood, and Caroline S. Zeind

62

Principles of Infectious Diseases

Joshua A. Garcia and B. Joseph Guglielmo

CORE PRINCIPLES		CHAPTER CASES
1	Although acute infection generally is associated with an increased white blood cell count, fever, and localizing signs, these symptoms may be absent in less severe disease. More severe infection, including sepsis, may be associated with hypotension, disseminated intravascular coagulation, and end-organ dysfunction.	**Case 62-1 (Questions 1, 2), Figure 62-1**
2	Other disease states, particularly autoimmune disease and malignancy, may mimic infectious diseases. Although it should be considered a diagnosis of exclusion, drug-induced fever should be ruled out, particularly in patients without other classic signs and symptoms of infection.	**Case 62-1 (Question 3)**

3	Site-specific signs and symptoms and host factors generally predict the most likely pathogens, and empirical antimicrobial therapy should be directed against these organisms. Rapid detection tests improve the efficiency of identifying a pathogen; however, they are more costly than traditional methodology.	**Case 62-1 (Questions 4, 5), Tables 62-1, 62-2**
4	Isolation of an organism may reflect infection; however, colonization and contamination must be ruled out to avoid unnecessary antimicrobial exposure. Once a pathogen is identified, susceptibility tests, particularly disk diffusion or broth dilution, can demonstrate the most active antimicrobial agents.	**Case 62-1 (Questions 6, 7), Tables 62-3–62-7**
5	Once the site of infection is confirmed and the likely pathogens are identified, drug distribution to the site of infection, dosage, route of administration, antimicrobial toxicity, side effects, and costs, must be considered before selection of therapy. Therapy should be tailored to the narrowest-spectrum agents and the shortest effective duration of therapy to minimize bacterial resistance and superinfection.	**Case 62-1 (Questions 8–10), Table 62-8**
6	Antimicrobial dosing should reflect the site of infection, route of elimination, and	**Case 62-1 (Questions 11–13), Table 62-9**

	pharmacokinetics and pharmacodynamics.	
7	Antimicrobial failure may be related to pharmacologic factors (inadequate dosing, insufficient penetration to the site of infection, and inadequate duration) and host factors (presence of prosthetic material, undrained focus of infection, and immune status). Adjunct therapies, including pressors and volume repletion, may improve outcomes in patients who are critically ill.	**Case 62-1 (Questions 14–17)**

INTRODUCTION

The appropriate choice, dose, and duration of antimicrobial therapy are based on several factors. Before initiating therapy, confirmation of an infectious versus noninfectious process must take place. Once infection has been documented, the most likely site must be identified, and signs and symptoms (eg, erythema associated with cellulitis) generally direct the clinician to the likely source. Because certain pathogens are known to be associated with a specific site of infection, empirical therapy often is directed against these organisms. Additional laboratory tests, including the Gram stain, serologic analysis, and antimicrobial susceptibility testing, generally identify the primary pathogen and most active agents. Spectrum of activity, established clinical efficacy, adverse effect profile, pharmacokinetic disposition, and cost considerations ultimately guide the choice of therapy. Once an agent has been selected, the dosage and duration should be based on the size of the patient, site of infection, route of elimination, and other factors.

ESTABLISHING THE PRESENCE OF AN INFECTION

CASE 62-1

QUESTION 1: R.G., a 63-year-old, 154.32 pounds (70 kg) male in the intensive care unit (ICU) underwent emergency resection of his large bowel. He has been mechanically ventilated throughout his postoperative course. On day 20 of his hospital stay, R.G. suddenly becomes confused; his blood pressure (BP) drops to 70/30 mm Hg, with a heart rate of 130 beats/minute. His extremities are cold to the touch, and he presents with circumoral pallor. His temperature spikes to 104 °F (40 °C) (axillary), and his respiratory rate is 24 breaths/minute. Copious amounts of yellow-green secretions are suctioned from his endotracheal tube.

Physical examination reveals sinus tachycardia with no rubs or murmurs. Rhonchi with decreased breath sounds are observed upon auscultation. The abdomen is distended, and R.G. experiences new abdominal pain. No bowel sounds can be heard, and the stool is guaiac positive. Urine output from the urinary catheter has been 10 mL/hour for the past 2 hours. Erythema is noted around the central venous catheter.

A chest radiograph demonstrates bilateral lower lobe infiltrates, and urinalysis reveals >50 white blood cells/high-power field (WBC/HPF) (normal <10), few casts (normal, none), and a specific gravity of 1.015. Blood, endotracheal aspirate, and urine cultures are pending. Other laboratory values include the following:

Sodium (Na), 131 mEq/L (normal, 135–147)
Potassium (K), 4.1 mEq/L (normal, 3.5–5)
Chloride (Cl), 110 mEq/L (normal, 95–105)
CO_2, 16 mEq/L (normal, 20–29)
Blood urea nitrogen (BUN), 58 mg/dL (normal, 8–18)
Serum creatinine (SCr), 3.8 mg/dL (increased from 0.9 mg/dL at admission; normal, 0.6–1.2)
Glucose, 320 mg/dL (normal, 70–110)
Serum albumin, 2.1 g/dL (normal, 4–6)
Hemoglobin (Hgb), 10.3 g/dL (13.5–17.5 g/dL male patients)
Hematocrit (Hct), 33% (normal, 39%–49% [male patients])
WBC count, 15,600/μL (normal, 4500–10,000/μL) with bands present
Platelets, 40,000/μL (normal, 130,000–400,000)
Prothrombin time (PT), 18 seconds (normal, 10–12)
Erythrocyte sedimentation rate (ESR), 65 mm/hour (normal, 0–20)
Procalcitonin, 1 μg/L (normal <0.25 μg/L)

Which of R.G.'s signs and symptoms are consistent with infection?

R.G. demonstrates numerous signs and symptoms consistent with infection. His WBC count (15,600/μL) is increased, and a “shift to the left” (presence of bands, ie, immature neutrophils) is observed on the differential. An increased WBC count is commonly observed with infection, particularly with bacterial pathogens. The WBC differential in patients with a bacterial infection often demonstrates a shift to the left associated with the acute bone marrow response to infection. Although infection is usually associated with an increased WBC, overwhelming sepsis can also be associated with a markedly decreased WBC count. In less-acute infection (eg, uncomplicated urinary tract infection, localized abscess), the WBC count may remain within the normal range because a less vigorous bone marrow response would be anticipated.

R.G.’s temperature is 104 °F (40 °C) by axillary measurement. Fever is a common manifestation of infection, with oral temperatures generally >100.40 °F (38 °C). Oral and axillary temperatures tend to be ~32.72 °F (0.4 °C) lower compared with rectal measurement. As a result, R.G.’s temperature would be expected to be 104.72 °F (40.4 °C) if his temperature had been taken rectally. In general, rectal measurement of temperature is a more reliable determination of fever. Some patients with overwhelming infection, however, may present with hypothermia with temperatures <96.80 °F (36 °C). Furthermore, patients with localized infections (eg, uncomplicated urinary tract infection, chronic abscesses) may be afebrile.

The bilateral lower lobe infiltrates on R.G.’s chest radiograph, the presence of copious amounts of yellow-green secretions from his endotracheal tube, and the erythema surrounding his central venous catheter are also compatible with one or more infectious processes. Furthermore, R.G. has signs and symptoms consistent with sepsis.

ESTABLISHING THE SEVERITY OF AN INFECTION

CASE 62-1, QUESTION 2: What signs and symptoms manifested by R.G. are consistent with a serious systemic infection?

The term *sepsis*, although a poorly defined syndrome, generally suggests more systemic infection with the presence of pathogenic microorganisms and/or their toxins in the blood. A uniform system for defining the spectrum of disorders associated with sepsis has been established, but it remains difficult to precisely define.[1]

The pathogenesis of sepsis is complex (**Fig. 62-1**) and only partially understood.[2,3] Gram-negative aerobes produce endotoxin that results in a cascade of endogenous mediator release, including tumor necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6), platelet-activating factor (PAF), and various other substances from mononuclear phagocytes and other cells. Although this initial stimulus commonly is associated with gram-negative endotoxin, other substances, including gram-positive exotoxin and fungal cell wall constituents, may also be associated with cytokine release. After release of TNF, IL-1, and PAF, arachidonic acid is metabolized to form leukotrienes, thromboxane A_2, and prostaglandins, particularly prostaglandin E_2 and prostaglandin I_2. IL-1 and IL-6 activate the T cells to produce interferon, IL-2, IL-4, and granulocyte–macrophage colony-stimulating factor. Increased endothelial permeability ensues. Subsequently, the endothelium releases two hemodynamically active substances: endothelium-derived relaxing factor (EDRF) and endothelin-l. Activation of the complement cascade (fragments C3a and C5a) follows, with additional vascular abnormalities and neutrophil activation. Other potentially important agents in this cascade include adhesion molecules, kinins, thrombin, myocardial depressant substance, endorphins, and heat shock protein. The net result of this cascade involves several hemodynamic, renal, acid–base, and other disorders. Uncontrolled inflammation and coagulation have a particularly important role in this sepsis cascade.[3]

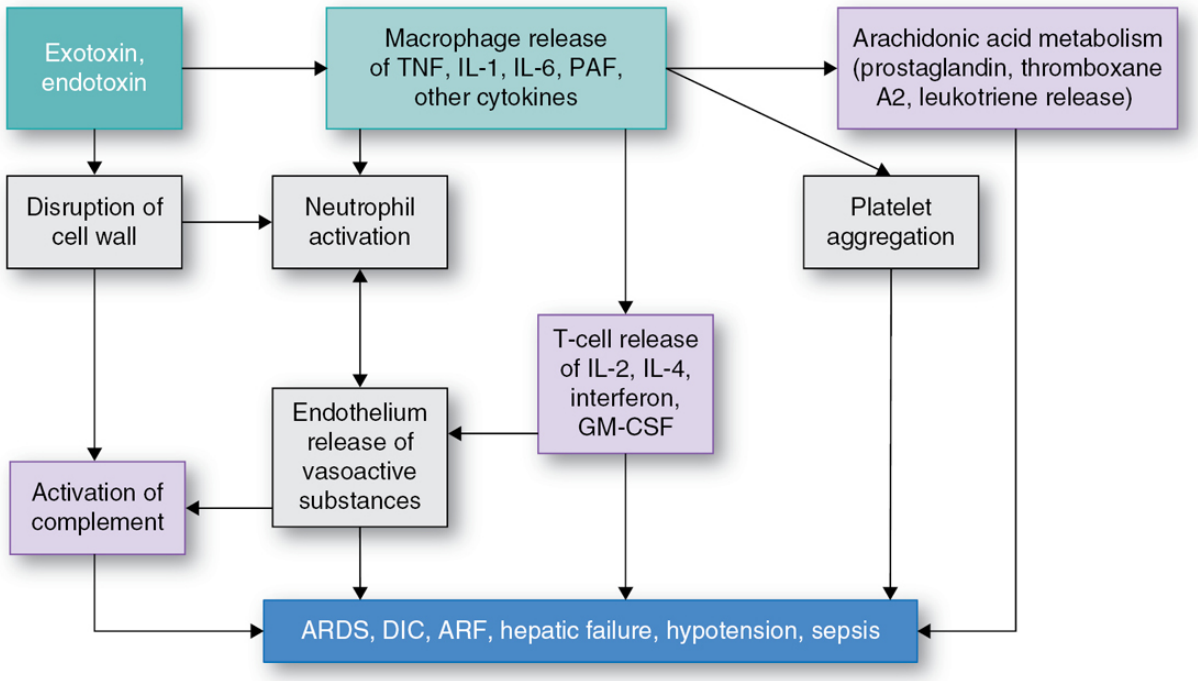


Figure 62-1 The sepsis cascade. ARDS, acute respiratory distress syndrome; ARF, acute renal failure; DIC, disseminated intravascular coagulation; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL-1, interleukin-1; IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; PAF, platelet-activating factor; TNF, tumor necrosis factor.

Hemodynamic Changes

Patients who are critically ill often have central intravenous (IV) lines in place for measuring cardiac output and systemic vascular resistance (SVR). These central lines are placed in the pulmonary artery resulting in a more precise measurement of critical hemodynamics. A normal SVR of 800 to 1200 dyne·s·cm^{-5} may fall to 500 to 600 dyne·s·cm^{-5} in septic shock because of extensive vasodilation. In response to vasodilation, the heart rate generally increases, resulting in increased cardiac output from a normal 4 to 6 L/minute to up to 11 to 12 L/minute in patients with sepsis; stroke volume remains unchanged or decreased. In addition to reflex tachycardia because of vasodilatation, stress-induced catecholamine

release (norepinephrine, epinephrine) also contributes to the rise in heart rate. The initial increase in cardiac output generally is insufficient to overcome the vasodilatory state, and hypotension ensues. In overwhelming septic shock, myocardial depression may result, resulting in a decreased cardiac output. The combination of decreased cardiac output and decreased SVR results in severe hypotension unresponsive to pressors and IV fluids. R.G. has hemodynamic evidence of septic shock. He is hypotensive (BP, 70/30 mm Hg) and tachycardic (HR, 130 beats/minute), presumably in response to vasodilation and catecholamine release.

Although vasodilation commonly occurs in sepsis, this dilation is unequal and chaotic. Some vascular beds constrict and others dilate, resulting in maldistribution of blood flow. In sepsis, blood generally is shunted away from the kidneys, mesentery, and extremities.

When sepsis has progressed to septic shock, blood flow to most major organs is decreased. Normal urine output of ~0.5 to 1.0 mL/kg/hour (30–70 mL/hour for a 154.32-pound [70 kg] patient) can decrease to <20 mL/hour in sepsis. The urine output for R.G. has decreased to 10 mL/hour, consistent with sepsis-induced perfusion abnormalities. Decreased blood flow to the kidney as well as mediator-induced microvascular failure can cause acute-tubular necrosis. R.G.'s uremia (BUN, 58 mg/dL) and increased serum creatinine concentration (3.8 mg/dL) are consistent with sepsis-induce decreased renal perfusion. Decreased blood flow to the liver may result in "shock liver," in which liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase, become elevated. The liver function tests for R.G. are not available; however, his serum albumin concentration is low (2.1 g/dL) and his PT of 18 seconds is prolonged. Decreased blood flow to the musculature classically is characterized by cool extremities, and decreased blood flow to the brain is often associated with decreased mentation. R.G. is confused, his extremities are cold, and the area around his mouth appears pale. All these signs and symptoms strongly suggest he is in septic shock.

Cellular Changes

The sepsis syndrome is associated with significant abnormalities in cellular metabolism. Glucose intolerance commonly is observed in sepsis, and patients with previously normal blood glucose levels may experience sudden increases in blood sugar. In some cases, a rise in glucose is one of the first signs of an infectious process. R.G.'s increased blood glucose concentration (320 mg/dL) is, therefore, consistent with infection. Other sensitive indicators of sepsis-associated inflammation include the ESR, C-reactive protein, and procalcitonin, nonspecific tests that are commonly elevated in various inflammatory states, including infection. The ESR, C-reactive protein, or procalcitonin can be used to follow the progression of infection; currently, R.G.'s ESR is elevated at 65 mm/hour. With appropriate management of infection, the ESR should decrease; inadequate treatment is associated with persistent elevation of the ESR and C-reactive protein. Procalcitonin is a more specific indicator for infection than ESR or C-reactive protein and has been used as a tool to discontinue antibiotics in patients with noninfectious inflammation.[4] At present, R.G.'s procalcitonin is 1.0 μg/L, which is consistent with infection-associated inflammation.

Respiratory Changes

Production of organic acids, such as lactate, increased glycolysis, decreased fractional extraction of oxygen, and abnormal delivery-dependent oxygen consumption are observed in sepsis.[3] This process leads to metabolic acidosis, with accompanying decreased serum bicarbonate levels. The lungs normally respond to metabolic acidosis in a compensatory manner with an increased respiratory rate (tachypnea), resulting in an increased elimination of arterial carbon dioxide. R.G.'s acid–base status is consistent with sepsis-associated metabolic acidosis (CO_2, 16 mEq/L) and compensatory respiratory alkalosis (respiratory rate, 24 breaths/minute).

A late complication of the above-mentioned sepsis cascade is acute respiratory distress syndrome (ARDS). ARDS initially was described as noncardiogenic pulmonary edema with severe hypoxemia caused by right-to-left intrapulmonary shunting resulting from atelectasis and edema-filled alveoli. The primary pathophysiology of ARDS is a breakdown in the natural integrity of the alveolar capillary network in the lung.[5] In the early phase of ARDS, patients have severe alveolar edema with large numbers of inflammatory cells, primarily neutrophils. The chronic phase of ARDS (10–14 days after the development of the syndrome) is associated with significant lung destruction. Emphysema, pulmonary vascular obliteration, and fibrosis commonly are observed. Severe ARDS is associated with ratios of arterial oxygen level to fraction of inspired oxygen (Pa_{O_2}/F_{IO_2}) of <100, low lung compliance, a need for high positive end-expiratory pressure (PEEP), and other respiratory maneuvers. At present, the treatment for this syndrome primarily is supportive, including mechanical ventilation, high-inspired oxygen, and PEEP. If patients fail to show improved gas exchange by day 7, the mortality associated with ARDS is high (>80%).[6] Although R.G. currently does not have ARDS, the severity of his sepsis strongly suggests that he may develop this complication.

Coagulation Changes

Disseminated intravascular coagulation (DIC) is a well-recognized sequel of sepsis because of bacterial and serious viral infections, including COVID-19 infections. Huge quantities of clotting factors and platelets are consumed in DIC as widespread coagulation and inflammation take place throughout the circulatory system.[3] As a result, the ratio of prothrombin time (PT) to international normalized ratio (INR) and the activated partial thromboplastin time (aPTT) are prolonged, and the platelet count commonly is decreased in sepsis. Decreased fibrinogen levels and increased fibrin split products generally are diagnostic for DIC. The PT of 18 seconds and the

decreased platelet count of 40,000/μL in R.G. are consistent with sepsis-induced DIC.[3]

Neurologic Changes

Central nervous system (CNS) changes, including lethargy, disorientation, confusion, and psychosis, are common in patients with sepsis. Altered mental status is also a well-recognized symptom associated with CNS infections, such as meningitis and brain abscess. These changes, however, are also commonly observed with other sites of infection. R.G.'s confused state is consistent with septic shock.[2–3]

PROBLEMS IN THE DIAGNOSIS OF AN INFECTION

Case 62-1, Question 3: R.G.'s medical history includes temporal arteritis and seizures chronically treated with corticosteroids and phenytoin. He recently received perioperative "stress doses" of hydrocortisone because of his surgical procedure. What medications or disease states confuse the diagnosis of infection?

Confabulating Variables

Various factors, including major surgery, acute myocardial infarction, and initiation of corticosteroid therapy, are associated with an increased WBC count. Unlike infection, however, a shift to the left does not occur with these disease states or drugs. In R.G., the stress dose of hydrocortisone and his recent surgical procedure might have contributed to the increased WBC count. The presence of bands in this patient, however, strongly suggests an acute bone marrow response to an infectious process.

Drug Effects

The ability of corticosteroids to mimic or mask infection is noteworthy. Corticosteroids are associated with an increased WBC count and glucose intolerance with the initiation of therapy or with increased doses. Furthermore, some patients experience corticosteroid-induced mental status changes that may mimic those associated with sepsis. Although corticosteroids mimic infection, their anti-inflammatory properties can also mask infection. For example, bowel perforation in a patient with ulcerative colitis would result in significant bacterial peritoneal contamination. Considering their potent anti-inflammatory effects, concomitant receipt of glucocorticoids may, however, reduce the classic findings of peritonitis. Furthermore, corticosteroids can reduce and sometimes ablate the febrile response. Thus, these corticosteroid-treated patients may be asymptomatic but are at great risk for gram-negative septic shock.

Another example of the influence of corticosteroids on the diagnosis of infection relates to neurosurgical procedures. Certain neurosurgical procedures are associated with significant trauma to the meninges, and steroids are often used to decrease the inflammation associated with this trauma. Dexamethasone, a corticosteroid commonly used to reduce the inflammation and swelling associated with neurosurgical procedures, is generally initiated at high doses. When the dexamethasone dose is decreased, such patients may subsequently experience classic meningismus, including stiff neck, photophobia, and headache. The lumbar puncture may demonstrate cloudy cerebrospinal fluid (CSF), an elevated WBC count, high CSF protein, and low CSF glucose. Although the signs and symptoms are consistent with infectious bacterial meningitis, if the CSF sample is sterile, this disease state represents an aseptic meningitis (ie, inflammation of the meninges without an infectious origin).[7] Certain drugs may cause aseptic meningitis, including nonsteroidal anti-inflammatory agents, sulfonamides, and certain antiepileptics.[8]

Fever

Fever is also a common finding with autoimmune diseases, such as systemic lupus erythematosus and temporal arteritis, or with sarcoidosis, chronic liver disease, and familial Mediterranean fever.[9],[10] Acute myocardial infarction, pulmonary embolism, postoperative pulmonary atelectasis, and certain cancers are also commonly associated with fever. Factitious fever or self-induced disease must be considered in certain patients. More recent evaluations of fever of unknown origin (FUO) have resulted in an inability to diagnose the ultimate etiology of the fever; in many instances, FUO results in the unnecessary use of antibiotics.[10] After infection, autoimmune disease, and malignancy have been ruled out, drug fever should be considered. Drugs, including certain antimicrobials and antiepileptics, have been associated with drug fever. Drug fever generally occurs after 7 to 10 days of therapy and resolves within 48 hours of drug discontinuation.[11] Some clinicians claim that patients with drug fever generally feel "well" and are unaware of their fever. A rechallenge with the offending agent usually results in the recurrence of fever. Drug fever should be considered a diagnosis of exclusion, however, and only after eliminating the presence of other disease states.

In summary, R.G. has an autoimmune disease, temporal arteritis, which is known to cause fever. Similarly, his corticosteroids (anti-inflammatory effects) and phenytoin (possible drug fever) use may confound the diagnosis of infection. His other signs and symptoms, however, strongly suggest an infectious origin of R.G.'s problems.

ESTABLISHING THE SITE OF THE INFECTION

Case 62-1, Question 4: What are the most likely sources of R.G.'s infection?

Independent of the presumed site of infection, drawing a series of blood samples may determine the presence of bacteremia in patients with sepsis. A thorough physical examination often documents the source of infection. Urosepsis, the most common cause of nosocomial infection, may be associated with dysuria, flank pain, and abnormal urinalysis.[12] Tachypnea, increased sputum production, altered chest radiograph, and hypoxemia may direct the clinician toward a pulmonary source. Evidence for an infected IV line might include pain, erythema, and purulent discharge around the IV catheter. Other potential sites of infection include the peritoneum, pelvis, bone, and CNS.

R.G. has several possible sites of infection. The copious production of yellow-green sputum, tachypnea, and the altered chest radiograph suggest the presence of pneumonia. The abdominal pain, absent bowel sounds, and recent surgical procedure, however, suggest an intra-abdominal source.[13] Further, the abnormal urinalysis (>50 WBC/HPF) and the erythema around the central venous catheter suggest urinary tract and intravenous catheter infections, respectively.

DETERMINING LIKELY PATHOGENS

CASE 62-1, QUESTION 5: What are the most likely pathogens associated with R.G.'s infection(s)?

R.G. has several possible sources of infection and likely pathogens. **Table 62-1** provides a classification of infectious organisms (eg, gram-positive, gram-negative, aerobic, and anaerobic), and **Table 62-2** lists the most likely organisms associated with sites of infection. Bacterial pneumonia is caused by various pathogens, including *Streptococcus pneumoniae*, *Enterobacteriaceae*, and "atypical" pathogens (eg, *Legionella pneumophila*).[14] However, empirical antimicrobial therapy directed

against all the above organisms is not necessary in all patients. Bacterial community-acquired pneumonia in normal hosts is generally associated with *S. pneumoniae*, *Haemophilus influenzae*, and "atypical" bacterial pathogens.[15] However, viral etiology, including pneumonia because of COVID-19, should always be considered. In contrast to community-acquired, nosocomial (acquired in hospital or in other health care facilities, eg, nursing home) pneumonia is frequently associated with gram-negative bacilli (eg, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, and *Pseudomonas aeruginosa*) and *Staphylococcus aureus*. If the pneumonia is the result of a gastric aspiration, empirical antibacterial treatment of mouth anaerobes generally takes place; however, their true pathogenicity in aspiration pneumonia is not clear. For the empirical treatment of hospital-associated pneumonia or ventilator-associated pneumonia, knowledge of a hospital epidemiology is useful. If *P. aeruginosa* or *Enterobacter cloacae* predominate in an institution, then broad-spectrum agents should be used directed against these pathogens. Similarly, prior or concurrent receipt of antimicrobial therapy significantly impacts the choice of empirical therapy. Age is an important determinant in the epidemiology of infection. For example, meningitis in a neonate is commonly caused by group B streptococci, *E. coli*, and *Listeria monocytogenes*, whereas these bacteria are uncommon pathogens in normal healthy adults. The presence of concomitant diseases, such as chronic obstructive pulmonary disease (COPD) or alcohol and IV drug abuse, also increases the likelihood for infection because of certain pathogens. As an example, patients with COPD-associated community-acquired pneumonia more likely are infected by *S. pneumoniae* and *H. influenzae*, whereas chronic alcoholics more likely have *Klebsiella* species as a source of pneumonia.

Table 62-1
Classification of Infectious Organisms

1. BACTERIA
   Aerobic
   Gram-positive

Cocci
Streptococci: pneumococcus, viridans streptococci; group A streptococci
Enterococcus
Staphylococci: *Staphylococcus aureus, Staphylococcus epidermidis*
Rods (bacilli)
Corynebacterium
Listeria
Gram negative
Cocci
Moraxella
Neisseria (Neisseria meningitidis, Neisseria gonorrhoeae)
Rods (bacilli)
Enterobacteriaceae (*Escherichia coli, Klebsiella, Enterobacter, Citrobacter, Proteus, Serratia, Salmonella, Shigella, Morganella, Providencia*)
Campylobacter
Pseudomonas
Helicobacter
Haemophilus (coccobacilli morphology)
Legionella
Anaerobic
Gram-positive
Cocci
Peptococcus
Peptostreptococcus
Rods (bacilli)
Clostridia (*Clostridium perfringens, Clostridium tetani, Clostridioides difficile*)
Propionibacterium acnes
Gram negative
Cocci
None
Rods (bacilli)
Bacteroides (*Bacteroides fragilis, Bacteroides melaninogenicus*)
Fusobacterium
Prevotella

2. FUNGI
   Aspergillus, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucor, Tinea, Trichophyton
3. VIRUSES
   Influenza; hepatitis A, B, C, D, E; human immunodeficiency virus (HIV); rubella; herpes; influenza; cytomegalovirus; respiratory syncytial virus; Epstein–Barr virus; severe acute respiratory syndrome (SARS) virus, COVID-19
4. CHLAMYDIAE
   Chlamydia trachomatis

Chlamydia psittaci
Chlamydophila pneumoniae
Lymphogranuloma venereum (LGV)

5. RICKETTSIAE
   Rocky Mountain spotted fever, Q fever
   Ureaplasma
6. MYCOPLASMAS
   Mycoplasma pneumoniae, Mycoplasma hominis
7. SPIROCHETES
   Treponema pallidum, Borrelia burgdorferi (Lyme disease)
8. MYCOBACTERIA
   Mycobacterium tuberculosis
   Mycobacterium avium intracellulare

Table 62-2
Site of Infection: Suspected Organisms

Site/Type of Infection	Suspected Organisms
1. Respiratory	
Pharyngitis	Viral, group A streptococci
Otitis	Viral, *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis*
Acute sinusitis	Viral, *S. pneumoniae, H. influenzae, M. catarrhalis*
Chronic sinusitis	Anaerobes, *Staphylococcus aureus* (as well as suspected organisms associated with acute sinusitis)
Epiglottitis	Viral, *H. influenza*
Pneumonia	
Community-acquired	
Normal host	*S. pneumoniae*, viral, mycoplasma
Aspiration	Normal aerobic and anaerobic mouth flora
Pediatrics	*S. pneumoniae, H. influenzae*
COPD	*S. pneumoniae, H. influenzae, Legionella, Chlamydia, Mycoplasma*
Alcoholic	*S. pneumoniae, Klebsiella*
Hospital-	

acquired	
Aspiration	Mouth anaerobes, aerobic gram-negative rods, *S. aureus*
Neutropenic	Molds, aerobic gram-negative rods, *S. aureus*
HIV	Molds, *Pneumocystis, Legionella, Nocardia, S. pneumoniae, Pseudomonas*
2. Urinary Tract	
Community-acquired	*Escherichia coli*, other gram-negative rods, *S. aureus, Staphylococcus epidermidis*, enterococci
Hospital-acquired	Resistant aerobic gram-negative rods, enterococci
3. Skin and Soft Tissue	
Cellulitis	Group A streptococci, *S. aureus*
IV catheter infection	*S. aureus, S. epidermidis*
Surgical wound	*S. aureus*, gram-negative rods
Diabetic ulcer	*S. aureus*, gram-negative aerobic rods, anaerobes
Furuncle	*S. aureus*
4. Intra-abdominal	*Bacteroides fragilis, E. coli*, other aerobic gram-negative rods, enterococci
5. Gastroenteritis	*Salmonella, Shigella, Helicobacter, Campylobacter, Clostridioides difficile*, enterotoxigenic-hemorrhagic *E. coli, Giardia*, amoeba, viral
6. Endocarditis	
Preexisting valvular disease	*Viridans streptococci*
IV drug user	*S. aureus*, aerobic gram-negative rods, enterococci, fungi
Prosthetic valve	*S. epidermidis, S. aureus*
7. Osteomyelitis and Septic Arthritis	*S. aureus*, aerobic gram-negative rods
8. Meningitis	
<2 months	*E. coli*, group B streptococci, *Listeria*
2 months–12 years	*S. pneumoniae, Neisseria meningitidis, H. influenzae*

Adults	*S. pneumoniae, N. meningitidis*
Hospital-acquired	*S. pneumoniae, N. meningitidis*, aerobic gram-negative rods
Post-neurosurgery	*S. aureus*, aerobic gram-negative rods

COPD, chronic obstructive pulmonary disease; IV, intravenous.

Immune status is an important predictor for certain pathogens. Patients with human immunodeficiency virus (HIV) infection/AIDS or those receiving Atgam, cyclosporine (or tacrolimus), sirolimus, and corticosteroids have quantitative and/or qualitative lymphocyte deficiency and are at risk for infections because of cytomegalovirus, *Pneumocystis jirovecii*, atypical mycobacteria, and *Cryptococcus neoformans.* Patients with leukemia and neutropenia are at risk for infection caused by aerobic gram-negative bacilli, including *P. aeruginosa*, *Candida* species, and *Aspergillus* species, as well as the above-mentioned pathogens.

In 2019, several cluster cases of viral pneumonia were reported from Wuhan City, China. Cases continued to emerge rapidly, increasing to 282 confirmed cases within 10 days with 51 patients who are severely ill, 12 patients in critical condition, and 6 deaths.[16] The pathogen responsible for the severe respiratory syndrome known as COVID-19 (coronavirus disease 2019) was later identified as a novel coronavirus, SARs-CoV-2 (severe acute respiratory syndrome coronavirus 2). The virus spread throughout the world in the ensuing months, requiring massive quarantine and leading to economic shutdown and social unrest unseen in recent history.[17] COVID-19 is associated with a wide range of severity of the disease. Although the majority of patients infected with COVID-19 have mild symptoms or are asymptomatic, many patients require hospitalization including ICU care and mechanical intubation. Patients at risk for more severe disease include those with advanced age, cancer, chronic kidney disease, COPD, other immunocompromised states, obesity, serious heart conditions, sickle cell disease, and diabetes mellitus.[18] Commonly observed symptoms

include fever/chills, cough, shortness of breath, fatigue, muscle aches, headache, loss of taste or smell, sore throat, congestion, nausea, vomiting, and diarrhea. These symptoms can appear 2 to 14 days after initial exposure to the virus.[19]

In R.G., the abdomen, respiratory tract, urinary tract, and IV catheter are all potential sites of infection. Intra-abdominal infection is likely caused by aerobic gram-negative enteric bacteria, *Bacteroides fragilis*, and possibly enterococcus; nosocomial urinary tract infection is usually caused by aerobic gram-negative bacteria. R.G.'s pneumonia could be because of gram-negative bacilli and staphylococci, as well as other organisms including SARS-CoV-2. Furthermore, his long-term use of corticosteroids may predispose him to infection caused by more opportunistic organisms, including *Legionella*, *P. jirovecii*, and certain fungi. Lastly, his IV catheter infection suggests infection caused by staphylococci, including *Staphylococcus epidermidis* and *Staphylococcus aureus.*

MICROBIOLOGIC TESTS AND SUSCEPTIBILITY OF ORGANISMS

Case 62-1, Question 6: A Gram stain of R.G.'s tracheal aspirate shows gram-negative bacilli. What tests may assist with the identification of the pathogen(s)?

Once the site of infection has been determined and host defense and other epidemiologic factors have been evaluated, additional tests can be performed to identify the pathogen. The Gram stain uses crystal violet solution and iodine staining bacteria gram positive or gram negative; some organisms are gram variable. In addition, the shape of the organism (cocci, bacilli) is readily apparent with the use of the Gram stain. Streptococci and staphylococci are gram-positive cocci, whereas *E. coli*, *E. cloacae*, and *P. aeruginosa* appear as gram-negative bacilli (see Table 62-1).[20] If the Gram stain of the tracheal aspirate demonstrates gram-positive cocci in clusters,

empirical antistaphylococcal therapy is indicated. In contrast, if the Gram stain shows gram-negative rods, antimicrobials with activity against these pathogens should be used.

Similar to the Gram stain in bacterial infection, the India ink and potassium hydroxide stains are helpful in the identification of certain fungi. The acid-fast bacilli stain is critical in the diagnosis of infection caused by *Mycobacterium tuberculosis* or atypical mycobacteria.

In R.G.'s case, the Gram stain suggests that antimicrobials active against gram-negative bacilli should be used. **Table 62-3** provides a classification of antibacterials (eg, different generations of cephalosporins). **Tables 62-4**, **62-5**, and **62-6** list in vitro susceptibilities of aerobic gram-positive, gram-negative, and anaerobic bacteria, respectively.

Table 62-3
Classification of Antibacterials

a-Lactam Antibiotics
***b**-Lactam and **b**-Lactamase Inhibitors Combinations*
Amoxicillin plus clavulanic acid (Augmentin)
Ampicillin plus sulbactam (Unasyn)
Ceftazidime plus avibactam (Avycaz®)
Ceftolozane plus tazobactam (Zerbaxa)
Imipenem/cilastatin plus relebactam (Recarbrio™)
Meropenem plus vaborbactam (Vabomere)
Piperacillin plus tazobactam (Zosyn)
Ticarcillin plus clavulanic acid (Timentin)[a]
Carbacephem
Loracarbef (Lorabid)[a]
Carbapenems
Doripenem (Doribax®)
Ertapenem (Invanz)
Imipenem/cilastatin (Primaxin)
Meropenem (Merrem)
Cephalosporins
First Generation
Cefadroxil (Duricef)
Cefazolin (Ancef)
Cephalexin (Keflex)
Second Generation

Cefaclor (Ceclor)
Cefamandole (Mandol®)[a]
Cefonicid (Monocid)
Ceforanide (Precef)
Cefotetan (Cefotan®)
Cefoxitin (Mefoxin)
Cefprozil (Cefzil)
Cefuroxime (Zinacef)
Cefuroxime axetil (Ceftin)
Third Generation
Cefdinir (Omnicef)
Cefditoren (Spectracef)
Cefixime (Suprax)
Cefotaxime (Claforan)
Cefpodoxime proxetil (Vantin)
Ceftazidime (Fortaz)
Ceftibuten (Cedax)
Ceftizoxime (Cefizox®)
Ceftriaxone (Rocephin)
Fourth Generation
Cefepime (Maxipime)
Fifth Generation
Ceftaroline (Teflaro™)
Siderophore Cephalosporins
Cefiderocol (Fetroja®)
Penicillins
Natural Penicillins
Penicillin G
Penicillin V
Aminopenicillins
Ampicillin (Omnipen)
Amoxicillin (Amoxil)
Bacampicillin (Spectrobid)[a]
Penicillinase-Resistant Penicillins
Isoxazolyl penicillins (dicloxacillin, oxacillin, cloxacillin)
Nafcillin (Unipen)
Monobactams
Aztreonam (Azactam)

Non–a-Lactam Antibiotics

Aminoglycosides
Amikacin (Amikin)
Gentamicin (Garamycin)
Neomycin (Mycifradin)
Netilmicin (Netromycin)[a]

Plazomicin (Zemdri®)
Streptomycin
Tobramycin (Nebcin)
Folate inhibitors
Sulfadiazine
Sulfadoxine (Fansidar)
Trimethoprim (Trimpex)
Trimethoprim-sulfamethoxazole (Bactrim, Septra)
Glycopeptides
Dalbavancin (Dalvance)
Oritavancin (Orbactiv®)
Telavancin (Vibativ®)
Vancomycin (Vancocin)
Lincosamides
Clindamycin (Cleocin)
Macrolides
Azithromycin (Zithromax)
Clarithromycin (Biaxin®)
Dirithromycin (Dynabac®)[a]
Erythromycin (Erythrocin)
Fidaxomicin (Dificid)
Ketolides
Telithromycin (Ketek)[a]
Oxazolidinones
Linezolid (Zyvox)
Tedizolid (Sivestro®)
Pleuromutilins
Lefamulin (Xenleta®)
Quinolones
Ciprofloxacin (Cipro)
Delafloxacin (Baxdela®)
Gemifloxacin (Factive)
Levofloxacin (Levaquin)
Moxifloxacin (Avelox)
Norfloxacin (Noroxin®)
Ofloxacin (Floxin)
Tetracyclines
Doxycycline (Vibramycin)
Eravacycline (Xerava)
Minocycline (Minocin)
Omadacycline (Nuzyra®)
Tetracycline (Sumycin)
Tigecycline (Tygacil)
Others

Chloramphenicol (Chloromycetin)
Dalfopristin/Quinupristin (Synercid)
Daptomycin (Cubicin®)
Metronidazole (Flagyl)

[a]Not on the U.S. market.

Table 62-4
In Vitro Antimicrobial Susceptibility: Aerobic Gram-Positive Cocci

Drugs	*Staphylococcus aureus*	*Staphylococcus aureus* (MR)	*Staphylococcus epidermidis*	*Staphylococcus epidermidis* (MR)	Streptococci[a]	Enterococci[b]	Pneumococci
Ampicillin	+		+		++++	++	+++
Augmentin	++++	+	++++		++++	++	++++
Cefazolin	++++		++++		++++		++
Cefepime	++++		++++		++++		+++
Cefiderocol					++		++
Cefoxitin/cefotetan	++		++		++		+
Ceftaroline	++++	++++	++++	++++	++++	+	++++
Cefuroxime	++++		++++		++++		+++
Ciprofloxacin[c]	+++	+	+++	++	+	+	++
Clindamycin	++++	++	++++	+	+++		+++
Cotrimoxazole	++++	+++	++	+	++	+	+
Dalbavancin	++++	++++	++++	++++	++++	++	++++
Daptomycin[d]	++++	++++	++++	++++	++++	++++	++++
Delafloxacin	+++	++	+++	++	++++	+	++++
Eravacycline	++++	++++	++++	++++	++++	++++	++++
Erythromycin (azithromycin, clarithromycin)	++		+		+++		++
Ertapenem	++++		++++		++++		+++
Imipenem (doripenem, meropenem)	++++		++++		++++	++	+++
Imipenem/cilastatin-relebactam	++++		++++		++++	++	+++
Lefamulin	++++	+++	+++	+++	++++		++++
Levofloxacin (gemifloxacin, moxifloxacin)	++++	++	+++	++	+++	++	++++
Linezolid[d] (tedizolid)	++++	++++	++++	++++	++++	++++	++++
Meropenem-vaborbactam	++++		++++		++++	++	+++
Nafcillin (oxacillin)	++++		++++		++++		++
Omadacycline	++++	++++	++++	++++	++++	++++	++++
Oritavancin[d]	++++	++++	++++	++++	++++	++++	++++
Penicillin	+		+		++++	++	+++
Quinupristin/dalfopristin[d,e]	++++	++++	++++	++++	++++	++++	++++
TGC[f]	+++		++		++++		+++
Telavancin	++++	++++	++++	++++	++++	++++	++++
Tigecycline[d]	++++	++++	++++	++++	++++	++++	++++
Timentin	++++		++++		++++	+	+
Unasyn	++++		++++		++++	++	+++
Vancomycin	++++	++++	++++	++++	++++	+++	++++
Zosyn	++++		++++		++++	++	+++

MR, methicillin-resistant; TGC, third-generation cephalosporin.

[a]Nonpneumococcal streptococci.

[b]Usually requires combination therapy (eg, ampicillin plus gentamicin or ampicillin plus ceftriaxone) for endocarditis.

[c]Levofloxacin (eg, gemifloxacin, moxifloxacin) is more active than ciprofloxacin against staphylococci and streptococci.

[d]Active versus vancomycin-resistant *E. faecium*.

[e]Active against *Enterococcus faecium* but unpredictable against *E. faecalis.*

[f]Cefotaxime, ceftizoxime, ceftriaxone, and cefoperazone. Ceftazidime has comparatively inferior antistaphylococcal and antipneumococcal activity compared to cefotaxime or ceftriaxone. Cefotaxime, ceftriaxone, and cefepime are the most reliable cephalosporins versus *Streptococcus pneumoniae*.

Table 62-5
In Vitro Antimicrobial Susceptibility: Gram-Negative Aerobes

Drugs	*Escherichia coli*	*Klebsiella pneumoniae*	*Enterobacter cloacae*	*Proteus mirabilis*	*Serratia marcescens*	*Pseudomonas aeruginosa*	*Haemophilus influenzae*	*Haemophilus influenzae*[a]
Ampicillin	++			+++			++++	
Amikacin	++++	++++	++++	++++	++++	++++	++	++
Augmentin	+++	++		++++			++++	++++
Aztreonam	++++	++++	+	++++	++++	+++	++++	++++
Cefazolin	+++	+++		++++			+	
Cefepime	++++	++++	+++	++++	++++	+++	++++	++++
Cefiderocol	+++++	+++++	+++++	+++++	+++++	++++	+++++	+++++
Ceftazidime	+++	+++	+	++++	++++	+++	++++	++++
Ceftazidime-avibactam	+++++	+++++	+++++	+++++	+++++	++++	+++++	+++++
Ceftolozane-tazobactam	++++	++++	++++	++++	++++	+++++	++++	++++
Ceftaroline	++++	++++	+	++++	++	+++	++++	++++
Cefuroxime	+++	+++		++++	+		++++	++++
Cotrimoxazole	++	+++	+++	++++	+++		++++	++++
Eravacycline	+++++	+++++	+++++	+++++	+++++	++++	+++++	+++++
Ertapenem	++++	++++	++++	++++	++++	+	++++	++++
Gentamicin	++++	++++	++++	++++	++++	+++	++	++
Imipenem (meropenem, doripenem)	++++	++++	++++	+++	++++	+++	++++	++++
Imipenem/cilastatin-relebactam	+++++	+++++	+++++	+++++	+++++	+++++	+++++	+++++
Lefamulin							+++	+++
Plazomicin	+++++	+++++	+++++	+++++	+++++	+++++	+++++	+++++
Meropenem-vaborbactam	+++++	+++++	+++++	+++++	+++++	+++++	++++	+++++
Quinolones	+++	++++	+++	++++	++++	++	++++	++++
TGC[b]	++++	++++	+	++++	++++	+	++++	++++
Tigecycline	++++	++++	++++	++	++++	–	++++	++++
Timentin	+++	++	+	++++	+++	+++	++++	++++
Tobramycin	++++	++++	++++	++++	+++	++++	++	++
Unasyn	+++	+++		++++	++		++++	++++
Zosyn	++++	++++	++	++++	++++	++++	++++	++++

TGC, third-generation cephalosporin.

[a]β-Lactamase-producing strains.

[b]Cefotaxime, ceftizoxime, and ceftriaxone.

Table 62-6
Antimicrobial Susceptibility: Anaerobes

Drugs	*Bacteroides fragilis*	*Peptococcus*	*Peptostreptococcus*	Clostridia (Non-difficile)
Ampicillin	+	++++	++++	+++
Cefazolin		+++	+++	
Cefepime	+	+++	+++	+
Cefotaxime	++	+++	+++	+
Cefoxitin/cefotetan	+++	+++	++++	+
Ceftazidime		+	+	+
Ceftizoxime	+++	+++	+++	+
Ciprofloxacin	+	+	+	+
Clindamycin	+++	++++	++++	++
Imipenem/doripenem/ertapenem/ meropenem	++++	++++	++++	++
Metronidazole	++++	+++	++	+++
Moxifloxacin	+++	+++	+++	++
Penicillin	+	++++	++++	++++
Piperacillin-tazobactam, amoxicillin-clavula-nate, ticarcillin-clavulanate	++++	++++	+++	+++
Tigecycline	++++	++++	+++	+++
Unasyn	++++	++++	++++	++++
Vancomycin		+++	+++	+++

Culture and Susceptibility Testing

Culture and susceptibility testing provides final identification of the pathogen, as well as information regarding the likely effectiveness of various antimicrobials. Although these tests further clarify the pathogen, they generally require 18 to 24 hours to complete. Once the pathogen has been identified, the most effective agents (**Table 62-7**) and institution-specific susceptibility data allow for the selection of the most appropriate antimicrobial.

Table 62-7
Antimicrobials of Choice in the Treatment of Bacterial Infection

Organism	Drug of Choice	Alternatives	Comments
Aerobes			
Gram-Positive Cocci			
Streptococcus pyogenes (group A streptococci)	Penicillin	Clindamycin, macrolide, cephalosporin	Clindamycin is the most reliable alternative for patients who are allergic to penicillin.
Streptococcus pneumoniae	Ceftriaxone, ampicillin, oral amoxicillin	Macrolide, cephalosporin, doxycycline	Although the incidence of penicillin–*non*-susceptible pneumococci is 20%–30%, high-dose penicillin or amoxicillin is active against most of these isolates.
			Penicillin-resistant pneumococci commonly demonstrate resistance to other agents, including erythromycin, tetracyclines, and cephalosporins.
			Anti-pneumococcal quinolones (gemifloxacin, levofloxacin, moxifloxacin), ceftriaxone, and cefotaxime are options for treatment of high-level penicillin-resistant isolates.
Enterococcus faecalis	Ampicillin with or without gentamicin Ampicillin with or without ceftriaxone	Piperacillin-tazobactam; vancomycin with or without gentamicin; daptomycin, linezolid, tedizolid, tigecycline	Most commonly isolated enterococcus (80%–85%). Most reliable anti-enterococcal agents are ampicillin (penicillin, piperacillin-tazobactam), vancomycin, and linezolid. Monotherapy generally inhibits but does not kill the enterococcus. Daptomycin is unique in its bactericidal activity against enterococci. Aminoglycosides or ceftriaxone must be added to ampicillin to provide bactericidal activity. High-level aminoglycoside resistance should be determined for endocarditis.
Enterococcus faecium	Vancomycin with or without gentamicin	Linezolid, tedizolid, daptomycin, dalfopristin/quinupristin (D/Q), oritavancin, tigecycline	Second most common enterococcal organism (10%–20%) and is more likely than *E. faecalis* to be resistant to multiple antimicrobials. Most reliable agents are daptomycin, D/Q, oritavancin, and linezolid. Monotherapy generally inhibits but does not kill the enterococcus. Aminoglycosides or ceftriaxone must be added to cell wall–active agents to provide bactericidal activity. Ampicillin and vancomycin resistance is common. Daptomycin, D/Q, and linezolid are drugs of choice for vancomycin-resistant isolates.

Organism	Drug of Choice	Alternatives	Comments
Staphylococcus aureus methicillin-resistant	Nafcillin, oxacillin, dicloxacillin, cefazolin	Vancomycin, clindamycin, dalbavancin, linezolid, oritavancin	Isolates of 80%–85% are resistant to penicillin. Most isolates are susceptible to nafcillin, cephalosporins, trimethoprim-sulfamethoxazole, and clindamycin. First-generation cephalosporins are equal to nafcillin. Most second- and third-generation cephalosporins are adequate in the treatment of infection (exceptions include ceftazidime and cefonicid). Methicillin-resistant *S. aureus* must be treated with vancomycin or alternatives (eg, linezolid, daptomycin, delafloxacin, ceftaroline, D/Q, the vancins); trimethoprim-sulfamethoxazole, doxycycline, or minocycline can be used for community-acquired MRSA.
	Vancomycin	Trimethoprim-sulfamethoxazole, minocycline, doxycycline, daptomycin, tigecycline, telavancin, oritavancin, dalbavancin, ceftaroline, delafloxacin	
Staphylococcus epidermidis methicillin-resistant	Nafcillin, oxacillin	Cefazolin, vancomycin, clindamycin	Most isolates are resistant *to* β-lactam, clindamycin, and trimethoprim–sulfamethoxazole. Most reliable agents are vancomycin, daptomycin, D/Q, and linezolid. Rifampin is active and can be used in conjunction with other agents; however, monotherapy with rifampin is associated with the development of resistance.
	Vancomycin	Daptomycin, linezolid, D/Q	
Gram-Positive Bacilli			
Diphtheroids	Penicillin	Cephalosporin	
Corynebacterium jeikeium	Vancomycin	Erythromycin, quinolone	
Listeria monocytogenes	Ampicillin (with or without gentamicin)	Trimethoprim-sulfamethoxazole	
Gram-Negative Cocci			
Moraxella catarrhalis	Trimethoprim-sulfamethoxazole	Amoxicillin-clavulanic acid, erythromycin, doxycycline, second- or third-generation cephalosporin	
Neisseria gonorrhoeae	Ceftriaxone		
Neisseria meningitidis	Penicillin	Third-generation cephalosporin	
Gram-Negative Bacilli			
Campylobacter fetus	Imipenem/cilastatin	Gentamicin	
Campylobacter jejuni	Azithromycin	Tetracycline, amoxicillin-clavulanic acid, quinolone	
Enterobacter	Carbapenem	Quinolone, aminoglycoside	Not predictably inhibited by third-generation cephalosporins. Carbapenems, quinolones, trimethoprim-sulfamethoxazole, cefepime, and aminoglycosides are most active agents.
Escherichia coli	Third-generation cephalosporin	First- or second-generation cephalosporin, gentamicin	ESBL producers should be treated with a carbapenem/β-lactamase combination, later-generation cephalosporin/β-lactamase combinations (ie, ceftolozane–tazobactam, ceftazidime-avibactam), plazomicin, eravacycline, or cefiderocol
Haemophilus influenzae	Third-generation cephalosporin	β-Lactamase inhibitor combinations, second-generation cephalosporin, trimethoprim-sulfamethoxazole	
Helicobacter pylori	PPI + clarithromycin + amoxicillin *or* metronidazole	PPI + bismuth subsalicylate + tetracycline + nitroimidazole	
Klebsiella pneumoniae	Third-generation cephalosporin	First- or second-generation cephalosporin, gentamicin, trimethoprim-sulfamethoxazole	ESBL producers should be treated with a carbapenem β-lactamase combination, later-generation cephalosporin/β-lactamase combinations (ie, ceftolozane-tazobactam, ceftazidime-avibactam), plazomicin, eravacycline, or cefiderocol

Organism	Drug of Choice	Alternatives	Comments
Legionella	Fluoroquinolone	Macrolide with or without rifampin, doxycycline	
Proteus mirabilis	Ampicillin	First-generation cephalosporin, trimethoprim-sulfamethoxazole	
Other *Proteus*	Third-generation cephalosporin	β-Lactamase inhibitor combination, aminoglycoside, trimethoprim-sulfamethoxazole	
Pseudomonas aeruginosa	Antipseudomonal penicillin or antipseudomonal cephalosporin with or without aminoglycoside (or quinolone)	Quinolone or imipenem with or without aminoglycoside	Most active agents include aminoglycosides, doripenem, imipenem, meropenem, ceftazidime, ceftazidime-avibactam, cefepime, ceftolozane-tazobactam, aztreonam, imipenem-relebactam, and the extended-spectrum penicillins. Monotherapy is adequate for most pseudomonal infections.
Salmonella typhi	Quinolone	Ceftriaxone	
Serratia marcescens	Third-generation cephalosporin	Trimethoprim-sulfamethoxazole, aminoglycoside, carbapenem	
Shigella	Quinolone	Trimethoprim-sulfamethoxazole, ampicillin	
Stenotrophomonas maltophilia	Trimethoprim-sulfamethoxazole	Ceftazidime, minocycline, β-lactamase inhibitor combination (Timentin)	
Anaerobes			
Bacteroides fragilis	Metronidazole	β-Lactamase inhibitor combinations, carbapenems	Most active agents (95%–100%) include metronidazole, the β-lactamase inhibitor combinations ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanic acid, and carbapenems. Clindamycin, cefoxitin, cefotetan, cefmetazole, ceftizoxime have good activity but not to the degree of metronidazole.
Clostridioides difficile	Vancomycin, fidaxomicin		Fidaxomicin is superior to other agents in the prevention of relapse.
Fusobacterium	Penicillin	Metronidazole, clindamycin	
Other Oropharyngeal			
Prevotella	β-Lactamase inhibitor combination	Metronidazole, clindamycin	
Peptostreptococcus	Penicillin	Clindamycin, cephalosporin	Most β-lactams active (exceptions include aztreonam, nafcillin, ceftazidime)
Other			
Actinomyces israelii	Penicillin	Tetracyclines	
Nocardia	Trimethoprim-sulfamethoxazole	Amikacin, minocycline, imipenem	
Chlamydia trachomatis	Doxycycline	Azithromycin	
Chlamydophila pneumoniae	Doxycycline	Azithromycin, clarithromycin	
Mycoplasma pneumoniae	Doxycycline	Azithromycin, clarithromycin	
Borrelia burgdorferi	Doxycycline	Ampicillin, second- or third-generation cephalosporin	
Treponema pallidum	Penicillin	Doxycycline	

ESBL, extended-spectrum β-lactamase.

DISK DIFFUSION

The most widely used tests for bacterial susceptibility are the disk diffusion and the broth dilution methods. The disk diffusion (Kirby–Bauer) technique uses an agar plate on which an inoculum of the organism is placed. After inoculation, several antimicrobial-laden disks are placed on the plate, and evidence of bacterial growth is observed after 18 to 24 hours. If the antimicrobial is active against the pathogen, a zone of growth inhibition around the disk is observed. Based on the guidelines provided by the Clinical and Laboratory Standards Institute (CLSI), the diameter of inhibition is reported as susceptible, intermediate, or resistant. CLSI zones of inhibitions are determined considering known achievable antimicrobial concentrations in vivo. However, broth dilution (see below) minimum inhibitory concentration (MIC) allows for a better comparison with achievable antimicrobial concentrations.

BROTH DILUTION

The broth dilution method introduces a bacterial inoculum into several tubes or wells filled with broth. Serial dilutions of antimicrobials (eg, nafcillin 0.5, 1.0, and 2.0 µg/mL) are placed in the respective wells. After bacterial incubation for 18 to 24 hours, the wells are examined for bacterial growth. If the well is cloudy, bacterial growth has occurred, suggesting resistance to the specific antimicrobial at that concentration. As an example, if bacterial growth is observed with *S. aureus* at 0.5 µg/mL of nafcillin but not at 1.0 µg/mL, then 1.0 µg/mL would be considered the MIC for nafcillin against *S. aureus.*

Similar to the disk diffusion method, the CLSI provides guidelines[21] that also take into account antimicrobial pharmacokinetics to determine whether the MIC should be reported as susceptible, intermediately susceptible, or resistant. MIC interpretations are both pathogen- and antimicrobial-specific. For example, ciprofloxacin achieves serum concentrations of only 1 to 4 µg/mL, whereas the fourth-generation cephalosporin, cefepime, achieves peak serum concentrations of 75 to 100 µg/mL; consequently, an MIC of 4.0

μg/mL for *P. aeruginosa* would be interpreted by CLSI as resistant to ciprofloxacin but susceptible to cefepime.

Although these tests provide an accurate assessment of in vitro susceptibility, the time delay (18–24 hours) can hinder streamlining of therapy. An alternative efficient, but more expensive, MIC test is the E test, which uses an antibiotic-laden plastic strip with increasing concentrations of a specific antimicrobial from one end to the other. The strip is placed on an agar plate with the actively growing pathogen. Inhibition of growth observed at specific marks on the strip coincides with the MIC of the organism. Numerous studies have confirmed that the E test is as effective as traditional susceptibility testing. Several automated antimicrobial susceptibility systems are available in the United States, including Phoenix (Becton Dickinson, Franklin Lakes, NJ), Vitek (bioMérieux, Durham, NC), MicroScan WalkAway (Siemens Healthcare Diagnostics, Tarrytown, NY), and Sensititre (Trek Diagnostics, Cleveland, OH). These systems generally use a computerized algorithm for interpreting results and determine the antibiotic MIC for the organism by using specialized decision technology. Two major advantages of automated susceptibility methodologies include a reduction in labor and faster reporting of susceptibility results, potentially leading to the earlier initiation of appropriate antibiotic therapy. Although these represent advantages, disadvantages exist, particularly with cystic fibrosis isolates. Most clinical microbiology laboratories use automated susceptibility testing systems. Although these automated antimicrobial susceptibility systems are an improvement over traditional broth dilution and disc diffusion methods, other emerging technologies including polymerase chain reaction (PCR) and other “next-generation” systems are likely to result in more rapid identification of pathogens and their associated antimicrobial susceptibility. In the context of COVID-19, the most reliable method of identification and diagnosis is a viral PCR of antigen or nucleic acid via respiratory sample (ie, nasal or oral swabs or saliva) to determine if a patient is infected with SARS-CoV-2.[22]

Although susceptibility testing is relatively well standardized for aerobic gram-negative and gram-positive organisms, its utility is not

as established for anaerobes[23] and fungi.[24] In general, despite improvements in the standardization of testing in anaerobes, institutions do not routinely perform susceptibility testing for these bacteria. In contrast, susceptibility testing is available for *Candida* species, and these in vitro data have demonstrated to predict clinical success in the patient care setting.

The consensus of the CLSI and other experts is that anaerobic isolates from blood, bone and joint sources, brain abscesses, empyemic fluid, and other body fluids that are normally sterile should be considered for susceptibility testing. However, in general, these susceptibilities are rarely performed.[23] Progress has been made in developing a standardized test for determining fungal susceptibility, but the emphasis has been on the susceptibility of *Candida* species to azoles in the treatment of candidiasis.[24] Although CLSI and other organizations have established standardized susceptibility testing for molds, the correlation with clinical outcome is variable. The best correlation between antifungal susceptibility testing and efficacy lies with the use of azoles in the treatment of disseminated aspergillosis.[25]

DETERMINATION OF ISOLATE PATHOGENICITY

CASE 62-1, QUESTION 7: *Serratia marcescens* grows from a culture of R.G.'s endotracheal aspirate. How can it be determined whether an isolate represents a true bacterial infection versus colonization or contamination?

A positive culture may represent colonization, contamination, or infection. Colonization indicates that bacteria are present at the site; however, they are not actively causing infection. If the bacterium is determined to be a colonizer, antibacterials are not indicated. Poor sampling techniques or inappropriate handling of specimens can result in contamination. Contamination differs from colonization in

that these isolates are not truly at the site in question and were inadvertently introduced with the handling of the specimen. The *S. marcescens* growing from R.G. could represent infection, colonization, or contamination. If a suction catheter was used to sample R.G.'s endotracheal aspirate, the infecting organism likely would be cultured; however, other nonpathogenic flora would also appear in the culture medium (colonization). Furthermore, if the sample is not handled aseptically by the clinician or the microbiology laboratory, bacterial contamination is possible.

In summary, culture results do not solely identify true pathogens. In R.G., the *Serratia* may be a pathogen, contaminant, or colonizer. Nevertheless, considering the severity of R.G.'s illness and his associated respiratory symptoms, treatment directed against this pathogen is necessary.

ANTIMICROBIAL TOXICITIES

CASE 62-1, QUESTION 8: Considering the positive culture for *Serratia*, his increased respiratory secretions, and a worsening chest radiograph, ventilator-associated pneumonia is likely present. Pending antibacterial susceptibility results, R.G. is supposed to receive an empiric regimen of imipenem-cilastatin and gentamicin. A review of his medical records indicates that R.G. has no known allergies. Are there equally effective, less toxic options for this patient?

Adverse Effects and Toxicities

Before starting antimicrobial therapy, it is important to elicit an accurate drug and allergy history. When the patient has reported "allergy," it is necessary to determine whether the reaction was intolerance, toxicity, or true allergy. For example, gastric intolerance caused by oral doxycycline is common; however, this adverse effect does not represent an allergic manifestation. Although R.G. has no known allergies, neither imipenem nor gentamicin are optimal choices. Imipenem-cilastatin is associated with seizures, particularly

in patients with renal failure and in doses in excess of 50 mg/kg/day. Considering R.G.'s acute onset of renal failure and his history of seizures, other carbapenems, such as meropenem or doripenem, or alternative classes of antibacterials would be preferable. Gentamicin similarly may not be a good choice for R.G. His increased age and declining renal function predispose him to aminoglycoside nephrotoxicity and ototoxicity (cochlear and vestibular).[26] A reasonable recommendation pending susceptibility results would be to discontinue imipenem and gentamicin and treat with meropenem or doripenem with or without a fluoroquinolone. **Table 62-8** lists common antimicrobial adverse effects and toxicities.

Table 62-8
Antimicrobial Adverse Effects and Toxicities

Antibiotics	Side Effects	Comments
β-Lactams (penicillin, cephalosporins, monobactams, carbapenems)	*Allergic:* anaphylaxis, urticaria, serum sickness, rash, fever	Many patients will have "ampicillin rash" or "β-lactam rash" with no cross-reactivity with any other penicillins/β-lactams. Classically maculopapular rash and most commonly observed in patients with concomitant EBV disease. Likelihood of IgE-mediated cross-reactivity between penicillins and cephalosporins <5% (first and second generation) and <3% (third and fourth generation). Most recent data strongly suggest minimal IgE cross-reactivity between penicillins and imipenem/meropenem. No IgE cross-reactivity between aztreonam and penicillins.

Antibiotics	Side Effects	Comments
	Diarrhea	Particularly common with ampicillin, Augmentin, ceftriaxone. Antibiotic-associated colitis can occur with most antimicrobials.
	Hematologic: anemia, thrombocytopenia, antiplatelet activity, hypoprothrombinemia	Hemolytic anemia more common with higher doses. Antiplatelet activity (inhibition of platelet aggregation) most common with the antipseudomonal penicillins and high serum levels of other β-lactams. hypoprothrombinemia more often associated with those cephalosporins with the methyl-tetrazole-thiol side chain (cefamandole, cefotetan). Reaction preventable and reversible with vitamin K
	Hepatitis or biliary sludging	Hepatitis most common with oxacillin. Biliary sludging and stones reported with ceftriaxone
	Phlebitis	
	Seizure activity	Associated with high levels of β-lactams, particularly penicillins and imipenem
	Potassium load	Penicillin G (K^+)
	Sodium load	Piperacillin-tazobactam
	Nephritis	Interstitial nephritis reported for most β-lactams
	Neutropenia	Nafcillin
	Disulfiram reaction	Associated with cephalosporins with methyl-tetrazole-thiol side chain (cefamandole, cefotetan)

Antibiotics	Side Effects	Comments
	Hypotension, nausea	Associated with rapid infusion of imipenem
Aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin)	Nephrotoxicity	Incidence 10%–15%. Generally reversible, usually occurs after 5–7 days of therapy. *Risk factors:* dehydration, age, dose, duration, concurrent nephrotoxins, renal disease
	Ototoxicity	Incidence 1%–5%, often irreversible. Both cochlear and vestibular toxicity occur
	Neuromuscular paralysis	Rare, most common with large doses administered via intraperitoneal instillation or in patients with myasthenia gravis
Macrolides (erythromycin, azithromycin, clarithromycin)	Nausea, vomiting, “burning” stomach, cholestatic jaundice, ototoxicity, prolonged QT interval	Oral administration: azithromycin and clarithromycin associated with less nausea than erythromycin Cholestatic jaundice reported for all erythromycin salts, most common with estolate Ototoxicity most common with high doses in patients with renal or hepatic failure Torsades de Pointes and increased risk of cardiac death associated with increased QT interval
Telithromycin	Hepatotoxicity; upper GI	Severe, sometimes fatal hepatotoxicity associated with telithromycin
Clindamycin	Diarrhea	Most common adverse effect. High association with antibiotic-associated colitis and *Clostridioides difficile*
Tetracyclines (including	Allergic	

Antibiotics	Side Effects	Comments
tigecycline)		
	Photosensitivity	
	Drug interactions	Decreased oral bioavailability with multivalent cations (less so with doxycycline). Similar to that stated in the Quinolones section
	Teeth and bone deposition and discoloration	Avoid in pediatrics (<8 years old), pregnancy, and breast-feeding
	GI	Upper GI predominates
	Hepatitis	Primarily in pregnancy or the elderly
	Vestibular	Associated with minocycline, particularly high doses
Vancomycin	“Red man syndrome”: hypotension, flushing	Associated with rapid infusion of vancomycin. More common with higher doses
	Nephrotoxicity	Reversible nephrotoxicity with high doses or in combination with other nephrotoxins
	Ototoxicity	Only with receipt of concomitant ototoxins such as aminoglycosides
	Phlebitis	Needs large volume dilution
Dalfopristin/quinupristin	Phlebitis	Generally requires central line administration
	Myalgia	Moderate to severe in many patients
	Increased bilirubin	
Daptomycin	Myalgia	Primarily at high doses and reversible

Antibiotics	Side Effects	Comments
Linezolid (tedizolid)	Thrombocytopenia, neutropenia, anemia, MAO inhibition, neuropathy	Bone marrow suppression and neuropathy duration- and dose-dependent with linezolid. Tedizolid may have less association with bone marrow suppression and neuropathy.
Dalbavancin, oritavancin, telavancin	Renal toxicity and prolonged QT with telavancin	
Sulfonamides	GI	Nausea, diarrhea
	Hepatic	Cholestatic hepatitis
	Rash	Exfoliative dermatitis, Stevens–Johnson syndrome. Rash more common in HIV
	Hyperkalemia	Hyperkalemia because of trimethoprim (as a component of trimethoprim-sulfamethoxazole)
	Bone marrow	Neutropenia, thrombocytopenia. More common in HIV
	Kernicterus	Caused by unbound drug in the neonate. Premature liver cannot conjugate bilirubin. Sulfonamide displaces bilirubin from protein, resulting in excessive free bilirubin and kernicterus
Chloramphenicol	Anemia	Idiosyncratic irreversible aplastic anemia (rare). Reversible dose-related anemia
	Gray syndrome	Caused by inability of neonates to conjugate chloramphenicol
Quinolones	GI	Nausea, vomiting, diarrhea

Antibiotics	Side Effects	Comments
	Prolonged QT	Moxifloxacin; possibly all quinolones as a class
	Drug interactions	Decreased oral bioavailability with multivalent cations
	CNS and peripheral neuropathy	Altered mental status, confusion, seizures. Neuropathy can be long term.
	Cartilage toxicity	Toxic in animal model. Despite this toxicity, appears safe in children including patients with cystic fibrosis
	Tendonitis or tendon rupture	Common in elderly, renal failure, concomitant glucocorticoids
	Dysglycemia	Hypo- and hyperglycemia
Antifungals		
Amphotericin B products	Nephrotoxicity	Common. May depend on patient sodium load. Caution with concomitant nephrotoxins (eg, aminoglycosides, cyclosporine)
	Hypokalemia	Predictable. Likely associated with renal tubular excretion of potassium. More common in patients receiving concomitant piperacillin-tazobactam
	Hypomagnesemia	Less commonly observed than hypokalemia
	Anemia	Long-term adverse effect. Similar to anemia of chronic disease
Caspofungin, micafungin, anidulafungin	Mild LFT increase with concomitant cyclosporine	Anidulafungin is reconstituted with alcohol (about the equivalent of a beer)

Antibiotics	Side Effects	Comments
Flucytosine	Neutropenia, thrombocytopenia	Secondary to metabolism of flucytosine to fluorouracil. More commonly observed with flucytosine levels >100 µg/mL. More common in patients with HIV
	Hepatitis	Usually moderate increase in LFT. Rarely clinical hepatitis but higher associations at levels >100 µg/mL
Ketoconazole (fluconazole, isavuconazole, itraconazole, posaconazole, voriconazole)	Drug interactions	Decreased oral bioavailability of ketoconazole tablet, and itraconazole capsules with increased gastric pH. Azoles are CYP450 substrates and also inhibitors of CYP450 3A4 and other CYP isoenzymes. voriconazole most likely to be associated with CYP drug interactions
	Upper GI	Dose-dependent and associated with all azoles
	Hepatitis	Ranges from mild increase in LFTs (AST, ALT) to occasional fatal hepatitis. More likely with voriconazole than other azoles
	Gynecomastia, decreased libido	More common with high-dose ketoconazole (>400 mg/day). Less common with other azoles
	Visual disturbance	Unique to voriconazole, particularly first week of therapy
	Squamous cell carcinoma	Long-term voriconazole
	Periostitis	Long-term voriconazole
Antivirals (Excluding Antiretrovirals and Hepatitis Antivirals)		

Antibiotics	Side Effects	Comments
Acyclovir	Phlebitis	Caused by poor solubility of IV preparation. Reported in 1%–20% of cases
	Renal failure	Low solubility of acyclovir associated with renal failure. Dehydrated patients, as well as rapid infusions, predispose to toxicity
	CNS	1% incidence in AIDS. Increased incidence with doses in excess of 10 mg/kg/day
Cidofovir	Nephrotoxicity	Commonly observed and often severe
Foscarnet	Nephrotoxicity	Occurs in up to 60% of patients. May be prevented with normal saline bolus before dose. Frequent monitoring of renal function imperative
	Mineral and electrolyte abnormalities	Hypo- or hypercalcemia, hypo- and hyperphosphatemia, hypomagnesemia, hypokalemia. Increased risk of cardiomyopathy and seizures
	Anemia	Anemia in 33%; usually manageable with transfusions and discontinuation of foscarnet
	Nausea, vomiting	
Ganciclovir	Neutropenia, thrombocytopenia	Increased incidence in AIDS. Increased incidence with doses in excess of 10 mg/kg/day
	Hepatitis	Usually mild to moderate increase in LFT

Antibiotics	Side Effects	Comments
Letermovir	Drug interactions Bloating, swelling, rapid weight gain, tingling of hands and feet	Substrate of CYP450 and p-glycoprotein
Oseltamivir	Nausea	
Ribavirin	Oral ribavirin: anemia Inhaled ribavirin: bronchospasm Inhaled ribavirin: bronchospasm Environmental concerns	Environmental concerns with inhaled ribavirin stem from the potential safety of the drug and exposure to health care personnel

AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; EBV, Epstein–Barr virus; GI, gastrointestinal; HIV, human immunodeficiency virus; IV, intravenous; LFT, liver function tests; MAO, monoamine oxidase.

Concomitant Disease States

Concomitant disease states should also be considered in the selection of therapy. As discussed, older patients with hearing deficits are poor candidates for potentially ototoxic aminoglycoside therapy. Patients with diabetes or kidney transplant with candidemia may be better treated with fluconazole or an echinocandin rather than nephrotoxic amphotericin. Patients with a preexisting seizure history should not receive imipenem if safer choices are available. In summary, drug toxicity must always be considered in the selection of antimicrobial therapy.

ANTIMICROBIAL COSTS OF THERAPY

CASE 62-1, QUESTION 9: What factors should be included in calculating the cost of R.G.'s antimicrobial therapy?

The true cost of antimicrobial therapy is difficult to quantify.[27] Although acquisition cost traditionally has been the primary factor in the overall cost of therapy, drug administration labor costs (ie, nursing and pharmacy) and the use of IV sets, piggyback bags, and infusion control devices must be included in the analysis. As a result, a drug administered several times daily, such as intravenous penicillin, will incur increased administration costs compared with one that requires once-a-day dosing, such as ceftriaxone.

Some drugs, such as aminoglycosides, with a high potential for toxicity, are associated with additional costs because of pharmacokinetic and laboratory monitoring (eg, aminoglycoside serum concentrations, serum creatinine, and audiometry) that are not required for other agents,[28] such as the third-generation cephalosporins and quinolones. If meropenem with or without ciprofloxacin had been selected for R.G., this therapy would be expected to be associated with relatively few laboratory costs. However, the broad spectrum of activity[29] of these agents, potential for misuse, and development of resistance and superinfection could ultimately result in increased costs, including those to society.

Costs that are difficult to quantitate include those associated with failure of antimicrobial therapy and antimicrobial toxicity. Ineffective or toxic therapy can prolong hospitalization and may require expensive interventions, such as hemodialysis,[28] mechanical ventilation, and ICU admission. The net effect of these latter costs is usually significantly greater than the acquisition and administration costs of antimicrobial therapy.

In summary, determining the true cost of antimicrobial therapy is complex. Acquisition cost, IV bags, infusion controllers, and labor must be incorporated into the analysis. Although they are difficult to estimate, other costs, including because of antibiotic toxicity, superinfection and failure of therapy, should also be considered.

ROUTE OF ADMINISTRATION

Case 62-1, Question 10: The *Serratia* was determined to be susceptible to ciprofloxacin. Oral ciprofloxacin was considered for the treatment of R.G.'s presumed *Serratia* pneumonia, but the IV route was prescribed. Is the selection of the oral route of administration of ciprofloxacin reasonable?

The proper route of antibiotic administration depends on many factors, including the severity of infection, antimicrobial oral bioavailability, and other patient factors. In patients who appear "septic," blood flow often is shunted away from the mesentery and extremities, resulting in unreliable bioavailability from the gastrointestinal (GI) tract and muscles, respectively. Consequently, hemodynamically unstable patients should always receive antimicrobials by the IV route to ensure therapeutic antimicrobial levels. Furthermore, drug interactions with certain oral agents can result in subtherapeutic serum concentrations (eg, reduced bioavailability associated with concomitant quinolone and antacid administration, and decreased absorption of itraconazole with concurrent proton-pump inhibitor [PPI] therapy). Although clinical practice for some diseases states (such as endocarditis and osteomyelitis) has historically required that antibiotics be administered intravenously for the entire duration of therapy (4–6 weeks), a short initial course of IV therapy, followed by oral therapy for the remainder of the treatment is a reasonable option.[30,31] Early switch to oral therapy has potential benefits, including reduced IV catheter infection, greater adherence to the antimicrobial therapy, and increased patient satisfaction and quality of life.

R.G. is clinically septic with a possible *Serratia* pneumonia. Considering his unstable state, the bioavailability of oral ciprofloxacin cannot be guaranteed; thus, he should be treated with IV antimicrobials.

ANTIMICROBIAL DOSING

Case 62-1, Question 11: What dose of IV ciprofloxacin should be given to R.G.? What factors must be taken into account in determining a proper antimicrobial dose?

The choice of antimicrobial dose is based on many factors. **Table 62-9** provides a guide for the dosing of more commonly administered antimicrobials. The appropriate dosage should be based on well-designed trials in the treatment of a specific infection. Patient-specific factors, including weight, site of infection, and route of elimination, must also be considered in dosage selection. The patient's weight is important, particularly for agents with a low therapeutic index (eg, aminoglycosides, liposomal amphotericin, vancomycin); these drugs should be dosed on a milligram per kilogram per day basis. Obesity may require dosing based on an adjusted weight for some antibiotics. Other agents with a more favorable adverse effect profile, such as cephalosporins, are less likely to require weight-specific dosing in most disease states.

Table 62-9
Adult Antimicrobial Dosing Guidelines for Hospitalized Patients (Selected Drugs)[a]

Drug	CrCl >50 mL/minute	CrCl 10–50 mL/minute	CrCl <10 mL/minute (ESRD not on HD)	Dialysis (HD or CRRT)
Acyclovir	*Herpes simplex infections* 5 mg/kg/dose IV every 8 hours	5 mg/kg/dose IV every 12–24 hours	2.5 mg/kg IV every 24 hours	HD: 2.5 mg/kg IV × 1 now; then 2.5 mg/kg every evening (give after HD on HD days) CRRT: 5 mg/kg every 24 hours
	HSV encephalitis/Herpes zoster 10 mg/kg/dose IV every 8 hours	10 mg/kg/dose IV every 12–24 hours	5 mg/kg IV every 24 hours	HD: 5 mg/kg IV ×1 now; then 5 mg/kg every evening (give after HD on HD days) CRRT: 5–10 mg/kg every 12–24 hours
Ampicillin	*Meningitis or endovascular infection* 2 g IV every 4 hours *Uncomplicated infection* 2 g IV every 6 hours	2 g IV every 6 hours	1 g IV every 8–12 hours	HD: 1–2 g IV every 12 hours CRRT: 1–2 g IV every 6 hours
Ampicillin/sulbactam	3 g IV every 6 hours	1.5 g IV every 6 hours	1.5 g IV every 12 hours	HD: 1.5–3 g IV every 12 hours CRRT: 1.5 g IV every 6 hours
Aztreonam	2 g IV every 8 hours	2 g IV every 12 hours	1 g IV every 12 hours	HD: 1 g IV ×1 now; then 1 g every evening (give after HD on HD days) CRRT: 2 g IV every 12 hours
Cefazolin	*Gram negative or complicated gram positive* 2 g IV every 8 hours *Uncomplicated gram positive* 1–2 g IV every 8 hours	1–2 g IV every 12 hours	1 g IV every 24 hours	HD: 2 g after HD only CRRT: 2 g IV every 12 hours
Caspofungin Severe hepatic dysfunction: 70 mg LD, then 35 mg IV daily	LD: 70 mg × 1, then 50 mg every 24 hours Increase maintenance dose to 70 mg when given with phenytoin, rifampin, carbamazepine, dexamethasone, nevirapine, efavirenz	No change	No change	No change
Cefepime *Less severe infections* *Febrile neutropenia, meningitis, pseudomonas infections, patients who are critically ill*	>60 mL/minute 2 g IV every 12 hours 2 g IV every 8 hours	30–60 mL/minute: 2 g IV every 24 hours 2 g IV every 12 hours 10–30 mL/minute: 1 g IV every 24 hours 2 g IV every 24 hours	<10 mL/minute 500 mg IV every 24 hours 1 g IV every 24 hours	HD: 2 g after HD only CRRT: 2 g IV every 12 hours
Ceftazidime	2 g IV every 8 hours	2 g IV every 12–24 hours	500 mg IV every 24 hours	HD: 1 g after HD only CRRT: 2 g IV every 12 hours
Ceftriaxone *Meningitis*: 2 g every 12 hours *Endocarditis and osteomyelitis*: 2 g every 24 hours	1 g IV every 24 hours	No change	No change	No change

Drug	CrCl >50 mL/minute	CrCl 10–50 mL/minute		CrCl <10 mL/minute (ESRD not on HD)	Dialysis (HD or CRRT)
Ciprofloxacin[IV-PO] *Pseudomonas infections* *Severe infections*	400 mg IV every 12 hours 500–750 mg PO every 12 hours 400 mg IV every 8 hours 750 mg PO every 12 hours	30–50 mL/minute No change 250-500 mg PO every 12 hours No change		<30 mL/minute 200–400 mg IV every 24 hours 250–500 mg PO every 24 hours 200–400 mg IV every 12–24 hours 750 mg PO every 24 hours	HD: 400 mg IV every 24 hours or 500 mg PO every 24 hours (give after HD on HD days) CRRT: 400 mg IV every 12 hours
Clindamycin	600–900 mg IV every 8 hours	No change		No change	No change
Daptomycin Not effective in the treatment of pneumonia	4–10 mg/kg IV every 24 hours Dose depends on indication	<30 mL/minute 4–10 mg/kg IV every 48 hours			HD: 4–10 mg/kg IV every 48 hours CRRT: 4–10 mg/kg IV every 48 hours
Doxycycline[IV-PO]	100 mg IV/PO every 12 hours	No change		No change	No change
Ertapenem	1 g IV every 24 hours	<30 mL/minute 500 mg IV every 24 hours			HD: 500 mg every 24 hours CRRT: 500 mg every 24 hours
Ethambutol	15–20 mg/kg PO every 24 hours	<30 mL/minute 15–25 mg/kg three times/week			HD: 15–25 mg/kg three times/week (after HD) CRRT: 15–25 mg/kg three times/week
Fluconazole[IV-PO]	*Oropharyngeal candidiasis* 100 mg every 24 hours *Esophageal candidiasis* 200 mg every 24 hours *Severe infection* Loading dose of 800 mg then 400 mg every 24 hours	50–200 mg IV/PO every 24 hours		50–100 mg IV/PO every 24 hours	HD: 400 mg after HD only CRRT: 400–800 mg every 24 hours
Flucytosine (5FC)	*Meningitis* 25 mg/kg/dose PO every 6 hours	25–50 mL/minute 25 mg/kg/dose PO every 12 hours	10–25 mL/minute 25 mg/kg/dose PO every 24 hours	12.5 mg/kg/dose PO every 24 hours	HD: 12.5–25 mg/kg PO every 24 hours CRRT: 12.5–37.5 mg/kg/dose PO every 12–24 hours
Ganciclovir	>70 mL/minute 5 mg/kg/dose IV every 12 hours	50–69 mL/minute 2.5 mg/kg/dose IV every 12 hours	25–49 mL/minute 2.5 mg/kg IV every 24 hours	10–24 mL/minute 1.25 mg/kg IV every 24 hours	HD: 1.25 mg/kg after HD only CRRT: 2.5 mg/kg every 24 hours
Gentamicin	See Tobramycin	See Tobramycin		See Tobramycin	See Tobramycin
Imipenem	500 mg IV every 6–8 hours max 50 mg/kg/day	500 mg IV every 8 hours		<20 mL/minute 250–500 mg IV every 12 hours	HD: 250 mg IV every 12 hours CRRT: 500 mg IV every 8 hours
Isoniazid	300 mg PO every 24 hours	No change		No change	No change
Levofloxacin[IV-PO] *Urinary tract infection* *Pneumonia* *Pseudomonas infections*	250–500 mg IV/PO every 24 hours 750 mg IV/PO every 24 hours	500 mg ×1, then 250 mg IV/PO every 24 hours 750 mg ×1; then 750 IV/PO every 48 hours		500 mg ×1, then 250 mg IV/PO every 48 hours 750 mg ×1, then 500 mg IV/PO every 48 hours	HD: 500 mg ×1, then 250 mg every 48 hours CRRT: 500 mg ×1, then 250–500 mg every 24 hours

Drug	CrCl >50 mL/minute	CrCl 10–50 mL/minute		CrCl <10 mL/minute (ESRD not on HD)	Dialysis (HD or CRRT)
Linezolid[IV-PO]	600 mg IV/PO every 12 hours	No change		No change	No change
Meropenem *Meningitis, documented or suspected Pseudomonas infections or critically ill*	0.5–1 g IV every 8 hours 2 g IV every 8 hours	25–50 mL/minute 0.5–1 g IV every 12 hours 2 g IV every 12 hours	10–25 mL/minute 0.5 g IV every 12 hours 1 g IV every 12 hours	0.5 g IV every 24 hours 1 g IV every 24 hours	HD: 500 mg IV ×1 now then 500 mg every evening (give after HD on HD days) CRRT: 1 g IV every 12 hours
Metronidazole[IV-PO]	500 mg IV/PO every 8 hours	500 mg IV/PO every 8 hours		500 mg IV/PO every 12 hours ESRD not on HD	500 mg IV/PO every 8 hours
Moxifloxacin[IV-PO]	400 mg IV/PO every 24 hours	No change		No change	No change
Nafcillin *Meningitis, osteomyelitis, endovascular infection*	1–2 g IV every 4–6 hours 2 g IV every 4 hours	No change		No change	No change
Penicillin G *Meningitis, endovascular infection*	2–3 MU IV every 4–6 hours 3–4 MU IV every 4–6 hours	1–2 MU IV every 4–6 hours		1 MU IV every 6 hours	HD: 1 MU IV every 6 hours CRRT: 2 MU IV every 4–6 hours
Piperacillin/-tazobactam (Zosyn) *Documented/suspected Pseudomonas infections*	3.375–4.5 g IV every 6–8 hours 4.5 g every 6 hours for CrCl >20 mL/minute	3.375–4.5 g every 6–8 hours		2.25 g every 8 hours	HD: 2.25 g IV every 8 hours CRRT: 4.5 g IV every 8 hours or 3.375 g IV every 6 hours
Posaconazole Must be administered with high-fat meal or nutritional shake, eg, Ensure *Neutropenia prophylaxis*	400 mg PO every 12 hours or 200 mg PO every 6 hours 200 mg PO every 8 hours	No change		No change	No change
Pyrazinamide	20–25 mg/kg/day PO every 24 hours	<30 mL/minute 25–35 mg/kg three times/week			HD: 25–35 mg/kg three times/week after HD CRRT: 25–35 mg/kg three times/week
Rifampin *Mycobacterial infection* *Endocarditis* *Prosthetic device infection*	600 mg PO every 24 hours 300 mg PO every 8 hours 450 mg PO every 12 hours	No change		No change	No change
Tigecycline Severe hepatic disease: 100 mg IV ×1, then 25 mg IV every 12 hours	100 mg IV × 1, then 50 mg IV every 12 hours	No change		No change	No change
Tobramycin (and gentamicin) *Gram-negative infection* Dose is based on ideal body weight (IBW) except in patients who are obese or those under their IBW. Use actual body weight if patient weight is <IBW. Use adjusted body weight if patient is obese (calculations, see below).	For CrCl >60 mL/minute, not morbidly obese or fluid overloaded, give once-daily regimen: 7 mg/kg/dose IV every 24 hours. For those patients not qualifying for once-daily dosing, see conventional dosing below.				

Drug	CrCl >50 mL/minute		CrCl 10–50 mL/minute		CrCl <10 mL/minute (ESRD not on HD)	Dialysis (HD or CRRT)
For conventional dosing peak and trough levels should be monitored.	>60 mL/minute 1.6 mg/kg IV every 8 hours		40–60 mL/minute 1.2–1.5 mg/kg every 12–24 hours		<20 mL/minute 2 mg/kg loading dose, then follow drug levels	HD: 2 mg/kg IV × 1 then 1 mg/kg IV after HD CRRT: 2 mg/kg IV × 1 then 1.5 mg/kg IV every 24 hours
TMP/SMX[IV-PO] When switching to oral therapy, consider that a single-strength tablet has 80 mg of TMP, a double-strength tablet 160 mg of TMP.	*Systemic GNR infections* 10 mg TMP/kg/day IV divided every 6–12 hours *Pneumocystis pneumonia* 15–20 mg TMP/kg/day IV divided every 6–8 hours		5–7.5 mg TMP/kg/day IV divided every 12–24 hours 10–15 mg TMP/kg/day IV divided every 12–24 hours		2.5–5.0 mg TMP/kg IV every 24 hours 5–10 mg TMP/kg IV every 24 hours	HD: 2.5–5 mg TMP/kg/day every 24 hours CRRT: 5–7.5 mg TMP/kg/day divided every 12–24 hours
Vancomycin *Uncomplicated infections* *Serious infections*	>60 mL/minute 15–20 mg/kg IV every 8–12 hours	40–60 mL/minute 10–15 mg/kg IV every 12–24 hours	20–40 mL/minute 5–10 mg/kg IV every 24 hours	10–20 mL/minute 5–10 mg/kg IV every 24–48 hours	<10 mL/minute 10–15 mg/kg IV loading dose ×1; redose according to serum levels	HD: 15–20 mg/kg load, then 500 mg IV after HD only CRRT: 10–15 mg/kg IV every 24 hours
Round dose to 250 mg, 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g, or 2 g (maximum 2 g/dose). AUC should be calculated using Bayesian-derived monitoring software or hand calculated by using two levels (ideally a peak and trough from the same dosing interval at steady state). If using Bayesian-derived AUC monitoring software, a single level of vancomycin can be taken, regardless of timing (although a trough is preferable). If using hand calculation of AUC, peak levels should be obtained 1–2 hours after infusion and trough levels should be obtained within 30 minutes before the next dose (assuming steady state is achieved). AUC:MIC target is 400–600 m*h/L.						
Voriconazole[IV-PO]	LD = 400 mg every 12 hours × 1 day, then 200 mg every 12 hours (PO)		No change		No change[b]	No change[b]
PO should be used when possible, as oral bioavailability >95%. IV dose: LD = 6 mg/kg/dose every 12 hours × 1 day, then 4 mg/kg/dose every 12 hours.						

CrCl, creatinine clearance; CRRT, continuous renal replacement therapy (assumes an ultrafiltration rate of 2 L/hour with continuous venovenous hemofiltration and an ultrafiltration rate of 1 L/hour and dialysate flow rate of 1 L/hour with continuous venovenous hemodiafiltration and residual native glomerular filtration rate <10 mL/minute); ESRD, end-stage renal disease; GNR, gram-negative rod HD, intermittent (high-flux) hemodialysis (when administering a daily dose with HD, the drug should be administered after the HD session); HSV, herpes simplex virus; IV, intravenous; IV-PO, high oral bioavailability (consider initiating with or switching to PO therapy when patient tolerating orals); LD, loading dose; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, by mouth; SCr, serum creatinine.

[a]Doses are those recommended for systemic infections in hospitalized patients commonly treated with these agents for moderate/severe infections. More mild infection may require decreased doses compared with moderate-to-severe infection. Dosing guidelines may differ in other institutions.

Estimate of renal function using Cockcroft and Gault equation: CrCl (mL/minute) = (140 − age) × Wt (kg)/72 × SCr (mg/dL) (for females multiply by 0.85).

Ideal body weight equation:

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.

Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

Adjusted body weight (consider if >120% IBW): ABW = IBW + 0.4 (actual weight − IBW).

[b]The use of the IV formulation should be avoided in patients with CrCl <50 mL/minute owing to accumulation of IV vehicle and is contraindicated in ESRD and hemodialysis. May require dose adjustment in hepatic dysfunction.

Site of Infection

Different doses are required for different infections. An uncomplicated urinary tract infection requires lower doses considering the high urinary drug concentrations achieved with most renally cleared agents. In contrast, a more serious upper urinary tract infection, such as pyelonephritis, requires increased antibacterial doses to ensure therapeutic drug levels in both tissue and serum.

Anatomic and Physiologic Barriers

Anatomic and physiologic barriers must also be considered in recommending a dosing regimen. For example, penetration into CSF requires high antibacterial doses to ensure adequate drug concentrations at the site of infection.[32] Vitreous humor[33] and the prostate gland[34] are additional examples of sites in which therapeutic antimicrobial concentrations are more difficult to achieve.

Route of Elimination

Route of elimination is another consideration in the dosage calculation for those drugs that are dependent on the kidney for clearance. In general, antimicrobials are eliminated renally or nonrenally (metabolic and/or biliary). Renal function can be estimated via 24-hour urine collection or with equations, such as Cockcroft and Gault[35]:

$$\text{Creatinine clearance} = ([140 - \text{age}] \times [\text{weight in kg}])/(72 \times \text{SCr})$$

Many antimicrobials (eg, most β-lactams) are eliminated by the kidney (Table 62-9). In contrast, ceftriaxone and most antistaphylococcal penicillins (eg, nafcillin, oxacillin, and dicloxacillin) are eliminated both renally and nonrenally. Aminoglycosides, vancomycin, acyclovir, and ganciclovir are cleared primarily by the kidney. Thus, dosage adjustment is recommended for these drugs in patients with renal failure (Table 62-9). Because azithromycin, clindamycin, and metronidazole are primarily eliminated by the liver, no dose reduction is required in renal failure. Using the Cockcroft and Gault equation, R.G.'s age (63 years), weight (154.32 pounds [70 kg]), and current serum creatinine (3.8 mg/dL) result in a calculated creatinine clearance of 14 mL/minute. R.G. normally should receive an IV dosage of ciprofloxacin at 400 mg every 12 hours but because of his reduced kidney function, he needs a lower dose (eg, 200 mg every 12 hours).

(Eq. 62-1)

Although renal function can be approximated with the use of the Cockcroft and Gault equation (or a similar equation), hepatic function is more difficult to evaluate. No standard liver function test (AST, ALT, alkaline phosphatase) has been demonstrated to correlate well with hepatic drug clearance. Some tests, such as PT, INR, and albumin, are markers of hepatic function, but even these tests do not clearly predict drug clearance. Patients receiving hemodialysis or continuous hemofiltration provide additional dosing challenges. Table 62-9 includes dosing recommendations for inpatients receiving hemodialysis or continuous hemofiltration.

Patient Age

It is important to note that most dosing information is derived from a younger, relatively healthy patient population. The newborn and the elderly have a decreased ability to clear drugs; thus, dosages for many agents are lower in neonatal and geriatric patients.

Fever and Inoculum Effect

The impact of other factors on the selection of an antimicrobial dose is less clear. Fever can both increase and decrease blood flow to mesenteric, hepatic, and renal organ systems,[36] and it can either increase or decrease drug clearance. Inoculum effect has been demonstrated when higher concentrations of a bacterial inoculum result in an increase in the MIC.[37] As an example, piperacillin may demonstrate an MIC of 8.0 μg/mL against *P. aeruginosa* at a concentration of 10^5 colony-forming units/mL (CFU/mL); however, at 10^9 CFU/mL, the MIC may increase to 32 to 64 μg/mL. This phenomenon is well recognized, particularly with β-lactamase–producing bacteria treated with β-lactam antimicrobials. The more stable the antimicrobial is to β-lactamase, the less the influence of the inoculum effect. Aminoglycosides, quinolones, and imipenem appear to be less affected by the inoculum effect than β-lactams. The inoculum effect probably is most relevant in the treatment of a bacterial abscess, in which extremely high concentrations of bacteria usually are present. As a result, antimicrobials that are more susceptible to the inoculum effect may require increased drug dosages for optimal outcomes in the treatment of abscesses.

PHARMACOKINETICS AND PHARMACODYNAMICS

Case 62-1, Question 12: R.G.'s respiratory status remains unchanged; thus, the ciprofloxacin is discontinued and cefepime and gentamicin are started empirically. The use of a prolonged 3-hour IV infusion of cefepime is being considered in R.G. In addition, the use of single daily dosing of gentamicin is being discussed. What is the rationale for these approaches, and would either be advantageous for R.G.?

β-Lactams, such as cefepime, are not associated with increased bacterial killing with increasing drug concentrations. Pharmacodynamic activity with β-lactams best correlates with the duration of time that antimicrobial levels are maintained above the

MIC.[38] The animal model suggests that β-lactam antimicrobials should be dosed such that their serum levels exceed the MIC of the pathogen as long as possible.[38] This observation appears to be most important in the neutropenic model, in which the use of a constant infusion more reliably inhibits bacterial growth compared with traditional intermittent dosing. An additional benefit of the use of constant infusions of β-lactams is that smaller daily doses appear to be as effective as higher doses administered intermittently. Other than this latter outcome, it is unclear, however, whether constant infusions have any distinct advantages or disadvantages compared with usual dosing of β-lactams. The efficacy of quinolones, vancomycin, and daptomycin best correlates with the peak plasma concentration to MIC ratio, or area under the curve (AUC) to MIC ratio.[38] In light of this pharmacodynamic principle, it is possible that ciprofloxacin was underdosed in this patient and contributed to the therapeutic failure, particularly if the MIC was in the upper range of susceptibility for this agent.

In the past, aminoglycosides were administered every 8 to 12 hours to achieve optimal peak serum levels (ie, 5–8 μg/mL, for gentamicin) in the treatment of serious gram-negative infection.[39],[40] With this past dosing strategy, gentamicin troughs of >2 μg/mL resulted in an increased risk for nephrotoxicity.[40],[41] The correlation of serum levels with both efficacy and toxicity has been questioned.[26] For vancomycin, troughs of 10 to 20 μg/mL have been traditionally recommended[42]; however, current recommendations suggest direct monitoring and calculation of the AUC via Bayesian pharmacokinetic software to achieve an AUC:MIC ratio of 400 to 600 μg/L.[43]

Several antimicrobials (eg, aminoglycosides) have been associated with a pharmacodynamic phenomenon known as a post-antibiotic effect (PAE). PAE is delayed regrowth of bacteria after exposure to an antibiotic (ie, continued suppression of normal growth in the absence of antibiotic levels above the MIC of the organism).[38],[44] As an example, if *P. aeruginosa* is cultured in broth, it will multiply to a concentration of 10^9 CFU/mL. If piperacillin is added in a concentration above the MIC for the organism, a reduction in the bacterial concentration is observed. As described, a β-lactam

antibiotic should be present in concentrations above the MIC to optimize its time-dependent killing. When piperacillin is removed from the broth, immediate bacterial growth takes place. If the above experiment is repeated with gentamicin, a reduction in bacterial CFU is observed. In contrast to that observed with β-lactam antibiotics, if the gentamicin is removed from the system, a lag period of 2 to 6 hours takes place before characteristic bacterial growth occurs. This lag period is defined as the PAE. A PAE has also been observed with quinolones and imipenem against gram-negative bacteria. Although most β-lactam antibiotics, such as antipseudomonal penicillins or cephalosporins, do not exhibit PAE against gram-negative organisms, PAE has been demonstrated in β-lactams against gram-positive pathogens such as *S. aureus.*

Once-Daily Dosing of Aminoglycosides

Because of PAE and other pharmacodynamic factors, certain antimicrobials may be dosed less frequently. The greatest clinical experience has been with the aminoglycosides in the treatment of gram-negative infection.[45],[46] Earlier data suggested that the maximal aminoglycoside peak level to MIC ratio correlates well with clinical response. Thus, the higher the achievable peak, the greater likelihood of a favorable outcome. Consequently, greater, less frequent doses of aminoglycosides should work at least as well as the more traditional lower, more frequent doses. Once-daily dosing of aminoglycosides in the treatment of gram-negative infection is as efficacious as traditional multiple daily dosing.[26]

Single daily dosing of aminoglycosides (ie, 5–6 mg/kg IV gentamicin every 24 hours) has been investigated primarily in patients with normal renal function, and few patients who are critically ill have been treated with this nontraditional regimen. Thus, patients in septic shock are less clear candidates for once-daily dosing. The utility and proper timing of serum aminoglycoside concentrations and association with clinical outcomes are debatable with nontraditional once-daily aminoglycosides.

In summary, the use of a prolonged IV infusion of cefepime is possible in R.G., but the benefit of this mode of administration is not clear. Considering the severity of R.G.'s infection and his elevated serum creatinine level, he is not a candidate for single daily dosing of aminoglycosides independent of the aminoglycoside-associated PAE, his current renal function requires a reduced gentamicin dose to treat his infection.

Antimicrobial Protein Binding

Case 62-1, Question 13: Ceftriaxone (Rocephin), rather than cefepime, is being considered for the treatment of R.G.'s infection. Ceftriaxone is more highly protein-bound than cefepime. Why is protein binding important in the selection of therapy?

Free (ie, unbound) rather than total drug levels best correlate with antimicrobial activity,[47] and the degree of protein binding may have important clinical consequences in some patients. Chambers et al[48] reported treatment failures with the highly protein-bound cefonicid (98% protein-bound) in patients with endocarditis caused by *S. aureus.* Despite achievable serum drug concentrations well above the MIC of the organism, breakthrough bacteremia occurred in three of four patients. Although total drug concentrations greatly exceeded the MIC of the pathogen, free concentrations were consistently below the level necessary to inhibit bacterial growth. Similar experiences have been reported with daptomycin (90%–93% protein-bound).[49] Thus, clinical cure appears to be more likely if unbound antibiotic concentrations exceed the MIC of the infecting organism. For β-lactams, the longer free unbound drug levels remain above the MIC, the likely better outcome. Although ceftriaxone is 85% to 90% protein-bound, the free concentrations probably remain far above the MIC throughout the entire dosing interval to optimally treat the *Serratia* in R.G.

ANTIMICROBIAL FAILURE

Antibiotic-Specific Factors

CASE 62-1, QUESTION 14: Despite "appropriate" treatment, R.G. is unresponsive to antimicrobial therapy. What antibiotic-specific factors may contribute to "antimicrobial failure"?

Antimicrobials may fail for various reasons, including patient-specific host factors, drug or dosage selection, and concomitant disease states. One of the most common reasons for antimicrobial failure is drug resistance.[50–52] Several clinically important pathogens have been associated with the emergence of resistance during the past decade, including *M. tuberculosis*,[53] enterococci,[54] gram-negative rods,[50] *S. aureus*,[55] *S. pneumoniae*,[56] and others. Of particular concern is the isolation of glycopeptide-resistant *S. aureus*[55] and multidrug-resistant *Acinetobacter* and *Pseudomonas.*[57] Development of resistance during therapy, although less common than initial intrinsic resistance, may also account for failure to respond to therapy. Organisms that produce extended-spectrum β-lactamase or amp C β-lactamases may be unresponsive to β-lactam therapy despite associated in vitro susceptibility.[58]

Superinfection may also play a role in the unsuccessful treatment of infection. Superinfection has taken place when a new pathogen resistant to the current antimicrobial regimen is isolated. If R.G.'s ceftriaxone-treated *Serratia* pneumonia subsequently worsens and a tracheal aspirate returns positive for *P. aeruginosa*, then supercolonization and, perhaps, superinfection have occurred.

Combination Therapy

Most infections can be treated with monotherapy (eg, an *E. coli* wound infection is treatable with a cephalosporin). Some infections, however, require two-drug therapy, including most cases of

enterococcal endocarditis and perhaps certain *P. aeruginosa* infections. Hilf et al studied 200 consecutive patients with *P. aeruginosa* bacteremia and demonstrated a 47% mortality in those receiving monotherapy (antipseudomonal β-lactam or aminoglycoside) versus 27% in those in whom two-drug therapy was used.[59] Thus, monotherapy appeared to contribute to antimicrobial failure in this specific study.

In contrast to the findings of the previous trial, almost all later investigations do not support the use of two drugs over monotherapy in the treatment of serious gram-negative infection, including *P. aeruginosa*.[60–62] An exception to this rule is bacteremia caused by *P. aeruginosa* in patients with neutropenia.

If two antimicrobials are used in the treatment of infection, one of three sequelae will result: indifference, synergism, or antagonism.[63] Indifference occurs when the antimicrobial effect of drug A plus that of drug B equals the anticipated sum activity of the two drugs. Although numerous definitions exist, synergism generally occurs when the addition of drug A to drug B results in a total antibiotic activity greater than the expected sum of the two agents. Antagonism occurs if the addition of drug A to drug B results in a combined activity less than the sum of drug A plus drug B. An example of antagonism is the combination of imipenem with a less β-lactamase–stable β-lactam, such as piperacillin.[64] If *P. aeruginosa* is exposed to imipenem and piperacillin, the imipenem induces the bacteria to increase its production of β-lactamase. Imipenem is remarkably β-lactamase–stable and is not degraded by this β-lactamase. In direct contrast, piperacillin is easily degraded by the β-lactamase. Thus, imipenem antagonizes the activity of piperacillin. Antagonism is not unique to antibacterials; itraconazole may antagonize amphotericin B in the treatment of certain fungal infections.[65]

Pharmacologic Factors

Case 62-1, Question 15: What pharmacologic or pharmaceutical factors can lead to failure of therapy?

Subtherapeutic dosing regimens are likely for agents with a low therapeutic index, such as the aminoglycosides. For example, a serious gram-negative pneumonia may not respond to aminoglycoside therapy with peak gentamicin serum levels of only 3 to 4 µg/mL.[26],[39] Considering that only 20% to 30% of the aminoglycoside penetrates from serum into bronchial secretions, only 0.5 to 1.0 µg/mL may exist at the site of infection,[66] a likely inadequate level to treat pneumonia. Another example of dosing contributing to antimicrobial failure centers on the lack of use of loading doses. Aminoglycosides or vancomycin regimens should be initiated with a loading dose, particularly in patients with renal failure. If the clinician neglects to use a loading dose, it may take several days before a therapeutic level is achieved. As described, another potential etiology for subtherapeutic antimicrobial levels and potential drug failure is reduced oral absorption because of drug interactions (eg, concomitant oral ciprofloxacin with antacids or iron).

An emerging problem relates to the use of vancomycin in the treatment of serious methicillin-resistant *S. aureus* (MRSA) infection. By CLSI standards, MRSA isolate with an MIC of 2 µg/mL is considered susceptible. Current vancomycin dosing schemes should achieve an AUC:MIC ratio of ≥400 to ensure maximal efficacy. However, similar patient outcomes have been observed with MRSA isolates with a vancomycin MIC of either ≥1.5 µg/mL or <1.5 µg/mL. Variability in susceptibility testing methods and documented failures with increased MICs[67] have led to the most current vancomycin guidelines recommending the use of alternative agents if the vancomycin MIC is ≥2 mg/L for MRSA isolates.[43] As described, the site of infection could also contribute to antimicrobial failure. Most antimicrobials concentrate in the urine, resulting in therapeutic levels even with receipt of low doses. However, in some infections, such as meningitis, prostatitis, and osteomyelitis, antimicrobial penetration to

the site of infection may be inadequate. Agents that penetrate well into these sites are associated with a more favorable outcome.

Another potential reason for antimicrobial failure is inadequate therapy duration. A female with a first-time uncomplicated cystitis may respond adequately to a 3-day course of an antibiotic. In contrast, patients with recurrent urinary tract infections are not candidates for this length of therapy, and failure is more likely with only 3 days of therapy.

Host Factors

Case 62-1, Question 16: What host factors may contribute to the failure of antimicrobial therapy?

Several host factors may limit the ability of an antibiotic to cure infection. Infection of prosthetic material (eg, IV catheters, orthopedic prostheses, mechanical cardiac valves, and vascular grafts) is difficult to eradicate without removal of the hardware. In most cases, surgical intervention is required for successful resolution of the infection. Consequently, to optimally treat R.G.'s IV catheter infection, removal of his central intravenous catheter should take place. Similar to infected prostheses, large, undrained abscesses are difficult, if not impossible, to treat with antimicrobial therapy. Such infections generally require surgical drainage for successful outcome.

Diabetic foot ulcer–associated cellulitis may not respond adequately to antimicrobial therapy. Reasons for antimicrobial failure in patients with diabetes include poor wound healing and reduced delivery of antibiotics to the infection site.

Immune status, particularly neutropenia or lymphocytopenia, can also influence infection treatment. Profoundly patients with neutropenia with disseminated *Aspergillus* infections are unlikely to respond to even the most appropriate antifungal therapy. Similarly, eradication of opportunistic infections (eg, because of cytomegalovirus, atypical mycobacteria, and cryptococci) in patients

with HIV/AIDS with extremely low CD4 lymphocyte counts, is difficult.

Once these factors have been eliminated as causes for antimicrobial failure, noninfectious sources (eg, malignancy, autoimmune disease, drug fever, as discussed) must be ruled out in the treatment of presumed and documented infection.

CASE 62-1, QUESTION 17: Other than initiation of adequate antimicrobial therapy, what adjunct measures can be considered in this patient with septic shock?

The 2016 Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock consultants developed key recommendations toward the early goal-directed resuscitation of the patient with sepsis.[68] These recommendations include the use of "sepsis bundles" (ie, multiple interventions taking place at the same time). Recommended key adjuncts include administration of broad-spectrum antibiotics within 1 hour of diagnosis of septic shock, administration of either crystalloid or colloid fluid resuscitation, and norepinephrine or dopamine to maintain mean arterial pressure of at least 65 mm Hg. In addition, stress-dose steroid therapy can be given to those patients whose BP is poorly responsive to fluid resuscitation and vasopressors. Although improved survival might be expected with adherence to such guidelines, the results have been mixed. Performance improvement programs have shown increased adherence to resuscitation and management sepsis bundles and reduced mortality in patients with sepsis, severe sepsis, or septic shock.[69] In contrast, in patients with early-identified septic shock who received intravenous antibiotics and adequate fluid resuscitation, an early, strict, goal-directed hemodynamic management protocol did not result in an improvement in outcomes.[70]

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840–851. (3)

Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(1):1–12. (50)

Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: the evolution in definition, pathophysiology, and management. *SAGE Open Med*. 2019;7:205031211983504. doi:10.1177/2050312119835043 (1)

Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(5):625–663. (12)

Horowitz HW. Fever of unknown origin or fever of too many origins? *N Engl J Med*. 2013;368(3):197–199. (10)

Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. *JAMA*. 2014;312(15):1552–1564. (67)

Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45–e67. doi:10.1164/rccm.201908-1581S (15)

Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and pharmacodynamic principles of anti-infective dosing. *Clin Ther*. 2016;38(9):1930–1947. doi:10.1016/j.clinthera.2016.06.015 (38)

Pepper DJ, Sun J, Rhee C, et al. Procalcitonin-guided antibiotic discontinuation and mortality in critically ill adults: a systematic review and meta-analysis. *Chest*. 2019;155(6):1109–1118. doi:10.1016/j.chest.2018.12.029 (4)

Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Intensive Care Med*. 2017;43(3):304–377. doi:10.1007/s00134-017-4683-6 (68)

Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System

Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864. doi:10.1093/ajhp/zxaa036 (43)

Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America [published correction appears in *Clin Infect Dis*. 2010;50(12):1695]. *Clin Infect Dis*. 2010;50(2):133–164. (13)

Weisfelt M, de Gans J, van de Beek D. Bacterial meningitis: a review of effective pharmacotherapy. *Expert Opin Pharmacother*. 2007;8(10):1493–1504. (32)

COMPLETE REFERENCES CHAPTER 62 PRINCIPLES OF INFECTIOUS DISEASES

1. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: the evolution in definition, pathophysiology, and management. *SAGE Open Med*. 2019;7:2050312119835043. doi:10.1177/2050312119835043
2. Lee WL, Slutsky AS. Sepsis and endothelial permeability. *N Engl J Med*. 2010;363(7):689–691.
3. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840–851.
4. Pepper DJ, Sun J, Rhee C, et al. Procalcitonin-guided antibiotic discontinuation and mortality in critically ill adults: a systematic review and meta-analysis. *Chest*. 2019;155(6):1109–1118. doi:10.1016/j.chest.2018.12.029
5. Máca J, Jor O, Holub M, et al. Past and present ARDS mortality rates: a systematic review. *Respir Care.* 2017;62(1):113–122. doi:10.4187/respcare.0471
6. Zambon M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest*. 2008;133(5):1120–1127.
7. Jarrin I, Sellier P, Lopes A, et al. Etiologies and management of aseptic meningitis in patients admitted to an internal medicine department. *Medicine (Baltimore)*. 2016;95(2):e2372. doi:10.1097/MD.0000000000002372
8. Shukla B, Aguilera EA, Salazar L, Wootton SH, Kaewpoowat Q, Hasbun R. Aseptic meningitis in adults and children: diagnostic and management challenges. *J Clin Virol.* 2017;94:110–114. doi:10.1016/j.jcv.2017.07.016
9. Hayakawa K, Ramasamy B, Chandrasekar PH. Fever of unknown origin: an evidence-based review. *Am J Med Sci*. 2012;344(4):307–316.

10. Horowitz HW. Fever of unknown origin or fever of too many origins? *N Engl J Med.* 2013;368(3):197–199.
11. Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010;30(1):57–69.
12. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(5):625–663.
13. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America [published correction appears in *Clin Infect Dis*. 2010;50(12):1695]. *Clin Infect Dis*. 2010;50(2):133–164.
14. Chalmers JD, Rother C, Salih W, Ewig S. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. *Clin Infect Dis*. 2014;58(3):330–339.
15. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45–e67. doi:10.1164/rccm.201908-1581S
16. Chaplin S. COVID-19: a brief history and treatments in development. *Prescriber*. 2020;31(5):23–28. doi:10.1002/psb.1843
17. Chakraborty I, Maity P. COVID-19 outbreak: migration, effects on society, global environment and prevention. *Sci Total Environ*. 2020;728:138882. doi:10.1016/j.scitotenv.2020.138882
18. Centers for Disease Control and Prevention. COVID-19 information for specific groups of people. Published February 11, 2020. http://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html
19. Centers for Disease Control and Prevention. Symptoms of COVID-19. Published May 13, 2020. http://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html
20. Bennett JE, Dolin R, Blaster MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019.
21. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*. 30th ed. CLSI Document M100-S25. CLSI; 2020.
22. Centers for Disease Control and Prevention. Overview of testing for SARS-CoV-2, the virus that causes COVID-19. Published February 11, 2020. http://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html
23. Scheutz AN. Antimicrobial resistance and susceptibility testing of anaerobic bacteria. *Clin Infect Dis*. 2014;59(5):698–705.

24. Berkow EL, Lockhart SR, Ostrosky-Zeichner L. Antifungal susceptibility testing: current approaches. *Clin Microbiol Rev*. 2020;33(3):e00069-19. doi:10.1128/CMR.00069-19
25. Pfaller MA, Diekema DJ, Ghannoum MA, et al. Wild-type MIC distribution and epidemiological cutoff values for *Aspergillus fumigatus* and three triazoles as determined by the Clinical and Laboratory Standards Institute broth microdilution methods. *J Clin Microbiol*. 2009;47(10):3142–3146.
26. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. *Clin Infect Dis*. 2007;45(6):753–760.
27. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis*. 2006;42(suppl 2):S82–S89.
28. Bhavnani SM, Prakhya A, Hammel JP, Ambrose PG. Cost-effectiveness of daptomycin versus vancomycin and gentamicin for patients with methicillin resistant *Staphylococcus aureus* bacteremia and/or endocarditis. *Clin Infect Dis*. 2009;49(5):691–698.
29. Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46(2):155–164.
30. Li HK, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med*. 2019;380(5):425–436. doi:10.1056/NEJMoa1710926
31. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med*. 2018;380(5):415–424. doi:10.1056/NEJMoa1808312
32. Weisfelt M, de Gans J, van de Beek D. Bacterial meningitis: a review of effective pharmacotherapy. *Expert Opin Pharmacother*. 2007;8(10):1493–1504.
33. López-Cabezas C, Muner DS, Massa MR, Mensa Pueyo JM. Antibiotics in endophthalmitis: microbiological and pharmacokinetic considerations. *Curr Clin Pharmacol*. 2010;5(1):47–54.
34. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. *Clin Infect Dis*. 2010;50(12):1641–1652.
35. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
36. Mackowiak PA. Influence of fever on pharmacokinetics. *Rev Infect Dis*. 1989;11(5):804–807.
37. Brook I. Inoculum effect. *Rev Infect Dis*. 1989;11(3):361–368.
38. Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and pharmacodynamic principles of anti-infective dosing. *Clin Ther*. 2016;38(9):1930–1947. doi:10.1016/j.clinthera.2016.06.015

39. Moore RD, Smith CR, Lietman PS. Association of aminoglycoside levels with therapeutic outcome in gram-negative pneumonia. *Am J Med*. 1984;77(4):657–662.
40. Mattie H, Craig WA, Pechère JC. Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother*. 1989;24(3):281–293.
41. Matzke GR, Lucarotti RL, Shapiro HS. Controlled comparison of gentamicin and tobramycin nephrotoxicity. *Am J Nephrol*. 1983;3(1):11–17.
42. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-system Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis*. 2009;49(3):325–327.
43. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-system Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864. doi:10.1093/ajhp/zxaa036
44. Pea F, Viale P. The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? *Clin Infect Dis*. 2006;42(12):1764–1771.
45. Hatala R, Dinh TT, Cook DJ. Single daily dosing of aminoglycosides in immunocompromised adults: a systematic review. *Clin Infect Dis*. 1997;24(5):810–815.
46. Ferriols-Lisart R, Alos-Alminana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. *Am J Health Syst Pharm*. 1996;53(10):1141–1150.
47. Schmidt S, Röck K, Sahre M, et al. Effect of protein binding on the pharmacological activity of highly bound antibiotics. *Antimicrob Agents Chemother*. 2008;52(11):3994–4000.
48. Chambers HF, Mills J, Drake TA, Sande MA. Failure of a once-daily regimen of cefonicid for treatment of endocarditis due to *Staphylococcus aureus*. *Rev Infect Dis*. 1984;6(suppl 4):S870–S874.
49. Schwartz BS, Ngo PD, Guglielmo BJ. Daptomycin treatment failure for vancomycin-resistant *Enterococcus faecium* infective endocarditis: impact of protein binding? *Ann Pharmacother*. 2008;42(2):289–290.
50. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(1):1–12.
51. Giamarellou H, Poulakou G. Multidrug-resistant gram negative infections: what are the treatment options? *Drugs*. 2009;69(14):1879–1901.

52. Qureshi ZA, Hittle LE, O'Hara JA, et al. Colistin-resistant *Acinetobacter baumanii: beyond carbapenem resistance*. *Clin Infect Dis*. 2015;60(9):1295–1303.
53. Jassal M, Bishai WR. Extensively drug-resistant tuberculosis. *Lancet Infect Dis*. 2009;9(1):19–30.
54. Reik R, Tenover FC, Klein E, McDonald LC. The burden of vancomycin-resistant enterococcal infections in US hospitals, 2003 to 2004. *Diagn Microbiol Infect Dis*. 2008;62(1):81–85.
55. Sievert DM, Rudrik JT, Patel JB, McDonald LC, Wilkins MJ, Hageman JC. Vancomycin-resistant *Staphylococcus aureus* in the United States, 2002–2006. *Clin Infect Dis*. 2008;46(5):668–674.
56. Richter SS, Heilmann KP, Dohrn CL, Riahi F, Beekmann SE, Doern GV. Changing epidemiology of antimicrobial resistant *Streptococcus pneumoniae* in the United States, 2004–2005. *Clin Infect Dis*. 2009;48(3):e23–e33.
57. Zavascki AP, Carvalhaes CG, Picão RC, Gales AC. Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: resistance mechanisms and implications for therapy. *Expert Rev Anti Infect Ther*. 2010;8(1):71–93.
58. Yang K, Guglielmo BJ. Diagnosis and treatment of extended-spectrum and AmpC ß-lactamase-producing organisms. *Ann Pharmacother*. 2007;41(9): 1427–1435.
59. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. *Am J Med*. 1989;87(5):540–546.
60. Paul M, Leibovici L. Combination antimicrobial treatment versus monotherapy: the contribution of meta-analyses. *Infect Dis Clin North Am*. 2009;23(2):277–293.
61. Leibovici L, Vidal L, Paul M. Aminoglycoside drugs in clinical practice: an evidence-based approach. *J Antimicrob Chemother*. 2009;63(2):246–251.
62. Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al. Optimal management therapy for *Pseudomonas aeruginosa*–ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. *Crit Care Med*. 2007;35(8):1888–1895.
63. Fantin B, Carbon C. In vivo antibiotic synergism: contribution of animal models. *Antimicrob Agents Chemother*. 1992;36(5):907–912.
64. Bertram MA, Young LS. Imipenem antagonism of the in vitro activity of piperacillin against Pseudomonas aeruginosa. *Antimicrob Agents Chemother*. 1984;26(2):272–274.
65. Sugar AM, Liu XP. Interactions of itraconazole with amphotericin B in the treatment of murine invasive candidiasis. *J Infect Dis*. 1998;177(6):1660–1663.
66. Bergogne-Berezin E. New concepts in the pulmonary disposition of antibiotics. *Pulm Pharmacol*. 1995;8(2–3):65–81.

67. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. *JAMA*. 2014;312(15):1552–1564.
68. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Intensive Care Med*. 2017;43(3):304–377. doi:10.1007/s00134-017-4683-6
69. Damiani E, Donati A, Serafini G, et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. *PLoS One*. 2015;10(5):e0125827. doi:10.1371/journal.pone.0125827
70. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372(14):1301–1311.

63

Antimicrobial Prophylaxis for Surgical Procedures

Daniel J. G. Thirion

CORE PRINCIPLES		CHAPTER CASES
1	Assessment of the risk of infection is based on patient and procedure risk factors.	**Case 63-1 (Question 1)**
2	Surgical antibiotic prophylaxis is indicated for patients at high risk for infection or in those at high risk for complications from postoperative infection. A contaminated wound requires presumptive therapy and an infected wound requires empiric therapy.	**Case 63-2 (Question 1)** **Case 63-7 (Question 1)**
3	The choice of prophylactic agent is based on the most likely pathogen associated with the surgical site infection. Institutional patterns of	**Case 63-2 (Question 2)** **Case 63-3 (Questions 1, 2)**

	pathogens, their resistance profiles, and antibiotic profiles impact agent selection.	**Case 63-4 (Question 1)** **Case 63-5 (Question 1)**
4	To maximize the benefit of prophylaxis, antibiotic administration should be completed in the 1 hour before incision to achieve adequate drug levels at the surgical site.	**Case 63-5 (Question 2)** **Case 63-8 (Question 1)**
5	The optimal dose for antimicrobials is based on weight, volume of distribution, and clearance rate.	**Case 63-2 (Question 3)**
6	Intravenous administration is most commonly used. Coadministration of an oral regimen is recommended in colorectal surgery.	**Case 63-6 (Question 3)**
7	Antimicrobials with shorter half-lives may require administration of an additional intraoperative dose in prolonged surgical cases.	**Case 63-5 (Question 3) Case 63-6 (Question 2)**
8	Single-dose preoperative prophylaxis is sufficient for most surgical procedures.	**Case 63-6 (Questions 1, 2)** **Case 63-8 (Question 1)**
9	Continuation of postoperative prophylaxis for up to 24 hours in cardiac surgery has been recommended by some professional organizations.	**Case 63-7 (Question 1)**
10	Continuation of prophylaxis beyond these time frames is not associated with improved outcomes and increases the	**Case 63-8 (Question 2)**

	risk of superinfections, emergence of resistance, adverse effects, and cost.	
11	Surgical site infections are classified as superficial or deep incisional and usually occur within 30 days of the surgical procedure. Deep organ or space infections can occur up to several months after surgery and up to a year after implantation of the prosthetic material.	**Case 63-9 (Question 1)**
12	Continuous quality improvement is critical in the prevention of surgical infection and should be overseen by a multidisciplinary team.	**Case 63-10 (Question 1)**

INTRODUCTION

Surgical site infection (SSI) occurs when a pathogenic organism multiplies in a surgical wound, leading to local and sometimes systemic signs and symptoms. They are among the most common health care–associated infections.[1,2] In developed countries, SSIs complicate surgical procedures in about 1% to 3% of cases but can be as high as 10%, depending on the surgical procedure and the patient.[2–4] In developing countries, infections occur in 6% to 15% of procedures, with data quality depending on the presence of postdischarge follow-up.[5] They put patients at risk for death, increase morbidity, extend the duration of hospitalization,[6,7] and are among the most expensive conditions encountered in U.S. hospitals,[8] associated with an estimated annual cost of $3.5 billion to $10 billion.[9]

Risk Factors for Infection and Implicated Pathogens

Risk factors for SSIs can be classified according to procedure-specific factors and patient characteristics.[7],[10],[11] Procedure-specific factors such as the surgeon's experience and technique, the duration of the procedure, and the operating room (OR) environment have an important influence on SSI rates (**Table 63-1**). The risk of SSI is influenced by host factors such as extremes of age, obesity, tobacco use, malnutrition, and comorbid states, including diabetes mellitus, glycemic control in patients with diabetes, remote infection, ischemia, oxygenation and body temperature during the procedure, colonization with microorganisms, immune status, and immunosuppressive therapy.[12]

Table 63-1
National Research Council Wound Classification

	Classification	Criteria	Infection Rate (%) Without Antibiotic Prophylaxis	Infection Rate (%) With Antibiotic Prophylaxis
I	Clean	No acute inflammation or entry into GI, respiratory, GU, or biliary tracts; no break in aseptic technique occurs; wounds primarily closed	>5	0.8
II	Clean-contaminated	Elective, controlled opening of GI, respiratory, biliary, or GU tracts without significant spillage; clean wounds with a major break in sterile technique	>10	1.3
III	Contaminated	Penetrating trauma (<4 hours old); major technique break or major spillage from GI tract; acute, nonpurulent inflammation	15–20	10.2
IV	Dirty	Penetrating trauma (>4 hours old); purulence or abscess (active infectious process); preoperative perforation of viscera	30–100	Therapeutic antibiotics

GI, gastrointestinal; GU, genitourinary.

Adapted with permission from Berard F, Gandon J. Postoperative wound infections: the influence of ultraviolet irradiation of the operating room and of various other factors. *Ann Surg*. 1964;160(suppl 2):1–192.

The likelihood of the development of an SSI is related to the degree of bacterial contamination during surgery, the virulence of the infecting organism, and host defenses.[7] Bacterial contamination can occur from exogenous sources (eg, the operative team, instruments, airborne organisms) or from endogenous sources (eg, the patient's

microflora of the skin, respiratory, genitourinary, or gastrointestinal [GI] tract).[11] Microbial flora of the skin from the point of entry and manipulation of colonized sites such as the GI tract are the most common causes of SSIs. *Staphylococcus aureus* is the leading causing pathogen, followed by *Escherichia coli*, *Enterococcus faecalis*, and coagulase-negative staphylococci.[13] Implicated pathogens vary according to surgical site. *E. coli* is the most common pathogen associated with abdominal surgical infection, whereas *S. aureus* is commonly associated with cardiac, orthopedic, and obstetric/gynecologic surgical infections and coagulase-negative staphylococci is often associated with transplant surgical infection.[13] Fungal infections are especially of concern in patients with risk factors (ie, immunosuppression). *Candida* species are the predominant fungi causing SSIs in solid organ transplant recipients.[14,15] Less frequently, *Aspergillus* species have been associated with infections following lung transplantation.[15] **Tables 63-2** and **63-3** list pathogens commonly associated with specific surgical procedures.[12,13]

Table 63-2
Suggested Prophylactic Antimicrobial Regimens for Clean Surgical Procedures

Procedure	Predominant Organisms	Recommended Agent(s)[a,b,c,d]	Alternative Agents[a,b]
Neurosurgery			
Craniotomy and cerebrospinal fluid–shunting procedures and implantation of intrathecal pumps	*Staphylococcus aureus*, coagulase-negative staphylococci, *Propionibacterium acnes*	Cefazolin	Clindamycin, vancomycin
Ophthalmic Surgery			
Cataract procedures	Coagulase-negative staphylococci	Neomycin–polymyxin B–gramicidin, gatifloxacin, or moxifloxacin[d,e]	None
Cardiac Surgery			
All with sternotomy, cardiopulmonary bypass, pacemaker, and automated defibrillator placement	*S. aureus*, coagulase-negative staphylococci, gram-negative bacilli	Cefazolin	Cefuroxime, clindamycin, vancomycin
Vascular Surgery			
Vascular (aortic resection, groin incision, prosthesis)	*S. aureus*, coagulase-negative staphylococci, gram-negative enterics	Cefazolin	Clindamycin, vancomycin
Orthopedic Surgery			
Spinal procedure, total joint replacement, internal fixation of fractures	*S. aureus*, coagulase-negative staphylococci, enterococci, gram-negative bacilli	Cefazolin	Clindamycin, vancomycin
Plastic Surgery			
Tissue transplantation and skin grafts and flaps	*S. aureus*, other staphylococci, streptococci, gram-negative enterics	Cefazolin, ampicillin–sulbactam	Clindamycin, vancomycin

[a]Dosing of antibiotics is ampicillin–sulbactam 3 g, cefazolin 2 g in patients weighing up to 264 pounds (120 kg) and 3 g if weighing >264.55 pounds (120 kg), cefuroxime 1.5 g, cefoxitin 2 g, ciprofloxacin 400 mg, clindamycin 900 mg, gentamicin 5 mg/kg based on dosing weight and single dose, levofloxacin 500 mg, metronidazole 500 mg, moxifloxacin 400 mg, and vancomycin 15 mg/kg.

[b]Vancomycin and ciprofloxacin require longer infusion times and administration should be started in the 2 hours before the incision.

[c]Addition of vancomycin to the antimicrobial regimen is recommended for patients with known methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or prior MRSA infection, and addition of linezolid is recommended if there is known vancomycin-resistant enterococci (VRE) or prior VRE infection. If patient is colonized with MRSA and VRE, only administer linezolid.

[d]Addition of fluconazole to the antibiotic regimen is recommended for patients at high risk for fungal infection.

[e]Neomycin–polymyxin B–gramicidin, gatifloxacin, and moxifloxacin require topical administration of one drop every 5 to 15 minutes for five doses.

Table 63-3
Suggested Prophylactic Antimicrobial Regimens for Clean-Contaminated Surgical Procedures

Procedure	Predominant Organisms	Recommended Agent(s)[a,b,c,d]	Alternative Agents[a,b]
Head and neck surgery involving incisions through mucosa	Viridans group streptococci, *Staphylococcus aureus*, coagulase-negative staphylococci	Cefazolin + metronidazole	Ampicillin–sulbactam, clindamycin
Thoracic Surgery			
Lung resection, pneumonectomy, lobectomy, thoracotomy, thoracoscopy	*S. aureus*, coagulase-negative staphylococci, viridans group streptococci	Cefazolin	Clindamycin, vancomycin
Esophageal resection	Gram-negative enterics, gram-positive cocci, oropharyngeal anaerobes	Cefazolin[e]	Vancomycin + tobramycin
General Surgery			
Gastroduodenal surgery (only for procedures entering the stomach and the intestines)	Streptococci, *Candida albicans*, *S. aureus*, gram-negative enterics	Cefazolin	Clindamycin or vancomycin + aminoglycoside
Small bowel surgery[f]	*Escherichia coli*, *E. faecalis*, *Klebsiella* spp.	Cefazolin	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone
Appendectomy (uncomplicated)	*E. coli*, *Bacteroides fragilis*, viridans group streptococci, *Pseudomonas aeruginosa*	Cefoxitin	Cefazolin + metronidazole, metronidazole + aminoglycoside
Hernioplasty and herniorrhaphy (open repair)	*S. aureus*, *E. coli*, *E. faecalis*, other gram-negative enterics, other gram-positive organisms	Cefazolin	Clindamycin, vancomycin
Pancreatic surgery (pancreaticoduodenectomy and pancreatectomy)	*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *E. faecalis*	Ceftriaxone + ampicillin	Vancomycin + aminoglycoside
Hepatic (hepatectomy)	*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *E. faecalis*	Ceftriaxone + ampicillin	Tobramycin + vancomycin
Biliary tract surgery (including cholecystectomy)	*E. coli*, *Klebsiella* spp., *S. aureus*, *E. faecalis*	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone

Procedure	Predominant Organisms	Recommended Agent(s)[a,b,c,d]	Alternative Agents[a,b]
Colorectal surgery[g]	*E. coli*, *E. faecalis*, *B. fragilis*, *S. aureus*, other gram-negative enterics	Cefazolin + metronidazole	Ampicillin–sulbactam, metronidazole + aminoglycoside
Gynecologic Surgery			
Cesarean section	*S. aureus*, *E. coli*, coagulase-negative staphylococci, *E. faecalis*	Cefazolin	Clindamycin + aminoglycoside
Hysterectomy (abdominal and vaginal)	*S. aureus*, *E. coli*, *E. faecalis*, *Bacteroides* spp.	Cefazolin	Clindamycin or vancomycin + aminoglycoside
Genitourinary Surgery			
With open or laparoscopic entry of the abdomen	*S. aureus*, *S. epidermidis*, gram-negative enterics, enterococci	Cefazolin	Clindamycin + aminoglycoside
With entry of the urinary tract (ureterectomy, prostatectomy, cystectomy)	*E. coli*, other gram-negative enterics, enterococci	Cefazolin	Fluoroquinolone, aminoglycoside with or without clindamycin
With entry of the gastrointestinal tract (use of bowel segments)	Gram-negative enterics, anaerobes, *S. aureus*	Cefazolin + metronidazole	Fluoroquinolone or aminoglycoside + metronidazole or clindamycin
Renal surgery (nephrectomy, percutaneous nephrolithotomy)	*E. coli*, *S. aureus*, coagulase-negative staphylococci	Cefazolin	Vancomycin
Transplant Surgery			
Heart and lung transplantations	Staphylococci, *Enterobacter* spp., *P. aeruginosa*	Cefazolin	Clindamycin, vancomycin
Pancreas transplantation (with or without kidney transplantation)	Staphylococci, *E. coli*, *Klebsiella* spp.	Cefazolin	Clindamycin or vancomycin + gentamicin or aztreonam or a fluoroquinolone
Liver transplantation	*Enterococcus* spp., staphylococci, *E. coli*	Piperacillin–tazobactam, cefotaxime + ampicillin	Clindamycin or vancomycin + gentamicin or aztreonam or fluoroquinolone
Kidney transplantation	Coagulase-negative staphylococci, *E. coli*, *P. aeruginosa*, enterococci	Cefazolin	Clindamycin or vancomycin + gentamicin or aztreonam or a fluoroquinolone

spp., species.

[a]Dosing of antibiotics is ampicillin–sulbactam 3 g, cefazolin 2 g in patients weighing up to 264.55 pounds (120 kg) and 3 g if weighing >264.55 pounds (120 kg), cefuroxime 1.5 g, cefoxitin 2 g, ciprofloxacin 400 mg, clindamycin 900 mg, gentamicin 5 mg/kg based on dosing weight and single dose, levofloxacin 500 mg, metronidazole 500 mg, moxifloxacin 400 mg, and vancomycin 15 mg/kg.

[b]Vancomycin and ciprofloxacin require longer infusion times and should be administered in the 2 hours before surgery.

[c]Addition of vancomycin to antimicrobial regimen is recommended for patients with known methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or prior MRSA infection, and addition of linezolid is recommended if there is known vancomycin-resistant enterococci (VRE) or prior VRE infection. If patient is colonized with MRSA and VRE, only administer linezolid.

[d]Addition of fluconazole to the antibiotic regimen is recommended for patients at high risk for fungal infection.

[e]For esophageal resection with mucosal breach, add metronidazole to the antimicrobial regimen.

[f]For obstructed small bowel, cefazolin plus metronidazole is recommended.

[g]An oral regimen of neomycin plus erythromycin or metronidazole the day before surgery is recommended.

Microbial contamination can also occur from remote infections or colonized sites. Treatment of ongoing infections before surgery is recommended in an effort to minimize risks of contamination.[4],[11] The current consensus is that SSIs are caused either by endogenous pathogens adjacent to the surgical site or exogenous pathogens present in the surgical environment. Current guidelines recommend antimicrobial regimens covering pathogens likely to be encountered at the surgical site.[12] However, the majority of patients with positive wound culture do not develop postoperative infections, implying that wound culture is not the best predictive factor for SSIs.[16] The hypothesis of pathogens being carried from remote sites (eg, GI tract) to the damaged tissue as possible pathogenesis for SSIs is being proposed but remains to be validated.[16],[17]

Clinical Presentation

SSIs can be defined as superficial incisional (involving the skin and subcutaneous fat), deep incisional (involving fascia and muscle), or organ space.[18],[19] Typically, an infected incision site wound is red, warm, and purulent and sometimes swollen, tender, or painful. Poor wound healing or dehiscence (reopening of the incision) is highly suggestive of infection. An SSI can also involve any part of the anatomy (eg, organs or spaces), other than the incision, which was opened or manipulated during an operation.[4] The purulent drainage, if present, should be cultured to identify the causative pathogen and direct antimicrobial therapy. Empiric therapy directed against the most likely pathogens should be instituted while awaiting culture and sensitivity test results. Although most incision site infections are diagnosed shortly after surgery (within 30 days), some deep-seated infections present indolently for weeks to months.[4] Infection of surgically implanted prosthetic hardware may take place up to a year after the surgical procedure.[4]

Nonpharmaceutical Recommendations and Prevention Programs

SSIs are mostly preventable health care–associated infections. In addition to the administration of antimicrobial prophylaxis before surgery, preoperative, intraoperative, and postoperative interventions can reduce rates of infection related to surgical procedures.[4] In 2014, the Surgical Infection Prevention (SIP) project became the Surgical Care Improvement Project (SCIP) in an effort to include interventions that are not restricted to prophylactic antibiotic use. These evidence-based recommendations cover proper hair removal at the surgical site, glycemic control, and normothermia control.[4,7] Moreover, infection control procedures to minimize all sources of bacterial contamination, including patient and surgical team preparation, operative technique, and incision care, are compiled in appendix 1 of the Centers for Disease Control and Prevention guidelines for SSI.[4] The aim of international initiatives such as the World Health Organization (WHO) Global Guidelines for Prevention of Surgical Site Infections is to encourage best surgical practices and improve patient outcomes.[3] Implementation of adapted strategies nationally and locally is critical to reduce the risk of SSIs. Among institutions, such strategies should focus on engagement and education of medical teams as well as execution and evaluation of procedures.[7] Following American national recommendations, institution prevention programs should consider the Centers for Disease Control and Prevention guidelines, as well as the Society for Hospital Epidemiologists for America (SHEA) and the Infectious Disease Society of America (IDSA) guidelines.[4,20]

ANTIMICROBIAL PROPHYLAXIS

Prophylactic antibiotics are widely used in surgical procedures and account for substantial antibiotic use in hospitals worldwide.[21] The purpose of surgical antibiotic prophylaxis is to reduce the prevalence of postoperative wound infection. Appropriate use of prophylactic antimicrobial agents results in decreased patient morbidity and

hospitalization costs for many surgical procedures.[22] However, the benefits of prophylaxis are questionable for surgical procedures at low risk for infection (eg, urologic operations in patients with sterile urine).[12] Consequently, inappropriate or indiscriminate use of prophylactic antibiotics can expose the patient to unnecessary risk of drug toxicity and superinfections, promotes the selection of resistant organisms, and increases cost.[23–26]

ASSESSING ANTIMICROBIAL PROPHYLAXIS

Steps for assessment of surgical antimicrobial prophylaxis include indication for prophylaxis, choice of antibiotic, dosing, timing of administration, route of administration, redosing during the surgical procedure, and duration of prophylaxis. The selection of a prophylactic regimen should be based on the spectrum of activity of the agents and the most likely pathogens associated with the given surgical procedure, pharmacokinetic characteristics (eg, half-life), adverse event profile, selective pressure for bacterial resistance, and cost.[12] These principles are usually adapted into guidelines and recommendations according to local bacterial resistance patterns. At the bedside, agent selection should also be adapted according to patient characteristics including allergies, risk of specific adverse events, colonization status, and procedure-related events.[12] Optimal prophylaxis ensures that adequate concentrations of an appropriate antibiotic are present in the serum and tissue during the entire time the surgical wound is open and at risk for bacterial contamination.[4]

DETERMINING RISK FACTORS FOR INFECTION

CASE 63-1

QUESTION 1: C.P., a 78-year-old female with osteoarthritis, is hospitalized for an elective hip surgery. She is 65 inches (165 cm) tall, weighs 198 pounds (89.8

kg), and is a nonsmoker. The surgery is planned to last within the usual time frame of the operation, which is about 1 to 2 hours.

What is the risk of infection following surgery for her?

Measuring and predicting the risk of infection determines which patients should receive antibiotic prophylaxis. The Centers for Disease Control and Prevention Study on the Efficacy of Nosocomial Infection Control (SENIC) developed an index that included the level of wound contamination and three other criteria based on procedure-related and patient-related factors.[27] Modification of this tool has led to the National Nosocomial Infection Surveillance (NNIS) System Risk Index that takes into account the patient's preoperative assessment (American Society of Anesthesiologists Assessment),[28] the level of contamination of the procedure, the duration of the procedure, and the use of a laparoscope.[10] This last criterion was added because of the associated decreased incidence of infection with the introduction of laparoscopic procedures. Indexes such as these are particularly useful for comparison of performance among institutions and public reporting.

The evaluation of the level of risk of infection according to the NNIS Risk Index System is helpful to predict preoperative risk and justify surgical antibiotic prophylaxis use. It can be summarily understood by going through three steps. The first step is to determine the surgical wound class. Each surgical wound class is defined in Table 63-1. Surgical wound class II, III, or IV counts for 1 point. The second step is to determine the American Society of Anesthesiologists Assessment score. One point is assigned if the patient has nonincapacitating severe systemic disease, has life-threatening incapacitating systemic disease, or is not expected to survive without operation.[29] The third step is to determine whether the duration of the operation exceeds the standard T point as determined by the NNIS database.[30] Surgeries that last longer than the standard time are assigned 1 point. The addition of these risk factors results in a score ranging from 0 to 3.

C.P. is at relatively low risk for infection. There are no points as attributed according to the NNIS score because she will undergo a

clean surgery within the average time frame. Her American Society of Anesthesiologists score is 2, being known with mild systemic disease (obese, rheumatoid arthritis, age older than 60).

CLASSIFICATION OF SURGICAL SITE INFECTIONS

From 1960 to 1964, the National Academy of Sciences National Research Council conducted a landmark study of SSIs and formulated a widely used standard classification based on the risk of intraoperative bacterial contamination (see Table 63-1).[31] Current recommendations for surgical prophylaxis pertain to clean surgeries at high risk for complications and/or involving implantation of prosthetic material, clean-contaminated surgeries, and select contaminated wounds. Antimicrobials for dirty surgeries in which infection is already established are considered treatment instead of prophylaxis and are not discussed further in this chapter. Recommendations for site-specific prophylactic antimicrobial regimens according to suspected pathogens are listed in Tables 63-2 and 63-3; a detailed examination of clinical trials supporting these recommendations is presented elsewhere.[12]

Decision to Use Antimicrobial Prophylaxis

CASE 63-2

QUESTION 1: M.R., a 62-year-old 265-pound (120.2-kg) male, is admitted to the hospital with severe abdominal pain, nausea and vomiting, and temperature of 102.7 °F (39.3 °C). A diagnosis of acute cholecystitis is made, and M.R. is scheduled for open biliary tract surgery (cholecystectomy).

Why is antimicrobial prophylaxis warranted for M.R.?

Based on the risk factors for infection previously discussed, the decision whether a given patient should receive antimicrobial

prophylaxis depends on a number of factors. Antimicrobial prophylaxis should be given for surgical procedures (a) with a high rate of infection (ie, clean-contaminated or contaminated procedures), (b) involving the implantation of prosthetic materials, or (c) in which an infection would have catastrophic consequences.[12] Open biliary tract surgery is considered a clean-contaminated procedure and, therefore, carries a risk of surgical wound infection approaching 10% (see Tables 63-1 and 63-3). The risk factors for infection include age older than 70 years, diabetes mellitus, acute cholecystitis, obstructive jaundice, common duct stones, emergency procedures, pregnancy, immunosuppression, nonfunctioning gallbladder, or insertion of prosthetic device. Prophylaxis is recommended for all patients undergoing open biliary tract surgery.[12] Prophylaxis is not recommended for low-risk procedures such as elective laparoscopic cholecystectomy. Thus, prophylaxis is warranted in M.R.

Selection of an Antimicrobial Agent

Case 63-2, Question 2: An order for intravenous (IV) cefazolin 2 g on call to the OR is written for M.R. Why is this an appropriate (or inappropriate) antibiotic selection?

The selected prophylactic agent should be directed against likely infecting organisms (see Tables 63-2 and 63-3) but need not eradicate every potential pathogen. In general, pathogens associated with infection originate from the skin or the associated structures contiguous to the regions involved in the surgical procedure. Cefazolin has been proved effective for most surgical procedures, including biliary tract surgery, given that the goal of prophylaxis is to decrease bacterial counts below critical levels necessary to cause infection. Broad-spectrum agents, such as third-generation cephalosporins, should be avoided for prophylaxis because they are no more effective than is cefazolin and may alter microbial flora, increasing the emergence of microbial resistance to

these otherwise valuable agents. Therefore, cefazolin is an appropriate antibiotic selection.

Case 63-2, Question 3: The nurse mentions that the patient is obese. Would you make any dosing recommendations?

Given the need for appropriate concentrations effective against likely pathogens at the incision site, drug pharmacokinetic parameters must be considered. Physiologic changes in patients who are obese can alter drug pharmacokinetics and consequently impact the distribution, metabolism, and clearance of the drugs.[12] In patients who are obese, the altered drug distribution can result in a decrease in drug concentration in tissues that can lead to suboptimal drug concentration at incision time. Therefore, current guidelines suggest a 2-g cefazolin dose for all adults weighing <264.55 pounds (120 kg) and a 3-g dose for patients ≥264.55 pounds (120 kg).[12] Because M.R. falls into the ≥264.55-pound (120-kg) category, the recommended dose is 3 g.

Selection of an Antimicrobial Agent

CASE 63-3

Question 1: L.T., a 46-year-old female, has a recent history of abnormal uterine bleeding and vaginal discharge. Endometrial biopsy finding is positive for squamous cell carcinoma; however, there does not appear to be an invasive disease. The diagnosis is carcinoma in situ, and a vaginal hysterectomy is scheduled.

What would be an appropriate surgical prophylaxis antimicrobial regimen for L.T.?

The selection of a prophylactic regimen should be based on the spectrum of activity of the agents and the most likely pathogens associated with the given surgical procedure (see Tables 63-2 and 63-3), pharmacokinetic characteristics (eg, half-life), adverse event profile, impact on bacterial resistance selection, and cost.

The usefulness of antimicrobial prophylaxis in vaginal hysterectomies is well established and should be directed against vaginal microflora, including gram-positive and gram-negative aerobes and anaerobes (see Table 63-3).[32] The most-effective, yet most narrow-spectrum agent should be selected considering that the goal of prophylaxis is not to eradicate every potential pathogen but to reduce bacterial counts below a critical level necessary to cause infection. Cefazolin has been proved to be as effective a prophylactic agent as ceftriaxone for vaginal hysterectomy.[33] This finding reinforces the fact that a more broad-spectrum agent (eg, a third-generation cephalosporin) is unwarranted.

Similar to vaginal hysterectomy, cefazolin and numerous agents (cefotetan, cefoxitin, ampicillin–sulbactam, etc) decrease the incidence of postoperative surgical infection when the abdominal approach is used.[32],[34] As with vaginal hysterectomy, most trials have not revealed significant differences between first- and second-generation cephalosporins.[34] In contrast, Hemsell et al[35] observed a significantly higher incidence of major postoperative surgical infections in patients receiving the first-generation agent cefazolin when compared with the second-generation cephalosporin, cefotetan. Cefazolin exhibits a favorable toxicity profile and has a relatively long half-life (~1.8 hours), and a single dose has proven prophylactic efficacy.[33] Cefazolin also is considerably less expensive than are broader-spectrum agents and is currently recommended by the American College of Obstetricians and Gynecologists.[36] Although it has a broader spectrum of coverage, a single dose of cefoxitin would also be an appropriate choice for this patient.[32],[34]

Case 63-3, Question 2: Because cefoxitin has an increased spectrum of activity against the anaerobe *Bacteroides fragilis*, it is being considered as an alternative to cefazolin prophylaxis for L.T. Is this change in prophylaxis appropriate?

The second- and third-generation cephalosporins and ampicillin–sulbactam generally are not more effective than the first-generation cephalosporins for surgical prophylaxis in vaginal hysterectomy or in

gastroduodenal, biliary, and clean surgical procedures.[12] One exception to these findings is in the prevention of infection after colorectal procedures and, perhaps, hysterectomy. Several investigations have documented the failure of first-generation agents when used as prophylaxis in colorectal procedures, probably a consequence of their weak anaerobic coverage.[37] As stated previously, second- and third-generation agents and ampicillin–sulbactam generally are no more efficacious than is cefazolin and should not be used for surgical prophylaxis in most procedures. Cefoxitin, however, would be a reasonable choice in colorectal surgery or hysterectomy. Considering that this patient is having a hysterectomy, either cefazolin or cefoxitin is appropriate.

CASE 63-4

QUESTION 1: S.N., a 57-year-old female with rheumatoid arthritis and degenerative joint disease, has been admitted for total hip arthroplasty. She states that she had an anaphylactic reaction to penicillin in the past.

How does this allergy history impact the selection of surgical prophylaxis for S.N.?

Cefazolin is the preferred prophylactic agent for most clean procedures, including cardiac, neurologic, vascular, and orthopedic procedures (see Table 63-2). Although the risk of cefazolin cross-allergenicity to penicillin is relatively low, S.N. experienced a serious, accelerated reaction (hives, shortness of breath [SOB]) with penicillin; consequently, she should not receive cefazolin. The organisms most likely to cause postoperative infection after total hip replacement are *S. aureus* and coagulase-negative staphylococci (see Table 63-2). Nafcillin, cefazolin, and vancomycin possess excellent activity against *S. aureus*; however, the β-lactams have only marginal activity against coagulase-negative staphylococci such as *S. epidermidis*. Regardless, nafcillin (and cefazolin) should be avoided because of the penicillin allergy, and the preferred agent for S.N. is vancomycin.

Preoperative vancomycin 15 mg/kg should be administered IV slowly, for at least 60 minutes. This slow rate of infusion is necessary to reduce the risk of infusion-related hypotension.[38]

CASE 63-5

QUESTION 1: B.K., an 18-year-old female, reports severe acute abdominal pain and nausea; the pain is localized to the periumbilical region. B.K. has a temperature of 103.1 °F (39.5 °C). After initial examination by her pediatrician, she is admitted to the hospital with presumed appendicitis, and an exploratory laparotomy is scheduled.

What surgical antimicrobial prophylaxis should be ordered for B.K.?

As with colorectal surgery, the most likely infecting organisms in appendectomy are *Bacteroides* species and gram-negative enterics (see Table 63-3). On surgical inspection, if the appendix appears normal (not inflamed, without perforation), then antimicrobial prophylaxis is unnecessary.[39] If the appendix is inflamed without perforation, a single preoperative antibiotic dose is necessary. If the appendix is perforated or gangrenous (complicated), infection is already established, and postoperative treatment is warranted. The status of the appendix, however, cannot be determined before surgery; therefore, all patients should receive at least one preoperative dose of an appropriate antibiotic.[40] After surgical inspection of the appendix, the need for postoperative antibiotic therapy can be determined.

Based on the pathogens likely to be encountered, an antimicrobial agent with both aerobic and anaerobic activity should be used. Consequently, cefoxitin is an acceptable choice for prophylaxis.[41]

Timing of Antimicrobial Administration

CASE 63-5, QUESTION 2: The administration of IV cefoxitin for B.K. is scheduled on call to the OR. Why is the administration time for this antimicrobial appropriate (or inappropriate) for B.K.?

Classic animal studies conducted by Burke[42] and others[43] clearly demonstrated the need for therapeutic antibiotic concentrations in the bloodstream and in vulnerable tissue at the time of wound contamination. Bacteria were most likely to enter the tissue beginning with the initial surgical incision and continuing until the wound was closed; antibiotics administered >3 hours after bacterial contamination were ineffective in decreasing the rate of wound infection.[42],[43] This 2- to 3-hour period after the surgical incision was deemed the “effective” or “decisive” period for prophylaxis, when the animal’s wound was most susceptible to the beneficial effects of the antibiotic. This decisive period for administration of prophylactic antibiotics has been confirmed in humans to be somewhere in the 2 hours before incision as compared to earlier administration or any time after incision.[44–47] Investigation of the precise window for optimal outcomes demonstrated that narrowing the window from 60 to 30 minutes before incision for antimicrobials with a short half-life (eg, cephalosporins) does not reduce infection rates.[48]

For maximal efficacy, an antibiotic should be present in therapeutic concentrations at the incision site as early as possible during the decisive period and continuing until the wound is closed. Because an antibiotic administered postoperatively cannot achieve therapeutic concentrations during the decisive period, postoperative administration does not prevent postoperative wound infections, and infection rates are similar to those in patients who receive no antibiotics.[49]

Consequently, prophylactic antibiotics should be administered before the surgical procedure in the operative suite.[12] Prophylactic antibiotics are most effective when given within the 1-hour window before surgical incision; rates of infection increase significantly if antibiotics are administered >1 hour before incision or postoperatively.[46],[47] Administration of vancomycin and fluoroquinolones should begin in the 120 minutes before surgical incision because of the prolonged infusion times required for these drugs.[12] If a tourniquet is required to control blood flow to a limb during surgery, the evidence is insufficient to recommend administering the dose before or after inflation of the tourniquet.[4]

The “on-call” prescribing practice for surgical prophylaxis, as with B.K., has fallen into disfavor because the time between antibiotic administration and the actual incision may exceed 1 hour. This delay may result in subtherapeutic antibiotic concentrations during the decisive period.[12],[50] B.K.’s cefoxitin should be ordered preoperatively and should be administered in the OR within 1 hour of the surgical incision.

Case 63-5, Question 3: Will B.K. require a second dose of cefoxitin during the surgical procedure?

The duration of the surgical procedure and the half-life of the administered antibiotic should be considered when determining the need for an additional intraoperative dose. The longer the duration of the surgical procedure, particularly with short half-life antibacterials, the greater the incidence of postoperative infection.[45],[51],[52] Cefoxitin, with a half-life of ~ 0.7 to 1 hour, is effective in a single preoperative dose for most surgical procedures. For prolonged procedures, or those with major blood loss,[53],[54] additional intraoperative doses should be administered every two half-lives of the drug.[12] B.K. should require an additional intraoperative cefoxitin dose only if the surgical procedure is prolonged (>2 hours).

Route of Administration

CASE 63-6

Question 1: G.B., a 55-year-old female recently diagnosed with carcinoma of the large bowel, is admitted to the hospital for an elective colorectal surgical resection; the surgery is expected to last 5 hours. Physical examination reveals a cachectic female with a 20-pound (9.1-kg) weight loss during the previous 3 months (current weight, 132 pounds [59.9 kg]). Increased frequency of bowel movements and chronic fatigue are noted; all other systems are normal. Laboratory data include the following:

Hemoglobin (Hgb), 10.4 g/dL (normal, 12.1–15.3 g/dL; SI units, 104 g/L)
Hematocrit (Hct), 29.7% (normal, 36%–45%; SI units, 0.297)

Prothrombin time (PT), 15 seconds (normal, 10–13 seconds)

Stool guaiac test result is positive. Vital signs are within normal limits. G.B. is taking no medications and has no history of drug allergies. The following orders are written to begin at home on the day before surgery: (a) clear liquid diet; (b) mechanical bowel cleansing with polyethylene glycol–electrolyte lavage solution (CoLYTE®, GoLYTELY®); and (c) neomycin sulfate 1 g and erythromycin 1 g orally (PO) at 1:00, 2:00, and 11:00 PM.

Is the oral route of administration appropriate antibiotic prophylaxis for G.B.?

In general, oral administration of surgical antimicrobial prophylaxis is not recommended because of unreliable or poor absorption of oral agents in the anesthetized bowel. Oral nonabsorbable agents, however, function effectively as GI decontaminants because high intraluminal drug concentrations are sufficient to decrease bacterial counts.[55] The concentration of bacteria in the colon may approach 10^{16} bacteria/μL, and colorectal procedures, such as the one G.B. will undergo, carry a relatively high risk of postoperative infection. Antimicrobial regimens with activity against aerobic and anaerobic bacterial fecal flora (*E. coli* and other Enterobacteriaceae and *B. fragilis*) are effective in preventing postoperative wound infections.[55]

A widely used oral antimicrobial regimen is 1 g each of the nonabsorbable antibiotics neomycin sulfate (for gram-negative aerobes) and erythromycin base (for anaerobes), given 1 day before surgery at the times indicated for G.B.[56] Mechanical bowel cleansing, such as with polyethylene glycol–electrolyte or sodium phosphate lavage solution, precede administration of this regimen; the purpose of bowel purging is to evacuate the colonic contents as completely as possible to decrease colonic bacterial counts. Effective oral prophylaxis includes an aminoglycoside, such as neomycin or kanamycin, plus either erythromycin or metronidazole.[57–59] Thus, the regimen selected for G.B. is highly appropriate.

CASE 63-6, QUESTION 2: The surgical resident has canceled the oral neomycin–erythromycin bowel regimen for G.B. Instead, he orders cefoxitin (Mefoxin®) 2 g IV preoperatively. Is this change in therapy an effective and a rational choice for G.B.?

Numerous parenteral regimens, specifically with agents that possess both aerobic and anaerobic activity, are effective as surgical prophylaxis in colorectal procedures. The second-generation cephalosporins with significant anaerobic activity (eg, cefoxitin) are superior to first-generation cephalosporins, which lack sufficient anaerobic activity.[60] Mechanical bowel preparation with the combination of oral and IV antibiotics is superior to oral or IV agents alone.[56]

Also, the cefoxitin order for G.B. would be unacceptable if the surgery lasts >3.5 hours (the relatively short half-life of cefoxitin could be associated with inadequate antibacterial levels and predispose her to infection).[61] For prolonged procedures (>3 hours) such as anticipated for G.B., an alternative agent with a longer half-life, such as ertapenem, or a second dose of cefoxitin should be considered. Ertapenem has been found to be superior to cefotetan in preventing infection after colorectal surgery.[62] This improved efficacy may be because of the long half-life or broader antibacterial activity.[63] Ertapenem may offer certain advantages as a prophylactic antibiotic, but its use in this indication is discouraged by most clinicians.[12] Although unproved, the potential impact of widespread ertapenem utilization on subsequent carbapenem resistance is of concern.[64] The increased acquisition cost of ertapenem also needs to be considered. Thus, for G.B., the importance of redosing IV regimens with short half-lives in prolonged surgery should be stressed to the resident.

Case 63-6, Question 3: The surgical resident has reconsidered the cefoxitin order and decides to prescribe both the oral and parenteral prophylactic regimens for G.B. Will the combination significantly reduce the rate of postoperative wound infection compared with either regimen administered singly?

Coadministration of an oral regimen followed by a parenteral antibiotic before incision is equivalent or superior to administration of either regimen alone in reducing infection rates.[56],[57],[65] Oral antibiotics, however, have only been evaluated in combination with

mechanical bowel preparation. The optimal agents and regimens as prophylaxis in colorectal surgery remain to be adequately determined. For now, a combination of oral and parenteral antimicrobial prophylaxis with mechanical bowel preparation is recommended for colorectal surgery.[12]

Duration of Administration

CASE 63-7

QUESTION 1: L.G., a 28-year-old male with a history of rheumatic heart disease, has a 12-year history of a heart murmur consistent with mild mitral stenosis and mitral regurgitation. During the past 4 months, his murmur has become much more prominent. In addition, he has experienced severe dyspnea with light physical activity and 3+ pitting edema over both lower legs. Physical examination is notable for coarse rales and an S_3 gallop. For the past 6 weeks, he has been maintained on digoxin and diuretics without significant relief of his SOB. The cardiothoracic surgeon recommends mitral valve replacement and orders the following surgical antibiotic prophylaxis regimen: cefazolin 2 g IV preoperatively, then every 8 hours for 24 hours.

Is cefazolin the most appropriate antimicrobial for L.G.? Why was prophylaxis ordered for only 24 hours?

Although the incidence of postoperative wound infection for cardiothoracic procedures is low (<5%), the devastating consequences of a postoperative endocarditis (after valve replacement) and mediastinitis or sternal osteomyelitis (after sternotomy) warrant antimicrobial prophylaxis.[66–68] Common pathogens associated with cardiothoracic surgery include *S. aureus* and coagulase-negative staphylococci (particularly with hardware placement) (see Table 63-2); based on these potential pathogens, successful prophylactic regimens include cefazolin and cefuroxime. When cefazolin has been compared with cefuroxime or cefamandole, a statistical trend in favor of the second-generation cephalosporins has been noted, and collective wound infection rates were slightly higher in the cefazolin group.[69–71] In contrast, a comparison of prophylactic cefazolin and cefuroxime in patients

having open heart surgery noted a significantly greater incidence of sternal wound infection and mediastinitis in the cefuroxime group.[72] Other studies similarly have not observed improved efficacy with cefuroxime compared with cefazolin.[72–74] Other studies similarly have not observed improved efficacy with cefuroxime compared with cefazolin.[73,74] In conclusion, cefazolin probably is at least as effective as second-generation cephalosporins; therefore, the choice of agent should be based on an institution's antimicrobial susceptibility and cost data. Hospital-specific antimicrobial resistance patterns are especially important in determining the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE) SSI rates. Although vancomycin has not been determined to be superior to cefazolin, it is the drug of choice for prophylaxis in patients colonized with MRSA.[12,75] Patients are at higher risk for MRSA carriage if they are frequently hospitalized or have a prolonged hospital stay, are exposed to broad-spectrum antibiotics, are known for comorbid conditions, or have severe underlying illness. The population to be screened for MRSA carriage and undergo decolonization with mupirocin is still being debated but is mostly considered for patients undergoing an orthopedic or a cardiac procedure. Surveillance of susceptibility of *S. aureus* isolated from SSIs should be done if mupirocin is used for decolonization.[76]

Meta-analyses reveal no differences between first- and second-generation cephalosporins or between β-lactams and glycopeptides in the prevention of surgical wound infection.[77,78] Thus, the cefazolin prophylaxis selected for L.G. is acceptable, provided the patient is not colonized with MRSA or MRSE. Additional empiric coverage with an aminoglycoside, a fluoroquinolone, or aztreonam may be considered when gram-negative pathogens are a concern according to local epidemiology and risk factors including hospital admission >48 hours before surgery, diabetes, and ventilator dependency.[12,79]

With regard to duration, the shortest effective prophylactic course of antibiotics should be used (ie, single dose preoperatively or not > 24 hours postoperatively for most procedures).[80] Postoperative doses after wound closure are usually not required and may

increase the risk of resistance. Single-dose prophylaxis given preoperatively, a viable option for many surgical procedures (see Case 63-8, Question 1), is still being evaluated for cardiac procedures.[12,81] In practice, cardiothoracic antimicrobial prophylaxis often is continued up to 24 hours after surgery, as in the case of L.G. No benefit is seen to prolonging prophylaxis to >24 hours, and such use should be discouraged. The duration of antimicrobial prophylaxis ordered for L.G. is appropriate.

CASE 63-8

QUESTION 1: G.J., a 27-year-old female, is admitted to the obstetrics unit at term with her first pregnancy. She is scheduled for a cesarean section because the baby is in a breech presentation. Cefazolin 1 g IV to be administered after the cord is clamped and every 8 hours for 24 hours is ordered.

Is this surgical prophylaxis appropriate or inappropriate?

As noted previously, the shortest effective duration of prophylaxis should be used. In the past, 1- to 5-day antimicrobial regimens were commonly used for cesarean section, but single-dose regimens have been proved to be as effective as these longer regimens.[82] Faro et al[82] demonstrated that a single 2-g dose of cefazolin was superior to either a single 1-g dose or a three-dose, 1-g prophylactic regimen. Others have noted similar results (ie, a single cefazolin dose administered after the umbilical cord is clamped is sufficient in preventing postoperative wound infections in cesarean section).[83–85] Single-dose prophylaxis is less costly and minimizes the development of bacterial resistance.[26] Antibiotic prophylaxis has traditionally been administered after clamping of the umbilical cord to minimize infant drug exposure. This early exposure could theoretically mask the signs of neonatal sepsis and favor the acquisition of resistant organisms. However, administration before initial incision and cord clamping decreases the incidence of maternal infections without adverse consequences to the child.[86] Thus, G.J. should receive a single 2-g dose of cefazolin before incision, without the three additional doses.

Single-dose prophylaxis has been found to be effective in a variety of GI tract, orthopedic, and gynecologic procedures.[51] A single dose of an antibiotic with a short half-life, however, may provide insufficient antimicrobial coverage during a prolonged surgical procedure. Repeated intraoperative dosing or selection of an agent with a longer half-life is recommended when the duration of surgery is long to maintain adequate tissue concentrations throughout the procedure.[12],[52]

Risks of Indiscriminate Antimicrobial Use

Case 63-8, Question 2: G.J. was to receive 24 hours of cefazolin. What are the risks of indiscriminate use of antimicrobials for surgical prophylaxis?

The risks of indiscriminate use of antimicrobials include the potential for adverse effects and superinfection. The administration of any β-lactam agent poses the risk of a hypersensitivity reaction, and many antibiotics, especially broad-spectrum agents, predispose patients to *Clostridioides difficile*–associated disease.[87] The risk of developing this superinfection increases with the duration of antibiotic exposure.[25] Avoiding unnecessary initial and prolonged exposure reduces the risk of this superinfection and its associated complications and could reduce rates of mortality associated with inadequate antibiotic use.[87],[88] In addition, prolonged use of antimicrobials increases the selection of resistant organisms in a given patient that could be spread to other hospitalized patients.[89]

Signs of Surgical Site Infection

CASE 63-9

Question 1: A.L., a 78-year-old female with peripheral venous disease, underwent a left femoral endarterectomy. Three weeks later, she is admitted to the emergency room after developing fever and chills at home, as well as groin redness and swelling. A.L. is diagnosed with left groin abscess that tested

positive for MRSA and antibiotic therapy of IV vancomycin is started. She is then brought to the OR for incision, drainage, and washout of the infected area.

What typical signs of site infection is A.L. presenting? Is she in the typical time course for manifestation of signs of site infection?

The presentation at 3 weeks falls within the typical 30-day time frame for an acute SSI. Abscess formation and deep-seated or indolent infections may take several months before presentation.[4] In addition to redness and swelling, it is pertinent to assess the wound for other warmth, tenderness, localized pain, purulent drainage, and spontaneous wound dehiscence. A surgeon's intervention to open the wound for drainage and debridement is considered diagnostic for infection.[19] Fever, chills, fatigue, and loss of appetite are systemic signs and symptoms that may indicate a more severe or extensive presentation. Complete workup should also include evaluation for deep incisional or organ space involvement.

OPTIMIZING SURGICAL ANTIMICROBIAL PROPHYLAXIS

CASE 63-10

QUESTION 1: As the new infectious disease pharmacist of the institution, you are informed by the infection control team that the antibiotic prophylaxis prescribed by the surgeons is not the same as what is indicated in the institution guidelines.

Which criteria would you want to measure antibiotic prophylaxis prescription performance? What interventions could improve how antibiotics are used in prophylaxis?

Antibiotic control strategies have improved the appropriate use of antimicrobial agents for surgical prophylaxis. Numerous factors including individual knowledge, attitudes, beliefs, and practice; team communication and allocation of responsibilities; and institutional support for promoting and monitoring practice influence antibiotic

prophylaxis measures.[90] Interventions for improvement are focused on education of practitioners, standardization of the ordering, the delivery and the administration processes, and providing feedback on performance as measured by infection rates and compliance with improvements. The SCIP, a national multidisciplinary initiative developed by the Centers for Medicare and Medicaid Services, aims at improving surgical care. Reducing SSIs is one among the targeted goals of this initiative.[91] Prophylactic antimicrobial received within 1 hour of surgical incision, prophylactic antimicrobial consistent with published guidelines, and prophylactic antimicrobial discontinued within 24 hours of surgery end time are three performance measures included in this quality improvement process. The first two, antibiotic timing of administration and appropriate antibiotic selection, are associated with a decrease in the SSI rate.[22]

Smaller scale projects have also been successful in improving antibiotic use and decreasing infection rates. A multidisciplinary team generated electronic quick orders allowing for a computer-enhanced decision-making process and developed an antibiotic administration protocol. Appropriate selection of antibiotics increased from 78% to 94%, timely administration improved from 51% to 98%, and clean wound infection rate decreased from 2.7% to 1.4%.[92]

In collaboration with other health care providers, pharmacists should be responsible for optimizing the timing, choice, and duration of antimicrobial surgical prophylaxis. Education of surgical, anesthesia, and nursing staff, supported by hospital policy changes initiated by pharmacists, improved appropriate timing from 68% to 97% and resulted in significant cost avoidance.[93] Postdischarge surveillance is also critical in reducing SSIs.[94]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references

and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Anderson DJ, Podgorny K, Berríos-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35(6):605–627. (7)

Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70(3): 195–283. (12)

Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis.* 2006;43(3):322–330. (91)

Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med*. 1992;326(5):281–286. (47)

Key Websites

ASA Physical Status Classification System. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system

Centers for Diseases Control and Prevention. Healthcare-Associated Infections. Surgical Site Infection (SSI). http://www.cdc.gov/HAI/ssi/ssi.html

Centers for Diseases Control and Prevention. Healthcare Infection Control Practices Advisory Committee (HICPAC). General Guidelines. https://www.cdc.gov/infectioncontrol/guidelines/ssi/index.html

Centers for Diseases Control and Prevention. National Healthcare Safety Network. Data and Statistics. http://www.cdc.gov/nhsn/datastat.html

National Institute for Health and Care Excellence. Surgical Site Infection. http://www.nice.org.uk/guidance/CG74

World Health Organization. Global guidelines for the prevention of surgical site infections. https://www.who.int/publications/i/item/global-guidelines-for-the-prevention-of-surgical-site-infection-2nd-ed

COMPLETE REFERENCES CHAPTER 63 ANTIMICROBIAL PROPHYLAXIS FOR SURGICAL PROCEDURES

1. Magill SS, O'Leary E, Janelle SJ, et al. Changes in prevalence of health care-associated infections in U.S. hospitals. *N Engl J Med*. 2018;379(18):1732–1744.
2. European Centre for Disease Prevention and Control. *Annual Epidemiological Report for 2017. Healthcare-Associated Infections: Surgical Site Infections*. European Centre for Disease Prevention and Control; 2019.
3. WHO. *Global Guidelines for the Prevention of Surgical Site Infection*. World Health Organization; 2018.
4. Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg.* 2017;152(8):784–791.
5. Curcio D, Cane A, Fernández F, Correa J. Surgical site infection in elective clean and clean-contaminated surgeries in developing countries. *Int J Infect Dis.* 2019;80:34–45.
6. Awad SS. Adherence to surgical care improvement project measures and post-operative surgical site infections. *Surg Infect (Larchmt).* 2012;13(4):234–237.
7. Anderson DJ, Podgorny K, Berríos-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.* 2014;35(6):605–627.
8. Liang L, Moore B, Soni A. *National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2017.* Agency for Healthcare Research and Quality; 2020.
9. Scott RD. *The Direct Medical Costs of Healthcare-Associated Infections in US Hospitals and the Benefits of Prevention*. 2009.
10. Culver DH, Horan TC, Gaynes RP, et al. Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. *Am J Med.* 1991;91(3b):152s–157s.
11. Waltz PK, Zuckerbraun BS. Surgical site infections and associated operative characteristics. *Surg Infect (Larchmt).* 2017;18(4):447–450.
12. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm.* 2013;70(3): 195–283.
13. Weiner-Lastinger LM, Abner S, Edwards JR, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015–2017. *Infect Control Hosp Epidemiol.* 2020;41(1):1–18.
14. Chea N, Sapiano MRP, Zhou L, et al. Rates and causative pathogens of surgical site infections attributed to liver transplant procedures and other hepatic, biliary, or pancreatic procedures, 2015–2018. *Transpl Infect Dis.* 2021:e13589.

15. Abbo LM, Grossi PA. Surgical site infections: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant.* 2019;33(9):e13589.
16. Alverdy JC, Hyman N, Gilbert J. Re-examining causes of surgical site infections following elective surgery in the era of asepsis. *Lancet Infect Dis.* 2020;20(3):e38–e43.
17. Krezalek MA, Hyoju S, Zaborin A, et al. Can methicillin-resistant *Staphylococcus aureus* silently travel from the gut to the wound and cause postoperative infection? modeling the “Trojan Horse Hypothesis.” *Ann Surg.* 2018;267(4):749–758.
18. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control.* 2008;36(5):309–332.
19. National Healthcare Safety Network. *Surgical Site Infection (SSI) Event*. Centers for Disease Control and Prevention; 2022:39.
20. Yokoe DS, Anderson DJ, Berenholtz SM, et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals: 2014 updates. *Infect Control Hosp Epidemiol.* 2014;35(8):967–977.
21. Magill SS, O’Leary E, Ray SM, et al. Antimicrobial use in US hospitals: comparison of results from emerging infections program prevalence surveys, 2015 and 2011. *Clin Infect Dis.* 2021;72(10):1784–1792.
22. Cataife G, Weinberg DA, Wong HH, Kahn KL. The effect of Surgical Care Improvement Project (SCIP) compliance on surgical site infections (SSI). *Med Care.* 2014;52(2 Suppl 1):S66–S73.
23. Branch-Elliman W, O’Brien W, Strymish J, Itani K, Wyatt C, Gupta K. Association of duration and type of surgical prophylaxis with antimicrobial-associated adverse events. *JAMA Surg.* 2019;154(7):590–598.
24. Balch A, Wendelboe AM, Vesely SK, Bratzler DW. Antibiotic prophylaxis for surgical site infections as a risk factor for infection with *Clostridium difficile*. *PLoS One.* 2017;12(6):e0179117.
25. Carignan A, Allard C, Pépin J, Cossette B, Nault V, Valiquette L. Risk of *Clostridium difficile* infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. *Clin Infect Dis.* 2008;46(12):1838–1843.
26. Harbarth S, Samore MH, Lichtenberg D, Carmeli Y. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation.* 2000;101(25):2916–2921.
27. Haley RW, Culver DH, Morgan WM, White JW, Emori TG, Hooton TM. Identifying patients at high risk of surgical wound infection. A simple multivariate index of patient susceptibility and wound contamination. *Am J Epidemiol.* 1985;121(2):206–215.

28. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology.* 1978;49(4):239–243.
29. *ASA Physical Status Classification System*. ASA House of Delegates. 2014. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system
30. National Nosocomial Infections Surveillance. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control.* 2004;32(8):470–485.
31. Berard F, Gandon J. Postoperative wound infections: the influence of ultraviolet irradiation of the operating room and of various other factors. *Ann Surg.* 1964;160(Suppl 2):1–192.
32. Mittendorf R, Aronson MP, Berry RE, et al. Avoiding serious infections associated with abdominal hysterectomy: a meta-analysis of antibiotic prophylaxis. *Am J Obstet Gynecol.* 1993;169(5):1119–1124.
33. Hemsell DL, Menon MO, Friedman AJ. Ceftriaxone or cefazolin prophylaxis for the prevention of infection after vaginal hysterectomy. *Am J Surg.* 1984;148(4a):22–26.
34. Kamat AA, Brancazio L, Gibson M. Wound infection in gynecologic surgery. *Infect Dis Obstet Gynecol.* 2000;8(5–6):230–234.
35. Hemsell DL, Johnson ER, Hemsell PG, Nobles BJ, Little BB, Heard MC. Cefazolin is inferior to cefotetan as single-dose prophylaxis for women undergoing elective total abdominal hysterectomy. *Clin Infect Dis.* 1995;20(3):677–684.
36. ACOG practice bulletin No. 104: antibiotic prophylaxis for gynecologic procedures. *Obstet Gynecol.* 2009;113(5):1180–1189.
37. Condon RE, Bartlett JG, Nichols RL, Schulte WJ, Gorbach SL, Ochi S. Preoperative prophylactic cephalothin fails to control septic complications of colorectal operations: results of controlled clinical trial. A Veterans Administration cooperative study. *Am J Surg.* 1979;137(1):68–74.
38. Dajee H, Laks H, Miller J, Oren R. Profound hypotension from rapid vancomycin administration during cardiac operation. *J Thorac Cardiovasc Surg.* 1984;87(1):145–146.
39. Górecki WJ, Grochowski JA. Are antibiotics necessary in nonperforated appendicitis in children? A double blind randomized controlled trial. *Med Sci Monit.* 2001;7(2):289–292.
40. Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendectomy. *Cochrane Database Syst Rev.* 2001;(3):CD001439.
41. Liberman MA, Greason KL, Frame S, Ragland JJ. Single-dose cefotetan or cefoxitin versus multiple-dose cefoxitin as prophylaxis in patients undergoing appendectomy for acute nonperforated appendicitis. *J Am Coll Surg.* 1995;180(1):77–80.

42. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery.* 1961;50:161–168.
43. Miles AA, Miles EM, Burke J. The value and duration of defence reactions of the skin to the primary lodgement of bacteria. *Br J Exp Pathol.* 1957;38(1):79–96.
44. van Kasteren ME, Manniën J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. *Clin Infect Dis.* 2007;44(7):921–927.
45. Steinberg JP, Braun BI, Hellinger WC, et al. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the trial to reduce antimicrobial prophylaxis errors. *Ann Surg.* 2009;250(1):10–16.
46. Garey KW, Dao T, Chen H, et al. Timing of vancomycin prophylaxis for cardiac surgery patients and the risk of surgical site infections. *J Antimicrob Chemother.* 2006;58(3):645–650.
47. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med.* 1992;326(5):281–286.
48. Weber WP, Mujagic E, Zwahlen M, et al. Timing of surgical antimicrobial prophylaxis: a phase 3 randomised controlled trial. *Lancet Infect Dis.* 2017;17(6): 605–614.
49. Stone HH, Hooper CA, Kolb LD, Geheber CE, Dawkins EJ. Antibiotic prophylaxis in gastric, biliary and colonic surgery. *Ann Surg.* 1976;184(4):443–452.
50. Wong-Beringer A, Corelli RL, Schrock TR, Guglielmo BJ. Influence of timing of antibiotic administration on tissue concentrations during surgery. *Am J Surg.* 1995;169(4):379–381.
51. Scher KS. Studies on the duration of antibiotic administration for surgical prophylaxis. *Am Surg.* 1997;63(1):59–62.
52. Zelenitsky SA, Ariano RE, Harding GK, Silverman RE. Antibiotic pharmacodynamics in surgical prophylaxis: an association between intraoperative antibiotic concentrations and efficacy. *Antimicrob Agents Chemother.* 2002;46(9):3026–3030.
53. Markantonis SL, Kostopanagiotou G, Panidis D, Smirniotis V, Voros D. Effects of blood loss and fluid volume replacement on serum and tissue gentamicin concentrations during colorectal surgery. *Clin Ther.* 2004;26(2):271–281.
54. Swoboda SM, Merz C, Kostuik J, Trentler B, Lipsett PA. Does intraoperative blood loss affect antibiotic serum and tissue concentrations? *Arch Surg.* 1996;131(11): 1165–1171; discussion 1171–1162.
55. Bartlett JG, Condon RE, Gorbach SL, Clarke JS, Nichols RL, Ochi S. Veterans Administration Cooperative Study on Bowel Preparation for Elective Colorectal Operations: impact of oral antibiotic regimen on colonic flora,

wound irrigation cultures and bacteriology of septic complications. *Ann Surg.* 1978;188(2):249–254.
56. Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev.* 2014;2014(5):CD001181.
57. McSorley ST, Steele CW, McMahon AJ. Meta-analysis of oral antibiotics, in combination with preoperative intravenous antibiotics and mechanical bowel preparation the day before surgery, compared with intravenous antibiotics and mechanical bowel preparation alone to reduce surgical-site infections in elective colorectal surgery. *BJS Open.* 2018;2(4):185–194.
58. Goldring J, McNaught W, Scott A, Gillespie G. Prophylactic oral antimicrobial agents in elective colonic surgery. A controlled trial. *Lancet.* 1975;2(7943): 997–1000.
59. Mulder T, Kluytmans-van den Bergh M, Vlaminckx B, et al. Prevention of severe infectious complications after colorectal surgery using oral non-absorbable antimicrobial prophylaxis: results of a multicenter randomized placebo-controlled clinical trial. *Antimicrob Resist Infect Control.* 2020;9(1):84.
60. Jones RN, Wojeski W, Bakke J, Porter C, Searles M. Antibiotic prophylaxis of 1,036 patients undergoing elective surgical procedures. A prospective, randomized comparative trial of cefazolin, cefoxitin, and cefotaxime in a prepaid medical practice. *Am J Surg.* 1987;153(4):341–346.
61. Morita S, Nishisho I, Nomura T, et al. The significance of the intraoperative repeated dosing of antimicrobials for preventing surgical wound infection in colorectal surgery. *Surg Today.* 2005;35(9):732–738.
62. Itani KM, Wilson SE, Awad SS, Jensen EH, Finn TS, Abramson MA. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. *N Engl J Med.* 2006;355(25):2640–2651.
63. Goldstein EJ, Citron DM, Merriam CV, Abramson MA. Infection after elective colorectal surgery: bacteriological analysis of failures in a randomized trial of cefotetan vs. ertapenem prophylaxis. *Surg Infect (Larchmt).* 2009;10(2):111–118.
64. Sexton DJ. Carbapenems for surgical prophylaxis? *N Engl J Med.* 2006;355(25):2693–2695.
65. Chen M, Song X, Chen LZ, Lin ZD, Zhang XL. Comparing mechanical bowel preparation with both oral and systemic antibiotics versus mechanical bowel preparation and systemic antibiotics alone for the prevention of surgical site infection after elective colorectal surgery: a meta-analysis of randomized controlled clinical trials. *Dis Colon Rectum.* 2016;59(1):70–78.
66. Gårdlund B, Bitkover CY, Vaage J. Postoperative mediastinitis in cardiac surgery—microbiology and pathogenesis. *Eur J Cardiothorac Surg.* 2002;21(5):825–830.
67. Regueiro A, Linke A, Latib A, et al. Association between transcatheter aortic valve replacement and subsequent infective endocarditis and in-hospital

death. *JAMA.* 2016;316(10):1083–1092.
68. Sears ED, Wu L, Waljee JF, Momoh AO, Zhong L, Chung KC. The impact of deep sternal wound infection on mortality and resource utilization: a population-based study. *World J Surg.* 2016;40(11):2673–2680.
69. Slama TG, Sklar SJ, Misinski J, Fess SW. Randomized comparison of cefamandole, cefazolin, and cefuroxime prophylaxis in open-heart surgery. *Antimicrob Agents Chemother.* 1986;29(5):744–747.
70. Kaiser AB, Petracek MR, Lea JW 4th, et al. Efficacy of cefazolin, cefamandole, and gentamicin as prophylactic agents in cardiac surgery. Results of a prospective, randomized, double-blind trial in 1030 patients. *Ann Surg.* 1987;206(6):791–797.
71. Geroulanos S, Oxelbark S, Donfried B, Recker F, Turina M. Antimicrobial prophylaxis in cardiovascular surgery. *Thorac Cardiovasc Surg.* 1987;35(4):199–205.
72. Doebbeling BN, Pfaller MA, Kuhns KR, Massanari RM, Behrendt DM, Wenzel RP. Cardiovascular surgery prophylaxis. A randomized, controlled comparison of cefazolin and cefuroxime. *J Thorac Cardiovasc Surg.* 1990;99(6):981–989.
73. Wellens F, Pirlet M, Larbuisson R, De Meireleire F, De Somer P. Prophylaxis in cardiac surgery. A controlled randomized comparison between cefazolin and cefuroxime. *Eur J Cardiothorac Surg.* 1995;9(6):325–329.
74. Curtis JJ, Boley TM, Walls JT, Hamory B, Schmaltz RA. Randomized, prospective comparison of first- and second-generation cephalosporins as infection prophylaxis for cardiac surgery. *Am J Surg.* 1993;166(6):734–737.
75. Finkelstein R, Rabino G, Mashiah T, et al. Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections. *J Thorac Cardiovasc Surg.* 2002;123(2):326–332.
76. Calfee DP, Salgado CD, Milstone AM, et al. Strategies to prevent methicillin-resistant *Staphylococcus aureus* transmission and infection in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.* 2014;35(Suppl 2):S108–S132.
77. Bolon MK, Morlote M, Weber SG, Koplan B, Carmeli Y, Wright SB. Glycopeptides are no more effective than beta-lactam agents for prevention of surgical site infection after cardiac surgery: a meta-analysis. *Clin Infect Dis.* 2004;38(10):1357–1363.
78. Kriaras I, Michalopoulos A, Turina M, Geroulanos S. Evolution of antimicrobial prophylaxis in cardiovascular surgery. *Eur J Cardiothorac Surg.* 2000; 18(4):440–446.
79. Frenette C, Sperlea D, Tesolin J, Patterson C, Thirion DJ. Influence of a 5-year serial infection control and antibiotic stewardship intervention on cardiac surgical site infections. *Am J Infect Control.* 2016;44(9):977–982.

80. Bucknell SJ, Mohajeri M, Low J, McDonald M, Hill DG. Single-versus multiple-dose antibiotics prophylaxis for cardiac surgery. *Aust N Z J Surg.* 2000;70(6):409–411.
81. van Oostveen RB, Romero-Palacios A, Whitlock R, et al. Prevention of Infections in Cardiac Surgery study (PICS): study protocol for a pragmatic cluster-randomized factorial crossover pilot trial. *Trials.* 2018;19(1):688.
82. Faro S, Martens MG, Hammill HA, Riddle G, Tortolero G. Antibiotic prophylaxis: is there a difference? *Am J Obstet Gynecol.* 1990;162(4):900–907; discussion 907–909.
83. Jakobi P, Weissman A, Zimmer EZ, Paldi E. Single-dose cefazolin prophylaxis for cesarean section. *Am J Obstet Gynecol.* 1988;158(5):1049–1052.
84. Chelmow D, Ruehli MS, Huang E. Prophylactic use of antibiotics for nonlaboring patients undergoing cesarean delivery with intact membranes: a meta-analysis. *Am J Obstet Gynecol.* 2001;184(4):656–661.
85. Sullivan SA, Smith T, Chang E, Hulsey T, Vandorsten JP, Soper D. Administration of cefazolin prior to skin incision is superior to cefazolin at cord clamping in preventing postcesarean infectious morbidity: a randomized, controlled trial. *Am J Obstet Gynecol.* 2007;196(5):e451–e455.
86. Bollig C, Nothacker M, Lehane C, et al. Prophylactic antibiotics before cord clamping in cesarean delivery: a systematic review. *Acta Obstet Gynecol Scand.* 2018;97(5):521–535.
87. Teng C, Reveles KR, Obodozie-Ofoegbu OO, Frei CR. *Clostridium difficile* infection risk with important antibiotic classes: an analysis of the FDA Adverse Event Reporting System. *Int J Med Sci.* 2019;16(5):630–635.
88. Rhee C, Kadri SS, Dekker JP, et al. Prevalence of antibiotic-resistant pathogens in culture-proven sepsis and outcomes associated with inadequate and broad-spectrum empiric antibiotic use. *JAMA Netw Open.* 2020;3(4):e202899.
89. Guillemot D, Carbon C, Balkau B, et al. Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae*. *JAMA.* 1998;279(5):365–370.
90. Gagliardi AR, Fenech D, Eskicioglu C, Nathens AB, McLeod R. Factors influencing antibiotic prophylaxis for surgical site infection prevention in general surgery: a review of the literature. *Can J Surg.* 2009;52(6):481–489.
91. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis.* 2006;43(3):322–330.
92. Webb AL, Flagg RL, Fink AS. Reducing surgical site infections through a multidisciplinary computerized process for preoperative prophylactic antibiotic administration. *Am J Surg.* 2006;192(5):663–668.
93. Frighetto L, Marra CA, Stiver HG, Bryce EA, Jewesson PJ. Economic impact of standardized orders for antimicrobial prophylaxis program. *Ann*

Pharmacother. 2000;34(2):154–160.

94. Brandt C, Sohr D, Behnke M, Daschner F, Rüden H, Gastmeier P. Reduction of surgical site infection rates associated with active surveillance. *Infect Control Hosp Epidemiol.* 2006;27(12):1347–1351.

64

Vaccinations

Molly G. Minze and Katie D. Ellis

CORE PRINCIPLES		CHAPTER CASES
GENERAL VACCINE PRINCIPLES		
1	Adverse effects: Immunization adverse effects are in part dependent upon the type of vaccine preparation used. Adverse effects from live attenuated vaccines mimic the disease but are less severe and occur 7 to 10 days postvaccination. Inactivated (killed whole virus) vaccination adverse effects include soreness at the site of administration within 24 hours of the vaccination. Vaccination adverse effects are significantly less severe than is the disease itself.	**Case 64-1 (Question 1)**
2	Immunization schedules: Recommended immunization schedules	**Case 64-2 (Question 1)**

	are designed to optimize immune response, standardize regimens, and enhance immunization rates. Birth to 18 years and adult immunization schedules are reviewed and updated annually.	
3	Catch-up immunization schedules: To catch up within an immunization series, it is not necessary to restart from the first dose of the schedule. A delay in receiving subsequent doses does not interfere with final immunity gained from the vaccination.	**Case 64-3 (Question 1)**
	INACTIVATED VACCINES	
1	Hepatitis B: Hepatitis B vaccination is effective for both pre-exposure and postexposure prophylaxis. To prevent vertical transmission to an infant from a mother, it is key to provide vaccination within 12 hours of birth along with hepatitis B immunoglobulin for those mothers who test hepatitis B–positive.	**Case 64-4 (Question 1)**
2	Hepatitis B: Rates of hepatitis B are low in children and adolescents. Over half of acute hepatitis B infections occur in patients ages 30 to 49. Hepatitis B vaccination is recommended for adults who participate in high-risk behaviors, those in close contact with the infected persons, and patients with chronic liver disease.	**Case 64-4 (Question 2)**
3	Hepatitis A: Hepatitis A immunization is targeted toward toddlers with the aim of	**Case 64-5 (Question 1)**

	preventing transmission to adolescents and adults. It is also recommended for patients traveling to countries with high or intermediate endemic hepatitis A.	
4	Diphtheria, tetanus, and acellular pertussis/pertussis booster: Waning immunity against pertussis has resulted in outbreaks of pertussis in the United States. Adolescents and adults, particularly those with close contact with young infants, should receive a single dose of pertussis booster vaccine.	**Case 64-6 (Question 1)**
5	*Haemophilus influenzae b*: Immunization recommendations for *H. influenzae* type b are age dependent. The older an infant is at presentation, the fewer the doses needed to elicit a response. A single vaccine dose may be considered in children and adults with underlying diseases that place them a risk for infection.	**Case 64-7 (Question 1)**
6	Polio: Inactivated polio vaccine is recommended over the oral attenuated vaccine for polio vaccination in the United States because inactivated vaccine is associated with a lower incidence of vaccine-associated paralytic polio.	**Case 64-8 (Question 1)**
7	Polio: Routine vaccination of adults against polio with inactivated poliovirus vaccine is not recommended unless individuals plan travel to endemic areas.	**Case 64-9 (Question 1)**

	Oral polio vaccine may be considered only in unique situations.	
8	Meningococcal: Vaccination is recommended within populations at increased risk for contracting *Neisseria meningitidis*, including travelers to endemic areas, patients with specific immunodeficiencies, functional/anatomic asplenia, laboratory personnel dealing with meningococcus, and college students.	**Case 64-10 (Question 1)**
9	Human papillomavirus: This two- or three-dose vaccination series is recommended for adolescent patients for the prevention of anogenital cancers, anogenital warts, and head and neck cancers, in males and females. It is also recommended for the prevention of cervical cancers in females.	**Case 64-11 (Question 1)**
10	Pneumococcus: *Streptococcus pneumoniae* mostly affects young children and the elderly. The conjugate vaccines protect against 80% (pneumococcal conjugate vaccine [PCV 7]) and 90% (PCV 13) of infectious strains that cause disease in children younger than 6 years old.	**Case 64-12 (Question 1)**
11	Pneumococcus: The polysaccharide vaccine does not elicit immune response in children younger than 2 years old, and protects against 23	**Case 64-12 (Question 2)**

	strains of *S. pneumoniae* that typically cause adult disease.	
12	Influenza: Vaccination is recommended for anyone older than 6 months of age who does not have a current contraindication. The inactivated vaccine is delivered intramuscularly or intradermally, whereas the live attenuated vaccine is delivered as a nasal spray formulation.	**Case 64-13 (Question 1)**
LIVE ATTENUATED VACCINES		
1	Rotavirus: Infants vaccinated with the rotavirus vaccine shed the virus in the feces after immunization; however, the risk of transmission to an immunocompromised contact is relatively low with appropriate precautions.	**Case 64-14 (Question 1)**
2	Measles, mumps, rubella (MMR): Parents are fearful of the risk of autism that has been falsely associated with the MMR vaccine. Pharmacists must provide counseling to overcome parental fears and ensure protection against measles.	**Case 64-15 (Question 1)**
3	Varicella: Postexposure vaccination with the varicella vaccine is recommended within 5 days of exposure for those unvaccinated or who have not received a second dose of vaccine.	**Case 64-16 (Question 1)**
4	Varicella: Herpes zoster vaccination is	**Case 64-16 (Question 2)**

	recommended in adults older than 50 years of age to prevent reactivation of previously acquired wild-type varicella zoster infections.	
COVID-19 VACCINES		
1	COVID-19: COVID 19 vaccination is recommended for people 6 months and older.	**Case 64-17 (Question 1)**
IMMUNIZATION PRACTICES		
1	Vaccine administration: Intramuscular vaccinations are administered at a 90-degree angle into the muscle using a 1-inch needle. Subcutaneous vaccinations are administered at a 45-degree angle into the subcutaneous tissue by pinching this tissue up to prevent insertion into the muscle. When multiple injections are given at the same site, separate each injection by 1 inch.	**Case 64-18 (Question 1)**
2	Advocacy and establishing services: Pharmacists have an important role as immunization advocates to positively increase immunization rates. Pharmacist immunization training is widespread throughout the United States, but pharmacists must adhere to guidelines and principles established by their state Pharmacy Practice Act when administering immunizations to patients.	**Case 64-19 (Question 1)**

INTRODUCTION

The use of immunizations to control common infectious diseases is a major public health achievement. Children, adolescents, and adults are now routinely immunized against 17 infectious diseases.[1] Immunization rates are high overall and have remained stable in the United States, with >80% of children age 3 years receiving all the recommended vaccines.[2] As a result, low levels of vaccine-preventable diseases are occurring. Rates of immunization for adults against influenza and pneumococcus range from 23% to 45%, with higher coverage for individuals older than age 65 years.[3] Unfortunately, despite the overall high rates of immunization coverage, disparities still exist in vaccination coverage for the socioeconomically disadvantaged and by ethnicity.[2] Clearly, there is room for improvement and an opportunity for all health professionals to have an impact.

The need for timely immunization administration is key to preventing disease resurgences.[4] As the incidence of vaccine-preventable disease continues to decrease, patients are becoming less aware of the significance and severity of the diseases that could be prevented.[5–9] This, along with parental concerns regarding vaccine safety, may jeopardize previous vaccination achievements.[7,8] Health care providers play a vital role in clarifying misconceptions and educating parents and other health professionals about the importance of proper and complete immunizations.[7] Any contact with a patient represents an opportunity to promote immunization, and thus every medication history should include a review of immunization status to detect any deficiencies.[9]

VACCINE PRINCIPLES

General Principles

The principle of vaccination against disease is that the introduction of a small amount of the pathogen to the body produces protective immunologic memory (active immunity) and, if the pathogen is reintroduced at a later date, a greater immunologic response is elicited but without inducing disease.[10] The ideal vaccine would present a nonvirulent form of a pathogen that produces a strong immunologic response once in the body.[11]

Vaccine types include live attenuated, killed (inactivated) whole organism, subcellular/subunit, and DNA-based vaccines[11] (see **Table 64-1** for a listing of common vaccines and their formulation type). In addition, recent COVID-19 vaccine types include messenger ribonucleic acid (mRNA), adenovirus, and subunit protein vaccines.[12–15] Live attenuated vaccines contain weakened or inactivated forms of the pathogen, which causes replication within the host and ultimately elicits antibody- and cell-mediated immunity within the body via B-cell and T-cell responses.[11,12,16,17] Live vaccine administration produces a mild, typically asymptomatic infection at the time of vaccination followed by long-lived immunity from a single immunization.[18,19]

Table 64-1
Vaccine Overview

	Vaccines	Recommended Regimens	Comment
Diphtheria, tetanus, pertussis (inactivated; intramuscular)	<7 years: DTaP, DT ≥7 years: Tdap, Td	DTaP: 2, 4, 6, 15–18 months; booster at 4–6 years Tdap routine vaccination: 11–12 years Td or Tdap booster: Every 10 years	Minimum age 6 weeks; fourth dose can be administered at 12 months of age if at least 6 months since third dose Minimum age 10 years (Boostrix® and Adacel®)
Haemophilus influenzae type b (Hib; inactivated; intramuscular)	Hib	2, 4, 6, 12–15 months	Minimum age 6 weeks If PRP-OMP (PedvaxHIB®) at 2 and 4 months, no 6-month dose indicated (2, 4, and 12–15 months) PRP-T (ActHIB® and Hiberix®) is a four-dose series.
Hepatitis B (inactivated; intramuscular)	Hep B	Birth, 1–2 months, 6–18 months	Monovalent vaccine to be administered for any doses before 6 weeks Administer birth dose within 12 hours if HBsAg-positive mother Final dose should not be given before 6 months of age.
Hepatitis A (inactivated; intramuscular)	Hep A	Two doses 6 months apart	Minimum age 12 months
Human papillomavirus vaccine (inactivated; intramuscular)	HPV9	Two doses 9–14 years Three doses 15–26 years Second dose 1–2 months after first Third dose 6 months after first	Administer before sexual activity.
Influenza (IIV4 = inactivated; intramuscular) (LAIV 4 = live attenuated; intranasal)	IIV4, LAIV4	Annually Two doses 4 weeks apart at first annual vaccination	Minimum age IIV4 6 months Minimum age LAIV4 2 years Two doses required for patients ages 6 months–8 years at first annual vaccination
Measles, mumps, rubella (MMR; live attenuated; subcutaneous)	MMR	12–15 months; repeat dose 4–6 years	Minimum age 12 months; second dose may be administered as early as 4 weeks after previous dose.
Meningococcal serogroup A, C, W, Y vaccination (MCV = inactivated; intramuscular)	MCV4 (Menactra®, Menveo®, MenQuadfi®)	Two-dose series: 11–12 years, 16 years	Minimum age for Menveo® = 8 weeks; Menactra® = 9 months; MenQuadfi® = 2 years First-year college students not previously vaccinated at age 16 or older: one dose Menactra®, Menveo®, or MenQuadfi®
Meningococcal serogroup B vaccination (inactivated; intramuscular)	MenB-4C, Bexsero®; MenB-FHbp, Trumenba®	If not at increased risk: Bexsero® = two-dose series 1 month apart Trumenba® = two-dose series 6 months apart	In special situations in patients at increased risk, Trumenba® is a three-dose series. The two vaccines are not interchangeable.

	Vaccines	Recommended Regimens	Comment
Pneumococcal (inactivated polysaccharide; usually intramuscular, but subcutaneous ok) Pneumococcal (conjugate; intramuscular)	PCV 13, 15, 20 PPSV 23	2, 4, 6, 12–15 months If decided, 1 PCV 13 dose one dose ≥65 years PCV 20 If PCV 15 used, follow with PPSV 23 1 year later	PCV minimum age 6 weeks PPSV minimum age 2 years Administer PCV 13 dose before PPSV 23.
Polio (inactivated; usually intramuscular, but subcutaneous ok)	IPV	2, 4, 6–18 months	IPV minimum age 6 weeks If four or more doses given before 4 years of age, repeat booster at 4–6 years. Final dose should be after fourth birthday and at least 6 months after previous dose.
Rotavirus (live attenuated; oral)	RV1 RV5	2, 4 months 2, 4, 6 months	Initial dose: minimum age 6 weeks, maximum age 14 weeks 6 days Final dose: maximum age 8 months Rotarix® (RV1): 6-month dose not indicated
Varicella (live attenuated; subcutaneous)	VZV	12–15 months; repeat dose at 4–6 years	Minimum age 12 months; second dose may be administered as early as 3 months from previous dose.
Zoster (recombinant; intramuscular)	RZV	50 years of age	Two-dose series 2–6 months apart, minimum interval 4 weeks. Delay RZV until after pregnancy.

HBsAG positive +, hepatitis B surface antigen positive; PRP-OMP, PedvaxHIB or Comvax™ (Hep B-Hib).

Sources: National Center for Immunization and Respiratory Diseases. General recommendations on immunizations—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60:1–61; Wodi AP, Murthy N, Bernstein H, McNally V, Cineas S, Ault K. Advisory Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger—United States, 2022. *MMWR Morb Mortality Wkly Rep*. 2022;71:234–237; Murthy N, Wodi AP, Bernstein H, McNally V, Cineas S, Ault K. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older—Unites States, 2021. *MMWR Morb Mortality Wkly Rep*. 2022;71:229–233.

Killed whole organism and subcellular/subunit vaccines do not replicate within the host, nor can they revert to pathogenicity, but they often require adjuvants and/or multiple doses to increase the duration of immune response to the antigen.[11,16] Because the organisms in whole-pathogen vaccines are inactivated (killed), their effectiveness may be impaired by circulating antibodies, maternal antibodies (in infants), or concomitant infections. Toxoids are a specific kind of inactivated vaccine formed by modifying a biologic toxin (eg, diphtheria and tetanus), usually by mixing it with formaldehyde.

Subunit vaccines contain either a protein or polysaccharide antigen within the vaccine and elicit less reaction than do whole-pathogen vaccines; thus, immune responses are weaker and require multiple doses similar to that of inactivated vaccines.[11] Conjugate subunit vaccines, consisting of a polysaccharide protein conjugate where the protein is the antigenic toxin, produce improved immune responses because of B-cell activation by the polysaccharide component and T-cell activation by the protein component. Recombinant vaccines available include hepatitis B, human papillomavirus (HPV), recombinant and live influenza, live typhoid vaccine, meningococcal serogroup B vaccine, and live rotavirus.[20]

mRNA vaccines use nonviral vector nucleic acid–based genetic encoding in a protein to be incorporated and expressed at the level of the cell membrane, which causes a coordinated immune response in the host.[21],[22] These vaccines express a specific antigen to produce a directed humoral and cell-mediated response.[23] mRNA vaccines available at this time are for COVID-19.

Adenovirus vaccines are viral vector vaccines that use a weakened, nonvirulent, nonreplicating virus to deliver genetic material to encode proteins for specific antigen production in the host cells.[22],[24] These vaccines are in development for COVID-19, Ebola, human immunodeficiency virus (HIV), tuberculosis, and malaria.[22] A limitation of these vaccines is if the host has any preexisting immunity to the viral vector.[22]

Adverse Effects

CASE 64-1

Question 1: H.P. is a 38-year-old female concerned about the side effects of the annual influenza "shot."

What information can be provided regarding expected adverse effects for H.P.?

Vaccine adverse events are classified as local, systemic, or allergic.[1] Adverse reactions to inactivated vaccines include pain at the injection site and fever within 48 to 72 hours of administration.[25–27] In contrast, adverse effects from live attenuated vaccines occur 7 to 10 days after immunization, after the virus has replicated and the immune system has responded. Adverse reactions to live attenuated vaccines mimic the symptoms of disease. Transient rash occurs in 5% of patients receiving measles, mumps, rubella (MMR) immunizations, and a mild varicella-like rash (median of five lesions) occurs in <5% of patients receiving the varicella vaccine. Syncope, usually occurring within 30 minutes of immunization, has been reported, with 70% of syncopal episodes occurring within 15 minutes of immunization, and occurs more commonly in female patients and adolescents.

Although anaphylactic reactions to vaccines are rare, an allergic reaction may occur as a result of specific allergy to the vaccine itself or to trace components in the vaccine (eg, preservatives, antibiotics).[27] The best practice to prevent allergic reactions is through screening and obtaining a history of any previous allergic reactions to vaccinations, vaccine components, or hypersensitivities.[1] Patients with egg allergy can receive vaccines produced in chick-embryo-fibroblast tissue culture (eg, MMR) because the risk factor for serious reaction to these vaccines in egg-allergic individuals is very low.[28–31] MMR should be used cautiously in individuals with a history of a severe reaction to gelatin, which is a stabilizer in the MMR vaccine. Trace amounts of streptomycin, bacitracin, and neomycin are present in oral polio virus vaccine, inactivated polio vaccine (IPV), and MMR; therefore, these vaccines should not be administered to individuals with a history of an anaphylactic reaction to these antibiotics.[31]

Overall, vaccinations are safe, especially when compared with the risks of the diseases that these vaccines prevent, and the safety of immunizations are scrutinized continually.[31–33] In response to concerns about vaccine safety, the National Vaccine Injury Compensation Act mandated an ongoing review of evidence

regarding the possible adverse effects of vaccines and established a no-fault injury compensation program for selected vaccines.

Contraindications

Misconceptions about contraindications and precautions for immunization often result in missed opportunities to provide needed immunizations.[1,34] Acute, severe febrile illness; history of anaphylaxis to the vaccine or vaccine components; and history of a severe reaction to an immunization are clear contraindications to immunizations. Immunizations, however, should not be delayed in a patient who has a minor illness (eg, upper respiratory tract infection, otitis media, diarrhea), even in the presence of a low-grade fever. A family history of seizures, allergies, and sudden infant death syndrome are not contraindications for immunizations. Immunization of a patient with a history of anaphylaxis to a vaccine or vaccine component should be withheld until he or she has undergone desensitization. Preterm infants should begin to receive routine immunizations based on their chronologic age for all vaccines, although initiation of the hepatitis B series should begin at age 1 month.

Allergic reaction to previous exposure to vaccine components, immunosuppression (eg, immunosuppressive therapy, immunodeficiencies), encephalopathy, recent administration of blood products, and pregnancy (although the risk in pregnancy is largely theoretic) are contraindications to live attenuated virus or live bacterial vaccines. Pooled blood products (eg, immunoglobulins [Igs], packed red blood cells, platelet transfusions) can impair the immune response to a live vaccine because these products contain antibodies that can prevent one's immune system from mounting an adequate response.[1] The impairment of an immune response to an immunization varies, depending on the type and amount of blood product administered, and immunizations may need to be delayed for up to 12 months if pooled blood products have been administered recently.[1] With any question about immune response, antibody titers

can be obtained to determine whether a patient needs to be reimmunized.

GUIDELINES

Schedule for Immunizations

CASE 64-2

QUESTION 1: K.C., a 2-month-old female, is brought to the clinic for a scheduled well-baby visit. K.C.'s mother inquires about immunizations for her daughter.

What are the current recommendations for immunizing pediatric patients? When should these immunizations be given to K.C.?

The goal of immunization is to prevent specific infectious diseases and their sequelae. For maximal effectiveness, a vaccine must be administered to the susceptible population before anyone has been exposed to the pathogen. The age at which immunizations are administered to specific individuals depends on several factors (eg, age-specific risks of the disease, risks of complications, presence of maternal antibodies transferred through the placenta, maturity of the immune system). Usually, immunizations are administered at the youngest age that the child is able to develop an adequate antibody response.

The recommended childhood and adolescent immunization schedules are reviewed annually by the Advisory Committee on Immunization Practice (ACIP) and the American Academy of Pediatrics (AAP), and supported by the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), and published within the Morbidity and Mortality Weekly Report [35,36] and are available online (http://www.cdc.gov/vaccines/schedules). A partial summary of vaccination schedules is included in Table 64-1, but the reader is referred to the online publication of immunization schedules for a

more complete listing of the most current recommendations. The minimal immunization requirements for entry into public schools and day care centers vary with each state and the departments of health of individual states need to be consulted for these guidelines. The ACIP reviews the adult immunization schedule annually as supported by the American College of Physicians (ACP), AAFP, and the American College of Nurse-Midwives (ACNM) and published within the Annals of Internal Medicine and the Morbidity and Mortality Weekly Report [37,38] (available online at https://www.cdc.gov/vaccines/schedules/index.html). The respective schedules for children and adults should be reviewed annually, and the policies and procedures revised to ensure compliance.

A review of the childhood immunization schedule reveals that the recommended vaccines to be administered at 2 months of age include diphtheria, tetanus, and acellular pertussis (DTaP), IPV, *Haemophilus influenzae* type b (Hib), pneumococcal conjugate vaccine (PCV 13), and rotavirus vaccine. A second dose of the hepatitis B (Hep B) vaccine should also be administered if the first dose was given at birth. If Hep B vaccine was not given to K.C. at birth, the first dose should be given today, then repeated 4 weeks later, and again at 6 months (see Case 64-4, Question 1).

CASE 64-3

QUESTION 1: K.C.'s mother also mentions that she personally received two doses of an HPV vaccine series. Her physician asked her to receive a third dose in December, and it is now March.

Does K.C.'s mother need to restart the vaccination series for HPV?

Immunization schedules can be adjusted to meet individual needs and may begin at any time of the year. Vaccines should not be administered at time intervals shorter than those recommended to allow for maximal immune responses before the administration of subsequent doses.[1] A "catch-up" schedule for immunizations of children and adolescents who begin their immunizations late or who are >1 month behind schedule in their immunizations and

recommendations for minimal intervals between doses for the administration of various vaccines can be implemented.[1,35,36] It is not necessary for adults who delay administration of a subsequent dose of an immunization series to restart the vaccination series. An interruption or a delay in the recommended schedule does not interfere with the final immunity gained.

Alternative immunization recommendations are available for patients with altered immunocompetence to ensure protection from vaccine-associated disease, yet prevent adverse effects or acquiring disease from the vaccine itself in the case of live attenuated vaccines.[1,37–39] As an adult, K.C.'s mother should receive a third dose of HPV vaccine as soon as possible, but she does not need to restart the whole series.

INACTIVATED VACCINES

Hepatitis B

CASE 64-4

QUESTION 1: A.G. is an infant (weight 4.63 pounds [2.1 kg]) born to a mother in whom the hepatitis B surface antigen (HBsAg) status is unknown.

How should A.G. be managed?

Hepatitis B virus (HBV) can be transmitted via exposure to contaminated blood (eg, blood products or medical instruments, nonsterilized needles used in intravenous drug abuse, or tattooing), exposure to body fluids (eg, sexual intercourse), and transplacentally from an HBsAg-positive mother.[40] The prevention of HBV maternal transmission to an infant is essential because acute disease can progress to a chronic carrier state, which can lead to chronic liver disease and primary hepatocellular carcinoma. Children acquiring HBV infection before 5 years of age are at an especially high risk for

developing chronic infection.[40] All pregnant females should be tested for HBsAg, and HBsAg-positive pregnant females should be tested for hepatitis B virus deoxyribonucleic acid (HBV DNA). Infants born to HBsAg-positive mothers should receive their first vaccine dose in addition to hepatitis B immune globulin (HBIG) within 12 hours of birth, regardless of birth weight, to prevent vertical transmission.[41] When combined, HBIG plus HBV vaccine are 99% effective in preventing acute and chronic infection in infants born to HBsAg-positive mothers.[41] If the mother's HBsAg status is unknown, the infant should be also immunized with the Hep B vaccine within 12 hours of birth regardless of birth weight. For infants weighing <4.41 pounds (2 kg), HBIG should also be administered within 12 hours of birth. The mother's HBsAg status should be determined at the first opportunity. If the mother is HBsAg positive, HBIG should be administered to infants weighing ≥4.41 pounds (2 kg) as soon as possible, but no later than day 7 of life.[41] Medically stable infants weighing ≥4.41 pounds (2 kg) born to HBsAg-negative mothers should begin their immunization series within 24 hours of birth. Infants weighing <4.41 pounds (2 kg) and born to HBsAg-negative mothers should have their first vaccine dose delayed to the time of hospital discharge or age 1 month (even if weight is still <4.41 pounds [2 kg]). In all situations, subsequent vaccine doses should be administered at age 1 to 2 months and again at age 6 months. All unimmunized children should receive HBV vaccine as soon as they are identified.[41]

A.G. should receive Hep B vaccine within 12 hours of birth and the mother's status should be determined. If her mother is found to be HBsAg positive, HBIG should also be administered within 7 days of birth. A.G. can receive her subsequent doses of HBV vaccine according to the childhood immunization schedule. Three Hep B vaccines are currently available for use in the United States. Recombivax-HB® and Engerix-B® are yeast-derived recombinant vaccines administered as a three-dose series.[41,42] Either formulation can be used because the immune response from an immunization series using different vaccines is comparable to that of a full series using a single vaccine.[1,43] Heplisav-B® (Hep B CpG) is a two-dose

series indicated for adults ages 18 years and older as an option for unvaccinated or incompletely vaccinated individuals. The two-dose series only applies when both doses consist of Hep B CpG, and the doses should be administered 4 weeks apart. Revaccination is not recommended in patients with a normal immune system who were vaccinated as infants, children, adolescents, or adults. However, if anti-HBs <10 mIU/mL, revaccination is recommended for infants born to HBsAg-positive mothers, patients on hemodialysis, and other immunocompromised persons.[35,36]

CASE 64-4, QUESTION 2: A.G.'s mother (age 17 years) has not herself been immunized against hepatitis B. Should she begin receiving the Hep B series as well?

Despite a decline in hepatitis B infections in the United States after universal childhood immunization, more than a million adults are living with chronic hepatitis B infection. The highest incidence of acute hepatitis B in the United States occurs in adults ages 30 to 49 years, the majority of which occur in individuals with high-risk behaviors including multiple sexual partners, anal intercourse, and injectable drug abuse.[42] Individuals who have close contact with patients infected with hepatitis B, including health care workers, are also at risk of infection.[42] Children and adolescents not vaccinated during infancy should be given a three-dose series of intramuscular (IM) injections. Hep B vaccine is now universally recommended for all adults ages 19 through 59 years, and a two-, three-, or four-dose series should be recommended for routine vaccination. For patients ages 60 and older at risk for hepatitis B infection, a two- or three-dose series should be recommended. Patients ages 60 and older considered at risk include patients with chronic liver disease, HIV infection, sexual exposure risk, current or recent injection drug use, percutaneous or mucosal risk for exposure to blood, incarcerated persons, or those who travel in countries with high or intermediate endemic hepatitis B. Anyone age 60 or older who does not meet the recommendations based on risk may still receive hepatitis B

vaccination.[37,38] Antibody screening after immunization is only recommended in high-risk groups in whom future clinical management may depend on knowledge of immune status (eg, health care workers). Recommendations for serologic testing and revaccination and postexposure prophylaxis for such situations are available.[42] Patients on dialysis and other immunocompromised patients may require a fourth dose if the anti-HBs level is <10 mIU/mL 2 months after the third dose.[42]

A.G.'s mother should begin a three-dose series of Hep B vaccine. Monovalent vaccines are preferred for the initial vaccination; however, combination vaccines may be used[1,43] (see **Table 64-2**). Combination vaccines should not be used for infants younger than age 6 weeks; therefore, only single-antigen doses should be used for birth doses.[41] Of note, Heplisav-B® is not recommended during pregnancy owing to lack of safety data.[37,38]

Table 64-2
Combination Vaccines

Combination Vaccine[a]	Antigens[b]	Age Indicated	Regimen
Kinrix®	DTaP-IPV	4–6 years	Only for fourth dose of IPV and fifth dose of DTaP
Quadracel®	DTaP-IPV	4–6 years	Only for fourth dose of IPV and fifth dose of DTaP
Pediarix®[c]	DTaP-Hep B-IPV	6 weeks–<7 years	2, 4, 6 months
Pentacel®	DTaP-IPV-Hib	6 weeks–4 years	2, 4, 6, 15–18 months An extra monovalent IPV recommended for IPV at 4–6 years (total, five doses)
ProQuad®[d]	MMR-V	12 months–12 years	12–15 months, 4–6 years
Twinrix®	Hep A-Hep B	18 years+	0, 1, 6 months
Vaxelis®	DTaP-Hep B IPV-Hib	6 weeks–5 years	2, 4, 6 months

DTaP, diphtheria, tetanus, and acellular pertussis; Hep A hepatitis A; Hep B, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus vaccine; MMR, measles, mumps, and rubella vaccine; V, varicella vaccine.

[a]Vaccine interchangeability: If combination and single-antigen vaccines are used to complete an immunization series, it is preferred to use products from the same manufacturer. Immunogenicity of vaccine antigens between different manufacturers is unknown.

[b]Extra antigens: Administration of extra antigens using combination vaccines should be avoided. Availability of monovalent vaccines should be provided to avoid giving extra antigens and increase risk of adverse effects, particularly for inactivated vaccines which are reactogenic (eg, DTaP vaccine).

[c]Hepatitis B: Combination vaccines not recommended for hepatitis B birth doses (<6 weeks).

[d]ProQuad®: MMRV may be associated with an increased risk of febrile seizures when used at age 12 to 47 months. The use of MMR is preferred during this time.

Sources: National Center for Immunization and Respiratory Diseases. General recommendations on immunizations—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60:1–61; Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Practice (AAFP). *Pediatrics*. 1999;103:1064–1077; Marin M, Broder KR, Temte JL, et al. Use of combination measles, mumps, rubella and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2010;59(RR-3):1–12.

Hepatitis A

CASE 64-5

Question 1: A mother presents with her 2-year-old to her pediatrician for a well-child visit. Her pediatrician encourages her to have her child immunized against hepatitis A.

What are the differences between hepatitis B and hepatitis A infections, and what are the immunization recommendations?

Hepatitis A infection can present as either an acute or a chronic illness, but it is often asymptomatic in infants and young children. However, infections in older children and adults typically present with fever, malaise, anorexia, nausea, abdominal discomfort, and jaundice.[44] Clinical illness usually lasts 1 to 2 months, but it may be relapsing and can last up to 6 months. In 2017, adults ages 30 to 39 years had the highest reported incidence of hepatitis A.[45] Among all reported cases, the most common source of infection is household or sexual contact, followed by day care attendance or employment, international travel, and food or waterborne outbreaks. Asymptomatic children serve as a source of infection, especially for household or other close contacts.[45]

Vaccination programs targeting toddlers and young children are important because children are often asymptomatic and unwittingly transmit the virus to adolescents and adults. In addition, data suggest a “herd effect” when vaccination of children is widespread (ie, large population immunization programs indirectly protect those who are not immunized because the risk of being exposed to an infected individual is reduced).[46] A program aimed exclusively at toddlers in an endemic area reduced the prevalence of hepatitis A by >90%, not only in the 2- to 4-year-old vaccine recipients but in all age groups.[46]

There are two hepatitis A (Hep A) vaccines on the market, Havrix® and Vaqta®, each with adult and pediatric formulations. The pediatric formulations of the vaccine for routine vaccination are indicated for infants 12 months and older, and contain half the antigen of the adult formulations.[44] Vaccination involves a two-dose regimen, with the second dose to be administered 6 to 18 months after the initial dose, depending on the formulation (see Table 64-1). Two doses of hepatitis A vaccine should be administered to all children ages 2 to 18 years who have not previously received the Hep A vaccine. All patients age 1 year and older with HIV should be vaccinated. Persons with chronic liver disease, pregnant patients who are identified to be at risk for infection during pregnancy, or patients at risk for having a severe outcome from Hep A infection should be vaccinated. Vaccination during hepatitis A outbreaks of persons ages 1 year and older who are at risk for Hep A infection (eg, persons who use injection or noninjection drugs [ie, all those who use illegal drugs], persons experiencing homelessness, or men who have sex with men [MSM]) or who are at risk for severe disease from HAV (eg, persons with chronic liver disease or who are infected with HIV) is recommended. Additional groups of individuals who should be vaccinated include people in settings providing services to adults in which a high proportion of persons have risk factors for Hep A infection (eg, health care settings with a focus on those who use injection or noninjection drugs, group homes, and nonresidential day care facilities for developmentally disabled persons). Vaccination of persons who receive blood products for clotting disorders is no

longer recommended.[47] Adults for whom Hep A vaccination is recommended include those with high-risk behaviors, individuals who work with hepatitis A virus–infected primates or in a hepatitis A research laboratory setting, patients with chronic liver disease, and those traveling to areas where hepatitis A is endemic.[37],[38],[47] A combination vaccine containing both Hep A and Hep B is available and indicated in individuals older than age 18 years on a three-dose schedule (see Table 64-2).

Diphtheria, Tetanus, Pertussis Vaccines

CASE 64-6

Question 1: N.R. is a nurse who cares for children in a hospital setting. She calls with confusion regarding the need for her to receive a "pertussis booster." She indicates that she received her DTaP immunization series as recommended during childhood and her last tetanus shot was 3 years ago.

Should N.R. receive the pertussis booster (Tdap)?

Pertussis ("whooping cough"), an infectious disease caused by *Bordetella pertussis*, is characterized by a paroxysmal cough with a whoop-like, high-pitched inspiratory noise; vomiting; and lymphocytosis.[48] It is a highly communicable infection, which can affect 90% of infants and young children in nonimmunized households, and can be associated with serious sequelae, particularly in young infants. An estimated 0.3% to 14% of patients with pertussis experience encephalopathy, 0.6% to 2% have permanent neurologic damage, and about 0.1% to 4% die.[49] This serious childhood infection has been mitigated by the availability of an acellular pertussis vaccine (aP), which commonly is administered in combination with diphtheria (D) and tetanus (T) vaccines (DTaP). A primary series of four doses of DTaP is recommended at 2, 4, 6, and 15 to 18 months followed by a booster dose at school entry or 4 to 6 years of age.[35],[50] The efficacy of the DTaP vaccines against pertussis after primary immunization (three doses) is >80%.[50] Protection increases to 90% after the last booster (age 4–6 years)

and then decreases during the next 12 years, after which protection is minimal.[51,52]

Historically, DTaP vaccines contained whole-cell pertussis antigens. However, because of concerns regarding adverse effects, products currently available contain acellular pertussis antigens (see Table 64-1). Despite a more favorable adverse effect profile, the DTaP vaccine is contraindicated in anyone experiencing an anaphylactic reaction or encephalopathy within 7 days of immunization with DTaP when these symptoms cannot be attributed to another cause.[50] In addition, careful consideration of subsequent doses should be given to infants experiencing a temperature of 105 °F (40.56 °C; not resulting from another cause) or persistent, inconsolable crying lasting >3 hours within 48 hours of the administration of a pertussis-containing vaccine.[50] The pertussis component of the DTaP vaccine should be eliminated (ie, continue vaccination with DT) in any child experiencing collapse or a hypotonic–hyporesponsive episode. If an evolving neurologic disorder is present, pertussis immunization should be deferred until the neurologic problem has been fully evaluated. Preexisting, stable neurologic conditions (eg, well-controlled seizures) are not contraindications because the benefits of pertussis immunization outweigh the risks. A family history of seizures or other central nervous system (CNS) disorders is not a contraindication to vaccination.[51]

Two DTaP vaccines (Infanrix® and Daptacel®) are approved for the primary vaccination series. Combination vaccines may also be used; however, their use for primary vaccination is product dependent (Table 64-2).[48] If possible, the same DTaP product should be used for all five doses because the immunity, safety, and efficacy associated with the interchanging of different DTaP vaccines are unknown.[1,35] If the product information is unknown or unavailable from prior vaccinations, however, any licensed DTaP vaccine can be used to complete the vaccination series.[1,35]

Despite the availability of an effective vaccine and a high rate of vaccine coverage, pertussis continues to cause morbidity in patients of all ages in the United States.[48] Decreased immunity in

adolescents and adults is believed to contribute to this problem. About 12% of adult patients with a cough lasting >2 weeks have pertussis.[53] Although the illness is typically mild in adults and adolescents, they serve as a source of transmission to unprotected infants. This has led to the development and recommendation of acellular pertussis booster vaccines for adolescents and adults with a tetanus and diphtheria toxoid and acellular pertussis vaccine (Tdap).[1,35,54] (Note the designation as *dap* compared with *DaP* for primary vaccines.)

All pregnant females should receive one dose of Tdap during each pregnancy, irrespective of their history of receiving the vaccine.[54] Tdap should be administered at 27 to 36 weeks' gestation, preferably during the earlier part of this period, although it may be administered at any time during the pregnancy. The routine use of a single dose of pertussis booster (Tdap) is recommended for adolescents at ages 11 to 18 years. This population should receive a single dose of Tdap, preferably at a preventive care visit at ages 11 to 12 years. To ensure continued protection against tetanus and diphtheria, one booster dose of either Td or Tdap should be administered every 10 years throughout life. Regardless of the interval since their last tetanus or diphtheria toxoid–containing vaccine, persons ages 19 years or older who have never received a dose of Tdap should receive one dose of Tdap. To ensure continued protection against tetanus and diphtheria, booster doses of either Td or Tdap should be administered every 10 years throughout life.

A tetanus toxoid–containing vaccine is indicated for wound management when >5 years have passed since the last tetanus toxoid–containing vaccine dose.[54] If a tetanus toxoid–containing vaccine is indicated for persons ages 11 years or older, Tdap is preferred for persons who have not previously received Tdap or whose Tdap history is unknown. If a tetanus toxoid–containing vaccine is indicated for a pregnant female, Tdap should be used. For nonpregnant persons with documentation of previous Tdap vaccination, either Td or Tdap may be used if a tetanus toxoid–containing vaccine is indicated.[35,37,54] The pertussis booster (Tdap) may be administered regardless of the time since receipt of a

tetanus booster (Td). Two Tdap vaccine formulations (Boostrix® and Adacel®) are U.S. Food and Drug Administration (FDA) approved for use as a booster dose for children ages 10 to 18 years.[54] Recommendations for catch-up immunization of unvaccinated or undervaccinated individuals with DTaP/Tdap are available.[1,35,37] N.R. should receive the Tdap vaccination, particularly because she works in an environment with young children and she has not received a booster since her childhood DTaP series. She may be given a dose without regard to her prior tetanus booster vaccination.

Diphtheria and tetanus toxoids have been administered in combination with pertussis vaccination in the United States since the 1940s. Both diphtheria and tetanus are rare diseases in the United States as a result of universal childhood immunization. When disease does occur, it does so primarily in the elderly or those who were inadequately vaccinated.[48] For both diseases, it is the toxin-producing strains (toxigenic *Corynebacterium diphtheriae* and *Clostridium tetani*) that result in severe disease and, therefore, the vaccine antigens target the toxoids that they produce. The concentration of diphtheria toxoid in vaccine preparations for adults (designated as *d* as compared with *D* in primary vaccination) is reduced relative to those for children owing to increased reactions with repeated injections and improved response to lower antigen doses.[48] DTaP and diphtheria and tetanus toxoids (DT) are to be used for primary vaccination in children younger than age 7 years, whereas the tetanus and diphtheria toxoids (Td) are for use in children older than age 7 years and in adults. Booster doses of tetanus (Td) should be administered every 10 years.[48]

Haemophilus Influenzae b

Hib was the most common cause of bacterial meningitis and a leading cause of serious, systemic bacterial diseases in children younger than age 5 years until an effective vaccine was added to the routine immunization schedule.[55–57] The mortality rate associated with Hib meningitis was ~5%, with neurologic sequelae observed in

25% to 35% of survivors.[58,59] Epiglottitis, cellulitis, septic arthritis, osteomyelitis, pericarditis, and pneumonia also were commonly caused by *H. influenzae.* Although *H. influenzae* is associated with otitis media and respiratory tract infections, type b strains account for only 5% to 10% of these infections.[32,60]

CASE 64-7

QUESTION 1: P.M. is a 12-month-old child who has not been immunized against Hib. His parents wish to enroll him in day care and are now trying to catch him up on his immunizations.

How many doses of vaccine against Hib should he receive?

The Hib vaccine is a conjugate polysaccharide vaccine that is associated with a 95% reduction in the incidence of Hib disease in children younger than age 5 years.[60] The three currently available monovalent conjugate Hib vaccines are as follows: Hib meningococcal protein conjugate vaccine or PRP-OMP (PedvaxHIB®), Hib tetanus toxoid conjugate vaccine or PRP-T (ActHIB® and Hiberix®).[61] The immunogenicity of the conjugate vaccines are age dependent (ie, older children have an improved immune response).[60,61] The three conjugate vaccines are all approved for use in infants, the group at greatest risk for *H. influenzae* infection; however, they vary in their dosing regimens. The HbCV immunization series requires a priming series followed by a booster dose at 12 to 15 months. PRP-OMP's primary series is administered at ages 2 and 4 months in contrast to a schedule of 2, 4, and 6 months' primary series for the other vaccines.[1,35,61] Ideally, the primary series should be completed with the same HbCV; however, data support the interchangeability of the products for the priming and booster doses.[35,62] If PRP-OMP is used in a priming series with another HbCV, the number of doses necessary to complete the series for the other product should be administered.[62] Combination vaccines may also be used according to indications for each (see Table 64-2).[35,62]

The number of doses of HbCV vaccine needed in previously unimmunized older infants and children depends on their age at presentation. Children who begin HbCV at ages 7 to 11 months should receive a primary series of two doses of a vaccine containing PRP-T, or PRP-OMP followed by a booster dose at age 12 to 18 months administered at least 2 months after the previous dose.[35,62] Children ages 12 to 15 months should receive a primary series of one dose followed by a booster dose 2 months later. If a child reaches age 15 months without receiving HbCV, only one dose is necessary.[35,62] HbCV is not routinely recommended in children younger than age 5 years or in adults. Adults who have anatomic or functional asplenia or sickle cell disease, or are undergoing elective splenectomy should receive one dose of Hib vaccine if they have not previously received Hib. Adults with a hematopoietic stem cell transplant (HSCT) should receive three doses of Hib in at least 4-week intervals 6 to 12 months after transplant regardless of their Hib history. Hib is not routinely recommended for adults with HIV infection because their risk factor for Hib infection is low.

Polio

Polio, an infectious disease caused by a highly contagious enterovirus, can strike at any age, but primarily affects children younger than age 3 years (>50% of cases). The three identified serotypes of poliovirus are transmitted person to person by direct fecal–oral contact or indirect exposure to infectious saliva, feces, or contaminated water.[63,64] After household exposure, 90% of susceptible contacts become infected.[63] The poliovirus enters through the mouth and then multiplies in the throat and intestines. Once established in the intestines, the poliovirus can enter the bloodstream and invade the CNS, which may result in paralysis.[63–65]

Immunity to polio can be achieved after natural infection with poliovirus; however, infection by one serotype of the poliovirus does not protect an individual against infection from the other two serotypes.[63] Immunity can also be achieved through immunization,

and the development of effective vaccines to prevent paralytic polio was one of the major medical breakthroughs of the 20th century. Since the advent of the trivalent oral polio vaccine (OPV) and IPV, the incidence of paralytic poliomyelitis has been reduced dramatically.[65]

CASE 64-8

QUESTION 1: H.G., the mother of a 2-month-old infant, is surprised when the nurse brings in a polio vaccine injection. She remembers that she had received an oral form of the vaccine as a child.

Why is H.G.'s infant receiving a form of polio vaccine different from what she had received?

Historically, the live attenuated OPV (or Sabin vaccine) was the formulation of choice in the United States. Its advantages include low cost, ease of administration, and induction of lifelong immunity.[63] In addition, OPV provides a high level of gastrointestinal immunity, thus preventing the carrier state. The fecal shedding of the attenuated OPV virus after vaccination is also an effective way to immunize or boost the preexisting immunity in close contacts.[63],[65] Despite these benefits, OPV carries the risk of vaccine-associated paralytic polio (VAPP), especially after the first dose in immunocompromised patients such as those with B-lymphocyte disorders (eg, agammaglobulinemia, hypogammaglobulinemia).[64] In contrast to OPV, the enhanced IPV (IPOL®), which is administered IM, has not been associated with VAPP or other reactions.[64],[66] Although IPV provides systemic immunity similar to that of OPV, it induces less immunity in the gastrointestinal tract.[63],[64] The risks of VAPP from OPV, despite its high efficacy, have resulted in the recommendation of IPV as the preferred dosage form for childhood immunization.[1],[35],[65]

The ACIP and AAP guidelines recommend that all children should receive four doses of IPV at ages 2 months, 4 months, 6 to 18 months, and 4 to 6 years. The first dose of vaccine should be administered no sooner than 6 weeks of life.[66] The last dose of the

four-dose series should be administered after age 4 years and at least 6 months after the previous dose.[35],[66] Combination vaccines containing IPV are available and may be used to provide the initial four IPV doses. When Pentacel® is used, an additional IPV booster dose is recommended to ensure adequate immunity. The IPV booster dose should be administered at ages 4 to 6 years, which results in a total of five doses; this is acceptable as long as it is delivered at least 6 months after the fourth dose[65] (see Table 64-2).

CASE 64-9

QUESTION 1: L.G. is a 28-year-old graduate student who is planning extensive travel through the African continent and is concerned about polio because she had not been immunized as a child.

What would be a prudent immunization schedule for her if her trip includes travel to a polio-endemic area?

Routine poliovirus vaccination of persons older than age 18 years is not necessary in the United States because U.S. residents are at minimal risk for exposure. Vaccination, however, should be considered for adults at high risk for polio exposure (eg, travel to an area endemic for polio, close contact with children who will be receiving OPV, close contact with patients who may be excreting wild polioviruses, or work that requires handling poliovirus specimens).[65],[66] IPV is the vaccine of choice because adults have a higher incidence of VAPP from OPV than do children. Ideally, L.G. should receive two doses of IPV, administered 4 to 8 weeks apart, followed by a third dose 6 to 12 months later. If exposure is likely in <8 weeks, two doses of IPV should be administered at least 4 weeks apart.[65] If L.G.'s travel must be undertaken on short notice (<4 weeks) she should receive one dose of IPV, with receipt of the remaining doses at a later date according to schedule.[65] Even if L.G. had been immunized as a child, a single dose of IPV may be considered for booster effect.[65]

Currently, OPV is recommended only in special circumstances, such as vaccination to control outbreaks of paralytic polio,

unvaccinated infants traveling in <4 weeks to areas endemic for polio, and children of parents who reject the number of vaccine injections.[65],[66] In parents who are concerned about the number of injections, OPV may be considered for the third and fourth vaccination after receiving systemic protection with IPV for the first two doses.[65] IPV is the only poliovirus vaccine that should be used in patients with an immunodeficiency disorder, those receiving immunosuppressive chemotherapy, or those living with a person who is known or suspected to have these conditions.[65],[66]

Meningococcus

CASE 64-10

Question 1: J.C. is a 12-year-old female who presents for a checkup with her pediatrician. In discussion, it is found that her cousin attends a university where an outbreak of meningococcal disease recently occurred.

Should J.C. receive meningococcal vaccine?

After dramatic reductions of *Streptococcus pneumoniae* and Hib strains of meningitis secondary to conjugate vaccines, *Neisseria meningitidis* has become a more prominent cause of bacterial meningitis. The ACIP recommends routine vaccination of adolescents, with first dose at age 11 to 12 years and a booster at 16 years, persons ages older than 2 months at increased risk for meningococcal disease, and patients in at-risk groups to control outbreaks.[67] Patients with increased risk factors for meningococcal disease include those with persistent complement deficiencies, functional or anatomic asplenia, travel to countries where meningococcal disease is hyperendemic or endemic, or who are at risk during an outbreak. Patients ages 2 months to 55 years not previously vaccinated should receive the vaccination if they have persistent complement deficiency, complement inhibitor use, functional or anatomic asplenia, have HIV, are first-year college students in residential housing, military recruits, travel to countries

where meningococcal disease is hyperendemic or endemic, or who are at risk during an outbreak, or are microbiologists who are routinely exposed to *N. meningitides*.[67]

The available meningococcal vaccine (MCV) options include two different conjugate vaccines covering serotypes A, C, Y, and W-135 of *N. meningitides.* The two conjugate vaccines available (Menactra® and Menveo®), both MCV4 conjugate vaccines, are indicated for individuals ages 11 to 55 years.[67] The ACIP recommends administration of this vaccine to all persons at age 11 to 12 years (or at high school entry if there is no history of vaccination) and to unvaccinated college freshmen residing in dormitories. In addition, as stated earlier, the ACIP recommends a booster dose at around age 16 years and a two-dose primary vaccination for patients with reduced response to a single dose.

Meningococcal serogroup B vaccination is available as Bexsero® or Trumenba®.[67] It is indicated in children ages 10 years and older, with a preferred age of 16 to 18 years for administration. It may be administered to adolescents and young adults ages 16 to 23 not at increased risk based on shared clinical decision-making. Both vaccines are a two-dose series; however, they are not interchangeable. The same product should be used for all doses in a series. Patients older than age 10 years with anatomic or functional asplenia, persistent complement deficiency, or complement inhibitor use should receive a two-dose series of Bexsero®, or a three-dose series of Trumenba®. In 2019, the ACIP recommended that persons with certain medical conditions and microbiologists routinely exposed to *N. meningitidis* isolates receive a MenB booster dose 1 year after primary series completion, then every 2 to 3 years thereafter. During an outbreak, a single MenB booster dose was recommended if it had been ≥1 year since primary series completion. In both the adult and pediatric population, MenACWY vaccines may be administered simultaneously with MenB vaccines in a different injection site, if indicated.[35]

Adverse effects (eg, fever, headache, chills, malaise, and arthralgias) are relatively rare; however, the Centers for Disease Control and Prevention (CDC) and the FDA issued a warning

regarding the potential for increased risk of Guillain–Barré syndrome in patients receiving the Menactra® conjugate vaccine.[68] Over the course of a 16-month period beginning in June 2005, 15 cases were reported in the 11- to 19-year-old age group, and two cases in those older than age 20 years. All patients recovered. Despite this apparent small increased risk of Guillain–Barré syndrome, current recommendations remain the same, but monitoring of this development will continue. No cases of Guillain–Barré syndrome have been reported with Menveo®; however, surveillance is ongoing. At this time, J.C. should receive one of the two MCV4 vaccines and be advised to receive a booster dose at age 16.

Human Papillomavirus

CASE 64-11

Question 1: J.S. is a 12-year-old female who is healthy and not currently sexually active. Her mother and she would like background information including the role of the HPV vaccine and recommendations for use of the vaccine in J.S.

What information can you give them?

HPV commonly infects the genital tract and is primarily transmitted by sexual contact. Infection with HPV has been associated with cervical cancer as well as other anogenital cancers (vulvar and vaginal cancers in females and penile cancers in males), anogenital warts, and recurrent respiratory papillomatosis, and it is estimated to be the most common sexually transmitted infection in the United States.[69–71] HPV affects both sexes with similar infection rates, and it is usually asymptomatic, unrecognized, or subclinical.[69,72] Acute HPV infections typically resolve without clinical complications within 1 year; however, 10% to 15% of infections remain persistent and pose a risk of invasive cervical carcinoma and other anogenital carcinomas.[73] Although not all HPV infections cause cervical cancer, almost all (99%) cervical cancer in females is associated with a previous HPV infection.[70,71] The majority of disease associated with

HPV is caused by the HPV types 6, 11, 16, and 18, with HPV strains 16 and 18 accounting for 64% of invasive HPV-associated cancers and ~50% of cervical cancer precursors.[71,74,75] In contrast, HPV strains 6 and 11 account for the cause of 90% of genital warts and most cases of recurrent respiratory papillomatosis.[76,77] Infection with one strain of HPV does not prevent infection from other strains; thus, repeated infections can occur through one's lifetime, and those with prior HPV infections benefit from immunization as well.[73]

A nine-valent vaccine (Gardasil® 9) is available for the prevention of HPV infection in both males and females ages 9 to 45 years old.[78] Gardasil® is indicated for the purpose of prevention of genital warts; anal, oropharyngeal, and head and neck cancers; and other precancerous lesions.[78]

Routine vaccination with any HPV vaccine is recommended for patients at age 11 to 12 years and may begin at age 9 years.[71,79] Vaccination at this age attempts to achieve an immune response before the sexual debut and involves a two-dose series administered at intervals of 0 and 6 to 12 months for patients initiating vaccine before 15 years old.[69,71] Immunization against HPV is 90% effective in reducing persistent HPV infections and 100% effective in preventing HPV-related diseases such as genital warts or lesions.[76,77] The vaccine dosing schedule is set at two or three doses, depending on the age of initial vaccination.[71] If initial vaccination is given at age 9 to 14 years, a two-dose series at 0 and 6 to 12 months is recommended. If initial vaccination is given at 15 years or older, a three-dose series at 0, 1 to 2 months, and 6 months is recommended, with the minimum interval between doses one and two of 4 weeks, between doses two and three of 12 weeks, and doses one and three of 5 months. There is no need to restart the series if the schedule is interrupted, and the number of recommended doses is dependent on the age at patient's first dose.[71] ACIP recommends that victims of sexual abuse or assault begin vaccination at age 9, that patients with immunocompromising conditions receive the three-dose series, and that HPV vaccination should be delayed until after pregnancy.[79] For patients older than age 27 years through age 45 years who have been adequately

vaccinated, discussion of the benefit of catch-up vaccination through shared decision-making should occur.[79]

The current vaccination rates for HPV vaccination increased between 2018 and 2019, and more teens are beginning the vaccination series on time. This is likely secondary to efforts at the local, state, and federal levels and simplifying the dosing schedule.[80] The CDC recommends immunization for adolescents, regardless of current sexual activity, to decrease the lifetime risk of HPV infections and HPV-associated diseases to protect against infection when the time that an individual chooses to become sexually active comes.[77],[79] Based on the current recommendations, J.S. should receive the HPV vaccine.

Pneumococcus

CASE 64-12

QUESTION 1: M.T. is a 5-year-old male with a history of asthma. His pediatrician recommends that he receive the pneumonia vaccine.

What is the evidence behind this recommendation?

S. pneumoniae (pneumococcus) infection can cause meningitis, pneumonia, sinusitis, and otitis media, and it is a major source of illness and death among children and adults.[81–83] Infants, young children, and older patients are at highest risk for exhibiting pneumococcal infections.[81] The risk factor for disseminated pneumococcal infections is increased by underlying medical conditions (heart failure, chronic obstructive pulmonary diseases), chronic liver disease (eg, cirrhosis), functional or anatomic asplenia (eg, sickle cell disease, splenectomy), and acquired or inherited immunosuppressive conditions (eg, HIV, cancer, immunosuppressive therapy).

Several pneumococcal vaccines are available: the original polysaccharide vaccine (Pneumovax®, PPSV 23) and conjugate pneumococcal vaccines (Prevnar®, PCV 13; Vaxnuevance™, PCV

15, and Prevnar 20™, PCV 20).[81,82,84] Pneumovax® contains 23 of the most prevalent or invasive purified capsular-polysaccharide antigen types of *S. pneumoniae.* Antibody response to Pneumovax® is inconsistent in children younger than age 2 years partially because the antigens included in Pneumovax® protect against strains that typically cause adult disease, but not childhood disease. In contrast, the conjugate pneumococcal vaccines (Prevnar 13®) improve immunogenicity and efficacy in infants and toddlers.[82] The PCV 13 vaccine provides protection against the 13 pneumococcal strains that cause 90% of all pneumococcal invasive diseases in children younger than age 6 years.[85] The ACIP recommends giving the conjugate 13 vaccine (PCV 13) to all children ages 2 to 59 months and children ages 60 to 71 months with underlying medical conditions that place them at high risk for experiencing pneumococcal disease or its complications.[82] Because M.T. has already passed the recommended age for vaccination and has asthma, he should receive the PCV 13 vaccine today.

Immunocompromised patients typically have an unreliable response to vaccines, but because of the potential benefits, the pneumococcal vaccines should be administered. PCV 13 and PPSV 23 are recommended for children 6 to 18 years old with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants.[83,86] In children, PCV 13 should be administered first, followed by PPSV 23 after 8 weeks, and a second PPSV 23 dose 5 years later.[86]

Case 64-12, Question 2: M.T.'s grandfather is 68 years old, a previous smoker, and has cardiovascular disease. Should M.T.'s grandfather receive pneumococcal vaccine?

PCV 13 vaccination in children has caused significant decline in PCV 13–type pneumococcal disease in adults.[87] In the adult population, one dose of PCV 15 or 20 is recommended to be administered to adults ages 65 years and older who have not received a PCV vaccine in the past or whose vaccination history is

unknown and in adults ages 19 to 64 years with certain underlying medical conditions or other risk factors.[84] These underlying medical conditions or risk factors include immunocompetent patients with chronic heart disease, chronic lung disease, diabetes mellitus, cerebrospinal fluid leaks, cochlear implants, alcoholism, chronic liver disease, functional or anatomic asplenia, cigarette smoking, sickle cell disease or other hemoglobinopathies, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, multiple myeloma, and solid organ transplants.[37],[38],[84] If PCV 15 is used, a dose of PPSV 23 should be given 1 year later.[84] Adults who received PPSV 23 previously may receive a PCV vaccine 1 year after their last PPSV 23 dose.[84] If PCV 15 is used, there is no need to deliver another dose of PPSV 23.[84]

M.T.'s grandfather (a previously unvaccinated 68-year-old male) should receive one dose of PCV 15 or 20. If PCV 15 is used, it should be followed by a PPSV 23 vaccine 1 year later.

Influenza

Annual influenza vaccination is the most effective method for preventing influenza viral infections, complications, and sequelae.[88] Recommendations for influenza vaccination include anyone older than age 6 months who does not have a contraindication.[88] Routine vaccination has been supported since 2010, and clinical evidence confirms that annual influenza vaccination is a safe and effective preventative health measure with potential benefit for all ages of the population.[88] Vaccination should occur before the onset of influenza virus within the community and patients should receive their dose as soon as available, preferably by the end of October.[88]

Each year, the influenza vaccine is formulated to contain four inactivated influenza virus strains (usually, two type A and one or two type B) predicted to be in circulation within the United States during the upcoming flu season.[88] The vaccine is available in IM-administered formulations including the following: a quadrivalent

inactivated influenza vaccine (IIV) standard-dose formulation, a quadrivalent recombinant influenza vaccine (RIV4), a quadrivalent cell-culture–based inactivated vaccine (ccIIV4), a quadrivalent inactivated high-dose formulation, a quadrivalent adjuvant inactivated influenza vaccine (aIIV4), and a quadrivalent intranasal live attenuated influenza vaccine (LAIV4).[88] Each season, the composition of the vaccine is evaluated; all vaccines available in the United States are quadrivalent vaccines that contain two type A strains and two type B strains.[88]

The injectable IIV is indicated for use in children at least 6 months old to adults, including those with high-risk conditions.[88] Standard- and high-dose nonadjuvanted IIV are available.[88] The LAIV4 (intranasal) is indicated for use in healthy nonpregnant patients ages 2 to 49 years old.[88] The RIV4 and ccIIV4 are considered safe for use in patients with a history of anaphylactic egg allergy.[88] The RIV4 is indicated in patients older than 18 years, whereas the ccIIV4 is indicated in patients 2 years or older.[88]

Influenza vaccine should be administered annually for adequate protection. Children younger than 9 years old require two doses of the vaccine administered 1 month apart to achieve adequate antibody response during the first season they are vaccinated.[88] Influenza vaccine contains a small amount of egg protein, and historically it has been contraindicated in patients with a severe egg allergy.[88] Evidence indicates that even patients with severe egg allergies, including hives, or those who can eat lightly cooked eggs can safely receive the influenza vaccine in the setting of health care personnel in case anaphylactic treatment is necessary. The RIV4 and ccIIV4 are alternatives to patients with egg allergies.

One IIV4 vaccine, Afluria®, is licensed for delivery via a microinjection system into the dermis and is recommended for patients ages 18 to 64 years.[88]

CASE 64-13

Question 1: H.N. is a 72-year-old male inquiring about an influenza vaccine for older adults.

Is there a recommended vaccine for H.N.? Could he be given the LAIV instead?

Two IIV4 vaccines are indicated for patients ages 65 years and older: the high-dose IIV4 (Fluzone High-Dose®) and adjuvant IIV4 (Fluad Quadrivalent®).[88] Standard-dose inactivated quadrivalent influenza vaccines contain a total of 60 µg (15 µg of each of the four recommended strains) of influenza virus antigen per 0.5-mL dose. In contrast, Fluzone High-Dose® has four times the activity and is formulated to contain a total of 240 µg (60 µg of each strain) of influenza virus antigen in each 0.5-mL dose. The older than 65 population is targeted to receive the high-dose formulation because older patients respond with a lower antibody titer to the conventional IIV.[89],[90] Original data that supported the use of a high-dose formulation in older adults showed significantly higher antibody titers for all three influenza strains present when antibody titers were measured in patients who received a trivalent high-dose vaccine.[90–93] In a study to confirm that the high-dose influenza IIV3 improved protection against laboratory-confirmed illness, the high-dose IIV3 produced a higher antibody response and provided improved protection compared to the standard-dose IIV3.[93] The high-dose recipient rates for pneumonia, cardiorespiratory conditions, hospitalizations, nonroutine medical visits, and medication use were lower than were the standard-dose recipients, thus concluding an estimate of improved relative efficacy for the high-dose IIV3 versus the standard-dose IIV3. The safety and efficacy of the high-dose IIV4 was compared to two formulations of high-dose IIV3, with improved immunogenicity against the fourth strain of influenza as compared to the high-dose IIV3.[94] High-dose IIV4 was noninferior to high-dose IIV3 for all four strains in terms of hemagglutination inhibition geometric mean titers and seroconversion rates, but was superior at inducing higher hemagglutination inhibition geometric mean titers and seroconversion rates for both B strains when compared to high-dose IIV3.[88],[94] The safety profiles were similar in each group, with higher injection site reactions and systemic adverse reactions in the

high-dose IIV4, although categorized as mild to moderate with resolution in 3 days.[88,94]

The adjuvant IIV4 (Fluad Quadrivalent®) is also licensed for older adults ages 65 years or older.[88] The adjuvant IIV4 was compared to adjuvant IIV3, where it produced a similar immune response and was noninferior to adjuvant IIV3.[95] However, neither group met seroconversion criteria and titer thresholds for the influenza B strains.[88,95] The safety profiles were similar between the adjuvant IIV4 and adjuvant IIV3 groups, with higher injection site reactions and systemic adverse reactions in the adjuvant IIV4 group. Most of these were mild to moderate and resolved within 2 to 4 days.[88,95]

The LAIV4 (FluMist®) is available for use in healthy, nonpregnant patients ages 2 to 49 years.[96] After administration, recipients become infected with attenuated virus strains, which stimulates both local IgA and circulating IgG antibodies.[97–100] Because live attenuated influenza viral particles are present within the LAIV4, recipients may experience mild signs or symptoms related to influenza infection, such as rhinorrhea, nasal congestion, fever, or sore throat.[96] Those who should not receive or may not be able to receive the live vaccine include patients who are or have the following [88,96]:

- Severe allergy to eggs or inactive ingredients such as monosodium glutamate, gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, gentamicin, or ethylenediaminetetraacetic acid
- Life-threatening reactions to previous influenza vaccinations
- Current wheezing or a history of wheezing if younger than 5 years of age
- Older than age 5 years with asthma
- Pediatric and adolescent patients currently taking aspirin therapy
- Known or suspected immunodeficiency
- History of Guillain–Barré syndrome within 6 weeks of influenza vaccine
- A history of heart, kidney, or lung disease or diabetes

- Pregnant or nursing
- Close contacts and caregivers to someone severely immuno-compromised
- Taken antiviral medications recently (oseltamivir or zanamivir within 48 hours, peramivir within 7 days, or baloxavir within 17 days)
- Cerebrospinal fluid leaks or cochlear implants
- Mild-to-moderate illness at time of vaccination
- Any underlying medical condition that predisposes to complications after influenza infection

Because of his age, H.N. should not be given the intranasal vaccine, but he could receive either the standard- or high-dose inactivated vaccine.

LIVE ATTENUATED VACCINES

Besides the live attenuated flu vaccine discussed previously, there are several other live attenuated vaccines currently available for use (see Table 64-1).

Rotavirus

Rotavirus is a major cause of gastroenteritis and subsequent dehydration in the United States. Almost all children in the United States experience rotavirus gastroenteritis within the first 5 years of their lives and up to 50% of hospitalizations secondary to gastroenteritis in children are caused by rotavirus infection.[101],[102] The AAP and the CDC currently recommend routine immunization of infants with the rotavirus vaccine.[35] There are two oral, live attenuated rotavirus vaccines currently commercially available: Rotateq® (RV5), a pentavalent vaccine, and Rotarix® (RV1), a monovalent vaccine.[103] Both vaccines are believed to be equally effective despite the lack of head-to-head comparison trials. The

RV5 vaccine is administered in a three-dose series at 2, 4, and 6 months, whereas the RV1 vaccine follows a two-dose series at 2 and 4 months.[35],[103] Initial vaccination should begin at a minimum of age 6 weeks and the maximum age at which to administer the last dose is at age 8 months.[103] It is preferred that all doses be administered with the same product; however, if a combination of RV5 and RV1 is used, a total of three doses should be administered.[103] Although immunization against rotavirus does not prevent all future episodes of rotavirus infection, it can significantly reduce the severity of infections and reduce hospitalization rates.

CASE 64-14

QUESTION 1: J.M., a 24-year-old mother, presents her 2-month-old infant to receive immunizations. She is concerned about the administration of the rotavirus vaccine because the infant's grandmother is undergoing chemotherapy for breast cancer.

Will the vaccine put her mother at risk for infection and/or cause "bowel problems" for her baby?

Because the rotavirus vaccine is a live attenuated vaccine and infants can shed the virus after administration, the immunocompromised person (the grandmother) should avoid contact with the infant's feces and adhere to good handwashing procedures, particularly during the first week after vaccine administration.[101–103] Although an immunized infant can spread the rotavirus to an immunocompromised person, the risk is believed to be small relative to the benefits and risks to the immunocompromised individual. For example, if not immunized, the infant may become infected with rotavirus and shed much higher amounts of the virus in their stool with a greater potential of spreading the illness to others. Thus, rotavirus immunization of infants under this circumstance still is strongly encouraged.[101]

The immunization of infants who themselves are immunocompromised is more controversial. Rotavirus immunization in this circumstance requires the medical practitioner to discuss risks and benefits with the infant's parents.

Despite being a live attenuated vaccine, the rotavirus vaccine may be administered at any time relative to the administration of blood products and antibody-containing products.[103] There appears to be no interference with the antibody response to the vaccine with the use of these products because much of the immune response is local within the gastrointestinal tract, which leads to protection from gastroenteritis.

Measles, Mumps, Rubella

CASE 64-15

Question 1: J.C. is a 15-month-old female who is scheduled to receive her MMR vaccination. J.C.'s mother is concerned about the risks of autism and other adverse effects from the vaccine.

How should the mother be counseled?

Measles, historically a highly contagious and common disease of childhood, often is associated with symptoms such as high fever, rash, cough, rhinitis, and conjunctivitis.

Complications, although uncommon, include pneumonia and encephalitis. Live attenuated measles virus vaccine produces a benign infection that is thought to produce lifelong immunity. Infections with measles, mumps, or rubella are uncommon in the United States secondary to a significant decrease in the incidence of measles when American children were required to receive the vaccine before entering school.[104],[105] During the 1985 to 1988 epidemic, most measles transmission occurred in areas with 95% immunization rates, indicating that some children fail to respond adequately to the initial vaccine dose.[106] In addition, up to 47% of reported cases of measles in the United States result from international importation; the remaining cases result from outbreaks in school-age children who did not receive a second dose of the vaccine.[105],[107] Unfortunately, many parents are refusing immunization

of their infants with the MMR vaccine because of unfounded media reports about the risk of autism.

The concern regarding the risk from autism after vaccination with the MMR vaccine stems from a report by Wakefield et al published in 1998. This report identified a causal relationship with the administration of the MMR vaccine and the subsequent development of autism in 12 children.[108] The results of this report became highly publicized and sparked fear in parents across the world. Further investigation revealed numerous counts of scientific misconduct for financial gains by Dr. Wakefield, which led to 10 of the 12 coinvestigators retracting their claims. The CDC has coordinated numerous investigations to uncover any relationship between the vaccine and autism, but despite years of research have been unable to find any association.

J.C.'s mother should be counseled regarding the lack of an association between autism and the MMR vaccine. If she still decides to refuse vaccination, appropriate forms for documenting such are available through the respective state's Department of Health.

The first dose of the MMR vaccine should be administered to children at age 12 to 15 months, followed by a second dose at entrance to grade school (age 4–6 years).[1,35,105] Studies indicate that infants receiving the vaccine may be at higher risk for exhibiting a febrile seizure during the 2 weeks after vaccination when peak virus replication occurs.[109] The risk appears to be higher with the combination vaccine ProQuad®. Because of this concern, the CDC recommends the preferential use of the MMR vaccine in children ages 12 to 47 months. Although studies have not shown a benefit with the use of antipyretics for preventing febrile seizures from the vaccine, it is recommended that caregivers be counseled regarding the management of fever. No increased risk of febrile seizures has been noted with the second dose of the vaccine administered at ages 4 to 6 years; thus, the use of the combination vaccine is recommended at this age to reduce the number of injections and enhance compliance.[105]

Adult vaccination with MMR vaccine is also important for protection from epidemics. Adults should receive a second dose of MMR if they were born between 1963 and 1967, previously vaccinated with killed measles vaccine, are students in postsecondary institutions, work in health care facilities, travel internationally, or were recently exposed to a measles outbreak.[105] Persons born after 1957 should receive one dose of a measles-containing vaccine.[35],[37],[105] Health care workers must show documentation of having receipt of the appropriate number of doses or laboratory evidence of immunity to comply with infection control policies.[110]

Mumps and rubella antigens are combined with measles in the MMR vaccine in the United States. Mumps illness in children rarely produces complications.[105] Meningoencephalitis generally is a benign meningitis, and postinfectious encephalitis, a serious complication, is extremely rare (1 of 6000). Deafness, commonly considered a risk of mumps, occurs rarely (1 of 15,000) and is usually unilateral. Orchitis, another complication, occurs in ~3% to 10% in postpubertal males since the postvaccine era and rarely causes sterility. The most significant consequences of rubella infection occur in pregnant patients (eg, spontaneous abortions, miscarriages, stillbirths, fetal anomalies), especially when infection occurs during the first trimester; however, the MMR vaccine is contraindicated in pregnancy.[105]

Varicella

CASE 64-16

Question 1: J.T. is a 6-year-old female who comes home from school with a note from the school nurse indicating that a child in her kindergarten class has been diagnosed with chickenpox. J.T.'s mother is quite concerned because J.T. has not been immunized with the varicella vaccine.

Will administration of the vaccine at this time protect J.T. from becoming infected?

Varivax®, a live attenuated vaccine against varicella zoster (chickenpox), is the first herpesvirus vaccine to be widely tested in healthy and high-risk children and adults.[111–113] Chickenpox is a highly contagious, mild childhood disease in healthy children, but it can be severe and even fatal, especially in the immunocompromised patient. Unusual complications (eg, severe bacterial superinfections, Reye syndrome, encephalopathies) are markedly reduced with an immunization program.[111] Before the vaccine was available, ~4 million cases of chickenpox were reported annually, with 4000 to 9000 hospitalizations and 100 deaths.[111] Historically, 55% of varicella-related deaths occurred in adults, many of whom were infected by exposure to unvaccinated preschool-aged children with typical cases of varicella.[114]

Despite high vaccine coverage rates and 85% vaccine efficacy with the previous single-dose vaccination, outbreaks of breakthrough varicella continued to occur in the United States.[111] As a result, current guidelines recommend a two-dose series for all children, adolescents, and adults without evidence of immunity.[1,35,111] The first varicella vaccine dose should be administered at ages 12 to 15 months, followed by the second dose at ages 4 to 6 years. For persons ages 7 to 12 years who have not received varicella vaccine, two doses of varicella vaccine should be administered at least 3 months apart. For persons older than age 13 years, administer two doses of varicella vaccine at least 4 weeks apart.[111]

Postexposure varicella vaccination should be considered for J.T. Chickenpox infection can be prevented or symptoms reduced if varicella vaccine is administered within 3 days of exposure and may provide some protection within 5 days.[111,113] If J.T. also needs MMR vaccination, the quadrivalent combination vaccine ProQuad® containing measles, mumps, rubella, and varicella antigens may be considered. A second dose of varicella vaccine in 3 months should be recommended to ensure long-term protection.

The most common adverse effect associated with varicella vaccine administration is rash. Transmission of the virus from the vaccine is low and caution should be used when patients exhibit a

rash postvaccination to avoid contact with immunocompromised individuals until rash resolution.[111]

Although the varicella vaccine might not entirely prevent the occurrence of chickenpox in an immunocompromised patient, it can modify the disease. In the National Institutes of Health's Collaborative Varicella Vaccine Study, a seroconversion rate of only 85% was observed after a single dose in adults, compared with 95% in healthy children and 90% in children with leukemia.[115] Varicella vaccine is generally not recommended in children who have cellular immunodeficiencies, but it can be used in those with impaired humoral immunity.[116] The vaccine should be avoided in children with symptomatic HIV, but it may be considered in asymptomatic or mildly symptomatic patients.[111]

CASE 64-16, QUESTION 2: If the varicella vaccine is now universally recommended, what is the role of the herpes zoster vaccine (HZ)?

After a primary infection with varicella, 15% to 30% of the population experiences a latent infection in the sensory nerve ganglia that reactivates, causing HZ.[111,116,117] HZ typically occurs decades after the initial varicella infection. This reactivation can result in postherpetic neuralgia or dissemination that results in skin eruptions ("shingles") and potential CNS, pulmonary, or hepatic complications.[111,116] Although some have theorized that universal varicella vaccination should eventually reduce the incidence of HZ because it prevents primary infection, others debate that the attenuated virus may have greater potential for becoming latent and reactivating.[111,116] Still others argue that with the elimination of wild-type virus in the community, the exposure of individuals with latent wild-type varicella to help boost immunity and prevent HZ is reduced. In this situation, the risk of HZ may be increased.[111,116] Routine varicella immunization began in 1995, and only long-term studies of vaccinated individuals will answer the questions about the impact of the varicella vaccination upon the incidence of HZ. However, currently, the majority of adults are not immunized against varicella

(unless required as a health care worker) and have previously acquired wild-type varicella infections. Therefore, most adults in the United States are at risk for exhibiting HZ as they age.

The zoster vaccine (Shingrix®) is a recombinant adjuvanted varicella zoster vaccine. It is approved by the FDA for all individuals older than age 50 years as a two-dose IM injection administered 2 to 6 months apart, regardless of previous HZ or history of live zoster vaccination.[35,37,116–118] Live zoster vaccine (Zostavax®) was previously marketed for patients older than age 60 years.[116,118] The recombinant adjuvanted varicella zoster vaccine (Shingrix®) is now the only zoster vaccine on the market and is recommended for patients 50 years and older, including those previously vaccinated with live zoster vaccine.[117] Shingrix® exhibits high efficacy and less waning of protection at ~4 years, even in patients older than 50 years.[117,119,120] The zoster vaccine is recommended for use in patients ages 19 and older who are (or will be) immunodeficient or immunosuppressed because of disease or therapy.[37] It has been studied in patients older than age 70 years with >90% efficacy toward HZ and 88.8% efficacy against postherpetic neuralgia.[120] It may be given to patients with a previous history of HZ, but it is not indicated to treat acute zoster, postherpetic neuralgia, or prevent further complications during an acute episode.[121] If the patient has been vaccinated with live zoster vaccine, administer Shingrix® at least 5 years afterward.[117]

COVID-19

CASE 64-17

Question 1: C.D. is a 46-year-old male inquiring about a COVID-19 vaccine for himself.

Which vaccines are recommended for C.D.?

The acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2020 to cause a global pandemic of COVID-19 that

produces mild, moderate, or severe illness in patients of all ages with a variety of symptoms ranging from cough, fever, anosmia, ageusia, fatigue, headache, myalgias, malaise, sore throat, and diarrhea.[122–125] SARS-CoV-2 is spread by respiratory transmission of aerosols and droplets from an infected person and has an incubation period of ~4 to 5 days and symptoms within 11.5 days of infection.[124] Severe illness presents with dyspnea usually 7 days after symptom onset and can progress to acute respiratory distress syndrome, severe hypoxemia, respiratory failure, and death, most especially in older adults.[123] Because of this high morbidity and mortality and to help control the global pandemic, an accelerated development of several vaccines occurred.[15,122]

The FDA issued Emergency Use Authorization (EUA) for the first COVID-19 vaccine, the Pfizer-BioNTech COVID-19 (BNT162b2) on December 11, 2020, with full approval on August 23, 2021.[126,127] It is an mRNA vaccine that encodes the prefusion spike glycoprotein of SARS-CoV-2 into host cells to produce an immune response.[126,128] Vaccination consists of two 30-μg (0.3 mL) or 10-μg (0.2 mL) doses administered IM 3 weeks apart for patients ages 12 or older and 6 months to 11 years, respectively.[126,128] Currently, it is indicated for patients 16 and older and marketed under the brand name Comirnaty®.[128] It is also available for use under EUA for patients 6 months and older.[128–130] After two doses, 95% protection against COVID-19 after 2 months of follow-up in patients ages 16 years and older and reduced risk for severe outcomes of hospitalization and death occurred.[126,131] Immune response in patients ages 5 to 15 years was at least as high as the response observed in patients ages 16 to 25 years.[129,130,132] Local reactions including mild-to-moderate pain within 7 days of administration and redness and swelling at the injection site were more frequently reported in patients who received BNT162b2. Systemic adverse effects such as fatigue, headache, and fever were also more frequent in patients receiving the vaccine, but few had severe adverse events.[131] The BNT162b2 vaccine must be stored in an ultralow temperature freezer between −80 and −60 °C.[128] It can be stored at −25 to −15 °C

for up to 2 weeks. Refer to the product information for further storage and handling.

The FDA also issued EUA to the Moderna COVID-19 (mRNA-1273) mRNA vaccine on December 18, 2020, with full approval on January 31, 2022.[133],[134] Like the BNT162b2, the mRNA-1273 is an mRNA vaccine that encodes a spike glycoprotein to produce an immune response.[133],[135] Vaccination consists of two doses 100-µg (0.5 mL) doses administered IM 4 weeks apart.[133],[136] An extended-interval dosing series of 8 weeks between primary series doses may be optimal for some patients ages 12 years or older, especially males ages 12 to 39 years.[134] The Moderna COVID-19 mRNA vaccine is indicated for patients ages 18 years and older and marketed under the brand name Spikevax™.[136] After two doses, 94% effectiveness against COVID-19 was seen in preventing the first occurrence of symptomatic COVID-19.[135] The mRNA-1273 prevented severe illness 100%; severe illness was a secondary end point in the trial.[135] Mild-to-moderate injection site reactions after the first and second doses, most commonly an injection site reaction, occurred more frequently in patients receiving the vaccine compared to placebo.[133],[135] Local and systemic reactions, such as headache and fatigue, occurred 1 to 2 days after the vaccine dose and resolved in 2 to 3 days.[135] The incidence of severe adverse reactions was low.[135] The mRNA-1273 vaccine must be stored frozen between −50 and –15 °C.[136] It can be stored in a refrigerator between 2 and 8 °C for up to 30 days before first use, and 8 to 25°C for a total of 24 hours. Refer to the product information for further storage and handling.

In June of 2021, ACIP issued an information regarding an elevated risk factor for myocarditis among male patients ages 12 to 29 years old who received an mRNA COVID-19 vaccine.[137] ACIP reviewed the data and determined that the benefits of mRNA COVID-19 vaccines outweigh the risk of myocarditis after vaccination. However, continuing to monitor myocarditis after vaccination is necessary, and the CDC and FDA are continuing to monitor reports of myocarditis after mRNA COVID-19 vaccines.

On February 27, 2021, the FDA issued EUA to the Janssen COVID-19 (Ad26.COV2.S) adenovirus vector vaccine.[138] It is a recombinant replication-incompetent adenovirus vector vaccine that encodes a spike glycoprotein to produce an immune response.[122],[138] Vaccination is a single 0.5-mL dose administered IM and indicated for patients 18 years and older.[138] After one dose, the Ad26.COV2.S vaccine produced 66.9% effectiveness against moderate- to severe-critical COVID-19 disease.[122] Also, participants who received this vaccine and contracted moderate COVID-19 reported fewer symptoms.[122] Patients who received the vaccine did report more adverse effects compared to placebo, with the most common local reaction being an injection site reaction; the most common systemic reactions were headache, fatigue, myalgia, and nausea.[122] The incidence of severe adverse reactions was low.[122] In April of 2021, the FDA paused the use of the Ad26.COV2.S vaccine secondary to reports of thrombosis with thrombocytopenia syndrome (TTS) in patients who received this vaccine.[139] Fifteen cases of TTS were reported among 7.98 million patients who had received the Ad26.COV2.S vaccine as of April 21, 2021.[139] All patients affected were females. ACIP reviewed data and determined that the benefits of resuming the use of Ad26.COV2.S in patients 18 years or older outweighed the risks. It did add a new warning for rare clotting events among females 18 to 49 years old. In addition, cases of Guillain–Barré syndrome have also been reported after the Janssen COVID-19 vaccine.[140] Because of these events, the ACIP has made a preferential recommendation for the use of mRNA COVID-19 vaccines over the Janssen adenovirus-vectored COVID-19 vaccine.[140] The Ad26.COV2.S vaccine must be stored between 2 and 8 °C, and may be stored between 9 and 25 °C for up to 12 hours.[14] Refer to the product information for further storage and handling.

Booster doses that enhance or restore protection that has waned over time after primary vaccination are recommended for the two mRNA vaccines and the Janssen COVID-19 vaccine.[141] Conditions for a single booster of the mRNA vaccines 6 months after completion of the primary series include all adult patients ages 18 years or

older.[142] In addition, recipients 18 years or older who received the Janssen COVID-19 vaccine should receive a booster >2 months after primary vaccination. Any approved or authorized COVID-19 vaccine may be used for the booster dose. The dose and volume for the booster are the same as that for the primary vaccination for the Pfizer-BioNTech and Janssen vaccines, whereas the Moderna dose and volume of the booster is one-half of the primary series (50 μg; 0.25 mL).

The Novovax COVID-19 (NVX-CoV2373) vaccine is a recombinant nanoparticle vaccine with a Matrix-M1 adjuvant that elicits an immune response against COVID-19.[143] It is administered in two IM doses of 5 μg 3 weeks apart.[15] After two doses, 89.7% efficacy was observed against COVID-19 in preventing symptomatic mild, moderate, or severe infection.[15] The NVX-CoV2373 vaccine prevented COVID-19 hospitalization or death in the vaccine group.[15] Local injection site reactions were the most common local adverse events, and the most common systemic adverse events were headache, muscle pain, and fatigue in patients who received the vaccine.[15] It is currently not available in the United States.

Currently, C.D. would be able to receive the Pfizer-BioNTech COVID-19 (BNT162b2), the Moderna COVID-19 (mRNA-1273), or the Janssen COVID-19 (Ad26.COV2.S) vaccine.

ADMINISTRATION TECHNIQUES

Vaccines or other biologic agents are typically administered as either an IM or a subcutaneous injection.

Because appropriate administration by the correct route and technique is critical to the effectiveness of the specified vaccine, it is essential to consult the prescribing and administration information for each specific vaccination administered to a patient (see also Table 64-1). The technique of vaccine administration by either route should include sterilizing the skin surface, drawing up the vaccine from the vial into a syringe using a sterile technique, protecting the patient

and health care provider from biologic hazards, performing proper disposal of biohazardous/sharp materials (needles and blood-borne products), observing for adverse effects after administration, and reassuring the patient post the vaccine administration. **Table 64-3** includes general guidelines for safe and effective parenteral administration.

Table 64-3
Subcutaneous and Intramuscular Vaccine Administration Techniques

Patient Age	Site	Injection Area	Typical Needle Length (inch)	Needle Gauge
Birth to 12 months	Subcutaneous	Fatty tissue over the anterolateral thigh muscle	5/8	23–25
12 months and older	Subcutaneous	Fatty tissue over anterolateral thigh or fatty tissue over triceps	5/8	23–25
Newborn (0–28 days)	Intramuscular	Anterolateral thigh muscle	5/8	22–25
Infant (1–12 months)	Intramuscular	Anterolateral thigh muscle	1	22–25
Toddler (1–3 years)	Intramuscular	Anterolateral thigh muscle or Deltoid muscle of arm if muscle mass is adequate	1–1¼ 5/8–1	22–25
Children (3–18 years)	Intramuscular	Deltoid muscle or Anterolateral thigh muscle	5/8–1 1–1¼	22–25
Adults ≥19 years	Intramuscular	Deltoid muscle or Anterolateral thigh muscle	1–1½	22–25

Sources: National Center for Immunization and Respiratory Diseases. General recommendations on immunizations-recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60:1–61; Immunization Action Coalition. How to administer intramuscular (IM) route. https://www.immunize.org/catg.d/p2020.pdf. Immunization Action Coalition. Administering vaccines: dose, route, site, and needle size. Accessed November 21, 2021. http://www.immunize.org/catg.d/p3085.pdf.

CASE 64-18

QUESTION 1: B.D., a nurse from a family medicine clinic, frantically calls you because she mistakenly administered a Pneumovax® vaccination subcutaneously.

How do you respond to B.D.'s call?

The majority of vaccines, including Pneumovax®, specify IM administration. This technique involves penetration of the

appropriate muscle at a 90-degree angle. For a graphic illustration of IM vaccine administration, see http://www.immunize.org/catg.d/p2020.pdf. Sites of IM injections include the anterolateral thigh muscle in infants and toddlers and the deltoid (upper arm) muscle in children and adults.[1,144] The typical needle used to administer an IM injection is 1 inch long and 22 to 25 gauge. A shorter needle (eg, 5/8 inch) may be used for newborns, whereas a 1- to 1/2-inch needle may be needed for adults weighing >198.42 pounds (90 kg) for females and 260.15 pounds (118 kg) for males.[144,145] Multiple IM injections given in the same extremity during the same time period should be placed at least 1 inch apart.[1] Although most vaccine products specify the route of administration, Pneumovax® may be administered either IM or into subcutaneous tissue.[146] Therefore, B.D. should be reassured that she has been administered the Pneumovax® correctly because it is acceptable to administer this vaccination by either route.

Subcutaneous vaccinations involve injection of the vaccine into fatty subcutaneous tissue between the layer of skin and the layer of muscle.[1,144] Subcutaneous vaccinations are administered with a 5/8-inch needle, 23 to 25 gauge, inserted at a 45-degree angle to the skin, while pinching up on the subcutaneous tissue to prevent injection into the muscle. For a graphic illustration of subcutaneous vaccination administration, see http://www.immunize.org/catg.d/p2020.pdf. Sites of subcutaneous injections include the fatty tissue over the anterolateral thigh muscle in newborn to 1-year-old children, and fatty tissue over the triceps in 1-year-old children to adults. Multiple subcutaneous injections given in the same extremity during the same time period should be placed at least 1 inch apart.

Other routes of administration for vaccinations include the oral, intranasal, and intradermal routes. Rotavirus and oral typhoid are the only orally administered vaccines in the United States.[1] LAIV is the only intranasal vaccine, and it is administered via a nasal sprayer with a dose divider. Intradermal influenza vaccine is the only intradermally administered vaccine, and it is administered in the area of the deltoid at a 90-degree angle into the skin.[145]

LEGAL REQUIREMENTS

CASE 64-19

QUESTION 1: C.M. wants to be able to deliver immunizations at her pharmacy. What are the requirements necessary to become a pharmacist immunizer?

How are pharmacists advocates for improving population immunization rates?

Pharmacists have varying authority to administer vaccinations within the United States based on each state's Pharmacy Practice Act. The rationale for pharmacists to deliver immunizations to the public includes pharmacist accessibility in every community and overall low vaccination rates throughout the population.[147] The Department of Health & Human Services and the CDC recognized the pharmacists' unique position to promote vaccines and also influence vaccination in diverse populations through a letter from the Assistant Surgeon General.[148] This letter also acknowledged the pharmacists' contribution to increase immunization awareness in the past, but it also requested continued assistance in this endeavor through the following:

- Increasing vaccine awareness in the adult and adolescent population
- Ensuring patients' vaccine requirements are assessed when they visit pharmacies
- Offering vaccinations to patients with certain medical conditions (high risk)
- Entering adult immunizations into vaccine registries where possible
- Partnering and collaborating with local and state health departments, immunization coalitions, medical providers, and other vaccination outreach programs

The American Pharmacists Association (APhA) has developed a national competency-based certificate training program for pharmacists, and most schools of pharmacy across the country

contain or provide an opportunity to learn immunization administration within their curriculum.[149] These programs include both didactic and hands-on training and prepare the learners to be public health educators regarding immunizations, to promote vaccinations within their community, and to administer vaccines at their practice sites. APhA also provides an immunization center with resources for the practitioner (https://www.pharmacist.com/immunization-center).

Although each state's requirements regarding necessary training, protocols, and notification systems may differ, there are some standardized requirements that a pharmacist immunizer must follow. Current cardiopulmonary resuscitation certification is a common requirement for pharmacist immunizers. Immunization administration curricula typically contain information regarding basic immunology, specifics regarding vaccine information, practice implementation, legal and regulatory issues, and administration techniques.[149],[150] Each state stipulates the statutes on patient age that may receive a pharmacist-administered vaccination; what types of vaccinations pharmacists are able to administer; and the mechanism by which pharmacists are authorized to administer vaccines by physicians, such as through a prescription, collaborative drug therapy management agreement, protocol, or standing order.[151] Some states require continuing education credit maintenance specific to immunizations or vaccinations for pharmacists who immunize; some states are very specific in their requirements, and others are more general. It is important to check with the state licensing board regarding specific statutes and regulations relating to pharmacist immunization practices. In addition, all states and territories have adopted legislation allowing pharmacy interns to administer vaccines, given the student has completed an immunization certificate program and operates only under supervision of an immunizing pharmacist.[151]

Patient consent forms for immunization and vaccine information sheets are important aspects for patient safety that pharmacists are required to use as part of an approved immunization program. Consent forms should include screening questionnaires specific for

each vaccine, should be signed before vaccine administration, and should be reviewed by the pharmacist with the patient present. Vaccine information sheets have patient information developed by the CDC providing specific individual vaccine information benefits and risks, and they are required to be distributed to the patient with each vaccine by the National Childhood Vaccine Injury Act of 1986. Resources for pharmacists are available through the CDC, Immunization Action Coalition, and APhA.[150],[152],[153]

More recently, under the Public Readiness and Emergency Preparedness Act (PREP Act), the Department of Health & Human Services authorized the state-licensed pharmacists (and pharmacy interns working under a pharmacist supervisor as long as the intern is licensed and/or registered by their state board of pharmacy) to order and administer vaccines to patients ages 3 to 18 years old as long as[154]:

- The vaccine is approved by the FDA.
- The vaccine is administered according to the CDC's ACIP immunization schedules.
- The licensed pharmacist has completed the required training by the American Council for Pharmacy Education (ACPE) to administer vaccines. The training must contain at least 20 hours of ACPE training that includes hands-on injection technique, clinical evaluation of vaccine indications and contraindications, and recognition and treatment of vaccine emergency reactions.
- The licensed or registered pharmacy intern has completed the practical training by ACPE to administer vaccines. The training must include hands-on injection technique, clinical evaluation of vaccine indications and contraindications, and recognition and treatment of vaccine emergency reactions.
- The licensed pharmacist and licensed or registered pharmacy intern must have a current certificate in basic cardiopulmonary resuscitation.
- The licensed pharmacist must complete at least 2 hours of ACPE-approved immunization-related continuing education during each

state licensure period.

- The licensed pharmacist must comply with record keeping and reporting requirements of the jurisdiction of which they administer vaccines, including the patient's primary care provider when available, submitting the required immunization information to the state or local immunization information system (vaccine registry), complying with the requirement regarding reporting adverse events, and complying with requirements that the person administering a vaccine must review the vaccine registry or other vaccine records before administering the vaccine.
- The licensed pharmacist must inform their childhood vaccine patients and adult caregivers accompanying the child of the importance of well-child visits with a pediatrician or other licensed primary care provider and refer patients as appropriate.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Centers for Disease Control and Prevention. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23*). MMWR Morb Mortal Wkly Rep*. 2010;59:1102–1106. (81)

Cortese MM, Parashar UD; Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP) [published correction appears in *MMWR Recomm Rep*. 2010;59:1074]. *MMWR Recomm Rep*. 2009;58(RR-2):1–25. (103)

Grohskopf L, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on

Immunization Practices, United States, 2021–2022 influenza season. *MMWR Recomm Rep*. 2021;70(No. RR-70):1–28. (88)

Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1–30; quiz CE2–CE4. (116)

Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;69:77–83. (54)

Kobayashi M, Farrar JL, Giercke R, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022; 71:10–117. (84)

Marin M, Broder KR, Temte JL, et al. Use of combination measles, mumps, rubella and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-3):1–12. (109)

Marin M, Güris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1–40. (111)

Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate the transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2007;56:1114]. *MMWR Recomm Rep*. 2006;55(RR-16):1–33; CE1–CE4. (42)

Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal vaccination: recommendations of the Advisory Committee of Immunization Practices, United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(*9*):1–41. (67)

Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68:698–702. (79)

Murthy N, Wodi AP, Bernstein H, McNally V, Cineas S, Ault K. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:229–233. (37)

National Center for Immunization and Respiratory Diseases. General recommendations on immunizations—recommendations of the Advisory Committee on Immunization Practices (ACIP*). MMWR Recomm Rep*. 2011;60:1–61. (1)

Nuorti JP, Whitney CG; Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-11): 1–22. (82)

Wodi AP, Murthy N, Bernstein H, McNally V, Cineas S, Ault K. Advisory Committee on Immunization Practices recommended immunization Schedule for children and adolescents aged 18 years or younger—United States, 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71:234–237. (35)

Key Websites

American Pharmacists Association. Immunization center. https://www.pharmacist.com/immunization-center (150)

American Pharmacists Association. Pharmacist-administered vaccines: APhA/NASPA survey of state IZ Laws/Rules. Updated June 2020. Accessed November 21, 2021. https://aphanet.pharmacist.com/sites/default/files/files/practice/07-2020/pharmacist-administered-vaccines-june-2020.pdf (151)

Centers for Disease Control and Prevention. Vaccine information statements. Published October 15, 2021. Accessed November 21, 2021. http://www.cdc.gov/vaccines/hcp/vis/index.html (152)

Centers for Disease Control and Prevention. Immunization schedules: adult immunization schedule. Recommendations for ages 19 years or older, United States, 2022. http://www.cdc.gov/vaccines/schedules/hcp/adult.html

Centers for Disease Control and Prevention. Immunization schedules: child and adolescent immunizations schedule. Recommendations for ages 18 or younger, United States, 2022. http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html

Immunization Action Coalition. Administering vaccines: dose, route, site, and needle size. Accessed November 21, 2021. http://www.immunize.org/catg.d/p3085.pdf (145)

Immunization Action Coalition. Handouts: screening checklists. Updated September 10, 2021. http://www.immunize.org/handouts/screening-vaccines.asp (153)

Immunization Action Coalition. How to administer intramuscular (IM) route. http://www.immunize.org/catg.d/p2020.pdf (144)

COMPLETE REFERENCES CHAPTER 64 VACCINATIONS

1. National Center for Immunization and Respiratory Diseases. General recommendations on immunizations-recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60:1–61.
2. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang Y. Vaccination coverage among children aged 19–35 months—United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(40):1123–1128.
3. Williams WW, Lu PJ, O'Halloran A, et al. Surveillance of vaccination coverage among adult populations: United States, 2015. *MMWR Surveill Summ.* 2017;66(No. SS-11):1–28.
4. Luman ET, Barker LE, Shaw KM, McCauley MM, Buehler JW, Pickering LK. Timeliness of childhood vaccinations in the United States: days undervaccinated and number of vaccines delayed. *JAMA*. 2005;293:1204–1211.
5. Constable C, Blank NR, Caplan AL. Rising rates of vaccine exemptions: problems with current policy and more promising remedies. *Vaccine*. 2014;32:1793–1797.
6. Siddiqui M, Salmon DA, Omer SB. Epidemiology of vaccine hesitancy in the United States. *Hum Vaccin Immunother*. 2013;9:2643–2648.
7. Omer SB, Salmon DA, Orenstein WA, deHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *N Engl J Med*. 2009;360:1981–1988.
8. Kempe A, Saville AW, Albertin C, et al. Parenteral hesitancy about routine childhood and influenza vaccinations: a national survey. *Pediatrics*. 2020;146(1):e20193852.
9. Keeton VF, Chen AK. Immunization updates and challenges. *Curr Opin Pediatr*. 2010;22:234–240.
10. Zepp F. Principles of vaccine design—lessons from nature. *Vaccine*. 2010;28S: C14–C24.
11. Moser M, Leo O. Key concepts in immunology. *Vaccine*. 2010;28S:C2–C13.
12. Pfizer BioNTech. Comirnaty (COVID-19 Vaccine, mRNA). Package insert. Revised August 2021. Accessed August 2, 2021. https://www.fda.gov/media/144413/download
13. Moderna COVID-19 Vaccine. Package insert. Revised November 19, 2021. Accessed November 21, 2021. https://www.fda.gov/media/144637/download
14. Janssen COVID-19 Vaccine. Package insert. Revised November 19, 2021. Accessed November 21, 2021. https://www.fda.gov/media/146304/download
15. Heath PT, Galiza EP, Baxter DN, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *N Engl J Med*. 2021;385(13):1172–1183. doi:10.1056/NEJMoa2107659
16. Lee S, Nguyen MT. Recent advances of vaccine adjuvants for infectious diseases. *Immune Netw*. 2015;15:51–57.

17. Jennings GT, Bachmann MF. Designing recombinant vaccines with viral properties: a rational approach to more effective vaccines. *Curr Mol Med*. 2007;7:143–145.
18. Coffman RL, Sher A, Seder RA, et al. Vaccine adjuvants: putting innate immunity to work. *Immunity*. 2010;33:492–503.
19. Wodi AP, Morelli V. Principles of vaccination. In: Hall E, Wodi AP, Hamborsky J, et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 14th ed. Centers for Disease Control and Prevention. Public Health Foundation; 2021. Accessed November 21, 2021. https://www.cdc.gov/vaccines
20. Braun MM, Patriarca PA, Ellenberg SS. Syncope after immunization. *Arch Pediatr Adolesc Med*. 1997;151:255–259.
21. Kowalzik F, Schreiner D, Jensen C, Teschner D, Gehring S, Zepp F. mRNA-based vaccines. *Vaccines (Basel)*. 2021;9(4):390.
22. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 vaccines. *JAMA*. 2021;325(13): 1318–1320. doi:10.1001/jama.2021.3199
23. Rosa SS, Prazeres DMF, Azevedo AM, Marques MPC. mRNA vaccines manufacturing: challenges and bottlenecks. *Vaccine*. 2021;39(16):2190–2200.
24. Ndwandwe D, Wiysonge CS. COVID-19 vaccines. *Curr Opin Immunol*. 2021;71:111–116.
25. Centers for Disease Control and Prevention. Syncope after vaccination—United States, January 2005–July 2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:457–460.
26. Babl FE, Lewena S, Brown L. Vaccination-related adverse events. *Pediatr Emerg Care*. 2006;22:514–519.
27. Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics*. 2003;112:815–820.
28. Kemp A, Van Asperen P, Mukhi A. Measles immunization in children with clinical reactions to egg protein. *Am J Dis Child*. 1990;144:33–35.
29. Fasano MB, Wood RA, Cooke SK, Sampson HA. Egg hypersensitivity and adverse reactions to measles, mumps, and rubella vaccine. *J Pediatr*. 1992;120:878–881.
30. James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. *N Engl J Med*. 1995;332:1262–1266.
31. Advisory Committee on Immunization Practices. Update: vaccine side effects, adverse reactions, contraindications, and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP) [published correction appears in *MMWR Morb Mortal Wkly Rep.* 1997;46:227]. *MMWR Recomm Rep*. 1996;45(RR-12):1–35.
32. Centers for Disease Control and Prevention. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children—United

States, 1987–1995. *JAMA*. 1996;276:1542–1544.
33. Smith MH. National childhood vaccine injury compensation act. *Pediatrics*. 1988;82:264–269.
34. Saari TN; American Academy of Pediatrics Committee on Infectious Disease. Immunization of preterm and low birth weight infants. *Pediatrics*. 2003;112:193–198.
35. Wodi AP, Murthy N, Bernstein H, McNally V, Cineas S, Ault K. Advisory Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:234–237.
36. Centers for Disease Control and Prevention. Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2022. Accessed July 10, 2022. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
37. Murthy N, Wodi AP, Bernstein H, McNally V, Cineas S, Ault K. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:229–233.
38. Centers for Disease Control and Prevention. Recommended adult immunization schedule for ages 19 years or older, United States, 2022. Accessed April 2, 2022. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
39. Foster SL, Short CT, Angelo LB. Vaccination of patients with altered immunocompetence. *J Am Pharm Assoc*. 2013;53:438–440.
40. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. *Semin Liver Dis*. 1991;11:84–92.
41. Schillie S, Murphy TV, Fenlon N, Ko S, Ward JW. Update: shortened interval for postvaccination serologic testing of infants born to hepatitis b-infected mothers. *MMWR Morb Mortal Wkly Rep*. 2015;64(39):1118–1120.
42. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate the transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2007;56:1114]. *MMWR Recomm Rep*. 2006;55(RR-16):1–33; CE1–CE4.
43. Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Practice (AAFP). *Pediatrics*. 1999;103:1064–1077.
44. Advisory Committee on Immunization Practices. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-7):1–23.

45. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR Recomm Rep*. 2020;69(5):1–38.
46. Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. *JAMA*. 2005;294(2):202–210.
47. Foster MA, Haber P, Nelson NP. Hepatitis A. In: Hall E, Wodi AP, Hamborsky J, et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 14th ed. Centers for Disease Control and Prevention. Public Health Foundation; 2021. Accessed April 2, 2022. https://www.cdc.gov/vaccines/pubs/pinkbook/hepa.html
48. Liang JL, Tiwari T, Moro P, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2018;67(No. RR-2):1–44.
49. Advisory Committee on Immunizations Practices. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunizations Practices (ACIP) [published correction appears in *MMWR Morb Mortal Wkly Rep*. 1997;46:706]. *MMWR Recomm Rep*. 1997;46(RR-7):1–25.
50. Broder KR, Cortese MM, Iskander JK, et al. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-3):1–34.
51. Kretsinger K, Broder KR, Cortese MM, et al. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-17):1–37.
52. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) vaccine from the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:13–15.
53. Nennig ME, Shinefield HR, Edwards KM, Black SB, Fireman BH. Prevalence and incidence of adult pertussis in an urban population. *JAMA*. 1996;275(21):1672–1674.
54. Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;69:77–83.
55. Fraser DW. Haemophilus influenzae in the community and the home. In: Sell SH, Wright PF, eds. *Haemophilus Influenzae: Epidemiology, Immunology, and Prevention of Disease*. Elsevier Science; 1982:11.

56. Schlech W III, Ward JI, Band JD, Hightower A, Fraser DW, Broome CV. Bacterial meningitis in the United States, 1978 through 1981. The National Bacterial Meningitis Surveillance Study. *JAMA*. 1985;253:1749–1754.
57. Dajani AS, Asmar BI, Thirumoorthi MC. Systemic *Haemophilus influenzae* disease: an overview. *J Pediatr*. 1979;98:355–364.
58. Taylor HG, Michaels RH, Mazur PM, Bauer RE, Liden CB. Intellectual, neuropsychological, and achievement outcomes in children six to eight years after recovery from *Haemophilus influenzae* meningitis. *Pediatrics*. 1984;74:198–205.
59. Peltola H, Käyhty H, Virtanen M, Mäkelä PH. Prevention of *Haemophilus influenzae* type b bacteremic infections with the capsular polysaccharide vaccine. *N Engl J Med*. 1984;310:1561–1566.
60. Polysaccharide vaccine for prevention of *Haemophilus influenzae* type b disease. *JAMA*. 1985;253:2630,2636–2637.
61. Lepow ML, Barkin RM, Berkowitz CD, et al. Safety and immunogenicity of *Haemophilus influenzae* type b diphtheria toxoid conjugate vaccine (PRP-D) in infants. *J Infect Dis*. 1987;156:591–596.
62. Briere EC, Rubin L, Moro PL, et al. Prevention and control of *Haemophilus influenzae* Type B disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63(RR-01):1–14.
63. Estivariz CF, Link-Gelles R, Shimabukuro T. Poliomyelitis. In: Hall E, Wodi A.P, Hamborsky J, et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 14th ed. Centers for Disease Control and Prevention. Public Health Foundation; 2021. Accessed November 21, 2021. https://www.cdc.gov/vaccines/pubs/pinkbook/chapters.html
64. Sutter RW, Prevots DR. Vaccine-associated paralytic poliomyelitis among immunodeficient persons. *Infect Med*. 1994;11:426.
65. Prevots DR, Burr RK, Sutter RW, Murphy TV; Advisory Committee on Immunization Practices. Poliomyelitis prevention in the United States: updated recommendations of the Advisory Committee on Immunization Practices (AICP). *MMWR Recomm Rep.* 2000;49(No. RR-5):1–22.
66. Centers for Disease Control and Prevention. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. *MMWR Morb Mortal Wkly Rep*. 2009;58:829–830.
67. Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal vaccination: recommendations of the Advisory Committee of Immunization Practices, United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020; 69(9):1–41.
68. Centers for Disease Control and Prevention. Update: Guillain-Barre syndrome among recipients of Menactra meningococcal conjugate vaccine—United States, June 2005–September 2006. *MMWR Morb Mortal Wkly Rep*. 2006;55:1120–1124.

69. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010 [published correction appears in *MMWR Recomm Rep*. 2011;60:18]. *MMWR Recomm Rep*. 2010;59(RR-12):1–110.
70. Dunne EF, Markowitz LE, Saraiya M, et al. CDC Grand Rounds: reducing the burden of HPV-associated cancer and disease. *MMWR Morb Mortal Wkly Rep*. 2014;63;69–72.
71. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2016;65:1405–1408.
72. Guiliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males [published correction appears in *N Engl J Med*. 2011;364:1481]. *N Engl J Med*. 2011;364:401–411.
73. Saslow D, Castle PE, Cox JT, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin*. 2007;57:7–28.
74. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007;356:1928–1943.
75. Kahn JA. HPV vaccination for the prevention of cervical intraepithelial neoplasia. *N Engl J Med*. 2009;361:271–278.
76. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007;356:1915–1927.
77. Centers for Disease Control and Prevention. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP) [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2010;59:1184]. *MMWR Morb Mortal Wkly Rep*. 2010;59:626–629.
78. Gardasil 9. Package insert. Merck & Co; 2020. Accessed October 11, 2020. https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf
79. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019;68:698–702.
80. Elam-Evans LD, Yankey D, Singleton JA, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;69:1109–1116.
81. Centers for Disease Control and Prevention. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-

valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR Morb Mortal Wkly Rep*. 2010;59:1102–1106.

82. Nuorti JP, Whitney CG; Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-11):1–22.
83. Centers for Disease Control and Prevention. Use of 12-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
84. Kobayashi M, Farrar JL, Giercke R, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022; 71:109–117.
85. Esposito S, Tansey S, Thompson A, et al. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine compared to those of a 7-valent pneumococcal conjugate vaccine given as a three-dose series with routine vaccines in healthy infants and toddlers. *Clin Vaccine Immunol*. 2010;17:1017–1026.
86. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6–18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62:521–524.
87. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63:822–826.
88. Grohskopf L, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2021–2022 influenza season. *MMWR Recomm Rep.* 2021;70(No. RR-70):1–28.
89. Centers for Disease Control and Prevention. Licensure of a high-dose inactivated influenza vaccine for persons aged >65 years (Fluzone High-Dose) and guidance for use—United States, 2010. *MMWR Morb Mortal Wkly Rep*. 2010;59:485–486.
90. Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine*. 2007;25:7656–7663.

91. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis*. 2009;200:172–180.
92. Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med*. 2006:1121–1127.
93. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med*. 2014;371:635–645.
94. Chang LJ, Meng Y, Janosczyk H, Landolfi V, Talbot HK; QHD00013 Study Group. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults ≥65 years of age: a phase 3 randomized clinical trial. *Vaccine.* 2019;37:5825–5834.
95. Essink B, Fierro C, Rosen J, et al. Immunogenicity and safety of MF59-adjuvanted quadrivalent influenza vaccine versus standard and alternate B strain MF59-adjuvanted trivalent influenza vaccines in older adults. *Vaccine.* 2020;38:242–250.
96. Flumist Quadrivalent. Package insert. MedImmune; 2020.
97. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. *N Engl J Med*. 1998;338:1405–1412.
98. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis*. 1994;169:68–76.
99. Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults. *JAMA*. 1999;282:137–144.
100. Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. *J Pediatr*. 2000;136:168–175.
101. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of rotavirus disease: updated guidelines for the use of rotavirus vaccine. *Pediatrics*. 2009;123(5):e764–e769.
102. Parashar UD, Alexander JP, Glass RI; Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2006;55(RR-12):1–13.
103. Cortese MM, Parashar UD; Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices

(ACIP) [published correction appears in *MMWR Recomm Rep*. 2010;59:1074]. *MMWR Recomm Rep*. 2009;58(RR-2):1–25.

104. Robbins KB, Brandling-Bennett D, Hinman AR. Low measles incidence: association with enforcement of school immunization laws. *Am J Public Health*. 1981;71:270–274.
105. Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(R-4):1–34.
106. Gustafson TL, Lievens AW, Brunell PA, Moellenberg RG, Buttery CM, Sehulster LM. Measles outbreak in a fully immunized secondary-school population. *N Engl J Med*. 1987;316:771–774.
107. Centers for Disease Control and Prevention. Measles outbreak among internationally adopted children arriving in the United States, February–March 2001. *MMWR Morb Mortal Wkly Rep*. 2002;51:1115–1116.
108. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, nonspecific colitis, and pervasive developmental disorder in children [retraction appears in *Lancet*. 2010;375:445]. *Lancet*. 1998;351:637–641.
109. Marin M, Broder KR, Temte JL, et al. Use of combination measles, mumps, rubella and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-3):1–12.
110. Centers for Disease Control and Prevention. Immunization of health-care personnel: recommendations of the Advisory Council on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(R-07):1–45.
111. Marin M, Güris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1–40.
112. Gershon AA. Live attenuated varicella vaccine. *Pediatr Ann*. 1984;13:653–656.
113. Arbeter AM, Granowetter L, Starr SE, Lange B, Wimmer R, Plotkin SA. Immunization of children with acute lymphoblastic leukemia with live attenuated varicella vaccine without complete suspension of chemotherapy. *Pediatrics*. 1990;85:338–344.
114. Centers for Disease Control and Prevention. Varicella-related deaths among adults—United States 1997. *MMWR Morb Mortal Wkly Rep*. 1997:46:409–412.
115. Gershon AA, Steinberg SP, Gelb L. NIAID Varicella Vaccine Collaborative Study Group: live attenuated varicella vaccine in immuno-compromised children and healthy adults. *Pediatrics*. 1986;78:757–762.
116. Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention.

Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1–30; quiz CE2–CE4.

117. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67(3):103–108.
118. Hales CM, Harpaz R, Ortega-Sanchez I, Bialek SR; Centers for Disease Control and Prevention. Update on recommendations for use of herpes zoster vaccine. *MMWR Morb Mortal Wkly Rep*. 2014;63:729–731.
119. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med.* 2015;372:2087–2096.
120. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med.* 2016;375:1019–1032.
121. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271–2284.
122. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV_2.S vaccine against Covid-19. *N Engl J Med*. 2021;384(23):2187–2201.
123. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med*. 2020;383(25):2451–2460.
124. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. *N Engl J Med*. 2020;383(18):1757–1766.
125. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological features of Covid-19. *N Engl J Med*. 2020;383(10):989–992.
126. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine—United States, December 2020. *MMWR Morb Mortal Wkly Rep 2020*;69:1922–2924.
127. U.S. Food & Drug Administration. FDA approves first COVID-19 vaccine. Published August 23, 2021. Accessed September 1 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine
128. Comirnaty. Package insert. Pfizer BioNTech; 2021. Accessed July 10, 2022. https://www.fda.gov/media/144413/download
129. Wallace M, Woodworth KR, Gargano JW, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine in adolescents aged 12–15 years—United States, May 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:749–752.
130. Woodworth KR, Moulia D, Collins JP, et al. The Advisory Committee on Immunizations Practices' interim recommendation for the use of Pfizer-

BioNTech COVID-19 vaccine in children aged 5–11 years—United States, November 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1579–1583.
131. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615.
132. Frenck RW Jr, Klein NP, Kitchin N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med*. 2021;385(3):239–250.
133. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Moderna COVID-19 vaccine—United States, December 2020. *MMWR Morb Mortal Wkly Rep*. 2021;69:1653–1656.
134. Wallace M, Moulia D, Blain AE, et al. The Advisory Committee on Immunization Practices' recommendation for the use of Moderna COVID-19 vaccine in adults aged >18 years and considerations for extended intervals for administration of primary series doses of mRNA COVID-19 vaccines—United States, February 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:416–421.
135. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403–416.
136. Spikevax (COVID-19 vaccine, mRNA). Package insert. 2022. Accessed April 2, 2022. https://www.fda.gov/media/155675/download
137. Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices—United States, June 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:977–982.
138. Oliver SE, Gargano JW, Scobie H, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Janssen COVID-19 vaccine—United States, February 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:329–332.
139. MacNeil JR, Su JR, Broder KR, et al. Updated recommendations from the Advisory Committee on Immunization Practices for use of the Janssen (Johnson & Johnson) COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome among vaccine recipients—United States, April 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:651–656.
140. Oliver SE, Wallace M, See I, et al. Use of Janssen (Johnson & Johnson) COVID-19 vaccine: updated interim recommendations from the Advisory Committee on Immunization Practices—United States, December 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71:90–95.
141. Mbaeyi S, Oliver SE, Collins JP, et al. The Advisory Committee on Immunizations Practices' interim recommendation for additional primary and booster doses of COVID-19 vaccines—United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1545–1552.

142. Centers for Disease Control and Prevention. CDC expands eligibility for COVID-19 booster shots to all adults. Published November 19, 2021. Accessed November 21, 2021. https://www.cdc.gov/media/releases/2021/s1119-booster-shots.html
143. Keech C, Albert G, Cho I, et al. Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *N Engl J Med*. 2020;383(24):2320–2332.
144. Immunization Action Coalition. How to administer intramuscular (IM) route. Accessed November 21, 2021. http://www.immunize.org/catg.d/p2020.pdf
145. Immunization Action Coalition. Administering vaccines: dose, route, site, and needle size. Accessed November 21, 2021. http://www.immunize.org/catg.d/p3085.pdf
146. Pneumovax (Pneumococcal Vaccine Polyvalent). Package insert. Merk & Co; May 2015.
147. Centers for Disease Control and Prevention. Adult immunization programs in nontraditional setting: quality standards and guidance for program evaluation-a report of the National Vaccine Advisory Committee and Use of standing orders programs to increase adult vaccination rates: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2000;49(No. RR-1):4–22.
148. Pharmacy Times. CDC praises pharmacist's vaccine efforts. Published October 10, 2015. Accessed November 21, 2021. https://www.pharmacytimes.com/view/cdc-praises-pharmacists-vaccine-efforts
149. American Pharmacists Association. Pharmacy-based immunization delivery. Accessed November 21, 2021. https://aphanet.pharmacist.com/pharmacy-based-immunization-delivery
150. American Pharmacists Association. Immunization center. Accessed November 21, 2021. https://www.pharmacist.com/immunization-center
151. American Pharmacists Association. Pharmacist-administered vaccines: APhA/NASPA survey of state IZ Laws/Rules. Updated June 2020. Accessed November 21, 2021. https://aphanet.pharmacist.com/sites/default/files/files/practice/07-2020/pharmacist-administered-vaccines-june-2020.pdf
152. Centers for Disease Control and Prevention. Vaccine information statements. Published October 15, 2021. Accessed November 21, 2021. http://www.cdc.gov/vaccines/hcp/vis/index.html
153. Immunization Action Coalition. Handouts: screening checklists. Updated September 10, 2021. Accessed October 11, 2020. http://www.immunize.org/handouts/screening-vaccines.asp
154. U.S. Department of Health & Human Services. Guidance for licensed pharmacists and pharmacy interns regarding COVID-19 vaccines and immunity under the PREP Act. Accessed November 21, 2021.

https://www.hhs.gov/sites/default/files/licensed-pharmacists-and-pharmacy-interns-regarding-covid-19-vaccines-immunity.pdf

65

Central Nervous System Infections

Deanna J. Buehrle and Gregory A. Eschenauer

CORE PRINCIPLES		CHAPTER CASES
1	The most common symptoms of meningitis include the triad of fever, stiff neck, and altered mental status. In neonates and infants, irritability and poor feeding may be reported along with fever. In the elderly, signs may be absent or more subtle.	**Case 65-1 (Question 1)**
2	Cerebrospinal fluid (CSF) is essential in confirming the diagnosis of meningitis. The CSF typically contains many white blood cells (WBCs) with a predominance of neutrophils. In addition, CSF protein is typically elevated to >100 mg/dL with a low CSF glucose concentration (either <50 mg/dL	**Case 65-1 (Question 2)**

	or <50%–60% of a simultaneously obtained serum glucose value).	
3	Adjunctive dexamethasone should be initiated in all patients with suspected bacterial meningitis either before or concomitant with the first dose of antibiotic.	**Case 65-1 (Question 4)**
4	The choice of empiric therapy in patients with meningitis is primarily driven by age and the presence of predisposing conditions (postneurosurgical, head trauma, immunocompromised).	**Case 65-1 (Question 3)**
5	Intraventricular antibiotics should be considered for patients with meningitis who have an external drainage device in place. Such therapy should be used in combination with systemically administered therapy.	**Case 65-4 (Question 4)**
6	Brain abscess is associated with a different spectrum of pathogens, including oral anaerobes, staphylococci, and aerobic gram-negative bacilli, depending on the patient. The barrier from the blood to brain parenchyma differs from that between blood and CSF. Consequently, the choice of antimicrobial for brain abscess may differ from that associated with meningitis.	**Case 65-5 (Questions 1–3)**
7	Response to therapy should be monitored by resolution of fever, altered	**Case 65-1 (Question 6)**

mental status, and stiff neck. A baseline level of mental status should be evaluated for this reason. Delays in response to therapy may require a repeat lumbar puncture to reexamine CSF cultures, which are usually sterile after 18 to 24 hours of therapy. Clinical response should be seen between 24 and 48 hours of initiation of therapy.

INTRODUCTION

The pharmacotherapy of central nervous system (CNS) infections presents numerous challenges. Antibiotic penetration often is limited, and host defenses are absent or inadequate. Thus, morbidity and mortality from infections of the CNS remain high despite the availability of highly potent, bactericidal antibiotics. In a review of 3155 episodes of bacterial meningitis between 1998 and 2007, the mortality rate was 15%.[1] Although eradication of bacteria is essential, it is only one of the variables that affects mortality from CNS infections. In an attempt to decrease morbidity and mortality, the pathophysiologic mechanisms of CNS infections continue to be studied.[2]

A number of infectious processes can occur within the CNS (eg, meningitis, encephalitis, meningoencephalitis, brain abscess, subdural empyema, and epidural abscess). In addition, prosthetic devices placed into the CNS (eg, cerebrospinal fluid [CSF] shunts for management of hydrocephalus) often are complicated by infection. Many etiologic agents are capable of inducing CNS infections, including bacteria, viruses, fungi, and certain parasites. This chapter focuses primarily on bacterial infections of the CNS, with an emphasis on the pharmacotherapy of bacterial meningitis and brain abscess. (Also see Chapter 76, Pharmacotherapy of Human

Immunodeficiency Virus Infection, and Chapter 77, Opportunistic Infection in Patients Living With HIV, for presentations pertaining to CNS infections in these populations.)

REVIEW OF CENTRAL NERVOUS SYSTEM

Anatomy and Physiology

MENINGES

Proper therapy for CNS infections requires an understanding of anatomic and physiologic characteristics. The brain and spinal cord are ensheathed by a protective covering known as the *meninges* and suspended in CSF, which acts as a shock absorber to outside trauma. The meninges consist of three layers of fibrous tissue: the *pia mater*, *arachnoid*, and *dura mater*. The pia mater, the innermost layer of the meninges, is a thin, delicate membrane that closely adheres to the contours of the brain. Separating the pia mater from the more loosely enclosed arachnoid membrane is the subarachnoid space, in which the CSF resides. The pia mater and arachnoid, known collectively as the *leptomeninges,* lie interior to the dura mater, a tough outer membrane that adheres to the periosteum and vertebral column. *Meningitis* is a term describing inflammation (often the result of infection) of the subarachnoid space. Abscesses also can form outside the dural space (epidural abscess), often with devastating consequences.[3]

CEREBROSPINAL FLUID

CSF is produced and secreted by the choroid plexus in the lateral ventricles and, to a lesser extent, by the choroid plexuses within the third and fourth ventricles. CSF flows unidirectionally from the lateral ventricles through the foramina of the third and fourth ventricles into the subarachnoid space, then over the cerebral hemispheres, and downward into the spinal canal. CSF is absorbed through villous

projections (arachnoid villi) into veins, primarily the cerebral venous sinuses. About 0.35 to 0.4 mL of CSF is secreted per minute, with 50% of the total volume of CSF being replaced every 5 to 6 hours.[4] The flow of CSF is unidirectional from the ventricles to the intralumbar space. Therefore, intralumbar injection of antibiotics results in little, if any, antibiotic reaching the cerebral ventricles.[3,5] This unidirectional flow of CSF presents a problem because ventriculitis commonly occurs in conjunction with bacterial meningitis. Direct intraventricular instillation of antibiotics, usually by means of a reservoir, is preferable in the setting of ventriculitis (see Case 65-4, Question 4).[6]

In adults, children, and infants, the volume of CSF is ~150 mL, 60 to 100 mL, and 40 to 60 mL, respectively.[4,7] Knowledge of approximate CSF volume facilitates estimation of the CSF concentration of a drug subsequent to intrathecal administration. For example, administration of gentamicin 5 mg (5000 µg) intrathecally should result in a CSF concentration of ~33 µg/mL in an adult shortly after administration.

The composition of CSF differs from other physiologic fluids. The pH of CSF is slightly acidic (normal pH, 7.3), and with the exception of chloride ion, electrolyte concentrations are slightly less than those in serum.[6] Under normal conditions, the protein concentration in CSF is 15 to 45 mg/dL, CSF glucose values are 50 to 80 mg/dL (~60% those of plasma), and few if any WBCs are present (<5 cells/µL).[3] When the meninges become inflamed (ie, in meningitis), the composition of the CSF is altered. In particular, the protein concentration in the CSF increases, and the glucose concentration in the CSF usually declines with meningitis. Therefore, careful evaluation of CSF chemistries is useful when establishing a diagnosis of meningitis.

BLOOD–BRAIN BARRIER

The blood–brain barrier plays a crucial role in protecting the brain and maintaining homeostasis within the CNS.[3,4] Actually, two distinct barriers exist within the brain: the blood–CSF barrier and the blood–

brain barrier. The blood–CSF barrier is characterized morphologically by porous capillaries (**Fig. 65-1**). This allows proteins and other molecules (including antibiotics) to pass freely into the immediate interstitial space. Diffusion of substances into the CSF is restricted by tightly fused cells lining the ventricular side of the choroid plexus (Fig. 65-1). Cerebral capillary endothelial cells make up the blood–brain barrier, which separates blood from the interstitial fluid of the brain. Unlike capillaries in other areas of the body, the capillary endothelia of the brain are packed closely together, forming tight junctions that, in effect, produce a barrier physiologically similar to a continuous lipid bilayer. The surface area of the blood–brain barrier is >5000 times than that of the blood–CSF barrier; thus, the blood–brain barrier plays a more important role in protecting the brain and regulating its chemical composition.[8] Many antimicrobials traverse the blood–brain barrier with difficulty (see the subsequent section on Antimicrobial Penetration into the Cerebrospinal Fluid).

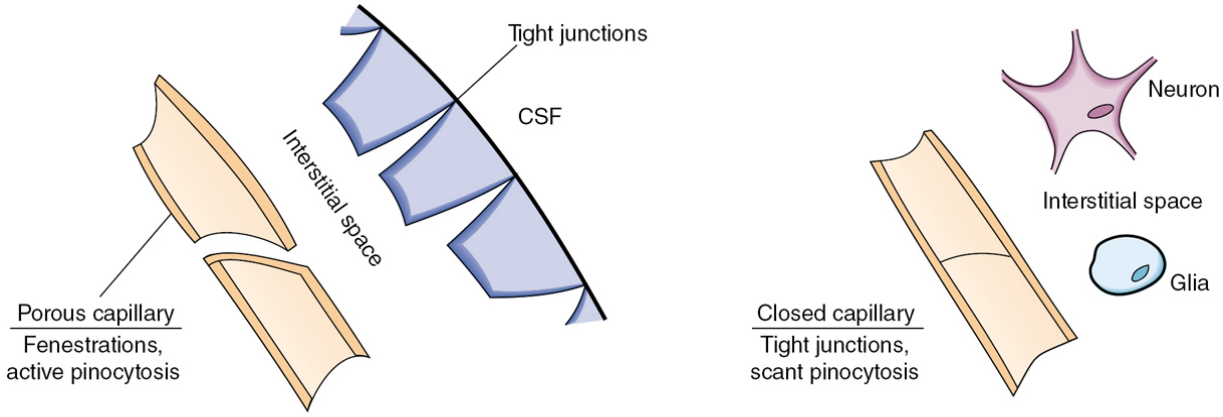


Figure 65-1 The two membrane barrier systems in the central nervous system: the blood-cerebrospinal fluid (CSF) barrier (A) and the blood-brain barrier (B). Blood-brain barrier: interface between internal medicine and the brain.

MENINGITIS

Meningitis is the most common type of CNS infection. The signs and symptoms associated with bacterial meningitis usually are acute in onset, evolving over the course of a few hours. Prompt recognition and early institution of therapy are essential to ensuring beneficial outcomes.[9] In contrast, a diverse group of infectious (eg, viruses, fungi, and mycobacteria) and noninfectious (eg, chemical irritants) agents produce a meningitic picture often of a less acute or chronic nature.[9,10] Drugs that can induce aseptic meningitis include trimethoprim–sulfamethoxazole (TMP-SMX), intravenous (IV) immunoglobulins, OKT3 antibodies, and nonsteroidal anti-inflammatory drugs such as ibuprofen, naproxen, and sulindac.[10]

Microbiology

Generally, meningitis is a disease of the very young and very old: Most cases occur in children younger than 2 years of age and in elderly adults.[1] The bacterial causes of meningitis correlate well with age and underlying conditions (**Table 65-1**).[11]

Table 65-1
Microbiology of Bacterial Meningitis

Age Group or Predisposing Condition	Most Likely Organismsa
Neonates (<1 month)	Group B streptococcus *(Streptococcus agalactiae)*, *Escherichia coli*, *Klebsiella species*, *Listeria monocytogenes*
Infants and children (1–23 months)	*S. pneumoniae, Neisseria meningitidis, S. agalactiae*, *Haemophilus influenzae*,[b] *E. coli*
Children and adults (2–50 years)	*N. meningitidis, S. pneumonia*
Adults (>50 years)	*S. pneumoniae, N. meningitidis, L. monocytogenes, E. coli*, *Klebsiella* species, and other aerobic gram-negative bacilli

Postneurosurgical	*Staphylococcus aureus*, aerobic gram-negative bacilli (eg, *E. coli, Klebsiella* species, *Pseudomonas aeruginosa*), *S. epidermidis*[c]
Closed head trauma	*S. pneumoniae*, *H. influenzae*, group A β-hemolytic streptococci
Penetrating trauma	*S. aureus, S. epidermidis*, aerobic gram-negative bacilli (eg, *E. coli, Klebsiella* species, *P. aeruginosa*)
CSF shunt	Coagulase-negative staphylococci (particularly *S. epidermidis*), *S. aureus*, aerobic gram-negative bacilli (including *P. aeruginosa*), *Propionibacterium acnes*

CSF, cerebrospinal fluid.

[a]Organisms listed in descending order of frequency.

[b]Need to consider this pathogen only in children not vaccinated with Hib.

[c]Most commonly seen in association with prosthetic devices (eg, cerebrospinal fluid shunts).

Neonates (infants younger than 1 month) are at an especially high risk for experiencing meningitis. Meningitis in preterm neonates is most often caused by *Escherichia coli*, whereas meningitis in term neonates is most often caused by group B streptococci (*Streptococcus agalactiae*). These highly virulent pathogens usually are acquired during passage through the birth canal or from the hospital environment and are associated with significant morbidity and mortality, particularly in premature infants.[1],[12] Consensus recommendations regarding intrapartum administration of penicillin to females colonized with group B streptococci have led to an 80% decrease in early-onset infection due to this pathogen.[13] *Listeria monocytogenes* is another important and often overlooked pathogen in neonates.[1] Because *L. monocytogenes* is resistant to many antimicrobial agents, including third-generation cephalosporins, selection of initial (empiric) therapy in neonates must be approached with this pathogen in mind.[11]

Infants and children 2 to 23 months old are also at a high risk for meningitis. Historically, in this age group, the disease was caused predominantly by three pathogens: *Haemophilus influenzae*, *S. pneumoniae*, and *Neisseria meningitidis*. Up to 45% of all cases of

meningitis in the United States before 1985 were caused by *Haemophilus influenzae* type b (Hib).[14] From 1991 to 1996, however, Hib invasive disease incidence in children age younger than 5 years decreased by >99%. This reduction in *H. influenzae*–induced meningitis correlates with the widespread vaccination of children against invasive *H. influenzae* disease with the Hib polysaccharide–protein conjugate vaccines.[15]

In adults and children who have received the conjugated Hib vaccine, community-acquired meningitis most often is caused by *S. pneumoniae* (the pneumococcus) and *N. meningitidis* (the meningococcus). Meningococci more commonly are implicated in individuals ages 2 to 34 years, whereas pneumococci are the predominant pathogens in adults older than age 34 years.[1] The incidence of pneumococcal meningitis has decreased by 26% from 1998 to 2006–2007 with the introduction of pneumococcal conjugate vaccines, with a decrease of 92% if only serotypes contained in the seven-valent conjugate vaccine are considered.[16] Unfortunately, use of the 13-valent conjugate vaccine has not resulted in further decreases in meningitis cases in children, with nonvaccine serotypes replacing those contained in the vaccine.[17] The incidence of meningococcal disease has decreased by 73% from 1996 to 2011. Interestingly, most of this decline in incidence occurred before the routine use of meningococcal conjugate vaccines.[18]

Patients of advanced age and those who undergo neurosurgical procedures or experience head trauma are also susceptible to meningitis. The most likely causative pathogens in these patient populations are listed in Table 65-1.

Pathogenesis and Pathophysiology

In general, meningitis can develop from *hematogenous* spread of organisms, by *contiguous* spread from a parameningeal focus (eg, sinusitis or otitis media), or by direct bacterial *inoculation*, as occurs with head trauma or neurosurgery. In contiguous spread, colonization of mucosal surfaces is a necessary first step in the

pathogenesis of meningitis. Meningeal pathogens then adhere to, and penetrate through, the epithelial surface and enter the intravascular space. Eventually, organisms that allow invasion of the blood–brain barrier multiply to sufficient numbers.[2,20,21]

Once bacteria gain entry into the CSF, host defenses are inadequate to contain the infection, and bacteria replicate rapidly. Humoral immunity (both complement and immunoglobulin) essentially is absent within the CSF. In addition, opsonic activity in CSF is negligible, and although leukocytosis ensues shortly after bacterial invasion, phagocytosis also is inefficient. Therefore, this relative immunodeficiency state necessitates the initiation of bactericidal therapy.[2,19,20]

Inflammation of the meninges is initiated by contents within the bacterial cell wall. Release of these contents (lipopolysaccharide for gram negatives and teichoic acid for gram positives) induces the production and secretion of inflammatory cytokines, which promote the adherence of leukocytes to cerebral capillary endothelial cells and facilitate the migration of leukocytes into the CSF. This results in the characteristic CSF leukocytosis as well as an eventual increase in blood–brain barrier permeability.[2,19,20]

Inflammation of the blood–brain barrier may lead to brain edema, which, combined with obstruction of CSF outflow, increases intracranial pressure and alters cerebral blood flow. Resultant hyperperfusion or hypoperfusion of the brain may ultimately result in neuronal injury, cerebral ischemia, and irreversible brain damage. The inflammatory response in meningitis also can be aggravated by some antibiotics, notably the penicillins and cephalosporins.[19] When the β-lactam antibiotics lyse bacterial cell walls, large amounts of cell wall products are liberated, and these products amplify the inflammatory response. The long-term benefits of β-lactam therapy far outweigh such detrimental effects, and the use of adjunctive corticosteroids in certain patient populations can substantially reduce inflammation and the subsequent neurologic sequelae of meningitis.[2,19,20]

In a systemic review of approximately three decades of data surrounding neurologic sequelae, the median risk of developing at

least one major or minor sequela was 19.9% (12.3%–35.3%).[21] The type and severity of neurologic complications vary with the specific infecting organism, the severity of the infection, and the susceptibility of the host. In a long-term prospective study of 185 children with acute bacterial meningitis, permanent hearing loss occurred in 6%, 10.5%, and 31% of children with meningitis caused by *H. influenzae*, *N. meningitidis*, and *S. pneumoniae*, respectively. Although seizures are fairly common on initial presentation, long-term epilepsy occurs in ~7% of patients. Other important long-term complications include spastic paraparesis, behavioral disorders, and learning deficits.[22]

Diagnosis and Clinical Features

CLINICAL AND LABORATORY FEATURES OF BACTERIAL MENINGITIS

CASE 65-1

Question 1: S.C., a 5-year-old male, is brought to the emergency department (ED) by his mother, who says her son has a temperature of 102.2 °F (39 °C), is irritable and lethargic, and has a rash. S.C. was in his usual state of good health until last night, when he awoke crying. When she went to investigate, her son began to stiffen up and rock back and forth in his bed. Because he was not arousable, S.C.'s mother rushed him to the hospital. S.C.'s medical history is noncontributory except for an allergy to amoxicillin described as a skin rash. S.C., his parents, and his 7-year-old brother recently moved to the United States. S.C.'s vaccination history currently is unknown. S.C. and his brother currently attend a community day care center.

On physical examination, S.C. was in marked distress, with a temperature of 104 °F (40 °C), blood pressure of 90/60 mm Hg, and a respiratory rate of 32 breaths/minute. His weight on admission was 44.09 pounds (20 kg). Neurologic examination showed evidence of nuchal rigidity; he was lethargic and difficult to arouse. Brudzinski and Kernig sign findings were positive. On head, eyes, ears, nose, and throat examination, S.C. demonstrated photophobia (he squinted severely when the examiner shone a light in his eyes), but no evidence was noted of papilledema. A petechial rash was visible on his extremities. The remainder of S.C.'s examination was essentially normal.

Blood drawn for laboratory tests revealed the following results:

Sodium (Na^+), 128 mEq/L

Potassium (K^+), 3.2 mEq/L
Chloride (Cl^-), 100 mEq/L
Bicarbonate (HCO_3^-), 25 mEq/L
Blood urea nitrogen (BUN), 16 mg/dL
Serum creatinine (SCr), 0.6 mg/dL
Serum glucose, 80 mg/dL

The WBC count was 18,000 cells/μL with 95% polymorphonuclear (PMN) cells; the hemoglobin (Hgb), hematocrit (Hct), and platelet counts all were within normal limits.

What clinical and laboratory features that are suggestive of meningitis does S.C. display?

The clinical features of bacterial meningitis are summarized in **Table 65-2**. The most common symptoms include the triad of fever, stiff neck (nuchal rigidity), and altered mental status. When all three of these features are present, as in S.C.'s case, meningitis should be strongly suspected. Other less common signs and symptoms include headache, photophobia (unusual intolerance to light), and focal neurologic deficits, including cranial nerve palsies.[23] A positive Brudzinski sign (reflex flexion of the hips and knees produced on flexion of the neck when lying in the recumbent position) and Kernig sign (pain on extension of the hamstrings when lying supine with the thighs perpendicular to the trunk) provide physical evidence of meningeal irritation.[24] Brudzinski and Kernig signs both were positive in S.C. Seizures occur on initial presentation in up to 60% of patients and may be focal or generalized.[23] The presence of seizures or a severely depressed mental status (ie, obtundation or coma) generally is associated with a poorer prognosis.[25] According to the most recent practice guidelines for the management of bacterial meningitis, a computed tomographic (CT) scan should be obtained before lumbar puncture in patients with specific criteria. These include immunocompromised state, history of CNS disease, new-onset seizure, papilledema, abnormal level of consciousness, and focal neurologic deficit. Although controversial, brain herniation can occur when lumbar puncture is performed in patients with elevated intracranial pressure because of the pressure changes induced within the cranial vault.[11]

Table 65-2

Signs and Symptoms of Acute Bacterial Meningitis

Fever	Anorexia
Nuchal rigidity (stiff neck)	Headache
Altered mental status	Photophobia
Seizures	Nausea and vomiting
Brudzinski sign[a]	Focal neurologic deficits
Kernig sign[a]	Septic shock
Irritability[b]	

[a]See text for description of sign.

[b]Symptoms seen in infants with meningitis.

S.C. has many of the clinical features associated with acute bacterial meningitis. Furthermore, the low blood pressure (hypotension) and increased respiratory rate are characteristic findings in severe, life-threatening types of bacterial infection (eg, septic shock, meningitis) and are likely the result of endotoxin release.

The signs and symptoms of meningitis in the very young and very old differ from those in older children and adults. In neonates, signs of meningeal irritation may be absent; fever, irritability, and poor feeding are often the only symptoms manifested.[23] Because S.C. is 5 years old, accurate assessment of his mental status is challenging. Irritability (crying), as was manifested by S.C., is an important finding that suggests an altered mental status.

In elderly patients, many of the classic signs of meningeal irritation are absent as well, and the disease presentation can be subtler.[23] Therefore, given the grave consequences of a misdiagnosis, clinicians caring for infants and elderly patients must have a particularly high index of suspicion for meningitis.

Laboratory evaluation of meningitis should include serum chemistries and a hemogram as well as a detailed examination of the CSF.[23] The peripheral WBC count often is markedly elevated in acute bacterial meningitis, usually with a left shift evident on the

differential. This finding, however, is nonspecific and occurs in many acute inflammatory and infectious diseases. S.C. has a marked leukocytosis with a predominance of PMN cells on the differential.

The abrupt onset of S.C.'s clinical symptoms is consistent with an acute bacterial process rather than a fungal or viral etiology. Given his age (5 years) and the community-acquired nature of the infection, the most likely pathogens for his meningitis are *H. influenzae*, *N. meningitidis*, and *S. pneumoniae*. The presence of maculopapular lesions argues for *N. meningitidis* as the causative pathogen because this is a common finding in cases of meningococcemia or meningococcal meningitis.[20] To make an accurate clinical and microbiologic diagnosis in S.C., it is necessary to obtain CSF for analysis. Thus, a lumbar puncture is required as soon as possible.

CEREBROSPINAL FLUID EXAMINATION

Case 65-1, Question 2: The resident physician in the ED performs a lumbar puncture, which yielded the following:

Opening pressure, 300 mm Hg (normal, <20)
CSF glucose, 20 mg/dL (normal, 50%–60% of plasma glucose)
Protein, 250 mg/dL (normal, <50 mg/dL)
WBC count, 1200 cells/μL, with 90% PMN, 4% monohistiocytes, and 6% lymphocytes

The CSF red blood cell (RBC) count was 50/μL. A STAT Gram stain of CSF revealed numerous WBCs but no organisms. CSF, blood, and urine culture results are pending. How should these CSF results be interpreted?

Careful examination of the CSF is essential to confirm the diagnosis of meningitis.[7] **Table 65-3** compares the typical findings in CSF obtained from patients with acute bacterial meningitis with those seen with fungal or viral causes.[11,26,27] In acute bacterial meningitis, the CSF is often purulent, containing numerous WBCs with a predominance of PMNs, and often is turbid. CSF protein nearly always is elevated, and the CSF glucose concentration is low.[11] In contrast, CSF obtained in viral and fungal cases of meningitis usually is clear and characterized by a much lower WBC

count with a mononuclear or lymphocyte predominance. Although the CSF protein concentration often is elevated, it may be normal. A variable effect is observed with CSF glucose.[11,26,27]

Table 65-3
Cerebrospinal Fluid Findings in Various Types of Meningitis

Microbial Etiology	WBC Count (cells/μL)	Predominant Cell Type	Protein	Glucose
Bacterial	>500	PMN	Elevated	Low
Fungal	10–500	MN	Elevated	Variable
Viral	10–200	PMN or MN	Variable	Normal

MN, mononuclear cells; PMN, polymorphonuclear neutrophils; WBC, white blood cell.

MICROBIOLOGIC EVALUATION

Microbiologic evaluation should include examination of CSF by Gram stain and culture as well as cultures obtained from other potential sites of infection (eg, blood, sputum, urine). The presence of organisms on smear is indicative of a high bacterial inoculum (ie, inoculum $>10^5$ colony-forming units/mL) and is associated with a more fulminant disease.[22] The absence of organisms on Gram stain by no means rules out infection, but does make selection of empiric therapy more difficult. Although a positive Gram stain should prompt a reevaluation of empiric therapy to ensure appropriate coverage, Gram stain results should not, by themselves, prompt a narrowing of appropriate empiric therapy.[9]

S.C. has a negative Gram stain finding, which may be the result of previous antibiotic therapy or the early detection of disease. Given the negative CSF Gram stain result, S.C. must receive antibacterial therapy sufficiently broad to cover all pathogens associated with meningitis in his age group until the results from his CSF culture are available (usually within 24–48 hours). The CSF culture nearly always is positive in purulent meningitis, although CSF cultures can

be negative in a patient who clearly has meningitis, particularly with antecedent receipt of antibiotic therapy.[7] Finally, results from cultures of other sites, such as the blood, urine, and sputum (when appropriate), can yield useful microbiologic information. In 2015, a multiplex polymerase chain reaction (PCR) panel (FilmArray® Meningitis/Encephalitis Panel, BioFire Diagnostics, LLC, Salt Lake City, Utah) was marketed, which detects 14 bacterial, viral, and yeast pathogens in about an hour from a CSF sample. Unfortunately, the test is currently limited by concerns regarding sensitivity (eg, with *S. agalactiae*) and specificity (eg, false-positive results for *S. pneumoniae*).[28] Although this panel does not replace current testing approaches, technologic innovations enabling rapid and reliable pathogen identification remain a focus of ongoing research.[29]

The CSF findings in S.C. also strongly support the diagnosis of bacterial meningitis. He has a markedly elevated opening CSF pressure, CSF leukocytosis (with a predominance of PMNs), an elevated CSF protein concentration, and a depressed CSF glucose value. A few RBCs are present in the CSF, which suggests contamination with peripheral blood caused by the traumatic nature of the lumbar puncture. Precise identification of the offending organism is not possible until CSF culture results are available.

Treatment Principles

Prompt institution of appropriate antimicrobial therapy is essential when treating meningitis. Delay in antibiotic administration is associated with increased morbidity and mortality.[9] When choosing antimicrobial therapy, a number of factors must be considered. First, the antibiotics selected must penetrate adequately into the CSF. In addition, the regimen chosen must have potent activity against known or suspected pathogens and exert a bactericidal effect.[28]

ANTIMICROBIAL PENETRATION INTO THE CEREBROSPINAL FLUID

The ability of antimicrobials to penetrate the CSF is affected by lipid solubility, degree of ionization, molecular weight, protein binding, and susceptibility to active transport systems operative within the choroid plexus. In general, the penetration of most antibiotics into the CSF is increased when the meninges are inflamed. Antimicrobial penetration into the CSF is most commonly reported as a ratio of CSF to serum antimicrobial levels. **Table 65-4** summarizes the CSF penetration characteristics of various antimicrobials during acute bacterial meningitis.[28],[30] Metronidazole, sulfamethoxazole, and trimethoprim are small, highly lipophilic compounds and penetrate into the CSF well, achieving adequate concentrations even when meningeal inflammation is absent. Rifampin is lipophilic but is a larger compound with a high degree of protein binding. Thus, it achieves satisfactory CSF penetration and may be combined with vancomycin to treat coagulase-negative staphylococcal infections in the CNS. Because β-lactams usually are ionized at physiologic pH, they are more polar and do not penetrate the CSF as well. β-Lactams penetrate poorly when the meninges are intact, but when the meninges are inflamed, most penicillins and the third- and fourth-generation cephalosporins achieve CSF concentrations sufficient to treat meningitis (~10%–30% of simultaneously obtained serum concentrations). First- and second-generation cephalosporins are not recommended in the treatment of meningitis owing to inadequate penetration and/or inferior efficacy.[31],[32] Ceftriaxone achieves sustained, reliable bactericidal activity within the CSF despite its high protein binding and has been used successfully to treat meningitis in both children and adults. An additional factor working against maintenance of therapeutic concentrations of β-lactams in the CSF is the active transport system of the choroid plexus, which pumps these organic acids out of the CSF. Meropenem achieves CSF levels 10% to 40% of serum levels.[28],[30] Regarding β-lactamase inhibitors, there is sparse clinical data exploring their use in the treatment of CNS infections, and limited pharmacokinetic data with tazobactam and clavulanic acid raise concerns for inadequate CSF concentrations. High-dose sulbactam has been used with success in some patients with *Acinetobacter baumannii* meningitis.[30] However,

this is a unique scenario because sulbactam alone displays activity against *Acinetobacter*, and as such maintaining a ratio of β-lactam:β-lactamase inhibitor is not necessary. At the present time, data are too limited to draw conclusions on the utility of the newer agents such as ceftaroline or cefiderocol in the treatment of CNS infections.

Table 65-4
Cerebrospinal Fluid Penetration Characteristics of Various Antimicrobials

Very Good[a]
Commonly recommended: metronidazole (brain abscess), TMP-SMX (second line to ampicillin for empiric coverage of *Listeria*) Uncommonly utilized; reserve use for specific scenarios[b]: linezolid, rifampin, fluoroquinolones (ciprofloxacin, moxifloxacin, levofloxacin)
Good[c]
Penicillins: penicillin G, ampicillin, piperacillin, nafcillin
Other β-*lactams:* aztreonam, clavulanate, imipenem, meropenem, sulbactam, tazobactam
Third- and fourth-generation cephalosporins[d]: cefotaxime, ceftazidime, ceftriaxone, cefepime
Other agents: vancomycin, doxycycline
Fair to Poor[e]
Aminoglycosides: amikacin, gentamicin, tobramycin *Polymyxins: colistin, Polymyxin B*
First-generation cephalosporins: Cefazolin *Other agents:* macrolides (azithromycin, clarithromycin, erythromycin), clindamycin, daptomycin

TMP-SMX, trimethoprim–sulfamethoxazole.

[a]Generally achieve levels ≥20% of serum concentrations; generally penetrate cerebrospinal fluid (CSF) well regardless of meningeal inflammation.

[b]See text for details.

[c]Generally achieve levels 10% to 20% of serum concentrations; adequate CSF penetration achieved when the meninges are inflamed.

[d]Cefuroxime has similar central nervous system (CNS) penetration but is not recommended owing to inferior efficacy.

[e]Penetration often inadequate even when the meninges are inflamed.

The aminoglycosides have a low therapeutic index, and adequate CSF concentrations are difficult to achieve with IV dosing alone without risking significant toxicity. Thus, when aminoglycoside therapy is initiated for adults with CNS infections, concomitant intrathecal therapy is usually required. Similarly, the polymyxins are large hydrophilic compounds with substantial toxicity, and thus intrathecal administration is preferred.[28],[30]

Vancomycin is a large hydrophilic compound with moderate protein binding (50%) and as such does not diffuse well across the blood–CSF barrier. Therapeutic concentrations in the CSF (up to 30% of serum concentrations) may be attained with systemic vancomycin therapy when the meninges are inflamed. Other studies have found much lower penetration, however, and, as such, concomitant intraventricular therapy also may be necessary in selected circumstances.[28],[30] Consensus guidelines, which were revised in 2020, recommend targeting a vancomycin area under the curve over 24 hours to a minimum inhibitory concentration (AUC/MIC) of 400 to 600 when treating serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections including meningitis.[33] However, as with trough targets espoused in a prior iteration of the guidelines, the optimal target AUC is not defined for this indication. Loading doses of 20 to 35 mg/kg should be strongly considered for patients with CNS infections.

Fluoroquinolones are moderately lipophilic, have a molecular weight of ~300 Da, and are not protein bound to a large extent. As would be expected, they penetrate reasonably well into the CSF on a percentage basis (~40%–60% or higher).[28],[30] Despite this, clinical data supporting the use of fluoroquinolones for bacterial CNS infections are lacking, although some hypotheses may be made. First, given its potent activity against *S. pneumoniae*, moxifloxacin may be an option for pneumococcal infections with limited therapeutic options, such as infections caused by penicillin- and ceftriaxone-resistant isolates.[34] Second, CSF concentrations attained are likely inadequate for infection caused by bacteria with higher

MICs (≥0.125–0.5 μg/mL, depending on the specific organism and drug).[35] This is especially relevant because concerns regarding CNS toxicity have generally limited the study and practice of nonstandard, increased fluoroquinolone dosages for bacterial CNS infections.[28,30] Finally, given the high rates of gram-negative resistance to fluoroquinolones, these agents should not be considered reliable as empiric therapy options in patients considered at risk for infections caused by such organisms.[36] Taken together, the fluoroquinolones are rarely utilized for the treatment of bacterial CNS infections.

Macrolides such as erythromycin and clarithromycin have a relatively high molecular weight and are substrates for a transporter that is abundant at the blood–brain barrier, P-glycoprotein. As such, they do not reach adequate concentrations when meningeal inflammation is lacking, and their lack of bactericidal activity further limits their utility in the treatment of bacterial meningitis. Bacteriostatic activity against *S. pneumoniae* also limits the utility of the tetracyclines and tigecycline. Clindamycin penetrates the CSF poorly and should not be used in the treatment of meningitis. Linezolid is also generally bacteriostatic, but because it often retains activity against multiresistant gram-positive pathogens and achieves CSF levels comparable to those in plasma, it may be considered an option for infections caused by gram-positive infections that are resistant or refractory to frontline options. Daptomycin is generally bactericidal and active against multiresistant gram-positive pathogens, but it is a large, highly protein-bound compound, and, thus, CSF penetration is low (≤10% of plasma levels). Use of higher doses and intrathecal administration is being actively explored, but current utility is limited.[28,30]

EMPIRIC THERAPY FOR CHILDHOOD MENINGITIS

Case 65-1, Question 3: A detailed medication and vaccination history reveals that S.C. and his brother appropriately received vaccination for Hib when they were 2 months old. What constitutes appropriate empiric therapy for childhood meningitis? Which antibiotic would be appropriate for S.C.? What dose and route of administration should be used?

Because results from culture and sensitivity testing of CSF will not be available for >24 hours, empiric therapy must be instituted promptly. The regimen should take into consideration the patient's age, any predisposing conditions, results from the CSF Gram stain, history of allergy, and the presence of organ dysfunction. **Table 65-5** gives recommendations for empiric antimicrobial therapy for acute bacterial meningitis.[11,37]

Table 65-5
Empiric Therapy for Bacterial Meningitis

Age Group or Predisposing Condition	Recommended Therapy	Alternative Therapy
Neonates (<1 month)	Ampicillin + cefotaxime	Ampicillin + gentamicin
Infants and children (1–23 months)	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + aztreonam/meropenem
Older children and adults (2–50 years)	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + aztreonam/meropenem
Elderly (>50 years)	Ampicillin, cefotaxime, or ceftriaxone + vancomycin	Vancomycin + TMP-SMX + aztreonam or vancomycin + meropenem
Postneurosurgical	Vancomycin + ceftazidime/cefepime	Vancomycin + meropenem
Closed head trauma	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + aztreonam/meropenem
Penetrating head trauma	Vancomycin + ceftazidime/cefepime	Vancomycin + meropenem
Immunocompromised	Vancomycin + cefepime + ampicillin	Vancomycin + TMP-SMX + aztreonam or vancomycin + meropenem

TMP-SMX, trimethoprim–sulfamethoxazole.

S.C. is 5 years old and has a negative CSF Gram stain result. Therefore, therapy with a third-generation cephalosporin, such as

ceftriaxone or cefotaxime, is preferred. Either of these two agents will provide excellent coverage of the most likely pathogens in this age group (*S. pneumoniae* and *N. meningitidis*).[11,37] Of these two pathogens, S.C.'s rash suggests that *N. meningitidis* is likely.[38] *H. influenzae* is not very likely because he was vaccinated against Hib. Thus, initiation of ceftriaxone plus vancomycin would be appropriate for S.C. at this time.

Use of a cephalosporin in this case is appropriate despite the allergic history with amoxicillin (history of skin rash). Patients with a documented penicillin allergy carry an ~2% risk of cross-reactivity when cephalosporins are prescribed, depending on the agent. In this setting, the type of reaction to penicillin is important to consider. Patients with a history of accelerated hypersensitivity reactions (eg, hives, shortness of breath [SOB], or anaphylaxis) to penicillins should not be given cephalosporins in most instances. Conversely, a benign skin rash would not contraindicate use of a cephalosporin.[39] If S.C. had experienced an accelerated reaction to penicillin, vancomycin plus aztreonam, or meropenem would be the best alternative choice (Table 65-5).[11]

DOSING CONSIDERATIONS

In general, therapy for meningitis requires the use of high dosages of antimicrobials administered by the IV route. **Table 65-6** lists the recommended dosing regimens for the treatment of CNS infections. S.C. should receive ceftriaxone in a dosage of 100 mg/kg/day given in one or two doses. A ceftriaxone regimen of 1000 mg IV every 12 hours is reasonable for S.C.

Table 65-6
Suggested Antibiotic Dosing Regimens for Treatment of Central Nervous System Infections

Antibiotic	Daily Dose (interval in hours)[a]			
	Neonates 0–7 Days Old	Neonates 8–28 Days Old	Infants and Children	Adults
Ampicillin	150 mg/kg (8)	200 mg/kg (6–8)	300 mg/kg (6)	12 g (4)
Aztreonam				8 g (6)
Nafcillin	75 mg/kg (8–12)	100–150 mg/kg (6–8)	200 mg/kg (6)	12 g (4)
Penicillin G	0.15 mU/kg (8–12)	0.2 mU/kg (6–8)	0.3 mU/kg (4–6)	24 mU (4)
Meropenem			120 mg/kg (8)	6 g (8)
Cephalosporins				
Cefotaxime	100–150 mg/kg (8–12)	150–200 mg/kg (6–8)	225–300 mg/kg (6–8)	12 g (4)
Ceftriaxone			80–100 mg/kg (12–24)	4 g (12)
Ceftazidime	100–150 mg/kg (8–12)	150 mg/kg (8)	150 mg/kg (8)	6 g (8)
Cefepime			150 mg/kg (8)	6 g (8)
Aminoglycoside[b,c]				
Gentamicin	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5–7 mg/kg (8–24)
Tobramycin	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5–7 mg/kg (8–24)
Amikacin	15–20 mg/kg (12)	30 mg/kg (8)	20–30 mg/kg (8)	15 mg/kg (8–24)
Others				
Moxifloxacin				400 mg (24)
Linezolid				1200 mg (12)
Rifampin		10–20 mg/kg (12)	10–20 mg/kg (12–24)	600 mg (24)
TMP-SMX[d]			10–20 mg/kg (6–12)	10–20 mg/kg (6–12)
Vancomycin[c,e]	10–20 mg/kg (8–48) depending on postmenstrual age, weight, and serum creatinine	10–20 mg/kg (8–48) depending on postmenstrual age, weight, and serum creatinine	**Ages 1–3 months:** 10–20 mg/kg (8–48) **Ages 3 months to <12 years:** 60–80 mg/kg (6) **Ages ≥12 years:** 60–70 mg/kg (6–8)	30–60 mg/kg (8–12)

[a]Recommended daily dose when renal and hepatic functions are normal.

[b]Concurrent intraventricular doses of 5 to 10 mg (gentamicin, tobramycin) or 20 mg (amikacin) often required when treating gram-negative bacillary meningitis.

[c]Dose should be individualized based on serum level monitoring.

[d]Dose is based on the trimethoprim component.

[e]Concurrent intraventricular doses of 5 to 20 mg recommended if response to intravenous (IV) therapy is inadequate.

Sources: Adapted from Tunkel AR, Hartman BJ, Kaplan L, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39(9): 1267–1284. Reproduced by permission of Infectious Diseases Society of America; Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(9):835–864.

ADJUNCTIVE CORTICOSTEROID THERAPY

Case 65-1, Question 4: What is the rationale for adjunctive corticosteroid therapy in acute bacterial meningitis, and would it be appropriate for S.C.? How should dexamethasone be dosed and monitored for S.C.?

Corticosteroids, particularly dexamethasone, can reduce cerebral edema and lower intracranial pressure.[40] In addition, corticosteroids reduce the synthesis and release of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-1β from monocytes and astrocytes. These two cytokines play a central role in initiating the cascade of events that leads to neuronal tissue damage and neurologic sequelae.[41] Theoretically, then, inhibition of cytokine synthesis by corticosteroids in meningitis should lead to a decreased risk of hearing loss and other neurologic sequelae. Indeed, a prospective, randomized, double-blind multicenter trial evaluating the use of dexamethasone in adults with acute bacterial meningitis supported this theory.[42] A total of 301 patients were randomized to receive dexamethasone or placebo 15 to 20 minutes before or with the first dose of antibiotic every 6 hours for 4 days. Dexamethasone reduced the risk of an unfavorable outcome, defined as a Glasgow Outcome Scale score of 1 to 4 at 8 weeks (relative risk [RR], 0.59; *P* = .03), and of death (RR, 0.48; *P* = .04). When the outcomes were analyzed based on culture results, mortality reduction (14% vs 34%) and all unfavorable outcomes (26% vs 52%) were only seen with dexamethasone therapy in patients with meningitis caused by *S. pneumoniae*. Outcomes in patients with meningitis caused by organisms other than *S. pneumoniae* were independent of whether they received dexamethasone or not. Neither gastrointestinal (GI) bleeding nor other adverse effects were increased in the dexamethasone group.

In children, several studies have also evaluated the role of adjunctive dexamethasone therapy in bacterial meningitis. Some prospective placebo-controlled, randomized trials have demonstrated that adjunctive dexamethasone therapy significantly reduces audiologic and neurologic sequelae in children older than 2 months. *H. influenzae*, however, was the causative pathogen in most of these meningitis cases, whereas the number of children with

streptococcal and meningococcal meningitis in these trials was small.[2],[43]–[47] As previously mentioned, the number of Hib cases has decreased dramatically, making the data from these trials difficult to apply to the present day. More recently, of the 166 patients enrolled in a trial comparing dexamethasone to placebo, 35 and 26 cases were caused by *S. pneumoniae* and *N. meningitides*, respectively, in the treatment arm. Fewer audiologic and neurologic sequelae were observed in the dexamethasone-treated group compared with the placebo group, but the difference did not reach statistical significance.[48]

More recently, a 2015 Cochrane meta-analysis evaluated data from 25 randomized trials that included over 4000 children and adults. In the overall population, glucocorticoid administration did not significantly reduce mortality. However, glucocorticoids did reduce mortality in the subgroup of patients with meningitis caused by *S. pneumoniae* (RR, 0.84; 95% confidence interval [CI], 0.72–0.98). In studies conducted in high-income countries, glucocorticoids reduced severe hearing loss (RR, 0.51; 95% CI, 0.35–0.73), any hearing loss (RR, 0.58; 95% CI, 0.45–0.73), and short-term neurologic sequelae (RR, 0.64; 95% CI, 0.48–0.85). In the subgroup of over 2000 children, the administration of dexamethasone did not affect mortality but did reduce the incidence of severe hearing loss, particularly in those with *H. influenzae* meningitis.[49]

The 2004 Infectious Diseases Society of America (IDSA) meningitis guidelines recommend that dexamethasone be initiated before (or concomitant with the first dose of) antimicrobial therapy in all adult patients with suspected or proven pneumococcal meningitis.[11] Controversy remains over whether dexamethasone should be continued in adults if the causative agent is found not to be pneumococcus because the number of patients in the studies with meningitis caused by other organisms was small.[50] However, the guidelines do recommend discontinuing dexamethasone if the organism is found to be something other than *S. pneumonia*.[11] Regarding pediatrics, the American Academy of Pediatrics (AAP) Committee on Infectious Diseases suggests that dexamethasone therapy may be beneficial in children with Hib meningitis if given

before or at the same time as the first dose of antimicrobial therapy.[51] The AAP Committee on Infectious Diseases also suggests that the decision to use adjunctive dexamethasone therapy should be individualized but considered for infants and children older than 6 weeks with pneumococcal meningitis.[52] At this time, there can be no firm recommendation as to whether steroids should be continued in children if the pathogen is found not to be *H. influenzae* or *S. pneumoniae.*

Thus, S.C. should receive dexamethasone therapy, 0.15 mg/kg/dose given IV every 6 hours for 2 to 4 days. For S.C., who is 44.09 pounds (20 kg), this would be 3 mg every 6 hours, with the first dexamethasone dose given 15 minutes before initiating ceftriaxone therapy.

Potential adverse effects associated with dexamethasone include GI bleeding, mental status changes (eg, euphoria or encephalopathy), increases in blood glucose, and, possibly, elevations in blood pressure. For S.C., the complete blood count (CBC), serum chemistries, and stool guaiac should be monitored daily while he is receiving dexamethasone. He also should be questioned about possible GI upset and assessed for changes in mental status (eg, confusion, combativeness). Given the short duration of corticosteroid therapy, dexamethasone can be discontinued abruptly without tapering.

EFFECT ON CENTRAL NERVOUS SYSTEM PENETRATION OF ANTIBIOTICS

Another important issue to consider is whether dexamethasone, a potent anti-inflammatory agent, reduces the ability of antimicrobials to penetrate across the blood–brain barrier into CSF. Because CSF penetration of the penicillins, cephalosporins, and vancomycin is greatest when the meninges are inflamed, a hypothetical concern is that concomitant dexamethasone may reduce CSF concentrations of these agents, resulting in reduced efficacy. Early animal models suggest that vancomycin penetration into the CSF is reduced in dexamethasone-treated animals compared with animals not treated

with steroids.[53] In a rabbit meningitis model, the coadministration of dexamethasone and vancomycin resulted in 29% less penetration of vancomycin into the CSF. By increasing the daily dose of vancomycin in these rabbits, however, therapeutic CSF levels were achieved, suggesting that giving larger daily doses of vancomycin circumvents the steroid effect on CNS penetration.[54] In addition, current human data suggest that CSF penetration of vancomycin or ceftriaxone is not diminished with concomitant administration of dexamethasone.[55–58] Based on these encouraging findings, it is recommended that dexamethasone be utilized in all patients.[11]

Neisseria meningitidis Meningitis

DEFINITIVE THERAPY

Case 65-1, Question 5: Twenty-four hours after admission, S.C.'s culture results from his blood and CSF samples are available. The CSF culture is growing *N. meningitidis* (penicillin MIC, 0.06 mg/L), and *N. meningitidis* is also growing in both the collected blood cultures. What modification in S.C.'s antimicrobial therapy is necessary at this time?

Once culture and sensitivity results become available, definitive therapy can be instituted, often with a single agent (**Table 65-7**).[11,37] As suspected, S.C.'s CSF culture result is positive for *N. meningitidis.* Cefuroxime, a second-generation cephalosporin, has activity against *N. meningitides*; however, it is less effective for meningitis than are third-generation cephalosporins and should not be used.[59,60] The reason for the inferiority of cefuroxime relative to ceftriaxone most likely is related to reduced potency.[59]

Table 65-7
Definitive Therapy for Bacterial Meningitis

Pathogen	Recommended Treatment	Alternative Agents
Haemophilus influenza		

β-Lactamase negative	Ampicillin	Cefotaxime or ceftriaxone; aztreonam
β-Lactamase positive	Cefotaxime or ceftriaxone	Aztreonam
Neisseria meningitidis	Penicillin MIC <0.1 μg/mL: penicillin G or ampicillin	Cefotaxime or ceftriaxone; meropenem
	Penicillin MIC 0.1–1.0 μg/mL: cefotaxime or ceftriaxone	
Streptococcus pneumoniae	Penicillin MIC ≤0.06 μg/mL: penicillin G or ampicillin	Cefotaxime or ceftriaxone
	Penicillin MIC ≥0.12 μg/mL: cefotaxime or ceftriaxone if susceptible	Vancomycin or meropenem
	Penicillin and cefotaxime/ceftriaxone nonsusceptible: vancomycin + cefotaxime/ceftriaxone ± rifampin	Vancomycin + moxifloxacin
Streptococcus agalactiae	Penicillin G or ampicillin + gentamicin	Cefotaxime or ceftriaxone
Listeria monocytogenes	Penicillin G or ampicillin ± gentamicin	TMP-SMX or meropenem
Enterobacteriaceae		
Escherichia coli, Klebsiella species	Cefotaxime or ceftriaxone	Cefepime; aztreonam; meropenem
Enterobacter, *Serratia* species	Cefepime; meropenem	TMP-SMX; aztreonam
Pseudomonas aeruginosa	Cefepime or ceftazidime; meropenem	Aztreonam
Staphylococcus aureus[a]		
Methicillin-susceptible (MSSA)	Nafcillin or oxacillin	Vancomycin ± rifampin; meropenem
Methicillin-resistant (MRSA)	Vancomycin ± rifampin	TMP-SMX; linezolid
Staphylococcus	Vancomycin ± rifampin	TMP-SMX;

epidermidis[a]		linezolid

MIC, minimum inhibitory concentration; TMP-SMX, trimethoprim–sulfamethoxazole.

[a]Concomitant intrathecal therapy may be required for optimal response (most commonly an intrathecal aminoglycoside for gram-negative or intrathecal vancomycin for gram-positive infections).

Because *N. meningitidis* is susceptible to penicillin and ampicillin currently, penicillin is the drug of choice. However, S.C.'s questionable history of amoxicillin rash makes the use of ceftriaxone a reasonable choice (see Table 65-6 for dosing).

MONITORING THERAPY

Case 65-1, Question 6: What subjective and objective data should be monitored to evaluate the efficacy and toxicity of treatment of patients with meningitis, and what specifically should be monitored in S.C.?

Clinical signs and symptoms attributable to the disease, such as fever, altered mental status, and stiff neck, should be checked periodically throughout the day and monitored for resolution. S.C.'s temperature and mental status should be assessed often. Accurate assessment of S.C.'s mental status can be difficult because of his young age. Thus, his baseline level of mental status should be evaluated (eg, whether he is awake and alert, or lethargic and difficult to arouse). If awake and alert, S.C. should be observed for irritability, because this often is the only sign of altered mentation. Questions can be used to assess his orientation: Does he know where he is? Does he know his name? Can he recognize his mother or other family members? In general, signs of clinical improvement should be evident within 24 to 48 hours in most uncomplicated cases of acute bacterial meningitis, with defervescence of fever achieved in a mean of 3.3 days in one trial of cefotaxime in children.[61]

Laboratory tests should be monitored as well. A CBC with differential, serum electrolytes (eg, Na^+, K^+, Cl^-, HCO_3^-), blood glucose, and renal function tests (eg, BUN, SCr) should be

performed daily. Abnormal electrolyte results may require more frequent monitoring. Laboratory abnormalities, such as leukocytosis and hyponatremia, may take longer to normalize than do clinical symptoms. CSF chemistries usually improve within 48 hours of starting therapy, although CSF WBC and protein may remain elevated for a week or more.[62,63] With effective therapy, the CSF culture usually is sterile after about 18 to 24 hours of therapy.[59,61] Delays in CSF sterilization are associated with a higher propensity for neurologic complications.[59] If S.C. responds to therapy in a straightforward manner, he need not have a repeat lumbar puncture. If the response is inadequate, as evidenced by persistent fever or deteriorating mental status, S.C. will require a repeat lumbar puncture to reexamine the CSF parameters.[11]

In addition to monitoring the therapeutic response, side effects of the antimicrobial regimen also need to be assessed frequently. Meningitis requires high-dose therapy, making the likelihood of adverse effects much greater. Currently, S.C. is being treated with ceftriaxone. The adverse effects most often associated with ceftriaxone include hypersensitivity reactions, mild pain and phlebitis at the injection site, and GI problems.[64] S.C. should be observed for the formation of an antibiotic-related skin rash or evidence of an accelerated allergic reaction (eg, hives, wheezing). The IV catheter site should be observed daily for redness, tenderness, or pain on palpation of the vein. S.C. should be watched closely for loose stools or diarrhea. Although mild diarrhea is a common side effect of most antimicrobials that rarely requires a change in therapy, diarrhea that is severe, persistent, or accompanied by fever, unexplained leukocytosis, or abdominal cramping should prompt testing for *Clostridium difficile* colitis.[60,65]

CEFTRIAXONE-INDUCED BILIARY PSEUDOLITHIASIS

Case 65-1, Question 7: After 5 days of treatment, the nurse caring for S.C. notes that his appetite is markedly diminished, and he has an upset stomach. S.C. was afebrile and alert and oriented, but abdominal examination revealed

"guarding," with pain localized in the right upper quadrant area. Laboratory data at this time are as follows:

WBC count, 6000 cells/μL
Hgb, 12.5 g/dL
Hct, 34%
Platelets, 120,000/μL
Na, 135 mEq/L
K, 3.6 mEq/L
Cl, 98 mEq/L
Aspartate aminotransferase (AST), 35 units/L
Alanine aminotransferase (ALT), 33 units/L
Alkaline phosphatase, 110 IU/dL
Total bilirubin, 1.2 mg/dL
Amylase, 70 units/L

A stool guaiac test result is negative. What are the possible causes of S.C.'s abdominal discomfort?

A number of possible causes exist for S.C.'s abdominal discomfort. His corticosteroid therapy may have caused acute GI bleeding; however, the dexamethasone was discontinued 3 days ago and S.C.'s hemoglobin and hematocrit values are in the low-normal range. The negative stool guaiac result also argues strongly against a GI bleed. Acute pancreatitis is unlikely given the normal amylase result. Viral or drug-induced hepatitis is another possibility but also is unlikely given his normal AST, ALT, and bilirubin results. An intra-abdominal infection also is possible, but this is improbable because he is afebrile and has a normal WBC count. Other causes, such as acute cholecystitis or appendicitis, require further diagnostic evaluation.

Case 65-1, Question 8: An abdominal ultrasound reveals sludge in the gallbladder. What is the significance of this finding in S.C., and how should this abnormality be managed?

The abnormality on S.C.'s abdominal ultrasound explains his right upper quadrant pain. S.C. has what appears to be a condition known as biliary pseudolithiasis (ie, biliary "sludging"). Biliary sludging can occur under conditions of gallbladder hypomotility (eg, recent

surgery, burns, total parenteral nutrition) and, in some instances, can be drug induced. S.C. has been receiving ceftriaxone for treatment of his meningitis, and this drug can cause biliary pseudolithiasis.[66]

Antibiotic-associated biliary pseudolithiasis is seen almost exclusively with ceftriaxone. The biliary excretion associated with ceftriaxone results in very high concentrations of the drug in gallbladder bile. In selected circumstances, the biliary concentration of ceftriaxone may exceed solubility limits, resulting in the formation of a fine, granular precipitate (ie, sludge), which differs in composition and ultrasound features from true gallstones. The precipitate is composed of a ceftriaxone–calcium complex, the formation of which is dose dependent. Given the high dosages required for meningitis therapy, it is not surprising that this adverse effect has occurred in S.C.[66] In the comparative randomized trial between ceftriaxone and cefuroxime cited previously, evidence of biliary pseudolithiasis on abdominal ultrasonography was observed in 16 of 35 (46%) patients who received ceftriaxone and in none of 35 patients receiving cefuroxime.[59] Pseudolithiasis usually appears 3 to 10 days following the start of therapy and, in most instances, it is clinically asymptomatic. Symptoms similar to acute cholecystitis are evident in some individuals and include nausea with or without vomiting and abdominal right upper quadrant pain.[66]

Prompt recognition of this adverse effect and discontinuation of ceftriaxone therapy are required to effectively manage biliary pseudolithiasis. Once S.C.'s ceftriaxone is discontinued, the condition should resolve gradually over a period of weeks to months; the clinical symptoms should disappear within a few days.[66] Cefotaxime can be substituted for ceftriaxone; cefotaxime is not associated with biliary complications, and the efficacy of these two agents is equivalent.[64] For S.C., the cefotaxime dosage would be 1000 mg IV every 6 hours (Table 65-6).

DURATION OF THERAPY

CASE 65-1, QUESTION 9: What is the recommended duration of antimicrobial therapy for S.C.?

The optimal duration of therapy for meningitis is difficult to ascertain because few trials have been designed to address this issue.[67] Although general guidelines exist, the duration should be individualized based on the response to therapy, the presence of complicating factors (eg, immunosuppression), and the specific causative pathogen. **Table 65-8** lists the recommended treatment durations for uncomplicated cases of bacterial meningitis according to the specific pathogen. Patients such as S.C. with meningitis caused by *N. meningitidis* should be treated for 7 days.[11] Complicated cases, such as those with delayed CSF sterilization, require therapy for longer periods (up to 2 weeks or more).

Table 65-8
Duration of Therapy for Bacterial Meningitis

Etiology	Duration of Therapy (days)
Haemophilus influenzae	7
Neisseria meningitidis	7
Streptococcus pneumoniae	10–14
Group B streptococci *(Streptococcus agalactiae)*	14–21
Listeria monocytogenes	≥21
Gram-negative bacilli	21

PREVENTION OF NEISSERIA MENINGITIDIS MENINGITIS

CASE 65-1, QUESTION 10: S.C. is ready to be discharged home. How can the potential spread of meningococcal disease be prevented in persons with whom S.C. has contact?

Despite an excellent response to therapy, S.C. still may harbor *N. meningitidis* in his nasopharynx and could transmit this organism to individuals with whom he has close contact.[18],[68],[69] Therefore,

chemoprophylaxis to prevent secondary cases of *N. meningitidis* is indicated for S.C. and his close contacts. In this context, close contacts include the following: a household member including roommates and young adults in dormitories, child care center contacts, and any person directly exposed to the patient's oral secretions (eg, through kissing, mouth-to-mouth resuscitation, or endotracheal intubation) in the 7 days before symptom onset and until 24 hours after initiation of appropriate antibiotics.[68,70] Health care personnel and any passenger on a flight who had direct contact with respiratory secretions or anyone seated directly next to an index patient on a prolonged flight (eg, one lasting ≥8 hours) should also receive chemoprophylaxis.[70]

S.C.'s 7-year-old brother, the children at the day care center, and close contacts at the hospital who have been caring for S.C. are at risk for invasive *N. meningitidis* disease and should receive chemoprophylaxis. Because the risk of secondary disease is greatest immediately after onset of disease in the index patient, chemoprophylaxis should be instituted as soon as possible and ideally within 24 hours.[68] Administering chemoprophylaxis ≥14 days after identification of the index case is of little value. Regimens to reduce nasopharyngeal carriage of *N. meningitidis* include rifampin, ciprofloxacin, and ceftriaxone. The most frequently used regimen for children 1 month or older is rifampin, given every 12 hours in a dosage of 10 mg/kg/dose for 2 days. For adults, rifampin given every 12 hours in a dosage of 600 mg for 2 days is commonly used. The index patient should also receive prophylaxis if they were treated with an agent other than a third-generation cephalosporin as soon as he/she is able to tolerate oral medications and before being discharged from the hospital.[70]

Because S.C. is receiving ceftriaxone, he does not need chemoprophylaxis. S.C.'s brother, parents, and day care contacts should be treated with appropriate doses of rifampin as soon as he is diagnosed. Because rifampin is not recommended for pregnant females, ceftriaxone would be a viable alternative.

Streptococcus pneumoniae Meningitis

CLINICAL FEATURES, PREDISPOSING FACTORS, AND DIAGNOSIS

CASE 65-2

QUESTION 1: A.L., a 58-year-old male with a long history of alcohol abuse, is admitted to the ED febrile and unresponsive. During the past several days, A.L. has experienced intermittent episodes of fever, chills, SOB, and a worsening productive cough. A friend visiting A.L. called 911 when he could not arouse him. A.L.'s medical records indicate that he has hypertension, adult-onset diabetes mellitus, peptic ulcer disease (PUD), and chronic obstructive pulmonary disease (COPD). A splenectomy was performed 10 years ago after trauma to the abdomen. A.L. is divorced and lives alone in a low-income apartment. He has no known drug allergies. His records show him to be a smoker for >30 years. Current medications include hydrochlorothiazide 50 mg every other day, glipizide 5 mg orally (PO) twice daily, famotidine 20 mg PO every day at bedtime, and doxycycline PO twice daily as needed for cough and increased sputum production.

On admission to the ED, A.L. had a temperature of 104 °F (40 °C), blood pressure of 90/50 mm Hg, and pulse and respiratory rates of 115 beats/minute and 25 breaths/minute, respectively. His weight is 130.07 pounds (59 kg). A.L. was unresponsive but withdrew all extremities to painful stimuli. His pupils were equal and sluggishly reactive to light; papilledema and evidence of meningismus were present. Wheezes and crackles were heard throughout both lung fields, with dense consolidation noted in the left lower lobe. The remainder of his physical examination was noncontributory.

Stat laboratory tests revealed the following:

WBC count, 18,000 cells/μL, with 80% PMN, 15% bands, 3% lymphocytes, and 2% basophils
Hgb, 10.5 g/dL
Hct, 34%
Platelet count, 250,000/μL
K, 3.0 mEq/L
Glucose, 250 mg/dL
AST, 190 mg/dL
ALT, 140 mg/dL
BUN, 35 mg/dL
SCr, 2.4 mg/dL

The prothrombin time was high normal, and albumin was 3.1 mg/dL. A STAT blood alcohol level of 100 mg/dL was reported, and a urine toxicology screen

result was negative. A.L.'s serum theophylline concentration was 18 mg/dL. Stool guaiac test result was positive.

A CT scan showed no evidence of mass lesions or cerebral hematoma. Lumbar puncture yielded the following results:

CSF opening pressure, 200 mm Hg
Protein, 120 mg/dL
Glucose, 100 mg/dL
WBC count, 8500 cells/μL, with 92% PMN, 4% monohistiocytes, and 4% lymphocytes
RBC count, 400/μL

Gram-positive, lancet-shaped diplococci were visible on CSF Gram stain. In addition, a sputum Gram stain test revealed numerous WBCs, few epithelial cells, and numerous gram-positive cocci in pairs and in short chains. Blood, CSF, urine, and sputum culture results are pending.

What are the clinical and laboratory features of pneumococcal meningitis? What features of pneumococcal meningitis are present in A.L.?

A.L. presents to the ED with many signs and symptoms suggestive of pneumococcal meningitis. He is 56 years old, and *S. pneumoniae* is the most common bacterial etiology for meningitis in adults age older than 30 years (Table 65-1). As is evidenced by A.L.'s presentation, invasive pneumococcal disease often is associated with significant morbidity, and mortality rates remain high.[1] However, likely due to the introduction of conjugate vaccines, the incidence of *S. pneumoniae* meningitis in the United States has significantly decreased, from 0.8 cases per 100,000 people in 1997 to 0.3/100,000 in 2010.[71] Predisposing factors to invasive pneumococcal disease include advanced age, cigarette smoking, alcoholism, diabetes, chronic pulmonary disease, and functional (sickle cell disease) or anatomic (splenectomy) asplenia. In addition, individuals infected with the human immunodeficiency virus (HIV) or with other immunocompromising conditions (such as solid organ or bone marrow transplantation) are at higher risk. Patients with CSF otorrhea or rhinorrhea induced by closed head trauma or neurosurgical procedures are more susceptible to develop pneumococcal meningitis as well.[72]

A.L. has many predisposing factors for pneumococcal meningitis. He smokes, has a long history of alcohol abuse, has had a

splenectomy, and has diabetes and COPD. A diagnosis of pneumococcal meningitis in A.L. is supported by the high fever, stiff neck (meningismus), and altered mental status. He is unresponsive, which is a definite negative prognostic factor.[73] Results from CSF chemistries and microbiologic analysis are highly suggestive of pneumococcal meningitis. A.L. has an elevated opening CSF pressure and a markedly elevated CSF protein and WBC count with a predominance of neutrophils on differential examination. The normal CSF glucose level (100 g/dL) is misleading because A.L. is diabetic. The calculated ratio of CSF to serum glucose for A.L. is <50%, which is consistent with acute bacterial meningitis (Table 65-3). The presence of gram-positive, lancet-shaped diplococci in pairs on the CSF Gram stain result strongly supports the diagnosis of pneumococcal disease. The signs and symptoms of pneumococcal pneumonia (cough, SOB, increased sputum production, and pulmonary consolidation) as well as the sputum Gram stain result also lend support to a diagnosis of invasive pneumococcal infection.

EMPIRIC THERAPY IN ADULTS

CASE 65-2, QUESTION 2: What would be appropriate therapy for A.L.?

Table 65-7 provides therapy recommendations for pneumococcal meningitis based on penicillin and ceftriaxone/cefotaxime susceptibility. Resistance among pneumococci to penicillin G (MIC ≥0.12 μg/mL) is a significant concern. In a surveillance study from 2006 to 2007, 27.5% of *S. pneumoniae* isolates from patients with meningitis were resistant to penicillin.[74] *S. pneumoniae* strains in CSF with MIC >0.5 μg/mL to cefotaxime or ceftriaxone are intermediate (1 μg/mL) or resistant (≥2 μg/mL). Reduced activity of ceftriaxone and cefotaxime against penicillin-resistant pneumococci affects the therapeutic ratio achieved in CSF and has been associated with clinical failure. Optimal therapy for fully penicillin-resistant pneumococcal meningitis should include vancomycin. The combination of vancomycin and ceftriaxone was superior to either

agent given alone in a rabbit model of penicillin-resistant pneumococcal meningitis. Ceftriaxone or vancomycin combined with rifampin also may be superior to either drug given alone.[75] With its potent pneumococcal activity and satisfactory CNS penetration, moxifloxacin may be an option for pneumococcal meningitis caused by penicillin- and ceftriaxone-resistant isolates.[34] However, clinical data supporting the use of moxifloxacin in this scenario are lacking. Thus, until more information is available, the combination of ceftriaxone or cefotaxime with vancomycin represents the most reasonable approach to empiric therapy for potential penicillin-resistant pneumococcal meningitis.

Until culture and susceptibility results are available, the recommended antibiotic in this situation is ceftriaxone 2 g given IV every 12 hours and vancomycin 30 to 60 mg/kg/day IV divided every 8 to 12 hours. A.L. weighs 130.07 pounds (59 kg), and because his renal function is not normal (SCr, 2.4 mg/dL; creatinine clearance, 30 mL/minute), a dosage adjustment was made.

CORTICOSTEROID THERAPY FOR ADULT MENINGITIS

CASE 65-2, QUESTION 3: Should A.L. receive corticosteroid therapy in addition to his antibiotic therapy?

A.L. presents with profoundly altered mental status, and his signs and symptoms are consistent with a fulminant course of disease. His age, underlying medical problems, likely streptococcal meningitis, and deteriorating clinical status all point to a poor prognosis and argue for the use of adjunctive dexamethasone. On the other hand, A.L. is diabetic and has an elevated glucose concentration. He also has PUD, which may be active given that he is anemic and has a positive stool guaiac result. High-dose dexamethasone therapy may impact on his mental status, making assessment even more difficult. Although each of these issues is a concern, none is so critical as to preclude the use of corticosteroids. Therefore, dexamethasone given in a dosage of 10 mg IV every 6 hours could be instituted before

starting ceftriaxone therapy provided that the diagnosis of bacterial meningitis is confirmed. Dexamethasone can be continued for up to 4 days if *S. pneumoniae* is found to be the causative pathogen. Dexamethasone may be discontinued if *S. pneumoniae* is not the causative pathogen.[11] To control blood glucose, a sliding scale dosing schedule of regular insulin is recommended. A.L.'s PUD should be properly worked up and treated if necessary.

TREATMENT OF PENICILLIN-SUSCEPTIBLE PNEUMOCOCCAL MENINGITIS

Case 65-2, Question 4: Results from A.L.'s CSF, blood, and sputum cultures are available and are positive for *S. pneumoniae* at each site. Sensitivity testing in CSF revealed an MIC of 0.06 µg/mL to penicillin, 0.25 µg/mL to cefotaxime and ceftriaxone, and 0.25 µg/mL to vancomycin. What therapy is indicated for A.L.?

A.L. is infected with a strain of *S. pneumoniae* that is susceptible to penicillin G (see Table 65-7).[76] The dosage usually is 24 million units/day in adults with normal renal function (see Table 65-6). A.L. has renal impairment, however, which means he should receive a reduced penicillin dosage. For A.L., who has a calculated creatinine clearance of ~28 mL/minute (according to the method of Cockcroft and Gault), the daily dose would be 12 to 16 million units, or 3 to 4 million units every 6 hours. This revised regimen should provide penicillin serum concentrations similar to those achieved with high-dose therapy when kidney function is normal. Failure to adjust the dosage appropriately is equivalent to providing excessive doses of penicillin, and seizures may result.[77] In patients unable to tolerate penicillin G, the best alternatives are ceftriaxone or cefotaxime (Table 65-7).[11,37]

Gram-Negative Bacillary Meningitis

CASE 65-3

QUESTION 1: R.R., a 40-year-old, 176.37-pound (80-kg) male, is admitted to the hospital for a cervical laminectomy with vertebral fusion. His surgical procedure was complicated by a dural tear. On the third postoperative day, drainage at his surgical excision site was noted, and R.R. was febrile to 100.76 °F (38.2 °C). The result of the Gram stain of the drainage revealed moderate gram-negative bacilli. Therapy with IV cefazolin 2 g every 8 hours was begun. The following morning, R.R. was oriented to person, place, and time, but he was slightly obtunded and had a temperature of 104 °F (40 °C). Neck stiffness could not be assessed because of his recent surgery. A magnetic resonance imaging (MRI) scan of the head and neck returned a negative finding, and lumbar puncture yielded the following CSF results:

WBC count, 3000 cells/μL, with 95% PMN
Glucose, 20 mg/dL
Protein, 280 mg/dL

What important clinical and laboratory features of gram-negative bacillary meningitis are manifested in R.R.?

EPIDEMIOLOGY

R.R. has developed gram-negative meningitis as a complication of his recent neurosurgical procedure. In the 2017 IDSA guidelines for health care–associated ventriculitis and meningitis, postneurosurgical CNS infections are classified as health care–associated ventriculitis and meningitis.[78] Gram-negative organisms are important pathogens particularly after neurosurgical procedures such as craniotomy.[71] Historically, mortality rates from gram-negative bacillary meningitis have been extremely high, ranging from 40% to 70%. With the availability of third-generation cephalosporins, some studies report that fatalities have declined to <40%; however, a recent study of 40 adults with spontaneous gram-negative meningitis reported a mortality rate of 53%.[79] Increasing resistance among certain gram-negative bacilli, such as *Enterobacter* species and *P. aeruginosa*, presents a therapeutic dilemma in that mortality associated with these pathogens is high and therapeutic options are fewer.

PREDISPOSING FACTORS

Individuals at greatest risk for gram-negative bacillary meningitis include neonates, the elderly, patients with underlying conditions such as diabetes mellitus or malignancy, patients with open trauma to the head, and individuals such as R.R. undergoing neurosurgical procedures.[78],[80] Although meningitis is a rare complication of clean neurosurgical procedures (eg, craniotomy, laminectomy), the consequences can be devastating when it does happen.[79]

MICROBIOLOGY

E. coli and *K. pneumoniae* have historically been the most common gram-negative bacteria causing meningitis; however, rates of pseudomonal meningitis appear to be increasing.[79],[81] *E. coli* is the most common gram-negative cause of neonatal meningitis, whereas *K. pneumoniae* is isolated more often in the elderly population.[82],[83] The remaining cases are generally divided evenly among *Proteus*, *Serratia*, *Enterobacte*r, *Citrobacter*, *Pseudomonas*, and other less common bacilli.[79]

CLINICAL FEATURES

In general, clinical laboratory features of gram-negative bacillary meningitis are similar to that of other types of bacterial meningitis.[1],[11] Because of high virulence, gram-negative bacillary meningitis often is a fulminant, rapidly progressive disease. An exception to this rule is meningitis after neurosurgery.[83] As is evidenced by R.R.'s clinical presentation, postneurosurgical gram-negative bacillary meningitis can present in a more subtle manner. In such patients, many of the symptoms of meningitis (eg, altered mental status, stiff neck) are masked by underlying neurologic disease. Thus, a high index of suspicion is warranted in the postsurgical setting. In addition to gram-negative bacilli, staphylococci also are associated with postneurosurgical meningitis.[78],[84]

TREATMENT OF GRAM-NEGATIVE BACILLARY MENINGITIS

Case 65-3, Question 2: What empiric therapy is appropriate for R.R. at this time?

Fewer choices are available for the treatment of gram-negative bacillary meningitis than for other meningitides. Ampicillin is active against only *E. coli*, *P. mirabilis*, and *Salmonella* species, but resistance has essentially eliminated its use. Aminoglycosides are limited by their inability to achieve therapeutic CSF concentrations, as well as reduced activity in the acidic milieu of purulent CSF.[85] Intraventricular administration, which results in therapeutic CSF concentrations, is usually reserved for difficult-to-eradicate shunt infections in combination with IV therapy because of the absence of data supporting their use.[21,44] As such, the 2017 IDSA guidelines recommend that intraventricular antimicrobials considered for the treatment of health care–associated ventriculitis and meningitis that responds poorly to systemic antimicrobials alone.[78] Unlike intraventricular administration, intralumbar injections will not result in therapeutic CSF concentrations in the ventricle.[44]

Health care–associated meningitis and ventriculitis include infections associated with CSF shunts or drains, intrathecal drug therapy such as baclofen infusions, deep brain stimulation hardware, and neurosurgery or head trauma.[78] Empiric antimicrobial regimens should include an agent with activity against *P. aeruginosa* and vancomycin in patients with health care–associated meningitis and ventriculitis. Because R.R. recently had a neurosurgical procedure, his empiric therapy should include an antipseudomonal agent such as cefepime, ceftazidime, or meropenem (see Table 65-5).[11] Because his surgical incision Gram stain revealed gram-negative bacilli, vancomycin may be withheld. Cefepime has excellent activity against *E. coli* and *K. pneumoniae* and is active against other enteric gram-negative bacilli as well (see Table 65-7).[32] Resistance to third-generation cephalosporins among *Enterobacter*, *Citrobacter*, and *Serratia* is so prevalent that these agents cannot be relied on for the treatment of meningitis caused by these pathogens.[86] With this in mind, therapy of gram-negative meningitis in situations where third-

generation cephalosporin resistance is likely (eg, nosocomial or postneurosurgical meningitis) should result in the use of cefepime or meropenem. If a pathogen is isolated, therapy may be tailored based on culture results, antibiotic sensitivities, and antibiotic penetration into the CNS. For example, success rates exceed 80% with cefotaxime and ceftriaxone for gram-negative bacillary meningitis caused by *E. coli* or *K. pneumoniae*.[87],[88] For R.R., cefazolin should be discontinued, and treatment with cefepime (2 g IV every 8 hours) should be instituted until the return of culture and sensitivity results.

TREATMENT OF ENTEROBACTER MENINGITIS

CASE 65-3, QUESTION 3: Culture results from R.R.'s wound drainage and CSF are both positive for *Enterobacter cloacae.* Sensitivity data reveal resistance to ceftriaxone, cefepime, ceftazidime, piperacillin–tazobactam, and aztreonam. Drugs to which the isolate is sensitive include imipenem, meropenem, TMP-SMX, gentamicin, tobramycin, and ciprofloxacin. What alteration in antimicrobial therapy is most appropriate for R.R. at this time?

Treatment of meningitis caused by *Enterobacter* and related species (eg, *Serratia*, *Citrobacter* species) presents a particular challenge.[32],[89] Furthermore, some isolates that are sensitive to third-generation cephalosporins can become resistant during therapy by virtue of selecting for derepressed mutants.[90] Thus, in contrast to gram-negative bacillary meningitis caused by *E. coli* and *Klebsiella* species, alternative therapies are needed when treating meningitis caused by *Enterobacter*, *Serratia*, *Citrobacter*, and *Pseudomonas* species. The isolate is sensitive to imipenem, but the higher propensity for seizures compared with other β-lactams (including penicillin G) argues against its use in R.R.[39] Meropenem is not considered to be epileptogenic and should be used preferentially to imipenem for meningitis.[91] Clinical trials have evaluated the efficacy and safety of meropenem versus cefotaxime in the treatment of meningitis in children. Clinical outcomes were similar among the patients randomized to either group, and the incidence of seizures was similar in the treatment groups.[92],[93] Thus, after consideration of

the aforementioned options, meropenem appears to be the best choice of therapy for R.R. and carries U.S. Food and Drug Administration (FDA) approval for this indication; however, TMP-SMX, although not FDA approved, may be an option as well.[94] Cefepime should be discontinued and, if confirmed to be susceptible, therapy started with meropenem 2 g IV every 8 hours adjusted for renal insufficiency.

DURATION OF THERAPY

The 2017 IDSA guidelines recommend a duration of 10 to 14 days for the treatment of health care–associated meningitis and ventriculitis caused by gram-negative bacilli, with some experts recommending longer courses of 21 days. Because of the high mortality and morbidity associated with these pathogens and the reduced susceptibility of enteric pathogens to antimicrobial agents, 21 days has been suggested by some experts. R.R. should be provided with at least 10 to 14 days of therapy (see Table 65-8).[11]

Staphylococcus epidermidis Meningitis or Ventriculitis

CLINICAL PRESENTATION OF CEREBROSPINAL FLUID SHUNT INFECTIONS

CASE 65-4

Question 1: T.A., a 21-year-old female with a history of congenital hydrocephalus, is admitted to the neurosurgery unit for worsening mental status and fever. T.A. has a history of multiple revisions and placements of intraventricular shunts for control of hydrocephalus. Currently, she has a ventriculoperitoneal (VP) shunt, which was placed 1 month ago and previously had been functioning normally. During the past few days, T.A. has exhibited worsening obtundation, stiff neck, and a temperature of 103.1 °F (39.5 °C). A CT scan performed today reveals enlarged ventricles consistent with acute hydrocephalus.

T.A.'s medical history is noncontributory except for a seizure disorder for which she takes phenytoin 400 mg PO at bedtime. She also takes Lo-Ovral® as

an oral contraceptive. T.A. is allergic to sulfa drugs (severe skin rash). Her weight on admission is 132.28 pounds (60 kg).

Laboratory analysis was significant for the following:

WBC count, 14,000 cells/μL, with a differential of 85% PMNs and 10% lymphocytes
BUN, 19 mg/dL
SCr, 0.9 mg/dL

A tap of T.A.'s shunt was performed, and the ventricular fluid was notable for the following results:

Total protein, 150 mg/dL
Glucose, 40 mg/dL
WBC count, 200 cells/μL, with 85% PMNs and 10% lymphocytes

The result of the Gram stain of the ventricular fluid showed numerous gram-positive cocci in clusters.

What are the subjective and objective findings of CSF shunt infections, and what manifestations of this type of infection are present in T.A.?

T.A. likely has health care–associated meningitis with ventriculitis secondary to infection of her VP shunt. The most important way to manage hydrocephalus involves the use of devices that divert (shunt) CSF from the cerebral ventricles to other areas of the body such as the peritoneum (VP shunts) or atrium (ventriculoatrial shunts).[95] This approach alleviates increased CSF pressure and substantially reduces morbidity and mortality.[96] Infection of these devices, however, is a common cause of shunt malfunction, as seen in T.A. The reported incidence of CSF shunt infections in children is ~11% in recent studies and varies in adults from 2.5% to 15% depending on patient factors, surgical technique, and the type and duration of the procedure performed (ie, shunt revision vs placement of a new device).[97–99] T.A., who has been hydrocephalic since birth and has a history of multiple shunt procedures, is at high risk for such an infection.

Clinical symptoms associated with infected CSF shunts vary widely from asymptomatic colonization to fulminant ventriculitis with meningitis. Fever is common and, in many instances, is the only presenting symptom. CSF findings also are slightly different in shunt infection compared with acute meningitis: The WBC count usually is

not as elevated, the decrease in CSF glucose is less pronounced, and the protein value may be normal or slightly elevated. CSF culture result is positive in most patients.[100] T.A.'s clinical presentation, CSF findings, and radiographic evidence of hydrocephalus are highly suggestive of a VP shunt infection. She is febrile and has altered mental status. The presence of a stiff neck strongly suggests meningeal involvement. Evaluation of T.A.'s ventricular fluid reveals a slightly elevated WBC count, with a predominance of PMNs, an elevated protein concentration, and a slightly lower than normal glucose concentration.

Skin microflora are the most common causes of CSF shunt infections. Coagulase-negative staphylococci (usually *Staphylococcus epidermidis*) account for roughly 50% of all cases and *S. aureus* accounts for roughly one-fourth of all cases. Other less common pathogens include diphtheroids, enterococci, and *Propionibacterium acnes*. Enteric gram-negative bacilli are responsible for a small percentage of cases; these cases usually occur when the distal end of the shunt is inserted improperly into the peritoneal cavity.[100,101] The gram-positive cocci in clusters on the Gram stain of T.A.'s CSF strongly suggest a staphylococcal shunt infection. Determining the coagulase status of the isolate will allow differentiation between *S. aureus* and coagulase-negative staphylococci, likely *S. epidermidis.*

TREATMENT OF CEREBROSPINAL FLUID SHUNT INFECTIONS

Case 65-4, Question 2: Culture and sensitivity tests of T.A.'s ventricular fluid are positive for *S. epidermidis.* The isolate is resistant to nafcillin but sensitive to vancomycin, rifampin, and TMP-SMX. How should T.A.'s CSF shunt infection be treated?

For T.A.'s CSF shunt infection to be optimally treated, a combined medical and surgical approach is required. Studies have demonstrated poorer outcomes for systemic antibiotic therapy alone versus systemic antibiotic therapy plus shunt removal.[102] Because many patients cannot tolerate the complete removal of their shunt for

long, externalization of the distal end of the shunt, or shunt removal and placement of an external drainage device, often is necessary during systemic antibiotic therapy.[78] The presence of an externalized device permits sequential sampling of ventricular fluid and also provides a convenient way to administer antibiotics intraventricularly (see the following discussion entitled Intraventricular Dosing of Vancomycin).

Glycocalyx

Although *S. epidermidis* is not as virulent a pathogen as *S. aureus*, it is extremely difficult to eradicate this organism from prosthetic devices such as CSF shunts. This is because many strains of *S. epidermidis* produce a mucous film or slime layer known as *glycocalyx*, which allows the staphylococci to adhere tightly to the shunt material, protecting them against phagocytosis.[99] As expected, antibiotic failures are much more likely with slime-producing strains of *S. epidermidis.*

Vancomycin is the drug of choice for treatment of shunt infections caused by *S. epidermidis* and should be instituted immediately in T.A.[11],[78] This is because a high percentage (>60%) of coagulase-negative staphylococci are resistant to methicillin (eg, methicillin-resistant *Staphylococcus epidermidis* [MRSE]). T.A.'s isolate also is sensitive to TMP-SMX, as is the case with many strains of MRSE (and also MRSA), but it must be avoided because T.A. is allergic to this drug combination. Although not considered a first-line therapy, linezolid has been shown to be effective for VP shunt infections in small case series and may be considered in patients who are allergic to vancomycin.[103],[104] In addition, many staphylococcal isolates (both *S. epidermidis* and *S. aureus*) are susceptible to rifampin, but monotherapy with this drug is not recommended because of rapid emergence of resistance. However, rifampin may be used in addition to an antistaphylococcal agent to enhance bactericidal activity, especially if the prosthesis is retained.[78]

Vancomycin therapy

CASE 65-4, QUESTION 3: What would be an appropriate IV dosage for vancomycin in T.A.? What subjective or objective data should be monitored to evaluate the efficacy and toxicity of the treatment?

Vancomycin therapy for T.A.'s CSF shunt infection requires the use of doses similar to those used for bacterial meningitis. For adults such as T.A., vancomycin dosages of 30 to 60 mg/kg/day have been endorsed.[11,33,78] For children ages 3 months to younger than 12 years with meningitis or infected shunts, the recommended dosage of vancomycin is 60 to 80 mg/kg/day, given IV in divided doses every 6 hours. For children ages 12 years and older, the recommended dosage of vancomycin is 60 to 70 mg/kg/day, given IV in divided doses every 6 to 8 hours (see Table 65-6).[33,78,105] An individualized target of the AUC/MIC ratio of 400 to 600 is recommended.[33] For neonates and infants up to 3 months of age, doses recommended to achieve an AUC of 400 range from 10 to 20 mg/kg every 8 to 48 hours, depending on postmenstrual age, weight, and serum creatinine.[11,33]

T.A., who weighs 132.28 pounds (60 kg), should be started on a vancomycin regimen of 1 g IV every 8 to 12 hours because her renal function is normal. In either case, trough serum concentrations should be obtained at steady state to assess whether the initial dosing regimen is adequate. Another consideration for T.A. is the addition of rifampin to her vancomycin regimen. This is based on the excellent staphylococcal activity of rifampin, its moderate CSF penetration, and the potential for synergy between these two agents.[106] Whether rifampin plus vancomycin is superior to vancomycin alone has not been determined. For T.A., it is best to avoid rifampin because evidence supporting its efficacy is weak, and she currently is taking phenytoin and oral contraceptives. Rifampin is a potent inducer of hepatic microsomal enzymes, which can lower serum phenytoin concentrations (possibly resulting in seizure activity) and increase the possibility of an unplanned pregnancy (from reduced effectiveness of the oral contraceptive pill).

Intraventricular Dosing of Vancomycin

Case 65-4, Question 4: Should T.A. receive intraventricular vancomycin? If so, what would be an appropriate dosage?

T.A. should receive IV vancomycin. In addition, T.A. has a long history of hydrocephalus and will require placement of an external drainage device after removal of her VP shunt. The external drainage device allows for intraventricular administration of vancomycin, and such treatment should be instituted promptly. Although dosage recommendations vary from 5 to 20 mg/day, most use 20 mg/day and this dose should be used for T.A. Also, serial (daily) cultures of CSF are recommended to monitor her response to therapy. Therapy should be continued for at least 10 days after sterilization of her ventricular fluid is documented, at which time a new VP shunt can be placed.[11]

In contrast to T.A.'s situation, vancomycin therapy for patients with MRSA meningitis not associated with a CSF shunt or indwelling ventricular catheter is more problematic. The 2017 IDSA guidelines endorse a 10- to 14-day course of IV vancomycin 30 to 60 mg/kg daily divided every 8 to 12 hours, with the potential addition of rifampin 600 mg daily. In addition, in seriously ill patients, including those with meningitis, a loading dose of 25 to 35 mg/kg of actual body weight may be considered. An individualized target of an AUC of 400 to 600 is recommended.[30] In the setting of drug allergy, intolerance, or adverse events, alternatives include linezolid 600 mg PO or IV every 12 hours, or TMP-SMX 5 mg/kg/dose IV every 8 to 12 hours.[107]

BRAIN ABSCESS

Epidemiology

Although not nearly as common as meningitis, abscesses of the brain parenchyma (brain abscess) remain an important type of CNS infection. The reported incidence of brain abscess caused by any type of organism ranges from 0.4 to 0.9 cases per 100,000 population.[108],[109] On a busy neurosurgical service, 4 to 10 cases a year typically are seen.[110],[111] For reasons that are not entirely clear, males are more likely to develop abscesses within the brain than are females.[109],[110] Brain abscess can occur at any age, but the mean age most recently reported is 34 years of age, with a minority of cases occurring in children.[112]

Despite advances in antimicrobial therapy over the past several decades, mortality rates from brain abscess have remained above 40% until recently. Developments in imaging techniques (eg, CT and MRI scanning), which allow early recognition of abscesses and the ability to serially monitor the radiographic response to antimicrobial therapy, have had the most profound impact on reducing morbidity and mortality from brain abscess. A meta-analysis of 123 studies found case fatality rates declined from 40% to 10% over the decades from 1970 to 2013, whereas the rates of full recovery increased from 33% to 70%. With the combined medical and surgical approach currently recommended, mortality rates continue to average <10%.[116]

Predisposing Factors

Brain abscesses most commonly arise from a contiguous suppurative source of infection (eg, sinusitis, otitis, mastoiditis, or dental infections).[112] The formation of a single abscess cavity usually is found when infection develops from a contiguous source. In addition, the abscess nearly always is formed in close proximity to the primary focus of infection (**Table 65-9**). For example, abscesses of sinusitic origin more commonly involve the frontal lobe, whereas otitic infections often lead to temporal lobe abscess formation.[113] Brain abscess also occurs as a consequence of hematogenous spread of organisms from a primary site of infection (eg, lung

abscess, endocarditis, osteomyelitis, pelvic, and intra-abdominal infections). Multiple abscesses suggest a metastatic source of infection. As with meningitis, brain abscess occurs as an infrequent complication of head trauma or neurosurgery.[116] No identifiable source (cryptogenic abscess) is detected in as many as 30% of cases.[113]

Table 65-9
Predisposing Conditions, Microbiology, and Recommended Therapy for Bacterial Brain Abscess

Predisposing Condition	Usual Location of Abscess	Most Likely Organisms	Recommended Therapy
Contiguous Site			
Otitis media	Temporal lobe or cerebellum	Streptococci (anaerobic and aerobic), *Bacteroides fragilis*, gram-negative bacilli	Ceftriaxone + metronidazole
Sinusitis	Frontal lobe	Streptococci (predominantly), *Bacteroides* species, gram-negative bacilli, *Staphylococcus aureus*, *Haemophilus* species	Vancomycin + ceftriaxone + metronidazole
Dental infection	Frontal lobe	*Fusobacterium* species, *Bacteroides* species, and streptococci	Ceftriaxone + metronidazole
Primary Infection			
Head trauma or neurosurgery	Related to the site of wound	Gram-negative bacilli, staphylococci, streptococci, *Clostridium*	Vancomycin + cefepime + metronidazole

Staging

Once an intracranial focus of infection is established, the evolution of brain abscess involves two distinct stages: cerebritis and capsule formation. The cerebritis stage evolves gradually over the first 9 to 10 days of infection and is characterized by an area of marked inflammatory infiltrate that contains a necrotic center surrounded by an area of cerebral edema. Capsule formation occurs about 10 to 14 days after the initiation of infection, and once formed, the capsule continues to thicken over a period of weeks. The stage of abscess development has important implications for therapy. Although it is best to wait until the capsule is fully formed before attempting any type of surgical intervention, antimicrobial therapy alone may resolve the infection if discovered in the early cerebritis stage.[114]

Microbiology

The microbiology of brain abscess is distinctly different from that of meningitis. Streptococci are implicated in 50% to 70% of cases and include anaerobic as well as microaerophilic streptococci of the *S. milleri* group.[112] Other anaerobes, particularly *Bacteroides* species (including *B. fragilis*) and *Prevotella* species, are the second most common cause of brain abscess and are usually in mixed culture.[110],[112] These organisms are followed by staphylococci and gram-negative bacteria as other common pathogens.[112] Although somewhat imprecise, a reasonable correlation exists between the various predisposing conditions and the microbiologic etiology of brain abscess (see Table 65-9).[113]

In the immunocompromised patient, a diverse group of microorganisms can induce abscesses within the brain. In patients with AIDS, *Toxoplasma gondii* is the most common infectious cause of focal brain lesions.[115] Transplant recipients and those receiving immunosuppressive therapy are susceptible to infection from *Nocardia* species and fungi (eg, *Aspergillus* or *Candida* species).[116] In Mexico and other Central American countries, cysticercosis remains a common cause of intracerebral infection.[117]

Clinical and Radiologic Features

CASE 65-5

Question 1: L.Y., a 40-year-old male, is brought to the ED by a friend. L.Y. reports severe headache, fever, weakness in his left arm and leg, and increasing drowsiness. During the past week, L.Y. has suffered from headaches, which have gradually worsened in intensity, and from intermittent episodes of fever. Despite getting plenty of sleep, L.Y. has been feeling increasingly drowsy during the past several days. When he noticed weakness in his left arm and difficulty concentrating this morning, he called a friend and asked to be taken in for evaluation.

L.Y. has a history of chronic sinusitis that has been treated with a variety of oral antibiotics. His last episode of sinusitis, which occurred about 1 month ago, was treated with a 10-day course of cephalexin. He denies any nausea or vomiting and has not experienced any seizures in the recent past. L.Y. was tested for HIV 6 months ago, and the result of his antibody test was negative. He takes no current medications, denies smoking and use of recreational drugs,

and drinks alcohol only on social occasions a few times a month. L.Y. has no known drug allergies.

Physical examination reveals L.Y. to be in mild distress, with a temperature of 100.76 °F (38.2 °C). He is slightly lethargic and is oriented to person and place but not time. The strength in L.Y.'s left arm is 3/5; the strength in his left leg is 4/5. The remainder of his neurologic examination is grossly normal. L.Y. described moderate pain on palpation of his frontal sinuses, and a purulent discharge is noted.

Laboratory evaluation shows the following:

WBC count, 8000 cells/μL, with 70% PMN, 25% lymphocytes, and 5% monocytes
BUN, 16 mg/dL
SCr, 1.2 mg/dL
Erythrocyte sedimentation rate (ESR), 40 mm/hour
Hgb, Hct, platelets, and serum chemistries are within normal limits.

A CT scan with contrast dye reveals a right frontal ring-enhancing lesion with a small amount of surrounding cerebral edema. L.Y. is admitted to the neurosurgery unit for further evaluation and treatment.

What clinical signs and symptoms that are suggestive of bacterial brain abscess does L.Y. display? How can brain abscess be diagnosed in L.Y.?

L.Y. has presented to the ED with many signs and symptoms suggestive of bacterial brain abscess. He is 40 years old and male, both of which place him in a group with the highest likelihood of having a brain abscess. In contrast to the diffuse nature of meningitis, brain abscess presents as a focal neurologic process. Notable in L.Y.'s presentation is left-sided (arm and leg) weakness. Symptoms of brain abscess range in severity from indolent to fulminant, and in most patients, the duration of symptoms at the time of presentation is ≤2 weeks.[113] Headache is the most common symptom of brain abscess, occurring in ~70% of cases. L.Y.'s clinical manifestations have become gradually worse over the past week, and his worsening headaches, increasing drowsiness, and difficulty in concentrating all are consistent with bacterial brain abscess.

L.Y. presents with the classic triad of fever, headache, and focal neurologic deficits. Although this triad should always be looked for, fewer than half of patients with confirmed bacterial brain abscess present in this manner.[112]

The absence of fever does not rule out infection because fever is found in <50% of patients.[110],[113] Focal neurologic deficits are present in ~50% of patients and vary in nature and severity in relation to the location and size of the abscess and surrounding cerebral edema. Although L.Y. does not have a history of seizure activity, ~25% of patients experience partial seizures that often become generalized. Papilledema and nuchal rigidity occur in ≤25% of cases and often are not useful in confirming the diagnosis. Symptoms associated with a contiguous focus of infection should always be sought, and in some situations, they may dominate the clinical picture.[112] L.Y. has a history of sinus infection, and the pain on palpation of his sinuses coupled with the purulent sinus drainage suggests active infection at this site.

As can be seen from L.Y.'s test results, laboratory evaluation usually is not very helpful when diagnosing brain abscess. L.Y. does not have a peripheral leukocytosis, but he does have an elevated ESR. A normal peripheral WBC count is not unusual in patients with intracranial suppuration. The ESR often is elevated in brain abscess, but this test is nonspecific and only indirectly supports the diagnosis.

L.Y. did not have a lumbar puncture because this procedure is contraindicated for diagnosing brain abscess. The diagnostic yield from CSF is low because chemistries (eg, protein, glucose, WBC) usually are normal and culture of the CSF in patients with brain abscess is unlikely to yield the causative pathogen. More important, performing a lumbar puncture in patients with space-occupying lesions of the brain can produce cerebral herniation as a consequence of the shifting pressure gradient induced within the cranial vault after insertion of the lumbar puncture needle.[118]

Of paramount importance is the abnormality detected on the CT scan of L.Y.'s brain. When dye is injected before the CT scan, brain abscesses will appear to "ring enhance." Furthermore, cerebral edema can be identified as a variable hypodense region immediately surrounding the abscess cavity. As stated earlier, CT and MRI scanning techniques have revolutionized the diagnosis and treatment of brain abscess.[112],[119] In general, a good correlation exists

between the clinical and radiologic response to therapy of bacterial brain abscess.

TREATMENT

CASE 65-5, QUESTION 2: How should L.Y.'s brain abscess be treated?

SURGICAL TECHNIQUES

A combined medical and surgical approach is the best form of therapy for L.Y.'s brain abscess. Response rates to antimicrobial therapy alone have been disappointing, and with a few exceptions, surgical intervention is necessary to ensure optimal results. Modern stereotactic neurosurgical techniques allow almost any brain abscess that is ≥1 v in diameter to be drained via stereotactic aspiration, regardless of location. Primary medical therapy may be indicated if imaging does not show a central cavity in the abscess or if surgery is withheld for other reasons such as poor health status.[113]

The two types of surgical approaches for brain abscess are (a) stereotactic navigation with needle aspiration and (b) intraoperative ultrasonography through a burr hole or craniotomy for direct abscess drainage.[113] Stereotactic aspiration of abscess is highly effective and is associated with lower morbidity and mortality than is craniotomy.[120] Modern medical advances leave total resection with a very limited role unless an abscess is superficial or when there is high suspicion of fungal or tuberculous infection.[113]

ANTIMICROBIAL PENETRATION INTO BRAIN ABSCESS

Antimicrobial therapy is an essential component of brain abscess therapy. Penetration of antibiotics into brain abscess fluid has not been studied as carefully as penetration into CSF, and as discussed earlier, the barrier involved is different (see Fig. 65-1).[8] Penicillins and cephalosporins penetrate adequately into abscess fluid, but certain agents (eg, penicillin G) may be susceptible to degradation

by enzymes present within the abscess milieu.[110] Third-generation cephalosporins (eg, cefotaxime, ceftriaxone) penetrate sufficiently into the abscess and thus are appropriate choices when gram-negative bacteria are present.[110],[121] Metronidazole achieves abscess fluid concentrations equal to or in excess of serum levels and is bactericidal against strict anaerobes. The unique mechanism of action of metronidazole makes it particularly useful in the necrotic core of the cavity, where the oxidation-reduction potential is low and bacteria replicate slowly or are dormant. For these reasons, metronidazole is the drug of choice for anaerobic gram-negative bacterial brain abscess.[110] Vancomycin and carbapenems also penetrate sufficiently into brain abscess fluid.[110],[122] Although specific abscess-penetration data are unavailable, successful treatment of cerebral nocardiosis with TMP-SMX and CNS toxoplasmosis with clindamycin suggests that these compounds also achieve adequate penetration into cerebral abscess cavities.[123],[124]

ANTIBIOTIC THERAPY

When antibiotic therapy should be instituted depends on the status of the patient and the stage of abscess development. For patients diagnosed during the cerebritis stage, before formation of a well-circumscribed capsule, surgery should be delayed and antimicrobial therapy begun in patients with significant symptoms.[110],[121] If capsule formation already has taken place and if the patient's clinical status allows, it is reasonable to delay initiation of antibiotics until after surgery if surgery is to be performed within hours to increase the microbiologic yield from tissue and fluid samples. If the disease is fulminant, antibiotics must be instituted promptly and surgical intervention performed as quickly as possible.[113]

L.Y.'s clinical presentation suggests an advanced brain abscess. The presence of ring enhancement on CT and the onset of symptoms over 2 weeks support this conclusion. Because he is not critically ill, antibiotic therapy may be delayed until surgery is performed. Specimens obtained from the surgical procedure should

be sent for aerobic and anaerobic culture and an immediate Gram stain.

Initial antibiotic therapy for brain abscess needs to be sufficiently broad to cover the most likely pathogens (Table 65-9). When the implicated source is contiguous such as oral, otogenic, or sinus, metronidazole plus ceftriaxone (with the addition of vancomycin with a sinus source) is recommended.[110,113] Metronidazole will provide coverage for strict anaerobes, including *Bacteroides* and *Prevotella* species. When the implicated source is head trauma with skull fracture or is associated with a neurosurgical procedure, empiric therapy should consist of vancomycin, metronidazole, and a third- or fourth-generation cephalosporin. For hematogenous sources, a third-generation cephalosporin, metronidazole, and vancomycin are recommended.[113] Vancomycin is added to cover staphylococcal infection.

For L.Y., therapy with ceftriaxone 2 g IV every 12 hours, vancomycin 1 g IV every 8 hours, and metronidazole 500 mg IV every 8 hours should be started postoperatively (see Table 65-6).

ADJUNCTIVE CORTICOSTEROID THERAPY

Adjunctive corticosteroid therapy for bacterial brain abscess is controversial. Steroids can interfere with antibiotic penetration into abscesses and obscure the interpretation of serial CT scans when assessing response to therapy. Therefore, steroids are indicated only if significant cerebral edema is present, particularly if it is accompanied by rapid neurologic deterioration.[110,121] L.Y. should not receive dexamethasone because his mental status is only mildly depressed and the cerebral edema seen on CT scan is not massive.

ADJUNCTIVE ANTICONVULSANT THERAPY

L.Y. has shown no sign of seizure activity thus far and, therefore, does not require anticonvulsant therapy. However, anticonvulsants should be used in the acute setting when seizures are present.[110,121] Agents with activity against partial and complex partial seizures are preferred (eg, phenytoin, carbamazepine, and, potentially,

levetiracetam). The long-term use of anticonvulsants depends on whether seizure activity persists. Insufficient information exists regarding how long to continue anticonvulsants in such cases. Therefore, discontinuation of these agents must be individualized.

No formal guidelines are available regarding the optimal duration of therapy for bacterial brain abscess. Given the serious nature of the infection and the difficulty associated with antibiotic penetration, high-dose IV therapy should continue for at least 6 to 8 weeks.[110,113] The duration of therapy should be evaluated on a case-by-case basis. In an attempt to ensure complete eradication of infection, some experts recommend long-term (2–6 months) oral antibiotics after the IV course, provided agents with good oral absorption and activity against the offending pathogens are available.[110]

MONITORING THERAPY

Case 65-5, Question 3: How should L.Y. be monitored for therapeutic response and toxicity?

Although L.Y. is on antibiotic therapy, weekly or biweekly CT scans should be obtained to evaluate abscess resolution. His clinical response to therapy also should be assessed daily. If therapy is effective, L.Y.'s mental status should improve gradually (eg, he will become more alert and oriented) over a period of several days. L.Y.'s headaches and hemiparesis (weakness in his arm and leg) also should resolve eventually. It may take a week or longer, however, to see a complete resolution of symptoms.[110] In general, radiologic improvement (ie, reduction in abscess size) correlates reasonably well with clinical response, but not always. Persistent symptoms or failure to detect a reduction in abscess size on CT scan or the appearance of new abscesses may indicate improper antimicrobial therapy or the need for more surgery.[110,121] Repeated surgical intervention with appropriate reculturing may be required in some instances to optimize therapy.

Adverse effects associated with the penicillin G therapy that L.Y. is receiving are similar to those of other β-lactam antibiotics. Seizures are a potential complication when high doses of penicillin are used in the presence of a mass lesion in the brain.[125] L.Y. should be observed closely by those providing care and questioned regularly for any evidence of seizure activity. Metronidazole usually is well tolerated, but may cause neurotoxicity, most commonly peripheral neuropathy. L.Y. should be assessed for the presence of numbness or tingling in his hands or feet. Seizures, although uncommon, occasionally occur with metronidazole. If L.Y. experiences peripheral neuropathy or seizures, a switch to meropenem would be appropriate. Other adverse effects associated with metronidazole include mild nausea, brownish discoloration of the urine, peripheral neuropathies, and the potential for a disulfiram-like reaction with concomitant ethanol ingestion.[126] L.Y. should be counseled regarding the possibility of gastric upset and discoloration of the urine, and he should be strongly cautioned to avoid alcoholic beverages while receiving metronidazole. Given his young age, the absence of significant underlying diseases, and the relative early detection of his brain abscess, there is every reason to expect a good response to his treatment and, eventually, a complete resolution of his abscess.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and website for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2013;6:CD004405. (51)

Brouwer MC, Tunkel AR, McKhann GM 2nd, van de Beek D. Brain abscess. *N Engl J Med*. 2014;371:447–456. (113)

Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. *Lancet Infect Dis.* 2014;14:813–819. (71)

de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med.* 2002;347:1549–1556. (42)

Nau R, Blei C, Eiffert H. Intrathecal antibacterial and antifungal therapies. *Clin Microbiol Rev.* 2020;33(*3*):e00190-19. (5)

Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev.* 2010;23:858–883. (30)

Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med.* 2011;364:2016–2025. (1)

Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39:1267–1284. (11)

Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64(*6*):e34–e65. (78)

COMPLETE REFERENCES CHAPTER 65 CENTRAL NERVOUS SYSTEM INFECTIONS

1. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med*. 2011;364:2016–2025.
2. Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. *J Infect Dis*. 2002;186(Suppl 2):S225–S233.
3. Kurrus TA, Tauber MG. Meningitis. In: Jong EC, Stevens DL, eds. *Netter's Infectious Diseases*. Elsevier/Saunders; 2012:202–213.
4. Mancall EL. Ventricular system and cerebrospinal fluid. In: *Gray's Clinical Neuroanatomy: The Anatomic Basis for Clinical Neuroscience*. Elsevier/Saunders; 2010:83–91.
5. Nau R, Blei C, Eiffert H. Intrathecal antibacterial and antifungal therapies. *Clin Microbiol Rev*. 2020;33(3):e00190-19.
6. Cook AM, Mieure KD, Owen RD, Pesaturo AB, Hatton J. Intracerebroventricular administration of drugs. *Pharmacotherapy*. 2009;29:832–845.

7. Bonadio WA. The cerebrospinal fluid: physiologic aspects and alterations associated with bacterial meningitis. *Pediatr Infect Dis J*. 1992;11:423–431.
8. Pardridge WM, Oldendorf WH, Cancilla P, Frank HJ. Blood-brain barrier: interface between internal medicine and the brain. *Ann Intern Med*. 1985;105:82–95.
9. Van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. *N Engl J Med*. 2006;354:44–53.
10. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. *Arch Intern Med*. 1999;159:1185–1194.
11. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.
12. Basmaci R, Bonacorsi S, Bidet P, et al. *Escherichia coli* meningitis features in 325 children from 2001 to 2013 in France. *Clin Infect Dis*. 2015;61:779–786.
13. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. *JAMA*. 2008;299:2056–2065.
14. Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group. *J Infect Dis*. 1990;162:1316–1323.
15. Centers for Disease Control and Prevention (CDC). Progress toward elimination of *Haemophilus influenzae* type b invasive disease among infants and children—United States, 1998–2000. *MMWR Morb Mortal Wkly Rep*. 2002;51:234–237.
16. McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. *Lancet*. 2012;380:1703–1711.
17. Olarte L, Barson WJ, Barson RM, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis in US children. *Clin Infect Dis*. 2015;61:767–775.
18. Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease. *MMWR Morb Mortal Wkly Rep*. 2013;62:1–32.
19. Quagliarello VJ, Scheld WM. New perspectives on bacterial meningitis. *Clin Infect Dis*. 1993;17:603–608.
20. Quagliarello VJ, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. *N Engl J Med*. 1992;327:864–872.
21. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and metaanalysis. *Lancet Infect Dis*. 2010;10:317–328.
22. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. *N Engl J Med*. 1990;323:1651–1657.
23. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev*.

2010;23:467–492.
24. Verghese A, Gallemore G. Kerning's and Brudzinski's signs revisited. *Rev Infect Dis*. 1987;9:1187–1192.
25. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcomes and effect of antibiotic timing. *Ann Intern Med*. 1998;129:862–869.
26. Studahl M, Lindquist L, Eriksson BM, et al. Acute viral infections of the central nervous system in immunocompetent adults: diagnosis and management. *Drugs*. 2013;73:131–158.
27. Black KE, Baden LR. Fungal infections of the CNS. Treatment strategies for the immunocompromised patient. *CNS Drugs*. 2007;21:292–318.
28. Ramanan P, Bryson AL, Binnicker MJ, Pritt BS, Patel R. Syndromic panel-based testing in clinical microbiology. *Clin Microbiol Rev*. 2017;31(1):e00024-17.
29. Wilson MR, Sample HA, Zorn KC, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. *N Engl J Med*. 2019;80:2327–2340.
30. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev*. 2010;23:858–883.
31. Lutsar I, Friedland IR. Pharmacokinetics and pharmacodynamics of cephalosporins in cerebrospinal fluid. *Clin Pharmacokinet*. 2000;39:335–343.
32. Cherubin CE, Corrado ML, Nair SR, Gombert ME, Landesman S, Humbert G. Treatment of gram-negative bacillary meningitis: role of the new cephalosporin antibiotics. *Rev Infect Dis*. 1982;4(Suppl):S453–S464.
33. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864.
34. Kanellakopoulou K, Pagoulatou A, Stroumpoulis K, et al. Pharmacokinetics of moxifloxacin in non-inflamed cerebrospinal fluid of humans: implication for a bactericidal effect. *J Antimicrob Chemother*. 2008;61:1328–1331.
35. Frei CR, Wiederhold NP, Burgess DS. Antimicrobial breakpoints for Gram-negative aerobic bacteria based on pharmacokinetic–pharmacodynamic models with Monte Carlo simulation. *J Antimicrob Chemother*. 2008;61:621–628.
36. Eagye KJ, Kuti JL, Sutherland CA, Christensen H, Nicolau DP. In vitro activity and pharmacodynamics of commonly used antibiotics against adult systemic isolates of *Escherichia coli* and *Pseudomonas aeruginosa* at Forty US Hospitals. *Clin Ther*. 2009;31:2678–2688.
37. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. *Lancet*. 2012;380:1693–1702.

38. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*. *Lancet*. 2007;369:2196–2210.
39. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321(2):188–199.
40. Fishman R. Steroids in the treatment of brain edema. *N Engl J Med*. 1982;306:359–360.
41. Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin Microbiol Rev*. 2011;24:557–591.
42. de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2002;347:1549–1556.
43. Syrogiannopoulos GA, Lourida AN, Theodoridou MC, et al. Dexamethasone therapy for bacterial meningitis in children: 2-versus 4-day regimen. *J Infect Dis*. 1994;169:853–858.
44. Odio CM, Faingezicht I, Paris M, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. *N Engl J Med*. 1991;324:1525–1531.
45. Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgwood J. Dexamethasone therapy for bacterial meningitis in children. Swiss Meningitis Study Group. *Lancet*. 1993;342:457–461.
46. Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. *Pediatr Infect Dis J*. 1989;8:848–851.
47. Saez-Lloren X, McCracken GH Jr. Antimicrobial and antiinflammatory treatment of bacterial meningitis. *Infect Dis Clin North Am*. 1999;13:619–636.
48. Peltola H, Roine I, Fernández J, et al. Adjuvant glycerol and or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2007;45:1277–1286.
49. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2015;2015(9):CD004405.
50. Nudelman Y, Tunkel AR. Bacterial meningitis: epidemiology, pathogenesis, and management update. *Drugs*. 2009;69:2577–2596.
51. American Academy of Pediatrics. *Haemophilus influenzae* infections. In: Pickering LK, ed. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. American Academy of Pediatrics; 2012:345.
52. American Academy of Pediatrics. Pneumococcal infections. In: Pickering LK, ed. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. American Academy of Pediatrics; 2012:571.
53. Martinez-Lacasa J, Cabellos C, Martos A, et al. Experimental study of the efficacy of vancomycin, rifampicin and dexamethasone in the therapy of

pneumococcal meningitis. *J Antimicrob Chemother*. 2002;49:507–513.
54. Ahmed A, Jafri H, Lutsar I, et al. Pharmacodynamics of vancomycin for the treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother*. 1999;43:876–881.
55. Ricard JD, Wolff M, Lacherade JC, et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. *Clin Infect Dis*. 2007;44(2):250–255.
56. Gaillard JL, Abadie V, Cheron G, et al. Concentrations of ceftriaxone in cerebrospinal fluid of children with meningitis receiving dexamethasone therapy. *Antimicrob Agents Chemother*. 1994;38(5):1209–1210.
57. Buke AC, Cavusoglu C, Karasulu E, Karakartal G. Does dexamethasone affect ceftriaxone (corrected) penetration into cerebrospinal fluid in adult bacterial meningitis. *Int J Antimicrob Agents*. 2003;21(5):452–456.
58. Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant *Streptococcus pneumoniae* in cerebrospinal fluid of children with acute bacterial meningitis. *Antimicrob Agents Chemother*. 1995;39:1988–1992.
59. Schaad UB, Suter S, Gianella-Borradori A, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. *N Engl J Med*. 1990;322:141–147.
60. Lebel MH, Hoyt MJ, McCracken GH Jr. Comparative efficacy of ceftriaxone and cefuroxime for treatment of bacterial meningitis. *J Pediatr*. 1989;114:1049–1054.
61. Odio CM, Faingezicht I, Salas JL, Guevara J, Mohs E, McCracken GH Jr. Cefotaxime vs. conventional therapy for the treatment of bacterial meningitis of infants and children. *Pediatr Infect Dis*. 1986;5:402–407.
62. Valmari P, Peltola H, Kataja M. Cerebrospinal fluid white cell, glucose and protein changes during the treatment of *Haemophilus influenzae* meningitis. *Scand J Infect Dis*. 1986;18:39–43.
63. Bonadio WA, Smith D. Cerebrospinal fluid changes after 48 hours of effective therapy for *Haemophilus influenzae* type B meningitis. *Am J Clin Pathol*. 1990;94:426–428.
64. Neu HC. Third-generation cephalosporins: safety profiles after 10 years of clinical use. *J Clin Pharmacol*. 1990;30:396–403.
65. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431–455.
66. Bickford CL, Spencer AP. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: case report and review of the literature. *Pharmacotherapy*. 2005;25:1389–1395.

67. Radetsky M. Duration of treatment in bacterial meningitis: a historical inquiry. *Pediatr Infect Dis J*. 1990;9:2–9.
68. Peltola H. Prophylaxis of bacterial meningitis. *Infect Dis Clin North Am*. 1999;13:685–710.
69. Gardner P. Clinical practice. Prevention of meningococcal disease. *N Engl J Med*. 2006;355:1466–1473.
70. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(RR-2):1–28.
71. Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. *Lancet Infect Dis*. 2014;14:813–819.
72. Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR Morb Mortal Wkly Rep*. 2010;59:1102–1106.
73. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis [published correction appears in *N Engl J Med*. 2005;352:950]. *N Engl J Med*. 2004;351:1849–1859.
74. Centers for Disease Control and Prevention (CDC). Effects of new penicillin susceptibility breakpoints for *Streptococcus pneumoniae*—United States, 2006–2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:1353–1355.
75. Kaplan SL, Mason EO Jr. Management of infections due to antibiotic-resistant *Streptococcus pneumoniae. Clin Microbiol Rev*. 1998;11:628–644.
76. Musher DM, Bartlett JG, Doern GV. A fresh look at the definition of susceptibility of *Streptococcus pneumoniae* to β-lactam antibiotics. *Arch Intern Med*. 2001;161:2538–2544.
77. Barrons RW, Murray KM, Richey RM. Populations at risk for penicillin-induced seizures. *Ann Pharmacother*. 1992;26:26–29.
78. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64(6):e34–e65.
79. Pomar V, Benito N, López-Contreras J, Coll P, Gurguí M, Domingo P. Spontaneous gram-negative bacillary meningitis in adult patients: characteristics and outcome. *BMC Infect Dis*. 2013;13(1):451.
80. Lu CH, Chang WN, Chuang YC, Chang HW, et al. The prognostic factors of adult gram-negative bacillary meningitis. *J Hosp Infect*. 1998;40(1):27–34.
81. Cherubin CE, Marr JS, Sierra MF, Becker S. Listeria and gram-negative bacillary meningitis in New York City, 1972–1979. Frequent cases of meningitis in adults. *Am J Med*. 1981;71(2):199–209.

82. Domingo P, Pomar V, de Benito N, Coll P. The spectrum of acute bacterial meningitis in elderly patients. *BMC Infect Dis*. 2013;13:108.
83. Gaschignard J, Levy C, Romain O, et al. Neonatal bacterial meningitis: 444 cases in 7 years. *Pediatr Infect Dis J*. 2011;30:212–217.
84. Tenney JH. Bacterial infections of the central nervous system in neurosurgery. *Neurol Clin*. 1986;4:91–114.
85. Kaiser AB, McGee ZA. Aminoglycoside therapy of gram-negative bacillary meningitis. *N Engl J Med*. 1975;293:1215–1220.
86. Wong VK, Wright HT Jr, Ross LA, Mason WH, Inderlied CB, Kim KS. Imipenem/cilastatin treatment of bacterial meningitis in children. *Pediatr Infect Dis J*. 1991;10:122–125.
87. Wolff MA, Young CL, Ramphal R. Antibiotic therapy for *Enterobacter* meningitis: a retrospective review of 13 episodes and review of the literature. *Clin Infect Dis*. 1993;16:772–777.
88. Calandra G, Lydick E, Carrigan J, Weiss L, Guess H. Factors predisposing to seizures in seriously ill infected patients receiving antibiotics: experience with imipenem/cilastatin. *Am J Med*. 1988;84:911–918.
89. Eng RH, Munsif AN, Yangco BG, Smith SM, Chmel H. Seizure propensity with imipenem. *Arch Intern Med*. 1989;149:1881–1883.
90. Ralph ED, Behme RJ. Enterobacter meningitis-treatment complicated by emergence of mutants resistant to cefotaxime. *Scand J Infect Dis*. 1987;19:577–579.
91. Miller AD, Ball AM, Bookstaver PB, Dornblaser EK, Bennett CL. Epileptogenic potential of carbapenem agents: mechanism of action, seizure rates, and clinical considerations. *Pharmacotherapy*. 2011;31:408–423.
92. Klugman K, Dagan R. Randomized comparison of meropenem with cefotaxime for treatment of bacterial meningitis. Meropenem Meningitis Study Group. *Antimicrob Agents Chemother*. 1995;39:1140–1146.
93. Odio CM, Puig JR, Feris JM, et al. Prospective, randomized, investigator-blinded study of the efficacy and safety of meropenem vs. cefotaxime therapy in bacterial meningitis in children. Meropenem Meningitis Study Group. *Pediatric Infect Dis J*. 1999;18:581–590.
94. Foster DR, Rhoney DH. Enterobacter meningitis: organism susceptibility, antimicrobial therapy and related outcomes. *Surg Neurol*. 2005;63:533–537.
95. Bhimraj A. Cerebrospinal fluid shunt and drain infections. In: Mandell GL, Douglas RG, Bennett JE, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Churchill Livingstone; 2015:1186–1192.
96. Casey AT, Kimmings EJ, Kleinlugtebeld AD, Taylor WA, Harkness WF, Hayward RD. The long-term outlook for hydrocephalus in childhood. A ten-year cohort study of 155 patients. *Pediatr Neurosurg*. 1997;27(2):63–70.
97. Simon TD, Hall M, Riva-Cambrin J, et al. Infection rates following initial cerebrospinal fluid shunt placement across pediatric hospitals in the United

States. *J Neurosurg Pediatr*. 2009;4:156–165.
98. Lam CH, Villemure JG. Comparison between ventriculoatrial and ventriculoperitoneal shunting in the adult population. *Br J Neurosurg*. 1997;11(1):43–48.
99. Lishner M, Perrin RG, Feld R, et al. Complications associated with Ommaya reservoirs in patients with cancer. The Princess Margaret Hospital experience and a review of the literature. *Arch Intern Med*. 1990;150(1):173–176.
100. Conen A, Walti LN, Merlo A, Fluckiger U, Battegay M, Trampuz A. Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective analysis over an 11-year period. *Clin Infect Dis*. 2008;47:73–82.
101. Arnell K, Cesarini K, Lagerqvist-Widh A, Wester T, Sjölin J. Cerebrospinal fluid shunt infections in children over a 13-year period: anaerobic cultures and comparison of clinical signs of infection with *Propionibacterium acnes* and with other bacteria. *J Neurosurg Pediatr*. 2008;5:366–372.
102. Tamber MS, Klimo P Jr, Mazzola CA, Flannery AM; Pediatric Hydrocephalus Systematic Review And Evidence-Based Guidelines Task Force. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 8: management of cerebrospinal fluid shunt infection. *J Neurosurg Pediatr*. 2014;14(Suppl 1):60–71.
103. Yilmaz A, Dalgic N, Müslüman M, Sancar M, Colak I, Aydin Y. Linezolid treatment of shunt-related cerebrospinal fluid infections in children. *J Neurosurg Pediatr*. 2010;5:443–448.
104. Gill CJ, Murphy MA, Hamer DH. Treatment of *Staphylococcus epidermidis* ventriculo-peritoneal shunt infection with linezolid. *J Infect*. 2002;45:129–132.
105. Thompson JB, Einhaus S, Buckingham S, Phelps SJ. Vancomycin for treating cerebrospinal fluid shunt infections in pediatric patients. *J Pediatr Pharmacol Ther*. 2005;10:14–25.
106. Morris A, Low DE. Nosocomial bacterial meningitis, including central nervous system shunt infections. *Infect Dis Clin North Am*. 1999;13:735–750.
107. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
108. Nicolosi A, Hauser WA, Musicco M, Kurland LT. Incidence and prognosis of brain abscess in a defined population: Olmsted County, Minnesota, 1935–1981. *Neuroepidemiology*. 1991;10:122–131.
109. Helweg-Larsen J, Astradsson A, Richhall H, Erdal J, Laursen A, Brennum J. Pyogenic brain abscess, a 15 year survey. *BMC Infect Dis*. 2012;12:332.
110. Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis*. 1997;25:763–779.
111. Mampalam TJ, Rosenblum ML. Trends in the management of bacterial brain abscesses: a review of 102 cases over 17 years. *Neurosurgery*.

1988;23:451–458.
112. Brouwer MC, Coutinho JM, van de Beek D. Clinical characteristics and outcome of brain abscess: systematic review and meta-analysis. *Neurology*. 2014; 82:806–813.
113. Brouwer MC, Tunkel AR, McKhann GM 2nd, van de Beek D. Brain abscess. *N Engl J Med*. 2014;371:447–456.
114. Britt RH, Enzmann DR, Yeager AS. Neuropathological and computerized tomographic findings in experimental brain abscess. *J Neurosurg*. 1981;55:590–603.
115. Tan IL, Smith BR, von Geldern G, Mateen FJ, McArthur JC. HIV-associated opportunistic infections of the CNS. *Lancet Neurol*. 2012;11:605–617.
116. Baddley JW, Salzman D, Pappas PG. Fungal brain abscess in transplant recipients: epidemiologic, microbiologic, and clinical features. *Clin Transplant*. 2002;16:419–424.
117. Del Brutto OH, Sotelo J, Roman GC. Therapy for neurocysticercosis: a reappraisal. *Clin Infect Dis*. 1993;17:730–735.
118. Heilpern KL, Lorber BS. Focal intracranial infections. *Infect Dis Clin North Am*. 1996;10(4):879–898.
119. Reddy JS, Mishra AM, Behari S, et al. The role of diffusion-weighted imaging in the differential diagnosis of intracranial cystic mass lesions: a report of 147 lesions. *Surg Neurol*. 2006;66:246–250.
120. Fitch MT, van de Beek D. Emergency diagnosis and treatment of adult meningitis. *Lancet Infect Dis*. 2007;7:191–200.
121. Rosenblum ML, Mampalam TJ, Pons VG. Controversies in the management of brain abscesses. *Clin Neurosurg*. 1986;33:603–632.
122. Levy RM, Gutin PH, Baskin DS, Pons VG. Vancomycin penetration of a brain abscess: case report and review of the literature. *Neurosurgery*. 1986;18:632–636.
123. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). *Cochrane Database Syst Rev*. 2006;3:CD005420.
124. Simpson GL, Stinson EB, Egger MJ, Remington JS. Nocardial infections in the immunocompromised host: a detailed study in a defined population. *Rev Infect Dis*. 1981;3:492–507.
125. Snavely SR, Hodges GR. The neurotoxicity of antibacterial agents. *Ann Intern Med*. 1984;101:92–104.
126. Carroll MW, Jeon D, Mountz JM, et al. Efficacy and safety of metronidazole for pulmonary multidrug resistant tuberculosis. *Antimicrob Agents Chemother*. 2013;57:3903–3909.

66

Endocarditis

Annie Wong-Beringer, Rachid Douglas-Louis, and Emi Minejima

CORE PRINCIPLES		CHAPTER CASES
1	Infective endocarditis (IE) is a microbial infection of the heart valves or other endocardial tissue, usually associated with an underlying cardiac defect. Between 2000 and 2011, IE incidence has increased, accounting for ~29,000 to 47,000 cases per year. *Streptococcus viridans*, *Staphylococcus aureus*, and *Enterococcus* species are common causes of IE. Other rare pathogens affecting special populations include *S. epidermidis*, *Pseudomonas aeruginosa*, and *Candida* species.	**Case 66-1 (Question 1) Case 66-2 (Question 1) Case 66-3 (Question 1) Case 66-4 (Question 1) Case 66-5 (Questions 1, 4, 6)**
2	Clinical presentation may be highly variable and characterized by nonspecific symptoms such as fever, weight loss, fatigue, night sweats, and	**Case 66-1 (Question 1) Case 66-2 (Question 2), Figures 66-1–66-3**

	arthralgias. Peripheral manifestations specific to IE include conjunctival petechiae, Janeway lesions, and splinter hemorrhages. Major embolic episodes and infarction involving other organs can develop in up to one-third of cases. Congestive heart failure (CHF) is the most common cause of death in IE and the most common indication for surgery.	
3	The American Heart Association (AHA) recommends use of the modified Duke criteria as the primary diagnostic schema to evaluate patients suspected of having IE. The most important factor confirming IE is positive blood culture findings. Transesophageal echocardiogram (TEE) is a valuable tool to strengthen diagnosis and identify patients at risk for complications and need for surgical interventions.	**Case 66-1 (Question 2), Tables 66-1, 66-2**
4	General treatment approach to organism eradication requires the administration of parenteral bactericidal antibiotics at high doses for a prolonged duration of 4 to 6 weeks. Combination therapy is common to achieve synergy for some pathogens. Selection of regimen should be based on organism sensitivity, tissue penetration, and host tolerance of the antibiotic agent(s). The AHA treatment guideline by organisms should be followed.	**Case 66-1 (Questions 3–5) Case 66-2 (Question 3) Case 66-3 (Questions 2–4) Case 66-4 (Questions 1–5) Case 66-5 (Questions 2, 3, 5, 7), Tables 66-3–66-5**

5	Treatment of IE caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and by enterococci presents significant challenges owing to the emergence of resistance to standard therapy, vancomycin. Higher doses of vancomycin targeting an area under the 24-hour plasma concentration–time curve to the minimum inhibitory concentration (AUC_{24hr}/MIC) ≥400 mg*hour/L are advocated for treatment of MRSA IE but may be associated with increased incidence of nephrotoxicity. Alternative agents for the treatment of IE caused by vancomycin-resistant enterococci have limited clinical success or lack of clinical evidence.	**Case 66-3 (Questions 3, 4) Case 66-4 (Question 5)**
6	Fungal endocarditis is rare but carries poor prognosis. It occurs primarily in intravenous drug users (IVDUs), patients with prosthetic heart valves or intravenous (IV) catheters, and those with a compromised immune system. Management generally requires early valve replacement and combination antifungal therapy.	**Case 66-5 (Questions 1–3)**
7	The AHA recommends the use of antibiotic prophylaxis in select patients with specific cardiac conditions associated with the highest risk of adverse outcomes from endocarditis, who are undergoing dental or respiratory procedures known to cause	**Case 66-6 (Questions 1, 2), Tables 66-6, 66-7**

significant bacteremia. Antimicrobial prophylaxis should be directed against viridans group streptococci.

INTRODUCTION

Infective endocarditis (IE) is a microbial infection of the heart valves or other endocardial tissue, often associated with an underlying cardiac defect. IE is classified based on the causative organism to provide information on the probable microbial cause and course of the disease (acute or subacute), the likelihood of underlying heart disease, and the appropriate antimicrobial regimens.[1]

Pathogenesis

The pathogenesis of endocarditis involves a complex series of events that ultimately result in the formation of an infected platelet-β-fibrin thrombus on the valve surface.[1,2] This thrombus is called a *vegetation.*

The first step in the formation of the vegetation involves modification of the endocardial surface, which is normally nonthrombogenic. Valvular insufficiency, for example, caused by aortic stenosis or ventricular septal defects, can produce regurgitant blood flow, high-pressure gradients, or narrow orifices, resulting in turbulence and endocardial damage.[1,2] In patients with rheumatic heart disease, endocardial injury (eg, mitral valve stenosis) occurs as a result of immune complex deposition or hemodynamic disturbances. Once the endocardial surface of the valve is traumatized, small, sterile thrombi consisting of platelets and fibrin are deposited, forming the lesion called nonbacterial thrombotic endocarditis (NBTE).[1,2] NBTE occurs most commonly on the atrial surfaces of the mitral and tricuspid valves and on the ventricular surface of the aortic valve. NBTE serves as a nidus for microbial

colonization during periods of bacteremia (eg, procedures involving perforation of the oral mucosa, respiratory tract, genitourinary tract, or infected skin). Organisms such as viridans group streptococci (VGS), *Enterococcus* spp., *Staphylococcus aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, and *Candida albicans* possess adherence factors that facilitate their pathogenicity. In particular, platelet aggregation is an important virulence factor in experimental streptococcal endocarditis, potentially leading to larger vegetations and multifocal embolic spread.[3]

Once the NBTE lesion becomes colonized by microorganisms, the surface is rapidly covered with a sheath of fibrin and platelets. This avascular encasement provides an environment protected from host defenses and is conducive to further bacterial replication and vegetation growth.[2] The bacterial colony count can be as high as 10^4 to 10^5 bacteria per gram of valvular vegetation. Endocarditis can result in life-threatening hemodynamic disturbances and embolic episodes affecting many organs. Without antimicrobial therapy and surgical intervention, IE is virtually 100% fatal. Because of bacterial proliferation to high densities in the fibrin mesh protected from normal host defenses, cure of infection requires prolonged therapy of 4 to 6 weeks with relapse not uncommon.

Epidemiology

Between 2000 and 2011, there were >450,000 IE-related hospitalizations in the United States alone. Over that decade, the incidence has increased from 11 to 15 cases per 100,000 persons, with an associated mortality of 11% to 26%.[4–6] Health care–associated IE has emerged as a result of increased use of invasive medical devices and procedures (eg, intravenous [IV] catheters, total parenteral nutrition [TPN] IV lines, hemodialysis shunts or fistulas, intracardiac prosthesis, and central venous pressure monitoring lines).[1] With the exception of intravenous drug users (IVDUs), the mean patient age has shifted from younger than 30 years in the 1920s to older than 55 years at the turn of the century.[7–9] This

increase in age is likely attributable to (a) a decline in the incidence of acute rheumatic fever and rheumatic heart disease, counterbalanced by degenerative valvular disease in an increasing elderly population, (b) the increasing longevity of the general population, and (c) increased exposure to more intense and invasive medical procedures in both, the overall and the aging population. Males are infected more often than are females (roughly 2:1), and the disease remains uncommon in children, occurring primarily in association with underlying congenital cardiac defect and nosocomial catheter-related bacteremia.[1]

Predisposing Factors

In general, any structural cardiac defect that leads to the turbulence of blood flow predisposes to the development of IE. Rheumatic heart disease was at one time the most common underlying cardiac defect associated with endocarditis; however, cases related to rheumatic heart disease have declined to ≤25% in developed countries while remaining the predominant defect in developing countries.[7,8] Mitral valve prolapse with thickened leaflets and valvular redundancy is a recognized predisposing risk for IE, with a documented occurrence rate of 10%. Clinical presentation is often subtle, with lower associated mortality in these individuals compared with left-sided IE of other types. In the absence of underlying valvular defects, degenerative cardiac lesions, such as calcified mitral annulus secondary to atherosclerotic cardiovascular disease and post-myocardial infarction thrombus, may be a significant risk factor for the elderly. IVDUs constitute a unique population at greatest risk for recurrent and polymicrobial IE.[7] Hemodialysis dependency (8%), diabetes mellitus (16%), and congenital heart disease (12%) are the most common demographic characteristics associated with IE.[10] Up to 25% of all cases are acquired in health care–related settings, whereas community acquisition accounts for the majority of the cases. Between 2000 and 2014, there have been an increased proportion of community-associated IE cases due to IVDU,

accounting for 12% to >50% in certain regions in the United States.[11–13]

Bacteriology

Streptococci and staphylococci cause 80% to 90% of cases of IE. VGS remain the predominant cause of IE in children and in young females with isolated mitral valve involvement.[1] During the past decades, staphylococci have become increasingly prevalent as a cause of IE, and *S. aureus* is the leading cause of IE.[10] Acquisition of IE in nearly half of these cases was likely health care related, supporting a low threshold to evaluate underlying IE in the setting of health care–related *S. aureus* bacteremia. More importantly, methicillin-resistant strains account for up to 40% of IE cases involving *S. aureus*.[7–9] Endocarditis in IVDUs often is caused by *S. aureus*, whereas prosthetic valve endocarditis (PVE) is more commonly caused by coagulase-negative staphylococci, such as *S. epidermidis*. Gram-negative bacilli and fungi together account for <10% of all endocarditis cases and usually are associated with IV drug use, valvular prostheses, and hospital IV access procedures. Endocarditis caused by anaerobes and other organisms is rare. Polymicrobial IE (caused by at least two organisms), although uncommon, is being recognized more frequently in IVDUs and certain postoperative patients. *Candida* species, *S. aureus*, *P. aeruginosa*, *Serratia marcescens*, and non-β hemolytic group D streptococci are the organisms involved most frequently in these populations.

Site of Involvement

The site of heart valve involvement is determined by the underlying cardiac defect and the infecting organism.[2,7,9,10] The mitral valve is affected in >85% of cases caused by VGS with underlying rheumatic heart disease. The tricuspid valve is the common site of involvement in staphylococcal endocarditis associated with IVDU. Overall, the

distribution ranges from 28% to 45% for mitral valve, 5% to 36% for aortic valves, and 0% to 6% for tricuspid valves, and the pulmonary valve is rarely affected.[14] Multiple heart valves may be affected simultaneously.

CASE 66-1

QUESTION 1: A.G., a 57-year-old, 132.28-pound (60-kg) male with fatigue, a persistent low-grade fever, night sweats, arthralgias, and a 15.43-pound (7-kg) unintentional weight loss, is admitted to the hospital for evaluation. Visual inspection reveals a cachectic, ill-appearing male in no acute distress. Physical examination is significant for a grade III/IV diastolic murmur with mitral regurgitation (insufficiency), increased from preexisting murmur, a temperature of 100.50 °F (38.05 °C), petechial skin lesions, subungual splinter hemorrhages, and Janeway lesions on the soles of both feet (**Figs. 66-1, 66-2, and 66-3**). Nail clubbing, Roth spots, or Osler nodes are not evident. The remainder of his physical examination is unremarkable. A.G.'s medical history is significant for mitral valve prolapse and, more recently, a dental procedure involving the extraction of four wisdom teeth. The history of his present illness is noteworthy for the development of symptoms 2 weeks after the dental procedure (about 2 months before admission). His only current medication is ibuprofen 600 mg orally four times a day.

Figure 66-1 Janeway lesions. Extensive ecchymotic embolic lesions in a case of acute bacterial endocarditis.

Figure 66-2 Splinter hemorrhages in the nail bed.

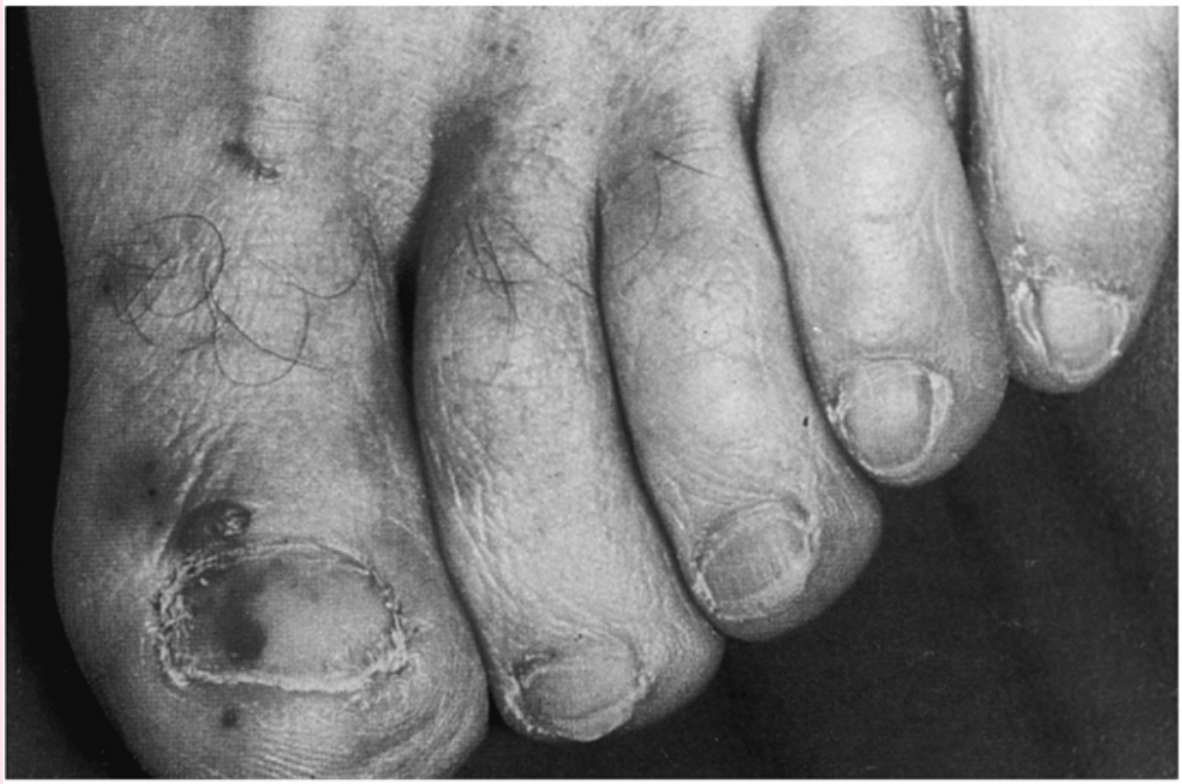


Figure 66-3 Petechial skin lesions in a case of acute staphylococcal endocarditis.

Relevant laboratory results include the following:

Hemoglobin (Hgb), 11.4 g/dL (SI units, 114 g/L [normal, 140–180])
Hematocrit (Hct), 34% (SI units, 0.34 [normal, 0.39–0.49])
Reticulocyte count, 0.5% (SI units, 0.005 [normal, 0.001–0.024])
White blood cell (WBC) count, 35,000/μL with 65% polys and 1% bands (SI units, 35 × 10/L with 0.65 polys and 0.01 bands [normal, 3.2–9.8 with 0.54–0.62 polys and 0.03–0.05 bands])
Blood urea nitrogen (BUN), 21 mg/dL (SI units, 7.5 mmol/L of urea [normal, 2.9–8.9])
Serum creatinine (SCr), 1.2 mg/dL (SI units, 159 mmol/L [normal, 53–133])

A urinalysis (UA) reveals 2+ proteinuria and 10 to 20 red blood cells (RBCs) per high-power field (HPF). The erythrocyte sedimentation rate (ESR) is elevated at 66 mm/hour (normal, ≤30 mm/minute), and the rheumatoid factor (RF) finding is positive. Results from a transthoracic echocardiogram (TTE) were unrevealing. Three blood cultures were obtained over 24 hours, and all cultures obtained on day 1 are growing gram-positive cocci in pairs and chains, presumed α-hemolytic streptococci. Although confirmation and speciation of the organism is being performed, A.G. is started empirically on penicillin G, 2 million units IV every 4 hours (12 million units per day), and IV gentamicin, 120 mg

(loading dose) followed by 60 mg every 8 hours. Antimicrobial susceptibility results are pending.

What clinical manifestations and laboratory abnormalities in A.G. are consistent with IE?

VIRIDANS GROUP *STREPTOCOCCUS* ENDOCARDITIS

Clinical Presentation

The clinical presentation of IE is highly variable and can involve almost any organ system.[1] A.G. appears pale and chronically ill and represents the typical patient with subacute disease (eg, that caused by VGS). Nonspecific symptoms consistent with endocarditis in A.G. include fatigue, weight loss, fever, night sweats, and arthralgias. Fever alone is present in most (90%) patients with endocarditis. The fever is characteristically low grade and remittent, with peaks in the afternoon and evening. Fever may be absent or minimal in patients with CHF, chronic renal and liver failure, prior use of antimicrobial agents, or IE caused by less virulent organisms.[1] Musculoskeletal symptoms (eg, arthralgias, myalgias, and back pain) are common and may mimic rheumatic disease. Other symptoms can include lethargy, anorexia, malaise, nausea, and vomiting.[1] Because signs and symptoms are nonspecific and subtle, diagnosis is often difficult to make. In addition, the time from bacteremia to diagnosis is often prolonged because of the insidious progression of symptoms.[1] Delayed diagnosis occurs more commonly in the elderly. Fever may be absent in 30% to 40% of patients older than age 60 years, whereas it can be present in >90% of patients younger than age 40 years.

Elderly patients are less likely to have new or changed heart murmurs. The most common presenting symptoms in the elderly with endocarditis are confusion, anorexia, fatigue, and weakness, which may be readily attributable to stroke, heart failure, or syncope.

The temporal relationship between A.G.'s dental procedure and the onset of symptoms suggests it was the etiology of bacteremia and subsequent endocarditis. Although one assumes that prophylactic antibiotics were administered before the procedure, endocarditis can develop despite receipt of adequate chemoprophylaxis.[1,10,14] A.G. has an increase in his preexisting diastolic murmur with mitral insufficiency, a finding consistent with endocarditis. Cardiac murmurs are present in >85% of patients with endocarditis. Murmurs frequently are absent in patients with acute disease (eg, staphylococcal endocarditis), right-sided disease (eg, endocarditis in IVDUs), or mural infection.[1]

A.G. exhibits several peripheral manifestations of IE, including conjunctival petechiae, Janeway lesions, and splinter hemorrhages. Overall, peripheral manifestations are observed in 10% to 50% of cases, but none of these is pathognomonic for IE.[1] These manifestations are usually a result of septic embolization of vegetations to distal sites or immune complex deposition. Mucocutaneous petechial lesions of the conjunctiva, mouth, or pharynx are present in 20% to 40% of patients, especially those with long-standing disease.[1] These lesions generally are small, nontender, and hemorrhagic in appearance, and result from vasculitis or peripheral embolization. Janeway lesions are painless, hemorrhagic, macular plaques most commonly found on the palms and soles (Fig. 66-1). Splinter hemorrhages are nonspecific findings that appear as red to brown linear streaks in the proximal portion of the fingers or toenails (Fig. 66-2). Other findings can include Roth spots (small, flame-shaped retinal hemorrhages with pale white centers found near the optic nerve) and Osler nodes (purplish, nonhemorrhagic, painful nodules that develop on the subcutaneous pads of the fingers and toes or on the palms and soles). Clubbing (broadening and thickening) of the nails also may be observed in patients with prolonged disease. Petechial skin lesions are also seen (Fig. 66-3).

Several laboratory findings are consistent with IE in A.G. A low Hgb and Hct with normal red cell indices suggest anemia of chronic disease. Of patients with subacute disease, 70% to 90% will have a

normochromic, normocytic anemia. Leukocytosis with a left shift, although not evident in A.G., commonly is seen in those with acute, fulminant disease such as staphylococcal endocarditis. The ESR nearly always is elevated in IE, but this finding is nonspecific and can be associated with several other disease entities. RF (an immunoglobulin M antiglobulin) and circulating immune complexes are detected in most patients with long-standing disease, but both are nonspecific findings.[1] Major embolic episodes and infarction involving the kidney, spleen, lung, and brain may develop as secondary complications in up to one-third of cases.[1] A.G. exhibits some degree of renal damage, as evidenced by moderate hematuria and proteinuria. Alterations in A.G.'s renal function (increased BUN and creatinine) probably are a result of immune complex deposition (diffuse glomerulonephritis) or secondary to renal embolization (focal glomerulonephritis). Erythrocyte and leukocyte cast formation also may be present. Renal impairment usually is reversible with the institution of effective antimicrobial therapy.[1,15] Cardiac complications occur most frequently. CHF from infection-induced valvular damage is the most common cause of death in IE and is the most common indication for surgery.[1,15] As many as two-thirds of patients with endocarditis develop CHF. Aortic valve infection is more frequently associated with CHF than is mitral valve infection. Other manifestations include paravalvular abscesses, pulmonary edema, and pericarditis.[15] Mitral valve injury caused by VGS generally is better tolerated hemodynamically than is aortic valve injury caused by staphylococci. Although A.G. has no apparent signs of overt heart failure, he should be monitored closely for the development of hemodynamic instability. Neurologic complications, most commonly stroke, rank second to cardiac complications in frequency, but they may be the leading cause of death in patients with endocarditis.[15] A stroke syndrome in a patient with underlying valvular abnormalities should prompt the clinician to rule out IE. Other clinical manifestations include headache, mental status change, transient ischemic attack, seizures, brain abscess, or intracranial mycotic aneurysms.[1,15] Neurologic symptoms associated with high mortality can be observed in up to 35% of patients with *S. aureus* endocarditis

who are non-IVDUs.[16] Metastatic abscesses (eg, in the spleen, kidney, liver, and iliac and mesenteric arteries) can develop in virtually any organ secondary to systemic septic embolization[15] Splenomegaly, although not part of A.G.'s findings, occurs in 20% to 60% of all cases and is more common in subacute disease.

Diagnosis

Case 66-1, Question 2: How was the diagnosis of IE established in A.G.?

BLOOD CULTURES

Although A.G.'s medical history (mitral valve prolapse, recent dental procedure) and clinical presentation are highly suggestive of IE, blood culture is the single most important diagnostic workup for IE.[1] Bacteremia (when present) secondary to endocarditis is continuous and low grade; >50% of the cultures show only 1 to 30 bacteria per milliliter. Despite the low concentration of organisms, at least one of the first two blood culture results is positive in 95% of cases.[1] To achieve a high yield, at least three sets of blood cultures collected by separate venipunctures should be obtained, with the first and third set of blood cultures taken at least 1 hour apart.[1] Administration of antibiotics within the previous 2 weeks may significantly decrease this yield.[17] It is also important to establish the exact microbiologic cause before initiating antimicrobial therapy. In patients who are acutely ill, empiric therapy should start as soon as the appropriate cultures are obtained to avoid further valvular damage or other complications.[1]

ECHOCARDIOGRAPHY

Echocardiography is a valuable tool in establishing early diagnosis (eg, the presence and size of vegetations), identifying patients at high risk for complications, and optimizing the timing and mode of surgical intervention by detecting and monitoring associated pathologic changes such as valvular abscess.[1],[18],[19] The transducer

may be placed on the chest (TTE) or in the esophagus (transesophageal echocardiogram [TEE]).[19] TTE is a rapid and noninvasive procedure with 98% specificity for vegetations. Sensitivity for vegetations may be <60% to 70%, however, for adult patients with obesity, hyperinflated lungs caused by emphysema, or a prosthetic valve. TEE is more costly and invasive but is significantly more sensitive in detecting vegetations and abscesses while maintaining high specificity. All patients with suspected IE should have echocardiography on admission and repeated during their course, to help guide future medical management and timing of intervention.[19] Compared with TTE, TEE is superior in the diagnosis of pacemaker IE and IE in the elderly. A.G. has a negative TTE result on admission. Given the high clinical suspicion for IE in A.G., a follow-up TEE is recommended to rule out a false-negative TTE result.

Diagnostic criteria for IE that integrate clinical, laboratory, microbiologic, and echocardiographic data are listed in **Tables 66-1** and **66-2**.[10],[20] Based on published evidence involving nearly 2000 patients, the 2015 AHA guidelines suggest that the modified Duke criteria be used as the primary diagnostic schema to evaluate patients suspected of having IE.[10] A.G. possesses one major criterion (positive blood cultures) and three minor criteria (fever, predisposing heart condition, and vascular and immunologic phenomena); therefore, he meets the diagnostic criteria for definite IE.[20]

Table 66-1

Definition of Infective Endocarditis According to the Modified Duke Criteria

Definite IE[a]
Pathologic Criteria
Microorganisms: demonstrated by culture or histology examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; *or*
Pathologic lesions: vegetation or intracardiac abscess confirmed by histologic

examination showing active endocarditis
Clinical Criteria
Using specific definitions listed in Table 66-2; two major criteria *or* one major and three minor criteria *or* five minor criteria
Possible IE
One major criterion and one minor criterion; *or* three minor criteria
Rejected
Firm alternative diagnosis explaining evidence of IE; *or*
Resolution of IE syndrome with antibiotic therapy for >4 days; *or*
No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for >4 days; *or* not meet criteria for possible IE as above

IE, infective endocarditis.

[a]Modifications shown in bold.

Adapted from Li JS, Sexton DJ, Nettles R, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638. Reproduced by permission of Infectious Diseases Society of America.

Table 66-2
Definitions of Terminology Used in the Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Major Criteria[a]
Blood Culture Positive for IE
▪ Typical microorganisms consistent with IE from two separate blood cultures: **1.** Viridans streptococci, *Streptococcus bovis*, HACEK group; *or* **2.** *Staphylococcus aureus* or community-acquired enterococci in the absence of a primary focus; *or* ▪ Microorganisms consistent with IE from persistently positive blood cultures defined as follows: **1.** At least two positive blood cultures drawn >12 hours apart; *or* **2.** All of three or a majority of four separate blood cultures (with first and last sample drawn at least 1 hour apart) ▪ **Single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800**
Evidence of Endocardial Involvement

- Echocardiogram positive for IE **(TEE recommended for patients with prosthetic valves, rated at least "possible IE" by clinical criteria or complicated IE [paravalvular abscess]; TEE as first test in other patients)** defined as follows:
  1. Oscillating intracardiac Masson valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; *or*
  2. Abscess; *or*
  3. New partial dehiscence of prosthetic valve
- New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

- Predisposition: predisposing heart condition or IV drug use
- Fever >100.40 °F (38 °C)
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, RF
- Microbiologic evidence: positive blood culture but not meeting major criterion as noted earlier[b] or serologic evidence of active infection with organism consistent with IE
- **Echocardiographic minor criteria eliminated**

HACEK, *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*; IE, infective endocarditis; IgG, immunoglobulin G; IV, intravenous; RF, rheumatoid factor; TEE, transesophageal echocardiography.

[a]Modifications shown in bold.

[b]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

From Li JS, Sexton DJ, Nettles R, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638. Reproduced by permission of Infectious Diseases Society of America.

Antimicrobial Therapy

GENERAL PRINCIPLES

Case 66-1, Question 3: What would be a reasonable duration of antibiotic therapy for A.G.?

The avascular nature of the vegetation results in an environment that is devoid of normal host defenses (eg, phagocytic cells and complement); this permits uninhibited growth of bacteria.[2] Therefore, to eradicate the causative organism, high doses of an IV bactericidal antibiotic generally are administered for 4 to 6 weeks.[1,10]

Table 66-3
Suggested Regimens for Therapy of Native Valve Endocarditis Caused by *Streptococcus viridans* Group and *Streptococcus gallolyticus*

Antibiotic	Dose[a,b] and Route	Duration
Penicillin-Susceptible (minimum inhibitory concentration [MIC] ≤0.12 µg/mL)		
Aqueous crystalline penicillin G[c] *or*	*Adult*: 12–18 million units/24 hour IV either continuously or in four to six equally divided doses	4 weeks
	Pediatric: 200,000 units/kg/24 hour IV (max: 20 million units/24 hour) either continuously or in four to six equally divided doses	
Ceftriaxone sodium[c]	*Adult*: 2 g once daily IV or IM	4 weeks
	Pediatric: 100 mg/kg once daily IV or IM	
Or		
Aqueous crystalline penicillin G *or*	See penicillin-susceptible dosing for penicillin given earlier	2 weeks
Ceftriaxone sodium	See penicillin-susceptible dosing for ceftriaxone given earlier	2 weeks
With gentamicin sulfate[d]	*Adult*: 3 mg/kg once daily IV or IM	2 weeks
	Pediatric: 3 mg/kg once daily IV or IM or in three equally divided doses	
Relatively Penicillin G Resistant (MIC >0.12 and <0.5 µg/mL)		
Aqueous crystalline penicillin G	*Adult*: 24 million units/24 hour IV either continuously or in four to six equally divided doses	4 weeks

	Pediatric: 200,000–300,000 units/kg/24 hour IV (max: 20 million units/24 hour) either continuously or in four to six equally divided doses	
With gentamicin sulfate[d]	*Adult*: 3 mg/kg once daily IV or IM *Pediatric*: 3 mg/kg once daily IV or IM or in three equally divided doses	2 weeks
Or		
Ceftriaxone sodium[c]	*Adult*: 2 g once daily IV or IM *Pediatric*: 100 mg/kg once daily IV or IM	4 weeks
β-*Lactam Allergic*		
Vancomycin hydrochloride[e]	*Adult*: 15–20 mg/kg every 8–12 hours (adjust dose based on AUC-guided monitoring)	4 weeks
	Pediatric (3 months to <12 years): 60–80 mg/kg/24 hour IV in four equally divided doses (max: 3 g/24 hour; adjust dose based on AUC-guided monitoring) *Pediatric (≥12 years):* 60–70 mg/kg/24 hour IV in three to four equally divided doses (max: 3 g/24 hour; adjust dose based on AUC-guided monitoring)	

AUC, area under the curve; IM, intramuscular; IV, intravenous.

[a]Pediatric doses should not exceed that of a normal adult.

[b]Antibiotic doses for patients with impaired renal function should be modified appropriately.

[c]Preferred in most patients older than 65 years of age and in those with impairment of the eighth nerve or renal function.

[d]Two-week regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/minute, impaired eighth cranial nerve function or *Abiotrophia*, *Granulicatella*, or *Gemella* infection. Gentamicin nomogram should be used for preferred single daily dosing; when three divided doses are used, dosage should be adjusted to achieve peak serum concentrations of 3–4 μg/mL and trough serum concentrations of <1 μg/mL. Other potential nephrotoxic drugs should be used with caution in patients receiving gentamicin therapy.

[e]Vancomycin dosage should be reduced in patients with impaired renal function. In obese adult patients, a loading dose of 20 to 25 mg/kg based on actual body weight, with a maximum dose of 3000 mg, should be considered. Each dose of vancomycin should be infused for at least 1 hour to reduce the risk of the histamine-release red man syndrome. Peak and trough concentrations should be

measured to improve accuracy of vancomycin AUC_{24hr}/MIC and to optimize subsequent maintenance doses. Early and frequent monitoring of AUC values is recommended for maintenance dose adjustment.

Sources: Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435–1486. doi:10.1161/cir.0000000000000296; Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864. doi:10.1093/ajhp/zxaa036.

Case 66-1, Question 4: When is determination of minimum bactericidal concentration (MBC) and minimum inhibitory concentration (MIC) useful in treating bacterial endocarditis?

In some IE cases, it is necessary to use two antibiotics to achieve synergistic activity against the organism. Once an organism is identified, its in vitro susceptibility pattern is determined by the MIC for various antibiotics. Standard Kirby–Bauer disk diffusion testing is inadequate in the setting of IE to aid in the selection of antibiotics without the quantitative information provided by the MIC.[1] In addition, the MBC may be useful in detecting tolerant strains, particularly in the setting of unexplained slow response or treatment failure. However, routine MBC determination is not recommended.[1] Treatment of endocarditis requires antibiotics with bactericidal activity; therefore, the serum concentration of the antibiotic must greatly exceed the MBC for the particular organism. For endocarditis caused by community-acquired VGS, this usually is achieved without much difficulty because most isolates are sensitive to penicillin at an MIC of <0.12 μg/mL[10]; corresponding MBCs are, at most, one or two tube dilutions higher.[14] The emergence of strains with resistance to penicillin and related β-lactams, such as ceftriaxone, is a significant problem, particularly among bloodstream isolates obtained from the nosocomial setting and patients with cancer having neutropenia.[14,21,22] The increasing prevalence of β-lactam–resistant

clinical isolates highlights the importance of determining the MIC and continued close monitoring of the antibiotic susceptibility of VGS.

Several studies have investigated whether vancomycin MIC was associated with treatment failure and mortality, and the data are mixed. Some studies showed suboptimal response and poor clinical outcome with vancomycin therapy for the treatment of invasive infection caused by MRSA strains with high vancomycin MIC of 2 μg/mL[23–28]; whereas others found no significant difference in clinical outcome such as mortality and infection recurrence when compared to MRSA strains with MIC of ≤1 μg/mL.[29,30] The heterogeneity of an individual's immune response may contribute to the different outcomes observed. Given the conflicting reports, vancomycin MIC alone should not be used to guide therapy decisions; instead, a patient's initial clinical response should determine whether to continue with vancomycin or switch to an alternative therapy.[31]

REGIMEN SELECTION

Case 66-1, Question 5: What factors must be considered in selecting a regimen for A.G.? Which regimen should A.G. receive?

Patients with endocarditis caused by penicillin-sensitive strains of VGS and non-enterococcal group D streptococci (eg, *S. gallolyticus*; MIC ≤0.12 μg/mL) can be treated with any one of three regimens, as outlined in the 2015 AHA treatment guidelines.[10] The suggested regimens (**Table 66-3**) are associated with cure rates of up to 98% and include (a) high-dose parenteral penicillin for 4 weeks, (b) high-dose parenteral ceftriaxone for 4 weeks, and (c) 2 weeks of combined therapy with high-dose parenteral penicillin and an aminoglycoside.[10,32–35] Ceftriaxone with an aminoglycoside for 2 weeks appears to be equally effective.[10,36]

HIGH-DOSE PENICILLIN FOR 4 WEEKS

Ten to 20 million units per day of IV penicillin G for 4 weeks resulted in a cure rate of 100% for 66 patients with non-enterococcal

streptococcal endocarditis.[33] Another study using penicillin monotherapy reported relapse in only 2 of 49 patients; however, both of these patients received <4 weeks of therapy.[34] The large range of 12 to 18 million units per day of penicillin is recommended to allow flexibility in dosing based on the patient's renal function and disease severity. Ampicillin IV (2 g every 4 hours) is a reasonable alternative.

SINGLE DAILY CEFTRIAXONE FOR 4 WEEKS

Ceftriaxone is active against viridans streptococcal strains isolated from patients with endocarditis. In one study, all 49 strains of VGS and 11 strains of *S. bovis* were inhibited at an MIC <0.125 µg/mL of ceftriaxone; one strain of *S. sanguinis* was inhibited at an MIC of 0.25 µg/mL.[37] Although no direct comparative trials have been performed evaluating ceftriaxone against high-dose penicillin for the treatment of streptococcal endocarditis, it appears to be comparable to high-dose penicillin when given for 4 weeks.[38],[39] Of 70 assessable patients who received ceftriaxone 2 g as a single daily dose for 4 weeks, all were cured, except for 1 patient who had a probable relapse 3 months after completion of therapy. Ceftriaxone inhibited all strains of VGS at an MIC of 0.25 µg/mL in both studies. Although the simplicity of single daily treatment with ceftriaxone is attractive for outpatient use, careful patient selection based on microbiologic, clinical, and host factors is critical to treatment success and proper and timely management of potential complications. (See Case 66-6, Question 1, for a detailed discussion of outpatient therapy.)

HIGH-DOSE PENICILLIN OR CEFTRIAXONE PLUS AN AMINOGLYCOSIDE FOR 2 WEEKS

The combination of 2 weeks of streptomycin (or gentamicin) with 4 weeks of penicillin is synergistically bactericidal for highly penicillin-susceptible and relatively penicillin-resistant streptococci, and enterococci (see Case 66-4, Question 4).[40],[41]A shortened combination regimen consisting of high-dose penicillin G and streptomycin for 2 weeks is an effective alternative to the previously described regimens. The reported cure rate in 104 patients treated at

the Mayo Clinic with this regimen was 99%.[40,42] Although clinical experience with combination therapy has been primarily with penicillin and streptomycin, in vitro and animal data support that streptomycin and gentamicin are reasonably interchangeable. Of note, streptomycin is rarely used presumably due to lack of clinician familiarity with this drug and laboratory access to streptomycin serum assays.[10] Administration of gentamicin once daily versus three times daily when added to penicillin appears equally effective in the treatment of VGS endocarditis.[32]

Combination therapy with once-daily ceftriaxone 2 g plus netilmicin or gentamicin at 3 mg/kg for 2 weeks has also been evaluated and clinical cure rates of 87% to 96% were observed in patients infected with penicillin-susceptible streptococci.[34,43] Although the aminoglycoside agent was administered as a single daily dose, all of the patients had measurable serum trough levels.[34,43] Therefore, the efficacy of "extended-interval dosing" of aminoglycoside (whereby trough levels are not detectable, allowing a drug-free interval) in short-course combination therapy remains uncertain. Based on available data, the 2-week regimen of penicillin or ceftriaxone plus an aminoglycoside appears to be efficacious for (rare) uncomplicated cases of highly penicillin-susceptible VGS and *S. gallolyticus* (MIC ≤0.12 µg/mL) native valve endocarditis. It is not recommended for patients with extracardiac complications or intracardiac abscesses, those with creatinine clearance <20 mL/minute, or those with impaired eighth cranial nerve function. Patients infected with *Abiotrophia*, *Granulicatella*, or *Gemella* spp. or those who have prosthetic valve infections should not receive short-course therapy.[10]

Patients with native valve endocarditis caused by relatively resistant VGS and *S. gallolyticus* with penicillin MIC >0.12 to <0.5 µg/mL should receive a 4-week regimen of high-dose penicillin plus 2 weeks of gentamicin (3 mg/kg IV every 24 hours). Alternatively, ceftriaxone (2 g IV every 24 hours) may be used alone for 4 weeks if the organism is susceptible to ceftriaxone. Patients allergic to β-lactams should receive vancomycin 15 to 20 mg/kg IV (based on actual body weight) every 8 to 12 hours for a duration of 4 weeks.[10]

SPECIAL CONSIDERATIONS

The risk of relapse may be higher in patients who have had symptoms for >3 months before the initiation of treatment. These patients should be treated with 4 to 6 weeks of penicillin combined with an aminoglycoside for the first 2 weeks.[1,10,38]

Abiotrophia defectiva and *Granulicatella* spp. (*G. elegans*, *G. adiacens*, *G. paraadiacens*, and *G. balaenopterae*), formerly known as nutritionally variant streptococci (NVS) are slow-growing, fastidious organisms that are responsible for ~5% of IE cases.[44] *A. defectiva* and *Granulicatella* spp. are less susceptible (MIC 0.2–2.0 μg/mL) or highly resistant (MIC >4 μg/mL) to penicillin when compared with other streptococci. In addition, many strains may be tolerant to penicillin.[14] Even in strains highly susceptible to penicillin, high rates of bacteriologic failure and relapse may occur in patients despite completion of the treatment course.[14] An animal model of endocarditis indicates that a penicillin–aminoglycoside (streptomycin or gentamicin) combination is significantly better than is penicillin alone in reducing bacterial counts.[45] Therefore, patients infected with *A. defectiva*, *Granulicatella* spp., and VGS with penicillin MIC ≥0.5 μg/mL should receive high-dose penicillin or ceftriaxone (2 g IV every 24 hours) in combination with gentamicin (1 mg/kg every 8 hours) for a duration of 4 to 6 weeks, usually determined with infectious diseases consultation.[10] A 6-week course of combination therapy with penicillin and gentamicin is recommended for patients with symptoms lasting >3 months in duration and for those with PVE caused by these strains.[10,14] Patients allergic to β-lactams should receive vancomycin 15 to 20 mg/kg IV (based on actual body weight) every 8 to 12 hours for a duration of 4 to 6 weeks.[10]

Assuming the isolated VGS strain from A.G. is not resistant to penicillin and he has no other complicating factors, any of the suggested regimens would be appropriate. Although A.G. has mild renal impairment, this is most likely secondary to the endocarditis and should improve once adequate antimicrobial therapy has been instituted. A.G. was begun on 12 million units per day of penicillin G, which would be reasonable for his age and mild renal impairment. If

nephrotoxicity were a major concern in A.G., ceftriaxone alone for 4 weeks is reasonable. If gentamicin is used, A.G.'s renal function should be monitored, and the dose should be adjusted appropriately if not using a single daily regimen. Multiple aminoglycoside dosing requires frequent monitoring for signs of toxicity by taking periodic peak and trough aminoglycoside concentrations.

STAPHYLOCOCCUS EPIDERMIDIS: PROSTHETIC VALVE ENDOCARDITIS

Etiology

CASE 66-2

Question 1: F.T., a 65-year-old male, presents with anorexia, fever, chills, and weight loss. His medical history is significant for replacement of his mitral and aortic heart valves (both porcine) 1 month ago for aortic stenosis, mitral regurgitation, and mitral stenosis secondary to rheumatic heart disease. Two weeks post discharge he presented to the emergency department (ED) with fever, a right pleural effusion, a pericardial friction rub, and pericarditis. The impression at that time was either post-pericardiotomy or Dressler syndrome. F.T. was sent home on anti-inflammatory agents but failed to improve. After continued symptoms of anorexia, nausea, chills, and fever of 101 °F (38.33 °C), he returned to the hospital. On readmission, his physical examination was noteworthy for a systolic ejection murmur at the left sternal border and 3+ pedal edema. Blood cultures were obtained, and routine laboratory studies were performed. His history and clinical presentation were strongly suggestive of PVE.

What are the most likely organisms responsible for PVE in F.T.?

PVE is a life-threatening infectious complication of artificial heart valve implantation that accounts for 7% to 25% of cases of IE in developed countries.[46–48] The prevalence of complications resulting in death has been as high as 20% to 40%.[47] The risk of PVE after surgery is ~1% at 12 months and 2% to 3% at 60 months. PVE is categorized as early or late, depending on the onset of clinical

manifestations after cardiac surgery.[46–48] Early PVE occurs within 2 months of surgery and is thought to represent infection by skin organisms implanted into the valve annulus (suture site where the valve is attached to cardiac muscle during valve placement).[46–48] The most common organisms cultured from patients such as F.T. with early PVE are coagulase-negative staphylococci (primarily *S. epidermidis* [>30%], most of which are resistant to methicillin), followed by *S. aureus* (20%), and gram-negative bacilli (10%–15%). Miscellaneous organisms, such as diphtheroids and fungi, account for the remainder. In contrast, streptococci are a more common cause of late PVE (>2 months after surgery).[46–48]

Prophylaxis

Case 66-2, Question 2: What measures can be taken to prevent early PVE?

The overall frequency of early PVE, despite antibiotic prophylaxis, is 1% to 4%.[49] Complications are severe and include valve dehiscence, acute heart failure, arrhythmias, and outflow obstruction. Although antibiotic prophylaxis before valve surgery (a "clean" procedure) does not seem to reduce the frequency of early PVE, it is indicated nevertheless because the complications of infection are catastrophic. The antimicrobial regimen used most commonly for cardiac surgery prophylaxis (see Chapter 63, Antimicrobial Prophylaxis for Surgical Procedures) consists of an antistaphylococcal cephalosporin, such as cefazolin, given in the operating room at the time of induction of anesthesia or in the 60 minutes before the procedure. Vancomycin is considered the prophylactic agent of choice for cardiovascular procedures, including prosthetic valve replacement and implantation of prosthetic grafts, for the following: (a) documented penicillin allergy, (b) prior receipt of broad-spectrum antimicrobial therapy and high likelihood of colonization with cephalosporin-resistant staphylococci or enterococci, or (c) performance of the procedure in a center

experiencing outbreaks or a high endemic rate of surgical infection with methicillin-resistant staphylococci.[50]

Antimicrobial Therapy

Case 66-2, Question 3: What are the treatment options for F.T.?

As noted earlier, F.T. most likely is infected with coagulase-negative staphylococci. For those rare coagulase-negative staphylococci that remain sensitive to β-lactams (<20%), a penicillinase-resistant penicillin (nafcillin or oxacillin) is the drug of choice (**Table 66-4**).[51] For the treatment of PVE caused by methicillin-resistant, coagulase-negative staphylococci, vancomycin should be used.[51] Most staphylococci are sensitive to vancomycin with MIC of 2 μg/mL or less; however, strains of staphylococci with intermediate susceptibility to vancomycin have emerged.[52] Refer to the American Society of Health-System Pharmacists-Infectious Diseases Society of America (ASHP-IDSA) guidelines for area under the curve (AUC)-guided dosing and monitoring of vancomycin.[23]

Table 66-4
Treatment of Staphylococcal Endocarditis

Antibiotic	Dosage and Route	Duration
Without Prosthetic Material[a,b]		
Oxacillin/Methicillin-Susceptible Staphylococci		
Patients with Nonpenicillin Allergy		
Nafcillin *or* oxacillin	*Adult*: 2 g IV every 4 hours	6 weeks
	Pediatric: 150–200 mg/kg/24 hour IV (max: 12 g/24 hour) in four to six equally divided doses	
Patients with Penicillin Allergy		
Cefazolin[c] *or*	*Adult*: 2 g IV every 8 hours	6 weeks
	Pediatric: 100 mg/kg/24 hour IV (max: 6 g/24 hour) in equally divided doses every 8 hour	

Vancomycin[d,e,f]	*Adult*: 15–20 mg/kg every 8–12 hours (adjust dose based on AUC-guided monitoring)	6 weeks
	Pediatric (3 months to <12 years): 60–80 mg/kg/24 hour IV in four equally divided doses (max: 3g/24 hour; adjust dose based on AUC-guided monitoring) *Pediatric (≥12 years):* 60–70 mg/kg/24 hour IV in three to four equally divided doses (max: 3g/24 hour; adjust dose based on AUC-guided monitoring)	
Oxacillin/Methicillin-Resistant Staphylococci		
Vancomycin[d,e,f]	See abovementioned dosing of vancomycin in patients with penicillin allergy without prosthetic material	6 weeks
With Prosthetic Valve or Other Prosthetic Material[g]		
Oxacillin/Methicillin-Resistant Staphylococci		
Vancomycin[d,e,f]	See abovementioned dosing of vancomycin in patients with penicillin allergy without prosthetic material	≥6 weeks
With rifampin[h]	*Adult*: 300 mg IV/PO every 8 hours	≥6 weeks
	Pediatric: 20 mg/kg/24 hour PO (max: 900 mg/24 hour) in three equally divided doses	
With gentamicin[d,g,i]	*Adult*: 3 mg/kg IV or IM in two or three equally divided doses	2 weeks
	Pediatric: 3 mg/kg IV or IM in three equally divided doses	
Oxacillin/Methicillin-Susceptible Staphylococci		
Nafcillin *or* oxacillin[j,k]	*Adult*: 2 g IV every 4 hours	≥6 weeks
	Pediatric: 150–200 mg/kg/24 hour IV (max: 12 g/24 hour) in four to six equally divided doses	
With rifampin[h]	See prosthetic valve dosing for rifampin earlier	≥6 weeks
With gentamicin[d,g,i]	See prosthetic valve dosing for gentamicin earlier	2 weeks

IM, intramuscular; IV, intravenous; PO, orally.

[a]Antibiotic doses should be modified appropriately for patients with impaired renal function. Shorter antibiotic courses have been effective in some intravenous drug users (IVDUs) with right-sided endocarditis caused by *Staphylococcus aureus.* (See text for comments on the use of daptomycin and rifampin.)

[b]The benefit of additional aminoglycoside has not been established. The risk of toxic reactions because of these agents is increased in patients older than 65 years of age or those with renal or eighth nerve impairment.

[c]There is potential cross-allergenicity between penicillins and cephalosporins. Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin.

[d]Dosing of aminoglycosides and vancomycin on a milligram per kilogram basis will give higher serum concentrations in obese than in lean patients.

[e]Targeted area under the 24-hour plasma concentration–time curve to the minimum inhibitory concentration (AUC_{24hr}/MIC) ratio should be in the range of 400 to 600 mg*hour/L. (See text for detailed discussion on AUC-guided monitoring for vancomycin.) Each vancomycin dose should be infused for 1 hour.

[f]Vancomycin and gentamicin doses must be modified appropriately in patients with renal failure.

[g]Serum concentration of gentamicin should be monitored, and the dose should be adjusted to obtain a peak level of ~3 μg/mL.

[h]Rifampin is recommended therapy for infections caused by coagulase-negative staphylococci. Its use in coagulase-positive staphylococcal infections is controversial. Rifampin increases the amount of warfarin sodium required for antithrombotic therapy.

[i]Use during initial 2 weeks. (See text on alternative aminoglycoside therapy for organisms resistant to gentamicin.)

[j]First-generation cephalosporins or vancomycin should be used in patients with penicillin allergy.

[k]Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin and those infected with oxacillin-resistant staphylococci.

Sources: Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435–1486. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of

Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864. doi:10.1093/ajhp/zxaa036.

The AHA currently recommends the use of triple-drug combination (vancomycin, gentamicin, and rifampin) therapy for the treatment of PVE caused by methicillin-resistant, coagulase-negative staphylococci (methicillin-resistant *Staphylococcus epidermidis* [MRSE]).[10] Rifampin plays a role in the sterilization of the prosthetic material.[10,53–55] When isolates of MRSE are resistant to all available aminoglycosides, aminoglycoside treatment should be omitted. A fluoroquinolone that is active against the isolate may substitute for the aminoglycoside in the three-drug regimen. In addition to medical therapy, most patients also require valve replacement surgery.[46,47,51] Although alternative agents such as quinupristin/dalfopristin, linezolid, daptomycin, telavancin, ceftaroline, dalbavancin, and oritavancin have shown potent in vitro activity against coagulase-negative staphylococci, clinical experience in the treatment of IE caused by these strains is lacking.[51,56,57]

STAPHYLOCOCCUS AUREUS ENDOCARDITIS

Intravenous Drug User Versus Nonintravenous Drug User

CASE 66-3

Question 1: T.J., a 36-year-old human immunodeficiency virus (HIV)-seropositive male with a long history of IV drug abuse, was admitted to the hospital 4 months after being released from the state prison. His chief symptoms included fever, night sweats, pleuritic chest pain, shortness of breath, dyspnea on exertion, and fatigue. Physical examination was remarkable for a temperature of 101.2 °F (38.44 °C), splenomegaly, and a pansystolic ejection murmur at the left sternal border, best heard during inspiration. The chest radiograph revealed diffuse nodular infiltrates. TTE finding was positive for a small vegetation on the tricuspid valve leaflet. Significant laboratory results included the following:

WBC count, 14,000/μL with 65% polys and 5% bands

CD4 cell count, 350/μL
Hgb, 13.1 g/dL
Hct, 39%
ESR, 55 mm/hour (Westergren)

IE was suspected. Six samples of blood culture results were positive for coagulase-positive, gram-positive cocci, later identified as methicillin-sensitive *Staphylococcus aureus* (MSSA).

How do the clinical presentation and prognosis of endocarditis in an IVDU differ from that of a non-IVDU? What impact does HIV infection have on the risk and outcomes of endocarditis in an IVDU?

The incidence rate of endocarditis among IVDUs increased from 48 per 10,000 in 2002 to 79 per 10,000 persons in 2016 in the United States, attributable in part to the opioid epidemic.[6] The presentation, pathophysiology, and prognosis of endocarditis in IVDUs differ from those in non-IVDUs.[1,58,59] *S. aureus* is 10-fold more likely than are other pathogens to cause infection in this population.[10] *S. aureus* is part of the normal skin flora and is introduced when the illicit drug is injected. Compared to non-IVDUs with *S. aureus* endocarditis, IVDUs with *S. aureus* endocarditis are significantly younger; have fewer underlying diseases and more right-sided (tricuspid) involvement (in contrast to the predominance of left-sided disease in non-IVDUs); are less likely to have heart failure or central nervous system complications; and exhibit fewer signs of peripheral involvement and have a lower incidence of death.[59] Among patients without history of IV drug use, MRSA was involved in one-third of a cohort of 424 patients with definite *S. aureus* IE. Clinical features that characterized MRSA IE were persistent bacteremia, chronic immunosuppressive therapy, health care–associated infection (HAI), a presumed intravascular device source, and diabetes mellitus.[9] Prevalence of HIV seropositivity may be 40% to 90% among IVDUs with IE.[58,60] HIV-related immunosuppression may be an independent risk factor for the development of endocarditis.[61]

Antimicrobial Therapy

METHICILLIN-SENSITIVE STAPHYLOCOCCUS AUREUS

Case 66-3, Question 2: What are the therapeutic options for treating *S. aureus* endocarditis in T.J.?

The susceptibility of *S. aureus* to methicillin is the major determinant of antibiotic selection to treat T.J.'s endocarditis. T.J. is infected with MSSA. Therapy of choice for methicillin-sensitive strains is a penicillinase-resistant penicillin, such as nafcillin or oxacillin (Table 66-4).[10] Penicillin G rarely is appropriate because nearly all isolates of *S. aureus* produce penicillinase. A 6-week course of therapy with high-dose (12 g/day) oxacillin is the therapy of choice.[62,63] Vancomycin may be less efficacious than is oxacillin as an antistaphylococcal agent.[10,62] IVDUs, for the reasons previously identified, have a higher response rate to appropriate therapy compared with non-IVDUs.

IVDUs with uncomplicated right-sided endocarditis caused by MSSA have been treated successfully with a 2-week course of combination therapy with a penicillinase-resistant penicillin and an aminoglycoside.[64–67] In one study, 47 of 50 patients (94%) were cured after treatment with the combination of IV nafcillin (1.5 g every 4 hours) and tobramycin (1 mg/kg every 8 hours) for a total of 2 weeks. Notably, two of three patients treated with vancomycin relapsed, resulting in early termination of this arm of the study. Thus, vancomycin should not be used as a substitute for nafcillin in this regimen. An abbreviated treatment course is possible in a defined group of IVDUs with right-sided endocarditis with these characteristics: (a) clinical and bacteriologic response within 96 hours of initiation of therapy; (b) no evidence of hemodynamic compromise, metastatic infection, or neurologic or systemic embolic complications at either the initiation or completion of 2 weeks of therapy; (c) no echocardiographically demonstrable vegetations >2 cm^3; (d) not infected with MRSA; and (e) not receiving antibiotics

other than penicillinase-resistant penicillins, first-generation cephalosporins, and glycopeptides.[10],[66] HIV-seropositive patients (CD4 counts >300 × 10^6 cells) with tricuspid valve involvement included in the abovementioned studies also responded favorably to these short-course regimens; thus, a short-course regimen is an option for T.J.[66]

Recent studies suggest that the addition of an aminoglycoside to the treatment regimen does not improve the overall response for patients who meet the abovementioned criteria for short-course therapy and is associated with increased toxicity. Therefore, the AHA guidelines no longer favor the antibiotic combination. Also, all patients receiving the short regimen should be carefully evaluated for evidence of continuing infection or complications before discontinuing therapy at the end of the 2-week treatment course; extension of therapy with a β-lactam agent to at least a 4- to 6-week duration is recommended with any evidence of active disease or complications. Although the response to antibiotic therapy has been shown to be similar between asymptomatic HIV-seropositive and HIV-seronegative IVDUs, short-course therapy should be avoided in more immunosuppressed individuals (CD4 cell counts <200 μL) until more definitive outcome data are available in this subgroup.[58]

Oral regimen

An oral treatment regimen consisting of ciprofloxacin (750 mg every 12 hours) plus rifampin (300 mg every 12 hours) for 4 weeks has also been evaluated in IVDUs with uncomplicated right-sided endocarditis. In one small, noncomparative study, 10 IVDUs were successfully treated with ciprofloxacin (300 mg IV every 12 hours for the first 7 days followed by 750 mg orally [PO] every 12 hours for the remaining 21 days) in combination with rifampin (300 mg PO every 12 hours for 28 days).[68],[69] In another prospective study, IVDUs were randomized to receive oral ciprofloxacin plus rifampin versus standard parenteral therapy for 28 days.[69],[70] One of 19 patients in the oral group versus 3 of 25 patients in the parenteral group failed treatment; notably, approximately half of the study patients in either

group had possible endocarditis. Given the small number of patients who completed treatment, the comparative effectiveness between the oral and parenteral regimens will need confirmation in larger trials.[68–70] In addition, fluoroquinolone and rifampin resistance in *S. aureus*, compliance issues, and therapeutic monitoring in the outpatient setting are of concern.[68–70]

Other oral combination regimens have recently been evaluated in a randomized, multicenter noninferiority trial in Denmark.[71] The Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis (POET) trial included 400 patients in stable condition with left-sided native and prosthetic valve IE due to *Streptococcus* spp. (*n* = 196), *E. faecalis* (*n* = 97), *S. aureus* (*n* = 87), or coagulase-negative staphylococci (*n* = 23). After receipt of standard IV treatment for at least 10 days and meeting criteria for clinical stability, patients were randomized to either continue with full IV treatment course (*n* = 199) or switch to an oral regimen (*n* = 201) consisting of two antibiotics from a different class and with moderate to high oral bioavailability. Clinical stability was defined as a temperature of <100.40 °F (<38 °C) for >48 hours, a decrease of C-reactive protein (CRP) to <25% of peak level or <20 mg/L, WBC count of <14,000/μL, and no sign of abscess or valve abnormalities requiring surgery seen on echocardiography. Patients were followed up until 6 months after completing their treatment to assess a composite end point of all-cause mortality, unplanned cardiac surgery, clinically evident embolic event, and relapse of bacteremia with the primary pathogen. The most common combination regimens were dicloxacillin 1 g PO four times daily plus rifampin 600 mg PO bid for *S. aureus*; amoxicillin 1 g PO four times daily plus moxifloxacin 400 mg PO once a day for *E. faecalis;* amoxicillin 1 g PO four times daily plus rifampin 600 mg PO bid for streptococci; and fusidic acid 750 mg PO bid plus linezolid 600 mg PO bid for coagulase-negative staphylococci. The primary composite outcome occurred in 12% of patients in the IV treatment group versus 9% of patients in the oral treatment group (odds ratio [OR] 0.72, 95% confidence interval [CI] [0.37–1.36]). A similar number of patients in each group had an unplanned cardiac surgery (3%), embolic event (1.5%), or relapse of bacteremia (2.5%).

Incidence of adverse events was similar in both groups. Notable limitations in this trial were that none of the patients had drug-resistant gram-positive cocci such as MRSA or vancomycin-resistant enterococci (VRE) as the causative pathogen, and only 20% of screened patients were included in the outcome analysis.[71] However, this study demonstrated that partial oral treatment in clinically stable patients with IE, with no signs of abscess or valve abnormalities, caused by susceptible streptococci, enterococci, and staphylococci was noninferior to full course of IV treatment.

Patients with penicillin allergy

Treatment of patients allergic to penicillin with *S. aureus* endocarditis is somewhat controversial. First-generation cephalosporins have been used with some success for the treatment of patients with mild penicillin allergy, but treatment failures with cefazolin are difficult to explain.[72] The stability of cefazolin when exposed to staphylococcal β-lactamase has been proposed as a mechanism for these failures.[73] Notably, staphylococci are capable of producing four β-lactamase (blaZ) subtypes A, B, C, and D, to which the stability of cefazolin varies.[74] These susceptibility differences are apparent on MIC testing only if a larger than usual inoculum is used (eg, $>10^6$ organisms).[73] It is possible that treatment failures with cefazolin are caused by a combination of the recalcitrant nature of the infection and the instability of cefazolin against a particular subtype of penicillinase produced by the staphylococcal strain, which is not readily detectable via routine MIC testing. For patients with endocarditis caused by *S. aureus* who have immediate-type hypersensitivity to penicillin, vancomycin or daptomycin may be used.[10]

Combination therapy

An enhanced response to combination therapy in the experimental animal model of MSSA endocarditis has prompted clinical trials to evaluate whether the addition of gentamicin to nafcillin confers any additional benefit. The combination of nafcillin and gentamicin resulted in more rapid clearing of organisms from the blood, but the

response rates were similar to that of patients treated with nafcillin alone.[62] As expected, the group receiving gentamicin had a higher incidence of nephrotoxicity. Thus, for the routine management of endocarditis caused by MSSA, the addition of a second drug does not appear to offer additional benefit when a penicillinase-resistant penicillin is used and is discouraged owing to the lack of clearly established efficacy and aminoglycoside toxicity (see Case 66-3, Question 2, previous discussion). For patients who remain bacteremic or who fail to improve clinically (usually non-IVDUs), imaging studies are often performed to identify metastatic sites of infection (ie, occult abscess) with possible need for surgical intervention.

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS: VANCOMYCIN

Case 66-3, Question 3: How would T.J.'s therapy differ if he were infected with MRSA?

S. aureus IE involving MRSA has become increasingly common and accounts for up to 40% of cases.[7–9] Patients infected with MRSA are more likely to have chronic comorbid conditions (eg, diabetes mellitus, hemodialysis dependency) and HAI (76% vs 37%). They also more likely have an indwelling intravascular catheter or hemodialysis fistula as the presumed source of infection when compared with patients infected with MSSA (60% vs 31%).[7–9] Persistent bacteremia was more common with MRSA IE than with MSSA. In a recent prospective observational study, in patients with *S. aureus* IE, the median duration of bacteremia was 5 days (interquartile range [IQR], 3–8) for MRSA versus 4 days (IQR, 2–5) for MSSA. In this study, each additional day of bacteremia increased the risk of mortality by 16%.[75]

MRSA infection is traditionally associated with health care contact in the nosocomial setting, but it is now becoming more prevalent in the community (community-associated methicillin-resistant

Staphylococcus aureus [CA-MRSA]), especially in young and otherwise healthy individuals without the traditional risk factors.[9],[75],[76] CA-MRSA strains are distinct from health care–associated strains in that some strains possess a distinct virulence gene encoding for Panton-Valentine leukocidin (PVL). This pore-forming toxin causes severe necrosis in polymorphonuclear neutrophil cells in a rabbit model and has been associated with invasive infections, including necrotizing pneumonia and skin abscesses.[77–83] Specifically, CA-MRSA PVL-producing strains causing IE have been reported.[84] Although PVL plays a role in the virulence of certain MRSA strains, subsequent reports have demonstrated that the presence of PVL was not associated with disease severity or clinical outcome in patients presenting with infections due to CA-MRSA PVL-producing strains.[85–87]

Treatment options

Vancomycin has been the accepted standard of treatment for MRSA endocarditis. Response to treatment, however, is slower than that with semisynthetic penicillins (eg, nafcillin) for MSSA endocarditis. The mean duration of bacteremia in patients with MSSA endocarditis reportedly is 3.4 days for nafcillin alone and 2.9 days for the combination of nafcillin and gentamicin.[65] In contrast, the median duration of bacteremia for MRSA endocarditis was 7 days for vancomycin alone. Failure rates of up to 40% may occur in patients even with right-sided involvement. Of great concern is the emergence of resistant strains of *S. aureus* after repeated and prolonged exposure to vancomycin therapy.[52]

Either vancomycin or daptomycin at 8 mg/kg IV once daily (up to 12 mg/kg/day) may be used to treat patients with MRSA endocarditis.[31] The AHA recommends daptomycin 8 mg/kg/dose. Vancomycin 15 to 20 mg/kg IV based on actual body weight every 8 to 12 hours for a total of 6 weeks is recommended for adults with normal renal function. Traditionally, for serious MRSA infections (eg, endocarditis, bacteremia, meningitis, osteomyelitis, and pneumonia), the ASHP-IDSA guidelines recommended a target trough of 15 to 20

µg/mL as a surrogate for the ratio of the area under the 24-hour plasma concentration–time curve to the MIC (AUC_{24hr}/MIC) for vancomycin.[10,31] However, recent evidence demonstrated that a single trough level was not an optimal surrogate for determining AUC_{24hr}/MIC because of significant interpatient variability. Thus, the 2020 ASHP-IDSA vancomycin guidelines no longer recommend trough-only monitoring and instead recommend AUC-guided dosing, targeting an AUC_{24hr}/MIC ratio of 400 to 600 mg*hour/L, assuming that the *S. aureus* isolate has an MIC of 1 ug/ml from broth microdilution testing.[23] This range is recommended to maximize efficacy and minimize the risk of nephrotoxicity. The data to support the minimum AUC_{24hr}/MIC threshold of 400 mg*hour/L are based on studies of *S. aureus* bacteremia and endocarditis; however, the minimum needed for other gram-positive cocci or other sources of infections has yet to be clearly defined. AUC-guided monitoring requires the use of a Bayesian software program or the collection of two vancomycin concentrations obtained near steady state, a peak concentration at 1 to 2 hours postinfusion and a trough concentration at the end of the same dosing interval to estimate the 24-hour AUC.[23,88] Both methods used to estimate the AUC_{24hr}/MIC have been shown to significantly decrease the risk of vancomycin-induced nephrotoxicity compared to trough-guided monitoring[23,89,90]; however, whether attainment of AUC_{24hr}/MIC >400 mg*hour/L improves clinical outcomes in *S. aureus* endocarditis has not yet been demonstrated in prospective clinical trials.[23,88]

Persistent bacteremia

Case 66-3, Question 4: T.J. has been treated with vancomycin 1 g IV every 12 hours for 5 days for his MRSA endocarditis but does not seem to be clinically improving. His blood culture results are still positive, and his WBC count remains elevated at 12,500/µL with 55% polys and 7% bands. He continues to have a low-grade fever since starting vancomycin. His vancomycin AUC_{24hr}/MIC ratio on the second day of therapy was 417 mg*hour/L. The infected MRSA strain had a vancomycin MIC of 1.5 µg/mL as determined by the

Epsilometer test (E-test). What factors may be contributing to T.J.'s poor response to treatment? What other therapeutic options are available for T.J.?

In a large multinational study of nearly 1800 patients with definite IE, persistent bacteremia, receipt of vancomycin, and health care contact were significantly more common in patients with MRSA IE from the United States compared with those from other geographic regions.[6] The authors speculated that the higher rates of persistent bacteremia in U.S. patients are attributable in part to the receipt of vancomycin therapy. Vancomycin MIC values for *S. aureus* have been increasing over the years.[91] In response to increasing reports of vancomycin clinical failure caused by MRSA strains with high MIC values, the vancomycin breakpoint for susceptibility was reduced from 4 to 2 μg/mL for *S. aureus* in 2005 per the Clinical and Laboratory Standards Institute.[92],[93] Previous data have suggested that higher clinical failure rates in MRSA bacteremia were seen in patients treated with vancomycin when the MRSA isolate had a vancomycin MIC of 1.5 or 2 μg/mL compared to patients infected with MRSA isolates with MIC of 1 μg/mL or less[25–28]; however, a meta-analysis of 38 studies that included >8000 patients found no significant difference in mortality compared to those with MIC <1.5 μg/mL.[29] Another prospective cohort study involving >400 patients with *S. aureus* bacteremia, including 188 patients with MRSA bacteremia investigated whether the MIC value was a determinant of clinical outcomes. In the subgroup analysis for MRSA bacteremia that compared MIC of 2 μg/mL with MIC of <2 μg/mL, a higher MIC value was not associated with the composite outcome of bacteremia recurrence, all-cause readmission, and death at 30 and 90 days. Results from this study provided further support that vancomycin MIC at the higher end of the susceptibility range is not a primary determinant of treatment failure and is not associated with worse outcomes.[30]

Widespread use of vancomycin has led to the emergence of glycopeptide-intermediate *Staphylococcus aureus* (GISA) or heteroresistant glycopeptide-intermediate *Staphylococcus aureus* (hGISA) strains.[52] Reduced susceptibility to glycopeptides results

from an increase in the production of peptidoglycan precursors, leading to a thickened bacterial cell wall and decreased penetration of glycopeptides into the bacterial cell membrane.[94] An in vitro pharmacodynamic model demonstrated that vancomycin activity is also reduced in the presence of high inoculum.[95] In the absence of vancomycin, hGISA strains may revert to glycopeptide susceptibility, making it difficult to detect these strains in vitro. As such, several investigators have found that hGISA strains have an MIC range that overlaps with the currently defined susceptible range and that the prevalence among hospitalized patients is increasing.[96–98] Routine susceptibility testing methods performed in the clinical laboratory are unreliable in detecting MRSA strains with hGISA phenotype.[99] MIC determined by E-test best predicts treatment outcome with vancomycin.[23],[31],[100]

Despite attaining a goal AUC_{24hr}/MIC >400 mg*hour/L, T.J. fails to clinically improve and has persistent bacteremia. It is possible that T.J. is infected with an heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA) strain. IE is an infection with high bacterial load or large vegetation size. T.J. may have a vancomycin heteroresistant subpopulation that was undetected by microbiology laboratory and selected for in the setting of multiple prolonged courses of vancomycin treatment[101],[102]; thus, a change in therapy is warranted.

Daptomycin (Cubicin®) is a cyclic lipopeptide approved for the treatment of *S. aureus* bacteremia and right-sided endocarditis. In vivo, it has a wide spectrum of activity against gram-positive bacteria, including *S. aureus* (including MRSA), *E. faecalis*, *E. faecium*, streptococci, and most other species of aerobic and anaerobic gram-positive bacteria. It was approved for the treatment of *S. aureus* bacteremia and endocarditis in a noninferiority study in patients receiving daptomycin or standard therapy consisting of an antistaphylococcal penicillin or vancomycin in addition to low-dose gentamicin.[103] Successful outcome was seen in 46% (41 of 90) of patients who had presumed or definite staphylococcal endocarditis as their baseline diagnosis. Of those, MRSA endocarditis was

successfully treated in 42% (15 of 36) of cases. In patients with confirmed uncomplicated and complicated right-sided endocarditis, treatment success was similar between the daptomycin group (8 of 18) and the group receiving standard therapy (7 of 16) at 44%.

The use of daptomycin for the treatment of left-sided endocarditis is not established because only nine patients were treated and only one had treatment success. Daptomycin at >8 mg/kg/day for a total duration of 6 weeks should be used for the treatment of endocarditis. Considering its concentration-dependent effects, some recommended higher doses (up to 12 mg/kg/day) appear to be safe.[31],[104],[105] High-dose daptomycin should be considered in patients who have previously failed vancomycin treatment, who are severely ill, or who are infected with an isolate with elevated vancomycin MICs. Daptomycin should be dosed based on total body weight because patients with obesity have a larger volume of distribution as well as increased clearance compared with the nonobese population.[106] Creatine kinase levels should be obtained at baseline and weekly to monitor for elevations, and more frequently in patients who may be at risk for developing skeletal muscle dysfunction.[107] High-dose daptomycin at 8 to 12 mg/kg daily should be considered as an alternative therapy in T.J. Emergence of cross-resistance to daptomycin after vancomycin exposure has been documented.[108],[109] Similar to a thickened cell wall contributing to decreased susceptibility to vancomycin, the same mechanism is thought to contribute to daptomycin resistance in *S. aureus*.[110] Therefore, it is important to confirm MRSA susceptibility to daptomycin when used in a patient who had prior vancomycin exposure.

A potential treatment option for T.J., if his infected MRSA strain demonstrates reduced susceptibility to daptomycin, is the addition of an antistaphylococcal β-lactam agent such as nafcillin, oxacillin, or ceftaroline to daptomycin.[111],[112] Combining daptomycin with a β-lactam may enhance the binding effect of daptomycin, owing to the β-lactam altering the surface charge of MRSA.[111],[113] In a recent prospective study of 40 patients with MRSA bacteremia, the patients were given a combination of daptomycin plus ceftaroline versus vancomycin monotherapy, although it is unclear whether source

control was similarly performed in both groups. In a subgroup analysis of the seven patients with proven or suspected MRSA endocarditis, those who received vancomycin monotherapy had a significantly increased risk of mortality compared to those in the combination therapy group.[114] Although the results appeared promising, additional data involving a larger number of patients are needed before the combination can be recommended for routine use.

Addition of rifampin to standard treatment is not recommended for native valve endocarditis without secondary complications (eg, prosthetic joint, central nervous system involvement) given reports of worse outcomes and emerging resistance compared to rifampin-free regimens.[55],[115]

Once daptomycin therapy is initiated, continued monitoring of clinical response and organism susceptibility to daptomycin is warranted because resistance development has been reported during prolonged therapy.[116–118] Daptomycin MIC increase during therapy for *S. aureus* (especially MRSA) endocarditis was demonstrated in six patients. Baseline MIC increased from 0.25 to 2 μg/mL in five isolates, and from 0.5 to 4 μg/mL in one isolate.[117]

Linezolid (Zyvox®), an oxazolidinone, is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of IE, but it has been used in cases of treatment failures, intolerability to standard therapy, or in infections with multidrug-resistant gram-positive cocci.[119] In a review article that included 33 case reports of IE treated with linezolid, 63.6% of patients had successful outcomes at the end of the follow-up period.[119] MRSA and vancomycin-intermediate *S. aureus* were the most common pathogens, accounting for 24% and 30% of cases, respectively. Failure with linezolid treatment was documented in seven cases, including four deaths attributed to endocarditis and three owing to persistent positive blood cultures. Thrombocytopenia was the most common adverse effect, occurring in eight of nine patients. In a compassionate-use program, linezolid achieved 50% clinical and microbiologic cure rates at 6-month follow-up in 32 patients with definite IE; MRSA was the causative agent in seven of those

patients. The most common adverse events reported in this group were gastrointestinal system effects and thrombocytopenia, each occurring in 15% of patients.[120] The degree of thrombocytopenia associated with linezolid correlates with the extent of drug exposure, as measured by area under the concentration curve and duration of treatment.[121] Of note, treatment failure with linezolid for MRSA endocarditis caused by persistent bacteremia has been described in two patients and in one patient with relapse of infection.[122],[123] Thus, additional efficacy data are needed before linezolid can be recommended for the treatment of IE caused by MRSA. Tedizolid (Sivextro®), a novel oxazolidinone, was shown to have only moderate bactericidal activity in vivo in a rabbit model of MRSA endocarditis and was less active than either vancomycin or daptomycin.[124] At this time, tedizolid cannot be recommended as a primary agent in the treatment of endocarditis.

ENTEROCOCCAL ENDOCARDITIS

Antimicrobial Therapy

ANTIBIOTIC SYNERGY

CASE 66-4

QUESTION 1: G.S., a 35-year-old female, has had anorexia, weight loss, and fever for the past 2 months. Her medical history is significant for an aortic aneurysm with insufficiency that resulted in an aortic valve replacement (porcine) 3 years before admission. Approximately 2 months before admission, G.S. had a cesarean section followed by tubal ligation. She did not receive antibiotic prophylaxis for either procedure. Physical examination revealed a thin female (60 inches [152.40 cm], 105.82 pounds [48 kg]) in no acute distress with evidence of a systolic heart murmur, splinter hemorrhages, and petechiae on her soft palate. Her temperature was 100.2 °F (37.88 °C). Her WBC count was 14,000/μL with a slight left shift; all other laboratory results were within normal limits. She was not taking any medications, and she has a documented allergy to penicillin (rash, urticaria, and wheezing). The working clinical diagnosis was

probable bacterial endocarditis, which was confirmed when four sets of blood cultures grew gram-positive cocci. Antibiotic therapy with gentamicin (50 mg IV every 8 hours) and vancomycin (1000 mg IV every 12 hours) was initiated. Biochemical testing subsequently identified the organism as *E. faecalis*, highly resistant to streptomycin (MIC >2000 µg/mL).

Why were two antibiotics prescribed for the treatment of enterococcal endocarditis in G.S.?

Enterococci, unlike streptococci, are inhibited but not killed by penicillin or vancomycin alone.[125,126] Relapse rates are unacceptably high if penicillin is used alone for the treatment of enterococcal endocarditis.[10,125,130] The synergistic combination of penicillin (or ampicillin, or piperacillin/tazobactam) or vancomycin with an aminoglycoside is required to produce the desired bactericidal effect.[127,128] The mechanism of synergy against enterococci is explained by an increased cellular uptake of the aminoglycoside with agents that inhibit cell wall synthesis (eg, β-lactams and vancomycin).[127] Numerous in vivo and clinical studies have confirmed the in vitro synergy for penicillin in combination with streptomycin or gentamicin for enterococcal endocarditis.[21,125–127] Because G.S. is allergic to penicillin, vancomycin was prescribed with an aminoglycoside.

Streptomycin resistance

Of the aminoglycosides, gentamicin and streptomycin are often tested with penicillin (or ampicillin) for synergistic bactericidal activity. As many as 55% of all enterococcal blood isolates are highly resistant to streptomycin (MIC >2000 µg/mL), and the combination of streptomycin with penicillin is not synergistic for those isolates. In contrast, gentamicin in combination with penicillin, ampicillin, or vancomycin is synergistic for most blood isolates of enterococci, regardless of their susceptibility to streptomycin.[1,125,128] In addition, ototoxicity in the form of vestibular dysfunction secondary to streptomycin therapy occurs in nearly 30% of patients in the treatment of enterococcal endocarditis and is most often irreversible. High peak concentrations and prolonged drug therapy have been

associated with ototoxicity, but laboratory assays for streptomycin levels are not readily available. Therefore, gentamicin in combination with penicillin (or ampicillin) or vancomycin is recommended by most authorities for the treatment of aminoglycoside-susceptible and, in particular, streptomycin-resistant enterococcal endocarditis, as it was for G.S.[10] Of note, other aminoglycosides cannot be used to substitute for gentamicin or streptomycin because of the uncertain correlation between in vitro synergy and in vivo efficacy.[10] **Table 66-5** lists the suggested regimens for the treatment of enterococcal endocarditis.

Table 66-5
Therapy for Endocarditis Caused by Enterococci (or Streptococci Viridans With an MIC $0.5 mg/mL)

Antibiotic[a,b]	Dose and Route	Duration
Patients with Nonpenicillin Allergy		
Penicillin G	*Adult*: 18–30 million units/24 hour IV given continuously or in six equally divided doses	4–6 weeks
	Pediatric: 300,000 units/kg/24 hour IV (max: 30 million units/24 hour) given continuously or in four to six equally divided doses	4–6 weeks
With gentamicin[c,d]	*Adult*: 1 mg/kg IM or IV every 8 hours	4–6 weeks
	Pediatric: 1 mg/kg IM or IV every 8 hours	4–6 weeks
Or		
Ampicillin	*Adult*: 12 g/24 hour IV given continuously or in six equally divided doses	4–6 weeks
	Pediatric: 300 mg/kg/24 hour IV (max: 12 g/24 hour) in four to six equally divided doses	4–6 weeks
With gentamicin[c,d] *or*	See nonpenicillin-allergic dosing for gentamicin earlier	4–6 weeks
With ceftriaxone	4 g/24 hour IV in two equally divided doses	6 weeks

Patients with Penicillin Allergye		
Vancomycin[f]	*Adult*: 15–20 mg/kg every 8–12 hours (adjust dose based on AUC-guided monitoring)	6 weeks
	Pediatric (3 months to <12 years): 60 to 80 mg/kg/24 hour IV in four equally divided doses (max: 3 g/24 hour; adjust dose based on AUC-guided monitoring) *Pediatric (≥12 years):* 60–70 mg/kg/24 hour IV in three to four equally divided doses (max: 3 g/24 hour; adjust dose based on AUC-guided monitoring)	6 weeks
With gentamicin[c,d]	*Adult*: 1 mg/kg IM or IV (max: 80 mg) every 8 hours	6 weeks
	Pediatric: 1 mg/kg IM or IV (max: 80 mg) every 8 hours	6 weeks

AUC, area under the curve; IM, intramuscular; IV, intravenous; MIC, minimum inhibitory concentration.

[a]Antibiotic doses should be modified appropriately in patients with impaired renal function.

[b]Enterococci should be tested for high-level resistance (gentamicin: MIC ≥500 µg/mL).

[c]Serum concentration of gentamicin should be monitored and dosage adjusted to obtain a peak level of ~3 µg/mL. (For shorter course gentamicin therapy for enterococcal endocarditis, see comment in text.)

[d]Dosing of aminoglycosides and vancomycin on a milligram per kilogram basis gives higher serum concentrations in obese than in lean patients.

[e]Desensitization should be considered; cephalosporins are *not* satisfactory alternatives.

[f]Targeted area under the 24-hour plasma concentration–time curve to the minimum inhibitory concentration (AUC_{24hr}/MIC) ratio should be in the range of 400 to 600 mg*hour/L. (See text for detailed discussion on AUC-guided monitoring for vancomycin.) Each dose should be infused over 1 hour; 6 weeks of vancomycin therapy recommended because of decreased activity against enterococci.

Sources: Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435–1486. doi:10.1161/cir.0000000000000296; Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society,

and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864. doi:10.1093/ajhp/zxaa036.

Dual β-lactam combination

In light of the increasing prevalence of enterococci with high-level aminoglycoside resistance, the potential synergistic interaction between ampicillin or amoxicillin and a third-generation cephalosporin was explored in vitro and in experimental models of IE.[129] A bactericidal synergistic effect was shown between amoxicillin and cefotaxime against 50 strains of *E. faecalis*. Amoxicillin MIC decreased from 0.25 to 1 µg/mL to 0.01 to 0.25 µg/mL for 48 of 50 strains tested.[130] In addition, Brandt et al[131] demonstrated a synergistic bactericidal effect for amoxicillin in combination with imipenem against vancomycin–aminoglycoside-resistant *E. faecium* strains. The authors speculated that saturation of different penicillin-binding proteins by different β-lactam agents may be the underlying mechanism for the synergy observed. In an observational, nonrandomized multicenter study, 159 patients were treated with ampicillin (2 g IV every 4 hours) plus ceftriaxone (2 g IV every 12 hours) and 87 were treated with ampicillin plus gentamicin.[132] There were no differences in mortality (while on antibiotics and at 3-month follow-up), treatment failure, and relapses. In a subsequent retrospective study of 85 patients with *E. faecalis* IE, 18 patients were treated with the ceftriaxone-based combination and 67 patients with the gentamicin-based combination. The investigators found no significant difference in 1-year mortality or IE relapse between the ceftriaxone and gentamicin groups. One case of relapse occurred in each group after completion of treatment, 37 days and 210 days for the ceftriaxone- and gentamicin-based combination, respectively. Although this was a small retrospective study, it demonstrated results comparable to previous studies with regard to mortality and relapse of IE.[133] The 2015 AHA guidelines recommend double β-lactam therapy with ampicillin and ceftriaxone as a reasonable option for infections caused by aminoglycoside-resistant *E. faecalis* strains.

GENTAMICIN

Dosing

Case 66-4, Question 2: What is the optimal dosage of gentamicin for G.S.?

Because patients with enterococcal endocarditis require prolonged therapy with aminoglycosides, the optimal serum concentration should minimize toxicity without jeopardizing clinical cure. Early in vitro data indicated that the bactericidal activity of gentamicin against enterococci was not significantly different between peak concentrations of 5 and 3 μg/L; however, the differences between 3 and 1 μg/mL were significant.[129] Animal models of endocarditis show discordant results in bacterial counts per gram of vegetation in animals on low-dose versus high-dose aminoglycosides.[134,135] In experimental enterococcal endocarditis, multiple daily dosing is more effective than is single daily dosing in reducing bacterial titers in vegetations.[136–138] In contrast, VGS endocarditis can be managed with single daily dosing[43] (see Case 66-1, Question 4). Thus, single daily dosing of aminoglycosides is not recommended for the treatment of enterococcal endocarditis at this time.

The only study comparing high-dose (>3 mg/kg/day) and low-dose (<3 mg/kg/day) gentamicin with penicillin in humans with enterococcal endocarditis evaluated 56 patients during a 12-year period (36 with streptomycin-susceptible and 20 with streptomycin-resistant infections).[139] The relapse rate of patients infected with streptomycin-resistant organisms (n = 20) was not significantly different between the high- and low-dose treatment groups (n = 10 each). Furthermore, patients who received the higher doses of gentamicin experienced a greater prevalence of nephrotoxicity (10 of 10 vs 2 of 10; $P < .001$). Mean peak and trough concentrations of gentamicin in patients who received the high doses were 5 and 2.1 μg/mL, respectively; corresponding levels for patients receiving the low-dose regimen were 3.1 and 1 μg/mL.

Given the available data, it would be reasonable to start G.S. on a gentamicin dosage of 1 mg/kg every 8 hours (assuming her renal

function is normal) and to maintain peak concentrations of 3 to 5 μg/mL and trough concentrations of <1 μg/mL.

In combination with vancomycin

Case 66-4, Question 3: Why was vancomycin used in combination with gentamicin in G.S.? Is this combination effective against enterococci?

G.S. has a history of penicillin allergy. Most clinicians favor a combination of vancomycin and gentamicin for patients allergic to penicillin with enterococcal endocarditis.[10,125,139] The combination of vancomycin and gentamicin demonstrates bactericidal synergy for about 95% of enterococci strains. Because G.S. has PVE, she should receive ~15 to 20 mg/kg IV every 8 to 12 hours of vancomycin in combination with gentamicin (3 mg/kg/day) in divided doses. Serum concentrations of vancomycin and gentamicin should be monitored as previously discussed.

DURATION OF THERAPY

Case 66-4, Question 4: For how long should G.S. be treated?

Historically, enterococcal endocarditis has been treated with penicillin plus an aminoglycoside for 6 weeks, with an overall cure rate of about 85%.[10] Four weeks of therapy is probably adequate for most patients with enterococcal endocarditis.[10,139,140] One study evaluated the efficacy of a treatment regimen involving shorter course aminoglycoside therapy (median of 15 days) in combination with a cell wall–active agent for a median of 42 days in patients with PVE and native valve enterococcal endocarditis.[140] Clinical cure was observed in 75 of 93 (81%) patients overall, 78% of patients with PVE, and 82% of patients with native valves. Among those who had a clinical cure, 52% received a β-lactam, 12% received vancomycin, and 36% received a combination of both. Ampicillin was given in 88% of patients receiving a β-lactam. The causative organism was

E. faecalis in 78 patients and *E. faecium* in 5 patients. Clinical success was also achieved in all eight patients with native valve IE who received vancomycin (50%), ampicillin (25%), or a combination of both (25%) without synergistic aminoglycoside therapy.[140]

Patients with complicated courses should receive 6 weeks of therapy, including patients infected with streptomycin-resistant organisms (such as G.S.), those who have had symptoms for >3 months before the initiation of antibiotics, and patients with PVE (such as G.S.).[10],[17] Some clinicians recommend 6 weeks of therapy for all patients in whom the duration of illness cannot be firmly established (eg, many patients who present with subacute disease).

CASE 66-4, QUESTION 5: How do enterococci develop resistance to vancomycin? What are the therapeutic implications if G.S. is infected with glycopeptide-resistant enterococci?

GLYCOPEPTIDE RESISTANCE IN ENTEROCOCCI

VRE, particularly *E. faecium,* have emerged in the United States since 1987.[141],[142] The increased use of vancomycin since the mid-1980s has coincided with the increased resistance to this class of antibiotic. More recently, in a 2014 review of HAIs that included 4000 acute care hospitals in the United States, ~30% of enterococci were reported as vancomycin resistant.[143]

Although *E. faecalis* is responsible for 80% to 90% of infections caused by enterococci, *E. faecium* is more likely to exhibit resistance to glycopeptides compared with *E. faecalis*; >95% of VRE recovered in the United States are *E. faecium.* Glycopeptide-resistant enterococci synthesize abnormal peptidoglycan precursors that lower the binding affinity of glycopeptides to peptidoglycans.[140] VRE can be broadly classified into three separate phenotypes (A, B, and C) based on three structurally different genes and gene products (eg, altered ligases).[140] Most (~70%) of resistant enterococci are of the VanA phenotype, which are resistant to high levels of vancomycin (MIC >256 μg/mL). Expression of resistance is inducible, usually plasmid mediated, and transferable to other

organisms via conjugation. The VanB strains exhibit moderate vancomycin resistance (MIC 16–64 µg/mL), and the VanC strains are the least resistant (vancomycin MIC 8–16 µg/mL), because of chromosomal-mediated constitutive expression (eg, not inducible as are VanA and VanB); however, VanC isolates usually are associated with the much less common *E. gallinarum* and *E. casseliflavus* infections.

Vancomycin, extended-spectrum cephalosporins, and drugs with potent anti-anaerobic activity are risk factors for VRE.[140,144] Few therapeutic alternatives exist for VRE, and synergistic combinations are required for bactericidal activity and clinical cure in endocarditis. The treatment of choice is unknown, and practitioners must make decisions using the available data from in vitro synergy studies, experimental models of endocarditis, and scattered case reports. Of additional concern, glycopeptide-resistant isolates often exhibit concomitant high-level resistance to aminoglycosides and β-lactams (eg, ampicillin, penicillin) secondary to either β-lactamase production or alteration in the target penicillin-binding proteins. Several antibiotic combinations appear promising in vitro and in preliminary animal models of endocarditis, but few data are currently available in humans. Combination therapy with daptomycin plus ceftaroline or ampicillin have demonstrated successful synergy against VRE endocarditis in vitro via enhancement of the peptide cathelicidin LL37 activity, thereby increasing daptomycin surface binding to VRE.[145–147]

Streptogramin and oxazolidinone

Quinupristin/dalfopristin (Synercid®) and linezolid (Zyvox®) are two agents with activity and proven efficacy against some infections caused by VRE. Quinupristin/dalfopristin received accelerated approval by the FDA in late 1999 specifically for the treatment of vancomycin-resistant *E. faecium* bacteremia. However, in 2010, with other therapies available for the treatment of VRE, this FDA-labeled indication was removed. The fixed product is generally bactericidal against susceptible streptococci and staphylococci (including

methicillin-resistant strains), but it is bacteriostatic against *E. faecium.*

Linezolid has bacteriostatic activity against enterococci, including vancomycin-resistant *E. faecium* and *E. faecalis.* It is also active against other gram-positive cocci, including *S. pneumoniae* and methicillin-resistant staphylococci.[147] Vancomycin-resistant *E. faecium* isolates resistant to linezolid have been isolated.[148],[149] Treatment experience with linezolid under the compassionate-use protocol reported clinical and microbiologic cure rates of 50% at 6-month follow-up for patients with endocarditis. Vancomycin-resistant *E. faecium* was the causative organism for 19 of the 32 patients treated.[141] Common adverse effects associated with linezolid include nausea, headache, diarrhea, rash, and altered taste. Of greater concern is its potential to cause myelosuppression. Thrombocytopenia, leukopenia, anemia, and pancytopenia have all been reported. Up to 30% of treated patients experience thrombocytopenia (platelet counts <100,000 platelets/μL).[147] Linezolid given orally or via enteral feedings is completely bioavailable.[150] A dosage of 600 mg IV or orally twice daily for a duration >6 weeks is recommended for adults with IE caused by *Enterococcus* spp. strains resistant to penicillin, aminoglycosides, and vancomycin.[10] However, in a retrospective study of >600 patients with VRE bloodstream infections, including 39 patients with IE, linezolid therapy compared to daptomycin was associated with worse outcomes such as higher risk of treatment failure (adjusted relative risk [RR] 1.15, 95% CI [1.02–1.30]) and 30-day mortality (RR 1.17, 95% CI [1.04–1.32]).[151]

Daptomycin

Daptomycin has demonstrated activity against enterococci in vitro, with an MIC range of 0.25 to 4 μg/mL and MIC_{90} of 4 μg/mL for 219 vancomycin-resistant *E. faecium* isolates from the United States. For 40 vancomycin-resistant *E. faecalis* isolates, the MIC range was 0.015 to 2 μg/mL, with an MIC_{90} of 2 μg/mL. Of concern is the emergence of daptomycin resistance during therapy for VRE

infections.[152–154] In a patient with vancomycin-resistant *E. faecium* pyelonephritis, the initial isolate had an MIC of 2 µg/mL which increased to 32 µg/mL after 17 days of treatment.[155] There is a lack of clinical evidence to support the use of daptomycin monotherapy for multidrug-resistant enterococcal endocarditis. If daptomycin monotherapy is chosen, a higher dose of 10–12 mg/kg/day is recommended. Combination therapy with a higher dose of daptomycin plus ampicillin, ceftaroline, gentamicin, rifampin, or tigecycline can also be considered.[10]

FUNGAL ENDOCARDITIS CAUSED BY *CANDIDA ALBICANS*

Prognosis and Treatment

CASE 66-5

Question 1: B.G., a 35-year-old male heroin addict, was admitted to the hospital with pleuritic chest pain and dyspnea on exertion. Physical examination revealed a cachectic male with a temperature of 104 °F (40 °C), a diastolic regurgitant heart murmur heard loudest during inspiration, splenomegaly, and pharyngeal petechiae. On the chest radiograph, several pulmonary infiltrates with cavitation were evident. UA was significant for microscopic hematuria and RBC casts. A TEE demonstrated vegetations on both the tricuspid and aortic heart valves. B.G. had evidence of moderate heart failure, although his hemodynamic status at that time was "stable." Six sets of blood cultures were drawn over the course of 2 days, and broad-spectrum empiric coverage consisting of vancomycin, gentamicin, and ceftazidime was initiated. Two days later, two of the cultures grew *Candida albicans*, and a diagnosis of fungal endocarditis was established.

What is B.G.'s prognosis, and how should his fungal endocarditis be treated?

Fungal endocarditis is a rare but life-threatening infection that is difficult to diagnose and even more difficult to treat.[1] Most cases are caused by *Candida* and *Aspergillus* species. Fungal endocarditis

occurs primarily in IV drug users, patients with prosthetic heart valves, immunocompromised patients, those with IV catheters, or patients receiving broad-spectrum antibiotics.[156–159]

Management of fungal endocarditis generally requires early valve replacement and aggressive fungicidal therapy with liposomal amphotericin B (3–5 mg/kg IV daily) with or without 5-flucytosine (5-FC) (25 mg/kg orally qid), or monotherapy with a high-dose echinocandin (micafungin 150 mg IV daily, caspofungin 150 mg IV daily, or anidulafungin 200 mg IV daily).[160]

These antifungal agents should be prescribed for B.G., and his broad-spectrum antibiotic should be discontinued. B.G.'s clinical presentation and chest radiograph indicate that fragments of vegetation have already embolized to his lungs and possibly to other vital organs (eg, spleen, kidneys). Because of the morbidity and mortality associated with major emboli and valvular insufficiency, B.G. should undergo surgery within 48 to 72 hours of starting antifungal therapy. The prognosis for B.G. is dismal even with proper medical and surgical treatment. In a series analyzing 270 cases of fungal IE occurring during a 30-year period, mortality for those who received combined medical and surgical management was 45%, compared with 64% for those who received antifungal therapy alone.[156] Despite initial response to treatment, the rate of relapse is high (30%–40%), and relapse can occur up to 9 years after the initial episode of infection.[156–159] Most deaths in IVDUs with endocarditis are secondary to heart failure, a finding already evident in B.G.[1] In addition, replacement of a heart valve for fungal endocarditis in a heroin addict carries a significant risk of late morbidity and mortality.[156]

COMBINATION THERAPY WITH 5-FLUCYTOSINE AND AMPHOTERICIN B

Case 66-5, Question 2: Why is it important to treat B.G.'s fungal endocarditis with the combination of 5-FC and lipid-based amphotericin B? What is the optimal duration of therapy?

The poor prognosis associated with fungal endocarditis warrants the administration of 5-FC in combination with amphotericin B, despite its potential for causing bone marrow suppression and hepatotoxicity.[156] The vegetations from B.G.'s tricuspid or aortic heart valves already have broken off and caused pulmonary cavitation and, possibly, splenomegaly. His clinical presentation is consistent with a potentially fatal outcome; therefore, his blood isolates should be tested for in vitro susceptibility to amphotericin, 5-FC, and azoles. Fungi resistant to 5-FC alone may still be susceptible to the synergistic effect of the 5-FC–amphotericin B combination.[161] If the organism is resistant to 5-FC, in vitro synergy testing between these two antifungals should be performed or therapy with an echinocandin is warranted. The optimal dose and duration of antifungal therapy for fungal endocarditis have not been determined by clinical studies; however, postoperative treatment with liposomal amphotericin B (3–5 mg/kg IV daily) and 5-FC (25 mg/kg orally qid) for a minimum of 6 weeks is recommended.[160,162]

In patients with fungal PVE, some experts advocate secondary prophylaxis for a minimum of 2 years or lifelong suppressive treatment with an oral antifungal agent for nonsurgical candidates in light of the high rates of relapse.[1,156,158,161–164] Nephrotoxicity caused by amphotericin B is often a serious dose-limiting factor to completion of therapy, particularly in patients who require a prolonged treatment course. Renal dysfunction secondary to the conventional formulation of amphotericin B may stabilize or improve with the switch to lipid-formulated amphotericin B products (eg, Abelcet®, AmBisome®).[165] In addition, the lipid formulation appears more potent against *Candida* biofilm in vitro.[166,167]

ALTERNATIVE ANTIFUNGALS

Case 66-5, Question 3: If B.G. experiences significant toxicities because of prolonged combination treatment with amphotericin and 5-FC, what alternative antifungal agent(s) can be used to treat his fungal endocarditis?

Alternative antifungal agents, including echinocandins and azoles, are potential options in patients who experience significant renal toxicities. Echinocandins are fungicidal against most *Candida* species, including those in biofilms. A limited, but growing, number of case reports and small observational studies describe successful outcomes with use of the echinocandins in patients with *Candida* IE. An echinocandin-based treatment with caspofungin, micafungin, or anidulafungin was found to be as effective and with similar mortality rate as an amphotericin-based regimen.[168–171]

Another alternative is fluconazole (Diflucan®), a triazole compound that is active against *Candida* species, particularly *C. albicans* and *C. parapsilosis.* It also has a favorable toxicity profile compared with amphotericin and 5-FC.[172] Successful outcome with fluconazole treatment of fungal endocarditis in humans has been described in only a few case reports.[173–176] Patients with various *Candida* species were treated with 200 to 600 mg of fluconazole daily for 45 days to 6 months or until death. Fluconazole therapy reduced or completely removed all cardiac vegetations and resolved clinical symptoms. Because of the lack of adequate clinical experience, however, the use of fluconazole in treating fungal endocarditis cannot be advocated except in patients who require lifelong therapy because of the following situations: (a) The patient is a poor surgical candidate, (b) the patient has relapsed at least once since the initial infection episode, or (c) the patient has PVE.

Gram-Negative Bacillary Endocarditis Caused by *Pseudomonas aeruginosa*

Risk Factors

Case 66-5, Question 4: Fourteen months after completing his course of antifungal therapy, B.G. was readmitted to the hospital with a 48-hour history of fever, shaking chills, rigors, and night sweats. His vital signs at that time were

blood pressure, 100/60 mm Hg; pulse, 120 beats/minute; respirations, 24/minute; and temperature, 103.70 °F (39.83 °C). A new-onset systolic murmur was noted on auscultation. Two-dimensional echocardiography revealed two small vegetations on the prosthetic valve. Empiric therapy consisting of amphotericin B, 5-FC, vancomycin, and gentamicin was initiated. Three blood cultures drawn on the day of admission had positive findings for *P. aeruginosa* with the following antibiotic susceptibilities: gentamicin (8 µg/mL), tobramycin (2 µg/mL), piperacillin–tazobactam (16 µg/mL), and ceftazidime (2 µg/mL). A presumptive diagnosis of PVE caused by *P. aeruginosa* was made. Was the finding of *Pseudomonas* expected in B.G.?

Gram-negative endocarditis is commonly associated with health care exposure, especially in patients with prosthetic heart valves, and less commonly now in IVDUs.[10] Most gram-negative endocarditis cases are caused by *Pseudomonas* species, *S. marcescens*, and *Enterobacter* species, although numerous other gram-negative organisms have been known to cause endocarditis.[177–180]

Antimicrobial Therapy

Case 66-5, Question 5: How should B.G.'s gram-negative endocarditis be treated and monitored?

The previous empirical antimicrobials should be discontinued because *P. aeruginosa* has been cultured from B.G.'s blood. A bactericidal combination of antibiotics usually is required to provide in vivo synergy and to prevent resistant subpopulations from emerging during therapy.[1,181] Endocarditis caused by *P. aeruginosa* (as in B.G.) should be treated for at least 6 weeks with a combination of an aminoglycoside and an antipseudomonal penicillin (piperacillin–tazobactam) or cephalosporin (eg, ceftazidime).[1,10,180,182–184] B.G., therefore, should be treated with ceftazidime (2 g IV every 8 hours) with concurrent high-dose tobramycin (5–7 mg/kg IV every 24 hours). Aminoglycosides (tobramycin or gentamicin) at high-dose extended interval should

achieve peak and trough serum concentrations of 15 to 20 μg/mL and <2 μg/mL, respectively, to ensure maximum efficacy, in conjunction with surgical excision of the infected valve.[1,10]

There is very limited clinical data regarding the use of other antipseudomonal antibiotics such as imipenem, meropenem, aztreonam, and ciprofloxacin in the treatment of endocarditis.[185–188] Newer β-lactam and β-lactamase combinations (eg, ceftolozane/tazobactam [Zerbaxa®], ceftazidime/avibactam [Avycaz®]) meropenem/vaborbactam [Vabomere®], imipenem-cilastatin/relebactam [Recarbrio®]) as well as cefiderocol (Fetroja®) may be considered as alternative treatment options for multidrug-resistant *Pseudomonas* infections based on documented in vitro susceptibility. However, their efficacy for the treatment of endocarditis has not yet been demonstrated.

CULTURE-NEGATIVE ENDOCARDITIS

CASE 66-5, QUESTION 6: B.G.'s history, clinical presentation, and imaging studies are strongly suggestive of IE. If his blood culture results had been negative after 48 hours of incubation, the working diagnosis would have been culture-negative endocarditis. What are the possible reasons for culture-negative endocarditis, and what measures should be taken to establish a microbiologic etiology?

Culture-negative endocarditis occurs in 5% to 20% of patients, which may be due to inappropriate microbiologic culture techniques, prior administration of antimicrobials, slow-growing and fastidious organisms, such as gram-negative bacilli in the *Haemophilus–Actinobacillus–Cardiobacterium–Eikenella–Kingella* (HACEK) group, *Brucella*, *Coxiella*, *Chlamydiae*, strict anaerobes, and fungi. Other diagnostic tests such as special culture media, serologic or polymerase chain reaction (PCR) tests can be used to identify difficult-to-cultivate organisms.[10,189] Of note, previously, *Abiotrophia* has been the cause of most of the cases of endocarditis diagnosed

as culture negative, initially because of its requirement for the addition of vitamin B_6 (pyridoxal HCl) to the culture media for laboratory growth; however, laboratory identification is no longer a significant problem with current culture media and laboratory techniques.[14]

Empiric Therapy

Case 66-5, Question 7: Considering that the causative organism remains unidentified, what antimicrobial regiment do you recommend for the empiric treatment of B.G.'s presumed culture-negative endocarditis?

In the hemodynamically stable patient, antibiotic therapy should be withheld until positive blood cultures are obtained.[1] Based on B.G.'s clinical presentation and echocardiographic findings, empiric antibiotics should be initiated as soon as necessary cultures have been collected. Because staphylococci (often MRSA) and gram-negative bacilli account for most cases of endocarditis in IVDUs with a prosthetic heart valve, B.G. should be started on a broad-spectrum four-drug regimen: vancomycin targeting an AUC_{24hr}/MIC ratio of 400 to 600 mg*hour/L, gentamicin targeting a peak of 3 to 4 µg/mL, cefepime 2 g IV every 8 hours, and rifampin 300 mg IV/PO every 8 hours.[10,19] Depending on the gram-negative pathogens common to the region and their anticipated susceptibilities, a third-generation cephalosporin (ceftriaxone or ceftazidime) or piperacillin–tazobactam could be used. The combination of an aminoglycoside with piperacillin–tazobactam also will provide coverage for enterococci. Because B.G. may be experiencing a relapse caused by *C. albicans*, the addition of liposomal amphotericin B and 5-FC would be appropriate.

B.G.'s clinical status and the positive echocardiogram finding indicate that early surgical valve excision and replacement are necessary. Cultures obtained from the excised valve may allow for identification of the causative organism and subsequent alteration of his antimicrobial regimen depending on susceptibilities.

PROPHYLACTIC THERAPY

Rationale and Recommendations

CASE 66-6

QUESTION 1: B.B., a 74-year-old male with poor dentition, is scheduled to have all his remaining teeth extracted for subsequent fitting of dentures. His medical history is significant for numerous infections of the oral cavity and prosthetic valve replacement 2 years ago. His only current medications are oral digoxin (Lanoxin®) 0.125 mg/day and furosemide (Lasix®) 40 mg every morning and he has no known drug allergy.

What is the rationale for antibiotic prophylaxis?

Because IE is associated with significant mortality and long-term morbidity, prevention in susceptible patients is of paramount importance.[1] Estimates are, however, that <10% of all cases are preventable.[190] The incidence of endocarditis in patients undergoing procedures known to cause significant bacteremia, even without antibiotic prophylaxis, is low. In addition, endocarditis may develop after the administration of seemingly appropriate chemoprophylaxis. Therefore, it is not surprising that the efficacy of prophylaxis has never been established through placebo-controlled clinical trials. Approximately 6000 patients would be necessary to demonstrate a statistical difference (if one exists) between untreated controls and a group receiving prophylaxis.[191] Without conclusive clinical data from prospective trials, recommendations for antibiotic prophylaxis are based largely on in vitro susceptibility data, evaluation of antibiotic regimens using animal models of endocarditis, and anecdotal experiences.[191] Prophylactic antibiotics are thought to provide protection by decreasing the number of organisms reaching the damaged heart valve from a primary source. Thus, antibiotics theoretically prevent bacterial multiplication on the valve and interfere with bacterial adherence to the cardiac lesion.[191]

The 2007 AHA recommendations for antibiotic prophylaxis before common medical procedures are outlined in **Table 66-6**.[191] Compared with previous (1997) guidelines, the current guidelines only recommend the use of prophylaxis in patients with specific cardiac conditions (associated with the highest risk of adverse outcomes from endocarditis) who are undergoing only dental or respiratory tract procedures. The use of prophylaxis for patients undergoing genitourinary or gastrointestinal procedures is not recommended because of a continuing lack of evidence to support efficacy.

Table 66-6

Cardiac Conditions for Which Prophylaxis Is Recommended

Cardiac Conditions

▪ Prosthetic cardiac valves
▪ Previous bacterial endocarditis
▪ Congenital heart disease
  ▪ Unrepaired cyanotic CHD, including palliative shunts and conduits
  ▪ Completely repaired congenital heart defect with prosthetic material device during the first 6 months after the procedure
  ▪ Repaired CHD with residual defects at or adjacent to the site of the prosthetic device or patch
  ▪ Mitral valve prolapse with valvular regurgitation and/or thickened leaflets
▪ Cardiac transplantation recipients who develop cardiac valvulopathy

CHD, congenital heart disease.

Source: Reprinted with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736–1754.

DENTAL AND UPPER RESPIRATORY TRACT PROCEDURES

Analysis of published data shows that VGS bacteremia can result from any procedure that involves the manipulation of the gingival tissue or the periapical region of the teeth or perforation of the oral

mucosa. Placement or removal of prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, taking dental radiographs, bleeding from trauma to the lips or oral mucosa, and instantaneous shedding of deciduous teeth do not require chemoprophylaxis. Endotracheal intubation also does not require prophylactic therapy.

Antimicrobial prophylaxis should be directed against VGS because these organisms are the most common cause of endocarditis after dental procedures. Invasive surgical procedures involving the upper respiratory tract, such as incision or biopsy of the respiratory mucosa (eg, tonsillectomy, adenoidectomy), can cause transient bacteremia with organisms that have similar antibiotic susceptibilities to those that occur after dental procedures; therefore, the same regimens are suggested. Prophylaxis is not recommended for bronchoscopies unless the procedure involves incision of the respiratory mucosa. Amoxicillin is the current recommendation for oral prophylaxis in susceptible persons having dental or upper respiratory tract surgery. Oral clindamycin, clarithromycin, or azithromycin are alternatives for patients with immediate-type hypersensitivity reaction to penicillins. Only patients with outlined cardiac conditions should receive prophylactic antibiotics.

Most cases of endocarditis caused by bacterial flora from the mouth do not follow dental procedures but rather are the result of poor oral hygiene. The cumulative exposure to random bacteremias from daily oral activities is estimated to be 5730 minutes during a 1-month period compared with only 6 to 30 minutes for a dental procedure. Furthermore, the cumulative exposure to bacteremia from routine daily activities may be up to 5.6 million times greater than a single tooth extraction.[191] Based on the study results, concerns for antimicrobial resistance, and cost, changes to restrict the use of antibiotic prophylaxis before dental procedures to the highest risk patients may be expected with future AHA guidelines.

Indications and Choice of Agent

Case 66-6, Question 2: Is prophylactic antibiotic therapy indicated for B.B.? If so, which antibiotic(s) should be used?

Based on the current recommendations, B.B. is a candidate for antibiotic prophylaxis. Presence of a prosthetic aortic valve while undergoing multiple tooth extractions, procedures likely to result in bacteremia, places him at high risk for experiencing endocarditis. According to **Table 66-7**, B.B. should receive a single 2-g oral dose of amoxicillin 1 hour before the procedure.

Table 66-7
Endocarditis Prophylaxis Regimen Indicated for Patients With Cardiac Conditions

Drug[a]	Dose
DENTAL or UPPER RESPIRATORY TRACT PROCEDURES	Single dose 30–60 minutes before the procedure
Standard Oral Regimen	
Amoxicillin	*Adult*: 2 g
	Pediatric: 50 mg/kg
Allergic to Penicillin or Ampicillin	
Clindamycin	*Adult*: 600 mg
	Pediatric: 20 mg/kg
Cephalexin[b,c]	*Adult*: 2 g
	Pediatric: 50 mg/kg
Azithromycin or clarithromycin	*Adult*: 500 mg
	Pediatric: 15 mg/kg
Unable to Take Oral Medications	
Ampicillin	*Adult*: 2 g IM or IV
	Pediatric: 50 mg/kg IM or IV
Allergic to Penicillin or Ampicillin	
Clindamycin	*Adult*: 600 mg IM or IV
	Pediatric: 20 mg/kg IV

Cefazolin[b]	*Adult*: 1 g IM or IV
	Pediatric: 50 mg/kg IM or IV

IM, intramuscular; IV, intravenous.

[a]See Table 66-6.

[b]Cephalosporins should not be used in individuals with immediate-type hypersensitivity reaction (eg, urticaria, angioedema, or anaphylaxis) to penicillin or ampicillin.

[c]Other first- or second-generation oral cephalosporins in equivalent adult or pediatric dose.

Source: Reprinted with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736–1754.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435–1486. doi:10.1161/cir.0000000000000296 (10)

Fowler VG, Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355(7):653–665. doi:10.1056/NEJMoa053783 (103)

Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA.* 2005;293(24):3012–3021. doi:10.1001/jama.293.24.3012 (9)

Holland T, Bayer A, Fowler V. Endocarditis and intravascular infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019. (1)

Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clin Microbiol Rev*. 2010;23(1):99–139. doi:10.1128/cmr.00042-09 (52)

Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638. doi:10.1086/313753 (20)

Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52(3):285–292. doi:10.1093/cid/cir034 (31)

Palraj R, Knoll B, Baddour L, Wilson W. Prosthetic valve endocarditis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019. (47)

Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1–e50. doi:10.1093/cid/civ933 (160)

Rupp M, Fey P. *Staphylococcus epidermidis* and other coagulase-negative staphylococci. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019. (51)

Sexton DJ, Tenenbaum MJ, Wilson WR, et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. *Clin Infect Dis*. 1998;27(6):1470–1474. doi:10.1086/515038 (36)

Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736–1754. doi:10.1161/circulationaha.106.183095 (191)

COMPLETE REFERENCES CHAPTER 66 ENDOCARDITIS

1. Holland T, Bayer A, Fowler V. Endocarditis and intravascular infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019.
2. Sullam PM, Drake TA, Sande MA. Pathogenesis of endocarditis. *Am J Med*. 1985;78(6b):110–115. doi:10.1016/0002-9343(85)90373-0
3. Manning JE, Hume EB, Hunter N, Knox KW. An appraisal of the virulence factors associated with streptococcal endocarditis. *J Med Microbiol*. 1994;40(2):110–114. doi:10.1099/00222615-40-2-110
4. Wang A, Gaca JG, Chu VH. Management considerations in infective endocarditis: a review. *JAMA*. 2018;320(1):72–83. doi:10.1001/jama.2018.7596
5. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. 2015;65(19):2070–2076. doi:10.1016/j.jacc.2015.03.518
6. Kadri AN, Wilner B, Hernandez AV, et al. Geographic trends, patient characteristics, and outcomes of infective endocarditis associated with drug abuse in the United States from 2002 to 2016. *J Am Heart Assoc*. 2019;8(19):e012969. doi:10.1161/jaha.119.012969
7. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169(5):463–473. doi:10.1001/archinternmed.2008.603
8. Bor DH, Woolhandler S, Nardin R, Brusch J, Himmelstein DU. Infective endocarditis in the U.S., 1998–2009: a nationwide study. *PLoS One*. 2013;8(3):e60033. doi:10.1371/journal.pone.0060033
9. Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA*. 2005;293(24):3012–3021. doi:10.1001/jama.293.24.3012
10. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435–1486. doi:10.1161/cir.0000000000000296
11. Fleischauer AT, Ruhl L, Rhea S, Barnes E. Hospitalizations for endocarditis and associated health care costs among persons with diagnosed drug dependence—North Carolina, 2010–2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(22):569–573. doi:10.15585/mmwr.mm6622a1
12. Hedegaard H, Minino AM, Warner M. Drug overdose deaths in the United States, 1999–2017. *NCHS Data Brief*. 2018;(329):1–8.

13. Wurcel AG, Anderson JE, Chui KK, et al. Increasing infectious endocarditis admissions among young people who inject drugs. *Open Forum Infect Dis*. 2016;3(3):ofw157. doi:10.1093/ofid/ofw157
14. Cunha C. Viridans streptococci and groups C and G streptococci and *Gamelia* species. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019.
15. Sexton DJ, Spelman D. Current best practices and guidelines. Assessment and management of complications in infective endocarditis. *Cardiol Clin*. 2003;21(2):273–282, vii–viii. doi:10.1016/s0733-8651(03)00031-6
16. Roder BL, Wandall DA, Espersen F, Frimodt-Moller N, Skinhoj P, Rosdahl VT. Neurologic manifestations in *Staphylococcus aureus* endocarditis: a review of 260 bacteremic cases in nondrug addicts. *Am J Med*. 1997;102(4):379–386. doi:10.1016/s0002-9343(97)00090-9
17. Pazin GJ, Saul S, Thompson ME. Blood culture positivity: suppression by outpatient antibiotic therapy in patients with bacterial endocarditis. *Arch Intern Med*. 1982;142(2):263–268.
18. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32(1):1–64. doi:10.1016/j.echo.2018.06.004
19. Sachdev M, Peterson GE, Jollis JG. Imaging techniques for diagnosis of infective endocarditis. *Infect Dis Clin North Am*. 2002;16(2):319–337, ix. doi:10.1016/s0891-5520(02)00003-x
20. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638. doi:10.1086/313753
21. Knoll B, Tleyjeh IM, Steckelberg JM, Wilson WR, Baddour LM. Infective endocarditis due to penicillin-resistant viridans group streptococci. *Clin Infect Dis*. 2007;44(12):1585–1592. doi:10.1086/518174
22. Carratala J, Alcaide F, Fernandez-Sevilla A, Corbella X, Linares J, Gudiol F. Bacteremia due to viridans streptococci that are highly resistant to penicillin: increase among neutropenic patients with cancer. *Clin Infect Dis*. 1995;20(5):1169–1673. doi:10.1093/clinids/20.5.1169
23. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864. doi:10.1093/ajhp/zxaa036
24. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus*

infections: efficacy and toxicity. *Arch Intern Med*. 2006;166(19):2138–2144. doi:10.1001/archinte.166.19.2138

25. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol*. 2004;42(6):2398–2402. doi:10.1128/jcm.42.6.2398-2402.2004
26. Soriano A, Marco F, Martinez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2008;46(2):193–200. doi:10.1086/524667
27. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. *Antimicrob Agents Chemother*. 2008;52(9): 3315–3320. doi:10.1128/aac.00113-08
28. Van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis*. 2012;54(6):755–771. doi:10.1093/cid/cir935
29. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. *JAMA*. 2014;312(15):1552–1564. doi:10.1001/jama.2014.6364
30. Baxi SM, Clemenzi-Allen A, Gahbauer A, et al. Vancomycin MIC does not predict 90-day mortality, readmission, or recurrence in a prospective cohort of adults with *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2016;60(9): 5276–5284. doi:10.1128/aac.00658-16
31. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52(3):285–292. doi:10.1093/cid/cir034
32. Bisno AL, Dismukes WE, Durack DT, et al. Antimicrobial treatment of infective endocarditis due to viridans streptococci, enterococci, and staphylococci. *JAMA*. 1989;261(10):1471–1477.
33. Karchmer AW, Moellering RC Jr, Maki DG, Swartz MN. Single-antibiotic therapy for streptococcal endocarditis. *JAMA*. 1979;241(17):1801–1806.
34. Malacoff RF, Frank E, Andriole VT. Streptococcal endocarditis (nonenterococcal, non-group A): single vs combination therapy. *JAMA*. 1979;241(17): 1807–1810.
35. Sande MA, Irvin RG. Penicillin-aminoglycoside synergy in experimental *Streptococcus viridans* endocarditis. *J Infect Dis*. 1974;129(5):572–576. doi:10.1093/infdis/129.5.572

36. Sexton DJ, Tenenbaum MJ, Wilson WR, et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. *Clin Infect Dis*. 1998;27(6):1470–1474. doi:10.1086/515038
37. Francioli P, Etienne J, Hoigne R, Thys JP, Gerber A. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone sodium for 4 weeks. Efficacy and outpatient treatment feasibility. *JAMA*. 1992;267(2):264–267.
38. Hoen B. Special issues in the management of infective endocarditis caused by gram-positive cocci. *Infect Dis Clin North Am*. 2002;16(2):437–452, xi. doi:10.1016/s0891-5520(01)00004-6
39. Stamboulian D, Bonvehi P, Arevalo C, et al. Antibiotic management of outpatients with endocarditis due to penicillin-susceptible streptococci. *Rev Infect Dis.* 1991;13(suppl 2):S160–S163. doi:10.1093/clinids/13.supplement_2.s160
40. Wilson WR, Thompson RL, Wilkowske CJ, Washington JA 2nd, Giuliani ER, Geraci JE. Short-term therapy for streptococcal infective endocarditis. Combined intramuscular administration of penicillin and streptomycin. *JAMA*. 1981;245(4):360–363.
41. Le T, Bayer AS. Combination antibiotic therapy for infective endocarditis. *Clin Infect Dis*. 2003;36(5):615–621. doi:10.1086/367661
42. Wilson WR, Geraci JE, Wilkowske CJ, Washington JA 2nd. Short-term intramuscular therapy with procaine penicillin plus streptomycin for infective endocarditis due to viridans streptococci. *Circulation*. 1978;57(6):1158–1161. doi:10.1161/01.cir.57.6.1158
43. Francioli P, Ruch W, Stamboulian D. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone and netilmicin for 14 days: a prospective multicenter study. *Clin Infect Dis*. 1995;21(6):1406–1410. doi:10.1093/clinids/21.6.1406
44. Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. *Clin Microbiol Rev*. 2001;14(1):177–207. doi:10.1128/cmr.14.1.177-207.2001
45. Henry NK, Wilson WR, Roberts RB, Acar JF, Geraci JE. Antimicrobial therapy of experimental endocarditis caused by nutritionally variant viridans group streptococci. *Antimicrob Agents Chemother*. 1986;30(3):465–467. doi:10.1128/aac.30.3.465
46. Karchmer AW, Longworth DL. Infections of intracardiac devices. *Infect Dis Clin North Am*. 2002;16(2):477–505, xii. doi:10.1016/s0891-5520(01)00005-8
47. Palraj R, Knoll B, Baddour L, Wilson W. Prosthetic valve endocarditis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019.

48. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007;297(12):1354–1361. doi:10.1001/jama.297.12.1354
49. Hoen B, Duval X, Durack D. Prevention of infective endocarditis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019.
50. Maki DG, Bohn MJ, Stolz SM, Kroncke GM, Acher CW, Myerowitz PD. Comparative study of cefazolin, cefamandole, and vancomycin for surgical prophylaxis in cardiac and vascular operations. A double-blind randomized trial. *J Thorac Cardiovasc Surg*. 1992;104(5):1423–1434.
51. Rupp M, Fey P. Staphylococcus epidermidis and other coagulase-negative staphylococci. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2019.
52. Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clin Microbiol Rev*. 2010;23(1):99–139. doi:10.1128/cmr.00042-09
53. Lucet JC, Herrmann M, Rohner P, Auckenthaler R, Waldvogel FA, Lew DP. Treatment of experimental foreign body infection caused by methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 1990;34(12):2312–2317. doi:10.1128/aac.34.12.2312
54. Chuard C, Herrmann M, Vaudaux P, Waldvogel FA, Lew DP. Successful therapy of experimental chronic foreign-body infection due to methicillin-resistant *Staphylococcus aureus* by antimicrobial combinations. *Antimicrob Agents Chemother*. 1991;35(12):2611–2616. doi:10.1128/aac.35.12.2611
55. Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2008;52(7):2463–2467. doi:10.1128/aac.00300-08
56. Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Schentag JJ. Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. *Clin Infect Dis*. 2003;36(2): 159–168. doi:10.1086/345744
57. Livermore DM. Quinupristin/dalfopristin and linezolid: where, when, which and whether to use? *J Antimicrob Chemother*. 2000;46(3):347–350. doi:10.1093/jac/46.3.347
58. Miro JM, del Rio A, Mestres CA. Infective endocarditis in intravenous drug abusers and HIV-1 infected patients. *Infect Dis Clin North Am*. 2002;16(2): 273–295, vii–viii. doi:10.1016/s0891-5520(01)00008-3
59. Chambers HF, Korzeniowski OM, Sande MA. *Staphylococcus aureus* endocarditis: clinical manifestations in addicts and nonaddicts. *Medicine (Baltimore)*. 1983;62(3):170–177.

60. Siddiq S, Missri J, Silverman DI. Endocarditis in an urban hospital in the 1990s. *Arch Intern Med*. 1996;156(21):2454–2458.
61. Manoff SB, Vlahov D, Herskowitz A, et al. Human immunodeficiency virus infection and infective endocarditis among injecting drug users. *Epidemiology*. 1996;7(6):566–570. doi:10.1097/00001648-199611000-00001
62. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. *Ann Intern Med*. 1982;97(4):496–503. doi:10.7326/0003-4819-97-4-496
63. Pulvirenti JJ, Kerns E, Benson C, Lisowski J, Demarais P, Weinstein RA. Infective endocarditis in injection drug users: importance of human immunodeficiency virus serostatus and degree of immunosuppression. *Clin Infect Dis*. 1996;22(1):40–45. doi:10.1093/clinids/22.1.40
64. Fortun J, Navas E, Martinez-Beltran J, et al. Short-course therapy for right-side endocarditis due to *Staphylococcus aureus* in drug abusers: cloxacillin versus glycopeptides in combination with gentamicin. *Clin Infect Dis*. 2001;33(1):120–125. doi:10.1086/320869
65. Chambers HF, Miller RT, Newman MD. Right-sided *Staphylococcus aureus* endocarditis in intravenous drug abusers: two-week combination therapy. *Ann Intern Med*. 1988;109(8):619–624. doi:10.7326/0003-4819-109-8-619
66. DiNubile MJ. Short-course antibiotic therapy for right-sided endocarditis caused by *Staphylococcus aureus* in injection drug users. *Ann Intern Med*. 1994;121(11):873–876. doi:10.7326/0003-4819-121-11-199412010-00009
67. Torres-Tortosa M, de Cueto M, Vergara A, et al. Prospective evaluation of a two-week course of intravenous antibiotics in intravenous drug addicts with infective endocarditis. Grupo de Estudio de Enfermedades Infecciosas de la Provincia de Cadiz. *Eur J Clin Microbiol Infect Dis*. 1994;13(7):559–564. doi:10.1007/bf01971306
68. Dworkin RJ, Lee BL, Sande MA, Chambers HF. Treatment of right-sided *Staphylococcus aureus endocarditis in intravenous drug users with ciprofloxacin and rifampicin. Lancet*. 1989;2(8671):1071–1073. doi:10.1016/s0140-6736(89)91083-0
69. Al-Omari A, Cameron DW, Lee C, Corrales-Medina VF. Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review. *BMC Infect Dis*. 2014;14:140. doi:10.1186/1471-2334-14-140
70. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. *Am J Med*. 1996;101(1):68–76. doi:10.1016/s0002-9343(96)00070-8
71. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med*. 2019;380(5):415–424. doi:10.1056/NEJMoa1808312

72. Bryant RE, Alford RH. Unsuccessful treatment of staphylococcal endocarditis with cefazolin. *JAMA*. 1977;237(6):569–570.
73. Livermore DM. beta-Lactamases in laboratory and clinical resistance. *Clin Microbiol Rev*. 1995;8(4):557–584. doi:10.1128/cmr.8.4.557-584.1995
74. Nannini EC, Stryjewski ME, Singh KV, et al. Inoculum effect with cefazolin among clinical isolates of methicillin-susceptible *Staphylococcus aureus*: frequency and possible cause of cefazolin treatment failure. *Antimicrob Agents Chemother*. 2009;53(8):3437–3441. doi:10.1128/aac.00317-09
75. Minejima E, Mai N, Bui N, et al. Defining the breakpoint duration of *Staphylococcus aureus* bacteremia predictive of poor outcomes. *Clin Infect Dis*. 2020;70(4):566–573. doi:10.1093/cid/ciz257
76. Gorwitz R, Jernigan D, Powers J, Jernigan J. Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention. 2006. https://www.cdc.gov/mrsa/pdf/mrsa-strategies-expmtgsummary-2006.pdf
77. Boussaud V, Parrot A, Mayaud C, et al. Life-threatening hemoptysis in adults with community-acquired pneumonia due to Panton-Valentine leukocidin-secreting *Staphylococcus aureus. Intensive Care Med*. 2003;29(10):1840–1843. doi:10.1007/s00134-003-1918-5
78. Dufour P, Gillet Y, Bes M, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: emergence of a single clone that produces Panton-Valentine leukocidin. *Clin Infect Dis*. 2002;35(7):819–824. doi:10.1086/342576
79. Francis JS, Doherty MC, Lopatin U, et al. Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidin genes. *Clin Infect Dis*. 2005;40(1):100–107. doi:10.1086/427148
80. Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet*. 2002;359(9308):753–759. doi:10.1016/s0140-6736(02)07877-7
81. Micek ST, Dunne M, Kollef MH. Pleuropulmonary complications of Panton-Valentine leukocidin-positive community-acquired methicillin-resistant *Staphylococcus aureus*: importance of treatment with antimicrobials inhibiting exotoxin production. *Chest*. 2005;128(4):2732–2738. doi:10.1378/chest.128.4.2732
82. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med*. 2005;352(14):1445–1453. doi:10.1056/NEJMoa042683
83. Diep BA, Chan L, Tattevin P, et al. Polymorphonuclear leukocytes mediate *Staphylococcus aureus* Panton-Valentine leukocidin-induced lung inflammation and injury. *Proc Natl Acad Sci USA*. 2010;107(12):5587–5592. doi:10.1073/pnas.0912403107

84. Bahrain M, Vasiliades M, Wolff M, Younus F. Five cases of bacterial endocarditis after furunculosis and the ongoing saga of community-acquired methicillin-resistant *Staphylococcus aureus* infections. *Scand J Infect Dis*. 2006;38(8):702–707. doi:10.1080/00365540500447150
85. Peyrani P, Allen M, Wiemken TL, et al. Severity of disease and clinical outcomes in patients with hospital-acquired pneumonia due to methicillin-resistant *Staphylococcus aureus* strains not influenced by the presence of the Panton-Valentine leukocidin gene. *Clin Infect Dis*. 2011;53(8):766–771. doi:10.1093/cid/cir541
86. Hamilton SM, Bryant AE, Carroll KC, et al. In vitro production of Panton-Valentine leukocidin among strains of methicillin-resistant *Staphylococcus aureus* causing diverse infections. *Clin Infect Dis*. 2007;45(12):1550–1558. doi:10.1086/523581
87. Tong A, Tong SY, Zhang Y, et al. Panton-Valentine leukocidin is not the primary determinant of outcome for *Staphylococcus aureus* skin infections: evaluation from the CANVAS studies. *PLoS One*. 2012;7(5):e37212. doi:10.1371/journal.pone.0037212
88. Lodise TP, Rosenkranz SL, Finnemeyer M, et al. The Emperor's New Clothes: PRospective Observational Evaluation of the Association Between Initial VancomycIn Exposure and Failure Rates Among ADult HospitalizEd Patients With Methicillin-resistant *Staphylococcus aureus* Bloodstream Infections (PROVIDE). *Clin Infect Dis*. 2020;70(8):1536–1545. doi:10.1093/cid/ciz460
89. Rhodes NJ, Prozialeck WC, Lodise TP, et al. Evaluation of vancomycin exposures associated with elevations in novel urinary biomarkers of acute kidney injury in vancomycin-treated rats. *Antimicrob Agents Chemother*. 2016;60(10):5742–5751. doi:10.1128/aac.00591-16
90. Neely MN, Kato L, Youn G, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother*. 2018;62(2):e02042-17. doi:10.1128/aac.02042-17
91. Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. *J Clin Microbiol*. 2006;44(11):3883–3886. doi:10.1128/jcm.01388-06
92. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 2020. CLSI supplement M100.
93. Wootton M, Walsh TR, MacGowan AP. Evidence for reduction in breakpoints used to determine vancomycin susceptibility in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2005;49(9):3982–3983.
94. Howe RA, Wootton M, Walsh TR, Bennett PM, MacGowan AP. Expression and detection of hetero-vancomycin resistance in *Staphylococcus aureus*. *J Antimicrob Chemother*. 1999;44(5):675–678. doi:10.1093/jac/44.5.675

95. Rose WE, Leonard SN, Rossi KL, Kaatz GW, Rybak MJ. Impact of inoculum size and heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) on vancomycin activity and emergence of VISA in an in vitro pharmacodynamic model. *Antimicrob Agents Chemother*. 2009;53(2):805–807. doi:10.1128/aac.01009-08
96. Charles PG, Ward PB, Johnson PD, Howden BP, Grayson ML. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. *Clin Infect Dis*. 2004;38(3):448–451. doi:10.1086/381093
97. Jones RN. Microbiological features of vancomycin in the 21st century: minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical outcomes or detect resistant strains. *Clin Infect Dis*. 2006;42(suppl 1):S13–S24. doi:10.1086/491710
98. Sancak B, Ercis S, Menemenlioglu D, Colakoglu S, Hascelik G. Methicillin-resistant *Staphylococcus aureus* heterogeneously resistant to vancomycin in a Turkish university hospital. *J Antimicrob Chemother*. 2005;56(3):519–523. doi:10.1093/jac/dki272
99. Wootton M, MacGowan AP, Walsh TR, Howe RA. A multicenter study evaluating the current strategies for isolating *Staphylococcus aureus* strains with reduced susceptibility to glycopeptides. *J Clin Microbiol*. 2007;45(2):329–332. doi:10.1128/jcm.01508-06
100. Hsu DI, Hidayat LK, Quist R, et al. Comparison of method-specific vancomycin minimum inhibitory concentration values and their predictability for treatment outcome of meticillin-resistant *Staphylococcus aureus* (MRSA) infections. *Int J Antimicrob Agents*. 2008;32(5):378–385. doi:10.1016/j.ijantimicag.2008.05.007
101. Deresinski S. Vancomycin heteroresistance and methicillin-resistant *Staphylococcus aureus*. *J Infect Dis*. 2009;199(5):605–609.
102. Boucher H, Miller LG, Razonable RR. Serious infections caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2010;51(suppl 2): S183–S197. doi:10.1086/653519
103. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355(7):653–665. doi:10.1056/NEJMoa053783
104. Smith JR, Claeys KC, Barber KE, Rybak MJ. High-dose daptomycin therapy for staphylococcal endocarditis and when to apply it. *Curr Infect Dis Rep*. 2014;16(10):429. doi:10.1007/s11908-014-0429-6
105. Moise PA, Hershberger E, Amodio-Groton MI, Lamp KC. Safety and clinical outcomes when utilizing high-dose (> or =8 mg/kg) daptomycin therapy. *Ann Pharmacother*. 2009;43(7):1211–1219. doi:10.1345/aph.1M085
106. Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. *J Clin Pharmacol*. 2005;45(1):48–56. doi:10.1177/0091270004269562

107. Norris AH, Shrestha NK, Allison GM, et al. 2018 infectious diseases society of America clinical practice guideline for the management of outpatient parenteral antimicrobial therapy. *Clin Infect Dis*. 2019;68(1):e1–e35. doi:10.1093/cid/ciy745
108. Cui L, Tominaga E, Neoh HM, Hiramatsu K. Correlation between reduced daptomycin susceptibility and vancomycin resistance in vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2006;50(3):1079–1082. doi:10.1128/aac.50.3.1079-1082.2006
109. Patel JB, Jevitt LA, Hageman J, McDonald LC, Tenover FC. An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in *Staphylococcus aureus*. *Clin Infect Dis*. 2006;42(11):1652–1653.
110. Moise PA, North D, Steenbergen JN, Sakoulas G. Susceptibility relationship between vancomycin and daptomycin in *Staphylococcus aureus*: facts and assumptions. *Lancet Infect Dis*. 2009;9(10):617–624. doi:10.1016/s1473-3099(09)70200-2
111. Dhand A, Bayer AS, Pogliano J, et al. Use of antistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*: role of enhanced daptomycin binding. *Clin Infect Dis*. 2011;53(2):158–163. doi:10.1093/cid/cir340
112. Rand KH, Houck HJ. Synergy of daptomycin with oxacillin and other beta-lactams against methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2004;48(8):2871–2875. doi:10.1128/aac.48.8.2871-2875.2004
113. Dhand A, Sakoulas G. Daptomycin in combination with other antibiotics for the treatment of complicated methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Ther*. 2014;36(10):1303–1316. doi:10.1016/j.clinthera.2014.09.005
114. Geriak M, Haddad F, Rizvi K, et al. Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2019;63(5):e02483-18. doi:10.1128/aac.02483-18
115. Miro JM, Garcia-de-la-Maria C, Armero Y, et al. Addition of gentamicin or rifampin does not enhance the effectiveness of daptomycin in treatment of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2009;53(10):4172–4177. doi:10.1128/aac.00051-09
116. Kaatz GW, Lundstrom TS, Seo SM. Mechanisms of daptomycin resistance in *Staphylococcus aureus*. *Int J Antimicrob Agents*. 2006;28(4):280–287. doi:10.1016/j.ijantimicag.2006.05.030
117. Mariani PG, Sader HS, Jones RN. Development of decreased susceptibility to daptomycin and vancomycin in a *Staphylococcus aureus* strain during prolonged therapy. *J Antimicrob Chemother*. 2006;58(2):481–483.

118. Skiest DJ. Treatment failure resulting from resistance of *Staphylococcus aureus* to daptomycin. *J Clin Microbiol*. 2006;44(2):655–656. doi:10.1128/jcm.44.2. 655-656.2006
119. Falagas ME, Manta KG, Ntziora F, Vardakas KZ. Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. *J Antimicrob Chemother*. 2006;58(2):273–280. doi:10.1093/jac/dkl219
120. Dresser L. Results of treating infective endocarditis with linezolid (LNZ). presented at: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 2000; Toronto, Ontario, Canada.
121. Forrest A. Pharmacostatistical modeling of hematologic effects of linezolid in seriously ill patients. Presented at: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 2000; Toronto, Ontario, Canada.
122. Sperber SJ, Levine JF, Gross PA. Persistent MRSA bacteremia in a patient with low linezolid levels. *Clin Infect Dis*. 2003;5:675–676.
123. Corne P, Marchandin H, Macia JC, Jonquet O. Treatment failure of methicillin-resistant *Staphylococcus aureus* endocarditis with linezolid. *Scand J Infect Dis*. 2005;37(11–12):946–949. doi:10.1080/00365540500263110
124. Chan LC, Basuino L, Dip EC, Chambers HF. Comparative efficacies of tedizolid phosphate, vancomycin, and daptomycin in a rabbit model of methicillin-resistant *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother*. 2015;59(6):3252–3256. doi:10.1128/aac.04376-14
125. Watanakunakorn C. Penicillin combined with gentamicin or streptomycin: synergism against enterococci. *J Infect Dis*. 1971;124(6):581–586. doi:10.1093/infdis/124.6.581
126. Wilkowske CJ, Facklam RR, Washington JA 2nd, Geraci JE. Antibiotics synergism: enhanced susceptibility of group D streptococci to certain antibiotic combinations. *Antimicrob Agents Chemother (Bethesda)*. 1970;10:195–200.
127. Moellering RC Jr, Weinberg AN. Studies on antibiotic syngerism against enterococci. II. Effect of various antibiotics on the uptake of 14 C-labeled streptomycin by enterococci. *J Clin Invest*. 1971;50(12):2580–2584. doi:10.1172/jci106758
128. Eliopoulos GM. Aminoglycoside resistant enterococcal endocarditis. *Infect Dis Clin North Am*. 1993;7(1):117–133.
129. Matsumoto JY, Wilson WR, Wright AJ, Geraci JE, Washington JA 2nd. Synergy of penicillin and decreasing concentration of aminoglycosides against enterococci from patients with infective endocarditis. *Antimicrob Agents Chemother*. 1980;18(6):944–947. doi:10.1128/aac.18.6.944
130. Mainardi JL, Gutmann L, Acar JF, Goldstein FW. Synergistic effect of amoxicillin and cefotaxime against *Enterococcus faecalis*. *Antimicrob Agents Chemother*. 1995;39(9):1984–1987. doi:10.1128/aac.39.9.1984

131. Brandt CM, Rouse MS, Laue NW, Stratton CW, Wilson WR, Steckelberg JM. Effective treatment of multidrug-resistant enterococcal experimental endocarditis with combinations of cell wall-active agents. *J Infect Dis*. 1996;173(4):909–913. doi:10.1093/infdis/173.4.909
132. Fernandez-Hidalgo N, Almirante B, Gavalda J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *Enterococcus faecalis* infective endocarditis. *Clin Infect Dis*. 2013;56(9):1261–1268. doi:10.1093/cid/cit052
133. El Rafei A, DeSimone DC, Narichania AD, et al. Comparison of dual β-lactam therapy to penicillin-aminoglycoside combination in treatment of *Enterococcus faecalis* infective endocarditis. *J Infect*. 2018;77(5):398–404. doi:10.1016/j.jinf.2018.06.013
134. Carrizosa J, Levison ME. Minimal concentrations of aminoglycoside that can synergize with penicillin in enterococcal endocarditis. *Antimicrob Agents Chemother*. 1981;20(3):405–409. doi:10.1128/aac.20.3.405
135. Wright AJ, Wilson WR, Matsumoto JY, Washington JA 2nd, Geraci JE. Influence of gentamicin dose size on the efficacies of combinations of gentamicin and penicillin in experimental streptomycin-resistant enterococcal endocarditis. *Antimicrob Agents Chemother*. 1982;22(6):972–975. doi:10.1128/aac.22.6.972
136. Fantin B, Carbon C. Importance of the aminoglycoside dosing regimen in the penicillin-netilmicin combination for treatment of *Enterococcus faecalis*-induced experimental endocarditis. *Antimicrob Agents Chemother*. 1990;34(12):2387–2391. doi:10.1128/aac.34.12.2387
137. Marangos MN, Nicolau DP, Quintiliani R, Nightingale CH. Influence of gentamicin dosing interval on the efficacy of penicillin-containing regimens in experimental *Enterococcus faecalis* endocarditis. *J Antimicrob Chemother*. 1997;39(4):519–522. doi:10.1093/jac/39.4.519
138. Wilson WR, Wilkowske CJ, Wright AJ, Sande MA, Geraci JE. Treatment of streptomycin-susceptible and streptomycin-resistant enterococcal endocarditis. *Ann Intern Med*. 1984;100(6):816–823. doi:10.7326/0003-4819-100-6-816
139. Olaison L, Schadewitz K. Enterococcal endocarditis in Sweden, 1995–1999: can shorter therapy with aminoglycosides be used? *Clin Infect Dis*. 2002;34(2): 159–166. doi:10.1086/338233
140. Murray BE. Vancomycin-resistant enterococcal infections. *N Engl J Med*. 2000;342(10):710–721. doi:10.1056/nejm200003093421007
141. Rice LB. Emergence of vancomycin-resistant enterococci. *Emerg Infect Dis*. 2001;7(2):183–187. doi:10.3201/eid0702.010205
142. Weiner LM, Fridkin SK, Aponte-Torres Z, et al. Vital signs: preventing antibiotic-resistant infections in hospitals—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2016;65(9):235–241. doi:10.15585/mmwr.mm6509e1

143. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A review of combination antimicrobial therapy for *Enterococcus Faecalis* bloodstream infections and infective endocarditis. *Clin Infect Dis*. 2018;67(2):303–309. doi:10.1093/cid/ciy064
144. Sakoulas G, Bayer AS, Pogliano J, et al. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2012;56(2):838–844. doi:10.1128/aac.05551-11
145. Sakoulas G, Nonejuie P, Nizet V, Pogliano J, Crum-Cianflone N, Haddad F. Treatment of high-level gentamicin-resistant *Enterococcus faecalis* endocarditis with daptomycin plus ceftaroline. *Antimicrob Agents Chemother*. 2013;57(8):4042–4045. doi:10.1128/aac.02481-12
146. Sakoulas G, Rose W, Nonejuie P, et al. Ceftaroline restores daptomycin activity against daptomycin-nonsusceptible vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2014;58(3):1494–1500. doi:10.1128/aac.02274-13
147. Eliopoulos GM. Quinupristin-dalfopristin and linezolid: evidence and opinion. *Clin Infect Dis*. 2003;36(4):473–481. doi:10.1086/367662
148. Gonzales RD, Schreckenberger PC, Graham MB, Kelkar S, DenBesten K, Quinn JP. Infections due to vancomycin-resistant *Enterococcus faecium* resistant to linezolid. *Lancet*. 2001;357(9263):1179.
149. Herrero IA, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin-resistant *Enterococcus faecium. N Engl J Med*. 2002;11:867–869.
150. Beringer P, Nguyen M, Hoem N, et al. Absolute bioavailability and pharmacokinetics of linezolid in hospitalized patients given enteral feedings. *Antimicrob Agents Chemother*. 2005;49(9):3676–3681. doi:10.1128/aac.49.9.3676-3681.2005
151. Britt NS, Potter EM, Patel N, Steed ME. Comparison of the effectiveness and safety of linezolid and daptomycin in vancomycin-resistant enterococcal bloodstream infection: a National Cohort Study of Veterans Affairs Patients. *Clin Infect Dis*. 2015;61(6):871–878. doi:10.1093/cid/civ444
152. Kanafani ZA, Federspiel JJ, Fowler VG Jr. Infective endocarditis caused by daptomycin-resistant *Enterococcus faecalis*: a case report. *Scand J Infect Dis*. 2007;39(1):75–77. doi:10.1080/00365540600786465
153. Munoz-Price LS, Lolans K, Quinn JP. Emergence of resistance to daptomycin during treatment of vancomycin-resistant *Enterococcus faecalis* infection. *Clin Infect Dis*. 2005;41(4):565–566.
154. Schwartz BS, Ngo PD, Guglielmo BJ. Daptomycin treatment failure for vancomycin-resistant *Enterococcus faecium* infective endocarditis: impact of protein binding? *Ann Pharmacother*. 2008;42(2):289–290.
155. Lewis JS 2nd, Owens A, Cadena J, Sabol K, Patterson JE, Jorgensen JH. Emergence of daptomycin resistance in *Enterococcus faecium* during

daptomycin therapy. *Antimicrob Agents Chemother*. 2005;49(5):1664–1665.
156. Ellis ME, Al-Abdely H, Sandridge A, Greer W, Ventura W. Fungal endocarditis: evidence in the world literature, 1965–1995. *Clin Infect Dis*. 2001;32(1):50–62. doi:10.1086/317550
157. Melgar GR, Nasser RM, Gordon SM, Lytle BW, Keys TF, Longworth DL. Fungal prosthetic valve endocarditis in 16 patients. An 11-year experience in a tertiary care hospital. *Medicine (Baltimore)*. 1997;76(2):94–103. doi:10.1097/00005792-199703000-00002
158. Pierrotti LC, Baddour LM. Fungal endocarditis, 1995–2000. *Chest*. 2002;122(1): 302–310. doi:10.1378/chest.122.1.302
159. Rubinstein E, Noriega ER, Simberkoff MS, Holzman R, Rahal JJ Jr. Fungal endocarditis: analysis of 24 cases and review of the literature. *Medicine (Baltimore)*. 1975;54(4):331–334.
160. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1–e50. doi:10.1093/cid/civ933
161. Shadomy S, Wagner G, Espinel-Ingroff E, Davis BA. In vitro studies with combinations of 5-fluorocytosine and amphotericin B. *Antimicrob Agents Chemother*. 1975;8(2):117–1121. doi:10.1128/aac.8.2.117
162. Rubinstein E, Noriega ER, Simberkoff MS, Rahal JJ Jr. Tissue penetration of amphotericin B in *Candida* endocarditis. *Chest*. 1974;66(4):376–377. doi:10.1378/chest.66.4.376
163. Gilbert HM, Peters ED, Lang SJ, Hartman BJ. Successful treatment of fungal prosthetic valve endocarditis: case report and review. *Clin Infect Dis*. 1996;22(2): 348–354. doi:10.1093/clinids/22.2.348
164. Muehrcke DD, Lytle BW, Cosgrove DM 3rd. Surgical and long-term antifungal therapy for fungal prosthetic valve endocarditis. *Ann Thorac Surg*. 1995;60(3): 538–543. doi:10.1016/0003-4975(95)00469-2
165. Wong-Beringer A, Jacobs RA, Guglielmo BJ. Lipid formulations of amphotericin B: clinical efficacy and toxicities. *Clin Infect Dis*. 1998;27(3):603–618. doi:10.1086/514704
166. Kuhn DM, George T, Chandra J, Mukherjee PK, Ghannoum MA. Antifungal susceptibility of *Candida* biofilms: unique efficacy of amphotericin B lipid formulations and echinocandins. *Antimicrob Agents Chemother*. 2002;46(6): 1773–1780. doi:10.1128/aac.46.6.1773-1780.2002
167. Melamed R, Leibovitz E, Abramson O, Levitas A, Zucker N, Gorodisher R. Successful non-surgical treatment of *Candida tropicalis* endocarditis with liposomal amphotericin-B (AmBisome). *Scand J Infect Dis*. 2000;32(1):86–89. doi:10.1080/00365540050164281
168. Arnold CJ, Johnson M, Bayer AS, et al. *Candida* infective endocarditis: an observational cohort study with a focus on therapy. *Antimicrob Agents Chemother*. 2015;59(4):2365–2373. doi:10.1128/aac.04867-14

169. Talarmin JP, Boutoille D, Tattevin P, et al. *Candida* endocarditis: role of new antifungal agents. *Mycoses*. 2009;52(1):60–66. doi:10.1111/j.1439-0507.2008.01533.x
170. De Rosa FG, D'Avolio A, Corcione S, et al. Anidulafungin for *Candida glabrata* infective endocarditis. *Antimicrob Agents Chemother*. 2012;56(8):4552–4553.
171. Falcone M, Barzaghi N, Carosi G, et al. *Candida* infective endocarditis: report of 15 cases from a prospective multicenter study. *Medicine (Baltimore)*. 2009;88(3): 160–168. doi:10.1097/MD.0b013e3181a693f8
172. Terrell CL. Antifungal agents. Part II. The azoles. *Mayo Clin Proc*. 1999;74(1): 78–100. doi:10.4065/74.1.78
173. Hernandez JA, Gonzalez-Moreno M, Llibre JM, Aloy A, Casan CM. Candidal mitral endocarditis and long-term treatment with fluconazole in a patient with human immunodeficiency virus infection. *Clin Infect Dis*. 1992;15(6): 1062–1063. doi:10.1093/clind/15.6.1062
174. Isalska BJ, Stanbridge TN. Fluconazole in the treatment of candidal prosthetic valve endocarditis. *BMJ*. 1988;297(6642):178–179. doi:10.1136/bmj.297.6642.178
175. Roupie E, Darmon JY, Brochard L, Saada M, Rekik N, Brun-Buisson C. Fluconazole therapy of candidal native valve endocarditis. *Eur J Clin Microbiol Infect Dis*. 1991;10(5):458–459. doi:10.1007/bf01968030
176. Venditti M, De Bernardis F, Micozzi A, et al. Fluconazole treatment of catheter-related right-sided endocarditis caused by *Candida albicans* and associated with endophthalmitis and folliculitis. *Clin Infect Dis*. 1992;14(2):422–426. doi:10.1093/clinids/14.2.422
177. Cohen PS, Maguire JH, Weinstein L. Infective endocarditis caused by gram-negative bacteria: a review of the literature, 1945–1977. *Prog Cardiovasc Dis*. 1980;22(4):205–242. doi:10.1016/0033-0620(80)90010-9
178. Tunkel AR, Fisch MJ, Schlein A, Scheld WM. Enterobacter endocarditis. *Scand J Infect Dis*. 1992;24(2):233–240. doi:10.3109/00365549209052618
179. Cooper R, Mills J. Serratia endocarditis. A follow-up report. *Arch Intern Med*. 1980;140(2):199–202.
180. Ellner JJ, Rosenthal MS, Lerner PI, McHenry MC. Infective endocarditis caused by slow-growing, fastidious, Gram-negative bacteria. *Medicine (Baltimore)*. 1979;58(2):145–158. doi:10.1097/00005792-197903000-00003
181. Weinstein MP, Stratton CW, Ackley A, et al. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. *Am J Med*. 1985;78(2):262–269. doi:10.1016/0002-9343(85)90436-x
182. Reyes MP, Lerner AM. Current problems in the treatment of infective endocarditis due to *Pseudomonas aeruginosa*. *Rev Infect Dis*. 1983;5(2):314–321. doi:10.1093/clinids/5.2.314

183. Archer G, Fekety FR Jr. Experimental endocarditis due to *Pseudomonas aeruginosa*. II. Therapy with carbenicillin and gentamicin. *J Infect Dis*. 1977;136(3):327–335. doi:10.1093/infdis/136.3.327
184. Lerner SA, Dudek EJ, Boisvert WE, Berndt KD. Effect of highly potent antipseudomonal beta-lactam agents alone and in combination with aminoglycosides against *Pseudomonas aeruginosa*. *Rev Infect Dis*. 1984;6(suppl 3):S678–S688. doi:10.1093/clinids/6.supplement_3.s678
185. Scully BE, Neu HC. Use of aztreonam in the treatment of serious infections due to multiresistant gram-negative organisms, including *Pseudomonas aeruginosa*. *Am J Med*. 1985;78(2):251–261. doi:10.1016/0002-9343(85)90435-8
186. Dickinson G, Rodriguez K, Arcey S, Alea A, Greenman R. Efficacy of imipenem/ cilastatin in endocarditis. *Am J Med*. 1985;78(6a):117–121. doi:10.1016/0002-9343(85)90113-5
187. Brown NM, Korner RJ, Zollman CE, Martin RP, Millar MR. Ciprofloxacin treatment of bacterial endocarditis involving prosthetic material after cardiac surgery. *Arch Dis Child*. 1997;76(1):68–69. doi:10.1136/adc.76.1.68
188. Strunk RW, Gratz JC, Maserati R, Scheld WM. Comparison of ciprofloxacin with azlocillin plus tobramycin in the therapy of experimental *Pseudomonas aeruginosa* endocarditis. *Antimicrob Agents Chemother*. 1985;28(3):428–432. doi:10.1128/aac.28.3.428
189. Hoen B, Selton-Suty C, Lacassin F, et al. Infective endocarditis in patients with negative blood cultures: analysis of 88 cases from a one-year nationwide survey in France. *Clin Infect Dis*. 1995;20(3):501–506. doi:10.1093/clinids/20.3.501
190. Child JS. Risks for and prevention of infective endocarditis. *Cardiol Clin*. 1996;14(3):327–343. doi:10.1016/s0733-8651(05)70287-3
191. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736–1754. doi:10.1161/circulationaha.106.183

67

Respiratory Tract Infections

Jason Cross, Evan Horton, and Dinesh Yogaratnam

CORE PRINCIPLES	CHAPTER CASES
ACUTE BRONCHITIS	
1 Acute bronchitis is a commonly encountered clinical diagnosis exhibited by cough for more than 5 days and generally does not require treatment with antimicrobial agents.	**Case 67-1 (Questions 1-7)**
ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE	
1 Antibiotics should be provided to patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) if three primary symptoms (increased dyspnea, increased sputum volume, and increased sputum purulence) are present, if two primary symptoms are present and increased sputum purulence is one of the	**Case 67-2 (Question 3, 4)**

	symptoms, or if mechanical ventilation is required.	
2	Hospitalized patients with AECOPD should both be optimally treated and their chronic obstructive pulmonary disease (COPD) management should be assessed to decrease the likelihood of readmission. Baseline COPD medications should be reviewed and adjusted based on disease severity. Additionally, an assessment of patients' understanding of the role of medications (maintenance therapy vs rescue medications), their ability to use inhalers correctly and access to prescribed medications, and discussions regarding pulmonary rehabilitation should take place. Pharmacologic venous thromboembolism prophylaxis should also be considered in this high-risk population.	**Case 67-2 (Question 1, 2, 5, 6)**
3	Vaccinations against influenza and *Streptococcus pneumoniae* in patients with COPD or with previous pneumonia reduce disease-associated morbidity.	**Case 67-2 (Question 7)**
	COMMUNITY-ACQUIRED PNEUMONIA	
1	The first decision after a diagnosis of community-acquired pneumonia (CAP) is to determine the need for hospitalization and severity of disease. Several predictive rules including the pneumonia severity index (PSI) and CURB-65 (confusion, uremia, increased respiratory rate, low blood pressure, and age ≥65 years) have	**Case 67-3 (Question 2)**

	been developed to facilitate site-of-care decision-making.	
2	The most frequently isolated bacterial pathogen causing CAP, regardless of epidemiologic factors and severity of illness, is *S. pneumoniae.*	**Case 67-3 (Question 4)**
3	The most important consideration when selecting empiric therapy is to identify patients at risk for infection with drug-resistant *S. pneumoniae* (DRSP).	**Case 67-3 (Question 5)**
4	Patients who continue to have a positive laboratory test result for influenza more than 48 hours after the onset of illness are at high risk of requiring hospitalization; those who are not improving should be treated.	**Case 67-4 (Question 2)**
	HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA	
1	Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs at least 48 hours after hospital admission. Ventilator-associated pneumonia (VAP) refers to pneumonia that arises 48 to 72 hours after endotracheal intubation.	**Case 67-5 (Question 1)**
2	The major difference in the bacteriology between CAP and HAP/VAP is a shift to gram-negative pathogens, multidrug-resistant (MDR) pathogens, and methicillin-resistant *Staphylococcus aureus* (MRSA) in HAP/VAP.	**Case 67-5 (Question 1)**
3	Risk factors for pneumonia caused by	**Case 67-5**

	MDR pathogens include antimicrobial therapy in the previous 90 days, current hospitalization of 5 days or more, or immunosuppressive disease or therapy.	**(Question 1)**
4	Patients with early-onset pneumonia (<5 days) and no MDR risk factors can be treated with a single agent, including a non-antipseudomonal third-generation cephalosporin or ertapenem, ampicillin/sulbactam, or an antipneumococcal fluoroquinolone. Empiric therapy in those with late-onset pneumonia (≥5 days) or MDR risk factors should include a combination of antibiotics active against *Pseudomonas aeruginosa.* This regimen usually includes an antipseudomonal β-lactam, plus either an aminoglycoside or ciprofloxacin/levofloxacin. Vancomycin or linezolid should be added if MRSA risk factors are present or if there is a high incidence at the health care facility.	**Case 67-5 (Question 2)**

ACUTE BRONCHITIS

Definition and Incidence

Acute bronchitis (AB) is defined as an acute, self-limiting respiratory illness of the upper bronchi accompanied by cough for more than 5 days.[1–3] AB may be associated with or without purulent sputum production, and fever is rare.[2] Patients may be diagnosed with AB when there is no evidence of pneumonia and when acute asthma, an acute exacerbation of chronic obstructive pulmonary disease

(AECOPD), or the common cold have been ruled out as the cause of cough.[3] Although the true incidence of AB is unknown, it is considered to be one of the most common conditions encountered in clinical practice, accounting for ~7.7 million outpatient visits per year.[1,4]

Pathophysiology and Epidemiology

AB is characterized by the inflammatory response to infection in the epithelium of the bronchi. Further progression of this inflammation leads to thickening of the tracheal mucosa.[1,2] Sloughing of cells from the tracheobronchial epithelium and inflammatory mediators causes bronchospasm and reduced forced expiratory volume in 1 second (FEV_1) that usually improves after 5 weeks. Spread of pathogen and inflammatory response correlate with patient symptoms. Although bacteria can be isolated from sputum, bacterial invasion of the bronchial tree rarely occurs, and the role of bacterial pathogens in AB is limited.[5] The vast majority of cases of AB are presumed to be caused by viruses.[2,5–7]

Clinical Presentation

Cough lasting for more than 5 days is the hallmark sign of AB. Although the illness is self-limited, cough can last for up to 3 weeks (typical duration 10–20 days). Sputum production occurs in up to 50% of cases, but it does not indicate bacterial infection.[3] Fever is unusual in most cases; when present, it should prompt investigation for influenza (during appropriate seasons) or for pneumonia (if other clinical signs are present).

Overview of Drug Therapy

CASE 67-1

Question 1: A.R. is a 50-year-old male presenting with a cough. His symptoms have persisted for 8 days, and he now produces yellow sputum with each cough. He has had no recent illnesses; however, his 14-year-old son in high school has experienced recent mild colds. A.R. denies nausea, vomiting, or fever and chills. A review of systems reveals fatigue and difficulty sleeping because of cough. Past medical history includes hypertension managed with lisinopril and hyperlipidemia for which he takes atorvastatin. He also takes low-dose aspirin for stroke prevention. Vital signs indicate a temperature of 98.78 °F (37.1 °C), heart rate of 70 beats/ minute, blood pressure of 130/70 mm Hg, and respiratory rate of 18 breaths/minute with accompanying oxygen saturation of 98% on room air. His physical examination is normal, except for positive for coarse breath sounds that clear with coughing.

What signs and symptoms in A.R. are consistent with AB?

A.R.'s persistent cough for more than 5 days in the absence of other symptoms including fever or myalgia is typical with AB.[3] Pneumonia must be ruled out; however, normal oxygen saturation and lack of focal signs on pulmonary physical examination makes this diagnosis less likely. Sputum production is common, although not present in all cases of AB. Symptoms can be present at night, contributing to A.R.'s symptoms of fatigue.

Microbiology

Case 67-1, Question 2: What are the most likely causes of A.R.'s AB?

The causative agent for AB is identified in a minority of cases; however, when pathogens are isolated, they are usually of viral etiology.[2,5–7] The most common viruses associated with AB include influenza, parainfluenza, respiratory syncytial virus (RSV), coronavirus, adenovirus, and rhinovirus. The bacterial pathogens associated with AB include *Bordetella pertussis, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*. Bacterial infection causing AB should primarily be considered in patients with underlying COPD, mechanical ventilation (tracheobronchitis), or in cases of outbreaks and exposures (e.g., *Bordetella pertussis*).[2]

Sick contacts, duration of incubation (2–7 days for viruses vs weeks for atypical bacteria), and previous exposures should be considered when determining the etiologic agent responsible for AB. Specific symptoms reveal infection caused by specific pathogens, such as an inspiratory whoop and posttussive emesis (*B. pertussis*), pharyngitis and cough lasting longer than 4 weeks (*Mycoplasma pneumoniae*), hoarseness with low-grade fever (*Chlamydophila pneumoniae*), or cough with fever and myalgias (influenza).[2] Given A.R.'s lack of sick contacts with bacterial infections (his son's recent colds are most likely of viral etiology), time course of present illness, and absence of symptoms suggestive of influenza, a viral etiology (other than influenza) is most likely to be the cause of his symptoms.

Clinical Diagnosis and Treatment

Case 67-1, Question 3: Should A.R. be provided an antimicrobial agent for his AB?

Antibiotics have not been shown to substantially reduce the duration or severity of AB.[8] Thus, expert guidelines in the United States and abroad recommend against the routine use of antimicrobial agents for the treatment of AB in patients who are immunocompetent.[3,6,7,9] Despite these recommendations, antimicrobials are frequently prescribed.[10] Inappropriate use of antimicrobial therapy is a public health concern because it may lead to unnecessary adverse events and increased antimicrobial resistance.

One exception to avoidance of antimicrobial therapy in AB is if *Bordetella pertussis* infection (whooping cough) is suspected. In these cases, antibiotic therapy with a macrolide antibiotic is recommended, and patients should remain in isolation for the first 5 days of treatment to prevent disease transmission.[1,3] In A.R.'s case, no antimicrobial agent is warranted.

Case 67-1, Question 4: Should a sputum culture be obtained from A.R.? What other diagnostics should be considered?

Obtaining a sputum sample for culture to determine the presence of the causative agent or diagnostic screening for atypical pathogens is not routinely indicated for AB. The rationale is that most of the identified pathogens have no specific treatment (viral illnesses), and the isolated organisms often are not true pathogens. Diagnostic screening, however, should be performed during influenza season or during outbreaks of *B. pertussis* or other atypical pathogens for infection control purposes. The use of biomarkers, such as procalcitonin or C-reactive protein (CRP), for the diagnosis of bacterial infection, may decrease inappropriate antimicrobial use in AB, but their routine use is not recommended at this time.[3,11,12]

Case 67-1, Question 5: What symptom-guided therapies should be offered to A.R.?

Symptom-guided therapies include the use of inhaled β_2-agonists (albuterol) for shortness of breath, particularly in patients with underlying reactive airway disease; inhaled or systemic steroids for persistent cough; nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or acetaminophen to alleviate myalgias or fever; or antihistamines (brompheniramine), antitussives (codeine, dextromethorphan, or benzonatate), or mucolytics (guaifenesin) for cough. These symptom-guided treatments, however, are not backed by strong evidence demonstrating a clear benefit in patients with AB.[1–3,13,14] As such, using each of these treatments should consider the balance between perceived benefit and risk of adverse events. Given A.R.'s troublesome cough that has kept him up at night, a trial of an antitussive such as dextromethorphan is a reasonable first option. NSAIDs should be avoided given his concurrent aspirin use and lack of clear indication. An inhaled β_2-agonist or steroid is also not necessary at this time.[12,15]

Case 67-1, Question 6: Should a chest radiograph be ordered for A.R.? What other illnesses may be considered as the cause of his symptoms?

It is important to distinguish AB from pneumonia with chest radiograph or other imaging tests in the presence of fever, tachycardia, and tachypnea; physical examination findings such as egophony or rales; hypoxemia; or mental status changes (especially in the elderly).[2,3] Clinical differentiation of AB from AECOPD, postnasal drip, gastroesophageal reflux disorder (GERD), and asthma must also be made (discussed separately in this chapter and in Chapter 23, Upper Gastrointestinal Disorders, and in Chapter 18, Asthma, respectively). In A.R.'s case, no signs of pneumonia are present on physical examination or on reviewing symptomatology; therefore, no chest radiograph is warranted. Frequent or persistent symptoms or risk factors for COPD would warrant an investigation for chronic bronchitis. Wheezing or frequent AB outbreaks and GERD symptoms would guide evaluations for asthma or gastrointestinal disorders, respectively.

Patient Education

Case 67-1, Question 7: What education would you provide to A.R. to dissuade his perceived need for an antibiotic?

An evaluation of A.R.'s expectations for therapy is important to alleviate his potential concerns about the physician's decision to not prescribe antimicrobials. Overuse of antibiotics in AB is often driven by prescribers' acquiescence to patient requests for antibacterial drug therapy. Communication is key with each patient to provide insight into the potential causative agents of AB, the natural course of the disease, the role of symptomatic relief, and reasons for avoiding prescriptions for antibiotics.

ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition, Incidence, and Epidemiology

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is a persistent and progressive reduction in airflow that results from repeated exposure to noxious particles. The chronic inflammation in the lungs results in a narrowing of the small airways, destruction of alveoli, and loss of elastic recoil. Of note, COPD may or may not be accompanied by increased sputum production and chronic cough. This disease is also characterized by acute exacerbations (AECOPD), which is defined as a worsening of symptoms that is more severe than the typical day-to-day variations that patients experience during the stable phase of their disease. Acute exacerbations of COPD typically require a change in medication to relieve symptoms and improve outcomes.[16] Maintenance therapy for COPD (discussed separately in Chapter 19, Chronic Obstructive Pulmonary Disease) is often targeted to reduce the severity and frequency of AECOPD.

COPD is associated with high health care expenditures, decreased quality of life, significant morbidity, and high mortality around the world. The global prevalence and annual death rate of COPD have been estimated to be 11.7% and 3 million deaths, respectively. Although COPD is a chronic illness, acute exacerbations are responsible for most of the economic and societal burden. AECOPD is associated with a decrease in quality-of-life measurements and an increase in the rate of decline in lung function, particularly if not treated early.[16,17]

The primary precipitating factors for AECOPD are infection of the bronchial tree and air pollution.[16,18–20] As many as one-third of the cases of AECOPD do not have a cause identified.

Pathophysiology

Bacteria, viruses, and pollutants lead to inflammatory responses.[20] Airway inflammation, associated with increases in interleukin-8, tumor necrosis factor-α, and neutrophils, contributes to pulmonary remodeling, decreased ciliary clearance of mucus, worsening airflow obstruction, and the respiratory symptoms associated with AECOPD.

Viruses have been identified as the etiologic cause of AECOPD in up to one-third of the cases, whereas bacteria have been identified in up to one-half of cases.[20] The microorganisms most commonly associated with AECOPD include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. In patients with GOLD 3 (severe) or GOLD 4 (very severe) COPD, *Pseudomonas aeruginosa* is more prevalent.[16] Many patients with COPD are also colonized with bacteria during the stable phase of their illness.[21] Evidence suggests that either an increased burden of the same colonizing microorganism(s) or acquisition of a new bacterial species may be associated with exacerbating COPD symptoms.[16,21] Decreases in adaptive immune responses occur as COPD disease progresses, making patients susceptible to more frequent exacerbations caused by bacterial pathogens. Additionally, pathogens associated with exacerbations tend to increase in virulence and antimicrobial resistance as the underlying disease progresses.[16,19,20,22] A possible mechanism for prolonged infection and colonization in patients with COPD is suggested by interactions between both viruses and bacteria altering immune response.[20]

Clinical Presentation and Diagnosis

Common features of AECOPD include the following: breathlessness, increased cough, increased sputum volume, and increased sputum purulence. In contrast to AB, purulent sputum in AECOPD is associated with an acute bacterial infection.[22] Less specific symptoms include insomnia, fatigue, tachycardia, tachypnea, and a decrease in exercise tolerance. Patients often report a decrease in ability to conduct activities of daily living.[16]

Diagnostic considerations in the evaluation of patients with AECOPD include pulse oximetry and arterial blood gases, electrocardiogram, and complete blood count including white blood cell (WBC) differential. Chest radiographs are helpful to rule out pneumonia, pneumothorax, or pleural effusion. An assessment of comorbidities, such as the presence of heart failure or lung diseases (eg, asthma or lung cancer), should be performed to aid in both prognosis and diagnosis.[16],[18] Collection of sputum samples for Gram stain and culture are not generally recommended, but it may be helpful if patients are failing initial therapies. There is growing evidence that the bacterial infection biomarkers procalcitonin and CRP are useful to curtail antibiotic prescribing in patients with AECOPD. Similarly, evidence suggests that patients with AECOPD who have lower blood eosinophil levels may not experience clinical benefit from glucocorticoid administration. However, more robust supportive data are needed before these blood tests can be routinely recommended in the management of patients with AECOPD.[16]

Overview of Treatment

Pharmacotherapy directed at AECOPD includes bronchodilators and supplemental oxygen, antimicrobial therapy to decrease the burden of microorganisms, and corticosteroids targeting the inflammatory response.[16],[18] Methylxanthines (aminophylline or theophylline) are rarely used owing to conflicting and limited evidence of efficacy and concerns about toxicity.[16] Nonpharmacologic AECOPD treatment considerations include decisions regarding the site of care and the level of respiratory support. These nondrug considerations are not discussed in detail in this chapter but are available in the GOLD guidelines.[16]

Disease Severity

CASE 67-2

Question 1: T.H. is an 81-year-old White female presenting to the emergency department (ED) because she "cannot catch my breath." At baseline she is on 4 L of oxygen continuously via nasal cannula. However, during the last week, she has experienced worsening dyspnea necessitating help with daily activities including bathing and feeding. Her daughter had contacted T.H.'s primary care physician who directed the patient to the ED when T.H. seemed "out of it" and was difficult to arouse. T.H.'s daughter indicates that T.H. has been "having a cold" with increased sputum that is more yellow than in the past with frequent coughing spells. Past medical history is significant for very severe COPD, atrial fibrillation, depression, obstructive sleep apnea, morbid obesity, and a left humerus fracture. No medication allergies are noted. Medications at home include aspirin 81 mg PO daily, citalopram 20 mg PO daily, diltiazem extended-release capsule 240 mg PO daily, salmeterol–fluticasone dry powdered inhaler 50/250 one puff twice daily, and albuterol inhaler four puffs every 6 hours as needed for shortness of breath. Social history is significant for a >80-pack-year history of cigarette smoking, but she quit 4 to 5 years ago. In the ED she was afebrile, heart rate was 96 beats/minute, respiratory rate was 23 breaths/minute, blood pressure was 135/75 mm Hg, and oxygen saturation was 60% on 4 L of oxygen. T.H. is alert and oriented. She appears to be in respiratory distress, and she is using accessory muscles for breathing. Initial physical examination was significant for distant breath sounds and decreased air movement bilaterally, a noted absence of lower extremity edema, and an irregularly irregular heartbeat. Laboratory findings are as follows:

Arterial blood gases: pH, 7.34, P_{CO_2}, 60 mm Hg, P_{O_2}, 72 mm Hg
WBC, 9.8 × 10^3/μL (neutrophils 71%)
Hemoglobin, 12 g/dL
Platelets, 319 × 10^3/μL
Sodium, 135 mmol/L
Potassium, 3.7 mmol/L
Chloride, 91 mmol/L
Bicarbonate, 39 mmol/L
Blood urea nitrogen (BUN), 15 mg/dL
Serum creatinine (SCr), 1.21 mg/dL
Glucose, 104 mg/dL
Brain natriuretic peptide, 66 pg/mL
Troponin, >0.07 ng/mL
Thyrotropin, 1.63 μIU/mL

Chest radiograph indicated small pleural effusions, but it was otherwise negative for infiltrates or consolidation. An electrocardiogram indicated the presence of atrial fibrillation. Pulmonary function tests (obtained 1 year ago) indicated an FEV_1 to forced vital capacity ratio of 0.39 and an FEV_1 of 37% predicted.

How would you stage the severity of this exacerbation for T.H.?

T.H. has several risk factors for a poor outcome, including the presence of atrial fibrillation and severe COPD defined by her high home oxygen requirement, chronic carbon dioxide retention (as evidenced by her elevated partial pressure of carbon dioxide [P_{CO_2}]), and low baseline FEV_1.[16]

Clinical signs and symptoms consistent with a severe exacerbation include the use of accessory respiratory muscles, paradoxical chest wall movements, worsening or new cyanosis, peripheral edema, hemodynamic compromise, signs of right heart failure, and alterations in mental status.[16],[18] T.H. has two of these factors: reduced alertness and use of accessory muscles.

Disease Prevention

Case 67-2, Question 2: Which therapies should T.H. receive to alleviate her shortness of breath?

Supplemental oxygen to alleviate hypoxemia is a foundation of treatment for AECOPD. Controlled provision of oxygen is crucial to provide an oxygen saturation of >90% or a Pa_{O_2} of >60 mm Hg. Hypoxia that is not easily reversible warrants further examination for venous thromboembolism, pneumonia, or other causes. A repeat arterial blood gas should be obtained within 1 hour of initiation of supplemental oxygen to assess for carbon dioxide retention or acidosis.

Short-acting bronchodilators should be initiated promptly in all patients with AECOPD. Inhaled β_2-agonists, such as albuterol, with or without an anticholinergic agent (ipratropium), are the preferred agents.[16] If the patient does not respond, a methylxanthine (theophylline or aminophylline) may be considered as second-line therapy. There is no role for long-acting bronchodilators in AECOPD at this time.

Case 67-2, Question 3: Does T.H. need to be treated with antimicrobial therapy?

The "cardinal" symptoms of AECOPD include increases in sputum purulence, sputum volume, and dyspnea.[23] The use of cardinal symptoms as a method of staging AECOPD severity and deciding on antibiotic initiation has been used in several prospective studies and is recommended in the GOLD guidelines.[16],[24]

Experts advocate for the use of antibiotics for AECOPD, particularly when two or three cardinal symptoms are present.[16],[18] Specifically, the GOLD guidelines recommend antibiotics for patients with three cardinal symptoms (increased dyspnea, increased sputum volume, and increased sputum purulence); two cardinal symptoms, if increased sputum purulence is one of the symptoms; with the need for mechanical ventilation for their AECOPD.[16]

T.H. is exhibiting all three of the cardinal symptoms and, therefore, she should receive antibiotics. Likely benefits would be enhanced treatment success, improvement in pulmonary function, prevention of relapse, decreased risk for rehospitalization, and reduction of the severity of her exacerbation.

Case 67-2, Question 4: Which antimicrobial agent should be selected for treating T.H.? What duration of treatment is recommended?

Given T.H.'s history, diminished mental status, and risk factors for poor outcomes, intravenous (IV) administration seems appropriate for the initial antibiotic administration. Potential risk factors for *P. aeruginosa* should be evaluated. If T.H. demonstrates risk factors for *P. aeruginosa*, an antipseudomonal β-lactam, such as cefepime, ceftazidime, or piperacillin/tazobactam, would be an appropriate initial agent. If no risk factors for *P. aeruginosa* exist, a β-lactam/β-lactamase inhibitor such as ampicillin/sulbactam, or a third-generation cephalosporin such as ceftriaxone should be selected. If necessary, a respiratory fluoroquinolone such as moxifloxacin or levofloxacin could be considered, but the risks of adverse reactions

to this class of antibiotic, especially in the elderly, should be weighed carefully. All these therapies are active against drug-resistant *Streptococcus pneumoniae* (DRSP). If T.H. improves on one of these parenteral agents and is ready for discharge, T.H. could transition to an oral agent, such as high-dose amoxicillin/clavulanate.

Another important consideration for initial selection of antimicrobials is an evaluation of antibiotic history. Alternative antimicrobials from another class should be considered if patients have been previously treated in the last 3 months.[16] Additionally, if no improvements in symptoms occur within 72 hours, consider obtaining a sputum sample for directed therapy.[16]

The optimal duration of antibiotic therapy for AECOPD remains unknown. A duration of 5 to 10 days has been suggested, but this is an area in need of further research.[16]

Case 67-2, Question 5: Should T.H. be treated with corticosteroids? If so, which dose and duration is recommended?

In the setting of AECOPD, systemic corticosteroids help to improve lung function, shorten recovery time, and prevent relapses. Based on available evidence, the GOLD guidelines recommend a corticosteroid regimen of 40 mg/day of prednisone for 5 days in patients with AECOPD.[16] This regimen would be appropriate for T.H., although an equivalent intravenous regimen could be considered if she was not able to take an oral regimen. Higher doses and longer durations of therapy have not been found to confer a clinical advantage, and intravenous and oral regimens are considered equally effective.[25],[26] In those patients having received more than 3 weeks of steroids or multiple course of steroids in the previous months, tapering the dose should be considered. Although it is more expensive, nebulized budesonide is an alternative to oral corticosteroids for treatment of AECOPD.[16]

Enhancing Patient Outcomes

Case 67-2, Question 6: What factors should be assessed for T.H. during her hospitalization, and what follow-up should be planned to help assure she recovers fully and is not readmitted for COPD?

Hospitalized patients with AECOPD should both be optimally treated and their COPD management be assessed to decrease the likelihood of readmission. T.H.'s baseline COPD medications should be examined and adjusted based on disease severity (see Chapter 19, Chronic Obstructive Pulmonary Disease for details). Additionally, an assessment of her understanding of the role of medications (maintenance therapy vs rescue medications), ability to use inhalers correctly, access to her prescribed medications, and discussions regarding pulmonary rehabilitation should take place.[16,17] Consideration for pharmacologic venous thromboembolism prophylaxis (see Chapter 11, Thrombosis) should also be made in this high-risk population.[16,27]

PREVENTION OF COMMON RESPIRATORY INFECTIONS BY VACCINATION

Case 67-2, Question 7: Which vaccines should T.H. receive as part of her COPD management?

Vaccination records for influenza and *S. pneumoniae* should be evaluated in T.H. All patients with COPD should receive annual influenza vaccination to reduce the risk of serious illness, lower the frequency of AECOPD, and improve mortality.[16,17] Vaccination against *S. pneumoniae* with the 23-valent polysaccharide vaccine (PPSV23) is recommended for patients with COPD age 19 years and older, whereas vaccination with both the 13-valent conjugated pneumococcal vaccine (PCV13) and PPSV23 is recommended for all patients ages 65 years and older. Unlike with the influenza vaccine, however, there is no strong evidence for reduced AECOPD

risk with vaccination against *S. pneumoniae*. Despite this shortcoming, the guidelines recommend the pneumococcal vaccine as part of the overall health plan of the patient.

COMMUNITY-ACQUIRED PNEUMONIA

Definition, Incidence, and Epidemiology

Pneumonia is an infection of the lung parenchyma. Community-acquired pneumonia (CAP) refers to pneumonia acquired in the absence of health care system exposure (ie, hospital, long-term care, chronic antibiotic exposure). Diagnosis is dependent on clinical features and radiologic evidence of an infiltrate, and it is further supported by physical examination and/or hypoxemia.

Pneumonia accounts for ~3 million deaths per year worldwide and is leading in infectious causes of death.[28] Current estimates show that CAP accounts for 24.8 cases per 10,000 discharges in the U.S. adult population, and it affects primarily the elderly (65 to 79 years: incidence 63/10,000; 80 years and older: incidence 164.3/10,000).[29] In the pediatric population, CAP accounts for 15.7 cases per 10,000 discharges, with infants and young children showing increased risk (<2 years: incidence 62.2/10,000).[30] The overall mortality rate for patients 65 years and older is 5.6% and is more pronounced in hospitalized patients (8.5%) compared to outpatients (3.8%).[31]

Pathophysiology

Development of CAP occurs through the inhalation of infectious particles via droplets or aerosols, or the aspiration of oral flora. Rarely, hematogenous spread of bacteria from distant sources into the lungs may occur, as well as direct extension of infection to the lung from contiguous areas, such as the pleural or subdiaphragmatic spaces.

Once bacteria reach the tracheobronchial tree, defects in local pulmonary defenses facilitate infection. Contributing factors include inflammation-mediated injury to bronchial epithelium leading to depressed mucociliary clearance and a blunted cellular and humoral response. Patients with underlying or acquired immunodeficiencies are at an increased risk.

Clinical Presentation and Diagnosis

In the majority of CAP cases, patients present acutely with high fever, chills, tachypnea, tachycardia, and productive cough. Physical examination findings are usually localized to a specific lung zone and can include crackles, rhonchi, bronchial breath sounds, dullness, or egophony. On rare occasions, CAP exhibits a subacute presentation with fever, nonproductive cough, constitutional symptoms, and absent or diffuse findings on lung examination. Children with CAP may present with vomiting.

A chest radiograph or other imaging technique revealing an infiltrate is required for the diagnosis of CAP.[32] Radiographic manifestations of diseases such as congestive heart failure and malignancy can obscure the infiltrate, reinforcing the need to utilize both clinical and chest radiographic findings.

Based on updated recommendations from the most recent American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) guideline, pretreatment blood cultures and expectorated sputum cultures should only be obtained in patients presenting with severe CAP or in patients being empirically treated for suspicion of pneumonia because of methicillin-resistant *Staphylococcus aureus* (MRSA) or *P. aeruginosa*.[33]

Overview of Drug Therapy

Antibiotic therapy for CAP is empirical in the majority of cases and should always consider the most likely pathogen(s), underlying patient characteristics, and the severity of disease. Based on these

variables, clinicians can triage patients for risk of infection caused by antibiotic-resistant pathogens and appropriately tailor therapy.

CLINICAL PRESENTATION

CASE 67-3

QUESTION 1: J.T. is a 45-year-old female presenting to the ED with fevers, chills, and chest pain. Her symptoms have persisted for 4 days, and she has a productive cough with rust-colored sputum and dyspnea on exertion. She has had no recent illnesses and no known sick contacts, but she was recently released from a 2-year period of incarceration. She has tried acetaminophen to alleviate her fever and chest pain. Past medical history is positive for asthma, for which she is prescribed fluticasone and albuterol, and depression, for which she takes paroxetine. Vital signs reveal a temperature of 104.18 °F (40.1 °C), heart rate of 128 beats/minute, blood pressure of 130/76 mm Hg, and respiratory rate of 32 breaths/minute with accompanying oxygen saturation of 85% on 5 L of oxygen by nasal cannula. The remainder of the physical examination is notable for orientation to person but not place or time and for diffuse crackles bilaterally, which are most apparent on the right side. Laboratory results include the following:

WBC count, 15,500 cells/μL
Hematocrit, 29.3%
Platelets, 150,000 cells/μL
Sodium, 133 mmol/L
Potassium, 3.8 mmol/L
BUN, 23 mg/dL
SCr, 0.8 mg/dL
HCO_3, 28 mEq/L
Glucose 148, mg/dL
Arterial blood gases: pH 7.42, P_{O_2}, 61 mm Hg, P_{CO_2}, 46 mm Hg

A test for human immunodeficiency virus is negative. Chest radiograph reveals a right lower lobe infiltrate. Upon interview, J.T. reveals an allergy to penicillin that she states led to a rash following exposure about 15 years ago.

What signs, symptoms, and tests are consistent with CAP in J.T.?

Most patients with CAP present with cough with sputum production, dyspnea, and pleuritic chest pain.[34] Patients may show signs of the systemic inflammatory response syndrome, including tachycardia, tachypnea, fever, and an abnormal WBC count.[35]

Auscultatory examination often reveals decreased breath sounds, crackles or rhonchi, or egophony in patients with consolidation. Signs and symptoms associated with severe pneumonia are grouped into minor and major criteria as defined by the ATS/IDSA guidelines.[32,33] Minor criteria include respiratory rate >30 breaths/minute at admission; ratios of the Pa_{O_2} to fraction of inspired oxygen (F_{IO_2}), (Pa_{O_2}/F_{IO_2}), <250 mm Hg; systolic blood pressure (SBP) <90 mm Hg, or diastolic blood pressure (DBP) <60 mm Hg; confusion; multilobar infiltrates; SBP <90 mm Hg, despite aggressive fluid resuscitation; BUN of at least 20 mg/day; leukopenia; thrombocytopenia; and hypothermia. Major criteria include requirement of mechanical ventilation and requirement of vasopressors for more than 4 hours.

Clinical findings and a positive infiltrate by chest radiograph or other imaging technique is required for the diagnosis of pneumonia.[32] Patients who are hospitalized based on clinical symptoms absent of positive imaging should have repeat imaging performed 24 to 48 hours postadmission.

Disease Severity

Case 67-3, Question 2: Given the clinical condition of J.T. in the ED, where should her care be continued?

The first decision after a diagnosis of CAP is to determine whether the patient requires hospitalization. Several predictive rules facilitate site-of-care decision-making. The two best-studied tools that are endorsed by the ATS/IDSA guidelines are the pneumonia severity index (PSI) and the CURB-65 rule, with preference given to PSI.[33]

The PSI uses individually scored demographic characteristics (age, gender, nursing home residence), comorbidities (liver disease, CHF, renal disease, neoplasm), physical examination findings (mental status, RR, SBP, temp, HR), and laboratory data (sodium, glucose, Hct, BUN). The total PSI score categorizes patients into

one of five classes that are associated with an escalating risk of death (**Table 67-1**).[36]

Table 67-1
Predicted Pneumonia Mortality and Recommended Site of Care

System and Score	Predicted 30-Day Mortality (%)	Recommended Site of Care
PSI strata I–II (≤70)	0.1–0.7	Outpatient
PSI strata III (71–90)	0.9–2.8	Admit to hospital ward
PSI strata IV–V (≥91)	9.3–27	Admit to hospital; consider ICU
CURB-65 score 0–1	0.7–2.1	Outpatient
CURB-65 score 2	9.2	Admit to hospital ward
CURB-65 score ≥3	14.5–57	Admit to ICU

CURB-65, confusion, uremia, increased respiratory rate, low blood pressure, and age ≥65 years; ICU, intensive care unit; PSI, pneumonia severity index.

Source: Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.

The CURB-65, developed by the British Thoracic Society, is a simple tool that focuses on five assessments: confusion (owing to pneumonia), uremia (BUN > 19 mg/dL), respiratory rate of at least 30 breaths/minute, SBP <90 mm Hg systolic or DBP <60 mm Hg, and age of at least 65 years.[37] Each criteria receives one point, and the cumulative score is associated with a specific (rising with higher score) 30-day mortality risk. Based on the score, subsequent care should be as follows: 0–1 = outpatient; 2 = admission to ward; ≥3 = intensive care unit (ICU) care.

Both scales identify patients at low risk of death, but the PSI was found to have a higher sensitivity and negative predictive value for identifying mortality.[37] The need for ICU admission can be subjective; however, the ATS/IDSA guidelines recommend that patients with three or more minor criteria, or at least one major criteria for severe CAP, be admitted to the ICU.[33]

Using the PSI, patient J.T.'s CAP severity can be assessed as: 45-year-old female (35 points [45 for age − 10 for gender female]); respiratory rate >30 breaths/minute (20 points); heart rate >125 beats/minute (20 points); temperature >40 °C (15 points); hematocrit <30% (10 points); and altered mental status (20 points). A total score of 120 points places J.T. in risk strata IV (30-day mortality risk: 9.3%–27%), and she should be admitted to the hospital, potentially to the ICU.

Using the CURB-65, J.T. has a score of 3 (30-day mortality of 9.2%) based on uremia, confusion, and increased respiratory rate, and she should be admitted to the ICU.

Case 67-3, Question 3: What testing should be performed to obtain a microbiologic diagnosis in J.T.?

J.T. has no major criteria for severe sepsis, but at least three minor criteria, qualifying her to have severe CAP (BUN >20 [23], RR >30 [32], confusion [A & O × 1]). Based on this, J.T. should get both blood and expectorated sputum cultures collected before treatment initiation.

Microbiologic testing is not routinely recommended for patients in either the outpatient or inpatient setting unless they are diagnosed with severe CAP or suspected of being infected with MRSA or *Pseudomonas*.[33] Urine antigen tests for pneumococcus and *Legionella pneumophila* serogroup 1 are only indicated in severe CAP or in cases where epidemiologic factors warrant testing (eg, travel or exposure to an outbreak). Because of conflicting evidence, procalcitonin levels are not currently recommended as a means to determine the utility of antibiotic therapy.

Current guidelines recommend influenza testing during traditional "flu season" utilizing a rapid influenza molecular assay.[33]

Microbiology

Case 67-3, Question 4: What pathogens are most likely in J.T.?

Pathogens are only identified in 38% of CAP, with bacterial causes identified in only 14% of patients.[29] The top three pathogens responsible for CAP are rhinovirus, influenza, and *S. pneumoniae.* The major pathogens for CAP are summarized in **Table 67-2**. *Streptococcus pneumoniae* uses two survival strategies.[38] The first pertains to a noninvasive phenotype that uses surface adhesions, immune evasion strategies, and secretory defenses to promote long-term carriage within the nasopharynx. Deficits in host defense, such as an immunocompromised state, allow colonizing strains of low virulence to cause invasive disease. The second survival strategy depends on efficient person-to-person transmission and associated rapid disease induction by an invasive phenotype. Risk factors for the invasive pneumococcal phenotype are age younger than 2 years or older than 64 years, asplenia, alcoholism, diabetes mellitus, antecedent influenza, defects in humoral immunity, and human immunodeficiency virus infection.[39] Other risk factors less likely to be associated with invasive disease include poverty and crowding, cigarette smoking, chronic lung disease, severe liver disease, recent exposure to antibiotics, and chronic proton-pump inhibitor use.[39]

Table 67-2
Common Pathogens in Community-Acquired Pneumonia

Ambulatory	Hospitalized, Non-ICU	Hospitalized, ICU
Streptococcus pneumoniae	*S. pneumoniae*	*S. pneumoniae*
Mycoplasma pneumoniae	*M. pneumoniae*	*Staphylococcus aureus*
Haemophilus influenzae	*C. pneumoniae*	*Legionella* species
Chlamydophila pneumoniae	*Staphylococcus aureus*	Gram-negative bacilli
Respiratory viruses[a]	*H. influenzae*	*H. influenzae*
	Legionella species	
	Respiratory viruses[a]	

[a]Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

Source: Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Disease Society of America. *Am J Respir Crit Care Med*. 2019;200:e45–e67.

Following the introduction of the first pneumococcal conjugate vaccine (PCV7) in 2000 and the expanded PCV13 in 2010, the incidence of invasive disease and all-cause pneumonia have significantly fallen.[40] However, the advent of these vaccines has not led to a significant pneumonia decline in high-risk pediatric patients, specifically children younger than 5 years with moderate-to-severe asthma, or in adults with asthma and one or more of the following comorbid conditions: heart disease, lung disease, diabetes, or neuromuscular disease.[40] Current Centers for Disease Control and Prevention (CDC) guidelines recommend PCV13 for patients younger than age 2 years or patients ages 2 to 64 years who are high risk for pneumococcal disease and the pneumococcal polysaccharide vaccine (PPSV23) for high-risk populations and all patients 65 years and older.[40]

Atypical pathogens, including *L. pneumophila*, *C. pneumoniae*, and *M. pneumoniae*, account for ~25% of CAP worldwide.[41] However, atypical pathogens may be present in up to 60% of CAP episodes because of coinfection.[42] Polymicrobial infection including atypical pathogens may lead to a more complicated course with extended lengths of hospital stay. Several studies have shown that antibiotic regimens that include coverage against these pathogens demonstrate a survival benefit over regimens that do not.[43–46] Legionnaires' disease, caused primarily by *L. pneumophila* serogroup 1, accounts for 2% to 7% of CAP and is considered more severe among hospitalized patients.[41] Patients may present with high fever, nonproductive cough, low serum sodium concentration, high concentration of lactate dehydrogenase, and low platelet counts.[47]

Epidemiologic factors may favor the presence of certain bacterial pathogens and are listed in **Table 67-3**.[32] This highlights the importance of performing a thorough patient history to assist in the direction of therapy. Additional factors such as chronic oral steroid

use (≥10 mg prednisone/day), immunosuppression, and frequent antibiotic therapy will require augmented therapy.[48]

Table 67-3

Community-Acquired Pneumonia: Underlying Conditions and Commonly Encountered Pathogens

Condition	Commonly Encountered Pathogen(s)
Alcoholism	Oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Mycobacterium tuberculosis*
COPD or smoking	*Pseudomonas aeruginosa*, *Legionella* spp.
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis*, atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
HIV infection (early)	*M. tuberculosis*
HIV infection (late)	*M. tuberculosis*, *Pneumocystis jirovecii*, *Cryptococcus* spp., *Histoplasma* spp., *Aspergillus* spp., atypical mycobacteria (especially *Mycobacterium kansasii*), *Pseudomonas aeruginosa*
Hotel or cruise ship stay in previous 2 weeks	*Legionella* spp.
Travel to or residence in southwestern United States	*Coccidioides* spp., hantavirus

Travel to or residence in Southeast and East Asia	*Burkholderia pseudomallei*, avian influenza, SARS
Cough >2 weeks with whoop or posttussive vomiting	*Bordetella pertussis*
Structural lung disease (eg, bronchiectasis)	*P. aeruginosa*, *Burkholderia cepacia*, *Staphylococcus aureus*
Injection drug use	*S. aureus*, anaerobes, *M. tuberculosis*
Endobronchial obstruction	Anaerobes, *S. aureus*
In context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *F. tularensis* (tularemia)

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; SARS, severe acute respiratory syndrome.

Source: Adapted from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72. Reproduced by permission of Infectious Diseases Society of America.

Staphylococcus aureus is a major cause of nosocomial pneumonia; however, its significance in CAP is less clear. Traditionally, *S. aureus* has not been considered a common cause of CAP (~2.5% of cases), but it most likely occurs in association with influenza or in patients with lung abscess.[32],[49] Community-associated MRSA (CA-MRSA) is significantly different from the typical hospital-acquired strain. These differences include susceptibility to non–β-lactam antibiotics (eg, clindamycin and doxycycline) and clinical syndrome (necrotizing radiographic presentation, empyema formation, hemoptysis, and profound hypoxemia) associated with toxins including Panton–Valentine leukocidin.[50] Toxin-producing strains are also part of methicillin-sensitive *S. aureus*'s (MSSA) virulence.[51] The outcomes of patients

with MRSA and MSSA CAP are similarly poor, with prolonged length of hospital stay and a nearly 25% mortality.[52]

Respiratory virus can be the primary cause of CAP (22% in the United States) and may predispose patients to infection by another pathogen, often bacterial.[53] Respiratory viruses that cause CAP include influenza A and B, respiratory syncytial virus, rhinovirus, parainfluenza, adenovirus, human metapneumovirus, and coronavirus.[54] In patients coinfected with both viral and bacterial pathogens, the most common bacteria are *S. pneumoniae*, *S. aureus*, and atypicals.

Possible microbes causing J.T.'s CAP include *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, *S. aureus*, *H. influenzae*, *Legionella* species, and respiratory viruses.

Antibiotic Therapy

Case 67-3, Question 5: Which antimicrobial agent(s) should be chosen for the initial management of J.T.?

An approach to the patient with CAP and recommended antibiotic regimens based on the patient's site of care and severity of illness is provided in **Figure 67-1**. Delayed antibiotic therapy has been associated with an increased length of hospital stay and decreased survival in CAP; therefore, a rapid and correct diagnosis is imperative.[55],[56] ATS/IDSA CAP treatment guidelines recommend the first dose of antibiotic be given in the ED in an effort to avoid treatment delays associated with the hospital admission process.[33]

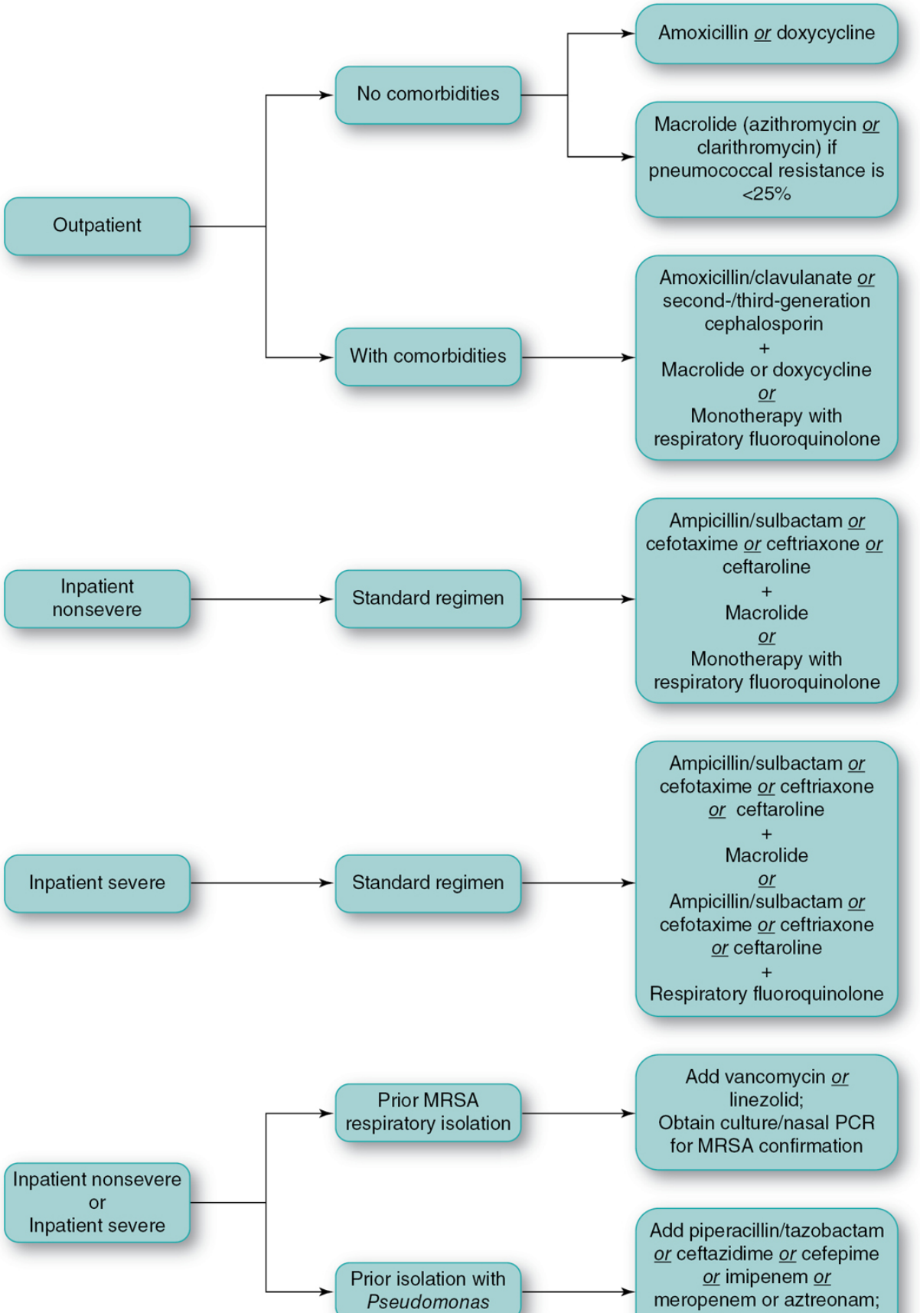

Outpatient
No comorbidities
Amoxicillin or doxycycline
Macrolide (azithromycin or clarithromycin) if pneumococcal resistance is <25%
With comorbidities
Amoxicillin/clavulanate or second-/third-generation cephalosporin + Macrolide or doxycycline or Monotherapy with respiratory fluoroquinolone
Inpatient nonsevere
Standard regimen
Ampicillin/sulbactam or cefotaxime or ceftriaxone or ceftaroline + Macrolide or Monotherapy with respiratory fluoroquinolone
Inpatient severe
Standard regimen
Ampicillin/sulbactam or cefotaxime or ceftriaxone or ceftaroline + Macrolide or Ampicillin/sulbactam or cefotaxime or ceftriaxone or ceftaroline + Respiratory fluoroquinolone
Inpatient nonsevere or Inpatient severe
Prior MRSA respiratory isolation
Add vancomycin or linezolid; Obtain culture/nasal PCR for MRSA confirmation
Prior isolation with Pseudomonas
Add piperacillin/tazobactam or ceftazidime or cefepime or imipenem or meropenem or aztreonam;

Figure 67-1 Approach to empiric antibiotic therapy in patients with community-acquired pneumonia. MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction. (From Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Disease Society of America. *Am J Respir Crit Care Med*. 2019;200:e45–e67.)

All adult patients, regardless of treatment setting, require at least empiric treatment for pneumococcus and atypical pathogens.[33] The choice of the initial regimen should be based on medical comorbidities or epidemiologic factors, including the possibility of antibiotic-resistant causative organisms. Pediatric patients should be treated with ampicillin or amoxicillin if younger than 5 years old, with a macrolide added for atypical coverage for children five years and older.[57] Children who are unvaccinated or have risk factors for DRSP should receive ceftriaxone in place of ampicillin or amoxicillin. Factors that increase the risk of DRSP are located in **Table 67-4**.

Table 67-4
Risk Factors for β-Lactam–Resistant *Streptococcus pneumoniae*

Age >2 or >65 years
β-Lactam therapy within the previous 3 months
Alcoholism
Medical comorbidities
Immunosuppressive illness or therapy
Exposure to a child in a day-care center
Recent hospitalization

Source: Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management

of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.

For patients without comorbidities, the preferred treatment in the outpatient setting is high-dose amoxicillin (1 g PO tid) or doxycycline (100 mg PO bid). Macrolide antibiotics (azithromycin 500 mg PO day 1, 250 mg PO days 2 to 5; clarithromycin 500 mg PO bid or 1 g ER PO daily) are recommended only when local pneumococcal isolates exhibit <25% resistance.[33] Adults with comorbidities should be treated with a combination of β-lactam plus macrolide or doxycycline, or with respiratory fluoroquinolone monotherapy (levofloxacin, moxifloxacin, or gemifloxacin). Amoxicillin/clavulanate is often the preferred β-lactam of choice. Amoxicillin (90 mg/kg/day) is the preferred outpatient treatment in children.[57]

β-Lactam resistance occurs through alteration of one or more of the penicillin-binding proteins that mediate bacterial cell wall production.[58] Penicillin-binding protein alterations in resistant strains decrease the affinity to all β-lactams such that higher concentrations are required for binding and inhibition of the enzyme. This further justifies the need for appropriate dosing of β-lactams in the treatment of CAP to minimize the development of resistance and promote optimal clinical outcomes.[59]

Adults with nonsevere CAP requiring inpatient admission, but without previous risk factors for or respiratory isolation of MRSA or *P. aeruginosa,* should be treated with a combination β-lactam (ampicillin/sulbactam, cefotaxime, ceftriaxone, or ceftaroline) plus a macrolide, or with a respiratory fluoroquinolone monotherapy.[33] Patients with no previous respiratory isolates, but with risk factors for MRSA or *P. aeruginosa,* should have cultures obtained, but should hold off any additional therapies until positive results are reported. Adults with severe CAP requiring inpatient admission without previous respiratory isolation of or risk factors for MRSA or *P. aeruginosa* can be treated with either a β-lactam plus a macrolide or a β-lactam plus a respiratory fluoroquinolone. Patients with severe disease and risk factors for MRSA, or any patient with a previous respiratory isolate of MRSA, should have either vancomycin (15

mg/kg IV q12h; dosing adjusted based on serum levels and renal function) or linezolid (600 mg IV q12h) added to the standard regimen. Sputum cultures and a nasal polymerase chain reaction (PCR) should be ordered to guide the remainder of therapy.[33] Patients with severe disease and risk factors for *P. aeruginosa,* or any patient with a prior respiratory isolation of *P. aeruginosa,* should have an antipseudomonal antibiotic (piperacillin/tazobactam 4.5 g IV q6h, cefepime 2 g IV q8h, ceftazidime 2 g IV q8h, imipenem 500 mg IV q6h, meropenem 1 g IV q8h, or aztreonam 2 g IV q8h; dosing adjusted on renal function) added to the standard regimen. Sputum cultures should be ordered to guide the remainder of therapy.

Children requiring hospitalization for CAP who are up-to-date with vaccinations should be treated with intravenous ampicillin monotherapy if they are younger than age 5 years, with azithromycin added for patients 5 and older. Patients who are unvaccinated should receive ceftriaxone in place of ampicillin because of both pneumococcal and *Haemophilus* concerns.[57]

For patients with contraindications to macrolides or fluoroquinolones, doxycycline may be added to β-lactam treatments. This is most commonly because of cardiac abnormalities, as both classes of medications can prolong the QTc interval. In patients with severe allergic reactions to β-lactams, fluoroquinolones are the preferred agents. Fluoroquinolones are often avoided as first-line therapy because of increasing concerns of resistance mediated by mutations in the DNA gyrase gene *gyrA* and the topoisomerase IV genes *parC* and *parE*, as well as efflux pump–mediated means.[60] Resistance is primarily the result of overuse in clinically nonrelevant situations. This is a common target of institutional antimicrobial stewardship programs. ATS/IDSA guideline-concordant therapy for hospitalized patients has been associated with improved patient outcomes including decreases in time to achieve clinical stability, total duration of parenteral therapy, and hospital length of stay, as well as improved in-hospital survival.[61],[62]

J.T.’s qualifies for severe CAP based on her three minor criteria noted before. Treatment should be started in the ED after obtaining a respiratory specimen and pretreatment blood cultures for Gram stain

and culture. As far as we know, J.T. does not possess risk factors for specific bacteria, such as MRSA or *P. aeruginosa*, but she does have a noted allergy to penicillin that resulted in a rash. This allergy should not necessitate deviation from guideline-directed therapy given the length of time since the allergy was noted (15 years ago) and the low likelihood of cross-sensitivity between β-lactams. J.T. should receive a β-lactam (ceftriaxone) plus a macrolide (azithromycin) or a respiratory fluoroquinolone (levofloxacin) intravenously for empiric treatment. J.T.'s recent incarceration is a risk factor for CA-MRSA infection but more information regarding where she was jailed would be needed to make a definitive decision on adding MRSA coverage to her regimen. J.T. should at the very least have a nasal PCR swab performed to determine MRSA colonization, which could augment the direction of her treatment.

Case 67-3, Question 6: What is the appropriate length of therapy for J.T.?

Although some recent evidence has suggested that shorter courses of therapy (5–7 days) are equally efficacious to extended durations (10–14 days), the 2019 ATS/IDSA guidelines recommend that treatment duration be guided by clinical improvement: normalization of vital signs including oxygen saturation, ability to eat, and resolution of any cognitive dysfunction.[33] Treatment should be no <5 days, and it is understood that some patients may require longer courses of antibiotics based on their underlying health prior to admission and how quickly clinical improvement begins. Patients should be afebrile for at least 48 to 72 hours before therapy is discontinued. Follow-up chest radiographs are no longer indicated if a patient achieves clinical stability within 5 to 7 days.

CASE 67-4

Question 1: F.E. is a 56-year-old male presenting to the ED with fever, chills, nausea, and vomiting for the last 7 days, and more recently, shortness of breath with productive cough with white sputum for the past 4 days. He visited his family ~2 days prior to symptoms, where two of his relatives were thought to

have an unconfirmed viral illness. Initial assessment reveals the patient to be alert and oriented times three, but falling asleep during assessment, pulses present with brisk capillary refill, decreased lung sounds bilaterally, and no peripheral edema. Past medical history is significant for hypertension and diabetes mellitus. The patient has no known drug allergies. Medications at home include aspirin 81 mg PO daily, hydrochlorothiazide 25 mg PO daily, lisinopril 20 mg PO daily, and atorvastatin 40 mg PO daily. Social history is significant for smoking one pack of cigarettes per week.

In the ED, he had a temperature of 102.02 °F (38.9 °C), heart rate of 112 beats/minute, respiratory rate of 22 breaths/minute, SBP/DBP of 126/80 mm Hg, and oxygen saturation of 93% on 2 L of oxygen via nasal cannula. Laboratory results include the following:

WBC count, 2900 cells/μL
Hematocrit, 47.1%
Platelets, 129,000 cells/μL
Sodium, 127 mmol/L
Potassium, 4.6 mmol/L
BUN, 7 mg/dL
SCr, 0.73 mg/dL
Glucose, 117 mg/dL

Chest radiograph showed bilateral interstitial infiltrates; real-time (RT)–PCR was positive for influenza A.

What is the most likely reason for F.E.'s influenza infection?

Influenza viruses spread when a person who is infected coughs or sneezes near a susceptible person.[63] The usual incubation period for influenza is 1 to 4 days, and the time between onset among patients who have come into contact with one another is likely to be 3 to 4 days.[64] Adults can shed influenza virus from the day before symptoms begin through 5 to 10 days after illness onset.[65] Young children shed virus several days before illness onset, and they can be infectious for 10 days or more after onset of symptoms. Prolonged viral replication can occur in adults with severe disease, including those with comorbidities or those receiving corticosteroid therapy.[66,67] Severely immunocompromised persons can shed virus for weeks to months.[68,69]

Case 67-4, Question 2: Should F.E. be treated with antiviral agents?

Patients with laboratory-confirmed or suspected influenza virus meeting the following criteria should be treated with antiviral therapy within 48 hours of symptom onset: persons of any age hospitalized because of respiratory illness; outpatients of any age with severe or progressive illness; those at high-risk for complications from influenza infection (**Table 67-5**); children younger than age 2 years and adults ages 65 years and older; and pregnant females and those within 2 weeks postpartum.[70] Nonimproving high-risk patients or those with symptoms >48 hours and requiring hospitalization should also be considered for antiviral treatment. F.E. falls into the latter category and should be treated for influenza A. Antibiotic treatment is recommended for hospitalized patients with CAP, even if influenza is suspected, and therapy should be directed at likely bacterial pathogens based on the patient's disease severity, previous respiratory isolates, and known risk factors.[33]

Table 67-5

Patients at High Risk of Complications From Influenza

Unvaccinated infants ages 12–24 months
Persons with asthma or other chronic pulmonary diseases (eg, COPD, cystic fibrosis)
Persons with hemodynamically significant cardiac disease
Persons with immunosuppressive disorders or who are receiving immunosuppressive therapy
Persons who are HIV-infected
Persons with sickle cell anemia and other hemoglobinopathies
Persons with diseases that require long-term, high-dose aspirin therapy, such as rheumatoid arthritis
Persons with chronic renal dysfunction
Persons with cancer
Persons with chronic metabolic disease, such as diabetes mellitus
Persons with central nervous system disorders that may compromise the handling of secretions such as neuromuscular disorders, cerebral vascular accidents, or seizure disorders
Adults ages ≥65 years

Residents of any age of nursing homes or other long-term care institutions

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

Source: Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;6:895–902.

Antiviral Therapy

Case 67-4, Question 3: Which antiviral agent(s) should F.E. receive?

Influenza susceptibility profiles to antiviral agents evolve rapidly, and treating clinicians should be familiar with updated resistance data found at the CDC website: www.cdc.gov/flu. There are currently four Food and Drug Administration (FDA)-approved antiviral medications indicated for influenza treatment. Three of these drugs, all recommended by the 2018 IDSA guideline update, are neuraminidase inhibitors: oseltamivir, zanamivir, and peramivir.[70] The inhibition of neuraminidase prevents cleavage of sialic acid residues on the cell surface of the virus, thereby preventing the release of virus from infected cells. The fourth drug, baloxavir, was approved in October 2018, too late to be included in the most recent guideline update.[71] Baloxavir inhibits viral replication by inhibiting the endonuclease activity of the polymerase acidic protein, which is required for viral gene transcription. Information on the currently available influenza antiviral therapies is included in **Table 67-6**. Because of high rates of resistance, adamantines (amantadine and rimantadine) are no longer recommended for treatment of influenza. FE could be treated with any of the four available antiviral medications with oseltamivir administered by mouth bid for 5 days, zanamivir inhaled bid for 5 days, peramivir administered IV in a single dose, and baloxavir by mouth in a single dose.

Table 67-6

Comparison of Current Antiviral Treatment for Influenza

	Oseltamivir	Zanamivir	Peramivir	Baloxavir
Drug class	Neuraminidase inhibitor	Neuraminidase inhibitor	Neuraminidase inhibitor	Influenza cap-dependent endonuclease inhibitor
Route of administration	PO	Inhalation	IV	PO
FDA-approved treatment age	All ages	≥7 years	≥13 years	≥12 years
Treatment duration	bid for 5 days	bid for 5 days	Single dose over 15 minutes	Single dose
Side effects	Nausea, vomiting, abdominal pain	Nasal and throat discomfort, headache, bronchospasm	Diarrhea; serious skin reactions; sporadic, transient neuropsychiatric events	Diarrhea, bronchitis, rhinorrhea, headache, nausea

bid, two times a day; IV, intravenous; PO, by mouth.

Source: Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;6:895–902.

Antiviral therapies should be initiated as soon as possible after illness onset, ideally within 48 hours, as this is when the majority of viral replication occurs. However, treatment of any person with confirmed or suspected influenza requiring hospitalization is recommended for up to 96 hours postillness onset.[72],[73] For patients whose illness is prolonged, treatment regimens may need to be extended beyond 5 days.

Resistance to neuraminidase inhibitors oseltamivir and zanamivir has been identified during treatment of seasonal influenza, caused by a specific mutation leading to a histidine to tyrosine substitution (H275Y) in neuraminidase.[74],[75] Oseltamivir resistance, which can occur within one week of treatment initiation, was reported particularly among immunocompromised patients infected with the 2009 H1N1 virus.[76],[77]

HOSPITAL-ACQUIRED PNEUMONIA AND VENTILATOR-ASSOCIATED PNEUMONIA

Definitions and Incidence

Despite advances in therapy and prevention, hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are associated with significant morbidity and mortality. HAP is defined as pneumonia that occurs at least 48 hours after hospital admission. VAP refers to pneumonia that arises 48 to 72 hours after endotracheal intubation.[48]

Epidemiology

HAP is the second most common nosocomial infection in the United States, with urinary tract infections as the most common.[48] Based on a prospective cohort study, ~7% of ICU patients developed HAP and over 75% of them had VAP.[78] A retrospective cohort study of 4543 hospitalized patients with culture-positive pneumonia observed that HAP accounted for 18.4% and VAP for 11%. Mortality rates associated with HAP groups were comparable (19.8% and 18.8%, respectively) and were significantly lower than those for VAP (29.3%). Mean lengths of stay also differed between patients with HAP and VAP (15.2 ± 13.6 days, and 23 ± 20.2 days, respectively).[79]

The disease onset is an important epidemiologic variable and risk factor for specific pathogens and outcomes in patients with HAP and VAP. Early-onset HAP and VAP are defined as occurring within the first 4 days of hospitalization, usually carry a better prognosis, and are more likely caused by antibiotic-sensitive bacteria. Late-onset HAP and VAP (occurring after ≥5 days of hospitalization) are more likely to be caused by multidrug-resistant (MDR) pathogens and are associated with increased morbidity and mortality.[48]

Pathogenesis

Microorganisms gain access into the lower respiratory tract via aspiration of oropharyngeal pathogens and leakage of secretions around the endotracheal tube cuff in intubated patients.[80],[81] Invasive-care devices, contaminated equipment, and transfer of microorganisms among staff and patients serve as the primary

pathogen sources,[82] and although more controversial, the gastrointestinal tract may also play a role in bacterial colonization.[83]

Clinical Presentation and Diagnosis

HAP and VAP are diagnosed based on radiographic findings, clinical features, and health care setting when there is initial evidence of infection. Patients must demonstrate new or progressive infiltrates on imaging as well as two of three of the following signs: fever >100.40 °F (>38 °C), leukopenia or leukocytosis, and purulent sputum. Patients will often experience declines in oxygen saturation, but this finding is less specific for determining the need for empiric antimicrobial agents.[84]

Respiratory cultures may be taken from endotracheal aspirates, bronchoalveolar lavage, or protected-specimen brush samples. Blood cultures lack sensitivity, and when positive, a potential extrapulmonary source should be considered.[85]

Overview of Treatment

The IDSA/ATS have published guidelines for the treatment of HAP.[48] The five major principles in the management of HAP and VAP include the following: (a) failure to initiate prompt, appropriate therapy is associated with increased mortality; (b) the variability of bacteriology from one institution to another, as well as within specific sites in a hospital, can be significant; (c) the overuse of antibiotics should be avoided by focusing on accurate diagnosis; (d) therapy should be tailored based on lower respiratory tract cultures and the duration of therapy should be shortened; and (e) prevention strategies directed at modifiable risk factors should be applied. Antimicrobial choice considers the likelihood of an infection with a potential pathogen based on the time to onset of HAP, severity of the condition, and underlying risk factors. In general, patients with early-onset disease who are not severely ill and have no risk factors for MDR organisms can be treated with a single agent, including a non-

antipseudomonal third-generation cephalosporin or an antipneumococcal fluoroquinolone (**Table 67-7**). Empiric therapy in those with late-onset or severe disease should include a combination of antibiotics active against *Pseudomonas.* This regimen usually includes an antipseudomonal β-lactam, such as cefepime, imipenem, meropenem, or piperacillin–tazobactam, plus either an aminoglycoside or ciprofloxacin/levofloxacin. Vancomycin or linezolid should be added if MRSA risk factors are present or there is a high institutional incidence (**Table 67-8**).[48]

Table 67-7

Empiric Therapy for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia in Patients With No Known Risk Factors for Multidrug-Resistant Pathogens and Onset >5 Days

Possible Pathogens	Recommended Therapy	Dosage
Streptococcus pneumoniae[a] *Haemophilus influenza* MSSA Antibiotic-sensitive enteric GNB *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter* spp. *Proteus* spp. *Serratia marcescens*	Ceftriaxone	1–2 g IV every 24 hours
	Or	
	Levofloxacin	750 mg IV every 24 hours
	Or	
	Moxifloxacin	400 mg IV every 24 hours
	Or	
	Ertapenem	1 g IV every 24 hours
	Or	
	Ampicillin–sulbactam	3 g IV every 6 hours

GNB, gram-negative bacilli; IV, intravenous; MSSA, methicillin-sensitive *Staphylococcus aureus.*

[a]The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae is* increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin.

Source: Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice

guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:1–51.

Table 67-8
Empiric Therapy for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia in Patients With Late-Onset Infection (≥5 days) or Risk Factors for Multidrug-Resistant Pathogens

Possible Pathogens	Recommended Combination Therapy	Adult Dosage[a]
MDR pathogens *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL+)[b] *Acinetobacter* spp.[b]	*Antipseudomonal cephalosporin* Cefepime Ceftazidime *Or* *Antipseudomonal carbapenem* Imipenem–cilastatin Doripenem Meropenem *Or* β-*Lactam*/β-*lactamase inhibitor* Piperacillin–tazobactam *Plus* *Antipseudomonal fluoroquinolone*[d] Ciprofloxacin *Or* Levofloxacin *Or* *Aminoglycoside* Amikacin Gentamicin Tobramycin	 1–2 g IV every 8–12 hours 2 g IV every 8 hours 500 mg IV every 6 hours or 1 g IV every 8 hours 500 mg IV every 6–8 hours[c] 1 g IV every 8 hours 3.375–4.5 g IV every 8 hours (infused over 4 hours) 400 mg IV every 8 hours 750 mg IV every 24 hours 15–20 mg/kg IV every 24 hours[e] 5–7 mg/kg IV every 24 hours[e] 5–7 mg/kg IV every 24 hours[e]
MRSA[d]	*Plus* Vancomycin *Or* Linezolid	15 mg/kg every 12 hours[f] 600 mg every 12 hours
Legionella pneumophila[g]	Azithromycin	500 mg IV every 24 hours

ESBL, extended-spectrum β-lactamase; IV, intravenous; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus.*

[a]Dosages are based on normal renal and hepatic function.

[b]If an ESBL+ strain, such as *K. pneumoniae*, or *Acinetobacter* spp. is suspected, a carbapenem alone or in combination with a β-lactamase inhibitor (eg, meropenem–vaborbactam) is a reliable choice, or one of the newer third-generation cephalosporin combinations with a β-lactamase inhibitor (ie, ceftazidime–avibactam, ceftolozane–tazobactam), or cefiderocol alone.

[c]Studied infusion times range from 30 minutes to 4 hours.

[d]If MRSA risk factors are present, or there is a high incidence locally.

[e]Trough levels for gentamicin and tobramycin should be based on drug levels.

[f]Trough levels for vancomycin should be 15–20 µg/mL; newer guidelines recommend using a target AUC/MIC ratio of 400 to 600 for therapeutic vancomycin monitoring.

[g]If *L. pneumophila* is suspected, a combination antibiotic regimen including a macrolide (eg, azithromycin) or a fluoroquinolone (eg, ciprofloxacin or levofloxacin) should be used.

Sources: Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:1–51; Rybak M, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77:835–864.

Microbiology

The major difference in the bacteriology between CAP and HAP or VAP is a shift to gram-negative pathogens, MDR pathogens, and MRSA. Gram-negative bacilli commonly colonize oropharyngeal secretions of patients with moderate-to-severe (acute and chronic) diseases without exposure to broad-spectrum antibiotics.[86] Patients admitted to the hospital with acute illnesses are rapidly colonized with gram-negative organisms. Approximately 20% are colonized on the first hospital day, and this number increases with the duration of

hospitalization and severity of illness. The respiratory tract of ~35% to 45% of hospitalized patients and up to 100% of patients who are critically ill will be colonized within 3 to 5 days of admission.[86,87]

In the past, gram-negative bacteria accounted for 50% to 70% of all cases of HAP and VAP[48,88–92]; however, gram-positive organisms have become increasingly common, with *S. aureus* responsible for upward of 40% of cases of HAP and VAP. This is in stark contrast to CAP bacteriology, in which *S. aureus* represents 25% or less of cases. *Pseudomonas aeruginosa* remains the most prevalent gram-negative organism in HAP and VAP, accounting for ~20% to 25% of infections.[93] In patients who are ventilator-dependent, *Acinetobacter* species is an increasingly common gram-negative pathogen. Other organisms with special risk factors include *Legionella*, which is associated with high-dose corticosteroid use and outbreaks secondary to water supplies and cooling systems,[87,94] and *Aspergillus*, which is associated with neutropenia or organ transplantation.[95]

Risk factors for MDR pathogens include patient-specific factors such as antimicrobial therapy in the previous 90 days, current hospitalization of 5 days or more, and immunosuppressive disease or therapy. Coverage for MDR organisms should also be initiated if there is a high frequency of community, hospital, or health care facility (ie, nursing home) antibiotic resistance.[96]

CASE 67-5

QUESTION 1: M.L. is a 71-year-old male admitted to the hospital for a deep vein thrombosis. His past medical history is significant for chronic kidney disease (CrCl 40 mL/minute), diabetes mellitus, COPD, GERD, hypertension, and a recent diagnosis of non–small cell lung cancer for which he is not currently receiving chemotherapy. M.L.'s home medications include lisinopril, famotidine, aspirin, insulin glargine, insulin aspart, tiotropium, fluticasone/salmeterol, and as-needed albuterol.

What characteristics does M.L. exhibit that place him at risk for HAP?

Several risk factors for HAP have been identified, including intubation and mechanical ventilation, aspiration, a patient's body

position, the administration of enteral feeding, prior use of antibacterial agents, gastrointestinal bleeding prophylaxis (ie, histamine type-2 antagonists and proton-pump inhibitors), immunosuppressive therapy, and poor nutrition status or glucose control. Other nonmodifiable risk factors associated with developing HAP include age older than 70 years and chronic lung disease.

An important factor in the cause of pneumonia is colonization of the oropharynx, common in alcoholism and with prolonged hospitalization, and previous antimicrobial exposure.[48] Several factors may contribute to the colonization of M.L.'s oropharynx with gram-negative bacteria. In addition to his pulmonary disease, an altered immune response in diabetics and being elderly can predispose M.L. to respiratory infection. The use of drugs that inhibit the production of gastric acid, such as famotidine and omeprazole, increases the possibility of oropharyngeal colonization and pneumonia; yet acid-suppressive medications are commonly used to prevent gastric stress ulcers in mechanically ventilated patients.[97–100]

Antibiotic Therapy

Case 67-5, Question 2: Three days after admission, while receiving anticoagulation for the deep vein thrombosis, M.L. exhibits a fever to 102.74 °F (39.3 °C). Antibiotics are inappropriately delayed, and over the next 24 hours, his respiratory function declines significantly requiring intubation (Pa_{O_2}/F_{IO_2} 250). Additionally, objective findings show elevated WBC count (17,200 cells/μL), left shift (immature leukocytes, bands 18%), and a new infiltrate on his daily chest radiograph. Sputum cultures are sent, and the decision is made to start M.L. on antibiotics. How should antimicrobial therapy be managed for M.L.?

Because delays in the administration of appropriate therapy have been associated with increased hospital mortality from HAP, the prompt administration of empiric therapy is essential. Importantly, changing therapy once culture results are available may not reduce the excess risk of hospital mortality if inappropriate initial therapy is selected.[48] To this end, available and frequently updated local bacteriologic patterns and in vitro susceptibility data should be

consulted to allow for appropriate selection of initial empirical therapy. In addition to choosing an appropriate agent, the selection of adequate dosing regimens will optimize the pharmacodynamic properties of the antibacterial agent(s) and improve clinical outcomes and mortality rates.[48]

Resolution of HAP can be defined both clinically and microbiologically. Clinical improvement usually is apparent after the first 48 to 72 hours of therapy. During this time, the selected antibacterial regimen should not be changed unless progressive deterioration takes place or microbiologic studies confirm the pathogen.

If culture results are negative or inconclusive (because of known specimen contamination with mouth flora), the patient's response to the initial antibiotic therapy should guide potential modification of the antibiotic regimen. If the patient responds to the initial regimen, narrowing coverage to the most likely causative pathogens is recommended.

If the patient is not responding to the initial antibiotic therapy, one should consider whether (a) the pathogen is not covered in the initial choice of antibiotic therapy, (b) the dose of antibiotic is insufficient, and (c) any other factors are responsible for the failure to respond to therapy. Such factors include poor pulmonary clearance of necrotic tissue and cellular debris, lung abscesses or empyema, and severely altered host defenses leading to a rapidly fatal underlying disease.

Of note, if microorganisms such as *Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, or *Enterobacter* species are isolated, in vitro susceptibility reports should be carefully evaluated, as these organisms often possess an inducible β-lactamase gene (also referred to as a type-I β-lactamase enzyme).[101] In vitro testing may demonstrate susceptibility to third-generation cephalosporins and extended-spectrum penicillins, but this may not translate into efficacy in the clinical setting. As a possible scenario of infection with these organisms, after initiation with one of the above agents, the patient may initially respond; however, after ~1 week, the patient's condition begins to worsen. Because treatment with the β-lactam agent induces the expression of the type-I enzyme, a subsequent

sputum specimen (sent after ~1 week) is now likely to demonstrate resistance to the third-generation cephalosporins and extended-spectrum penicillins.[101] Although cefepime is more likely to be active against these isolates, a large inoculum of organisms (eg, present in pneumonia) can result in β-lactamase degradation of this agent as well.[102] Considering that this phenomenon will not be identified by usual in vitro testing, cefepime should be used cautiously in these patients.[103] The preferred therapy in these patients includes trimethoprim–sulfamethoxazole, a fluoroquinolone, or a carbapenem.[101] *Acinetobacter* species are increasingly resistant to many commonly used antibacterial agents. Treatment of this often MDR pathogen requires the use of very high doses of ampicillin–sulbactam (up to 24 g/day) or colistin.[104],[105] Since publication of the 2016 IDSA guidelines on managing HAP and VAP, there have been several newer β-lactam/β-lactamase inhibitors that have been approved for MDR gram-negative pathogens including ceftazidime–avibactam, ceftolozane–tazobactam, and cefiderocol.

Case 67-5, Question 3: Seventy-two hours after initiation of empiric antibiotics, the microbiology laboratory reports that >100,000 colonies/mL of MRSA have grown on M.L.'s sputum culture. Antibiotics are de-escalated to vancomycin therapy alone, to which the isolate is susceptible. After a loading dose and aggressive maintenance regimen, vancomycin trough concentrations are 17 to 22 µg/mL. However, M.L. remains febrile, demonstrates progression of his infiltrates on chest radiograph, and has acute worsening of renal function requiring dialysis and necessitating vancomycin dose adjustment. Repeat tracheal cultures again grow only *S. aureus* with susceptibility to vancomycin, sulfamethoxazole–trimethoprim, daptomycin, and linezolid. Should M.L.'s antibiotic therapy be modified?

The first IDSA MRSA infection treatment guidelines[106] were published in 2011, and vancomycin therapeutic monitoring guidelines were jointly developed and recently updated by the American Society of Health-System Pharmacists, the Society of Infectious Diseases Pharmacists, and the IDSA.[107]

For MRSA pneumonia, IV vancomycin, or linezolid 600 mg by mouth (PO) or IV twice daily, or clindamycin 600 mg PO or IV three

times daily (if the strain is susceptible) is recommended for 7 to 21 days, depending on the extent of infection. Daptomycin should not be used for the treatment of MRSA pneumonia, because its activity is inhibited by pulmonary surfactant, rendering it inactive in the treatment of lung infection.[106]

VANCOMYCIN

The recommended dosing of IV vancomycin is 15 to 20 mg/kg/dose (actual body weight) every 8 to 12 hours, not to exceed 2 g/dose, for patients with normal renal function. A loading dose of 25 to 30 mg/kg (actual body weight) may be considered. Some patients may experience an adverse event during the infusion of vancomycin known as red man syndrome. Extending the infusion time to 2 hours for larger doses or premedicating patients who have experienced this phenomenon with an antihistamine may alleviate this adverse event.[106] Updated guidelines recommend the shift away from trough-only monitoring to area under the curve to minimum inhibitory concentration (AUC/MIC) ratio in patients with suspected or definitive serious MRSA infections. Assuming a vancomycin MIC of 1 mg/L, the target AUC/MIC ratio is 400:600 using Bayesian software programs to achieve clinical efficacy and maximize patient safety.[107]

LINEZOLID

Linezolid achieves higher concentrations in lung epithelial fluid than in plasma[108] and serves as an alternative to vancomycin for the treatment of MRSA pneumonia. A retrospective analysis of two prospective trials[109],[110] for the treatment of HAP found that patients in the subgroup of MRSA cases randomly assigned to linezolid experienced higher cure rates and lower mortality compared with vancomycin.[111] In contrast, a meta-analysis of eight randomized control trials comparing glycopeptide antibiotics to linezolid for suspected MRSA pneumonia found no evidence to support superiority of linezolid.[112] The ZEPHyR study compared linezolid with vancomycin in patients with proven nosocomial MRSA pneumonia in a randomized, double-blind fashion. This is the largest trial

conducted in this population to date, and it showed a statistical improvement with linezolid in clinical outcomes at the end of study; yet the confidence interval was close to no significance and only showed a benefit with linezolid in identified nosocomial MRSA pneumonia.[113] These results make it difficult for initial selection over vancomycin for empiric therapy of MRSA coverage. Therefore, it remains uncertain whether linezolid or vancomycin should be considered superior.

M.L. is at risk for MDR pathogens (current hospitalization of 5 days or more and immunosuppressive diseases) and should be started empirically on an anti-MRSA agent (vancomycin), and double coverage for resistant gram-negative pathogens (cefepime and gentamicin or ciprofloxacin) (Table 67-8). Dosing and frequency of antimicrobial agents will require renal adjustments because of M.L.'s chronic renal issues. When culture results are known, the antibiotic regimen can be modified and individualized. For patients with uncomplicated HAP or VAP, who have received appropriate empiric antibiotics with a satisfactory subsequent clinical response, 7 to 10 days of therapy is recommended.[48] However, patients infected with nonfermenting gram-negative bacilli (eg, *Pseudomonas* and *Acinetobacter*) may benefit from longer courses (14 days or greater) to prevent recurrence.[114] M.L.'s clinical response should be monitored to determine whether the selected antibiotics are effective in treating this infection. These parameters include the ability to discontinue mechanical intubation and decreases in temperature and WBC count with resolution of the left shift.

Because M.L. remains febrile despite MRSA sensitivities to vancomycin with appropriate trough concentrations, it is appropriate to consider alternative MRSA coverage. Despite MRSA susceptibility to daptomycin, the drug does not penetrate lung surfactant, and therefore it is not appropriate to use in the treatment of pneumonia. Sulfamethoxazole–trimethoprim is a less appealing option owing to the patient's dialysis requirement. M.L. should receive linezolid. Linezolid quickly reaches high lung concentrations and is safe to use in the setting of acute renal failure. Linezolid has been associated with thrombocytopenia and neutropenia. Platelet counts and WBC

should be monitored at baseline and at least every 7 days during treatment.

ALTERNATIVE AGENTS

Doxycycline, clindamycin, and sulfamethoxazole–trimethoprim are not reliably active against MRSA strains, and recent research has focused on novel agents. Although active against MRSA, tigecycline has been associated with worsened clinical outcomes when used for the treatment of HAP, including MRSA pneumonia.[115] Telavancin has been compared with vancomycin in the treatment of HAP caused by gram-positive pathogens. Treatment with telavancin achieved higher clinical cure rates in patients with monomicrobial *S. aureus* infection and in those with isolates that demonstrated a vancomycin MIC of at least 1 μg/mL. However, lower cure rates were observed in the telavancin group in those who had mixed infections. Telavancin use was also associated with a higher incidence in serum creatinine elevation; yet in 2013, the U.S. FDA approved the drug for HAP when other alternatives are not suitable.[116]

AMINOGLYCOSIDES

Individualization of aminoglycoside dosing is imperative as the therapeutic outcome (efficacy and toxicity) of aminoglycosides correlates with plasma concentrations in patients with gram-negative pneumonia.[117–120] In patients receiving multiple daily doses of gentamicin or tobramycin and achieving a 1-hour postinfusion peak plasma concentration of >7 μg/mL, a successful outcome occurs more often than in those with lower plasma concentrations.

The aminoglycosides are concentration-dependent killing antibiotics. The rate and extent of killing organisms is maximized by increasing their peak serum concentration as high as possible relative to the MIC of the pathogen. In addition to maximizing bactericidal activity, in vitro evidence has demonstrated that this concentration goal also minimizes the development of resistance. The use of once-daily dosing strategies to minimize nephrotoxicity of the aminoglycosides has been studied extensively. Single doses of

gentamicin and tobramycin (5–7 mg/kg/day) and of amikacin (15–20 mg/kg/day) have been reported to be as effective as standard dosing (smaller single doses given every 8 or 12 hours) of these agents in controlled clinical trials. However, none of the trials has enrolled a sufficient number of patients required to demonstrate a lower incidence of nephrotoxicity. There are several advantages of once-daily dose aminoglycoside therapy: (a) it is not more nephrotoxic than traditional dosing; (b) clinicians are ensured that a therapeutic peak serum level will be achieved with the first dose; (c) it is the only safe and effective way to achieve serum peak levels of 10 to 20 times the MIC for difficult-to-treat organisms such as *P. aeruginosa*; and (d) it is a more efficient dosing regimen (fewer doses and administration times per day; fewer serum level measurements are required).[48]

Despite the use of individualized aminoglycoside dosing, morbidity and mortality rates attributable to gram-negative pneumonia remain high. This is because the success of antibiotic therapy depends on the ability of the antibiotic to reach the site of infection and remain biologically active.[120] Concentrations of the aminoglycosides in bronchial secretions range from 1 to 5 µg/mL (30%–40% of serum concentrations) 2 to 4 hours after parenteral administration.[121],[122] These concentrations may be insufficient to inhibit the growth of many gram-negative organisms, especially *Pseudomonas*. Lastly, aminoglycosides bind to purulent exudates and cellular debris and are inactivated by these agents.[123–125]

In summary, the aminoglycosides penetrate poorly into bronchial secretions and are less active at the site of infection because of local pH effects and binding to cellular debris. These properties may result in the need for increased dosages, placing patients at increased risk for ototoxicity and nephrotoxicity. Therefore, unless no reasonable alternative exists, aminoglycoside monotherapy for the treatment of pneumonia should be avoided.

INHALED AGENTS FOR MULTIDRUG-RESISTANT PATHOGENS

Because of the growing incidence of pneumonia caused by MDR gram-negative organisms, there is renewed interest in the use of inhaled aminoglycosides and polymyxin products. When given systemically, both classes have been associated with poor pulmonary penetration and with nephrotoxicity, with polymyxin carrying the additional risk of neurotoxicity, and with aminoglycosides ototoxicity. However, the proposed high drug concentrations at the site of pulmonary infection, minimal systemic exposure after nebulized administration, and data showing benefit in both the prevention and treatment of *Pseudomonas* pulmonary infection in patients with cystic fibrosis make aerosolized antibiotic therapy an appealing strategy for the treatment of VAP. The IDSA/ATS guidelines state that aerosolized antimicrobials be considered in patients with MDR organisms not responding well to IV therapy.[48]

The use of adjunctive inhaled antibiotics in VAP has been evaluated in several studies. A systematic review of 16 observational studies and randomized trials without blinding revealed that aerosolized colistin was associated with microbial eradication (OR, 1.61; 95% CI, 1.11–2.35) and improved clinical response (OR, 1.57; 95% CI, 1.14–2.15) but the results were limited by several biases.[126] A systematic review of 12 observational and randomized trials with some blinding showed that nebulized antibiotics in patients with VAP had some benefit in patient outcomes. Nebulized antibiotics were associated with increased rate of clinical cure (RR, 1.23; 95% CI, 1.05–1.43).[127] Neither study showed an improvement in mortality, duration of mechanical ventilation, or length of stay in the intensive care unit.

ALTERNATIVE DOSING OF ANTIBIOTICS FOR MULTIDRUG-RESISTANT PATHOGENS

Carbapenems, cephalosporins, and extended-spectrum penicillins or β-lactamase inhibitors demonstrate time-dependent killing, and it is known that bactericidal killing for these drug classes is optimized if their free drug concentrations are greater than the MIC for 30% to 40%, 50% to 60%, and 60% to 70% of the time, respectively.

Prolonged or continuous infusions have been used to increase the time that free drug concentrations are greater than the MIC, theoretically leading to improved patient outcomes.[128]

Continuous infusions were first used in the late 1970s with suggested improvement in clinical cure rates,[129] but until recently they were largely abandoned owing to logistical concerns about medication stability, drug compatibility, and limited IV access. These concerns are lessened by use of contemporary prolonged infusions. This latter strategy is supported primarily by Monte Carlo simulation, a mathematical modeling technique that estimates the probability of pharmacodynamic target attainment at each MIC for a given MIC range.

Patients diagnosed with VAP and treated with cefepime 2 g every 8 hours (3-hour infusion) have been evaluated using the Monte Carlo methodology. Investigators found that at an MIC of 1 μg/mL, all regimens had a probability of target attainment >90%. However, at an MIC of 8 μg/mL, when compared with 30-minute intermittent infusions of 1 to 2 g every 8 hours and 2 g every 12 hours, only the prolonged infusion (3 hours) of 2 g every 8 hours maintained 90% probability of target attainment. As one might predict, this phenomenon was only demonstrated in patients with preserved renal function as defined as a creatinine clearance of 50 to 120 mL/minute.[129]

A comparison of intermittent and continuous infusion dosing strategies was also done with piperacillin–tazobactam to treat *Pseudomonas* infections. Lodise et al retrospectively compared intermittent infusions of 3.375 g IV piperacillin–tazobactam (infused over 30 minutes every 6 hours) versus extended infusions of 3.375 g IV piperacillin–tazobactam (infused over 4 hours every 8 hours).[130] Results indicated a shorter length of hospital stay (21 vs 38 days; P = .02) and lower 14-day mortality rate among patients with Acute Physiological and Chronic Health Evaluation-II scores >17 (12.2% vs 31.6%; P = .04) in patients receiving extended infusion therapy.[130]

Ventilator-Associated Pneumonia Prophylaxis

The substantial risk of pneumonia in the ICU has prompted aggressive methods to prevent this disease.[131],[132] The most important recommendations include the use of the semi-upright position to reduce the risk of aspiration, infection control (including hand washing) to prevent the spread of pathogens from one patient to the next, and surveillance for ICU infections.[132]

Several strategies for the prevention of VAP are controversial, including selective decontamination of the digestive tract (SDD), selective oral decontamination (SOD), and topical antiseptics applied to the oral mucosa. These three strategies address the concept that VAP occurs after colonization of the upper respiratory tract. Because digestive tract flora may play a role in this colonization, the impact of various decontamination approaches has been studied. For SDD, a combination therapy including topical tobramycin, polymyxin E, and, sometimes, amphotericin B is administered to the stomach and oropharynx four times daily in combination with IV administration of ciprofloxacin or a second-generation cephalosporin. SOD uses a similar antimicrobial strategy to SDD, except that the IV agents are omitted, and the combination therapy is applied to the oropharynx.

Historically, SDD and SOD are more widely used in Europe, and most of the literature investigating these techniques in thousands of patients and supporting their use results from outside the United States. In 2009, De Smet et al performed a large crossover study comparing standard of care ventilation bundles versus SDD versus SOD in mechanically ventilated patients and found a statistically reduced risk of 28-day mortality with an OR of 0.83 (95% CI, 0.72–0.97) for SDD and 0.86 (95% CI, 0.74–0.99) for SOD.[133]

In 2015, Roquilly et al produced the largest meta-analysis of VAP prevention techniques to decrease mortality.[134] More than 37,000 patients were involved from 157 randomized trials. Although the overall mortality reduction was 5% in the intervention group, in a subgroup analysis only SDD significantly decreased mortality compared to control with an RR of 0.84 (95% CI, 0.76–0.92).[134] Despite the overwhelming evidence supporting SDD, leading clinicians suggest there are still concerns of North American practitioners who fear that widespread use of antibiotics for SDD will

increase antibiotic resistance and *Clostridioides difficile* infections, particularly in the United States where drug resistance is more prevalent than in Northern Europe.[135]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbation of COPD. American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147:894–942. (17)

Global Initiative for Chronic Lung Disease. Global strategy for the diagnosis, management and prevention of COPD. 2020. Accessed November 17, 2020. http://goldcopd.org (16)

Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background. *Ann Intern Med*. 2001;134:479–486. (7)

Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:1–51. (48)

Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2019;68:1069–1075. doi:10.15585/mmwr.mm6846a5 (40)

Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Disease Society of America. *Am J Respir Crit Care Med*. 2019;200:e45–e67. (33)

Smith MP, Lown M, Singh S, et al. Acute cough due to acute bronchitis in immunocompetent adult outpatients: *Chest*. 2020;157:1256–1265. (3)

Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev*. 2017;(6):CD000245. (8)

Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;6:895–902. (70)

Key Websites

Centers for Disease Control and Prevention. Seasonal influenza vaccination resources for health professionals. http://www.cdc.gov/flu/professionals/vaccination/ (most recent 2020–2021)

Global Initiative for Chronic Lung Disease. Global strategy for the diagnosis, management, and prevention of COPD. 2020. Accessed November 17, 2020. http://goldcopd.org (16)

COMPLETE REFERENCES CHAPTER 67 RESPIRATORY TRACT INFECTIONS

1. Kinkade S, Long NA. Acute bronchitis. *Am Fam Physician*. 2016;94:560–565.
2. Wenzel RP, Fowler AA 3rd. Clinical practice. Acute bronchitis. *N Engl J Med*. 2006;355:2125–2130.
3. Smith MP, Lown M, Singh S, et al. Acute cough due to acute bronchitis in immunocompetent adult outpatients: CHEST Expert Panel Report. *Chest*. 2020;157:1256–1265.
4. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey: 2017 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2017_ed_web_tables-508.pdf
5. Clark TW, Medina MJ, Batham S, Curran MD, Parmar S, Nicholson KG. Adults hospitalized with acute respiratory illness rarely have detectable bacteria in the absence of COPD or pneumonia; viral infection predominates in a large prospective UK sample. *J Infect*. 2014;69:507–515.
6. Snow V, Mottur-Pilson C, Gonzales R, et al. Principles of appropriate antibiotic use for treatment of acute bronchitis in adults. *Ann Intern Med*. 2001;134:518–520.

7. Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background. *Ann Intern Med*. 2001;134:479–486.
8. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev*. 2017;6(6):CD000245.
9. National Institute for Health and Care Excellence. Cough (acute): antimicrobial prescribing (NICE guideline 120). 2019. https://www.nice.org.uk/guidance/ng120/resources/cough-acute-antimicrobial-prescribing-pdf-66141652166341
10. Barnett ML, Linder JA. Antibiotic prescribing for adults with acute bronchitis in the United States, 1996–2010. *JAMA*. 2014;311:2020–2022.
11. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2017;10(10):CD007498.
12. Pfister R, Kochanek M, Leygeber T, et al. Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review, and individual patient data meta-analysis. *Crit Care*. 2014;18:R44.
13. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. *Cochrane Database Syst Rev*. 2014;2014(11):CD001831.
14. Becker LA, Hom J, Villasis-Keever M, van der Wouden JC. Beta2-agonists for acute cough or a clinical diagnosis of acute bronchitis. *Cochrane Database Syst Rev*. 2015;2015(9):CD001726.
15. El-Gohary M, Hay AD, Coventry P, Moore M, Stuart B, Little P. Corticosteroids for acute and subacute cough following respiratory tract infection: a systemic review. *Fam Pract*. 2013;30:492–500.
16. Global Initiative for Chronic Lung Disease. Global strategy for the diagnosis, management and prevention of COPD. 2020. Accessed November 17, 2020. http://goldcopd.org
17. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbation of COPD. American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147:894–942.
18. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systemic review and meta-analysis. *Chest*. 2008;133:756–766.
19. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med.* 2019;381:1257–1266.
20. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:2355–2365.
21. Rosell A, Monsó E, Soler N, et al. Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med*. 2005;165:891–897.

22. Soler N, Agustí C, Angrill J, Puig De la Bellacasa J, Torres A. Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2007;62:29–35.
23. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106:196–204.
24. Vollenweider DJ, Frei A, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2018;10(10):CD010257.
25. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;(9):CD001288.
26. Walters JA, Tan DJ, White CJ, Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2018;3(3):CD006897.
27. Rutschmann OT, Cornuz J, Poletti PA, et al. Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax*. 2007;62:121–125.
28. World Health Organization Fact Sheet. The top 10 causes of death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Updated 5/2018
29. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415–427. doi:10.1056/NEJMoa1500245
30. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;373(9):835–845.
31. Yu H, Rubin J, Dunning S, Li S, Sato R. Clinical and economic burden of community-acquired pneumonia in the Medicare fee-for-service population. *J Am Geriatr Soc*. 2012;60(11):2137–2143.
32. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.
33. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Disease Society of America. *Am J Respir Crit Care Med*. 2019;200:e45–e67.
34. Halm EA, Teirstein AS. Clinical practice. Management of community-acquired pneumonia. *N Engl J Med*. 2002;347:2039–2045.
35. Laterre PF, Garber G, Levy H, et al. Severe community-acquired pneumonia as a cause of severe sepsis: data from the PROWESS study. *Crit Care Med*. 2005;33:952–961.

36. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377–382.
37. Aujesky D, Auble TE, Yealy DM, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. *Am J Med*. 2005;118:384–392.
38. Kadioglu A, Weiser JN, Paton JC, Andrew PW. The role of *Streptococcus pneumoniae* virulence factors in host respiratory colonization and disease. *Nat Rev Microbiol*. 2008;6:288–301.
39. van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. *Lancet*. 2009;374:1543–1556.
40. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2019;68:1069–1075. doi:10.15585/mmwr.mm6846a5
41. Arnold FW, Summersgill JT, Lajoie AS, et al. A worldwide perspective of atypical pathogens in community-acquired pneumonia. *Am J Respir Crit Care Med*. 2007;175(10):1086–1093.
42. Lieberman D, Schlaeffer F, Boldur I, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. *Thorax*. 1996;51:179–184.
43. Tessmer A, Welte T, Martus P, Schnoor M, Marre R, Suttorp N. Impact of intravenous β-lactam/macrolide versus β-lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia. *J Antimicrob Chemother*. 2009;63:1025–1033.
44. Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med*. 2010;36:612–620.
45. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. *Ann Pharmacother*. 2000;34:446–452.
46. Restrepo MI, Mortensen EM, Waterer GW, Wunderink RG, Coalson JJ, Anzueto A. Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *Eur Respir J*. 2009;33:153–159.
47. Fiumefreddo R, Zaborsky R, Haeuptle J, et al. Clinical predictors for *Legionella* in patients presenting with community-acquired pneumonia to the emergency department. *BMC Pulm Med*. 2009;9:4.
48. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice

guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:1–51.

49. Hageman JC, Uyeki TM, Francis JS, et al. Severe community-acquired pneumonia due to *Staphylococcus aureus*, 2003–04 influenza season. *Emerg Infect Dis*. 2006;12:894–899.
50. Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet*. 2002;359:753–759.
51. Rasigade JP, Laurent F, Lina G, et al. Global distribution and evolution of Panton-Valentine leukocidin-positive methicillin-susceptible *Staphylococcus aureus*, 1981–2007. *J Infect Dis*. 2010;201:1589–1597.
52. Taneja C, Haque N, Oster G, et al. Clinical and economic outcomes in patients with community-acquired *Staphylococcus aureus* pneumonia. *J Hosp Med*. 2010;5:528–534.
53. Jennings LC, Anderson TP, Beynon KA, et al. Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax*. 2008;63:42–48.
54. Lieberman D, Shimoni A, Shemer-Avni Y, Keren-Naos A, Shtainberg R, Lieberman D. Respiratory viruses in adults with community-acquired pneumonia. *Chest*. 2010;138:811–816.
55. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA*. 1997;278:2080–2084.
56. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med*. 2004;164:637–644.
57. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Disease Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53(7):e25–e76.
58. Hakenbeck R, Kaminski K, König A, et al. Penicillin-binding proteins in beta-lactam-resistant *Streptococcus pneumoniae*. *Microb Drug Resist*. 1999;5:91–99.
59. Yu VL, Chiou CC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. *Clin Infect Dis*. 2003;37:230–237.
60. Lynch JP 3rd, Zhanel GG. Escalation of antimicrobial resistance among *Streptococcus pneumoniae*: implications for therapy. *Semin Respir Crit Care Med*. 2005;26:575–616.
61. Arnold FW, LaJoie AS, Brock GN, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. *Arch Intern Med*. 2009;169:1515–1524.

62. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med*. 2009;169:1525–1531.
63. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. *Lancet Infect Dis*. 2007;7:257–265.
64. Cowling BJ, Chan KH, Fang VJ, et al. Comparative epidemiology of pandemic and seasonal influenza A in households. *N Engl J Med*. 2010;362:2175–2184.
65. Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol*. 2008;167:775–785.
66. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis*. 2009;200:492–500.
67. Giannella M, Alonso M, Garcia de Viedma D, et al. Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. *Clin Microbiol Infect*. 2011;17(8):1160–1165.
68. Englund JA, Champlin RE, Wyde PR, et al. Common emergence of amantadine and rimantadine-resistant influenza A viruses in symptomatic immunocompromised adults. *Clin Infect Dis*. 1998;26:1418–1424.
69. Boivin G, Goyette N, Bernatchez H. Prolonged excretion of amantadine-resistant influenza A virus quasi species after cessation of antiviral therapy in an immunocompromised patient. *Clin Infect Dis*. 2002;34:E23–E25.
70. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;6:895–902.
71. Xofluza. Package insert. Genentech USA, Inc.; 2018.
72. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis*. 2007;45:1568–1575.
73. Lee N, Choi KW, Chan PK, et al. Outcomes of adults hospitalised with severe influenza. *Thorax*. 2010;65:510–515.
74. Stephenson I, Democratis J, Lackenby A, et al. Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. *Clin Infect Dis*. 2009;48:389–396.
75. Dharan NJ, Gubareva LV, Meyer JJ, et al. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA*. 2009;301:1034–1041.
76. Kidd IM, Down J, Nastouli E, et al. H1N1 pneumonitis treated with intravenous zanamivir. *Lancet*. 2009;374:1036.
77. Gaur AH, Bagga B, Barman S, et al. Intravenous zanamivir for oseltamivir resistant 2009 H1N1 influenza. *N Engl J Med*. 2010;362:88–89.

78. Alp E, Güven M, Yildiz O, Aygen B, Voss A, Doganay M. Incidence, risk factors and mortality of nosocomial pneumonia in intensive care units: a prospective study. *Ann Clin Microbiol Antimicrob*. 2004;3:17.
79. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia [published correction appears in *Chest*. 2006;129:831]. *Chest*. 2005;128:3854–3862.
80. Cameron JL, Reynolds J, Zuidema GD. Aspiration in patients with tracheostomies. *Surg Gynecol Obstet*. 1973;136:68–70.
81. Valles J, Artigas A, Rello J, et al. Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann Intern Med*. 1995;122:179–186.
82. Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep*. 2004;53(RR-3):1–36.
83. Bonten MJ, Bergmans DC, Ambergen AW, et al. Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. *Am J Respir Crit Care Med*. 1996;154:1339–1346.
84. Raoof S, Baumann MH; Critical Care Societies Collaborative. An official multi-society statement: ventilator-associated events: the new definition. *Chest*. 2014;145:10–12.
85. Luna CM, Videla A, Mattera J, et al. Blood cultures have limited value in predicting severity of illness and as a diagnostic tool in ventilator-associated pneumonia. *Chest*. 1999;116:1075–1084.
86. Johanson WG Jr, Pierce AK, Sanford JP, Thomas GD, et al. Nosocomial respiratory infections with gram-negative bacilli: the significance of colonization of the respiratory tract. *Ann Intern Med*. 1972;77:701–706.
87. Tillotson JR, Finland M. Bacterial colonization and clinical super-infection of the respiratory tract complicating antibiotic treatment of pneumonia. *J Infect Dis*. 1969;119:597–624.
88. Rouby JJ, Martin De Lassale E, Poete P, et al. Nosocomial bronchopneumonia in the critically ill: histologic and bacteriologic aspects. *Am Rev Respir Dis*. 1992;146:1059–1066.
89. Bartlett JG, O'Keefe P, Tally FP, Louie TJ, Gorbach SL. Bacteriology of hospital-acquired pneumonia. *Arch Intern Med*. 1986;146:868–871.
90. Prod'hom G, Leuenberger P, Koerfer J, et al. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: a randomized controlled trial. *Ann Intern Med*. 1994;120:653–662.
91. Rello J, Ausina V, Ricart M, Castella J, Prats G. Impact of previous antimicrobial therapy on etiology and outcome of ventilator-associated pneumonia. *Chest*. 1993;104:1230–1235.

92. Fridkin SK, Welbel SF, Weinstein RA. Magnitude and prevention of nosocomial infections in the intensive care unit. *Infect Dis Clin North Am*. 1997;11:479–496.
93. Jones R. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia [published correction appears in *Clin Infect Dis*. 2010;51:1114]. *Clin Infect Dis*. 2010;51:S81–S87.
94. Edelstein PH. Legionnaires' disease. *Clin Infect Dis*. 1993;16:741–747.
95. Rhame FS. Prevention of nosocomial aspergillosis. *J Hosp Infect*. 1991;18(suppl A):466–472.
96. Maruyama T, Fujisawa T, Okuno M, et al. A new strategy for healthcare-associated pneumonia: a 2 year prospective multicenter cohort study using risk factors for multidrug-resistant pathogens to select initial empiric therapy. *Clin Infect Dis*. 2013;57:1373–1383.
97. Muscroft TJ, Deane SA, Youngs D, Burdon DW, Keighley MR. The microflora of the postoperative stomach. *Br J Surg*. 1981;68:560–564.
98. du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. *Lancet*. 1982;1:242–245.
99. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: systematic review and meta-analysis. *CMAJ*. 2011;183:310–319.
100. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301:2120–2128.
101. Chow JW, Fine MJ, Shlaes DM, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med*. 1991;115:585–590.
102. Medeiros AA. Relapsing infection due to *Enterobacter* species: lessons of heterogeneity. *Clin Infect Dis*. 1997;25:341–342.
103. Acar J. Rapid emergence of resistance to cefepime during treatment. *Clin Infect Dis*. 1998;26:1484–1486.
104. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. *Clin Infect Dis*. 2003;36:1111–1118.
105. Smolyakov R, Borer A, Riesenberg K, et al. Nosocomial multi-drug resistant *Acinetobacter baumannii* bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. *J Hosp Infect*. 2003;54:32–38.
106. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52: e18–e55.

107. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77:835–864.
108. Conte JE Jr, Golden JA, Kipps J, Zurlinden E. Intrapulmonary pharmacokinetics of linezolid. *Antimicrob Agents Chemother.* 2002;46:1475–1480.
109. Rubinstein E, Cammarata S, Oliphant T, Wunderink R; Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32:402–412.
110. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH; Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25:980–992.
111. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*. 2003;124:1789–1797.
112. Walkey AJ, O'Donnell MR, Wiener RS. Linezolid vs glycopeptide antibiotics for the 5 treatment of suspected methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a meta-analysis of randomized controlled trials. *Chest*. 2011;139:1148–1155.
113. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis*. 2012;54:621–629.
114. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA*. 2003;290:2588–2599.
115. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis*. 2010;68:140–151.
116. Torres A, Rubinstein E, Corey GR, Stryjewski ME, Barriere SL. Analysis of Phase 3 telavancin nosocomial pneumonia data excluding patients with severe renal impairment and acute renal failure. *J Antimicrob Chemother*. 2014;69:1119–1126.
117. Barza M, Brown RB, Shen D, Gibaldi M, Weinstein L. Predictability of blood levels of gentamicin in man. *J Infect Dis*. 1975;132:165–174.
118. Zaske DE, Irvine P, Strand LM, Strate RG, Cipolle RJ, Rotschafer J. Wide interpatient variations in gentamicin dose requirements for geriatric patients. *JAMA*. 1982;248:3122–3126.

119. Flint LM, Gott J, Short L, Richardson JD, Polk HC Jr. Serum level monitoring of aminoglycoside antibiotics. Limitations in intensive care unit-related bacterial pneumonia. *Arch Surg*. 1985;120:99–103.
120. Moore RD, Smith CR, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. *Am J Med*. 1984;77:657–662.
121. Bergogne-Berezin E. Pharmacokinetics of antibiotics in respiratory secretion. In: Pennington JE, ed. *Respiratory Infections: Diagnosis and Management.* Raven Press; 1983.
122. Bodem CR, Lampton LM, Miller DP, Tarka EF, Everett ED. Endobronchial pH. Relevance of aminoglycoside activity in gram-negative bacillary pneumonia. *Am Rev Respir Dis*. 1983;127:39–41.
123. Vaudaux P. Peripheral inactivation of gentamicin. *J Antimicrob Chemother*. 1981;8(suppl A):17–25.
124. Levy J, Smith AL, Kenny MA, Ramsey B, Schoenknecht FD. Bioactivity of gentamicin in purulent sputum from patients with cystic fibrosis or bronchiectasis: comparison with activity in serum. *J Infect Dis*. 1983;148:1069–1076.
125. Mendelman PM, Smith AL, Levy J, Weber A, Ramsey B, Davis RL. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. *Am Rev Respir Dis*. 1985;132:761–765.
126. Valachis A, Samonis G, Kofteridis DP. The role of aerosolized colistin in the treatment of ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2015;43:527–533.
127. Zampieri FG, Nassar AP Jr, Gusmao-Flores D, Taniguchi LU, Torres A, Ranzani OT. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care*. 2015;19:150.
128. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of “bug and drug.” *Nat Rev Microbiol*. 2004;2:289–300.
129. Nicasio AM, Ariano RE, Zelenitsky SA, et al. Population pharmacokinetics of high-dose, prolonged-infusion cefepime in adult critically ill patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother.* 2009;53:1476–1481.
130. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis*. 2007;44:357–363.
131. Kollef MH. The prevention of ventilator associated pneumonia. *N Engl J Med.* 1999;340:627–634.
132. Torres A, Serra-Batlles J, Ros E, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med*. 1992;116:540–543.
133. De Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patient. *N Engl J Med*. 2009;360: 20–

31.
134. Roquilly A, Marret E, Abraham E, Asehnoune K. Pneumonia prevention to decrease mortality in intensive care unit: a systematic review and meta-analysis. [published correction appears in *Clin Infect Dis*. 2015;60:1449]. *Clin Infect Dis*. 2015;60:64–75.
135. Klompas M. Editorial commentary: evidence vs instinct for pneumonia prevention in hospitalized patients. *Clin Infect Dis*. 2015;60:76–78.

68

Tuberculosis

Michael B. Kays

CORE PRINCIPLES		CHAPTER CASES
1	Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis,* and the most common site of infection is the lungs. Active disease is characterized by fever, chills, cough, night sweats, weight loss, and changes on chest radiography. Several risk factors have been identified, including immune suppression, exposure to infected close contacts, and smoking.	**Case 68-1 (Questions 1, 2)**
2	Diagnosis of active disease includes chest radiography, sputum collection for acid-fast bacilli smear microscopy and culture, and nucleic acid amplification tests. Tuberculin skin testing and interferon-γ release assays may aid in the diagnosis of tuberculosis. Human	**Case 68-1 (Questions 3–7)**

	immunodeficiency virus (HIV) screening is recommended for all patients with tuberculosis.	
3	Goals of therapy include cure, prevention of transmission, and prevention of resistance of *M. tuberculosis*. Treatment of active pulmonary disease requires administration of multiple-drug therapy for a minimum of 26 weeks. Rapid molecular drug susceptibility testing for rifampin is recommended. Directly observed therapy is a core management strategy for all patients to ensure adherence to therapy.	**Case 68-1 (Questions 8–13)**
4	Patients should be monitored for resolution of symptoms and questioned about the occurrence of adverse events, especially hepatitis. Sputum smears and cultures should be obtained every 2 to 4 weeks initially and then monthly after culture results become negative. If treatment failure occurs, at least three new drugs should be added to the treatment regimen.	**Case 68-1 (Questions 14, 15)**
5	Patients with latent tuberculosis infection have a positive tuberculin skin test or interferon-γ release assay result but no clinical symptoms or radiographic evidence of active disease. Isoniazid for 6 to 9 months has been preferred historically, but rifampin for 4 months	**Case 68-2 (Questions 1, 2)**

	and weekly isoniazid plus rifapentine for 12 weeks are acceptable alternatives.	
6	Adverse events associated with isoniazid include hepatotoxicity and peripheral neuropathy. Rifampin is associated with hepatotoxicity, flulike syndrome, thrombocytopenia, and discoloration of body fluids. Pyrazinamide can cause hepatotoxicity and increased uric acid, whereas ethambutol can cause optic neuritis.	**Case 68-3 (Questions 1–3) Case 68-4 (Question 1)**
7	The case rate for tuberculosis in persons age 65 years or older is greater than that in all other age groups. Principles of treatment of tuberculosis in the elderly are the same as those for other age groups.	**Case 68-5 (Question 1)**
8	Multidrug-resistant tuberculosis can develop as a result of nonadherence to treatment. Successful treatment of multidrug-resistant tuberculosis is possible depending on the host, adherence to therapy, and the number of drugs to which the organism remains susceptible. Treatment with at least five drugs may be required in the intensive phase.	**Case 68-6 (Questions 1, 2)**
9	HIV infection is an important risk factor for tuberculosis. Clinical manifestations in HIV-infected persons will vary depending on the severity of immunodeficiency at presentation.	**Case 68-7 (Questions 1–3) Case 68-8 (Question 1)**

	Principles and recommendations for treatment of active disease and latent infection in HIV-infected persons are the same as those for HIV-negative persons.	
10	In antiretroviral-naive patients, the optimal timing for initiating antiretroviral therapy is dependent on the patient's $CD4^+$ cell count. Antiretroviral therapy may be delayed to decrease the potential for immune reconstitution inflammatory syndrome. If patients are receiving antiretroviral therapy, treatment of tuberculosis should begin immediately with modification of antiretroviral therapy as needed.	**Case 68-7 (Questions 4, 5)**
11	Treatment of active disease in pregnant females is the same as that for nonpregnant females. Pyrazinamide is not recommended in pregnancy in the United States owing to insufficient safety data. However, pyrazinamide is frequently utilized in other countries. Minimum duration of therapy is 9 months without pyrazinamide.	**Case 68-9 (Question 1)**
12	Infants and children have a higher risk of disseminated tuberculosis, and treatment should be initiated promptly. Ethambutol is generally avoided because it is difficult to assess visual acuity in children. Many experts prefer to initiate therapy in children with three	**Case 68-10 (Question 1)**

	drugs and treat for a minimum duration of 6 months.	
13	Extrapulmonary tuberculosis may require longer durations of therapy. Tuberculous meningitis may require 9 to 12 months of therapy, and corticosteroids reduce sequelae and improve survival.	**Case 68-11 (Question 1)**

INTRODUCTION

Tuberculosis (TB) is an ancient disease with evidence of spinal TB in pre-Columbian and early Egyptian remains. TB emerged as a major health problem in the 17th and 18th centuries when crowded living conditions of the Industrial Revolution contributed to its epidemic spread throughout Europe and the United States. Early physicians referred to TB as *phthisis,* derived from the Greek term for wasting, because its clinical presentation consisted of weight loss, cough, fevers, and hemoptysis. The etiologic agent was identified in 1882 when Robert Koch isolated and cultured *Mycobacterium tuberculosis* and demonstrated its infectious nature. With this knowledge, early treatment in the mid-1800s to the early 1900s consisted of placing patients with TB in a sanatorium for bed rest and fresh air. With the advent of radiographic film, pulmonary cavitary lesions were found to be a pivotal component in the evolution of the disease. Therapy included pneumoperitoneum, thoracoplasty, and plombage to reduce the size of the cavitary lesion, and some of these therapies are still used today for severe and refractory cases.

The modern era of medical TB therapy began in 1944 with the discovery of streptomycin and, shortly thereafter, *p*-aminosalicylic acid. Addition of isoniazid in 1952 and rifampin in the late 1960s greatly increased treatment success and provided hope for the eventual elimination of TB. However, multidrug-resistant tuberculosis

(MDR-TB) emerged in the 1990s as a threat to the control of TB in the United States and other countries.[1–3] In the subsequent decade, published reports described the worldwide emergence of extensively drug-resistant tuberculosis (XDR-TB)[4–6] and, more recently, the emergence of totally drug-resistant (TDR) or super XDR-TB strains.[7] As TB strains become increasingly resistant to currently available agents, the likelihood of achieving global control and elimination of this disease is diminished. Therefore, a high index of suspicion for TB, rapid pathogen identification, susceptibility testing, patient isolation, and appropriate antimicrobial therapy are critical to prevent further development and spread of drug-resistant TB.

Incidence and Epidemiology

Assuming lifelong infection, ~2.0 billion people (30% of the world's population) are infected with *M. tuberculosis.*[8] TB is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent, ranking above human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS).[9] Globally, there were an estimated 10 million new cases of TB in 2019; the majority of these new cases were identified in Southeast Asia, Africa, and the Western Pacific.[9] Approximately 8.2% of the new TB cases in 2019 were identified in persons living with HIV, with the African region accounting for 86% of these cases.[9] In 2019, ~1.2 million deaths were reported among HIV-negative cases (decreased from 1.7 million in 2000) and 0.21 million deaths were reported among HIV-positive cases (decreased from 0.68 million in 2000).[9]

In the United States, 7163 cases of TB were provisionally reported in 2020, and the incidence rate was 2.2/100,000 population, which represents the lowest recorded rate since national reporting began in 1953.[10] However, the incidence rate remained higher than the national goal for elimination of TB (<1 case per 1,000,000 population). Thirty-nine states and the District of Columbia reported decreased TB cases in 2020, and four states (California, Texas, New York, and Florida) accounted for >50% of all TB cases.[10] The number

of TB cases and incidence rates declined for both foreign-born and U.S.-born persons, but foreign-born and ethnic and racial minorities continue to be disproportionally affected by TB in the United States. In 2020, 71% and 29% of all TB cases were reported in foreign-born and U.S.-born persons, respectively, and the incidence rate was >16 times higher in foreign-born persons compared with U.S.-born persons (11.5 vs 0.7 per 100,000 population).[10] Mexico, the Philippines, India, Vietnam, and China were the most frequently reported countries of birth among foreign-born persons.[10] Among U.S.-born persons, the greatest number of TB cases was reported in non-Hispanic Blacks. Among persons with TB whose HIV status was known, 4.7% of these patients were coinfected with HIV in 2019.[11]

In the United States, 9.2% of isolates from patients with no previous history of TB were resistant to isoniazid in 2019; resistance was 6.5% in U.S.-born individuals and 10.2% in foreign-born individuals.[11] In 2019, there were ~206,000 global cases of MDR-TB, defined as resistance to both isoniazid and rifampin, and 3.3% of new TB cases and 17.7% of previously treated cases were caused by MDR-TB.[9] The largest number of MDR-TB cases were reported in India, China, and the Russian Federation.[9] In the United States, 90 cases of MDR-TB were reported in 2019, and foreign-born persons accounted for 86% of these MDR-TB cases.[11] The percentage of MDR-TB cases is approximately five times higher for persons with a previous history of TB compared with persons with no previous history of TB.[11] Several conditions and risk factors for persons with increased risk of infection with drug-resistant TB are shown in **Table 68-1**.

Table 68-1
Conditions and Risk Factors for Persons With Increased Risk of Drug-Resistant Tuberculosis

History of treatment for latent tuberculosis infection or active disease
Patients from areas with high prevalence of initial or primary drug resistance (urban population, northeast United States, Florida, California, Texas, United States–Mexico border)

Foreign-born persons from areas with high prevalence of drug-resistant tuberculosis (Southeast Asia, Mexico, South America, Africa)
Contact with persons with active infection caused by drug-resistant *Mycobacterium tuberculosis*
Tuberculosis in persons who are homeless, abusers of intravenous drugs, and HIV infected
Patients with positive sputum smear and culture results after 2 months of treatment

HIV, human immunodeficiency virus.

In the mid-2000s, XDR-TB emerged as another major threat to global health.[4–6] The definition of XDR-TB is resistance to isoniazid and rifampin among first-line agents, resistance to any fluoroquinolone, and resistance to at least one second-line injectable drug (amikacin, kanamycin, or capreomycin).[12] Globally, 12,350 cases of TB were caused by XDR-TB strains in 2019.[9] One of the first reports described 53 patients infected with XDR-TB from South Africa.[13] HIV status was known in 44 patients, and all of these patients were HIV positive. Fifty-five percent of the patients had no prior history of TB treatment, and 98% died with a median survival period of only 16 days after collection of the first sputum specimen.[13] In the United States, 63 cases of XDR-TB were identified between 1993 and 2011, and mortality was strongly associated with concomitant HIV infection.[14] In 2019, four cases of XDR-TB were reported in the United States.[11]

Risk factors for XDR-TB include previous treatment for TB, HIV infection, homelessness, and alcohol use.[15] In a retrospective analysis of patients with documented MDR-TB, emergence of XDR-TB was associated with baseline chronic disease and nonadherence to MDR-TB therapy.[16] Treatment success is significantly lower for XDR-TB, and XDR-TB is associated with increased all-cause and TB-related mortality.[17] However, treatment outcomes are significantly improved when later generation fluoroquinolones are added to the treatment regimen, even if fluoroquinolone resistance was demonstrated on susceptibility testing.[18]

The evolution of TB resistance continued in 2009 with the identification of strains that were reported to be TDR, which was defined as resistance to all first-line and second-line agents.[7] Fifteen (10.3%) of 146 MDR-TB strains tested were found to be TDR-TB in Iran, and culture results remained positive in these cases after 18 months of treatment with second-line agents.[7] All of these TDR-TB cases were HIV negative. This report illustrates the critical need to develop new and effective agents for the treatment of TB caused by MDR, XDR, and TDR strains.

Etiology

TB is caused by *M. tuberculosis,* an aerobic, non-spore–forming bacillus that resists decolorization by acid alcohol after staining with basic fuchsin. For this reason, the organism is often referred to as an acid-fast bacillus (AFB).

M. tuberculosis is different from other bacteria in that it replicates slowly—once every 24 hours instead of every 20 to 40 minutes as with some other bacteria. The organism thrives in environments in which the oxygen tension is relatively high, such as the apices of the lung, the renal parenchyma, and the growing ends of bones.

Transmission

M. tuberculosis is transmitted through the air by aerosolized droplet nuclei that are produced when a person with pulmonary or laryngeal TB coughs, sneezes, speaks, or sings. Droplet nuclei may also be produced by other methods, such as aerosol treatments, sputum induction, bronchoscopy, endotracheal intubation, suctioning, autopsy, and through manipulation of lesions or processing of secretions in the hospital or laboratory.[19] These droplet nuclei, which contain one to three *M. tuberculosis* organisms, are small enough (1–5 μm) to remain airborne for prolonged periods and reach the alveoli within the lungs when inhaled. Tubercle bacilli are not

transmitted on inanimate objects, and organisms deposited on skin or intact mucosa do not invade tissues.

Several factors influence the likelihood of transmission of *M. tuberculosis,* including the number of organisms expelled into the air by the index patient, the concentration of organisms in the air determined by the volume of the space and its ventilation, the length of time an exposed person breathes the contaminated air, location of the exposure (small room vs outdoors), and the immune status of the exposed individual.[20] Family household contacts, especially children, and persons working or living in an enclosed environment (eg, hospitals, nursing homes, prisons) with an infected person are at increased risk for becoming infected. If the index case finding is smear positive, 50% of household contacts will have a conversion of the tuberculin skin test (TST) result from negative to positive; however, if the index case finding is smear negative, only 5% will become infected.[20] Individuals with impaired cell-mediated immunity, such as HIV-infected persons or patients who underwent transplant, are more likely to become infected with *M. tuberculosis* after exposure than are persons with normal immune function.[20] Travelers to TB-endemic areas with international medical exchange programs are also at risk for TB infection, regardless of the involvement in direct patient care activities or duration of stay.[21]

Several techniques are effective in limiting airborne transmission of *M. tuberculosis* by reducing the number of droplet nuclei in a given airspace. Adequate room ventilation with fresh air is very important, especially in the health care setting, in which six or more room air exchanges per hour are desirable.[19],[22] New construction or renovation of existing facilities should be designed so that airborne infection isolation rooms achieve ≥12 room air exchanges per hour.[22] Ultraviolet irradiation of air in the upper part of the room can also reduce the number of viable airborne tubercle bacilli. All health care workers and visitors who enter the room of a patient with infectious TB should wear at least N95 disposable respirators, and the mask should be molded to fit tightly around the nose and mouth.[22] Patients with presumed or confirmed infectious TB should wear a protective mask when being transferred to another area of the institution or

after hospital discharge until they are noninfectious.[22] However, the most important means of reducing transmission of *M. tuberculosis* is by treating the infected patient with effective antituberculosis therapy.

Pathogenesis

LATENT INFECTION VERSUS ACTIVE DISEASE

Latent infection

A clear distinction should be made between latent infection and active disease. Latent infection occurs when the tubercle bacilli are inhaled into the body. After inhalation, the droplet nuclei containing *M. tuberculosis* settle into the bronchioles and alveoli of the lungs. Development of infection in the lung is dependent on the inoculum of organisms inhaled, the virulence of the organism, and the innate immune response of the host.[23–25] In the nonimmune (susceptible) host, the bacilli initially multiply unopposed by normal host defense mechanisms. Organisms are then phagocytized by alveolar macrophages and resident dendritic cells, but they may remain viable, multiplying within the cells for extended periods.[25] After 14 to 21 days of replication, the tubercle bacilli spread via the lymphatic system to the hilar lymph nodes and through the bloodstream to other organs of the body.

Fortunately, certain organs and tissues in the body, such as the bone marrow, liver, and spleen, are resistant to subsequent multiplication of these bacilli. Organs with high blood flow and Pa_{O_2}, such as the apices of the lungs, kidneys, bones, and brain, are favorable for organism growth and may lead to extrapulmonary disease. Organisms replicate for 2 to 12 weeks until they reach a concentration of 10^3 to 10^4, plateauing coincident with the development of T-cell–mediated immunity in the host.[25] $CD4^+$ T cells produce interferon-***γ***, which is an essential cytokine for activation of macrophages and mycobacterial killing.[25] At this point, the patient has developed cell-mediated immunity, which can be detected by a reaction to the TST or interferon-γ release assay (IGRA), and bacterial replication is halted.[25]

In persons with intact cell-mediated immunity, activated T cells and macrophages may result in granuloma formation, a hallmark of TB, that is thought to represent a physical and immunologic barrier to control the infection and limit dissemination of the bacilli to the surrounding environment.[25] Cells found within the granuloma include $CD4^+$ and $CD8^+$ T cells, B cells, neutrophils, macrophages, multinucleated giant cells, and fibroblasts.[25] Organisms tend to localize in the center of the granuloma, which is frequently necrotic, and the tubercle bacilli may remain viable indefinitely within the granuloma. In addition, maintenance of the integrity of the granuloma allows for control of bacterial replication and depends on the immune status of the patient.[25] Tumor necrosis factor (TNF) is a critical cytokine for the integrity of the granuloma.[26] Most patients with latent TB infection are asymptomatic, with no radiographic evidence of the infection.[23] In some patients, there may be a healed, calcified lesion on the chest radiograph, but bacteriologic studies return negative results. A positive TST or IGRA finding is the only indication that the person has been infected with *M. tuberculosis.* Individuals with latent TB infection are not infectious and thus cannot transmit the organism to other individuals.[19]

Active disease

In the majority of patients, active TB disease results from reactivation of a previously controlled latent infection, termed *reactivation TB*. It has been estimated that ~10% of individuals who acquire TB infection and do not receive therapy for the latent infection will develop active TB disease, and the risk of developing active disease is greatest during the first 2 years after infection.[18,23,24] In a population-based TST survey conducted in Florida between 1997 and 2001, the rate of reactivation with latent TB infection without HIV coinfection was 0.040 to 0.058 cases per 100 person-years.[27] However, another study reported that one in four cases of active TB in the United States may be caused by recent transmission.[28] This study included patients with TB whose culture result was positive, and *M. tuberculosis* isolates were fully characterized by genotype.

Clusters were defined as cases with *M. tuberculosis* that were an exact match by genotype within specific geospatial zones. Cases that were both genotypically and spatially clustered were considered recent TB transmission, and cases that were not genotypically and spatially clustered were considered reactivation TB. Of the 36,860 cases where genotyping was performed, 8499 cases (23.1%) met the criteria for recent TB transmission.[28] Groups at greatest risk for recent transmission were HIV-infected individuals, members of a minority group or ethnic race, males, individuals born in the United States, children ages 4 years and younger, substance abusers, and the homeless.[28] These patients may have limited access to health care, resulting in delayed diagnosis and extended periods of infectivity.

Reactivation of TB in persons with latent TB infection is primarily a function of the immune status of the host. The ability of the host to respond to *M. tuberculosis* infection is reduced by certain diseases, such as diabetes mellitus, silicosis, chronic renal failure, and diseases or drugs associated with immunosuppression (eg, HIV infection, anti-TNF-α agents, organ and hematologic transplantation, corticosteroids, and other immunosuppressive agents). The likelihood of progression from latent TB infection to active TB disease is greater in persons with these conditions.[23–25] HIV-infected persons, especially those with low $CD4^+$ T-cell counts, develop active TB disease rapidly after becoming infected; up to 50% of these individuals may develop active disease in the first 2 years after infection.[29] In addition, a person with untreated latent TB infection who acquires HIV infection will progress to active TB disease at an approximate rate of 5% to 10% per year.[30,31] The relative risk of progression from latent infection to active disease is 1.6 to 25 times higher in patients treated with anti-TNF-α agents, depending on the clinical setting and the agents used.[32] Physical or emotional stress, gastrectomy, intestinal bypass surgery, alcohol abuse, hematologic disease, reticuloendothelial disease, and intravenous (IV) drug use are risk factors for development of active disease. The elderly, adolescents, and children younger than age 5 years are also at increased risk for developing active disease.[19,23–25,33]

Overview of Drug Therapy

Drug treatment is the cornerstone of the management of patients with TB. In a patient with active TB, the overall treatment goals are to cure the individual patient and to minimize transmission of *M. tuberculosis.* Primary goals of chemotherapy are rapid bacterial killing, prevent emergence of drug resistance, and eliminate persistent tubercle bacilli to prevent relapse.[34] To accomplish these goals, treatment must be tailored to each patient's clinical and social circumstances to ensure adherence to and completion of treatment (patient-centered care). Effective TB treatment requires a prolonged period of drug therapy, and optimization of the initial treatment phase prevents emergence of resistance and ensures success of therapy. Current guidelines recommend four drugs for the initial 8-week treatment phase: rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE).[34] The drug regimen and duration of the continuation phase depends on patient response, susceptibility of the isolate, host factors, extent of the disease (pulmonary vs extrapulmonary, cavitation on chest radiography), and drug tolerability.[34] The shortest duration of therapy is 6 months, but longer durations may be required in certain situations and with drug-resistant strains.[34,35] Because patients must be treated for months, directly observed therapy (DOT) is the preferred core management strategy to ensure adherence.[34–37] In patients with latent TB infection, monotherapy with isoniazid, monotherapy with rifampin, or a combination of isoniazid plus rifapentine is among the recommended options.

Clinical Presentation of Active Disease

CASE 68-1

Question 1: H.G. is a 35-year-old Hispanic male who presents with a 4-week history of a productive cough. The cough was initially nonproductive but became productive of yellow sputum after 2 weeks. The patient has been self-medicating with over-the-counter antitussives without relief, and he experienced hemoptysis this morning. He reports subjective fevers, chills, night sweats,

dyspnea on exertion, fatigue, and an unintentional 15-pound (6.80-kg) weight loss during the past 2 months. He immigrated to the United States from Mexico when he was 12 years old, but he has not traveled outside the United States for more than a decade. He currently works as a laborer on new home construction projects, and several of his coworkers, who moved to the United States from Mexico within the past year, have similar respiratory symptoms. He is currently married with three children. The patient has a 20-pack-year smoking history and drinks alcohol on weekends but denies illicit drug use.

On physical examination, H.G. is a thin-appearing male in mild respiratory distress. His heart rate is 94 beats/minute, his respiratory rate is 24 breaths/minute, and his temperature is 102.02 °F (38.9 °C). Bronchial breath sounds are noted in the right upper lobe on chest auscultation, and chest radiography shows extensive patchy infiltrates in the right upper lobe. Significant laboratory data include the following:

White blood cell count, 13,200/μL (72% polymorphonuclear leukocytes, 3% bands, 12% lymphocytes, 13% monocytes)
Red blood cell count, 3.7×10^6/μL
Hemoglobin, 11.2 g/dL
Hematocrit, 34%
Platelets, 269×10^3/μL

Serum electrolytes, renal function, and hepatic function are within normal limits.

He is 69 inches (175.26 cm) tall, and his weight is 149.91 pounds (68 kg). The remainder of his physical examination is unremarkable.

What signs and symptoms consistent with active TB disease are present in H.G.?

H.G.'s history of cough (which gradually became productive), fever, night sweats, fatigue, and weight loss are classic symptoms of active TB.[19] Cough may be nonproductive early in the course of the illness, but with subsequent inflammation and tissue necrosis, sputum is usually produced and is key to the diagnostic studies. Sputum may contain blood (hemoptysis) in patients with advanced cavitary disease, which is particularly worrisome because cavitary lesions harbor high concentrations of organisms and the pulmonary location facilitates airborne transmission. Dyspnea is unusual unless there is extensive disease.[19] Other symptoms of TB may include pleuritic chest pain and general malaise.

In pulmonary TB, the chest radiograph usually reveals patchy or nodular infiltrates in the apical or posterior segments of the upper

lobes, but changes may be observed in any segment.

The patchy infiltrates on H.G.'s chest radiograph are consistent with pulmonary TB. Cavitary lesions may be seen; however, these were absent in this patient. Moderate elevation of the white blood cell count with increased monocytes and eosinophils and anemia are the most common hematologic manifestations of TB.[19] H.G. had an elevated white blood cell count with increased monocytes, and he was also anemic.

Many patients with active pulmonary TB have no acute symptoms, and a lack of symptoms may hinder diagnosis. In one study, ~50% of active TB cases without classic symptoms were misdiagnosed.[38] More than one-third of the patients with active TB had no sweats, chills, or malaise, and <50% were febrile. Cough was evident in 80% of these patients, and only 25% had hemoptysis. Although dullness over the apices of the lungs and posttussive rales are expected in TB, less than one-third of these patients had any abnormal pulmonary signs. Similar findings were reported in another study.[39] Absence of specific clinical symptoms underscores the importance of skin testing, sputum smears for AFB, and chest radiographs in suspected TB. Lastly, cases of active TB are often found after routine chest radiographs for other illnesses.

Because many of the symptoms of TB also occur in persons with preexisting pulmonary disease or pneumonia, they may be overlooked and not attributed to TB.

CASE 68-1, QUESTION 2: What risk factors for TB are present in H.G.?

The close contact with his coworkers, who have similar respiratory symptoms, and their geographic origin from Mexico are risk factors for TB in H.G. In addition, studies have implicated cigarette smoking as a risk factor for TB.[40–42] In a cohort study conducted in Taiwan, smoking was associated with a twofold increase in the risk of active TB. Furthermore, a significant dose–response relationship was identified for number of cigarettes smoked per day, number of years of smoking, and number of pack-years smoked.[42] Smoking impairs

mucociliary clearance, decreases phagocytic pulmonary alveolar macrophage function, decreases intracellular production of TNF-α, and causes iron overload in macrophages.[43–46] These defects in host defense mechanisms increase the risk of active disease after exposure to *M. tuberculosis.*

Diagnosis of Active Tuberculosis

Case 68-1, Question 3: A tuberculin purified protein derivative (PPD) skin test (5 test units [TU]) is ordered and placed on the volar aspect of H.G.'s left arm. Sputum is collected and sent for AFB stain, culture, and susceptibility testing. His smear finding is positive for AFB, and the result of the TST, read at 48 hours, was a palpable induration of 14 mm. What is tuberculin PPD skin testing? How should the result be interpreted in H.G.'s case?

The TST (Mantoux method) has been used as a diagnostic tool for infection with *M. tuberculosis* for decades, but a positive skin test result is not necessary for the diagnosis of active TB disease. The test is frequently referred to as the PPD test, which contains a protein prepared from a culture of the tubercle bacilli. Skin testing is performed by injecting 0.1 mL of solution containing 5 TU of PPD *intracutaneously* into the volar or dorsal surface of the forearm.[19,47] The injection is made using a 1/4- to 1/2-inch, 27-gauge needle and a tuberculin syringe. The solution should be injected just beneath the surface of the skin, avoiding subcutaneous tissue.[19,48] A discrete, pale elevation of the skin (a wheal) 6 to 10 mm in diameter is produced when the injection is performed correctly. If the first injection was administered improperly, another test dose can be given at once, selecting a site several centimeters away from the original injection site.[19]

If the patient has been infected with *M. tuberculosis,* sensitized T cells are recruited to the skin site where they release cytokines.[49] These cytokines induce an induration (raised area) through local vasodilatation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area.[19] Typically, the reaction to the

tuberculin protein begins 5 to 6 hours after the injection, with maximal induration observed at 48 to 72 hours. Therefore, the test should be read between 48 and 72 hours after the injection because tests read after 72 hours underestimate the actual size of the induration.[19],[24] For standardization, the diameter of the induration should be measured transversely to the long axis of the forearm and recorded in millimeters.[19] The diameter of the induration should be measured and not the erythematous zone surrounding the induration.

An induration of at least 5 mm in diameter read 48 to 72 hours after the injection is a positive reaction in an individual with a recent history of close contact with a person with active TB, a person with fibrotic changes on chest radiograph consistent with previous TB, patients who have undergone organ transplant and other immunosuppressed patients (receiving the equivalent of ≥15 mg/day of prednisone for >1 month), or HIV-infected persons.[19],[47],[50],[51]

An induration of at least 10 mm in diameter is a positive reaction with clinical conditions associated with increased risk of TB, such as diabetes mellitus, silicosis, chronic renal failure, malnutrition, leukemia, lymphoma, gastrectomy, jejunoileal bypass, and weight loss of >10% of ideal body weight.[19],[47],[51] In addition, an induration of at least 10 mm is considered to be a positive finding in recent immigrants (>5 years) from countries with a high prevalence of TB, injection drug users, residents and employees of high-risk congregate settings (eg, prisons, nursing homes, homeless shelters), health care workers, mycobacteriology laboratory personnel, and children younger than age 4 years or infants, children, and adolescents exposed to adults in high-risk categories.[19],[47],[51] The TST result is also considered positive for persons with an increase in induration diameter of at least 10 mm within a 2-year period.[47],[51] For individuals with no risk factors for TB, an induration of at least 15 mm is required for a positive reaction.[47],[51]

It is very likely that H.G. has been in close contact with persons with active TB, that is, his coworkers, even though they have not yet been diagnosed with active TB. When all factors are considered, the PPD of 14 mm should be considered to be a positive reaction in H.G.

Case 68-1, Question 4: Because H.G.'s PPD skin test result is positive, does this confirm his diagnosis of active TB? What other laboratory tests may be performed to aid in the diagnosis of TB in H.G.?

H.G.'s positive reaction to 5 TU of PPD alone does not imply active TB disease. It only confirms that he has previously been infected with *M. tuberculosis.* To confirm the diagnosis of active TB disease in H.G., *M. tuberculosis* must be detected and isolated from sputum, gastric aspirate, spinal fluid, urine, or tissue biopsy, depending on the site of infection.[19] As was performed in H.G., detection of AFB in stained sputum smears examined microscopically should be the first test to confirm the presence of mycobacteria in a clinical specimen. It is the easiest and fastest procedure that can be performed and allows preliminary confirmation of the diagnosis. Three appropriate sputum samples should be collected 8 to 24 hours apart, and at least one sample should be tested using a rapid molecular test.[34] Sputum samples for AFB stain and culture are best obtained early in the morning because the cough reflex is usually suppressed at night. The first early morning expectoration represents secretions accumulated in the chest overnight. The number of organisms in the morning sample is greater, and the diagnostic yield is higher. If a patient is not spontaneously producing sputum, induction of sputum using aerosolized hypertonic saline or bronchoscopy may be needed.[34] Smears may be prepared directly from clinical specimens or from concentrated preparations by placing the specimen on a glass slide under a microscope with a Ziehl–Neelsen or fluorochrome stain (not a Gram stain).[19] Sensitivity of sputum smear microscopy is low because 5000 to 10,000 bacilli/mL of specimen must be present for AFB detection in stained smears.[19,52] Therefore, a negative AFB smear result does not rule out active TB disease, and patients with active TB and negative AFB smear results may facilitate transmission of *M. tuberculosis.* Additional limitations of the AFB smear are its inability to differentiate among mycobacterial species and between viable and nonviable organisms. In many areas of the

United States, *M. avium* complex organisms are commonly isolated from the sputum of patients in whom a diagnosis of TB is highly probable, such as the elderly and patients with HIV infection.[53] This finding has resulted in a marked decrease in the specificity and positive predictive value of the sputum smear, in some cases to as low as 50%.[54]

The gold standard for laboratory confirmation of TB is culture.[55] Some patients may have a negative AFB smear result, but a sufficient number of organisms may be present to produce a positive culture result. Only 10 to 100 organisms are needed for a positive culture result.[19] As a result of the limitations of the AFB smear, a positive culture finding for *M. tuberculosis* is necessary to definitively diagnose TB in H.G. and all patients, even if the AFB smear result is positive. In addition, culture allows for genotyping and susceptibility testing of the isolate.[53] Because *M. tuberculosis* grows slowly (ie, once every 24 hours), it may take several weeks for the culture results to become positive.[19] Broth-based culture systems, when combined with DNA probes, can result in positive cultures in 2 weeks or less for sputum smear-positive specimens and in 3 weeks or less for smear-negative specimens.[53]

Nucleic acid amplification (NAA) tests are available to enhance and expedite direct identification of *M. tuberculosis* in clinical specimens independent of mycobacterial culture.[56],[57] These tests amplify the specific target sequences of nucleic acids in *M. tuberculosis* that can be detected by a nucleic acid probe within 24 to 48 hours. Compared with AFB smears, benefits of NAA testing include the ability to rapidly confirm the presence of *M. tuberculosis* in many AFB-negative smears and the positive predictive value of >95% for AFB-positive specimens in settings where nontuberculous mycobacteria are common.[55] NAA tests are cost-effective because they prioritize contact investigations, improve decision-making regarding respiratory isolation, and decrease unnecessary TB treatment.[58],[59] Current guidelines recommend NAA testing on at least one respiratory specimen from a patient with signs and symptoms of pulmonary TB for whom a diagnosis has not been established and for whom the test result would alter case

management and infection control activities.[55] If the NAA test result and the AFB smear result are positive, the patient is presumed to have TB, and drug treatment should be initiated while awaiting culture results.[55] If the NAA test result is positive and the AFB smear result is negative, clinical judgment should be exercised regarding initiating drug therapy, and additional diagnostic testing may be needed. If the NAA test result is negative and the AFB smear result is positive, a test for inhibitors should be performed and additional specimens should be tested with NAA. Sputum specimens (3%–7%) might contain inhibitors that prevent or reduce amplification and cause false-negative NAA results.[55] If the NAA test result and the AFB smear result are negative, clinical judgment is recommended in the decision to begin drug therapy because NAA tests lack the sensitivity in AFB smear-negative specimens needed to exclude the diagnosis of TB.[55]

Case 68-1, Question 5: Would a negative TST result have eliminated the possibility of infection with *M. tuberculosis* in H.G.?

A negative response to 5 TU of PPD in H.G. would not exclude active infection with *M. tuberculosis.* The PPD skin test has a reported false-negative rate of 25% during the initial evaluation of persons with active tuberculosis.[19] This high false-negative rate is attributable to poor nutrition and general health, overwhelming acute illness, or immunosuppression. False-negative results usually occur in persons who have only recently been infected or are anergic. Anergy, the decreased ability to respond to antigens, may be caused by severe debility, advanced age, immaturity in newborns, high fever, sarcoidosis, corticosteroids, immunosuppressive drugs, hematologic disease, HIV infections, overwhelming TB, recent viral infection, live-virus vaccinations, and malnutrition.[19] If anergy is suspected, control skin tests (*Candida,* mumps, or *Trichophyton*) may be placed in the contralateral arm. If the control test results are positive and the PPD test result is negative, infection with *M. tuberculosis* is less likely. The Centers for Disease Control and Prevention (CDC) changed its

recommendations regarding anergy skin testing in HIV-infected patients with a negative PPD test result. They cite problems with standardization and reproducibility, a low risk for TB associated with a diagnosis of anergy, and the lack of apparent benefit of therapy for latent TB infection in anergic HIV-infected patients. Therefore, the use of anergy testing in conjunction with PPD is no longer routinely recommended in this population or in other patients who are immunocompromised.[50,60,61]

Case 68-1, Question 6: On further questioning, H.G. informs the medical team that he received the bacillus Calmette–Guérin (BCG) vaccine when he was a child in Mexico. What is the BCG vaccine? What effect does the BCG vaccine have on the results of the TST? What other test may be performed in H.G. for detection of *M. tuberculosis* infection?

BCG is a live vaccine derived from an attenuated strain of *M. bovis,* and it is used in many foreign countries with a high prevalence of TB to prevent the disease in persons who are tuberculin negative. Many different BCG vaccines are available worldwide, and they differ with respect to immunogenicity, efficacy, and reactogenicity. Additional factors, such as genetic variability in the vaccinated subjects, the nature of the mycobacteria endemic in different parts of the world, and the use of different doses and immunization schedules, may contribute to the varied degrees of protection provided by the vaccine. The protective effect derived from BCG vaccines in case–control studies ranges from 0% to 80%.[62] Two meta-analyses calculated estimates of the protective efficacy of BCG vaccination for preventing TB. Results from the first meta-analysis indicated a 75% to 86% protective effect against meningeal and miliary TB in children.[63] In the second meta-analysis, the overall protective effect of BCG vaccines was ~50%.[64] Vaccine efficacy was higher in studies in which persons were vaccinated during childhood in contrast with those vaccinated at older ages.[64] Unfortunately, neither study could confirm vaccine efficacy for preventing pulmonary TB.

Prior vaccination with BCG usually results in a false-positive TST finding in patients who are not infected with *M. tuberculosis,* but skin test reactivity does not correlate with protection against TB.[19,62] There is no reliable method of distinguishing TST reactions caused by BCG vaccination from those caused by natural mycobacterial infections.[19,62] Therefore, it is prudent to consider "positive" reactions to 5 TU of PPD in BCG-vaccinated persons as indicating infection with *M. tuberculosis,* especially among persons from countries with a high prevalence of TB.[19] Even though H.G. received the BCG vaccine when he was a child, the results of the PPD skin test should still be considered positive, especially in light of his symptoms.

In general, BCG vaccination is not recommended for routine prophylaxis in the United States because the risk of exposure to TB is relatively low. BCG vaccination should be considered only for very select persons who meet specific criteria and in consultation with a TB expert. BCG vaccination should only be considered for infants or children whose PPD test result is negative and are continually exposed to a highly infectious, untreated patient with active TB or a child who is continually exposed to a person with infectious pulmonary TB caused by *M. tuberculosis* strains resistant to isoniazid and rifampin.[62] BCG vaccination of health care workers should be considered on an individualized basis in settings in which a high prevalence of patients is infected with MDR-TB, transmission of MDR-TB strains to health care workers and subsequent infection are likely, and comprehensive infection control precautions have been unsuccessful.[62] BCG vaccination is contraindicated in pregnancy and in persons who are immunocompromised (eg, HIV infection) or persons who are likely to become immunocompromised (eg, organ transplantation).[62] Adverse reactions to the BCG vaccine vary according to the type, dose, and age of the vaccine. Osteitis, prolonged ulceration at the vaccination site, lupoid reactions, regional suppurative lymphadenitis, disseminated BCG infection, and death have been reported.[62]

An IGRA is preferred over the TST for persons who have received the BCG vaccine.[65] Two IGRAs are currently approved by the FDA as an aid for diagnosing both latent and active *M. tuberculosis*

infection: the QuantiFERON®-TB Gold test (Qiagen) and the T-SPOT®.TB test (Oxford Immunotec). These IGRAs assess response to synthetic peptides that represent specific proteins, early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10), that are present in all *M. tuberculosis* strains.[65] In sensitized patients, ESAT-6 and CFP-10 are recognized by T cells and stimulate release of interferon-γ. The QuantiFERON®-TB Gold test measures the interferon-***γ*** concentrations released using an enzyme-linked immunosorbent assay. The T-SPOT®.TB test uses an enzyme-linked immunospot assay (ELISpot) to detect increases in the number of cells that secrete interferon-γ. However, ESAT-6 and CFP-10 are not present in BCG vaccine strains and most nontuberculous mycobacteria; therefore, IGRAs have improved specificity in BCG-vaccinated persons compared with the TST.[65] Results are available within 24 hours compared to 2 to 3 days for TST. IGRAs have essentially replaced TST for all patients because of the high rate of false-negative results and delay in availability of results with TST.

CASE 68-1, QUESTION 7: Should H.G. be tested for HIV infection?

The CDC recommends HIV screening for all patients with TB as well as those persons suspected of having TB disease and contacts of patients with TB.[66] Therefore, H.G. should be tested for HIV. HIV infection is the most important risk factor for progression of latent TB infection to active disease, and progression is more rapid in HIV-infected persons. Unlike other AIDS-related opportunistic infections, CD4 count is not a reliable predictor of increased risk of TB disease in HIV-infected persons.[67] TB may be the first manifestation of HIV infection because patients can have a relatively high CD4 count when TB disease develops.[67]

TREATMENT OF ACTIVE DISEASE

Initial Therapy

Case 68-1, Question 8: H.G.'s HIV test result is negative. How should treatment be initiated in H.G., pending the results of sputum culture and susceptibility testing? Can he transmit *M. tuberculosis* to others during treatment?

There are four basic regimens recommended for the treatment of adult patients with active TB caused by organisms that are known or presumed to be drug susceptible (**Table 68-2**).[34] Because H.G. has not been treated previously for TB, he should be started on the RIPE regimen. However, he has been in close contact with persons with symptoms resembling TB who are from an area (Mexico) with a high prevalence of drug-resistant TB. Therefore, H.G. must be closely monitored for resolution of symptoms, results of repeated sputum smears, and culture and susceptibility results, regardless of the initial treatment regimen. Previous guidelines recommended the addition of ethambutol only if the local prevalence of isoniazid-resistant *M. tuberculosis* is at least 4%.[36,68] In the United States, 9.2% of *M. tuberculosis* isolates recovered from patients with no previous history of TB were resistant to isoniazid in 2019.[11] The prevalence of isoniazid resistance was higher in foreign-born persons (10.2%) compared with U.S.-born persons (6.5%).[11] In patients with a previous history of TB, 14.1% of strains were resistant to isoniazid in 2019, with 15.4% resistance in foreign-born persons versus 9.7% resistance in U.S.-born persons.[11] Because of the relatively high likelihood of TB caused by isoniazid-resistant organisms, four drugs are necessary in the initial 8-week treatment phase.[34]

Table 68-2
Treatment Regimens for Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Initial Phase		Continuation Phase			
Regimen	Drugs	Interval and Doses[a] (Minimal Duration)	Drugs	Interval and Doses[a,b] (Minimal Duration)	Range of Total Doses (Minimal Duration)	Comments [b,c]
1	RIF INH PZA EMB	7 days per week for 56 doses (8 weeks) *or* 5 days per week for 40 doses (8 weeks)	RIF INH	7 days per week for 126 doses (18 weeks) *or* 5 days per week for 90 doses (18 weeks)	182–130 (26 weeks)	Preferred regimen for newly diagnosed pulmonary tuberculosis
2	RIF INH PZA EMB	7 days per week for 56 doses (8 weeks) *or* 5 days per week for 40 doses (8 weeks)	RIF INH	Three times weekly for 54 doses (18 weeks)	110–94 (26 weeks)	Preferred alternative regimen in situations where more frequent DOT is a concern
3	RIF INH PZA EMB	Three times weekly for 24 doses (8 weeks)	RIF INH	Three times weekly for 54 doses (18 weeks)	78 (26 weeks)	Use with caution in patients with HIV or cavitary disease. Missed doses may lead to treatment failure, relapse, and/or acquired drug resistance.
4	RIF INH PZA EMB	7 days per week for 14 doses, then twice weekly for 12 doses	RIF INH	Twice weekly for 36 doses (18 weeks)	62 (26 weeks)	Do not use twice-weekly regimens in patients with HIV or smear-positive and/or cavitary disease.

DOT, directly observed therapy; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

[a]Drugs may be given 5 days per week with adjustment of the total number of doses when directly observed therapy (DOT) is used. No studies have compared 5 days per week to 7 days per week, but extensive experience supports 5 days per week administration with DOT.

[b]The continuation phase should be extended to 31 weeks for patients with cavitary disease on initial chest radiograph and positive culture results at the end of 2 months of intensive therapy.

[c]Pyridoxine 25 to 50 mg daily is given with isoniazid to decrease the risk of peripheral neuropathy. The dose should be increased to 100 mg daily for patients with peripheral neuropathy.

The initial four-drug regimen should be administered for 8 weeks and may be administered daily for 7 or 5 days/week (regimens 1 and 2), thrice weekly (regimen 3), or daily for the first 2 weeks and then twice weekly for 6 weeks (regimen 4).[34] The preferred administration schedule is daily by DOT. Based on clinical experience, 5 days per week administration is considered to be equivalent to 7 days per week administration and either regimen 1 or 2 may be considered "daily." However, 5-day-a-week administration should always be given by DOT.[34] Thrice-weekly dosing (regimen 3) may be considered in HIV-uninfected patients with noncavitary disease if

daily treatment is not feasible or poorly tolerated. However, thrice-weekly dosing has been associated with higher rates of treatment failure, relapse, and acquired drug resistance.[34] Regimen 4 is generally not recommended owing to lack of high-quality supporting evidence and concern for missed doses resulting in once-weekly dosing, which is inferior. This regimen may be considered if daily- or thrice-weekly DOT is not feasible in patients who are HIV uninfected and at low risk for relapse (drug susceptibility known, noncavitary and/or smear result negative). Drug dosages for these recommended regimens are listed in **Table 68-3**. H.G. should be started on rifampin 600 mg daily, isoniazid 300 mg daily, pyrazinamide 1500 mg daily, and ethambutol 1200 mg daily. He should also receive pyridoxine 25 to 50 mg/day to minimize the risk of developing isoniazid-induced peripheral neuropathy. For patients with peripheral neuropathy, pyridoxine 100 mg daily may be given.[34] If the TB strain is susceptible to both rifampin and isoniazid, ethambutol is not necessary, and the intensive phase may be completed with rifampin, isoniazid, and pyrazinamide.[34]

Table 68-3
Drugs Used in the Treatment of Tuberculosis in Adults and Children

Drug	Dosing (Maximum Dose)	Primary Side Effects	Dose Adjustment in Renal Impairment	Comments
First-Line Agents				
Isoniazid	Adults: 5 mg/kg (300 mg) daily; 15 mg/kg (900 mg) once, twice, or thrice weekly Children: 10–15 mg/kg (300 mg) daily; 20–30 mg/kg (900 mg) once or twice weekly	Increased aminotransferases (asymptomatic), clinical hepatitis, peripheral neuropathy, CNS effects, lupus-like syndrome, hypersensitivity reactions	No	Peripheral neuropathy preventable with pyridoxine 25–50 mg. Hepatitis more common in older patients and alcoholics. Potent inhibitor of CYP2C9, CYP2C19, CYP2E1. ↑ serum level of phenytoin
Rifampin	Adults: 10 mg/kg (600 mg) once daily, twice weekly, or thrice weekly Children: 15–20 mg/kg (600 mg) once daily or thrice weekly	Pruritus, rash, hepatotoxicity, GI (nausea, anorexia, abdominal pain), flulike syndrome, thrombocytopenia, renal failure	No	Orange-red discoloration of body secretions (sweat, saliva, tears, urine). Potent inducer of CYP3A4, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A5.
Rifabutin	Adults: 5 mg/kg (300 mg) once daily, twice weekly, or thrice weekly Children: unknown; estimated 5 mg/kg	Neutropenia, uveitis, GI symptoms, polyarthralgias, hepatotoxicity, rash	No	Orange-red discoloration of body secretions (sweat, saliva, tears, urine). Weaker inducer of hepatic microsomal enzymes than is rifampin.
Rifapentine	Adults: Active disease, 10–20 mg/kg (600 mg) once weekly during continuation phase; latent infection, 15 mg/kg (900 mg) once weekly Children 2–11 years: 15 mg/kg (900 mg) once weekly	Similar to rifampin	Unknown	Drug interactions due to induction of hepatic microsomal enzymes (see rifampin)
Pyrazinamide	Adults: 40–55 kg: 1 g daily, 2 g twice weekly, 1.5 g thrice weekly; 56–75 kg: 1.5 g daily, 3 g twice weekly, 2.5 g thrice weekly; 76–90 kg: 2 g daily, 4 g twice weekly, 3 g thrice weekly Children: 30–40 mg/kg (2 g) daily; 50 mg/kg (2 g) thrice weekly	Hepatotoxicity, nausea, anorexia, polyarthralgias, rash, hyperuricemia, dermatitis	Yes	Monitor aminotransferases monthly.
Ethambutol	Adults: 40–55 kg: 800 mg daily, 2 g twice weekly, 1.2 g thrice weekly; 56–75 kg: 1.2 g daily, 2.8 g twice weekly, 2 g thrice weekly; 76–90 kg:1.6 g daily, 4 g twice weekly, 2.4 g thrice weekly Children: 15–25 mg/kg (1 g) daily; 50 mg/kg (2.5 g) twice weekly	Optic neuritis, skin rash, drug fever	Yes	Routine vision tests recommended; 50% excreted unchanged in urine
Second-Line Agents				
Cycloserine	Adults: 10–15 mg/kg/day (1 g), usually 500–750 mg/day in 2 divided doses Children: 10–15 mg/kg/day (1 g)	CNS toxicity (psychosis, seizures), headache, tremor, fever, skin rashes	Yes	May exacerbate seizure disorders or mental illness. Some toxicity preventable by pyridoxine (100–200 mg/day). Monitor serum concentrations (peak 20–35 μg/mL desirable).

Drug	Dosing (Maximum Dose)	Primary Side Effects	Dose Adjustment in Renal Impairment	Comments
Ethionamide	Adults: 15–20 mg/kg/day (1 g), usually 500–750 mg/day in one daily dose or 2 divided doses Children: 15–20 mg/kg/day (1 g)	GI effects (metallic taste, nausea, vomiting, anorexia, abdominal pain), hepatotoxicity, neurotoxicity, endocrine effects (alopecia, gynecomastia, impotence, hypothyroidism), difficulty in diabetes management	Yes	Must be given with meals and antacids. Monitor aminotransferases and thyroid-stimulating hormone monthly.
Streptomycin	Adults: 15 mg/kg/day (1 g); ≥60 years, 10 mg/kg/day (750 mg) Children: 20–40 mg/kg/day (1 g)	Vestibular or auditory dysfunction of eighth cranial nerve, renal dysfunction, skin rashes, neuromuscular blockade	Yes	Audiometric and neurologic examinations recommended; 60%–80% excreted unchanged in urine. Monitor renal function.
Amikacin	Adults: 15 mg/kg/day (1 g); ≥60 years, 10 mg/kg/day (750 mg) Children: 15–30 mg/kg/day (1 g)	Ototoxicity, nephrotoxicity	Yes	Less vestibular toxicity than with streptomycin. Monitoring similar to that for streptomycin
Capreomycin	Adults: 15 mg/kg/day (1 g); ≥60 years, 10 mg/kg/day (750 mg) Children: 15–30 mg/kg/day (1 g) as single dose or twice-weekly dose	Nephrotoxicity, ototoxicity	Yes	Monitoring similar to that for streptomycin
p-Aminosalicylic acid (PAS)	Adults: 8–12 g/day in 2–3 doses Children: 200–300 mg/kg/day in 2–4 divided doses	GI intolerance, hepatotoxicity, malabsorption syndrome, hypothyroidism	Yes	Liver enzymes and thyroid function should be monitored.
Levofloxacin	Adults: 500 to 1000 mg/day	Nausea, diarrhea, abdominal pain, anorexia, headache, dizziness, QT prolongation, tendon pain or rupture	Yes	Do not give with divalent or trivalent cations (aluminum, magnesium, iron, etc).
Moxifloxacin	Adults: 400 mg/day	Nausea, diarrhea, abdominal pain, anorexia, headache, dizziness, QT prolongation, tendon pain or rupture	No	See levofloxacin.
Bedaquiline	Adults: 400 mg once daily for 2 weeks, then 200 mg thrice weekly for 22 weeks	Nausea, arthralgias, headache, increased transaminases, hemoptysis, chest pain, anorexia, rash, QT prolongation	No	Take with food. CYP3A4 substrate, avoid concomitant administration with inducers and inhibitors. Increased mortality compared to that of placebo

CNS, central nervous system; CYP, cytochrome P450; GI, gastrointestinal.

Fixed-dose combinations of drugs have been advocated to improve adherence to the prescribed regimen, especially during the critical initial treatment phase. There are two fixed-dose combination preparations available in the United States: Rifamate®, which contains isoniazid 150 mg and rifampin 300 mg/capsule, and Rifater®, which contains isoniazid 50 mg, rifampin 120 mg, and pyrazinamide 300 mg/tablet. These formulations are a means of minimizing inadvertent monotherapy, especially when DOT is not possible, and they may decrease the risk of acquired drug resistance while reducing the number of capsules or tablets that must be ingested each day.[34] Safety and efficacy of a four-drug fixed-dose

combination regimen was compared, with each drug administered separately in patients with pulmonary TB.[69] The combination tablet contained isoniazid 75 mg, rifampin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg, and two to five tablets were ingested per day based on body weight. The number of patients whose results were culture negative at 18 and 24 months was similar between the treatment groups, in addition to the number of treatment failures, relapses, and death. The four-drug fixed-dose combination was noninferior to each drug administered separately.[69] It should be noted that there was no difference in outcomes based on HIV status, but <7% of the study subjects were HIV positive.[69]

The high risk of transmission of *M. tuberculosis* to other persons mandates that hospitalized persons with suspected or confirmed infectious TB be placed in respiratory isolation until they are determined not to have TB, they are discharged from the hospital, or they are confirmed to be noninfectious.[36] Based on H.G.'s subjective and objective findings, he should be placed in respiratory isolation. H.G.'s symptoms should improve within the first 4 weeks. He would be considered to be noninfectious when he is receiving effective drug therapy, is improving clinically, and has had negative results for three consecutive sputum AFB smears collected on different days.[36] Patients who have responded clinically may be discharged to home despite positive smear results if their household contacts have already been exposed and these contacts are not at increased risk for TB (eg, infants, HIV-positive and immunosuppressed persons). In addition, patients discharged to home with positive smear results must agree not to have contact with other susceptible persons.[36]

Fluoroquinolones as Initial Therapy

Interest in fluoroquinolones for the treatment of TB dates back >30 years, with a report describing the use of ofloxacin in 19 patients with chronic, drug-resistant TB disease.[70] Several fluoroquinolones possess in vitro activity against *M. tuberculosis*, but moxifloxacin is four- to eightfold more potent than is levofloxacin.[71] Moxifloxacin was

compared with ethambutol in the first 2 months of treatment in adults with smear result–positive pulmonary TB.[72] Patients were randomly assigned to receive moxifloxacin 400 mg daily or ethambutol (based on body weight), and all patients received rifampin, isoniazid, and pyrazinamide. Patients receiving moxifloxacin were more likely to have negative sputum culture results at 4 and 6 weeks, but the 2-month conversion rates were equal in each group.[72] In another study, sputum culture conversion at 8 weeks was significantly greater in patients treated with moxifloxacin when compared with ethambutol (80% vs 63%).[73] Culture conversion rates were also significantly higher in the moxifloxacin group at weeks 1, 2, 3, and 4, and the median time to consistently negative culture results was 35.0 days in the moxifloxacin group and 48.5 days in the ethambutol group.[73]

Moxifloxacin has been compared with isoniazid during the intensive phase of treatment of pulmonary TB.[74] Patients were randomly assigned to receive moxifloxacin 400 mg or isoniazid 300 mg daily, and all patients received rifampin, pyrazinamide, and ethambutol.[74] After 8 weeks, negative sputum culture results were observed in 60.4% of the patients in the moxifloxacin group and 54.9% of patients in the isoniazid group, but this difference was not statistically significant.[74]

Despite the reported efficacy of fluoroquinolones in the treatment of TB, clinicians must be cognizant of the potential development of resistance to this important drug class. Fluoroquinolone resistance in *M. tuberculosis* has been described, occurring more frequently in multidrug-resistant isolates.[9,75] Globally, resistance to any fluoroquinolone was 20.1% in MDR-TB cases in 2019.[9] Fluoroquinolones are widely used in the United States, and outpatient use for infections other than TB could be a potential risk factor for TB resistance in a patient who becomes infected with *M. tuberculosis.* In a study evaluating risk factors for fluoroquinolone-resistant *M. tuberculosis,* investigators identified newly diagnosed patients with culture-confirmed TB in a Medicaid population.[76] Of the 640 patients evaluated, 116 (18%) patients had fluoroquinolone exposure in the 12 months before diagnosis with TB, and 16 (2.5%) patients were infected with *M. tuberculosis* strains that were

fluoroquinolone resistant.[76] The study found that receipt of a fluoroquinolone for >10 days, occurring >60 days before diagnosis of TB, was associated with the highest risk for fluoroquinolone resistance.[76] Therefore, judicious use of fluoroquinolones, especially in patients at risk for TB infection, is mandatory to maintain the utility of fluoroquinolones in the treatment of TB.

Susceptibility Testing

Drug susceptibility testing is essential to ensure proper treatment of patients with active disease and should be performed on the initial isolate of *M. tuberculosis* from all patients.[19] Susceptibility testing should also be performed if culture results remain positive after 3 months of therapy or if negative culture results become positive after a period of time. Traditionally, susceptibility testing is performed by growing the organism on solid or in liquid media containing the drug. The agar proportion method allows for quantitation of the proportion of organisms that are resistant to a given drug, which is expressed as a percentage of the total organism population tested.[19] A drug will not be useful for therapy if ≥1% of the total population is resistant to the drug. Unfortunately, susceptibility results may not be available for several weeks because of the slow growth of the organism and the need to isolate the pathogen before susceptibility testing can be performed.[19]

To expedite susceptibility reporting, molecular drug resistance tests have been developed to detect mutations in the chromosomal sequence encoding for resistance to a specific drug directly on clinical specimens without the need for growth on culture.[56],[57] For example, mutations in the *rpoB* gene block the activity of rifampin by preventing the drug from binding to RNA polymerase. Approximately 95% of rifampin-resistant *M. tuberculosis* carry this mutation, and treatment failures have been associated with the presence of *rpoB* mutations.[77],[78] The molecular drug resistance test amplifies the target genetic sequence using polymerase chain reaction, and a second assay, such as DNA sequencing and hybridization assays, is

used to determine whether the sequence contains a mutation associated with drug resistance. If a mutation is detected, the organism is considered to be drug resistant, but the organism is presumed to be drug susceptible if a mutation is not detected. Molecular tests can reliably detect the presence of known mutations within 1 to 2 days, which may result in earlier initiation of effective therapy, shorter durations of infectivity, and reduced spread of TB. However, these molecular drug resistance tests can only detect a specific set of known mutations and cannot identify novel mutations conferring resistance.[57] Therefore, traditional susceptibility testing continues to play an important role in confirming results of molecular testing.[56]

The Xpert® MTB/RIF assay (Cepheid) is an automated molecular-based test that uses nested real-time polymerase chain reaction, allowing for simultaneous detection of *M. tuberculosis* and rifampin resistance. The test is approved for diagnostic testing of raw sputum samples, and results are available within 2 hours.[56] Sensitivity was 95% to 98.2% in AFB culture or smear specimens that returned positive results, but performance was correlated with bacterial load because sensitivity was only 55% to 72.5% in smear specimens with negative results.[79],[80] Specificity was 94% to 99.2% in patients with negative culture results.[79],[80] A recent, large meta-analysis demonstrated pooled sensitivity and specificity of 85% and 98%, respectively, for the Xpert® MTB/RIF assay with a sensitivity of 98% in AFB smear-positive sample results and 67% in AFB smear-negative, culture-positive sample results.[81] Sensitivity was lower in patients with HIV infection (81%) compared to patients without HIV infection (88%), with no difference in specificity (98%).[81] The sensitivity and specificity of the Xpert® MTB/RIF test for detection of rifampin resistance was 96% and 98%, respectively.[81] The Xpert® MTB/RIF Ultra assay demonstrated higher sensitivity and lower specificity for detection of TB with similar sensitivity and specificity for detection of rifampin resistance compared to the Xpert® MTB/RIF assay.[81]

Case 68-1, Question 9: Is H.G. a risk to the community and does anyone need to know?

Yes! Each case of active TB disease must be reported to the local, state, or both public health departments.[19,36,82] This not only results in optimal therapy by monitoring adherence to therapy but it also ensures that contact and source-case investigations will be performed. All individuals who have been in close contact with H.G. should be evaluated for latent TB infection or active disease. Considering their close contact with H.G. and his coworkers, his family members should be evaluated. Reporting of cases also permits record-keeping and surveillance to determine whether public health TB control efforts are achieving their goal of preventing the spread of TB.[36,82]

Continuation Therapy

REGIMENS

Case 68-1, Question 10: Four weeks later, H.G.'s initial sputum culture results were reported to be positive for *M. tuberculosis*. Drug susceptibility testing to rifampin and isoniazid revealed susceptibility to both agents. What drug regimen should be used for continued treatment of H.G.? How long should treatment be continued? What microbiologic testing should be performed during treatment?

Successful treatment of uncomplicated TB can be achieved in 6 months (26 weeks) if the RIPE regimen is used for the first 2 months (8 weeks) and if patient adherence to the regimen and organism susceptibility can be assured.[34] Therefore, after 8 weeks of DOT with the RIPE regimen, H.G.'s regimen may be streamlined to rifampin and isoniazid daily (5 or 7 days per week) or twice- or thrice-weekly administration under continued DOT for an additional 18 weeks (Table 68-2). Three times a week is preferred over twice-weekly administration because of concerns for missed doses resulting in an inferior once-weekly regimen. Once-weekly treatment with isoniazid

900 mg and rifapentine 600 mg is generally not recommended but may be considered only in HIV-uninfected patients without cavitary lesions and negative sputum culture results at the end of the intensive phase.[34]

The effectiveness of a primarily twice-weekly treatment regimen has been demonstrated in both pulmonary and extrapulmonary TB.[83] The regimen consisted of rifampin 600 mg, isoniazid 300 mg, pyrazinamide 1.5 to 2.5 g, and streptomycin 750 to 1000 mg intramuscularly daily for 2 weeks, followed by the same drugs twice weekly for an additional 6 weeks. The regimen was then reduced to isoniazid and rifampin twice weekly for the remaining 16 weeks (4 months). At 3 months, 75% of patients had negative sputum culture results, and all patients returned culture-negative results at 20 weeks.[83] Relapse occurred in two patients and only minor adverse effects were reported. An important feature is that this regimen is highly cost-effective primarily because of the lowest number of patient–health care worker encounters (62 directly observed doses). However, adherence must be ensured for twice-weekly administration.

If pyrazinamide cannot be included in the initial regimen, therapy should be initiated with rifampin, isoniazid, and ethambutol for the first 8 weeks. Therapy should be continued with rifampin and isoniazid for 7 months (31 weeks) given either daily or thrice weekly.[34]

Daily administration of rifampin 600 mg and isoniazid 300 mg is preferred for continuation therapy for H.G.; however, he is HIV negative and chest radiography does not demonstrate cavitary lesions. Thus, thrice-weekly dosing of rifampin 600 mg and isoniazid 900 mg could be considered for H.G. because this approach requires fewer doses and may result in substantial cost savings.[34] However, negative AFB culture results must be documented at the end of the 8-week intensive phase. Relapse rates for the twice- and thrice-weekly rifampin and isoniazid continuation regimens are significantly lower than is the once-weekly regimen of isoniazid 900 mg and rifapentine 600 mg.[84],[85] Five characteristics were associated with increased relapse risk in the isoniazid/rifapentine group: sputum

culture result positive at 2 months; cavitation on chest radiograph; underweight; bilateral pulmonary involvement; and non-Hispanic Caucasian race.[85] A potential explanation for these results is the high protein binding of rifapentine (98%). A study evaluated the safety and tolerability of rifapentine 600, 900, and 1200 mg once weekly (with isoniazid 15 mg/kg) in 150 HIV-negative patients.[86] A trend toward more adverse events was observed in the 1200-mg treatment arm (P = .051), but the 900-mg dose was well tolerated.[86] However, relapse rates for the higher dose weekly rifapentine regimens with isoniazid are unknown. A subsequent study demonstrated that low plasma concentrations of isoniazid were associated with failure or relapse with once-weekly isoniazid and rifapentine.[87] Two patients who relapsed with *M. tuberculosis* monoresistant to rifamycin had very low isoniazid concentrations. Rapid acetylation status was a risk factor in those patients who failed or relapsed.[87] However, rifamycin pharmacokinetics did not influence patient outcomes.[87]

Treatment with rifampin and isoniazid should be continued for a minimum total duration of 26 weeks. A full course of therapy can be more accurately determined by the total number of doses ingested, not solely by the duration of therapy.[34] Thus, 26 weeks is the minimum duration of treatment and accurately indicates the amount of time the drugs are given only if there are no interruptions in drug administration.[34] During treatment of pulmonary TB, sputum samples for AFB smear and culture should be obtained at least monthly until two consecutive samples return culture-negative results. If the patient has AFB-positive smear results at diagnosis, as in the case of H.G., follow-up samples for AFB smears may be obtained every 2 weeks until two consecutive sample results are negative.[34] On occasion, AFB culture results may be negative despite positive AFB smear results, but the positive smears likely contain dead organisms and does not represent treatment failure. Duration of the continuation phase is dependent on the microbiologic status of the patient at the end of the intensive phase. If AFB culture results remain positive after the intensive phase, the continuation phase should be continued for 7 months (31 weeks).[34]

Pyridoxine 25 to 50 mg/day should be continued throughout the treatment period. If H.G. is symptomatic or has smear- or culture-positive results after 3 months of therapy, he should be reevaluated for possible nonadherence with his therapy, malabsorption of the drugs, or infection with drug-resistant organisms. Evaluation should include a second culture and a second susceptibility test, consideration of DOT (if not already instituted), and consultation with experts in the treatment of TB.[36]

Case 68-1, Question 11: H.G. is concerned about the long duration required for treatment of his infection. He asks whether there is any way to shorten the length of treatment. Are there any effective treatment regimens that may be administered for <26 weeks?

Treatment of active TB for 26 weeks is a challenge to ensure that patients adhere to the prescribed regimen for the total duration of therapy. Shorter course treatment regimens, if efficacious, could be helpful in improving adherence rates, decreasing treatment costs, and reducing adverse events. Three published studies evaluated the treatment of drug-susceptible TB for a total duration of 4 months using modified regimens that included a fluoroquinolone (moxifloxacin or gatifloxacin).[88–90] The control regimen was the same in each study and consisted of 8 weeks of RIPE followed by rifampin and isoniazid for 18 weeks. In all three studies, unfavorable outcomes and culture-confirmed relapse/recurrence were more common in patients receiving the short-course regimens; therefore, noninferiority was not demonstrated for any of the 4-month regimens.[88–90] Based on these studies, H.G. should receive 26 weeks of therapy, and every effort should be made to ensure adherence to the treatment regimen.

Directly Observed Therapy

Case 68-1, Question 12: What is DOT, and why is it important for H.G. to be treated using DOT?

DOT is the practice of a health care provider or other responsible person observing as the patient ingests *and* swallows the TB medications. DOT is the preferred core management strategy for *all* patients with TB.[34–37] The purpose of DOT is to ensure adherence to TB therapy. DOT not only ensures completion of therapy but it may also reduce the risk of developing drug resistance. By improving these two factors, it also reduces the risk of transmission of TB to the community. DOT can be administered with daily or twice- and thrice-weekly regimens. It can be administered to patients in the office or clinic setting, or it can be given at the patient's home, school, or work.[34],[68] Often, enablers or incentives, such as food, clothing, or transportation, are used to improve adherence to DOT. A comprehensive review of DOT-related articles found that the completion rate of TB therapy exceeds 90% when DOT is used along with enablers.[37],[91] A study found that patients with positive culture results treated for active pulmonary TB with DOT had significantly higher cure rates (97.8% vs 88.6%; $P > .002$) and lower TB-related mortality (0% vs 5.5%; $P = .002$) compared with patients treated using self-administered therapy.[92] Although DOT is recommended for all patients, public health departments may not be able to provide DOT for all patients because of the associated costs. The initial cost of DOT is greater than self-administered therapy; however, when costs of relapse and failure are included in a cost-effectiveness analysis, DOT is significantly less expensive than is self-administered therapy.[93] When drug resistance develops (in those instances in which DOT is not used), the cost of salvage therapy increases to $180,000.00 per patient.[94] It is, therefore, widely accepted that patients with TB should receive DOT.[93],[95]

Multiple-Drug Therapy

Case 68-1, Question 13: Why are multiple drugs recommended for treatment of active TB disease? What is the role of each drug in the treatment of active TB?

The key to treating active TB disease is multiple-drug therapy for a period sufficient to kill the organisms and to prevent development of resistant strains of *M. tuberculosis.* Most cavitary lesions contain a concentration of 10^9 to 10^{12} organisms, and the frequency of mutations that confer resistance to a single drug is ~10^{-6} for isoniazid and streptomycin, 10^{-8} for rifampin, and 10^{-5} for ethambutol. Considering the inoculum of organisms involved, patients with active TB disease likely harbor organisms with random mutations that confer drug resistance to a given drug. If a single drug is given, it would reduce the number of drug-susceptible organisms but allow the drug-resistant organisms to replicate. By using multiple-drug therapy, the likelihood of encountering organisms with mutations to multiple drugs is reduced. For example, the frequency of concurrent mutations to isoniazid and rifampin would be 10^{-14} (10^{-6} for isoniazid and 10^{-8} for rifampin), making simultaneous resistance to both drugs an unlikely event in an untreated patient. Therefore, monotherapy should never be used in the treatment of active TB disease.[34],[94]

Multiple-drug therapy also serves to sterilize the sputum and lesions as quickly as possible. The drugs available for the treatment of TB vary in their ability to accomplish this task.[34] Drugs effective against tubercle bacilli can be divided into first-line and second-line agents (Table 68-3). The foundation of treatment should be with first-line agents, such as RIPE. Of the various agents, isoniazid has the most bactericidal activity versus rapidly multiplying *M. tuberculosis* during the initial phase of therapy (early bactericidal activity), followed by ethambutol, rifampin, and streptomycin.[96–98] Drugs that have potent early bactericidal activity more rapidly decrease the infectiousness of the patient and reduce the likelihood of developing resistance. Pyrazinamide has weak early bactericidal activity during the first 2 weeks of therapy and is less effective in preventing emergence of drug resistance than are isoniazid, rifampin, and ethambutol.[96],[99] Therefore, pyrazinamide should not be combined with only one other agent when treating active TB disease. Rifampin also has activity against intracellular organisms that are usually dormant but undergo periods of active growth. This ability to

penetrate and destroy the persistent intracellular organisms makes rifampin extremely valuable in short-course chemotherapy regimens.[100]

Pyrazinamide is most effective against tubercle bacilli in the acidic environment within the macrophage or areas of tissue necrosis. In addition, it is most effective in sterilizing lesions when used in the first 2 months of treatment, but it does not offer substantial sterilizing activity after 2 months. Pyrazinamide should be considered an essential component of short-course regimens.[34,68]

Ethambutol is bacteriostatic at low doses, but bactericidal at higher doses. It is moderately effective against the fast-growing bacilli. It has little sterilizing activity and is primarily used to prevent the emergence of drug-resistant organisms.[68]

Other drugs used in the treatment of TB (bedaquiline, capreomycin, amikacin, cycloserine, ethionamide, *p*-aminosalicylic acid) are usually reserved for cases involving drug-resistant organisms, treatment failures, drug toxicity, or patient intolerance to the other agents. Their use is discussed later in the chapter.

Monitoring Drug Therapy

Case 68-1, Question 14: What subjective and objective findings should be followed to ensure therapeutic efficacy and to minimize drug toxicity? Should H.G. be followed up closely after completion of his treatment regimen?

H.G. should be questioned about the occurrence of adverse reactions associated with his therapy (see Table 68-3). Specifically, he should be asked about anorexia, nausea, vomiting, or abdominal pain, which may be an indication of possible hepatitis secondary to isoniazid, rifampin, or pyrazinamide. He should be questioned about numbness and tingling in his extremities; however, isoniazid-induced peripheral neuropathy should not be a problem in H.G. because he is also taking pyridoxine, which should prevent this adverse effect. H.G. also should be examined for, and questioned about, petechiae or bruises, because thrombocytopenia occurs occasionally with

rifampin therapy. This effect purportedly occurs more frequently with intermittent rifampin therapy, but it is rare at the currently recommended intermittent rifampin dose of 10 mg/kg/day (≈600 mg).[68]

In a study comparing 6- versus 9-month antituberculosis therapies of mostly isoniazid and rifampin, the incidence of side effects was similar between the two groups. Adverse effects occurred in 7.7% of patients in the 6-month arm compared with 6.4% in the 9-month arm, which was not statistically significant.[101] Hepatic abnormalities occurred in 1.6% of patients in the 6-month regimen and 1.2% in the 9-month regimen (not statistically significant). Hematologic events were rare at 0.2% and 0.0% in the 6- and 9-month groups, respectively. Other reported effects, gastrointestinal (GI) problems, rash, and arthralgias were minor and infrequent in both regimens.[101]

OBJECTIVE SIGNS

A pretreatment complete blood count, platelet count, blood urea nitrogen, hepatic enzymes (serum aminotransferases), bilirubin, and serum uric acid should be evaluated. Baseline visual examination should also be considered for patients receiving ethambutol. These tests are performed to detect any abnormality that may complicate or necessitate modification of the prescribed regimen. These tests should be repeated if the patient experiences any evidence of drug toxicity or has abnormalities at baseline.[34,68]

H.G. is 35 years old and at increased risk for development of drug-induced hepatotoxicity. Isoniazid can cause asymptomatic increases in serum transaminases as well as overt hepatitis.[34] Pyrazinamide has also been associated with hepatotoxicity, but the incidence is less common at doses of ≤25 mg/kg/day. Transient asymptomatic hyperbilirubinemia and cholestatic hepatitis can occur in patients receiving rifampin.[34] Therefore, it is important that H.G. be educated about possible symptoms of hepatotoxicity, primarily nausea, vomiting, abdominal pain, anorexia, and jaundice. Monthly serum liver function tests (LFTs) are no longer recommended because they are costly, and transient, asymptomatic elevations in LFTs may

occur, which could result in unnecessary discontinuation of optimal therapy. The CDC recommends that medical personnel question patients about symptoms once monthly.[68]

Sputum cultures and smears for AFB should be ordered every 2 to 4 weeks initially and then monthly after the sputum culture results become negative. With appropriate therapy, sputum culture results should become negative in >85% of patients after 2 months. Radiologic examination (chest radiographs) is not as important as sputum examination, but it may be useful at the completion of therapy to serve as a comparison for any future films.

Patients whose culture results are positive at 2 months need to be carefully reexamined. Drug susceptibility testing should be performed to rule out acquired drug resistance, and special attention should be given to drug adherence (ie, DOT should be used). If drug resistance is demonstrated, the regimen should be modified as needed. Sputum cultures should also be obtained monthly until result negativity is achieved.[68]

As was the case for H.G., weight loss and nutritional depletion are common in patients with active TB disease. In a large TB treatment study, 7.1% of patients experienced relapse, with relapse greatest in patients who were underweight at diagnosis or with a body mass index <18.5 kg/m^2.[102] In patients underweight at diagnosis (defined as ≥10% below ideal body weight), weight gain of ≤5% between diagnosis and completion of 2 months of therapy was independently associated with relapse.[102] In addition, the relapse rate was 50.5% in underweight patients with a cavitary lesion on chest radiograph, positive sputum culture results after 2 months of therapy, and a ≤5% weight gain in the first 2 months of therapy.[102] Therefore, it may be prudent to monitor H.G.'s body weight during the initial 2 months of therapy, and he may need to receive more intensive therapy or a longer duration of therapy.

Routine follow-up usually is not required after the successful completion of chemotherapy with isoniazid and rifampin. It may be prudent, however, to reexamine the patient 6 months after completion of therapy or at the first sign of any symptoms suggestive of active TB. This is especially important in patients who were slow

to respond to therapy or who have significant radiologic findings at completion of therapy. These recommendations are only for those patients with organisms fully susceptible to the medications being used.[68]

Patients whose culture results are negative but have radiographic abnormalities consistent with TB should have an induced sputum or bronchoscopy performed to establish a microbiologic diagnosis and be monitored radiographically. Patients with extrapulmonary TB should be evaluated according to the site of involvement.[34,68]

Treatment Failure

Case 68-1, Question 15: If H.G. does not respond to his currently prescribed treatment regimen, should one additional drug be added to his regimen?

No! Adding a single drug to a failing regimen is the most common and devastating prescribing error in TB therapy. This practice is essentially monotherapy because the assumption is that the organisms are resistant to the medications currently being used. Resistance to the new drug will eventually develop, further reducing the patient's chance of cure. At least two, and preferably three, new drugs to which susceptibility can be inferred should be added to lessen the probability of further acquired drug resistance. Empiric retreatment regimens may include a fluoroquinolone, bedaquiline, an injectable agent (eg, streptomycin, amikacin, or capreomycin), and an additional oral agent (eg, *p*-aminosalicylic acid, cycloserine, or ethionamide).[34] New drug susceptibility testing should be performed and treatment adjusted accordingly.[34,94]

TREATMENT OF LATENT TUBERCULOSIS INFECTION

CASE 68-2

QUESTION 1: J.G., the 32-year-old wife of H.G., and their children are tested to determine whether they have been infected with *M. tuberculosis.* For J.G., the induration from 5 TU of PPD was 12 mm, a result that is reported as positive. J.G. states that she has never received the BCG vaccine. The PPD results for the children were negative. J.G. does not have any clinical symptoms or radiographic findings suggestive of active TB at this time, and her current weight is 132.28 pounds (60 kg).

Is she at risk for developing active disease? What are the current recommendations for drug therapy for persons with latent TB infection? Should J.G. receive treatment?

Because J.G. is a household contact of a person with active TB disease and has a positive TST finding, she is at great risk for developing active disease.[23],[24],[50],[51] During the first year after infection from the index case, a household contact's risk of developing active disease is 2% to 4%, and contacts with a positive TST finding are at the greatest risk.[68] As with active disease, the TST is usually performed to detect the presence of latent TB infection. However, for contact investigation, studies have demonstrated that IGRAs are a more accurate indicator of the presence of latent TB infection than is TST.[103],[104] Therefore, many health departments in the United States have adopted IGRAs as screening tests for contact investigations.[105] The majority of people with a negative IGRA result after exposure to a person with active TB disease do not have TB infection; however, the immune reaction to TB can take several weeks to develop, so the IGRA should be repeated 8 to 12 weeks after the last exposure to rule out infection.[24],[105] TST is preferred for screening children younger than 5 years old.[24]

Treatment of latent TB infection is effective in preventing active TB disease in patients with a positive TST or IGRA result and in those at risk for reactivation of active TB; therefore, it is *strongly* recommended.[23],[24] Treatment decreases the population of tubercle bacilli and reduces future morbidity from TB in the groups at high risk for developing active disease. Because J.G. is infected with *M.*

tuberculosis but does not currently have active TB disease, she should be treated for latent TB infection.

There are four approved regimens for the treatment of latent TB.[23],[24] Isoniazid monotherapy prevents active TB in 90% of patients who complete a 9-month regimen compared to 60% to 80% of patients who complete a 6-month regimen.[106] Therefore, isoniazid 300 mg daily or 900 mg twice weekly for 9 months is preferred. The twice-weekly regimen should be administered by DOT to ensure patient adherence.[20] A 6-month regimen is an acceptable alternative in patients who cannot complete 9 months of therapy.[23] The benefits of treating latent TB infection outweigh the risks of isoniazid-induced hepatitis because all persons infected with TB are at risk for developing active disease throughout their lifetime. All patients receiving isoniazid should receive pyridoxine 25 mg/day to minimize the risk of peripheral neuropathy.

Unfortunately, patient adherence to these isoniazid regimens is very poor. In a population of patients beginning isoniazid treatment for latent TB, only 64% of patients completed at least 6 months of therapy.[107] Younger age, Hispanic ethnicity, and non-U.S. country of birth were associated with greater likelihood of completing therapy.[107] Lower completion rates were associated with homelessness, excess alcohol intake, and experiencing an adverse event.[107] In another study, 52.7% of patients receiving treatment for latent TB infection failed to complete the prescribed course of therapy.[108] More than 93% of these patients were receiving isoniazid. Risk factors for failing to complete therapy included receipt of a 9-month isoniazid regimen, residence in a congregate setting (nursing home, shelter, jail), injection drug use, and employment at a health care facility.[108] In addition, this study reported that employees at health care facilities were more likely to decline treatment for latent TB infection.[108]

Because of concerns for isoniazid toxicity and abysmal adherence rates, shorter rifampin-based regimens may be utilized. Daily isoniazid plus rifampin for 3 months and daily rifampin monotherapy for 4 months are acceptable alternatives to isoniazid therapy.[23],[24],[106] For the patients randomly assigned to receive daily rifampin for 4 months, 91% took 80% of the doses, and 86% took >90% of the

doses at 20 weeks.[109] For the patients randomly assigned to receive daily isoniazid for 9 months, 76% took 80% of the doses, and only 62% took >90% of the doses at 43 weeks.[109] Discontinuation of therapy because of adverse events was more common in the isoniazid group (14%) versus the rifampin group (3%).[109] Another study reported significantly fewer grade 3 to 4 adverse events and hepatitis and significantly higher treatment completion rates with 4 months of rifampin compared with 9 months of isoniazid.[110] Rifampin for 4 months is an effective, safe, and cost-effective strategy to consider when treating latent TB infection in selected populations of patients.[109–113]

An attractive alternative for the treatment of latent TB infection is the combination of isoniazid and rifapentine administered once weekly for 12 weeks.[23],[24] In one study, patients received either isoniazid 15 to 25 mg/kg (maximal dose 900 mg) plus rifapentine 900 mg (with adjustments for patients weighing <50 kg) once weekly for 12 weeks by DOT or isoniazid 5 mg/kg (maximal dose 300 mg) once daily for 9 months.[114] Completion of therapy was significantly higher in the isoniazid/rifapentine group (82% vs 69%; $P > .001$). Overall, TB developed in 7 of 3986 patients receiving isoniazid/rifapentine and 15 of 3745 patients receiving isoniazid (hazard ratio 0.38 for the combination; 95% CI 0.15–0.99; $P = .05$).[114] Hepatotoxicity was higher in the isoniazid group (2.7% vs 0.4%; $P > .001$), whereas hypersensitivity reactions were higher in the combination group (3.8% vs 0.5%; $P > .001$). Permanent drug discontinuation for any reason was higher in the isoniazid group (31.0% vs 17.9%; $P > .001$), but permanent drug discontinuation owing to an adverse event was higher in the combination group (4.9% vs 3.7%; $P = .009$).[114] This combination is recommended as an equal alternative to daily isoniazid for 9 months in patients ages 12 years and older with a greater risk of developing active TB disease.[115] These patients include those with recent exposure to a person with active TB, conversion of the TST or IGRA result from negative to positive, or radiographic evidence of healed pulmonary TB. Isoniazid/rifapentine may also be considered in patients unlikely to complete 9 months of isoniazid or in a setting where the combination offers practical

advantages (eg, correctional facilities, homeless shelters). The combination is not recommended in females who are pregnant or who expect to become pregnant during treatment.

J.G. should be placed on isoniazid 300 mg/day or 900 mg twice weekly for at least 6 months and preferably up to 9 months, rifampin 600 mg for 4 months, or isoniazid 900 mg plus rifapentine 900 mg weekly for 12 weeks.[23],[24],[115] She should be educated and questioned frequently about the clinical symptoms of hepatitis. Pretreatment serum aminotransferases and bilirubin should be assessed to rule out preexisting liver disease. The American Thoracic Society and the CDC do not recommend routine monitoring of LFTs unless symptoms suggest hepatotoxicity.[68]

ADVERSE DRUG EVENTS

Isoniazid

HEPATOTOXICITY

Case 68-2, Question 2: J.G. is started on daily isoniazid. After 2 months of therapy, she presents to the clinic with nausea, vomiting, and abdominal pain. LFTs were ordered, and her aspartate aminotransferase (AST) was 150 IU/L. Discuss the presentation, prognosis, and mechanism of isoniazid-induced hepatitis. What are the risk factors for developing hepatitis? Should isoniazid be discontinued to prevent further liver damage?

Approximately 10% to 20% of patients treated with isoniazid alone for latent TB infection will develop elevated serum aminotransferases, which are generally transient and asymptomatic.[34],[116] Most patients with mild, subclinical hepatic damage do not progress to overt hepatitis and recover completely even while continuing isoniazid. In contrast, continuation of isoniazid in patients with symptoms of hepatitis increases the risk of mortality compared with immediate discontinuation.[34] The risk of death from

TB, however, is estimated to be 11 times higher than is the risk of death from isoniazid hepatotoxicity.[117]

Isoniazid-induced hepatotoxicity generally occurs within weeks to months of initiating therapy; 60% of cases occur in the first 3 months and 80% occur in the first 6 months.[116] Constitutional symptoms may be seen early and may last from days to months. Nausea, vomiting, and abdominal pain are seen in 50% to 75% of patients with severe hepatotoxicity.[116] Jaundice, dark urine, and clay-colored stools may also be seen. Recovery may take weeks after discontinuing isoniazid therapy. Development of isoniazid hepatotoxicity has been linked to several factors, including acetylator phenotype, age, daily alcohol consumption, and concurrent rifampin use. In addition, females may be at higher risk for death, especially during the postpartum period.[117]

The mechanisms responsible for isoniazid hepatotoxicity remain unclear. Previously, it was thought that rapid acetylators had a greater risk for isoniazid hepatotoxicity than do slow acetylators. Rapid acetylators of isoniazid form monoacetylhydrazine, a compound that can cause liver damage, more rapidly than do slow acetylators.[118] Rapid acetylators, however, would eliminate monoacetylhydrazine at a faster rate, and this should equalize the risk of toxicity between slow and fast acetylators.[119] One study demonstrated a different incidence of hepatitis between Asian males and females. Because both groups were fast acetylators, this study suggests that hepatitis is associated with factors other than acetylator phenotype.[120] Some evidence supports the theory that isoniazid-induced hepatitis is a hypersensitivity reaction; however, many patients tolerate isoniazid on rechallenge, discounting this theory.[121,122]

Age and concurrent daily alcohol ingestion are the most consistent risk factors for isoniazid hepatitis.[68] Progressive liver damage is rare in persons younger than age 20 years. It occurs in ~0.3% of persons between ages 20 and 34 years, 1.2% of those between ages 35 and 49 years, and 2.3% of persons older than age 50 years.[68] One prospective cohort study, however, demonstrated a low incidence of isoniazid hepatitis. Of 11,141 patients receiving isoniazid alone for

the treatment of latent TB infection, only 11 (0.1% of those starting and 0.15% of those completing therapy) developed clinical hepatitis.[123] Previous studies suggested a higher incidence of clinical hepatitis in patients receiving isoniazid alone, and a meta-analysis of six studies estimated the rate to be 0.6%.[34] However, severe hepatotoxicity may occur with isoniazid treatment of latent TB infection. The CDC reported 17 severe hepatic adverse events with isoniazid in 15 adults and 2 children (ages 11 and 14 years).[124] Five patients, including one child, underwent liver transplantation, and five adults died (including one patient who underwent liver transplant).

High-risk patients should be followed up with routine monitoring of LFTs. These patients include those who consume alcohol daily, persons older than age 35 years, those taking other hepatotoxic drugs, those with preexisting liver disease, IV drug users, Black and Hispanic females, and all postpartum females. In these high-risk patients, isoniazid should be discontinued if the AST level exceeds three to five times the upper limit of the normal value.[68] Because J.G. is experiencing nausea, vomiting, and abdominal pain and her AST is greater than three times the upper range of the normal value, isoniazid should be discontinued temporarily until the AST returns to normal. At that time, isoniazid should be resumed, and her LFTs rechecked. If the AST increases again, the drug should be discontinued, and J.G. should be followed up frequently for development of active TB.

CASE 68-3

Question 1: C.M., a 176.37-pound (80-kg), 35-year-old female, is being treated for active TB disease with rifampin 900 mg and isoniazid 1200 mg twice weekly.

Is 1200 mg of isoniazid twice weekly an appropriate dose for a 176.37-pound (80-kg) patient? What isoniazid side effects, other than hepatotoxicity, should be anticipated?

The usual twice-weekly isoniazid dose is 15 mg/kg, with a maximal dose of 900 mg. Even though she weighs 176.37 pounds (80 kg), C.M. should be receiving no more than 900 mg rather than 1200 mg

of isoniazid twice weekly. Although high doses or increased serum concentrations have not been linked with hepatitis, elevated serum isoniazid concentrations have been associated with increased central nervous system (CNS) events, ranging from somnolence to psychosis and seizure. GI side effects are also more commonly observed at doses >20 mg/kg.

PERIPHERAL NEUROPATHY

Although uncommon at the recommended daily and intermittent doses, isoniazid can cause peripheral neuropathy by interfering with pyridoxine (vitamin B_6) metabolism.[33,50] As many as 20% of patients may experience this problem with isoniazid doses >6 mg/kg/day. Numbness or tingling in the feet or hands is the most common neuropathic symptom. In patients with medical conditions in which neuropathy is common, including diabetes mellitus, alcoholism, HIV infection, malnutrition, and renal failure, supplemental pyridoxine 25 to 50 mg/day should be given with isoniazid.[34,50] Females who are pregnant or breast-feeding and persons with seizure disorders should also receive supplemental pyridoxine with isoniazid.[50]

ALLERGIC AND OTHER REACTIONS

Allergic reactions consisting of arthralgias, skin rash, swelling of the tongue, and fever have also been reported. Isoniazid has been associated with arthritic symptoms and systemic lupus erythematosus; ~20% of patients receiving isoniazid develop antinuclear antibodies.[34] Other less common reactions reported with isoniazid are dry mouth, epigastric distress, CNS stimulation and depression, psychoses, hemolytic anemia, pyridoxine-responsive anemia, and agranulocytosis.[121]

DRUG INTERACTIONS

Isoniazid is a relatively potent inhibitor of several cytochrome P450 ([CYP] 2C9, CYP2C19, CYP2E1) isoenzymes, but has minimal effects on CYP3A.[34] Isoniazid inhibits the hepatic metabolism of phenytoin and carbamazepine, resulting in increased plasma

concentrations of these drugs. Patients receiving either of these two drugs with isoniazid should be observed for signs of phenytoin or carbamazepine toxicity, such as nystagmus, ataxia, headache, nausea, or drowsiness. Plasma phenytoin and carbamazepine concentrations should be monitored periodically so that the doses can be adjusted if necessary. Carbamazepine also may induce isoniazid hepatitis by inducing its metabolism to toxic metabolites.[125] In addition, isoniazid inhibits the metabolism of diazepam and triazolam. It is important to note that rifampin has the exact opposite effect on hepatic metabolism. Rifampin is a stronger inducer than isoniazid is an inhibitor, as documented by the fact that isoniazid–rifampin combination therapy induces the metabolism of diazepam, phenytoin, and other agents metabolized by the CYP system.[126]

Rifampin

FLULIKE SYNDROME

A flulike syndrome has been reported in 1% of patients receiving intermittent rifampin administration. This syndrome is rarely seen with usual doses of 600 mg twice weekly, but the incidence increases with twice-weekly doses >900 mg. The incidence also increases if the dosing interval is increased to ≥1 week.[127],[128] Unless the symptoms are severe, discontinuation of the drug is unnecessary. Because C.M. is receiving rifampin 900 mg twice weekly, her dose should be reduced to 600 mg and administered daily until the symptoms subside. Temporary administration of a nonsteroidal anti-inflammatory drug has been used to alleviate the flulike symptoms. Twice-weekly therapy may then be resumed as long as the dose of rifampin does not exceed 600 mg.

Case 68-3, Question 2: One month after beginning her twice-weekly DOT regimen, C.M. exhibited symptoms of myalgias, malaise, and anorexia. Laboratory data were normal except for a slightly decreased platelet count. Could C.M.'s symptoms be related to her drug therapy? What adverse reactions other than hepatotoxicity should be anticipated in a patient receiving rifampin?

HEPATOTOXICITY

Rifampin (rifapentine) is associated with a <1% rate of hepatotoxicity. Therefore, the risk of drug-induced hepatotoxicity is greater with isoniazid than that with rifampin. On occasion, rifampin can cause hepatocellular injury and potentiate hepatotoxicity of other antituberculosis drugs.[116] Although elevations of liver enzymes may be seen, rifampin is more likely to produce cholestasis, as manifested by increases in alkaline phosphatase and hyperbilirubinemia without hepatocellular injury.[116] Elevations of all LFTs may be seen transiently during the first month of rifampin therapy, but they are usually benign.[34]

THROMBOCYTOPENIA

Thrombocytopenia is more frequently associated with intermittent or interrupted rifampin administration, likely caused by production of immunoglobulin G and immunoglobulin M antibodies to rifampin. These antibodies likely fix complement onto platelets, resulting in platelet destruction. Hypothetically, intermittent or interrupted rifampin therapy results in increased antibody production. Once thrombocytopenia occurs with rifampin, its subsequent use is contraindicated because the problem will likely recur.[129],[130]

MISCELLANEOUS REACTIONS

In addition to the side effects associated with high-dose, intermittent therapy, 3% to 4% of patients taking normal doses of rifampin may experience adverse reactions.[129] The most common of these are nausea, vomiting, fever, and rash. Other reactions to rifampin include the hepatorenal syndrome, hemolysis, leukopenia, anemia, and arthralgias as part of a suspected drug-induced lupus syndrome.[34],[131] Development of these latter reactions requires discontinuation of the drug.

ACUTE RENAL FAILURE

Acute renal failure has been reported rarely with rifampin. This hypersensitivity reaction may occur with both intermittent and daily

administration and may last as long as 12 months.[127] Rifampin should be discontinued, and other drugs (eg, pyrazinamide and ethambutol) should be given. Doses of ethambutol and pyrazinamide should be adjusted for renal dysfunction, if necessary. Both rifampin and isoniazid may, however, be given in normal dosages to patients with preexisting renal failure.[132],[133]

DISCOLORATION OF BODY FLUIDS

Another important characteristic of rifampin relates to its chemical makeup. It is an orange-red crystalline powder that is widely distributed in body fluids. As a result, it can discolor saliva, tears, urine, sweat, and cerebrospinal fluid (CSF).[34] Patients using rifampin should be warned of this effect and cautioned not to use soft contact lenses because of possible discoloration. This effect may also be used to monitor adherence to rifampin therapy.

DRUG INTERACTIONS

Rifampin is a very potent inducer of CYP3A4 and also induces other CYP isoenzymes, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A5.[34],[134],[135] Rifampin induces phase 2 drug-metabolizing enzymes (eg, uridine 5'-diphospho-glucuronosyltransferase, sulfotransferases) and expression of transporter proteins (eg, P-glycoprotein, multiple-drug resistance protein 2, organic anion-transporting polypeptide).[134] Complete induction of these isoenzymes and transport proteins occurs ~1 week after starting rifampin and returns to baseline ~2 weeks after discontinuing the drug.[134] Rifamycins differ in their ability to induce CYP isoenzymes, in which rifampin is the most potent, rifapentine is intermediate, and rifabutin is the least potent enzyme inducer.[34] Rifampin increases the metabolism of protease inhibitors, integrase strand inhibitors, certain non-nucleoside reverse transcriptase inhibitors (NNRTIs), macrolide antibiotics, azole antifungal agents, corticosteroids, oral contraceptives, methadone, warfarin, cyclosporine, tacrolimus, theophylline, phenytoin, quinidine, diazepam, propranolol, metoprolol, sulfonylureas, verapamil,

nifedipine, diltiazem, enalapril, and simvastatin.[34,126] Although the patient is receiving rifampin, it may be necessary to monitor serum concentrations of the aforementioned drugs, when appropriate, or increase their dosages. Also, females who are taking rifampin and oral contraceptives should use an alternative method of birth control. When treating any patient with rifampin, the health care professional should carefully evaluate all concomitant medications for the possibility of drug–drug interactions.

Isoniazid–Rifampin

HEPATOTOXICITY

Case 68-3, Question 3: Will the combination of isoniazid and rifampin increase the risk of hepatotoxicity in C.M. to a greater extent than does either drug alone?

Some initial evidence suggested that the concomitant use of isoniazid and rifampin was associated with a greater incidence of hepatotoxicity. The mechanism was thought to be attributable to rifampin induction of the metabolism of isoniazid to either monoacetylhydrazine or to other hepatotoxic products of hydrolysis. Steele et al[122] performed a meta-analysis reviewing the incidence of hepatitis using regimens that contained isoniazid without rifampin, rifampin without isoniazid, and regimens containing both drugs. They found the incidence of clinical hepatitis was greater in regimens containing both isoniazid and rifampin (2.7%) versus regimens of isoniazid alone (1.6%), but this effect was additive, not synergistic, and therefore expected.[122] The use of the two drugs together, therefore, is not contraindicated, but caution should be used in high-risk groups such as the elderly, alcoholics, those receiving concomitant hepatotoxic agents, and those with preexisting liver disease.[116]

Ethambutol

OPTIC NEURITIS

CASE 68-4

QUESTION 1: S.E., a 65-year-old female, was placed on daily rifampin 600 mg, isoniazid 300 mg, pyrazinamide 1500 mg, and ethambutol 1200 mg for initial treatment of active pulmonary TB. Two months after the initiation of therapy, she began to report blurred vision. A routine eye examination and visual field tests yielded a diagnosis of optic neuritis. No evidence was seen of glaucoma, cataracts, or retinal damage. Laboratory tests were within normal limits except for an elevated serum uric acid (9.7 mg/dL) and a slightly elevated serum creatinine (1.6 mg/dL). No symptoms of joint pain were associated with the elevated serum uric acid, and there was no history of gout. Her estimated creatinine clearance based on her weight of 143.30 pounds (65 kg) was 36 mL/minute.

Could the visual problem and increased uric acid levels be related to her medications?

S.E.'s decrease in visual acuity is compatible with ethambutol-induced optic neuritis. This condition is characterized by central scotomas, loss of red-green color vision, or, less commonly, a peripheral vision defect. The intensity of these ocular effects is related to the duration of continued therapy after decreased visual acuity is first noted. Optic neuritis is related to both dose and duration, and it rarely occurs at doses of 15 mg/kg.[136–138] The incidence is estimated to be 6% for doses of 25 mg/kg and increases to 15% for doses in excess of 35 mg/kg. Recovery, which may take months, is usually, but not always, complete when the drug is discontinued.

The optic neuritis manifested in S.E. is probably caused by the use of an increased ethambutol dose (18.5 mg/kg) in a patient with impaired renal function. Because ethambutol adds no additional benefit to isoniazid and rifampin after the first 2 months for susceptible organisms, it can be discontinued. Ethambutol is excreted by the kidney (50%–80%), and her ethambutol dosing interval should have been increased based on the decline in creatinine clearance.[132] Her visual acuity should be monitored closely through periodic eye examinations, and she should be

instructed to contact her physician immediately if she experiences any further visual changes.

S.E.'s elevated serum uric acid also may be attributed to her ethambutol and a decline in her renal function, but it is more likely caused by pyrazinamide, which decreases the tubular secretion of urate.[101] Asymptomatic hyperuricemia secondary to drugs usually does not require treatment.

SPECIAL TREATMENT CONSIDERATIONS

Elderly Patients

INCIDENCE

CASE 68-5

QUESTION 1: G.H., a 75-year-old, 176.37-pound (80-kg) male who resides in a nursing home, becomes disoriented, refuses to eat, and has a productive cough. Physical examination reveals a thin male with slight difficulty breathing. Laboratory findings are essentially normal, with the exception of a slightly elevated blood urea nitrogen of 25 mg/dL and serum creatinine of 1.3 mg/dL. Chest radiography reveals infiltrates in the right lower lobe. He has a history of congestive heart failure, which is well controlled. Blood, urine, and sputum samples are sent for culture and susceptibility testing. The initial Gram stain finding is negative. Because the nursing home has recently had two cases of active TB, a PPD skin test and sputum smear for AFB are ordered. The PPD skin test induration is 16 mm, and the sputum smear result is positive for AFB. G.H.'s admission skin test result several months ago was negative.

What is the typical presentation of TB in the elderly? What is the appropriate treatment of active disease in G.H.? Is the incidence of drug side effects higher in the elderly? Should other patients in close contact with G.H. receive isoniazid therapy?

In 2019, the overall case rate of TB in adults ages 65 years or older was higher than all other age groups (4.5/100,000 population).[11] Similar to other age groups, the case rate for persons ages 65 years or older has declined every year since 1993 when the

case rate was 17.7/100,000 population.[11] In 2019, 1.8% of TB cases were reported in residents of long-term care facilities,[11] and the case rate for nursing home residents was 1.8 times higher than that for elderly persons living in the community.[139] Active TB disease in the elderly has been attributed to decreased immune function followed by reactivation of an earlier infection, but active disease is a common, endemic infection in nursing home patients with no previous immunity (negative skin test) to *M. tuberculosis.*[139],[140] The incidence of positive TST results increases after patients have been in the nursing home >1 month. Therefore, all patients entering a nursing home should be tested with 5 TU of PPD. If the initial test result is negative and a source case is present in the nursing home (as illustrated by this case), this test should be repeated in 1 month. The rate of TST conversion (from negative to positive test results) in this population is ~5%. If these recent converters are not treated with isoniazid, ~17% will develop progressive pulmonary TB.[141]

DIAGNOSIS

Diagnosis of active TB in elderly patients is difficult because classic symptoms of cough, fever, night sweats, and weight loss are often absent, and elderly patients may describe their symptoms poorly. The chest radiograph and PPD skin test results may be the only signs of TB infection.[139],[141] Frequently, the chest radiograph finding is atypical, resembling pneumonia or worsening heart failure. Chest radiographs in the elderly are less likely to reveal upper lobe infiltration; however, more commonly they will show extensive infiltration of both lungs.[142] If the patient's clinical disease is caused by reactivation, the chest radiograph often shows apical infiltrates or nodules. If the disease is progressing from an initial infection, as in the case of G.H., lower lobe infiltrates may be present.[139] TB in this population may present clinically with changes in activities of daily living, chronic fatigue, cognitive impairment, anorexia, or unexplained low-grade fever. Nonspecific signs and symptoms that range in severity from subacute to chronic and that persist for weeks to months must alert clinicians to the possibility that unrecognized

TB is present.[143] Sputum examination for *M. tuberculosis,* and AFB smear and culture should be performed in all patients, including the elderly.

TREATMENT OF ACTIVE DISEASE IN THE ELDERLY

The principles of TB treatment are the same for the elderly as that for any other age group.[34],[139] Because G.H. has clinical symptoms of a respiratory infection, positive sputum smear results for AFB, and a positive TST result, he should be treated with a four-drug regimen for active TB disease. Most TB cases in elderly patients are caused by drug-susceptible strains of *M. tuberculosis;* however, notable exceptions would be older patients who are from a country or region where the prevalence of drug-resistant strains is high, persons who have been inadequately treated in the past, or persons who acquired the infection from a recent contact known to be infected with drug-resistant *M. tuberculosis.*[143] G.H.'s drug regimen should include rifampin 600 mg, isoniazid 300 mg, pyrazinamide 2000 mg, and ethambutol 1600 mg daily for 8 weeks followed by rifampin and isoniazid daily or thrice weekly for 16 weeks (DOT). Another option might be isoniazid, rifampin, pyrazinamide, and ethambutol daily for 2 weeks, followed by twice weekly for 6 weeks, then isoniazid and rifampin twice weekly for 16 weeks.[143] Some clinicians prefer treating the elderly with 9-month regimens of rifampin and isoniazid. G.H. should also receive pyridoxine 10 to 50 mg daily.[68]

ADVERSE DRUG EFFECTS

Although isoniazid-induced hepatitis is more common in elderly patients, both rifampin and isoniazid are generally well tolerated within this age group, with major hematologic or hepatic side effects occurring in 3% to 4% of patients.[144] Therefore, serum aminotransferases should be assessed at baseline, and G.H. should be observed monthly for clinical signs of hepatitis. As discussed earlier, routine monitoring of LFTs remains controversial because transient, asymptomatic elevations do occur among the elderly.[144]

Although uncommon at 600 mg, rifampin given twice weekly may cause a greater incidence of flulike symptoms. Because potential drug interactions with isoniazid and rifampin are possible, any medication added to the patient's regimen should be carefully evaluated. Considering that G.H. has age-related decreased renal function, signs of ethambutol-induced visual dysfunction should be monitoring carefully.

TREATMENT OF LATENT INFECTION IN THE ELDERLY

Treatment of elderly patients with positive TST or IGRA results but no active TB disease with isoniazid 300 mg daily for 6 to 9 months is essential if a source case is present in the nursing home. Stead et al[141] reported only 1 case of active disease in patients receiving therapy for latent TB infection compared with 69 cases in untreated patients. In patients with recently converted skin tests, one patient in the group receiving isoniazid therapy had active disease compared with 45 who received no treatment.[141] Daily rifampin for 4 months or weekly isoniazid plus rifapentine for 12 weeks are also acceptable regimens in the elderly.[115],[139]

Multidrug-Resistant Organisms

DEFINITION AND ETIOLOGY

CASE 68-6

QUESTION 1: M.S., an ill-appearing 29-year-old Asian male, is admitted to the hospital with signs and symptoms of pneumonia. He is coughing, and his chest radiograph indicates bilateral infiltrates. He is placed in respiratory isolation pending the results of sputum testing for *M. tuberculosis.* He states that he was diagnosed with TB ~3 months ago, and treatment was initiated with the RIPE regimen. However, he stopped taking his medication after 1 month. An HIV test was performed 3 months ago, the result of which was negative.

What is the likelihood of acquired drug resistance in *M. tuberculosis*?

In the United States, isoniazid resistance was 14.1% and resistance to both isoniazid and rifampin was 5.4% in patients with

previous TB in 2019.[11] Resistance in *M. tuberculosis* is either primary or acquired. Primary drug resistance occurs when a patient harbors a resistant strain before any drugs have been administered. Acquired drug resistance occurs when resistant subpopulations are selected as a result of treatment errors, such as addition of a single drug to a failing regimen, inadequate primary regimen, failure to recognize resistance, and, most importantly, nonadherence to the prescribed regimen. Sporadic ingestion, inadequate dosages, or malabsorption of medications can cause susceptible *M. tuberculosis* strains to become resistant to multiple drugs within a few months.[145],[146] These resistant organisms can then be transmitted to persons who have never received treatment and lead to primary resistance in those patients.

M.S. is a foreign-born person of Asian ethnicity and may have primary resistance from his country of origin, making a detailed exposure history essential for the treatment of his infection. M.S. is also an example of the problem of treatment failure caused by nonadherence and the potential development of drug-resistant organisms. Homelessness and lack of awareness of the severity of TB have been shown to be significantly associated with interruptions in TB therapy.[147] Therefore, educational efforts to improve a patient's understanding of TB disease are critical for appropriate treatment of the disease.

Many factors can affect the outcome of therapy for MDR-TB, including HIV status, treatment adherence, the number of drugs to which the tubercle bacilli remain susceptible, and the time since the first diagnosis of TB.[148–150] In one study, 77% of patients with MDR-TB had sputum cultures convert to a negative finding in a median time of 60 days (range, 4–462 days), but 23% of patients never converted to negative culture results.[150] Of the patients who converted, 60% converted after 4 months of therapy.[150] Predictors of a longer time for sputum culture conversion were high initial sputum colony counts, bilateral cavitation on chest radiograph, previous treatment of MDR-TB, and the number of drugs the initial isolate was resistant to at the beginning of therapy.[150]

Case 68-6, Question 2: Can M.S. be cured by drug therapy, and, if so, how should he be treated?

According to the World Health Organization, overall treatment success for MDR-TB is 57%, which is lower than is the treatment success for drug-susceptible TB (85%).[9] Because his recent HIV test result was negative, M.S. may have a higher probability of treatment success. In HIV-negative patients, 32 (97%) of 33 patients with MDR-TB were cured, and these patients received an average of five second-line drugs.[149] Only one relapse occurred 5 years after treatment.[149] Therefore, M.S.'s current regimen should be reevaluated, drug susceptibility testing determined, and the patient referred to a specialist or consultation at a specialized treatment center.[35] Molecular drug resistance testing should be performed to evaluate resistance to rifampin, which is a reliable surrogate for MDR-TB. If rifampin resistance is detected, the patient should begin therapy for MDR-TB, and susceptibility testing should be performed for all first-line agents, fluoroquinolones, and aminoglycosides, although results may not be available for several weeks.[35] Globally, fluoroquinolone resistance was 20.1% in MDR-TB isolates, so resistance to fluoroquinolones must be excluded.[9]

Treatment guidelines for MDR-TB recommend initiating therapy with at least five drugs with documented susceptibility or with high likelihood of susceptibility against the patient's isolate.[35] It is preferable to avoid drugs that were previously used for treatment. Bedaquiline and either levofloxacin or moxifloxacin should be included in the initial treatment regimen. Additional drugs for treatment of MDR-TB include linezolid, clofazimine, cycloserine, amikacin, ethambutol, and pyrazinamide. The intensive phase should be continued for 5 to 7 months after culture conversion. The continuation phase should include four drugs with a total treatment duration of 15 to 21 months.[35] Treatment should be given by DOT, but only 40% of patients with MDR-TB complete a full 18 to 24 months of therapy.[151]

The efficacy of a standardized treatment regimen for a shorter duration of therapy has been evaluated in patients with documented MDR-TB.[152],[153] A recent study compared a short-course regimen for 9 to 11 months to an individualized regimen for 18 to 24 months for treatment of MDR-TB.[153] The study population consisted of 424 patients, of which 32.6% were infected with HIV with a median $CD4^+$ count of 248 cells/μL and 77.2% had cavitary lesions. The short-course regimen consisted of high-dose moxifloxacin, clofazimine, ethambutol, and pyrazinamide for a total of 40 weeks, and kanamycin, isoniazid, and prothionamide were also administered for the first 16 weeks.[153] The intensive phase could be extended to 20 or 24 weeks if AFB smear results were still positive at 16 or 20 weeks, respectively. Daily moxifloxacin doses were 400, 600, and 800 mg for body weights <33 kg, 33 to 50 kg, and >50 kg, respectively. The longer course regimen was the standard regimen of the World Health Organization for the treatment of MDR-TB. The primary outcome (favorable status) was reported in 78.8% in the short-course group and 79.8% in the longer course regimen, which demonstrated noninferiority.[153] Unfavorable bacteriologic outcomes were more common in the short-course group (10.6% vs 5.6%), and death was more common in the short-course group (8.5% vs 6.4%).[153] Median time to negative AFB and culture results did not differ significantly between groups. These results suggest that it may be possible to adequately treat patients with MDR-TB with shorter courses of therapy. However, prothionamide and kanamycin are unavailable, and clofazimine is difficult to procure in the United States.

Fluoroquinolones are active against mycobacteria, including *M. tuberculosis,* and they penetrate rapidly into macrophages and exhibit intracellular mycobactericidal activity.[148] Fluoroquinolones inhibit DNA gyrase in *M. tuberculosis,* but the other molecular target of these agents, topoisomerase IV, is absent.[148] Ciprofloxacin, ofloxacin, and levofloxacin have been used long term for the treatment of mycobacterial infections and were well tolerated with few serious adverse effects.[154],[155] Limited data suggest that moxifloxacin is an acceptable option in the treatment of MDR-TB.[156]

Selection of fluoroquinolone resistance has been observed in vivo, and complete cross-resistance within the class is the accepted rule.[148]

Bedaquiline was FDA approved in late 2012 as part of combination therapy with at least three or four other drugs in adults with pulmonary MDR-TB when other alternatives are not available. Bedaquiline is a novel drug that inhibits mycobacterial adenosine 5′-triphosphate synthase, thereby inhibiting energy production in *M. tuberculosis*.[157] The drug is available as 100-mg tablets, and the recommended dosage is 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks.[157] Bioavailability of bedaquiline is increased twofold when administered with food, and each dose should be administered by DOT.[157] Bedaquiline is metabolized by CYP3A4, and it is recommended to avoid concomitant administration of bedaquiline with moderate (eg, efavirenz) and strong (eg, rifamycins) CYP3A4 inducers. Strong CYP3A4 inhibitors may increase systemic exposure and adverse events of bedaquiline, and use of strong CYP3A4 inhibitors for >14 consecutive days should be avoided while the patient is receiving bedaquiline.[157] Bedaquiline can cause QT prolongation, and additive prolongation may occur with other drugs known to prolong the QT interval, such as fluoroquinolones.

Bedaquiline received accelerated FDA approval based on the surrogate marker of time to sputum culture conversion in phase 2 studies. In the first study, 47 patients with MDR-TB received bedaquiline or placebo added to a preferred background regimen of kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone for 8 weeks.[158] After 8 weeks, the background regimen was continued for a total of 96 weeks. Time to sputum culture conversion was significantly reduced in the bedaquiline group, and sputum culture results were negative in 48% of patients in the bedaquiline group compared to 9% in the placebo group at 8 weeks.[158] After 24 weeks, 81% of patients in the bedaquiline group had negative sputum culture results compared to 65.2% in the placebo group.[159] However, after 104 weeks, treatment success was

achieved in 52.4% and 47.8% of patients in the bedaquiline and placebo groups, respectively.[159]

In the second study, 160 patients with pulmonary MDR-TB received either placebo or bedaquiline 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks with the same background regimen described previously.[160] After 24 weeks, patients continued the background regimen for a total of 18 to 24 months. The median time to sputum culture conversion was 83 days in the bedaquiline group compared to 125 days in the placebo group ($P > .001$).[160] Compared to placebo, significantly more patients in the bedaquiline group had negative culture results at 24 weeks (79% vs 62%, $P = .008$) and at 120 weeks (62% vs 44%, $P = .04$).[160] However, mortality was significantly higher in patients receiving bedaquiline (13% vs 2%, $P = .02$).[160]

Pretomanid is an oral nitroimidazole that was approved by the FDA in 2019 as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary XDR-TB and treatment-intolerant or nonresponsive MDR-TB.[161] It blocks cell wall production by inhibiting mycolic acid biosynthesis. The dose is 200 mg daily for 26 weeks, and the drug should be taken with food. Compared with the fasting state, maximum serum concentrations and area under the serum concentration–time curve were increased by 76% and 88%, respectively, when administered with a high-fat, high-calorie meal. Pretomanid is metabolized via multiple pathways, and CYP3A4 is responsible for 20% of metabolism. Only 1% of pretomanid is excreted in the urine as unchanged drug.

Human Immunodeficiency Virus Infection

TREATMENT OF ACTIVE DISEASE

CASE 68-7

Question 1: F.R. is a 32-year-old male who presents to the emergency department with mild pleuritic chest pain and a productive cough. He also has experienced weight loss, fatigue, and night sweats for the past 3 weeks. On

questioning, F.R. states that he is bisexual and frequently engages in unprotected sex. Chest radiography finding reveals bilateral interstitial infiltrates. Sputum samples are ordered, and the workup includes AFB smear and culture. A PPD skin test is placed, and an HIV test is ordered. The results of the AFB smear and HIV test are positive, and the induration from the PPD is 6 mm. A $CD4^+$ count is ordered, which is 150 cells/μL.

What are the clinical manifestations of active TB in patients infected with HIV? How effective is skin testing in the diagnosis of TB infection in patients infected with HIV? What diagnostic tests should be performed in F.R.?

HIV infection is an important risk factor for active TB disease because HIV infects and destroys $CD4^+$ cells, leading to impaired cell-mediated immunity. The immunodeficiency allows for rapid development of active TB disease in a person who is infected with *M. tuberculosis.* TB is a common opportunistic infection in persons infected with HIV, but unlike other opportunistic infections in this population, $CD4^+$ cell count is not a reliable predictor for risk for TB disease.[67] Active TB disease can occur at any $CD4^+$ cell count, but the risk increases as a patient's immunodeficiency progresses.

Common symptoms of active disease (productive cough, fever, sweats, weight loss, fatigue) may be present in HIV-infected individuals, but the clinical manifestations of TB depend on the severity of the immunodeficiency at the time of presentation. TB in an HIV-infected person will clinically resemble TB in an HIV-uninfected person if the immunodeficiency is less severe ($CD4^+$ count >200 cells/μL).[162] The disease will primarily be limited to the lungs in these patients, and upper lobe involvement with or without cavitation will be seen on chest radiography findings. However, the findings on chest radiography are markedly different in patients with advanced HIV disease ($CD4^+$ count <200 cells/μL). Lower lobe, middle lobe, interstitial, and miliary infiltrates are common, whereas cavitation is seen infrequently.[67],[162] In these patients, TB may be difficult to distinguish from other HIV-related pulmonary opportunistic infections (*Pneumocystis jirovecii, M. avium* complex), and TB should be ruled out in any HIV-infected patient with pulmonary symptoms. Patients with advanced HIV disease may also have normal chest radiograph findings but still have positive sputum

smear results for AFB and positive cultures for *M. tuberculosis*.[162] Therefore, a normal chest radiograph finding does not exclude the possibility of active TB disease. Extrapulmonary TB is more common in HIV-infected persons with $CD4^+$ counts <200 cells/μL.[67],[162] Because of F.R.'s clinical presentation and positive HIV test result, a high index of suspicion and diagnostic workup for active TB are appropriate.

A PPD skin test may be placed on HIV-infected patients with suspected TB infection, but sensitivity and specificity of skin testing are poor in patients with HIV infection. Only about 30% to 50% of patients with AIDS and TB will respond to a PPD skin test with an induration >10 mm. Therefore, an induration of ≥5 mm is considered to be a positive reaction in this population.[50] F.R.'s reaction of 6 mm to the TST should be considered positive. Theoretically, the sensitivity and specificity of IGRAs are also limited in patients with HIV infection because the tests depend on adequately functioning $CD4^+$ cells. In a study of 294 HIV-infected subjects, indeterminate results were more likely to occur in subjects with a $CD4^+$ count <100 cells/μL compared with those with a $CD4^+$ count of ≥100 cells/μL.[163] Additional studies found only 64% sensitivity for detection of active TB disease, and false-negative results occurred in ~25% of HIV-infected patients with documented pulmonary TB.[164],[165] These studies suggest that IGRAs should not be used alone to exclude active TB in this population.

The diagnostic workup for HIV-infected persons is similar to that for HIV-uninfected persons. Chest radiography and sputum samples for AFB smear and culture of three sputum specimens should be obtained.[162],[166] AFB smear results may be negative in patients with pulmonary TB who have advanced immunodeficiency and noncavitary disease.[162] NAA tests can be used to assist in evaluation of HIV-infected persons with positive AFB smear results, and a positive NAA test result in a patient whose AFB smear result is positive likely represents active TB.[67],[162] Drug susceptibility testing for all first-line agents should be performed on the initial isolate for all patients, and testing should be repeated if sputum culture results remain positive after 4 months of treatment or become positive after

at least 1 month of negative culture results.[162] Susceptibility testing of second-line agents should be limited to specimens from patients who have received prior therapy, are contacts of persons with drug-resistant TB disease, have demonstrated resistance to rifampin or other first-line agents, have positive culture results after 3 months of therapy, or are from regions with a high prevalence of MDR-TB or XDR-TB.[167] Molecular drug resistance tests may also be used to yield faster results. Patients with symptoms of extrapulmonary TB should undergo needle aspiration or tissue biopsy of skin lesions, lymph nodes, or pericardial or pleural fluid, and blood cultures for AFB should be obtained.[67]

Case 68-7, Question 2: What is the preferred treatment regimen for TB in F.R.?

Given his symptoms and positive AFB smear result, F.R. should be started on multiple-drug therapy for treatment of active TB disease. DOT is recommended for all patients with HIV-related TB.[34],[67],[162] F.R.'s treatment plan should be based on completion of the total number of doses ingested rather than on the duration of therapy. Principles and recommendations for treatment of TB in HIV-infected adults are similar to those for HIV-uninfected adults, with a notable exception (Table 68-2). The initial 8-week treatment phase in F.R. should include rifampin or rifabutin, isoniazid, pyrazinamide, and ethambutol administered daily by DOT (7 days/week for 56 doses or 5 days/week for 40 doses).[34],[162] Ethambutol may be discontinued when rifampin and isoniazid susceptibility are confirmed. However, twice- or thrice-weekly dosing regimens during the intensive or continuation phase have been associated with increased risk of treatment failure or relapse with acquired rifamycin resistance; therefore, intermittent dosing regimens are not recommended.[162] F.R. should also receive supplemental pyridoxine. After the initial phase, if no drug resistance is evident on susceptibility or molecular testing, F.R. can be treated with rifampin (or rifabutin) and isoniazid daily by DOT for a minimum of 18 weeks.[162]

Case 68-7, Question 3: How should TB therapy be monitored in F.R.?

If F.R. had cavitary disease on chest radiography finding or if culture results are positive after 2 months of intensive therapy, treatment with rifampin or rifabutin and isoniazid should be continued to complete a total of 9 months (39 weeks) of therapy. If F.R. was suspected of having extrapulmonary disease caused by drug-susceptible strains, the recommended treatment is rifampin or rifabutin, isoniazid, pyrazinamide, and ethambutol for 2 months followed by isoniazid and rifampin for 4 to 7 months. However, longer durations of therapy are recommended for extrapulmonary TB involving the CNS (meningitis or tuberculoma) or bone and joints. For these infections, many experts recommend 9 to 12 months of therapy.[162]

Baseline and monthly evaluations of hepatic function, renal function, complete blood count, and $CD4^+$ cell count are recommended in all HIV-infected patients with active TB disease.[67] In the absence of symptoms, elevations of alanine transaminase (ALT) more than three times the upper limit of normal should not cause a change in therapy.[162] If the ALT is more than three times the upper limit of normal in a patient with symptoms, more than five times the upper limit of normal regardless of symptoms, or if a significant increase in alkaline phosphatase and/or bilirubin occurs, hepatotoxic drugs should be stopped and the patient evaluated.[162] At least three anti-TB drugs should be initiated (eg, ethambutol, fluoroquinolone, aminoglycoside) as a bridging regimen until the etiology of hepatotoxicity can be determined and a long-term regimen designed. After the patient's ALT decreases to two and a half times the upper limit of normal, the first-line hepatotoxic agents may be restarted by adding back each individual drug to the bridging regimen at 7-day intervals, and ALT should be monitored frequently.[162] For pulmonary TB, at least one sputum specimen should be obtained monthly for AFB smear and culture until two consecutive specimen results are culture negative.[67],[162] If the AFB smear result is positive at the initiation of treatment, AFB smears

may be obtained every 2 weeks to provide an early assessment of bacteriologic response to therapy.[34],[67] Results of sputum samples obtained after the initial 8-week treatment phase are important because determination of the duration of the continuation phase will be based on these results. Susceptibility testing should be performed on all isolates, and susceptibility testing should be repeated on a newly obtained sputum sample if cultures are positive for *M. tuberculosis* after 3 months of therapy.[67] Patients with positive culture results at or after 4 months of therapy should be considered treatment failures.

At every visit, patients should be questioned about adherence to therapy and possible adverse events to the treatment regimen. If a patient is experiencing adverse events, the first-line drugs should not be discontinued permanently without strong evidence that a specific agent is the cause of the adverse event.[67],[162] Drug concentration monitoring may be useful to help guide therapy in patients who respond slowly to the prescribed treatment regimen.[168]

CASE 68-7, QUESTION 4: When should antiretroviral therapy (ART) be initiated in F.R.?

Optimal management of active TB disease in patients infected with HIV requires treatment of both infections. TB in HIV-infected patients with advanced immunodeficiency can be rapidly progressing and fatal; therefore, sequential treatment of TB followed by treatment of HIV is not recommended.[162] In patients with HIV infection, $CD4^+$ cells multiply in response to *M. tuberculosis,* and then HIV replication accelerates within the lymphocytes and macrophages, which leads to progression of HIV disease. Therefore, initiation of ART can prevent progression of HIV disease and reduce morbidity and mortality associated with TB and other opportunistic infections.[67],[162] However, this approach may be associated with cumulative drug toxicities, significant drug interactions, higher pill burden, and the potential for development of immune reconstitution inflammatory syndrome (IRIS).[67],[162]

Three studies addressed the optimal timing to initiate ART during treatment of active TB disease.[169–171] In ART-naive patients, ART should be initiated within 2 weeks of starting TB therapy in patients with a $CD4^+$ count <50 cells/μL.[162] Early initiation of ART significantly reduces mortality in these patients, but the risk of IRIS is increased. In patients with $CD4^+$ counts of ≥50 cells/μL who present with severe TB disease (low Karnofsky score, low body mass index, low hemoglobin, low albumin, organ system dysfunction, or extensive disease), studies suggest that ART should be initiated within 2 to 4 weeks of starting TB therapy. In patients with $CD4^+$ counts of ≥50 cells/μL who do not have severe TB disease, ART should be initiated within 8 to 12 weeks of initiating TB therapy.[169–171] Guidelines recommend initiation of ART within 8 weeks of starting TB treatment in patients with $CD4^+$ counts of ≥50 cells/μL.[162] If IRIS develops, neither therapy for TB nor HIV should be discontinued. Because F.R. is ART naive and his $CD4^+$ count is 150 cells/μL, ART should be initiated within 8 weeks of starting treatment for active TB.

If F.R. was receiving ART when diagnosed with TB, treatment for TB should be started immediately, and ART should be modified to maintain virologic suppression while reducing the risk for drug–drug interactions.[162] ART should not be withheld simply because the patient is being treated for TB, and a rifamycin should not be excluded from the treatment regimen for fear of interactions with certain antiretroviral agents.[34,162] Exclusion of a rifamycin will likely delay sputum conversion, prolong the duration of therapy, and possibly result in a poor outcome.

Case 68-7, Question 5: Because F.R.'s $CD4^+$ count is 150 cells/μL, the decision is made to begin ART after the initial 8-week intensive phase to decrease the potential for IRIS. What is IRIS? What drug interactions are likely in an HIV-infected patient receiving treatment for TB and HIV?

IRIS occurs in ~30% of patients who begin therapy for both HIV and TB in close temporal proximity.[162,172] This syndrome is thought to reflect recovery of immune responses to *M. tuberculosis* and usually occurs in the first 1 to 4 weeks after initiation of ART.[162] IRIS lasts for

2 to 3 months on average, but some patients may experience IRIS symptoms for months. The immune response can be an exaggerated inflammatory response during TB therapy in a patient known to have TB infection, or it may unmask a previously undiagnosed TB infection. The risk of IRIS is greater when ART is initiated within the first 2 months of TB therapy and when the $CD4^+$ count is <50 to 100 cells/μL.[67],[162] Symptoms include high fever, malaise, and local reactions in organs, depending on the location of the mycobacterial infection (eg, lungs, lymph nodes, CNS). IRIS is usually self-limiting, but supportive therapy may be required if symptoms are severe. Moderate IRIS reactions should be treated with nonsteroidal anti-inflammatory drugs without any changes to TB therapy or ART.[67] No specific treatment recommendations are available for severe IRIS; however, prednisone or methylprednisolone at doses of 1 mg/kg body weight and tapered for 1 to 2 weeks has been beneficial.[67]

Simultaneous treatment of TB and HIV can be complicated by drug interactions with the rifamycins and ART.[134],[162] Rifampin is a potent inducer of CYP isoenzymes, but rifabutin is not a potent inducer.[34],[67] Rifabutin is highly active against *M. tuberculosis,* and data from clinical trials suggest equal efficacy with rifampin- and rifabutin-based treatment regimens.[34],[162] Because of fewer drug interactions and documented efficacy, rifabutin is recommended in place of rifampin for the treatment of active TB in HIV-infected patients receiving ritonavir-boosted protease inhibitors or NNRTIs.[33],[161] However, some antiretroviral agents may either induce or inhibit CYP isoenzymes, depending on the specific drug, and may alter rifabutin serum concentrations.[34],[162]

For the NNRTIs, rifampin has been shown to decrease efavirenz exposures by 26%, but two additional studies did not show a significant effect of rifampin on efavirenz exposure.[173–175] Therefore, the preferred treatment regimens are rifampin-based TB therapy with an ART regimen consisting of efavirenz plus two nucleoside reverse transcriptase inhibitors.[162] The efavirenz dose should be 600 mg daily.[162] Efavirenz decreases rifabutin exposure by 38%, necessitating a dosage increase for rifabutin to 450 to 600 mg

daily.[162] For patients unable to take efavirenz because of early pregnancy or intolerance, nevirapine-based ART can be used, but rifampin significantly decreases nevirapine exposures.[162] If used concomitantly, the nevirapine dose should be 200 mg twice daily.[162] However, rifabutin-based TB therapy may be considered with a nevirapine-based ART regimen because dosage adjustments are not needed for either agent.[162] Concomitant administration of doravirine, etravirine, and rilpivirine with rifampin should be avoided because of significant reduction in exposures of these NNRTIs.[162]

Rifampin should not be used in patients receiving protease inhibitor– based ART, regardless of boosting with ritonavir or cobicistat, because rifampin causes a dramatic decrease in exposures of the protease inhibitors.[67],[162] Rifabutin has a negligible effect on ritonavir-boosted lopinavir or atazanavir and only moderate increases in darunavir and fosamprenavir concentrations.[162] For patients unable to tolerate efavirenz or nevirapine or if the HIV strain is resistant to NNRTIs, a rifabutin-based TB regimen is preferred with an ritonavir-boosted protease inhibitor regimen.[162] However, all protease inhibitors markedly increase rifabutin concentrations. If doses of rifabutin are not adjusted, adverse drug events, such as uveitis, neutropenia, arthralgias, and skin discoloration, may occur.[67] Therefore, the rifabutin dose should be decreased to 150 mg daily when administered with boosted protease inhibitors.[162]

HIV nucleoside and nucleotide reverse transcriptase inhibitors (tenofovir disoproxil fumarate, abacavir, emtricitabine, lamivudine) and the fusion inhibitor enfuvirtide are not metabolized by CYP isoenzymes. As a result, these agents can be administered with the rifamycins.[134],[162] Tenofovir alafenamide (TAF) is a substrate for P-glycoprotein, but intracellular concentrations of tenofovir diphosphate are higher when administered with rifampin compared to administration of tenofovir disoproxil fumarate alone. Thus, TAF may be given with rifampin-based TB regimens without dose adjustment.[162]

Rifampin decreases the concentrations of the integrase strand inhibitors. For raltegravir, the dose should be increased to 800 mg twice daily if given with rifampin, but no dosage adjustment is

recommended with rifabutin.[162] Dolutegravir may be given with rifampin, but the dose should be increased to 50 mg twice daily, which provides exposure similar to that with 50 mg daily without rifampin. Dose adjustment is not needed for dolutegravir if given with rifabutin.[176] Coadministration with elvitegravir or bictegravir with rifampin and rifabutin should be avoided.[162] Maraviroc, a CCR5 antagonist, is a substrate for CYP3A and P-glycoprotein, and concomitant administration with rifampin significantly decreases exposures.[134] The maraviroc dose should be increased to 600 mg twice daily, but no dosage adjustment is needed with rifabutin.

TREATMENT OF LATENT TUBERCULOSIS INFECTION IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION

CASE 68-8

QUESTION 1: N.M. is the 32-year-old partner and roommate of F.R. Because of his close contact with F.R., he is evaluated for exposure to TB by an infectious diseases specialist. N.M.'s HIV test result is positive, and a TST produces an induration of 8 mm, which is a positive reaction. All other studies return negative findings for active TB.

Should N.M. receive treatment for latent TB infection? If so, what therapy should he receive?

The risk of N.M. developing active TB disease is significant; therefore, he should receive treatment for latent TB infection. HIV-infected persons, regardless of age, should be treated for latent TB infection.[67] In addition, HIV-infected persons who are in close contact with anyone with active TB should receive treatment for latent TB infection, regardless of TB screening test results.[162] Pape et al conducted a randomized, placebo-controlled trial of isoniazid therapy in HIV-infected patients.[177] Patients receiving placebo were six times more likely to develop active TB than were those receiving isoniazid, and patients receiving isoniazid were also less likely to develop AIDS.[177] Treatment of latent TB infection, in conjunction with ART, decreases the risk of progression from latent infection to active disease by 76%.[162] The preferred treatment for latent TB infection in

N.M. is isoniazid 300 mg daily for 9 months.[162] Isoniazid does not increase the risk of hepatitis when used with efavirenz- or nevirapine-based ART regimens.[162] N.M. should also receive pyridoxine 25 to 50 mg daily to prevent peripheral neuropathy. Rifampin for 4 months is an alternative to isoniazid, but the potential for drug interactions should be considered. Weekly isoniazid plus rifapentine is only recommended for patients receiving efavirenz- or raltegravir-based ART regimens.[162]

Pregnancy

CASE 68-9

Question 1: E.F. is a 25-year-old Hispanic female who is being treated with isoniazid 900 mg and rifampin 600 mg twice weekly for pulmonary TB. She completed 2 months of therapy with RIPE, and began the continuation regimen 2 months ago. She recently became pregnant, and her obstetrician is concerned about the possible teratogenic effects of her TB regimen.

What are the risks of TB and its treatment to the mother and the fetus? Are these drugs teratogenic?

Although concerns about the use of any medication during pregnancy always exist, it is now recognized that untreated TB represents a far greater risk to a pregnant female and her fetus than does the treatment.[34,68] TB is one of the leading nonobstetric causes of maternal mortality.[178] The World Health Organization recommends that treatment of TB in pregnant females should be the same as that for nonpregnant females, with a few exceptions.[178] Although TB drugs cross the placenta, those in the RIPE regimen are not teratogenic in humans.[179,180] In the United States, inclusion of pyrazinamide is controversial, but it has not been recommended for use during pregnancy because of insufficient safety data.[34] Pyrazinamide has been used extensively in high-burden countries and is recommended by the World Health Organization for treatment of TB in pregnancy.[34] If pyrazinamide is not included in the initial treatment regimen, the minimal duration of therapy is 9 months.[34] All

pregnant females receiving isoniazid should also receive pyridoxine 25 to 50 mg/day because of the possibility of peripheral neuropathy.

Streptomycin should not be used during pregnancy except as a last alternative because it has been associated with mild-to-severe ototoxicity in the fetus.[178] Ototoxicity can occur throughout the gestational period and is not confined to the first trimester. With the exception of streptomycin ototoxicity, the occurrence of birth defects in females being treated for TB with the abovementioned agents is no greater than that in healthy pregnant females.[181],[182] Therefore, administration of antituberculosis drugs is not an indication for termination of pregnancy.[34] Because E.F. likely became pregnant after completing the first 2 months of therapy, she should continue her current regimen for a total of 6 months because she received pyrazinamide as part of the initial regimen.

MULTIDRUG-RESISTANT TUBERCULOSIS IN PREGNANCY

Little is known about the efficacy and safety of second-line drugs for the treatment of MDR-TB during pregnancy. Two reports with small numbers of patients have suggested that treatment is effective, with no adverse effects to mother or child.[183],[184] In a study of seven females treated for MDR-TB during pregnancy, no obstetric complications or perinatal transmission of MDR-TB was observed. Five females were cured, one experienced treatment failure, and one stopped therapy prematurely.[183] No evidence of drug toxicity was seen among their children exposed to second-line drugs in utero, although one child was diagnosed with MDR-TB.[184] There are no well-controlled studies with bedaquiline in pregnancy; therefore, the drug should only be used in pregnancy if clearly needed. More data are needed, but pregnancy should not be a limitation to the treatment of MDR-TB.

LACTATION

Breast-feeding is encouraged for females who are deemed noninfectious and are receiving first-line therapy. Low concentrations of TB drugs have been measured in breast milk but have not been

reported to produce adverse effects in the nursing infant.[34] When the baby is born, E.F. may breastfeed while continuing her medication. Drug concentrations in breast milk are minimal and do not provide sufficient quantities for the treatment or prevention of TB in the nursing infant.[34],[68]

Pediatrics

CASE 68-10

QUESTION 1: A.M., a 3-year-old African American boy, is suspected of having TB. His father has been receiving treatment for TB for the past 2 months. A.M. has a productive cough, fever, and general malaise. His sputum test result is positive for AFB, and his PPD skin test result is positive (10 mm).

What is the incidence of TB in children? How should A.M. be treated?

The incidence of TB in children younger than age 5 years has declined from 1014 cases (4.0/100,000 population) in 1993 to 215 cases (2.4/100,000 population) in 2019.[11] Children commonly develop active TB disease as a complication of the initial infection with *M. tuberculosis* (primary TB), and the disease is characterized by intrathoracic lymphadenopathy, middle and lower lung lobe infiltrates, and the absence of cavitation on chest radiography.[34],[185] Because of the high risk of disseminated TB in infants and children, treatment should be started as soon as the diagnosis of TB is suspected. In general, regimens recommended for adults are also recommended for infants, children, and adolescents, with the exception that ethambutol has not been used routinely in children historically.[34] Ethambutol is often avoided because it is difficult to assess visual acuity in young children. However, the American Academy of Pediatrics does not exclude ethambutol from the initial four-drug intensive phase.[186] A.M. should be started on rifampin 15 to 20 mg/kg/day, isoniazid 10 to 15 mg/kg/day, pyrazinamide 30 to 40 mg/kg/day, and ethambutol 15 to 25 mg/kg/day (after assessment of risk versus benefit) for 2 months, followed by rifampin and isoniazid for 4 months.[34],[186] Thrice-weekly dosing is also

recommended in children.[186] If ethambutol is started and the initial isolate is drug susceptible, ethambutol should be discontinued. Many experts prefer to treat children with three drugs (rather than with four) in the initial phase because the bacillary population is usually lower than that in an adult and it may be difficult for an infant or child to ingest four drugs. Pyridoxine is recommended for infants, children, and adolescents who are receiving isoniazid.[34],[186]

A.M. should be monitored monthly for visual acuity and red-green color discrimination, and he should be examined routinely for signs and symptoms of hepatitis. Although antituberculosis medications are generally well tolerated in children, LFT results are commonly two to three times the upper limit of normal during therapy. These are often benign and transient; however, the incidence of hepatitis in children from rifampin with isoniazid may be four to six times more common than in children receiving isoniazid alone. Most hepatitis cases occur within the first 3 months of therapy and generally are associated with higher than recommended doses of isoniazid or rifampin.[122],[187]

Children and adolescents should be screened for risk factors for TB using a questionnaire, and they should be skin tested with 5 TU of PPD or an IGRA if one or more risk factors are present.[186],[188] For children younger than age 2 years, TST is preferred, and either TST or IGRA can be used in children ages 2 years and older. However, IGRA is preferred in children previously vaccinated with BCG. For latent TB infection, isoniazid plus rifapentine weekly for 12 weeks is the preferred regimen for children ages 2 years and older.[186] This regimen is not recommended in children younger than age 2 years owing to lack of pharmacokinetic data. Isoniazid for 9 months has been most commonly recommended for treatment of latent TB in this population, but adherence is poor and completion rates are low.[186] Daily rifampin for 4 months is an acceptable alternative, especially in children who cannot tolerate isoniazid or those exposed to a source case whose isolate was isoniazid resistant.[186]

Extrapulmonary Tuberculosis and Tuberculous Meningitis

CASE 68-11

Question 1: R.U. is a 64-year-old, 180.78-pound (82-kg) male who is brought to the emergency department after a 4-day period during which he became progressively disoriented, febrile to 104.90 °F (40.5 °C), and obtunded. He also had severe headaches during this time. Physical examination revealed moderate nuchal rigidity and a positive Brudzinski sign (neck resistant to flexion). An initial diagnosis of possible meningitis was made, and a lumbar puncture was ordered. The CSF appeared turbid, and laboratory analysis revealed an elevated protein concentration of 200 mg/dL, a decreased glucose concentration of 30 mg/dL, and a white blood cell count of 500/μL (85% lymphocytes). A Gram stain of the spinal fluid and a sputum smear result for AFB were negative, but the AFB smear result of the CSF was positive. Other laboratory test results were within normal limits. A diagnosis of tuberculous meningitis was made. What is the presentation and prognosis of tuberculous meningitis?

How should R.U. be treated?

Tuberculous meningitis is only one of the extrapulmonary complications of infection with *M. tuberculosis.* It is a potentially devastating disease and is associated with increased morbidity and mortality, regardless of HIV status. Successful treatment of extrapulmonary TB can usually be accomplished in 6 to 9 months with an acceptable relapse rate.[34,68,188] Some forms, such as bone or joint TB, miliary TB, or tuberculous meningitis, may require 9 to 12 months of therapy.[34] Because specimens for culture and susceptibility testing may be difficult or impossible to obtain from a site, response to treatment must be based on clinical and radiographic improvement.

Tuberculous meningitis in older persons is usually caused by hematogenous dissemination of the tubercle bacilli from a primary site, most commonly the lungs. In its early stages, tuberculous meningitis often is confused with aseptic meningitis because the Gram stain finding is negative. The most common symptoms of tuberculous meningitis are headache, fever, restlessness, irritability,

nausea, and vomiting. A positive Brudzinski sign and neck stiffness may be present. As illustrated in R.U.'s case, the CSF is usually turbid, with increased protein and decreased glucose concentrations. There is an increase in the CSF white blood cell count with a predominance of lymphocytes. Culture results of the CSF for *M. tuberculosis* may not be helpful because rates of positivity for clinically diagnosed cases range from 25% to 70%.[189] Early recognition and treatment are essential for a favorable outcome. Thus, empirical treatment before receipt of confirmatory culture and susceptibility results is common in suspected tuberculous meningitis. Multiple-drug therapy should be used because irreversible brain damage or death can occur as soon as 2 weeks after the onset of infection (not clinical symptoms).[189]

TREATMENT

Treatment should be initiated in R.U. with daily administration of rifampin 600 mg, isoniazid 300 mg, pyrazinamide 2000 mg, and ethambutol 1600 mg for the first 8 weeks.[34] After this initial phase of treatment, R.U. should receive daily rifampin and isoniazid for an additional 7 to 10 months, although the optimal duration of therapy is unknown.[34] In addition, because R.U. is older, pyridoxine 25 to 50 mg/day should be given to prevent the occurrence of peripheral neuropathy from isoniazid. It should be reiterated that rifampin can impart a red to orange color to the CSF.

Isoniazid readily penetrates into the CSF, with CSF concentrations reaching up to 100% of those in the serum. Rifampin is often included in tuberculous meningitis regimens and may be associated with reduced morbidity and mortality; however, even with inflammation, CSF concentrations of rifampin are only 6% to 30% of those found in the serum. Ethambutol should be used in the highest dosage to achieve bactericidal concentrations in the CSF because its CSF concentrations are only 10% to 54% of those in the serum. Streptomycin penetrates into the CSF poorly even with inflamed meninges.[190]

CORTICOSTEROIDS

Corticosteroids in moderate-to-severe tuberculous meningitis appear to reduce sequelae and prolong survival.[191] The mechanism for this benefit is likely owing to reduction of intracranial pressure. Dexamethasone 8 to 12 mg/day (or prednisone equivalent) for 6 to 8 weeks should be used and then tapered slowly after symptoms subside.[34],[191] Corticosteroids are likely indicated for R.U.

THERAPEUTIC DRUG MONITORING

Pharmacokinetics of the drugs used to treat tuberculosis are highly variable and depend on weight, sex, genetic traits, and underlying comorbidities. Subtherapeutic concentrations may be associated with a delayed response to therapy, increased risk of relapse, or acquired drug resistance. Several studies measured drug concentrations in patients with slow clinical response to TB treatment and found subtherapeutic concentrations for isoniazid, rifampin, ethambutol, and rifabutin in a substantial percentage of patients evaluated.[87],[192–194] In one study, time to sputum culture result conversion was longer in patients with low serum concentrations.[194] In a prospective observational study, 2-hour plasma concentrations were measured in 35 patients, and plasma concentrations were below the normal ranges in 71%, 58%, 46%, and 10% of patients for isoniazid, rifampin, ethambutol, and pyrazinamide, respectively.[195] In addition, 45% of patients had subtherapeutic concentrations for both isoniazid and rifampin. Treatment failure occurred significantly more frequently when concentrations of isoniazid and rifampin were below the normal ranges (P = .013) and below the median 2-hour drug concentration achieved in the study (P = .005).[195] In 142 patients with active TB, poor long-term outcomes were predicted by a 24-hour area under the concentration–time curve (AUC) ≤363 mg × hour/L for pyrazinamide, ≤13 mg × hour/L for rifampin, and ≤52 mg × hour/L for isoniazid.[196] Poor outcomes occurred in 32/78 patients with at least one drug with an AUC below these threshold values

compared to 3/64 patients without any low AUCs (odds ratio = 14.14; 95% confidence interval [CI] 4.08–49.1). Low rifampin and isoniazid peak concentrations and AUCs predicted acquired drug resistance in all cases.[196]

Based on these studies, therapeutic drug monitoring may be useful in patients with poor or slow clinical response to therapy and allow for dosage adjustment to achieve therapeutic drug concentrations. Additional patients who may benefit from therapeutic drug monitoring include those with severe disease, diabetes, HIV infection, renal dysfunction, and hepatic dysfunction.[197] A 2-hour postdose blood sample can be obtained to estimate the peak concentration for most drugs, whereas a 3-hour postdose blood sample would be needed for rifabutin.[197] A second blood sample at 6 hours postdose (7 hours for rifabutin) may also be obtained. Trough concentrations for most agents are below the detection limit of the assays at the end of a dosing interval and are not clinically useful.[197] Blood samples should be collected in red-top test tubes and processed immediately because some drugs are not stable at room temperature in blood or serum. Once the drug concentrations are known, comparisons can be made to the normal ranges for each drug and doses adjusted accordingly. However, normal ranges for drug concentrations have not been studied with regard to clinical outcome, and optimal drug concentrations for clinical and microbiologic efficacy are not known.[195] Although therapeutic drug monitoring may provide useful information, clinicians must remember that serum concentrations are only one factor among multiple factors affecting treatment outcomes.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs.* 2014;74:839–854. (197)

American Academy of Pediatrics, Committee on Infectious Diseases. *2021 Red Book: Report of the Committee on Infectious Diseases*. 32nd ed. American Academy of Pediatrics; 2021. (186)

Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin and rifabutin drug interactions. *Am J Med Sci*. 2008;335:126–136. (126)

Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *Morb Mortal Wkly Rep*. 2011;60: 1650–1653. (115)

Centers for Disease Control and Prevention. Reported tuberculosis in the United States 2019. Accessed August 30, 2021. http://www.cdc.gov/tb/statistics/reports/2019/national_data.htm (11)

Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med*. 2014;371:723–732. (160)

Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* infection. *N Engl J Med*. 2015;372:2127–2135. (23)

Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371: 1577–1587. (88)

Lin SYG, Desmond EP. Molecular diagnosis of tuberculosis and drug resistance. *Clin Lab Med*. 2014;34:297–314. (56)

Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines. Treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195. (34)

Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. *Am J Respir Crit Care Med.* 2020;200:e93–e142. (35)

Prahl JB, Johansen IS, Cohen AS, Frimodt-Møller N, Andersen ÅB. Clinical significance of 2 h plasma concentrations of first-line anti-tuberculosis drugs: a prospective observational study. *J Antimicrob Chemother*. 2014;69:2841–2847. (195)

Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–2166. (114)

Wlodarsha M, Johnston JC, Gardy JL, Tang P. A microbiological revolution meets an ancient disease: improving the management of tuberculosis with genomics. *Clin Microbiol Rev*. 2015;28:523–539. (57)

Worley MV, Estrada SJ. Bedaquiline: a novel antitubercular agent for the treatment of multidrug-resistant tuberculosis. *Pharmacotherapy*. 2014;34: 1187–1197.

(157)

Key Websites

Centers for Disease Control and Prevention. Tuberculosis (TB). http://www.cdc.gov/tb

Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Mycobacterium tuberculosis infection and disease. Accessed August 30, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/mycobacterium-tuberculosis-infection-and?view=full (162)

World Health Organization. Global tuberculosis report 2020. Accessed August 30, 2021. https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf (9)

COMPLETE REFERENCES CHAPTER 68 TUBERCULOSIS

1. Dooley SW, Jarvis WR, Marione WJ, Snider DE. Multidrug-resistant tuberculosis. *Ann Intern Med*. 1992;117:257–259.
2. Frieden TR, Sterling T, Pablos-Mendez A, Kilburn JO, Cauthen GM, Dooley SW. The emergence of drug-resistant tuberculosis in New York City [published correction appears in *N Engl J Med*. 1993;329:148]. *N Engl J Med*. 1993;328:521–526.
3. Riley LW. Drug-resistant tuberculosis. *Clin Infect Dis*. 1993;17(suppl 2):S442–S446.
4. Centers for Disease Control and Prevention. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. *Morb Mortal Wkly Rep*. 2006;55:301–305.
5. Raviglione MC, Smith IM. XDR tuberculosis—implications for global public health. *N Engl J Med*. 2007;356:656–659.
6. Shah NS, Wright A, Bai GH, et al. Worldwide emergence of extensively drug-resistant tuberculosis. *Emerg Infect Dis*. 2007;13:380–387.
7. Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. *Chest*. 2009;136:420–425.
8. Corbett EL, Watt CJ, Walker N, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis. Global trends and interactions with the HIV

epidemic. *Arch Intern Med*. 2003;163:1009–1021.
9. World Health Organization. Global tuberculosis report 2020. Accessed August 30, 2021. https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf
10. Deutsch-Feldman M, Pratt RH, Price SF, Tsang CA, Self JL. Tuberculosis—United States, 2020. *Morb Mortal Wkly Rep*. 2021;70:409–414.
11. Centers for Disease Control and Prevention. Reported tuberculosis in the United States 2019. Accessed August 30, 2021. http://www.cdc.gov/tb/statistics/reports/2019/national_data.htm
12. Centers for Disease Control and Prevention. Notice to readers: revised definition of extensively drug-resistant tuberculosis. *Morb Mortal Wkly Rep*. 2006;55:1176.
13. Gandhi NR, Moll A, Willem Sturm A, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet*. 2006;368:1575–1580.
14. Centers for Disease Control and Prevention. Extensively drug-resistant tuberculosis (XDR TB). Accessed August 30, 2021. http://www.cdc.gov/tb/publications/factsheets/drtb/xdrtb.htm
15. Kliiman K, Altraja A. Predictors of extensively drug-resistant pulmonary tuberculosis. *Ann Intern Med*. 2009;150:766–775.
16. Shin SS, Keshavjee S, Gelmanova IY, et al. Development of extensively drug-resistant tuberculosis during multidrug-resistant tuberculosis treatment. *Am J Respir Crit Care Med*. 2010;182:426–432.
17. Kim DH, Kim HJ, Park SK, et al. Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2008;178:1075–1082.
18. Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis*. 2010;51:6–14.
19. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med*. 2000;161(4, Pt 1):1376–1395.
20. Gordin FM, Masur H. Current approaches to tuberculosis in the United States. *JAMA*. 2012;308:283–289.
21. Gardner A, Cohen T, Carter EJ. Tuberculosis among participants in an academic global health medical exchange program. *J Gen Intern Med*. 2011;26: 841–845.
22. Jensen PA, Lambert LA, Iademarco MF, Ridzon R; Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *Morb Mortal Wkly Rep*. 2005;54(RR-17):1–141.

23. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* infection. *N Engl J Med*. 2015;372:2127–2135.
24. Hartman-Adams H, Clark K, Juckett G, et al. Update on latent tuberculosis infection. *Am Fam Physician*. 2014;89:889–896.
25. Lin PL, Flynn JL. Understanding latent tuberculosis: a moving target. *J Immunol*. 2010;185:15–22.
26. Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? *Clin Infect Dis*. 2005;41(suppl 3):S199–S203.
27. Horsburgh CR Jr, O'Donnell M, Chamblee S, et al. Revisiting rates of reactivation tuberculosis: a population-based approach. *Am J Respir Crit Care Med*. 2010;182:420–425.
28. Moonan PK, Ghosh S, Oeltmann JE, Kammerer JS, Cowan LS, Navin TR. Using genotyping and geospatial scanning to estimate recent *Mycobacterium tuberculosis* transmission, United States. *Emerg Infect Dis*. 2012;18:458–465.
29. Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. *N Engl J Med*. 1992;326:231–235.
30. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320:545–550.
31. Markowitz N, Hansen NI, Wilcosky TC, et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med*. 1993;119:185–193.
32. Solovic I, Sester M, Gomez-Reino JJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J*. 2010;36:1185–1206.
33. Nelson LJ, Schneider E, Wells CD, Moore M. Epidemiology of childhood tuberculosis in the United States, 1993–2001: the need for continued vigilance. *Pediatrics*. 2004;114:333–341.
34. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines. Treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63:e147–e195.
35. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. *Am J Respir Crit Care Med.* 2020;200:e93–e142.
36. Horsburgh CR Jr, Feldman S, Ridzon R; Infectious Diseases Society of America. Practice guidelines for the treatment of tuberculosis. *Clin Infect Dis*. 2000;31:633–639.
37. Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. *Proc Am Thorac Soc*. 2006;3:103–110.

38. MacGregor RR. A year's experience with tuberculosis in a private urban teaching hospital in the post-sanatorium era. *Am J Med*. 1975;58:221–228.
39. Counsell SR, Tan JS, Dittus RS. Unsuspected pulmonary tuberculosis in a community teaching hospital. *Arch Intern Med*. 1989;149:1274–1278.
40. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167:335–342.
41. Slama K, Chiang CY, Enarson DA, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2007;11:1049–1061.
42. Lin HH, Ezzati M, Chang HY, Murray M. Association between tobacco smoking and active tuberculosis in Taiwan: prospective cohort study. *Am J Respir Crit Care Med*. 2009;180:475–480.
43. Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M. Regulation of mucociliary clearance in health and disease. *Eur Respir J*. 1999;13:1177–1188.
44. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol*. 2002;2:372–377.
45. Wang H, Yu M, Ochani M, et al. Nicotinic acetylcholine receptor alpha 7 subunit is an essential regulator of inflammation. *Nature*. 2003;421:384–388.
46. Boelaert JR, Gomes MS, Gordeuk VR. Smoking, iron, and tuberculosis. *Lancet*. 2003;362:1243–1244.
47. Myers JP. New recommendations for the treatment of tuberculosis. *Curr Opin Infect Dis*. 2005;18:133–140.
48. Howard A, Mercer P, Nataraj HC, Kang BC. Bevel-down superior to bevel-up in intradermal skin testing. *Ann Allergy Asthma Immunol*. 1977;78:594–596.
49. Tsicopoulos A, Hamid Q, Varney V, et al. Preferential messenger RNA expression of Th1-type cells (IFN-gamma+, IL-2+) in classical delayed-type (tuberculin) hypersensitivity reactions in human skin. *J Immunol*. 1992;148:2058–2061.
50. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *Morb Mortal Wkly Rep*. 2000;49(RR-6):1–51.
51. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. *N Engl J Med*. 2002;347:1860–1866.
52. Hobby GL, Holman AP, Iseman MD, Jones JM. Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. *Antimicrob Agents Chemother*. 1973;4:94–104.
53. Schluger NW. Changing approaches to the diagnosis of tuberculosis. *Am J Respir Crit Care Med*. 2001;164:2020–2024.
54. Wright PW, Wallace RJ Jr, Wright NW, Brown BA, Griffith DE. Sensitivity of fluorochrome microscopy for detection of *Mycobacterium tuberculosis* versus nontuberculous mycobacteria. *J Clin Microbiol*. 1998;36:1046–1049.

55. Centers for Disease Control and Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *Morb Mortal Wkly Rep*. 2009;58:7–10.
56. Lin SYG, Desmond EP. Molecular diagnosis of tuberculosis and drug resistance. *Clin Lab Med*. 2014;34:297–314.
57. Wlodarska M, Johnston JC, Gardy JL, Tang P. A microbiological revolution meets an ancient disease: improving the management of tuberculosis with genomics. *Clin Microbiol Rev*. 2015;28:523–539.
58. Taegtmeyer M, Beeching NJ, Scott J, et al. Clinical impact of nucleic acid amplification tests on the diagnosis and management of tuberculosis in a British hospital. *Thorax*. 2008;63:317–321.
59. Guerra RL, Hooper NM, Baker JF, et al. Use of the amplified *Mycobacterium tuberculosis* direct test in a public health laboratory: test performance and impact on clinical care. *Chest*. 2007;132:946–951.
60. Centers for Disease Control and Prevention. Anergy skin testing and tuberculosis [corrected] preventive therapy for HIV-infected persons: revised recommendations. *Morb Mortal Wkly Rep*. 1997;46(RR-15):1–10.
61. American Thoracic Society. Targeted tuberculin skin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2000;161(4, Pt 2):S221–S247.
62. Advisory Council for the Elimination of Tuberculosis. The role of BCG vaccine in the prevention and control of tuberculosis in the United States. A joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. *Morb Mortal Wkly Rep*. 1996;45(RR-4):1–18.
63. Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *Int J Epidemiol*. 1993;22:1154–1158.
64. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. *JAMA*. 1994;271:698–702.
65. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *Morb Mortal Wkly Rep*. 2010;59(RR-5):1–25.
66. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in healthcare settings. *Morb Mortal Wkly Rep*. 2006;55(RR-14):1–17; quiz CE1–CE4.
67. Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Morb Mortal Wkly Rep*. 2009;58 (RR-4):1–207; quiz CE1–CE4.

68. Bass JB Jr, Farer LS, Hopewell PC, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and the Centers for Disease Control and Prevention. *Am J Respir Crit Care Med*. 1994;149:1359–1374.
69. Lienhardt C, Cook SV, Burgos M, et al. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis. The Study C randomized controlled trial. *JAMA*. 2011;305:1415–1423.
70. Tsukamura M, Nakamura E, Yoshii S, Amano H. Therapeutic effect of a new antibacterial substance ofloxacin (DL8280) on pulmonary tuberculosis. *Am Rev Respir Dis*. 1985;131:352–356.
71. Alvirez-Freites EJ, Carter JL, Cynamon MH, et al. In vitro and in vivo activities of gatifloxacin against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 2002;46:1022–1025.
72. Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med*. 2006;174:331–338.
73. Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet*. 2009;373:1183–1189.
74. Dorman SE, Johnson JL, Goldberg S, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. *Am J Respir Crit Care Med*. 2009;180:273–280.
75. Bozeman L, Burman W, Metchock B, Welch L, Weiner M; Tuberculosis Trials Consortium. Fluoroquinolone susceptibility among *Mycobacterium tuberculosis* isolates from the United States and Canada. *Clin Infect Dis*. 2005;40:386–391.
76. Devasia RA, Blackman A, Gebretsadik T, et al. Fluoroquinolone resistance in *Mycobacterium tuberculosis*. The effect of duration and timing of fluoroquinolone exposure. *Am J Respir Crit Care Med*. 2009;180:365–370.
77. Johnson R, Streicher EM, Louw GE, Warren RM, van Helden PD, Victor TC. Drug resistance in *Mycobacterium tuberculosis*. *Curr Issues Mol Biol*. 2006;8:97–111.
78. Williamson DA, Roberts SA, Bower JE, et al. Clinical failures associated with rpoB mutations in phenotypically occult multidrug-resistant *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis*. 2012;16:216–220.
79. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363:1005–1015.
80. Theron G, Peter J, van Zyl-Smit R, et al. Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in a high HIV prevalence setting. *Am J Respir Crit Care Med*. 2011;184:132–140.
81. Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults.

Cochrane Database Syst Rev. 2019;6(6):CD009593. doi:10.1002/14651858.CD009593.pub4

82. American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America. Controlling tuberculosis in the United States. *Am J Respir Crit Care Med*. 2005;172:1169–1227.
83. Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis: a twice-weekly, directly observed, and cost-effective regimen. *Ann Intern Med*. 1990;112:407–415.
84. Tam CM, Chan SL, Lam CW, et al. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis. Initial report. *Am J Respir Crit Care Med*. 1998;157(6, Pt 1):1726–1733.
85. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002;360:528–534.
86. Bock NN, Sterling TR, Hamilton CD, et al. A prospective, randomized, double-blind study of the tolerability of rifapentine 600, 900, and 1,200 mg plus isoniazid in the continuation phase of tuberculosis treatment. *Am J Respir Crit Care Med*. 2002;165:1526–1530.
87. Weiner M, Burman W, Vernon A, et al. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. *Am J Respir Crit Care Med*. 2003;167:1341–1347.
88. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371:1577–1587.
89. Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med*. 2014;371:1588–1598.
90. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371:1599–1608.
91. Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis: consensus statement of the Public Health Tuberculosis Guidelines Panel [published correction appears in *JAMA*. 1998;280:134]. *JAMA*. 1998;279:943–948.
92. Jasmer RM, Seaman CB, Gonzalez LC, Kawamura LM, Osmond DH, Daley CL. Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy. *Am J Respir Crit Care Med*. 2004;170:561–566.
93. Burman WJ, Dalton CB, Cohn DL, Butler JR, Reves RR. A cost-effectiveness analysis of directly observed therapy vs. self-administered therapy for treatment of tuberculosis. *Chest*. 1997;112:63–70.

94. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis. Common errors and their association with the acquisition of drug resistance. *JAMA*. 1993;270:65–68.
95. Iseman MD, Cohn DL, Sbarbaro JA. Directly observed treatment of tuberculosis: we can't afford not to try it. *N Engl J Med*. 1993;328:576–578.
96. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *Am Rev Respir Dis*. 1980;121:939–949.
97. Chan SL, Yew WW, Ma WK, et al. The early bactericidal activity of rifabutin measured by sputum viable counts in Hong Kong patients with pulmonary tuberculosis. *Tuber Lung Dis*. 1992;73:33–38.
98. Sirgel FA, Botha FJ, Parkin DP, et al. The early bactericidal activity of rifabutin in patients with pulmonary tuberculosis measured by sputum viable counts: a new method of drug assessment. *J Antimicrob Chemother*. 1993;32:867–875.
99. Botha FJ, Sirgel FA, Parkin DP, van de Wal BW, Donald PR, Mitchison DA. The early bactericidal activity of ethambutol, pyrazinamide, and the fixed combination of isoniazid, rifampicin, and pyrazinamide (Rifater) in patients with pulmonary tuberculosis. *S Afr Med J*. 1996;86:155–158.
100. Dickinson JM, Mitchison DA. Experimental models to explain the high sterilizing activity of rifampin in the chemotherapy of tuberculosis. *Am Rev Respir Dis*. 1981;123(4, Pt 1):367–371.
101. Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med*. 1990;112:397–406.
102. Khan A, Sterling TR, Reves R, Vernon A, Horsburgh CR. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. *Am J Respir Crit Care Med*. 2006;174:344–348.
103. Arend SM, Thijsen SF, Leyten EM, et al. Comparison of two interferon-gamma assays and tuberculin skin test for tracing tuberculosis contacts. *Am J Respir Crit Care Med*. 2007;175:618–627.
104. Diel R, Loddenkemper R, Meywald-Walter K, Gottschalk R, Nienhaus A. Comparative performance of tuberculin skin test, QuantiFERON-TB-Gold In Tube assay, and T-Spot. TB test in contact investigations for tuberculosis. *Chest*. 2009;135:1010–1018.
105. Schluger NW, Burzynski J. Recent advances in testing for latent TB. *Chest*. 2010;138:1456–1463.
106. Horsburgh CR, Rubin EJ. Latent tuberculosis infection in the United States. *N Engl J Med*. 2011;364:1441–1448.
107. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. *Am J Respir Crit Care Med*. 2003;168:443–447.
108. Horsburgh CR Jr, Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*.

2010;137:401–409.
109. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. *Am J Respir Crit Care Med*. 2004;170:445–449.
110. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2008;149:689–697.
111. Reichman LB, Lardizabal A, Hayden CH. Considering the role of four months of rifampin in the treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2004;170:832–835.
112. Fountain FF, Tolley EA, Jacobs AR, Self TH. Rifampin hepatotoxicity associated with treatment of latent tuberculosis infection. *Am J Med Sci*. 2009;337:317–320.
113. Holland DP, Sanders GD, Hamilton CD, Stout JE. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. *Am J Respir Crit Care Med*. 2009;179:1055–1060.
114. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–2166.
115. Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *Morb Mortal Wkly Rep*. 2011;60:1650–1653.
116. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174:935–952.
117. Moulding T. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis*. 1992;146:1643–1644.
118. Ellard GA. Variations between individuals and populations in the acetylation of isoniazid and its significance for the treatment of pulmonary tuberculosis. *Clin Pharmacol Ther*. 1976;19(5, Pt 2):610–625.
119. Ellard GA, Mitchison DA, Girling DJ, Nunn AJ, Fox W. The hepatic toxicity of isoniazid among rapid and slow acetylators of the drug. *Am Rev Respir Dis*. 1978;118:628–629.
120. Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *Am Rev Respir Dis*. 1978;117:991–1001.
121. Girling DJ. Adverse effects of antituberculosis drugs. *Drugs*. 1982;23:56–74.
122. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. *Chest*. 1991;99:465–471.
123. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic.

JAMA. 1999;281:1014–1018.
124. Centers for Disease Control and Prevention. Severe isoniazid-associated liver injuries among persons being treated for latent tuberculosis infection—United States, 2004–2008. *Morb Mortal Wkly Rep*. 2010;59:224–229.
125. Wright JM, Stokes EF, Sweeney VP. Isoniazid-induced carbamazepine toxicity and vice versa: a double drug interaction. *N Engl J Med*. 1982;307:1325–1327.
126. Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin and rifabutin drug interactions. *Am J Med Sci*. 2008;335:126–136.
127. Sanders WE Jr. Rifampin. *Ann Intern Med*. 1976;85:82–86.
128. Zierski M, Bek E. Side-effects of drug regimens used in short-course chemotherapy for pulmonary tuberculosis: a controlled clinical study. *Tubercle*. 1980;61:41–49.
129. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J Antimicrob Chemother*. 1977;3:115–132.
130. Lee CH, Lee CJ. Thrombocytopenia—a rare but potentially serious side effect of initial daily and interrupted use of rifampicin. *Chest*. 1989;96:202–203.
131. Berning SE, Iseman MD. Rifamycin-induced lupus syndrome. *Lancet*. 1997;349:1521–1522.
132. Bennett WM, Muther RS, Parker RA, et al. Drug therapy in renal failure: dosing guidelines for adults. Part I: antimicrobial agents, analgesics. *Ann Intern Med*. 1980;93:62–89.
133. Andrew OT, Schoenfeld PY, Hopewell PC, Humphreys MH. Tuberculosis in patients with end-stage renal disease. *Am J Med*. 1980;68:59–65.
134. Semvua HH, Kibiki GS, Kisanga ER, Boeree MJ, Burger DM, Aarnoutse R. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. *Ther Drug Monit*. 2015;37:22–32.
135. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet*. 2003;42:819–850.
136. Citron KM, Thomas GO. Ocular toxicity from ethambutol. *Thorax*. 1986;41:737–739.
137. Schild HS, Fox BC. Rapid-onset reversible ocular toxicity from ethambutol therapy. *Am J Med*. 1991;90:404–406.
138. Alvarez KL, Krop LC. Ethambutol-induced ocular toxicity revisited. *Ann Pharmacother*. 1993;27:102–103.
139. Van den Brande P. Revised guidelines for the diagnosis and control of tuberculosis: impact on management in the elderly. *Drugs Aging*. 2005;22:663–686.
140. Rajagopalan S, Yoshikawa TT. Tuberculosis in long-term-care facilities. *Infect Control Hosp Epidemiol*. 2000;21:611–615.

141. Stead WW, Lofgren JP, Warren E, Thomas C. Tuberculosis as an endemic and nosocomial infection among elderly in nursing homes. *N Engl J Med*. 1985;312:1483–1487.
142. Chan CH, Woo J, Or KK, Chan RC, Cheung W. The effect of age on the presentation of patients with tuberculosis. *Tuber Lung Dis*. 1995;76:290–294.
143. Rajagopalan S. Tuberculosis and aging: a global health problem. *Clin Infect Dis*. 2001;33:1034–1039.
144. van den Brande P, van Steenbergen W, Vervoort G, Demedts M. Aging and hepatotoxicity of isoniazid and rifampin in pulmonary tuberculosis. *Am J Respir Crit Care Med*. 1995;152(5, Pt 1):1705–1708.
145. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med*. 1993;328:527–532.
146. Berning SE, Huitt GA, Iseman MD, Peloquin CA. Malabsorption of antituberculosis medications by a patient with AIDS. *N Engl J Med*. 1992;327: 1817–1818.
147. Driver CR, Matus SP, Bayuga S, Winters AI, Munsiff SS. Factors associated with tuberculosis treatment interruption in New York City. *J Public Health Manag Pract*. 2005;11:361–368.
148. Di Perri G, Bonora S. Which agents should we use for the treatment of multidrug-resistant *Mycobacterium tuberculosis*? *J Antimicrob Chemother*. 2004;54:593–602.
149. Burgos M, Gonzalez LC, Paz EA, et al. Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. *Clin Infect Dis*. 2005;40:968–975.
150. Holtz TH, Sternberg M, Kammerer S, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. *Ann Intern Med*. 2006;144:650–659.
151. Winston CA, Mitruka K. Treatment duration for patients with drug-resistant tuberculosis, United States. *Emerg Infect Dis*. 2012;18:1201–1202.
152. Van Deun A, Maug AK, Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010;182:684–692.
153. Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med.* 2019;380:1201–1213.
154. Berning SE, Madsen L, Iseman MD, Peloquin CA. Long-term safety of ofloxacin and ciprofloxacin in the treatment of mycobacterial infections. *Am J Respir Crit Care Med*. 1995;151:2006–2009.
155. Peloquin CA, Berning SE, Huitt GA, Iseman MD. Levofloxacin for drug-resistant *Mycobacterium tuberculosis. Ann Pharmacother*. 1998;32: 268–269.
156. Codecasa LR, Ferrara G, Ferrarese M, et al. Long-term moxifloxacin in complicated tuberculosis patients with adverse reactions or resistance to first

line drugs. *Respir Med*. 2006;100:1566–1572.
157. Worley MV, Estrada SJ. Bedaquiline: a novel antitubercular agent for the treatment of multidrug-resistant tuberculosis. *Pharmacotherapy*. 2014;34: 1187–1197.
158. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med*. 2009;360:2397–2405.
159. Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother*. 2012;56:3271–3276.
160. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med*. 2014;371:723–732.
161. Pretomanid. Prescribing information. Accessed August 31, 2021. https://www.tballiance.org/sites/default/files/assets/Pretomanid_Full-Prescribing-Information.pdf
162. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Mycobacterium tuberculosis infection and disease. Accessed August 30, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/mycobacterium-tuberculosis-infection-and?view=full
163. Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am J Respir Crit Care Med*. 2007;175:737–742.
164. Dewan PK, Grinsdale J, Kawamura LM. Low sensitivity of a whole-blood interferon-γ release assay for detection of active tuberculosis. *Clin Infect Dis*. 2007;44:69–73.
165. Menzies D, Pai M, Comstock G. New tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research [published correction appears in *Ann Intern Med*. 2007;146:688]. *Ann Intern Med*. 2007;146:340–354.
166. Monkongdee P, McCarthy KD, Cain KP, et al. Yield of acid-fast smear and mycobacterial culture for tuberculosis diagnosis in people with human immunodeficiency virus. *Am J Respir Crit Care Med*. 2009;180:903–908.
167. Rich ML, Socci AR, Mitnick CD, et al. Representative drug susceptibility patterns for guiding design of retreatment regimens for MDR-TB. *Int J Tuberc Lung Dis*. 2006;10:290–296.
168. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs*. 2002;62:2169–2183.
169. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365:1471–1481.
170. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365:1482–1491.

171. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011;365:1492–1501.
172. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society—USA panel. *JAMA*. 2006;296:827–843.
173. López-Cortés LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet*. 2002;41:681–690.
174. Cohen K, Grant A, Dandara C, et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antivir Ther*. 2009;14:687–695.
175. Ramachandran G, Hemanth Kumar AK, Rajasekaran S, et al. CYP2B6 G516T polymorphism but not rifampin coadministration influences steady-state pharmacokinetics of efavirenz in human immunodeficiency virus-infected patients in South Africa. *Antimicrob Agents Chemother*. 2009;53:863–868.
176. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr.* 2013;62:21–27.
177. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet*. 1993;342:268–272.
178. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. *Br J Obstet Gynecol*. 2011;118:226–231.
179. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. *Obstet Gynecol Clin North Am*. 1997;24:659–673.
180. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. *Lancet*. 2003;362:887–899.
181. Vallejo JG, Starke JR. Tuberculosis and pregnancy. *Clin Chest Med*. 1992;13:693–707.
182. Bergeron KG, Bonebrake RG, Gray CJ. Tuberculosis in pregnancy: current recommendations for screening and treatment in the USA. *Expert Rev Anti Infect Ther*. 2004;2:589–598.
183. Shin S, Guerra D, Rich M, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: a report of 7 cases. *Clin Infect Dis*. 2003;36:996–1003.
184. Drobac PC, del Castillo H, Sweetland A, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. *Clin Infect Dis*. 2005;40:1689–1692.
185. Powell DA, Hunt WG. Tuberculosis in children: an update. *Adv Pediatr*. 2006;53:279–322.

186. American Academy of Pediatrics, Committee on Infectious Diseases. *2021 Red Book: Report of the Committee on Infectious Diseases*. 32nd ed. American Academy of Pediatrics; 2021.
187. Starke JR, Correa AG. Management of mycobacterial infection and disease in children. *Pediatr Infect Dis J*. 1995;14:455–470.
188. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. *Am Fam Physician*. 2005;72:1761–1768.
189. Garg RK. Tuberculosis of the central nervous system. *Postgrad Med J*. 1999; 75:133–140.
190. Holdiness MR. Cerebrospinal fluid pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet*. 1985;10:532–534.
191. Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal of the literature. *Clin Infect Dis*. 1997;25:872–887.
192. Heysell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA. *Emerg Infect Dis*. 2010;16:1546–1553.
193. Magis-Escurra C, van den Boogaard J, Ijdema D, Boeree M, Aarnoutse R. Therapeutic drug monitoring in the treatment of tuberculosis patients. *Pulm Pharmacol Ther*. 2012;25:83–86.
194. Babalik A, Babalik A, Mannix S, Francis D, Menzies D. Therapeutic drug monitoring in the treatment of active tuberculosis. *Can Respir J*. 2011;18:225–229.
195. Prahl JB, Johansen IS, Cohen AS, Frimodt-Møller N, Andersen ÅB. Clinical significance of 2 h plasma concentrations of first-line anti-tuberculosis drugs: a prospective observational study. *J Antimicrob Chemother*. 2014;69:2841–2847.
196. Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. *J Infect Dis*. 2013;208:1464–1473.
197. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs*. 2014;74:839–854.

69

Infectious Diarrhea

Rupali Jain and David T. Bearden

CORE PRINCIPLES		CHAPTER CASES
1	The most common complication of any diarrheal illness is loss of fluids and electrolytes, which in extreme cases can lead to hypovolemia, shock, and death. Depending on the degree of dehydration, fluid and electrolyte losses are replaced intravenously or orally.	**Case 69-1 (Questions 1, 2)**
2	Classification of infectious diarrheas as either an inflammatory or a noninflammatory diarrheal illness provides a basis for a focused list of suspected pathogens, thus guiding the overall diagnostic and therapeutic plan.	**Case 69-1 (Questions 3, 4)** **Case 69-4 (Question 1)** **Case 69-5 (Question 1)** **Case 69-6 (Question 1)** **Case 69-16 (Questions 1, 4)**
3	*Vibrio cholerae* 01 and 0139 are	**Case 69-2 (Questions**

	toxigenic strains of *Vibrio* species, which cause epidemic cholera; severe dehydration requiring vigorous fluid replacement may be necessary. Noncholera *Vibrio* species do not possess the virulence factors required to cause epidemic cholera. Antimicrobial treatment differs between toxigenic and nontoxigenic *Vibrio* species.	**1–3)** **Case 69-3 (Questions 1, 2)**
4	*Salmonella* species are classified as nontyphoidal and typhoidal salmonellae. Nontyphoidal salmonellae may cause the clinical syndromes of gastroenteritis, bacteremia, and localized infection, whereas typhoidal salmonellae may cause typhoid fever and chronic carriage. The role of antimicrobials in the management of salmonellosis is based on the clinical syndrome, its severity, and underlying health problems of infected persons.	**Case 69-7 (Question 1)** **Case 69-8 (Questions 1, 2)** **Case 69-9 (Question 1)** **Case 69-10 (Question 1)** **Case 69-11 (Questions 1–7)**
5	Severe dysentery caused by *Shigella* species is most commonly caused by *Shigella dysenteriae*, whereas a milder illness is typically caused by *S. sonnei*. Antimicrobials alleviate the symptoms of shigellosis and decrease the period of time that shigellae can be spread by person-to-person contact.	**Case 69-12 (Questions 1–5)** **Case 69-13 (Question 1)**
6	Fluoroquinolone resistance in *Campylobacter* species is a common finding in both developed and underdeveloped areas of the world;	**Case 69-14 (Questions 1–3)**

	when indicated, macrolide antimicrobials are recommended.	
7	Travelers to destinations where acquisition of travelers' diarrhea (TD) is a concern should bring a travel kit including medications (eg, loperamide and antimicrobials) and instructions for self-treatment at the onset of illness. The selected antimicrobial depends on the area of travel. Long-term postinfectious complications of TD may occur in some returning travelers.	**Case 69-15 (Questions 1–6)**
8	*Escherichia coli* O157:H7 is a specific toxin-producing strain of *E. coli* bacteria that can lead to the severe sequelae of hemolytic uremic syndrome.	**Case 69-16 (Questions 2, 3)**
9	*Clostridioides difficile* infection causes a wide range of severity of illness. Most cases are treated orally with vancomycin or fidaxomicin as first-line therapy.	**Case 69-17 (Questions 1-8)** **Case 69-18 (Questions 1, 2)** **Case 69-20 (Questions 1, 2)**
10	Severe *C. difficile* infection can be life-threatening and often necessitates multiple therapeutic interventions.	**Case 69-19 (Questions 1, 2)**

INTRODUCTION

Worldwide, diarrhea accounts for >2.5 million deaths annually,[1],[2] mainly affecting infants and children lacking access to clean water and improved sanitation.[3] Prolonged episodes of diarrhea lead to dehydration and malnutrition, and in children contribute to impaired

growth and developmental delay and death.[3] In the United States, about 178 million foodborne diarrheal illnesses occur each year, resulting in ~473,000 hospitalizations and 5000 deaths.[4]

Infectious diarrhea is primarily caused by the ingestion of food or water contaminated with pathogenic microorganisms (eg, bacteria, viruses, protozoa, or fungi) or their toxins (**Table 69-1**).[3] In the United States, noroviruses account for about 59% of diarrheal outbreaks, whereas common bacterial pathogens include *Campylobacter*, nontyphoidal *Salmonella*, *Shigella*, and Shiga toxin–producing *Escherichia coli*.[5]

Table 69-1
Exposures, Symptoms, and Therapy for Gastrointestinal Infections

Pathogen	Exposures	Symptoms	Diagnostic Evaluations	Drug of Choice[a,b]	Alternatives[a,b]
Salmonella (nontyphoidal)[c]	Ingestion of contaminated poultry, unpasteurized milk, juices, vegetables custards, and cream fillings; foreign travel	Nausea, vomiting, diarrhea, cramps, fever, tenesmus *Incubation*: 6–72 hours	Stool culture, NAAT	Supportive therapy only	
Salmonella (typhoidal)	Ingestion of contaminated food; uncooked eggs, foreign travel	High fever, abdominal pain, headache, dry cough, blood in stool	Stool culture, blood culture	Fluoroquinolone, third-generation cephalosporins	TMP-SMX, amoxicillin, or azithromycin
Shigella	Ingestion of contaminated salad, raw vegetables, swimming in water contaminated with sewage; foreign travel	Fever, dysentery, cramps, abdominal pain tenesmus; blood in stool *Incubation*: 24–48 hours	Stool culture or NAAT	Fluoroquinolone, azithromycin, ceftriaxone	TMP-SMX, ampicillin, if susceptible
Campylobacter	Contaminated eggs, raw milk, or poultry; foreign travel	Mild-to-severe diarrhea; blood in stool fever, systemic malaise *Incubation*: 24–72 hours	Stool culture or NAAT	Azithromycin	Ciprofloxacin
Clostridioides difficile	Antibiotics, antineoplastics	Mild-to-severe diarrhea, cramps	NAAT, GDH antigen with or without toxin detection	Oral vancomycin or fidaxomicin	Metronidazole (for mild cases)
Staphylococcal food poisoning	Custard-filled bakery products, canned food, processed meat, ice cream	Nausea, vomiting <24 hours, salivation, cramps, diarrhea; usually resolves in 8 hours *Incubation*: 2–6 hours	—	Supportive therapy only	—
Travelers' diarrhea (enterotoxigenic *Escherichia coli*, *Campylobacter*)	Contaminated food (vegetables and cheese), water; travel	Nausea, vomiting, mild-to-severe diarrhea, cramps	—	See Table 69-3	—
Shiga toxin–producing *Escherichia coli* (*E. coli* O157:H7)	Beef, raw milk, water	Diarrhea, headache, bloody stools *Incubation*: 48–96 hours	Stool cultures on MacConkey's sorbitol, molecular assays, NAAT	Supportive therapy only	—
Cryptosporidiosis	Immunosuppression, day care centers, contaminated water, animal handlers	Mild-to-severe diarrhea (chronic or self-limited); large fluid volume	Stool screening for oocytes, NAAT, EIA	See Chapter 77, Opportunistic Infections in Patients Living With HIV	—
Viral gastroenteritis (norovirus)	Community-wide outbreaks, contaminated food	Nausea, diarrhea (for 2–3 days), cramps *Incubation*: 16–48 hours	NAAT	Supportive therapy only	—

EIA, enzyme-linked immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; TMP-SMX, trimethoprim–sulfamethoxazole.

[a]Sources: Navaneethan U, Giannella RA. Mechanisms of infectious diarrhea. *Nat Clin Pract Gastroenterol Hepatol.* 2008;5:637–647; DuPont HL. Acute infectious diarrhea in immunocompetent adults. *N Engl J Med.* 2014;370:1532; Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65(12):e45–e80. See text for doses and duration of therapy.

[b]If susceptible. See text for details.

[c]Not all cases require antibiotic therapy. See text for details.

This chapter focuses on the diagnosis and management of the common microbial causes of acute infectious diarrhea in the United States.

DEFINITIONS

Diarrhea is often defined as three or more episodes of loose stools or any loose stool with blood during a 24-hour period, which may be accompanied by nausea, vomiting, or abdominal cramping.[5] The duration of illness is considered acute if symptoms are present for <2 weeks' duration, persistent if symptoms last for 14 to 29 days, and chronic if symptoms last ≥30 days.[5] The clinical presentation (eg, the specific symptoms, the severity, and duration of symptoms), along with the history of present illness (eg, risk factors for infection), allows for the classification of diarrheal syndromes as noninflammatory versus inflammatory illnesses. Such a classification allows the physician to consider a more focused list of potential enteropathogen(s), and based on the list of suspected organisms, a diagnostic and therapeutic plan can be developed.[1]

PATHOGENESIS

The pathogenesis of infectious diarrhea involves an interplay among bacterial virulence factors, host factors, and predisposing factors to infection. Diarrhea is more likely to occur in the setting in which an imbalance among these factors favors the enteropathogen.

Bacterial Virulence Factors

Enteropathogens possess various virulence factors that contribute to the organism's pathogenicity.[3] Enterotoxins targeting the small bowel cause net movement of fluid into the gut lumen, leading to

voluminous watery stools and potentially life-threatening dehydration. Cytotoxins targeting the colon cause direct mucosal damage, leading to fever and bloody diarrhea. Invasive properties of *Shigella* species and invasive strains of *E. coli* allow these bacteria to invade and destroy epithelial cells in the distal small bowel and colon, causing bloody or mucoid stools. Some enteropathogens induce a vigorous host response through the release of proinflammatory cytokines from intestinal epithelial cells, leading to diarrhea. Finally, enteropathogens attach and colonize the gastrointestinal (GI) mucosa, facilitating toxin delivery, invasion, dissemination, or host cell lysis.[3]

Host Defenses

The human GI tract possesses numerous defense mechanisms to protect against enteric infection. Normal bacterial flora compete for space and nutrients with potentially pathogenic organisms or produce substances, for example, short-chain fatty acids, that are inhibitory to enteropathogens.[3] Gastric acidity of the stomach prevents acid-susceptible pathogens from passing from the stomach into the intestinal tract, whereas GI mucus and mucosal tissue integrity provide physical barriers against infection. Intestinal immunity includes defensins that are bactericidal to some enteropathogens, local production of antibodies, and toll-like receptors that recognize enteropathogens and activate the immune response.[3] Intestinal peristalsis moves bacteria and their toxins along and out of the GI tract. Finally, specific host genetic factors are protective against enteric infection.[5]

Predisposing Factors

Inadequate sanitation facilities increase the risk that local inhabitants and travelers will be exposed to contaminated food and water. Outbreaks of foodborne or waterborne illnesses in both industrialized and developing countries facilitate the spread of infectious

organisms. Industrialized countries that rely on imported food items risk the possibility of importation of contaminated food products.[6] Immunocompromised hosts, such as organ transplant recipients and patients receiving immunosuppressive therapies, are more susceptible to intestinal infection. Congregate settings such as day care centers, hospitals, and extended-care facilities are high-risk settings for dissemination of disease. Other risk factors include global travel, animal exposure (in public venues), and certain sexual practices.[7]

The use of pharmacologic agents, for example, drugs that increase gastric pH, increases the risk of infection with acid-susceptible pathogens such as *Salmonella* species and *Vibrio cholerae*.[7]

MANAGEMENT OVERVIEW

Rehydration Therapy

The most acute diarrhea episodes in healthy, immunocompetent people are of limited duration and are usually self-resolving.[7] The most common complication of any diarrheal illness is loss of fluids and electrolytes, which in extreme cases can lead to hypovolemia, shock, and death.[1] Depending on the degree of dehydration, fluid and electrolyte losses are replaced intravenously or orally. Once replacement of fluid and electrolyte losses is completed, additional laboratory tests and drug therapies can be considered.

Laboratory Tests

Inflammatory diarrheal illnesses are characterized by the presence of bloody or mucoid stools. Therefore, stool specimens with red blood cells (RBCs) or occult blood, or those that contain large numbers of white blood cells, suggest infection attributable to invasive pathogens.[8]

Identification of bacterial toxins in stool specimens is a useful diagnostic tool. For example, only the toxigenic strains of *Clostridioides difficile* are pathogenic, so the presence or absence of bacterial toxins in stool specimens is more important than is a positive culture for the organism.[9]

In clinical practice, routine microbiologic identification of pathogens utilizes selective media that favor the growth of suspected pathogens.[9] Stool cultures are recommended for patients with one of the following: acute diarrhea that is severe or associated with a temperature >101.3 °F (38.5 °C); dysentery—which is an inflammatory diarrheal illness characterized by bloody or mucoid stools with abdominal cramps; profuse cholera-like watery diarrhea; dehydration; elderly or immunocompromised patients; patients in nursing homes; food handlers; and day care workers.[5] Hospitalized patients and those with recent antimicrobial exposure should be evaluated for *Clostridioides difficile* infection (CDI). Culture results of specimens from extraintestinal sites of infection (eg, blood cultures) can be used to identify the microbial etiology, especially in young children and immunocompromised hosts.

Polymerase chain reaction (PCR)-based diagnostic tests are widely available, offering improved sensitivity but focusing on genes versus virulence factors.[5]

Drug Therapy

Drug therapy for infectious diarrhea includes medications to provide symptomatic relief or to eradicate the causative pathogen.

LOPERAMIDE AND DIPHENOXYLATE/ATROPINE

Loperamide and diphenoxylate/atropine reduce the frequency of diarrheal stools by slowing intestinal transit time; in addition, loperamide possesses antisecretory properties.[10] Loperamide is preferred over diphenoxylate/atropine because of its greater efficacy, better tolerance, and over-the-counter availability. Diphenoxylate/atropine causes drowsiness, dizziness, dry mouth,

and urinary retention owing to the atropine component, and its use in the elderly is not recommended (see Chapter 107, Geriatric Drug Use).

The use of antimotility drugs is not recommended in persons with fever, bloody diarrhea,[5] or when invasive pathogens are suspected.[1] The primary concern is that prolongation of clearance of pathogens from the intestinal tract could worsen the severity of the illness. However, in patients who are not critically ill with bacillary dysentery, loperamide was not harmful when administered with antimicrobials to which the infecting pathogen was susceptible.[11]

BISMUTH SUBSALICYLATE

Bismuth subsalicylate's (BSS) antidiarrheal properties comprise antisecretory, adsorbent, and antimicrobial properties.[12] Problems with BSS include the inconvenience of dosing four times per day and adverse effects such as darkening of the tongue and stools, possible tinnitus, and GI bleeding risk secondary to its high salicylate component and absorption. Each recommended antidiarrheal dose of BSS of 526 mg contains 263 mg of salicylate, and this needs to be considered in patients already taking salicylate products.

PROBIOTICS

There has been growing interest in probiotic supplementation and its effect on intestinal microbiology. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits on the host (eg, restoring normal intestinal flora as a natural defense against intestinal colonization with pathogens and inhibiting the action of microbial toxins).[13] They are not regulated in the United States or Europe in a manner similar to that of pharmaceutical agents. The most commonly available and studied probiotics include the *Lactobacillus* and *Bifidobacterium* genera as well as *Lactococcus* species, and the yeast, *Saccharomyces boulardii.* The variability of the probiotic formulations and the inconsistent analytic rigor of the studies with varying methodologies and clinical end points have led to the lack of

definitive indication for probiotics.[13] Currently, the American Gastrointestinal Association recommends against the routine use in children with acute infectious diarrhea,[14] whereas other associations recommend probiotics for this indication.[7],[15] Probiotics are generally safe in healthy adults, but their use has been associated with a higher risk of infection in young infants and neonates with very low birth weight, critically ill adults and infants, and immunosuppressed individuals.[15]

ANTIMICROBIALS

In selected cases, antimicrobials are prescribed to decrease the duration and the severity of diarrheal illnesses, to prevent the progression to invasive infection, and to prevent person-to-person transmission of pathogens. Antimicrobials are generally recommended for the severely ill, for patients with conditions compromising normal enteric defenses, for immunocompromised patients, and for the treatment of extraintestinal infection.[5]

Ongoing surveillance of antimicrobial resistance is important to guide treatment recommendations. Extensively used in the past and resulting in widespread resistance to common enteropathogens, trimethoprim–sulfamethoxazole (TMP-SMX), the aminopenicillins, nalidixic acid, and tetracyclines are unsuitable empiric choices for the treatment of many enteropathogens. Depending on the circumstances surrounding the diarrheal illness, including where the pathogen was acquired (eg, domestic vs travel related), age, and allergy history of the patient, commonly recommended antimicrobials include selected third-generation cephalosporins (eg, ceftriaxone or cefotaxime), azithromycin, rifaximin, fluoroquinolones, and others.[5]

The fluoroquinolones, although still recommended because of their efficacy against susceptible organisms[5] and their availability as oral formulations, must be used cautiously because common enteropathogens, for example, *Shigella*, *Salmonella*, and *Campylobacter* species, are frequently fluoroquinolone resistant.[16] Another consideration with using fluoroquinolones is that they are not U.S. Food and Drug Administration (FDA) approved for use in

children because lesions on cartilage tissue have been reported in juvenile animals. Nevertheless, because of the emergence of multidrug-resistant (MDR) enteropathogens in some geographic areas, clinical trials using fluoroquinolones in children have been performed,[17] and the available data suggest that a short course of these agents is safe. Finally, all antimicrobial use should be limited to instances where their benefits outweigh their risks for adverse effects and furthering antimicrobial resistance.

Prevention

Good personal hygiene along with proper food handling, cooking, and storage are essential to prevent the spread of enteropathogens. When visiting areas with inadequate facilities for the disposal of sewage, travelers should follow the rule, "boil it, cook it, peel it, or forget it." Effective vaccines are available to prevent typhoid fever, rotavirus, and cholera.[1] To prevent spread to other individuals, people with diarrhea who attend or work in child care, long-term care centers, patient care, food service, or recreational water venues should follow local public health guidance and public health reporting requirements.[7]

EVALUATION AND TREATMENT OF PATIENTS WITH INFECTIOUS DIARRHEA

CASE 69-1

Question 1: B.K. is a 78-year-old male presenting to his physician with a diarrheal illness for 1 day. His illness began with vomiting, followed by abdominal pain, nausea, and watery, nonbloody diarrhea. Despite not feeling well, he is able to drink fruit juices. B.K.'s history of present illness is significant for eating a potato salad at a picnic, and he has since learned that other picnic guests are experiencing a similar illness. B.K. has no significant medical history. He denies recent hospitalization, contact with small children, recent travel, or recent use of antimicrobials. On physical examination, B.K. is alert and oriented,

afebrile, and has stable vital signs. The remainder of his examination is significant for decreased skin turgor and dry mucous membranes.

What is your general approach to the management of B.K.'s diarrheal illness?

Because infectious diarrhea is typically a self-limiting illness, patients may never seek medical attention, and, in many cases, replacement of fluids and electrolytes is all that is required. In general, medical evaluation is warranted for patients with profuse watery diarrhea with dehydration, bloody stools, temperature >101.3 °F (38.5 °C), or illness of >48 hours' duration. Other persons requiring medical evaluation include patients older than age 50 years with severe abdominal pain and immunocompromised patients (eg, those with acquired immunodeficiency syndrome, organ transplant recipients, or patients being treated with cancer chemotherapies). Noninfectious causes for the illness such as medications (eg, laxatives), inflammatory bowel disease, consumption of poorly absorbable carbohydrates (eg, sugarless candies or chewing gum), or malabsorption syndromes should also be considered.[8]

Case 69-1, Question 2: What rehydration plan would you recommend for B.K.?

B.K.'s physical examination is significant for decreased skin turgor and dry mucous membranes, findings consistent with mild-to-moderate volume depletion.[18] Given that B.K. has stable vital signs, and is tolerating oral liquids, oral beverages containing glucose (eg, lemonades, sweet sodas, or fruit juices) or soups rich in electrolytes are appropriate.[19] In developing countries, reductions in dehydration-related mortality are attributed to the utilization of oral replacement therapy solutions containing optimal concentrations of sodium, potassium, chloride, bicarbonate, and glucose; the glucose content of these solutions is responsible for accelerating the absorption of sodium.[7]

IV replacement therapy is warranted for severe dehydration—characterized by lethargy; very sunken and dry eyes; a very dry tongue and mouth; poor skin turgor; a pulse that is fast, weak, or

nonpalpable; poor urine output; and low blood pressure or for persons with intestinal ileus or who are unable to drink on their own.[18]

CLINICAL PRESENTATION

CASE 69-1, QUESTION 3: How does B.K.'s clinical presentation as a noninflammatory versus inflammatory diarrheal illness help guide further treatment?

Classifying diarrheal syndromes as either a noninflammatory (watery diarrhea) or an inflammatory (bloody diarrhea, dysentery) illness provides a basis for predicting the most likely microbial cause for the intestinal illness.[1]

B.K.'s history of present illness and clinical presentation are consistent with a noninflammatory diarrheal illness. Voluminous, watery, nonbloody diarrhea is characteristic of pathogens targeting the small bowel (responsible for absorption of most fluids entering the GI tract), and it is a consequence of bacterial enterotoxins that promote the secretion of water and electrolytes into the intestinal lumen or of viruses infecting and damaging the absorptive villus tips.[9] Noninflammatory diarrheas are typically caused by viruses (eg, rotaviruses and noroviruses), bacteria (eg, *Staphylococcus aureus*, *Bacillus cereus*, and *C. perfringens)*, or parasites (eg, *Cryptosporidium parvum* and *Giardia lamblia*).[1] As with B.K., patients with noninflammatory diarrheal illnesses are not usually severely ill, are afebrile, and without significant abdominal pain[3],[9]; most patients require only supportive therapies.

In contrast, inflammatory diarrheas are generally a more severe illness characterized by diarrhea (with or without dysentery), abdominal pain, and fever.[3] Pathogens targeting the distal small bowel and colon disrupt the epithelial barrier, causing the bloody or mucoid stools.[3] The clinical manifestations are a consequence of the production of cytotoxins (eg, as produced by *C. difficile*, Shiga toxin–

producing *E. coli*, and enteroaggregative *E. coli*), or of the pathogen's ability to invade the intestinal mucosa (eg, *Campylobacter jejuni*, *Shigella* species, and *Salmonella* species).[20] In addition to supportive therapies, selected persons with inflammatory diarrheal illnesses may benefit from antimicrobial therapy directed at the causative pathogen.

VIRAL GASTROENTERITIS

Clinical Presentation and Treatment

CASE 69-1, QUESTION 4: With B.K.'s history of dining at the same restaurant as other patrons having a similar illness, the physician calls the local Health Department to find out if similar illnesses are being reported throughout the city. The physician is informed that an outbreak of norovirus (previously called Norwalk-like virus) gastroenteritis was confirmed at the restaurant where B.K. had dined. Why is B.K.'s history of present illness and clinical presentation consistent with the presumptive diagnosis of viral gastroenteritis, specifically the norovirus? What supportive therapies are recommended?

Noroviruses are responsible for major outbreaks of foodborne viral illnesses in both adults and children, usually in association with restaurants, schools, day care centers, and cruise ships. The virus is spread by eating contaminated foods (eg salads, sandwiches), inadequately cooked clams and oysters harvested from contaminated waters, by person-to-person contact, or by exposure to contaminated recreational waters.[21] As with B.K., within 12 to 48 hours of exposure to the virus, patients report nausea, vomiting, diarrhea, and abdominal cramps. B.K. will likely experience a mild intestinal illness lasting 1 to 3 days. Supportive therapies to correct fluid and electrolyte losses and to replace ongoing losses are the mainstay of treatment for viral gastroenteritis. Preventing future outbreaks will require the restaurant to ensure proper food-handling practices.[21]

Other common causes of viral gastroenteritis are rotaviruses and astroviruses that are responsible for 30% to 60% of all cases of severe, watery diarrhea in children. After an incubation period of 1 to 3 days, patients experience fever, vomiting, and nonbloody, watery diarrhea; otherwise healthy persons are typically ill for 5 to 7 days.

In the United States, two oral rotavirus vaccines are available for the prevention of rotavirus gastroenteritis in infants and children, a pentavalent (three-dose series) and a monovalent (two-dose series). Vaccine effectiveness in high- and upper-middle-income countries ranges from 79% to 100%, with the benefit of vaccination outweighing vaccine risks, for example, intussusception (when a part of the intestine folds into another adjacent part of the intestine, referred to as *telescoping*, which can lead to intestinal obstruction).[22] Because rotaviruses are spread by the fecal–oral route, proper handwashing and disposal of contaminated items are essential to limit the spread of infection.

VIBRIO SPECIES

Vibrio species are curved gram-negative rods whose natural habitats are the environmental waters throughout the world. *V. cholerae* 01 and 0139 are noninvasive enteropathogens responsible for epidemic cholera in humans. The ongoing seventh cholera pandemic began in 1961, subsequently spreading through Asia to Africa, Europe, and Latin America.[7] Prevention of cholera relies on the provision of safe drinking water and adequate sanitation. Cholera vaccines are not routinely incorporated into cholera control efforts, in part related to financial and logistical reasons.[7] Noncholera *Vibrio* species (eg, *V. parahaemolyticus*) do not possess the virulence factors required to cause epidemic cholera but do cause gastroenteritis, wound infections, and, in susceptible hosts, fulminant sepsis.[23] A live-attenuated, oral cholera vaccine is available in the United States for adults ages 18 to 64 who are traveling to endemic areas.[24]

Vibrio cholerae

RISK FACTORS AND CLINICAL PRESENTATION

CASE 69-2

QUESTION 1: M.M. is a 50-year-old male hospitalized for severe watery diarrhea, vomiting, muscle cramping with weakness, and confusion, notably unable to recognize his family members. His history of present illness is significant for returning 1 day ago from Haiti where he visited his relatives, several of whom were recovering from diarrheal illnesses caused by *V. cholerae*. Approximately 24 hours before admission, he noted the onset of watery diarrhea and immediately began drinking the oral rehydrating solution remaining from his trip to Haiti. However, over the past several hours he has been unable to drink on his own, and his family noticed "white flecks" in his stools. M.M. lives in Florida, and his past medical history is significant for peptic ulcer disease for which he takes a proton-pump inhibitor.

In the emergency department (ED), M.M.'s vital signs are as follows: afebrile, blood pressure is 70/40 mm Hg, and heart rate is 130 beats/minute. Physical examination reveals a severely ill-appearing male with altered mental status, sunken eyes, poor skin turgor, and dry mucous membranes. The physician's assessment is severe dehydration because of massive diarrhea, most likely caused by *V. cholerae*.

What are his risk factors for cholera and why is his clinical presentation consistent with this diagnosis?

Risk factors

M.M. has two risk factors to explain his presumed diagnosis of cholera.[25] In developed countries, cholera has been virtually eliminated because of water and sewage treatment systems. However, sporadic cases, similar to M.M.'s, occur in travelers returning from areas where cholera is epidemic or endemic, or from the consumption of contaminated and undercooked seafood (eg, improperly preserved fish, raw oysters, and shellfish) from the waters off the Gulf Coast states or imported from endemic areas.[26] Second, M.M.'s daily use of a proton-pump inhibitor reduces his stomach's acidity, thus allowing the acid-susceptible *V. cholerae* to pass from the stomach into the small intestine.[7]

Clinical presentation

Cholera epidemics are caused by toxin-producing strains of *V. cholerae* 01 or 0139.[7] The characteristic voluminous, watery, and colorless stools with "white flecks" of mucus (referred to as rice-water stools because of their similarity to the appearance of water after washing rice) are caused by the cholera toxin that promotes the intestinal secretion of fluids and electrolytes.[7]

The severity of cholera and likelihood of infection is influenced by host factors and the setting in which it occurs.[7] Severe disease is more common in previously unexposed persons such as M.M. who are immunologically naive (eg, epidemic cholera), whereas less severe disease occurs in areas where cholera is endemic.[7] Following ingestion of contaminated foods, a watery diarrheal illness begins within 18 hours to 5 days and may progress to life-threatening dehydration.[7]

TREATMENT

Case 69-2, Question 2: What are the signs and symptoms suggesting that M.M. is severely dehydrated, and how should his dehydration be treated?

M.M. is one of the 2% to 5% of persons with *V. cholerae* infection who experience severe dehydration (≥10% dehydration), losing up to 1 L/hour of fluid, and whose condition may, within hours, progress to hypovolemic shock and death.[7] M.M. shows signs of severe dehydration as manifested by his altered mental status, sunken eyes, poor skin turgor, dry mucous membranes, low blood pressure, and increased heart rate. Acidosis may occur as a result of massive bicarbonate losses through diarrheal stools, and it may be exacerbated by lactic acidosis from shock and hypovolemic renal failure.[7] M.M. should receive vigorous IV hydration with lactated Ringer solution to replace the large quantities of sodium, potassium, and bicarbonate lost through his watery stools; his muscle weakness could be attributed to depletion of electrolytes, specifically potassium

and calcium.[7] Monitoring of blood pressure and normalization of heart rate are critical interventions.

Once M.M. is able to drink fluids, oral hydration can be started, even with ongoing IV hydration.[7] Oral rehydration solutions can be made by mixing together 1/2 tsp salt, 6 tsp sugar, and 1 L of safe water.[7]

CASE 69-2, QUESTION 3: Would M.M. benefit from the administration of antimicrobials, and what antimicrobial treatment options are available?

Antimicrobials are recommended for patients with moderate-to-severe dehydration from cholera infection.[7] Effective antimicrobial therapy decreases the volume of diarrheal losses, reduces the volume of stool, and reduces the period of shedding infectious organisms.[7] Antimicrobials should be administered after the initial fluid deficit has been corrected and, if applicable, after vomiting has resolved.[7]

Antimicrobials

If susceptible, the following single- and multiple-dose regimens are effective treatments for *V. cholerae*; single-dose regimens are preferred because of their ease of administration, and compared to multiple doses of erythromycin, they are better tolerated.[7],[27]

- Adults: doxycycline 300 mg PO × 1 dose, or azithromycin 1 g PO × 1 dose, or ciprofloxacin 500 mg PO twice a day × 3 days
- Children: ciprofloxacin 15 mg/kg/dose PO twice a day × 3 days, or azithromycin 20 mg/kg PO × 1 dose. Pediatric doses should not exceed maximum adult doses.

For M.M., a single 300-mg PO dose of doxycycline is a good empiric choice because the strain of *V. cholerae* circulating in Haiti is currently susceptible to tetracycline (indicative of susceptibility to doxycycline).[28] Empiric ciprofloxacin is not recommended because the circulating strain in Haiti has reduced susceptibility to ciprofloxacin.[29] In addition, until M.M. has recovered from this

cholera infection, he should refrain from taking his proton-pump inhibitor because it reduces his stomach's acidity, allowing for the acid-susceptible *V. cholerae* to pass from the stomach to the small intestine.

Vibrio parahaemolyticus

CLINICAL PRESENTATION

CASE 69-3

QUESTION 1: C.T. is a 45-year-old male presenting to his physician with 1 day of nonbloody, watery diarrhea. Two days before his illness, he ate raw oysters at a restaurant specializing in fresh local seafood. C.T. lives along the coast of Florida and has no significant medical history. His physical examination reveals no evidence of dehydration.

Why is C.T.'s history of present illness and clinical presentation consistent with noncholera *Vibrio* gastroenteritis?

A key piece of information from C.T.'s history of present illness consistent with the presumptive diagnosis of noncholera *Vibrio* gastroenteritis is the consumption of raw oysters harvested from the coastal areas of Florida, where *V. parahaemolyticus* species have been identified. Diarrhea, abdominal cramps, nausea, vomiting, and fever begin after a median incubation period of 17 hours (range, 4–90 hours); bloody diarrhea occurs in 9% to 29% of cases.[23]

TREATMENT

CASE 69-3, QUESTION 2: Should a course of antibiotics be prescribed for C.T.?

In otherwise healthy adults such as C.T., *V. parahaemolyticus* gastroenteritis is usually a mild, self-limiting illness lasting for a median of 2 to 6 days.[23] There are no data to support the benefit of antibiotics in this setting, although patients with diarrhea lasting >5 days may benefit from treatment with tetracycline or a

fluoroquinolone; doxycycline 100 mg PO every 12 hours and ceftriaxone have also been recommended.[7,23]

Individuals with liver disease or alcoholism are at risk for severe *Vibrio* infections including bacteremia[23]; such individuals should avoid eating raw or undercooked shellfish, and avoid exposure of open wounds to seawater especially during the warmer months when water temperatures favor the growth of *Vibrio* species. Infectious diarrhea caused by *Vibrio* species should be reported to local and/or national reporting mechanisms.[7]

STAPHYLOCOCCUS AUREUS, BACILLUS CEREUS, AND *CLOSTRIDIUM PERFRINGENS*

S. aureus, *B. cereus*, and *C. perfringens* are important causes of toxin-mediated foodborne illnesses. GI symptoms typically begin within 24 hours of the ingestion of contaminated foods, which is in contrast to the longer incubation periods for illnesses caused by *Salmonella*, *Shigella*, and *Campylobacter* species. *B. cereus* causes two different intestinal syndromes: the short-incubation disease characterized by vomiting and a long-incubation disease characterized by a diarrheal illness.[1,30]

Clinical Presentation and Treatment

CASE 69-4

QUESTION 1: S.A. is an otherwise healthy 23-year-old college student who presents to the Student Health Center with an acute GI illness after eating at the school cafeteria. S.A. recalled eating a salad and cream-filled pastries and stated that within 3 hours she felt nauseous and began vomiting.

Why is S.A.'s history of present illness and clinical presentation consistent with food poisoning caused by *S. aureus* or *B. cereus*?

Foodborne illnesses are often grouped by their usual incubation period: <6 hours, 8 to 16 hours, and >16 hours.[30] The rapid onset (within 6 hours) of S.A.'s intestinal symptoms after eating suggests the illness is caused by preformed toxins, such as those produced by *S. aureus* or *B. cereus* (short-incubation disease form, emetic syndrome). Diarrhea and abdominal cramps may also occur. Although cooking kills the toxin-producing bacteria, it does not destroy toxin that has already been produced. Foods implicated in staphylococcal food poisoning include salads, cream-filled pastries, and meats, whereas foods implicated in *B. cereus* food poisoning generally include fried rice, dried foods, and dairy products.[30]

CASE 69-5

QUESTION 1: C.P. is also an otherwise healthy 22-year-old college student presenting to the same Student Health Center as S.A. (see Case 69-4) with an acute GI illness. C.P. recalled having lunch at the cafeteria, selecting a fish and poultry meal. Approximately 10 hours after eating, she experienced diarrhea and abdominal cramps.

Why is C.P.'s history of present illness and clinical presentation consistent with food poisoning caused by *C. perfringens* or *B. cereus*? Should empiric antibiotics be prescribed to either of these students?

In contrast to S.A., the longer incubation period before the onset of symptoms is consistent with illness caused by *C. perfringens* or *B. cereus* (long-incubation disease form, diarrheal syndrome). These bacteria are associated with an incubation period of 8 to 16 hours and symptoms of diarrhea and abdominal cramps; vomiting is not a prominent symptom in these illnesses.[30]

C. perfringens or *B. cereus* (long-incubation disease) produce heat-labile toxins after the ingestion of contaminated foods, explaining the longer incubation period compared with illness caused by the ingestion of preformed toxins. Foods implicated in *C. perfringens* food poisoning include improperly stored beef, fish, poultry dishes, pasta salads, and dairy products, whereas foods implicated in long-incubation *B. cereus* food poisoning include meats, vanilla sauce, cream-filled baked goods, and salads.[30]

Foodborne illnesses caused by these toxin-producing bacteria usually resolve within 24 hours; therefore, antibiotic therapy is not indicated for either student.

CRYPTOSPORIDIUM PARVUM

The protozoan parasite *C. parvum* is an important cause of human intestinal illness in both healthy and immunocompromised persons.[31] The role of antiprotozoal agents and the clinical response to antiprotozoal therapy depends on the competence of the host's immune system.

Clinical Presentation

CASE 69-6

QUESTION 1: C.K. is a 35-year-old, previously healthy male presenting to his physician with 15 days of watery diarrhea and a 5-pound (2.27-kg) weight loss. He is concerned that his illness is related to the announcement by the local Health Department notifying the community of an outbreak of cryptosporidiosis from contaminated water supplies.

Why is C.K.'s history of present illness and clinical presentation consistent with cryptosporidiosis? Should antiprotozoal agents be prescribed to treat cryptosporidiosis in otherwise healthy persons such as C.K.?

C.K. is presenting with persistent diarrhea, that is, diarrhea lasting >14 days. A key finding from C.K.'s history is his exposure to water supplies known to be contaminated with cryptosporidium oocysts; other modes of spreading cryptosporidiosis include animal contact (cattle and sheep) and person-to-person contact.[31] Common microbial causes of persistent watery diarrhea include parasites, such as *Isospora belli*, *Microsporidia*, *G. lamblia*, and *C. parvum*. The spectrum of infection with *C. parvum* ranges from asymptomatic carriage to a persistent, noninflammatory diarrheal illness; vomiting, abdominal cramps, weight loss, and fever may also occur.[31]

Immunocompetent patients such as C.K. can generally expect a self-limiting illness lasting ~2 weeks.[31]

In contrast, in immunocompromised patients (historically in many patients infected with the human immunodeficiency virus [HIV]) and in children, cryptosporidiosis can be a chronic, debilitating, diarrheal illness associated with malnutrition, increased mortality, and long-term cognitive impairment.[32]

Treatment

For immunocompetent hosts with cryptosporidiosis, other than replacement of fluids and electrolytes no specific therapy directed at the organism is generally required. Nitazoxanide, a broad-spectrum antiparasitic, is an FDA-approved treatment for diarrhea caused by *C. parvum and G. lamblia,* including for children older than age 1 year. In adults, a dose of nitazoxanide 500 mg PO twice daily for 3 to 14 days is recommended for the treatment of cryptosporidiosis.[31] The efficacy of nitazoxanide in malnourished children and patients with HIV is limited.

For persons infected with HIV, reconstitution of the immune system with effective antiretroviral therapies is the mainstay of treatment for cryptosporidiosis.[33]

SALMONELLA

Salmonellae are enteric gram-negative bacilli belonging to the *Enterobacteriaceae* family. Widely found in nature colonizing animal hosts including mammals, reptiles, and birds,[34] they are major causes of foodborne illness as a consequence of consuming contaminated foods including poultry and dairy products. Worldwide, the annual incidence of salmonellosis is about 1.3 billion cases, and of the nearly 3 million persons who die,[35] most live in developing areas of the world.

The role of antimicrobials in the management of salmonellosis depends on the clinical syndrome, its severity, and underlying health problems of infected persons. Nontyphoidal salmonellae (eg, *Salmonella typhimurium*, *S. enteritidis*, *S. choleraesuis*, and many others) cause the clinical syndromes of gastroenteritis, asymptomatic carriage in the stool, bacteremia, and localized infection.[36] Typhoidal salmonellae (*S. typhi* and *S. paratyphi* A, B, and C) cause the syndromes of enteric fever (also referred to as typhoid or paratyphoid fever) and chronic carriage.[34]

Nontyphoidal Salmonellosis

CASE 69-7

QUESTION 1: An outbreak of *Salmonella* gastroenteritis being investigated by the Department of Public Health has traced the source of the outbreak to Restaurant A, specifically the popular turkey dinner special.

Anticipating that infected diners with specific clinical syndromes associated with *Salmonella* infection will benefit from antimicrobial treatment, and that antimicrobial-resistant *Salmonella* species are increasingly problematic, the Department of Health has a question for you.

"What antimicrobials are available for the treatment of nontyphoidal salmonellosis?"

DRUG RESISTANCE AND ANTIBIOTIC THERAPY

Trimethoprim–sulfamethoxazole and ampicillin

Until the late 1980s, standard treatments for nontyphoidal *Salmonella* were chloramphenicol, TMP/SMX, or ampicillin. By the early 1990s, widespread multidrug resistance, defined as simultaneous resistance to ampicillin, chloramphenicol, streptomycin, tetracyclines, and sulfonamides, precluded their use as empiric therapies for the treatment of salmonellosis.[34] Depending on the geographic area, rates of MDR *Salmonella* species are as high as 80% in East Asia and southern Europe and 30% to 40% in the United States.[35] As MDR *Salmonella* species remained

susceptible to the fluoroquinolones, these antimicrobials became the agents of choice for the treatment of salmonellosis.[35]

Fluoroquinolones

With the advent of MDR nontyphoidal *Salmonella*, fluoroquinolones were widely prescribed for the empiric treatment of nontyphoidal salmonellosis.[34] During the 1990s, suboptimal clinical responses following treatment with fluoroquinolones were noted when isolates were resistant to nalidixic acid. Both nalidixic acid and the fluoroquinolones are related compounds belonging to the quinolone family of antimicrobials. Because these isolates also displayed elevated ciprofloxacin minimum inhibitory concentrations (MICs) compared to nalidixic acid–susceptible strains (ie, 0.12–1 μg/mL vs ≤0.06 μg/mL, respectively), they were referred to as having decreased ciprofloxacin susceptibility (DCS).[37] Consequently, nalidixic acid resistance became a surrogate marker for isolates with DCS, for which ciprofloxacin was not an optimal antimicrobial choice.

In 2012, the Clinical Laboratory Standards Institute (CLSI) lowered for *Salmonella* species the breakpoint for resistance to ciprofloxacin from >1 to >0.06 μg/mL, to reliably detect *Salmonella* with DCS. The CLSI also recognized that not all laboratories (eg, resource-limited settings) would be able to institute the new ciprofloxacin breakpoints. Nalidixic acid–susceptible isolates with concurrent decreased susceptibility to ciprofloxacin are still uncommon, so CLSI allowed for the continued use of nalidixic acid screening,[37] although prescribers should be made aware of its limitations as a marker for isolates with DCS. Currently, nalidixic acid–resistant nontyphoidal *Salmonella* are prevalent in Asia and increasingly more common in the United States, reportedly 0.4% in 1996 and 2.3% in 2003. Antimicrobial treatment options for nalidixic acid–resistant *Salmonella* include azithromycin and selected third-generation cephalosporins.[37]

β-Lactams

Nontyphoidal Salmonella resistance to ceftriaxone is currently uncommon, but it has been reported worldwide, including in Africa,

Europe, Asia, the Philippines, and the United States,[34] some isolates are also simultaneously resistant to fluoroquinolones.[35],[38] Carbapenems[38] have been successfully used for the treatment of invasive infection (ie, bloodstream infection) caused by ceftriaxone- and ciprofloxacin-resistant *S. choleraesuis*,[39] although carbapenem-resistant *Salmonella* have also been reported.[34]

Azithromycin

Azithromycin displays good in vitro activity against nontyphoidal *S. enterica*[40] and is a recommended treatment for nontyphoidal salmonellosis requiring antimicrobial treatment,[5] including the treatment of nalidixic acid–resistant isolates.

Anticipating recommendations to guide prescribers regarding which diners with salmonellosis should receive antimicrobial therapy, the Department of Health has asked you to address the following question: "Considering a diner's severity of illness and underlying health problems, should antimicrobials be prescribed for diners with the following clinical syndromes: (a) uncomplicated gastroenteritis in the immunocompetent host, (b) asymptomatic stool carriage, or (c) extraintestinal *Salmonella* infection? If appropriate, what specific antimicrobial therapies would you recommend?"

UNCOMPLICATED GASTROENTERITIS IN THE IMMUNOCOMPETENT HOST

Clinical presentation and treatment

CASE 69-8

QUESTION 1: B.B., a 35-year-old, otherwise healthy male presents with a 1-day history of fever, abdominal pain, nausea, vomiting, and nonbloody stools. B.B. has no significant medical history. Physical examination is significant for a non-ill-appearing, febrile male; his presumptive diagnosis is mild, uncomplicated nontyphoidal *Salmonella* gastroenteritis.

Should he receive antimicrobial therapy?

As with B.B., within 6 to 72 hours of ingesting contaminated foods, patients begin experiencing the clinical manifestations of *Salmonella* gastroenteritis including acute onset of fever, diarrhea, and abdominal cramping; in more severe illness, bloody diarrhea and dehydration may occur.

In otherwise healthy individuals with uncomplicated nontyphoidal *Salmonella* gastroenteritis, antimicrobials are not recommended because salmonellosis is typically a self-limiting illness lasting for 2 to 5 days. Antimicrobials do not reduce the duration or severity of illness and may be harmful by placing patients at risk for adverse drug reactions, prolonging the asymptomatic carriage of salmonellae, and promoting the emergence of antimicrobial-resistant bacteria.[36],[41] Most individuals such as B.B. will only require replacement of lost fluids and electrolytes.

ASYMPTOMATIC STOOL CARRIAGE

Clinical presentation and treatment

CASE 69-8, QUESTION 2: Three weeks after resolution of B.B.'s episode of *Salmonella* gastroenteritis, follow-up testing reveals *Salmonella* bacteria from his stool, despite remaining asymptomatic. Should antimicrobials be prescribed to eliminate B.B.'s intestinal carriage of nontyphoidal *Salmonella*?

Antimicrobials should not be prescribed to eliminate asymptomatic intestinal carriage of nontyphoidal *Salmonella*.[20] Outbreaks related to known carriers are rare, so proper hand hygiene remains the mainstay of prevention.[7] A randomized, double-blind trial in healthy, asymptomatic adults from areas where nontyphoidal *Salmonella* infection is endemic found that neither norfloxacin nor azithromycin was better than placebo in eradicating intestinal carriage of *Salmonella* species.[20] The median duration of fecal shedding of nontyphoidal *Salmonella* is about 1 month in adults and 7 weeks in

children younger than 5 years of age.[42] Some health departments may require food handlers to have negative stool cultures before resuming work, so in these cases, treatment may be considered.[7]

GASTROENTERITIS IN PATIENTS AT RISK FOR EXTRAINTESTINAL SALMONELLA INFECTION

Clinical presentation and treatment

CASE 69-9

Question 1: W.M., a 50-year-old male with a past medical history significant for a recently diagnosed malignancy, presents with a 1-day history of fever, severe abdominal pain, nausea, vomiting, and nonbloody stools. One day before the onset of these symptoms, he ate cream-filled pastries from a bakery that has since been closed by the Department of Health because of its association with an ongoing outbreak of *Salmonella* gastroenteritis.

Should antimicrobials be prescribed for his presumed diagnosis of *Salmonella* gastroenteritis, and, if so, what would you recommend?

Antimicrobials are indicated for patients at risk for developing extraintestinal *Salmonella* infection such as persons with malignancy (such as W.M.), diabetes, rheumatologic disorders, HIV infection,[7],[35] persons receiving immunosuppressive therapies, very young age, low gastric pH (eg, as in infancy, pernicious anemia, or medication-induced), severe infection,[36] and persons older than age 50 years who may have atherosclerotic lesions that could become hematogenously infected.[43] Overall, <5% of patients with nontyphoidal *Salmonella* gastroenteritis become bacteremic, although infection with some serotypes, for example, *S. choleraesuis* and *S. dublin* are more likely to cause bloodstream infection.[36] Once in the bloodstream, extraintestinal complications include osteomyelitis, septic arthritis, meningitis, or infectious endarteritis. Lastly, antimicrobials have been used when rapid interruption of fecal excretion of organisms is needed to control outbreaks of salmonellosis in institutionalized persons.[43]

For patients at risk for extraintestinal infection or with severe diarrhea, antimicrobial options include fluoroquinolone (eg,

levofloxacin 500 mg PO once daily) for 7 to 10 days, azithromycin 500 mg PO once daily for 7 days, or parenteral ceftriaxone 1 to 2 g daily for 7 to 10 days (14 days is recommended for immunocompromised patients).[5]

EXTRAINTESTINAL SALMONELLA INFECTION

Clinical presentation and treatment

CASE 69-10

QUESTION 1: B.T., an "ill-appearing" 70-year-old male with a history significant for eating the same cream-filled pastries as W.M. (see Case 69-9, Question 1) is hospitalized for severe abdominal pain, bloody diarrhea, new-onset right hip pain, high fever, and low blood pressure. His past surgical history is significant for a right hip prosthesis.

Would B.T. benefit from antibiotic therapy, and, if so, what would you recommend?

B.T. is presenting with signs and symptoms of *Salmonella* gastroenteritis, bacteremia (fever, low blood pressure), and possible localized infection of his right hip prosthesis (new-onset hip pain).

Treatment of *Salmonella* bacteremia is generally successful after 10 to 14 days of antimicrobial therapy.[5,35] If infection of B.T.'s hip prosthesis is confirmed, surgery may be required to cure his infection.[42] Recommended treatment durations for extraintestinal nontyphoidal salmonellosis are available.[43]

Considering the antimicrobial resistance patterns from where the *Salmonella* infection was acquired (eg, travel history), prior antimicrobial therapy, and site of infection, empiric therapy options until susceptibilities are available include selected IV third-generation cephalosporins (eg, ceftriaxone 1 g IV every 24 hours, cefotaxime 1 g IV every 8 hours),[44] an IV or PO fluoroquinolone (eg, ciprofloxacin 400 mg IV every 12 hours, ciprofloxacin 500–750 mg PO every 12 hours, levofloxacin 750 mg IV or PO every 24 hours), or the combination of a third-generation cephalosporin with a fluoroquinolone.[43] For patients who are bacteremic, some experts prefer the IV route of administration,[43] particularly until the patient

has stabilized,[35] whereas other experts recommend either the IV or oral route of administration.[44]

Typhoidal Salmonellosis—Typhoid Fever (Enteric Fever)

CLINICAL PRESENTATION

CASE 69-11

Question 1: B.C. is a 49-year-old obese female, presenting to the ED with a 1-week history of fever, confusion and delirium, severe abdominal pain, headache, anorexia, and diarrhea and, for the past 1 day, a red rash on her chest. Her history of present illness is significant for returning 10 days ago from travel to the Indian subcontinent where she stayed with relatives, some of whom were recovering from typhoid fever. B.C.'s medical history is significant for gallstones. She lives in California with her husband. Admission vital signs show a temperature of 101 °F (38.33 °C), a heart rate of 60 beats/minute, and a stable blood pressure. Physical examination is significant for an unstable appearance, a red rash on her chest, splenomegaly, and hepatomegaly. Laboratory tests include the following: white blood cell (WBC) count is 3.0 × 10^6/μL, liver function tests are mildly elevated, and the results of two sets of blood cultures are pending. B.C. is given the presumptive diagnosis of severe enteric fever and encephalopathy most likely attributable to *S. typhi*.

Why is her history of present illness, clinical presentation, and laboratory results consistent with this diagnosis?

A key piece of information from B.C.'s history of present illness supporting the diagnosis of typhoid fever is her recent travel to the Indian subcontinent, where typhoid fever is endemic, and her contact with relatives recovering from this infection. Other developing countries with endemic typhoid fever include Southeast Asia, Africa, and Latin America.[45] In developed countries, enteric fever is a sporadic disease occurring mainly in travelers returning from areas where the disease is endemic; in the United States, 85% of cases of typhoid fever are travel related.[46]

B.C.'s clinical presentation and laboratory findings are classic for enteric fever. During the 7- to 14-day incubation period,[45]

salmonellae multiply within macrophages and monocytes, and systemic manifestations of infection appear after the release of bacteria into the bloodstream. Patients usually present with fever, abdominal pain, anorexia, diarrhea or constipation, headache, dry cough, splenomegaly, and hepatomegaly, whereas severe illness is characterized by concomitant GI bleeding, encephalopathy, and shock. Bacteremia may be followed by localized infection to the liver, spleen, bone marrow, gallbladder, and Peyer patches of the terminal ileum.[45] Laboratory abnormalities consistent with typhoid fever include B.C.'s low WBC count and mildly elevated liver function test results.[34]

TREATMENT

Case 69-11, Question 2: Would B.C. benefit from a course of antimicrobials to treat her presumptive diagnosis of typhoid fever? If so, what options are available?

B.C. would benefit from effective antimicrobial treatment for typhoid fever in the following ways: (a) shortening the resolution of fever from 3 to 4 weeks to 3 to 5 days,[47] with clearing of all symptoms within 7 to 10 days,[48] (b) decreasing mortality from usually 5% to 10% to <1%,[34] (c) eradicating fecal shedding of *S. typhi*, thereby limiting further spread of infection,[48] and (d) preventing recurrence of the infection. Most cases of typhoid fever are effectively treated with oral antimicrobials; IV therapy is reserved for severely ill patients or patients with persistent vomiting and severe diarrhea.[45]

Fluoroquinolones

Short-treatment courses (<5 days) of oral fluoroquinolones were once as effective or better than previously used treatments (eg, TMP-SMX, ampicillin, or chloramphenicol) for *S. typhi*.[49] By the late 1990s, short-course fluoroquinolone therapies used in parts of Asia were associated with clinical failures in up to 50% of patients.[46]

Microbiologic evaluation revealed these isolates were resistant to nalidixic acid and had higher ciprofloxacin MICs (0.125–1 μg/mL) compared to *Salmonella* that was fully susceptible to ciprofloxacin (MICs < 0.12 μg/mL).[50]

In areas with a high prevalence of nalidixic acid–resistant *S. typhi*, alternatives to fluoroquinolones include azithromycin and selected third-generation cephalosporins.

Azithromycin

Azithromycin is effective for patients with mild-to-moderate typhoid fever.[51] Azithromycin (20 mg/kg/day) for 7 days cured >95% of children with uncomplicated typhoid fever in Vietnam where 96% of *S. typhi* are nalidixic acid resistant; fever clearance time was 106 hours, and there were no recurrences.[17] In contrast, lower azithromycin doses (10 mg/kg/day) in the setting of nalidixic acid resistance are associated with lower cure rates (82%).[52] The identification of azithromycin-resistant *S. typhi*[53] and nonresponse to azithromycin is a current concern.[54]

β-Lactams, carbapenems, and tigecycline

Cefixime, an oral third-generation cephalosporin, is variably effective in the treatment of typhoid fever. Failure rates range from 4% to 27%[53] and some experts do not recommend its use for the treatment of typhoid fever.[46] The lower clinical response to cefixime may be related to the poor intracellular penetration of the β-lactam because the intracellular compartment is the primary site of *S. typhi* colonization.[55]

Ceftriaxone, an intravenous (IV) third-generation cephalosporin, is recommended for the treatment of severe typhoid fever[47] with the caveat that longer treatment courses are recommended to prevent recurrence of infection. In patients with bacteremia caused by ceftriaxone-susceptible isolates, recurrence of infection was higher among patients treated with a 7-day course of ceftriaxone versus azithromycin, 14% versus 0%, respectively.[56] No recurrences were reported when a longer course (14 days) of ceftriaxone was used for

infection caused by MDR *S. typhi*.[57] Patients treated with ceftriaxone may remain febrile for as long as 10 days.[58] Ceftriaxone-resistant *S. typhi* have been reported in India, the Philippines, China, the United States, and elsewhere.[59] Potential alternatives to ceftriaxone include carbapenems (imipenem, meropenem, and ertapenem) and tigecycline, although clinical data are lacking.[51]

TREATMENT—SEVERE VERSUS UNCOMPLICATED TYPHOID FEVER

Case 69-11, Question 3: What specific empiric antibiotic regimen would you recommend for the treatment of B.C.'s complicated (severe) typhoid fever? How would her treatment differ if she had uncomplicated typhoid fever?

For complicated typhoid fever, empiric therapy with ceftriaxone is recommended.[60] Once susceptibility data are available, treatment options include 10 to 14 days of ceftriaxone (1–2 g IV once daily) continued for at least 7 days after defervescence to minimize the risk for recurrence,[51] or a fluoroquinolone for 10 to 14 days.[47]

Uncomplicated typhoid fever is typically treated in the outpatient setting.[47] Empiric oral regimens include azithromycin 500 mg daily × 5 to 7 days,[47] or a fluoroquinolone (eg, levofloxacin 500 mg once daily or ciprofloxacin 500 mg twice daily) for 7 days.[5] For children, azithromycin or ceftriaxone is recommended.[5]

ADJUNCTIVE TREATMENT

Case 69-11, Question 4: Besides the administration of antibiotics, what adjunctive therapies could benefit B.C. for the treatment of severe typhoid fever?

Enteric encephalopathy, that is, altered mental status, is associated with a mortality rate as high as 56% if effective treatment is not promptly administered.[61] In patients with enteric encephalopathy, retrospective data report improved survival when

appropriate antimicrobial therapy is combined with high-dose dexamethasone (3 mg/kg IV followed by 1 mg/kg every 6 hours IV for eight doses).[61] The exact mechanism of action of dexamethasone in enteric encephalopathy is not known but hypothesized to reduce inflammation.[61]

CASE 69-11, QUESTION 5: Fourteen months after discharge from the hospital, B.C. remains free of symptoms associated with typhoid fever, but follow-up testing reveals that she continues to excrete *S. typhi* in her stools. In addition, their adult son who has dinner with them every Sunday presents to his clinic doctor with fever, headache, and chills, and is confirmed to have uncomplicated typhoid fever. He has no significant past medical history and has no recent travel history. How might her son have acquired typhoid fever? What treatment recommendations can be provided to this family?

Unlike his mother, B.C.'s son has no travel history to an area where typhoid fever is endemic. Instead, he is likely to have contracted typhoid fever from consuming foods prepared by his mother who is now a chronic carrier of *S. typhi*. Most patients with typhoid fever continue to excrete *S. typhi* in their stools for 3 to 4 weeks after recovery from their illness. However, 1% to 3% of persons such as B.C. become chronic carriers who continue to excrete *Salmonella* from stool or urine for >1 year after infection and serve as reservoirs for spreading infection. Unlike for nontyphoidal salmonellae, humans are the only natural host and reservoir for *S. typhi*.[58] B.C.'s risk factor for becoming a chronic carrier is her history of gallstones that allows the sequestration of organisms within her abnormal biliary tract.

CHRONIC TYPHOID CARRIERS

Treatment

CASE 69-11, QUESTION 6: What therapeutic options are available to cure B.C.'s chronic carrier state?

Treatment options for chronic *S. typhi* carriers such as B.C. include a prolonged course of antibiotics, cholecystectomy, or suppressive antimicrobial therapy.[45] Fifty percent to 90% of chronic carriers may be cured after prolonged courses of antibiotics,[62–65] although efficacy may be lessened when anatomic abnormalities (eg, cholelithiasis) are present.[62] Recurrence is usually detected within the first several months of completing antimicrobial therapy[66] but can occur up to 24 months after completing therapy.[67] For susceptible *S. typhi*, curative oral antimicrobial regimens include amoxicillin 2 g three times daily for 28 days,[64] ampicillin 1 g four times daily for 90 days,[63] ampicillin 1.5 g four times daily plus probenecid for 6 weeks,[62] TMP-SMX 160/800 mg twice a day for 3 months,[65] ciprofloxacin 500 to 750 mg twice a day for 3 to 4 weeks,[65–69] or norfloxacin 400 mg twice daily for 4 weeks.[70]

Prevention

Case 69-11, Question 7: B.C.'s sister is planning a trip to the Indian subcontinent and is concerned about acquiring typhoid fever. What can she do to reduce her risk of becoming infected?

The U.S. Centers for Disease Control and Prevention recommends vaccination for travel to areas where the risk for *S. typhi* is increased, including many Asian, African, and Latin American countries.[71] In the United States, two licensed vaccines are available to protect against *S. typhi* but not against *S. paratyphi*. The intramuscular vaccine for persons older than age 2 years is 55% effective in preventing typhoid fever; adverse effects include local pain and swelling, fever, and headache.[71] The oral live-attenuated vaccine Ty21a vaccine (a series of four doses) for persons older than age 6 years is well tolerated, and it affords a protective efficacy rate around 55%. The vaccine series should be completed 1 week before travel.[71] The oral vaccine is a live-attenuated vaccine, and therefore should not be administered to immunocompromised persons. In addition, to ensure full vaccine activity, the live-

attenuated vaccine should not be given until at least 3 days after the last dose of an antimicrobial, and, if possible, antimicrobials should not be initiated within 3 days of the last dose of the oral vaccine; longer intervals should be considered for long-acting agents such as azithromycin.[71]

Finally, because the protective efficacy of available vaccines against *S. typhi* is incomplete and because neither vaccine is licensed to protect against *S. paratyphi*, which in some Asian countries accounts for up to 50% of blood isolates from patients with enteric fever,[72] it is still necessary to reinforce the importance of good hygiene and the avoidance of foods with a high risk of being contaminated with enteropathogens.

SHIGELLA SPECIES

Shigella are gram-negative intracellular bacterial pathogens belonging to the *Enterobacteriaceae* family. They are the most frequent cause of dysentery, which is an inflammatory diarrheal illness characterized by bloody or mucoid stools with abdominal cramps. Of the four *Shigella* species, severe dysentery is most commonly caused by *Shigella dysenteriae* followed by *S. flexneri*, whereas milder illness characterized by watery diarrhea with or without blood is typically caused by *S. sonnei* and *S. boydii*.[73]

Shigellosis—Severe Illness

CLINICAL PRESENTATION

CASE 69-12

QUESTION 1: M.T. is a 60-year-old, ill-appearing male hospitalized for bloody diarrhea and fever. Two days before admission he noted the onset of fever, abdominal cramps, and 6 to 7 nonbloody, watery stools. His diarrhea has since worsened to 10 to 12 small-volume stools with blood and mucus, and he now reports painful straining while passing his stools. His history of present illness is

significant for returning 3 days ago from a business trip to the Indian subcontinent. During the business portion of the trip, he remained at the hotel where all his meals were prepared by hotel staff well trained in the sanitary preparation of foods. However, on the day of his departure, he opted to mingle with local residents to get a first-hand taste of native foods and beverages from street vendors. M.T. lives alone in Florida, has no significant medical history or drug allergies, and takes no medications. On admission, his temperature is 101 °F (38.33 °C) and physical examination reveals a critically ill male with severe abdominal tenderness.

Why is M.T.'s history of present illness and clinical presentation consistent with the diagnosis of dysentery, most likely caused by *S. dysenteriae type 1*?

M.T.'s diagnosis of dysentery, likely caused by *S. dysenteriae type 1*, is consistent with his recent travel to the Indian subcontinent where *S. dysenteriae type 1* is both epidemic and endemic,[73] primarily a consequence of inadequate systems for sewage disposal.[73] M.T. likely became infected from the consumption of contaminated foods or beverages prepared by local street vendors, by person-to-person contact with symptomatic persons with diarrhea, or from asymptomatic persons continuing to excrete shigellae from their stool.[74] As few as 10 to 100 individual shigellae organisms can cause illness[73] in healthy hosts, explaining why shigellosis is a very contagious infection.

Once ingested, virulence factors allow shigellae to evade detection by the immune system and invade colonic and rectal epithelium. Enterotoxin production causes fluid secretion into the intestinal lumen and cytotoxin production causes cell death; both toxins lead to the severe clinical manifestations of shigellosis.[73]

As with M.T., within 24 to 48 hours of ingestion of *Shigella* bacteria, symptoms of dysentery begin and include fever, fatigue, malaise, and anorexia.[74] Watery diarrhea generally precedes dysentery and frequently is the only manifestation of mild infection.[74] Progression to dysentery may follow within hours to days and is characterized by frequent, small-volume, bloody, and mucoid stools; abdominal cramps; and tenesmus that is described as painful straining when passing stools.[74] Hemolytic uremic syndrome (HUS) is a serious complication of shigellosis, occurring in up to 13% of patients with dysentery caused by *S. dysenteriae type 1*. HUS is a

consequence of the production of Shiga toxin 1, most commonly produced by *S. dysenteriae* but also rarely by *S. flexneri*.[73] Longer term health complications of diarrheal illness caused by invasive pathogens such as *Shigella* species, as well as *Salmonella* and *Campylobacter* species, include postinfectious irritable bowel syndrome (PI-IBS)[75] or reactive arthritis.[76]

TREATMENT

Case 69-12, Question 2: Would M.T. benefit from antimicrobials to treat bloody diarrhea and fever (dysentery), presumably caused by *S. dysenteriae type 1*?

M.T. would benefit from antimicrobial therapy for dysentery presumably caused by *S. dysenteriae type 1*: First, effective antimicrobial therapy reduces the average duration of illness from 5 to 7 days to about 3 days[74] and reduces the risk of death and serious infection-related complications. Within 48 hours of starting treatment, M.T. should notice a reduction in stool frequency, volume of bloody stools, and fever. Second, effective antimicrobial therapy quickly reduces the carriage and excretion of shigellae, thus limiting the spread of infection. Despite the benefits of antimicrobial therapy, there has been concern that antimicrobials could increase the risk of developing HUS. However, Bennish et al[77] reported that early administration of effective antimicrobials (ie, within 3–4 days of the onset of dysentery) is associated with a low risk of developing HUS. Supportive management with fluids is imperative with antimicrobial therapy.

Case 69-12, Question 3: What empiric antimicrobial regimens are available for the treatment of shigellosis?

Shigella species are well known for rapidly developing resistance following exposure to antimicrobials; therefore, selection of empiric therapy should be based on local antimicrobial susceptibility

patterns.[73] For information on susceptibility data in the United States, see National Antimicrobial Resistance Monitoring system (NARMS; http://www.cdc.gov/narms).

Antibiotic therapy: fluoroquinolones, azithromycin, β-lactams

During the 1960s to 1980s, ampicillin, TMP-SMX, or nalidixic acid was the standard treatment for shigellosis. During the 1990s, MDR (ie, resistance to ampicillin, TMP-SMX, and chloramphenicol) *Shigella* precluded their empiric use for shigellosis, but because these MDR isolates remained susceptible to fluoroquinolones, these agents became the drugs of choice for this infection.[73] In adults, ciprofloxacin 500 mg PO twice daily for 3 to 5 days is effective against MDR *S. dysenteriae type 1* infection in the setting where all isolates are susceptible to ciprofloxacin and nalidixic acid.[12] With the widespread introduction of fluoroquinolones as the drugs of choice for the treatment of shigellosis, quinolone-resistant shigellae have emerged.[78] Ciprofloxacin resistance in *Shigella* species from Asia and Africa has progressively increased from 0.6% before 2000 to 29.1% during 2007 to 2009.[79] Although the prevalence of ciprofloxacin-resistant *Shigella* remains low (<5%) in Europe and the Americas,[79] international travel is strongly associated with the importation and subsequent circulation, within the United States, of ciprofloxacin-resistant *S. sonnei*[80] and other MDR *Enterobacteriaceae*.[81]

In the setting of epidemic dysentery caused by *S. dysenteriae type 1*, similar clinical outcomes were observed in adults treated with a single 1-g PO dose of azithromycin or multiple doses of ciprofloxacin (500 mg PO twice daily for 3 days). In this study, the mean number of days until resolution of symptoms after starting therapy was similar (2.5 days for azithromycin vs 2.3 days of ciprofloxacin) but only 17% of isolates were nalidixic acid resistant.[82]

In adults with moderate-to-severe shigellosis caused by MDR *Shigella* species, clinical efficacy is similar to that with azithromycin (500 mg PO on day 1, then 250 mg PO daily for 4 days) or ciprofloxacin (500 mg PO every 12 hours for 5 days), 89% versus

82%, respectively ($P > .2$).[83] In a subgroup analysis, a greater proportion of patients infected with *S. dysenteriae type 1* failed therapy with either azithromycin (29%) or ciprofloxacin (17%), compared with patients infected with other *Shigella* species (failure rate of 6% for both antibiotics).[83] Intercontinental spread through sexual transmission of azithromycin-resistant shigellosis and treatment failure following azithromycin therapy has been reported.[84] *S. sonnei* with reduced susceptibility to azithromycin remains susceptible to ceftriaxone,[85] and ceftriaxone has successfully treated a patient with azithromycin-resistant shigellosis failing azithromycin therapy.[86]

The oral third-generation cephalosporin cefixime is unreliable for the treatment of shigellosis, with failures reported in 11% to 47% of patients.[87] Parenteral ceftriaxone and cefotaxime have excellent in vitro activity against *Shigella* species and have been used alone or with amikacin[87] for patients failing ciprofloxacin therapy. Although uncommon, ceftriaxone-resistant *Shigella* have been reported in Asia.[73] Ongoing surveillance to detect changes in antimicrobial susceptibility among *Shigella* species is needed to direct local empiric treatment recommendations.

CASE 69-12, QUESTION 4: Should loperamide be started in patients with dysentery?

The role of antimotility drugs in patients with dysentery has been debated, the concern being that prolonging the clearance of pathogens from the intestinal tract could worsen the severity of illness. However, loperamide (in combination with ciprofloxacin) has been safely used in adults who are not critically ill with bacillary dysentery primarily caused by *Shigella* species, decreasing the number of unformed stools and shortening the duration of diarrhea; fever was not prolonged in these patients.[11] However, the authors stress that all *Shigella* isolates in the study were susceptible to the antimicrobial used (ie, all isolates were susceptible to ciprofloxacin and nalidixic acid) and none of the patients were critically ill; thus, it

would not be prudent to extrapolate the findings from this study to patients who are critically ill such as M.T.[11]

Case 69-12, Question 5: What empiric antimicrobial regimen could be started in patients such as M.T. with severe dysentery, likely caused by *Shigella* species?

Ciprofloxacin, azithromycin, and ceftriaxone are the primary agents used for the treatment of shigellosis,[5,78] although resistance to all of these agents has been reported. In the setting of severe dysentery associated with nausea and vomiting, parenteral ceftriaxone is a reasonable empiric option.[73] Fluoroquinolones are a less desirable option given the widespread prevalence of fluoroquinolone-resistant *Shigella* species in areas including the Indian subcontinent[79] where M.T. likely became infected.

Shigellosis—Mild Illness

CLINICAL PRESENTATION

CASE 69-13

Question 1: F.F. is a 30-year-old, previously healthy female, presenting to her physician with nonbloody, watery diarrhea of 3 days' duration. Her history of present illness is significant for the following: 2 days before the onset of her GI symptoms, she visited her 4-year-old nephew who was recovering from an intestinal illness caused by *S. sonnei* acquired at his day care center. F.F. has no significant medical history. Overall, she feels better compared to the previous day and is afebrile.

How does F.F.'s clinical presentation of shigellosis differ from that of M.T. (see Case 69-12, Question 1)? Should F.F. be treated with antimicrobials for her presumed, mild case of shigellosis?

TREATMENT

Compared to M.T., F.F. is experiencing a much milder, and likely self-limiting case of shigellosis. In industrialized countries, risk factors for shigellosis include settings where individuals are in close contact

such as in child care centers, military barracks, and institutional housing.[74] International travel[80] and sexual transmission in males who have sex with males[84] are other means of spreading shigellosis. Secondary attack rates as high as 40% occur within 1 to 4 days of exposure to the primary case; infected persons may continue to asymptomatically shed *Shigella* in stool following recovery from their illness.

S. sonnei accounts for 90% of shigellosis in developed countries. Because most patients have a mild and self-limiting illness, antimicrobials are not generally required. However, from a public health standpoint, they are often prescribed to shorten the duration of illness to reduce the infectious period.[88] On the other hand, with the emergence of MDR *Shigella* species, some experts favor reserving antimicrobials for only severely ill persons.[89]

Empiric antimicrobial options include a 3-day course of either ciprofloxacin 500 mg PO twice daily or azithromycin 500 mg PO once daily; ceftriaxone can also be used.[89] Clinical improvement may be evident within 24 hours.[73]

PREVENTION

Prevention of shigellosis requires good hygiene, including proper handwashing and reducing fecal–oral exposure during sexual contact.[90] Development of an effective vaccine has been limited by poor vaccine immunogenicity, decreased vaccine protection because of the changing prevalence of infection caused by nonvaccine serotypes, and adverse effects.[73]

CAMPYLOBACTER JEJUNI

Clinical Presentation

CASE 69-14

Question 1: M.U. is a 20-year-old, previously healthy female presenting to the Student Health Center with malaise, fever, diarrhea, abdominal pain, and bloody diarrhea for the past 24 hours. One day before the onset of symptoms, she dined at a restaurant near campus, noting that the chicken she ate was perhaps not thoroughly cooked. She has no significant medical history, no recent travel history, and is a full-time student at a university in the United States. On physical examination, M.U. is not ill appearing. The physician tells her that during the past week several students with GI symptoms similar to hers have been diagnosed with *C. jejuni* gastroenteritis, and all had recently eaten at the same restaurant.

Why is M.U.'s history of present illness and clinical presentation consistent with *Campylobacter* gastroenteritis?

M.U.'s presumptive diagnosis of *Campylobacter* gastroenteritis is consistent with her recent history of eating undercooked chicken at a restaurant associated with an ongoing outbreak of *Campylobacter* gastroenteritis. In industrialized nations, the most important risk factor for acquiring *Campylobacter* infection is the consumption of contaminated undercooked poultry, dairy products, unpasteurized foods, or contaminated water.[91] Prevention of *Campylobacter* infection involves careful food preparation and cooking practices.[92]

Beginning 24 to 72 hours after consumption of contaminated foods, clinical manifestations of *Campylobacter* gastroenteritis typically include diarrhea, fever, and abdominal cramps with either loose and watery or bloody stools.[91] Postinfectious complications of *C. jejuni* gastroenteritis include Guillain–Barré syndrome, reactive arthritis, and PI-IBS; the latter associated with diarrhea lasting >7 days.[91]

Treatment

Case 69-14, Question 2: Would M.U. benefit from antimicrobial therapy to treat her *Campylobacter* gastroenteritis?

Because *C. jejuni* gastroenteritis is typically an acute, self-limiting illness resolving within 3 to 7 days,[93] antibiotic therapy is usually not

necessary.[91] Antibiotics are recommended for patients with symptoms lasting >1 week, high fevers, bloody stools, pregnant females, or immunocompromised hosts.[94] Because M.U.'s clinical presentation includes fever with bloody stools, antimicrobial therapy is warranted. Effective antimicrobial therapy shortens the duration and the severity of illness by a mean of 1.3 days, and it is most beneficial when started within 3 days of the onset of illness.[91]

CASE 69-14, QUESTION 3: What empiric antimicrobial therapies could be initiated to treat M.U.'s presumed case of *C. jejuni* gastroenteritis?

MACROLIDES

Macrolides remain the drugs of choice for the treatment of *Campylobacter* gastroenteritis.[3] Macrolide resistance has remained relatively stable around 5%,[91] but depending on geographic location, higher macrolide resistance has been reported from Eastern Europe and China (5%–11%)[95] and India (22%).[96]

FLUOROQUINOLONES

Once considered the drugs of choice for *Campylobacter* infection, fluoroquinolones are no longer first-line options as a consequence of widespread fluoroquinolone resistance, largely attributed to their use in veterinary medicine and food animals (eg, poultry); the latter practice has since been banned in the United States.[95] Fluoroquinolone-resistant *C. jejuni* exceeds 80% in Spain, Thailand, and Hong Kong, and it is about 50% in selected European Union States.[97] In the United States, the prevalence of ciprofloxacin-resistant *C. jejuni* remained between 20% and 30% from 2007 to 2011.[91,95,98] However, higher quinolone resistance among *Campylobacter* isolates in international travelers returning to the United States compared to nontravel-associated isolates (60% vs 13%)[95] underscores the need to consider local resistance patterns from where infection was acquired when selecting empiric antimicrobial therapy for returning travelers.

Recommended oral treatments for *C. jejuni* gastroenteritis for adults are azithromycin 500 mg once daily for 3 days or erythromycin 500 mg four times daily for 5 days.[5] On the basis of M.U.'s medical history and clinical presentation, empiric therapy with oral azithromycin can be started.

TRAVELERS' DIARRHEA

Of the nearly one billion people traveling each year from industrialized countries to developing areas of the world, ~10% to 60% will experience an acute self-limiting episode of travelers' diarrhea (TD).[16,99] TD is usually viewed from the perspective of individuals originating in high-income countries and traveling to lower and middle-income countries. TD is defined as a disease where patients develop three or more unformed stools per 24 hours plus one additional symptom such as abdominal cramps, tenesmus, nausea, vomiting, fever, fecal urgency, or the passage of bloody or mucoid stools. Often, a diagnosis is made on the clinical presentation and travel history and a microbiologic diagnosis is not made.[16] Long-term postinfectious complications occur in a small proportion of returning travelers.[16] Experts recommend pretravel education focusing on the prevention of TD and instructions for the self-treatment of TD at the onset of illness.[100]

CASE 69-15

QUESTION 1: W.D. and B.D. are healthy 23-year-old females beginning a 2-week backpacking trip through Latin America. Before their departure, both travelers attended a travel clinic where they received instructions to minimize their risk factors for TD and a travel kit including instructions and medications for the self-treatment of TD. On the day of their arrival, both travelers seek out local street vendors, sampling their fresh fruits, vegetables, prepared foods, and unbottled beverages.

On the second day of their vacation, both travelers are not feeling well. W.D. notes only the passing of two to three watery stools without blood and mild nausea. In contrast, B.D. is feeling much worse, noting the passing of six to

seven loose, bloody stools, abdominal cramps, and feeling “feverish.” Neither traveler feels dizzy or thirsty, and both are able to continue drinking unbottled water and juices.

What are their risk factors for TD and why are their clinical presentations consistent with this diagnosis?

Risk Factors

Both travelers have several risk factors for acquiring TD. First, their travel to Latin America, a destination considered “high risk” for TD; other high-risk destinations include South Asia and West/Central Africa.[16] Second, because the highest risk for TD is during the first 2 weeks of travel, their recent arrival to an at-risk destination increases the likelihood of infection; the risk factor for TD lessens during the second (9.9% risk) and third (3.3% risk) weeks of travel.[16] Third is their travel style of eating foods with a high risk of contamination with enteropathogens such as foods from local street vendors and drinking unbottled beverages. Additional high-risk foods include ice cubes, raw milk, unpeeled fruits and vegetables, uncooked foods, moist foods; foods remaining at room temperature for prolonged periods of time, allowing bacteria to multiply or release their enterotoxins[101]; use of acid-inhibiting medications allowing acid-susceptible enteropathogens to pass through to the intestines; and genetic predisposition.[16]

Clinical Presentation

W.D. has symptoms consistent with TD. In travelers, illness typically begins within 24 to 48 hours of consuming fecally contaminated foods. Left untreated, TD is generally a self-limiting illness lasting 4 to 5 days.[16]

Severity of the diarrhea can be classified into three categories[102]:

Mild (acute): diarrhea that is tolerable, is not distressing, and does not interfere with planned activities

Moderate (acute): diarrhea that is distressing or interferes with planned activities

Severe (acute): diarrhea that is incapacitating or completely prevents planned activities; all dysentery (passage of grossly bloody stools) is considered severe.

Persistent: diarrhea lasting ≥2 weeks

General Management

Case 69-15, Question 2: What general approach should W.D. and B.D. take to manage their diarrheal illnesses?

Realizing that their symptoms are consistent with TD, both travelers review their pretravel information for the self-management of TD.

HYDRATION

To replace fluid and electrolyte losses, they should continue to drink only bottled or boiled liquids such as tea, broth, carbonated beverages, and fruit juices.[101] Electrolytes can be replaced by eating salted crackers or similar sources of sodium chloride. For travelers able to drink fluids ad libitum, a modified World Health Organization oral rehydration solution offers no additional benefit over the administration of loperamide alone.[103] Neither traveler has symptoms indicative of significant dehydration such as thirst, dizziness, or altered mental status.

SAFE FOODS—"PEEL IT, BOIL IT, OR FORGET IT"

Travelers should avoid consuming foods with a high risk of contamination with enteropathogens that include raw vegetables and fruits that are not peeled or cooked, food not served steaming hot, and tap water.[104] Instead, they should only eat fruits that they have themselves peeled or that have been adequately washed, and well-cooked foods served steaming hot. Enteropathogens are killed at 100 °C and foods served piping hot at 60 °C are generally safe.[16]

Despite adherence to dietary restrictions and precautions, prevention of TD is not always possible, likely reflecting the difficulty with adhering to sanitary standards for the preparation and serving of foods, the lack of facilities for employees to wash their hands after going to the bathroom, or the lack of screens or windows to prevent flies from contaminating foods.[16]

SELF-TREATMENT OF TRAVELERS' DIARRHEA

Antimotility agents alone provide rapid relief of symptoms but do not cure the infection, whereas antimicrobials alone will cure the infection but symptoms may persist for a longer time.[101] In the appropriate setting, antimotility drugs plus antibiotics provide the fastest relief of diarrheal symptoms.[101] Selection of a self-treatment plan is, in part, based on the traveler's severity of illness and manifestations of their diarrheal illness.

Microbial Etiology, Clinical Manifestations, and Treatment Options

Case 69-15, Question 3: For travelers with the following manifestations of TD, (a) watery diarrhea without blood or fever, (b) bloody diarrhea or fever, or (c) diarrhea while taking chemoprophylaxis, what are the common microbial etiologies, and what treatment options are available to manage these diarrheal syndromes?

The microbial etiology of TD is recognized in 50% to 94% of patients, with bacteria most commonly identified; viruses and parasites are less frequently isolated.[16] For travelers to developing countries, the most common enteropathogen is enterotoxigenic *Escherichia coli* (ETEC), followed by enteroaggregative *Escherichia coli* (EAEC), diffusely adherent *E. coli*, noroviruses, rotaviruses, *Salmonella* species, *C. jejuni*, and *Shigella* species.[16] The likely enteropathogen afflicting individual travelers can in part be predicted by the clinical manifestations of the diarrheal illness and the travel destination information (provided by the Centers for Disease

Control), which is helpful for selecting an appropriate self-treatment plan).[105]

WATERY DIARRHEA WITHOUT FEVER OR BLOODY DIARRHEA

ETEC is suspected in the setting of acute watery diarrhea, especially in travelers to Latin America and the Caribbean (≥35% of reported pathogens), Africa (25%–35% of reported pathogens), and South Asia (15%–25% of reported pathogens).[16] ETEC produces enterotoxins that stimulate the intestinal mucosa to secrete fluid into the gut lumen, leading to diarrheal stools.

Loperamide, diphenoxylate/atropine, bismuth preparations

Loperamide alone can be considered in patients with a mild diarrheal illness, for example, two loose stools and mild symptoms,[106] without fever or bloody stools.[104] Loperamide rapidly relieves diarrheal symptoms, often within >24 hours[104] and is better tolerated than is diphenoxylate/atropine. Mild diarrheal illness may be less likely to be infectious in etiology, but instead because of noninfectious causes such as anxiety, diet changes, and stress.[106] BSS is moderately effective in improving diarrheal symptoms.[16]

Alternatively, travelers on a short and critical trip (eg, business) might consider the addition of an antibiotic. However, the potential adverse consequences of antimicrobial therapy such as the risk of adverse drug events, additional cost, and antimicrobial resistance should also be considered. A recent prospective study reported that depending on the travel destination, the risk factor for a traveler with diarrhea becoming colonized with extended-spectrum β-lactamase–producing *Enterobacteriaceae* was greatest (28%–80%) if an antimicrobial was taken versus if no antibiotic was taken (8%–47%).[81] After returning home, up to 24% of travelers remain colonized at 6 months and 10% remain colonized at 3 years.[81] Consequently, some experts do not recommend antimicrobials for mild-to-moderate disease nor for the prevention of TD.[81]

Antimicrobials alone

Rifaximin, ciprofloxacin or levofloxacin, or azithromycin are recommended for travelers with moderate or severe TD[102],[105] (**Table 69-2**). For travelers to Mexico[107],[108] or Kenya,[109] where ETEC is a frequent cause of TD, a single dose of ciprofloxacin 500 mg, azithromycin 1 g, or levofloxacin 500 mg decreased the median time to passage of the last unformed stool to 22 to 33 hours versus 54 to 66 hours for travelers given placebo.[110] For travelers to Mexico or India, oral rifaximin 200 mg three times daily or ciprofloxacin 500 mg twice daily for 3 days significantly reduced the median time to passage of the last unformed stool to 32 and 29 hours, respectively, versus 66 hours for travelers taking placebo.[111] Rifaximin is not systemically absorbed, is well tolerated, and has a low potential for the development of antibiotic resistance.[112]

Table 69-2
Therapy for Travelers' Diarrhea in Adults

Drug	Treatment
Ciprofloxacin	500 mg PO twice daily or 750 mg PO once daily × 1–3 days[a]
Azithromycin	1000 mg PO in a single dose or 500 mg PO once daily × 3 days
Rifaximin	200 mg PO three times daily × 3 days

PO, orally.

[a]Single dose may be effective. If diarrhea improves 12 to 24 hours after the first dose, the antibiotic can be stopped; otherwise, may continue antibiotic for up to 3 days.

Sources: Steffen R, Hill DR, DuPont HL. Traveler's diarrhea. A clinical review. *JAMA.* 2015;313(1):71–80; DuPont HL. Acute infectious diarrhea in immunocompetent adults. *N Engl J Med.* 2014;370:1532–1540.

Antimotility drugs plus antimicrobials

The combination of antimotility drugs plus antimicrobials provides the fastest relief of diarrheal symptoms. The antimotility drug quickly acts to reduce the number of stools, whereas the antimicrobial cures the infection.[107] In military personnel stationed in Turkey with TD primarily caused by ETEC, the median time to the passage of the

last unformed stool was shortened to as little as 3 hours in recruits taking loperamide (4 mg PO initially, then 2 mg PO as needed; maximum 16 mg/day) plus either levofloxacin (single 500-mg dose) or azithromycin (single 1-g dose).[113] In otherwise healthy U.S. students at least 18 years old attending school in Mexico, the combination of rifaximin (200 mg PO three times daily for 3 days) plus loperamide (4 mg initially, then 2 mg after each unformed stool) relieved diarrheal symptoms faster (27 ± 4.13 hours) than did rifaximin alone (32.5 ± 4.14 hours) or loperamide alone (69 ± 4.11 hours).[112]

BLOODY DIARRHEA WITH OR WITHOUT FEVER, OR DIARRHEA

Invasive pathogens including *Shigella*, *Campylobacter*, and, less commonly, *Salmonella*, noncholera *Vibrios*, and *Aeromonas* species are suspected in the setting of acute bloody diarrhea with fever. *Campylobacter* species are frequent causes of TD in travelers to Southeast Asia (25%–35% of reported pathogens) and South Asia (15%–25% of reported pathogens).[16]

Antimicrobials alone

A comparative study reported the highest cure rate with a single dose of azithromycin 1 g (96%), followed by 3 days of either azithromycin 500 mg daily (85%) or levofloxacin 500 mg daily (71%).[113] The lower cure rate with levofloxacin was because of infection with levofloxacin-resistant *Campylobacter* species. Nausea during the 30 minutes after receipt of the first antimicrobial dose was more common in persons given 1 g of azithromycin versus the other regimens (14% vs >6%, respectively).[113]

Rifaximin should not be used in patients with diarrhea complicated by fever and bloody stools, being ineffective against invasive enteropathogens, for example, *Salmonella*, *Shigella*, and *Campylobacter* species.[105]

Case 69-15, Question 4: Based on the symptoms each traveler is experiencing, what drug therapies are available for W.D. and B.D. that can be considered to reduce the duration and severity of their TD?

For travelers with *mild* watery diarrhea without fever or bloody stools (as with W.D.), loperamide can be used, often relieving symptoms in <24 hours.[104] If improvement is not evident within 12 hours, an antimicrobial could be started.[106]

For travelers with moderate-to-severe diarrhea with fever or bloody stools (as with B.D.), antimicrobial therapy is recommended to shorten the duration and severity of the diarrheal illness.[104] Treatment options include fluoroquinolone or azithromycin (**Table 69-3**). Azithromycin is recommended for travelers to areas with a high prevalence of fluoroquinolone-resistant *Campylobacter* species,[104] including Thailand (93%), Nepal (71%), Asia (70%), Latin America (61%), and Africa (31%),[105] or for travelers not responding within 48 hours to a fluoroquinolone.[104] Rifaximin is not effective for TD caused by invasive enteropathogens[16] and is not recommended for B.D.

Table 69-3
Dosing of Agents Commonly Used in *Clostridioides difficile* Infection

Agent	Standard Dosing
Antibacterials	
Vancomycin	125–500 mg orally four times daily for 10 days
Fidaxomicin	200 mg orally twice daily for 10 days
Metronidazole	500 mg orally three times daily for 10–14 days
Adjunctive Agents	
Bezlotoxumab	10 mg/kg IV infusion over 60 minutes, one time

IV, intravenous.

Source: Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis*. 2021;73(5):e1029–e1044.

POSTINFECTIOUS COMPLICATIONS OF TRAVELER'S DIARRHEA

Case 69-15, Question 5: Three weeks after returning from their trip, unlike W.D. who is free of intestinal symptoms, B.D. continues to have episodes of loose stools and abdominal discomfort, for which she seeks medical attention. On physical examination, her vital signs are stable and she is afebrile. The physician believes her symptoms are consistent with PI-IBS. What are B.D.'s risk factors for PI-IBS and why is her clinical presentation consistent with this diagnosis? What therapies can be recommended to manage her symptoms?

Clinical Presentation and Risk Factors

Postinfectious complications of TD include reactive arthritis and Guillain–Barré syndrome that are associated with *C. jejuni* infection and PI-IBS, which may occur in 3% to 17% of travelers following a diarrheal episode[16] by invasive pathogens including *Campylobacter*, *Salmonella*, and *Shigella* species.[9] Risk factors for PI-IBS include a severe episode of TD (as with B.D.), the number of episodes, pretravel diarrhea, pretravel adverse life events, and infection with heat-labile toxin-producing ETEC.[16]

Management

Treatment of PI-IBS is aimed at providing symptomatic relief; antimicrobials have not been proven to be beneficial and may be harmful.[114] Diarrheal symptoms can be managed with loperamide; if postprandial fecal urgency is problematic, taking loperamide 30 minutes before meals is recommended. Bloating and abdominal discomfort can be managed with simethicone or antispasmodic agents[75]; chronic abdominal symptoms can be managed with low doses of amitriptyline and selective serotonin reuptake inhibitors.[114] About 50% of patients with PI-IBS recover within 6 years, although recovery is less likely in the setting of persistent depression or anxiety.[114]

Prevention of PI-IBS with chemoprophylaxis of TD has not been proved. A recent randomized, double-blind, placebo-controlled study evaluating prophylactic rifaximin for the prevention of diarrhea in travelers to South and Southeast Asia did not find rifaximin to reduce the occurrence of new-onset irritable bowel syndrome (IBS). The absence of a benefit could be attributed to inadequate power of the study to detect a true difference; more studies are needed to address this issue.[115]

Prophylaxis

Case 69-15, Question 6: On hearing of the travels of W.D. and B.D., friends J.G. and T.M. begin planning a similar vacation to Central America, but they want to prevent the occurrence of any diarrheal illness. Neither friend has any significant medical history. Should prophylaxis be recommended for these travelers? What drug therapies can be recommended for the chemoprophylaxis of TD?

CANDIDATES FOR ANTIMICROBIAL PROPHYLAXIS AND SPECIFIC AGENTS

Antimicrobial prophylaxis for TD is considered when the benefit of prophylaxis outweighs the risks of drug therapy including adverse drug reactions such as photosensitivity with fluoroquinolones, bacterial resistance, and expense.[102],[115] In otherwise healthy persons, TD is typically a self-limiting illness lasting several days, and should it occur, traveler's self-management of TD reduces the time to the last unformed stool to within 24 hours of the onset of illness.[116] For these reasons, routine chemoprophylaxis for TD is not recommended.

Chemoprophylaxis could be considered for travelers at greatest risk for infection or its complications: persons in whom a diarrheal illness could complicate an underlying medical problem (eg, insulin-dependent diabetes mellitus, congestive heart failure, reactive arthritis, inflammatory bowel disease, advanced cancer, or HIV infection); and persons with conditions that increase the risk of

enteric infection (eg, genetic predisposition, gastric disease, or surgery).[102],[107] If offered, chemoprophylaxis should not extend beyond 2 to 3 weeks.[16],[104] Thus, these travelers are not candidates to receive antimicrobial prophylaxis for TD. Instead, at the onset of illness, they should follow their self-treatment plan for TD they received from their pretravel clinic visit.

For travelers who are candidates for chemoprophylaxis of TD, the following options are available.

Antimicrobials

Chemoprophylaxis with a fluoroquinolone (ciprofloxacin 500 mg or levofloxacin 500 mg given daily during travel but not exceeding 2–3 weeks and for 2 days after return) is recommended to reduce the incidence of diarrheal illness.[16],[104] However, the current efficacy of fluoroquinolones should be viewed with caution, given the rising fluoroquinolone resistance in common enteropathogens[115] including ETEC and EAEC in India, and *Campylobacter* species in Asia and Latin America.[105] Azithromycin 250 mg daily is an alternative chemoprophylactic agent and preferred for travel to destinations where *Campylobacter* species is a common cause of TD, for example, South and Southeast Asia.[104]

Rifaximin is not FDA approved for the prophylaxis of TD, but it has been effective for the prevention of TD in students traveling from the United States to Mexico where ETEC is a common enteropathogen.[117] A more recent randomized, double-blind, placebo-controlled study showed only a modest (48% protection) benefit of rifaximin compared to placebo in otherwise healthy travelers to South and Southeast Asia—areas where enteroinvasive pathogens are frequent causes of TD.

Miscellaneous agents

BSS, two tablets (526 mg/dose) four times daily for a maximum of 3 weeks has a protective efficacy of 65% against TD.[118] The problems with BSS because of inconvenient dosing, salicylate content, and unpleasant adverse effects (eg, grayish black fecal and dark tongue

discoloration) should be considered. BSS avoids the acquisition of MDR organisms and changes in the microbiome; therefore, it is recommended for prophylaxis by some organizations.[102]

Probiotics have been studied on the basis of their ability to prevent enteropathogen colonization. The effectiveness of probiotics has not been determined and more studies are needed before these agents can be routinely recommended.[102,105]

ESCHERICHIA COLI O157:H7

Epidemiology

CASE 69-16

QUESTION 1: P.J., a 3-year-old female, is brought to the ED because of "stomach pains" and diarrhea that has progressed from nonbloody to bloody over the past 48 hours. Five days before the onset of diarrhea, the family celebrated her birthday at a fast-food restaurant; P.J.'s parents ate fish sandwiches, and P.J. ate a hamburger. P.J.'s mother noted that the hamburger was not thoroughly cooked because the juices from the hamburger were still pinkish. P.J. has no significant medical history. During the week, she attended a day care center.

On physical examination P.J. is afebrile, with signs of mild-to-moderate dehydration. A stool sample is negative for fecal leukocytes. The physician assesses her illness as bloody diarrhea, possibly caused by Shiga toxin–producing *Escherichia coli* (STEC). The plan is to admit P.J. to the hospital for hydration, observation, and further workup.

What clinical and laboratory findings and epidemiologic history are consistent with the diagnosis of STEC as the cause of P.J.'s illness?

E. coli O157:H7 is a strain of *E. coli* that produces Shiga toxins as one of its mechanisms of causing GI illness. A second virulence factor of STEC strains is their ability to attach to and damage the intestinal mucosa.[119] These *E. coli* bacteria cause a wide spectrum of illness, including asymptomatic carriage, mild and nonbloody

diarrhea, bloody diarrhea (hemorrhagic colitis), HUS, and thrombotic thrombocytopenia purpura.[120]

E. coli O157:H7 should be suspected in the setting of abdominal cramps with nonbloody diarrhea that progresses to bloody diarrhea over 1 to 2 days.[121] Unlike bloody diarrhea associated with *Shigella* or *Campylobacter* species, fever is often absent or of low grade because this pathogen is not invasive.[122] However, patients with severe illness are more likely to have fever.[123]

STEC is most commonly spread by consumption of undercooked beef products that are contaminated with *E. coli* O157:H7, although other modes of acquiring this infection have been reported. The incubation period for this infection is usually 3 to 4 days, which is consistent with P.J.'s recent history of eating undercooked hamburger. In most instances, the illness resolves in 5 to 8 days.[124] Fecal leukocytes may or may not be found in stool samples.[125]

Hemolytic Uremic Syndrome

Case 69-16, Question 2: Forty-eight hours after admission to the hospital, P.J. is pale and has developed several "bruises" on her extremities. The nurse recorded only a minimal output of darkened urine during the past 24 hours. New laboratory test results reveal blood urea nitrogen (BUN), 150 mg/dL; serum creatinine (SCr), 6 mg/dL; serum potassium (K), 6.8 mEq/L; WBC count, 20,000 cells/mm^3; hemoglobin (Hgb), 5 g/dL; platelets, 50,000 cells/mm^3; and urinalysis finding is positive for blood and protein. The stool specimen sent on admission returns a positive result for *E. coli* O157:H7. What complication of *E. coli* O157:H7 infection does P.J. now display?

The new clinical and laboratory findings support the diagnosis of HUS, a well-known complication of STEC infection. HUS is characterized by the triad of thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure with oliguria.[126] On physical examination, P.J.'s "bruises" on her extremities are consistent with thrombocytopenia, which is confirmed by the low platelet count. Her pale appearance is consistent with anemia and is confirmed by the low Hgb. The dark urine is caused by the color

imparted from bilirubin because of red cell lysis (hemolytic anemia). Finally, P.J.'s decreased urine output and increased SCr and BUN concentrations are consistent with renal failure.[127] P.J. has several risk factors for HUS: her age (ie, children age older than 5–15 years, median age 4–8 years), fever, increased peripheral WBC count, and the season of the year (ie, summer).[123],[126],[128–131] Although not present in this case, other possible risk factors for developing HUS are age older than 65 years[125] and treatment with antimotility or antidiarrheal agents,[132] although this has not been universally confirmed.[123],[131] The progression of *E. coli* O157:H7 gastroenteritis to HUS typically becomes apparent about 1 week after the onset of diarrhea.[123],[126],[128] Of children, 3% to 7%[132] may develop HUS, with a mortality rate ranging from 3% to 5%.

In adults, *E. coli* O157:H7 infection progresses to HUS in as many as 27% of patients, with a higher rate in patients age older than 65 years.[123] HUS-related mortality has reached 42% in patients age older than 15 years[123]; elderly patients in nursing homes have a mortality rate of up to 88%.[133]

Treatment

Case 69-16, Question 3: Would P.J. benefit from drug therapy, including antimicrobial, antimotility, or antidiarrheal agents?

Other than supportive measures to manage the complications associated with illness caused by *E. coli* O157:H7, no specific drug therapy for this infection exists.[121] In retrospective and prospective studies, antibiotics have not influenced the severity of illness, the duration of diarrhea or other GI symptoms.[134] When TMP-SMX was started a mean of 7 days after the onset of diarrhea, the duration of *E. coli* O157:H7 excretion was not altered.[135]

The effect of antibiotic administration on the risk of *E. coli* O157:H7 complications (eg, HUS) remains also controversial. A meta-analysis of 17 studies revealed no association between antibiotic administration and development of HUS when all studies

were pooled.[136] This lack of association was similar to an earlier meta-analysis of studies.[137] However, when restricting the newer meta-analysis to higher quality studies with more rigorous definitions, the analysis suggests antibiotic use to increase HUS risks.[136]

Therefore, currently, clinicians do not generally recommend antibiotic treatment for STEC. However, according to active U.S. surveillance reports, nearly two-thirds of patients with this diagnosis receive antimicrobial therapy at some point in their infection, including 29% of patients receiving therapy after confirmed diagnosis.[138] Despite these numbers, P.J. should not receive antibiotic therapy at this time. Clinicians must carefully weigh empiric antibiotic treatment before an organism has been identified.[136]

Antimotility drugs are not recommended for patients with *E. coli* O157:H7 infection because they have been variably associated with an increased risk of progression to HUS,[132] although other studies have failed to find an association.[123],[131] Despite these concerns, recent reports suggest that up to 31% of patients continue to receive antimotility agents for this infection.[138] Although the explanation for the increased risk is unknown, the reduction in bowel motility may decrease the clearance of organisms from the GI tract, thereby increasing the absorption of toxins. Administration of antimotility drugs within the first 3 days of illness has been associated with a longer duration of bloody diarrhea.[139]

Prevention

Case 69-16, Question 4: P.J.'s family members want to know what they could have done to prevent this infection. On discharge from the hospital, is it safe for P.J. to return to her day care center?

STEC is often spread to humans by consumption of contaminated beef products that are not thoroughly cooked.[120] Because thorough cooking kills this organism, meat should be well cooked (ie, juices from meat should be clear, not pink). In addition, this infection can be

acquired by consuming other contaminated foods, including water, unpasteurized milk, apple cider, lettuce, and sprouts.[120],[121]

Finally, because contact with infected persons commonly results in transmission of this infection to others,[132],[133] P.J. should not return to day care until at least 48 hours after her diarrhea has ceased.[134]

CLOSTRIDIOIDES (CLOSTRIDIUM) DIFFICILE INFECTION

Mild-to-Moderate Infection

CLINICAL PRESENTATION AND DIAGNOSIS

CASE 69-17

QUESTION 1: B.W., a 35-year-old female, is admitted to a 10-bed medical ward for the treatment of *Streptococcus pneumoniae* meningitis. On arrival, she is started on ceftriaxone (Rocephin®) 2 g IV every 12 hours and improves over the next few days. On day 7 of antibiotic therapy, she reports feeling warm, with cramping abdominal pain and diarrhea. She begins passing mucoid, greenish, foul-smelling watery stools and has a temperature of 101 °F (38.33 °C). Microscopic examination result of a stool sample is positive for fecal leukocytes. The physician's assessment of B.W.'s clinical and laboratory findings is antibiotic-associated diarrhea (AAD), most likely caused by *C. difficile*.

What is the most likely mechanism for this patient's AAD?

AAD is a common complication of antimicrobial therapy.[140] The mechanisms by which antibiotics cause diarrhea include direct allergic and toxic effects on intestinal mucosa, and alterations of GI motility (eg, erythromycin) and of normal intestinal flora. Changes in the normal bowel flora can lead to changes in carbohydrate or bile acid metabolism by intestinal bacteria or to overgrowth of pathogenic bacteria, either of which may be followed by diarrhea.[140] Bacteria known to be associated with AAD include *C. perfringens*, *S. aureus*,

Klebsiella oxytoca, *Candida* species, and *C. difficile.* CDI is the most clinically relevant microbial cause and the focus of this section.

A spore-forming, gram-positive anaerobic bacillus, *C. difficile* can cause a wide spectrum of syndromes, including asymptomatic carriage, diarrhea of varying severity, colitis with or without formation of pseudomembranes, toxic megacolon, colonic perforation, and death.[140]

The overall incidence of CDI has been decreasing with lower health care–associated infections, but the number of community-associated infections remains stable, now representing nearly half of all CDI infections.[141] The pathogenesis of CDI involves disruption of the normal colonic flora, most commonly by antibiotics. An increasing number of cases in the outpatient setting have been identified without any antibiotic exposure, making additional risk factors difficult to find, although food and pet exposure has been suggested.[141],[142] Recent data suggest that proton-pump inhibitors may be associated with CDI.[143],[144] Alteration of the colonic microflora allows for overgrowth of toxin-producing strains of *C. difficile.* These toxins, primarily toxins A and B, are responsible for causing colonic inflammation and the clinical manifestations of this infection.[140],[141]

A highly pathogenic strain of *C. difficile* has been described in outbreaks in the United States and around the world.[141],[145] This strain, labeled BI/NAP1 (or ribotype 027), generally causes more severe disease. Among its increased virulence factors are an increased production of both toxins A and B and a binary toxin. This ribotype has become endemic in some facilities and appears to cause more severe disease even in nonoutbreak situations, although national rates seem to be decreasing.[141],[146]

Case 69-17, Question 2: Why is B.W.'s history and presentation consistent with AAD caused by *C. difficile*?

B.W.'s major risk factor for acquiring CDI is her receipt of an antibiotic within the last 2 weeks. *C. difficile* is a common cause of nosocomial diarrhea. The clinical and laboratory findings consistent

with CDI include nonbloody, mucoid, greenish, foul-smelling watery stools and crampy abdominal pain. Patients usually present with low-grade fevers, but temperature may be >104 °F (40 °C).[147] Peripheral leukocytosis is common with CDI, sometimes with WBC >30,000 cells/mm^3.[147],[148] Fecal leukocytes are variably present in CDI and are not clinically useful for diagnosis.[149]

The onset of symptoms of CDI varies widely from a few days after the start of antibiotic therapy to 8 weeks after the agent is discontinued.[147] Other risk factors for acquiring CDI are admission to a hospital in which *C. difficile* is endemic, including asymptomatic carriage, or in which there is an ongoing outbreak of CDI.

Case 69-17, Question 3: How can B.W.'s diagnosis of CDI be confirmed?

Finding toxins in unformed stool of symptomatic patients is the gold standard for diagnosis. A two-step diagnostic method is currently recommended. The two-step test first looks for the presence of glutamate dehydrogenase (GDH) antigen as a quick and inexpensive screening test. GDH is produced by all *C. difficile* strains, so positive GDH tests are then followed by toxin-detecting nucleic acid amplification testing (NAAT) or enzyme-linked immunoassay (EIA).[150] Samples with negative results for GDH are considered negative and not tested further. Culture, although helpful, is complicated by the fact that of the *C. difficile* strains isolated from various populations, 5% to 25% do not produce toxins (nontoxigenic) and do not cause colitis or diarrhea.[147] Routine testing for specific *C. difficile* strains such as ribotype 027 is not typically available in most settings.[150]

Colonoscopy with biopsy may be used to diagnose *C. difficile* colitis through its characteristic colonic changes, which are raised, yellowish nodules or plaque-like pseudomembranes, often with skip areas of normal mucosa.[147]

Case 69-17, Question 4: How can B.W.'s CDI be differentiated from enigmatic AAD?

Only 10% to 20% of cases of AAD have positive findings for toxigenic *C. difficile*; the remaining cases have an unknown cause and are referred to as simple, benign, or "nuisance" diarrhea.[140] Benign diarrhea is a self-limited illness that resolves with nonspecific supportive measures and discontinuation of antibiotics. These clinical entities can be differentiated from one another by several objective measures. In hospitalized patients, watery diarrhea, low functional capacity, acid suppression, low albumin, and a WBC >13,000 cells/mm^3 were significant predictors of CDI.[151] Other clinical features that suggest CDI rather than enigmatic diarrhea are constitutional symptoms, lack of an antibiotic dose relationship to the illness, and hospital-wide epidemics of diarrhea.[152]

TREATMENT

Case 69-17, Question 5: B.W.'s stool sample is positive for both GDH and *C. difficile* toxin. What is the general plan to treat B.W.'s CDI?

After replacement of fluids and electrolytes, there are several steps to most effectively manage B.W.'s CDI. The first is to discontinue the offending drug (if possible), which in B.W.'s case is probably the antibiotic ceftriaxone. Although some data suggest that withdrawal of the precipitating antibiotic and supportive care may be sufficient for mild disease, all available guidelines suggest specific antimicrobial treatment.[153]

Because B.W. is being treated for bacterial meningitis, a life-threatening infection, discontinuing antibiotics is not an option. A second option is to change her antimicrobial therapy to an agent less likely to cause CDI. B.W. is taking a cephalosporin, which, as with ampicillin, amoxicillin, clindamycin, and the fluoroquinolones, is frequently implicated as a cause of *C. difficile* diarrhea. In contrast, antibiotics, such as TMP-SMX, and aminoglycosides, are less commonly associated with CDI.[154–156] None of these antimicrobials, however, is a suitable alternative for treating *S. pneumoniae* meningitis.

B.W. should also receive therapy directed against *C. difficile* while continuing to take ceftriaxone for the treatment of her bacterial meningitis.

Specific *Clostridioides difficile*–directed antimicrobials

Case 69-17, Question 6: What antibiotic should be selected to treat B.W.'s CDI?

The oral agents currently used to treat CDI are vancomycin, fidaxomicin, and metronidazole (if none of the previous agents is available) (Table 69-3). The differentiation between these three agents is complex and evolving, but it is guided in part by severity of illness and concern for recurrence.[157–161] The most optimal definition of severe disease is not well established, but general markers of instability of vital signs with high white counts and changes in albumin and SCr are suggested[150] (**Table 69-4**). In patients categorized as having mild-to-moderate disease severity, vancomycin or fidaxomicin are generally recommended as the preferred initial agents, a major change from earlier guidance that suggested metronidazole as the first-line agent.[150,158] Two major trials comparing metronidazole and vancomycin[162,163] in contemporary *C. difficile* settings reported superiority of vancomycin to metronidazole in mild/moderate disease, prompting the relegation of metronidazole as a second-line agent. This hierarchy of efficacy for vancomycin and fidaxomicin over metronidazole was confirmed in a Cochrane review of 22 studies on *C. difficile* treatment.[153] Recent reports have shown increases in *C. difficile* resistance to both metronidazole and vancomycin, but the clinical significance in treatment selection is unknown.[164] Antibiotic sensitivities, therefore, are not routinely performed on *C. difficile*.

Table 69-4
***Clostridioides difficile* Infection Severity of Disease**

	Published Guidelines

Severity	*ESCMID 2014*	*SHEA/ISDA 2017*
Mild-to-moderate	Diarrhea plus signs and symptoms that do not meet severe or complicated criteria	White blood count ≤15,000 cells/mL *and* Serum creatinine <1.5 mg/dL
Severe	CDI with (one or more specific signs and symptoms of) severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy or death; or one or more of the following: 1. Marked leucocytosis (leucocyte count >15 × 10^9/L) 2. Decreased blood albumin (<30 g/L) 3. Rise in serum creatinine level (≥133 μM or ≥1.5 times the premorbid level)	White blood count ≥15,000 cells/mL *or* Serum creatinine >1.5 mg/dL
Fulminant	N/A	Hypotension or shock, ileus, megacolon

ICU, intensive care unit; N/A, not applicable.

Sources: McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):987–994; Debast SB, Bauer MP, Kuijper EJ, European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology (ESCMID) and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect*. 2014;20 Suppl 2:1–26.

Oral vancomycin produces fecal concentrations that are several 100 times the concentration needed to inhibit toxin-producing strains of *C. difficile.*[161] A 10-day course of oral vancomycin (125 PO four times daily) is recommended for the treatment of mild/moderate CDI.[150] IV vancomycin is not effective for treatment. Although oral

vancomycin is not well absorbed, measurable serum concentrations have been found in patients with both normal and compromised renal function, although higher and longer dose regimens, severe infection, and renal dysfunction were more associated with serum concentrations.[165]

Fidaxomicin is the newest antimicrobial indicated for the treatment of CDI.[166],[167] Fidaxomicin is a macrocyclic antibiotic active against *C. difficile* that is poorly absorbed and achieves high colonic concentrations.[168] It has limited antimicrobial spectrum and largely preserves colonic flora. In the clinical trials, patient outcomes on initial infection were similar when compared with vancomycin.[167] Although at a significantly higher cost of therapy, one potential advantage for fidaxomicin is in recurrence rates, which were found to be significantly lower with fidaxomicin compared to vancomycin (15.4% vs 25.3%, P = .005). Some clinicians and the most recent IDSA guidelines are now suggesting this advantage is large enough to prefer fidaxomicin over vancomycin in many patient groups.[169],[170] A recent meta-analysis suggests fidaxomicin may have better outcomes than does vancomycin in all but severe infection.[169] Although recurrence is a concern in CDI treatment, it is not yet clear if it is possible to identify patients for whom the higher cost would provide an additional benefit from this effect.

Metronidazole is well absorbed after oral administration and is excreted through the biliary tract before reaching the colon. Because metronidazole is a carcinogen and, in some animal species, a mutagen, it should be used in pregnancy only if clearly needed. Similarly, metronidazole's safety in children has not been proved, and many prefer not to use it in this population if other options exist.[154]

Because B.W. is not critically ill, vancomycin (125 mg PO four times daily) for 10 days is recommended as first-line treatment.[150] Oral fidaxomicin is generally considered equally efficacious in mild-to-moderate disease, with some suggestions of superiority to vancomycin in pooled analyses.[150],[170],[171] Oral vancomycin capsules and a prepared oral solution are expensive but less than fidaxomicin and more than a course of oral metronidazole. Some of this cost

differential can be offset using the IV vancomycin preparation to prepare an oral solution that can be flavored and prepared as directed in the package insert. Once therapy directed against *C. difficile* is initiated, diarrhea or cramping should subside within 2 to 4 days.

ALTERNATIVE THERAPIES

Probiotics

Using probiotics introduces probiotic microorganisms into the normal flora to counteract disturbances and reduce the colonization with pathogenic species.[172] Orally administered *Lactobacillus* species and the yeast *S. boulardii* have been used to treat CDI, but no good data support the use of probiotics alone. Adjunctive use has been suggested to prevent CDI and its recurrences. A hospital trial looking at prevention of all AAD with *Lactobacillus* reported positive results for the prevention of CDI.[173] A Cochrane review of 31 studies looking at probiotics for the prevention of CDI found a positive benefit, particularly in patients with a higher baseline risk of CDI.[174] Although positive results have been suggested, there is caution to the widespread use of probiotics, with reports of isolated adverse effects, including fungemia, with ingestion of viable *S. boulardii* being reported.[158],[175]

Antidiarrheals

CASE 69-17, QUESTION 7: Should B.W. be given any antidiarrheal agent to relieve her symptoms?

Opiates and other antiperistaltic agents should be avoided in patients with CDI. Although these types of drugs may relieve diarrheal symptoms, they may also delay toxin removal from the GI tract. Evidence supporting these negative effects is minimal because data are scarce,[11] but caution would suggest avoiding any antimotility agent in B.W.

Case 69-17, Question 8: Following resolution of B.W.'s CDI, is it necessary to send a follow-up stool sample to determine whether it is negative for *C. difficile* toxin?

After resolution of diarrhea, obtaining a follow-up stool sample to determine whether it is negative for *C. difficile* toxin is not recommended as part of routine practice because many test results may remain positive for an extended duration and most patients with continued positive test results will not develop a recurrence of their diarrhea.[150] In addition, up to 3% of healthy adults carry small numbers of *C. difficile* in their feces, whereas colonization rates are much higher (31%–37%) in hospitalized patients and infants under 1 month.[176],[177]

Transmission

CASE 69-18

Question 1: Over the next few days, five patients on the ward with B.W. are found to have *C. difficile* toxin in their stools. Three patients have diarrhea and the other two are asymptomatic.

What is the role of hospital-wide stewardship interventions in controlling this outbreak?

Controlling overall antibiotic use in the hospital is considered a very useful strategy. Antimicrobial stewardship is increasingly seen as a major control mechanism for CDI.[150] Restricting the use of agents such as clindamycin and fluoroquinolones can be an effective component in efforts to control nosocomial outbreaks of CDI, especially with the emergence of the BI/NAP1 strain.[178],[179] A meta-analysis of antibiotic stewardship impacts on *C. difficile* revealed a 32% reduction in incidence when implemented.[180]

Thorough cleaning and disinfecting of the hospital environment is important to limit spread. In addition, hand hygiene remains of particular importance. It should be noted that, in addition to alcohol-based hand sanitizers, soap and water hand hygiene is

recommended because alcohol-based hand sanitizers do not reliably kill *C. difficile* spores that can be spread from patient to patient.[150]

Finally, the overuse of acid-suppressive therapy in the hospital setting, particularly proton-pump inhibitors, has been linked to increases in CDI.[180] Efforts to control the use of these drugs have been increasingly recommended.[181]

Case 69-18, Question 2: What effect will the current CDI outbreak have on the outcomes of the infected patients and on health care costs?

In a prospective study, hospitalized patients who developed CDI had a 3.6-day increase in length of stay.[182] A large retrospective cohort study in the Veterans Affairs Administration reported a 2.3-day increase in hospitalization, with an increase of 4.4 days with severe disease.[183] A review of available economic data suggests additional hospital costs of $8900 to $30,000 for each case of CDI.[184] In addition, CDI has been shown to decrease the likelihood that hospitalized patients be discharged to home, with a significant increase in hospice or long-term care transfers.[185] The current outbreak on the hospital ward is likely to increase both hospital costs and individual lengths of stay and may impact patient discharge locations.

Severe *Clostridioides difficile* Infection

CASE 69-19

Question 1: H.T. is a 76-year-old who has also developed CDI on the ward. His temperature is 102 °F (38.89 °C), WBC is 22,000 cells/mL, and he is hypotensive. He currently has severe abdominal pain, a computed tomography (CT) scan result is showing pseudomembranes, and he is being evaluated for possible surgical intervention.

What treatment is recommended for H.T. who is critically ill from a CDI? What criteria should be used to characterize patients as “critically ill”?

Up to 57% of patients with antibiotic-associated pseudomembranous colitis who require surgical intervention (colectomy) die.[186] Although the precise definition of "critically ill" is not clear, it has variably included patients with pseudomembranes, age older than 60, serum albumin >2.5 mg/dL, fever >100.94 °F (38.3 °C), severe abdominal pain, and marked leukocytosis (>15,000–20,000 cells/mL).[147],[162] Guidelines from the Society for Healthcare Epidemiology of America and the IDSA have suggested the definition of severity as the presence of either of the following two parameters: WBC count ≥15,000 cells/mL or SCr >1.5 mg/dL. An additional definition of "fulminant" disease has been suggested for patients such as H.T. who have hypotension, shock, ileus, or megacolon[150] (see Table 69-4). The recommended therapy for H.T. would be a combination of high-dose vancomycin (500 mg) PO four times daily and metronidazole 500 mg IV every 8 hours.[150] This combination therapy was shown to reduce mortality from 36.4% to 15.9% when compared with monotherapy in a small observational study.[187] The combination of high-dose therapies is theorized to overcome the difficulties for either medication to get to the site of action in the colon.

NONORAL TREATMENT

CASE 69-19, QUESTION 2: Three days after oral vancomycin and IV metronidazole is initiated, H.T. develops an ileus and cannot take anything by mouth. What therapeutic options are available to treat H.T.'s pseudomembranous colitis?

Adequate antibiotic levels in the colon are necessary to treat *C. difficile*–associated pseudomembranous colitis. If the oral route is not feasible (eg, patients with an ileus or bowel obstruction), the clinician must choose an agent that is either secreted or excreted into the GI tract in its active form. IV vancomycin is not a desirable agent in this situation because it is not secreted into the GI tract. In contrast, IV metronidazole is eliminated by both renal and hepatic routes, and bactericidal concentrations are achieved in both serum and bile.[188]

The literature contains few reports of successful attempts to treat CDI or pseudomembranous colitis with IV metronidazole (500 mg every 6–8 hours) alone.[189–191] Likewise, unsuccessful attempts to treat CDI with IV metronidazole have been reported.[189,192] The clinical response of CDI to PO vancomycin in a patient who did not survive was difficult to ascertain.[161]

In adults, enteral vancomycin 500 mg four times daily can be given through a nasogastric tube, or an ileostomy or colostomy (if present). Several reports of successful outcomes using intracolonic vancomycin (as an adjunct to oral/enteral vancomycin or to IV metronidazole) in patients with CDI have been documented, and this approach is currently recommended.[150,170] Rectal doses of vancomycin have varied from 500 mg every 4 to 8 hours to 1000 mg/L every 8 hours.[193] Rectal vancomycin administration volumes of 500 mL are suggested to better ensure delivery to the transverse and distal colon.[150] Saline can be used as a carrier, but electrolytes should be monitored because absorption can occur. Lactated Ringer solution may be preferred if hyperchloremia is present.[7]

Because patients with CDI are at risk for colonic perforation, some clinicians suggest that enteral vancomycin be administered cautiously.

Recurrence

CASE 69-20

Question 1: P.V. is a 57-year-old male who acquired CDI on the same ward as the other infected patients. P.V. was treated with vancomycin 125 mg PO four times daily for 10 days while in the hospital. Two weeks after discharge from the hospital, P.V. once again developed abdominal pain and diarrhea. His clinic physician assumed these symptoms could not be related to a recurrence of his CDI because he had responded so well to vancomycin.

What is the likelihood that CDI has recurred?

Regardless of the antibiotic regimen prescribed for CDI, symptomatic recurrence occurs in 5% to 30% of patients who

respond to their initial treatment regimen.[150],[155] Recurrences occur 2 weeks to 2 months (median of 7 days) after treatment has been discontinued.[194] In most instances, recurrences are caused by germination of dormant spores that are intrinsically resistant to antibiotics. Reinfection with *C. difficile* from external sources, however, may account for up to half of all second episodes.[195] In rare instances, either vancomycin[196] or metronidazole[197] may have caused CDI.

Risk factors for recurrent CDI include increasing age (≥65 years), immune dysfunction, renal insufficiency, use of proton-pump inhibitors, continued use of antimicrobials during CDI treatment, glucocorticoid use, and certain *C. difficile* strains.[198–200] Further refinement of these risk factors may allow for the prediction of recurrences and guide tailored treatment options or the addition of other therapeutics in high-risk patients.

Data suggest that patients with a poor immune response to *C. difficile* toxin A are more likely to have a recurrence of CDI.[200] It is not clinically helpful in the case of P.V. because no standard tests are currently available for this immune response. The influence of the immune system, however, has led to the usage of IV immune globulin in refractory or severe cases of CDI.[201],[202] However, utility of the usage of immune globulins is still debated. Immune globulins would not be considered the next line of therapy for P.V.

Case 69-20, Question 2: How should P.V.'s CDI recurrence be treated?

Most infections resulting from recurrence are not related to bacterial resistance, and they may respond to retreatment with the same antibiotic used for initial treatment of the CDI.[155],[203] However, current recommendations suggest switching agents and considering alternate dosing strategies.[150],[170] Thus, an appropriate approach for P.V. is to administer a 10-day course of fidaxomicin 200 mg PO twice daily.

For patients with multiple recurrences of CDI, the optimal management plan is unresolved. Different approaches have been

tried, including (a) high-dose vancomycin (2000 mg/day PO)[204]; (b) a 4- to 6-week course with vancomycin, after which the dose is tapered over a 1- to 2-month period[204],[205]; (c) exchange resins[206],[207] with or without antibacterials; (d) “pulse” dosing of vancomycin every 2 to 3 days[204]; or a combination of vancomycin and rifampin (600 mg PO twice daily).[208] Tapered and pulse therapy with vancomycin was shown to be most effective in a clinical trial comparing multiple strategies and is now recommended.[170],[204]

When combined with standard antibiotic therapy, a clinical trial with the probiotic *S. boulardii* for cases of relapsing CDI noted a 65% response rate versus a 36% response rate for combination therapy with placebo.[209] The recurrence rate was reduced to 17% when *S. boulardii* was combined with high-dose vancomycin.[210]

Following treatment with vancomycin, a “chaser” course of rifaximin, a poorly absorbed rifamycin derivative, was successful in separate case series for patients with multiple recurrences.[211],[212] The most recent guidelines suggest rifaximin 400 mg PO three times daily for 20 days after a 10-day course of vancomycin 125 mg PO four times daily as an alternative for second or subsequent CDI recurrence.[170] Concern must be raised that the single failure occurred in concert with emerging rifaximin resistance.[211]

Because of its more minimal impact on fecal flora, fidaxomicin is recommended for recurrent infections, although there is less evidence for its use in recurrence compared to other recommended agents.[150],[170] Despite its much higher cost, fidaxomicin’s inherent advantage in limiting recurrence with initial treatment and treatment of first recurrences may lie in overall cost savings.[213],[214] A recent trial in older adults suggested that extended pulsed use of fidaxomicin 200 mg twice daily for 5 days followed by every other day dosing from days 7 to 25 led to low recurrence rates of 6% at 90 days versus 19% with conventional vancomycin dosing.[215]

Bezlotoxumab is a newly approved monoclonal antibody infusion directed against *C. difficile* toxin B. Bezlotoxumab does not have direct antibacterial activity against *C. difficile*, but it has been shown to reduce recurrence rates when combined with antimicrobial therapy in high-risk patients. In published studies, bezlotoxumab 10

mg/kg as a single infusion during antimicrobial treatment for *C. difficile* resulted in an absolute 10% reduction in recurrence rates of disease.[216] Further evaluation was completed for patients stratified by number of risk factors for recurrence, for example, age 65 years or older, history of CDI in the previous 6 months, compromised immunity, severe CDI, and isolation of a strain associated with poor outcomes (ribotypes 027, 078, or 244).[200] In this analysis, having three or more risk factors for recurrence showed the greatest benefit from bezlotoxumab with a 24.8% absolute reduction in recurrence, compared to a 14.2% reduction with one or two risk factors. Patients without known risk factors for recurrence did not gain a significant benefit from bezlotoxumab treatment. The cost of this therapy is significant (~$3800), and bezlotoxumab's exact place in therapy is currently under debate.[217] The new IDSA guidelines suggest its co-use to standard CDI treatment in patients with a recurrent CDI episode within the past 6 months as risk reduction of a subsequent CDI recurrence after initial clinical cure, whereas the American College of Gastroenterology (ACG) guidelines suggest its use as CDI prevention only in patients at high risk for recurrence.[170],[218] Further, owing to the potential for exacerbating heart failure, bezlotoxumab should be given with caution in patients with this disease.

Finally, fecal microbiota transplant (FMT) therapy has been more widely investigated in second and third recurrences and has shown significant promise.[219] Healthy fecal donors, often family members, are the usual source of fecal microbiota, although frozen "banks" of FMT samples have been increasing along with newly lyophilized versions.[220],[221] Administration of FMT can be provided through nasogastric or nasojejunal tubes, colonoscopy, or colonic enemas. Although published data overall remain small, a systematic review of the literature supports the efficacy (85% cure rates) and limited adverse effects of this therapy.[219] Long-term follow-up from 137 patients treated with FMT found an 82% durable response rate without recurrence.[222] A single cost-effectiveness model, using literature-based data, found FMT to be more cost-effective compared to treatment of recurrences with vancomycin.[223] The current CDI

guidelines recommend FMT after at least the second CDI recurrence to prevent further recurrent CDI.[218]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key Reference

Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. *Lancet*. 2017;390(10101):1539–1549. (25)

Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive salmonella infections. *Clin Microbiol Rev*. 2015;28(4):901–937. (34)

DuPont HL. Acute infectious diarrhea in immunocompetent adults. *N Engl J Med.* 2014;370(16):1532–1540. (5)

Goldstein EJ, Johnson S, Maziade PJ, et al. Pathway to prevention of nosocomial *Clostridium difficile* infection. *Clin Infect Dis*. 2015;60(Suppl 2):S148–S158. (181)

Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis*. 2021;73(5):e1029–e1044. (170)

Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. *Am J Gastroenterol*. 2021;116:1124–1147. (218)

McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):987–994. (150)

Meltzer E, Schwartz E. Enteric fever: a travel medicine oriented view. *Curr Opin Infect Dis.* 2010;23(5):432–437. (58)

Navaneethan U, Giannella RA. Mechanisms of infectious diarrhea. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5(11):637–647. (3)

Pawlowski SW, Warren CA, Guerrant R. Diagnosis and treatment of acute or persistent diarrhea. *Gastroenterology.* 2009;136(6):1874–1886. (9)

Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis.* 2017;65(12):e45–e80. (7)

Key Websites

Centers for Disease Control and Prevention. www.cdc.gov

COMPLETE REFERENCES CHAPTER 69 INFECTIOUS DIARRHEA

1. Barr W, Smith A. Acute diarrhea. *Am Fam Physician*. 2014;89(3):180–189.
2. Troeger C, Blacker BF, Khalil IA, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Infectious Diseases*. 2018;18(11):1211–1228. https://doi.org/10.1016/S1473-3099(18)30362-1
3. Navaneethan U, Giannella RA. Mechanisms of infectious diarrhea. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5(11):637–647.
4. Scallan E, Griffin PM, Angulo FJ, Tauxe R, Hoekstra RM. Foodborne illness acquired in the United States—unspecified agents. *Emerg Infect Dis*. 2011;17(1):16–22.
5. DuPont HL. Acute infectious diarrhea in immunocompetent adults. *N Engl J Med*. 2014;370(16):1532–1540.
6. Dickinson B, Surawicz CM. Infectious diarrhea: an overview. *Curr Gastroenterol Rep*. 2014;16(8):399.
7. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65(12):e45–e80.
8. Corinaldesi R, Stanghellini V, Barbara G, Tomassetti P, De Giorgio R. Clinical approach to diarrhea. *Intern Emerg Med*. 2012;7(Suppl 3):S255–S262.
9. Pawlowski SW, Warren CA, Guerrant R. Diagnosis and treatment of acute or persistent diarrhea. *Gastroenterology*. 2009;136(6):1874–1886.
10. DuPont HL. Clinical practice. Bacterial diarrhea. *N Engl J Med*. 2009;361(16): 1560–1569.

11. Murphy GS. Ciprofloxacin and loperamide in the treatment of bacillary dysentery. *Ann Intern Med*. 1993;118(8):582–586.
12. Bierer DW. Bismuth subsalicylate: history, chemistry, and safety. *Rev Infect Dis*. 1990; 12(Suppl 1):S3–S8.
13. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med.* 2019;25:716–729.
14. Su GL, Ko CW, Bercik P, et al. AGA clinical practice guidelines on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology*. 2020;159(2):697–705.
15. Dylag K, Hubalewska-Mazgaj M, Surmiak M, Szmyd J, Brzozowski T. Probiotics in the mechanism of protection against gut inflammation and therapy of gastrointestinal disorders. *Curr Pharm Des*. 2014;20(7):1149–1155.
16. Steffen R, Hill DR, DuPont HL. JAMA patient page. Traveler's diarrhea. *JAMA*. 2015;313(1):108.
17. Dolecek C, Phi La TT, Rang NN, et al. A multi-center randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. *PLoS One*. 2008;3(5):e2188.
18. Swerdlow DL, Ries AA. Cholera in the Americas. Guidelines for the clinician. *JAMA*. 1992;267(11):1495–1499.
19. King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep*. 2003;52(RR-16):1–16.
20. Sirinavin S, Thavornnunth J, Sakchainanont B, Bangtrakulnonth A, Chongthawonsatid S, Junumporn S. Norfloxacin and azithromycin for treatment of nontyphoidal *Salmonella* carriers. *Clin Infect Dis*. 2003;37:685–691.
21. Robilotti E, Deresinski S, Pinsky BA. Norovirus. *Clin Microbiol Rev*. 2015;28(1): 134–164.
22. Tate JE, Parashar UD. Rotavirus vaccines in routine use. *Clin Infect Dis*. 2014;59(9):1291–1301.
23. Morris JG Jr. Cholera and other types of vibriosis: a story of human pandemics and oysters on the half shell. *Clin Infect Dis*. 2003;37(2):272–280.
24. Centers for Disease Control and Prevention. Cholera vaccine for travelers. Accessed January 27, 2021. https://wwwnc.cdc.gov/travel/news-announcements/cholera-vaccine-for-travelers
25. Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. *Lancet*. 2017;390(10101):1539–1549.
26. Fillion K, Mileno MD. Cholera in travelers: shifting tides in epidemiology, management, and prevention. *Curr Infect Dis Rep*. 2015;17(1):455.
27. Nelson EJ, Nelson DS, Salam MA, Sack DA. Antibiotics for both moderate and severe cholera. *N Engl J Med*. 2011;364(1):5–7.

28. Khan WA, Saha D, Rahman A, Salam MA, Bogaerts J, Bennish ML. Comparison of single-dose azithromycin and 12-dose, 3-day erythromycin for childhood cholera: a randomised, double-blind trial. *Lancet*. 2002;360(9347):1722–1727.
29. Ryan ET, Madoff LC, Ferraro MJ. Case records of the Massachusetts General Hospital. Case 20-2011. A 30-year-old man with diarrhea after a trip to the Dominican Republic. *N Engl J Med*. 2011;364(26):2536–2541.
30. McMullan R, Edwards PJ, Kelly MJ, Millar BC, Rooney PJ, Moore JE. Food-poisoning and commercial air travel. *Travel Med Infect Dis*. 2007;5(5):276–286.
31. Chen XM, Keithly JS, Paya CV, LaRusso NF. Cryptosporidiosis. *N Engl J Med*. 2002;346(22):1723–1731.
32. Sparks H, Nair G, Castellanos-Gonzalez A, White AC. Treatment of cryptosporidium: what we know, gaps, and the way forward. *Curr Trop Med Rep*. 2015;2(3):181–187
33. Abubakar I, Aliyu SH, Arumugam C, Usman NK, Hunter PR. Treatment of cryptosporidiosis in immunocompromised individuals: systematic review and meta-analysis. *Br J Clin Pharmacol*. 2007;63(4):387–393.
34. Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive *Salmonella* infections. *Clin Microbiol Rev*. 2015;28(4):901–937.
35. Chimalizeni Y, Kawaza K, Molyneux E. The epidemiology and management of non typhoidal *Salmonella* infections. *Adv Exp Med Biol*. 2010;659:33–46.
36. Gordon MA. *Salmonella* infections in immunocompromised adults. *J Infect*. 2008;56(6):413–422.
37. Humphries RM, Fang FC, Aarestrup FM, Hindler JA. In vitro susceptibility testing of fluoroquinolone activity against *Salmonella*: recent changes to CLSI standards. *Clin Infect Dis*. 2012;55(8):1107–1113.
38. Kariuki S, Gordon MA, Feasey N, Parry CM. Antimicrobial resistance and management of invasive *Salmonella* disease. *Vaccine*. 2015;33(Suppl 3):C21–C29.
39. Ko WC, Yan JJ, Yu WL, et al. A new therapeutic challenge for old pathogens: community-acquired invasive infections caused by ceftriaxone- and ciprofloxacin-resistant *Salmonella* enterica serotype choleraesuis. *Clin Infect Dis*. 2005;40:315.
40. Gunell M, Kotilainen P, Jalava J, Huovinen P, Siitonen A, Hakanen AJ. In vitro activity of azithromycin against nontyphoidal *Salmonella* enterica. *Antimicrob Agents Chemother*. 2010;54(8):3498–3501.
41. Onwuezobe IA, Oshun PO, Odigwe CC. Antimicrobials for treating symptomatic non-typhoidal *Salmonella* infection. *Cochrane Database Syst Rev*. 2012;11:CD001167.

42. Hohmann EL. Nontyphoidal salmonellosis. *Clin Infect Dis*. 2001;32(2):263–269.
43. Pegues DA, Miller SI. *Salmonella* species. In: Bennett JE, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Vol 2. 9th ed. Elsevier Saunders; 2019:2725–2736.
44. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV*. Department of Health and Human Services. Accessed January 27, 2021. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines
45. Sanchez-Vargas FM, Abu-El-Haija MA, Gómez-Duarte OG. *Salmonella* infections: an update on epidemiology, management, and prevention. *Travel Med Infect Dis*. 2011;9(6):263–277.
46. Butler T. Treatment of typhoid fever in the 21st century: promises and shortcomings. *Clin Microbiol Infect*. 2011;17(7):959–963.
47. Dupont HL, Okhuysen PC. Bacillary dysentery: *Shigella* and enteroinvasive *Escherichia coli*. In: Bennett JE, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Vol 1. 9th ed. Elsevier Saunders; 2019:2737–2742.
48. Parry CM. The treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Viet Nam. *Trans R Soc Trop Med Hyg*. 2004;98(7):413–422.
49. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *N Engl J Med*. 2002;347(22):1770–1782.
50. Crump JA, Kretsinger K, Gay K, et al; Emerging Infections Program FoodNet and NARMS Working Groups. Clinical response and outcome of infection with *Salmonella* enterica serotype typhi with decreased susceptibility to fluoroquinolones: a United States Foodnet multicenter retrospective cohort study. *Antimicrob Agents Chemother*. 2008;52(4):1278–1284.
51. Parry CM, Basnyat B, Crump JA. The management of antimicrobial-resistant enteric fever. *Expert Rev Anti Infect Ther*. 2013;11(12):1259–1261.
52. Parry CM, Ho VA, Phuong LT, et al. Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. *Antimicrob Agents Chemother*. 2007;51(3):819–825.
53. Mahmud AK, Chowdhury AJ, Sarker ZM, et al. Typhoid fever. *Mymensingh Med J*. 2008;17(2):236–244.
54. Rai S, Jain S, Prasad KN, Ghoshal U, Dhole TN. Rationale of azithromycin prescribing practices for enteric fever in India. *Indian J Med Microbiol*. 2012;30(1):30–33.
55. Pandit A, Arjyal A, Day JN, et al. An open randomized comparison of gatifloxacin versus cefixime for the treatment of uncomplicated enteric fever. *PLoS One*. 2007;2(6):e542.

56. Frenck RW, Nakhla I, Sultan Y, et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clin Infect Dis*. 2000;31(5):1134–1138.
57. Bhutta ZA, Khan IA, Shadmani M. Failure of short-course ceftriaxone chemotherapy for multidrug-resistant typhoid fever in children: a randomized controlled trial in Pakistan. *Antimicrob Agents Chemother*. 2000;44(2):450–452.
58. Meltzer E, Schwartz E. Enteric fever: a travel medicine oriented view. *Curr Opin Infect Dis*. 2010;23(5):432–437.
59. Sjolund-Karlsson M, Rickert R, Matar C, et al. *Salmonella* isolates with decreased susceptibility to extended-spectrum cephalosporins in the United States. *Foodborne Pathog Dis*. 2010;7(12):1503–1509.
60. Dave J, Sefton A, de Pinna E, et al. Trends in antibiotic susceptibility of enteric fever isolates in East London. *Travel Med Infect Dis*. 2015;13(3):230–234.
61. Chisti MJ, Bardhan PK, Huq S, et al. High-dose intravenous dexamethasone in the management of diarrheal patients with enteric fever and encephalopathy. *Southeast Asian J Trop Med Public Health*. 2009;40(5):1065–1073.
62. Kaye D, Merselis JG, Connolly S, Hook EW. Treatment of chronic enteric carriers of *Salmonella* typhosa with ampicillin. *Ann N Y Acad Sci*. 1967; 145:429–435.
63. Phillips WE. Treatment of chronic typhoid carriers with ampicillin. *JAMA*. 1971;217(7):913–915.
64. Nolan CM, White PC Jr. Treatment of typhoid carriers with amoxicillin. Correlates of successful therapy. *JAMA*. 1978;239(22):2352–2354.
65. Pichler H, Knothe H, Spitzy KH, Vieliind G. Treatment of chronic carriers of *Salmonella* typhi and *Salmonella* paratyphi B with trimethoprim-sulfamethoxazole. *J Infect Dis*. 1973;128(Suppl):743–744.
66. Ferreccio C, Morris JG, Valdivieso C, et al. Efficacy of ciprofloxacin in the treatment of chronic typhoid carriers. *J Infect Dis*. 1988;157(6):1235–1239.
67. Kaye D, Eyckmans L, Rocha H, Prata A, Hook EW. Comparison of parenteral ampicillin and parenteral chloramphenicol in the treatment of typhoid fever. *Ann N Y Acad Sci*. 1967;145(2):423–428.
68. Diridl G, Pichler H, Wolf D. Treatment of chronic *Salmonella* carriers with ciprofloxacin. *Eur J Clin Microbiol*. 1986;5(2):260–261.
69. Sammalkorpi K, Lähdevirta J, Mäkelä T, Rostila T. Treatment of chronic *Salmonella* carriers with ciprofloxacin. *Lancet*. 1987;2(8551):164–165.
70. Gotuzzo E, Guerra JG, Benavente L, et al. Use of norfloxacin to treat chronic typhoid carriers. *J Infect Dis*. 1988;157:1221–1225.
71. Jackson BR, Iqbal S, Mahon B; Centers for Disease Control and Prevention (CDC). Updated recommendations for the use of typhoid vaccine—advisory

committee on immunization practices, United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):305–308.
72. Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. *Clin Infect Dis*. 2010;50(2):241–246.
73. Zaidi MB, Estrada-Garcia T. *Shigella*: a highly virulent and elusive pathogen. *Curr Trop Med Rep*. 2014;1(2):81–87.
74. Niyogi SK. Shigellosis. *J Microbiol*. 2005;43(2):133–143.
75. DuPont AW. Postinfectious irritable bowel syndrome. *Clin Infect Dis*. 2008;46(4):594–599.
76. Carter JD, Hudson AP. Reactive arthritis: clinical aspects and medical management. *Rheum Dis Clin North Am*. 2009;35(1):21–44.
77. Bennish ML, Khan WA, Begum M, et al. Low risk of hemolytic uremic syndrome after early effective antimicrobial therapy for *Shigella dysenteriae* Type 1 infection in Bangladesh. *Clin Infect Dis*. 2006;42(3):356–362.
78. Klontz KC, Singh N. Treatment of drug-resistant *Shigella* infections. *Expert Rev Anti Infect Ther*. 2015;13(1):69–80.
79. Gu B, Cao Y, Pan S, et al. Comparison of the prevalence and changing resistance to nalidixic acid and ciprofloxacin of *Shigella* between Europe–America and Asia–Africa from 1998 to 2009. *Int J Antimicrob Agents*. 2012;40(1):9–17.
80. Bowen A, Hurd J, Hoover C, et al. Importation and domestic transmission of *Shigella sonnei* resistant to ciprofloxacin—United States, May 2014–February 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(12):318–320.
81. Kantele A, Lääveri T, Mero S, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing Enterobacteriaceae. *Clin Infect Dis*. 2015;60(6):837–846.
82. Shanks GD, Smoak BL, Aleman GM, et al. Single dose of azithromycin or three-day course of ciprofloxacin as therapy for epidemic dysentery in Kenya. Acute Dysentery Study Group. *Clin Infect Dis*. 1999;29(4):942–943.
83. Khan WA, Seas C, Dhar U, Salam MA, Bennish ML. Treatment of shigellosis: V. Comparison of azithromycin and ciprofloxacin. A double-blind, randomized, controlled trial. *Ann Intern Med*. 1997;126(9):697–703.
84. Baker KS, Dallman TJ, Ashton PM, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. *Lancet Infect Dis*. 2015;15(8):913–921.
85. Sjolund Karlsson M, Bowen A, Reporter R, et al. Outbreak of infections caused by *Shigella sonnei* with reduced susceptibility to azithromycin in the United States. *Antimicrob Agents Chemother*. 2013;57(3):1559–1560.
86. Hassing RJ, Melles DC, Goessens WH, Rijnders BJ. Case of *Shigella flexneri* infection with treatment failure due to azithromycin resistance in an HIV-positive patient. *Infection*. 2014;42(4):789–790.
87. Williams PCM, Berkley JA. Guidelines for the treatment of dysentery (shigellosis): a systematic review of the evidence. *Paediatr Int Child Health*.

2018;38(sup1):S50–S65.
88. Shiferaw B, Solghan S, Palmer A, et al. Antimicrobial susceptibility patterns of *Shigella* isolates in Foodborne Diseases Active Surveillance Network (FoodNet) sites, 2000–2010. *Clin Infect Dis*. 2012;54(Suppl 5):S458–S463.
89. Lima AAM, Warren CA, Guerrant RL. Acute dysentery syndromes (diarrhea with fever). In: Bennett JE, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Vol 1. 9th ed. Elsevier Saunders; 2019:1357–1364.
90. Heiman KE, Karlsson M, Grass J, et al; Centers for Disease Control and Prevention (CDC). Notes from the field: *Shigella* with decreased susceptibility to azithromycin among men who have sex with men—United States, 2002–2013. *MMWR Morb Mortal Wkly Rep*. 2014;63(6):132–133.
91. Kirkpatrick BD, Tribble DR. Update on human *Campylobacter jejuni* infections. *Curr Opin Gastroenterol*. 2011;27(1):1–7.
92. Ternhag A, Asikainen T, Giesecke J, Ekdahl K. A meta-analysis on the effects of antibiotic treatment on duration of symptoms caused by infection with campylobacter species. *Clin Infect Dis*. 2007;44(5):696–700.
93. Epps SV, Harvey RB, Hume ME, Phillips TD, Anderson RC, Nisbet DJ. Foodborne *Campylobacter*: infections, metabolism, pathogenesis and reservoirs. *Int J Environ Res Public Health*. 2013;10(12):6292–6304.
94. Acheson D, Allos BM. *Campylobacter jejuni* infections: update on emerging issues and trends. *Clin Infect Dis*. 2001;32(8):1201–1206.
95. Ricotta EE, Palmer A, Wymore K, et al. Epidemiology and antimicrobial resistance of international travel-associated *Campylobacter* infections in the United States, 2005–2011. *Am J Public Health*. 2014;104(7):e108–e114.
96. Platts-Mills JA, Liu J, Gratz J, et al. Detection of *Campylobacter* in stool and determination of significance by culture, enzyme immunoassay, and PCR in developing countries. *J Clin Microbiol*. 2014;52(4):1074–1080.
97. Ge B, Wang F, Sjölund-Karlsson M, McDermott PF. Antimicrobial resistance in *Campylobacter*: susceptibility testing methods and resistance trends. *J Microbiol Methods*. 2013;95(1):57–67.
98. Allos BM. *Campylobacter jejuni* infections: update on emerging issues and trends. *Clin Infect Dis*. 2001;32:1201–1206.
99. Kendall ME, Crim S, Fullerton K, et al. Travel-associated enteric infections diagnosed after return to the United States, Foodborne Diseases Active Surveillance Network (FoodNet), 2004–2009. *Clin Infect Dis*. 2012;54(Suppl 5):S480–S487.
100. Bomsztyk M, Arnold RW. Infections in travelers. *Med Clin North Am*. 2013;97(4):697–720, xi.
101. Dupont HL. Systematic review: the epidemiology and clinical features of travellers' diarrhoea. *Aliment Pharmacol Ther*. 2009;30(3):187–196.
102. Riddle MS, Connor BA, Beeching NJ, et al. Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report. *J Travel Med*.

2017;24(suppl_1):S57–S74.
103. Caeiro JP, DuPont HL, Albrecht H, Ericsson CD. Oral rehydration therapy plus loperamide versus loperamide alone in the treatment of traveler's diarrhea. *Clin Infect Dis*. 1999;28(6):1286–1289.
104. Advice for travelers. *Med Lett Drugs Ther*. 2015;57(1466):52–58.
105. Paredes-Paredes M, Flores-Figueroa J, Dupont HL. Advances in the treatment of travelers' diarrhea. *Curr Gastroenterol Rep*. 2011;13(5):402–407.
106. Riddle MS, Arnold S, Tribble DR. Effect of adjunctive loperamide in combination with antibiotics on treatment outcomes in traveler's diarrhea: a systematic review and meta analysis. *Clin Infect Dis*. 2008;47(8):1007–1014.
107. DuPont HL, Ericsson CD, Farthing MJ, et al. Expert review of the evidence base for prevention of travelers' diarrhea. *J Travel Med*. 2009;16(3):149–160.
108. Infante RM, Ericsson CD, Jiang ZD, et al. Enteroaggregative *Escherichia coli* diarrhea in travelers: response to rifaximin therapy. *Clin Gastroenterol Hepatol*. 2004;2(2):135–138.
109. Steffen R, Sack DA, Riopel L, et al. Therapy of travelers' diarrhea with rifaximin on various continents. *Am J Gastroenterol*. 2003;98(5):1073–1078.
110. Adachi JA, Ericsson CD, Jiang ZD, et al. Azithromycin found to be comparable to levofloxacin for the treatment of US travelers with acute diarrhea acquired in Mexico. *Clin Infect Dis*. 2003;37(9):1165–1171.
111. Taylor DN, Bourgeois AL, Ericsson CD, et al. A randomized, double-blind, multicenter study of rifaximin compared with placebo and with ciprofloxacin in the treatment of travelers' diarrhea. *Am J Trop Med Hyg*. 2006;74(6):1060–1066.
112. Dupont HL, Jiang ZD, Belkind-Gerson J, et al. Treatment of travelers' diarrhea: randomized trial comparing rifaximin, rifaximin plus loperamide, and loperamide alone. *Clin Gastroenterol Hepatol*. 2007;5(4):451–456.
113. Sanders JW, Frenck RW, Putnam SD, et al. Azithromycin and loperamide are comparable to levofloxacin and loperamide for the treatment of traveler's diarrhea in United States military personnel in Turkey. *Clin Infect Dis*. 2007;45(3):294–301.
114. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology*. 2009;136(6):1979–1988.
115. Zanger P, Nurjadi D, Gabor J, Gaile M, Kremsner PG. Effectiveness of rifaximin in prevention of diarrhoea in individuals travelling to south and southeast Asia: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2013;13(11):946–954.
116. Connor BA, Keystone JS. Editorial commentary: antibiotic self-treatment of travelers' diarrhea: helpful or harmful? *Clin Infect Dis*. 2015;60(6):847–848.
117. DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med*. 2005;142(10):805–812.

118. DuPont HL. Travelers' diarrhea: contemporary approaches to therapy and prevention. *Drugs*. 2006;66:303.
119. Pennington H. *Escherichia coli* O157. *Lancet*. 2010;376(9750):1428–1435.
120. Karch H, Bielaszewska M, Bitzan M, Schmidt H. Epidemiology and diagnosis of Shiga toxin-producing *Escherichia coli* infections. *Diagn Microbiol Infect Dis*. 1999;34(3):229–243.
121. Mead PS, Griffin PM. *Escherichia coli* O157:H7. *Lancet*. 1998;352(9135):1207–1212.
122. Ericsson CD, Nicholls-Vasquez I, DuPont HL, Mathewson JJ. Optimal dosing of trimethoprim-sulfamethoxazole when used with loperamide to treat traveler's diarrhea. *Antimicrob Agents Chemother*. 1992;36(12):2821–2824.
123. Dundas S, Todd WT, Stewart AI, Murdoch PS, Chaudhuri AK, Hutchinson SJ. The central Scotland *Escherichia coli* O157:H7 outbreak: risk factors for the hemolytic uremic syndrome and death among hospitalized patients. *Clin Infect Dis*. 2001;33(7):923–931.
124. Davis TK, McKee R, Schnadower D, Tarr PI. Treatment of Shiga toxin-producing *Escherichia coli infections. Infect Dis Clin North Am*. 2013;27(3):577–597.
125. Klein EJ, Stapp JR, Clausen CR, et al. Shiga toxin-producing *Escherichia coli* in children with diarrhea: a prospective point-of-care study. *J Pediatr*. 2002;141(2):172–177.
126. Banatvala N, Griffin PM, Greene KD, et al; Hemolytic Uremic Syndrome Study Collaborators. The United States national prospective hemolytic uremic syndrome study: microbiologic, serologic, clinical, and epidemiologic findings. *J Infect Dis*. 2001;183(7):1063–1070.
127. Besbas N, Karpman D, Landau D, et al; European Paediatric Research Group for HUS. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. *Kidney Int*. 2006;70(3):423–431.
128. Ikeda K, Ida O, Kimoto K, Takatorige T, Nakanishi N, Tatara K. Predictors for the development of haemolytic uraemic syndrome with *Escherichia coli* O157:H7 infections: with focus on the day of illness. *Epidemiol Infect*. 2000;124(3):343–349.
129. Tarr PI, Gordon CA, Chandler WL. Shiga-toxin-producing *Escherichia coli* and haemolytic uraemic syndrome. *Lancet*. 2005;365(9464):1073–1086.
130. Tserenpuntsag B, Chang H, Smith PF, Morse DL. Hemolytic uremic syndrome risk and *Escherichia coli* O157:H7. *Emerg Infect Dis*. 2005;11(12):1955–1957.
131. Wong CS, Jelacic S, Habeeb RL, Watkins SL, Tarr PI. The risk of the hemolytic–uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *N Engl J Med*. 2000;342(26):1930–1936.
132. Slutsker L, Ries AA, Maloney K, Wells JG, Greene KD, Griffin PM. A nationwide case-control study of *Escherichia coli* O157:H7 infection in the

United States. *J Infect Dis*. 1998;177(4):962–966.
133. Carter AO, Borczyk AA, Carlson JA, et al. A severe outbreak of *Escherichia coli* O157:H7–associated hemorrhagic colitis in a nursing home. *N Engl J Med*. 1987;317(24):1496–1500.
134. Thomas DE, Elliott EJ. Interventions for preventing diarrhea-associated hemolytic uremic syndrome: systematic review. *BMC Public Health*. 2013;13:799.
135. Proulx F, Turgeon JP, Delage G, Lafleur L, Chicoine L. Randomized, controlled trial of antibiotic therapy for *Escherichia coli* O157:H7 enteritis. *J Pediatr*. 1992;121(2):299–303.
136. Freedman SB, Xie J, Neufeld MS, et al; Alberta Provincial Pediatric Enteric Infection Team (APPETITE). Shiga toxin-producing *Escherichia coli* infection, antibiotics, and risk of developing hemolytic uremic syndrome: a meta-analysis. *Clin Infect Dis.* 2016;62(10):1251–1258.
137. Safdar N, Said A, Gangnon RE, Maki DG. Risk of hemolytic uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 enteritis: a meta-analysis. *JAMA*. 2002;288:996–1001.
138. Nelson JM, Griffin PM, Jones TF, Smith KE, Scallan E. Antimicrobial and antimotility agent use in persons with Shiga toxin-producing *Escherichia coli* O157 infection in FoodNet sites. *Clin Infect Dis*. 2011;52(9):1130–1132.
139. Bell BP, Griffin PM, Lozano P, Christie DL, Kobayashi JM, Tarr PI. Predictors of hemolytic uremic syndrome in children during a large outbreak of *Escherichia coli* O157:H7 infections. *Pediatrics*. 1997;100(1):e12–e12.
140. Bartlett JG. Antibiotic-associated diarrhea. *N Engl J Med*. 2002;346(5):334–339.
141. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. *N Engl J Med*. 2020;382(14):1320–1330.
142. Wilcox MH, Mooney L, Bendall R, Settle CD, Fawley WN. A case-control study of community-associated *Clostridium difficile* infection. *J Antimicrob Chemother*. 2008;62(2):388–396.
143. Turco R, Martinelli M, Miele E, et al. Proton pump inhibitors as a risk factor for paediatric *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2010;31(7):754–759.
144. Dalton BR, Lye-Maccannell T, Henderson EA, Maccannell DR, Louie TJ. Proton pump inhibitors increase significantly the risk of *Clostridium difficile* infection in a low-endemicity, non-outbreak hospital setting. *Aliment Pharmacol Ther*. 2009;29(6):626–634.
145. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene–variant strain of *Clostridium difficile*. *N Engl J Med*. 2005;353(23):2433–2441.
146. Rao K, Micic D, Natarajan M, et al. *Clostridium difficile* ribotype 027: relationship to age, detectability of toxins A or B in stool with rapid testing, severe infection, and mortality. *Clin Infect Dis*. 2015;61(2):233–241.

147. Bartlett JG. The case for vancomycin as the preferred drug for treatment of *Clostridium difficile* infection. *Clin Infect Dis*. 2008;46(10):1489–1492.
148. Wanahita A, Goldsmith EA, Musher DM. Conditions associated with leukocytosis in a tertiary care hospital, with particular attention to the role of infection caused by *Clostridium difficile*. *Clin Infect Dis*. 2002;34(12):1585–1592.
149. Savola KL, Baron EJ, Tompkins LS, Passaro DJ. Fecal leukocyte stain has diagnostic value for outpatients but not inpatients. *J Clin Microbiol*. 2001;39(1):266–269.
150. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):987–994.
151. Peled N, Pitlik S, Samra Z, Kazakov A, Bloch Y, Bishara J. Predicting *Clostridium difficile* toxin in hospitalized patients with antibiotic associated diarrhea. *Infect Control Hosp Epidemiol*. 2007;28(4):377–381.
152. Bartlett JG. Antibiotic-associated diarrhea. *Clin Infect Dis*. 1992;15(4):573–581.
153. Nelson R. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database Syst Rev*. 2007:CD004610.
154. Fekety R. Guidelines for the diagnosis and treatment of *Clostridium difficile*-associated diarrhea and colitis. *Am J Gastroenterol*. 1997;92:739.
155. Johnson S, Gerding DN. Clostridium difficile--associated diarrhea. *Clin Infect Dis*. 1998;26(5):1027–1034.
156. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*. 2005;41(9):1254–1260.
157. Al-Nassir WN, Sethi AK, Nerandzic MM, Bobulsky GS, Jump RL, Donskey CJ. Comparison of clinical and microbiological response to treatment of *Clostridium difficile*-associated disease with metronidazole and vancomycin. *Clin Infect Dis*. 2008;47(1):56–62.
158. Cohen Stuart H, Gerding DN, Johnson S, et al; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431–455.
159. Pépin J, Valiquette L, Gagnon S, Routhier S, Brazeau I. Outcomes of *Clostridium difficile*-associated disease treated with metronidazole or vancomycin before and after the emergence of NAP1/027. *Am J Gastroenterol*. 2007;102(12):2781–2788.

160. Teasly DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium-difficile*-associated diarrhoea and colitis. *Lancet*. 1983;2:1043–1046.
161. Tedesco F, Markham R, Gurwith M, Christie D, Bartlett JG. Oral vancomycin for antibiotic-associated pseudomembranous colitis. *Lancet*. 1978;312(8083):226–228.
162. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45:302–307.
163. Johnson S, Louie TJ, Gerding DN, et al; Polymer Alternative for CDI Treatment (PACT) Investigators. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59:345–354.
164. Peng Z, Jin D, Kim HB, et al. Update on antimicrobial resistance in *Clostridium difficile*: resistance mechanisms and antimicrobial susceptibility testing. *J Clin Microbiol*. 2017;55(7):1998–2008.
165. Pettit NN, DePestel DD, Fohl AL, Eyler R, Carver PL. Risk factors for systemic vancomycin exposure following administration of oral vancomycin for the treatment of *Clostridium difficile* infection. *Pharmacotherapy*. 2015;35(2):119–126.
166. Cornely OA, Nathwani D, Ivanescu C, Odufowora-Sita O, Retsa P, Odeyemi IA. Clinical efficacy of fidaxomicin compared with vancomycin and metronidazole in *Clostridium difficile* infections: a meta-analysis and indirect treatment comparison. *J Antimicrob Chemother*. 2014;69(11):2892–2900.
167. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364(5):422–431.
168. Crawford T, Huesgen E, Danziger L. Fidaxomicin: a novel macrocyclic antibiotic for the treatment of *Clostridium difficile* infection. *Am J Health Syst Pharm*. 2012;69(11):933–943.
169. Beinortas T, Burr NE, Wilcox MH, Subramanian V. Comparative efficacy of treatments for *Clostridium difficile* infection: a systematic review and network meta-analysis. *Lancet Infect Dis*. 2018;18(9):1035–1044.
170. Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis*. 2021;73(5):e1029–e1044.
171. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for *Clostridium difficile*-associated diarrhoea in adults. *Cochrane Database Syst Rev*. 2017; (3):CD004610.
172. Sullivan A. Probiotics in human infections. *J Antimicrob Chemother*. 2002;50(5):625–627.

173. Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic *Lactobacillus* preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ*. 2007;335(7610):80.
174. Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev*. 2017(12):CD006095.
175. Munoz P, Bouza E, Cuenca-Estrella M, et al. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. *Clin Infect Dis*. 2005;40(11):1625–1634.
176. Jangi S, Lamont JT. Asymptomatic colonization by *Clostridium difficile* in infants: implications for disease in later life. *J Pediatr Gastroenterol Nutr*. 2010;51(1):2–7.
177. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. *N Engl J Med*. 2000;342(6):390–397.
178. Climo MW. Hospital-wide restriction of clindamycin: effect on the incidence of *Clostridium difficile*-associated diarrhea and cost. *Ann Intern Med*. 1998;128(12, part 1):989–995.
179. Kazakova SV. A hospital outbreak of diarrhea due to an emerging epidemic strain of *Clostridium difficile*. *Arch Intern Med*. 2006;166(22):2518–2524.
180. Baur D, Gladstone BP, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2017;17(9):990–1001.
181. Goldstein EJ, Johnson S, Maziade PJ, et al. Pathway to prevention of nosocomial *Clostridium difficile* infection. *Clin Infect Dis*. 2015;60(Suppl 2):S148–S158.
182. Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. *Clin Infect Dis*. 2002;34(3):346–353.
183. Stevens VW, Khader K, Nelson RE, et al. Excess length of stay attributable to *Clostridium difficile* infection (CDI) in the acute care setting: a multistate model. *Infect Control Hosp Epidemiol*. 2015;36(9):1024–1030.
184. Nanwa N, Kendzerska T, Krahn M, et al. The economic impact of *Clostridium difficile* infection: a systematic review. *Am J Gastroenterol*. 2015;110(4):511–519.
185. Reveles KR, Dotson KM, Gonzales-Luna A, et al. *Clostridioides* (formerly *Clostridium*) *difficile* infection during hospitalization increases the likelihood of nonhome patient discharge. *Clin Infect Dis*. 2019;68(11):1887–1893.
186. Dallal RM, Harbrecht BG, Boujoukas AJ, et al. Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. *Ann Surg*. 2002;235(3):363–372.

187. Rokas KE, Johnson JW, Beardsley JR, Ohl CA, Luther VP, Williamson JC. The addition of intravenous metronidazole to oral vancomycin is associated with improved mortality in critically ill patients with *Clostridium difficile* infection. *Clin Infect Dis*. 2015;61(6):934–941.
188. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet*. 1999;36(5):353–373.
189. Friedenberg F, Fernandez A, Kaul V, Niami P, Levine GM. Intravenous metronidazole for the treatment of *Clostridium difficile* colitis. *Dis Colon Rectum*. 2001;44(8):1176–1180.
190. Kleinfeld DI, Sharpe RJ, Donta ST. Parenteral therapy for antibiotic-associated pseudomembranous colitis. *J Infect Dis*. 1988;157(2):389–389.
191. Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. *Gut*. 1986;27(10):1169–1172.
192. Guzman R, Kirkpatrick J, Forward K, Lim F. Failure of parenteral metronidazole in the treatment of pseudomembranous colitis. *J Infect Dis*. 1988;158(5):1146–1146.
193. Apisarnthanarak A, Razavi B, Mundy LM. Adjunctive intracolonic vancomycin for severe *Clostridium difficile* colitis: case series and review of the literature. *Clin Infect Dis*. 2002;35(6):690–696.
194. McFarland LV, Surawicz CM, Rubin M, Fekety R, Elmer GW, Greenberg RN. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. *Infect Control Hosp Epidemiol*. 1999;20(1):43–50.
195. Barbut F, Richard A, Hamadi K, Chomette V, Burghoffer B, Petit JC. Epidemiology of recurrences or reinfections of *Clostridium difficile*-associated diarrhea. *J Clin Microbiol*. 2000;38:2386–2388.
196. Hecht JR, Olinger EJ. *Clostridium difficile* colitis secondary to intravenous vancomycin. *Digest Dis Sci*. 1989;34(1):148–149.
197. Saginur R, Hawley CR, Bartlett JG. Colitis associated with metronidazole therapy. *J Infect Dis*. 1980;141(6):772–774.
198. Abdelfatah M, Nayfe R, Nijim A, et al. Factors predicting recurrence of *Clostridium difficile* infection (CDI) in hospitalized patients: retrospective study of more than 2000 patients. *J Investig Med*. 2015;63(5):747–751.
199. Deshpande A, Pasupuleti V, Thota P, et al. Risk factors for recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2015;36(4):452–460.
200. Gerding DN, Kelly CP, Rahav G, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection in patients at increased risk for recurrence. *Clin Infect Dis*. 2018;67(5):649–656.
201. Kyne L, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. *Lancet*. 2001;357(9251):189–193.

202. Juang P, Skledar SJ, Zgheib NK, et al. Clinical outcomes of intravenous immune globulin in severe *Clostridium difficile*-associated diarrhea. *Am J Infect Control*. 2007;35(2):131–137.
203. Pepin J, Routhier S, Gagnon S, Brazeau I. Management and outcomes of a first recurrence of *Clostridium difficile*-associated disease in Quebec, Canada. *Clin Infect Dis*. 2006;42(6):758–764.
204. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol*. 2002;97(7):1769–1775.
205. Tedesco F, Gordon D, Fortson WC. Approach to patients with multiple relapses of antibiotic-associated pseudomembranous colitis. *Am J Gastroenterol*. 1985;80:867–868.
206. Ariano RE, Zhanel GG, Harding GK. The role of anion-exchange resins in the treatment of antibiotic-associated pseudomembranous colitis. *CMAJ*. 1990;142:1049–1051.
207. Pruksananonda P, Powell KR. Multiple relapses of *Clostridium difficile*-associated diarrhea responding to an extended course of cholestyramine. *Pediatr Infect Dis J*. 1989;8:175–178.
208. Buggy BP, Fekety R, Silva J. Therapy of relapsing *Clostridium difficile* associated diarrhea and colitis with the combination of vancomycin and rifampin. *J Clin Gastroenterol*. 1987;9(2):155–159.
209. McFarland LV. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *JAMA*. 1994;271(24):1913.
210. Surawicz Christina M, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high dose vancomycin combined with *Saccharomyces boulardii*. *Clin Infect Dis*. 2000;31(4):1012–1017.
211. Johnson S, Schriever C, Galang M, Kelly CP, Gerding DN. Interruption of recurrent *Clostridium difficile*-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clin Infect Dis*. 2007;44(6):846–848.
212. Garey KW, Jiang ZD, Bellard A, Dupont HL. Rifaximin in treatment of recurrent *Clostridium difficile*-associated diarrhea: an uncontrolled pilot study. *J Clin Gastroenterol*. 2009;43(1):91–92.
213. Gallagher JC, Reilly JP, Navalkele B, Downham G, Haynes K, Trivedi M. Clinical and economic benefits of fidaxomicin compared to vancomycin for *Clostridium difficile* infection. *Antimicrob Agents Chemother*. 2015;59(11):7007–7010.
214. Nathwani D, Cornely OA, Van Engen AK, Odufowora-Sita O, Retsa P, Odeyemi IAO. Cost-effectiveness analysis of fidaxomicin versus vancomycin in *Clostridium difficile* infection. *J Antimicrob Chemother*. 2014;69(11):2901–2912.

215. Guery B, Menichetti F, Anttila V, et al. EXTEND Clinical Study Group extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis*. 2018;18(3):296–307.
216. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med*. 2017;376(4):305–317.
217. Bezlotoxumab (Zinplava) for prevention of recurrent *Clostridium difficile* infection. *Med Lett Drugs Ther*. 2017;59:49–50.
218. Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. *Am J Gastroenterol*. 2021;116:1124–1147.
219. Drekonja D, Reich J, Gezahegn S, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: a systematic review. *Ann Intern Med*. 2015;162(9):630–638.
220. Han S, Shannahan S, Pellish R. Fecal microbiota transplant: treatment options for *Clostridium difficile* infection in the intensive care unit. *J Intensive Care Med*. 2016;31(9):577–586.
221. Jiang Z-D, Jenq RR, Ajami NJ, et al. Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent *Clostridium difficile* infection: a randomized clinical trial. *PLoS ONE*. 2018;13(11):e0205064.
222. Aroniadis OC, Brandt LJ, Greenber A, et al. Long-term follow-up study of fecal microbiota transplantation for severe and/or complicated *Clostridium difficile* infection: a multicenter experience. *J Clin Gastroenterol*. 2016;50(5):398–402.
223. Varier RU, Biltaji E, Smith KJ, et al. Cost-effectiveness analysis of fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Infect Control Hosp Epidemiol*. 2015;36:438–444.

70

Intra-Abdominal Infections

Christie M. Bertram and Sheila K. Wang

CORE PRINCIPLES		CHAPTER CASES
1	Acute cholecystitis is the acute inflammation of the gallbladder, presenting with fever, prolonged abdominal pain, and positive Murphy's sign of the right upper quadrant followed by nausea and vomiting. Acute cholangitis is an acute inflammation of the common bile duct with the accompanying classic Charcot triad: fever, jaundice, and right upper quadrant pain.	**Case 70-1 (Question 1)**
2	Enterobacterales (aerobic enteric gram-negative rods) are most commonly associated with biliary tract infections, which include pathogens such as *Escherichia coli (E. coli), Klebsiella* species, and *Enterobacter* species. The	**Case 70-1 (Question 2)**

	choice of antibacterial agents is largely empiric covering these common pathogens.	
3	Empiric therapy for severe biliary tract infections may include combination therapy with ciprofloxacin, levofloxacin, or cefepime plus metronidazole or monotherapy with piperacillin/tazobactam or an antipseudomonal carbapenem (imipenem/cilastatin or meropenem) if multidrug-resistant gram-negative rods are suspected.	**Case 70-1 (Question 3)**
4	Adequate serum concentrations of recommended antibacterial agents coupled with targeted source control (ie. biliary drainage) are most important when managing biliary tract infections. Duration of therapy for intra-abdominal infections typically ranges from 4 to 7 days. Clinical response and source control influence duration of therapy.	**Case 70-1 (Question 4)**
5	Spontaneous bacterial peritonitis (SBP) is largely a monomicrobial infection commonly caused by Enterobacterales.	**Case 70-2 (Question 1)**
6	Empiric therapy for SBP may include a third-generation cephalosporin such as ceftriaxone or cefotaxime or parenteral fluoroquinolone with activity versus *Streptococcus pneumoniae*. Length of therapy depends on the reduction in polymorphonuclear leukocyte counts	**Case 70-2 (Question 2)**

	(<250 cells/μL) in peritoneal fluid, generally occurring in ≤5 days.	
7	Due to the selection of resistant bacteria, long-term prophylaxis to prevent SBP is recommended for those at high risk for developing SBP (eg. previous episodes of SBP, cirrhosis with GI bleed, low ascitic protein of < 1.0 g/dL).	**Case 70-2 (Question 3)**
8	Empiric therapy for Continuous Ambulatory Peritoneal Dialysis (CAPD)-associated peritonitis should target the most common causative organisms which included gram-positive bacteria such as *Staphylococcus* and *Streptococcus* species, followed by gram-negative Enterobacterales, with *E.coli* being the most common. The intraperitoneal (IP) route is preferred except in the setting of systemic sepsis.	**Case 70-3 (Question 1)**
9	In general, fluconazole is the agent of choice for *Candida albican*-associated CAPD peritonitis with temporary catheter removal.	**Case 70-3 (Question 2)**
10	Signs and symptoms of secondary peritonitis may include moderate to severe abdominal pain with anorexia, nausea, vomiting, fevers with or without chills, tachycardia, faint or absent bowel sounds, abdominal distention, and an elevated WBC count.	**Case 70-4 (Question 1)**
11	The most likely pathogens for	**Case 70-4 (Question**

	secondary peritonitis are facultative gram-negative organisms such as *E. coli, Proteus* species, *Klebsiella* species, or *Enterobacter* species or an anaerobe such as *Bacteroides fragilis*.	**2)**
12	Therapy for secondary peritonitis should include antimicrobial coverage directed at gram-negative bacteria and anaerobes. Therapy may include (a) certain extended-spectrum β-lactams or β-lactamase inhibitor combinations, (b) carbapenems, or (c) a fluoroquinolone with metronidazole stratified according to severity of infection (ie, mild-to-moderate risk vs high risk).	**Case 70-4 (Question 3)**
13	In general, coverage of *Enterococcus* species is warranted if it is present in blood cultures or is the sole organism on culture.	**Case 70-5 (Question 1)**
14	*Candida* species should be treated when isolated surgically or directly from an intra-abdominal collection in patients with severe community-acquired or healthcare-associated infections.	**Case 70-5 (Question 2)**
15	Definitive culture and susceptibility reports for anaerobes may take days to weeks to finalize; therefore, empiric antibiotic regimens should cover for anaerobes when suspected.	**Case 70-5 (Question 3)**
16	Optimal antimicrobial therapy for the treatment of intra-abdominal abscesses should penetrate the abscess in	**Case 70-6 (Question 1)**

	adequate concentrations and have an adequate spectrum of activity.	
17	Antimicrobial therapy targeting both aerobic and anaerobic pathogens should be used in the treatment of infections due to penetrating trauma.	**Case 70-7 (Question 1)**
18	Acute penetrating abdominal trauma requires a short course (<24 hours) of antimicrobial therapy. Delay in therapy or development of infection necessitates a 5- to 7-day course of therapy.	**Case 70-7 (Question 2)**
19	Antimicrobial therapy for appendicitis follows the recommendations for community-acquired intra-abdominal infections.	**Case 70-8 (Question 1)**

INTRODUCTION

Despite the introduction of new antimicrobial agents and improvements in diagnostic and surgical techniques, the treatment of intra-abdominal infections remains a therapeutic challenge. However, advances in radiographic and interventional techniques with timely source control, improved fluid and nutritional management, and the selection of appropriate antimicrobial agents have decreased mortality in intra-abdominal infections.[1]

Intra-abdominal infections are those contained within the peritoneal cavity, which extends from the undersurface of the diaphragm to the floor of the pelvis or the retroperitoneal space. Intra-abdominal infections can present as a localized infection (eg, appendicitis), a diffuse inflammation throughout the peritoneum (eg, peritonitis), or as abscesses, which can form anywhere within the

abdomen, between bowel loops, or in solid organs such as the liver, biliary tract, spleen, pancreas, or female pelvic organs. Antibiotic selection will depend on the type of intra-abdominal infection. Most intra-abdominal infections are community acquired (80%), which can be either mild-to-moderate risk or high risk depending on the severity of the infection, comorbidities, and involvement of drug-resistant pathogens. Health care–associated intra-abdominal infections generally involve more nosocomial bacteria and fungi with a greater risk factor for multidrug resistance. Intra-abdominal infections can also be categorized as uncomplicated and complicated. Uncomplicated intra-abdominal infections involve a single organ without spread to the peritoneum, whereas complicated intra-abdominal infections (cIAIs) extend beyond the hollow viscus of origin into the peritoneal space (eg, abscess or peritonitis).[2]

Empiric antimicrobial therapy should be initiated as soon as an intra-abdominal infection is suspected. In addition to the type of infection, therapy should be selected on the basis of the suspected pathogens; however, antimicrobial therapy alone may be insufficient, especially in the setting of diffuse peritonitis. *Source control* is a term used to involve all physical measures needed to eradicate an infection, such as debridement of necrotic tissue or drainage of an abscess or fluid collection. If adequate source control is delayed, bacteremia, multiple organ failure, and mortality are more likely to occur.[3]

Normal Gastrointestinal Flora

The stomach of fasting individuals contains very few bacteria as a result of gastric motility and the bactericidal activity of normal acidic gastric fluid.[1] The bacterial population of the stomach can be altered by drugs or diseases that increase gastric pH or decrease gastric motility. Not surprisingly, patients with bleeding or obstructing duodenal ulcers, gastric ulcers, gastric carcinomas, or those receiving proton-pump inhibitors or histamine-2 (H_2) receptor

antagonists have an increased number of oral bacteria colonizing the stomach.

The upper small intestine (duodenum and jejunum) usually contains relatively few bacteria and harbors mainly oral flora. The lower small intestine serves as a transitional zone between the sparsely populated stomach and the abundant microbial flora of the colon.[2,4]

In the ileum, facultative gram-negative and gram-positive species, as well as obligate anaerobes, are encountered. As the distal ileum is approached, the quantity and variety of bacteria increase. Substantial numbers of anaerobic bacteria are present, including *Bacteroides* species, as well as *Escherichia coli* (*E.coli*) and *Enterococcus* species.[1,2]

In the large bowel, anaerobic bacteria, particularly *Bacteroides* species, predominate. In the distal colon, bacterial counts average 10^{10} colony-forming unit (CFU)/mL of feces, with anaerobes outnumbering other organisms by a ratio of 1000 to 10,000:1.[2] Among the facultative aerobes, *E. coli* is the most frequently isolated species.[1,2] Given these differences in regional microflora populations, it is not surprising that trauma to the colon carries a much higher risk of intra-abdominal infection in comparison with the stomach or jejunum[5] (**Fig. 70-1; Table 70-1**).

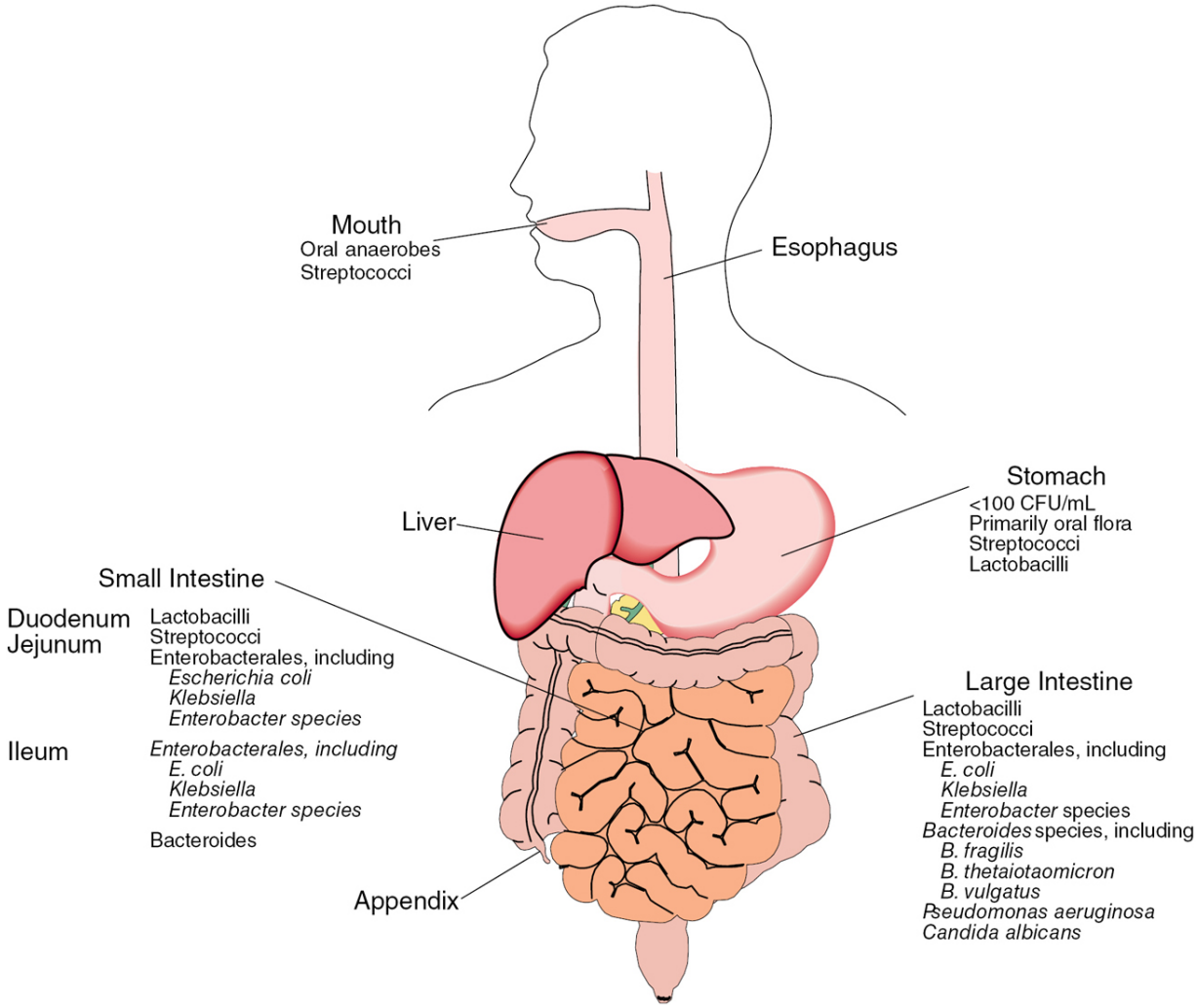


Figure 70-1 Microflora of the gastrointestinal tract.

Table 70-1
Common Pathogens in Intra-Abdominal Infection

Disease	Common Pathogens	Comments
Cholecystitis, cholangitis	*Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus*, and anaerobes	*Enterococcus* species and anaerobes are less frequently isolated, but they have been associated with nosocomial infections and chronic surgical infections, particularly in patients receiving broad-spectrum antimicrobials.
Primary peritonitis	*E. coli*, *K. pneumoniae*, *Streptococcus*	Also known as spontaneous bacterial peritonitis presented in patients with

	pneumoniae, occasional anaerobes	cirrhosis. Often monomicrobial. Anaerobes less likely than aerobes.
Secondary peritonitis	*E. coli*, *Bacteroides fragilis*, *Enterococcus*, and anaerobes	Generally polymicrobial with both aerobic and anaerobic pathogens. *Enterococcus* species should be considered in the setting of health care–associated infections.
Chronic ambulatory peritoneal dialysis	*Staphylococcus epidermidis*, *S. aureus*, diphtheroids, gram-negative rods	Dwell time of exchange with intraperitoneal antibiotics must be a minimum of 6 hours.

As noted earlier, resistant flora are more common in health care–associated infections, including *Pseudomonas aeruginosa*, *Acinetobacter* species, extended-spectrum β-lactamase (ESBL)-producing organisms, carbapenemase-producing *E. coli* and *Klebsiella* species, methicillin-resistant *Staphylococcus aureus* (MRSA), enterococci, and *Candida* species.[6–10]

INFECTIONS OF THE BILIARY TRACT

Cholecystitis and Cholangitis

Cholecystitis and cholangitis originate as inflammatory conditions, usually as a result of obstruction in the gallbladder or common bile duct, respectively. The obstruction is typically caused by the presence of stones. The biliary tract is sterile under normal conditions, and the flow of bile, along with its bacteriostatic properties, functions to maintain the sterility. Infection typically occurs as a secondary event to obstruction.[4,5] The location, degree, and length of time of the obstruction can influence the development of pancreatitis, cholangitis, or hepatic abscesses.[11]

Acute cholecystitis is the acute inflammation of the gallbladder. The presence of gallstones in >90% of cases prevents the outflow of gallbladder drainage by obstructing the neck of the gallbladder, the Hartmann pouch, or the cystic duct.[4] The obstruction causes an increase in intraluminal pressure, gallbladder distension, and edema, which triggers an acute inflammatory response. The potential consequences of this obstruction and inflammation include infection, ischemia, perforation, and necrosis.[4,12] The reduction in gallbladder outflow leads to biliary stasis, which provides an ideal environment for bacterial proliferation and subsequent infection (see **Fig. 70-2**).

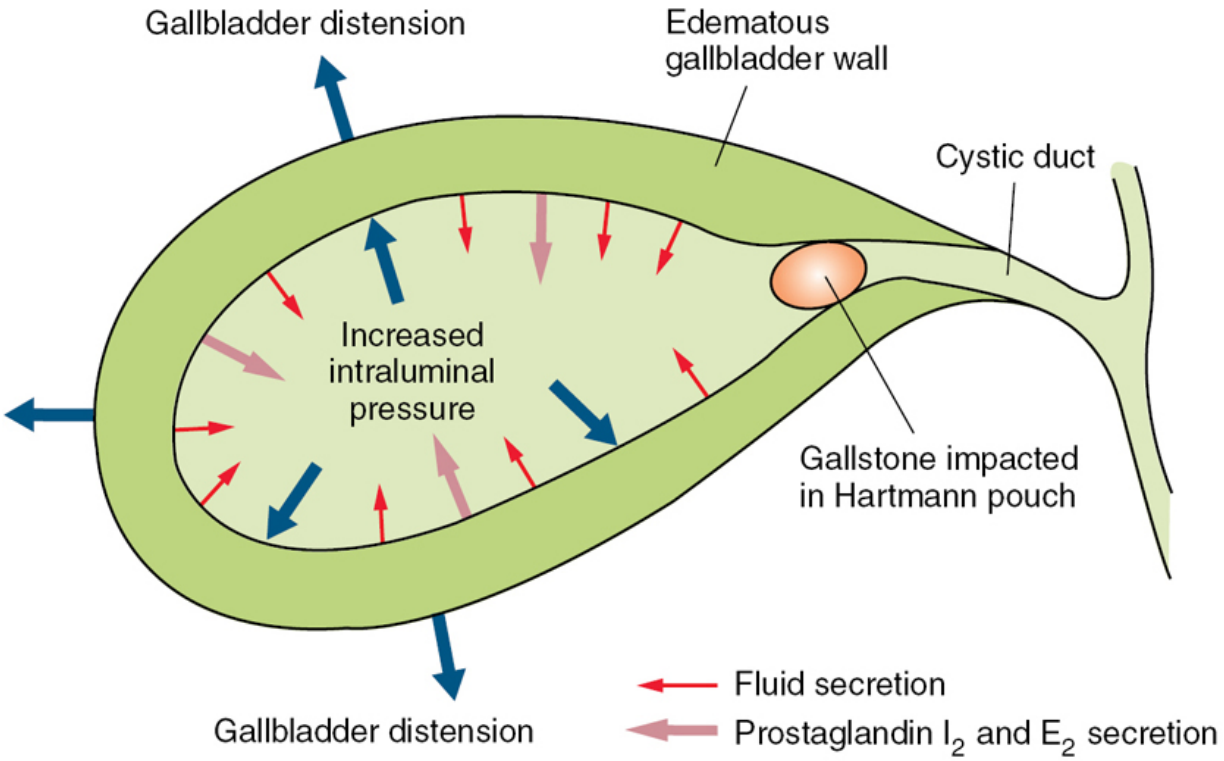


Figure 70-2 Pathogenesis of acute cholecystitis.

Acute cholangitis is an acute inflammation of the common bile duct. The most common cause of cholangitis in the United States is common bile duct obstruction as a consequence of choledocholithiasis (gallstones). Less common causes include neoplastic obstruction, postoperative obstruction after biliary intervention, benign strictures, and primary sclerosing cholangitis.[4] The decrease in biliary outflow results in biliary stasis and bacterial

proliferation. Infection results in a rapid rise in biliary pressure, which facilitates the spread of bacteria into lymphatics and the bloodstream via alterations in membrane permeability. In comparison with cholecystitis, acute cholangitis generally carries a poorer prognosis, approaching a mortality of 100% if untreated.[4,13]

CLINICAL PRESENTATION AND DIAGNOSIS

CASE 70-1

Question 1: D.S., a 54-year-old male, presents to the hospital with a 1-week history of abdominal pain and tenderness, localized to the right upper quadrant, fever of 102.02 °F (38.9 °C), and chills. He reports nausea, with three episodes of emesis occurring in the past 24 hours. D.S. appears jaundice and reports dark-colored urine. His laboratory values are the following:

White blood cell (WBC) count, 17 × 10^3/μL
Serum creatinine (SCr), 1.1 mg/dL
Total bilirubin, 6 mg/dL
Alkaline phosphatase, 270 U/L

What evidence of cholangitis exists in D.S.? How does the presentation of cholecystitis differ from that of cholangitis?

The clinical manifestations of acute cholangitis vary, but the classic presentation involves the Charcot triad, which consists of fever, jaundice, and right upper quadrant abdominal pain. Nausea and vomiting can follow.[4,12] Fever is present in 90% of cases, and jaundice and abdominal pain occur in 60% to 70% of cases.[4] On physical examination, tenderness in the right upper quadrant and a positive Murphy's sign (inspiration inhibited by pain on palpation) are often present. A smaller percentage of patients with more severe disease, generally with gram-negative bacteremia, may present with changes in mental status and hypotension.[4] The addition of these two signs to the Charcot triad is often referred to as Reynold pentad. Laboratory findings of acute cholangitis include leukocytosis, elevated bilirubin (>2 mg/dL), and alkaline phosphatase, and mildly elevated liver transaminases.[4,14] The clinical signs and symptoms of cholangitis, as exemplified by D.S., include high fevers 102.02 °F

(38.9 °C), chills, jaundice, and right upper quadrant abdominal pain. Laboratory evidence supportive of cholangitis includes leukocytosis with WBC of 17 × 10^3/μL, increased bilirubin of 6 mg/dL, and elevated alkaline phosphatase of 270 U/L. Jaundice and significant elevations in transaminases are less common with cholecystitis compared to cholangitis.[4,12]

Diagnostic imaging for acute cholecystitis and cholangitis involves ultrasonography. Findings for acute cholecystitis may reveal pericholecystic fluid, distension of the gallbladder, thickening of the gallbladder wall, stones, and a sonographic Murphy's sign.[15] Ultrasound is less sensitive for choledocholithiasis, but it may reveal biliary dilation with stones. Hepatobiliary scintigraphy is another diagnostic tool used to identify obstruction of the cystic duct. After intravenous (IV) injection with technetium hepatobiliary iminodiacetic acid (Tc-HIDA), failure to observe gallbladder filling suggests acute cholecystitis.[6,15] Computed tomography (CT) imaging may be superior in determining the extent of biliary obstruction.[4] Endoscopic retrograde cholangiopancreatography (ERCP) is an alternative mode of imaging for cholangitis.[4,14]

ETIOLOGY

Case 70-1, Question 2: What are the most likely organisms causing infection in D.S.? What clinical specimens are helpful to identify the causative pathogen(s)?

The most common pathogens associated with acute cholangitis include *Enterobacterales* such as *E. coli*, *Klebsiella* species, and *Enterobacter* species. However, *P. aeruginosa*, skin flora (*Staphylococcus* species, *Streptococcus* species), and oropharynx bacteria may be implicated. Anaerobic organisms, commonly *Bacteroides* species, are associated with ~15% of infections, particularly in elderly patients undergoing biliary tract surgery.[4,16] The etiology of cholecystitis typically involves *E. coli*, *Klebsiella* species,

and *Enterococcus* species. Anaerobes are less commonly isolated (see Table 70-1).[4,12]

As described earlier, the stasis of bile flow results in proliferation of bacteria within the gallbladder or common bile duct. Acute cholangitis results in increased pressure within the common bile duct with dissemination of bacteria from the biliary tree to the bloodstream. Blood culture results may be positive in up to 40% of patients with symptomatic acute cholangitis.[4] Acute cholecystitis may reveal positive bile culture results in 20% to 75% of patients with symptomatic disease, whereas 59% to 93% of bile culture results have generally been found positive for acute cholangitis.[2] In contrast to cholangitis, bacteremia is unlikely with cholecystitis. The choice of antibacterial agents is largely empiric covering the aforementioned common causative pathogens.

TREATMENT

Definitive therapy for both cholangitis and cholecystitis must involve source control, using surgery, percutaneous drainage, or endoscopic intervention. Empiric antibacterial therapy should be added owing to the likelihood of secondary infection and to prevent complications. Supportive measures include fluid and electrolyte supplementation and analgesia.[4,5,12,14]

To decompress or drain the biliary ductal system in cholangitis, ERCP is used with a success rate of >90% in the treatment of cholangitis.[4] Alternatively, percutaneous transhepatic biliary drainage or endoscopic sphincterotomy can be used to drain the contents. Open surgery is a less favored option to decompress the biliary tree because it is associated with increased mortality.[4] Acute symptomatic cholecystitis requires removal of the gallbladder (cholecystectomy). The procedure of choice is laparoscopic cholecystectomy within 48 to 72 hours of onset of symptoms. Early intervention is associated with decreased morbidity and length of hospital stay compared with delayed surgical intervention.[4,12] In high-risk patients, in whom the risks outweigh the benefits of early surgery, percutaneous cholecystostomy can be performed to drain

the contents of the gallbladder. The procedure improves the clinical symptoms in 75% to 90% of patients who cannot undergo surgery. Cholecystectomy, however, should take place once the patient is stable enough for surgery.[4] For acute uncomplicated cholecystitis with no infection outside the gallbladder, antibiotics can be discontinued within 24 hours of cholecystectomy.[15]

CASE 70-1, QUESTION 3: Based on the most likely causative pathogen(s), what empiric antimicrobial therapy is recommended for D.S., given a diagnosis of cholangitis?

Empiric antimicrobial therapy for acute cholangitis and cholecystitis should be initiated after blood cultures have been collected. The empiric choice of therapy should cover enteric gram-negative pathogens, particularly *E. coli* (**Table 70-2**).[5,6] In general, the addition of anaerobic coverage is not mandatory for cholecystitis; however, it should be considered in the setting of severe cases such as acute cholangitis, biliary-enteric anastomosis, or health care–associated infections.[6] Empiric coverage for *Enterococcus* species should be considered for patients at risk for health care–associated infections, such as immunocompromised patients, patients who have required long-term hospitalization, patients who have received broad-spectrum antimicrobial therapy, or patients with valvular heart disease or prosthetic intravascular materials.[6] Antimicrobial therapy must be guided by drug pharmacokinetics and pharmacodynamics, local resistance patterns, and patient factors, such as drug allergies, renal or hepatic dysfunction, and cost.

Table 70-2
Treatment Options for Intra-Abdominal Infections

Infection	Agents and Regimens	Agent Dosing[a]
Mild-to-moderate in severity: Community-acquired perforated or abscessed appendicitis or	**Single agent** Cefoxitin Ertapenem Moxifloxacin[b]	Cefoxitin 2 g IV every 6 hours Ertapenem 1 g IV every 24 hours

Acute cholecystitis	Tigecycline **Combination** Cefazolin or Ceftriaxone or Cefotaxime or Ciprofloxacin[b] or Levofloxacin[b] + metronidazole	Tigecycline 100 mg initially, then 50 mg IV every 12 hours Cefazolin 1–2 g IV every 8 hours Ceftriaxone 1–2 g IV every 12–24 hours Cefotaxime 1–2 g IV every 6–8 hours Ciprofloxacin 400 mg IV every 12 hours Levofloxacin 750 mg IV every 24 hours Moxifloxacin 400 mg IV every 24 hours Metronidazole 500 mg IV every 8–12 hours Cefepime 1–2 g IV every 8 hours *and* Ceftazidime 1–2 g IV every 8–12 hours Piperacillin–tazobactam 3.375 g IV every 4–6 hours or 4.5 g IV every 6 hours[c] Imipenem–cilastatin 500 mg IV every 6 hours or 1 g every 8 hours Meropenem 1 g IV every 8 hours Vancomycin[d] 15–20 mg/kg IV every 8–12 hours (normal renal function) Aztreonam[e] 1–2 g IV every 6–8 hours Ceftazidime/avibactam 2.5 g IV every 8 hours or Ceftolozane/tazobactam 1.5 g IV every 8 hours + Metronidazole 500 mg IV every 8–12 hours
High risk in severity: Community-acquired acute cholecystitis with severe physiologic disturbance, advanced age, or immunocompromised state or Acute cholangitis associated with biliary-enteric anastomosis or Health care–associated intra-abdominal infections	**Single agent** Imipenem–cilastatin Meropenem Piperacillin–tazobactam **Combination** Cefepime or Ceftazidime or Ciprofloxacin[b] or Levofloxacin[b] + metronidazole	

		Imipenem–cilastatin/relebactam 1.25 g IV every 6 hours Eravacycline 1 mg/kg IV every 12 hours

IV, intravenous.

[a]Normal renal function dosing.

[b]Selection of fluoroquinolones should be based on local antibiogram or susceptibility reports.

[c]Extended infusion: 3.375 g IV every 8 hours over 4 hours.

[d]May be added to each regimen in the setting of health care–associated intra-abdominal infections (eg, methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcal infection).

[e]For patients who are intolerant of β-lactams, aztreonam may be considered as an alternative agent for gram-negative coverage.

Sources: Sifri CD, Madoff LC. Infections of the liver and biliary system (liver abscess, cholangitis, cholecystitis). In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2020; e-book; Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by Surgical Infection Society and the Infectious Diseases Society of America [published correction appears in *Clin Infect Dis.* 2010;50:1695. Dosage error in article text]. *Clin Infect Dis*. 2010;50:133–164; Montravers P, Zappella N, Tran-Dinh A. Eravacycline for the treatment of complicated intra-abdominal infections. *Expert Rev Anti Infect Ther.* 2019;17(11):851–863. doi:10.1080/14787210.2019.168197; Sotto A, Lefrant JY, Fabbro-Peray P, et al. Evaluation of antimicrobial management of 120 consecutive patients with secondary peritonitis. *J Antimicrob Chemother.* 2002;50:569–576; Bassetti M, Marchetti M, Chakrabarti A, et al. A research on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. *Intensive Care Med.* 2013;39:2092–2106.

Considering their activity versus multidrug-resistant gram-negative bacilli, carbapenems generally should be reserved for infection caused by these pathogens. Vancomycin may be added empirically in health care–associated biliary infections in which ampicillin-resistant enterococci and MRSA are of concern. Linezolid or daptomycin may be considered in cases of known vancomycin-resistant *Enterococcus* species (VRE). Empiric broad-spectrum

antimicrobial regimens should be narrowed, when possible, based on culture and susceptibility findings. For mild-to-moderate community-acquired acute cholecystitis, monotherapy with cefazolin, cefuroxime, or ceftriaxone is recommended. Because of a wide prevalence of ampicillin–sulbactam-resistant *E. coli*, this agent is no longer recommended for empiric use.[6,16] Resistance to fluoroquinolones is problematic with unpredictable susceptibility of *E. coli* to ciprofloxacin and levofloxacin.[17] Current guidelines for cIAIs suggest that fluoroquinolones be considered for therapy when institutional antibiograms indicate >90% susceptibility of *E. coli*.[6] Use of aminoglycosides is not routinely recommended because of the need for therapeutic drug monitoring and potential nephrotoxicity and ototoxicity.[6] Furthermore, in comparison with other regimens, aminoglycoside-based regimens are inferior in the treatment of intra-abdominal infections.[18] However, some argue the decreased efficacy of aminoglycosides has been caused by inadequate dosing. An appropriate empiric regimen for D.S. would be piperacillin–tazobactam 3.375 g IV every 6 hours.

BILIARY CONCENTRATIONS

Case 70-1, Question 4: The physician caring for D.S. questions the need for an antibiotic that concentrates in the bile. Is there a benefit to using an antibiotic that is extensively excreted into bile?

Common bile duct obstruction prevents the entry of antibiotics into the bile, and the need for high biliary concentrations of antibiotics in the treatment of cholangitis has been debated.[19] Nagar and Berger[20] concluded that a number of antibiotics with excellent in vitro susceptibility, but poor biliary excretion, are still clinically effective. Biliary antibacterial concentrations do not correlate with an improved clinical outcome.[4] Highly biliary-excreted versus moderately biliary-excreted antibiotics have been compared.[19] Serum concentrations are more important than are biliary levels in reducing the septic

complications of biliary tract surgery. Furthermore, biliary excretion of any antibiotic is minimal in the presence of obstruction.[19]

The treatment of D.S.'s biliary tract infection must include biliary drainage. Piperacillin–tazobactam should be continued for 4 to 7 days.

PRIMARY PERITONITIS

Peritonitis is inflammation of the peritoneum as a result of infectious or chemical inflammation within the peritoneal cavity.[2,21] Infectious peritonitis can be classified as primary, secondary, or tertiary. Primary peritonitis involves the development of infection in the peritoneal cavity in the absence of other intra-abdominal pathology.[21,22] Secondary peritonitis classically results from other intra-abdominal abnormalities leading to contamination of the peritoneum with gastrointestinal (GI) or genitourinary microorganisms due to the loss of mucosal barrier integrity (eg, trauma or perforation). Tertiary peritonitis is clinical peritonitis along with signs of sepsis and multiorgan dysfunction persisting or recurring after the treatment of secondary peritonitis, often involving multidrug-resistant pathogens.[2,21] Tertiary peritonitis has a poor prognosis with a mortality rate of 30% to 64%.[23]

Primary peritonitis is also known as spontaneous bacterial peritonitis (SBP) and is most frequently identified in adults with cirrhosis and ascites. Nearly 10% to 30% of patients hospitalized with cirrhosis and ascites have SBP.[2,22,24] Primary peritonitis is associated with postnecrotic cirrhosis, chronic acute hepatitis, acute viral hepatitis, congestive heart failure, metastatic malignancy, or systemic lupus erythematosus.[2,21] In addition to advanced cirrhosis, other risk factors for primary peritonitis include GI hemorrhage, history of primary peritonitis, low protein in ascetic fluid (<1 g/dL), elevated serum bilirubin (>2.5 mg/dL), and proton-pump inhibitors.[2]

Spontaneous Bacterial Peritonitis in Patients With Cirrhosis

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients with SBP may present with fever, signs of peritonitis, including abdominal pain, altered mental status, changes in GI motility, nausea, vomiting, diarrhea, or ileus.[24] Fever is common, occurring in 50% to 80% of patients.[2] Some patients have an atypical presentation or even lack symptoms.[24] The diagnosis of SBP is made on clinical presentation and examination of the peritoneal fluid via paracentesis. The ascitic fluid is tested for cell counts with WBC differential, and the presence of microorganisms is based on Gram stain and culture. Fluid analysis should be collected before the start of antibiotics. A positive ascitic fluid bacterial culture result with an elevated polymorphonuclear (PMN) count (≥250/μL) is diagnostic for SBP. Empiric treatment for SBP should be initiated with a significant elevation in ascitic fluid PMN, even if the ascitic fluid culture result is negative.[23]

ETIOLOGY AND PATHOGENESIS

CASE 70-2

Question 1: M.W., a 51-year old male with alcoholic cirrhosis, history of SBP, and significant abdominal ascites, presents with a 4-day history of fever of 101.12 °F (38.4 °C) and abdominal pain. Ascitic fluid obtained by paracentesis was cloudy, and culture of the ascitic fluid is pending. Laboratory values include ascitic fluid PMN count, 450/μL; serum WBC count, 12.2 × 10^3/μL; and total bilirubin, 4.4 mg/dL.

What organisms are likely to be cultured from M.W.'s ascitic fluid?

An estimated 70% of cases of SBP are caused by aerobic enteric organisms considered normal flora of the GI tract.[24] *E. coli* is the most common pathogen, followed by *Klebsiella pneumoniae*.[2] Other common causes of SBP include *Streptococcus pneumoniae* and other *Streptococcus* species, accounting for 20% of cases.

Enterococcus species are isolated in ~5% of cases.[24] *Staphylococcus* species, anaerobes, and microaerophilic organisms are rarely reported in community-acquired SBP. SBP is largely a monomicrobial infection.

One of the main mechanisms of pathogenesis associated with the development of SBP is bacterial translocation, which is the migration of microorganisms through the GI wall to mesenteric lymph nodes and other structures outside the intestine, including the bloodstream. Bacteria then infect the ascitic fluid by hematogenous or lymphogenous spread.[24],[25] Certain characteristics of patients with cirrhosis facilitate the pathogenesis of SBP, including bacterial overgrowth, decreased motility, structural intestinal damage, and decreased host-defense mechanisms that normally function to eliminate microorganisms. Bacterial overgrowth in the face of decreased motility and increased gut wall permeability, secondary to structural damage, facilitates subsequent systemic infection. Reduced opsonic activity and phagocytosis allow the microorganisms to escape the hosts' defenses and subsequently infect the ascitic fluid.[25] SBP with underlying cirrhosis was previously associated with a >90% mortality rate, but with the advances in antibacterial therapy, the rate has been reduced to ~30% to 40%.[2],[24] Gram-negative pathogens are associated with increased mortality compared with gram-positive pathogens.[2] Early diagnosis and effective antibacterial treatment of SBP are associated with reduced rates of mortality.[26] Patient characteristics associated with increased mortality include renal insufficiency, hypothermia, hyperbilirubinemia, and hypoalbuminemia. To decrease the rate of renal dysfunction associated with SBP, IV albumin at 1.5 g/kg within 6 hours of diagnosis and 1 g/kg on day 3 may be administered. Albumin acts as a volume expander to lessen hemodynamic changes, thereby preserving renal function. Albumin is recommended in patients with an SCr >1 mg/dL, blood urea nitrogen (BUN) >30 mg/dL, or total bilirubin >4 mg/dL.[24]

ANTIMICROBIAL THERAPY

Case 70-2, Question 2: Pending ascitic fluid culture results, what empiric antimicrobial therapy should be recommended for M.W.? What is an appropriate duration of therapy, and how should the response to therapy be monitored?

Although a positive Gram stain and culture result guides antibacterial therapy, nearly 60% of patients with signs and symptoms of SBP have negative culture results.[2,26] Initial antibacterial therapy for patients with a diagnosis of SBP is typically empiric and targeted toward the most likely pathogens, as described previously. Ampicillin plus an aminoglycoside was the traditional choice for empiric therapy; however, third-generation cephalosporins (cefotaxime and ceftriaxone) represent safer and more effective options.[27,28] A fluoroquinolone may be considered an alternative in patients with β-lactam allergies. Levofloxacin and moxifloxacin are preferred over ciprofloxacin, because of their superior activity against *S. pneumoniae*, the most commonly isolated gram-positive bacterial pathogen. Although parenteral therapy is preferred, oral fluoroquinolones may be as effective in patients with uncomplicated SBP.[27] As described earlier, aminoglycosides are not recommended in cirrhotic SBP therapy because of the risk of nephrotoxicity, and the decision whether to use fluoroquinolones should be based on institutional antibiogram reports.[24] Fluoroquinolones should be avoided if used previously for SBP prophylaxis.[29]

Antibiotic therapy is recommended until the PMN count from the ascitic fluid falls <250 cells/μL, which normally occurs within 5 days.[26] França et al[30] concluded that a 5-day course of cefotaxime for the treatment of SBP was as effective as a 10-day course. In general, follow-up fluid analysis is not necessary if clinically improving.

M.W. should receive empiric therapy with an antimicrobial agent effective against *E. coli* and other common pathogens such as *Klebsiella* species and *S. pneumoniae*. Any of the abovementioned options would be reasonable empiric choices. Therapy can continue for at least 5 days with signs of clinical improvement.

PROPHYLAXIS

CASE 70-2, QUESTION 3: After treatment is completed, should prophylactic antimicrobial therapy be initiated in M.W.?

Recurrence rates for SBP are high. Patients with cirrhosis who survive an episode of SBP have a 1-year recurrence rate of nearly 70%. Owing to the high risk of mortality from primary peritonitis, antibiotic prophylaxis should be administered to the following patients because they are considered high risk for the development of SBP: patients who have had one or more episodes of SBP; patients with cirrhosis with GI bleeding; patients with cirrhosis with ascites, who have impaired renal or liver function; or patients with cirrhosis with a low ascitic protein (<1.0 g/dL).[24]

Antibiotic prophylaxis in patients with cirrhosis is typically initiated to provide selective decontamination of the GI tract. The goal of this therapy is to reduce the burden of bacteria and subsequently prevent bacterial translocation and infection and reduce the risk of rebleeding.[24],[25] Prospective, randomized studies in subjects with cirrhosis with ascites support the use of oral antibacterial agents to reduce the rate of recurrence. The agents studied include oral norfloxacin[31] (no longer available in the United States), ciprofloxacin,[32] and trimethoprim–sulfamethoxazole.[33] Rifaximin, a nonabsorbable derivative of rifamycin, has also been shown to significantly reduce the occurrence of SBP.[34] Clinical trials have provided evidence to support the use of short-course therapy (7 days) with IV ceftriaxone 1 g/day to prevent peritonitis in hospitalized patients with cirrhosis presenting with GI hemorrhage.[25],[35] Transition to oral therapy (ciprofloxacin or trimethoprim–sulfamethoxazole) to complete 7 days is reasonable once bleeding has stopped and the patient is stable. Several cost analyses have been performed, demonstrating that prophylactic therapy in high-risk groups of patients with cirrhosis is cost-effective.[25] Long-term prophylaxis is recommended based on the significant reduction in rates of recurrence in clinical trials. However, the rising prevalence of gram-

positive bacteria and multidrug-resistant organisms parallel with concerns for gut microbiota dysbiosis question the risk versus benefit of long-term prophylaxis for SBP, particularly in vulnerable patients with cirrhosis.[36] Long-term prophylaxis in patients with low ascitic protein, elevated bilirubin, or both may also be beneficial, but it has not been associated with decreased overall infection or mortality and, therefore, is not uniformly recommended.[24,25,31–33]

Because rates of fluoroquinolone-resistant and trimethoprim–sulfamethoxazole-resistant organisms are more prevalent in patients who receive long-term prophylactic therapy, its long-term use must be considered when initiating antibacterial therapy for the treatment of new infections in this patient population.[37,38]

M.W. has cirrhosis, a previous episode of SBP, and a high total bilirubin; thus, he is at high risk for recurrence. Prophylactic antimicrobial therapy should be considered and may be a cost-effective measure. M.W. would benefit from ciprofloxacin 500 mg PO daily. The use of trimethoprim–sulfamethoxazole would depend on local resistance patterns.

Continuous Ambulatory Peritoneal Dialysis–Associated Peritonitis

PATHOGENESIS AND CLINICAL PRESENTATION

CASE 70-3

Question 1: H.M., a 33-year-old female with human immunodeficiency virus (HIV) and end-stage renal disease, has undergone continuous ambulatory peritoneal dialysis (CAPD) daily for the past year. She presents with abdominal pain and a cloudy dialysate fluid. H.M. has negligible residual urine output.

What are the most common causative organisms related to CAPD-associated peritonitis? What empiric antimicrobial therapy should be initiated? How should antimicrobial agents be administered?

Following SBP, peritoneal dialysis (PD) is another cause of primary peritonitis. Historically, an estimated 45% of patients

undergoing CAPD will experience at least one episode of peritonitis in the first 6 months of dialysis. Approximately 60% to 70% of patients exhibit peritonitis during the first year of dialysis, and recurrent infection occurs in 20% to 30% of patients.[2] CAPD-associated peritonitis is theorized to originate from contamination of the catheter by organisms of the normal skin flora, contamination of the peritoneum from an exit-site or subcutaneous-tunnel infection, contamination of the dialysate fluid, or bacterial translocation.[2] Nasal carriers of *Staphylococcus aureus* may have a higher incidence of PD-associated peritonitis.[39] Alterations in host defenses of the peritoneum may also have a role in the development of CAPD-associated peritonitis.[2]

Clinical manifestations of CAPD-associated peritonitis include abdominal pain and tenderness, which is observed in 60% to 80% of patients. Nausea and vomiting occur in ~30% to 50% of patients, whereas 10% will have diarrhea and 10% to 20% will present with fever. The diagnosis of peritonitis is made on the basis of clinical signs and symptoms along with examination of the dialysate fluid for cell counts, Gram stain, and culture. Characteristically, the dialysate fluid will be cloudy and have a WBC count >100 cells/μL (85% have >500 cells/μL) after a dwell time of 2 hours with a neutrophilic predominance (at least 50%).[2,40] A low leukocyte count may suggest a tunnel infection and eosinophilic peritonitis may represent an allergy to tubing or drug or presence of fungal and parasitic peritonitis.[3] The Gram stain result may be positive in 9% to 50% of cases, and blood culture results are typically negative.[2,41] In most cases, peritonitis is commonly caused by a single organism.[42]

ETIOLOGY

The most common causative organisms have historically involved gram-positive bacteria, accounting for 60% to 80% of isolates. Coagulase-negative *Staphylococcus* species (*S. epidermidis*) have been the most common, followed by *S. aureus* and *Streptococcus* species. Gram-negative bacilli are isolated in ~15% to 30% of cases, with *E. coli* being the most common. Other common gram-negative

organisms include *Klebsiella* species, *Enterobacter* species, *Proteus* species, and *P. aeruginosa*. Cases due to gram-negative organisms have been on the rise largely owing to contaminated water; skin, urinary, or bowel sources; and animal contacts. Nosocomial pathogens such as VRE are also increasing, and, if isolated, should raise concerns for concomitant intra-abdominal processes. Anaerobes, fungi, and mycobacteria constitute the less commonly encountered pathogens.[2]

ANTIMICROBIAL THERAPY

Antimicrobial therapy aims to resolve inflammation and preserve the function of the peritoneal membrane. In general, empiric antibiotic therapy should be directed against the most common causative organisms, both gram-positive and gram-negative organisms, until culture results of peritoneal fluid are available. Intraperitoneal (IP) delivery of antibacterial agents is the preferred route of administration for the treatment of CAPD-associated peritonitis, except in the setting of systemic sepsis. The IP route provides very high local concentrations of antibacterial agents as well as the ability to avoid a venipuncture and allow the patient to self-administer therapy at home.[40]

Empiric IP administration of antibiotics should be given when CAPD-associated peritonitis is suspected. When culture and susceptibility results are available, antibacterial therapy should be adjusted as necessary. With appropriate therapy, a clinical response should be expected within the first 48 hours.[40]

Treatment guidelines for CAPD-associated peritonitis provide a systematic approach for antimicrobial selection, dosing guidelines, and duration of therapy.[40] Dosing regimens are targeted to maintain drug concentrations above the minimum inhibitory concentration (MIC) of the causative pathogen in the peritoneal cavity fluid for majority of the dosing interval. Intermittent dosing should dwell for at least 6 hours; however, intermittent versus continuous dosing regimens have been found to be relatively equivalent in results.[43] Empiric IP therapy recommendations include vancomycin or a first-

generation cephalosporin for gram-positive coverage plus an antibacterial agent with antipseudomonal coverage.[40] Because of the increasing rates of MRSA and methicillin-resistant *Staphylococcus epidermidis*, vancomycin may be the most appropriate initial empiric agent for gram-positive organisms.[42–45] Empiric gram-negative antipseudomonal therapy can be initiated with a third-generation cephalosporin (ceftazidime) or an aminoglycoside. Alternatively, cefepime, piperacillin–tazobactam, or a carbapenem may also be used.[2,40,46] For patients who are intolerant of β-lactams, aztreonam may be considered as an alternative agent for gram-negative coverage.[40,46] IP fluoroquinolones represent an option for CAPD-associated peritonitis; however, avoidance of fluoroquinolone use should be considered when local fluoroquinolone-resistant rates are >10%.[47,48]

Refractory peritonitis, presence of cloudy effluent after 5 days of IP therapy, may require removal of the catheter, as well as cases of relapse and recurrent and repeat peritonitis. When concomitant *S. aureus* exit-site or tunnel infection is identified, the infection usually necessitates the removal of the dialysis catheter. Vancomycin is recommended for MRSA. Conversely, cefazolin alone is adequate for methicillin-susceptible *Staphylococcus aureus* (MSSA). Coagulase-negative *Staphylococcus* species do not require prompt catheter removal because they typically respond well to antimicrobial therapy. Methicillin resistance is common for *S. epidermidis*; thus, vancomycin is normally used. *Enterococcus* species or *Streptococcus* species should be treated with ampicillin if susceptible. Vancomycin should be used for ampicillin-resistant enterococcus; however, VRE requires treatment with daptomycin, linezolid, or quinupristin–dalfopristin. In the case of peritonitis where the culture result was negative with clinical improvement after 3 days of empiric coverage, a single agent directed toward gram-positive organisms may be continued for a total of 2 weeks.[40]

When a single gram-negative organism is cultured (eg, *E. coli*, *Klebsiella* species, or *Proteus* species), therapy can be narrowed based on susceptibility. Isolation of *P. aeruginosa* most often indicates a severe infection, involving the dialysis catheter (exit site

and tunnel infection) with a high rate of relapse and treatment failure, in which case catheter removal is recommended.[2] Therapy options include an antipseudomonal β-lactam such as ceftazidime, cefepime, or piperacillin–tazobactam. Double coverage with antipseudomonal agents (using a fluoroquinolone or an aminoglycoside) pending susceptibilities may be needed in the setting of hemodynamic instability; however, ongoing dual therapy has not been found to be of benefit.[2] In general, IP β-lactam antimicrobials achieve peritoneal fluid concentrations exceeding typical minimum inhibitory concentrations for most commonly encountered facultative gram-negative and anaerobic bacteria.[40],[49],[50]

Polymicrobial peritonitis is uncommon and may indicate a more complicated intra-abdominal process requiring surgery if clinical response is not obtained from medical management. Anaerobic coverage is recommended. Duration of therapy generally lasts 2 to 3 weeks.[2] **Table 70-3** lists antimicrobial dosing guidelines for the treatment of peritonitis associated with CAPD.[40]

Table 70-3
Intraperitoneal Antibiotic Dosing Recommendations for Patients With Peritoneal Dialysis

	Intermittent Dosing[a]	Continuous Dosing[b] (mg/L)	
		LD	MD
Amikacin	2 mg/kg daily	25	12
Amoxicillin			150
Ampicillin			125
Ampicillin/sulbactam	2 g/1 g every 12 hours	750–100	100
Aztreonam	2 g daily	1000	250
Cefazolin	15–20 mg/kg daily	500	125
Cefepime	1000 mg daily	250–500	100–125
Cefotaxime	500–1000 mg daily		
Ceftazidime	1000–1500 mg daily	500	125
Ceftriaxone	1000 mg daily		
Ciprofloxacin			50
Clindamycin			600 mg/bag
Daptomycin		100	20
Fluconazole	200 mg every 24–28 hours		
Gentamicin	0.6 mg/kg daily	8	4
Imipenem/cilastatin	500 mg in alternate exchange	250	50
Meropenem	1000 mg daily		
Penicillin G		50,000 units/L	25,000 units/L
Piperacillin/tazobactam		4 g/0.5 g	1 g/0.125 g
Polymyxin B			300,000 unit (30 mg)/bag
Quinupristin/dalfopristin	25 mg/L in alternate exchange[c]		
Tobramycin	0.6 mg/kg	3 mg/kg	0.3 mg/kg
Vancomycin	15–30 mg/kg every 5–7 days[d]	30 mg/kg	1.5 mg/kg/bag
Voriconazole	2.5 mg/kg daily		

Empiric doses for patients with residual renal function (>100 mL/day urine output) should be increased by 25%.

LD, loading dose; MD, maintenance dose.

[a]Per exchange, once daily.

[b]All exchanges.

[c]Given in conjunction with 500 mg intravenously (IV) twice daily.

[d]Supplemental doses may be needed for patients with ambulatory peritoneal dialysis (APD).

Source: Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016;36(5):481–508. © 2016 SAGE Publications. Reprinted by permission of SAGE Publications, Inc.

An example of an appropriate ‘empiric’ regimen for H.M may include vancomycin plus cefepime or an aminoglycoside given IP.

The clinician should monitor culture and susceptibility results to adjust therapy based on guidelines, local sensitivity patterns, and therapeutic response.

FUNGAL CONTINUOUS AMBULATORY PERITONEAL DIALYSIS–ASSOCIATED PERITONITIS

CASE 70-3, QUESTION 2: Two years later, H.M. presents with abdominal pain and cloudy dialysate fluid. *Candida albicans* is cultured from the dialysate fluid. No other organisms are present. How should H.M. be treated?

Fungal peritonitis is a rare complication of CAPD that is associated with significant morbidity and mortality. The rate of mortality in fungal peritonitis is ~25%.[40] Considering the high rate of failure of therapy, patients with CAPD with fungal peritonitis should have their catheters removed.[44] Patients who have received prolonged or multiple courses of antibiotics; are on immunosuppressant therapy for a malignancy, a transplant, or an inflammatory disease; or have a postoperative or recurrent intra-abdominal infection are at increased risk for fungal peritonitis and should be treated with antifungals.[2],[5],[51] Most cases are caused by *Candida* species, most commonly *C. albicans*; however, an increase in infection attributable to non-albicans species has emerged in many areas.[51] Empiric antifungal therapy should be broad and include most *Candida* species; echinocandins such as caspofungin, micafungin, or anidulafungin are the empiric drugs of choice. Amphotericin B may be administered via IV or IP, but when given IP, conventional amphotericin B is very irritating to the peritoneum.[40] The azole antifungal agents can be administered orally or via IV or IP. Fluconazole is active against *C. albicans*, but it has dose-dependent activity against certain types of non-albicans species, such as *C. glabrata*. In general, fluconazole is the drug of choice for *C. albicans*; however, other options, such as a polyene or echinocandin, may be needed for azole-resistant *Candida* species. Therapy should continue for a minimum of 2 weeks after catheter removal, and the

total duration may be based on severity and clinical response.[40] Owing to the azotemic state of the patient and its high renal elimination, flucytosine should not be used because of the risk of severe toxicity to the colon and bone marrow.[2]

H.M.'s treatment should include temporary catheter removal and administration of antifungal agents. Antifungal therapy with oral fluconazole 400 mg daily should be continued for at least 14 days.

SECONDARY PERITONITIS

Pathogenesis and Epidemiology

Secondary peritonitis usually occurs after fecal or urinary contamination of the peritoneal cavity or its surrounding structures.[3] The process leading to an infection commonly includes an acute perforation associated with appendicitis, diverticulitis, the uterus, neoplasm, and inflammatory bowel disease (IBD). Secondary peritonitis can also result from postoperative or posttraumatic perforation of the GI or genitourinary tract related to blunt trauma or ingestion of foreign material.[52,53]

Localization of infection without eradication of bacteria results in IP or visceral abscesses. IP abscesses occur most often in the right lower quadrant in association with appendicitis or a perforated peptic ulcer. Other causes can include diverticulitis, pancreatitis, IBD, trauma, and abdominal surgery. Visceral abscesses generally are found in the pancreas but may also occur in the liver, spleen, or kidney.[2]

Mortality with secondary peritonitis can be as high as 68%.[54] Timely source control with surgical intervention is imperative for clinical success of infections resulting from secondary peritonitis. Management with appropriate antimicrobial therapy, intensive care support, and the overall health of the patient are also critical for the outcome.[53]

Clinical Presentation and Diagnosis

CASE 70-4

QUESTION 1: R.C., a 48-year-old male, presents with severe abdominal pain and nausea. He states he has been taking nonsteroidal anti-inflammatory drugs (NSAIDs) for joint pain daily for the past 2 weeks. An esophagogastroduodenoscopy reveals a perforated peptic ulcer. Significant vital signs include a temperature of 101.66 °F (38.7 °C) and tachycardia (pulse, 105 beats/minute). Bowel sounds are absent. Pertinent laboratory values include WBC count, 16.5 × 10^3/μL and BUN, 34 mg/dL.

What signs and symptoms of secondary peritonitis does R.C. display?

Making the diagnosis of a localized intra-abdominal infection may be difficult, despite the presence of signs and symptoms typical of infection. Moderate-to-severe abdominal pain with anorexia, nausea, and vomiting are commonly experienced. Fevers with or without chills, tachycardia, sparse urination secondary to fluid loss into the peritoneum, faint or absent bowel sounds, and abdominal distension may accompany primary GI symptoms associated with peritonitis. Inflammation around the intestines and peritoneal cavity results in local paralysis and reflex rigidity of the abdominal wall muscles and the diaphragm, causing rapid and shallow respirations.[2] These signs are usually accompanied by an elevated WBC count with a predominance of neutrophils (left shift). The hematocrit (Hct) and BUN may be elevated as a result of dehydration. Initially, patients are usually alkalotic owing to emesis and hyperventilation, but in the later stages of peritonitis, acidosis usually occurs. Untreated or partially treated peritonitis can result in generalized sepsis and hypovolemic shock, in addition to a gradual development of IP abscesses. Therefore, patients with a sudden turn in disposition after treatment and recovery from peritonitis or abdominal surgery should be assessed for IP abscess formation.[3,2]

R.C. is likely to have a community-acquired intra-abdominal infection suggestive of a secondary peritonitis resulting from an acute perforated peptic ulcer after NSAID use for 2 weeks. His current clinical status is highlighted by severe abdominal pain and

nausea, fever with tachycardia, a significant elevation in WBC, and signs of dehydration with a BUN of 34 mg/dL.

CASE 70-4, QUESTION 2: Given these findings, what are the most likely pathogens for R.C.'s secondary peritonitis?

ETIOLOGY

The normal flora consistent with the perforated segment of the GI tract determines the most likely pathogens, consisting of both aerobes and anaerobes (anaerobes become more prevalent the more distal the source).[55] In general, the stomach and small bowel consist of few microbes, such as *Candida* species, lactobacilli, and oral streptococci, in the fasting state. However, the number and variety of gastric microbiota can increase with meals, achlorhydria (use of H_2 blockers or proton-pump inhibitors), obstruction, and presence of blood.[2] The most common facultative bacterium is *E. coli*, which is found in ~50% of cultures. A variety of other facultative gram-negative bacteria include *Klebsiella* species, *P. aeruginosa*, *Proteus* species, and *Enterobacter* species (**Table 70-4**).[3,56–59] *E. coli*, enterococci, and a predominant presence of obligate anaerobes, including *Bacteroides fragilis*, *Prevotella* species, *Peptococcus* species, *Peptostreptococcus* species, and *Fusobacterium* species, are found in the ileum and colon of the large bowel. *B. fragilis* is the most frequently isolated obligate anaerobe after perforation of the colon.[2,60] Anaerobic cocci (*Peptostreptococcus*) and facultative gram-positive cocci, such as streptococci, are also isolated.[2,6,57,60] *Enterococcus* species are isolated less frequently.[2,6,57,60] *B. fragilis* and *E. coli* are the most common pathogens found in blood culture samples after bacteremia related to an intra-abdominal infection.[2] Highly antibiotic-resistant strains of *P. aeruginosa*, Enterobacterales-producing ESBLs or carbapenemases, *Acinetobacter* species, and *Enterococcus*, as well as *Candida* species, are often isolated from hospitalized patients who experience secondary peritonitis.[2,6]

Table 70-4
Bacteriology of Intra-Abdominal Infections

Bacteria	Patients (%)
Facultative and Aerobic Gram Negatives	
Escherichia coli[a]	71
Klebsiella species	14
Pseudomonas aeruginosa	14
Proteus mirabilis	5
Enterobacter species	5
Anaerobes	
Bacteroides fragilis[a]	35
Other *Bacteroides* species	71
Clostridium species	29
Prevotella species	12
Peptostreptococcus species	17
Fusobacterium species	9
Eubacterium species	17
Aerobic Gram Positives	
Streptococcus species	38
Enterococcus faecalis	12
Enterococcus faecium	3
Staphylococcus aureus	4

[a]Most common in community-acquired intra-abdominal infections.

Source: Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(2):133–164. Reproduced by permission of Infectious Diseases Society of America; Paterson DL, Rossi F, Baquero F, et al. In vitro susceptibilities of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART). *J Antimicrob Chemother*. 2005;55(6):965–973.

Gram stain and culture do not need to be routinely obtained in community-acquired intra-abdominal infections before the initiation of antimicrobial therapy. It may be useful in health care–associated infections for detection of gram-positive cocci, yeast, or multidrug-resistant pathogens.[2,6] The presence of pleomorphic gram-negative bacilli, a strong odor, or tissue gas is strongly suggestive of infection with anaerobes, particularly *B. fragilis.*

R.C.'s secondary peritonitis is likely due to the presence of a facultative gram-negative organism, such as *E. coli*, *Proteus* spp., *Klebsiella* spp., or *Enterobacter* spp., or possibly an obligate anaerobe, such as *B. fragilis*. R.C. does not present with a history of hospitalization or recent receipt of broad-spectrum antimicrobials; therefore, an infection caused by more resistant health care–associated pathogens (eg, *P. aeruginosa*, ESBLs, carbapenemases) is less likely.

Case 70-4, Question 3: What empiric antimicrobial therapy is appropriate for R.C. at this time?

Antimicrobial Therapy

EMPIRIC THERAPY

Therapy for secondary peritonitis should include early administration of antimicrobial agents directed at facultative gram-negative bacteria and obligate anaerobes, fluid therapy, and support of vital organ function, as well as source control measures. Antibiotics should be administered within 1 hour of presentation of septic shock and within 8 hours of hospital admission in those with stable hemodynamic or organ status.[6] Adequate source control involving surgical debridement and drainage, in conjunction with appropriate antimicrobial therapy, decreases morbidity and mortality and should always be performed when possible.[2,3,61] In general, when an intra-abdominal infection is suspected, antimicrobial agents should be started immediately after appropriate specimens (eg, blood, peritoneal fluid) have been obtained and before any surgical

procedures are performed.[2,3,6,62] The parenteral route should be used to ensure adequate systemic and tissue concentrations, especially in patients in whom shock or poor perfusion of the muscles or GI tract precludes the use of oral administration. Table 70-2 outlines dosing recommendations for antibiotics commonly used in the treatment of intra-abdominal infections.

For mild-to-moderate community-acquired infections, empiric monotherapy with ertapenem, moxifloxacin, tigecycline, or cefoxitin is recommended. Ertapenem provides coverage against gram-positive, gram-negative, and anaerobic organisms with the notable exceptions of *Acinetobacter* spp., *P. aeruginosa,* and *Enterococcus* spp. In comparative trials of ertapenem versus piperacillin–tazobactam, the two agents were shown to be similar in efficacy and safety.[63–65] Moxifloxacin has coverage against gram-positive and gram-negative aerobic organisms (excluding *P. aeruginosa*), in addition to anaerobic organisms, and penetrates well into inflamed GI tissue, peritoneal exudates, and abscesses.[59,66,67] Earlier concerns for resistance among *Bacteroides* species to moxifloxacin were reevaluated in recent studies and moxifloxacin was found to be a safe and effective monotherapy option for mild-to-moderate community-acquired cIAI.[6,57,68,69] However, moxifloxacin should be used cautiously in infections with recent fluoroquinolone use owing to concerns of acquired bacterial resistance.

Tigecycline offers added in vitro activity against resistant pathogens such as MRSA, VRE, and penicillin-resistant *S. pneumoniae*; however, tigecycline lacks activity against *Proteus* species and *P. aeruginosa*. Caution should be practiced when using tigecycline for severe infections, including cIAI because the U.S. Food and Drug Administration announced a boxed warning of increased risk for mortality and noncure rates. Therefore, the use of tigecycline should be considered when alternative antibiotic options are not available. Cefoxitin is a cephamycin antibiotic that covers gram-positive, gram-negative, and anaerobic bacteria. Owing to concerns of increasing resistance from anaerobes, most notably *B. fragilis,* cefoxitin has fallen out of favor compared to other guideline-recommended agents for use as monotherapy.[70] Combination

therapy with either a cephalosporin or a fluoroquinolone (ciprofloxacin or levofloxacin) plus metronidazole is also reasonable.[6]

For severe community-acquired intra-abdominal infections, meropenem, imipenem–cilastatin, and piperacillin–tazobactam are empiric monotherapy options that may be used. An antipseudomonal third- or fourth-generation cephalosporin, fluoroquinolone (ciprofloxacin or levofloxacin), or aztreonam in combination with metronidazole represent alternative options for severe infections.[6,63]

Empiric use of ampicillin–sulbactam is no longer recommended for cIAIs because of increasing rates of *E. coli* resistance.[6,71] In addition, clindamycin and cefotetan are not recommended for community-acquired cIAI because of rising resistance rates from *B. fragilis*. The association of clindamycin with *Clostridioides difficile*–associated diarrhea has also resulted in the use of other options.[6,56,63–65,72,73] With the risk of nephrotoxicity and ototoxicity with aminoglycosides, safer agents are now considered first-line treatment options. Caution should be taken when using fluoroquinolones empirically, particularly if hospital antibiograms indicate <90% susceptibility of *E. coli* because fluoroquinolone-resistant *E. coli* has become more common in the community.[6] Susceptibility patterns within the community and institutional antibiograms may assist with selection of optimal empiric antimicrobials when managing community-acquired cIAIs.

Tertiary peritonitis is described as persistent peritonitis with systemic signs of sepsis even after appropriate management of the infection has been initiated.[2] As a health care–associated infection, tertiary peritonitis often presents in critically ill or immunocompromised patients where adequate source control may be improbable. With tertiary peritonitis, pathogens can vary from those that are less virulent such as enterococci, including VRE, coagulase-negative *Staphylococcal* species, and *Candida* species to the more resistant health care–associated pathogens with little to no antibiotic options. Empiric use of meropenem, imipenem–cilastatin, or piperacillin–tazobactam[6] should be reserved for health care–associated infections in cases of sepsis and presumed or documented multidrug-resistant pathogens.

Multiple new antibiotics with activity against resistant pathogens were recently approved for the treatment of cIAI (see Table 70-2).[74,75] Ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, and imipenem–cilastatin/relebactam offer in vitro activity against challenging resistant gram-negative pathogens, including ESBLs and AmpC-producing *Enterobacterales* and multidrug-resistant *P. aeruginosa*.[76,77,78,79] Ceftazidime/avibactam and imipenem–cilastatin/relebactam also have in vitro activity against *K. pneumoniae* carbapenemases. Because they lack adequate anaerobic coverage on their own, both ceftolozane/tazobactam and ceftazidime/avibactam must be combined with metronidazole when treating an intra-abdominal source. Eravacycline is a new synthetic fluorocycline antibiotic that covers pathogens commonly implicated in intra-abdominal infections including enterococci, ESBL-producing *Enterobacterales*, *Acinetobacter baumannii*, and anaerobes.[80]

R.C. should receive antimicrobial therapy with activity against facultative gram-negative bacteria and anaerobes, including *B. fragilis.* Ertapenem 1 g IV every 24 hours would be an appropriate treatment for R.C.'s mild-to-moderate cIAI.

ENTEROCOCCAL INFECTION

CASE 70-5

QUESTION 1: B.B. is a 58-year-old, nonobese female with gangrene of the bowel. One day after undergoing surgical resection of the duodenum, she has a fever of 102.02 °F (38.9 °C), shaking chills, and abdominal pain. Laboratory values include a WBC count of 18.4 × 10^3/μL and creatinine of 1.1 mg/dL. B.B.'s peritoneal fluid cultures grew *E. coli*, *B. fragilis*, *C. albicans*, and *Enterococcus*. Blood culture results are negative. She is currently receiving ertapenem 1g IV every 24 hours.

Should B.B. receive additional antimicrobial therapy active against *Enterococcus*?

Although *Enterococcus* is commonly cultured in patients with secondary peritonitis, its pathogenicity has been questioned.

Enterococcus can cause serious infections (eg, endocarditis, urinary tract infections), but it is less virulent in the setting of polymicrobial infections such as intra-abdominal infections.

An important issue is whether empiric treatment should include antibiotics with activity against *Enterococcus.* Some investigators believe that *Enterococcus* species are commensal organisms that need not be treated in most clinical settings. They point to clinical studies in which antibiotic regimens lacking in vitro activity against *Enterococcus* have been successful. The pathogenicity of *Enterococcus* lies in its ability to enhance the formation of abscesses.[2,3] The presence of enterococci suggests active disease; however, use of anti-enterococcal antibiotics has not shown to improve outcomes.[3,81]

In general, coverage is warranted if *Enterococcus* is present in blood cultures or is the sole organism on culture.[2,6] Anti-enterococcal therapy is recommended in patients with nosocomial or health care–associated infections,[6] particularly those who received antibiotics selecting for *Enterococcus* spp. (eg, cephalosporins), are immunocompromised, have postoperative infection, or have valvular heart disease or prosthetic intravascular materials.[6] If susceptible, *Enterococcus* species should be treated with ampicillin or piperacillin/tazobactam. Vancomycin should be reserved for ampicillin-resistant enterococcus, whereas VRE can be treated with linezolid or daptomycin. Because B.B.'s blood culture results are negative and ascitic culture has demonstrated mixed pathogens, *Enterococcus* coverage may not be necessary. B.B. should be treated with an antimicrobial regimen that has activity against gram-negative pathogens and anaerobes

Case 70-5, Question 2: Should B.B.'s antimicrobial therapy include an agent with antifungal activity?

ANTIFUNGAL THERAPY: TREATMENT OF CANDIDA

The need to treat *Candida* species as a solitary isolate or as part of a polymicrobial infection is controversial. Certainly, *Candida* has the

potential to cause peritonitis, IP abscesses, and subsequent candidemia. Mortality resulting from *Candida* peritonitis ranges from 25% to 60%.[82] Risk factors for *Candida* peritonitis include recent abdominal surgery; GI tract perforation, particularly in those untreated within the first 24 hours; surgical drains; IV and urinary catheters; severe sepsis; and colonization by *Candida* species.[82,83] Significance of intra-abdominal candidiasis worthy of treatment rises when *Candida* species are isolated surgically or directly from an intra-abdominal collection (eg, within 24 hours of drain placement) in patients with severe community-acquired or health care–associated infections.[6,84] This may include patients who recently received immunosuppressive therapy for neoplasm; have a perforated gastric ulcer while on acid suppression; have a malignancy, transplantation, or inflammatory disease; or a postoperative or recurrent intra-abdominal infection.

Echinocandins and azoles are initial options for fungal peritonitis.[6,21] Concerns about the toxicity of conventional amphotericin B have limited the use of this agent. Fluconazole is considered an appropriate drug of choice for *C. albicans*.[6] For *C. glabrata* or other fluconazole-resistant species, an echinocandin (caspofungin, micafungin, or anidulafungin) or an amphotericin product is an appropriate option.[6] If critically ill, initial therapy with an echinocandin is recommended.

Therapy with an antifungal agent such as fluconazole 400 mg daily is acceptable for B.B. and the *C. albicans* can be isolated.

CASE 70-5, QUESTION 3: The surgical resident decides to continue ertapenem for the treatment of B.B.'s intra-abdominal infection. Should culture and susceptibility results be used to monitor for anaerobic activity?

ANAEROBIC BACTERIA

With the introduction of broad-spectrum antimicrobial agents with in vitro activity against *B. fragilis* and a significant problem of increasing resistance, the choice of a specific anti-anaerobic agent has become more complex. Multiple mechanisms of resistance are encountered,

and resistance rates differ among various geographic areas in the United States. Although *Bacteroides* resistance to metronidazole is rare,[21,85] resistance to clindamycin has increased substantially.[21] Although the carbapenems and the β-lactamase inhibitor combinations are exquisitely active against *Bacteroides*, occasional resistance has been reported.

Because most anaerobes are cultured in the setting of mixed flora, isolation of individual components of a complex mixture can be time consuming. In addition, most anaerobes are very slow growing, and it may take days to weeks for a definitive culture and susceptibility report. If specimens are not collected and transported in optimal media or in a timely manner, inaccurate or misleading results may be reported. The methods for susceptibility testing of anaerobic bacteria are not well standardized, and many hospital laboratories do not have resources to perform extensive culture and susceptibility testing. Routine cultures rarely impact the choice of antibiotic regimen, and thus the empiric choice of therapy usually determines the outcome.[86] Routine susceptibility testing for patient-specific cases is not recommended because of the prolonged time needed to achieve results, but it may be useful when resistant organisms are suspected or high-risk patients have been identified.[87]

Intra-Abdominal Abscess

CASE 70-6

Question 1: R.K. is a 28-year-old female with a history of diverticulitis who presents with abdominal pain and distension, fever, and chills. An intra-abdominal abscess is visualized by CT scan.

How did this abscess develop? What considerations should be taken into account in the selection of appropriate antimicrobial agents?

Abscesses are collections of necrotic tissue, bacteria, and WBCs that form during a period of days to years. They generally result from chronic inflammation and the body's attempt to localize organisms and toxic substances by the formation of an avascular fibrous wall.

This process isolates bacteria and the liquid core from opsonins and antimicrobial agents.

MICROBIOLOGY

Pathogens encountered in intra-abdominal abscesses often include facultative aerobic gram-negatives (eg, *E. coli*) and obligate anaerobes (eg, *B. fragilis*).[52] Mixed infections involving *E. coli* or enterococci with *B. fragilis* have been associated with a synergistic mechanism responsible for late IP abscess development.[88,89]

ANTIMICROBIAL THERAPY

Abscesses pose a therapeutic challenge because they typically contain large bacterial inocula that are likely to include subpopulations of resistant bacteria.[61] Furthermore, the rate of penetration of antibiotics into abscesses is hindered by the low surface-to-volume ratio, low pH, and decreased permeability. Although percutaneous drainage or surgical debridement of R.K.'s abscess is crucial, adjunctive therapy with antimicrobial agents is warranted. The optimal antimicrobial agent should penetrate into the abscess in adequate concentrations and have an adequate spectrum of activity.[21,61] R.K. should be placed on an antimicrobial regimen, such as piperacillin–tazobactam 3.375 g IV every 6 hours, that covers gram-negative bacteria and anaerobes.

INFECTIONS AFTER ABDOMINAL TRAUMA AND POSTOPERATIVE COMPLICATIONS

Risk factors for infection after penetrating abdominal trauma include the number, type, and location of injuries; the presence of hypotension; large transfusion requirements; prolonged operation; advanced age; and the mechanism of injury.[90]

Most investigators stress the importance of instituting antimicrobial therapy as close to the time of trauma as possible. Bozorgzadeh et

al[91] demonstrated a significant reduction in the incidence of postoperative infections when antibiotics were administered before surgical repair of the penetrating abdominal trauma.

Penetrating Trauma

CASE 70-7

Question 1: T.I., a 19-year-old male, is admitted to the emergency department within 1 hour of sustaining a gunshot wound to the stomach and colon. He is to undergo emergency laparotomy.

What antimicrobial therapy is appropriate at this time?

As with other types of intra-abdominal infections, antibiotics active against both aerobic and anaerobic pathogens should be used.

Anti-infective therapy has been studied in patients who have sustained penetrating trauma to the abdomen (usually from knife or gunshot wounds). In several comparative trials, single-drug therapy with cefoxitin was as effective as the combination of clindamycin or metronidazole plus an aminoglycoside.[92] In evaluating these studies, however, it is important to note that most patients did not sustain injuries to the colon, where the risk of infection is highest. Although the age of this patient suggests he would be more likely to tolerate aminoglycoside therapy, monotherapy with cefoxitin or one of the β-lactamase inhibitor combinations would be appropriate.

Consensus guidelines regarding the duration of therapy were published by the Eastern Association for the Surgery of Trauma (EAST) Practice Management Group. These investigators reviewed all literature from 1976 to 1997 regarding the duration of antimicrobial use after penetrating abdominal trauma. They concluded that antimicrobial use should not exceed 24 hours in this patient population.[90]

Case 70-7, Question 2: How long should antibiotic therapy be administered to T.I.?

The shortest duration of antimicrobial therapy that has been shown to be effective has been 12 hours with the possibility that a short course (eg, 48 hours) is as efficacious as a 5- to 7-day course if antimicrobial therapy is promptly instituted.[6] Several other trials have confirmed that no additional benefit exists in providing a longer treatment duration.[6,86,90,93–95]

Because antimicrobial therapy carries a risk of adverse reactions, development of resistance, and unnecessary costs, short-term therapy seems warranted as long as it is instituted soon after the injury.[90,96] If the initial dose of antibiotic is administered >3 to 4 hours after injury, therapy should be continued for 3 to 7 days because the incidence of infection in this circumstance is high.

Antimicrobial therapy was instituted soon after T.I. sustained the colonic injury; therefore, a short course of antimicrobial therapy is appropriate. Therapy should be continued for 24 hours.

Appendectomy

CASE 70-8

QUESTION 1: S.R. is a 12-year-old female with a 2-day history of periumbilical pain migrating to the right lower quadrant, abdominal distension, fever of 102.2 °F (39 °C), diarrhea, and decreased bowel sounds. Her WBC count is 15.8 × 10^3/μL. A presumptive diagnosis of acute appendicitis is made.

What antimicrobial therapy is indicated?

Clinical manifestations commonly encountered with acute appendicitis include right lower quadrant abdominal pain, rebound tenderness, and low-grade fever complicated by nausea, vomiting, and anorexia.[2,6,40]

A variety of antimicrobial agents are effective in the treatment of acute appendicitis.[97–101] Antimicrobial therapy selection for uncomplicated appendicitis can follow those recommended for community-acquired intra-abdominal infection where therapy for <24 hours is sufficient.[6] Patients with gangrenous or perforated appendices are associated with the highest risk of infection. In

several well-designed, randomized, placebo-controlled trials, therapy with imipenem–cilastatin, β-lactams, and β-lactamase inhibitor combinations has been found to be as effective as the combination of clindamycin or metronidazole plus an aminoglycoside.[30,98,100] Patients with gangrenous or perforated appendices who were afebrile for 48 hours have been treated for durations ranging from a single dose[101] to 3 to 5 days.[99]

S.R. should receive a preoperative dose of β-lactam antimicrobials with activity against facultative gram-negative and anaerobic bacteria, such as cefoxitin alone or cefazolin plus metronidazole (see Table 70-2). Cost, potential side effects, and ease of administration guide selection of a specific agent. If a gangrenous or perforated appendix is found during surgery, antimicrobial therapy should be continued for a minimum of 3 to 5 days or until S.R. has been afebrile for 48 hours.

DURATION OF ANTIMICROBIAL THERAPY

Recommendations for the duration of therapy for intra-abdominal infection vary from 4 to 7 days and depend primarily on the patient's clinical response to therapy and the need for surgical drainage.[6] In general, antimicrobial therapy should be continued until resolution of signs of infection, including return of WBC count to normal and elimination of fever. The STOP-IT trial (Trial of Short-Course Antimicrobial Therapy for Intra-Abdominal Infection) published in 2015 evaluated the composite outcome of surgical-site infection, recurrent intra-abdominal infection, or death within 30 days in patients with cIAI and adequate source control randomized to either antibiotic therapy until 2 days after the resolution of fever, leukocytosis, and ileus with a maximum of 10 days of therapy or a fixed antibiotic course of 4 ± 1 calendar days. The study found that in patients who had undergone an adequate source control procedure, there was no difference in outcomes between the groups, suggesting that a fixed course of ~4 days should be recommended after source

control is achieved.[102] Another randomized clinical trial evaluated duration of therapy for postoperative intra-abdominal infections in patients in the ICU who are critically ill. This study concluded that a longer course of antibiotics (15 days) was not associated with any clinical benefit when compared to a short course of antibiotics (8 days).[103] Without adequate source control, antimicrobial therapy will likely need to be continued for longer durations.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Bush LM, Levison ME. Peritonitis and intraperitoneal abscesses. *In: Bennett* JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practices of Infectious Diseases*. 9th ed. Elsevier Saunders; 2020; e-book. (2)

Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Gastroenterology.* 2001;120:726–748. (24)

Hoban DJ, Bouchillon SK, Hawser SP, Badal RE, Labombardi VJ, DiPersio J. Susceptibility of gram-negative pathogens isolated from patients with complicated intra-abdominal infections in the United States, 2007–2008: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART*). Antimicrob Agents Chemother.* 2010;54:3031–3034. (17)

Kimura Y, Takada T, Kawarada Y, et al. Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo guidelines. *J Hepatobiliary Pancreat Surg*. 2007;14:15–26. (13)

Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int.* 2016;36(*5*): 481–508. (40)

Luchette FA, Borzotta AP, Croce MA, et al. Practice management guidelines for prophylactic antibiotic use in penetrating abdominal trauma: the EAST Practice Management Guidelines Work Group. *J Trauma.* 2000;48:508–518. (85)

Sifri CD, Madoff LC. Infections of the liver and biliary system (liver abscess, cholangitis, cholecystitis). In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2020; e-book. (5)

Sirinek KR. Diagnosis and treatment of intra-abdominal abscesses. *Surg Infect (Larchmt)*. 2000;1:31–38. (61)

Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by Surgical Infection Society and the Infectious Diseases Society of America [published correction appears in *Clin Infect Dis*. 2010;50:1695. Dosage error in article text]. *Clin Infect Dis.* 2010;50:133–164. (6)

COMPLETE REFERENCES CHAPTER 70 INTRA-ABDOMINAL INFECTIONS

1. Marshall JC. Intra-abdominal infections. *Microbes Infect*. 2004;6:1015–1025.
2. Bush LM, Levison ME. Peritonitis and intraperitoneal abscesses. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practices of Infectious Diseases*. 9th ed. Elsevier Saunders; 2020; e-book.
3. Wacha H, Hau T, Dittmer R, Ohmann C. Risk factors associated with intraabdominal infections: a prospective multicenter study. Peritonitis Study Group. *Langenbecks Arch Surg*. 1999;384:24–32.
4. Yusoff IF, Barkun JS, Barkun AN. Diagnosis and management of cholecystitis and cholangitis. *Gastroenterol Clin North Am*. 2003;32:1145–1168.
5. Sifri CD, Madoff LC. Infections of the liver and biliary system (liver abscess, cholangitis, cholecystitis). In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Saunders; 2020; e-book.
6. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by Surgical Infection Society and the Infectious Diseases Society of America [published correction appears in *Clin Infect Dis*. 2010;50:1695. Dosage error in article text]. *Clin Infect Dis*. 2010;50:133–164.
7. Montravers P, Gauzit R, Muller C, Marmuse JP, Fichelle A, Desmonts JM. Emergence of antibiotic-resistant bacteria in cases of peritonitis after intraabdominal surgery affects the efficacy of empirical antimicrobial therapy. *Clin Infect Dis*. 1996;23:486–494.
8. Montravers P, Dupont H, Gauzit R, et al. Candida as a risk factor for mortality in peritonitis. *Crit Care Med*. 2006;34:646–652.

9. Montravers P, Chalfine A, Gauzit R, et al. Clinical and therapeutic features of non-postoperative nosocomial intra-abdominal infections. *Ann Surg*. 2004;239:409–416.
10. Hawser SP, Badal RE, Bouchillon SK, et al. Susceptibility of gram-negative aerobic bacilli from intra-abdominal pathogens to antimicrobial agents collected in the United States during 2011. *J Infect*. 2014;68:71–76.
11. Williams EJ, Green J, Beckingham I, Parks R, Martin D, Lombard M. Guidelines on the management of common bile duct stones (CBDS). *Gut*. 2008;57:1004–1021.
12. Greenberg NJ, Paumgartner G. Diseases of the gallbladder and bile ducts. In: Kasper DL, Hauser SL, Jameson JL, Fauci AS, Long DL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 19th ed., Vol. 1. McGraw-Hill Education; 2006: 6–16. 219–226.
13. Kimura Y, Takada T, Kawarada Y, et al. Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo guidelines. *J Hepatobiliary Pancreat Surg.* 2007;14:15–26.
14. Carpenter HA. Bacterial and parasitic cholangitis. *Mayo Clin Proc*. 1998; 73:473–478.
15. Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis. *J Hepatobiliary Pancreat Sci*. 2018;25(1):41–54.
16. Podnos YD, Jimenez JC, Wilson SE. Intra-abdominal sepsis in elderly persons. *Clin Infect Dis*. 2002;35:62–68.
17. Hoban DJ, Bouchillon SK, Hawser SP, Badal RE, Labombardi VJ, DiPersio J. Susceptibility of gram-negative pathogens isolated from patients with complicated intra-abdominal infections in the United States, 2007–2008: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART*)*. *Antimicrob Agents Chemother*. 2010;54:3031–3034.
18. Bailey JA, Virgo KS, DiPiro JT, Nathens AB, Sawyer RG, Mazuski JE. Aminoglycosides for intra-abdominal infection: equal to the challenge? *Surg Infect (Larchmt)*. 2002;3:315–335.
19. Keighley MR, Drysdale RB, Quoraishi AH, Burdon DW, Alexander-Willians J. Antibiotics in biliary disease: the relative importance of antibiotic concentrations in the bile and serum. *Gut*. 1976;17:495–500.
20. Nagar H, Berger SA. The excretion of antibiotics by the biliary tract. *Surg Gynecol Obstet*. 1984;158:601–607.
21. Johnson CC, Baldessarre J, Levison ME. Peritonitis: update on pathophysiology, clinical manifestations, and management. *Clin Infect Dis*. 1997;24:1035–1045.
22. Ginès P, Cárdenas A, Arroyo V, Rodés J. Management of cirrhosis and ascites. *N Engl J Med*. 2004;350:1646–1654.
23. Evans HL, Raymond DP, Pelletier SJ, Crabtree TD, Pruett TL, Sawyer RG. Diagnosis of intra-abdominal infection in the critically ill patient. *Curr Opin*

Crit Care. 2001;7(2):117–121.
24. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Gastroenterology*. 2001;120:726–748.
25. Riordan SM, Williams R. The intestinal flora and bacterial infection in cirrhosis. *J Hepatol*. 2006;45:744–757.
26. Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. *Gastroenterology*. 1991;100:1737–1742.
27. Tuncer I, Topcu N, Durmus A, Turkdogan MK. Oral ciprofloxacin versus intravenous cefotaxime and ceftriaxone in the treatment of spontaneous bacterial peritonitis. *Hepatogastroenterology*. 2003;50:1426–1430.
28. Ricart E, Soriano G, Novella MT, et al. Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. *J Hepatol*. 2000;32:596–602.
29. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology*. 2009;49(6):2087–2107.
30. França A, Giordano HM, Sevá-Pereira T, Soares EC. Five days of ceftriaxone to treat spontaneous bacterial peritonitis in cirrhotic patients. *J Gastroenterol*. 2002;37:119–122.
31. Ginés P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology*. 1990;12:716–724.
32. Rolachon A, Cordier L, Bacq Y, et al. Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial. *Hepatology*. 1995;22:1171–1174.
33. Alvarez RF, Mattos AA, Corrêa EB, Cotrim HP, Nascimento TV. Trimethoprim-sulfamethoxazole versus norfloxacin in the prophylaxis of spontaneous bacterial peritonitis in cirrhosis. *Arq Gastroenterol*. 2005;42:256–262.
34. Mantry PS, Munsaf S. Rifaximin for the treatment of hepatic encephalopathy. *Transplant Proc*. 2010;42:4543–4547.
35. Fernández J, Ruiz del Arbol L, Gómez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology*. 2006;131:1049–1056.
36. Gonzalez SA. Antibiotoic prophylaxis for spontaneous bacterial peritonitis: benefit or risk? *Am J Gastroenterol*. 2019;114:553–555. https://doi.org/10.14309/ajg.0000000000000208
37. Fernández J, Navasa M, Gómez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology*. 2002;35:140–148.

38. Frazee LA, Marinos AE, Rybarczyk AM, Fulton SA. Long-term prophylaxis of spontaneous bacterial peritonitis in patients with cirrhosis. *Ann Pharmacother*. 2005;39:908–912.
39. Nouwen J, Schouten J, Schneebergen D, et al. *Staphylococcus aureus* carriage patterns and the risk of infections associated with continuous peritoneal dialysis. *J Clin Microbiol*. 2006;44:2233–2236.
40. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016;36(5):481–508.
41. Rubin J, Rogers WA, Taylor HM, et al. Peritonitis during continuous ambulatory peritonitis dialysis. *Ann Intern Med*. 1980;92:7–13.
42. Toussaint N, Mullins K, Snider J, Murphy B, Langham R, Gock H. Efficacy of a non-vancomycin-based peritoneal dialysis peritonitis protocol. *Nephrology (Carlton)*. 2005;10:142–146.
43. Wiggins KJ, Craig JC, Johnson DW, et al. Treatment of peritoneal dialysis-associated peritonitis: a systemic review of randomized controlled trials. *Am J Kidney Dis*. 2007;50:967–988.
44. Salzer W. Antimicrobial-resistant gram-positive bacteria in PD peritonitis and the newer antibiotics used to treat them. *Perit Dial Int*. 2005;25:313–319.
45. Khairullah Q, Provenzano R, Tayeb J, Ahmad A, Balakrishnan R, Morrison L. Comparison of vancomycin versus cefazolin as initial therapy for peritonitis in peritoneal dialysis patients. *Perit Dial Int*. 2002;22:339–344.
46. Leung CB, Szeto CC, Chow KM, et al. Cefazolin plus ceftazidime versus imipenem/cilastatin monotherapy for treatment of CAPD peritonitis—a randomized controlled trial. *Perit Dial Int*. 2004;24:440–446.
47. Passadakis P, Oreopoulos D. The case for oral treatment of peritonitis in continuous ambulatory peritoneal dialysis. *Adv Perit Dial*. 2001;17:180–190.
48. Goffin E, Herbiet L, Pouthier D, et al. Vancomycin and ciprofloxacin: systemic antibiotic administration for peritoneal dialysis-associated peritonitis. *Perit Dial Int*. 2004;24:433–439.
49. Gerding DN, Hall WH. The penetration of antibiotics into peritoneal fluid. *Bull N Y Acad Med*. 1975;51:1016–1019.
50. Wittman DH, Schassan HH. Penetration of eight betalactam antibiotics into the peritoneal fluid. A pharmacokinetic investigation. *Arch Surg*. 1983;118:205–213.
51. Prasad N, Gupta A. Fungal peritonitis in peritoneal dialysis patients. *Perit Dial Int*. 2005;25:207–222.
52. Wittmann DE, Schein M, Condon RE. Management of secondary peritonitis. *Ann Surg*. 1996;224(1):10–18.
53. Doklestic SK, Bajec DD, Djukic´ RV, et al. Secondary peritonitis—evaluation of 204 cases and literature review. *J Med Life*. 2014;7(2):132–138.
54. Ruiter J, Weel J, Manusama E, Kingma WP, van der Voort PH. The epidemiology of intra-abdominal flora in critically ill patients with secondary and tertiary abdominal sepsis. *Infection*. 2009;37:522–527.

55. Skrupky LP, Tellor BR, Mazuski JE. Current strategies for the treatment of complicated intra-abdominal infections. *Expert Opin Pharmacother*. 2013;14(14):1933–1947.
56. Dupont H, Carbon C, Carlet J. Monotherapy with a broad-spectrum betalactam is as effective as its combination with an aminoglycoside in treatment of severe generalized peritonitis: a multicenter randomized controlled trial. The Severe Generalized Peritonitis Study Group. *Antimicrob Agents Chemother*. 2000;44:2028–2033.
57. Malangoni MA, Song J, Herrington J, Choudhri S, Pertel P. Randomized controlled trial of moxifloxacin compared with piperacillin-tazobactam and amoxicillin-clavulanate for the treatment of complicated intra-abdominal infections. *Ann Surg*. 2006;244:204–211.
58. Erasmo AA, Crisostomo AC, Yan LN, Hong YS, Lee KU, Lo CM. Randomized comparison of piperacillin/tazobactam versus imipenem/cilastatin in the treatment of patients with intra-abdominal infection. *Asian J Surg*. 2004;27:227–235.
59. Goldstein EJ, Citron DM, Warren YA, Tyrrell KL, Merriam CV, Fernandez H. In vitro activity of moxifloxacin against 923 anaerobes isolated from human intra-abdominal infections. *Antimicrob Agents Chemother*. 2006;50:148–155.
60. Nathens AB. Relevance and utility of peritoneal cultures in patients with peritonitis. *Surg Infect (Larchmt)*. 2001;2:153–160.
61. Sirinek KR. Diagnosis and treatment of intra-abdominal abscesses. *Surg Infect (Larchmt)*. 2000;1:31–38.
62. Minton J, Stanley P. Intra-abdominal infections. *Clin Med*. 2004;4:519–523.
63. Solomkin J, Teppler H, Graham DR, et al. Treatment of polymicrobial infections: post hoc analysis of three trials comparing ertapenem and piperacillin-tazobactam. *J Antimicrob Chemother*. 2004;53(Suppl 2):ii51–ii57.
64. Namias N, Solomkin JS, Jensen EH, Tomassini JE, Abramson MA. Randomized, multicenter, double-blind study of efficacy, safety, and tolerability of intravenous ertapenem versus piperacillin/tazobactam in treatment of complicated intra-abdominal infections in hospitalized adults. *Surg Infect (Larchmt)*. 2007;8:15–28.
65. Solomkin JS, Yellin AE, Rotstein OD, et al. Ertapenem versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections: results of a double-blind, randomized comparative phase III trial. *Ann Surg*. 2003;237:235–245.
66. Edmiston CE, Krepel CJ, Seabrook GR, et al. In vitro activities of moxifloxacin against 900 aerobic and anaerobic surgical isolates from patients with intra-abdominal and diabetic foot infections. *Antimicrob Agents Chemother*. 2004; 48:1012–1016.
67. Ackermann G, Schaumann R, Pless B, Claros MC, Goldstein EJ, Rodloff AC. Comparative activity of moxifloxacin in vitro against obligately anaerobic bacteria. *Eur J Clin Microbiol Infect Dis*. 2000;19:228–232.

68. Mu YP, Liu RL, Wang LQ, et al. Moxifloxacin monotherapy for treatment of complicated intra-abdominal infections: a meta-analysis of randomized controlled trials. *Int J Clin Pract*. 2012;66(2):210–217.
69. Goldstein EJ, Solomkin JS, Citron DM, Alder JD. Clinical efficacy and correlation of clinical outcomes with in vitro susceptibility for anaerobic bacteria in patients with complicated intra-abdominal infections treated with moxifloxacin. *Clin Infect Dis*. 2011;53(11):1174–1180.
70. Mazuski JE, Tessier JM, May AK, et al. The surgical infection society revised guidelines on the management of intra-abdominal infection. *Surg Infect*. 2017;18(1):1–76.
71. Paterson DL, Rossi F, Baquero F, et al. In vitro susceptibilities of aerobic and facultative gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART). *J Antimicrob Chemother*. 2005;55:965–973.
72. Cohn SM, Lipsett PA, Buchman TG, et al. Comparison of intravenous/oral ciprofloxacin plus metronidazole versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections. *Ann Surg*. 2000;232:254–262.
73. Matthaiou DK, Peppas G, Bliziotis IA, Falagas ME. Ciprofloxacin/metronidazole versus beta-lactam-based treatment of intra-abdominal infections: a meta-analysis of comparative trials. *Int J Antimicrob Agents*. 2006;28:159–165.
74. Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). *Clin Infect Dis*. 2015;60(10):1462–1471.
75. Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults; results of a randomized, double-blind, phase II trial. *J Antimicrob Chemother*. 2013;68:1183–1192.
76. AVYCAZ ceftazidime-avibactam injection. Package insert. Forest Pharmaceuticals, Inc; 2015. Accessed May 11, 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206494s005,s006lbl.pdf
77. ZERBAXA ceftolozane-tazobactam injection. Package insert. Cubist Pharmaceuticals, U.S.; 2015. Accessed May 11, 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206829lbl.pdf
78. VABOMERE meropenem-vaborbactam [package insert]. Melinta Therapeutics, U.S.; 2021. http://www.vabomere.com/media/pdf/vabomere-us-prescribing-information.pdf
79. RECARBRIO imipenem-cilastatin-relebactam [package insert]. Merck Sharp & Dohme, U.S.;2022. https://www.merck.com/product/usa/pi_circulars/r/recarbrio/recarbrio_pi.pdf

80. Montravers P, Zappella N, Tran-Dinh A. Eravacycline for the treatment of complicated intra-abdominal infections. *Expert Rev Anti Infect Ther*. 2019;17(11):851–863. doi:10.1080/14787210.2019.168197.
81. Sotto A, Lefrant JY, Fabbro-Peray P, et al. Evaluation of antimicrobial therapy management of 120 consecutive patients with secondary peritonitis. *J Antimicrob Chemother*. 2002;50:569–576.
82. Bassetti M, Marchetti M, Chakrabarti A, et al. A research on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. *Intensive Care Med*. 2013;39:2092–2106.
83. Rebolledo M, Sarria JC. Intra-abdominal fungal infections. *Curr Opin Infect Dis*. 2013;26:441–446.
84. Ubeda A, Vázquez AL, Gil CL. Candida peritonitis. *Enferm Infecc Microbiol Clin*. 2010;28(Suppl 2):42–48.
85. Snydman DR, Jacobus NV, McDermott LA, et al. National survey on the susceptibility of *Bacteroides fragilis* group: report and analysis of trends in the United States from 1997 to 2004. *Antimicrob Agents Chemother*. 2007;51:1649–1655.
86. Dougherty SH. Antimicrobial culture and susceptibility testing has little value for routine management of secondary bacterial peritonitis. *Clin Infect Dis*. 1997;25(Suppl 2):S258–S261.
87. Nicoletti G, Nicolosi D, Rossolini GM, Stefani S. Intra-abdominal infections: etiology, epidemiology, microbiological diagnosis and antibiotic resistance. *J Chemother*. 2009;21(Suppl 1):5–11.
88. Onderdonk AB, Bartlett JG, Louie T, Sullivan-Seigler N, Gorbach SL. Microbial synergy in experimental intra-abdominal abscess. *Infect Immun*. 1976;13:22–26.
89. Rotstein OD, Pruett TL, Simmons RL. Mechanisms of microbial synergy in polymicrobial surgical infections. *Rev Infect Dis*. 1985;7:151–170.
90. Luchette FA, Borzotta AP, Croce MA, et al. Practice management guidelines for prophylactic antibiotic use in penetrating abdominal trauma: the EAST Practice Management Guidelines Work Group. *J Trauma*. 2000;48:508–518.
91. Bozorgzadeh A, Pizzi WF, Barie PS, et al. The duration of antibiotic administration in penetrating abdominal trauma. *Am J Surg*. 1999;177:125–131.
92. Fabian TC. Infection in penetrating abdominal trauma: risk factors and preventive antibiotics. *Am Surg*. 2002;68:29–35.
93. Delgado G Jr, Barletta JF, Kanji S, Tyburski JG, Wilson RF, Devlin JW. Characteristics of prophylactic antibiotic strategies after penetrating abdominal trauma at a level I urban trauma center: a comparison with the EAST guidelines. *J Trauma*. 2002;53:673–678.
94. Demetriades D, Lakhoo M, Pezikis A, Charalambides D, Pantanowitz D, Sofianos C. Short-course antibiotic prophylaxis in penetrating abdominal injuries: ceftriaxone versus cefoxitin. *Injury*. 1991;22:20–24.

95. Fabian TC, Croce MA, Payne LW, Minard G, Pritchard FE, Kudsk KA. Duration of antibiotic therapy for penetrating abdominal trauma: a prospective trial. *Surgery*. 1992;112:788–794.
96. Bratzler DW, Houck PM; Surgical Infection Prevention Guidelines Writers Workgroup. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis*. 2004;38:1706–1715.
97. Berne TV, Yellin AE, Appleman MD, Gill MA, Chenella FC, Heseltine PN. Surgically treated gangrenous or perforated appendicitis. A comparison of aztreonam and clindamycin versus gentamicin and clindamycin. *Ann Surg*. 1987;205:133–137.
98. Lau WY, Fan ST, Chu KW, Suen HC, Yiu TF, Wong KK. Randomized, prospective, and double-blind trial of new beta-lactams in the treatment of appendicitis. *Antimicrob Agents Chemother*. 1985;28:639–642.
99. Heseltine PN, Yellin AE, Appleman MD, et al. Imipenem therapy for perforated and gangrenous appendicitis. *Surg Gynecol Obstet*. 1986;162:43–48.
100. Lau WY, Fan ST, Chu KW, et al. Cefoxitin versus gentamicin and metronidazole in prevention of post-appendicectomy sepsis: a randomized, prospective trial. *J Antimicrob Chemother*. 1986;18:613–619.
101. Foster MC, Kapila L, Morris DL, Slack RC. A randomized comparative study of sulbactam plus ampicillin vs. metronidazole plus cefotaxime in the management of acute appendicitis in children. *Rev Infect Dis*. 1986;8(Suppl 5):S634.
102. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med*. 2015;372:1996–2005. doi:10.1056/NEJMoa1411162
103. Montravers P, Tubach F, Lescot T, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. *Intensive Care Med*. 2018;44:300–310. doi:10.1007/s00134-018-5088-x

71

Urinary Tract Infections

Douglas N. Fish

CORE PRINCIPLES		CHAPTER CASES
1	Urinary tract infection (UTI) is usually bacterial in etiology, may be either acute or chronic, and may affect any part of the upper or lower urinary system. UTI is classified as either uncomplicated or complicated based on patient characteristics and on the clinical setting in which the infection is acquired (eg, community-acquired vs health care–acquired infection).	**Case 71-1 (Questions 1–6)** **Case 71-2 (Questions 1, 2)**
2	Uncomplicated UTI occurs in females who are otherwise healthy and have normal urinary tract structure and function. These infections are primarily caused by *Escherichia coli* (75%–95% of infections) and other gram-negative bacilli, as well as gram-positive	**Case 71-1 (Questions 1–3)**

	organisms such as *Staphylococcus saprophyticus* and *Enterococcus.*	
3	Symptoms commonly associated with lower UTI (eg, cystitis) include dysuria, frequent urination, suprapubic pain, and hematuria. Patients with upper tract infection (eg, acute pyelonephritis) often present with similar findings as well as loin pain, costovertebral angle tenderness, fever, chills, nausea, and vomiting.	**Case 71-1 (Questions 1, 2)** **Case 71-5 (Questions 1–3)**
4	The cornerstone of effective UTI treatment is appropriate selection and use of antibiotics. Resistance among *E. coli* and other uropathogens is increasing and is an important consideration in antibiotic selection. Consensus clinical guidelines recommend trimethoprim–sulfamethoxazole (TMP-SMX) for 3 days, nitrofurantoin for 5 days, or a single dose of fosfomycin as preferred first-line antibiotics for treatment of acute uncomplicated cystitis in females.	**Case 71-1 (Questions 1–6)** **Case 71-2 (Question 1), Tables 71-1–71-3**
5	Fluoroquinolones are commonly used for treatment of UTI and are highly effective. However, concerns regarding increased resistance and potential adverse effects limit the use of fluoroquinolones in uncomplicated UTI to patients unable to receive other preferred agents because of drug resistance, allergies, or other	**Case 71-1 (Question 3)** **Case 71-2 (Questions 1, 2)** **Case 71-3 (Question 1), Tables 71-1–71-3**

	contraindications. Similar recommendations restrict the use of β-lactam antibiotics for uncomplicated UTI.	
6	Complicated UTI is associated with abnormalities of the urinary tract that interfere with normal urine flow or function; males, children, patients with diabetes, pregnant females, and hospitalized patients are examples of commonly affected populations. Complicated infections are frequently caused by drug-resistant gram-negative bacilli or other pathogens with reduced antibiotic susceptibility. Antibiotic selection for complicated UTI should be guided by culture and susceptibility testing, and patients usually require longer durations of antibiotic therapy (7–14 days).	**Case 71-1 (Questions 1–4)** **Case 71-2 (Question 1)** **Case 71-4 (Question 1)** **Case 71-10 (Question 1)** **Case 71-11 (Questions 1–3)**
7	Pyelonephritis may be more severe in presentation and often associated with bacteremia and other complications. However, most cases are uncomplicated and can be treated on an outpatient basis with oral antibiotics such as fluoroquinolones. Patients who cannot take oral antibiotics or who are clinically unstable should be hospitalized for initial treatment with intravenous antibiotics.	**Case 71-5 (Questions 1–5), Tables 71-1, 71-2, 71-5**
8	Recurrent UTI may be caused by either reinfection or relapse because of	**Case 71-6 (Questions 1–3, 6–8)**

	treatment failure. Relapse usually occurs within 2 weeks of the original infection and is caused by the same pathogen. Selection of antibiotics for treatment of relapsed UTI should be guided by culture and susceptibility testing, and the duration of antibiotic therapy should be at least 2 weeks in length.	**Case 71-7 (Questions 1, 2)**
9	Recurrent UTI, which occurs >2 weeks after the original infection, is treated as a new infection with antibiotic considerations similar to those for the initial infection. Females with frequent infections (≥3/year) may be considered for chronic prophylaxis therapy. Females with identifiable causes of reinfection (eg, associated with sexual intercourse) may self-administer prophylactic antibiotics.	**Case 71-6 (Questions 4, 5, 7, 8), Tables 71-3, 71-4**
10	Asymptomatic bacteriuria (≥10^5 bacteria per milliliter of urine in the absence of clinical signs/symptoms of UTI) is particularly common in children, the elderly, pregnant females, and in patients with diabetes. Treatment of asymptomatic bacteriuria for prevention of subsequent infection and associated complications is routinely recommended in children and pregnant females. However, treatment of the elderly and patients with diabetes has not shown	**Case 71-7 (Questions 3, 4)** **Case 71-8 (Question 1)** **Case 71-9 (Question 1)**

	clear benefits and is not currently recommended.	
11	Prostatitis is a relatively common infection in males and is caused by bacteria similar to those causing uncomplicated UTI in females. Acute bacterial prostatitis is usually treated with either a fluoroquinolone or TMP-SMX for a period of 2–4 weeks. Chronic prostatitis persists in a small percentage of males after acute infection and is usually treated for 4–6 weeks, although longer courses may sometimes be required.	**Case 71-12 (Questions 1, 2)**

INTRODUCTION

Incidence, Prevalence, and Epidemiology

Urinary tract infection (UTI) is an acute or a chronic infection, usually bacterial in origin, that may affect any part of the upper or lower urinary system.

Infections of the bladder are referred to as *cystitis*, and infections involving the parenchyma of the kidneys are known as *pyelonephritis*. UTIs occur frequently in both community and hospital environments and are the most common bacterial infections in humans.[1–3] The term UTI encompasses a spectrum of clinical entities ranging in severity from asymptomatic infection to acute pyelonephritis with sepsis.[1–4] Approximately 8 to 9 million cases of acute cystitis and 250,000 cases of acute pyelonephritis occur annually in the United States, resulting in >100,000 hospitalizations.[2,5,6] Direct costs associated with the diagnosis and

treatment of UTI have been estimated at ~$3 billion annually in the United States.[3,6,7] UTI is predominantly a disease of females, with >50% of all females experiencing at least one infection during their lifetime.[2,5] The overall likelihood of developing a UTI is ~30 times greater in females than in males because of anatomic and physiologic differences.[3,7,8] The female urethra is relatively short and allows bacteria easy access to the bladder. In contrast, males are partly protected because the urethra is longer and antimicrobial substances are secreted by the prostate.[1,3,7,8]

Approximately 1% of boys and 3% to 5% of girls experience at least one UTI during childhood and 30% to 50% of these will have at least one recurrence.[9] The incidence of UTI in neonates is about 1% and is more frequent in male neonates, frequently because of congenital structural abnormalities.[10] UTIs in males also occur with increased frequency after age 50, when prostatic obstruction, urethral instrumentation, and surgery influence the infection rate. Infection in younger males is rare and requires careful evaluation for urinary tract pathology.[11,12]

Of females between the ages of 15 and 24 years, 1% to 5% have asymptomatic bacteriuria (ASB). This is defined as two consecutive voided urine specimens showing $\geq 10^5$ bacteria/milliliter (mL) of urine in females, or as a single clean-catch voided specimen in males without signs or symptoms of UTI. ASB prevalence increases 1% to 2% for each decade of life, and ~10% to 16% of females have ASB after age 70.[1,8,13,14] The prevalence of ASB in the elderly living at home is 5% to 20%, increasing to 20% to 50% in extended care facilities and 30% in hospitals.[3,13,15,16] The incidence of actual UTI also continues to rise with increasing age.[15,16] Reasons for higher ASB and UTI rates in elderly persons include the high prevalence of prostatic hypertrophy in males, incomplete bladder emptying caused by underlying diseases or medications, dementia, and urinary and fecal incontinence.[8,15–17] Whether ASB in older age is associated with decreased survival remains controversial[17,18]; however, the presence of ASB is associated with decreased functional ability of institutionalized persons,[13,15] and symptomatic UTI has been

independently associated with a threefold increased risk of vertebral fractures.[19]

Etiology

UNCOMPLICATED VERSUS COMPLICATED INFECTIONS

An important distinction in the characterization and treatment of UTI is that of uncomplicated versus complicated infections. Uncomplicated UTI, either cystitis or pyelonephritis, occurs in females who have normal structure and function of the genitourinary tract and who have no other factors that would put them at risk for more severe or complex infections.[3,5,20] By contrast, complicated infections are associated with conditions that increase the risk of acquiring infection, the potential for serious outcomes, or the risk of therapeutic failure. Such conditions include genitourinary tract abnormalities that may interfere with normal urine flow. Infections in males, children, and pregnant females, and those that are health care–associated in origin are automatically considered complicated. Other examples of complicated infections include those associated with structural and neurologic abnormalities of the urinary tract, metabolic or hormonal abnormalities, impaired host responses, instrumentation and catheterization of the urinary tract, and those caused by unusual pathogens (eg, yeasts, *Mycoplasma*).[3,5,20] Uncomplicated infections are always community acquired and are caused by the organisms typical to that etiology. Complicated UTI may be caused by pathogens associated with either community-acquired or health care–associated infections, depending on the source of bacterial acquisition and specific underlying patient risk factors. Complicated infections are also more often polymicrobial in etiology, associated with more antibiotic-resistant pathogens, and generally require a longer duration of therapy.

COMMUNITY-ACQUIRED INFECTIONS

Most UTIs are caused by gram-negative aerobic bacilli from the intestinal tract. *Escherichia coli* causes 75% to 95% of community-

acquired, uncomplicated UTIs.[1,3,20] Coagulase-negative staphylococci (eg, *Staphylococcus saprophyticus*) account for 5% to 20% of UTIs in younger females.[1,3,5] Other Enterobacterales (eg, *Proteus mirabilis*, *Klebsiella*) and *Enterococcus faecalis* also are common pathogens.[1,3,20] Uncomplicated infections are nearly always caused by a single pathogen.

HEALTH CARE–ASSOCIATED INFECTIONS

UTIs occur in up to 10% of hospitalized patients and represent 20% to 30% of all nosocomial infections.[21–23] *E. coli* remains the most common pathogen in hospital-acquired or other complicated UTI but is responsible for only 20% to 30% of these infections. Other gram-negative organisms, such as *Pseudomonas aeruginosa*, *Klebsiella*, *Proteus*, *Enterobacter*, and *Acinetobacter*, cause significantly more infections (up to 25%) compared to the community setting.[5,22,23] *Enterococcus* is also a common pathogen in hospital-acquired UTIs and accounts for ~15% of infections.[22,23] UTIs caused by *S. aureus* are usually the result of hematogenous spread but are also associated with urinary catheterization.[1,22–24] *Candida* is a common pathogen in hospital-acquired infections and may be involved in 20% to 30% of cases.[21–23] In contrast to the usually monomicrobial uncomplicated infections, UTIs associated with structural abnormalities or indwelling urinary catheters are often caused by multiple pathogens.[1,21–24]

Pathogenesis and Predisposing Factors

The spread of bacteria to the urinary tract typically occurs via the ascending route. A UTI usually begins with heavy and persistent colonization of the introitus (ie, vaginal vestibule and urethral mucosa) with intestinal bacteria. Colonization of the urethra then leads to retrograde infection of the bladder and the development of cystitis.[25,26]

The bladder has defense mechanisms that prevent spread of the infection after urethral colonization has occured.[1,3,22] Urination

effectively washes bacteria out of the bladder if the urine flows freely and the bladder is emptied completely. Substances in the urine, including organic acids (which contribute to low pH) and urea (which contributes to high osmolality), are antibacterial. The bladder mucosa also has antibacterial properties.[1,3,22] Other substances, including immunoglobulin A and glycoproteins (eg, Tamm–Horsfall protein), are actively secreted into the urine and prevent adherence of bacteria to uroendothelial cells.[22,25,26]

Focal renal involvement leading to pyelonephritis may result from the spread of bacteria via the ureters and may be facilitated by vesicoureteral reflux or decreased ureteral peristalsis. Ureteral peristalsis is decreased in pregnancy, by ureteral obstruction, or by gram-negative bacterial endotoxins.[1,25,26] Reflux can be produced by cystitis alone or by anatomic defects.

Bacterial virulence factors contributing to the development of UTI include expression of specific adhesin molecules, bacterial polysaccharides, and bacterial enzymes. Other factors predisposing to the development of UTI are dependent on the host and may include extremes of age, female sex, sexual activity, use of contraception, pregnancy, urinary tract instrumentation or catheterization, urinary tract obstruction, neurologic dysfunction, renal disease, previous antimicrobial use, and expression of A, B, and H blood group oligosaccharides on the surface of epithelial cells.[1–3,17,25,27]

The incidence of ASB in pregnant females is as high as 17%, which is approximately twice that of similarly aged nonpregnant females.[1,13,28,29] The incidence of acute symptomatic UTI, both cystitis and pyelonephritis, in pregnant females with untreated bacteriuria also is high and may reach 40%.[3] Many factors contribute to the increased susceptibility of the pregnant female to colonization and infection; these include hormonal changes, anatomic changes, progressive urinary stasis, and glucose in the urine.[28,29] Hormonal changes have also been linked to a significantly higher risk of UTI in menopausal females.[3] Estrogen promotes an acidic vaginal pH and proliferation of normal flora such as *Lactobacillus*, both factors that reduce pathogenic colonization of the vagina. Likewise, reduction of

estrogen production during menopause allows significant colonization of the vaginal tract with *E. coli* and other enteric bacilli, thus predisposing to subsequent infection.[3]

Renal disease increases the susceptibility of the kidney to infection.[1] The incidence of UTI among renal transplant recipients ranges from 35% to 80% without prophylactic antibiotic therapy.[30] Patients with spinal cord injuries, stroke, atherosclerosis, or diabetes may have neurologic dysfunction that predisposes to UTI as a result of urinary retention and/or need for catheterization. Furthermore, prolonged immobilization facilitates hypercalciuria and stone formation in some of these patients.[1,5,25]

Prior antimicrobial use (within the previous 15–28 days) for UTI or other infections increases the relative risk of UTI in females threefold to sixfold.[3] The proposed mechanism for this is alteration of normal flora of the urogenital tract and subsequent colonization with pathogenic bacterial strains.[2,3]

Diabetes mellitus is associated with a higher risk factor for UTI because glucose in the urine is promoting bacterial growth and impairing leukocyte function. Anatomic, neurologic, and immunologic abnormalities of the urinary tract in patients with diabetes contribute to the risk of infection, often because of more frequent urinary tract instrumentation.[31,32] Several studies have documented a twofold to threefold increase in UTI in females with diabetes compared to those without; rates of relapses and reinfections, as well as complications such as pyelonephritis, are also higher.[31–33]

Studies have supported an association between sexual intercourse and UTI among otherwise healthy females.[2,3,25,34] Specific contraceptive practices, particularly the use of spermicides, and the use of a diaphragm, cervical cap, or condom in combination with spermicidal jelly increases the risk of UTI compared with the use of the barrier method alone.[2,27,34] Diaphragm users are approximately three times more likely to experience a UTI than are females using other contraceptive methods, especially when the diaphragm is used in conjunction with spermicidal jelly.[2,27] The exact mechanisms of infection related to sexual intercourse and contraceptive methods are unclear but appear to be related to

alterations in vaginal flora allowing for bacterial overgrowth and subsequent infection.[1–3]

URINARY CATHETERS

Instrumentation or catheterization of the urinary tract is an important predisposing factor for health care–associated UTI. Catheter-associated urinary tract infection (CAUTI) occurs in up to 30% of patients who have been catheterized and is the most common type of hospital-acquired infection.[23] CAUTIs also are major causes of nosocomial gram-negative bacteremia.[21,23] Other urologic procedures, such as cystoscopy, transurethral surgery, prostate biopsy, and upper urinary tract endoscopy, are much less likely to result in infection, unless there is preexisting bacteriuria or bacterial colonization in other sites (eg, prostate, renal stones). Any obstruction to the free flow of urine (eg, urethral stenosis, stones, tumor) or mechanical difficulty in evacuating the bladder (eg, prostatic hypertrophy, urethral stricture) also predisposes patients to UTI and potential complications such as sepsis.[1]

CAUTI can occur by bacterial entry from several routes. The urethral meatus and the distal third of the urethra normally are colonized by bacteria; therefore, initial catheter insertion can introduce bacteria into the bladder. Bacteria contaminating catheter junctions and the urine collection bag can migrate through the catheter lumen to the bladder, initiating infection.[23] The extraluminal space in the urethra also has been considered a potential route of contamination and subsequent infection. The risk of infection is directly related to the catheter insertion technique, care of the catheter, duration of catheterization, and the susceptibility of the patient. A diagnostic or single, short-term catheterization is associated with a much lower risk of infection than is indwelling, long-term catheterization.[23] Despite careful technique, the risk of contaminating a sterile bladder with urethral bacteria is always present; each reinsertion of the catheter also increases risk of infection.[23]

CAUTIs have been markedly reduced by the closed sterile drainage system, the most common type of catheter currently in use, in which the drainage tube leads from the catheter directly to a closed plastic collection bag. The overall incidence of infection with the closed system using careful insertion and maintenance is about 20%; the risk increases to 50% after 14 days of catheterization.[23] Condom catheters are associated with a lower incidence of bacteriuria than are indwelling urethral catheters. These catheters avoid problems associated with insertion of a tube directly into the urinary tract; nevertheless, urine within the catheters may have high concentrations of organisms so that colonization of the urethra and subsequent cystitis may still develop.[23]

Application of antibacterial substances to the collection bag or exterior surface of the drainage tube does not decrease the incidence of bacteriuria.[23,35,36] The use of antimicrobial-impregnated catheters (eg, silver, rifampin plus minocycline) may decrease rates of bacteriuria and UTI.[23,35,36] The overall effects of antibiotic-impregnated catheters on infection rates, patient outcomes, and antibiotic resistance are not known, however, and their routine use is not currently recommended.[23,35]

Clinical Presentation

Symptoms commonly associated with lower tract UTI (eg, cystitis) include burning on urination (dysuria), frequent urination, suprapubic pain, and blood in the urine (hematuria). Patients with upper tract infection (eg, pyelonephritis) may also present with loin pain, costovertebral angle (CVA) tenderness, fever, chills, nausea, and vomiting.[1–5,37]

Clinical signs and symptoms correlate poorly with either the presence or the extent of the infection. Symptoms common to lower UTI often are the only positive findings in upper UTI (ie, subclinical pyelonephritis).[1,4] The probability of true infection in females who present with one or more symptoms of UTI is only about 50%.[38] The presence of dysuria, back pain, pyuria, hematuria, bacteriuria, and a

history of previous UTI may enhance the probability of true infection; the absence of dysuria or back pain, and history of vaginal discharge or irritation significantly decrease the likelihood of bacterial infection.[38],[39] The combination of dysuria plus urgency or frequency in the absence of vaginal discharge or irritation increases the probability of true infection to >90%.[38],[39] Fever, chills, flank and back pain, nausea and vomiting, or CVA tenderness are highly suggestive of acute pyelonephritis rather than of cystitis.[4],[5],[37] Many elderly patients with UTI are asymptomatic without pyuria. Likewise, nonspecific symptoms such as failure to thrive and fever may be the only manifestations of UTI in neonates and children younger than age 2 years.[1]

Diagnosis

Diagnosis of UTI based on clinical findings alone is accurate in only ~70% of patients.[38],[39] Urinalysis (UA) is a series of laboratory tests commonly performed in patients suspected of having a UTI. In combination with appropriate clinical findings, the UA effectively improves the overall diagnostic accuracy for UTI.[38],[39] Macroscopic analysis using a rapid “dipstick” method describes the color of the urine; measures its specific gravity; and estimates the pH, glucose, protein, ketone, blood, and bilirubin contents as well as presence of leukocytes and nitrite (see subsequent text). Microscopic analysis of urine sediment, obtained by centrifugation, determines the presence and quantity of leukocytes, erythrocytes, epithelial cells, crystals, casts, and bacteria. In patients with UTI, microscopic examination of urine sediment reveals many bacteria (usually >20 per high-power field [HPF]). Gram staining of uncentrifuged (“unspun”) urine shows at least one organism per immersion oil field and usually correlates with a positive urine culture result. Pyuria (ie, eight or more white blood cells [WBC] per milliliter of unspun urine or two to five WBC/HPF of centrifuged urine) is frequently seen in patients with UTI. WBC casts in the urine strongly suggest acute pyelonephritis.[1],[38],[39]

Rapid diagnostic dipstick tests are widely available and easily performed. The nitrite test detects nitrite formation from the reduction of nitrates by bacteria. Although a positive nitrite reading is useful, false-negative results do occur.[38],[39] The leukocyte esterase test detects the esterase activity of activated leukocytes in the urine. A positive test result correlates well with significant pyuria[40]; however, both false-negative and false-positive findings can occur with the leukocyte esterase test as well.[38] Nitrite and leukocyte esterase tests are useful in ruling out the presence of infection if results of both tests are negative, whereas positive results of both tests in combination are highly suggestive of the presence of infection.[38]

The gold standard criterion for the diagnosis of UTI is the urine culture with a positive UA finding.[1–3,37,38] Proper interpretation of these cultures depends, however, on appropriate urine collection techniques. Urinating into a sterile collection cup using the midstream clean-catch technique is the most practical method of urine collection. This method of urine specimen collection is especially useful for male patients, but it is less useful in female patients because bacterial contamination is extremely difficult to avoid.[1] The external urethral area must first be thoroughly cleaned and rinsed, then the urine specimen must be collected after initiation of the urine stream (hence “midstream”).

Urinary catheterization for a urine culture sample yields reliable results if performed carefully. Suprapubic bladder aspiration generally is not painful and is quite reliable. It is not practical for routine office or clinic practice, but it may be useful when voided urine samples yield questionable results or when patients have voiding problems. Because contamination is negligible, any number of bacteria found by this method reflects infection.[1–3]

Urine must be plated on culture media within 20 minutes of collection to avoid erroneously high colony counts from bacterial growth in urine at room temperature. Otherwise, urine should be promptly refrigerated until it can be cultured. Colony counts are also affected by the concentration of bladder urine; bacterial counts are higher in first-voided morning urine samples compared with those obtained from the same patient later in the day.[1],[37],[38]

Greater than 10^5 colonies of bacteria per mL cultured from a midstream urine specimen confirms a UTI. A single, carefully collected urine specimen provides 80% reliability, and two consecutive cultures of the same organism are virtually diagnostic.[1–3] However, the classic definition of UTI as $\geq 10^5$ bacteria/mL is inaccurate in diagnosing patients with true UTI. Approximately 30% to 50% of patients with acute cystitis have $<10^5$ bacteria/mL.[5,13] In a symptomatic patient, using a definition of $\geq 10^2$ bacteria/mL is more accurate and avoids failure to diagnose infection in many patients.[5]

Diagnosis of UTI in males also requires different interpretation of laboratory data. Contamination of urinary specimens is much less likely to occur in males compared with females, and numbers of bacterial colonies in specimens are therefore much lower. Greater than 10^3 bacteria/mL is thus highly suggestive of UTI in males.[11,12,38] In addition, although a positive nitrite test result in a symptomatic male is highly indicative of the presence of an acute UTI, a negative nitrite test result does not necessarily exclude infection, and a urine culture should be performed.[38,41]

Diagnosis of UTI in children is particularly problematic because of the difficulties and high contamination rates associated with commonly used methods of urine specimen collection. Suprapubic aspiration is the most accurate method in children, followed by urinary bladder catheterization.[3,37] Although clean-catch and bag methods (ie, collecting urine into a bag placed around the urogenital area) are susceptible to contamination and inaccurate results, they are also the most preferred methods for parents and health care personnel because they are simple and noninvasive. The choice of diagnostic tests for children will therefore vary based on the experience, skill, and preferences of those involved with the child.[37]

Simplified culture methods are as reliable as traditional laboratory methods for bacterial identification and quantification. The dip-slide (eg, Uricult®) and pad-culture (Microstix®) methods are accurate, differentiate between gram-positive and gram-negative organisms, and are similar in cost. The dip-slide method has the added advantages of ease of storage and a nitrite indicator pad.

Overview of Drug Therapy

The cornerstone of effective treatment of UTI is the appropriate selection and use of antibiotics. Antibiotic treatment of UTI is well studied and antibiotic choice and duration of therapy for acute, uncomplicated infections are reasonably clear. Consensus guidelines from the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESMID) recommend a 5-day course of nitrofurantoin, 3 days of trimethoprim–sulfamethoxazole (TMP-SMX), or a single dose of fosfomycin trometamol as first-line antibiotic treatment of acute uncomplicated cystitis in females.[20] Nitrofurantoin and TMP-SMX are familiar agents, whereas fosfomycin is a lesser known antibiotic that has made a resurgence in clinical use because of low rates of resistance among common uropathogens.[20,42]

Fluoroquinolones and β-lactam antibiotics, such as amoxicillin–clavulanate and various cephalosporins, are recommended by the IDSA/ESMID guidelines as alternative agents for treating acute uncomplicated cystitis.[20] The recommended durations of therapy for fluoroquinolones and β-lactams are 3 days and 3 to 7 days, respectively. Fluoroquinolones, cephalosporins, aminoglycosides, TMP-SMX, extended-spectrum penicillins (ie, piperacillin–tazobactam), or a carbapenem are recommended by the IDSA/ESMID for the treatment of acute pyelonephritis in females.[20] The choice of a specific agent for pyelonephritis depends primarily on whether the patient is hospitalized or treated as an outpatient, local susceptibility patterns, and whether therapy is empiric or based on known susceptibilities. The duration of therapy for acute pyelonephritis ranges from 5 to 14 days and is dependent on which specific antibiotic is being used.[20] Parameters for monitoring response to treatment of either uncomplicated cystitis or pyelonephritis are primarily resolution of clinical signs and symptoms; repeat urinary cultures are not usually required. Patients with complicated UTI or recurrent infections may require additional monitoring and long-term follow-up, and antibiotic selection must be guided by culture and susceptibility (C&S) testing. Patient monitoring

related to the safety and tolerability of antibiotic therapy is required regardless of type of infection, as is effective patient counseling.

LOWER URINARY TRACT INFECTION

Initial Patient Evaluation and Determining Goals of Therapy

CASE 71-1

QUESTION 1: V.Q., a 20-year-old female with no previous history of UTI, reports burning on urination, frequent urination of a small amount, and bladder pain. She has no fever or CVA tenderness. A clean-catch midstream urine sample shows gram-negative rods on Gram stain. A urine sample for C&S testing is ordered, and the results of a UA are as follows:

Appearance, straw-colored (normal, straw)
Specific gravity, 1.015 (normal, 1.002–1.028)
pH, 8.0 (normal, 5.5–7.0)
Protein, glucose, ketones, bilirubin, and blood, all negative (normal, all negative)
WBC, 10 to 15 cells/low-power field (LPF; normal, 0–2 cells/LPF)
Red blood cells (RBCs), 0 to 1 cells/LPF (normal, 0–2 cells/LPF)
Bacteria, many (normal, 0 to rare)
Epithelial cells, 3 to 5 cells/LPF (normal, 0 to few cells/LPF)
Based on these findings, V.Q. is presumed to have a lower UTI.

What should be the goals of therapy of V.Q.'s infection at this time? What factors should be considered before selecting an antibiotic for V.Q.?

The goals of therapy for treatment of acute cystitis are to effectively eradicate the infection and prevent associated complications, while minimizing adverse effects and costs associated with drug therapy. Selection of a specific antimicrobial agent should be made after considering several factors: (a) most likely pathogens, (b) resistance rates within the specific geographic area, (c) desired duration of therapy, (d) clinical efficacy and toxicity profiles of various agents, (e) cost and availability of specific agents,

and (f) patient characteristics such as allergies, compliance history, and underlying comorbidities.[20] Because resistance rates among various pathogens vary considerably among geographic areas, clinicians must be familiar with those prevalent within their specific practice area.[20,43,44]

Drug treatment of a lower UTI often is started empirically or before C&S results are known because the most probable infecting organisms and their susceptibility to antibiotics can be predicted reasonably well (**Table 71-1**). Approximately 75% to 95% of community-acquired infections are caused by Enterobacterales, particularly *E. coli*. Although these organisms may be sensitive to ampicillin, amoxicillin, and the sulfonamides (such as TMP-SMX), resistance to these agents is common.[43–47] Ampicillin resistance occurs in 25% to 70% of community-acquired isolates[43–47]; overall resistance in the United States is currently 30% to 50%. Ampicillin and amoxicillin are therefore not recommended as first-line empiric agents for UTI.[1,5,20,43–47] TMP-SMX has been an agent of choice for many years; however, TMP-SMX resistance has significantly increased in recent years and may be 20% to 45% among community-acquired *E. coli* isolates in some geographic areas.[20,43–47] Although traditionally associated with hospital-acquired infections, *E. coli* and *Klebsiella* resistance, caused by production of ESBL enzymes that confer resistance to penicillins and cephalosporins, has also been steadily increasing among community-acquired pathogens.[48,49] Another relatively common organism is *S. saprophyticus.* Most strains are susceptible to sulfonamides, TMP-SMX, penicillins, and cephalosporins. Commonly used medications and doses are shown in **Table 71-2**.

Table 71-1

Overview of Treatment of Urinary Tract Infections

Common Uropathogens	Antibacterial of Choice
Uncomplicated Urinary Tract Infection	
Escherichia coli	TMP-SMX[a]

Proteus mirabilis	TMP-SMX[a]
Klebsiella pneumoniae	TMP-SMX[a]
Enterococcus faecalis	Ampicillin, amoxicillin
Staphylococcus saprophyticus	First-generation cephalosporin or TMP-SMX
Complicated Urinary Tract Infection[b,c]	
E. coli	First-, second-, or third-generation cephalosporin; TMP-SMX[c]
P. mirabilis	First-, second-, or third-generation cephalosporin
K. pneumoniae	First-generation cephalosporin; fluoroquinolone
ESBL-producing organisms[d]	Nitrofurantoin, fosfomycin, carbapenem, amikacin, ceftolozane–tazobactam, ceftazidime–avibactam
Enterococcus faecalis	Ampicillin or vancomycin ± aminoglycoside
Pseudomonas aeruginosa	Antipseudomonal penicillin ± aminoglycoside; ceftazidime; cefepime; fluoroquinolone; carbapenem[e]
Enterobacter	Fluoroquinolone; TMP-SMX; carbapenem
Indole-positive Proteus	Third-generation cephalosporin; fluoroquinolone
Serratia	Third-generation cephalosporin; fluoroquinolone
Acinetobacter	Carbapenem; TMP-SMX
Staphylococcus aureus	Penicillinase-resistant penicillin; first-generation cephalosporin; vancomycin

ESBL, extended-spectrum β-lactamase; TMP-SMX, trimethoprim–sulfamethoxazole.

[a]Caution in communities with increased resistance (>10%–20%).

[b]Drug selection based on culture and susceptibility testing when possible.

[c]Oral therapy when appropriate. Nitrofurantoin, fosfomycin, fluoroquinolones, or cephalosporins should be used in areas with increased TMP-SMX resistance.

[d]Choice of specific antibiotic should be guided by susceptibility reports.

[e]Ertapenem has no activity against *Pseudomonas*.

Table 71-2
Commonly Used Oral Antimicrobial Agents for Acute Urinary Tract Infections

Drug	Usual Dose[a]		Pregnancy[b]	Breast Milk[b]	Comments[c]
	Adult	Pediatric			Pediatric
Amoxicillin	500 mg every 8 or 12 hours or 3 g single dose	20–40 mg/kg/day in three doses	Crosses placenta (cord) = 30% (maternal)[d]	Small amount present	High resistance rates, not for empiric use
Amoxicillin/ potassium clavulanate	500/125 mg every 12 hours	20–40 mg/kg/day (amoxicillin content) in three doses	Unknown	Unknown	
Cephalexin	250–500 mg every 6 hours	25–50 mg/kg/day in two to four doses	Crosses placenta	Enters breast milk	Cephalosporins are alternative choices for patients allergic to penicillins, although cross-hypersensitivity can occur. May be associated with higher failure rates compared to other drug classes
Cefaclor	250–500 mg every 8 hours	20–40 mg/kg/day in two to three doses	Crosses placenta	Small amount present	
Cefpodoxime proxetil	100 mg every 12 hours	10 mg/kg/day in two doses	Crosses placenta	Variable amounts; milk = 0%–16% of serum	
Cefdinir	300 mg every 12 hours (or 600 mg every 24 hours)	14 mg/kg/day in one or two doses	Crosses placenta	Not detectable after single 600-mg dose	
Norfloxacin[e]	400 mg every 12 hours	Avoid	Arthropathy in immature animals	Unknown	Avoid concomitant administration of antacids, divalent and trivalent cations, and sucralfate[f]
Ciprofloxacin[e]	250–500 mg every 12 hours Extended release: 500 mg to 1 g every 24 hours	Avoid	Arthropathy in immature animals	Unknown	Alternative choice for patients allergic to β-lactams.[f] Useful for pseudomonal infection. *Caution with concomitant use of QTc-prolonging agents.*
Levofloxacin	250 or 750 mg every 24 hours	Avoid	Arthropathy in immature animals	Milk = 100% of serum[d]	*Caution with concomitant use of QTc-prolonging agents.*
Nitrofurantoin	100 mg every 12 hours (eg, Macrobid®) 50–100 mg every 6 hours (eg, Macrodantin®)	5–7 mg/kg/day in four doses (eg, Macrodantin®)	Hemolytic anemia in newborn	Variable, but up to 30%; may cause hemolysis in G6PD-deficient baby	Alternative choice *To be taken with food or milk. May cause brown or rust-yellow discoloration of urine.*
Trimethoprim (TMP)	100 mg every 12 hours	4–6 mg/kg/day in two doses	Crosses placenta (cord) = 60%; (maternal) folate antagonism, avoid during first trimester; teratogenic in rats	Milk > serum[d]	Alternative choice

Drug	Usual Dose[a]		Pregnancy[b]	Breast Milk[b]	Comments[c]
	Adult	Pediatric			Pediatric
TMP-SMX	160–800 mg every 12 hours	10 (6–12) mg/kg/day (TMP component in two doses)	SMX crosses placenta (cord) = 60%; maternal folate antagonism, avoid during first trimester; displacement of bilirubin may lead to hyperbilirubinemia and kernicterus in newborn; avoid after 32 weeks of gestation; teratogenic in some animal studies.	SMX enters breast milk in concentrations greater than serum; displacement of bilirubin may lead to neonatal jaundice; may cause hemolysis in G6PD-deficient baby.	*To be taken on an empty stomach with a full glass of water. Photosensitivity may occur.* Monitor HIV-infected patients closely for development of adverse hematologic reactions. First-line agent for prostatitis
Fosfomycin	3-g single dose	2-g single dose (children <12 years)	Crosses placenta	Present in breast milk	Recommended option for uncomplicated cystitis

G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus; TMP-SMX, trimethoprim–sulfamethoxazole.

[a]Where dosing ranges are provided, lower doses are often used for uncomplicated infections and higher doses reserved for complicated infections.

[b]Also see Chapter 49, Obstetric Drug Therapy.

[c]Includes unique patient consultation information in italics.

[d]Denotes drug concentration.

[e]May increase theophylline and warfarin concentrations when given concurrently. Carefully monitor theophylline serum concentrations and international normalized ratio (INR) during quinolone use.

[f]Same comments apply to all fluoroquinolones.

Sources: Sobel JD, Brown P. Urinary tract infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier, Inc.; 2020:962–989; Hooton TM Jr. Uncomplicated urinary tract infection. *N Engl J Med*. 2012;366:1028–1037; Kolman KB. Cystitis and pyelonephritis: diagnosis, treatment, and prevention. *Prim Care Clin Off Pract*. 2019;46:191–202; Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am.* 2008;35:1–12; Lumbiganon P, Laopaiboon M, Thinkhamrop J. Screening and treating asymptomatic bacteriuria in pregnancy. *Curr Opin Obstet Gynecol.* 2010;22:95–99; Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant gram-negative bacteria causing urinary tract infections: a review. *J Chemother*. 2017;29(Suppl 1):2–9; Perletti G, Magri V, Cai T, Stamatiou K, Trinchieri A, Montanari E. Resistance of uropathogens to antibacterial agents: emerging threats, trends, and treatments. *Arch Ital Urol Androl*. 2018;90(2):85–96.

ROLE OF URINE CULTURES

Case 71-1, Question 2: Is it necessary to order a pretreatment urine C&S test for V.Q.?

Many investigators question the value of pretreatment urine cultures for acute uncomplicated UTI.[1,2,5,20] Females with lower UTI usually have pyuria on UA and respond rapidly to appropriate antimicrobial treatment. Pyuria may be a better predictor of treatable infection than the colony count obtained on urine culture. Furthermore, the urine culture accounts for a large portion of the cost of treating a patient with a UTI.[50] Consequently, in patients such as V.Q. with uncomplicated, acute, lower UTI, it is more cost-effective to order a UA and, if pyuria is present on UA, to forego a urine culture and empirically start a conventional course of antibiotic therapy. If V.Q. remains symptomatic 48 hours later, a C&S test can then be ordered. Considerations are different in patients with complicated infections. In complicated UTI, predisposing factors that lead to infection and history of frequent previous antibiotic use make both causative pathogens and associated antibiotic susceptibilities much less predictable. Use of C&S testing is therefore commonly recommended for treatment of complicated UTI to guide appropriate antibiotics.[1–3,5,20]

INITIAL ANTIBIOTIC SELECTION

Case 71-1, Question 3: What antibiotics may be appropriate for treatment of V.Q.'s infection?

IDSA/ESMID guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis were published in 2011 and serve as the basis for antibiotic selection in V.Q.[20] (**Table 71-3**). The recommended first-line agents for treatment of this patient's uncomplicated cystitis include TMP-SMX, nitrofurantoin, and

fosfomycin trometamol; a fourth recommended antibiotic, pivmecillinam, is not commercially available in the United States.

Table 71-3

Summary of Evidence-Based Recommendations for Treatment of Acute Uncomplicated Cystitis and Pyelonephritis

Recommendations	Recommendation Grades[a]
Cystitis	
Preferred Agents	
Nitrofurantoin monohydrate/macrocrystals 100 mg PO twice daily × 5 days	A-1
TMP-SMX 160/800 mg (1 double-strength tablet) PO twice daily × 3 days	A-1
Trimethoprim 100 mg PO twice daily × 3 days is considered equivalent to TMP-SMX and is the preferred agent in some regions.	A-3
Fosfomycin trometamol 3 g PO × 1 dose	A-1, but appears to have inferior microbiologic efficacy compared with standard short-course therapies with agents such as trimethoprim or nitrofurantoin
Pivmecillinam 400 mg PO twice daily × 3–7 days (not commercially available in the United States)	A-1, but may have inferior efficacy compared with other available therapies
Resistance Considerations	
A specific antibiotic is no longer recommended for empirical treatment when the prevalence of resistance is ≥20%.	B-3 for TMP-SMX No recommendation for other agents
Alternative agents	
Fluoroquinolones	
Fluoroquinolones (ciprofloxacin or levofloxacin) PO × 3 days are highly efficacious for acute cystitis.	A-1

Recommendations	Recommendation Grades[a]
Fluoroquinolones should be reserved for other important clinical uses because of propensity for collateral damage.	A-3
β-*Lactams*	
β-Lactams (including amoxicillin–clavulanate, cefdinir, cefaclor, and cefpodoxime– proxetil) PO × 3–7 days are appropriate when other recommended agents cannot be used.	B-1
Other β-lactams such as cephalexin are less well studied but may also be appropriate in certain settings.	B-3
β-Lactams generally have inferior efficacy and more adverse effects compared with other antimicrobials for UTI.	B-1
Pyelonephritis	
All Patients	
Urine culture and susceptibility testing should be performed, and initial empirical antibiotic therapy tailored appropriately based on results.	A-3
Outpatient Treatment	
Fluoroquinolones	
Ciprofloxacin 500 mg PO twice daily × 7 days, ± an initial IV dose of ciprofloxacin 400 mg, a long-acting parenteral cephalosporin (eg, ceftriaxone 1 g) or a consolidated 24-hour dose of an aminoglycoside (eg, gentamicin 5–7 mg/kg)	A-1
Ciprofloxacin 1000 mg extended-release tablet PO once daily × 7 days, or levofloxacin 750 mg PO once daily × 5 days	B-2
If the local prevalence of fluoroquinolone resistance among uropathogens is >10%, an initial one-time IV dose of a long-acting parenteral cephalosporin or a consolidated 24-hour dose of an aminoglycoside should be administered.	B-3
Alternative agents	

Recommendations	Recommendation Grades[a]
TMP-SMX 160/800 mg (1 double-strength tablet) PO twice daily × 14 days	A-1
If TMP-SMX susceptibility is not known, an initial IV dose of a long-acting parenteral cephalosporin or a consolidated 24-hour dose of an aminoglycoside should be administered.	B-2 for a cephalosporin B-3 for an aminoglycoside
Oral β-lactams × 10–14 days are less effective than are other available agents.	B-3
If an oral β-lactam is used, an initial IV dose of a long-acting parenteral cephalosporin or a consolidated 24-hour dose of an aminoglycoside should be administered.	B-2 for a cephalosporin B-3 for an aminoglycoside
Hospitalized Patients	
One of the following antibiotic options may be used initially, based on local resistance data and on susceptibility results: IV fluoroquinolone; IV aminoglycoside ± IV ampicillin; extended-spectrum IV cephalosporin or extended-spectrum IV penicillin ± aminoglycoside; or IV carbapenem.	B-3

Quality of evidence: 1 = evidence from ≥1 properly randomized controlled trial; 2 = evidence from ≥1 well-designed clinical trial without randomization, from cohort or case–control analytic studies, from multiple time series, or from dramatic results from uncontrolled experiments; 3 = evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

IV, intravenous; PO, orally; TMP-SMX, trimethoprim–sulfamethoxazole; UTI, urinary tract infection.

[a]Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation for or against use, respectively.

Source: Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis.* 2011;52:e103–e120.

TMP-SMX is effective as therapy for uncomplicated cystitis.[1–3,20,51] Gram-positive and gram-negative uropathogens, with the notable

exceptions of *Enterococcus* and *P. aeruginosa*, are generally susceptible to TMP-SMX.[20],[52] Although TMP-SMX may appear active against enterococci in vitro, clinical efficacy against this pathogen does not always correlate well and is variable. Furthermore, this combination is almost uniformly successful in the treatment of uncomplicated UTI, even against organisms that are resistant to either agent alone. Although resistance to trimethoprim has increased,[20],[43–48] resistance rates remain relatively low in some geographic areas and trimethoprim alone may be effective in managing UTI in many patients.

The ratio of trimethoprim to sulfamethoxazole in the available tablet products is 1:5 (eg, 80 mg trimethoprim and 400 mg sulfamethoxazole). This combination will achieve peak serum concentrations of the two drugs that approximate a 1:20 ratio. This ratio is optimal for synergistic activity against most microorganisms, although the drugs remain synergistic and bactericidal in ratios ranging from 1:5 to 1:40 in vitro.[52] Urinary concentrations of trimethoprim and sulfamethoxazole far exceed the minimum inhibitory concentrations (MIC) for most susceptible urinary pathogens. Therefore, good in vitro activity, excellent clinical success against susceptible strains (similar to that of the fluoroquinolones and other alternative agents), relatively low resistance rates among common pathogens, and low cost make TMP-SMX a reasonable choice in V.Q.[20] The 2011 IDSA/ESMID guidelines recommend TMP-SMX as an appropriate initial agent of choice in the treatment of acute, uncomplicated lower UTI in geographic areas where the incidence of TMP-SMX resistance among *E. coli* is <20%.[20]

Nitrofurantoin is also recommended as an appropriate agent for empirical treatment of acute uncomplicated cystitis.[20] Nitrofurantoin is almost completely absorbed after oral administration, but it barely reaches detectable levels in the plasma because it is rapidly eliminated (half-life, 20–60 minutes) into the urine and bile; the resulting high urine levels of 50 to 250 mg/L are well in excess of the MIC for most common pathogens causing UTI.[53],[54] Food substantially decreases the rate of absorption, but it increases the total bioavailability of nitrofurantoin by about 40%. This effect

lengthens the duration of therapeutic urine concentrations by about 2 hours.[53,54]

Nitrofurantoin's spectrum of activity includes *E. coli*, some *Pseudomonas* strains, *S. saprophyticus*, streptococci, and enterococci, whereas *Proteus*, *Enterobacter*, and *Klebsiella* are more likely to be resistant (susceptibility <60%).[20,54] Nitrofurantoin does not significantly alter the fecal or introital flora, and the development of resistance in previously sensitive strains does not often occur.[20,53,54] In contrast to ampicillin, TMP-SMX, and other drugs with relatively high resistance rates, nitrofurantoin has maintained excellent activity against most uropathogens; susceptibility rates among *E. coli* range from 90% to 99% in most geographic areas.[20,43–47,54] Nitrofurantoin has shown effectiveness similar to that of TMP-SMX, fluoroquinolones, or fosfomycin in the treatment of acute uncomplicated cystitis, and thus is recommended in the most recent clinical guidelines as an appropriate choice for treatment of uncomplicated UTI in patients such as V.Q. (Table 71-3).[20]

Fosfomycin trometamol has been successfully used for the treatment of UTI in many parts of the world for a number of years.[20,42] Fosfomycin is a phosphonic acid derivative that irreversibly blocks bacterial cell wall synthesis through inhibition of early cytoplasmic stages of peptidoglycan synthesis.[42,53] It has bactericidal activity against a broad range of gram-negative and gram-positive organisms including *E. coli* and other Enterobacterales, *P. aeruginosa*, and *Enterococcus.* Fosfomycin is also useful against methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) pathogens including vancomycin-resistant enterococci (VRE), and extended spectrum β-lactamase (ESBL)-producing gram-negative bacteria that are becoming more common in certain practice settings.[20,42] Fosfomycin is ~40% absorbed after oral administration (granules marketed in a sachet form are dissolved in cold water) and is rapidly and almost completely excreted unchanged in the urine. Fosfomycin achieves mean urinary concentrations >500 mg/L within 6 to 8 hours of administration and maintains concentrations >100 mg/L for >24 hours after a single oral dose.[42,53] Single 3-g oral doses of

fosfomycin are clinically as effective as trimethoprim and nitrofurantoin, although microbiological efficacy may be less.[20] Fosfomycin is currently recommended for treatment of acute uncomplicated cystitis in the 2011 IDSA/ESMID guidelines (Table 71-3), and is substantially more expensive than is either TMP-SMX or nitrofurantoin.[20]

Alternative agents for the treatment of UTI in V.Q. include the fluoroquinolones and various oral β-lactam antibiotics.[20] The fluoroquinolones remain highly effective in the treatment of UTI. However, increasing rates of resistance among common uropathogens, and the potential for significant collateral effects on normal flora leading to complications such as *Clostridioides difficile* infection have led to recent recommendations that the fluoroquinolones not be routinely used as preferred agents in the treatment of uncomplicated UTI such as that present in V.Q.[20] Further details regarding the use of fluoroquinolones for UTI are discussed in Case 71-2.

Amoxicillin–clavulanate and several oral cephalosporins have been studied for the treatment of uncomplicated UTI. β-Lactams are generally comparable to TMP-SMX, but less clinically or microbiologically effective than are the fluoroquinolones.[20] β-Lactams require longer durations of treatment (see Case 71-1, Question 4), which makes them less attractive from the standpoint of ensuring patient adherence and may also predispose them to higher rates of drug-related adverse effects.[20] These relatively broad-spectrum agents may be associated with more frequent emergence of bacterial resistance, including ESBL-producing gram-negative bacilli.[20] Thus, the β-lactam antibiotics (with the exception of pivmecillinam) are currently only recommended for empirical treatment of uncomplicated cystitis when none of the other agents previously discussed can be used (Table 71-3).[20] Ampicillin and amoxicillin are specifically discouraged for empirical treatment of UTI because of the high resistance rates previously noted.[20]

V.Q. could be appropriately treated with TMP-SMX, nitrofurantoin, or fosfomycin. She has no apparent patient characteristics that would favor the use of one agent over another. In this case, the most

important factor to consider would be local antibiotic susceptibilities among community-acquired uropathogens, particularly *E. coli.* Local costs and availability of the different options would also be important to consider in V.Q.

Note that the current IDSA/ESMID guidelines do not apply to the empirical selection of antibiotics for complicated UTI. Complicated infections are often associated with more difficult pathogens (eg, *P. aeruginosa*) and increased risk of antibiotic resistance; fluoroquinolones are therefore considered preferred agents for initial treatment of complicated UTI with subsequent antibiotic therapy guided by the results of C&S testing.[1–3,5,24]

DURATION OF ANTIBIOTIC THERAPY

Case 71-1, Question 4: V.Q. is started on TMP-SMX for treatment of her infection. What would be the preferred duration of antibiotic therapy for V.Q.?

Outpatients with acute, uncomplicated UTI can be treated successfully with a single dose, a 3- to 5-day course of therapy, or a 7- to 14-day course of oral medications; the latter is considered excessive for most patients with uncomplicated infections and is seldom used.[1–3,5,20,55] A 3- to 5-day antibiotic regimen is just as effective as a 10-day regimen in achieving clinical cures and eradicating uropathogens, although this is antibiotic class specific.[1–3,5,20,55] TMP-SMX is recommended as the preferred agent for 3-day treatment regimens; the fluoroquinolones may also be used in this shorter duration (Table 71-3).[20] A 5-day course of nitrofurantoin is as effective as a 3-day course of TMP-SMX for acute uncomplicated cystitis, and the 5-day treatment duration is currently recommended.[20,56] β-Lactam antibiotics are more appropriately reserved for treatment courses of 3 to 7 days.[5,20] Longer treatment courses are also used in cases of treatment failure after regimens of shorter duration, as well as in the treatment of complicated UTI where longer courses of therapy (7–14 days) are associated with higher clinical success rates and improved outcomes.[1–3,24]

Even a single dose of an antibiotic may be effective. Bacteria disappear from the urine within hours of antibacterial therapy being initiated.[20] This, coupled with the urinary bladder's ability to defend itself through micturition, acidification, and inherent antibacterial activity, gives theoretic support to the clinical evidence that a large single dose of an antibiotic can eradicate a UTI. Fosfomycin trometamol is a perfect example of this principle: very high urinary concentrations of this bactericidal agent are maintained for >24 hours after a single 3-g oral dose and contribute to the favorable clinical efficacy observed in comparative trials.[20,42,53]

Although not recommended in the current guidelines, single doses of antibiotics other than fosfomycin are also occasionally used in treating acute, lower UTI in young females.[5,8,20] Examples of regimens used are TMP-SMX (two or three double-strength tablets), trimethoprim 400 mg, amoxicillin–clavulanate 500 mg, amoxicillin 3 g, nitrofurantoin 200 mg, ciprofloxacin 500 mg, and norfloxacin 400 mg.[1,20] The advantages of single-dose treatment of UTI include improved compliance, reduced cost, proven efficacy in a defined population of patients (ie, young females with acute, uncomplicated lower UTI), minimal side effects, and a potentially decreased incidence of bacterial resistance associated with antibiotic overuse. However, several concerns also exist regarding single-dose therapy.[5,8,20] First, sample sizes in most comparative studies were relatively small. Consequently, it is difficult to determine whether differences in effectiveness or incidence of side effects between single-dose and multiple-dose therapy are clinically significant. Meta-analysis of studies comparing single-dose versus longer regimens of TMP-SMX has demonstrated that single-dose therapy is significantly less effective in eradicating bacteriuria than are regimens of ≥5 days (83% vs 93%, respectively, $P > .001$) or ≥7 days in duration (87% vs 94%, respectively; $P = .014$).[20,51,55] Although fewer studies have directly compared single-dose versus 3-day therapies, numerous studies have shown that 3-day courses are as effective as courses of longer duration.[20,55] As discussed in Case 71-1, Question 3, reduced microbiologic efficacy was also observed with single-dose fosfomycin[20] and single-dose therapies have been associated with

higher rates of recurrence compared with therapies of longer duration.[5] A 3- or 5-day course of therapy is therefore currently recommended by the IDSA/ESMID for uncomplicated cystitis; a large single dose of fosfomycin is the sole single-dose regimen endorsed by the guidelines.[20]

Female patients with history or clinical presentation suggestive of complicated infection (eg, systemic manifestations of infection, renal disease, anatomic abnormalities of the urinary tract, diabetes mellitus, pregnancy), a history of antibiotic resistance, or a history of relapse after single-dose therapy should not receive single-dose regimens. Single-dose therapy is also not appropriate for male patients with UTI. Because V.Q. does not have any of these contraindications, she could theoretically receive single-dose therapy with an appropriate agent. Based on the preceding information, and according to current guidelines, a 3-day course of TMP-SMX, a 5-day course of nitrofurantoin, or a single dose of fosfomycin would be most appropriate for treatment of V.Q.'s infection (Table 71-3).[20]

When using short-course regimens, it is important to counsel the patient that the clinical signs and symptoms of infection may often not be completely resolved for 2 to 3 days after initiation of therapy. Therefore, symptoms that persist for a short while after beginning therapy (or actually completing therapy, in the case of single-dose regimens) are not necessarily indicative of treatment failure.

PHENAZOPYRIDINE

Case 71-1, Question 5: Along with TMP-SMX, phenazopyridine is also prescribed because of V.Q.'s reports of significant dysuria. Is phenazopyridine appropriate for this patient?

Phenazopyridine, a urinary tract analgesic, may occasionally be administered together with an antibacterial agent for the symptomatic relief of dysuria. Although phenazopyridine at a dose of 200 mg orally three times a day may relieve dysuria, it is ineffective in the actual eradication of true UTI. Phenazopyridine plus an

antibiotic is not any better than an antibiotic alone in terms of treatment efficacy; therefore, the drug is not likely of significant value in V.Q. and should not be routinely recommended. However, although most patients have resolution of symptoms within 24 to 48 hours of beginning therapy, certain patients with severe dysuria or delayed response to antibiotic therapy may benefit symptomatically from a short trial (1–2 days) of phenazopyridine.[5] The need for, and duration of, analgesic therapy must be individualized.

Phenazopyridine is an azo dye and may discolor the urine to an orange–red, orange–brown, or red color that can stain clothes. Other adverse effects of phenazopyridine occur after acute overdose, or as a result of accumulation in older patients or in patients with decreased renal function who take the drug chronically. In vivo, about 50% of phenazopyridine is metabolized to aniline, which can cause methemoglobinemia and hemolytic anemia. Hemolytic anemia associated with phenazopyridine occurs primarily in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[57] Cases of reversible acute renal failure and allergic hepatitis have also been rarely reported after brief exposure to phenazopyridine.[57]

INTERPRETATION OF URINE CULTURE AND SUSCEPTIBILITY TEST RESULTS

Case 71-1, Question 6: Two days after V.Q. begins treatment for her infection with TMP-SMX, results of the C&S studies become available and reveal $>10^5$ bacteria/mL of *P. mirabilis*, which is susceptible to ampicillin, amoxicillin–clavulanate, cephalosporins, and gentamicin. The *Proteus* is intermediately susceptible to nitrofurantoin, and resistant to TMP-SMX and ciprofloxacin. V.Q. reports that she is symptomatically better since starting antibiotic therapy and that her dysuria and bladder pain are now almost completely resolved. How should these test results be interpreted? Is a change in V.Q.'s antibiotic therapy necessary?

Most females with either lower or upper UTI have $>10^5$ bacterial colonies/mL of urine. However, a major revision in the diagnostic criteria for symptomatic UTI has been the abandonment of the absolute requirement for growth of $\geq 10^5$ bacterial colonies/mL of

urine. The criterion of ≥100 bacteria/mL results in excellent sensitivity and specificity in correctly diagnosing and treating females with symptomatic infection.[13] This same criterion should also be applied to lower UTI when *S. saprophyticus* is isolated, because UTIs caused by this pathogen often are associated with low urine bacterial colony counts, suboptimal growth on commonly used media, and negative findings on nitrite screening.

Mixed flora (more than two organisms) is unusual in uncomplicated cystitis except in severely debilitated persons and other complicated infections. Thus, mixed flora in the setting of uncomplicated infection frequently suggests contamination, and a repeat specimen should be obtained.

Bacterial susceptibility to different antimicrobial drugs is usually determined by referencing interpretive criteria that correlate with achievable serum concentrations of those drugs. However, drugs useful in the treatment of UTI are excreted primarily by the kidney, and urine concentrations of these drugs may be 20 to 100 times greater than are serum concentrations. Therefore, infections caused by organisms that are only intermediately susceptible, or even "resistant" to the tested concentration of antibacterial drug, might still be effectively treated with the high concentration of drug achieved in the urine.

Although in vitro susceptibility testing is not always predictive of patient response to therapy for UTI, studies clearly show that patients infected with a resistant pathogen are at increased risk for treatment failure.[49,58–60] Clinical response to infection occurred in only 24% to 61% of patients with organisms resistant to TMP-SMX compared to 83% to 92% of patients infected with susceptible organisms[49,58,59]; furthermore, patients infected with TMP-SMX–resistant pathogens were 17 times more likely to fail therapy compared to patients with susceptible strains.[61] Infections with drug-resistant organisms also result in longer median times to symptom resolution (14 vs 7 days, $P = .0002$), more frequent clinic visits within 1 week (36% vs 6%, $P > .0001$), more frequent need for subsequent antibiotic therapy (36% vs 4%, $P > .0001$), and higher rates of significant bacteriuria after 1 month (42% vs 20%, $P = .04$).[59]

Although up to 75% of patients with organisms resistant to TMP-SMX may experience treatment failure with TMP-SMX, empiric antimicrobial therapy is usually chosen without C&S testing results. Appropriateness of antibiotic therapy is thus usually judged according to subsequent clinical response. If the infecting organism is susceptible, the urine will usually be sterile within 24 to 48 hours. If the urine specimen is sterile and the patient is symptomatically improved, the chosen antimicrobial is appropriate (regardless of susceptibility studies), and the full course of therapy should be completed. If a urine specimen collected 48 hours after initiation of therapy is not sterile and the patient has been taking the medication properly, the antibiotic may be inappropriate or the focus of infection may be deeper (eg, pyelonephritis, abscess, obstruction). Because V.Q. reports significant improvement in her subjective symptoms, she should complete her 3-day course of TMP-SMX as originally ordered and V.Q. should be closely monitored for any evidence of relapse. A repeat C&S test should be performed in the event that V.Q. reports any new signs or symptoms consistent with antibiotic failure and relapse of her infection, and a different antibiotic should be selected for treatment at that time.

FLUOROQUINOLONE THERAPY

CASE 71-2

QUESTION 1: I.B., a 48-year-old female, presents with a community-acquired UTI. She has a past medical history significant only for several previous episodes of UTI. A UA returns with the following results:

Appearance, straw-colored and turbid
Specific gravity, 1.028
pH, 6.3
Glucose, ketones, and bilirubin, all negative
Blood and protein, both trace positive by dipstick
WBC, 10 to 15 cells/LPF
RBC, 5 to 10 cells/LPF
Bacteria, many
Epithelial cells, 3 to 5 cells/LPF
Leukocyte esterase and nitrite test results by dipstick, both positive

Of note, I.B. has experienced a rash with TMP-SMX and a type I hypersensitivity reaction to penicillins in the past.

What is the role of fluoroquinolones in the treatment of I.B.'s community-acquired UTI?

Fluoroquinolones indicated for the treatment of uncomplicated or complicated UTI include norfloxacin, ciprofloxacin, and levofloxacin. They are usually administered orally in the treatment of UTI and have excellent in vitro activity against most gram-negative organisms, including *P. aeruginosa*.[62] They are also active in vitro against many gram-positive organisms including *S. saprophyticus*.[62] The in vitro activity of many fluoroquinolones is antagonized by acidic pH and divalent cations in urine; however, this is unlikely to be clinically significant because urine concentrations are several hundredfold greater than are serum levels.[62] Many clinical trials have demonstrated that fluoroquinolones are very effective in the treatment of acute uncomplicated UTI, with efficacy rates typically >90%.[20,51]

Although the fluoroquinolones are as effective as TMP-SMX, nitrofurantoin, or β-lactams in treatment of uncomplicated UTI, they are no longer recommended as first-line empirical therapy because they are more expensive and provide no additional treatment benefits.[5,8,20,51,62] Concerns also exist regarding the overuse of fluoroquinolones and the promotion of drug resistance among community-acquired uropathogens. Resistance to fluoroquinolones among organisms causing acute uncomplicated UTI is usually <1% to 2%.[21] Fluoroquinolone resistance may, however, be more frequent in some geographic areas and in complicated infections.[43–48] Recent studies revealed resistance to ciprofloxacin in 2% to 20% of acute uncomplicated infections, whereas it is 8% to 60% in complicated UTI.[20,43–48] Furthermore, these quinolone-resistant strains often are resistant to multiple other antimicrobials.[43–48] Concerns also exist regarding the potential for fluoroquinolones to produce collateral effects on normal flora, leading to increased risk of infection owing to MRSA and *C. difficile.*[20]

Fluoroquinolones are recommended as appropriate alternatives for patients with allergies or other contraindications to the use of recommended first-line agents or for patients infected with organisms resistant to multiple antibiotics, such as *P. aeruginosa.* Fluoroquinolones are appropriate initial therapy in geographic areas with >20% resistance of *E. coli* to TMP-SMX[20]; however, many patients in such areas may be appropriately treated with nitrofurantoin or other options (Table 71-3).[20] Further, the fluoroquinolones are effective in treating patients with structural or functional abnormalities of the urinary tract and other complicated infections.[20,62]

A fluoroquinolone may be considered for I.B. because she has experienced previous adverse reactions to penicillins and sulfonamides. However, nitrofurantoin or fosfomycin should be preferentially considered for I.B. based on current IDSA/ESMID recommendations.[20] If a fluoroquinolone was deemed appropriate for I.B. based on availability, cost, or tolerability issues with other treatment options, the individual fluoroquinolones are similar in efficacy, and the choice would be based on comparative costs and compliance considerations.[20] The duration of fluoroquinolone therapy in I.B. would be 3 days.[20]

NITROFURANTOIN-INDUCED ADVERSE EFFECTS

Case 71-2, Question 2: The decision is made to begin I.B. on nitrofurantoin rather than on a fluoroquinolone. After starting Macrobid® (nitrofurantoin monohydrate/macrocrystals) 100 mg twice daily (bid), she reports nausea and gastrointestinal (GI) upset after the ingestion of each dose. How can these GI effects be minimized in I.B.? What other important adverse effects are associated with nitrofurantoin?

Nausea is a common complication of nitrofurantoin therapy, and this may affect the patient's adherence with the prescribed regimen. It is unknown whether the mechanism by which nitrofurantoin produces nausea is central or local. Taking nitrofurantoin with food may reduce nausea, either by serving as a buffer or slowing the rate

of absorption and reducing peak concentrations of the drug. The macrocrystalline preparation (Macrodantin®) reduces GI adverse effects through slowing rates of dissolution and absorption and producing lower serum levels. Its disadvantage, however, is four times daily dosing and higher cost than the monohydrate/macrocrystalline preparation. The best-studied and clinically effective dose of nitrofurantoin is 100 mg bid,[20] which I.B. is currently receiving. I.B. should remain on her current product and dose; taking the drug with food should allow her to successfully finish her course of nitrofurantoin.

Several hundred cases of nitrofurantoin-induced acute, subacute, or chronic pulmonary reactions have been reported.[63] Acute toxicity often manifests with a sudden flulike syndrome consisting of fever, dyspnea, and cough within several days of initiating the drug; eosinophilia may also be present. The subacute form (fever and dyspnea) usually occurs after at least a month of exposure. The chronic form tends to be more insidious, with milder dyspnea and low-grade fever. In all forms, rales are common and pulmonary infiltrates may be present on chest radiograph.[63] Discontinuation of nitrofurantoin results in complete symptomatic recovery after several weeks; however, permanent fibrotic changes may persist with chronic pulmonary reactions. Rechallenge with oral nitrofurantoin results in rapid reappearance of pulmonary symptoms in those who have had an acute reaction; therefore, the drug must be avoided in patients with a history of nitrofurantoin-induced pulmonary toxicity.[63]

Peripheral neuropathy may also occur during prolonged nitrofurantoin therapy and is characterized by symmetric dysesthesia and paresthesia in the distal extremities, which progresses in a central and an ascending manner.[53],[64] Neuropathy usually occurs within the first 60 days of chronic nitrofurantoin treatment and is rarely seen during shorter courses of therapy.[53],[64] Symptom severity is not dose related and is generally reversible, although more severe cases may require up to several months to resolve completely. Renal failure is a risk factor for both neurotoxicity and pulmonary toxicity, but neuropathy has also been reported in patients with normal renal function.[53],[64]

FLUOROQUINOLONE USE IN PEDIATRIC INFECTIONS

CASE 71-3

QUESTION 1: C.S. is a 2-year-old female with a history of multiple recurrent UTIs caused by congenital urinary tract abnormalities that have not been corrected. She has had at least nine UTIs since birth and has received multiple courses of antibiotics, including ampicillin, amoxicillin, amoxicillin–clavulanate, and TMP-SMX. She has also been on chronic, low-dose antibiotic prophylaxis with TMP-SMX. C.S. was brought to her pediatrician 48 hours ago with signs and symptoms consistent with a new UTI. Suprapubic aspiration was performed, and urine samples sent for C&S testing at that time; C.S. was empirically begun on amoxicillin–clavulanate pending laboratory test results. C&S results, however, are now available and show $>10^5$ colonies/mL of *P. mirabilis.* The organism is susceptible to ciprofloxacin, gentamicin, and ertapenem and resistant to ampicillin, trimethoprim, TMP-SMX, cephalexin, cefaclor, cefpodoxime, tetracycline, nitrofurantoin, and erythromycin. C.S. has not clinically improved while receiving empiric amoxicillin–clavulanate.

What antibiotic therapy would be most appropriate for continued management of this acute infection in C.S.?

This case illustrates the serious dilemmas caused by antibiotic resistance among uropathogens. The pathogen isolated from C.S. is resistant to all commonly used, orally administered antibiotics that have been proved effective in the treatment of UTI in pediatric patients. Penicillins, cephalosporins, nitrofurantoin, and sulfonamides are frequently recommended for treatment of pediatric UTI; however, multiple past treatment regimens and chronic antibiotic prophylaxis make these agents less suitable for treatment of this new infection in C.S. Although in vitro susceptibility testing does not accurately predict clinical response to therapy in all cases, the risk of treatment failure and poor patient outcome is significantly increased when agents to which isolates are resistant are administered.[58,59] Alternative treatment is required; however, few desirable options exist for C.S.

The recommended duration of antibiotic therapy in C.S. would be at least 2 weeks for the treatment of this complicated and recurrent infection (refer to subsequent sections of this chapter). Although the organism isolated from C.S. is susceptible to gentamicin and this

drug would be effective, parenteral (intramuscular or intravenous [IV]) administration would be required and the lengthy required treatment duration makes this far from ideal. Use of aminoglycosides would also be less desirable because of toxicity concerns. Although ertapenem would also likely be effective, there is relatively little clinical experience with this agent in the pediatric population, and ertapenem would also require parenteral administration for the duration of the treatment regimen.

Fluoroquinolones are contraindicated in children and adolescents younger than 18 years of age because of concerns regarding potential musculoskeletal toxicities in juvenile populations. Although not approved for pediatric use, fluoroquinolones have been formally studied for febrile neutropenia, infectious gastroenteritis, otitis media, bacterial meningitis, and other uses in pediatric patients.[65–68] Use of fluoroquinolones has substantially increased in children and adolescents, most likely owing to resistance to other antimicrobials. Approximately 520,000 prescriptions were written in the United States for patients younger than age 18 years during 2002, including nearly 3000 prescriptions for children younger than 2 years, whereas an estimated 6.2 million additional prescriptions were written for children between 2006 and 2015.[65,66] Several reviews summarized data related to the safety of fluoroquinolones in children. Although tendinopathy or other musculoskeletal toxicities have been recorded, these toxicities were usually mild, reversible, and occurring at rates comparable to that seen in adults.[65,67,68] Based on currently available information and in consideration of antimicrobial resistance, the American Academy of Pediatrics has published recommendations regarding the use of fluoroquinolones in children and adolescents.[65] These indicate that fluoroquinolones may be considered in special circumstances including (a) infections caused by MDR pathogens for which there are no other safe and effective alternatives and (b) times when parenteral therapy is not feasible and no other effective oral agent is available. Treatment of UTI caused by MDR, gram-negative pathogens are specifically mentioned as a potentially appropriate use for fluoroquinolones in pediatric patients.[65]

Selection of a specific agent for the treatment of UTI in C.S. should be based on careful consideration of potential risks and benefits of available antibiotic options. The feasibility, risks, expenses, and inconvenience associated with prolonged (≥2 weeks) parenteral administration of an aminoglycoside or carbapenem are problematic; however, the ease of oral fluoroquinolone administration must be carefully balanced against the possible risks of using these agents in C.S. Clearly, no antibiotic of choice exists for treatment of C.S. and both the providers and the child's parents must be involved in development of an acceptable and well-informed treatment plan.

TREATMENT OF LOWER TRACT INFECTION IN RENAL FAILURE

CASE 71-4

QUESTION 1: K.M., a 55-year-old male with a history of hypertension and chronic renal failure, experiences a UTI. His creatinine clearance, determined from a recent 24-hour urine collection, is 20 mL/minute.

What antimicrobial agent should be prescribed?

The major problem in treating UTI in patients with renal failure is how to achieve adequate urine concentrations of the drug without causing systemic toxicity. The ideal drug would be (a) inherently nontoxic, even at high serum concentrations, making dosage adjustments unnecessary; (b) excreted unchanged in the urine (ie, not metabolized); and (c) eliminated by renal tubular secretion rather than by glomerular filtration. Because renal tubular secretion remains active in all but the most severe cases of renal failure, antibiotics eliminated by this mechanism would reach adequate urinary levels; however, no such ideal drug exists.

Nitrofurantoin and many sulfonamides are substantially metabolized by the liver and generally produce low urine levels in uremic patients. The aminoglycosides are eliminated almost

exclusively by the kidneys, but patients with uremia are at high risk for drug-induced toxicities and alternative agents are usually recommended. Penicillins, cephalosporins, and trimethoprim are partially metabolized by the liver but are also eliminated by the kidney to a significant extent. These agents are suitable for use in renal failure according to the criteria described earlier. Certain fluoroquinolones, specifically ciprofloxacin and levofloxacin, are highly excreted in the urine through a combination of filtration and tubular secretion and reach extremely high urinary concentrations. These agents are also considered safe and effective in the treatment of UTI in patients with renal failure. For suitable antibiotics, appropriate dosing for reduced renal function needs to be considered.

Acute Pyelonephritis

SIGNS AND SYMPTOMS

CASE 71-5

Question 1: L.B., a 45-year-old female with type 1 diabetes mellitus, comes to the emergency department with severe nausea, frequent vomiting, frequent urination, fever, shaking chills, and flank pain. Positive physical findings include a temperature of 103 °F (39.44 °C), a pulse of 110 beats/minute, blood pressure of 90/60 mm Hg, and CVA tenderness. A Gram stain of L.B.'s urine reveals gram-negative rods, and a UA demonstrates glucosuria, macroscopic hematuria, 20 to 25 WBC/LPF, numerous bacteria, and WBC casts. She also has a blood glucose level of 400 mg/dL. L.B. is admitted to the hospital with a diagnosis of acute bacterial pyelonephritis, and routine laboratory tests including a blood chemistry profile, complete blood count with differential, and specimens of urine and blood for C&S are ordered. L.B. is started on IV normal saline, ampicillin 1 g IV every 6 hours, and a sliding scale schedule of regular insulin based on every 6-hour blood glucose levels.

Which signs and symptoms in L.B. are consistent with pyelonephritis?

It is not always possible to differentiate clinically between upper and lower UTIs. Symptoms common in lower UTI often are the only positive findings in upper UTI (ie, subclinical pyelonephritis).[1–5,38,69]

L.B., however, does manifest signs and symptoms of systemic infection consistent with acute bacterial pyelonephritis, including tachycardia, hypotension, fever, nausea and vomiting, shaking chills, flank pain, CVA tenderness, hematuria, and WBC casts. In addition, her diabetes predisposes her to various renal infections, including pyelonephritis.[2–5,69]

Treatment

TRIAGE FOR HOSPITALIZATION

Case 71-5, Question 2: Why was L.B. hospitalized?

Most patients with pyelonephritis have relatively mild infection and can be treated as outpatients. The need for hospitalization often is determined by the patient's social situation and ability to maintain an adequate fluid intake and tolerate oral medications.[2–5,8,20] Patients who experience significant nausea and/or vomiting may not be able to maintain adequate hydration and thus may be at higher risk for cardiovascular complications of infection. Such patients may also require parenteral therapy initially for adequate empirical treatment. Finally, patients such as L.B. with diabetes should be hospitalized because acute pyelonephritis may predispose her to diabetic ketoacidosis.

Although blood cultures are usually obtained in patients with moderate-to-severe pyelonephritis, one study found that blood cultures were of low yield in the setting of acute uncomplicated pyelonephritis. They rarely provided any additional information not already obtained from the urine culture and were not helpful in the clinical management of such cases.[70] Blood cultures may be positive in up to 25% of patients with severe or complicated pyelonephritis, however, and they are still recommended for hospitalized patients such as L.B.[2–5,69,70]

ANTIMICROBIAL CHOICE FOR PYELONEPHRITIS

Case 71-5, Question 3: Was ampicillin appropriate treatment for L.B.?

Ampicillin is not an appropriate choice for L.B. because patients with diabetes (and patients treated with corticosteroids) are susceptible to colonization with unusual or more resistant organisms. As with lower tract UTI, pyelonephritis is often classified as uncomplicated or complicated. L.B.'s infection would be classified as a complicated infection because of her underlying diabetes.[2–5,8,20,69]

E. coli remains the predominant pathogen in complicated pyelonephritis, but other gram-negative organisms (eg, *Klebsiella*, *Proteus*, *Pseudomonas*) are frequently found.[2–5,8] Because L.B. is acutely ill and has gram-negative organisms in her urine, she should be treated with an antibiotic that has a better spectrum of activity against gram-negative organisms. Because of high rates of ampicillin resistance among common uropathogens, ampicillin and amoxicillin are inappropriate as empirical therapy for UTI, including pyelonephritis.[20] Current IDSA/ESMID recommendations for the initial oral management of acute pyelonephritis are shown in Table 71-3. Because L.B. is hospitalized, broad-spectrum parenteral antibiotics appropriate for initial therapy include third-generation cephalosporins (eg, ceftriaxone), fluoroquinolones (eg, ciprofloxacin, levofloxacin), extended-spectrum penicillins (eg, piperacillin–tazobactam), or carbapenems.[2–5,8,20] Aminoglycosides may be used empirically as either monotherapy or in combination with various β-lactams: in combination with ampicillin to provide better activity against suspected enterococci, or together with cephalosporins or piperacillin–tazobactam to provide enhanced gram-negative activity.[20] The choice of a specific regimen is based on local susceptibility patterns and should be tailored according to C&S test results.[20] It is not always necessary to initially treat patients with antipseudomonal therapy; thus, agents such as ceftriaxone with little activity against *Pseudomonas* are often appropriate as initial therapy in patients such as L.B.[4,8,20] Most hospital laboratories can report C&S results within 48 hours, and, accordingly, initial antibiotics can be replaced with more specific ones.

SERUM VERSUS URINE CONCENTRATIONS

CASE 71-5, QUESTION 4: Is it necessary to achieve bactericidal concentrations of antimicrobials in the serum, or are high urinary concentrations adequate for L.B.? How long should she be treated? How should therapeutic success be determined?

In patients with pyelonephritis and infection of the renal parenchyma, adequate tissue concentrations of antimicrobial agents are necessary. Therefore, antibiotics that achieve bactericidal concentrations in serum and kidney tissues as well as in the urine should be selected.[20,71] Patients requiring hospitalization should be treated with parenteral antibiotics until fluids and medications can be taken orally and the patient is symptomatically improved and afebrile for 24 to 48 hours.[2–5,38] This should be followed with a course of oral antibiotics for a total duration of antimicrobial therapy for ~14 days; less severe infections not requiring hospitalization are usually treated with 7- to 14-day courses, depending on the specific agent chosen.[20,38] Although it is customary to observe the patient in the hospital for 24 hours after switching from parenteral to oral antibiotics before discharge, this is probably of limited benefit.[2–5,8,38] Specimens for C&S testing should be obtained on the second day of therapy (to rule out treatment failure), 2 to 3 weeks after the completion of therapy, and again at 3 months.[1,4]

For patients who have relapsed after 14 days, retreatment for 6 weeks usually is curative. There have been reports of successful retreatment of relapsed infection with only 5 days of treatment[70]; however, longer courses are recommended.[4,8,70]

ORAL THERAPY FOR PYELONEPHRITIS

CASE 71-5, QUESTION 5: Would oral therapy have been appropriate for the initial treatment of acute pyelonephritis in L.B.?

Patients with mild, acute pyelonephritis (no nausea, vomiting, or signs of sepsis) can be treated with oral antibiotics such as fluoroquinolones for 5 to 7 days, or with TMP-SMX for 14 days.[2–5,20] Oral fluoroquinolones are preferred agents for initial empirical therapy of acute pyelonephritis in patients not requiring hospitalization because of lower resistance rates among common uropathogens compared to TMP-SMX, and higher rates of clinical and microbiological efficacy compared to β-lactams.[20] Fluoroquinolones may be particularly useful for patients potentially infected with resistant organisms because of their excellent in vitro activity against gram-negative organisms and high kidney tissue concentrations (2- to 10-fold greater than serum).[38,62] However, fluoroquinolone resistance and risk of inappropriate initial therapy may be more common in certain geographic areas. If fluoroquinolone resistance among *E. coli* exceeds 10%, treatment for acute pyelonephritis should be initiated with an IV dose of extended-spectrum cephalosporin (ie, ceftriaxone) or an aminoglycoside, until C&S test results are known (Table 71-3).[20,38] Oral agents such as amoxicillin–clavulanate, cefuroxime, cefpodoxime proxetil, or cefdinir also can be used in this setting, but the most recent guidelines suggest that oral β-lactams are less effective than are other available options and their use is discouraged as first-line treatment options.[20,38]

Patients such as L.B. with evidence of bacteremia (eg, fever, shaking chills) or sepsis (eg, hypotension) should be hospitalized and treated with parenteral antibiotics[4,8,20] (see **Table 71-4**). L.B.'s frequent vomiting and potential inability to receive oral antibiotics would also make initial therapy with parenteral antibiotics more favorable. Although L.B. will be initially treated with parenteral antibiotics, early switch to oral therapy after as few as 1 to 4 days of treatment is recommended; clinical outcomes with oral antibiotics are similar to those achieved with continued parenteral therapy (ie, ≥5 days).[38,72]

Table 71-4
Parenteral Antimicrobial Agents Commonly Used in the Treatment of Urinary Tract Infections

Class	Drug	Average Adult Total Daily Dose[a]		Usual Dosage Interval[b]	Comments
		UTI	Maximum Dose		
Penicillins	Ampicillin	2–4 g	8 g	Every 4–6 hours	Use should be based on local susceptibility patterns.
	Ampicillin–sulbactam	6 g	12 g	Every 6 hours	
	Piperacillin–tazobactam	12 g (piperacillin component)	16 g (piperacillin component)	Every 6 hours	
First-generation cephalosporins	Cefazolin	1–3 g	6 g	Every 8–12 hours	More effective than second- or third-generation cephalosporins against gram-positive organisms
Second-generation cephalosporins	Cefuroxime	2.25 g	4.5 g	Every 8 hours	Intermediate between first- and third-generation cephalosporins against gram-negative organisms
Third-generation cephalosporins	Cefotaxime	3–4 g	8 g	Every 6–8 hours	Better coverage than first- and second-generation cephalosporins against gram-negative organisms Ceftazidime and cefepime most effective against *Pseudomonas*. All generations of cephalosporins ineffective against *Enterococcus faecalis* and methicillin-resistant staphylococci. *(Exception: ceftaroline; see subsequent text.)*
	Ceftriaxone	1 g	1g	Every 24 hours	
	Ceftazidime	1–3 g	6 g	Every 8 hours	

Class	Drug	Average Adult Total Daily Dose[a]		Usual Dosage Interval[b]	Comments
		UTI	Maximum Dose		
Fourth-generation cephalosporins	Cefepime	1–2 g	4 g	Every 12 hours	Ceftaroline has activity against methicillin-resistant staphylococci.
	Ceftaroline	1.2 g	1.2 g	Every 12 hours	
Carbapenems	Imipenem–cilastatin	1 g	2 g	Every 6 hours	The most broad-spectrum coverage of any antibiotics listed. Ertapenem is not active against *Pseudomonas*. Resistance may develop, especially with *Pseudomonas*. Toxic in some pregnant animals
	Meropenem	1.5–3 g	3 g	Every 8 hours	
	Ertapenem	0.5–1 g	1 g	Every 24 hours	
Monobactam	Aztreonam	1–3 g	6–8 g	Every 8–12 hours	Active against gram-negative aerobic pathogens, including *Pseudomonas* sp.
Aminoglycosides	Gentamicin	3–5 mg/kg	5 mg/kg	Every 24 hours	Potent against gram-negative bacteria including *Pseudomonas*. Associated with possible eighth nerve toxicity in the fetus. Amikacin should be reserved for multiresistant bacteria.
	Tobramycin	3–5 mg/kg	5 mg/kg	Every 24 hours	
	Amikacin	7.5 mg/kg	15–20 mg/kg	Every 24 hours	
Quinolones	Ciprofloxacin	400–800 mg	800 mg	Every 12 hours	Use for resistant organisms. Change to oral therapy when indicated.
	Levofloxacin	500 mg	750 mg	Every 24 hours	

UTI, urinary tract infection.

[a]Higher doses are reserved for severe, potentially life-threatening infections or infections caused by organisms with reduced antibiotic susceptibilities and limited treatment options.

[b]Assuming normal renal function. Dose adjustments necessary in patients with compromised renal function (see Chapter 62, Principles of Infectious Diseases).

Sources: Sobel JD, Brown P. Urinary tract infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier, Inc.; 2020:962–989; Hooton TM Jr. Uncomplicated urinary tract infection. *N Engl J Med*. 2012;366:1028–1037; Kolman KB. Cystitis and pyelonephritis: diagnosis, treatment, and prevention. *Prim Care Clin Off Pract.* 2019;46:191–202; Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am.* 2008;35:1–12; Johnson JR, Russo TA. Acute pyelonephritis in adults. *N Engl J Med.* 2018;378:48–59; Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis.* 2011;52:e103–e120; Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-

resistant gram-negative bacteria causing urinary tract infections: a review. *J Chemother.* 2017;29(Suppl 1):2–9; Perletti G, Magri V, Cai T, Stamatiou K, Trinchieri A, Montanari E. Resistance of uropathogens to antibacterial agents: emerging threats, trends, and treatments. *Arch Ital Urol Androl.* 2018;90(2):85–96.

RECURRENT URINARY TRACT INFECTIONS

Relapse Versus Reinfection

CASE 71-6

QUESTION 1: T.W. is a 28-year-old female with a history of recurrent UTIs who now exhibits a new *E. coli* UTI. Her last episode occurred 5 months ago. Her current infection is treated with TMP-SMX for 10 days. A repeat UA was scheduled but she canceled her appointment because she "felt fine." Twelve weeks later, she returns to the clinic with signs and symptoms of another UTI. The only other medication she has taken is an oral contraceptive.

Why would C&S testing of a urine sample be especially useful at this time?

Recurrent infections develop in ~20% to 30% of females with acute cystitis.[3,5,34,38,73,74] Repeat C&S data should help determine whether this infection represents a relapse or a reinfection. Relapse refers to a recurrence of infection caused by the same microorganism that was present before initial therapy. Most relapses occur within 1 to 2 weeks of the completion of therapy and are caused by persistence of the organism in the urinary tract. Relapses often are associated with an inadequately treated upper UTI (eg, medication nonadherence), structural abnormalities of the urinary tract, or acute or chronic bacterial prostatitis in males.[1,34,38,73,74]

Reinfection implies recurrence of UTI with a different organism than was present before therapy. Reinfections can occur at any time during or after the completion of treatment, but most appear several weeks to several months later. Approximately 80% of recurrences are caused by reinfection.[1,34,38] Reinfection is generally caused by introital colonization with Enterobacterales from the lower intestinal

tract[1]; of these, *E. coli* is the most common. Certain *E. coli* strains have been shown to adhere to vaginal epithelial cells and, in females with recurrent UTI, adherence of these organisms to epithelial cells is increased.[26] Considering T.W. was symptom free for 8 weeks suggests that this is a reinfection, rather than a relapse. Patients with reinfection should be evaluated for modifiable predisposing factors such as use of a diaphragm with or without spermicides. Other risk factors for frequent reinfections include anatomic abnormalities, undiagnosed glucose intolerance, or diabetes.

Treatment for Reinfection

Case 71-6, Question 2: Pending the C&S test results, what therapy should be instituted in T.W.?

T.W. has a history of recurrent infections and now probably has a reinfection. Because reinfection is not caused by failure of previous therapy, TMP-SMX may be a reasonable choice once again. The probability that a resistant organism will be responsible for the infection increases when the interval between infectious episodes is short. If several months elapse between each episode of antimicrobial therapy, normal fecal bacterial flora becomes reestablished, and this reduces the risk of infection with resistant pathogens.

The alteration of fecal flora caused by the sulfonamides makes these drugs poor choices for repeated use in cases of frequent reinfection, especially when C&S results are unknown. The development of bacterial resistance also may limit the usefulness of these agents for chronic antimicrobial therapy.[20,34,38,73–75] However, because T.W.'s most recent infection was 12 weeks ago and the UTI before that was 5 months earlier, TMP-SMX would again be a reasonable choice at this time.

Case 71-6, Question 3: If T.W. exhibited an adverse reaction to TMP-SMX, what are the other therapeutic alternatives?

Nitrofurantoin is highly effective against *E. coli* with relatively low rates of resistance (<10%) in most geographic areas. It does not significantly alter the fecal or introital flora, and the emergence of resistance in previously sensitive strains does not often occur.[20,38,73–75] Therefore, it is generally a useful agent for the treatment of recurrent *E. coli*, *S. saprophyticus*, and *Enterococcus* infections.[20]

The fluoroquinolones also are useful in this setting, especially in geographic areas with high rates of TMP-SMX resistance.[34,72,74] However, their widespread use should be discouraged for reinfections as in T.W. in light of their high cost and concern regarding selection of resistant organisms.[20,34,74] Cephalosporins (eg, cefpodoxime proxetil) and trimethoprim have also been recommended as alternative agents in this setting.[3,73,74]

Antibiotic Selection for Treatment of Relapse

Case 71-6, Question 4: Greater than 10^5 bacteria/mL of *P. mirabilis*, sensitive to amoxicillin/clavulanate and TMP-SMX are cultured from T.W.'s urine. One week after completing her second course of TMP-SMX therapy, signs and symptoms of a UTI again appear. Pending C&S results, TMP-SMX is again prescribed. Is this still a reasonable medication for T.W. at this time?

Because the *P. mirabilis* cultured during the last recurrence was still susceptible to TMP-SMX, this agent would again be a reasonable choice until C&S test results are available. Alternatively, use of a different agent (eg, amoxicillin/clavulanate, nitrofurantoin, fluoroquinolone) could be considered because the relapse occurred within 1 week of completing the previous treatment and resistance may have developed.[5,34,75] Additional reasons for treatment failure, including failure to adhere to previously prescribed medication regimens, should also be investigated in patients with apparent recurrent infections.

Case 71-6, Question 5: How long should antibiotic therapy be continued in T.W. for her relapsed infection?

The duration of therapy for relapsing infections usually is 14 days. In patients who relapse after a second 2-week course of therapy, treatment for 6 weeks should be instituted.[1–3,34] If relapse occurs after a 6-week course, some experts recommend longer courses of 6 months to 1 year.[1–3] These prolonged courses should be reserved for children, adults with continuous symptoms, or adults at high risk for experiencing progressive renal damage. Asymptomatic adults without evidence of obstruction should not receive these longer courses. T.W. should be treated for at least 2 weeks and perhaps as long as 6 weeks.[34,74,75]

Case 71-6, Question 6: Although T.W. tolerated TMP-SMX well during her previous treatment, on this occasion she experiences significant nausea and vomiting after taking the medication. Would trimethoprim alone be an appropriate substitute for TMP-SMX in the treatment of T.W.'s infection?

Trimethoprim alone, and in combination with sulfamethoxazole, is active in vitro against many Enterobacterales associated with UTI and is an effective alternative to TMP-SMX in the management of both acute and chronic UTI.[1–3,5] It would be especially appropriate for T.W. because GI intolerance to TMP-SMX is most commonly attributed to the sulfamethoxazole component, and trimethoprim is associated with a lower incidence of side effects. Some concern exists for the potential development of resistant organisms, but studies using trimethoprim alone have failed to demonstrate a significant increase in bacterial resistance.[73,75] Trimethoprim is used for the treatment of acute, uncomplicated UTI in an oral dosage of 200 mg/day.

Chronic Prophylaxis

Case 71-6, Question 7: T.W. was treated successfully with trimethoprim for 6 weeks. Is prophylactic antimicrobial therapy indicated? If so, how long should it be continued?

Cases of chronic UTI in adult patients may be managed by treating each recurrent infection with an appropriate antibacterial drug or by administering chronic, low-dose prophylactic therapy. The frequency of urinary infections is the main determinant of whether chronic suppressive therapy should be used.[1,34,38,73–75] Long-term prophylactic therapy clearly reduces the frequency of symptomatic infections in nearly all patients.[15,34,38,73–75]

From a cost-effectiveness standpoint, females having more than one episode of cystitis per year may benefit from antimicrobial prophylaxis.[73] For females with three or more episodes of cystitis per year, prophylaxis clearly is more cost-effective than treating individual infections. Therefore, it is recommended that chronic antimicrobial prophylaxis may be considered in any adult patient with two or more episodes of UTI per year.[2,34,38,73–75]

The duration of prophylactic therapy also depends on the frequency of infection. Females with three or more UTIs in the 12 months before a 6-month course of antimicrobial prophylaxis have a significantly higher recurrence rate (75%) in the 6 months after prophylaxis is stopped compared to females with only two infections in the 12 months before prophylaxis (26% recurrence rate).[38] Therefore, prophylaxis should be continued for 6 months in patients with fewer than three UTIs per year, and for at least 12 months in adult patients with three or more UTIs per year.

Before initiating chronic antimicrobial suppressive therapy, active infections must be completely eradicated with a full course of appropriate antibiotic therapy. The low doses of antimicrobials used for chronic prophylaxis suppress bacterial growth but do not eliminate active infection. Furthermore, surgically correctable anatomic abnormalities that predispose the patient to recurrent infections (eg, obstruction, stones) should be ruled out.[34,38,73,75] Age also should be considered when contemplating chronic antimicrobial

therapy. An asymptomatic, elderly patient taking many other medications is usually not an ideal candidate for chronic prophylactic treatment because of problems of nonadherence, cost, and potential drug interactions or toxicities.[73,75] Younger patients, however, are good candidates for long-term suppressive therapy.[74,75]

Because T.W., a 28-year-old female, has had at least three UTIs in the past few months, has undergone extensive evaluation, and has just been successfully treated with a standard course of trimethoprim, a 12-month course of antimicrobial prophylaxis would seem reasonable. She also should be evaluated at regular intervals for recurrent UTI and for the development of resistant organisms.

Although the foregoing discussion applies to antimicrobial prophylaxis in adults, the use of long-term prophylaxis of recurrent UTI in children remains controversial. Individual studies have shown conflicting outcomes with respect to whether risk of recurrent UTI was significantly decreased. However, prophylaxis was associated with substantially increased risk of infection caused by resistant bacteria without any benefits related to decreased hospitalization, secondary infections, or evidence of parenchymal disease on renal scans.[76–80] A meta-analysis of 11 studies evaluating long-term antibiotic prophylaxis in children found no significant benefits of antibiotic administration overall.[76–80] Current recommendations are that long-term antimicrobial prophylaxis should not be routinely recommended for prevention of recurrent UTI in children.[1–3,73,74,76–80]

Case 71-6, Question 8: What drugs could be appropriately used for long-term suppressive therapy in T.W.?

Although numerous drugs are used for prophylaxis, TMP-SMX may be the drug of choice for chronic antimicrobial therapy owing to extensive experience, proven efficacy, infrequent toxicities, and low cost.[34,38,73–75] TMP-SMX also has the effect of decreasing vaginal colonization with uropathogens.[34,75] TMP-SMX single strength, either one-half or one full tablet daily, is commonly prescribed for chronic UTI prophylaxis and is an effective, well-tolerated, and convenient

prophylactic regimen.[34],[38],[73–75] Successful prophylaxis is significantly decreased in patients with urologic abnormalities or renal dysfunction. Also, infections that are not eradicated by a short-term therapeutic trial of TMP-SMX are not likely to respond to a long-term prophylaxis regimen.[38],[73] Finally, introital colonization with enterococci may occur in patients taking chronic TMP-SMX.[75]

Fluoroquinolones are effective for chronic suppressive therapy but should be used only when antimicrobial resistance or intolerance to other recommended drugs is present. Cephalosporins also have been recommended, but they are best reserved for patients intolerant to or failing prophylaxis with other agents.[73],[75]

When selecting a drug for chronic antimicrobial therapy, it is important to consider efficacy, the likelihood that resistant organisms will develop, long-term toxicity, convenience, and cost to the patient. The most commonly used agents are listed in **Table 71-5**.

Table 71-5

Antimicrobial Agents Commonly Used for Chronic Prophylaxis Against Recurrent Urinary Tract Infections

Agent	Adult Dose	Comments[a]
Nitrofurantoin	50–100 mg nightly	Contraindicated in infants <1 month of age. *To be taken with food or milk. May cause brown or rust-yellow discoloration of urine.*
Trimethoprim	100 mg nightly	Not recommended in children age <12 years.
Trimethoprim 80 mg + sulfamethoxazole 400 mg	0.5–1 tablet nightly *or* 3/week	Not recommended for use in infants ≤ 2 months. *To be taken on an empty stomach with a full glass of water. Photosensitivity may occur.*
Norfloxacin	200 mg/day	*To be taken on an empty stomach with a full glass of water; give at least 1 hour before or 2 hours after meal or dairy products. Do not coadminister with antacids or supplements/multivitamins containing di- or trivalent ions (give 2 hours before or after).* Monitor INR in patients receiving warfarin.

Cephalexin	125–250 mg/day	
Cefaclor	250 mg/day	

INR, international normalized ratio.

[a]Includes unique patient consultation information in italics.

Sources: Sobel JD, Brown P. Urinary tract infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier, Inc.; 2020:962–989; Hooton TM Jr. Uncomplicated urinary tract infection. *N Engl J Med*. 2012;366:1028–1037; Kolman KB. Cystitis and pyelonephritis: diagnosis, treatment, and prevention. *Prim Care Clin Off Pract*. 2019;46:191–202; Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am*. 2008;35:1–12; Wagenlehner FM, Weidner W, Naber KG. Emergence of antibiotic resistance amongst hospital-acquired urinary tract infections and pharmacokinetic/pharmacodynamic considerations. *J Hosp Infect*. 2005;60:191–200; Vouloumanou EK, Rafailidis PI, Kazantzi MS, Athanasiou S, Falagas ME. Early switch to oral versus intravenous antimicrobial treatment for hospitalized patients with acute pyelonephritis: a systematic review of randomized controlled trials. *Curr Med Res Opin*. 2008;24:3423–3434; Kodner CM, Thomas Gupton EK. Recurrent urinary tract infections in women: diagnosis and management. *Am Fam Physician*. 2010;82:638–643.

Based on the available information, T.W. could be switched to TMP-SMX. Although she has a history of GI distress because of this drug, it may not be a problem with the lower doses used for prophylaxis. If she is intolerant, trimethoprim alone, nitrofurantoin, or a fluoroquinolone also should be effective.

Cranberries and probiotics have long been of interest for their potentially beneficial effects in preventing UTI. Cranberries contain known compounds (ie, flavanols, anthocyanidins, proanthocyanidins-tannins) that prevent *E. coli* from adhering to uroepithelial cells in the urinary tract and may also inhibit bacterial motility.[74,80–83] A wide variety of cranberry products (eg, juice concentrate, juice cocktail, cranberry extracts in capsules and tablets) and different dosing regimens have been evaluated in the prophylaxis of UTI, but the overall inconclusive results preclude formal recommendations.[38,74,80–82] A 2012 meta-analysis found benefits of

cranberry-containing products in females (51% reduction in risk of infections), females with recurrent UTI (47% reduced risk of recurrences), and children (67% reduction in UTI risk).[81] However, this analysis also noted that available studies are quite heterogeneous, and the results of the meta-analysis should be interpreted with caution.[81] Recent consensus guidelines from the American Urological Association, Canadian Urological Association, and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (AUA/CUA/SUFU) state that cranberries may be offered for prophylaxis for recurrent UTIs, but this recommendation is conditional (ie, evidence indicates that there is no apparent net benefit or harm) and has a low strength of evidence.[74] Probiotics (particularly *Lactobacillus* strains) may prevent colonization with uropathogens.[38,80–83] Studies of probiotics for prophylaxis, however, are also inconclusive at this time. Lack of standardization of ingredients (ie, purity, dosage strengths) among available products and paucity of well-designed clinical studies are among the reasons for lack of clear recommendations regarding probiotics for this use. Further research is required to clarify unanswered questions regarding the role of cranberries or probiotics in the prevention of UTI.[38,80–83]

Urinary Tract Infection and Sexual Intercourse

CASE 71-7

Question 1: On routine screening, ASB is noted in W.W., a 30-year-old pregnant female in her first trimester. Five years ago, during her first pregnancy, she experienced acute bacterial pyelonephritis, which required hospitalization and treatment with parenteral antibiotics. Since that time, she has had recurrent UTIs, apparently related to sexual intercourse. These subsided when she began taking a single dose of nitrofurantoin after coitus, but she discontinued the practice before this pregnancy because she was afraid of the potential effects of this drug on the fetus.

What is the association between sexual intercourse and the occurrence of UTI?

Studies strongly support an association between sexual intercourse and UTI.[1–3,27] A direct relationship seems to exist between the number of days with intercourse within the previous week and the risk of developing a UTI.[1–3,27] One study found the relative risk of infection in females with 1, 4, and 7 days of intercourse within the previous week to be 1.4, 3.5, and 9.0, respectively, compared with females who were sexually inactive within the previous week. Another study found that the risk of UTI was doubled in females having intercourse more than four times a month compared with those females who did not.[27] Studies also indicate that introital colonization by fecal bacteria has a definite role in recurrent infections related to intercourse. The migration of these colonizing bacteria into the bladder appears to be facilitated during intercourse, but the exact mechanism remains unclear.[1–3] Because UTIs are uncommon in males, transmission of an infection from the male is unlikely. Occasionally, bacteria harbored under the foreskin of an uncircumcised male may be transmitted to his partner through intercourse.[25]

Case 71-7, Question 2: Was it rational to treat W.W.'s repeated infections with a single dose of an antibiotic after intercourse?

Postcoital antibiotic prophylaxis is useful when recurrent UTI results from sexual intercourse. Theoretically, a single dose of an antimicrobial agent produces bactericidal activity in the urine before bacteria have a chance to multiply, and the infection is averted. Patients should be instructed to empty their bladder just after intercourse and before taking the medication to minimize the number of bacteria present in the bladder and to reduce dilution of the drug in the urine. Because most drugs effective for UTI are rapidly excreted by the kidney and quickly reach high urinary concentrations, this regimen is reasonable and decreases the incidence of postcoital infections.[38,74] However, this practice is not recommended in patients with structural abnormalities of the urinary

tract or decreased renal function. Symptomatic infection must be completely treated before beginning prophylaxis.

Depending on the frequency of intercourse, postcoital prophylaxis may result in less antibiotic use compared with continuous prophylaxis. TMP-SMX and nitrofurantoin are the most commonly recommended agents; however, other agents such as fluoroquinolones and cephalexin may be used.[38,74]

Urinary Tract Infection and Pregnancy

Case 71-7, Question 3: Because W.W. is asymptomatic at this time, should treatment be withheld because of her pregnancy?

W.W. should be treated because acute symptomatic lower UTI or pyelonephritis may develop in pregnant females with untreated ASB. A clear cause-and-effect relationship between UTI and maternal or infant risk has not been definitely established.[84,85] However, treatment with an appropriate antimicrobial agent is currently recommended for all pregnant patients with significant bacteriuria, even when asymptomatic.[13,28,29]

The penicillins and cephalosporins are considered safe for use during pregnancy. However, these drugs, along with the others listed in Tables 71-3 and 71-5, cross the placental barrier; thus, the risk of toxicity or teratogenicity to the fetus must always be considered before deciding to treat a pregnant patient with a UTI.[88] Nitrofurantoin is often recommended during pregnancy because teratogenic effects have not been observed clinically and W.W. was previously using this agent for prophylaxis.[13,28,29,86] In vitro and retrospective investigations, however, suggest a mutagenic potential during the first trimester.[87,88] Although only small amounts of nitrofurantoin have been detected in breast milk, the drug could cause hemolytic anemia in a G6PD-deficient nursing infant.[88] Nitrofurantoin should therefore be used with caution during the first and late third trimesters. The fluoroquinolones are contraindicated in

pregnancy because of the arthropathy observed in immature animals.[62,88]

In this case, a cephalosporin or fosfomycin could be safely prescribed for treatment of W.W. Trimethoprim alone and TMP-SMX should be avoided in the first trimester because of the folate antagonist actions of trimethoprim and concerns regarding neural tube and cardiovascular defects potentially associated with maternal folate deficiency during the first trimester.[88] Although TMP-SMX may be an option during the second trimester, it should not be used after 32 weeks of gestation because of concerns regarding neonatal hyperbilirubinemia, jaundice, and kernicterus. W.W. was correct in discontinuing her nitrofurantoin before pregnancy because the risk to the fetus, although small, tends to offset the advantage of antimicrobial prophylaxis. W.W. must receive proper follow-up care.

Case 71-7, Question 4: For how long should W.W. be treated?

Few studies have compared single-dose and 3-day therapy with conventional 7-day therapy in pregnant patients. Although some clinical trials have shown single-dose therapy to effectively eradicate bacteriuria in pregnancy, most data suggest that cure rates of single-dose therapy were lower than 7- to 10-day therapy.[13,27–29,85] Therefore, similar to other populations, it is recommended that pregnant patients receive either a 3-day regimen or a prolonged (5- to 10-day regimen).[13,27–29,85]

Irrespective of the duration of therapy, appropriate follow-up of patients is crucial. Clinicians must document elimination of pathogens 1 to 2 weeks after therapy and follow up the patient monthly for the remainder of gestation. If bacteriuria recurs, therapy should be given for relapse or reinfection and the patient evaluated radiologically for structural abnormalities.[1,27]

ASYMPTOMATIC BACTERIURIA

Antibiotic Treatment

CASE 71-8

QUESTION 1: A.K., an asymptomatic 6-year-old female, is found to have significant bacteriuria on routine screening.

Should she be treated with an antimicrobial agent?

The treatment of patients with ASB depends on the clinical setting in which it is found. Recommendations for management of ASB are thus based on specific age, sex, and clinical characteristics and should consider the risk factors for development of acute UTI and subsequent long-term complications.[1,10,13,27–29] Generally, patients who benefit most from antibiotic treatment are those with urinary tract structural abnormalities, immunosuppressive therapy, and procedures requiring urinary tract instrumentation or manipulation.[1–3,13] Short-course regimens (ie, single-dose or 3-day ones) are usually recommended when treatment is desired,[3] although longer regimens have also been recommended.[13]

Although UTIs in infants and preschool children (predominantly females) are occasionally associated with renal tissue damage, its incidence is as low as 0.4% in children with previously normal renal function, and the overall risk of UTIs in this population is controversial.[9,89–91] However, ASB of childhood may be a manifestation of an anatomic or a mechanical defect in the urinary tract. Therefore, it should be evaluated fully. Because most cases of renal scarring as a result of bacteriuria occur within the first 5 years of life, it is controversial whether treatment should be limited to infants and preschool children or whether children should be treated regardless of age. Screening for bacteriuria in children and treating those with positive culture results, regardless of their clinical presentation, seems reasonable and is frequently recommended.[89–91] Treatment of A.K. seems prudent because any renal damage resulting from ASB generally occurs during childhood. Should the decision be made to treat, principles of therapy are similar to those for symptomatic infections.

Pregnant Patients, the Elderly, and Other Adult Populations

CASE 71-9

Question 1: B.F., a 65-year-old female, is found to have significant bacteriuria on routine screening before an elective surgery not involving the urinary tract. She has no symptoms associated with the bacteriuria.

Should she be treated with an antimicrobial agent? What other population groups should be treated for ASB?

Without urinary tract obstruction, UTIs in adults rarely lead to progressive renal damage.[3,5] Therefore, ASB does not require treatment in most adult patients without evidence of mechanical obstruction or renal insufficiency. As previously discussed, antimicrobial therapy is appropriate during pregnancy because as many as 40% of pregnant females with ASB later develop symptomatic UTI, particularly pyelonephritis.[13] In addition, studies have confirmed associations between acute pyelonephritis during pregnancy with increased rates of preterm labor, premature delivery, and lower birth-weight infants.[27] The treatment of ASB in pregnancy is therefore justified to decrease the risk of associated complications.[13]

Bacteriuria in elderly individuals such as B.F. is common; about 20% of all females and 10% of all males ages 65 years and older have bacteriuria.[14–16] Although bacteriuria in this population often leads to symptomatic infection, clinical studies have not consistently documented beneficial outcomes in treated patients compared with untreated patients.[13,15] Consequently, therapy is not recommended for the asymptomatic older patient because the expense, side effects, and potential complications of drug therapy appear to outweigh the benefits.[13,15] Patients experiencing symptomatic infections should be treated as usual.

The treatment of ASB in females with diabetes does not reduce complications and is not currently recommended.[13,28]

HOSPITAL-ACQUIRED ACUTE URINARY TRACT INFECTION

CASE 71-10

QUESTION 1: P.M., an alert, 70-year-old female with chest pain, was hospitalized to rule out acute myocardial infarction. This is her third hospitalization for chest pain in the past 6 months. A urinary catheter was temporarily placed as part of her routine medical care. Two days after admission and one day after removal of the urinary catheter, she reported burning on urination and bladder pain. TMP-SMX double-strength, one tablet bid was ordered after the microscopic examination of the urine indicated a UTI.

Was this empiric therapy appropriate?

Hospital-acquired (or nosocomial) UTIs occur in about 500,000 patients per year, and most are associated with the use of indwelling bladder catheters. Approximately 10% to 30% of catheterized patients experience infection.[23] Complications of CAUTI are considerable and include bloodstream infections with increased mortality rates, increased hospital length of stay, and increased hospital costs. Prevention is the best way to manage nosocomial UTI, but antibiotic treatment is usually initiated in hospitalized patients who exhibit UTI symptoms.

The susceptibility of hospital-acquired pathogens to antimicrobial agents differs from community-acquired bacteria, and these susceptibilities frequently vary from one hospital to another. Therefore, the microbiology department of a particular hospital should be consulted to determine current trends in the antibiotic susceptibility of bacteria acquired in that setting. In general, *E. coli* is still the predominant urinary tract pathogen. An increased proportion of infections is caused, however, by other gram-negative bacteria such as *Proteus* and *Pseudomonas*, gram-positive pathogens such as *Staphylococcus* and *Enterococcus*, and yeast (eg, *Candida*).[21,23]

Repeated courses of antibiotic therapy, anatomic defects of the urinary tract, old age, increased length of hospital stay, and repeated hospital admissions are associated with a higher incidence of

infection with antibiotic-resistant organisms.[21,23,92] *Pseudomonas*, *Proteus*, *Providencia*, *Morganella*, *Klebsiella*, *Enterobacter*, *Citrobacter*, and *Serratia* and ESBL uropathogens are particularly difficult to eradicate because they usually are less susceptible to commonly used antimicrobial agents.

P.M. is elderly, hospitalized, and has been repeatedly exposed to potentially resistant organisms during her previous hospitalizations. Oral fluoroquinolones are most commonly used as empiric therapy in this setting because of their greater activity against potentially resistant pathogens compared to TMP-SMX; however, fluoroquinolone use is often discouraged in older patients owing to a greater risk of adverse effects such as central nervous system toxicities and QTc interval prolongation. Therefore, TMP-SMX is an acceptable empirical therapy in P.M. as long as her clinical and laboratory data are appropriately monitored.[21,23,93] A C&S test of P.M.'s urine should be performed and once results are known, therapy promptly changed accordingly. To achieve the most cost-effective therapy, oral agents should be administered to all patients capable of taking medications by mouth, unless the isolated pathogens are resistant to oral medications, or underlying GI dysfunction makes adequate absorption of oral antibiotics questionable.[23,69,93] The recommended duration of antibiotic therapy for patients such as P.M., who present with mild-to-moderate symptoms, is 5 to 7 days; patients who do not respond promptly to treatment may be treated for a total of 10 to 14 days.[23]

In seriously ill patients with possible sepsis, broad-spectrum parenteral antibiotics with activity against *P. aeruginosa* are usually preferred as initial therapy (Table 71-4). In general, antipseudomonal β-lactam antibiotics remain the empiric drugs of choice for nosocomial urologic sepsis.[93] Because many patients may be at risk for infection caused by MDR pathogens, C&S test results should carefully monitored, and therapy adjusted accordingly. Although combination therapy may be useful initially in patients with neutropenia with urologic sepsis, it should be narrowed to single-agent therapy once culture results are available.[93] The

recommended duration of antibiotic therapy in seriously ill patients is 10 to 14 days.[23]

Catheter-Associated Urinary Tract Infection

CASE 71-11

QUESTION 1: J.W., an 18-year-old female, was hospitalized after a diving accident that resulted in a spinal cord injury with paralysis. Included among several initial interventions was insertion of an indwelling catheter with a closed drainage system because of bladder incontinence. Two weeks after admission to the hospital, J.W. has developed ASB.

Should this be treated?

A systemic antibiotic selected specifically for the infecting organism will temporarily result in sterile urine. Reinfection, often by a resistant organism, then occurs in 30% to 50% of these cases if closed drainage catheterization is continued during therapy.[1,23] For this reason, it generally is recommended that systemic antimicrobial therapy be initiated after or just before catheter removal in those patients in whom antibiotics are needed.[1,23,94] Because long-term catheterization is necessary in many patients and because bacteriuria is an inevitable consequence, asymptomatic patients (such as J.W.) should be left untreated to avoid the complications of recolonization and potential infection with resistant organisms.[1,13,23,94] Therapy must be started, however, if fever, flank pain, or other symptoms indicative of an actual UTI develop.[1,23]

CASE 71-11, QUESTION 2: Is systemic antimicrobial prophylaxis useful for J.W.?

The benefits of systemic antibiotics in preventing CAUTI are not clear. Studies using closed drainage systems with diligent catheter care indicate that systemic antibiotics decrease the daily and overall incidence of infection in patients with sterile urines before catheterization.[35,36] The preventive effect of antimicrobials is greatest

for short-term catheterizations or during the first 4 to 7 days of long-term catheterization.[35],[36] Thereafter, the rate of infection increases despite antibiotics. Although the overall infection rate remains lower than in untreated patients, the emergence of resistant organisms is significant. Therefore, in deciding to use systemic antimicrobials, it is important to consider the patient's underlying diseases, risk factors, probable duration of catheterization, and potential complications of drug toxicity or resistant organisms that can result from the chronic use of antimicrobials. Because long-term catheterization is anticipated for J.W., antimicrobial prophylaxis for J.W. is not recommended.[23]

Case 71-11, Question 3: J.W. eventually regains urinary continence and the catheter is removed. However, 2 days after removal of the catheter, she still has ASB. How should she be managed?

Because ASB in patients with urinary catheters is very common (~25% with short-term catheterization and virtually 100% long term) but is associated with few complications, antibiotic therapy for ASB is not recommended as long as the catheter remains in place.[23] However, antibiotic treatment may be considered in asymptomatic females with catheter-acquired bacteriuria that persists >48 hours after catheter removal.[13],[23] Such patients can be treated with either a single large dose or a 3-day regimen of TMP-SMX, even if the patient is asymptomatic.[13],[23],[24] Older females (older than 65 years) probably should be treated with a 10-day course; however, the optimal duration in this age group is unknown. Whether these same treatment regimens are advisable in male patients requires further study.[23]

PROSTATITIS

Incidence, Prevalence, and Epidemiology

Prostatitis is an acute or chronic inflammatory condition affecting the prostate, with ~5% of cases being caused by proven bacterial infections.[11,12] Other noninfectious types of prostatitis include chronic calculus prostatitis, nonbacterial prostatitis, and prostatodynia.[11,12] Chronic bacterial prostatitis, defined as prostatitis in which symptoms persist for at least 3 months, is one of the most common causes of recurrent UTI in males. The lifetime probability of a male being diagnosed with prostatitis is >25%; recurrence rates reportedly range from 20% to 50%.[11,12] Approximately 5% of males with acute prostatitis will experience chronic infection.[11]

Etiology, Pathogenesis, and Predisposing Factors

ACUTE BACTERIAL PROSTATITIS

Acute bacterial prostatitis in most patients probably begins as an ascending infection of the urethra. A simple UTI then eventually involves reflux of infected urine into the ejaculatory and prostatic ducts through the prostate gland, where bacteria are difficult to eradicate.[12] Acute prostatitis may also result from urethral stricture or after instrumentation of the urinary tract or prostate biopsy, especially in the presence of bacteriuria at the time of the procedure.[12] Bacterial prostatitis is predominantly caused by aerobic gram-negative bacilli, with *E. coli* causing 50% to 90% of cases. Other Enterobacterales such as *Proteus* and *Klebsiella* account for an additional 10% to 30% of cases, followed by *Enterococcus* (5% to 10%) and *Pseudomonas* (>5%); less common causes include staphylococci, streptococci, and atypical organisms such as *C. trachomatis*, *T. vaginalis*, and *Ureaplasma urealyticum*.[11,12]

CHRONIC BACTERIAL PROSTATITIS

Chronic prostatitis is commonly associated with spinal cord injuries, infectious stones, anatomic or physiologic abnormalities of the urinary tract such as obstruction or voiding dysfunction, and immune dysfunction. However, recurrent infections are also commonly

caused by relapses of acute prostatitis due to persistent bacteria in the prostate.[11,12] Normally, males secrete a prostatic antibacterial factor; however, this substance is often absent or significantly reduced in males with chronic prostatitis. The most common pathogens isolated from chronic bacterial prostatitis are *E. coli* (>80% of cases) and other gram-negative bacilli, although atypical bacteria have also been more commonly reported in chronic prostatitis compared to acute infections.[11,12]

Clinical Presentation and Diagnosis

ACUTE BACTERIAL PROSTATITIS

Acute bacterial prostatitis is characterized by the sudden onset of chills and fever; perineal and low back pain; urinary urgency and frequency; nocturia, dysuria, and generalized malaise; and prostration. Patients may also report myalgias, arthralgias, and symptoms of bladder outlet obstruction. Rectal examination usually discloses an exquisitely tender, swollen prostate that is firm and warm to the touch. Culture of the voided urine generally identifies the pathogens. In patients with acute bacterial prostatitis, prostatic massage (see following discussion) should be avoided because of patient discomfort and the risk of bacteremia.[11,12] The diagnosis of acute prostatitis is therefore usually based on clinical presentation and physical examination.

CHRONIC BACTERIAL PROSTATITIS

The clinical manifestations of chronic bacterial prostatitis are highly variable, and many patients are asymptomatic. The disease usually is suspected when a male patient treated for UTI or acute prostatitis relapses. The diagnosis of chronic prostatitis is confirmed by examination of expressed prostatic secretions.[11,12] To ensure accurate localization (ie, to distinguish prostatic from urethral bacteria), segmented urine samples are taken. The first 10 mL of collected voided urine represents the urethral sample, the midstream urine represents the bladder sample, and the first 10 mL voided

immediately after prostatic massage represents the prostate sample. When the bladder sample is sterile or nearly so, bacterial prostatitis is diagnosed if the bacterial count in the prostate sample is at least one logarithm greater than that in the urethral sample.[11,12]

Overview of Treatment

Treatment of bacterial prostatitis is challenging because of poor penetration of many antibiotics across the nonfenestrated prostatic capillaries and through prostatic epithelium into infected tissues and fluids. Most acidic antibiotics do not readily cross the prostatic epithelium into the alkaline prostatic fluid except in the presence of acute inflammation. Theoretically, the high alkalinity of prostatic fluids should impair the diffusion of trimethoprim and enhance the diffusion of tetracyclines, certain sulfonamides, and macrolide antibiotics, such as erythromycin. TMP-SMX is commonly used in the treatment of both acute and chronic prostatitis. Fluoroquinolones are often considered the preferred antibiotics for treatment of acute or chronic prostatitis because of good penetration into the prostate (10%–50% of serum concentrations) and good activity against most causative pathogens, although fluoroquinolone resistance has become a growing problem.[11,12] β-Lactams, tetracyclines, macrolides, and clindamycin have also been successfully used in the treatment of both acute and chronic infections, but their penetration into the prostatic tissues and fluids may be somewhat less than that of the fluoroquinolones or TMP-SMX. In addition, the antimicrobial activity of these drugs is not ideal for covering the most common causative pathogens.[11,12]

The duration of antibiotic therapy in acute prostatitis is 2 to 4 weeks, depending on the severity of the infection and rate of response to treatment.[11,12] Chronic prostatitis is usually treated for 4 to 6 weeks, although longer courses may be required in the presence of prostate stones or other types of genitourinary pathology, and long-term suppressive therapy is sometimes used for patients with a history of rapid and/or multiple recurrences.[11,12]

Monitoring parameters consist primarily of clinical signs and symptoms, and the treatment end point is complete resolution of clinical findings.[11,12]

Supportive treatment for prostatitis consists primarily of drugs for symptomatic relief such as acetaminophen or nonsteroidal anti-inflammatory agents; warm compresses to the perineal area are also recommended, although there are few data to support this practice.[11,12] Other supportive measures for symptomatic relief in patients with acute bacterial prostatitis include liberal hydration, sitz baths, and stool softeners.

CASE 71-12

QUESTION 1: D.G., a 60-year-old male, experienced his first UTI at age 40, with symptoms of frequency, dysuria, nocturia, perineal pain, fever and chills but no flank pain, and acute prostatitis being diagnosed. *E. coli* was cultured from the urine, and treatment with TMP-SMX was successful. Two more *E. coli* infections that responded to TMP-SMX therapy occurred during the next 8 years.

Why was TMP-SMX appropriate treatment for D.G.'s repeated acute episodes of bacterial prostatitis?

Many antibacterial drugs appropriate for UTI, including sulfonamides, can be used to treat acute bacterial prostatitis because the diffuse, intense inflammation of the prostate gland allows many of these drugs to readily penetrate into the prostatic fluid and tissues. In the case of D.G., these repeated episodes occurred far enough apart to be considered reinfections rather than relapses, which are often associated with treatment failures and development of antimicrobial resistance. The overall risk of D.G. developing resistance to sulfonamides subsequently remained relatively low. Antimicrobial therapy should be continued for at least 2 to 4 weeks to prevent the development of chronic prostatitis.[11,12,24]

CASE 71-12, QUESTION 2: Three years after the last episode of prostatitis, D.G. again starts to experience urinary frequency, dysuria, perineal pain, and fever. He is again diagnosed with acute bacterial prostatitis. What would be a reasonable choice of therapy for D.G.'s current episode of prostatitis?

In retrospect, sulfonamides were previously appropriate for D.G. because they effectively treated his past infections; a sulfonamide would potentially again be appropriate for future episodes. TMP-SMX historically has the best-documented cure rates in the treatment of acute and chronic bacterial prostatitis. Long-term therapy for chronic bacterial prostatitis with TMP-SMX for 4 to 16 weeks is associated with a cure rate of 32% to 71%, which significantly exceeds the cure rate associated with short-term therapy for ≤2 weeks.[11,12]

The fluoroquinolones are alternatives to TMP-SMX and are now considered by many to be the agents of choice for the treatment of prostatitis.[11,12,24] A number of studies have documented bacteriologic cure in 80% to 90% of patients treated with norfloxacin, ciprofloxacin, or levofloxacin for 4 to 12 weeks, rates comparable to or substantially higher than those achieved with TMP-SMX.[11,12] The fluoroquinolones are also excellent alternatives to other agents in patients who are unresponsive or intolerant to conventional therapy, or in those infected with resistant organisms.[11,12,24] Fluoroquinolones also have been used for chronic suppressive therapy (one-half normal doses) in patients who relapse after conventional treatment.[1]

D.G. should be treated with TMP-SMX for a minimum of 6 weeks; some authorities recommend a 2- to 3-month total course of therapy. If an adequate trial of TMP-SMX is unsuccessful, fluoroquinolone therapy can be used. Alternatively, a fluoroquinolone could be used as initial therapy for this or future episodes.[11,12,24]

If D.G. continues to experience recurrent infections after a trial of fluoroquinolone therapy, chronic low-dose treatment with TMP-SMX, fluoroquinolones, or nitrofurantoin can alleviate the symptoms of episodic bladder infection associated with chronic bacterial prostatitis. Infections eventually recur with greater frequency in most of these patients. Chronic, low-dose antibacterial therapy sterilizes the bladder, alleviates symptoms, confines bacteria to the prostate, and prevents infection of and damage to the rest of the urinary tract. Chronic bacterial prostatitis is one of the few indications for continuous antibiotic therapy.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children [published correction appears in *N Engl J Med*. 2010;362:1250]. *N Engl J Med.* 2009;361:1748–1759. (76)

Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis.* 2011;52:e103–e120. (20)

Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50:625–663. (23)

Hooton TM Jr. Uncomplicated urinary tract infection. *N Engl J Med.* 2012;366(11):1028–1037. (2)

Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. *Clin Infect Dis.* 2010;50:1641–1652. (11)

Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant gram-negative bacteria causing urinary tract infections: a review. *J Chemother*. 2017;29(Suppl 1):2–9. (45)

Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am.* 2008;35:1–12. (5)

Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guidelines for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68:e83–e110. (13)

Pietrucha-Dilanchian P, Hooton TM. Diagnosis, treatment, and prevention of urinary tract infection. *Microbiol Spectrum*. 2016;4(6):1–20. (38)

Raynor MC, Carson CC 3rd. Urinary infections in men. *Med Clin North Am.* 2011;95:43–54. (7)

Schito GC, Naber KG, Botto H, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. *Int J Antimicrob Agents.* 2009;34: 407–413. (43)

Shuman EK, Chenoweth CE. Recognition and prevention of healthcare-associated urinary tract infections in the intensive care unit. *Crit Care Med.* 2010;38(Suppl):S373–S379. (22)

Tullus K, Shaikh N. Urinary tract infections in children. *Lancet*. 2020;395: 1659–1668. (9)

Vouloumanou EK, Rafailidis PI, Kazantzi MS, Athanasiou S, Falagas ME. Early switch to oral versus intravenous antimicrobial treatment for hospitalized patients with acute pyelonephritis: a systematic review of randomized controlled trials. *Curr Med Res Opin.* 2008;24:3423–3434. (72)

Zhanel GG, Walkty AJ, Karlowsky JA. Fosfomycin: a first-line oral therapy for acute uncomplicated cystitis. *Can J Infect Dis Med Microbiol*. 2016;2016:1–10. (42)

COMPLETE REFERENCES CHAPTER 71 URINARY TRACT INFECTIONS

1. Sobel JD, Brown P. Urinary tract infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier, Inc.; 2020:962–989.
2. Hooton TM Jr. Uncomplicated urinary tract infection. *N Engl J Med*. 2012;366:1028–1037.
3. Kolman KB. Cystitis and pyelonephritis: diagnosis, treatment, and prevention. *Prim Care Clin Off Pract*. 2019;46:191–202.
4. Schneeberger C, Holleman F, Geerlings SE. Febrile urinary tract infections: pyelonephritis and urosepsis. *Curr Opin Infect Dis*. 2016;29:80–85.
5. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am*. 2008;35:1–12.
6. Johnson JR, Russo TA. Acute pyelonephritis in adults. *N Engl J Med*. 2018;378:48–59.
7. Raynor MC, Carson CC 3rd. Urinary infections in men. *Med Clin North Am*. 2011;95:43–54.
8. Schaeffer AJ, Nicolle LE. Urinary tract infections in older men. *N Engl J Med*. 2016;374:562–571.
9. Tullus K, Shaikh N. Urinary tract infections in children. *Lancet*. 2020;395:1659–1668.
10. Beetz R. Evaluation and management of urinary tract infection in the neonate. *Curr Opin Pediatr*. 2012;24(2):205–211.
11. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. *Clin Infect Dis*. 2010;50:1641–1652.

12. Coker TJ, Dierfeldt DM. Acute bacterial prostatitis: diagnosis and management. *Am Fam Phys*. 2016;93(2):114–120.
13. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guidelines for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68:e83–e110.
14. Rodriguez-Manas L. Urinary tract infections in the elderly: a review of disease characteristics and current treatment options. *Drugs Context*. 2020;9:4–13.
15. Rowe TA, Juthani-Mehta M. Diagnosis and management of urinary tract infection in older adults. *Infect Dis Clin North Am*. 2014;28:75–89.
16. Al Salman J, Al Agha RA, Mussayab YA, Hassan AF. Infection in long term care facility in the Kingdom of Bahrain. *J Infect Public Health*. 2014;7:392–399.
17. Nicolle LE. Urinary tract infections in the elderly. *Clin Geriatr Med*. 2009;25: 423–436.
18. Richards CL. Urinary tract infections in the frail elderly: issues for diagnosis, treatment and prevention. *Int Urol Nephrol*. 2004;36:457–463.
19. Eriksson I, Gustafson Y, Fagerstrom L, Olofsson B. Prevalence and factors associated with urinary tract infections (UTIs) in very old women. *Arch Gerentol Geriatr*. 2010;50:132–135.
20. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52:e103–e120.
21. Bagshaw SM, Laupland KB. Epidemiology of intensive care unit-acquired urinary tract infections. *Curr Opin Infect Dis*. 2006;19:67–71.
22. Shuman EK, Chenoweth CE. Recognition and prevention of healthcare-associated urinary tract infections in the intensive care unit. *Crit Care Med*. 2010;38(Suppl):S373–S379.
23. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:625–663.
24. Wagenlehner FM, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. *Clin Microbiol Infect*. 2006;12(Suppl 3):67–80.
25. Kalita A, Hu J, Torres AG. Recent advances in adherence and invasion of pathogenic *Escherichia coli*. *Curr Opin Infect Dis*. 2014;27:459–464.
26. Agarwal J, Srivasatva S, Singh M. Pathogenomics of uropathogenic *Escherichia coli*. *Indian J Med Microbiol*. 2012;30:141–149.
27. Arnold JJ, Hehn LE, Klein DA. Common questions about recurrent urinary tract infections in women. *Am Fam Phys*. 2016;93(7):560–569.

28. Schneeberger C, Kazemier BM, Geerlings SE. Asymptomatic bacteriuria and urinary tract infections in special patient groups: women with diabetes mellitus and pregnant women. *Curr Opin Infect Dis*. 2014;27:108–114.
29. Lumbiganon P, Laopaiboon M, Thinkhamrop J. Screening and treating asymptomatic bacteriuria in pregnancy. *Curr Opin Obstet Gynecol*. 2010;22:95–99.
30. Golebiewska JE, Debska-Slizien A, Rutkowski B. Urinary tract infections during the first year after renal transplantation: one center's experience and a review of the literature. *Clin Transplant*. 2014;28:1263–1270.
31. Chen SL, Jackson SL, Boyko EJ. Diabetes mellitus and urinary tract infection: epidemiology, pathogenesis and proposed studies in animal models. *J Urol*. 2009;182:S51–S56.
32. Kamei J, Yamamoto S. Complicated urinary tract infections with diabetes mellitus. *J Infect Chemother*. 2021;27:1131–1136.
33. Gorter KJ, Hak EH, Zuithoff NPA, Hoepelman AIM, Rutten GEHM. Risk of recurrent acute lower urinary tract infections and prescription pattern of antibiotics in women with and without diabetes in primary care. *Fam Pract*. 2010;27:379–385.
34. Storme O, Saucedo JT, Garcia-Mora A, Dehesa-Davila M, Naber KG. Risk factors and predisposing conditions for urinary tract infection. *Ther Adv Urol*. 2019;11:19–28.
35. Majeed A, Sagar F, Latif A, et al. Does antimicrobial coating and impregnation of urinary catheters prevent catheter-associated urinary tract infection? A review of clinical and preclinical studies. *Expert Rev Med Devices*. 2019;16(9):809–820.
36. Tenke P, Koves B, Johansen TEB. An update on prevention and treatment of catheter-associated urinary tract infections. *Curr Opin Infect Dis*. 2014;27:102–107.
37. Geerlings SE. Clinical presentations and epidemiology of urinary tract infections. *Microbiol Spectrum*. 2016;4(5):1–11.
38. Pietrucha-Dilanchian P, Hooton TM. Diagnosis, treatment, and prevention of urinary tract infection. *Microbiol Spectrum*. 2016;4(6):1–20.
39. Medina-Bombardo D, Jover-Palmer A. Does clinical examination aid in the diagnosis of urinary tract infections in women? A systematic review and meta-analysis. *BMC Fam Pract*. 2011;12:111–125.
40. Deville WLJM, Yzermans JC, van Dujin NP, Bezemer PD, van der Windy DA, Bouter LN. The urine dipstick test useful to rule out infections: a meta-analysis of the accuracy. *BMC Urol*. 2004;4:4.
41. Koeijers JJ, Kessels AGH, Nys S, et al. Evaluation of the nitrite and leukocyte esterase activity tests for the diagnosis of acute symptomatic urinary tract infection in men. *Clin Infect Dis*. 2007;45:894–896.
42. Zhanel GG, Walkty AJ, Karlowsky JA. Fosfomycin: a first-line oral therapy for acute uncomplicated cystitis. *Can J Infect Dis Med Microbiol*. 2016;2016:1–

10.
43. Schito GC, Naber KG, Botto H, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. *Int J Antimicrob Agents*. 2009;34:407–413.
44. Kranz J, Helbig S, Mandrake F, Schmidt S, Naber KG. The revival of old antibiotics for treatment of uncomplicated urinary tract infections in the era of antibiotic stewardship. *Curr Opin Urol*. 2017;27:127–132.
45. Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant gram-negative bacteria causing urinary tract infections: a review. *J Chemother*. 2017;29(Suppl 1):2–9.
46. Perletti G, Magri V, Cai T, Stamatiou K, Trinchieri A, Montanari E. Resistance of uropathogens to antibacterial agents: emerging threats, trends, and treatments. *Arch Ital Urol Androl*. 2018;90(2):85–96.
47. Asadi Karam MR, Habibi M, Bouzari S. Urinary tract infection: pathogenicity, antibiotic resistance and development of effective vaccines again uropathogenic *Escherichia coli*. *Molecular Immunol*. 2019;108:56–67.
48. Kot B. Antibiotic resistance among uropathogenic *Escherichia coli*. *Pol J Microbiol*. 2019;4:403–415.
49. Oteo J, Perez-Vazquez M, Campos J. Extended-spectrum β-lactamase producing *Escherichia coli*: changing epidemiology and clinical impact. *Curr Opin Infect Dis*. 2010;23:3206–3213.
50. Alam MF, Cohen D, Butler C, et al. The additional costs of antibiotics and reconsultations for antibiotic-resistant *Escherichia coli* urinary tract infections managed in general practice. *Int J Antimicrob Agents*. 2009;33:255–257.
51. Trestioreanu AZ, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev*. 2010;(10):CD007182.
52. Zinner SH, Mayer KH. Sulfonamides and trimethoprim; trimethoprim-sulfamethoxazole. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier, Inc.; 2020:416–452.
53. Horton JM. Urinary tract agents: nitrofurantoin, fosfomycin, and methenamine. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier, Inc.; 2020:461–465.
54. Kashanian J, Hakimian P, Blute M, et al. Nitrofurantoin: the return of an old friend in the wake of growing resistance. *BJU Int*. 2008;102:1634–1637.
55. Dawson-Hahn EE, Mickan S, Onakpoya I, et al. Short-course versus long-course oral antibiotic treatment for infections treated in outpatient settings: a review of systematic reviews. *Fam Pract*. 2017;34(5):511–519.
56. Gupta K, Hooton TM, Roberts PI, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med*.

2007;167:2207–2212.
57. Eastham JH, Patel P. Phenazopyridine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 35593852. Last accessed June 4, 2022.
58. Raz R, Chazan B, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. *Clin Infect Dis*. 2002;34:1165–1169.
59. McNulty CAM, Richards J, Livermore DM, et al. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *J Antimicrob Chemother*. 2006;58:1000–1008.
60. Gupta K, Stamm WE. Outcomes associated with trimethoprim/sulfamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. *Int J Antimicrob Agents*. 2002;19:554–556.
61. Brown PD, Freeman A, Foxman B. Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. *Clin Infect Dis*. 2002;34:1061–1066.
62. Hooper DC, Strahilevitz J. Quinolones. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier, Inc.; 2020:426–448.
63. Lin DC, Bhally H. Nitrofurantoin-induced interstitial lung disease. *N Z Med J*. 2007;120:U2753.
64. Kammire LD, Donofrio PD. Nitrofurantoin neuropathy: a forgotten adverse effect. *Obstet Gynecol*. 2007;110(2, pt 2):510–512.
65. Jackson MA, Schutze GE; AAP Committee on Infectious Diseases. The use of systemic and topical fluoroquinolones. *Pediatrics*. 2016;138(5):e20162706.
66. Etminan M, Guo MY, Carleton B. Oral fluoroquinolone prescribing to children in the United States from 2006 to 2015. *Pediatr Infect Dis J*. 2019;38:268–270.
67. Patel K, Goldman JL. Safety concerns surrounding quinolone use in children. *J Clin Pharmacol*. 2016;59:1060–1075.
68. Bacci C, Galli L, de Martino M, Chiappini E. Fluoroquinolones in children: update of the literature. *J Chemother*. 2015;27(5):257–265.
69. Scholes D, Hooton TM, Roberts PL, Gupta K, Stapleton AE, Stamm WE. Risk factors associated with acute pyelonephritis in healthy women. *Ann Intern Med*. 2005;142:20–27.
70. Spoorenberg V, Prins JM, Opmeer BC, de Reijke TM, Hulscher ME, Geerlings SE. The additional value of blood cultures in patients with complicated urinary tract infections. *Clin Microbiol Infect*. 2014;20:O476–O479.
71. Wagenlehner FM, Weidner W, Naber KG. Emergence of antibiotic resistance amongst hospital-acquired urinary tract infections and

pharmacokinetic/pharmacodynamic considerations. *J Hosp Infect*. 2005;60:191–200.
72. Vouloumanou EK, Rafailidis PI, Kazantzi MS, Athanasiou S, Falagas ME. Early switch to oral versus intravenous antimicrobial treatment for hospitalized patients with acute pyelonephritis: a systematic review of randomized controlled trials. *Curr Med Res Opin*. 2008;24:3423–3434.
73. Kodner CM, Thomas Gupton EK. Recurrent urinary tract infections in women: diagnosis and management. *Am Fam Physician*. 2010;82:638–643.
74. Anger J, Lee U, Ackerman AL, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. *J Urol*. 2019;202:282–289.
75. Taich L, Zhao H, Cordero C, Anger JT. New paradigms in the management of recurrent urinary tract infections. *Curr Opin Urol*. 2020;30:833–837.
76. Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children [published correction appears in *N Engl J Med*. 2010;362:1250]. *N Engl J Med*. 2009;361:1748–1759.
77. Dai B, Liu Y, Jia J, Mei C. Long-term antibiotics for the prevention of recurrent urinary tract infection in children: a systematic review and meta-analysis. *Arch Dis Child*. 2010;95:499–508.
78. Korbel L, Howell M, Spencer JD. The clinical diagnosis and management of urinary tract infections in children and adolescents. *Paediatr Int Child Health*. 2017;37(4):273–279.
79. Khan AK, Jhaveri R, Seed PC, Arshad M. Update on associated risk factors, diagnosis, and management of recurrent urinary tract infections in children. *J Ped Infect Dis Soc*. 2019;8(2):152–159.
80. Alsubaie SS, Barry MA. Current status of long-term antibiotic prophylaxis for urinary tract infections in children: an antibiotic stewardship challenge. *Kidney Res Clin Pract*. 2019;38(4):441–454.
81. Wang C-H, Fang C-C, Chen N-C, et al. Cranberry-containing products for prevention of urinary tract infections in susceptible populations. *Arch Intern Med*. 2012;172:988–996.
82. Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2008;(2):CD001321.
83. Barea BM, Veeratterapillay R, Harding C. Nonantibiotic treatments for urinary cystitis: an update. *Curr Opin Urol*. 2020;30:845–852.
84. Henderson JT, Webber E, Bean SI. *Screening for Asymptomatic Bacteriuria in Adults: An Updated Systematic Review for the U.S. Preventive Services Task Force*. Evidence Synthesis No. 183. Agency for Healthcare Research and Quality; 2019.
85. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev.* 2019;2019(11):CD000490.
86. Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev*. 2010;(9):CD007855.

87. Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA, Hu DJ. Antibacterial medication use during pregnancy and risk of birth defects. *Arch Pediatr Adolesc Med*. 2009;163:978–985.
88. Briggs GG, Freeman RK, Towers CV, Forinash AB, eds. *Drugs in Pregnancy and Lactation*. 12th ed. Lippincott Williams & Wilkins; 2021.
89. Hewitt IK, Pennesi M, Morello W, Ronfani L, Montini G. Antibiotic prophylaxis for urinary tract infection-related renal scarring: a systematic review. *Pediatrics*. 2017;139(5):e20163145.
90. Murugapoopathy V, McCusker C, Gupta IR. The pathogenesis and management of renal scarring in children with vesicoureteral reflux and pyelonephritis. *Pediatr Nephrol*. 2020;35:349–357.
91. Dahiya A, Goldman RD. Management of asymptomatic bacteriuria in children. *Can Fam Phys*. 2018;64:821–824.
92. Chen YH, Ko W-C, Hsueh P-R. Emerging resistance problems and future perspectives in pharmacotherapy for complicated urinary tract infections. *Exp Opin Pharmacother*. 2013;14:587–596.
93. Liu H, Mulholland SG. Appropriate antibiotic treatment of genitourinary infections in hospitalized patients. *Am J Med*. 2005;118(Suppl 7A):14S–20S.
94. Marschall J, Carpenter CR, Fowler S, Trautner BW; CDC Prevention Epicenters Program. Antibiotic prophylaxis for urinary tract infections after removal of urinary catheter: meta-analysis. *BMJ*. 2013;346:f3147.

72

Sexually Transmitted Diseases

Albert Bach, Anne Walsh, and Karl M. Hess

CORE PRINCIPLES		CHAPTER CASES
GONORRHEA		
1	Gonorrhea is initially characterized in males by a purulent discharge associated with dysuria. Discharge may become more profuse and blood tinged as the infection progresses. Some strains of gonorrhea have a propensity to cause asymptomatic or minimally symptomatic infections.	**Case 72-1 (Questions 1–3)** **Case 72-2 (Questions 1, 2)**
2	In females, the most common symptom of gonorrhea is vaginal discharge. Many females infected with gonorrhea have abnormalities of the cervix, including purulent or mucopurulent endocervical discharge, erythema, friability, and edema of the zone of ectopy. Pelvic	**Case 72-1 (Questions 4, 5)**

	inflammatory disease (PID) is a serious complication and can lead to infertility and chronic pelvic pain.	
3	The standard of treatment for gonorrhea is a third-generation cephalosporin such as ceftriaxone. Fluoroquinolones should not be used owing to high levels of resistance.	**Case 72-1 (Questions 6–8)** **Case 72-2 (Questions 3–5)**
4	In a small percentage of patients, gonococcal infections may invade the bloodstream and cause infections at distant sites in the body causing disseminated gonococcal infections (DGIs). The recommended treatment for DGI is ceftriaxone.	**Case 72-4 (Questions 1–4)**
	PELVIC INFLAMMATORY DISEASE	
1	PID may be treated on an inpatient or outpatient basis. Those with mild-to-moderate PID can be admitted and treated with parenteral antibiotics; however, clinical efficacy and overall outcomes are equal between parenteral and oral therapies.	**Case 72-3 (Question 1)**
	NONGONOCOCCAL URETHRITIS	
1	Nongonococcal urethritis (NGU) is a common sexually transmitted infection in males and is frequently caused by *Chlamydia trachomatis*.	**Case 72-5 (Question 1)**
2	NGU typically produces less severe and less frequent dysuria and less penile discharge as compared with gonococcal	**Case 72-5 (Question 2)**

	urethritis. NGU and gonococcal urethritis cannot be reliably differentiated on the basis of symptoms and signs.	
3	NGU may be treated with either azithromycin or doxycycline; however, azithromycin is superior in its coverage of both *Mycoplasma genitalium* and *Chlamydia*.	**Case 72-5 (Questions 3–5)**
	LYMPHOGRANULOMA VENEREUM	
1	Lymphogranuloma venereum is characterized by three stages of infection and may be treated with doxycycline, erythromycin base, or azithromycin.	**Case 72-6 (Questions 1, 2)**
	SYPHILIS	
1	Syphilis is characterized by four stages of infection: primary, secondary, latent, and tertiary. Penicillin G is the drug of choice for all stages of syphilis.	**Case 72-7 (Questions 1–5) Case 72-8 (Questions 1, 3)**
2	The Jarisch–Herxheimer reaction is a benign, self-limited complication of antibiotic therapy that may develop after treatment of primary and secondary syphilis.	**Case 72-8 (Question 2)**
	CHANCROID	
1	Uncircumcised males have an increased risk of infection and may not respond to therapy as well as circumcised males do. Current	**Case 72-9 (Questions 1, 2)**

	treatment options include azithromycin, ceftriaxone, ciprofloxacin, and erythromycin base.	
	VAGINITIS	
1	Common causes of vaginitis include bacterial vaginosis, trichomoniasis, and vulvovaginal candidiasis. General symptoms may include itching, burning, irritation, and abnormal discharge and can be differentiated based on signs, symptoms, and laboratory testing.	**Case 72-10 (Question 1) Case 72-11 (Questions 2–4) Case 72-12 (Question 1)**
2	Vulvovaginal candidiasis may be effectively treated with nonprescription medications; however, patients must be assessed fully before self-treatment is initiated.	**Case 72-11 (Questions 1–4, 6–9)**
	GENITAL HERPES	
1	Genital herpes, transmitted either from symptomatic or asymptomatic individuals, often presents with painful vesicles in those with herpes simplex virus type 2 primary infection, and recurrent infections are common, although the frequency decreases with time.	**Case 72-14 (Questions 1–3)**
2	Genital herpes is best treated with oral antivirals, such as acyclovir or valacyclovir, and prevented with either suppressive or standby antivirals.	**Case 72-14 (Question 5)**
	GENITAL WARTS	

1	Human papillomavirus is highly contagious and may now be prevented by vaccination, in addition to condoms.	**Case 72-17 (Question 1)**
2	Genital warts often recur even with treatment, which is primarily local, including antimitotics, immune modulators, chemical and surgical ablation, and cryotherapy.	**Case 72-17 (Question 1)**

INTRODUCTION

Sexually transmitted diseases (STDs) are discussed in the earliest written records. However, only in the past several decades have the common STDs been differentiated from each other; unique STD syndromes continue to be described today. For example, of the common STDs, herpes simplex virus (HSV) type 2 (the cause of genital herpes) was not differentiated from HSV type 1 until the 1960s; the spectrum of genital chlamydial infections was not defined until the 1970s; and the human immunodeficiency virus (HIV), as an STD, was not recognized until the 1980s. Since 1980, eight additional sexually transmitted pathogens have been identified. They include the human papillomaviruses (HPVs), human T-lymphotropic virus (HTLV-I and -II), *Mycoplasma genitalium, Mobiluncus* species, HIV-1 and -2, and the human herpesvirus type 8 (associated with Kaposi sarcoma).[1] More recently, the Centers for Disease Control and Prevention (CDC) reports that although hepatitis C virus (HCV) infection is not efficiently transmitted through sexual contact, MSM (men who have sex with men) coinfected with HIV are more likely to transmit HCV than through heterosexual contact.[2] See https://www.cdc.gov/std/training/default.htm for general resources from the CDC for various STDs.

GONORRHEA

Gonorrhea[3] is caused by *Neisseria gonorrhoeae,* a gram-negative diplococcus. Depending on the site of exposure, this disease can cause uncomplicated cervical, urethral, rectal, and oropharyngeal infections in both males and females. *N. gonorrhoeae* infection in females is also a major cause of pelvic inflammatory disease (PID). Disseminated gonococcal infection (DGI), the bacteremic spread of *N. gonorrhoeae* to joints and other tissues, can lead to complicated gonorrhea infections that cause pustular acral skin lesions, tenosynovitis, polyarthralgia, or arthritis. DGI may lead to rare cases of perihepatitis, endocarditis, or meningitis. In the 1930s, sulfonamides became the first form of effective antimicrobial therapy for gonorrhea until penicillins and tetracyclines became the mainstays of therapy; however, the high levels of resistance to these two antimicrobial agents have eliminated their use in the treatment of this disease state.

In the United States, the incidence of gonorrhea fell 74.3% between 1975 and 1997 after the establishment of national gonorrhea control programs. From 1996 to 2006, the rate fluctuated at around 115 cases per 100,000 individuals, and from 2006 to 2009, the rates declined to a historic low of 98.1 cases per 100,000 individuals in 2009.[4],[5] In 2018, gonorrhea cases yielded a rate of 179.1 cases per 100,000 population. From 2017 to 2018, the rate of reported gonorrhea cases increased 5.0% and increased 82.6% since the historic low in 2009.[6] From 2014 to 2018, the rates of reported gonorrhea cases increased for each of the 5 years among all race/Hispanic ethnicity groups. As of the 2018 Sexually Transmitted Disease Surveillance Report, rates of gonorrhea were highest among Blacks, followed by American Indians/Alaska Natives and Native Hawaiians/Other Pacific Islanders (**Fig. 72-1**).[6]

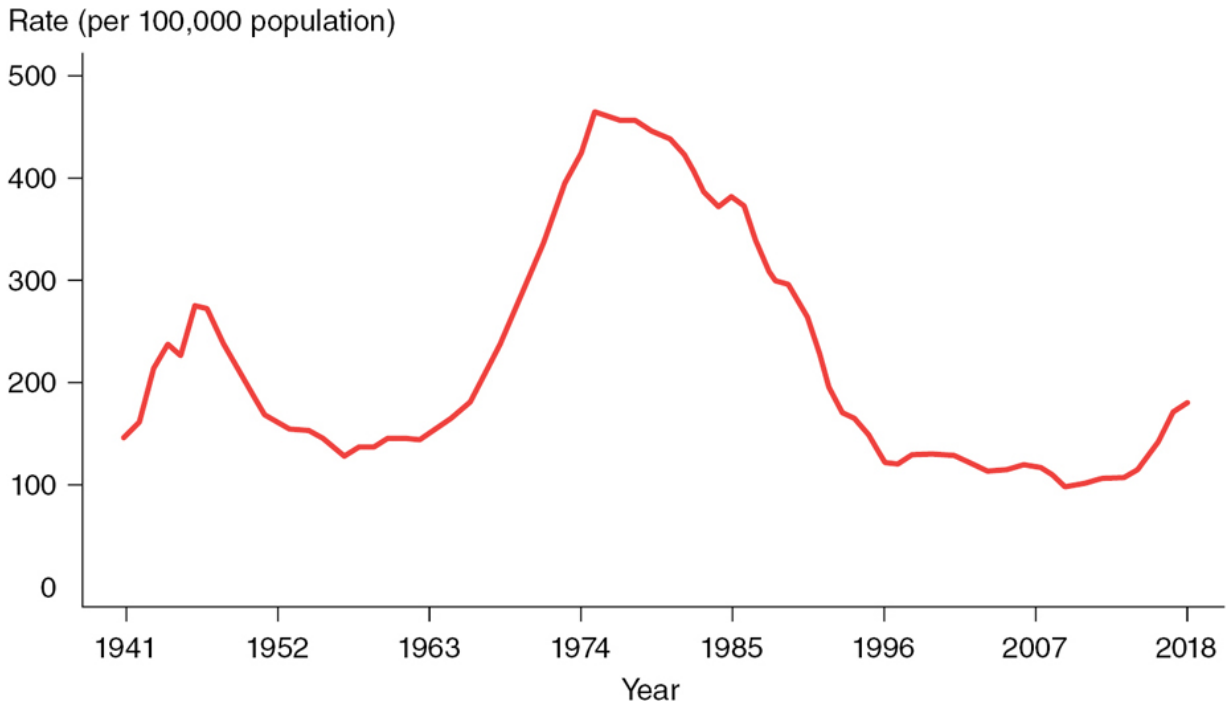


Figure 72-1 Gonorrhea rates by year in the United States. Line graph showing rates of reported cases of gonorrhea in the United States by year from 1941 to 2018. In 2018, gonorrhea cases yielded a rate of 179.1 cases per 100,000 population. From 2017 to 2018, the rate of reported gonorrhea cases increased 5.0% and increased 82.6% since the historic low in 2009. (From Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. https://www.cdc.gov/std/stats18/figures/14.htm.)

In 2018, the highest incidence of gonorrhea was in males ages 20 to 24 years and in females ages 20 to 24 years.[6] Additional risk factors for females acquiring gonorrhea include a previous gonococcal or other STD infection, new or multiple sex partners, inconsistent condom use, or engaging in commercial sex work or drug use.[7] Although the risk of gonorrhea was greater in MSM than in MSW in the past, the incidence dropped in homosexual males during the 1980s AIDS epidemic because of a reduction in sexual risk behaviors. Currently, the incidence of gonorrhea in MSM continues to rise, with an estimated 375.5% increase during 2010 to 2018 from 1368.6 cases per 100,000 MSM in 2010 to 6508.0 cases

per 100,000 MSM in 2018. Comparing this to men who have sex with women (MSW) over the same period, case rates among MSW and women increased by 69.3% and 95.2%, respectively.[6]

Uncomplicated Gonorrhea

TRANSMISSION

CASE 72-1

Question 72-1: D.S., a 23-year-old male naval officer recently stationed in the Philippines, presents with dysuria, meatal pain, and a profuse yellow urethral discharge for 2 days. He admits to having sex with a sex worker during the past week. He is accompanied by his pregnant wife, C.S., who is asymptomatic. D.S. engages in insertive vaginal sex, but there is no history of oral or anal sex with either partner.

Assuming the sex worker has gonorrhea, what is the likelihood that D.S. and C.S. have been infected?

After one or two episodes of unprotected vaginal intercourse with an asymptomatic infected sex worker, a male has an ~50% risk of acquiring a urethral infection; the risk increases with repeated exposures and high prevalence among commercial sex workers.[8] The prevalence of infection in females who are secondary sex contacts of infected males is as high as 80% to 90%.[9] Therefore, the likelihood that D.S. and C.S. are infected is high. Because D.S. had sex with a sex worker, both D.S. and C.S. should also be tested for HIV infection.

SIGNS AND SYMPTOMS: MALES

Case 72-1, Question 2: What signs and symptoms in D.S. are consistent with the diagnosis of gonorrhea? Describe D.S.'s anticipated clinical course if he remains untreated.

In males, gonorrhea usually becomes clinically apparent 1 to 7 days after contact with an infected source. A purulent discharge associated with dysuria is the first sign of infection; D.S. exhibits both. The discharge, which is presumably caused by chemotactic factors such as C5a released when antigonococcal antibody binds complement, may become more profuse and blood tinged as the infection progresses. Some strains of gonorrhea have a propensity to cause asymptomatic or minimally symptomatic infection with negative Gram stain.

Patients with asymptomatic or minimally symptomatic disease may serve as reservoirs for the infection, evading treatment for prolonged periods.[10] At one time, only females were thought to have asymptomatic gonorrhea, but now it is known that males may be asymptomatic carriers as well.[11]

In the era before antimicrobials, gonococci occasionally spread to the epididymis, causing unilateral epididymitis; the prevalence was 5% or more in patients in some studies. Currently, epididymitis occurs in <1% of males with gonorrhea. Urethral stricture after repeated attacks and sterility after epididymitis are now rare complications of gonococcal infection owing to the effectiveness of antibiotics.

DIAGNOSIS: MALES

Case 72-1, Question 3: Intracellular gram-negative diplococci were seen on the Gram stain of D.S.'s urethral exudate. Is any further diagnostic testing required?

Demonstration of intracellular gram-negative diplococci in the gram-stained exudate confirms the diagnosis in symptomatic males. Until recently, some experts recommended that cultures be reserved for individuals with negative Gram stain finding of urethral exudate. However, today, cultures are recommended for all patients to permit isolation and testing of the bacteria for antibiotic susceptibility. Cultures usually are performed on Thayer–Martin medium, an

enriched chocolate agar to which vancomycin, colistimethate, and nystatin have been added. Cultures from the throat should be obtained if D.S. were exposed by cunnilingus to the prostitute. In D.S.'s case, symptomatic urethritis with the presence of polymorphonuclear leukocytes (PMNs) with intracellular gram-negative diplococci on a Gram stain of the urethral specimen does not require further testing and is sufficient to establish a diagnosis of gonorrhea. See Case 72-1, Question 5, for situations where further testing may be needed with a nucleic acid amplification test (NAAT).

SIGNS AND SYMPTOMS: FEMALES

Case 72-1, Question 4: C.S., D.S.'s wife, is asymptomatic. What symptoms would be consistent with gonorrhea in C.S.? Do the symptoms differ because she is pregnant? What is the natural course of gonorrhea in females if left untreated?

Urogenital gonococcal infections in females are commonly asymptomatic. Because the endocervical canal is the primary site of urogenital gonococcal infection in females, the most common symptom is vaginal discharge. Many females infected with gonorrhea have abnormalities of the cervix, including purulent or mucopurulent endocervical discharge, erythema, friability, and edema of the zone of ectopy.[9] The incubation period for urogenital gonorrhea in females is variable.[12] PID is a serious complication in 10% to 20% of females with acute gonococcal infection and can lead to infertility and chronic pelvic pain.[2,9] The assessment of signs and symptoms in females with gonorrhea often is confounded by nonspecific signs and symptoms and a high prevalence of coexisting infection, especially with *Chlamydia trachomatis* or *Trichomonas vaginalis.*

Although lower genital tract symptoms in females may disappear, they remain carriers of *N. gonorrhoeae* and should be treated. Complications of urogenital gonorrhea in pregnancy include spontaneous abortion, premature rupture of the fetal membranes, premature delivery, and acute chorioamnionitis.[13–15] Other

complications include gonococcal arthritis (see Case 72-4, Question 1), conjunctivitis, and ophthalmia neonatorum in the newborn.[16] For these reasons, it is critical that C.S. be worked up thoroughly for gonorrhea.

DIAGNOSIS: FEMALES

Case 72-1, Question 5: How should gonorrhea be ruled out in C.S.?

NAATs, such as the polymerase chain reaction (PCR), are recommended for the detection of *N. gonorrhoeae* in males and females from urogenital sites regardless of whether symptoms are present.[17] Although NAATs are not FDA approved for the detection of *N. gonorrhoeae* at nonurogenital (or extragenital) sites, laboratories should meet Clinical Laboratory Improvement Amendments (CLIA) requirements and performance specifications for use with rectal and oropharyngeal specimens; NAATs are the recommended detection method for rectal and orophyaryngeal specimens. Although culture for *N. gonorrhoeae* is not ideal for routine diagnosis, cultures should be performed for isolation and identification, antibiotic susceptibility, and resistance surveillance. Cultures should also be performed in cases of suspected treatment failures, defined as those that have received CDC-recommended treatment and subsequently have a positive *N. gonorrhoeae* test result 7 days after treatment, and did not engage in sexual activity during those 7 days.[17] In C.S., a NAAT from the anal specimen also could be performed because the rectum can serve as a reservoir for gonococci.

TREATMENT

Case 72-1, Question 6: What are the various drug regimens used for uncomplicated gonorrhea?

The CDC recommendations are summarized in **Table 72-1**. The CDC recommends a single dose of intramuscular (IM) ceftriaxone

500 mg as the preferred treatment of gonorrhea.[18] Cefixime 800 mg orally (PO) as a single dose is no longer recommended as a first-line treatment by the CDC, but as an alternative option when ceftriaxone cannot be used. Many strains of *N. gonorrhoeae* exhibit plasmid-mediated resistance to penicillin and tetracycline (penicillinase-producing *Neisseria gonorrhoeae* [PPNG] and/or tetracycline-resistant *Neisseria gonorrhoeae* [TRNG], respectively; **Fig. 72-2**). In addition, significant levels of chromosomally mediated resistance to penicillin, tetracycline, and cefoxitin have been reported.[2]

Table 72-1
CDC Recommendations for Treatment of Uncomplicated Gonorrhea

Presentation	Drugs of Choice (% Cured)	Dosage	Alternative Regimens
Urethritis, cervicitis, rectal[a]	Ceftriaxone (99.2)	500 mg IM once	Cephalosporin single-dose regimens[b]
Pharyngeal[a]	Ceftriaxone (98.9)	500 mg IM once	

IM, intramuscularly: PO, orally.

[a]Because a high percentage of patients with gonorrhea have coexisting *Chlamydia trachomatis* infections, a course of doxycycline 100 mg twice daily for 7 days should be given with recommended gonorrhea treatment if chlamydia has not been excluded.

[b]Additional cephalosporin regimens include cefixime 800 mg orally (PO), ceftizoxime 500 mg intramuscularly (IM), cefoxitin 2 g IM (administered with probenecid 1 g PO), and cefotaxime 500 mg IM.

Source: Adapted from Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4): 1–187. doi:10.15585/mmwr.rr7004a1.

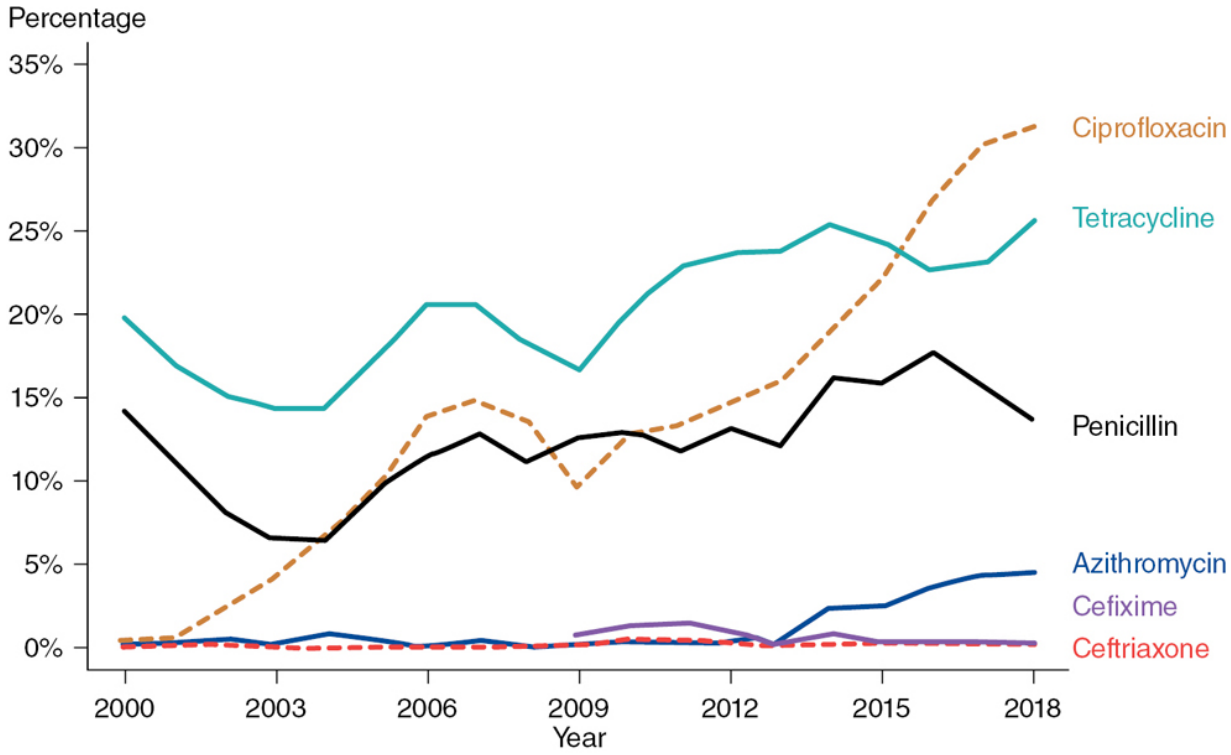


Figure 72-2 Prevalence of minimum inhibitory concentrations (MICs) of common antibiotics to *Neisseria gonorrhoeae*. In 2018, 31.2% of isolates collected from the Gonococcal Isolate Surveillance Project (GISP) sites were resistant to ciprofloxacin, 25.6% to tetracycline, and 13.7% to penicillin. (Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. https://www.cdc.gov/std/stats18/figures/31.htm.)

Failure of penicillin to eradicate the gonococcus can be the result of plasmid (eg, PPNG) or chromosomally mediated resistant *Neisseria gonorrhoeae* (CMRNG) antibiotic resistance. PPNG contain plasmids that determine the production of lactamase, an enzyme that hydrolyzes the lactam ring of penicillin G or ampicillin. Chromosomally mediated resistance does not involve β-lactamase production and often is associated with increased resistance to other β-lactams. The clinical significance of CMRNG is questionable because serum levels of approved antibiotics are achieved far above the minimum inhibitory concentration, such that treatment failure is unlikely. However, to date, CMRNG remain largely susceptible to

ceftriaxone. High-level tetracycline resistance is defined by gonococci that carry plasmid-encoded resistance to 16 g/mL or more of tetracycline. These strains are known as *TRNG*. Although not of major concern in the United States, development of resistance to alternative therapies is a continuing concern.

Quinolone-resistant *Neisseria gonorrhoeae* (QRNG) was first reported in 1990 and was reported to be 0.2% of isolates in the continental United States.[4],[19] In 2007, increasing emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States prompted the CDC to cease recommending fluoroquinolones for treatment of gonorrhea.[20] Resistance to fluoroquinolones is associated with mutations of *GyrA* and is commonly identified in strains that produce β-lactamase and strains exhibiting chromosomally mediated resistance to penicillin and tetracycline.[21],[22] *N. gonorrhoeae* strains may therefore exhibit decreased susceptibility or complete resistance to the recommended dose of quinolones, and the clinical importance of strains with decreased susceptibility is unknown.[23]

Owing to the emergence of high levels of resistance to these antibiotics, the CDC no longer recommends the use of fluoroquinolones, tetracycline, or penicillin for the treatment of gonorrhea.[2],[20] Because a high percentage of patients with gonorrhea are also coinfected with *C. trachomatis*, a 7-day course of doxycycline is recommended to be taken concurrently when chlamydia infection has not been excluded (see Case 72-1, Question 7). Since 2020, the CDC no longer recommends presumptive *Chlamydia trachomatis* treatment with azithromycin due to increasing azithromycin resistance for gonorrhea and other organisms.[18],[24]

The antibiotic resistance profile for gonorrhea is defined as fluoroquinolone (ciprofloxacin): minimum inhibitory concentration (MIC) ≥1.0 μg/mL; penicillin: MIC ≥2.0 μg/mL or β-lactamase positive; tetracycline: MIC ≥0 μg/mL. Elevated MICs = azithromycin: MIC ≥1.0 μg/mL (2000–2004), ≥2.0 μg/mL (2005–2018); ceftriaxone: MIC ≥0.125 μg/mL; cefixime: MIC ≥0.25 μg/mL.

IM spectinomycin, which traditionally had been used in individuals who could not tolerate fluoroquinolones or cephalosporins, is still

unavailable from the manufacturer.[25] Although limited data exist for the treatment of gonorrhea in patients with cephalosporin or immunoglobulin (Ig)E-mediated penicillin allergy, potential alternative treatments are a single dose of gentamicin 240 mg IM plus azithromycin 2 g PO.[18],[26] Individuals who have either penicillin or cephalosporin allergies should be desensitized to cephalosporins before treatment begins.[27]

Ceftriaxone and other cephalosporins

Ceftriaxone, a third-generation cephalosporin, is given as a single, small-volume IM injection that eradicates gonorrhea at all anatomic sites and is also safe in pregnancy (U.S. Food and Drug Administration [FDA] pregnancy category B). Ceftriaxone is ineffective against *C. trachomatis* and in the prevention of postgonococcal urethritis, whereas ofloxacin and levofloxacin for 7 days have similar efficacy to doxycycline.[15] Other injectable cephalosporins (notably ceftizoxime, cefoxitin, and cefotaxime) have been found to be safe and highly effective, but do not offer any advantage over ceftriaxone for urogenital infections, and their efficacy in pharyngeal infections is not as well established. A single oral dose of cefixime is also effective in curing 92.3% of uncomplicated urogenital and anorectal gonorrhea infections.[2],[18] However, the CDC no longer recommends cefixime as a first-line regimen owing to recent concerns about declining cefixime susceptibility among urethral *N. gonorrhoeae* isolates in the United States.[2],[18] Other oral cephalosporins such as cefpodoxime and cefuroxime are not recommended owing to inferior efficacy and less favorable pharmacodynamics; however, they are FDA approved to treat uncomplicated *N. gonorrhoeae*. Although ceftriaxone is used as a first-line regimen, there is increasing concern for resistance. In 2018, 0.2% of isolates had elevated ceftriaxone MIC, and MICs have fluctuated between 0.1% and 0.4% between 2009 and 2018.[6] These concerns of ceftriaxone resistance prompted the CDC in 2020 to increase the ceftriaxone dose for uncomplicated gonorrhea from 250 to 500 mg.[18]

Prescribing patterns

The CDC's 2018 Sexually Transmitted Disease Surveillance Program observed that 96.5% of treated patients received ceftriaxone. The number of those treated with cefixime decreased from 0.3% in 2015 to 0.1% in 2018. This decrease in cefixime use was expected as CDC recommendations were to avoid the use of cefixime at any dose as first-line therapy.[18] Treatment with gentamicin 240 mg increased from 0.2% in 2015 to 1.4% in 2018. Prescribed treatment for gonorrhea, in order of most frequently used, was ceftriaxone, gentamicin, azithromycin, and cefixime (**Fig. 72-3**).

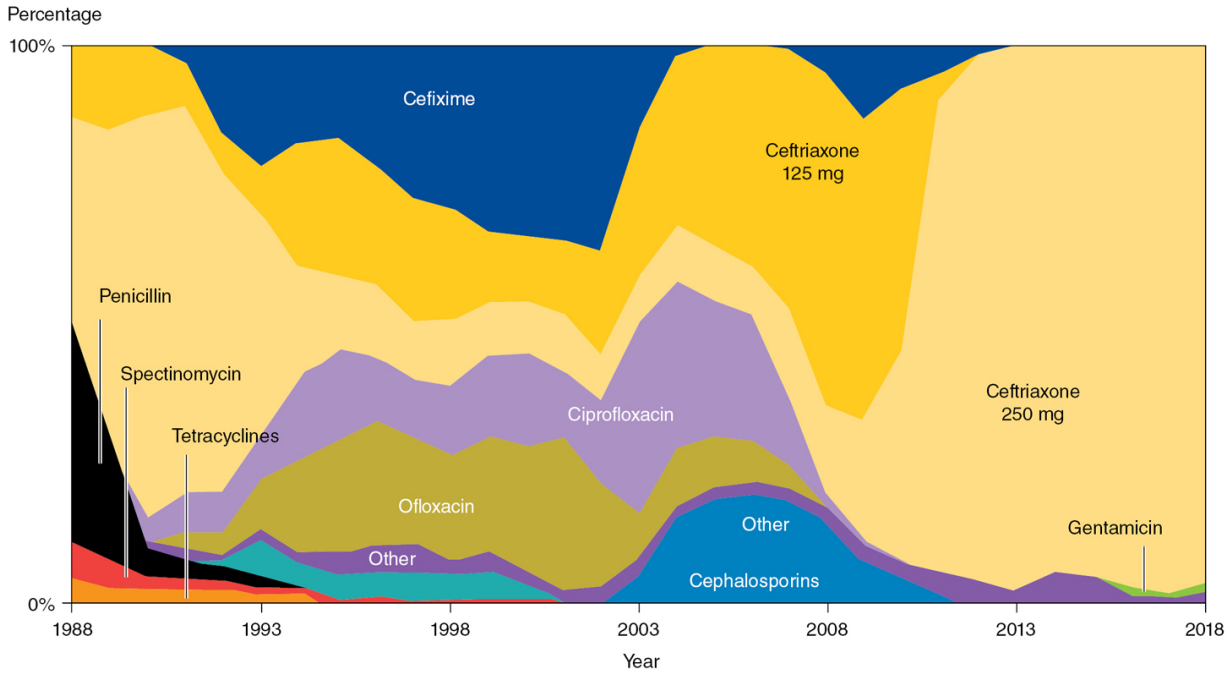


Figure 72-3 Area graph showing the distribution of primary antimicrobial drug used to treat gonorrhea among Gonococcal Isolate Surveillance Project (GISP) participants from 1988 to 2018. (From Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. https://www.cdc.gov/std/stats18/figures/33.htm.)

Case 72-1, Question 7: How should D.S.'s urethritis be treated? Because C.S. is totally asymptomatic and the results of her cultures are pending, should she be treated empirically? If so, what drug(s) would you recommend?

Because D.S. has gonococcal infection limited to the urethra (uncomplicated), a few treatment regimens are possible, as outlined in Case 72-1, Question 6. Ceftriaxone is the preferred treatment, with cefixime as an alternative, only if ceftriaxone is not available. Quinolones should be avoided because of increased resistance in *N. gonorrhoeae* and because D.S.'s infection was likely obtained in the Philippines, where quinolone resistance occurs in more than half of all isolates.[20],[28] Patients with gonorrhea may also be coinfected with chlamydia, and therefore presumptive cotreatment with doxycycline 100 mg PO twice daily for 7 days could be initiated if coinfection is suspected.[29],[30]

Sexual partners

C.S. also should be treated even though she appears asymptomatic. All partners who have had sexual exposure to patients with gonorrhea within 60 days should be treated. If the patient has not been sexually active for 60 days, the most recent sexual partner should be treated. This is especially true when the partner is pregnant because gonorrhea during pregnancy is associated with chorioamnionitis and prematurity, as well as neonatal infection. Pregnant females can be treated safely with cephalosporins and azithromycin for gonorrhea and chlamydia. Doxycycline should be avoided during pregnancy.

Follow-up

Case 72-1, Question 8: How does one determine whether the drug therapy of gonorrhea has been effective in D.S. and C.S.?

If recommended therapies are used for the treatment of uncomplicated gonorrhea, a test of cure is not necessary for either C.S. or D.S. because cure rates are close to 100%.[2] However, a test of cure should be done 7 to 14 days after treatment in those with pharyngeal infection using culture or NAATs regardless of treatment regimen.[2],[18] If symptoms persist in D.S., who was treated with

ceftriaxone, cultures should be done to determine antibiotic susceptibility, and to rule out other causes of urethritis.

Anorectal and Pharyngeal Gonorrhea

EPIDEMIOLOGY

CASE 72-2

Question 1: M.B. is a 24-year-old, sexually active MSM with a 2-month history of perianal itching, painful defecation, constipation, a bloody mucoid rectal discharge, and a sore throat. Sigmoidoscopy revealed rectal mucosal inflammation but no apparent ulcers or fissures. Stool examination for parasites returned a negative result and a Venereal Disease Research Laboratory (VDRL) test result was nonreactive. Both rectal and pharyngeal culture results revealed *N. gonorrhoeae.*

How does gonorrhea infection in MSM compare with gonorrhea infection in MSW?

Rectal infection occurs rarely in strictly MSW, whereas in the MSM population, anorectal (25%) and pharyngeal (10%–25%) gonococcal infections occur more often.[9,31] CDC data in 2018 from STD clinics saw a median positivity of 14.8% rectal and 12.9% pharyngeal gonorrhea among MSM.[6] Because pharyngeal[31,32] and anorectal gonococcal infections are often asymptomatic, a large reservoir of carriers in the homosexual male population may exist, and annual screening should be done if they have engaged in receptive oral or anal intercourse in the preceding year. By comparison, very few urethral gonococcal infections are asymptomatic. In addition, data indicate that pharyngeal infections may be an important source of urethral gonorrhea in homosexual males, spread by fellatio.[31,33]

SIGNS AND SYMPTOMS

Case 72-2, Question 2: Are M.B.'s signs and symptoms consistent with gonorrhea?

Rectal gonorrhea produces the syndrome of proctitis with anorectal pain, mucopurulent anorectal discharge, constipation, tenesmus, and anorectal bleeding. The differential diagnosis of proctitis in MSM includes rectal infection with *N. gonorrhoeae, C. trachomatis*, HSV, and syphilis. Proctitis, limited to the distal rectum, should be differentiated from proctocolitis, which is often caused by *Shigella* species, *Campylobacter* species, or *Entamoeba histolytica* in homosexual males. The incidence of rectal gonorrhea and chlamydia has risen dramatically since 1996.[34] Rectal chlamydia is often asymptomatic and observed more often than is gonorrhea, necessitating testing for both pathogens.[35] Although pharyngeal gonorrhea is often asymptomatic, a review of the system and physical exam may reveal a sore throat, pharyngeal exudates, or cervical lymphadenitis.

TREATMENT

Case 72-2, Question 3: How should M.B.'s diagnosis be managed?

The treatment of choice for patients such as M.B. with anorectal or pharyngeal gonorrhea is ceftriaxone 500 mg IM as a single dose (see Table 72-1).[2] Doxycycline should also be given to treat possible coexisting rectal chlamydial infection. Patients such as M.B. with either anorectal or pharyngeal gonorrhea should be advised to avoid further unprotected sexual activity and should be counseled and tested for infection with HIV.

Case 72-2, Question 4: What are alternative regimens for patients with isolated anal or pharyngeal gonorrhea?

Patients with anorectal gonorrhea alone should be treated with ceftriaxone. Oral cefixime is a recommended alternative but should not be used as a first-line agent. As with urogenital infections, alternative regimens for isolated anorectal infection include a single-dose cephalosporin regimen such as ceftizoxime. Because

spectinomycin is unavailable, patients with anorectal gonorrhea who are allergic to penicillin or cephalosporins should be desensitized before treatment is initiated. Patients with gonococcal infections of the pharynx should be treated with ceftriaxone; however, infections of this nature are more difficult to eradicate than are infections at urogenital and anorectal sites. Treatment for gonorrheal infections at these sites should also include doxycycline for presumptive chlamydial coinfection if it has not been excluded.[2,18]

PREVENTION

CASE 72-2, QUESTION 5: What measures have been used to prevent the sexual transmission of infection?

Condoms, when used properly, seem to provide a high degree of protection against the acquisition and transmission of STDs.[2,36] Previous studies indicated that the use of the spermicide nonoxynol-9 had activity against gonorrhea and chlamydia; however, in light of recent evidence suggesting that nonoxynol-9 might actually increase the risk of acquiring HIV and other STDs, the FDA currently requires manufacturers of nonoxynol-9 products to include a warning statement on the product's label that it does not protect against HIV or other STDs.[15,37] Topical antibacterial agents, urinating, and washing after intercourse are of little value in preventing the transmission of STDs. Douching may increase the risk of other STDs such as trichomoniasis.[38]

The prophylactic administration of antibiotics immediately before or soon after sexual intercourse is not recommended owing to increased costs and antimicrobial resistance. Use of rapid, specific tests and empiric symptomatic management should be used to enhance detection and treatment of gonorrhea.

PELVIC INFLAMMATORY DISEASE

The term *pelvic inflammatory disease (PID)* refers to a variety of inflammatory disorders of the upper female reproductive tract. This term does not denote the primary infection site (the fallopian tubes) nor the causative microorganisms. PID also has been used to connote an infection that occurs acutely when either vaginal or cervical microorganisms traverse the sterile endometrium and ascend to the fallopian tubes. Acute salpingitis also may be used to describe an acute infection of the fallopian tubes. Therefore, the terms *PID* and *salpingitis* are used interchangeably in this discussion to denote an acute infection involving the fallopian tubes.

PID affects ~2.5 million females annually in the United States.[39] However, the National Disease and Therapeutic Index (NDTI) estimates that from 2007 to 2016, the number of initial visits to physicians for PID for females ages 15 to 44 years decreased 38.3% from 146,000 to 90,000 visits. Many cases of acute PID occur by sexual transmission, especially in females ages 16 to 24 years who are more likely to have multiple sexual partners.[40] Risk factors for the development of PID include unprotected sexual intercourse before age 15, douching, bacterial vaginosis (BV), sex while menstruating, and smoking.[41] It is unclear whether an intrauterine device (IUD) increases the risk of PID, but it may be prudent to avoid placement when the patient has chlamydial or gonococcal cervicitis.[42] Two-thirds of PID cases resulting in infertility are asymptomatic, and up to one-third are incorrectly diagnosed owing to low specificity of diagnostic techniques. In the United States, infertility occurs in about 12.1% of females after the first episode of PID.[43] The estimated costs for treatment of PID and its sequelae exceed $4.2 billion annually.[44]

Etiology

Most cases of PID are caused by *C. trachomatis* and *N. gonorrhoeae.* Some microorganisms that make up the vaginal flora are also associated with PID including *Gardnerella vaginalis, Haemophilus influenzae*, and *Streptococcus agalactiae. M. hominis,*

Ureaplasma urealyticum, M. genitalium, and cytomegalovirus (CMV) have also been associated with PID, but a causative role is unclear.[15] Cases of PID are also associated with polymicrobial infection, BV, and anaerobic gram-negative rods.[45] Facultative enteric gram-negative bacilli and a variety of anaerobic bacteria have also been isolated from the upper genital tract of up to 70% of females with acute PID.[45] Females diagnosed with acute PID should be tested for *C. trachomatis* and *N. gonorrhoeae* using NAAT and screened for HIV.[2]

Signs and Symptoms

The variations in presentation and nonspecific signs and symptoms of PID make it a complex disease to diagnose. The onset of abdominal pain attributable to PID caused by either gonococci or chlamydia often occurs soon after the menstrual period. Additional symptoms, if present, are often non-specific, which can create a delay in or failure of diagnosis. Vaginal discharge, menorrhagia, dysuria, and dyspareunia are commonly associated with PID. Pelvic examination findings include cervical motion tenderness, uterine tenderness, or adnexal tenderness. Temperatures >101 °F (38.33 °C), abnormal cervical or vaginal mucopurulent discharge, white blood cells (WBCs) on saline microscopy of vaginal secretions, elevated erythrocyte sedimentation rate, elevated C-reactive protein, or laboratory documentation of cervical infection with *N. gonorrhoeae or C. trachomatis* support a diagnosis of PID.[2] Clinical diagnosis has a sensitivity for PID of 65% to 90%, whereas laparoscopy and a newer technique, transvaginal Doppler ultrasound, are 100% specific, resulting in the combination of laparoscopy and clinical impression serving as the gold standard.[2,46,47] Unfortunately, laparoscopy and Doppler ultrasound are costly and often not readily available for acute cases and they are not diagnostic for endometritis; thus, clinical impression is critical. A key to reducing the incidence of PID may be through active screening of *Chlamydia* in young, sexually active females.[48,49]

Clinical Sequelae

An abscess may form in the pelvic or abdominal cavity and or one or both fallopian tubes. Chronic abdominal pain develops in 18% of females with PID and may be the result of pelvic adhesions surrounding the tubes and ovaries. After a single episode of PID, tubal occlusion and fibrosis secondary to fallopian tube inflammation (salpingitis) result in 12% infertility, 25% infertility after two episodes, and 50% infertility after three or more episodes.[43] Other sequelae include ectopic pregnancy (9%) and chronic pelvic pain (18%).[50] The risk of ectopic pregnancy is increased approximately eightfold after one or more episodes of PID.

Diagnosis and Treatment

CASE 72-3

Question 1: H.C., a 19-year-old, sexually active female, presents with mild dysuria, a purulent vaginal discharge, fever, and moderately severe, bilateral, lower abdominal pain of 3 days duration. Examination confirms uterine and adnexal tenderness, a purulent cervical exudate, and a temperature of 102.20 °F (39 °C). Laboratory examinations show a nonreactive VDRL and negative urinalysis. A pregnancy test performed returned a negative result. The peripheral WBC count was mildly elevated (11,000/μL), with 70% PMNs.

Does H.C. have PID? How should she be treated?

Although fever and leukocytosis are often absent in mild or subacute PID, these findings in a female with uterine and adnexal tenderness with cervical exudate increases the likelihood of acute PID. Recommended treatment regimens for PID are listed in **Table 72-2** and should be initiated immediately after diagnosis of PID to prevent clinical sequelae; confirmation of the actual pathogen rarely takes place. Patients such as H.C. with mild-to-moderate PID can be hospitalized and treated with parenteral antibiotics; however, clinical efficacy and overall outcomes are equal between parenteral and oral therapy, and H.C. could also be treated on an outpatient basis. For inpatient treatment, the CDC recommends either intravenous (IV)

cefotetan 2 g every 12 hours or IV cefoxitin 2 g every 6 hours for at least 24 hours beyond the first signs of clinical improvement along with doxycycline 100 mg every 12 hours. Once clinical improvement is noted, parenteral therapy may be discontinued, and PO doxycycline 100 mg every 12 hours can continue to complete 14 days of therapy. For outpatient treatment, the CDC guidelines recommend either IM ceftriaxone 250 mg as a single dose or IM cefoxitin 2 g as a single dose (with probenecid 1 g PO for one dose) plus PO doxycycline 100 mg twice a day for 14 days with or without PO metronidazole 500 mg twice daily for 14 days.[2] A tetracycline derivative or an alternative agent that is active against *C. trachomatis* should be included in the treatment of PID; however, monotherapy with a tetracycline is not recommended because of the lack of activity against gram-negative aerobic and anaerobic organisms and *N. gonorrhoeae.* The addition of metronidazole, which covers anaerobic bacteria, should also be considered; anaerobes have been isolated from the upper reproductive tract of females with PID and may cause tubal and epithelial destruction.[2,51] Metronidazole is widely used by clinicians because BV is frequently associated with PID.[2] Fluoroquinolones such as levofloxacin and ofloxacin are no longer recommended for the treatment of PID because of the increase in the prevalence of QRNG in the United States.[20]

Table 72-2
Antimicrobial Regimens Recommended by the CDC for Treatment of Acute Pelvic Inflammatory Disease

Treatment Setting, Drugs, Schedule	Advantage	Disadvantage	Clinical Considerations
Inpatient (Parenteral) Therapy			
Regimen A			
Cefotetan 2 g IV every 12 hours *or* cefoxitin 2 g IV every 6 hours *plus* doxycycline 100 mg IV or PO[a] every 12 hours Continue doxycycline (100 mg PO twice daily) after discharge to complete 14 days of therapy.	Optimal coverage of *Neisseria gonorrhoeae* (including resistant strains) and *Chlamydia trachomatis*	Possible suboptimal anaerobic coverage	Penicillin-allergic patients also may be allergic to cephalosporins; doxycycline use in pregnant patients may cause reversible inhibition of skeletal growth in the fetus and discoloration of teeth in young children.
Regimen B			
Clindamycin 900 mg IV every 8 hours *plus* gentamicin loading dose IV or IM (2 mg/kg) followed by a maintenance dose of 1.5 mg/kg every 8 hours[b]	Optimal coverage of anaerobes and gram-negative enteric rods	Possible suboptimal coverage of *N. gonorrhoeae* and *C. trachomatis*	Patients with decreased renal function may not be good candidates for aminoglycoside treatment or may need a dosage adjustment.
Alternative Regimen			
Ampicillin/sulbactam 3 g IV every 6 hours *plus* doxycycline 100 mg PO or IV every 12 hours	Optimal coverage of *N. gonorrhoeae* and *C. trachomatis*	Inadequate coverage of anaerobes necessitates the use of metronidazole or ampicillin/sulbactam.	Not appropriate in pregnancy or in young children
Outpatient (Intramuscular or Oral) Therapy[c]			
Ceftriaxone 500 mg IM in a single dose *plus* doxycycline 100 mg PO twice daily for 14 days *with* metronidazole 500 mg PO twice daily for 14 days *or* Cefoxitin 2 g IM in a single dose and probenecid, 1 g PO administered concurrently in a single dose *plus* doxycycline 100 mg PO twice daily for 14 days *with* metronidazole 500 mg PO twice daily for 14 days *or* Other parenteral third-generation cephalosporins (eg, ceftizoxime or cefotaxime) *plus* doxycycline 100 mg PO twice daily for 14 days *with* metronidazole 500 mg PO twice daily for 14 days	Good to excellent coverage of *N. gonorrhoeae* and optimal coverage of *C. trachomatis*	Possible suboptimal anaerobic coverage necessitating the addition of metronidazole	Optimal cephalosporin is unclear; more complicated regimen requiring a combination of parenteral and oral therapies

CDC, Centers for Disease Control and Prevention; IM, intramuscular; IV, intravenous; PID, pelvic quality disease; PO, orally.

[a]Considering the oral bioavailability of doxycycline, oral (PO) therapy should be preferentially used over intravenous (IV).

[b]Single daily dosing (3–5 mg/kg) may be substituted.

[c]Consider for mild-to-moderate acute PID.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1–187. doi:10.15585/mmwr.rr7004a1.

Both oral and IV doxycycline have similar bioavailability; therefore, doxycycline should be given PO whenever possible.[2] Substantial clinical improvement is usually seen within 3 days of initiation of therapy. Clindamycin plus gentamicin can be used alternatively in penicillin-allergic and pregnant females.[2] Because H.C. is sexually active, any sexual partners within the previous 60 days (or if >60 days, then the most recent sexual partner) should be empirically treated because of the risk of gonococcal or chlamydial urethritis as well as to reduce the risk of reinfection.[2]

COMPLICATED GONORRHEA

Disseminated Gonococcal Infection

SIGNS AND SYMPTOMS

CASE 72-4

QUESTION 1: S.P., a 28-year-old, sexually active female, was seen for stiffness and pain of the right wrist and left ankle and fever (100.40 °F [38 °C]). On physical examination, the knee and wrist joints were found to be hot, red, and swollen; papules and pustular lesions were observed on S.P.'s legs and forearms. A latex fixation test result for rheumatoid factor was negative. A tap of the right knee yielded an effusion with a WBC count of 34,000/μL (80% PMNs). Culture results of the skin lesions were negative, but *N. gonorrhoeae* was isolated from the throat, cervix, blood, and synovial fluid. A chest radiograph, echocardiogram, and electrocardiogram findings all were normal, and no murmur could be appreciated.

What do you make of S.P.'s clinical presentation?

S.P.'s signs, symptoms, and laboratory findings are consistent with gonococcal bacteremia, which today occurs in <1% of patients with gonorrhea. The most common manifestation of gonococcemia is the gonococcal arthritis–dermatitis syndrome or DGI exhibited by S.P. Symptoms include fever, occasional chills, a mild tenosynovitis of the

small joints, and skin lesions; the latter, primarily involving the distal extremities, are petechial, papular, pustular, and hemorrhagic in appearance.[2]

Diagnosis of DGI is made by NAAT or culture of specimen from routine sites of gonococcal infections (eg, urethra, cervix, pharynx, and rectum), as well as culture from disseminated sites of infection (eg, synovial fluid, blood, skin, and CNS). However, blood culture results are positive in only 33% of DGI cases, even when culture samples are obtained early in the course of the infection.[15] The low positive yield from blood cultures may be attributable to the low inoculum or intermittent bacteremic period.

TREATMENT

Case 72-4, Question 2: How should S.P. be managed? How quickly will she respond to therapy?

Patients such as S.P. with gonococcal arthritis and bacteremia should be hospitalized for treatment with ceftriaxone 1 g IV or IM daily until substantial clinical improvement is sustained for 24 to 48 hours, at which time therapy may be switched to an oral agent guided by antimicrobial susceptibility for a total treatment course of at least 7 days (**Table 72-3**).[2] Initiation of treatment should also include doxycycline 100 mg twice daily for 7 days. Symptoms and signs of tenosynovitis should be improved markedly within 48 hours. Septic gonococcal arthritis with purulent synovial fluid may require repeated aspiration and resolves more slowly.

Table 72-3
Treatment of Disseminated Gonococcal Infection[a] (No Penicillin Allergy)

No Penicillin Allergy
Parenteral
Recommended[b]: Ceftriaxone 1 g IV or IM every 24 hours

Alternative[b]: Cefotaxime 1 g IV Q 8 hours or ceftizoxime 1 g IV Q 8 hours
Oral[c]: Cefixime 400 mg PO twice daily

IM, intramuscular; IV, intravenous; PO, orally; Q, every.

[a]Parenteral treatment should be continued for 24 to 48 hours beyond clinical improvement.

[b]Doxycycline 100 mg twice daily for 7 days.

[c]Treat for 7 days after switching from parenteral therapy.

Source: Adapted from Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1–187. doi:10.15585/mmwr.rr7004a1.

Treatment of Gonococcal Endocarditis and Meningitis

Case 72-4, Question 3: How should gonococcal endocarditis and meningitis be treated?

Gonococcal endocarditis and meningitis, occurring in only 1% to 3% of DGIs, require high-dose IV therapy such as ceftriaxone (1–2 g IV every 12–24 hours) for 10 to 14 days in the case of meningitis and for at least 4 weeks in the case of endocarditis.[2] As with other gonococcal infections, a single dose of azithromycin 1 g PO should be given.

Neonatal Disseminated Gonococcal Infection: Treatment

Case 72-4, Question 4: How should neonatal DGI and meningitis be managed?

Neonatal DGI and meningitis can be treated with either ceftriaxone 25 to 50 mg/kg (IV or IM) daily or cefotaxime 25 mg/kg (IV or IM) every 12 hours. Treatment is for 7 days for DGI; however, meningitis

requires 10 to 14 days of treatment.[2] Although ceftriaxone is also effective in the treatment of neonatal DGI and meningitis, cefotaxime is considered a safer choice in the neonatal population.

CHLAMYDIA TRACHOMATIS

The rate of reported *Chlamydia* infections has climbed steadily each year since the 1980s and is the most commonly reported STD in the United States. From 2000 to 2018, the reported rate of chlamydial infections increased from 254.1 to 539.9 cases per 100,000 individuals.[6] This increase may be attributable to the increased development and use of more sensitive screening tests, improved national reporting efforts, or a true increase in the incidence of disease.[15] Females are three times more likely than are males to be infected with *Chlamydia*—692.7 cases versus 380.6 cases per 100,000 individuals, respectively, in 2018. However, from 2014 to 2018, the infection rate among males increased 37.8% compared with 11.4% in females. The highest rate of infection is in females 20 to 24 years (4064.6 cases per 100,000 females) and in males 20 to 24 years (1784.5 cases per 100,000 males).[6] If left untreated, chlamydial infection in females can lead to serious sequelae such as PID, ectopic pregnancy, and infertility. Asymptomatic infection is also observed in both males and females; however, routine screening is recommended for sexually active females up to 25 years of age and older females with risk factors for infection (eg, multiple sexual partners or having a new sexual partner). Screening sexually active males for *C. trachomatis* can be considered in settings or populations with a high prevalence of the infection (eg, MSM population).[2]

C. trachomatis, an obligate intracellular bacterium, can be diagnosed by culture, direct immunofluorescence assay (DFA), enzyme immunoassay (EIA), or NAAT of endocervical or male urethral swabs.[15] However, *C. trachomatis* is a difficult organism to demonstrate in clinical specimens because cell culture techniques

are not readily available to the practitioner. Because few practitioners have access to facilities for isolation of *C. trachomatis,* most chlamydial infections are diagnosed and treated based on clinical impression and laboratory techniques. NAATs are recommended for detecting *C. trachomatis* because it is the most sensitive nonculture diagnostic test method. Ligase chain reaction and PCR are two NAATs with wide commercial availability, are relatively simple to use, can be performed using urine or genital swab specimens, and are more sensitive than are non-NAATs.[16] NAATs are ~20% to 35% more sensitive than are EIAs and DFAs, and they are the recommended test method for the detection of *C. trachomatis* in patients with and without symptoms.[2,17] A test of cure is not necessary unless patient adherence is questionable, symptoms persist, or reinfection is suspected. Repeat testing with NAATs <3 weeks after initiation of treatment is not recommended because false-negative results may occur as a result of undetectable *C. trachomatis* organisms. Moreover, false positives may occur with repeat NAATs with the continued excretion of dead organisms.

A variety of clinical syndromes are caused by *C. trachomatis,* including cervicitis, urethritis, bartholinitis, endometritis, salpingitis, and perihepatitis in females, and urethritis, epididymitis, prostatitis, proctitis, and Reiter syndrome in males.[15] The spectrum of chlamydial infections closely resembles those caused by gonococcus, which is why many patients presenting with these syndromes are treated with drugs effective against both organisms.

There is controversy over how *C. trachomatis* is cultured and what the in vitro results mean clinically, especially in the 10% to 15% of cases that fail treatment.[52] The CDC thus uses cure rates instead of microbial susceptibilities to make treatment recommendations. Only azithromycin and doxycycline have 97% and 98% cure rates, respectively.[2,53] Alternatives include erythromycin, ofloxacin, and levofloxacin. Other quinolones should not be used because they have not been evaluated adequately or are not reliably effective.[2]

Nongonococcal Urethritis

ETIOLOGY

CASE 72-5

QUESTION 1: T.K., a 26-year-old, sexually active male, presents with mild dysuria and a mucoid urethral discharge beginning 15 days after his last intercourse. He has no fever, lymphadenopathy, penile lesions, or hematuria. A Gram stain smear of an anterior urethral specimen showed 20 PMNs per oil immersion (1000) field and no gram-negative diplococci.

What pathogens are associated with nongonococcal urethritis (NGU)?

In the United States, NGU is the most common STD in males.[54],[55] *C. trachomatis* is a frequent cause of NGU, representing 15% to 40% of all cases. Other agents that have been associated with NGU include *M. genitalium*, *T. vaginalis, HSV, and adenovirus*; however, the cause for the majority of NGU cases is unknown.[15] The variety of pathogens and disparity among identification techniques require sound clinical judgment and an algorithmic laboratory testing approach to accurately identify and treat the cause. A NAAT, if available, should be performed to rule out the presence of *C. trachomatis* and *N. gonorrhoeae*.

SIGNS AND SYMPTOMS

CASE 72-5, QUESTION 2: Describe the clinical presentation of a person with NGU. Is T.K.'s presentation consistent with NGU? How can NGU be differentiated from gonococcal urethritis?

T.K.'s presentation is typical. Compared with gonococcal urethritis, NGU typically produces less severe and less frequent dysuria and less penile discharge. Chlamydial urethral infection is completely asymptomatic more often than is gonococcal urethral infection. The incubation period for gonococcal urethritis is 2 to 7 days, whereas the incubation period for NGU is typically 2 to 3 weeks.

Nonetheless, NGU and gonococcal urethritis cannot be reliably differentiated solely on the basis of symptoms and signs. If there is

objective evidence of a urethral discharge (expressed by milking the urethra), a Gram stain of the urethral discharge with ≥2 WBCs per oil immersion field, or urinalysis of first voided urine with positive leukocyte esterase or >10 WBC per high power field, the diagnosis of NGU is made by excluding the presence of *N. gonorrhoeae* by Gram stain and/or culture.

TREATMENT

CASE 72-5, QUESTION 3: How should T.K. be treated?

If *C. trachomatis* cannot be ruled out, therapy with azithromycin 1 g PO for one dose or doxycycline 100 mg PO twice daily for 7 days should be ordered. Compared to doxycycline, *M. genitalium* responds better to azithromycin because doxycycline does not effectively eradicate *M. genitalium*.[2] Azithromycin also has the advantage of a single-dose regimen, which may aid in patient adherence. If adherence is a concern, or the patient is receiving a multidose regimen, all doses of the medication should be dispensed on-site in the clinic, and the first dose should be directly observed. Erythromycin base 500 mg PO four times a day or erythromycin ethylsuccinate 800 mg PO four times a day for 7 days is an alternative CDC-approved regimen. In addition, ofloxacin 300 mg PO twice daily or levofloxacin 500 mg PO every day for 7 days is another alternative, but they offer no significant advantages compared with the previously mentioned agents, may not treat *U. urealyticum* adequately, and are significantly more expensive.[2,56] Ciprofloxacin should be avoided because treatment failures have been reported.[57] Patient counseling should emphasize the need for abstinence from sexual intercourse at least until the prescribed course of therapy has been completed (or 7 days after single-dose therapy) by the patient and his sexual partner(s).[2] There is some indication that the proportion of NGU caused by *C. trachomatis* is declining, potentially being replaced by an increased proportion of *U.*

urealyticum, which is variably cured at 2 weeks by azithromycin (73%) and doxycycline (65%).[58]

Recurrent infection

Case 72-5, Question 4: T.K. was treated with doxycycline 100 mg twice daily for 7 days. He remained asymptomatic for 14 days after completion of his therapy when he again noticed similar symptoms of dysuria and a mucoid urethral discharge. How should T.K.'s recurrent infection be treated?

The major problem encountered in the treatment of NGU is the high rate of recurrent infections. Males receiving treatment should follow up if symptoms persist or recur after completion of therapy. Approximately 20% to 60% of patients experience recurrent or persistent urethritis within 1 to 2 weeks of treatment.[59] The rate of recurrence is highest in patients with idiopathic urethritis, that is, those not infected with *C. trachomatis* or *U. urealyticum.* Recurrence suggests reexposure to an untreated partner, whereas persistent urethritis (without improvement during therapy) suggests the presence of other organisms including *M. genitalium*, *U. urealyticum,* or *T. vaginalis*.[2],[60],[61] NGU that persists or recurs should be retreated with the initial regimen if the patient was not compliant or the sexual partner was not treated. For patients with persistent symptoms who were compliant with the initial regimen and were not reexposed, the CDC recommends using a single 1-g dose of azithromycin if not used for the initial episode or moxifloxacin 400 mg PO daily for 7 days if the patient has failed azithromycin.[2]

Males with acute epididymitis often have a chlamydial or gonococcal infection, particularly if they are younger than age 35 years or have a urethral discharge. *Escherichia coli* and *Pseudomonas* species are common pathogens in homosexual males. In older males, sexually transmitted epididymitis is less common and is more commonly caused by urinary tract instrumentation, surgery, systemic disease, or immune suppression.[2] If testicular tenderness is present with urethritis, and the clinical

impression is consistent with epididymitis caused by *Chlamydia* or gonorrhea, the CDC recommends a single dose of ceftriaxone 250 mg IM plus doxycycline 100 mg PO twice for 10 days. For acute epididymitis caused by enteric organisms or with a negative gonococcal culture or NAAT, ofloxacin 300 mg PO twice daily or levofloxacin 500 mg PO once daily for 10 days may be used.[2,51] In males who practice insertive anal sex, where the most likely cause of acute epididymitis is caused by chlamydia, gonorrhea, and enteric organisms, the CDC recommends ceftriaxone 250 mg IM in a single dose plus levofloxacin 500 mg PO daily or ofloxacin 300 mg PO bid for 10 days.[2]

SEXUAL PARTNERS

Case 72-5, Question 5: A.C., T.K.'s girlfriend, comes into the clinic 3 weeks after T.K.'s last visit. She is worried that she may have a similar infection, although she has no signs or symptoms. What clinical manifestations of chlamydial infections are seen in females? Should A.C. be treated for suspected chlamydial infection?

In the absence of cultures for chlamydia, empirical treatment against chlamydia in females who are sexual partners of males with NGU is recommended. Many partners are asymptomatic, but from 30% to 70% return positive culture results if tested. A.C. should be examined carefully for mucopurulent cervicitis and salpingitis. Although many females with chlamydial infection of the cervix are asymptomatic, up to one-quarter have evidence of mucopurulent discharge.[62] A Gram stain of appropriately collected mucopurulent endocervical discharge from patients with chlamydia infection shows many PMNs and no gonococci.

Regardless of findings, treatment should be initiated with the same azithromycin or doxycycline regimen used for NGU. However, if A.C. is pregnant, tetracyclines and fluoroquinolones should be avoided. Azithromycin 1 g PO as a single dose or amoxicillin 500 mg PO three times a day for 7 days could be used instead. Alternatively, either erythromycin base 500 mg PO four times a day for 7 days,

erythromycin base 250 mg PO four times a day for 14 days, erythromycin ethylsuccinate 800 mg PO four times a day for 7 days, or erythromycin ethylsuccinate 400 mg PO four times a day for 14 days can be used.[2] Erythromycin estolate should be avoided in pregnancy because of the increased risk of hepatotoxicity. Azithromycin is safe and effective during pregnancy.[63],[64] High rates of gastrointestinal (GI) side effects limit the use of erythromycin. In pregnant females, a repeat NAAT is recommended 3 weeks after completion of therapy to ensure therapeutic cure.[2] Coinfection with chlamydia is common in heterosexual males and females with gonorrhea. Therefore, drug regimens effective against both organisms are recommended in patients with gonorrhea to prevent postgonococcal chlamydial morbidity (epididymitis, mucopurulent cervicitis, salpingitis) and to reduce the genital reservoir of *C. trachomatis.*

Lymphogranuloma Venereum

ETIOLOGY AND SIGNS AND SYMPTOMS

CASE 72-6

Question 1: S.F., a 32-year-old male student who reports having sex with females, presents to the STD clinic with pain and swelling in the groin. He reports the appearance of a small ulcer on his penis about 2 weeks ago, which resolved rapidly. On examination, he has a bubo (inflammatory swelling of one or more lymph nodes in the groin) with surrounding erythema on his right side. S.F. also has a fever (102.20 °F [39 °C]). Laboratory findings are remarkable for a mild leukocytosis (WBC count, 12,000 cells/μL).

What organisms are responsible for lymphogranuloma venereum (LGV)? What is its clinical course? What subjective and objective manifestations in S.F. are consistent with LGV?

LGV or Nicolas–Favre disease has historically been considered a rare disease in the United States and other developed nations; however, outbreaks have been recently reported in the Netherlands and Great Britain as well as in the United States in New York, Texas,

and San Francisco.[65],[66] Since 2003, the number of cases of LGV, especially proctocolitis, in MSM in developed countries has been increasing.[67],[68] The cause of LGV is usually *C. trachomatis* serovars L1, L2, or L3, which are different from those serovars responsible for chlamydia urethritis.[69] Three stages of LGV infection are recognized in MSW.[70]

Stage I is characterized by a small genital papule or vesicle that appears between 3 and 30 days after exposure. The patient usually is asymptomatic; the ulcer heals rapidly and leaves no scar. This primary lesion is consistent with that reported by S.F. Many patients with LGV recall no primary lesion. Stage II is characterized by acute, painful lymphadenitis with bubo formation (the inguinal syndrome); it often is accompanied by pain and fever, as illustrated by S.F. Without treatment, the buboes may rupture, forming numerous sinus tracts that drain chronically. Adenopathy above and below the inguinal ligament results in the "groove sign." Healing occurs slowly, and most patients suffer no serious sequelae. Patients in this stage also may present with an anogenitorectal syndrome, which is accompanied by proctocolitis and hyperplasia of intestinal and perirectal lymphatic tissue. Stage III is characterized by perirectal abscesses, rectovaginal fistulae (in females), rectal strictures, and genital elephantiasis.[70] Appropriate treatment of stage II LGV usually prevents these late complications.

An acute anorectal syndrome of LGV occurs in MSM who acquire the infection through rectal receptive intercourse. In these cases, a primary anal ulcer may be noted with associated inguinal adenopathy (anal lymphatics drain to inguinal nodes). Subsequently, acute hemorrhagic proctocolitis occurs with tenesmus, rectal pain, constipation, and a copurulent, bloody rectal discharge. Rectal biopsy findings may show granulomatous colitis, mimicking Crohn disease. Perirectal pelvic adenopathy also occurs.

TREATMENT

Case 72-6, Question 2: How should S.F. be treated?

Current CDC recommendations for LGV include doxycycline 100 mg PO twice daily or, as an alternative, erythromycin base 500 mg PO four times a day for 21 days.[2] Surgical intervention may be needed for later forms of the disease. Azithromycin 1 g weekly for 3 weeks may be effective as well as fluoroquinolones, but clinical data on its use are lacking.[2]

SYPHILIS

Epidemiology

Syphilis is caused by the spirochete *Treponema pallidum.* The rates of primary and secondary syphilis in the United States increased in the late 1980s secondary to crack cocaine use (and associated unsafe sex practices), but from 1990 to 2000, rates have decreased to those reported in 1941 when reporting began, representing an 89.7% decrease since 1990.[5,71,72] However, the number of cases of primary and secondary syphilis have steadily risen since 2000, reaching a high of 35,063 cases in 2018 (**Fig. 72-4**). MSM continue to account for the majority of primary and secondary syphilis cases in 2018. Another concern is that syphilis facilitates the transmission of HIV, thus the high proportion of syphilis reported in HIV-positive MSM.[5,73] Since 2008, rates of congenital syphilis did not increase until 2013 and have continued to rise since then to a total of 1306 cases in 2018.[6] In 2018, the total case count of reported syphilis for all stages combined was the highest recorded since 1991.

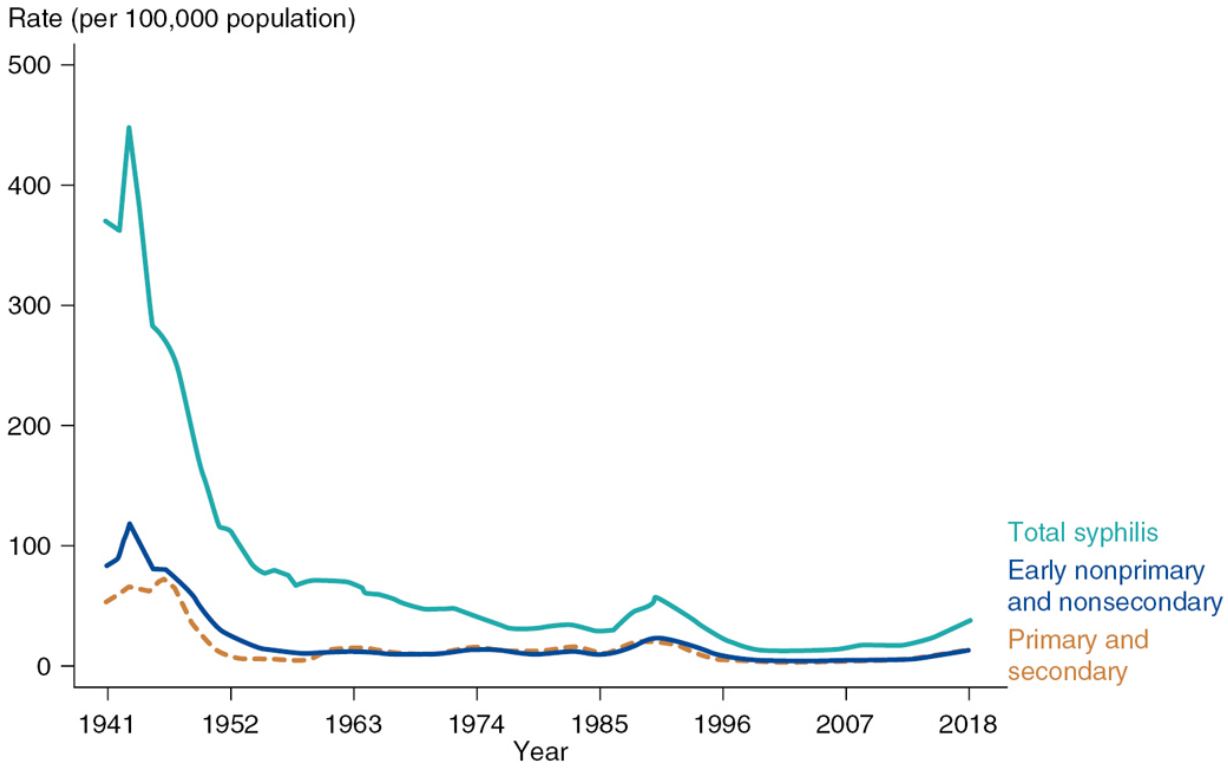


Figure 72-4 In 2018, a total of 35,063 cases of primary and secondary syphilis were reported in the United States, yielding a rate of 10.8 cases per 100,000 population. This rate represents a 14.9% increase compared with that in 2017 (9.4 cases per 100,000 population), and a 71.4% increase compared with that in 2014 (6.3 cases per 100,000 population). (Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. https://www.cdc.gov/std/stats18/figures/35.htm.)

The clinical manifestations of syphilis have not changed appreciably since their first description. However, early diagnosis, treatment, and greater physician/patient awareness of the disease have reduced the incidence of its severe forms. Penicillin continues to be the mainstay of therapy.

Clinical Stages

CASE 72-7

QUESTION 1: D.M., a 27-year-old MSM presents to the STD clinic with malaise, headache, and fever of 4 days' duration. He also reveals that he had a sore on his penis about 8 weeks ago, but it has since resolved. Upon examination, he is afebrile and has a widespread maculopapular skin rash that involves the soles of his feet; general lymphadenopathy also is appreciated. Medical history is unremarkable except for one episode of gonorrhea 2 years ago that was treated with procaine penicillin. Laboratory findings include a normal peripheral WBC count, negative serum for HIV antigen, and a positive rapid plasma reagin (RPR) and fluorescent treponemal antibody absorption (FTA-ABS) test results.

What is the clinical course of syphilis? Are D.M.'s symptoms consistent with this infection?

PRIMARY STAGE

The average incubation period for syphilis is 3 weeks and ranges from 10 to 90 days.[74] During this incubation period, *T. pallidum* can be demonstrated in the lymph and blood. The primary chancre develops at the site of inoculation as a painless papule that becomes ulcerated and indurated. The ulcer is nontender and filled with spirochetes. The chancre usually involves the penis in the MSW; the penis or anus in the MSM; and the vulva, perineum, or cervix in the female. Occasionally, the lip or tongue is involved. Regional lymph nodes are enlarged, firm, and nontender. Unfortunately, the typical chancre described earlier often is missed, particularly in females or MSM.[75] Without treatment, the primary chancre resolves spontaneously, usually in 2 to 6 weeks. The differential diagnosis of genital ulcers also includes chancroid and genital herpes. As with chancroid, genital herpes produces painful, superficial, nonindurated ulcers with tender inguinal adenopathy. However, unlike chancroid, lesions of genital herpes characteristically proceed through a vesicular state and often are associated with urethritis, cervicitis, and constitutional symptoms, such as fever and chills. Syphilis can be differentiated from herpes by a nonpainful versus painful lesion, a papular versus vesicular appearance, and single versus multiple lesions. Chancroid is more difficult to differentiate from syphilis, although chancroid tends to have a more tender lesion, jagged border, and striking inguinal lymphadenopathy.[74]

SECONDARY STAGE

Approximately 6 weeks after a chancre first appears, the untreated patient manifests signs and symptoms of the secondary stage of syphilis. This stage is currently evidenced by D.M. Skin lesions of secondary syphilis may erupt in a variety of patterns and are usually widespread in distribution. A macular lesion often is the earliest manifestation in this stage. The lesion is round or oval, occurs primarily on the trunk, and is rose or pink in color. As lesions mature, they become papular or nodular with scaling (the so-called papulosquamous rash). The differential diagnosis of diffuse papulosquamous rashes includes psoriasis, pityriasis rosea, and lichen planus. In syphilis, the palms and soles are characteristically involved, and oral lesions (mucous patches) may occur. Generalized lymphadenopathy usually is present, and patchy alopecia may be seen. The most infectious lesion of secondary syphilis is condyloma latum. Condylomata lata are characteristically wet, indurated lesions occurring primarily in the perineum or around the anus as a result of direct spread from the primary lesion. Laboratory study findings sometimes reveal anemia, leukocytosis, or an increased erythrocyte sedimentation rate. Other manifestations of secondary syphilis include mild hepatitis, aseptic meningitis, uveitis, neuropathies, and glomerulonephritis.[76]

LATENT STAGE

By definition, untreated, asymptomatic persons with serologic evidence for syphilis have latent syphilis. The latent stage is divided into two phases: the early latent (<1 year's duration) and late latent (>1 year's duration). In the Oslo study of patients with untreated syphilis, 25% experienced secondary relapses, usually within the first year.[77] Patients who relapse to the secondary stage are infectious; those in the late latent stage are not infectious and are immune to reinfection with *T. pallidum.*

TERTIARY STAGE

Serious morbidity and mortality are caused by pathologic progresses involving the skin, bones, central nervous system, and cardiovascular system. Infectious granulomas (gummas), the characteristic lesions of tertiary syphilis, are observed infrequently. Most gummas respond quickly to specific therapy, although if critical organs are involved (heart, brain, liver), they can be fatal.[78] The most common manifestations of syphilitic cardiovascular disease are aortic insufficiency and aortitis, with aneurysm of the ascending aorta.

Neurosyphilis may be classified as asymptomatic early or late, meningeal, parenchymatous, or gummatous. Although neurosyphilis has been a rare complication for >40 years because of the widespread use of penicillin, syphilitic meningitis, an early form of neurosyphilis, may be more common in patients who are HIV positive.[74],[79] Late neurosyphilis may be asymptomatic or accompanied by a variety of manifestations; the most common syndromes are meningovascular syphilis, general paresis, tabes dorsalis (locomotor ataxia), and optic atrophy. In patients with asymptomatic neurosyphilis, examination of the cerebrospinal fluid (CSF) typically reveals mononuclear pleocytosis, an elevated protein concentration, and a positive VDRL reaction.

Patients with asymptomatic neurosyphilis are at increased risk for experiencing neurologic disease. Meningovascular syphilis, accounting for almost 38% of all cases of neurosyphilis, typically begins abruptly with hemiparesis or hemiplegia, aphasia, or seizures.[80] General paresis is characterized by extensive parenchymal damage and includes abnormalities associated with the mnemonic PARESIS (personality, affect, reflexes [hyperactive], eye [Argyll Robertson pupil], sensorium [hallucination, delusions, illusions], intellect [decreased recent memory, calculations, judgment], and speech). Tabes dorsalis occurs after demyelinization of the spinal cord. Symptoms observed include an ataxic, wide-based gait and foot slap; paresthesias; bladder irregularities; impotence; areflexia; and loss of position, deep pain, and temperature sensation. The Argyll Robertson pupil, seen in both

paresis and tabes dorsalis, is a small, irregular pupil that reacts to accommodation but not to light.

Laboratory Tests

Case 72-7, Question 2: Evaluate D.M.'s laboratory findings.

DARK-FIELD EXAMINATION

Exudate expressed from the chancre or from condyloma latum is examined with a dark-field microscope. The diagnosis of syphilis is made if spirochetes with characteristic corkscrew morphology and mobility are present. Three dark-field examinations on consecutive days should be performed before considering the test negative in suspected primary syphilis. This technique and other methods, such as DFA and PCR, which detect *T. pallidum* directly from exudate or tissue, are definitive diagnostic methods for syphilis. Dark-field examination is the most specific and sensitive method but only with an experienced microscopist.[81,82] Because of the special methods and equipment and experience needed for this direct method of diagnosis, a presumptive diagnosis of syphilis requires use of two serologic tests.[2]

SEROLOGIC TESTS

Two types of tests are used for the diagnosis of syphilis: nontreponemal tests, which measure serum concentrations of reagin (antibody to cardiolipin-cholesterol-lecithin), and treponemal tests, which detect the presence of antibodies specific for *T. pallidum.* When the history or examination suggests primary syphilis, a nontreponemal test and a treponemal test should be performed in a clinic (see discussion on nontreponemal tests, next). The use of one test can lead to false positives and is insufficient for diagnosis.[2]

Serologic test results become reactive during the primary stage, but they may be negative at the time of presentation with primary syphilis. If initial serology and dark-field examination results are

negative, the serology should be repeated in 1 to 4 weeks to exclude primary syphilis. If the dark-field examination result is positive, an RPR may still be ordered to establish a baseline for follow-up after treatment. Serologic test results are uniformly positive in secondary syphilis.[74]

Nontreponemal tests

Nontreponemal tests detect reactivity to a cardiolipin-cholesterol-lecithin antigen, which is not specific for *T. pallidum* but can be quantified. They are inexpensive and useful for screening large numbers of people. The most widely used nontreponemal tests are the VDRL test and the RPR Card Test. The RPR Test is the most widely used because it is simpler to perform than is the VDRL. Although equally valid assays, results of the VDRL and RPR are not interchangeable; thus, the same test should be used throughout the posttreatment monitoring period.[2,83]

The result reported in the quantitative VDRL test is the most dilute serum concentration with a positive reaction. This test may be used to follow the decline in VDRL titer after effective therapy (see Case 72-7, Question 5). In some individuals, a serofast reaction occurs in which nontreponemal antibodies may remain at a low titer for up to their entire lives. When false-positive tests occur, the titer usually is low (eg, VDRL or RPR titer of 1:8).[84] In secondary syphilis, sensitivity of the RPR and VDRL approaches 100% owing to the high antibody concentrations.[85]

Treponemal tests

Specific treponemal tests, such as FTA-ABS, *Treponema pallidum* particle agglutination (TP-PA) assay, and various EIAs, confirm a positive nontreponemal test. The FTA-ABS test is the most commonly used treponemal test. Although treponemal tests are qualitative, they tend to be more specific than are nontreponemal tests because they test for specific treponemal antigens. Traditionally, treponemal tests are relatively difficult and expensive to perform and were not used for screening. However, with advances in

methods for testing, new devices have eased the use of treponemal tests, and these tests are now recommended as part of the diagnostics for syphillis.[2]

Treatment

Case 72-7, Question 3: How should D.M. be treated?

The CDC recommends penicillin G for the treatment of all stages of syphilis (**Table 72-4**).[2] Every effort should be made to rule out penicillin allergy before choosing alternative agents. Considering that penicillin-resistant *T. pallidum* has never been observed, treatment regimens for syphilis have changed relatively little during the years.

Table 72-4
Treatment Guidelines for Syphilis

Stage	Recommended Regimen	Alternative Regimen
Early (primary, secondary, or early latent)[a]	Benzathine penicillin G 2.4 million units single dose IM	Doxycycline 100 mg PO bid for 14 days *or* Tetracycline 500 mg PO qid for 14 days *or* Ceftriaxone 1 g IM/IV every day for 8 to 10 days *or* Azithromycin 2 g PO × 1 dose
Latent (>1 year) or latent syphilis of unknown duration	If CSF normal: benzathine penicillin G 2.4 million units /week × 3 week IM	If CSF normal: doxycycline 100 mg PO bid for 28 days *or*

		Tetracycline 500 mg PO qid for 28 days
	If CSF abnormal: treat as neurosyphilis	If CSF abnormal: treat as neurosyphilis
Neurosyphilis[b] (asymptomatic or symptomatic)	Aqueous crystalline penicillin G 18–24 million units IV every day × 10–14 days[c]	Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO qid, both for 10–14 days
Congenital	Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV Q 12 hour during the first 7 days of life, and every 8 hours thereafter for a total of 10 days[d]	If CSF normal: benzathine penicillin G 50,000 units/kg/dose IM in a single dose
	or	
	Procaine penicillin G 50,000 units/kg/dose IM a day in a single dose for 10 days	
Syphilis in pregnancy	According to stage	According to stage

bid, twice a day; CSF, cerebrospinal fluid; IM, intramuscular; IV, intravenous; PO, orally; Q, every; qid, four times a day.

[a]Some experts recommend repeating this regimen after 7 days for HIV-infected patients.

[b]Because of the shorter duration of therapy as compared with latent syphilis, some experts recommend giving benzathine penicillin G, 2.4 million units/week for up to 3 weeks, after the completion of these neurosyphilis regimens to provide a comparable total duration of therapy.

[c]Administered as 3 to 4 million units IV every 4 hours or continuous infusion.

[d]All infants born to females treated during pregnancy with erythromycin must be treated with penicillin at birth.

Source: Adapted from Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1–187. doi:10.15585/mmwr.rr7004a1.

As shown in Table 72-4, recommended therapy for primary, secondary, or early latent syphilis (with negative findings in the CSF) of <1 year's duration is a single, IM 2.4 million unit dose of benzathine penicillin G. If penicillin is contraindicated, tetracycline 500 mg PO four times a day or doxycycline 100 mg PO twice a day for 14 days is the main alternative. If the patient is allergic to penicillin, is not pregnant, and cannot receive tetracycline or doxycycline, a 10- to 14-day regimen of ceftriaxone 1-g IM or IV every day or a single 2-g dose of azithromycin is an option.[2] The use of erythromycin as an alternative is no longer recommended by the CDC because of its poor efficacy. The optimal dose, duration, and efficacy of these alternative regimens are not well defined, necessitating close follow-up of patients. Recent studies, however, have shown that azithromycin 2 g PO as a one-time dose is at least equivalent to benzathine penicillin G.[86,87] Skin testing should be performed for individuals who claim an allergy to penicillin. If the patient is truly allergic, they should be desensitized.[2]

Late latent syphilis (>1 year's duration) and tertiary syphilis (gummas or cardiovascular syphilis with negative findings in the CSF) are treated with IM benzathine penicillin G 2.4 million units weekly for a total of 3 weeks.[2]

NEUROSYPHILIS

Case 72-7, Question 4: Would D.M.'s treatment differ if his CSF test had yielded a positive result for syphilis?

Neurosyphilis can present at any stage of syphilis. When conventional IM doses of benzathine penicillin G are administered, measurable levels of penicillin are not obtainable in the CSF. However, this does not mean that penicillin does not concentrate in meningeal tissue.[88] Treatment failures, as well as late clinical progression to neurosyphilis, can occur after treatment with the recommended IM regimen. After one dose, benzathine penicillin reaches peak plasma concentrations slower (13–24 hours) but with

more prolonged treponemicidal plasma concentrations (7–10 days) when compared with procaine penicillin (1–4 hours to peak; 12- to 24-hour treponemicidal plasma concentrations).[88] Reports of benzathine penicillin failures in the 1970s resulted in the CDC recommending treatment with aqueous crystalline penicillin G, 3 to 4 million units IV every 4 hours, or 18 to 24 million units per day continuous infusion, for 10 to 14 days. Alternatively, neurosyphilis can be treated with concurrent procaine penicillin (2.4 million units IM daily) and probenecid (500 mg PO four times a day) for 10 to 14 days. Some experts add benzathine penicillin G (2.4 million units IM once a week for up to 3 weeks) after the completion of aqueous penicillin G or procaine penicillin.[2] Penicillin-allergic patients should be skin tested to confirm allergy and, if confirmed, the patient should be desensitized and treated with an appropriate penicillin regimen. Some data suggest that ceftriaxone 2 g IM or IV daily for 10 to 14 days can be used as an alternative in patients whose concern for cross-sensitivity between ceftriaxone and penicillin is negligible.[2] Alternatively, the World Health Organization recommends penicillin-allergic nonpregnant patients receive either doxycycline 200 mg PO twice a day or tetracycline 500 mg PO four times a day for 30 days.[89]

FOLLOW-UP

Case 72-7, Question 5: D.M. was treated with a single IM dose of benzathine penicillin (2.4 million units). How should his response to therapy be monitored?

Physical examination and a quantitative VDRL or RPR test for primary and secondary syphilis should be repeated at least 6 and 12 months after therapy.[2] Retreatment should be considered when the RPR or VDRL titer does not decline fourfold in 6 months. Patients with HIV coinfection should receive periodic serologic testing.[74] Patients with latent syphilis should be retested 6, 12, and 24 months after treatment. Close serologic monitoring is necessary if antibiotics other than penicillin are used; CSF examination should be performed in these patients at their last follow-up visit. Patients with

neurosyphilis should be monitored serologically every 6 months; CSF examinations should be repeated at 6-month intervals until normal. If results are still abnormal at 2 years, retreatment should be considered. Return of lesions, a fourfold increase in titer, or a titer of 1:8 that does not fall at least fourfold within 12 months necessitates retreatment. Suspected treatment failures, especially with abnormal CSF, should be treated as described for neurosyphilis. However, false-positive serologic results should be ruled out.

Within 2 years, most patients with early syphilis become seronegative. However, if the disease is treated during the late stages, complete seroreversion may not occur. Patients treated with oral doxycycline or erythromycin are less likely to become seronegative.[90] Therapy is considered adequate in patients who never become seronegative as long as the titer decreases fourfold. Although the disease process may be halted in patients with tertiary syphilis, existing damage to the cardiovascular or nervous systems cannot be reversed.

PREGNANCY

CASE 72-8

Question 1: N.W., a 27-year-old female in her 19th week of gestation, has a positive VDRL and FTA-ABS.

How should N.W. be managed? How would management be altered in the face of penicillin allergy?

Although pregnancy may be associated with false-positive nontreponemal test results,[76] the presence of both a positive treponemal test result (eg, FTA-ABS) and a nontreponemal test result (eg, RPR) virtually excludes a false-positive reaction.[82] The next step is to determine whether N.W. already has been treated adequately. If she has previously received adequate treatment and follow-up and shows no evidence of persistence or recurrence of syphilis, then she requires no further therapy. Pregnancy has no known effect on the clinical course of syphilis.[91] However, her infant

should be observed carefully. If N.W. has not been treated previously for syphilis, then she should be treated with penicillin in the same doses recommended for nonpregnant females; some experts recommend a second dose 1 week later of 2.4 million units of benzathine penicillin.[2]

The goal of therapy should be to treat the mother with syphilis as soon as possible. Syphilis transmission can occur transplacentally as early as 9 to 10 weeks' gestation via direct contact with lesions in the birth canal.[91],[92] If the mother is left untreated, 70% to 100% of fetuses born to mothers with primary or 40% with secondary syphilis may be aborted, stillborn, or born with congenital syphilis (see Case 72-8, Question 3).[93],[94]

There is no completely satisfactory alternative for the pregnant female with an accelerated allergic reaction to penicillin. Tetracycline, as well as doxycycline, should be avoided during pregnancy, especially during the second or third trimester, because of tetracycline's known effects on the fetus (tooth staining and inhibition of bone growth).[95] Erythromycin has been used to treat pregnant patients with syphilis; however, the transplacental transfer rate of erythromycin is inadequate[96] potentially explaining the increased rate of aborted or stillborn infants in erythromycin-treated patients. Erythromycin and azithromycin are not recommended as an alternative therapy for syphilis during pregnancy.[2] A female with a history of allergy to penicillin should be skin tested; if allergy is confirmed, she should be desensitized and treated with penicillin.[2] It is possible that the newer cephalosporins may ultimately prove to be acceptable alternatives to penicillin G in the pregnant female with syphilis who is allergic to penicillin, but there is insufficient evidence for the CDC to recommend their use. Adequate treatment with penicillin can prevent up to 98% of fetal infections.[97],[98] Serologic titers, at a minimum, should be followed up at 28 to 32 weeks' gestation and at delivery. Monthly serologic titers may be considered in females at high risk for reinfection or those in geographical areas of high syphilis rates; thereafter, she should be followed up as any other patient with syphilis.[2]

JARISCH–HERXHEIMER REACTION

Case 72-8, Question 2: N.W. was treated with an IM injection of 2.4 million units of benzathine penicillin G. Six hours later, N.W. experienced diffuse myalgias, chills, headache, and an exacerbation of her rash. She was tachypneic, but normotensive. What is this reaction? How should N.W. be managed?

N.W. has developed the Jarisch–Herxheimer reaction (JHR), a usually benign, self-limited complication of antitreponemal antibiotic therapy that develops within hours of treatment of early syphilis.[2] The cause of JHR is not well understood but is probably related to release of cytokines.[99] Clinical manifestations include fever, chills, myalgias, headache, tachycardia, and hypotension. The pathogenesis of the syndrome is uncertain, but the reaction should not be interpreted as an allergic reaction to penicillin. It typically begins within the first 24 hours of antibiotic administration and normally subsides spontaneously, generally subsiding even while antibiotics are continued.[2,100] Notably, JHR can occur after administration of many antimicrobials and is not exclusive to penicillins, nor is it exclusive to syphilis treatment, occurring in other spirochetal diseases such as Lyme disease and relapsing fever.[101] Usually self-limiting in nonpregnant patients, the primary risk of this reaction in pregnant females is miscarriage, premature labor, or fetal distress.[2,102] Pregnant females should seek medical attention if contractions or a change in fetal movements are noted. Close monitoring of JHR should be observed in patients with ophthalmic or neurologic syphilis. For these patients, prednisolone 10 to 20 mg three times a day for 3 days given 24 hours before syphilis treatment may prevent fever, but it will not control local inflammation.[88] Tumor necrosis factor-α has been demonstrated to have some success in the prevention of JHR in spirochete disease.[103] Although there is no proven effective preventive therapy, some experts still recommend antipyretics, hydration, and patient education; antibiotic therapy should not be discontinued.

NEONATAL SYPHILIS

CASE 72-8, QUESTION 3: How should N.W.'s baby be treated if a diagnosis of congenital syphilis is confirmed?

Infants born to mothers who have been treated for syphilis during pregnancy should be carefully examined at birth with a quantitative nontreponemal serologic test. If tests are reactive, the infant should be followed up and have serologic testing done every 2 to 3 months until nontreponemal tests are nonreactive.[2] Newborn serology is difficult to interpret because of transplacental transfer of nontreponemal and treponemal IgG to the infant. Treatment decisions are largely based on evidence of syphilis in the mother, adequacy of maternal treatment, comparison of maternal and neonatal nontreponemal serology, and/or presence of clinical or laboratory evidence of syphilis in the neonate. In addition, infants should be treated at birth, even if they are asymptomatic, when maternal treatment is unknown or inadequate, or when infant follow-up cannot be guaranteed. In most cases, a CSF examination should be performed before treatment is begun to rule out neurosyphilis.

CHANCROID

Chancroid or soft chancre is a painful genital ulcer disease that often is associated with tender inguinal adenopathy. It is caused by *H. ducreyi,* a gram-negative bacillus. Chancroid is endemic in developing countries, but its incidence in the United States has steadily declined. Since 2011, cases of chancroid in the United States have been <100; and in 2018, only three cases were reported.[6] Chancroid and other genital ulcers have also been implicated in the acquisition and transmission of HIV.

Signs and Symptoms

CASE 72-9

QUESTION 1: T.G., a 31-year-old uncircumcised sexually active male, presents to the STD clinic with tender lesions on the penis and inguinal regions. He noticed the penile lesions on the external surface of the prepuce (foreskin) 2 days before his visit. The lesions were sharply demarcated but were not indurated; the base of the penile ulcer was covered by a yellow-gray purulent exudate. Right inguinal adenitis was present and extremely painful on palpation. A dark-field examination result of the purulent exudate was negative. Gram stain revealed a mixture of gram-positive and gram-negative flora. T.G. claims to have an allergy to penicillin, but no other drug allergies are reported.

What is the natural course of chancroid? Does T.G. have signs or symptoms consistent with chancroid? What diagnostic procedures are necessary?

Uncircumcised males may have an increased risk of chancroid infection and may not respond to therapy as well as circumcised males do. In fact, evidence suggests circumcision is protective against nearly all STDs, including HIV, as well as protecting females against *T. vaginalis* and BV.[2] A painful genital ulcer appears 3 to 10 days after exposure and begins as a tender, red papule that becomes pustular and ulcerates within 2 days. Chancroid can be suspected if all of the following criteria are met: (a) one or more painful genital ulcers present, (b) regional lymphadenopathy, (c) no evidence of T. *pallidum* by dark-field examination, and (d) a negative result in the HSV PCR test or HSV culture. As illustrated by T.G., the ulcer may be covered by a grayish or yellow exudate. A Gram stain can be misleading because of the polymicrobic nature of the ulcer and culture and because isolation of *H. ducreyi* is difficult, requiring specialized specimen collection and growth media.[2]

Treatment

CASE 72-9, QUESTION 2: How should T.G.'s chancroid be treated?

Most strains of *H. ducreyi* produce a TEM-type β-lactamase, and many strains are resistant to the antimicrobials that traditionally were used to treat chancroid, such as sulfonamides and tetracycline.[104,105]

Currently recommended CDC treatment regimens include azithromycin 1 g PO for 1 dose, ceftriaxone 250 mg IM once, ciprofloxacin 500 mg PO twice a day for 3 days, or erythromycin base 500 mg PO three times a day for 7 days. Ciprofloxacin is contraindicated in pregnant and lactating females. Because T.G. has a history of penicillin hypersensitivity, azithromycin as a single oral dose is a preferred treatment regimen. Treatment may not be as effective for patients who are coinfected with HIV or who are uncircumcised and, therefore, HIV testing should occur at the time of chancroid diagnosis. If the result is negative, the test should be repeated 3 months after the diagnosis. Follow-up should occur 3 to 7 days after treatment is initiated. Depending on the size of the ulcer, the time required until complete recovery will vary; larger ulcers may require longer than 2 weeks. Because T.G. is also sexually active, his sexual partner should be evaluated and treated if they had contact during the 10 days before the onset of symptoms.[2]

VAGINITIS

Approximately 10 million physician office visits are made annually in the United States for females seeking evaluation and treatment of vaginitis.[106] The term *vaginitis* refers to such nonspecific vaginal symptoms as itching, burning, irritation, and abnormal discharge that may be caused by infection or other medical conditions. The most common vaginal infections are BV (22%–50% of cases), vulvovaginal candidiasis (VVC; 17%–39% of cases), and trichomoniasis (4%–35% of cases). However, up to 30% of cases of vaginitis remain undiagnosed.[107]

Bacterial Vaginosis

BV was not described clearly as a syndrome (initially called *H. vaginalis* vaginitis) until the 1950s. BV is the most common genital tract disorder among reproductive age females.[108] Although the

exact prevalence of BV varies based on race/ethnicity, the National Health and Nutrition Examination Survey (NHANES) data estimate it to be 29.2%. Many females harbor *G. vaginalis*, the most commonly implicated organism, yet up to 84% are asymptomatic.[108] During an episode of BV, normally predominant lactobacilli are replaced with an overgrowth of *G. vaginalis*, *Atopobium vaginae, and other* anaerobic species such as *Mobiluncus*, *Prevotella*, *Bacteroides*, *Fusobacterium*, *Ureaplasma*, and *Mycoplasma.* This shift in vaginal flora results in a malodorous discharge, and the paucity of lactic acid and peroxide-producing lactobacilli leaves the mucosa vulnerable to other infections.

BV may be more accurately described as vaginal ecosystem imbalance, in which multiple organisms are implicated. The evidence for definitive risk factors in BV is inconclusive. Multiple sexual partners, a new sexual partner, douching, smoking, lack of condom use, and antibiotic use have been associated with BV. Any female may develop BV, although nonsexually active females are rarely affected.[2] In addition, studies among females who have sex primarily with females show evidence for sexual transmission.[109] The routine treatment of male sexual partners is not recommended because a female's response to therapy, as well as her likelihood of relapse or recurrence is not impacted by treatment of her sexual partner(s).[2]

SIGNS, SYMPTOMS, AND DIAGNOSIS

CASE 72-10

Question 1: H.H. is a 24-year-old, sexually active female with a 1-week history of moderate vaginal discharge that has a "fishy" odor, most notable after coitus. She has no vaginal pruritus or burning. On examination, the discharge appears thin, white, homogeneous, and notably malodorous. A wet mount of the vaginal secretion revealed rare leukocytes and numerous "clue cells." The vaginal pH was 5.0, and a characteristic fishy odor was noted when the discharge was mixed with 10% potassium hydroxide (KOH).

Does H.H. have signs and symptoms consistent with BV? Are additional diagnostic tests required?

H.H.'s signs and symptoms are typical of BV. The gold standard diagnostic test is a Gram stain of the vaginal discharge showing overgrowth of *G. vaginalis* and other anaerobes with low numbers of lactobacilli (Nugent score). Clinical diagnosis is confirmed by noting the presence of at least three of four Amsel criteria: (a) 10% KOH solution mixed with the vaginal discharge yields a fishy odor from increased biogenic diamines (positive "whiff" test); (b) saline mount of the specimen reveals >20% "clue cells" (vaginal epithelial cells with adherent coccobacilli); (c) vaginal pH measures >4.5; and (d) vaginal discharge is characteristically thin, milky-gray, and homogeneous.[110] Vaginal cultures are not helpful because up to 60% of the results from healthy, asymptomatic females will be positive for *G. vaginalis*. DNA probes for *G. vaginalis* and immunochromatographic testing for vaginal sialidase are available but add to the cost of diagnosis. If there are many white cells on wet mount, other infections (eg, *T. vaginalis*) should be suspected, because BV, by definition, is noninflammatory. Self-diagnosis is correct only 3% to 4% of the time because most females attribute symptoms to poor hygiene.[111]

TREATMENT

CASE 72-10, QUESTION 2: How should H.H. be treated?

Females with symptomatic disease require treatment. CDC-recommended regimens include oral metronidazole 500 mg twice a day for 7 days, metronidazole gel 0.75% intravaginally daily for 5 days, or clindamycin cream 2% intravaginally at bedtime for 7 days.[2] The FDA has approved metronidazole extended release 750 mg PO once daily for 7 days and a single dose of clindamycin intravaginal cream for the treatment of BV; however, limited data have been published comparing these regimens to established therapies. Alternatively, the CDC recommends either tinidazole 2 g PO every day for 2 days, tinidazole 1g PO every day for 5 days, clindamycin 300 mg PO two times a day for 7 days, or clindamycin ovules 100

mg intravaginally once at bedtime for 3 days.[2] Patients should be instructed to avoid consuming alcohol during treatment with metronidazole and for 72 hours afterward to avoid disulfiram-like reactions. In addition, clindamycin cream is oil based and may weaken latex condoms or diaphragms. Alternative products include oral probiotics, which have been evaluated in nonpregnant females and have shown to improve cure rates and reduce the reoccurrence of BV, although more studies are needed to establish their role in treatment.[111]

BV has been associated with preterm labor and premature delivery, and treatment is recommended for all symptomatic pregnant females. The CDC recommends metronidazole 250 mg PO three times daily for 7 days or 500 mg PO twice a day for 7 days, or clindamycin 300 mg PO twice daily for 7 days. Teratogenic studies suggest that metronidazole is not harmful to the fetus, and more recent data suggest that the use of intravaginal clindamycin cream is also safe to use for pregnant females.[2]

Vulvovaginal Candidiasis

Candida albicans is the causative organism of VVC in 80% to 92% of cases, with *C. glabrata* and *C. tropicalis* accounting for most of the remaining cases.[2] The latter have been identified increasingly as the causative agents of VVC during the past two decades. Approximately 75% of females will experience at least one episode of VVC during their reproductive years, and 40% to 45% will have two or more episodes within their lifetime.[107] Less than 5% of females who have VVC have recurrent episodes (defined as four or more episodes of VVC in 1 year). VVC is not usually described as an STD because celibate females may also experience it; however, the incidence of VVC increases when females become sexually active.[112] Because of this, VVC is often diagnosed during evaluation for a suspected STD when females present with vaginal symptoms.

ASSESSING SELF-TREATMENT

CASE 72-11

QUESTION 1: L.L., a 23-year-old female, purchases a nonprescription antifungal agent to relieve vaginal symptoms that she believes are caused by a vaginal yeast infection. L.L. asks the pharmacist for assistance in the selection of an antifungal agent.

What information should be obtained from L.L. before a medication is recommended?

The pharmacist should ask L.L. if this is her first episode of vaginitis or whether she has experienced similar symptoms previously that have been diagnosed and treated as a vaginal yeast infection by a qualified medical practitioner. The nonprescription antifungal agents are indicated for the treatment of VVC in females who previously were diagnosed and treated by a clinician. Additional questions that should be asked by the pharmacist include current symptoms, whether she is pregnant, other current medical conditions or medications, and medication allergies. Patients should be referred to a medical practitioner if any of the following are present: a first episode of VVC; four or more episodes of VVC within the past 12 months; last episode was <2 months ago; pregnancy; age younger than 12; or the presence of fever, lower abdominal or back pain, severe symptoms, or a malodorous vaginal discharge.[113]

SIGNS AND SYMPTOMS

CASE 72-11, QUESTION 2: L.L. has experienced two episodes of vaginal yeast infections, with the most recent case occurring ~1 year ago. On both occasions, she was diagnosed by a physician as having VVC and responded to antifungal therapy. L.L. currently describes vaginal and vulvar itching, vaginal soreness, and vulvar burning accompanied by a thick, white vaginal discharge that has the consistency of cottage cheese. She has been unable to have sexual intercourse because of pain. These symptoms are similar to those she experienced with her previous vaginal yeast infections. L.L. has no underlying major health problems. Her current medications include oral tetracycline for acne and Ortho Tri-Cyclen® for birth control. She has regular menstrual cycles and her last menstrual period ended 4 days ago. What clinical manifestations does L.L. exhibit that are consistent with VVC? What are other common manifestations?

L.L. exhibits signs and symptoms associated with VVC: vulvar and vaginal pruritus, vaginal soreness, vulvar burning, dyspareunia, and a thick, white nonodorous vaginal discharge that appears to be curdlike. Vulvar erythema may also be present.

DIFFERENTIAL DIAGNOSIS

Case 72-11, Question 3: How can VVC be differentiated from other vaginal infections?

VVC should be differentiated from other vaginal infections because a nonprescription antifungal agent could delay the appropriate treatment of other vaginal infections. The physical appearance of the vaginal discharge may be useful in predicting VVC if it is a viscous, nonodorous, white, curdlike discharge and the patient has a normal vaginal pH (pH <4.5). The quantity of the discharge may be scanty to profuse. Some females with VVC exhibit only vulvovaginal erythema with minimal discharge or an increased amount of normal vaginal secretion. **Table 72-5** characterizes the vaginal discharges associated with VVC, BV, and trichomoniasis. The vaginal discharge from a female with signs and symptoms of VVC should be examined microscopically for the presence of *Candida* using a wet-mount preparation with 10% KOH. The use of KOH improves the visualization of yeast or pseudohyphae that are seen in ~70% of females diagnosed with VVC. If the wet-mount finding is negative, the patient's vaginal discharge should be cultured for *Candida* in an appropriate growth medium. Isolation of *Candida* without signs and symptoms should not result in treatment, because *Candida* is part of normal vaginal flora in ~10% to 20% of females. It is the proliferation of *C. albicans* or other yeasts that lead to vulvovaginitis symptoms. Nonprescription home screening tests that measure pH levels of the vaginal discharge (eg, Vagisil Screening Kit® and Fem-V®) are also available; they are highly sensitive to pH changes but lack diagnostic specificity.

Table 72-5
Characteristics of Vaginal Discharge

Characteristics	Normal	Candidiasis	Trichomoniasis	Bacterial Vaginosis
Color	White or clear	White	Yellow-green	White to gray
Odor	Nonodorous	Nonodorous	Malodorous	Fishy smell
Consistency	Floccular	Floccular	Homogeneous	Homogeneous
Viscosity	High	High	Low	Low
pH	<4.5	4–4.5	5–6.0	>4.5
Other characteristics		Thick, curdlike	Frothy	Thin

Sources: Ries AJ. Treatment of vaginal infections: candidiasis, bacterial vaginosis, and trichomoniasis. *J Am Pharm Assoc (Wash).* 1997;NS37(5):563–569; Sobel JD. Vaginitis. *N Engl J Med.* 1997;337(26):1896–1903; Carr PL, Felsenstein D, Friedman RH. Evaluation and management of vaginitis. *J Gen Intern Med.* 1998;13(5):335–346.

Physiologic vaginal discharge and symptomatic normal pH vulvovaginitis

Case 72-11, Question 4: Do females such as L.L., who have an increased vaginal discharge and symptoms consistent with VVC, necessarily have a vaginal infection?

Although the possibility of vaginal infection must be addressed when a female presents with an increased vaginal discharge with or without symptoms, other conditions are associated with an increased discharge. First, a physiologic vaginal discharge must be distinguished from a pathologic discharge. Physiologic discharges (Table 72-5) characteristically are nonodorous, white or clear, highly viscous or floccular, and acidic (pH ~4.5). Physiologic discharge may also become more profuse at midcycle secondary to increased cervical mucus or vaginal epithelial cell exfoliation. Other non-infectious conditions resulting in excessive vaginal discharge include retention of foreign bodies (eg, tampons) and allergic reactions or contact dermatitis secondary to the use of vaginal spermicidal agents, soaps, deodorants, douches, vaginal lubricants, and condoms. Episodes of vulvovaginitis-like symptoms can be associated with frequent use of hot tubs, Jacuzzi baths, or swimming

pools that contain chemically treated water with high levels of chlorine.[114]

RISK FACTORS FOR VULVOVAGINAL CANDIDIASIS

CASE 72-11, QUESTION 5: What specific groups of females are most susceptible to VVC? Does L.L. fit into any group at high risk for VVC?

C. albicans colonization and symptomatic VVC increase during pregnancy and with use of high-estrogen–containing oral contraceptives. Estrogens increase binding affinity of vaginal epithelial cells to *C. albicans*.[115] Females with high glycogen concentrations (eg, uncontrolled or poorly controlled diabetes mellitus), females with depressed cell-mediated immunity secondary to disease (eg, cancer, HIV infection), and females receiving broad-spectrum antibiotics or immunosuppressive drugs (eg, cytotoxic agents, corticosteroids) are also at risk for VVC.[113] Individual cases of VVC, although not related to intercourse, may be related to orogenital sex.

L.L. is taking tetracycline, which may increase her risk for VVC. Antibacterials increase the risk for *C. albicans* overgrowth by suppressing the normal vaginal flora (eg, lactobacilli), which are normally protective. L.L. is also taking a low-estrogen–containing oral contraceptive; however, low-dose oral contraceptives have not been consistently associated with an increased risk of VVC. The use of diaphragms, vaginal sponges, and IUDs also may be risk factors for VVC.[113]

Stress-induced VVC and an increased incidence of VVC before menstruation have been described.[115] The cause of both is currently unknown. Although various dietary factors have been postulated as a cause of vaginal yeast overgrowth, the role of diet in the development of VVC remains inconclusive.[115]

TREATMENT OF VULVOVAGINAL CANDIDIASIS

Vaginally administered azoles

Case 72-11, Question 6: What vaginally administered therapy is effective for L.L.'s VVC?

L.L. is an appropriate candidate for nonprescription therapy (Table 72-6) because she had previous vaginal yeast infections with symptoms similar to those she currently is experiencing and her VVC is uncomplicated (defined as sporadic disease with mild-to-moderate symptoms in an immunocompetent host). When a patient's VVC appears complicated (defined as a recurrent infection, severe symptoms, non-*C. albicans* infection, or the presence of uncontrolled diabetes, immunosuppression, and/or pregnancy), she should be referred to her medical practitioner.[2] L.L. should respond well to short-term topical azole therapy. In addition, L.L. should ask her physician whether continuation of antibiotics is truly needed. If L.L. had been evaluated by her physician, a prescription for single-dose oral fluconazole or 3-day intravaginal therapy might have been an option.

The available azole antifungals are equally effective in treating VVC with cure rates between 80% and 90% when a full course of therapy is completed.[2] All the azole antifungal products listed in **Table 72-6** are superior to nystatin, which is no longer recommended by the CDC.[2] The medication used to treat L.L.'s VVC should be selected based on response or failure to previous therapy, convenience, ease of use, length of therapy, dosage form, and cost. L.L. should select a non–oil-based product if a latex condom or a diaphragm is used as a form of contraception (Table 72-6).

Table 72-6
Recommended Regimens for the Treatment of Candida Vulvovaginitis

Drug	Availability	Trade Names	Dosing Regimens
Nonprescription Products			
Butoconazole	2% vaginal cream[a]	Femstat 3®	Nonpregnant females: Administer 1 applicatorful intravaginally qhs for 3 consecutive days.
			Pregnant females during second and third trimesters: Administer 1 applicatorful intravaginally qhs for 7 consecutive days.
Clotrimazole	1% vaginal cream[a]	Gyne-Lotrimin 7®; Mycelex-7®; Clotrimazole 7®; various generics	Administer 1 applicatorful intravaginally qhs for 7–14 consecutive days.
	2% vaginal cream[a]	Gyne-Lotrimin 3®; various generics	Administer 1 applicatorful intravaginally qhs for 3 consecutive days.
Miconazole	2% cream[a]	Monistat 7®; Femizol-M®; various generics	Administer 1 applicatorful intravaginally qhs for 7 consecutive days.
	4% cream[a]	Monistat 3®; various generics	Administer 1 applicatorful intravaginally qhs for 3 consecutive days.
	100-mg vaginal suppositories[a]	Monistat 7®	Insert 1 suppository intravaginally qhs for 7 consecutive days.
	200-mg vaginal suppositories[a]	Monistat 3®	Insert 1 suppository intravaginally qhs for 3 consecutive days.
	1200-mg vaginal suppositories[a]	Monistat 1 Daytime Ovule	Insert 1 suppository intravaginally qhs for 1 dose only.
Tioconazole	6.5% vaginal ointment	Vagistat-1®	Administer 1 applicatorful intravaginally at qhs for 1 dose only.
Prescription Products			
Butoconazole	2% vaginal cream[a]	Gynazole 1®	Nonpregnant females: Administer 1 applicatorful qhs for 1 dose only.
Fluconazole	150-mg oral tablet	Diflucan®	Take 1 tablet PO for 1 dose only.
Terconazole	0.4% vaginal cream[a]	Terazol 7®	Administer 1 applicatorful intravaginally qhs for 7 consecutive days.
	0.8% vaginal cream[a]	Terazol 3®	Administer 1 applicatorful intravaginally qhs for 3 consecutive days.
	80-mg vaginal suppositories[a]	Terazol 3®	Insert 1 suppository intravaginally qhs for 3 consecutive days.

PO, orally; qhs, at bedtime.

[a]The Centers for Disease Control and Prevention (CDC) states that the use of vaginally administered oil-based preparations may weaken latex products such as condoms and diaphragms.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4): 1–187. doi:10.15585/mmwr.rr7004a1.

Other treatments for acute vulvovaginal candidiasis

Oral lactobacillus and lactobacillus-containing yogurt are advocated for the treatment of VVC; however, evidence in support of this treatment is inconclusive.[116] Boric acid 600 mg capsules inserted in the vagina at bedtime for 14 days are effective for the treatment of recurrent VVC with eradication rates of 70%, but vaginal burning and irritation are common side effects and it is poisonous if inadvertently

ingested.[2],[116] Gentian violet preparations also have limited use in the treatment of candidiasis because they stain clothing and bed linens and cause local irritation and edema.

Oral azoles

Case 72-11, Question 7: How effective are orally administered azoles in the treatment of an acute VVC infection such as the one L.L. is experiencing?

Fluconazole is the only oral antifungal agent currently recommended by the CDC for the treatment of acute VVC. A single 150-mg oral dose of fluconazole is as effective as a 3- to 6-day regimen of intravaginal clotrimazole.[117] Patient preference should be a factor in treatment choice, and many females may prefer the convenience of an oral over intravaginal therapy; however, systemic therapy for mild-to-moderate VVC is of some concern because of the potential for systemic adverse effects.[118]

Adverse Effects Associated With Azoles

Case 72-11, Question 8: What adverse effects might L.L. experience from intravaginally or orally administered azoles?

When used intravaginally, azoles are associated with dose-dependent adverse reactions similar to symptoms females report from VVC. Thus, it can be difficult to differentiate disease symptoms from adverse drug reactions. If the vaginal symptoms worsen after therapy is started, the patient should contact her health care provider. In addition, if symptoms have not improved within 3 days of initiation of therapy or continue past 7 days, the patient should contact her provider to rule out more severe disease or treatment of the wrong disease.[113] Topical azole therapy is generally well tolerated but has been associated with a variety of side effects including headaches, allergic contact dermatitis, vulvovaginal pruritus and irritation, dyspareunia, and general burning, soreness,

and genital pain. Oral fluconazole is also well tolerated but has been associated with headaches, nausea, abdominal pain, diarrhea, dyspepsia, dizziness, taste perversion, angioedema, Stevens–Johnson syndrome, anaphylaxis, and cardiac arrhythmia. It has also been associated with drug–drug interactions with several commonly prescribed drugs (eg, sulfonylureas, statins, proton-pump inhibitors, benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants). Intravaginal miconazole has been reported to interact with warfarin, increasing the risk of bleeding and bruising.[119]

PATIENT COUNSELING

Case 72-11, Question 9: How should L.L. be counseled about the use of a nonprescription vaginal antifungal product?

The details of intravaginal administration should be reviewed with L.L., including instructions on how to clean the applicator. To minimize leakage and annoyance, L.L. should apply the product at bedtime, which increases vaginal retention. She should be advised that the nonprescription vaginal antifungal creams and suppositories are oil based and thus may weaken condoms or diaphragms, thereby reducing their effectiveness.

L.L. should be informed about the importance of completing a full course of therapy even if her symptoms subside beforehand and to continue her antifungal treatment through her menstrual period should it occur. In addition, L.L. should be instructed to see her medical provider if her symptoms persist, if she experiences symptoms that may signal a more serious problem (eg, abdominal pain, fever, a foul-smelling or bloody vaginal discharge), and/or if another yeast infection occurs within 2 months.

L.L. may be advised to avoid wearing tight-fitting, unventilated underwear (eg, nylon panties or pantyhose) and tight-fitting jeans because a warm, moist environment can facilitate fungal growth. However, one study addressing risk factors for VVC found no relation between type of underwear and the incidence of VVC.[120] In

fact, many risk factors for VVC are not consistently associated with this infection.[113] L.L. also could be alerted to the possible relation between candidiasis and swimming in a heavily chlorinated pool or frequent use of a Jacuzzi or hot tub.

Complicated Vulvovaginal Candidiasis

Case 72-11, Question 10: How would the management of L.L.'s VVC differ if she had poorly controlled diabetes?

VVC in a female with uncontrolled diabetes is usually considered to be complicated VVC. A diagnosis of complicated VVC is also warranted when the VVC is severe, recurrent, caused by non-C. *albicans* species, or when VVC occurs in an immunosuppressed, debilitated, or pregnant female. The treatment of complicated VVC varies depending on the underlying reason. Severe VVC (eg, extensive vulvar erythema, edema, excoriation, and fissures) may be treated with either a 7- to 14-day course of topical azoles or two oral doses of fluconazole 150 mg given 72 hours apart. Infection with non-*C. albicans* species should be treated with a 7- to 14-day course of an oral or intravaginal azole; however, the optimal treatment is unknown. Oral fluconazole has poor activity against non-*C. albicans* species and should not be used. Boric acid 600 mg capsules administered intravaginally once daily for 14 days can also be used, showing eradication rates of 70%.[2]

Recurrent Vulvovaginal Candidiasis

Case 72-11, Question 11: L.L. experiences another case of VVC 1 month later. Does she have recurrent VVC? How should she be treated?

Most females have only occasional episodes of VVC, but ~5% experience recurrent VVC infections. To determine whether L.L. has recurrent VVC, a diagnosis of *Candida* needs to be confirmed by

vaginal cultures. Then, underlying risk factors for VVC, such as HIV infection, uncontrolled diabetes mellitus, consumption of excess sugars, IUD placement, and use of antibiotics, must be ruled out.[121] Based on the timing of L.L.'s episodes and the absence of risk factors, L.L. does not meet the definition for recurrent VVC. If a patient meets the criteria for recurrent VVC, an underlying cause of the problem may not be determined. In addition, the role of sexual transmission is not currently well understood.[112] In most patients, the pathogenesis of recurrent VVC cannot be determined.

Treatment of recurrent (more than four episodes in 12 months) *C. albicans* vulvovaginitis should include a prolonged, 7- to 14-day course of topical therapy or a three-dose regimen of oral fluconazole (100, 150, or 200 mg) administered every 3 days. A 6-month maintenance regimen should be initiated after remission has been achieved (**Table 72-7**). Despite the efficacy of these regimens, discontinuation of therapy after 6 months can result in relapse in 30% to 50% of females.[2] Azole-resistant strains of *C. albicans* are rare; therefore, culture and sensitivity testing is not usually performed to help guide treatment before initiation.

Table 72-7
Maintenance Regimens for Recurrent Vulvovaginal Candidiasis

	Dose	Frequency
Topical agents[a]		
Clotrimazole	200 mg	Intermittently
Clotrimazole vaginal suppositories	500 mg	Intermittently
Oral agents		
Fluconazole tablets	100, 150, or 200 mg	Weekly for 6 months

[a]Given as examples only; the Centers for Disease Control and Prevention (CDC) does not indicate a preferred regimen.

Vulvovaginal Candidiasis During Pregnancy

Case 72-11, Question 12: What teratogenic risks are associated with the use of azole preparations?

Vaginal colonization with *Candida* and symptomatic VVC are common during pregnancy.[120] Asymptomatic colonization is not associated with increased maternal or fetal risks and need not be treated; however, symptomatic VVC should be treated.[122] Although doses of oral fluconazole used to treat VVC have not been associated with increased fetal defects, higher doses may be teratogenic. Therefore, topical antifungal agents are preferred for the treatment of VVC in pregnant females. The CDC currently recommends a 7-day course of topical antifungal therapy for VVC during pregnancy; however, a 3-day regimen with appropriate follow-up to assess efficacy has been shown to be effective in mild-to-moderate cases. Clotrimazole is also classified as a category B drug for fetal risk, and the remaining vaginally administered azoles are designated as category C.[122]

Trichomoniasis

SIGNS AND SYMPTOMS

CASE 72-12

Question 1: N.B. is a 31-year-old female with a recent history of profuse vaginal discharge and irritation. Examination confirms the presence of an increased, yellow-green vaginal discharge. A wet-mount examination of vaginal secretions revealed numerous motile flagellates.

What subjective and objective clinical data support a diagnosis of trichomoniasis?

Trichomoniasis is the most common curable (nonviral) STD in the United States; it is caused by the protozoan *T. vaginalis.*[2] The overall prevalence is estimated at 3.1%, with the highest prevalence among African Americans at 13.3%. Trichomoniasis in females is

asymptomatic or with minimal symptoms about 70% to 85% of the time. In males, *T. vaginalis* most commonly infects the urethra, although it may also cause epididymitis and prostatitis. Classic symptoms of trichomoniasis in females include a profuse, frothy, yellow-green malodorous discharge with pruritus and dysuria. On speculum exam, a "strawberry" cervix (cervical microhemorrhages) may be noted in 2% to 25% of cases.[123] In almost all cases of trichomoniasis, a vaginal pH >5 is observed.[124] Although trichomonads are easily visualized on a Papanicolaou (Pap) test, it is associated with a 48.4% error in diagnosis when used alone.[123] Direct microscopic observation of trichomoniasis using a wet mount is inexpensive and yields a high specificity, but it has a low sensitivity.[26] Other testing options include culture, rapid antigen tests, and NAATs.

Treatment

METRONIDAZOLE AND TINIDAZOLE

Case 72-12, Question 2: How should N.B.'s trichomoniasis be treated?

The only class of drugs that is effective for the treatment of trichomoniasis is nitroimidazoles. In the United States, metronidazole and tinidazole are the only available nitroimidazoles, and both are CDC-recommended first-line agents given as a single 2-g oral dose. Sexual partners should be simultaneously treated to prevent reinfection. Although females should be tested for reinfection in 3 months, there are currently no data to support retesting males posttreatment. Metronidazole cure rates are reported to be 84% to 98%, whereas tinidazole cure rates are reported to be 92% to 100%; concurrently treating sexual partners might increase these rates. Tinidazole offers other advantages such as higher serum and genitourinary levels, a longer half-life, and fewer GI adverse reactions.[2]

Approximately 4% to 10% of *T. vaginalis* isolates exhibit a low-level resistance to metronidazole therapy and 1% to tinidazole therapy; however, higher level resistance appears to be rare.[2] If metronidazole 2 g PO for one dose fails and reinfection is excluded, metronidazole 500 mg PO twice daily for 7 days can be used. However, if this regimen fails, either metronidazole or tinidazole 2 g PO as a single dose for 7 days should be used. In the case of allergy to nitroimidazole compounds, patients should be desensitized to metronidazole and subsequently treated.[2]

ADVERSE EFFECTS

Case 72-12, Question 3: N.B. was treated with metronidazole 2 g as a single dose; however, while attending a party, N.B. experienced a severe headache, followed by nausea, sweating, and dizziness. Could N.B.'s symptoms be caused by metronidazole?

Minor side effects associated with metronidazole therapy include nausea, vomiting (especially with single-dose therapy), headache, skin rashes, and alcohol intolerance. The alcohol intolerance may be attributable to a metronidazole-induced inhibition of aldehyde dehydrogenase, which results in the buildup of high serum acetaldehyde levels, although the true risk of this interaction has been debated.[125] According to the manufacturer, patients should be warned about the possibility of nausea, vomiting, flushing, and respiratory distress after alcohol consumption, although reliable evidence is lacking.[120] As a general rule, patients should avoid alcohol ingestion during treatment and for 72 hours after metronidazole or tinidazole therapy. In those patients who cannot otherwise tolerate oral metronidazole or tinidazole, a combination of intravaginal miconazole and metronidazole may be an effective alternative.[126]

PREGNANCY

CASE 72-13

QUESTION 1: S.G., a 31-year-old female, is in her first trimester of pregnancy and has a history of recurrent trichomoniasis. She now has a profuse, yellow vaginal discharge. The preliminary diagnosis of trichomoniasis is confirmed by a wet-mount examination of vaginal secretions revealing numerous trichomonads. S.G. has read much lay press on metronidazole and is concerned about the health of her fetus.

Can metronidazole be used for S.G.?

During pregnancy, trichomoniasis infection is associated with premature rupture of the membranes, preterm delivery, and low birth weight; thus, current guidelines recommend treatment in all symptomatic pregnant females in any trimester.[2] Historically, there has been concern about the administration of metronidazole during the first trimester; it is mutagenic in facultative bacteria, and long-term, high-dose metronidazole in laboratory mice is associated with the development of pulmonary and hepatic tumors. Although midline facial defects have been documented in humans, numerous recent studies have found that metronidazole is not a teratogen.[127] The use of metronidazole in asymptomatic females has not been shown to decrease rates of preterm labor despite eliminating the organism from its host.[127]

Treatment

CASE 72-13, QUESTION 2: How should S.G. be treated?

All symptomatic pregnant females should be treated with metronidazole 2 g PO as a single dose, and sexual partners should also be treated. Metronidazole is classified as pregnancy category B. Tinidazole 2 g PO as a single dose could be suggested as an alternative regimen; however, it is classified as pregnancy category C.[2]

GENITAL HERPES

The word *herpes* is of Greek origin and means "to creep."[128] HSV is a DNA-containing virus that consists of two antigenically distinct serotypes: HSV-1 and HSV-2. The primary cause of herpes labialis (cold sores), herpes keratitis, and herpetic encephalitis is HSV-1. Genital herpes and neonatal herpes primarily are the result of HSV-2 infections. Among males who were diagnosed with genital herpes between 2011 and 2016, 25.2% were HSV-2 positive/HSV-1 negative, which is similar to previously reported rates from 1999 to 2010. However, the percentage of females diagnosed during this same time frame found that 31.6% were HSV-2 positive/HSV-1 negative, a significant increase, whereas HSV-2 seropositivity declined significantly to 63.3%.[6]

Etiology

Most people are exposed to HSV-1 early in life, with more than half being positive for HSV-1 antibodies before 18 years and >90% of the population positive by age 70 years.[129] The infection is often asymptomatic and generally acquired through primary infection of mucocutaneous surfaces. The initial, primary disease is a gingivostomatitis characterized by vesicles in the oral cavity and, occasionally, an elevated temperature; life-threatening encephalitis or keratoconjunctivitis may also occur. Usually after primary exposure, HSV-1 enters cells of the trigeminal ganglion, where it may remain latent for the lifetime of the host.[130] Initial HSV-2 infections usually occur after puberty and coincide with the onset of sexual activity, although transfer to a neonate from an infected mother can occur. After primary infection, the virus enters a state of latency in the sacral dorsal root ganglia in many infected individuals; a high percentage of infected persons may never manifest the disease clinically.[131],[132] In both HSV-1 and HSV-2 infections, reactivation can occur, even when circulating antibody and sensitized lymphocytes are present. Clinically, the lesions

periodically erupt usually at the same location, and the interval between episodes varies widely between individuals.

Epidemiology

Although herpes was recognized several thousand years ago, genital herpes was not described until the 18th century. Overall, the seroprevalence of genital herpes (HSV-2) in the United States has declined from 18% in 1999 to 12.1% in 2016; however, seroprevalence remains highest in non-Hispanic Blacks at ~40%.[6] Fifty million individuals are estimated to have HSV-2, making it one of the most common STDs in the United States.[2,6] In 2013, U.S. physicians saw >300,000 new patients presenting with genital herpes simplex, with nearly 20% of non-Hispanic White females and more than double that in non-Hispanic Black females seropositive in the United States.[6]

Demographic characteristics indicate that the risk of genital HSV-2 infection increases from 2% to 5% with one sexual partner, to between 19% and 37% in those with ≥10 partners. Other demographic characteristics that increase the risk of acquisition include Black non-Hispanic race (three to four times the prevalence of non-Hispanic Whites); female sex (twice the prevalence of males); and presence of other STDs (increases odds ratio for viral shedding to 3.1).[133] The time range from exposure to disease onset is ~4 days (range 2–12 days).[134] HSV-2 infection increases the risk of HIV acquisition by up to threefold, possibly due to the presence of open ulcers or lymphocytes at the site, which may aid transmission. Of recent concern, although the seroprevalence of HSV-1 in 14- to 19-year-olds has been reported to have declined by 23% from 1999 to 2010, other studies have found HSV-1 infections actually increasing in this age group as a result in part of not having protective HSV-1 antibodies at sexual debut.[6,135]

Signs and Symptoms

CASE 72-14

QUESTION 1: R.A., a 28-year-old, sexually active male, presents with painful penile lesions and tender inguinal adenopathy. The lesions are vesicular and limited to the scrotum, glands, and shaft of the penis. The onset of the lesions was preceded by a 1-week period of fever, malaise, headache, and itching. Viral culture result of the lesions was positive for HSV infection.

What is the typical course and clinical presentation of herpes genitalis in males and females? What subjective and objective clinical data in R.A. are compatible with herpes genitalis?

Most initial episodes of genital herpes are symptomatic. As illustrated by R.A., the symptoms usually start ~1 week after initial exposure, with prodromal signs of tingling, itching, paresthesia, or genital burning. The prodromal stage, which can last from a few hours to several days, is followed by the appearance of numerous vesicles. The vesicles eventually erupt, resulting in painful genital ulcers. The pain and edema associated with genital herpetic lesions, especially if they are infected secondarily, can be severe enough to result in dysuria and urinary retention. Bilaterally distributed lesions of the external genitalia are characteristic. The lesions usually are limited to the glands, corona prepuce, and shaft of the penis in males and to the vulva and vagina in females. However, lesions can occur on the buttocks, thighs, and urethra.[132],[133] Asymptomatic or mucopurulent cervicitis may occur in about 15% to 20% of females with primary HSV-2 infections.[136] Rectal and perianal HSV-2 infections are more common in MSM and immunocompromised individuals.[137] Symptoms may include anorectal pain and discharge, tenesmus, and constipation.

Prior infection may ameliorate the severity of the first episode of genital herpes but does not impact the rate of recurrence.[138] In primary infections, the local symptoms of pain, itching, and urethral or vaginal discharge last up to 14 days, with a complete disappearance of lesions in 3 to 6 weeks.[132],[139] The clinical course of primary herpes is presented in **Figure 72-5**. Most patients have minor symptoms or are asymptomatic and are often unaware of being infected; however, individuals are most infectious within the

first year of acquisition of the virus.[133],[140] Asymptomatic individuals may also intermittently shed virus particles to others, which represents the primary way genital HSV2 is spread.[2]

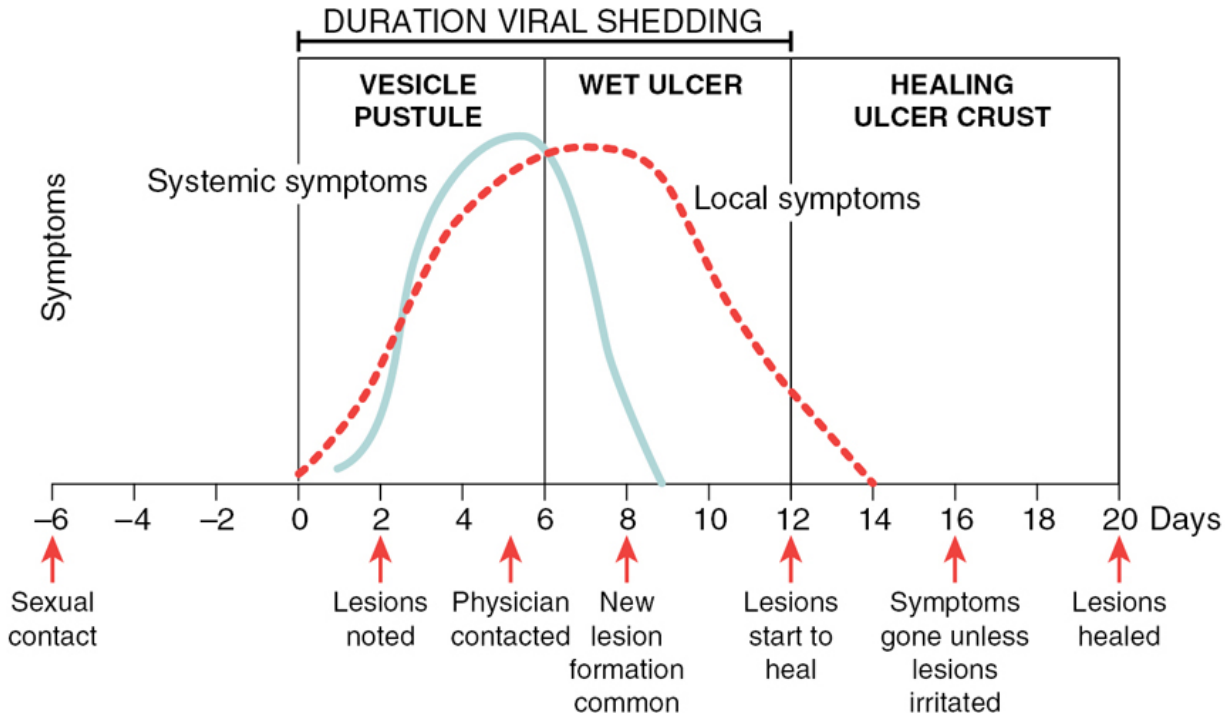


Figure 72-5 The clinical time course of primary genital herpes infections. (Adapted with permission of McGraw Hill LLC from Corely L, Wald A. Genital herpes. In: Holmes K, Sparling PF, Stamm WE, et al, eds. *Sexually Transmitted Diseases*. 4th ed. McGraw-Hill; 2008:399; permission conveyed through Copyright Clearance Center, Inc.)

Recurrence

CASE 72-14, QUESTION 2: Is R.A.'s infection likely to recur?

Most first-episode HSV-2 symptomatic patients experience a recurrence of their initial infection.[2] However, the rate of recurrent infections varies among individual patients. Approximately 38% can experience 6 or more episodes, and 20% can have >10.[139] Natural infection with HSV-2 induces type-specific immunity against

exogenous reinfection, but does not affect recurrences.[141] The severity of the primary episode and recurrence appear to be influenced by the host's immune status, especially a depressed T-cell response.[132] Recurrent infections usually appear at or near the site of the initial infection, and prodromal symptoms are reported by about 50% of persons with recurrent infection. Males experience recurrence more frequently than do females. In contrast with primary infections, there are fewer lesions and they are often unilateral.[132] Constitutional symptoms such as lymphadenopathy, fever, and malaise generally are also milder. Recurrent infections are also shorter in duration (average, 1 week); local symptoms such as pain and itching last 4 to 5 days and the lesions themselves last 7 to 10 days.[132] Although there is some variability, patients may have four to five recurrences during the first year, but reactivation frequency slowly declines over time.[133]

Transmission

Case 72-14, Question 3: R.A. states that this is the first time he has had such lesions and that he has had only one sexual partner for the past 14 months. His sexually active female partner has no history of herpes genitalis or any other STD. The couple is very curious as to how R.A. acquired his infection. How is HSV transmitted?

Transmission of HSV occurs by direct contact with active lesions or from a symptomatic or asymptomatic person shedding virus at a peripheral site, mucosal surface, or secretion.[142] Genital HSV-2 infections usually are acquired through sexual (vaginal or anorectal) intercourse, whereas genital HSV-1 infections are acquired through orogenital sexual practices. Consistent condom use has been shown to result in a 30% reduction in the risk of acquiring HSV-2, but there does not appear to be any differences in effectiveness between males and females. However, for every 25% of the time that condoms are used during vaginal or anal sex, the risk of HSV-2 acquisition decreases by 7%.[143] Regardless, patients with

seropositive HSV should be counseled to practice safer sex, using male or female condoms, at all times, not just during symptomatic episodes.[144]

A patient with genital herpes is contagious only when shedding the virus. The patient begins to shed virus during the prodromal phase, which may be several hours to days before the actual lesions first appear. Patients can, however, be asymptomatically diagnosed by serology and subsequently develop clinical lesions or be symptomatic on diagnosis and have recurrent episodes of clinical lesions. Symptomatic viral shedding occurs twice as often than in asymptomatic HSV-2 seropositive individuals, but subclinical viral shedding (ie, no lesions present) still occurs ~10% of days, regardless of gender.[145],[146] From a public health standpoint, unrecognized subclinical shedding may indicate a greater need for serologic testing to reduce further transmission and initiate therapy; however, it may also result in high false-positive rates and cause psychosocial harms.[147] Lesions are most contagious during the ulcerative phase. The median duration of viral shedding, as defined from onset to the last positive culture result, is about 12 days.[132] The mean time from the onset of vesicles to the appearance of the crust stage (~10.5 days) correlates well with the duration of viral shedding. However, there is considerable overlap between the duration of viral shedding and the duration of crusting. Females require a longer healing time than do males, 19.5 and 16.5 days, respectively.[132] The mean duration of viral shedding from genital lesions is 11 to 12 days following a primary infection and 4 days following a recurrent infection.[145] Therefore, patients should be advised to refrain from sexual activity until the lesions have completely healed; however, subclinical viral shedding may also transmit HSV-2.

A genital herpes infection may be acquired from an individual who has never had symptomatic genital lesions. States of asymptomatic or subclinical viral shedding occur in the majority of females with recurrent genital herpes as a result of reactivation of latent infection. These recurrent infections can have a primary disease presentation, causing the patient to blame the most proximate sexual partner when, in actuality, the exposure could have occurred in the distant

past.[148] Serologic and virologic typing can be used to determine whether this is a true primary infection. Sensitive detection techniques such as PCR may detect the presence of HSV; however, the relationship between a PCR-positive HSV test result and true communicability has yet to be fully determined because shedding can be intermittent.[149–151] In addition, asymptomatic spread can occur from multiple anatomic genital sites and in a bilateral manner, even with previous outbreaks of unilateral lesions.[152]

Diagnostic Tests

Case 72-14, Question 4: Viral culture result was negative for R.A., but HSV-2 point-of-care (POC) serology finding was positive for both R.A. and his sexual partner. How should these laboratory tests be interpreted?

The accuracy with which herpes genitalis can be diagnosed without the aid of laboratory tests generally is difficult to achieve, especially if the infection is not symptomatic. Thus, because of the potentially severe psychological and physiologic ramifications of such a diagnosis, either virologic and/or serologic confirmation of the diagnosis may be obtained.

The laboratory diagnosis of HSV-1 or HSV-2 infection depends on isolation of the virus using viral culture, whereas HSV DNA detection by PCR is more expensive than is viral culture and may not be as widely available for HSV antigen detection using ELISA (enzyme-linked immunosorbent assay) or DFA. Both PCR and ELISA can differentiate HSV-1 from HSV-2. Currently, HSV DNA PCR is the most sensitive method for detecting mucocutaneous herpes simplex infection rather than is simple viral culture in those with genital ulcers and is the preferred method for CSF samples.[151] Tests that measure serologic response or antibody production are valuable in documenting primary infection, but they are not useful in recurrent infections or determining when the initial infection occurred. It is possible to differentiate between antibodies to HSV-1 and HSV-2 by means of type-specific serologic assay. POC devices using HSV-2–

specific antibody testing kits offer ease, reduced time, differentiation between HSV-1 and HSV-2, and high sensitivities and specificities.[15,153,154]

Viral culture is more likely to yield false-negative results than do other testing methods because sensitivity is low.[2] A better antigen detection test could have been used, such as an ELISA or DFA. The lack of a positive viral culture result does not rule out the diagnosis of a primary infection in R.A., especially because the antibody test result was positive. The fact that R.A.'s partner's antibody test result was positive without a history of symptomatic disease suggests a distant infection with asymptomatic shedding.

Treatment

Case 72-14, Question 5: How should R.A.'s lesions be managed? Because the likelihood of recurrence of genital herpes is high, what treatment and prevention measures are recommended currently?

A diagnosis of genital herpes is concerning because there is no cure for the condition. Therapies ranging from antiviral agents to photoinactivation to investigational vaccines to supplements have been tried. Currently, only acyclovir (ACV), famciclovir (FCV), and valacyclovir (VCV) are approved agents for the treatment of symptomatic genital herpes and suppression of latent infection

The ideal anti-HSV agent should prevent infection, shorten the clinical course, prevent the development of latency, prevent recurrence in patients with established latency, decrease transmission of disease, and eradicate established latent infection.[132] To date, no agent has been successful in achieving all of these goals.

All three agents, ACV, FCV, and VCV, are effective for the short-term treatment of some HSV infections. ACV, a nucleoside analog, is a substrate for HSV-specific thymidine kinase. Through a series of phosphorylation steps, ACV is transformed to ACV-triphosphate, a competitive inhibitor of viral DNA polymerase. ACV has potent in

vitro activity against both HSV-1 and HSV-2, but it is far less active against varicella-zoster and CMV.[155] FCV, a prodrug of penciclovir, has increased oral bioavailability compared with acyclovir. Once converted in the intestine and liver to the active form, penciclovir, it is quickly phosphorylated in HSV in a manner similar to that of ACV. VCV is the L-valyl ester prodrug of ACV. The oral bioavailability of VCV is also significantly better than that of ACV, producing plasma levels of ACV comparable to those attained with IV-administered ACV, often eliminating the need for parenteral therapy.[156] All three antiviral drugs are equally effective for genital herpes infections.

IV ACV has been shown to reduce the median number of symptomatic days and duration of lesions.[157] Similar findings have been shown in the immunocompromised patient population.[158] IV and oral ACV or VCV also prevent HSV reactivation in seropositive immunocompromised patients who are undergoing bone marrow transplantation.[159] For patients with HIV, ACV 400 to 800 mg PO two to three times daily, FCV 500 mg twice daily, or VCV 500 mg twice daily for 5 to 10 days has been used for daily suppressive therapy.[2] Currently, IV therapy is recommended only for patients with severe genital or disseminated infections (eg encephalitis) who cannot take oral medications.

Topical ACV has minimal effect on the duration of symptoms in first-episode primary genital herpes, has low-quality evidence supporting its use, and is therefore not recommended for primary genital herpes.[157] Penciclovir 1% cream applied every 2 hours while awake for 4 days is an effective treatment option for herpes simplex labialis, but it is not currently indicated for genital herpes infections.

Oral antivirals speed the healing and resolution of symptoms of first and recurrent episodes of genital HSV-2 infections.[133] Treatment of primary infection after the first week of infection does change the natural history of recurrent outbreaks; thus, patients should be educated about the risk of sexual transmission, and prompt recognition of signs and symptoms and the early use of antivirals.[2],[160] The frequency of recurrence decreases with time in most patients. Recurrent episodes of genital HSV-2 infection can be

treated with any of the three available oral antivirals (**Table 72-8**). Rather than having to go into clinic, patients with recurrent infections could instead be provided with a supply of antiviral medication with them to allow early initiation of therapy, which may abort or reduce symptoms by 1 to 2 days.[161],[162]

Table 72-8
Antiviral Chemotherapy of Genital HSV-2 Infections

	Acyclovir	Valacyclovir	Famciclovir	Duration	Comments
First clinical episode	400 mg PO tid *or* 200 mg PO five times per day	1 g PO bid	250 mg PO tid	7–10 days	May extend treatment duration if healing is incomplete
Episodic recurrent infection	400 mg PO tid *or* 800 mg PO bid or 800 mg PO tid × 2 days	1 g PO QD *or* 500 mg PO bid × 3 days	125 mg PO bid or 1 g PO bid × 1 day or 500 mg PO × 1, then 250 mg bid × 2 days	5 days	Most effective if initiated within the first 24 hours of onset of lesions or during the prodrome
Daily suppressive therapy	400 mg PO bid[a]	500 mg PO QD[b] or 1 g PO QD	250 mg PO bid	Daily	Reduces the frequency of genital herpes recurrences by ≥75% among patients who have frequent recurrences (ie, ≥6 recurrences per year); use should be reevaluated at 1 year
Severe disseminated	5–10 mg/kg IV Q 8 hours	Not indicated	Not indicated	2–7 days[c]	Hospitalize and treat until clinical resolution of symptoms. Follow-up IV therapy with PO ACV to complete 10 days
HIV-infected: episodic	400 mg PO tid *or* 200 mg 5/day	1 g PO bid[d]	500 mg PO bid	5–10 days	Treat until clinical resolution of lesions
HIV-infected: suppressive	400–800 mg PO bid or tid	500 mg PO bid[e]	500 mg PO bid		

Note: Regimen recommendations derived from the 2021 Centers for Disease Control and Prevention (CDC) Recommendations.[2]

ACV, acyclovir; bid, twice a day; HIV, human immunodeficiency virus; IV, intravenous; PO, orally; tid, three times a day; QD, on prescription.

[a]Safety and efficacy of up to 6 years have been documented with the use of acyclovir.

[b]Valacyclovir 500 mg on prescription (QD) seems less effective in patients with >10 episodes per year. Thus, 1 g QD should be used in these patients.

[c]Or until clinical improvement is observed.

[d]Dosages up to 8 g/day have been used, but an association with a syndrome resembling either hemolytic uremic syndrome or thrombotic thrombocytopenic purpura was observed.

[e]Effective in decreasing both the rate of recurrences and the rate of subclinical shedding among HIV-infected patients.

Source: Adapted from Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1–187. doi:10.15585/mmwr.rr7004a1.

Daily suppressive therapy with ACV, FCV, or VCV reduces the frequency of recurrent episodes up to 70% to 80% among patients with frequent (eg, five to eight episodes per year) genital herpes.[2,163] Recurrent outbreaks diminish with time; thus, after each year of continuous suppressive therapy, an effort should be made to discuss discontinuing therapy with the patient. The use of suppressive therapy does not eliminate viral transmission. However, a randomized, controlled clinical trial of serodiscordant HSV-2–positive couples found a statistically significant decrease in the rate of transmission to the uninfected partner when the infected partner took VCV 500 mg QD.[164] In such couples, suppressive therapy should be considered to help prevent transmission, in addition to condom use and refraining from sexual activity during recurrences. The CDC recommends various dosing regimens for VCV; however, one meta-analysis found a consistent prophylactic benefit if VCV was dosed at 250 mg twice daily or 500 mg once daily.[165] Immunocompromised patients may require higher doses or more frequent intervals for suppression.[166]

Most cases of ACV-resistant HSV occur in the immunocompromised host; however, the resistance is <5%.[167] All ACV-resistant strains are also resistant to VCV, and most are resistant to FCV as well. Foscarnet 40 to 80 mg/kg IV every 8 hours or cidofovir 5 mg/kg once weekly until clinical resolution may be used for severe ACV-resistant genital HSV infections.[2] Cidofovir 1% gel (not commercially available in the United States) applied once daily for 5 days may be an alternative for mucocutaneous HSV resistant to ACV, but more studies are needed.[2,168]

R.A. is not yet a candidate for daily suppressive ACV therapy. A summary of the indications for ACV, FCV, and VCV is outlined in Table 72-8.

ADVERSE EFFECTS

Case 72-14, Question 6: What adverse effects associated with ACV, FCV, or VCV should be anticipated?

Overall, all forms of ACV, including VCV and FCV, are associated with relatively few adverse reactions largely because of the drugs' affinity for viral thymidine kinase over cellular kinase.

Hematuria and an increase in blood urea nitrogen and serum creatinine may occur, primarily in patients with underlying renal disease or in those receiving concomitant nephrotoxic agents. However, this complication is almost entirely associated with the IV route. In addition, severe local reactions are possible with IV administration. In patients with HIV/AIDS, VCV at a dosage of 8 g/day was associated with a hemolytic uremic syndrome or thrombotic thrombocytopenic purpura-like syndrome. However, this complication has not been observed with normal therapeutic doses. As described previously, when given as IV in high doses or with significant dehydration, ACV crystallizes in the renal collecting tubules of animals, leading to renal insufficiency.[169] ACV should not be rapidly infused or administered at concentrations >10 mg/mL. Dose adjustment is necessary for all three antiviral agents in patients with decreased renal function.

Although neurotoxicity is a rare side effect, case reports of coma and delirium have been reported in patients with renal failure.[170,171]

IV ACV occasionally has been associated with cutaneous irritation and phlebitis, reversible leukopenia,[172] and transient elevations of liver transaminases. Oral ACV and VCV are relatively safe and do not produce any serious side effects at normal doses. Patients receiving oral ACV, VCV, or FCV may experience nausea, dizziness, diarrhea, and headaches.

Patient Education and Counseling

Case 72-14, Question 7: What are the roles for education and counseling in patients with genital herpes? Are other forms of local or symptomatic care useful?

Most genital herpes infections are benign, and lesions heal spontaneously unless the patient is immunocompromised, or the lesions have become infected secondarily. The patient should be instructed to keep the affected areas clean and dry. To prevent autoinoculation, the patient should be told not to touch the lesions and to wash hands immediately afterward if they come in contact with the lesion. Local anesthetics provide relief from the pain of genital lesions, but they should be avoided if possible because they counteract efforts to keep the lesions dry. Local corticosteroid therapy is contraindicated because it may predispose the patient to secondary infections.

Patient counseling should include the source contact and any future partner. Health care practitioners should attempt to relieve patients' feelings of guilt and anxiety; discussion of long-term consequences should take place after the acute symptoms of the infection have resolved.

For individuals with frequent recurrences, efforts should be made to identify and avoid stimulatory factors such as sunlight, trauma, or emotional stress. The limitations of therapy and the decreased severity and frequency of recurrences with time should be explained to the patient. The periods of infectivity and the need to avoid sexual activity even when lesions are not present should be emphasized, indicating the need for continuous barrier protection during sexual intercourse. Females with herpes genitalis should be scheduled for routine Pap tests and be instructed to discuss their HSV with their physicians if they become pregnant.

Currently, there is no completely effective way to prevent the transmission of HSV-2 infection. Barrier forms of contraception, in particular condoms, may reduce the transmission of HSV, but this may be limited only to male-to-female transmission owing to the large area that herpes lesions may occupy on the female.[173] However, greater use of condoms by males can increase protection and is recommended to prevent HSV infections.[174] Nonoxynol-9, a spermicide that has in vitro anti-HSV activity, is ineffective in the prevention of established genital HSV infection and may actually

increase the risk of transmission of HSV by causing genital ulceration.[175] Herpes simplex vaccines have been extensively studied,[176] but no candidate vaccine has been submitted for approval.

Complications

CASE 72-15

QUESTION 1: M.F. is a 23-year-old, sexually active female student with a history of frequent and severe recurrences of genital herpes since her initial infection 3 years ago. M.F. has tried numerous therapies, including suppressive and episodic antivirals. None of these therapies has provided M.F. with any relief of her symptoms, nor have they decreased the frequency of her recurrences. M.F. has read much in the lay press about herpes and is concerned about the possible complications of the disease, especially cervical cancer.

What are the potential complications of herpes genitalis?

Previous research suggested that HSV-2 might be an oncogenic agent responsible for carcinoma of the cervix. However, a large longitudinal nested case–control study using nearly 20 years of seroepidemiologic and epidemiologic data combined with a meta-analysis concluded that it is very unlikely that HSV-2 is associated with the development of invasive cervical carcinoma.[177] Severe complications of herpes genitalis include meningitis and encephalitis as well as disseminated disease.[2,132]

PREGNANCY

CASE 72-16

QUESTION 1: A.P., a 26-year-old female in her 32nd week of gestation, was hospitalized with painful genital lesions, headache, fever, increased vaginal discharge, and dysuria of 1 week's duration. Multiple ulcerative lesions consistent with genital herpes were present on the cervix, vulva, labia minora, and thighs.

How should A.P. be treated?

Herpes genitalis seropositivity in pregnant females occurs more frequently than in nonpregnant females, with 20% to 30% of all pregnant females having serologic evidence of HSV-2 infection.[178] When HSV is acquired by the mother near the time of delivery, transmission to the neonate can be 30% to 50%, but it is <1% in those who acquired it early in pregnancy or had recurrent infection.[2] Unfortunately, a large proportion of those infections occurring during pregnancy are limited to the cervix and are totally asymptomatic, often eluding diagnosis.

Pregnant patients with a history of recurrent genital herpes should be examined carefully when they present in labor for evidence of active disease. The safety of systemic ACV, VCV, and FCV in pregnant females has not been established in controlled trials, but the CDC cites the lack of documented fetal harm to assert that ACV can be used safely in all stages of pregnancy (and during breast-feeding).[2] Thus, it is reasonable to recommend ACV to treat HSV in this patient and possibly VCV and FCV because of data from animal trials showing a low risk in pregnancy, although the data are limited.[2] Some small studies suggest ACV administered for several weeks before delivery may decrease recurrent outbreaks and lessen the need for herpes-related cesarean section,[179] whereas a larger randomized clinical trial did not show a benefit in reducing the need for a cesarean delivery with primary infection.[180] In general, it does seem that patients with symptomatic genital herpes benefit from cesarean section.[181] The manufacturer of Zovirax® (ACV) maintained an extensive database of fetal complications related to ACV use that showed no link between ACV and birth defects has been established.[182] The decision to treat HSV with ACV during pregnancy should depend on the clinical severity of infection. If the mother has an active herpes genitalis infection at the time of delivery (either active genital lesions or HSV-2 cervicitis) or is experiencing a recurrent, the baby should be delivered by cesarean section to help minimize the risk of exposure to the newborn. However, if no genital lesions are present at the time of labor, vaginal delivery may be recommended.[2] There is evidence that up to 70% of neonatal herpes cases occur in asymptomatic females and the use of ACV or VCV

after 36 weeks gestation may decrease clinical disease and viral shedding to the fetus.[183]

Neonatal herpes is a devastating systemic infection of the newborn, associated with high morbidity and mortality, especially when infected with HSV-2 versus HSV-1.[184] HSV is usually transmitted to the newborn during passage through an infected birth canal, ~300 times greater than when HSV is not present.[181] The risk of transmission to the newborn is greatest in mothers who acquire an initial infection late in the third trimester and lower in mothers with recurrent infection or those who acquire herpes in the first trimester (25% –50% vs <1% for preexisting infection).[184]

GENITAL WARTS

CASE 72-17

QUESTION 1: S.L., a 21-year-old female, presents to the health clinic for her annual examination. One week later, her Pap test result is read as low-grade squamous intraepithelial lesion (LGSIL) with koilocytosis. A colposcopy is subsequently performed, revealing changes consistent with cervical flat warts, and biopsy finding of the lesion reveals low-grade cervical intraepithelial neoplasia (CIN).

What is the cause of S.L.'s infection? How should she be managed?

HPV is the cause of genital warts or condylomata acuminata. Types 6 and 11 account for >90% of genital warts. Other types of HPV, including 16 and 18, account for 66% of cervical cancer in the United States.[6] They are associated with changes in Pap test findings, including koilocytosis and cervical dysplasia. In the United States, the seroprevalence of any HPV serotype causing genital infection is 42.5% among adults 18 to 59 years of age; however, prevalence is significantly higher in sexually active non-Hispanic White and Black males.[185],[186]

CIN is a common cervical cancer grading system using histologic changes to classify specimens in three categories, CIN-1, -2, and -3.

The higher the number, the greater is the chance of progressing to invasive cervical cancer. Most new cases of HPV infection spontaneously regress, but with progressive histologic changes, the chance of spontaneously regressing diminishes (CIN1, 60%; CIN2, 30%; and CIN3, 10%).[187] Types of HPV are also classified as high risk, or those likely to cause cancer, and low risk, those less likely to cause cancer. HPV types 16, 18, 31, 33, 45, 52, and 58 are considered high risk and types 6 and 11 are low risk, the latter mostly resulting in genital warts. In females, visible warts occur on the labia, introitus, and vagina. Subclinical lesions also commonly occur on these sites and on the cervix, as in S.L.'s case. They are visible only by colposcopy after applying acetic acid. Males can sexually transmit HPV infections to females as well as exhibit genital warts, and anal and penile cancers are associated with oncogenic HPV types, especially type 16.[188] The goal of HPV therapy is the removal of symptomatic warts. Several therapeutic options are available and include patient-administered treatments to visible warts such as podofilox 0.5% solution or gel, imiquimod 3.75% or 5% cream, and sinecatechins 15% ointment; provider-administered therapies include topical treatments (bichloroacetic or trichloroacetic acid 80%–90%, cryotherapy) and surgical removal (laser or excision).[2] However, it is important to note that none of these treatments can eradicate HPV infection or alter the natural history of HPV. It is important to individualize therapy, considering location and number of warts, patient preference, cost, and convenience.

Podophyllin resin, compounded as a 10% to 25% solution in tincture of benzoin, can be applied by the health care provider to visible warts; however, this is generally no longer recommended because of severe systemic toxicity if the resin is applied to large surface areas and not washed off after 4 hours of application.[2] Podophyllin is potentially neurotoxic if absorbed in large amounts. In addition, the rate of wart recurrence after podophyllin therapy is also extremely high, around 50%. As an alternative to podophyllin resin, podofilox 0.5% solution or gel, the active component of podophyllin resin, may be applied by the patient (after the health care provider demonstrates proper application technique) with a cotton swab, or

podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. A total of four cycles, 0.5 mL/day, or application of an area >10 cm^2 should not be exceeded. Podofilox solution is not suitable for use with perianal warts; the gel is more practical for this region. Podofilox has the advantage over podophyllin resin in that it has a longer shelf life, does not need to be washed off, and has less systemic toxicity.[189] However, it should still be applied in limited doses and should also be avoided in pregnancy.

Imiquimod induces cytokines and activates the cell-mediated immune system. In initial trials, complete clearance of warts took place in 37% to 50% of immunocompetent patients, but up to 20% experienced recurrence.[190] The 5% cream is optimally applied by finger at bedtime three times per week and the 3.5% cream once daily for up to 16 weeks.[191],[192] It is usually left on for 6 to 10 hours before it is washed off with soap and water. Imiquimod may take as long as 8 weeks before the warts are cleared. Mild-to-moderate local irritation occurs in more than half of the patients who use it, especially when used daily instead of three times weekly as directed. The cream may weaken condoms and diaphragms.

Sinecatechins are green-tea extracts that contain active catechins with purported immunostimulatory, antiproliferative, and antitumor properties. There are limited data on this product, but it may be more effective than is imiquimod or podofilox by clearing up to 55% of external genital warts.[193] A 15% topical solution can be applied by finger directly to the wart three times a day up to 16 weeks, with the most common side effects being local erythema, pruritus, burning, and pain. Individuals who are immune suppressed, have genital herpes, or are pregnant should not use sinecatechins because their safety and efficacy have not been fully evaluated.[2]

Cryotherapy by application of liquid nitrogen can be more effective than is podophyllin but requires special equipment and trained personnel. Pain and skin blistering after treatment is common. Cryotherapy is associated with minimal systemic toxicity and is useful against oral, anal, urethral, and vaginal warts.

Trichloroacetic acid (80%–90%) is used topically in the treatment of some genital warts, but its efficacy is uncertain. To date,

interferons are not recommended because of expense and toxicity. Cases refractory to topical drug therapy should be considered for surgical treatment.

Prevention

Prevention and control of STDs have largely revolved around education and antimicrobials. Immunization, however, holds the promise of protecting large numbers of people before they are at risk for STDs as well as targeting those who already have the infection. Hepatitis B is an example of an STD with a highly effective vaccine that is now mandatory for school-aged children.

In 2006, the first vaccine to prevent HPV types 6, 11, 16, and 18 was approved in the United States. This quadrivalent vaccine was tested in females from 15 to 26 years of age and demonstrated 98% to 100% protection against HPV types contained in the vaccine.[194,195] In males, the quadrivalent vaccine efficacy was 62.1% to 89.4% against genital warts, depending on previous HPV exposure, leading to its approval for males and boys 9 to 26 years old.[196] Using bridging data, it is estimated that 99% to 100% of 9- to 15-year-olds will seroconvert. In 2014, a 9-valent HPV vaccine was approved to replace the discontinued quadrivalent vaccine. The extra five types (31, 33, 45, 52, and 58) add 15% more cervical cancer coverage protection to the 66% covered by types 16 and 18 in the quadrivalent.[197] The 9-valent HPV vaccine can be administered as a two-dose series as early as age 9 years, but is CDC recommended at 11 to 12 years as part of a routine adolescent health care visit (and ideally before the commencement of sexual activity). If this vaccine is administered past age 15 years, then it needs to be administered as the usual three-dose series instead. Because there are >30 types of HPV associated with anogenital disease, a previous HPV infection is not a contraindication to vaccination. Although the HPV vaccine may be of minimal benefit to older individuals, it may still be recommended and administered on an individual basis to adults ages 27 to 45 years who may not be adequately vaccinated

under a shared clinical decision model. It is also important to note that receipt of the HPV vaccine does not change the recommendation for Pap tests. Lastly, it should not be considered as a therapeutic option because it has no impact on active HPV infection.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and website for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1–187. doi:10.15585/mmwr.rr7004a1 (2)

Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2018*. Department of Health and Human Services; 2019. http://www.cdc.gov/std/stats (6)

Key Website

Division of STD Prevention (DSTDP) at the Centers for Disease Control and Prevention. https://www.cdc.gov/std/default.htm

COMPLETE REFERENCES CHAPTER 72 SEXUALLY TRANSMITTED DISEASES

1. Institute of Medicine: Committee on Prevention and Control of Sexually Transmitted Diseases. *The Hidden Epidemic: Confronting Sexually Transmitted Diseases*. National Academy Press; 1997.

2. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1–187. doi:10.15585/mmwr.rr7004a1
3. Centers for Disease Control and Prevention. STD clinical slides. http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm
4. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2009*. U.S. Department of Health and Human Services; 2010.
5. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2013*. U.S. Department of Health and Human Services; 2014.
6. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2018.* U.S. Department of Health and Human Services; 2019.
7. Nelson HD, Zakher B, Cantor A, Deagas M, Pappas M. *Screening for Gonorrhea and Chlamydia: Systematic Review to Update the U.S. Preventive Services Task Force Recommendations.* Agency for Healthcare Research and Quality; 2014.
8. Holmes KK, Johnson DW, Trostle HJ., et al. An estimate of the risk of men acquiring gonorrhea by sexual contact with infected females. *Am J Epidemiol*. 1970;91:170–174.
9. Hook AEW, Hansfield H. Gonococcal infections in the adult. In: Holmes KK, Sparling PF, Stamm WE, et al, eds. *Sexually Transmitted Diseases (electronic version)*. 4th ed. McGraw-Hill Health Professions Division; 2008.
10. Turner CF, Rogers SM, Miller HG, et al. Untreated gonococcal and chlamydial infection in a probability sample of adults. *JAMA*. 2002;287:726–733.
11. Mehta SD, Rothman RE, Kelen GD, Quinn TC, Zenilman JM. Unsuspected gonorrhea and chlamydia in patients of an urban adult emergency department: a critical population for STD control intervention. *Sex Transm Dis*. 2001;28:33–39.
12. Emmert DH, Kirchner JT. Sexually transmitted diseases in women. Gonorrhea and syphilis. *Postgrad Med*. 2000;107:181–197.
13. Centers for Disease Control and Prevention. Control of *Neisseria gonorrhoeae* infection in the United States: report of an external consultants' meeting convened by the division of STD prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention (CDC). *CDC*. 2001:19.
14. Watts D. Pregnancy and viral sexually transmitted infections. In: Holmes KK, ed. *Sexually Transmitted Diseases*. 4th ed. McGraw-Hill Health Professions Division; 2008.
15. Workowski KA, Berman S; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1–110. doi:rr5912a1 [pii]
16. Brocklehurst P. Update on the treatment of sexually transmitted infections in pregnancy–2. *Int J STD AIDS*. 1999;10:636–643.

17. Centers for Disease Control and Prevention. Recommendations for the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*—2014. *MMWR Recomm Rep*. 2014;63(RR-02):1–19.
18. St Cyr S, Barbee L, Workowski KA, et al. Update to CDC's treatment guidelines for gonococcal infection, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(50): 1911–1916. doi:10.15585/mmwr.mm6950a6
19. U.S. Department of Health & Human Services. Sexually Transmitted Disease Surveillance 2005 Supplement: Gonococcal Isolate Surveillance Project (GISP) Annual Report 2005. http://www.cdc.gov/std/GISP2005
20. Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2007;56:332–336.
21. Knapp JS, Mesola VP, Neal SW, et al. Molecular epidemiology, in 1994, of *Neisseria gonorrhoeae* in Manila and Cebu City, Republic of the Philippines. *Sex Transm Dis*. 1997;24:2–7.
22. Yahara K, Nakayama SI, Shimuta K, et al. Genomic surveillance of *Neisseria gonorrhoeae* to investigate the distribution and evolution of antimicrobial-resistance determinants and lineages. *Microb Genom*. 2018;4(8):e000205. doi:10.1099/mgen.0.000205
23. Fox KK, Knapp JS, Holmes KK, et al. Antimicrobial resistance in *Neisseria gonorrhoeae* in the United States, 1988–1994: the emergence of decreased susceptibility to the fluoroquinolones. *J Infect Dis*. 1997;175:1396–1403.
24. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(Rr-03):1–137.
25. Centers for Disease Control and Prevention. Discontinuation of spectinomycin. *MMWR Morb Mortal Wkly Rep*. 2006;55(RR-13):370.
26. Kirkcaldy RD, Weinstock HS, Moore PC, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. *Clin Infect Dis*. 2014;59(8):1083–1091.
27. Park MA, Li JTC. Diagnosis and management of penicillin allergy. *Mayo Clin Proc*. 2005;80:405–410.
28. Aplasca De Los Reyes MR, Pato-Mesola V, Klausner JD, et al. A randomized trial of ciprofloxacin versus cefixime for treatment of gonorrhea after rapid emergence of gonococcal ciprofloxacin resistance in the Philippines. *Clin Infect Dis*. 2001;32:1313–1318.
29. Lyss SB, Kamb ML, Peterman TA, et al. *Chlamydia trachomatis* among patients infected with and treated for *Neisseria gonorrhoeae* in sexually transmitted disease clinics in the United States. *Ann Intern Med*. 2003;139(3):178–185. doi:10.7326/0003-4819-139-3-200308050-00007 [pii]
30. Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no

longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2012;61(31):590–594.
31. Lafferty WE, Hughes JP, Handsfield HH. Sexually transmitted diseases in men who have sex with men. Acquisition of gonorrhea and nongonococcal urethritis by fellatio and implications for STD/HIV prevention. *Sex Transm Dis*. 1997;24:272–278.
32. Jebakumar SP, Storey C, Lusher M, Nelson J, Goorney B, Haye KR. Value of screening for oro-pharyngeal *Chlamydia trachomatis* infection. *J Clin Pathol*. 1995;48:658–661.
33. Bernstein KT, Stephens SC, Barry PM, et al. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* transmission from the oropharynx to the urethra among men who have sex with men. *Clin Infect Dis*. 2009;49(12):1793–1797. doi:10.1086/648427
34. Geisler WM, Whittington WL, Suchland RJ, Stamm WE. Epidemiology of anorectal chlamydial and gonococcal infections among men having sex with men in Seattle: utilizing serovar and auxotype strain typing. *Sex Transm Dis*. 2002;29:189–195.
35. Kent C, Chaw JK, Wong W, et al. Prevalence of rectal, urethral, and pharyngeal Chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. *Clin Infect Dis*. 2005;41:67–74.
36. Feldblum PJ, Morrison CS, Roddy RE, Cates W Jr. The effectiveness of barrier methods of contraception in preventing the spread of HIV. *AIDS*. 1995;9(suppl A):S85–S93.
37. US Food and Drug Administration. CFR –Code of Federal Regulations Title 21. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.325
38. Sutton M, Sternberg M, Koumans EH, McQuillan G, Berman S, Markowitz L. The prevalence of *Trichomonas vaginalis* infection among reproductive age women in the United States, 2001–2004. *Clin Infect Dis*. 2007;45:1319–1326.
39. Kreisel K, Torrone E, Bernstein K, Hong J, Gorwitz R. Prevalence of pelvic inflammatory disease in sexually experienced women of reproductive age—United States, 2013–2014. *MMWR Morb Mortal Wkly Rep*. 2017;66(3):80–83. doi:10.15585/mmwr.mm6603a3
40. Sutton MY, Sternberg M, Zaidi A, St Louis ME, Markowitz LE. Trends in pelvic inflammatory disease hospital discharges and ambulatory visits, United States, 1985–2001. *Sex Transm Dis*. 2005;32:778–784.
41. Barrett S, Taylor C. A review on pelvic inflammatory disease. *Int J STD AIDS*. 2005;16:715–720.
42. Mohllajee AP, Curtis KM, Peterson HB. Does insertion and use of an intrauterine device increase the risk of pelvic inflammatory disease among

women with sexually transmitted infection? A systematic review. *Contraception*. 2006;73:145–153.
43. Paavonen J, Westrõm L, Eschenbach D. Pelvic inflammatory disease. In: Holmes K, ed. *Sexually Transmitted Diseases*. 4th ed. McGraw-Hill; 2008.
44. Centers for Disease Control and Prevention. Pelvic inflammatory disease: guidelines for prevention and management. *MMWR Recomm Rep*. 1991;40(RR-5):1–25.
45. Haggerty C, Ness R. Newest approaches to treatment of pelvic inflammatory disease: a review of recent randomized clinical trials. *Clin Infect Dis*. 2007;44:953–960.
46. Ross JD. An update on pelvic inflammatory disease. *Sex Transm Infect*. 2002;78:18–19.
47. Gaitan H, Angel E, Diaz R, Parada A, Sanchez L, Vargas C. Accuracy of five different diagnostic techniques in mild-to-moderate pelvic inflammatory disease. *Infect Dis Obstet Gynecol*. 2002;10:171–180.
48. Scholes D, Stergachis A, Heidrich FE, Andrilla H, Holmes KK, Stamm WE. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. *N Engl J Med*. 1996;334:1362–1366.
49. Addiss DG, Vaughn ML, Ludka D, Pfister J, Davis JP. Decreased prevalence of *Chlamydia trachomatis* infection associated with a selective screening program in family planning clinics in Wisconsin. *Sex Transm Dis*. 1993;20:28–35.
50. Westrom L, Joesoef R, Reynolds G, Hagdu A, Thompson SE. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. *Sex Transm Dis*. 1992;19:185–192.
51. Centers for Disease Control and Prevention. Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6950a6.htm
52. Wang S, Papp JR, Stamm WE, Peeling RW, Martin DH, Holmes KK. Evaluation of antimicrobial resistance and treatment failures for *Chlamydia trachomatis*: a meeting report. *J Infect Dis*. 2005;191:917–923.
53. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis*. 2002;29:497–502.
54. Stamm WE. *Chlamydia trachomatis* infections of the adult. In Holmes KK, ed. *Sexually Transmitted Diseases (electronic version)*. 4th ed. McGraw-Hill Health Professions Division; 2008.
55. Hughes G, Simms I, Rogers PA, Swan AV, Catchpole M. New cases seen at genitourinary medicine clinics: England 1997. *Commun Dis Rep CDR Suppl*. 1998;8:S1–S11.
56. Tartaglione TA, Hooton TM. The role of fluoroquinolones in sexually transmitted diseases. *Pharmacotherapy*. 1993;13:189–201.

57. Hooton TM, Rogers ME, Medina TG, et al. Ciprofloxacin compared with doxycycline for nongonococcal urethritis. Ineffectiveness against *Chlamydia trachomatis* due to relapsing infection. *JAMA*. 1990;264:1418–1421.
58. Stamm WE, Hicks CB, Martin DH, et al. Azithromycin for empirical treatment of the nongonococcal urethritis syndrome in men. A randomized double-blind study. *JAMA*. 1995;274:545–549.
59. Horner P, Thomas B, Gilroy CB, Egger M, Taylor-Robinson D. Role of *Mycoplasma genitalium* and *Ureaplasma urealyticum* in acute and chronic nongonococcal urethritis. *Clin Infect Dis*. 2001;32:995–1003.
60. Sena AC, Lensing S, Rompalo A, et al. *Chlamydia trachomatis, Mycoplasma genitalium*, and *Trichomonas vaginalis* infections in men with nongonococcal urethritis: predictors and persistence after therapy. *J Infect Dis*. 2012;206(3):357–365.
61. Schwebke JR, Rompalo A, Taylor S, et al. Re-evaluating the treatment of nongonococcal urethritis: emphasizing emerging pathogens—a randomized clinical trial. *Clin Infect Dis*. 2011;52(2):163–170.
62. Meyers DS, Halvorson H, Luckhaupt S; U.S. Preventive Services Task Force. Screening for chlamydial infection: an evidence update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2007;147:135.
63. Wehbeh HA, Ruggeirio RM, Shahem S, Lopez G, Ali Y. Single-dose azithromycin for Chlamydia in pregnant women. *J Reprod Med*. 1998;43:509–514.
64. Adair CD, Gunter M, Stovall TG, McElroy G, Veille JC, Ernest JM. *Chlamydia* in pregnancy: a randomized trial of azithromycin and erythromycin. *Obstet Gynecol*. 1998;91:165–168.
65. Kapoor S. Re-emergence of lymphogranuloma venereum. *J Eur Acad Dermatol Venereol*. 2008;22(4):409–416.
66. van Hal SJ, Hillman R, Stark DJ, Harkness JL, Marriott D. Lymphogranuloma venereum: an emerging anorectal disease in Australia. *Med J Aust*. 2007;187:309–310.
67. de Vrieze NH, de Vries HJ. Lymphogranuloma venereum among men who have sex with men. An epidemiological and clinical review. *Expert Rev Anti Infect Ther*. 2014;12(6):697–704. doi:10.1586/14787210.2014.901169
68. Martin-Iguacel R, Llibre JM, Nielsen H, et al. Lymphogranuloma venereum proctocolitis: a silent endemic disease in men who have sex with men in industrialised countries. *Eur J Clin Microbiol Infect Dis*. 2010;29(8):917–725. doi:10.1007/s10096-010-0959-2
69. Stamm W. Lymphogranuloma venereum. In Holmes KK, ed. *Sexually Transmitted Diseases (electronic version)*. 4th ed. McGraw-Hill; 2008.
70. Mabey D, Peeling RW. Lymphogranuloma venereum. *Sex Transm Infect*. 2002;78:90–92.
71. Centers for Disease Control and Prevention. Primary and secondary syphilis —United States, 1998. *MMWR Morb Mortal Wkly Rep*. 1999;48:873–878.

72. Centers for Disease Control and Prevention. Primary and secondary syphilis —United States, 2000–2001. *MMWR Morb Mortal Wkly Rep*. 2002;51:971–973.
73. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2006 Supplement: Syphilis Surveillance Report*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. http://www.cdc.gov/std/Syphilis2006/Syphilis2006Short.pdf
74. Sparling P, Swartz M, Musher D, Healy B. Clinical manifestations of syphilis. In Holmes KK, ed. *Sexually Transmitted Diseases (electronic version)*. 4th ed. McGraw-Hill; 2008.
75. Chapel TA. The variability of syphilitic chancres. *Sex Transm Dis*. 1978;5:68–70.
76. Birnbaum NR, Goldschmidt RH, Buffett WO. Resolving the common clinical dilemmas of syphilis. *Am Fam Physician*. 1999;59:2233–2246.
77. Gjestland T. The Oslo study of untreated syphilis: an epidemiologic investigation of the natural course of syphilitic infection based on a restudy of the Boeck-Bruusgaard material. *Acta Derm Venereol*. 1955;35(suppl 34):3–368; I–LVI.
78. Garnett GP, Aral SO, Hoyle DV, Cates W Jr, Anderson RM. The natural history of syphilis. Implications for the transmission dynamics and control of infection. *Sex Transm Dis*. 1997;24:185–200.
79. Flood JM, Weinstock HS, Guroy ME, Bayne L, Simon RP, Bolan G. Neurosyphilis during the AIDS epidemic, San Francisco, 1985–1992. *J Infect Dis*. 1998;177:931–940.
80. Pezzini A, Gulletta M, Pinelli L, et al. Meningovascular syphilis: a vascular syndrome with typical features? *Cerebrovasc Dis*. 2001;11:352–353.
81. Association of Public Health Laboratories. Expert Consultation Meeting Summary Report: Laboratory Diagnostic Testing for *Treponema pallidum.* Published January 13–15, 2009. https://www.aphl.org/programs/infectious_disease/std/Documents/ID_2009Jan_Laboratory-Guidelines-Treponema-pallidum-Meeting-Report.pdf
82. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev*. 1995;8:1–21.
83. Clyne B, Jerrard DA. Syphilis testing. *J Emerg Med*. 2000;18:361–367.
84. Farnes SW, Setness PA. Serologic tests for syphilis. *Postgrad Med*. 1990;87:37–46.
85. Hook EW 3rd, Marra CM. Acquired syphilis in adults. *N Engl J Med*. 1992;326:1060–1069.
86. Bai ZG, Wang B, Yang K, et al. Azithromycin versus penicillin G benzathine for early syphilis. *Cochrane Database Syst Rev*. 2012;(6):CD007270. doi:10.1002/14651858.CD007270.pub2
87. Hook EW 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. *J*

Infect Dis. 2010;201(11):1729–1735. doi:10.1086/652239
88. Pao D, Goh BT, Bingham JS. Management issues in syphilis. *Drugs*. 2002;62:1447–1461.
89. World Health Organization. *Guidelines for the Management of Sexually Transmitted Infections*. World Health Organization; 2003.
90. Felman YM, Nikitas JA. Syphilis serology today. *Arch Dermatol*. 1980;116:84–89.
91. Genc M, Ledger WJ. Syphilis in pregnancy. *Sex Transm Infect*. 2000;76:73–79.
92. Nathan L, Bohman VR, Sanchez PJ, Leos NK, Twickler DM, Wendel GD Jr. In utero infection with *Treponema pallidum* in early pregnancy. *Prenat Diagn*. 1997;17:119–123.
93. Doroshenko A, Sherrard J, Pollard AJ. Syphilis in pregnancy and the neonatal period. *Int J STD AIDS*. 2006;17:221–228.
94. Larkin JA, Lit L, Toney J, Haley JA. Recognizing and treating syphilis in pregnancy. *Medscape Womens Health*. 1998;3:5.
95. Niebyl JR. *Teratology and Drugs in Pregnancy. Danforth's Obstetrics and Gynecology*. Lippincott Williams & Wilkins; 1999.
96. Heikkinen T, Laine K, Neuvonen PJ, Ekblad U. The transplacental transfer of the macrolide antibiotics erythromycin, roxithromycin and azithromycin. *BJOG*. 2000;107:770–775.
97. Mascola L, Pelosi R, Blount JH, Binkin NJ, Alexander CE, Cates W Jr. Congenital syphilis. Why is it still occurring? *JAMA*. 1984;252:1719–1722.
98. Alexander JM, Sheffield JS, Sanchez PJ, Mayfield J, Wendel GD Jr. Efficacy of treatment for syphilis in pregnancy. *Obstet Gynecol*. 1999;93:5–8.
99. Radolf JD, Arndt LL, Akins DR, et al. *Treponema pallidum* and *Borrelia burgdorferi* lipoproteins and synthetic lipopeptides activate monocytes/macrophages. *J Immunol*. 1995;154:2866–2877.
100. Silberstein P, Lawrence R, Pryor D, Shnier R. A case of neurosyphilis with a florid Jarisch-Herxheimer reaction. *J Clin Neurosci*. 2002;9:689–690.
101. Negussie Y, Remick DG, DeForge LE, Kunkel SL, Eynon A, Griffin GE. Detection of plasma tumor necrosis factor, interleukins 6, and 8 during the Jarisch-Herxheimer reaction of relapsing fever. *J Exp Med*. 1992;175:1207–1212.
102. Klein VR, Cox SM, Mitchell MD, Wendel GD Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol*. 1990;75:375–380.
103. Fekade D, Knox K, Hussein K, et al. Prevention of Jarisch-Herxheimer reactions by treatment with antibodies against tumor necrosis factor alpha. *N Engl J Med*. 1996;335:311–315.
104. Knapp JS, Back AF, Babst AF, Taylor D, Rice RJ. In vitro susceptibilities of isolates of *Haemophilus ducreyi* from Thailand and the United States to

currently recommended and newer agents for treatment of chancroid. *Antimicrob Agents Chemother*. 1993;37:1552–1555.

105. National guideline for the management of chancroid. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). *Sex Transm Infect*. 1999;75(suppl 1):S43–S45.
106. Taylor B, Darville T, Haggerty C. Does bacterial vaginosis cause pelvic inflammatory disease?. *Sex Transm Dis*. 2013;40(2):117–122.
107. Koumans EH, Sternberg M, Bruce C, et al. The prevalence of bacterial vaginosis in the United States, 2001–2004; associations with symptoms, sexual behaviors, and reproductive health. *Sex Transm Dis*. 2007;34(11):864–869. doi:10.1097/OLQ.0b013e318074e565
108. Verstraelen H, Verhelst R, Vaneechoutte M, Temmerman M. The epidemiology of bacterial vaginosis in relation to sexual behaviour. *BMC Infect Dis*. 2010;10:81–92.
109. Vodstrcil LA, Walker SM, Hocking JS, et al. Incident bacterial vaginosis (BV) in women who have sex with women is associated with behaviors that suggest sexual transmission of BV. *Clin Infect Dis*. 2015;60(7):1042–1053. doi:10.1093/cid/ciu1130
110. Ling Z, Liu X, Chen W, Luo Y, Yuan L, Xia Y. The restoration of the vaginal microbiota after treatment for bacterial vaginosis with metronidazole or probiotics. *Microb Ecol*. 2013;65:773–780.
111. Munteanu B, Cirstoiu C, Secara D, Cirstoiu M. Probiotics: a helpful additional therapy for bacterial vaginosis. *J Med Life*. 2013;6(4):434–436.
112. Sobel JD. Vulvovaginitis: when *Candida* becomes a problem. *Dermatol Clin*. 1998;16:763–768.
113. Carr PL, Felsenstein D, Friedman RH. Evaluation and management of vaginitis. *J Gen Intern Med*. 1998;13:335–346.
114. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists, Number 72, May 2006: Vaginitis. *Obstet Gynecol*. 2006;107:1195–1206.
115. Van Kessel K, Assefi N, Marrazzo J, Eckert L. Common complementary and alternative therapies for yeast vaginitis and bacterial vaginosis: a systematic review. *Obstet Gynecol Surv*. 2003;58:351–358.
116. Mikamo H, Kawazoe K, Sato Y, Hayasaki Y, Tamaya T. Comparative study on the effectiveness of antifungal agents in different regimens against vaginal candidiasis. *Chemotherapy*. 1998;44:364–368.
117. Kovac M, Mittic G, Kovac Z. Miconazole and nystatin used as topical antifungal drugs interact strongly with warfarin. *J Clin Pharm Ther.* 2012;37:45–48.
118. Sobel JD. Factors involved in patient choice of oral or vaginal treatment for vulvovaginal candidiasis. *Patient Prefer Adherence*. 2013;8:31–34. doi:10.2147/ppa.S38984

119. Sobel JD. Management of patients with recurrent vulvovaginal candidiasis. *Drugs*. 2003;63:1059–1066.
120. Cotch MF, Hillier SL, Gibbs RS, Eschenbach DA. Epidemiology and outcomes associated with moderate to heavy *Candida* colonization during pregnancy. *Am J Obstet Gynecol*. 1998;178:374–380.
121. Sobel JD. Use of antifungal drugs in pregnancy: a focus on safety. *Drug Saf*. 2000;23:77–85.
122. Haefner HK. Current evaluation and management of vulvovaginitis. *Clin Obstet Gynecol*. 1999;42:184–195.
123. Nye M, Schwebke J, Body B. Comparison of APTIMA *Trichomonas vaginalis* transcription-mediated amplification to wet mount microscopy, culture, and polymerase chain reaction for diagnosis of trichomoniasis in men and women. *Am J Obstet Gynecol*. 2009;200(188):e1–e188.e7.
124. Meites E, Llata E, Braxton J, et al. *Trichomonas vaginalis* in selected US sexually transmitted disease clinics: testing, screening, and prevalence. *Sex Transm Dis*. 2013;40(11):865–869.
125. Klebanoff M, Carey J, Hauth JC, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic *Trichomonas vaginalis* infection. *N Engl J Med*. 2001;345:487–493.
126. Schwebke J, Lensing S, Sobel J. Intravaginal metronidazole/miconazole for the treatment of vaginal trichomoniasis. *Sex Transm Dis*. 2013;40(9):710–714.
127. Koss CA, Baras DC, Lane SD, et al. Investigation of metronidazole use during pregnancy and adverse birth outcomes. *Antimicrob Agents Chemother*. 2012;56(9):4800–4805.
128. Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. *Neurotherapeutics*. 2016;13(3):493–508. doi:10.1007/s13311-016-0433-7
129. Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. *J Infect Dis*. 2002;186(suppl 1):S3–S28.
130. Petti S, Lodi G. The controversial natural history of oral herpes simplex virus type 1 infection. *Oral Dis*. 2019;25(8):1850–1865. doi:10.1111/odi.13234
131. Whitley RJ, Miller RL. Immunologic approach to herpes simplex virus. *Viral Immunol*. 2001;14:111–118.
132. Corey L, Wald A. Genital herpes. In Holmes KK, ed. *Sexually Transmitted Diseases*. McGraw-Hill Health Professions Division; 2008.
133. Groves MJ. Genital herpes: a review. *Am Fam Physician*. 2016;93(11):928–934.
134. Kimberlin DW, Rouse DJ. Clinical practice. Genital herpes. *N Engl J Med*. 2004;350(19):1970–1977. doi:10.1056/NEJMcp023065
135. Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999–2010. *J Infect Dis*.

2014;209(3):325–333. doi:10.1093/infdis/jit458
136. Marrazzo JM, Martin DH. Management of women with cervicitis. *Clin Infect Dis*. 2007;44(suppl 3):S102.
137. Lavery E, Coyle W. Herpes simplex virus and the alimentary tract. *Curr Gastroenterol Rep*. 2008;10(4):417–423.
138. Xu F, Sternberg M, Kottiri B, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA*. 2006;296(8):964–973. doi:10.1001/jama.296.8.964
139. Benedetti J, Corey L, Ashley R., et al. Recurrence rates in genital herpes after symptomatic first-episode infection. *Ann Intern Med*. 1994;121:847–854.
140. Sen P, Barton SE. Genital herpes and its management. *BMJ*. 2007;334:1048–1052.
141. Koelle DM, Schomogyi M, Corey L. Antigen-specific T cells localize to the uterine cervix in women with genital herpes simplex virus type 2 infection. *J Infect Dis*. 2000;182:662–670.
142. Wald A, Zeh J, Selke S, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med*. 1995;333:770–775.
143. Martin ET, Krantz E, Gottlieb SL, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. *Arch Intern Med*. 2009;169(13): 1233–1240. doi:10.1001/archinternmed.2009.177
144. Stanaway JD, Wald A, Martin ET, Gottlieb SL, Magaret AS. Case-crossover analysis of condom use and herpes simplex virus type 2 acquisition. *Sex Transm Dis*. 2012;39(5):388–393. doi:10.1097/OLQ.0b013e318248aa8a
145. Johnston C, Corey L. Current concepts for genital herpes simplex virus infection: diagnostics and pathogenesis of genital tract shedding. *Clin Microbiol Rev*. 2016;29(1):149–161. doi:10.1128/cmr.00043-15
146. Tronstein E, Johnston C, Huang ML, et al. Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection. *JAMA*. 2011;305(14):1441–1449. doi:10.1001/jama.2011.420
147. Feltner C, Grodensky C, Ebel C, et al. Serologic screening for genital herpes: an updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;316(23):2531–2543. doi:10.1001/jama.2016.17138
148. Diamond C, Selke S, Ashley R, Benedetti J, Corey L. Clinical course of patients with serologic evidence of recurrent genital herpes presenting with signs and symptoms of first episode disease. *Sex Transm Dis*. 1999;26:221–225.
149. Singh A, Preiksaitis J, Ferenczy A, Romanowski B. The laboratory diagnosis of herpes simplex virus infections. *Can J Infect Dis Med Microbiol*. 2005;16(2):92–98. doi:10.1155/2005/318294

150. Wald A. Herpes. Transmission and viral shedding. *Dermatol Clin*. 1998; 16:795–797.
151. LeGoff J, Péré H, Bélec L. Diagnosis of genital herpes simplex virus infection in the clinical laboratory. *Virol J*. 2014;11:83. doi:10.1186/1743-422x-11-83
152. Tata S, Johnston C, Huang M, et al. Overlapping reactivations of herpes simplex virus type 2 in the genital and perianal mucosa. *J Infect Dis*. 2010;201(4):499–504. doi:10.1086/650302
153. Ashley-Morrow R, Krantz E, Wald A. Time course of seroconversion by HerpeSelect ELISA after acquisition of genital herpes simplex virus type 1 (HSV-1) or HSV-2. *Sex Transm Dis*. 2003;30:310–314.
154. Wald A, Ashley-Morrow R. Serological testing for herpes simplex virus (HSV)-1 and HSV-2 infection. *Clin Infect Dis*. 2002;35(suppl 2):S173–S182.
155. Balfour HH Jr. Antiviral drugs. *N Engl J Med*. 1999;340:1255–1268.
156. MacDougall C, Guglielmo BJ. Pharmacokinetics of valaciclovir. *J Antimicrob Chemother*. 2004;53:899–901.
157. Heslop R, Roberts H, Flower D, Jordan V. Interventions for men and women with their first episode of genital herpes. *Cochrane Database Syst Rev*. 2016; (8):CD010684. doi:10.1002/14651858.CD010684.pub2
158. Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high-dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. *J Infect Dis*. 1998;178:349–359.
159. Eisen D, Essell J, Broun ER, Sigmund D, DeVoe M. Clinical utility of oral valacyclovir compared with oral acyclovir for the prevention of herpes simplex virus mucositis following autologous bone marrow transplantation or stem cell rescue therapy. [See comment]. *Bone Marrow Transplant*. 2003;31:51–55.
160. Nadelman CM, Newcomer VD. Herpes simplex virus infections. New treatment approaches make early diagnosis even more important. *Postgrad Med*. 2000;107:189–195.
161. Drake S, Taylor S, Brown D, Pillay D. Improving the care of patients with genital herpes. *BMJ*. 2000;321:619–623.
162. Strand A, Patel R, Wulf HC, Coates KM; International Valaciclovir HSV Study Group. Aborted genital herpes simplex virus lesions: findings from a randomised controlled trial with valaciclovir. *Sex Transm Infect*. 2002;78:435–439.
163. Fuchs J, Celum C, Wang J, et al. Clinical and virologic efficacy of herpes simplex virus type 2 suppression by acyclovir in a multicontinent clinical trial. *J Infect Dis*. 2010;201(8):1164–1168. doi:10.1086/651381
164. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med*. 2004;350:11–20.
165. Lebrun-Vignes B, Bouzamondo A, Dupuy A, Guillaume J, Lechat P, Chosidow O. A meta-analysis to assess the efficacy of oral antiviral

treatment to prevent genital herpes outbreaks. *J Am Acad Dermatol*. 2007;57(2):238–246. doi:10.1016/j.jaad.2007.02.008

166. Conant MA, Schacker TW, Murphy RL, et al. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. *Int J STD AIDS*. 2002;13:12–21.
167. Reyes M, Shaik N, Graber J, et al. Acyclovir-resistant genital herpes among persons attending sexually transmitted disease and human immunodeficiency virus clinics. *Arch Intern Med*. 2003;163(1):76–80. doi:10.1001/archinte.163.1.76
168. Lalezari J, Schacker T, Feinberg J, et al. A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. *J Infect Dis*. 1997;176:892–898.
169. Perazella MA. Crystal-induced acute renal failure. *Am J Med*. 1999;106: 459–465.
170. Revankar SG, Applegate AL, Markovitz DM. Delirium associated with acyclovir treatment in a patient with renal failure. *Clin Infect Dis*. 1995;21:435–436.
171. Kitching AR, Fagg D, Hay NM, Hatfield PJ, Macdonald A. Neurotoxicity associated with acyclovir in end stage renal failure. *N Z Med J*. 1997;110: 167–169.
172. Straus SE, Smith HA, Brickman C, de Miranda P, McLaren C, Keeney RE. Acyclovir for chronic mucocutaneous herpes simplex virus infection in immunosuppressed patients. *Ann Intern Med*. 1982;96:270–277.
173. Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA*. 2001;285:3100–3106.
174. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. *JAMA*. 2005;143:707–713.
175. Wilkinson D, Ramjee G, Tholandi M, Rutherford G. Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men. *Cochrane Database Syst Rev*. 2002;(4):CD003939.
176. Johnston C, Gottlieb SL, Wald A. Status of vaccine research and development of vaccines for herpes simplex virus. *Vaccine*. 2016;34(26):2948–2952. doi:10.1016/j.vaccine.2015.12.076
177. Lehtinen M, Koskela P, Jellum E, et al. Herpes simplex virus and risk of cervical cancer: a longitudinal, nested case-control study in the Nordic countries. *Am J Epidemiol*. 2002;156:687–692.
178. Brown Z, Gardella C, Wald A, Morrow R, Corey L. Genital herpes complicating pregnancy. *Obstet Gynecol*. 2005;106(4):845–856. doi:10.1097/01.AOG.0000180779.35572.3a
179. Tyring SK, Baker D, Snowden W. Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience

with acyclovir. *J Infect Dis*. 2002;186(suppl 1):S40–S46.
180. Watts DH, Brown ZA, Money D, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. *Am J Obstet Gynecol*. 2003;188:836–843.
181. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA*. 2003;289:203–209.
182. Reiff-Eldridge R, Heffner CR, Ephross SA, Tennis PS, White AD, Andrews EB. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment. *Am J Obstet Gynecol*. 2000;182:159–163.
183. Sheffield JS, Hill JB, Hollier LM, et al. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. *Obstet Gynecol*. 2006;108:141–147.
184. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med*. 2009;361(14):1376–1385. doi:10.1056/NEJMra0807633
185. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER, Paulose-Ram R. Prevalence of HPV in adults aged 18–69: United States, 2011–2014. *NCHS Data Brief.* 2017;(280):1–8.
186. Lewis RM, Markowitz LE, Gargano JW, Steinau M, Unger ER. Prevalence of genital human papillomavirus among sexually experienced males and females aged 14–59 years, United States, 2013–2014. *J Infect Dis*. 2018;217(6):869–877. doi:10.1093/infdis/jix655
187. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol*. 1993;12:186–192.
188. Giuliano AR, Tortolero-Luna G, Ferrer E, et al. Epidemiology of human papillomavirus infection in men, cancers other than cervical and benign conditions. *Vaccine*. 2008;26(suppl 10):K17–K28. doi:10.1016/j.vaccine.2008.06.021
189. Longstaff E, von Krogh G. Condyloma eradication: self-therapy with 0.15%–0.5% podophyllotoxin versus 20%–25% podophyllin preparations—an integrated safety assessment. *Regul Toxicol Pharmacol*. 2001;33:117–137.
190. Perry CM, Lamb HM. Topical imiquimod: a review of its use in genital warts. *Drugs*. 1999;58:375–390.
191. Gotovtseva EP, Kapadia AS, Smolensky MH, Lairson DR. Optimal frequency of imiquimod (aldara) 5% cream for the treatment of external genital warts in immunocompetent adults: a meta-analysis. *Sex Transm Dis*. 2008;35(4): 346–351. doi:10.1097/OLQ.0b013e31815ea8d1
192. Baker DA, Ferris DG, Martens MG, et al. Imiquimod 3.75% cream applied daily to treat anogenital warts: combined results from women in two randomized, placebo-controlled studies. *Infect Dis Obstet Gynecol.* 2011;2011:806105. doi:10.1155/2011/806105

193. Tatti S, Stockfleth E, Beutner KR, et al. Polyphenon E: a new treatment for external anogenital warts. *Br J Dermatol*. 2010;162(1):176–184. doi:10.1111/j.1365-2133.2009.09375.x
194. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007;356:1928–1943.
195. Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56:1–24.
196. Centers for Disease Control and Prevention. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59(20):630–632.
197. Petrosky E, Bocchini JA, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):300–304.

73

Osteomyelitis and Septic Arthritis

Jacqueline L. Olin, Linda M. Spooner, and Karyn M. Sullivan

CORE PRINCIPLES		CHAPTER CASES
OSTEOMYELITIS		
1	Acute hematogenous osteomyelitis is characterized by the abrupt onset of localized pain and tenderness at a single site, fever, and increased inflammatory markers (erythrocyte sedimentation rate, C-reactive protein). Imaging techniques and blood and bone cultures (if done) may reveal findings consistent with bone changes in osteomyelitis and the responsible pathogen.	**Case 73-1 (Questions 1, 2), Table 73-1**
2	Initial empiric antibiotic therapy for acute hematogenous osteomyelitis should be	**Case 73-1 (Question 3), Table 73-2**

	directed at gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* (MRSA). Protein binding and bone concentrations of antibiotics are not critical factors in predicting successful treatment, as long as the responsible pathogen is susceptible to the chosen therapy, and treatment is given in high doses for a long duration.	
3	If blood or bone cultures grow the likely pathogen, then therapy should be de-escalated when possible based on organism susceptibilities. Assuming no allergies, methicillin-sensitive *Staphylococcus aureus* (MSSA) should be treated with oxacillin or nafcillin. The overall duration of therapy (by intravenous [IV] route and possibly orally) should be at least 4 weeks.	**Case 73-1 (Questions 4–6), Tables 73-2, 73-3**
4	Osteomyelitis associated with a contiguous focus of infection typically occurs after trauma and the consequent orthopedic corrective surgery. Common symptoms are pain, tenderness, erythema, and drainage at the site of injury or infection. Imaging studies usually show bone changes consistent with infection. It is often polymicrobial.	**Case 73-2 (Question 1), Table 73-1**
5	With contiguous osteomyelitis, surgical efforts should be instituted to reassess the site of bone injury and infection, with deep tissue or bone samples obtained	**Case 73-2 (Questions 2, 3)**

	for culture. Treatment is IV therapy for at least 4 weeks, and the antibiotics chosen should depend on the cultured organisms and their antibiotic susceptibilities.	
6	Osteomyelitis associated with vascular insufficiency most often occurs in patients with diabetes mellitus. Neuropathy and impaired blood flow are risk factors for the development of chronic lower extremity cellulitis and underlying osteomyelitis. Multiple gram-positive and gram-negative aerobic and anaerobic bacteria may be involved; an initial empiric treatment typically includes vancomycin and an antipseudomonal β-lactam. Definitive therapy is based on the results of deep surgical cultures. Duration of treatment should be 6 weeks, with chronic suppressive therapy considered thereafter.	**Case 73-3 (Questions 1, 2)**
7	Chronic osteomyelitis can present years later at a site of previous bone infection and is usually characterized by a draining sinus tract from bone to skin. Chronically infected dead (necrotic) bone needs to be surgically removed when possible. Chronic osteomyelitis is often polymicrobial, and the same organism (especially *S. aureus*) that was causative of a previous bone infection could still be involved in	**Case 73-4 (Questions 1–4)**

	chronic infection. High-dose IV therapy directed at the results of bone culture and the sensitivity results for 6 weeks is recommended to offer the best chances of preventing the extension of infection to the adjacent uninfected bone.	
8	Orthopedic implant–associated infections with adjacent bone osteomyelitis usually require surgical removal of the infected prosthesis for cure. Antibiotics should be directed at the cultured bacteria from a joint aspirate or from deep surgical specimens. The most common pathogens are *S. aureus* and coagulase-negative staphylococci. If the prosthesis cannot be totally removed, lifelong, chronic suppressive oral therapy may be necessary.	**Case 73-5 (Questions 1–3)**
	SEPTIC ARTHRITIS	
1	Nongonococcal septic arthritis is characterized by fever and the acute onset of joint pain and effusion in a single joint. Infection is typically acquired hematogenously from an originating site that may not always be easily identified. *S. aureus* is the most common pathogen. Duration of treatment should be 6 weeks, with oral therapy for the final 2 weeks.	**Case 73-6 (Questions 1, 2)**
2	*Neisseria gonorrhoeae* is the most common cause of polyarticular arthritis	**Case 73-7 (Questions 1–3)**

in a young, sexually active adult. Skin lesions may also be present in disseminated gonococcal infection (DGI). The diagnosis is frequently based on the clinical syndrome and sexual history because joint fluid aspirate and blood culture results are frequently negative. IV ceftriaxone is the treatment of choice and should be continued for 1 to 2 days after improvement begins. Treatment duration is 7 to 14 days.

INTRODUCTION

Osteomyelitis is an inflammation of the bone marrow and surrounding bone associated with infection. Any bone can be involved, and substantial morbidity is possible even with early diagnosis and treatment. Despite the continued refinement of diagnostic procedures (eg, radionuclide imaging, computed tomography, magnetic resonance imaging), advances in antimicrobial therapy, and the use of prophylactic antibiotics before orthopedic procedures, osteomyelitis continues to be difficult to cure.

Osteomyelitis can affect all age groups. The most common causative microorganisms of acute osteomyelitis have historically been streptococci and staphylococci. *Staphylococcus aureus* remains the most causative organism, accounting for >50% of all cases, although the prevalence of infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing across all age groups. In addition, osteomyelitis caused by gram-negative and anaerobic bacilli is becoming more common.[1]

Bone may be infected by three routes: hematogenous spread of bacteria from a distant infection site, direct infection of bone from an adjacent or contiguous source of infection, and infection of bone

secondary to vascular insufficiency. **Table 73-1** summarizes characteristics associated with osteomyelitis.[1–3] Patients with recurrent osteomyelitis are considered to have chronic osteomyelitis.

Table 73-1
Features of Osteomyelitis

Feature	Hematogenous	Adjacent/Contiguous Site of Infection	Vascular Insufficiency
Usual onset: pediatric or adult	Predominantly pediatric	Adult	Adult
Sites of infection	Tibia, femur (children); vertebrae (adults)	Femur, fibula, tibia, skull, mandible	Foot
Risk factors	Bacteremia	Surgery, trauma, cellulitis, joint prosthesis	Diabetes, peripheral vascular disease
Common bacteria	*Staphylococcus aureus*, gram-negative bacilli; usually *one* organism	*S. aureus*, streptococci, gram-negative bacilli, anaerobic organisms; often *polymicrobial*	*S. aureus*, coagulase-negative staphylococci, streptococci, gram-negative bacilli, anaerobic organisms; often *polymicrobial*
Clinical findings	Fever, chills, local tenderness, swelling; limitation of motion	Fever, warmth, swelling; unstable joint	Pain, swelling, drainage, ulcer formation

Bone Anatomy and Physiology

The bone is divided into three sections: the epiphysis, located at the end of the bone; the metaphysis (adjacent to the epiphysis and part of the epiphyseal growth plate); and the diaphysis (midsection of the bone). Surrounding most of the bone is a fibrous, cellular envelope. The external portion of this envelope is the periosteum, and the internal portion is the endosteum.

Blood vessels that supply bone tissue and support bone growth are located predominantly in the epiphysis and metaphysis of the bone. Nutrient arteries enter the bone at the metaphyseal side of the epiphyseal growth plate and lead to capillaries that form sharp loops within the growth plate. These capillaries lead to large sinusoidal veins that eventually exit the metaphysis through a nutrient vein. Within the sinusoidal veins, blood flow is slowed considerably, and infection is possible with bacterial colonization.[4]

Differences in the vasculature of bone in different age groups lead to different forms of osteomyelitis. In neonates and adults, vascular communications are present between the metaphysis and epiphysis, which can allow infection to spread from bone to the adjacent joint.

During childhood, however, this area often is protected from infection because the epiphyseal plate separates the vascular supply for these two regions.[4]

Hematogenous Osteomyelitis

Hematogenous osteomyelitis predominantly occurs in prepubertal children but may be seen in older adults, patients with indwelling central catheters, and intravenous (IV) drug users.[1] Osteomyelitis in children tends to be acute, hematogenous, and often responsive to antibiotic therapy alone. It can be difficult to identify all pathogens.[5] In comparison, osteomyelitis in adults tends to be subacute or chronic; commonly results from trauma, infection of prosthetic devices, or other insult; and often requires surgical debridement in addition to antimicrobial therapy.[1–3]

Hematogenous infection in children develops primarily in the metaphysis of the rapidly growing long bones of the body, usually with a single focus in the femur and tibia, where the slowed blood flow allows bacteria to colonize and multiply. Hematogenous osteomyelitis in neonates is an especially serious disease that often involves multiple bones, especially the long bones. The acute infectious process (eg, edema, inflammation, small vessel thrombosis) increases bone pressure, which compromises blood flow and eventually leads to necrosis. Released cytokines alter bone integrity by promoting osteoclast activity. Eventually, the elevated pressure and necrosis cause devitalized bone to fragment from healthy bone (sequestra). With continued spread of the infection into the outer layers of the bone and soft tissue, abscess and draining sinus tracts may form.[1,3]

Rapid infection spreading across the epiphyseal plate to the adjacent joint can lead to septic arthritis, necessitating immediate and aggressive treatment. Vertebrae involvement is seen more frequently in adults.[1–3]

The most common organism causing hematogenous osteomyelitis is *S. aureus*, responsible for up to 85% of pediatric cases.[4] The

emergence of both hospital- and community-associated strains of MRSA has challenged the management of osteomyelitis. MRSA infections are associated with an increased risk of antibiotic treatment failures and complications, including abscess formation, deep vein thrombosis, and septic emboli.[6] The most common streptococcal pathogen for hematogenous osteomyelitis is *Streptococcus pyogenes.*[1] Gram-negative bacilli (*Escherichia coli*, *Klebsiella*, *Proteus*, *Salmonella*, and *Pseudomonas*) are responsible for an increasing number of cases of osteomyelitis as well. *Pseudomonas aeruginosa* is more commonly seen in patients with indwelling central catheters and in IV drug users, whereas *S. aureus* and *Salmonella* species are common causes in patients with sickle cell anemia.[1]

Clinical features of hematogenous osteomyelitis vary, depending on the patient's age and the infection site. In children, infection usually is characterized by an abrupt onset of high fever and chills, localized pain, tenderness, and swelling. Systemic symptoms often are absent in neonates, potentially delaying the diagnosis. A diagnosis, therefore, is based on localized symptoms such as edema and restricted limb movement. Systemic symptoms are also less common in adults, although patients with vertebral osteomyelitis can present with the insidious onset of localized back pain and tenderness.[1,3]

Acute Osteomyelitis

USUAL CLINICAL PRESENTATION

CASE 73-1

Question 1: L.D., a 7-year-old girl, is unable to go to school today because of fever and worsening leg pain. Her upper left leg started to hurt 3 to 4 days ago, and last night she began limping. Her parents report no history of trauma to the area. Her past medical history is significant only for two episodes of otitis media at ages 2 and 5. In the pediatrician's office, maximal tenderness is localized over the left distal femur without knee joint effusion. No signs of swelling,

warmth, or trauma are seen. Her white blood cell (WBC) count is 8000/μL with a normal WBC differential. Plain radiographic study findings of the left leg are normal, but the erythrocyte sedimentation rate (ESR) is 58 mm/hour (normal ≤30 mm/hour). Two blood samples are obtained for culture and sensitivity testing, and L.D. is sent home with directions for bed rest and use of acetaminophen as needed for fever. Two days later, she is admitted to the hospital with severe pain and tenderness in her left leg and a fever of 101.84 °F (38.8 °C). The blood cultures obtained 2 days ago are positive for *S. aureus*, with susceptibilities still pending. C-reactive protein (CRP) is 14 mg/dL (normal, <2 mg/dL). Another plain radiographic study finding is normal, but a magnetic resonance imaging (MRI) scan reveals inflammation in her left distal femur.

What findings in L.D. are consistent with hematogenous osteomyelitis?

L.D. displays the usual signs and symptoms of acute hematogenous osteomyelitis in children. She is a previously healthy child who experienced acute localized pain and tenderness of the left distal femur, abrupt onset of high fever, and an elevated ESR and CRP. Her plain radiographic study findings were normal on two occasions; however, destructive changes to bone often do not appear on plain radiographs for at least 10 to 14 days after onset of infection.[1] Hence, a normal plain film does not rule out acute osteomyelitis if obtained within the first 2 weeks of infection. Diagnosis includes radionuclide imaging (bone scans), computed tomography (CT), or MRI.[1,4] MRI is more sensitive than is CT for the assessment of soft tissue and detecting early bone marrow edema; however, it often requires sedation for children.[4] The sensitivity of bone scan detection of osteomyelitis has been lowest when the infection was caused by community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[4] L.D.'s MRI scan on hospitalization detected inflammation in the left distal femur. Although L.D. did not have a bone biopsy sent for culture, her clinical picture, a positive MRI scan result, and blood culture results positive for *S. aureus* establish the diagnosis of osteomyelitis. The specific event that caused bacteremia with dissemination to bone is unknown, as is often the case in children.[4]

Laboratory tests that should be routinely obtained in every child suspected of having osteomyelitis include a complete blood count (CBC), ESR, and serum CRP. Although these tests are not specific

for the diagnosis of osteomyelitis, they help confirm the clinical diagnosis. An increased WBC count is consistent with osteomyelitis, but leukocytosis is absent in many children with osteomyelitis at the initial examination. Thus, L.D.'s WBC count of 8000/μL is not unusual. In adults, leukocytosis is more common in an acute infection rather than with recurrent or chronic disease. Both ESR and CRP are nonspecific markers of systemic inflammation when elevated.

Predisposing factors for hematogenous osteomyelitis include any risk factors for bacteremia, for example, indwelling catheters such as hemodialysis shunts and chronic central venous catheters, IV drug use, and a distant focus of infection in the gastrointestinal or urinary tract. None of these factors exist in L.D. In children such as L.D. who have no history of trauma, fractures, or penetrating injury, the most common cause of acute hematogenous osteomyelitis is *S. aureus*, and the possibility of CA-MRSA must be considered.[1,6]

PATIENT WORKUP

CASE 73-1, QUESTION 2: What additional patient and diagnostic information should be obtained before L.D. receives her first dose of antibiotics?

Before L.D. receives antibiotic therapy, she should be assessed for drug allergies, especially penicillin allergy. Patient interviews, discussions with her parents, and a comprehensive review of her medical record are necessary, especially with a history of allergy. Details of an allergic reaction, including symptoms, onset of the reaction, probable causative agent, treatment, and exposure to related antimicrobials should be evaluated. Cultures of blood and bone aspirate material optimally identify the pathogen and must be part of the initial workup before the start of antibiotics. Cultures taken after initiation of antibiotics can decrease culture yield.[5]

In L.D.'s case, the positive blood culture and MRI findings establish the diagnosis of osteomyelitis. If the blood culture results had been negative, however, a bone aspirate would be

recommended to identify the pathogen.[1] Once material has been obtained for culture and sensitivity testing, empiric antibiotic therapy should start as soon as possible.

TREATMENT

Empiric antibiotic therapy

Case 73-1, Question 3: L.D. has no history of drug allergies. She took amoxicillin for the previous episodes of acute otitis media without incident. What empiric antibiotic(s) should be started? What is the relevance of bone concentrations or protein binding of antibiotics in the selection of therapy for osteomyelitis?

Treatment should be initiated as soon as possible to improve the chances for complete eradication of infection and to avoid the need for surgery. Thus, empiric antibiotic therapy is often administered while bacterial culture results are pending or before antibiotic susceptibility results are known. The chosen agent should be administered IV at high doses to optimize drug concentration in infected bone.

Even if culture results are pending or have returned negative results, the age of the child can predict the likely pathogen and guide empiric antibiotic selection. For example, *S. aureus* and *Streptococcus* species are commonly responsible for osteomyelitis in the neonate.[1] *Kingella kingae*, a facultatively anaerobic, gram-negative hemolytic bacillus, is being detected with increasing frequency in children younger than age 3 years, especially in the day care setting.[7] **Table 73-2** summarizes the common causative organisms of acute hematogenous osteomyelitis in children and recommended drugs and doses for treatment.[2,4,5,8–10]

Table 73-2

Empiric Intravenous Antibiotics for Acute Osteomyelitis in Children

Host	Likely Organisms	Antibiotics	Dose	
			(mg/kg/day)	(doses/day)
Neonate	*Staphylococcus aureus* Group B streptococci Gram-negative bacilli	Oxacillin (or nafcillin) *with* cefotaxime	25–50	2–4
			50	2–4
<3 years	*S. aureus*	Vancomycin *or*	40–60	4
		Linezolid *or*	30	3
		Daptomycin	6–10	1
	Haemophilus influenzae type b	Oxacillin (*or* nafcillin) *with* cefotaxime	150–200	4
			100–180	4–6
	Kingella kingae	Cefazolin *or*	100–150	3
		Ampicillin-sulbactam	100–200	4
≥3 years	*S. aureus*	Vancomycin *or*	40–60	4
		Linezolid		
		≤12 years	30	3
		>12 years *or*	600 mg dose	2
		Daptomycin *or*	6–10	1
		Oxacillin (or nafcillin) *or*	150–200	4
		Cefazolin *or*	60–150	3–4
		Clindamycin	40	3–4
	S. pyogenes	Cefazolin	60–150	3–4
After puncture wound through shoe	*Pseudomonas aeruginosa*	Ceftazidime	100–150	3
Child with sickle cell disease	*Salmonella* sp. *S. aureus*	Oxacillin (or nafcillin) *with* cefotaxime *or*	150–200	4
			100–180	4–6
		Vancomycin *with* cefotaxime	40–60	4
			100–180	4–6

Considering the epidemiology of L.D.'s infection and the blood culture results, she should be treated for *S. aureus* osteomyelitis. Because in both children and adults, the number of acute osteomyelitis cases caused by MRSA continues to increase, empiric IV vancomycin should be administered pending susceptibility results.[4,8] Alternative empiric therapy for L.D. with MRSA coverage includes daptomycin or linezolid.[9] Owing to limited clinical experience, these two agents should be reserved for vancomycin-intolerant cases. Clindamycin is not an option for L.D. but may be used empirically for stable patients without bacteremia or intravascular infection.[9]

The importance of antibiotic bone concentration when treating osteomyelitis is unclear, and bone concentrations do not always predict the outcome of therapy.[2,11] Theoretically, protein binding could influence clinical efficacy because only free drug is thought to diffuse from plasma into bone tissue and protein-bound drug does not. However, cefazolin (for sensitive gram-positive cocci) and

ceftriaxone (for sensitive gram-negative rods and streptococci), both highly protein-bound drugs, are well-established treatments for osteomyelitis when appropriate doses and duration are used. Therefore, antibiotic bone concentrations and protein binding of antibiotics (in appropriate doses) are not significant factors in the selection of appropriate therapy for osteomyelitis.[2,11]

Directed antibiotic therapy

CASE 73-1, QUESTION 4: The *S. aureus* grown from L.D.'s blood culture is methicillin sensitive. Considering these results, what is the optimal antibiotic regimen? Would other antibiotics given less frequently also be adequate?

L.D. is not allergic to penicillin. Although vancomycin is active against MSSA, it is inferior to β-lactams and likely to be associated with treatment failure; thus, β-lactam–based therapy should be used for susceptible organisms.[1,6] De-escalating from vancomycin to oxacillin (or nafcillin) at 150 mg/kg/day every 6 hours is appropriate.[2] Nafcillin and oxacillin are therapeutically equivalent and are given in similar doses; therefore, selection typically depends on hospital formulary considerations. Her prior exposure to amoxicillin is irrelevant except to establish the absence of a penicillin allergy.

Continuing to treat L.D. with IV oxacillin (or nafcillin) every 6 hours follows treatment recommendations for MSSA osteomyelitis. Antistaphylococcal penicillins are effective therapy with appropriate doses and duration. Changing L.D. to cefazolin would allow slightly less frequent dosing (every 8 hours), a potential advantage for home treatment. In the absence of susceptibility results or of methicillin resistance, IV vancomycin would be required for the duration of therapy. Although the logistics of outpatient parenteral antibiotic therapy (OPAT) in L.D. are being investigated, she should remain on oxacillin while in the hospital.

Duration of therapy

Case 73-1, Question 5: Both of L.D.'s parents are employed, and their work schedules prevent them from leaving their jobs to transport her to an outpatient antibiotic treatment center. Is L.D. a candidate for OPAT at home, or is oral antibiotic treatment an option? Must L.D. remain in the hospital to receive her oxacillin?

Initially, all patients should receive IV antibiotics because early, aggressive therapy offers the best chance to cure the infection. L.D., however, does not necessarily need to stay in the hospital for the duration of therapy. A peripherally inserted central catheter (PICC) can be placed, and antibiotics can be administered in an outpatient setting. The decision to use OPAT must be decided in concert with L.D.'s parents. If L.D.'s parents do not have the resources or are unwilling to oversee home therapy, L.D. should remain hospitalized for a minimum of 1 week to assess the efficacy of IV treatment. De-escalation to oral antibiotic therapy should be considered at discharge because of the frequency of PICC line complications and the cost and inconvenience of several weeks of IV therapy at home.[7,12]

As discussed in Case 73-1, Question 6, L.D. can complete most of her treatment with oral antibiotics, but oral therapy should not be given until the effectiveness of IV therapy can be assessed. Children with uncomplicated acute osteomyelitis are candidates for oral therapy when clinically improved, and the CRP has normalized, typically between 3 and 7 days.[5,8] Total duration of antibiotic therapy should be 3 to 4 weeks; however, the Infectious Diseases Society of America (IDSA) guidelines recommend 4 to 6 weeks of therapy for children with MRSA osteomyelitis.[9] Adults may receive a longer duration of IV therapy because of the chronic nature of osteomyelitis.[5] Neonatal cases warrant 4 weeks of IV antibiotics.[13]

Oral antibiotics

Case 73-1, Question 6: After 1 week of IV nafcillin, L.D. is afebrile and reports that the pain and tenderness in her left leg are much improved. Her ESR is 40 mm/hour, and CRP is 6 mg/dL. The plan is to switch L.D. to oral antibiotics

to complete a 4-week course of therapy at home. What would be an appropriate oral antibiotic regimen for L.D.? How often should she return to the clinic for evaluation?

As mentioned, oral antibiotics are only appropriate if a clear clinical response has occurred within the first week of IV therapy, the patient's parents are aware of the vital importance of medication adherence, and the patient can swallow and tolerate oral therapy.

Assuming her parents agree to supervise treatment outside of the hospital, L.D. is a candidate for oral therapy. She has responded promptly to the IV therapy: her symptoms have improved, and the ESR and CRP are trending downward. Oral therapy will be effective only if L.D. consistently takes her medications; therefore, assurances must be in place to facilitate adherence. L.D.'s parents have made arrangements with her teacher to help her take her oral antibiotic during the day.

L.D. can complete her 4-week course of antibiotics with oral cephalexin capsules or suspension, which is more palatable (and usually better tolerated) than is dicloxacillin suspension. Cephalexin should begin at 150 mg/kg/day, divided into four doses. Weekly follow-up is necessary to monitor L.D.'s adherence and clinical response to therapy. If this is not optimal, symptoms recur, or ESR or CRP increases, parenteral therapy should be reinitiated, and reevaluation is warranted.[4] Oral antibiotic doses for children with osteomyelitis are summarized in **Table 73-3**.[4,5,8,9]

Table 73-3
Oral Antibiotic Doses for the Treatment of Osteomyelitis in Children

Drug	Dose (mg/kg/day)	Doses/day
Penicillin V	125	6
Dicloxacillin	100	4
Amoxicillin	100	4
Cephalexin	150	4
Clindamycin	40	3

Linezolid		
≤12 years	30	3
>12 years	600 mg dose	2

Osteomyelitis Associated With a Contiguous Source of Infection

CLINICAL PRESENTATION

CASE 73-2

QUESTION 1: M.K., a 30-year-old male, suffered an open left femur fracture 3 weeks ago in a motorcycle accident. His fracture was stabilized by open reduction and internal fixation. His postoperative course was unremarkable until yesterday when he experienced left leg pain and spontaneous drainage from the surgical wound. On presentation, his left thigh is tender and warm, but he is afebrile. Laboratory data, including WBC count, serum creatinine, and blood urea nitrogen (BUN), are normal, but the ESR is 38 mm/hour and CRP is 8 mg/dL. Plain bone films and bone MRI show inflammation and no healing of the femur fracture.

What findings in M.K. are characteristic of secondary osteomyelitis? What organisms are most likely causing infection in M.K.?

Few of the systemic signs and symptoms associated with acute osteomyelitis are seen in contiguous-spread osteomyelitis. Some findings in acute contiguous osteomyelitis include pain in the area of infection and drainage. Considering several weeks to months might pass before the patient becomes symptomatic, radiographic study findings at the time of diagnosis might reveal abnormalities consistent with bone deterioration.[1] M.K.'s case is consistent with contiguous-spread osteomyelitis. Infection likely is at the site of surgical repair of the left femur fracture. M.K.'s localized symptoms, along with the absence of fever and leukocytosis, are characteristic of osteomyelitis after a contaminated fracture. In these cases, bone becomes infected from an exogenous source or through the spread of an infection from adjacent tissue to bone. Infection can result from

any trauma with or without subsequent orthopedic procedure to fix a bone fracture. The lower extremity bones are most commonly involved.[1] Acute contiguous infection occurs more often in adults than in children. This finding is explained by the higher incidence of precipitating factors within this age group, such as trauma, hip fractures, and orthopedic procedures.[1] Other conditions potentially associated with contiguous-spread osteomyelitis include gunshot wounds, punctures, or soft tissue infections.

Polymicrobial infection is common in contiguous-spread osteomyelitis. Although *S. aureus* is the most common pathogen, it is often part of a mixed infection. Other common pathogens include *Pseudomonas*, *Proteus*, *Streptococcus*, and *Klebsiella* species, *E. coli*, and *S. epidermidis*. Anaerobes also are associated with contiguous-spread osteomyelitis, and most commonly isolated are *Bacteroides* species and anaerobic cocci. Adjacent soft tissue infections can also lead to anaerobic bone infections, as in the case of sacral osteomyelitis secondary to severe decubitus ulcers. To identify the true pathogen(s), M.K. should have a surgical reevaluation and a biopsy of the involved bone at the probable site of infection.[1] Bone films and MRI scan will help localize the possible infectious process to direct the surgical biopsy.

Initial treatment

Case 73-2, Question 2: M.K. returns to the operating room for surgical exploration, and bone tissue is obtained for culture. He has no drug allergies, weighs 187.39 pounds (85 kg), and is 72 inches (182.88 cm) tall. The initial postoperative antibiotic order is for vancomycin, 1 g IV every 12 hours. Is this adequate antibiotic treatment for M.K.?

M.K. has had surgery to obtain bone material for culture because cultures of adjacent wound or sinus tract material are not always predictive of the bacteria actually infecting the bone.[1] Broad empiric antibiotic coverage is necessary because *S. aureus* and gram-negative aerobic bacilli most likely are causing this infection.[1]

M.K. was started on vancomycin for possible MRSA infection while awaiting results of bone tissue cultures. Given his normal renal function and weight, M.K. will likely require at least 1.25 g IV every 12 hours of vancomycin (15 mg/kg/dose) with goal area under the concentration–time curve to the minimum inhibitory concentration (AUC/MIC) ratio of 400 to 600 mg × hour/L.[14] Newer agents such as ceftaroline, dalbavancin, oritavancin, delafloxacin, and omadacycline cover MRSA and have been approved for skin infections but require further study in osteomyelitis.

To cover possible pathogenic gram-negative aerobic bacilli, a third- or fourth-generation cephalosporin (ceftriaxone, ceftazidime, or cefepime) or a quinolone (ciprofloxacin, levofloxacin) could be added. The choice of agent should, in part, be based on local susceptibility patterns. Some experts recommend avoiding quinolones, if possible, in osteomyelitis associated with fractures, citing potential concerns with bone healing.[1]

Anaerobic coverage should be initiated if an anaerobe is cultured from bone or anaerobes are suspected. Vancomycin has activity against gram-positive anaerobes, but not against the gram-negative anaerobe, *Bacteroides fragilis.* If *B. fragilis* is cultured from bone, additional therapy with metronidazole is indicated. Alternatively, a β-lactam/β-lactamase inhibitor combination therapy with piperacillin/tazobactam, or a carbapenem could provide broad-spectrum aerobic (including *Pseudomonas)* and anaerobic gram-negative coverage.

While cultures are pending, M.K. is receiving vancomycin 1.25 g IV every 12 hours and cefepime 2 g IV every 8 hours.

DIRECTED THERAPY

Case 73-2, Question 3: The bone biopsy from M.K. grows MRSA that is sensitive to vancomycin, linezolid, and trimethoprim/sulfamethoxazole. His leg pain is no worse than it was 2 days ago, and he remains afebrile. How should M.K. now be treated? Is he a candidate for oral therapy?

Because no gram-negative organisms grew on culture, cefepime should be discontinued. Therapy should be directed against MRSA. Thus, it is justified to continue treating M.K. with vancomycin as long as he is monitored closely, following up on his symptoms, periodic vancomycin serum concentrations that permit AUC-guided dosing and monitoring, weekly ESR or CRP concentrations, CBC, and metabolic panel.[14] Vancomycin can be administered as OPAT. Alternatively, studies have shown that oral antibiotics can achieve adequate concentrations in bone and that they may be noninferior to parenteral agents, permitting partial oral antibiotic therapy in selected patients with osteomyelitis.[15] Based on clinical improvement and provider preference, M.K. may be transitioned to oral linezolid (600 mg twice daily) for 6 total weeks of therapy.[1] He should be followed up closely for at least 2 years to detect recurrent infection.

Osteomyelitis Associated With Vascular Insufficiency

CLINICAL PRESENTATION

CASE 73-3

Question 1: M.S., a 55-year-old female, presents to the diabetes clinic with an ulcer 2 cm wide × 1 cm deep on the left lateral aspect of her foot that she first noted a month ago. Her primary care physician had prescribed a 2-week course of ciprofloxacin and gave her instructions for regular wound care. A few days before her clinic visit, the callus surrounding the ulcer cracked open and a small piece of bone protruded from the wound. She reports mild swelling and redness but denies any pain, fever, or chills. Her past medical history includes type 2 diabetes mellitus, hypertension, peripheral neuropathy, and chronic kidney disease requiring hemodialysis three times a week. Laboratory findings include WBC 5200/μL with normal differential, BUN 56 mg/dL, serum creatinine 5.6 mg/dL, fasting blood glucose 240 mg/dL, hemoglobin $A1_c$ (HbA_{1c}) 12.4%, and ESR 45 mm/hour.

What findings in M.S. are consistent with osteomyelitis secondary to vascular insufficiency?

M.S. has chronic lower extremity vascular insufficiency because of type 2 diabetes. Patients with impaired blood flow may develop osteomyelitis in the toes or small bones of the feet. Infection often first presents as cellulitis, as in M.S.'s case, progressing to deep ulcers and, finally, to the underlying bone.

Similar to contiguous-spread osteomyelitis, systemic signs of infection (eg, fever and leukocytosis) are often absent in patients who experience bone infection secondary to vascular insufficiency. Local symptoms such as pain, swelling, and erythema usually predominate, but there are no specific clinical findings.[15]

M.S. may have a bone infection under the chronic, cutaneous ulcer on the bottom of her left great toe. Because of peripheral neuropathy, the skin lesion may not be painful, and poor blood supply to the site likely contributed to the development of a chronic infection and possibly secondary osteomyelitis. The true depth of an ulcer is not always clinically apparent, so careful physical examination and evaluation of patient risk factors are essential for diagnosis.[16] Infection is suggested by her elevated ESR, fasting glucose (consistent with infection), and HbA_{1c} (indicating uncontrolled diabetes). In addition, diabetic foot ulcers with an area >2 cm^2 or that penetrate to bone are often predictive of underlying osteomyelitis.[16]

ANTIBIOTIC SELECTION

Case 73-3, Question 2: M.S. is admitted into the hospital for diagnosis, wound care, and antibiotics. Plain films show destruction of the distal left fifth metatarsal with bony changes consistent with osteomyelitis. Her wound is debrided, and material obtained from a bone biopsy is sent to the microbiology laboratory for cultures. She has no drug allergies and is started on vancomycin (1 g IV every 12 hours) and oral ciprofloxacin (750 mg every 12 hours). Is this appropriate initial, empiric therapy?

In many cases of osteomyelitis associated with vascular insufficiency, multiple pathogens will be cultured from surgical specimens or the wound. The most commonly isolated pathogen is

S. aureus; however, gram-negative and anaerobic bacteria are also often recovered. The bacteria isolated from a wound or soft tissue culture may not correlate with bacteria found in a concomitant bone biopsy, so bone biopsy is preferred when possible.[16],[17] Empiric antibiotic therapy for osteomyelitis associated with vascular insufficiency should be active against both gram-positive and gram-negative aerobic bacteria and possibly anaerobes. No specific regimens have demonstrated superiority, so a broad-spectrum empiric regimen can be chosen based on local sensitivity patterns.[1] Frequently used empiric regimens for gram-negative and anaerobic coverage are an antipseudomonal β-lactam (piperacillin-tazobactam, cefepime) or quinolone (ciprofloxacin, levofloxacin) with metronidazole.

M.S. has risk factors for MRSA and resistant gram-negative bacilli because of her diabetes, hemodialysis, and recent course of antibiotics. The initial regimen of vancomycin and ciprofloxacin for M.S. is not optimal for several reasons. Because of her recent, prolonged ciprofloxacin exposure, a quinolone-resistant organism may be responsible for infection and a β-lactam–based antibiotic regimen would be more appropriate. Secondly, IV antibiotics should be used during initial treatment. Lastly, M.S. is dialysis dependent, and the antibiotic regimen selected should be dose adjusted according to her renal function. Vancomycin should be intermittently dosed based on her dialysis regimen and maintaining predialysis serum drug concentrations to achieve the desired AUC.[14] The dose for M.S.'s cefepime is 1 g IV every 24 hours, with the dose administered after dialysis on dialysis days.

Antibiotic de-escalation should occur after the results of the deep wound swab culture are available. The optimal duration of IV therapy for diabetic foot osteomyelitis is patient dependent. Some patients may require longer-term, oral suppressive therapy depending on the degree of surgical debridement and the healing rate of the ulcer.[16] The overall duration varies and generally should not exceed 6 weeks.[1],[16] Oral linezolid (600 mg every 12 hours) has been used to treat MRSA osteomyelitis in patients with diabetes, although long-term therapy can be associated with hematologic and neuropathic

adverse effects.[18] Osteomyelitis associated with diabetic foot ulcers is difficult to treat. Despite adequate surgical debridement of the infection followed by appropriate treatment with long-term IV and oral antibiotic therapy, cure rates are low.

Chronic Osteomyelitis

CLINICAL PRESENTATION

CASE 73-4

Question 1: J.F., a 52-year-old male, sustained a fracture of the right humerus in a farming accident 6 years ago. That fracture clinically healed without any immediate consequences; however, 1 year ago, a draining sinus tract developed at the site of the previous fracture without any antecedent events. Two weeks ago, he noted increased sinus drainage, pain, swelling, and erythema of his left upper arm, and levofloxacin was restarted. A swab culture of the sinus drainage grew *S. epidermidis*, *E. coli*, *Peptostreptococcus micros*, and *Bacteroides* species. Surgical debridement of bone and tissue was performed because of increased drainage and poor appearance of the wound. Gentamicin-impregnated polymethylmethacrylate (PMMA) beads were placed in the tissue adjacent to the debrided bone during surgery. Bone cultures grew *Proteus mirabilis* and *B. fragilis.* The *Proteus* was resistant to ampicillin, cefazolin, levofloxacin, and tigecycline but sensitive to cefotaxime, ceftriaxone, imipenem, gentamicin, and trimethoprim-sulfamethoxazole. Antibiotic susceptibilities for the *Bacteroides* were not tested.

What aspects of J.F.'s case are characteristic of chronic osteomyelitis?

Despite appropriate initial therapy, osteomyelitis can reactivate, even with organisms different from the initial episode. Some propose that previously infected bone might be a risk for reinfection. Persistent symptoms or signs lasting >10 days are consistent with chronic osteomyelitis and the development of necrotic bone. Draining sinus tracts often develop from the bone to the skin with chronic osteomyelitis.[19] J.F. probably experienced a chronic bone infection after the farming accident. The reappearance of sinus tract drainage in his left upper arm indicates an indolent infection of the bone that was periodically suppressed, but not completely treated by

oral antibiotics. Cultures of sinus drainage now reveal multiple organisms including normal skin flora. These sinus tract cultures usually do not correlate with the organisms actually causing bone infection. J.F.'s recurrent course of bone involvement with drainage and local symptoms, and lack of any remarkable systemic symptoms, suggest chronic osteomyelitis.[19]

SURGERY AND ORAL ANTIBIOTICS

Case 73-4, Question 2: Oral levofloxacin was started 2 weeks ago when J.F.'s left arm became more painful, and drainage increased. Was his poor response to therapy unexpected? How should his case have been managed?

J.F.'s poor response should have been expected for at least two reasons: Antibiotic therapy was started before surgical debridement of avascular tissue, and he was given an antibiotic that was inactive against the cultured bone organisms.

Surgery plays an important role in the treatment of chronic osteomyelitis. Bone necrosis will continue to progress if decompression and drainage of the infected area are not carried out as soon as possible. Furthermore, without dead space management including initial surgical removal of necrotic bone (sequestrum) and other poorly vascularized, infected material, even the most optimal IV antibiotics are likely to fail.[20]

After surgery, antibiotic therapy directed against the pathogens isolated in the surgical specimens should be started. The regimen choice should not be based on the sinus tract culture results because these isolates may not correlate with the actual causative organisms. J.F. should be treated initially with IV antibiotics because of relatively poor blood flow at the infection site. Although the optimal duration of antibiotic therapy for chronic osteomyelitis is not well established, the standard recommendation has been 6 weeks. The susceptibility of the organism to the antibiotic is more relevant than is the route of administration.[15],[21],[22] J.F. should continuously be

evaluated by an orthopedic surgeon because he may require further surgical treatment to eradicate chronically infected bone.

INTRAVENOUS ANTIBIOTICS

Case 73-4, Question 3: What would be reasonable antibiotic therapy for J.F.?

Based on the bone culture and sensitivity results, J.F. needs high-dose therapy directed at *P. mirabilis* and *B. fragilis.* For convenience and possible future home therapy, ceftriaxone (2 g IV every 24 hours) could be started for coverage of *Proteus* with metronidazole (500 mg IV every 8 hours) for coverage of *B. fragilis*. Because of excellent oral bioavailability, metronidazole can be rapidly converted to oral therapy at the same dose before discharge. Ertapenem is an alternative choice for home IV therapy assuming that the *Proteus* isolate is sensitive. This agent also provides excellent anaerobic activity, and its once-daily dosing (1 g IV every 24 hours) is convenient for OPAT. J.F. should be evaluated for response. If symptoms have abated, treatment with oral antibiotics (trimethoprim-sulfamethoxazole and metronidazole) may commence and should continue for a total of ≥6 weeks depending on resolution of the sinus tract drainage, pain, and tenderness in J.F.'s arm. Under these circumstances, he should be monitored closely for possible long-term adverse drug effects (eg, hepatitis, cytopenias, neuropathy). If the sinus tract does not heal or if J.F. remains symptomatic, surgical exploration and bone cultures must be repeated.

LOCAL ANTIBIOTICS

Case 73-4, Question 4: What is the rationale for and effectiveness of local antibiotic administration (the PMMA beads) inserted during J.F.'s orthopedic surgery?

To deliver high concentrations of antibiotics to poorly vascularized bone infection sites, various materials containing antibiotics can be

placed at the infection site during surgery. Plaster pellets, fibrin, collagen, hydroxyapatite, and PMMA impregnated with antibiotic, usually an aminoglycoside or vancomycin, are used. The dosage form is designed for the slow release of antibiotics from the material. The most commonly reported experience with local antibiotic delivery has been with antibiotic-impregnated PMMA cement or beads inserted during joint arthroplasty. Local delivery of antibiotics should not replace systemic antibiotics in the treatment of chronic osteomyelitis.[20]

Orthopedic Implant–Associated Infections

USUAL CLINICAL PRESENTATION

CASE 73-5

Question 1: A.T., a 47-year-old female, had a left knee replacement 1 year ago for osteoarthritis. She presents today to the orthopedic clinic because of increasing left knee pain for the past 2 months. The knee is painful and warm. She is afebrile, and her peripheral WBC count is 9800/μL. Aspiration of fluid from the knee reveals a total nucleated cell count of 78,000/μL with 90% neutrophils. A Gram stain of this fluid shows 4+ polymorphonuclear leukocytes (PMNs) and 1+ gram-positive cocci. She is started on antibiotic therapy with vancomycin and ciprofloxacin pending culture results, and she is scheduled for operative evaluation and possible removal of her prosthetic joint.

Does A.T. have a periprosthetic joint infection?

Joint replacement surgery is commonly performed in patients with significant joint destruction as a result of arthritis and other disabling diseases. Prosthetic knee, shoulder, elbow, or hip devices made of metallic alloys are cemented to the adjacent bone to reestablish joint function. Infection of these foreign bodies can occur because of exogenous inoculation of bacteria perioperatively, via hematogenous dissemination of bacteria, or by contiguous spread from a topical wound. Bacterial infection of bone adjacent to the joint prosthesis, including the bone–cement interface, may result in a loosened and less functional prosthesis.[23] *Staphylococcus* species including

coagulase-negative species such as *S. epidermidis* are most commonly involved in prosthetic joint infections, followed by *Streptococcus* species, gram-negative bacilli, and anaerobes. Although coagulase-negative staphylococci are usually considered a contaminant in culture, this organism readily adheres to prosthetic material and should be considered pathogenic when cultured from prostheses. Coagulase-negative staphylococci are often methicillin resistant but susceptible to vancomycin.

Chronic pain, swelling, erythema, and tenderness over a prosthetic joint are typical findings associated with prosthetic joint infection. Persistent wound drainage may also be present. A.T. has had a relatively lengthy duration of symptoms associated with her left knee, which could be caused by joint loosening, but the cell count and differential from the joint aspirate suggest joint infection. Consistent with infected prosthesis is also the predominance of neutrophils in her joint fluid and gram-positive cocci on a Gram stain finding. As is often the case, she has no obvious preceding source of infection from which bacteria may have originated. Occasionally, sources of infection with hematogenous dissemination to the prosthetic joint are identified, such as dental infections, cellulitis, or urinary tract infections. Given the Gram stain result, A.T. should receive coverage for *Staphylococcus* and *Streptococcus* species with vancomycin while awaiting the results of cultures and sensitivities. Because gram-negative bacteria also can infect these joints, gram-negative coverage is reasonable until the results of joint fluid cultures are available.

SURGERY

CASE 73-5, QUESTION 2: Does A.T. need surgery and antibiotics to cure her infection?

Surgical removal of A.T.'s knee prosthesis in conjunction with systemic antibiotics for 6 weeks is the current recommendation for optimal eradication of prosthetic joint infection.[23],[24] A two-stage

orthopedic procedure that involves removal of the infected prosthesis, placement of an antibiotic-filled spacer, joint immobilization, and antibiotics for 6 weeks is frequently used. If the joint space culture result remains negative after 2 weeks of antibiotics, a new joint prosthesis is then reinserted. Because avascular bone cement and prosthetic material can become seeded with bacteria, complete removal of this material is necessary to have the greatest chance of curing the infection. Six weeks of systemic antibiotic therapy in combination with orthopedic surgery results in restoration of joint function in >80% of cases. High rates of treatment failure occur if the joint prosthesis is not removed, the antibiotic duration is too short, and if chronic suppressive antibiotics are not given.[23],[24]

ANTIBIOTICS

CASE 73-5, QUESTION 3: The surgeon is unable to completely remove A.T.'s prosthetic joint. The removed lining material and three swabs of the left knee prosthesis grow MRSA. What antibiotic regimen could be used? How long should A.T. be treated?

Because A.T.'s prosthesis cannot be removed, she will need 2 to 6 weeks of vancomycin (15 mg/kg IV every 12 hours) plus oral rifampin (450 mg orally [PO] bid), followed by 6 months of oral antibiotics plus rifampin.[24] Daptomycin (6–10 mg/kg IV daily) or linezolid (600 mg PO/IV every 12 hours) are alternatives to vancomycin, depending on pathogen susceptibility, drug allergies or intolerances, and potential drug–drug interactions.[24],[25] However, these agents are not U. S. Food and Drug Administration (FDA) approved for prosthetic joint infections, and they require monitoring for adverse effects, such as creatine kinase elevations (daptomycin) and bone marrow suppression and neuropathy (linezolid).[23] Combination therapy with rifampin should be used for prosthetic joint infection caused by staphylococci, particularly if removal of the infected prosthesis is not possible, because rifampin penetrates bacterial membranes and biofilms to enhance the bactericidal activity

of the antibiotic regimen. Monotherapy with rifampin should never be used because of the rapid development of resistance.[26,27] Rifampin induces the metabolism of multiple other agents (eg, warfarin, anticonvulsants, azole antifungals); therefore, a thorough review of A.T.'s medication profile is critical. A.T.'s baseline liver function should also be evaluated and rechecked at least monthly while she is taking rifampin.[28] In addition, weekly assessment of A.T.'s CBC and renal function along with periodic vancomycin serum concentrations that permit AUC-guided dosing and monitoring should be performed.[14]

SEPTIC ARTHRITIS

Septic arthritis or infectious arthritis is usually acquired hematogenously. The highly vascular synovium of the joint allows easy passage of bacteria from blood into the synovial space. Bacteremia, secondary to *Neisseria gonorrhoeae* or *S. aureus* in particular, often is associated with joint infections. Septic arthritis also can develop secondary to inoculation of pathogens because of trauma, including puncture (eg, animal bites, nail) or surgery, as well as via contiguous spread from osteomyelitis.[29]

Several factors predispose patients to the development of infectious arthritis. Patients with abnormal joint structure, including rheumatoid arthritis (RA), prosthetic joints, or recent joint surgery, are more susceptible to the development of infection. Patients 80 years or older and having diabetes mellitus and chronic illnesses such as malignancy and chronic renal failure are also at an increased risk. Gonococcal arthritis may occur in those who have been exposed to or are infected with *N. gonorrhoeae*.[29,30]

Clinical Presentation of Nongonococcal Arthritis

CASE 73-6

Question 1: C.H., a 45-year-old male, is referred to the rheumatology clinic for left knee swelling. Two days ago, his left knee became painful and swollen, and he is unable to flex the joint. He also recorded temperatures at home of 100.7 °F (38.17 °C) to 102 °F (38.89 °C) for at least 4 days. In clinic, a joint effusion is noted, and fluid is aspirated for cell count, Gram stain, and culture. His medical history is unremarkable. C.H.'s WBC count is 16,000/μL, and his ESR is 42 mm/hour. The synovial fluid from his right knee contains 30,000 WBC/μL with 90% neutrophils, and the Gram stain finding shows gram-positive cocci in clusters. Culture and sensitivity results are pending. His current temperature is 101.3 °F (38.5 °C).

What findings in C.H. are consistent with septic arthritis?

C.H. has an acute onset of monoarticular joint pain and swelling, with a reduced range of motion and fever. These findings are classic for septic, nongonococcal arthritis. The joint effusion shows a predominance of neutrophils, which confirms the diagnosis. C.H.'s knee has been infected hematogenously from a distant, unrecognized, source of infection, and the most common causative pathogens are gram positive, including *Staphylococcus* and *Streptococcus* species.

A single joint, most frequently the knee, is infected in 80% to 90% of nongonococcal arthritis cases. Other possible sites of infectious arthritis in adults include the hip, shoulder, elbow, ankle, and wrist joints.[29,30] Patients commonly present with fever, pain, swelling, redness, and decreased mobility of the involved joint.

As illustrated by C.H., most patients have joint effusion on physical examination. When evaluating a patient with possible septic arthritis, any purulent joint effusion should be considered septic until proven otherwise. Alternatively, noninfectious conditions may be present, such as acute RA, gout, or chondrocalcinosis.[29]

Aspirated joint fluid should be cultured because isolation of bacteria is the only definitive diagnostic test for bacterial arthritis. C.H.'s joint fluid picture is typical. The leukocyte count in the synovial fluid usually is elevated significantly, often with counts >50,000/μL with a predominance of neutrophils (>75%). Blood culture results are positive in 25% to 70% of patients, and 80% to 90% of patients will have positive synovial fluid culture results.

Another laboratory finding in C.H. consistent with infectious arthritis is the elevated ESR and peripheral WBC count. CRP is frequently elevated as well, although both ESR and CRP are nonspecific markers of inflammation and can be elevated owing to causes other than infectious arthritis.

The patient's age impacts the most common bacterial cause of infection. In adults older than age 30 years, such as C.H., and in children older than age 2 years, *S. aureus* is the most common bacterial source. In sexually active young adults, *N. gonorrhoeae* is more likely to be the causative agent. Streptococci, such as group A β-hemolytic streptococci, can cause infection in children and adults. Group B streptococci, anaerobic streptococci, and gram-negative bacteria can also cause infection. Gram-negative bacilli are responsible for ~5% to 20% of cases and often infect multiple joints. Infections with gram-negative bacteria usually are associated with predisposing factors, such as RA, osteoarthritis, history of joint surgery, intra-articular injections, or IV drug use. An organism commonly isolated from patients with bacterial arthritis and a history of IV drug use is *P. aeruginosa*.[29,30]

Initial Antimicrobial Therapy

Case 73-6, Question 2: How should C.H. be treated, and for how long? How should the treatment efficacy be monitored?

Treatment of nongonococcal arthritis includes drainage of purulent joint fluid (by needle aspiration or surgery) and appropriate antibiotic therapy guided by patient presentation and synovial fluid Gram stain. Because of the increasing frequency of health care–associated and community-acquired MRSA causing infection, initial empiric therapy with vancomycin (15–20 mg/kg/dose IV every 12 hours in normal renal function, goal AUC/MIC ratio of 400–600 mg-h/L) should be initiated to provide coverage for this and streptococci in C.H.[14] Daptomycin and linezolid are typically reserved for patients with vancomycin intermediate-susceptible or resistant gram-positive

organisms, or those patients with intolerance, allergy, or nonresponse to vancomycin. More data assessing use in septic arthritis are needed before other antibiotics with MRSA coverage can be recommended, such as dalbavancin, oritavancin, ceftaroline, delafloxacin, or omadacycline. Vancomycin can be changed on the basis of sensitivity testing to oxacillin, nafcillin, or cefazolin if the isolated organism is susceptible.[29],[30]

DURATION OF THERAPY

Optimal duration of therapy for bacterial arthritis remains unknown.[29] Previous recommendations based on early clinical trials recommended treating for 2 to 3 weeks.[31] Current recommendations are to treat with 2 to 4 weeks of antibiotics, initially parenteral, followed by oral antibiotics (if possible, based on susceptibilities and drug bioavailability).[29],[32] Injections of antibiotics into the joint space are of no value. Most systemic antibiotics readily penetrate the joint space and enter the synovial fluid.

C.H. should be treated for at least 4 weeks if his infection is caused by *S. aureus*.[29] His response to therapy should be monitored clinically (resolution of symptoms, fever, and falling ESR, CRP, or both) as well as by periodic evaluation of joint fluid. Frequent aspirations of joint fluid via closed-needle aspiration or following arthroscopic lavage, and debridement and insertion of drains are needed in more severe cases and will permit daily evaluation of cell count and fluid culture. Effective therapy should result in a decreasing WBC count in the joint fluid and negative culture findings.[29]

Joint inflammation and other symptoms also should diminish during the first week of treatment. The duration of articular symptoms before antibiotic therapy begins correlates with the subsequent time required to sterilize the synovial fluid. Therefore, delay in initiating antibiotic treatment may necessitate a longer course of therapy.

Gonococcal Arthritis

Polyarticular arthritis in a young, sexually active adult is frequently caused by *N. gonorrhoeae.* Arthritis in multiple joints is a common feature of disseminated gonococcal infection (DGI). Unlike nongonococcal arthritis, which is almost exclusively monoarticular, gonococcal arthritis involves multiple joints in 42% to 85% of cases. Females have a fourfold increased risk of developing gonococcal arthritis as compared with males, often due to delays in diagnosis of genital infection.[29,33] Clinically, patients present with a migratory polyarthralgia and often with fever, dermatitis, and tenosynovitis. Skin lesions are an important clue to the diagnosis of DGI and often begin as tiny erythematous papules that develop into larger vesicles. As in hematogenously acquired nongonococcal arthritis, the synovial fluid leukocyte count usually is elevated, but often to a lesser degree. *N. gonorrhoeae* is recovered in ~50% of purulent joint effusions and is detected using polymerase chain reaction (PCR) assays with ~80% sensitivity. These laboratory studies, coupled with the patient's clinical presentation, can be used to make a definitive diagnosis.[29,33]

CLINICAL PRESENTATION OF GONOCOCCAL ARTHRITIS

CASE 73-7

Question 1: E.D., a 21-year-old female, presents to the walk-in clinic with right knee and right shoulder pain, nausea, and vomiting. On physical examination, her right knee is swollen, and she has decreased range of motion of her right shoulder. Several erythematous, papular skin lesions are noted on both hands. She also has a vaginal discharge. Her temperature is 100.76 °F (38.2 °C), and her WBC count is 15,000/μL. She gives a history of having two recent sexual partners. Culture results of blood, joint fluid, and vaginal discharge are obtained; a joint fluid Gram stain shows 4+ PMNs, but no organisms are seen.

Why is E.D. considered to have gonococcal arthritis?

E.D. has systemic signs of infection (fever, nausea, vomiting, leukocytosis), skin lesions, and multiple joint involvement, which are classic for DGI. Her history of recent sexual activity and the presence of a vaginal discharge are consistent with gonococcal

infection, although evidence of mucosal infection with *N. gonorrhoeae* is not necessary for disseminated infection to occur.[29],[33]

PATIENT WORKUP AND TREATMENT IN THE CLINIC

Case 73-7, Question 2: What additional workup should be done in E.D.? Can she be treated immediately in the clinic?

A nucleic acid amplification test (NAAT) should be performed using a specimen obtained from E.D.'s cervix. E.D. should also be evaluated for other sexually transmitted infections, specifically syphilis and HIV infection. Serologic testing for syphilis (rapid plasma reagent [RPR] or venereal disease research laboratory [VDRL] testing) and for antibody to HIV should be obtained. In addition, she should have a pregnancy test because some of the antibiotics that may be used are contraindicated during pregnancy, including doxycycline.

Because of possible penicillinase production and widespread fluoroquinolone resistance with *N. gonorrhoeae*, recommended therapy is with ceftriaxone (1 g intramuscularly or IV every 24 hours). E.D. should receive her first dose of ceftriaxone in the clinic today. Conversion to oral antibiotics should be guided by antimicrobial susceptibility testing following 24 to 48 hours of clinical improvement by the patient.[34]

E.D.'s sexual partners should also be evaluated and treated for relevant sexually transmitted infections. She should also be counseled on utilization of barrier methods (eg, condoms) to prevent sexually transmitted infections.

FULL COURSE OF THERAPY

Case 73-7, Question 3: Results of RPR and pregnancy testing in E.D. are negative. How should she complete her course of therapy?

E.D.'s DGI should be treated for at least 7 days. E.D. also should begin treatment with azithromycin (1 g PO once) or doxycycline (100 mg PO twice daily for 7 days) for the possibility of concomitant chlamydial infection. Azithromycin is preferred because of its increasing resistance to tetracyclines.[35] Treatment guidelines for DGI are also included in the section on Gonorrhea in Chapter 72, Sexually Transmitted Diseases.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and website for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. *Cochrane Database Syst Rev*. 2013;9:CD004439. (22)

Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. *Clin Microbiol Rev*. 2010;23(1):14. (26)

Keren R, Shah SS, Srivastava R, et al. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr*. 2015;169(2):120–128. (12)

Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54(12):e132–e173. (16)

Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18–e55. (9)

Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56(1):e1–e25. (24)

Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System

Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm*. 2020;77:835–864 (14)

Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54(3):393–407. (21)

Tande AJ, Steckelberg JM, Osmon DR, Berbari EF. Osteomyelitis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Churchill Livingstone; 2019:1418. (1)

Zimmerli W, Sendi P. Orthopedic implant-associated infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Churchill Livingstone; 2019:1430–1441. (23)

Key Websites

Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. Accessed May 14, 2021. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6403a1.htm

COMPLETE REFERENCES CHAPTER 73 OSTEOMYELITIS AND SEPTIC ARTHRITIS

1. Tande AJ, Steckelberg JM, Osmon DR, Berbari EF. Osteomyelitis. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Churchill Livingstone; 2019:1418.
2. Petolta H, Paakkonen M. Acute osteomyelitis in children. *N Engl J Med*. 2014;370:352–360.
3. Eid AJ, Berbari EF. Osteomyelitis: review of pathophysiology, diagnostic modalities and therapeutic options. *J Med Liban*. 2012;60:51–60.
4. Krogstad P. Osteomyelitis. In: Feigin RD, Harrison GJ, Kaplan SL, Hotez PJ, Steinbach WJ, eds. *Textbook of Pediatric Infectious Diseases*. 7th ed. WB Saunders; 2014:711.
5. DeRonde KJ, Girotto JE, Nicolau DP. Management of pediatric acute hematogenous osteomyelitis, part I: antimicrobial stewardship approach and review of therapies for methicillin-susceptible *Staphylococcus aureus, Streptococcus pyogenes*, and *Kingella kingae*. *Pharmacotherapy*. 2018;38:947–966.

6. Mantadakis E, Plessa E, Vouloumanou EK, Michailidis L, Chatzimichael A, Falagas ME. Deep venous thrombosis in children with musculoskeletal infections: the clinical evidence. *Int J Infect Dis*. 2012;16(4):e236–e243.
7. Principi N, Esposito S. *Kingella kingae* infections in children. *BMC Infect Dis*. 2015;15:260.
8. DeRonde KJ, Girotto JE, Nicolau DP. Management of pediatric acute hematogenous osteomyelitis, Part II: a focus on methicillin-resistant *Staphylococcus aureus*, current and emerging therapies. *Pharmacotherapy*. 2018;38:1021–1037.
9. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18–e55.
10. Garcia C, McCracken GH. Antibacterial therapeutic agents. In: Feigin RD, Harrison GJ, Kaplan SL, Hotez PJ, Steinbach WJ, eds. *Textbook of Pediatric Infectious Diseases*. 7th ed. WB Saunders; 2014:3182.
11. Landersdorfer CB, Bulitta JB, Kinzig M, Holzgrabe U, Sörgel F. Penetration of antibacterials into bone: pharmacokinetic, pharmacodynamics and bioanalytical considerations. *Clin Pharmacokinet*. 2009;48(2):89–124.
12. Keren R, Shah SS, Srivastava R, et al. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr*. 2015;169(2):120–128.
13. Howard-Jones AR, Issacs D. Systematic review of duration and choice of systemic antibiotic therapy for acute haematogenous bacterial osteomyelitis in children. *J Paediatr Child Health*. 2013;49(9):760–768.
14. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77:835–864.
15. Li HK, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med.* 2019;380:425–436.
16. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54(12):e132–e173.
17. Lázaro Martínez JL, García Álvarez Y, Tardáguila-García A, García Morales E. Optimal management of diabetic foot osteomyelitis: challenges and solutions. *Diabetes Metab Syndr Obes*. 2019;12:947–959.
18. Falagas ME, Siempos II, Papagelopoulos PJ, Vardakas KZ. Linezolid for the treatment of adults with bone and joint infections. *Int J Antimicrob Agents*. 2007;29(3):233–239.

19. Lowenberg DW, Rupp, M, Alt V. Understanding and treating chronic osteomyelitis. In: Browner BD, Jupiter JB, Kretteck C, Anderson PA, eds. *Skeletal Trauma: Basic Science, Management, and Reconstruction*. 6th ed. WB Saunders; 2020:707–742.
20. Pincher B, Fenton C, Jeyapalan R, Barlow G, Sharma HK. A systematic review of the single-stage treatment of chronic osteomyelitis. *J Ortho Surg Res.* 2019;14:393.
21. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54(3):393–407.
22. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. *Cochrane Database Syst Rev*. 2013;9:CD004439.
23. Zimmerli W, Sendi P. Orthopedic implant-associated infections. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Churchill Livingstone; 2019:1430–1441.
24. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56(1):e1–e25.
25. Hermsen ED, Mendez-Vigo L, Berbari EF, Chung T, Yoon M, Lamp KC. A retrospective study of outcomes of device-associated osteomyelitis treated with daptomycin. *BMC Infect Dis*. 2016;16(310):1–5.
26. Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. *Clin Microbiol Rev*. 2010;23(1):14–34.
27. Perlroth J, Kuo M, Tan J, Bayer AS, Miller LG. Adjunctive use of rifampin for the treatment of *Staphylococcus aureus* infections: a systematic review of the literature. *Arch Intern Med*. 2008;168(8):805–819.
28. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. *JAMA*. 1998;279(19):1537–1541.
29. Ohl CA, Forster D. Infectious arthritis of native joints. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Elsevier Churchill Livingstone; 2019:1430–1441.
30. Long B, Koyfman A, Gottlieb M. Evaluation and management of septic arthritis and its mimics in the emergency department. *West J Emerg Med*. 2019;20(2): 331–341.
31. Syrogiannopoulos GA, Nelson JD. Duration of antimicrobial therapy for acute suppurative osteoarticular infections. *Lancet*. 1988;1(8575–8576):37–40.
32. Ross JJ. Septic arthritis of native joints. *Infect Dis Clin N Am*. 2017;31:203–218.
33. Garcia-Arias M, Balsa A, Mola EM. Septic arthritis. *Best Pract Res Clin Rheumatol*. 2011;25:407–421.

34. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines 2015. Accessed May 14, 2021. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6403a1.htm
35. Centers for Disease Control and Prevention. Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. Accessed May 14, 2021. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm

74

Skin and Soft Tissue Infections

Cheryl R. Durand and Kristine C. Willett

CORE PRINCIPLES		CHAPTER CASES
SKIN AND SOFT TISSUE INFECTIONS		
1	Cellulitis (an acute inflammation of the skin and subcutaneous fat) is characterized by local tenderness, pain, swelling, warmth, and erythema with or without a definite entry point.	**Case 74-1 (Question 1, 5)**
2	Cellulitis is most often caused by group A β-hemolytic streptococci (*Streptococcus pyogenes*) and, less often, *Staphylococcus aureus.*	**Case 74-1 (Question 1), Table 74-1**
3	Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) may be a causative pathogen, especially in high-risk patients (children, competitive athletes, prisoners, soldiers,	**Case 74-1 (Question 1) Case 74-3 (Question 1)**

	selected ethnic populations, Native Americans/Alaska Natives, Pacific Islanders, intravenous drug users, men who have sex with men [MSM]), and empiric treatment should have activity against CA-MRSA.	
4	For most cases of cellulitis requiring antibiotics, the least expensive of dicloxacillin or cephalexin should be chosen. Cases of cellulitis as evidenced by signs of systemic infection require parenteral antibiotics. The duration of therapy should be at least 5 days.	**Case 74-1 (Questions 1–4, 6) Case 74-2 (Question 1, 2)**
5	Conversion to oral antibiotic therapy should be considered when patients show signs of clinical improvement and are afebrile for at least 24 hours.	**Case 74-2 (Questions 3, 4)**
6	Abscesses, furuncles, and carbuncles are commonly caused by *S. aureus* and should be managed with incision and drainage. Antibiotic therapy is warranted when systemic inflammatory response syndrome is present.	**Case 74-3 (Questions 2, 3), Table 74-1**
	ERYSIPELAS	
1	Oral or parenteral penicillins, with activity against group A streptococci, are the drugs of choice for treatment.	**Case 74-4 (Question 1), Table 74-1**
	SKIN AND SOFT TISSUE INFECTIONS IN PATIENTS WITH DIABETES	
1	Skin and soft tissue infections are very common in patients with diabetes, with	**Case 74-5 (Question 1)**

	~25% of patients reporting a history of skin and soft tissue infection.	
2	Mild infections in patients with diabetes can be treated similar to cellulitis (gram-positive coverage), whereas moderate-to-severe infections require broad-spectrum coverage.	**Case 74-5 (Questions 1–4), Table 74-1**
	NECROTIZING SOFT TISSUE INFECTIONS	
1	Necrotizing soft tissue infections can progress rapidly to cause local (eg, necrosis and loss of skin sensation) and severe systemic (eg, hypotension, shock) effects.	**Case 74-6 (Question 1)**
2	Initial treatment of necrotizing soft tissue infections involves extensive debridement to remove all necrotic tissue, fluid resuscitation, and broad-spectrum antibiotics.	**Case 74-6 (Question 1), Table 74-1**
	ANIMAL BITES	
1	Animal bites (eg, from cats, dogs) necessitate irrigation of the wound to reduce the risk of infection and treatment may include coverage against aerobic or anaerobic organisms (oral flora of the animals). Amoxicillin/clavulanate is the preferred first-line agent.	**Case 74-7 (Questions 1, 2), Table 74-1**
	HUMAN BITES	
1	Treating a human bite is similar to that of any other laceration, including	**Case 74-8 (Question 1), Table 74-1**

cleansing, irrigating, exploring, debriding, draining, excising, and suturing, as required. Human-bite infections may be caused by aerobic and anaerobic organisms and should be treated with amoxicillin/clavulanate or ampicillin/sulbactam, or ertapenem.

INTRODUCTION

Skin and soft tissue infections may involve any or all layers of the skin (epidermis, dermis), subcutaneous fat, fascia, or muscle. Many terms or classifications describe various skin and soft tissue infections, and these often are based on the site of infection and causative organism(s).[1] This chapter focuses on skin and soft tissue infections that are primarily the result of a break in the skin after an abrasion, skin puncture, ulceration, surgical wound, intentional or unintentional insertion of a foreign body, or blunt soft tissue contusion. Treatment of skin and soft tissue infections often is empiric and based on the severity and site of infection, presence of purulence, the patient's underlying immunocompetence, and the triggering event (eg, abrasion, bite, insertion of a foreign object) because attempts to isolate the causative organism often are futile.

SKIN AND SOFT TISSUE INFECTIONS

Cellulitis (an acute inflammation of the skin and subcutaneous fat) is characterized by local tenderness, pain, swelling, warmth, and erythema with or without a definite entry point. Cellulitis is usually secondary to trauma or an underlying skin lesion that allows bacterial penetration into the skin and underlying tissues. Cellulitis is most often caused by group A β-hemolytic streptococci

(*Streptococcus pyogenes*) and other streptococcus species (B, C, F, or G), and less often, *Staphylococcus aureus* (**Table 74-1**).[2] However, if the patient presents with abscess, purulence, or penetrating trauma, coverage of *S. aureus* is indicated.[2] Coverage for community-acquired methicillin-resistant *Streptococcus aureus* (CA-MRSA) may be warranted because the incidence has been increasing.[3] Gram-negative organisms (eg, *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*) also can cause cellulitis but should be suspected only in patients who are immunocompromised or in patients who fail to respond to antibiotics with activity limited to gram-positive organisms. Wound cultures often are negative and fail to identify the causative organism.

Table 74-1

Potential Organisms Causing Skin and Soft Tissue Infections

	Gram Positive		Gram Negative		Anaerobes			
	Staphylococci	Streptococci	*Escherichia coli*, *Klebsiella* Species, *Proteus* Species	*Pasteurella multocida*	*Eikenella corrodens*	Oral Anaerobes	*Clostridium* Species	*Bacteroides fragilis*
Cellulitis	X	X						
Diabetic soft tissue	X	X	X					X
Necrotizing infections	X	X	X			X	X	X
Erysipelas		X						
Animal bites	X	X	X	X		X		
Human bites	X	X	X		X	X		

X, organisms that should be covered empirically with appropriate antibiotic therapy.

Sources: Esposito S, Noviello S, Leone S. Epidemiology and microbiology of skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29:109–115; Esposito S, Bassetti M, Concia E, et al. Diagnosis and management of skin and soft tissue infections (SSTI). A literature review and consensus statement: an update. *J Chemother*. 2017;29:197–214; Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10–e52; Lipsky BA, Berendt AR, Cornia PB, et al. Clinical practice guidelines for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:e132–e173.

Severity of infection is based on the presence of systemic signs of infection, failure of oral antibiotics, and immunocompetence. Cases

of mild cellulitis without signs of systemic infection often require treatment with antibiotics active against streptococci. Patients with evidence of a systemic infection, suggesting a moderate-to-severe infection, will require intravenous (IV) antibiotics, in addition to local wound care. Severe infections occur in patients who have failed oral antibiotic therapy or those who are immunocompromised. Antibiotic selection is based on the suspected etiology as well as severity of infection.

In addition to cellulitis, skin and soft tissue infections include abscesses, furuncles, and carbuncles. A skin abscess is an infection and results in a collection of pus within the dermis and deep skin tissues.[2] Furuncles are abscesses that initiate in the hair follicle and penetrate into the surrounding subcutaneous tissue, whereas carbuncles are a coalescence of furuncles.

CASE 74-1

QUESTION 1: N.P., a 25-year-old female, presents to her family doctor with a 2- to 3-day history of worsening pain, redness, and swelling on her left leg following an abrasion that occurred after falling while jogging in the park. The area is red, painful, nonpurulent, and warm to the touch. During the past 24 to 36 hours, the leg has become increasingly painful and "tight." N.P. denies having fever or chills. The presumptive diagnosis is a mild cellulitis, and dicloxacillin is prescribed.

Why is dicloxacillin appropriate empiric treatment for N.P.?

Oral dicloxacillin is appropriate empiric therapy for cellulitis in an otherwise healthy individual with no signs or symptoms of systemic infection, regardless of the presence of purulence. Dicloxacillin has predictable activity against streptococci and methicillin-sensitive staphylococci and is better tolerated than is erythromycin or clindamycin. Because the patient presents with nonpurulent cellulitis, penicillin VK is also an option; however, it lacks coverage against staphylococcus. If the cellulitis is well demarcated and nonpurulent, penicillin alone can be appropriate because the causative organism is likely to be *Streptococcus*. Many other available antibiotics that have activity against staphylococci and streptococci have been

evaluated for effectiveness in skin and soft tissue infections. A recent review concluded that the available evidence does not allow specific recommendations for the best antibiotic regimen for cellulitis.[3,4] Cephalexin is probably as effective and as well tolerated as dicloxacillin and is comparable in cost. However, the gram-negative activity of cephalexin (not present with dicloxacillin) is not required for most cases of cellulitis in otherwise healthy patients. For N.P., antibiotic treatment is required, and she can receive dicloxacillin or cephalexin.

In geographic areas with higher incidence of CA-MRSA (>10% of isolates), particularly in patients with additional risk factors (children, competitive athletes, prisoners, soldiers, selected ethnic populations, Native Americans/Alaska Natives, Pacific Islanders, IV drug users, men who have sex with men [MSM]), empiric treatment should include antibiotics with activity against CA-MRSA.[5] In cases of an abscess without signs of systemic infection, drainage is often all that is needed because antibiotic therapy has not been shown to be better than is placebo for uncomplicated skin abscesses in a population at risk for CA-MRSA infection.[6] At present, most CA-MRSA are still susceptible to trimethoprim-sulfamethoxazole, clindamycin, and doxycycline.[2] Although trimethoprim-sulfamethoxazole has good activity against *S. aureus*, its activity against *S. pyogenes* (group A streptococci), is weak, rendering this antibiotic undesirable alone as empiric therapy. If these agents are used, a reasonable suggestion would be to reevaluate (by the patient if they are competent) within 24 to 48 hours to verify that an improvement is occurring. Some clinicians avoid the use of clindamycin because of concerns of inducible resistance. In areas with a clinically important incidence of CA-MRSA, laboratories should test for inducible clindamycin resistance. If N.P. is from an area of high CA-MRSA prevalence and has associated risk factors, the combination of trimethoprim-sulfamethoxazole or doxycycline with β-lactam (penicillin, cephalexin, amoxicillin) would provide therapy for the anticipated pathogens. However, even in areas of high CA-MRSA prevalence, some investigations have found cephalexin to be as effective as therapy specifically targeted for CA-

MRSA, although this has not been supported in all studies.[7–9] If CA-MRSA does not require antibacterial coverage, this practice may reduce antibacterial selection pressure and expense.[10]

Case 74-1, Question 2: What agents could be chosen if N.P. is allergic to penicillin?

Clindamycin could be selected for patients with a documented history of penicillin or cephalosporin allergy.[2] In certain geographic areas, group A streptococci macrolide resistance approaches 15% to 20%, decreasing the potential value of this agent. Clindamycin is superior to macrolides with respect to group A streptococcal coverage; however, it may cause diarrhea in 20% of patients and is one of the commonly used agents responsible for antibiotic-associated colitis. Moxifloxacin and levofloxacin are potential alternatives that have the convenience of once-daily dosing.

Case 74-1, Question 3: What dose should be prescribed for N.P.?

The recommended dosage of dicloxacillin is 500 mg orally every 6 hours. The dosage for penicillin V is 250 to 500 mg orally every 6 hours; for oral clindamycin, the dosage is 300 to 450 mg every 6 hours. Because dicloxacillin is the drug chosen for N.P., a dosage of 500 mg orally every 6 hours is appropriate. The dose for doxycycline is 100 mg orally every 12 hours, and the dose for trimethoprim-sulfamethoxazole is one to two double-strength tablets orally every 12 hours. The recommended dose for moxifloxacin is 400 mg orally every 24 hours and for levofloxacin 500 mg orally every 24 hours.

Case 74-1, Question 4: What is the appropriate duration of therapy for N.P.?

Although the recommended duration of therapy for cellulitis is 5 days, treatment may be extended if clinical improvement is not seen.[2] A reasonable recommendation to the patient would be to

continue oral antibiotics for 2 to 3 days after the patient has become afebrile and has clinically improved. Counseling points for N.P. should be to expect a response within 1 to 2 days of therapy beginning (although erythema may persist longer) and to return for reevaluation if the condition does not improve or worsens during the next few days.

CASE 74-1, QUESTION 5: What further diagnostic evaluation should be undertaken for N.P.?

In otherwise healthy individuals, identification of the causative organism in cases of mild cellulitis is unnecessary. Needle aspiration, fine-needle aspiration biopsy, and punch biopsy identify the causative organism in only 20% to 30% of patients.[2] Appropriate empiric treatment is effective in most patients, and an attempt to isolate the organism does not improve the success of treatment and adds significantly to the cost of care. However, patients with moderate-to-severe purulent infection, patients who failed initial empiric therapy, patients who are immunocompromised, patients with potential joint or tendon damage, or patients with life-threatening infections requiring hospitalization may benefit from additional cultures. In these cases, blood cultures, a swab of the primary wound, and a needle aspiration or punch biopsy of the leading edge of the cellulitis should be obtained for Gram stain and culture before initiating antimicrobial therapy. Anaerobic cultures need to be drawn only when the wound contains necrotic tissue, is foul smelling, or crepitus is present. Even if wound and blood cultures are obtained, many infections will return culture-negative results (74%). Blood culture results are positive in ~5% of cellulitis cases. Culture information, in conjunction with clinical course, is used to modify subsequent treatment. Because N.P. has only a mild cellulitis, cultures are not required, and she should receive empiric therapy. In addition to systemic therapy, N.P. should be instructed to keep the area clean with soap and water (if an open wound is present) and to protect the area. Treatment of cellulitis should also include rest,

immobilization and elevation of the infected area, and surgical drainage or debridement, as required. The wound should be assessed daily for local tenderness, pain, erythema, swelling, ulceration, necrosis, and wound drainage.

Case 74-1, Question 6: Could topical antibiotics be used to treat N.P.'s cellulitis?

The value of topical antibiotics in treating skin infections is questionable.[11] Most topical antibiotics have not been evaluated in appropriately designed trials. Although mupirocin is superior to placebo in treating some types of wound infections, its value in more severe disease is uncertain. In patients with moderate-to-severe infections, mupirocin, or any topical antibiotics (neomycin, bacitracin, polymyxin B) should not be used to replace or augment systemic antibiotics. Topical antibiotics likely do little but add to the cost of therapy, and they occasionally cause a contact dermatitis. Therefore, N.P. should not be treated with topical antibiotics because her cellulitis should be managed adequately with systemic antimicrobial therapy.

CASE 74-2

Question 1: O.A., a 49-year-old male, presents to the ED with a 3- to 4-day history of increasing pain around his left hip, secondary to an injury he sustained falling on the sidewalk. Examination reveals a swollen, warm, and extremely tender hip. O.A. has a temperature of 103.64 °F (39.8 °C). He is diagnosed with moderate cellulitis and is hospitalized to receive IV antibiotics. O.A. has no other underlying medical problems.

What empiric antibiotic regimen would be reasonable for O.A.?

The parenteral agent of choice in this case is nafcillin or oxacillin.[2]

Cefazolin (1–2 g IV every 8 hours) would be an appropriate alternative if it is less expensive than nafcillin. Second- and third-generation cephalosporins (cefuroxime, ceftriaxone, cefotaxime) and some quinolones may be as effective as nafcillin, but provide no

clinical advantages for most cellulitis. Patients with risk factors for MRSA (penetrating trauma, history of MRSA, nasal colonization, IV drug abuse, presence of systemic inflammatory response syndrome) should be treated with vancomycin or agents with activity against *Streptococci* and MRSA. One potential option is linezolid, but its use is limited by the potential for drug–drug interactions with serotonergic agents. Other agents include daptomycin, telavancin, dalbavancin, oritavancin, ceftaroline, and delafloxacin. Although these agents are as effective in severe cellulitis, they are not used as commonly as vancomycin because of cost and formulary availability.

Therefore, O.A. should receive nafcillin, oxacillin, or cefazolin, whichever is less expensive and more tolerable for the patient. Once O.A. has become afebrile and has evidence of clinical improvement, the parenteral antibiotic should be discontinued, and appropriate oral therapy should be initiated to complete at least a 5-day course (or longer until clinical improvement is seen).

Case 74-2, Question 2: Two days after starting therapy, O.A. develops a maculopapular skin rash. What alternative therapy should be chosen?

Regardless of when during the course of therapy a drug rash occurs (early or late), the precipitant drug should be discontinued because there is a chance, although small, that the reaction could worsen. In patients who have a penicillin allergy and who still require parenteral therapy, clindamycin, vancomycin, linezolid, moxifloxacin, levofloxacin, or delafloxacin could be chosen. Because all of these agents are equally effective, the choice should be based on cost and dosing convenience and presence of risk factors for MRSA.

Case 74-2, Question 3: After 48 hours of therapy, culture and sensitivity results are available. What changes, if any, should be made in O.A.'s treatment?

If culture results show only streptococcus species in a patient who is not allergic to penicillin, therapy should be de-escalated to

penicillin because it is effective, well tolerated, and less expensive than is nafcillin. If cultures grow staphylococcus species (*S. aureus*) that are sensitive to methicillin/oxacillin, the initial empiric therapy should be continued. If the organisms are resistant to methicillin/oxacillin, therapy should be switched to vancomycin 15 mg/kg IV every 12 hours or an alternative agent as previously described. Because O.A. has a presumed penicillin allergy (due to maculopapular rash) and does not require therapy for MRSA, he should continue with clindamycin or vancomycin. Cefazolin may also be an option for penicillin-allergic patients who do not experience severe allergic reactions, such as urticaria and anaphylaxis.

Case 74-2, Question 4: After 72 hours of therapy, O.A. has improved considerably and has been afebrile for 24 hours. Can he be switched to oral therapy?

Once O.A. has been afebrile for at least 24 hours and has significantly improved, he can be switched to oral therapy, if tolerated. Clinicians should select the oral agent on the basis of culture results (if available), anticipated pathogens (if no culture results), convenience, and cost.

Case 74-2, Question 5: What is the role of anti-inflammatory agents as adjunctive treatment of cellulitis?

Anti-inflammatory agents, such as nonsteroidal anti-inflammatory agents and corticosteroids, have been shown to decrease the time to resolution of cellulitis when given in conjunction with antibiotics to patients without diabetes.[2] Although supporting evidence is weak, a significantly quicker resolution of symptoms in patients on prednisolone 5 to 30 mg/day has been seen.[2,12,13]

CASE 74-3

Question 1: M.C. is a 22-year-old college football player who presents to the emergency department (ED) with a 3- to 4-day history of pain in his left thigh.

On examination, he has a swollen, erythematous, and purulent 2 × 3 cm abscess in the inner left thigh. The area is warm and tender to the touch. M.C. is afebrile with no signs of lymphangitis.

What tests are needed to confirm the diagnosis?

In patients with abscesses, large furuncles (superficial skin abscess), and carbuncles (clusters of furuncles), Gram stain and culture of pus is recommended; however, typically, patients may be adequately treated without further testing.[2] M.C. has risk factors for CA-MRSA (competitive athlete); if CA-MRSA is identified, infection control measures should be implemented to prevent an outbreak.[14] In febrile patients, blood cultures should be drawn before antibiotics are started to maximize the ability to isolate the pathogen.

Case 74-3, Question 2: Are the suspected organisms in M.C. similar to those found in other patients with cellulitis?

Abscess, furuncles, and carbuncles are most commonly caused by staphylococci, predominately *S. aureus.*[2,6] Abscesses may also be polymicrobial. For patients who are IV drug abusers and present with abscess or cellulitis, the infecting bacteria are similar to those found in normal hosts. IV drug use is also a risk factor for infection with CA-MRSA, and this should be particularly considered if the patient has had recurrent infections or has failed to respond to methicillin-sensitive *Staphylococcus aureus* (MSSA)-directed antibiotic therapy.[14] Although *S. epidermidis,* gram-negative organisms, including *P. aeruginosa,* and anaerobes are rarely pathogens, they may be present, particularly in patients who do not respond to initial therapy.

Case 74-3, Question 3: What is the appropriate empiric therapy for M.C.?

Antibiotic therapy is often not required. Incision and drainage should be performed for all abscesses, large furuncles, and carbuncles.[2] Antibiotics may be considered as an adjunct to incision

and drainage when systemic inflammatory response syndrome is present but has not been shown to improve cure rates in patients with cutaneous abscess. Antibiotic therapy should be directed toward suspected CA-MRSA and based on the severity of infection. Mild-to-moderate infection can be adequately treated with doxycycline or sulfamethoxazole/trimethoprim, whereas more severe disease should be empirically treated with agents such as vancomycin, daptomycin, linezolid, telavancin, or ceftaroline.[2,14] Several newer agents have been approved for the treatment of drug-resistant *S. aureus* infections; however, their current role in clinical therapy is not yet clear. If treatment does not result in some resolution of inflammation within 48 hours, antimicrobial coverage should be expanded to cover gram-negative organisms and resistant streptococci.

ERYSIPELAS

Erysipelas is a superficial skin infection caused by streptococci, predominantly group A, although groups C and G (and group B in children) also may cause the infection.[15,16] This skin infection affects ~1 in 1000 persons/year and is associated with diabetes mellitus, chronic venous insufficiency, and cardiovascular disease.[16] Erysipelas is diagnosed based on characteristics of the skin lesion and concurrent systemic symptoms.[15] The lesion is a continuous, indurated, edematous area, with a clearly defined raised edge.[16] Early in the course, the lesion is bright red, but it may turn to brown as the lesion ages or grows. The initial lesion results from a small break in the skin that becomes infected, although signs of the initial wound often are not evident. Aspiration of the lesion or a superficial swab is not recommended because this has not been shown useful in detecting the pathogen.[15] Patients with erysipelas have associated systemic symptoms of high fever, chills, frequent history of rigors, and general malaise. This constellation of systemic symptoms differentiates erysipelas from other local skin disorders.

CASE 74-4

Question 1: D.D., a 70-year-old male, presents to the ED with a red, swollen face. He describes the area as "a swollen red spot" that has appeared during the past 2 days. He also describes feeling unwell for the previous 3 days and having a fever. On examination, D.D. has a bright red, shiny, edematous lesion on his right cheek that is 0.4 cm wide. It is a continuous lesion with a clearly demarcated border.

What antibiotic therapy should D.D. receive?

Erysipelas responds promptly to antibiotics with activity against group A streptococci.[17] Oral penicillin V 250 to 500 mg every 6 hours and in severe cases parenteral penicillin G (2–4 million units IV every 6 hours) generally reduce the systemic symptoms (eg, fever, malaise) within 24 to 48 hours[17]; however, it will take several more days for the skin lesion to resolve. If D.D.'s condition does not improve within 72 hours of initiation of antibiotics, he should be instructed to return for reassessment. If D.D. has an allergy to penicillins, then a macrolide, clindamycin, or an oral fluoroquinolone, such as moxifloxacin, is a reasonable alternative.[15],[17] Ceftriaxone may also be an alternative in patients who are allergic to penicillin (without anaphylaxis) because of low (<3%) cross-sensitivity risk.[18] If the community has increased macrolide resistance to group A streptococci, these agents should not be part of empiric therapy. Antibiotic therapy should be continued for 10 days even if signs and symptoms resolve quickly to avoid a relapse, which could lead to chronic infection or scarring.

SKIN AND SOFT TISSUE INFECTIONS IN DIABETES

Skin and soft tissue infections are common in patients with diabetes mellitus. Approximately 25% of patients with diabetes report a history of skin and soft tissue infections, and 5% to 15% of patients with diabetes may undergo limb amputation.[19] In addition to the cost

associated with treating skin and soft tissue infections, functional disability may occur, which can significantly decrease the patient's quality of life. Patients with diabetes are at particular risk for foot problems, primarily because of the neuropathies and peripheral vascular diseases associated with long-standing diabetes. The decreased pain sensation allows the patient to continue to bear weight in the presence of skin damage, thereby promoting the formation of an ulcer. In addition, minor trauma (eg, cuts, foreign body insertion) can go unnoticed and, when left untreated, can become infected and extensive. Although these infections are common, preventive measures could reduce the frequency of amputations. Mild infections can be treated empirically with those agents used for soft tissue infections in patients with diabetes because these are commonly caused by aerobic gram-positive cocci. In moderate-to-severe infections, antibiotic coverage should be expanded because multiple organisms may be responsible for the infection. Although it is often difficult to differentiate colonizers from true pathogens, an average of two to six organisms are cultured from foot ulcers in patients with diabetes.[19,20] The following organisms (in no particular order) have been isolated in >20% of diabetic wounds: *S. aureus, S. epidermidis,* other streptococci, *Enterococcus faecalis, Proteus* species, *E. coli, Klebsiella* species, *Peptococcus* species, *Peptostreptococcus* species, and *Bacteroides* species.[19] Although these infections are often polymicrobic, empiric treatment can be effective even if not all cultured pathogens are covered.[19] To determine the true pathogens in the wound most accurately, a specimen of infected deep tissue (vs superficial swab), or cultures of purulent exudate or curettage should be obtained after the wound has been cleaned.[18] Although antibiotics have an important role, drainage and surgical debridement to remove necrotic tissue are essential.[19] Although anaerobic organisms often are difficult to culture, they must be considered if an abscess or devitalized, necrotic, foul-smelling tissue is present.

CASE 74-5

Question 1: T.U. is a 67-year-old male with diabetes presenting to his general practitioner for a routine checkup and has no specific issues to report. T.U. has a 15-year history of poorly controlled type 2 diabetes and a 3-year history of recurrent foot ulcers. On examination, the physician observes that an ulcer on the underside of the foot, which had previously healed over, is open and inflamed; purulent fluid can be expressed from the wound. T.U. reports no pain around the area and was unaware that the ulcer had worsened. He is currently febrile, and physical examination reveals mild lymphadenopathy and elevated white blood cell count.

Does T.U. have an active infection, and is antibiotic therapy required?

All open wounds, in patients with diabetes and those without, will become colonized with bacteria, but only infected wounds should be treated with antibiotic therapy.[19],[20] Often, it is difficult to determine whether an open wound is infected, but signs and symptoms (eg, purulent drainage, erythema, pain, and swelling around the area) are suggestive of infection. Based on his symptoms, T.U. has an infection that requires treatment.

Case 74-5, Question 2: What treatment should T.U. receive?

Before initiating antibiotic therapy, the presence of a clinically infected wound must first be confirmed because often diabetic wounds may not be infected and thus do not require antimicrobial therapy. When determining appropriate antibiotic therapy for infected wounds, clinicians must consider the severity of infection (mild vs moderate to severe), the patient's risk factors for MRSA or *P. aeruginosa* or if the patient has received any antibiotics within the past month. Mild diabetic foot infections should not be treated with topical antibiotic preparations because of limited evidence of their efficacy, insufficient penetration of antibiotic into the tissues, and potential detriment to wound healing.[21] Mild infections can be treated empirically in a way similar to that of other soft tissue infections because these are commonly caused by aerobic gram-positive cocci.[19] A penicillinase-resistant penicillin (eg, dicloxacillin) or cephalexin will be effective in most cases. The choice between these

agents should be based on tolerability and cost. Alternative agents include clindamycin, amoxicillin/clavulanate, or levofloxacin. If anaerobes are suspected (based on malodorous aroma, if the infection is severe or long-standing or has recently been treated with antibiotics), clindamycin or amoxicillin/clavulanate monotherapy can be used, or metronidazole can be added to the regimen.[18] If metronidazole is selected, concurrent use of an antibiotic with good activity against aerobic pathogens is required (eg, levofloxacin) because metronidazole has no activity against aerobic bacteria. In patients with significant vascular compromise, crepitus (gas in the subcutaneous tissues), or gangrene (dead tissue), a radiograph should be taken to identify any bone involvement suggestive of osteomyelitis.

For treatment of moderate-to-severe infections, oral or parenteral antibiotics (IV recommended for severe) with a broad spectrum of activity against gram-positive and gram-negative organisms should be selected based on suspected organisms. For staphylococci, streptococci, and enterobacteriaceae, therapeutic options include levofloxacin, cefoxitin, ceftriaxone, ampicillin/sulbactam, moxifloxacin, ertapenem, and imipenem/cilastatin.[20],[21] Levofloxacin and ceftriaxone have no anaerobic coverage; thus, clindamycin or metronidazole should be added if anaerobes are suspected (ischemic or necrotic wounds).[22] It is important to consider that clindamycin may be more likely to cause *Clostridioides difficile*–associated diarrhea.

Antibiotic selection should include coverage against MRSA or *P. aeruginosa* when risk factors are present. Infections due to MRSA can be treated with vancomycin, daptomycin, or linezolid. Newer antibiotics, including dalbavancin, telavancin, oritavancin, ceftaroline, and delafloxacin have activity against MRSA skin and soft tissue infections, but there is a lack of efficacy data in diabetic foot infections.[23] Infections due to *P. aeruginosa* may be more common in patients in areas with high local prevalence, warmer climates, and frequent exposure of foot to water, and can be treated with piperacillin/tazobactam. Other antibiotics with activity against *P. aeruginosa* include cefepime, ceftazidime, aztreonam,

imipenem/cilastatin, meropenem, doripenem, or an antipseudomonal fluoroquinolone (eg, ciprofloxacin). Aminoglycosides are associated with serious toxicity if used for an extended period and should probably be avoided in patients with diabetes.

Because T.U. is an elderly patient with diabetes with systemic signs and symptoms of infection (moderate to severe), empiric therapy with cefoxitin, ceftriaxone, ampicillin/sulbactam, levofloxacin, moxifloxacin, or ertapenem would be appropriate because he does not have risk factors for MRSA or *P. aeruginosa* infection.

CASE 74-5, QUESTION 3: Despite aggressive antibiotic therapy and debridement, T.U.'s infection spreads, and an amputation is required. How long should antibiotics be prescribed for T.U. after surgery?

Antibiotics may be continued until signs and symptoms of infection have resolved. Typical treatment duration is 1 to 2 weeks; however, longer treatment duration (2–4 weeks) may be necessary in patients with moderate-to-severe infections or in patients with infections that are slow to resolve.[20] Oral therapy should be considered once the patient has clinically improved; treatment can be stopped even if the underlying ulcer has not completely healed.[18,20]

The best option for uncontrollable, life-threatening infections often is amputation to remove the infected area. Once the infected area has been removed, antibiotic therapy should be continued for 2 to 5 days.[20]

CASE 74-5, QUESTION 4: What measures could have been taken to prevent this complication in T.U.?

Many of the foot problems associated with diabetes can be prevented with proper foot care (**Table 74-2**), and these preventive measures must be emphasized. Patients with diabetes with neuropathies or those who are elderly should carefully examine their feet every 1 to 2 days.

Table 74-2

Foot Care for the Patient With Diabetes

Inspect feet daily for cuts, blisters, or scratches. Pay particular attention to the area between the toes and use a mirror to examine the bottom of the foot.
Wash feet daily in tepid water and dry thoroughly.
Apply lotion to feet to prevent calluses and cracking.
Ensure that shoes fit properly (not too tight or too loose) and inspect them daily.
Trim nails regularly, making sure to cut straight across the nail.
Do not walk barefoot.
Do not use chemical agents to remove corns or calluses.

Source: Schaper NC, van Netten JJ, Apelqvist J, et al. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diab Metab Res Rev*. 2020;36(suppl 1):e3266.

Necrotizing Soft Tissue Infections

Skin and soft tissue infections are described as *necrotizing* when the inflammation is rapidly progressing and necrosis of the skin or underlying tissue is present. The following clinical signs suggest necrotizing infections, as opposed to simple cellulitis: edema beyond the area of erythema, skin blisters or bullae, localized pallor or discoloration, crepitus, and the absence of lymphangitis and lymphadenitis. Common clinical features include high temperature, disorientation, lethargy, or the hard wood feel of the infected area.[2] Occasionally, a broad erythematous track along the route of infection may be present. Necrotizing soft tissue infections can progress rapidly, causing additional local effects (eg, necrosis and loss of skin sensation) and severe systemic effects (eg, hypotension, shock).[24] Necrotizing soft tissue infections are rare, with ~1000 cases/year in the United States, but they can be lethal.[25],[26] Necrotizing infections can occur in healthy individuals but are more commonly associated with IV or subcutaneous injections of illicit drugs.[27]

Necrotizing cellulitis involves the skin and subcutaneous tissues. Necrotizing fasciitis involves both superficial and deep fascia, and necrotizing infections involving the muscle are termed *myonecrosis.*

Group A β-hemolytic streptococci, *S. aureus,* other staphylococci, *Pseudomonas* species, other gram-negative organisms, *Clostridium perfringens, Peptostreptococcus*, *B. fragilis,* and *Vibrio* species can cause necrotizing infections.[24],[28] Gas gangrene is myonecrosis caused by a *Clostridium* subspecies, most commonly *C. perfringens* (70%).[24] Gas in a wound is not necessarily indicative of gas gangrene caused by *C. perfringens.* Gram-negative organisms (eg, *E. coli, Proteus* species, *Klebsiella* species) or anaerobic streptococci can produce gas in a wound. Air also could have been introduced at the time of the injury. Gas gangrene is characterized by acute onset of worsening pain that is usually out of proportion to the degree of injury. The primary treatment for necrotizing soft tissue infections involves extensive debridement of the area to remove all necrotic tissue and drainage. Early fluid resuscitation and broad-spectrum antibiotics are also imperative.[25]

CASE 74-6

QUESTION 1: M.T., a 45-year-old alcoholic homeless male, presents to the ED with a broken nose and facial lacerations, which he received after a fight outside one of the local taverns. On examination, in addition to the facial wounds, an area of severe inflammation, erythema, and necrosis is evident on his left calf. The area is very painful, crepitation is felt over the area, and a purulent discharge is present. M.T. states he believes the infection is because of a knife wound he experienced ~1 week ago.

What antibacterial treatment should be provided?

A Gram stain and culture of the purulent discharge should be ordered before initiating antimicrobial therapy. Because crepitus is present, the area should be incised, and a specimen of the infected tissue should be obtained for Gram stain and culture. Because the presence of crepitus may suggest a necrotizing infection, an immediate surgical consultation will be required for M.T. Pending the surgical evaluation, fluid resuscitation and IV antibiotics should be initiated. Gas in the tissues could be caused by many organisms, and empiric broad-spectrum antibiotic therapy with coverage against gram-positive organisms, enterobacteriaceae, and *B. fragilis* should

be started. Initial therapy should consist of an antibiotic with activity against MRSA (eg, vancomycin, daptomycin, or linezolid) plus either piperacillin/tazobactam, ampicillin/sulbactam, or ertapenem.[2] Clindamycin is often added for suspicion of group A streptococci, not for its antibacterial effects but because it inhibits protein synthesis, which may reduce toxin expression by the bacteria and cytokine response by the host.[2,29] Alternative options include ceftriaxone plus metronidazole, or a fluoroquinolone plus metronidazole. If a Gram stain of the infected tissue clearly shows the predominance of gram-positive cocci, consideration of narrowing the spectrum of antibiotic therapy is appropriate. Flesh-eating disease is usually a necrotizing fasciitis caused by virulent strains of group A streptococci. High-dose penicillin G (3 million units every 4 hours) plus clindamycin (900 mg IV every 8 hours) are the drugs of choice for this condition, as well as for gas clostridial myonecrosis.[2,29]

Potential adjunctive therapy for streptococcal necrotizing skin infections includes IV immunoglobulin G (IVIG) 2 g/kg as a single dose or 0.4 g/kg daily for 2 days. Alternative dosage regimens have included 1 g/kg on day 1 with 0.5 g/kg on days 2 and 3.[30] No clinical trials have proved the definitive benefit of IVIG, and the optimal dose, if used, is unknown. If it truly provides benefit, IVIG is thought to work by binding to the superantigens released by the streptococcal bacteria that are involved in the systemic effects of the infection.[30,31]

ANIMAL BITE WOUNDS

Any wound caused by an animal that results in the skin being cut or punctured should be examined to ensure no underlying tissue damage has occurred. This is especially true in patients with bites on the hand or around other joints. The wound should be washed thoroughly with clean water as soon as possible after the bite.[32] Irrigation of the wound, including puncture sites, should be extensive

to reduce the risk of infection. Obtaining specimens for cultures is not required, and wound irrigation should begin as soon as possible.

Animal bites may develop bacterial infections due to aerobic or anaerobic organisms in up to 18% of cases.[33] Purulent wounds or abscesses likely contain mixed aerobic and anaerobic organisms, whereas nonpurulent wounds are more frequently caused by streptococci or staphylococci.[2] *Pasteurella multocida* is a commonly isolated pathogen and is particularly significant in cat bites because it is present in up to 75% of the oral flora of cats.[2],[33] Although antibiotic treatment is not required for some dog bites, reports of a >75% incidence of infection after cat bites suggest that all patients with cat bites should receive antibiotics.[32]

CASE 74-7

QUESTION 1: P.J., an 18-year-old male, presents to the ED 3 hours after being bitten on the leg by a neighbor's dog. He has a laceration, 14 cm long, on his medial calf. Four distinct puncture marks, suggestive of teeth marks, also are present on the calf. P.J. was healthy before the attack and has no chronic illness.

Should P.J. receive any treatment other than suturing of his laceration?

The standard of care for all bites involves wound irrigation and decontamination of the wound.[32] P.J.'s wound should be evaluated for deep tissue injury, devascularization of any tissue, and bone injury. Loose suturing or closure with adhesive strips is appropriate for lacerations after irrigation.[32]

CASE 74-7, QUESTION 2: Because P.J. has several punctures that are difficult to irrigate, he is a candidate for prophylactic antibiotic therapy. Which antibiotic(s) should he receive?

The need for antibiotics is controversial and guided by wound severity and patient immunocompetency.[2],[33] The patient should receive a prophylactic course of antibiotics if the wound involves the hand or is near joints, if it involves deep punctures or is difficult to

irrigate, if the patient is immunocompromised (eg, diabetes, splenectomy), or if the wound is not well perfused. Antibiotics are not required for dog bites in which no deep tissue injury is present, and the wound can be well irrigated, particularly if the wound is on the lower extremities in healthy adults or children.[32]

The selection of the appropriate antibiotic is based on the most likely pathogens from the specific animal bite. Although *P. multocida* often is considered the primary pathogen of dog bites, antibiotic coverage also must address the other common pathogens. Monotherapy with amoxicillin/clavulanate 875/125 mg orally every 12 hours is recommended.[2],[32] Alternative options include second-generation cephalosporins (eg, cefuroxime plus an agent with anaerobic coverage such as clindamycin or metronidazole) or cefoxitin alone. If the patient is allergic to penicillin, doxycycline, moxifloxacin, or a carbapenem (eg, ertapenem) provides adequate coverage.[2] In all cases, patients should be instructed to watch for improvement; if the wound does not heal or it worsens within 48 hours, the patient needs to be reevaluated. Prophylactic antibiotic treatment should not extend beyond 5 days unless signs of an infection have occurred. If the patient presents with an established infection, parenteral therapy is warranted if the infection is over a joint, has lymphatic spread, or involves the hand or head. Parenteral therapy should be continued until the infection has resolved, and therapy should then be continued with oral antibiotics for at least 7 days or until all clinical signs of the infection have resolved.

Prophylaxis for rabies is required only if the animal is from an area with endemic rabies or if the bite was the result of an unprovoked attack by a wild animal.[32] The local health board should be contacted to determine the recent rabies risk in the area. In addition, immunization status of the animal should be obtained, if possible. If P.J. has not received a tetanus toxoid booster within the past 5 years, a booster should be administered. If P.J. has never been immunized for tetanus, tetanus immune globulin should be administered in addition to the tetanus toxoid.

HUMAN BITE WOUNDS

CASE 74-8

QUESTION 1: C.K., a 40-year-old male, presents with a sore arm 24 hours after receiving a bite to his left forearm by his neighbor in a "discussion over property boundaries." C.K. was previously healthy and has no chronic diseases. A 6 × 8 cm area of his left forearm is swollen and erythematous and includes several distinct puncture marks consistent with a human bite. No joint deformity or bone abnormality is detected on clinical examination.

How should C.K. be treated?

Treating a human bite is similar to that of any other laceration, including cleansing, irrigating, exploring, debriding, draining, excising, and suturing, as required.[32] All human bites should be cleansed as soon as possible, and any lacerations or punctures irrigated copiously. Surgical exploration with debridement, drainage, or excision should be undertaken in case of potential injury of deeper tissues or pus collection. If there is evidence of pus accumulation, the area should be explored and drained. C.K. should receive systemic antibiotic therapy to eradicate potential infecting organisms. If the wound is severe (ie, involves subcutaneous tissues, a joint, or a large area) or if the patient is unlikely to be compliant with oral antibiotics, parenteral administration of antibiotics is required. The most common pathogens in human bites are β-hemolytic streptococci, *S. aureus, Eikenella corrodens, Fusobacterium, Peptostreptococcus, Prevotella*, *Porphyromonas* spp., and *Corynebacterium* subspecies.[2] Treatment with amoxicillin/clavulanate, ampicillin/sulbactam, or ertapenem is appropriate. For patients who are allergic to penicillin, alternatives include ciprofloxacin or levofloxacin plus metronidazole or moxifloxacin alone.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Aziz H, Rhee P, Pandit V, Tang A, Gries L, Joseph B. The current concepts in management of animal (dog, cat, snake, scorpion) and human bite wounds. *J Trauma Acute Care Surg.* 2015;78:641–648. (33)

Bonnetblanc JM, Bedane C. Erysipelas: recognition and management. *Am J Clin Dermatol.* 2003;4:157–163. (15)

Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev*. 2010;(6):CD004299. (4)

Lipsky BA, Berendt AR, Cornia PB, et al. Clinical practice guidelines for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis.* 2012;54:e132–e173. (21)

Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011; 52:e18–e55. (5)

Matthews PC, Berendt AR, Lipsky BA. Clinical management of diabetic foot infection: diagnostics, therapeutics and the future. *Expert Rev Anti Infect Ther*. 2007;5:117–127. (19)

Moran GJ, Talan DA, Abrahamian FM. Antimicrobial prophylaxis for wounds and procedures in the emergency department. *Infect Dis Clin North Am*. 2008;22:117–143. (32)

Schaper NC, van Netten JJ, Apelqvist J, et al. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diab Metab Res Rev*. 2020;36(suppl 1):e3266. (23)

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Disease Society of America. *Clin Infect Dis*. 2014;59(2):e10–e52. (2)

COMPLETE REFERENCES CHAPTER 74 SKIN AND SOFT TISSUE INFECTIONS

1. Esposito S, Noviello S, Leone S. Epidemiology and microbiology of skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29:109–115.
2. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10–e52.
3. Moellering RC Jr. The growing menace of community-acquired methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med*. 2006;144:368–370.
4. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev*. 2010;(6):CD004299.
5. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
6. Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant *Staphylococcus aureus* infection. *Antimicrob Agents Chemother*. 2007;51:4044–4048.
7. Wells RD, Mason P, Roarty J, Dooley M. Comparison of initial antibiotic choice and treatment of cellulitis in the pre and post-community-acquired methicillin-resistant *Staphylococcus aureus* eras. *Am J Emerg Med*. 2009;27:436–439.
8. Madaras-Kelly KJ, Remington RE, Oliphant CM, Sloan KL, Bearden DT. Efficacy of oral beta-lactam versus non-beta-lactam treatment of uncomplicated cellulitis. *Am J Med*. 2008;121:419–425.
9. Khawcharoenporn T, Tice A. Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis. *Am J Med*. 2010;123: 942–950.
10. Jenkins TC, Sabel AL, Sarcone EE, Price CS, Mehler PS, Burman WJ. Skin and soft-tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship. *Clin Infect Dis*. 2010;51:895–903.
11. Pangilinan R, Tice A, Tillotson G. Topical antibiotic treatment for uncomplicated skin and skin structure infections: review of the literature. *Expert Rev Anti Infect Ther*. 2009;7(8):957–965.
12. Bergkvist PI, Sjobeck K. Antibiotic and prednisolone therapy of erysipelas: a randomized double blind placebo controlled study. *Scand J Infect Dis*. 1997;29:377–382.
13. Dall L, Peterson S, Simmons T, Dall A. Rapid resolution of cellulitis in patients managed with combination antibiotic and anti-inflammatory therapy. *Cutis*. 2005; 75:177–180.

14. Esposito S, Bassetti M, Concia E, et al. Diagnosis and management of skin and soft tissue infections (SSTI). A literature review and consensus statement: an update. *J Chemother*. 2017;29:197–214.
15. Bonnetblanc JM, Bedane C. Erysipelas: recognition and management. *Am J Clin Dermatol*. 2003;4:157–163.
16. Pereira de Godoy JM, Galacini Massari P, Yoshino Rosinha M, Marinelli Brandão R, Foroni Casas AL. Epidemiological data and comorbidities of 428 patients hospitalized with erysipelas. *Angiology*. 2010;61:492–494.
17. Bernard P. Management of common bacterial infections of the skin. *Curr Opin Infect Dis*. 2008;21:122–128.
18. Picard M, Robitaille G, Karam F, et al. Cross-reactivity to cephalosporins and carbapenems in penicillin-allergic patients: two systematic reviews and meta-analyses. *J Allergy Clin Immunol Pract.* 2019;7:2722–2738.
19. Matthews PC, Berendt AR, Lipsky BA. Clinical management of diabetic foot infection: diagnostics, therapeutics and the future. *Expert Rev Anti Infect Ther*. 2007; 5:117–127.
20. Grigoropoulou P, Eleftheriadon I, Jude EB, Tentolouris N. Diabetic foot infections: an update in diagnosis and management. *Curr Diab Rep*. 2017;17:3.
21. Lipsky BA, Berendt AR, Cornia PB, et al. Clinical practice guidelines for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:e132–e173.
22. Thurber EG, Kisuula F, Humbyrd C, Townsend J. Inpatient management of diabetic foot infections: a review of the guidelines for hospitalists. *J Hosp Med*. 2017;12:984–1000.
23. Schaper NC, van Netten JJ, Apelqvist J, et al. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diab Metab Res Rev*. 2020;36(suppl 1):e3266.
24. Kihiczak GG, Schwartz RA, Kapila R. Necrotizing fasciitis: a deadly infection. *J Eur Acad Dermatol Venereol*. 2006;20:365–369.
25. Stevens DL, Bryant AE. Necrotizing soft-tissue infections. *N Engl J Med*. 2017; 377:2253–2265.
26. Sarani B, Strong M, Pascual J, Schwab CW. Necrotizing fasciitis: current concepts and review of the literature. *J Am Coll Surg*. 2009;208:279–288.
27. Phan HH, Cocanour CS. Necrotizing soft tissue infections in the intensive care unit. *Crit Care Med*. 2010;38(suppl):S460–S468.
28. Wong CN, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO. Necrotizing fasciitis: clinical presentation, microbiology and determinants of mortality. *J Bone Joint Surg Am*. 2003;85(8):1454–1460.
29. Seal DV. Necrotizing fasciitis. *Curr Opin Infect Dis*. 2001;14:127–132.
30. Bonne SL, Kadri SS. Evaluation and management of necrotizing soft tissue infections. *Infect Dis Clin N Am*. 2017;31:497–511.

31. Johansson L, Thulin P, Low DE, Norrby-Teglund A. Getting under the skin: the immuno-pathogenesis of *Streptococcus pyogenes* deep tissue infections. *Clin Infect Dis*. 2010;51:58–65.
32. Moran GJ, Talan DA, Abrahamian FM. Antimicrobial prophylaxis for wounds and procedures in the emergency department. *Infect Dis Clin North Am*. 2008;22:117–143.
33. Aziz H, Rhee P, Pandit V, Tang A, Gries L, Joseph B. The current concepts in management of animal (dog, cat, snake, scorpion) and human bite wounds. *J Trauma Acute Care Surg*. 2015;78:641–648.

75

Prevention and Treatment of Infections in Neutropenic Cancer Patients

Richard H. Drew and Steven W. Johnson

CORE PRINCIPLES	CHAPTER CASES
DEFINITIONS	
1 As a consequence of select cancer chemotherapies, patients may experience neutropenia (defined as an absolute neutrophil count <500 cells/μL or anticipated to drop <500 cells/μL within 48 hours) and fever (defined as a single oral temperature of ≥101 °F [38.3 °C] or a temperature of ≥100.4 °F [38.0 °C] for >1 hour).	**Case 75-1 (Question 4)**
2 Bacteria are the primary pathogens associated with infection in patients with	**Case 75-1 (Questions 1, 6)**

	febrile neutropenia (especially those occurring early); however, fungal pathogens and reactivation of viruses may be a concern in select patient populations.	
CLINICAL PRESENTATION OF FEBRILE NEUTROPENIA		
1	Fever is usually the earliest (and often the only) sign of infection.	**Case 75-1 (Question 4)**
	A systematic assessment should be performed to maximize the chances of establishing a clinical and microbiologic diagnosis that may determine antimicrobial choice and prognosis.	**Case 75-1 (Question 5)**
2	Before antibiotics are initiated, two sets of blood cultures (with each set consisting of two culture bottles) should be obtained. Additional site-specific cultures should also be obtained if such infections are suspected. A complete blood count, comprehensive metabolic panel, coagulation, urinalysis, and assessment of organ function (eg, liver and kidney function) should be assessed.	**Case 75-1 (Question 5)**
KEY PREVENTION INFORMATION		
1	Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high-risk for febrile neutropenia or profound, protracted neutropenia (eg, most patients with	**Case 75-1 (Question 2)**

	acute myeloid leukemia/myelodysplastic syndrome [AML/MDS], or hematopoietic stem cell transplantation [HSCT] treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with solid tumors.	
2	Antifungal prophylaxis is recommended with an oral triazole or parenteral echinocandin for patients who are at high risk for febrile neutropenia or profound, protracted neutropenia. Antifungal prophylaxis is not routinely recommended for patients with solid tumors. The choice of the agent depends largely on the risk of mold infections.	**Case 75-1 (Question 3)**

KEY TREATMENT INFORMATION

1	Risk stratification should be undertaken to identify patients most likely to experience significant infection-related complications. Patients at highest risk include those with prolonged (>7 days) and profound (<100 cells/μL) neutropenia or select comorbidities (hypotension, severe mucositis interfering with swallowing or causing diarrhea, pneumonia, new-onset abdominal pain, hepatic or renal insufficiency, or neurologic changes).	**Case 75-1 (Question 7)**
2	In the absence of evidence of site- or pathogen-specific etiologies or clinical	**Case 75-1 (Questions 7–9)**

	instability, typical initial empiric therapy for high-risk individuals is monotherapy with an intravenous antipseudomonal β-lactam, such as cefepime, a carbapenem (eg, imipenem–cilastatin or meropenem) or piperacillin–tazobactam. Additional agents may be added (eg, vancomycin, an aminoglycoside, or fluoroquinolone) to initial therapy in high-risk patients for management of complications (eg, hemodynamically unstable, or pneumonia). Antiviral therapy is generally restricted to patients with serologic or clinical evidence of active viral infection. For low-risk individuals managed in the outpatient setting, consideration of an oral antibiotic regimen such as ciprofloxacin plus amoxicillin-clavulanate is commonly utilized. The first dose of empiric therapy should be administered within 1 hour of triage from initial presentation.	**Case 75-2 (Questions 1–5)** **Case 75-4 (Question 4)**
MONITORING PARAMETERS		
1	The need for (and timing of) modification of the initial empiric therapy is dependent on the risk group (ie, low vs high risk), establishment of an infection site or causative pathogen, persistence or resolution of fever, and clinical stability.	**Case 75-2 (Question 6)** **Case 75-4 (Question 3)**
2	Highest risk patients unresponsive to initial empiric antibacterial therapy	**Case 75-3 (Questions 1, 2)**

	should be considered for the addition of antifungal therapy at days 4 through 7. In addition to coverage for *Candida* species, highest risk patients with persistent or recurrent fever after 4 to 7 days of appropriate antibacterial therapy with prolonged (ie, >10 days) neutropenia should be considered for antimold therapy. Low-risk patients who are clinically stable do not routinely need antifungal therapy.	**Case 75-4 (Questions 1, 2, 4)**
THERAPEUTIC CONTROVERSIES		
1	Although hematopoietic colony-stimulating factors prevent neutropenia in high-risk patients with cancer, use of these agents as treatment of febrile neutropenia unresponsive to antibiotics remains controversial.	**Case 75-1 (Question 3)** **Case 75-4 (Question 5)**

INTRODUCTION

Many patients with both solid tumor and hematologic malignancies have had their lives prolonged through therapeutic advances in chemotherapy, immunotherapy, and hematologic stem cell transplantation (HSCT). Despite such advances, infectious complications continue to be a major cause of morbidity and mortality in these patients. Risk assessment, prevention, rapid detection, and effective management of infections, although a major challenge, can lead to improved outcomes in such immunocompromised hosts.[1,2]

This chapter focuses on infectious complications in patients with immunosuppression as a consequence of cancer. The following

topics are addressed: risks and epidemiology of infection, principles of prophylactic antimicrobials, empiric initial antibacterial selection, modification and duration of therapy, empiric antifungal and antiviral use, and the use of hematopoietic growth factors.

RISK FACTORS FOR INFECTION

Patients are rendered immunocompromised when there is a significant disruption or deficiency of one or more of the host defenses as a result of the underlying disease or chemotherapy. These risk factors include neutropenia and impairment in both humoral (antibody and complement) and cell-mediated immune defenses. In addition, disruption of barriers to infection resulting from chemotherapy-related damage to skin and mucosal barriers further increases the risk of infection. As a result, bacteria, fungi, and (less commonly) protozoa and viruses may infect various sites depending on the specific immunodeficiency.

Neutropenia

Granulocytes, or granular leukocytes, represent an important defense against bacterial and fungal infections. *Neutropenia* (a reduction in the number of circulating granulocytes or neutrophils) predisposes the host to infections. The terms *granulocytopenia* and *neutropenia* are often used interchangeably. The degree of neutropenia is expressed in terms of the absolute neutrophil count (ANC) or the total number of granulocytes (polymorphonuclear leukocytes [PMNs] and band forms) present in the circulating pool of white blood cells (WBCs). For purposes of guideline development and clinical trials, neutropenia is most commonly defined as an ANC <500 cells/μL or <1000 cells/μL with an anticipated drop to <500 cells/μL within 48 hours.[3],[4] The risk, severity, and type of infection in the patient with neutropenia is proportional to the severity, rate of decline, and duration of neutropenia.[5] In general, the relative risk of

infection is low when the ANC is >1000 cells/μL, with the frequency and severity of infection inversely proportional to the ANC. As the ANC drops to <500 cells/μL, the risk of infection rapidly increases.[5,6] Conversely, recovery of the ANC is one of the most important factors determining the outcome of infectious complications in the patient with neutropenia. Febrile patients with short durations of neutropenia (≤7 days) or in whom neutropenia is not severe (<100 cells/μL) less frequently experience serious, life-threatening infections.[1,7] In contrast, patients with severe neutropenia lasting >7 days are at significant risk for infection.[1]

Damage to Physical Barriers

The intact skins and mucosal surfaces of the body (gastrointestinal [GI], sinus, pulmonary, and genitourinary) constitute the host's primary physical defense against microbial invasion. The integrity of this physical barrier may be disrupted by tumor, treatment (eg, surgery, radiation), or various medical procedures (eg, insertion of intravenous [IV] or urinary catheters, venipuncture, measurement of rectal temperature). Device-related infections, including those associated with central venous catheters, are commonly caused by migration of skin flora (eg, staphylococci) through the cutaneous insertion site. Infections secondary to damaged mucosal lining of the GI tract such as mucositis (usually secondary to chemotherapy or graft-versus-host disease [GVHD]) are usually caused by enteric bacteria and fungi such as *Candida* species.

Malignancy-Related Alterations in the Immune System

Malignancies such as leukemia (acute and chronic), lymphoma (eg, non-Hodgkin lymphoma) and myelodysplastic syndrome (MDS) may invade bone marrow, resulting in leukopenia. This is most notable in patients with advanced or refractory malignancy, which may reflect either bone marrow invasion or as a consequence of multiple

courses of immunosuppressive chemotherapy. In contrast, predisposition to infection in patients with solid tumors is often associated with anatomic abnormalities (eg, obstruction or erosion). Such risks may be enhanced as a consequence of surgery, chemotherapy, and/or radiation to correct the underlying tumor.

Patients with immunoglobulin (Ig) deficiencies (eg, hypogammaglobulinemia, chronic lymphocytic leukemia [CLL], or splenectomy) are at increased risk for infections with encapsulated bacteria, which undergo antibody opsonization for efficient phagocytosis. Such bacteria include *Neisseria meningitidis, Haemophilus influenzae*, and *Streptococcus pneumoniae*. Hodgkin's disease, organ transplantation, and human immunodeficiency virus (HIV) disease can disrupt the cellular immune system, increasing the risk of infections with obligate and facultative intracellular organisms such as mycobacteria, *Listeria*, *Toxoplasma*, viruses, and fungi. Certain hematologic malignancies and MDSs may also be associated with immunodeficiencies secondary to replacement of leukocytes with malignant cells.

Medications Impacting Host Defenses

Some chemotherapeutic agents (eg, fludarabine) have profound effects on both cellular and humoral defenses.[8,9] Corticosteroids exert their immunosuppressive effects on the cellular immune system, particularly at the T-lymphocyte and macrophage levels. Therefore, patients receiving corticosteroids (eg, HSCT recipients with GVHD) have increased susceptibility to viral, bacterial, protozoal, and fungal infections.[10] Infectious complications secondary to glucocorticoids are dose dependent. The risk of infection increases with daily doses >10 mg or cumulative doses >700 mg of prednisone or its equivalent.[10] Thus, patients receiving corticosteroids in either high doses (>20 mg prednisone or its equivalent daily) or for prolonged periods are at increased risk for infections caused by opportunistic pathogens. In addition, corticosteroids may blunt the usual signs of infection such as fever

and inflammation. Severe cell-mediated immunodeficiency may also be caused by GVHD and its treatment.[1,8] Chemotherapeutic monoclonal options (eg, alemtuzumab) significantly weaken the immune system, predisposing recipients to viral, bacterial, and fungal infections.[11,12]

Colonization or Prior Infection

Colonization is characterized as isolation of an organism from any particular site (eg, stool, nasopharynx) without clinical signs of infection. Most infections in patients with neutropenia are caused by either the host's endogenous microflora or hospital-acquired pathogens that have colonized the alimentary tract, upper respiratory tract, or skin. Therefore, microbial colonization can be a prerequisite to infection in patients with neutropenia. This is perhaps best studied in patients colonized with methicillin-resistant *Staphylococcus aureus* (MRSA). Prior infection (especially in the pre-engraftment phase of HSCT recipients) is a risk factor for infection during immunosuppression, particularly for viral infections (eg, cytomegalovirus [CMV], herpes simplex virus [HSV], and varicella zoster virus [VZV]). Infections with these pathogens during immunosuppression are generally considered to be a consequence of latent infection rather than of new infection.[1,2,8]

Hematopoietic Stem Cell Transplantation

Transplantation of bone marrow predisposes patients to the development of opportunistic infections secondary to both intensive immunosuppressive therapy and transmission.[8] These infections may be acquired or may represent reactivation of latent host infection. The introduction of new therapeutic approaches for treatment of the underlying malignancy (including nucleoside analogs and monoclonal antibodies to CD20 and CD52), along with use of unrelated stem cell donors, has increased the potential for infections in these patients.[8] When compared with autologous or

syngeneic HSCT recipients, patients with allogeneic HSCT have an increased risk of infection, particularly in those undergoing therapy for GVHD.[8] The pathogens causing infections vary with the time since transplantation. The use of immunosuppressives after transplantation (eg, corticosteroids, antithymocyte globulin, and alemtuzumab) also significantly increases the risk of infection.[8]

Radiation Therapy

Side effects associated with the use of radiation therapy for the treatment of malignancy (eg, mucositis, skin breakdown, or reduction in blood counts) also predispose a patient with neutropenia to infection.

Functional Asplenia

The spleen is responsible for the production of opsonizing antibodies, assisting in protection against encapsulated bacteria (eg, *S. pneumoniae, H. influenzae,* and *N. meningitidis*). Functional asplenia may occur secondary to irradiation or as a complication of GVHD.

MOST COMMON PATHOGENS

CASE 75-1

Question 1: B.C., a 41-year-old female, was admitted to the cancer center for placement of a central IV catheter for administration of chemotherapy to treat acute nonlymphocytic leukemia in relapse. She was diagnosed 2 years ago and was treated with cytarabine plus daunorubicin, which resulted in a complete remission for 33 months. This admission, she will be treated with high-dose cytarabine plus mitoxantrone for reinduction.

What are the most likely pathogens to cause infection in patients such as B.C. during periods of chemotherapy-induced neutropenia?

Bacteria are the primary pathogens associated with infection in patients with febrile neutropenia, especially those occurring early.[13] Bacteremia, reported in ~25% of patients with febrile neutropenia, is most often caused by aerobic gram-negative bacilli (including *Pseudomonas aeruginosa, Escherichia coli,* and *Klebsiella pneumoniae*) or aerobic gram-positive cocci (ie, coagulase-negative staphylococci, *S. aureus,* enterococci, viridans streptococci).[14] Since the mid-1990s, the proportion of gram-negative infections has decreased with a proportional increase in gram-positive infections.[1] Gram-positive bacteria now account for ~60% to 70% of microbiologically documented infections in neutropenic cancer patients.[3],[15] This is likely attributable (in part) to the frequent use of indwelling IV catheters, intensive chemotherapy, and widespread use of broad-spectrum antibiotics.

S. aureus (including MRSA) and coagulase-negative staphylococci, streptococci (including *S. pneumoniae* and viridans streptococci), and *Corynebacterium* species are increasingly important pathogens.[15] Moreover, enterococcal infections (including vancomycin-resistant enterococci [VRE]) are increasing in frequency. Meningitis caused by the intracellular organism *Listeria monocytogenes* can be observed in patients with defective cellular immunity caused by disease or prolonged corticosteroid use. In general, anaerobic bacteria are an infrequent cause of infection in patients with granulocytopenia having hematologic malignancies.[16] However, they should be suspected in patients with GI malignancies or with significant disruption of the GI tract.[16] *Clostridioides difficile* is another anaerobic pathogen that may cause infection in this population.

Pneumocystis jiroveci (formerly known as *Pneumocystis carinii* that causes *Pneumocystis carinii* pneumonia or PCP [now *Pneumocystis jiroveci* pneumonia or PJP]) is a pathogen responsible for lung infections primarily in patients with HIV infection. However, PJP can also be responsible for lung infections in some patients with cancer.[17],[18] Seen predominantly in patients with solid tumors or hematologic malignancies receiving long-term corticosteroids, PJP

may present as subacute, febrile, hypoxemic, and diffuse pulmonary involvement.[17],[18]

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality among neutropenic cancer patients and patients undergoing HSCT.[19] The incidence of IFIs in patients with febrile neutropenia varies widely because of differences in definitions, methods of detection, patient populations, and prior use of antifungal prophylaxis. In general, patients with hematologic malignancies have a higher incidence of fungal infections than do those with solid tumors.[20] Similar to the risk of bacterial infections, the risk of IFIs is also related to the degree and duration of neutropenia. IFIs tend to occur later in the illness. Patients with prolonged neutropenia (>7 days) or with AML undergoing intensive induction therapy, allogeneic HSCT recipients, and those undergoing therapy for GVHD are at increased risk for acquiring systemic fungal infections.[19],[21] Up to 50% of patients who die during prolonged periods of neutropenia have evidence of deep-seated mycoses.[19] Before the use of fluconazole prophylaxis in selected populations, *Candida* species were responsible for most IFIs. Most fungal infections in neutropenic cancer patients are caused by *Candida* and *Aspergillus* species.[22–24] In addition to the risk factors mentioned earlier, specific risk factors for mold infections include, but are not limited to, older age, cytopenias, CVM disease, and iron overload. Other less common but important pathogenic fungi are those associated with zygomycosis (eg, *Mucor* and *Rhizopus* species) and other emerging pathogens (non-albicans *Candida, Trichosporon beigelii, Malassezia* species, *Cryptococcus neoformans,* and *Fusarium* species).[22–24] Today, invasive infections attributable to *Aspergillus* species and other molds are a major cause of IFI-related death (particularly in those with prolonged neutropenia and GVHD).[19],[25] Recent reports of improved survival from IFIs are likely related to newer prophylactic and treatment options and advances in cancer chemotherapy.[26]

As previously stated, most viral infections in neutropenic cancer patients are caused by a reactivation of latent infection rather than a new infection.[1],[2],[8] These may include hepatitis B virus (HBV), HSV, and VZV. Other viruses, such as CMV, can be either reactivation or

newly acquired during HSCT. The risk of viral reactivation in these patients increases in those who are seropositive before transplant. Respiratory viruses (eg, respiratory syncytial virus [RSV], influenza, parainfluenza), GI viruses (eg, rotavirus and norovirus), and other seasonal viruses may occasionally cause infection in this population.

STRATIFICATION FOR RISK OF INFECTION

Risk stratification to identify patients most likely to experience neutropenia has important implications for decisions about prevention, diagnostic strategies, empiric therapy (selection, route of administration, duration), and site of care.[1,8,27,28] In general, the underlying malignancy, status of disease (ie, active vs remission), degree and duration of neutropenia, and chemotherapy type (including select immune targeting agents) impact both risk intensity and pathogen(s). Patients at highest risk for complications include those with prolonged (>7 days) and profound (<100 cells/μL) neutropenia or with select comorbidities (hypotension, severe mucositis interfering with swallowing or causing diarrhea, pneumonia, new-onset abdominal pain, hepatic or renal insufficiency, or neurologic changes).[4] In contrast, patients with shorter (≤7 days) anticipated durations of neutropenia without significant comorbidities are generally considered at low risk for complications of infection.[2,4] Patients without fever but exhibiting new signs of infection should also be treated as high risk. Presenting signs and symptoms, cancer type, chemotherapy regimen, medical comorbidities, and prior history of febrile neutropenia (especially if severe or prolonged) should also be considered. Chemotherapeutic regimens associated with the highest (>20%) incidence are summarized in detail elsewhere[28] (see Section 16, Hematology and Oncology).

The factors impacting risk have been utilized by the consensus guidelines in assigning infection risk in patients with cancer as low, intermediate, and high. Other risk assessment tools have been

proposed,[1,2] including the Multinational Association for Supportive Care in Cancer (MASCC) Index.[29] Age of at least 60 years, presence of hematologic malignancies with a history of prior fungal infections, severe symptoms (particularly hypotension), inpatient site of care, organ dysfunction (hepatic and renal), and presence of chronic obstructive pulmonary disease are important variables that result in a low MASCC score (ie, <21), and (consequently) patients with any of these factors are considered at highest risk. Young patients (younger than 20 years) with solid tumors and no or mild symptoms (including the absence of hypotension) or organ dysfunction are generally at low risk for complications.

PROPHYLAXIS AGAINST INFECTION

Infection Control

CASE 75-1, QUESTION 2: Should B.C. receive antimicrobial prophylaxis during the neutropenic period? If yes, which agents should be used?

Exogenous contamination can be prevented by strict protective isolation of patients in specially designed rooms that maintain a sterile environment. These laminar airflow rooms are ventilated with air that is passed through a high-efficiency particulate air filter, which removes >99% of all particles >3 μm. Total protective isolation is accomplished by strict isolation in conjunction with the administration of sterile food and water, local skin care, and intensive microbial surveillance. However, this regimen is burdensome, difficult to accomplish, and expensive, and is recommended only for high-risk patients (ie, allogeneic HSCT recipients).[4] HSCT recipients and candidates undergoing conditioning therapy should avoid exposure to plants, flowers, and certain foods (eg, uncooked fruits and vegetables), which increase the risk of exposure to fungi.[8,30] Close attention and adherence to adequate handwashing procedures is

essential. In addition, contact isolation is advocated in circumstances in which the patient may be colonized or infected with resistant organisms (eg, MRSA, VRE, or multidrug-resistant gram-negative pathogens). Finally, isolating the patients from family or caregivers with potentially contagious respiratory viral illnesses is advocated.[27]

Antimicrobial Prophylaxis

Early administration of antimicrobials (ie, antibacterials, antifungals, and antivirals) during the afebrile, neutropenic period in select high-risk patients may result in a reduction in the number of febrile episodes and subsequent risk of infection. The goals of such prophylactic regimens are intended to reduce pathogenic endogenous microflora or prevent the acquisition of new microorganisms. The potential benefits of such prophylaxis must outweigh the risks of antimicrobial-related adverse effects including drug interactions, the development of resistance (including multidrug resistance most notable with antibacterials), disruption of the gut microbiome and the potential for superinfection. Use of agents for prophylaxis (ie, fluoroquinolones) may also preclude the use of the class as empiric therapy for subsequent suspected or documented infections.

In general, lowest risk patients with cancer (ie, those receiving standard chemotherapy for many solid tumors and whose neutropenia is anticipated to be <7 days) should not routinely receive antibacterial and antifungal prophylaxis.[27] Prophylactic administration of antivirals in such patients is generally restricted to those with a history of prior infection (eg, HSV). In contrast, highest risk patients (eg, allogeneic HSCT recipients and those with acute leukemia, receipt of alemtuzumab therapy, GVHD requiring high-dose steroids, and prolonged [>10 days] neutropenia) should receive antibacterial, antifungal, and (in select cases) antiviral prophylaxis.[27] PJP prophylaxis should also be considered in these patients.

ANTIFUNGALS

Case 75-1, Question 3: Should antifungal prophylaxis be used in B.C.? What is the role of hematopoietic growth factors?

The use of primary antifungal prophylaxis in patients with cancer having neutropenia should be reserved for those at intermediate or high risk for IFIs.[27] Patients with acute lymphocytic leukemia (ALL) receiving remission or salvage induction chemotherapy are at intermediate risk and should be considered for prophylaxis. Although autologous HSCT recipients may not routinely benefit from fungal prophylaxis (most notably those without evidence of mucositis), those with prolonged neutropenia, mucosal damage, or receipt of purine analogs should receive primary prophylaxis.[8] In patients for whom antifungal prophylaxis is indicated, the choice of the agent depends largely on the additional risk of invasive mold infection (eg, patients with AML/MDS, or those with GVHD receiving intensive immunosuppressive therapy regardless of neutropenia). Acceptable options for prophylaxis against *Candida* species include fluconazole and the echinocandin, micafungin (although caspofungin and anidulafungin would be considered interchangeable).[27] In the setting of colonization with fluconazole-resistant *Candida* species (ie, *C. krusei or C. glabrata*), an echinocandin is preferred.[8,27,31] In contrast, patients with higher risk factors for mold infections should be considered for prophylaxis with mold-active drugs (ie, posaconazole, voriconazole, echinocandins, or [less commonly] amphotericin B) during periods of risk.[8,27] Mold-active agents are also recommended in the setting of anticipated periods of prolonged (at least 2 weeks) neutropenia, or prolonged neutropenia immediately before HSCT.[27] Prophylactic use of antifungals may also be used in patients with a prior history of invasive disease due to *Candida* spp. or filamentous fungi. Such prevention (known as *secondary prophylaxis*) should be considered in these patients during subsequent chemotherapy or stem cell transplantation for the duration of immunosuppression.

Nonabsorbable antifungal agents

Nonabsorbable antifungal agents, such as oral nystatin,[32,33] clotrimazole,[34] and oral amphotericin B[35] have been studied. Although oral amphotericin B and clotrimazole reduce the frequency of oropharyngeal candidiasis, none of these antifungals has a role as primary prophylaxis in IFIs.[8] In attempts to enhance activity while minimizing side effects associated with IV administration, aerosolized delivery of amphotericin B deoxycholate (AmBd) has been investigated for the prevention of IFIs in this patient population,[36] and aerosolized liposomal amphotericin B (LAmB) has been used in patients with leukemia and HSCT.[37] Although promising, the optimal dose, delivery device, and duration of aerosol administration of amphotericin B preparations have not yet been determined.

Amphotericin B

The use of systemic antifungals for prophylaxis has been summarized elsewhere.[38] Many of the earlier studies evaluated the prophylactic role of IV amphotericin B.[39–41] In general, use of AmBd is limited in this setting because of its toxicities (ie, infusion-related reactions, nephrotoxicity, and electrolyte disturbances) relative to available options for prophylaxis. Consequently, amphotericin B is generally discouraged for primary prophylaxis in high-risk patients, unless the patient is unable to receive other mold-active prophylactic agents. If required, a lipid-based formulation would be preferred, especially in patients at increased risk for amphotericin B–induced nephrotoxicity.

Systemic azole antifungals

Systemic azole antifungals (eg, fluconazole, itraconazole, voriconazole, posaconazole) may also be considered in select patients, but differ considerably in their spectrum of activity, adverse reaction profile, drug interactions, and need for serum concentration monitoring. The newest member of this ciass, isavuconazole, represents potential advantages over comparator agents. Isavuconazole, approved for the treatment of invasive aspergillosis

and mucormycosis, is now considered an option for IFI prevention in patients undergoing allogeneic HSCT at intermediate or high risk of IFI.[42–44]

Fluconazole prophylaxis decreases the frequency of both superficial (eg, oropharyngeal candidiasis) and systemic fungal infections in HSCT recipients[45,46] but not in patients with leukemia.[7,47,48] Fluconazole is available as both oral and IV formulations, and its oral bioavailability is not significantly influenced by changes in gastric acidity. The IV formulation enables fluconazole to be administered to critically ill patients or patients who have difficulty swallowing. Relative to the alternate systemic azoles (itraconazole, voriconazole, and posaconazole), fluconazole is a less potent inhibitor of cytochrome P450 3A4 isoenzymes that may interact with select chemotherapeutic agents (such as vincristine). Historically, among the triazoles, fluconazole offers the most favorable pharmacokinetic profile (now challenged with the addition of isavuconazole). Fluconazole administration results in a predictable serum concentration, unlike other triazoles, which exhibit significant variability in drug concentration, most notably following oral administration. Consequently, serum concentration monitoring of these agents (itraconazole, voriconazole, posaconazole) may help ensure optimal drug exposure while reducing the potential for concentration-related toxicities. However, determination of definitive target concentrations for prophylactic use is hampered by the lack of controlled, prospective clinical trials. For itraconazole, steady-state trough concentrations of >0.5 μg/mL have been recommended. Voriconazole steady-state serum concentrations of >0.5–4 μg/mL have been recommended for use as prophylaxis. Studies regarding the optimal trough concentration of posaconazole for prophylaxis differ, but range between 0.5 and 0.7 μg/mL.[49,50] Adverse effects associated with fluconazole, similar to that of other triazoles include GI (nausea, vomiting, hepatic enzyme elevations) and cardiovascular (ie, QTc prolongation [shortening for isavuconazole]) effects. Although fluconazole is useful prophylactically, concern about its lack of reliable in vitro activity against molds limits its use in intermediate- and high-risk patients (notably those with neutropenia

and MDS, AML, or GVHD). An increased frequency of isolation of non-albicans *Candida* (eg, *C. krusei, C. glabrata, and C. parapsilosis*) has also been noted in some institutions.[51]

Itraconazole has been well studied as an antifungal prophylaxis. In addition to in vitro activity against many *Candida* species (eg, *C. albicans*), itraconazole is active in vitro against *Aspergillus* species and reduces systemic *Candida* infections.[52–54] Although itraconazole oral solution demonstrates improved bioavailability over the capsule formulation, it is associated with significant GI intolerance.[55],[56] Itraconazole is contraindicated in patients with reduced cardiac ejection fraction because of its negative inotropic effect. Use of newer azoles (such as posaconazole and voriconazole) has largely replaced the use of itraconazole for prophylaxis in patients at increased risk for mold infections.

Voriconazole's use as antifungal prophylaxis in patients with cancer at increased risk for mold infections is not well supported by clinical data despite its established use in the treatment of invasive aspergillosis.[57],[58] Side effects (most notably hepatotoxicity, rash, and phototoxicity) and the increased potential (relative to other azoles and the echinocandins) for drug interactions with voriconazole may limit its prophylactic use to patients at highest risk for mold infections. Similar to IV posaconazole, the use of IV voriconazole should be avoided in patients with significant renal impairment because of the potential toxicity of the vehicle. Oral voriconazole should be administered either 1 hour before or after a meal to optimize its absorption.

Posaconazole has demonstrated improved survival, a reduction in proven or probable IFI, and a reduction in invasive aspergillosis when compared with standard prophylaxis (either itraconazole or fluconazole) for the prevention of fungal infection in patients undergoing chemotherapy for AML or MDS.[59] Posaconazole was also effective prophylaxis in allogeneic HSCT recipients undergoing therapy for GVHD.[60] Posaconazole is currently available in both oral (solution and tablet) and parenteral (IV) formulations. The oral solution has been largely replaced by the tablet formulation because of its improved bioavailability and reduced dependency on the need

for coadministration with high-fat meals for optimal absorption.[61,62] Absorption of oral posaconazole may be reduced in patients with mucositis and in patients receiving acid-suppressing therapy.[63] In addition, the use of IV posaconazole is not recommended in patients with significant renal impairment because of the potential toxicity of the vehicle, betadex sulfobutyl ether sodium (SBECD).

Echinocandins

The echinocandins (eg, caspofungin, micafungin, and anidulafungin) may be useful as a prophylactic strategy in high-risk patients. Micafungin has been compared with fluconazole in autologous and allogeneic HSCT recipients.[31] Based on a composite endpoint (which included absence of breakthrough fungal infection and absence of empiric modifications to the antifungal regimen owing to neutropenic fever), micafungin was found to be superior. Although breakthrough candidemia, survival, and adverse events were similar in both groups, a trend toward a reduction in invasive aspergillosis in the allogeneic HSCT population was noted in the micafungin group. Micafungin is currently U.S. Food and Drug Administration (FDA) approved for the prevention of *Candida* infections in HSCT patients.

DURATION OF PROPHYLACTIC ANTIFUNGALS

Prophylaxis is generally continued during the period of neutropenia. In those with acute leukemia, MDS, or in autologous HSCT recipients, prophylaxis should continue until day 75 after transplant or through induction therapy for patients with leukemia.[64] Patients with a history of documented *Aspergillus* infection undergoing intensive chemotherapy should be considered for voriconazole.[8] Although the addition of a second prophylaxis (eg, echinocandin) may be considered, the benefits of combination therapy for secondary prophylaxis are unknown. Those patients with GVHD should continue prophylaxis until GVHD-related symptoms resolve.

NONABSORBABLE ANTIBACTERIALS

Because the GI tract is an important reservoir of potential pathogens, gut decontamination has been investigated.[15] However, the use of nonabsorbable antibacterial agents has been replaced by oral, absorbable antibiotics.[27]

ABSORBABLE (SYSTEMIC) ANTIBACTERIALS

The use of antibiotic prophylaxis is recommended for patients who are at high risk for febrile neutropenia or profound, protracted neutropenia (eg, AML/MDS), or HSCT treated with myeloablative conditioning regimens. Antibiotic prophylaxis is not routinely recommended for patients with solid tumors.

Trimethoprim–sulfamethoxazole

Although trimethoprim–sulfamethoxazole (TMP-SMX) decreases bacterial infections in patients with neutropenia,[65],[66] it may not reduce mortality in this patient population. The potential benefits of TMP-SMX prophylaxis must be carefully balanced against the potential for drug-induced bone marrow suppression, hypersensitivity reactions, hyperkalemia, nephrotoxicity, pancreatitis, the emergence of resistant organisms (eg, *E. coli*), and the development of superinfections. In addition, patients with leukemia receiving mucotoxic chemotherapy and TMP-SMX prophylaxis may be at increased risk for infections caused by viridans streptococci.[67],[68] However, TMP-SMX prevents PJP in patient populations with ALL and in those undergoing HSCT. Patients with malignancy at highest risk for experiencing PJP (ie, patients with ALL receiving intensive chemotherapy), allogeneic HSCT recipients, and those receiving alemtuzumab or phosphoinositide 3-kinase inhibitors (eg, alpelisib, idelalisib, copanlisib, and duvelisib) with or without rituximab or prolonged/high-dose corticosteroids (>20 mg of prednisone or its equivalent daily for ≥4 weeks) or temozolomide with radiation therapy should receive TMP-SMX prophylaxis.[8] Recipients of T-cell–depleting agents (eg, fludarabine or cladribine) and autologous HSCT recipients should also be considered for prophylaxis with TMP-SMX. In such settings, primary prevention should be continued

for up to 6 months (in the case of HSCT recipients) or longer (in cases in which immunosuppression is continued). In the setting of alemtuzumab therapy, such prophylaxis would generally continue for at least 2 months and until the CD4 count exceeded 200 cells/μL.[3] In patients requiring PJP prophylaxis but unable to tolerate TMP-SMX, patients should receive alternate prophylaxis with either atovaquone, dapsone, or pentamidine (either IV or via aerosol).[8] TMP-SMX is a preferred therapy for the prevention of PJP; however, it may be considered for use as primary prophylaxis for other typical microorganisms when unable to use a fluoroquinolone.

Fluoroquinolones

The fluoroquinolones ciprofloxacin and levofloxacin are used by some centers as prophylaxis for adult patients at high risk for infection.[69],[70] Of concern, however, is the increasing frequency of gram-positive infections (including viridans streptococci) and resistant gram-negative bacilli (most notable in *P. aeruginosa* and *E. coli*)[71] in patients receiving fluoroquinolone prophylaxis.[67],[68],[72],[73] Meta-analyses report reductions in mortality in high-risk patients receiving prophylaxis with these fluoroquinolones.[69],[74] Because fluoroquinolone prophylaxis is offset by the emergence of resistant organisms, routine prophylactic use in low-risk patients should generally be avoided.[27] However, those at intermediate or high-risk for bacterial infections (ie, those patients with an ANC ≤100 neutrophils/μL for >7 days) should be considered for fluoroquinolone prophylaxis until either the onset of fever (at which time empiric antibacterials would be started) or resolution of severe neutropenia.[27] Levofloxacin is preferred over ciprofloxacin in patients with or at increased risk for oral mucositis–related infection because of the potential of invasive viridans streptococci.[4] Regardless of the fluoroquinolone chosen, local resistance patterns should be closely monitored before such prophylaxis is chosen.

Penicillin

Because of the increased risk of invasive pneumococcal infections, select patient populations (notably patients with asplenia, allogeneic HSCT recipients [owing to functional asplenia and impaired B-cell immunity], and those undergoing immunosuppression for GVHD) should be considered for prophylaxis with penicillin. In patients with chronic GVHD, penicillin prophylaxis may be continued during the administration of immunosuppressive agents. In HSCT recipients, prophylaxis should begin 3 months after transplant and continue for 1 year after transplant. Alternative prophylaxis (eg, TMP-SMX) should be considered in areas where penicillin resistance in pneumococci is significant.

ANTIVIRALS

Most HSV disease in patients with cancer is a consequence of reactivation from latent infection. High-risk patients (eg, seropositive for HSV undergoing allogeneic HSCT or induction or reinduction therapy for acute leukemia, or has GVHD requiring steroid treatment, or a patient receiving alemtuzumab therapy) or intermediate-risk patients (eg, seropositive for HSV and undergoing autologous HSCT; or a patient with lymphoma, multiple myeloma, and CLL; or receiving purine analog therapy [eg, fludarabine]); or low-risk patients previously requiring treatment for HSV reactivation should be given antiviral prophylaxis. Both oral or IV acyclovir and oral valacyclovir are appropriate initial choices in most patients. Published data for famciclovir for this indication are lacking. Those receiving foscarnet or ganciclovir (most commonly for prevention and treatment of CMV infection) do not require additional prophylaxis for HSV, given the activity of these against Herpes simplex. Prophylaxis should be administered during periods of neutropenia, and for at least 1 month after HSCT.[27] The duration may be extended in those undergoing allogeneic HSCT with GVHD. Patients receiving alemtuzumab may also require extended prophylaxis of up to 2 months after completion of therapy or recovery of $CD4^+$ cell counts >200 cells/μL, whichever is later.

Similar to HSV, VZV in patients with cancer is most commonly reactivation. HSCT patients who are seropositive for VZV should also be given long-term prophylaxis (6–12 months for autologous HSCT and at least 1 year for allogeneic HSCT), particularly with receipt of either bortezomib or alemtuzumab. Extending prophylaxis in allogeneic HSCT patients should be considered in the setting of continued immunosuppressive therapy. As with HSV, patients receiving alemtuzumab may also require extended prophylaxis of up to 2 months after completion of therapy or recovery of $CD4^+$ cell counts >200 cells/μL, whichever is later. Patients receiving proteasome inhibitors (eg, bortezomib, carfilzomib, ixazomib) should also receive VZV prophylaxis during active therapy including periods of neutropenia. Agents active against HSV are also useful for VZV prevention. In one study, low-dose (ie, 500 mg/day three times weekly) valacyclovir prophylaxis after a 35-day course of IV acyclovir is safe and effective in allogeneic HSCT recipients.[75]

CMV infections frequently occur in patients with cancer who undergo allogeneic HSCT or who receive alemtuzumab. Infection may result from reactivation (immunocompromised, CMV-seropositive individuals) or primary infection (CMV-seronegative individuals). The highest risk of CMV reactivation occurs in individuals undergoing allogeneic HSCT who are CMV seropositive before transplant. Allogeneic HSCT recipients should undergo a surveillance period (typically for at least 1–6 months after transplant in donor or recipient CMV IgG seropositive cases or GVHD requiring therapy) and should be considered for primary antiviral prophylaxis with letermovir. CMV surveillance consists of weekly monitoring by polymerase chain reaction (PCR). CMV surveillance is also recommended for individuals receiving alemtuzumab for a minimum of 2 months after therapy. Preemptive CMV therapy (administration of antiviral agents to asymptomatic patients with laboratory markers of viremia to prevent CMV disease) is recommended in high-risk individuals for at least 2 weeks and until CMV is no longer detected. Preferred preemptive therapy includes valganciclovir (orally [PO]) or ganciclovir (IV). Foscarnet (IV) or cidofovir (IV) are generally reserved as second-line agents for preemptive therapy (such as in

the setting of ganciclovir-resistant CMV or neutropenia secondary to ganciclovir).[76–80] Letermovir is not indicated for preemptive therapy or treatment of CMV. Furthermore, letermovir does not have activity against other herpes group viruses (HSV or VZV). Therefore, acyclovir is also needed in such patients. Maribavir is a new antiviral agent currently approved for solid organ transplant recipients with CMV infection refractory to ganciclovir/valganciclovir, foscarnet, and cidofovir. It lacks activity against HSV, VZV, or HHV-6.

Patients with prior infections with HBV or hepatitis C virus (HCV) can experience reactivation of infection secondary to immunosuppressive therapy. Reactivation of infection can occur in patients infected with HBV undergoing immunosuppressive therapy (most notably in allogeneic HSCT recipients or those receiving B-cell depleting therapy). Therefore, serologic screening (utilizing testing for hepatitis B surface antigen [HBsAg] and hepatitis B core antibody [HBcAb]) is generally performed in patients at increased risk for infection. Prophylaxis should be considered in patients with positive test results. Patients with one or more of these screening test results that are positive often undergo further testing for active viral replication (utilizing a quantitative PCR test for HBV DNA). Preemptive therapy should be considered in patients with evidence of viral replication. Entecavir and tenofovir are considered preferred options and have largely replaced lamivudine monotherapy in such settings because of the high incidence of viral resistance.

Respiratory tract infections caused by RSV, influenza, and parainfluenza are less commonly observed in patients with neutropenia. Although response to influenza virus vaccine may be attenuated, patients undergoing cancer treatment should receive annual vaccinations with inactivated influenza vaccine. Whenever possible, the timing of such vaccinations may be best between cycles (>7 days after or >2 weeks before the next treatment). In contrast, immunocompromised patients should not receive the intranasal live virus vaccine.

Hematopoietic Growth Factors

Hematopoietic colony-stimulating factors (CSFs) such as granulocyte colony-stimulating factor (G-CSF; filgrastim or tbo-filgrastim), pegylated G-CSF (pegfilgrastim), or granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) are important adjuncts in patients with cancer.[81] Since 2009, several biosimilar G-CSFs have been approved (eg, filgrastim-sndz, filgrastim-aafi, pegfilgrastim-jmdb, pegfilgrastim-cbqv, and pegfilgrastim-bmez). Studies in patients with cancer receiving myelosuppressive or myeloablative chemotherapy have demonstrated that concurrent prophylactic use of the CSFs can reduce the incidence, duration, and severity of neutropenia.

Risk factors for neutropenia include age (ie, older than 65 years), medical history (including prior history of febrile neutropenic episodes, nutritional status, unstable comorbidities, and presence of active infections), disease characteristics (especially those involving the bone marrow resulting in cytopenias), and myelotoxicity of the regimen (including both chemotherapy and radiation) used to treat the underlying malignancy.[9],[28],[81] Many studies have shown that the prophylactic use of hematopoietic growth factors (more specifically G-CSF) reduces the incidence of chemotherapy-induced febrile neutropenia.[9],[28],[81] However, routine use of CSFs for the prevention of febrile neutropenia is discouraged in patients at low risk (<10%) for febrile neutropenia. Use as primary prophylaxis in patients at high risk (>20%) for fever and neutropenia is recommended. In addition, some guidelines also recommend the administration of CSFs for primary prevention for patients 65 years or older with diffuse aggressive lymphoma treated with curative chemotherapy (especially in the setting of significant comorbidities and in those receiving select dose-dense chemotherapy regimens). Although the benefits of CSFs are less clear in patients at intermediate risk (10%–20% risk of febrile neutropenia), they should be considered on a case-by-case basis. CSFs are generally avoided as prophylaxis in patients undergoing radiation therapy concomitant with chemotherapy because of the potential for thrombocytopenia[82] or reductions in tumor response.[83] Administration is generally continued 3 to 4 days after chemotherapy administration and continued until a

sufficient and stable post-nadir ANC recovery is established. Pegylated G-CSF may be preferred in some settings owing to the convenience of single administration.[28,84]

Consideration of the use of CSFs as secondary prophylaxis (ie, prevention of febrile neutropenia in patients undergoing second or subsequent cycles of chemotherapy) should be based on repeated assessments of patient risk of febrile neutropenia. Patients experiencing prior episodes of febrile neutropenia or neutropenia limiting the dose of chemotherapy without prior CSFs should be considered for secondary prophylaxis.

Other Agents

Although beyond the scope of this chapter, select vaccinations have also been recommended for both autologous and allogeneic HSCT recipients (primarily caused by a decline in antibody titers to many vaccine-preventable diseases).[8] These include (but are not limited to) administration of pneumococcal, influenza virus, and *H. influenzae* vaccines. Live vaccinations should be avoided in this population. However, because immune response may be altered immediately after transplant, delays of up to 3 months after cessation of immunosuppressive chemotherapy is recommended for many vaccines. This is most notable in patients receiving consolidation therapy for acute leukemia. Data regarding the safe use of vaccines in patients with cancer receiving immunostimulants are sparse. In addition, serologic testing of antibody response is recommended in selected settings.[8]

Although data to support use are limited, intravenous immunoglobulins (IVIGs) have been recommended for HSCT recipients with severe hypogammaglobulinemia (ie, serum IgG level <400 mg/dL) and recurrent infections.[8] IVIGs have been used as adjuncts in the prevention and treatment of CMV infections. In contrast, granulocyte transfusions have not been proved to be effective in either prevention or treatment of infection in the neutropenic cancer patient.[85]

INFECTIONS IN NEUTROPENIC CANCER PATIENTS

Clinical Signs and Symptoms

Case 75-1, Question 4: Seven days after completing chemotherapy, B.C. experienced a fever of 102 °F (38.9 °C; orally). Vital signs are blood pressure, 109/70 mm Hg; pulse, 102 beats/minute; and respirations, 25 breaths/minute. Physical examination demonstrates a clear oropharynx without exudates or plaques. Chest and cardiac examinations are normal. The exit site for the Hickman catheter is clean and nontender without signs of erythema or induration. The perineum and rectum are nontender, and no masses are noted. Laboratory data are as follows:

Hematocrit, 20%
Hemoglobin, 7 g/dL
WBC count, 1400 cells/μL, with 3% PMNs, 1% band forms, 70% lymphocytes, and 22% monocytes
Platelet count, 17,000 cells/L
Blood glucose, 160 mg/dL
Serum creatinine (SCr), 1.1 mg/dL
Blood urea nitrogen (BUN), 24 mg/dL

What are the signs and symptoms of infection in B.C.? What are the most common sites and sources of infection in patients such as B.C.?

B.C. has an ANC of 48 cells/μL (1400 WBCs/μL × [0.03 PMNs + 0.01 bands]) and is therefore at high risk for infection.

Fever in patients with neutropenia is defined as a single oral temperature of at least 101 °F (38.3 °C) or an oral temperature of at least 100.4 °F (38.0 °C) for >1 hour in the absence of an obvious cause.[4] It is the earliest (and often the only) sign of infection in patients with neutropenia, because typical signs can be modified or absent in this patient population. However, only 50% to 60% of patients with febrile neutropenia have occult or documented infections. Noninfectious sources of fever in the neutropenic cancer patient include inflammation, tumor progression, tumor lysis, adverse drug reactions, and transfusion reactions.[2,86] Signs and symptoms

consistent with a diagnosis of infection without fever should be considered to be infection in the neutropenic host until proved otherwise.

In patients with documented infections, the most common sites are skin, mouth, throat, esophagus, sinuses, abdomen, rectum, liver, vascular access, lungs, and urinary tract.[87] Although the lung is the most common site of serious infection in neutropenic cancer patients, fever and dry cough are often the only presenting signs of pneumonia.[87] The impaired inflammatory response results in scant sputum production, and sputum Gram stains often contain few PMNs. Radiologic evidence of a pulmonary infection can be minimal or absent, and the chest examination is frequently not diagnostic.[88] Pneumonia is associated with high mortality in patients with neutropenia, particularly in the setting of bacteremia. In the presence of shock, a mortality rate of ~80% has been observed in these patients.[89]

Invasive procedures such as venipuncture, central IV catheter placement (eg, Hickman catheter), and skin biopsies are associated with cellulitis and systemic infections. However, the typical signs and symptoms of infection (eg, pain, heat, erythema, and swelling) are often absent in part owing to inadequate granulocytes.[87] Colonization of these lesions may result in local infection and the potential for systemic dissemination of bacteria and fungi. Bacteremia occurs primarily from entry of bacteria through the skin or through unrecognized ulcerations in the GI and perirectal areas.

Confirmation of Infection

Case 75-1, Question 5: How can a suspected infection be confirmed in patients such as B.C.?

Because of the frequent lack of “typical” physical signs and symptoms of infection, an accurate history (including the cancer type and treatment regimen, new signs of infection, antimicrobial prophylaxis, prior infections, and comorbidities) should be obtained

and a thorough physical examination performed at the first sign of fever. Further procedures generally depend on the level of infection risk and its complications (low vs high risk [refer to section on Initial Empiric Antibiotic Selection for details]). A detailed search for subtle signs and symptoms of inflammation at the most common sites, such as the oropharynx, bone marrow aspiration sites, lung, periodontium, skin, vascular catheter access sites, nail beds, and perineum (including the anus) is necessary. Before antibiotics are initiated, two sets of blood cultures (with each set consisting of two culture bottles) should be obtained if possible, but should not delay the start of antibiotics if the patient is clinically unstable.[2,4] In patients with indwelling central venous catheters, one of the two sets of blood cultures should be obtained from the catheter to help rule out catheter-related infection.[4] Diarrheal stools may be tested for the presence of *C. difficile*. Additional Gram stain and cultures (eg, stool, urine, skin, IV site, respiratory specimens) should be obtained depending on signs and symptoms. The yield from such cultures, however, may be affected by the prior or concurrent administration of prophylaxis.[3] Chest radiographs and oximetry should be obtained in the presence of respiratory symptoms.[4] Respiratory virus testing should take place for patients with upper respiratory tract infection symptoms (ie, coryza) or cough.[4] In settings in which pulmonary aspergillosis is suspected, further radiologic evaluations (such as computed tomography scans) should be considered.[25] A complete blood count, comprehensive metabolic panel, coagulation, C-reactive protein, urinalysis, and assessment of organ function (eg, liver and kidney function) should be obtained to assist in drug dosing and to establish baseline values to monitor for treatment-related toxicities.[2]

Recent advances have been made in nonculture-based diagnostic tests that help support (or, in some cases, eliminate) the diagnosis of infection in these patients.[90] Such biomarkers include C-reactive protein[91–93] and procalcitonin.[93–95] However, these tests are not routinely ordered, and their role in the treatment of the neutropenic cancer patient has not yet been established.[2] Galactomannan

(specific for aspergillosis)[96] and β-D-glucan testing may assist in the diagnosis of fungal infections.[97],[98] Serial galactomannan testing has also been used preemptively to initiate antifungal therapy before overt signs and symptoms of IFIs occur.[99] In addition to other issues regarding sensitivity and specificity of these assays, both galactomannan and β-D-glucan are affected by prior or current receipt of antifungals.[25] At present, the use of these tests should be restricted to persistent fever despite other etiologic investigations.[4]

Significance of Colonization

Case 75-1, Question 6: Routine surveillance cultures of swabs taken from B.C.'s axillae, nasopharynx, and rectum grew *Corynebacterium jeikeium* (axillae), *S. aureus* (axillae and nasopharynx), and *Enterococcus faecium* (rectum). What is the significance of these culture results? Should routine, serial surveillance cultures be performed in patients such as B.C.?

Several factors influence the colonization and subsequent infection by microorganisms in patients with cancer. Organisms isolated from infected patients can be found in endogenous flora or acquired during hospitalization. Factors leading to colonization include staff-to-staff and patient-to-patient transmission (eg, lack of frequent and adequate hand hygiene), direct transmission from the environment (eg, inadequately disinfected bathtubs, sinks, toilet bowls), foods (eg, raw fruits and vegetables), inhalation from contaminated fomites (eg, respirators, ventilating systems), and IV access devices. In addition to immunosuppression, the underlying malignancy and associated chemotherapy diminish the resistance of the patient with cancer to colonization and infection.

The acquisition of and subsequent colonization by potentially pathogenic microbes may be detected by serial surveillance cultures of specimens obtained from various body sites such as the nasopharynx, axilla, and rectum, besides from urine. Such surveillance cultures may be useful for infection control purposes. However, little clinically useful information is gained in the absence

of infection. Therefore, routine use of surveillance cultures is generally restricted to select patients for infection control purposes. In such cases, culture of the anterior nares (for MRSA) or rectal samples (for VRE or multidrug-resistant gram-negative bacilli) may be performed.

In summary, B.C.'s surveillance culture results indicate that she is colonized with several potential pathogens associated with infection in the immunocompromised host, but these results are probably not useful in selecting empiric antibiotics for her fever.

EMPIRIC ANTIBIOTIC THERAPY

Rationale

Case 75-1, Question 7: Should B.C. be started on antibiotic therapy immediately considering that neither the source of her fever nor the pathogen has been established?

Neutropenic cancer patients with fever and/or other signs and symptoms of infection should undergo prompt risk assessment and initiation of antibiotic therapy. Once culture results are obtained, these patients should be emergently started on broad-spectrum antibacterials (within 1 hour of triage). Prompt institution should not be delayed if culture results cannot be obtained. Early studies confirmed high mortality in patients with neutropenia with untreated gram-negative infections up to 24 to 48 hours after the onset of fever. Crude mortality rates secondary to *P. aeruginosa* bacteremia approached 91%.[6] Prompt use of empiric, broad-spectrum antibiotics has resulted in significant reductions in infectious mortality rates.

Initial Empiric Antibiotic Regimens

Case 75-1, Question 8: What pathogen- and patient-specific factors should be considered when initiating empiric therapy for B.C.?

Consensus guidelines prepared by the Infectious Diseases Society of America[2,4] and the European Society of Medical Oncology[1] identify antimicrobial options for the treatment of fever in the neutropenic cancer patient. The ideal antibiotic regimen for empiric management in this setting (ie, those without evidence of site- or pathogen-specific infections) remains controversial. Determination of patient risk of infection aids in determining the site of care and (therefore) the therapeutic options for management. High-risk patients are those with an MASCC Risk Index score <21 or a clinical index of stable febrile neutropenia (CISNE) score ≥3, inpatient status at the time of development of fever, significant medical comorbidity or clinically unstable, allogeneic HSCT, anticipated prolonged severe neutropenia, hepatic insufficiency, renal insufficiency, uncontrolled/progressive cancer, pneumonia or other complex infections at clinical presentation, receiving alemtuzumab, or mucositis grades 3 to 4. These patients generally receive IV therapy in a hospitalized setting. In contrast, low-risk patients are generally characterized by outpatient status at time of development of fever, no associated acute comorbid illness, anticipated short duration of severe neutropenia, good performance status (Eastern Cooperative Oncology Group [ECOG] 0–1), no hepatic or renal insufficiency, an MASCC Risk-Index Score of ≥21 or a CISNE score of <3) and may be candidates for oral therapy at home or in alternate care settings (such as an ambulatory clinic).

In addition to the assessment of a patient's risk factor for infection, selecting an initial empiric regimen for a given patient should take into account likely pathogens, infection site–specific antibiotic efficacy, and institutional susceptibility patterns. This point is especially true in areas experiencing a growing frequency of multidrug-resistant organisms, such as MRSA, VRE, and extended-spectrum β-lactamase (ESBL)-producing organisms (such as *K. pneumoniae* and *E. coli*).[100] Additional patient-related considerations

should include allergies and prior and concomitant antimicrobials. Finally, dosing schedules, acquisition costs, and the potential for significant toxicities should be considered. In addition to broad-spectrum activity, antibacterial regimens should be bactericidal against the infecting pathogen. However, no adequately controlled comparative trials of bacteriostatic versus bactericidal antibiotics have been conducted in humans.

Optimal Antibacterial Spectrum

Case 75-1, Question 9: Given the lack of site-specific signs and symptoms of infection, what would be a reasonable initial empiric antibiotic regimen for B.C.?

Despite continued development in antibacterial drugs, the empiric management of patients with febrile neutropenia is complicated by the changing spectrum of bacterial pathogens and their antimicrobial susceptibilities. Empiric antibiotic regimens should provide broad-spectrum coverage against the potential gram-negative bacilli most commonly isolated from neutropenic cancer patients (eg, *E. coli, K. pneumoniae, P. aeruginosa*), staphylococci, and viridans streptococci. Because mortality from untreated bacteremia caused by *P. aeruginosa* is so high,[6] empiric regimens have traditionally included antimicrobials with antipseudomonal activity.

In summary, many organisms, including those recovered from surveillance cultures, may be pathogens in B.C. Those associated with a high mortality rate during the first 48 hours should be empirically treated pending culture and sensitivity results. Therefore, an empiric regimen with optimal activity against commonly isolated gram-negative bacilli (including *P. aeruginosa*) should be promptly administered to B.C.

ORAL ANTIBIOTICS

Carefully selected (ie, low risk) adult patients with febrile neutropenia may be candidates for oral antibiotic therapy, either as initial therapy

or as follow-up to IV antibiotics (sequential therapy).[1,2,101–103] Patients must be able to tolerate oral medications. In general, patients considered for oral therapy must be without microbiologic or clinical evidence of infection (other than fever), clinically stable, and closely observed. Patients with severe (ANC <100 cells/μL), or lasting anticipated >7 days, or those receiving prior fluoroquinolone prophylaxis would not be eligible. This would also exclude patients with any of the following: serious comorbidities, inpatient acquisition of infection, uncontrolled malignancy, pneumonia, recent HSCT, dehydration, hypotension, chronic lung disease, abnormal liver (more than three times the upper limit of normal) or renal function (SCr >2 mg/dL), or signs and symptoms lasting >7 days.[2] An international collaborative study established and validated a risk scoring system in adults that incorporated these principles to identify low-risk patients for whom oral therapy may be an option.[29]

Cefixime has been used effectively as an alternative regimen in low-risk pediatric patients initially receiving IV therapy,[104] but there is not adequate experience to recommend it at this time. It also lacks activity against *Pseudomonas*. Fluoroquinolone-containing regimens have been the mainstay of most oral regimens used in this setting. Patients already receiving fluoroquinolones as prophylaxis should be excluded from receiving this regimen. Oral ciprofloxacin (500–750 mg every 12 hours) in combination with amoxicillin–clavulanate (875 mg administered every 12 hours) is useful in low-risk adult patients with febrile neutropenia[105,106] and is the most commonly used oral regimen.[2] Oral levofloxacin may be used in place of ciprofloxacin, and oral clindamycin may be used in place of amoxicillin–clavulanate if the patient is allergic to β-lactam antibiotics. More recently, moxifloxacin has been evaluated in this patient population and demonstrates efficacy comparable to combination regimens containing ciprofloxacin.[107,108] Both levofloxacin and moxifloxacin demonstrate superior activity in vitro when compared to ciprofloxacin against *S. pneumoniae.* Although moxifloxacin permits simplification of the regimen, it lacks activity against *Pseudomonas.* Therefore, levofloxacin is generally the preferred fluoroquinolone in such

settings. Moxifloxacin use should be restricted to patients at low risk for pseudomonal infections.

Low-risk patients with adequate home support (eg, access to emergency facilities, phone access) and the desire for home treatment may be treated as outpatients (with either IV or oral therapy). Therapy is usually initiated in a clinic or hospital setting.[2] Monitoring in the outpatient setting should include either home nursing or office visits daily for 3 days to review progress and to screen for problems. Patients who are stable and responding after the initial observation period may continue to receive monitoring by phone contact.

Continued administration of antimicrobials in the outpatient setting initiated as an inpatient has been suggested in a subset of low-risk patients. The criteria used to define eligibility for outpatient therapy are generally similar to those established and previously discussed for oral therapy. Therefore, continued outpatient administration of parenteral antibiotics can be considered in a subset of low-risk patients with close medical follow-up.[2]

INTRAVENOUS MONOTHERAPY

High-risk patients requiring IV therapy are often candidates for monotherapy regimens, including an antipseudomonal β-lactam such as a fourth-generation cephalosporin (eg, cefepime), or a carbapenem (eg, imipenem–cilastatin or meropenem).[2] Initial, empiric use of additional antibiotics (eg, fluoroquinolones, aminoglycosides, and vancomycin) may be added for patients who are clinically unstable.[2] For patients with severe β-lactam allergies, the use of vancomycin plus aztreonam may be considered. Alternative initial empiric parenteral regimens (excluding those containing vancomycin) have been investigated in this patient population.[1,2,4,86] However, because no significant differences exist among any of these empiric approaches, monotherapy is employed and recommended in most patients. There are no convincing data to support one choice over the others as empiric monotherapy.

Antipseudomonal cephalosporins

Although ceftazidime monotherapy has been found to be as effective as is combination therapy, its efficacy as monotherapy in patients with documented staphylococcal and streptococcal infections was suboptimal. Select clinical trials have empirically added antistaphylococcal coverage with a glycopeptide (eg, vancomycin) and have shown improved outcomes in these patients. In addition, pathogens (particularly gram-negative pathogens) that produce either type 1 β-lactamase or ESBL (eg, *K. pneumoniae*) are not likely to respond to ceftazidime monotherapy. These organisms are more likely with prolonged hospitalization or receipt of antimicrobial therapy. Local in vitro susceptibilities of common gram-negative pathogens should be examined before the routine use of ceftazidime as monotherapy. Therefore, despite extensive experience for use as empiric treatment of fever in patients with neutropenia, concerns with weak gram-positive coverage and breakthrough infections limit its utility and therefore is no longer generally considered a preferred monotherapy agent given the availability of alternate effective and well-tolerated monotherapy options.[2]

Cefepime is a fourth-generation cephalosporin with an FDA-approved indication for monotherapy for empiric management of infection in patients with febrile neutropenia. The potential advantage of this agent compared with third-generation cephalosporins is its low affinity for major chromosomally mediated β-lactamases. Compared with ceftazidime, cefepime has more potent activity in vitro against select gram-positive bacteria (methicillin-susceptible *Staphylococcus* species, viridans streptococci, and *S. pneumonia*e). Similar to ceftazidime, numerous randomized, comparative studies have evaluated the role of cefepime as monotherapy in both adults and children with febrile neutropenia. The improved gram-positive activity (relative to ceftazidime) may decrease the empiric need for vancomycin in some patients. However, this advantage is less likely in institutions with a high rate of MRSA because cefepime and other cephalosporins (with the exception of ceftaroline) are inactive against this pathogen. Although a meta-analysis published in 2007

suggested increased all-cause mortality in patients with neutropenia treated empirically with cefepime,[109],[110] subsequent analysis by the FDA concluded that no such differences existed when compared with control patients.

Carbapenems

The carbapenems are a unique class of antibiotics with broad-spectrum activity against numerous gram-positive and gram-negative bacteria, including anaerobes. In addition, carbapenems may be used in the setting in which the patient is at increased risk for ESBL-producing gram-negative pathogens (such as *K. pneumoniae* or *E. coli*). Agents with increased anaerobic activity (including carbapenems) might be used as empiric therapy in cases in which an intra-abdominal infection is suspected. Imipenem (in combination with the dehydropeptidase inhibitor cilastatin) and meropenem are two currently available agents in this class that have been studied as monotherapy for patients with febrile neutropenia.

Clinical outcomes with imipenem–cilastatin monotherapy have been comparable with those of the β-lactam plus aminoglycoside combinations. Although effective, imipenem–cilastatin has generally been associated with a higher incidence of nausea and vomiting compared with ceftazidime or meropenem.[111],[112] The GI side effects are generally dose related (3–4 g/day) and associated with the rate of IV administration. Therefore, dosages of 2 g/day (divided every 6 hours) are generally given to patients with normal renal function.

Meropenem monotherapy for febrile neutropenia has been evaluated in both adults and children, and the results have supported the value of meropenem as empiric monotherapy for use in patients with febrile neutropenia. Meropenem may have advantages over imipenem–cilastatin in the treatment of central nervous system infections (owing to less associated seizure activity).

Although ertapenem possesses microbiologic activity comparable to that of the other carbapenems, it lacks in vitro activity against *Acinetobacter* species and *Pseudomonas,* including *P. aeruginosa.*

Therefore, ertapenem would not be appropriate as empiric therapy for patients with febrile neutropenia.

Routine carbapenem use may be associated with increased drug acquisition cost (relative to cephalosporins) and increased potential for the development of carbapenem resistance. Therefore, many institutions have elected to reserve the carbapenems for patients who have failed to respond to prior empiric therapy, have a history of infections with pathogens resistant to fourth-generation cephalosporins, are clinically unstable, or have need for expanded anaerobic coverage.

β-Lactam/β-lactamase inhibitors

Randomized trials have compared piperacillin–tazobactam monotherapy to various antibiotics. Published trials have documented that piperacillin–tazobactam is not inferior to cefepime in this patient population.[113],[114] Although experience with this agent as monotherapy is limited relative to that for the antipseudomonal carbapenems and antipseudomonal cephalosporins, it is considered to be an adequate choice for monotherapy.[2] Higher doses of piperacillin–tazobactam (ie, 3.375 g IV every 4 hours or 4.5 g IV every 6 hours in adult patients with normal renal function) should be used because of the risk of pseudomonal infections. More recently, many institutions utilize an extended-infusion protocol for the administration of piperacillin–tazobactam (ie, 4.5 g IV infused over 3–4 hours every 8 hours) to maximize its time-dependent effects. Piperacillin–tazobactam may interfere with the galactomannan assay used in the diagnosis of select IFIs, including aspergillosis.

INITIAL ANTIBACTERIAL COMBINATIONS (EXCLUDING VANCOMYCIN)

CASE 75-2

QUESTION 1: B.L., a 13-year-old male, presented with a 3-week history of "always being tired" and a persistent sore throat. Initial evaluation revealed anemia, thrombocytopenia, and a WBC count of 130,000 cells/L, with a

predominance of immature lymphoblasts. Further evaluation demonstrated that B.L. had high-risk ALL. Remission induction treatment was initiated with teniposide plus cytarabine followed by prednisone, vincristine, and L-asparaginase. Seven days after induction chemotherapy, B.L. experienced a fever of 102 °F (38.89 °C) and chills. The ANC was 48 cells/μL. SCr and BUN were 1.0 and 15 mg/dL, respectively. The physician wants to empirically start B.L. on cefepime plus gentamicin combination regimen.

What is the role of this combination in the empiric management of febrile neutropenia? Are there any differences in efficacy between these combinations?

Before the introduction of third- and fourth-generation cephalosporins and carbapenems, the empiric use of antibacterial combinations in febrile neutropenic cancer patients was favored because these regimens offered a broader spectrum of activity against bacteria commonly infecting patients with cancer.[115] In addition, these combinations offered the potential for an expanded empiric coverage.[115],[116] However, infections in patients with neutropenia have shifted largely from gram-negative to gram-positive pathogens, for which these traditional combination regimens have limited efficacy. Despite this concern, some clinicians continue to favor antibiotic combinations as initial empiric therapy, especially in patients who are clinically unstable or at increased risk for multidrug-resistant pathogens. Until the 1980s, most patients with febrile neutropenia were treated with two-drug combination regimens that contained an aminoglycoside (gentamicin, tobramycin, or amikacin) plus a β-lactam antibiotic, such as antipseudomonal penicillin, or a third-generation cephalosporin. This combination is one of the most established empiric treatment regimens for the management of febrile neutropenia.

Numerous studies have been conducted to evaluate the efficacy of combination therapy of an aminoglycoside with an antipseudomonal cephalosporin (ceftazidime and cefepime). Antipseudomonal penicillins plus β-lactamase inhibitors (in combination with an aminoglycoside) would also be considered a comparable regimen. A better outcome was demonstrated with full-course amikacin plus ceftazidime than with a short course (3 days) of amikacin plus a full

course of ceftazidime.[117] However, the longer course of the aminoglycoside is likely to be associated with more toxicity.

Because carbapenem antibiotics are more frequently evaluated as monotherapy in this patient population, there are limited studies examining the combination of an aminoglycoside with either imipenem–cilastatin or meropenem. However, in one such evaluation, the combination of imipenem–cilastatin plus amikacin was found to be superior to imipenem–cilastatin monotherapy.[118] Carbapenems (in combination with aminoglycosides and vancomycin) have been recommended as empiric initial therapy for patients who are clinically unstable.

Aminoglycosides have generally been considered the backbone of combination regimens because of their potential for bactericidal action against various bacteria. However, the addition of an aminoglycoside is associated with increased costs for therapeutic monitoring. The benefit of an aminoglycoside for empiric therapy has not been consistently demonstrated.[118,119] In addition, there is an increased potential for the development of nephrotoxicity and ototoxicity.[119] This concern is especially relevant in patients receiving concomitant nephrotoxins (such as cisplatin and cyclosporine).

In summary, the use of initial empiric therapy with combination antibiotic therapy is generally reserved for patients who are clinically unstable (eg, hypotension, tachycardia, tachypnea, mental status changes). In such settings, IV therapy with an antipseudomonal β-lactam is generally combined with an aminoglycoside and vancomycin. Therefore, B.L. may be treated with IV cefepime monotherapy. The addition of an aminoglycoside may not have an additional benefit and may increase the risk of harm by causing significant adverse effects.

Case 75-2, Question 2: Seven days into therapy, despite rehydration, B.L.'s SCr and BUN rose to 2.0 g/dL and 45 mg/dL, respectively. Because B.L. has nephrotoxicity (believed to be secondary to the aminoglycoside), what other combination regimens (excluding those containing aminoglycosides) could be used? Are these regimens as effective as aminoglycoside-containing regimens?

As stated, ciprofloxacin has been studied in combination with other antibacterials (either an aminoglycoside or a β-lactam, including an antipseudomonal penicillin) as initial empiric therapy for the treatment of suspected infection in patients with febrile neutropenia.[120–123] Ciprofloxacin in combination with clindamycin may also be useful in patients unable to receive β-lactam–containing combinations owing to the presence of immediate-type hypersensitivity reactions.[4] These studies, however, were associated with increased gram-positive infections in patients treated with ciprofloxacin. In addition, the in vitro activity of ciprofloxacin against *P. aeruginosa* has declined significantly (to <70% in many institutions). Therefore, if used as part of combination therapy, ciprofloxacin should be combined with an antimicrobial with favorable in vitro activity against this pathogen. Alternatively, the combination of aztreonam and vancomycin has been recognized as reasonable empiric combination therapy in patients with immediate-type hypersensitivity reactions to penicillin.[4]

In summary, the use of initial empiric therapy with combination antibiotic therapy is generally reserved for patients who are clinically unstable. These patients may receive IV therapy with an antipseudomonal β-lactam generally combined with an aminoglycoside and vancomycin. Systemic antifungals (such as fluconazole or an echinocandin) may also be added in such settings, especially in patients not receiving antifungal prophylaxis. This is discussed further in the upcoming section on Antifungal Therapy.

EMPIRIC VANCOMYCIN

Case 75-2, Question 3: B.L. is started on a two-drug regimen of cefepime and vancomycin. What is the rationale for adding vancomycin to the regimen?

As discussed, gram-positive bacteria are important pathogens in these patients. Because cephalosporins lack activity against methicillin-resistant staphylococci, vancomycin is often added to empiric regimens. A growing proportion of *S. aureus* infections are

methicillin resistant (as many as 60% in some institutions). However, widespread use of vancomycin may be one factor associated with the rise in vancomycin resistance among enterococci. Furthermore, vancomycin intermediate–resistant *S. aureus* and rare case reports of *S. aureus* fully resistant to vancomycin have been reported. Vancomycin use has also been associated with a modest increase in the incidence of nephrotoxicity.

Primarily because of differences in the measured endpoints, the need for vancomycin as initial empiric therapy continues to be debated.[124] For example, patients with cancer with febrile neutropenia had more rapid resolution of fever, fewer days of bacteremia, and a lower frequency of treatment failure when vancomycin was added to an initial regimen of antipseudomonal penicillin plus an aminoglycoside.[125],[126] Similarly, the addition of vancomycin to ceftazidime showed improved results compared with ceftazidime alone or with a three-drug combination.[127] However, other studies have concluded that mortality was not increased when vancomycin therapy was delayed.[128–131] The mortality from staphylococcal (generally coagulase-negative staphylococci) infections is generally considered to be low (<4%) during the first 48 hours after the onset of fever. In contrast, the mortality associated with viridans streptococcal infections is higher among patients who are not initially treated with vancomycin.[132] Some strains of viridans streptococci are either resistant or tolerant to penicillin.[132],[133] In general, vancomycin would represent a reasonable alternative treatment of such infections or in patients allergic to penicillins.

There continues to be considerable debate about whether vancomycin should be included in the initial empiric regimen for patients with febrile neutropenia.[124] In general, routine use of empiric vancomycin should be discouraged.[2] However, for institutions frequently isolating invasive gram-positive bacterial pathogens (eg, those caused by viridans streptococci), vancomycin should probably be included in the initial empiric regimen. In addition, patients at highest risk of serious, invasive infections with gram-positive organisms should be considered for initial vancomycin therapy. Such patients include suspected catheter-related infections, skin or soft

tissue infections, or pneumonia, those receiving intensive chemotherapy (eg, high-dose cytarabine) resulting in substantial mucosal damage, patients receiving prior fluoroquinolone or TMP-SMX prophylaxis, those with prior history of colonization with β-lactam–resistant pneumococci or MRSA or with gram-positive bacteria in blood cultures (before identification and susceptibility testing), and those with sepsis without an identified pathogen should also be considered for vancomycin therapy.[4] The addition of vancomycin to an aminoglycoside-containing regimen should be done with caution because data support an increased risk of aminoglycoside-induced nephrotoxicity in patients receiving these agents concomitantly with vancomycin.[134] More recently, vancomycin has been shown to increase the risk of nephrotoxicity in patients receiving piperacillin–tazobactam.[135–138]

Alternatives to vancomycin with activity against gram-positive pathogens

Options exist for the treatment of invasive gram-positive infections. Linezolid is an oxazolidinone that can be administered via IV or orally. A randomized, double-blind trial comparing the use of linezolid with vancomycin for empiric therapy demonstrated comparable safety and efficacy.[139] It is associated with thrombocytopenia and secondary neutropenia, especially when given for prolonged periods (ie, >14 days according to the product's package insert). Considering the reduced bone marrow reserve in patients undergoing cancer chemotherapy, these adverse events are of particular concern. In addition, it is currently not recommended for patients with catheter-related infections (including bacteremia). The emergence of linezolid-resistant enterococci is of concern in this patient population. Therefore, its primary role in this patient population would be as a treatment for select gram-positive infections (such as suspected or documented MRSA pneumonia or infections due to VRE). Tedizolid, an oxazolidinone for IV and oral therapy, has more recently been approved in the United States. Although advantages over linezolid include a potential reduction in hematologic adverse events and drug

interactions, data are lacking to support tedizolid use in this population. In addition, tedizolid is not currently recommended in patients with neutropenia.

Quinupristin–dalfopristin is available for IV administration only, and concerns about potential drug interactions and patient tolerability (including myalgias and arthralgias) limit its use as empiric therapy in this setting. Daptomycin provides potent in vitro activity against many multidrug-resistant gram-positive pathogens (including VRE and MRSA). Compared to historical controls treated with vancomycin, daptomycin use in patients with cancer with gram-positive catheter-related bacteremia was associated with earlier and overall improved response.[140],[141] Daptomycin requires IV therapy, and should not be used for the treatment of pneumonia. Tigecycline possesses activity in vitro against both MRSA and VRE (in addition to many gram-negative and anaerobic pathogens). However, it lacks activity against *P. aeruginosa,* and therefore would not be considered a viable option for empiric monotherapy. Telavancin is a new lipoglycopeptide with potent activity in vitro against select gram-positive pathogens (including MRSA). However, experience to date in this population has not been published. Ceftaroline is a cephalosporin with activity against MRSA recently approved for the treatment of complicated skin and skin structure infections and community-acquired pneumonia. However, reports of the use of ceftaroline in this patient population are sparse. In addition, ceftaroline has infrequently been associated with neutropenia, most notably at higher doses and/or for prolonged courses of therapy.[142–144] Data are also lacking for the use of oritavancin and dalbavancin (also approved for IV therapy of MRSA infections) in these patients. Therefore, these alternative agents (daptomycin and linezolid) are generally reserved for situations in which vancomycin is inappropriate (because of resistance or intolerance).[2]

In the case of B.L., empiric use of vancomycin is not warranted based on the previous discussion and it should be discontinued unless cultures indicate the need for this antibiotic.

ANTIBIOTIC DOSING, ADMINISTRATION, AND MONITORING CONSIDERATIONS

Intermittent Versus Continuous Versus Prolonged Infusion of Intravenous Antibiotics

Case 75-2, Question 4: Should B.L.'s antibiotics be given intermittently (ie, divided doses) or as a continuous infusion?

β-Lactam antibiotics exhibit time-dependent (ie, concentration independent) pharmacodynamic activity, and in vitro models of infection suggest that prolonged exposure of bacteria to drug concentrations above the minimum inhibitory concentration is linked with improved bacterial killing and survival. On the basis of these observations and the poor prognosis of neutropenic cancer patients with bacteremia, noncomparative, open-label trials were conducted to evaluate the role of continuous infusions of β-lactams (ie, ceftazidime) in the empiric treatment of suspected infection in patients with cancer.[145–147] Additional studies in patients with febrile neutropenia have also been performed with meropenem, suggesting a potential benefit of prolonged infusion over traditional administration.[148] However, this method of administration would require an IV line dedicated for continuous drug administration and limit B.L.'s ability to receive intermittent tobramycin infusions unless additional IV ports or lines are available for use. In contrast to continuous infusions, prolonged infusions (ie, 3–4 hours) of select β-lactams (notably carbapenems, third- or fourth-generation cephalosporins, or piperacillin–tazobactam) have shown promise in a variety of pharmacodynamic models of infection (specifically with elevated minimum inhibitory concentrations) and tend to show better outcomes in observational studies. However, this has not been verified in prospective randomized controlled trials. Prolonged infusions of β-lactams also have the potential to reduce the total

dose, and therefore result in drug acquisition cost savings. Although only limited clinical data exist to support this kind of a strategy, such evaluations have not been tested specifically in the setting of infections in the neutropenic host.

Consolidated Interval Aminoglycoside Dosing

Case 75-2, Question 5: What is the role of consolidated (once-daily) aminoglycoside dosing in patients with febrile neutropenia such as B.L.?

Because of the concentration-dependent pharmacodynamic properties of aminoglycosides and the convenience of administration, studies have been conducted to describe both the pharmacokinetic properties and efficacy of consolidated dosing of aminoglycosides in animals and in patients with neutropenia. Pharmacokinetic studies with amikacin[149,150] and gentamicin[151,152] have not revealed pharmacokinetic differences when compared with other populations. Several clinical studies have included consolidated aminoglycoside dosing for amikacin, gentamicin, and tobramycin.[153] However, most of the studies in this population were not designed to evaluate differences between consolidated aminoglycoside dosing compared with similar regimens using intermittent dosing. In general, the various studies suggest that consolidated dosing is as effective and possibly less nephrotoxic than is traditional dosing. Therefore, consolidated dosing of aminoglycosides appears reasonable in empiric therapy of patients with neutropenia.[153]

HOST FACTORS INFLUENCING RESPONSE TO THERAPY

Case 75-2, Question 6: What factors may have influenced B.L.'s clinical response to antimicrobial therapy?

The most important prognostic determinants of a favorable outcome in patients with neutropenia and infection are the recovery of the granulocyte count and (for the patient with infection) proper selection of antimicrobial therapy. Patients with profound, persistent neutropenia (<100 cells/μL) that does not rise during therapy or an initial ANC of 100 to 500 cells/μL that declines during therapy respond to antibiotics less favorably than in patients whose bone marrow recovers. The initial granulocyte count appears to be less important than is the trend toward granulocyte recovery. Although other evidence of bone marrow recovery (such as the absolute phagocyte count, absolute monocyte count, or reticulocyte fraction) may precede the ANC target of 500 cells/μL by several days, they are not as widely used clinically. The site of infection also influences outcome. Septic shock and pneumonia are associated with high mortality in patients with bacteremic neutropenia.

MODIFYING INITIAL EMPIRIC ANTIBIOTIC THERAPY

CASE 75-3

Question 1: M.H., a 24-year-old female with a recent diagnosis of ovarian cancer, exhibited neutropenia (ANC <150 cells/μL) after chemotherapy. Five days after becoming neutropenic, she experienced a fever of 101 °F (38.3 °C) and was started on an empiric antibiotic regimen of cefepime 2 g IV every 8 hours. Although she remained febrile, her initial cultures remained negative at 48 hours.

Should M.H. be continued on the same regimen, or should modifications be made? How do the culture results influence this decision? How long should empiric therapy be continued?

The need for modification of the initial empiric therapy is dependent on the risk group (ie, low vs high risk), establishment of an infection site or causative pathogen, response to initial therapy, and clinical stability. In the absence of an identification of the infection site, worsening of clinical status, or onset of new signs and symptoms of infection, 3 to 5 days of empiric treatment are generally required to determine initial efficacy after initiation of empiric antibiotics.[4] Defervescence in patients with hematologic malignancies, as well as HSCT recipients, may be delayed (up to 5 days). During this time, daily assessments should include history and physical examinations, review of laboratory results, assessment of response, and evaluation of any antibiotic-related toxicity. Adjustments to initial empiric antibiotic therapy should be made if a site-specific infection is identified, antimicrobial resistance is suspected or documented, or the patient's condition deteriorates.

Premature discontinuation of antibiotics may predispose these patients to recrudescence of bacterial infection and increase the risk of infection-related morbidity and mortality. Patients with cancer with unexplained fever who became afebrile after empiric antibiotics were randomly assigned to continue or discontinue antibiotic therapy after 7 days.[154] The patients whose neutropenia resolved had no infectious sequelae regardless of whether antibiotics were continued or discontinued. However, for patients with persistent neutropenia randomly assigned to continue or discontinue antibiotic therapy until their ANC was >500 cells/μL, the percentages of patients remaining febrile without infectious complications were 94% and 41%, respectively. Therefore, initial empiric therapy in responding patients without an identified source should be continued until the patient's ANC is >500 cells/μL and increasing, and the patient is well and afebrile for at least 24 hours. Patients who are afebrile and stable but whose neutropenia persists may be considered for continuation with oral antibiotics (such as ciprofloxacin plus amoxicillin-clavulanate). Patients whose initial empiric regimen appropriately included vancomycin should continue receiving such therapy. In contrast, those initiated inappropriately on vancomycin, or in whom culture,

diagnosis, or condition does not support continued use should have the vancomycin therapy discontinued.

Documented Infections

Case 75-3, Question 2: On day 3, M.H.'s temperature is normal (97.6 °F [36.4 °C]). However, two sets of blood cultures drawn 3 days ago have grown *S. aureus* resistant to methicillin and susceptible to vancomycin. Her ANC is 170 cells/μL. How should therapy be modified in M.H.? For how long should antibiotics be continued?

As previously stated, modification of initial empiric therapy should be made based on culture results as well as site-specific signs and symptoms of infection (**Table 75-1**). For example, anaerobic coverage (often with a carbapenem or piperacillin–tazobactam if not used for initial monotherapy) may be expanded in the setting of abdominal pain. Oral vancomycin should be initiated in the setting of diarrhea when *C. difficile* is suspected.[4] Vesicular lesions may be suggestive of viral infections (such as HSV or VZV) and may respond to the addition of acyclovir.[1] Suspected IV catheter infections should be managed with catheter removal (whenever possible), and this as well as skin and skin structure infections should be managed with treatment directed at MRSA.[4] For pneumonia, antibiotic coverage should be consistent with published guidelines (see Chapter 67, Respiratory Tract Infections).[155,156] In the setting of severe or life-threatening pulmonary infections, antifungal therapy should also be included (Table 75-1). Modifications of therapy may also be based on isolation of a resistant pathogen. For example, resistant gram-positive infections such as MRSA may be treated with vancomycin, linezolid, or daptomycin, whereas linezolid or daptomycin may be used for the treatment of VRE. For multidrug-resistant gram-negative pathogens, carbapenems are often used to treat ESBL-producing organisms, whereas carbapenem-resistant Enterobacteriaceae may require therapy with newer β-lactam/ β-lactamase combinations, polymyxin, colistin, or tigecycline.

Table 75-1
Antimicrobials in Patients With Neutropenia and Fever[a]

Condition	Therapy[b]
Initial Empiric Therapy (Site Unknown)	
Low-Risk (Anticipated Neutropenia ≤7 Days, Clinically Stable, No Medical Comorbidities)	
Candidate for oral therapy	Adults: ciprofloxacin[a] + amoxicillin–clavulanate (alternative is clindamycin if penicillin allergic), moxifloxacin, levofloxacin Children: cefixime
Requires IV therapy	(See *High-Risk* subsequently)
High-Risk (Anticipated Neutropenia >7 Days, Clinically Unstable, Or Medical Comorbidities)	
	Piperacillin–tazobactam, antipseudomonal carbapenem,[c] or cefepime Clinically unstable: Consider addition of aminoglycoside, fluoroquinolone, or vancomycin to above mentioned regimen.
Modifications of Initial Therapy	
Unexplained Fever	
Defervescence with negative culture results	Continue antibiotics. Low-risk patients: If IV therapy initially, consider switch to oral therapy.
Persistent fever (2–4 days) without clinical or microbiologic evidence of infection	Clinically stable: Continue antibiotics.
	Unstable: Hospitalize (if outpatient), IV therapy (if initially treated with oral), broaden antibacterial coverage to include anaerobes, resistant gram-negative rods, and resistant gram-positive organisms. Consider antifungal therapy for *Candida* species, or antimold therapy if previously receiving azole prophylaxis.

Condition	Therapy[b]
	Consider empiric antifungal therapy on days 4–7, especially if neutropenia is expected to continue >7 days or the patient has other risk factors for fungal infections.
	If initial regimen did not include vancomycin: Reevaluate risk factors for gram-positive infection, consider adding vancomycin.
Documented Infection(s)	
Multidrug-resistant pathogen	MRSA: Add vancomycin, linezolid, or daptomycin. VRE: Add linezolid or higher doses of daptomycin. ESBLs: Switch to a carbapenem, carbapenemase-producing Enterobacteriaceae (other than KPC): polymyxin-colistin or tigecycline.
Head, Eyes, Ears, Nose, Throat	
Necrotizing ulceration	If initial regimen did not include anaerobic therapy (carbapenem or β-lactam/β-lactamase inhibitor; ie, piperacillin–tazobactam), consider adding clindamycin or metronidazole or switch to antipseudomonal carbapenem (imipenem–cilastatin or meropenem). Consider adding antifungal and antiviral therapy for HSV.
Oral vesicular lesions	Add antiviral therapy for HSV.
Oral thrush	Add antifungal therapy (fluconazole). Consider extended-spectrum azoles (posaconazole, voriconazole) or an echinocandin if refractory to fluconazole.
Esophagus	(See antifungal therapy for oral thrush.) Consider acyclovir for HSV if laboratory or clinical suspicion of disease. Assess CMV risk and (if high) consider ganciclovir or foscarnet.
Sinus tenderness, periorbital cellulitis, nasal ulceration	If suspicion of mold infection: Add lipid-based formulation of amphotericin B. Reassess antistaphylococcal activity of empiric regimen; consider vancomycin. Vancomycin for periorbital cellulitis
Gastrointestinal Tract	

Condition	Therapy[b]
Acute abdominal pain/perianal	If initial regimen did not include carbapenem or β-lactam/β-lactamase inhibitor (ie, piperacillin–tazobactam), consider adding metronidazole, or switch to imipenem–cilastatin or meropenem. Ensure pseudomonal coverage for perirectal infection. For perirectal pain: Consider enterococcal coverage for infection (not colonization). Consider antifungal.
Diarrhea	If *Clostridioides difficile* documented, discontinue unnecessary antibiotics and add oral vancomycin or fidaxomicin. Contact isolation of rotavirus or norovirus documented
Respiratory Tract	
Pneumonia	Add fluoroquinolone, azithromycin, or doxycycline for atypical pathogens *(Mycoplasma, Legionella).* Add vancomycin or linezolid. (Note: daptomycin is *not* indicated for pneumonia due to inactivation by lung surfactant.) For patients with additional (pathogen-specific) risk factors or clinical/lab evidence of infection: Consider the addition of a mold-active antifungal (seasonal) Consider oseltamivir against influenza. PCP: Institute TMP-SMX or (atovaquone, dapsone, or pentamidine for patients who are sulfa allergic). CMV: Add ganciclovir if high risk Consider growth factors (G-CSF, GM-CSF)
Vesicular lesions	HSV, VZV treatment: acyclovir, famciclovir, or valacyclovir
Cellulitis, wound infection	Consider adding vancomycin (or alternative MRSA) therapy
Vascular access device infection, tunnel tract infection	Remove catheter whenever possible. Add empiric vancomycin (or alternative MRSA) therapy. Adjust based on culture and susceptibility results.
Documented Infection(s) (continued)	
Central nervous system	Antipseudomonal β-lactam (cefepime or meropenem) + vancomycin. Add ampicillin if meropenem is not used.
Encephalitis	High-dose acyclovir

Condition	Therapy[b]
Urinary tract	Change based on pathogen identification and susceptibility.
Bloodstream infections	Gram-negative: Add aminoglycoside and switch to antipseudomonal carbapenem. Gram-positive: Add vancomycin, linezolid, or daptomycin.

CMV, cytomegalovirus; ESBL, extended-spectrum β-lactamase; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; IV, intravenous; KPC, *Klebsiella*-producing carbapenemases; MRSA, methicillin-resistant *Staphylococcus aureus;* PCP, *Pneumocystis jiroveci;* TMP-SMX, trimethoprim–sulfamethoxazole; VRE, vancomycin-resistant enterococcus; VZV, varicella zoster virus.

[a]Exclude option if patient received fluoroquinolone prophylaxis.

[b]All modifications should be based on clinical and microbiologic data.

[c]Antipseudomonal carbapenem is imipenem–cilastatin or meropenem.

Freifeld A, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56–e93; Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018;36(14):1443–1453. doi:10.1200/JCO.2017.77.6211.

The duration of therapy is based on the infecting organism and site of infection (often up to 14 days) and should continue at least until the ANCs are ≥500/μL and rising.[4]

For patients with documented infections unresponsive to modification of therapy, new or worsening sites of infection should be suspected. Clinical, laboratory, and radiographic investigations should be undertaken or repeated. For hemodynamically unstable patients, antimicrobial therapy should be broadened, and the patient should be considered for empiric antifungal therapy.[4]

No Etiology Identified

CASE 75-4

Question 1: S.B. is a 55-year-old female with chronic myelogenous leukemia. She was admitted to the hospital with a 4-day history of fevers and night sweats. On admission, her temperature was 102.3 °F (39.1 °C), and her WBC count was 100,000 cells/μL, with an ANC of 500 cells/μL. Blood and urine cultures were obtained, and cefepime was empirically started. For the next 3 days, S.B. remained persistently febrile and neutropenic. All culture results remained negative.

How should she be treated?

Persistent fevers may be from noninfectious sources or from untreated infection. With the exception of consideration for antifungal therapy in some patients, those with persistent fever who are clinically stable do not routinely require a change in empiric therapy unless guided by clinical changes or culture results.[2] However, outpatients with persistent fever should be hospitalized and receive IV therapy. Empiric addition of vancomycin in patients with persistent fever does not decrease the time to fever resolution in this population,[157] and should therefore be discouraged.[2] In contrast, persistently febrile patients who are hemodynamically unstable without a clear source of infection should have their initial therapy modified to broaden coverage against resistant gram-positive and gram-negative organisms, as well as anaerobes. Patients with initial monotherapy with cefepime can be switched to vancomycin with an antipseudomonal carbapenem (such as imipenem–cilastatin or meropenem) in combination with either an aminoglycoside, aztreonam, or ciprofloxacin. Antifungal therapy targeting *Candida* species should also be considered (see Case 75-4, Question 3).

Case 75-4, Question 2: S.B., on day 4, continues to feel "lousy" and has started to report abdominal pains. What is the significance of this report? Should her antibiotic regimen be modified again?

Because S.B. has new abdominal pains suggestive of enterocolitis, her antibiotic regimen should be modified. Although cefepime provides excellent coverage against the common gram-negative pathogens, it has limited activity against select gram-

positive pathogens (eg, MRSA or VRE) and anaerobes. A change from cefepime to imipenem–cilastatin or another broad-spectrum regimen with both aerobic and anaerobic activity should be considered.

Case 75-4, Question 3: S.B.'s antibiotic regimen was changed to imipenem–cilastatin. Despite the change, she continues to have a low-grade fever and does not feel better. What is S.B.'s risk of having a systemic fungal infection? What is the significance of fungal infections in neutropenic cancer patients?

ANTIFUNGAL THERAPY

Early diagnosis and prompt treatment of systemic fungal diseases are critical to patient survival. However, significant challenges exist in making an accurate and timely diagnosis of IFIs. Therefore, patients who are neutropenic with protracted (4–7 days) fever despite the administration of broad-spectrum antibiotics should be considered for empiric antifungal therapy, especially patients whose neutropenia is anticipated to exceed 7 days.[2,158] Patients at highest risk for mold infections (ie, those with prolonged neutropenia, allogeneic HSCT recipients, and/or those receiving high-dose corticosteroids) should be initiated on antifungals after 4 days of persistent fever unless they are currently receiving antimold prophylaxis. Considerations for earlier empiric antifungal therapy (ie, days 2–4) should be made in patients with persistent fever and hemodynamic instability.[4]

Newer diagnostic tests (eg, β-D-glucan tests or galactomannan assays), along with additional diagnostic support, may allow for early preemptive therapy (ie, institution of therapy based on biomarker evidence of disease before the development of symptoms).[159] Such approaches may also be used to support decisions to withhold empiric antifungal therapy. As an example, persistently febrile patients on appropriate antibacterials who are clinically stable without clinical or radiographic signs of fungal infection, have had negative serologic assay results for IFI, and have had no recovery of fungi from any body site may have empiric antifungal agents withheld.[4,99]

Considerations about the choice of empiric antifungals should include prior or current antifungal prophylaxis, risk of mold infections, risks of antifungal-related toxicities, drug interactions, route of administration, clinical stability, and costs.[19] It is difficult to compare data among clinical trials evaluating empiric antifungal therapy in neutropenic cancer patients because of differences in trial design. Such differences may include inclusion of low-risk patients, lack of blinding, changes in concomitant antibacterials obscuring antifungal therapy end points, prior antifungal prophylaxis, use of composite end points of safety and efficacy, and different end point criteria.[20] Although select studies have also demonstrated that empiric antifungal therapy can decrease fungal-related deaths, overall mortality has not been affected.[19] This is the case particularly for patients with invasive disease and persistent neutropenia.

In patients requiring therapy, antifungal coverage should be directed at *Candida* species. Highest risk patients with persistent or recurrent fever after 4 to 7 days of appropriate antibacterial therapy and anticipated to have prolonged (ie, >10 days) neutropenia should be considered for antimold therapy.[4]

CASE 75-4, QUESTION 4: Should amphotericin B or acyclovir therapy be considered in S.B.?

Historically, AmBd was most commonly used in this setting because of its reliable activity in vitro against most *Candida* and *Aspergillus* species. Comparative trials have also evaluated the role of lipid-based formulations of amphotericin B in the treatment of suspected or documented infections in this population. LAmB,[160–163] amphotericin B lipid complex,[162] and amphotericin B colloidal dispersion[164] have demonstrated reductions in nephrotoxicity compared with AmBd. In addition, LAmB is least likely to be associated with infusion-related side effects.[161] Although there are limited data to suggest that the continuous infusion of AmBd may also reduce nephrotoxicity,[165] efficacy regarding this method of administration in patients with documented infections has not been

established. Therefore, continuous infusion of AmBd cannot be routinely recommended at this time. Considering the availability of other agents, empiric amphotericin B products are generally reserved for patients at highest risk for mold infections unable to receive alternative antifungals. When initiated as empiric therapy, amphotericin B administration is often preceded by attempts to minimize nephrotoxicity (eg, saline loading) and premedications to minimize infusion-related reactions. Close monitoring of tolerability, renal function, and electrolytes is required during administration.

In stable patients at low risk for mold infections or drug-resistant *Candida* species (eg, *C. krusei* and some strains of *C. glabrata*), fluconazole may be preferable to amphotericin B.[4,166,167] Patients with suspected mold infections (eg, aspergillosis), hemodynamic instability, or in whom an azole was used as prophylaxis should not receive fluconazole. Although itraconazole possesses enhanced activity in vitro against *Aspergillus* species and has reduced toxicity relative to amphotericin B, issues regarding tolerability with the oral solution, erratic bioavailability with the capsule formulation, potential for cross-resistance with other azoles, lack of a parenteral treatment option, and considerations of alternative treatment options generally limit its usefulness. A new formulation of itraconazole (SUBA-itraconazole) demonstrates improved absorption after oral administration. Posaconazole possesses a broad spectrum of activity in vitro against a variety of yeasts and molds. It is currently available in both an oral and IV formulation. Voriconazole (an azole antifungal agent with increased activity against *Aspergillus* and non-albicans *Candida* relative to fluconazole) has been tested in this population. When compared with LAmB, voriconazole failed to meet the preestablished criteria for noninferiority.[163] However, some believe that voriconazole should be considered as an alternative to amphotericin B preparations for empiric therapy in patients requiring initial empiric antifungal therapy who are at increased risk for mold infections (owing to receipt of prior azole prophylaxis) or for those patients suspected of having invasive candidiasis.[158] Because of the increased potential (relative to fluconazole) for drug interactions (including immunosuppressives and chemotherapy) and adverse

events (eg, phototoxicity, hepatotoxicity), voriconazole therapy should be monitored closely. IV use of voriconazole is contraindicated in patients with severe renal dysfunction. In addition, serum drug concentration monitoring for itraconazole, posaconazole, and voriconazole should be considered in select, high-risk patients receiving these triazoles to ensure adequate target concentrations.[4,8] These agents demonstrate significant intra- and interpatient variability in serum concentrations secondary to alterations in absorption, metabolism, elimination, or drug–drug interactions. Drug- and indication-specific recommended target concentrations for the triazoles are discussed extensively elsewhere.[49] Briefly, samples for analysis are obtained once steady state has been achieved (usually 5–7 days after initiation of therapy) before the next dose (trough concentration). Typical drug serum concentration for the treatment of IFIs include 1 to 2 μg/mL (toxicity >5 μg/mL) for itraconazole, >0.7 μg/mL (toxicity not established) for posaconazole, and >1 μg/mL (toxicity >5 μg/mL) for voriconazole.

Most recently, isavuconazole has been FDA approved for both oral and IV administration for the treatment of invasive aspergillosis and mucormycosis.[168] Potential advantages (relative to voriconazole) include improved oral bioavailability, predictable pharmacokinetics (no need for serum drug monitoring), and a reduction in the potential for drug interactions. For treatment of invasive aspergillosis, isavuconazole's efficacy was noninferior to that of voriconazole.

The echinocandins (eg, caspofungin, micafungin, anidulafungin) possess in vitro activity against *Candida* species (including non-albicans *Candida*) and *Aspergillus* species. Caspofungin is at least as effective and better tolerated than is LAmB as empiric therapy in this patient population.[169,170] Because of their safety profile and in vitro activity, echinocandins are often considered for patients requiring initial empiric antifungal therapy and who are at increased risk for mold infections (owing to receipt of prior azole prophylaxis). Caspofungin is currently FDA approved for such use. Published experience with other echinocandins (eg, micafungin, anidulafungin) as empiric therapy in the patient with febrile neutropenia is lacking at present; however, many would consider them interchangeable.

In summary, empiric antifungal therapy is indicated for persistent (4–7 days) or recurrent fever on appropriate antibacterials if the duration of neutropenia exceeds 7 days. Low-risk patients who are clinically stable do not routinely need antifungal therapy. Persistently febrile patients who are clinically stable without computed tomography signs of infection and have no serologic or culture results suggestive of infection may have antifungal therapy withheld. Patients receiving fluconazole prophylaxis requiring the addition of empiric antifungals should be considered for antifungals with activity against azole-resistant *Candida* species and mold infections. In the setting in which an antimold agent was used for prophylaxis, switching antifungal classes or conversion to IV therapy should be performed.

ANTIVIRAL THERAPY

Empiric use of antiviral agents in the patient with febrile neutropenia is not indicated without evidence of such disease.[4] In contrast, clinical evidence of HSV or VZV involving the skin or mucous membranes should be treated with antivirals (eg, acyclovir, valacyclovir).[4] When oral therapy is used, valacyclovir is favored over acyclovir because of improved oral bioavailability and need for less frequent dosing. With the exception of patients undergoing bone marrow transplantation,[171] CMV is an uncommon source of infection in the patient with febrile neutropenia. However, ganciclovir, valganciclovir, foscarnet, or, less commonly, cidofovir treatment should be initiated in patients with documented CMV infections (antigenemia, PCR for CMV DNA, or detection of CMV mRNA). Because both ganciclovir and valganciclovir can cause or worsen existing neutropenia, caution and close monitoring is warranted when these agents are prescribed in this setting. Treatment with neuraminidase inhibitors (such as oseltamivir or zanamivir) may be initiated empirically for influenza in the setting of exposure or outbreaks if the patient is presenting with an influenza-like illness.[4] Peramivir IV may be used in individuals unable to take oral oseltamivir or inhaled zanamivir. Baloxavir may be effective in this

population; however, its role is yet to be determined. Likewise, if RSV is identified, appropriate antiviral therapy should be initiated.[4]

ANTIMICROBIAL ADJUVANTS

CASE 75-4, QUESTION 5: S.B. became afebrile 2 days after micafungin was initiated, yet she remained neutropenic with an ANC of 480 cells/μL. An induction chemotherapy regimen consisting of idarubicin plus cytarabine was initiated for her chronic myelogenous leukemia. Because the chemotherapy will further reduce her ANC 7 to 10 days after treatment, is there any way to facilitate marrow recovery and reduce the duration of neutropenia in S.B.?

As previously discussed, the duration of neutropenia is the most important factor affecting outcome in neutropenic cancer patients. Because of this, there has been considerable interest in enhancing the immune system in these patients.

Granulocyte Transfusions

One of the earliest approaches used to boost the patient's defense against infections was the transfusion of WBCs. In the 1970s, granulocyte transfusions were used adjunctively in patients with persistent neutropenia and documented infections who, despite appropriate antibiotics, failed to respond after 24 to 48 hours. This approach had limited value because of the difficulties in obtaining adequate cells for transfusion, as well as the problems with alloimmunization and risk of infection transmission. In addition, the questionable efficacy of WBC transfusions has decreased the use of this strategy.[172] Therefore, granulocyte transfusions are not routinely indicated in this population. However, patients with progressive bacterial or fungal infections unresponsive to appropriate antimicrobial therapy may be considered as candidates.

Hematopoietic Growth Factors

Because these agents have not demonstrated a consistent and significant effect on other infection-related parameters (eg, duration of fever, use of antibiotics, costs of treatment), the use of CSFs as adjunctive therapy to antibiotics for patients with febrile neutropenia is controversial.[4,28] Patients already receiving CSFs for primary or secondary prevention may be continued during treatment of febrile neutropenia. Those patients administered pegfilgrastim for primary or secondary prevention should not require subsequent doses of CSFs because of the persistence of high CSF concentrations for prolonged periods.

Patients at high risk for infection-related complications not receiving CSFs for prophylaxis may be considered for therapy. Such risks include expected prolonged (>7 days) and profound (<100 cells/μL) neutropenia in clinically unstable patients unresponsive to initial empiric therapy, age older than 65 years, uncontrolled malignancy, pneumonia, sepsis and multiorgan dysfunction (characteristic of sepsis syndrome), and IFI.[9]

Immunoglobulins

Data regarding the use of Igs as adjunctive therapy for the treatment of select infections in the neutropenic cancer patient are primarily limited to case reports. Patients with pneumonia secondary to CMV may benefit from adjunctive Ig therapy (in combination with ganciclovir). In addition, IVIG should be considered in those patients with hypogammaglobulinemia.

G-CSF administration, although likely to reduce the duration of her chemotherapy-induced neutropenia, is not indicated in S.B., who is otherwise stable.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Crawford J, Caserta C, Roila F; ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO clinical practice guidelines for the applications. *Ann Oncol*. 2010;21 Suppl 5:248. doi:10.1093/annonc/mdq195 (9)

Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):e56–e93. doi:10.1093/cid/cir073 (4)

Klastersky J, de Naurois J, Rolston K, et al; ESMO Guidelines Committee. Management of febrile neutropaenia: ESMO clinical practice guidelines. *Ann Oncol*. 2016;27(suppl 5):v111–v118. doi:10.1093/annonc/mdw325 (1)

Smith TJ, Bohlke K, Armitage JO. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Oncol Pract*. 2015;11(6):511–513. (81)

Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018;36(14):1443–1453. doi:10.1200/JCO.2017.77.6211 (2)

Key Websites

American Society of Clinical Oncology. www.asco.org

Infectious Diseases Society of America. idsociety.org

COMPLETE REFERENCES CHAPTER 75 PREVENTION AND TREATMENT OF INFECTIONS IN NEUTROPENIC CANCER PATIENTS

Klastersky J, de Naurois J, Rolston K, et al; ESMO Guidelines Committee.
1. Management of febrile neutropaenia: ESMO clinical practice guidelines. *Ann Oncol*. 2016;27(suppl 5):v111–v118. doi:10.1093/annonc/mdw325
2. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018;36(14):1443–1453. doi:10.1200/JCO.2017.77.6211
3. de Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F; ESMO Guidelines Working Group. Management of febrile neutropenia: ESMO clinical practice guidelines. *Ann Oncol*. 2010;21 Suppl 5:252. doi:10.1093/annonc/mdq196
4. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):56–93. doi:10.1093/cid/cir073
5. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med*. 1966;64(2):328–340. doi:10.7326/0003-4819-64-2-328
6. Schimpff SC, Greene WH, Young VM, Wiernik PH. Significance of *Pseudomonas aeruginosa* in the patient with leukemia or lymphoma. *J Infect Dis*. 1974;130 Suppl(0):24. doi:10.1093/infdis/130.supplement.s24
7. Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. A randomized, controlled trial. *Ann Intern Med*. 2001;135(6):412–422. doi:200109180-00010
8. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143–1238. doi:10.1016/j.bbmt.2009.06.019
9. Crawford J, Caserta C, Roila F; ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO clinical practice guidelines for the applications. *Ann Oncol*. 2010;21 Suppl 5:248. doi:10.1093/annonc/mdq195
10. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis*. 1989;11(6):954–963. doi:10.1093/clinids/11.6.954
11. Zanfi C, Lauro A, Cescon M, et al. Daclizumab and alemtuzumab as induction agents in adult intestinal and multivisceral transplantation: rejection and infection rates in 40 recipients during the early postoperative period. *Transplant Proc*. 2010;42(1):35–38. doi:10.1016/j.transproceed.2009.12.019
12. Park SH, Choi SM, Lee DG, et al. Infectious complications associated with alemtuzumab use for allogeneic hematopoietic stem cell transplantation:

comparison with anti-thymocyte globulin. *Transpl Infect Dis*. 2009;11(5):413–423. doi:10.1111/j.1399-3062.2009.00414.x

13. Barton TD, Schuster MG. The cause of fever following resolution of neutropenia in patients with acute leukemia. *Clin Infect Dis*. 1996;22(6):1064–1068. doi:10.1093/clinids/22.6.1064
14. Rolston KV. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. *Clin Infect Dis*. 2005;40 Suppl 4:S246–S252. doi:10.1086/427331
15. Cordonnier C, Buzyn A, Leverger G, et al. Epidemiology and risk factors for gram-positive coccal infections in neutropenia: toward a more targeted antibiotic strategy. *Clin Infect Dis*. 2003;36(2):149–158. doi:10.1086/345435
16. Mathur P, Chaudhry R, Kumar L, Kapil A, Dhawan B. A study of bacteremia in febrile neutropenic patients at a tertiary-care hospital with special reference to anaerobes. *Med Oncol*. 2002;19(4):267–272. doi:10.1385/MO:19:4:267
17. Bollee G, Sarfati C, Thiery G, et al. Clinical picture of *Pneumocystis jiroveci* pneumonia in cancer patients. *Chest*. 2007;132(4):1305–1310. doi:S0012-3692(15)36728-3
18. Thomas CF, Limper AH. Pneumocystis pneumonia. *N Engl J Med*. 2004;350(24):2487–2498. doi:10.1056/NEJMra032588
19. Wingard JR. Empirical antifungal therapy in treating febrile neutropenic patients. *Clin Infect Dis*. 2004;39 Suppl 1:38. doi:10.1086/383052
20. Bennett JE, Powers J, Walsh T, et al. Forum report: issues in clinical trials of empirical antifungal therapy in treating febrile neutropenic patients. *Clin Infect Dis*. 2003;36(Suppl 3):117. doi:CID21209
21. Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Bohme A, Ruhnke M, et al. Treatment of invasive fungal infections in cancer patients—recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol*. 2009;88(2):97–110. doi:10.1007/s00277-008-0622-5
22. Hagen EA, Stern H, Porter D, et al. High rate of invasive fungal infections following nonmyeloablative allogeneic transplantation. *Clin Infect Dis*. 2003;36(1):9–15. doi:CID020847
23. Martino R, Subira M. Invasive fungal infections in hematology: new trends. *Ann Hematol*. 2002;81(5):233–243. doi:10.1007/s00277-002-0466-3
24. Ninin E, Milpied N, Moreau P, et al. Longitudinal study of bacterial, viral, and fungal infections in adult recipients of bone marrow transplants. *Clin Infect Dis*. 2001;33(1):41–47. doi:CID000689
25. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1–e60. doi:10.1093/cid/ciw326

26. Hahn-Ast C, Glasmacher A, Muckter S, et al. Overall survival and fungal infection-related mortality in patients with invasive fungal infection and neutropenia after myelosuppressive chemotherapy in a tertiary care centre from 1995 to 2006. *J Antimicrob Chemother*. 2010;65(4):761–768. doi:10.1093/jac/dkp507
27. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol*. 2018;36(30):3043–3054. doi:10.1200/JCO.18.00374
28. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011;47(1):8–32. doi:10.1016/j.ejca.2010.10.013
29. Klastersky J, Paesmans M, Rubenstein EB, et al. The multinational association for supportive care in cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol*. 2000;18(16):3038–3051. doi:10.1200/JCO.2000.18.16.3038
30. Feld R, Paesmans M, Freifeld AG, et al. Methodology for clinical trials involving patients with cancer who have febrile neutropenia: updated guidelines of the immunocompromised host society/multinational association for supportive care in cancer, with emphasis on outpatient studies. *Clin Infect Dis*. 2002;35(12):1463–1468. doi:CID020419
31. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis*. 2004;39(10):1407–1416. doi:CID32144
32. Schimpff SC, Greene WH, Young VM, et al. Infection prevention in acute nonlymphocytic leukemia. Laminar air flow room reverse isolation with oral, nonabsorbable antibiotic prophylaxis. *Ann Intern Med*. 1975;82(3):351–358. doi:10.7326/0003-4819-82-3-351
33. Young GA, Bosly A, Gibbs DL, Durrant S. A double-blind comparison of fluconazole and nystatin in the prevention of candidiasis in patients with leukaemia. antifungal prophylaxis study group. *Eur J Cancer*. 1999;35(8):1208–1213. doi:S0959804999001021
34. Owens NJ, Nightingale CH, Schweizer RT, Schauer PK, Dekker PT, Quintiliani R. Prophylaxis of oral candidiasis with clotrimazole troches. *Arch Intern Med*. 1984;144(2):290–293.
35. Akiyama H, Mori S, Tanikawa S, Sakamaki H, Onozawa Y. Fluconazole versus oral amphotericin B in preventing fungal infection in chemotherapy-induced neutropenic patients with haematological malignancies. *Mycoses*. 1993;36(11–12): 373–378. doi:10.1111/j.1439-0507.1993.tb00725.x
36. Drew R. Potential role of aerosolized amphotericin B formulations in the prevention and adjunctive treatment of invasive fungal infections. *Int J*

Antimicrob Agents. 2006;27 Suppl 1:36–44. doi:S0924-8579(06)00099-9

37. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2008;46(9):1401–1408. doi:10.1086/586739
38. Maertens JA, Girmenia C, Bruggemann RJ, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. *J Antimicrob Chemother*. 2018;73(12):3221–3230. doi:10.1093/jac/dky286
39. Gotzsche PC, Johansen HK. Routine versus selective antifungal administration for control of fungal infections in patients with cancer. *Cochrane Database Syst Rev*. 2014;(9):CD000026. doi:10.1002/14651858.CD000026.pub2
40. Bodey GP, Anaissie EJ, Elting LS, Estey E, O'Brien S, Kantarjian H. Antifungal prophylaxis during remission induction therapy for acute leukemia fluconazole versus intravenous amphotericin B. *Cancer*. 1994;73(8):2099–2106. doi:10.1002/1097-0142(19940415)73:83.0.co;2-n
41. Mattiuzzi GN, Estey E, Raad I, et al. Liposomal amphotericin B versus the combination of fluconazole and itraconazole as prophylaxis for invasive fungal infections during induction chemotherapy for patients with acute myelogenous leukemia and myelodysplastic syndrome. *Cancer*. 2003;97(2):450–456. doi:10.1002/cncr.11094
42. Bowen CD, Tallman GB, Hakki M, Lewis JS. Isavuconazole to prevent invasive fungal infection in immunocompromised adults: initial experience at an academic medical centre. *Mycoses*. 2019;62(8):665–672. doi:10.1111/myc.12924
43. Fontana L, Perlin DS, Zhao Y, et al. Isavuconazole prophylaxis in patients with hematologic malignancies and hematopoietic cell transplant recipients. *Clin Infect Dis*. 2020;70(5):723–730. doi:10.1093/cid/ciz282
44. Bose P, McCue D, Wurster S, et al. Isavuconazole as primary antifungal prophylaxis in patients with acute myeloid leukemia or myelodysplastic syndrome: an open-label, prospective, phase 2 study. *Clin Infect Dis*. 2021;72(10): 1755–1763. doi:10.1093/cid/ciaa358
45. Chandrasekar PH, Gatny CM. Effect of fluconazole prophylaxis on fever and use of amphotericin in neutropenic cancer patients. Bone marrow transplantation team. *Chemotherapy*. 1994;40(2):136–143. doi:10.1159/000239184
46. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med*. 1992;326(13):845–851. doi:10.1056/NEJM199203263261301
47. Ellis ME, Clink H, Ernst P, et al. Controlled study of fluconazole in the prevention of fungal infections in neutropenic patients with haematological

malignancies and bone marrow transplant recipients. *Eur J Clin Microbiol Infect Dis*. 1994;13(1):3–11. doi:10.1007/BF02026116

48. Winston DJ, Chandrasekar PH, Lazarus HM, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. *Ann Intern Med*. 1993;118(7):495–503. doi:10.7326/0003-4819-118-7-199304010-00003
49. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother*. 2014;69(5):1162–1176. doi:10.1093/jac/dkt508
50. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. *Antimicrob Agents Chemother*. 2009;53(1):24–34. doi:10.1128/AAC.00705-08
51. Safdar A, Perlin DS, Armstrong D. Hematogenous infections due to *Candida parapsilosis*: changing trends in fungemic patients at a comprehensive cancer center during the last four decades. *Diagn Microbiol Infect Dis*. 2002;44(1):11–16. doi:S0732889302004236
52. Nucci M, Biasoli I, Akiti T, et al. A double-blind, randomized, placebo-controlled trial of itraconazole capsules as antifungal prophylaxis for neutropenic patients. *Clin Infect Dis*. 2000;30(2):300–305. doi:CID990673
53. Menichetti F, Del Favero A, Martino P, et al. Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a randomized, placebo-controlled, double-blind, multicenter trial. GIMEMA Infection Program. Gruppo Italiano Malattie Ematologiche dell' Adulto. *Clin Infect Dis*. 1999;28(2):250–255. doi:10.1086/515129
54. Harousseau JL, Dekker AW, Stamatoullas-Bastard A, et al. Itraconazole oral solution for primary prophylaxis of fungal infections in patients with hematological malignancy and profound neutropenia: a randomized, double-blind, double-placebo, multicenter trial comparing itraconazole and amphotericin B. *Antimicrob Agents Chemother*. 2000;44(7):1887–1893. doi:10.1128/aac.44.7.1887-1893.2000
55. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. *Ann Intern Med*. 2003;138(9):705–713. doi:200305060-00006
56. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood*. 2004;103(4):1527–1533. doi:10.1182/blood-2003-08-2644
57. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010;116(24):5111–5118. doi:10.1182/blood-2010-02-268151

58. Vehreschild JJ, Bohme A, Buchheidt D, et al. A double-blind trial on prophylactic voriconazole (VRC) or placebo during induction chemotherapy for acute myelogenous leukaemia (AML). *J Infect*. 2007;55(5):445–449. doi:S0163-4453(07)00693-7
59. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356(4):348–359. doi:356/4/348
60. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356(4): 335–347. doi:356/4/335
61. Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. *Antimicrob Agents Chemother*. 2009;53(3):958–966. doi:10.1128/AAC.01034-08
62. Duarte RF, Lopez-Jimenez J, Cornely OA, et al. Phase 1b study of new posaconazole tablet for prevention of invasive fungal infections in high-risk patients with neutropenia. *Antimicrob Agents Chemother*. 2014;58(10):5758–5765. doi:10.1128/AAC.03050-14
63. Gubbins PO, Krishna G, Sansone-Parsons A, et al. Pharmacokinetics and safety of oral posaconazole in neutropenic stem cell transplant recipients. *Antimicrob Agents Chemother*. 2006;50(6):1993–1999. doi:50/6/1993
64. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood*. 2000;96(6):2055–2061.
65. Trimethoprim-sulfamethoxazole in the prevention of infection in neutropenic patients. EORTC international antimicrobial therapy project group. *J Infect Dis*. 1984;150(3):372–379. doi:10.1093/infdis/150.3.372
66. Hughes WT, Rivera GK, Schell MJ, Thornton D, Lott L. Successful intermittent chemoprophylaxis for pneumocystis carinii pneumonitis. *N Engl J Med*. 1987;316(26):1627–1632. doi:10.1056/NEJM198706253162604
67. Arning M, Wolf HH, Aul C, Heyll A, Scharf RE, Scheider W. Infection prophylaxis in neutropenic patients with acute leukaemia—a randomized, comparative study with ofloxacin, ciprofloxacin and co-trimoxazole/colistin. *J Antimicrob Chemother*. 1990;26 Suppl D:137–142. doi:10.1093/jac/26.suppl_d.137
68. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. *Clin Infect Dis*. 1992;14(6):1201–1207. doi:10.1093/clinids/14.6.1201
69. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. *J Antimicrob Chemother*. 2007;59(1):5–22. doi:dkl425

70. Cullen M, Baijal S. Prevention of febrile neutropenia: use of prophylactic antibiotics. *Br J Cancer*. 2009;101 Suppl 1:11. doi:10.1038/sj.bjc.6605270
71. Carratala J, Fernandez-Sevilla A, Tubau F, Callis M, Gudiol F. Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis*. 1995;20(3):557–560. doi:10.1093/clinids/20.3.557
72. Horvathova Z, Spanik S, Sufliarsky J, et al. Bacteremia due to methicillin-resistant staphylococci occurs more frequently in neutropenic patients who received antimicrobial prophylaxis and is associated with higher mortality in comparison to methicillin-sensitive bacteriemia. *Int J Antimicrob Agents*. 1998;10(1):55–58. doi:S0924-8579(98)00009-0
73. Oppenheim BA, Hartley JW, Lee W, Burnie JP. Outbreak of coagulase negative staphylococcus highly resistant to ciprofloxacin in a leukaemia unit. *BMJ*. 1989;299(6694):294–297. doi:10.1136/bmj.299.6694.294
74. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med*. 2005;142(12 Pt 1):979–995. doi:142/12_Part_1/979
75. Oshima K, Takahashi T, Mori T, et al. One-year low-dose valacyclovir as prophylaxis for varicella zoster virus disease after allogeneic hematopoietic stem cell transplantation. A prospective study of the Japan Hematology and Oncology Clinical Study Group. *Transpl Infect Dis*. 2010;12(5):421–427. doi:10.1111/j.1399-3062.2010.00541.x
76. Takenaka K, Eto T, Nagafuji K, et al. Oral valganciclovir as preemptive therapy is effective for cytomegalovirus infection in allogeneic hematopoietic stem cell transplant recipients. *Int J Hematol*. 2009;89(2):231–237. doi:10.1007/s12185-008-0249-2
77. Einsele H, Reusser P, Bornhauser M, et al. Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood*. 2006;107(7):3002–3008. doi:2005-09-3786
78. Ayala E, Greene J, Sandin R, et al. Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2006;37(9):851–856. doi:1705341
79. Busca A, de Fabritiis P, Ghisetti V, et al. Oral valganciclovir as preemptive therapy for cytomegalovirus infection post allogeneic stem cell transplantation. *Transpl Infect Dis*. 2007;9(2):102–107. doi:TID183
80. van der Heiden PL, Kalpoe JS, Willemze R, Kroes AC, Schippers EF. Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. *Bone Marrow Transplant*. 2006;37(7):693–698. doi:1705311
81. Smith TJ, Bohlke K, Armitage JO. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology clinical

practice guideline update. *J Oncol Pract*. 2015;11(6):511–513. doi:10.1200/JOP.2015.006742

82. Bunn PA, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. *J Clin Oncol*. 1995;13(7):1632–1641. doi:10.1200/JCO.1995.13.7.1632
83. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy—results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;50(5):1161–1171. doi:S0360301601015449
84. Aapro M, Crawford J, Kamioner D. Prophylaxis of chemotherapy-induced febrile neutropenia with granulocyte colony-stimulating factors: where are we now? *Support Care Cancer*. 2010;18(5):529–541. doi:10.1007/s00520-010-0816-y
85. Seidel MG, Peters C, Wacker A, et al. Randomized phase III study of granulocyte transfusions in neutropenic patients. *Bone Marrow Transplant*. 2008;42(10):679–684. doi:10.1038/bmt.2008.237
86. Marti FM, Cullen MH, Roila F; ESMO Guidelines Working Group. Management of febrile neutropenia: ESMO clinical recommendations. *Ann Oncol*. 2009;20 Suppl 4:166–169. doi:10.1093/annonc/mdp163
87. Bodey GP. Unusual presentations of infection in neutropenic patients. *Int J Antimicrob Agents*. 2000;16(2):93–95. doi:S0924-8579(00)00241-7
88. Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients. *Arch Intern Med*. 1975;135(5):715–719.
89. Malik I, Hussain M, Yousuf H. Clinical characteristics and therapeutic outcome of patients with febrile neutropenia who present in shock: need for better strategies. *J Infect*. 2001;42(2):120–125. doi:10.1053/jinf.2001.0798
90. Chen SC, Kontoyiannis DP. New molecular and surrogate biomarker-based tests in the diagnosis of bacterial and fungal infection in febrile neutropenic patients. *Curr Opin Infect Dis*. 2010;23(6):567–577. doi:10.1097/QCO.0b013e32833ef7d1
91. Sato M, Kako S, Oshima K, et al. Prediction of infectious events by high-sensitivity C-reactive protein level before undergoing chemotherapy for acute myeloid leukaemia. *Scand J Infect Dis*. 2010;42(2):97–101. doi:10.3109/00365540903331019
92. Avabratha KS, Rau AT, Venkataravanamma P, Rau A. Significance of C-reactive protein during febrile neutropenia in pediatric malignancies. *Indian Pediatr*. 2009;46(9):797–799. doi:S097475790800159-2
93. Martinez-Albarran M, Perez-Molina Jde J, Gallegos-Castorena S, et al. Procalcitonin and C-reactive protein serum levels as markers of infection in a

pediatric population with febrile neutropenia and cancer. *Pediatr Hematol Oncol*. 2009;26(6):414–425. doi:10.3109/08880010903044797

94. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: review of the literature. *Infection*. 2008;36(5):396–407. doi:10.1007/s15010-008-7374-y
95. Carnino L, Betteto S, Loiacono M, et al. Procalcitonin as a predictive marker of infections in chemoinduced neutropenia. *J Cancer Res Clin Oncol*. 2010;136(4):611–615. doi:10.1007/s00432-009-0699-9
96. Penack O, Rempf P, Graf B, Blau IW, Thiel E. Aspergillus galactomannan testing in patients with long-term neutropenia: implications for clinical management. *Ann Oncol*. 2008;19(5):984–989. doi:10.1093/annonc/mdm571
97. Verweij PE, Maertens J. The changing face of febrile neutropenia-from monotherapy to moulds to mucositis. Moulds: diagnosis and treatment. *J Antimicrob Chemother*. 2009;63 Suppl 1:31. doi:10.1093/jac/dkp080
98. Girmenia C, Micozzi A, Gentile G, et al. Clinically driven diagnostic antifungal approach in neutropenic patients: a prospective feasibility study. *J Clin Oncol*. 2010;28(4):667–674. doi:10.1200/JCO.2009.21.8032
99. Maertens J, Deeren D, Dierickx D, Theunissen K. Preemptive antifungal therapy: still a way to go. *Curr Opin Infect Dis*. 2006;19(6):551–556. doi:10.1097/QCO.0b013e3280106854
100. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. *Clin Infect Dis*. 2004;39 Suppl 1:25. doi:10.1086/383048
101. Castagnola E, Paola D, Giacchino R, Viscoli C. Clinical and laboratory features predicting a favorable outcome and allowing early discharge in cancer patients with low-risk febrile neutropenia: a literature review. *J Hematother Stem Cell Res*. 2000;9(5):645–649. doi:10.1089/15258160050196687
102. Koh A, Pizzo PA. Empirical oral antibiotic therapy for low risk febrile cancer patients with neutropenia. *Cancer Invest*. 2002;20(3):420–433. doi:10.1081/cnv-120001186
103. Vidal L, Ben Dor I, Paul M, Pokroy E, Soares-Weiser K, Leibovici L. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. *Cochrane Database Syst Rev*. 2013;(10):CD003992. doi(10):CD003992. doi:10.1002/14651858.CD003992.pub3
104. Paganini HR, Sarkis CM, De Martino MG, et al. Oral administration of cefixime to lower risk febrile neutropenic children with cancer. *Cancer*. 2000;88(12):2848–2852. doi:10.1002/1097-0142(20000615)88:123.0.CO;2-2
105. Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med*. 1999;341(5):305–311. doi:10.1056/NEJM199907293410501

106. Kern WV, Cometta A, De Bock R, Langenaeken J, Paesmans M, Gaya H. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment Of Cancer. *N Engl J Med*. 1999;341(5):312–318. doi:10.1056/NEJM199907293410502
107. Rolston KV, Frisbee-Hume SE, Patel S, Manzullo EF, Benjamin RS. Oral moxifloxacin for outpatient treatment of low-risk, febrile neutropenic patients. *Support Care Cancer*. 2010;18(1):89–94. doi:10.1007/s00520-009-0634-2
108. Kern WV, Marchetti O, Drgona L, et al. Oral antibiotics for fever in low-risk neutropenic patients with cancer: a double-blind, randomized, multicenter trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy—EORTC infectious diseases group trial XV. *J Clin Oncol*. 2013;31(9):1149–1156. doi:10.1200/JCO.2012.45.8109
109. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis*. 2007;7(5):338–348. doi:S1473-3099(07)70109-3
110. Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2006;57(2):176–189. doi:dki448
111. Freifeld AG, Walsh T, Marshall D, et al. Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. *J Clin Oncol*. 1995;13(1):165–176. doi:10.1200/JCO.1995.13.1.165
112. Raad II, Abi-Said D, Rolston KV, Karl CL, Bodey GP. How should imipenem-cilastatin be used in the treatment of fever and infection in neutropenic cancer patients? *Cancer*. 1998;82(12):2449–2458. doi:10.1002/(SICI)1097-0142(19980615)82:123.0.CO;2-O
113. Bow EJ, Rotstein C, Noskin GA, et al. A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. *Clin Infect Dis*. 2006;43(4):447–459. doi:CID38991
114. Corapcioglu F, Sarper N, Zengin E. Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. *Pediatr Hematol Oncol*. 2006;23(3):177–186. doi:R2511236J110Q241
115. Ohyashiki K. Monotherapy versus dual therapy based on risk categorization of febrile neutropenic patients. *Clin Infect Dis*. 2004;39 Suppl 1:56. doi:10.1086/383056
116. De Jongh CA, Joshi JH, Newman KA, et al. Antibiotic synergism and response in gram-negative bacteremia in granulocytopenic cancer patients. *Am J Med*. 1986;80(5C):96–100.

117. EORTC International Antimicrobial Therapy Cooperative Group, Calandra T, Klastersky J, Glauser MP, Meunier F, Zinner SH. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. *N Engl J Med*. 1987;317(27):1692–1698. doi:10.1056/NEJM198712313172703
118. Furno P, Bucaneve G, Del Favero A. Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: a meta-analysis. *Lancet Infect Dis*. 2002;2(4):231–242. doi:S1473309902002414
119. Paul M, Soares-Weiser K, Grozinsky S, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia. *Cochrane Database Syst Rev*. 2003;(3):CD003038. doi:10.1002/14651858.CD003038
120. Griggs JJ, Blair EA, Norton JR, et al. Ciprofloxacin plus piperacillin is an equally effective regimen for empiric therapy in febrile neutropenic patients compared with standard therapy. *Am J Hematol*. 1998;58(4):293–297. doi: 10.1002/(SICI)1096-8652(199808)58:43.0.CO;2-L
121. Peacock JE, Herrington DA, Wade JC, et al. Ciprofloxacin plus piperacillin compared with tobramycin plus piperacillin as empirical therapy in febrile neutropenic patients. A randomized, double-blind trial. *Ann Intern Med*. 2002;137(2):77–87. doi:200207160-00005
122. Flaherty JP, Waitley D, Edlin B, et al. Multicenter, randomized trial of ciprofloxacin plus azlocillin versus ceftazidime plus amikacin for empiric treatment of febrile neutropenic patients. *Am J Med*. 1989;87(5A):278S–282S. doi:10.1016/0002-9343(89)90080-6
123. Chan CC, Oppenheim BA, Anderson H, Swindell R, Scarffe JH. Randomized trial comparing ciprofloxacin plus netilmicin versus piperacillin plus netilmicin for empiric treatment of fever in neutropenic patients. *Antimicrob Agents Chemother*. 1989;33(1):87–91. doi:10.1128/aac.33.1.87
124. Paul M, Dickstein Y, Borok S, Vidal L, Leibovici L, Paul M. Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer. *Cochrane Database Syst Rev*. 2017; (6):CD003914. doi:10.1002/14651858.CD003914.pub4
125. Shenep JL, Hughes WT, Roberson PK, et al. Vancomycin, ticarcillin, and amikacin compared with ticarcillin-clavulanate and amikacin in the empirical treatment of febrile, neutropenic children with cancer. *N Engl J Med*. 1988;319(16):1053–1058. doi:10.1056/NEJM198810203191604
126. Karp JE, Dick JD, Angelopulos C, et al. Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. *Am J Med*. 1986;81(2):237–242. doi:0002-9343(86)90257-3
127. Kramer BS, Ramphal R, Rand KH. Randomized comparison between two ceftazidime-containing regimens and cephalothin-gentamicin-carbenicillin in

febrile granulocytopenic cancer patients. *Antimicrob Agents Chemother*. 1986;30(1):64–68. doi:10.1128/aac.30.1.64

128. Dompeling EC, Donnelly JP, Deresinski SC, Feld R, Lane-Allman EF, De Pauw BE. Early identification of neutropenic patients at risk of grampositive bacteraemia and the impact of empirical administration of vancomycin. *Eur J Cancer*. 1996;32A(8):1332–1339. doi:0959-8049(96)00050-0
129. Koya R, Andersen J, Fernandez H, et al. Analysis of the value of empiric vancomycin administration in febrile neutropenia occurring after autologous peripheral blood stem cell transplants. *Bone Marrow Transplant*. 1998;21(9):923–926. doi:10.1038/sj.bmt.1701201
130. Granowetter L, Wells H, Lange BJ. Ceftazidime with or without vancomycin vs. cephalothin, carbenicillin and gentamicin as the initial therapy of the febrile neutropenic pediatric cancer patient. *Pediatr Infect Dis J*. 1988;7(3): 165–170. doi:10.1097/00006454-198803000-00006
131. Paul M, Borok S, Fraser A, Vidal L, Cohen M, Leibovici L. Additional anti-gram-positive antibiotic treatment for febrile neutropenic cancer patients. *Cochrane Database Syst Rev*. 2005;(3):CD003914. doi:10.1002/14651858.CD003914.pub2
132. Shenep JL. Viridans-group streptococcal infections in immunocompromised hosts. *Int J Antimicrob Agents*. 2000;14(2):129–135. doi:S0924-8579(99)00172-7
133. Kennedy HF, Gemmell CG, Bagg J, Gibson BE, Michie JR. Antimicrobial susceptibility of blood culture isolates of viridans streptococci: relationship to a change in empirical antibiotic therapy in febrile neutropenia. *J Antimicrob Chemother*. 2001;47(5):693–696. doi:10.1093/jac/47.5.693
134. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother*. 1999;43(7):1549–1555. doi:10.1128/AAC.43.7.1549
135. Gomes DM, Smotherman C, Birch A, et al. Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime. *Pharmacotherapy*. 2014;34(7):662–669. doi:10.1002/phar.1428
136. Burgess LD, Drew RH. Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. *Pharmacotherapy*. 2014;34(7):670–676. doi:10.1002/phar.1442
137. Dilworth TJ, Sliwinski J, Ryan K, Dodd M, Mercier RC. Evaluation of vancomycin in combination with piperacillin-tazobactam or oxacillin against clinical methicillin-resistant *Staphylococcus aureus* isolates and vancomycin-intermediate *S. aureus* isolates in vitro. *Antimicrob Agents Chemother*. 2014;58(2):1028–1033. doi:10.1128/AAC.01888-13
138. Moenster RP, Linneman TW, Finnegan PM, Hand S, Thomas Z, McDonald JR. Acute renal failure associated with vancomycin and beta-lactams for the

treatment of osteomyelitis in diabetics: piperacillin-tazobactam as compared with cefepime. *Clin Microbiol Infect*. 2014;20(6):384. doi:10.1111/ 1469-0691.12410

139. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. *Clin Infect Dis*. 2006;42(5):597–607. doi:CID37669
140. Chaftari AM, Hachem R, Mulanovich V, et al. Efficacy and safety of daptomycin in the treatment of gram-positive catheter-related bloodstream infections in cancer patients. *Int J Antimicrob Agents*. 2010;36(2):182–186. doi:10.1016/ j.ijantimicag.2010.03.015
141. Rolston KV, Besece D, Lamp KC, Yoon M, McConnell SA, White P. Daptomycin use in neutropenic patients with documented gram-positive infections. *Support Care Cancer*. 2014;22(1):7–14. doi:10.1007/s00520-013-1947-8
142. Rimawi RH, Frenkel A, Cook PP. Ceftaroline—a cause for neutropenia. *J Clin Pharm Ther*. 2013;38(4):330–332. doi:10.1111/jcpt.12062
143. Varada NL, Sakoulas G, Lei LR, Chua J. Agranulocytosis with ceftaroline high-dose monotherapy or combination therapy with clindamycin. *Pharmacotherapy*. 2015;35(6):608–612. doi:10.1002/phar.1596
144. Yam FK, Kwan BK. A case of profound neutropenia and agranulocytosis associated with off-label use of ceftaroline. *Am J Health Syst Pharm*. 2014;71(17):1457–1461. doi:10.2146/ajhp130474
145. Dalle JH, Gnansounou M, Husson MO, Lambilliotte A, Mazingue F, Nelken B. Continuous infusion of ceftazidime in the empiric treatment of febrile neutropenic children with cancer. *J Pediatr Hematol Oncol*. 2002;24(9):714–716. doi:10.1097/00043426-200212000-00006
146. Egerer G, Goldschmidt H, Salwender H, et al. Efficacy of continuous infusion of ceftazidime for patients with neutropenic fever after high-dose chemotherapy and peripheral blood stem cell transplantation. *Int J Antimicrob Agents*. 2000;15(2):119–123. doi:S0924-8579(00)00155-2
147. Marshall E, Smith DB, O'Reilly SM, Murray A, Kelly V, Clark PI. Low-dose continuous-infusion ceftazidime monotherapy in low-risk febrile neutropenic patients. *Support Care Cancer*. 2000;8(3):198–202. doi:10.1007/s005200050285
148. Feher C, Rovira M, Soriano A, et al. Effect of meropenem administration in extended infusion on the clinical outcome of febrile neutropenia: a retrospective observational study. *J Antimicrob Chemother*. 2014;69(9):2556–2562. doi:10.1093/jac/dku150
149. Krivoy N, Postovsky S, Elhasid R, Ben Arush MW. Pharmacokinetic analysis of amikacin twice and single daily dosage in immunocompromised pediatric patients. *Infection*. 1998;26(6):396–398. doi:10.1007/BF02770843

150. Tod M, Lortholary O, Seytre D, et al. Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. *Antimicrob Agents Chemother*. 1998;42(4):849–856. doi:10.1128/AAC.42.4.849
151. MacGowan AP, Bedford KA, Blundell E, et al. The pharmacokinetics of once daily gentamicin in neutropenic adults with haematological malignancy. *J Antimicrob Chemother*. 1994;34(5):809–812. doi:10.1093/jac/34.5.809
152. Peterson AK, Duffull SB. Population analysis of once-daily dosing of gentamicin in patients with neutropenia. *Aust N Z J Med*. 1998;28(3):311–315. doi:10.1111/j.1445-5994.1998.tb01954.x
153. Mavros MN, Polyzos KA, Rafailidis PI, Falagas ME. Once versus multiple daily dosing of aminoglycosides for patients with febrile neutropenia: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2011;66(2):251–259. doi:10.1093/jac/dkq451
154. Pizzo PA, Robichaud KJ, Gill FA, et al. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. *Am J Med*. 1979;67(2):194–200. doi:0002-9343(79)90390-5
155. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45–e67. doi:10.1164/rccm.201908-1581ST
156. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61–e111. doi:10.1093/cid/ciw353
157. Wade JC, Glasmacher A. Vancomycin does not benefit persistently febrile neutropenic people with cancer. *Cancer Treat Rev*. 2004;30(1):119–126. doi:10.1016/j.ctrv.2003.11.008
158. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):1. doi:10.1093/cid/civ933
159. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis*. 2005;41(9):1242–1250. doi:CID36798
160. Prentice HG, Hann IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol*. 1997;98(3):711–718. doi:10.1046/j.1365-2141.1997.2473063.x
161. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of

Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med*. 1999;340(10):764–771. doi:10.1056/NEJM199903113401004

162. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A; L Amph/ABLC Collaborative Study Group. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L amph/ABLC Collaborative Study Group. *Clin Infect Dis*. 2000;31(5):1155–1163. doi:CID994069
163. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med*. 2002;346(4):225–234. doi:10.1056/NEJM200201243460403
164. White MH, Bowden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. *Clin Infect Dis*. 1998;27(2):296–302. doi:10.1086/514672
165. Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *BMJ*. 2001;322(7286):579–582. doi:10.1136/bmj.322.7286.579
166. Malik IA, Moid I, Aziz Z, Khan S, Suleman M. A randomized comparison of fluconazole with amphotericin B as empiric anti-fungal agents in cancer patients with prolonged fever and neutropenia. *Am J Med*. 1998;105(6):478–483. doi:S000293439800326X
167. Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. *Am J Med*. 2000;108(4):282–289. doi:S0002-9343(99)00457-X
168. Miceli MH, Kauffman CA. Isavuconazole: a new broad-spectrum triazole antifungal agent. *Clin Infect Dis*. 2015;61(10):1558–1565. doi:10.1093/cid/civ571
169. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 2004;351(14):1391–1402. doi:10.1056/NEJMoa040446
170. Maertens JA, Madero L, Reilly AF, et al. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. *Pediatr Infect Dis J*. 2010;29(5):415–420. doi:10.1097/INF.0b013e3181da2171
171. Fassas AB, Bolanos-Meade J, Buddharaju LN, et al. Cytomegalovirus infection and non-neutropenic fever after autologous stem cell transplantation: high rates of reactivation in patients with multiple myeloma and lymphoma. *Br J Haematol*. 2001;112(1):237–241. doi:bjh2487

172. Illerhaus G, Wirth K, Dwenger A, et al. Treatment and prophylaxis of severe infections in neutropenic patients by granulocyte transfusions. *Ann Hematol*. 2002;81(5):273–281. doi:10.1007/s00277-002-0439-6

76

Pharmacotherapy of Human Immunodeficiency Virus Infection

Aaron S. Devanathan, Allison E. Symonds, Jessica L. Adams, and Mackenzie L. Cottrell

CORE PRINCIPLES		CHAPTER CASES
1	Acute retroviral syndrome is characterized by nonspecific symptoms, such as fever, lymphadenopathy, rash, fatigue, and night sweats that coincide with an initial burst of viremia. These symptoms, as well as the presence of an opportunistic infection, and high-risk sexual or drug-using behaviors, warrant human immunodeficiency virus (HIV) testing. With current antigen/antibody laboratory tests, HIV can be diagnosed as early as 2 weeks after infection. In patients in whom very early infection (older than 2 weeks) is suspected, nucleic acid tests for HIV RNA may be considered for diagnostic purposes.	**Case 76-1 (Question 1)**
2	HIV RNA viral load is measured to quantify the level of viral replication in the body, and CD4 cell counts are followed to assess immune system function.	**Case 76-1 (Question 2)**
3	Antiretroviral therapy (ART) should be initiated as soon as possible after diagnosis in all patients after discussion of the lifelong benefits and importance of adherence. Early ART initiation is especially important in the following clinical situations:	**Case 76-1 (Question 3)**

	acquired immunodeficiency syndrome (AIDS)-defining condition such as an opportunistic infection, acute/recent HIV infection, and pregnancy. U.S. Department of Health and Human Services (DHHS) guidelines provide recommendations for optimal ART.	
4	Goals of ART include suppression of viral load, preservation and strengthening of the immune system, limitation of drug adverse events, promotion of adherence, prevention of HIV-related morbidity and mortality, prevention of HIV transmission, and reduction of latent reservoir.	**Case 76-1 (Question 4)**
5	General rules of therapy involve selection of ART-based regimen, optimization of the selected agents, and inclusion of quality of life in decisions.	**Case 76-1 (Questions 5, 6)**
6	After initiating an ART regimen, short-term goals include resolution of symptoms, undetectable HIV RNA levels at 8 to 24 weeks, and an increase in CD4 count at 3 to 4 months. Long-term assessments include the monitoring of HIV RNA and CD4 count every 3 to 6 months—and potentially every 12 months—to identify treatment failures, assessment of medication adherence, and determination of tolerability and quality of life.	**Case 76-1 (Questions 7, 8)**
7	General rules for changing failing regimens include switching to at least two new active drugs (although all new drugs are preferable), as quickly as possible after treatment failure to avoid accumulation of resistance mutations. To avoid the development of further resistance, a single drug should never be added to a failing regimen. If one drug must be discontinued, the whole regimen should be stopped simultaneously. Finally, previously failed regimens should never be restarted because of the potential of archived resistance mutations.	**Case 76-1 (Questions 9, 10)**
8	Considerations for treatment of antiretroviral-experienced patients include regimen tolerability, comorbid conditions, associated pharmacokinetic properties, antiretroviral histories, and resistance testing. Resistance testing should be performed	**Case 76-2 (Questions 1–3)**

	only when HIV RNA is >1000 copies/mL because of assay sensitivity constraints. Antiretroviral drug resistance is assessed through two methods: genotyping evaluates mutations in the virus genetic code and phenotyping involves growing virus in various concentrations of drug to determine viral susceptibilities. DHHS guidelines provide recommendations for treating antiretroviral-experienced patients.	
9	Drug interactions between ART and coadministered medications are common with certain classes of ART and should always be screened with the addition of any new medication.	**Case 76-3 (Question 1)**
10	ART is used in pregnancy for the health of the mother and to prevent transmission of HIV to the child. There are specific DHHS guidelines for antiretroviral use in pregnancy.	**Case 76-4 (Question 1)**
11	The use of ART for preexposure prophylaxis (PrEP) in individuals who are HIV-negative, but at high risk for acquiring HIV, has been shown to be safe and effective in clinical studies. Two combination products of emtricitabine with tenofovir disoproxil fumarate (FTC/TDF) or with tenofovir alafenamide (FTC/TAF) are Food and Drug Administration (FDA)-approved for this use, and the Centers for Disease Control and Prevention (CDC) and International AIDS Society–USA Panel have issued guidelines on the use and monitoring of the combination for this indication. Importantly, FTC/TAF is not recommended for use in cisgender females to prevent HIV acquisition through vaginal transmission.	**Case 76-5 (Question 1)**
12	The use of ART for occupational (eg, needle sticks) and nonoccupational (eg, high-risk behaviors) postexposure prophylaxis (PEP) may be warranted if initiated within 48 hours but no longer than 72 hours after exposure. There are CDC guideline recommendations for the choice of ART for PEP.	**Case 76-6 (Question 1)**

INTRODUCTION

Antiretroviral therapy (ART) is the combination of potent ART and has been shown to dramatically alter the natural progression of human immunodeficiency virus (HIV) infection, significantly improve patients' quality of life, and restore life expectancy of people living with HIV (PLWH) to that of an uninfected person. As a result, the number of newly acquired immunodeficiency syndrome (AIDS)– related opportunistic infections and deaths has declined.[1,2] In most instances, the use of ART has shifted HIV infection from a fatal disease to a manageable chronic disease. The most recent advances in HIV therapy include new and more potent ART in existing therapeutic drug classes, novel combinations of ART, new single tablet once-daily regimens, and the development of long-acting formulations.

Despite the drastic improvements in HIV treatment over the last decade, successfully managing the HIV epidemic remains a challenge because of suboptimal adherence to ART and the development of resistance, long-term adverse events, the price of ART, and the rampant spread of HIV throughout resource-poor countries.

This chapter focuses on the antiretroviral treatment of HIV infection. Although many therapeutic options now exist, a thorough understanding of viral pathogenesis is essential for managing patients infected with HIV. By understanding the principles of therapy as they relate to viral pathogenesis, clinicians can rapidly assimilate new data as they become available. Consensus panel recommendations provide a framework for clinical decision-making.[3–5] Given the complexity of therapy, this chapter focuses on treating adult HIV infections. A cursory introduction to the clinical concepts of perinatal transmission, preexposure prophylaxis (PrEP), and postexposure prophylaxis (PEP) for both occupational and nonoccupational HIV exposures are also provided. For more in-depth discussion of these concepts and the treatment of pediatric HIV, the reader is referred to the various consensus panel guidelines (https://clinicalinfo.hiv.gov/en/guidelines).

EPIDEMIOLOGY

In recent years, AIDS-related opportunistic infections and deaths in industrialized countries have dramatically declined in part because of ART and increasing access to health care.[2,6] However, access to newer, more potent antiretroviral regimens and monitoring are often limited by economics and politics. Infected patients residing in countries with a strong economic standing (North America, Western Europe, Australia, and New Zealand) have reasonable access to medications, and in recent years, patients residing in countries previously known to have scarce resources (Africa, south and southeast Asia, the Pacific, and the Caribbean) have had increasing access to medications. Regions that have made less progress are those in which the epidemic is predominantly concentrated in populations with lower access

and utilization of services, such as sex workers, injecting drug users, and males who have sex with males.[6]

As of 2019, the worldwide estimate of PLWH was 38 million: 36.2 million adults (53% of which are females) and 1.8 million children younger than age 15 years.[7] The estimated incidence (1.7 million new HIV infections) decreased by 25% from 2010, and the estimated number of AIDS-related deaths (690,000) decreased by 59%. Approximately two-thirds (68%) of all HIV-infected adults and children live in Africa, and approximately two-thirds (64%) of all AIDS-related deaths occurred there in 2019. Increasing access to HIV treatment in this region has led to a 63% reduction in the number of AIDS-related deaths since 2001. Universal access to ART became a global priority in 2000 when the United Nations Millennium Declaration called for unprecedented action to halt and begin to reverse the AIDS epidemic. This call to action resulted in an increase of more than 17.8 million PLWH in Africa (~13%) accessing ART in 2019 (increased from <1% in 2000). With these global efforts, the percentage of all PLWH worldwide on ART is 67%.

In the United States, the availability of ART resulted in a drastic decline (67%) in AIDS-related death rates between 1994 and 2007, and this percentage continues to drop albeit at a slower rate (54% decline from 2009 to 2018). Despite this success, ~7800 people in the United States still died from HIV attributable causes in 2018.[2] Racial and ethnic minorities continue to be disproportionately affected by HIV because of a complicated combination of poverty, disproportionate incarceration, and social and sexual network segregation.[8] In 2018, African Americans (who represented 13% of the U.S. population) accounted for ~42% of all new HIV infections in adult and adolescents and Hispanics/Latinos (who constitute 18% of the U.S. population) accounted for 27%. Compared with White males and females, the lifetime risk of HIV seroconversion is six times higher in African American males, 20 times higher in African American females, three times higher in Hispanic/Latino males, and four times higher in Hispanic/Latino females.[9] Gender is also an important factor linked to HIV prevalence, and transgender females are most vulnerable with a 49- to 80-fold increased risk of infection when compared to cisgender populations. Transmission through sexual intercourse remains a predominant route of infection, with rectal transmission from unprotected anal sex accounting for ~66% of cases and vaginal or penile transmission from unprotected heterosexual sex accounting for ~24% of cases in the United States.[9]

PATHOPHYSIOLOGY

Infection with HIV can be acquired through unprotected sexual intercourse (both anal and vaginal), injection drug use, receipt of tainted blood products, and mother-to-infant transmission (both perinatal infection and postpartum through breast-feeding).[3] Infection can also be acquired from occupational exposures among health care workers after needle sticks or infected blood splashes from patients infected with HIV

onto vulnerable mucosal membranes. Rarely, HIV infection has been documented following oral sex.[10,11]

Unprotected sexual intercourse accounts for ~80% of all documented HIV infections to date.[2,7] Infectivity via receptive anal intercourse represents the greatest sexual risk factor followed by male-to-female vaginal transmission and then female-to-male penile transmission.[12] Transmission between sexual partners depends on a number of factors, including the HIV viral subtype, stage of infection in the index partner, genetic susceptibility to infection of the potential host, and the viral fitness (or pathogenicity) of the infecting strain. Perhaps one of the most important predictors of transmission is the amount of HIV RNA in the blood of the infected index patient (ie, viral load). In 2011, the HPTN 052 trial demonstrated >95% reduction in risk of transmission when PLWH were started on ART immediately versus waiting for a decline in CD4 count or the onset of HIV-related symptoms. Since this landmark study, additional studies have demonstrated negligible transmission risk (0.00 transmissions/ 100 person-years with a 95% confidence interval of 0.00–0.28) from PLWH who have an undetectable viral load on ART.[13–15]

During transmission, HIV binds to specific immune cells, including Langerhans cells, dendritic cells, T-cell lymphocytes (also known as $CD4^+$ T cells, helper T cells, or T cells), and macrophages.[12,16–18] HIV primarily enters target immune cells that express specific receptor proteins known as CD4 receptors to which HIV binds. Once bound to the CD4 receptor, co-receptor proteins (CCR5, CXCR-4) are required for fusion of the viral membrane to the immune cell membrane.[19,20] CCR5 co-receptors are found on both monocytes and T lymphocytes and are more abundant in patients newly infected with HIV.[21,22] CXCR-4 co-receptors are predominantly found on T lymphocytes and are more abundant in patients who have been on long-term ART. The CD4–co-receptor complex causes conformational changes to key HIV proteins (gp41 and gp120) allowing for a more close association between the virus and the host cell.[22,23] HIV fuses with the cell and releases its contents into the host cell's cytoplasm: this includes the virus's RNA and specific enzymes necessary for replication (**Fig. 76-1**; see online animated images of HIV life cycle and where the drugs act at http://scienceofhiv.org/wp/?page_id=20). The single-stranded viral RNA is transcribed via reverse transcriptase into a double-stranded proviral DNA that is subsequently incorporated into the host cell's genetic material via the integrase enzyme. HIV then uses the infected cell's machinery to translate, transcribe, and produce immature viral particles that bud and break from the infected cell. For these immature virions to become infectious, the HIV protease enzyme must cleave large precursor polypeptides into functional proteins.[24,25] Once complete, the mature virion is free to infect new host cells and subsequently produce more infectious virus.

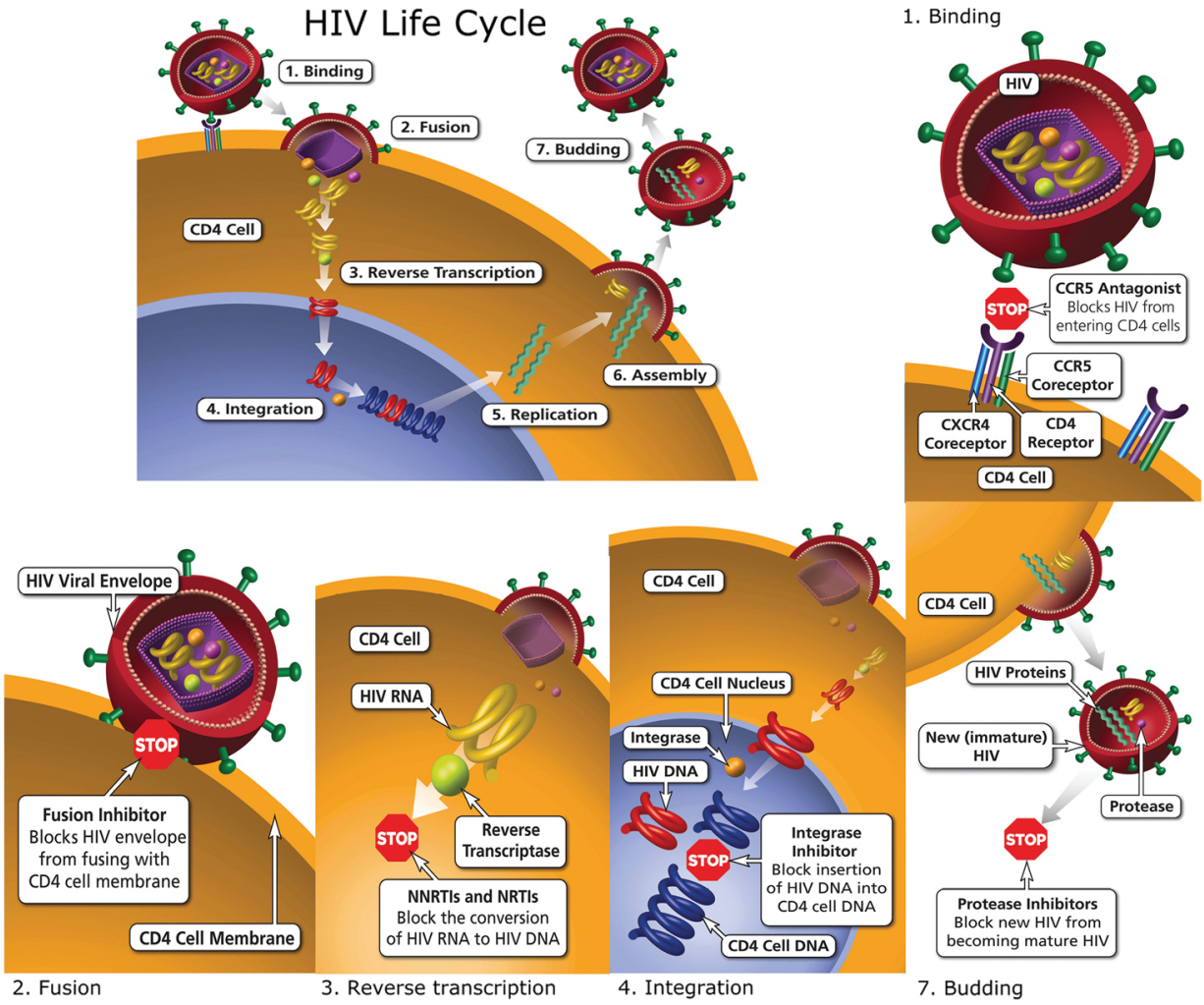


Figure 76-1 Schematic representation of the HIV-1 life cycle. Five classes of antiretroviral drugs are available at present. CCR5 antagonists and fusion inhibitors inhibit the entry of virions into a new target cell. The step of reverse transcription can be targeted, using nucleoside nucleotide analogs or non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs, respectively). The class of integrase inhibitors prevents integration of viral DNA into host cell DNA. The class of PIs interferes with the last state of the life cycle, the proteolytic processing of the viral proteins, which results in the production of noninfectious particles. (Adapted from education materials provided by the National Institutes of Health available on https://clinicalinfo.hiv.gov/en/guidelines.)

Over time, HIV-infected host cells can be destroyed by a number of mechanisms: (a) a direct cytolytic effect of the virus (eg, formation of syncytium induction, cellular dysfunction); (b) the identification and elimination of the infected cell by the host's immune response (eg, via cytotoxic T-cell lymphocytes); or (c) the cell's natural life cycle coming to completion.[26] In addition, HIV infection can inhibit the production of new $CD4^+$ cells.[27]

Once a patient becomes infected, an initial burst of viremia occurs and causes latent infection in various tissues (eg, lymph nodes) and cells (CD4, macrophages, and monocytes).[26,28] Most infectious HIV virions (~99%) reside inside lymph nodes and other immune-cell–rich tissues found throughout the body.[16,26,29,30] The immune system reacts by producing antibodies against HIV; however, given the rapid production of new HIV particles and the development of many new and genetically diverse viral strains (a result of the error-prone HIV reverse transcriptase), the antibody response is inadequate.[31] After this burst of viremia, a transient depletion of $CD4^+$ cells occurs (**Fig. 76-2**). Initially, patients may raise concerns of nonspecific symptoms, such as fever, lymphadenopathy, rash, fatigue, and night sweats.[3] This phase of infection is known as the acute retroviral syndrome.

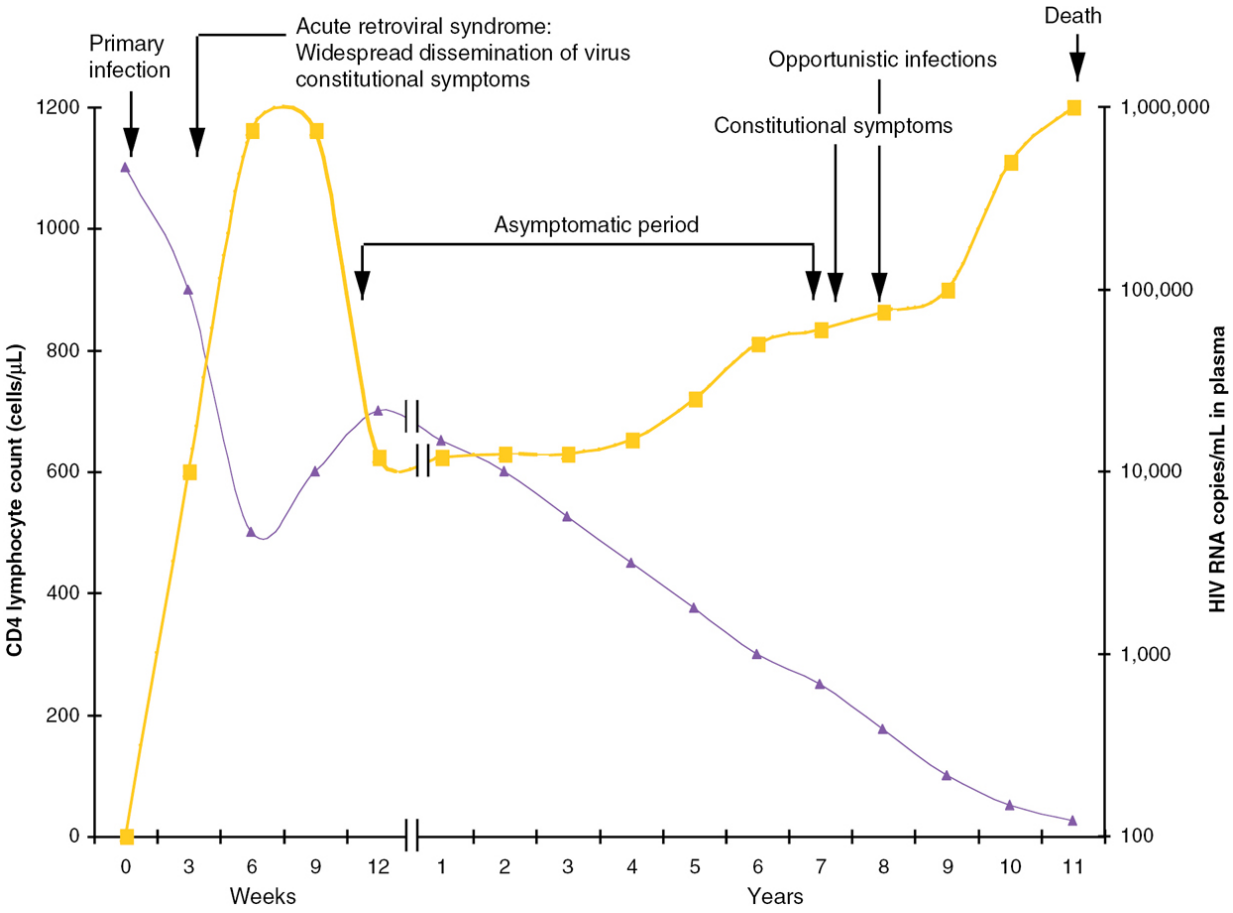


Figure 76-2 Sample disease course for an untreated HIV-infected individual showing the relationships among immunologic, virologic, and clinical outcomes over time. Constitutional symptoms include fever, night sweats, and weight loss. Viral load values; CD4 T lymphocytes. (Source: From Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. *Ann Intern Med*. 1996;124(7):654–663. © 1996 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc; Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion

clearance rate, infected cell life-span, and viral generation time. *Science.* 1996;271(5255):1582–1586.)

In most cases, patients are unaware that they are infected. Within 6 months, the host's immune response is able to control the infection to a point where the number of virus particles produced per day equals the number of particles destroyed per day. This steady state is often referred to as the patient's viral "set point."

The higher a patient's viral set point, the greater the risk for disease progression. This is because there is a greater chance for more widespread viral infection and immune cell destruction with a larger replicating viral population. Why some patients establish higher or lower viral set points is currently under investigation, but this may be a consequence of differences in immune responses, cellular receptor populations, viral subtypes, viral fitness, or a combination of these factors. This understanding of viral pathogenesis has led to a new paradigm of therapy that prioritizes initiating ART in the acute phase of infection to lower viral set points and reduce the size of the viral reservoir (ie, long-lived, latently infected memory T cells believed to be responsible for repopulating the virus in infected patients who stop ART).[3] A significant challenge is to identify these patients with acute infection who have nonspecific symptoms.[32]

Once the initial burst of viremia has been controlled and the viral set point established, infection with HIV results in a constant battle between viral replication and suppression of that replication by the immune system. Mathematical models have calculated the production of HIV at 10 billion particles per day.[16,33–35] To keep the infection controlled, the body must produce an equal immune response. Over time, HIV depletes the body of T cells, which places the host at an increased risk for opportunistic infections. Direct measurements of HIV RNA concentrations in plasma (also called "viral load") can predict disease progression (see subsequent discussion).[36–38] Higher viral load measurements represent an inability of the host to control viral replication and a greater risk for immune cell destruction. Long-term "nonprogressors" (eg, patients with asymptomatic HIV infection for >10 years; 5% of all HIV-infected patients) consistently have lower baseline viral loads than patients with rapidly progressive disease (eg, AIDS within 5 years of infection; 20% of all HIV-infected patients).[39,40]

Without intervention, the natural progression of HIV infection results in depletion of 50 to 100 T cells/μL/year.[26] The severity of immune dysfunction, as evidenced by T-cell loss, is highly predictive of the potential for the development of specific types of opportunistic infections. For example, *Pneumocystis jirovecii* pneumonia rarely occurs when T-cell counts are >200 cells/μL, whereas retinitis from cytomegalovirus infection rarely occurs in patients with CD4 counts >75 cells/μL. The diagnosis of AIDS is made when a significant amount of immune deterioration has occurred, either by depletion of $CD4^+$ cells to <200 cells/μL or because of the development of new opportunistic infections (**Table 76-1**). It is important to recognize that not every patient with HIV has a diagnosis of AIDS. On average, without appropriate drug therapy, death occurs within 10 to 15 years after infection.[26]

Table 76-1

CDC MMWR Revised Surveillance Case Definition for HIV Infection—United States, 2014

HIV infection stage[a] based on age-specific $CD4^+$ T-lymphocyte count or $CD4^+$ T-lymphocyte percentage of total lymphocytes						
Stage	Age on date of $CD4^+$ T-lymphocyte test					
		<1 year		1–5 years		≥6 years
	Cells/μL	%	Cells/μL	%	Cells/μL	%
0[b]	Staging independent of CD4 count/% and age					
1	≥1500	≥34	≥1000	≥30	≥500	≥26
2	750–1499	26–33	500–999	22–29	200–499	14–25
3	>750	>26	>500	>22	>200	>14

[a]Stage is based first on the $CD4^+$ T-lymphocyte count, and then on percentage if the count is unavailable. Three situations can dictate that staging is not based on count or percentage: (1) Stage 0 criteria are met, meaning that the stage is 0 regardless of $CD4^+$ T-lymphocyte test results and the diagnosis of opportunistic infection; (2) if the criteria for stage 0 are not met and a stage-3 defining opportunistic illness has been diagnosed (see Table 76-2), meaning that the stage is 3 regardless of $CD4^+$ T-lymphocyte test results; or (3) if the criteria for stage 0 are not met and information on the above criteria for other stages is missing, then the stage is classified as unknown.

[b]Stage 0 can be established either:

Based on testing history (previous negative/indeterminate test results): a negative or indeterminate HIV test (antibody, combination antigen/antibody, or NAT) result within 180 days before the first confirmed positive HIV test result of any type. The first positive test result could be any time before the positive supplemental test result that confirms it.

Based on a testing algorithm: a sequence of tests performed as part of a laboratory testing algorithm that demonstrate the presence of HIV-specific viral markers such as p24 antigen or nucleic acid (RNA or DNA) 0 to 180 days before or after an antibody test that had a negative or indeterminate result. Adapted from http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm.

The interplay between viral load and CD4 T-cell counts is often compared with that of a train heading toward a particular destination. If the destination is immune system destruction (and eventually death), then the T-cell count is the distance of the train from this destination, and the viral load (concentration of HIV RNA in plasma) is the speed of the train. As both higher speeds and shorter distances reach destinations faster, so does a high viral load and low T-cell count result in quicker onset of immune destruction (and death). Potent ART regimens decrease viral replication and dramatically alter the natural course of infection by prolonging the time to opportunistic infection and death.[41]

PHARMACOTHERAPY

Pharmacotherapy of HIV has been directed at inhibiting key areas of the HIV life cycle (Fig. 76-1 and animations found at http://biosingularity.wordpress.com/2007/03/04/3d--animation-of--hiv-replication/; **Table 76-2**).

Table 76-2

CDC MMWR Revised Surveillance Case Definition for HIV Infection—United States, 2014. Appendix Stage-3 Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent[a]
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive[b]
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV[c]
Herpes simplex: chronic ulcers (>1 month duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary[b], disseminated or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii (previously known as *Pneumocystis carinii*) pneumonia
Pneumonia, recurrent[b]
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV[c]

[a]Only among children ages >6 years.

[b]Only among adults, adolescents, and children ages ≥6 years.

[c]Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: CDC. 1994 Revised classification system for human immunodeficiency virus infection in children age younger than 13 years. *MMWR*. 1994;43(RR-12):1–10; CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 1992;41(RR-17):1–19. Adapted from http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm.

Nucleoside reverse transcriptase inhibitors (NRTIs) include abacavir (ABC), emtricitabine (FTC), lamivudine (3TC), and zidovudine (AZT). NRTIs currently only include tenofovir, which is available in two Food and Drug Administration (FDA)–approved prodrug formulations, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). These agents inhibit this enzyme by incorporating false nucleic acids into the newly forming proviral DNA.[42] This results in an HIV DNA strand that cannot continue to elongate. Non-nucleoside reverse transcriptase inhibitors (NNRTIs; doravirine [DOR], efavirenz [EFV], etravirine [ETR], nevirapine [NVP], and rilpivirine [RPV]) inhibit reverse transcriptase by directly binding to the enzyme itself and prevent DNA transcription from RNA.[43]

Integrase strand transfer inhibitors (INSTIs; bictegravir [BIC], dolutegravir [DTG], elvitegravir [EVG], and raltegravir [RAL]) prevent the integrase enzyme from integrating HIV DNA into the immune cell's genome.[44]

Protease inhibitors (PIs; atazanavir [ATV], darunavir [DRV], and ritonavir [RTV]) directly bind to the catalytic site of HIV protease, inactivating the enzyme and preventing maturation of the HIV virion.[45],[46] Unlike reverse transcription, which occurs early in the course of the HIV life cycle, protease enzyme activity occurs late in virion development. As a result, inactivation of the protease enzyme inhibits viral replication in any infected cell regardless of the current stage of HIV replication within that cell. In contrast, reverse transcriptase inhibitors can protect newly infected cells from becoming latently infected cells before the formation and insertion of proviral DNA into the host cell's genetic material. However, these agents provide no benefit for those infected cells that are actively producing new strains of virus.

Pharmacokinetic (PK) enhancers are drugs that strongly inhibit CYP3A4, a liver enzyme responsible for metabolizing several PIs, NNRTIs, and INSTIs.[47] These agents are used with certain PIs and EVG to impede metabolism and increase serum drug concentrations in order to decrease dosing requirements. RTV, a PI itself, is now used primarily for its boosting effect rather than its anti-HIV activity. The newest PK enhancer, cobicistat (COBI), does not directly affect HIV replication.

Fusion inhibitors (enfuvirtide [T-20], fostemsavir, and ibalizumab [IBA]) prevent HIV and $CD4^+$ T cells from being pulled closer together after HIV binds to CD4 and CCR5 or CXCR-4 co-receptors. Enfuvirtide prevents fusion of the virus with the T cell by binding to a double coil–coil complex at the gp41–gp120–CD4 receptor area.[48] Because of the development of antiretroviral resistance, patients who have failed multiple ART regimens have few options to manage their disease.[49] In 2018, the FDA-approved IBA (Trogarzo), a novel monoclonal antibody dosed once every two weeks as an intravenous infusion in combination with other oral ART, for highly treatment-experienced patients who are failing on their current ART regimen.[50] Fostemsavir is a prodrug of the active moiety, temsavir, which is dosed orally twice daily in combination with other ART.[51] Maraviroc (MVC) is the only FDA-approved CCR5 co-receptor blocker, which prevents HIV from fully binding to cells and causing infection.[52]

With the development of newer, more potent ART regimens in the 2000s, researchers speculated about the possibility of completely eradicating HIV from an

infected patient (see video of challenges to curing HIV/AIDS at http://scienceofhiv.org/wp/?page_id=18). However, even in patients who have been virally suppressed for years on ART, HIV quickly re-emerges (within 2–3 weeks) in the blood (a phenomena known as viral rebound) following ART treatment interruption.[53] It is now widely recognized that the main barrier to eradication is HIV's ability to suppress its own replication and maintain this latent infection within extremely long-lived central memory T cells that have half-lives lasting more than 6 to 44 months. Given this half-life, complete suppression of HIV replication in all anatomical compartments for 60 years or more may be necessary to eradicate HIV in the presence of ART alone.[54–56] Another complicating factor is the potential for HIV to reside in sites that achieve low antiretroviral concentrations, thereby serving as sanctuaries for HIV replication (eg, central nervous system [CNS], testes). Once therapy is discontinued, these sites could theoretically release unaffected virions and repopulate the host.[57] As a result, research has shifted toward immune-based therapies that can identify and destroy HIV-infected cells, in addition to preventing HIV acquisition.[58],[59]

DIAGNOSIS

CASE 76-1

QUESTION 1: E.J. is a 27-year-old male who presents with fevers, night sweats, weight loss, and white patches in his mouth. He states that these symptoms have been present for the past 4 to 6 weeks. E.J. admits to intravenous drug use in the past; however, he states that he has been in recovery for 3 years. E.J. is diagnosed with thrush caused by *Candida albicans*. HIV infection is suspected and consent for an HIV test is obtained.

Why is HIV suspected and how is it confirmed?

In otherwise healthy, immunocompetent individuals, opportunistic infections, such as thrush, are rare because an intact cell-mediated immunity protects against infection. In immunosuppressed individuals, such as those infected with HIV, the immune system is significantly compromised and places patients at risk for opportunistic infections. Infections such as shingles (herpes zoster), tuberculosis, thrush, and recurrent candidal vaginal infections in an otherwise healthy person warrant further evaluation for the possibility of HIV infection. More advanced diseases, such as *P. jirovecii* pneumonia, *Mycobacterium avium* bacteremia, and cytomegalovirus retinitis infections, among others, generally occur in patients with severely depressed immune systems and strongly suggest HIV infection. This suggestion is especially true for those patients with risk factors for HIV infection.[3] Despite E.J.'s discontinuation of intravenous drugs, his prior use places him at risk for HIV infection. Given his social history and current clinical presentation, an HIV test is warranted.

Laboratory methods used to diagnose HIV infection rely on detecting antigens produced by HIV viral replication or antibodies produced by the host's immune response to HIV infection. After HIV infection, there is an initial eclipse period where no antigen or antibody laboratory markers can be consistently detected.[60] The first laboratory marker that can be reliably detected in the plasma after infection is HIV RNA by nucleic acid tests (NATs) ~10 days after infection, then p24 (a protein produced during viral replication) ~4 to 10 days after HIV RNA can be detected. The immune response to HIV infection is characterized first by the production of anti-HIV immunoglobulin (Ig)M proteins (10–13 days after HIV RNA can be detected) then IgG (18–38 days after HIV RNA can be detected). The period between infection with HIV and the ability to detect these antibodies is known as the seroconversion window, and the duration of this window can vary based on assay sensitivity or antibody type. Established infection is characterized by a fully developed IgG response.

Although early laboratory methods that utilized enzyme-linked immunosorbent assays (ELISA) and confirmatory Western blot to detect anti-HIV IgG antibodies were highly sensitive (>99%), the turnaround time for test results could be up to 1 to 2 weeks and the seroconversion window was 1 to 2 months long, making it difficult to diagnose early infections.[60] Third-generation HIV assays decreased the seroconversion window by including anti-HIV IgM.[60] Fourth-generation antigen/antibody combination assays further reduced this timeframe by testing for p24 antigen and anti-HIV-1 and 2 IgM/IgG. Fifth-generation assays further built on these advances and have allowed for fully automated procedures to differentiate among p24 antigen, HIV-1, and HIV-2 antibodies in 45 minutes, a process aligned with the Centers for Disease Control and Prevention's (CDC) 2018 quick reference guide for HIV testing algorithm in serum or plasma specimens.[61–63] Updated in January 2018—and to be used in conjunction with the 2014 recommendations—the quick reference states that unless there is reason to suspect very early infection, no further testing is required for a nonreactive antigen/antibody combination assay.[60,62] Specimen with reactive antigen/antibody results should be further tested with an immunoassay to differentiate HIV-1 and HIV-2 antibodies. NATs for HIV RNA should be used to confirm an indeterminate antibody differentiation immunoassay or a negative antigen/antibody tests in patients where there is reason to suspect very early infection.[60,62]

SURROGATE MARKER DATA

Although current guidelines recommend initiating therapeutic interventions for all HIV-infected persons ready to begin treatment, the severity of immune damage and potential for disease progression should still be assessed.[3] As stated previously, HIV predominantly infects and destroys T cells. The larger the viral load, the greater the risk for T-cell destruction and opportunistic infections. Therefore, quantitative measurements of E.J.'s HIV viral load and T-cell counts will assist in determining the

severity of infection, assessing the risk for disease progression, and providing a reference point (ie, baseline) for future therapeutic decisions.

Identification and measurement of T-lymphocyte subsets (eg, CD4, CD8) are based on flow cytometry readings of fluorescent-labeled monoclonal antibodies.[64] These values can vary widely on repeated laboratory evaluations, even in clinically stable patients. Patient samples can display up to 30% intralaboratory and interlaboratory variabilities.[3] Consequently, it is important to realize that assessment of T-cell measurements should always be interpreted as trends and not as individual values. Variability can also be minimized by using the same laboratory and by sampling patients at a consistent time of day.

The measurement of HIV viral load can be performed by one of three methods: reverse transcriptase–polymerase chain reaction (RT-PCR), branched-chain DNA assay, or nucleic acid sequence–based amplification.[65] Measurements using RT-PCR are obtained when viral RNA is amplified and counted. In contrast, branched-chain DNA amplifies and enumerates the signal from target probes attached to the viral RNA. Nucleic acid sequence–based amplification allows real-time, high-throughput amplification of viral RNA. All methods report HIV RNA in plasma as the number of copies per milliliter but have differing lower limits of quantitation.[3] It should be recognized that plasma viral RNA values measure the amount of free virus in the periphery and not the lymph nodes. Because viral concentrations are substantially greater in the lymph node, plasma measurements of HIV indirectly reflect spillover from replication in that compartment.[66,67]

Similar to CD4 counts, viral load measurements (copies/milliliter) can vary by as much as threefold (0.5 log) in either direction.[3] When obtaining a patient's baseline value, a number of issues must be considered. On initial infection with HIV, a burst of viremia occurs until the host's immune responses are able to control the infection. Consequently, viral load measurements obtained during the first 6 months of infection may not accurately reflect a true baseline value.[3] In addition, factors that activate the immune system, such as the development of a new opportunistic infection or immunizations,[68] can result in transient elevations of viral load measurements. In these situations, concentrations obtained within 4 weeks of the event may not accurately reflect the baseline viral load measurement.[3]

Some clinicians would recommend that at least two separate viral load measurements, which are obtained within 1 to 4 weeks of each other, be performed before making decisions regarding therapeutic options.[3] As with T-cell values, viral load measurements should be evaluated as trends.

In addition to quantifying the viral load, baseline resistance testing should be performed, using either genotypic or phenotypic testing, to guide the selection of the initial regimen. Resistance testing is recommended in most clinical situations before beginning treatment, because the rate of transmission of virus resistant to at least one drug (ie, transmitted drug resistance) has been noted in up to 10% to 17% of HIV-infected patients who have never been on ART in high-income countries (see Resistance, Viral Genotyping, Phenotyping, and Viral Fitness section, for further discussion).[3]

Case 76-1, Question 2: E.J.'s HIV-1/2 antigen/antibody combination immunoassay is reactive, and the antibody differentiation immunoassay detects HIV-1 antibodies. He is informed of his HIV status the next day at his follow-up examination. Before making any decisions regarding therapeutic options, what additional laboratory tests should be obtained?

E.J. should have a baseline T-cell count, viral load measurement, and viral genotype obtained. A complete blood count, electrolyte panel, renal and liver function tests, and hepatitis B and C serology should be performed. If specific therapies are being considered, such as ABC and MVC, specific testing is available to guide the appropriate use of these agents. HLA-B5701 screening is performed before starting a patient on ABC because of an increased risk for exhibiting a hypersensitivity reaction in patients positive for this allele. Co-receptor tropism assay is performed before initiating MVC to determine whether the patient has a virus that predominantly uses CCR5 receptors (versus ones that use primarily CXCR-4 receptors or ones that can use both).[3] These laboratory results help in selecting therapeutic options (see subsequent discussion) and establish baseline values in the event that problems are encountered in the future.

ANTIRETROVIRAL THERAPY

Case 76-1, Question 3: E.J.'s T-cell count and viral load measurement return at 225 cells/μL and 145,000 copies/mL (by RT-PCR assay), respectively. Should ART be initiated?

ART should be offered to all patients who are willing and able to commit to lifelong treatment after an in-depth discussion of the benefits and risks of ART and the importance of adherence. This recommendation is based on the results of two large randomized clinical trials (START; The Strategic Timing of AntiRetroviral Treatment and the TEMPRANO ARNS 12136 Study). These trials investigated the risks and benefits of initiating ART at a CD4 count >500 cell/μL versus delaying until the CD4 count declined to >350 cell/μL. A significant increase in morbidity and mortality was observed when ART was delayed.[3] In further support of starting ART regardless of baseline CD4 count, the guidelines recognize the benefits of initiating ART for HIV prevention and support initiating ART to prevent perinatal and heterosexual transmission (AI evidence rating) or other transmission risks (AIII evidence rating). Understanding logistical concerns related to the linkage of care between initial HIV diagnosis and ART prescribing, there are recommendations regarding rapid ART initiation on the same day of HIV diagnosis. This is intended to enhance the uptake of ART and promote the engagement in clinical care to achieve viral suppression, which has been demonstrated in numerous studies, both in the United States and in resource-limited settings.[69–72] Certain clinical situations favor urgent initiation of ART include pregnancy: AIDS-defining condition such as an opportunistic infection and acute/early HIV infection.[3] In patients who are asymptomatic, assessment of the

patient's surrogate marker data (T-cell count, viral load measurements), concurrent medical conditions, medication adherence history (if any), and motivation to initiate therapy are necessary.

In otherwise healthy, immunocompetent persons, T-cell measurements are >1200 cells/μL. In patients who have been chronically infected with HIV, significant T-cell destruction occurs. When T-cell counts fall to <500 cells/μL, patients are at increased risk for opportunistic infections. The risk of disease progression is closely tied to CD4 cell counts, with low CD4 counts (<200 cells/μL) predicting both short-term and long-term risk of disease progression.[73–75] High viral load (>100,000 copies/mL), increasing age, acquisition of infection through intravenous drug use, and a previous AIDS diagnosis also increase the risk of disease progression in observational cohorts.

The decision to initiate ART should not be taken lightly. ART regimens may improve the quality and duration of a patient's life, but they are not without risks. Patients should be counseled that ART should be continued indefinitely without interruption to improve and preserve the immune system. For some patients, this may be a difficult realization, particularly if the patient is relatively healthy. In addition, the risk of adverse events/toxicities and the costs of ART should be considered before beginning treatment. These guidelines, therefore, should be used to initiate discussions with the patient regarding the risks and benefits of therapy. It is critical for practitioners to talk openly with patients about their fears and concerns and make an assessment about their motivation to initiate therapy and ability to adhere to a lifelong regimen, and the U.S. Department of Health and Human Services (DHHS) guidelines support this discussion.[3] The patient should always make the final decision after careful discussions with the practitioner.

E.J. has a number of significant risk factors for disease progression. He is clinically symptomatic with oral thrush and nonspecific constitutional symptoms (eg, fevers, night sweats, and weight loss). His surrogate marker data place him at risk for greater disease progression (T-cell count <500 cells/μL and viral load >100,000 copies/mL). Based on these values, E.J. should be counseled on his risk of disease progression, potential adverse events associated with both starting and deferring treatment, and his willingness to adhere to a regimen.

Before developing a patient-specific regimen, it is important to recognize the benefits and limitations of ART and identify obtainable and realistic goals.

Case 76-1, Question 4: After careful discussions, E.J. agrees to initiate ART. What should be the goals of therapy? What other factors or information should be considered in selecting an appropriate regimen?

Goals of Therapy

GOAL 1: MAXIMALLY AND DURABLY SUPPRESS VIRAL LOAD

Maximal viral suppression often results in significant increases in T-cell counts and improved clinical outcomes. Based on our understanding of viral pathogenesis, this finding is not surprising. Lower amounts of replicating virus result in decreased risk for T-cell infection and destruction and, subsequently, a more intact immune response. Therefore, therapy should suppress viral replication to undetectable levels in the plasma (>50 copies/mL), for as long as possible.[3–5] The development of new ART with improved potency, higher genetic barrier to resistance, low adverse event profiles, and more convenient dosing regimens (including once-daily single tablet regimens) makes viral suppression a reasonable goal in most patients, even those who previously have received multiple suboptimal regimens or failed therapy. In the treatment-experienced patient, however, special care must be given to designing a regimen that will suppress viral load, yet not contribute to the development of drug resistance that limits future treatment options. Consultation with an expert in ART resistance patterns is critical to designing a salvage regimen in such patients.

The development of drug resistance is also a consideration in the selection of regimens for patients who have not previously used ART (ART naive). In any given viral population, the potential exists for a spontaneous mutation to occur, which results in a resistant isolate. The larger the population, the greater the risk for mutations. HIV replication is a highly error-prone process, especially with the reverse transcriptase enzyme. Given the high rate of viral replication, the potential exists for the daily production of thousands of replication-competent viral mutations to each and every site on the HIV genome (~10,000 nucleotides in length).[4,35] Under selective pressures from inadequate ART, spontaneously produced isolates with reduced susceptibility to the given regimen eventually flourish and repopulate the host. This fact is of particular concern, given the potential for cross-resistance between ART (see the following discussion of resistance). Therefore, the use of a regimen that fully suppresses viral replication reduces the potential for mutations and the development of cross-resistance.

Although >30 FDA-approved ART agents are currently available to use in combination therapies, many of these agents display similar resistance profiles. Developing resistance to one or more agents in a given regimen may result in the loss of activity to other agents with similar resistance profiles (ie, cross-resistance).[4] Whether drug resistance develops is determined by the genetic barrier associated with the individual antiretroviral drugs. Some drugs have low genetic barriers; that is, only one or two critical changes in the virus are necessary for resistance to occur. An example of a class of agents with a low genetic barrier is the NNRTIs. Although a number of individual point mutations in the viral genome can confer the loss of activity for the first-generation NNRTIs (EFV and NVP), second-generation NNRTIs (DOR, ETR, and RPV) exhibit improved barriers to resistance compared to these first-generation agents. In contrast, the PIs have a wide genetic barrier, which requires multiple changes to the viral genome to incur resistance.[4]

It should be recognized, however, that just because an agent has a low genetic barrier does not mean it is virologically inferior or less potent. Potent regimens containing NNRTIs are highly effective and provide durable treatment responses. The

potency of the entire regimen is critical to determining whether drug resistance develops.[3] If viral replication is suppressed, the development of resistance will be minimal. When viral replication does occur, the greater the replication, the greater the risk for development of resistance. In situations in which viral replication does occur, inclusion of a drug with a low genetic barrier in the ART regimen may be risky and could result in the loss of activity of the drug, the development of cross-resistance to other drugs, or both. As a result, an ART regimen should be selected that has a high likelihood of suppressing viral replication and to which the patient will strictly adhere.

GOAL 2: PRESERVE AND STRENGTHEN THE IMMUNE SYSTEM

Decreasing viral replication usually leads to increased CD4 cell counts, which strengthens and preserves the immune system. With increased cell counts, patients are at lower risk for exhibiting opportunistic infections and death. With newer and improved regimens, strengthening and preserving the immune system may be possible even in treatment-experienced patients, although drug regimens must be designed carefully to prevent developing further resistance. Full immune reconstitution may not be possible if the CD4 cell count is low for a long period of time; however, it is reasonable to try and restore immune function as fully as possible. Despite advances in drug therapy, it is important to remember that HIV remains an incurable condition.

GOAL 3: LIMIT DRUG ADVERSE EVENTS, PROMOTE ADHERENCE, AND IMPROVE QUALITY OF LIFE

Treatment with combination therapy has been shown to be highly effective in suppressing HIV replication and improving survival among PLWH. Lifelong adherence to an ART is required and can be a complex and difficult task, although advances in co-formulation of drug products have simplified HIV treatment considerably. Several once-daily regimens and single tablet regimens are recommended as first-line therapy (**Tables 76-2** and **76-3**), and long-acting injectable therapies will likely be available soon. The patient's ability to adhere to therapy may, however, still be the difference between a regimen that fails and one that results in a clinical benefit. The first regimen generally provides the best chance for treatment success. Although newer ART tend to exhibit better adverse event profiles compared to the early ART, adverse events can still make tolerating these regimens difficult and affect drug adherence and response to therapy. Changes in body composition (known as lipodystrophy), increases in lipids and triglycerides, decreases in bone mineral density, increased risks for cardiac disease, and the development of lactic acidosis are serious concerns.[3]

Table 76-3

Characteristics of Antiretroviral Agents for the Treatment of Adult Human Immunodeficiency Virus Infection

Drug	Dose	Pharmacokinetic Parameters	Administration Considerations
Nucleoside Reverse Transcriptase Inhibitors			
Abacavir (ABC) **Ziagen** *Preparations* Tablets: 300 mg Oral solution: 20 mg/mL Epzicom: ABC 600 mg + 3TC 300 mg Trizivir: ABC 300 mg + ZDV 300 mg + 3TC 150 mg Triumeq: ABC 600 mg + 3TC 300 mg + DTG 50 mg	300 mg every 12 hours, or 600 mg daily Epzicom: one tablet daily Trizivir: one tablet bid Triumeq: one tablet daily	*Oral bioavailability*: 83% *Serum* $t_{1/2}$: 1.5 hours *Intracellular* $t_{1/2}$: 12–26 hours *Elimination*: alcohol dehydrogenase and glucuronyltransferase; 82% renal elimination of metabolites	Can be administered without regard to meals Alcohol raises abacavir exposure by 41% HLA testing required before administration
Lamivudine (3TC) **Epivir** *Preparations* Tablets: 150, 300 mg Solution: 10 mg/mL Combivir: 3TC 150 mg + ZDV 300 mg Epzicom: 3TC 300 mg + ABC 600 mg Trizivir: 3TC 150 mg + ZDV 300 mg + ABC 300 mg Triumeq: ABC 600 mg + 3TC 300 mg + DTG 50 mg	150 mg PO bid or 300 mg PO daily Combivir: one tablet bid Epzicom: one tablet bid Trizivir: one tablet bid Triumeq: one tablet daily	*Oral bioavailability*: 86% *Serum* $t_{1/2}$: 5–7 hours *Intracellular* $t_{1/2}$: 18–22 hours *Elimination*: 70% unchanged in urine	Can be administered without regard to meals
Emtricitabine (FTC) **Emtriva** *Preparations* Capsules: 200 mg Oral solution: 10 mg/mL Truvada: FTC 200 mg + TDF 300 mg Atripla: FTC 200 mg + TDF 300 mg + EFV 600 mg Complera: FTC 200 mg + RPV 25 mg + TDF 300 mg Stribild: FTC 200 mg + EVG/c 150/150 mg + TDF 300 mg Descovy: FTC 200 mg + TAF 300 mg Odefsey: FTC 200 mg + RPV 25 mg + TAF 25 mg Genvoya: FTC 200 mg + EVG/c 150/150 mg + TAF 10 mg	200 mg daily for patients with calculated CrCl >50 mL/minute Dose needs to be adjusted for renal dysfunction: CrCl 30–49 mL/minute: 200 mg every 48 hours CrCl 15–29 mL/minute: 200 mg every 72 hours CrCl >15 mL/minute: 200 mg every 96 hours Truvada: one tablet daily. Not for patients with CrCl >30 mL/minute Atripla: one tablet daily. Not for patients with CrCl >50 mL/minute Complera: one tablet daily Stribild: one tablet daily. Not for patients with CrCl >70 mL/minute Stribild: one tablet daily. Not for patients with CrCl >70 mL/minute	*Oral bioavailability*: 93% *Serum* $t_{1/2}$: 10 hours *Intracellular* $t_{1/2}$: >20 hours *Elimination*: 86% recovered in urine	Can be administered without regard to meals
Tenofovir Disoproxil Fumarate (TDF) **Viread** *Preparations* Tablets: 150, 200, 250, 300 mg Oral powder: 40 mg/g Truvada: TDF 300 mg + FTC 200 mg Atripla: TDF 300 mg + FTC 200 mg + EFV 600 mg Complera: FTC 200 mg + RPV 25 mg + TDF 300 mg Stribild: FTC 200 mg + EVG/c 150/150 mg + TDF 300 mg	300 mg daily for patients with CrCl >60 mL/minute Truvada: one tablet daily. Not for patients with CrCl >30 mL/minute Atripla: one tablet daily. Not for patients with CrCl >50 mL/minute Complera: one tablet daily Stribild: one tablet daily. Not for patients with CrCl >70 mL/minute	*Oral bioavailability*: 25% fasting; 39% with high-fat meal *Serum* $t_{1/2}$: 17 hours *Intracellular* $t_{1/2}$: >60 hours *Elimination:* primarily by glomerular filtration and active tubular secretion	Can be administered without regard to meals

Drug	Dose	Pharmacokinetic Parameters	Administration Considerations
Nonpreferred Nucleoside Reverse Transcriptase Inhibitors			
Tenofovir alafenamide (TAF) *Preparations* Descovy: TAF 25 mg + FTC 200 mg Odefsey: FTC 200 mg + RPV 25 mg + TAF 25 mg Genvoya: FTC 200 mg + EVG/c 150/150 mg + TAF 10 mg	25 mg for patients with CrCl >30 mL/minute Descovy: one tablet daily Odefsey: one tablet daily Genvoya: one tablet daily	*Oral bioavailability:* 40% *Serum* $t_{1/2}$: 0.51 hours *Intracellular* $t_{1/2}$: 150–180 hours *Elimination*: primarily by glomerular filtration and active tubular secretion	Can be administered without regard to meals
Zidovudine (ZDV) **Retrovir (R)** *Preparations* Oral solution: 10 mg/mL Capsule: 100 mg Tablet: 300 mg IV solution: 10 mg/mL Combivir: ZDV 300 mg + 3TC 150 mg Trizivir: ZDV 300 mg + 3TC 150 mg + ABC 300 mg	300 mg bid or 200 mg tid Combivir (R) or Trizivir (R): one tablet bid	*Oral bioavailability*: 60% *Serum* $t_{1/2}$: 1.1 hours *Intracellular* $t_{1/2}$: 3 hours *Elimination*: hepatic glucuronidation; renal excretion of glucuronide metabolite	Can be administered without regard to meals (manufacturer recommends administration 30 minutes before or 1 hour after a meal.)
Didanosine (ddI) **Videx** *Preparations* Videx EC (R): 125, 200, 250, 400 mg capsule Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL Generic ddI enteric-coated capsule also available	>60 kg: 400 mg daily (with TDF, use 250 mg daily) >60 kg: 250 mg daily (with TDF, use 200 mg daily)	*Oral bioavailability*: 30%–40% *Serum* $t_{1/2}$: 1.6 hours *Intracellular* $t_{1/2}$: 25–40 hours *Elimination:* renal excretion ~50%	Food decreases absorption (decreases 55%); administer ddI on empty stomach (1 hour before or 2 hours after meal) Separate ATV and TPV/r administration by at least 2 hours.
Stavudine (d4T) **Zerit** *Preparations* Solution: 1 mg/mL Capsules: 15, 20, 30, 40 mg	>60 kg: 40 mg bid >60 kg: 30 mg bid Sustained release: >60 kg use 100 mg daily; >60 kg use 75 mg daily	*Oral bioavailability*: 86% *Serum* $t_{1/2}$: 1.0 hour *Intracellular* $t_{1/2}$: 3.5 hours *Elimination*: renal excretion ~50%	Can be administered without regard to meals
Non-Nucleoside Reverse Transcriptase Inhibitorsa			
Rilpivirine (RPV) **Edurant** *Preparations* Tablets: 25 mg Complera: RPV 25 mg + TDF 300 mg + FTC 200 mg Odefsey: RPV 25 mg + TAF 25 mg + FTC 200 mg	25 mg daily Complera: one tablet daily	*Oral bioavailability*: not established *Serum* $t_{1/2}$: ~50 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism primarily by CYP3A4 with 85% fecal excretion	Take with moderate-to-high calorie meal (increases absorption 40%).
Efavirenz (EFV) **Sustiva®** *Preparations* Capsules: 50, 100, 200 mg Tablets: 600 mg Atripla: EFV 600 mg + TDF 300 mg + FTC 200 mg	600 mg at bedtime Atripla one tablet at bedtime. Not for patients with CrCl >50 mL/minute	*Oral bioavailability*: ~60%–70% *Serum* $t_{1/2}$: 40–55 hours *Intracellular* $t_{1/2}$: unknown *Elimination:* hepatically metabolized by CYP2B6 and CYP3A4 (also CYP3A4 mixed inhibitor/inducer)	Avoid taking with high-fat meals, concentrations increases 50% (increased risk for CNS toxicity).
Etravirine (ETV) **Intelence** *Preparations* Tablets: 100, 200 mg	200 mg bid	*Oral bioavailability*: unknown *Serum* $t_{1/2}$: 40 ± 20 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatically metabolized by CYP3A4, CYP2C9, CYP2C19 (also 3A4 inducer, 2C9 and 2C19 inhibitors)	Take after a meal.

Drug	Dose	Pharmacokinetic Parameters	Administration Considerations
Nonpreferred Non-Nucleoside Reverse Transcriptase Inhibitors[a]			
Nevirapine (NVP) **Viramune** *Preparations* Suspension: 50 mg/5 mL Tablets: 200 mg	200 mg PO daily × 14 days, then 200 mg PO bid	*Oral bioavailability*: >90% *Serum* $t_{1/2}$: 25–30 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: metabolized by CYP2B6 and CYP3A4 (also a CYP3A4 inducer) with 80% excreted in urine as the glucuronide metabolite	Can be administered without regard to meals
Protease Inhibitors			
Darunavir (DRV) **Prezista** *Preparations* Tablet: 75, 150, 600, 800 mg Suspension: 100 mg/ml Prezcobix®: DRV 800 mg + COBI 150 mg	DRV 800 mg + RTV 100 mg daily In patients with ≥1 DRV resistance mutations: DRV 600 mg + RTV 100 mg bid Prezcobix®: one tablet daily	*Oral bioavailability*: 37% alone, 82% with RTV *Serum* $t_{1/2}$: 15 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism via CYP3A4 (inhibitor)	Food increases C_{max} and AUC by 30%: administer with food.
Atazanavir (ATV) **Reyataz** *Preparations* Capsules: 100, 150, 200, 300 mg Evotaz®: ATV 300 mg + COBI 150 mg	400 mg daily Atazanavir/RTV: 300/100 daily Evotaz®: one tablet daily	*Oral bioavailability*: 60%–70% *Serum* $t_{1/2}$: 6–7 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism via CYP3A4 (modest inhibitor)	Take with food, and avoid acid suppressing agents (which prevent ATV solubility and absorption).
Lopinavir (LPV)/ritonavir (RTV) **Kaletra** *Preparations* Tablet: LPV 200 mg + RTV 50 mg Solution: LPV 80 mg+ RTV 20 mg per mL	Two tablets or 5 mL bid or Four tablets or 10 mL daily (recommended for treatment-naive patients only)	*Oral bioavailability*: not determined *Serum* $t_{1/2}$: 5–6 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism via CYP3A4 (inhibitor)	Take with food (increases AUC by 48%). Tablet stable at room temperature.
Nonpreferred Protease Inhibitors			
Indinavir (IDV) **Crixivan** *Preparations* Capsule: 200, 333, 400 mg	800 mg every 8 hours (bid dosing ineffective when sole protease inhibitor) IDV/RTV: IDV 800 mg + 100 mg or 200 mg RTV bid	*Oral bioavailability*: 65% *Serum* $t_{1/2}$: 1.5–2 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatically metabolized via CYP3A4 (also inhibitor of CYP3A4)	Must be taken on empty stomach (1 hour before or 2 hours after a meal); may be taken with skim milk or low-fat meal Adequate hydration necessary (at least 1.5 L/24 hours of liquid) to minimize risk of nephrolithiasis
Nelfinavir (NFV) **Viracept** *Preparations* Powder for oral suspension: 50 mg per one level scoop (200 mg per one level teaspoon) Tablets: 250 and 625 mg	750 mg tid or 1250 mg bid	*Oral bioavailability*: 20%–80% *Serum* $t_{1/2}$: 3.5–5 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism via CYP3A4	Administer with meal or light snack (exposure increased two- to threefold).
Saquinavir (SQV) **Invirase** (hard gel capsules) *Preparations* Hard gel capsule: 200 mg Tablets: 500 mg	Unboosted saquinavir not recommended Saquinavir/ritonavir: 1000/100 bid; 1600/100 daily under investigation	*Oral bioavailability*: 4% (as the sole PI) *Serum* $t_{1/2}$: 1–2 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism via CYP3A4 (inhibitor)	Take within 2 hours of a meal and take with RTV.

Drug	Dose	Pharmacokinetic Parameters	Administration Considerations
Fosamprenavir (FPV) **Lexiva** Tablet: 700 mg	In ARV-naive patients: FPV 1400 mg bid or FPV 1400 mg + RTV 200 mg daily or FPV 700 mg + RTV 100 mg bid In PI-experienced patients: FPV 700 mg + RTV 100 mg bid	*Oral bioavailability*: not determined *Serum* $t_{1/2}$: 7.1–10.6 hours (APV) *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism via CYP3A4 (inhibitor)	Can be taken without regard to meals but should not be taken with high-fat meals
Tipranavir (TPV) **Aptivus®** Capsules: 250 mg	TPV 500 mg + RTV 200 mg bid DO NOT USE WITHOUT RTV	*Oral bioavailability*: not determined *Serum* $t_{1/2}$: 6 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism via CYP3A4 (inhibitor and inducer)	Administer with food to increase bioavailability.
Entry Inhibitors			
Enfuvirtide (T-20) Fuzeon	90 mg SC bid in upper arm, thigh, or abdomen	*Oral bioavailability*: 84.3% compared with IV *Serum* $t_{1/2}$: 3.8 hours *Intracellular* $t_{1/2}$: not applicable *Elimination*: nonrenal, nonhepatic	Reconstitute with 1.1 mL sterile water for injection; gently tap vial for 10 seconds and then roll gently between hands to avoid foaming and ensure all drug is off vial walls. After reconstitution, use immediately or refrigerate for 24 hours. Refrigerated T-20 should be brought to room temperature before injection.
Chemokine Receptor Antagonists (CCR5)			
Maraviroc (MVC) **Selzentry** *Preparations* Tablet: 150, 300 mg	300 mg bid (with all NRTIs, NVP, TPV, ENF), 150 mg bid with CYP3A inhibitors (with or without a CYP3A inducer) including protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, and other strong CYP3A inhibitors (eg, nefazodone, telithromycin) 600 mg bid with CYP3A inducers (without a strong CYP3A inhibitor) including Efavirenz, etravirine (TMC125), rifampin, carbamazepine, phenobarbital, and phenytoin	*Oral bioavailability*: ~33% *Serum* $t_{1/2}$: 14–18 hours *Elimination*: hepatic metabolism by CYP3A; 20% recovered in urine, 76% recovered in feces	Can be administered without regard to meals (high-fat meal decreases C_{max} and AUC by ~30%) Trofile assay must be performed before administration.
Integrase Inhibitors			
Dolutegravir (DTG) **Tivicay** *Preparations* Tablet: 50 mg Triumeq: DTG 50 mg + ABC 600 mg + 3TC 300 mg	50 mg once daily 50 mg bid when coadministered with EFV, FPV/r, TPV/r, or rifampin 50 mg bid when INSTI mutations present Triumeq: one tablet daily	*Oral bioavailability*: unknown *Serum* $t_{1/2}$: ~14 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism by UGT1A1 (major) CYP3A4 (minor); 31% recovered in urine, 53% recovered in feces	Increased serum creatinine because of inhibition of tubular secretion not decreased renal glomerular filtration. Mean (range) increase from baseline = 0.15 (−0.32 to 0.65) mg/dL

Drug	Dose	Pharmacokinetic Parameters	Administration Considerations
Elvitegravir (EVG) **Vitekta** *Preparations* Tablet: 85, 150 mg Stribild: EVG 150 mg + COBI 150 mg + FTC 200 mg + TDF 300 mg Genvoya: EVG 150 mg + COBI 150 mg + FTC 200 mg + TAF 10 mg	85 mg once daily if coadministered with ATV/r or LPV/r 150 mg once daily if coadministered with DRV/r 600/100 mg bid, FPV/r 700/100 mg bid, or TPV/r 500/200 mg bid 50 mg bid when INSTI mutations present Stribild: one tablet daily	*Oral bioavailability*: not established *Serum* $t_{1/2}$: 9 hours when administered with RTV *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism by CYP3A, and UGT1A1/3; 6.7% recovered in urine, 94.8% recovered in feces	Vitekta must be administered with ritonavir unboosted. EVG is not recommended. Take with food.
Raltegravir (RAL) **Isentress®** *Preparations* Tablet: 400 mg, 1200 mg HD Chewable tablet: 25, 100 mg Single packet for oral suspension: 100 mg	400 mg bid or 1200 mg (HD) daily	*Oral bioavailability*: not established *Serum* $t_{1/2}$: 9 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: hepatic metabolism by UGT1A1 glucuronidation; 32% recovered in urine, 51% recovered in feces	Can be administered without regard to meals (high-fat meal decreases C_{max} by ~34% and increases AUC by ~19%)
Pharmacokinetic Enhancers			
Ritonavir (RTV) **Norvir®** *Preparations* Oral solution: 80 mg/mL Capsules: 100 mg Tablets: 100 mg	RTV is a PI currently used as a pharmacokinetic enhancer for other PIs and EVG, using 100–400 mg/day in one to two divided doses	*Oral bioavailability*: Not determined *Serum* $t_{1/2}$: 3–5 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: extensive hepatic metabolism via CYP3A4 (also potent CYP3A4 inhibitor and mixed inhibitor/inducer of other isozymes)	Take with food if possible to improve tolerability Dose should be titrated upward to minimize gastrointestinal adverse events Refrigerate capsules but not liquid or tablets Solution contains 43% alcohol.
Tybost **(COBI)** **Cobicistat** *Preparations* Tablets: 150 mg Stribild: EVG 150 mg + COBI 150 mg + FTC 200 mg + TDF 300 mg Prezcobix®: DRV 800 mg + COBI 1 50 mg Evotaz®: ATV 300 mg + COBI 150 mg	150 mg daily when coadministered with ATV 300 mg daily 150 mg daily when coadministered with DRV 800 mg daily Stribild: one tablet daily. Not for patients with CrCl >70 mL/minute Prezcobix®: one tablet daily Evotaz®: one tablet daily	*Oral bioavailability*: Not determined *Serum* $t_{1/2}$: 3–5 hours *Intracellular* $t_{1/2}$: unknown *Elimination*: extensive hepatic metabolism via CYP3A4 (also potent CYP3A4 inhibitor and mixed inhibitor/inducer of other isozymes) 8.2% recovered in urine, 86.2% recovered in feces	Not interchangeable with RTV Increased serum creatinine because of inhibition of tubular secretion not decreased renal glomerular filtration. Monitor for renal safety if increased from baseline >0.4 mg/dL.

ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; AUC, area under the curve; bid, twice daily; CNS, central nervous system; COBI, cobicistat; CrCl, creatinine clearance; ddI, didanosine; d4T, stavudine; DLV, delavirdine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ENF, enfuvirtide; ETV, etravirine; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; HLA, human leukocyte antigen; IDV, indinavir; IV, intravenous; LPV, lopinavir; MVC, maraviroc; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PI, protein inhibitor; PO, orally; qid, four times daily; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SC, subcutaneously; SQV, saquinavir; 3TC, lamivudine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; tid, three times daily; TPV, tipranavir; TPV/r, tipranavir/ritonavir; T-20, enfuvirtide; ZDV, zidovudine.

[a]In clinical trials, the NNRTIs were discontinued because of rash in 7% of patients taking nevirapine, 4.3% of patients taking delavirdine, and 1.7% of patients taking efavirenz. Rare cases of Stevens–Johnson syndrome have been reported with all three NNRTIs.

Sources: U.S. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines; Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2020;324(16):1651–1669. doi:10.1001/jama.2020.17025.

Limit adverse events

Although new ART offers marked improvement over early generation agents' toxicity profiles, lifelong ART is not without risk. Historically, metabolic complications from older ART include abnormal distribution of body fat, lipid abnormalities (eg, hypercholesterolemia, hypertriglyceridemia, increases in low-density lipoprotein [LDL] and decreases in high-density lipoprotein [HDL]), and new-onset diabetes.[76–78] Concerning modern ART, there are risks related to cardiovascular outcomes (ABC and PIs), renal and bone mineral density concerns (tenofovir-based regimens), and weight gain (INSTIs), which are discussed below.

With more modern ART, cardiovascular risks exist. For instance, ABC has been associated with myocardial infarctions after adjustment for known risk factors and the Framingham risk scores.[79] PIs are also implicated in cardiovascular risk. In a large international prospective multicohort study, it was noted that the cumulative use of boosted DRV—and not boosted ATV, was associated with the risk of cardiovascular disease after adjustment for factors, including those already at high risk of cardiovascular disease.[80]

TAF, a novel formulation of tenofovir, is associated with improved long-term bone and renal outcomes compared to TDF in patients initiating therapy, and this has been seen in a double-blind, multicenter, noninferiority trial between FTC/TAF and FTC/TDF after 48 and 96 weeks of follow-up.[81] However, with the availability of generic TDF (FDA approved in June 2017), balancing lower cost versus improved safety will be an important consideration for clinicians in selecting a tenofovir-based regimen, especially considering that both formulations are equally recommended by the guidelines.

The INSTI-based regimens, which are first-line ART, have been associated with weight gain.[82] Additionally, the weight gain is differentially based on the specific INSTI. In a large observational study, the adjusted average weight gain was higher after 6 and 18 months for RAL (3.0 and 3.4 kg, respectively) but not for EVG (0.6 and 0.5 kg, respectively).[83] The majority of the reports of weight gain have been related to DTG, which has received more scrutiny, particularly in lower-income countries. On average, the increase in body weight is ~3 to 4 kg but can be as high as 6.0 kg after 18 months.[83] Furthermore, in the New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries (NASMAL) and the ADVANCE studies, participants were randomized to a DTG-based regimens in both with findings supporting a 10% increase in body weight and statistically significantly higher weight gain compared to control NNRTI-based ART.[84],[85] Lastly, the weight gain associated with BIC is comparable to that seen in DTG in noninferiority trials compared to DTG-based regimens with median weight gain of 7.71 pounds (3.5 kg) after 96 weeks.[86],[87]

Promote adherence

Although the exact degree of adherence required for clinical success is currently unknown and varies by antiretroviral class, taking 90% to 95% of prescribed doses is generally believed to be necessary to prevent the development of resistance. Data

from studies evaluating adherence among HIV-infected patients indicate that ~62% of patients take ≥90% of the prescribed doses of ART.[88] Although it is important to note that adherence patterns vary widely based on patient-specific factors. Poor adherence is multifactorial and related to behavioral, structural, and psychosocial concerns.[89–91] Factors associated with poor adherence include (a) patient's social situation and clinical condition, (b) prescribed regimen (once-daily regimens vs multiple pills per day), and (c) quality of the patient–provider relationship.

To better address the complex, multidimensional, patient-specific structures that can influence adherence behavior and retention in care, the DHHS HIV treatment guidelines recommend that clinics adopt a multidisciplinary team approach that provides access to trustworthy case managers, pharmacists, social workers, nurses, psychiatric care providers, and so on.[3] Additionally, before selecting an ART regimen, clinicians should provide adherence-related education (including information regarding why adherence is important) and involve the patient in the ART selection process. Selecting a treatment plan that the patient can (a) understand and (b) commit to for the long term is critical for fostering lifelong adherence. Thus, considering the patient's daily schedule and their ability to comply with antiretroviral-specific requirements (ie, food requirements, drug interactions) is important. For example, DTG should be administered 2 hours before polyvalent cation supplements. When DTG and iron-containing supplements are administered simultaneously under fasting conditions, DTG exposure decreases by 54%. For this reason, it is recommended to administer DTG together with food or to administer DTG at least 2 hours before or at least 6 hours after the polyvalent-containing supplement. Involving patients in the selection of their antiretroviral regimen maximizes the possibility of selecting a regimen that is least burdensome to their daily routine and helps to reduce certain barriers that lead to poor adherence. After the ART regimen has been selected and treatment is initiated, quickly identifying patients who are struggling with adherence (via patient self-report, pharmacy records, pill counts, etc), identifying their specific barriers to adherence (eg, pill fatigue, high co-pays, forgetfulness) and employing targeted interventions to improve adherence are essential. A recent technological strategy is the utilization of mobile applications (apps), which focuses on consistent daily alarms and text messaging reminders. Although recent meta-analyses of adherence apps and text messages reminders have indicated mixed efficacy results, cellular phones that support apps are now more globally available and may more readily promote adherence in clinical trials.[92,93] Of note, the CDC has promoted a free mobile app called Ever Dose Every Day (E2D2; available at https://npin.cdc.gov/pages/new-resource-every-dose-every-day-e2d2-toolkit-and-app). Examples of other specific strategies to improve adherence can be found in Table 16 (https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AA_Tables.pdf) of the 2019 DHHS HIV treatment guidelines.[3]

Finally, considering the importance of adherence in suppressing viral replication, long-acting (LA) injectables are a promising option for HIV treatment that offer less burdensome dosing compared to daily oral medications. The FDA recently approved

the first LA injectable regimen consisting of the novel INSTI cabotegravir (CAB) and RPV. LA-CAB/RPV is indicated for patients currently suppressed (HIV RNA <50 copies/mL) on an ART regimen with no history of treatment failure and no known or suspected resistance to either agent. As of this writing, patients should be prescribed a month-long course of oral CAB/RPV prior to receiving the injectable formulation to ensure they are well-tolerated. However, as safety data accumulates, forthcoming guidelines are anticipated to omit the recommendation or an oral lead-in period. LA-CAB/RPV was approved for HIV treatment on the basis of three phase III randomized clinical trials. The ATLAS study randomized virologically suppressed patients 1:1 to either continue current oral ART or to switch to monthly intramuscular injections of LA-CAB/RPV following a 4-week oral lead-in period consisting of CAB 30 mg plus RPV 25 mg once daily with food to assess safety and side effects.[94] At 48 weeks, LA-CAB/RPV was noninferior with 92.5% of participants maintaining viral suppression.[94] Similarly, in the FLAIR study, participants received DTG/ABC/3TC for 20 weeks to achieve virologic suppression, then were randomized 1:1 to receive monthly intramuscular injections of LA-CAB/RPV following a 4-week oral CAB/RPV lead-in or to continue oral DTG/ABC/3TC.[95] At 96 weeks, LA-CAB/RPV was noninferior with 87% of participants maintaining viral suppression in the per-protocol analyses.[95] Finally, the initial LATTE-2 study examined every 4- and 8-week administrations of LA-CAB/RPV following oral CAB/RPV lead-in. The authors noted that at week 96, 87% and 94%, respectively, maintained viral suppression, which were both as effective as oral treatment with conventional ART.[96] In the study, the every 4-week administration group had a lower rate of virologic nonresponse (defined as HIV-1 RNA ≥50 copies/mL per the FDA Snapshot Algorithm) than the every 8-week group (0% and 4%, respectively).[96] This led to the selection of the 4-week dosing regimen in the ATLAS and FLAIR trials. Future approval decision-making may invite every 8-week LA-CAB/RPV administration to the armamentarium.

GOAL 4: PREVENT HUMAN IMMUNODEFICIENCY VIRUS–RELATED MORBIDITY AND MORTALITY

By successfully treating HIV (suppressing viral load and restoring immune function), patients are at decreased risk for acquiring HIV-associated opportunistic infections. By achieving goals 1 through 3, goal 4 naturally follows, and this is the ultimate goal of the pharmacotherapy of HIV infection. With modern-day ART, patients infected with HIV are dying more frequently from non–HIV-related conditions common in the general population (ie, cardiovascular disease, hepatic disease, non–HIV-associated malignancies).[97] Although this represents a significant achievement in care, it also provides increased complexity in caring for those who are both at risk for HIV-related illness and also receiving treatment for comorbid conditions. This increases the potential for drug–drug and drug–disease interactions.

The selection of a patient-specific regimen can be a complex decision. Many potential combinations can be used, but a number of general principles should be followed.[3,5]

GOAL 5: PREVENT HUMAN IMMUNODEFICIENCY VIRUS TRANSMISSION

Maintaining a plasma HIV RNA of <200 copies/mL—related to goal 1 above—prevents the sexual transmission of HIV to partners. This is represented by "Undetectable = Untransmittable" or "U=U" and the cornerstone of treatment as prevention (TasP). This has been seen in the PARTNER and PARTNER-2 studies, in which there were zero transmissions in serodiscordant partners.[98,99] In order for U=U to be achieved, high levels of ART adherence must be maintained as transmission may be possible during stretches of less than optimal adherence and/or treatment interruption. This was seen in the HPTN 052 study, which noted in its 2016 analysis that no phylogenetically linked sexual transmission occurred over 5.5 years among couples with a partner on ART and maintaining viral loads <400 copies/mL.[100] In addition, a recent systematic review of 12 clinical studies exploring the association between risk of transmission and undetectable viral load found no transmissions across 10,511 person-years of follow-up when viral load of an infected partner was <200 copies/mL across consecutive measurements regardless of condom use.[14] It must be noted that while adherence to ART prevents transmission of HIV, sexually transmitted infections (STIs) must be routinely screened.

GOAL 6: REDUCE THE LATENT RESERVOIR

It is important for both clinicians and patients to understand that ART will not cure HIV. One barrier to a cure is the establishment of the latent reservoir, a term indicating the persistence of replication-competent virus. The establishment of the latent reservoir occurs within days of initial infection.[101] Because of the time lag between infection and diagnosis, the latent reservoir may already be established. As a result, early initiation of ART will help reduce the size of the latent reservoir as it prevents further cells from being infected with HIV. In the context of future HIV cure strategies that may rely on immunomodulation agents and/or therapies to bring out virus, early initiation of and consistent adherence to ART may be complementary in ultimately eradicating HIV.

General Rules of Therapy

Initiation of therapy should occur soon after diagnosis in most patients.[3,5] Many of the current regimens reduce viral replication to less than detectable levels and result in durable treatment responses. Reasons for the current improved response rates include the simplification of the regimens (eg, fewer pills per day, less frequent dosing per day, use of fixed-dose combination products), improvement in overall potency of the regimens, and minimization of short-term side effects. Consequently, if the correct patient-specific ART regimen is selected as initial therapy, the patient should be able to adhere to therapy and gain both virologic and clinical benefits from the regimen.

Case 76-1, Question 5: On questioning, E.J. admits to having an occasional drink with dinner, but he is not currently using any illicit drugs and has not in 3 years. E.J. has no known drug allergies and is currently taking only omeprazole to help with stomach acid. He is employed as a

construction worker and is extremely busy during the day, so he prefers to take medications only one time daily. His complete blood count, electrolyte, and liver and renal panel all return within normal limits. His baseline genotype does not indicate any transmitted drug resistance, and he is HLA-B*5701-negative. E.J. has no particular preference for a specific regimen and appears highly motivated to take control of his disease. What factors should be considered when selecting an appropriate antiretroviral regimen?

Select the type of antiretroviral regimen. ART regimens typically consist of a combination of two to three agents from at least two classes. In general, INSTI-based ART regimens are preferred (**Table 76-4**). Patient-specific factors, such as comorbid disease states, concomitant medications, and pill burden should be considered.

Table 76-4
Recommended Antiretroviral Agents for Initial Treatment of Established Human Immunodeficiency Virus Infection

	Preferred[a]	Alternatives
PIs (one or two PIs + two NRTIs)	Darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate or emtricitabine/tenofovir alafenamide	Darunavir/ritonavir + abacavir/lamivudine[b]
		Darunavir/cobicistat[c] + abacavir/lamivudine[b] or emtricitabine/tenofovir disoproxil fumarate or emtricitabine/tenofovir alafenamide
		Atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate or emtricitabine/tenofovir alafenamide
		Atazanavir/cobicistat[c] + emtricitabine/tenofovir disoproxil fumarate or emtricitabine/tenofovir alafenamide
Integrase inhibitors	Raltegravir twice daily + emtricitabine/tenofovir disoproxil fumarate or emtricitabine/tenofovir alafenamide	
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate[c] or elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	
	Dolutegravir + emtricitabine/tenofovir disoproxil fumarate or emtricitabine/tenofovir alafenamide	
	Dolutegravir/abacavir/lamivudine[b]	
NNRTIs (one NNRTI + two		Efavirenz/emtricitabine/tenofovir disoproxil fumarate

NRTIs)		Rilpivirine/emtricitabine/tenofovir disoproxil fumarate[d] or rilpivirine/emtricitabine/tenofovir alafenamide
Not recommended: Should not be offered	All monotherapies, dual-nucleoside regimens, triple-NRTI regimens	

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; NRTI, nucleos(t)ide analog reverse transcriptase inhibitor; NNRTI, non-nucleos(t)ide analog reverse transcriptase inhibitor; PI, protease inhibitor.

[a]This table provides a guide to the use of available treatment regimens for individuals with no prior or limited experience on HIV therapy. In accordance with the established goals of HIV therapy, priority is given to regimens in which clinical trial data suggest the following: sustained suppression of HIV plasma RNA (particularly in patients with high baseline viral load), sustained increase in $CD4^+$ T-cell count (in most cases >48 weeks), and favorable clinical outcome (ie, delayed progression to AIDS and death). Additional consideration is given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens. It is important to note that all antiretroviral agents have potentially serious toxic and adverse events associated with their use.

[b]Only for patients who are HLA-B*5701 negative.

[c]Only for patients with pretreatment estimated CrCl >70 mL/minute.

[d]Only for patients with pretreatment HIV RNA >100,000 copies/mL and CD4 count >200 cells/μL.

Avoid regimens that are not virologically additive or synergistic. 3TC and FTC should not be used together because they have similar resistance profiles, and concomitant use will not confer any additional virologic benefit.

If PI-based ART is desired, regimens combined with a pharmacoenhancer (eg, RTV and COBI) are preferred. RTV, a potent inhibitor of cytochrome P-450 metabolism and P-glycoprotein (PGP) activity, interacts significantly with a number of agents, including other PIs. This inhibition can be exploited to decrease the metabolism or increase the absorption of the other PIs. In some cases, such as in the use of LPV and DRV, the use of a coadministered pharmacoenhancer is required for virologically relevant concentrations. The result is a regimen with more potent viral suppression. In addition, boosting concentrations with a pharmacoenhancer allows for less frequent dosing, often lowers the total daily pill burden, and removes the need for drug/food restrictions. The pharmacoenhancer, COBI, can also be combined with ATV or DRV (as well as the INSTI, EVG) to provide a similar boosting effect as RTV without providing any antiviral effect. Because RTV and COBI are potent inhibitors of CYP3A4, they interact with a number of medications. Concomitant medications may require dosage adjustments, depending on the severity of the interaction.[3,5]

CASE 76-1, QUESTION 6: What initial ART regimen should E.J. receive?

When selecting a patient-specific regimen, the following steps should be followed.

STEP 1: DETERMINE WHICH ANTIRETROVIRAL CLASS WILL BE USED

A careful review of the advantages and disadvantages of each regimen should occur (**Table 76-5**). For example, PIs may be less favored with a current medical condition consisting of coronary artery disease, hyperlipidemia, or diabetes mellitus because of their potential metabolic side effects.[3,77]

Table 76-5
Advantages and Disadvantages of Antiretroviral Components for Initial Antiretroviral Therapy

ARV[a] Class	Possible Advantages	Possible Disadvantages
Dual NRTI	▪ Established backbone of combination antiretroviral therapy ▪ Less fat maldistribution and dyslipidemia than PI-based regimens	▪ Rare but serious cases of lactic acidosis with hepatic steatosis reported (d4T > ddI = ZDV > TDF or TAF = ABC = 3TC = FTC) ▪ Low genetic barrier to resistance (single mutation confers resistance)
NNRTI	▪ Long half-lives ▪ Single tablet regimens available with EFV and RPV	▪ Low genetic barrier to resistance ▪ Cross-resistance among first-generation NNRTIs ▪ Skin rash ▪ Potential for cytochrome P-450 drug interactions ▪ Transmitted resistance to NNRTIs more common than with PIs and INSTIs
PI	▪ Higher genetic barrier to resistance ▪ PI resistance uncommon with failure (boosted PIs) ▪ More forgiving to intermittent adherence	▪ Metabolic complications (fat maldistribution, dyslipidemia, insulin resistance) ▪ Cytochrome P-450 substrates, inhibitors, and inducers (potential for drug interactions)
INSTI	▪ Well-tolerated ▪ Single tablet regimens available with EVG and DTG ▪ Fewer drug–drug interactions with RAL and DTG than PI- or NNRTI-based regimens ▪ Achieve rapid viral load suppression	▪ Less long-term experience than with boosted PI-based regimens ▪ Lower genetic barrier to resistance than boosted PI-based regimens

ABC, abacavir; ARV, antiretroviral; DHHS, Department of Health and Human Services; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

[a]Adapted from DHHS treatment guidelines July 2016. See full guidelines for discussion of the advantages and disadvantages of each individual ARV agent.

After discussions with E.J., it appears that he is highly motivated to take control of his disease and is willing to initiate therapy. Subsequently, the use of a combination

ART regimen with an INSTI-based regimen is appropriate. Potential initial treatment options are listed in Table 76-4.

In the most recent updates to the guidelines, an additional option for first-line regimens is a two-drug regimen. To date, the only recommended combination is DTG/3TC. The rationale of this inclusion was based on the 96-week data from the GEMINI-1 and GEMINI-2 trials.[102] These analyses showed that the rates of virologic control in treatment-naive patients were similar to those of a conventional three-drug regimen consisting of DTG plus FTC/TDF. Of note, this dual regimen is not recommended for individuals with HIV RNA >500,000 copies/mL, hepatitis B virus (HBV) coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

STEP 2: OPTIMIZE AGENTS IN THE REGIMEN

The next step requires the selection of agents for the ART regimen. In many situations, absolute contraindications and significant drug–drug interactions limit the agents available for use in the regimen. The nucleoside or nucleotide reverse transcriptase inhibitors, including 3TC, TDF or TAF, FTC, and ABC, are all potential options for E.J. With respect to drug interactions, an INSTI can be administered safely with omeprazole.

STEP 3: QUALITY-OF-LIFE CONSIDERATIONS

When selecting an ART regimen, assessment of quality-of-life issues, potential adverse drug events, and patient preference should receive as much consideration as drug–drug interactions and absolute contraindications. In some situations, these issues could mean the difference between a regimen that is effective and one that is not. Considering E.J.'s lifestyle and work requirements, it is best to select a regimen that will minimally interfere with his daily activities. The selection of a regimen with once-daily or twice-daily dosing is appropriate (see Table 76-2), although once-daily dosing might be preferred. Potential regimens include INSTI-based regimens such as BIC/FTC/TAF, RAL twice daily with FTC/TDF or FTC/TAF once daily, DTG plus FTC/TDF or FTC/TAF all once daily, DTG/ABC/3TC as a combination tablet once daily, or DTG/3TC pending the HBV serology and HIV-1 resistance testing results.

Case 76-1, Question 7: E.J. is starting BIC/FTC/TAF. How should therapy be monitored? Are any additional laboratory tests necessary? What adherence support should be provided?

Short-Term Assessments

Three important criteria determine whether an ART regimen is effective: clinical assessment, surrogate marker responses, and regimen tolerability, including a patient's ability to adhere to the regimen.[3,5] In patients who are clinically symptomatic (eg, constitutional symptoms such as fatigue, night sweats, and weight loss; new opportunistic infections), the initiation of an appropriate antiretroviral regimen often

results in resolution of symptoms, increased strength and energy, and improvement in overall well-being. In some patients, however, the effect may not be as prominent. A careful assessment of clinical symptoms should therefore be regularly performed at all follow-up appointments.

In all patients, repeat viral load and T-cell measurements are necessary. This early value allows clinicians to assess the magnitude of response and ensures declining viral load measurements. ART with an effective regimen will generally result achieve viral suppression 8 to 24 weeks after initiation. Therapy with an effective regimen will result in at least a threefold (0.5 log) and tenfold decrease (1.0 log) in viral load counts by weeks 4 and 8, respectively.[3,5] The viral load should continue to decline during the next 12 to 16 weeks, and, in most patients, it will become undetectable.[3,5] Long-term response to therapy correlates with the magnitude of viral suppression on initiation of a regimen. The greater the suppression, the greater the durability of response to that regimen.[103] The speed and magnitude of suppression, however, can be affected by a number of factors, including clinical status of the patient (eg, more advanced disease–low T-cell counts, high viral load value), adherence to therapy, and overall potency of the regimen.[3,5]

In response to declining viral replication, T-cell destruction slows, and eventually cellular repopulation occurs. The magnitude of this T-cell increase can vary significantly, with some patients experiencing large increases (≥500 cells/μL) and others experiencing little or no change. Given that T-cell changes do not occur rapidly, once therapy is initiated, repeat T-cell counts should be obtained at 3-to 4-month intervals.[3,5]

A seemingly worsening of symptoms may also occur after the initiation of potent antiretroviral therapies because of immune reconstitution.[104–106] In patients with advanced HIV disease (ie, CD4 <100 cells/μL), significant immune dysfunction results in an inability to mount an appropriate response to subclinical infections. As a result, these infections replicate unimpeded and often undetected by the host (also known as quiescent disease). During the first 12 weeks of therapy, an increased immune response results from redistribution of memory cells,[107–109] and inflammation occurs at the site of infection. The immune reconstitution inflammatory syndrome can present in any organ system where quiescent disease exists (eg, CNS, eyes, lymph nodes). Most cases occur within 1 to 4 weeks after the initiation of potent antiretroviral therapies.[3]

A patient's tolerability of the regimen, which includes involvement in the decision of what therapy to initiate, ease of administration, and avoidance of intolerable side effects, is vital to a patient's willingness and ability to adhere to an antiretroviral regimen. If the patient is not adherent, they are at risk for clinical failure and the development of resistance. Adherence should be evaluated at every clinic visit, and the type and reason for identified nonadherence should be assessed. If adherence is not a present concern, then positive reinforcement and encouragement are recommended.[3]

Case 76-1, Question 8: After initiation of therapy, E.J.'s viral load values are 7000 copies/mL at 4 weeks and <50 copies/mL (undetectable) at 12 weeks. His T-cell counts have increased from 225 to 475 cells/μL. In addition, E.J. states that his night sweats and fevers have disappeared, he "feels great," and that he has had no drug-related problems. Is the therapy effective? How should therapy be monitored?

E.J.'s response to BIC/FTC/TAF does indicate efficacy. Clinically, his symptoms have subsided, and his overall health is much improved. His viral load measurements have responded appropriately and are now less than the level of assay detection. T-cell counts have increased by 250 cells/μL. Finally, E.J. has experienced no drug-related adverse events. Given the response to date, no changes are required, and the current regimen should be continued.

Long-Term Assessments

Once the prescribed regimen has been stabilized, the long-term goals are to maintain maximal viral suppression, sustain clinical and immunologic improvements, and maintain drug safety and tolerability. Periodic assessments should be made of viral load and T-cell counts (every 3–6 months), and potentially even annually after demonstrating a consistent and reliable history of undetectable viral load assessments[3,5] These surrogate marker data allow clinicians to monitor trends in viral activity and immunologic status and assist them in identifying early regimen failure. Clinical assessment of the patient questioning of tolerability and adherence to the prescribed regimen should occur at the 3- to 6-month follow-up visits. Lastly, routine laboratory safety monitoring should occur as part of the clinical care and more frequently as warranted.

Treatment Failure

Case 76-1, Question 9: E.J. has remained on BIC/FTC/TAF for more than a year. To date, his T-cell counts have remained stable at 550 cells/μL, and his viral load measurements have remained less than the limit of assay detection. He presents with new complaints of fevers and malaise. E.J. reports that he has been concerns with therapy and has not started any new medications. Repeat laboratory tests now show E.J.'s viral load is 3000 copies/mL and his T-cell count is 375 cells/μL (both repeated and validated). Should E.J.'s regimen be changed?

Assessment of regimen failure should be based on (a) clinical symptoms, (b) surrogate marker data, and (c) regimen tolerability and adherence.[3–5]

In some patients, the first sign of failure is a change in signs and symptoms. These changes can be subtle (eg, increase in constitutional symptoms, new onset of oral thrush) or more severe (eg, new opportunistic infections) and suggest a failing regimen and need to change therapy.

Assessment of efficacy should also involve evaluation of surrogate marker data (eg, T cells and viral load). In many situations, changes to these markers occur

before any noticeable clinical signs and symptoms. Therefore, careful evaluation of surrogate marker data may allow for intervention before any significant immune destruction occurs. Virologic failure, defined as new or continued viral replication despite appropriate ART, suggests a failing regimen. For example, patients with repeated detection of virus in plasma after initial suppression to undetectable levels should be evaluated as potential treatment failures. In patients who do not achieve viral suppression to less than detectable levels, a significant increase in viral replication should also be viewed as a treatment failure.[3],[4]

When assessing viral load, it is important to recognize that these values can increase from vaccinations or other concurrent infections (see Case 76-1, Question 2). Therefore, a thorough medical history should be taken to rule out other causes of increasing viral load. In addition, laboratory values should be interpreted as trends over time and not necessarily as individual measurements. A repeat viral load should be performed and evaluated within 4 weeks of the initial viral load increase. In some cases, transient viral "blips" occur (increases in viral load measurements just above the level of assay detection (eg, 50–1000 copies/mL), which become undetectable at the next visit.[109],[110] The clinical significance of viral blips is unknown, and, although they may not directly reflect treatment failure, they may represent near-future viral breakthrough because of either patient nonadherence or insufficient antiretroviral potency.[111],[112] Careful follow-up of these patients is required, because changes to the current ART regimen may be necessary.

In response to increasing viral replication, T-cell destruction occurs. Persistently declining T-cell counts, with or without increasing viral load measurements, represent treatment failure and suggest a change in therapy is warranted.

Other potential causes for failure include nonadherence and drug–drug interactions. In the event of nonadherence, discussions regarding tolerability, number of doses missed, duration of nonadherence, and lifestyle changes should take place. The decision to reinitiate a prescribed regimen should take into account the future likelihood of adherence and the potential development of resistant strains. In those patients with a history of long-standing nonadherence, the success of reinitiating the prescribed regimen may be limited. Stopping all ART at once poses less risk for the development of resistance than intermittent adherence to some or all of a regimen. The precise effect of the duration and extent of nonadherence on the development of resistance cannot be fully anticipated and is dependent on the barrier to resistance of the patient's ART. For the virus to mutate, sufficient drug pressure must be placed on the virus.

Significant drug interactions could also contribute to reduction in oral bioavailability or increased metabolism of the HIV medications leading to low serum concentrations, resulting in failure.[3] In addition, many medications require certain food requirements to allow maximal drug absorption. A careful review of all new medications and their potential for clinically significant drug interactions should be evaluated at all visits (Table 76-5).

Currently, E.J. has a number of signs and symptoms that suggest a failing regimen. E.J. is experiencing new symptoms of fevers and malaise not attributable to any

other cause. E.J.'s viral load value has become detectable at 3000 copies/mL without evidence of concurrent infections or vaccinations in the past 4 weeks. E.J.'s T-cell counts have declined from 550 to 375 cells/μL. Finally, it appears that E.J. has been adhering to his therapy and has not started any new medications that could affect the efficacy of his current regimen. Therefore, a change in therapy is necessary.

CASE 76-1, QUESTION 10: What potential antiretroviral regimen(s) can be considered for E.J.?

In addition to the general rules of therapy described in Case 76-1, Question 5, other issues should be considered when selecting an alternative regimen for a patient failing therapy.[3,4]

GENERAL RULES FOR CHANGING THERAPIES

1. If possible, the new regimen should contain at least two, preferably three, fully active agents. The potential for cross-resistance between ART should be considered when choosing new regimens, and therefore resistance testing should provide useful information (see Case 76-2, Question 2).
2. Given that antiretroviral drug resistance is more likely to occur with increased and prolonged viral replication in the presence of ART, changes to therapy should occur close to the time of treatment failure. Prolonged treatment with a failing regimen is likely to result in the accumulation of resistance mutations (particularly with PIs), which may limit future treatment options.
3. Resistance testing is recommended to guide the selection of future drug regimens. Optimally, testing via genotype, phenotype, or virtual phenotype should occur while the patient is taking the failing regimen or within 4 weeks of discontinuation to increase the likelihood of detecting resistant isolates. These tests cannot reliably detect mutations at viral concentrations <1000 copies/mL and may have limited usefulness in patients with persistent low-level viremia.
4. To prevent the development of resistance, one new drug should never be added to a failing regimen. An exception to this rule is if the initial response to a first regimen has been inadequate (eg, undetectable viral load at 16–20 weeks). In this situation, some clinicians may intensify therapy with an additional agent provided that the viral load measurements were trending downward since initiation of therapy.
5. If possible, a regimen that has failed in the past should not be reinitiated, because an isolate resistant to the failed regimen could continue to reside within various compartments of the body. If a regimen to which the patient had previously failed were restarted, unimpeded viral replication of the resistant strain would occur, repopulate the host, and eventually result in treatment failure. In some situations (eg, patients with advanced disease, limited treatment options, and prior exposure to most ART), it may be necessary to reinitiate agents or regimens in combination with additional new agents with the goal of suppressing viral replication.

6. When treatment failure is a direct result of drug toxicity (rather than poor drug efficacy), the offending agent should be replaced with an alternative drug from a similar class, provided that the potential for cross-resistance is minimal.
7. If an agent in a given regimen must be stopped, it is recommended that all agents in the regimen be stopped and restarted simultaneously to prevent the development of resistance.

It should be recognized that many alternative regimens are based on theoretical benefits or limited data. In addition, many potential options could be limited in some patients based on prior antiretroviral use, toxicity, or past intolerances. Therefore, the clinician should carefully discuss these issues with the patient before changing therapy.

Because E.J. is failing to respond to his current regimen, a new ART regimen must be chosen. In addition to selecting susceptible agents from resistance testing, the new regimen should take into consideration quality-of-life issues. In E.J.'s situation, it is reasonable to switch to a PI-based ART regimen, with two or more nucleoside agents as dictated by the viral resistance profile.

Considerations in Antiretroviral-Experienced Patients

CASE 76-2

Question 1: H.G. is a 56-year-old male infected with HIV with an extensive history of ART with a variety of ART. He took AZT monotherapy in the late 1980s and early 1990s. When 3TC became available, he took the combination of AZT and 3TC until he failed therapy about 25 years ago. At that time, he began experiencing AZT-induced myopathies. Since that time, H.G. has been "on and off" various regimens without sustained clinical benefit. He is currently taking FTC/TDF and ATV/r with a CD4 count and viral load measurement of 55 cells/μL and 48,000 copies/mL, respectively. These laboratory values have been stable for the last 9 months.

How do patients with extensive antiretroviral histories differ from antiretroviral-naive patients? Are there any special considerations when selecting therapeutic regimens for patients such as H.G.?

Patients who have been infected for 20 or more years may have been treated with many different regimens, both experimental and FDA approved. As a result, many potential regimens have already been exhausted; thus, there are fewer viable choices left. Agents with higher barriers to resistance that do not have cross-resistance with older agents and agents with novel mechanisms of action are useful in these patients. Although, DRV was specifically marketed for highly treatment-experienced patients because of its high genetic barrier to resistance and limited cross-resistance with other PIs.[3,4] The second-generation NNRTIs, DOR, ETR, and RPV, have minimal cross-resistance with the first-generation NNRTIs, EFV and NVP.[3,4] MVC, the first CCR5 receptor antagonist approved by the FDA, is also an option for treatment-experienced patients infected with HIV-1 utilizing this co-receptor and failing current treatment. MVC is not recommended for use in patients with dual-tropic viral populations (ie, able to use CXCR-4 or CCR5 as co-receptors) or CXCR-

4–trophic virus, and, thus, patients with extensive treatment histories should undergo tropism testing before MVC is initiated. Although INSTIs had historically been used in patients with extensive reverse transcriptase or PIs mutations, INSTI-based regimens have been first-line agents for years and therefore treatment-experienced patients may have started on INSTIs. Some highly treatment-experienced individuals will have extensive resistance patterns that limit their therapeutic options. In such patients, full suppression of viral load and immune reconstitution may not be possible.[3],[4] Two newer agents have been approved for the management of patients with virologic failure: ibalizumab and fostemsavir. Patients with ongoing detectable viremia who have exhausted first- and second-line treatment options could be candidates for ibalizumab.[3] Fostemsavir has been studied in clinical trials in treatment-experienced subjects with multiclass resistance with viral loads of at least 400 copies/mL.[51],[113] Recommendations for fostemsavir, however, have not been formalized in the guidelines.

Patients who have experienced several antiretroviral regimens present other unique challenges for clinicians and require consideration of the following factors.

1. *Regimen tolerability*: Patients with advanced HIV disease display decreased tolerability to many medications, including ART. Although this is not fully understood, it is probably a result of HIV-induced immune alterations and cytokine dysregulations. Subsequently, clinicians evaluating patients with advanced disease should be alert for possible drug-induced adverse events.
2. *Drug interactions*: Many patients with advanced disease take numerous medications for primary or secondary prophylaxis of various opportunistic infections, as well as other medications for comorbid disease states. Subsequently, the risk for a drug–drug interaction is increased. The addition of any new medication, either prescription or over-the-counter, should be carefully evaluated for potential interactions with the patient's current ART regimen (see **Table 76-6**). In addition, any change to the current ART regimen should also be checked against the patient's current medication list.
3. *Altered bioavailability*: Patients with advanced HIV infection may have unreliable absorption of many medications because of severe diarrhea, anorexia, weight loss, wasting, and gastric achlorhydria. As a result, the bioavailability of some agents may be affected (Table 76-2). Any changes in dietary habits or bowel function should be carefully assessed in light of the potential impact on the ART regimen.
4. *Antiretroviral drug histories and resistance testing*: The most useful information to guide the choice of alternative ART regimens is a detailed drug history, in conjunction with appropriate resistance testing. Among patients with extensive prior antiretroviral use, it is critical to identify previously failed regimens and determine the precise cause of the failures. In an experienced patient who has taken many different regimens over a lifetime, the number of remaining viable agents and regimens may be limited. Therefore, it is important to determine whether prior regimens truly failed for virologic reasons or some other cause (eg, regimen intolerability, nonadherence, or an inadequate trial period). In addition, detailed

knowledge of regimen intolerabilities and which agent(s) caused the adverse event will help in the selection of a new, appropriate ART regimen. In some situations, the offending agent may be reinitiated if the adverse event was minimal or can be appropriately managed.

Table 76-6
Metabolism and Drug–Drug Interaction Potential of Antiretroviral Classes

Class	General Metabolism and Drug–Drug Interaction Considerations	Exceptions
NRTIs	Renally eliminated, few drug–drug interactions	ABC is metabolized by alcohol dehydrogenase and competes with alcohol for metabolism.
NNRTIs	CYP3A4 substrates CYP3A4 inducers	RPV is a CYP3A4 substrate only. ETR is also a CYP2C9, CYP2C19 substrate/inhibitor.
PIs	CYP3A4 and PGP substrates CYP3A4 inhibitors	RTV is also a CYP2D6 substrate/inhibitor. ATV also inhibits UGT1A1. TPV is also a CYP2D6 inhibitor and PGP inducer.
INSTI	UGT1A1	EVG is a CYP3A4 substrate, given with COBI a potent CYP3A4 inhibitor. DTG is also a UGT1A3 and PGP substrate.
CCR5	CYP3A4 substrate	

ABC, abacavir; CCR5, chemokine co-receptor 5; COBI, cobicistat; DTG, dolutegravir; EVG, elvitegravir; ETR, etravirine; INSTI, integrase strand transfer inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PGP, P-glycoprotein; PI, protease inhibitor; RPV, rilpivirine; RTV, ritonavir; TPV, tipranavir.

RESISTANCE, VIRAL GENOTYPING, PHENOTYPING, AND VIRAL FITNESS

CASE 76-2, QUESTION 2: Will viral genotyping and phenotyping assist in selecting an appropriate therapeutic regimen for H.G.? What are these tests? What are their limitations and when should they be used? What is viral fitness, and does it have a role in clinical decision-making?

Viral genotyping and phenotyping reveal resistance patterns to ART. Genotyping evaluates mutations in the virus's genetic material, whereas phenotyping assesses the ability of the virus to grow in the presence of increasing concentrations of ART. The three potential causes for the development of resistance are as follows.

1. Initial infection with a resistant isolate[114–116]
2. Natural selection of a resistant isolate as a consequence of inefficient, error-susceptible viral replication[35]
3. Generation of resistant isolates via selective pressures from ART that does not fully suppress viral replication[3,4]

Mutations are generated when naturally occurring amino acids in the HIV genome are replaced with alternative amino acids. For example, resistance to 3TC occurs when the amino acid methionine (M) is replaced by valine (V) at the 184th amino acid in the protein chain.[117],[118] This mutation is subsequently referred to as an M184V mutation. These amino acid substitutions change the proteins that are produced and may alter the shape, size, or charge of the viral enzyme's substrate or primer.[118] Subsequently, antiretroviral drug binding to the active site is decreased, affinity for natural substrates is increased, or there is an increased removal of the antiretroviral agent from the enzyme by the virus (known as pyrophosphorylation).[116] Whether a mutation results in a clinically resistant, less viable, or indifferent isolate depends on which amino acid(s) is replaced. In addition, certain mutations or combination of mutations have been shown to produce viral isolates that display increased sensitivity to various ART (known as hypersusceptibility). Alterations to certain key amino acids can also result in cross-resistance between various ART.[4],[117]

Key enzymes have been extensively studied regarding their potential for development of resistance: reverse transcriptase (RT), protease, and, more recently, integrase. Replication by the RT enzyme is highly susceptible to errors. Given that the HIV genome is ~10,000 nucleotides in length and that mutations via the RT enzyme occur approximately once in every 10,000 nucleotides copied, it has been estimated that a mutation occurs with every viral replication cycle. With up to 10 billion particles of virus being produced per day, the potential exists for 1000 to 10,000 mutations occurring at each site in the HIV genome every day.[35] Key mutations to the ART are updated periodically by expert panels of clinicians.[4]

Over time, countless viral subpopulations known as "quasi-species" develop. In any given host, at any given time, many different quasi-species can exist. In addition, within any compartment of the body (eg, CNS, testes, lymph nodes), many different quasi-species can also exist. Because these mutant strains represent only a small number of isolates in the total viral population, they must have some replicative disadvantage when compared with the "wild-type" virus.[117] Under selective pressures from ART, however, these mutant isolates can replicate. For example, if wild-type viral replication is inhibited by an ART regimen, and if any one viral strain of the quasi-species is more fit for growth in the presence of that regimen, then the viral mutant will have a competitive advantage.[117] It should be recognized that for resistance to develop, viral replication must occur. When viral replication is completely inhibited, the development of resistant isolates is unlikely.

Genotypic analysis involves sequencing the viral genetic material via PCR amplification. Mutations are identified by analysis of key sequences of the RT or protease enzymes. These tests can be rapidly processed; however, they detect mutations present only in more than 25% of all HIV isolates in the body and can only reliably detect resistance patterns in samples with HIV RNA >1000 copies/mL. Because pressure from ART selects resistant isolates, these tests may not provide information regarding rare, yet potentially clinically significant, isolates.[3],[4]

Phenotypic analysis involves growing virus in the presence of various concentrations of drug and then determining viral susceptibilities (eg, half-maximal

inhibitory concentration [IC_{50}]). Phenotyping is limited because it evaluates only one viral isolate at a time and could fail to identify other clinically relevant isolates.[3]

In the case of ART-experienced patients with suspected drug resistance and limited or incomplete antiretroviral and resistance history, obtaining medical records —if possible—alongside resistance testing is helpful to identify mutations.[3] Clinicians should keep in mind that it is possible that specific mutations may not be detected with the absence of drug pressure (eg, resistance testing of replicating virus from genotyping may not reflect "older," mutated virus). Similar to other resistance mechanisms, the goal here is resuppression.

One other measure available to clinicians is "viral fitness" or "replication capacity." The genetic changes that occur in a virus to become resistant to ART often impair the virus' ability to replicate.[119],[120] This measure is called "fitness" and is quantified as replication capacity during phenotypic evaluation. During amplification of the virus before the phenotype is measured, the replication capacity of the virus is evaluated and compared to a reference wild-type, drug-sensitive virus. A virus with normal fitness has a replication capacity between 70% and 120% of the reference viral strain; isolates with values <70% are considered to be less fit than wild-type virus. In general, the more mutations that occur to the virus, the more compromised the virus becomes, and the lower the fitness (although, in some situations, the interplay between mutations can result in a viral isolate that is relatively fit). Recent data have shown that, despite persistent viral replication, unfit viruses may not cause the same degree of immune destruction as fit viruses.[118] This finding is important for patients with limited treatment options because it may allow for continuation of an ART regimen that is not completely suppressive, but that produces an unfit virus, with less T-cell depletion.

As with all clinical decisions made for PLWH, careful assessment of the results in combination with the treatment history are essential for proper clinical decision-making. Consultation with an expert in antiretroviral drug resistance patterns is highly recommended. Furthermore, specific actions for ART options for patients with virologic failure can be found in Table 11 (https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AA_Tables.pdf) of the 2019 DHHS HIV treatment guidelines.

Given H.G.'s extensive antiretroviral drug history and his current failure, a genotype or phenotype will likely provide some insights into potential therapeutic options.

SPECIAL CIRCUMSTANCES

Poor CD4 Cell Recovery

Case 76-2, Question 3: H.G. was started on a regimen of TAF, FTC, DTG, and DRV boosted with RTV. During the following 6 months, H.G.'s T-cell counts increased to 325 cells/μL and his viral load value declined to 5000 copies/mL. At the last two clinic visits, H.G.'s viral load and CD4 counts were 2000 copies/mL/275 cells/μL and <20 copies/mL/225 cells/μL, respectively. H.G. reports no new clinical complaints or adverse drug events. In addition, H.G. states that he has been concerns with therapy. Are changes to therapy necessary?

In most cases, declines in viral load result in increases in CD4 cell counts; however, in some cases, CD4 cells fail to recover with viral load suppression.[5] In this situation, it may be wise to continue current treatment and monitor the patient closely. Adding an additional drug to intensify the regimen or changing to a different ART regimen does not consistently increase the CD4 cell count and is not recommended.[3]

Therapeutic Drug Monitoring

PK evaluations of various ART have shown interpatient variability in drug exposures among cohorts of patients taking the same dose of drug under the same conditions.[3,120–123] Many factors contribute to interpatient variability in drug exposure, such as pharmacogenetics, environment, different physiologic conditions, regimen adherence, and drug interactions. For most ART, a drug exposure–response relationship exists (eg, the higher the exposure, the faster and more prolonged the viral suppression). In addition, most ART also have well-defined exposure–toxicity relationships.

Therapeutic drug monitoring (TDM) is currently recommended for limited clinical situations, including the use of concomitant medications with known drug interactions, clinical scenarios of impaired drug absorption, and certain clinical scenarios of pregnancy.[3,122] For patients with these scenarios of altered absorption, distribution, metabolism, or clearance, drug concentrations may help identify low or high exposure that can be corrected with a dosage adjustment. For proper interpretation of the concentrations, patients should provide a dosing history from the last several days, a list of concomitantly administered drugs to screen for interactions, and the exact time the last dose was taken. The exact time the TDM sample was collected should also be recorded. Clinicians should consult a pharmacology expert to determine a maximally informative TDM sampling strategy and select a laboratory that routinely measures ART and participates in both internal and external quality control programs to minimize laboratory variability and error in measuring these concentrations. A list of such laboratories can be obtained from the Clinical Pharmacology Quality Assurance and Quality Control Program (https://www.fstrf.org/apps/cfmx/apps/cpqa/cpqaDocs/public/index.html).

Drug Interactions

CASE 76-3

Question 1: J.F. is a 37-year-old male infected with HIV who has been taking EVG/c, TDF, and FTC for the past 4 years. His most recent lipid panel showed markedly elevated triglycerides, LDL, and total cholesterol.

What needs to be considered when starting a lipid-lowering medication for J.F.?

Drug interactions are very common with certain classes of ART, including PIs, PK enhancers, and NNRTIs, but less common with INSTIs and NRTIs. The potential for interactions should be considered when changing HIV-related or nonrelated drug regimens. In this case, COBI will significantly increase the concentrations of HMG-CoA reductase inhibitors that are metabolized by CYP3A4 through inhibition of the CYP3A4 isoenzyme.[3] Increased concentrations of the HMG-CoA reductase inhibitor could put J.F. at risk for myalgias and rhabdomyolysis. If J.F.'s lipids require treatment with an HMG-CoA reductase inhibitor, one that is only partially metabolized by CYP3A4 or metabolized by another pathway should be considered. Simvastatin and lovastatin are contraindicated in combination with the PK enhancer, COBI, but pravastatin, pitavastatin, rosuvastatin, and atorvastatin can be used at reduced doses.[3] The DHHS HIV adult treatment guidelines have extensive tables outlining specific drug interactions and recommendations for concomitant use of medications with the ART.[3] Table 76-6 gives the general metabolism and transport effects of each of the classes of ART and gives an idea of the drug interaction potential of each class.

Pregnancy and Breast-Feeding

CASE 76-4

Question 1: T.D. is a 32-year-old female infected with HIV, whose ART includes the combination tablet DTG/ABC/3TC once daily. Her virus is fully suppressed, and her CD4 cells count is 786 cells/μL. She has had a positive home pregnancy test result, and her last period was 2 months ago.

Is her current antiretroviral regimen appropriate for use during pregnancy and for prevention of mother-to-child transmission?

The current perinatal HIV guidelines[124] recommend that females receiving and tolerating a currently suppressive regimen when they become pregnant continue on that regimen as long as there are no risks to the female or fetus. EFV is the only antiretroviral that is currently pregnancy category D and is not recommended during the first 8 weeks of pregnancy. It has been shown to be teratogenic in animal studies, particularly in the first trimester of pregnancy, and retrospective case reports of neural tube defects in humans have been documented.[125–128] In 2019, a birth-outcomes surveillance study of 119,477 deliveries in hospitals throughout Botswana found a slightly higher rate of neural tube defects among infants born to females taking DTG containing versus non–DTG-containing ART (3 vs 1 per 1000 deliveries, respectively).[129] Importantly there is no folate fortification of food in Botswana as in the United States. It is uncertain how folate fortification might impact these findings

and whether these findings in Botswana translate to other geographical regions like the United States.

Perinatal transmission prevention guidelines recommend ABC/3TC, FTC/TDF, or 3TC with TDF as first-line NRTIs for ART initiation in pregnancy. ATV/r and darunavir/r are the recommended PIs for initiation in pregnancy, and RAL and DTG are the recommended INSTIs for initiation in pregnancy. However, given the possible increased risk of neural tube defects, DTG is considered an alternative INSTI that may be considered in certain clinical situations in females who are trying to conceive. Alternative agents for initiation in pregnancy include AZT/3TC, LPV/r, EFV as long as it is initiated after 8 weeks of pregnancy, and RPV.[124] Many of the pregnancy recommendations are based on those drugs that have the most safety and efficacy data available during pregnancy (both animal and human).[124]

In females who have a viral load persistently >1000 copies/mL, it is recommended that a planned 38-week cesarean section be performed to reduce the risk of mother-to-child transmission. In females with a viral load <1000 copies/mL, there is little evidence to show that cesarean section decreases transmission rates compared to vaginal delivery. In this case, the decision is made at the discretion of the physician in consultation with the mother. Additionally, if the mother's viral load is >1000 copies/mL or unknown at the time of delivery, it is recommended that intravenous AZT be administered to the mother at 2 mg/kg intravenously (IV) for 1 hour at the onset of labor, then given as a continuous infusion of 1 mg/kg/hour during the intrapartum period (during labor and postpartum). Once delivered, newborns that are at low risk for perinatal transmission (ie, those born to females with suppressed viral load near the time of delivery) should receive oral AZT at 4 mg/kg every 12 hours for 4 weeks. Newborns at higher risk for perinatal transmission (ie those born to females who did not receive antepartum ART or those who did not achieve viral suppression or had acute HIV infection at the time of birth) should receive up to 6 weeks of presumptive HIV therapy with oral AZT plus 3TC with either NVP or RAL (see the Perinatal guidelines[124] for age- and weight-based dosing recommendations). It is recommended that the infant undergo diagnostic virologic testing using either HIV DNA PCR or RNA virologic assays at a minimum at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months. Antibody testing should not be considered a definitive exclusion or confirmation of HIV infection in a perinatally exposed infant because maternal HIV antibody crosses the placenta and may be detectable in an HIV-exposed infants for up to 24 months of age.[124]

It is not recommended that females infected with HIV breast-feed their children in resource-rich settings where clean water and formula are reasonably available. However, with clear evidence that virologically suppressed individuals do not transmit HIV,[13] guidelines from these resource-rich settings now indicate that mothers who receive adequate counseling about the risks of HIV transmission via breast-feeding and still choose to breast-feed should be supported in their choice. Recommendations to mitigate risk of transmission through breast-feeding include monitoring maternal plasma viral loads every 1 to 2 months during breast-feeding to ensure virologic suppression; exclusive breast-feeding for 6 months before the

introduction of solids, at least 6 weeks of AZT with or without NVP prophylaxis for the infant; promptly identifying and treating maternal mastitis and infant thrush; and monitoring the infant for HIV infection every 3 months throughout breast-feeding, followed by monitoring at 4 to 6 weeks, 3 months, and 6 months after cessation of breast-feeding.

J.F. presents at 2 to 3 months of pregnancy on a fully suppressive ART regimen that she is tolerating well. Although limited evidence suggests that DTG may confer a slight increase in the risk of neural tube defects, these defects most frequently occur before the neural tube closes at 4 weeks postconception or ~6 weeks post-last menstrual period. After 6 weeks gestation, the additional risk of neural tube defects developing is thought to be much less likely. Thus, J.F. should continue on her current ART regimen, and if she remains undetectable throughout her pregnancy, the decision of whether to have a cesarean or a vaginal delivery will be at the discretion of J.F. and her physician.

Preexposure Prophylaxis

CASE 76-5

Question 1: F.C. is a 22-year-old, healthy female who is HIV-uninfected with multiple male sex partners. She reports infrequent condom use but would like to consider therapeutic options to mitigate her risk of pregnancy and STIs.

What prevention methods can be offered to F.C.?

PrEP is the use of ART in HIV-uninfected individuals to prevent HIV infection. The PrEP Clinical Practice Guidelines recommend PrEP as one prevention option for adults at substantial risk of HIV acquisition through sexual behaviors or injection practices.[130] Substantial risk is defined as any individual not in a monogamous partnership with a recently tested HIV-negative partner who in the last 6 months has engaged in condomless receptive or insertive anal sex, who frequently engages in condomless receptive or insertive vaginal sex, or who was diagnosed with a bacterial STI. Additionally, PrEP may be discussed with HIV-uninfected heterosexual females and males whose partners are HIV-infected as one of several options to protect the uninfected partner during conception and pregnancy. Fixed-dose combination tablets of FTC 200 mg with TDF 300 mg (FTC/TDF) and FTC 200 mg with TAF 25 mg (FTC/TAF) have been FDA approved for use as PrEP.[131],[132] Although FTC/TDF is indicated to reduce the risk of any type of sexually acquired HIV infection, FTC/TAF's indication excludes receptive vaginal sex. This distinction is because the study population of the phase III trial demonstrating FTC/TAF's noninferiority to FTC/TDF excluded cisgender females.[81] Event-driven PrEP (ie, two pills within 24 hours prior to sex and one pill at 24 and 48 hours post sex) may also be considered to protect against sexual acquisition for males who have sex with males.[5] HIV testing should be done immediately before PrEP is prescribed and every 3 months while taking PrEP. If a patient is found to be HIV-infected, PrEP should be immediately converted to an

HIV treatment regimen without waiting for additional laboratory results. PrEP should always be provided in conjunction with behavioral risk reduction support and medication adherence counseling. In addition to regular HIV testing and risk reduction counseling, renal function testing should be performed at baseline, 3 months, and then every 6 months thereafter, and STIs should be screened for at baseline and every 6 months.[130] The continued need for PrEP should be evaluated every 12 months, and patients wishing to discontinue PrEP should be counseled that protection will wane over 7 to 10 days following cessation. Alternative methods to reduce risk for HIV acquisition should be discussed.

Although not yet approved for PrEP, LA-CAB has been studied in two phase III trials. HPTN 083 enrolled HIV-uninfected males who have sex with males and transgender females who have sex with males to assess noninferiority of the investigational treatment (5 weeks of daily oral CAB followed by IM injections every 8 weeks of LA-CAB) versus daily oral TDF/FTC standard of care.[133] The study was terminated early because of LA-CAB demonstrating a 66% reduction in HIV incidence when compared to oral PrEP.[133] Importantly, on average nearly 25% of the participants in the daily oral PrEP arm were taking less than 4 doses per week.[133] Suboptimal adherence is likely linked to the inferior protection and evidences the need for less burdensome dosing modalities in HIV PrEP. Additionally, HPTN 084 had an identical study design as HPTN 083 but enrolled HIV-uninfected cisgender females.[134] The blinded trial was stopped in November 2020 after LA-CAB was shown to be superior to the oral PrEP arm (89% reduction).[134] It was noted that only 62% of the plasma samples had detectable TDF/FTC, and <50% of them were consistent with daily dosing.[134] Given these contrasting results, time will tell how regulatory agencies will adjudicate potential approval of LA-CAB for PrEP in different patient populations.

FTC/TDF one tablet daily can be considered for F.C. to reduce her risk of acquiring HIV through receptive vaginal sex. She will need to have baseline HIV, STI, and renal function testing as well as medication adherence and behavioral risk reduction counseling. She will need to follow up 3 months after FTC/TDF prescribing for monitoring and repeat HIV testing. She should be counseled that PrEP does not protect against the risk of other STIs or pregnancy.

Postexposure Prophylaxis

CASE 76-6

Question 1: L.T. is a 47-year-old female nurse at an HIV clinic. While drawing routine labs on a newly diagnosed PLWH, not yet started on ART, she accidently stuck herself with a contaminated needle.

Are interventions available to prevent L.T. from contracting HIV from the needle stick? What drugs should be utilized, and for how long?

PEP is the use of ART to prevent HIV infection in individuals who have had an exposure to blood or body fluid either known to be infected with HIV or potentially infected with HIV. Occupational exposures require immediate evaluation with a first dose of ART offered within the first 2 hours following exposure.[135],[136] PEP is more effective the earlier it can be initiated, and it should always be started within 72 hours of exposure. Percutaneous exposure poses more of a concern than mucous membrane exposure. A needle stick with a large hollow-bore needle is higher risk than a solid needle, a deep penetrating wound is considered a high-risk exposure compared to a superficial injury, and an exposure to a large volume of infectious fluid is more concerning than exposure to a low volume. Patient-specific factors must also be considered, such as whether the PLWH is on ART therapy and has a suppressed viral load or whether the PLWH currently has a high viral load. Regardless of the type of exposure or risk factors, current guidelines recommend that PEP be offered to all health care workers with an exposure. If the source patient is known to be HIV-infected or the HIV status is not known, PEP should be continued for a total of 4 weeks, or 28 days. If the source patient's status is unknown but is later determined to be HIV-negative, then PEP can be discontinued prior to 28 days.[135],[136]

Three-drug PEP is recommended for all health care workers exposed or possibly exposed to HIV. Recommended regimens include two NRTIs with RAL (400 mg twice daily), RAL-HD (1200 mg once daily), or DTG. Females of childbearing potential should be counseled on the potential risk of DTG, as described in the Pregnancy and Breast-Feeding section. Alternative regimens include two NRTIs with a boosted PI.[136]

In instances where the source patient is a known treatment-experienced patient with HIV, the choice of agents to use for PEP is generally dependent on the patient's ART regimen and resistance profile.[135],[136]

L.T. should start a PEP regimen immediately, preferably FTC/TDF once daily with RAL (once- or twice daily depending on formulation) or DTG (once daily). This entire regimen should be continued for a total of 4 weeks. It would also be a good idea to look at the specific patient from which the exposure occurred. If he had a great deal of known antiretroviral drug resistance, then L.T. may need to be put on different ART according to the patient's resistance profile. HIV antibody testing using ELISA should be performed on L.T. at baseline exposure, 6 weeks, 12 weeks, and 6 months after exposure. She should also have baseline and follow-up labs performed to assess antiretroviral toxicity. At a minimum, these should include a complete blood count, renal and hepatic function tests, and fasting glucose while on the PI. Additional laboratory tests should be performed based on the individual drugs chosen.[135],[136]

Additional guidelines exist for nonoccupational HIV exposures and follow similar risk and stratification treatment paradigms. In those instances where a person seeks care within 72 hours of exposure to blood, genital secretions or other potentially infected body fluids of persons known to be HIV-infected and the exposure represents a substantial risk for HIV transmission then the person is started on PEP in a similar fashion as with an occupation exposure and continued for 4 weeks with similar monitoring and HIV testing.[135]

In 2019, California Senate Bill 159 (CA SB 159) sought to improve and expedite access to PrEP and PEP by allowing pharmacists with special credentialing to dispense up to a 60-day supply without a prescription.[137] Additionally, the bill barred insurance companies from requiring prior authorization for PrEP coverage.

KEEPING CURRENT

The management of HIV infection continues to evolve. Additional important emerging data are in HIV prevention and cure. One example of a rapidly changing clinical landscape within the HIV treatment and prevention fields is the development of LA formulations of ART. With the development of newer, more potent ART, efficacious LA treatment strategies such as monthly intramuscular injections of CAB/RPV have the potential to dramatically simplify the provision of HIV treatment.[138] New technologies in development such as drug-eluting implants that administer up to a year of HIV PrEP offer promise beyond once-daily oral ART for HIV prevention.[139]

The overwhelming data presented at scientific meetings and in journals within this exciting and dynamic clinical environment have made staying informed about current issues and new developments a daunting task. As a result, many clinicians, even those actively caring for PLWH, remain cautious and often confused regarding therapeutic options.

New technologies for the dissemination of medical information are constantly evolving. The Internet has allowed clinicians worldwide to exchange ideas, teach new concepts, and obtain access to limited resources. In addition, many research centers, patient advocacy groups, and academic institutions have posted sites on the Internet that have resulted in access to large amounts of high-quality medical information. This new technology has also allowed, however, for the dissemination of incomplete, misleading, or inaccurate information. Therefore, clinicians must remain cautious and carefully evaluate the information obtained from various websites.

When evaluating the quality of a website, clinicians should look for a few basic standards.

- *Author qualifications.* Is the author qualified to write the article or perform the research? Is their affiliation or relevant credentials provided?
- *Attribution.* Are references provided to confirm statements? Is all relevant copyrighted information noted?
- *Currency.* When was the content posted? Is the website updated regularly?
- *Disclosure.* Who owns the website? Is there a conflict of interest between what is being posted and any commercial interest?

Any Internet site that fails to meet these basic competencies should be viewed with caution. In general, the most accurate and informative websites for HIV-specific information come from academic institutions, government organizations, medical societies, and patient advocacy groups. **Table 76-7** lists high-quality websites that

provide timely and accurate information. A periodic evaluation of these sites often provides sufficient information to stay up-to-date on current issues and controversies.

Table 76-7
Human Immunodeficiency Virus Internet Resources

Government Sites
American Foundation for AIDS Research: http://www.amfar.org
Centers for Disease Control and Prevention: http://www.cdc.gov
Consensus Panel Guidelines Online: https://hivinfo.nih.gov/
National Prevention Information Network: https://npin.cdc.gov/
United Nations AIDS: http://www.unaids.org/
University Sites
University of Stanford. HIV Drug Resistance Database: http://hivdb.stanford.edu/
AIDS Treatment/Advocacy Groups
San Francisco AIDS Foundation: http://www.sfaf.org/index.html
Other Relevant Sites
The AIDS Map: http://www.aidsmap.com
Clinical Care Options: http://www.clinicalcareoptions.com
HIV Drug Interactions: http://www.hiv-druginteractions.org
HIV and Hepatitis: http://hivandhepatitis.com
HIV Treatment Information: http://i-base.info/
Medscape: http://www.medscape.com
Physician's Research Network: http://www.prn.org
The Body for Clinicians: http://www.thebodypro.com

CONCLUSION

Given the significant advances in ART over the past 30 years, HIV-1 infection is now a manageable chronic disease for those who have access to ART. The pharmacologic management of HIV continues to rapidly evolve, but a basic understanding of viral pathogenesis and drug interactions provides a framework that can be used to evaluate new information as it becomes available. Although a cure is still out of reach, methods for preventing infection via TasP, PrEP, PEP, and through the prevention of perinatal transmission have become increasingly effective as alternative strategies for curbing the epidemic.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Coffey S, Bacchetti P, Sachdev D, et al. RAPID antiretroviral therapy: high virologic suppression rates with immediate antiretroviral therapy initiation in a vulnerable urban clinic population. *AIDS*. 2019;33(5):825–832. doi:10.1097/QAD.0000000000002124 (72)

Eisinger RW, Dieffenbach CW, Fauci AS. HIV viral load and transmissibility of HIV infection: undetectable equals untransmittable. *JAMA*. 2019;321(5):451–452. doi:10.1001/jama.2018.21167 (13)

Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. *Lancet HIV*. 2015;2(4):e127–e136.

Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2020;324(16):1651–1669. doi:10.1001/jama.2020.17025 (5)

U.S. Department of Health and Human Services. Panel on Antiretroviral Guidelines. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Accessed October 5, 2020. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines (3)

U.S. Department of Health and Human Services. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines (124)

U.S. Public Health Service and Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 update. Accessed October 1, 2020. https://clinicalinfo.hiv.gov/themes/custom/aidsinfo/documents/cdc-hiv-prep-guidelines-2017.pdf (130)

Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2019 update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2019;27(3):111–121. (4)

Key Websites

Centers for Disease Control and Prevention. HIV surveillance report. Published July 2020. Accessed September 30, 2020. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html (2)

U.S. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Accessed October 5, 2020. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines (3)

U.S. Public Health Service and Centers for Disease Control and Prevention. Preexposure Prophylaxis for the prevention of HIV infection in the United States—2017 update. Accessed October 1, 2020. https://clinicalinfo.hiv.gov/themes/custom/aidsinfo/documents/cdc-hiv-prep-guidelines-2017.pdf (130)

COMPLETE REFERENCES CHAPTER 76 PHARMACOTHERAPY OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

1. Murphy EL, Collier AC, Kalish LA, et al. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. *Ann Intern Med*. 2001;135(1):17–26. doi:10.7326/0003-4819-135-1-200107030-00005
2. Centers for Disease Control and Prevention. HIV surveillance report. Published July 2020. Accessed September 30, 2020. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html
3. U.S. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Accessed October 5, 2020. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines
4. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2019 update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2019;27(3):111–121.
5. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2020;324(16):1651–1669. doi:10.1001/jama.2020.17025
6. World Health Organization. Antiretroviral therapy (ART) coverage among all age groups. Accessed October 29, 2020. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/estimated-antiretroviral-therapy-coverage-among-people-living-with-hiv-(-)
7. World Health Organization. HIV/AIDS data and statistics. Accessed September 30, 2020. http://www.who.int/hiv/data/en/
8. Adimora A. Sexual networks, social forces, and the HIV epidemic: written congressional testimony for the September 16, 2008 hearing (p 111). Accessed August 7, 2017. https://www.gpo.gov/fdsys/pkg/CHRG-110hhrg56578/pdf/CHRG-110hhrg56578.pdf
9. Centers for Disease Control and Prevention. HIV in the United States and Dependent Areas. https://www.cdc.gov/hiv/statistics/overview/ataglance.html
10. Lane HC, Holmberg SD, Jaffe HW. HIV seroconversion and oral intercourse. *Am J Public Health*. 1991;81(5):658. doi:10.2105/ajph.81.5.658
11. Page-Shafer K, Shiboski CH, Osmond DH, et al. Risk of HIV infection attributable to oral sex among men who have sex with men and in the population of men who have sex with men. *AIDS*. 2002;16(17):2350–2352. doi:10.1097/00002030 -200211220-00022
12. Shaw GM, Hunter E. HIV transmission. *Cold Spring Harb Perspect Med*. 2012;2(11):a006965. doi:10.1101/cshperspect.a006965
13. Eisinger RW, Dieffenbach CW, Fauci AS. HIV viral load and transmissibility of HIV infection: undetectable equals untransmittable. *JAMA*. 2019;321(5):451–452. doi:10.1001/jama.2018.21167
14. LeMessurier J, Traversy G, Varsaneux O, et al. Risk of sexual transmission of human immunodeficiency virus with antiretroviral therapy, suppressed viral load and condom use: a systematic review. *Can Med Assoc J*. 2018;190(46):E1350–E1360. doi:10.1503/cmaj.180311
15. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493–505. doi:10.1056/NEJMoa1105243
16. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science*. 1996;271(5255):1582–1586. doi:10.1126/science.271.5255.1582
17. Fahey JL, Prince H, Weaver M, et al. Quantitative changes in T helper or T suppressor/cytotoxic lymphocyte subsets that distinguish acquired immune deficiency syndrome from other immune subset disorders. *Am J Med*. 1984;76(1):95–100. doi:10.1016/0002-9343(84)90756-3
18. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. *N Engl J Med*. 2011;364(20):1943–1954. doi:10.1056/NEJMra1011874
19. Deng H, Liu R, Ellmeier W, et al. Identification of a major co-receptor for primary isolates of HIV-1. *Nature*. 1996;381(6584):661–666. doi:10.1038/ 381661a0
20. Dragic T, Litwin V, Allaway GP, et al. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature*. 1996;381(6584):667–673. doi:10.1038/381667a0

21. Berson JF, Long D, Doranz BJ, Rucker J, Jirik FR, Doms RW. A seven-transmembrane domain receptor involved in fusion and entry of T-cell-tropic human immunodeficiency virus type 1 strains. *J Virol*. 1996;70(9):6288–6295. doi:10.1128/JVI.70.9.6288-6295.1996
22. Levy JA. Infection by human immunodeficiency virus—CD4 is not enough. *N Engl J Med*. 1996;335(20):1528–1530. doi:10.1056/NEJM199611143352011
23. Wild C, Greenwell T, Matthews T. A synthetic peptide from HIV-1 gp41 is a potent inhibitor of virus-mediated cell-cell fusion. *AIDS Res Hum Retroviruses*. 1993;9(11):1051–1053. doi:10.1089/aid.1993.9.1051
24. Bugelski PJ, Kirsh R, Hart TK. HIV protease inhibitors: effects on viral maturation and physiologic function in macrophages. *J Leukoc Biol*. 1994;56(3):374–380. doi:10.1002/jlb.56.3.374
25. Kohl NE, Emini EA, Schleif WA, et al. Active human immunodeficiency virus protease is required for viral infectivity. *Proc Natl Acad Sci U S A*. 1988;85(13):4686–4690. doi:10.1073/pnas.85.13.4686
26. Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. *Ann Intern Med*. 1996;124(7):654–663. doi:10.7326/0003-4819-124-7 -199604010-00006
27. Hellerstein M, Hanley MB, Cesar D, et al. Directly measured kinetics of circulating T lymphocytes in normal and HIV-1-infected humans. *Nat Med*. 1999;5(1):83–89. doi:10.1038/4772
28. Daar ES, Moudgil T, Meyer RD, Ho DD. Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. *N Engl J Med*. 1991;324(14):961–964. doi:10.1056/NEJM199104043241405
29. Fox CH, Tenner-Rácz K, Rácz P, Firpo A, Pizzo PA, Fauci AS. Lymphoid germinal centers are reservoirs of human immunodeficiency virus type 1 RNA. *J Infect Dis*. 1991;164(6):1051–1057.
30. Pantaleo G, Graziosi C, Demarest JF, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. *Nature*. 1993;362(6418):355–358. doi:10.1038/362355a0
31. Richman DD, Wrin T, Little SJ, Petropoulos CJ. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. *Proc Natl Acad Sci U S A*. 2003;100(7): 4144–4149. doi:10.1073/pnas.0630530100
32. Pilcher CD, Eron JJ, Galvin S, Gay C, Cohen MS. Acute HIV revisited: new opportunities for treatment and prevention. *J Clin Invest*. 2004;113(7):937–945. doi:10.1172/JCI21540
33. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*. 1995;373(6510):123–126. doi:10.1038/373123a0
34. Wei X, Ghosh SK, Taylor ME, et al. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature*. 1995;373(6510):117–122. doi:10.1038/373117a0
35. Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. *Science*. 1995;267(5197):483–489. doi:10.1126/science .7824947
36. Mellors JW, Rinaldo CR, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*. 1996;272(5265):1167–1170. doi:10.1126/science.272.5265.1167
37. O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS. *N Engl J Med*. 1996;334(7):426–431. doi:10.1056/NEJM199602153340703
38. Mellors JW, Muñoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997;126(12):946–954. doi:10.7326/0003-4819-126-12-199706150-00003
39. Pantaleo G, Menzo S, Vaccarezza M, et al. Studies in subjects with long-term nonprogressive human immunodeficiency virus infection. *N Engl J Med*. 1995; 332(4):209–216. doi:10.1056/NEJM199501263320402
40. O'Brien TR, Blattner WA, Waters D, et al. Serum HIV-1 RNA levels and time to development of AIDS in the Multicenter Hemophilia Cohort Study. *JAMA*. 1996;276(2):105–110.

41. Sepkowitz KA. Effect of HAART on natural history of AIDS-related opportunistic disorders. *Lancet*. 1998;351(9098):228–230. doi:10.1016/S0140-6736(05)78279-9
42. Yarchoan R, Broder S. Development of antiretroviral therapy for the acquired immunodeficiency syndrome and related disorders. A progress report. *N Engl J Med*. 1987;316(9):557–564. doi:10.1056/NEJM198702263160925
43. Merluzzi VJ, Hargrave KD, Labadia M, et al. Inhibition of HIV-1 replication by a nonnucleoside reverse transcriptase inhibitor. *Science*. 1990;250(4986):1411–1413. doi:10.1126/science.1701568
44. Adams JL, Greener BN, Kashuba ADM. Pharmacology of HIV integrase inhibitors. *Curr Opin HIV AIDS*. 2012;7(5):390–400. doi:10.1097/COH.0b013e328356e91c
45. Deeks SG, Smith M, Holodniy M, Kahn JO. HIV-1 protease inhibitors. A review for clinicians. *JAMA*. 1997;277(2):145–153.
46. Acosta EP, Kakuda TN, Brundage RC, Anderson PL, Fletcher CV. Pharmacodynamics of human immunodeficiency virus type 1 protease inhibitors. *Clin Infect Dis*. 2000;30(suppl 2):S151–S159. doi:10.1086/313852
47. Larson KB, Wang K, Delille C, Otofokun I, Acosta EP. Pharmacokinetic enhancers in HIV therapeutics. *Clin Pharmacokinet*. 2014;53(10):865–872. doi:10.1007/s40262-014-0167-9
48. Reeves JD, Piefer AJ. Emerging drug targets for antiretroviral therapy. *Drugs*. 2005;65(13):1747–1766. doi:10.2165/00003495-200565130-00002
49. World Health Organization. HIV drug resistance report 2019. Published July 2019. Accessed October 29, 2020. https://www.who.int/publications/i/item/WHO-CDS-HIV-19.21
50. Beccari MV, Mogle BT, Sidman EF, Mastro KA, Asiago-Reddy E, Kufel WD. Ibalizumab, a novel monoclonal antibody for the management of multidrug-resistant HIV-1 infection. *Antimicrob Agents Chemother*. 2019;63(6):e00110-19. doi:10.1128/AAC.00110-19
51. Kozal M, Aberg J, Pialoux G, et al. Fostemsavir in adults with multidrug-resistant HIV-1 infection. *N Engl J Med*. 2020;382(13):1232–1243. doi:10.1056/NEJMoa1902493
52. Westby M, van der Ryst E. CCR5 antagonists: host-targeted antivirals for the treatment of HIV infection. *Antivir Chem Chemother*. 2005;16(6):339–354. doi:10.1177/095632020501600601
53. Chun TW, Davey RT, Engel D, Lane HC, Fauci AS. Re-emergence of HIV after stopping therapy. *Nature*. 1999;401(6756):874–875. doi:10.1038/44755
54. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med*. 1999;5(5):512–517. doi:10.1038/8394
55. Zhang L, Ramratnam B, Tenner-Racz K, et al. Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. *N Engl J Med*. 1999;340(21):1605–1613. doi:10.1056/NEJM199905273402101
56. Pomerantz RJ. Residual HIV-1 disease in the era of highly active antiretroviral therapy. *N Engl J Med*. 1999;340(21):1672–1674. doi:10.1056/NEJM199905273402110
57. Chun T-W, Fauci AS. HIV reservoirs: pathogenesis and obstacles to viral eradication and cure. *AIDS*. 2012;26(10):1261–1268. doi:10.1097/QAD.0b013e328353f3f1
58. Vansant G, Bruggemans A, Janssens J, Debyser Z. Block-and-lock strategies to cure HIV infection. *Viruses*. 2020;12(1):84. doi:10.3390/v12010084
59. Olson A, Basukala B, Lee S, Gagne M, Wong WW, Henderson AJ. Targeted chromatinization and repression of HIV-1 provirus transcription with repurposed CRISPR/Cas9. *Viruses*. 2020;12(10):1154. doi:10.3390/v12101154
60. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: updated recommendations. 2014. Accessed November 10, 2020. http://stacks.cdc.gov/view/cdc/23447
61. U.S. Food & Drug Administration. BioPlex 2200 HIV Ag-Ab assay. Accessed November 10, 2020. https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/bioplex-2200-hiv-ag-ab-assay
62. Centers for Disease Control and Prevention. 2018 Quick reference guide: recommended laboratory HIV testing algorithm for serum or plasma specimens. Accessed November 9, 2020.

https://stacks.cdc.gov/view/cdc/50872/Share
63. Centers for Disease Control and Prevention. Advantages and disadvantages of FDA-approved HIV assays used for screening, by test category. Accessed November 10, 2020. https://www.cdc.gov/hiv/pdf/testing/hiv-tests-advantages-disadvantages_1.pdf
64. World Health Organization. Laboratory guidelines for enumerating CD4 T lymphocytes in the context of HIV/AIDS. Published 2007. Accessed November 10, 2020. https://apps.who.int/iris/bitstream/handle/10665/205403/B3180.pdf?sequence=1&isAllowed=y
65. Peter JB, Sevall JS. Molecular-based methods for quantifying HIV viral load. *AIDS Patient Care STDS*. 2004;18(2):75–79. doi:10.1089/108729104322802506
66. Lafeuillade A, Poggi C, Profizi N, Tamalet C, Costes O. Human immunodeficiency virus type 1 kinetics in lymph nodes compared with plasma. *J Infect Dis*. 1996;174(2):404–407. doi:10.1093/infdis/174.2.404
67. Harris M, Patenaude P, Cooperberg P, et al. Correlation of virus load in plasma and lymph node tissue in human immunodeficiency virus infection. INCAS Study Group. Italy, Netherlands, Canada, Australia, and (United) States. *J Infect Dis*. 1997;176(5):1388–1392. doi:10.1086/517328
68. Brichacek B, Swindells S, Janoff EN, Pirruccello S, Stevenson M. Increased plasma human immunodeficiency virus type 1 burden following antigenic challenge with pneumococcal vaccine. *J Infect Dis*. 1996;174(6):1191–1199. doi:10.1093/infdis/174.6.1191
69. Rosen S, Maskew M, Fox MP, et al. Initiating antiretroviral therapy for HIV at a patient's first clinic visit: the RapIT randomized controlled trial. *PLoS Med*. 2016;13(5):e1002015. doi:10.1371/journal.pmed.1002015
70. Koenig SP, Dorvil N, Dévieux JG, et al. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: a randomized unblinded trial. *PLoS Med*. 2017;14(7):e1002357. doi:10.1371/journal.pmed.1002357
71. Colasanti J, Sumitani J, Mehta CC, et al. Implementation of a rapid entry program decreases time to viral suppression among vulnerable persons living with HIV in the southern United States. *Open Forum Infect Dis*. 2018;5(6):ofy104. doi:10.1093/ofid/ofy104
72. Coffey S, Bacchetti P, Sachdev D, et al. RAPID antiretroviral therapy: high virologic suppression rates with immediate antiretroviral therapy initiation in a vulnerable urban clinic population. *AIDS*. 2019;33(5):825–832. doi:10.1097/QAD.0000000000002124
73. Gras L, Kesselring AM, Griffin JT, et al. CD4 cell counts of 800 cells/mm^3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm^3 or greater. *J Acquir Immune Defic Syndr*. 2007;45(2):183–192. doi:10.1097/QAI.0b013e31804d685b
74. Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. *Clin Infect Dis*. 2005;41(3):361–372. doi:10.1086/431484
75. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441–446. doi:10.1086/510746
76. Calvo M, Martinez E. Update on metabolic issues in HIV patients. *Curr Opin HIV AIDS*. 2014;9(4):332–339. doi:10.1097/COH.0000000000000075
77. Dube MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV medicine association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2003;37:613–627.
78. Dubé MP, Parker RA, Tebas P, et al. Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides. *AIDS*. 2005;19(16):1807–1818. doi:10.1097/01.aids.0000183629.20041.bb
79. Elion RA, Althoff KN, Zhang J, et al. Recent abacavir use increases risk of type 1 and type 2 myocardial infarctions among adults with HIV. *J Acquir Immune Defic Syndr*. 2018;78(1):62–72. doi:10.1097/QAI.0000000000001642

80. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. *Lancet HIV*. 2018;5(6):e291–e300. doi:10.1016/S2352-3018(18)30043-2
81. Mayer KH, Molina J-M, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet*. 2020;396(10246):239–254. doi:10.1016/S0140-6736(20)31065-5
82. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. *Curr Opin Infect Dis*. 2020;33(1):10–19. doi:10.1097/QCO.0000000000000616
83. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis*. 2020;70(7):1267–1274. doi:10.1093/cid/ciz407
84. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N Engl J Med*. 2019;381(9):803–815. doi:10.1056/NEJMoa1902824
85. NAMSAL ANRS 12313 Study Group, Kouanfack C, Mpoudi-Etame M, et al. Dolutegravir-based or low-dose efavirenz-based regimen for the treatment of HIV-1. *N Engl J Med*. 2019;381(9):816–826. doi:10.1056/NEJMoa1904340
86. Stellbrink H-J, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2019;6(6):e364–e372. doi:10.1016/S2352-3018(19)30080-3
87. Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2019;6(6):e355–e363. doi:10.1016/S2352-3018(19)30077-3
88. Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. *AIDS Behav*. 2011;15(7):1381–1396. doi:10.1007/s10461-011-9942-x
89. Schneider J, Kaplan SH, Greenfield S, Li W, Wilson IB. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med*. 2004;19(11):1096–1103. doi:10.1111/j.1525-1497.2004.30418.x
90. Halkitis PN, Shrem MT, Zade DD, Wilton L. The physical, emotional and interpersonal impact of HAART: exploring the realities of HIV seropositive individuals on combination therapy. *J Health Psychol*. 2005;10(3):345–358. doi:10.1177/1359105305051421
91. Stirratt MJ, Remien RH, Smith A, et al. The role of HIV serostatus disclosure in antiretroviral medication adherence. *AIDS Behav*. 2006;10(5):483–493. doi:10.1007/s10461-006-9106-6
92. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: a systematic review and meta-analysis. *PLoS One*. 2018;13(9):e0204091. doi:10.1371/journal.pone.0204091
93. Shah R, Watson J, Free C. A systematic review and meta-analysis in the effectiveness of mobile phone interventions used to improve adherence to antiretroviral therapy in HIV infection. *BMC Public Health*. 2019;19(1):915. doi:10.1186/s12889-019-6899-6
94. Swindells S, Andrade-Villanueva J-F, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med*. 2020;382(12):1112–1123. doi:10.1056/NEJMoa1904398
95. Orkin C, Oka S, Philibert P, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. *Lancet HIV*. 2021;8(4):e185–e196. doi:10.1016/S2352-3018(20)30340-4
96. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-

label, phase 2b, non-inferiority trial. *Lancet*. 2017;390(10101):1499–1510. doi:10.1016/S0140-6736(17)31917-7

97. Palella FJ, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. 2006;43(1):27–34. doi:10.1097/01.qai.0000233310.90484.16
98. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316(2):171–181. doi:10.1001/jama.2016.5148
99. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet*. 2019;393(10189):2428–2438. doi:10.1016/S0140-6736(19)30418-0
100. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830–839. doi:10.1056/NEJMoa1600693
101. Churchill MJ, Deeks SG, Margolis DM, Siliciano RF, Swanstrom R. HIV reservoirs: what, where and how to target them. *Nat Rev Microbiol*. 2016;14(1):55–60. doi:10.1038/nrmicro.2015.5
102. Cahn P, Madero JS, Arribas JR, et al. Durable efficacy of dolutegravir plus lamivudine in antiretroviral treatment-naive adults with HIV-1 infection: 96-week results from the GEMINI-1 and GEMINI-2 randomized clinical trials. *J Acquir Immune Defic Syndr*. 2020;83(3):310–318. doi:10.1097/QAI.0000000000002275
103. Powderly WG, Saag MS, Chapman S, Yu G, Quart B, Clendeninn NJ. Predictors of optimal virological response to potent antiretroviral therapy. *AIDS*. 1999;13(14):1873–1880. doi:10.1097/00002030-199910010-00009
104. Jacobson MA, Zegans M, Pavan PR, et al. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet*. 1997;349(9063):1443–1445. doi:10.1016/S0140-6736(96)11431-8
105. Kempen JH, Min Y-I, Freeman WR, et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology*. 2006;113(4):684–694. doi:10.1016/j.ophtha.2005.10.067
106. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet*. 1998;351(9098):252–255. doi:10.1016/S0140-6736(97)04352-3
107. Lederman MM, Connick E, Landay A, et al. Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and ritonavir: results of AIDS Clinical Trials Group Protocol 315. *J Infect Dis*. 1998;178(1):70–79. doi:10.1086/515591
108. Pakker NG, Notermans DW, de Boer RJ, et al. Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. *Nat Med*. 1998;4(2):208–214. doi:10.1038/nm0298-208
109. Roederer M. Getting to the HAART of T cell dynamics. *Nat Med*. 1998;4(2):145–146. doi:10.1038/nm0298-145
110. Lee PK, Kieffer TL, Siliciano RF, Nettles RE. HIV-1 viral load blips are of limited clinical significance. *J Antimicrob Chemother*. 2006;57(5):803–805. doi:10.1093/jac/dkl092
111. Sungkanuparph S, Overton ET, Seyfried W, Groger RK, Fraser VJ, Powderly WG. Intermittent episodes of detectable HIV viremia in patients receiving nonnucleoside reverse-transcriptase inhibitor-based or protease inhibitor-based highly active antiretroviral therapy regimens are equivalent in incidence and prognosis. *Clin Infect Dis*. 2005;41(9):1326–1332. doi:10.1086/496985
112. Macias J, Palomares JC, Mira JA, et al. Transient rebounds of HIV plasma viremia are associated with the emergence of drug resistance mutations in patients on highly active antiretroviral therapy. *J Infect*. 2005;51(3):195–200. doi:10.1016/j.jinf.2004.11.010
113. Lataillade M, Lalezari JP, Kozal M, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. *Lancet HIV*. 2020;7(11):e740–e751. doi:10.1016/S2352-3018(20)30240-X

114. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. *JAMA*. 1999;282(12):1135–1141. doi:10.1001/jama.282.12.1135
115. Hecht FM, Grant RM, Petropoulos CJ, et al. Sexual transmission of an HIV-1 variant resistant to multiple reverse-transcriptase and protease inhibitors. *N Engl J Med*. 1998;339(5):307–311. doi:10.1056/NEJM199807303390504
116. Yerly S, Kaiser L, Race E, Bru JP, Clavel F, Perrin L. Transmission of antiretroviral-drug-resistant HIV-1 variants. *Lancet*. 1999;354(9180):729–733. doi:10.1016/S0140-6736(98)12262-6
117. Tang MW, Shafer RW. HIV-1 antiretroviral resistance: scientific principles and clinical applications. *Drugs*. 2012;72(9):e1–e25. doi:10.2165/11633630-000000000-00000
118. Deeks SG, Grant RM, Wrin T, et al. Persistence of drug-resistant HIV-1 after a structured treatment interruption and its impact on treatment response. *AIDS*. 2003;17(3):361–370. doi:10.1097/00002030-200302140-00010
119. Leigh Brown AJ, Frost SDW, Mathews WC, et al. Transmission fitness of drug-resistant human immunodeficiency virus and the prevalence of resistance in the antiretroviral-treated population. *J Infect Dis*. 2003;187(4):683–686. doi:10.1086/367989
120. Acosta EP, Gerber JG, Adult Pharmacology Committee of the AIDS Clinical Trials Group. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses*. 2002;18(12):825–834. doi:10.1089 /08892220260190290
121. Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit*. 2011;33(3):265–274. doi:10.1097/FTD.0b013e31821b42d1
122. Moltó J, Blanco A, Miranda C, et al. Variability in non-nucleoside reverse transcriptase and protease inhibitors concentrations among HIV-infected adults in routine clinical practice. *Br J Clin Pharmacol*. 2007;63(6):715–721. doi:10.1111/j.1365-2125.2006.02834.x
123. Nettles RE, Kieffer TL, Parsons T, et al. Marked intraindividual variability in antiretroviral concentrations may limit the utility of therapeutic drug monitoring. *Clin Infect Dis*. 2006;42(8):1189–1196. doi:10.1086/501458
124. U.S. Department of Health and Human Services. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Accessed October 5, 2020. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines
125. Chersich MF, Urban MF, Venter FWD, et al. Efavirenz use during pregnancy and for women of child-bearing potential. *AIDS Res Ther*. 2006;3:11. doi:10.1186/1742-6405-3-11
126. De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med*. 2002;162(3):355. doi:10.1001/archinte.162.3.355
127. Fundarò C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. 2002;16(2): 299–300.
128. Saitoh A, Hull AD, Franklin P, Spector SA. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol*. 2005;25(8):555–556. doi:10.1038/sj.jp.7211343
129. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381(9):827–840. doi:10.1056/NEJMoa1905230
130. U.S. Department of Health and Human Services and Center for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 update. Accessed October 1, 2020. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf
131. Truvada. Package insert. Gilead Sciences, Inc. Accessed October 5, 2020. https://www.gilead.com/~/media/Files/pdfs/medicines/hiv/truvada/truvada_pi.pdf
132. Descovy. Package insert. Gilead Sciences, Inc. Accessed October 2, 2020. https://www.gilead.com/~/media/Files/pdfs/medicines/hiv/descovy/descovy_pi.pdf
133. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med*. 2021;385(7):595–608. doi:10.1056/NEJMoa2101016

134. Landovitz RJ. HPTN 083 FINAL RESULTS: Pre-exposure prophylaxis containing long-acting injectable cabotegravir is safe and highly effective for cisgender men and transgender women who have sex with men. Presented at the International AIDS Conference 2020; July 8, 2020. Accessed July 16, 2021. https://natap.org/2020/IAC/IAC_28.htm
135. Dominguez KL, Smith DK, Vasavi Thomas, et al. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. Accessed November 10, 2020. https://stacks.cdc.gov/view/cdc/38856
136. New York State Department of Health AIDS Institute. HIV prophylaxis following occupational exposure. Published 2014. Accessed May 31, 2015. https://www.hivguidelines.org/pep-for-hiv-prevention/
137. California Legislative Information. SB-159 HIV: preexposure and postexposure prophylaxis. Published October 8, 2019. Accessed June 20, 2020. https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201920200SB159
138. Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med*. 2020;382(12):1124–1135. doi:10.1056/NEJMoa1909512
139. Matthews R. First-in-human trial of MK-8591-eluting implants demonstrates concentrations suitable for HIV prophylaxis for at least one year. Presented at the 10th IAS Conference on HIV Science (IAS 2019); July 21, 2019; Mexico City, Mexico.

77

Opportunistic Infections in Patients Living With HIV

Emily L. Heil and Amanda H. Corbett

CORE PRINCIPLES		CHAPTER CASES
1	Acquired immunodeficiency syndrome (AIDS) is characterized by the gradual erosion of immune competence and the development of opportunistic infections (OIs) and malignancies. A decline in OIs and OI-related malignancies has been observed, which is associated with combined antiretroviral therapy (ART).	
2	*Pneumocystis jirovecii* pneumonia (PCP) should be treated with trimethoprim–sulfamethoxazole (TMP-SMX). Patients intolerant of sulfonamides should be treated with alternatives such as dapsone, atovaquone, or pentamidine. Steroids	**Case 77-1 (Questions 1–5)**

	should be used to treat patients with moderate-to-severe diseases. Primary prophylaxis with these agents is recommended for patients with CD4 counts <200.	
3	Toxoplasmosis typically occurs in patients with CD4 counts <100, and primary prophylaxis is indicated in these patients who are also *Toxoplasma* immunoglobulin G (IgG)-positive. Alternatives for prophylaxis include TMP-SMX, dapsone + pyrimethamine + leucovorin, and atovaquone ± pyrimethamine + leucovorin. Treatment options include sulfadiazine + pyrimethamine + leucovorin, clindamycin + pyrimethamine + leucovorin, and TMP-SMX.	**Case 77-2 (Questions 1–8)**
4	Cytomegalovirus (CMV) typically causes retinitis in persons living with HIV (PLWH) with CD4 counts <50. Primary prophylaxis is usually not indicated, and treatment options include intravenous (IV) ganciclovir, valganciclovir, IV foscarnet, and IV cidofovir.	**Case 77-3 (Questions 1–4)**
5	Cryptococcal meningitis occurs typically in patients with CD4 counts <50, and primary prophylaxis is not typically recommended. First-line treatment includes liposomal amphotericin B + flucytosine for induction therapy with subsequent addition of fluconazole for maintenance.	**Case 77-4 (Questions 1–8)**

6	*Mycobacterium tuberculosis* infects PLWH at any CD4 count, sometimes with an atypical presentation. Isoniazid for 9 months is the preferred regimen for latent tuberculosis (TB) in PLWH. Initial treatment in drug-susceptible TB is with rifampin (or rifabutin) + isoniazid + pyrazinamide + ethambutol.	**Case 77-5 (Question 1, 2) Case 77-6 (Question 1), and Case 77-7 (Question 1)**
7	*Mycobacterium avium* complex (MAC) can be localized to the lung or with disseminated infection in PLWH with CD4 counts <50. Primary prophylaxis is not indicated for patients on effective ART. First-line treatment for acute infection consists of clarithromycin (or azithromycin) + ethambutol ± rifampin (or rifabutin).	**Case 77-8 (Questions 1–6)**

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is characterized by the gradual erosion of immune competence and the development of opportunistic infections (OIs). Since the advent of antiretroviral therapy (ART), which is the use of a combination of potent antiretroviral medications, AIDS-related mortality has declined in the United States.[1,2] The overall 5-year survival probability after the first OI diagnosis has increased dramatically from 7% in the pre-HAART (highly active antiretroviral therapy) to 65% in the ART era.[3] This decline in mortality has been associated with a decline in OIs and an increase in non-AIDS-related causes of mortality.[4] Persons living with HIV (PLWH) infection are susceptible to an array of diseases, but most OIs are caused by a few common pathogens, including

Pneumocystis jirovecii (*carinii*), cytomegalovirus (CMV), fungi, and mycobacteria.[5]

The revised classification system for human immunodeficiency virus (HIV) infection and expanded surveillance case definition for AIDS included stratification for the CD4 lymphocyte count, as well as subgrouping by clinical categories (see Chapter 76, Pharmacotherapy of Human Immunodeficiency Virus Infection, Table 76-1). These AIDS-defining OIs may also occur in asymptomatic PLWH.[5]

Natural History of Opportunistic Infections

DECLINE OF THE CD4 LYMPHOCYTE

Within the immune system, the CD4 lymphocyte functions as a "helper cell" that modulates the actions of the other key cellular components of the immune system. The eventual loss of CD4 lymphocytes is the underlying pathophysiology that leads to AIDS. (See Chapter 76, Pharmacotherapy of Human Immunodeficiency Virus Infection, and comprehensive immunology texts for a more detailed explanation of immune function and inflammation associated with HIV infection.) The infected CD4 lymphocyte can function normally for a time, but eventually becomes dysfunctional, as manifested by an abnormal response to soluble mitogens. It is this cellular functional deficit, compounded by the eventual decline in the absolute number of CD4 lymphocytes that leads to OIs and neurologic dysfunctions. The CD4 lymphocyte count declines gradually during several years in the untreated PLWH. The average rate of decline in CD4 lymphocyte cells (CD4 slope) is ~40 to 80 cells/μL/year in the absence of ART. An accelerated decline in the CD4 count occurs at 1.5 to 2 years, just before an AIDS-defining diagnosis.[6] Without therapy, the course of infection averages ~10 years from the time of initial infection to an AIDS-defining diagnosis.

The CD4 count dictates the need for OI prophylaxis, influences the differential diagnosis of the OI, and is an independent indicator of prognosis. For these reasons, the CD4 count has become a primary

surrogate marker of immune suppression and antiretroviral activity. HIV-1 ribonucleic acid (RNA) is the other clinical surrogate marker, most predictive of survival and antiretroviral activity.

OIs range from relatively minor events (eg, oral candidiasis or oral hairy leukoplakia) to sight-threatening episodes of CMV retinitis or life-threatening *Pneumocystis jirovecii* pneumonia (PCP). The risk of specific OIs varies with the degree of immunosuppression.[7] Asymptomatic patients with moderate immunosuppression (CD4 counts, 200–500) may become infected with herpes viruses and *Candida* species or develop pneumonia, enteric infection, and meningitis with more common pathogens. Massive destruction of the immune system occurs when the CD4 count drops <200, which increases the risk of opportunistic pathogens (eg, PCP), opportunistic tumors, wasting, and neurologic complications. With a CD4 count of 50 to 100, invasive candidiasis, cerebral toxoplasmosis, cryptococcosis, and various protozoal infections are observed. When the CD4 count falls <50, the patient is in an advanced immunosuppressed state, which is associated with non-Hodgkin lymphoma, CMV, and disseminated *Mycobacterium avium* complex (MAC; **Fig. 77-1**). Without treatment, the 5-year probability of survival associated with a CD4 count <100 is 43%, and the time to an AIDS-defining infection ranges from 18 to 24 months.[7,8]

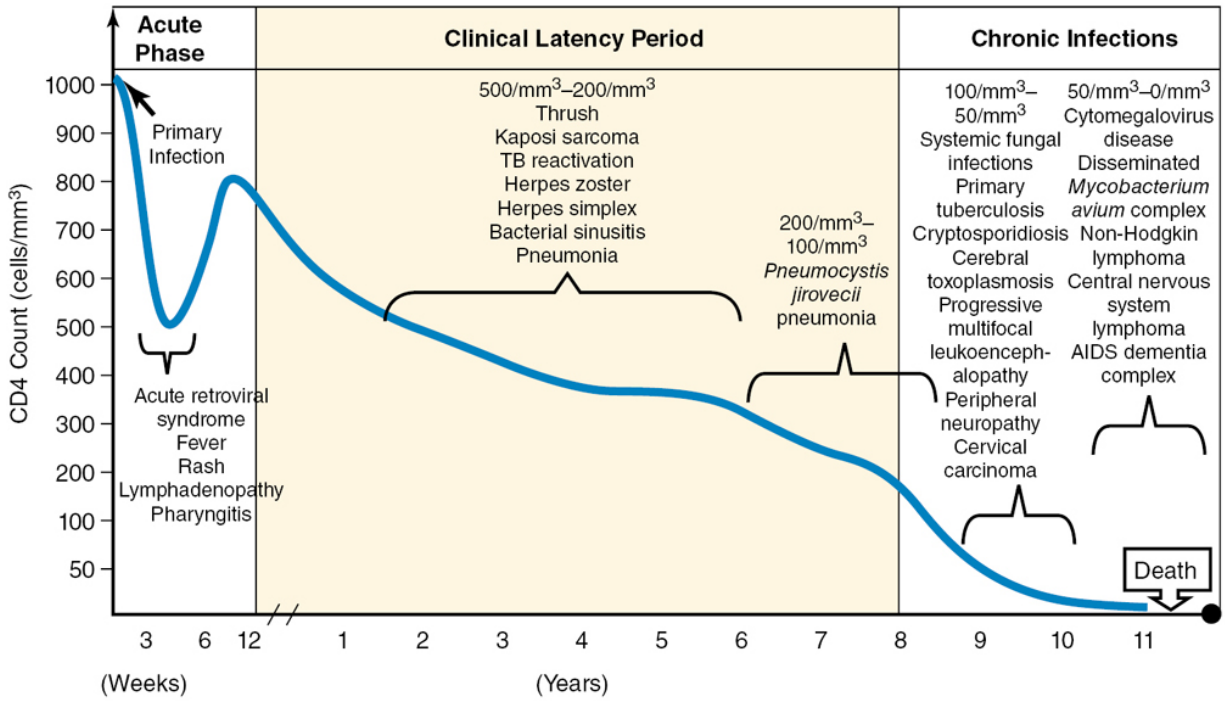


Figure 77-1 Natural history of CD4 cell count in the average patient living with HIV without antiretroviral therapy, from the time of HIV transmissions to death. (Illustration by Mary Van, PharmD.)

EFFECT OF OPPORTUNISTIC INFECTIONS ON VIRAL LOAD AND SURVIVAL

Acute OIs upregulate HIV replication, resulting in higher HIV-1 RNA concentrations in the plasma and lymphoid tissues of PLWH. This enhanced replication is presumably caused by antigen-mediated activation of HIV-1 replication in latently infected cells. To assess the impact of OIs on survival, data from a cohort of 2081 PLWH followed up (in the pre-ART era) for a mean of 30 months were analyzed.[9] CD4 counts and incidence of opportunistic disease were used as independent variables. These investigators found that PCP, CMV, MAC, esophageal candidiasis, Kaposi sarcoma (KS), non-Hodgkin lymphoma, progressive multifocal leukoencephalopathy (PML), dementia, wasting syndrome, toxoplasmosis, and cryptosporidiosis were independently associated with death.[9] In addition, data from a prospective longitudinal study of HIV infection in same-gender–loving males initiated in 1984 (Multicenter AIDS Cohort Study)

demonstrated that plasma HIV-1 RNA concentrations strongly predict the rate of decline in the absolute CD4 count and clinical progression to AIDS and death.[10] More recent investigations in the era of ART have demonstrated that CD4 count is the strongest prognostic factor in patients starting therapy.[8]

IMPACT OF ANTIRETROVIRAL AGENTS ON THE NATURAL HISTORY OF OPPORTUNISTIC INFECTIONS

Reduction in the incidence of opportunistic infections and death

The introduction of protease inhibitors, combination therapy, prophylaxis therapy, and improved medical care has reduced the incidence of OIs and death resulting from AIDS in patients living with HIV. ART generally refers to an antiretroviral regimen that can be expected to reduce the viral load in antiretroviral-naive patients to <50 copies/mL. A panel of experts convened by the U.S. Department of Health and Human Services recommended ART as the standard of care for all PLWH.[11] These potent antiretroviral agents and effective management of OIs have led to an improved quality of life and prolonged survival among PLWH in patients in the United States.[12]

CHANGES IN THE NATURAL HISTORY OF OPPORTUNISTIC INFECTIONS

OIs result from long-standing immunosuppression from HIV infection.[7] For example, before ART, ~40% of all patients with AIDS exhibited CMV retinitis, with the most cases occurring at CD4 counts <100. Since the implementation of ART, a decrease in the incidence and progression of CMV retinitis have been noted.[13],[14]

Ironically, ART has also been associated with a worsening or an unmasking of occult OIs in patients with an advanced stage of AIDS. When ART strengthens the immune system, inflammatory symptoms in response to infection are more clinically pronounced.[12] This syndrome has been referred to as *immune reconstitution inflammatory syndrome (IRIS)*. IRIS incidence is estimated to be

10% to 40% in patients starting ART, based primarily on retrospective observational data.[15–18] During IRIS, there is typically a rapid increase in CD4 lymphocytes; however, this does not represent fully functional cells, but rather an increase in memory subtypes.

The initiation of ART typically results in an increase in CD4 lymphocytes and a decrease in HIV RNA to undetectable levels. This initial increase in CD4 T cells after the initiation of therapy involves an increase in memory T cells with low proliferation and a decrease in functional or effector cells. As a result, infections that are present in tissues are allowed to proliferate once the immune system is recovering, allowing IRIS to occur.[19]

IMPROVEMENT IN OR RESOLUTION OF OPPORTUNISTIC INFECTIONS

With the initiation of ART, reports of improvement in or resolution of some OIs can occur.[20–24] These OIs include KS,[24] PML,[22] CMV,[13,14] microsporidiosis, cryptosporidiosis,[21] and molluscum contagiosum,[23] a viral infection caused by a member of the *Poxviridae* family. Furthermore, there are reports of restored immunity and clinical improvement in patients with chronic hepatitis B infection (not classified as a Centers for Disease Control and Prevention [CDC]-defined AIDS indicator condition) with the initiation of ART.[20] However, these infections were not eradicated, and, in some cases, improvement was only transient. Clinical resolution most likely results from immunologic improvement, and the protective immunity against OI is sustained only as long as ART remains effective.

Pharmacotherapeutic Management of Opportunistic Infections

Successful pharmacotherapeutic management of OIs requires an understanding of the natural history of HIV-associated OIs, including the recognition that OIs occur with declining CD4 lymphocyte counts, the clinical presentation of each disease, diagnostic techniques, and effective treatment and preventive strategies. Management issues,

complicated by multiple-drug therapy for OIs and HIV suppression, include adherence, toxicities, resistance, drug interactions, and cost. PLWH are usually less tolerant to drugs such as flucytosine, trimethoprim–sulfamethoxazole (TMP-SMX), and pyrimethamine; however, alternative agents are available to overcome these barriers to treatment.

A panel from the CDC, the National Institutes of Health (NIH), and the HIV Medicine Association of the Infectious Diseases Society of America (IDSA) maintain comprehensive guidelines for preventing exposure to opportunistic pathogens, preventing first episodes of the disease by chemoprophylaxis or vaccination (primary prophylaxis), and preventing disease recurrence (secondary prophylaxis). Current guidelines and any archived guidelines can be found at www.clinicalinfo.hiv.gov/guidelines.[12]

PRIMARY PROPHYLAXIS

Primary prophylaxis is defined as a therapy that is initiated before the appearance of an OI in high-risk asymptomatic persons to prevent the initial occurrence of an infection. Primary prevention of OIs is important, considering the inevitable immune depletion associated with chronic HIV infection.[25] PCP and MAC prophylaxis have significantly prolonged survival and delayed the onset of illness (see sections on Prophylaxis for both PCP and MAC).[26,27]

The guidelines strongly recommend primary prophylaxis against PCP, toxoplasmosis, latent tuberculosis infection (LTBI), and MAC (in patients not starting ART). Vaccinations to prevent *Streptococcus pneumoniae*, hepatitis B virus, hepatitis A virus, varicella-zoster virus (VZV), and influenza virus infection are generally recommended for all PLWH. Primary prophylaxis for fungal infections (*Cryptococcus neoformans* and *Histoplasma capsulatum*), CMV, and bacterial infections are not routinely recommended for most patients, except in unusual circumstances (**Table 77-1**).

Table 77-1
Primary Prophylaxis of Opportunistic Infections in HIV-Infected

Adults and Adolescents

	Preventive Regimens			
Pathogen	**Indication**	**First Choice**	**Alternatives**	**Discontinue Prophylaxis**
Strongly Recommended as Standard of Care				
Pneumocystis jirovecii (carinii)	CD4 count <200 or CD4 <14%	TMP-SMX, 1 DS PO daily or TMP-SMX 1 SS PO daily	TMP-SMX 1 DS tiw Dapsone 50 mg bid or 100 mg/day; dapsone 50 mg daily + pyrimethamine 50 mg qw + leucovorin 25 mg PO qw; aerosolized pentamidine 300 mg qm via Respirgard II® nebulizer, atovaquone 1500 mg PO daily; atovaquone 1500 mg PO + pyrimethamine 25 mg PO + leucovorin 25 mg PO daily	Patients on HAART with sustained CD4 >200 cells for ≥3 months may discontinue PCP prophylaxis. Reintroduce if CD4 >200.
Mycobacterium tuberculosis				
Isoniazid sensitive	+ Diagnostic test for TB with no evidence of active TB, no prior treatment *or* close contact with a person with active TB, with no evidence of active TB	Isoniazid 300 mg PO daily *or* isoniazid 900 mg PO biw × 9 months both with pyridoxine 50 mg PO daily ART recommended for all persons with HIV and LTBI	Rifapentine plus isoniazid 900 mg plus pyridoxine 50 mg once weekly for 12 weeks Rifampin 600 mg PO daily × 4 months	
Drug-resistant TB	Same; high probability of exposure to isoniazid-resistant TB	Choice of drugs requires consultation with public health authorities.	None	
Toxoplasma gondii	IgG antibody to *Toxoplasma* and CD4 count <100	TMP-SMX, 1 DS PO daily	TMP-SMX, 1 SS PO daily; TMP-SMX 1 DS PO tiw; dapsone 50 mg PO daily + pyrimethamine 50 mg PO qw + leucovorin 25 mg PO qw; dapsone 200 mg PO qw + pyrimethamine 75 mg PO qw + leucovorin 25 mg PO qw; atovaquone 1500 mg PO daily with or without pyrimethamine 25 mg PO daily + leucovorin 10 mg PO daily	Patients on HAART with sustained CD4 >200 for ≥3 months may discontinue toxoplasmosis prophylaxis. Restart if CD4 >100–200.
MAC	CD4 <50 in those who are not on fully suppressive ART after ruling out disseminated MAC	Azithromycin, 1200 mg PO qw; clarithromycin 500 mg PO bid; azithromycin 600 mg PO biw	Rifabutin, 300 mg PO daily	Patients on HAART with sustained CD4 >100 for ≥3 months may discontinue MAC prophylaxis. Restart if CD4 >50.
VZV	Pre-exposure prevention: Patients with CD4 ≥200 who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV Postexposure prevention: Significant exposure to chicken pox or shingles for patients who are susceptible	Pre-exposure: Primary varicella vaccination, two doses administered 3 months apart Postexposure prevention: VZIG 125 IU per 10 kg (maximum of 635 IU) IM administered 96 hours after exposure		

	Preventive Regimens			
Pathogen	**Indication**	**First Choice**	**Alternatives**	**Discontinue Prophylaxis**
Usually Recommended				
Streptococcus pneumoniae	Regardless of CD4 count followed by:	PCV13 0.5 mL × 1 Followed by: PPV23 0.5 mL IM at least 8 weeks after PCV13 if CD4 ≥200 If CD4 <200, PPV23 can be offered at least 8 weeks after receiving PCV13 or can wait until CD4 ≥200	None	
HBV	All susceptible (anti-HBc-negative) patients	Hepatitis B vaccine series (depends on the vaccine used)	None	
HPV	Females and males ages 13–26 years	HPV recombinant vaccine 9 valent at 0, 1–2, and 6 months		
Influenza virus	All patients (annually before influenza season)	Inactivated influenza vaccine per recommendation for the season (note, live attenuated influenza vaccine is contraindicated in all PLWH)		
HAV	All susceptible (anti-HAV-negative) patients at increased risk for HAV or patients with chronic liver disease (including HBV or HCV) or who are injection drug users	Hepatitis A vaccine; two doses	None	
Not Recommended for Most Patients; Indicated for Use Only in Unusual Circumstances				
Histoplasma capsulatum	CD4 count ≤150 and at high risk owing to endemic geographic areas	Itraconazole 200 mg PO daily	None	
Coccidioidomycosis	Positive IgM or IgG serologic test in patients in an endemic area with CD4 <250	Fluconazole 400 mg daily	None	

ART, antiretroviral therapy; bid, twice a day; biw, twice weekly; DS, double strength; HAART, highly active antiretroviral therapy; HAV, hepatitis A virus; HBc, hepatitis B core; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; IgG, immunoglobulin G; IgM, immunoglobulin M; IM, intramuscularly; IU, international units; LTBI, latent tuberculosis infection; MAC, *Mycobacterium avium* complex; PCP, *Pneumocystis jirovecii* pneumonia; PCV13, 13-valent pneumococcal conjugate vaccine; PLWH, persons living with HIV; PO, orally; PPV23, 23-valent pneumococcal polysaccharides vaccine; qm, monthly; qw, weekly; SS, single strength; tiw, three times a week; TMP-SMX, trimethoprim–sulfamethoxazole; VZIG, varicella-zoster immune globulin; VZV, varicella-zoster virus.

Source: Panel on Opportunistic Infections in HIV-infected Adults and Adolescents. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of

America. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/.

Discontinuation of primary prophylaxis therapy

ART has diminished the incidence of several OIs.[14,21,24] Therefore, it may be possible to discontinue prophylactic OI therapy when CD4 counts rise above the threshold associated with the risk of infection. These data have been particularly encouraging in patients who had PCP prophylaxis discontinued with an increase in CD4 counts.[12] In one observational PCP prophylaxis study, no episodes of PCP were observed after the discontinuation of primary and secondary PCP prophylaxis.[28] These studies suggest that patients who respond to ART with a sustained increase in CD4 count can have their primary prophylaxis safely discontinued. The OI prophylaxis guidelines suggest that primary PCP prophylaxis may be discontinued for patients on ART when the CD4 count is >200 for at least 3 months. In addition, the guidelines suggest discontinuing primary prophylaxis for toxoplasmosis when the CD4 count increases to >200 for at least 3 months.[12]

ACUTE THERAPY

Prompt diagnosis and immediate initiation of therapy are essential for the management of acute infections. Most common OIs can be classified into one of two groups. The first group consists of infections that can be treated by conventional or investigational agents. These include PCP, TB, cryptococcosis, CMV, MAC, and histoplasmosis. Treatment may result in either effective or moderately effective resolution. These infections may recur if chronic suppressive or secondary prophylaxis is discontinued without an accompanying elevation in the CD4 count and viral load suppression. The second group includes pathogens for which no therapeutic regimen is currently effective. These include cryptosporidiosis, microsporidiosis, and PML.

SECONDARY PROPHYLAXIS OR CHRONIC SUPPRESSIVE THERAPY

Secondary prophylaxis is used to prevent the recurrence of an OI once the patient has developed signs and symptoms of active infection. In some cases, secondary prophylaxis regimens can be discontinued after patients achieve a certain CD4 level. The OI guidelines strongly recommend secondary prophylaxis for PCP, toxoplasmosis (reduced dosage), MAC, CMV, and infections caused by endemic fungi and *C. neoformans.*[12]

Discontinuation of secondary prophylaxis or chronic suppressive therapy

The OI guidelines recommend discontinuing primary or secondary prophylaxis for certain pathogens with ART-related increases in CD4 count to specified threshold levels.[12] Criteria for discontinuing chemoprophylaxis are based on specific clinical studies and vary by duration of CD4 count increase and duration of treatment of the initial episode of disease (in the case of secondary prophylaxis).

Secondary PCP prophylaxis may be discontinued among patients whose CD4 counts have increased to >200 for >3 months while on ART. Secondary prophylaxis for disseminated MAC may be discontinued among patients who have completed 12 months of MAC therapy, have no signs or symptoms of MAC, and have had a CD4 count of >100 for ≥6 months in response to ART. Similarly, secondary prophylaxis for toxoplasmosis may be discontinued in patients who have completed initial therapy, have no signs or symptoms of infection, and have had CD4 counts of >200 for >6 months in response to ART. Patients with cryptococcal meningitis can discontinue prophylaxis after completing their initial therapy if they have received at least 1 year of maintenance therapy, remain asymptomatic, and have a CD4 count >100 for at least 3 months on ART. Maintenance therapy for CMV can be discontinued safely in patients who have maintained a CD4 count of >100 for >6 months on ART.[12,14] The decision to stop CMV prophylaxis should be made in consultation with an ophthalmologist and is influenced by factors

such as the magnitude and duration of CD4 increases and viral load suppression, anatomic location of retinal lesions, and vision in the contralateral eye.

Although there are considerable data concerning the discontinuation of primary and secondary prophylaxis, there are no data regarding restarting prophylaxis if the CD4 count decreases again to levels at which the patient is likely to again be at risk for OIs. For primary prophylaxis, the same CD4 count threshold for stopping or restarting therapy is recommended. For PCP prophylaxis, the current guidelines use a CD4 count of 200 as the threshold for restarting both primary and secondary prophylaxis. For toxoplasmosis, the CD4 threshold is 100 to 200, and for MAC, it is 50 in patients not on suppressive ART.[12]

PNEUMOCYSTIS JIROVECII PNEUMONIA

As an indication of the relative obscurity of this organism, no comprehensive text on PCP was available until 1983.[29] Since that time, this organism has been reclassified from a protozoan to a fungus on the basis of ribosomal RNA sequence comparisons. The morphologic resemblance of *P. carinii* to a protozoan has led to its life cycle being described as a cyst form, with up to eight sporozoites per cyst. The trophozoite or extracystic form has different staining characteristics (ie, it does not stain with Toluidine Blue O or Grocott-Gomori stains) compared with the cyst or sporozoites. In addition, current literature refers to PCP as *P. jirovecii* as opposed to the original terminology of *Pneumocystis carinii.* The former species is the one responsible for infectivity in humans. *P. jirovecii* pneumonia is the second leading OI affecting PLWH in the United States.[2] Hospitalizations and hospital mortality for AIDS-associated PCP have decreased significantly in the past 20 years; however, there has been a shift in the overall population at risk for PCP over time, with a greater proportion of patients with PCP who are Black, female, or from the southern region of the United States.[30]

Clinical Presentation

CASE 77-1

QUESTION 1: J.R. is a 38-year-old, HIV-seropositive male who was diagnosed 5 years ago when he had an outbreak of herpes zoster. He has not been on any ART or prophylaxis since his diagnosis because of ongoing socioeconomic challenges. J.R. developed a mild, nonproductive cough that has persisted for the past 4 weeks. He has also had a low-grade fever, but denies any chills or pleuritic chest pain. His chest radiograph demonstrates a diffuse, symmetric, interstitial infiltrate. Arterial oxygen partial pressure (Pa_{O_2}) is 80 mm Hg. His last CD4 count ~3 months ago was 180 cells/μL, and his viral load was 60,000 copies/mL, After hypertonic saline nebulization for sputum induction and subsequent bronchoalveolar lavage, examination of the specimens with the modified Giemsa stain revealed both intracystic bodies and extracystic trophozoites.

How is the clinical presentation of J.R. consistent with PCP?

The clinical features of PCP in patients with AIDS differ from those of patients with no AIDS in that a more subtle onset, with mild fever, a cough, tachypnea, and dyspnea, is typically seen in PLWH.[12] J.R.'s low-grade fever and mild, nonproductive cough of 4 weeks' duration are consistent with this description of PCP. His history of HIV infection and the finding of trophozoites on Giemsa stain further support a diagnosis of PCP. The characteristic diffuse interstitial pulmonary infiltrates on J.R.'s chest radiograph are consistent with PCP. Limited data exist with regard to the latent state of *P. jirovecii* after host infection. Some investigators hypothesize that most persons are asymptomatic unless the host immune system becomes impaired. Others believe that the infection is caused by reinfection as opposed to reactivation.[31]

Antimicrobial Selection

CASE 77-1, QUESTION 2: A diagnosis of PCP is made and J.R. agrees to be treated. What patient factors are important to consider when selecting an

antimicrobial? What would be a reasonable drug for J.R., and how might his course of PCP be monitored?

The treatment of acute PCP is determined by the degree of clinical severity on presentation. The arterial oxygen status on presentation is an important indicator of overall outcome. Key factors to consider when initiating therapy for PCP include arterial blood gas findings, whether it is an initial or a repeat episode of PCP, the need for parenteral therapy, and a prior history of adverse drug reactions or hypersensitivity. Concomitant therapy must also be considered.

Patients with PCP often can be classified as having mild, moderate, or severe disease, based on their oxygenation. Patients with mild PCP often have a room air alveolar-arterial (A-a) oxygen gradient of <35 or Pa_{O_2} >70 mm Hg, and patients with moderate or severe disease have an A-a >35 mm Hg or Pa_{O_2} <70 mm Hg. With the advent of corticosteroid use for moderate-to-severe cases of PCP (discussed later), it is useful to calculate the A-a gradient or Pa_{O_2}. The A-a gradient (normal range, 5–15 mm Hg) can be calculated as $P_{IO_2} - (1.25 \times Pa_{CO_2}) - Pa_{O_2}$, where P_{IO_2} is the partial pressure of inspired oxygen (150 mm Hg in room air), and Pa_{CO_2} and Pa_{O_2} are arterial levels of CO_2 and O_2, respectively, expressed in mm Hg.

Several other clinical tests have been used to identify and monitor PCP. The lactate dehydrogenase concentration in serum or bronchoalveolar lavage fluid has been used to aid in diagnosis, monitor therapy, and to predict the outcome of PCP. However, it is a nonspecific value and should not be used alone. Chest radiographs also vary with PCP. The most common picture is one of bilateral diffuse interstitial pneumonitis, but atypical patterns, such as pleural effusion, cavities, pneumatoceles, and nodules, may also occur. A normal chest radiograph is associated with improved clinical outcome.

The natural course of PCP among untreated PLWH is progressive dyspnea and hypoxemia. Increasing patient age, a subsequent episode of PCP, low hemoglobin, low partial pressure of oxygen

breathing room air, the presence of medical comorbidity, and pulmonary KS are all early predictors of mortality from PCP at hospital admission.[32] The treatment of PCP in patients with AIDS (compared with non-PLWH) indicates that a longer duration of therapy is needed.[29] Some patients may experience worsening hypoxemia during the first 3 to 5 days after the treatment is initiated. This period of clinical worsening is least tolerated by those patients with moderate-to-severe PCP (Pa_{O_2} ≤70 mm Hg). In patients who are extremely sick, this period may lead to respiratory failure and the need for intubation. Although many would associate the need for intensive care unit admission as a poor prognostic factor, many patients do well despite the need for mechanical ventilation and IV antibiotics. In light of the role of corticosteroids, patients with PCP and respiratory failure may be viewed as manageable if treated aggressively (**Table 77-2**).

Table 77-2
Treatment of *Pneumocystis jirovecii* Pneumonia

Regimen	Dose	Route	Adverse Effects/Comments
Approved			
TMP-SMX	15–20 mg/kg TMP (75–100 mg/kg SMX) daily administered IV or PO every 6–8 hours or two DS tablets tid	IV, PO	Hypersensitivity, hyperkalemia, rash, fever, neutropenia ↑LFTs, and nephrotoxicity (15 mg/kg/day preferred to 20 mg/kg/day because of reduced toxicity)
Pentamidine isethionate	4 mg/kg IV daily for 60–90 minutes × 21 days	IV	Pancreatitis, hypotension, hypoglycemia, hyperglycemia, and nephrotoxicity
Atovaquone[a]	750 mg bid with meals × 21 days (suspension)	PO	Headache, nausea, diarrhea, rash, fever, and ↑LFTs
TMP[a] + dapsone	15 mg/kg/day	PO	Pruritus, GI intolerance, and bone marrow suppression
	100 mg/day × 21 days	PO	Methemoglobinemia and hemolytic anemia (contraindicated in G6PD deficiency)
Clindamycin + primaquine	600 mg IV every 8 hours or 300–450 mg PO every 6 hours	PO or IV	Rash and diarrhea
	15–30 mg (base) daily × 21 days	PO	Methemoglobinemia and hemolytic anemia (contraindicated in G6PD deficiency)
Prednisone	Within 72 hours of anti-*Pneumocystis* therapy 40 mg every 12 hours × 5 days, then 40 mg daily × 5 days, then 20 mg/day × 11 days	PO	Initiation in patients with moderately severe or severe disease (Pa_{O_2} <70 mm Hg or A-a gradient ≥35 mm Hg) in combination with one of the abovementioned antibiotic regimens

A-a, alveolar-arterial gradient; bid, twice a day; DS, double strength; GI, gastrointestinal; G6PD, glucose-6 phosphate dehydrogenase; IV, intravenous; PO, oral; Pa_{O_2}, arterial partial pressure of oxygen; LFTs, liver function tests; tid, three times a day; TMP-SMX, trimethoprim–sulfamethoxazole.

[a]Used only in mild-to-moderate *Pneumocystis jirovecii* pneumonia.

TRIMETHOPRIM–SULFAMETHOXAZOLE

The decision to hospitalize a patient is based on the severity of his or her illness. Patients who present with mild PCP with reasonable oxygenation and without evidence of clinical deterioration can be managed as outpatients. Patients with reasonably good gas exchange (ie, Pa_{O_2} >70 mm Hg) but with signs of clinical deterioration most often are admitted to the hospital and given oxygen by nasal cannula and are usually started on IV TMP-SMX (15–20 mg/kg/day TMP) for 21 days.[12,33] The dosing of IV TMP-SMX must be modified in patients with renal dysfunction. TMP reversibly inhibits dihydrofolate reductase, and sulfamethoxazole competes with para-aminobenzoic acid in the production of dihydrofolate, synergistically blocking thymidine biosynthesis.

TMP-SMX is the drug of choice for PCP unless the patient has a history of life-threatening intolerance. In the treatment of PCP, TMP-SMX is either as effective as or superior to all alternative agents. A good response may be expected in >70% of patients receiving TMP-SMX. TMP-SMX is often prescribed orally (PO) because of its high bioavailability. The usual dose is 15 mg/kg (dosed by the TMP component) divided every 8 hours for 21 days. Because one double-strength tablet of TMP-SMX contains 160 mg TMP plus 800 mg SMX, a standard regimen is two double-strength tablets three times per day (tid; or every 8 hours).

Although the TMP-SMX regimen is very efficacious, 25% to 50% of patients may be intolerant. Adverse effects include an erythematous, maculopapular, morbilliform rash, and, less commonly, severe urticaria, exfoliative dermatitis, and Stevens–Johnson syndrome. Gastrointestinal (GI) intolerance (nausea, vomiting, and abdominal pain) is common.[12] Hematologic side effects may include leukopenia, anemia, and thrombocytopenia. Neurologic toxicities, acute kidney injury, hyperkalemia, and hepatitis may also occur. Most patients who exhibit a mild hypersensitivity (skin rash) reaction can be managed with antipruritics or antihistamines without discontinuation of TMP-SMX. In some patients with mild hypersensitivity reactions, the agent can be

restarted after the rash has resolved, using gradual dosage escalation or rapid oral desensitization to reduce adverse effects.[34] Patients with severe adverse reactions should be switched to another agent rather than being rechallenged with this drug (see also Chapter 32, Drug Hypersensitivity Reactions).

Because J.R. seems to have a mild-to-moderate case of PCP (PaO_2, 80 mm Hg), has not previously experienced an episode of PCP, and has no history of adverse effects to TMP-SMX, an outpatient course of TMP-SMX would be reasonable.

ALTERNATIVES TO TRIMETHOPRIM–SULFAMETHOXAZOLE

CASE 77-1, QUESTION 3: J.R. experienced exfoliative dermatitis on day 7 of TMP-SMX treatment. What other drugs could be prescribed to treat his PCP?

Because J.R. presents with a serious adverse effect to TMP-SMX, it should be discontinued, and he should not be rechallenged or desensitized. Instead, he should be treated with an alternative regimen (Table 77-2).

Atovaquone suspension, 750 mg twice a day (bid), is available for the treatment of mild-to-moderate PCP. Atovaquone interrupts protozoan pyrimidine synthesis and demonstrates activity against *P. jirovecii* and *Toxoplasma gondii* in animal models. Atovaquone is approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild-to-moderate PCP in patients intolerant of TMP-SMX. Atovaquone is also an alternative for primary and secondary prophylaxis for both PCP and toxoplasmosis.[12] Atovaquone is well tolerated compared with other PCP therapies. Adverse effects include rash, fever, elevated liver function tests (LFTs), and emesis. Atovaquone is safer, but less effective, than is TMP-SMX in patients with mild-to-moderate PCP.[35] When compared with IV pentamidine in the treatment of mild-to-moderate PCP, atovaquone and pentamidine were equally efficacious; however, pentamidine was significantly more toxic.[36] Most atovaquone studies were performed using the moderately absorbed oral tablets; reformulation of this drug as a

suspension has improved bioavailability by at least 30%, although patients may find the taste and texture unpleasant. Concomitant administration of fatty foods with atovaquone doubles the absorption.

An oral regimen of dapsone plus TMP is another alternative to TMP-SMX. Dapsone–TMP can be used to treat mild-to-moderate PCP in patients intolerant of TMP-SMX. Dapsone is a sulfone antimicrobial that is used for leprosy. Although monotherapy (200 mg/day) with dapsone is ineffective for the treatment (not prophylaxis) of PCP, the addition of TMP (20 mg/kg/day) to dapsone (100 mg/day) is an effective alternative regimen.[37] In a small comparative trial of TMP–dapsone versus TMP-SMX, the response rates of 93% and 90% were observed, respectively.[38] When dapsone is coadministered with TMP, the resulting plasma concentrations for both drugs are higher than when either drug is taken alone. In combination with TMP, a pyrimidine, synergistic inhibition of folic acid synthesis occurs.[39] Dapsone–TMP should not be used in patients with sulfonamide allergy with a history of type I hypersensitivity reaction, toxic epidermal necrolysis, or Stevens–Johnson syndrome. Dapsone is associated with hematologic toxicities, including hemolytic anemia, methemoglobinemia, neutropenia, and thrombocytopenia. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency cannot detoxify hydrogen peroxide and are at an increased risk for hematologic toxicity from dapsone.

Success rates of 70% to 100% have been reported with clindamycin (600 mg IV every 6 hours or 600 mg PO tid given in conjunction with 30 mg/day of primaquine base). Although skin rashes are common with this combination, these often subside with continued therapy. Some patients experience toxicities (fever, rash, granulocytopenia, and methemoglobinemia), requiring discontinuation.[40–42] As with dapsone, before starting primaquine, patients should be screened for G6PD deficiency. Patients who test positive for G6PD deficiency are at risk for developing hemolytic anemia.

A double-blind efficacy and toxicity study of 181 patients with mild-to-moderate PCP compared three oral drug regimens: TMP-SMX

versus dapsone–TMP versus clindamycin–primaquine. The doses of TMP-SMX and dapsone–TMP were weight based, and the dosage of clindamycin–primaquine was 600 mg clindamycin tid and primaquine 30 mg/day. All patients with moderately severe PCP (A-a oxygen gradient >45) were treated with prednisone (40 mg bid for 5 days, then once daily for 3 weeks). Rash was the most frequent dose-limiting toxicity (TMP-SMX, 19%; dapsone–TMP, 10%; and clindamycin–primaquine, 21%). Hematologic toxicities were observed more frequently in the clindamycin–primaquine arm. Elevated LFTs (five times above baseline) were more frequent in the TMP-SMX arm. The clindamycin–primaquine group demonstrated better quality of life scores at day 7, but by day 21, these differences became less significant.[37] TMP-SMX, dapsone–TMP, and clindamycin–primaquine demonstrated equal efficacy in patients with mild-to-moderate PCP.

A last-line option for acute PCP is IV pentamidine isethionate. The mechanism of action is unknown, but it may be related to interference with oxidative phosphorylation, inhibition of nucleic acid biosynthesis, or interference with dihydrofolate reductase. Pentamidine is generally more toxic than is TMP-SMX.[43] In a 5-year review of 106 courses of IV pentamidine, 76 (72%) patients had adverse reactions (nephrotoxicity, dysglycemia, hepatotoxicity, hyperkalemia, and hyperamylasemia). Drug discontinuation occurred in 31 of the 174 adverse drug events reported in the study. Nephrotoxicity and hypoglycemia were the most common causes of drug discontinuation. Nephrotoxicity occurred in 25% to 50% of the patients with dehydration and concurrent nephrotoxic drugs among the risk factors. Hypoglycemia was noted in 5% to 10% of patients after 5 to 7 days of treatment or several days after discontinuation of treatment. Hyperglycemia is a consequence of decreased β-cells and results in diabetes mellitus in 2% to 9% of patients. Other less common adverse effects and toxicities include thrombocytopenia, orthostatic hypotension, ventricular tachycardia, leukopenia, nausea, vomiting, abdominal pain, and anorexia.[43] Nebulized pentamidine should not be considered as an alternative to IV pentamidine for the treatment of PCP.[44]

J.R. should be hospitalized to better manage his severe adverse reaction and to complete his treatment of PCP. Because of his severe reaction to TMP-SMX, dapsone–TMP should not be administered because dapsone is a sulfone with a risk of cross-reactivity in patients with severe sulfonamide allergies. IV pentamidine is an option for J.R., but its toxicity suggests that it should be reserved for patients with more severe PCP presentation. Atovaquone is a reasonable option for patients with mild PCP who are intolerant of TMP-SMX and have no evidence of GI dysfunction, but it is not as effective as TMP-SMX or IV pentamidine. Clindamycin–primaquine is as efficacious as TMP-SMX for the treatment of mild-to-moderate PCP and can be administered PO. Consequently, it is the drug of choice in this patient.

The decision was made to start J.R. on oral clindamycin–primaquine for his mild-to-moderate PCP. J.R. tested negative for G6PD deficiency and was treated with clindamycin–primaquine for 14 days, completing a 21-day course of PCP therapy (Table 77-2).

Initiation of Corticosteroids

Case 77-1, Question 4: Should J.R. receive corticosteroid therapy with PCP treatment? If so, when should corticosteroids be initiated, and what would be a reasonable regimen for patients with PCP?

Corticosteroids have an important role in the management of patients with acute PCP who are clinically ill and have a low Po_2 (<70 mm Hg) or an A-a oxygen gradient >35.[12] Many patients who are started on PCP therapy have an acute period of clinical deterioration, which may be associated with an acute inflammatory reaction to the rapid killing of *Pneumocystis.* Particularly among patients with moderate-to-severe PCP (A-a oxygen gradient ≥35 mm Hg or Pao_2 <70 mm Hg on room air), the use of prednisone during the first 72 hours of treatment may prevent fatal acute deterioration.[45] Corticosteroids may also have some benefits in patients exhibiting acute respiratory failure after 72 hours of

conventional PCP therapy.[46] The recommended dose of prednisone is 40 mg given PO bid for 5 days, then 40 mg/day for 5 days, and then 20 mg/day for 11 days, for a total of 21 days.[47] Patients requiring IV corticosteroids may receive methylprednisolone at 75% of the prednisone dose. The major concern using glucocorticoids is the activation of latent infections (such as TB) or exacerbation of an active undiagnosed condition (especially fungal infections). However, the beneficial role of corticosteroids as adjunctive therapy outweighs the relative risk of short-term steroid use in this population.[48] More common side effects of short-term corticosteroids include hyperglycemia, ulcerative esophagitis, increased appetite, weight gain, sodium and fluid retention, headache, and elevated LFTs. Corticosteroids should be used with caution in the presence of uncontrolled diabetes, active GI bleeding, and uncontrolled hypertension.

Considering his mild hypoxemia (Pa_{O_2}, >70 mm Hg), J.R. is not a candidate for corticosteroid therapy.

Prophylaxis

Case 77-1, Question 5: J.R. was hospitalized and responded well to treatment. He now is a candidate for secondary prophylaxis. What secondary prophylaxis would be a good choice for J.R. when he is discharged from the hospital?

The early recognized efficacy of TMP-SMX prophylaxis[41] led to the eventual widespread application of prophylaxis and the development of guidelines for PCP prophylaxis (Table 77-2).[12] PLWH not receiving ART or *Pneumocystis* prophylaxis were associated with a PCP prevalence of 8.4%, 18.4%, and 33.3% at 6, 12, and 36 months, respectively, in patients with a CD4 count of <200.[49] These data have formed the basis on which patients receive PCP prophylaxis. In addition to patients with CD4 counts of <200, other patients at risk for PCP include those with a CD4 count of <14%, a history of an AIDS-defining illness, a history of oropharyngeal candidiasis, and

possibly those with CD4 counts of 200 to 250.[12] J.R. refused primary prophylaxis and developed PCP. Secondary prophylaxis is necessary for J.R. to prevent recurrence and should be continued for life or until immune reconstitution occurs as a result of ART.

The same agents and dosing schedules are recommended for primary (before an acute event) and secondary (after an acute event) prophylaxis of PCP.[12] TMP-SMX, one double-strength tablet daily, is the most efficacious prophylactic regimen; a single-strength tablet given daily is less toxic and nearly as efficacious. Patients with a history of non–life-threatening rash or fever caused by TMP-SMX may benefit from rechallenge with the original (or half) dose, or a dose escalation technique (desensitization regimen). Desensitization is preferred to switching to an alternative agent and is more successful than is the direct rechallenge method.[50] Desensitization involves initiating very low doses of TMP-SMX and gradually increasing to the maximum dose over the course of days to weeks. In addition, patients who develop PCP while receiving prophylactic doses of TMP-SMX usually respond to full therapeutic doses for acute therapy. However, J.R. had a life-threatening reaction to TMP-SMX and should not be rechallenged or desensitized, and another agent should be chosen for prophylaxis.

The alternative agents used for prophylaxis include dapsone, dapsone plus pyrimethamine (with leucovorin), atovaquone suspension, and aerosolized pentamidine administered by the Respirgard II® nebulizer (Table 77-2). TMP-SMX confers additional protection against toxoplasmosis and certain bacterial infections. Regimens containing dapsone plus pyrimethamine or atovaquone with or without pyrimethamine also protect against toxoplasmosis.[12] Although yet to be confirmed in clinical trials, other options include oral clindamycin–primaquine, intermittently administered IV pentamidine, oral pyrimethamine–sulfadiazine, and aerosolized pentamidine administered by other nebulizing devices.[12] TMP-SMX is more efficacious than is dapsone or aerosolized pentamidine in the prevention of PCP.[51]

Extrapulmonary (eg, lymph nodes, spleen, liver, bone marrow, adrenal gland, and GI tract) *P. carinii* has been noted in patients

receiving inhaled pentamidine prophylaxis,[52] a finding rarely observed with IV administration. In addition, aerosolized pentamidine alters the usual chest radiograph findings associated with PCP, potentially complicating the diagnosis of this disease. Upper lobe infiltrates, cystic lesions, pneumothoraces, cavitary lesions with nodular infiltrates, and pleural effusions have been associated with aerosolized pentamidine prophylaxis.

The guidelines for primary prophylaxis suggest that prophylactic antimicrobial therapy can be discontinued when CD4 counts rise above the threshold associated with a risk for infection (ie, >200 for PCP).[12] Many studies support the practice of discontinuing secondary PCP prophylaxis in patients whose CD4 counts have increased to >200 for at least 3 months.[12] A European cohort study found that primary PCP rates were very low in patients with CD4 counts of 101 to 200 cells/μL and a viral load of <400 copies/mL regardless of prophylaxis, indicating that discontinuation of prophylaxis may be safe in patients with a CD4 count >100 cells/μL who are on effective antiretrovirals.[53] The guidelines recommend that prophylaxis be reintroduced if the CD4 count decreases to <100 or if CD4 100 to 200 and HIV RNA is detectable.[12] J.R. responded well to his PCP treatment with clindamycin–primaquine in the hospital. However, because this regimen is unproved for secondary prophylaxis, it cannot be recommended. Considering his severe intolerance to TMP-SMX, the best selection would be atovaquone suspension.

TOXOPLASMA GONDII ENCEPHALITIS

Clinical Presentation

CASE 77-2

Question 1: W.O. is a 40-year-old male discovered to be HIV positive during admission to a detoxification program for alcohol and heroin dependency. W.O. presented to the HIV clinic with esophageal candidiasis, a CD4 count of 60 cells/μL (normal, ~1000 cells/μL), a viral load of 150,000 copies/mL, and a *Toxoplasma* IgG titer of 1:256. W.O. was started on ART. He remained well until 2 years later when he presented to the emergency department reporting two seizures in the past 24 hours. His home medications at that time included daily emtricitabine, tenofovir alafenamide, dolutegravir, and inhaled pentamidine 300 mg monthly, although the patient reported nonadherence for the past 6 months. His temperature was 100.1 °F (37.83 °C), and he was observed to have difficulty walking. His CD4 count is 90 cells/μL (previously 230 cells/μL), viral load is 70,000 copies/mL (previously 200), and white blood cell (WBC) count is 4200 cells/L (normal, 3800–9800). A magnetic resonance imaging (MRI) of the head reveals several ring-shaped lesions in the brainstem. *Toxoplasma* encephalitis is presumptively diagnosed.

Should W.O. be isolated from other patients and health care workers to prevent the spread of this organism?

T. gondii is a parasitic protozoan that can infect people and is spread by environmental factors, such as the consumption of raw or undercooked meats and contact with cat feces. Immunocompetent persons infected with *T. gondii* may develop mild symptoms resembling infectious mononucleosis. However, these symptoms are generally transient and not associated with significant sequelae in patients who are immunocompetent (except in pregnant females). Recrudescent disease from *T. gondii* is problematic in patients with a suppressed cellular immune system, including those infected with HIV. Any PLWH infected with *T. gondii* is at risk for developing clinical disease, particularly at CD4 counts <100, as illustrated by W.O.[12] W.O. presents with encephalitis (an inflammation of the brain or brainstem), the most frequent manifestation of *T. gondii* in PLWH.

All PLWH should be tested for IgG antibody to *T. gondii* after HIV diagnosis to detect latent infection. In the United States, as many as 70% of healthy adults are seropositive to *Toxoplasma.* The prevalence of *Toxoplasma* encephalitis among patients who are HIV positive varies depending on the geographic region. In the United States, only 3% to 10% of patients with AIDS actually develop encephalitis. In countries such as France, El Salvador, and Tahiti,

where uncooked meat commonly is ingested, seropositivity is >90% by the fourth decade of life. *Toxoplasma* encephalitis may develop in as many as 25% to 50% of patients with AIDS in these countries.[54]

The two major routes of transmission of *Toxoplasma* to humans are oral and congenital. W.O. need not be isolated from other patients and health care workers. PLWH should be advised not to eat raw and undercooked meat (internal temperature of meat should be at least 165 °F–170 °F), especially patients who are IgG negative for *T. gondii.* Patients should wash their hands after touching uncooked meats and soil, and fruits and vegetables must be washed before eating. PLWH should avoid stray cats, keep their cats inside, and change the litter box daily. If no one else is available to change the litter box, patients should wash their hands thoroughly afterward.[12]

Diagnosis

Case 77-2, Question 2: Is there sufficient clinical evidence to establish a presumptive diagnosis of *Toxoplasma* encephalitis in W.O.?

The diagnosis of *Toxoplasma* encephalitis usually is presumptive because demonstration of cysts or trophozoites in brain tissue is required for a definitive diagnosis. The clinical signs and symptoms of *Toxoplasma* encephalitis can be either focal (indicating a specific region of the brain that is infected or inflamed) or generalized (indicating diffuse inflammation of the brain). *Toxoplasma* encephalitis usually occurs in patients with CD4 counts of <100. Serum titers of antibodies against *T. gondii* typically reflect past infection with the organism and unfortunately do not help delineate whether acute infection is present. In addition, cerebrospinal fluid (CSF) polymerase chain reaction for *Toxoplasma* is not always a reliable diagnostic tool. Most patients with encephalitis have single or multiple ring-enhancing lesions demonstrated on computed tomography scan or MRI of the head. Brain biopsy is reserved for patients with symptoms of encephalitis who are seronegative and for

those who do not respond to presumptive antitoxoplasmosis therapy.[55] Because of the nonspecific diagnosis of *Toxoplasma* encephalitis, a high index of suspicion for other causes of encephalitis (eg, central nervous system [CNS] lymphoma or TB) should be maintained throughout the treatment period for presumed *Toxoplasma* encephalitis. W.O. has overwhelming clinical evidence suggestive of *Toxoplasma* encephalitis. He is HIV positive, has a CD4 count of <100, a positive *Toxoplasma* titer of 1:256 IgG, and a ring-shaped lesion in the brainstem on MRI.

Prophylaxis

Case 77-2, Question 3: Should W.O. have been receiving prophylactic therapy for *T. gondii*?

Similar to many other OIs associated with HIV, therapy for toxoplasmosis can be categorized into primary prophylaxis, treatment of acute disease, and secondary prophylaxis. Primary prophylaxis is currently recommended for PLWH with CD4 counts of <100 who are also IgG-positive for *T. gondii* (see Table 77-1). Many of the agents used to prevent PCP have activity against *T. gondii*: TMP-SMX, dapsone–pyrimethamine–leucovorin, and atovaquone with or without pyrimethamine/leucovorin are effective as primary prophylaxis for *T. gondii.*[12] The increased use of prophylaxis with these agents has significantly decreased the incidence of *Toxoplasma* encephalitis.[2],[12] The double-strength TMP-SMX tablet once daily is recommended as the first-line prophylaxis. Data do not support the use of macrolides or aerosolized pentamidine for *Toxoplasma* prophylaxis. Similarly, data are conflicting regarding the efficacy of pyrimethamine as monotherapy for primary prophylaxis.[56],[57]

Primary prophylaxis may be discontinued in patients who have responded to ART with an increase in the CD4 counts to >200 for >3 months. In addition, data support reinstituting primary prophylaxis when CD4 counts drop <200.

W.O. is currently receiving inhaled pentamidine for PCP prophylaxis. Considering his CD4 count and IgG seropositivity, he should have received primary prophylaxis for *T. gondii.*

Treatment

ACUTE THERAPY

Case 77-2, Question 4: How should W.O.'s presumptive *Toxoplasma* encephalitis be treated?

The first-line treatment of acute *Toxoplasma* encephalitis consists of a combination of sulfadiazine 4 g/day in three or four daily divided doses and pyrimethamine as a single 200-mg loading dose, followed by 50 to 75 mg/day as a single daily dose plus leucovorin 10 to 25 mg PO every day (qd).[12] Induction therapy should be continued for 6 weeks after resolution of symptoms (a treatment course of ~8 weeks) followed by maintenance therapy (secondary prophylaxis). Sulfadiazine toxicity may limit the completion of a full course of therapy in as many as 40% of patients.[58] However, successful desensitization has been documented.[59] W.O.'s clinical and radiologic response should be monitored closely, and other diagnoses should be considered if there is no improvement.

Alternative therapy includes pyrimethamine plus leucovorin with clindamycin 600 to 900 mg IV every 6 hours or 600 mg PO every 6 hours for at least 6 weeks. One controlled trial compared the efficacy and tolerability of pyrimethamine plus sulfadiazine versus pyrimethamine plus clindamycin. Although both regimens were effective, pyrimethamine–sulfadiazine was superior to pyrimethamine–clindamycin. The rate of adverse events was similar with both regimens; however, pyrimethamine–clindamycin led to fewer discontinuations than did pyrimethamine–sulfadiazine (11% vs 30%, respectively).[60] TMP-SMX may be considered a treatment option, particularly in patients who cannot take an oral regimen because the only widely available parenteral sulfonamide is the

sulfamethoxazole component of TMP-SMX. However, there is less in vitro activity and less clinical data to support the use of TMP-SMX as monotherapy for toxoplasmosis.[61] In addition, anticonvulsants should be given to patients with *Toxoplasma* encephalitis and a history of seizures, and corticosteroids may be warranted for focal lesions or edema but should be used cautiously.

Case 77-2, Question 5: W.O. is treated with sulfadiazine–pyrimethamine. What are the limitations to the use of the sulfadiazine component for the treatment of *Toxoplasma* encephalitis?

As with other sulfonamides in PLWH, rashes commonly occur with sulfadiazine therapy.[58] Similar to TMP-SMX, various desensitization regimens have been recommended[34],[59]; however, it may be simpler to use alternative regimens.

Renal function should be monitored throughout therapy. Elevated serum creatinine (SCr) levels, hematuria, or decreased urine output may occur secondary to sulfadiazine-induced crystalluria. The water solubility of sulfadiazine is less than that of other sulfonamides; therefore, hydration (2–3 L/day) is needed to prevent crystalline nephropathy, and aggressive hydration and alkalinization can be used in cases of crystal formation.

Case 77-2, Question 6: What toxicities are associated with the pyrimethamine component?

Pyrimethamine can suppress bone marrow function; thus, concomitant therapy with other medications that suppress marrow function (eg, valganciclovir) may not be tolerated. Leucovorin (10–25 mg/day) is always given in conjunction with pyrimethamine to maintain bone marrow function, although it may not always be successful. Leucovorin doses can be increased to 50 to 100 mg/day in divided doses, if needed, to reverse bone marrow suppression.[12] Folic acid (not folinic acid) should be avoided because it can be used for growth by protozoal organisms, potentially antagonizing

pyrimethamine–sulfadiazine activity.[62] Vitamin preparations containing large quantities of folic acid should be discontinued during therapy for *T. gondii.*

W.O. is not taking any medications that would make him particularly susceptible to the myelosuppressive effects of pyrimethamine, and he is not neutropenic. Consequently, he should be given sulfadiazine and pyrimethamine.

SUPPRESSIVE THERAPY (SECONDARY PROPHYLAXIS)

CASE 77-2, QUESTION 7: Once W.O. has completed acute therapy for his *Toxoplasma* encephalitis, should he receive suppressive therapy?

Most antiprotozoal agents do not eradicate the cyst form of *T. gondii.* Therefore, patients should be administered lifelong suppressive therapy unless immune reconstitution occurs as a consequence of ART.[12] A commonly used regimen for patients who cannot tolerate sulfonamides is pyrimethamine plus clindamycin. However, only the combination of pyrimethamine plus sulfadiazine provides protection against PCP as well. In addition, two small studies of patients receiving maintenance therapy for *Toxoplasma* encephalitis have suggested that sulfadiazine–pyrimethamine is more effective than is clindamycin–pyrimethamine or pyrimethamine alone.[60] The use of atovaquone with or without pyrimethamine is also effective as prophylaxis for both *Toxoplasma* and PCP, but it is significantly more expensive and is only available as a less palatable liquid formulation.

Patients receiving secondary prophylaxis are at low risk for recurrence of *Toxoplasma* encephalitis when they have completed their initial therapy, remain asymptomatic, and have a sustained increase in their CD4 count to >200 after >6 months of ART. Clinicians may obtain a brain MRI as part of the evaluation to determine the end point of therapy. Discontinuation of primary and secondary toxoplasmosis prophylaxis is safe if patients are receiving ART and their CD4 count has increased to >200 for at least 6

months. Secondary prophylaxis should be reintroduced if the CD4 count decreases to <200.[12]

W.O. will be continued on sulfadiazine–pyrimethamine for suppressive therapy for his *Toxoplasma* encephalitis because his CD4 count has decreased to <100. W.O. is currently receiving aerosolized pentamidine for PCP prophylaxis, but because sulfadiazine– pyrimethamine is also protective against PCP, the aerosolized pentamidine can be discontinued. Clindamycin–pyrimethamine is an inferior option because it does not protect against PCP.[12]

ALTERNATIVE THERAPIES

Case 77-2, Question 8: What treatment options exist for patients who cannot tolerate sulfadiazine and do not wish to undergo desensitization?

Clindamycin 600 mg PO every 8 hours plus pyrimethamine and leucovorin at standard doses.[12] Combination therapy with pyrimethamine and leucovorin plus clarithromycin (1 g bid), or atovaquone (750 mg PO four times a day) has shown promise in a limited number of patients.[12]

CYTOMEGALOVIRUS DISEASE

Diagnosis

CASE 77-3

Question 1: P.P.Z. is a 58-year-old male living with AIDS who describes experiencing floating spots, light flashes, and difficulty reading road signs when he drives to his physician. His most recent laboratory results were as follows:

Blood urea nitrogen (BUN), 17 mg/dL
SCr, 0.8 mg/dL
CD4 count, 40 cells/μL

Viral load, 80,000 copies/mL (3 months ago)
WBC count, 1200 cells/L, with 63% polymorphonuclear neutrophil leukocytes

His current weight is 138.89 pounds (63 kg). P.Z.'s medications include a coformulated antiretroviral regimen of tenofovir alafenamide/emtricitabine/bictegravir and dapsone (PCP prophylaxis), although he reports being nonadherent to his medications. He has a history of hematologic intolerance to TMP-SMX. P.Z. is known to have a positive CMV IgG antibody titer. Funduscopic examination reveals alternating areas of hemorrhage and scar tissue (a "cottage cheese and ketchup" appearance) in the proximity of the retina in his left eye.

What is the likely cause of P.Z.'s visual problems?

P.Z. has an inflammation of the retina (retinitis), most likely because of CMV. Many PLWH have been previously infected with CMV, and reactivation typically occurs when CD4 counts are <50. Before ART, the prevalence of CMV disease in patients with AIDS was 30%; however, the incidence of new cases of CMV end-organ disease has declined by 75% to 80% and is estimated to be <6 cases per 100 person-years.[12,63] Although CMV can cause colitis, pneumonitis, esophagitis, hepatitis, and neurologic disease, retinitis is the most common manifestation of active infection in patients with AIDS, accounting for 75% to 85% of CMV end-organ disease. One investigation describing patients with CMV retinitis in the post-ART era found a diverse demographic group with infection; most of them had received ART, and as expected, they had very low CD4 counts.[64] In addition, the characteristics of the disease in this group were similar to those in the pre-ART era. Diagnosis is usually presumptive because biopsy is difficult given the inaccessibility of the retina. Serology is indicative of previous CMV infection, but not an active disease. Cultures (serum, urine, and saliva) may be useful for monitoring therapy, considering that patients frequently have disseminated CMV disease. Patients with positive cultures for CMV while receiving therapy may be at a higher risk for relapse.[65] Typically, the diagnosis of CMV retinitis is based on observations made during a dilated retinal examination and indirect ophthalmoscopy, as was done for P.Z. Lesions appear as fluffy, white retinal patches with retinal hemorrhage.

Once CMV retinitis is diagnosed, the patient should be thoroughly examined for extraocular CMV disease. P.Z. will require regular ophthalmologic examinations, along with retinal photographs, for life. As with HIV therapy, CMV deoxyribonucleic acid (DNA) quantification in plasma or blood cells by polymerase chain reaction may have a role in evaluating treatment efficacy and predicting symptomatic development of CMV disease.[12]

Drug Therapy

Case 77-3, Question 2: What are the treatment options for CMV retinitis, and which one would be preferred for P.Z.?

Several treatment options exist for CMV retinitis: oral valganciclovir, IV ganciclovir, IV ganciclovir followed by oral valganciclovir, IV foscarnet, and IV cidofovir. Alternatives include combined IV ganciclovir plus foscarnet or intraocular injections of ganciclovir, foscarnet, or cidofovir.[12] The efficacy of combined parenteral ganciclovir and foscarnet is similar to that in monotherapy, but it is more toxic. This latter therapy should be reserved for patients with refractory disease.[66]

Intraocular implants (not currently available) and intraocular injections of ganciclovir have similar efficacy in the treatment of CMV retinitis, but their benefit is localized to the infected eye and may lead to an increased risk of contralateral retinitis and extraocular CMV disease. Regimens consisting of systemic anti-CMV therapy have been associated with a 50% reduction in mortality compared with those using intraocular therapy alone.[67] Therefore, concomitant systemic anti-CMV therapy is recommended (eg, oral valganciclovir or IV ganciclovir). The use of ganciclovir intraocular implants with oral valganciclovir has shown to be more effective in preventing relapse of retinitis than is IV ganciclovir and likely oral valganciclovir.[12] Many providers prefer this (or the intraocular injections because the implants are not currently available) as the first-line therapy in patients with immediate sight-threatening lesions,

although others chose oral valganciclovir as the first-line treatment. The choice of agents typically depends on drug efficacy, toxicity, stage of disease, and quality-of-life issues.

GANCICLOVIR

Ganciclovir is an acyclic nucleoside with CMV activity superior to acyclovir. Similar to other nucleosides, ganciclovir must be taken into cells and phosphorylated before it can compete with endogenous nucleotides for binding to viral DNA polymerase. Ganciclovir is poorly absorbed PO (bioavailability, ~5%–9%), and the oral form is no longer marketed. The disposition of ganciclovir is biexponential after IV administration (terminal half-life, ~2.5 hours). The total body clearance is highly dependent on glomerular filtration and tubular secretion.

The dose-limiting toxicity is bone marrow suppression, with neutropenia occurring in ~50% of patients. Thrombocytopenia is also observed. Absolute neutrophil counts (ANCs) and platelets should be monitored weekly during ganciclovir therapy. If the ANC falls to <1000 cells/μL or the platelet count falls to <50,000/μL, the monitoring frequency should be increased to twice weekly.[68] Dosage adjustments must be made in patients with renal dysfunction.

VALGANCICLOVIR

Valganciclovir is an oral monovalyl ester prodrug that is rapidly hydrolyzed to ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir is 60%, and a dose of 900 mg results in ganciclovir blood concentrations similar to those obtained with a dose of 5 mg/kg of IV ganciclovir. Oral valganciclovir and IV ganciclovir are equally effective as induction therapy for newly diagnosed CMV retinitis in patients with AIDS.[69] The frequency and severity of adverse events were similar in the two groups. Based on these data, oral valganciclovir is as effective as and no more toxic than is IV ganciclovir, and the convenience of the oral route suggests it be the drug of choice for the long-term management of CMV retinitis in patients with AIDS.

CIDOFOVIR

Cidofovir is a nucleotide analog that is phosphorylated intracellularly to an active diphosphate metabolite. It is the most potent of all the available anti-CMV compounds and is active against herpes simplex virus (HSV) and VZV, including acyclovir-resistant isolates. Cidofovir does not require viral activation. Because nucleotide analogs do not require virally encoded kinases for their activity, they remain a treatment option for patients who have failed to respond to ganciclovir. Cidofovir is poorly absorbed PO (bioavailability, >5%) and has an intracellular half-life of 17 to 65 hours, resulting in once-weekly induction and every-other-week maintenance therapy.

Eighty percent of this poorly soluble agent is excreted unchanged in the urine via filtration and tubular secretion. Cidofovir is nephrotoxic; however, the administration of probenecid (2 g administered 3 hours before the start of infusion and two 1-g doses administered at 2 and 8 hours after infusion) blocks tubular secretion and reduces nephrotoxicity. Prehydration with 1 L of normal saline is required 1 hour before each dose and, if tolerated, repeated concomitantly with or after the cidofovir infusion. Because nephrotoxicity is the most significant dose-limiting toxicity, other nephrotoxic agents should be discontinued (eg, nonsteroidal anti-inflammatory drugs, and aminoglycosides), and renal function should be carefully monitored throughout therapy (BUN, SCr, and proteinuria). Dosage adjustment must accompany any deterioration in renal function.

The complete blood count (CBC) should be checked at baseline because neutropenia has been reported in ~20% of patients in clinical trials. Hypotony (reduction in intraocular pressure) and uveitis (inflammation of the uveal tract of the eye) have also been reported. Thus, monthly ophthalmologic examinations of the retina are necessary.[12]

The role of cidofovir is limited. Although it offers the advantage of weekly and biweekly dosing, its toxicity greatly limits its utility. Cidofovir appears to be as efficacious as foscarnet and ganciclovir in the treatment of CMV retinitis, but limited comparative studies have

been performed. Finally, the efficacy of cidofovir in the treatment of extraocular CMV (eg, GI disease, pneumonitis, and encephalitis) remains to be established.

FOSCARNET

Foscarnet is a pyrophosphate analog that acts by selectively inhibiting viral DNA polymerases and reverse transcriptase. At doses currently recommended for induction therapy (60 mg/kg every 8 hours or 90 mg/kg IV every 12 hours), peak plasma foscarnet concentrations are higher than those that inhibit CMV in vitro.[70] The dose-limiting toxicity of foscarnet is nephrotoxicity, probably because its poor solubility results in crystallization in nephrons.[68] In one trial, when compared with ganciclovir, patients treated with foscarnet survived ~4 months longer; however, patients treated with foscarnet with reduced creatinine clearance (>1.2 mL/minute/kg) had a poorer survival rate.[71]

Because P.Z. has a low ANC, the bone marrow–suppressive effects of ganciclovir and valganciclovir are of concern. Because he has good renal function (SCr, 0.8 mg/dL), foscarnet or cidofovir would be an option.

Case 77-3, Question 3: P.Z. completes 21 days of foscarnet induction therapy. How can his CMV retinitis be suppressed in future?

The currently available antiviral agents used to treat CMV disease are not curative. After induction therapy, chronic maintenance therapy is indicated for the remainder of P.Z.'s life, unless immune reconstitution occurs as a result of ART. Effective suppressive regimens include valganciclovir, parenteral ganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. The ganciclovir implant was also effective, but is no longer manufactured. Oral valganciclovir is approved for both acute induction and maintenance therapy, but the published clinical data are limited. In uncontrolled case series, repeated intravitreal injections of ganciclovir, foscarnet, and cidofovir have been shown to

be effective for prophylaxis of CMV retinitis. However, because this therapy is effective only locally and does not protect the contralateral eye or other organ systems, it is usually combined with oral valganciclovir.

Guidelines suggest that discontinuation of prophylaxis may be considered in patients with CMV retinitis who are taking ART with a sustained (>3–6 months) increase in the CD4 count to >100 and have remained disease free for >30 weeks. The decision to discontinue suppression should be done in consultation with an ophthalmologist and be based on the magnitude and duration of the CD4 increase and viral load suppression, the anatomic location of the retinal lesions, and the degree of vision loss.[12] All patients who have had anti-CMV maintenance therapy discontinued should continue to undergo regular ophthalmologic monitoring for early detection of CMV relapse and for immune reconstitution uveitis.

Relapse or Refractory Cytomegalovirus Retinitis

Case 77-3, Question 4: After 5 months of maintenance therapy with foscarnet, a routine funduscopic examination reveals retinal CMV disease progression. How should P.Z.'s retinitis be managed at this time?

Most patients with CMV not receiving ART while undergoing maintenance treatment eventually relapse.[12] For the first relapse, repeat induction therapy followed by maintenance therapy with the same drug is beneficial in most patients. Because P.Z. has tolerated foscarnet therapy thus far, he should receive another course of induction therapy. After reinduction, P.Z. should receive a higher maintenance dosage (120 mg/kg/day).[12]

It is important to distinguish between relapse and refractory disease. Relapse, as in the case of P.Z., is defined as the recurrence of clinically apparent viral activity and is usually caused by a decline in immune function, insufficient delivery of drug into the eye, or resistant CMV strains. Relapse can effectively be managed by repeat induction therapy of the same drug. If the relapse is caused

by a resistant virus, the patient may benefit from a change in therapy. Ganciclovir-resistant CMV strains occur by two mechanisms. DNA polymerase mutation at the *UL54* gene is observed in ~20% of ganciclovir-resistant strains. This mutation usually confers resistance to cidofovir and, to a lesser extent, foscarnet.[12] Most ganciclovir-resistant CMV strains have *UL97* mutations. *UL97* mutations are incapable of monophosphorylating ganciclovir. Cidofovir and foscarnet are appropriate alternatives to treat strains with *UL97* mutations. Patients who receive extensive ganciclovir treatment (>6–9 months) may present with highly ganciclovir-resistant strains containing *UL54* and *UL97* mutations.[72] Cidofovir may be considered in most patients who relapse while receiving ganciclovir or foscarnet. Although ganciclovir-resistant and foscarnet-resistant strains of CMV have been reported, their precise role in the clinical failure of these regimens is not known. Because of the different mechanisms of action of ganciclovir and foscarnet, strains resistant to one drug may retain sensitivity to the other.[73] Resistant or relapsing CMV retinitis may be treated by the administration of local ocular therapy via intravitreal injection of ganciclovir or foscarnet (see the section on Local Treatment).

Refractory CMV retinitis is defined by disease progression because of ineffective therapy. This phenomenon is observed in two clinical situations: when the disease persists with minimal or no response during induction therapy and when long-term control is inadequate with maintenance therapy. Refractory CMV disease has been defined in clinical trials as two relapses occurring within 10 weeks despite repeat induction and maintenance therapy. Treatment options for refractory CMV retinitis include reinduction with ganciclovir at higher dosages (7.5 mg/kg/dose every 12 hours, followed by maintenance doses of 10 mg/kg/day) or reinduction using combination therapy (IV ganciclovir plus foscarnet).[12] Refractory CMV retinitis can be treated with local ocular therapy via intravitreal injection of ganciclovir or foscarnet.[12]

Local Treatment

Case 77-3, Question 5: What is the role of intravitreal injections in CMV retinitis?

INTRAVITREAL INJECTIONS

Intravitreal administration of ganciclovir or foscarnet through a small-gauge needle is a method of selectively delivering the drug to the site of infection. Ganciclovir and foscarnet doses of 0.2 to 2 mg and 1.2 to 2 mg, respectively, are administered two or three times per week for active disease, followed by weekly maintenance injections.[12] Potential complications of intravitreal injections include bacterial endophthalmitis, vitreous hemorrhage, and retinal detachment. Importantly, in contrast to systemic therapy, local instillation of a drug is associated with a higher risk of CMV disease developing in the contralateral eye as well as extraocular sites.

CRYPTOCOCCOSIS

Clinical Presentation and Prognosis

CASE 77-4

Question 1: A.S. is a 28-year-old female with congenital HIV. She weighs 105.82 pounds (48 kg). She presents with a fever (103 °F [39.44 °C]) and a 2-week history of "splitting headaches." Laboratory test results include the following:

Hemoglobin, 11.2 g/dL
WBC count, 4100 cells/μL
Platelets, 73,000/L
SCr, 0.9 mg/dL
Glucose, 94 mg/dL
CD4 count, 47 cells/μL

A.S. has been out of care for more than a year; the last time she was seen in clinic, she was prescribed a single-tablet regimen consisting of darunavir/cobicistat/tenofovir alafenamide/emtricitabine. Physical examination

reveals no nuchal rigidity. With the exception of moderate lethargy, her neurologic examination is unremarkable. Her chest radiograph and three sets of blood culture results for bacteria and fungi are negative. A computed tomography scan is nondiagnostic. Lumbar puncture reveals the following CSF findings:

Glucose, 45 mg/dL
Protein, 90 mg/dL
WBC count, 10 cells/μL
Cryptococcal antigen titer, 1:2048 IU
Intracranial pressure (ICP), 24 cm H_2O (normal, 8–22 cm H_2O)

How is A.S.'s clinical presentation typical of a patient with AIDS and cryptococcal meningitis? What is her likely prognosis?

In the pre-ART era, cryptococcosis developed in ~6% to 10% of patients with AIDS in the United States, with meningitis being the most common clinical presentation.[74] In the era of ART and azole prophylaxis, a significant decline in the incidence of cryptococcosis has been observed.[74] The initial portal of entry is the lungs, where the organism is normally contained by an intact immune system. Cryptococcal disease typically develops in patients with profound defects in cell-mediated immunity (ie, CD4 counts, <50). Unlike bacterial meningitis, cryptococcal CNS infection has a much more insidious onset; the most common symptoms are fever and headache. Less frequent signs and symptoms include nausea and vomiting, meningismus, photophobia, and altered mental status. Focal neurologic deficits and seizures are observed in <10% of patients. CSF glucose is decreased, whereas CSF proteins are usually elevated. CSF cryptococcal antigen titer and CSF culture results are frequently positive. These findings, along with the clinical presentation, form the basis for the diagnosis. The overall outcome is poor, with a mean survival of 5 months in patients not receiving ART. Relapse within 6 months occurs in 50% of patients who do not receive suppressive therapy. Altered mental status at baseline, CSF WBC count of <20 cells/μL, high CSF cryptococcal antigen titer (>1:1,000), and an elevated initial CSF opening pressure of >20 cm H_2O have all been associated with a poor prognosis.[74]

A.S.'s CD4 count is 47. She has a temperature of 103 °F (39.44 °C) and has experienced "splitting headaches" for about a week. Her clinical presentation is typical of cryptococcal meningitis in patients living with AIDS. The CSF WBC count of 10 cells/μL, high cryptococcal antigen titer, and ICP >20 cm H_2O suggest a poor prognosis.[75] If left untreated, cryptococcal meningitis is fatal.

Treatment

AMPHOTERICIN B

Case 77-4, Question 2: How should A.S.'s acute cryptococcal meningitis be managed?

The current treatment recommended for cryptococcal meningitis is liposomal amphotericin B, 3 to 4 mg/kg/day IV, plus flucytosine (100 mg/kg/day) given PO in four divided doses as induction therapy for 14 days. Once the patient is stable (eg, afebrile, with the resolution of symptoms), then consolidation therapy with oral fluconazole 400 mg/day for 8 weeks or until CSF cultures are sterile can be initiated. After consolidation therapy, daily suppressive therapy with fluconazole 200 mg should be continued indefinitely unless immune reconstitution occurs with ART. Owing to lower rates of nephrotoxicity and infusion-related reactions, lipid-based amphotericin B, specifically liposomal amphotericin B, has supplanted amphotericin B deoxycholate as the agent of choice.[76,77]

Although the aforementioned regimen is highly effective, the ability to rapidly reduce A.S.'s ICP will also significantly improve her clinical course. Removal of 10 to 20 mL of spinal fluid by repeat lumbar puncture is recommended for patients with an ICP >20 cm H_2O (A.S.'s ICP is 24 cm H_2O). An additional intervention to consider reducing A.S.'s elevated ICP is the insertion of an intraventricular shunt.[12]

CASE 77-4, QUESTION 3: What is the evidence for adding flucytosine to amphotericin B in the acute treatment of A.S.? What are the disadvantages of this combination?

Amphotericin B binds to sterols in the fungal cell membrane, resulting in leakage of cytoplasmic contents. Flucytosine is an antimetabolite type of antifungal drug that is activated by deamination within the fungal cells to 5-fluorouracil. It inhibits fungal protein synthesis by replacing uracil with 5-fluorouracil in fungal RNA, and it also inhibits thymidylate synthase via 5-fluorodeoxy-uridine monophosphate, interfering with fungal DNA synthesis. Flucytosine, a purine analog, is ~10% converted to 5-fluorouracil, an antimetabolite, which is the mechanism for its potential bone marrow toxicity.

A classic prospective study conducted in patients who are HIV negative favored the use of the combination.[78] The protocol randomly assigned patients to receive either amphotericin B monotherapy (0.4 mg/kg/day IV for 6 weeks followed by 0.8 mg/kg/day IV every other day for 4 weeks) or amphotericin B plus flucytosine (150 mg/kg/day PO divided every 6 hours) for 6 weeks. Fewer failures or relapses, more rapid CSF sterilization, and less nephrotoxicity occurred in the combination group, although overall mortality was not different. However, approximately one-fourth of the patients in the combination arm developed leukopenia, thrombocytopenia, or both.

If flucytosine is chosen as adjunctive therapy, renal function and CBCs should be monitored closely for these adverse effects. A.S. is at increased risk for granulocytopenia because of her HIV infection.

The comparative trial forming the basis for the current recommendations for the treatment of acute cryptococcal meningitis in PLWH evaluated a higher dose of IV amphotericin B (0.7 mg/kg/day) with or without flucytosine given at a lower dose (25 mg/kg/dose PO every 6 hours) for 2 weeks.[75] The study evaluated 381 patients with an acute first episode of cryptococcal meningitis. The second part of this trial randomly reassigned patients who were

stable or had improved to either a fluconazole or an itraconazole treatment arm for an additional 8 weeks as consolidation therapy. Sixty percent and 51% of patients receiving amphotericin B plus flucytosine, and amphotericin B alone, respectively, had sterile CSF culture findings at 2 weeks of therapy. No significant differences were noted between groups in the percentage of patients who had negative culture results at 2 weeks. Importantly, the addition of flucytosine to amphotericin B was not associated with a significant increase in drug toxicities at 2 weeks. Fluconazole and itraconazole were similar in efficacy. However, multivariate analysis revealed two factors that were independently associated with a higher rate of CSF sterilization: the addition of flucytosine and the randomization to fluconazole. A more recent trial randomized 299 patients to amphotericin B (1 mg/kg/day) for 4 weeks, amphotericin B (1 mg/kg/day) plus flucytosine (100 mg/kg/day divided) for 2 weeks, or amphotericin B (1 mg/kg/day) plus fluconazole (400 mg bid) for 2 weeks. Patients receiving amphotericin B and flucytosine had lower mortality rates and significantly increased rates of yeast clearance from CSF. Rates of adverse events were similar between groups, with the exception of more frequent neutropenia in patients receiving a combination therapy. The addition of fluconazole provided no survival benefit.[79]

FLUCONAZOLE

CASE 77-4, QUESTION 4: Could A.S. be treated with fluconazole instead of amphotericin B for acute cryptococcal meningitis?

Fluconazole, one of the triazole antifungal agents, inhibits a fungal cytochrome P-450 (CYP) enzyme necessary for the conversion of lanosterol to ergosterol. Without ergosterol, the fungal cell membrane becomes defective and loses its selective permeability properties. Unlike itraconazole, fluconazole is well absorbed PO even in the presence of an elevated gastric pH. Fluconazole has excellent CNS penetration and a good safety profile, but it is likely a

secondary choice in the initial treatment of cryptococcal meningitis. In a prospective, randomized, multicenter trial, the National Institute of Allergy and Infectious Diseases Mycoses Study Group and the AIDS Clinical Trial Group compared amphotericin B with 200 mg/day of oral fluconazole (after a 400-mg loading dose) for 10 weeks in 194 patients.[80] The dose of amphotericin B (mean dose, 0.4–0.5 mg/kg/day) and the possible addition of flucytosine were left to the discretion of the individual investigators. Although the overall mortality was similar (14% for amphotericin B vs 18% for fluconazole), more patients treated with fluconazole died during the first 2 weeks of treatment (15% vs 8%; $P = 0.25$). Furthermore, the median time to the first negative CSF culture finding in the successfully treated patients was shorter in the amphotericin B group compared with fluconazole (16 vs 30 days). In a small, prospective, randomized trial of 20 male patients with AIDS, oral fluconazole (400 mg/day) for 10 weeks was compared with IV amphotericin B (0.7 mg/kg/day for 1 week, followed by the same dose three times weekly for 9 weeks) combined with flucytosine (150 mg/kg/day).[81] There were four deaths in the fluconazole group and none in the amphotericin B group ($P = 0.27$). Eight of the 14 patients in the fluconazole group failed to respond to treatment, whereas none in the amphotericin B group failed to respond. The mean duration of positive CSF cultures was 41 days in the fluconazole group and 16 days in the amphotericin B group ($P = 0.02$). These results, taken together, have led most clinicians to choose amphotericin, with or without flucytosine, as initial treatment for severe cryptococcal meningitis. Although increased doses of fluconazole have been proposed, it is unknown whether these will result in improved outcomes. High doses of fluconazole are being investigated further for patients in the developing world where the use of IV amphotericin may not always be feasible. Considering the severity of her meningitis, A.S. should be treated acutely with liposomal amphotericin B and not with fluconazole.

DURATION OF THERAPY

CASE 77-4, QUESTION 5: How long should treatment continue for A.S.'s cryptococcal meningitis?

Once A.S. completes 2 weeks of acute induction therapy with liposomal amphotericin B and flucytosine, she should be switched, if stable, to oral fluconazole 400 mg/day for consolidation therapy. Consolidation should be continued for an additional 8 to 10 weeks, followed by lifelong suppressive therapy with fluconazole 200 mg/day[75] (see the section on Maintenance Therapy).

MAINTENANCE THERAPY

CASE 77-4, QUESTION 6: Should A.S. receive maintenance therapy after successful treatment?

After induction and consolidation treatment of cryptococcal meningitis, A.S. and all patients with AIDS should receive maintenance therapy indefinitely, unless immune reconstitution occurs as a result of ART.[12],[74],[75] A higher relapse rate and a shorter life expectancy have been observed in patients who did not receive chronic secondary prophylaxis.[82] Fluconazole (200 mg once daily) has emerged as the suppressive treatment of choice. In a randomized, placebo-controlled trial of 61 patients with AIDS, four recurrent cases of meningitis developed in the placebo group and none in the fluconazole group.[83] A multicenter, comparative trial randomized patients to receive either weekly amphotericin B 1 mg/kg/day IV or 200 mg/day of fluconazole PO.[84] Of 189 patients enrolled, 18% of the patients in the amphotericin B group relapsed, compared with 2% in the fluconazole group. Serious toxicities were more frequent in the amphotericin B group.[75] The newer triazole antifungals, posaconazole and voriconazole, have limited experience as primary or maintenance therapy for patients with cryptococcosis and are associated with many drug interactions with ART.[12]

According to the OI guidelines,[12] adult and adolescent patients are at a low risk for recurrence of cryptococcosis when they have

completed a course of initial therapy, remain asymptomatic, and have a sustained increase (eg, >6 months) in their CD4 counts to at least 200 after ART. Thus, discontinuing chronic maintenance therapy among such patients is reasonable. Recurrences may occur, and some specialists recommend a repeat lumbar puncture to determine whether the CSF culture result is negative before stopping therapy. Maintenance therapy should be reinitiated if the CD4 count decreases to <200.

Primary Prophylaxis

Case 77-4, Question 7: What is the role of primary prophylaxis in cryptococcal meningitis?

Primary prophylaxis against cryptococcal disease in PLWH has been studied in a few clinical trials.[85],[86] In an open-label study, fluconazole (100 mg/day) was administered to all patients (329 PLWH) with CD4 counts <68. These results were compared with 337 historical controls from the pre-ART era.[85] Sixteen cases of cryptococcal meningitis occurred in the historical controls (4.8%) compared with only one case in the fluconazole group (0.3%). In a prospective, randomized AIDS Clinical Trial Group study, fluconazole 200 mg/day was compared with clotrimazole troches (10 mg five times a day) for the prevention of fungal infections in 428 patients with advanced HIV disease. After a median follow-up of 35 months, 32 cases of invasive fungal infection were confirmed. Of these, the majority (17 of 32) were cryptococcosis: 2 cases in the fluconazole group and 15 cases in the clotrimazole group. The greatest benefit derived from fluconazole was observed in patients with CD4 counts of <50.[86] However, no effect on survival was noted. A randomized, double-blind, placebo-controlled trial of fluconazole 200 mg three times weekly versus placebo in Ugandan adults with CD4 counts <200 found fluconazole prophylaxis to be effective prophylaxis against cryptococcal disease, with 18 patients in the placebo group developing cryptococcal disease versus one patient in the

fluconazole group. There was no difference in all-cause mortality between the groups.[85]

Fluconazole resistance has been reported in PLWH receiving a long-term therapy.[87] In addition to the potential for resistance, other concerns include the lack of survival benefits associated with prophylaxis, the possibility of drug interactions, and cost. In light of these concerns, the guidelines currently do not recommend primary prophylaxis for this disease (see Table 77-1).[12]

MYCOBACTERIUM TUBERCULOSIS

Clinical Presentation

CASE 77-5

QUESTION 1: C.J., a 45-year-old male prison inmate with AIDS, presents with fever, cough, and occasional night sweats. A tuberculin purified protein derivative (PPD) skin test result is negative. Two acid-fast bacilli (AFB) sputum smears also return negative results. Chest radiograph reveals hilar adenopathy with a questionable right middle lobe localized infiltrate. No cavitary lesions are seen. His antiretroviral medications include abacavir, lamivudine, and dolutegravir. Three months ago, his CD4 count was 120 cells/μL, and his viral load was 5200 copies/mL.

Why is infection with *Mycobacterium tuberculosis* a strong possibility in C.J.?

TB is the third leading cause of mortality attributed to infection worldwide, with nearly 2 million deaths in 2016.[88] Low- to middle-income countries account for 95% of deaths from *M.* tuberculosis. In the United States, 8916 cases of TB occurred in 2019, which is the lowest number of TB cases on record.[89] The recognized link between HIV and TB, along with an increase in clinical and public health resources, has subsequently resulted in a decline in the incidence of TB in the United States.[89]

C.J. presents with fever, cough, night sweats, and a right middle lobe infiltrate with hilar adenopathy, consistent with TB. Furthermore,

his HIV status in combination with his incarceration increases the probability of *M. tuberculosis* infection, including multidrug-resistant isolates. C.J. will be started with the standard four-drug regimen: isoniazid, rifampin (or rifabutin), pyrazinamide, and ethambutol.[12] (See Chapter 68, Tuberculosis, for a more comprehensive approach to TB treatment.)

Case 77-5, Question 2: Why are the negative tuberculin skin test result, negative sputum smear findings for AFB, and lack of cavitary lesions in C.J. still consistent with *M. tuberculosis* infection?

PLWH with CD4 counts <200 commonly present with extrapulmonary TB, along with or in the absence of pulmonary disease. These extrapulmonary sites include lymph nodes, bone marrow, spleen, liver, CSF, and blood.[12] The chest radiograph in PLWH may reveal hilar or mediastinal adenopathy or localized infiltrates in the middle or lower lung fields.

In PLWH, it is unusual to see typical apical infiltrates or cavitations. Furthermore, concomitant PCP may confuse the interpretation of chest radiographs. Finally, anergy (a state of immune unresponsiveness) is common in HIV disease. Thus, definitive diagnosis of TB rests on positive culture findings from sputum or other tissue and body fluid specimens.[12] Unlike many other AIDS-related OIs, CD4 count is not a reliable predictor of an increased risk for TB diseases, and patients can have relatively high CD4 counts at the time of TB development.

PLWH: DRUG-SUSCEPTIBLE TUBERCULOSIS

CASE 77-6

Question 1: K.D., a 26-year-old male living with HIV, comes in for a routine clinic visit. It is discovered that he is a household contact of a person known to have active, untreated, drug-susceptible TB. His CD4 count is 350 cells/μL. A tuberculin skin test (five tuberculin units of PPD) is administered, and he is instructed to return to the clinic in 48 hours. His PPD has returned negative

findings in the past, and he has demonstrated delayed hypersensitivity responsiveness.

How should the results of K.D.'s skin tests be interpreted, and should he be treated for latent TB considering his known exposure to TB?

Current guidelines recommend 9 months of isoniazid prophylaxis (300 mg/day PO) plus pyridoxine (50 mg/day PO) for all PLWH who have at least a 5-mm induration reaction to PPD and no evidence of active TB (negative chest radiograph and no clinical symptoms), unless otherwise contraindicated and regardless of Bacillus Calmette–Guerin vaccination status.[12] Alternatively, patients can receive rifapentine plus isoniazid plus pyridoxine once weekly for 12 weeks. The administration of Bacillus Calmette–Guerin vaccine to PLWH is contraindicated because of the potential to cause disseminated disease.[12] A >5-mm reaction in PLWH is considered positive.[12] Few isoniazid prophylaxis failures have been reported, although this finding has not been systematically studied. Persons who cannot take isoniazid or who have been exposed to a known isoniazid-resistant strain should use either rifampin or rifabutin alone for 4 months as alternatives, being mindful of potential drug interactions with ART.[12] All PLWH, irrespective of age, PPD results, or prior course of chemoprophylaxis, should be given chemoprophylaxis if they are in close contact with persons who have active TB. Prophylaxis also should be given for anergic, PLWH who have been in contact with patients known to have active TB.[12] Before the treatment of latent TB is begun, active TB needs to be ruled out. K.D. should undergo chest radiography and clinical evaluation to rule out active disease. The CDC no longer recommends routine anergy testing in these patients.[12]

PLWH: PROTEASE INHIBITORS, NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS, CCR5 ANTAGONISTS, AND INTEGRASE INHIBITORS

CASE 77-7

Question 1: F.C., a 36-year-old female living with HIV, diagnosed 6 months ago, was found to have active TB (pulmonary infiltrates on chest radiographs, sputum AFB stain and positive culture finding, and culture pansensitive). She is taking tenofovir alafenamide, emtricitabine, darunavir, cobicistat, and fluconazole, and her CD4 count is 300 cells/μL.

What factors must be considered when selecting TB therapy for F.C.?

The use of protease inhibitors in the treatment of PLWH coinfected with TB increases the potential for drug interactions with rifamycin derivatives (rifampin and rifabutin). Because the rifamycins are potent inducers of the hepatic CYP system (eg, CYP3A4), they can induce metabolism of the protease inhibitors, resulting in subtherapeutic levels. Conversely, the protease inhibitors elevate rifamycin serum levels by inhibiting their metabolism and increasing toxicities, such as rifabutin-associated uveitis (inflammation of the uveal tract of the eye; see Chapter 68, Tuberculosis).

According to recent guidelines, rifampin should not be coadministered with any standard protease inhibitors (boosted or not with ritonavir or cobicistat), etravirine, nevirapine, rilpivirine, or elvitegravir.[11,88] Dolutegravir should be dosed 50 mg bid if combined with rifampin.[11] Rifabutin should be given at 50% of the usual dose (ie, reduced from 300 to 150 mg/day or 300 mg three times a week) with ritonavir- or cobicistat-boosted protease inhibitors.[11] Rifabutin can be used in full doses with nevirapine, etravirine, and rilpivirine; however, the rilpivirine dose should be increased to 50 mg daily.[90] If etravirine is coadministered with a ritonavir-boosted protease inhibitor, rifabutin should not be coadministered.[11] Tenofovir/emtricitabine/elvitegravir/cobicistat should not be coadministered with rifabutin; however, no dose adjustment is needed when combined with dolutegravir or raltegravir.[11] Sequential treatment of TB followed by HIV treatment is not recommended.[12] Three clinical trials have demonstrated a reduction in mortality and HIV-related diseases when antiretrovirals are given during TB treatment.[91–93]

If a change in her ART regimen is not possible, a reduced dose of rifabutin (150 mg daily or 300 mg three times per week) is

recommended when coadministered with darunavir/cobicistat. She will receive isoniazid, rifabutin, pyrazinamide, and ethambutol daily for 8 weeks followed by isoniazid and rifabutin daily or three times weekly for 6 months.

MYCOBACTERIUM AVIUM COMPLEX DISEASE

Clinical Presentation

CASE 77-8

QUESTION 1: M.E., a 38-year-old female living with HIV who has a history of IV drug use, presents with fevers, drenching night sweats, a poor appetite, and a 20-pound (9.07-kg) weight loss (>15% of baseline) during the past 4 months. M.E. has been off all ART for the past year because of drug intolerance. She has a past medical history of recurrent herpes zoster, PCP, and cryptococcal meningitis. Her current medications include one TMP-SMX double-strength tablet once daily and an occasional valacyclovir dose when she feels the herpes zoster "is beginning to start"; she is not on MAC prophylaxis therapy. Physical examination reveals a cachectic female with mild hepatosplenomegaly. Pertinent laboratory test results include the following:

Hematocrit, 23%
WBC count, 3500 cells/L, with 68% neutrophils, 2% bands, 22% lymphocytes, and 8% monocytes
Absolute CD4 count, 25 cells/μL
Viral load, 400,000 copies/mL
Aspartate transferase, 135 IU/L
Alanine aminotransferase, 95 IU/L
Alkaline phosphatase, 186 IU/L

The chest radiograph is unremarkable. Based on these findings, a presumptive diagnosis of MAC infection is made.

Why is M.E.'s clinical presentation consistent with MAC infection?

Disseminated MAC infection is common in patients with end-stage AIDS. On autopsy, MAC organisms are observed in the lungs and multiple other bodily tissues.[94] The predominant organism in PLWH

is *M. avium* (>95% of typeable isolates).[12] The risk of developing disseminated MAC infection is highest in patients with a CD4 count <50.[12] Poor prognostic indicators include prior OI, high plasma HIV RNA levels, previous colonization of the respiratory or GI tract with MAC, and reduced in vitro lymphoproliferative immune responses to *M. avium* antigens.[12]

M. avium is a ubiquitous organism found in food, water, soil, and house dust. The most likely portal of entry is either the GI or respiratory tract. Common presenting symptoms associated with MAC infection include fever, night sweats, anorexia, malaise, profound weight loss (>10% body weight), anemia, lymphadenopathy, and diarrhea.[12] M.E.'s fevers, drenching night sweats, poor appetite, 20-pound (9.07-kg) weight loss, and mild hepatosplenomegaly are consistent with MAC infection. In particular, her CD4 count of 25 puts her at risk for this OI.

Treatment

INITIATION

Case 77-8, Question 2: Why is it appropriate to initiate M.E.'s drug therapy before blood culture results have documented the presence of MAC?

Disseminated MAC is best diagnosed by peripheral blood cultures. However, initial testing often includes AFB on a blood smear.[12] Conventional culture methods using solid media may have a turnaround time of as long as 8 weeks; however, radiometric broth systems signaling the release of carbon 15-labeled CO_2 from mycobacteria may detect bacterial growth in 7 to 10 days.[95] Identification of the organism (*M. tuberculosis* vs atypical mycobacteria) by conventional biochemical methods may take weeks to months. Techniques using DNA probes make diagnosis possible within several hours.[95] Quantitative blood cultures have been useful to monitor the effects of drug therapy, but may not be

practical on a routine clinical basis. Radiometric broth methods also may provide in vitro drug susceptibility in another 7 to 10 days. Even with the availability of all these laboratory tests, results generally are not available for 2 to 3 weeks. In view of this lag time, empiric therapy should be initiated as quickly as possible. Although MAC is typically isolated from blood, the organism can also be demonstrated via acid-fast smears of lymph node, liver, or bone marrow biopsies. Because these organs are rich in monocytes (the target cells for MAC infection), the organism load may be high (up to 10^{11} colony-forming units/mL).

DRUG SUSCEPTIBILITY AS A BASIS FOR TREATMENT

CASE 77-8, QUESTION 3: Should M.E.'s therapy be based on in vitro drug susceptibility results?

Correlation between in vitro drug susceptibility results and clinical efficacy has not been clearly established for MAC.[95],[96] In addition, drug susceptibility studies also may not correlate with clinical efficacy because in vitro results for individually tested drugs may show resistance, but combination therapy may be additive or synergistic. Finally, some antimycobacterial agents exhibit large differences between the minimum inhibitory concentration and maximum bactericidal concentration. This finding may reflect the difficulty in eradicating this organism, particularly in a severely immunocompromised host. Despite these limitations, in vitro drug susceptibility testing is only recommended for macrolide antibiotics because of the correlation with clinical outcomes.[97]

DRUG THERAPY

CASE 77-8, QUESTION 4: What drug regimens could be selected to treat M.E.?

The guidelines recommend a two-drug or more MAC regimen because monotherapy can lead to breakthrough bacteremia and

resistance; at least one of these drugs must be a macrolide. Clarithromycin (500 mg PO bid) is the preferred agent because there are more clinical data; however, if intolerable or significant drug interactions need to be avoided, azithromycin 500 to 600 mg PO qd is an alternative. Doses of clarithromycin >1 g/day in the treatment of MAC have been associated with increased mortality.[12] Ethambutol (15 mg/kg/day PO) is recommended as the second agent. Several drugs can be used as the third agent, including rifabutin (300 mg/day), amikacin (10–15 mg/kg/day), and fluoroquinolones. The choice of the third agent depends on the severity of the illness, including high mycobacterial loads, CD4 count <50, drug interactions, hepatic and renal function, patient tolerability, patient compliance, and cost. Long-term therapy may be discontinued in patients who have completed a course of >12 months of treatment for MAC, remain asymptomatic, and have a sustained increase (eg, >6 months) in their CD4 count to >100 after ART.[12]

Although four-drug regimens have been used, one study observed that a three-drug macrolide regimen (clarithromycin, ethambutol, and rifabutin) was more effective than was a four-drug regimen (ciprofloxacin, clofazimine, ethambutol, and rifampin).[98] Benefits of the macrolide regimen included more rapid clearing of MAC bacteremia and a longer duration of survival. Rifabutin, at 600 mg/day, induced uveitis in approximately one-third of patients. Subsequently, the rifabutin dosage was lowered to 300 mg/day, and the incidence of uveitis decreased to 5.6%. Although clearance of bacteremia was superior at the higher rifabutin dose, no differences in survival were observed.

IRIS can also occur with MAC disease. IRIS-associated fever and lymphadenitis are difficult to differentiate from active MAC disease. IRIS most commonly occurs in patients with MAC and very low CD4 counts with the initiation of ART. The disease is often self-limiting and requires no therapy; however, steroid therapy may be warranted in severe disease. For this reason, for patients not taking ART, it may be warranted to administer MAC therapy for 2 weeks before the initiation of ART to minimize the risk of IRIS.[12]

M.E. is placed on a regimen of azithromycin 600 mg daily and ethambutol 15 mg/kg/day. Considerations for the addition of a third-line agent include the severity of the illness, potential drug interactions, tolerability, hepatic and renal function, and cost. M.E. must be counseled regarding the slow response to treatment. If she improves, therapy should be continued, and ART should be reinstituted.

Monitoring therapy

CASE 77-8, QUESTION 5: How should M.E. be monitored?

The primary goals of MAC therapy are to eradicate or reduce the number of ***M. avium*** organisms, decrease symptoms, enhance quality of life, and prolong survival. M.E. should be monitored for symptomatic relief (temperature spikes and frequency of night sweats), as well as for a microbiologic response (colony-forming units/mL). Clinical response, as well as a decline in the quantity of mycobacteria, is expected in 2 to 4 weeks but may be delayed in patients with extensive disease. If no clinical response is seen in 4 to 8 weeks, repeat blood cultures for MAC should be obtained along with repeat susceptibility testing for clarithromycin and azithromycin. If resistance is observed or suspected, two new drugs should be added based on susceptibility testing with or without the macrolide. If the organism is found to be susceptible to macrolides, therapy should be continued and adherence, absorption, tolerance, and drug interactions should be considered.[12] If the problem is determined to be drug absorption, IV agents can be considered. M.E. should also be followed up for the development of toxicities related to drug therapy. Furthermore, because many drugs used to treat MAC infections are associated with drug interactions, this issue must be considered each time a new drug is prescribed. In some cases, drug doses need to be modified or alternative drugs should be selected to prevent adverse events or therapeutic failures.[12,97]

Case 77-8, Question 6: What drug(s) should be used to provide primary prophylaxis against MAC infection?

Prophylaxis

MAC prophylaxis is not recommended for patients who are initiated on ART and is only recommended for those who are not on fully suppressive ART after active disseminated MAC has been ruled out.[12] Options include clarithromycin (500 mg bid) or azithromycin 1200 mg every week or 600 mg twice weekly for persons with a CD4 count <50. Although the combination of azithromycin and rifabutin is more effective than is azithromycin alone, the increased cost, adverse events, potential for drug interactions with rifabutin, and the absence of a survival benefit preclude this regimen from being routinely recommended. If neither clarithromycin nor azithromycin is tolerated, rifabutin 300 mg/day may be used (Table 77-1).[12]

The decision to use clarithromycin or azithromycin (both first-line recommendations for primary prophylaxis) is based on patient compliance and the potential for drug interactions. Azithromycin (1200 mg once weekly or 600 mg twice weekly) may be preferable for a patient who has difficulty with adherence. In contrast to clarithromycin, azithromycin does not affect the CYP enzyme system and is therefore less likely to interact with other drugs. M.E. would have benefited from MAC prophylaxis when her CD4 count decreased to <50 because she was not on ART.

MAC prophylaxis can be discontinued when they initiate effective ART and would be reinitiated if CD4 <50 only if not on suppressive ART.[12]

MUCOCUTANEOUS CANDIDIASIS

CASE 77-9

Question 1: P.J. is a 45-year-old male living with HIV who was started on dolutegravir and tenofovir alafenamide/emtricitabine when he was diagnosed 1 year ago. P.J. has not been seen in the clinic since his initial presentation. He appears today with difficult, painful swallowing and diffuse pain. On examination, localized white plaques are observed in the oral cavity. His CD4 count is 280 cells/μL.

What is the most likely cause of this patient's dysphagia and odynophagia?

Candida can cause both oropharyngitis and esophagitis in PLWH typically when CD4 counts are >200 cells/μL. In addition, patients can present with CMV, HSV, or aphthous ulcers in the oropharynx. Symptoms include dysphagia, odynophagia, and thrush (with *Candida* infections). Oral ulcers are common with HSV, rare with *Candida*, and uncommon with CMV or aphthous ulcers. Pain is usually diffuse in *Candida* infections and more focused with HSV, CMV, and aphthous ulcers. Fever is primarily associated with CMV.[12]

Most infections are caused by *Candida albicans*; however, because of the exposure of fluconazole, emergence of non-*albicans* species such as *C. glabrata* has been seen, and in some cases led to refractory candidiasis.[12] Patients with localized white plaques in the oral cavity likely have oral candidiasis (thrush), and should be started on antifungal therapy. Oral fluconazole (100 mg once daily) is considered the drug of choice for the treatment of oropharyngeal candidiasis because it is more convenient and better tolerated than are topical therapies. Patients may also be treated with local antifungal therapy (eg, "swish and swallow" nystatin suspension, 1 tsp four or five times daily, or clotrimazole troches four or five times daily). The preferred therapy for esophageal candidiasis is 14 to 21 days of fluconazole at higher doses (up to 400 mg PO or IV daily). Alternative therapies include itraconazole and posaconazole (for oropharyngeal disease) and voriconazole, isavuconazole, anidulafungin, caspofungin, micafungin, and amphotericin B (for esophageal disease).[12] Primary prophylaxis is not recommended for candidiasis.[12]

A presumptive diagnosis of *Candida* esophagitis can be made for P.J. because he presents with oral pharyngeal candidiasis,

dysphagia, and odynophagia. P.J. should be empirically treated with fluconazole 200 mg/day for 14 to 21 days. If he is unresponsive to fluconazole, endoscopy with biopsy and culture should be performed to confirm the diagnosis as well as *Candida* speciation. If candidiasis is confirmed, P.J. should be checked for medication adherence and potential drug interactions. If the patient is adherent and does not have malabsorption, posaconazole suspension or itraconazole solution should be considered. In addition, higher doses of fluconazole could be considered before the initiation of alternative IV therapy. Relapse is common in patients who do not receive secondary prophylaxis. Chronic suppressive therapy (fluconazole, 100–200 mg/day) could be considered in patients responsive to fluconazole therapy who have frequent or severe recurrent esophagitis; however, the risks of fluconazole resistance should be considered.[12]

ACKNOWLEDGMENTS

The authors acknowledge Angela D.M. Kashuba, Gene D. Morse, Alice M. O'Donnell, Marjorie Robinson, and Mark J. Shelton for their contributions to this chapter in the previous editions.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and website for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Buchacz K, Armon C, Palella FJ Jr, et al. The HIV Outpatient Study—25 years of HIV patient care and epidemiologic research. *Open Forum Infect Dis.* 2020;7(5):ofaa123. (4)

Panel on Opportunistic Infections in HIV-infected Adults and Adolescents. Guidelines for prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines (12)

Selik RM, Mokotoff ED, Branson B, Owen MS, Whitmore S, Hall HI. Revised surveillance case definition for HIV infection, United States, 2014. *MMWR Recomm Rep*. 2014;63(RR03);1–10. (5)

Key Websites

Centers for Disease Control and Prevention. HIV/AIDS. http://www.cdc.gov/hiv

Centers for Disease Control and Prevention. Managing drug interactions in the treatment of HIV-related tuberculosis. Published June 2013. Accessed July 2015. http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/pdf/tbhiv.pdf

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/ (11)

COMPLETE REFERENCES CHAPTER 77 Opportunistic Infections in Patients Living with HIV

1. Glynn MK, Lee LM, McKenna MT. The status of national HIV case surveillance, United States 2006. *Public Health Rep*. 2007;122(suppl 1):63–71.
2. Buchacz K, Baker RK, Palella FJ Jr, et al. AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study. *AIDS*. 2010;24:1549–1559.
3. Djawe K, Buchacz K, Hsu L, et al. Mortality risk after AIDS-defining opportunistic illness among HIV-infected persons—San Francisco, 1981–2012. *J Infect Dis*. 2015;212(9):1366–1375.
4. Buchacz K, Armon C, Palella FJ Jr, et al. The HIV Outpatient Study— 25 years of HIV patient care and epidemiologic research. *Open Forum Infect*

Dis. 2020;7(5):ofaa123.
5. Selik RM, Mokotoff ED, Branson B, Owen MS, Whitmore S, Hall HI. Revised surveillance case definition for HIV infection, United States, 2014. *MMWR Recomm Rep*. 2014;63(RR03):1–10.
6. Pantaleo G, Graziosi C, Fauci AS. New concepts in the immunopathogenesis of human immunodeficiency virus infection. *N Engl J Med*. 1993;328:327–335.
7. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. *Ann Intern Med*. 1996;124:633–642.
8. The HIV-CAUSAL Collaboration; Ray M, Logan R, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS.* 2010;24(1):123–137.
9. Chaisson RE, Gallant JE, Keruly JC, Moore RD. Impact of opportunistic disease on survival in patients with HIV infection. *AIDS*. 1998;12:29–33.
10. Mellors JW, Muñoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997;126:946–954.
11. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Accessed October 28, 2020. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/
12. Panel on Opportunistic Infections in HIV-infected Adults and Adolescents. Guidelines for prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Accessed October 28, 2020. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/
13. Jacobson MA, Zegans M, Pavan PR, et al. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet*. 1997;349:1443–1445.
14. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. *J Infect Dis*. 1998;177:1080–1083.
15. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin Infect Dis*. 2004;39:1709–1712.
16. Murdoch DM, Venter WD, Feldman C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. *AIDS*. 2008;22:601–610.
17. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. *Clin Infect Dis*. 2006;42:418–427.

18. Shelburne SA, Visnegarwala F, Darcourt J, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS*. 2005;19:399–406.
19. Mori S, Levin P. A brief review of potential mechanisms of immune reconstitution inflammatory syndrome in HIV following antiretroviral therapy. *Int J STD AIDS*. 2009;20:447–452.
20. Carr A, Cooper DA. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. *Lancet*. 1997;349:995–996.
21. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet*. 1998;351:256–261.
22. Elliot B, Aromin I, Gold R, Flanigan T, Mileno M, et al. 2.5 year remission of AIDS-associated progressive multifocal leukoencephalopathy with combined antiretroviral therapy. *Lancet*. 1997;349:850.
23. Hicks CB, Myers SA, Giner J, et al. Resolution of intractable molluscum contagiosum in a human immunodeficiency virus-infected patient after institution of antiretroviral therapy with ritonavir. *Clin Infect Dis*. 1997;24:1023–1025.
24. Murphy M, Armstrong D, Sepkowitz KA, Ahkami RN, Myskowski PL. Regression of AIDS-related Kaposi's sarcoma following treatment with an HIV-1 protease inhibitor. *AIDS*. 1997;11:261–262.
25. Whitley RJ, Jacobson MA, Friedberg DN, et al. Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS in the era of potent antiretroviral therapy: recommendations of an international panel. International AIDS Society-USA. *Arch Intern Med*. 1998;158:957–969.
26. Fischl MA, Dickinson GM, La Voie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for Pneumocystis carinii pneumonia in AIDS. *JAMA*. 1988;259:1185–1189.
27. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated Mycobacterium avium complex infection in patients with advanced acquired immunodeficiency syndrome. *N Engl J Med*. 1996;335:384–391.
28. Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for Pneumocystis carinii pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet*. 1999;353:201–203.
29. Young L. Pneumocystis carinii pneumonia. In: Walzer PD, ed. *Pneumocystis carinii Pneumonia*. 2nd ed. Marcel Dekker; 1994:vii.
30. Kelley CF, Checkley W, Mannino DM, Franco-Paredes C, Del Rio C, Holguin F. Trends in hospitalizations for AIDS-associated Pneumocystis jirovecii pneumonia in the United States (1986 to 2005). *Chest*. 2009;136:190–197.
31. Montgomery AB. Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. Pathophysiology and therapy. *AIDS*

Clin Rev. 1991: 127–143.

32. Walzer PD, Evans HE, Copas AJ, Edwards SG, Grant AD, Miller RF. Early predictors of mortality from Pneumocystis jirovecii pneumonia in HIV-infected patients: 1985–2006. *Clin Infect Dis*. 2008;46:625–633.
33. Sattler R, Jelliffe R. Pharmacokinetic and pharmacodynamic considerations for drug dosing in the treatment of Pneumocystis carinii pneumonia. In: Walzer PD, ed. *Pneumocystis carnii Pneumonia*. Rev ed. Marcel Dekker; 1993:467.
34. Gluckstein D, Ruskin J. Rapid oral desensitization to trimethoprim-sulfamethoxazole (TMP-SMZ): use in prophylaxis for Pneumocystis carinii pneumonia in patients with AIDS who were previously intolerant to TMP-SMZ. *Clin Infect Dis*. 1995;20:849–853.
35. Hughes W, Leoung G, Kramer F, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. *N Engl J Med*. 1993;328:1521–1527.
36. Dohn MN, Weinberg WG, Torres RA, et al. Oral atovaquone compared with intravenous pentamidine for Pneumocystis carinii pneumonia in patients with AIDS. Atovaquone Study Group. *Ann Intern Med*. 1994;121:174–180.
37. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med*. 1996;124:792–802.
38. Medina I, Mills J, Leoung G, et al. Oral therapy for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med*. 1990;323:776–782.
39. Lee BL, Medina I, Benowitz NL, Jacob P 3rd, Wofsy CB, Mills J 5th. Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of Pneumocystis pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). Evidence of drug interactions. *Ann Intern Med*. 1989;110:606–611.
40. Benfield T, Atzori C, Miller RF, Helweg-Larsen J. Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr*. 2008;48:63–67.
41. Helweg-Larsen J, Benfield T, Atzori C, Miller RF. Clinical efficacy of first and second-line treatments for HIV-associated Pneumocystis jirovecii pneumonia: a tri-centre cohort study. *J Antimicrob Chemother*. 2009;64:1282–1290.
42. Kim T, Kim SH, Park KH, et al. Clindamycin-primaquine versus pentamidine for the second-line treatment of Pneumocystis pneumonia. *J Infect Chemother*. 2009;15: 343–346.

43. O'Brien JG, Dong BJ, Coleman RL, Gee L, Balano KB. A 5-year retrospective review of adverse drug reactions and their risk factors in human immunodeficiency virus-infected patients who were receiving intravenous pentamidine therapy for Pneumocystis carinii pneumonia. *Clin Infect Dis*. 1997;24:854–859.
44. Conte JE Jr, Chernoff D, Feigal DW Jr, Joseph P, McDonald C, Golden JA. Intravenous or inhaled pentamidine for treating Pneumocystis carinii pneumonia in AIDS. A randomized trial. *Ann Intern Med*. 1990;113:203–209.
45. Sistek CJ, Wordell CJ, Hauptman SP. Adjuvant corticosteroid therapy for Pneumocystis carinii pneumonia in AIDS patients. *Ann Pharmacother*. 1992;26:1127–1133.
46. LaRocco A Jr, Amundson DE, Wallace MR, Malone JL, Oldfield EC 3rd. Corticosteroids for Pneumocystis carinii pneumonia with acute respiratory failure. Experience with rescue therapy. *Chest*. 1992;102:892–895.
47. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323:1451–1457.
48. Bozzette SA, Morton SC. Reconsidering the use of adjunctive corticosteroids in Pneumocystis pneumonia? *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995;8:345–347.
49. Ioannidis JP, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Arch Intern Med*. 1996;156:177–188.
50. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for Pneumocystis carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. 2001;184:992–997.
51. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332:693–699.
52. Noskin GA, Murphy RL. Extrapulmonary infection with Pneumocystis carinii in patients receiving aerosolized pentamidine. *Rev Infect Dis*. 1991;13:525.
53. Mocroft A, Reiss P, Kirk O, et al. Is it safe to discontinue primary Pneumocysitis jiroveci pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. 2010;51(5):611–9.
54. Montoya J, Remington J. Toxoplasma gondii. In: Mandell G, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 5th ed. Churchill Livingstone; 2000:2858.

55. Mathews C, Barba D, Fullerton SC. Early biopsy versus empiric treatment with delayed biopsy of non-responders in suspected HIV-associated cerebral toxoplasmosis: a decision analysis. *AIDS*. 1995;9:1243–1250.
56. Jacobson MA, Besch CL, Child C, et al. Primary prophylaxis with pyrimethamine for toxoplasmic encephalitis in patients with advanced human immunodeficiency virus disease: results of a randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS. *J Infect Dis*. 1994;169:384–394.
57. Leport C, Chêne G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. ANRS 005-ACTG 154 Group Members. Agence Nationale de Recherche sur le SIDA. AIDS. Clinical Trial Group. *J Infect Dis*. 1996;173:91–97.
58. de la Hoz Caballer B, Fernandez-Rivas M, Fraj Lazaro J, et al. Management of sulfadiazine allergy in patients with acquired immunodeficiency syndrome. *J Allergy Clin Immunol*. 1991;88:137–138.
59. Tenant-Flowers M, Boyle MJ, Carey D, et al. Sulphadiazine desensitization in patients with AIDS and cerebral toxoplasmosis. *AIDS*. 1991;5:311–315.
60. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis*. 1996;22: 268–275.
61. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. *Antimicrob Agents Chemother*. 1998;42:1346–1349.
62. Frenkel JK, Hitchings GH. Relative reversal by vitamins (p-aminobenzoic, folic, and folinic acids) of the effects of sulfadiazine and pyrimethamine on Toxoplasma, mouse and man. *Antibiot Chemother (Northfield)*. 1957;7:630–638.
63. Jabs DA, Van Natta ML, Holbrook JT, et al. Longitudinal study of the ocular complications of AIDS: 1. Ocular diagnoses at enrollment. *Ophthalmology*. 2007;114: 780–786.
64. Holland GN, Vaudaux JD, Shiramizu KM, et al. Characteristics of untreated AIDS-related cytomegalovirus retinitis. II. Findings in the era of highly active antiretroviral therapy (1997 to 2000). *Am J Ophthalmol*. 2008;145:12–22.
65. Jennens ID, Lucas CR, Sandland AM, Maclean H, Hayes K. Cytomegalovirus cultures during maintenance DHPG therapy for cytomegalovirus (CMV) retinitis in acquired immunodeficiency syndrome (AIDS). *J Med Virol*. 1990;30:42–44.
66. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. The Cytomegalovirus Retreatment Trial. The Studies of Ocular Complications of

AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. *Arch Ophthalmol*. 1996;114:23–33.

67. Jabs DA, Ahuja A, Van Natta M, Dunn JP, Yeh S; Studies of the Ocular Complications of AIDS Research Group. Comparison of treatment regimens for cytomegalovirus retinitis in patients with AIDS in the era of highly active antiretroviral therapy. *Opthalmology*. 2013;120:1262–1270.
68. Morbidity and toxic effects associated with ganciclovir or foscarnet therapy in a randomized cytomegalovirus retinitis trial. Studies of ocular complications of AIDS Research Group, in collaboration with the AIDS Clinical Trials Group. *Arch Intern Med*. 1995;155:65–74.
69. Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med*. 2002;346:1119–1126.
70. Aweeka F, Gambertoglio J, Mills J, Jacobson MA. Pharmacokinetics of intermittently administered intravenous foscarnet in the treatment of acquired immunodeficiency syndrome patients with serious cytomegalovirus retinitis. *Antimicrob Agents Chemother*. 1989;33:742–745.
71. Studies of Ocular Complications of AIDS Research Group, in collaboration with the AIDS Clinical Trials Group. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. . *N Engl J Med*. 1992;326:213–220.
72. Smith IL, Cherrington JM, Jiles RE, Fuller MD, Freeman WR, Spector SA. High-level resistance of cytomegalovirus to ganciclovir is associated with alterations in both the UL97 and DNA polymerase genes. *J Infect Dis*. 1997;176:69–77.
73. Baldanti F, Underwood MR, Stanat SC, et al. Single amino acid changes in the DNA polymerase confer foscarnet resistance and slow-growth phenotype, while mutations in the UL97-encoded phosphotransferase confer ganciclovir resistance in three double-resistant human cytomegalovirus strains recovered from patients with AIDS. *J Virol*. 1996;70:1390–1395.
74. Powderly WG. Cryptococcal meningitis and AIDS. *Clin Infect Dis*. 1993;17: 837–842.
75. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med*. 1997;337:15–21.
76. Baddour LM, Perfect JR, Ostrosky-Zeichner L, et al. Successful use of amphotericin B lipid complex in the treatment of cryptococcosis. *Clin Infect Dis*. 2005; 40(suppl 6):S409–S413.
77. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS*. 1997;11:1463–1471.

78. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med*. 1979;301:126–131.
79. Day JN, Chau TTH, Wolbers M, et al. Combination therapy for cryptococcal meningitis. *N Engl J Med*. 2013;368:1291–1302.
80. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. *N Engl J Med*. 1992;326:83–89.
81. Larsen RA, Leal MA, Chan LS. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS. A randomized trial. *Ann Intern Med*. 1990;113:183–187.
82. Chuck SL, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. *N Engl J Med*. 1989;321:794–799.
83. Bozzette SA, Larsen RA, Chiu J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1991;324:580–584.
84. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. *N Engl J Med*. 1992;326:793–798.
85. Parkes-Ratanshi R, Wakeham K, Levin J, et al. Primary prophylaxis of cryptococcal disease with fluconazole in HIV-positive Ugandan adults: a double-blind randomised, placebo controlled trial. *Lancet Infect Dis*. 2011;11(12):933-41.
86. Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332:700–705.
87. Berg J, Clancy CJ, Nguyen MH. The hidden danger of primary fluconazole prophylaxis for patients with AIDS. *Clin Infect Dis*. 1998;26:186–187.
88. World Health Organization. Top 10 causes of death fact sheet. May 24, 2018. Accessed November 4, 2020. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death/
89. Centers for Disease Control and Prevention. *TB Incidence in the United States 1953–2019*. Centers for Disease Control and Prevention; 2019. Accessed June 20, 2017. https://www.cdc.gov/tb/statistics/default.htm
90. Centers for Disease Control and Prevention. Managing drug interactions in the treatment of HIV-related tuberculosis. Published June 2013. Accessed July 2015. http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/pdf/tbhiv.pdf

91. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362:697–706.
92. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365(16):1482–1491. Accessed June 20, 2017. http://www.ncbi.nlm.nih.gov/pubmed/22010914
93. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365(16):1471–1481. Accessed June 20, 2017. http://www.ncbi.nlm.nih.gov/pubmed/22010913
94. Chaisson RE, Moore RD, Richman DD, Keruly J, Creagh T. Incidence and natural history of Mycobacterium avium-complex infections in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. *Am Rev Respir Dis*. 1992;146: 285–289.
95. Woods GL. Disease due to the Mycobacterium avium complex in patients infected with human immunodeficiency virus: diagnosis and susceptibility testing. *Clin Infect Dis*. 1994;18(suppl 3):S227–S232.
96. Inderlied C. Microbiology and minimum inhibitory concentration testing for Mycobacterium avium complex prophylaxis. *Am J Med*. 1997; 102(suppl 3):2–10.
97. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175:367–416.
98. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. Canadian HIV Trials Network Protocol 010 Study Group. *N Engl J Med*. 1996;335:377–383.

78

Fungal Infections

John Cleary and Russell E. Lewis

CORE PRINCIPLES		CHAPTER CASES
1	Owing to increased numbers of immunocompromised patients, the use of invasive devices, and an aging patient population, invasive fungal infections are the fourth most common nosocomial infection.	
2	Yeast infections are generally easier to treat than mold infections. However, mortality is still significant for both types of infection, even when treated appropriately.	**Table 78-2**
3	Most common risk factors for acquiring mycotic infections include immunocompromised host, the use of broad-spectrum antibacterials, and	**Case 78-3 (Questions 1, 3)**

	breakdown of physical barriers including invasive catheterization.	
4	Diagnostic tools (ie, serum galactomannan or β-glucan) can be useful as monitoring parameters for therapeutic outcome assessment.	**Case 78-3 (Question 2)**
5	The Infectious Disease Society of America (IDSA) and the Mycoses Study Group are important sources for guidelines and evidence-based approaches to therapy.	**Case 78-5 (Question 1)**
6	Dermatophyte infection is most commonly associated with *Tinea* ringworm, and the most effective antifungal agents include itraconazole and terbinafine.	**Case 78-1 (Questions 1–3)**
7	Sporothrix is one of the most common fungal pathogens associated with subcutaneous infections. Amphotericin, terbinafine, and itraconazole are useful treatments.	**Case 78-2 (Questions 1–3), Figure 78-1**
8	Candida represents the most common cause of systemic fungal infection in hospitalized patients. Candidemia must be treated promptly and appropriately. Delay in treatment or failure to adhere to IDSA guidelines results in a significant increase in mortality. Fluconazole and echinocandins are the most recommended prophylaxis and therapies for disseminated candidiasis.	**Case 78-3 (Questions 1–4, 11), Tables 78-4–78-6**

9	Fluconazole, although reliable against *Candida albicans*, is less reliable against certain non-albicans Candida species, including *Candida glabrata* and *Candida krusei*.	**Case 78-3 (Question 5)**
10	Conventional amphotericin is associated with significant infusion-related adverse events, nephrotoxicity, and electrolyte abnormalities. Consequently, other agents, including lipid-based amphotericin B, triazoles, and echinocandins, are drugs of choice for most deep-seated fungal infections.	**Case 78-3 (Questions 6–10), Table 78-3**
11	In patients with yeast identified in urine, the selection of drug therapy for a simple candiduria versus organ infection as a result of disseminated candidiasis is complicated by difficulties with diagnostics.	**Case 78-4 (Question 1)**
12	Blastomycosis, histoplasmosis, and coccidioides are associated with endemic infection from specific geographic areas. Long-term treatment with polyenes and/or azole antifungals is useful in the management of these diseases.	**Case 78-5 (Questions 1–3)** **Case 78-6 (Questions 1–3)** **Case 78-7 (Questions 1–3), Figures 78-2–78-4, Table 78-7**
13	Aspergillus is the most significant fungal pathogen associated with severely immunocompromised patients. Aggressive, immediate treatment with voriconazole alone or in combination with other antifungals is the most	**Case 78-8 (Questions 1–3), Figure 78-5, Table 78-8**

	effective therapy for disseminated disease.	
14	*Cryptococcus neoformans* is associated with opportunistic infection, particularly in acquired immunodeficiency syndrome (AIDS), and the central nervous system (CNS) is a common site of infection. Initial treatment of meningitis in AIDS should include amphotericin B plus flucytosine, followed by long-term fluconazole.	**Case 78-9 (Questions 1–3)**

INTRODUCTION

Mycotic (fungal) infections are now the fourth most commonly encountered nosocomial infection. Attributable mortality associated with invasive yeast infections can approximate 40%, whereas molds typically double that observed rate (ie, invasive aspergillosis). This increase can be attributed, in part, to the growing numbers of immunocompromised hosts as a result of organ transplants, cancer-chemotherapy–associated neutropenia, and acquired immunodeficiency syndrome (AIDS). This chapter reviews the mycology, diagnosis, and pharmacotherapeutics for common mycotic infections. For a more in-depth presentation of the basic biology of fungi, as well as the epidemiology, pathogenesis, immunology, diagnosis, and monitoring of mycotic infections, see *Clinical Mycology*.[1] Referred to Chapter 65, Central Nervous System Infections; Chapter 66, Endocarditis; Chapter 70, Intra-Abdominal Infections; Chapter 73, Osteomyelitis and Septic Arthritis; Chapter 75, Prevention and Treatment of Infections in Neutropenic Patients; Chapter 76, Pharmacotherapy of Human Immunodeficiency Virus Infection; and Chapter 77, Opportunistic Infections in Patients Living With HIV, for detailed pharmacotherapy in these human pathologies.

MYCOLOGY

Morphology

The pathogenic fungi that infect humans are nonmotile eukaryotes that are reproduced by sporulation, and they exist in two forms: filamentous molds and unicellular yeasts. These forms are not mutually exclusive, and depending on the growth conditions, a fungus may exist in one or even both of these forms (**Table 78-1**).

Table 78-1
Organism Classification

Hyphae (Molds)
Hyalohyphomycoses *Aspergillus* species, *Pseudallescheria boydii* *Dermatophytes*: *Epidermophyton floccosum, Trichophyton* species, *Microsporum* species **Phaeohyphomycoses** *Alternaria* species, *Anthopsis deltoidea*, *Bipolaris hawaiiensis, Cladosporium* species, *Curvularia geniculata*, *Exophiala* species, *Fonsecaea pedrosoi*, *Phialophora* species, *Fusarium* species **Zygomycetes** *Rhizopus* spp., *Mucor* spp., *Rhizomucor* spp. *Absidia corymbifera*
Dimorphic Fungi
Blastomyces species, *Coccidioides* species, *Paracoccidioides* species, *Histoplasma* species, *Sporothrix* species
Yeasts
Candida species, *Cryptococcus neoformans*

The dimorphic fungi (eg, *Histoplasma capsulatum* and *Blastomyces dermatitidis*) grow as a mold in nature (27 °C) but quickly convert to the pathogenic yeast form after infecting the host (37 °C). This mycelium-to-yeast conversion is an important factor in the pathogenesis of disease caused by these organisms. Other pathogenic fungi, such as *Aspergillus* species, grow only in a mold

form, whereas *Cryptococcus neoformans* usually grows in a yeast form. *Candida* species grow with a modified form of budding, whereby newly budded cells remain attached to the parent cells and form pseudohyphae. Fungi are aerobic and are easily grown on routine culture media similar to that used to grow bacteria. Most fungi grow best at 25 °C to 35 °C. Fungi that cause only cutaneous and subcutaneous disease grow poorly at temperatures >37 °C. This temperature-selective growth explains, at least in part, why these organisms rarely disseminate from a primary focus in the skin or subcutaneous tissues.

Classification

Fungal infections are best classified by the area of the body infected (**Table 78-2**). Superficial mycoses involve only the outermost keratinized layers of the skin (stratum corneum) and hair. The cutaneous mycoses extend deeper into the epidermis and may also infect the nails. The subcutaneous mycoses infect the dermis and subcutaneous tissues; entry into these sites is by the inoculation or implantation of dirt or vegetative matter. The systemic mycoses cause disease of the internal organs of the body. Standard definitions that are useful in daily patient care for invasive fungal infections have been developed for epidemiologic and clinical trials. The guidelines are referenced under each infection. The respiratory tract is the most common primary portal of entry, and lung infection may be symptomatic or asymptomatic. Systemic infection with *Candida* usually results from a primary focus on the gastrointestinal (GI) tract or skin. In each case, the organism may spread hematogenously from the primary focus throughout the body, resulting in disseminated disease. The opportunistic mycoses occur primarily in the immunocompromised host and require immediate and aggressive treatment. The list of fungi that cause opportunistic infection has expanded, especially with the AIDS epidemic; however, the now commonplace use of highly active antiretroviral therapy has resulted in some decrease in this incidence.[2] The nonopportunistic

fungi (primary pathogens) usually cause disease in the immunologically normal host. Some primary pathogens, however, result in unique clinical syndromes when infection occurs in the immunocompromised host, such as histoplasmosis in AIDS.[1]

Table 78-2
Clinical Classification of Mycoses

Classification	Site Infected	Example	Potential Gene Deficiency
Superficial	Outermost skin and hair	Malasseziasis (tinea versicolor)	
Cutaneous	Deep epidermis and nails	Dermatophytosis	
Subcutaneous	Dermis and subcutaneous tissue	Sporotrichosis	
Systemic	Disease of more than one internal organ		
Opportunistic		Candidiasis	Mannose-binding lectin-1 Toll-like receptor 4
		Cryptococcosis	Dectin-1
		Aspergillosis	
		Mucormycosis	
Nonopportunistic		Histoplasmosis	
		Blastomycosis	
		Coccidioidomycosis	Interferon-γ receptor 1 Dectin-1 Mannose-binding lectin-1

Pathogenesis of Infection

ENDOGENOUS

Fungal infection can be acquired from both exogenous and endogenous sources. The only pathogenic fungi identified as commensals within the human microbiome are *Pityrosporum orbiculare*, which causes the noninflammatory superficial condition of tinea versicolor, and *Candida* species. Infections with these yeasts primarily develop from the patient's own normal flora (endogenous infection). These endogenous fungal infections of the skin or mucous membranes generally occur when host resistance is lowered, and the organism proliferates in high numbers. Excess heat and humidity, oral contraceptive use, pregnancy, diabetes, malnutrition, and immunosuppression facilitate endogenous local infection by both *Pityrosporum* and *Candida*. Systemic candidal infections occur in the immunocompromised or genetic deficient host (see **Table 78-2**)[3],[4]

when the organism colonizing the patient's skin or GI tract disseminates hematogenously throughout the body.

EXOGENOUS

Exogenous infections occur when the fungus is acquired from an environmental source. In the case of dermatophytes (ringworm fungi), the organism can be acquired from dirt, animals, or another infected individual. The subcutaneous mycoses result from direct inoculation of infected material, often a thorn or other vegetable matter, through the skin. Infections of the skin and subcutaneous tissues by *Aspergillus* and zygomycetes (eg, *Rhizopus*, *Absidia*, and *Mucor*) have resulted from contaminated wound dressings and cast materials.[1,5] Drug-induced disease has been observed secondary to *Saccharomyces cerevisiae* (nutraceutical) administration to healthy and immunocompromised patients or secondary to the administration of a contaminated sterile product (ie, *Exserohilum rostratum*).

Exogenous fungi colonized or carried on the hands of health care workers can infect patients; therefore, handwashing is emphasized for health care workers, particularly in critically ill patients.[6] Other than candidal infections, the systemic mycoses are primarily the result of inhalation of dust contaminated by the infectious spores, with a primary focus on infection in the lungs.

If local or systemic host defenses do not control the primary infection, the organism can spread hematogenously to other organs. Some of the systemic mycoses have defined geographic (endemic) areas where the fungus is more commonly encountered. For example, histoplasmosis and blastomycosis occur most often in the regions of the Red, Mississippi, and Ohio River valleys, whereas coccidioidomycosis is endemic to the southwestern United States and the Central Valley of California.

Host Defenses

Host defenses against fungal infection involve both nonimmune (also known as nonspecific or natural resistance) and immune (also known as specific or acquired resistance) mechanisms. Nonimmune resistance plays a primary role in preventing colonization and invasion of a susceptible tissue. The normal bacterial flora of the skin and mucous membranes prevent colonization (colonization resistance) by more pathogenic bacteria and fungi. Patients treated with broad-spectrum antibiotics are at a greater risk for colonization and infection by fungi. The barrier function of the intact skin and mucous membranes is also an important defense. Skin defects (intravenous [IV] catheters, burns, surgery, or trauma) are risk factors for local invasion and fungemia, especially with *Candida* species. The translocation of yeast from the gut into the peritoneum during the trauma of a motor vehicle accident or post-GI surgery is also commonly associated with these infections. When these physical barriers are breached, the polymorphonuclear leukocyte (neutrophil) and monocytes along with defensive lectins (ie, mannose-binding protein) provide early host defense. The antifungal activity of neutrophils not only involves phagocytosis and intracellular killing but also can include extracellular killing by secreted lysosomal enzymes. Neutropenia is the most common neutrophil defect predisposing to fungal infection, but functional defects of neutrophils, such as those occurring in patients with chronic granulomatous disease of childhood and myeloperoxidase deficiency, have also been associated with an increased frequency of fungal infections, especially with *Candida* and *Aspergillus*. Finally, endothermy/homeothermy and ultimately febrile responses are potent nonspecific immune defenses.

Antibody and complement have a potential role in the prevention of certain fungal infections, but they are not the primary effectors of acquired resistance. Cellular immunity, mediated by antigen-specific T lymphocytes, cytokines, and activated macrophages, is the primary acquired (immune) host defense against fungi. Patients with defective cellular immunity (eg, immunosuppressed organ transplant recipients, patients with lymphoma and leukemia, patients with AIDS, and those treated with corticosteroids or cytotoxic agents) are at the

greatest risk for fungal infection. Severe immunodeficiency often results in poor therapeutic outcome despite appropriate antifungal therapy. An additional factor associated with an increased risk for fungal infection is the use of total parenteral nutrition (TPN).[1] Interestingly, patients with specific T-cell dysfunction (ie, human immunodeficiency virus [HIV] infection) appear to be at an isolated risk for mucosal *Candida* infection, but not systemic infections.

ANTIMYCOTICS

Mechanisms of Action

Table 78-3 lists the U.S. Food and Drug Administration (FDA)-approved topical and systemic antimycotics for the treatment of fungal infections. Griseofulvin and potassium iodide have limited clinical utility and are not used to treat systemic fungal infections. Griseofulvin inhibits growth by inhibiting fungal cell mitosis caused by the polymerization of cell microtubules, thereby disrupting mitotic spindle formation. It has activity only against the dermatophyte fungi. The antifungal mechanism of potassium iodide is unclear. It is effective only in the treatment of lymphocutaneous sporotrichosis.

Table 78-3
Antifungal Agents Approved for Use

Agent (Brand Name)	Formulation
Systemic Agents	
Amphotericin B (Abelcet®, AmBisome®, Amphotec®)	IV
Amphotericin B-deoxycholate (generic)	IV
Anidulafungin (Eraxis®)	IV
Caspofungin (Cancidas®)	IV

Fluconazole (Diflucan®)	IV, tablet, oral suspension
Fluorocytosine (Flucytosine) (Ancobon®)	Capsule
Griseofulvin (generic)	Tablet, oral suspension
Isavuconazole (Cresemba®)	IV, oral capsule
Itraconazole (Sporanox®)	IV, capsule, oral solution
Ketoconazole (Nizoral®)	Tablet
Micafungin (Mycamine)	IV
Posaconazole (Noxafil®)	IV, oral suspension, oral gastroresistant tablet
Potassium iodide	Solution
Terbinafine (Lamisil®)	Tablet, oral granules
Voriconazole (Vfend®)	IV, tablet, oral suspension
Topicals, Class I	
Amphotericin B	Cream, lotion, ointment, oral suspension[a]
Butenafine (Lotrimin Ultra®)	Cream
Butoconazole (Gynazole®)	Vaginal cream
Ciclopirox (Loprox®)	Cream, gel, lotion, shampoo, solution, suspension
Clioquinol (Vioform®)	Cream, ointment
Clotrimazole	Cream, lotion, lozenge, solution, tablet, vaginal cream
Econazole (Spectazole®)	Cream
Ketoconazole (Nizoral®)	Cream, foam, gel, shampoo
Miconazole	Aerosol liquid and powder, buccal tablet, cream, lotion, ointment, powder, suppository, vaginal tablet
Naftifine (Naftin®)	Cream, gel
Nystatin	Cream, mouthwash, ointment, powder, suspension, tablet
Oxiconazole (Oxistat®)	Cream, lotion

Povidone iodine	Aerosol, douche, gel, ointment, solution, suppository
Sodium thiosulfate (Exoderm®)	Lotion
Sulconazole (Exelderm®)	Cream, solution
Terbinafine (Lamisil®)	Cream, spray
Terconazole (Terazol® 7)	Cream, suppository
Tioconazole (Vagistat®)	Ointment
Tolnaftate (generic)	Aerosol, cream, gel, powder, solution
Undecylenic acid	Powder

IV, intravenous.

[a]No longer available in the United States.

The 12 antifungal drugs used commonly for systemic disease fall into five structural classes that act by four mutually exclusive mechanisms. Amphotericin B (AmB) and nystatin (a polyene macrolide) act principally by binding to ergosterol in the fungal cell membrane, effectively creating pores in the cell membrane and leading to the depolarization of the membrane and cell leakage.[7] AmB binds with greater affinity to ergosterol than to cholesterol.[8] This phenomenon is believed to be mediated through both hydrophilic hydrogen bonding and hydrophobic, nonspecific van der Waals forces. Investigations using P(^{32}) nuclear magnetic resonance spectroscopy document that the presence of the double bond in the side chain of ergosterol (not present in cholesterol) accounts for the greater affinity of AmB for ergosterol.[7] AmB, however, also binds to sterols of mammalian cells (ie, cholesterol), which may account for most of the toxic effects of AmB or reduced toxicity (ie, circulating cholesterol). Alteration in the lipid content of the pathogen's membrane may play a role in the development of resistance,[9] although other factors are also important.[10] The fungicidal effects of AmB are, however, not only owing to cell leakage resulting from ergosterol binding, but also owing to immune stimulation and oxygen-dependent killing.[8],[11]

5-Flucytosine, a fluorinated cytosine analog, acts principally by inhibiting nucleic acid synthesis. It is actively transported into susceptible cells by the enzyme cytosine permease, where it is deaminated to the toxic metabolite 5-fluorouracil. Fluorouracil, when converted to 5-fluorouridine triphosphate, functions as an antimetabolite. It is incorporated into fungal RNA, where it is substituted for uracil and thereby disrupts protein synthesis. 5-Fluorouracil can also be converted to fluorodeoxyuridine monophosphate, which inhibits thymidylate synthase and thus disrupts DNA synthesis.[12]

The azole antifungals and the allylamines (naftifine and terbinafine) inhibit sterol biosynthesis by interference with either cytochrome (CYP) P450–dependent lanosterol C14-demethylase (azoles) or squalene epoxidase (allylamines), critical enzymes in the biosynthesis of ergosterol.[13],[14] The superior affinity of the triazoles (fluconazole, itraconazole, isavuconazole, posaconazole, and voriconazole) for fungal versus mammalian enzymes, as compared with the imidazoles (ketoconazole and miconazole), accounts for their reduced toxicity and improved efficacy.[13] The consequence of sterol biosynthesis inhibition is a faulty cell membrane with altered permeability. In general, the allylamines and older azoles are fungistatic. The newer triazoles (voriconazole and posaconazole) demonstrate fungicidal activity against some fungal species. The clinical relevance of in vitro fungicidal versus fungistatic action is the subject of considerable debate. Nevertheless, it seems logical that fungicidal action, if it can also be achieved in vivo, is preferred in immunosuppressed hosts.[15]

Lipopeptides, which are potent antifungal agents, include the structural class of echinocandins (anidulafungin, micafungin, and caspofungin). All share a common mechanism. They act by interfering with 1,3-β-D-glucan, preventing the synthesis of essential cell wall polysaccharides that protect the cell from osmotic and structural stresses. The result is inhibition of fungal cell wall biosynthesis. Targeting the cell wall (as opposed to the cell membrane, which is the target of polyene, azole, and allylamine

antifungals) imparts greater selectivity for fungal versus mammalian cells; thus, echinocandins class of antifungals has fewer toxicities than other antifungal classes.[16]

Antifungal Spectrum and Susceptibility Testing

The Clinical and Laboratory Standards Institute (CLSI) recommends standardized broth dilution (M27-A3) and disk diffusion (M44-A2, M44-S3, and M51-A) methods for determining in vitro antifungal susceptibilities for yeasts.[17] These methods stipulate test medium, inoculum size and preparation, incubation time and temperature, end point reading, and quality control limits for AmB, flucytosine, fluconazole, ketoconazole, and itraconazole. Minimum inhibitory concentration (MIC) values for use in clinical interpretation are specified for fluconazole, voriconazole, itraconazole, flucytosine, and the echinocandins against *Candida* species after 24 hours of incubation. For azoles, a susceptible-dose-dependent (S-DD) break point was developed based on data supporting a trend toward better response with higher drug concentrations for isolates with higher MIC.[18] The fluconazole S-DD range is 4 to 8 µg/mL for *C. albicans*, *Candida parapsilosis*, and *Candida tropicalis* and ≤32 mg/L for *C. glabrata*. Itraconazole and voriconazole S-DD ranges are 0.25 to 0.5 mg/L for *C. albicans*. Owing to the rapid development of resistance and limited data on correlation of MIC with outcome for flucytosine monotherapy, proposed interpretive break points for this agent are based on a combination of historic data and results from animal studies. *Candida* isolates with a flucytosine MIC ≤4 µg/mL are considered susceptible, and isolates with MIC >16 µg/mL are considered resistant. Limitations of the M27-A methodology have precluded the development of AmB interpretive break points nor have interpretive criteria been proposed for ketoconazole MIC. Candida are generally susceptible to MIC >0.25 µg/mL and resistant to >1 µg/mL, except for *C. parapsilosis* and *Candida guilliermondii* that have higher susceptibility (>2 µg/mL) and resistant (>8 µg/mL) values. Commercial kits are available for antifungal susceptibility

testing, which use broth microdilution, colorimetric, and agar-based techniques.[19–21] The University of Texas Health Science Fungal Testing Laboratory has historically tested fungi susceptibilities and reports current break points and epidemiologic cutoff values.

An E-Test (AB Biodisk; Piscataway, NJ) is a commercially available antifungal gradient strip. Difficulties in end point determination using this method result from frequent, nonuniform growth of the fungus on the agar medium; yet, when properly performed, correlation between the E-Test and M27-A methods has been satisfactory for the azole antifungal agents against most *Candida*.[19] Other techniques under development for antifungal susceptibility testing for yeasts include flow cytometry and direct measurement of alterations in ergosterol synthesis.[20] Flow cytometry detects the activity of the test antifungal drug through identification of subtle dosage–response effects on specific cell parameters as cells within the prepared inoculum pass through a beam of light. Test results may be available in as few as 4 hours. Interlaboratory reproducibility or correlation between test results and clinical outcomes has not been well studied.[21]

The CLSI-recommended standardized broth dilution method for determining in vitro antifungal susceptibilities for certain spore-producing molds, namely *Aspergillus* species, *Fusarium* species, *Rhizopus* species, *Pseudallescheria boydii*, and *Sporothrix schenckii*, is the M38-A2 method.[15] An E-Test to evaluate mold susceptibilities is also commercially available (AB Biodisk) and correlates well with the CLSI M38-A method for AmB and itraconazole.[22] Colorimetric microdilution, flow cytometry, and agar-based testing methods are under development. Despite these recent advances, the determination of in vitro susceptibilities or resistance in clinical practice is of limited utility and not readily available for yeasts or molds in most institutions.

Susceptibility testing for clinical isolates is not routinely recommended because susceptibility is usually predictable. However, published data on the susceptibility of the identified species of yeasts or molds should guide the clinician’s therapeutic choice. Clinical isolates from patients failing high-dose therapy (ie,

refractory oral pharyngeal candidiasis) or unusual pathogenic yeasts in patients with AIDS can be sent for testing.[20] Testing should be performed in a laboratory where the staff is trained in mycoses. Despite these limitations, certain patterns are common. First, AmB has broad in vitro activity and clinical efficacy against the yeasts and filamentous molds. The echinocandins have cidal activity in vitro versus *Candida* species and static activity for *Aspergillus* species; they are not active in vitro against *Cryptococcus* species and many endemic mycoses.[23] The azole antifungals are generally reliable against the yeasts and most dimorphic fungi. Additionally, itraconazole, voriconazole, and posaconazole have excellent in vitro activity against *Aspergillus* species, with associated clinical efficacy. Unlike other azoles, posaconazole and isavuconazole have some activity in vitro and reported clinical evidence of efficacy against zygomycetes, for which previously only AmB formulations were therapeutic options.[24,25]

Routine susceptibility testing of fluconazole, voriconazole, and an echinocandin against *C. glabrata* is increasingly recommended, especially for isolates from blood normally sterile fluids, tissue, or abscess owing to recent reports of increasing echinocandin and multidrug resistance.[26–28] Additionally, any patient with invasive disease and clinical failure of initial therapy should be considered for susceptibility following consultation with an experienced microbiologist.

New Frontiers for Antifungal Therapy

Various investigative efforts have been directed toward enhancing efficacy, reducing the toxicity, and improving the oral bioavailability of older antifungal drugs. Aerosol delivery of AmB products, itraconazole, voriconazole, and caspofungin in immunocompromised patients has been investigated for the prevention of invasive pulmonary aspergillosis. Reduction in invasive pulmonary aspergillosis was demonstrated in a randomized, placebo-controlled trial of aerosolized liposomal AmB.[29] Additional well-designed clinical

trials are still needed to establish the role of aerosolized delivery of antifungal agents. Optimal antifungal dose and nebulized system required for effective prophylaxis have yet to be established compared with traditional GI regimens (**Table 78-4**).[29–31]

Table 78-4
Antimycotic Prophylaxis Regimens and Approximate Costs

Agent	Dose/Day	Formulation	Recommended Regimen	Cost ($)/day
Selective GI Decontamination				
Amphotericin B	400 mg	Oral suspension	Swish and swallow qid	9.75
Nystatin	4–12 million units	Oral suspension	Swish and swallow qid	38.50–115.25
Systemic				
Clotrimazole	30–80 mg	Troche	tid–qid	125–450
Ketoconazole	200–400 mg	Oral	Daily	0.75–1.50
Itraconazole	200–400 mg	Oral	Daily	18–36.25
Fluconazole	50–400 mg	Oral	Daily	4.50–35.25
Posaconazole	600–800 mg suspension 300 mg daily tablet 300 mg IV	Oral	Daily	175 636

GI, gastrointestinal; qid, four times daily; tid, three times daily.

Source: *Red Book*. PDR Network, LLC; 2011.

Identification of new antifungal compounds has been challenging. One significant barrier is that both mammalian cells and fungal cells are eukaryotes and share many similar biochemical processes, unlike bacterial cells, which are prokaryotes. Traditionally, the drug discovery process depended on the ability to detect compounds (either natural products or synthetic compounds) that selectively inhibit or destroy fungal cells. This process is accomplished by either or both of two approaches: (a) the evaluation of existing compounds (natural or synthetic) for potentially useful antifungal activity and (b) the design and synthesis of new compounds that selectively block fungal targets. Recent advances in genomic sequencing of *C. albicans*, *C. glabrata*, *Aspergillus fumigatus*, *Rhizopus oryzae* (delmar), and *C. neoformans* have facilitated the search for new targets. Other less conventional drug discovery approaches include targeting known traditional virulence factors (eg, adhesions and secreted enzymes). This approach is based on the principle that killing of the microbe need not occur for an anti-infective agent to be

efficacious. Promising lead compounds include nikkomycins, sordarins, lytic peptides, hydroxypyridones, and cathelicidins.[32–35]

SUPERFICIAL AND CUTANEOUS MYCOSES

Tinea Pedis: Treatment

CASE 78-1

QUESTION 1: C.W., a 28-year-old male construction worker, is evaluated for a chronic case of "athlete's foot." He wears boots all day at work and notes intense itching of both feet throughout the day. He has been using tolnaftate powder for 1 week with no real therapeutic benefit. On examination, the web spaces between all the toes are white, macerated, and cracked. A few vesicles are also present over the dorsum of the foot at the base of the toes. Scrapings of the lesions examined as a potassium hydroxide (KOH) preparation reveal branching, filamentous hyphae compatible with a dermatophyte infection. The diagnosis of athlete's foot is made.

What therapeutic options are available for C.W.?

Selection of antifungal therapy should be based on the extent and type of infection.

Superficial or cutaneous infections should initially be approached topically. Any follicular, nail, or widespread (>20% of body surface area) infection should be treated systemically under medical supervision owing to poor penetration of topical applications. Topical antifungals have been reviewed as a class by the FDA advisory review panel on over-the-counter (OTC) antimicrobial drug products and on an individual basis as newer products have been released. To receive a class I recommendation, each agent (or combination) must have been tested in well-designed clinical trials that show that the drug is microbiologically and clinically effective against dermatophytosis or candidiasis with insignificant toxicity (irritation). Class I agents are listed in **Table 78-3**. Class II agents (camphor, candicidin, coal tar, menthol, phenolates, resorcinol, tannic acid,

thymol, and tolindate) are considered to have higher risk–benefit ratios associated with their pharmacotherapy. Class III agents (benzoic acid, borates, caprylic acid, oxyquinolines, iodines, propionic acid, salicylates, triacetin, and gentian violet) lack adequate scientific data to determine efficacy. Topical therapy with any class I agent applied twice daily to the affected area for 2 to 6 weeks should be adequate. Therapy should be titrated to response.

C.W. could continue tolnaftate powder for 2 to 6 weeks or switch to an antifungal cream or lotion (eg, miconazole and terbinafine), and these products should be applied to the web spaces between all the affected toes twice daily. C.W. should also be careful to use nonocclusive footwear (eg, cotton rather than synthetic fiber socks and leather rather than vinyl boots). Application of an absorbent or antifungal powder to his footwear would also be helpful (see Chapter 39, Dermatotherapy and Drug-Induced Skin Disorders).

Tinea Unguium (Onychomycosis): Treatment

Case 78-1, Question 2: If C.W. also had an infection of the toenail (onychomycosis), what additional therapy could be offered to him?

Onychomycosis is typically caused by a dermatophyte, a hyphal fungi, or *Candida*.

Nail scrapings and culture should be performed to help plan initial therapy. Once culture results are known, therapy can be initiated with either terbinafine 250 mg/day or itraconazole 200 mg/day for 6 (fingernail) to 12 (toenail) weeks. In some cases, however, successful therapy of tinea unguium can require 3 to 6 months for fingernails and 6 to 12 months for toenails. Therapy should be considered successful when several millimeters of healthy nail have emerged from the nailfold to the margin of the infected nail or when a 25% reduction in the size of the infected site has been achieved.

For dermatophyte nail or paronychial infections, griseofulvin therapy could be used if an azole or allylamine is contraindicated. Griseofulvin (microsized or ultramicrosized) administered orally at 10

mg/kg/day and titrated to response should be effective.[25] Owing to the large doses given for prolonged periods, C.W. should be monitored closely at each prescription refill for signs and symptoms of adverse reactions. The most common adverse events associated with terbinafine or itraconazole are headache, rash, and GI distress. Griseofulvin is more toxic, often causing hypersensitivity (urticaria, angioedema, and type II hypersensitivity reactions), photosensitivity dermatitis, GI distress, and neurologic complications (headache, paresthesias, and altered sensorium).[25]

Antimycotic pulse therapy is a novel approach to the treatment of onychomycosis. An FDA-approved alternative to daily therapy can now include a course of itraconazole 200 mg twice daily for 1 week in 2 consecutive months for fingernail infections. Double-blind, placebo-controlled trials revealed that this regimen was associated with a 77% clinical response and 73% mycologic response.[36] Overall responses and toxicity to therapy were more desirable with pulse regimens than with traditional regimens. Comparative studies demonstrate promising results for itraconazole pulse therapy for toenail infections[37] and fluconazole pulse therapy administered as a 150- to 450-mg dose once weekly for up to 12 months for mild disease.[38],[39] Relapse rates after pulse (intermittent) terbinafine for 4 months have been frequent, and longer courses of therapy are under study to enhance long-term efficacy.[40] Longer courses of therapy are being evaluated.

Removal of the nail as the sole therapy is not recommended because of the high relapse rate without concomitant systemic therapy. Likewise, IV antifungals are not indicated.

Case 78-1, Question 3: Describe the role of corticosteroids, antibacterials, or other additives to the antimycotic regimen in C.W.

Many patients with superficial, cutaneous, or nail fungal infections will have local inflammation and secondary bacterial infections. Inflammation is primarily a type IV hypersensitivity reaction. Topical corticosteroids in conjunction with antifungals can relieve itching and

erythema secondary to inflammation. Bacterial (*Proteus* or *Pseudomonas* species) superinfection can also occur in these inflamed or macerated areas requiring concomitant topical antibacterial therapy. Pharmaceutical manufacturers of OTC preparations often combine a drying agent or astringent (eg, alcohol, starch, talc, and camphor) to their preparations to increase the desquamation of the stratum corneum. Hyperhidrosis also can be relieved by these pharmaceutical additions. Such combination treatments should not be used routinely, however, because they increase the risk of toxicity and do not increase efficacy. If required for symptomatic relief, they should be used only for the initial days of treatment.

The affected web spaces between C.W.'s toes are macerated and cracked, and vesicles are present at the base of his toes. A topical corticosteroid cream will probably facilitate the healing process and make him more comfortable during the first few days of antifungal therapy. The selection of topical corticosteroid formulations is presented in Chapter 39, Dermatotherapy and Drug-Induced Skin Disorders.

SUBCUTANEOUS MYCOSES

Sporotrichosis

TREATMENT OPTIONS

CASE 78-2

Question 1: O.M., a 62-year-old male, has had a painless, slowly enlarging ulcer on his left hand for the past 4 months. He is an avid gardener but can identify no antecedent local trauma. The primary lesion began as a red papule that slowly enlarged and then ulcerated. At the same time that the ulcer developed, O.M. also noted painless, red nodules that spread proximally up his arm. He denies any chills, fever, weight loss, or cough. The ulcer has slowly enlarged despite the daily application of a povidone iodine ointment and 2

weeks of cephalexin treatment. On physical examination, O.M. is afebrile. A 1.5 cm^2 ulcer is present on the dorsum of the left hand. Extending proximally from the ulcer are a palpable cord and multiple nontender, erythematous nodules distributed linearly up the forearm, elbow, arm, and axilla. A culture of this ulcer obtained 4 weeks ago is now growing *S. schenckii*.

What is the recommended therapy for O.M.?

S. schenckii is the dimorphic fungi found in the soil and on many plants. Infection is usually secondary to inoculation into the skin from a thorn or sharp plant matter. *S. schenckii* infection most commonly causes lymphocutaneous disease (**Fig. 78-1**) as illustrated by this case. Rarely, extracutaneous disease may occur and usually involves the lungs, bones, or joints.

Figure 78-1 Lymphocutaneous sporotrichosis.

HEAT TREATMENT

In the 1930s and 1940s, local heat was applied to very mild plaque or lymphocutaneous disease. Germination rates of this dimorphic fungus can actually be decreased by increased temperature, and heat therapy 1 hour/day for 3 months is effective in 90% of patients with plaques (very mild disease).[41] Heat treatment could be particularly useful in pregnant patients when pharmacotherapy may be contraindicated.

ITRACONAZOLE

Itraconazole is more active in vitro against *S. schenckii* than other imidazoles or saturated solution of potassium iodide. Saturated solution of potassium iodide is seldom used for therapy secondary to treatment-limiting toxicity. Cure rates for sporotrichosis cutaneous and lymphocutaneous disease are >90% with itraconazole 100 to 200 mg/day for 3 to 6 months. For extracutaneous disease, higher dosages of itraconazole (200 mg twice a day [bid]) for 1 to 2 years achieve response rates of 81%, but relapse frequently occurs (27%) after therapy is stopped.[41],[42] Itraconazole is well tolerated in these patients. Patients with extracutaneous disease who are unable to tolerate the higher itraconazole dosages or whose disease continues to progress should be treated with AmB or a lipid-based amphotericin product. A total dose of 2.0 to 2.5 g is most often recommended if conventional AmB is used. Although voriconazole, posaconazole, and ravuconazole demonstrate in vitro activity against *S. schenckii* (albeit less than itraconazole), their role in the treatment of sporotrichosis has not been defined.[43] Neither ketoconazole nor fluconazole is effective in the treatment of sporotrichosis.

TERBINAFINE

Terbinafine has a good in vitro activity against *S. schenckii* and has been used clinically with some success.[44] An unpublished clinical trial comparing 250 or 500 mg bid for 3 months for lymphocutaneous disease appeared clinically equivalent to itraconazole. Adverse reactions include GI distress (dysgeusia, dyspepsia, and diarrhea), skin rash, and weight gain.

Therefore, in the case of lymphocutaneous disease, itraconazole 100 mg/day for a minimum of 3 months is the treatment of choice. If significant improvement is not observed in the first 6 weeks, the itraconazole dosage should be increased to 200 mg/day and continued for 6 months or until both the ulcer and lymphangitis have resolved. Most patients will respond to this dosage, but an occasional patient may require dosages of 300 or 400 mg/day.

Itraconazole Dosing

Case 78-2, Question 2: What instructions should O.M. receive for taking his antifungal agent?

The peak serum concentrations of itraconazole capsules are ninefold higher when the drug is taken with food (0.18 µg/mL with food vs 0.02 µg/mL in fasting subjects).[45] The influence of food on absorption appears to be dependent on food type. High-carbohydrate meals decrease the absorption of itraconazole, and high-lipid-content meals increase itraconazole absorption.[46] Patients who have difficulty eating (eg, patients with AIDS and those with cancer receiving antineoplastic therapy) or with hypochlorhydria may not absorb a sufficient amount from the capsule to achieve therapeutic plasma concentrations after a typical oral dose.[47] Although itraconazole manifests nonlinear serum pharmacokinetics (ie, administering the total dose in two divided doses is associated with higher peak serum concentrations than a single larger dose), there is no clinical benefit in splitting the dose. Therefore, O.M. could be instructed to take his itraconazole capsule with his highest-fat-content meal of the day or itraconazole solution could be substituted to improve absorption.

Itraconazole oral solution is a cyclodextrin formulation that has 55% bioavailability in a fed patient; this increases in a fasting patient (**Table 78-5**). Furthermore, bioavailability of this formulation is not affected by the level of gastric acidity. Average serum concentration in a cohort of patients with advanced HIV infection was 2.7 µg/mL

after a 28-day twice-daily dosing regimen.[48] O.M. should take his itraconazole solution on an empty stomach bid if this formulation is selected.

Table 78-5
Pharmacokinetic Properties of Systemically Active Non-Polyene Antifungals

	Imidazoles			Triazoles				Echinocandins			Other	
Characteristic	**MCZ**	**KCZ[a]**	**ITZ[a]**	**FCZ[a]**	**PCZ[a] Suspension/ tablet**	**ICZ[a] (Cap)**	**VCZ[a]**	**AFG[a]**	**CFG[a]**	**MFG[a]**	**5FC[a]**	**TBF[a]**
Absorption												
Relative bioavailability	>10	75[b]	99.8 (40)[b]	(85–92)[b]		>90	>90[d]	>10	>10	>10	75–90[b]	70
C_{max} (µg/mL)	1.9	3.29	0.63	1.4	0.851/2.76	7.50	2.3–4.7[d]	7.5	12	7.1	70–80	1.34–1.7
T_{max} (hours)	1.0	2.6	4.0	1.0–4.0	3/4	3	>2	1	1	1	>2	1.5
AUC[c] (µg/hour/mL)	ND	12.9 (13.6)	1.9(0.7)	42	8.619/51.62	121.4	9–11 (13)[d]	104.5	97.63–100.5	59.9	ND	4.74–10.48
Distribution												
Protein binding (%)	91–93	99	99.8	11	99	95	58	80	96.5	99.5	2–4	>99
CSF or serum concentration (%)	>10	>10	>10	60	ND	ND	~50	ND	ND	ND	60	>10
Excretion												
β-$t_{1/2}$ (hours)	2.1	8.1[d]	17[d]	23–45	31	130	6	25.6	10	13	2.5–6.0	36
Active drug in urine (%)	1	2	>10	60–80	13	>1	>2	>1	2	1	0	80

AUC, area under the concentration–time curve; C_{max}, maximum concentration; CSF, cerebrospinal fluid; ND, no data; T_{max}, time of maximum concentration; $t_{1/2}$, half-life.

[a]Given parameters are estimated from the administration of currently recommended doses. Miconazole (MCZ) 7.4–14.2 mg/kg/day (500–1000 mg) parenterally; ketoconazole (KTZ) 2.8 mg/kg/day orally (200 mg); itraconazole (ITZ) 1.4–2.8 mg/kg/day orally (100–200 mg); fluconazole (FCZ) 0.7–1.4 mg/kg/day orally; voriconazole (VCZ) and posaconazole (PCZ) 400 mg twice-daily orally; or 300 mg twice-daily day 1, then 300 mg daily; isavuconazole (ICZ) 200 mg (372 mg isavuconazonium sulfate) three times daily for 48 hours, then 300 mg daily anidulafungin (AFG) 200 mg parenterally; caspofungin (CFG) 70 (50) mg parenterally on day 1 (2–14); micafungin (MFG) 70 mg parenterally; flucytosine (5FC) 150 mg/day parenterally; and terbinafine (TBF) 250 mg/day orally.

[b]With meals (fasting), absorption altered by gastric acidity.

[c]Dose-dependent and/or infusion-dependent.

[d]Absorption decreased when administered with high-fat meal; C_{max} and AUC reduced by 34% and 24%, respectively.

Case 78-2, Question 3: How would instructions for taking itraconazole capsules be modified if O.M. were achlorhydric as a result of medications or AIDS gastropathy? Should azole serum concentrations be monitored for an assessment of efficacy?

Itraconazole capsules, as with ketoconazole, require an acidic environment for dissolution and absorption. Thus, patients who are achlorhydric, as a result of medications, surgery, or underlying disease (eg, AIDS gastropathy), may not absorb itraconazole capsules adequately.[47],[49] The use of ketoconazole in achlorhydric patients has historically required concomitant administration of 4 mL, 0.2 N hydrochloric acid aqueous solution. Etching of tooth enamel by the acid can occur; thus, other alternatives have been explored. The administration of ketoconazole and itraconazole with a low pH liquid (eg, 8–16 fluid ounces of a carbonated cola beverage or orange juice) improves absorption in 65.2% of healthy patients who are achlorhydric or taking H_2-blockers.[49] Refer to Azole–Drug Interactions section for more detailed information on problematic therapeutic combinations.

Voriconazole does not require an acidic environment for adequate oral absorption, but voriconazole should be administered 1 hour before or after meals because high-fat meals may reduce voriconazole serum concentrations.[50] In contrast, posaconazole plasma concentrations are fourfold higher after administration with food or a high-fat nutritional supplement. A newer formulation of posaconazole, which releases the drug in a pH-dependent manner in the duodenum, is not dependent on low gastric pH for dissolution and does not require administration with food to achieve therapeutic levels.[51–53] Isavuconazole is unique among triazole antifungals because it is administered IV or orally as a prodrug (isavuconazonium sulfate), which is rapidly cleaved by plasma esterases to the active antifungal, isavuconazole. Absorption of the prodrug is relatively complete (>90% bioavailability) and does not require low gastric pH or coadministration with food. IV isavuconazonium is water-soluble and, unlike voriconazole or posaconazole parenteral formulations, is not solubilized in hydroxypropyl-β-cyclodextrin.

Because serum ketoconazole, itraconazole, and voriconazole concentrations <0.25 to 1.0 μg/mL have been associated with an increased risk of treatment failure and increased mortality in

neutropenic patients, therapeutic drug monitoring is justified in patients in whom therapy is failing or suspected risk factors for low blood levels (ie, poor gut function, drug interactions, and pediatric patients) or, in the case of voriconazole, suspected CNS toxicity, which is more frequent in patients with trough levels exceeding 5.5 μg/mL.[54] Similarly, posaconazole serum concentrations <0.7 μg/mL have been associated with an increased risk of breakthrough infection during prophylaxis, and trough or random levels approaching 1.5 μg/mL have been associated with an improved probability of treatment response in documented invasive aspergillosis.[54] Serum antimycotic concentrations may be more easily monitored in the future because assays, potentially performed at the point of care (patient bedside or clinic), become available, and correlations between concentration and efficacy or toxicity are more clearly established.[55]

SYSTEMIC MYCOSES

Candida Infection

CASE 78-3

Question 1: L.K., a 21-year-old, 68-inch (172.72 cm), 170-pound (77.11 kg), otherwise healthy male, was admitted to the hospital 16 days ago after a gunshot wound to the abdomen. He has undergone three exploratory laparotomies with repair and resection of damaged small intestine. He was placed on TPN to allow his bowel to rest and received stress doses of methylprednisolone since day 6 in the hospital. Three days ago, he exhibited a fever of 102.38 °F (39.1 °C) and chills; his blood pressure of 100/70 mm Hg had dropped more than 30 mm Hg (systolic). Vancomycin and meropenem were promptly begun after obtaining blood cultures. Despite 3 days of antibiotics, he remains febrile. His physical examination reveals a Hickman catheter in the right subclavian vein that is functioning normally; no inflammatory changes are evident at the exit site. A single erythematous nodule about 0.5 cm wide is noted near the left wrist. The funduscopic examination of both eyes is normal. A

chest radiograph is also normal. The white blood cell (WBC) count is currently 10,950 cells/μL, and renal function is normal.

What subjective and objective data in this case suggest a possible *Candida* infection?

EPIDEMIOLOGY

Although it is possible that L.K. might be infected with bacterial pathogens not susceptible to vancomycin and meropenem, the possibility of a candidal infection should be considered. *Candida* species are the most common nosocomial fungal pathogens. *Candida* species were responsible for 72.2% of mycoses in hospitalized cases, and *C. albicans* accounted for 55% of these cases in the Centers for Disease Control, National Nosocomial Infections Surveillance System. Attributable mortality associated with disseminated candidiasis from all species is 38% and it is ~12% for extremely low-birth-weight neonates.[56] These statistics may underestimate the true occurrence because systemic candidiasis is difficult to diagnose. To reinforce this point, the diagnosis of systemic candidal infection is made in 30% to 50% of neutropenic patients with hematologic malignancies at postmortem.[57] Therefore, the morbidity for systemic candidiasis may be even higher because of the limited ability to diagnose systemic disease.

CHARACTERISTICS

The diagnosis and monitoring of therapeutic outcomes for systemic candidal infection are difficult because the characteristics of systemic candidal infection are subtle. Salient clinical features include constitutional symptoms (eg, fever, chills, and hypotension) and evidence of end-organ dissemination, such as nodular erythematous skin lesions, endophthalmitis, liver abscess, and spleen abscess. In addition, 50% of patients or fewer will have a single positive *Candida* blood culture. The Mycoses Study Group uses a single positive culture from a sterile body site and hypotension (systolic blood pressure [SBP] <100 mm Hg or an SBP decrease >30 mm Hg) or abnormal temperature (<35.5 °C or >38.6 °C) on one occasion or

>37.8 °C on two separate occasions more than 4 hours apart), or inflammation at an infected site as diagnostic criteria.

RISK FACTORS

Risk factors for candidemia include central venous catheters, broad-spectrum antibiotic use, extensive surgical procedures, *Candida* colonization, TPN, pancreatitis, neutropenia or neutrophil dysfunction, and immunosuppression (eg, premature infants, burn patients, patients with mannose-binding lectin deficiency, and patients with AIDS).[58]

L.K. has chills, a temperature of 102.38 °F (39.1 °C), and is hypotensive. He is probably immunosuppressed as a result of multiple surgical procedures and receipt of corticosteroids. His Hickman catheter is a possible portal of entry, and his broad-spectrum antibiotic therapy with vancomycin and meropenem should be adequate for most bacterial pathogens. Because L.K. still has manifestations of an infection despite 3 days of antibiotics, additional diagnostic studies are warranted.

DIAGNOSTIC TESTS

Case 78-3, Question 2: What diagnostic tests could be ordered for L.K. to evaluate a possible fungal infection?

The diagnosis of fungal infection may be made with varying levels of certainty. Sometimes, the diagnosis is absolutely certain, such as the isolation of a pathogenic fungus from a clinical specimen in an immunocompromised patient. Such a finding is referred to as a definitive or microbiologically confirmed diagnosis. At other times, only a high probability of infection can be determined, that is, a presumptive diagnosis. To illustrate this, a patient with a chest radiograph showing nodular lesions and a high complement fixation (CF) antibody against *H. capsulatum* would have a presumptive diagnosis of histoplasmosis. This finding may be as certain a diagnosis as is possible without performing a more invasive

procedure to obtain lung tissue. In this event, a trial of drug therapy can be undertaken on the presumptive diagnosis alone. A diverse spectrum of tests is available for clinicians to diagnose and monitor therapeutic responses.

Direct examination

Direct examination of the specimen is often useful in diagnosing fungal infection. Traditionally, the specimen is treated with 10% KOH to digest the cells and debris, resulting in clear visualization of the hyphae or yeast. Treatment of cerebrospinal fluid (CSF) specimens with KOH is not necessary because this fluid is naturally clear. India ink can be added to CSF to increase contrast and outline the organisms. Calcofluor white, a fluorescent fabric brightener that binds to fungi and fluoresces brilliantly when viewed under the ultraviolet microscope, can also be used to assist in the recognition of fungal elements.

Histologic examination of biopsy specimens is an important tool for diagnosing and monitoring fungal infection, but identifying the exact fungus may be difficult. This is because only the tissue phase can be observed, and the fungal organisms in the specimen may be few. Because recognizing a fungus in hematoxylin-stained or eosin-stained sections may be difficult, a number of special stains have been developed.[58] Periodic acid–Schiff staining binds linked sugar groups in the fungal cell wall. This intense magenta staining makes visualization of the fungal form easier. Likewise, several silver precipitation stains (eg, Gomori methenamine silver) rely on the presence of a charged fungal surface to reduce oxidized silver to metallic silver. This process coats the fungus with a black layer, again outlining the form.[59] The mucicarmine stain imparts a deep red color to complex polysaccharides, such as mucin, which can stain the thick capsule of *C. neoformans*. Because no other yeast has a positive mucicarmine stain, the definitive diagnosis of cryptococcosis can be made.[60] The size of the organism, manner of budding, and the presence or absence of septae all assist in the diagnosis.

Monoclonal antibodies against many fungi are now available. Immunohistochemical procedures using these sera on biopsy specimens allow for the identification of a number of fungal pathogens.[60] Reagents for in situ oligonucleotide probe hybridization to detect fungi in tissue are being developed and will also be extremely helpful.[61]

Culture

The most definitive method for diagnosing or monitoring a fungal infection is using culture. Specimens should be inoculated onto several different types of fungal media, some of which contain antibiotics to inhibit bacterial overgrowth. Swab specimens have a very low yield, especially for hyphal fungi, and should be avoided in follow-up cultures. Yeast may grow rapidly and be isolated within 24 to 48 hours, but many fungi grow slowly, and 4 to 6 weeks of incubation may be necessary to isolate and identify the organism. After growth, yeasts are usually recognized by their patterns of metabolic activity on a variety of substrates, whereas mycelial organisms may produce characteristic spores and fruiting bodies that are used for identification. Occasionally, a mycelial organism will be slow in producing recognizable spores, and immunologic testing for a characteristic isoantigen may be used for identification. A peptide nucleic acid fluorescence in situ hybridization test more rapidly identifies *C. albicans* from blood-culture bottles.[62] It is unclear how cost-effective this test will be compared with traditional germ-tube testing.

Antigen detection

Fungi synthesize polysaccharides that cannot be broken down by human enzymatic systems. These polysaccharides can accumulate within the body and can be excreted in the urine. These fungal antigens can be detected by using antibodies that specifically recognize a particular species of fungus, thereby providing a diagnosis. The most commonly used antigen detection test is a latex agglutination test for cryptococcal antigen. This assay can be

performed on serum or CSF. Antigenemia is present in 80% to 100% of patients with culture-proved cryptococcal meningitis. This test can also be used to monitor patient response to therapy by determining the end point dilution for the positive reaction and following this end point over time when the patient is treated. If treatment is successful, the titer will decline.[63],[64]

Tests (quantitative polymerase chain reaction, enzyme-linked immunosorbent assay [ELISA], and latex agglutination) for other fungal antigens are also not established. Latex particle agglutination tests to detect candidal antigens are available, but their use has not been clearly demonstrated. Assays for detecting *H. capsulatum* antigen in serum and urine have been reported.[65] Antigen can be detected in the blood of 50% of patients and in the urine of 80% to 90% of patients with systemic histoplasmosis. Patients with blastomycosis and paracoccidioidomycosis, however, may also have positive cross-reactions. The ELISA for the detection of *Aspergillus* galactomannan antigen and *Candida* (1–3)-β-D-glucan has reported sensitivity (63%) and specificity (96%) of two consecutive (1–3)-β-D-glucan results >7 pg/mL, which is clinically useful. Using these tests can result in a shorter time to diagnosis and leads to a significantly shorter time of illness compared with other diagnostic tests. β-Glucan is most valuable for its negative predictive value.[66] Considering the presence of false-positives or false-negatives, it is unknown whether these assays will improve diagnostic capability for patients at a risk for these infections. False-positives may be caused by a myriad of products (IgG, albumin, cellulose filters, or gauze bandages) with variable outcomes associated with piperacillin/tazobactam. Increasing or decreasing values can be used to monitor clinical response to antifungal therapy.[62]

Antibody detection

The detection of antibody can be useful for some fungal diseases, but not for others. Serologic diagnosis of systemic candidiasis is complicated because most people have anti-*Candida* antibodies. A rising titer is not specific for infection and may indicate only

colonization. Furthermore, dissemination of *Candida* is most likely in people who are immunocompromised and, therefore, may not respond by producing antibody.[67] On the other hand, seropositivity can be demonstrated in more than 90% of patients with symptomatic histoplasmosis.[68] The most important serologic tests use the CF, immunodiffusion, and enzyme immunoassay (EIA) techniques. The appropriate evolution of serologic results requires an understanding of the sensitivity, specificity, and predictive value of each methodology. In general, serologic tests allow only a presumptive diagnosis of mycotic infections.

Although any of the aforementioned tests could be ordered for L.K., a direct examination of his blood and urine specimens along with an assessment of signs and symptoms of disseminated candidiasis is a reasonable first step in his evaluation. A blood specimen from L.K. should also be cultured on different fungal media. Because a candidal infection is suspected, the culture could isolate *Candida* within 24 to 48 hours. Cultures and histopathologic examination of a biopsy specimen of skin lesions are often helpful not only in confirming a diagnosis of disseminated candidal infection but also in monitoring response to therapy. The other fungal tests previously described need not be ordered immediately and should await the results from the direct examination and culture.

NECESSITY OF TREATMENT

Case 78-3, Question 3: The clinical laboratory reports that a single blood culture obtained 2 days ago is growing *Candida* species. Why is therapy necessary in L.K. with only a single positive blood culture?

Case–control studies of candidemia report an 85.6% mortality rate in untreated patients compared with a 41.8% mortality rate in patients who received early treatment. Isolation of *Candida* from a patient's bloodstream requires the initiation of immediate antifungal therapy. Delays in therapy are associated with a significant increase in mortality. In fact, delaying therapy 24 hours from the time a blood

culture is positive or failure to follow the Infectious Disease Society of America (IDSA) treatment guidelines increases mortality by nearly 50%.[69–71] Elimination of risk factors may improve the clinical outcome of candidemia, and the removal of central venous catheters reduces morbidity and mortality.[72],[73] Although discontinuation of a centrally inserted catheter may complicate drug administration, it still should be removed. L.K.'s other risk factors (eg, broad-spectrum antibacterials) are perhaps of even greater importance.

TREATMENT OPTIONS AND COMBINATION THERAPY

CASE 78-3, QUESTION 4: What therapeutic options are available to treat candidemia? Which option would be best for L.K.?

Therapeutic options are individualized and based on the competence of a patient's host defenses. In immunocompetent patients, AmB formulations, an echinocandin, or a triazole decreases morbidity and mortality associated with this disease.[74–78] Echinocandins have been demonstrated as effective as AmB formulations in neutropenic and non-neutropenic patients; however, AmB clears the bloodstream more rapidly.[79],[80] In the largest, well-controlled comparative trial, 206 non-neutropenic patients were randomly assigned to AmB 0.5 to 0.6 mg/kg/day or fluconazole 400 mg/day for 14 days. Mortality was <9% in both the groups with no significant difference in successful outcomes (AmB, 80%; fluconazole, 72%). Less toxicity was noted in the fluconazole group, however.[75] Therefore, fluconazole 400 mg/day is as effective as AmB for non-neutropenic patients infected with susceptible *Candida*. Candidemic (or other mycotic infections discussed in this chapter) patients who are clinically stable and have no evidence of deep-seated infection should be initiated on a triazole or an echinocandin for at least 14 days. Patients who cannot be treated with an echinocandin or an azole can be treated with AmB 0.5 to 1.0 mg/kg/day or 3 to 5 mg/kg/day of a lipid formulation of AmB. Alternatively, a comparison of micafungin (100 or 150 mg) with

caspofungin revealed no difference with micafungin 100 mg and caspofungin after 10 days of therapy. However, micafungin 150 mg trended toward poorer responses.[81]

High-dose fluconazole (12 mg/kg/day) alone or in combination with AmB for a minimum of 3 days, followed by step-down therapy to fluconazole, was evaluated. Outcomes were not different between treatment groups and consistent with the previously reported success rates. Notably, the fluconazole treatment group had higher Acute Physiology and Chronic Health Evaluation (APACHE II) scores, making the evaluation of the comparison difficult.[79] In contrast, in another clinical trial, the combination of AmB and flucytosine was suggested to be more effective than single-agent therapy.[82,83] An AmB-containing regimen may be more effective in patients with APACHE II scores between 10 and 22.[79]

L.K. could be treated with an echinocandin, with the total duration based on clinical response and resolution of positive cultures (see Case 78-3, Question 6). Therapy typically should be continued for 14 days post–last positive blood culture. Some clinicians check cultures daily to assess this end point. Efficacy should be monitored using patient-specific signs and symptoms of candidemia. Combination therapy can be considered in those patients who are not responding clinically. More importantly, a complete examination for focal sites of infection (septic thrombi or intra-abdominal abscess) should take place.

CASE 78-3, QUESTION 5: This fungal species has now been identified as *C. non-albicans*. How does this affect the therapeutic options for L.K.?

Historically, the isolation of a non-albicans *Candida* from blood has resulted in a therapeutic dilemma caused by common in vitro resistance, which has been associated with poor clinical outcomes in animal models and uncontrolled case reports. Intrinsic resistance (ie, *Candida lusitaniae* to AmB, *C. parapsilosis* to echinocandins, and *Candida krusei* to fluconazole) or acquired resistance (*C. tropicalis* or *glabrata* against fluconazole) has been reported.[76,82,83] Acquired

in vitro fluconazole drug resistance is probably associated with altered fungal cell membrane permeability, antifungal efflux pumps, and changes in CYP450 enzymes. In observational studies, fluconazole resistance in vitro has been 9%.[76],[82],[83] A large, multicenter study of 232 non-neutropenic patients was unable, however, to demonstrate a relationship between yeast MIC and patient outcome.[76] An inability to demonstrate a relationship is probably a result of a limited understanding or inadequate management of risk factors for infection. For example, the removal of a colonized IV catheter is probably a more important predictor of outcome than the MIC of the isolated yeast. A disturbing increase in acquired *C. glabrata* resistance to the echinocandins via an *FKS* gene, first reported in 2008, should be suspected in echinocandin treatment failures.[27],[84]

Therefore, the true rate of acquired clinical resistance to azoles and ultimate failure is unknown. Vigilant monitoring and aggressive therapy of infections caused by *Candida non-albicans* are recommended. In patients in whom susceptibilities are available, fluconazole should be avoided when the MIC is >16 µg/mL.

AMPHOTERICIN FORMULATIONS

Dosing

Case 78-3, Question 6: How should amphotericin B formulation be dosed and administered to L.K.?

The AmB formulation dose and duration of therapy should be individualized based on the severity of infection and immunocompetence of the patient. Once the patient is stable, therapy should be changed to one of the applicable regimens discussed previously. The dose of AmB formulations should be based on lean body mass. Owing to the difficulty in measuring lean body mass, many clinicians, however, use ideal body weight. Tissues that contain large numbers of macrophages sequester significant amounts of AmB (liver, 17.5%–40.3%; spleen, 0.7%–

15.6%; kidney, 0.6%–4.1%; and lung, 0.4%–13%), but it does not distribute well into adipose tissue (>1.0%).[77],[78] In fact, AmB formulations bound to cholesterol have been shown to bind to clathrin-coated pits (low-density lipoprotein receptors or receptors of endocytosis) on cells, facilitating intracellular incorporation and possibly reducing renal toxicity.[85] Because L.K. is 68 inches (172.72 cm) tall and not obese, his ideal body weight should be about 154.32 pounds (70 kg). Therefore, generic AmB 35 mg/day (0.5 mg/kg) should be initiated because L.K. is not clinically stable and may require increased doses. Half of the full dose should be given on the first day of therapy and the full dose given on subsequent days. In more seriously ill patients, the full dose of generic AmB can be initiated immediately. Although the optimal dosing regimen to initiate generic AmB is not well established, most clinicians gradually titrate the dose upward to minimize infusion-related reactions. Peak AmB serum concentrations achieved after parenteral administration are a function of dose, frequency of dosing, and the rate of infusion. When the AmB total dose is <50 mg, the serum concentration is directly proportional to the dose; doses >50 mg are associated with a plateau in serum concentrations. After administration, AmB undergoes biphasic elimination: Peak serum concentrations drop rapidly (initial $t_{1/2}$, 24–48 hours), but low concentrations (0.5–1.0 μg/mL) are detectable for up to 2 weeks (terminal $t_{1/2}$, 15 days).[86] The long terminal elimination half-life has been used as a justification for the common practice of less frequent AmB dosing, in which twice the daily dose is given every other day. Every-other-day regimens have not been carefully evaluated but are rationalized based on the potential for reduced nephrotoxicity. Administration of generic AmB 0.5 mg/kg/day or 1.0 mg/kg every other day results in trough AmB concentrations with sufficient postdose antifungal effects that inhibit the common pathogenic fungi.[87] Once L.K.'s clinical status has improved, the potential for renal toxicity could outweigh the concerns of potential reduced efficacy, and implementation of AmB every-other-day therapy should be considered.

Infusion reactions

Case 78-3, Question 7: L.K. has no problems except for fevers and shaking chills that occur during his 6- to 8-hour AmB infusion for the past 3 days. He has been receiving acetaminophen 650 mg 30 minutes before AmB infusion, but he has refused today's AmB dose. What measures can be taken to minimize these infusion-related reactions?

Adverse reactions, which are common with AmB formulation administration, are best classified as infusion-related, dose-related, or idiosyncratic reactions. Infusion-related reactions include an acute symptom complex of fever, chills, nausea, vomiting, headache, hypotension, and thrombophlebitis. Dose-related reactions also can be acute (eg, cardiac arrhythmias) or chronic (eg, renal dysfunction with secondary electrolyte imbalances and anemia). Premedication to prevent AmB formulation, infusion-related reactions, and a test dose of AmB formulations are not needed for L.K. Most practices of premedicating are performed out of ritual rather than predicated on a scientific study.[88] Test dosing with 1 mg before the first dose is not currently used because of the immeasurably low incidence of anaphylactoid reactions. Until clinical trials clarify the risk–benefit ratio of premedications, concomitant therapy should be restricted to acetaminophen for fever or headache and heparin to prevent thrombophlebitis when possible.

Many infusion-related reactions are mediated by AmB-induced cytokine (interleukin-1β, tumor necrosis factor, and prostaglandin E_2) expression by mononuclear cells.[89,90] Hydrocortisone is extremely effective in suppressing cytokine expression,[89] and it also blunts the fever and chills associated with AmB formulations.[91] Hydrocortisone, however, does not reduce the frequency of chronic dose-related toxicity such as renal insufficiency, and corticosteroid-induced immunosuppression could decrease AmB fungicidal activity.[92] Nonsteroidal anti-inflammatory drugs (NSAIDs) also prevent fever, most likely by the suppression of prostaglandin E_2 expression.[93] NSAIDs, however, cannot be recommended for routine use because

of their potential for additive nephrotoxicity when used with AmB formulations.

The mild-to-moderate elevations in temperature and the other infusion-related symptoms usually subside when the infusion is completed, and tolerance to these effects develops over 3 to 5 days. L.K. initially should be counseled that these reactions will abate over the next few days without intervention. If assessment of the reactions suggests the need for more aggressive premedication, a short course of hydrocortisone 0.7 mg/kg prior to AmB or added to the infusion bag should be initiated.[91] Meperidine 25 to 50 mg by rapid IV infusion reduces AmB-induced rigors and can be repeated every 15 minutes as required while monitoring for signs and symptoms of opiate toxicity. Administration of an average meperidine dose of 45 mg has been found to resolve chills three times faster than placebo.[94]

Fast generic AmB infusion rates (> normal 4–6 hours) are associated with the earlier onset of infusion-related reactions, but not with more severe infusion reactions.[95],[96] Many patients prefer rapid infusions (1–2 hours) because the infusion-related reactions abate quickly on the completion of the AmB infusion. Electrocardiographic evaluations of 1-hour infusions indicate that this rate of polyene infusion is safe at currently recommended doses in patients without renal or heart disease. Rapid infusions are not safe in all patients, however, because cardiac arrhythmias appear to be dose- and infusion rate–related. If infused too rapidly, high serum concentrations of AmB can precipitate severe cardiac adverse events. Arrhythmias have been reported most often in patients who are anuric or who have previous cardiac disease.[97] Continuous infusion is not recommended based on the pharmacodynamics of this agent and the concentration dependence of activity.

Nephrotoxicity

Case 78-3, Question 8: On day 4 of therapy with AmB, L.K.'s serum creatinine (SCr) and blood urea nitrogen (BUN) are 2.3 mg/dL (SI units, 203.32

μmol/L) and 42 mg/dL (SI units, 14.99 mmol/L), respectively. How could AmB exacerbate L.K.'s renal dysfunction and how could it be prevented from worsening?

Renal dysfunction is the adverse event that most often limits treatment with AmB formulations. The renal toxicity results from AmB-mediated damage to renal tubules, which causes electrolyte wasting and disrupts the tubuloglomerular feedback mechanism. The clinical manifestations of AmB-induced renal damage include azotemia, renal tubular acidosis, hypokalemia, and hypomagnesemia.[88] The renal insult along with infusion-related reactions appears less severe in patients with higher serum cholesterol. This may be associated with the clathrin binding discussed earlier. Generally, AmB-related renal toxicity is reversible within 2 weeks after therapy has been discontinued. Administration of normal saline (250 mL) immediately before AmB administration reduces the risk for AmB-induced nephrotoxicity[98] and should be initiated before L.K.'s next dose. AmB formulations should not be admixed with normal saline, however, because sodium causes AmB to precipitate into an inactive particulate in IV admixture formulations.[99] Other nephrotoxins should be avoided (especially diuretics), and patients with already-compromised renal function should be closely monitored and alternate therapy should be considered.[99] Hypokalemia and hypomagnesemia should also be monitored closely. These measures to prevent further renal deterioration should be implemented, and the AmB therapy continued cautiously in this patient with systemic candidiasis. Anemia, associated with decreased renal production of erythropoietin, should resolve after AmB is discontinued and need not be treated.[100]

Case 78-3, Question 9: L.K. has exhibited significant renal dysfunction resulting from acute tubular necrosis. How should his dose of systemic antifungal drugs be altered?

Renal elimination of the antimycotics varies tremendously. For systemically administered AmB, only 5% to 10% of unchanged drug is eliminated in urine and bile during the first 24 hours,[88] and no evidence indicates that it is metabolized to a significant extent. Therefore, no substantial dosage adjustment is required for patients with chronic renal or hepatic failure. Although many clinicians will withhold AmB doses if acute renal dysfunction develops during therapy, concerns of drug-induced nephrotoxicity in L.K. must be balanced against the high likelihood of mortality in untreated patients with deep-seated infections.[55],[56] Alternative systemic antifungal therapy (ie, azoles or echinocandins) that is less nephrotoxic should also be considered. Dosing recommendations for echinocandins are unchanged in renal dysfunction or liver dysfunction, except for caspofungin. For patients with moderate hepatic insufficiency (Child–Turcotte–Pugh score 7–9), a change in the maintenance dose of caspofungin to 35 mg/day is recommended, even though the higher exposures expected with the standard dose are generally well tolerated. No data are available for caspofungin used in severe hepatic impairment, and a further dosage reduction should be considered.

Ketoconazole and itraconazole undergo first-pass metabolism and have a biphasic dose-dependent elimination.[45],[46] These agents are extensively metabolized and excreted in the bile; small amounts of unchanged drug are excreted in the urine; therefore, no need exists to adjust dosages in patients with renal dysfunction or in patients undergoing dialysis.[101] Voriconazole is extensively metabolized by cytochrome P450 2C19 and to a lesser extent CYP3A4 to inactive metabolites excreted in the urine. However, the IV formulations of voriconazole and posaconazole are solubilized in sulfobutylether-β-cyclodextrin, which is eliminated via the kidneys. Accumulation of the cyclodextrin vehicle is associated with a theoretical potential for renal toxicity not reported to date in patients including those with renal impairment.[102],[103] Therefore, oral therapy (or possibly isavuconazole) may be preferred in patients who require a broad-spectrum triazole but have impaired renal function. Fluconazole, unlike ketoconazole and itraconazole, is not extensively metabolized. More than 90% of a

fluconazole dose is excreted in urine, of which about 80% is measured as unchanged drug and about 20% as metabolites.[104] Because fluconazole is excreted primarily unchanged in the urine, dosages should be adjusted in patients with renal insufficiency (see **Table 78-5**).[23,24,45–48,88,101–111] Fluconazole or voriconazole may be reasonable alternatives in L.K., but the dosage must be adjusted for renal function based on published nomograms.[105]

CASE 78-3, QUESTION 10: What is the role of an AmB formulated with a lipid?

Lipid formulations of AmB have been approved by the FDA for patients who are unable to tolerate generic AmB (**Table 78-6**). In addition, the admixture of AmB in 10% or 20% lipid emulsion has been used for treating systemic mycotic infections. The lipid carriers differ tremendously for each of the amphotericin formulations. The liposomal formulation is a spherical carrier that contains AmB on both the inside and outside of the vesicle. Imagine the lipid complex as a snowflake shape and the colloidal dispersion shaped like a Frisbee with AmB bound to the structure. The differences in structure appear to have no effect on therapeutic outcome but exhibit markedly different pharmacokinetics and rates of AmB release in vivo, which may account for difference in the rates of adverse effects observed with each formulation.[112] AmB admixture with a lipid emulsion cannot be recommended until a stable formulation can be established.[113] Yet, similar in concept, some clinicians administer AmB formulations with breakfast (high-cholesterol meals) to simulate or enhance “lipid” coadministration, macrophage clathrin pit binding, and subsequent decreases in toxicity.

Table 78-6
Amphotericin B Formulations

Category	Amphotericin B (Fungizone)	Amphotericin B Lipid Complex (Abelcet®)	Amphotericin B Colloidal Dispersion (Amphotec®)	Liposomal Amphotericin B (AmBisome®)		Amphotericin B in Lipid Emulsion
FDA-approved indication	Life-threatening fungal infections Visceral leishmaniasis	Refractory or intolerant to AmB	Invasive Aspergillosis in patients refractory or intolerant to AmB	Empirical therapy in neutropenic FUO Refractory or intolerant to AmB Visceral leishmaniasis		NA
Formulation						
Sterol	None	None	Cholesterol sulfate	Cholesterol sulfate (5)[a]		Safflower and soybean oils
Phospholipid	None	DMPC and DMPG (7:3)[a]	None	EPC and DSPG (10:4)[a]		10–20 g/100 mL
						EPC > 2.21 g/100 mL
						Glycerin > 258 g/100 mL
Amphotericin B (mole%)	34	33	50	10		Variable
Particle size (nm)	>10	1600–11,000	122 (±48)	80–120		333–500
Manufacturer	Generic	Enzon	Intermune	Fujisawa Pharmaceuticals		Not applicable
Stability	1 week at 2 °C –8 °C or 24 hours at 27 °C	15 hours at 2 °C–8 °C or 6 hours at 27 °C	24 hours at 2 °C–8 °C	24 hours at 2 °C–8 °C		Unstable
Dosage and rate	0.3–0.7 mg/kg/day during 1–6 hours[b]	5 mg/kg/day at 2.5 mg/kg/hour	3–4 mg/kg/day during 2 hours	3–5[c] mg/kg/day during 2 hours		Investigational: 1 mg/kg/day during 1–8 hours
Lethal dose 50%	3.3 mg/kg	10–25 mg/kg	68 mg/kg	175 mg/kg		Unknown
Pharmacokinetic Parameters						
Dose	0.5 mg/kg	5 mg/kg × 7 days	5 mg/kg × 7 days	2.5 mg/kg × 7 days	5 mg/kg × 7 days	0.8 mg/kg/day × 13 days
Serum Concentrations						
Peak (µg/mL)	1.2	1.7	3.1	31.4	83.0	2.13
Trough (µg/mL)	0.5	0.7		4.0		0.42
Half-life (hours)	91.1	173.4	28.5	6.3	6.8	7.75
Volume of distribution (L/kg)	5.0	131.0	4.3	0.16	0.10	0.45
Clearance (mL/hour/kg)	38.0	436.0	0.117	22.0	11.0	37.0
AUC (µg/mL·hour)	14	17	43.0	197	555	26.37

AmB, amphotericin B; AUC, area under the curve; DMPC, dimyristoylphosphatidylcholine; DMPG, dimyristoylphosphatidylglycerol; DSPG, distearolyphosphatidylglycerol; EPC, egg phosphatidylcholine; FDA, U.S. Food and Drug Administration; FUO, fever of unknown origin; NA, not applicable.

[a]Molar ratio of each component, respectively.

[b]No benefit for longer infusions.

[c]Doses >10 mg/kg have no benefit.

Limited data on AmB formulation comparisons are available to assist in the management of this case. A single, large controlled trial has evaluated AmB lipid complex for the treatment of disseminated candidiasis. Generic AmB 0.6 to 1.0 mg/kg/day for 14 days was slightly, but not significantly, superior to the lipid complex formulation at 5 mg/kg/day for mycologic efficacy (68% vs 63%) or survival.[114] Renal dysfunction defined as a doubling in SCr, however, was 47% with AmB and 28% with this lipid formulation. Because of the significant cost, some health care facilities reserve lipid formulations for patients who have preexisting renal dysfunction or those who have severe adverse reactions to generic AmB. However, most centers use lipid formulations as their formulary polyene owing to patient acceptance and cost of AmB-associated renal dysfunction. Indications for the lipid formulations are further reviewed in the discussion of sections on aspergillosis, histoplasmosis, and cryptococcosis.

ANTIMYCOTIC PROPHYLAXIS

CASE 78-3, QUESTION 11: What measures could have been undertaken to prevent invasive fungal infections in L.K.?

In 2014, the National Institutes of Allergy and Infectious Diseases (NIAID)/Mycoses Study Group completed a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis initiated on the basis of an antigen diagnostic test (β-D-glucan) among high-risk patients in the intensive care unit (ICU) setting.[115] The study used a validated risk prediction score for invasive candidiasis that identified 18% of subjects admitted to the ICU with a predicted invasive candidiasis incidence rate of >10%. Caspofungin prophylaxis was not associated with a reduction in the incidence of proven or probable invasive candidiasis or patient mortality. Therefore, prophylaxis among non-neutropenic patients at this time should be restricted to patient populations with proven benefit: post-GI perforation, severe

pancreatitis, liver/pancreas or small bowel transplant recipients, and extreme low-birth-weight neonates.[57]

Selective GI decontamination or systemic antimycotic pharmacotherapy can be used in high-risk, immunocompromised, or surgical patients to prevent the development of fungal infections and could have been used for L.K. In critically ill surgical patients, the risk of invasive infection, but not mortality, may be reduced by more than 50% with fluconazole prophylaxis.[116] Alternatively, a nonabsorbable antifungal such as AmB or nystatin is a possible option. Oral AmB decreases systemic candidal infections threefold to fivefold in high-risk patients.[117] Yet the problems of unreliable antifungal stool concentrations,[118] decreasing azole cost associated with the availability of generics, and poor compliance have led to preferential azole use. Azoles are also more effective in preventing oral pharyngeal candidiasis than placebo.[119],[120] At the present time, no well-designed studies have compared azoles with polyene antifungals (eg, AmB) for the prevention of oropharyngeal or systemic candidiasis.

Prophylaxis could be initiated and continued until L.K. is no longer immunocompromised. If L.K. is discharged from the hospital and treated as an outpatient, a systemic azole (imidazole or triazole) administered once daily is preferable to a polyene to improve adherence. To reemphasize, however, systemic therapy increases the risk of resistance, adverse effects, drug interactions, and potentially cost (see **Table 78-4**). Therapeutic drug monitoring may be necessary in these patients.

Candiduria

TREATMENT

CASE 78-4

QUESTION 1: M.Y., a 24-year-old male, has been hospitalized in the surgical ICU with multiple traumatic injuries resulting from a motor vehicle accident. Shortly after admission, he underwent an exploratory laparotomy for a ruptured spleen

and lacerated liver. He subsequently suffered from respiratory and renal failure. M.Y. is currently intubated and on mechanical ventilation. Since admission, he has been nutritionally supported with central hyperalimentation and has been receiving broad-spectrum antibiotics (gentamicin, ampicillin, and metronidazole). A Foley catheter is in place. Two recent urinalyses (UAs) show budding yeast, and cultures were positive for >100,000 colony-forming units of *C. albicans*. M.Y. is currently afebrile, his funduscopic examination is normal, and no macronodular skin lesions are present. The WBC count is 8900 cells/μL (SI units, WBC count, 8.9×10^9/L), and three sets of blood cultures drawn during the past 2 days are negative.

How should M.Y.'s candiduria be treated?

It is difficult to differentiate among cystitis, urethritis, or systemic infection in the presence of funguria. Similarly, it is difficult to differentiate colonization from infection because candiduric patients are usually asymptomatic. Funguria cannot be used to determine the location or severity of invasion. Signs and symptoms of systemic disease should be monitored diligently until a diagnosis of colonization, cystitis, or urethritis is confirmed and the risk of dissemination is excluded.

Eradication of fungi in the urine (specifically *C. albicans*) should begin with the removal of the indwelling urinary catheter and alleviation of risk factors for fungal disease. If catheter removal does not clear the urine within 48 hours, pharmacotherapy should be considered. If M.Y. is scheduled for a genitourinary procedure, he should receive systemic therapy because the rate of candidemia after surgery is high (10.8%) in candiduric patients. In addition, any patient at a high risk for dissemination into the blood should be considered for treatment (eg, patients with immunosuppression).[121]

Bladder irrigation with AmB has been used in the past at concentrations of 150 μg/mL, however, has limited clinical utility, and is not recommended by the Infectious Diseases Society of America.[122] In two comparative studies, bladder irrigation for 5 days with AmB 50 μg/mL was superior to fluconazole 100 mg/day as measured by microbiologic cure rates. Clinical cure rates at 2 to 4 weeks were equal—however, mortality rates were higher in the AmB-treated groups. It was suggested that AmB failures may have

been associated with the dissemination of yeast from the urinary tract.[123],[124] Systemic antifungal therapy with flucytosine 100 to 150 mg/kg/day for 7 days[125] and azoles (fluconazole 0.6–1.4 mg/kg/day for 7 days)[126],[127] also has been used in noncomparative or nonrandomized studies. Newer triazoles (voriconazole, posaconazole, and isavuconazole) or echinocandins are not recommended for the treatment of candiduria owing to their low concentrations in urine, even though some case series have suggested that clearance of positive cultures is possible on echinocandin therapy.[128]

Blastomycosis

ETIOLOGY

CASE 78-5

QUESTION 1: C.P., a 17-year-old female from Arkansas, is admitted to the hospital with a chronic pneumonia that has not responded to antibiotics. Three months ago, she began to exhibit a chronic cough that eventually became productive of purulent sputum, which was occasionally streaked with blood. Two months ago, she began to exhibit "boils" on her lower extremities and back, which drained spontaneously. She was hospitalized at another hospital but failed to respond to amoxicillin and clarithromycin. C.P. denies fever, chills, or night sweats but has lost 11 pounds (4.99 kg). Her temperature is 100.76 °F (38.2 °C). A 2-cm^2 subcutaneous, fluctuant, tender mass is seen over the right mandible and a second fluctuant mass about 4 cm wide on the lower back. In addition, several 0.5- to 1-cm^2 ulcers with heaped-up, hyperkeratotic margins are noted on the lower extremities (**Fig. 78-2**). Rales are heard at the right lung base. C.P.'s leukocyte count is slightly elevated at 13,500 cells/μL (SI units, WBC count, 13.5 × 10^9/L). A chest radiograph shows a mass-like infiltrate in the right mid-lung field (**Fig. 78-3**). A wet preparation of ulcer scrapings and material aspirated from a subcutaneous abscess reveal numerous broad-based, budding yeast forms with refractile cell walls and multiple nuclei typical of *B. dermatitidis*.

Cultures of sputum, skin scrapings, and abscess material eventually confirmed the diagnosis.

What was the likely portal of entry for C.P.'s disseminated blastomycosis? Why should it be treated?

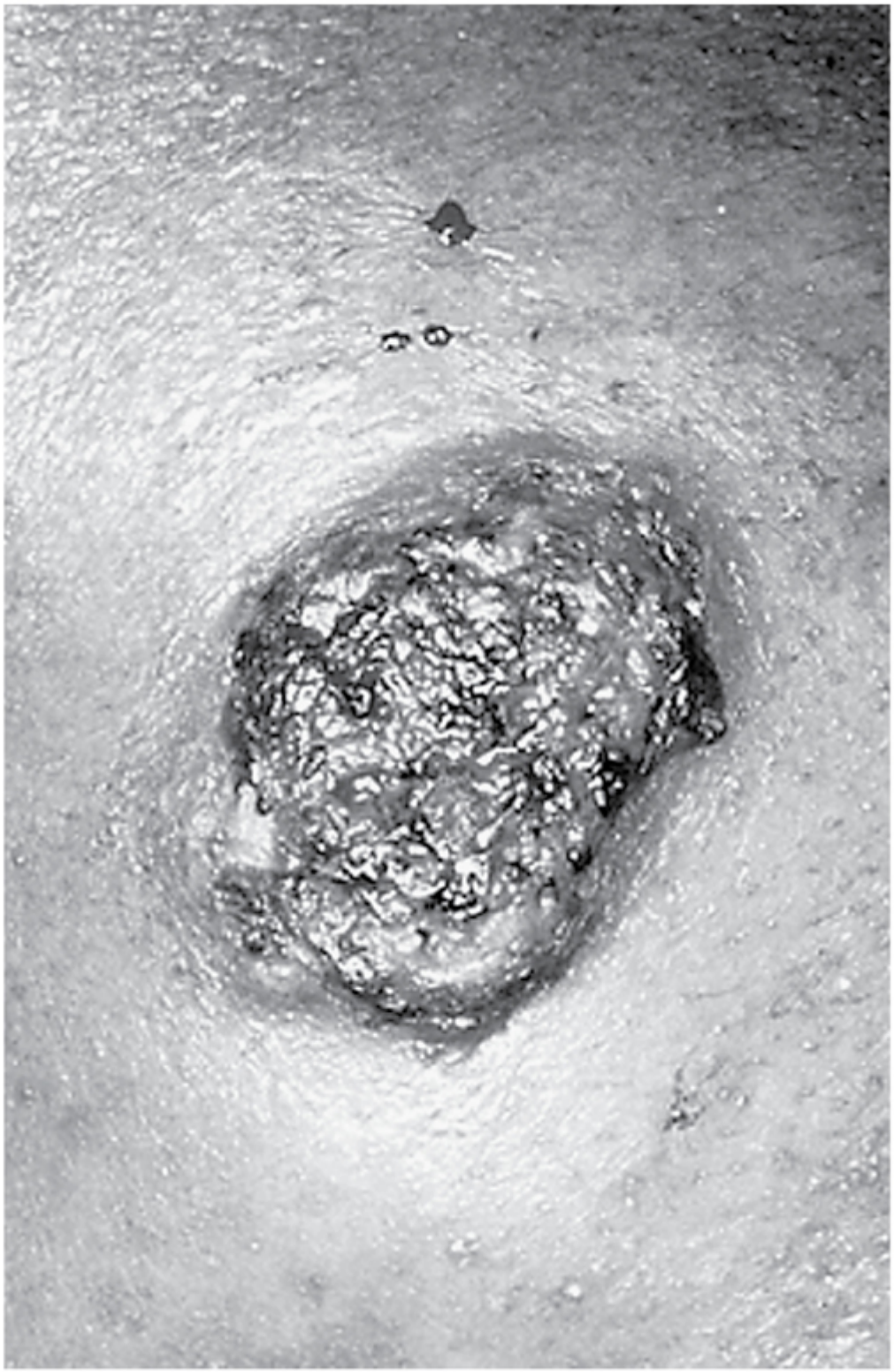


Figure 78-2 Disseminated Blastomyces dermatitidis skin ulcers.

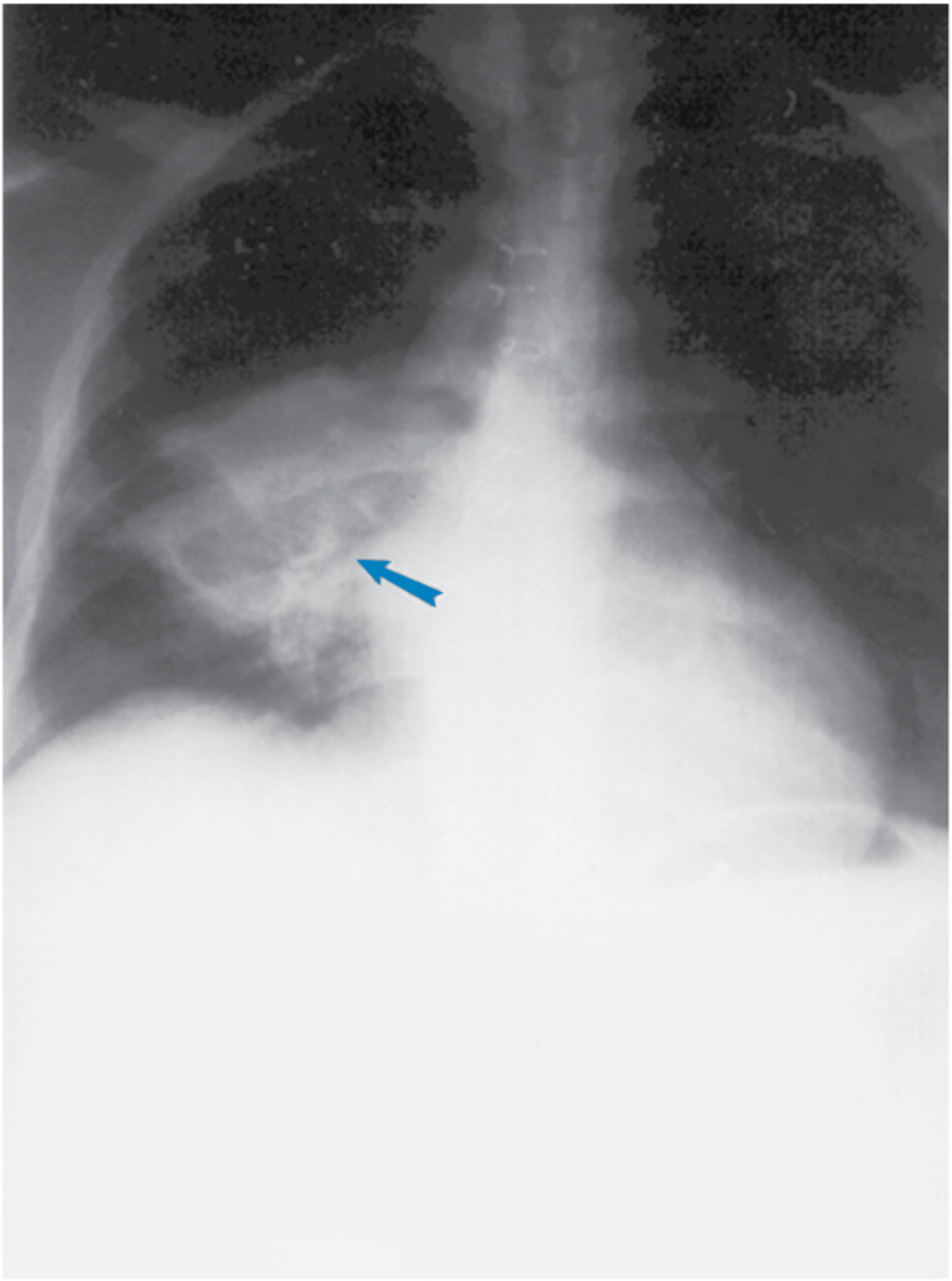


Figure 78-3 Chest radiograph of pulmonary Blastomyces dermatitidis. Arrow marks abnormality.

Typical of the other endemic mycoses, the primary portal of entry for *B. dermatitidis* is the lungs. A pulmonary origin for C.P.'s infection is supported by her history of cough with purulent, blood-streaked sputum, followed a month later with cutaneous lesions on her legs and back. An acute pulmonary infection is most often asymptomatic and, when symptomatic, usually requires only observation. Chronic pulmonary or extrapulmonary blastomycosis will develop in an unknown number of these patients. C.P.'s rales at the base of her right lung and persistent pneumonia unresponsive to antibacterials suggest a chronic pulmonary infection and a need for treatment. Chronic pulmonary disease often presents with radiographic studies often mistaken for tuberculosis or cancer; the mass-like infiltrate in her right lung on chest radiograph also is consistent with chronic pulmonary disease. Extrapulmonary infections can involve the skin (verrucous or ulcerative lesions), bone, genitourinary system (prostatitis and epididymo-orchitis), or CNS (meningitis or brain abscess). If untreated, these chronic pulmonary or extrapulmonary infections are fatal in at least 21% of patients.[129] Because C.P. presents with pulmonary and cutaneous evidence of blastomycosis, she should be treated.

TREATMENT

Case 78-5, Question 2: What specific therapy should be initiated for C.P.?

Historically, AmB formulations were considered the treatment of choice for blastomycosis, and total doses of more than 2 g were associated with 97% cure rates, low relapse rates, but also, however, substantial associated toxicity.[129] Ketoconazole and itraconazole are safe, effective alternatives to AmB in patients with non–life-threatening, non-CNS infections. The NIAID–Mycoses Study Group[130] confirmed the effectiveness of azoles for the

treatment of chronic pulmonary and extrapulmonary disease associated with blastomycosis and histoplasmosis. In uncontrolled evaluations of chronic pulmonary and extrapulmonary infections (excluding life-threatening or CNS), ketoconazole at dosages of 400 to 800 mg/day resulted in cure rates of about 89%, failure rates of about 6%, and relapse rates of about 5%.[130] In similar studies, itraconazole capsules of 200 to 400 mg/day for a median of 6.2 months resulted in cure rates of 88% to 95%.[131] Fluconazole was ineffective at dosages <400 mg/day. Higher dosages (400–800 mg/day), however, are as effective as ketoconazole in non–life-threatening diseases.[132] Although these trials are neither comparative nor controlled, itraconazole is less toxic than ketoconazole and with the best benefit (efficacy) to risk (toxicity) ratio.

C.P. has mild-to-moderate disease and can be treated with an initial itraconazole dosage of 200 mg/day. If no clinical improvement is seen within 2 weeks or if the disease progresses, the dosage of itraconazole can be titrated upward in 100-mg increments to a maximal dosage of 400 mg/day. Treatment should be continued for at least 6 months. If C.P. experiences severe or meningeal disease, itraconazole should be discontinued and AmB or a lipid-based AmB product should be initiated. C.P. should be followed up for 12 months owing to the risk of relapse. Unlike histoplasmosis, skin test and serologic testing are not sufficiently sensitive to diagnose blastomycosis or evaluate the effectiveness of treatment.[130,133] Rather, patients should be evaluated closely for resolution of symptoms (constitutional and pulmonary), negative microbiologic samples, and improvement in radiographic studies.

ANTIFUNGALS IN PREGNANCY

Case 78-5, Question 3: C.P. reports she has not menstruated in 3 months, and a urine pregnancy test is positive. How does this information change the therapeutic options for her?

Data on the safety of antimycotics for treating patients who are pregnant or lactating are limited but are comprehensively reviewed according to FDA categories of the teratogenic risks of drugs (see Chapter 49, Obstetric Drug Therapy).[134],[135] The systemic azoles are categorized with risk factor C. A recent Danish registration study did not find evidence of birth defects in females who took itraconazole during their first trimester.[136],[137] However, the majority of females analyzed in this registry received low cumulative doses of triazoles for thrush. However, these agents should be avoided in pregnant or lactating females who are breast-feeding because of their potential teratogenicity and endocrine toxicity in the fetus or newborn. As with the azoles, griseofulvin and flucytosine have been classified with risk factor C. These agents should not be used in C.P. because the risk clearly outweighs the therapeutic benefit. Few or no data exist on the secretion of these agents in breast milk. Therefore, breast-feeding should be discouraged in females receiving these antifungal agents.

AmB and terbinafine are classified as risk factor B. Therapeutic agents in this category have no fetal risk based on animal studies, or when risk has been found in animals, controlled human studies have not confirmed the results. There are limited data regarding the use of terbinafine in pregnancy. Consequently, clinicians should avoid terbinafine use in pregnancy until published data support a B classification. Furthermore, considerable clinical experience with AmB formulations in pregnant females has documented successful treatment of systemic mycoses with no excess toxicity to either the mother or the fetus. Thus, AmB formulations have been the mainstay of antifungal therapy in pregnancy.

Histoplasmosis

TREATMENT

CASE 78-6

QUESTION 1: J.N., a 47-year-old male with severe rheumatoid arthritis, has been maintained on daily prednisone for the past 6 years; his current dosage is

20 mg/day. For the past 4 weeks, he has experienced daily fevers to 101.12 °F (38.4 °C), drenching night sweats, anorexia, and an 18.08-pound (8.2-kg) weight loss. His prednisone dosage was increased to 40 mg/day with little clinical effect. On admission to the hospital, J.N. appears chronically ill and has many of the stigmata of chronic steroid therapy. His temperature is 100.04 °F (37.8 °C) with an associated rapid heart rate of 105 beats/minute. A shallow mouth ulcer is present on the hard palate. The liver is enlarged to a total span of 18 cm, and the spleen is palpable 3 cm below the left costal margin. Stool is positive for occult blood. A chest radiograph shows bilateral interstitial infiltrates (**Fig. 78-4A**). He is pancytopenic, with the following laboratory results:

Hematocrit, 29% (normal, 39%–45% SI units, 0.29)
WBC count, 3500 cells/μL (normal, 4000–11,000 cells/μL) (SI units, 3.5×10^9/L)
Platelet count, 78,000 cells/μL (normal, 130–400,000 cells/μL)
UA, 8 to 10 WBC/high-power field
SCr, 1.9 mg/dL (SI units, 167.96 μmol/L)
BUN, 42 mg/dL (SI units, 14.99 mmol/L urea)

The bilirubin is normal, but the aminotransferases are elevated to about 1.5 times normal, and serum lactate dehydrogenase is 10 times greater than normal. A bone marrow aspirate and biopsy of the mouth ulcer reveal multiple, small intracellular yeast forms compatible with *H. capsulatum* in macrophages and polymorphonuclear leukocytes (**Fig. 78-4B**). Cultures of blood and urine, bone marrow aspirate, and mouth ulcer biopsy grew *H. capsulatum*.

What is the optimal antifungal therapy in this case of systemic *H. capsulatum*? What clinical parameters should be monitored to assess the efficacy and toxicity of J.N.'s therapy?

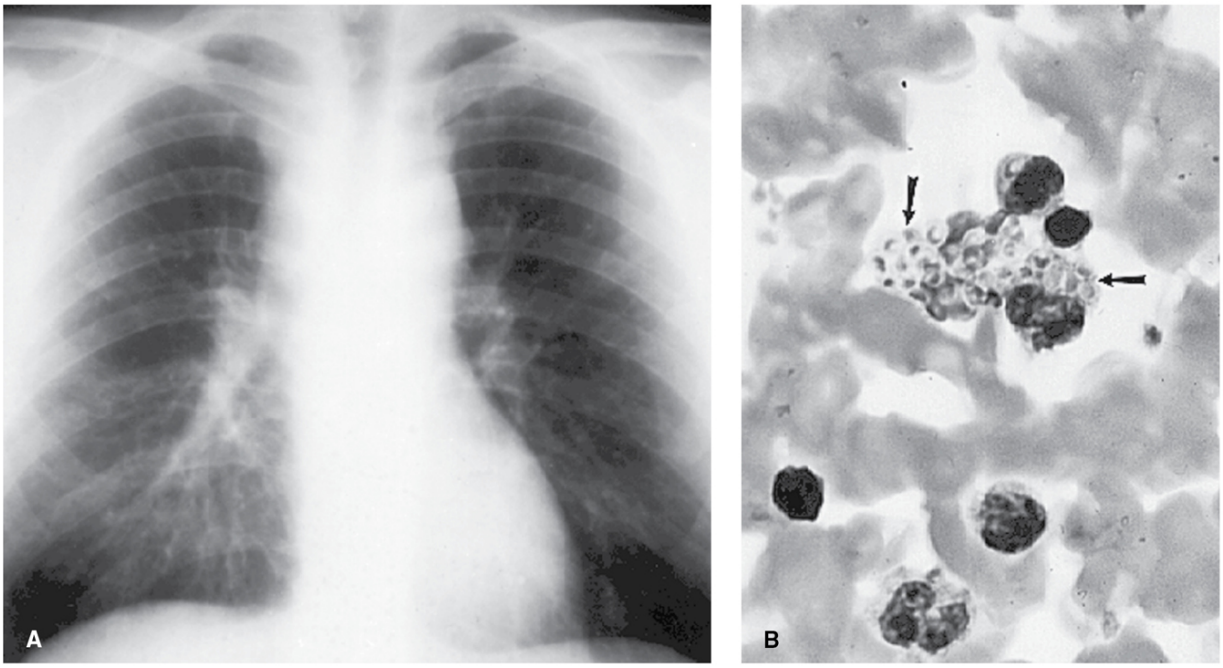


Figure 78-4 Histoplasmosis infection. A, Chest radiograph showing bilateral interstitial infiltrate. B, Gram stain of peripheral blood showing leukocytes with intracellular organisms.

The treatment benefits of antifungal therapy in systemic histoplasmosis have not been well investigated. Treatment options for histoplasmosis are outlined in **Table 78-7**.[138] Accordingly, J.N. should be treated with an IV amphotericin product or itraconazole 2.8 mg/kg/day, and his course of therapy should be monitored for both efficacy and toxicity. The decision was made to use conventional amphotericin for J.N.

Table 78-7
Treatment of Histoplasmosis

Disease	Primary	Secondary
Acute Pulmonary		
Prolonged symptomatology (>2 weeks)	Resolves spontaneously	N/A
Immunocompromised[a]	ITZ 50–100 mg/day (3–6 months)[b]	AmB 0.3–0.5 mg/kg/day[b]

Respiratory distress	AmB lipid formulation 3–5 mg/kg/day[a]	AmB 0.3–0.5 mg/kg/day
(Pa_{O_2} >70 mm Hg)	AmB 0.5–1.0 mg/kg/day	ITZ 1.5–2.8 mg/kg/day (≥6 months)[b]
	(TD 250–500 mg) ± corticosteroids (methylprednisolone 0.5–1 mg/kg) × 1–2 weeks	ITZ (has not been investigated in life-threatening situations)
Chronic Pulmonary		
Active	ITZ (1.5–2.8 mg/kg/day 9 months)[b,c]	AmB 0.5 mg/kg/day[c]
Inactive		or KTZ 400 mg/day (≈6 months)
Histoplasmoma	No treatment	N/A
Mediastinal fibrosis	Surgery[d]	N/A
Systemic Disease		
	AmB (TD recommended: 35 mg/kg) or lipid AmB then ITZ 2.8 mg/kg/day × up to 12 months[b]	Fluconazole 400–800 mg/day[e]

AmB, amphotericin B-deoxycholate; ITZ, itraconazole; KTZ, ketoconazole; TD, total dose.

[a]Lipid formulations of amphotericin B are preferable to generic amphotericin B in patients infected with HIV.[148]

[b]Treatment should be continued until the patient is symptom-free and culture-negative for 3 months. The recommendations for duration of therapy or total doses should be used only as guides for initial therapy based on the IDSA 2007 guideline.[147]

[c]Indicated only for serious symptoms (ie, hemoptysis).

[d]ITZ 200 mg daily or twice a day for 6–18 months for most patients.

[e]Fluconazole should only be used in patients who cannot take ITZ.

Blood and urine cultures, WBC and platelet counts (histoplasma is associated with pancytopenia), constitutional symptoms, serum lactate dehydrogenase, and hepatosplenomegaly are useful

measures for evaluating the outcome of antifungal therapy of J.N.'s histoplasmosis. Anemia and chest radiographs are poor measures of treatment response. Chest radiographs often reflect calcified granulomas in chronic disease with scarring, which rarely resolve even with extensive therapy. Therefore, evaluation of deterioration on radiograph, but not of improvement, is possible. In addition, AmB-induced renal disease with secondary anemia can confuse evaluation of disease resolution. Anemia must be excluded as a prognostic indicator in patients receiving AmB for durations of 3 weeks regardless of the dose.[100]

Diligent follow-up of patients is required because relapses occur in 5% to 15% of AmB-treated patients within 3 years. Relapses have occurred in patients who received <30 mg/kg total dose of generic AmB or had concomitant untreated Addison disease, immunosuppression, vascular infections (endocarditis, grafts, and aneurysms), or meningeal infections.[138] More than 90% of HIV-positive patients experience a relapse of histoplasmosis subsequent to adequate AmB therapy. A double-blind trial in immunocompromised patients (HIV) revealed that liposomal AmB was superior to AmB deoxycholate. It is not known how itraconazole is compared with liposomal AmB in those coinfected with HIV. If this patient was coinfected with HIV, a lipid-based amphotericin is preferred.[139] Even the initiation of subsequent immunosuppressive therapy is of particular concern because of the potential for reactivation (relapse) and dissemination of histoplasmosis from dormant foci, especially in patients with residual granulomas. The residual disease has been hypothesized to lead to chronic inflammatory responses and secondary strokes.[140]

Potential adverse effects to AmB should also be monitored in J.N. (eg, infusion-related reactions, nephrotoxicity, anemia, hypokalemia, neurotoxicity, and thrombophlebitis). In addition, J.N.'s adrenal status should be monitored closely because of his long-term corticosteroid therapy and his histoplasmosis. Patients who are addisonian secondary to histoplasmosis infections appear to experience more episodes of AmB-induced acute hypotension.

AZOLE ADVERSE EFFECTS

CASE 78-6, QUESTION 2: After treatment with a total AmB dose of 750 mg, clinical improvement in J.N.'s histoplasmosis is subjectively and objectively documented. The clinician selected ketoconazole 400 mg/day as an oral substitute for his AmB regimen because of the patient's economic circumstances. Six weeks later, J.N. reports impotence and wonders whether this could be caused by his medication. What is the likelihood that ketoconazole is the cause of J.N.'s impotence?

Ketoconazole has been associated with more adverse reactions and greater potential for drug interactions compared with itraconazole and fluconazole. The most common side effects of ketoconazole, however, are nausea and vomiting. GI distress is dose-related, with fewer GI effects with 400 mg/day compared with 800 mg/day.[138] Endocrine and hepatic toxicities are the most significant adverse effects of ketoconazole. Dose-splitting from daily to twice daily may decrease nausea and vomiting. Dose-related endocrinologic toxicities (hypoadrenalism, oligospermia, and diminished libido) have been observed during ketoconazole therapy secondary to the inhibition of mammalian sterol synthesis[13,141] and usually have been resolved with drug discontinuation. Therefore, J.N.'s impotence might well be attributed to his ketoconazole. Liver enzymes should also be monitored because an approximate 10% risk exists of elevation in transaminases and an occasional case of serious hepatitis and hepatic failure.[13,141]

The triazoles—itraconazole, fluconazole, and voriconazole—are much better tolerated and require less monitoring than ketoconazole therapy. This result has been attributed to the greater affinity of the triazoles for fungal cytochrome enzymes and less interference with mammalian enzymes.[142] Itraconazole, fluconazole (6 mg/kg/day), and voriconazole do not exhibit antiandrogenic effects, and nausea and vomiting are less common when compared with imidazoles. Abnormal elevations in liver function have been reported in 2.7% of patients receiving voriconazole during clinical trials. Abnormalities in liver function tests may be associated with higher azole dosages or

serum concentrations but generally resolve either with continued therapy or dosage modification, including drug discontinuance. Liver function should be determined before and periodically throughout azole therapy because cases of serious hepatic reactions have been reported.[142] A unique adverse event associated with voriconazole is enhanced perception to light, which may be associated with higher plasma concentrations or doses. Generally, drug discontinuance is not required, although monitoring of visual acuity, visual field, and color perception is advised if therapy lasts longer than 28 days. Diarrhea, asthenia, flatulence, and eye pain have been reported with posaconazole therapy.[53] Based on these data, J.N. should be given a trial of itraconazole.

AZOLE–DRUG INTERACTIONS

Case 78-6, Question 3: J.N. chose to continue his ketoconazole therapy. He now returns with Cushingoid signs and symptoms. What potential drug or disease state interaction could be implicated as a cause of this serious problem in J.N.?

Drug interactions with systemic azoles and polyenes vary from mild inconveniences to life-threatening events. Historically, the interaction between azoles and nonsedating H_1-selective antihistamines has been serious, leading to QT prolongation and ventricular arrhythmias.[143] Although it is possible that concomitant use of corticosteroids could reduce antifungal efficacy, no clinical trial has addressed this important question. Corticosteroid serum concentrations can double with concomitant use of ketoconazole, leading to recommendations to decrease the steroid dose by 50% when ketoconazole is used. The interaction has been suggested between glucocorticoids and other azoles.[144] In addition, dexamethasone has been demonstrated to increase the clearance of caspofungin.

Other significant drug interactions with the azole antifungals involve their ability to inhibit the CYP450 enzyme system. All azoles

inhibit CYP3A4, but with varying potency: Ketoconazole is the most potent inhibitor, followed by itraconazole and voriconazole, then posaconazole and fluconazole. Data on relative inhibition potency for isavuconazole are still pending. In addition to therapeutic interactions, numerous other agents are substrates to cytochrome CYP3A4 but have yet to be evaluated. Because azole antifungals could increase serum concentrations with associated potential toxicity, caution should be exercised during concomitant use. Adding complexity to voriconazole's interactions includes its propensity to inhibit CYP2C9 and CYP2C19, two isoenzymes exhibiting polymorphism, thus increasing concentrations of CYP2C9 or CYP2C19 substrates. Conversely, agents that either induce or inhibit the CYP450 system may decrease or increase, respectively, antifungal drug concentrations. Posaconazole is a substrate for *p*-glycoprotein efflux and is metabolized via uridine diphosphate glucuronidation; therefore, inhibitors or inducers of these clearance pathways may affect posaconazole concentrations.[51–53]

Although hundreds of drug interactions have been documented with antifungals (particularly azoles), the number of theoretical interactions probably exceeds 2000.[145] Therefore, patient medication profiles should be carefully screened before initiating and stopping antifungal therapy to assess the risk for serious drug interactions. Preferably, this screening should be performed with a frequently updated computerized interaction database, which are available commercially (Lexicomp) or free of cost (www.fungalpharmacology.org), including software for use on smartphones.

Coccidioidomycosis

SEROLOGIC TESTS

CASE 78-7

Question 1: F.W., a 32-year-old Filipina female and a lifelong resident of the Central Valley in California, is admitted to the hospital with a third recurrence of

coccidioidal meningitis. Approximately 4 years ago, she was treated with a total AmB dose of 2.2 g, which resulted in a good clinical response. Nine months later, she relapsed and received a second course of AmB to a total of 1.6 g. She did well during the next 18 months and was able to return to work as a secretary. Over the past 4 months, however, F.W. has had chronic headaches, has been unable to concentrate at work, and is reported by family members to have a very labile personality. A computed tomography (CT) scan of the brain reveals mild hydrocephalus. An opening pressure of 19 mm Hg (normal, 10 mm Hg) was documented at lumbar puncture. Analysis of the CSF showed:

110 WBC/μL (normal, 0 WBC/μL)
Glucose, 18 mg/dL (normal, 60% of serum glucose)
Protein, 190 mg/dL (normal, >50 mg/dL)
CF antibodies were positive in the CSF at a titer of 1:32.

How should serologic tests for coccidioidomycosis be interpreted?

The most important serologic tests for fungal infections use CF, immunodiffusion, and EIA techniques. Tests for complement-fixing antibodies (ie, CF) to the dimorphic fungi (see **Table 78-1**) are well established, and various antigens have been used. Coccidioidin is the mycelial-phase antigen for *Coccidioides immitis*. Of patients with coccidioidomycosis, 61% will have coccidioidin CF titers of at least 1:32, and 41% will have titers of 1:64. Rising titers are a bad prognostic sign, and falling titers indicate clinical improvement. Therefore, F.W.'s CSF CF titer of 1:32 is consistent with active coccidioidomycosis. Immunodiffusion testing for coccidioidomycosis using coccidioidin reveals that seropositive results appear 1 to 3 weeks after the onset of primary infection in 75% of patients, and this positivity usually disappears within 4 months if the infection resolves.[146] IgG-specific and IgM-specific EIAs using a combination of antigens for *C. immitis* have been developed. These tests offer sensitivities of more than 92% and specificities of 98% for serum and CSF. EIA reactivity appears earlier than CF reactivity.[147,148]

ANTIFUNGAL CENTRAL NERVOUS SYSTEM PENETRATION

CASE 78-7, QUESTION 2: What is a pharmacokinetic explanation for the treatment failure of F.W.? How might this problem be overcome?

F.W. has received prolonged parenteral AmB administration, and the CSF still contains fungal organisms. Treatment failures in this case may partly be owing to the limited penetration of free AmB into the CSF.[88] Because generic AmB or lipid formulation–dissociated AmB is highly bound to lipid (90%–95%), CSF concentrations achieved are only 2% to 4% of the serum concentration[88],[142]; peritoneal, synovial, and pleural fluid concentrations are <50% of the serum concentrations (see **Table 78-5**). Flucytosine is not significantly bound to protein and penetrates the CSF, vitreous, and peritoneal fluids; its volume of distribution approximates that of total body water.[149] Flucytosine concentration in the CSF is 74% of the serum concentration, resulting in its extensive use in the treatment of CNS mycoses, particularly cryptococcal meningitis. Flucytosine, however, has no activity in coccidioidomycosis and, therefore, cannot be used in F.W.

The volume of distribution of fluconazole approaches that of total body water,[150] and concentrations of fluconazole in CSF are ~60% of simultaneous serum concentrations. Ketoconazole penetrates CSF poorly because it is highly bound to plasma proteins (>80%) and to erythrocytes (15%). Itraconazole is similar to ketoconazole in that it is >99% protein bound. Itraconazole concentrates intracellularly in host alveolar macrophages, which may account for its efficacy against some fungal CNS infections despite its inability to penetrate into the CSF.[151] Echinocandins also poorly (>5%) penetrate into the CSF. Reliable data on terbinafine, isavuconazole, and posaconazole penetration are currently unavailable. Therefore, fluconazole might be an alternative to CNS instillation of AmB based on pharmacokinetic considerations.[152],[153]

Fluconazole, investigated at dosages of 400 mg/day, is useful in patients with coccidioidomycosis meningitis. Similar to amphotericin products, relapse rates are high once fluconazole therapy is stopped. Oral itraconazole 200 mg twice daily was not found to be superior to fluconazole in a controlled trial of nonmeningitis disease; however, a trend toward greater efficacy was observed, particularly in skeletal disease.[154]

INTRATHECAL AMPHOTERICIN

CASE 78-7, QUESTION 3: What adverse events might be observed with the intrathecal administration of an antifungal in F.W.?

Augmentation of systemic antifungal administration with intraventricular or intrathecal administration may improve the outcome for antifungals with poor penetration into the CSF. Intrathecal generic AmB doses in adults normally range from 0.25 to 0.5 mg diluted in 5 mL of 5% glucose.[155],[156] A few studies suggest that doses larger than 0.7 mg improve the cure rate and decrease relapse. Cisternal or intraventricular administration is recommended as the routes of choice because of flow characteristics of CSF from the ventricles to the spinal cord. When lumbar administration has been necessary, agents are administered in a hypertonic solution of 10% glucose, and the patient is placed in a Trendelenburg position in an attempt to improve distribution of the drug to the basilar meninges and ventricles and reduce local toxicity. Voriconazole, caspofungin, and the lipid amphotericin formulations have been used, but not evaluated in controlled trials.

Cisternal antifungal administration has been associated with headaches, nausea, vomiting, cranial nerve paresis, and cisternal hemorrhage caused by needle trauma. An Ommaya reservoir often is used to facilitate intraventricular administration of AmB formulations. Common complications of these devices include shunt occlusion, bacterial colonization or bacterial meningitis, Parkinsonian symptoms, and seizures.[156–158] In the past, lumbar administration was used because it is simpler, but it often must be discontinued because of chemical arachnoiditis, headache, transient radiculitis, paresthesia, nerve pulses, difficulty voiding, impaired vision, vertigo, and tinnitus. Acute toxic delirium, demyelinating peripheral neuropathy, and spinal cord injury have also been reported.[159–162] Regardless of the substantial and serious adverse effects, intraventricular administration may be effective in treating patients

with meningitis who have severe disease or who are pharmacologic nonresponders.

Aspergillosis

EMPIRIC THERAPY (NEUTROPENIC HOST)

CASE 78-8

QUESTION 1: M.Z., an otherwise healthy 29-year-old male, received an allogeneic stem cell transplantation 12 days ago. He has had no serious complications associated with his chloroquine-induced aplastic anemia during his 7-month wait for transplant. On transplant Days 5 to 2, induction therapy was initiated with cyclophosphamide (50 mg/kg) and total body irradiation, and then bone marrow from his human leukocyte antigen–compatible brother was infused on day 0. The onset of neutropenia was noted on day 3, and the WBC count was 50 cells/μL. M.Z. has reported only of stomatitis and diarrhea before day 5. On that morning, he was reporting fever, chest pain, and headache. On physical examination, his temperature was 98.6 °F (37 °C). Empiric antibiotics were added, but by day 8, he was not clinically improving. A CT scan of the chest and sinuses revealed a nodular pleural–based opacity with ground-glass attenuation (halo sign) in his right lung.

What therapeutic options should be considered for this patient?

Empiric antifungal therapy in a neutropenic host should be initiated when a patient is febrile for more than 96 hours on appropriate antibiotics. Routine empiric therapy for a patient without evidence of deep-seated fungal infection was historically generic AmB 0.3 to 0.6 mg/kg/day or fluconazole 200 to 400 mg/day until the absolute neutrophil count is >500 cells/μL.[163] Therapy results in the resolution of signs and symptoms in up to 64% of patients.

CASE 78-8, QUESTION 2: What is the role of lipid formulations of AmB?

Because mold infections are of concern in this neutropenic patient who received an allogeneic stem cell transplant, mold-active antifungal therapy should be started immediately. In a large, well-controlled, double-blind study, AmB 0.6 mg/kg/day was compared

with liposomal AmB 3.0 mg/kg/day in febrile neutropenic patients. Patients who were febrile for more than 96 hours and neutropenic (>500 cells/μL) experienced equal survival and clinical success of ~50% for both the agents.[164] Success rates have been similar with other agents, including liposomal AmB (34%), caspofungin (34%),[165] voriconazole, or itraconazole.[166],[167] It is important to remember that fever is a late and insensitive measure of infection. Prevention of breakthrough invasive fungal infection may be the most important indicator of an agent's efficacy. Using this measure comparing the various trials, voriconazole appears to be the most effective agent (voriconazole vs liposomal AmB [1.9% vs 5%] and AmB versus liposomal AmB [3.2% vs 7.8%]), although crude mortality rates were similar in the two patient groups (8% vs 6%, respectively).[164],[167] Selection of expensive, but less toxic, agents should be weighed against the morbidity and mortality associated with invasive fungal disease.

TREATMENT OF ASPERGILLOSIS

CASE 78-8, QUESTION 3: Fiber optic bronchoscopy performed to evaluate the nodular lesion in chest CT revealed eroded bronchioles with necrotic tissue, and methenamine silver nitrate stain of a biopsy sample revealed fragmented, closely septated hyphal bodies branched at 45° angles. The samples were sent to microbiology for cultures. A galactomannan test from the bronchial wash was positive at an index of 1.1. All previous blood and sputum cultures have been negative. The diagnosis at this time is probable aspergillosis. What treatment steps should be taken?

Drug therapy should be approached by first determining whether the infection is likely to be invasive or noninvasive disease (**Fig. 78-5**). Most patients inhale *Aspergillus* species and never become symptomatic or exhibit only mild hypersensitivity pneumonitis. Pepper can be a common food source for *Aspergillus* exposure. Invasive infections are more likely to occur in immunocompromised patients, especially those with prolonged neutropenia or patients who receive high dose (ie, more than 1 mg/kg/day prednisone

equivalent) or corticosteroids or other T-cell immunosuppressive therapy (ie, alemtuzumab and anti-thymocyte globulin) to treat acute graft-versus-host disease following stem cell transplantation or organ rejection after solid organ transplantation. Allogeneic hematopoietic stem cell transplantation (HSCT) has a much greater infection rate and mortality compared with autologous HSCT.[168] A classic observation reported by radiology is a “halo” sign or a “crescent” sign identified on CT, which is highly suggestive of invasive aspergillosis. However, the halo sign is not specific, because other bacterial viral, malignant, or autoimmune conditions can produce similar radiographic findings. The halo sign is also transient and is less common after 1 week of infection. Typically, these nodular lesions will enlarge (even with effective antifungal therapy) and then cavitate when a patient’s neutrophil count recovers, forming another distinguishing CT abnormality for invasive mold disease—the air crescent sign.[169]

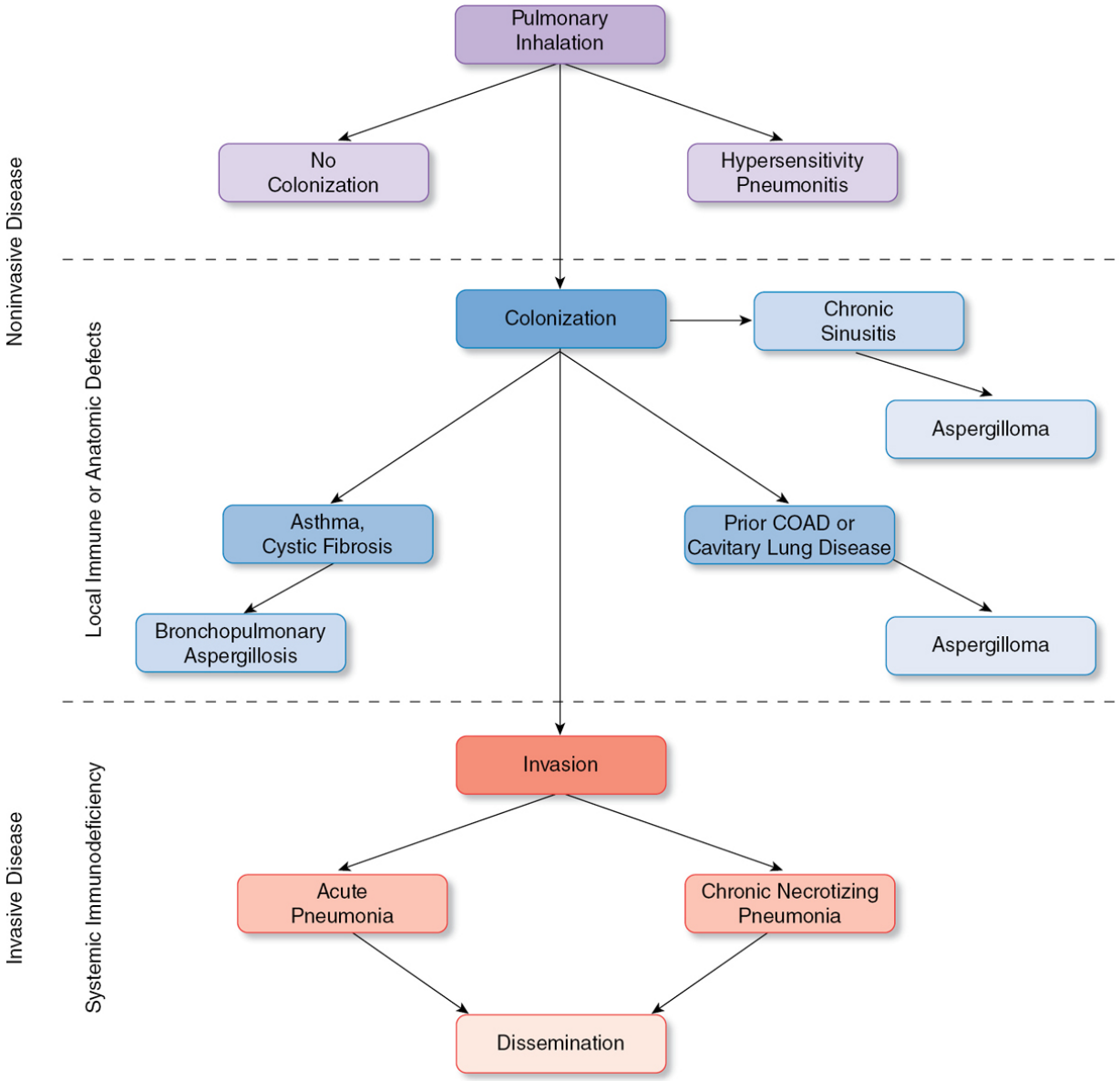


Figure 78-5 Classification of aspergillosis infections. COAD, chronic obstructive airway disease.

A majority invasive aspergillosis cases are now diagnosed based on a compatible clinical and radiographic picture described above and the results of an ELISA antigen test for a cell wall polysaccharide in *Aspergillus* spp.-galactomannan. Serum galactomannan test is a fairly sensitive and specific test (80%–90%) in neutropenic patients with aspergillosis who rapidly progress to angioinvasive disease in the lung. The test is less sensitive in non-neutropenic patients who initially present with bronchial invasive

patterns of pneumonia before angioinvasion or in patients receiving mold-active antifungal therapy.[170] In these populations, testing of bronchial alveolar lavage fluid for galactomannan antigen has better sensitivity than serum. False-positive test findings have been associated with *Bifidobacterium* spp. colonization in pediatric GI tracts, other eukaryotic infections (ie, *Trichosporon*, *Fusarium*, *Saccharomyces*, *Histoplasma*, or *Acremonium*), and administration of piperacillin–tazobactam or calcium gluconate, which is of concern for clinicians using this test for screening in areas with low case rates. Galactomannan antigen is a useful prognostic indicator for therapeutic outcome in confirmed cases or as a screen in areas with high case rates. The subjective and objective data in this case clearly represent invasive symptomatic disease necessitating aggressive treatment.

Aspergillosis is a model for invasive mold infections that have a propensity to invade blood vessels and tissue. Antifungal therapy should be initiated rapidly and aggressively (**Table 78-8**) in conjunction with the removal or reversal of immunosuppression if possible. Definite or probable invasive aspergillosis should be treated with voriconazole, isavuconazole, or lipid amphotericin B formulation (ie, liposomal AmB 3–5 mg/kg/day), or combination therapy.[171–173] In a recent European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) trial performed in patients with probable or proven aspergillosis, a combination therapy with voriconazole plus anidulafungin for at least 2 weeks was associated with an 8% reduction in 6-week all-cause mortality versus voriconazole monotherapy alone, although this difference was not statistically different in the context of the design of the clinical trial.[174] Therefore, the optimal approach for using combination therapy in invasive aspergillosis remains unresolved. Despite early and intensive therapy, mortality from invasive aspergillosis can be >50%.[175] In unresponsive patients, a lipid AmB formulation in combination therapy or possibly triazole should be considered.[171–177] Importantly, some less common molds intrinsically resistant to several antifungal classes (ie, Mucorales, *Fusarium* spp., *Scedosporium* spp.) occasionally present as infections or

breakthrough infections that may be indistinguishable from invasive aspergillosis.

Table 78-8
Therapeutic Options for Treatment of Aspergillosis

Disease	Primary	Secondary
Hyalohyphomycetes		
Aspergillosis		
Allergic bronchopulmonary	Prednisone 1 mg/kg/day followed by 0.5 mg/kg/day or every other day × 3–6 months; no antifungal therapy	ITZ 200 mg bid × 4 months[a]
Aspergilloma	Observation	Surgery[b]
Systemic (invasive)	Isavuconazole 300 mg IV three times daily for 48 hours LD, then 300 mg daily	Amphotericin B lipid formulation[c], or Posaconazole 300 mg twice-daily LD, then 300 mg daily or/and Combination therapy with an echinocandin[d]

AmB, amphotericin B; bid, twice daily; ITZ, itraconazole; LD, loading dose; tid, three times daily.

[a]Treatment should be continued until the patient is symptom-free and culture-negative for 3 months. Noted durations or total doses should be used only as a compass to help guide therapy.

[b]Indicated only for serious symptoms (eg, hemoptysis).

[c]Lipid formulations of amphotericin B should be utilized preferentially in these patients.

[d]Anidulafungin (AFG) 200 mg parenterally; caspofungin (CFG) 70 (50) mg parenterally on day 1 (2–14); micafungin (MFG) 70 mg parenterally; flucytosine (5FC) 150 mg/day parenterally.

Patients with mild-to-moderate *Aspergillus* should be treated with voriconazole or isavuconazole.[166] Clinical and microbiologic cure

rates of 50% to 71% have been reported for voriconazole- or isavuconazole-treated invasive aspergillosis. In a comparative trial of voriconazole versus isavuconazole for patients with proven or probable aspergillosis, patients randomized to receive isavuconazole had similar clinical response and mortality rates as voriconazole-treated patients with lower rates of ocular, hepatic, and cutaneous adverse reactions.[178],[179]

Cryptococcosis

CASE 78-9

Question 1: D.W., a 48-year-old male, was hospitalized with fever and severe headache. His history was significant for Hodgkin lymphoma, which is in remission. Lumbar puncture revealed the following:

Opening pressure of 280 mm Hg (normal, 10 mm Hg)
WBC count, 50 leukocytes/μL (normal, 0 leukocytes/μL)
Positive India ink preparation
Cryptococcal antigen titer, 1:4096
Serology for HIV infection was negative. Culture of the CSF eventually grew *C. neoformans*. The presumptive diagnosis is cryptococcal meningitis.

What are the treatment options for D.W.?

Currently, only two therapeutic options exist for meningeal cryptococcal disease: an AmB formulation with or without flucytosine and fluconazole. Flucytosine cannot be used alone for therapy or prophylaxis because of the rapid development of resistance. This yeast is also resistant to echinocandins. Patients, whether infected with HIV or not, have improved treatment outcomes when the combination of AmB and flucytosine is used.[180],[181] Furthermore, when flucytosine (100–150 mg/kg/day divided into four daily doses) is used in combination therapy, the dose of AmB may be reduced to 0.3 to 0.6 mg/kg/day, which decreases the frequency of dose-related AmB toxicity. In patients who cannot be treated with flucytosine, the dosage of AmB must be increased to more than 0.6 mg/kg/day. AmB 1 mg/kg/day is more rapidly fungicidal than 0.7 mg/kg/day when

used with 5FC. Liposomal AmB 3 mg/kg/day can and probably should be used instead of the nonlipid formulations in this disease owing to presumed increase in safety.[182]

Fluconazole is an alternative to AmB in patients infected with HIV with cryptococcal meningitis. It is important to be mindful of the following caveats, however: Sterilization of the CSF occurs more rapidly, and mortality is lower during the first 2 weeks of therapy in patients treated with AmB as compared with fluconazole.[182] Early mortality was especially high in fluconazole-treated patients who presented with altered mental status.[183–185] Thus, initial therapy of cryptococcal meningitis in patients with mental status changes should be initiated with AmB for at least 2 weeks or until the patient has stabilized clinically.

A landmark study on patients with cryptococcal meningitis compared patients randomized to receive either amphotericin B 1 mg/kg/day for 4 weeks or a 2-week induction regimen of amphotericin B 1 mg/kg/day plus flucytosine (1 mg/kg/day) or fluconazole (400 mg twice daily).[185] At day 70 after randomization, significantly fewer deaths were observed in patients receiving amphotericin B plus flucytosine versus patients receiving amphotericin B alone (hazard ratio: 0.61, 95% CI, 0.39–0.97, P = .04). Combination therapy with fluconazole did not significantly impact survival over amphotericin B monotherapy. Notably, the amphotericin B-flucytosine combination was associated with more rapid clearance of yeast from the CSF versus other regimens. Rates of adverse effects were similar in all groups even though neutropenia was slightly more common in patients receiving amphotericin B-flucytosine or amphotericin B-fluconazole combinations versus amphotericin B monotherapy (34% and 32% vs 19%, P = .04).

Fluconazole 400 mg/day may be an acceptable option in patients with less severe disease in all other patients. Another alternative may include liposomal AmB 4 to 6 mg/kg/day for 21 days. Until larger clinical studies have been completed, however, this regimen cannot be recommended over generic AmB (see Chapter 77, Opportunistic Infections in Patients Living With HIV).[181]

In D.W., initial treatment should focus on the elimination of all factors leading to immunosuppression. Antifungal therapy should be initiated immediately with AmB 0.3 to 0.6 mg/kg/day plus flucytosine 100 to 150 mg/kg/for a minimum of 6 weeks to optimize the chance of a cure, especially in transplant recipients.[185] In addition, CSF hypertension, usually presenting as headache, should be resolved through therapeutic spinal tap. Acetazolamide should be avoided in these cases.[186] An unfortunate consequence of eliminating immune suppression is immune reconstitution syndrome (IRIS). This syndrome is most commonly observed in patients infected with HIV started on antiretrovirals who experience complications secondary to new onset inflammatory reactions from replenished leukocytes. IRIS may make it appear these patients are failing antifungal therapy.

CASE 78-9, QUESTION 2: What parameters should be monitored while D.W. is treated with flucytosine?

The most common side effect of flucytosine is GI distress (eg, nausea, vomiting, and diarrhea). Although flucytosine is not metabolized per se by mammalian cells, gut flora may be responsible for metabolism of flucytosine to fluorouracil. This toxic metabolite has been speculated to account, in part, for the GI distress and bone marrow toxicity associated with flucytosine therapy.[187] Other flucytosine adverse effects include leukopenia, thrombocytopenia, and hepatotoxicity. Dose-dependent bone marrow suppression, which can be fatal, generally is seen in patients whose serum concentration of flucytosine is >100 µg/mL. Thus, it is important to monitor blood concentrations and maintain concentrations below this level.[181,183] If assays for flucytosine serum concentrations are unavailable, signs and symptoms of bone marrow suppression or worsening renal function should result in a dosage reduction or discontinuation of the drug. Flucytosine is eliminated by glomerular filtration, with 80% to 95% of the dose excreted unchanged in the urine. Renal excretion of flucytosine is directly related to creatinine clearance, and dosages should be adjusted

based on creatinine clearance to prevent the accumulation of toxic concentrations in patients with renal impairment.[101] Patients with creatinine clearances of 10 to 40 mL/minute should have the dosage of flucytosine reduced by 50% (usual dose, 37.5 mg/kg every 12 hours). For patients with creatinine clearance <10 mL/minute, dosing should be initiated at 37.5 mg/kg/day, with frequent monitoring of flucytosine serum concentrations. Dosage adjustment and close monitoring also are required for patients receiving hemodialysis, and it is recommended that the dose be given postdialysis.

CASE 78-9, QUESTION 3: When is combination antifungal therapy indicated?

In vitro results of antifungal combinations against many common mycotic pathogens have been variable. These incomplete and inconsistent findings have been attributed to variable incubation times, variable concentrations of antifungal agents, and the sequence of antifungal addition. As a result, clinical decisions about combination therapy should be based on patient-specific in vivo evaluations. Because of the limited clinical data, combination antifungal therapy should be initiated cautiously. Except for the treatment of cryptococcal meningitis and disseminated aspergillosis, combination therapy should be reserved for cases of treatment failure (disseminated candidiasis) with no other established pharmacologic options for therapy or mold infections with high mortality rates.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and website for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med.* 2002;347:408–415. (176)

Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med.* 2002;137:105–109. (139)

Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother.* 2005;49:3640–3645. (71)

Odom RB, Aly R, Scher RK, et al. A multicenter, placebo-controlled, double-blind study of intermittent therapy with itraconazole for the treatment of onychomycosis of the fingernail. *J Am Acad Dermatol.* 1997;36:231–235. (36)

Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62(4):e1–e50. (57)

Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;63(4):e1–e60. (179)

Pelz RK, Hendrix CW, Swoboda SM, et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg.* 2001;233:542–548. (116)

Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50(3):291–322. (182)

Rex JH, Pfaller MA, Walsh TJ, et al. Antifungal susceptibility testing: practical aspects and current challenges. *Clin Microbiol Rev.* 2001;14:643–658. (20)

Shepard JR, Addison RM, Alexander BD, et al. Multicenter evaluation of the *Candida albicans*/*Candida glabrata* peptide nucleic acid fluorescent in situ hybridization method for simultaneous dual-color identification of *C. albicans* and *C. glabrata* directly from blood culture bottles. *J Clin Microbiol.* 2008;46:50–55. (62)

COMPLETE REFERENCES CHAPTER 78 FUNGAL INFECTIONS

1. Anaissie E, McGinnis MR, Pfaller MA, eds. *Clinical Mycology*. Churchill Livingstone; 2009.
2. Rinaldi MG. Emerging opportunists. *Infect Dis Clin North Am*. 1989;3:65–76.
3. Vinh D, Masannat F, Dzioba RB, Galgiani JN, Holland SM. Refractory disseminated coccidioidomycosis and mycobacteriosis in interferon-gamma receptor 1 deficiency. *Clin Infect Dis*. 2009;49:e62–e65.
4. Netea MG, Marodi L. Innate immune mechanisms for recognition and uptake of Candida species. *Trends Immunol*. 2010;31:346–353.
5. Khardori N, Hayat S, Rolston K, Bodey GP. Cutaneous Rhizopus and Aspergillus infections in five patients with cancer. *Arch Dermatol*. 1989;125:952–956.
6. Wingard JR. Importance of Candida species other than *C. albicans* as pathogens in oncology patients. *Clin Infect Dis*. 1995;20:115–125.
7. Brajtburg J, Powderly WG, Kobayashi GS, Medoff G. Amphotericin B: current understanding of mechanisms of action. *Antimicrob Agents Chemother*. 1990;34:183–188.
8. Gruda I, Nadeau P, Brajtburg J, Medoff G. Application of differential spectra in the ultraviolet-visible region to study the formation of amphotericin B-sterol complexes. *Biochem Biophys Acta*. 1980;602:260–268.
9. Hitchcock CA, Barrett-Bee KJ, Russell NJ. The lipid composition and permeability to azole of an azole-and polyene-resistant mutant of *Candida albicans*. *J Med Vet Mycol*. 1987;25:29–37.
10. Pierce AM, Pierce HD Jr, Unrau AM, Oehlschlager AC. Lipid composition and polyene antibiotic resistance of *Candida albicans*. *Can J Biochem*. 1978;56:135–142.
11. Brajtburg J, Elberg S, Medoff J, Kobayashi GS, Schlessinger D, Medoff G. Stimulatory, permeabilizing, and toxic effects of amphotericin B on L cells. *Antimicrob Agents Chemother*. 1984;26:892–897.
12. Chouini-Lalanne N, Malet-Martino MC, Martino R, Michel G. Study of the metabolism of flucytosine in Aspergillus species by 19F nuclear magnetic resonance spectroscopy. *Antimicrob Agents Chemother*. 1989;33:1939–1945.
13. Bodey GP. Azole antifungal agents. *Clin Infect Dis*. 1992;14(suppl 1):S161–S169.
14. Petranyi G, Ryder NS, Stütz A. Allylamine derivatives: new class of synthetic antifungal agents inhibiting fungal squalene epoxidase. *Science*. 1984;244:1239–1241.
15. Manavathu EK, Cutright JL, Chandrasekar PH. Organism-dependent fungicidal activities of azoles. *Antimicrob Agents Chemother*. 1998;42:3018–3021.
16. Walsh TJ, Viviani MA, Arathoon E, et al. New targets and delivery systems for antifungal therapy. *Med Mycol*. 2000;38(suppl 1):335–347.

17. Clinical Laboratory Standards Institute. *Approved Standard CLSI Document M27-A3, M38A, M44-A2, M44-S3, and M51A*. Clinical Laboratory Standards Institute; 2011.
18. Rex JH, Pfaller MA, Galgiani JN, et al. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole, and Candida infections. *Clin Infect Dis*. 1997;24:235–247.
19. Morace G, Amato G, Bistoni F, et al. Multicenter comparative evaluation of six commercial systems and the national committee for Clinical Laboratory Standards M27-A broth microdilution method for fluconazole susceptibility testing of Candida species. *J Clin Microbiol*. 2002;40:2953–2958.
20. Rex JH, Pfaller MA, Walsh TJ, et al. Antifungal susceptibility testing: practical aspects and current challenges. *Clin Microbiol Rev*. 2001;14:643–658.
21. Vale-Silva LA, Buchta V. Antifungal susceptibility testing by flow cytometry: is it the future? *Mycoses*. 2006;49:261–273.
22. Lass-Florl C, Perkhofer S. In vitro susceptibility-testing in Aspergillus species. *Mycoses*. 2008;51:437–446.
23. Wagner C, Graninger W, Presterl E, Joukhadar C. The echinocandins: comparison of their pharmcokinetics, pharmcodynamics and clinical applications. *Pharmacology*. 2006;78:161–177.
24. Posaconazole (Noxafil) for invasive fungal infections. *Med Lett Drugs Ther*. 2006;48:93–95.
25. Fulvicin (griseofulvin). Package insert. Schering-Plough Healthcare Products; 1994.
26. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. *Clin Infect Dis*. 2013;56:1724–1732.
27. Beyda ND, John J, Kilic A, Alam MJ, Lasco TM, Garey KW. FKS mutant *Candida glabrata*; risk factors and outcomes in patients with candidemia. *Clin Infect Dis*. 2014;59:819–825.
28. Pham CD, Iqbal N, Bolden CB, et al. The role of FKS mutations in *C. glabrata*: MIC values, echinocandin resistance and multidrug resistance. *Antimicrob Agents Chemother*. 2014;58:4690–4696.
29. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal AmB for the prevention of pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2008;46:1401–1408.
30. Drew RH, Dodds Ashley E, Benjamin DK Jr, Duane Davis R, Palmer SM, Perfect JR. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. *Transplantation*. 2004;77:232–237.
31. Le J, Schiller DS. Aerosolized delivery of antifungal agents. *Curr Fungal Infect Rep*. 2010;4:96–102.

32. Nix DE, Swezey RR, Hector R, Galgiani JN. Pharmacokinetics of nikkomycin Z after single rising oral doses. *Antimicrob Agents Chemother*. 2009;53(6): 2517–2521.
33. Benincasa M, Scocchi M, Pacor S, et al. Fungicidal activity of five cathelicidin peptides against clinically isolated yeasts. *J Antimicrob Chemother*. 2006;58:950–959.
34. Lopez-Garcia B, Lee PH, Gallo RL. Expression and potential function of cathelicidin antimicrobial peptides in dermatophytosis and tinea versicolor. *J Antimicrob Chemother*. 2006;57:877–882.
35. Pachl J, Svoboda P, Jacobs F, et al. A randomized, blinded, multicenter trial of lipid-associated amphotericin B alone versus in combination with an antibody-based inhibitor of heat shock protein 90 in patients with invasive candidiasis. *Clin Infect Dis*. 2006;42:1404–1413.
36. Odom RB, Aly R, Scher RK, et al. A multicenter, placebo-controlled, doubleblind study of intermittent therapy with itraconazole for the treatment of onychomycosis of the fingernail. *J Am Acad Dermatol*. 1997;36:231–235.
37. Havu V, Brandt H, Heikkilä H, et al. A double-blind, randomized study comparing itraconazole pulse therapy with continuous dosing for the treatment of toenail onychomycosis. *Br J Dermatol*. 1997;36:230–234.
38. Scher RK, Breneman D, Rich P, et al. Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol*. 1998;38:S77–S86.
39. Ling MR, Swinyer LJ, Jarratt MT, et al. Once-weekly fluconazole (450 mg) for 4, 6, or 9 months of treatment for distal subungual onychomycosis of the toenail. *J Am Acad Dermatol*. 1998;38:S95–S102.
40. Gupta AK, Lynde CW, Konnikov N. Single-blind, randomized, prospective study of sequential itraconazole and terbinafine pulse compared with terbinafine pulse for the treatment of toenail onychomycosis. *J Am Acad Dermatol*. 2001;44:485–491.
41. Kauffman CA. Endemic mycoses: blastomycosis, histoplasmosis, and sporotrichosis. *Infect Dis Clin North Am*. 2006;20:645–662.
42. Breeling JL, Weinstein L. Pulmonary sporotrichosis treated with itraconazole. *Chest*. 1993;103:313–314.
43. McGinnis MR, Nordoff N, Li RK, Pasarell L, Warnock DW. Sporothrix schenckii sensitivity to voriconazole, itraconazole, and amphotericin B. *Med Mycol*. 2001;39:369–371.
44. Chapman SW, Pappas P, Kauffmann C, et al. Comparative evaluation of the efficacy and safety of two doses of terbinafine (500 and 1000 mg day(-1)) in the treatment of cutaneous or lymphocutaneous sporotrichosis. *Mycoses*. 2004;47:62–68.
45. Wishart JM. The influence of food on the pharmacokinetics of itraconazole in patients with superficial fungal infection. *J Am Acad Dermatol*. 1987;17(2):220–223.

46. Barone JA, Koh JG, Bierman RH, et al. Food interaction and steady state pharmacokinetics of itraconazole capsules in healthy male volunteers. *Antimicrob Agents Chemother*. 1993;37:778–784.
47. Smith D, van de Velde V, Woestenborghs R, Gazzard BG. The pharmacokinetics of oral itraconazole in AIDS patients. *J Pharm Pharmacol*. 1992;44:618–619.
48. Zhao Q, Zhou H, Pesco-Koplowitz L. Pharmacokinetics of intravenous itraconazole followed by itraconazole oral solution in patients with human immunodeficiency virus infection. *J Clin Pharmacol*. 2001;41:1319–1328.
49. Sporonox (itraconazole) oral suspension. Package insert. Janssen Pharmaceuticals; 1998.
50. Tatro DS, ed. *Drug Interaction Facts 2015*. 1st ed. Lippincott, Williams, and Wilkins; 2014.
51. Kraft WK, Chang PS, van Iersel ML, Waskin H, Krishna G, Kersemaekers WM. Posaconazole tablet pharmacokinetics: lack of effect of concomitant medications altering gastric pH and gastric motility in healthy subjects. *Antimicrob Agents Chemother*. 2014;58:4020–4025.
52. Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single-and multiple-dose pharmacokinetics and safety in healthy volunteers. *J Antimicrob Chemother*. 2012;67:2725–2730.
53. McKeage K. Posaconazole: a review of the gastro-resistant tablet and intravenous solution in invasive fungal infections. *Drugs*. 2015;75:397–406.
54. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother*. 2014;69:1162–1176.
55. Smith J, Andes D. Therapeutic drug monitoring of antifungals: pharmacokinetic and pharmacodynamic considerations. *Ther Drug Monit*. 2008;30:167–172.
56. Arendrup MC, Fisher BT, Zaoutis TE. Invasive fungal infections in the paediatric and neonatal population: diagnostics and management issues. *Clin Microbiol Infect*. 2009;15:613–624.
57. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1–e50.
58. Woods GL, Gutierrez Y. *Diagnostic Pathology of Infectious Diseases*. Lea & Febiger; 1993.
59. Arrington JB. Bacteria, fungi, and other microorganisms. In: Prophet EB, Mills B, Arrington JB, Sobin LH, eds. *Laboratory Methods in Histotechnology. Armed Forces Institute of Pathology*. American Registry of Pathology; 1992:203.

60. Jensen HE, Salonen J, Ekfors TO. The use of immunohistochemistry to improve sensitivity and specificity in the diagnosis of systemic mycoses in patients with haematologic malignancies. *J Pathol*. 1997;181:100–105.
61. Lischewski A, Kretschmar M, Hof H, Amann R, Hacker J, Morschhäuser J. Detection and identification of Candida species in experimentally infected tissue and human blood by rRNA-specific fluorescent in-situ hybridization. *J Clin Microbiol*. 1997;35:2943–2948.
62. Shepard JR, Addison RM, Alexander BD, et al. Multicenter evaluation of the *Candida albicans/Candida glabrata* peptide nucleic acid fluorescent in situ hybridization method for simultaneous dual-color identification of *C. albicans* and *C. glabrata* directly from blood culture bottles. *J Clin Microbiol*. 2008; 46:50–55.
63. Coovadia YJ, Solwa Z. Sensitivity and specificity of a latex agglutination test for detection of cryptococcal antigen in meningitis. *S Afr Med J*. 1987;71:510–512.
64. Koshi G, Anandi V, Shastry JC, Cheriyan AM, Abraham J. Coagglutination (CoA) test for the rapid diagnosis of cryptococcal meningitis. *J Med Microbiol*. 1989;29:189–194.
65. Wheat LJ, Kohler RB, Tewari RP. Diagnosis of disseminated histoplasmosis by detection of *Histoplasma capsulatum* antigen in serum and urine specimens. *N Engl J Med*. 1986;314:83–88.
66. Pasqualotto AC, Sukiennik TC. Beta-glucan in the diagnosis of invasive fungal disease. *Clin Infect Dis*. 2008;47:292–293.
67. Crislip MA, Edwards JE Jr. Candidiasis [published correction appears in *Infect Dis Clin North Am*. 1989;3:ix]. *Infect Dis Clin North Am*. 1989;2:103–133.
68. Wheat LJ. Systemic fungal infections: diagnosis and treatment. I. Histoplasmosis. *Infect Dis Clin North Am*. 1988;2:841–859.
69. Gudiaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis*. 2003;37:1172–1177.
70. Patel M, Kunz DF, Trivedi VM, Jones MG, Moser SA, Baddley JW. Initial management of candidemia at an academic medical center: evaluation of the IDSA guidelines. *Diagn Microbiol Infect Dis*. 2005;52:29–34.
71. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother*. 2005;49:3640–3645.
72. Walsh TH, Rex JH. All catheter-related candidemia is not the same: assessment of the balance between the risks and benefit of removal of vascular catheters. *Clin Infect Dis*. 2002;34:600–602.
73. Nucci M, Anaissie E. Should vascular catheters be removed from all patients with candidemia? An evidence-based review. *Clin Infect Dis*. 2002;34:591–599.

74. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med*. 2002;347:2020–2029.
75. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *N Engl J Med*. 1994;331:1325–1330.
76. Rex JH, Pfaller MA, Barry AL, Nelson PW, Webb CD. Antifungal susceptibility testing of isolates from a randomized, multicenter trial of fluconazole versus amphotericin B as treatment of nonneutropenic patients with candidemia. NIAID Mycoses Study Group and the Candidemia Study Group. *Antimicrob Agents Chemother*. 1995;39:40–44.
77. Christiansen KJ, Bernard EM, Gold JW, Armstrong D. Distribution and activity of amphotericin B in humans. *J Infect Dis*. 1985;152:1037–1043.
78. Collette N, van der Auwera P, Lopez AP, Heymans C, Meunier F. Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericin B-deoxycholate. *Antimicrob Agents Chemother*. 1989;33:362–368.
79. Rex JH, Pappas PG, Karchmer AW, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo vs. fluconazole plus amphotericin B as therapy of candidemia and its consequences in nonneutropenic patients. *Clin Infect Dis*. 2003;36:1221–1228.
80. Cappelletty D, Eiselstein-McKitrick K. The echinocandins. *Pharmacotherapy*. 2007;27:369–388.
81. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis [published correction appears in *Clin Infect Dis*. 2008;47:302]. *Clin Infect Dis*. 2007;45:883–893.
82. Abele-Horn M, Kopp A, Sternberg U, et al. A randomized study comparing fluconazole with amphotericin B/5-flucytosine for the treatment of systemic Candida infections in intensive care patients. *Infection*. 1996;2496:426–432.
83. Wingard JR. Infections due to resistant Candida species in patients with cancer who are receiving chromotherapy. *Clin Infect Dis*. 1994;19(suppl 1):S49–S53.
84. Cleary JD, Garcia-Effron G, Chapman SW, Perlin DS. Reduced *Candida glabrata* susceptibility secondary to an FKS1 mutation developed during candidemia treatment. *Antimicrob Agents Chemother*. 2008;52:2263–2265.
85. Cleary JD, Wasan K. Amphotericin B: a new look at cellular binding. *Open Antimicrob Agents*. 2011;3:30–36.
86. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. *Clin Pharmacokinet*. 1983;8:17–42.
87. Ernst EJ, Klepser ME, Pfaller MA. Postantifungal effects of echinocandin, azole, and polyene antifungal agents against *Candida albicans* and *Cryptococcus neoformans*. *Antimicrob Agents Chemother*. 2000;44:1108–1111.

88. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. *Rev Infect Dis*. 1990;12:308–329.
89. Cleary JD, Nolan RL, Chapman SW. Inhibition of interleukin 1 release from endotoxin or amphotericin B-stimulated monocytes. *Antimicrob Agents Chemother*. 1992;36:977–981.
90. Cleary JD, et al. Pharmacologic modulation of prostaglandin E2 (PGE2) production by bacterial endotoxin. Presented at: LPSat 31st Annual Interscience Conference on Antimicrobial Agents and Chemotherapy Meeting; September 19, 1991; Chicago, IL.
91. Tynes BS, Utz JP, Bennett JE, Alling DW. Reducing amphotericin B reactions. *Am Rev Respir Dis*. 1963;87:264–268.
92. Hoeprich PD. Clinical use of amphotericin B and derivative: lore, mystique, and fact. *Clin Infect Dis*. 1992;14:S114–S119.
93. Gigliotti F, Shenep JL, Lott L, Thornton D. Induction of prostaglandin synthesis as the mechanism responsible for the chills and fever produced by infusing amphotericin B. *J Infect Dis*. 1987;156:784–789.
94. Burks LC, Aisner J, Fortner CL, Wiernik PH. Meperidine for the treatment of shaking chills and fever. *Arch Intern Med*. 1980;140:483–484.
95. Cleary JD, Weisdorf D, Fletcher CV. Effect of infusion rate on amphotericin B-associated febrile reactions. *Drug Intell Clin Pharm*. 1988;22:769–772.
96. Oldfield EC III, Garst PD, Hostettler C, White M, Samuelson D. Randomized, double-blind trial of 1-versus 4-hour amphotericin B infusion durations. *Antimicrob Agents Chemother*. 1990;34:1402–1406.
97. Cleary JD, Hayman J, Sherwood J, Lasala GP, Piazza-Hepp T. Amphotericin B overdose in pediatric patients with associated cardiac arrest. *Ann Pharmacother*. 1993;27:715–719.
98. Branch RA. Prevention of amphotericin B-induced renal impairment: a review on the use of sodium supplementation. *Arch Intern Med*. 1988;148:2389–2394.
99. Fisher MA, Talbot GH, Maislin G, McKeon BP, Tynan KP, Strom BL. Risk factors for amphotericin B-associated nephrotoxicity. *Am J Med*. 1989;87:547–552.
100. Lin AC, Goldwasser E, Bernard EM, Chapman SW. Amphotericin B blunts erythropoietin response to anemia. *J Infect Dis*. 1990;161:348–351.
101. Bennett WM, Aronoff GR, Morrison G, et al. Drug prescribing in renal failure: dosing guidelines for adults. *Am J Kidney Dis*. 1983;3:155–193.
102. Abel S, Allan R, Gandelman K, Tomaszewski K, Webb DJ, Wood ND. Pharmacokinetics, safety and tolerance of voriconazole in renally impaired subjects. *Clin Drug Investig*. 2008;28:409–420.
103. Oude Lashof AM, Sobel JD, Ruhnke M, et al. Safety and tolerability of voriconazole in patients with baseline renal insufficiency and candidemia. *Antimicrob Agents Chemother*. 2012;56:3133–3137.

104. Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in superficial and systemic mycoses [published correction appears in *Drugs*. 1990;40:862]. *Drugs*. 1990;39:877–916.
105. Graybill JR. New antifungal agents. *Eur J Clin Microbiol Infect Dis*. 1989;8:402–412.
106. Van Cauteren H, Heykants J, De Coster R, Cauwenbergh G. Itraconazole pharmacologic studies in animals and humans. *Rev Infect Dis*. 1987;9(suppl 1):S43–S46.
107. Hardin TC, Graybill JR, Fetchick R, Woestenborghs R, Rinaldi MG, Kuhn JG. Pharmacokinetics of itraconazole following oral administration to normal volunteers. *Antimicrob Agents Chemother*. 1988;32:1310–1313.
108. Schwartz S, Milatovic D, Thiel E. Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukaemia. *Br J Haematol*. 1997;97:663–665.
109. Grasela DM, Olsen SJ, Mummaneni V, et al. Ravuconazole: multiple ascending oral dose study in healthy subjects. Paper presented at: 42nd Interscience Conference on Antimicrobial Agents Chemotherapy; September 27, 2002; San Diego, CA.
110. Ullmann AJ, Cornely OA, Burchardt A, et al. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. *Antimicrob Agents Chemother*. 2006;50:658–666.
111. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet*. 2006;45:649–663.
112. Wong-Beringer A, Jacobs RA, Guglielmo BJ. Lipid formulations of amphotericin B: clinical efficacy and toxicities. *Clin Infect Dis*. 1998;27:603–618.
113. Cleary JD. Amphotericin B formulated in a lipid emulsion. *Ann Pharmacother*. 1996;30:409–412.
114. Anaissie EJ, et al. Amphotericin B lipid complex versus amphotericin B (AMB) for treatment of hematogenous and invasive candidiasis: a prospective, randomized, multicenter trial [abstract LM21]. In: *Program and Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy*. American Society for Microbiology; 1995:330.
115. Ostrosky-Zeichner L, Shoham S, Vazquez J, et al. MSG-01: a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high-risk adults in the critical care setting. *Clin Infect Dis*. 2014;58:1219–1226.
116. Pelz RK, Hendrix CW, Swoboda SM, et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg*. 2001;233:542–548.

117. Ezdinli EZ, O'Sullivan DD, Wasser LP, Kim U, Stutzman L. Oral amphotericin for candidiasis in patients with hematologic neoplasms. *JAMA*. 1979;242:258–260.
118. DeGregorio MW, Lee WM, Ries CA. Candida infections in patients with acute leukemia: ineffectiveness of nystatin prophylaxis and relationship between oropharyngeal and systemic candidiasis. *Cancer*. 1982;50:2780–2784.
119. Cuttner J, Troy KM, Funaro L, Brenden R, Bottone EJ. Clotrimazole treatment for prevention of oral candidiasis in patients with acute leukemia undergoing chemotherapy. *Am J Med*. 1986;81:771–774.
120. Yeo E, Alvarado T, Fainstein V, Bodey GP. Prophylaxis of oropharyngeal candidiasis with clotrimazole. *J Clin Oncol*. 1985;3:1668–1671.
121. Ang BS, Telenti A, King B, Steckelberg JM, Wilson WR. Candidemia from a urinary tract source: microbiological aspects and clinical significance. *Clin Infect Dis*. 1993;17:662–666.
122. Fong IW, Cheng PC, Hinton NA. Fungicidal effect of amphotericin B in urine: in vitro study to assess feasibility of bladder washout for localization of site of candiduria. *Antimicrob Agents Chemother*. 1991;35:1856–1859.
123. Vergis EN, et al. A randomized controlled trial of oral fluconazole and local amphotericin B for treatment of Candida funguria in hospitalized patients. Paper presented at: Infectious Diseases Society Meeting; September 14, 1997; San Francisco, CA.
124. Jacobs LG, Skidmore EA, Freeman K, Lipschultz D, Fox N. Oral fluconazole compared with bladder irrigation with amphotericin B for treatment of fungal urinary tract infections in elderly patients. *Clin Infect Dis*. 1996;22:30–35.
125. Fujihiro S, Ehara H, Saito A, et al. Flucytosine in the treatment of urinary fungal infections: clinical efficacy and background factors. *Jpn J Antibiot*. 1991;44:14–21.
126. Graybill JR, Galgiani JN, Jorgensen JH, Strandberg DA. Ketoconazole therapy for fungal urinary tract infections. *J Urol*. 1983;29:68–70.
127. Ikemoto H. A clinical study of fluconazole for the treatment of deep mycoses. *Diagn Microbiol Infect Dis*. 1989;12(suppl 4):239S–247S.
128. Lagrotteria D, Rotstein C, Lee CH. Treatment of candiduria with micafungin: a case series. *Can J Infect Dis Med*. 2007;18:149–150.
129. Parker JD, Doto IL, Tosh FE. A decade of experience with blastomycosis and its treatment with amphotericin B. *Am Rev Respir Dis*. 1969;99:895–902.
130. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Treatment of blastomycosis and histoplasmosis with ketoconazole: results of a prospective, randomized clinical trial. *Ann Intern Med*. 1985;103: 861–872.
131. Bradsher RW. Blastomycosis in systemic fungal infections: diagnosis and treatment I. *Infect Dis Clin North Am*. 1988;2:877–898.
132. Pappas PG. Treatment of blastomycosis with higher doses of fluconazole. *Clin Infect Dis*. 1997;25:200–205.

133. Chapman SW. Blastomyces dermatitidis. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. Churchill Livingstone; 1990:1999.
134. U.S. Food and Drug Administration. Content and format of labeling for human prescription drugs and biological products; Requirements for pregnancy and lactation labeling. *Fed Reg*. 1980;44:37434–37467.
135. King CT, Rogers PD, Cleary JD, Chapman SW. Antifungal therapy during pregnancy. *Clin Infect Dis*. 1998;27:1151–1160.
136. Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. 2013;369:830–839.
137. Pursley TJ. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. 1996;22:336–340.
138. Wheat LJ. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807–825.
139. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med*. 2002;137:105–109.
140. Cleary JD, Pearson M, Oliver J, Chapman SW. Association between Histoplasma exposure and stroke. *J Stroke Cerebrovasc Dis*. 2008;17:312–319.
141. Pont A, Williams PL, Loose DS, et al. Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med*. 1982;97:370–372.
142. Lyman CA, Walsh TJ. Systemically administered antifungal agents. *Drugs*. 1992;44:9–35.
143. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Terfenadine-ketoconazole interactions: pharmacokinetic and electrocardiographic consequences [published correction appears in *JAMA*. 1993;269:2088]. *JAMA*. 1993;269:1513–1518.
144. Glynn AM, Slaughter RL, Brass C, D'Ambrosio R, Jusko WJ. Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion. *Clin Pharmacol Ther*. 1986;39:654–659.
145. Brüggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clin Infect Dis*. 2009;48:1441–1458.
146. Saubolle MA, McKellar PP, Sussland D. Epidemiologic, clinical, and diagnostic aspects of coccidioidomycosis. *J Clin Microbiol*. 2007;45:26–30.
147. Peter JB. *Use and Interpretation of Tests in Medical Microbiology*. 3rd ed. Specialty Laboratories; 1992.
148. Galgiani JN, Grace GM, Lundergan LL. New serologic tests for early detection of coccidioidomycosis. *J Infect Dis*. 1991;163:671–674.

149. Vermes A, Guchelaar HJ, Dankert J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *J Antimicrob Chemother*. 2000;46:171–179.
150. Brammer KW, Farrow PR, Faulkner JK. Pharmacokinetics and tissue penetration of fluconazole in humans. *Rev Infect Dis*. 1990;12(suppl 3):S318–S326.
151. Phillips P, Fetchick R, Weisman I, Foshee S, Graybill JR. Tolerance to and efficacy of itraconazole in treatment of systemic mycoses: preliminary results. *Rev Infect Dis*. 1987;9(suppl 1):S87–S93.
152. Dodds AE, Zaas AK, Fang AF, Damle B, Perfect JR. Comparative pharmacokinetics of voriconazole administered orally as either crushed or whole tablets. *Antimicrob Agents Chemother*. 2007;51:877–880.
153. Bowden R, Chandrasekar P, White MH, et al. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis*. 2002;35:359–366.
154. Galgiani JN, Catanzaro A, Cloud GA, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. *Ann Intern Med*. 2000;133:676–686.
155. Ratcheson RA, Ommaya AK. Experience with the subcutaneous cerebrospinal fluid reservoir: a preliminary report of 60 cases. *N Engl J Med*. 1968;279:1025–1031.
156. Harrison HR, Galgiani JN, Reynolds AF Jr, Sprunger LW, Friedman AD. Amphotericin B and imidazole therapy for coccidioidal meningitis in children. *Pediatr Infect Dis*. 1983;2:216–221.
157. Witorsch P, Williams TW Jr, Ommaya AK, Utz JP. Intraventricular administration of amphotericin B. *JAMA*. 1965;194:109.
158. Sung JP, Grendahl JG, Levine HB. Intravenous and intrathecal miconazole therapy for systemic mycoses. *West J Med*. 1977;126:5–13.
159. Fisher JF, Dewald J. Parkinsonism associated with intraventricular amphotericin B. *J Antimicrob Chemother*. 1983;12:97–99.
160. Winn RE, Bower JH, Richards JF. Acute toxic delirium: neurotoxicity of intrathecal administration of amphotericin B. *Arch Intern Med*. 1979;139:706–707.
161. Haber RW, Joseph M. Neurological manifestations after amphotericin B therapy. *BMJ*. 1962;1:230–231.
162. Carnevale NT, Galgiani JN, Stevens DA, et al. Amphotericin-induced myelopathy. *Arch Intern Med*. 1980;140:1189–1192.
163. Anaissie EJ, Darouiche RO, Abi-Said D, et al. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. *Clin Infect Dis*. 1996;23:964–972.

164. Prentice HG, Hann IM, Herbrecht R, et al. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol*. 1997;98:711–718.
165. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy inpatients with persistent fever and neutropenia. *N Engl J Med*. 2004;351:1391–1402.
166. Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. A randomized, controlled trial. *Ann Intern Med*. 2001;135:412–422.
167. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever [published correction appears in *N Engl J Med*. 2007;356:760]. *N Engl J Med*. 2002;346:225–234.
168. Pagano L, Caira M, Nosari A, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study—Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. *Clin Infect Dis*. 2007;45:1161–1170.
169. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol*. 1997;15:139–147.
170. Nucci M, Nouér SA, Cappone D, Anaissie E. Early diagnosis of invasive pulmonary aspergillosis in hematologic patients: an opportunity to improve the outcome. *Haematologica*. 2013;98:1657–1660.
171. Denning DW, Marr KA, Lau WM, et al. Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis. *J Infect*. 2006;53:337–349.
172. Walsh TJ, Goodman JL, Pappas P, et al. Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with Aspergillus species and other filamentous fungi: maximum tolerated dose study. *Antimicrob Agents Chemother*. 2001;45:3487–3496.
173. Maertens J, Glasmacher A, Herbrecht R, et al. Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. *Cancer*. 2006;107:2888–2897.
174. Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis*. 2004;39:797–802.
175. Ellis M, Spence D, de Pauw B, et al. An EORTC international multicenter randomized trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. *Clin Infect Dis*. 1998;27:1406–1412.

176. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347:408–415.
177. Segal BH, Almyroudis NG, Battiwalla M, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis*. 2007;44:402–409.
178. Maertens J, et al. A phase 3 randomized, double-blind trial evaluating isavuconazole versus voriconazole for the primary treatment of invasive fungal infections caused by Aspergillus spp. and other filamentous fungi. In: European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); May 13, 2004.
179. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1–e60.
180. Larsen RA, Leal MA, Chan LS. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS: a randomized trial. *Ann Intern Med*. 1990;113:183–187.
181. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med*. 1979;301:126–131.
182. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(3):291–322.
183. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS associated cryptococcal meningitis. *N Engl J Med*. 1992;326:83–89.
184. Day JN, Chau TTH, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. 2013;368:1291–1302.
185. Hibberd PL, Rubin RH. Clinical aspects of fungal infection in organ transplant recipients. *Clin Infect Dis*. 1994;19:S33–S40.
186. Newton PN, Thai le H, Tip NQ, et al. A randomized, double-blind, placebo controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis*. 2002;35:769–772.
187. Kauffman CA, Frame PT. Bone marrow toxicity associated with 5-fluorocytosine therapy. *Antimicrob Agents Chemother*. 1977;11:244–247.

79

Viral Infections

Sandra Benavides, Neeta Bahal O'Mara, and Milap C. Nahata

CORE PRINCIPLES		CHAPTER CASES
1	Herpes simplex virus (HSV) encephalitis is associated with significant morbidity and mortality. Intravenous acyclovir for a 21-day period is the therapy of choice.	**Case 79-1 (Questions 1–4)**
2	Neonatal herpes can present with mucocutaneous and ocular infection, as well as encephalitis and disseminated HSV infection. Transmission can be acquired during the first trimester of pregnancy or during vaginal delivery in an infected mother.	**Case 79-2 (Questions 1–3)**
3	Herpes labialis is the most common oral–facial HSV infection and is usually self-limiting in an immunocompetent host. Patients who are immunocompromised must be treated	**Case 79-3 (Question 1)** **Case 79-4 (Questions 1, 2)** **Case 79-5 (Question 1)**

	with antiviral therapy, primarily oral or intravenous acyclovir or oral valacyclovir.	
4	Individuals with progressive varicella, those with extracutaneous complications, or those at high risk for developing complications to varicella infection benefit from antiviral therapy.	**Case 79-6 (Question 1)** **Case 79-7 (Questions 1, 2)**
5	The goal of pharmacotherapy of herpes zoster is to reduce pain and duration of rash and to prevent the development of postherpetic neuralgia (PHN). These outcomes can be accomplished with the use of oral acyclovir, famciclovir, or valacyclovir. For the treatment of PHN, topical capsaicin gels, creams and patches, topical lidocaine patches, and oral gabapentin and pregabalin are efficacious.	**Case 79-8 (Questions 1–3)** **Case 79-9 (Question 1, 2)**
6	Neuraminidase inhibitors, such as zanamivir, oseltamivir, and peramivir, are indicated for the treatment of influenza if used within 48 hours of the onset of symptoms.	**Case 79-10 (Question 1, 2)** **Case 79-11 (Question 1)**
7	Influenza vaccination is the most effective mechanism to prevent the flu. However, certain high-risk populations may require additional prophylaxis with oseltamivir or zanamivir.	**Case 79-11 (Question 2)** **Case 79-12 (Questions 1–3)**
8	Infants at high risk for severe disease caused by respiratory syncytial virus (RSV) should receive monthly	**Case 79-13 (Questions 1, 2)**

	intramuscular injections of palivizumab for a total of five doses during the RSV season.	
9	West Nile virus can cause disease ranging from a febrile infection to encephalitis. Treatment is supportive; however, ribavirin and interferon-α-2b have been tried in this patient population.	**Case 79-14 (Questions 1, 2)**
10	Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a highly transmissible virus that causes COVID-19. Patients can be asymptomatic or have viral pneumonia with multisystem organ dysfunction. Preventive and treatment strategies continue to be developed.	**Case 79-15 (Questions 1–3)**
11	The common cold is the most prevalent viral infection. Numerous pathogens can cause this respiratory infection, including rhinovirus, coronavirus, parainfluenza, RSV, adenovirus, and enterovirus. There are currently no products that have been conclusively shown to prevent or treat the common cold.	**Case 79-16 (Question 1)**

INTRODUCTION

Viral infections are common causes of human disease. An estimated 60% of illnesses in developed countries result from viruses,

compared with only 15% from bacteria. These include the common cold, chickenpox, measles, mumps, influenza, bronchitis, gastroenteritis, hepatitis, poliomyelitis, rabies, and numerous diseases caused by the herpesviruses. Upper respiratory tract infections, such as the common cold or influenza, are among the most common reasons for visits to a health care professional.[1] Most of these patients have a self-limiting illness; however, certain viral infections, such as influenza, can cause significant mortality, particularly in the elderly. During the worldwide Spanish influenza epidemic of 1918 to 1920, 50 to 100 million people died.[2] At the writing of this chapter, the world is enduring a pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has caused millions of deaths worldwide and unknown long-lasting health consequences. Although influenza and SARS-CoV-2 vaccines reduce the morbidity and mortality associated with these diseases, for many other potentially severe viral infections, including herpes encephalitis and neonatal herpes, no vaccine is available.

Substantial progress has been made in antiviral chemotherapy as a result of advances in molecular virology and genetic engineering. Antiviral agents can be designed to inhibit functions specific to viruses, which maximize their therapeutic benefits and minimize adverse effects.

Current technology also permits rapid diagnosis of viral diseases. It is now possible to make a specific diagnosis of several viral illnesses within hours to a few days; previously, a specific diagnosis often took days to months. These improved diagnostics have facilitated rapid selection of an appropriate antiviral drug.

This chapter describes the etiology, pathogenesis, and treatment of common viral infections. Specific case presentations illustrate the optimal use of antiviral drugs in patients with viral infections.

HERPES SIMPLEX VIRUS INFECTIONS

Herpes viruses are responsible for a broad spectrum of diseases including acute life-threatening illness (herpes encephalitis and neonatal herpes), as well as more chronic, recurrent infection (genital herpes). Antivirals significantly decrease the morbidity and mortality in most of these infections.[3]

Herpes Encephalitis

Herpes simplex virus (HSV) encephalitis is the most common sporadic viral infection of the central nervous system (CNS). HSV encephalitis occurs in up to 500,000 people yearly, although this may be an underestimate owing to difficulties in diagnosis. It typically occurs in two populations, those ages 6 months to 20 years and those older than 50 years. It is characterized by the acute onset of fever, headache, decreased consciousness, and seizures. Any child with fever and altered behavior should be evaluated for HSV encephalitis. Without treatment, mortality approaches 70% and some morbidity is evident in up to 90% of survivors. Only 2.5% of patients recover to baseline neurologic function.[4]

Herpes simplex virus type 1 (HSV-1) is the etiologic agent in most patients with herpes encephalitis, but herpes simplex virus type 2 (HSV-2) is more common in newborns. The infection may be localized to the brain or involve cutaneous and mucous membranes. Although any area of the brain can be involved, the orbital region of the frontal lobes and the temporal lobes are most often affected.[5]

Herpes encephalitis is often difficult to diagnose. A magnetic resonance imaging (MRI) can identify brain abnormalities in 80% to 100% of patients with herpes encephalitis.[6] If an MRI is unavailable, a computed tomography (CT) scan can be used to rule out other conditions such as brain abscess or other space-occupying lesions.

Cerebrospinal fluid (CSF) examination usually reveals pleocytosis (predominately lymphocytes) with 50 to 2000 white blood cells (WBCs)/μL. Polymorphonuclear leukocytosis and red blood cells (RBCs) may also be seen. Many patients have an elevated protein

level in the CSF (median, 80 mg/dL; normal values differ per age, eg, if 6 months or older, 15–45 mg/dL).

The electroencephalogram (EEG) is the most sensitive but least specific test. There are usually CT or brain scan abnormalities, but these may take a day or two longer to appear. The EEG, MRI, CT, and brain scan findings compatible with HSV encephalitis can be mimicked by other conditions, and a brain biopsy is required to clearly establish the diagnosis. Rapid diagnosis of herpes encephalitis by a polymerase chain reaction (PCR) assay of HSV DNA in the CSF is available at most medical centers. This is a highly sensitive, specific, and rapid method for diagnosing herpes encephalitis.[7]

CLINICAL PRESENTATION

CASE 79-1

Question 1: R.F., a 7-year-old male weighing 44.09 pounds (20 kg), was seen in the emergency department (ED) after a seizure. For the previous 3 days, R.F. had decreased appetite, headache, fever of 101 to 102 °F (38.33–38.89 °C), and was lethargic and disoriented. His leukocyte count was 13,000/μL with a shift to the left. Ceftriaxone (50 mg/kg intravenously [IV] every 12 hours) and dexamethasone (0.15 mg/kg IV every 6 hours) were initiated for presumed bacterial meningitis. Levetiracetam (10 mg/kg IV every 12 hours) was given for seizure control. The CSF finding was normal, and no bacteria could be cultured. Acyclovir 20 mg/kg IV every 8 hours was started immediately. A PCR analysis of HSV-1 returned a positive result.

What findings in R.F. are consistent with the diagnosis of herpes encephalitis?

Fever, headache, lethargy, and disorientation are common features of herpes encephalitis. As illustrated by R.F., the CSF examination can be normal in some patients. A negative CSF culture result suggests the absence of a bacterial infection.[8] However, the positive HSV-1 DNA finding by PCR analysis confirms the diagnosis of herpes encephalitis.

TREATMENT: ACYCLOVIR

Case 79-1, Question 2: What is the treatment of choice for R.F.'s herpes encephalitis?

Two studies comparing acyclovir and vidarabine (no longer marketed in the United States) have demonstrated that IV acyclovir (10 mg/kg every 8 hours for 10 days) is the treatment of choice in patients with herpes encephalitis.[9,10] The 12-month all-cause mortality was 25% in the acyclovir-treated group and 59% in the vidarabine-treated group. Notably, nearly one-third of the patients treated with acyclovir returned to normal life, compared with only 12% of those treated with vidarabine.[11]

Acyclovir is the treatment of choice for R.F. because it has been shown to decrease morbidity in patients with herpes encephalitis. Acyclovir should be started as soon as HSV encephalitis is suspected because early initiation of therapy is associated with improved outcome. Therapy should be continued for 14 to 21 days.[12,13] The role of corticosteroids in the treatment of herpes encephalitis is not well defined. One small, nonrandomized trial found that corticosteroid therapy, in combination with IV acyclovir, was associated with an improved outcome.[14] However, prospective, randomized trials are needed before routine use of corticosteroids can be recommended.[15] Acyclovir-resistant herpes is not an important consideration in the management of herpes encephalitis in most patients.

Adverse effects

Case 79-1, Question 3: What adverse effects can occur with IV acyclovir therapy in R.F.? How should these be monitored, and how can they be minimized?

Acyclovir is a relatively safe drug, but renal toxicity associated with IV acyclovir is well described (**Table 79-1**). Blood urea nitrogen (BUN) and serum creatinine (SCr) levels can increase in 5% to 10% of patients; however, these changes are generally reversible.

Acyclovir is relatively insoluble: maximal urine solubility at 98.6 °F (37 °C) is 1.3 mg/mL. Consequently, the mechanism of acyclovir-associated renal disease is a transient crystal nephropathy, which may occur at high acyclovir concentrations.[11]

Table 79-1
Adverse Effects of U.S. Food and Drug Administration–Indicated Drugs for Various Viral Infections

Drug	Adverse Effects
Acyclovir[11]	Local irritation, phlebitis; increased SCr, BUN; nausea, vomiting; itching, rash; increased liver transaminases; CNS toxicity; hematologic abnormalities
Baloxivir[85]	Facial swelling, dysphonia, angioedema, anaphylaxis reactions; rash, urticaria, erythema multiforme, vomiting, bloody diarrhea, melena, colitis, delirium, abnormal behavior, hallucination
Cidofovir[185]	Nephrotoxicity; neutropenia; rash; headache; alopecia; anemia; abdominal pain; fever; infection; ocular hypotonia; nausea, vomiting; asthenia; diarrhea
Famciclovir[42]	Headache; nausea; diarrhea
Foscarnet[186]	Fever, nausea, vomiting; renal dysfunction; anemia; diarrhea; headache; electrolyte abnormalities; bone marrow suppression; seizure; anorexia; abdominal pain; mental status changes; paresthesia, peripheral neuropathy; cough, dyspnea; rash; first-degree AV block, ECG changes
Ganciclovir[187]	Increased SCr; anemia; neutropenia, pancytopenia, thrombocytopenia; abdominal pain, anorexia; diarrhea; nausea, vomiting; retinal detachment, vitreous hemorrhage, cataracts, corneal opacification; neuropathy; rash
Oseltamivir[84]	Nausea, vomiting; diarrhea; abdominal pain; dizziness, vertigo, insomnia; self-injury and psychosis
Peramivir[86]	Diarrhea, constipation, insomnia, AST elevation, hypertension, hyperglycemia, elevated CPK, elevated neutrophils, anaphylaxis, Stevens–Johnson syndrome, behavioral abnormalities
Ribavirin[110]	Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, ventilator dependence; cardiac arrest, hypotension; rash; conjunctivitis

Remdesivir[188]	Hypersensitivity reactions (ie, infusion related, anaphylaxis), elevated AST and ALT, seizure (<2%), rash (<2%)
Trifluridine[189]	Burning or stinging on instillation (4.6%); palpebral edema (2.8%); keratopathy; hypersensitivity reaction; stromal edema; hyperemia; increased intraocular pressure
Valacyclovir[41]	Headache (14%); nausea (15%); vomiting (6%); dizziness (3%); abdominal pain (3%)
Valganciclovir[190]	Neutropenia; thrombocytopenia; diarrhea; nausea, vomiting; abdominal pain; increased SCr; insomnia; peripheral neuropathy; paresthesias; CNS (ataxia, dizziness, seizures, psychosis, hallucinations, confusion, drowsiness); retinal detachment (during treatment of CMV retinitis); hypersensitivity
Zanamivir[83]	Bronchospasm; decline in respiratory function, especially if underlying respiratory disease; nasal or throat irritation or congestion; headache; cough; diarrhea; nausea, vomiting

ALT, alanine transaminase; AST, aspartate transaminase; AV, atrioventricular; BUN, blood urea nitrogen; CMV, cytomegalovirus; CNS, central nervous system; CPK, creatine phosphokinase; ECG, electrocardiogram; SCr, serum creatinine.

Other common adverse effects include gastrointestinal (GI) problems, such as nausea and vomiting and, less commonly, neurologic disturbances, including lethargy, tremors, confusion, hallucinations, and seizures.[11,16] Neurotoxicity appears to be more common in patients with impaired renal function and is reversible. Finally, IV acyclovir can cause phlebitis and pain at the injection site.[11,16] This complication can be minimized by administering acyclovir at a concentration of 5 mg/mL (maximum, 7 mg/mL).[16]

Renal function tests, including BUN, SCr, and urine output, should be monitored in R.F. To minimize the risk of acyclovir nephrotoxicity, R.F. should be well hydrated, and each acyclovir dose should be infused for 1 hour. In addition, the IV infusion site should be inspected for inflammation and pain, and R.F. should be asked about pain at the infusion site.

Conversion to oral therapy

Case 79-1, Question 4: After 7 days of IV acyclovir, R.F. is alert, responsive, actively moving about, and eating a normal diet. The intern suggests switching him to oral acyclovir and discontinuing IV therapy. Is this appropriate?

Oral acyclovir therapy is inappropriate for R.F. On the basis of studies in adults, the absorption of acyclovir after oral administration is variable, slow, and incomplete. The relative bioavailability (*F*) of acyclovir is low (*F* = 0.1–0.2) and decreases with increasing doses.[17] The mean peak plasma concentration has ranged from only 0.83 to 1.61 μg/mL after multiple acyclovir doses of 200 to 800 mg.[18] Thus, with only ~50% of acyclovir penetrating the blood–brain barrier, the concentrations of acyclovir in the CSF may be inadequate for R.F. There is only very limited information regarding the use of oral valacyclovir for therapy. A small pharmacokinetic trial of oral valacyclovir in patients with HSV encephalitis found that while therapeutic CSF concentrations of valacyclovir were achieved, CSF concentrations dropped over time, likely because of resolution of inflammation of the blood–brain barrier.[18] Consequently, switching to oral therapy cannot be recommended at this time and therapy with IV acyclovir should be continued to complete a 14- to 21-day course (**Table 79-2**).[12,13]

Table 79-2
Food and Drug Administration–Indicated Drugs for Various Viral Infections

Disease	Drug	Dosage (Age Group)	Route	Duration
COVID-19	Remdesivir (Veklury®)	≥12 years and ≥88.18 pounds (40 kg): 200 mg on day 1, followed by 100 mg daily	IV	3 days for nonhospitalized patients; 5 days for patients not requiring invasive mechanical ventilation and/or ECMO; 10 days if patient does not exhibit clinical improvement at day 5
Herpes encephalitis	Acyclovir (Zovirax®)[a]	>12 years: 10 mg/kg every 8 hours	IV	14–21 days
		3 months–12 years: 20 mg/kg every 8 hours	IV	14–21 days
Neonatal herpes	Acyclovir (Zovirax®)	Birth–3 months: 10–20 mg/kg every 8 hours[a]	IV	14–21 days
Oral–facial herpes (for treatment of recurrent infection)	Acyclovir (Zovirax®) Famciclovir (Famvir®) Valacyclovir (Valtrex®)	Adults: 400 mg five times per day Adults: 1500 mg Adults: 2000 mg bid	PO PO PO	5 days One dose 1 day
Oral–facial herpes[b] (immunocompromised patients)	Acyclovir (Zovirax®)	>12 years: 5 mg/kg every 8 hours <12 years: 10 mg/kg every 8 hours	IV IV	7 days 7 days
	Famciclovir (Famvir®)	Adults: 500 mg bid	PO	7 days
Herpes zoster[b] (immunocompetent patients)	Acyclovir (Zovirax®) Famciclovir (Famvir®) Valacyclovir (Valtrex®)	Adults: 800 mg five times per day Adult: 500 mg every 8 hours Adult: 1000 mg every 8 hours	PO PO PO	7–10 days 7 days 7 days
Herpes zoster[b] (immunocompromised patients)	Acyclovir (Zovirax®)	>12 years: 10 mg/kg every 8 hours <12 years: 20 mg/kg every 8 hours	IV IV	7 days 7 days
Varicella (immunocompetent patient)	Acyclovir (Zovirax®)	>88.18 pounds (40 kg): 800 mg qid >2 years and <88.18 pounds (40 kg): 20 mg/kg (max 800 mg) qid	PO PO	5 days 5–10 days
Varicella (immunocompromised patients)	Acyclovir (Zovirax®)	<12 years: 10 mg/kg every 8 hours >12 years: 500 mg/m^2 every 8 hours	IV IV	7–10 days 7–10 days
Cytomegalovirus retinitis (immunocompromised patients)	Ganciclovir (Cytovene®)	5 mg/kg every 12 hours; then 5 mg/kg/day, 7 days a week or 6 mg/kg/day, 5 days a week	IV	14–21 days for induction; maintenance
	Cidofovir (Vistide®)	5 mg/kg every week for 2 weeks, then every 2 weeks	IV	Maintenance
	Foscarnet (Foscavir®)	90 mg/kg every 12 hours; then 90 mg/kg every day	IV	Induction for 2 weeks; maintenance
	Valganciclovir (Valcyte®)	900 mg bid; 900 mg every day	PO	Induction for 21 days; maintenance
Influenza A and B	Baloxavir (Xofluza®)	88.18 pounds (40 kg) to <176.37 pounds (80 kg): 40 mg once	PO	Single dose
		≥176.37 pounds (80 kg): 80 mg once	PO	Single dose
	Oseltamivir (Tamiflu®)	>13 years (or >88.18 pounds [40 kg]): 75 mg bid	PO	5 days (treatment)
		>13 years (or >88.18 pounds [40 kg]): 75 mg every day	PO	10 days (prophylaxis)
				Up to 6 weeks (community outbreaks)
		52.91–88.18 pounds (24–40 kg): 60 mg bid	PO	5 days (treatment)
		35.27–50.71 pounds (16–23 kg): 45 mg bid		

Disease	Drug	Dosage (Age Group)	Route	Duration
		>1 year (33.07 pounds [15 kg]): ≤15–30 kg bid		
		52.91–88.18 pounds (24–40 kg): 60 mg every day	PO	10 days (prophylaxis)
		2 weeks to 1 year: 3 mg/kg bid	PO	5 days
		35.27–50.71 pounds (16–23 kg): 45 mg every day		
		>1 year–33.07 pounds (15 kg): 30 mg every day		
	Peramivir (Rapivab®)	2–12 years: 12 mg/kg (maximum 600 mg)	IV	Single dose
		≥13 years: 600 mg	IV	Single dose
	Zanamivir (Relenza®)	>7 years: 10 mg (two inhalations) bid	Inhalation	5 days (treatment)
		Adolescent and adult: 10 mg (two inhalations) every day	Inhalation	10 days (prophylaxis) 28 days (community outbreak)
		>5 years: 10 mg (two inhalations) every day	Inhalation	10 days (prophylaxis)
Respiratory syncytial virus	Ribavirin (Virazole®)	6 g in 300 mL for 12–18 hour/day	Inhalation	3–7 days

ECMO, extracorporeal membrane oxygenation; bid, two times day; IV, intravenously; PO, orally; qid, four times a day.

[a]FDA-approved dose is 10 mg/kg. Although doses of 15 to 20 mg/kg have been used, safety has not been established at these doses.

[b]Foscarnet 40 mg/kg IV every 8 hours is recommended for acyclovir-resistant herpes simplex virus or varicella zoster virus.

Neonatal Herpes

Most neonates acquire herpes from the infected genital secretions of the mother at delivery, and most can be caused by HSV-1 or HSV-2 virus.[19] In the United States, there are ~1500 cases annually.[19] The infection can present in one of three forms: localized to the skin, eye, and mouth (SEM) (45%); encephalitis (30%); or disseminated disease (25%).[19] The effects of neonatal herpes can be devastating, and severe disabilities persist in many afflicted children.[20] With currently available antivirals, the mortality has ranged from 4% in those with CNS involvement to 29% in those with other disseminated disease.[20] Neonatal HSV-1 infections may also be acquired after birth through contact with family members with symptomatic or asymptomatic oral–labial HSV-1 infection or from nosocomial transmission. When the virus is transmitted from the mother, clinical

evidence of infection in the neonate usually is present 5 to 17 days after birth. Although skin vesicles are the hallmark of infection, up to 40% of neonates never have skin lesions.[20] In 70% of patients, the disease may progress from isolated skin lesions to involve other organs, including the lungs, liver, spleen, CNS, and eyes.

Diagnosis can be made by direct fluorescent antibody examination of epithelial cells from the infant or the mother. Examination of the base of a vesicular lesion may show giant cells and intranuclear inclusions, which are characteristic of HSV infections. Serologic test results can support a diagnosis of neonatal herpes.

RISK FACTORS

CASE 79-2

Question 1: S.P., an 18-year-old pregnant female, was admitted to labor and delivery with premature rupture of the membranes. Four hours later, S.P. vaginally delivered a 5.51-pound (2.5-kg) infant, R.P., who had an estimated gestational age of 33 weeks. Twenty-four hours after delivery, S.P. reported the onset of vesicles in the genital area; she had a history of previous episodes of genital herpes. The last infection was during her first trimester of pregnancy.

Is R.P. at risk for developing herpes infection?

R.P. is at risk for acquiring herpes infection because the mother had genital herpes during the first trimester and because he was delivered vaginally rather than by cesarean section.[20] The risk of a newborn acquiring the disease from an infected mother with primary disease is about 35%; that from a mother who has reactivation of disease is 3%.[20]

TREATMENT: ACYCLOVIR

Case 79-2, Question 2: Ten days after birth, R.P. exhibited poor feeding patterns, irritability, and respiratory distress. Three days later, skin lesions appeared. How should R.P. be treated?

R.P. is manifesting signs of HSV infection and should be treated with antiviral therapy (see Table 79-2). The drug of choice for neonatal HSV infections is IV acyclovir.[19,20] Vidarabine was the first antiviral agent used in the treatment of neonatal HSV. Because of the drastic reduction in morbidity, it became the standard of therapy to which other antiviral agents were compared. In clinical trials comparing vidarabine with acyclovir, acyclovir was shown to be as effective as vidarabine in infants with SEM involvement, encephalitis, and disseminated HSV infection.[21] Although both agents were equally effective, acyclovir was safer and easier to administer, making it the standard of care for neonatal HSV.

Acyclovir administration

Case 79-2, Question 3: What dosage of acyclovir should R.P. receive?

Although an IV dosage of 30 mg/kg given in three divided doses has been shown to be effective in the treatment of neonatal herpes, the use of 60 mg/kg given in three divided doses is superior in decreasing morbidity and mortality. The higher dose of acyclovir is associated with a higher frequency of hematologic abnormalities, especially neutropenia.[11,16,20] The minimum duration of therapy should be 14 days for neonates with only SEM involvement, whereas longer courses (eg, 21 days) are indicated in infants with CNS involvement or disseminated disease.[19,20]

The role of prolonged oral suppressive therapy in newborns with SEM involvement has been investigated.[22–24] Acyclovir, given orally (PO) at 300 mg/m^2 per dose three times a day (tid), resulted in a reduction in the recurrences of lesions and improved neurodevelopmental outcomes. The demonstrated improvement in neurodevelopmental outcomes supports the use of suppressive acyclovir for 6 months. Owing to the high incidence of neutropenia in infants on suppressive treatment, monitoring of the absolute neutrophil counts (ANCs) is recommended at 2 weeks, 4 weeks, and

monthly after the initiation of treatment.[19] It is important to adjust the dose as the infant gains weight.

Oral–Facial Herpes (Herpes Labialis)

Both primary and recurrent oral–facial HSV-1 infections can be asymptomatic. Gingivostomatitis and pharyngitis are the most common clinical manifestations of a first episode of HSV-1 infection, and recurrent herpes labialis is most commonly caused by reactivated HSV infection. Clinical features include fever, malaise, myalgia, inability to eat, and irritability. Immunocompromised patients with oral–facial herpes have severe pain, extensive lesions, and prolonged viral shedding; thus, they are candidates for antiviral therapy.

Herpes labialis (cold sores) is the most common oral–facial HSV infection. Clinical features include pain or paresthesia and erythematous or papular lesions followed by vesiculation and swelling. These lesions usually crust and heal in a few days. Viral culture results generally are positive within 2 to 3 days. Rapid diagnosis can be made by visualizing viral particles in vesicular fluid with electron microscopy or fluorescent antibody staining of cells from vesicles.

INDICATIONS FOR ANTIVIRAL TREATMENT

CASE 79-3

Question 1: M.K., a 26-year-old male, experienced pain and erythematous skin lesions on his face and around his mouth during a 2-day period after contact with a person with active herpetic lesions. For the next 2 days, significant swelling was noted. He remembers similar episodes in the past. M.K. has no previous history of any other illness.

Should he be treated with antiviral drugs?

Most patients with herpes labialis have a self-limiting benign course and the lesions heal within 10 days. Antiviral drugs (eg,

acyclovir, valacyclovir, famciclovir) are indicated when the patient has a primary infection, an underlying illness, or a compromised immune system that may lead to prolonged illness, dissemination, or recurrent infections.[25] In patients with severe disease, such as those undergoing a solid organ transplant, IV therapy may be necessary.[26]

M.K. should not receive antiviral therapy. However, acetaminophen or nonsteroidal anti-inflammatory agents (NSAIDs) can be considered for symptomatic relief. Although ice, ether, lysine, silver nitrate, and smallpox vaccine have been used to treat cold sores, no data support their efficacy.

CASE 79-4

QUESTION 1: P.L., a 16-year-old male diagnosed with acute lymphocytic leukemia 8 months ago, is now admitted for a bone marrow transplant. Admission laboratory tests reveal that he has antibodies against HSV-1 and that 4 months ago, during a course of chemotherapy, he developed an oral–facial herpes infection.

What is the significance of these findings for P.L., who is about to undergo a bone marrow transplant?

Immunosuppressed patients have more frequent and severe mucocutaneous HSV infections. Therefore, IV acyclovir should be considered to suppress the reactivation of oral–facial HSV infections.[26] Oral therapy with famciclovir is approved for use in patients with human immunodeficiency virus (HIV) infection,[27] but efficacy in other immunocompromised patients is not yet established.

Antiviral treatment

CASE 79-4, QUESTION 2: P.L. did not receive antiviral therapy. Two weeks later, he developed malaise and painful oral mucosal and skin lesions on his face. HSV was identified from the lesion by immunofluorescence. What is the treatment of choice for P.L.?

Acyclovir should be administered IV at 5 mg/kg every 8 hours for 7 days[11] or until the lesions are healed, followed by oral acyclovir 200

mg tid.[26] For patients with bothersome or multiple recurrences, the daily use of antiviral therapy is recommended to suppress the infection until the immunosuppression can be decreased.[27] In patients with marrow transplants and culture-proven recurrent mucocutaneous herpes simplex, oral acyclovir (400 mg five times daily for 10 days) is significantly more effective than is placebo in reducing pain, virus shedding, new lesion formation, and lesion healing time.[28] Valacyclovir and famciclovir have also been used in the transplant population.[29]

CASE 79-5

QUESTION 1: N.B., a 43-year-old female, experiences 8 to 10 cold sores a year. These are typically preceded by "colds" or sun exposure. She requests a prescription for acyclovir to prevent cold sores when she feels one coming on.

What is the role of antiviral medications in the acute treatment and prevention in immunocompetent patients with recurrent herpes labialis?

Topical agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of recurrent herpes labialis in immunocompetent patients include acyclovir 5% cream (Zovirax®), acyclovir 5% and hydrocortisone 1% cream (Xerese®), docosanol 10% cream (Abreva®), and penciclovir 1% cream (Denavir®). Clinical trials demonstrate that each agent modestly decreases the healing time of herpes lesions when started at the first sign or symptom of a cold sore.[30–36] Although penciclovir cream may be more effective than is acyclovir cream, the benefit is small.[33,34] An advantage of docosanol cream compared with the other agents is its availability without a prescription. Topical acyclovir and docosanol require administration five times a day, whereas penciclovir must be applied within 1 hour of the first sign or symptom of a cold sore and then every 2 hours for 4 days while awake.

Studies evaluating the use of oral antiviral agents have produced conflicting results. In some studies, oral antiviral medications have shown to decrease the duration of pain and healing time in immunocompetent patients. One study demonstrated that oral

acyclovir 200 mg five times daily for 5 days had no benefit.[37] However, 400 mg five times daily for 5 days started within 1 hour of the development of a cold sore significantly decreased duration of pain and healing time in immunocompetent patients.[38] Valacyclovir 2 g at the first signs of a cold sore followed by 2 g 12 hours later, and famciclovir 1500 mg as a single dose showed similar clinical efficacy.[39],[40] No studies have directly compared the efficacy of the different oral antiviral medications.[40] Frequency of dosing and cost should be considered when choosing a particular agent.[17],[41],[42]

Daily suppressive therapy may be recommended in patients with six or more recurrences per year, in patients with frequent infection who do not experience a prodrome, or in patients with severe episodes. In immunocompetent patients with six or more episodes of herpes labialis, oral acyclovir 400 mg twice a day (bid) for 4 months was more effective than was placebo in decreasing the number of recurrences.[43] Oral valacyclovir, 500 or 1000 mg once daily, is efficacious in decreasing the number of recurrences.[44] Controlled trials of famciclovir for chronic suppressive therapy of herpes labialis have not been performed.

N.B. should be treated with either a topical antiviral medication or an oral antiviral for the acute episode of herpes labialis. She should be instructed to start treatment as soon as the first sign or symptom of the cold sore appears. If suppressive therapy is desired, N.B. should be treated with oral acyclovir or valacyclovir.

RESISTANCE

The incidence of acyclovir-resistant herpes in patients with herpes labialis is greater in immunocompromised patients compared with immunocompetent patients. Current estimates of HSV resistance in the immunocompromised population are about 6.4%; some populations, such as bone marrow transplant patients, have a resistance rate of 34%.[45] IV foscarnet 40 mg/kg every 8 hours is more effective and less toxic than is IV vidarabine 15 mg/kg/day in patients with acquired immunodeficiency syndrome (AIDS) and mucocutaneous herpetic lesions unresponsive to IV acyclovir.[46] More

concerning, however, are the reports of foscarnet-resistant HSV, particularly in the bone marrow transplant population.[45],[47] Cidofovir has been used with moderate success in such cases. In patients with recurrent acyclovir-resistant genital herpes, limited evidence suggests that topical imiquimod 5% cream may be effective.[48]

VARICELLA ZOSTER INFECTIONS

Chickenpox

Chickenpox used to be a common childhood infection; however, its incidence has decreased by up to 81% and by 92% in patients receiving one or two doses of the varicella zoster virus (VZV) vaccine, respectively.[49] This vaccine is now considered a routine childhood vaccine by the American Academy of Pediatrics. Unimmunized adolescents and adults who have not had chickenpox should also be vaccinated. Before the vaccine was available, ~4 million cases occurred per year in the United States: 90% of cases occurred in children and adolescents younger than age 15 years, with the majority of cases occurring between ages 1 and 4 years.[50],[51] In addition to a decline in cases of chickenpox, complications and mortality have also declined.[50],[51] The population at risk for complications such as pneumonia and encephalitis, because of VZV, include immunocompromised individuals and pregnant females. Children with HIV are at an increased risk for mortality from VZV.[51]

Chickenpox is a contagious disease; the average incubation period is 14 to 16 days. Children are considered contagious from 1 to 2 days before the onset of rash until all vesicles have crusted (usually 4–6 days after the onset of rash).[51]

After household exposure, >90% of susceptible individuals become infected. Thus, a history of exposure is useful in making a diagnosis. A smear of cells scraped from the lesions will show multinucleated giant cells. Viruses also can be identified in vesicular

lesions by electron microscopy, or antigen can be detected by countercurrent immunoelectrophoresis. Chickenpox is a primary varicella zoster infection, whereas herpes zoster (shingles) is caused by reactivation of VZV.[52]

CLINICAL PRESENTATION

CASE 79-6

QUESTION 1: A.V., a 10-year-old male, was admitted to the hospital for evaluation and treatment of possible recurrent chickenpox. According to his mother and his physician, he had a mild case of chickenpox at age 4 years and has not received the vaccine. At admission, A.V. had a 10-day history of progressive vesicular and pustular lesions that began on his neck and spread to his back, trunk, extremities, and face. Although he had been febrile (up to 104.9 ° F [40.5 °C] orally) for the past 3 days, his temperature on admission was 98.6 ° F (37 °C). A.V. had episodes of vomiting during the 4 days before admission. On admission, he was alert, cooperative, and well oriented but had overt ataxia with abnormal cerebellar signs. Lesions consistent with VZV infection were extensive and confluent over the face, neck, chest, and back. Stages of lesions varied from tiny thin-walled vesicles with an erythematous base to umbilicated vesicles. Few crusted lesions were present. Blood analysis revealed the following results:

BUN, 9 mg/dL (normal, 5–18 mg/dL; 1.8–6.4 mmol/L)
SCr, 0.2 mg/dL (normal, 0.5–0.8 mg/dL; 44–71 μmol/L)
Serum aspartate aminotransferase, 65 IU/L (normal, 0–34 units/L)
Serum alanine aminotransferase 122 IU/L (normal, 0–34 units/L)

Because of the possibility of cerebellar involvement with VZV infection, therapy with acyclovir 550 mg IV every 8 hours (1500 mg/m^2/day) was instituted. Oral diphenhydramine was also prescribed for itching, but A.V. required only two doses on the first hospital day.

New lesions were noted on the second day of acyclovir therapy, but by the third day no new lesions appeared and previous lesions were healing. The ataxia improved daily. He was discharged on day 7 with no further nausea and vomiting. Follow-up serologic evaluation demonstrated a fourfold rise in the optical density for the VZV enzyme-linked immunosorbent assay (ELISA) from day 20 to day 60 after the onset of infection. These results suggested primary VZV infection.

Why is the use of acyclovir in A.V. appropriate?

ANTIVIRAL TREATMENT

Neonates, adults, immunocompromised hosts, patients with progressive varicella, and those with extracutaneous complications benefit from acyclovir therapy. Acyclovir is effective in preventing dissemination of VZV infection, accelerating cutaneous healing, and reducing mortality.[53] A.V. had a prolonged progressive course of varicella and demonstrated an extracutaneous manifestation of varicella infection (eg, ataxia with abnormal cerebellar signs). Because of the concern of possible cerebellar involvement, the use of IV acyclovir was appropriate in A.V.

CASE 79-7

QUESTION 1: C.J., an 8-year-old male, developed a case of chickenpox and was kept home from school. Four days later, his 15-year-old brother, K.J., began to exhibit similar symptoms.

What is the role of acyclovir in immunocompetent patients with chickenpox? Should C.J. or K.J. be treated with acyclovir?

Three studies in children (2–18 years old) have shown that oral acyclovir 20 mg/kg (when initiated within 24 hours of disease onset) four times a day (qid) for 5 to 10 days accelerates healing and decreases the formation of new lesions, fever, and itching. However, the benefit is modest (usually healing 1 day sooner than does placebo) and does not reduce the complications of varicella.[53] Thus, the American Academy of Pediatrics does not consider routine use of acyclovir in healthy children justified, and it is not indicated for C.J.[54]

Adolescents and adults are more likely to develop complications (eg, pneumonia, encephalitis) than do children. Others at higher risk for developing complications include those with chronic cutaneous or pulmonary disease, patients receiving chronic salicylate therapy, and patients receiving short, intermittent, or aerosolized corticosteroid therapy.[54] In these patients, acyclovir therapy may be warranted. Acyclovir 800 mg PO qid for 5 days in adolescents and adults (initiated within 24 hours of disease onset) decreases the number of

lesions and reduces time for healing, fever, and itching. The effect of acyclovir on prevention of severe complications is unknown.[55–57] Thus, acyclovir therapy should be considered in those at increased risk for severe chickenpox, for example, those similar to K.J. who are older than 14 years or those with chronic respiratory or skin disease.[55] There are no published clinical trials to support the use of famciclovir and valacyclovir in the treatment of chickenpox. However, valacyclovir or famciclovir may be preferred because of the need for less frequent administration for adolescents and adults at risk for moderate-to-severe complications.

SUPPORTIVE TREATMENT

CASE 79-7, QUESTION 2: What is the role of supportive treatment in C.J. and K.J.?

Cool baths and application of calamine or other topical antipruritic agents may decrease itching. Fingernails should be trimmed to avoid scratching and secondary bacterial infections. In severe cases, a systemic antipruritic and antihistamine preparation may be useful because some degree of sedation may be desired. In C.J. and K.J., aspirin should not be used because Reye syndrome has been associated with the use of salicylates in chickenpox or flu-like illness (see Chapter 102, Pediatric Pharmacotherapy).

Shingles (Herpes Zoster)

Herpes zoster infections are caused by the reactivation of dormant VZV in the sensory neurons. Reactivation is believed to occur because of waning immunity. The incidence of herpes zoster is higher in immunocompromised patients (eg, those with HIV or cancer or those receiving immunosuppressive medications), and the incidence of zoster increases with age. It tends to be more severe in the elderly.[58]

Acute herpes zoster infection is characterized by pain, which is described as a deep aching or burning pain. It may be accompanied by excessive sensitivity to touch. Many patients exhibit a rash that presents initially as erythematous patches and progresses to vesicles that crust in 7 to 10 days. By 1 month, the rash is usually gone, but scarring can occur.[58]

Postherpetic neuralgia (PHN) is the most common complication of acute herpes zoster characterized by pain that continues for >1 month after the onset of the rash. It is estimated that 20% of patients experience PHN, although the incidence can be as high as 90% in individuals older than age 50 years.[58] Prevention is important because PHN pain is difficult to treat.

The goal of pharmacotherapy in acute herpes zoster is to inhibit viral replication, to reduce the pain and duration of the rash. Ultimately, by inhibiting the virus, nerve damage can be prevented and the incidence and severity of PHN can be decreased. Unfortunately, no therapy can prevent all cases of PHN.

The herpes zoster vaccines (Shingrix® and Zostavax®) significantly reduce the incidence of herpes zoster and the associated resulting PHN (see Chapter 64, Vaccinations).

ANTIVIRAL THERAPY IN IMMUNOCOMPETENT PATIENTS

CASE 79-8

QUESTION 1: E.O. is a 72-year-old, previously healthy male who reports a burning pain under his left arm for the past 2 days. The pain radiates across his chest. The pain is worse when the area is touched. This morning, he noticed a rash that starts under his arm and continues to his midline. Pertinent laboratory findings include BUN of 15 mg/dL (normal, 8–18) and SCr of 2.0 mg/dL (normal, 0.6–1.2). He has not received the herpes zoster vaccine. A diagnosis of herpes zoster is made.

What therapy should be initiated?

Acyclovir is the standard antiviral agent against which new VZV therapies are compared. In immunocompetent patients, oral acyclovir 800 mg five times daily for 10 days is moderately beneficial

in reducing acute pain during the first 28 days. Acyclovir therapy should be initiated within 72 hours of the onset of the rash. The benefit of acyclovir in reducing PHN and chronic pain is modest at best. Although a number of trials showed no benefit from acyclovir in reducing PHN, a meta-analysis of acyclovir treatment in herpes zoster concluded that acyclovir was effective, but that 6.3 patients would need to be treated to prevent one patient from having PHN 6 months after the outbreak of VZV.[59]

Famciclovir (Famvir®) is approved for the treatment of acute herpes zoster infection. Famciclovir is a prodrug and is rapidly absorbed and converted to the active drug penciclovir in the intestine. The bioavailability of famciclovir is greater than that of acyclovir, resulting in higher concentrations of active drug in the infected cells. In addition, the intracellular half-life (10 hours) of penciclovir allows for less frequent administration.[60] Famciclovir 500 mg tid is as effective as acyclovir 800 mg five times a day in reducing the duration of acute pain and healing of the rash.[61] Although famciclovir does not decrease the incidence of PHN, it may reduce the duration of PHN.[62]

To overcome the poor oral bioavailability of acyclovir, valacyclovir (Valtrex®), a prodrug of acyclovir, was developed. Valacyclovir is rapidly and extensively absorbed and converted to acyclovir after oral administration. Valacyclovir 1 g tid is as effective as acyclovir 800 mg five times a day in terms of reducing rash progression and time to rash healing, and valacyclovir is more effective than is acyclovir in relieving zoster-associated pain.[63] Valacyclovir is comparable to famciclovir with respect to decreasing the duration of acute zoster-associated pain and PHN.[64]

E.O. should be started on acyclovir, famciclovir, or valacyclovir. Famciclovir or valacyclovir may be preferred because adherence with a tid regimen will likely be better than with acyclovir, which must be administered five times a day. Therapy should be initiated within 72 hours of the rash onset and continued for 10 days; the duration of therapy for famciclovir and valacyclovir is 7 days. Although therapy may not prevent PHN, it may decrease the duration of pain. Because

these agents are renally eliminated, the dosage should be adjusted based on E.O.'s reduced creatinine clearance (**Table 79-3**).

Table 79-3
Clinical Pharmacokinetics of Antiviral Drugs

Drug	Type of Patient	Peak Serum Concentration (µg/mL)	VD	Elimination			Comments
				% Recovered Unchanged in Urine	Total Clearance	Half-Life (hours)	
Acyclovir[11,16,17,191–194]	Adults	3.4–22.9 (based on a dose of 2.5–10 mg/kg IV) 0.83–1.61 (based on a dose of 200–800 mg PO)	59 L/1.73 m^2	69–91	327 mL/minute/1.73 m^2	2.5–3.3	Use 100% of recommended dose, but extend dosage interval to 12 and 24 hours if CrCl ranges from 25 to 50 and 10 to 25 mL/minute/1.73 m^2, respectively; use 50% of recommended dose every 24 hours if ClCr ranges from 0 to 10 mL/minute/1.73 m^2
	Neonates	N/A	24–30 L/1.73 m^2	N/A	98–122 mL/minute/1.73 m^2	3.2–4.1	
Baloxivir[85,195]	Adolescents and adults	0.0491 fasting (based on a dose of 20 mg)	1180 L	3.3%	4.38 L/hour	79.1	
Famciclovir[41,196,197]	Adults	0.8–6.6 (based on a dose of 125–1000 mg PO)	1.1 L/kg	73–94[a]	0.37–0.48 L/hour/kg	2.2–3.0	Use 100% of recommended dose, but extend dosage interval to 12 and 24 hours if ClCr ranges from 40 to 59 and 20 to 39 mL/minute, respectively; use 250 mg every 24 hours if ClCr >20 mL/minute
Oseltamivir[84,198–200]	Adults	0.6–3.5[b] (based on a dose of 75 mg PO)	23–26 L	99[b]	18.8 L/hour	6.0–10	Use 75 mg/day in patients if ClCr 10–30 mL/minute. The effect of hepatic impairment has not been determined.
	Pediatrics (1–12 years)	0.06–0.8[b] (based on a dose of 2 mg/kg PO)	N/A	N/A	0.63 L/hour/kg	3.2–7.8	Dosage recommendations are based on body weight and age.
	Adolescents	N/A	N/A	N/A	0.32 L/hour/kg	8.1	
Peramivir[86,201]	Adults	0.0468 µg/mL after a single 600-mg dose	12.56 L	90	6.19–7.58 L/hour/kg	20	In adolescents 13 years and older and adults, use 200 mg if ClCr is 30–49 mL/minute and 100 mg if ClCr is 10–29 mL/minute. In pediatric patients ages 2–12 years, use 4 mg/kg if ClCr is 30–49 mL/minute and 2 mg/kg if the ClCr is 10–29 mL/minute.
Remdesivir[188,202]	Adults	2.23 (based on multiple doses of 100 mg IV)	85.5 L (based on multiple doses of 150 mg/day for 7–14 days)	10%	N/A	1 hour	In patients with an eGFR <30 mL/minute, remdesivir is not recommended.
Valacyclovir[42,203] (see Acyclovir [prodrug of acyclovir])	Adults	5.7–6.7[c] (based on a dose of 1000 mg PO)	N/A	46–80[c]	N/A	2.5–3.3[c]	Use 100% of recommended dose, but extend dosage interval to 12 and 24 hours if ClCr ranges from 30 to 49 and 10 to 29 mL/minute, respectively; use 500 mg every 24 hours if ClCr >10 mL/minute.
Zanamivir[83,204,205]	Adults	0.02–0.1 (based on a dose of 10 mg INH)	15.9 L	7–17	2.5–10.9 L/hour	2.5–5.1	4%–17% of inhaled dose systemically absorbed. Although only limited studies with renal or hepatic impairment, dosing adjustment likely unnecessary

bid, twice a day; ClCr, creatinine clearance; eGFR, estimated glomerular filtration rate; INH, inhalation; IV, intravenously; N/A, not available; PO, orally; VD, volume of distribution.

[a]Pharmacokinetic properties of active metabolite penciclovir.

[b]Active metabolite oseltamivir carboxylate.

[c]Pharmacokinetic properties of active metabolite acyclovir.

For acute illness, E.O. may require pain control with medications such as nonsteroidal anti-inflammatory agents, opioids, topical lidocaine, or tramadol.[47] In addition, E.O. should be counseled to

keep the area of the rash clean and dry and to avoid topical antibiotics. If the rash worsens or fever develops, he should contact his health care professional.

Case 79-8, Question 2: Should E.O. receive a corticosteroid to treat or prevent the pain associated with herpes zoster?

The decision to use corticosteroids, such as prednisone or prednisolone, remains controversial.[65] A number of studies have examined the effect of steroids on pain during acute neuralgia and on the development of PHN. Early studies revealed that steroids are effective for both acute pain and PHN, but these studies were small and uncontrolled, and used various corticosteroid regimens. Most studies suggest relief of the acute pain but no decrease in PHN.[66–68] Because of recent studies demonstrating a lack of benefit in preventing PHN, the theoretical concerns of herpes zoster dissemination, the development of secondary bacterial infections, and the beneficial effects of antiviral agents such as acyclovir, famciclovir, and valacyclovir for acute pain, corticosteroids should not be used in E.O.

Case 79-8, Question 3: Two months after the onset of the rash, E.O. continues to report pain. A diagnosis of PHN is made. What FDA-approved treatments for PHN should be prescribed for E.O.?

Although many different agents have been studied, the only FDA-approved treatments for PHN are topical capsaicin cream or gel, capsaicin patch 8% (Qutenza®), topical lidocaine 5% patches (Lidoderm®), and oral gabapentin (Neurontin®) and pregabalin (Lyrica®). Capsaicin depletes substance P, a mediator that transmits pain from the periphery to the CNS. The largest double-blind, placebo-controlled trial of capsaicin evaluated 143 patients with PHN for at least 6 months.[68] After 6 weeks of treatment with capsaicin 0.075% cream, pain scores were reduced in 21% and 6% of the capsaicin and placebo groups, respectively. After the double-blind

phase of the study ended, a subset of patients continued to use capsaicin cream for up to 2 years, and most patients experienced prolonged pain relief.[68] Capsaicin should be applied three or four times per day. Qutenza® is a capsaicin patch that is applied by a health care professional. The patch is applied for 1 hour and cannot be repeated more frequently than every 3 months. Lidocaine 5% patches have only been compared with placebo and have been shown to relieve pain for 4 to 12 hours after administration. Currently, an over-the-counter lidocaine 4% patch is the only available product. Either capsaicin cream or gel or lidocaine patches can be considered as a first-line option for E.O. A common adverse effect is a burning sensation after application of capsaicin, which is intolerable in up to one-third of patients. The burning sensation usually lessens with continued use.

If lidocaine patches are prescribed, E.O. should be instructed to apply up to three patches to the painful area. Patients should be instructed to wear the patches for a maximum of 12 hours a day, and proper disposal of used patches should be emphasized. Even a used patch contains a large amount of lidocaine, and small children or pets could suffer serious consequences from chewing or swallowing a used patch.[69]

Gabapentin at doses >1200 mg/day has demonstrated up to a 50% decrease in PHN compared to placebo.[70] However, adverse effects limit the ability for patients to reach this dose. Pregabalin is approved for the treatment of PHN, but it is associated with a greater risk of adverse effects. Pregabalin binds to a subunit of calcium channels, thereby decreasing calcium influx at nerve terminals and reducing the release of several neurotransmitters, including glutamate, norepinephrine, and substance P.[71] In clinical trials, dizziness was experienced by 29% of patients treated with pregabalin compared with 9% of placebo-treated patients; somnolence was noted in 22% of patients who received pregabalin compared with 8% of placebo-treated patients. Dizziness and somnolence usually occur soon after the pregabalin is started and is dose dependent.[71]

Other agents that have been used in the treatment of PHN include tricyclic antidepressants (eg, amitriptyline, desipramine) and opioids.[47]

ANTIVIRAL THERAPY IN IMMUNOCOMPROMISED PATIENTS

CASE 79-9

QUESTION 1: R.F. is a 68-year-old female with vesicles on her face associated with severe pain. She has a history of polymyalgia rheumatica and possible temporal arteritis with headaches that are responsive to steroids. She had been having increasing headaches on the right side of her forehead 5 days before admission. Two days before admission, her family physician increased the dosage of prednisone from 30 to 60 mg/day. Vesicles developed on her face 1 day before admission. She was admitted for pain control and diagnosed with herpes zoster infection. Six hours after admission, R.F. began having visual hallucinations, hearing noises, and talking to herself. A lumbar puncture was performed with the following results:

WBCs, three (two lymphocytes and one monocyte)
RBCs, three
Protein, 84 mg/dL
Glucose, 86 mg/dL
VZV was isolated from the CSF and IV acyclovir was started at a dosage of 10 mg/kg every 8 hours.

Why is antiviral therapy indicated in R.F.? Should her prednisone be continued or discontinued?

Antiviral therapy is indicated for R.F. Acyclovir may halt the progression of acute herpes zoster infection in immunocompromised hosts such as R.F., who has been taking large doses of corticosteroids.[72]

IV acyclovir 10 mg/kg every 8 hours is effective in severely immunocompromised patients. Alternatively, in less severely immunocompromised patients, oral therapy with acyclovir 800 mg five times a day, valacyclovir 1000 mg tid, or famciclovir 500 mg tid, along with close monitoring, can be used.[73] Antiviral therapy is associated with more rapid clearance of the herpes zoster virus from the vesicles. Acyclovir has little to no benefit in resolution of pain or

prevention of PHN.[74] Initial data indicate that famciclovir or valacyclovir are effective in severe herpes zoster infection in an immunocompromised host.[74,75]

Systemic corticosteroids are of unproven usefulness and may slow the healing of lesions. Therefore, if possible, R.F.'s prednisone should be slowly tapered.

Acyclovir toxicity

CASE 79-9, QUESTION 2: On the fourth day of acyclovir therapy, R.F. developed severe nausea and vomited three times. The laboratory data showed a BUN of 45 mg/dL and SCr of 3.2 mg/dL (baseline BUN, 10 mg/dL and SCr, 1.0 mg/dL). Why must R.F.'s acyclovir dosage be altered?

Nausea and vomiting have been reported with acyclovir therapy in patients with herpes zoster infections.[11] Similarly, elevations of SCr and BUN can occur in association with acyclovir therapy. This may be secondary to acyclovir crystallization in the renal tubules, particularly when fluid intake is inadequate (see Table 79-1). Because R.F.'s creatinine clearance is between 10 and 25 mL/minute/1.73 m^2, the acyclovir dosage interval should be extended to 24 hours. Every effort should be made to maintain adequate hydration for the duration of acyclovir therapy. (See Table 79-3 and Chapter 2, Interpretation of Clinical Laboratory Tests, for creatinine clearance calculation.)

INFLUENZA

Influenza is an acute infection caused by the virus of the Orthomyxoviridae family. Epidemics of influenza are usually caused by the type A virus; type B virus is generally associated with more sporadic infection. Infection is transmitted by the inhalation of virus-containing droplets ejected from the respiratory tract of a person with influenza. Influenza can be spread by direct contact, large droplets,

or items recently contaminated by nasopharyngeal secretions. The incubation period is typically 2 days (range, 1–4 days).

Influenza A viruses are classified into subtypes of hemagglutinin (H) and neuraminidase (N) surface antigens. Three subtypes of hemagglutinin (H1, H2, H3) and two subtypes of neuraminidase (N1, N2) have caused influenza in humans. Infection with a virus of one subtype may confer little or no protection against viruses of other subtypes. In addition, significant antigenic variation (antigenic drift) within a subtype may occur with time. Thus, infection or vaccination with one strain may not protect against a distantly related strain of the same subtype. This is why major epidemics of influenza continue to occur, and influenza vaccines must be reformulated each year with the most likely viral strains to maximize vaccine benefit.[76]

The influenza vaccine is indicated for all individuals ages 6 months and older. However, there are a number of populations for which vaccination is vital. Persons at highest risk for influenza infection (**Table 79-4**) should receive the influenza vaccine each year. The majority of influenza vaccine products are the quadrivalent vaccines that contain two strains of type A and type B.[77] In addition, there are a number of influenza virus vaccine products available that are indicated for patients 65 years or older, a population known to have a suboptimal response to the standard-dose influenza vaccine. These vaccine formulations contain either a higher dose of antigen or have a different adjuvant and are designed to produce a stronger immune response than do standard influenza vaccines. For example, a high-dose vaccine product contains four times the amount of antigen relative to other influenza vaccine products. Early trials with the higher strength vaccine found the high-dose vaccine was 24.2% more effective in preventing influenza in adults ages 65 years and older relative to a standard-dose vaccine.[78] The high-dose and adjuvanted flu vaccines may result in more of the temporary, mild adverse effects that occur with standard-dose influenza vaccines. Adverse effects can include pain, redness, or swelling at the injection site; headache; muscle ache; and malaise, and typically resolve within 1 to 3 days.[76]

Table 79-4
Persons Who Should Receive the Influenza Vaccine

Groups in which the influenza vaccine is indicated in:

- All persons ages 6 months and older

Individuals for which the influenza vaccine is vital for:

- All persons ages 50 years or older
- Nursing home or chronic care facility residents
- Adults and children who have chronic pulmonary (eg, asthma) or cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes)
- People who are immunocompromised because of any condition including HIV infection or those taking medications that cause immunosuppression
- Children (6 months–18 years) receiving long-term aspirin therapy or salicylate-containing medications
- Females who will be pregnant during influenza season
- American Indians/Alaska Natives
- Persons who are extremely obese (BMI ≥40 for adults)
- Health care workers
- Persons who take care of people at high risk for influenza-related complications including health care workers and household contacts and caregivers of these individuals.

BMI, body mass index; HIV, human immunodeficiency virus.

Source: Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices (ACIP)—United States, 2021–22 influenza season. *MMWR Morb Mortal Wkly Rep*. 2021;70:1–28.

The efficacy of the influenza vaccine depends on the similarity of the components of the vaccine to the circulating viruses that year and the immunocompetence of the host. If there is a good match with the circulating viruses, the inactivated injectable influenza vaccines can prevent illness in ~60% of healthy adults and children, can prevent 50% to 60% of hospitalization among elderly persons, and prevent 80% of deaths among the elderly.[76] Despite the lower efficacy, vaccination is still associated with less severe illness and fewer complications in vaccinated individuals.

Individuals at high risk for transmission to patients include health care personnel in the hospital and ambulatory settings; employees of nursing homes and chronic care facilities; providers of home care services; and household members, including children. It is vital that all these individuals should be vaccinated annually. In addition, considering the morbidity and mortality associated with influenza, all individuals older than 6 months of age should receive an annual influenza vaccination.

The optimal time for vaccine administration is between mid-October and mid-November because influenza activity peaks between late December and early March in the United States. Vaccinating an individual too early in the season could result in waning antibody concentrations before the influenza season is over. However, influenza vaccine should be offered throughout the influenza season, even if outbreaks of influenza have already been documented in the community.[77]

Because the parenteral influenza vaccine is an inactivated vaccine and contains no infectious viruses, it cannot cause influenza. The most common adverse effect is soreness at the administration site lasting for up to 2 days.[79] Fever, malaise, myalgia, and other systemic reactions occur infrequently; these may develop within 6 to 12 hours of the vaccine being given and persist for 1 to 3 days.[79,80] Immediate hypersensitivity to egg protein (hives, angioedema, allergic asthma, or systemic anaphylaxis) rarely occurs. However, there are influenza vaccine products that are not manufactured in embryonated eggs and use of these vaccines should be considered in those with a history of egg allergy. Minor illnesses with or without fever are not contraindications to the influenza vaccine, particularly in children with a mild upper respiratory tract infection or allergic rhinitis. When the vaccine is contraindicated, an oral antiviral agent should be used for prophylaxis.[77] Amantadine and rimantadine are no longer recommended for prophylaxis of influenza because of widespread resistance in the United States.[77]

Clinically, it is impossible to differentiate between influenza A and B. Definitive diagnosis can be made by isolating the virus from throat

washings or sputum and by a significant increase in antibody titers during the convalescent period.

Clinical Presentation

CASE 79-10

QUESTION 1: K.B., a 40-year-old female, comes into the pharmacy claiming she has "the flu." She recently started a new job and is afraid she will lose her job if she misses too many days from work.

What questions would you ask her to differentiate the common cold from an influenza infection?

Although it can be difficult to differentiate the common cold from influenza, there are some clues that may suggest one viral infection from the other. Influenza infections typically occur from December through March in the United States. Patients with influenza generally experience more systemic symptoms, such as fever >102 °F (38.89 °C), headache, myalgia, and cough. Rhinorrhea, nasal congestion, and sneezing are more pronounced in patients with the common cold. Sore throat can occur with both a cold and the flu. Bacterial sore throat (eg, strep throat) is somewhat differentiated from a viral sore throat in that a viral sore throat usually has a slower onset and the throat pain is less severe. Lymph nodes are only slightly enlarged and not tender in a viral sore throat, whereas with a bacterial sore throat, lymph nodes are large and tender.[81]

K.B. should be questioned about her symptoms and exposure to ill contacts, and investigation into whether influenza has been documented in the community should be performed to help differentiate an influenza infection from the common cold.

Treatment

CASE 79-10, QUESTION 2: K.B. describes symptoms consistent with an influenza infection for the past 24 hours. What treatment options exist for the

treatment of influenza? Why is she a candidate for an antiviral agent?

Persons with suspected or confirmed influenza virus infection who are at high risk for developing complications (eg, those with preexisting cardiac or pulmonary disease, unvaccinated infants and children, elderly, immunocompromised) may benefit from antiviral therapy. Treatment is recommended regardless of influenza vaccination status and severity of illness in all patients who develop symptoms of influenza and who require hospitalization.[82] Antiviral therapy should also be used in outpatients with severe or progressive illness, those at high risk for complications, children younger than age 2 years and adults ages 65 years and older, and in outpatient females who are pregnant or within 2 weeks' postpartum.[82] Treatment can be considered in outpatients within 48 hours of onset of symptoms, symptomatic outpatients who are household contacts of people who are at high risk for complications, and symptomatic health care providers who care for patients who are at high risk for complications of influenza infection.[82] Therapy will shorten the duration of illness and decrease the risk of transmission to others in close contact with persons at high risk for complications secondary to influenza infection. The benefits are less clear in patients who have had symptoms >48 hours.[82]

The neuraminidase inhibitors, zanamivir (Relenza®), oseltamivir (Tamiflu®), and peramivir (Rapivab®), and the polymerase acidic endonuclease inhibitor baloxavir marboxil (Xofluza®) are the currently available agents that are active against influenza A and B. Neuraminidase inhibitor agents work by selectively inhibiting the enzyme neuraminidase, an enzyme necessary for viral replication and spread. Baloxavir inhibits the endonuclease activity of the polymerase acidic protein, an influenza virus–specific enzyme necessary for virus replication. Oral oseltamivir is currently indicated for the prevention and treatment of influenza in patients ages 1 year and older; oral zanamivir is indicated for the prevention of influenza in patients ages 7 years and older and for the treatment of influenza in patients ages 5 years and older; and baloxavir is indicated for the

treatment of influenza in patients ages 12 years and older who have been symptomatic for no more than 48 hours.[83–85] Peramivir, a parenteral formulation, is indicated in adults older than ages 18 years and in patients who cannot tolerate or absorb orally administered oseltamivir or inhaled zanamivir.[86]

Zanamivir is available as an oral powder for inhalation. For the treatment of influenza infection in adults, 10 mg (two inhalations) bid for 5 days should be used. Patients should inhale two doses, separated by at least 2 hours, on the first day and then two doses, separated by 12 hours, on days 2 through 5.[83] Bronchospasm after use can occur, and if bronchodilators are also prescribed, the bronchodilator should be used before zanamivir.[83] Proper use of the delivery system (Rotadisk®/Diskhaler®) is important, and thus patients should be instructed by the pharmacist on proper delivery technique, with a demonstration device.

Oseltamivir is pharmacologically related to zanamivir but has significantly better oral bioavailability, allowing oral dosing. It is approved for children older than age 1 year and for adults. The dosage of oseltamivir for the treatment of influenza in adults is 75 mg bid for 5 days.[84] Oseltamivir is available as a suspension with pediatric dosing recommendations. As with zanamivir, treatment with oseltamivir must be started within 48 hours of the onset of symptoms. Common side effects include nausea, vomiting, and headache.[84] Of concern is that oseltamivir-resistant influenza has been reported.[87] In addition, there are reports, predominantly in children, of self-injury and delirium after the administration of oseltamivir.[76]

Baloxavir, the newest antiviral approved for the treatment of influenza infection, is administered as a single oral dose within 48 hours of symptom onset, with or without food. The dose varies with weight: 40 mg (two 20-mg tablets) for patients weighing between 88.18 pounds (40 kg) and <176.37 pounds (80 kg) and 80 mg (two 40-mg tablets) for those weighing at least 176.37 pounds (80 kg). Coadministration with dairy products, calcium-fortified beverages, polyvalent cation–containing laxatives, antacids, or oral supplements (eg, calcium, iron, magnesium, selenium, or zinc) should be avoided

because of chelation leading to decreased baloxavir absorption. The most commonly noted adverse effects include diarrhea and nausea.[85]

Peramivir is dosed at 600 mg once and is administered intramuscularly (IM) or IV as an infusion over 15 to 30 minutes. As the agent was primarily studied in patients with influenza A and moderate disease, efficacy is unknown for patients infected with influenza B or patients with severe infection requiring hospitalization. The most common side effect is diarrhea; however, severe dermatologic reactions and abnormal behaviors have been reported with its use.[86]

Resistance to amantadine and rimantadine has increased dramatically in recent years; consequently, these agents are no longer recommended for the routine prevention or treatment of influenza infections.[88]

When administered within 48 hours of onset of illness, zanamivir, oseltamivir, and baloxavir reduce influenza symptoms by ~1 day.[85,89–91] Information regarding the effectiveness of the neuraminidase inhibitors in preventing serious complications of influenza, such as pneumonia or worsening of chronic diseases, is limited.[77] Considering the causative agent is unknown and symptoms have been present for only 24 hours, K.B. may benefit from an antiviral agent. Oral oseltamivir or oral baloxavir is easier to administer than is inhaled zanamivir, and the patient has no reason to not tolerate this drug. Although no antiviral agent will cure influenza, these medications may reduce the severity and duration of symptoms by about 1 day. She should be treated with a 5-day course of oseltamivir or a single dose of baloxavir.

CASE 79-11

Question 1: J.T., a 74-year-old male, is brought to the ED from a nursing home with fever (103 °F [39.44 °C]), shaking chills, cough, headache, malaise, anorexia, and photophobia. He has been ill for the past 48 hours but is much worse this evening. On physical examination, he appeared flushed, his skin was hot and moist, and he was having difficulty breathing. Vital signs included blood pressure, 150/90 mm Hg; pulse, 108 beats/minute; respiratory rate (RR), 22

breaths/minute; and temperature, 103 °F (39.44 °C). Rales were audible on auscultation of both lungs. A chest roentgenogram showed bilateral infiltrates but no consolidation. His viral respiratory panel finding was positive for influenza A. Results of blood gas studies showed significant hypoxia, with a partial pressure of oxygen (Pa_{O_2}) of 50 mm Hg and a partial pressure of carbon dioxide (Pa_{CO_2}) of 50 mm Hg. J.T.'s medical history was significant for chronic bronchitis and a stroke 16 months ago. Blood, sputum, and urine cultures were obtained, and J.T. was started on antibiotics (ceftriaxone 1 g IV every 24 hours and azithromycin 500 mg IV every 24 hours). Gram stain of the sputum sample showed many WBCs but no bacteria. He was started on oxygen therapy at 4 L/minute via nasal cannula. Twenty-four hours later, his respiratory symptoms worsened, and his arterial blood gases deteriorated slightly (Pa_{O_2}, 40 mm Hg; Pa_{CO_2}, 55 mm Hg) and J.T. was intubated. Blood, urine, and sputum culture results were all negative for bacterial pathogens.

Why is this presentation consistent with influenza infection? Is antiviral treatment appropriate in J.T.?

Although symptoms of influenza may vary depending on age, most patients with influenza A have an abrupt onset of fever, chills, cough, and headache. In elderly patients such as J.T. and those with underlying diseases, the course of influenza can worsen quickly, and patients are more likely to require hospitalization.

Antiviral therapy in J.T. is inappropriate. None of the antiviral agents has been studied in patients presenting with symptoms after 48 hours of onset. In addition, the antiviral agents have shown efficacy only in uncomplicated influenza.[92] However, owing to the severity of his illness, the administration of peramivir should be prescribed.[92]

Prevention

INFLUENZA VACCINES

Case 79-11, Question 2: During the next 3 weeks, two other nursing home patients develop influenza A infections. What measures should be taken to prevent a further outbreak of influenza among other residents?

The nursing home residents and staff should receive influenza vaccine plus chemoprophylaxis with oseltamivir or zanamivir. The Centers for Disease Control and Prevention (CDC) recommends immunization of all individuals 6 months of age or older, and especially those in high-risk groups, primarily all individuals who are at high risk for influenza-related complications and their household contacts (Table 79-4).[77] Second in priority are otherwise healthy adults ages 50 years and older and children with chronic metabolic diseases severe enough to warrant regular follow-up during the preceding year. Any child younger than age 9 years in whom the vaccine is indicated requires two doses of the vaccine for optimal effectiveness in the first year the vaccine is administered. The first dose should be administered as soon as the vaccine becomes available, if possible by October, and the second dose is given before influenza infection is present in the community. Vaccination should continue throughout the season and can be given as late as February or March, depending on the duration of the influenza season. However, the efficacy of the influenza vaccine is incomplete (70%).[91] Therefore, an oral antiviral agent should be considered for pre- and postexposure prophylaxis in high-risk individuals who may not develop an adequate antibody response (eg, patients with advanced HIV infection, residents of nursing homes) to supplement the protection by vaccine.[82],[88],[93]

A live, attenuated influenza vaccine (FluMist®) is an option for healthy, individuals between ages 2 and 49 years. In clinical studies with matched influenza strains, live, attenuated influenza vaccine was ~87% effective in preventing influenza in children and provided 85% efficacy in adults.[91],[94] Advantages of the intranasal route of administration include ease of administration and patient acceptability of an intranasal preparation compared with an IM injection. However, because the vaccine is live, viral shedding can occur for ≥2 days after vaccination. Consequently, patients who are immunosuppressed and close contacts of patients who are severely immunocompromised (including health care workers who care for them) should not receive the live vaccine. Others who should not receive the live vaccine include patients with asthma or other chronic

disorders of the pulmonary or cardiovascular systems, those with chronic metabolic diseases such as diabetes, renal dysfunction, or hemoglobinopathies, and children or adolescents who are receiving aspirin or other salicylates.[76]

OSELTAMIVIR, ZANAMIVIR, AND BALOXAVIR

Analysis of clinical trials of oseltamivir in the prevention of influenza showed a decreased incidence of laboratory-confirmed influenza: 4.8% in the placebo group and 1.2% in the treatment group.[95] The incidence of influenza in a skilled nursing facility was 4.4% in the placebo group and 0.4% in the oseltamivir group. In addition, oseltamivir lowered the rate of infection in patients exposed to influenza at home from 12% to 1%. Baloxavir has been shown to have efficacy similar to that of oseltamivir in high-risk outpatients.[96] Zanamivir has also been found to be effective in preventing infection.[97],[98]

Comparative studies between oral antiviral agents have not been published. Considering that oseltamivir and baloxavir are available in oral formulations and are easier to administer in patients in nursing homes compared with zanamivir, which requires proper use of the delivery device and a coordinated inspiratory effort, these agents may be preferred.

RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

Respiratory syncytial virus (RSV) causes bronchiolitis and bronchopneumonia in infants younger than age 2 years. More than one-half of affected infants are infected in the first 2 years of life. Of these infants, ~1% to 2% will require hospitalization.[99] Children who are severely premature, immunocompromised, or with underlying congenital heart disease or lung disease may be at increased risk for mortality because of RSV.[100] Patients with RSV infection before 3

years of age are at increased risk for wheezing and asthma during childhood.[101]

RSV infections usually occur in the winter. The chest radiograph and blood gas findings are often abnormal, and the virus can be isolated in the nasopharyngeal secretions.

Clinical Presentation and Ribavirin Therapy

CASE 79-12

QUESTION 1: J.R., a 6-month-old male infant who is lethargic, tachypneic, and cyanotic, is brought to the ED. J.R.'s medical history is significant for congenital HIV. He has a fever (102 °F [38.89 °C]), his breathing is labored, and wheezing is audible on expiration. The chest roentgenograms reveal a flattened diaphragm and hyperinflated lung parenchyma. Because of hypoxemia and hypercarbia, J.R. is placed on ambient oxygen to maintain the alveolar oxygen pressure at >60 mm Hg. RSV is identified in the viral respiratory panel collected in the ED.

What therapy is indicated for J.R.?

The goal of RSV therapy is to increase oxygen saturation and decrease airway resistance in patients such as J.R.[102] Treatment of RSV is highly individualized, depending on the presenting signs and symptoms and associated comorbidities. Oxygen is first-line therapy. Although decreases in airway resistance are often achieved with the use of bronchodilators or corticosteroids in other conditions, such as asthma, they have not proved to be effective in the treatment of bronchiolitis.[103],[104] Hypertonic saline, administered as a nebulized solution, is beneficial in increasing mucociliary clearance.[105] Adverse reactions of hypertonic saline include wheezing and excessive secretions.

Ribavirin (Virazole®) is active against many DNA and RNA viruses, including RSV. However, its clinical benefit remains controversial. Early studies with ribavirin showed significant clinical improvement compared with placebo in both healthy children and those with underlying disease.[106] These studies reported benefit in terms of clinical recovery and improvement in arterial oxygenation.

Subsequent studies found ribavirin to be ineffective in patients with a variety of risk factors.[107],[108] Consequently, the routine use in previously healthy infants and children has not been clearly established. Whether ribavirin decreases the long-term sequelae and severity of illness in high-risk groups (including premature infants, patients with bronchopulmonary dysplasia, congenital heart disease, cystic fibrosis, and immunodeficiency) has not been determined.[109] Current recommendations include consideration for use of ribavirin in infants at risk for severe life-threatening infection.[106] Because J.R. has an underlying immunodeficiency, ribavirin may be considered if J.R.'s condition worsens.

ADMINISTRATION OF RIBAVIRIN

CASE 79-12, QUESTION 2: How is ribavirin administered, and what precautions should be taken during drug administration in J.R.?

Ribavirin is administered as an aerosol through a collision generator that generates particles small enough (1–2 μm wide) to reach the lower respiratory tract. The concentration of the ribavirin solution in the reservoir is 20 mg/mL (6 g in 300 mL of sterile water). The dose is administered over the course of 12 to 18 hours, although in nonventilated patients, 2 g during 2 hours tid (using a 60-mg/mL solution) has been successfully used.[106] Ribavirin therapy is continued for 3 to 7 days.[110]

Ribavirin is approved for use in patients requiring mechanical ventilation. However, ribavirin is hygroscopic, and aerosol particles can deposit in the tubing and around the expiratory valve of a ventilator. The precipitated drug can obstruct the expiratory valve and alter the peak end-expiratory pressure.[110] Ribavirin has been safely used in such patients,[111],[112] but close monitoring of respiratory therapy is advised to prevent this problem. In addition to the inspection of the tubing, modifications of standard ventilatory circuits have been suggested.[110]

ADVERSE EFFECTS

CASE 79-12, QUESTION 3: What are the important adverse effects of ribavirin?

The most common adverse effects of ribavirin are rash, initial mild bronchospasm, and reversible skin irritation.[113] Although long-term follow-up data are limited, a study evaluating the effects of ribavirin in patients 1 year after administration showed a reduction in the incidence and severity of reactive airway disease, as well as in hospitalizations related to respiratory illness.[114] Further long-term evaluation is still necessary.

Ribavirin is contraindicated in females who are or may become pregnant during exposure to the drug. Although there are no human data, ribavirin has been found to be teratogenic or lethal to embryos in nearly all animal species in which it has been tested. Teratogenesis was evident after a single oral dose of 2.5 mg/kg in hamsters and after daily oral doses of 10 mg/kg in rats. Malformation of the skull, palate, eye, jaw, skeleton, and GI tract have been documented in animals. Ribavirin has reduced the survival of fetuses and offspring of animals tested. It is lethal to rabbit embryos in daily oral doses as small as 1 mg/kg. There are no studies that address teratogenicity in humans, but hospital personnel who are pregnant or may become pregnant should avoid exposure to this drug.[111]

It is important to consider the environmental effects of ribavirin on the personnel involved with its administration. One study found no detectable plasma or urine concentrations of ribavirin in 19 nurses, whereas another reported its presence in the RBCs of a nurse caring for a patient who received ribavirin via oxygen tent.[115] The ribavirin concentration in the air was highest when it was administered via oxygen tent, followed by mist mask, and was lowest after administration via endotracheal tubes of mechanically ventilated patients. This has led to several recommendations: (a) Ribavirin aerosol should be administered solely via endotracheal tube of mechanically ventilated patients in a closed filtered system[99]; (b) children receiving ribavirin should be placed in a containment

chamber equipped with a high-efficiency particulate air filter exhaust in an isolation room with negative air pressure[110]; (c) disposable full-body coverings and either a powered air-purifying respirator or disposable particulate respirator should be made available to all health care personnel[115]; and (d) males and females planning to have children should not care for patients receiving ribavirin via oxygen tents.[115] The manufacturer provides an aerosol delivery system for oxygen and ribavirin that decreases the liberation of ribavirin into the environment.[110]

Prevention

CASE 79-13

QUESTION 1: S.N. is a 7-month-old male born prematurely at 27 weeks' gestation. He has chronic lung disease (CLD) of prematurity and uses oxygen at home. RSV season will begin next month.

What treatments to prevent RSV infection are available? Why is S.N. a candidate for such treatment?

Palivizumab (Synagis®), a humanized monoclonal antibody made from recombinant DNA, is active against RSV and is indicated for children at risk for severe RSV respiratory tract infections (eg, infants with CLD or a history of premature birth before 29 weeks' gestation). The efficacy of palivizumab has been demonstrated in children with a history of prematurity or CLD.[116] Children receiving monthly IM injections of palivizumab for 5 months during RSV season had a reduction in hospitalizations and intensive care admissions for RSV disease. Palivizumab has replaced the use of RSV immunoglobulins (Igs) in infants because it is easier to administer (IM vs IV), does not interfere with the response of live vaccines such as measles–mumps–rubella or varicella vaccine, and is not likely to transmit blood-borne diseases because it is a synthetic product rather than one derived from human blood.[117]

Based on S.N.'s age and his CLD, he is a candidate for palivizumab therapy.[116]

PALIVIZUMAB DOSAGE AND ADMINISTRATION

CASE 79-13, QUESTION 2: How are the doses of palivizumab calculated, and how should it be administered?

The dose of palivizumab is 15 mg/kg given IM. The first dose is given before the start of the RSV season, and then monthly doses are given for a total of 5 months. In the Northern Hemisphere, the RSV season is typically November through April.

HANTAVIRUS

Infections

Rodents are the primary reservoir hosts of *Hantavirus*, and in the United States the deer mouse (*Peromyscus maniculatus*) is the main reservoir. These viruses apparently do not cause illness in the reservoir hosts, but infection in humans occurs when infected saliva, urine, and feces produced by the rodent are inhaled as aerosols. Most patients recall exposure to rodents or rodent feces within 6 weeks of the onset of illness.[118] Person-to-person transmission has not been documented.

The case definition includes clinical evidence of (a) febrile illness characterized by unexplained acute respiratory distress syndrome (ARDS) or acute bilateral pulmonary interstitial infiltrates, or (b) an autopsy finding of noncardiogenic pulmonary edema, resulting from an unexplained respiratory illness. In addition, laboratory evidence consists of (a) a positive serology (ie, presence of hantavirus-specific IgM or rising titers of IgG), (b) positive immunohistochemistry for hantavirus antigen in a tissue specimen, or (c) positive PCR for hantavirus RNA in a tissue specimen.[119] Hantavirus infection can cause three different clinical diseases: hemorrhagic fever with renal syndrome, nephropathia epidemica, and hantavirus pulmonary

syndrome (HPS). Hemorrhagic fever with renal syndrome and nephropathia epidemica occur in Asian and European countries. HPS occurs only in the Western Hemisphere, including North America.[118] From 1993 to 2018, 797 cases of HPS were reported in the United States, leading to 32% mortality rate.[120] Most cases have occurred in the southwestern United States during spring and summer.

Clinical Presentation

The clinical features of patients with HPS include fever, myalgia, headache, chills, dizziness, and nonproductive cough. Abdominal pain, nausea, or vomiting may also be present. The physical examination has been unreliable. Laboratory abnormalities may include leukocytosis, thrombocytopenia, and hypoalbuminemia. The chest radiograph may initially be normal, but rapid disease progress may show bilateral infiltrates and ARDS. Other viral pneumonias do not typically progress to ARDS as rapidly as hantavirus infections. Because of the nonspecific signs and symptoms, some patients may be misdiagnosed as having influenza.[121]

Treatment

Supportive treatment is important. Oxygen therapy and mechanical ventilation may be necessary. Hypotension can be treated with vasopressor agents and judicious use of IV crystalloids (ie, 0.9% NaCl) to prevent worsening of pulmonary edema. Universal precautions and respiratory isolation should be instituted.[118]

There is no FDA-approved drug to treat hantavirus infections. Based on one study in 242 patients, IV ribavirin was more effective than was placebo in reducing morbidity (oliguria and hemorrhage) and mortality. IV ribavirin was given as a loading dose of 33 mg/kg, followed by 16 mg/kg every 6 hours for 4 days, and 8 mg/kg every 8 hours for the next 3 days.[122]

Two other clinical trials, however, did not show similar clinical efficacy in the treatment of HPS. One open-label trial conducted by the CDC showed a mortality rate of 47% in patients who received ribavirin compared with 50% in those who did not.[123] In addition, a small trial conducted at the National Institutes of Health could not demonstrate any benefit from ribavirin.[124]

WEST NILE VIRUS

West Nile virus (WNV) was first identified in the United States in 1999 in New York City. Since then, the virus has had rapid geographic expansion and has infected individuals in all states in the continental United States and Puerto Rico.[125] Although WNV normally occurs in tropical climates, the increase in international travel and changes in weather patterns have led to its spread.

WNV is a member of the Flaviviridae family. Culicine mosquitoes (including *Culex pipiens*, *C. restuans*, and *C. quinquefasciatus*) are the vectors, and they infect both birds and humans.[126] Infection with the virus involves direct inoculation by the infecting mosquito. Birds are reservoir hosts. WNV can infect a number of vertebrates, including horses. Transmission usually occurs from a mosquito bite; however, reports indicate that transmission of the infection has occurred through transfusions, organ transplantation, placental transfer, and via breast milk.[126] Because of the seasonal variations in the life cycle of the mosquito, cases are most commonly seen during the summer and early fall.

Diagnosis is usually made by high clinical suspicion and laboratory tests. WNV can cause a wide range of illness, from an asymptomatic disease to West Nile fever to encephalitis or meningitis. Mortality is low except in the neuroinvasive forms of the infection. Mortality rates in the elderly, particularly those older than 70 years, can be nine times higher than that in the general population.[126] The CDC laboratory criteria for diagnosis of WNV include (a) isolation of the WNV antigen or genomic sequence from a tissue, blood, CSF, or

other body fluids; (b) WNV IgM antibody in a CSF sample; (c) a fourfold rise in the antibody titer to WNV; and (d) demonstration of an IgM or rising titers of IgG to WNV in a single serum sample.[127]

Clinical Presentation

CASE 79-14

Question 1: A.G. is an 84-year-old female. She is very active and runs the yearly flower festival in the community. She was brought to the ED by her granddaughter, who found her at home, confused and with a headache, fatigue, and increasing muscle weakness. She has a temperature of 103 °F (39.44 °C), and her Mini-Mental Status Examination score is 21 of 30. She has decreasing muscle strength and an erythematous, macular, papular rash on her arms and legs. The complete blood count and electrolytes are normal, with the exception of slightly decreased sodium. The CSF reveals increased WBCs, increased protein, normal glucose, and positive IgM antibody to WNV. A CT scan shows no abnormalities.

What signs and symptoms are indicative of WNV encephalitis?

Acute signs and symptoms of WNV include sudden onset of fever, anorexia, weakness, nausea, vomiting, eye pain, headache, altered mental status, and stiff neck. A rash may be present on the arms, legs, neck, and trunk. The rash is typically erythematous, macular, and papular with or without morbilliform eruption.[126] Laboratory parameters may show normal or elevated WBC counts. Low serum sodium concentrations may be seen in patients with encephalitis. CSF usually shows pleocytosis, mostly with an elevation of lymphocytes, elevated protein levels, and normal glucose levels.[126] MRI shows some enhancement of the leptomeninges or the periventricular areas in approximately one-third of patients, but no other abnormalities or evidence of acute disease are present on either CT or MRI examination.[126]

With disease progression, further muscle weakness and hyporeflexia may be observed. Patients may progress to a diffuse, flaccid paralysis similar to that of Guillain–Barré syndrome. Ataxia,

extrapyramidal symptoms, cranial nerve abnormalities, myelitis, optic neuritis, and seizures may be seen.

Treatment

Case 79-14, Question 2: What treatment options are available to A.G.?

Currently, treatment of WNV infection is supportive. Patients with febrile infection usually have a self-limiting course. In severe cases, patients with muscle weakness and signs of encephalitis will require admission to an intensive care unit (ICU), and many will need mechanical ventilation. The available antiviral medications do not have any activity against WNV in vivo, although ribavirin inhibits replication in vitro.[126] Combination therapy of high-dose ribavirin and interferon-α-2b has been used in patients with severe disease with limited success. Although optimal doses have not been established, the doses needed to inhibit the virus were 2 to 3 million units of interferon and 2400 mg of ribavirin daily.[128–130]

SEVERE ACUTE RESPIRATORY SYNDROME

Severe acute respiratory syndrome (SARS), a highly transmissible infectious disease caused by a SARS-associated coronavirus, was first identified in China in early 2003. During the 2003 outbreak, ~8000 cases were reported, with a case fatality rate of about 10%.[131],[132] No cases of SARS were reported worldwide after this outbreak was contained in 2004. In 2012, an outbreak of another severe respiratory illness caused by a coronavirus was identified in Saudi Arabia. As of December 2021, a total of 2583 cases with Middle East respiratory syndrome (MERS) have been reported, with a case fatality rate of 37.1%.[133] In December 2019 in Wuhan, China, an alarming number of patients presented with symptoms of viral pneumonia, with the initial 27 cases presumably associated with a

seafood market in downtown Wuhan. Since the initial identification of this novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus has spread to all countries in the world and been declared a pandemic by the World Health Organization on March 11, 2020.[134] The number of cases and deaths reported worldwide exceed 430 million and 5.9 million, respectively, as of March 1, 2022. In the United States, 78 million infections and 939,950 deaths have been reported as of March 1, 2022.[135]

Infection with SARS-CoV-2 is generally caused by exposure to airborne droplets from a symptomatic patient. Patients who are asymptomatic or presymptomatic may also transmit the virus, with estimates of at least 50% of infected individuals contracting the infection from an asymptomatic or presymptomatic individual.[136] Because the virus is easily transmitted by airborne microdroplets, precautions such as wearing a face mask, maintaining a distance of at least 72 inches (182.88 cm) from others and frequent handwashing can decrease the risk of infection. In December 2020, the first vaccine was granted Emergency Use Authorization (EUA) in the United States for protection against SARS-CoV-2.

SARS-CoV, responsible for the 2003 outbreak, was isolated from patients and identified as the causative agent of SARS. Although the natural reservoir of SARS-CoV has not been identified, the virus has been detected in the Himalayan masked palm civet, the Chinese ferret badger, and the raccoon dog. SARS-CoV-2 was isolated from bronchoalveolar lavage fluid samples in patients initially infected in Wuhan. The sequence of SARS-CoV-2 shares 79% of genome sequencing with SARS-CoV and 50% with Middle East Respiratory Syndrome coronavirus (MERS-CoV).[137] It is thought that the virus originated from the *Rhinolophus malayanus* bat indigenous in the Yunnan province in China. Bats are natural hosts to alphacoronaviruses and betacoronavirus, two of which (RaRTG13 and RmYN02) have been identified as sharing >90% of the genomic sequencing as the SARS-CoV-2. Viruses similar to SARS-CoV-2 have also been identified in pangolins that were smuggled from Southeast Asia into southern China.[137]

Clinical Presentation

CASE 79-15

Question 1: S.R. is a 75-year-old Black male. His past medical history is unremarkable except for hypertension controlled by lisinopril 20 mg daily. He is retired but spends many hours outdoors and at his church. S.R. enjoys the company of many of his fellow churchgoers who would visit his home frequently without masks or social distancing. S.R. does not have a history of smoking and does not drink alcohol. S.R. has not received a vaccine for COVID-19.

S.R. experienced a cough, headache, myalgia, and fever 2 days before his presentation to the ED. He began experiencing shortness of breath and weakness that prompted a visit to the ED. Upon arrival, his heart rate was 76 beats/minute, blood pressure 142/88, temperature 103.2 °F (39.56 °C), RR of 32 breaths/minute, and oxygen saturation of 92% on room air. His chest radiograph revealed ground glass opacities bilaterally in the middle and lower lung. The ED physician immediately quarantined S.R., started supplemental oxygen via nasal cannula, and obtained a nasopharyngeal swab to test for SARS-CoV-2. S.R. was admitted to the hospital.

What signs and symptoms are consistent with COVID-19? What severity of COVID-19 does S.R. present with?

The 2021 case definition of COVID-19 established by the CDC as of August 2021 includes clinical, laboratory, and epidemiologic criteria.[138] **Table 79-5** describes the symptoms required for diagnosis of COVID-19 named for coronavirus disease first identified in 2019 and caused by SARS-CoV-2. S.R. exhibits symptoms consistent with COVID-19, including cough, fever, headaches, myalgia, shortness of breath, and weakness. His oxygen saturation and chest radiograph are indicative of COVID-19. Based on his clinical presentation, he meets the clinical criteria for a probable infection. Despite not having known contact with someone infected with SARS-CoV-2, his lack of wearing a mask and social distancing may have increased his risk of contact. The reverse transcriptase polymerase chain reaction (RT-PCR) test will confirm the diagnosis of COVID-19 if the result is positive.

Table 79-5
2021 Case Definition for Diagnosis of Coronavirus Disease 2019

Case Classification

Suspect:

- Meets supportive laboratory evidence with no prior history of being a confirmed or probable case

Probable:

- Meets clinical criteria *and* epidemiologic linkage with no confirmation or presumptive laboratory evidence for SARS-CoV-2
- Meets presumptive laboratory evidence
- Meets vital records criteria with no confirmatory laboratory evidence for SARS-CoV-2

Confirmed:

Meets confirmatory laboratory evidence

Clinical Criteria	Laboratory Criteria	Epidemiologic Linkage
In the absence of a more likely diagnosis, acute onset or worsening of at least two of the following: ▪ Fever (measured or subjective) ▪ Chills ▪ Rigors ▪ Myalgia ▪ Headache ▪ Sore throat ▪ Nausea/vomiting ▪ Diarrhea ▪ Fatigue ▪ Congestion or rhinorrhea *or* *Acute onset or worsening of any one of the following:* ▪ Cough	*Confirmatory* ▪ Detection of SARS-CoV-2 RNA in a postmortem respiratory swab or clinical specimen using a diagnostic molecular amplification test *or* ▪ Detection of SARS-CoV-2 by genomic sequencing *Presumptive* ▪ Detection of SARS-CoV-2–specific antigen in a postmortem-obtained respiratory swab or clinical specimen using a diagnostic test *Supportive* ▪ Detection of antibody in serum, plasma, or whole blood specific to natural infection with SARS-CoV-2 ▪ Detection of SARS-CoV-2–specific antigen by immunocytochemistry in an autopsy specimen	*One or more of the following exposures in the prior 14 days:* ▪ Close contact with a confirmed or probable case of COVID-19 disease[a] ▪ Member of an exposed risk cohort as defined by public health authorities during an outbreak or a high community transmission

▪ Shortness of breath ▪ Difficulty breathing ▪ Olfactory disorder ▪ Taste disorder ▪ Confusion or change in mental status ▪ Persistent pain or pressure in chest ▪ Pale, gray, or blue-colored skin, lips, or nail beds, depending on skin tone ▪ Inability to wake or stay awake *or* *Severe respiratory illness with at least one of the following:* ▪ Clinical or radiographic evidence of pneumonia ▪ ARDS	*or* ▪ Detection of SARS-CoV-2 RNA or specific antigen	

ARDS, acute respiratory distress syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Close contact defined by being within 72 inches (182.22 cm) for at least 15 minutes (cumulative over a 24-hour period).

Source: Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) 2021 case definition. Updated August 24, 2021. Accessed October 29, 2020. https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/.

Virologic (ie, molecular and antigen) testing is available for patients suspected of having COVID-19 infection or for those at high-risk for contracting SARS-CoV-2. Treatment guidelines recommend a virologic test preferably from a nasopharyngeal, nasal, or an oropharyngeal sample for diagnostic purposes. A swab of the

nasopharynx has a higher yield, but concerns regarding aerosolization of the virus may limit this method in some settings; therefore, nasal or oropharyngeal samples are acceptable.[139] RT-PCR is the gold standard for detecting SARS-CoV-2 infection. Sensitivity varies, depending on time of symptom onset, collection of sample, and the sample tested for SARS-CoV-2.[140–142] A meta-analysis that determined the highest sensitivity for RT-PCR was obtained from the sputum (97.2%, 95% confidence interval [CI] 90.3%–99.7%), nasopharyngeal aspirate/swab or throat swab (73.3%, 95% CI 68.1%–78.0%) and saliva (62.3%, 95% CI 54.5%–69.6%).[142] Rapid, point-of-care antigen testing varies in sensitivity and specificity. A meta-analysis evaluated 18 cohorts utilizing rapid point-of care testing from North America (10), Europe (4), South America (2), China (1), and one conducted in several countries.[143] Average sensitivity for antigen point-of-care tests was 56.2% (95% CI 29.5%–79.8%) and specificity was 99.5% (95% CI 98.1%–99.9%). Patients with symptoms of COVID-19 who have a negative point-of-care test result should have an RT-PCR test for confirmation.

Probable or likely exposure to SARS-CoV-2 through a close contact or as a member of a high-risk cohort during an outbreak is a critical component of the SARS case definition.[138] A close contact is defined as being within 6 feet for at least 15 minutes at one time or cumulatively over a 24-hour period.

COVID-19 can present and progress to varying degrees of severity.[139] Patients can remain asymptomatic throughout infection or develop critical illness involving respiratory failure, shock, and multiple organ dysfunction resulting in death.[139] **Table 79-6** outlines the categories of severity based on the clinical guidelines developed by the National Institutes of Health. Patients considered to be at higher risk for developing severe disease include those older than age 65 years, underlying cardiovascular disease or CLD, sickle cell disease, diabetes, cancer, obesity, chronic kidney disease, being pregnant, being a cigarette smoker, being a transplant recipient, or an individual on immunosuppressant therapy.[139] Once a patient recovers from COVID-19, symptoms may persist. Although the

sequelae of the disease have not been clearly elucidated, reports have included fatigue, joint pain, chest pain, palpitations, shortness of breath, cognitive impairments, and worsened quality of life.[139] The CDC defines the syndrome of persistent symptoms (commonly referred to as “long COVID”) with sequelae that extend beyond 4 weeks after initial infection.[144] These may persist for at least 3 months, although long-term follow-up is still required to determine the associated COVID-19 morbidity. S.R. presents with severe illness based on his respiratory rate, oxygen saturation, and chest radiograph findings.

Table 79-6

Severity Categories for Adults Diagnosed With SARS-CoV-2

Category	Criteria
Asymptomatic or presymptomatic infection	Individuals whose test result is positive for SARS-CoV-2 using a virologic test (ie, a nucleic acid amplification test or an antigen test), but who have no symptoms that are consistent with COVID-19
Mild illness	Individuals who have any of the various signs and symptoms of COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (Spo_2) ≥94% on room air at sea level
Severe illness	Individuals who have Spo_2 <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (Pao_2/Fio_2) <300 mm Hg, respiratory frequency >30 breaths/minute, or lung infiltrates >50%
Critical illness	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Source: COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Accessed March 1, 2022. https://www.covid19treatmentguidelines.nih.gov/.

Treatment

Case 79-15, Question 2: What treatment is indicated for S.R. at this time?

Patients presenting with mild-to-moderate COVID-19 disease may be managed on an ambulatory basis with symptomatic treatment. Patients not hospitalized or not requiring oxygenation should not receive any specific antiviral, corticosteroid, or immunomodulatory therapy because clinical trials with these treatments have not found any benefit from antiviral therapy.[139] Antiviral therapies are available for patients at high risk for progression to severe COVID-19. The therapies (in order of preference based on efficacy and convenience of administration per guidelines) are ritonavir-boosted nirmatrelvir, sotrovimab, remdesivir, and molnupiravir.

Ritonavir-boosted nirmatrelvir (Paxlovid®) is an oral inhibitor against the SARS-CoV-2 main protease (M^{pro}) with activity against coronaviruses known to infect humans. It is boosted with ritonavir, a potent CYP3A4 inhibitor, to decrease its metabolism and thus increase concentrations of nirmatrelvir at the site of action. Clinical studies demonstrate an 87.8% ($P < 0.001$) reduced risk of hospitalization or death when administered within 3 days of symptom onset compared to placebo in patients at high risk for severe COVID-19 disease.[145] Use of ritonavir-boosted nirmatrelvir has resulted in rebound of COVID-19.Ritonavir-boosted nirmatrelvir is administered at a dose of 300 mg of nirmatrelvir and 100 mg of ritonavir every 12 hours for 5 days. Adverse effects attributed to nirmatrelvir included taste disturbances, diarrhea, and vomiting.[145] Owing to the ritonavir component in the therapy, a review of current medications the patient is taking is required to minimize drug–drug interactions. Dose reductions are required in patients with an estimated glomerular filtration rate (eGFR) between 30 and 60 mL/minute. Ritonavir-boosted nirmatrelvir is not recommended for use in patients with an eGFR <30 mL/minute or severe hepatic impairment (Child–Pugh class C). EUA for ritonavir-boosted nirmatrelvir was granted for

children 12 years old with a weight of at least 88.18 pounds (40 kg) and adults in December 2021.[146]

Sotrovimab is an IV therapy of anti-SARS-CoV-2 monoclonal antibodies approved for nonhospitalized patients with mild-to-moderate COVID-19 at risk for progression to severe disease.[139] Clinical trials demonstrated an 85% relative risk reduction (95% CI, 44%–96%) in risk of hospitalization or death in adult patients who received sotrovimab 500 mg IV within 5 days of symptom onset.[147] Sotrovimab received EUA for adults and children age older than 12 years and weighing >88.18 pounds (40 kg). Owing to the risk of hypersensitivity reactions, sotrovimab must be administered in a health care setting where a patient can be monitored during and for 1 hour after the infusion. Diarrhea was reported more frequently in patients receiving sotrovimab compared to placebo. Although the patients were treated within 5 days of symptom onset in the clinical trial, EUA is approved for up to 10 days of symptom onset.[148]

Remdesivir was the first antiviral granted FDA authorization for use in hospitalized patients with COVID-19. A clinical trial evaluated the efficacy of remdesivir in nonhospitalized patients (12 years or older) at high risk for progression to severe disease presenting within 7 days of symptom onset. The study found those randomized to receive IV remdesivir for 3 days had an 87% lower risk of COVID-19–related death or hospitalization (hazard ratio, 0.13; 95% CI 0.03%–0.59%; P = 0.008).[149] The most common adverse effects were nausea, headache, and cough. The dose of remdesivir is 200 mg IV on day 1, followed by 100 mg on days 2 and 3 for adults and pediatric patients older than 12 years and weighing >88.18 pounds (40 kg). EUA has been granted for nonhospitalized children younger than 12 years weighing at least 7.72 pounds (3.5 kg), but not ≥88.18 pounds (40 kg), at risk for progression to severe COVID-19.[150] For these patients, the dose is 5 mg/kg IV on day 1, followed by 2.5 mg/kg IV on day 2. Similar to sotrovimab, administration must occur in a health care setting to monitor and manage hypersensitivity reactions. The use of remdesivir is not recommended for patients with an eGFR <30 mL/minute.

Molnupiravir is a prodrug that is metabolized to its triphosphate form, subsequently serving as a substrate for RNA polymerases. Molnupiravir increases mutations in various viruses, including SARS-CoV-2, which results in nonfunctional viral genomes.[151] Owing to the mechanism of action, concern regarding genotoxicity in humans has been evaluated. Based on data and the short duration of treatment, the risk of genotoxicity is thought to be low. However, concern exists regarding the risk of molnupiravir on SARS-CoV-2 mutation rates. Although the manufacturer is mandated to monitor genomic databases for mutations of the virus, the use of molnupiravir is recommended only when no other therapies are available for prevention of severe disease in high-risk patients. A randomized controlled trial evaluated the efficacy of molnupiravir 800 mg orally twice daily for 5 days versus placebo on rates of hospitalization or death. The study was stopped early because it met the primary outcome at the interim analysis. Molnupiravir was found to decrease rate of hospitalization by 31% (hazard ratio, 0.69; 95% CI, 0.48–1.01) compared to placebo.[152] Molnupiravir has EUA for adults within 5 days of symptom onset.[153] Common adverse effects include diarrhea, nausea, and dizziness. No dose adjustments are recommended for patients with renal or hepatic dysfunction.

Patients with moderate-to-severe disease admitted to an acute care setting require aggressive management from an interprofessional health care team. Patients presenting with oxygenation saturation levels <94% on room air require supplemental oxygen. Current clinical guidelines recommend the use of remdesivir in patients requiring supplemental oxygen.[139] The Adaptive COVID-19 Treatment Trial evaluated 1062 patients older than 18 years treated with remdesivir at 200 mg IV on day 1, followed by 100 mg IV daily until day 10 or discharge. Patients treated with remdesivir had a recovery time of 10 days (95% CI, 9–11) in the treatment group compared to 15 days (95% CI, 13–19) in the placebo group. Patients randomized to remdesivir also had an improved clinical outcome compared to those in the placebo group.[154] The most common adverse events reported in the remdesivir group included anemia, acute kidney injury,

hyperglycemia, and increases in aminotransferase levels.[154] Another study evaluated the duration of therapy with remdesivir in patients 12 years or older.[155] Patients were randomized in this open-label trial to 5 or 10 days of treatment. Patients in the 10-day group, at baseline, were more critically ill than were those in the 5-day group. After adjusting for baseline clinical status, there was no difference in the length of hospitalization, or time to clinical improvement.[155] Patients on the 10-day course had a higher incidence of adverse events, including elevated liver enzymes, and decreased renal and hepatic function. In addition, 10% of the patients on the 10-day course discontinued treatment because of adverse events compared to 4% in the 5-day course.[155] Because the study did not demonstrate a difference in clinical outcomes with a 5-day course in patients who did not require mechanical ventilation at initiation of the study, the recommended treatment duration for nonintubated patients is 5 days.[155] For those who do not demonstrate clinical improvement after 5 days, the treatment may be extended to 10 days.[139] In addition, any patient progressing to administration of high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation should complete a 10-day course of remdesivir. Remdesivir was approved by the FDA on October 22, 2020.

Dexamethasone is recommended in patients requiring supplemental oxygen.[139] The randomised evaluation of COVID-19 therapy (RECOVERY) trial was a controlled, open-label multicenter trial evaluating the dexamethasone in hospitalized patients with COVID-19.[156] Patients randomized to dexamethasone received 6 mg IV or PO for 10 days or until discharge. The preliminary findings reported an improved survival benefit for patients requiring supplemental oxygen treated with dexamethasone compared to standard of care (22.9% vs 25.7% deaths at 28 days, rate ratio 0.83 [95% CI, 0.75–0.93] *P* <.001). In a subgroup analysis, patients not on supplemental oxygen did not appear to have a survival benefit (14.0% vs 17.8%), whereas patients on invasive mechanical ventilation had an improved survival benefit (41.4% vs 29.3%) compared to standard of care.[156] For this reason, dexamethasone, or

other corticosteroids if dexamethasone is unavailable, is recommended for patients on supplemental oxygen.[139]

S.R. is a candidate for remdesivir because his oxygen saturation is <94% and he is receiving supplemental oxygen. He should receive a 200 mg IV dose as soon as he is admitted, followed by 4 additional days of 100 mg IV every 24 hours. If he does not demonstrate clinical improvement in 5 days, a 10-day course of remdesivir is warranted. S.R. should also receive dexamethasone for 10 days or until discharge.

Case 79-15, Question 3: S.R. is on day 7 of remdesivir therapy. He is now intubated, with increasing oxygen demands. Which therapy could be considered in addition to remdesivir and dexamethasone?

Patients who are critically ill requiring rapidly increasing oxygen supplementation may benefit from an interleukin (IL)-6 inhibitor or Janus kinase (JAK) inhibitors. However, owing to lack of data on efficacy, the selection of an additional immunomodulator must be made on an individual basis. The addition of either baricitinib or tocilizumab to a regimen including corticosteroids may depend on the availability of the medication and the patient's comorbidities. It is not recommended to use baricitinib and tocilizumab together because of the risk of immunosuppression. If baricitinib is unavailable, clinicians may consider using tofacitinib. Similarly, if tocilizumab is unavailable, sarilumab may be considered. The use of corticosteroids and an IL-6 or JAK inhibitor, may potentially increase the risk of opportunistic infections regardless of the treatment duration.[139] Because S.R. requires increased oxygen, he may be a candidate for the addition of baricitinib or tocilizumab.

Patients with COVID-19 require management of other complications because of associations with bacterial pulmonary superinfections, septic shock secondary to cytokine storm, thromboembolic events, cardiac dysfunction, and renal or hepatic dysfunction. A critical aspect in managing patients with COVID-19 is prevention or treatment of thromboembolic events.

COVID-19 IN PEDIATRIC PATIENTS

Infection rates and disease severity due to SARS-CoV-2 appear to be lower in pediatric patients compared to that in the adult population. Initial reports of children infected with SARS-CoV-2 in China indicated that 2% of infections were in individuals younger than 19 years.[158] As of February 22, 2022, in the United States, over 10 million cases have been reported in individuals younger than 18 years. Of these, 1346 have died of COVID-19.[157] One epidemiologic study determined the highest hospitalization rates of COVID-19 between March 1, 2020 and August 14, 2021 were in children younger than 2 years (69.2 hospitalizations per 100,000 children and adolescents). An analysis of pediatric patients with or without a vaccine against SARS-CoV-2 found a hospitalization rate of 0.8 per 100,000 person-weeks (95% CI, 0.6–0.9) in unvaccinated children and adolescents compared to 0.1 per 100,000 person-weeks (95% CI, 3.7–27.9) in fully vaccinated children and adolescents.[158] Children at risk for severe disease include those with a history of concurrent medical conditions (eg, genetic disorders, neurologic impairment), obesity, chronic pulmonary or cardiac disease, or those who are immunocompromised.[159] Adolescents and non-White children also are at increased risk.

Children may be asymptomatic or have milder symptoms than do adults. Symptoms in pediatric patients are similar to that in adults (Table 79-6), with the most common symptoms being fever and cough.[160] Children may also present with only GI symptoms.[160] Fever, nausea/vomiting, cough, shortness of breath, and upper respiratory symptoms are the more common signs and symptoms in pediatric patients who are hospitalized.[139] Diagnostic tests in children are the same as that in adults.

Clinical guidelines have been published to provide recommendations for use of pharmacologic agents in the treatment of COVID-19 in pediatric patients.[139] Supportive care remains the main treatment for COVID-19 infection in pediatric patients because most children will not progress to severe disease. Although the recent clinical guidelines do not outline specific recommendations for

nonhospitalized children with COVID-19 at high risk for severe disease, ritonavir-boosted nirmatrelvir, sotrovimab, and remdesivir have received EUA for children and adolescents older than 12 years weighing ≥88.18 pounds (40 kg). In addition, remdesivir received EUA in January 2022 for children at least 7.72 pounds (3.5 kg) but not more than 88.18 pounds (40 kg) who do not require hospitalization but are at risk for progression of COVID-19.[150] The use of these agents must be considered on an individual basis given underlying risks in the child.[139]

For pediatric patients requiring hospitalization, guidelines recommend remdesivir in those 12 years or older with worsening respiratory disease requiring increased oxygen support and risk factors for severe disease. For children 16 years or older, remdesivir is recommended for all patients with an increased requirement of oxygen support, regardless of risk factors. In consultation with an infectious disease team, all children (regardless of age and risk factors) with worsening severity of COVID-19 can be considered for treatment with remdesivir.[139] Dosing for remdesivir for patients <88.18 pounds (40 kg) is 5 mg/kg IV on day 1 followed by 2.5 mg/kg IV every 24 hours. For patients >88.18 pounds (40 kg), the dose is 10 mg/kg IV on day 1 followed by 5 mg/kg IV every 24 hours. The duration of therapy is 5 to 10 days, with 10 days indicated for patients not improving at day 5.[161]

Corticosteroids are recommended for use in pediatric patients who are hospitalized and require high-flow oxygen, noninvasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation.[139] If available, dexamethasone is recommended at 0.15 mg/kg/dose (maximum 6 mg) once daily for 10 days. Prednisone, methylprednisolone, and hydrocortisone (at equivalent doses) can be used should dexamethasone be unavailable. Caution is warranted in immunocompromised patients. The guidelines do not recommend for or against the use of baricitinib or tocilizumab. However, the guidelines do not recommend the use of sarilumab or convalescent plasma in pediatric patients.

The guidelines also recommend enrolling children and adolescent patients in clinical trials when possible to expand the data on the

efficacy and safety of these agents in pediatric patients. Medical care for complications related to COVID-19 (eg, renal dysfunction, thromboembolic events) is necessary.

Another manifestation of SARS-CoV-2 in children and adolescents presents as hyperinflammatory shock with clinical characteristics similar to Kawasaki disease.[162] The multisystem inflammatory syndrome in children was described in children from Europe and appeared to be associated with SARS-CoV-2 but presenting 2 to 4 weeks after an acute infection. Patients presented with fever, rash, conjunctivitis, peripheral edema, GI symptoms, shock, and cardiac damage. Patients also presented with increased inflammatory markers and positive serology for SARS-CoV-2. Cases in the United States were first recognized in New York in May 2020.[162] As of January 31, 2022, 6851 cases have been reported in the United States, with 59 associated deaths.[163] The syndrome is referred to as pediatric multisystem inflammatory syndrome temporally related to SARS CoV-2 (PMIS-TS) or multisystem inflammatory syndrome in children (MISC-C).

The case definition for MISC-C includes (a) an individual younger than 21 years with fever, laboratory evidence of inflammation (eg, CRP, erythrocyte sedimentation rate [ESR], fibrinogen, D-dimer), and evidence of clinically severe illness requiring hospitalization with two or more organs involved, (b) no alternative plausible diagnosis, and (c) positive result for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test or COVID-19 exposure within the 4 weeks of the onset of symptoms. Fever is defined as a temperature ≥100.4 °F (38 °C) or a subjective fever for at least 24 hours.[164]

In the first 570 cases of MISC-C in the United States, 86.5% presented with some form of cardiac involvement including shock, increased cardiac enzymes, myocarditis, and cardiac dysfunction.[162] Patients will require intensive care with cardiac monitoring. In addition, 60.4% presented with elevated D-dimers, indicating an existing coagulopathy. Patients presenting with an elevated D-dimer may require anticoagulation for prevention or treatment of thromboembolism.[165]

Treatment for patients presenting with MIS-C includes supportive care and immunotherapy directed at antibodies responsible for the inflammatory response. Recommended treatment is IVIG (1–2 g/kg [not to exceed 100 g] over 12 hours) in combination with a moderate-dose corticosteroid such as methylprednisolone 1 to 2 mg/kg/day.[139] Data from nonrandomized clinical trials found that this combination improves recovery of cardiac function, shorter ICU stay, less treatment failure, and decreased need for escalation compared to IVIG alone.[139] However, no randomized clinical trials have been conducted for safety and efficacy of these agents. Other immunotherapies such as infliximab, anakinra, or tocilizumab have been used in patients with treatment failure to IVIG and corticosteroid therapy. Treatment failure is defined as persistent fever, ongoing organ dysfunction, and increasing levels of inflammatory markers. These patients may require intensification therapy with anakinra at a dose of 5 to 10 mg/kg/day, infliximab at a dose of 5 to 10 mg/kg/day, or higher dose corticosteroids (eg, methylprednisolone 10–30 mg/kg/day). A second dose of IVIG for intensification is not recommended.[139]

Because patients with MIS-C are not in an acute phase of an infection, remdesivir is not indicated. Most patients with MIS-C recover; however, long-term effects are currently unknown.

PREVENTION OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Prevention against infection with SARS-CoV-2 includes avoiding contact with infected individuals and vaccination against SARS-CoV-2. If the infected person is in the same household, it is recommended to maintain at least 72 inches (182.22 cm) between the infected person and others and limiting time to 15 minutes cumulatively. Avoid poorly ventilated areas and crowds when possible. A mask can prevent spreading infection to others and should be worn in public settings. Handwashing with soap and water for at least 20 seconds is recommended after sneezing or coughing. In the event soap and water are not available, hand sanitizer is a suitable

alternative. Surfaces that are touched daily (eg, tables, doorknobs, light switches, phones) should be disinfected daily with a household disinfectant. It is also important to monitor health daily for symptoms of COVID-19. It is important to monitor for signs and symptoms of COVID-19 and test if symptoms of COVID-19 occur after a close contact.[166]

As of February 2022, three vaccines are available in the United States to protect against COVID-19. The mRNA vaccines, Spikevax® (manufactured by ModernaTX, Inc.) and Comirnaty® (manufactured by BioNTech Manufacturing GmbH and Pfizer, Inc.) are recommended for primary and booster immunization over the COVID-19 vaccine (manufactured by Janssen Biotech Inc.) owing to improved effectiveness against severe COVID-19 requiring hospitalization and lower risk of serious adverse effects.[167] The primary series of the vaccine is recommended for everyone age 5 years and older and requires administration of two doses for the mRNA vaccines. Children 12 years and older should receive a booster of an mRNA vaccine 5 months after the completion of the primary series. Individuals who are immunocompromised may require an additional booster (fourth dose) 3 months after the first booster. The efficacy of the vaccines depends on the number of boosters an individual receives and the circulating variant. The CDC updates the risk of testing positive and risk of dying from COVID-19 based on vaccine status. The most recent data reported on January 22, 2022 indicated unvaccinated adults had 2.6 times the risk of testing positive for COVID-19 and 14 times the risk of dying from COVID-19 compared to fully vaccinated adults.[168] In the same time frame, compared to fully vaccinated adults with booster doses, unvaccinated adults had a 3.2 times greater risk of testing positive for COVID-19 and a 41 times greater risk of dying from COVID-19.

Adverse reactions to the vaccines range from mild to moderate in severity. Common side effects include pain, swelling and redness at the site of injection, fever, headache, fatigue, myalgia, chills, and nausea. More severe, rare adverse effects include anaphylaxis. An increased risk of thrombosis with thrombocytopenia syndrome (TTS) has been reported with all three vaccines but more often with the

Johnson & Johnson/Janssen vaccine. Females between ages 30 and 49 years may be at increased risk for TTS, which causes blood clots in large blood vessels and thrombocytopenia.[167] Cases of myocarditis and pericarditis have been reported after administration of the mRNA vaccines. The reported cases were mild and self-limiting, with more occurrences in male adolescents and young adults.[139]

Although vaccines are the most effective way to prevent COVID-19, people who have had a severe reaction to a vaccine or are unable to mount an adequate immune response (eg, immunocompromised) may require pre-exposure prophylaxis with anti-SARS-CoV-2 monoclonal antibodies tixagevimab plus cilgavimab (Evusheld®). Tixagevimab 150 mg with cilgavimab 150 mg administered as two IM injections can offer protection against COVID-19 for up to 6 months. Although no data are available on the use of repeated doses every 6 months, it is recommended that individuals meeting criteria for administration receive the monoclonal antibodies every 6 months. These monoclonal antibodies are not recommended for individuals able to receive vaccines safely but rather for individuals with a severe reaction to a vaccine or are severely immunocompromised.[139] Data demonstrated a 77% reduction in infection in patients receiving tixagevimab and cilgavimab compared to placebo (95% CI, 46%–90%; $P < 0.001$).[139] For patients who receive a COVID-19 vaccine, it is recommended to wait 2 weeks before administration of tixagevimab and cilgavimab. Serious adverse effects reported included anaphylaxis and rare serious cardiac events including myocardial infarction, cardiac failure, and arrhythmia. The cardiac events occurred in participants with underlying heart disease or risk factors for heart disease. Less serious reported adverse reactions included headache and fatigue.[169]

It is important to reference the most recent clinical guidelines by the National Institutes of Health and the CDC for updated prevention and treatment recommendations. The COVID-19 pandemic is continuing to evolve with the possibility of new variants. The Omicron variant spread quickly around the world and became the dominant

strain, replacing the Delta variant. Soon, data emerged on the effectiveness of diagnostic tests, vaccines, and treatments for the new variant. For example, during the Delta wave, monoclonal antibodies for postexposure prophylaxis, bamlanivimab plus etesevimab and casirivimab plus imdevimab received EUA for individuals at risk for progression to severe disease. However, when Omicron became the dominant variant, it was determined that these monoclonal antibodies were no longer effective against the new variant. As such, they are no longer available in the United States. Thus, preferred treatment would depend on the efficacy and safety of various medications for a specific COVID variant and should be based on the most recent evidence-based guidelines for the optimal management of patients.

MIDDLE EAST RESPIRATORY SYNDROME

MERS was first reported in 2012 in Saudi Arabia. As of January 2020, a total of 2519 cases have been reported with a case fatality rate of 34.3%, primarily in the Arabian Peninsula.[170] To date, only two cases have been reported in the United States, both in health care workers who lived in Saudi Arabia and traveled to the United States. Both received supportive care at a hospital and were discharged.[170]

The causative organism of MERS is the MERS-CoV. Symptoms of MERS include fever, cough, chills/rigors, lethargy, myalgia, headache, confusion, and shortness of breath. In some patients, GI symptoms such as nausea, diarrhea, and vomiting have been reported. The infection progresses to complications including progressive pneumonitis, respiratory failure, acute respiratory distress syndrome, septic shock, and multiorgan failure. Those at greatest risk for death are those older than 60 years and those with comorbid conditions, such as diabetes, cancer, lung disease, or chronic kidney disease. Individuals older than 60 years with a history of smoking, preexisting pneumonia, abnormal renal function, and comorbidities are at greatest risk for death.[171]

MERS-CoV appears to be transmitted through close contact with an infected individual, likely through respiratory droplets. Most infections reported have occurred in hospitals or in individuals caring for or living with an infected individual.[171] Treatment of MERS is directed as supportive care and management of symptoms and complications.

COMMON COLD

The most prevalent viral infection is the common cold. In the United States, ~62 million cases of the common cold occur annually.[172] An estimated 20 million and 22 million days of absence from work and school, respectively, occur. The frequency of the occurrence of a cold is greater in younger children and decreases with increasing age. Although the common cold is self-limiting, otitis media occurs in ~20% of children after infection.[173]

Many viruses have been isolated from patients with respiratory infections, but rhinovirus is the most common viral pathogen.[174] Rhinovirus accounts for 30% to 50% of all respiratory illnesses. More than 100 different serotypes of rhinovirus exist, and the prevalence of each varies with time and geography. Other pathogens include coronavirus, parainfluenza, RSV, adenovirus, and enterovirus. Because of the number of pathogens known to cause the common cold, development of an effective vaccine remains difficult.

Treatment for the common cold is directed at pharmacologic treatment of symptoms. Nonsteroidal anti-inflammatory drugs, oral or intranasal decongestants, antihistamines, and antitussives may be used. However, these products provide minimal relief of symptoms and do not shorten the natural course of infection.[175–177] In pediatric patients younger than 4 years, the use of cough and cold medications is not recommended by the FDA because of the lack of evidence for efficacy and deaths associated with their use.[178–180] Currently, there are no specific antiviral treatments for the common cold.

Prevention

CASE 79-16

QUESTION 1: J.C. comes into the pharmacy asking for an herbal product that will help him prevent colds this upcoming cold season. He states that last year he had three colds and his neighbor had none. His neighbor had mentioned an herbal product he had been taking. J.C. cannot remember the name of the product but wonders whether there are any products that may be helpful.

What can you recommend for J.C.?

ZINC

Zinc, a dietary supplement, has been studied in both the prevention and treatment of the common cold. The proposed mechanism of action is that the rhinovirus 3C protease is inhibited by zinc, and the inhibition of this enzyme prevents viral replication. In vitro, zinc has been shown to have antiviral activity. Several trials conducted in the past several decades have produced conflicting results on the benefits of zinc in decreasing symptom severity or duration. If started within 24 hours of symptom onset, zinc may shorten symptoms but not severity of the cold. Zinc lozenges, dosed at a minimum of 75 mg/day for the duration of cold symptoms, is recommended.[181] Patients who took zinc lozenges for the common cold reported mouth irritation, unpleasant taste, feeling sick, and diarrhea. Daily administration of zinc is not currently recommended for prophylaxis of the common cold.

ECHINACEA

Echinacea is an herbal product extracted from the *Echinacea* plant, which belongs to the Compositae family. Echinacea is believed to stimulate the immune system, specifically phagocytosis. Some clinical trials using echinacea have shown positive results in decreasing the incidence of infection when compared with placebo, but the data remain inconclusive.[182] One study showed no benefit of echinacea versus placebo but did show an increased incidence of rash in the treatment group.[183] Because the current data are

inconclusive for efficacy and owing to the variability of echinacea concentrations in the available products and their association with adverse effects, use of echinacea in the prevention and treatment of the common cold is not recommended.[182–184]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med.* 2020;383:1813–1826. (154)

Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP*). MMWR Morb Mortal Wkly Rep.* 2011;60:1–26. (88)

Godfred-Cato S, Bryant B, Leung J, et al. COVID-19 associated multisystem inflammatory syndrome in children—United States, March–July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1074–1080. (162)

Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med.* 2022;386:305–315. (149)

Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices (ACIP)—United States, 2020–21 influenza season. *MMWR Morb Mortal Wkly Rep*. 2021;70(5):1–28. (77)

Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1–30. (48)

Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis.* 2020;20:e276–e288. (165)

Lee DH, Zuckerman RA; AST Infectious Diseases Community of Practice. Herpes simplex virus infections in solid organ transplantation: guidelines from the

American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant.* 2019;33:e13526. (26)

Marin M, Güris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2007;56(RR-4):1–40. (52)

Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics.* 2014;134:e1474–e1502. (103)

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med.* 2020;384:693–704. (156)

Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis.* 2019;68:895–902. (82)

Key Websites

Centers for Disease Control and Prevention. Hantaviruses. https://www.cdc.gov/hantavirus/index.html

Centers for Disease Control and Prevention. West Nile virus. https://www.cdc.gov/westnile/

Centers for Disease Control and Prevention. SARS basic fact sheet. Updated December 6, 2017. Accessed March 1, 2022. http://www.cdc.gov/sars/about/fs-sars.html (131)

Centers for Disease Control and Prevention. COVID data tracker. https://covid.cdc.gov/covid-data-tracker/

Centers for Disease Control and Prevention. Post-COVID conditions. Updated September 16, 2021. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html (144)

Centers for Disease Control and Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. https://www.cdc.gov/mis-c/cases/index.html (163)

COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Accessed March 1, 2022. https://www.covid19treatmentguidelines.nih.gov/ (139)

World Health Organization. WHO Coronavirus disease (COVID-19) dashboard. Accessed March 1, 2022. https://covid19.who.int/table (135)

COMPLETE REFERENCES CHAPTER 79 VIRAL INFECTIONS

1. Rui P, Okeyode T. National Ambulatory Medical Care Survey: 2016 National summary tables. Accessed February 28, 2022. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2016_namcs_web_tables.pdf
2. Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. *Lancet*. 2006;368:2211–2218.
3. Whitley RJ, Roizman B. Herpes simplex virus infections. *Clin Infect Dis*. 2001;357:1513–1518.
4. Whitley RJ, Kimberlin DW, Roizman B. Herpes simplex virus. *Clin infect Dis*. 1998;26:541–555.
5. Schleede L, Bueter W, Baumgartner-Sigl S, et al. Pediatric herpes simplex virus encephalitis: a retrospective multicenter experience. *J Child Neurol*. 2013;28(3):321–331.
6. Stahl JP, Mailles A. Herpes simplex virus encephalitis update. *Curr Opin Infect Dis*. 2019;32:239–243
7. Aurelius E, Johansson B, Sköldenberg B, Staland A, Forsgren M. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. *Lancet*. 1991;337:189–192.
8. Gnann JW, Whitley RJ. Herpes simplex encephalitis: an update. *Curr Infect Dis Rep*. 2017;19:13.
9. Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med*. 1986;314:144–149.
10. Skoldenberg B, Forsgren M. Acyclovir versus vidarabine in herpes simplex encephalitis. *Lancet*. 1985;47:89–96.
11. Zovirax (acyclovir). Product information. GlaxoSmithKline; 2003.
12. James SH, Kimberlin DW, Whitley RJ. Antiviral therapy for herpesvirus central nervous system infections: neonatal herpes simplex virus infection, herpes simplex encephalitis, and congenital cytomegalovirus infection. *Antiviral Res*. 2009;83:207–213.
13. American Academy of Pediatrics. Herpes simplex. In: Kimberlin DW, Brady MT, Jackson MA, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. American Academy of Pediatrics; 2018.
14. Kamei S, Sekizawa T, Shiota H, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. *J Neurol Neurosurg Psychiatry*. 2005;76:1544–1549.

15. Ramos-Estebanez C, Lizarraga KJ, Merenda A. A systemic review on the role of adjunctive corticosteroids in herpes simplex virus encephalitis: is timing critical for safety and efficacy? *Antivir Ther*. 2014;19:133–139.
16. Wagstaff AJ, Faulds D, Goa KL. Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*. 1994;47:153–205.
17. Zovirax (acyclovir) oral. GlaxoSmithKline; 2005.
18. Pouplin T, Pouplin JN, Van Toi P, et al. Valacyclovir for herpes simplex encephalitis. *Antimicrob Agents Chemother*. 2011;55:3624–3626.
19. Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus infections. *Semin Perinatol*. 2018;42:168–175.
20. James SH, Kimberlin DW. Neonatal herpes simplex virus infection: epidemiology and treatment. *Clin Perinatol*. 2015;42:47–59.
21. Whitley R, Arvin A, Prober C, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. Infectious Diseases Collaborative Antiviral Study Group. *N Engl J Med*. 1991;324:444–449.
22. Kimberlin DW, Whitley RJ, Wan W, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. *N Engl J Med*. 2011;365:1284–1292.
23. Kimberlin DW, Powell D, Gruber W, et al. Administration of oral acyclovir suppressive therapy after neonatal herpes simplex virus disease limited to the skin, eyes, and mouth: results of a phase I/II trial. *Pediatr Infect Dis J*. 1996;15:247–254.
24. Gutierrez K, Arvin AM. Long term antiviral suppression after treatment for neonatal herpes infection. *Pediatr Infect Dis J*. 2003;22:371–372.
25. Chen F, Xu H, Liu J, et al. Efficacy and safety of nucleoside antiviral drugs for treatment of recurrent herpes labialis: a systematic review and meta-analysis. *J Oral Pathol Med*. 2017;46:561–568.
26. Lee DH, Zuckerman RA; AST Infectious Diseases Community of Practice. Herpes simplex virus infections in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33:e13526.
27. Schacker T, Hu HL, Koelle DM, et al. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. *Ann Intern Med*. 1998;128:21–28.
28. Shepp DH, Newton BA, Dandliker PS, Flournoy N, Meyers JD. Oral acyclovir therapy for mucocutaneous herpes simplex virus infections in immunocompromised marrow transplant recipients. *Ann Intern Med*. 1985;102:783–785.
29. Shiley K, Blumberg E. Herpes viruses in transplant recipients: HSV VZV human herpes viruses, and EBV. *Infect Dis Clin North Am*. 2010;24:373–393.
30. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized,

doubleblind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother*. 2002;46:2238–2243.

31. Raborn GW, Martel AY, Lassonde M, et al. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc*. 2002;133:303–309.
32. Sacks SL, Thisted RA, Jones TM, et al. Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol*. 2001;45:222–230.
33. Lin L, Chen XS, Cui PG, et al. Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double-blind, multicentre, aciclovir-controlled trial. *J Dermatolog Treat*. 2002;13:67–72.
34. Femiano F, Gombos F, Scully C. Recurrent herpes labialis: efficacy of topical therapy with penciclovir compared with acyclovir (aciclovir). *Oral Dis*. 2001;7:31–33.
35. Spruance SL, Rea TL, Thoming C, et al. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, doubleblind, placebo-controlled trial. Topical Penciclovir Collaborative Study Group. *JAMA*. 1997;277:1374–1379.
36. Raborn GW. Penciclovir cream for recurrent herpes simplex labialis: an effective new treatment. *Antimicrob Agents Chemother*. 1996;36:178.
37. Raborn GW, McGaw WT, Grace M, Tyrrell LD, Samuels SM. Oral acyclovir and herpes labialis: a randomized, double-blind, placebo-controlled study. *J Am Dent Assoc*. 1987;115:38–42.
38. Spruance SL, Stewart JC, Rowe NH, McKeough MB, Wenerstrom G, Freeman DJ. Treatment of recurrent herpes simplex labialis with oral acyclovir. *J Infect Dis*. 1990;161:185–190.
39. Spruance SL, Bodsworth N, Resnick H, et al. Single-dose, patient-initiated famciclovir: a randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. *J Am Acad Dermatol*. 2006;55:47–53.
40. Spruance SL, Hill J. Clinical significance of antiviral therapy for episodic treatment of herpes labialis: exploratory analyses of the combined data from two valaciclovir trials. *J Antimicrob Chemother*. 2004;53:703–707.
41. Valtrex. Product information. GlaxoSmithKline; 2019.
42. Famvir. Producto information. Novartis Pharmaceuticals Canada, Inc; 2016.
43. Rooney JF, Straus SE, Mannix ML, et al. Oral acyclovir to suppress frequently recurrent herpes labialis: a double-blind, placebo-controlled trial. *Ann Intern Med*. 1993;118:268–272.
44. Baker D, Eisen D. Valacyclovir for prevention of recurrent herpes labialis: 2 double-blind, placebo-controlled studies. *Cutis*. 2003;71:239–242.
45. Piret J, Boivin G. Antiviral resistance in herpes simplex virus and varicell-zoster infections: diagnosis and management. *Curr Opin Infect Dis*. 2016;29:654–662.

46. Safrin S, Crumpacker C, Chatis P, et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the aquired immunodeficiency syndrome. The AIDS Clinical Trials Group. *N Eng J Med*. 1991;325:551–555.
47. Cohen JI. Herpes zoster. *N Engl J Med*. 2013;369:255–263.
48. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1–30.
49. Shaw J, Gershon AA. Varicella virus vaccination in the United States. *Viral Immunol*. 2018;31:96–103.
50. Gershon AA, Breuer J, Cohen JI, et al. Varicella zoster virus infection. *Nat Rev Dis Primers*. 2017;1:15016.
51. Freer G, Pistello M. Varicella-zoster virus infection: natural history, clinical manifestations, immunity and current and future vaccination strategies. *New Microbiol*. 2018;41:95–105.
52. Marin M, Güris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1–40.
53. Klassen TP, Belseck EM, Wiebe N, Hartling L. Acyclovir for treating otherwise healthy children and adolescents. *Cochrane Database Syst Rev*. 2005;(4): CD002980.
54. American Academy of Pediatrics Committee on Infectious Diseases: the use of acyclovir in otherwise healthy children with varicella. *Pediatrics*. 1993;91:674–676.
55. Wallace MR, Bowler WA, Murray NB, Brodine SK, Oldfield EC 3rd. Treatment of adult varicella with oral acyclovir: a randomized placebo-controlled trial. *Ann Intern Med*. 1992;117:358–363.
56. Whitley RJ. Therapeutic approaches to varicella-zoster virus infections. *J Infect Dis*. 1992;166(suppl 1):S51–S57.
57. Feder HM Jr. Treatment of adult chickenpox with oral acyclovir. *Arch Intern Med*. 1990;150:2061–2065.
58. Saguil A, Kane S, Mercado M, Lauters R. Herpes zoster and postherpetic neuralgia: prevention and management. *Am Fam Physician*. 2017;96:656–663.
59. Jackson JL, Gibbons R, Meyer G, Inouye L. The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia: a metaanalysis. *Arch Intern Med*. 1997;157:909–912.
60. Diaz-Mitoma F, Sibbald RG, Shafran SD, Boon R, Saltzman RL. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. *JAMA*. 1998;280:887–892.
61. deGreef H; Famciclovir Herpes Zoster Clinical Group. Famciclovir, a new oral antiherpes drug; results of the first controlled clinical study demonstrating its

efficacy and safety in the treatment of uncomplicated herpes zoster in immunocompetent patients. *Int J Antimicrob Agents*. 1995;4:241–246.

62. Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia: a randomized, double-blind placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. *Ann Intern Med*. 1995;123:89–96.
63. Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL, Wood MJ. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother*. 1995;39:1546–1553.
64. Tyring SK, Beutner KR, Tucker BA, Anderson WC, Crooks RJ. Antiviraltherapy for herpes zoster: randomized, controlled trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. *Arch Fam Med*. 2000;9:863–869.
65. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2013; (3):CD005582.
66. Wood MJ, Johnson RW, McKendrick MW, Taylor J, Mandal BK, Crooks J. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *N Engl J Med*.1994;330:896–900.
67. Santee JA. Corticosteroids for herpes zoster: what do they accomplish? *Am J Clin Dermatol*. 2002;3:517–524.
68. Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Ther*. 1993;15:510–526.
69. Lidoderm. Product information. Endo Pharmaceuticals; 2018.
70. Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2014; (2):CD006866.
71. Lyrica. Product information. Pfizer Pharmaceuticals LLC; 2020.
72. Balfour HH Jr, Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med*. 1983;308:1448–1453.
73. Kim B, Maverakis E, Alexanian C, Wang JZ, Raychaudhuri SP. Incidence, clinical features, management and prevention of herpes zoster in patients receiving antitumor necrosis factor therapy: a clinical review. *J Cutan Med Surg*. 2020;24:278–284.
74. Tyring S, Belanger R, Bezwoda W, et al. A randomized, double-blind trial of famciclovir versus acyclovir for the treatment of localized dermatomal herpes zoster in immunocompromised patients. *Cancer Invest*. 2001;19:13–22.
75. Arora A, Mendoza N, Brantley J, Yates B, Dix L, Tyring S. Double-blind study comparing 2 dosages of valacyclovir hydrochloride for the treatment of

uncomplicated herpes zoster in immunocompromised patients 18 years of age and older. *J Infect Dis*. 2008;197:1289–1295.

76. Centers for Disease Control and Prevention. Influenza. In: Hamborsky J, Hall E, Wodi AP, Morelli V, Schillie S, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 13th ed. Public Health Foundation; 2015.
77. Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices (ACIP)—United States, 2021–22 influenza season. *MMWR Morb Mortal Wkly Rep*. 2021;70:1–28.
78. Diaz-Granados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard dose influenza vaccine in older adults. *N Engl J Med*. 2014;371:635–645.
79. Nichol KL, Margolis KL, Lind A, et al. Side effects associated with influenza vaccination in healthy working adults. A randomized, placebo controlled trial. *Arch Intern Med*. 1996;156:1546–1550.
80. Margolis KL, Poland GA, Nichol KL, et al. Frequency of adverse reactions after influenza vaccination. *Am J Med*. 1990;88:27–30.
81. Scolaro KL. Colds and allergy. In: Krinsky DL, Berardi RR, Ferrari SP, eds. *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care*. 20th ed. American Pharmacists Association; 2020.
82. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68:895–902.
83. Relenza (zanamivir). Product information. GlaxoSmithKline; 2018.
84. Tamiflu (oseltamivir). Product information. Genentech USA; 2019.
85. Xofluza (baloxivir). Product information. Genentech USA; 2019.
86. Rapivab (peramivir). Product information. BioCryst Pharmaceuticals; 2020.
87. Centers for Disease Control and Prevention. Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis—North Carolina, 2009. *Morb Mortal Wkly Rep*. 2009;58:969–972.
88. Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mortal Wkly Rep*. 2011;60:1–26.
89. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group [published corrections appear in *Lancet*. 1999;353:504; *Lancet*. 1999;353:1104]. *Lancet*. 1998;352:1877–1881.
90. Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy

adults. *Cochrane Database Syst Rev*. 2010;(2):CD001265.
91. Allison MA, Daley MF, Crane LA, et al. Influenza vaccine effectiveness in healthy 6-to 21-month-old children during the 2003–2004 season. *J Pediatr*. 2006;149:755–762.
92. Hayden FG, Treanor JJ, Fritz RS, et al. Use of oral neuraminidase inhibitor oseltamivir in experimental influenza: randomized controlled trials for prevention and treatment. *JAMA*. 1999;282:1240–1246.
93. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:1003–1032.
94. FluMist Quadrivalent. Product information. Med Immune LLC; 2020.
95. Hayden FG, Atmar RL, Schilling M, et al. Use of selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med*. 1999;341:1336–1343.
96. Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2020;20:1204–1214.
97. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. *N Engl J Med*. 2000;343:1282–1289.
98. Monto AS, Robinson DP, Herlocher ML, Hinson JM Jr, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza in healthy adults: a randomized controlled trial. *JAMA*. 1999;282:31–35.
99. Lugo RA, Nahata MC. Pathogenesis and treatment of bronchiolitis. *Clin Pharm*. 1993;12:95–116.
100. Barr R, Green CA, Sande CJ, Drysdale SB. Respiratory syncytial virus: diagnosis, prevention and management. *Ther Adv Infect Dis.* 2019;6:2049936119865798.
101. Mikhail I, Grayson MH. Asthma and viral infections: an intricate relationship. *Ann Allergy Asthma Immunol.* 2019;123:352–358.
102. Panitch HB. Respiratory syncytial virus bronchiolitis: supportive care and therapies designed to overcome airway obstruction. *Pediatr Infect Dis J*. 2003;22(2 suppl):S83–S88.
103. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134:e1474–e1502.
104. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev*. 2014;(6):CD001266.
105. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitits in infants. *Cochrane Database Syst Rev*. 2017;12(12):CD006458.

106. American Academy of Pediatrics Committee on Infectious Diseases: use of ribavirin in the treatment of respiratory syncytial virus infection. *Pediatrics*. 1993;92:501–504.
107. Englund JA, Piedra PA, Ahn YM, Gilbert BE, Hiatt P. High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection. *J Pediatr*. 1994;125:635–641.
108. Wheeler JG, Wofford J, Turner RB. Historical cohort evaluation of ribavirin efficacy in respiratory syncytial virus infection. *Pediatr Infect Dis J*. 1993;12:209–213.
109. Ventre K, Randolph AG. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev*. 2007;(1):CD000181.
110. Virazole. Product information. Bausch Health; 2019.
111. Meert KL, Sarnaik AP, Gelmini MJ, Lieh-Lai MW. Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double-blind, randomized trial. *Crit Care Med*. 1994;22:566–572.
112. Smith DW, Frankel LR, Mathers LH, Tang AT, Ariagno RL, Prober CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. *N Engl J Med*. 1991;325:24–29.
113. Janai HK, Marks MI, Zaleska M, Stutman HR. Ribavirin: adverse drug reactions, 1986 to 1988. *Pediatr Infect Dis J*. 1990;9:209–211.
114. Edell D, Khoshoo V, Ross G, Salter K. Early ribavirin treatment of bronchiolitis: effect on long-term respiratory morbidity. *Chest*. 2002;122:935–939.
115. Krilov LR. Safety issues related to the administration of ribavirin. *Pediatr Infect Dis J*. 2002;21:479–481.
116. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalizations from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics*. 1998;102(3, pt 1):531–537.
117. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn. *Pediatrics*. 1998;102:1211–1216.
118. Avsic-Supanc T, Saksida A, Korva M. Hantavirus infections. *Clin Microbiol Infect*. 2019;21:e6–e16.
119. Centers for Disease Control and Prevention. Hantavirus Pulmonary Syndrome (HPS) 2015 case definition. Accessed June 13, 2022. https://ndc.services.cdc.gov/case-definitions/hantavirus-pulmonary-syndrome-2015/

120. Centers for Disease Control and Prevention. Hantavirus. Reported cases of hantavirus disease. Accessed October 7, 2020. https://www.cdc.gov/hantavirus/surveillance/index.html
121. Mertz GJ, Chapman L. Hantavirus infections in the United States: diagnosis and treatment. *Adv Exp Med Biol*. 1996;394:153–162.
122. Huggins JW, Hsiang CM, Cosgriff TM, et al. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J Infect Dis*. 1991;164:1119–1127.
123. Chapman LE, Mertz GJ, Peters CJ, et al. Intravenous ribavirin for hantavirus pulmonary syndrome: safety and tolerance during 1 year of open-label experience. *Antivir Ther*. 1999;4(4):211–219.
124. Mertz GJ, Miedzinski L, Goade D, et al. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. *Clin Infect Dis*. 2004;39:1307–1313.
125. Centers for Disease Control and Prevention. West Nile virus. Statistics & maps. Accessed October 7, 2020. https://www.cdc.gov/westnile/statsmaps/index.html
126. Petersen LY, Brault AC, Nasci RS. West Nile virus: review of the literature. *JAMA*. 2013;330:308–315.
127. Centers for Disease Control and Prevention. Neuroinvasive and non-neuroinvasive domestic arboviral diseases. 2015 case definition. Accessed June 13, 2022. https://ndc.services.cdc.gov/case-definitions/west-nile-virus-disease-2015/
128. Lewis M, Amsden JR. Successful treatment of West Nile virus infection after approximately 3 weeks into the disease course. *Pharmacotherapy*. 2007;27:455–458.
129. Anderson JF, Rahal JJ. Efficacy of interferon alpha-2b and ribavirin against West Nile virus in vitro. *Emerg Infect Dis*. 2002;8:107–108.
130. Kalil AC, Devetten MP, Singh S, et al. Use of interferon-alpha in patients with West Nile encephalitis: report of 2 cases. *Clin Infect Dis*. 2005;40:764–766.
131. Centers for Disease Control and Prevention. SARS basic fact sheet. Updated December 6, 2017. Accessed March 1, 2022. https://www.cdc.gov/sars/about/fs-sars.html
132. World Health Organization. Global Alert and Response (GAR). Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Accessed June 13, 2022. https://www.who.int/publications/m/item/summary-of-probable-sars-cases-with-onset-of-illness-from-1-november-2002-to-31-july-2003
133. World Health Organization. MERS situation update, January 2020. Accessed June 13, 2022. http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-january-2020.html
134. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. Published March 11, 2020. Accessed October

12, 2020. https://who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
135. World Health Organization. WHO Coronavirus disease (COVID-19) dashboard. Accessed March 1, 2022. https://covid19.who.int/table
136. Johansson MA, Quandelacy TM, Kada S, et al. SARS-CoV-2 transmission from people without COVID-19 symptoms. *JAMA Netw Open*. 2021;4:e2035057.
137. Wang H, Li X, Li T, et al. The genetic sequence, origin, and diagnosis of SARS-CoV-2. *Eur J Clin Microbiol Infect Dis*. 2020;39:1629–1635.
138. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) 2021 case definition. Updated August 24, 2021. Accessed October 29, 2020. https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/
139. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Accessed March 1, 2022. https://www.covid19treatmentguidelines.nih.gov/
140. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. *Ann Intern Med*. 2020;173(4):262–267.
141. Tang Y, Schmitz JE, Persing DH, Stratton CW. Laboratory diagnosis of COVID-19: current issues and challenges. *J Clin Microbiol*. 2020;58:e00512-20.
142. Boger B, Fachi MM, Vilhena RO, Cobre AF, Tonin FS, Pontarolo R. Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. *Am J Infect Cont*. 2021;49(1):21–29.
143. Dinnes J, Deeks JJ, Adriano A, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database Syst Rev*. 2020;8(8):CD013705.
144. Centers for Disease Control and Prevention. Post-COVID conditions. Updated September 16, 2021. Accessed March 1, 2022. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html
145. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk nonhospitalized adults with Covid-19. *N Engl J Med*. 2022;386(15): 1397–1408.
146. U.S. Food & Drug Administration. Fact sheet for healthcare providers: emergency use authorization for paxlovid. 2021. Accessed March 1, 2022. https://www.covid19oralrx-patient.com/files/Final-Emergency-Use-Full-Prescribing-Info-HCP-Fact-Sheet-COVID-19-Oral-Antiviral.pdf
147. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385:1941–1950.

148. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization of sotrovimab. 2022. Accessed March 1, 2022. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Sotrovimab/pdf/SOTROVIMAB-EUA.PDF#nameddest=HCPFS
149. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med*. 2022;386:305–315.
150. U.S. Food & Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of Veklury (remdesivir) for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients weighting 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing who are: hospitalized, or not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Accessed March 1, 2022. https://www.fda.gov/media/137566/download
151. Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M. Molnupiravir promotes SARS-CoV-2 mutagenesis via the RNA template. *J Biol Chem*. 2021;297:100770.
152. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med*. 2022;386:509–520.
153. U.S. Food & Drug Administration. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. Accessed March 1, 2022. https://www.fda.gov/media/155054/download
154. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020;383:1813–1826.
155. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med*. 2020;383(19):1827–1837. https://www.ncbi.nlm.nih.gov/pubmed/32459919
156. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2020;384:693–704.
157. Centers for Disease Control and Prevention. COVID data tracker: demographic trends of COVID-19 cases and deaths in the US reported to CDC. Accessed March 1, 2022. https://covid.cdc.gov/covid-data-tracker/#demographics
158. Siegel DA, Reses HE, Cool AJ, et al. Trends in COVID-19 cases, emergency department visits, and hospital admissions among children and adolescents aged 0–17 years—United States, August 2020–August 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(36):1249–1254.
159. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19—COVID-NET, 14 States, March 1–July 25, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1081–1088.

160. Centers for Disease Control and Prevention. Information for pediatric healthcare providers care for children. Accessed March 1, 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html
161. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. *J Pediatr Infect Dis*. 2020;9:701–715.
162. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19 associated multisystem inflammatory syndrome in children—United States, March–July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1074–1080.
163. Centers for Disease Control and Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. Accessed October 29, 2020. https://www.cdc.gov/mis-c/cases/index.html
164. Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Accessed March 1, 2022. https://www.cdc.gov/mis/mis-c/hcp/
165. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children an adolescents. *Lancet Infect Dis*. 2020;20(11):e276–e288.
166. Center for Disease Control and Prevention. How to protect yourself and others. Accessed March 1, 2022. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html
167. Oliver SE, Wallace M, See I, et al. Use of the Janssen (Johnson & Jonhnson) COVID-19 vaccine: updated interim recommendations from the Advisory Committee on Immunization Practices—United States, December 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71:90–95.
168. Centers for Disease Control and Prevention. COVID data tracker: rates of COVID-19 cases and deaths by vaccination status. Accessed March 1, 2022. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status
169. Tixagevimab and cilgavimab (evusheld) for pre-exposure prophylaxis of COVID-19. *JAMA.* 2022;327(4):384–385.
170. Centers for Disease Control and Prevention. CDC announces second imported case of Middle East Respiratory Syndrome (MERS) in the United States. Accessed October 9, 2020. https://www.cdc.gov/media/releases/2014/p0512-US-MERS.html
171. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A. Middle East respiratory syndrome. *Lancet*. 2020;295:1063–1077.
172. Centers for Disease Control and Prevention, National Center for Health Statistics. Vital and health statistics: current estimates from the National Health Interview Survey, 1996. Published October 1999. Accessed October 9, 2020. http://www.cdc.gov/nchs/data/series/sr_10/sr10_200.pdf
173. Jaume F, Valls-Mateus M, Mullol J. Common cold and acute rhinosinusitis: up-to-date management in 2020. *Curr Allergy Asthma Rep*. 2020;20:28.

174. Heikkinen T, Järvinen A. The common cold. *Lancet*. 2003;361:51–59.
175. Eccles R. Efficacy and safety of over-the-counter analgesics in the treatment of common cold and flu. *J Clin Pharm Ther*. 2006;31:309–319.
176. Arroll B. Non-antibiotic treatments for upper-respiratory tract infections (common cold). *Respir Med*. 2005;99:1477–1484.
177. Kim SY, Chang YJ, Cho HM, Hwang YW, Moon YS. Non-steroidal anti-inflammatory drugs for the common cold. *Cochrane Database Syst Rev*. 2015;(9):CD006362.
178. Centers for Disease Control and Prevention. Revised product labels for pediatric over-the-counter cough and cold medicines. *MMWR Morb Mortal Wkly Rep*. 2008;57:1180.
179. Vassilev ZP, Kabadi S, Villa R. Safety and efficacy of over-the-counter cough and cold medicines for use in children. *Expert Opin Drug Saf*. 2010;9:233–242.
180. Centers for Disease Control and Prevention. Infant deaths associated with cough and cold medications—two states, 2005. *MMWR Morb Mortal Wkly Rep*. 2007;56:1–4.
181. Singh M, Das RR. Zinc for the common cold. *Cochrane Database Syst Rev*. 2013;6:CD001364.
182. Karsch-Volk M, Barrett B, Kiefer D, Bauer R, Ardjomand-Woelkart K, Linde K. Echinacea for preventing and treating the common cold. *Cochrane Database Syst Rev*. 2014;2:CD000530.
183. Taylor JA, Weber W, Standish L, et al. Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial. *JAMA*. 2003;290:2824–2830.
184. Caruso TJ, Gwaltney JM Jr. Treatment of the common cold with echinacea: a structured review. *Clin Infect Dis*. 2005;40:807–810.

Table References

185. Cidofovir. Product information. Mylan Institutional LLC; 2020.
186. Foscavir. Product information. Clinigen Healthcare Ltd; 2019.
187. Ganciclovir. Product information. Sagent Pharmaceuticals; 2019.
188. Remdesivir. Product information. Gilead Sciences, Inc; 2022.
189. Trifluridine ophthalmic solution. Product information. Pfizer Inc; 2018.
190. Valcyte (valganciclovir). Product information. Genentech USA, Inc; 2018.
191. Whitley RJ, Blum MR, Barton N, de Miranda P. Pharmacokinetics of acyclovir in humans following intravenous administration. A model for the development of parenteral antivirals. *Am J Med*. 1982;73(1A):165–171.

192. Blum MR, Liao SH, de Miranda P. Overview of acyclovir pharmacokinetic disposition in adults and children. *Am J Med*. 1982;73(1A):186–192.
193. Hintz M, Connor JD, Spector SA, Blum MR, Keeney RE, Yeager AS. Neonatal acyclovir pharmacokinetics in patients with herpes virus infections. *Am J Med*. 1982;73:210–214.
194. de Miranda P, Whitley RJ, Blum MR, et al. Acyclovir kinetics after intravenous infusion. *Clin Pharmacol Ther*. 1979;26:718–728.
195. Koshimichi H, Ishibashi T, Kawaguchi N, Sato C, Kawasaki A, Wajima T. Safety, tolerability and pharmacokinetics of the novel anti-influenza agent baloxavir marboxil in healthy adults: phase I study findings. *Clin Drug Investig*. 2018;38:1189–1196.
196. Filer CW, Allen GD, Brown TA, et al. Metabolic and pharmacokinetic studies following oral administration of 14C-famciclovir to healthy subjects. *Xenobiotica*. 1994;24:357–368.
197. Pue MA, Pratt SK, Fairless AJ, et al. Linear pharmacokinetics of penciclovir following administration of single oral doses of famciclovir 125, 250, 500, and 750 mg to healthy volunteers. *J Antimicrob Chemother*. 1994;33:119–127.
198. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. *Clin Pharmacokinet*. 1999;37:471–484.
199. Bardsley-Elliot A, Noble S. Oseltamivir. *Drugs*. 1999;58:851–860.
200. Oo C, Hill G, Dorr A, Liu B, Boellner S, Ward P. Pharmacokinetics of anti-influenza prodrug oseltamivir in children aged 1–5 years. *Eur J Clin Pharmacol*. 2003;59:411–415.
201. Mancuso CE, Gabay MP, Steinke LM, Vanosdol SJ. Peramivir: an intravenous neuraminidase inhibitor for the treatment of 2009 H1N1 influenza. *Ann Pharmacother*. 2010;44:1240–1249.
202. Deb S, Reeves AA, Hopefl R, Bejusca R. ADME and pharmacokinetic properties of remdesivir: its drug interaction potential. *Pharmaceuticals (Basel)*. 2021;14:655.
203. Soul-Lawton J, Seaber E, On N, Wootton R, Rolan P, Posner J. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. *Antimicrob Agents Chemother*. 1995;39:2759–2764.
204. Dunn CJ, Goa KL. Zanamivir: a review of its use in influenza. *Drugs*. 1999;58:761–784.
205. Cass LM, Efthymiopoulos C, Bye A, et al. Pharmacokinetics of zanamivir after intravenous, oral, inhaled, or intranasal administration to healthy volunteers. *Clin Pharmacokinet*. 1999;36(suppl 1):1–11.

80

Viral Hepatitis

Jerika T. Lam and Amy Kang

CORE PRINCIPLES		CHAPTER CASES
1	Hepatitis A virus (HAV) is a worldwide, acute self-limiting disease transmitted via the fecal–oral route. Hepatocyte injury is caused by a cytopathic and immunologic response, which can result in jaundice and increased liver function tests. Treatment measures are usually supportive and aimed toward prevention (pre-exposure and postexposure) through vaccination.	**Case 80-1 (Questions 1–3)** **Case 80-2 (Question 1)** **Case 80-3 (Question 1)**
2	Hepatitis B virus (HBV) is a bloodborne pathogen that is transmitted through percutaneous or perinatal exposure, blood products, or sexual contact. HBV has an acute phase with resolution and a chronic phase. Over the course of decades, the chronic phase can lead to	**Case 80-4 (Questions 1–4)** **Case 80-5 (Questions 1, 2)** **Case 80-6 (Questions 1–3)** **Case 80-7 (Question 1)**

	complications of the liver, hepatic cirrhosis, and death. Patients with chronic infection require treatment with pegylated interferon and nucleoside and nucleotide reverse transcriptase (RT) inhibitors. Several effective prophylactic strategies (immunizations and nucleoside or nucleotide RT inhibitors) are used to prevent HBV infection.	**Case 80-8 (Question 1)** **Case 80-9 (Question 1)** **Case 80-10 (Questions 1, 2)** **Case 80-11 (Question 1)** **Case 80-12 (Questions 1–14)**
3	Hepatitis C virus (HCV) is a bloodborne pathogen that is transmitted primarily through percutaneous exposure, blood products, or sexual contact. HCV has an acute and a chronic phase. The chronic phase can lead to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death. Acute clinical manifestations are similar to those for HAV and HBV. Current effective treatment of chronic HCV infection (genotypes 1–6) is with direct-acting antivirals (DAAs).	**Case 80-13 (Question 1)** **Case 80-14 (Questions 1–3)** **Case 80-15 (Questions 1–4)** **Case 80-16 (Questions 1–5)**
4	Hepatitis D virus (HDV) is a small RNA virus that requires coinfection with HBV for replication. HDV transmission is most likely associated with percutaneous exposure. HDV, in combination with HBV, leads to a much higher risk of acute liver failure. Prevention strategies rely on successful immunization of HBV. Pegylated interferon is the only medication used to treat HDV infection. An investigational	**No cases**

	injectable antiviral agent is under investigation to treat HDV infection.	
5	Hepatitis E virus is similar to HAV and is transmitted via the fecal–oral route, especially through contaminated water, which is found to be more common in developing countries. Recovery from acute illness usually occurs.	**No cases**
6	Immunizations for persons with viral hepatitis infections, specifically against HAV, HBV, and pneumococcal disease, are highly recommended.	**No cases**

INTRODUCTION

There are five distinctly separate hepatitis viruses that cause liver disease. A sixth virus also has been identified but has yet to be implicated in liver disease. Four of these viruses are RNA viruses, and one is a DNA virus.[1] The individual virus types can be distinguished by serologic assays and, in some instances, by genotyping. Although progress in the area of disease prevention has improved, advances in treatment of certain viral infections have been limited because of the large concentration of viruses produced and their rapid mutation. For instance, the hepatitis C virus (HCV) replicates ~1 trillion virus particles (virions) daily, compared with 100 billion hepatitis B virus (HBV) virions daily and 10 billion human immunodeficiency virus (HIV) virions daily.[1],[2] This chapter reviews the virology, epidemiology, pathogenesis, natural history, diagnosis, clinical manifestations, prevention, and treatment strategies for viral hepatitis A through E.

CAUSATIVE AGENTS AND CHARACTERISTICS

Viral hepatitis is a major cause of morbidity and mortality in the United States.[1–3] At least five distinct pathogens are responsible for viral hepatitis. These hepatotropic viruses are identified by the letters A through E, as follows: (a) type A hepatitis caused by hepatitis A virus (HAV), (b) type B hepatitis caused by hepatitis B virus (HBV), (c) type C hepatitis caused by HCV, (d) type D or delta hepatitis caused by the HBV-associated hepatitis D virus (HDV), and (e) type E hepatitis caused by the hepatitis E virus (HEV). Hepatitis A through E viruses differ in their immunologic characteristics and epidemiologic patterns (**Table 80-1**).[4,5] Fecal–oral transmission is the primary mode of infection for HAV and HEV, whereas parenteral and sexual transmission are characteristic of HBV, HCV, and HDV infections.[1–3] Several other viruses primarily affect nonhepatic organ systems and may secondarily induce a hepatitis-like syndrome. These include the Epstein–Barr virus (infectious mononucleosis), cytomegalovirus, herpes simplex viruses, varicella zoster virus, and rubella, rubeola, and mumps viruses.

Table 80-1

Characteristics of Hepatitis Viruses

Virus	Nucleic Acid	Routes of Transmission	Risk of Chronic Illness	Mortality
HAV	Nonenveloped SS RNA	Fecal–oral	None	Low
HBV	Enveloped DS DNA	Parenteral (sex, perinatal)	High	Moderate–high
HCV	Enveloped SS RNA	Parenteral (sex, perinatal)	High	Moderate–high
HDV	Enveloped SS RNA	Parenteral (sex, perinatal)	High	High
HEV	Nonenveloped SS RNA	Fecal–oral	None	Low–moderate

DNA, deoxyribonucleic acid; DS, double-stranded; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; RNA, ribonucleic acid; SS, single-stranded.

Sources: Davis S. Chronic hepatitis. In: Kaplowitz N, ed. *Liver and Biliary Diseases*. 2nd ed. Williams & Wilkins; 1996:327; Nelson KE, Thomas DL. Viral hepatitis. In: *Infectious Disease Epidemiology*. 2nd ed. Jones and Bartlett; 2007.

Definitions of Acute and Chronic Hepatitis

Viral hepatitis can present as either an acute or a chronic illness. Acute hepatitis is defined as an illness with a discrete date of onset with jaundice or increased serum aminotransferase concentrations >10 times the upper limit of normal (ULN)[1–3,5] and does not exceed 6 months. Chronic hepatitis is a prolonged inflammatory condition of the liver that involves ongoing hepatocellular necrosis for ≥6 months beyond the onset of acute illness.[4,5] The most common causes of chronic viral hepatitis are HBV and HCV.[3] Drug-induced and autoimmune chronic hepatitis occur less frequently; metabolic disorders and HDV chronic hepatitis are relatively uncommon in the United States.[6,7] HAV and HEV are self-limiting infections that rarely progress to chronic hepatitis.

Serologic Evaluation in Presumed Chronic Hepatitis

Serologies are useful in diagnosing viral hepatitis. Antibodies against HAV (anti-HAV), HBV (anti-HBs or HBsAb), and HCV (anti-HCV) are useful diagnostic markers. A diagnosis of acute HAV infection includes the presence of immune globulin (Ig) M anti-HAV. If HBsAb is present, further testing for hepatitis B surface antigen (HBsAg), hepatitis B envelope antigen (HBeAg), and HBV DNA confirm the presence of active viral replication and viral load, respectively. Testing for HDV antibody (anti-HDV) should also be performed in patients with HBV infection to evaluate the possibility of coinfection or superinfection. If the serology result is negative, rare but treatable causes of chronic active hepatitis should be further ruled out. These could include alcoholic liver disease, α-1-antitrypsin deficiency, and drug-induced hepatitis. Commonly reported drugs associated with reversible hepatitis syndrome include anticonvulsants, methyldopa,[8] nitrofurantoin,[9] isoniazid,[10] and, rarely, sulfonamides,[11] and propylthiouracil.[12]

HEPATITIS A VIRUS

Virology and Epidemiology

HAV is an icosahedral, nonenveloped virus measuring 28 nm in diameter. It is a single-stranded, positive-sense, linear RNA enterovirus of the *Picornaviridae* family in the *Hepatovirus* genus (Table 80-1).[2,4,5] HAV has a worldwide distribution.[13,14] The prevalence of infection is linked to the quality of the water supply, level of sanitation, and age.[14,15] Incidence data are unreliable because the disease is frequently mild and often unrecognized, resulting in underreporting. The primary mode of transmission is from person to person via the fecal–oral route.[15,16] The virus is sturdy and resists degradation by drying, environmental conditions (temperatures as high as 56 °C and as low as −20 °C), gastric acid (pH 3.0), and digestive enzymes in the upper gastrointestinal (GI) tract. Therefore, HAV is easily spread within a population. Direct contact with fecally contaminated water or food is a significant mode of transmission.[16,17] Children are considered a relatively common reservoir, but rarely exhibit clinical symptoms.[17,18]

In 2019, the estimated number of infections had increased to 5.6 times, or an estimated 37,000 infections in the United States.[19] The incidence of new HAV infections is mainly attributed to hepatitis A outbreaks among people who inject drugs (PWID) or are homeless. HAV infection could also occur from common-source outbreaks of fecally contaminated food or water, as well as uncooked HAV-contaminated foods. In developed countries with well-maintained sanitation and water supplies, waterborne outbreaks of HAV are uncommon.[19] Originally, HAV vaccination was recommended for persons at high risk for infection and children living in communities at high risk. However, owing to the significant number of cases of HAV disease still occurring in the United States, HAV vaccination recommendations have expanded. In 2020, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination

for all children and adolescents ages 2 to 18 years in the United States.[20]

Exceedingly rare causes of HAV include transfusion of blood or blood products collected from donors during the viremic phase of their infection and from contact with experimentally infected nonhuman primates.[16],[21] Percutaneous transmission is rare because no asymptomatic carrier state for HAV exists and the incubation period is brief.[16] Occupations at risk for HAV infection include sewage workers, hospital cleaning personnel, day care staff, and pediatric nurses.[18],[19] HAV is the most common preventable (eg, vaccination) infection in travelers visiting locations with poor hygienic conditions.[22]

Transmission

Before HAV vaccination prevalence and availability, asymptomatic children, as HAV carriers shedding viral contents, were thought to be one of the main sources of transmission primarily infecting via the fecal–oral route from direct person-to-person contact or from contaminated food or water. After the universal vaccination implementation in the United States, transmission of HAV predominantly occurs via susceptible adults who are unvaccinated, partially vaccinated, or nonresponders to vaccines.[20] HAV has been also detected in saliva, but data evaluating the transmissibility of saliva with HAV is lacking at this time.[23]

Pathogenesis

Although the exact mechanism of injury is unknown,[17],[18] viral replication occurs within the liver or hepatocytes. Subsequent hepatocyte death results in viral elimination and eventual resolution of the clinical illness.[18]

Natural History

After exposure to HAV, usually via ingestion of HAV from material contaminated with feces, the virus resides and replicates in the hepatocytes within hours and days of infection. Following the translational and replication processes, HAV is released into the bile canaliculi and is transported to the intestine, where it is excreted in the feces at concentrations ranging up to 10^9 infectious virions per gram of feces.[17] This occurs during the subclinical stage (incubation period) or anicteric prodromal period (14–21 days) of the infection before alanine aminotransferase (ALT) levels become elevated and clinical symptoms or jaundice occur.[18]

The contagiousness of the infection is highest during this period and is significantly reduced following the onset of symptoms or jaundice. HAV infection could occur in two clinical courses, varying from subclinical hepatitis (asymptomatic), usually observed in children, to anicteric hepatitis (symptoms without jaundice) or icteric hepatitis that occurs in adults and could result in fulminant hepatitis and death, especially among adults older than 50 years.[18] Chronic HAV infection usually does not manifest because of the robust humoral and cellular immune responses, particularly natural killer cells, $CD4^+$ and $CD8^+$ cytotoxic T cells.[18] More importantly, humoral immunity plays a pivotal role in viral clearance, leading to viremia declines after the presence of neutralizing antibodies.[24] Typically, the course of HAV includes an incubation phase, an acute hepatitis phase, and a convalescent phase. Complete clinical recovery is usually seen in all patients within 6 months of HAV infection.

Clinical Manifestations

CASE 80-1

Question 1: E.T., a 34-year-old medical sales representative, presents to the emergency department (ED) with acute onset of jaundice and “dark urine.” He was in good health until 2 weeks ago, when he noted feeling fatigued and weak, which he attributed to his demanding work schedule. He also recalled having a mild headache, loss of appetite, muscle pain, diarrhea, and low-grade fevers from 99 °F (37.22 °C) to 101 °F (38.33 °C). He attributed these symptoms to the

flu and took acetaminophen with plenty of fluids. His symptoms persisted until yesterday when they resolved unexplainably. He then noticed his urine was cola colored. This morning, he noted jaundice of his eyes and skin and sought medical attention.

E.T.'s medical history includes a recent respiratory tract infection, treated successfully with levofloxacin. His social history is significant for frequenting the local oyster bar, where he regularly ingests raw oysters. He denies smoking and recent travel outside the United States but admits to occasional alcohol consumption. E.T. has no history of sexual exposure, needle use, or transfusions. His current medications include oral diazepam 5 mg at bedtime as needed for "muscle spasms," but he has not taken diazepam for "several months." He also has a seizure disorder sustained after a motorcycle accident 2 years before admission, for which he takes phenytoin 400 mg orally (PO) at bedtime.

Physical examination is significant for a well-developed, well-nourished male in no acute distress. He is alert and oriented, with a temperature of 99 °F (37.22 °C). His sclerae and skin are icteric, and his abdomen is positive for a tender, enlarged liver and right upper quadrant pain. Laboratory test results reveal the following values:

Hemoglobin (Hgb): 16 g/dL
Hematocrit (Hct): 44%
White blood cell (WBC) count: 5500 cells/μL
Aspartate transaminase (AST): 120 units/L
ALT: 240 units/L
Alkaline phosphatase: 86 units/L
Total bilirubin: 3.2 mg/dL
Direct bilirubin: 1.5 mg/dL
Phenytoin concentration: 12 mg/L (normal: 10–20 mg/L)

The albumin, prothrombin time (PT), blood glucose, and electrolytes are all within normal (WNL) limits. E.T.'s test result is negative for anti-HCV, HBeAg, HBsAg, and hepatitis B core antibody (anti-HBc), but is positive for anti-HBs and IgM anti-HAV.

What clinical features and serologic markers are consistent with viral hepatitis in E.T.?

The incubation period for HAV is 15 to 50 days (average 28 days) after inoculation. The host is usually asymptomatic during this stage of the infection; thus, E.T. is beyond the inoculation phase of the disease. Because HAV titers are highest in the acute-phase fecal samples, the period of infectivity is 14 and 21 days before the onset of jaundice to 7 or 8 days after jaundice. Therefore, E.T. should be considered infectious at this time. In HAV infections, acute-phase

serum and saliva are less infectious than are fecal samples, whereas urine and semen samples are not infectious. Family members and persons recently in immediate contact with E.T. should be notified.[25]

The symptoms of acute viral hepatitis caused by HAV, HBV, HCV, HDV, and HEV are similar. The onset of symptoms in HAV infection, however, is less insidious than those seen with HBV and HCV infection.[5] Generally, symptoms of HAV infection present a week or more before the onset of jaundice. The likelihood of having symptoms is related to age. In children younger than age 6 years, 70% of infections are asymptomatic, whereas older children and adults have symptomatic disease with jaundice occurring in >70% of cases.[18] E.T. has signs and symptoms of acute HAV infection, including the nonspecific prodromal symptoms of fatigue, weakness, anorexia, nausea, and vomiting. Abdominal pain and hepatomegaly are common. Less common symptoms include fever, headache, arthralgias, myalgias, and diarrhea. Within 1 to 2 weeks of the onset of prodromal symptoms, patients may enter an icteric phase with symptoms, including clay-colored stools, dark urine, scleral icterus, and jaundice. The dark urine is caused by bilirubin (bilirubinuria), generally occurring shortly before the onset of jaundice. E.T. should be questioned about the presence of pale stools (light gray or yellow color), which usually is observed during the icteric phase. His scleral icterus is strongly suggestive of viral hepatitis. Icteric infections usually occur in adults and are 3.5 times more common than is the anicteric presentation that is seen in children.[16,25]

The results of E.T.'s liver function tests (eg, elevations in AST, ALT, and total bilirubin) also are consistent with viral hepatitis. Serum transaminase concentrations increase during the prodromal phase (usually ALT > AST) of HAV infection, peaking before the onset of jaundice. These concentrations are often >500 units/L and decline at an initial rate of 75%/week, followed by a slower rate of decline thereafter. Serum bilirubin peaks after aminotransferase activity and rarely exceeds 10 mg/dL. Total bilirubin levels decline more slowly than do aminotransferases and generally normalize within 3 months. Right upper quadrant tenderness, mild liver enlargement, and

splenomegaly may also be present in patients with acute HAV infection.[5,25]

Extrahepatic Manifestations

Case 80-1, Question 2: Are there any additional complications that E.T. could experience from his acute HAV infection?

With the appearance of jaundice, prodromal pruritus and extrahepatic manifestations can occur, usually in patients with a more protracted illness. E.T. should be monitored for additional manifestations of HAV infection, including immune complex–associated rash, leukocytoclastic vasculitis, glomerulonephritis, cryoglobulinemia (less likely than with HCV), and arthritis.[25]

Diagnosis and Serology

Diagnostic methods for detecting HAV antigen and anti-HAV are listed in **Figure 80-1**. Detection of IgM antibodies to HAV in a patient who presents with clinical characteristics of hepatitis, or in an asymptomatic patient with elevated transaminases, is consistent with acute HAV infection. HAV IgG appears after IgM and is indicative of previous exposure and immunity to HAV, whereas a rising IgG is consistent with recent exposure.[5,25] Anti-HAV IgM is commonly present throughout the disease course (16–40 weeks), usually peaking early and declining to undetectable levels 3 to 4 months after the initial infection.[25] One-quarter of patients infected with HAV have IgM present for up to 6 months and occasionally longer. HAV IgG appears early in the convalescent phase and is detectable for decades after the acute infection resolves, with a slowly declining titer.[16,25] Both enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay methods of antibody detection are sensitive, specific, and reliable to diagnose acute HAV infection. E.T. has a positive IgM anti-HAV, consistent with acute HAV infection. He has a negative IgM anti-HBc test, ruling out acute HBV infection.[16,25]

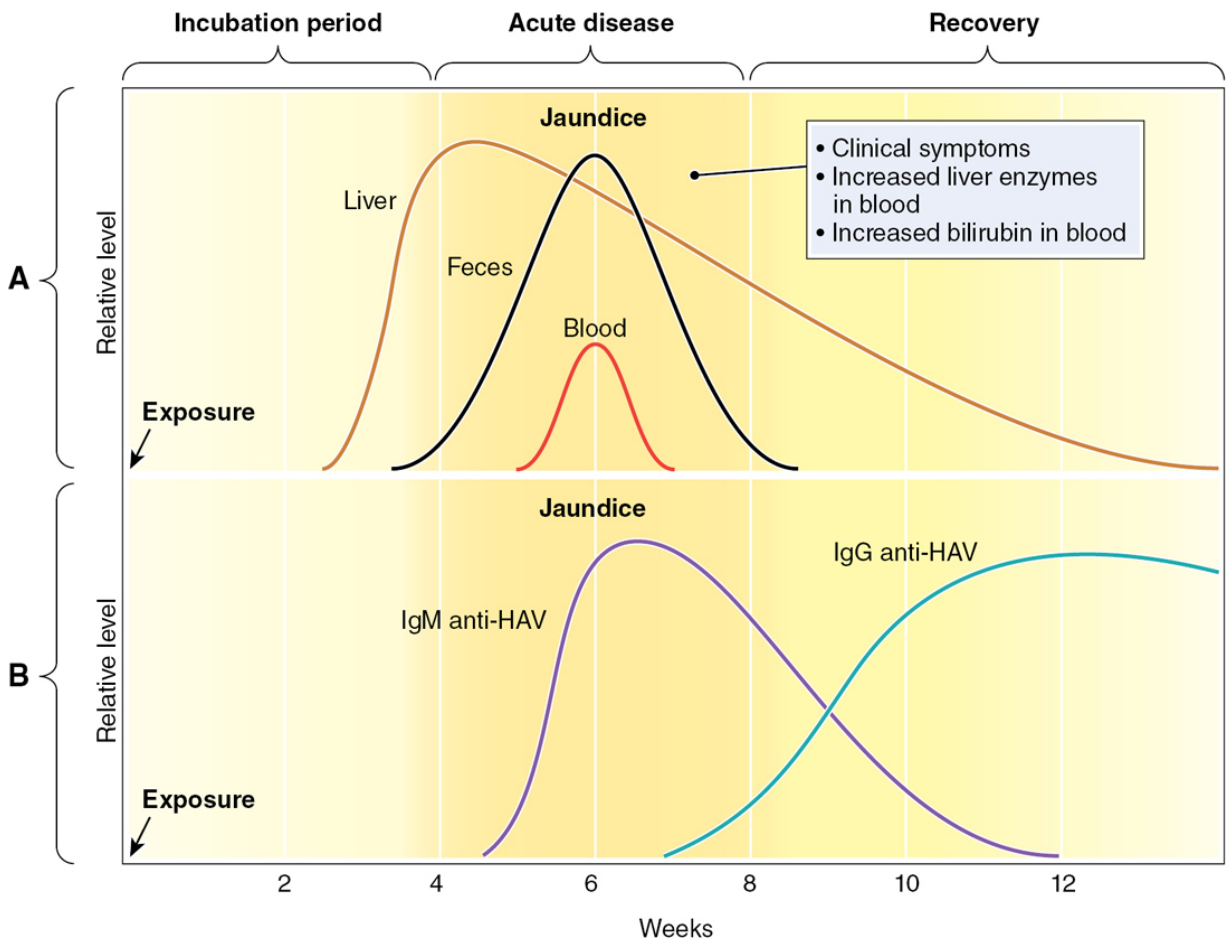


Figure 80-1 Typical course of hepatitis A. A, Presence of hepatitis A virus in liver, feces, and blood. B, Markers of hepatitis A virus in blood. Anti-HAV, antibody to HAV; HAV, hepatitis A virus. (Adapted with permission from McConnell TH. *The Nature of Disease: Pathology for the Health Professions*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2007.)

Treatment

GENERAL MEASURES

HAV infection is usually a self-limiting disease and rarely leads to serious complications including fulminant liver failure and death. Management involves supportive care and medical treatment of serious complications. Intravenous (IV) fluid and electrolyte replacement, nutritional support, and the use of antiemetics may be necessary for some patients. Antipyretics (acetaminophen) should

not be used because the risk of fulminant hepatic failure (FHF) could increase. Considering that hemolysis or acute kidney injury is possible, a regular assessment of renal function with a complete blood count (CBC) should be performed. Patients should abstain from alcohol during the acute phase of the disease. After resolution of symptoms and serum biochemical abnormalities, moderate alcohol intake is no longer contraindicated. In general, prognosis after HAV infection is very good. Long-term immunity accompanies HAV infection, and recurrence or chronic hepatitis usually does not occur.

Adjustment of Medication Doses

Case 80-1, Question 3: Should E.T.'s medications be adjusted during the acute phase of HAV infection?

Dosage adjustments for hepatically eliminated drugs in the setting of liver disease are difficult to predict. This is because hepatic metabolism is complex, involving numerous oxidative and conjugative pathways that are variably affected in hepatic disease. In renal disease, creatinine serves as an endogenous marker to predict the clearance of renally eliminated drugs. In hepatic disease, however, no reliable endogenous biomarkers exist to predict drug hepatic clearance. Laboratory tests that approximate the synthetic function of the liver (eg, albumin, PT) and biliary clearance (bilirubin) are used to estimate the degree of hepatic impairment, but these tests are not dependable in predicting alterations in pharmacokinetic parameters for hepatically metabolized drugs. Unnecessary and potentially hepatotoxic medications should be avoided during the acute phase of the illness. When drug therapy is indicated with agents that undergo hepatic elimination, it is prudent to use the lowest doses possible to achieve the desired therapeutic effect.

E.T. should be advised to discontinue diazepam because this medication undergoes extensive hepatic biotransformation and limited data suggest this agent accumulates in the setting of acute

viral hepatitis.[26] If E.T. should require drug therapy for muscle spasms, he should either decrease the diazepam dose or consider using an alternative agent (eg, lorazepam) that does not accumulate in acute viral hepatitis.[27] Patients with acute viral hepatitis do not require phenytoin dosage adjustments.[28] Because E.T.'s plasma phenytoin concentration is within the desired therapeutic range, no dosage adjustment is needed.

Prevention of Hepatitis A

Prevention of hepatitis A infection can be achieved through immunoprophylactic measures. Immunoprophylaxis may be passive, active, or a combination of both. In passive immunization, temporary protective antibody in the form of Ig is administered. In active immunization, a vaccine is administered to induce the formation of long-term protective antibodies.[20],[29] Prophylaxis can be administered before (pre-exposure prophylaxis) or after exposure (postexposure prophylaxis).

Pre-exposure Prophylaxis

CASE 80-2

QUESTION 1: M.D., a 22-year-old student, is preparing for a 2-week vacation to Thailand. He plans to travel 3 months from now.

Should he receive prophylaxis for HAV?

IMMUNE GLOBULIN

Before hepatitis A vaccine was available, the only therapy for pre-exposure prophylaxis of hepatitis A infection was Ig, which is a concentrated solution of antibodies prepared from pooled human plasma. Although passive immunization with Ig alone is highly effective in preventing HAV infection,[20] the duration of protection is short. For these reasons, hepatitis A vaccine is generally preferred to Ig for pre-exposure prophylaxis. However, when Ig is used for pre-

exposure prophylaxis in specific circumstances (eg, travelers who are allergic to a vaccine component decide against vaccination, or age younger than 1 year), a single dose of 0.1 mL/kg of Ig administered intramuscularly (IM) confers protection for up to 1 month of travel, and an IM dose of 0.2 mL/kg confers protection for up to 2 months, with a repeat dose every 2 months if >2 months of travel will occur.[19,20,25,30]

For selected populations, including those traveling in <2 weeks to intermediate-to-high HAV endemic countries, of older age (older than 40 years), have underlying immunocompromised conditions and chronic liver diseases, they may receive Ig in addition to hepatitis A vaccine administered at a separate anatomic site.

VACCINE

Active immunization with hepatitis A vaccine has largely supplanted the use of Ig for pre-exposure prophylaxis of infection caused by HAV. Two types of the inactivated, monovalent hepatitis A vaccines are available in the United States and globally: Havrix® and Vaqta®. Both vaccines are formalin-inactivated preparations of attenuated HAV strains.[31] The manufacturers use differing units to express antigen content of their respective vaccines. Havrix® dosages are expressed in ELISA units, and Vaqta® dosages are expressed as units of hepatitis A antigen. These vaccines are developed to provide long-term immunity. They contain an aluminum adjuvant, are free of thimerosal and mercury preservatives, and are safe and effective for children and adults.[32]

DOSING REGIMEN

Havrix® is available in two formulations that differ according to age: for persons 12 months to 18 years old, 720 ELISA units (0.5 mL) per dose in a two-dose schedule; and for persons 19 years and older, 1440 ELISA units (1.0 mL) per dose in a two-dose schedule (**Table 80-2**).[27,31,32] Havrix® is injected IM into the deltoid muscle, with a second dose administered 6 to 12 months later. The pediatric Havrix® formulation (three-dose schedule) is no longer available.

Vaqta® is available in two formulations that differ according to the person's age: for persons 12 months to 18 years old, 25 units (0.5 mL) per dose in a two-dose schedule; and for persons 19 years and older, 50 units (1.0 mL) per dose in a two-dose schedule (Table 80-2).[29,31,33] Likewise, this vaccine is injected IM into the deltoid muscle, with a second dose administered 6 to 18 months later.[20,29,31]

Table 80-2
Recommended Doses of Hepatitis A Vaccines

Age at Vaccination	Dose (Volume)[a]	Schedule (Months)[b]
Havrix®		
Children 12 months–18 years	720 ELISA units (0.5 mL)	0, 6–12
Adults >19 years	1440 ELISA units (1.0 mL)	0, 6–12
Vaqta®		
Children 12 months–18 years	25 units (0.5 mL)	0, 6–18
Adults >19 years	50 units (1.0 mL)	0, 6

[a]Enzyme-linked immunosorbent assay (ELISA) units.

[b]Zero months represent timing of the initial dose; subsequent numbers represent months after the initial dose.

Sources: Lu PJ, Euler GL, Hennessey KA, Weinbaum CM. Hepatitis A vaccination coverage among adults aged 18–49 years in the United States. Vaccine. 2009;27:1301–1305; American Academy of Pediatrics Committee on Infectious Diseases. Hepatitis A vaccine recommendations. *Pediatrics*. 2007;120:189–199; Craig AS, Schaffner W. Prevention of hepatitis A with the hepatitis A vaccine. *N Engl J Med*. 2004;350:476–481.

COMBINATION VACCINE

The U.S. Food and Drug Administration (FDA) has also licensed a combined HAV and HBV vaccine (Twinrix®) for use in persons ages 18 years and older. Twinrix® is composed of the same antigenic components used in Havrix® and Engerix-B®. Each dose of Twinrix® contains at least 720 ELISA units of inactivated HAV (half of the Havrix® adult dose) and 20 µg of recombinant HBsAg protein (same as the Engerix-B® adult dose).[34,35] Twinrix® does not contain

thimerosal and mercury as preservatives and is safe and effective for adults.[32]

Primary immunization consists of a series of three doses, given on a 0-, 1-, and 6-month schedule, the same that is used for single-antigen hepatitis B vaccine.[34],[35] Any person 18 years and older having an indication for both hepatitis A and hepatitis B vaccine can receive Twinrix®, including persons with chronic liver disease, PWID, men who have sex with men (MSM), persons who have occupational risk for infection (eg, who work with HAV-infected primates), and persons with clotting factor disorders who receive therapeutic blood products.[34],[35] For international travel, hepatitis A vaccine is recommended; hepatitis B vaccine is recommended for travelers to areas of high or intermediate hepatitis B endemicity who plan to stay for >6 months and have frequent close contact with the local population.[36]

EFFICACY, SAFETY, AND DURATION OF RESPONSE

The efficacy of the hepatitis A vaccine is well established, with a protective efficacy of 94% to 100%.[33],[34] The vaccine is well tolerated, with soreness at the injection site, headache, myalgias, and malaise as the most commonly reported adverse effects.

The duration of protection from the vaccines has not been studied extensively. However, protective levels of antibody to HAV could be present for at least 14 to 20 years in children and for at least 25 years in adults.[31],[34] The ACIP has no recommendations regarding the need for booster doses for healthy populations who completed the vaccination series at this time. The safety data of the HAV vaccine during pregnancy are limited. However, because the vaccine is produced from inactivated HAV, the theoretic risk to the developing fetus is low. The benefits versus risks associated with vaccination for HAV in females who might be at high risk for exposure to the infection should be discussed with her primary care physician and obstetrician.[19]

INDICATIONS

Universal HAV vaccination is recommended for all children and adolescents ranging from 2 to 18 years old if previously unvaccinated. In addition to universal recommendations, ACIP also recommends HAV vaccination for several high-risk groups, including HIV-infected populations if age 1 year or older, pregnant patients at risk for HAV infection (illicit drug users regardless of injection or noninjection, international travelers, close contact with an international adoptee, homelessness), 6- to 11-month-old infants traveling outside the United States, older adults (older than 40 years), immunocompromised conditions, travelers to countries with high endemicity of infection (South and Central America, Africa, South and Southeast Asia, Caribbean, and the Middle East),[37–39] travelers to countries with intermediate endemicity of infection (Eastern and Southern Europe and Russia), anyone age 1 year old or older during HAV outbreaks at risk for HAV infection (MSM, persons living with HIV), or living in communities with high rates of hepatitis A infection or periodic hepatitis A outbreaks (Alaskan Native villages, American Indian reservations), health care workers or settings providing services to those who are at risk for HAV infection, group homes, day care facilities for people with developmental disabilities, prisoners, and persons with chronic liver disease who are at increased risk for fulminant hepatitis A.[20,29,31,33]

Thus, M.D. should receive either Havrix® 1440 ELISA units or Vaqta® 50 units. This initial injection dose will provide adequate protection from HAV infection during his travel, and he can receive the second dose upon his return, at least 6 months after the first dose. If M.D. decides to travel within the next 2 weeks, he should receive both vaccination and Ig before departure.[36]

Postexposure Prophylaxis

CASE 80-3

Question 1: L.W., a 26-year-old male, was recently diagnosed with HAV infection. He attends college and works part-time as a retail clerk. He lives with his healthy, 25-year-old wife and 10-month-old infant daughter.

Which of L.W.’s contacts require postexposure prophylaxis for HAV?

Although Ig has been recommended in the past for unvaccinated people recently exposed to HAV, hepatitis A vaccines (Havrix® and Vaqta®) are effective in preventing secondary HAV infection in healthy people. Twinrix® is not recommended for postexposure prophylaxis because there are no data available for its use in this setting.[19] A vaccine, Ig, or both should be administered for people who have been exposed to HAV within the past 2 weeks and have not been vaccinated, particularly those age older than 1 year with immunocompromised condition or chronic liver disease.[20],[29],[36] For infants age younger than 1 year old, Ig should be administered instead of the vaccine. Of note, if Ig is administered, the measles, mumps, rubella (MMR) vaccination should be delayed until after a minimum of 6 months have passed owing to the concerns that Ig may interfere with live vaccines such as MMR.[30],[34] In addition, Ig of 0.1 mL/kg should be used for populations with existing contraindications for hepatitis A vaccines within 2 weeks of exposure.[20]

Therefore, L.W.’s wife should receive prophylactic administration of the HAV vaccine, and his 10-month-old infected daughter should receive hepatitis A Ig at a dose of 0.1 mL/kg IM as soon as possible but no later than 2 weeks after exposure. Contacts who have received a dose of hepatitis A vaccine at least 1 month before exposure do not need Ig because protective antibody titers are achieved in >95% of patients 1 month after vaccination.[20] Prophylaxis is not recommended for casual contacts at work or school.

Administration of Ig within 2 weeks of exposure to HAV is 80% to 90% effective in preventing acute HAV infection.[20],[25] In most cases, when given early, Ig prevents both clinical and subclinical HAV illness. Protection after Ig administration is immediate and complete, but a short-lived one. Other situations in which Ig administration may be indicated include hepatitis A infection in day care centers and in settings with infected persons who prepare and serve food. Ig is

recommended for all staff and children in day care settings when a case of HAV infection is confirmed among employees or attendees.[15,19,20] When a food handler is diagnosed with hepatitis A, Ig is recommended for other food handlers at the same location. Given the improbability of disease transmission to persons consuming food prepared or served by workers infected with hepatitis A, the routine administration of Ig in this setting is not recommended.[15,20]

When Ig is required for infants or pregnant patients, preparations free of thimerosal should be used.[15] Although Ig does not impede the immune response to inactivated vaccines, oral poliovirus vaccine or yellow fever vaccine, it may interfere with the response to live attenuated vaccines such as the MMR and varicella vaccines. Therefore, MMR and varicella vaccines should be delayed for at least 3 months after administration of Ig for HAV prophylaxis. Ig should not be given within 2 weeks of the administration of MMR or varicella vaccine. Finally, if Ig is administered within 2 weeks of MMR, the person requires revaccination, but not sooner than 3 months after the Ig administration for MMR.[15,19,20] Serologic tests for varicella vaccination should be performed 3 months after Ig administration to determine whether revaccination is required.

HEPATITIS B VIRUS

Virology

HBV is an icosahedral, enveloped, and encapsulated virus measuring 40 to 42 nm in diameter and belongs to the *Hepadnaviridae* family of viruses.[35–38] The viral genome is a partially double-stranded, circular DNA linked to a DNA polymerase. Unlike HAV, HBV carries various antigenic components, including HBsAg, hepatitis B core antigen (HBcAg), and HBeAg, potentially causing acute illness with or without a chronic disease state. HBV infection

can produce either asymptomatic or symptomatic infection. The average incubation period is 90 days (range: 60–150 days) from exposure to the onset of jaundice and 60 days (range: 40–90 days) from exposure to the onset of abnormal serum ALT levels because the liver is the primary site utilized for HBV replication.[37,38]

The life cycle of HBV is described in **Figure 80-2**. Elucidation of the HBV life cycle has resulted in opportunities for drug development. Of special importance, the viral DNA polymerase functions as both a reverse transcriptase (RT) for synthesis of the negative DNA strand from genomic RNA and as an endogenous DNA polymerase. Because the HBV polymerase is remotely related to the RT enzymes of retroviruses (eg, HIV), some inhibitors of HIV polymerase or RT also have activity against the HBV polymerase. Thus, several RT inhibitors (nucleosides and nucleotides) have been evaluated for treating and preventing HBV; however, rapid emergence of resistance occurs with many of these agents.

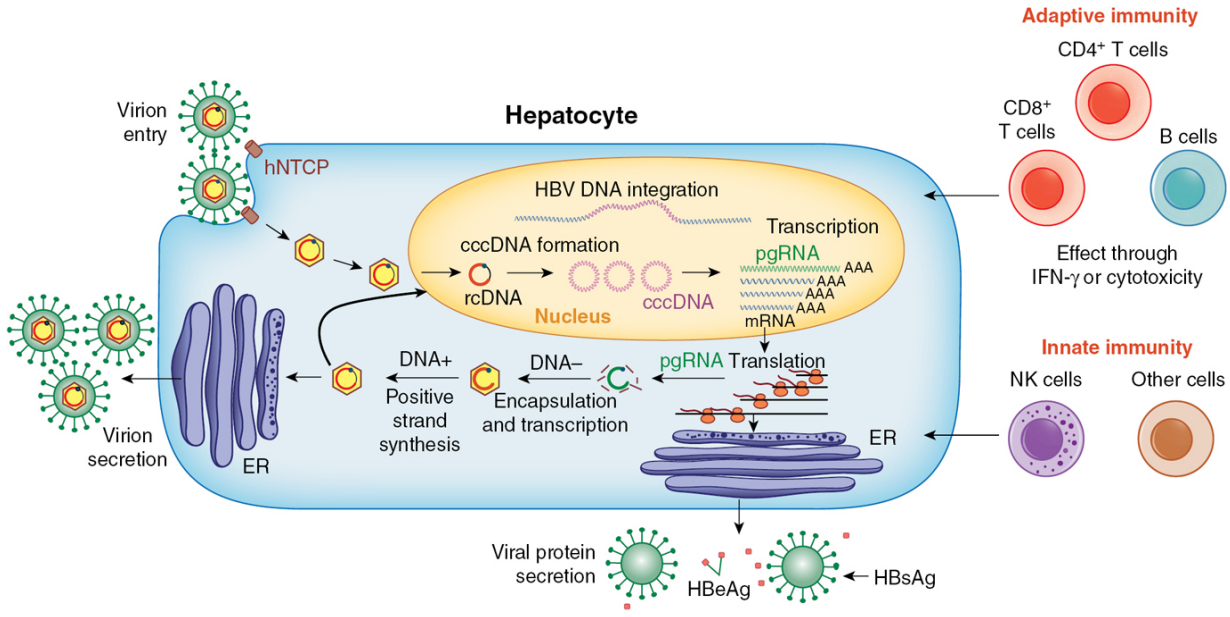


Figure 80-2 Life cycle of hepatitis B virus in the hepatocyte. cccDNA, covalently closed circular DNA; ER, endoplasmic reticulum; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; hNTCP, human sodium taurocholate cotransporting polypeptide; IFN, interferon; NL, natural killer cell; pgRNA, progenomic RNA. (Source: Reprinted with permission from Zoulim F,

Durantel D. Antiviral therapies and prospects for a cure of chronic hepatitis B. *Cold Spring Harb Perspect Med*. 2015;5(4):a021501. © 2015 Cold Spring Harbor Laboratory Press.)

Epidemiology

Globally, ~2 billion persons are infected with HBV, and between 350 and 400 million persons are living with chronic hepatitis B virus (CHB) infection.[39],[40] HBV disease causes ~1 million deaths from cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[41–43] In 2002, >600,000 persons died of HBV-associated acute and chronic liver disease.[39],[40] In the United States, an estimated 2.2 million persons are living with chronic HBV infection and ~5500 died annually from CHB-related complications and HCC.[42],[43]

Acute HBV infection is usually asymptomatic in infants and children younger than 5 years old compared to 30% to 50% of children older than 5 years and adults who could develop clinical signs and symptoms.[44] Clinical signs and symptoms can include anorexia, nausea, vomiting, abdominal pain, malaise, and jaundice. Extrahepatic manifestations of CHB disease may include skin rashes, arthralgias, and arthritis.[35] Approximately 95% of primary infections in immunocompetent adults are self-limiting, with elimination of the virus from the blood and subsequent lasting immunity to reinfection. Progression from acute to CHB infection is influenced by the person's age at acquisition of the virus. CHB infection occurs in ~30% of infected children younger than 5 years old, and <5% of infected persons older than 5 years.[44] Persons who are HBV infected and are at risk for developing CHB disease include immunosuppressed persons (eg, persons with diabetes, HIV, or on hemodialysis).[35]

With respect to HBV infection in certain parts of the world, it is commonly acquired perinatally in Asia. The cellular immune responses to hepatocyte-membrane HBV proteins that are associated with acute hepatitis do not occur, and chronic, lifelong infection is established in >90% of persons infected in Asia.[45] On the

other hand, most acute HBV infections that occur in the West are reported during adolescence and early adulthood because of behaviors and environments that favor the transmission of bloodborne infections, such as sexual activity, injection drug use, and occupational exposure. There are no specific treatments for acute HBV, and supportive care is the mainstay of therapy.[45,46]

Similar to HAV infection, CHB infection is defined as persons positive for HBsAg for >6 months (**Fig. 80-3**). The incidence of acute HBV infection has declined in the United States by ~82% since 1991.[40,46–48] This reduction in infection occurs in all age, racial, ethnic, and high-risk groups, particularly among children and health care workers, the groups with the highest rate of vaccination. Less high-risk behaviors also have led to decreased transmission of infection. High-risk groups in the United States for acquiring HBV infection include certain ethnic groups (eg, Alaskan Eskimos, Asian Pacific Islanders), first-generation immigrants from regions of high endemicity (eg, India, Central and Southeast Asia), PWID, MSM, African Americans, and males (more than females).[46–48] The most prominent risk factors associated with acute HBV infection include heterosexual contact (42%), MSM (15%), and injection drug use (21%).[46–48] HBV vaccination opportunities include clinics for sexually transmitted infections (STIs), correctional facilities, and holding centers for incarceration.

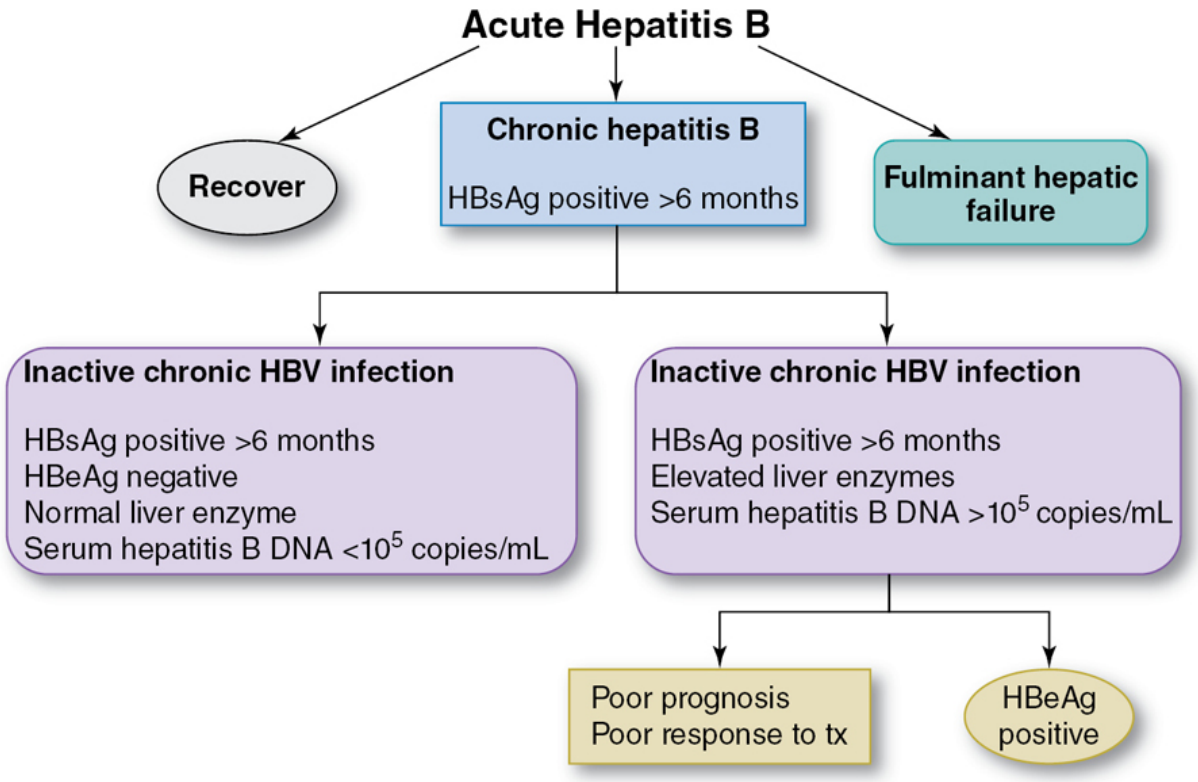


Figure 80-3 Acute hepatitis B virus infection. HbeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus. (AASLD/IDSA Guidelines.)

Transmission

HBV is known to be highly infectious and can be transmitted even when the presence of blood is invisible. Of note, the virus can live on an environmental surface for a minimum of 7 days.[47],[49],[50] The transmission of HBV is from exposure to blood, semen, and other body fluids infected with HBV. Furthermore, HBV transmission could occur among unvaccinated adults with risky behaviors, including sexual contact, and percutaneous or perinatal exposure to infectious blood or body fluids. HBV is most highly concentrated in serum with lower concentrations in semen, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid, all of which can potentially transmit the virus if contacted through percutaneous, mucosal, or nonintact skin.[44] Other body fluids, such as sweat, urine, fecal matter, sputum, breast milk, bile, and

nasopharyngeal washing, are unlikely to transmit HBV owing to low quantities of HBV unless they also contain blood.[51] The modes of HBV transmission include sexual, percutaneous, and perinatal routes, which are summarized in the following sections.

SEXUAL TRANSMISSION

Sexual activity, especially unprotected sex and having multiple sexual partners, is the most significant mode of HBV transmission worldwide, including North America where the prevalence of infection is low compared to Southeast Asia, Africa, and Europe.[46–48] Heterosexual intercourse accounts for the majority of U.S. infections (26%). In heterosexual persons, factors associated with an enhanced risk of HBV infection include duration of sexual activity, number of sexual partners, and history of STI. Sexual partners of PWID, sex workers, and clients of sex workers are at a very high risk for infection. Sexual partners of infected individuals are at high risk for infection, even in the absence of high-risk behavior. Because most patients with CHB infection are unaware of their infection and are "silent carriers," sexual transmission is a significant mode of transmission. Many of the HBV infections could have been prevented through universal vaccination. Furthermore, the use of condoms could reduce the risk of sexual transmission.[46–48]

From 1980 to 1985, a very high rate of HBV infection was observed in MSM, accounting for 20% of all reported cases of infection.[46–48] Having multiple sexual partners, anal-receptive intercourse, and duration of sexual activity were the most common factors associated with HBV acquisition in the MSM population. Fortunately, the current rates of HBV infection in the MSM population have fallen and are estimated to be about 8%, possibly as a result of modifications of sexual behavior in response to HIV transmission. Similar to heterosexuals, the use of condoms in the MSM population has also reduced the risk of sexual transmission of HBV.

PERCUTANEOUS TRANSMISSION

Another common mode of HBV transmission among adults is via the percutaneous route, primarily from injection drug use. Recreational and illicit drug use in the United States and globally is a significant mode of HBV transmission, accounting for ~23% of all patients.[46–48] The risk increases with the duration of injection drug use; thus, serologic markers of ongoing or prior HBV infection are usually positive after 5 years of drug use. In addition, use of contaminated needles including acupuncture, tattoo procedures, or needlestick injuries in health care settings can lead to HBV transmission.

PERINATAL TRANSMISSION

Early childhood exposure and perinatal exposure are additional modes of transmission of HBV infection. High serum concentrations of virus have been linked to increased risk of transmission by vertical routes and needlestick exposure. Infants born to HBeAg-positive mothers with high viral replication (>80 pg/mL) have a 70% to 90% risk of perinatal HBV acquisition compared with a 10% to 40% risk in infants born to mothers infected with HBV who are HBeAg negative.[46–48] Infection generally occurs via inoculation of the infant at the time of birth or soon thereafter; and even with active and passive immunization, 10% to 15% of infants acquire HBV infection at birth.

In developing countries with high prevalence rates and in regions of the United States with high endemicity, children born to HBsAg-positive mothers are at risk for acquiring HBV infection in the perinatal period, with infection rates reported to be between 7% and 13%.[35],[43],[44] In addition, children of HBsAg-positive mothers who are not infected at birth remain at very high risk for early childhood infection, with 60% of those born to HBsAg-positive mothers becoming infected by the age of 5 years. The mechanism of the later infection, which is neither perinatal nor sexual, is not known. Although HBsAg is detectable in breast milk, breast-feeding is not believed to be a primary mode of HBV transmission. HBV antibody treatment criteria and recommended agents to prevent perinatal

transmission in pregnant patients are discussed later in the section under management of HBV in pregnancy.

OTHER MODES OF TRANSMISSION

Other risk factors for transmission of HBV include personal contact, such as sharing a toothbrush or razor, exudates from skin lesions, or contact with HBV-contaminated surfaces. Dialysis, organ transplantation, traveling to regions of the world endemic for HBV infection, and living in correctional facilities or prisons can also serve as a possible source of transmission.[46–48] Sporadic cases of HBV transmission have been attributed to nonpercutaneous transmission by way of small breaks in the skin, biting, or mucous membranes. Transfusion-associated HBV infection is rare with the screening of blood (tests for HBsAg and anti-HBc), the exclusion of donors who engage in high-risk activities, and viral inactivation process before the transfusion. It is estimated that 1 of 50,000 transfused units could transmit HBV infection. Although HBsAg is found in bodily fluids (eg, saliva, tears, sweat, semen, vaginal secretions, breast milk, cerebrospinal fluid, ascites, pleural fluid, synovial fluid, gastric juice, and urine), only semen, saliva, and serum actually contain infectious HBV.[49–54]

Pathogenesis

Similar to HAV infection, clinical observations suggest that host immune responses are more important than are virologic factors in the pathogenesis of liver injury. Host cellular and humoral immune responses are linked to T lymphocytes, which enhance viral clearance from hepatocytes and cause liver injury.[49,52]

Diagnosis

The presence of HBsAg in serum is diagnostic for HBV infection. In 5% to 10% of acute cases in which the HBsAg levels fall below sensitivity thresholds of current assays, the presence of IgM anti-

HBc in serum confirms a recent acute HBV infection. Another highly reliable marker of active HBV replication and diagnosis is the presence of HBV DNA in serum through qualitative or quantitative assays, detectable early during the course of acute HBV infection.[53–55] Persistent levels of HBV DNA indicate ongoing infection and a high degree of active viral replication and infectivity.

Serology

Antigens and antibodies associated with HBV infection include HBsAg and surface antibody to hepatitis B (anti-HBs or HBsAb), HBcAg, anti-HBc, HBeAg, and antibody to hepatitis B envelope (anti-HBe). The serologic markers that differentiate between acute, resolving, and chronic infection are HBsAg, anti-HBc, and anti-HBs. HBeAg and anti-HBe screenings are used for the management of patients with chronic infection and used as markers for how infectious the person with HBV is.[44,56]

Serologic patterns, general definitions, and diagnostic criteria of HBV infection are depicted in **Table 80-3**. Within the first several weeks of exposure (range: 2–10 weeks), HBsAg appears in the blood and is present for several weeks before serum concentrations of aminotransferases increase and symptoms occur (**Fig. 80-4**).[53,54] Clinical illness usually follows HBV exposure by 1 to 3 months. HBsAg can be detected in serum until the clinical illness resolves and usually becomes undetectable after 4 to 6 months. Persistence of HBsAg beyond 6 months implies progression to CHB infection. The anti-HBs often appear after a short “window” period during which neither HBsAg nor anti-HBs are detectable. Therefore, screening should be performed using both HBsAg and anti-HBs. In most patients, anti-HBs persist for years after HBV infection, conferring immunity to reinfection (see Fig. 80-4).

Table 80-3
Hepatitis B Virus: Laboratory Markers and Interpretations

Laboratory Marker	Interpretation

Hepatitis B surface antigen (HBsAg)	Marker of infection; presence indicates person is infectious.
Hepatitis B surface antibody (HBsAb or anti-HBs)	Past infection, or person has been vaccinated.
Hepatitis B core antibody (anti-HBc)	Marker of previous or ongoing infection
IgM antibody to hepatitis B core antigen (IgM anti-HBc)	Indicates acute infection; first reaction of the body's immune response to HBV
Hepatitis B e antigen (HBeAg)	Marker of active replication of virus and infectiveness
Hepatitis B e antibody (HBeAb or anti-HBe)	Virus is no longer replicating; predictor of long-term clearance of HBV in patients undergoing antiviral therapy
Hepatitis B virus DNA (HBV DNA)	Indicates active replication of virus; more accurate than is HBeAg; used mainly for monitoring response to therapy

Sources: Dienstag JL. Hepatitis B virus infection. *N Engl J Med.* 2008;359: 1486–1500; Bertoletti A, Gehring AJ. The immune response during hepatitis B infection. *J Gen Virol*. 2006;87(Pt 6):1439–1449.

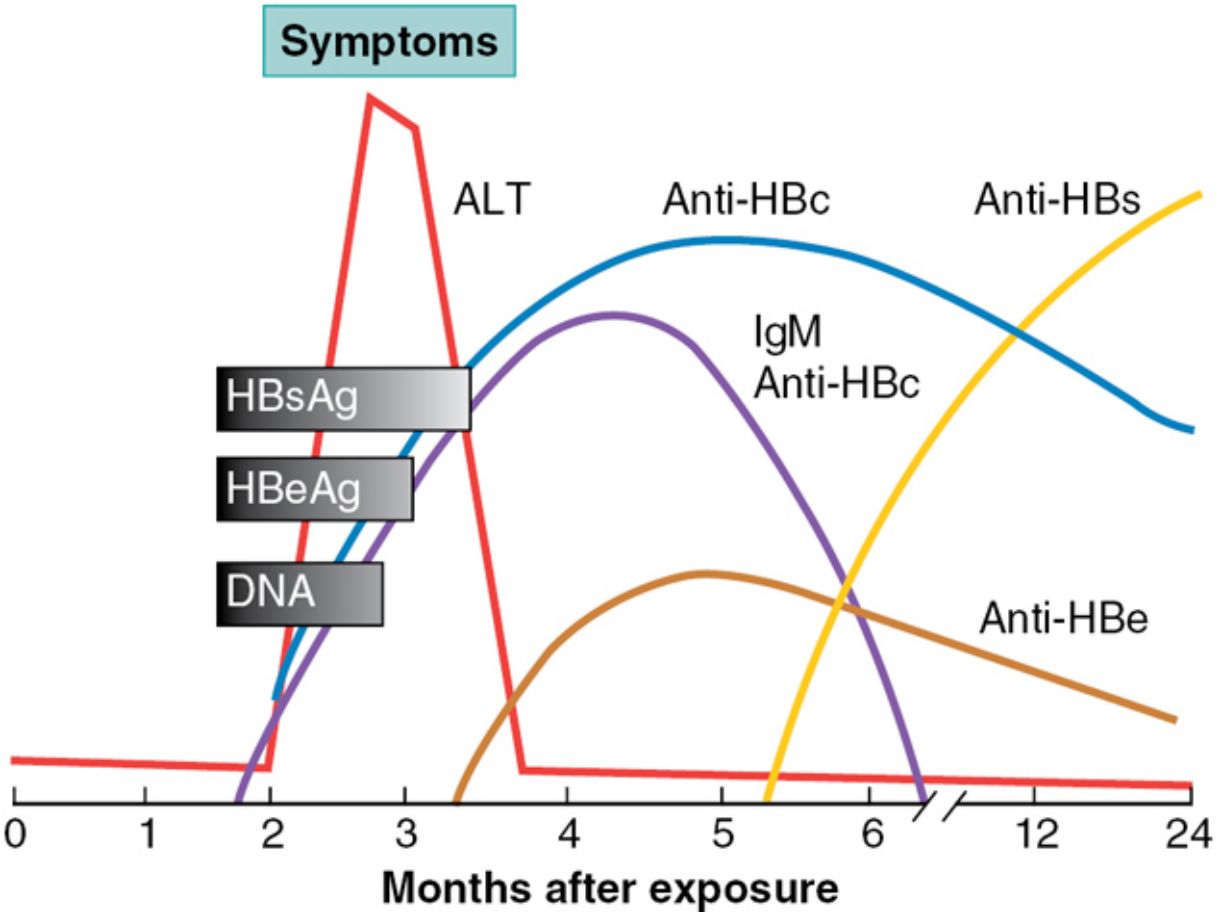


Figure 80-4 Sequence of events after acute hepatitis B virus infection with resolution. ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B envelope antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; IgM anti-HBc, immune globulin M antibody to hepatitis B core virus. (Adapted with permission from Perrillo RP, Regenstein FG. Viral and immune hepatitis. In: Kelley WN, ed. *Textbook of Internal Medicine*. 3rd ed. J.B. Lippincott; 1996.)

Interpretation of serologic markers is described in **Table 80-4**. A soluble viral protein, HBeAg, is detectable early during the acute phase of the disease and persists in chronic CHB infection. HBeAg is a marker of active HBV replication, and its presence correlates with circulating HBV particles. The presence of both HBeAg and HBsAg indicates high levels of viral replication and infectivity and a

need for antiviral therapy. Generally, seroconversion from HBeAg to hepatitis B envelope antibody (anti-HBe) results in a reduction in HBV DNA and suggests resolution of HBV infection. Some patients may, however, continue to have active liver disease and detectable serum HBV DNA levels as a result of the presence of wild-type virus or the presence of precore or promoter mutations that impair HBeAg secretion (patients who are HBeAg negative).

Table 80-4

Hepatitis B Virus: Interpretations of Laboratory Results

Laboratory Markers	Laboratory Results	Clinical Interpretation
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Immune because of natural infection
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune because of hepatitis B vaccination
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acute infection
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low-level” chronic infection 4. Resolving acute infection

Source: Dienstag JL. Hepatitis B virus infection. *N Engl J Med.* 2008;359:1486–1500.

HBcAg does not circulate freely in the bloodstream and is not measured. Anti-HBc, the antibody directed against HBcAg, is usually detected 1 to 2 weeks after the appearance of HBsAg and just

before the onset of clinical symptoms; and it persists for life. The detection of IgM anti-HBc is the most sensitive diagnostic test for acute HBV infection or recent infection with HBV ≤6 months. During the recovery phase of infection, the predominant form of anti-HBc is in the IgG class. The presence of this antibody suggests prior or ongoing infection with HBV. Furthermore, in areas where HBV is not endemic, isolated detection of anti-HBc in a patient's serum may correlate with low levels of HBV DNA. The presence of HBV DNA may enhance the risk of transmission of HBV and progression to cirrhosis and HCC. Patients immunized against HBV do not develop anti-HBc; therefore, the presence of this antibody differentiates successful vaccination from actual HBV infection. Previous testing modalities such as anti-HBc enzyme immunoassay and radioimmunoassay tests had limited specificity leading to frequent false-positive results, but newer tests have improved specificity for anti-HBc.

Natural History

Of those patients with acute HBV infection, only 1% develops FHF with associated coagulopathy, encephalopathy, and cerebral edema.[57],[58] The cause of fulminant infection is a heightened immune response to the virus, in the absence of HDV or HCV coinfection. Patients with acute liver failure (ALF) often have early clearance of HBsAg, which may complicate the diagnosis, but a positive IgM antibody to HBcAg generally confirms the diagnosis.

Four phases of CHB infection are present: immune tolerance, immune clearance, low-level replication or nonreplication phase (inactive carrier), and reactivation phase. Up to 12% (average 5%) of immunocompetent patients acutely infected with HBV remain chronically infected (historically defined as having detectable HBsAg in serum for ≥6 months).[55],[57] In these patients, HBsAg generally remains detectable indefinitely and anti-HBs fails to appear. The risk of chronicity after neonatally acquired infection is high (>90%), possibly because neonates have immature immune systems. Of the

infected neonates, 50% have evidence of active viral replication. Furthermore, patients who have a reduced ability to clear viral infections, including those receiving chronic hemodialysis, immunosuppression after transplantation or chemotherapy, or patients with HIV infection, may have a greater risk of developing CHB infection.[35,59]

Ultimate outcomes are linked to the presence or absence of viral replication and by the severity of liver damage. Approximately 50% of all chronic carriers have ongoing viral replication, especially with elevated aminotransferases, and 15% to 20% of these develop cirrhosis within 5 years.[35–38,59] Spontaneous loss of HBeAg (7%–20% per year) has been reported, possibly as a result of the use of antiviral therapy, whereas loss of HBsAg occurs less frequently (1%–2% per year). In general, chronic carriers remain infected throughout their life.[35–38,59] Five-year survival rates decline depending on the severity of disease (55% survival with cirrhosis).[59] Asymptomatic HBV carriers tend to have mild disease manifestations with few complications, even with a long period of follow-up. Finally, the risk of HCC is increased up to 300 times in chronic carriers with active viral replication (HBeAg positive).[59,60] The natural history of HBV is such that patients often clear HBeAg and become HBeAg negative with or without therapy. In patients who are HBeAg negative, there can also be chronic infection, which is defined by low levels of both HBV DNA and surface antigen. HBeAg-negative chronic hepatitis involves higher HBV DNA levels (>2000 IU/mL) with elevated ALT, liver disease, and a high potential for disease progression. Resolved HBV infection means that the individual has cleared the surface antigen and, again, this is the ultimate goal with or without antiviral treatment.

Clinical Manifestations

CASE 80-4

QUESTION 1: W.H. is a 35-year-old male who developed nausea, vomiting, anorexia, scleral icterus, and jaundice within the past month. Within the past week, he became increasingly lethargic, confused, disoriented, and lapsed into a grade IV coma. He is admitted to the ED intubated and transferred to the intensive care unit.

W.H.'s social history is significant for IV drug use for the past 10 years and alcohol misuse (none for the previous 5 years). Physical findings include an older than age appearing, hypertensive (blood pressure is 158/99 mm Hg), bradycardic (heart rate is 58 beats/minute) male in respiratory distress (respiratory rate is 26 breaths/minute) with severe jaundice, scleral icterus, and decreased hepatic dullness to percussion (reduced hepatic mass). He shows sluggish pupillary response and increasing muscle tone; neurologic examination reveals W.H. to be stuporous and nonarousable.

The laboratory evaluation shows the following results:

Hct: 42%
Hgb: 14 g/dL
Platelets: 85,000/μL
PT: 25.8 seconds
International normalized ratio (INR): 3.8
AST: 555 units/L
ALT: 495 units/L
Alkaline phosphatase: 101 units/mL
Total bilirubin: 8.4 mg/dL
HBV DNA: 6,000,000 IU/mL

Hepatitis serologic test results are positive for HBsAg, HBeAg, IgM anti-HBc, and HBV DNA. IgM anti-HAV, IgM anti-HDV, and anti-HCV test results are negative. STAT blood gases reveal a metabolic acidosis with a compensatory respiratory alkalosis profile. W.H.'s serum creatinine is 1.8 mg/dL with a recent reduction in urine output.

What clinical findings that support the diagnosis of acute hepatitis and ALF does W.H. have?

The clinical features of acute HBV infection are similar to those described for HAV infection. W.H.'s initial symptoms include a recent history of nausea, vomiting, anorexia, scleral icterus, and jaundice. These are consistent with diagnosis of acute HBV infection. His serologies, notably a positive IgM anti-HBc and HBV DNA, also support this diagnosis.

ACUTE LIVER FAILURE

The most significant complication of acute HBV infection is ALF, widely defined as a coagulation abnormality (INR >1.5) and any degree of mental alteration (encephalopathy) in a patient of <26 weeks' duration.[58,61] He has hepatic encephalopathy, lethargy, confusion, coma, coagulopathy, hemodynamic instability, declining liver function, and acidosis. Patients with ALF often have cerebral edema (80% mortality rate), a complication of a disrupted blood–brain barrier that allows protein-rich fluid to cross into the extracellular spaces of the brain tissue leading to edema and increased intracranial pressure (ICP) or intracranial hypertension (vasogenic model). Clinical symptoms (sluggish pupillary response and increasing muscle tone) develop when the ICP is >30 mm Hg.[58,62–64] Cerebral edema in the confinement of the cranial vault raises the ICP, which may reduce intracerebral perfusion. The edema can result in cerebral ischemia if the cerebral perfusion pressure (systemic blood pressure minus ICP) is not maintained at >40 mm Hg. Of note, intracranial hypertension in ALF is related to the severity of encephalopathy. Cerebral edema is rarely reported in patients with grade I or II encephalopathy, but occurs in up to 75% of patients with grade IV coma.[65] Diagnostic head imaging tests (computed tomography), elevation of the head of the bed, and intubation (and subsequent hyperventilation) may be necessary medical interventions in this setting.

W.H. has symptoms of cerebral edema and may benefit from 100 to 200 mL of a 20% solution of mannitol (0.5–1.0 g/kg) administered by rapid IV infusion to induce an osmotic diuresis with a subsequent decrease in ICP. The dose may be repeated at least once after several hours provided serum osmolality has not exceeded 320 mOsm/L.[66,67] Because W.H. has a blood pressure of 158/99 mm Hg and a heart rate of 58 beats/minute, and is at risk for intracranial hemorrhage, an ICP monitoring device should be placed.[64,65] Although placement of this device is invasive and bleeding is a potential complication, ICP monitoring devices provide important prognostic information. Patients with a cerebral perfusion pressure of >40 mm Hg that is refractory to mannitol therapy are not candidates for liver transplantation. W.H. also has a coagulopathy typical of ALF.

Decreased levels of clotting factors II, V, VII, IX, and X normally synthesized by the liver account for his prolonged PT and elevated INR.[61–63] Recombinant activated factor VII has been used selectively in patients with ALF, but is usually reserved for administration before any invasive procedures. In addition, consumption of clotting factors by low-grade disseminated intravascular coagulation is common in ALF.

W.H. is also thrombocytopenic and at risk for GI ulceration.[65,66] A platelet transfusion should be considered if his counts drop to <10,000/μL. Because he is not actively bleeding, fresh frozen plasma is not indicated at this time.[65,66] W.H. should also be monitored for cardiovascular and renal abnormalities as a result of his ALF.[61,64] Although W.H. is hypertensive, most patients with ALF are hypotensive and hypovolemic and present with interstitial edema owing to low levels of oncotic proteins. Functional renal failure, also known as hepatorenal syndrome or acute tubular necrosis, occurs in 43% to 55% of patients with ALF.[66,67] In hepatorenal syndrome, renal blood flow is reduced, renin and aldosterone levels are increased, and levels of atrial natriuretic factor are unchanged.[67]

As seen in W.H., patients may develop acid–base disturbances, including respiratory alkalosis as a result of central nervous system–mediated hyperventilation or a lactic acid–induced metabolic acidosis.[63,66] Hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, hypoglycemia, seizures, infections (bacterial and/or fungal), and pancreatitis are additional findings associated with ALF. Thus, sodium, potassium, calcium, magnesium, blood glucose, and amylase should be monitored closely in W.H.[63,66] Prophylactic antimicrobial therapy reduces the incidence of infections in selected groups of patients with ALF, but no survival benefit has been demonstrated.[63,66] Therefore, if antibiotics are not initiated, surveillance for infection (via chest radiography and blood, urine, and sputum cultures) should be undertaken while having a low threshold for initiating appropriate antibacterial or antifungal therapy. Finally, pulmonary complications (hypoxemia, aspiration, acute respiratory distress syndrome, and pulmonary edema) may also occur in patients with ALF.[66,67]

PROGNOSIS

Case 80-4, Question 2: What is W.H.'s prognosis?

Although the incidence of ALF is <1%, the prognosis for these patients is poor once encephalopathy has developed.[67,68] Survival depends on the etiology and degree of hepatic destruction, the ability of the remaining liver cells to regenerate, and the management of complications that may develop during the course of illness. Survival rates often depend on the etiology of ALF. Non-A, non-B (NANB) hepatitis and halothane- or drug-induced hepatotoxicity have been associated with worse survival rates compared to those with hepatitis A, hepatitis B, or acetaminophen overdose.[68] Age younger than 14 years, worsening grade of encephalopathy, reduced liver size, and significantly abnormal liver function test (LFT) values (eg, serum bilirubin, aminotransferases, alkaline phosphatase, PT, and serum albumin) are also poor prognostic indicators in patients with ALF.[67,68] W.H. has a poor prognosis because he has evidence of encephalopathy, cerebral edema, and abnormal LFT values.

TREATMENT

Case 80-4, Question 3: What is an appropriate treatment plan for W.H.'s ALF?

The primary therapy for ALF is supportive care for the patient who is comatose. Systemic therapies with heparin, prostaglandin, or insulin and glucagon have shown limited efficacy.[63] Blood or plasma exchange, hemodialysis, or other methods implemented to detoxify the blood or improve the coma grade do not result in long-term benefits if liver mass is not reconstituted as well. Thiopental may be useful in lowering ICP, but corticosteroids and prolonged hyperventilation are of no value.[63,66] W.H. could benefit from prophylactic histamine H_2-blockers because they have been shown to reduce the incidence of upper GI hemorrhage.[63] The role of

proton-pump inhibitors has not been clearly defined, although limited data have also supported their role in this setting. Blood products (packed red blood cells, fresh frozen plasma, or platelets) should be given as needed if W.H. develops active bleeding, and pulmonary artery monitoring should be implemented to guide management of intravascular volume and gas exchange. W.H. should be closely monitored for additional complications, especially cardiac abnormalities (eg, arrhythmias), hemodynamic changes, renal failure, acidosis, pulmonary complications, and sepsis.

In cases in which prognostic information indicates <20% chance of survival without transplantation, liver transplantation is indicated. Patients with acetaminophen poisoning resulting in ALF, a pH <7.3, a PT >100 seconds, and a serum creatinine >3.4 mg/dL, with grade III or IV encephalopathy, usually require transplantation.[68] Other causes of ALF, a PT >50 seconds, or any three of the following variables irrespective of grade of encephalopathy: age younger than 10 years or older than 40 years; liver failure caused by NANB hepatitis, halothane-induced hepatitis, or idiosyncratic drug reactions; duration of jaundice before encephalopathy >7 days; or serum bilirubin >17.5 mg/dL would indicate a need for transplantation.[67],[68] Although these criteria continue to be used worldwide, they are less reliable in patients with moderate illness; sensitivity is acceptable although specificity is poor. Therefore, other models and surrogate markers have emerged to predict survival, such as the model for end-stage liver disease, Acute Physiology and Chronic Health Evaluation II scoring system, and biomarkers such as Gc protein (also known as vitamin D_3–binding protein), α fetoprotein (AFP), or troponin.[68] To date, none of these methods have been flawless in their ability to accurately predict an outcome in ALF.

Coinfection With Human Immunodeficiency Virus

Case 80-4, Question 4: What is the likelihood of HIV and HBV coinfection for W.H.?

Coinfection with other viruses has been reported in patients with HBV infection. For example, markers of prior or active HBV infection are present in >80% of patients with acquired immunodeficiency syndrome, with ~10% of these cases seropositive for HBsAg.[37],[38] HIV has also been reported to coexist in up to 13% of patients with CHB infection.[37],[38] Compared to patients with CHB infection alone, patients coinfected with CHB and HIV have significantly higher levels of viral replication, lower ALT levels, and more severe histologic disease. CHB infection does not reduce survival in patients who are HIV positive; however, because these patients live longer with effective, potent antiretroviral regimens, hepatic decompensation and manifestations of CHB may still occur.[35],[46] In the setting of CHB and HIV coinfection, there are three nucleoside and nucleotide analogs that are active against both viruses—lamivudine, emtricitabine, and tenofovir. Although emtricitabine has activity against HBV based on its pharmacology, it has not been studied in clinical trials and is not FDA approved for CHB treatment. If treating an individual with CHB coinfected with HIV, it is recommended to utilize two antiretroviral drugs—tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) plus lamivudine or emtricitabine. Of note, lamivudine has been shown to be more resistance prone, demonstrating ~90% resistance at 4 years.[69] Generally, TAF is preferred over TDF because of its improved safety profile (less negative effect on the kidneys and bones), especially in older patients. In addition, entecavir is known to cause resistance to HIV via *M184V* mutation.[70] Therefore, entecavir should not be used unless the patient with coinfection of HIV and CHB is on a fully suppressive antiretroviral regimen.[71] These agents are covered in detail in the section on Treatment. Adefovir and telbivudine are not recommended in the setting of coinfection because they lack activity against HIV and *M204I* mutation in HBV, respectively.[71]

Prevention of Hepatitis B Virus Infection

Screening of high-risk patients (eg, being born in regions of high or intermediate HBV endemicity, PWID, MSM, immunosuppression, people with end-stage renal disease [ESRD] on dialysis, chronic liver disease or evidence of elevated liver enzymes [greater than twice ULN] of unknown etiology, pregnancy, patients with HIV, infants born to HBsAg-positive mothers, having more than one sex partner during the previous 6 months, patients seeking evaluation or treatment for an STI, travelers to countries with intermediate or high prevalence of HBV), high-risk settings (eg, any health care and public safety worker at risk for occupational exposure to blood or blood-contaminated bodily fluids, facilities for developmentally disabled persons, STI and HIV testing and treatment facilities, drug abuse treatment and prevention settings, health care settings targeting services to PWID or MSM, and correctional facilities), blood products, and developing needle exchange programs, cultural outreach, and education may have an impact on reducing HBV transmission. The goals of preventive therapy should be to identify all persons who require immunoprophylaxis for the prevention of infection and provide long-term protection through vaccination to decrease the risk of CHB infection and its subsequent complications. For patients undergoing immunosuppressive therapy, prophylaxis against HBV should be initiated if shown to be positive for HBsAg and anti-HBc and continued until at least 6 months after completion of immunosuppressive therapy. In addition, per updated *Morbidity and Mortality Weekly Report* (*MMWR*) recommendations, medically stable infants weighing ≥4.41 pounds (2 kg) should be administered universal HBV vaccination within 24 hours of birth.

PRE-EXPOSURE PROPHYLAXIS

CASE 80-5

QUESTION 1: P.G., a 55-year-old nursing student, is going to start her clinical rotations. She has no history of hepatitis and has not yet been immunized. She is 62 inches (157.48 cm) tall and weighs 176.37 pounds (80 kg).

What prophylactic regimen should P.G. receive to prevent hepatitis secondary to HBV infection?

Using recombinant DNA technology, Recombivax HB® (10 mg HBsAg/mL) and Engerix-B® (20 mg HBsAg/mL) are yeast-derived HBV vaccines that induce an immunologic response. Most recently, Heplisav-B® (HepB-CpG), a single-antigen recombinant HBV vaccine with a novel adjuvant, was approved in 2018 for use in adults ages 18 years and older. Heplisav-B® is given as a two-dose series with doses separated by 1 month.[72] Because P.G. will come in contact with potentially infectious bodily secretions during her rotations, she should be immunized against hepatitis B with either Recombivax HB®, Engerix-B®, or Heplisav-B®.[72–74]

Vaccine dosing regimen

Relative potency comparisons are not clinically important because comparative trials using Recombivax HB®, Engerix-B®, and Heplisav-B® in the recommended dosages have demonstrated comparable immunogenicity and tolerability. P.G. can be immunized with either product, provided she receives the manufacturer's recommended dosage with each injection. Hepatitis B vaccines are administered as an IM injection in the deltoid muscle of adults and children or in the anterolateral thigh muscle of neonates and infants. The immunogenicity of hepatitis B vaccines is significantly lower when injections are given in the buttocks, probably because the greater amount of fat tissue in the buttocks inhibits interfacing of vaccine and antigen-recognition leukocytes. The results of a small vaccination series suggest that healthy adults who do not respond to hepatitis B vaccine injection to the buttocks have a significantly higher response when vaccinated in the arm. P.G. should receive either the Recombivax HB® (1 mL), Engerix-B® (1 mL), or Heplisav-B® (0.5 mL) vaccine as an IM injection in the deltoid muscle.[75–77] The recommended vaccination schedule is shown in **Table 80-5**.

Table 80-5
Recommended Hepatitis B Vaccine Dosage and Schedules for Adults

Vaccine	Dosage	Dosing Schedule and Route
Hepatitis B Vaccines		
Engerix-B®	20 µg	Three-dose schedule: 1 mL given IM at 0, 1, and 6–12 months
Recombivax HB®	10 µg	Three-dose schedule: 1 mL given IM at 0, 1, and 6–12 months
Heplisav-B®	20 µg	Two-dose schedule: 1 mL given IM at 0 and 1 months
Combined Hepatitis A and B Vaccines		
Twinrix®	HAV: 720 ELISA units plus HBsAg: 20 µg	Standard three-dose schedule: 1 mL given IM at 0, 1, and 6 months *or* Accelerated four-dose schedule: 1 mL given IM on days 0, 7, and 21–30, followed by a booster dose at month 12

ELISA, enzyme-linked immunosorbent assay; HAV, hepatitis A virus; IM, intramuscular.

Sources: Kroger A, Bahta L, Hunter P. General best practice guidelines for immunization. Best practices guidance of the Advisory Committee on Immunization Practices (ACIP). Accessed September 19, 2020. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf; Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67:1–31.

Vaccine efficacy

Recombinant yeast-derived vaccines (eg, Recombivax HB®, Engerix-B®, and Heplisav-B®) produce similar results.[73,74,78,79] A protective antibody response is defined as having anti-HBs levels of at least 10 IU/mL.[80] This threshold was derived from early HBV vaccine trials in MSM, in which vaccine recipients with serum antibody levels of at least 10 sample ratio units (SRUs) were protected from HBV infection.[75,76] A serum antibody level of 10 SRU is roughly equivalent to 10 mIU/mL of anti-HBs when the international standard is used. For this reason, an anti-HBs level of at least 10 IU/mL is considered a protective antibody titer and is the standard used by the ACIP. Although HBV infections have occurred in vaccine recipients with a

detectable immune response, almost all infections have been asymptomatic, identified only through the presence of anti-HBc. These infections have been limited largely to patients with no response or a poor response to vaccination.[47]

Nonresponders

Case 80-5, Question 2: P.G. has completed her three-dose vaccination series with Engerix-B®. Routine hepatitis serology testing is performed before volunteering for a drug study and reveals that P.G. is anti-HBs negative. Why did P.G. not respond to the hepatitis B vaccine, and how should she be managed?

Two important determinants of vaccine efficacy appear to be the age at vaccination and underlying immune function. In healthy recipients, the immune response to vaccination decreases with advancing age. In one study, 99% of patients ages 0 to 19 years, 93% of those ages 20 to 49 years, and 73% of those older than 50 years of age achieved protective anti-HBs levels (>10 SRU) after three doses of the hepatitis B vaccine.[47] Immunocompromised patients, including those receiving hemodialysis, those infected with HIV, or children receiving cytotoxic chemotherapy, respond poorly to the hepatitis B vaccine. Patients who smoke or are obese also have a reduced response.[75],[76] P.G. has two risk factors for a poor response to the hepatitis B vaccine: She is older than age 50 years and she is moderately obese (ideal body weight for her height is 110.23 pounds [50 kg]).

Vaccine recipients who respond poorly to hepatitis B vaccine are classified either as hyporesponders who can probably be protected by additional doses of vaccine or as true nonresponders. Patients with inadequate initial response to the HBV vaccine series should be revaccinated. Of the hyporesponders (anti-HBs levels <10 IU/mL), 50% to 90% achieve a protective level after a single booster dose or after repeating the entire three-dose series.[77],[80] Of patients not responding to a primary vaccination series with Engerix-B®, 60% produced an immune response after a three-dose series with HBVax

II (Recombivax HB®), suggesting that a repeat course with the alternative HBV vaccine may be a reasonable approach in some patients.[77],[80] Revaccination of nonresponders (no detectable anti-HBs) is less successful, and protective levels, if achieved, are not sustained.[47] True nonresponders to HBV vaccination are rare in the immunocompetent population, and these persons may have a genetic predisposition toward nonresponsiveness.[75],[77] P.G. should be revaccinated with a booster dose of hepatitis B vaccine. Her anti-HBs levels can be rechecked 1 month after the injection. If she still has not responded, it is reasonable to administer an additional two injections to complete a second vaccination series. She could also be considered for the Heplisav-B® vaccination.

Interchangeability of hepatitis B virus vaccines

CASE 80-6

Question 1: T.M., a 32-year-old hospital laboratory technician, received the first two doses of Recombivax HB®. He has relocated recently and is due for the third dose. The employee health service at his new job uses only Engerix-B® for hepatitis B vaccination.

Can hepatitis B vaccines produced by different manufacturers be used interchangeably?

Although it is recommended that patients receive the complete vaccination series with the same product, it is not absolutely necessary if it is between Recombivax HB® and Engerix-B®. To determine whether a hepatitis B vaccination series initiated with Recombivax HB® could be completed with Engerix-B®, healthy adults received 10 µg of Recombivax HB® at baseline and at 1 month. At 6 months, the subjects were randomly assigned to receive either Engerix-B® 20 µg or Recombivax HB® 10 µg. One month after the third dose, 100% of those who had received Engerix-B® and 92% of those who had received Recombivax HB® had protective anti-HBs levels.[73],[74] Chan et al. studied the booster response to either recombinant hepatitis B vaccine or plasma-derived vaccine in

children who had originally been vaccinated with the plasma-derived product (Heptavax-B®). Children were randomly assigned to receive either 5 µg of the plasma-derived vaccine or 20 µg of Engerix-B®. One month after the booster dose, all vaccine recipients had significant elevations in their anti-HBs titers, suggesting recombinant hepatitis B vaccines elicit an adequate booster response in persons who originally received the plasma-derived vaccine.[81] According to ACIP, the immune response from one or two doses of a vaccine produced by one manufacturer, when followed by subsequent doses from a different manufacturer, is comparable with that resulting from a full course of vaccination with a single product type.[47]

T.M. may complete the hepatitis B vaccine series with Engerix-B® provided he receives the recommended dosage of 20 µg administered as a 1-mL IM injection to the deltoid region.

On the contrary, the interchangeable concept may not apply to the newer vaccine Heplisav-B®, which has limited data on immunogenicity and safety if used interchangeably with another vaccine to complete the series. When possible, the two-dose vaccine series of Heplisav-B® should be finished with the same manufacturer. However, if the same manufacturer of the vaccine is unavailable or unknown, it is recommended to complete the vaccination series regardless of the manufacturer to prevent delays.[34]

Duration of response

Case 80-6, Question 2: Does T.M. require a booster dose for sustained protection from HBV infection?

The duration of vaccine-induced immunity has been evaluated in many long-term studies.[82–85] The duration of detectable anti-HBs appears proportional to the peak antibody response achieved after vaccination, and protective anti-HBs levels were sustained in 68% to 85% of patients receiving the plasma-derived HBV vaccine from 6 to 12 years.[82–85] More importantly, the protective efficacy of the HBV vaccine in these trials was high even in patients with anti-HBs levels

>10 IU/mL. HBsAg was only rarely detected, and most HBV infection events consisted of asymptomatic seroconversion to anti-HBc. These studies suggest that successful HBV vaccination confers long-lasting protection without the need for additional booster doses for up to 12 years. The mechanism of sustained protection against HBV, despite low or undetectable anti-HBs levels, is thought to be related to the phenomenon of immunologic memory in previously sensitized B lymphocytes. This amnestic response, in combination with the long incubation period of HBV, may allow the synthesis of protective antibodies to quickly block infection in patients rechallenged with HBV.[80]

In summary, there is no need for routine administration of HBV vaccine booster doses to immunocompetent persons after successful vaccination. Immunocompromised patients may require a persistent minimal level of protective antibody, and ACIP recommends annual antibody testing for patients receiving chronic hemodialysis with administration of a booster dose when antibody levels are <10 IU/mL.[47] Based on the available evidence, T.M. does not require a scheduled booster dose of hepatitis B vaccine.

Indications

Case 80-6, Question 3: Why is it appropriate for T.M. to receive the hepatitis B vaccine, and who else should be vaccinated against HBV?

The ACIP recommends pre-exposure hepatitis B vaccination for the following high-risk groups: PWID, health care workers with exposure to blood, staff of institutions for the developmentally disabled, patients on hemodialysis, patients with chronic liver disease or HIV infection, recipients of blood products, household and sexual contacts of HBV carriers, international travelers to HBV-endemic areas, MSM, sexually active males or females who are in a polygamous relationship, males or females seeking evaluation or treatment for STIs, patients with diabetes ages 19 to 59 years, and inmates of long-term correctional facilities.[47],[86],[87] Because T.M. is a

hospital laboratory technician, he is at high risk for exposure to HBV and should be vaccinated.

Universal hepatitis B vaccination

In addition to the previously listed high-risk groups, all infants should receive hepatitis B vaccination. For all medically stable infants weighing ≥4.41 pounds (2 kg) born to an HBsAg-negative mother, it is recommended to administer the first dose of HBV vaccine within 24 hours of birth. It should be noted that only single-antigen HBV vaccine is to be considered when given to infants at birth. For infants weighing <4.41 pounds (2 kg) born to an HBsAg-negative mother, the time of vaccination should be delayed to the time of hospital discharge or age 1 month, even if the infant's weight is still <4.41 pounds (2 kg). For infants with complications who need to be transferred to a different facility for a higher level of care, it is critical for transferring and receiving facilities to communicate regarding the HBV vaccination and hepatitis B immune globulin (HBIG) status to ensure that proper prophylaxis against HBV occurs in a timely manner. The final dose is to be administered after the age of 24 weeks or 164 days.[51]

The practice of vaccinating only high-risk persons has resulted in little impact on the incidence of HBV disease in the United States. Populations at risk for HBV disease (eg, PWID, persons with multiple sexual partners) generally are not vaccinated before they begin engaging in high-risk behaviors. In addition, many persons who become infected have no identifiable risk factors for infection and, thus, would not be recognized as candidates for vaccination. A program designed to immunize children before they initiate high-risk behaviors is likely to have a greater impact in reducing the incidence of HBV infection. As a means to achieve this goal, the hepatitis B vaccine is now incorporated into the existing pediatric vaccination schedule. The first dose is administered during the newborn period, preferably before the infant is discharged from the hospital, but no later than 2 months of age.[34],[47],[51] The recommended vaccination schedule for infants is shown in **Table 80-6**. Routine vaccination of

previously unvaccinated children ages 18 months old and younger is also recommended by the ACIP.

Table 80-6

Recommended Schedules of Hepatitis B Vaccination for Infants Born to HBsAg-Negative Mothers

Hepatitis B Vaccine	Age of Infant
Option 1	
Dose 1	Birth (before hospital discharge)
Dose 2	1–2 months[a]
Dose 3	6–18 months[a]
Option 2	
Dose 1	1–2 months[a]
Dose 2	4 months[a]
Dose 3	6–18 months[a]

HbsAg, hepatitis B surface antigen.

[a]Hepatitis B vaccine can be administered simultaneously with diphtheria-tetanus-pertussis, *Haemophilus influenzae* type b conjugate, measles-mumps-rubella, and oral polio vaccines.

Sources: Sorrell MF, Belongia EA, Costa J, et al. National Institutes of Health consensus development conference statement: management of hepatitis B. *Hepatology*. 2009;49(5, Suppl):S4; Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67:1–31.

CASE 80-7

QUESTION 1: R.M. is a mother of two children ages 11 years and 2 months. Her infant daughter just received a second dose of hepatitis B vaccine as part of her routine well-baby care.

Should R.M.'s son, who did not receive the hepatitis B vaccine during his normal childhood immunizations, receive the vaccine now?

The Centers for Disease Control and Prevention (CDC) addresses the issue of immunizing children and adolescents born before 1991 who are potentially at risk for HBV infection. The current recommendations suggest that adolescents who have not received three doses of hepatitis B vaccine should initiate or complete the series at ages 11 to 15 years. A schedule of 0, 1 to 2, and 4 to 6 months is recommended.[34],[51] It is anticipated that universal vaccination of all infants and previously unvaccinated adolescents ages 11 to 12 years, in addition to ongoing immunization of high-risk persons, will reduce the incidence of acute HBV infection, hepatitis B–associated chronic liver disease, and HCC. R.M.'s son should receive either Recombivax HB® 5 µg or Engerix-B® 10 µg IM in the deltoid with repeat doses 1 to 2 months and 4 to 6 months from the initial dose.

Adverse effects

HBV vaccines have generally been well tolerated. The most common side effect is pain at the injection site, observed in 3% to 29% of patients. Transient febrile reactions, defined as temperature >99.9 °F (37.72 °C), occurred in <6% of recipients, and other reactions including nausea, rash, headache, myalgias, and arthralgias were observed in <1% of recipients. Ongoing monitoring of vaccine safety by the FDA and CDC is assessed through the Vaccine Safety Datalink project and Vaccine Adverse Events Reporting System.[46],[47] On the basis of these reporting systems, additional "causal" adverse effects associated with vaccination include anaphylaxis (one case per 1.1 million vaccine doses), Guillain–Barré syndrome, and multiple sclerosis. Additional rare adverse events that have been reported but remain to be validated are chronic fatigue syndrome, neurologic disorders (leukoencephalitis, optic neuritis, and transverse myelitis), rheumatoid arthritis, type 1 diabetes, and autoimmune disease.

POSTEXPOSURE PROPHYLAXIS

Percutaneous exposure

CASE 80-8

QUESTION 1: K.N., a 26-year-old phlebotomy student, presents to the ED after accidentally sticking herself with a contaminated needle while drawing blood from an HBsAg-positive patient. K.N. has not been vaccinated previously and has no known prior episodes of hepatitis or liver disease. Her tetanus status is current. She weighs 123.46 pounds (56 kg).

How should K.N. be treated for percutaneous exposure to HBV?

After possible exposure to HBV infection, prophylactic treatment with hepatitis B vaccination and passive immunization with HBIG should be considered.[34],[52] The ACIP recommends postexposure immunoprophylaxis after HBV exposure. K.N.'s percutaneous exposure warrants active immunization against HBV and passive immunization with HBIG. The source of K.N.'s exposure is HBsAg positive, and K.N. has not previously received hepatitis B vaccine. She should receive a single dose of HBIG 0.06 mL/kg (3.4 mL) as an IM injection in either the gluteal or deltoid region as soon as possible after the incident, preferably within 24 hours. HBIG is prepared from plasma of persons preselected for high titers of anti-HBs. The ratio of anti-HBs of HBIG in the United States is 1:100,000 as determined by radioimmunoassay. HBIG is superior to regular Ig in the prevention of HBV infection after percutaneous exposure. K.N. should also receive active immunization with HBV vaccine simultaneously with HBIG (at a separate injection site). The second and third doses should be given 1 month and 6 months later. Passively acquired antibodies against HBV from HBIG or Ig will not interfere with active immunization from the vaccine.[87]

If the HBsAg status of the donor source of the percutaneous exposure is unknown, recommendations for prophylaxis against HBV infection will depend on whether the donor source is at high risk or at low risk for being HBsAg positive. High-risk donor sources include MSM, PWID, patients undergoing hemodialysis, residents of mental institutions, immigrants from HBV-endemic areas, and household contacts of HBV carriers.

Sexual exposure

CASE 80-9

QUESTION 1: G.G. is a 20-year-old construction worker who had sexual contact with a partner who recently found out she is HBsAg positive.

What are the current recommendations for a person who has had sexual contact with an HBsAg-positive person?

Sexual transmission of HBV is an important cause of HBV infection, accounting for ~30% to 60% of all new cases annually.[37],[38] Passive immunization with a single 5-mL dose of HBIG was found to be highly effective in preventing HBV infection after sexual exposure when compared with a control globulin (with no anti-HBs activity).[34],[51],[87] The CDC recommends for the susceptible person exposed to HBV through sexual contact with a person who has acute or CHB infection to receive postexposure prophylaxis with 0.06 mL/kg of HBIG as a single IM dose within 14 days of the last exposure.[34],[86] Patients should also receive the standard three-dose immunization series with hepatitis B vaccine beginning at the time of HBIG administration.[34]

Perinatal exposure

CASE 80-10

QUESTION 1: S.L., a 7.95-pound (3.2-kg) male, was just born to an HBsAg-positive mother.

Is S.L. at risk for acquiring HBV infection, and how should he be treated?

In many Asian and developing countries, perinatal (vertical) transmission accounts for most HBV infections. Infants born to HBV-infected mothers have a >85% risk of acquiring HBV during the perinatal period. Of those who become infected, 80% to 90% become chronic HBsAg carriers.[85],[87] Although fulminant cases have been reported, most hepatitis infections in neonates are asymptomatic. Despite the usually innocuous initial disease, significant adverse consequences are associated with chronic

HBsAg carriage in neonates. CHB infection is associated with chronic liver disease and has been clearly implicated as a major risk factor in the development of primary HCC.[59,60]

Mothers who are HBsAg carriers can transmit HBV to their infants. The risk is related to the presence of HBsAg and HBeAg in the mother, which suggests a high degree of viral replication and infectivity. The likelihood that S.L. will develop HBV infection is high. S.L. requires immediate therapy with HBIG to provide immediate high titers of circulating anti-HBs, and simultaneous vaccination with hepatitis B vaccine to induce long-lasting protective immunity. Screening pregnant patients for the presence of HBeAg and administration of HBIG and hepatitis B vaccine is 85% to 98% effective in preventing HBV infection and the chronic carrier state.[60,80,86] This compares with a 71% efficacy rate with the administration of HBIG alone. Simultaneous administration of HBIG and hepatitis B vaccine does not adversely affect the production of anti-HBs in neonates.[46,47,60,86]

Infants born to mothers who are HBsAg positive should receive simultaneous IM injections of the appropriate doses of hepatitis B vaccine (see Table 80-5) and HBIG (0.5 mL) within 12 hours of birth. The injections should be administered at separate sites. S.L. should receive HBIG (0.5 mL) as soon as possible after birth, administered as an IM injection. He also should receive 0.5 mL of either Recombivax HB® (5 µg) or Engerix-B® (10 µg) as an IM injection at a separate site.

Case 80-10, Question 2: What would the management plan be if the HBsAg status of S.L.'s mother is unknown?

The ACIP has developed recommendations for the prevention of perinatal HBV infection. This includes the routine testing of all pregnant patients for HBsAg during an early prenatal visit. HBsAg testing should be repeated late in the pregnancy for patients who are HBsAg negative, but who are at high risk for HBV infection or who have had clinically apparent hepatitis. Patients admitted for delivery

who have not had prenatal HBsAg testing should have blood drawn for testing. While the mother's test results are pending, the infant should receive hepatitis B vaccine within 12 hours of birth. If the mother is found later to be HBsAg positive, her infant should receive HBIG as soon as possible within 7 days of birth. The second and third doses of the vaccine should be administered at 1 and 6 months, respectively. If the mother is found to be HBsAg negative, her infant should continue to receive hepatitis B vaccine as part of the routine vaccination series.[60]

Evaluation and Management of Patients With Chronic Hepatitis B Virus Infection

CASE 80-11

QUESTION 1: E.A. is a 58-year-old female who presents to the hepatology clinic with a recent history of mild jaundice. Her previous medical history is unremarkable except for a blood transfusion she received during childbirth in 1988.

What initial and follow-up tests should be performed to assess the extent of HBV infection in E.A.?

Initially, a thorough history and physical examination should be performed with greater emphasis placed on risk factors for coinfection, alcohol use, and family history of HBV and liver cancer. Laboratory tests should include assessment of liver disease, markers of HBV replication, and screening tests for HCV, HDV, or HIV. Vaccination against HAV should also be administered as mentioned earlier in the section on Hepatitis A Virus. The decision to treat should be made based on knowledge of the patient's age, ALT level, HBeAg status, HBV DNA levels, and additional clinical features suggestive of chronic liver disease and associated complications. See **Figures 80-5 and 80-6** for the algorithm descriptions. In Figure 80-5, there are three potential scenarios for E.A. if she is HBsAg positive and HBeAg positive without cirrhosis. In scenario one, if her ALT is at or less than the ULN and her HBV DNA >20,000 IU/mL,

then she does not need treatment at this time. Meanwhile, E.A.'s ALT and HBV DNA levels should be monitored every 3 to 6 months and her HBeAg every 6 to 12 months while hoping for seroconversion.[88] On the other hand, in scenario two, if E.A.'s ALT is at least twice the ULN with the HBV DNA >20,000 IU/mL, then she will require antiviral treatment. In scenario three (center part of the algorithm), if E.A.'s ALT level is above the ULN, but less than twice the ULN, and her HBV DNA >20,000 IU/mL, then exclusion of other causes of ALT elevation will need to be made. Treatment is warranted if her ALT continues to be elevated, especially because she is older than 40 years of age. In addition, E.A.'s level of liver staging (fibrosis score ≥F2 or inflammation score ≥A3) will need to be evaluated before initiating treatment. Of note, if HBeAg-positive persons have HBV DNA <20,000 IU/mL, then it represents that seroconversion (HBeAg to anti-HBe) is happening. Their HBV DNA should be checked every 1 to 3 months. They should also be treated if their HBV DNA remains >2000 IU/mL for >6 months.[88]

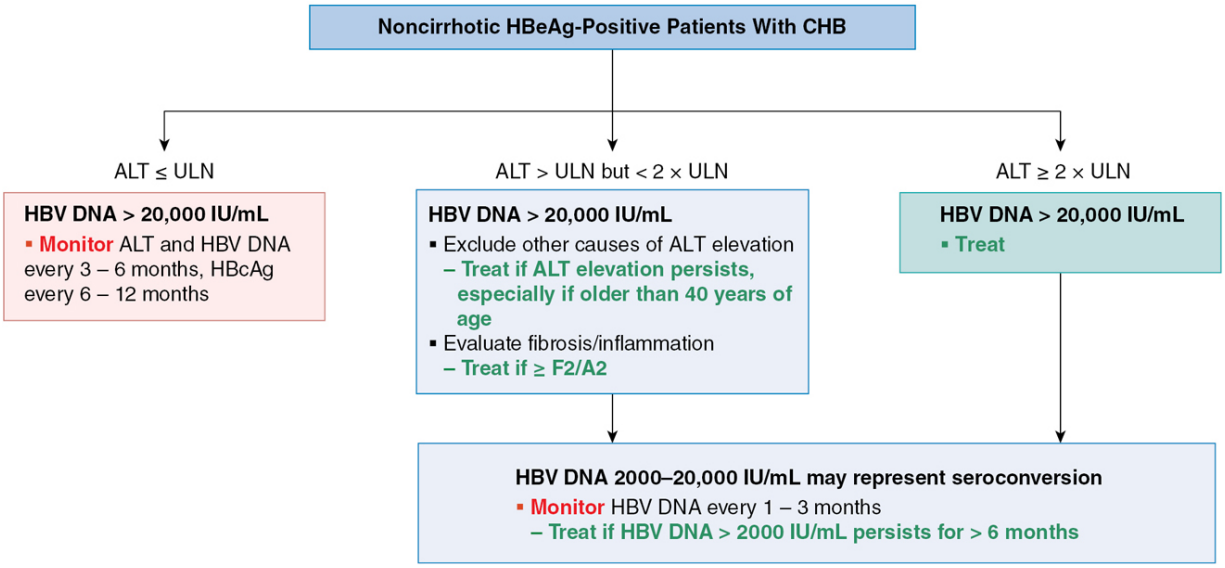


Figure 80-5 Algorithm for management of HBsAg-positive persons without cirrhosis who are HbeAg-positive. ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B envelope antigen; HBV DNA, hepatitis B virus DNA; ULN, upper limit of normal. (Source: Adapted from Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic

hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560–1599. © 2018 by the American Association for the Study of Liver Diseases. Reprinted by permission of John Wiley & Sons, Inc.)

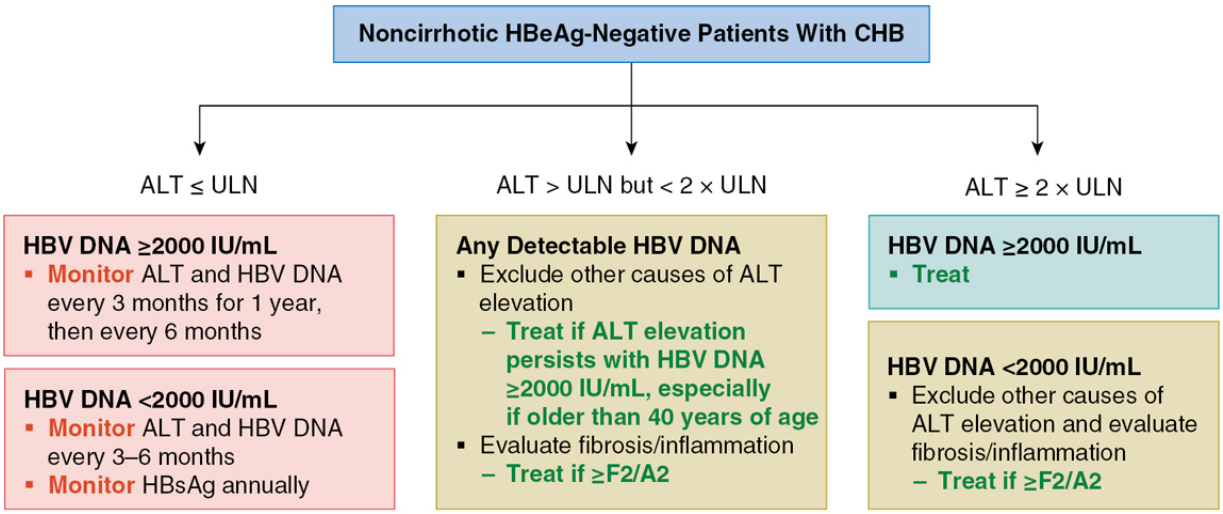


Figure 80-6 Algorithm for management of HBsAg-positive persons without cirrhosis who are HbeAg-negative. ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA; ULN, upper limit of normal. (Source: Adapted from Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560–1599. © 2018 by the American Association for the Study of Liver Diseases. Reprinted by permission of John Wiley & Sons, Inc.)

Similarly, Figure 80-6 describes three potential scenarios for E.A. who is HBsAg positive, but HBeAg negative without cirrhosis. In scenario one, E.A. has an ALT level below the ULN and does not require antiviral treatment regardless of her HBV DNA level. Her ALT and HBV DNA levels will still need to be monitored every 3 to 6 months and HBsAg annually. In scenario two, antiviral treatment is required if E.A.'s ALT level is at least twice above the ULN and her HBV DNA >2000 IU/mL. In this same scenario, if her HBV DNA <2000 IU/mL but she has elevated liver fibrosis and inflammatory

biomarkers (≥F2 and ≥A3, respectively), then E.A. will require antiviral treatment. In scenario three where the HBV DNA is at any detectable level (center part of the algorithm) and E.A.'s ALT level is above the ULN but less than twice the ULN, antiviral treatment is required especially if her ALT elevation persists with HBV DNA ≥2000 IU/mL because she is older than age 40 years. An evaluation of liver fibrosis or inflammation should also be performed.[88]

Periodic screening for HCC with ultrasound examination should also be performed in high-risk populations, such as Asian or African American males older than 40 and Asian females older than age 50 years, persons with cirrhosis, persons with a first-degree family history of HCC, and any HBsAg carrier older than 40 years with persistent or intermittent ALT or HBV DNA elevations.

CASE 80-12

Question 1: C.R., a 48-year-old male, presents to the ED with jaundice, incapacitating fatigue, and vague intermittent abdominal pain for the past month. C.R. was diagnosed with HBV infection 12 years ago. His social history includes injection drug use (none in the past 2 years) and alcohol misuse (none in the past 2 years). Several weeks ago, C.R. noticed darkening of his urine and yellowing of his eyes. In addition, C.R. has a history of severe depression, which is managed with escitalopram.

Physical examination reveals a thin male in no apparent distress. He is afebrile, and his blood pressure, heart rate, and respiratory rate are WNL. Moderate scleral icterus is noted. The abdomen is firm and distended. The liver is enlarged, nontender, and smooth with an edge palpable 5 cm below the costal margin and a span of 15 cm. The spleen is palpable. The cardiac, pulmonary, neurologic, and extremity examinations all are WNL.

C.R.'s laboratory evaluation is significant for the following:

Hct: 39%
Hgb: 11 g/dL
WBC count: 8.8 cells/μL
Platelets: 75,000/μL
PT: 15.4 seconds
INR: 2.1
AST: 326 units/L
ALT: 382 units/L
Alkaline phosphatase: 142 units/mL
Total bilirubin: 4.2 mg/dL

Albumin: 2.8 g/dL
BUN/SCr: 20/1.6 mg/dL (estimated glomerular filtration rate [eGFR] 45 mL/min/1.73)

Hepatitis serology test results are positive for HBsAg, HBeAg, and anti-HBc, and negative for IgM anti-HAV and anti-HCV. HBV DNA is reported as >20,000 IU/mL. A liver biopsy finding reveals periportal inflammation, as well as piecemeal and bridging necrosis.

What clinical findings that support the diagnosis of CHB infection does C.R. have?

The chronic occurrence of jaundice and hepatosplenomegaly with significantly elevated AST and ALT in a young patient such as C.R. is suggestive of chronic hepatitis. Although alcoholic hepatitis secondary to long-term alcohol use is consistent with these clinical features, his serology test results are positive for HBV. Hepatitis serology with positive HBsAg and HBeAg suggests ongoing viral replication and a high degree of infectivity. Serum concentrations of aminotransferases can range from slightly abnormal to greatly elevated, with ALT concentrations generally greater than AST. Serum bilirubin concentrations >3.0 mg/dL are common, serum concentration of alkaline phosphatase usually is increased, and the PT may be prolonged. Patients such as C.R. with a prolonged PT, thrombocytopenia, and low serum albumin concentration generally have a more severe form of chronic hepatitis and can be considered to have decompensated liver disease.

Liver biopsy is important for the diagnosis, treatment, and prognosis of patients with chronic hepatitis. C.R.’s liver biopsy finding reveals the classic triad of periportal inflammation, as well as piecemeal and bridging necrosis. The liver biopsy and hepatitis serology test results are consistent with a diagnosis of CHB infection. Treatment of CHB infection requires knowledge of the natural history of the untreated disease and the potential benefits of intervention. There are seven agents approved by the FDA for treating CHB infection, including six oral nucleoside/nucleotide analogs (entecavir, TDF, TAF, lamivudine, adefovir, telbivudine) and one parenteral formulation of interferon (pegylated interferon α-2a).

Case 80-12, Question 2: Does C.R. require treatment for CHB infection?

The decision to treat C.R. depends on the severity of symptoms, the serum biochemistries, and the liver biopsy results. C.R. has evidence of severe CHB infection and is diagnosed with decompensated cirrhosis. He is symptomatic with jaundice, severe fatigue, and abdominal pain. The results of his LFTs, HBV DNA, and pertinent biomarkers (decreased albumin, elevated PT, low platelets) suggest that his disease is advanced. More importantly, the current American Association for the Study of Liver Diseases (AASLD) guidelines recommend treating all patients with decompensated cirrhosis who are HBsAg positive regardless of their HBV DNA, HBeAg status, or ALT.[88] Therefore, C.R. should be treated to reduce the viral replication, resolve the hepatocellular damage, and prevent long-term adverse hepatic sequelae.[59,87]

GOALS OF THERAPY

Case 80-12, Question 3: What are the goals of therapy for CHB management?

Progression of chronic hepatitis to cirrhosis is likely because of continued replication of the HBV. Loss of active viral replication usually is associated with a decrease in infectivity, a reduction in inflammatory cells within the liver, and a decline in serum aminotransferase activities into the normal range. The disappearance of detectable HBeAg and HBV DNA is considered an indicator of loss of active viral replication.

The goals of therapy for CHB infection are to achieve sustained suppression of viral replication and remission of liver disease.[87,89] Ultimately, achieving these goals should lead to resolving ongoing hepatocellular damage and reducing the development of cirrhosis and HCC, and death. Clinical trials for CHB infection have used the following markers as end points for successful therapy: seroconversion from HBeAg positive to HBeAg negative (with

appearance of anti-HBe), reductions in serum ALT activity, elimination of circulating HBV DNA, and improvement in liver histology (**Fig. 80-7**). The elimination of HBsAg (termination of HBV carrier state) has been difficult to achieve in clinical trials. In addition, the responses to antiviral therapy of CHB can be categorized as biochemical, virologic or histologic, and as on therapy or sustained off therapy.

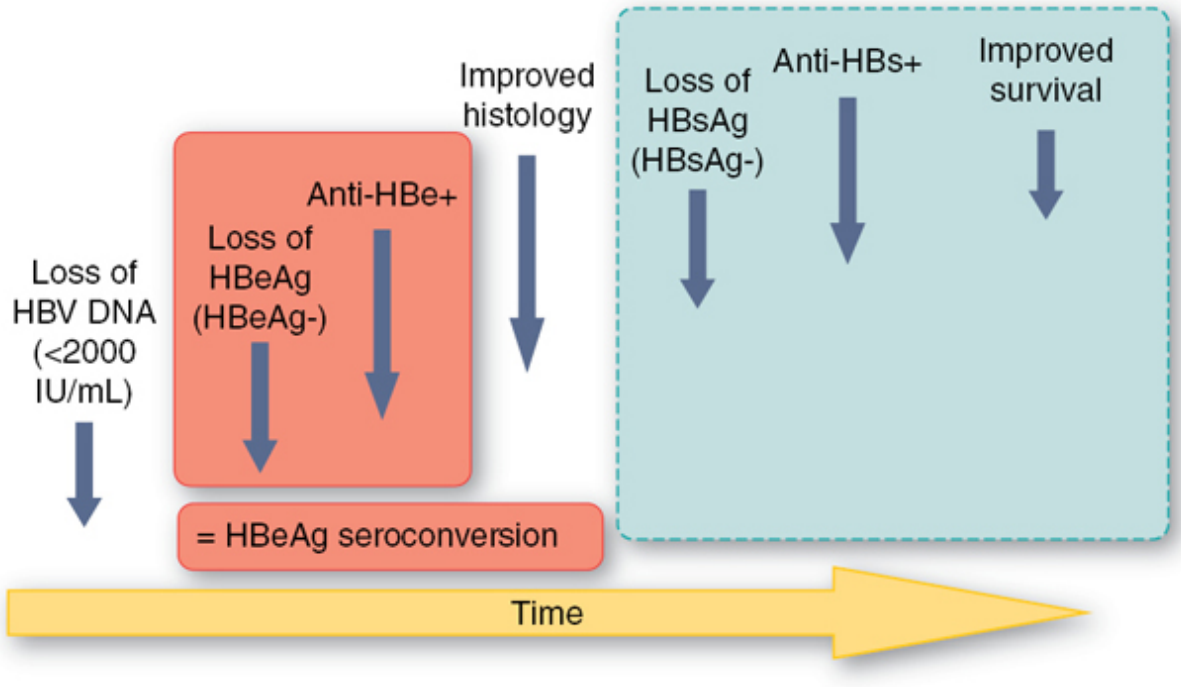


Figure 80-7 Therapeutic end points for management of chronic hepatitis B. Anti-HBe, hepatitis B envelope antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA.

DRUG THERAPY

CASE 80-12, QUESTION 4: Would initiating therapy during the acute phase of HBV infection benefit C.R.?

Pharmacologic interventions in the management of acute HBV infection have been disappointing. Early studies demonstrated a transient decrease in serum aminotransferase activity and bilirubin concentration associated with corticosteroids. More recent studies, however, have resulted in a higher incidence of relapse and mortality in patients receiving corticosteroids.[89–92] Other therapies, including HBIG and interferon (IFN) α, have been ineffective in managing acute viral hepatitis secondary to HBV.[60,93] Nucleoside and nucleotide RT inhibitors reduce HBV DNA levels in patients with chronic disease,[94–96] but their use in acute HBV infection requires further investigation. Thus, administration of antivirals during the acute phase of HBV infection would not have benefited C.R.

Interferon

Case 80-12, Question 5: What drug therapy should C.R. receive to treat his CHB infection?

Previously, IFN α-2a and α-2b were considered effective immunomodulating agents for treating CHB,[93–96] which appeared to activate their target cells by binding to specific cell-surface receptors to induce synthesis of effector proteins. These intracellular proteins induced the antiviral, antiproliferative, and immunomodulatory actions of the host's natural IFNs. Their antiviral activity possibly arose from their ability to abate viral entry into the host cells and modulate several steps of the viral replication cycle (eg, viral uncoating, inhibition of messenger RNA, and protein synthesis).[93–96] It is important to note that IFN should not be used in patients who are pregnant, have decompensated liver disease, or compensated cirrhosis and portal hypertension. The pegylated formulation involves adding polyethylene glycol to IFN α-2a that leads to an increased serum half-life, resulting in a prolonged antiviral effect. As a result, the frequency of administration is adjusted from three times weekly to once a week. The main place of therapy for pegylated interferon α-2a (PegIFN) is to treat younger patients without decompensated

liver disease or portal hypertension with a finite duration of treatment. PegIFN was the only available treatment for CHB infection before the oral nucleoside/nucleotide analogs were developed. Now, PegIFN should only be considered when the nucleoside/nucleotide analogs are unavailable, or their use is contraindicated.

Efficacy

Pegylated Interferon

PegIFN (Pegasys®) was the first and only pegylated interferon α-2a approved for the treatment of CHB infection in the United States, including both variations of the virus (HBeAg positive and HBeAg negative). PegIFN has the advantage of more convenient dosing and additional viral suppression for patients with CHB. Clinical data suggest that this agent has slightly enhanced efficacy than the conventional IFN formulations. An evaluation of monotherapy of PegIFN 180 µg subcutaneously (SQ) weekly was compared with PegIFN SQ weekly plus lamivudine 100 mg PO daily or lamivudine 100 mg PO daily alone.[94] At the end of the 24-week follow-up, significantly more patients who received PegIFN monotherapy or combination therapy had HBeAg conversion than did those who received lamivudine monotherapy. PegIFN (alone or in combination) resulted in HBsAg conversion in 16 patients compared with none in the lamivudine monotherapy group (P = .001). In addition, at the end of treatment, viral suppression was most pronounced in the group that received combination therapy. Similar results were reported in HBeAg-positive patients receiving PegIFN α-2b.[95] In the only published trial performed in HBeAg-negative patients, PegIFN 180 µg weekly (N = 177) was compared with either PegIFN 180 µg weekly plus 100 mg of lamivudine (N = 179) or 100 mg of lamivudine alone (N = 181). Viral suppression was greater in the combination group, but sustained response (HBV DNA and ALT levels at week 72) was comparable in the group that received PegIFN alone or in combination, and superior to the lamivudine monotherapy group. Loss of HBsAg occurred in 12 patients in the PegIFN groups

compared with none in the lamivudine group. Unfortunately, the addition of lamivudine to PegIFN did not improve posttherapy response rates.[96]

Dosing Considerations

The recommended dose of PegIFN is 180 µg SQ weekly for 48 weeks.[94],[96] It is possible that more severe flu-like symptoms and headache occur with thrice-weekly dosing when compared to once-weekly administration. In contrast, severe bone marrow suppression tends to occur less often with thrice-weekly administration.[94],[96]

Predictors of Response

CASE 80-12, QUESTION 6: Would C.R. be likely to respond to PegIFN therapy?

Certain patient variables can predict the response to therapy with PegIFN. The most reliable predictor of a positive response to PegIFN in HBeAg-positive patients is pretreatment ALT and HBV DNA levels.[94],[96] Patients with high pretreatment ALT more than two times the ULN and HBV DNA levels <20 IU/mL are more likely to respond to therapy.[94],[96] HBeAg seroconversion with PegIFN treatment is associated with improved survival and reduced complications. Other predictors of a positive response include a short duration of disease, negative HIV status, and a high histologic activity index as demonstrated by liver biopsy or other diagnostic tools. No consistent predictor of sustained response in patients who are HBeAg negative exists. Thus, C.R. is not a reasonable candidate for PegIFN therapy. His liver biopsy finding is consistent with chronic disease where he has high pretreatment aminotransferase levels, his HBV DNA is >20,000 IU/mL, and his duration of CHB infection is long.

Adverse Effects

Case 80-12, Question 7: What are some additional reasons for avoiding PegIFN therapy in C.R.?

Adverse effects associated with PegIFN therapy can be categorized as early adverse effects that rarely limit the use of PegIFN and late adverse effects that may necessitate dose reduction or discontinuation of therapy altogether.[94,96] The early adverse effects of PegIFN therapy generally appear hours after administration and resemble an influenza-like syndrome with fever, chills, anorexia, nausea, myalgias, fatigue, and headache. Virtually all patients receiving PegIFN experience these toxicities, and they tend to resolve after repeated exposure to the medication over time. Administration of PegIFN at bedtime may decrease the severity of early onset of the adverse effects. Acetaminophen can be used to treat early adverse effects of PegIFN therapy but should be limited to 2 g/day to minimize the risk of hepatotoxicity. The late onset of more serious adverse effects is usually observed after 2 to 4 weeks of therapy. These toxicities, which limit the use of PegIFN, include worsening of the flu-like syndrome, alopecia, bone marrow suppression, bacterial infections, thyroid dysfunction (both hypothyroidism and hyperthyroidism), and psychiatric disturbances (eg, emotional lability, irritability, depression, anxiety, delirium, and suicidal ideation). The use of PegIFN can also cause a flare (increase) in ALT levels in 30% to 40% of patients. These flares are considered to be a favorable prognostic indicator, but they have been reported to cause hepatic decompensation, especially in patients with cirrhosis. C.R.'s history of severe depression should be considered a precaution to treating him with PegIFN. Furthermore, the use of PegIFN in patients with decompensated liver disease may lead to FHF. Therefore, although approved for CHB treatment, PegIFN is not an optimal medication for C.R.[94,96]

Nucleoside/nucleotide analogs

Case 80-12, Question 8: What other antiviral therapies are available to treat C.R.'s CHB infection?

Although PegIFN has played an important role in the treatment of CHB infection, patients included in most clinical trials represented a highly select group of CHB carriers. Specifically, patients with decompensated liver disease were excluded because they often have leukopenia and thrombocytopenia as a result of hypersplenism, which limits the dose of PegIFN that can be administered. Aside from PegIFN, nucleoside analogs represent an alternative approach to CHB treatment in patients with decompensated liver disease.[89–91] The FDA has approved six oral antiviral agents for the treatment of CHB infection (lamivudine, entecavir, TDF, TAF, adefovir, and telbivudine). Of these agents, the preferred antivirals include entecavir, TDF, and TAF based on their potency and high barrier to viral resistance development. Of note, telbivudine is no longer available in the United States.

Lamivudine

Lamivudine (Epivir-HB®) is the first oral nucleoside analog approved by the FDA for use in patients with compensated liver disease who have evidence of active viral replication and liver inflammation caused by CHB infection. Lamivudine, the (−) enantiomer of 3′-thiacytidine, is an oral 2′-,3′-dideoxynucleoside that inhibits DNA synthesis by terminating the nascent proviral DNA chain and interferes with the RT activity of HBV.[97–99] For CHB treatment, Epivir-HB® is administered as 100 mg PO daily. Lamivudine is well tolerated and reduces serum levels of HBV DNA.[89–91,97,99] Lamivudine is also approved at a higher dosage (300 mg PO daily) in combination with other antiretroviral agents for HIV-1 treatment.

Lamivudine Resistance

CASE 80-12, QUESTION 9: What is the risk of developing lamivudine resistance in C.R.?

Considering the high rate of viral turnover and the error-prone nature of the polymerase, particularly the RT enzyme, acquisition of resistance mutations is common. The most common mutation leading to lamivudine resistance is a specific point mutation in the highly conserved methionine motif of the HBV DNA polymerase.[100,101] In this mutation, the methionine residue is changed to a valine or isoleucine. These genotypic mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) locus are associated with a reduced sensitivity to lamivudine and occur after long-term therapy (around 52 weeks). This motif is thought to be representative of the active site of the enzyme, similar to that associated with the HIV RT enzyme, leading to lamivudine resistance.[100,101] Lamivudine-resistant HBV mutants generally are detectable after ≥6 months of chronic therapy. Integrated data from four studies show a 16% to 32% incidence at 1 year, increasing to 47% to 56% at 2 years of therapy, and 69% to 75% at 3 years of therapy.[100,101] The presence of YMDD mutants results in a loss of the clinical response, a rise in ALT levels, and worsening of hepatic histology. Reports of continued improvement despite lamivudine resistance exist, but the long-term consequences of viral resistance, including hepatic decompensation and exacerbation of liver disease, are substantial. Thus, lamivudine has limited clinical utility in patients with CHB and is currently considered a second-line agent.

Adefovir

Adefovir dipivoxil (Hepsera®) is approved for the treatment of CHB in adults with wild-type or lamivudine-resistant virus.[102–104] Adefovir dipivoxil is the oral prodrug of an acyclic nucleotide monophosphate analog, 9-(2-phosphonylmethoxyethyl)-adenine. The active drug is a selective inhibitor of numerous species of viral nucleic acid polymerases and RTs. Previously, two trials reported the efficacy of adefovir 10 mg PO once daily for the treatment of patients who were

HBeAg negative[103] and HBeAg positive.[104] Resistance to adefovir occurred at a much slower rate compared to that with lamivudine. The cumulative probability of resistance in the HBeAg-negative patient trial was estimated to be 0%, 3%, 1%, 18%, and 29% at years 1, 2, 3, 4, and 5 years, respectively.[103] In the trial with HBeAg-positive patients, resistance was estimated to be 20% at 5 years.[104] Other reports have described adefovir resistance rates as high as 20% after 2 years of treatment.[102] Risk factors for adefovir resistance appear to be suboptimal viral suppression and its use as monotherapy. Adverse effects of adefovir include abdominal pain, diarrhea, dyspepsia, headaches, nausea, and nephrotoxicity. Adefovir is rarely used in the United States because of its high risk of causing nephrotoxicity.

Entecavir

Entecavir (Baraclude®) is an oral acyclic guanosine nucleoside derivative with potent activity against HBV.[105–107] The drug inhibits HBV replication at three different steps: (a) the priming of HBV DNA polymerase; (b) the RT of the negative-strand HBV DNA from the pregenomic RNA; and (c) the synthesis of positive-strand HBV DNA. In vitro studies have shown that the drug is more potent than are lamivudine and adefovir and is highly effective against lamivudine-resistant HBV mutants.

In two phase III clinical trials, the efficacy of entecavir was reported in patients with HBeAg-positive and HBeAg-negative CHB infection. Patients with compensated liver disease who had not previously received a nucleoside analog were assigned to receive either entecavir 0.5 mg or lamivudine 100 mg PO once daily for a minimum of 52 weeks. By week 48, HBeAg-positive patients receiving entecavir had higher rates of histologic (72% vs 62%), virologic (HBV DNA undetectable by polymerase chain reaction [PCR]; 67% vs 36%), and biochemical (ALT normalization; 68% vs 60%) responses when compared to that of lamivudine.[106] Of note, the seroconversion rates were similar among the two treatment groups (21% vs 18%; entecavir vs lamivudine, respectively). No viral

resistance to entecavir was detected during the study period, but follow-up data suggest a low rate of resistance (3% by week 96 of therapy).[106] The authors concluded that entecavir was safe and had significantly higher histologic, virologic, and biochemical response rates for HBeAg-positive patients versus HBeAg-positive patients who were treated with lamivudine. In patients who remained HBeAg positive with low levels of HBV DNA replication, a second year of entecavir and lamivudine therapy resulted in seroconversion in 11% and 13% of patients, respectively.[106]

In another trial of HBeAg-negative CHB infection, patients received either entecavir 0.5 mg or 100 mg of lamivudine PO daily for a minimum of 52 weeks. At week 48, patients receiving entecavir had significantly higher rates of histologic (70% vs 61%; *P* >.01), virologic (90% vs 72%), and biochemical (78% vs 71%) response rates.[107] No resistance was observed among patients receiving entecavir. Safety and adverse events were similar in the two groups. Thus, C.R. could receive entecavir 0.5 mg PO daily. As with all of the nucleoside agents, dosage adjustments should be implemented with changes in renal function. Furthermore, entecavir may be used for lamivudine-refractory or lamivudine-resistant patients. In these patients, lamivudine should be discontinued to reduce the risk of entecavir cross-resistance. Furthermore, the dose of entecavir is increased for lamivudine-resistant patients to 1 mg PO daily. In these patients, entecavir resistance has been reported to be 51% after 5 years of therapy. Thus, alternatives may be warranted for these patients.[108–112] With regard to histologic liver improvement, entecavir is ranked superior over TDF.[113]

Tenofovir Disoproxil Fumarate

TDF (Viread®) is approved for the oral treatment of CHB and HIV infections at a dose of 300 mg daily.[114–116] This agent is a potent nucleotide analog that is structurally similar, yet equipotent, but less nephrotoxic than is adefovir. TDF is a prodrug that gets metabolized to its active form, tenofovir. Clinical trials in HBeAg-positive and HBeAg-negative patients with CHB infection have demonstrated the

efficacy of TDF. In the first phase III trial of HBeAg-positive patients with compensated liver disease, a significantly higher proportion of TDF-treated patients had undetectable HBV DNA (76% vs 13%), ALT normalization (68% vs 54%), and HBsAg loss (3% vs 0%) at the end of therapy. Histologic response rates and HBeAg conversion were similar between the two groups. At the end of therapy, patients in the adefovir group were switched to TDF, and any patient who had detectable HBV DNA by week 72 had emtricitabine added to their regimen with subsequent additional serologic benefit.[115]

In the second trial, HBeAg-negative patients with compensated liver disease were given a similar regimen (300 mg of TDF or 10 mg of adefovir daily for 48 weeks).[115] By week 48, a higher percentage of TDF-treated patients had undetectable serum HBV DNA than did those treated with adefovir (93% vs 63%). The proportions of patients having ALT normalization (76% vs 77%) or histologic response (72% vs 69%) were similar. No patients in the study became HBsAg negative. Again, at week 48, patients receiving adefovir were switched to TDF. Patients in both groups who still had detectable HBV DNA by 72 weeks were given emtricitabine. Similar to the HBeAg-positive group, the change to TDF led to additional viral suppression in the patients initially treated with adefovir. In the previous two trials, only seven patients were observed to have virologic breakthrough during 96 weeks of therapy, but no tenofovir-resistant HBV mutations were detected. Current guidelines suggest and clinical data support TDF 300 mg PO daily as a viable first-line agent.[116] Generally, TDF is well tolerated, but it has been reported to cause Fanconi syndrome (rare), renal insufficiency, osteomalacia, and a decrease in bone density.[114] Similar to other agents in this class, the dose of TDF should be adjusted based on renal function (creatinine clearance [CrCl] <50 mL/minute).[114–116] More recent data show TDF to cause weight loss or is weight neutral compared to TAF.

Tenofovir Alafenamide

TAF (Vemlidy®) is the latest oral antiviral approved for the treatment of CHB infection. Similar to TDF, TAF is also approved for HIV-1 treatment as part of combination antiretroviral regimens. TAF is a nucleotide prodrug that is converted to tenofovir diphosphate in a two-step process, which inhibits the RT enzyme and the replication of HBV.[117] TAF has an antiviral profile similar to that of its sibling drug, TDF, but at a dose one-twelfth of TDF. Approved at 25 mg PO daily, TAF exhibits greater plasma stability and more efficiently delivers tenofovir to hepatocytes, resulting in lower tenofovir concentration in the bloodstream. Therefore, TAF leads to improved renal (eGFR and renal tubular function) and bone safety parameters (smaller declines in spine and hip bone mineral density) compared to TDF.[117–119] Interestingly, TAF has been reported to cause weight gain and an increase in triglycerides when used as part of a combination treatment regimen for HIV. The mechanisms behind these adverse effects are currently under investigation.

Two pivotal international phase III clinical studies (Studies 108 and 110) demonstrated TAF's efficacy among 1298 treatment-naive and treatment-experienced adults with CHB infection over 48 weeks. Study 108 was a randomized, double-blind, active-controlled trial that showed TAF was noninferior to TDF in treatment-naive and treatment-experienced patients with HBeAg-negative chronic HBV infection.[118] Study 110 randomized and treated 873 HBeAg-positive patients with either TAF or TDF. The study results were similar showing noninferiority to TDF based on the percentage of participants with a decline in HBV DNA below 29 IU/mL at 48 and 96 weeks.[119] Upon further data analysis through 96 weeks, higher rates of ALT normalization occurred with participants in the TAF study arm compared to those in the TDF arm. No viral resistance developed with either TAF or TDF in the studies.[118,119]

TAF was generally well tolerated by the study participants, and discontinuations from adverse events were 1% compared to 1.2% of participants in the TDF arm. The most common adverse events (incidence ≥5%) reported for TAF included headache, fatigue, abdominal pain, cough, nausea, and back pain. Similar to TDF, TAF has a safety warning of risk of lactic acidosis/severe hepatomegaly

with steatosis and posttreatment severe acute exacerbations of hepatitis B, especially upon discontinuation.[118],[119] There have been no reported cases of Fanconi syndrome or proximal renal tubulopathy associated with TAF. Nevertheless, renal monitoring of the serum creatinine, phosphorus, CrCl, urine glucose, and urine protein before initiating and during TAF treatment is clinically recommended. Even though TAF is less nephrotoxic than is TDF, it is not recommended for patients with CrCl <15 mL/minute or patients with ESRD not receiving chronic hemodialysis. TAF is also not recommended for patients with decompensated hepatic impairment (Child–Pugh class B or C).[117–119]

Regarding the drug interaction profile of TAF, it is not recommended to be coadministered with anticonvulsants (eg, oxcarbazepine, carbamazepine, phenobarbital, and phenytoin), antituberculosis medications (eg, rifabutin, rifampin, and rifapentine), or St. John wort. Such coadministration will result in significant decreased serum concentrations of TAF, thus reducing its therapeutic effect. TAF is also a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption.[117] Recommendations of the treatments for CHB can be found in **Table 80-7**.

Table 80-7
Treatments for Chronic Hepatitis B Virus Infection

Agent	Dosage Regimen[a]	Pregnancy Category	Approved for Use in Children	Potential ADRs	Potency Against HBV	Resistance Barrier to HBV
Preferred Agents						
Entecavir (Baraclude®)	*Treatment naive*: 0.5 mg PO daily *Lamivudine resistant*: 1 mg PO daily	C	Yes; for ≥2 years old	Lactic acidosis (decompensated cirrhosis only)	High	High
Tenofovir disoproxil fumarate (TDF, Viread®)	300 mg PO daily	B	Yes; for ≥2 years old	Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis	High	High
Tenofovir alafenamide (TAF, Vemlidy®)	25 mg PO daily with food	Limited human safety and efficacy data	No	Lactic acidosis	High	High
Pegylated interferon α-2a (PegIFN, Pegasys®)	180 µg SQ every week	C	Yes; for ≥3 years old	Flu-like symptoms, fatigue, mood disturbances, cytopenia, autoimmune disorders in adults	Moderate	NA
Not Preferred Agents						
Lamivudine (Epivir-HB®)	100 mg PO daily	C	Yes; for ≥2 years old	Pancreatitis, lactic acidosis	Moderate	Low
Adefovir (Hepsera®)	10 mg PO daily	C	Yes; for ≥12 years old	Acute renal failure, Fanconi syndrome, lactic acidosis	Low	Moderate

ADRs, adverse drug reactions; HBV, hepatitis B virus; NA, not applicable; PegIFN, pegylated interferon α-2a; PO, oral; SQ, subcutaneous; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide.

[a]Dosage regimen for adults.

Sources: Adapted from Terrault NA, Lok ASF, McMohan BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560–1599. Copyright © 2018 by the American Association for the Study of Liver Diseases. Reprinted by permission of John Wiley & Sons, Inc; Chang TT, Lai CL, Yoon SK, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology*. 2010;51(2):422–430.

Comparisons of PegIFN with the oral antivirals can be found in **Table 80-8**.

Table 80-8
Comparison of Drug Classes

	Pegylated Interferon α-2a	Nucleoside/Nucleotide Analogs
Advantages	Finite duration Lack or very little resistance Higher rates of HBeAg seroconversion within 12 months	Potent antiviral effect Well tolerated Oral route of administration

Disadvantages	Moderate antiviral effect Inferior tolerability Serious adverse effects Subcutaneous route of administration	Indefinite duration of therapy Risk of viral resistance Long-term safety unknown

HBeAg: hepatitis B envelope antigen.

Sources: Saravolatz LD, Bhattacharya D, Thio CL. Review of hepatitis B therapeutics. *Clin Infect Dis.* 2010;51:1201–1208; Hynicka LM, Yunker N, Patel PH. A review of oral antiretroviral therapy for the treatment of chronic hepatitis B. *Ann Pharmacother.* 2010;44:1271–1286; Ghany MG, Doo EC. Antiviral resistance and hepatitis B therapy. *Hepatology.* 2009;49(5 Suppl):S174–S184; Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. *Gastroenterology.* 2009;137:1593–1608.e1–2.

Case 80-12, Question 10: What other nucleoside or nucleotide therapies are available for managing C.R.'s CHB infection?

C.R. could benefit from one of the preferred oral antiviral agents recommended by the AASLD treatment guidelines for CHB infection, such as TAF or entecavir.[88] TAF would be the optimal treatment for C.R. because it is potent, safe, and effective to suppress the virus at its standard dose of 25 mg PO daily with food. If entecavir is selected, then its dose needs to be adjusted based on C.R.'s impaired renal function. TDF could be considered as a treatment option for C.R., but its dose would also need to be adjusted based on his impaired renal function. It is important to know that TDF would not be preferred for patients with renal impairment, especially when there are better choices because TDF could worsen the renal function. Adefovir should be avoided in patients with renal impairment because it could also exacerbate the condition. Of note, several combination therapies have been evaluated (PegIFN and lamivudine, lamivudine and adefovir, lamivudine and telbivudine), but none are superior to antiviral monotherapy.[120] Combination therapy is superior to lamivudine monotherapy in reducing the rate of resistance in patients. However, there is no such role for combination therapy for entecavir, TDF, and TAF against CHB. Therefore, combination therapy is not appropriate for C.R. at this time.

Laboratory Monitoring

CASE 80-12, QUESTION 11: How should C.R. be monitored while on treatment for CHB infection?

According to the guidance from the European Association for the Study of the Liver (EASL), patients should receive liver tests every 3 to 4 months in the first year and then every 6 months thereafter. Check HBV DNA levels every 3 to 4 months in the first year, then every 6 to 12 months thereafter. If the patient is HBeAg positive, then he/she should be assessed for seroconversion after the first year to see if they have cleared HBeAg and produced anti-HBe.[121] The HBsAg should be checked every 12 months in those with undetectable HBV DNA. If they do clear HBsAg, then they should be tested for anti-HBs. Periodic renal monitoring should be performed in those receiving TDF and in those who are at increased risk for renal disease, as well as anyone receiving a nucleoside/nucleotide analog. Renal monitoring should include assessing serum creatinine and serum phosphate levels every 3 months in the first year, and then every 6 months thereafter.[121]

LIVER TRANSPLANTATION

CASE 80-12, QUESTION 12: If C.R. fails therapy, continues to decompensate, and develops cirrhosis from his CHB infection, what nonpharmacologic interventions are available?

Liver transplantation should be considered for patients with decompensated cirrhosis. One-year survival rates for patients with cholestatic or alcoholic liver disease who undergo liver transplantation are >90% in most liver transplant centers.[122] Historical data for liver transplants in patients with CHB infection indicated that the spontaneous risk for allograft reinfection was ~80%.[122–125] This reinfection rate was associated with initial liver disease and the hepatitis B viral load at the time of transplantation,

and with allograft failure, retransplantation, or death. However, with appropriate posttransplant HBV prophylactic management, overall survival rates of patients who received a liver transplant for HBV-related cirrhosis have exceeded 85% at 1 year and 75% at 5 years, making liver transplantation a viable alternative for C.R.

CASE 80-12, QUESTION 13: What are the current recommendations for prevention of recurrent HBV infection after liver transplantation?

Historically, the most efficacious approach to prevent HBV recurrence after transplantation was with high-dose IV HBIG given in the anhepatic (recipient liver excised) and postoperative periods. Daily IV HBIG in the early postoperative period with maintenance of serum anti-HBs levels of ≥100 IU/L had an overall survival (84%) that approached what was observed in other transplant recipients without HBV infection.[124],[125] Furthermore, patients receiving long-term HBIG administration (>6 months) compared with patients receiving short-term HBIG (<6 months) had a lower risk factor for recurrent HBV infection (35% vs 75%) and longer 3-year actuarial survival (78% vs 48%).[124],[125]

HEPATITIS B IMMUNE GLOBULIN DOSAGE, ADMINISTRATION, AND ADVERSE EFFECTS

Over the years, many liver transplant centers routinely administered immunoprophylaxis with IV HBIG 10,000 IU (10 vials, 50 mL in 250 mL of saline) given in the anhepatic phase, then gave 10,000 IU (50 mL infused for 4–6 hours) for the next 6 days postoperatively. HBIG 10,000 IU is generally administered on a monthly basis for life, or discontinued if HBsAg becomes positive, indicating treatment failure.[124],[125] This regimen is able to achieve trough anti-HBs titers of ~500 IU/L and up to 2000 IU/L, which provided protection from HBV recurrence in the majority of transplanted patients. Patients who received HBIG oftentimes experience a serum sickness-like syndrome (fever, myalgias) and were managed by receiving premedication (eg, acetaminophen, diphenhydramine), thus

prolonging the HBIG infusion (up to 6 hours), or discontinuing HBIG therapy altogether.[124],[125]

Long-term concerns associated with HBIG administration may include the potential for treatment failure (HBV reinfection from extrahepatic sites despite adequate anti-HBs titers), emergence of mutant viruses, and the prohibitive high cost of therapy (>$60,000/year).[124],[125] Some data suggested that pharmacokinetic modeling and use of maintenance therapy with IM administration of HBIG (eg, 2.5–10 mL every 2–3 weeks) after a reduced induction dose (eg, 10,000 IU anhepatically, then 2000 IU via IV for six doses) could achieve similar outcomes and reduce the cost associated with IV administration of the drug.[124],[125]

Case 80-12, Question 14: What is the role of oral antiviral agents in liver transplant recipients with CHB infection?

The preferred nucleoside/nucleotide analogs include entecavir, TDF, and TAF based on their potent efficacy and high barrier to viral resistance. As discussed previously, TAF is not FDA approved for use in patients with decompensated cirrhosis. However, if a patient requiring tenofovir therapy is at risk for toxicities related to TDF, such as existing renal injury and/or bone toxicity, then it would be reasonable to initiate TAF to prevent recurrence of HBV in patients who undergo transplants for CHB infection.[125],[126] Several transplant centers, however, have implemented clinical protocols that administer entecavir, TDF, or TAF before transplantation to achieve undetectable HBV DNA viral loads at the time of transplant and then combine one of these agents with HBIG in the postoperative setting.[125],[126] Ultimately, these management strategies have emerged as a clinical standard in the preoperative and early postoperative periods because they are effective and have low rates of resistance. Future considerations for preventing recurrent HBV infection after transplantation include combining oral nucleoside (lamivudine, entecavir) with nucleotide (TDF, TAF) analogs, thus avoiding the use of HBIG altogether.[126]

MANAGEMENT OF HEPATITIS B VIRUS IN PREGNANCY

For HBsAg-positive pregnant patients with an HBV DNA level >200,000 IU/mL, the AASLD guidelines recommend initiating antiviral therapy to reduce risks associated with perinatal transmission. This is a conservative recommendation because the evidence for this specific DNA cutoff is limited. If the pregnant patient is HBsAg positive, but her HBV-DNA level is <200,000 IU/mL, then AASLD recommends against initiating HBV treatment. If treatment is warranted based on the criteria mentioned, the preferred agent is TDF owing to its high efficacy in preventing mother-to-child transmission and low viral resistance rate. Other anti-HBV agents studied in the pregnant patient population include lamivudine and telbivudine; however, they are not preferred antiviral agents. Telbivudine is also no longer available in the United States. Currently, there is limited data that show TAF is comparable to TDF with regard to safety and efficacy in the prevention of perinatal transmission.[127] Initiation of antiviral therapy is recommended for the pregnant female anywhere between 28 and 32 weeks of gestation, with continued antiviral therapy until delivery or 3 months after birth.

HEPATITIS C VIRUS

Virology

HCV is recognized as the most common cause of chronic transfusion-associated hepatitis.[128],[129] HCV is a positive-sense, single-stranded RNA virus in the *Flaviviridae* family that is 50 to 65 nm in diameter (see Table 80-1). It causes acute and chronic hepatitis C (CHC) infection in humans. If untreated, CHC can progress to cirrhosis and HCC in a subset of patients.[130] The infectious viral structure is composed of envelope glycoproteins in a lipid bilayer that contain the viral core protein and RNA.[131] After entry into the hepatocyte, the viral RNA is translated through the host

machinery into a polyprotein, which is cleaved during and after translation by both host- and viral-encoded proteases into mature viral proteins and nonstructural (NS) proteins (**Fig. 80-8**).

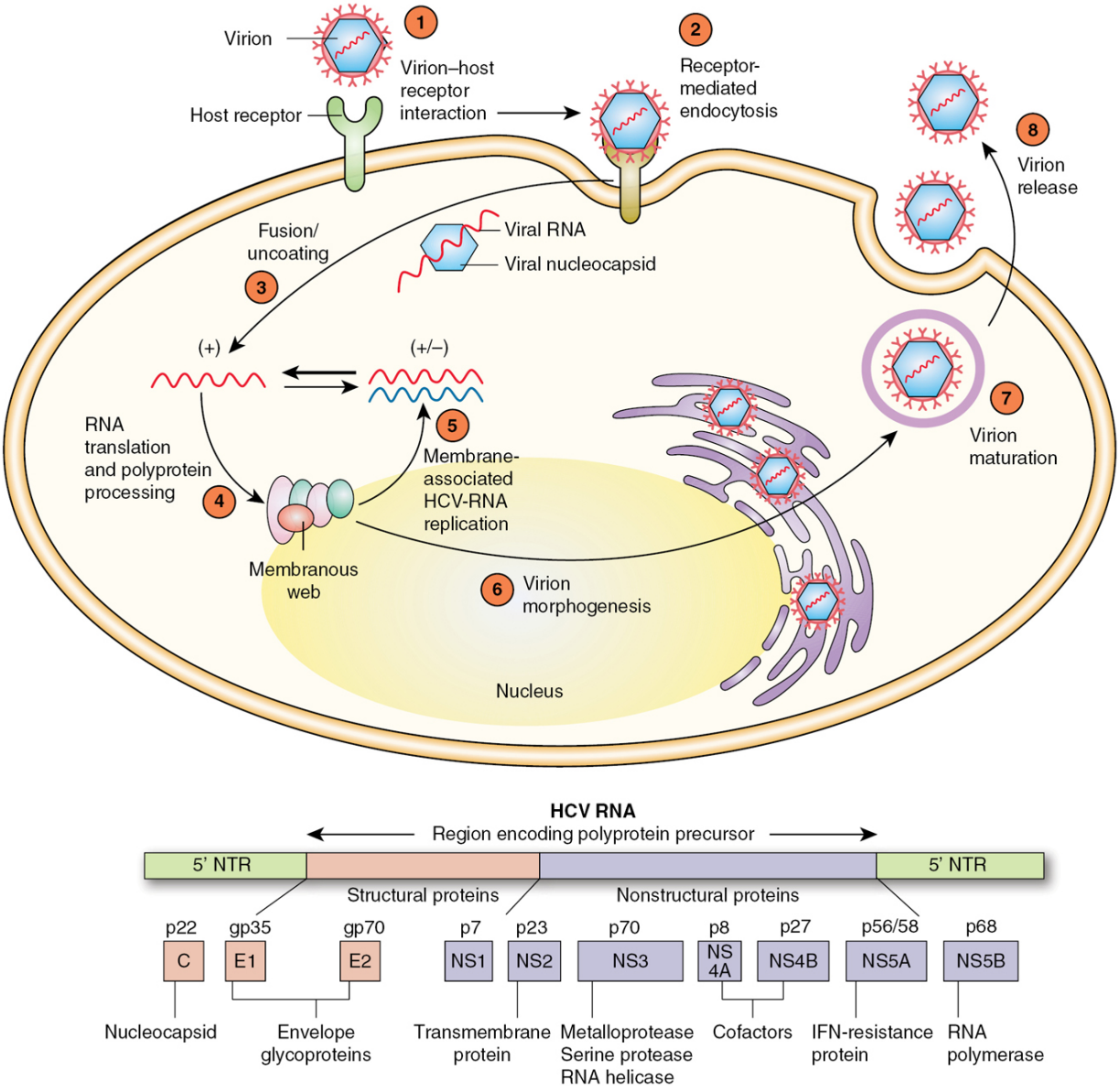


Figure 80-8 Hepatitis C virus life cycle. HCV RNA, hepatitis C virus RNA; IFN, interferon; NTR, nontranslated region. (Source: Reprinted by permission from Nature: Pereira AA, Jacobson IM. New and experimental therapies for HCV. *Nat Rev Gastroenterol Hepatol*. 2009;6(7):403–411. © 2009 Springer Nature.)

Epidemiology

The worldwide prevalence estimated that up to 180 million people are infected with CHC. This estimate includes high-risk populations, such as PWID, patients undergoing hemodialysis, patients with cancer, and blood donors. Excluding the high-risk populations, the global prevalence of HCV infection, based on anti-HCV, was 1.6% (1.3%–2.1%) corresponding to 115 (92–149) million past viremic infections.[132–134] The estimated prevalence is conservative because it did not include the abovementioned high-risk populations. The majority of these infections, 104 million, were among adults with an anti-HCV infection rate of 2.0%. Currently, there are six genotypes reported for HCV worldwide. Globally, genotype 1 distribution is most common, accounting for 46% of all infections, followed by genotype 3 (22%), and genotypes 2 and 4 (13% each). The genotype subtype 1b accounts for ~22% of all infections.[135] A further analysis of the genotype distribution across the global regions shows that genotype 1 is prevalent in Australia, Europe, Latin America, and North America (53%–71% of all cases), and genotype 3 accounting for 40% of all infections in Asia.[136–139] Genotype 4 is most prevalent (71%) in Egypt, northern and equatorial Africa, and the Middle East.[138] The prevalence of HCV genotype 5 is found in South Africa and scattered in regions of Europe and North and Eastern sub-Saharan Africa.[140,141] HCV genotype 6 is primarily found in Asia and Southeast Asia.[142]

In the United States, HCV infection is the most common bloodborne infection. Between 2013 and 2016, ~2.4 million people were living with active HCV infection, which corresponds to 1% HCV prevalence among the adult population in this country. Nearly 50% of them were unaware of their infection.[143] HCV infection occurs among persons of all ages, but the highest incidence (defined as the number of new infections in a specific time period) is among persons ages 20 to 39 years, with a male predominance. Blacks and Whites have similar incidence rates of acute disease, whereas persons of Hispanic ethnicity have higher rates. In the general population, the highest prevalence (defined as the number or percentage of persons

in the total population observed infected with HCV) rates of CHC infection are found among persons ages 30 to 49 years and among males.[130],[144],[145] Unlike the racial or ethnic pattern of acute disease, Blacks have a substantially higher prevalence of CHC infection than do Whites. In the United States, the predominant HCV genotype is type 1 (subtypes 1a and 1b) accounting for ~75% of the chronic cases.[144],[146] Historically, having knowledge of the HCV genotype or serotype (genotype-specific antibodies) was helpful in determining treatment, particularly when considering PegIFN and the first-generation protease inhibitors of the direct-acting antiviral (DAA) class. Once the genotype is identified, it need not be tested again; genotypes do not change during the course of infection. Because HCV has a high mutation rate during replication, several quasi-species, a heterogeneous population of HCV isolates that are closely related, may exist in an infected individual.[144],[146] The number of quasi-species increases during the course of infection, which allows HCV to escape the host's immune system, leading to persistent infection.

In 2020, the U.S. Preventive Services Task Force (USPSTF) and CDC expanded their one-time HCV screening recommendations from the "baby boomer" birth cohort (those born from 1945 through 1965) to include all adults regardless of age or setting prevalence (18–79 years) and all pregnant patients during each pregnancy.[143],[146] The USPSTF and CDC also suggest screening individuals younger than 18 and older than 79 years with behaviors, exposures, or conditions/circumstances associated with an increased risk of HCV infection. Similarly, the AASLD/Infectious Diseases Society of America (IDSA) recommends annual HCV testing for all PWID and MSM with HIV who have unprotected sex.[147] These recommendations are derived from several epidemiologic and surveillance health research data about new HCV infection rates. One was reported from two national laboratory companies representing the majority of patients screened for HCV antibody and/or tested for HCV RNA between 2013 and 2017. The data showed there was an increasing number of young patients and patients with milder HCV disease.[148] The CDC estimated a total

number of 44,700 new acute cases of HCV infection in 2017. This was a threefold increase in new cases since 2009 and reflected new infections associated with increasing rates of injection drug use from the opioid epidemic.[143] Furthermore, the National Notifiable Diseases Surveillance System data reported 3621 new acute HCV infection cases in 2018 among individuals younger than 40 years old.[143]

Similar to other hepatitis virus infections, acute HCV infection is defined as having an infection <6 months following acquisition of HCV. Six months is usually the period to define an acute infection based on evidence that most individuals who clear HCV will do so within 6 months. Acute HCV infection could occur whether the person develops clinical signs or symptoms of acute hepatitis. Oftentimes, patients with acute HCV infection are asymptomatic and most are unaware of their recent exposure to hepatitis C. If symptoms from acute infection develop, they usually develop within the first 4 to 12 weeks of infection and may persist between 2 and 12 weeks.[149],[150] The clinical manifestations of acute HCV infection are similar to that of other types of viral hepatitis (eg, jaundice, flu-like symptoms, dark urine and white stool, nausea, anorexia, abdominal pain, and malaise).[151] Approximately 15% to 20% of symptomatic acute liver disease in the United States is reported as resulting from acute HCV.[152] There are many potential sources of exposure to HCV, such as percutaneous transmission (eg, blood transfusion, injection drug use, procedures involving potentially reused needles, tattooing, body piercing, and acupuncture), and nonpercutaneous transmission (eg, perinatal transmission, MSM, high-risk sexual practices, noninjection drug use, and nosocomial exposure to contaminated equipment).

PERCUTANEOUS TRANSMISSION

Injection drug use is the most common route of HCV transmission. The incidence of HCV infection is 48% to 90% among PWID, and the risk of acquiring the infection in these individuals is as high as 90%.[130],[131],[144] Of the PWID with acute hepatitis, 75% are anti-HCV positive and, unlike transfusion-related hepatitis, the incidence of

HCV infection associated with injection drug use has not declined because of the opioid epidemic.[130],[131],[144] Additional risk factors for HCV infection include the presence of HBV or HIV coinfection. Other populations at risk for acquiring HCV include patients receiving chronic hemodialysis (up to 45%) and health care workers (0%–4% seroconversion after needlestick).[130],[131],[144]

NONPERCUTANEOUS TRANSMISSION

Nonpercutaneous transmission includes transmission between sexual partners engaged in physically traumatic or rough sex, and from mother to child during the perinatal period. The risk of sexual transmission appears to be highest with MSM exposures, particularly those infected with HIV.[149],[150] However, these routes of transmission are less efficient compared to the percutaneous or injection drug use route.

CASE 80-13

QUESTION 1: O.S. is a 30-year-old female who presents to the clinic 3 months after having a diagnosis of CHC infection. Her past medical history shows that she was injecting crystal methamphetamine intermittently for 6 years but denies using any drugs for 3 months. She is accompanied on the visit by her HCV-negative boyfriend. They would like to know what her risk is of transmitting HCV to others. The couple has been in a monogamous relationship for 2 years.

What is the boyfriend's risk of acquiring hepatitis C from O.S.?

The couple does not need to alter their sexual practices. According to the CDC, patients should be counseled not to share needles or any of the injection materials/paraphernalia, such as cookers, cottons, water, or the actual drug. The risk of HCV transmission among long-term, monogamous, serodiscordant couples is very low. Therefore, couples in a monogamous relationship do not need to change their sexual practices. The risk of HCV transmission among MSM is likely higher, especially with rough sexual activity. Household transmission of HCV can potentially occur via sharing razors or toothbrushes, but it is not considered a risk to share food, water, or eating utensils.[143]

Compared with the high incidence of perinatal transmission of HBV from mothers to infants, perinatal transmission of HCV infection is relatively low. In general, it is considered safe for patients infected with HCV to breast-feed their infants, with the exception that most experts recommend stopping breast-feeding if the mother's nipples (or the surrounding area) are cracked and bleeding. The mother can temporarily pump her breast milk (and discard it) and then resume breast-feeding after the nipple region has healed.[143] Additional concerns and areas for investigation related to mother-to-infant transmission of HCV include the timing of transmission (in utero, time of birth) and the natural history of perinatally acquired infection.

Natural History, Pathogenesis, and Risk Factors

Between 75% and 85% of persons who acquire HCV will develop chronic infection.[153] The rate of viral replication is high, between 10^{10} and 10^{12} virions daily, and the lack of proofreading by the viral polymerase leads to a broad genetic diversity. Among those who develop CHC infection, between 20% and 25% will develop cirrhosis 20 to 30 years after HCV acquisition.[154–156] As a result, the host immune system has a major challenge in its mechanisms to eradicate the virus.[157] Nevertheless, a small percentage of persons infected with HCV infection have spontaneously cleared the infection. The host factors or characteristics that are associated with a lower rate of chronicity or spontaneous clearance of acute HCV infection include jaundice, younger age (younger than 20 years), female gender, non-Black race, competent immune status, elevated ALT level, and genotype 1 infection with polymorphisms of the gene encoding the interferon-λ β subunit (IL28B).[158],[159] Of note, individuals with the CC allele of IL28B genotype are more likely to spontaneously clear HCV than do those with the CT or TT alleles.

The pathogenesis of liver damage from HCV infection most likely results from both direct and indirect immune-mediated responses instigated by the virus. In some studies, having genotype 3a has been associated with a higher prevalence of steatosis, which is

associated with fibrosis progression.[154],[160],[161] Hepatic fibrosis is a dynamic scarring process in which chronic inflammation stimulates production and accumulation of collagen and extracellular matrix proteins. Over time, with CHC infection, the total collagen content increases and fibrosis can develop, with potential progression to cirrhosis. Fibrosis is a precursor to cirrhosis.[160],[161] CHC is the leading cause of HCC in Western countries.[162] For persons infected with HCV infection, risk factors that can accelerate fibrosis progression include acquisition of HCV at an older age (older than 40 years), male sex, heavy alcohol intake (>50 g/day, which is ~3.5 drinks), marijuana use, coinfection with HIV or HBV, obesity, and metabolic factors (eg, steatosis and insulin resistance).[163–168] For persons who develop cirrhosis, there is an estimated 1% to 4% risk per year of developing HCC.[156],[169] On the other hand, risk factors that are less associated with the progression of liver fibrosis include HCV viral load, HCV genotype and subtype, geography, and smoking.[155]

Diagnosis and Screening

Before engaging persons with CHC infection in clinical care and treatment, an evaluation and staging of liver fibrosis should be performed. Two classes of assays are used in the diagnosis and management of HCV. These include serologic assays that detect specific anti-HCV and molecular assays that detect viral nucleic acid. These assays are not used to assess the severity of disease or predict prognosis in patients infected with HCV. Screening for additional causes, contributors of liver disease, and abnormal liver function tests should be part of the diagnostic process of liver disease. There are nonviral causes of hepatic inflammation, such as hereditary and acquired conditions. These may include alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), α-1 antitrypsin deficiency, hemochromatosis (excessive accumulation of iron in the liver), and autoimmune hepatitis.

NONINVASIVE SEROLOGIC ASSAYS AND IMAGING

Laboratory studies that are commonly used to evaluate HCV infection include HCV RNA, anti-HCV, and ALT. Persons who become infected with HCV may develop abnormal laboratory findings in the following order: detectable HCV RNA, elevation in ALT, and anti-HCV.[170],[171]

CASE 80-14

QUESTION 1: N.P. is a 27-year-old law student who presents to clinic for his routine medical evaluation. He reports having recent flu-like symptoms and nausea. He also reports noticing dark urine color and was told by his friends that he is looking "yellow and pale." N.P. has a remote history of injection drug and heavy alcohol use.

Recent laboratory tests reveal the following results:

ALT: 350 units/L
Anti-HCV: positive
HCV RNA level: 1,100,000 IU/mL

What are the clinical and serologic features of acute HCV infection in N.P.?

N.P. clearly presents with a clinical picture consistent with acute HCV infection, including symptoms of fatigue, headache, and dark urine color. His laboratory test results show elevated ALT, positive anti-HCV, and detectable HCV RNA levels.

HCV RNA is usually detected in blood within 1 to 2 weeks of infection by a nucleic acid test. Qualitative, quantitative, and genotype test results are also performed for the HCV RNA. The period from infection until HCV RNA is detectable in plasma (by a commercially available assay) is referred to as the *eclipse phase* or *previremic phase*. During this phase, the probability of establishment of HCV infection in susceptible hepatocytes is most likely. The eclipse phase is followed by an 8- to 10-day "ramp-up" phase in which HCV replication increases exponentially and readily becomes detectable in plasma. The "plateau phase" follows afterward with the HCV RNA viral load levels peaking 6 to 10 weeks after injection and remaining near these peak levels for ~40 to 60 days.[170],[171] During an

acute infection, detection of HCV RNA is not very reliable because RNA levels could fluctuate significantly. However, detectable HCV RNA levels are more uniform and present at the onset of symptoms.[149],[172]

Between 4 and 12 weeks after infection, patients may have liver cell injury resulting in an elevation in serum ALT levels. Increases in ALT can occur 1 to 2 weeks after detectable HCV RNA levels are present, and precede the development of anti-HCV. Usually, after an acute infection, the mean ALT could increase to the 800 units/L range. The CDC uses an ALT >200 units/L during the period of acute illness as part of the diagnostic criteria.[143] The last of the three abnormal laboratory findings associated with HCV infection is the presence of anti-HCV in the blood. Anti-HCV is usually detectable between 8 and 12 weeks after infection. Approximately after 12 weeks, >90% of patients will be positive for anti-HCV. This is referred to as the *serologic window period*, which describes the time period from initial infection until seroconversion.[150] Having detectable anti-HCV does not clearly differentiate acute from CHC infection. Moreover, anti-HCV is not a reliable marker to diagnose acute HCV because only 50% to 70% of patients have detectable anti-HCV at the onset of symptoms.[171],[172]

Case 80-14, Question 2: After N.P. or any other person becomes infected with HCV, what is the typical sequence of laboratory findings?

Laboratory findings will include detectable HCV RNA, then increased aminotransferase levels, and then anti-HCV positive. The gold standard for the laboratory diagnosis of acute HCV infection is anti-HCV seroconversion (negative anti-HCV [before suspected exposure] to positive anti-HCV [following exposure]) combined with a positive HCV RNA viral load test.[152],[171] However, because many patients are unaware of their exposure or risk of infection, they may not present to their health care providers early enough to be evaluated and diagnosed. Oftentimes, acute HCV is diagnosed based on the first-time detection of HCV RNA and newly elevated

ALT compared to negative laboratory results at baseline. Close follow-up of patients who have encountered high-risk exposures is recommended to establish the diagnosis and their treatment care. The laboratory testing for a known exposure to HCV includes measuring for the anti-HCV, HCV RNA, and ALT at initial presentation, 4 weeks from the time of suspected exposure, and 12 weeks from the time of suspected exposure.[143],[173]

Case 80-14, Question 3: According to the CDC 2020 case definition of acute hepatitis C, what level of increased ALT is required as part of the clinical description?

An ALT >200 units/L. N.P.'s ALT result is 350 units/L.

Acute HCV infection rarely causes a life-threatening illness. The CDC 2020 case definition of acute HCV infection includes clinical and laboratory criteria, case classification as probable or confirmed, and criteria to distinguish a new case from an existing case.[143] Clinical criteria of acute infection is described as an illness with an onset of any sign or symptom consistent with acute viral hepatitis (eg, fever, headache, abdominal pain, malaise, anorexia, nausea, vomiting, and diarrhea) combined with jaundice, a peak elevated serum ALT level >200 units/L, or a peak elevated total bilirubin level ≥3.0 mg/dL during the acute illness phase.[143],[172],[173] When the HCV RNA level persists beyond 6 months, the person is diagnosed with CHC infection. As part of the comprehensive patient workup, a complete laboratory and imaging evaluation of a patient with CHC infection includes the following[159],[172],[174]:

- *General*: CBC (platelet count), complete metabolic panel (serum creatinine), and thyroid function tests (thyroid-stimulating hormone [TSH]). Because some studies have shown that persons with vitamin D deficiency have reduced response to hepatitis C treatment, some experts recommend obtaining baseline vitamin D levels (1,25-OH vitamin D).
- *Hepatic inflammation and function*: ALT, aspartate aminotransferase (AST), total and direct bilirubin, alkaline

phosphatase, serum albumin, INR, and α-fetoprotein.

- *Assays to detect coinfections*: hepatitis A antibody, HBsAg, anti-HBc, hepatitis B surface antibody, and HIV antigen and antibody.
- *HCV RNA level (viral load)*: a quantitative HCV RNA level to confirm that the patient has CHC infection, and to establish a pretreatment baseline level. In the absence of treatment, it is not necessary to repeatedly assess the HCV RNA levels because monitoring values over time does not provide useful prognostic information.
- *HCV genotype*: HCV exists as one of six distinct genotypes with significantly different clinical characteristics, mostly with respect to treatment response rates. In the United States, HCV genotype 1 is the most common, accounting for ~75% of cases. During the IFN treatment era, knowing the HCV genotype was important because the response to antiviral therapy was very different among the different genotypes, and treatment protocols differ substantially. Since the FDA approval of DAA drugs and associated successful cure rates or sustained virologic response (SVR), especially with pangenotypic (has antiviral activity against all six genotypes) DAAs, obtaining the genotype is optional in the CHC treatment plan.
- *FibroSure*®: to stage the fibrosis of liver disease
- *Pregnancy*: if the female is of child-bearing age
- *Liver ultrasound or transient elastography*: if there is evidence of concern for advanced liver disease
- *IL28B allele*: This is a single-nucleotide polymorphism at the IL28B gene locus and strongly correlates with HCV treatment response, especially with IFN-based therapies. Because the DAAs have become the gold standard therapy for CHC treatment, testing for IL28B is now obsolete.

Noninvasive serologic assays include serum biomarkers that have clinical utility for predicting the presence or absence of significant fibrosis or cirrhosis. However, they may not be useful in differentiating between the intermediate stages of fibrosis. The

common indirect serum biomarkers used in the clinical setting include the AST to Platelet Ratio Index (APRI), FIB-4, and FibroSure® or FibroTest®. Other screening tools that have been used include the FibroIndex, Forns Index, HepaScore® (FibroScore®), and FIBROSpect® II.

APRI is easily calculated and could predict significant, severe fibrosis or cirrhosis. It is calculated using the patient's AST level and platelet count, and the ULN of the AST level. A meta-analysis of 40 studies found that an APRI cutoff of <0.5 represents the low likelihood of fibrosis (less than or equal to F2 by METAVIR). A cutoff score of >1.5 represents a high likelihood of severe fibrosis/cirrhosis (F3–F4 by METAVIR).[175–178] APRI has good diagnostic utility for predicting severe fibrosis or cirrhosis, but does not accurately differentiate intermediate fibrosis from mild or severe fibrosis. The liver guidelines recommend using APRI with other noninvasive markers of fibrosis.

The FIB-4 Index is a simple, quick, and an inexpensive test that provides results immediately. The result is generated from a formula using the person's age, AST, ALT, and platelet count. A cutoff value of <1.45 has a 90% negative predictive value for advanced liver disease, or low likelihood of fibrosis. A cutoff value >3.25 has a specificity (98%) in confirming cirrhosis and 65% positive predictive value for advanced liver disease. FIB-4 has valid utility in excluding or confirming cirrhosis; however, values between 1.45 and 3.25 do not clearly discriminate fibrosis.[179] Thus, additional methods to predict liver fibrosis are recommended.

FibroSure® and FibroTest® are identical noninvasive blood tests marketed in the United States and Europe, respectively. FibroSure® is the test available in the United States. These tests are utilized to assess liver inflammation and fibrosis. The FibroSure® provides estimates of the grade and stage of fibrosis. It includes the patient's age and gender along with a composite of six biochemical markers associated with hepatic fibrosis: α-2-macroglobulin, haptoglobin, γ-globulin, γ-glutamyltransferase (GGT), apolipoprotein A1, and total bilirubin. The score of >0.31 has a negative predictive value of 91% for the absence of clinically significant fibrosis. The positive

predictive value for the presence of significant fibrosis at a score of >0.48 was 61% and a score of 0.72 was 76%.[180] A score of >0.75 is consistent with cirrhosis (F4 score). The FibroSure® test is considered a fairly reliable "confirmatory test" when the clinical examination is consistent with cirrhosis. Ideally, the test should be performed under fasting conditions. However, there are contraindications to using the FibroSure® test (eg, patient having Gilbert disease, acute hemolysis, extrahepatic cholestasis, posttransplantation, or renal insufficiency), which may result in inaccurate quantitative calculations and predictions.

FibroIndex® is a simple scoring method comprising three biochemical markers: AST, platelet count, and γ-globulin. A cutoff value ≤1.25 has a sensitivity (40%) and specificity (94%) for mild fibrosis (F0 or F1 by METAVIR). In contrast, a cutoff value ≥2.25 has a sensitivity (36%) and specificity (97%) for significant fibrosis (F2 or F3 by METAVIR). Patients with F4 fibrosis were not included in the study.[181]

Forns Index uses a complicated calculation method. It incorporates parameters such as age, GGT, cholesterol, and platelet count. A cutoff value of >4.25 has a negative predictive value of 96% for excluding significant fibrosis (F2, F3, or F4). On the other hand, a cutoff of >6.9 has a positive predictive value of 66% for significant fibrosis (F2, F3, or F4). The Forns Index is useful and has good predictive value in selecting those with a low risk of significant fibrosis, but does not reliably predict more advanced fibrosis or cirrhosis.[182] Patients with genotype 3 HCV infection may have varying cholesterol levels. Hence, the Forns Index should not be used in these patients.

The HepaScore® or FibroScore® algorithm is more complex than are other indirect markers. Additional fibrosis markers (eg, age, sex, total bilirubin, GGT, α-2-macroglobulin, and hyaluronic acid levels) are included in the equation. A cutoff value ≤0.2 has a negative predictive value of 98% to exclude fibrosis. In contrast, a cutoff value ≥0.8 has a positive predictive value of 62% for predicting cirrhosis.[183] The HepaScore® has good utility at excluding significant fibrosis but is not as good at predicting cirrhosis.

Aside from the invasive, indirect markers for predicting liver fibrosis or cirrhosis, there are direct markers of fibrosis. Direct markers of fibrosis include procollagen types (II, III, IV), matrix metalloproteinases, cytokines, and chemokines. These markers exhibit variable effectiveness in predicting liver fibrosis. FIBROSpect® II is the only commercially available test that combines hyaluronic acid, tissue inhibitor of a metalloproteinase-1 (TIMP-1), and α-1-macroglobulin to predict fibrosis stages (F2–F4). An index score of >0.42 indicates the presence of stage F2 to F4 fibrosis. The cutoff values for sensitivity and specificity are 80.6% and 71.4%, respectively.[180],[184] The FIBROSpect® II test is a good tool to use to determine the presence or absence of cirrhosis in patients who have contraindications to liver biopsy, or those who refuse it. These markers may serve as reliable clinical alternatives in patients who are not candidates for liver biopsy. If noninvasive methods provide a clear assessment of hepatic fibrosis, then a liver biopsy may not be needed or warranted.

Noninvasive radiologic imaging of the liver has been an effective diagnostic tool for identifying cirrhosis and stratifying the stages of liver fibrosis. Several tools that are being used include hepatic ultrasound, transient elastography, and magnetic resonance imaging (MRI). Both the ultrasound and MRI should not be used for fibrosis staging unless the patient has cirrhosis. The transient elastography is a noninvasive imaging tool used to measure liver stiffness. Elastography is more accurate than is APRI or FIB-4 in predicting significant or advanced fibrosis. Furthermore, it is as accurate in measuring the degree of liver inflammation and fibrosis as a liver biopsy. Elastography is preferred over liver biopsy. However, there are potential patient factors that could confound the elastography results such as obesity, ascites, inflammation, alcohol intake, and food ingestion.

BIOPSY

Historically, liver biopsy with histologic analysis was the gold standard for establishing severity of fibrosis or fibrosis staging. It

provides information on both the grade (degree of inflammation associated with ongoing liver disease injury) and the stage (amount of currently established fibrosis). Some factors (eg, alcohol consumption, increased hepatic iron concentration, and steatosis) are associated with accelerated fibrosis progression and may elicit concern for advanced fibrosis.[185–187] Some limitations of a liver biopsy include its high cost, invasive technique, associated risks of bleeding and complications, and the probability of incorrectly staging fibrosis in about 20% of patients.[185–187] Because of these limitations and the development of noninvasive serologic tests that provide good estimates of hepatic fibrosis, liver biopsy is now optional.

IMMUNOCOMPROMISED PATIENTS

Approximately 5% of adults with CHC infection have coinfection with HIV.[188] Coinfection with HIV accelerates the progression of hepatic fibrosis and results in a more aggressive course of liver disease, resulting in cirrhosis.[189] Persons with HIV/CHC coinfection are more likely to develop cirrhosis 12 to 16 years earlier than do those who have CHC monoinfection.[190] Furthermore, liver-related morbidity and mortality is a prominent non–AIDS-related complication occurring in persons with HIV/CHC coinfection. In fact, up to 80% to 90% of liver-related deaths in those living with HIV are attributable to HCV infection.[191,192] Therefore, it is critical to treat the CHC infection in coinfected patients once their HIV infection is suppressed.

Kidney transplant recipients also have a high incidence of HCV infection (6%–28%), which may be acquired through dialysis before transplant, or from the allograft or blood products after transplantation.[193,194] After kidney transplantation, elevation in aminotransferases is more common in anti-HCV–positive compared with anti-HCV–negative patients (48% and 14%, respectively), and cirrhosis has been reported with the former.[193,194]

Clinical and Extrahepatic Manifestations

Most patients with acute HCV infection are asymptomatic.[132],[144],[145] In contrast, ~40% of patients with CHC infection will develop at least one extrahepatic manifestation. Specific extrahepatic conditions may vary, and their prevalence is derived from observational studies. Extrahepatic manifestations and conditions include cryoglobulinemic vasculitis, renal disorders with or without cryoglobulinemia, jaundice, arthralgias, neuropathy, pruritus, dermatologic manifestations (eg, cutaneous leukocytoclastic vasculitis and porphyria cutanea tarda), insulin resistance, and B-cell lymphomas.[195–202] Successful eradication of HCV could reduce the risk of some extrahepatic manifestations and complications (eg, B-cell lymphoma, diabetes, cryoglobulinemic vasculitis, and renal disease), decompensated cirrhosis (eg, ascites, encephalopathy, coagulopathy, or hyperbilirubinemia), and HCC.

Prevention of Hepatitis C

PRE-EXPOSURE PROPHYLAXIS

There are currently no vaccines against HCV, and current measures to prevent HCV infection have largely focused on identifying high-risk persons and counseling them on risk reducing strategies to prevent acquisition. The CDC and the National Institutes of Health have published recommendations that address these issues.[143] Suggested primary preventive measures include those implemented in health care settings, such as reinforcing adherence to universal precautions for the protection of medical personnel and patients, and educating HCV-positive individuals to refrain from donating blood, organs, tissues, or semen. In some situations, the use of organs and tissues from HCV-positive individuals may be considered. For example, in emergency situations, the use of a donor organ in which the HCV status is either positive or unknown may be considered in an HCV-negative recipient after full disclosure and informed consent. Strategies should be developed to identify prospective blood donors with any history of injection drug use. Such individuals must be deterred from donating blood.

Furthermore, safer sexual practices, including the use of latex condoms should be strongly encouraged in persons with multiple sexual partners. In monogamous long-term relationships, transmission is less common.[132–134] Although HCV-positive individuals and their partners should be informed of the potential for transmission, insufficient data exist to recommend changes in current sexual practice in persons with a steady partner. It is recommended that sexual partners of infected persons should be tested for anti-HCV.

In households with an HCV-positive member, sharing razors and toothbrushes should be avoided.[132–134] Covering open wounds is recommended. Injection needles should be carefully disposed of using universal precaution techniques. It is not necessary to avoid close contact with family members or to avoid sharing meals or utensils. No evidence justifies exclusion of HCV-positive children or adults from participation in social, educational, and employment activities. In addition, pregnancy is not contraindicated in HCV-infected individuals. Perinatal transmission from mother to baby occurs in <6% of instances.[132–134] No evidence indicates that breast-feeding transmits HCV from mother to baby; therefore, it is considered safe. Babies born to HCV-positive mothers should be tested for anti-HCV at 1 year.

Finally, needle exchange and other safer injection drug use programs may be beneficial in reducing parenterally transmitted infections.[132–134] Expansion of such programs should be considered in an effort to reduce the rate of transmission of HCV. It is important that clear and evidence-based information be provided to both patients and health care providers regarding the natural history, means of prevention, management, and therapy of HCV infection.

GOALS OF THERAPY

CASE 80-15

QUESTION 1: K.C., a 22-year-old female, presents to the hepatology clinic for evaluation of liver enzyme elevation. She recently saw her gynecologist and

laboratory results revealed marked ALT/AST increase. She denies any recent symptoms or change in health other than flu-like illness a few months ago. She currently works as a waitress at a restaurant. She denies prior medical problems and does not take any prescribed medications, herbal, and over-the-counter (OTC) medications. K.C. reports that she has been using IV heroin since she was 15 at a shopping center and that her best friend has died of an overdose. She went on a binge after he died and was not careful about needle sharing. She previously tested negative for HCV and HIV 1 year ago. Upon physical examination, she has multiple tattoos and body piercings, as well as a few track marks on her arms. Her physical examination is otherwise unremarkable. Liver is not enlarged, and there are no asterixis (no stigmata of liver disease), ascites, or jaundice. Abdominal ultrasound finding is normal. The hepatologist ruled out cirrhosis for K.C. Her laboratory results include the following:

ALT: 45 units/L	Anti-HCV: positive
AST: 64 units/L	HCV RNA level: 10,480,000 IU/mL
Platelets: 240 × 10^9/L	HCV genotype: 1a
Anti-HBs: positive	FibroSure®: 0.40 (F1)
HBsAg: negative	APRI: 0.67
Anti-HBc: negative	FIB-4: 0.87
Fibroscan/transient elastography: pending	HIV-1/2 Ag/Ab: negative

BUN/SCr: 18/0.6 mg/dL (eGFR 105 mL/minute/1.73 m^2)

K.C. wants to be treated for her HCV infection. She agrees to go to Narcotics Anonymous and to receive psychological and risk reduction counseling.

What is the goal of CHC therapy for K.C. and the definition of an SVR12?

K.C. clearly has a clinical presentation consistent with CHC infection including flu-like symptoms, an elevated ALT, positive anti-HCV, and detectable HCV RNA. She does not have HIV and HBV coinfection because her HIV-1/2 Ag/Ab is negative and HBsAg is negative. Coinfection with HIV or HBV could also accelerate the rate of liver fibrosis and progression of the disease for K.C. She has immunity against HBV via vaccination based on being positive for anti-HBs and negative for HBsAg and anti-HBc.

The primary goal of HCV therapy is to achieve virologic cure or SVR12, which is defined as having a negative HCV RNA level 12 weeks after completion of DAA therapy. A negative or undetectable HCV RNA level is <15 IU/mL, which is below the level of detection by sensitive laboratory assays.[132] Among persons who achieve SVR12, >99% proceed to achieve total eradication of HCV.[203–206] K.C. should be counseled that achieving SVR with DAA therapy does not mean that she will be immune from reinfection with HCV. After successfully completing DAA therapy, she should receive an annual test for HCV RNA to ensure that she does not get reinfected.

The impact of SVR is remarkably positive because patients will have an improvement in liver inflammation and fibrosis compared to those who do not achieve SVR. Other studies have also confirmed the long-term histologic benefit.[204–207] In a study involving the general population, patients with advanced fibrosis who underwent antiviral therapy and achieved SVR had reduction in overall mortality, liver-related death, liver failure, and HCC when compared to those who did not achieve SVR.[208],[209] Most of this survival benefit from successful treatment response was associated with improved clinical outcomes, primarily because of lower rates of liver failure. In a meta-analysis of 35 studies, investigators showed a clear benefit in the 5-year overall survival with HCV treatment, including patients with cirrhosis and HIV coinfection.[209] With regard to the extrahepatic manifestations, successful treatment of HCV is associated with improvement or remission of insulin resistance and diabetes mellitus.[210],[211] Overall, SVR is associated with reversal of hepatic inflammation and fibrosis, and can reduce the chance of dying from liver-related complications by at least 60%.[212]

FACTORS THAT PREDICT RESPONSE TO THERAPY

Case 80-15, Question 2: K.C. has heard about HCV infection and how treatment response may be affected by the person's genotype. She asks if her genotype could affect her successful response to HCV therapy?

In the DAA era, K.C.'s genotype should not really affect her response to treatment. Treatment responses are very high (≥98% SVR) across all genotypes when DAA therapies are used. Historically, there were viral and host factors that predicted a person's response to HCV therapy, such as the HCV genotype, HCV RNA level, IL28B genotype, race, age, gender, comorbid conditions, and the degree of hepatic fibrosis. During the IFN treatment era and before the emergence of the potent DAA drugs, the HCV genotype was the predictor of achieving an SVR, where genotype 1 has poor success rates and outcomes.[213–215] In contrast, the role of HCV genotype in predicting treatment response is modestly relevant because several DAAs are highly effective against all genotypes. In addition to the genotype, the HCV RNA level also influenced the successful treatment outcome during the IFN treatment era. Persons with genotype 1 HCV infection and very high HCV RNA levels had ~27% lower chance of achieving SVR.[216] However, the HCV RNA level has very little impact on the SVR in the era of DAA therapy.

Similarly, polymorphisms in the *IL28B* gene were associated with a difference in treatment response rates for persons receiving IFN-based therapies. In the DAA era, IL28B genotype, race, age, and gender do not significantly influence treatment response. The degree of hepatic fibrosis may still influence the SVR rates for persons receiving DAA therapies. Advanced fibrosis, defined as F3 (precirrhosis or bridging fibrosis), and F4 (cirrhosis) were associated with a much lower virologic cure rate across all genotypes (between 10% and 20% lower) during the IFN era.[213–215] This is similarly observed in patients receiving DAA therapies. Patients with decompensated cirrhosis (Child–Pugh class B or C) had lower SVR rates (86%–87%) with 12-week treatment of ledipasvir/sofosbuvir plus ribavirin compared with SVR rates of ≥98% in similarly treated patients with no cirrhosis.[217] Current strategies to improve the SVR rates for patients with cirrhosis include adding ribavirin to the DAA combination therapies and lengthening the duration of therapy.

Current Treatment Strategies

From 1998 to 2013, antiviral therapy evolved from IFN monotherapy to PegIFN monotherapy, to PegIFN plus ribavirin, and to triple therapy with PegIFN plus ribavirin plus a first-generation DAA (eg, boceprevir or telaprevir), which was part of the NS3/4A serine protease inhibitor class. At the time, research methodologies for enhancing the effectiveness of HCV treatments and improving SVR mainly focused on genotype 1, which is the most prevalent genotype in the United States. The DAAs are oral antiviral agents that directly target the specific steps within the replication genome of the HCV. Between 2013 and 2014, antiviral treatment against genotype 1 HCV infection included PegIFN and ribavirin plus either sofosbuvir or simeprevir, which modestly improved the SVR outcomes. Then in 2015, the HCV treatment paradigm significantly shifted to an IFN-free approach where the oral DAAs became the standard of care for CHC infection. The DAAs were superior to PegIFN and ribavirin therapy because of their outstanding SVR rates, better tolerability profiles, and much shorter treatment duration. The treatment duration was significantly reduced from 48 weeks with PegIFN plus ribavirin to between 8 and 24 weeks with DAA combination regimens. The three classes of DAAs are defined by their mechanism of action and therapeutic target. They include the nonstructural proteins 3/4A (NS3/4A) serine protease inhibitors, nonstructural protein 5B (NS5B) RNA-dependent RNA polymerase inhibitors, and nonstructural protein 5A (NS5A) inhibitors.[218]

According to the AASLD/IDSA HCV treatment guidelines, treatment should be offered to all persons with CHC infection because the DAAs are safer, better tolerated, and more effective in achieving virologic cure.[147] However, there are absolute contraindications for DAA treatment: persons with short life expectancies (<6 months); the use of DAA regimens plus ribavirin in pregnant patients, females who may become pregnant, or males whose female partners are pregnant.[219],[220] The main concern is with ribavirin, which is teratogenic. Persons with CHC infection who are of reproductive age and are to receive treatment that includes ribavirin should be strongly advised to use two forms of contraception during treatment and for at least 6 months following the end of treatment.

Similarly, there are relative contraindications when considering CHC treatment initiation. They include active severe substance abuse (eg, excess alcohol use, injecting drugs), psychiatric issues not controlled or stabilized, and social issues that may negatively affect a person's adherence to treatment, laboratory, and scheduled office visits.

DIRECT-ACTING ANTIVIRALS

CASE 80-15, QUESTION 3: Genotyping of K.C.'s HCV infection shows that she has genotype 1a. Which DAA therapy would be effective for patients with genotype 1a HCV infection?

K.C. has many treatment options with the DAA therapies. She has no signs of cirrhosis, or decompensated disease with splenomegaly, ascites, coagulopathy, or esophageal varices. The DAA combination therapies are highly potent and effective in achieving ≥98% SVR rates for persons with genotype 1 (1a and 1b subtypes) HCV infection (**Table 80-9**).[221,222]

Table 80-9
Comparison of Direct-Acting Antiviral Agents for Hepatitis C Virus Treatment

	NS3/4A Serine Protease Inhibitors	NS5B Polymerase Inhibitor	NS5B (Nonnucleoside) Polymerase Inhibitor	NS5A Inhibitors
DAA agents	Glecaprevir Grazoprevir Paritaprevir Voxilaprevir	Sofosbuvir	Dasabuvir	Daclatasvir (not available in the United States) Elbasvir Ledipasvir Ombitasvir Pibrentasvir Velpatasvir
MOA	Block RNA translation and polyprotein processing prevent viral maturation	Blocks viral replication and propagation	Blocks viral replication and propagation	Block the replication complex and virion assembly
Potency	High	Moderate-to-high	Moderate-to-high	High
Barrier to resistance	Moderate-to-high	High	High	Low
Potential for drug interactions	High	Low	Low	Variable
Adverse effects	Headache, fatigue, nausea	Headache, insomnia, pruritus, diarrhea	Minimal	Headache, nausea, fatigue

DAA, direct-acting antiviral; MOA, mechanism of action; NS3/4A, nonstructural proteins 3/4A serine protease inhibitors; NS5A, nonstructural protein 5A inhibitor; NS5B, nonstructural protein 5B RNA-dependent RNA polymerase inhibitor.

Sources: Zoulim F, Durantel D. Antiviral therapies and prospects for a cure of chronic hepatitis B. *Cold Spring Harb Perspect Med*. 2015;5(4):a021501; Pockros PJ. New direct-acting antivirals in the development for hepatitis C virus infection. *Therap Adv Gastroenterol.* 2010;3:191–202.

NS3/4A serine protease inhibitors

The NS3/4A protease is a trypsin-like serine enzyme, which is essential for the generation of components of the viral RNA replication complex. The NS3/4A serine protease is responsible for cleaving the polyprotein downstream of the NS3 site, allowing the release of functional proteins and the generation of mature proteins. The NS3/4 serine protease inhibitors are macrocyclic noncovalent peptidomimetic inhibitors that reversibly bind to the HCV NS3/4A protease and function through two mechanisms. They disrupt the virus replication process by blocking the NS3 catalytic site or the NS3/NS4A interaction.[222] The NS3/NS4A protease inhibitors also block the cleaving of two cellular proteins in the IFN cascade, thereby affecting IFN-α and IFN-β synthesis.[222] In short, the NS3/4A serine protease inhibitors exert two distinct effects: blocking viral replication by inhibiting viral polyprotein processing and restoring IFN signaling pathways that are believed to be disrupted by NS3/4A. As a result, the NS3/4A serine protease inhibitors prevent viral maturation.

First Generation

The first-generation protease inhibitors for CHC treatment included boceprevir and telaprevir. They were used in combination with PegIFN plus ribavirin for the treatment of genotype 1 infection. Their clinical importance substantially diminished because of the cumbersome administration, substantial adverse effects, drug–drug interactions, and a low barrier to viral resistance. As more potent and better-tolerated protease inhibitors were approved for CHC treatment without PegIFN and ribavirin, telaprevir and boceprevir became clinically obsolete and were removed from the U.S. market in 2014 and 2015, respectively.

Second Generation

The second-generation protease inhibitors were more favored because they have fewer drug–drug interactions, fewer severe adverse effects, and have improved dosing schedules. In spite of their improved efficacy against genotype 1 infection, the newer protease inhibitors have limited efficacy against other genotypes and a low barrier to resistance.[223] The second-generation protease inhibitors currently available in the United States include simeprevir, grazoprevir, paritaprevir, glecaprevir, and voxilaprevir.

Simeprevir Simeprevir (Olysio®) was the first DAA in the second-generation NS3/4A serine protease inhibitor class. It was approved for combination use with PegIFN plus ribavirin, or in combination with sofosbuvir, with or without ribavirin for chronic HCV genotype 1 infection.[224] No dose adjustment is required in patients with renal impairment. Simeprevir cannot be used in patients with moderate (Child–Pugh class B) or severe (Child–Pugh class C) hepatic impairment because of two- to fivefold increases in drug exposure. Higher simeprevir exposure was reported in patients of East Asian ancestry; thus, simeprevir should be used with caution for this patient population.[225] In clinical trials, simeprevir treatment discontinuations from adverse effects were uncommon. However, photosensitivity and rash that led to serious reactions requiring hospitalization for some patients have occurred in the trials.[226,227] Patients taking simeprevir should be cautioned about the risk of photosensitivity and rash, and to use sun-protective measures and/or limit sun exposure while on treatment. If a severe rash or photosensitivity reaction occurs, simeprevir should be discontinued.

Simeprevir is oxidatively metabolized by the hepatic and intestinal cytochrome P450 (CYP) 3A4 isoenzyme. Coadministration with potent inducers and inhibitors of CYP3A4 will affect the plasma concentration of simeprevir. The efficacy of simeprevir is affected by the presence of resistance mutations or polymorphisms of the NS3/4A protease. In particular, the presence of Q80K polymorphism was associated with a lower SVR rate (58% vs 84% if the Q80K was absent).[225] However, data suggest that the Q80K mutation does not

significantly affect SVR rates when simeprevir is coadministered with sofosbuvir, an NS5B polymerase inhibitor.[228] Owing to simeprevir's narrow spectrum of activity (against genotype 1 only) and its adverse effect profile, it is no longer a preferred option in the AASLD/IDSA treatment guidelines for CHC infection.

Grazoprevir Grazoprevir is coformulated in a fixed-dose combination with elbasvir, an NS5A inhibitor. Grazoprevir has activity against HCV genotypes 1, 4, and 6. However, it is only FDA approved for genotypes 1 and 4 because of the elbasvir component. It is a substrate of CYP3A4 isoenzyme and the OATP1B1/3 transporter. The drug–drug interactions with grazoprevir are different compared to other protease inhibitors, where its concentrations are increased by cyclosporine and HIV protease inhibitors via OAT1B1/3 inhibition[229] (see section on Elbasvir/Grazoprevir).

Paritaprevir Paritaprevir is hepatically metabolized by the CYP3A4 isoenzyme. It is coformulated with low-dose ritonavir, an HIV protease inhibitor, for pharmacokinetic-enhancing effects via inhibition of CYP3A-mediated metabolism. Ritonavir does not have any activity against HCV. Paritaprevir and ritonavir are coformulated as a fixed-dose combination with ombitasvir, an NS5A inhibitor (see section on Paritaprevir/Ritonavir/Ombitasvir Plus Dasabuvir).

Glecaprevir Glecaprevir is coformulated in a fixed-dose combination product with pibrentasvir, an NS5A inhibitor. Glecaprevir has pangenotypic antiviral activity against HCV genotypes 1 to 6. It is minimally metabolized and excreted via the bile.[230] The combination is approved for the treatment of persons with CHC infection without cirrhosis and with compensated cirrhosis (Child–Pugh class A) (see section on Glecaprevir/Pibrentasvir).

Voxilaprevir Voxilaprevir is coformulated in a fixed-dose combination with sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor). It also has pangenotypic antiviral activity against HCV genotypes 1 to 6. Voxilaprevir is a CYP3A4 and 2C8 substrate. It is also a substrate and inhibitor of OATP1B1, OATP1B3, P-gp, and BCRP.[231] Unlike the other combination DAA regimens, this triple combination regimen is intended to be used as salvage therapy for

DAA treatment failures (see section on Sofosbuvir/Velpatasvir/Voxilaprevir).

It is important to note that the FDA issued a safety announcement in 2019 regarding case reports of worsening liver function or liver failure associated with the use of second-generation NS3/4A protease inhibitors: grazoprevir, glecaprevir, and voxilaprevir.[232] These protease inhibitors are found in DAA combination regimens, such as elbasvir/grazoprevir (Zepatier®), pibrentasvir/glecaprevir (Mavyret®), and sofosbuir/velpatasvir/voxilaprevir (Vosevi®). Many of the case reports described liver failure that occurred in patients who were symptomatic with moderate-to-severe liver impairment (Child–Pugh class B or C), or have other serious liver problems. The FDA recommends the use of these DAA regimens for patients without liver impairment or with mild liver impairment (Child–Pugh class A) only. Zepatier® and Mavyret® should be avoided in persons with any history of prior hepatic decompensation. Vosevi® is indicated for persons who have previously failed DAA treatments and is not recommended in persons with a history of hepatic decompensation unless the benefits outweigh the risk of liver injury or fatality.[232]

NS5A inhibitors

The NS5A inhibitors block the protein complex that is involved in viral replication and the assembly of the virion.[233–235] The NS5A class is relatively potent and effective across all genotypes. However, it has a low barrier to viral resistance and a variable toxicity profile. When coadministered with PegIFN and ribavirin, NS5A inhibitors can substantially reduce HCV RNA levels and improve SVR.[235] The NS5A inhibitors are substrates of P-gp and BCRP drug transporters. They are also substrates of CYP3A4, except for ledipasvir.[236] The available NS5A inhibitors in fixed-dose combinations with other DAAs include ledipasvir, ombitasvir, elbasvir, and velpatasvir. Daclatasvir, the only stand-alone NS5A inhibitor, is no longer available in the United States.

Elbasvir is available in a fixed-dose combination with grazoprevir, an NS3/4A serine protease inhibitor. Before initiating this DAA

combination regimen for treatment of genotype 1a, baseline resistance testing is required to determine the presence of the virus with NS5A resistance-associated substitution (RAS) polymorphisms at the amino acid positions 28, 30, 31, or 93 and to determine dosage regimen and duration[237] (see section on Elbasvir/Grazoprevir).

Ledipasvir is available in a fixed-dose combination with sofosbuvir, an NS5B polymerase inhibitor. Its absorption is optimal in an acidic milieu. Therefore, drugs that increase gastric pH could decrease the plasma concentration of ledipasvir. Coadministration of ledipasvir is not recommended with antacids (eg, aluminum and magnesium hydroxide) and should be separated by 4 hours. On the other hand, ledipasvir could be administered simultaneously with H_2-receptor antagonists or given 12 hours apart. The dose of the H_2-receptor antagonists should not exceed doses comparable to famotidine 40 mg twice daily, which was used in the studies.[236] Ledipasvir can be given with omeprazole, but not >20 mg and under fasting conditions.[236] It is active against genotypes 1, 4, 5, and 6 (see the section on Ledipasvir/Sofosbuvir).

Ombitasvir is available in a fixed-dose combination with the protease inhibitors paritaprevir and ritonavir, and is administered in combination with dasabuvir, an NS5B nonnucleoside inhibitor (see section on Paritaprevir/Ritonavir/Ombitasvir Plus Dasabuvir).

Elbasvir is available in a fixed-dose combination with glecaprevir, an NS3/4A serine protease inhibitor. It is considered one of the newer generations of NS5A inhibitors with pangenotypic activity. Pibrentasvir has potent antiviral activity against common HCV NS5A single-position variants that confer resistance to first-generation NS5A inhibitors (eg, daclatasvir, ledipasvir, and ombitasvir) (see section on Glecaprevir/Pibrentasvir).

Velpatasvir has pangenotypic antiviral activity against genotypes 1 to 6. It is only available in a fixed-dose combination with sofosbuvir, an NS5B polymerase inhibitor. Similar to ledipasvir, velpatasvir requires an acidic milieu for optimal absorption. Its drug–drug interaction profile mirrors that of ledipasvir when velpatasvir is

administered with antacids (eg, aluminum and magnesium hydroxide) and H_2-receptor antagonists. Similar administration recommendations should be taken when using velpatasvir-based regimens. However, the coadministration of velpatasvir and proton-pump inhibitors is not recommended. If considered medically necessary, then velpatasvir-based regimens should be administered with food and taken 4 hours before omeprazole 20 mg[238] (see sections on Sofosbuvir/Velpatasvir and Sofosbuvir/Velpatasvir/Voxilaprevir).

NS5B RNA-dependent RNA polymerase inhibitors

The NS5B RNA-dependent RNA polymerase is involved in posttranslational processing that is necessary for HCV replication. The polymerase has a catalytic site for nucleoside binding and four other sites for nonnucleoside binding to cause an allosteric alteration. The enzyme structure is highly conserved across all six genotypes. The NS5B RNA-dependent RNA polymerase inhibitors essentially block viral replication and propagation. There are two subclasses of NS5B polymerase inhibitors: the nucleoside/nucleotide polymerase inhibitors (NPIs) and nonnucleoside polymerase inhibitors (NNPIs). The NPIs bind to the catalytic site of NS5B, whereas NNPIs function as allosteric inhibitors.[222,223]

Sofosbuvir

Sofosbuvir (Sovaldi®) is the first NS5B NPI available for HCV treatment and has pangenotypic activity. It should not be used as monotherapy against HCV and is most effective when used in DAA combination regimens. Sofosbuvir is available as a 400-mg tablet and is given daily with or without food. It is primarily renally eliminated; however, pharmacokinetic studies suggest that no dose adjustments are required for patients with mild or moderate renal impairment (eGFR >30 mL/minute/1.73 m^2).[239] Nevertheless, serum levels of sofosbuvir are increased in patients with severe renal impairment and receiving hemodialysis. There are insufficient data to recommend dose adjustments in these patients. Sofosbuvir can be

given to patients with moderate (Child–Pugh class B) or severe (Child–Pugh class C) hepatic impairment and cirrhosis without dose adjustments. Sofosbuvir is generally well tolerated. When given with PegIFN and ribavirin, the commonly reported adverse effects of sofosbuvir and ribavirin (with or without PegIFN) were fatigue, headache, nausea, insomnia, and anemia.[240,241]

As a substrate of the P-gp drug transporter, sofosbuvir has significant drug interactions with potent intestinal P-gp inducers that could decrease its plasma concentration. The coadministration of sofosbuvir with anticonvulsants (eg, carbamazepine, phenytoin, phenobarbital, oxcarbazepine), antituberculosis drugs (eg, rifampin, rifabutin, rifapentine), and St. John wort is contraindicated. Of note, the coadministration of sofosbuvir and amiodarone is also contraindicated. Concomitant use of sofosbuvir and sofosbuvir-based regimens with amiodarone are contraindicated because of episodes of severe bradycardia and fatal cardiac arrest.[242,243] The proposed mechanism for the major drug–drug interaction between amiodarone and sofosbuvir remains unclear.

Dasabuvir

Dasabuvir is an NS5B NNPI. The NNPI class is less potent than the NPI class, is more specific for genotype 1, and has a low-to-moderate barrier to viral resistance and a variable toxicity profile.[244] Dasabuvir is coadministered and packaged with paritaprevir/ritonavir/ombitasvir (see section on Paritaprevir/Ritonavir/Ombitasvir Plus Dasabuvir).

Case 80-15, Question 4: The current AASLD/IDSA guidelines endorse fixed-dose DAA combination regimens for effective HCV treatment. Which DAA regimen could K.C. benefit from and for what treatment duration?

There are currently four FDA-approved fixed-dose combinations that are effective against HCV genotype 1, as well as other genotypes. K.C. has genotype 1a HCV infection. She could benefit from any of the following regimens:

a. Glecaprevir 300 mg/pibrentasvir 120 mg (Mavyret®) three tablets PO with food once daily for 8 weeks
b. Elbasvir 50 mg/grazoprevir 100 mg (Zepatier®) one tablet PO once daily for 12 weeks
c. Ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni®) one tablet PO once daily for 12 weeks
d. Sofosbuvir 400 mg/velpatasvir 100 mg (Epclusa®) one tablet PO once daily for 12 weeks

Both glecaprevir/pibrentasvir (Mavyret®) and sofosbuvir/velpatasvir (Epclusa®) are DAA combination regimens that have pangenotypic activity against genotypes 1 to 6. Before starting elbasvir/grazoprevir (Zepatier®), K.C. will need to receive baseline resistance testing for the presence of the virus with NS5A RAS polymorphisms at the amino acid positions 28, 30, 31, or 93 to determine the duration and possible addition of ribavirin to the treatment regimen because of her genotype.[237] Ledipasvir/sofosbuvir (Harvoni®) could be considered for K.C.; however, the treatment duration would be for 12 weeks because her baseline HCV RNA level is >6,000,000 IU/mL. Of note, paritaprevir/ritonavir/ombitasvir plus dasabuvir (Viekira Pak®, Viekira Pak® XR) could be another possible treatment option for K.C. because it has activity only against genotype 1 HCV variants. However, this DAA regimen would not be preferred for K.C. because of the pill burden (three to four tablets daily) and a longer duration of treatment (24 months).

ORAL FIXED-DOSE DIRECT-ACTING ANTIVIRAL COMBINATIONS

Elbasvir/grazoprevir

As a fixed-dose combination single tablet, elbasvir 50 mg/grazoprevir 100 mg (Zepatier®) has activity against genotypes 1 and 4 HCV infection. It is a combination of an NS5A inhibitor and NS3/4A serine protease inhibitor. The DAA regimen is administered once daily for either 12 or 16 weeks.[245] This regimen is administered with or without weight-based ribavirin, depending on certain patient

characteristics. Elbasvir/grazoprevir has been studied and approved for the treatment of CHC and HIV coinfection. Patients should have documentation of baseline aminotransferases and be tested for current or previous CHB infection (HBsAg and anti-HBc) to ensure that there is no risk of HBV flares during HCV treatment. The regimen is the first of the newer DAA therapies that could be used in patients with renal impairment, including hemodialysis, without the need for dose adjustments. However, the regimen is contraindicated for use in patients with moderate-to-severe hepatic impairment (Child–Pugh class B or C).

Before administering elbasvir/grazoprevir, patients with genotype 1a infection should undergo baseline testing for the presence of NS5A RAS polymorphisms. Preexisting NS5A polymorphisms that are associated with elbasvir resistance and lower SVR rates with the regimen in patients with genotype 1a are found at amino acid positions M28, Q30, L31, and Y93.[237] Approximately 11% of genotype 1a viruses are estimated to harbor one of these polymorphisms before taking elbasvir/grazoprevir regimen. In the presence of one of the NS5A polymorphisms, ribavirin (weight based) could be added to the regimen and the treatment duration extended to improve SVR rates. Interestingly, the polymorphisms do not affect the SVR rates in persons with genotype 1b virus infection. The polymorphisms in the NS3 protein, especially the Q80L polymorphism in genotype 1a virus, do not appear to affect treatment response and SVR rates. The other difference between the NS5A and NS3 polymorphisms appears to be the long persistence of the NS5A resistance mutations in individuals after completing the DAA treatment.

Elbasvir/grazoprevir is overall well tolerated. From the large clinical trials, the most common adverse effects were headache, fatigue, and nausea.[237],[246] Approximately 1% of patients developed late aminotransferase elevations more than five times ULN without associated bilirubin increases that resolved once the regimen was stopped. Aminotransferase monitoring at baseline and at week 8 of therapy (and at week 12 if the total duration is 16 weeks) is recommended.[245] The regimen should be discontinued if

aminotransferase elevations are accompanied by other signs or symptoms of hepatic injury, such as jaundice, increased bilirubin, or INR. The regimen is primarily metabolized by CYP3A isoenzyme, and grazoprevir is a substrate of OATP1B1/3 transporters. Coadministration of elbasvir/grazoprevir is contraindicated with potent inducers (eg, rifampin, phenytoin, carbamazepine, St. John wort, cyclosporine), efavirenz, and HIV protease inhibitors (eg, atazanavir, darunavir, ritonavir). Furthermore, coadministration of the regimen is not recommended with ketoconazole, nafcillin, modafinil, and other antiretrovirals (etravirine or cobicistat).

Ledipasvir/sofosbuvir

Ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni®) is coformulated as a fixed-dose tablet that is administered with or without food.[222] It is a combination of an NS5A inhibitor and NS5B polymerase inhibitor. The regimen is given with or without weight-based ribavirin, depending on the patient population, and is active against HCV genotypes 1, 4, 5, and 6. The limited spectrum of antiviral activity is based on the ledipasvir component. The duration of therapy ranges between 8 and 24 weeks depending on the genotype, treatment exposure (naive or experienced), and the liver condition (fibrosis stage level). Based on the ION-3 trial, ledipasvir/sofosbuvir could be considered in treatment-naive patients with genotype 1 without cirrhosis who have pretreatment HCV RNA level <6 million IU/mL.[247] The levels of sofosbuvir and its inactive metabolite (GS-331007) might accumulate in the setting of severe renal impairment (eGFR <30 mL/minute/ 1.73 m^2). Therefore, the combination should not be used until further data are available. Otherwise, no dose adjustment is needed for mild or moderate renal impairment, or in the setting of moderate (Child–Pugh class B) or severe (Child–Pugh class C) hepatic impairment.[247]

The ledipasvir/sofosbuvir combination is well tolerated, and the common adverse effects include fatigue, headache, nausea, and insomnia. With regard to drug interactions, ledipasvir is a substrate of the P-gp drug transporter. Similar to sofosbuvir, ledipasvir should

not be coadministered with potent intestinal P-gp inducers because its plasma concentration will significantly decrease. The coadministration of ledipasvir with acid-suppressing agents could increase the gastric pH levels and decrease its solubility and absorption. Coadministration of ledipasvir is not recommended with antacids (eg, aluminum and magnesium hydroxide) and should be separated by 4 hours. On the other hand, ledipasvir could be administered simultaneously with H_2-receptor antagonists or given 12 hours apart. The dose of the H_2-receptor antagonists should not exceed doses comparable to famotidine 40 mg twice daily, which was used in the studies. Ledipasvir can be given with omeprazole, but not >20 mg and under fasting conditions.[236,239] The coadministration of amiodarone and sofosbuvir/velpatasvir is contraindicated because of severe bradycardia and cardiac arrest.[242,243]

The resistance profile of ledipasvir/sofosbuvir has been associated with several NS5A RAS polymorphisms that reduce the susceptibility to ledipasvir, such as Q30R, Y93H/N, and L31M for genotype 1a virus and Y93H for genotype 1b virus.[248] The presence of NS5A RASs does not require adjustment of the regimen's dosage or duration of treatment. Further data are warranted to make any clinical adjustments. The coadministration of amiodarone and ledipasvir/sofosbuvir is contraindicated because of severe bradycardia and cardiac arrest based on a major drug–drug interaction between amiodarone and sofosbuvir[242,243] (see section on Sofosbuvir).

Sofosbuvir/velpatasvir

Sofosbuvir 400 mg/velpatasvir 100 mg (Epclusa®) is a fixed-dose, pangenotypic regimen that comprises an NS5B polymerase inhibitor plus an NS5A inhibitor. It is coformulated as a once-daily single tablet administered for 12 weeks with or without ribavirin. The commonly reported adverse effects include headache, fatigue, nausea, nasopharyngitis, and insomnia.[249] Baseline viral resistance testing is required only for persons with genotype 3 HCV infection.

No dose adjustments are needed for this regimen in patients with mild-to-moderate renal impairment. There are insufficient data regarding the safety and efficacy of this regimen in patients with severe renal impairment (eGFR <30 mL/minute/1.73m^2) or ESRD requiring hemodialysis. For patients with moderate (Child–Pugh class B) or severe (Child–Pugh class C) hepatic impairment, no dosage adjustments are recommended. Thus, close monitoring is recommended for patients with decompensated cirrhosis who are receiving sofosbuvir/velpatasvir and ribavirin.[250]

Sofosbuvir and velpatasvir are substrates of the P-gp and BCRP drug transporters. Therefore, coadministration of the regimen with potent intestinal P-gp inducers can decrease both sofosbuvir and velpatasvir serum levels. The coadministration of this regimen is contraindicated with anticonvulsants, antituberculosis drugs, and St. John wort. Efavirenz can also significantly reduce the serum levels of velpatasvir and should not be coadministered. Velpatasvir is also an inhibitor of the P-gp transporter and thus may increase the absorption of P-gp substrates. Similar to ledipasvir, velpatasvir requires an acid gastric environment for enhanced solubility and absorption. Antacids, H_2-receptor antagonists, and proton-pump inhibitors will increase the gastric pH levels, resulting in decreased absorption of velpatasvir. The manufacturer recommends separating the administration time of 4 hours between sofosbuvir/velpatasvir and antacids (eg, aluminum and magnesium hydroxide). However, H_2-receptor antagonists could be administered simultaneously with or separated 12 hours apart from the DAA regimen at a dose that is comparable with famotidine 40 mg twice daily. Coadministration of velpatasvir and proton-pump inhibitors is not recommended. If considered medically necessary, then velpatasvir-based regimens should be administered with food and taken 4 hours before omeprazole 20 mg.[231,238] The coadministration of amiodarone and sofosbuvir/velpatasvir is contraindicated because of severe bradycardia and cardiac arrest based on a major drug–drug interaction between amiodarone and sofosbuvir[242,243] (see section on Sofosbuvir).

Paritaprevir/ritonavir/ombitasvir plus dasabuvir

The coformulated tablet of paritaprevir 75 mg/ritonavir 50 mg/ombitasvir 12.5 mg is given with dasabuvir 250 mg. It is the only combination regimen that contains ritonavir, an HIV protease inhibitor, as a pharmacokinetic enhancer. The regimen is often referred to as *PrOD* (Viekira Pak®, Viekira® XR). PrOD can be taken with or without weight-based ribavirin, depending on the patient population, for the treatment of genotype 1 (1a and 1b subtypes) without cirrhosis or with compensated cirrhosis. PrOD is also indicated in combination with ribavirin in liver transplant patients with HCV genotype 1 as long as hepatic function is normal and fibrosis is mild (METAVIR score ≤2).[251] Paritaprevir/ritonavir/ombitasvir, with or without dasabuvir, can be administered in CHC-infected patients with renal impairment. Dose adjustment for the regimens is not warranted for patients with mild hepatic impairment (Child–Pugh class A). However, the regimens are contraindicated in patients with moderate-to-severe hepatic impairment (Child–Pugh classes B and C). Hepatic decompensation was reported when the regimen is used, with or without dasabuvir, in patients with underlying cirrhosis.[252] Most of the reported cases occurred within 1 to 4 weeks of drug initiation, and some cases resulted in the need for liver transplantation or death.

PrOD is available in immediate-release and extended-release tablet formulations. For the immediate-release formulation (Viekira Pak®), two tablets (each containing ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg) are administered once daily. Dasabuvir is coadministered with the regimen as a single 250-mg tablet twice daily. In short, the number of pills for Viekira Pak® is four tablets a day. For the extended-release formulation (Viekira® XR), it is a four-drug combination tablet containing ombitasvir 8.33 mg/paritaprevir 50 mg/ritonavir 33.33 mg/dasabuvir 200 mg. The dosage regimen is three tablets administered once daily with ribavirin (weight-based dosing) in two divided doses. These regimens should be taken with food and are generally well tolerated. The commonly reported adverse effects in the trials that used the regimen with ribavirin

included nausea, pruritus, insomnia, diarrhea, and asthenia.[253],[254] Fatigue and headache were the most common side effects and may be attributable to the ribavirin component. Decreases in the hemoglobin level, by 2 to 2.5 g/dL, were observed in patients taking regimens with ribavirin. The incidence of severe anemia (hemoglobin <8 g/dL) is uncommon.[253],[254]

The components of PrOD are both substrates and inhibitors of CYP450 enzymes. The coadministration of paritaprevir/ritonavir/ombitasvir and dasabuvir is contraindicated with anticonvulsants, rifampin, St. John wort, and oral contraceptives containing ethinyl estradiol and salmeterol.[251] Close monitoring and dose adjustments of certain drugs (eg, 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA], cyclosporine, tacrolimus, and antiarrhythmics) are recommended when given with the PrOD regimen. The use of paritaprevir, ombitasvir, and dasabuvir can select for viral resistance mutations in NS3, NS5A, and NS5B, respectively, which will reduce the activity of a particular antiviral agent.

Glecaprevir/pibrentasvir

Glecaprevir 300 mg/pibrentasvir 120 mg (Mavyret®) is the first pangenotypic fixed-dose tablet comprising an NS3/4A serine protease inhibitor and NS5A inhibitor. It offers a potent 8-week treatment option for persons with no cirrhosis with renal disease or HIV coinfection.

Glecaprevir/pibrentasvir is administered as three tablets once daily with food to increase absorption. The manufacturer packages a daily packet containing three tablets to ensure medication adherence. For treatment-naive persons without cirrhosis, the treatment duration is 8 weeks for all genotypes. However, the treatment duration is extended to 12 weeks for treatment-naive persons with compensated cirrhosis (Child–Pugh class A). For treatment-experienced persons, the treatment duration will range between 8 and 16 weeks depending on their previous HCV regimen and genotype.[230],[255] Data from the clinical trials do not support the use of

glecaprevir/pibrentasvir for the treatment of patients with genotype 1 HCV infection who are both NS3/4A protease inhibitor and NS5A inhibitor experienced because of higher rates of virologic failure and treatment-emergent drug resistance.[255]

Table 80-10
Combination Direct-Acting Antiviral Regimens for Treatment-Naive Patients Without or With Compensated Cirrhosis

DAA Combination Therapy	Trade Name	Dosage Regimen	Genotype Coverage	Duration of Therapy	Safe in Decompensated Cirrhosis?	Use in CKD, ESRD
Preferred Therapies						
Glecaprevir 300 mg/pibrentasvir 120 mg	Mavyret®	Three tablets PO daily with food	1–6	8 weeks	No	Safe in HD
Sofosbuvir 400 mg/velpatasvir 100 mg	Epclusa®	One tablet PO daily	1–6	12 weeks	Yes	≥30 mL/minute
Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg	Vosevi®[a]	One tablet PO daily with food	1–6	12 weeks	No	≥30 mL/minute
Dependent on Patient's HCV Genotype						
Ledipasvir 90 mg/sofosbuvir 400 mg	Harvoni®	One tablet PO daily	1, 4, 5, 6	8 weeks[b] 12 weeks	Yes	≥30 mL/minute
Elbasvir 50 mg/grazoprevir 100 mg	Zepatier®[c]	One tablet PO daily	1 (1a[c], 1b), 4	12–16 weeks	No	Safe in HD
Paritaprevir 75 mg/ritonavir 50 mg/ombitasvir 12.5 mg + dasabuvir 250 mg	Viekira Pak®, Viekira Pak® XR	Dosing regimen variable depending on genotype and cirrhosis condition	1a, 1b	12–24 weeks	No	Safe in HD

CKD, chronic kidney disease; ESRD, end-stage renal disease; HD, hemodialysis.

[a]Vosevi®: not for first-line use, but only for salvage DAA therapy.

[b]Harvoni®: for patients with genotype 1, HIV-negative, and have HCV RNA level <6 million IU/mL.

[c]Zepatier® is eligible only if there are no baseline NS5A resistance-associated substitution (RAS) polymorphisms for genotype 1a; patients with genotypes 1b and 4 can use Zepatier® without screening for RAS.

Source: AASLD/IDSA HCV Guidance Panel. Recommendations for testing, managing, and treating hepatitis C. Updated August 27, 2020 [Internet]. 2020 [cited August 27, 2020]. Accessed October 1, 2020. http://hcvguidelines.org/

Before initiating glecaprevir/pibrentasvir, all persons should be tested for current or prior hepatitis B infection by measuring HBsAg and anti-HBc. Glecaprevir/pibrentasvir is not recommended in patients with moderate hepatic impairment (Child–Pugh class B) and

is contraindicated for use in patients with severe hepatic impairment (decompensated cirrhosis or Child–Pugh class C) because of higher exposures of the drugs, especially of glecaprevir.[255]

Nausea, fatigue, and headache were the more common adverse effects reported from the clinical trials. Regarding drug–drug interactions, glecaprevir and pibrentasvir are substrates and inhibitors of P-gp and BCRP transporters. They are weak inhibitors of CYP3A, CYP1A2, and UGT1A1 substrates. The coadministration of glecaprevir/pibrentasvir with potent CYP3A4 inducers (eg, rifampin, St. John wort, and carbamazepine) is not recommended because of reduced plasma concentrations of glecaprevir/pibrentasvir that could lead to decreased efficacy and potential treatment failure. The coadministration of atazanavir with glecaprevir/pibrentasvir is contraindicated because of an increased risk of ALT elevations and plasma concentrations of the drugs.[255] Similarly, the coadministration of glecaprevir/pibrentasvir is not recommended with HMG-CoAs that are metabolized by CYP3A4 enzyme (eg, atorvastatin, simvastatin, and lovastatin) because of their increased plasma concentrations that could lead to increased risk of myopathy. Alternative statins such as rosuvastatin, pitavastatin, and pravastatin could be considered with close monitoring for adverse effects.

Sofosbuvir/velpatasvir/voxilaprevir

Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg (Vosevi®) is the first pangenotypic fixed-dose combination tablet that includes one agent from each of the DAA class (NS3/4A serine protease inhibitor, NS5B RNA-dependent RNA polymerase inhibitor, and NS5A inhibitor), thereby targeting the essential steps of the virus life cycle. It is administered as one tablet once daily with food. Safety and efficacy have not been established in patients whose eGFR <30 mL/minute/1.73 m^2. This regimen plays an important role in patients who have experienced treatment failure with other DAA therapies. The presence of NS5A, NS3/4A, or NS5B RASs do not influence the likelihood of patients achieving SVR with Vosevi®.[256] Therefore,

sofosbuvir/velpatasvir/voxilaprevir is reserved as a viable option for patients. Unfortunately, the presence of voxilaprevir does not make this regimen an option for treatment-experienced patients who have moderate-to-severe hepatic disease (Child–Pugh class B or C cirrhosis).[257]

The common adverse effects reported from clinical trials include fatigue, headache, diarrhea, and nausea. The solubility of velpatasvir in the fixed-dose regimen depends on the gastric pH. Its solubility decreases as pH increases. Drugs that increase the gastric pH, such as antacids, H_2-receptor antagonists, and proton-pump inhibitors will decrease the plasma concentration of velpatasvir. They will increase the gastric pH levels, resulting in decreased solubility and absorption of velpatasvir. The manufacturer recommends separating the administration time of 4 hours between sofosbuvir/velpatasvir/voxilaprevir and antacids (eg, aluminum and magnesium hydroxide). However, H_2-receptor antagonists could be administered simultaneously with or separated 12 hours apart from the DAA regimen at a dose that is comparable with famotidine 40 mg twice daily. Coadministration of velpatasvir and proton-pump inhibitors is not recommended. If considered medically necessary, then velpatasvir-based regimens should be administered with food and taken 4 hours before omeprazole 20 mg.[231,238]

Sofosbuvir, velpatasvir, and voxilaprevir are metabolized by P-gp and BCRP drug transporters. Voxilaprevir is also a substrate of OATP1B1 and OATP1B3. In vitro observations have reported the metabolism of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 and of voxilaprevir by CYP1A2, CYP2C8, and CYP3A4 (mainly).[231] Therefore, potent inducers of P-gp, CYP2B6, CYP2C8, or CYP3A4 (eg, carbamazepine, rifampin, St. John wort) could significantly decrease the plasma concentrations of sofosbuvir, velpatasvir, and voxilaprevir resulting in a subtherapeutic effect of the regimen. Similarly, sofosbuvir/velpatasvir/voxilaprevir should not be coadministered with cyclosporine because of the risk of substantially increased exposure of voxilaprevir.[231] Similar to other sofosbuvir-based regimens, the coadministration of

sofosbuvir/velpatasvir/voxilaprevir with amiodarone is contraindicated because of severe bradycardia and cardiac arrest based on a major drug–drug interaction between amiodarone and sofosbuvir.[242],[243]

COINFECTION WITH HUMAN IMMUNODEFICIENCY VIRUS

CASE 80-16

QUESTION 1: F.X., a 32-year-old transgender female, presents to the Infectious Diseases clinic for medical care and medication management. She is newly diagnosed with HIV and CHC coinfection by her primary care physician. F.X. is treatment naive for both infections. She reports having condomless sex with multiple partners in the past few months and admits to nonadherence to TDF/emtricitabine (Truvada®) for pre-exposure prophylaxis. Her laboratory results are the following:

Hct/Hgb: 38/15.1	HIV-1/2 Ag/Ab: positive
Platelets: 200 × 10^9/L	HIV viral load: 68,000 copies/mL (5.2 logs)
Albumin: 4.0 g/dL	Absolute $CD4^+$: 358 cells/mm^3
ALT: 66 units/L	CD4%: 18%
AST: 54 units/L	FibroSure®: 0.50 (F2)
Anti-HCV: positive	APRI: 0.68
HCV RNA level: 22,510,000 IU/mL	FIB-4: 1.16
HCV genotype: 4	Elastography: results pending
Anti-HBs: positive	Anti-HAV: positive

HBsAg: negative
Anti-HBc: negative
BUN/SCr: 22/1.0 mg/dL (eGFR 115 mL/minute/1.73 m^2)

What is the treatment approach for managing F.X.'s HIV/CHC coinfection?

F.X. is immunized against HBV based on her serum anti-HBs, negative HBsAg, and negative anti-HBc levels. She is also immunized against HAV because she is positive for the antibodies.

As previously mentioned, coinfection of HIV with CHC accelerates the progression of hepatic fibrosis and could result in a more aggressive course of liver disease. Therefore, we should manage F.X.'s HIV infection first before initiating DAA therapy for her CHC infection. The Infectious Diseases team will initiate F.X. on bitegravir/TAF/emtricitabine (Biktarvy®) today as part of the rapid-start HIV treatment approach because they do not have her baseline HIV resistance result (genotype and phenotype) and HLA-B*5701 allele result (specific for abacavir). Medication education and adherence counseling are provided to F.X. She is scheduled for follow-up laboratory blood tests in 1 month.

Case 80-16, Question 2: F.X. returns to the Infectious Diseases clinic 6 weeks after starting her antiretroviral therapy for a follow-up routine visit. She reports tolerating the antiretroviral therapy well and admits to complete medication adherence. Her 1-month follow-up laboratory blood test results shows:

HIV viral load <20 copies/mL (undetectable)
Absolute $CD4^+$: 468 cells/mm^3
CD4%: 20%
ALT: 54 units/L
AST: 40 units/L
Elastography results: normal
Child–Pugh score: class A
CBC: WNL
Comprehensive metabolic panel: WNL
BUN/SCr: 20/0.9 mg/dL (eGFR 110 mL/minute/1.73 m^2)

Could F.X. be started on a DAA therapy for her CHC infection?

Because F.X.'s HIV is suppressed with the current antiretroviral therapy, she could begin therapy for her CHC infection. Moreover, her good medication adherence will help ensure her successful response to DAA therapy. There are multiple clinical trials that demonstrate high SVR rates in patients with HIV/CHC coinfection and taking DAA therapies. In these trials, the participants did not have cirrhosis, and most had CD4 counts above 200 cells/mm^3.[258–260] Similarly, there are observational cohort studies that report HIV/CHC

coinfected persons with advanced liver disease and lower CD4 cell counts also have SVR rates comparable to those with CHC monoinfection.[261–263] There are five key clinical trials that involve DAA therapy for patients with HIV/CHC coinfection: ION-4 (ledipasvir/sofosbuvir × 12 weeks for genotypes 1 or 4; SVR12 = 96%), C-EDGE CO-INFECTION (elbasvir/grazoprevir × 12 weeks for genotypes 1, 4, and 6; SVR12 = 96%), ASTRAL-5 (sofosbuvir/velpatasvir × 12 weeks for genotypes 1–4; SVR12 = 95%), EXPEDITION-2 (glecaprevir/pibrentasvir × 12 weeks for genotypes 1–4; SVR12 = 98%), NIAID ERADICATE (ledipasvir/sofosbuvir × 12 weeks for genotype 1; SVR12 = 98%).[258,259,264–266]

Case 80-16, Question 3: The Infectious Diseases team decides to initiate F.X. on DAA therapy. Which DAA therapy would be effective and appropriate for her?

F.X. has genotype 4 HCV infection, which is not a prevalent genotype in the United States but is more common in other countries such as Egypt, the Middle East, and parts of Africa. Approximately 75% of persons infected with HCV in the United States have genotype 1 (subtypes 1a or 1b). Based on the excellent potency of the DAAs, F.X. would most benefit from receiving the pangenotypic combination therapies, such as glecaprevir/pibrentasvir (Mavyret®) and sofosbuvir/velpatasvir (Epclusa®). Both are approved to treat HIV/CHC coinfection. F.X.'s Child–Pugh score and elastography result show that she does not have moderate-to-severe fibrosis. Therefore, she is eligible for glecaprevir/pibrentasvir (Mavyret®) three tablets PO daily with food for 8 weeks' duration. If sofosbuvir/velpatasvir (Epclusa®) is selected, then the regimen is dosed as one tablet PO daily with or without food for 12 weeks. In addition, F.X. could also benefit from taking elbasvir/grazoprevir (Zepatier®) one tablet PO daily for 12 weeks. Baseline RAS testing is not necessary before starting Zepatier® because F.X. has genotype 4 HCV infection. It is recommended only for patients with genotype 1a

HCV infection. The final treatment decision will depend on the type of insurance coverage that F.X. has.

Case 80-16, Question 4: Which DAA regimens are not preferred for F.X.?

The third pangenotypic DAA combination therapy, sofosbuvir/velptasvir/voxilaprevir (Vosevi®), would not be considered for F.X. because she is treatment naive. It is reserved for treatment-experienced persons with HCV infection who have failed previous DAA therapies. Ledipasvir/sofosbuvir (Harvoni®) is not approved for HIV/CHC coinfected persons with an HCV RNA level >6 million IU/mL. F.X. has an HCV RNA level of 22,510,000 IU/mL.

Case 80-16, Question 5: What counseling points should be provided to F.X. when she takes either Mavyret® or Epclusa®?

F.X. should take the DAA therapy as prescribed, either Mavyret® three tablets PO daily with food for 8 weeks, or Epclusa® one tablet PO daily with or without food for 12 weeks. She may experience fatigue, nausea, and headache during the treatment period, especially in the first month. F.X. should drink plenty of water and reduce her normal physical activities to manage the fatigue. She can take OTC ibuprofen or naproxen to alleviate the headache symptoms. For nausea, she could take Epclusa® with food, or take it with a light snack or nongreasy food. F.X. should avoid taking acetaminophen (>2 g/day) and iron supplements because they may damage her liver. She should be scheduled for follow-up quantitative HCV RNA levels at the end of her DAA therapy to determine treatment response. Subsequently, F.X. should be scheduled for the critical HCV RNA level 3 months after she completes the DAA therapy. If her HCV RNA level is negative or undetectable (<15 IU/mL) 3 months after treatment completion, then F.X. has achieved SVR12 or virologic cure.

HEPATITIS D VIRUS

Virology and Epidemiology

Hepatitis D (or "Delta") virus is a small, single-stranded circular RNA virus (36 nm) (see Table 80-1).[267–269] HDV is considered an incomplete virus that requires the presence of HBV to be pathogenic in humans.[270,271] Between 62 and 72 million persons are infected with HDV globally, particularly in the Mediterranean Basin, the Middle East, Asia, West and Central Africa, Colombia, Venezuela, and the South Pacific.[267–269,272] Vaccination for HBV significantly reduces the incidence of HDV. However, immigration from endemic areas, increased injection drug use, sexual practices, and body modification procedures have resulted in an increase in HDV prevalence in some regions. In the United States, an estimated 7500 HDV cases occur annually.[273,274] The prevalence of HDV is greatest among persons with percutaneous exposure (eg, PWID) and those with hemophilia (20%–53% and 48%–80%, respectively) and may be affected by additional factors such as the duration of infection.[273,274] The modes of transmission of HDV are similar to those reported for HBV infection. Therefore, HDV clearly represents a potential infectious hazard to patients susceptible to HBV and those who are CHB carriers. Generally, two major patterns of infection occur with HBV: coinfection and superinfection. Because infection by HDV requires the presence of active HBV, preventing HBV infection will prevent HDV infection in a susceptible patient.[274,275]

Pathogenesis

Although its prevalence is considered less common compared to other types of viral hepatitis, HDV is described as the most severe and rapidly progressive form of chronic viral hepatitis. Progression to cirrhosis occurs in 10% to 15% of patients within 2 years and in 70% to 80% within 5 to 10 years.[275,276] Limited data suggest that HDV

antigen and HDV RNA are cytotoxic to hepatocytes; however, the immune response may also be important.[274,275] Several autoantibodies associated with chronic HDV infection may play a role in propagating liver disease and could partially explain the differences in disease severity observed in persons with CHB/HDV coinfection compared to those with only CHB monoinfection. Furthermore, coinfection with CHB and HDV results in an increased risk of HCC and mortality compared to CHB monoinfection.[277–281]

Diagnosis and Serology

Quantitative measurement of the HDV RNA level by reverse transcription polymerase chain reaction (RT-PCR) confirms the presence of HDV and is currently the most accurate diagnostic tool available.[273,274] ELISA and radioimmunoassay tests for IgM anti-HDV are also commercially available. Measurement of anti-HDV is generally not useful for early diagnosis because detectable antibody levels are usually achieved late in the clinical course of the infection. Anti-HDV IgM is detectable before anti-HDV IgG in acute HDV coinfection and is diagnostic for acute HDV infection. Anti-HDV IgM levels are not sustained in self-limiting HDV infection but may persist in patients with chronic HDV infection. Also, anti-HDV IgM does not distinguish coinfection (HBV and HDV acquired simultaneously) from superinfection (HDV acquired in CHB carriers).

Differentiation between coinfection and superinfection is made by the presence or absence of anti-HBc IgM. In acute coinfection, serum anti-HDV IgM and HDV RNA appear together with anti-HBc IgM. On the other hand, in patients with superinfection, HDV biomarkers are present in the absence of anti-HBc IgM. The presence and titer level of anti-HDV, in the case of persistent infection, also correlate with the severity of the disease. Titers of anti-HDV IgG >1:1000 indicate ongoing viral replication.[275]

HDV antigen is present in the serum in the late incubation period of acute infection and lasts into the symptomatic phase in up to 20% of patients. Because this antigen is transient, repeat testing may be

required to detect its presence. HDV RNA is an early marker of infection in patients with both acute and chronic HDV infection.[273],[274] HDV RNA is detectable in 90% of patients during the symptomatic phase of HDV infection. HDV RNA levels are not detectable after symptomatic resolution but remain elevated in chronic infection.

Natural History

Coinfection with HDV and CHB is correlated with a higher risk of severe or fulminant liver disease than with any other human viral hepatitis.[275],[282] The rate of chronic disease after coinfection with HDV is similar to that of CHB infection alone, whereas superinfection with HDV is linked to a high rate of chronicity; however, the clinical course may be variable. Approximately 15% of patients superinfected with HDV develop rapidly progressive disease with hepatic decompensation or cirrhosis within 12 months of the infection. Another 15% of patients have a benign course of illness. Most patients (70%) have a slow progression to cirrhosis depending on age, injection drug use, and level of viral replication.[275] Finally, HBsAg-positive, HBeAg-positive patients who are superinfected with HDV are more likely to develop fulminant disease compared to those who are HBsAg-positive, anti-HBe, and are superinfected and develop chronic disease.[275],[282]

Prevention

HDV replication is dependent on HBV replication; therefore, successful immunization with HBV vaccine also prevents HDV infection.[267–269] No immunoprophylactic therapies are available for patients with CHB infection who are also at risk for superinfection with HDV. Prevention of HDV superinfection is based on behavioral modification, such as the use of condoms to prevent sexual transmission and use of needle exchange programs to minimize transmission by injection drug use.

Treatment

Currently, there is no FDA-approved treatment for HDV infection in the United States. The only treatment option available for chronic HDV infection is PegIFN, which has limited efficacy and a significant adverse effect profile (eg, flu-like symptoms, myalgias, and arthralgias).[88,121,283] On the other hand, bulevirtide is the first antiviral agent studied against CHB/HDV coinfected persons in Europe. It is an entry inhibitor that binds to and inactivates the human sodium taurocholate cotransporting polypeptide (NTCP) surface receptors. The NTCP surface receptors are found on the hepatocytes and serve as essential HBV and HDV entry receptors. As a result, bulevirtide prevents HBV and HDV from entering the hepatocytes. It was approved in July 2020 by the European Medicines Agency, the European equivalent of the FDA, as the first antiviral treatment for persons with HDV infection.

Bulevirtide was approved as 2 mg to be self-administered as a once-daily SQ injection with or without nucleoside/nucleotide analogs, such as TDF.[283,284] A more recent study was performed evaluating the efficacy and safety of high-dose bulevirtide (5 mg bid or 10 mg daily) as monotherapy or in combination with TDF or PegIFN. The study findings showed that monotherapy of bulevirtide 10 mg achieved a continuous HDV RNA decline and is generally safe and well tolerated. There was also strong synergistic antiviral activity observed when bulevirtide was given with PegIFN against HDV.[284] The potential promise of bulevirtide as an effective antiviral has paved the way for the development of other future investigational drugs against chronic HDV infection, such as peginterferon λ-1a, nucleic acid polymers, and viral assembly inhibitors. The goal of treatment is to eradicate HDV along with HBV. HDV is eradicated when both serum HDV RNA and HDV antigen in the liver become persistently undetectable. Notably, it is only when HBsAg clearance has taken place that complete clinical resolution occurs. Supportive care is the general strategy used to treat HDV infection. Because the development of FHF is more frequent with

HDV infection, close monitoring for evidence of severe liver failure is warranted.

In patients with decompensated cirrhosis caused by HDV, liver transplantation is the most appropriate intervention because PegIFN may precipitate hepatic decompensation.[285–288] The presence and amount of HBV DNA before transplantation is the most significant outcome marker, often predicting the posttransplant reinfection rate. Patients who receive a liver transplant for chronic HDV infection have a lower incidence of posttransplant HBV infection than do those with HBV infection alone (67% vs 32%, respectively).[287,288] This is thought to be related to an inhibitory effect of HDV on HBV replication. Furthermore, 3-year survival is higher for patients with HDV cirrhosis than that for patients undergoing transplantation for HBV cirrhosis alone (88% vs 44%, respectively) and is similar to that of patients having liver transplantation for other indications.[122–124]

HEPATITIS E VIRUS

Virology, Epidemiology, Transmission, and Pathogenesis

HEV is an icosahedral, nonenveloped virus of the Hepeviridae family (see Table 80-1). The HEV genome is a single-stranded polyadenylated RNA and, unlike HAV, has an RNA genome that encodes for NS proteins through overlapping open reading frames.[289,290] HEV sequences have been classified into four genotypes (1, 2, 3, and 4). Genotype 1 consists of epidemic strains in developing countries; genotype 2 has been found in Mexico; genotype 3 has been associated with acute cases of hepatitis and with domestic pigs in the United States, European countries, and Japan; and genotype 4 has been found in Asian countries.[291–294]

HEV occurs in endemic areas such as Africa, Southeast and Central Asia, Mexico, and Central and South America as both

epidemic and sporadic infections.[292],[293],[295],[296] Sporadic infections also occur in nonendemic areas and are usually associated with travel into areas of endemicity. The attack rate (the percentage of exposed patients who become infected) of HEV is low compared with HAV (1% vs 10%, respectively). In endemic areas, outbreaks usually occur between 5 and 10 years apart and are often associated with times of heavy rainfall, after floods or monsoons, or after the recession of flood waters.[294–296] The overall case fatality rate for the general endemic population is 0.5% to 4%, whereas for reasons unknown, pregnant patients have a much greater case fatality rate of 20%.[188] In particular, the fetal complication rate is increased, especially if the infection occurs in the third trimester of pregnancy. The frequency of death in utero and immediately after birth is also greater than that seen with acute hepatitis of other causes.[188]

Transmission of HEV is via the fecal–oral route, and the most common source of transmission is ingestion of fecally contaminated water.[295],[296] Poor climatic conditions in conjunction with inadequate personal hygiene and sanitation have led to epidemics of HEV infection. Additional routes of transmission include vertical and bloodborne transmission, as well as consuming raw or undercooked meat of infected animals such as boar or deer and domestic animals such as pigs.[292],[293]

Interference with the production of cellular macromolecules, alteration of cellular membranes, and alteration of lysosomal permeability are some of the proposed mechanisms of hepatic injury.[291],[293] In addition, immune-mediated mechanisms are believed to be responsible for lysis of virally infected hepatocytes by direct lymphocyte cytotoxicity or antibody-mediated cytotoxicity.

Diagnosis

Initial assays for detection of anti-HEV included electron microscopy to detect HEV antigen on the surface of HEV particles in the stool and serum and immunohistochemistry to detect the antigen in liver

tissue.[291],[293],[294] Fluorescent antibody-blocking assay is currently used to detect anti-HEV reacting to the HEV antigen in serum, but although highly specific, this assay lacks sensitivity (50%) in acute HEV infection.[291],[293],[294] Additional cloning and sequencing of HEV have led to the development of Western blot assays and ELISA that detect anti-HEV using recombinant expressed proteins from the structural region of the virus. RT-PCR has also been used to confirm the diagnosis of HEV by detecting HEV RNA from serum, liver, or stool.[291],[293],[294] Clinically, HEV is a diagnosis of exclusion.

Clinical Manifestations and Natural History

Typical HEV clinical symptoms include jaundice, dark urine, tender and enlarged liver, elevated liver enzymes, abdominal pain, nausea, vomiting, and fever. Protracted coagulopathy and cholestasis have also been reported in more severe cases, possibly related to genotype 4.[291–293] Two phases of illness exist, including a prodromal and preicteric phase. Peak serum aminotransferase levels reflect the onset of the icteric phase and generally return to baseline by 6 weeks.[291–293] Stool is often positive for HEV RNA at the onset of the icteric phase and persists for an additional 10 days beyond this period. Viral shedding may occur for up to 52 days after the onset of icterus. Detection in the serum occurs during the preicteric phase before detection of virus in the stool and becomes undetectable after the peak in aminotransferase activity. Because HEV RNA is not detectable in the serum during symptoms, diagnostic tests using HEV RNA have limited utility, and a correlation between PCR detection and infectivity has not been observed. Serologically, HEV IgM becomes detectable before the peak rise in ALT, whereas antibody titers peak with high ALT levels and subsequently decline. In most patients, HEV IgM is present for 5 to 6 months after the onset of illness. HEV IgG appears after HEV IgM and remains detectable for up to 14 years after acute infection. However, the duration of protective immunity has not been fully elucidated.[291–294] In nonfatal cases, acute HEV hepatitis is followed by complete recovery

without any chronic complications. There is protection from reinfection; however, the duration of protection is variable.

Prevention and Treatment

Currently, there are no immunoprophylactic measures for HEV disease, and effective prevention strategies are dependent on improved sanitation in endemic areas. Travelers going to endemic areas should be educated regarding the risks of drinking water, eating ice, or eating uncooked shellfish or uncooked and peeled fruits and vegetables. Drinking water should be boiled to inactivate HEV. No vaccines or postexposure prophylaxis treatments are available to prevent HEV infection.

IMMUNIZATIONS FOR PERSONS WITH VIRAL HEPATITIS

Hepatitis A Vaccines

HAV infection is generally self-limiting in healthy individuals. However, persons with CHC infection are more likely to develop severe manifestations of acute HAV infection. Therefore, they should receive the hepatitis A vaccine if they do not have immunity to HAV.[297] Hepatitis A immunization could be completed in a two-dose, single hepatitis A antigen vaccine (Havrix®, Vaqta®) or as a three-dose hepatitis A/B combination vaccine (Twinrix®).[34,36] It is not recommended to check postvaccination hepatitis A titers because of the very high response to hepatitis A vaccine.

Hepatitis B Vaccines

All persons with CHC infection should receive hepatitis B vaccine, unless they have immunity to hepatitis B or are chronically infected

with hepatitis B. There are a few vaccine options available including the three-dose series using recombinant HBV vaccines (Engerix-B®, Recombivax HB®), the two-dose hepatitis B vaccine series using the CpG 1018 adjuvant that can be completed in 1 month (Heplisav-B®), and a three-dose series hepatitis A/B combination vaccine (Twinrix®).[34,51]

Pneumococcal Vaccines

Persons ages 19 through 64 years with chronic liver disease should receive one dose of the 23-valent polysaccharide pneumococcal vaccine (PPSV23).[34] Adults ages 65 years and older, including those with liver disease, should receive one dose of pneumococcal conjugate vaccine (PCV13) and a dose of PPSV23, with the dose of PPSV23 given at least 1 year after the PCV13 and at least 5 years after any previous dose of PPSV23 they may have received.[34] Vaccine options for PCV13 and PPSV23 include Pneumovax 23® and Prevnar 13®, respectively. PCV13 and PPSV23 vaccines are typically spaced 1 year apart. ACIP does not have current recommendations for giving PCV13 specifically for chronic liver disease.

Other Adult Routine Vaccines

Adults with CHB and CHC infections should continue receiving the standard routine vaccinations, such as the annual influenza and a one-time tetanus diphtheria acellular pertussis (Tdap) or tetanus diphtheria (Td) booster every 10 years. If age 50 or older, Zoster vaccination is recommended. Depending on the comorbidities of the persons with viral hepatitis infection, there may be additional immunizations that should be considered. For example, *Haemophilus influenzae* type b (Hib), meningococcal ACWY (MenACWY), and meningococcal B (MenB) vaccines should be administered in persons with a high-risk condition such as asplenia.

SUMMARY

Viral hepatitis continues to be a significant infectious disease burden globally. To date, prevention strategies through universal vaccination are the most effective methods for minimizing the incidence of HAV, HBV, and HDV coinfected with HBV infections. Patient education about the common ways of spreading these infections may also result in behavioral modifications that could reduce the overall incidence of infection. Once HBV and HCV progress to chronic infection stage, more efficacious and better-tolerated antiviral therapies are required to treat these infections. Similarly, therapeutic modalities that reduce the progression of these infections are necessary to prevent end-stage liver disease and the development of additional complications (eg, encephalopathy, intractable ascites, coagulation disorders, and HCC). Newer therapeutic agents are becoming available as better understanding of viral replication is established, as well as appropriate models for viral hepatitis study. Furthermore, viral kinetics and genomic-based approaches could optimize responses to drug therapies, especially in CHB- and CHC-infected persons. The economic impact and quality of life of these newer antiviral therapeutics on this population and the health care system remain to be fully elucidated.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and website for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

AASLD/IDSA HCV Guidance Panel. Recommendations for testing, managing, and treating hepatitis C. Updated August 27, 2020 [Internet]. 2020 [cited August 27, 2020]. http://hcvguidelines.org/ (147)

Aggarwal R. Hepatitis E: historical, contemporary and future perspectives. *J Gastroenterol Hepatol.* 2011;26(Suppl 1):72–82. (289)

Au JS, Pockros PJ. Novel therapeutic approaches for hepatitis C. *Clin Pharmacol Ther.* 2014;95(*1*):78–88. (244)

European Association for the Study of the Liver (EASL). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67(*2*):370–398. (121)

Kroger A, Bahta L, Hunter P. General best practice guidelines for immunization. Best practices guidance of the Advisory Committee on Immunization Practices (ACIP). https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf (34)

Koh C, Da BL, Glenn JS. HBV/HDV coinfection: emerging therapeutic options for a challenging disease. *Clin Liver Dis*. 2019;23(*3*):557–572. (283)

Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology.* 2018;67(*4*):1560–1599. (88)

Zoulim F, Durantel D. Antiviral therapies and prospects for a cure of chronic hepatitis B. *Cold Spring Harb Perspect Med*. 2015;5(*4*):a021501. (221)

Key Website

American Association for the Study of Liver Diseases (AASLD). http://www.aasld.org

COMPLETE REFERENCES CHAPTER 80 VIRAL HEPATITIS

1. Alter MJ, Mast EE. The epidemiology of viral hepatitis in the United States. *Gastroenterol Clin North Am*. 1994;23:437–455.
2. Kudo M. Viral hepatitis A to E: an update in 2010. *Intervirology*. 2010;53:5–9.
3. Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin Liver Dis*. 2010;14:1–21.
4. Davis S. Chronic hepatitis. In: Kaplowitz N, ed. *Liver and Biliary Diseases*. 2nd ed. Williams & Wilkins; 1996:327.
5. Nelson KE, Thomas DL. Viral hepatitis. In: *Infectious Disease Epidemiology*. 2nd ed. Jones and Bartlett; 2007.

6. Døssing M, Sonne J. Drug-induced hepatic disorders. Incidence, management and avoidance. *Drug Saf*. 1993;9:441–449.
7. Hoofnagle JH, Di Bisceglie AM. Therapy of chronic delta hepatitis: overview. *Prog Clin Biol Res*. 1993;382:337–343.
8. Maddrey WC, Boitnott JK. Severe hepatitis from methyldopa. *Gastroenterology*. 1975;68:351–360.
9. Black M, Rabin L, Schatz N. Nitrofurantoin-induced chronic active hepatitis. *Ann Intern Med*. 1980;92:62–64.
10. Maddrey WC, Boitnott JK. Isoniazid hepatitis. *Ann Intern Med*. 1973;79:1–12.
11. Tönder M, Nordoy A, Elgio K. Sulfonamide-induced chronic liver disease. *Scand J Gastroenterol*. 1974;9:93–96.
12. Weiss M, Hassin D, Bank H. Propylthiouracil-induced hepatic damage. *Arch Intern Med*. 1980;140:1184–1185.
13. Shapiro CN, Margolis HS. Worldwide epidemiology of hepatitis A infection. *J Hepatol*. 1993;18 Suppl 2:S11–S14.
14. Melnick J. History and epidemiology of hepatitis A virus. *J Infect Dis*. 1995;171 (Suppl 1):S2–S8.
15. Gilroy RK. Hepatitis A. Medscape, 2016. Accessed July 12, 2017. https://emedicine.medscape.com/article/177484-overview#a3.
16. Cuthbert JA. Hepatitis A: old and new. *Clin Microbiol Rev*. 2001;14:38–58.
17. Hollinger FB, Martin A. Hepatitis A virus. In: Knipe DM, Howley PM, eds. *Fields Virology*. 6th ed. Lippincott Williams & Wilkins; 2013:550–581.
18. Phan C, Hollinger B. Hepatitis A: natural history, immunopathogenesis, and outcome. *Clin Liver Dis*. 2013;2:231–234.
19. Centers for Disease Control and Prevention. *Viral hepatitis surveillance—United States, 2019*. US Department of Health and Human Services, Centers for Disease Control and Prevention; 2021. Accessed September 13, 2021. https://www.cdc.gov/hepatitis/statistics/2019surveillance/index.htm
20. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the advisory committee on immunization practices, 2020. *MMWR Recomm Rep*. 2020;69:1–38.
21. Sheretz RJ, Russell BA, Reuman PD. Transmission of hepatitis A by transfusion of blood products. *Arch Intern Med*. 1984;144:1579–1580.
22. Steffen R, Kane MA, Shapiro CN, Billo N, Schoellhorn KJ, van Damme P. Epidemiology and prevention of hepatitis A in travelers. *JAMA*. 1994;272:885–889.
23. Mackiewicz V, Dussaix E, Le Petitcorps MF, Roque-Afonso AM. Detection of hepatitis A virus RNA in saliva. *J Clin Microbiol*. 2004;42:4329–4331.
24. Lemon SM, Murphy PC, Provost PJ, et al. Immunoprecipitation and virus neutralization assays demonstrate qualitative differences between protective antibody responses to inactivated hepatitis A vaccine and passive immunization with immune globulin. *J Infect Dis*. 1997;176:9–19.

Brundage SC, Fitzpatrick AN. Hepatitis A. *Am Fam Physician*.
25. 2006;73:2162–2168.
26. Klotz U, Avant GR, Hoyumpa A, Schenker S, Wilkinson GR. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J Clin Invest*. 1975;55:347–359.
27. Kraus JW, Desmond PV, Marshall JP, Johnson RF, Schenker S, Wilkinson GR. Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther*. 1978;24:411–419.
28. Blascke TF, Meffin PJ, Melmon KL, Rowland M. Influence of acute viral hepatitis on phenytoin kinetics and protein binding. *Clin Pharmacol Ther*. 1975;17:685–691.
29. Lu PJ, Euler GL, Hennessey KA, Weinbaum CM. Hepatitis A vaccination coverage among adults aged 18–49 years in the United States. *Vaccine*. 2009;27:1301–1305.
30. Nelson NP. Updated dosing instructions for immune globulin (human) GamaSTAN S/D for hepatitis A virus prophylaxis. *MMWR Morb Mortal Wkly Rep*. 2017;66:959–960.
31. American Academy of Pediatrics Committee on Infectious Diseases. Hepatitis A vaccine recommendations. *Pediatrics*. 2007;120:189–199.
32. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hall E, Wodi AP, Hamborsky J, et al. eds. 14th ed. Washington, D.C. Public Health Foundation, 2021. https://www.cdc.gov/vaccines/pubs/pinkbook/hepa.html
33. Craig AS, Schaffner W. Prevention of hepatitis A with the hepatitis A vaccine. *N Engl J Med*. 2004;350:476–481.
34. Kroger A, Bahta L, Hunter P. General best practice guidelines for immunization. Best practices guidance of the Advisory Committee on Immunization Practices (ACIP). Accessed September 19, 2020. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf
35. Dienstag JL. Hepatitis B virus infection. *N Engl J Med*. 2008;359:1486–1500.
36. Liang TJ. Hepatitis B: the virus and disease. *Hepatology*. 2009;49(5 Suppl):S13–S21.
37. Lok A, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50:661–662.
38. Doo EC, Ghany MG. Hepatitis B virology for clinicians. *Clin Liver Dis*. 2010;14:397–408.
39. CDC. *Pinkbook: HBV*. August 30, 2020. https://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html
40. CDC. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Morb Mortal Wkly Rep*. 2008;57(RR-8):9–11.

41. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. *N Engl J Med*. 2004;350:1118–1129.
42. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology*. 2007;45:507–539.
43. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology*. 2007;45:1056–1075.
44. CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the united states. 2006. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5516a1.htm?s_cid=rr5516a1_e
45. Dienstag JL, Isselbacher KJ. Acute viral hepatitis. In: Kasper DL, Braunwald E, Hauser S, Longo D, Jameson JL, Fauci A, eds. *Harrison's Principles of Internal Medicine*. 16th ed. Vol. 2. McGraw-Hill; 2005:1822–1838.
46. Sorrell MF, Belongia EA, Costa J, et al. National Institutes of Health consensus development conference statement: management of hepatitis B. *Hepatology*. 2009;49(5, Suppl):S4.
47. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2007;56:1114]. *MMWR Recomm Rep*. 2006;55(RR-16):1–33; quiz CE1–4.
48. Kim WR. Epidemiology of hepatitis B in the United States. *Hepatology*. 2009;49(5 Suppl):S28.
49. Chang JJ, Lewin SR. Immunopathogenesis of hepatitis B infection. *Immunol Cell Biol*. 2007;85:16–23.
50. Bond WW, Favero MS, Petersen NJ, Gravelle CR, Ebert JW, Maynard JE. Survival of hepatitis B virus after drying and storage for one week. *Lancet*. 1981;317:550–551.
51. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67:1–31.
52. Bertoletti A, Gehring AJ. The immune response during hepatitis B infection. *J Gen Virol*. 2006;87(Pt 6):1439–1449.
53. Valsamakis A. Molecular testing in the diagnosis and management of chronic hepatitis B. *Clin Microbiol Rev*. 2007;20:426–439.
54. Vivekanandan P, Singh OV. Molecular methods in the diagnosis and management of chronic hepatitis B. *Expert Rev Mol Diagn*. 2010;10:921–935.
55. Deny P, Zoulim F. Hepatitis B virus: from diagnosis to treatment. *Pathol Biol (Paris)*. 2010;58:245–253.
56. Allain JP. Occult hepatitis B virus infection. *Transfus Clin Biol*. 2004;11:18–25.

57. Bowden S. Serological and molecular diagnosis. *Semin Liver Dis*. 2006;26:97–103.
58. Lee WM. Etiologies of acute liver failure. *Semin Liver Dis*. 2008;28:142–152.
59. Chan HL, Sung JJ. Hepatocellular carcinoma and hepatitis B virus. *Semin Liver Dis*. 2006;26:153–161.
60. Lai M, Liaw YF. Chronic hepatitis B: past, present, and future. *Clin Liver Dis*. 2010;14:531–546.
61. Polson J, Lee WM; American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology*. 2005;41:1179–1197.
62. Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. *Liver Transpl*. 2008;14(Suppl 2):S67–S79.
63. Craig DG, Lee A, Hayes PC, Simpson KJ. Review article: the current management of acute live failure. *Aliment Pharmacol Ther*. 2010;31:345–358.
64. Lidofsky SD, Bass NM, Prager MC, et al. Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. *Hepatology*. 1992;16:1–7.
65. Larsen FS, Wendon J. Brain edema in liver failure: basic physiologic principles and management. *Liver Transpl*. 2002;8:983–989.
66. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. *Lancet*. 2010;376:190–201.
67. Munoz SJ. The hepatorenal syndrome. *Med Clin North Am*. 2008;92:813–837.
68. Dhiman RK, Jain S, Maheshwari U, et al. Early indicators of prognosis in fulminant hepatic failure: an assessment of the Model for End-Stage Liver Disease (MELD) and King's College Hospital criteria. *Liver Transpl*. 2007;13:814–821.
69. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus infected patients. *Hepatology*. 1999;30:1302–1306.
70. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med*. 2007;356:2614–2621.
71. US Department of Health and Human Services. Panel on Antiretroviral Guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Accessed September 22, 2020. https://aidsetc.org/resource/guidelines-use-antiretroviral-agents-hiv-1-infected-adults-and-adolescents
72. Food and Drug Administration. *Product Approval Information: Package Insert. Heplisav-B*. US Department of Health and Human Services, Food and Drug Administration; 2018. Accessed September 22, 2020. https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm584752.htm

73. Recombivax HB (hepatitis Bvaccine). Package insert. Merck and Company; 1998.
74. Engerix-B (hepatitis B vaccine). Package insert. Smith Kline Beecham Pharmaceuticals; 1998.
75. Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *N Engl J Med*. 1980;303:833–841.
76. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med*. 1986;315:209–214.
77. Goldwater PN. Randomized, comparative trial of 20 micrograms vs 40 micrograms Engerix B vaccine in hepatitis B vaccine non-responders. *Vaccine*. 1997;15:353–356.
78. Heyward WL, Kyle M, Blumenau J, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared to a licensed hepatitis B vaccine in healthy adults 40–70 years of age. *Vaccine*. 2013;31:5300–5305.
79. Jackson S, Lentino J, Kopp J, et al; HBV-23 Study Group. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. *Vaccine*. 2018;36:668–674.
80. West DJ, Calandra GB. Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccination. *Vaccine*. 1996;14:1019–1027.
81. Chan CY, Lee SD, Tsai YT, Lo KJ. Booster response to recombinant yeast derived hepatitis B vaccine in vaccinees whose anti-HBs responses were initially elicited by a plasma-derived vaccine. *Vaccine*. 1991;9:765–767.
82. Wainwright RB, Bulkow LR, Parkinson AJ, Zanis C, McMahon BJ. Protection provided by hepatitis B vaccine in a Yupik Eskimo population—results of a 10-year study. *J Infect Dis*. 1997;175:674–677.
83. Resti M, Azzari C, Mannelli F, Rossi ME, Lionetti P, Vierucci A. Ten-year follow-up study of neonatal hepatitis B immunization: are booster injections indicated? *Vaccine*. 1997;15:1338–1340.
84. Yuen MF, Lim WL, Cheng CC, Lam SK, Lai CL. Twelve-year follow-up of a prospective randomized trial of hepatitis B recombinant DNA yeast vaccine versus plasma-derived vaccine without booster doses in children. *Hepatology*. 1999;29:924–927.
85. Huang LM, Chiang BL, Lee CY, Lee PI, Chi WK, Chang MH. Long-term response to hepatitis B vaccination and response to booster in children born to mothers with hepatitis B e antigen. *Hepatology*. 1999;29:954–959.
86. Redeker AG, Mosley JW, Gocke DJ, McKee AP, Pollack W. Hepatitis B immune globulin as a prophylactic measure for spouses exposed to acute type B hepatitis. *N Engl J Med*. 1975;293:1055–1059.

87. Hollinger F, Lau DT. Hepatitis B: the pathway to recovery through treatment. *Gastroenterol Clin North Am*. 2006;35:895–931.
88. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560–1599.
89. Saravolatz LD, Bhattacharya D, Thio CL. Review of hepatitis B therapeutics. *Clin Infect Dis*. 2010;51:1201–1208.
90. Hynicka LM, Yunker N, Patel PH. A review of oral antiretroviral therapy for the treatment of chronic hepatitis B. *Ann Pharmacother*. 2010;44:1271–1286.
91. Rijckborst V, Sonneveld MJ, Janssen HL. Review article: chronic hepatitis B —antiviral or immunomodulatory therapy? *Aliment Pharmacol Ther*. 2011;33:501–513.
92. Lau GK. Current treatments for patients with HBeAg-positive chronic hepatitis B virus infection: a comparison focusing on HBeAg seroconversion. *Liver Int*. 2010;30: 512–520.
93. Perrillo R. Benefits and risks of interferon therapy for hepatitis B. *Hepatology*. 2009;49(5 Suppl):S103–S11.
94. Lau GKK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2005;352:2682–2695.
95. Janssen HLA, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet*. 2005;365:123–129.
96. Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2004;351:1206–1217.
97. Doong SL, Tsai CH, Schinazi RF, Liotta DC, Cheng YC. Inhibition of the replication of hepatitis B virus in vitro by 2′,3′-dideoxy-3′-thiacytidine and related analogues. *Proc Natl Acad Sci USA*. 1991;88:8495–8499.
98. Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology*. 2003;124:105–117.
99. Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med*. 1999;341:1256–1263.
100. Ghany MG, Doo EC. Antiviral resistance and hepatitis B therapy. *Hepatology*. 2009;49(5 Suppl):S174–S184.
101. Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. *Gastroenterology*. 2009;137:1593–1608.e1–2.
102. Dando T, Plosker G. Adefovir dipivoxil: a review of its use in chronic hepatitis B. *Drugs*. 2003;63:2215–2234.
103. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med*. 2003;348:800–807.

104. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med*. 2003;348:808–816.
105. Scott LJ, Keating GM. Entecavir: a review of its use in chronic hepatitis B. *Drugs*. 2009;69:1003–1033.
106. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2006;354:1001–1010.
107. Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2006;354:1011–1020.
108. Colonno RJ, Rose R, Baldick CJ, et al. Entecavir resistance is rare in nucleoside naive patients with hepatitis B. *Hepatology*. 2006;45:1656–1665.
109. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology*. 2009;49:1503–1514.
110. Gish RG, Lok AS, Chang TT, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology*. 2007;133:1437–1444.
111. Chang TT, Lai CL, Kew Yoon S, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology*. 2010;51:422–430.
112. Shim J, Suh DJ, Kim KM, et al. Efficacy of entecavir in patients with chronic hepatitis B resistant to both lamivudine and adefovir or to lamivudine alone. *Hepatology*. 2009;50:1064–1071.
113. Govan L, Wu O, Xin Y, Hutchinson SJ, Hawkins N. Comparative effectiveness of antiviral treatment for hepatitis B: a systematic review and Bayesian network meta-analysis. *Eur J Gastroenterol Hepatol*. 2015;27(8):882–894.
114. Perry CM, Simpson D. Tenofovir disoproxil fumarate: In chronic hepatitis B. *Drugs*. 2009;69:2245–2256.
115. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med*. 2008;359:2442–2455.
116. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology*. 2010;139:1218–1229.
117. VEMLIDY(R) oral tablets, tenofovir alafenamide oral tablets. Product information. Gilead Sciences, Inc (per manufacturer); 2016.
118. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1:196–206.

119. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1:185–195.
120. Terrault NA. Benefits and risks of combination therapy for hepatitis B. *Hepatology*. 2009;49(5, Suppl):S122.
121. European Association for the Study of the Liver (EASL). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370–398.
122. Beckebaum S, Sotiropoulos GC, Gerken G, Cicinnati VR. Hepatitis B and liver transplantation: 2008 update. *Rev Med Virol*. 2009;19:7–29.
123. Samuel D. The option of liver transplantation for hepatitis B: where are we? *Dig Liver Dis*. 2009;41(Suppl 2):S185–S189.
124. Katz LH, Paul M, Guy DG, Tur-Kaspa R. Prevention of recurrent hepatitis B virus infection after liver transplantation: hepatitis B immunoglobulin, antiviral drugs, or both? Systematic review and metaanalysis. *Transplant Infect Dis*. 2010;12:292–308.
125. Angus PW, Patterson SJ. Liver transplantation for hepatitis B: what is the best hepatitis B immune globulin/antiviral regimen? *Liver Transpl*. 2008;14(Suppl 2):S15–S22.
126. Saab S, Desai S, Tsaoi D, et al. Posttransplantation hepatitis B prophylaxis with combination oral nucleoside and nucleotide analog therapy. *Am J Transplant*. 2011;11:511–517.
127. Zeng QL, Yu ZJ, Ji F, et al. Tenofovir alafenamide to prevent perinatal hepatitis B transmission: a multicenter, prospective, observational study. *Clin Infect Dis*. 2021;73(9):e3324–e3332.
128. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*. 1989;244:359–362.
129. Bartenschlager R, Penin F, Lohmann V, André P. Assembly of infectious hepatitis C virus particles. *Trends Microbiol*. 2011;19:95–103.
130. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis*. 2000;20:17–35.
131. Scheel TK, Rice CM. Understanding the hepatitis C virus life cycle paves the way for highly effective therapies. *Nat Med*. 2013;19:837–849.
132. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management and treatment of hepatitis C: an update. *Hepatology*. 2009;49:1335–1374.
133. Seeff LB. The history of the “natural history” of hepatitis C (1968–2009). *Liver Int*. 2009;29(Suppl 1):89–99.
134. Chevaliez S, Pawlotsky JM. Hepatitis C virus: virology, diagnosis, and management of antiviral therapy. *World J Gastroenterol*. 2007;13:2641–

2466.
135. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol*. 2014;61:S45–S57.
136. Kershenobich D, Razavi HA, Sánchez-Avila JF, et al. Trends and projections of hepatitis C virus epidemiology in Latin America. *Liver Int*. 2011;31:18–29.
137. Cornberg M, Razavi HA, Alberti A, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada, and Israel. *Liver Int*. 2011;31:30–60.
138. Sievert W, Altraif I, Razavi HA, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia, and Egypt. *Liver Int*. 2011;31:61–80.
139. Hope VD, Eramova I, Capurro D, Donoghoe MC. Prevalence and estimation of hepatitis B and C infections in the WHO European Region: a review of data focusing on the countries outside the European Union and the European Free Trade Association. *Epidemiol Infect*. 2014;142:270–286.
140. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61:77–87.
141. Legrand-Abravanel F, Sandres-Sauné K, Barange K, et al. Hepatitis C virus genotype 5: epidemiological characteristics and sensitivity to combination therapy with interferon-alpha plus ribavirin. *J Infect Dis*. 2004;189: 1397–400.
142. Nguyen NH, Vutien P, Trinh HN, et al. Risk factors, genotype 6 prevalence, and clinical characteristics of chronic hepatitis C in Southeast Asian Americans. *Hepatol Int*. 2010;4:523–529.
143. Ryerson AB, Schillie S, Barker LK, Kupronis BA, Wester C. Vital signs: newly reported acute and chronic hepatitis C cases—United States, 2009–2018. *MMWR Morb Mortal Wkly Rep*. 2020;69:399–404.
144. Williams IT, Bell BP, Kuhnert W, Alter MJ. Incidence and transmission patterns of acute hepatitis C in the United States, 1982–2006. *Arch Intern Med*. 2011;171:242–248.
145. Wilkins T, Malcolm JK, Raina D, Schade RR. Hepatitis C: diagnosis and treatment. *Am Fam Physician*. 2010;81:1351–1357.
146. Bartenschlager R, Cosset FL, Lohmann V. Hepatitis C virus replication cycle. *J Hepatol*. 2010;53:583–585.
147. AASLD/IDSA HCV Guidance Panel. Recommendations for testing, managing, and treating hepatitis C. Updated August 27, 2020 [Internet]. 2020 [cited August 27, 2020]. Accessed October 1, 2020. http://hcvguidelines.org/
148. Chirikov VV, Marx SE, Manthena SR, Strezewski JP, Saab S. Development of a comprehensive dataset of hepatitis C patients and examination of disease epidemiology in the United States, 2013–2016. *Adv Ther*. 2018;35:1087–1102.
149. Chung RT. Acute hepatitis C virus infection. *Clin Infect Dis*. 2005;41 Suppl 1:S14–S17.
150. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. *Lancet*. 2008;372:321–332.

151. Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology*. 2003;125:80–88.
152. Hajarizadeh B, Grebely J, Dore GJ. Case definitions for acute hepatitis C virus infection: a systematic review. *J Hepatol*. 2012;57:1349–1360.
153. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000;284: 450–456.
154. Missiha SB, Ostrowski M, Heathcote EJ, et al. Disease progression in chronic hepatitis C: modifiable and nonmodifiable factors. *Gastroenterology*. 2008;134:1699–1714.
155. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol*. 2001;34:730–739.
156. Ryder SD, Irving WL, Jones DA, Neal KR, Underwood JC; Trent Hepatitis C Study Group. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. *Gut*. 2004;53:451–455.
157. Thomas DL, Seeff LB. Natural history of hepatitis C. *Clin Liver Dis*. 2005;9:383–398.
158. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat*. 2006;13:34–41.
159. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009;461:798–801.
160. Friedman SL. Evolving challenges in hepatic fibrosis. *Nat Rev Gastroenterol Hepatol*. 2010;7:425–436.
161. Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol*. 2011;6:425–456.
162. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology*. 2017;153:996–1005.e1.
163. Hui JM, Sud A, Farrell GC, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterology*. 2003;125:1695–1704.
164. Ishida JH, Peters MG, Jin C, et al. Influence of cannabis use on severity of hepatitis C disease. *Clin Gastroenterol Hepatol*. 2008;6:69–75.
165. Jamma S, Hussain G, Lau DT. Current concepts of HBV/HCV coinfection: coexistence, but not necessarily in harmony. *Curr Hepat Rep*. 2010;9:260–269.
166. Hezode C, Zafrani ES, Roudot-Thoraval F, et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. *Gastroenterology*. 2008;134:432–439.

167. Chen CM, Yoon YH, Yi HY, Lucas DL. Alcohol and hepatitis C mortality among males and females in the United States: a life table analysis. *Alcohol Clin Exp Res*. 2007;31:285–292.
168. Fartoux L, Chazouillères O, Wendum D, Poupon R, Serfaty L. Impact of steatosis on progression of fibrosis in patients with mild hepatitis C. *Hepatology*. 2005;41:82–87.
169. Benvegnu L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut*. 2004;53:744–749.
170. Dustin LB. Too low to measure, infectious nonetheless. *Blood*. 2012;119: 6181–6182.
171. McGovern BH, Birch CE, Bowen MJ, et al. Improving the diagnosis of acute hepatitis C virus infection with expanded viral load criteria. *Clin Infect Dis*. 2009;49:1051–1060.
172. Glynn SA, Wright DJ, Kleinman SH, et al. Dynamics of viremia in early hepatitis C virus infection. *Transfusion*. 2005;45:994–1002.
173. Mondelli MU, Cerino A, Cividini A. Acute hepatitis C: diagnosis and management. *J Hepatol*. 2005;42(Suppl 1):S108–S114.
174. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011;54:1433–1444.
175. Boursier J, de Ledinghen V, Zarski JP, et al; multicentric groups from SNIFF 32, VINDIAG 7, and ANRS/HC/EP23 FIBROSTAR studies. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. *Hepatology*. 2012;55:58–67.
176. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. *Gastroenterology*. 2012;142:1293–1302.e4.
177. Duarte-Rojo A, Altamirano JT, Feld JJ. Noninvasive markers of fibrosis: key concepts for improving accuracy in daily clinical practice. *Ann Hepatol*. 2012;11:426–439.
178. Holmberg SD, Lu M, Rupp LB, et al; Chronic Hepatitis Cohort Study (CHeCS) Investigators. Non-invasive serum fibrosis markers for screening and staging chronic hepatitis C virus (HCV) patients in a large U.S. cohort. *Clin Infect Dis*. 2013;57:240–246.
179. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology*. 2007;46:32–36.
180. Patel K, Benhamou Y, Yoshida EM, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during interferon alfa-2b combination therapy for chronic hepatitis C. *J Viral Hepat*. 2009;16:178–186.

181. Koda M, Matunaga Y, Kawakami M, Kishimoto Y, Suou T, Murawaki Y. FibroIndex, a practical index for predicting significant fibrosis in patients with chronic hepatitis C. *Hepatology*. 2007;45:297–306.
182. Forns X, Ampurdanès S, Llovet JM, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology*. 2002;36:986–992.
183. Becker L, Salameh W, Sferruzza A, et al. Validation of hepascore, compared with simple indices of fibrosis, in patients with chronic hepatitis C virus infection in United States. *Clin Gastroenterol Hepatol*. 2009;7:696–701.
184. Zaman A, Rosen HR, Ingram K, Corless CL, Oh E, Smith K. Assessment of FIBROSpect II to detect hepatic fibrosis in chronic hepatitis C patients. *Am J Med*. 2007;120:280.e9–e14.
185. Rockey DC, Caldwel SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology*. 2009;49:1017–1044.
186. Lefkowitch JH. Liver biopsy assessment in chronic hepatitis. *Arch Med Res*. 2007;38:634–643.
187. Theise ND. Liver biopsy assessment in chronic viral hepatitis: a personal, practical approach. *Mod Pathol*. 2007;20(Suppl 1):S3–S14.
188. Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. *Liver Int*. 2008;28:1190–1199.
189. Lo Re V, Kallan MJ, Tate JP, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. *Ann Intern Med*. 2014;160:369–379.
190. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001;33:562–569.
191. Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. *Lancet*. 2011;377:1198–1209.
192. Rosenthal E, Roussillon C, Salmon-Céron D, et al; Mortalité 2010 and GERMIVIC study groups. Liver-related deaths in HIV-infected patients between 1995 and 2010 in France: the Mortavic 2010 study in collaboration with the Agence Nationale de Recherche sur le SIDA (ANRS) EN 20 Mortalite 2010 survey. *HIV Med*. 2015;16:230–239.
193. Moghaddam SMH, Alavian SM, Kermani NA. Hepatitis C and renal transplantation: a review on historical aspects and current issues. *Rev Med Virol*. 2008;18:375–386.
194. Gane E, Pilmore H. Management of chronic viral hepatitis before and after renal transplantation. *Transplantation*. 2002;74:427–437.
195. Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2078–2085.

196. Dalrymple LS, Koepsell T, Sampson J, et al. Hepatitis C virus infection and the prevalence of renal insufficiency. *Clin J Am Soc Nephrol*. 2007;2:715–721.
197. Gisbert JP, García-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in porphyria cutanea tarda: systematic review and meta-analysis. *J Hepatol*. 2003;39:620–627.
198. Hanouneh IA, Feldstein AE, Lopez R, et al. Clinical significance of metabolic syndrome in the setting of chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol*. 2008;6:584–589.
199. Hartridge-Lambert SK, Stein EM, Markowitz AJ, Portlock CS. Hepatitis C and non-Hodgkin lymphoma: the clinical perspective. *Hepatology*. 2012;55:634–641.
200. Iannuzella F, Vaglio A, Garini G. Management of hepatitis C virus-related mixed cryoglobulinemia. *Am J Med*. 2010;123:400–408.
201. Kamar N, Rostaing L, Alric L. Treatment of hepatitis C virus-related glomerulonephritis. *Kidney Int*. 2006;69:436–439.
202. Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB; Italian Association of the Study of Liver Commission on Extrahepatic Manifestations of HCV infection. Extrahepatic manifestations of hepatitis C virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis*. 2007;39:2–17.
203. Burgess SV, Hussaini T, Yoshida EM. Concordance of sustained virologic response at weeks 4, 12 and 24 post-treatment of hepatitis C in the era of new oral direct-acting antivirals: a concise review. *Ann Hepatol*. 2016;15:154–159.
204. George SL, Bacon BR, Brunt EM, et al. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology*. 2009;49:729–738.
205. Maylin S, Martinot-Peignoux M, Moucari R, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. *Gastroenterology*. 2008;135:821–829.
206. Morisco F, Granata R, Stroffolini T, et al. Sustained virological response: a milestone in the treatment of chronic hepatitis C. *World J Gastroenterol*. 2013;19:2793–2798.
207. Pockros PJ, Hamzeh FM, Martin P, et al. Histologic outcomes in hepatitis C-infected patients with varying degrees of virologic response to interferon-based treatments. *Hepatology*. 2010;52:1193–1200.
208. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med*. 2007;147:677–684.
209. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. *Clin Infect Dis*. 2015;61:730–740.

210. Arase Y, Suzuki F, Suzuki Y, et al. Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. *Hepatology*. 2009;49:739–744.
211. Conjeevaram HS, Wahed AS, Afdhal N, Howell CD, Everhart JE, Hoofnagle JH; Virahep-C Study Group. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. *Gastroenterology*. 2011;140:469–477.
212. Butt AA, Wang X, Moore CG. Effect of hepatitis C virus and its treatment on survival. *Hepatology*. 2009;50:387–392.
213. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347:975–982.
214. Hadziyannis SJ, Sette H, Morgan TR, et al. Peginterferon alfa-2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140:346–355.
215. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358:958–965.
216. Zeuzem S, Rodríguez-Torres M, Rajender Reddy K, et al. Optimized threshold for serum HCV RNA to predict treatment outcomes in hepatitis C patients receiving peginterferon alfa-2a/ribavirin. *J Viral Hepat*. 2012;19:766–774.
217. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology*. 2015;149:649–659.
218. Poordad F, Dieterich D. Treating hepatitis C: current standard of care and emerging direct-acting antiviral agents. *J Viral Hepat*. 2012;19:449–464.
219. Feld JJ, Jacobson IM, Sulkowski MS, et al. Ribavirin revisited in the era of direct-acting antiviral therapy for hepatitis C virus infection. *Liver Int*. 2017;37:5–18.
220. Roberts SS, Miller RK, Jones JK, et al. The ribavirin pregnancy registry: findings after 5 years of enrollment, 2003–2009. *Birth Defects Res A Clin Mol Teratol*. 2010;88:551–559.
221. Zoulim F, Durantel D. Antiviral therapies and prospects for a cure of chronic hepatitis B. *Cold Spring Harb Perspect Med*. 2015;5(4):a021501.
222. Pockros PJ. New direct-acting antivirals in the development for hepatitis C virus infection. *Therap Adv Gastroenterol*. 2010;3:191–202.
223. Hunt D, Pockros P. What are the promising new therapies in the field of chronic hepatitis C after the first-generation direct-acting antivirals? *Curr Gastroenterol Rep*. 2013;15:303–313.
224. Olysio (simeprevir). US FDA approved product information. Janssen Therapeutics, Division of Janssen Products, LP; November 2013.
225. Lenz O, Fevery B, Verbinnen T, et al. Resistance analyses of HCV isolates from patients treated with simeprevir in phase 2b/3 studies. Presented at the

64th annual meeting of the American Association for the Study of Liver Diseases, Washington, DC, November 1–5, 2013. Abstract 1101.

226. Jacobson IM et al. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype 1 infection in treatment-naïve patients: results from QUEST-1, a phase III trial. Presented at the 48th annual meeting of the European Association for the Study of the Liver, Amsterdam, The Netherlands, April 24–28, 2013. Abstract 1425.
227. Lenz O, Fevery B, Verbinnen T, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naïve patients: results from QUEST-2, a phase III trial. Presented at the 48th annual meeting of the European Association for the Study of the Liver, Amsterdam, The Netherlands, April 24–28, 2013. Abstract 1413.
228. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomized study. *Lancet*. 2014;384:1756–1765.
229. Keating GM. Elbasvir/grazoprevir: first global approval. *Drugs*. 2016;76: 617–624.
230. Lin C-W, Dutta S, Asatryan A, et al. Pharmacokinetics, safety, and tolerability of single and multiple doses of ABT-493: a first-in-human study. *J Pharm Sci*. 2017;106: 645–651.
231. Kirby BJ, Taylor J, Stamm LM, et al. Evaluation of transporter and cytochrome P450-mediate drug-drug interactions with the pangenotypic HCV N23/4A protease inhibitor voxilaprevir (GS-9857) or sofosbuvir/velpatasvir/voxilaprevir and phenotypic probe drugs. Presented at the 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, June 8–10, 2016, Washington, DC, p.O-24.
232. U.S. Food & Drug Administration Drug Safety Communication. FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease. 2019. Accessed October 1, 2020. https://www.fda.gov/media/130351/download
233. Evans MJ, Rice CM, Goff SP. Phosphorylation of hepatitis C virus nonstructural protein 5A modulates its protein interactions and viral RNA replication. *Proc Natl Acad Sci USA*. 2004;101:13038–13043.
234. Tellinghuisen TL, Foss KL, Treadaway J. Regulation of hepatitis C virion production via phosphorylation of the NS5A protein. *PLoS Pathog*. 2008;4:e1000032.
235. Gao M, Nettles RE, Belema M, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. *Nature*. 2010;465:96–100.
236. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. *Gastroenterology*. 2016;151: 1131–1140.e5.

237. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naïve cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. *Ann Intern Med*. 2015;163:1–13.
238. Ahmed A, Lutchman GA, Kwo PY. Drug-drug interactions in hepatitis C virus treatment: do they really matter? *Clin Liver Dis*. 2017;10:111–115.
239. Sovaldi (sofosbuvir). US FDA approved product information. Gilead Sciences; December 2013.
240. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368:1878–1887.
241. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis*. 2013;13:401–408.
242. FDA hepatitis update—important safety information: Harvoni and Sovaldi. March 21, 2015. Accessed July 16, 2017. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-serious-slowing-heart-rate-when-antiarrhythmic-drug
243. Renet S, Chaumais MC, Antonini T, et al. Extreme bradycardia after first doses of sofosbuvir and daclatasvir in patients receiving amiodarone: 2 cases including a rechallenge. *Gastroenterology*. 2015;149:1378–1380.
244. Au JS, Pockros PJ. Novel therapeutic approaches for hepatitis C. *Clin Pharmacol Ther*. 2014;95(1):78–88.
245. Zepatier (elbasvir and grazoprevir). US FDA approved product information. Merck and Co, Inc; January 2016.
246. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK–5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomized, open-label phase 2 trial. *Lancet*. 2015;385:1075–1086.
247. Kowdley KV, An D, Pang PS, Wyles D. Analysis of subgroup difference in the ION-3 trial of ledipasvir-sofosbuvir in chronic hepatitis C infection. *Open Forum Infect Dis*. 2015;2:ofv056.
248. Wyles D, Dvory-Sobol H, Svarovskaia ES, et al. Post-treatment resistance analysis of hepatitis C virus from phase II and III clinical trials of ledispasvir/sofosbuvir. *J Hepatol*. 2017;66:703–710.
249. Jacobson IM, Brau N, Bourgeois S, et al. The tolerability of sofosbuvir/velpatasvir for 12 Weeks in >1000 patients treated in the ASTRAL-1, ASTRAL-2, and ASTRAL-3 studies: an integrated safety analysis. Presented at the 51st Annual Meeting of the European Association for the Study of the Liver (EASL), Barcelona, Spain, April 13–17, 2016.

250. Everson GT, Towner WJ, Davis MN, et al. Sofosbuvir with velpatasvir in treatment-naïve noncirrhotic patients with genotype 1 to 6 hepatitis C virus infection: a randomized trial. *Ann Intern Med*. 2015;163:818–826.
251. Viekira Pak. Product information: oral extended-release tablets, dasabuvir, ombitasvir, paritaprevir, ritonavir oral extended-release tablets. AbbVie Inc (per FDA); 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf
252. FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. October 22, 2015. Accessed July 16, 2017. http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm
253. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370: 1594–1603.
254. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370:1604–1614.
255. Mavyret. Prescribing information. AbbVie Inc.; August 2017. Accessed October 5, 2020. https://www.rxabbvie.com/pdf/mavyret_pi.pdf
256. Bourlière M, Gordon SC, Flamm S, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *N Engl J Med*. 2017;376:2134–2146.
257. Voaklander R, Jacobson IM. Sofosbuvir, velpatasvir and voxilaprevir combination for the treatment of hepatitis C. *Expert Rev Gastroenterol Hepatol*. 2017;11:789–795.
258. Naggie S, Cooper C, Saag M, et al. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. *N Engl J Med*. 2015;373:705–713.
259. Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *Lancet HIV*. 2015;2:e319–e327.
260. Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA*. 2015;313:1223–1231.
261. Bhattacharya D, Belperio PS, Shahoumian TA, et al. Effectiveness of all-oral antiviral regimens in 996 human immunodeficiency virus/hepatitis C virus genotype 1-coinfected patients treated in routine practice. *Clin Infect Dis*. 2017;64:1711–1720.
262. Sogni P, Gilbert C, Lacombe K, et al. All-oral direct-acting antiviral regimens in HIV/hepatitis C virus-coinfected patients with cirrhosis are efficient and safe: real-life results from the prospective ANRS CO13-HEPAVIH Cohort. *Clin Infect Dis*. 2016;763–770.
263. Patel M, Rab S, Kalapila AG, et al. Highly successful hepatitis C virus (HCV) treatment outcomes in human immunodeficiency virus/HCV-coinfected

patients at a large, urban, Ryan White clinic. *Open Forum Infect Ds*. 2017;4:ofx062.
264. Wyles D, Bräu N, Kottilil S, et al. Sofosbuvir and velpatasvir for the treatment of hepatitis C virus in patients coinfected with human immunodeficiency virus type 1: an open-label, phase 3 study. *Clin Infect Dis*. 2017;65:6–12.
265. Rockstroh JK, Lacombe K, Viani RM, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients coinfected with hepatitis C virus and human immunodeficiency virus type 1: the EXPEDITION-2 study. *Clin Infect Dis*. 2018;67:1010–1017.
266. Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA*. 2015;313:1232–1239.
267. Taylor JM. Hepatitis delta virus. *Virology*. 2006;344:71–76.
268. Rizzetto M. Hepatitis D: thirty years after. *J Hepatol*. 2009;50:1043–1050.
269. Pascarella S, Negro F. Hepatitis D virus: an update. *Liver Int*. 2011;31:7–21.
270. Rizzetto M, Canese MG, Aricò S, et al. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut*. 1977;18:997–1003.
271. Taylor JM. Structure and replication of hepatitis delta virus RNA. *Curr Top Microbiol Immunol*. 2006;307:1–23.
272. Chen HY, Shen DT, Ji DZ, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut*. 2018;68:512–521.
273. Rizzetto M. Hepatitis D: clinical features and therapy. *Dig Dis*. 2010;28:139–143.
274. Grabowski J, Wedemeyer H. Hepatitis delta: immunopathogenesis and clinical challenges. *Dig Dis*. 2010;28:133–138.
275. Yurdaydin C, Idilman R, Bozkaya H, Bozdayi AM. Natural history and treatment of chronic delta hepatitis. *J Viral Hepat*. 2010;17:749–756.
276. Rizzetto M, Verme G, Recchia S, et al. Chronic hepatitis in carriers of hepatitis B surface antigen, with intrahepatic expression of the delta antigen. An active and progressive disease unresponsive to immunosuppressive treatment. *Ann Intern Med*. 1983;98:437–441.
277. Kushner T, Serper M, Kaplan DE. Delta hepatitis within the veterans affairs medical system in the United States: prevalence, risk factors, and outcomes. *J Hepatol*. 2015;63:586–592.
278. Romeo R, Del Ninno E, Rumi M, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology*. 2009;136:1629–1638.
279. Fattovich G, Giustina G, Christensen E, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). *Gut*. 2000;46:420–426.

280. Abbas Z, Abbas M, Abbas S, Shazi L. Hepatitis D and hepatocellular carcinoma. *World J Hepatol*. 2015;7:777–786.
281. Beguelin C, Moradpour D, Sahli R, et al. Hepatitis delta-associated mortality in HIV/HBV coinfected patients. *J Hepatol*. 2017;66:297–303.
282. Farci P, Chessa L, Balestrieri C, Serra G, Lai ME. Treatment of chronic hepatitis D. *J Viral Hepat*. 2007;14(Suppl 1):58–63.
283. Koh C, Da BL, Glenn JS. HBV/HDV coinfection: emerging therapeutic options for a challenging disease. *Clin Liver Dis*. 2019;23:557–572.
284. Wedemeyer H, Schoneweis K, Bogomolov PO, et al. 48 Weeks of high dose (10 mg) bulevirtide as monotherapy or with peginterferon alfa-2a in patients with chronic HBV/HDV co-infection. *J Hepatol*. Supplement 1 [International Liver Congress], AS072, S52. 2020;73:S19–S57.
285. Castelnau C, Le Gal F, Ripault MP, et al. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up. *Hepatology*. 2006;44:728–735.
286. Niro GA, Ciancio A, Gaeta GB, et al. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. *Hepatology*. 2006;44:713–720.
287. Wedemeyer H, Yurdaydìn C, Dalekos GN, et al. Peginterferon plus adefovir versus either drug alone for hepatitis delta. *N Engl J Med*. 2011;364:322–331.
288. Mansour W, Ducancelle A, Le Gal F, et al. Resolution of chronic hepatitis delta after 1 year of combined therapy with pegylated interferon, tenofovir and emtricitabine. *J Clin Virol*. 2010;47:97–99.
289. Aggarwal R. Hepatitis E: historical, contemporary and future perspectives. *J Gastroenterol Hepatol*. 2011;26(Suppl 1):72–82.
290. Aggarwal R, Naik S. Epidemiology of hepatitis E: current status. *J Gastroenterol Hepatol*. 2009;24:1484–1493.
291. Khuroo MS, Khuroo MS. Hepatitis E virus. *Curr Opin Infect Dis*. 2008;21: 539–543.
292. Bihl F, Negro F. Hepatitis E virus: a zoonosis adapting to humans. *J Antimicrob Chemother*. 2010;65:817–821.
293. Mushahwar IK. Hepatitis E virus: molecular virology, clinical features, diagnosis, transmission, epidemiology, and prevention. *J Med Virol*. 2008;80: 646–658.
294. Teshale EH, Hu DJ, Holmberg SD. The two faces of hepatitis E virus. *Clin Infect Dis*. 2010;51:328–334.
295. Mahtab MA, Rahman S, Khan M, Karim MF. Hepatitis E virus is a leading cause of acute and chronic liver disease: experience from a tertiary centre in Bangladesh. *Hepatobiliary Pancreat Dis Int*. 2009;8:50–52.
296. Mahtab MA, Rahman S, Khan M, Karim F. HEV infection as an etiologic factor for acute hepatitis: experience from a tertiary hospital in Bangladesh. *J Health Popul Nutr*. 2009;27:14–19.

297. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med*. 1998;338:286–290.

81

Parasitic Infections

Sheila M. Seed, Janelle I. Herren, Samar E. Nicolas, Larry Goodyer, and Caroline S. Zeind

CORE PRINCIPLES		CHAPTER CASES
MALARIA		
1	Malaria in humans is caused by protozoan parasites of the genus *Plasmodium: Plasmodium falciparum*, *P. vivax*, *P. ovale*, or *P. malariae*. Early symptoms of malaria are nonspecific, with fever present in the majority of patients; and approximately two-thirds of persons who are infected may experience symptoms such as headache, muscle aches and pains, and malaise.	**Case 81-1 (Question 1)**
2	Travelers with symptoms of malaria should seek medical evaluation as soon as possible. *P. falciparum* is the species	**Case 81-1 (Questions 1–3, 5)**

	that is most likely to cause severe malaria and has the highest mortality. Mortality is higher in those with no immunity such as travelers from nonendemic areas, whereas adults living permanently in the country and exposed to malaria do develop semi-immunity. Suspected or confirmed malaria, especially *P. falciparum*, is a medical emergency necessitating early intervention. In instances when the traveler develops a febrile illness consistent with malaria and access to medical care is not readily available, a reliable supply of malaria treatment can be self-administered presumptively as a temporary measure.	
3	Travelers to malaria-endemic areas need to understand the risk of malaria and know how to best prevent it with mosquito-avoidance measures and chemoprophylaxis (where appropriate). Pregnant females are at greater risk for malaria and its associated complications. Females who are pregnant or likely to become pregnant should be advised to avoid travel to endemic areas if possible. If travel cannot be deferred, use of an effective chemoprophylaxis regimen is essential.	**Case 81-1 (Question 4), Case 81-2 (Questions 1–3), Case 81-3 (Question 1), Tables 81-1 and 81-2**
4	Several factors must be considered when selecting a chemoprophylactic drug regimen, including drug resistance,	**Case 81-1 (Question 4), Case 81-2 (Questions 1–3), Case**

	patient-specific factors, adverse effects, precautions, and contraindications and what to do in case of a missed dose.	**81-3 (Question 1), Tables 81-1 and 81-2**
	AMEBIASIS	
1	Amebiasis is caused by *Entamoeba histolytica*, and is implicated in amebic dysentery and hepatic abscesses. Diagnosis of amebic dysentery may include the following information: history of travel, stool and biopsy specimens, and ultrasound to exclude liver abscesses. Treatment for amebiasis calls for a combination of agents with both luminal-acting and extraintestinal effects. Amebic cyst passers and pregnant females must be treated to avoid invasive disease and transmission of the infection.	**Case 81-4 (Questions 1, 2), Case 81-5 (Questions 1, 2), Case 81-6 (Question 1), Case 81-7 (Question 1), Table 81-3**
	GIARDIASIS	
1	The signs and symptoms of giardiasis could be insidious and vague, but patients usually present with diarrhea and bulky, foul-smelling stools along with laboratory confirmation of *Giardia lamblia*.	**Case 81-8 (Question 1)**
2	The major treatments for giardiasis are metronidazole and tinidazole or nitazoxanide.	**Case 81-8 (Question 2), Table 81-3**
	ENTEROBIASIS	
1	The signs and symptoms of the infection may be subtle, but the specific	**Case 81-9 (Questions 1, 2),**

	diagnostic test for *Enterobius vermicularis* is the cellophane tape swab. Therapy for enterobiasis includes the antihelminthic agents: albendazole, pyrantel pamoate, or mebendazole. Household measures to eradicate the infection need to be addressed.	**Table 81-3**
CESTODIASIS		
1	Primarily, this includes *Taenia saginata* and *T. solium*, and symptoms of infections are nonspecific. It is critical to differentiate these two infections from other cestode infections. Praziquantel remains an effective agent for all species of cestodes. Cysticercosis, a complication caused by the larval cysts of *T. solium* that may be associated with central nervous system infection (neurocysticercosis), is serious and requires separate diagnostic testing and controversial therapy. Praziquantel, which is indicated for most cestodiasis, is well tolerated.	**Case 81-10 (Questions 1, 2), Table 81-3**
PEDICULOSIS		
1	Head and body lice are associated with dermatologic reactions, which can be treated with a number of agents: permethrin, pyrethrin, malathion, and ivermectin. Special attention needs to be focused on correct application procedures, drug resistance, and lice decontamination measures.	**Case 81-11 (Questions 1, 2), Tables 81-3 and 81-4**

SCABIES

1	Scabies produces pruritic rash and excoriations of the interdigital area of the upper and lower limbs. Treatment includes lindane, permethrin, and crotamiton. Clothes and personal items of person who is infected and their family members need to laundered >122 °F (>50 °C) to avoid reinfection.	**Case 81-12 (Question 1), Table 81-3**

INTRODUCTION

Parasitic infections affect individuals not only in developing countries but also in developed countries, contributing to an immense burden of disease globally. There are three main classes of parasites that cause disease in humans that will be reviewed in this chapter: protozoa, helminths, and ectoparasites. Of all the parasitic infections, malaria has the highest number of deaths.[1]

MALARIA

Epidemiology

According to World Health Organization (WHO) estimates, malaria was responsible for an estimated 228 million cases in 2018 with an estimated 405,000 deaths, predominately children in sub-Saharan African nations.[1] The global malaria burden continues to be disproportionately high, with ~93% of malaria cases and 94% of deaths in sub-Saharan Africa.[2] Within regions of high malaria transmission, children younger than 5 years of age are particularly susceptible, with 67% of all malaria deaths occurring in this age

group.[2] Although malaria is no longer an endemic infectious disease in the industrialized countries of North America, Europe, Australia, New Zealand, and Japan, travel to malaria-endemic regions, as well as immigration and refugee migrations into nonendemic areas, have resulted in increases in the numbers of imported cases of malaria in industrialized countries.[3],[4] Millions of U.S. travelers visit malaria-endemic areas each year, and ~2000 cases of malaria are diagnosed in the United States annually, mostly in returned travelers.[5]

Distribution of Malaria Species

Malaria in humans is caused by protozoan parasites of the genus *Plasmodium: Plasmodium falciparum*, *P. vivax*, *P. ovale*, or *P. malariae*.[6] The distribution of the four *Plasmodium* species of malaria varies worldwide. However, the vast majority of imported cases are caused by *P. falciparum* or *P. vivax*[3]; the proportion of imported cases caused by *P. falciparum* or *P. vivax* within a country reflects both the destinations that travelers select and, to a larger degree, the nature of immigrant communities.[3] In addition, *P. knowlesi*, a species normally found in monkeys, has been documented as a cause of human infections and some deaths in forest fringe areas of Southeast Asia.[6]

Life Cycle of the Malaria Parasite and Transmission

The life cycle of the malaria parasites in the human host is complex.[7] All species are transmitted by the bite of an infective female *Anopheles* mosquito that carries malaria-causing parasites and injects the asexual forms or sporozoites into the human bloodstream. Over a period of 5 to 16 days (depending on the species), the sporozoites grow, divide, and produce daughter cells, or merozoites, per liver cell. Infections caused by *P. vivax* and *P. ovale* may remain in a dormant stage for extended periods of time within the liver

(hypnozoites) and cause relapses by invading the bloodstream for months or years later. The merozoites exit the liver cells and reenter the bloodstream and begin a cycle of invading red blood cells and asexual replication, thus producing and releasing newly formed merozoites from the red blood cells. Through this process, symptoms can develop 1 week after being bitten by an infected mosquito, although in *P. falciparum* malaria, this can occur up to 3 months or occasionally longer. The characteristic malarial paroxysms of chills and fever usually coincide with the periodic release of merozoites and other pyrogens in the blood. In *P. falciparum* infections, this periodicity may not always be apparent. A subpopulation of merozoites differentiate into sexual forms of the parasite, resulting in male and female gametocytes that circulate in the bloodstream (**Fig. 81-1**). If the gametocytes in the host blood are ingested by a female *Anopheles* mosquito during a blood meal, fertilization and an asexual division occurs in the mosquito midgut, where they develop into oocysts. Each oocyst grows and divides, producing thousands of active haploid forms, called *sporozoites*; once mature, the oocyte bursts, releasing sporozoites, making their way to the mosquitos' salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle.

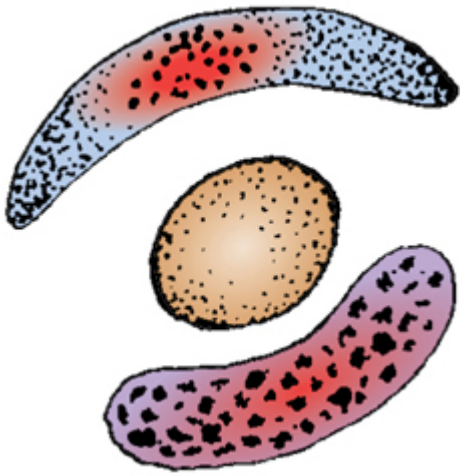


Figure 81-1 *Plasmodium falciparum* gametocytes.

Although the majority of cases of malaria are transmitted by the bite of an infective female *Anopheles* mosquito, occasional transmission has occurred by blood transfusion, needle sharing, organ transplantation, or congenitally from mother to fetus.[3]

Drug Resistance

The development of drug resistance has emerged as one of greatest threats to malaria control.[1–3] Resistance to antimalarial drugs has been confirmed for two malaria species, *P. falciparum* and *P. vivax*, whereas the development of drug resistance is currently unknown for *P. malariae* or *P. ovale*. Of note, there have been two cases of chloroquine-resistant *P. malariae* reported from Indonesia, although the clinical significance remains undefined.[8]

Chloroquine-resistant *Plasmodium falciparum* (CRPf) has become widespread, and is now found throughout most malaria-endemic areas, including all of sub-Saharan Africa, South America, the Indian subcontinent, Southeast Asia, and Oceania. Presently, CRPf, is not found in Mexico, the Caribbean, Central America, Argentina, and parts of the Middle East.[8] *P. falciparum* resistance has also developed to nearly all of the other currently available antimalarial agents, such as sulfadoxine/pyrimethamine, mefloquine, halofantrine, and quinine, along with the emergence of resistance to artemisinin derivatives in parts of Southeast Asia. In some parts of the world, the impact of multidrug-resistant malaria can be extensive.

Chloroquine-resistant *P. vivax* has also emerged as a global public health concern. First identified in 1989 among Australians living in or traveling to Papua New Guinea, chloroquine-resistant *P. vivax* has now been identified also in Southeast Asia, on the Indian subcontinent, and in South America. Because these areas are also coendemic for CRPf, this has had minimal impact on chemoprophylactic recommendations because the antimalarial choice for these areas is not chloroquine.[3]

Several online resources are available to retrieve updated malaria information and country-specific risks from several sources, including

the Centers for Disease Control and Prevention (CDC) and WHO.[1,3,7]

Acute Malaria

SIGNS AND SYMPTOMS

CASE 81-1

Question 1: P.T., a 26-year-old male college student, presents to the emergency department (ED) with malaise, myalgia, headache, and fever of 5 days' duration. A native of Uganda, he recently visited his parents who live in a remote area of Uganda, and he returned home to the United States 4 weeks ago. Two days before admission to the ED, he had an abrupt onset of coldness and chills, followed 1 hour later by a high fever, sweating, headache, nausea, and vomiting. The episode of chills and fever lasted about 24 hours, after which he became asymptomatic. On the afternoon of admission, he had another bout of chills that preceded a fever of 104 °F (40 °C).

When interviewed for his medical and travel history, he mentioned that he did not take malaria prophylaxis thinking that he was protected because he was born and raised in Uganda, and then as a teenager moved to the United States to live with relatives and to attend school. He also did not use mosquito-avoidance measures during his recent trip to Uganda.

Physical examination reveals a slender Black male who is acutely ill and has severe abdominal pain. Abdominal examination reveals a soft, tender spleen that is slightly enlarged. Blood pressure (BP) is 110/70 mm Hg; pulse, 120 beats/minute; respiration rate, 32 breaths/minute with crackles on pulmonary auscultation; and temperature, 104 °F (40 °C). Laboratory findings include the following:

Hemoglobin (Hgb), 11 g/dL
Hematocrit (Hct), 34%
White blood cell (WBC) count, 5300 cells/μL with 76% neutrophils (normal, 45%–65%), 23% lymphocytes (normal, 15%–35%), and 1% monocytes
Platelets, 26,000/μL
Creatinine, 1.5 mg/dL
C-reactive protein (CRP), 228.9 mg/dL
Bilirubin, 1.0 mg/dL

Urinalysis reveals trace amounts of albumin and the presence of urobilinogen. Thick and thin films of P.T.'s blood are prepared and a parasitemia of 20% is reported. A Giemsa stain of the thin film demonstrates *P. falciparum* gametocytes.

How is P.T.'s presentation consistent with *P. falciparum* malaria and what are his risk factors?

P.T. recently visited Uganda, where *P. falciparum* is endemic. The incubation period ranges between 1 week and 3 months, although it may occur later in rare cases.[9],[10] Early symptoms of malaria are nonspecific, with fever presenting in most patients and is often accompanied by rigors, as in P.T.'s presentation. Approximately two-thirds of persons who are infected usually experience symptoms such as headache, muscle aches and pains, and malaise, whereas about one-third of patients experience dry cough in the absence of other respiratory symptoms, diarrhea, and other gastrointestinal (GI) symptoms.[6] P.T.'s presentation is consistent with the majority of malaria-infected travelers because ~90% of them do not become symptomatic until they return home.[11–14] Given the nonspecific symptomatology with malaria, it is important that a good travel history is obtained as part of the evaluation. P.T.'s history of travel to an endemic area, the cyclical paroxysmal episodes of chills and fever, the presence of thrombocytopenia, abdominal pain, splenomegaly, and the identification of *P. falciparum* gametocytes in P.T.'s blood confirm the diagnosis of malaria.

Because P.T. grew up in Uganda in his early years but has been living for over a decade in the United States (a nonendemic country), he is considered to be in a high-risk group known as "travelers visiting friends and relatives" or VFR travelers.[15] When he returned to Uganda, an endemic country, to visit his parents, his loss of immunity over a period of time placed him in a high-risk group for malaria. Unfortunately, P.T. neglected to take malaria chemoprophylaxis because he thought his risk was low. Health care providers should raise awareness of the importance of malaria prophylaxis as well as other prevention strategies for VFR travelers.

TREATMENT

Case 81-1, Question 2: How should *P. falciparum* malaria in P.T. be treated?

Unfortunately, P.T. has acquired *P. falciparum* malaria, the species most likely to cause severe malaria with the highest mortality rate. Thus, P.T.'s treatment is a medical emergency, requiring immediate attention because mortality correlates with diagnostic and therapeutic delay.[9] P.T. would be classified as having severe malaria with complications, which could result in organ damage, including cerebral malaria. This is a particular feature of *P. falciparum*, which, unlike the other forms causes red blood cell adhesion to blood vessel walls, causing local damage and ischemia to end organs. His clinical symptoms along with the results of 20% parasitemia support the classification of severe *P. falciparum* malaria.

Specific treatment guidelines for treatment of malaria in the United States are provided by the CDC[16] at https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html, and those by the WHO[17] are available at https://apps.who.int/iris/rest/bitstreams/1411121/retrieve.

Because P.T.'s condition is critical, he should be admitted to an acute care unit and started on intravenous (IV) artesunate for at least 24 hours. According to the WHO and CDC guidelines for severe malaria, IV or intramuscular artesunate is the drug of choice for treatment of severe malaria.[18] In the United States, only the IV form of artesunate is used. Previously, quinidine was the only U.S. Food and Drug Administration (FDA)-approved IV antimalarial drug in the United States and required close cardiac monitoring.[16] Quinidine has been discontinued by the manufacturer, and will no longer be available in the United States. Therefore, as of May 2020, the FDA-approved injectable artesunate is the only treatment available. Until commercially available, it is only available through the CDC under the expanded-use investigational new drug (IND) protocol.[19] If parenteral artesunate is not available, the preferred oral therapy until artesunate can be obtained is artemether–lumefantrine (Coartem®) because of its fast onset of action.[16] For questions on the diagnosis and treatment of malaria, providers may call the CDC Malaria Hotline: 770-488-7788 or 855-856-4713(toll free), after hours 770-488-7100, or contact them via email: malaria@cdc.gov.

Once P.T. has received at least 24 hours of parenteral therapy and is able to tolerate oral therapy, he would complete 3 days of therapy with an artemisinin-based combination therapy (ACT), such as artemether–lumefantrine (Coartem®).[16] The artemisinin component is effective in rapidly clearing parasites from the blood. If an ACT is unavailable, other options are atovaquone–proguanil (Malarone®) and quinine plus doxycycline or clindamycin. If no other options are available, mefloquine is a last resort, because of the risk of neuropsychiatric adverse effects. The risk of death is greatest within the first 24 hours, requiring careful monitoring for management of complications as well as supportive care. P.T. should be monitored weekly up to 1 month after initiation of IV artesunate treatment for hemolytic anemia, a rare but delayed adverse reaction.

If P.T. presented with a case of uncomplicated malaria, he would only need to be treated with one of the abovementioned oral options.[16]

Managing other *Plasmodium* species

Case 81-1, Question 3: How would P.T.'s treatment of malaria differ if it had been a different *Plasmodium* species?

If P.T. had been infected with one of the other species of *Plasmodium* (*P. vivax*, *P. ovale*, or *P. malariae)*, treatment is dependent on whether it was acquired in a chloroquine-resistant area. Currently, there is no widespread evidence of chloroquine resistance with *P. malariae* infections; therefore, patients may be treated with chloroquine or hydroxychloroquine. *P*. *ovale* or *P. vivax* infections acquired in an area without chloroquine resistance may be treated with chloroquine or hydroxychloroquine plus primaquine or tafenoquine (Krintafel®).[16] Tafenoquine can only be used in infections treated with chloroquine and in patients age 16 years or older. For those infected with *P. vivax* or *P. ovale* acquired in an area with chloroquine resistance, they may be treated with artemether–lumefantrine or atovaquone–proguanil or quinine plus tetracycline or

doxycycline or clindamycin, or, if no other options, mefloquine plus primaquine.

Chloroquine-resistant *P. vivax* has been documented in Papua New Guinea and Indonesia, Brazil, Columbia, Ethiopia, Guatemala, Guyana, India, Myanmar, Peru, the Republic of Korea, Solomon Islands, Thailand, and Turkey.[9,17]

The use of primaquine or tafenoquine in patients with *P. ovale* and *P. vivax* is to prevent relapses from hypnozoites that remain dormant in the liver.[2] Before primaquine or tafenoquine is used in any patient, glucose-6-phosphate dehydrogenase (G6PD) deficiency must be ruled out by laboratory testing because it can cause hemolysis that can be fatal in G6PD-deficient individuals.

PREVENTION OF MALARIA

Case 81-1, Question 4: What malaria chemoprophylaxis recommendation would have been options for P.T. before his travel to visit his parents in Uganda? What guidance would you provide to P.T. regarding antimalarial options, adverse effects, counseling parameters, and mosquito-avoidance measures?

Travelers to malaria-endemic areas, such as P.T., should receive malaria prophylaxis and should follow mosquito-avoidance measures.[8] The goal of malaria prevention is to prevent malaria caused not only by *P. falciparum* but also by all species. It is important to assess an individual's level of risk, which includes the destination country, the detailed itinerary, including specific activities (eg, backpacking in the wilderness), types of accommodations, and style of travel.

Pregnancy, lactation, and other conditions, human immunodeficiency virus (HIV) disease, other immunocompromised diseases, as well as drug resistance at the destination will impact the risk assessment. Travelers should be made aware of the ABCD principles with regard to malaria protection: be made *A*ware of the risks, avoid *B*ites from mosquitoes (dusk to dawn), *C*hemoprophylaxis is needed to prevent infection, and prompt

*D*iagnosis and treatment if a fever develops after returning from malaria-endemic areas.[20]

Because P.T. is a first-generation immigrant living in a nonendemic country and was returning to Uganda, his country of origin, as a VFR traveler, he was considered at high risk for contracting malaria. Recommendations for drugs used for malaria prophylaxis are provided by the CDC[6] at https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria. It is important to understand that other countries may have differing guidelines with regard to prophylaxis recommendations for travelers going to the same region.

Given P.T.'s travel destination to Uganda with *P. falciparum* estimates at >85%, appropriate options for malaria prophylaxis are atovaquone–proguanil, doxycycline, mefloquine, or tafenoquine. It is important that P.T. understands the differences in the agents, including proper administration, their adverse effect profile, and potential drug interactions. **Table 81-1** provides a summary of the various agents for malaria prophylaxis and highlights adverse effects, contraindications, precautions, and potential drug interactions.[5,6,8,21] The importance of beginning chemoprophylaxis before travel should be emphasized. Although medications for malaria prophylaxis may be available at the destination location, travelers are strongly discouraged from obtaining chemoprophylaxis medications while abroad because the quality of these products is not known. These products may be counterfeit or may have been manufactured using substandard manufacturing practices or may contain contaminants.[22,23]

Table 81-1
Antimalarial Drugs Used for Malaria Prophylaxis

Drug	Usage	Adverse Effects	Contraindications and Precautions	Drug Interactions
Atovaquone–proguanil (fixed drug combination)	Prophylaxis in all areas Begin taking daily 3 days before travel to malarious area. Take daily (same time each day) while in malarious area and for 7 days after leaving such areas. Take with food or a milky drink. In the United States and European Union, a pediatric formulation is available (quarter strength = 62.5 mg atovaquone and 25 mg proguanil). CDC sanctions atovaquone/proguanil for infants >11 pounds (≥5 kg). WHO allows use in infants weighing >24.2 pounds (>11 kg). Partial doses may need to be prepared by a pharmacist and dispensed in capsules.	Nausea, vomiting, abdominal pain, increased transaminase, seizures, and rash	Contraindicated in severe renal impairment (creatinine clearance <30 mL/minute) Not recommended in pregnancy or breastfeeding (use only during pregnancy if potential benefits of therapy outweigh potential risk to infant) Contraindicated in children <5 kg	Tetracycline, rifampin, and rifabutin significantly decrease atovaquone level (avoid concurrent use). May interact with antiretroviral protease inhibitors ritonavir, darunavir, atazanavir, indinavir, and lopinavir, in addition to the non-nucleoside reverse transcriptase inhibitors nevirapine, etravirine, and efavirenz; monitor when used Metoclopramide: may reduce bioavailability of atovaquone; avoid use of this agent as an antiemetic to treat vomiting that may occur with atovaquone at treatment doses. Avoid use with cimetidine and fluvoxamine because of interference with proguanil's metabolism.
Chloroquine phosphate	Prophylaxis only in areas with chloroquine-sensitive malaria Begin 1–2 weeks before travel to malarious areas. Take weekly (same day of the week) while in malarious area and for 4 weeks after leaving such areas. Chloroquine sulfate (Nivaquine®) is not available in the United States and Canada, but it is available in most malaria-endemic countries in both tablet and syrup forms.	May exacerbate psoriasis; pruritus in black-skinned individuals, nausea, headache, skin eruptions, reversible corneal opacity, nail and mucous membrane discoloration, nerve deafness, photophobia, myopathy, retinopathy with daily use, blood dyscrasias, psychosis, seizures, and alopecia	Contraindications: persons hypersensitive to 4-aminoquinoline compounds and in G6PD-deficient individuals (hemolysis is rare when given at prophylactic and therapeutic doses). Preexisting retinopathy, diseases of the central nervous system, myasthenia gravis, disorders of the blood-producing organs, a history of epilepsy or psychosis Dosage reduction may be required: hepatic function impairments	May increase risk of prolonged QTc interval when given with other QT-prolonging agents (eg, sotalol, amiodarone, and lumefantrine); antiretroviral rilpivirine prolongs QTc; avoid combination of chloroquine with any of these agents. Chloroquine inhibits CYP2D6, and when used concomitantly with substrates of this enzyme (eg, metoprolol, propranolol, fluoxetine, paroxetine, and flecainide); increase monitoring for side effects. Chloroquine absorption may be reduced by antacids or kaolin; space apart by ≥4 hours. Avoid concomitant use of cimetidine and chloroquine because cimetidine can inhibit chloroquine's metabolism; avoid concurrent use of CYP3A4 inhibitors such as ritonavir, ketoconazole, and erythromycin because they may increase chloroquine levels. Chloroquine may increase digoxin levels, requiring careful monitoring. Use with caution with calcineurin inhibitors because their levels may be increased by chloroquine. Chloroquine inhibits bioavailability of ampicillin; space apart doses by 2 hours. Chloroquine may decrease the bioavailability of ciprofloxacin and methotrexate.

Drug	Usage	Adverse Effects	Contraindications and Precautions	Drug Interactions
Doxycycline	Prophylaxis in all areas Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas.	GI upset (nausea, vomiting, abdominal pain, and diarrhea (less frequent than with other tetracycline agents); esophageal ulceration; vaginal candidiasis, photosensitivity, allergic reactions, blood dyscrasias, azotemia in renal diseases, and hepatitis	Contraindicated in children ages younger than 8 years and in pregnant females Breastfeeding: excreted into breast milk; may cause permanent discoloration of teeth, damage to tooth enamel, impairment of skeletal growth, and photosensitivity in breastfed infants	Phenytoin, carbamazepine, and barbiturates may decrease doxycycline's half-life. Anticoagulants: may require reduction in anticoagulant dose while taking doxycycline; close monitoring of prothromb in time Absorption may be impaired by concomitant ingestion of bismuth subsalicylate, preparations containing iron, calcium, magnesium, or aluminum; avoid taking these preparations within 3 hours of taking doxycycline. Doxycycline may interfere with bactericidal activity of penicillin; avoid use of both drugs together.
Hydroxychloroquine sulfate	An alternative to chloroquine for prophylaxis only in areas with chloroquine-sensitive malaria Same frequency as chloroquine			
Mefloquine	Prophylaxis in areas with mefloquine-sensitive malaria Begin ≥2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas. Travelers should receive a copy of the FDA Medication Guide when receiving a prescription for mefloquine.	Dizziness, diarrhea, nausea, vivid dreams, nightmares, irritability, mood alterations, headache, insomnia, anxiety, seizures, and psychosis	Contraindicated in persons allergic to mefloquine or related compounds (quinine, quinidine) and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures Caution: in persons with psychiatric disturbances or a previous history of depression Not recommended for persons with cardiac conduction abnormalities Use with caution or avoid in individuals taking antiarrhythmic or β-blocking agents, calcium channel blockers, antihistamines, H1-blocking agents, tricyclic antidepressants, or phenothiazines. Use in second and third trimesters of pregnancy for females who cannot defer travel to high-risk areas is sanctioned by manufacturer, CDC, and WHO. Breastfeeding: small amounts secreted in breast milk; effect on breastfed infants is unknown.	May interact with antimalarial drugs that alter cardiac conduction; increased toxicities with lumefantrine (available in the United States in fixed combination to treat uncomplicated *Plasmodium falciparum* malaria); avoid or use with caution because of potentially causing fatal prolongation of the QTc interval. May lower plasma concentrations of anticonvulsant agents, such as valproic acid, carbamazepine, phenobarbital, and phenytoin; avoid concurrent use May increase levels of calcineurin inhibitors and mTOR inhibitors (tacrolimus, cyclosporine A, and sirolimus) Potent CYP3A4 inhibitors (eg, clarithromycin, erythromycin, ketoconazole, voriconazole, and itraconazole, ritonavir, lopinavir, darunavir, atazanavir, and cobicistat) may increase the levels of mefloquine, increasing the risk of QT prolongation. CYP3A4 inducers (eg, efavirenz, nevirapine, etravirine, rifampin, and rifabutin) may reduce plasma concentrations of mefloquine and concurrent use should be avoided. Boceprevir and telaprevir (drugs used to treat hepatitis C) may increase mefloquine levels.

Drug	Usage	Adverse Effects	Contraindications and Precautions	Drug Interactions
Primaquine	Prophylaxis for short-duration travel to areas with principally *Plasmodium vivax* Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease the risk of relapses of *P. vivax* and *P. ovale* Start therapy 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. A documented normal G6PD level should be obtained before starting primaquine therapy.	GI upset; hemolysis in G6PD deficiency, methemoglobinemia	Contraindicated in individuals with G6PD deficiency (G6PD level should be obtained before starting primaquine therapy because G6PD deficiency must be ruled out by laboratory testing.) Contraindicated during pregnancy and lactation (unless the infant being breastfed has a documented normal G6PD level)	Use with caution in medications that cause QT prolongation.
Tafenoquine	Prophylaxis in all areas Begin 3 days before travel to malarious area. Take weekly (same day of the week) while in malarious area and for 1 week after leaving such areas. Take with food to increase absorption, swallow whole do not break, crush, or chew tablets A documented normal G6PD level should be obtained before starting tafenoquine Used for presumptive anti-relapse therapy to decrease the risk of relapses of *P. vivax* and *P. ovale* (300 mg single dose)	Dizziness, nausea, vomiting, headache, back pain, diarrhea	Not for use in children <16 years old Contraindicated in patients with G6PD deficiency (G6PD level should be obtained before starting therapy-G6PD deficiency must be ruled out) Contraindicated in pregnancy and lactation (unless the infant being treated has a documented normal G6PD level) Not recommended on those with psychiatric disorders, meth	Co-administration with metformin may result in increased levels of metformin and increase risk of lactic acidosis. Monitor for adverse effects or reduce metformin dose. Co-administration of dofetilide is contraindicated may increase dofetilide concentrations and arrhythmias Penicillamine-increased risk of hematological and renal adverse effects

CDC, Centers for Disease Control and Prevention; CYP, cytochrome P450; FDA, U.S. Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; mTOR, mammalian target of rapamycin; WHO, World Health Organization.

Sources: Tan KR, Arguin PM. Malaria. In: Centers for Disease Control and Prevention. CDC Health Information for International Travel 2020. Oxford University Press. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria; Youngster I, Barnett ED. Interactions among travel vaccine & drugs. In: Centers for Disease Control and Prevention. CDC Health Information for International Travel 2020. Oxford University Press https://wwwnc.cdc.gov/travel/yellowbook/2020/preparing-international-travelers/interactions-between-travel-vaccines-and-drugs; Schlagenhauf P, Wilson ME, Taylor WR. Malaria prophylaxis. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier, Inc.; 2019:145–168.

P.T. should be counseled regarding mosquito-avoidance measures, not only for malaria but also for protection against *Aedes*

mosquitos (responsible for transmission of dengue, chikungunya, and the Zika viruses). Because malaria transmission occurs primarily between dusk and dawn, contact with mosquitos can be reduced by remaining in well-screened areas, using mosquito bed-nets (preferably insecticide-treated nets), using insecticide sprays, wearing clothes that cover most of the body, and treating clothing with permethrin. **Table 81-2** summarizes strategies to optimize protection against mosquitos and items that travelers can include in a travel kit for malaria prevention.[24],[25] In addition to mosquito-avoidance measures, it is important to emphasize to travelers, such as P.T., to inspect themselves and their clothing for ticks during outdoor activity and at the end of the day (see Chapter 82, Tick-Borne Diseases for further information).

Table 81-2
Mosquito Protection Measures

Protective Measures		Comments
Clothing	Wear a long-sleeved shirt, long pants, and socks. Treat clothing with permethrin 24–48 hours before travel to allow them to dry or purchase pretreated clothing.	Permethrin-treated clothing will retain repellant activity through multiple washes. Repellants used on skin can also be applied to clothing and must be reapplied after laundering. Clothing treated with other repellent products (eg, DEET) provides protection from biting arthropods, but will not last through washing and will require more frequent reapplications. Repellent still must be applied to exposed skin for maximum protection.
Insecticides	Permethrin: highly effective insecticide–acaricide and repellent	Other synthetic pyrethroids are available. Useful as an area repellent such as plug-in device/aerosol spray or burning coils
Repellents	Apply lotion, liquid, or spray	Repellents may be used with

for use on skin and clothing	repellent to exposed skin. Ensure adequate protection during times of the day when mosquitos are most active (*Anopheles* mosquitos responsible for malaria bite mainly from dusk to dawn; *Aedes* mosquitos responsible for yellow fever, Zika, Chikungunya bite more in daylight hours). Reapply repellants as protection wanes and mosquitos start to bite. The higher the percentage of active ingredient, the longer it will last. Purchase repellents before traveling.	sunscreen. General recommendation: use separate products, applying sunscreen first and then applying the repellent. Combination sunscreen and repellent products are not recommended, because sunscreen may need to be reapplied more frequently and in larger amounts than do repellents. Travelers may need to reapply sunscreen more often because limited data show a one-third decrease in the sun protection factor of sunscreens when DEET-containing insect repellents are used after a sunscreen is applied.
	DEET DEET formulations worldwide: concentrations range from 5% to 100%. For most activities, 10%–35% DEET will usually provide adequate protection. Higher percentage of active ingredient is recommended for mosquito-borne disease endemic areas.	Gold standard of insect repellents for several decades In the United States, registered for use by the general public since 1957 Can be applied to exposed skin, clothing, mesh insect nets or shelters, window screens, tents, or sleeping bags DEET should never be applied under clothing, avoid spraying on synthetic fabrics.
	Picaridin (KBR 3-23 [BayRepel®] and Picaridin outside of the United States; chemical name: 21-(2-hydroxyethylo)-1-piperidinecarboxylic acid 1-methylpropyl ester)	A reasonable alternative to DEET; concentration of ≥20% should be used in mosquito borne–disease endemic areas.
	OLE or PMD, the synthesized version of OLE	Note that EPA-registered repellent products contain the active ingredient OLE (or PMD)

		"Pure" OLE (essential oil is not formulated as a repellent) is not recommended because it has not undergone validated safety and efficacy testing and is not registered with the EPA as an insect repellent. Should use high concentrations of OLE or PMD in mosquito-borne disease endemic areas if using as an alternative to DEET
	IR3535® (chemical name: 3-[*N*-butyl-*N*-acetyl]-aminopropionic acid, ethyl ester)	Some evidence suggests it may not be reliable against *Anopheles* mosquitos.

DEET (chemical name): *N,N*-diethyl-m-toluamide or *N,N*-diethyl-3-methyl-benzamide; EPA, Environmental Protection Agency; OLE, oil of lemon eucalyptus; PMD (chemical name): para-menthane-3,8-diol.

Sources: Fradin MS. Insect protection. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier, Inc; 2019:43-52; Mutebi JP, Gimnig JE. Mosquitoes, ticks & other arthropods. In: Centers for Disease Control and Prevention. CDC Health Information for International Travel 2020. Oxford University Press. Accessed September 3, 2020. https://wwwnc.cdc.gov/travel/yellowbook/2020/noninfectious-health-risks/mosquitoes-ticks-and-other-arthropods; Schlagenhauf P, Wilson ME, Taylor WR. Malaria prophylaxis. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier Inc.; 2019:145–168.

STANDBY EMERGENCY TREATMENT

Given the risk of complications and death because of the delay initiating treatment of malaria, the concept of standby emergency treatment (SBET) was introduced in the late 1980s and then updated to provide travelers with a treatment dose of an appropriate antimalarial drug to be carried and taken in case of a febrile illness, when prompt medical attention is unavailable within 24 hours of the onset of symptoms.[26–28] The major issue with SBET is the difficulty for travelers to make a self-diagnosis of malaria based on clinical symptoms. For those situations in which the traveler does not have access to medical care and develops a febrile illness with symptoms

consistent with malaria, a supply of medications could be administered presumptively until medical evaluation is available.

Case 81-1, Question 5: Would P.T. have been a candidate for SBET because of his trip to Uganda?

In the United States, two malaria treatment regimens that could be prescribed for self-treatment are available: atovaquone–proguanil and artemether–lumefantrine. Because P.T. was traveling to a remote region in Uganda, discussing this option with a travel health provider would have been important in preparation for his trip. P.T. is a good candidate for SBET, and could have taken a reasonable supply of a full course of an approved malaria treatment regimen with him on his trip. It is important to note that the use of the same or related drugs that are taken for prophylaxis are not recommended to treat malaria. Thus, if P.T. was taking a reliable supply of atovaquone–proguanil as SBET, then atovaquone–proguanil would not be selected for malaria prophylaxis. Either mefloquine or doxycycline would be acceptable choices for malaria prophylaxis.

The introduction of rapid diagnostic tests (RDTs), which are based on the immunochromatographic detection of plasmodial proteins, has become an important component of the current global malaria control strategies, alongside ACTs for falciparum malaria across most areas of endemicity.[29] The use of RDTs is being evaluated as a tool for self-use by travelers to determine whether it will help them decide whether or not to use SBET.[26] Future directives will continue to evaluate the feasibility and utility of RDTs in providing guidance to travelers on whether to initiate SBET.

CASE 81-2

Question 1: L.P., a 32-year-old male who owns a small business in the United States, is planning to visit his seriously ill grandmother who lives in the eastern province of Maluku in Indonesia. L.P. immigrated to the United States when he was 21 years old, and he has not previously had a chance to go back to Indonesia. Given his concern for his grandmother's health, his wife, S.T., who is

26 weeks pregnant, wants to join him and also bring their 5-year-old daughter. S.T. is also from Indonesia and moved to the United States 7 years ago.

What are the malaria risks of each member of the family?

Malaria prevention strategies for both short-term and long-term travelers consist of a combination of mosquito-avoidance measures and chemoprophylaxis. It is important to assess the individual risk of each traveler, including a detailed itinerary of the specific cities, types of accommodations, and activities (eg, backpackers, adventure travelers).

Similar to the previous case of P.T. (Case 81-1), VFR travelers, such as L.P. and S.T., are at high risk because they are first-generation immigrants living in nonendemic countries who are returning to their countries of origin. They may consider themselves to be at no risk because they were raised in a malarious country (Indonesia) and consider themselves immune. They should be advised that any acquired immunity is lost quickly, and they are considered to have the same risk as nonimmune travelers. Because S.T. is pregnant, she should be advised that malaria infection in pregnant females can be more severe with increased risk for adverse pregnancy outcomes than that in nonpregnant females. In particular, falciparum malaria acquired during pregnancy has been associated with an increased risk of miscarriage and still birth, intrauterine growth retardation, as well as other complications, and maternal mortality.[7] She should be advised to avoid travel to eastern Indonesia because it is an endemic region. Their 5-year-old daughter should also follow preventive measures because infants, children, and adolescents of any age can contract malaria, and they are traveling to a malarious region.

Case 81-2, Question 2: L.P. and his wife S.T. have not finalized their decision if they will travel together to visit L.P.'s grandmother and bring their daughter. What resources are available to them to review options for malaria prevention, so that they can weigh the risks and benefits of traveling to Indonesia?

In eastern Indonesia, including Papua New Guinea, chemoprophylaxis is recommended for L.P. and his family that will protect them against CRPf infections. The CDC *Health Information for International Travel*[6] (commonly referred to as the *Yellow Book*) or the CDC Travelers Health website https://wwwnc.cdc.gov/travel serve as a useful resources for both travelers and clinicians regarding updated information on parasitic diseases and immunization requirements, based on length of stay, activities planned, and risk of disease in a particular country. In addition, the CDC Malaria Hotline mentioned previously provides malaria support. Other useful resources include the Morbidity and Mortality Weekly Reports and the WHO.

Non-falciparum prophylaxis/treatment

It is important to note that nearly all *P. falciparum* is chloroquine resistant and *P. vivax* and *P. falciparum* are the two most commonly encountered species in travelers to eastern Indonesia (refer to the section Prophylaxis for *Plasmodium falciparum*). There have been reports confirming a high prevalence of chloroquine-resistant *P. vivax* in Papua New Guinea and Indonesia.[15] Therefore, atovaquone–proguanil, doxycycline, mefloquine, or tafenoquine would be recommended as options for prophylaxis. Mefloquine is a first-line option for prophylaxis during pregnancy.[16]

With regard to treatment, there are three options for chloroquine-resistant *P. vivax* infections: atovaquone–proguanil, quinine sulfate plus doxycycline or tetracycline, or, if no other options are available, mefloquine can be considered. Mefloquine would be an appropriate choice during all trimesters of pregnancy. An alternative option for treatment of pregnant females in their second or third trimester is artemether–lumefantrine. Limited data suggest that atovaquone–proguanil can be used in pregnancy to treat malaria when other options are not suitable. In addition, infections with *P. vivax* and *P. ovale* can relapse as a result of hypnozoites that remain dormant in the liver. Therefore, a 14-day course of primaquine or a single dose (300 mg) of tafenoquine therapy is recommended with appropriate

screening for G6PD deficiency before treatment. Primaquine and tafenoquine are contraindicated during pregnancy.[16]

Prophylaxis for Plasmodium falciparum

There are several equally effective prophylactics for most regions where there is *P. falciparum*—atovaquone–proguanil, doxycycline, mefloquine, and tafenoquine. Selection of an antimalarial agent depends on individual factors, patient preference regarding the regimen, the side effect profile, and contraindications (see Table 81-1).[6]

Prophylaxis for *P. falciparum* can be achieved by taking the combination of atovaquone and proguanil administered once daily 1 to 2 days before entering malarious areas, continued for the duration of malaria exposure, and for 1 week after return. Mefloquine should be taken beginning ≥2 weeks before entering malarious areas, and continuing through 4 weeks after leaving the endemic area. A third option is doxycycline beginning 1 day before entering malarious areas, continued for the duration of the stay, and for 4 weeks after leaving the malarious area. Lastly, tafenoquine is not only highly effective for the prevention of *P. vivax* but also prevents *P. falciparum* infections. It should be taken daily 3 days before entering malarious areas, continued weekly for the duration of stay, and for 1 week after leaving the malarious area. Tafenoquine requires G6PD deficiency testing before use.

In pregnant patients, such as S.T., should she insist on traveling to CRPf areas, mefloquine is the only medication recommended for malaria prophylaxis during pregnancy. Atovaquone–proguanil is not recommended for use during pregnancy because data are still lacking to fully evaluate its safety, and tafenoquine and doxycycline are contraindicated in the United States. Given the prevalence of CRPf and chloroquine-resistant *P. vivax* in eastern Indonesia, chloroquine would not be recommended and mefloquine would be an appropriate option for S.T. who is in her second trimester.

Given the risks of acquiring malaria during pregnancy, L.P. and S.T. should reconsider their decision to travel together. With regard

to their 5-year-old daughter, mefloquine and atovaquone–proguanil are options because doxycycline is contraindicated in children age younger than 8 years, and tafenoquine is contraindicated in children age younger than 16 years. Practical advice should be emphasized, including physical barriers (eg, clothes, mosquito nets), insect repellent, and minimizing the stay in the endemic area also decrease the likelihood of transmission. Table 81-2 summarizes strategies to optimize protection against mosquitos and items that travelers can be advised to include in a traveler kit for malaria prevention. Considerations when selecting a drug for malaria prophylaxis are available by the CDC[6] at https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#:~:text=For%20destinations%20where%20malaria%20cases,Prophylaxis%20Information%2C%20by%20Country.

MALARIA VACCINE

CASE 81-2, QUESTION 3: Could L.P. be vaccinated as an alternative to chemoprophylaxis?

Currently, no malaria vaccine is available in the United States there have been numerous challenges in the development of a vaccine, including the technical complexity of developing a vaccine against a parasite and the lack of a traditional market.[29] As a result of successful in vitro *P. falciparum* cultivation and advances in genetic engineering and monoclonal antibody research, some progress has been made. In October 2021, WHO announced that the RTS,S/AS01 (RTS,S) malaria vaccine was recommended for broader use among children living in areas with moderate to high transmission of *P. falciparum* in sub-Saharan Africa and other regions based upon data from a pilot study conducted in Kenya, Ghana, and Malawi.[29] This vaccine may still be years from widespread use on a global scale and is dependent on whether a country decides to adopt this vaccine or not. The malaria parasite

undergoes many transformations during its development, and each stage expresses a different plasmodial genome that generates a large number of antigens. The development of a malaria vaccine relies on the identification and characterization of these antigens and the subsequent production of monoclonal antibodies. Presently, there are over a dozen vaccine candidates in clinical development that are being evaluated. A Malaria Vaccine Technology Roadmap has been designed by leading global health organizations that is focused on accelerating the development of a highly effective malaria vaccine.[30]

CASE 81-3

Question 1: G.S., a 30-year-old female, comes to the community pharmacy with a prescription for mefloquine that she obtained from a local travel medicine clinic. She explains that she will be traveling to sub-Saharan Africa for 6 weeks with a group of female friends, and she is concerned about experiencing adverse effects to mefloquine and what to do if she misses a dose while she is on her 1-month safari trip. She also wants your advice regarding malaria prevention. She currently takes an oral contraceptive and also a multivitamin daily and has no known drug allergies.

What guidance should be given to G.S. regarding mefloquine and advice on approaches to malaria prevention?

It is important to consider patient-specific factors in G.S. and drug-related factors. Given her concerns, G.S. can be advised to start early with mefloquine prophylaxis (2.5–3 weeks before her trip), which will be taken weekly on the same day.[7] This will allow her to assess her tolerability to mefloquine because the majority of adverse effects occur within the first three doses. If there are any tolerability issues that occur, this will enable her to switch to another agent.

In terms of overall malaria prevention strategies, the importance of adherence to malaria prophylaxis should be emphasized, because G.S. will begin mefloquine before her trip and will continue therapy while she is in the malarious region, and for 4 weeks after leaving the area.

Owing to the long half-life of mefloquine, should G.S. miss a prophylaxis dose by 1 to 2 days, the blood levels of the medication may still be sufficient. If 1 to 2 days late, she may take the dose as soon as possible and resume her regular weekly schedule. If she has missed her dose by more than 2 days, she needs to take a dose as soon as possible, and that day becomes her new scheduled weekly day. Prophylactic medications taken daily have a shorter half-life and are less likely to maintain sufficient blood levels. If a traveler is 1 to 2 days late, they should take the dose as soon as possible and resume the daily schedule at the new time of day.[6]

Personal protection measures should be reviewed with G.S., including habitat avoidance, the use of insect repellants, protective clothing, and bed-nets (see Table 81-2).[24],[25] For example, if G.S. selects a product containing *N,N*-diethyl-m-toluamide or *N,N*-diethyl-3-methylbenzamide (DEET), she should be counseled on using a sunscreen product separately (rather than a combination product). Sunscreen may need to be reapplied more often and in larger amounts than the insect repellent because limited data have shown a one-third decrease in the sun protection factor of sunscreens when DEET-containing insect repellents are used after a sunscreen is applied.[24]

AMEBIASIS

Prevalence and Mortality

Amebiasis is an infection caused by the intestinal protozoan parasite *Entamoeba histolytica* (**Fig. 81-2**), resulting in diarrhea or amebic dysentery. Extraintestinal infections may occur when the parasite spreads to other organs, the most common being the liver, resulting in hepatic abscesses.[31],[32] This parasitic infection is distributed globally, affecting >50 million people with >100,000 deaths annually.[33] Those most affected are people living in or traveling to

endemic areas, or recent immigrants from such areas where there are suboptimal sanitary conditions, particularly in tropical or subtropical developing countries. Symptoms may not appear until years after exposure to *E. histolytica*.[34] Transmission occurs by the fecal–oral route via direct person-to-person contact or by consumption of contaminated food and water.[35] Risk factors include poor sanitary conditions, anal sexual exposure, and household contact with a person who is infected. Other intestinal amebae are *E. dispar, E. moshkovskii*, and *E. bangladeshi*.[36] Most individuals are infected with *E. dispar* (80%) or *E. moshkovskii*, which are antigenically different strains from the pathogenic *E. histolytica* (10%). *E. dispar* does not cause symptomatic invasive disease.[37],[38] Further studies are needed to determine whether *E. moshkovskii* and *E. bangladeshi* are pathogenic in humans.[39],[40] Amebiasis can be asymptomatic, or it may present as colitis or dysentery. Extraintestinal lesions include abscesses in the liver, lungs, skin, and, rarely, the brain.[31],[32],[35–38]

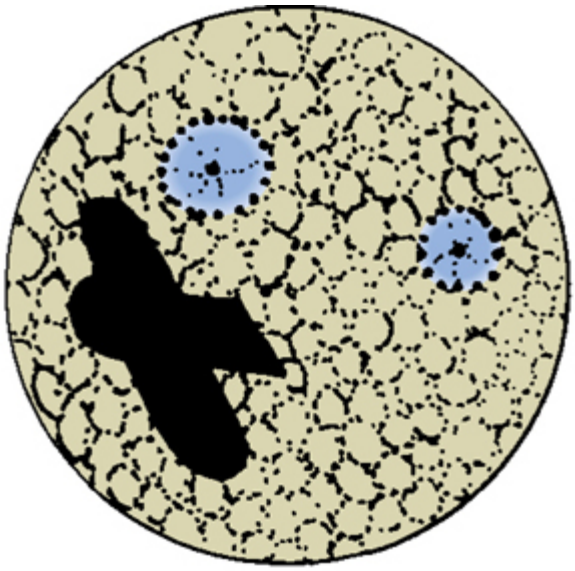


Figure 81-2 *Entamoeba histolytica*.

Life Cycle

Infection occurs by ingestion of mature cysts present in fecally contaminated water or food. Excystation occurs in the lumen of the small intestines where eight trophozoites are released from one cyst and migrate to the large intestine (**Fig. 81-3**). Trophozoites multiply by binary fission. In noninvasive infections, trophozoites remain in the intestinal lumen. In invasive infections, trophozoites invade the intestinal mucosa producing ulcerations, resulting in amebic dysentery.[41] Trophozoites may enter the bloodstream traveling to the liver, and, in rare instances, to the brain, lungs, and genitals forming abscesses. Both trophozoites and cysts are passed in the feces of an infected individual. Trophozoites do not survive outside the host body; if ingested, they will be destroyed by gastric juices. The cyst form can survive days to weeks in the external environment, only killed by temperatures in excess of 131 °F (55 °C) or hyperchlorinated water.[37],[38],[42]

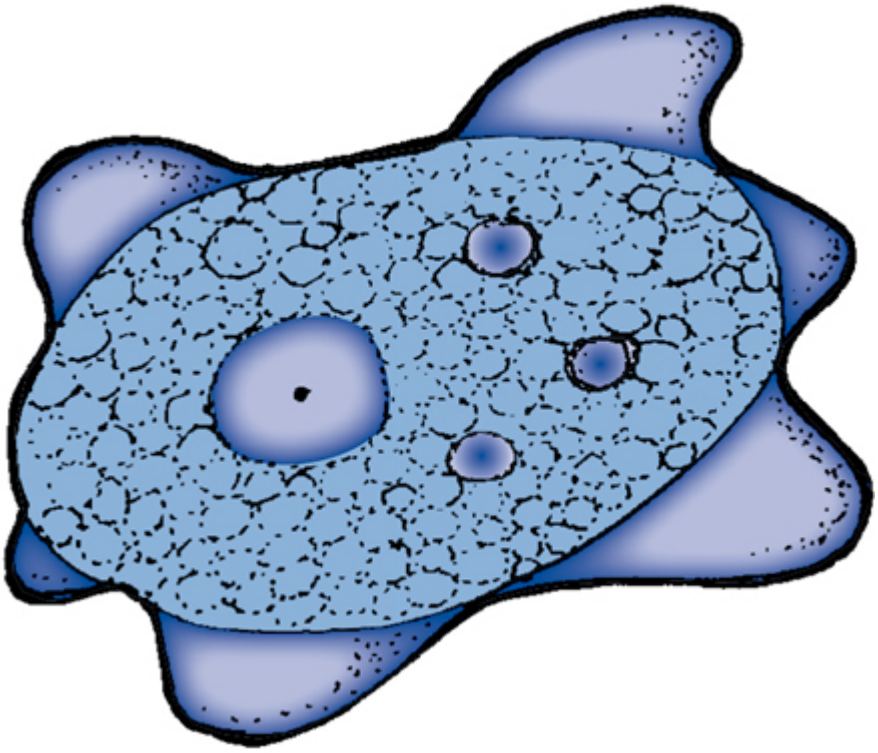


Figure 81-3 *Entamoeba histolytica* trophozoites.

Amebic Dysentery

DIAGNOSIS

CASE 81-4

QUESTION 1: J.D., a 45-year-old recent immigrant from Africa, presents to an urgent care clinic with a 12-day history of watery diarrhea with occasional blood, abdominal pain, and fever. On physical examination, he is a thin male with abdominal discomfort and occasional nausea. His vital signs include BP 150/90 mm Hg, heart rate 94 beats/minute, and temperature 99.68 °F (37.60 °C). He has no signs of jaundice or lymphadenopathy. Examination is remarkable for slight abdominal distension and rebound tenderness in the right lower quadrant. Liver function test results are normal. Stool samples collected reveal positive findings for occult blood. Microscopic examination of stool for ova and parasites is ordered; light microscopy result reveals trophozoites and cysts. Colonoscopy revealed flask-shaped intestinal mucosal ulcerations. The result of the tissue biopsy of the ulceration showed trophozoites. Antigenic testing of stool samples confirmed the presence of *E. histolytica*.

What clinical findings does J.D. have that support the diagnosis of amebic colitis?

Patients presenting with acute amebic colitis may present with bloody or watery diarrhea, abdominal pain, constipation, tenesmus, fever, rectal bleeding (especially in children), nausea, and anorexia.[34,43–45] On physical examination, patients may present with elevated temperature, tachycardia, and hypertension in cases of severe colitis. Intestinal amebic dysentery may be suspected in patients from endemic areas with bloody or watery diarrhea, abdominal pain, and fever. Diarrhea lasting >10 days should be evaluated for intestinal parasites.[46] Almost all patients presenting with amebic colitis will have heme-positive stools. Microscopic examination of stool samples can only identify the presence of trophozoites or cysts, but cannot differentiate between pathogenic and nonpathogenic strains of the *Entamoeba* species. Three stool samples from different days over a 10-day period need to be collected, because cysts are sporadically excreted in feces and may be missed if only one sample is tested. Serology tests detect antibodies against *E. histolytica*, but cannot determine between a current or past infection because antibodies are produced 7 to 10

days after infection and may last for years. A negative serology test result rules out *E. histolytica*.[47] There are various antigen assay detection kits commercially available, with varying specificity and sensitivity to differentiate the type of species found in the stool. J.D. is a recent immigrant from an endemic country and is presenting with symptoms consistent with amebic colitis. The stool antigen test finding confirmed J.D. has amebiasis, with the presence of *E. histolytica.*

CASE 81-4, QUESTION 2: What medications are available to treat J.D.'s symptomatic infection? What medication regimen is preferred?

Treatment is necessary if *E. histolytica* has been specifically identified to prevent disease progression and transmission to contacts.[34,45] Treatment is not necessary with *E. dispar* infections.[34,43,44] Treatment involves the elimination of both trophozoites and cysts from the intestinal lumen. There are two classes of drugs to treat J.D.'s amebiasis: tissue amebicides and intraluminal amebicides. Those presenting with mild-to-moderate intestinal symptoms or severe intestinal symptoms or extraintestinal disease should be treated with a tissue amebicide followed by a course of intraluminal amebicide therapy.[45] J.D.'s symptomatic amebic colitis needs to be treated with both a tissue amebicide and an intraluminal agent. Tissue amebicides include nitroimidazoles, nitazoxanide (Alinia®), and chloroquine. The drugs of choice with a 90% cure rate are the 5-nitroimidazoles, metronidazole (Flagyl®), and tinidazole (Tindamax®).[32,45] Nitazoxanide shows promise, but the data are limited; chloroquine is ineffective in intestinal illnesses. Metronidazole will kill the trophozoites in the intestines and the tissues, but it does not eradicate the cysts from the intestine. To eradicate colonization, therapy should be followed up with an intraluminal amebicide, such as paromomycin, diloxanide furoate (Furamide—not approved in the United States or Canada), or iodoquinol (Yodoxin®).

J.D.’s amebic colitis should be treated with metronidazole 750 mg orally or IV three times a day for 5 to 10 days.[41] Alternative treatment with tinidazole 2 g orally once daily for 3 days is often better tolerated because of its shorter duration of therapy. Common adverse effects of metronidazole are nausea, metallic taste, and abdominal discomfort. Patients should be warned of a possible disulfiram reaction with alcohol consumption during and up to 72 hours after the completion of therapy.[48] This should be followed by an intraluminal amebicide; the drug of choice is paromomycin 25 to 35 mg/kg/day orally in three divided doses for 5 to 10 days, and second-line agents include diloxanide or iodoquinol[31] (see **Table 81-3**). The most common adverse effects of paromomycin are abdominal pain/cramping, nausea, and diarrhea.

Table 81-3
Drug Therapy of Various Parasitic Infections[a]

Drug of Choice	Dosage	Adverse Effects	Warnings
Amebiasis			
Asymptomatic including cyst passers			
Luminal amebicides			
Paromomycin (drug of choice)	*Adults and children*: 25–35 mg/kg/day PO in three divided doses for 5–10 days	Nausea, vomiting, diarrhea, and cramps	Contraindicated in GI obstructions
Iodoquinol	*Adults*: 650 mg PO tid × 20 days *Children*: 30–40 mg/kg/day (max. 2 g/day) PO in three divided doses × 20 days	Nausea, vomiting, and headache	Avoid use in elderly because of optic nerve damage.
Diloxanide furoate (not available in the United States)	*Adults*: 500 mg PO tid × 10 days *Children*: 20 mg/kg/day in three divided doses × 10 days	Flatulence, nausea, and abdominal pain	
Symptomatic or invasive intestinal infections			
Tissue amebicides			
Metronidazole (drug of choice)	*Adults*: 750 mg PO/IV tid × 7–10 days *Children*: 35–50 mg/kg/day PO/IV in three divided doses × 7–10 days	Nausea, headache, metallic taste, disulfiram reaction with alcohol, and abdominal discomfort	Avoid use in first trimester of pregnancy.
Tinidazole	*Adults*: 2 g PO once daily × 3 days *Children >3 years:* 50 mg/kg (max. 2 g) once daily × 3 days	Metallic or bitter taste, anorexia, nausea, vomiting, epigastric discomfort, and fatigue	Contraindicated in first trimester of pregnancy and in those breastfeeding
Followed by luminal amebicide to eliminate intestinal colonization—see abovementioned for dosing.			
Amebic liver abscess			
Metronidazole (drug of choice)	*Adults*: 750 mg PO/IV tid × 7–10 days *Children*: 35–50 mg/kg/day in three divided doses × 7–10 days	Nausea, headache, metallic taste, disulfiram reaction with alcohol, and paresthesia	Avoid use in first trimester of pregnancy.
Tinidazole	*Adults*: 2 g PO once daily × 5 days *Children >3 years*: 50 mg/kg (max. 2 g) once daily × 5 days	Metallic or bitter taste, anorexia, nausea, vomiting, epigastric discomfort, and fatigue	Contraindicated in first trimester of pregnancy and in those breastfeeding
Followed by luminal amebicide agent to eliminate intestinal colonization—see abovementioned for dosing.			
Ascariasis (Roundworm)			
Albendazole	*Adults and children*: 400 mg PO once	Nausea, vomiting, headache, and abnormal liver function tests	Avoid during pregnancy.
Mebendazole (withdrawn from market in the United States)	*Adults and children*: 100 mg bid PO × 3 days *or* 500 mg PO single dose May repeat in 3 weeks if necessary	Headache, diarrhea, abdominal pain, and dizziness	Avoid during pregnancy. Use with caution in hepatic disease and inflammatory bowel diseases.
Enterobiasis (Pinworm)			
Mebendazole	*Adults and children*: 100 mg PO once; repeat in 2 weeks	Diarrhea and abdominal pain	Avoid during pregnancy. Use with caution in hepatic disease and inflammatory bowel diseases.
Pyrantel pamoate	*Adults and children*: 11 mg/kg PO once (max. 1 g), repeat in 2 weeks	Nausea, vomiting, headache, dizziness, diarrhea, and abdominal cramps	Avoid in pregnancy. Use with caution in hepatic disease.
Albendazole	*Adults and children*: 400 mg PO once; repeat in 2 weeks	Nausea, vomiting, headache, and abnormal liver function tests	Avoid during pregnancy.
Filariasis			
Diethylcarbamazine	*Adults*: day 1, 50 mg PO; day 2, 50 mg tid; day 3, 100 mg tid; days 4–14, 6 mg/kg/day in three doses *Children*: day 1, 25–50 mg; day 2, 25–50 mg tid; day 3, 50–100 mg tid; days 4–14, 6 mg/kg/day in three doses	Severe allergic or febrile reactions, GI disturbance, and, rarely, encephalopathy	

Drug of Choice	Dosage	Adverse Effects	Warnings
Albendazole	400 mg PO once daily for 10 days	Nausea, vomiting, headache, and abnormal liver function tests	Avoid during pregnancy.
Flukes (Trematodes)[b]			
Praziquantel	*Adults and children*: 40 mg/kg PO in two divided doses 4 hours apart (*Schistosoma haematobium*, *S. mansoni*, and *S. intercalatum*) 60 mg/kg PO in three divided doses 4 hours apart or two divided doses 6 hours apart (*S. japonicum* and *S. mekongi*)	Malaise, headache, dizziness, sedation, fever, and abdominal distress	Contraindicated with other strong CYP inducers (rifampin) Contraindicated in ocular cysticercosis
Giardiasis			
Metronidazole	*Adults*: 250 mg PO tid or 500 mg bid with meals × 5–7 days *Children*: 15 mg/kg/day PO tid × 5–7 days	Nausea, headache, metallic taste, and disulfiram reaction with alcohol	Avoid use in first trimester of pregnancy.
Tinidazole	*Adults*: 2 g PO single dose *Children*: 50 mg/kg single dose	Metallic or bitter taste, anorexia, nausea, vomiting, epigastric discomfort, and fatigue	Contraindicated in first trimester of pregnancy and those breastfeeding
Nitazoxanide	*Adults and children*: >12 years: 500 mg PO bid × 3 days *Children*: 7.5 mg/kg bid for 3 days in children >12 years old	Abdominal pain, diarrhea, vomiting, and headache	Has not been studied in those with hepatic or renal impairment
Paromomycin (drug of choice in first trimester of pregnancy)	*Adults*: 500 mg PO tid for 10 days *Children*: 25 mg/kg/day in three divided doses × 5–10 days	Nausea, vomiting, diarrhea, and cramps	Contraindicated in GI obstructions Use with caution in renal impairment.
Albendazole	400 mg PO daily × 5 days	Nausea, vomiting, headache, and abnormal liver function tests	Avoid during pregnancy.
Mebendazole	200 mg PO tid for 5 days	Headache, diarrhea, abdominal pain, dizziness	Avoid during pregnancy. Use with caution in hepatic disease and inflammatory bowel diseases.
Hookworm			
Mebendazole	*Adults and children*: 100 mg PO bid × 3 days *or* 500 mg PO single dose	Headache, diarrhea, abdominal pain, and dizziness	Avoid during pregnancy. Use with caution in hepatic disease and inflammatory bowel diseases.
Albendazole	400 g PO single dose	Nausea, vomiting, headache, and abnormal liver function tests	Avoid during pregnancy.
Lice			
1% Permethrin (Nix®)	See Table 81-4 for instructions.	Occasional allergic reaction, mild stinging, and erythema	Use with caution in those sensitive to chrysanthemums. Not recommended for eyebrow or eyelashes infestations.
Ivermectin	*Adults and children:* 200 μg/kg × 3, day 1, 2, and 10	Fever, pruritus, sore lymph nodes, headache, joint pains, and, rarely, hypotension	Use with caution in those with severe asthma.
Leishmaniasis			
Sodium stibogluconate	*Adults*: 20 mg /kg IV or IM × 20–28 days *Children*: Same as in adults	GI, malaise, headache arthralgias, myalgias, anemia, neutropenia, and thrombocytopenia; ECG abnormalities (ST- and T-wave changes)	Use with caution in those with cardiac disease. Use with caution in those with real or hepatic impairment.
Liposomal amphotericin B	Immunocompetent: 3 mg/kg/day on days 1–5, 14, and 21. Repeat if needed. Immunocompromised: 4 mg/kg/day on days 1 through 5, 10, 17, 24, 31, and 38. Seek advice if further therapy is needed.	Hypotension, chills, headache, anemia, thrombocytopenia, fever, and elevated serum creatinine	

Drug of Choice	Dosage	Adverse Effects	Warnings
Scabies			
5% Permethrin (Elimite® cream)	Apply topically to whole body. Remove cream by washing (shower or bath) after 8–14 hours.	Rash, edema, and erythema	Use with caution in those sensitive to chrysanthemums.
Alternatives for scabies			
Ivermectin	*Adults*: 200 µg/kg PO; repeat in 2 weeks	Nausea, diarrhea, dizziness, vertigo, and pruritus	Use with caution in those with severe asthma.
Lindane (Kwell®)	Apply topically once.	Not recommended in pregnant females, infants, and patients with massively excoriated skin. Second-line therapy when other alternatives have failed	Not recommended by American Academy of Pediatrics Second-line only US boxed warning because of neurologic toxicity Banned in California, United Kingdom, Australia
Crotamiton 10% (Eurax®)	Apply topically to whole body, especially to folds and creases. May repeat in 24 hours. Cleansing bath 48 hours after last application	Local skin irritation	Do not apply to raw, weeping skin. Not to be swallowed
Tapeworm[c,d]			
Praziquantel	*Adults and children*: 5–10 mg/kg PO single dose	Malaise, headache, dizziness, sedation, eosinophilia, and fever	Contraindicated with other strong CYP inducers (eg, rifampin) Contraindicated in ocular cysticercosis
Hydatid cysts[e]			
Albendazole	*Adults*: 400 mg bid × 8–30 days, repeat if necessary *Children*: 15 mg/kg/day × 28 days, repeat if necessary (surgical resection may precede drug therapy)	Diarrhea, abdominal pain, rarely hepatotoxicity, and leukopenia	Avoid use during pregnancy.
Trichomoniasis			
Metronidazole	*Adults*: 2 g PO × 1 day or 250 mg PO tid × 7 days *Children*: 15 mg/kg/day PO tid × 7 days	Nausea, headache, metallic taste, disulfiram reaction with alcohol, and paresthesia	Avoid use in first trimester of pregnancy.

bid, twice daily; CYP, cytochrome P450; ECG, electrocardiogram; GI, gastrointestinal; IM, intramuscularly; IV, intravenously; PO, orally; tid, three times daily.

[a]Does not include drugs used in the treatment and prophylaxis of malaria. (See Table 81-1 for the drugs used for malaria prophylaxis, as well as guidelines by the Centers for Disease Control [CDC] and World Health Organization [WHO] for treatment and prophylaxis of malaria.)

[b]*Schistosoma haematobium*, *S. mansoni*, *S japonicum*, *Clonorchis sinensis*, and *Paragonimus westermani*.

[c]Off-label use for tapeworms. Dose for *Hymenolepis nana* is 25 mg/kg single dose.

[d]*Diphyllobothrium latum* alternative treatment: adults, niclosamide 2 g orally once; children, 50 mg/kg (max. 2 g) orally once.

[e]*Echinococcus granulosus* and *E. multilocularis*.

Sources: *Drug Facts and Comparisons*. Accessed August 13, 2020. https://www.wolterskluwer.com/en/solutions/lexicomp/facts-and-comparisons. Wolters Kluwer Health, Inc; Drugs for parasitic infections. *Med Lett*. 2013;11 (suppl):e1–e31. Accessed August 31, 2020. https://www.uab.edu/medicine/gorgas/images/docs/syllabus/2015/03_Parasites/Rx

ParasitesMedicalLetter2013.pdf; Iodoquinol. Yodoxin. *Medscape*. Accessed August 18, 2020. https://reference.medscape.com/drug/yodoxin-iodoquinol-342656.

Paromomycin and metronidazole cause diarrhea, which may hinder evaluation of treatment efficacy and should therefore not be taken simultaneously.[49]

In those with a confirmed diagnosis of amebiasis, one study showed the addition of the probiotic *Saccharomyces boulardii* with metronidazole reduced the duration of bloody diarrhea and aided in the clearance of cysts when compared to metronidazole alone.[50]

J.D. must be monitored for the improvement of symptoms of diarrhea and abdominal pain. A follow-up stool sample should be examined to confirm response 1 week after completing therapy. Close contacts with J.D. should be screened for *E. histolytica* infection and receive treatment if their test result is positive. For contacts whose test result is negative, no treatment or follow-up screening is required.[51]

Amebic cyst carrier

CASE 81-5

Question 1: A.T., a 60-year-old female, presents to her primary care physician (PCP) for her annual examination after multiple trips to Southeast Asia. A.T. is currently asymptomatic, but her stool test result was positive for *E. histolytica* cysts.

Should A.T. be treated?

A.T. is an asymptomatic cyst passer. Cyst passers often do not develop invasive infections, and sometimes can clear the infection spontaneously.[32] Detection of the nonpathogenic cyst *E. dispar* does not require treatment, but all asymptomatic patients with positive test results of *E. histolytica* must be treated to reduce the transmission to others.[31,32]

Case 81-5, Question 2: What medications should be used to treat A.T.?

Intraluminal amebicides are the drugs of choice in the treatment of asymptomatic amebiasis. Paromomycin is the drug of choice, 25 to 35 mg/kg/day orally in three divided doses for 5 to 10 days with meals. Diloxanide furoate (not commercially available in the United States) or iodoquinol may also be recommended, but paromomycin has a higher efficacy rate when compared to diloxanide.[52] A.T.'s stools must be tested 1 week after completing therapy to ensure eradication of the infection.[51]

Close contacts with A.T. should be screened for *E. histolytica* infection and receive treatment if their test result is positive.[51]

Extraintestinal infections

CASE 81-6

Question 1: M.B. is a 29-year-old male presenting to the ED for worsening upper right quadrant abdominal pain, fever, and chills that started 2 days ago. Upon physical examination the patient shows signs of difficulty breathing during inspiration, with pain radiating to the shoulder and back and abdominal tenderness. Rales at the right base could be heard on examination. Laboratory results are significant for leukocytosis with neutrophilia, mild anemia, elevated alkaline phosphate, and alanine aminotransferase. Blood serology shows high antibody titers for *Entamoeba*. Computed tomography (CT) confirmed the presence of an abscess in the right lobe of the liver.

How should M.B. be managed?

Extraintestinal infections occur in <1% of patients with *E. histolytica*, of which liver abscesses are the most common. The right hepatic lobe is the most frequently affected area because of the portal circulatory system of the colon.[44] M.B.'s clinical presentation and laboratory findings are consistent with a hepatic abscess. Diarrhea is reported in ~50% of those with hepatic invasion.[44] The drug of choice for amebic liver abscess is metronidazole for 5 to 10 days followed with a luminal agent such as paromomycin.[34] Aspiration or drainage of the abscess is not recommended unless there is a failure to respond to therapy after 4 to 5 days, evidence of

a secondary infection, or impending rupture into the pericardium. After the completion of therapy, M.B. should be monitored for regression of the abscess with ultrasounds, and lesions may take up to 12 months to resolve. Complications of hepatic abscesses may include perforation of the abdominal cavity, septic shock, or superinfections. Infections outside of the intestines or liver are extremely rare, and dissemination of the amebae to the brain, lung, or skin is almost always associated with amebic liver abscess.[46,53]

Treatment During Pregnancy

CASE 81-7

Question 1: N.L., a 25-year-old female refugee from Sudan, presents to the clinic with an 8-day history of watery stools with blood streaks, abdominal cramping, and a fever. She is currently 11 weeks pregnant and has received no prenatal care before her arrival in the United States 4 weeks ago. Physical examination reveals a temperature of 100.4 °F (38 °C), HR 82 bpm, and BP 140/85 mm Hg. An examination of fresh stools is positive for occult blood and trophozoites. Stool antigen test confirmed the presence of *E. histolytica.* Bacteria culture results are negative for *Campylobacter*, *salmonellosis*, and *shigellosis*. Ultrasound imaging and CT findings are negative for the presence of liver abscesses. A diagnosis of intestinal amebiasis is made.

How would you manage N.L.'s infection? What are your concerns regarding her current condition?

N.L. needs to be treated for her intestinal amebiasis. The treatment of choice is metronidazole, but she is in her first trimester of pregnancy. Nitroimidazoles such as metronidazole and tinidazole should be avoided during the first trimester of pregnancy. Metronidazole readily crosses the placenta, and its effects on the development of the fetus are unknown.[48,54] N.L. should be treated with paromomycin 25 to 35 mg/kg/day orally in three divided doses for 5 to 10 days. Paromomycin is an aminoglycoside that is poorly absorbed in the bowel with an excellent safety profile. The most common adverse effects are nausea, vomiting, and abdominal

cramps.[34],[43] N.L.'s stools must be tested 1 week after completing therapy to ensure eradication of the infection.[51]

If N.L.'s infection does not resolve or progresses to fulminant colitis or amebic liver abscess, she will safely be beyond her first trimester, and should be treated appropriately with a tissue amebicide such as metronidazole followed by a luminal agent such as paromomycin, or second-line agents such as iodoquinol or diloxanide furoate. If iodoquinol is chosen, the most common adverse effects are headache, nausea, and vomiting. Optic nerve damage is a concern with elderly patients, so iodoquinol should be avoided in this population. Reported cases of peripheral neuropathy have occurred in doses in excess of the recommended dose. The most common adverse effect with diloxanide furoate is flatulence. It is not commercially available in the United States.[36],[45]

Close contacts with N.L. should be screened for *E. histolytica* infection and receive treatment if their test result is positive. For contacts whose test result is negative, no treatment or follow-up screening is required.[51]

GIARDIASIS

Prevalence and Transmission

Giardia is a globally endemic illness caused by the protozoa *Giardia lamblia*.[55] The highest number of cases are typically seen in developing countries with inadequate sanitary conditions, untreated water, or contaminated food. Although primarily seen in Asia, Africa, and South America, it is the most frequent parasitic intestinal disease in the United States.[55],[56] Those at greatest risk live in rural areas with poor sanitation, low socioeconomic conditions, and have contact with infected individuals or travel internationally. *Giardia* is most prevalent in children and immunocompromised individuals. Presentation of illness varies between individuals from self-limiting

diarrhea to more severe symptoms of chronic diarrhea, abdominal cramps, loose pale greasy stools that float, fatigue, weight loss, and malabsorption of fat, lactose, vitamins A and B_{12}, but many present with no symptoms.[56] In high-risk areas, children may experience impaired growth because of malabsorption, even in the absence of acute diarrhea.[56],[57] Severe *Giardia* infections may lead to mucosal damage in the small intestines.

Life Cycle

Infection occurs with the ingestion of cysts in contaminated water, food, or by the fecal–oral route. In the small intestine, excystation releases trophozoites (each cyst produces two trophozoites).[55] Trophozoites replicate in the lumen of the proximal small bowel, where they can be free or attached to the mucosa by a ventral sucking disk. Encystation occurs as the parasites transit toward the colon and are excreted in the feces. The cysts are hardy, surviving in environmental elements such as cold water and chlorination for weeks (**Fig. 81-4**).[56],[58]

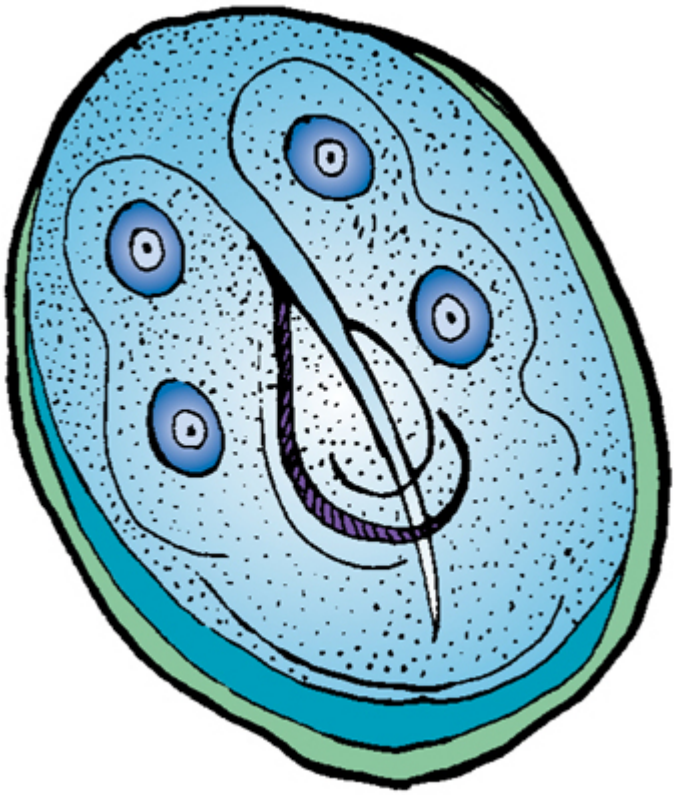


Figure 81-4 *Giardia lamblia* cyst.

Diagnosis

SIGNS AND SYMPTOMS

CASE 81-8

Question 1: K.P., a 32-year-old male who returned 2 weeks ago from a mission trip from Uganda, presents to the clinic with diarrhea, pale-colored foul-smelling greasy stools, bloating, and fatigue. He states he has been having diarrhea and flatulence for about 4 weeks. He experienced other bouts of diarrhea while on his year-long mission, but it resolved itself quickly, and his symptoms occurred typically after drinking out of one of the town's water sources. He has lost 15 pounds (6.80 kg) since the diarrhea started. He denies any blood or mucus in his stool and has no fever. Laboratory findings are the following: fecal fat content >9 g (normal 2-7 g over a 24-hour period), and complete blood count (CBC) results are anemia with thrombocytopenia and low levels of vitamin A. Three separate stool sample results were positive for *G. lamblia* cysts with antigenic tests confirming the presence of *G. lamblia*.

What clinical findings does K.P. have that support the diagnosis of giardiasis?

Patients with *Giardia* may be asymptomatic, and present with self-limiting diarrhea or with symptoms of chronic diarrhea with abdominal pain, yellowish greasy foul-smelling stools, abdominal distension, weight loss, or flatulence. Patients presenting with chronic diarrhea may suffer from dehydration and malabsorption of fat, lactose, and vitamins A and B_{12}.[56,59] The typical incubation period is 6 to 15 days after ingestion of the cysts. Infections may occur with as few as 10 cysts.[60] A giardiasis diagnosis is confirmed by signs and symptoms and the presence of cysts or trophozoites in stool samples. One stool sample may miss the presence of cysts, so multiple stool sample tests (at least three) are recommended.[58,61,62] Stool antigen test by either enzyme-linked immunosorbent assay (ELISA) or direct fluorescent antigen (DFA) are more sensitive than is traditional wet mount microscopy, and should be performed if a patient presents with symptoms consistent with giardiasis but have multiple negative results for cysts. A differential diagnosis ruling out bacterial (*Salmonella*, *Shigella*, *Campylobacter*) and viral (rotavirus, norovirus) causes should be made because the presentation may be similar. *Giardia* differs from these infections by its length of illness (7–10 days before first presentation) and evidence of weight loss.[58]

K.P.'s history of missionary work in Uganda is considered high risk. He may have consumed contaminated food or water, particularly if he drank untreated water from the town water source. His symptoms are consistent with chronic giardia: foul-smelling greasy stools, periods of diarrhea and constipation, fatigue, and bloating. Some patients will also present with flatulence, nausea or vomiting, or dehydration.[60] His laboratory results are consistent with malabsorption: fecal fat content is >9 g (normal fecal fat content is >7 g)[59]; a result >7 g is indicative of fat malabsorption resulting in steatorrhea.[61] Chronic infections may also present with anemia and low vitamin A and B_{12} levels. K.P. had *G. lamblia* cysts identified in the stool after three tests and confirmed with antigenic testing. A definitive diagnosis of *Giardia* can be made.

CASE 81-8, QUESTION 2: How should K.P. be treated?

Treatment of choice for K.P.'s giardiasis is a nitroimidazole. Tinidazole 2 g as a single oral dose with food may be preferred to metronidazole because of the single-dose treatment with similar rate of efficacy and better tolerance.[58],[62] Other first-line medications include metronidazole 250 mg orally three times a day for 5 to 7 days and nitazoxanide (Alinia®) 500 mg orally twice a day with food for 3 days. Paromomycin 500 mg orally three times daily with food for 10 days is an alternative treatment and is the drug of choice during the first trimester of pregnancy.[63] Albendazole (Albenza®) 400 mg orally once daily for 5 days is well tolerated and has activity against other parasites such as hookworm.[64],[65] Quinacrine[66] and Furazolidone[67] are effective options, but are not commercially available in the United States.

K.P. should be counseled to practice good hygiene, washing hands with soap and water for at least 20 seconds, to control transmission of disease.[65] Symptoms of diarrhea typically subside in 1 to 2 days and completely resolve in 10 days. Symptoms of malabsorption may take up to 4 to 8 weeks to resolve.[68],[69] If treatment failure occurs, another course of therapy is necessary. Refractory strains have been treated with success with either higher doses or a longer course of therapy.[68]

ENTEROBIASIS

Prevalence

Human enterobiasis or pinworm infection is caused by the intestinal nematode *Enterobius vermicularis.* It is the most common helminthic infection worldwide. The highest rate of infection occurs in school-age children (5–10 years), institutionalized persons, and household members or caretakers of an infected individual. Transmission occurs via the fecal–oral route, with finger sucking considered a

source of infection for children. If one family member is infected, all members of the family must be treated.[70–72]

Life Cycle

Humans are the only host of *E. vermicularis*. The entire life cycle occurs in the GI system for ~4 weeks. Infected eggs are ingested from food, water, or contaminated hands that have scratched the perianal area. Person-to-person transmission may occur from contaminated clothing or bed linen. Once eggs are ingested, they hatch in the small intestine.

Copulation occurs in the ileum, where the male typically dies and passes in the stool.[73] The gravid female settles into the large intestine and cecum. The female body fills with ~11,000 eggs and makes nocturnal migrations to the rectum and anus, where oxygen is needed for the maturation of eggs. Eggs are then deposited in the area around the anus, causing severe pruritus.[74]

SIGNS AND SYMPTOMS

CASE 81-9

Question 1: B.D. is a 5-year-old boy presenting to the pediatrician. B.D.'s mother states he has been scratching the perianal area for the past week. The intense itching has been keeping him up most of the night. B.D. is 45 inches (114.30 cm) tall and weighs 41.88 pounds (19 kg). A cellophane tape swab is placed over the skin of the perianal area, and evidence of *E. vermicularis* eggs are found under the microscope.

What signs and symptoms does B.D. exhibit to confirm a diagnosis of pinworm?

Many infected with pinworms are asymptomatic or present with mild symptoms; the most common symptom being nocturnal perianal pruritus and scratching because of the deposit of eggs to the perianal skin. The intense scratching may lead to secondary bacterial infections and sleep disturbances. Patients with major infestations may present with abdominal pain, anorexia, or insomnia.

Enterobiasis infections rarely cause serious disease, but it may result in dysuria or vaginal infections.[75,76]

B.D. is presenting with perianal itching, inability to sleep because of intense itching, and a positive "tape test" finding showing *E. vermicularis* eggs indicative of a pinworm infestation (**Fig. 81-5**).

Figure 81-5 Adult male *Enterobius vermicularis image*. (Source: Centers for Disease Control and Prevention. DpDx—Laboratory identification of parasitic diseases of public concern. Enterobiasis Image Gallery. Accessed October 26, 2020. https://www.cdc.gov/dpdx/enterobiasis/index.html.)

CASE 81-9, QUESTION 2: How should B.D.'s infection be managed? Should his parents be treated?

There are three options for the treatment of pinworm: albendazole (Albenza®), mebendazole (Emverm®), and pyrantel pamoate

(Reese's Pinworm Medicine®—available without a prescription). For B.D., any of the following regimens is appropriate: albendazole 400 mg orally in a single dose, mebendazole 100 mg orally in a single dose, or pyrantel pamoate 11 mg/kg (maximum 1 g) orally in a single dose. A second dose of the same agent must be repeated in 2 weeks.[76,77]

Albendazole and mebendazole are antihelminthic agents that selectively interfere with the microtubules of nematodes, leading to their death.[78] Because these medications do not kill existing eggs, a second dose should be repeated in 2 weeks to kill worms that hatch from these eggs.[75] Albendazole is considered the drug of choice in the treatment of enterobiasis with a 90% cure rate.[77,79] Both albendazole and mebendazole are well tolerated, with abdominal pain as the most common adverse effect reported.[80] Pyrantel pamoate is a depolarizing neuromuscular agent that acts by paralyzing adult worms, resulting in their expulsion in the stool. The most common adverse effects are nausea and vomiting. The liquid formulation must be shaken well before use, and may be mixed with fruit juice or milk.[81]

All members of B.D.'s family need to be treated simultaneously. Other preventative methods include proper hand hygiene, particularly after toilet use and before meals, trimming of fingernails, and frequent washing of bed linen and undergarments using hot water.[75]

CESTODIASIS

Description

Intestinal cestodes (tapeworms) are segmented worms; adults primarily live in the GI tract, but larvae can live in any organ.[82] There are several species that affect humans: *Taenia saginata* (beef tapeworm), *T. solium* (pork tapeworm), *Diphyllobothrium latum*

(broad or fish tapeworm), *T. asiatica* (Asian tapeworm), and *Hymenolepis nana* (dwarf tapeworm). Humans become infected by eating raw or undercooked meat (pork or beef) or fish (*D. latum*).[83]

A tapeworm attaches to the mucosa of the intestines by a scolex, the anterior portion of the tapeworm or the "head of the tapeworm."[82–84] The crown of the scolex is referred to as the *rostellum*; it may be armed with hooklets or unarmed (no hooklets). Proglottids or segments form behind a short neck. As each proglottid matures, they form a chain called a *strobili*, giving the tapeworm its ribbonlike appearance. The length of the strobili varies by species (*T. saginata* may have >2000 proglottids). Mature proglottids contain eggs that are indistinguishable between species. A definitive diagnosis is made by examining the scolex, proglottids, and eggs.

Tapeworms obtain nutrients through their skin directly from the host, and they do not invade the tissue mucosa or acquire blood; therefore, symptoms are often absent or mild in nature.[83] Typical symptoms involve the GI tract, and mild eosinophilia and elevated immunoglobulin (Ig)E levels may be detected. *T. solium* infections may lead to cysticercosis; neurocysticercosis, the most serious form, involves the central nervous system. It is important, therefore, to seek treatment with any tapeworm infection.

Life Cycle

Humans are the only definitive host for *T. saginata* and *T. solium*. Cattle or pigs are infected by ingesting vegetation contaminated with eggs or gravid proglottids passed in feces. Eggs hatch and invade the intestinal wall and migrate to the muscles, where they develop into cysticerci, thin-walled cysts that contain a single larval scolex.[85] Humans become infected by eating raw or undercooked meat. In humans, the cysticerci develop in the small intestines to an adult worm over a period of 2 months and can survive for years. Adult worms produce proglottids, which mature and become gravid, detach from the worm, and migrate to the anus or are passed in feces.[85]

Epidemiology

It is estimated that the prevalence of *Taenia* infections is ~170 to 200 million cases worldwide.[86],[87] *T. solium* occurs worldwide where pigs are raised, but it is most prevalent in Latin America, sub-Saharan Africa, China, India, and Southeast Asia.[82],[83] *T. saginata* can occur anywhere raw or undercooked beef is eaten. Most prevalent areas of occurrence are Eastern Europe, Russia, East Africa, Latin America, Indonesia, and China.[86] Rural and poor socioeconomic areas in developing countries with poor hygiene are at greatest risk.[87] Most cases of neurocysticercosis in industrial countries are primarily seen in refugees, immigrant populations, or travelers from endemic countries.

Cysticercosis

Cysticercosis is caused by the larval cysts of the *T. solium* tapeworm. The larvae migrate to muscle tissue, brain, subcutaneous tissue, or the eye. When the infection develops in the central nervous system, it is called *neurocysticercosis*, and is responsible for one-third of acquired epilepsy cases worldwide.[87] Signs and symptoms vary by location of the cyst. Clinical manifestations of cysts in the muscle may be absent other than a lump under the skin. Cysts that deposit in the eye may cause floaters in the eye or blurry vision.[88] Clinical manifestations of neurocysticercosis depends on how many cysts are found and the location; symptoms include seizures, focal neurologic deficits, cognitive decline, and increased intracranial pressure.[88],[89]

Diagnosis of neurocysticercosis is made by clinical presentation and radiologic imaging such as magnetic resonance imaging (MRI) or CT scans.[86] Treatment should be customized for each patient, depending on the size, location, and stage of the cysticerci. Treatment includes use of antihelminthic agents, such as praziquantel and/or albendazole. Coadministration of corticosteroids and antiepileptic drugs are used to manage seizures and the

inflammatory response because of the cysticidal activity of praziquantel therapy. Severe cases may require surgery.[89–92]

Taenia Saginata and *Taenia Solium*

SIGNS AND SYMPTOMS

CASE 81-10

QUESTION 1: P.R. is a 25-year-old missionary who lived 2 years in Ghana. She recently returned to the United States and is experiencing with perianal itching and diffuse abdominal discomfort (primarily cramping). She states she has lost about 15 pounds (6.80 kg) over the past few weeks. She reports no fever but mild constipation and nausea, and states that she sees "moving pieces of rice-looking objects" in her stool. Laboratory test results show slightly elevated eosinophil count and IgE levels and low levels of vitamin B_{12}. Three stool samples, obtained on separate days, and a cellophane tape test of the perianal area revealed the presence of *T. saginata eggs*.

Are P.R.'s symptoms consistent with *Taenia* infection? How can infections be differentiated?

Patients presenting with tapeworm infections may present with a range of symptoms. Many present with no symptoms, but if symptoms are present, then they are often mild. Symptoms include abdominal pain, cramps, flatulence, constipation, nausea, vomiting, headache, vitamin deficiency, or weight loss. More severe symptoms include appendicitis and pancreatitis. Patients may report the voiding of segments from the anus and in the feces. Some patients may present with moderate eosinophilia and elevated IgE because of the weak immunogenic activity of the adult worms.[84]

The eggs of *T. saginata* and *T. solium* are morphologically indistinguishable. A definitive diagnosis of species is made by examining the scolex (in rare cases) or, more likely, the mature gravid proglottids. Eggs and proglottids are only detected in the feces 2 to 3 months after the infection has been established. The CDC recommends three separate stool samples on different days to establish a diagnosis.[88] *T. solium* scolex is characterized by a scolex

with four large suckers and rostellum with two rows of hooks (see **Fig. 81-6**).[84,93,94] *T. saginata* has a scolex with four suckers, but no rostellum or hooks (see **Fig. 81-7**).[93] Biomolecular assays are more accurate than are microscopic stool examinations to distinguish between species, but are only available in a research laboratory setting.[94]

Figure 81-6 Scolex of *Taenia solium* image. (Source: Centers for Disease Control and Prevention. DpDx—Laboratory identification of parasitic diseases of public concern. Taeniasis Image Gallery. Accessed October 26, 2020. https://www.cdc.gov/dpdx/taeniasis/index.html.)

Figure 81-7 Scolex of *Taenia saginata* image. (Source: Centers for Disease Control and Prevention (CDC). DpDx—Laboratory identification of parasitic diseases of public concern. Taeniasis Image Gallery. Accessed October 26, 2020. https://www.cdc.gov/dpdx/taeniasis/index.html.)

Case 81-10, Question 2: How should P.R. be treated and how should treatment be evaluated?

The drug of choice for both *T. saginata* and *T. solium* infections is praziquantel (Biltricide®) 5 to 10 mg/kg as a single oral dose.[95] Other dosing is species dependent.[96] Praziquantel works by killing the adult worm but does not destroy the eggs. Typical adverse effects include malaise, headache, dizziness, abdominal discomfort, and, rarely, urticaria. P.R. should be advised to swallow the tablet whole

with water and a meal. The bitter taste of the tablet may cause P.R. to gag or vomit, so it is advisable to swallow the tablet promptly. Praziquantel cannot be chewed, but it may be halved or quartered. It is contraindicated to administer praziquantel with strong cytochrome P450 (CYP450) inducers, such as rifampin, because adequate blood levels of praziquantel may not be achieved.[95] P.R. should also be advised not to drive or operate heavy machinery on the day of treatment and the following day because of possible central nervous system effects. Praziquantel has a high cure rate (up to 98%) in *T. saginata* and *T. solium* infections.[96]

An alternative regimen is niclosamide 2 g as a single oral dose (chewed) for adults and 50 mg/kg in children. It is not available for human use in the United States. For those infections resistant to praziquantel and niclosamide, nitazoxanide has been used with success in *T. saginata* infections.[83] With any treatment, it is recommended to examine stool samples for eggs 1 and 3 months after treatment to confirm eradication of the infection.[94]

Recovery of the scolex for species identification may be necessary; purging of the bowel is recommended.[83] There are two options: Administer electrolyte–polyethylene glycol before therapy or administer castor oil or magnesium sulfate solution within 2 hours of taking the antihelminthic drug. The tapeworm and its fragments should pass within 6 to 12 hours. Patients should be instructed to collect all feces for up to 72 hours to collect all fragments.

PEDICULOSIS

Prevalence

Pediculosis (lice infections) can be caused by *Pediculus humanus capitis* (head lice) (**Fig. 81-8**), *P. humanus* (body lice), or *Pthirus pubis* (crab lice). Lice infections remain a major problem throughout the world, and infestations can be present in all socioeconomic

groups.[97] It is estimated that treatment costs for head lice may exceed $1 billion in the United States.[98]

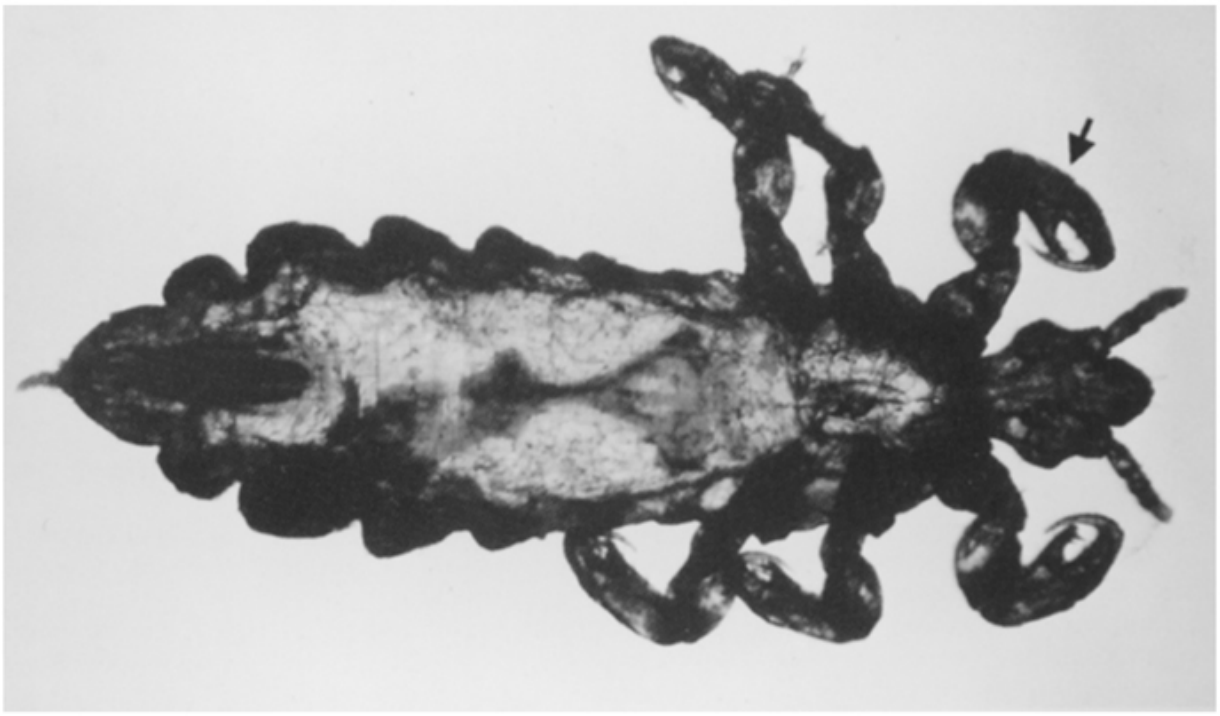


Figure 81-8 *Pediculus humanus capitis* (head lice).

Life Cycle

Head and body lice have similar life cycles, but their habitat preferences distinguish the two varieties. The life cycle of lice has three stages: egg, nymph, and adult. After fertilization, the female lays eggs (up to 10 a day), which attaches tightly to hair or seams of clothing. The eggs (nits) (see **Fig. 81-9**) hatch in 7 to 10 days and produce nymphs, which go through three molts to become adults. Lice feed by injecting a small amount of their saliva into the host and withdraw small amounts of blood; without these meals, they will die. The lice penetrate the host skin via stylets within their head and attach themselves by a circlet of teeth on their proboscis. Crab lice are usually found in pubic hair, less frequently on facial hair, eyebrows, eyelashes, and axillary hairs.[97],[99],[100]

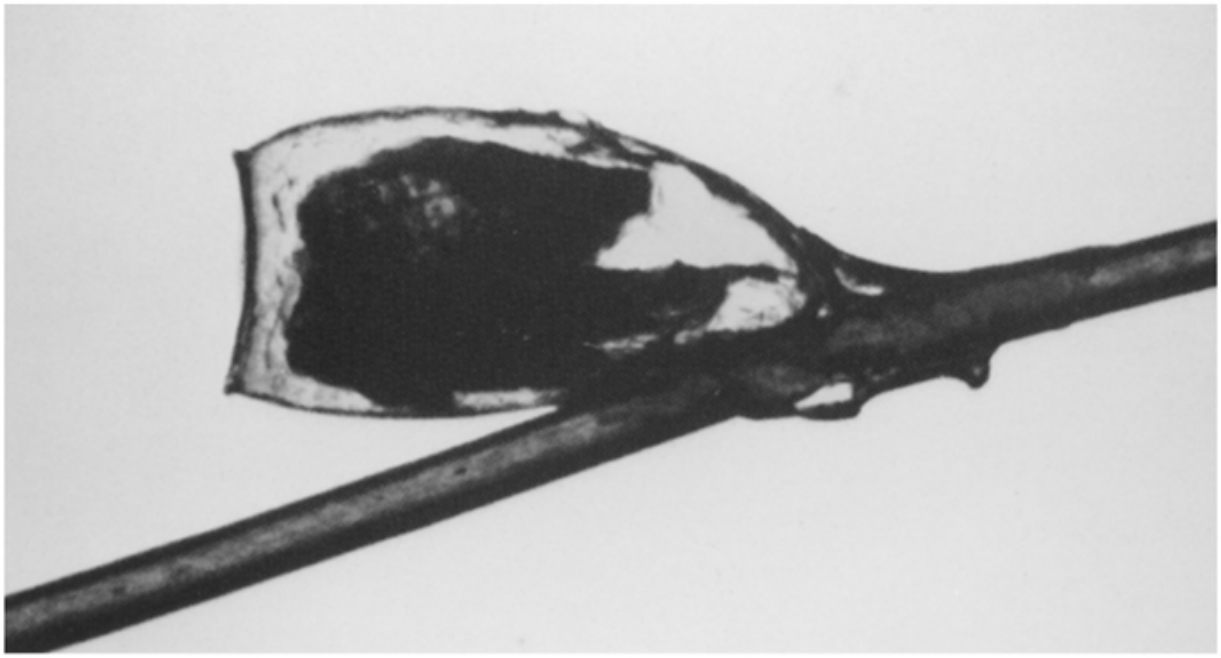


Figure 81-9 Nit or egg of lice on hair shaft.

Epidemiology

The highest incidence of head lice is seen among schoolchildren ages 3 to 12 years and in household members. It is less common in Black Americans because of different hair texture. The incidence of head lice infestation in the United States has been estimated to be between 6 and 12 million cases.[98] Body lice infest clothing by laying their eggs on the fabric. Head and crab lice infest hair by laying their eggs at the base of hair fibers. Hair and body lice are transferred between hosts by personal and clothing contact, whereas crab lice are transmitted by sexual contact.

SIGNS AND SYMPTOMS

CASE 81-11

Question 1: B.G., a 30-year-old homeless female who primarily lives in a tent city by the river, presents to a free clinic for intense itching all over her body. Upon examination, it is noted that she has a number of pustular lesions all over her body, and she complains of unbearable itchiness on her legs and abdomen.

The skin is particularly thick and discolored around her midsection. The triage nurse says she has "lice all over her body and in her hair."

Are the symptoms in B.G. consistent with lice infection?

The most common complaint of patients with head and body lice is pruritus of the scalp, ears, neck, and other body parts. Chronic infestations may result in hyperpigmentation and thickening of the skin. These changes are often seen in the waist, groin, and upper thigh areas ("vagabond's disease"). In severe infestations, intractable itching and scratching can result in folliculitis, hemorrhagic macules or papules, or secondary bacterial infections.[101–103] In contrast, schoolchildren who are exposed frequently to head lice may have only minor pruritus affecting the scalp, ears, and neck.[104] Lice infestation is diagnosed by identification of live nymph or adult lice on the scalp or body. The presence of live lice should be confirmed before initiating pharmacologic treatment.[102,103]

Treatment

Case 81-11, Question 2: How should B.G. be treated for lice infection of the head, body, and genital areas?

Concurrent treatment for the pustular bacterial lesions and lice infestation should be initiated in B.G. First-line treatment of head lice in adults, children, and pregnant and lactating females is permethrin 1% (Nix®) rinse. Alternative topical pediculicides are 0.5% malathion (Ovide®) lotion and pyrethrin 0.33% plus 4% piperonyl butoxide (Rid®). Permethrin and pyrethrins are well tolerated and the least expensive of the available agents.[103] Recent studies indicate that there may be differences in efficacy among the topical agents. Resistance of head lice to 0.5% malathion lotion has been documented in the United Kingdom. The formula used in the United States contains terpineol, dipentene, and pine needle oil, possibly responsible for delaying resistance in the United States.[98,105] Lindane

is FDA approved as a second-line therapy and should be used only when other alternatives have failed (and not for children under 110.23 pounds [50 kg]) because of neurologic toxicities (see **Table 81-4**).[98]

Table 81-4
Application of Nonprescription and Prescription Options for Head Lice[a,b]

Nonprescription Products	Application Directions
Permethrin 1% (Nix®)	Apply to damp hair that has been first shampooed with nonconditioning shampoo and towel dried. Leave on for 10 minutes and rinse off.
	Repeat in 7–10 days if live lice are seen (retreatment at 9 days is optimal). Alternative treatment schedule: 0, 7, and 13–15 days Conditioners and silicon-based products reduce residual effects of permethrin.
Pyrethrins plus piperonyl butoxide (Rid®) (available as mousse and shampoo)	Apply to dry hair and leave on for 10 minutes before rinsing off. Retreatment schedules same as permethrin. Significant resistance has been developed reducing its effectiveness.
Prescription Products	
Malathion 0.5% (Ovide®) lotion	Apply to dry hair, let air-dry, then wash off after 8–12 hours. Repeat in 7–9 days if live lice are seen. Highly flammable because of alcohol content. Instruct patients to let hair air-dry uncovered—do not use hair driers, curling irons, or flat irons while hair is wet. Resistance seen in the United Kingdom. Current U.S. formulation differs from European formulation—less resistance seen in the United States.
Benzyl alcohol 5% (Ulesfia™)	Apply a sufficient quantity to dry hair to saturate the scalp and the entire length of hair. Leave on for 10 minutes, then rinse off. Reapplication process is same as that for permethrin.
Spinosad 0.9% suspension	Apply to dry hair to saturate the scalp and work out to end of hair (may require the entire contents of bottle). Leave on for

(Natroba™)	10 minutes and rinse off. Retreat in 7 days if live lice are seen.
Ivermectin 0.5% lotion (Sklice™)	Apply to dry hair and scalp, leave on for 10 minutes, and rinse off. Only one application is needed.

There are various treatment options for head lice. Lack of adherence or failure to follow instructions may lead to resistance or failure to eradicate the louse.

[a]All topical products should be rinsed off over a sink with warm water—not in a shower or bath to limit exposure to the skin.

[b]Nits can be removed from the hair using a sturdy fine-tooth comb, especially for infants and young children.

Sources: Adapted from: Devore CD, Schutze GE, The Council on School Health and Committee on Infectious Diseases, American Academy of Pediatrics. Head lice [published correction appears in *Pediatrics*. 2015 Oct;136(4):781–782]. *Pediatrics*. 2015;135(5):e1355–e1365. doi:10.1542/peds.2015-0746; Centers for Disease Control and Prevention. Lice—Head lice—Treatment. Updated October 2019. Accessed August 12, 2020. http://www.cdc.gov/parasites/lice/head/treatment.html.

Body lice can be eliminated by bathing and laundering clothing in hot water. Because of B.G.'s severe infestation, she should also apply a topical pediculicide. Products for head lice may be used for body lice, with treatment repeated in 7 to 10 days.[97],[106] Oral medication such as ivermectin is not FDA approved, but has shown to be effective in some difficult-to-treat cases.[107] First-line treatment of pubic lice is permethrin 1% or pyrethrins plus piperonyl butoxide.[101] Alternative regimes include malathion 0.5% lotion to be rinsed off after 8 to 12 hours or ivermectin 250 µg/kg to be repeated in 14 days.[108] The pruritus in B.G. can be symptomatically treated with an antihistamine and a low-potency topical steroid.

Several "natural products" such as melaleuca plus lavender oil, coconut oil plus anise oil, tea tree oil, petrolatum shampoo, eucalyptus, mayonnaise, and Cetaphil® have been used in the management of lice.[109–111] None are FDA approved, and have not been proved to be more efficacious. Manual removal of nits by a fine-tooth comb can be a tedious task, but necessary because none of the pediculicides are 100% ovicidal. Application of vinegar-based

products 3 minutes before combing has been reported to make the process of “nit picking” easier.[98]

PETROLATUM

To remove lice from B.G.’s eyelids or eyelashes, ophthalmic-grade petrolatum ointment can be used.[101] Petrolatum is applied to the eyelashes and lid margins with cotton swabs two to four times daily for 10 days. This regimen will either suffocate the lice or physically remove them. Use of regular petrolatum may cause irritation to B.G.’s eyes.

DECONTAMINATION MEASURES

Treatment for pediculosis should include thorough decontamination to avoid reinfection. All personal articles of clothing, including bedding, should be washed and dried in temperatures >130 °F (54.44 °C).[98] Items that cannot be washed can be dry-cleaned or placed in a plastic bag for 2 weeks. Furniture and carpeting should be vacuumed; pediculicide spray is not recommended. Hairbrushes, combs, and other plastic articles can be decontaminated by soaking in hot water.[111] In institutions and schools where lice infestations are a problem, outer clothing (coats, hats, scarves) of individuals should be isolated in separate plastic bags at the beginning of the day. In addition, personal items (hats, combs) should not be shared. These measures will reduce reinfection significantly.

SCABIES

Prevalence

Scabies is a contagious skin infestation caused by the female mite, *Sarcoptes scabiei var. hominis*. Infestations occur throughout the world and across all ages and socioeconomic groups. The mite is transmitted by an infested individual through close skin contact; transmission through fomites (towels, clothing) is less likely, although

it may occur in crusted scabies.[112] Crusted scabies (Norwegian scabies), typically seen in immunocompromised individuals, is a more severe form that is highly infectious. Scabies outbreaks are often seen in institutional settings such as nursing homes and prisons.[112] Typical presentation is the presence of a pimple-like rash with intense itching that is often more severe at night. Most common sites of lesions are in the interdigital finger webs, wrists, elbows, buttock, and genitalia.[113–115] Those presenting with crusted scabies have thick crusts of skin containing a large number of mites and eggs.

Life Cycle

Adult females deposit eggs and feces (scybala) as they burrow under the skin. Once the eggs hatch, larvae are released, which eventually mature to nymphs and adult mites. The female mite can live up to 6 weeks producing two to four eggs daily. The classic presentation of skin lesions is a result of the burrowing action of the mites and hypersensitivity reactions to their excrement.

TREATMENT

CASE 81-12

QUESTION 1: A.H., a 30-year-old licensed practical nurse (LPN) working at a long-term care facility presents to her PCP with a pruritic rash with excoriations in the interdigital webs of her hands and wrists. Several patients and nurses in the same facility have similar symptoms as well as her husband and 10-year-old daughter. Burrows were present in her finger webs with a definitive diagnosis made from a skin scraping test. Microscopic examination revealed eggs of *S. scabiei* and scybala.

How should A.H. and her family be treated? What special instructions and precautions should accompany therapy?

There are several treatment options available for scabies. The treatment of choice in patients 2 months or older is permethrin 5% cream.[114] A thin layer must be applied to the skin from the neck to

the soles of feet for 8 to 14 hours and then washed off. A second application 1 to 2 weeks later may be necessary if living mites are still observed. Permethrin is considered safe for pregnant and lactating females.[114],[115] Although not FDA approved, oral ivermectin 200 mg/kg as a single dose and repeated in 2 weeks is also considered first-line treatment and has the advantage of ease of administration and low cost. A repeat dose is needed because of its limited ovicidal activity.[114] Ivermectin is not recommended for children age younger than 5 years, <33.06 pounds (<15 kg), or for pregnant or lactating females.[114] Lindane should be considered only as a second-line therapy because of reported toxicities and should not be used for children weighing 110.23 pounds (50 kg).[115],[116] Lindane is useful if first-line therapies are not tolerated or if treatment fails. Only Lindane shampoo is currently available in the United States; the lotion is no longer available. Other alternative agents include topical ivermectin, malathion, benzyl benzoate, and topical sulfur.[115],[117]

Symptoms after exposure to scabies may take several weeks to appear for first-time infections. Sexual partners and any other persons who have prolonged contact with an infested individual should be treated.[108] All members of the family should be treated at the same time to avoid reinfestation. Pruritus may persist, even with successful treatment, for up to 2 weeks; if symptoms persist after 2 weeks, evaluate for treatment failure. Combination treatment with topical permethrin and oral ivermectin is recommended for crusted scabies.[117]

A.H. must be educated on the nonpharmacologic measures to manage scabies. All bedding and clothing must be washed in hot water (140 °F [60 °C]) and hot dried or dry-cleaned. Items that cannot be washed, such as stuffed toys, may be placed in a sealed plastic bag for 48 to 72 hours because mites cannot survive for more than 72 hours away from human skin.[108],[117] Fumigation of living areas is not recommended.

ACKNOWLEDGMENT

The authors gratefully acknowledge Lin H. Chen, MD, Division of Infectious Diseases, Mount Auburn Hospital, for her expert review of this chapter.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Baird JK, Nelwan EJ, Taylor WR. Approach to the patient with malaria. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier Inc.; 2019:179–186. (10)

Choudhuri G, Rangan M. Amebic infections in humans. *Indian J Gastroenterol*. 2012;31(*4*):153–162. doi:10.1007/s12664-012-0192-2 (32)

Devore CD, Schutze GE, Council on School Health and Committee on Infectious Diseases, American Academy of Pediatrics. Head lice [published correction appears in *Pediatrics*. 2015 Oct;136(4):781–782]. *Pediatrics*. 2015; 135(*5*):e1355–e1365. doi:10.1542/peds.2015-0746 (98)

Escobedo AA, Almirall P, Robertson LJ, et al. Giardiasis: the ever-present threat of a neglected disease. *Infect Disord Drug Targets*. 2010;10(*5*):329–348. doi:10.2174/187152610793180821 (56)

Lalloo DG, Magill AJ. Malaria: epidemiology and risk to the traveler. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier Inc; 2019:137–144. (3)

Schlagenhauf P, Wilson ME, Petersen E, McCarthy A, Chen LH. Malaria chemoprophylaxis. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed.: Elsevier Inc.; 2019:145–168. (9)

Stanley SL Jr. Amoebiasis. *Lancet*. 2003;361(*9362*):1025–1034.doi:10.1016/S0140-6736(03)12830-9 (43)

Tan KR, Arguin PM. Malaria. In: Centers for Disease Control and Prevention. CDC Health Information for International Travel 2020. Accessed September 1, 2020. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria (6)

Vivancos V, González-Alvarez I, Bermejo M, Gonzalez-Alvarez M. Giardiasis: characteristics, pathogenesis and new insights about treatment. *Curr Top Med Chem*. 2018;18(*15*):1287–1303. doi:10.2174/1568026618666181002095314 (58)

White A Jr, Weller PF. Cestode infections. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 19 ed. McGraw-Hill; 2014. Accessed August 24, 2020. https://www.mhprofessional.com/medical/harrisons-principles-of-internal-medicine (82)

Key Websites

Centers for Disease Control and Prevention. Travelers' Health. http://www.cdc.gov/travel/

Centers for Disease Control and Prevention. Parasites. http://www.cdc.gov/parasites/index.html

Centers for Disease Control and Prevention. Sexually Transmitted Diseases 2021 Guidelines. https://www.cdc.gov/std/treatment-guidelines/toc.htm

World Health Organization. International travel and health. http://www.who.int/ith/en

World Health Organization. Neglected tropical disease–summary. https://www.who.int/health-topics/neglected-tropical-diseases#tab=tab_1

COMPLETE REFERENCES CHAPTER 81 PARASITIC INFECTIONS

1. World Health Organization. Health topics: malaria. Accessed September 1, 2020. https://www.who.int/health-topics/malaria#tab=tab_1
2. World Health Organization. The "World malaria report 2019" at a glance. Updated December 2019. Accessed August 31, 2020. https://www.who.int/news-room/feature-stories/detail/world-malaria-report-2019
3. Lalloo DG, Magill AJ. Malaria: epidemiology and risk to the traveler. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier Inc.; 2019:137–144.
4. World Tourism Organization. UNWTO World Tourism Barometer Nº18 January 2020. Accessed September 1, 2020. https://www.unwto.org/world-tourism-barometer-n18-january-2020

5. Centers for Disease Control and Prevention. Malaria and travelers for US residents. Updated February 12, 2020. Accessed September 1, 2020. http://www.cdc.gov/malaria/travelers/index.html
6. Tan KR, Arguin PM. Malaria. In: Centers for Disease Control and Prevention. CDC Health Information for International Travel 2020. Accessed September 1, 2020. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria
7. Centers for Disease Control and Prevention. Malaria—biology—lifecycle. Updated July 16 2020, Accessed September 1, 2020. https://www.cdc.gov/malaria/about/biology/index.html
8. Maguire JD, Sumawinata IW, Masbar S, et al. Chloroquine-resistant Plasmodium malariae in south Sumatra, Indonesia. *Lancet*. 2002;360(9326):58–60. doi:10.1016/S0140-6736(02)09336-4
9. Schlagenhauf P, Wilson ME, Petersen E, McCarthy A, Chen LH. Malaria chemoprophylaxis. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier Inc.; 2019:145–168.
10. Baird JK, Nelwan EJ, Taylor WR. Approach to the patient with malaria. In: Keystone JS, Kozarsky P, Connor B, Notfhdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier Inc.; 2019:179–186.
11. Genton B, D'Acremont V. Clinical features of malaria in returning travelers and migrants. In: Schlagenhauf-Lawlor P, ed. *Travellers' Malaria*. Decker; 2001:371–402.
12. Kain KC, Keystone JS. Malaria in travelers. Epidemiology, disease and prevention. *Infect Dis Clin North Am*. 1998;12:267–284. doi:10.1016/s0891-5520(05)70005-2
13. Baird JK, Hoffman SL. Prevention of malaria in travelers. *Med Clin North Am*. 1999;83:923–944.
14. Mace KE, Arguin PM, Tan KR. Malaria surveillance-United States, 2015. *MMWR Surveill Summ*. 2018;67(7):1–28. doi:10.15585/mmwr.ss6707a1
15. Leder K, Tong S, Weld L, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. *Clin Infect Dis*. 2006;43(9):1185–1193. doi:10.1086/507893
16. Centers for Disease Control and Prevention. Treatment of malaria: guidelines for clinicians (United States). Updated May 29, 2020. Accessed September 2, 2020. https://www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html
17. World Health Organization. *WHO Guidelines for Malaria, 16 February 2021*. Geneva: World Health Organization; 2021. Accessed March 23, 2022. https://apps.who.int/iris/rest/bitstreams/1332432/retrieve
18. Centers for Disease Control and Prevention. Artesunate now first-line treatment for severe malaria in the United States. Accessed September 1, 2020. https://www.cdc.gov/globalhealth/newsroom/artesunate.html?

CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fglobalhealth%2Fnewsroom%2Fartesunateupdate%2Findex.html

19. Centers for Disease Control and Prevention. Malaria: FDA approval of artesunate for injection for treatment of severe malaria. Accessed September 1, 2020. https://www.cdc.gov/malaria/new_info/2020/artesunate_approval.html
20. World Health Organization. International Travel and Health. Malaria. Accessed September 3, 2020. https://www.who.int/ith/diseases/malaria/en/
21. Youngster I, Barnett ED. Interactions between travel vaccine & drugs. Centers for Disease Control and Prevention. CDC Health Information for International Travel 2020. Oxford University Press. Accessed September 3, 2020. https://wwwnc.cdc.gov/travel/yellowbook/2020/preparing-international-travelers/interactions-between-travel-vaccines-and-drugs
22. Goodyer LI, Gibbs J. Medical supplies for travellers to developing countries. *J Travel Med*. 2004;11:208–212. doi:10.2310/7060.2004.19003
23. Centers for Disease Control and Prevention. Counterfeit and substandard Antimalarial drugs: information for travelers. Updated July 23, 2018. Accessed September 3, 2020. http://www.cdc.gov/malaria/travelers/counterfeit_drugs.html
24. Fradin MS. Insect protection. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier Inc.; 2019:43–52.
25. Mutebi JP, Gimnig JE. Mosquitoes, ticks & other arthropods. In: Centers for Disease Control and Prevention. CDC Health Information for International Travel 2020. Oxford University Press. Accessed September 3, 2020. https://wwwnc.cdc.gov/travel/yellowbook/2020/noninfectious-health-risks/mosquitoes-ticks-and-other-arthropods
26. Grobusch MP, Schlagenhauf P. Self-diagnosis and self-treatment of malaria by the traveler. In: Keystone JS, Kozarsky P, Connor B, Nothdurft H, Mendelson M, Leder K, eds. *Travel Medicine*. 4th ed. Elsevier Inc.; 2019:169–178.
27. World Health Organization. Development of recommendations for the protection of short-stay travellers to malaria-endemic areas: memorandum from two WHO Meetings. *Bull World Health Organ.* 1988;66:177–196.
28. World Health Organization. Malaria. In: *International Travel and Health.* Situation as on 1 January 2012. Accessed September 3, 2020. https://www.who.int/publications/i/item/9789241580472
29. Centers for Disease Control and Prevention. Malaria: how to reduce malaria's impact. Updated October 7, 2021. Accessed March 25, 2022. https://www.cdc.gov/malaria/malaria_worldwide/reduction/vaccine.html
30. Malaria Vaccine Initiative. Malaria vaccine technology roadmap: November 2013. Accessed September 3, 2020.

https://www.malariavaccine.org/sites/mvi/files/content/page/files/TRM_update_nov13.pdf
31. Bercu TE, Petri WA, Behm W. Amebic colitis: new insights into pathogenesis and treatment. *Curr Gastroenterol Rep*. 2007;9(5):429–433. doi:10.1007/s11894-007-0054-8
32. Choudhuri G, Rangan M. Amebic infections in humans. *Indian J Gastroenterol*. 2012;31(4):153–162. doi:10.1007/s12664-012-0192-2
33. Gunther J, Shafir S, Bristow B, Sorvillo F. Amebiasis-related mortality among United States residents, 1990–2007. *Am J Trop Med Hyg*. 2011;85(6):1038–1040. doi:10.4269/ajtmh.2011.11-0288
34. Pritt BS, Clark CG. Amebiasis. *Mayo Clin Proc.* 2008;83(10):1154–1160. doi:10.4065/83.10.1154
35. Centers for Disease Control and Prevention (CDC). Laboratory Identification of Parasites of Public Health Concern. Amebiasis. Accessed March 22, 2022. https://www.cdc.gov/dpdx/amebiasis/index.html.
36. Parija SC, Mandal J, Ponnambath DK. Laboratory methods of identification of *Entamoeba histolytica* and its differentiation from look-alike *Entamoeba* spp. *Trop Parasitol*. 2014;4(2):90–95. doi:10.4103/2229-5070.138535
37. Petri WA, Jr, Haque R. Entamoeba species, including amebiasis. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 7th ed. Churchill Livingstone; 2010:3411–3425.
38. Petri WA Jr, Singh U. Enteric amebiasis. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens, & Practice*. 2nd ed. Churchill Livingstone; 2006:967–990.
39. Heredia RD, Fonseca JA, López MC. *Entamoeba moshkovskii* perspectives of a new agent to be considered in the diagnosis of amebiasis. *Acta Trop*. 2012;123(3):139–145. doi:10.1016/j.actatropica.2012.05.012
40. Ali IK. Intestinal amebae. *Clin Lab Med*. 2015;35(2):393–422. doi:10.1016/j.cll.2015.02.009
41. Ross AG, Olds GR, Cripps AW, Farrar JJ, McManus D. Enteropathogens and chronic illness in returning travelers. *N Engl J Med*. 2013;368:1817–1825. doi:10.1056/NEJMra1207777
42. Centers for Disease Control and Prevention. DPDx: Amebiasis. Accessed August 31, 2020. https://www.cdc.gov/dpdx/amebiasis/
43. Stanley SL Jr. Amoebiasis. *Lancet.* 2003;361(9362):1025–1034. doi:10.1016/S0140-6736(03)12830-9
44. Ximenez C, Moran P, Rojas L, et al. Novelties on amoebiasis: a neglected tropical disease. *J Glob Infect Dis*. 2011;3(2):166–174. doi:10.4103/0974-777X.81695
45. Haque R, Huston CD, Hughes M, Houpt E, Petri WA. Amebiasis. *N Engl J Med*. 2003;348:1565–1573. doi:10.1056/NEJMra022710

46. Tanyuksel M, Petri WA Jr. Laboratory diagnosis of amebiasis. *Clin Microbiol Rev*. 2003;16(4):713–729. doi:10.1128/cmr.16.4.713-729.2003
47. Fotedar R, Stark D, Beebe N, Marriott D, Ellis J, Harkness J. Laboratory diagnostic techniques for *Entamoeba* species. *Clin Microbiol Rev*. 2007;20(3):511–532. doi:10.1128/CMR.00004-07
48. Product Information: FLAGYL(R) Oral Tablets, Metronidazole Oral Tablets. G.D. Searle (per FDA); 2013. Accessed August, 17, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/12623slr059_flagyl_lbl.pdf
49. McGuinness S, Leder K. Infectious diseases: Entamoeba. Infectious Disease Advisor Website. Accessed August, 31, 2020. https://www.infectiousdiseaseadvisor.com/home/decision-support-in-medicine/infectious-diseases/entamoeba/
50. Dinleyici EC, Eren M, Yargic ZA, Dogan N, Vandenplas Y. Clinical efficacy of Saccharomyces boulardii and metronidazole compared to metronidazole alone in children with acute bloody diarrhea caused by amebiasis: a prospective, randomized, open label study. *Am J Trop Med Hyg*. 2009;80(6):953–955.
51. Public Health England. Interim public health operational guidelines for Amoebiasis (*Entamoeba histolytica*). Published October 2017. Accessed August 31, 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/777437/Interim_Public_Health_Operational_Guidelines_for_Amoebiasis.pdf
52. Wolfe MS, Nondysenteric intestinal amebiasis. Treatment with diloxanide furoate. *JAMA*. 1973;224(12):1601–1604.
53. Centers for Disease Control and Prevention. Amebiasis. Updated October 15, 2020. Accessed August 31, 2020. https://www.cdc.gov/dpdx/amebiasis/index.html
54. U. S. Food and Drug Administration. Tinidazole. Accessed August 31, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021618s003lbl.pdf
55. Centers for Disease Control and Prevention. Giardia: pathogen and environment. Updated February 2017. Accessed August 14, 2020. http://www.cdc.gov/parasites/giardia/pathogen.html
56. Escobedo AA, Almirall P, Robertson LJ, et al. Giardiasis: the ever-present threat of a neglected disease. *Infect Disord Drug Targets*. 2010;10(5):329–348. doi:10.2174/187152610793180821
57. Centers for Disease Control and Prevention. Giardia: illness and symptoms. Updated July 2015. Accessed August 24, 2020. http://www.cdc.gov/parasites/giardia/illness.html
58. Vivancos V, González-Alvarez I, Bermejo M, Gonzalez-Alvarez M. Giardiasis: characteristics, pathogenesis and new insights about treatment. *Curr Top*

Med Chem. 2018;18(15):1287–1303. doi:10.2174/1568026618666181002095314

59. Ryan ET, Cronin CG, Branda JA. Case 38-2011: a 34-year-old man with diarrhea and weakness. *N Engl J Med*. 2011;365(24):2306–2316. doi:10.1056/NEJMcpc1011322
60. Hawrelak J. Giardiasis: pathophysiology and management. *Altern Med Rev*. 2003;8(2):129–142.
61. US National Library of Medicine. Fecal fat. *MedLine Plus*. Updated August 2020. Accessed August 24, 2020. http://www.nlm.nih.gov/medlineplus/ency/article/003588.htm
62. Escobedo AA, Cimerman S. Giardiasis: a pharmacotherapy review. *Expert Opin Pharmacother*. 2007;8(12):1885–1902. doi:10.1517/14656566.8.12.1885
63. Centers for Disease Control and Prevention. Parasites-Giardia: prevention and control. Updated November 15, 2018. Accessed August 24, 2020. https://www.cdc.gov/parasites/giardia/prevention-control-general-public.html
64. Hill DR, Nash TE. Intestinal flagellate and ciliate infections. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens, & Practice*. 2nd ed. Churchill Livingstone; 2006:984–1002.
65. Hill DR. Giardia lamblia. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 7th ed. Churchill Livingstone; 2010:3527–3534.
66. Mishra S. Hull KM. Orleans RJ. Quinacrine hydrochloride. Pharmacy compounding advisory committee meeting. Accessed March 30, 2022. https://www.fda.gov/media/96621/download
67. Furazolidone. Drugs.com. Updated January 17, 2022. Accessed March 30, 2022. https://www.drugs.com/search.php?searchterm=furazolidone&a=1
68. Farthing MJ. Treatment options for eradication of intestinal protozoa. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3:436–445. doi:10.1038/ncpgasthep0557
69. Ratanapo S, Mungthin M, Soontrapa S, et al. Multiple modes of transmission of giardiasis in primary schoolchildren of a rural community, Thailand. *Am J Trop Med Hyg*. 2008;78(4):611–615.
70. Centers for Disease Control and Prevention. Enterobiasis. Updated January 10, 2013. Accessed August 19, 2020. http://www.cdc.gov/parasites/pinworm
71. Wang L, Hwang K, Chen E. Enterobius vermicularis infection in schoolchildren: a large-scale survey 6 years after a population-based control. *Epidemiol Infect*. 2010;138(1):28–36. doi:10.1017/S0950268809002660
72. Stermer E, Sukhotnic I, Shaoul R. Pruritus ani: an approach to an itching condition. *J Pediatr Gastroenterol Nutr.* 2009;48(5):513–516. doi:10.1097/MPG.0b013e31818080c0
73. Caldwell JP. Pinworms (Enterobius Vermicularis). *Can Fam Physician*. 1982;28:306–309. https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC2306321&blobtype=pdf

74. Centers for Disease Control and Prevention. Enterobiasis: biology. Updated August 5, 2019. Accessed August 31, 2020. http://www.cdc.gov/parasites/pinworm/biology.html
75. Centers for Disease Control and Prevention. Enterobiasis: prevention and control. Updated January 19, 2013. Accessed August 31, 2020. https://www.cdc.gov/parasites/pinworm/prevent.html
76. Kucik CJ, Martin GL, Sorter BV. Common intestinal parasites. *Am Fam Physician*. 2004;69(5):1161–1168.
77. Drugs for parasitic infections. *Med Lett*. 2013;11(suppl):e1–e31. Accessed August 31, 2020. https://www.uab.edu/medicine/gorgas/images/docs/syllabus/2015/03_Parasites/RxParasitesMedicalLetter2013.pdf
78. Abongwa M, Martin RJ, Robertson AP. A brief review on the mode of action of antinematodal drugs. *Acta Vet (Beogr).* 2017;67(2):137–152. doi:10.1515/acve-2017-0013
79. Shoff WH, Shoff CT. Pediatric ascariasis medication. *Medscape*. Accessed August 31, 2020. https://emedicine.medscape.com/article/996482-medication
80. Wendt S, Trawinski H, Schubert S, Rodloff AC, Mossner J, Lubbert C. The diagnosis and treatment of pinworm infection. *Dtsch Arztebl Int*. 2019;116(13):213–219. doi:10.3238/arztebl.2019.0213
81. Prescriber's Digital Reference. Pyrantel pamoate—Drug Summary. Accessed August 31, 2020. https://www.pdr.net/drug-summary/Reese--39-s-Pinworm-Medicine-pyrantel-pamoate-2158
82. White A Jr, Weller PF. Cestode infections. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 19th ed. McGraw-Hill; 2014. Accessed August 24, 2020. https://www.mhprofessional.com/medical/harrisons-principles-of-internal-medicine
83. Craig P, Ito A. Intestinal cestodes. *Curr Opin Infect Dis*. 2007;20:524–532. doi:10.1097/QCO.0b013e3282ef579e
84. Centers of Diseases Control and Prevention. Taeniasis FAQs (Tapeworm). Updated January 2013. Accessed August 23, 2020. http://www.cdc.gov/parasites/taeniasis/gen_info/faqs.html
85. Centers for Disease Control and Prevention. Parasites-Taeniasis: biology. Updated January 2013. Accessed August 24, 2020. http://www.cdc.gov/parasites/taeniasis/biology.html
86. Ito A, Wandra T, Li T, et al. The present situation of human taeniases and cysticercosis in Asia. *Recent Pat Antiinfect Drug Discov*. 2014;9(3):173–185. doi:10.2174/1574891x10666150410125711
87. Coral-Almeida M, Gabriël S, Abatih EN, Praet N, Benitez W, Dorny P. Taenia solium human cysticercosis: a systematic review of Sero-epidemiological

data from Endemic Zones around the World. *PLoS Negl Trop Dis*. 2015;9(7):e0003919. doi:10.1371/journal.pntd.0003919

88. Centers for Disease Control and Prevention. Cysticercosis FAQs. Updated December 2019. Accessed August 24, 2020. http://www.cdc.gov/parasites/cysticercosis/gen_info/faqs.html
89. Jung-Cook H. Pharmacokinetic variability of anthelmintics: implications for the treatment of neurocysticercosis. *Expert Rev Clin Pharmacol*. 2012;5(1):21–30. doi:10.1586/ecp.11.72
90. World Health Organization. Taeniasis/cysticercosis. Updated June 2019. Accessed August 25, 2020. http://www.who.int/mediacentre/factsheets/fs376/en/
91. Garcia HH, Gonzales I, Lescano AG, et al. Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial. *Lancet Infect Dis*. 2014;14(8):687–695. doi:10.1016/S1473-3099(14)70779-0
92. Romo ML, Carpio A, Kelvin EA. Routine drug and food interactions during anthelminthic treatment of neurocysticerosis: a reason for the variable efficacy of albendazole and praziquantel? *J Clin Pharmacol*. 2014;54(4):361–367. https://doi,org/10.1002/jcph.269
93. Centers for Disease Control and Prevention. Parasites-Taeniasis. Updated January 2013. Accessed August 25, 2020. http://www.cdc.gov/parasites/taeniasis/index.html
94. Centers for Disease Control and Prevention. Parasites-Taeniasis: resources for health professionals. Updated July 2020. Accessed August 25, 2020. http://www.cdc.gov/parasites/taeniasis/health_professionals/index.html
95. Biltricide (praziquantel). Prescribing information. Schering; July 2017.
96. Chai JY. Praziquantel treatment in trematode and cestode infections: an update. *Infect Chemother*. 2013;45(1):32–43. doi:10.3947/ic.2013.45.1.32
97. Pollack RJ, Norton SA. Ectoparasite Infestations and Arthropod Injuries. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. eds. *Harrison's Principles of Internal Medicine 21e*. McGraw Hill; 2022. Accessed March 22, 2022. http://www.harrisonsim.com/index.php
98. Devore CD, Schutze GE, Council on School Health and Committee on Infectious Diseases, American Academy of Pediatrics. Head lice [published correction appears in *Pediatrics*. 2015 Oct;136(4):781–782]. *Pediatrics* 2015;135(5):e1355–e1365. doi:10.1542/peds.2015-0746
99. Centers for Disease Control and Prevention. Lice—body lice: biology. Updated September 2019. Accessed August 12, 2020. http://www.cdc.gov/parasites/lice/body/biology.html
100. Centers for Disease Control and Prevention. Lice—pubic "crab" lice. Updated June 2019. Accessed August 13, 2020. http://www.cdc.gov/parasites/lice/pubic/biology.html

101. Centers for Disease Control and Prevention. Lice—pubic “crab” lice: treatment. Updated September 2019. Accessed August 13, 2020. http://www.cdc.gov/parasites/lice/pubic/treatment.html
102. Centers for Disease Control and Prevention. Lice—head lice—general information: Frequently Asked Questions (FAQs). Updated September 2019. Accessed August 12, 2020. http://www.cdc.gov/parasites/lice/head/gen_info/faqs.html
103. Centers for Disease Control and Prevention. Lice—body lice: frequently asked questions. Updated September 2019. Accessed August 14, 2020. https://www.cdc.gov/parasites/lice/body/gen_info/faqs.html
104. Yetman RJ. The child with pediculosis capitis. *J Pediatr Health Care*. 2015;29(1):118–120. doi:10.1016/j.pedhc.2014.09.002
105. Ovide 0.5% Lotion. Package insert. TaroPharmaceutical; 2014.
106. Centers for Disease Control and Prevention. Lice—head lice—treatment. Updated October 2019. Accessed August 13, 2020. http://www.cdc.gov/parasites/lice/head/treatment.html
107. Chosidow O, Giraudeau B, Cottrell J, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice [published correction appears in *N Engl J Med.* 2010 April 29;362(17):1647]. *N Engl J Med*. 2010;362(10):896–905. doi:10.1056/NEJMoa0905471
108. Centers for Disease Control and Prevention. 2015 sexually transmitted diseases treatment guideline: ectoparasitic infections—pediculosis pubis. Updated June 2015. Accessed August 13, 2020. https://www.cdc.gov/std/treatment-guidelines/ectoparasitic.htm.
109. Centers for Disease Control and Prevention. Parasites—lice—head-lice: prevention & control. Updated September 2019. Accessed August 12, 2020. https://www.cdc.gov/parasites/lice/head/prevent.html
110. Diamantis SA, Morrell DS, Burkhart CN. Treatment of head lice. *Dermatol Ther*. 2009;22(4):273–278. doi:10.1111/j.1529-8019.2009.01242.x
111. National Pediculosis Association. Alternative treatment. Accessed August 14, 2020. http://www.headlice.org/faq/treatments/alternatives.htm
112. Centers for Disease Control and Prevention. Scabies: Epidemiology & risk factors. Updated November 2010. Accessed August 14, 2020. https://www.cdc.gov/parasites/scabies/epi.html
113. Centers for Disease Control and Prevention. Scabies: biology. Updated November 2010. Accessed August 14, 2020. http://www.cdc.gov/parasites/scabies/biology.html
114. Currie BJ, McCarthy JS. Permethrin and ivermectin for scabies. *N Engl J Med*. 2010;362(8):717–725. doi:10.1056/NEJMct0910329
115. Gunning K, Kiraly B, Pippitt K. Lice and scabies: treatment update. *Am Fam Physician*. 2019;99(10):635–642.
116. Nolan K, Kamrath J, Levitt J. Lindane toxicity: a comprehensive review of the medical literature. *Pediatr Dermatol*. 2012;29(2):141–146. doi:10.1111/j.1525-

1470 .2011.01519.x
117. Centers for Disease Control and Prevention. Scabies: prevention and control. Updated October 2018. Accessed August 14, 2020. http://www.cdc.gov/parasites/scabies/prevent.html

82

Tick-Borne Diseases

Caroline S. Zeind, Michelle Ceresia, and Lin H. Chen

CORE PRINCIPLES		CHAPTER CASES
LYME DISEASE		
1	Lyme disease is a multisystem spirochetal disease caused primarily by the bacterium *Borrelia burgdorferi* (and occasionally by *Borrelia mayonii*) and is transmitted to humans through the bite of infected black-legged ticks. Geography, tick species, and duration of attachment are used to guide clinical decision-making.	**Case 82-1 (Question 1)**
2	Although clinical features of Lyme disease are diverse and vary with the stage and duration of infection, the presence of an erythema migrans skin rash is universally the most common feature.	**Case 82-2 (Questions 1, 2)**

3	Most cases of localized (early) Lyme disease can be treated effectively with a few weeks of antibiotics (range of 10–21 days); however, if left untreated, infection can spread to the joints, the heart, and the nervous system.	**Case 82-2 (Questions 3, 4) Case 82-3 (Question 1) Case 82-4 (Question 1)**
	RELAPSING FEVER	
1	Relapsing fever is a bacterial infection caused by certain species of *Borrelia* spirochetes. Of the two types of relapsing fever, tick-borne relapsing fever occurs in the western United States and louse-borne relapsing fever is generally restricted to refugee settings in developing parts of the world.	**Case 82-6 (Question 1)**
	BORRELIA MIYAMOTOI	
1	The first human cases of *Borrelia miyamotoi* were described in the United States in 2013. *Borrelia miyamotoi* has been identified as a tick-borne organism transmitted by Ixodes ticks and is endemic in the same areas as Lyme disease, anaplasmosis, and babesiosis.	**Case 82-6 (Question 2)**
	SOUTHERN TICK-ASSOCIATED RASH ILLNESS	
1	Southern tick-associated rash illness is a tick-borne disease transmitted by the lone star tick and whose etiology is unknown. Patients bitten may occasionally develop a rash similar to the rash of Lyme disease.	**Case 82-7 (Question 1)**

ANAPLASMOSIS

1	Anaplasmosis, a tick-borne disease caused by the bacterium, *Anaplasma phagocytophilum*, was first recognized as a disease of humans in the United States in the mid-1990s. If not treated appropriately, illness can be severe and potentially fatal.	**Case 82-8 (Questions 1, 2)**

BABESIOSIS

1	Babesiosis is an illness caused by parasites that infect red blood cells and are spread by certain ticks, with symptoms ranging from asymptomatic disease to potential fatality, especially in immunocompromised patients.	**Case 82-9 (Questions 1, 2)**

COLORADO TICK FEVER, TICK-BORNE ENCEPHALITIS, AND OTHER VIRALLY MEDIATED TICK-BORNE DISEASES

1	Colorado tick fever is a virally mediated tick-borne disease that can be more severe in children than in adults. Other virally medicated tick-borne diseases include those caused by Powassan, Bourbon, and Heartland viruses.	**Case 82-10 (Question 1)**

TICK PARALYSIS

1	Tick paralysis occurs worldwide, affecting humans and livestock. It can be reversed by tick removal.	**Case 82-11 (Question 1)**

PREVENTION OF TICK-BORNE ILLNESSES

1	Prevention of tick-borne diseases is always preferable to acquisition. Personal protective measures and other methodologies aid in prevention.	**Case 82-5 (Question 1)**

INTRODUCTION

Currently, the majority of emerging infectious diseases are arthropod-borne and are caused by ticks and mosquitoes.[1] Unfortunately, with few exceptions, these emerging diseases cannot be prevented by vaccinations. Ticks belong to the class Arachnida, which includes scorpions, spiders, and mites.[2] Tick-borne diseases have become increasingly problematic worldwide, transmitting pathogens that cause diseases in humans and animals.[3] As a vector of human illness worldwide, disease can be spread by ticks, either by transmission of microorganisms or by injection of tick toxin into a host. Ticks can transmit bacterial, rickettsial, protozoal, and viral disease pathogens to humans and can often harbor more than one agent simultaneously (**Table 82-1**).[3–5] In the United States, major vector ticks are expanding their geographic range to new human populations, thus increasing the public health threat posed by ticks.[3]

Table 82-1
Tick-Borne Diseases

Disease	Causative Agent	Tick Vector	Host	Endemic Areas	Comments
Bacterial					
Anaplasmosis (HGA)	*Anaplasma phagocytophilum*	*Ixodes scapularis, Ixodes pacificus*	Deer, elk, wild rodents	North America (upper Midwest and northeastern United States)	Previously was known as HGE Reported in areas that correspond to the known geographic distribution of Lyme disease treatment: same as ehrlichiosis and RMSF
Ehrlichiosis	*Ehrlichia chaffeensis, Ehrlichia ewingii, EML*	*Amblyomma americanum*	Deer, dogs	North America (southeastern and south-central United States, from the eastern seaboard extending westward to Texas)	Similar clinical presentation as anaplasmosis but transmission by two different species of ticks and typically occur in different U.S. regions New species EML was identified in 2009 in patients in the upper Midwest. Treatment: same as anaplasmosis and RSMF
Lyme disease	*Borrelia burgdorferi, Borrelia mayonii*	*Ixodes scapularis, Ixodes pacificus*	Wild rodents	North America: *Borrelia burgdorferi; Borrelia mayonii* (new species identified in Midwestern United States; genetically distinct from *Borrelia burgdorferi, B. afzelii*, and *B. garinii*) Europe: more common in eastern and central Europe Asia: northern Asia, *B. afzelii* and *B. garinii*	Worldwide caused by three main species of bacteria: *Borrelia burgdorferi* (North America); and in Europe and Asia: *B. afzelii* and *B. garinii*
BMD	*Borrelia miyamotoi*	*Ixodes scapularis, Ixodes pacificus*			First BMD cases identified in North America in 2013
TBRF	*Borrelia* species *Borrelia hermsii, B. parkeri,* or *B. turicatae*	*Ornithodoros hermsii* ticks, *O. parkeri,* and *O. turicata*	Rodents	North America (western states in the United States); Central America, South America, the Mediterranean, Central Asia, and much of Africa	Most cases occur in summer months in rodent-infested cabins but can occur in winter months when fires warming a cabin activate ticks resting in the walls or woodwork.
Tick-borne spotted fever rickettsial infections, broadly grouped as "spotted fever group rickettsia" (SFGR)[a]	*Rickettsia* species: *Rickettsia parkeri* Worldwide*: Rickettsia* species including *R. conorii* and *R. africae*	Various ticks depending on *Rickettsia* species		North America: United States: *R. parkeri* (Eastern and southern United States), and *Rickettsia* species 364D (Northern California, Pacific coast) Worldwide: all continents except Antarctica; numerous Rickettsia species including *R. conorii and R. africae*	

Disease	Causative Agent	Tick Vector	Host	Endemic Areas	Comments
RMSF	*Rickettsia rickettsii*	*Dermacentor variabilis, Dermacentor andersoni, Rhipicephalus sanguineus*	Wild rodents, ticks	North America: United States >60% of cases occur in North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri; reports increasing in certain parts of Arizona	United States: reported throughout most of the contiguous states Treatment: same as anaplasmosis and ehrlichiosis
Tularemia	*Francisella tularensis*	*Dermacentor variabilis, Dermacentor andersoni, Amblyomma americanum*	Rabbits, hares, and rodents; domestic cats	Most common in the south-central United States, the Pacific Northwest, and parts of Massachusetts	United States: reported from all states except Hawaii Other transmission routes: inhalation and direct inoculation
Parasitic					
Babesiosis	*Babesia* species (most cases *Babesia microti*)	*Ixodes scapularis*	Mice, voles	North America (northeastern and upper Midwestern United States where *Babesia microti* is endemic); also sporadic cases on West Coast	Transmission of *Babesia* parasites can occur by transfusion.
Viral					
CTF	*Coltivirus* species	*Dermacentor andersoni*	Wild rodents, mammals	North America: western United States and southwestern Canada (at elevations of 4000–10,000 feet)	Transmission can occur from person to person (rare).
Heartland and Bourbon virus	Phleboviruses	*Amblyomma americanum*		United States: Midwest and the South	Worldwide
Tick-borne encephalitis	Member of virus family *Flaviviridae*	*Ixodes ricinus, Ixodes persulcatus*	Rodents	Europe: temperate regions, forested areas Asia: northern Asia (temperate regions, forested areas)	May also be acquired by ingestion of unpasteurized dairy products from infected cows, goats, and sheep
Powassan virus	*Member of virus family Flaviviridae*	*Ixodes scapularis, Ixodes cookei*		North America: United States (northeastern states and Great Lakes region), Canada Europe: Russia	
CCHF virus	Nairo virus. Family *Bunyaviridae*	Ixodid ticks		Asia, Africa, and Europe	May also be inquired by contact with infected blood, saliva, or inhalation
OHFV	Member of virus family *Flaviviridae*	*Dermacentor reticulatus, Dermacentor marginatus, Ixodes persulcatus*		Europe: southwestern Russia	
KFDV	Member of virus family *Flaviviridae*	*Hemaphysalis spinigera* (hard ticks)		Asia: southern India, Saudi Arabia (aka Alkhurma disease in Saudi Arabia)	Associated with exposure while harvesting agents
Other					
STARI		*Amblyomma americanum*		Eastern, southeastern, and south-central United States	

BMD, *Borrelia miyamotoi* disease; CCHF, Crimean–Congo hemorrhagic fever; CTF, Colorado tick fever; EML, *Ehrlichia muris*-like; HGA, human granulocytic anaplasmosis; HGE, human granulocytic ehrlichiosis; KFDV, Kyasanur forest disease virus; OHFV, Omsk hemorrhagic fever virus; RMSF, Rocky Mountain spotted fever; STARI, Southern tick-associated rash illness; TBRF, tick-borne relapsing fever.

[a]Refer to Centers for Disease Control and Prevention (CDC) for further information on other tick-borne SFGR transmitted internationally. Accessed January 1, 2021. http://www.cdc.gov/otherspottedfever/.

Source: Centers for Disease Control and Prevention. Diseases transmitted by ticks. Accessed January 1, 2021. http://www.cdc.gov/ticks/diseases/.

Tick Genus

Only two of the three families of ticks are of medical significance to humans: the soft-bodied ticks, Argasidae, and the hard-bodied ticks, Ixodidae.[2] Four of the 13 genera of Ixodidae transmit disease in the United States: *Dermacentor, Ixodes, Amblyomma,* and *Rhipicephalus.* Among the five genera of Argasidae, only *Ornithodoros* are known to transmit pathogens to humans in the United States. Most hard ticks have a 2- to 3-year life cycle, comprising the larval, nymphal, and adult stages.[2] They require one blood meal during each stage before they can mature into the next stage, and they usually remain attached to a host for hours or days. In contrast, soft ticks may have multiple nymphal stages, and both nymphal and adult forms can feast on blood multiple times, usually for only 30 minutes. However, Argasidae can survive many years without blood sustenance and are long-lived.[2] Humans are the inadvertent hosts for the life cycle of almost all ticks and tick-borne diseases.

LYME DISEASE

Lyme disease, or more accurately Lyme borreliosis, is a multisystem spirochetal disease caused by several genospecies of the spirochete

Borrelia burgdorferi sensu lato.[6,7] Lyme disease, which is transmitted by a tick bite, was first recognized in the United States in the mid-1970s, after a mysterious outbreak of arthritis near Lyme, Connecticut.[6] However, illness consistent with late manifestations of Lyme disease was described in Europe more than a century ago. In Europe and North America, Lyme disease is now recognized as the most commonly reported vector-borne disease.[4,7]

Etiologic Agent

Three genomic subgroups of *B. burgdorferi* worldwide account for most human infections: *Borrelia afzelii, Borrelia garinii*, and *B. burgdorferi* sensu stricto (hereafter referred to as *B. burgdorferi*).[7,8] Although all three groups have been found in Europe, most isolates are *B. garinii* or *B. afzelii,* the North American strains identified to date belong to the *B. burgdorferi* as the cause of Lyme disease.

Tick Vectors

There are four species of Ixodes ticks that commonly bite humans. In Europe and Asia, *Ixodes ricinus* and *Ixodes persulcatus* are principal vectors, respectively. In the United States, the black-legged or deer tick, *Ixodes scapularis,* is the principal vector in areas of the Northeastern, Mid-Atlantic, and North Central states, whereas *Ixodes pacificus,* the western black-legged tick, is the principal human-biting vector in the western United States.[7,8]

The tick acquires the *B. burgdorferi* spirochete from feeding on an infected reservoir host, such as mice, shrews, and other small mammals and various species of birds. The spirochete remains dormant in the tick's midgut until the tick feeds again. The spirochete then passes through the salivary ducts of the tick and is injected through the skin of the new host with the tick bite.[7,9,10] Few spirochetes are transmitted from the tick to its host during the first 24 to 36 hours of attachment. An infected nymphal tick, however,

invariably transfers spirochetes when attached to its host for more than 72 hours.

Most humans are infected through the bites of nymph ticks, which feed during the spring and summer months. Larval and nymph ticks are small, <3 mm, the size of a freckle or poppy seed. Therefore, the tick often goes unnoticed, and fewer than half of patients with Lyme disease recall having been bitten by a tick. The tick feeds on small, medium, or large mammals, lizards, or birds during its larval and nymphal (immature) stages.[2] Larval ticks are not relevant vectors for Lyme disease, however, because they are rarely infected and become so only after feeding on an infected host.[3] Adult ticks parasitize only medium or large mammals.[2] Although adult ticks can also transmit Lyme disease bacteria, because they are much larger, individuals are more likely to discover and remove them before transmission of bacteria.

Humans are inadvertent hosts of any stage of the tick. Although the tick can feed on many different animals, each tick species has preferred hosts. The complex interplay of spirochete, host, and vector in a particular area influences the risk of Lyme disease after a tick bite. Lyme disease is not transmitted directly between people, and there has not been substantive evidence of human transmission through sexual contact, semen, urine, or breast milk.[7]

Clinical Features and Diagnosis

LOCALIZED (EARLY) STAGE

Although clinical features of Lyme disease are diverse and vary with the stage and duration of infection, the presence of an erythema migrans (EM) skin rash is universally the most common feature, occurring in 60% to 90% of cases in North America.[7] The development of an EM rash at the site of the tick bite is typically the first indication of transmission and early infection in most North American patients.[9] The EM rash, which reflects the innate immune response, occurs at the site of the tick bite between 3 and 30 days (an average of 7 days) after the tick bite, typically before the onset of

fever.[4] Malaise, headache, fever, muscle and joint aches, swollen lymph nodes, and the characteristic EM skin rash are the typical early signs and symptoms.[6]

Lyme disease is diagnosed based on patient symptoms, physical findings (eg, EM rash), and the possibility of tick exposure.[5,9–11] Because it is a multisystem condition, if left untreated, infection can spread to the joints, the heart, and the nervous system. Although laboratory methods can be helpful if used correctly, serologic tests are insensitive during the first few weeks of infection. Although not necessary, in some cases, acute and convalescent titers may be helpful in some cases. During this stage, patient with an EM rash, systemic symptoms, and the possibility of tick exposure may be diagnosed clinically. Appropriate antibiotics should be initiated in early stages of Lyme disease.

DISSEMINATED STAGE

During the disseminated stage, serologic tests are usually positive and a conventional or modified two-tier testing protocol is recommended.[5,9,12] The Lyme disease presentation and testing can be complex, and the reader is referred to the Centers for Disease Control and Prevention (CDC) and other resources for further information.[5] During this stage, a variety of manifestations may occur (**Table 82-2**).

Table 82-2
Lyme Disease Clinical Manifestations

Early Localized Stage
▪ EM skin rash: red ring-like or homogenous expanding rash; classic rash not present in all cases ▪ Flu-like symptoms: malaise, headache, fever, myalgia, arthralgia ▪ Lymphadenopathy
Disseminated Stage
▪ Flu-like symptoms ▪ Lymphadenopathy ▪ Multiple secondary annular rashes

Cardiac Manifestations

- Myocarditis or pericarditis
- Conduction abnormalities, for example, atrioventricular node block

Neurologic Manifestations

- Bell palsy or other cranial neuropathy
- Meningitis
- Radiculoneuritis, myelitis
- Motor and sensory radiculoneuropathy, mononeuritis multiplex
- Subtle cognitive difficulties
- Encephalitis, encephalomyelitis, subtle encephalopathy, pseudotumor cerebri (all rare)

Rheumatologic Manifestations

- Transient, migratory arthritis, and effusion in one or multiple joints
- Migratory pain in tendons, bursae, muscle, and bones
- Baker cyst
- Arthritis may recur in same or different joints (if untreated)

Additional Manifestations

- Conjunctivitis, keratitis, uveitis
- Mild hepatitis
- Splenomegaly

EM, erythema migrans.

Source: Centers for Disease Control and Prevention. *Tickborne Diseases of the United States. A Reference Manual for Healthcare Providers*. 5th ed. 2018. Accessed January 1, 2021. https://www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf.

Treatment

The clinical manifestations of Lyme disease should govern the treatment strategy.[4,11] Patients who receive appropriate treatment in the early stages of Lyme disease usually recover rapidly and completely. Oral treatment regimens commonly used in early-stage disease include doxycycline, amoxicillin, or cefuroxime axetil (**Table 82-3**).[6] Patients with disseminated (late) Lyme disease should be evaluated for severity and may require intravenous (IV) treatment.[5,12]

Table 82-3
Treatment Recommendations for Localized (Early) Lyme Disease

Adults
Doxycycline 100 mg, twice per day orally (10–21 days)[a]
Or
Amoxicillin 500 mg three times per day orally (14–21 days)
Or
Cefuroxime axetil 500 mg twice per day orally (14–21 days)
Children
Amoxicillin 50 mg/kg per day orally, divided into three doses (maximum, 500 mg per dose) (14–21 days)
Cefuroxime axetil 30 mg/kg per day orally, divided into two doses (maximum, 500 mg per dose) (14–21 days)
(>8 years): may use Doxycycline 4 mg/kg per day orally, divided into two doses (maximum, 100 mg per dose) (10–21 days)[a]

Note: For patients intolerant of amoxicillin, doxycycline, and cefuroxime axetil, the macrolides azithromycin, clarithromycin, or erythromycin may be used, although they have a lower efficacy. Patients treated with macrolides should be closely observed to ensure resolution of clinical manifestations.

[a]Recent publications suggest the efficacy of shorter courses of treatment for early Lyme disease.

Source: Centers for Disease Control and Prevention. *Tickborne Diseases of the United States. A Reference Manual for Healthcare Providers*. 5th ed. 2018. Accessed January 1, 2021. https://www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf.

CASE 82-1

Question 1: C.T., a 57-year-old female, contacts her primary care physician (PCP) with symptoms of low-grade fever and muscle aches 2 days after camping in the western part of Massachusetts during the month of August. She explained that she was canoeing and hiking with her family in the woods, and on the last day of their trip, she noticed a small tick on her back and immediately destroyed it. A small, itchy spot that she felt at the site of the tick bite is no longer symptomatic. C.T. asks her PCP whether she needs any laboratory tests and/or preventive treatment.

Given her presentation and tick bite history, what would be appropriate steps to management?

The routine use of antibiotic prophylaxis or serologic testing is not recommended for Lyme disease prevention following a recognized tick bite.[5],[12] With regard to C.T.'s situation, the use of serologic testing is not recommended because the antibody response to *B. burgdorferi* is not detectable for the first few weeks after a tick bite. Therefore, the blood tests for antibodies to *B. burgdorferi* are unlikely to be positive, because C.T.'s tick bite occurred only 2 days ago.[9],[11],[12]

The risk of developing Lyme disease can be affected by the rate of transmission of the spirochete from infected ticks to humans, the length of time before the tick is removed during its bite, the degree of blood engorgement of the tick (scutal index), the prevalence of spirochete infestation of ticks in an area (which varies with the tick species), and the reservoir competency of host animals in the region.[3]

Although transmission rates of Lyme disease from an infected tick bite are estimated at ~10%, the risk is reduced dramatically if the tick is removed within 24 hours of attachment. The small, itchy spot experienced by C.T. may represent a hypersensitivity reaction to the bite. These erythematous, noninfectious skin lesions develop within 48 hours of tick detachment or may occur while the tick is still attached. They are usually <5 cm in diameter; they may have an urticarial appearance and usually disappear in 1 or 2 days.[5],[7]

Prophylactic antibiotic preventive therapy with a single dose of 200 mg of oral doxycycline (children age 8 years or older at 4 mg/kg to a maximum 200-mg dose) can be offered if all of the following criteria are met: (a) there are no contraindications to doxycycline use; (b) administration can start within 72 hours of tick removal; (c) the tick can be reliably identified as a nymphal or adult *I. scapularis* tick with certainty of the duration of attachment of 36 hours or more based on the degree of engorgement or time of exposure; and (d) the local rate of infection of ticks by *B. burgdorferi* in the area of exposure is

≥20% based on current ecologic evidence.[3] Routine testing of ticks themselves for tick-borne infections is not recommended.[12]

Antibiotic prophylaxis after *I. pacificus* tick bites is generally not necessary because of relatively low prevalence of *B. burgdorferi* infestation of *I. pacificus* ticks.[12] However, C.T. had exposure in a region where *B. burgdorferi* is highly prevalent among *I. scapularis* ticks. If there is uncertainty regarding the duration of tick attachment, she may be offered a dose of doxycycline prophylaxis.

ERYTHEMA MIGRANS

Signs, Symptoms, and Disease Course

CASE 82-2

QUESTION 1: M.W., a 30-year-old female, presents with right knee pain and multiple, large, discrete skin rashes that she has had for the past 10 days. Three months ago, in July, she visited friends in Cape Cod, Massachusetts, and spent much of her time engaged in outdoor activities. Two months ago, her husband noticed a circular area of intense redness, ~9 cm (~3.54 in) wide, in her left armpit. The rash grew considerably larger during the next 2 weeks and had a red outer border. M.W. attributed the expansion of the rash to having scratched the mildly itchy area. The rash gradually disappeared. In late August, M.W. experienced fatigue, nausea, and headache for a week and thought it was "summer flu." In early September, she experienced right knee pain; ibuprofen produced some relief.

On examination, she was afebrile and had mild soft tissue swelling of the right knee. Her white blood cell (WBC) count was normal. Serum samples contained antibody titers to *B. burgdorferi* demonstrated by a sensitive ELISA (enzyme-linked immunoassay) followed by immunoglobulin M (IgM) and IgG immunoblots. A Venereal Disease Research Laboratory (VDRL) test for syphilis and a pregnancy test were negative. M.W. has no contraindications to doxycycline and is started on a 4-week course of oral doxycycline 100 mg twice daily.

What characteristics of M.W.'s skin rash are consistent with the EM of Lyme disease?

The EM of Lyme disease usually develops within 3 to 30 days (average 7 days) of a usually asymptomatic tick bite at the site of inoculation of the spirochete. The rash begins as an erythematous (red) macule or papule typically on the thigh, back, shoulder, calf, groin, popliteal fossa, flank, axilla, buttock, or upper arm.[5,7,12] In children, EM is often found on the head at the hairline, neck, arms, or legs. It expands outwardly at 2 to 3 cm/day to a diameter of 5 to 70 cm (mean, 16 cm), occasionally with some central clearing. Some cases of EM in the United States lack central clearing. The rash may be warm to the touch and is usually painless, but some patients have mild burning or itching. Up to 50% of patients with EM have multiple secondary lesions that most likely represent blood-borne spread of the spirochete to other skin sites rather than multiple tick bites.[6] If untreated, EM generally fades within several weeks; if treated, it usually resolves in several days.[5,7,12]

Low-grade fever and other nonspecific symptoms, such as malaise, headache, myalgias, or arthralgias, may accompany EM.[5,7,12] Some individuals may have no symptoms. Cough, rhinitis, sinusitis, and other respiratory symptoms do not usually occur in Lyme disease.[4] Pitfalls in the diagnosis of EM exist. Lesions are sometimes misdiagnosed. M.W.'s skin rash was large (>9 cm), red, and had a red outer border. It gradually faded over the course of a few weeks. These characteristics are consistent with a diagnosis of EM.

Serologic Testing

Case 82-2, Question 2: What might have been the rationale for the laboratory tests that were undertaken in M.W.?

Guidelines currently recommend a modified two-tier approach of enzyme immunoassays (EIAs).[9,11,12] The sensitivity of such testing in Lyme arthritis cases is 97% to 100%.[9,11] However, routine use of serology testing for patients with early EM cannot be recommended presently. Syphilis and other known biologic causes (periodontal

spirochetes) of false-positive serologic testing should be excluded. Rheumatoid factor or antinuclear antibody tests usually are negative in Lyme disease. These tests help differentiate rheumatoid arthritis or systemic lupus erythematosus from Lyme disease. The WBC count is normal or mildly elevated in Lyme disease. M.W. had a normal WBC. Pregnancy was ruled out before initiating a tetracycline. Most interesting in M.W. is the presence of secondary EM lesions representing disseminated infection.

The presence of EM as an early indicator of Lyme disease gives clinicians the best opportunity for early diagnosis and treatment.[5,12] In the United States, the expression of EM is the *only* manifestation of Lyme disease that is sufficiently distinctive to allow clinical diagnosis in the absence of confirmatory laboratory information.[5,12] Early treatment can prevent sequelae of disseminated disease.

LYME DISEASE TREATMENT

Antibiotics

CASE 82-2, QUESTION 3: Why was doxycycline selected to treat M.W.?

Borrelia burgdorferi is susceptible to amoxicillin, tetracyclines, and some second- and third-generation cephalosporins. It is only moderately sensitive to penicillin G and is resistant to first-generation cephalosporins, rifampin, co-trimoxazole, aminoglycosides, chloramphenicol, and the fluoroquinolones.[5,12]

Penicillin, tetracycline, and erythromycin historically were the drugs of choice for the treatment of Lyme disease because they can be administered orally; they are relatively inexpensive and appear to have good in vitro activity. However, this in vitro activity does not translate to in vivo efficacy. Doxycycline is an agent of choice for treatment of Lyme disease. Amoxicillin and cefuroxime axetil are also first-line options. In Europe, in contrast, penicillin still is used

with continued success. A non–doxycycline regimen is preferred in pregnant or breast-feeding females and in children younger than 8 years of age.[5,12]

Compared with the third-generation cephalosporins, the oral second-generation drug cefuroxime axetil has good in vitro activity and efficacy. But it is more expensive than oral amoxicillin or doxycycline. Of the third-generation cephalosporins, ceftriaxone has the most potent in vitro activity and a long half-life for once-daily dosing in an outpatient program. Ceftriaxone is expensive, however, and has a higher incidence of diarrhea than other β-lactams, probably owing to extensive biliary excretion.

The macrolide azithromycin is considered second-line in the treatment of Lyme disease.[9] The combination of a macrolide with lysosomotropic agents, especially hydroxychloroquine, anecdotally has been suggested to be associated with increased symptom relief probably related to combined anti-inflammatory activity rather than direct antimicrobial activity.[3] Doxycycline is well absorbed orally and is less expensive than parenteral ceftriaxone or cefotaxime. Doxycycline has a long serum half-life of 18 to 22 hours. In addition, doxycycline penetrates the cerebrospinal fluid (CSF) at concentrations of ≥10% of serum levels, even in the absence of meningeal inflammation. Although not as significant as with tetracycline, doxycycline can complex with divalent or trivalent cations in the gut, with an associated decrease in oral absorption. On the other hand, administering doxycycline with food, to minimize nausea, is recommended.[3] Compared with other tetracyclines, doxycycline has the least affinity for divalent calcium cations, and oral absorption is reduced by only 20% if given with milk. The major side effect of doxycycline is phototoxicity, which is of concern because Lyme disease usually occurs during sunny times of the year. A less recognized side effect is the risk of doxycycline-induced esophageal ulceration. Patients should be instructed to never take doxycycline or other tetracyclines near bedtime and to take the medication while standing up with at least 240 mL of clear fluid, especially with the capsule formulation. Despite less in vitro activity compared with some β-lactam antibiotics, *B. burgdorferi* is

sufficiently susceptible to doxycycline, and clinical experience with doxycycline has been very favorable. In conclusion, doxycycline was a suitable choice for M.W.

Chronic Lyme Arthritis

Case 82-2, Question 4: M.W. continues to have knee inflammation for 3 months after receiving a second course of antibiotic treatment and is now considered to have Lyme arthritis. Should antibiotic therapy be repeated for M.W.'s arthritis?

Acute Lyme arthritis occurs from the accumulation of neutrophils, cytokines, immune complexes, complement, and mononuclear cells induced by the spirochete.[13] Appropriate antimicrobial treatment of acute Lyme arthritis is usually successful, and doxycycline, amoxicillin, or cefuroxime axetil is recommended for adult patients, such as M.W., if there is no clinical evidence of neurologic disease.[12] Treatment for Lyme arthritis typically requires 28 days of therapy.[12] A minority subset of patients may have persistent Lyme arthritis.[13] It is very unlikely that this is attributable to the continued presence of *B. burgdorferi* in the joint, but rather to the patient's continued inflammatory response or autoimmunity.[13] Polymerase chain reaction (PCR) testing of synovial fluid can be considered, and if negative, symptomatic therapies may be offered rather than repeated antibiotic courses. Such patients often respond well to synovectomy, suggesting that the presence of synovitis may not be the result of persistence of the infection. Nonsteroidal anti-inflammatory agents, disease-modifying antirheumatic agents, intra-articular corticosteroid injections, or synovectomy may be offered.[3],[12] However, it should be noted that before the antibiotic treatment era for Lyme disease, even the most prolonged cases of persistent Lyme arthritis eventually improved without treatment, although sometimes lasting for months to years.[13]

Neurologic Lyme Disease

CASE 82-3

QUESTION 1: E.S., a 60-year-old female, presents to her PCP with symptoms of early neurologic Lyme disease, including mild memory and cognitive deficits. Serum two-tier IgG seropositivity was confirmed.

Should E.S. be treated with antibiotics? If so, how long should she be treated? She has no known allergies.

Although rare, late neurologic complications of Lyme disease may present as encephalopathy, peripheral neuropathy, or encephalomyelitis.[5],[12] Although the Lyme *Borrelia* species found in Europe do not strictly overlap with those species found in the United States, there are no data to support a differential response to antibiotic.[11] Based on these studies, oral doxycycline can be considered as first-line therapy for neurologic Lyme disease in Europe and for ambulatory patients with early neurologic Lyme disease in the United States. An oral antibiotic treatment regimen may suffice in cases of early neurologic disease, but parenteral regimens are appropriate for severe cases.[14] The regimens may need to be adjusted depending on the person's age, medical history, underlying health conditions, and allergies.[5] In conclusion, E.S. can be treated with doxycycline administered orally with a duration range of 14 to 21 days and should be reassessed following treatment.

Post-Lyme Disease Syndromes

CASE 82-4

QUESTION 1: A friend who has been treated with a 4-week course of antibiotics for Lyme disease calls you to say that she has lingering symptoms and she thinks it is "chronic Lyme disease." She would like more information about it.

How should you respond?

Chronic Lyme disease is a confusing term, and most authorities agree that there may be “post-treatment Lyme disease syndrome” (PTLDS).[5] Although the exact cause is unknown, most medical experts believe that the lingering symptoms that can occur are the result of residual damage to tissues and the immune system. Clinical findings in patients may include fatigue, widespread musculoskeletal pain, cognitive difficulties, or subjective symptoms of such severity that a substantial reduction in quality of life has occurred. The subjective symptoms must include an onset within 6 months of the initial Lyme disease diagnosis and persistence for at least 6 months after completion of antimicrobial therapy. If adherence to a recommended Lyme treatment regimen is confirmed, the existence of symptomatic, chronic infection by *B. burgdorferi* is difficult to confirm. After appropriately targeted antibiotic therapy for early Lyme disease, treatment failure is exceedingly rare. The organism has not been shown to develop antibiotic resistance.[3] For these patients with chronic subjective symptoms for more than 6 months, repeated or prolonged antibiotic therapy is not useful or recommended.[5,12]

The friend should be encouraged to seek additional diagnostic workup for other diseases. Even in patients who have had verified Lyme disease, the aches and pains of daily living they experience appear to be more related to their post-treatment symptoms than to Lyme disease itself.[5]

Lyme Disease Prevention

CASE 82-5

Question 1: A family living in a Lyme disease endemic area is concerned regarding their risk for contracting the disease.

How would you advise them on Lyme disease prevention and overall protection from tick-borne disease?

Although some vector-borne diseases are prevented through vector control, this has proven difficult for tick-borne diseases

because of a lack of efficacy or environmental concerns with the use of pesticides. Evaluated methods include habitat destruction by fire, chemical spraying agents such as acaricides to achieve tick eradication, culling or removal of host deer, or protection of mice from tick infestation.[14]

Currently, there are limited vaccines available for tick-borne and mosquito-borne illnesses.[15] A Lyme disease vaccine for humans is no longer available in the United States. Citing low demand, the U.S. manufacturer discontinued production in 2002. Clinical trials are currently underway for candidate *Lyme borreliosis* vaccines.[16]

The first step in prevention of Lyme disease is personal protection and tick avoidance.[17],[18] Tick repellents may be applied to the skin or clothing. One basic chemical category of insect repellant is the synthetic agents, such as *N,N*-diethyl-*m*-toluamide (DEET), picaridin (also known as icaridin in Europe), and insect repellent (IR) 3535 (ethyl butylacetylaminopropionate). The second chemical category of repellant is the plant-derived oils and synthetics, such as oil of lemon eucalyptus or PMD (para-menthane-3,8-diol), which is an extract of the leaves of lemon eucalyptus, *Corymbia citriodora*, a synthesized version of oil of lemon eucalyptus.

The use of DEET skin repellent has evolved as the standard repellant for mosquito and tick-borne diseases. In combination with a permethrin clothing, DEET appears to offer adequate protection. DEET has been tested against *Ixodid* ticks for repellence and is more effective than dibutyl phthalate, dimethyl phthalate, pyrethrum, and two combination products.[17],[18] DEET is generally safe; however, excessive DEET application has been associated with seizures in children.[18],[19] These are rare events, however, and if the products are used according to their labeling, the adverse reaction risk is low, even for children age older than 2 months.[3] Prolonged or excessive application is not recommended. It may be prudent to use the lowest effective concentration of DEET-containing repellents, such as those containing 20% to 30%. To minimize DEET toxicity, the product should be applied sparingly, inhalation or introduction into the eyes should be avoided, repellent-treated skin should be washed when coming inside, use on children’s hands (that are likely to have

contact with the eyes or mouth) should be avoided, and it should be applied only to intact skin or clothing.

Picaridin was developed in Europe in the 1990s and released in the United States about 10 years ago. A couple of advantages over DEET include the lack of a chemical odor and its nonsticky or greasy feel. It is also safe to use on plastics, whereas DEET may damage certain synthetics including eyeglass frames. IR 3535, originally marketed in the United States as a skin emollient and moisturizer, was then adopted for use as an insect repellant. Plant-derived IRs, such as oil of lemon eucalyptus or PMD, have demonstrated efficacy against the tick vectors of Lyme disease (*I. scapularis*, *I. pacificus*) and Rocky Mountain spotted fever (RMSF, *Dermacentor andersoni*).[1]

A literature review between 2000 and 2012 on the efficacy of repellants against various mosquito and tick species noted that there are only limited studies conducted on tick behavior and repellant efficacy against the tick species *Ixodes.*[19,20] The use of picaridin, IR 3535, and PMD were also reviewed as part of this study. Results of this study found that the use of IR 3535 provided the longest protection against *I. scapularis*, whereas DEET and commercial products containing picaridin or PMD demonstrated a better response than IR 3535 against *I. ricinus*.[18] In situations in which environmental exposure to disease-transmitting ticks, biting midges, sandflies, or blackflies is anticipated, topical repellants containing IR 3535, picaridin, or oil of eucalyptus (or PMD) would offer better protection than topical DEET alone.[1] (Refer to Chapter 81, Parasitic Infections, Table 81-2, Mosquito Protection Measures for additional information on insect repellants.)

Physical barriers to ticks, such as wearing protective garments—long pants and long-sleeved shirts—tucking shirts into pants and pants into boots, and wearing closed-toed shoes, prevent infection.[1] Ticks are easier to spot on light-colored clothing. Checking the body for ticks regularly is recommended; any ticks that are found should be promptly removed. Avoiding tick habitats is the best protection against tick-borne diseases. Effective postexposure antibiotic prophylaxis can be administered in Lyme disease endemic areas after a tick bite.

The geographic range of Lyme disease in North America and elsewhere continues to expand rapidly with increases in the frequency of tick-borne diseases.[3,21] Although research to improve the diagnosis and treatment of Lyme disease and other tick-borne diseases has led to advancements, there have been fewer studies and resources allocated on avoidance and prevention of exposure.[3,21] To better understand the locations where people most frequently encounter infected ticks, a systematic review and meta-analysis was conducted on spatial risk factors for tick-borne disease and tick bites in eastern North America.[21] This study examined three scales: the residential yard, the neighborhood surrounding (but not including the yard), and outside the neighborhood. There were 19 studies that met inclusion criteria from 1237 citations with one additional study that was included by a reviewer. The total study population represented 2741 cases of tick-borne illness and 1447 individuals who experienced tick bites or ticks crawling on them. Using random effects models, study investigators derived pooled odds ratio estimates. The findings of this analysis revealed significant disease risk factors at all three scales. However, analysis of variance revealed that the risk at the neighborhood scale was 57% greater than risk at the yard sale and 101% greater than the risk outside the neighborhood. The results of this study highlight the need to better characterize sources of variation in risk at the neighborhood scale. Moreover, the meta-analyses suggest that implementation of risk-reducing interventions at each scale could be effective; however, those applied at the neighborhood scale are most likely to protect human health.

RELAPSING FEVER

Relapsing fever, a bacterial infection caused by a variety of *Borrelia* species, causes episodes of fever, nausea, headache, and muscle and joint aches. Of the two types of relapsing fever, tick-borne relapsing fever (TBRF) occurs in the western United States and

louse-borne relapsing fever (LBRF) is generally restricted to refugee settings in developing parts of the world.[7]

Tick Vector

The predominant tick vector for relapsing fever is of the genus *Ornithodoros,* a soft-bodied tick. These ticks feed on wild rodents or domestic animals and, incidentally, on humans. In North America, three tick species carry the agents of endemic relapsing fever with apparent strict specificity. In fact, the names of the responsible *Borrelia* species have been adopted from the three tick species that transmit them: *Ornithodoros hermsii, Ornithodoros parkeri,* and *Ornithodoros turicata.*[22] Although the ticks themselves may serve as reservoir hosts, the *Borrelia* usually circulate among wild rodents, ticks, and possibly birds.[6] Similar to Lyme disease, greater worldwide variations of endemic cycles and vectors for TBRF may exist than in North America.

TICK GEOGRAPHY

In North America, relapsing fever is an uncommon disease largely confined to the geographic distribution of the tick species that harbor the *Borrelia.* In the United States, most cases of TBRF have occurred in 14 western states and are caused by *Borrelia hermsii*.[6] These ticks are usually found in the remote natural settings of the mountains and semiarid plains of the far west and Mexico. TBRF can develop when people visit tick- or rodent-infested cabins or summer homes. Although TBRF is spread by multiple tick species, *O. hermsii* is the tick responsible for most cases in the United States usually at altitudes of 1500 to 8000 feet. The health significance of *O. parkeri* and *O. turicata* transmits its *Borrelia* at lower altitudes in the Southwest, where they inhabit caves and the burrows of ground squirrels, prairie dogs, and burrowing owls.

SPIROCHETAL BEHAVIOR

Ticks acquire spirochetes from blood feeding on small wild rodents. If high levels of *Borrelia* are present in the animal's blood, large numbers of spirochetes will be ingested by the tick and reside in the tick's midgut. During the next few days, the spirochetes invade the midgut wall, traverse the hemolymph system, and within a few weeks infect the salivary glands as well as other tick tissues and organs. Females may develop infected ovaries and transmit *Borrelia* to offspring in some *Ornithodoros* species, but this is rare in *O. hermsii.*[21] Having reached the tick's salivary glands, the spirochetes are poised to invade the tick's next host.

TICK BEHAVIOR

In contrast to the hard-bodied ticks, these soft ticks feed rapidly, often detaching after 30 to 90 minutes.[21],[22] They feed at night while people are sleeping, and their bite is usually painless. Therefore, most people are unaware that they have been bitten.[18]

Disease Characterization

The hallmark of endemic relapsing fever is an abrupt onset of high fever (often >102.2 °F [39 °C]) after an incubation period of 4 to 18 days.[21] The patient may experience shaking chills, severe headache, abdominal pain, myalgias, arthralgias, nausea, vomiting, and malaise. A few cases of acute respiratory distress syndrome have recently been recognized.[21] The fever usually breaks in 3 days (range, 12 hours to 17 days) in untreated patients.[21] After a variable afebrile period of 3 to 36 days (usually 7 days), cyclic periods of fever and constitutional symptoms reappear. Each febrile attack progressively diminishes in severity. Three to five relapses typically occur in untreated patients.

Routine laboratory testing is of little value. Moderate anemia and an increased erythrocyte sedimentation rate (ESR) are common. Leukocyte counts may be normal, yet moderate-to-severe thrombocytopenia is commonly observed but is considered nonspecific. The diagnosis of relapsing fever is made by direct

observation of the spirochete on a peripheral blood smear while the patient is febrile.[21] Observation of the smear is enhanced with Wright or Giemsa staining. Few diagnostic laboratories perform antibody serology tests; however, these tests lack specificity.[21] Skin biopsy of a rash to identify the spirochete is unreliable. Direct culture of the spirochete from the blood into a special culture medium is the most specific diagnostic tool, but this is a slow technique confined to research laboratories.

TREATMENT

These *Borrelia* have not demonstrated antibiotic resistance. Successful treatment regimens usually include a 7- to 10-day course of antibiotics.[6,21] Tetracycline (500 mg every 6 hours for 10 days) is the preferred regimen. Erythromycin is an effective alternative at a dose of 500 mg (or 12.5 mg/kg) every 6 hours for 10 days. For individuals experiencing central nervous system (CNS) involvement, ceftriaxone (2 g/day for 10–14 days) is preferred. Hospitalization and administration of IV antibiotics may be required in patients who are severely ill.

CASE 82-6

QUESTION 1: T.J. is a 49-year-old male who visits his PCP with a sudden onset of high fever, severe headache, malaise, nausea, vomiting, and myalgias. He returned a week ago, at the end of August, from a stay in a rustic cabin on the north rim of the Grand Canyon. His PCP orders a manual complete blood count (CBC) and chemistry panel and asks the laboratory to observe a blood smear with Giemsa staining. T.J.'s recent visit and outdoor activities are consistent with areas with prior outbreaks where relapsing fever has been documented. After confirming the presence of *Borrelia* in the blood smear, the PCP prescribes a 10-day course of tetracycline. Two hours after the first dose, T.J.'s wife calls the physician's office with concerns that the disease is worsening. T.J. experiences an increased temperature, faintness, and chills and has a rapid pulse and respiration rate.

What do these symptoms represent? Is this an adverse drug reaction?

Up to 54% of patients with relapsing fever experience a reaction, a Jarisch–Herxheimer reaction, to the first dose of antibiotic (see

Chapter 72, Sexually Transmitted Diseases).[22] It may occur in LBRF, TBRF, and in other spirochetal diseases such as syphilis or Lyme disease.[4] The dramatic reaction consists of a rise in temperature, chills, myalgias, tachycardia, hypotension, increased respiratory rate, and vasodilation.[21] Treatment of the reaction consists of supportive care. Severe reactions may require hospitalization for vital sign monitoring and management of hypovolemia. Although this is a reaction to the administration of an antibiotic drug, it is not an allergic response, and the antibiotic should be continued.

BORRELIA MIYAMOTOI

CASE 82-6, QUESTION 2: T.J. continues with antibiotic therapy and his symptom resolves. Given his clinical presentation and findings, his diagnosis and treatment were appropriate. How does *B. miyamotoi* typically present and what treatment options are available?

Borrelia miyamotoi is a bacterial species that is closely related to the bacteria that cause TBRF and distantly related to *B. burgdorferi* that causes Lyme disease. Although first identified in 1995 in ticks from Japan, *B. miyamotoi* has been detected in two species of North American ticks, the black-legged or deer tick (*I. scapularis*) and the western black-legged tick *I. pacificus*). The first human cases of infection were identified in Russia and described in 2011, followed by the first recognized cases in northeastern United States in 2013.[23] To date, there are <60 well-documented cases of *B. miyamotoi* in the United States. Because ticks are also known to transmit several diseases, including Lyme disease, anaplasmosis, and babesiosis, researchers and healthcare providers need to learn more about the transmission and signs and symptoms of this infection. Although Lyme disease most commonly occurs in June and July, *B. miyamotoi* infection occurs most commonly in July and August and may be spread by larval black-legged ticks.[5]

Patients with *B. miyamotoi* infection generally experience nonspecific symptoms such as fever, chills, headache, myalgia, and arthralgia.[23],[24] Unlike Lyme diseases, rash was an uncommon

finding, with only 4 out of 51 patients experiencing a rash. The blood tests that are used for Lyme disease are not helpful in the diagnosis of *B. miyamotoi* infections. Currently, the PCR tests that detect DNA from the organism or antibody-based tests are used for confirmatory diagnosis. Although studies have not yet been conducted to evaluate treatment regimens, in published case series, patients were successfully treated with antibiotics and dosages used for treatment of Lyme disease.[6] Patients with *B. miyamotoi* have been successfully treated with a 2- to 4-week course of doxycycline, and amoxicillin and ceftriaxone have also been used. *B. miyamotoi* disease will continue to be evaluated, and it may be an emerging tick-borne infection in the northeastern region of the United States.

SOUTHERN TICK-ASSOCIATED RASH ILLNESS

CASE 82-7

QUESTION 1: G.T., a 47-year-old male living in southern Missouri, recently experienced a rash resembling EM after a lone star tick bite.

Because this tick is not a vector for Lyme disease, what could be the cause and how should he be managed?

Amblyomma americanum (the lone star tick) is found throughout the southeast and south-central United States and along the Atlantic coast as far north as Maine, and its territory is expanding.[5] The lone star tick aggressively bites humans in the southern states, as opposed to *I. scapularis* ticks.[6,25] Spirochetes detected by microscopy and culture have been found in 1% to 5% of lone star ticks and are named *Borrelia lonestari.*[2,6,25] *Borrelia lonestari* and *B. burgdorferi,* however, were ruled out as the cause of EM like skin lesions known as Southern tick-associated rash illness (STARI) in one Missouri investigation.[6,25] Attempts to culture the agent of this Lyme-like illness, although exhaustive, have been unsuccessful.[25] The causative agent of STARI has not yet been confirmed. There are differences in the appearance and content of the rashes of STARI and the EM of Lyme disease. For example, Lyme EM rashes show

an abundance of plasma cells contrasted with a predominantly lymphocytic infiltrate seen in STARI.[25]

G.T.'s diagnosis was based on symptoms, geographic location, and tick bite information. Because the cause of STARI is unknown, no diagnostic tests are available, nor is it known if antibiotic treatment is necessary or beneficial for patients. However, because STARI resembles Lyme disease, limited data support treating STARI with regimens similar to those used for Lyme disease.[25] For example, doxycycline may be given for 10 to 30 days, with longer durations reserved for evidence of dissemination beyond the rash, such as fever, severe headache, lymphadenopathy, or multiple rashes.[26]

OTHER BACTERIAL DISEASES: TULAREMIA

Tularemia

ETIOLOGY AND EPIDEMIOLOGY

In 1911, George W. McCoy and Charles W. Chapin from the U.S. Public Health Service investigated a plague-like disease in wild ground squirrels harvested in Tulare County, California, and discovered the infectious etiology of tularemia.[26] The bacterium is a small, pleomorphic, catalase-positive, nonmotile, aerobic, nonencapsulated, gram-negative coccobacillus now named *Francisella tularensis* in honor of Edward Francis for his fieldwork and contributions to tularemia research. He proposed the terminology *tularemia* because the disease is associated with bacteremia.[26]

Although tularemia is found worldwide, it occurs primarily in the Northern Hemisphere.[23] The important reservoir hosts for *F. tularensis* are wild rabbits, ticks, and deer flies.[26] The North American tick vectors are *Dermacentor variabilis* (dog tick), *Amblyomma americanum* (lone star tick), and *Dermacentor*

andersoni (wood tick). Tick-borne tularemia occurs most often in the spring and summer, matching the likelihood of exposure.[5] Before 1950, most human cases of the disease developed from direct contact with infected animals, usually hares or rabbits, and tularemia cases that occurred in the fall or winter were usually associated with hunting season exposure. Tick bite transmission, however, now accounts for more than half of tularemia cases west of the Mississippi River in the United States. In summer months, tick or fly bites appear to be the main mode of transmission of tularemia to humans. Other animals, such as domestic cats, are susceptible to tularemia and are known to have transmitted tularemia to humans.[5] Tularemia outbreaks have also occurred among hamsters purchased from pet shops. Individuals should be careful when handling any sick or dead animal. Other modes of transmission include ingestion of, or contact with, infected meat, water, or soil; inhalation of aerosolized bacteria; or bites from infected animals, mosquitoes, or deerflies.[26] Direct person-to-person transmission has not been reported.

CLINICAL PRESENTATION

The clinical manifestations of tularemia are related to the mode of transmission, patient characteristics, and bacterial subspecies causing infection.[26] Classically, six types of tularemia presentation have been identified: ulceroglandular, glandular, typhoidal, oculoglandular, oropharyngeal, and pneumonic. The last three forms were presumably not tick-borne, reflecting alternative avenues of transmission. Today, the clinical manifestations fall into two main groups: ulceroglandular and typhoidal.[26]

Ulceroglandular is the most common form of tularemia, accounting for ~75% of cases.[26] Sixty percent of ulceroglandular cases are characterized by an ulcer that forms at the site of entry, usually on the lower extremities, perineum, buttocks, or trunk from arthropods that tend to bite the lower extremities or on the upper extremities from mammalian bites.[23] The lesion starts as a firm, erythematous papule that ulcerates and heals over the course of several weeks. It is accompanied by regional, painful lymphadenopathy, usually

inguinal or femoral. Typhoidal tularemia, occurring in ~25% of cases, is characterized by fever, chills, headache, debilitation, abdominal pain, and prostration. Fever and chills are common with all forms of tularemia.[26]

After exposure to the bacteria and an incubation period of 4 to 5 days, patients become ill with a sudden onset of fever, chills, headache, cough, arthralgias, myalgias, fatigue, and malaise. The severity of symptoms is quite variable, ranging from a mild, limited disease (probably type B tularemia) to rare cases of septic shock (probably type A tularemia). A hallmark manifestation is a high fever without an accompanying increase in pulse, or pulse–temperature disparity.[23] Common complications are mild hepatitis, secondary pneumonia, and pharyngitis. With antibiotic treatment of uncomplicated tularemia, mortality rates are only 1% to 3%. Increased morbidity and mortality are seen in the more rare typhoidal forms.[26] The most lethal form of tularemia is from pulmonary infection.[26] In the healthcare setting, standard precautions are all that is required when caring for patients who are infected with tularemia because they are not a source for secondary infection. However, any suspected outbreaks should be reported and investigated.[26]

DIAGNOSIS

Tularemia can be difficult to diagnose as routine laboratory testing is of little help in establishing a diagnosis and is limited to the demonstration of an antibody response to the bacteria. Because an antibody response to the illness requires 10 to 14 days for detection, treatment is usually empiric. The diagnosis is based on clinical suspicion from the epidemiologic history and the presence of compatible findings. The customary serologic test demonstrates *F. tularensis* antibody agglutination. Although a single-tube agglutination test with a titer of 1:160 or more (or 1:128 or more using a microagglutination study) in a suspected case is highly suggestive of a tularemia diagnosis, a fourfold or greater rise in titers between the acute and convalescent stages 2 weeks apart is

diagnostic.[27] After a bout of tularemia, detectable antibodies may persist for many years.[26]

TREATMENT

Antibiotic treatment options for tularemia have included streptomycin, gentamicin, doxycycline, and ciprofloxacin. Streptomycin was historically the drug of choice for tularemia, but it is often unavailable commercially. Some clinicians believe that gentamicin is the best alternative aminoglycoside for the treatment of nonmeningitic tularemia. Its advantages compared with streptomycin include lower minimal inhibitory concentrations (MICs), less vestibular toxicity, and wider commercial availability. Although considered comparable in efficacy to streptomycin, gentamicin has been associated with increased treatment failure and relapse. Tobramycin is inferior to gentamicin or streptomycin and should not be used.

In many of the reported studies of antimicrobial therapy for tularemia, short courses of treatment were used. To prevent tularemia from worsening or relapsing, longer regimens (10–14 days) should be used, especially in more severe cases. Jarisch–Herxheimer reactions can occur with antibiotic treatment of tularemia. Antibiotic prophylaxis for people exposed to those with tularemia is not recommended, but prophylactic antibiotics might be used for suspected bioterrorism attacks of tularemia. Acute febrile illness with pneumonia and other signs of infection occur 3 to 5 days after exposure to airborne tularemia organisms from an intentionally set weapon. No tularemia vaccines are available in the United States. A partially protective one was developed in the former Soviet Union but was only used for at-risk personnel such as for certain laboratory workers.[24] Personal protective measures, as discussed for Lyme disease, should be used when spending time outdoors in endemic areas.[26]

RICKETTSIA: ROCKY MOUNTAIN SPOTTED FEVER, *RICKETTSIA PARKERI* INFECTION, EHRLICHIOSIS, AND ANAPLASMOSIS

Rocky Mountain Spotted Fever

RMSF is the most prevalent and virulent rickettsial disease in the United States. As early as 1872, RMSF infected White settlers of the Northwest and it may have been prevalent in Native Americans of the region before that time. It was first described in residents of the Bitterroot, Snake, and Boise River valleys of Montana and Idaho in the late 1800s. Howard Ricketts discovered the causative agent, *Rickettsia rickettsii,* in 1908.[27] The rickettsia is a small (0.3 × 1 μm), pleomorphic, weakly gram-negative, obligate intracellular coccobacillus that can survive only briefly outside of a host.[27]

EPIDEMIOLOGY

RMSF is found throughout North America, including the United States, Canada, and Mexico, and in parts of Central and South America.[27] It has not been documented outside of the Western Hemisphere. The term “Rocky Mountain spotted fever” is actually a misnomer because the disease has shifted eastward from the Rocky Mountain states, and over 60% of the RMSF cases now occur in North Carolina, Missouri, Oklahoma, Arkansas, and Tennessee.[5,27,28] More recently (between 2013 and 2016), over 360 cases and 21 fatalities have occurred in Arizona.[5] Most RMSF infections arise from tick exposure in rural or suburban locations, although rare outbreaks in urban environments have occurred.

The prevalence of RMSF is highest in children ages 5 to 9 years.[29] Another peak prevalence is seen in males older than 60 years. Risk factors include male sex, residence in wooded areas, and exposure to tick-infected dogs. RMSF, like other tick-borne diseases, is highly seasonal, with greatest incidence in late spring and early summer.[27]

TICK VECTORS AND HOSTS

In the east, south, and west coasts of the United States, the tick vector for RMSF has been identified as the dog tick, *D. variabilis.*[2] In the Rocky Mountain states, the wood tick, *D. andersoni,* is the vector.[25] In Mexico, the tick vectors are *Rhipicephalus sanguineus* and *Amblyomma cajennense,* with the latter also being responsible in Central and South America.[25] The brown dog tick, *R. sanguineus*, has been identified as a new tick vector for RMSF in a defined area of Arizona.[27–29]

Dermacentor ticks feed on humans only during their adult stage.[27] Larval *Dermacentor* ticks may be infected while feeding on small mammals that have sufficient rickettsemia for transmission, such as chipmunks, ground squirrels, cotton rats, snowshoe hares, and meadow voles. Dogs are not considered reservoirs for *R. rickettsii* but are susceptible to RMSF and may introduce infected ticks into households.[27],[28] Adult ticks transmit the rickettsia transovarially to their progeny with high efficiency and establish newly infected tick lines. If the rickettsia burden is large in the adult tick, however, it may cause tick death, thereby reducing infected tick lines. Therefore, there must be nontick reservoirs, as mentioned previously, to develop newly infected tick generational lines; otherwise, RMSF would slowly disappear. In summary, ticks are both vectors and hosts for *R. rickettsii.*[27] Humans are dead-end accidental hosts of *R. rickettsii*.[27]

DISEASE COURSE, SYMPTOMS, AND FATALITIES

Rickettsia rickettsii is usually transmitted to humans from an infected tick bite.[27] The organism can also gain access to humans through broken skin if an infected tick is being crushed with bare fingers, and such crushing may generate infectious aerosols that might be inhaled. Conjunctival contact with infected tick tissues or feces provides another route for rickettsial entry. Contaminated blood transfusions and needle stick injuries have also transmitted *R. rickettsii*.[27]

After introduction of the organisms into the body, the rickettsia spread hematogenously with a predilection for the vascular endothelium, especially in capillaries and medium-sized blood vessels.[28] During an incubation period of 2 to 14 days, induced phagocytosis allows rickettsial entry into endothelial cells, where they replicate by binary fission in the cytoplasm and nuclei of infected cells. This induces a generalized vasculitis leading to activation of clotting factors, capillary leakage, and microinfarctions in various organs.[27] Exotoxins are not secreted by rickettsia; however, they do induce oxidative and peroxidative damage to host cell membranes, resulting in necrosis.[27] In severe infections, hypotension and intravascular coagulation may coexist and culminate in cell, tissue, or organ destruction.

Dehydration is an early sign of RMSF, followed by increased vascular permeability, edema, decreased plasma volume, hypoproteinemia, reduced serum oncotic pressure, and prerenal azotemia. RMSF is a multisystem disease, but a particular organ may be the major focus of the disease. If the brain or lungs are severely infected, death can ensue. An increased severity of illness is associated with edema, particularly in children, and hypoalbuminemia. Hypotension is present in 17% of patients and hyponatremia in 56%. Extensive infection of the pulmonary microvascular endothelium can cause noncardiogenic pulmonary edema.

A common finding in RMSF is myalgia (72%–83%) or muscular tenderness, which are manifestations of skeletal muscle necrosis. Striking creatinine kinase elevations have been described. Thrombocytopenia resulting from consumption of platelets during intravascular coagulation processes occurs in 35% to 52% of patients. True disseminated intravascular coagulation with attendant hypofibrinogenemia is exceptional, however, even in severe or fatal cases.[28] Blood loss or hemolysis in some may cause anemia, which is seen in 30% of patients and reflects blood vessel damage. Fatalities usually occur 8 to 15 days after illness onset if no treatment is given or is delayed. Long-term sequelae from severe forms of RMSF can include partial paralysis of the lower extremities,

gangrene of extremities requiring amputation, deafness or hearing loss, incontinence, and movement or speech disorders, but these occur in a minority of patients who receive prompt antibiotic therapy.[27]

"Fulminant" RMSF is best defined as a disease with a rapidly fatal course with death occurring in ~5 days. This form of disease is characterized by an early onset of neurologic signs and late or absent skin rash; it is highly associated with glucose-6-phosphate dehydrogenase deficiency, advanced age, male sex, and possibly heavy alcohol use.[27],[28] In the pre-antibiotic era, RMSF mortality rates were as high as 30%, but they have fallen to 5% in antibiotic-treated cases today.[2],[28]

The classically defined triad of RMSF symptoms at initial presentation is fever, rash, and headache, but this is found in only up to 5% of cases during the first 3 days of illness and up to ~60% of cases 2 weeks after exposure.[27],[29] The RMSF skin rash typically begins 2 to 4 days after fever onset as pink, 1- to 5-mm blanchable macules that later become papules.[28] It begins on the ankles, wrists, and forearms, and soon thereafter involves the palms or soles. It then spreads to the arms, thighs, and trunk, and typically evolves into a petechial exanthem. The utility of these findings in the differential diagnosis is limited because rash may be absent, transient, or late; it may never become petechial, or it may have an unusual distribution.

DIAGNOSIS

As for most tick-borne diseases, confirmatory serologic analysis is not particularly useful in early diagnosis of disease. The initial diagnosis is made based on clinical signs and symptoms and medical history. Because RMSF can be a severe or even fatal illness, antirickettsial treatment should begin immediately to prevent morbidity and mortality.[27],[28] *Rickettsia rickettsii* is difficult to culture. Immunohistologic demonstration of *R. rickettsii* in biopsy specimens of rash lesions is the only approach that can yield diagnostic results in a timely manner, but this approach is applicable only to those

presenting with a skin rash, and these tests are not readily available.[27]

The best serologic test for RMSF is the indirect immunofluorescence assay (IFA) test, but antibodies typically appear only after 10 to 14 days.[27] More striking laboratory abnormalities of RMSF disease include a normal leukocyte count with a shift to the left, hyponatremia, thrombocytopenia, elevated serum transaminases or creatinine kinase, and CSF pleocytosis. These findings are observed late in the disease course, however, and are not helpful in early disease recognition.

Clinical findings and history are essential to early diagnosis and successful treatment. Therapy must precede laboratory confirmation of RMSF.[27] In a febrile, tick-exposed person with a rash, RMSF should be considered. RMSF should be strongly considered in febrile children, adolescents, or males age older than 60 years, especially if they reside in or have traveled to the southern Atlantic or south-central United States from May through September. A delay in treatment for RMSF beyond 5 days of symptom onset can be rapidly fatal as the mortality rate increases from 5% to 22%.

TREATMENT

Doxycycline should be initiated immediately as first-line treatment for RMSF in both adults and children whenever RMSF is suspected. The recommended treatment is doxycycline 100 mg every 12 hours for children weighing <100 pounds (<45 kg): 2.2 mg/kg body weight given twice a day. The standard duration of treatment is 7 to 14 days, including at least 3 days after the temperature has normalized.[5],[6] The use of doxycycline to treat suspected RMSF in children is standard practice by the CDC and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases as the use of alternative antibiotics increases the risk of death. Contraindications to doxycycline use include history of severe hypersensitivity reactions to tetracyclines, and in some pregnant patients in which the case of RMSF seems mild, chloramphenicol may be considered as an alternative antibiotic.[27] However, oral formulations of

chloramphenicol are not available in the United States, and there are severe risks of adverse of effects with this agent, including gray baby syndrome and aplastic anemia.[27] The erythromycins, penicillins, sulfonamides, aminoglycosides, and cephalosporins are not effective for RMSF, and sulfa drugs may worsen infection.

A crucial component in the management of RMSF is appropriate supportive care.[5] Those with severe disease should be hospitalized and managed with hemodynamic, renal, pulmonary, and fluid support as needed.[5]

PREVENTION

In addition to the same guidelines for prevention of Lyme disease, keeping pets free of ticks can reduce exposure. Ticks must not be crushed in a way that might introduce rickettsia into cutaneous lesions, mucous membranes, or the conjunctiva. No RMSF vaccine is available.[27] Antirickettsial antibiotic prophylaxis after a tick bite is not warranted as there is no evidence that this approach is effective and it may delay the onset of the disease.

Spotted Fever Group *Rickettsia*

In addition to *R. rickettsii*, the agent of RMSF, many other rickettsial pathogens have been recognized and grouped broadly as "Spotted Fever group Rickettsia (SFGR)."[30] In the United States, these pathogens include *Rickettsia parkeri* and *Rickettsia* 364D, and internationally, there is a growing number of tick-borne SFGR that are pathogenic to humans.[5,31] Doxycycline treatment is effective and is the antibiotic of choice for tick-borne SFGR infections.[5]

Ehrlichiosis and Anaplasmosis

SPECIES IDENTIFICATION, TICK VECTORS, AND DISEASE HOSTS

Although ehrlichiosis and anaplasmosis are transmitted by two different species of ticks and generally occur in different regions of

the United States, patients may have a similar clinical presentation.[5],[6] The term “ehrlichiosis” may be more broadly applied to different infections, including *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, which are transmitted by the lone star tick generally in the southeastern and south-central United States, from the eastern seaboard extending westward to Texas. A third species, provisionally called *Ehrlichia muris*-like (EML), was identified among patients in the upper Midwest; however, the tick responsible for transmitting EML is unknown, and the clinical presentation is undifferentiated from other *Ehrlichia* species.

Anaplasmosis is a bacterial disease, caused by *Anaplasma phagocytophilum,* which was first recognized as a disease in humans in 1994.[5] Although previously known as human granulocytic ehrlichiosis (HGE), a taxonomic change in 2001 identified that this organism belongs to the genus *Anaplasma* and resulted in the name change to human granulocytic anaplasmosis (HGA). To date, the highest incidence of HGA in the United States is reported in the upper Midwest and northeastern states with transmission by the black-legged tick (*I. scapularis*). Along the West Coast, it is transmitted by the western black-legged tick *(I. pacificus*).

CLINICAL AND LABORATORY FINDINGS

Human ehrlichiosis and anaplasmosis usually present as nonspecific, febrile, flu-like illnesses resembling RMSF. The symptoms caused by infection generally develop 1 to 2 weeks following the bite of an infected tick and are variable. Patients who are immunocompromised (eg, receiving corticosteroids, cancer chemotherapy, long-term immunosuppressive therapy following organ transplant), or who have HIV infection or splenectomy may experience more severe disease and greater risk of mortality.

The following signs often are noted: hypertransaminemia, leukopenia (often with a shift to the left), and thrombocytopenia. A skin rash is an uncommon feature of ehrlichiosis and is rarely seen with anaplasmosis. However, up to 60% of children can experience a rash caused by *E. chaffeensis.* The diagnosis of ehrlichiosis and

anaplasmosis must be made based on clinical findings, as treatment should never be delayed pending the results of confirmatory laboratory testing or be withheld based on an initial negative laboratory result. In patients presenting with known tick exposure, fever, thrombocytopenia, and increased liver function test, a peripheral smear should be performed. A peripheral blood smear showing neutrophilic morulae supports a provisional diagnosis, although this characteristic finding is not present in most cases. Confirmatory testing by serology or PCR or direct culture is still required to establish a diagnosis.[32] As with many other tick-borne diseases, serologic findings of antibody response to ehrlichiosis or anaplasmosis assist only by retrospectively confirming the diagnosis.

TREATMENT AND PREVENTION

CASE 82-8

Question 1: G.T., a 65-year-old male living in northwest Wisconsin, presents with an influenza-like illness in late May. He has a 2-day history of fever, shaking chills, headache, myalgias, nausea, and anorexia. On examination, his temperature is 102.92 °F (39.40 °C), but other physical findings are unremarkable. No skin rashes are found. G.C. states that he had multiple tick bites 1 week ago while he was fur trapping. The physician suspects anaplasmosis. Blood is drawn for serology, CBC with differential, chemistry profile, and a Wright stain microscopic examination. Immediately available abnormal results include neutrophilic morulae on microscopy, a WBC count of 2500/μL, a platelet count of 80 × 10^3/μL, C-reactive protein of 136 mg/L (normal, 4–8 mg/L), aspartate aminotransferase (AST) of 150 IU/L, and lactate dehydrogenase of 700 IU/L. Serology is still pending.

What of G.T.'s history and symptoms are consistent with a diagnosis of HGA?

G.T.'s history is significant for HGA. He was in the right place, the upper Midwestern United States, and was outdoors during the right season; most patients are diagnosed with HGA in May through August, and his history fall within the usual 1- to 2-week incubation period from tick bite to onset of illness.

His symptoms are also important. Nearly 100% of patients with HGA have a fever of >99.68 °F (>37.60 °C). Other symptoms in G.C.

consistent with HGA are rigors (shaking chills), headache, myalgias, nausea, and anorexia. Matching laboratory findings include neutrophilic morulae. The laboratory findings of leukopenia and thrombocytopenia strongly support the diagnosis of anaplasmosis. Evidence of mild-to-moderate hepatic injury, as seen by the elevated liver enzyme results, is helpful in HGA diagnosis.

CASE 82-8, QUESTION 2: What antibiotic treatment should be initiated?

Doxycycline is the first-line treatment for G.T. and should be used for both adults and children of all ages whenever anaplasmosis or ehrlichiosis is suspected.[4],[5] In patients such as G.C. who are treated within the first 5 days of the disease, a good response to doxycycline occurs with fever resolution generally in 2 days.[32] Fever persisting for more than 2 days after doxycycline treatment suggests that the diagnosis is incorrect.

PROTOZOA: BABESIOSIS

Babesia, Ticks, and Hosts

There are more than 100 species of *Babesia* having a worldwide geographic range.[5] However, only relatively few species have caused documented cases of human infection, including *Babesia microti, Babesia divergens*, and *Babesia duncani* and currently an unnamed agent designated MO1.[5],[33] The most common cause of human babesiosis is *B. microti*, which is transmitted by *I. scapularis* ticks, primarily in the endemic regions in the Northeast and upper Midwest of the United States; however, sporadic cases of babesiosis have occurred in other regions, including the West Coast. In addition to the Ixodes ticks, *Babesia* species are also transmitted by *Dermacentor, Haemaphysalis,* and *Rhipicephalus* ticks. Because *B. microti* is typically transmitted by the nymphal stage of *I. scapularis*

tick (about the size of a poppy seed), infected patients may not recall a tick bite.

SYMPTOMS AND DIAGNOSIS

CASE 82-9

QUESTION 1: H.S., age 70 years, lives in Martha's Vineyard in Massachusetts. During the month of July, he enjoyed a day of boating, fishing, and hiking at a nearby lake. About a week later, he felt fatigued and lost his appetite. He presents to his local PCP in the middle of August with fever, headache, drenching sweats, aches, and pains and occasional dark-colored urine. He does not recall a tick bite. On physical examination, he has splenomegaly and hepatomegaly. Laboratory tests show a severe normochromic, normocytic anemia, decreased hemoglobin, hemoglobinuria, thrombocytopenia, and increased liver enzymes. His temperature is 104 °F (40 °C). Examination of a Giemsa-stained thin blood smear reveals the presence of unpigmented ring-shaped intraerythrocytic parasites in >5% of his erythrocytes.

What was the clue to the diagnosis of babesiosis?

The diagnosis of babesiosis was confirmed by the direct observation of the protozoan inside the red blood cells. Although the Giemsa-stain test is a commonly used tool, it is subject to false-negative results because the rate of parasitemia is typically low. Usually, multiple blood smears need to be examined because <1% of erythrocytes may be infected early in the course of the disease when most people seek medical help.[4,33] Because blood smear inspection is often not successful in diagnosing babesiosis or may only detect a few parasites, additional supportive laboratory results are advocated, such as serology using IFA for IgM and IgG antibabesial antibodies or PCR detection of babesial DNA in the blood.[3]

The clinical findings in patients with babesiosis are similar to those of malaria, ranging in severity from asymptomatic to severe complications and death.[12] Most patients with *B. microti* babesiosis are asymptomatic, although some people may develop nonspecific flu-like symptoms, such as fever, chills, sweats, headache, myalgias, and nausea. This form of babesiosis can be viewed as a distinct,

occult, asymptomatic disease with few known sequelae.[33] A number of transfusion-acquired infections have been documented, reflecting the existence of an asymptomatic form of babesiosis in blood donors. In 2018, the Food and Drug Administration (FDA) approved the first *B. microti* blood donor screening tests.[5]

A second form of babesiosis has been termed a "mild-to-moderate viral-like illness."[33] It has a gradual onset of fatigue and malaise and later fever accompanied by one or more of these symptoms: chills, sweats, headache, arthralgias or myalgias, anorexia, or cough.[33] Rash is rare. It can last weeks to months, sometimes with a prolonged recovery time of up to a year or more.[33]

A third form of babesiosis is a potentially life-threatening hemolytic one that occurs in people predisposed to severe infection because of advanced age, immune suppression as a result of HIV disease or immunosuppressants, malignancy, or prior splenectomy.[33] Although babesial infection is as prevalent in children as it is in adults, it is more severe in adults older than 50 years of age. Complications seen in severe babesiosis include acute respiratory failure, disseminated intravascular coagulation, congestive heart failure, coma, and renal failure, with a 5% to 9% mortality rate.[3,33]

In the northeastern United States, infections commonly occur in patients with spleens, as in H.S. Clinically apparent cases are most common in 50- to 60-year-old patients, many of whom do not recall a tick bite. Most symptoms of babesiosis are caused by hemolysis or the systemic inflammatory responses to parasitemia.[33] The usual incubation period is 1 to 6 weeks after a tick bite based on limited data.[33] Nonspecific, viral-like symptoms that are gradual in onset appear first, as in H.S.'s case, followed several days later by the other symptoms H.S. displayed. A hallmark of the disease is hemolytic anemia of varying severity. A high index of suspicion for babesiosis should be maintained in any patient with an unexplained febrile illness who lives in or has traveled to a region where the infection is endemic during June through August, as in H.S.'s case, particularly if there is a history of tick bite.

TREATMENT

CASE 82-9, QUESTION 2: The PCP institutes a regimen of atovaquone plus azithromycin for H.S. Is this an appropriate treatment regimen? What other drugs have been used?

The discovery of an original human babesiosis treatment regimen combining clindamycin and quinine was a fortuitous one. In 1982, an 8-week-old infant with presumed transfusion-acquired malaria was initially treated with chloroquine. Because of a lack of response, treatment was switched to quinine plus clindamycin, and the patient's fever decreased. A correct diagnosis of babesiosis was subsequently confirmed. Although this treatment combination is still used, frequent side effects (eg, tinnitus, vertigo, and diarrhea) occur, often resulting in dose reduction or discontinuation.[11,33] Treatment failures with this regimen have occurred in patients who underwent splenectomy, patients with HIV infection, or those receiving concurrent corticosteroids.[3]

For mild-to-moderate babesiosis, atovaquone plus azithromycin is the regimen of choice, as H.S. received. This regimen has also achieved cures in pediatric cases, although a controlled trial study has not been performed.[33] On the other hand, persistent relapsing babesiosis and emergence of resistance have occurred in immunocompromised patients receiving this regimen.[33,34] It has been suggested that the usual 7- to 10-day course treatment regimen may not be adequate in these patients.[34] Combination therapy of azithromycin with atovaquone is better tolerated than clindamycin–quinine combinations. The dosing is atovaquone 750 mg orally every 12 hours and azithromycin 500 to 1000 mg orally on day 1 and 250 to 1000 mg on subsequent days for 7 to 10 days.[12,33] Increased azithromycin doses of 600 to 1000 mg/day may be used in immunocompromised patients.[11,12] Children should receive atovaquone 20 mg/kg (maximum, 750 mg dose) every 12 hours and azithromycin 10 mg/kg (maximum, 500-mg dose) on day 1 and 5

mg/kg (maximum, 250-mg dose) orally thereafter for 7 to 10 days.[12,33]

For severe babesial illness, the IV clindamycin plus oral quinine should be given.[33] Dosing recommendations for adults are clindamycin 300 to 600 mg IV every 6 hours *plus* quinine 650 mg orally every 6 to 8 hours for 7 to 10 days; children should receive clindamycin 7 to 10 mg/kg (maximum, 600-mg dose) IV every 6 to 8 hours plus quinine 8 mg/kg (maximum, 650 mg dose) orally every 8 hours for 7 to 10 days.[11,12,33]

Antimicrobials should be used in all patients with symptomatic, active babesiosis once the diagnosis is confirmed by PCR or blood smear, owing to the risk of disease complications.[12] Antibody-seropositive, symptomatic patients without identifiable parasites on blood smear or PCR positivity should not be treated. Similarly, asymptomatic patients should not be treated regardless of serologic results, blood smear examinations, or PCR findings. A course of treatment should be considered in asymptomatic patients, however, if these tests are positive and repeat testing demonstrates persistent parasitemia for >3 months.[12]

Partial or complete red blood cell transfusions may be lifesaving in severe babesiosis for patients having high-grade parasitemia (10% or more infected erythrocytes), significant hemolysis, or pulmonary, renal, or hepatic compromise.[11] Rapidly increasing parasitemia leading to massive intravascular hemolysis and renal failure mandates immediate treatment for this form of the disease. Patients receiving antibiotic treatment, in particular those with severe or persistent symptoms, should be evaluated for co-infection with *B. burgdorferi* or *A. phagocytophilum* or both.

Babesiosis prevention is the same as for other tick-borne diseases. Asplenic patients should avoid areas where babesiosis is endemic. To date, no supportive data for the use of prophylactic antibiotics to prevent babesial infection after a tick bite are available.[33] Although developed for use in cattle, babesial vaccines are not available for humans.

VIRUSES: COLORADO TICK FEVER, TICK-BORNE ENCEPHALITIS, AND OTHER VIRALLY MEDIATED TICK-BORNE DISEASES

Colorado Tick Fever

VIRUS IDENTIFICATION, TICKS, AND HOST RESERVOIRS

"Mountain fever" has been described since the first immigrants arrived in the Rocky Mountains. It was later renamed Colorado tick fever (CTF), and the Colorado tick fever virus (CTFV) was identified as the cause.

CTF is caused by a double-stranded RNA *Coltivirus*. It is an intraerythrocytic virus. At least 22 strains of CTFV are known, but antigenic variation among human strains is low.[35] The virus is an arbovirus because it replicates inside ticks. The primary nidus of infection is thought to be CTFV invasion of hematopoietic progenitor erythroblasts, and it remains sheltered in mature erythrocytes.[35,36]

CTF is a viral illness transmitted by the bite of an infected tick.[35] Although at least eight tick species have been found to be infected with the virus, adult *D. andersoni* ticks are the primary tick vector that transmits CTF to humans.[35,36] *Dermacentor andersoni* feeds on numerous mammals, but ground squirrels, porcupines, and chipmunks are the primary reservoirs for CTFV as well as the ticks themselves.[35,36] Transstadial transmission of CTF virus within the tick ensures it is infected for life.[35]

PREVALENCE

CTF is contracted in forested mountain areas at higher elevations of the western Black Hills and Rocky Mountain regions of the United States and Canada, especially on the south-facing brush slopes and dry rocky surfaces of mountains east of the Continental Divide.[35,36] Although CTF can develop from March to October, May through July are peak incidence months.[5,6]

SYMPTOMS

CASE 82-10

QUESTION 1: P.J., a previously healthy 27-year-old graduate student living in Atlanta, Georgia, returns from a 1-week late-spring break camping trip with her friends in the eastern Colorado Rocky Mountains. Four days later, she experiences fever, chills, headache, myalgias, conjunctivitis, and lethargy. She recalls no tick bites and has no skin rashes. Suspecting RMSF, her physician prescribes doxycycline. P.J.'s symptoms and fever initially resolve, but 2 days later her symptoms return. Physical examination at this time reveals a temperature of 102.20 °F (39 °C). Routine laboratory tests are normal, although leukopenia is observed with a WBC count of 2400/μL.

How do P.J.'s symptoms suggest a diagnosis of CTF?

Symptoms of CTF usually start 3 to 5 days after a tick bite, although more than half of patients do not remember being bitten.[35],[36] The most common initial symptoms are fever of rapid onset, headache, chills without true rigors, and myalgias.[35] A rash, which may be petechial, maculopapular, or macular, can occur in 5% to 15% of patients.[39] About half of patients with fever experience a "biphasic" pattern of fever and other symptoms, which means they have several days of fever, then improve for several days, and then have a second period of fever and illness.[35],[36] Sequelae are rare, although fatigue and malaise may last for months.[36] One- to three-week periods of convalescence are usual. Children, however, experience complications more frequently than adults. Patients with suspected CTF should defer from donating blood or bone marrow for at least 6 months after their illness because the virus may stay in red blood cells for several months and can be passed to others via blood transfusions.

LABORATORY FINDINGS

Moderate-to-significant leukopenia is the most important finding in CTF. Leukocyte counts are usually normal on the first day, but decrease to 2000 to 4000/μL by the fifth or sixth day of illness with a lymphocytic predominance.[36] In one-third of confirmed CTF cases,

however, the leukocyte counts remained around 4500/μL. Counts return to normal within a week of fever abatement in most cases. Thrombocytopenia may occur.[35],[36] Although the CSF may show a lymphocytic pleocytosis, this does not distinguish CTF from other causes of meningoencephalitis.[36]

DIAGNOSIS AND TREATMENT

CTF diagnosis can be made serologically, either with IFA staining of erythrocytes, complement fixation, or ELISA.[35],[36] The most sensitive isolation system is intracerebral injection of infected blood into suckling mice.[35],[36] A reverse transcriptase PCR of specimens can be diagnostic within the first 5 days of illness, whereas serologic tests are more relevant for diagnosis 2 weeks after symptom onset.[36] There is no specific treatment available for patients with CTF infection, which is usually self-limiting. Supportive care should be provided. The best protection for CTF is tick prevention strategies.[36]

TICK-BORNE ENCEPHALITIS

Tick-borne encephalitis (TBE), a life-threatening neurologic disease, is a growing public health concern in Europe and Asia as the incidence of TBE virus has significantly increased in the past decade.[5],[37] TBE virus is divided into three subtypes: Central European (western subtype), Siberian, and Far Eastern (Russian spring–summer or eastern subtype) and is endemic to central and eastern Europe, Russia, and the Far East, with some overlap in geography.[5],[37]

The etiologic agents are spherical, lipid-enveloped RNA viruses in the genus *Flavivirus.*[5],[38] The western subtype is transmitted to humans by *I. ricinus,* and the Siberian and Far Eastern subtypes are transmitted by *I. persulcatus,* although *Ixodes ovatus* is the vector in Japan.[41] A minority of TBE cases have followed the consumption of infected unpasteurized milk or cheese directly without a tick vector.[38] The main virus reservoirs are small rodents.[38] Ticks are vectors, and humans are accidental hosts of the virus. Ticks can become infected for life by the virus at larval, nymphal, or adult stages; can acquire it

during mating; and can maintain the virus transovarially and transstadially.[38] TBE viruses are transmitted from the saliva of an infected tick very rapidly, within minutes of the bite, so early removal of the tick may not prevent subsequent encephalitis.

As the disease name implies, the ultimate outcome of the infectious process is manifested as CNS involvement, with symptoms of aseptic meningitis, meningoencephalitis, and meningoencephalomyelitis. TBE begins as a febrile headache with progression to CNS manifestations. There is no antiviral treatment available, and treatment is supportive, including management of any complications. Two inactivated cell culture–derived preventive human TBE vaccines are available in Europe, in adult and pediatric formulations (FSME-IMMUN and Encepur®).[5] The adult formulation of FSME-IMMUN is also licensed in Canada. Two other inactivated TBE vaccines are available in Russia (TBE-Moscow and EncVir®). The reader is referred to the CDC for information regarding vaccination to TBE-endemic countries.[5]

POWASSAN DISEASE

Powassan virus infection is an RNA virus belonging to the genus *Flavivirus* that is related to West Nile, St. Louis encephalitis, and TBE viruses.[5] Powassan disease is now recognized in the United States, Canada, and Russia. In the United States, ~60 cases have been reported in the past decade primarily from northeastern states and the Great Lakes region. The incubation period ranges from 1 week to 1 month. Many people who become infected are asymptomatic. Signs and symptoms of illness can include fever, headache, vomiting, and malaise. Because the Powassan virus can infect the CNS, progression of disease to meningoencephalitis with confusion, seizures, and memory loss may occur. There are currently no vaccines or treatment for Powassan disease. Supportive care should be provided to patients with suspected disease.

TOXINS: TICK PARALYSIS

Tick Paralysis

CASE 82-11

QUESTION 1: C.M., a 7-year-old girl residing in Spokane, Washington, tells her parents that both of her legs feel weak. The next day, her mother notices that C.M. has worsened and immediately takes her to the pediatrician. The physician finds that C.M. has begun experiencing flaccid paralysis in both legs and the lower trunk, although she is alert and oriented. The pediatrician finds that there is a tick attached to C.M.'s scalp under her hair and removes it. C.M. is back to full health in 2 days.

What happened?

Tick paralysis (tick toxicosis) occurs worldwide in humans and many animals, and was first described by the explorer Hovell in Australia in 1824.[39] Although 60 tick species worldwide can produce tick paralysis in animals and humans, it is predominantly caused in humans by *D. andersoni* and *D. variabilis* in North America.[39] In Australia, *Ixodes holocyclus* is the culprit.[39]

Most human cases occur during the spring and summer in Australia and North America. In the United States, it is most common in the Pacific Northwest and adjacent areas of southwestern Canada and in the Rocky Mountain states.[39] In children, girls are more commonly affected; however, in adults, more males are affected.[41] Of epidemiologic significance, a young girl's long hair provides camouflage for feeding ticks.[39]

The cause of tick paralysis is the secretion of a neurotoxin present in the large salivary glands of female ticks. They must usually be attached to a host for 4 to 5 days before symptoms develop.[39] The toxin affects motor neurons, decreases acetylcholine release, and may have a mechanistic similarity to botulinum toxin.[39] Paresthesias and symmetric weakness in the lower extremities with motor difficulties progress to an ascending flaccid paralysis in several hours or days. Cerebral sensorium is usually spared, pain is absent, and the blood and CSF are normal.[39] If the tick is not removed, the

toxicosis can progress to respiratory paralysis and death.[39] Initially reported mortality rates of 10% have fallen dramatically with our modern intensive care units and available respiratory care.[39] A Washington State case series of 33 patients conducted over the course of 50 years revealed a mortality rate of 6%, with the last two patients' deaths occurring in the 1940s.[39] Children are likely more vulnerable to tick paralysis than adults because the dose of neurotoxin present per kilogram of body weight is higher.[38] Diagnosis should include a complete body examination of the skin for the presence of an engorged tick.[38]

In North America, tick removal commonly results in complete recovery within hours to days. In Australia, the disease is more acute, and paralysis may continue to progress for 2 days after tick removal. Recovery from the disease in Australia may take several weeks. Treatment is supportive. Antitoxin derived from dogs is the treatment of choice for animals, but it also has been used occasionally in humans in Australia with severe tick paralysis.[39] Local experts must determine its use on a case-by-case basis because of the risk of serum sickness or acute allergic reactions.[38]

MIXED INFECTIONS

Because the tick vectors and mammalian hosts are the same for babesiosis, anaplasmosis, and Lyme disease in the northeastern United States, all three diseases, theoretically, could be transmitted to a human from one tick bite. Human co-infection by the agents of Lyme disease, babesiosis, or anaplasmosis can occur, especially in endemic areas.[6] Co-infection may alter the natural course for each disease or increase clinical manifestations, especially flu-like symptoms, in concurrent Lyme disease with babesiosis or HGA. Because the same tick vector in Europe and Russia can carry Lyme disease and TBE, dual infection may result in more severe disease.[38]

Dual infection may affect the choice of initial antibiotic therapy. For example, although amoxicillin is sometimes used to treat early Lyme disease, it is not effective for HGA. Doxycycline, however, is useful in both of these diseases. Thus, some cases of Lyme disease that were believed to be treatment failures may actually have been confounded by co-infection. Patients with concurrent Lyme disease and babesiosis have more symptoms and a longer duration of illness compared with patients with single infections. When moderate-to-severe Lyme disease is diagnosed, the possibility of concomitant babesial or anaplasma infection should be considered in regions where both diseases are endemic. Neutropenia and thrombocytopenia are associated with anaplasmosis, anemia and thrombocytopenia are associated with babesiosis, and neither is routinely found in Lyme disease.[6] For patients with Lyme disease who experience a prolonged flu-like illness that fails to respond to appropriate antiborrelial therapy in an endemic area, clinicians should consider testing for babesiosis and anaplasmosis.[6]

SUMMARY

Tick-borne diseases have become an increasingly complex and serious global problem. We continue to encounter growing numbers of cases of tick-borne human disease of known or unknown causes. Most of the research into tick-borne human disease demonstrates a close historical relationship of endemic tick–deer–rodent cycles for various microorganisms. Scientists continue to search for improvements in diagnosing, treating, and preventing tick-borne diseases, as well as controlling the tick populations that transmit microbes. The threat posed by human-biting ticks has become more widespread across various regions and, across tick species, more spatially diffuse (including backyards, neighborhood green spaces, and public recreation areas).[3,21] More research and coordinated strategies are needed to better understand and reduce tick-borne disease risk. Because patients present frequently with nonspecific

signs and symptoms, a high index of suspicion is crucial to include a tick-borne illness in the differential diagnosis of those presenting with symptoms compatible with a tick-borne illness. It is essential to obtain a careful history of possible tick exposure and consider the epidemiology of infected ticks when considering the possibility of tick-borne illnesses. It is also important to increase awareness of personal protection strategies and tick avoidance.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Alpern JD, Dunlop SJ, Dolan BJ, Stauffer WM, Boulware DR. Personal protection measures against mosquitoes, ticks, and other arthropods. *Med Clin North Am*. 2016;(*100*):303–313. (17)

Centers for Disease Control and Prevention. *Tickborne Diseases of the United States. A Reference Manual for Healthcare Providers*. 5th ed. 2018. Accessed January 1, 2021. https://www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf. (6)

Diaz JH. Chemical and plant-based insect repellents: efficacy, safety, and toxicity. *Wilderness Environ Med*. 2016;27(1):153–163. (1)

Madison-Antenucci S, Kramer LD, Gebhardt LL, Kauffman E. Emerging tick-borne diseases. *Clin Microbiol Rev*. 2020;33:e00083-18. doi:10.1128/CMR.00083-18 (4)

Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis*. 2021;72(1):e1-e48. (9)

Krause PJ, Auwaerter PG, Bannuru RR, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2020 Guideline on Diagnosis and Management of Babesiosis. *Clin Infect Dis*. 2021;72(2):e49-e64. doi:

10.1093/cid/ciaa1216. Erratum in: Clin Infect Dis. 2021 Jul 1;73(1):172-173. (33)

Key Websites

Centers for Disease Control and Prevention. Diseases transmitted by ticks. http://www.cdc.gov/ticks/diseases/ (5)

COMPLETE REFERENCES CHAPTER 82 TICK-BORNE DISEASES

1. Diaz JH. Chemical and plant-based insect repellents: efficacy, safety, and toxicity. *Wilderness Environ Med*. 2016;27(1):153–163.
2. Anderson JF, Magnarelli LA. Biology of ticks. *Infect Dis Clin North Am*. 2008;22(2):195–215, v.
3. Eisen L. Stemming the rising tide of human-biting ticks and tickborne diseases, United States. *Emerg Infect Dis*. 2020;26(4):641–647. doi:10.3201/eid2604.191629
4. Madison-Antenucci S, Kramer LD, Gebhardt LL, Kauffman E. Emerging tick-borne diseases. *Clin Microbiol Rev*. 2020;33:e00083-18. doi:10.1128/CMR.00083-18
5. Centers for Disease Control and Prevention. Diseases transmitted by ticks. Accessed January 1, 2021. http://www.cdc.gov/ticks/diseases/
6. Centers for Disease Control and Prevention. *Tickborne Diseases of the United States. A Reference Manual for Healthcare Providers*. 5th ed. 2018. Accessed January 1, 2021. https://www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf
7. Mead PS. Epidemiology of Lyme disease. *Infect Dis Clin North Am*. 2015;29(2): 187–210.
8. Maraspin V, Ruzic-Sablijic E, Strele F. Lyme Borreliosis and *Borrelia spielmanii*. *Emerg Infect Dis*. 2006;12:1177.
9. Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis*. 2021;72(1):e1-e48
10. Theel ES. The past, present, and (possible) future of serologic testing for Lyme disease. *J Clin Microbiol*. 2016;54(5):1191–1196.

11. Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review. *JAMA*. 2016;315(16):1767–1777.
12. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43:1089–1134.
13. Rivera Rivera KB, Blais CM. Tick-borne infections. *Hosp Med Clin*. 2015; 4:489–499.
14. Hinckley AF, Meek JI, Ray JAE, et al. Effectiveness of residential acaricides to prevent Lyme and other tick-borne diseases in humans. *J Infect Dis*. 2016; 214:183–188.
15. De la Fuente J, Contreras M. Tick vaccines: current status and future directions. *Expert Rev Vaccines*. 2015;14(10):1367–1376.
16. Plotkin SA. Need for a new Lyme disease vaccine. *N Engl J Med*. 2016;375: 911–913.
17. Alpern JD, Dunlop SJ, Dolan BJ, Stauffer WM, Boulware DR. Personal protection measures against mosquitoes, ticks, and other arthropods. *Med Clin North Am*. 2016;100:303–313.
18. Dantas-Torres F, Otranto D. Best practices for preventing vector-borne diseases in dogs and humans. *Trends Parasitol*. 2016;32(1):43–55.
19. Lupi E, Hatz C, Schlagenhauf P. The efficacy of repellents against *Aedes, Anopheles, Culex* and *Ixodes* spp.—a literature review. *Travel Med Infect Dis*. 2013; 11(6):374–411.
20. Bissinger BW, Roe RM. Tick repellents: past, present, and future. *Pestic Biochem Physiol*. 2010;96:63–79.
21. Dworkin MS, Schwan TG, Anderson DE Jr, Borchardt S. Tick-borne relapsing fever. *Infect Dis Clin North Am*. 2008;22(3):449–468, viii.
22. Schwan TG, Raffel SJ, Schrumpf ME, Porcella SF. Diversity and distribution of *Borrelia hermsii*. *Emerg Infect Dis*. 2007;13(3):436–442.
23. Molloy PJ, Telford SR III, Chowdri HR, et al. *Borrelia miyamotoi* disease in the northeastern United States. *Ann Intern Med*. 2015;163:91–98.
24. Hu LT, Tsibris AM, Branda JA. Case 24-2015-A 28-year-old pregnant woman with fever, chills, headache, and fatigue. *N Engl J Med*. 2015;373:468–475.
25. Masters EJ, Grigery CN, Masters RW. STARI, or Masters disease: lone star tick-vectored Lyme-like illness. *Infect Dis Clin North Am*. 2008;22(2):361–376, viii.
26. Nigrovic LE, Wingerter SL. Tularemia. *Infect Dis Clin North Am*. 2008;22(3): 489–504, ix.
27. Chen LF, Sexton DJ. What's new in Rocky Mountain spotted fever? *Infect Dis Clin North Am*. 2008;22(3):415–432, vii–viii.
28. Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other

Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis –United States. *MMWR Recomm Rep*. 2016;65(2):1-44.

29. Buckingham SC, Marshall GS, Shutze GE, et al. Clinical and laboratory features, hospital course, and outcome of Rocky Mountain spotted fever in children. *J Pediatr*. 2007;150(2):180–184.
30. Demma LJ, Traeger MS, Nicholson WL, et al. Rocky Mountain spotted fever from an unexpected tick vector in Arizona. *N Engl J Med*. 2005;353(6):587–594.
31. Shapiro MR, Fritz CL, Tait K, et al. Rickettsia 364D: a newly recognized cause of eschar-associated illness in California. *Clin Infect Dis*. 2010;50(4):541–548.
32. Bakken JS, Dumler S. Human granulocytic anaplasmosis. *Infect Dis Clin North Am*. 2008;22(3):433–448, viii.
33. Krause PJ, Auwaerter PG, Bannuru RR, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2020 Guideline on Diagnosis and Management of Babesiosis. *Clin Infect Dis*. 2021;72(2):e49-e64. doi: 10.1093/cid/ciaa1216. Erratum in: Clin Infect Dis. 2021 Jul 1;73(1):172-173.
34. Wormser GP, Prasad A, Neuhaus E, et al. Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with *Babesia microti* infection. *Clin Infect Dis*. 2010;50(3):381–386.
35. Attoui H, Jaafar FM, de Micco P, de Lamballerie X. Coltiviruses and seadornaviruses in North America, Europe, and Asia. *Emerg Infect Dis*. 2005;11(11):1673–1679.
36. Romero JR, Simonsen KA. Powassan encephalitis and Colorado tick fever. *Infect Dis Clin North Am*. 2008;22(3):545–559, x.
37. Ergunay K, Tkachev S, Kozlova I, Ruˇžek D. A review of methods for detecting tick-borne encephalitis virus infection in tick, animal, and human specimens. *Vector Borne Zoonotic Dis*. 2016;16(1):4–12.
38. Kaiser R. Tick-borne encephalitis. *Infect Dis Clin North Am*. 2008;22(3): 561–575, x.
39. Edlow JA, McGillicuddy DC. Tick paralysis. *Infect Dis Clin North Am*. 2008;22(3): 397–413, vii.

SECTION 15

Psychiatric Disorders and Substance Abuse

Section Editors: Michael C. Angelini and Michael G. Carvalho

83

Anxiety Disorders

Tamara Bystrak and Amanda Eloma

CORE PRINCIPLES	CHAPTER CASES
CLINICAL ASSESSMENT AND DIFFERENTIAL DIAGNOSIS	
1 Anxiety disorders are characterized by anxiety that is out of proportion to any actual threat and is excessive for the situation or distressing to the point that it interferes with daily functioning. Both medical and medication-related factors can cause or exacerbate anxiety.	**Case 83-1 (Question 1), Figure 83-1, Tables 83-1, 83-2**
GENERALIZED ANXIETY DISORDER	

CORE PRINCIPLES		CHAPTER CASES
1	Generalized anxiety disorder (GAD) is defined in the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition, (*DSM-5*) as a chronic state of waxing and waning anxiety that is associated with an inability to control symptoms of anxiety and worry. The severity of anxiety and the degree of impairment in daily activities are the main determinants of whether medication should be used to treat GAD.	**Case 83-2 (Question 1), Table 83-3**
2	First-line therapies for the treatment of GAD include psychotherapy or pharmacotherapy. Pharmacologic treatment options include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or buspirone. Benzodiazepines can be used for bridging purposes while awaiting the efficacy onset of the previously mentioned treatments, or as a rescue medication for patients currently in a high state of anxiety. Specific treatment for GAD should be chosen based on prior therapy, comorbid psychiatric and medical conditions, pharmacokinetic drug properties, and patient preference.	**Case 83-2 (Questions 2, 3), Tables 83-4–83-6**

CORE PRINCIPLES		CHAPTER CASES
3	When beginning treatment with benzodiazepines for GAD, patients should be educated about possible adverse effects, risk of abuse or dependence, and drug–drug interactions. Possible effects on pregnancy, teratogenicity, and breast-feeding should also be discussed with females of child-bearing potential.	**Case 83-2 (Questions 4) Case 83-3 (Question 1) Case 83-4 (Questions 1, 2) Case 83-5 (Questions 1–3), Table 83-7**
4	Patients beginning treatment with SSRIs or SNRIs should be counseled regarding possible adverse effects that may occur early in treatment, as well as those that may occur later and display a more chronic time course. In addition, all patients being treated with medications for GAD should be counseled regarding the duration of drug therapy.	**Case 83-2 (Questions 5, 6)**
PANIC DISORDER		
1	Panic disorder is characterized by short episodes of intense fear, associated with perceived physical symptoms such as increased heart rate, increased respiration, gastrointestinal disturbance, tremor, or feelings of bodily disassociation that may be misdiagnosed or remain undiagnosed because symptoms are attributed by the patient to a medical illness.	**Case 83-6 (Question 1), Table 83-8**

CORE PRINCIPLES		CHAPTER CASES
2	Therapy for panic disorder includes cognitive behavioral therapy (CBT), medications, or combination therapy. Medications used include SSRIs, venlafaxine extended release (XR), tricyclic antidepressants (TCAs), or benzodiazepines. The expected short-term adverse effects of antidepressants (eg, jitteriness) should prompt using a lower initial medication dose and be discussed with the patient.	**Case 83-6 (Questions 2–4), Table 83-6**
	SOCIAL ANXIETY AND SPECIFIC PHOBIAS	
1	Both social anxiety and specific phobias involve fears that are excessive and lead to avoidance behaviors to minimize fear. Social anxiety involves a generalized and intense anxiety involving social interactions, whereas specific phobias involve intense fear associated with specific objects or situations (eg, spiders or elevators). CBT and medications (SSRIs or venlafaxine XR) are both first-line treatment options.	**Case 83-7 (Questions 1–3), Tables 83-6, 83-9**
	POSTTRAUMATIC STRESS DISORDER AND ACUTE STRESS DISORDER	

CORE PRINCIPLES		CHAPTER CASES
1	Posttraumatic stress disorder (PTSD) and acute stress disorder occur in persons who have experienced a severely distressing traumatic event. Reexperiencing symptoms, avoidance, hyperarousal, and negative alterations in cognition and mood cause considerable psychological distress, as well as impairment in occupational functioning and personal relationships.	**Case 83-8 (Question 1), Table 83-10**
2	Trauma-focused psychotherapy is considered the preferred first-line treatment for PTSD, although there are also several first-line medication options (SSRIs or venlafaxine XR). Adjunctive treatment for psychiatric comorbidities such as depression or sleep is often indicated. Treatment goals include reducing the core symptoms of PTSD and improving patient functioning.	**Case 83-8 (Questions 2–4), Table 83-6**

OBSESSIVE–COMPULSIVE DISORDER

CORE PRINCIPLES		CHAPTER CASES
1	Obsessive–compulsive disorder (OCD) is characterized by chronic obsessions and/or compulsions that can be extremely disabling and usually consume at least an hour a day. OCD can be treated with medications (SSRIs preferred, venlafaxine XR, or clomipramine), psychotherapy (CBT with or without exposure therapy), or combined modalities for optimal therapy. Despite combination therapy, up to 40% of patients may continue to experience disabling symptoms.	**Case 83-9 (Questions 1–5), Table 83-6**
2	Owing to incomplete remission of symptoms with monotherapy in many patients suffering from OCD, augmentation strategies involving the combination of antidepressants or adjunctive antipsychotics may be considered with vigilant monitoring for increased adverse effects and drug–drug interactions.	**Case 83-10 (Questions 1–3)**

INTRODUCTION

Anxiety can be described as an uncomfortable feeling of vague fear or apprehension accompanied by characteristic physical sensations. It is a normal reaction to a perceived threat to one's physical or psychological well-being. Anxiety is normally provoked by stress and

involves activation of neurobiologic systems that, when activated, contribute to self-preservation. There are two basic components to anxiety: mental features (eg, worry, fear, difficulty concentrating) and physical symptoms (eg, racing heart, shortness of breath, trembling, pacing). Certain medical illnesses (eg, pheochromocytoma, hyperthyroidism) and/or substances (eg, sympathomimetics, caffeine) can result in both the physical and psychological manifestations of anxiety. However, when the anxiety is attributable to an external cause such as a medical illness or a medication, the anxiety abates when the physiologic cause is removed.[1]

If the anxiety is not the result of an external cause, is out of proportion to the actual threat, or persists beyond the presence of the threat, it may be classified as an anxiety disorder. To guide treatment, pathologic anxiety should be differentiated according to whether it occurs (a) as a primary anxiety disorder, (b) as a secondary anxiety disorder owing to medical causes or substances, (c) in response to acute stress (eg, loss of a loved one, marital or financial problems), or (d) as a symptom associated with other psychiatric disorders.[1]

Classification and Diagnosis of Anxiety Disorders

The *Diagnostic and Statistical Manual of Mental Disorders.* Fifth Edition (*DSM-5*) classifies primary anxiety disorders into seven types: generalized anxiety disorder (GAD), panic disorder, agoraphobia, specific phobia, social anxiety disorder, separation anxiety disorder, and selective mutism.[1] Obsessive–compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) are each classified under unique headings in the *DSM-5*. Each disorder involves an unhealthy level of anxiety, but the characteristic type and severity of symptoms, course of illness, and efficacy of drug and nondrug treatments vary, indicating underlying biologic differences. The *DSM-5* secondary anxiety disorders include “anxiety disorder due to a general medical condition” and “substance/medication-

induced anxiety disorder."[1] Anxiety disorders often present in addition to other psychiatric disorders, such as mood disorders. Both are associated with dysregulations in the limbic system and, therefore, share similar symptoms, including fatigue, impaired concentration, restlessness, difficulties with sleep, and somatic symptoms. However, mood disorders have a prominent mood component.[2]

Neurobiology of Anxiety

The limbic system, which is involved in emotion, learning, and memory, is composed of a set of structures integral to behavior, including the hippocampus and the amygdala. Hippocampal brain circuits are essential for conversion of short-term to long-term memory and for spatial memory, whereas the amygdala circuits are involved with emotion and its expression. A neurocircuit arising from the output pathways of the amygdala is believed to mediate fear and anxiety responses in humans.[3] Dysregulated or exaggerated output through various amygdala-related circuits may be a common element underlying the different anxiety disorders, but the specific type of dysfunction probably differs among the various disorders. If it is assumed that a dysregulation of the stress response is the basis of anxiety disorders, then the genesis of anxiety is probably related primarily to interactions between neural pathways in and between the limbic system structures, the sympathetic nervous system, and the hypothalamic–pituitary–adrenocortical (HPA) axis.[2,4] Many neurotransmitter and neuroendocrine systems interact to modulate the actions of the limbic pathways, including corticotrophin-releasing hormone (CRH); the monoamine neurotransmitters, epinephrine and norepinephrine (NE); the indolamine neurotransmitter, serotonin (5-hydroxytryptamine [5-HT]); the inhibitory amino acid, γ-aminobutyric acid (GABA); the excitatory amino acid, glutamate; and the neuropeptides, cholecystokinin (CCK), neuropeptide Y, and substance P.[3,5] As such, the genes from which these products are derived and regulated are an active area of research. Furthermore,

epigenetic mechanisms are being investigated to explore the complex relationship between gene–environment interactions.[6]

Interaction of the Hypothalamic–Pituitary–Adrenocortical, Noradrenergic, and Serotonergic Systems

In the event of an acute threat, a fear stimulus is transmitted via the thalamus to the amygdala, which then projects to both the hypothalamus and the brainstem. This results in various peripheral reactions such as increased heart rate, increased heart stroke volume, and vasodilation of blood vessels carrying blood to the muscles. This is accompanied by a release of NE by the locus coeruleus (LC), the main area of NE cell bodies in the brain. Central release of NE results in vigilance, arousal, the ability to focus attention on the threat, and symptoms of anxiety (eg, tachycardia, tremor, sweating). NE innervation of the hippocampus results in an increased state of memory formation, whereas innervation of the amygdala potentiates the formation of aversive memories.[4] Normally, this is important in allowing us to encode emotionally laden memories, but when overactive, it may result in a constant state of arousal and hypervigilance.

During a perceived threat, CRH is released in the hypothalamus, and it activates the anterior pituitary to release adrenocorticotropic hormone (ACTH). This stimulates the release of glucocorticoid steroids from the adrenal cortex. Although short-term elevation of glucocorticoids allows the body to adapt to a stressful situation by supporting HPA activation and mobilizing energy stores, prolonged elevation of the same glucocorticoids impairs neural plasticity and may even result in neuronal death. When CRH is infused into the LC in rodents, it causes anxiety-like behaviors.[2,4,7]

Although the inhibitory neurotransmitter 5-HT is involved in stress reactions, its role is not entirely clear. Serotonin has roles in sleep, appetite, memory, impulsivity, sexual behavior, mood, motor function, and seems to decrease aggressive behavior. The site of most 5-HT

cell bodies in the brain is the raphe nuclei. There is considerable interconnectivity between the raphe nuclei and the LC, and they tend to mutually inhibit one another. Under normal circumstances, 5-HT connections from the hippocampus decrease activity in the amygdala, which would dampen fear and anxiety responses. However, under conditions of stress, the LC accelerates firing, inhibits the raphe nuclei firing, and increases CRH release—all of which sensitize the limbic system and cause arousal and sensitivity to memory of any stressful or aversive stimuli. This primes the system to a state of arousal to deal with the threat.[2] Although the specific etiology of anxiety is only hypothesized, the current use of treatments activating the 5-HT system, or other inhibitory systems such as the GABA system, supports the hypothesis.

Epidemiology and Clinical Significance of Anxiety Disorders

As a group, anxiety disorders are the most common psychiatric illnesses. Epidemiologic surveys indicate that 13% to 28% of Americans suffer from an anxiety disorder at some time in their lives, with similar prevalence in other parts of the world.[8,9] Anxiety disorders are more common in females than in males.[9] Medical illness is associated with higher rates of anxiety compared with the general population.[10] In addition, 50% to 60% of people with major depressive disorder (MDD) have a lifetime history of one or more comorbid anxiety disorders.[7,11,12] Concurrent anxiety and depression are associated with greater disability, poorer treatment outcomes, and higher suicide rates than with either depression or anxiety alone.

Today, most anxiety disorders can be successfully treated with medications, cognitive or behavioral therapies, or combinations thereof. However, less than one-third of those affected seek help. Many who do seek help by reporting physical symptoms of anxiety to primary care providers are not properly diagnosed, and therefore remain untreated.[9] A significant portion of patients with anxiety also do not believe in taking medication for emotional problems.[13]

Because anxiety is a feeling with which everyone is familiar, there is a tendency to trivialize the impact it can have on the functioning and quality of life of those with anxiety disorders. Increased understanding about pathologic anxiety is needed in society and with health care professionals, so that people seek and receive appropriate treatment. A list of consumer and professional resources for information about anxiety disorders and treatment can be found in **Table 83-1**.

Table 83-1
Resource Organizations for Anxiety Disorders

Anxiety Coach: www.anxietycoach.com
Anxiety Disorders Association of America: www.adaa.org
Freedom From Fear: www.freedomfromfear.org
International OCD Foundation: www.iocdf.org
Mental Health America: www.nmha.org
National Alliance on Mental Illness: www.nami.org
PTSD Gateway: www.ptsdinfo.org

Clinical Assessment and Differential Diagnosis of Anxiety

CASE 83-1

Question 1: R.R., a 49-year-old female, reports to her provider about having trouble sleeping, feeling tired and nervous, and worrying constantly. R.R. was divorced 2 years ago, and she retained custody of their 15-year-old daughter. Since her divorce, R.R. has returned to work as a nurse, but she worries constantly that she will not be able to earn enough money to support herself and her daughter. She has hypertension, asthma, seasonal allergies, and gastroesophageal reflux disease, for which she is prescribed hydrochlorothiazide 12.5 mg/day, losartan 50 mg/day, montelukast 10 mg/day, albuterol one to two puffs every 4 to 6 hours as needed (PRN) wheezing and shortness of breath, and pantoprazole 40 mg/day. She also takes over-the-counter (OTC) loratadine 10 mg/day and pseudoephedrine 60 mg every 4 to 6 hours PRN for allergies, naproxen 200 mg every 8 to 12 hours PRN for

occasional back pain, and polyethylene glycol 17 g daily PRN for constipation. R.R. drinks three or four cups of coffee each morning and one or two glasses of wine 4 nights each week to help her calm down when she has had a stressful day. She denies any history of psychiatric illness, but states she has always been a “worrier.”

What factors should be considered in the clinical assessment and differential diagnosis of R.R.’s symptoms of anxiety?

A diagnostic decision tree such as that in **Figure 83-1** can be used to assist the clinician in differentiating among various causes of anxiety and different anxiety disorders. According to *DSM-5* criteria for primary anxiety disorders, the symptoms should not be secondary to any medical (drug or disease) causes (**Table 83-2**).

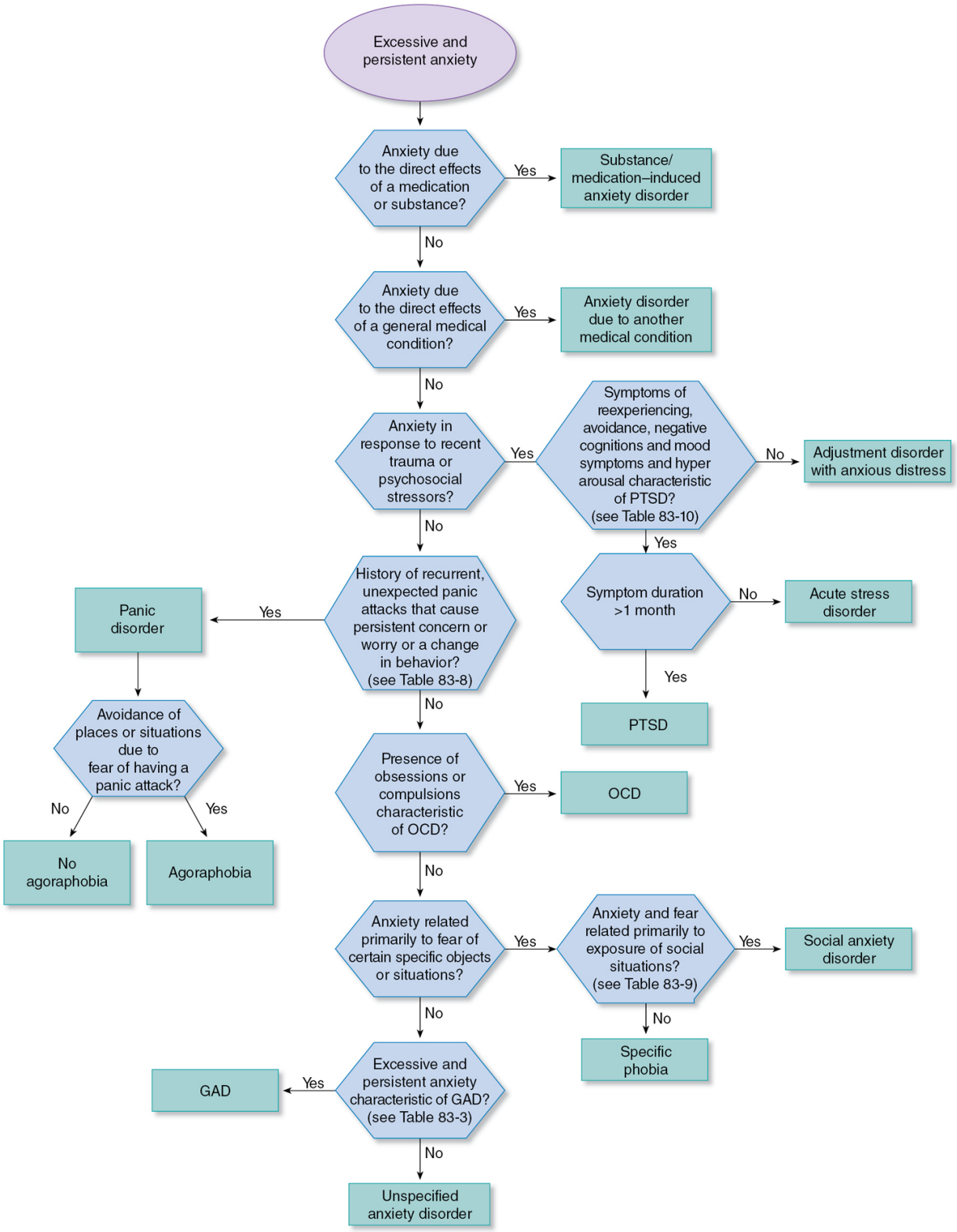


Figure 83-1 Diagnostic decision tree for anxiety disorders. GAD, generalized anxiety disorder; OCD, obsessive–compulsive disorder;

PTSD, posttraumatic stress disorder.

Table 83-2
Secondary Causes of Anxiety

Medical Illnesses
Endocrine and metabolic disorders: hyperthyroidism, hypoglycemia, Addison disease, Cushing disease, pheochromocytoma, PMS, electrolyte abnormalities, acute intermittent porphyria, anemia
Neurologic: seizure disorders, multiple sclerosis, chronic pain syndromes, traumatic brain injury, CNS neoplasm, migraines, myasthenia gravis, Parkinson disease, vertigo, essential tremor
Cardiovascular: mitral valve prolapse, CHF, arrhythmias, post-MI, hyperdynamic β-adrenergic state, hypertension, angina pectoris, postcerebral infarction
GI: PUD, Crohn disease, ulcerative colitis, irritable bowel syndrome
Respiratory: COPD, asthma, pneumonia, pulmonary edema, respirator dependence, pulmonary embolus
Others: HIV infection, systemic lupus erythematosus
Psychiatric
Depression, mania, schizophrenia, adjustment disorder, personality disorders, delirium, dementia, eating disorders
Drugs
CNS stimulants: amphetamines, methylphenidate, caffeine, cocaine, diethylpropion, ephedrine, MDMA (ecstasy), nicotine (and withdrawal), PCP, phenylephrine, pseudoephedrine
CNS depressant withdrawal: barbiturates, benzodiazepines, ethanol, opioids
Psychotropics: antipsychotics (akathisia), bupropion, buspirone, SNRIs, SSRIs, TCAs
Cardiovascular: captopril, enalapril, digoxin, disopyramide, hydralazine, procainamide, propafenone, reserpine
Others: albuterol, aminophylline, baclofen, bromocriptine, cycloserine, dapsone, dronabinol, efavirenz, fluoroquinolones, interferon-α, isoniazid, isoproterenol, levodopa, lidocaine, mefloquine, metoclopramide, monosodium glutamate, nicotinic acid, NSAIDs, pergolide, quinacrine, sibutramine, statins, steroids, theophylline, thyroid hormone, triptans, vinblastine, yohimbine

CHF, congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HIV, human immunodeficiency

virus; MDMA, 3,4-methylenedioxymethamphetamine; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; PCP, phencyclidine; PMS, premenstrual syndrome; PUD, peptic ulcer disease; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

SECONDARY CAUSES OF ANXIETY

A diagnosis of anxiety disorder attributable to a general medical condition is warranted when symptoms are believed to be the direct physiologic consequence of a medical condition, such as hyperthyroidism or hypoglycemia.[1] A complete physical and laboratory workup, with a thorough medical and psychiatric history, is needed to exclude reversible causes before a primary anxiety disorder diagnosis is considered. Because new onset of anxiety disorders in elderly persons is uncommon, this can often be attributed to a medical or substance-related cause. The presence of anxiety may complicate the medical picture and have a negative impact on the course of illness. Also, it should be noted R.R. is 49 years old, and the median age for onset of menopause is 52 years. Although not a medical illness, menopausal symptoms also may include sleep disturbances and mood swings.

When evaluating for possible causes of anxiety, it is also important to consider all medications a person is taking, including OTC drugs such as cough and cold preparations.[14] A diagnosis of substance-induced anxiety disorder is warranted when anxiety symptoms occur in relation to substance intoxication or withdrawal or when medication use causes the symptoms. Among the medications R.R. is taking, pseudoephedrine might be contributing to her anxiety. Other medications that can cause anxiety are listed in Table 83-2. Psychoactive substance abuse, withdrawal from central nervous system (CNS) depressants (eg, alcohol, barbiturates, benzodiazepines), excessive caffeine intake, and nicotine withdrawal may go unrecognized as underlying precipitants of anxiety. R.R.'s current pattern of alcohol use may become problematic if she uses alcohol to self-medicate her anxiety symptoms.

Anxiety in response to life stressors may be severe and functionally detrimental, but could be considered appropriate for the circumstances. Usually, this type of anxiety is self-limiting and brief, subsiding over days to weeks as the person adapts to the new situation. If the person has no history of an anxiety disorder and the symptoms last only a few months, a diagnosis of adjustment disorder with anxious mood may be appropriate. If the symptoms are severe and continue for a prolonged period, a primary anxiety disorder may be present.[1] The initial onset of a chronic anxiety disorder often occurs during a stressful period. Short-term or intermittent therapy with anxiolytic medication or counseling can be extremely beneficial in helping persons cope during times of acute stress. In contrast, management of primary anxiety disorders usually requires more extended treatment.[13]

In summary, the factors in R.R.'s case warranting further investigation include her medical illness (asthma), possible onset of menopause, use of pseudoephedrine and caffeine, and adjustment to recent life changes (divorce, returning to work, becoming a single mother). These factors need to be addressed and treated, if possible, before a diagnosis of an anxiety disorder can be applied and appropriately managed.

GENERALIZED ANXIETY DISORDER

Epidemiology and Clinical Course

GAD is one of the most common anxiety disorders, with a lifetime prevalence of about 9%. GAD is twice as common in females than in males.[1,15] Onset is usually gradual and may be associated with increased life stressors. GAD usually begins between the mid-teens and mid-50s, and the median age of onset is 30 years.[9,15] As such, GAD presents the latest of all anxiety disorders.[1] Whites are more likely to report anxiety symptoms than do Asians, Hispanics, and African Americans.[16] The typical course of GAD is described as

being chronic and recurrent, but much is unknown about the long-term course of illness. Without treatment, it appears that less than half of GAD cases undergo remission.

Most people with GAD have at least one other psychiatric disorder. Common comorbid disorders include panic or social anxiety disorder, simple phobia, OCD, and MDD.[8] Evidence suggests that GAD itself may be a risk factor for suicidal ideation, particularly among females.[17]

Diagnostic Criteria

GAD is characterized by excessive anxiety and worry about life issues for 6 months or longer.[1] The patient usually has great difficulty controlling the worry, which is accompanied by at least three of the associated symptoms listed in **Table 83-3**. Although some physical symptoms are similar between GAD and other anxiety disorders, if the anxiety is related solely to another anxiety disorder (eg, obsession with germs, fear of social situations), a diagnosis of GAD is not warranted.

Table 83-3
Symptoms of Generalized Anxiety Disorder

Anxiety and worry are associated with at least three of the following symptoms (or one in children):
Restlessness, feeling keyed up, or on edge
Easy fatigue
Difficulty concentrating or mind going blank
Irritability
Muscle tension
Sleep disturbances

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. American Psychiatric Association; 2013.

Etiology and Pathophysiology

Genetic factors play a significant role in the etiology of GAD. Genes involved in the hereditary development of GAD are believed to be the same as those for neuroticism and major depression, with environmental factors determining which disorder is expressed in an individual.[5,18,19] Biologic studies in GAD have found abnormalities in noradrenergic, serotonergic, and CCK and GABA-A receptor function.[5] Several studies report decreased α_2-adrenergic receptors in patients with GAD, and this is believed to represent downregulation of receptors in response to high catecholamine levels.

Treatment of Generalized Anxiety Disorder

NONPHARMACOLOGIC TREATMENTS

Management of GAD can involve both psychological and pharmacologic therapies. It is undetermined whether a combination of psychotherapy and pharmacotherapy is more or less efficacious than is each alone.[26] Nondrug treatments such as supportive psychotherapy, dynamic psychotherapy, cognitive behavioral therapy (CBT; including Internet- or computer-based programs), relaxation training, and meditation are often helpful in relieving anxiety and improving coping skills.[20–22] Cognitive therapy is aimed at identifying negative thought patterns provoking or worsening anxiety and making them more positive. CBT has been associated with significant reductions in anxiety that are maintained for 6 to 12 months, as well as decreased psychiatric comorbidity in GAD.[20]

BENZODIAZEPINES

Benzodiazepines are widely prescribed anxiolytic agents, and their efficacy in treating GAD and other anxiety disorders, particularly in the short term, is well established.[23] Benzodiazepines offer rapid symptom relief, but are associated with risks such as dependence, withdrawal, and cognitive impairment, and therefore are not recommended for the long-term management of GAD.

Mechanism of action

Benzodiazepines potentiate GABA by binding to sites on the central GABA-A receptor that serve as the main inhibitory neurotransmitter in the CNS.[24] Benzodiazepines have four distinct effects: anxiolytic, anticonvulsant, muscle relaxant, and sedative-hypnotic. Benzodiazepines with a rapid onset and short duration of action are commonly used to decrease anxiety as well as induce sedation before surgery and other medical procedures.

Clinical comparison of benzodiazepines

The 14 benzodiazepines commercially available in the United States are marketed for different indications, which reflect manufacturers' labeling decisions, because anxiolytics can be effective sedatives and vice versa. **Table 83-4** compares the indications, dosing, and clinical profiles of marketed oral benzodiazepines. Midazolam and clobazam are not included in Table 83-4 because these agents are not used in the treatment of anxiety. Approximate conversions between different benzodiazepines can also be found (**Table 83-5**); however, different resources report varying equivalency factors. Check multiple resources and consider using the most conservative conversion estimation. Also, in many circumstances, it may be appropriate to initiate the new drug at a slightly lower than equivalent dose, which can be titrated further if needed and tolerated.

Table 83-4
Clinical Comparison of Benzodiazepine Agents[a]

Generic (Brand Name)	FDA-Approved Indications	Usual Dosage Range	Rate of Onset Following Oral Administration	Half-Life (hours)[a]
Alprazolam (Xanax®)	Anxiety, anxiety associated with depression, panic disorder	0.5–6 mg/day (up to 10 mg/day for panic disorder)	Fast	12–15
Chlordiazepoxide (Librium®)	Anxiety, preoperative anxiety, acute alcohol withdrawal	15–100 mg/day	Intermediate	>100
Clonazepam (Klonopin®)	Anticonvulsant, panic disorder	0.5–12 mg/day	Intermediate	20–50
Clorazepate (Tranxene®)	Anxiety, alcohol withdrawal, anticonvulsant	15–60 mg/day	Fast	>100
Diazepam (Valium®)	Anxiety, muscle relaxant, acute alcohol withdrawal, preoperative anxiety, anticonvulsant	4–40 mg/day	Very fast	>100[b]
Estazolam (Prosom®)	Sedative-hypnotic	1–2 mg HS	Intermediate	24
Flurazepam (Dalmane®)	Sedative-hypnotic	15–30 mg HS	Fast	>100
Lorazepam (Ativan®)	Anxiety, anxiety associated with depression, anticonvulsant, premedication for anesthetic procedure	2–6 mg/day	Intermediate	10–20
Oxazepam (Serax®)	Anxiety, alcohol withdrawal	30–120 mg/day	Slow	5–14
Quazepam (Doral®)	Sedative-hypnotic	7.5–15 mg HS	Fast	47–100
Temazepam (Restoril®)	Sedative-hypnotic	15–30 mg HS	Intermediate	10–20
Triazolam (Halcion®)	Sedative-hypnotic	0.125–0.25 mg HS	Intermediate	1.5–5

Midazolam and clobazam are omitted because these agents not used in the treatment of anxiety.

FDA, U.S. Food and Drug Administration; HS, at bedtime

[a]Parent drug + active metabolite.

[b]Diazepam metabolizes to desmethyldiazepam, which metabolizes to temazepam, which metabolizes to oxazepam.[249–251]

Table 83-5
Benzodiazepine Approximate Dosage Equivalence[a]

Generic (Brand Name)	Approximate Dose Equivalence (mg)
Alprazolam (Xanax®)	0.5
Chlordiazepoxide (Librium®)	25
Clonazepam (Klonopin®)	0.5
Diazepam (Valium®)	10
Lorazepam (Ativan®)	1
Oxazepam (Serax®)	20
Temazepam (Restoril®)	20

[a]Reported dose equivalences are approximate because different resources quote varying equivalents.[249–251]

ANTIDEPRESSANT AGENTS

Antidepressants are the recommended first-line treatment for most patients with GAD. Although the anxiolytic effects of benzodiazepines occur almost immediately, the anxiolytic effects of antidepressants occur gradually over several weeks. Therefore, it is possible for short-term benzodiazepine therapy (<12 weeks) to be prescribed in combination with an antidepressant during initial treatment of many anxiety disorders, including GAD.[25]

As shown in **Table 83-6**, selective serotonin reuptake inhibitors (SSRIs) have since gained first-line status for treating all five primary anxiety disorders.[26] Use of these agents, in addition to serotonin norepinephrine reuptake inhibitors (SNRIs), first line is increasingly common when compared to alternatives owing to their tolerability profile. SSRIs and SNRIs also have utility in treating comorbid depression.

Table 83-6

Summary of Comparative Medication Treatment Options for Anxiety Disorders

Disorder	FDA-Approved First-Line Treatments (Unless Otherwise Noted)	Second-Line Treatments	Possible Alternatives
Generalized anxiety disorder	Benzodiazepines (short-term use only) Buspirone Duloxetine Escitalopram Paroxetine Venlafaxine XR	Citalopram Pregabalin Sertraline	Atypical antipsychotics[a] Fluoxetine Mirtazapine Tricyclic antidepressants[b]
Panic disorder	Citalopram[c] Escitalopram[c] Fluoxetine Fluvoxamine[c] Paroxetine Sertraline Venlafaxine XR	Benzodiazepines (eg, alprazolam, clonazepam, diazepam, lorazepam) Clomipramine Imipramine Mirtazapine	Anticonvulsants Atypical antipsychotics Phenelzine
Social anxiety disorder	Escitalopram[c] Fluvoxamine CR Paroxetine Sertraline Venlafaxine XR	Benzodiazepines (eg, alprazolam, clonazepam) Citalopram Pregabalin	Atypical antipsychotics Duloxetine Fluoxetine Gabapentin Mirtazapine Phenelzine[b] Tranylcypromine[b]
Posttraumatic stress disorder	Fluoxetine[c] Paroxetine Sertraline Venlafaxine XR[c]	Citalopram Escitalopram Fluvoxamine Mirtazapine	Amitriptyline[b] Anticonvulsants Atypical antipsychotics[a] Bupropion Duloxetine Imipramine[b] Nefazodone[b] Phenelzine[b] Prazosin
Obsessive–compulsive disorder	Escitalopram[c] Fluoxetine Fluvoxamine Fluvoxamine CR Paroxetine Sertraline	Citalopram Clomipramine[b] Venlafaxine	Anticonvulsants[a] Antipsychotic agents[a] Phenelzine

[a]Adjunctive therapy only.

[b]Documented efficacy, but not recommended for first-line treatment because of undesirable clinical properties (side effects, potential toxicity, drug interactions).

[c]Not U.S. Food and Drug Administration (FDA) approved for the indication, but evidence supports use.

Early GAD controlled studies found tricyclic antidepressants (TCAs) such as doxepin, imipramine, and amitriptyline comparably effective or superior to benzodiazepines in treating GAD.[23] However, TCAs are not widely used for treating anxiety disorders because attention has turned to other much safer and better tolerated antidepressants, including SSRIs and SNRIs.

Paroxetine and escitalopram are SSRIs approved for GAD by the U.S. Food and Drug Administration (FDA). Sertraline and citalopram

have also been studied for this indication, and sertraline is the preferred first-line agent according to one treatment guideline.[25] Overall, SSRIs and SNRIs are recommended for first-line use, and specific agents should be selected based on patient-specific factors (eg, risk for discontinuation syndrome, drug interactions, tolerability, and patient preference).[21,26] Patients with GAD may experience an initial increase in anxiety during SSRI treatment, especially fluoxetine. Therefore, lower than normal SSRI starting doses should be used in this population.[27]

Venlafaxine and duloxetine are FDA-approved SNRIs for the treatment of GAD. Newer SNRIs including levomilnacipran, and venlafaxine's active metabolite, desvenlafaxine, have not been well studied in the management of anxiety. Preliminary data suggest that these agents may be useful for the treatment of anxiety symptoms associated with depression, although further randomized controlled trials (RCTs) are needed to confirm this finding.[28–30] The side effect profile of SNRIs is similar to that of the SSRIs. Dose-related nausea is the most common side effect, which usually subsides after 1 to 2 weeks of continued therapy. Similar to SSRIs, vigilance for worsening anxiety is required on initiation of treatment with SNRIs. Low doses should be utilized to mitigate this potential effect. Unlike SSRIs, SNRIs can cause increased blood pressure. Significant increases in blood pressure with venlafaxine are not usually seen within the dosage range used for GAD (75–225 mg/day), but can occur with higher doses.

Long-term studies report remission of GAD during 6 months of continued treatment with venlafaxine XR.[31] Duloxetine's effectiveness has been demonstrated in short- and long-term trials, with the latter citing a decrease in relapse of GAD in patients treated with 60 to 120 mg/day.[32–36] In a comparison of duloxetine 60 to 120 mg/day and venlafaxine XR 75 to 225 mg/day, these agents achieved criteria for noninferiority and demonstrated comparable tolerability.[37]

Mirtazapine is a noradrenergic and specific serotonergic antidepressant with limited controlled data in the treatment of GAD, although there is some data supporting its use in patients with

comorbid MDD.[38,39] Mirtazapine is unlikely to cause anxiety as a side effect, owing to its 5-HT receptor type-2 blocking activity (see Chapter 86, Depressive Disorders, for more information regarding the clinical use of various antidepressant agents). Vilazodone is a serotonin reuptake inhibitor and partial 5-HT1A agonist. Although only FDA approved for MDD, vilazodone has displayed efficacy for the treatment of GAD in an 8-week placebo-controlled trial.[40] Vortioxetine, a serotonin reuptake inhibitor with additional effects at numerous serotonergic receptors, has been studied in short- and long-term treatment of GAD with mixed results.[41–45]

As mentioned previously, lower initial doses of antidepressants are recommended to avoid acute worsening of anxiety symptoms. Slow titration and patient education regarding adverse reactions associated with antidepressants, including the black box warning for suicidality, is also recommended.[46] Although decreases in anxiety symptoms during antidepressant treatment may appear within the first 2 weeks, response is gradual and generally continues for 8 to 12 weeks or longer. Therefore, optimal trials of antidepressants in GAD should allow at least 8 weeks of adequate doses before a lack of response is determined. Continued improvements may occur for 4 to 6 months in some patients with GAD treated with antidepressants.[47,48]

Overall, advantages of antidepressants compared with benzodiazepines in treating GAD include their superior efficacy for cognitive symptoms, such as excessive worry, as well as for common comorbid disorders such as depression and other anxiety disorders. Antidepressants also have a safer withdrawal syndrome and lack potential for abuse and dependence versus benzodiazepines.

OTHER AGENTS USED TO TREAT GENERALIZED ANXIETY DISORDER

Buspirone was marketed in the United States as the first of a nonbenzodiazepine class of anxiolytics, the azapirones, and is FDA approved for the treatment of GAD. Buspirone works as a partial

agonist of the 5-HT type 1A receptor, reducing 5-HT neurotransmission.[49] In addition, buspirone enhances dopaminergic neurotransmission by blocking presynaptic dopamine receptor-2 autoreceptors and also facilitates noradrenergic activity.[50] Buspirone is effective in treating cognitive anxiety symptoms, and is not associated with abuse or dependence; however, it has a delayed onset of anxiolytic effects, and is not appropriate for as-needed use. Buspirone can be used alone or in combination with an SSRI or SNRI. Because buspirone must be taken two or three times daily, it may not be the best choice for patients with a history of poor medication adherence.

Pregabalin, a schedule V controlled substance, may be recommended as a second-line agent following use of SSRIs or SNRIs.[21,25] Pregabalin binds to the α2-δ-subunit of voltage-gated calcium channels in the CNS to inhibit excitatory neurotransmitters (eg, glutamate, NE). Pregabalin appears to be efficacious in managing symptoms of GAD compared with active comparators, including benzodiazepines and venlafaxine.[46,51] Pregabalin is commonly used as an adjunctive agent in combination with SSRIs or SNRIs.[52] It may also be used as a second-line treatment option for patients who have failed or experienced intolerable side effects to antidepressants. Some guidelines support use of pregabalin as a first-line agent for GAD.[21,53] Considerations need to be made for individuals with renal disease or those with a history of substance abuse.[26] Pregabalin exhibits a dose–response effect that appears to plateau at 300 mg/day, although one long-term continuation study of up to 24 weeks suggests pregabalin 450 mg/day may be effective in preventing relapse compared with placebo.[54] Further, an open-label study of doses up to 600 mg/day maintained response for up to 1 year.[55]

Hydroxyzine is a first-generation histamine-1 receptor antagonist. Its anxiolytic effect is believed to be influenced by serotonergic antagonism. Hydroxyzine has displayed efficacy in several studies, although analysis of data suggests possible bias. It may be a reasonable second- or third-line option, but should not be used as monotherapy in patients with comorbid MDD.[21] Owing to its

anticholinergic side effects, exercise caution in the elderly and/or with other anticholinergic or CNS depressant medications. In addition, hydroxyzine is contraindicated in early pregnancy.[56]

Finally, atypical antipsychotics are utilized off label in patients with GAD, although current guidelines highlight that use of these agents should not be initiated in primary care and should be reserved after multiple antidepressant class failures.[25] Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone have been studied for treatment-resistant GAD, with the bulk of evidence and current guidelines supporting use of quetiapine.[21,26,57] These agents may be useful in patients who fail to respond to first-line treatment options; however, their side effects (eg, metabolic syndrome, extrapyramidal side effects) should be discussed before use.[21,25,26]

Clinical Presentation and Assessment of Generalized Anxiety Disorder

CASE 83-2

Question 1: L.V., a 32-year-old male, has been employed as a teacher for the past 10 years. He has had an excellent work record until 8 months ago, when excessive absences and a tendency to become easily upset at students and coworkers became noticeable. On clinical assessment, L.V. reports feeling "on edge," irritable, and tense, with frequent stomach upset and diarrhea. He has no history of mental illness; however, he admits to being stressed and worrying too much about "insignificant things." He cannot seem to control these symptoms regardless of how hard he tries. L.V. denies any symptoms indicative of panic disorder or OCD.

L.V.'s physical examination is unremarkable, and his family history is only notable for his sister who is described as a "nervous person." L.V. denies past or present use of any illicit substances and drinks three to four beers at social events, which he has not enjoyed recently. His mental status examination reveals the following:

- *Appearance and behavior:* L.V. is neatly groomed and dressed and speaks coherently, but he constantly fidgets and taps his right foot.
- *Mood:* L.V. is anxious and worried about the clinician's evaluation, and admits to occasionally feeling depressed and hopeless because of his

anxiety. He often has difficulty falling asleep, but generally remains asleep throughout the night.

- *Sensorium:* L.V. is oriented to person, place, and time.
- *Thoughts:* L.V. denies any auditory or visual hallucinations, or suicidal or homicidal ideation.

L.V. states, at times, that he is unable to relax, particularly in the classroom around his students. His work has been difficult for him lately, and the principal has told him that his job is in immediate jeopardy unless he improves his performance. L.V. states that he just wants to be able to perform his job as he used to and be able to "chill out" and get back to his old life. His insight and judgment are good, and he is motivated to obtain treatment. The provider's provisional diagnosis is GAD.

What clinical features of GAD are present in L.V., and how can his symptoms be assessed objectively?

L.V. exhibits the following target symptoms associated with GAD: excessive worry that is difficult to control, irritability, tension, and inability to relax. Other typical symptoms of anxiety present in L.V. include gastrointestinal (GI) problems (upset stomach and diarrhea), being startled easily, and fidgeting. These target symptoms are not necessarily diagnostic of any particular disorder, but other factors in association with these symptoms are consistent with GAD. The absence of physical or other psychiatric illnesses, as well as use of any illicit substances and lack of recent use of alcohol, excludes possible secondary causes of anxiety. The 8-month duration of symptoms is consistent with a diagnosis of GAD, and L.V.'s age is consistent with the usual onset of GAD. More importantly, the symptoms are causing significant occupational impairment for L.V. and interfering with his quality of life. Therefore, a diagnosis of GAD is appropriate in L.V.

The Hamilton Anxiety Rating Scale for Anxiety (HAM-A) is a useful assessment tool to evaluate clinical anxiety, and it is the standard instrument used in GAD clinical trials. A HAM-A score of >18 is generally correlated with significant anxiety. A reduction of the score to 7 to 10 is associated with no symptoms, defined as remission.[58] The HAM-A can be used to assess baseline anxiety symptoms in patients such as L.V. and to monitor response throughout treatment. The Sheehan Disability Scale is a patient-rated instrument

commonly used to assess functional impairment caused by GAD and other anxiety disorders. It measures three domains (eg, work/school, social life, and family life) from 1 to 10. A score of 1 reflects mild disability, whereas a score of 10 suggests severe impairment.[58]

Indications for and Selection of Treatment

Case 83-2, Question 2: Based on the information presented in L.V.'s case, how can it be determined whether treatment is indicated? What factors should be considered in choosing the most appropriate treatment for L.V.?

L.V. meets the diagnostic criteria for GAD, and is suffering significant disability in his work life from his anxiety disorder. He also has insight into his illness, and desires treatment that will enable him to improve his job performance and quality of life. Appropriate treatment of GAD can help achieve these goals, and is therefore indicated for L.V.

Treatment options for GAD include both pharmacologic and nondrug therapies. Psychosocial treatments such as CBT can be effective in treating GAD, but use of these therapies alone is generally reserved for patients with mild-to-moderate symptoms. In L.V.'s case, prompt treatment is needed because his job is in immediate jeopardy, owing to impairments associated with his anxiety. Therefore, pharmacotherapy in combination with psychological therapy, if available, is indicated for L.V.

Among potential drug therapies, short-term use of benzodiazepines and maintenance with SSRIs, SNRIs, or buspirone are all considered first-line treatments for GAD.[21,25,26] A primary consideration when choosing among these options is whether any comorbid psychiatric conditions are present. Antidepressants are the recommended initial choice, especially for patients with concurrent depression. Other medical or psychiatric disorders may also be present, which can guide selection toward a treatment that may be dually effective. Another consideration when selecting treatment for GAD is how quickly therapeutic effects are needed.

Benzodiazepines reduce anxiety within a few hours, whereas antidepressants and buspirone have delayed onsets of anxiolytic effects. Medication cost is another potential factor, and generic benzodiazepines or SSRIs are inexpensive options.

In L.V.'s case, a benzodiazepine may be a good initial choice because of the need for quick symptom relief relating to his problems at work. L.V. is young and healthy, with no past or present history of substance abuse or alcohol use that might make benzodiazepines unsuitable for him. Although L.V. drinks beer on occasion at social gatherings, he has not participated in these events recently, and he should continue to avoid alcohol if a benzodiazepine is initiated. GAD is often chronic, and antidepressants or buspirone are recommended over benzodiazepines for long-term treatment. Therefore, one of these agents would also be appropriate to use in this case.

Benzodiazepine Treatment

FACTORS INFLUENCING BENZODIAZEPINE SELECTION

Case 83-2, Question 3: The provider decides to treat L.V.'s GAD with paroxetine for maintenance and a benzodiazepine for quick control of his anxiety during the first several weeks until the onset of paroxetine's anxiolytic effects. What factors are important in the selection of a particular benzodiazepine agent for L.V.?

Of the available benzodiazepines, none have demonstrated clear superior efficacy in the treatment of GAD. However, certain agents have been used more extensively than others. Alprazolam, lorazepam, clonazepam, and diazepam have been successfully used in the treatment of GAD. Benzodiazepines differ in their pharmacokinetic properties, and these are generally the main factors considered in drug selection (see Table 83-4).

Benzodiazepines can be differentiated according to their elimination half-lives and metabolism to active or inactive compounds. Diazepam (Valium®) and chlordiazepoxide (Librium®)

have half-lives between 10 and 40 hours, and are metabolized by hepatic oxidative pathways to the active metabolite desmethyldiazepam (DMDZ).[24] The metabolite DMDZ has a long half-life of ~100 hours, and chronic dosing of benzodiazepines that get converted to DMDZ can result in drug accumulation and prolonged clinical effects.[59] This can be especially detrimental in the elderly, those with liver disease, those taking drugs that interfere with benzodiazepine metabolism, or poor metabolizers. Although long durations of action make once-daily dosing possible, small, divided daily doses are often used clinically to minimize side effects.

As highlighted in Table 83-4, the elimination half-life of clonazepam ranges from 20 to 50 hours, making once-daily dosing feasible. Alprazolam (Xanax®, Niravam®) and lorazepam (Ativan®) have intermediate half-lives of 10 to 20 hours, and oxazepam (Serax®) has a short to intermediate half-life of 5 to 14 hours. Alprazolam, lorazepam, and oxazepam usually need to be taken three or four times a day for sustained clinical effects, although an extended-release (XR) preparation of alprazolam allows daily or twice-daily dosing. Alprazolam XR may be associated with fewer CNS side effects than is the immediate-release (IR) form because peak alprazolam blood levels are lower.[60]

Notably, lorazepam, oxazepam, and temazepam (also referred to as the LOT benzodiazepines) are free of active metabolites and are unlikely to accumulate with chronic administration. These three benzodiazepines are preferred over longer acting agents in patients with liver disease and in the elderly. Unlike phase 1 oxidative metabolism, the phase 2 glucuronidation of the LOT benzodiazepines does not appear to decline with age.[61]

Benzodiazepines are readily absorbed after oral administration.[24] Lipid solubility varies among the agents, resulting in differences in rates of absorption and speed of onset, as well as in duration of clinical effects (see Table 83-4). Diazepam and clorazepate have the highest lipid solubilities and the quickest onset of action, which can be desirable when rapid anxiolysis is needed; however, both can produce a “drugged” or “high” feeling in some patients. Highly

lipophilic benzodiazepines are also more quickly redistributed out of the brain, which decreases their duration of action acutely.

Diazepam, lorazepam, and midazolam are also available for parenteral (intravenous [IV] and intramuscular [IM]) administration[24] for treatment of severe agitation or seizures, or for induction of preoperative sedation and anxiolysis. IM injection of diazepam can be very painful. Lorazepam is the preferred agent when IM dosing is needed for quick control of anxiety or agitation. Cost is another important factor in benzodiazepine selection. Brand-name benzodiazepines can be relatively expensive, but all are available in less costly generic versions. Potential drug interactions should also be considered in the selection of an agent because they can alter pharmacokinetics and clinical effects (see Case 83-4, Question 1).

Because L.V. is young and healthy and is not taking any other medications, the clinician could choose any benzodiazepine. A shorter acting high-potency agent, such as lorazepam or alprazolam, would be a reasonable as-needed option for L.V. Appropriate starting doses would be lorazepam 0.5 to 1 mg tid or alprazolam 0.25 to 0.5 mg tid. Dosages can be increased every 3 to 4 days, if needed, within the dosage ranges indicated in Table 83-4. L.V. should notice a decrease in his anxiety symptoms within the first few days of treatment. Prescription of a generic formulation is recommended to reduce treatment costs.

ADVERSE EFFECTS AND PATIENT COUNSELING

CASE 83-2, QUESTION 4: Alprazolam 0.25 mg tid is prescribed for L.V. in addition to paroxetine. What side effects may occur with benzodiazepine treatment, and how should L.V. be counseled regarding benzodiazepine therapy?

Sedation and feelings of tiredness are the most common side effects of benzodiazepines, although sedation may be beneficial in alleviating insomnia that often accompanies anxiety. Tolerance usually develops to the sedative effects of benzodiazepines within 1 to 2 weeks of continued treatment. Consequently, benzodiazepine

sedative-hypnotics are recommended for only short-term use.[21,24,26] Tolerance does not appear to develop to the anxiolytic or muscle relaxant effects of benzodiazepines.

Benzodiazepines can cause cognitive impairment and anterograde amnesia (decreased memory for new information after taking the drug), which is dose related and reversible on medication discontinuation. Tolerance often develops to the cognitive adverse effects, although these may also persist throughout therapy in some patients.[62] Newer studies have demonstrated a possible association with long-term benzodiazepine use and dementia.[63,64] Use of alcohol during benzodiazepine therapy greatly increases the risks of memory problems and sedation, as well as for other more dangerous effects, including respiratory depression. Elderly individuals are more sensitive to sedative, cognitive, and psychomotor effects of benzodiazepines, and tolerance to these effects may occur more slowly than in the younger population.[65,66]

Other psychomotor effects, such as poor coordination and delayed reaction time, can also occur during benzodiazepine treatment.[24] These effects are also dose related, but usually subside within a few weeks of continued treatment. Long-acting benzodiazepines taken at night may cause residual daytime effects, which could result in car accidents and hospitalization, especially in older individuals.[67] The link between benzodiazepine use and falls, especially in the elderly, is also well documented.[68] Rapid dosage escalation and use of high doses of benzodiazepines have been identified as major risk factors for falls. However, even use of low doses of short-acting agents greatly increases the risk of falling in the elderly.[68–70]

Respiratory depression is another potential adverse effect of benzodiazepines, but it is usually only clinically relevant in patients with severe respiratory disease, in overdose situations (see Case 83-5, Question 1), or when combined with alcohol or substances that depress breathing, such as opioids, gabapentin or pregabalin, muscle relaxants, or antihistamines.[71] It is recommended that benzodiazepines be avoided in patients with sleep apnea, especially those who are nonadherent with their positive airway pressure device. Respiratory complications are encountered most often with

IV administration. Severe and life-threatening cardiorespiratory depression has also occurred with the concurrent use of benzodiazepines and olanzapine IM (Zyprexa®), loxapine (Loxitane®), or clozapine (Clozaril®). Further, it should be noted that benzodiazepines increase the risk of death in prescription drug overdoses, typically in combination with other medications or drugs of abuse.[72]

Paradoxical disinhibition, with increased anxiety, irritability, and agitation, can occur infrequently with benzodiazepines,[24] primarily in elderly or developmentally disabled individuals.[73] Other unusual behaviors, such as increased anger, hostility, depression, suicidal ideation, and rage, have been attributed to benzodiazepine use in a small number of cases.[24,74] Most of these reports were anecdotal, and involved patients with preexisting psychiatric disorders such as bipolar disorder or schizophrenia.

Concerns related to abuse and dependence are one major drawback to the clinical use of benzodiazepines. These agents are classified as schedule IV controlled substances. Diazepam, alprazolam, and lorazepam are more likely to be abused than are oxazepam and chlordiazepoxide.[75] This difference is commonly attributed to the quicker onset of effect and high potency, which may be associated with a subjective euphoric sensation. The XR alprazolam formulation is reported to have a lower abuse potential than does IR alprazolam because of its slower onset of effect smaller peak-to-trough ratio and lower maximal plasma concentrations.[60] The potential problems with benzodiazepine abuse and dependence can be avoided or minimized in several ways. First, patients with GAD who have a history of alcohol or substance abuse should not be treated with benzodiazepines.[75] Second, patients should be counseled about directions for use, the anticipated duration of benzodiazepine use, the possibility of withdrawal symptoms, and the importance of gradual drug tapering when therapy is discontinued.

In summary, L.V. should be told that he may experience sedation and difficulties in thinking, concentration, or memory during the first week or so of therapy, but these side effects will likely resolve over time as he develops tolerance. He should be extremely careful while

driving or performing other tasks requiring psychomotor skills, especially during the first week. He should avoid the use of alcohol while he is taking benzodiazepines. The distinction between "addiction" and appropriate therapeutic use, which may be accompanied by some degree of physical dependence, should be explained.

DURATION OF TREATMENT

Case 83-2, Question 5: Two weeks later at his clinic appointment, L.V. is still doing well, and has shown further improvements in his GAD symptoms. He has been taking the prescribed alprazolam and paroxetine for 1 month, and his paroxetine has been increased to 40 mg/day during this time. How long should medication therapy continue?

GAD is a chronic disorder fluctuating in severity, and often requires long-term treatment. When benzodiazepines are used for acute anxiolytic effects during initiation of antidepressant treatment for GAD, they are commonly limited to short-term (2–6 weeks) therapy. L.V. has demonstrated good response after 1 month of combined alprazolam and paroxetine therapy. Because the anxiolytic effects of paroxetine usually occur between 2 and 4 weeks of therapy and he is taking a therapeutic paroxetine dose, it is appropriate to start discontinuing alprazolam at this time. Although it is unlikely, L.V. may experience significant withdrawal symptoms even after only 1 month of benzodiazepine treatment. Thus, the alprazolam dose should be gradually decreased for several weeks, according to tolerability of the taper.[76] In patients who are treated with short-acting benzodiazepines for longer durations, switching to an equivalent dose of a longer acting benzodiazepine, such as diazepam, may simplify the withdrawal schedule.[77]

There is no consensus about the optimal duration of drug therapy for GAD. However, recent recommendations suggest that effective medication treatment be continued for at least 6 to 12 months after initial response.[23,78] Continuation treatment with antidepressants significantly reduces the risk of GAD relapse in 6 months.[79]

Therefore, paroxetine therapy should be continued for another 5 to 11 months in L.V.'s case. After that time, gradual paroxetine discontinuation may be considered, and reinstitution of treatment is warranted if relapse occurs.

Case 83-2, Question 6: Two months later L.V. returns to the clinic after several "no shows." L.V. reports that he missed his appointments because he has started a new relationship and has been very busy. He self-discontinued paroxetine about 4 weeks ago after reading information online about the risk of sexual dysfunction with paroxetine. He denies experiencing sexual dysfunction, but did not want to take the chance. He refuses to be on an SSRI/SNRI, but would like another pharmacologic option because he has noticed return of some symptoms since stopping paroxetine. What should you discuss with L.V. and how should treatment proceed?

It is important to encourage L.V. to discuss any medication questions or concerns with his provider before making any self-directed changes. Among the SSRIs/SNRIs, paroxetine has been reported to have the highest potential for sexual dysfunction.[80,81] Given that L.V. is refusing an SSRI/SNRI, a reasonable next option would be pregabalin. Although GAD is an off-label indication for pregabalin, there is substantial evidence supporting its use, and it is recognized as second-line therapy in clinical practice guidelines.[25,54,55,82] Educate L.V. that pregabalin's incidence of treatment-emergent sexual dysfunction is uncertain and other possible side effects may occur (eg, drowsiness, dizziness).[83] Discuss the potential risk of dependence and abuse and to avoid alcohol use. Initiate pregabalin at 150 mg/day in two to three divided doses followed by weekly increases of up to 150 mg/day, based on patient response and tolerability.

SYMPTOMS AND MANAGEMENT OF BENZODIAZEPINE WITHDRAWAL

CASE 83-3

QUESTION 1: T.B., a 48-year-old female, is prescribed diazepam 10 mg bid for its muscle relaxant effects after sustaining back and other injuries from a collision between her road bike and an automobile 7 months ago. However, she has been taking diazepam 20 mg bid for the past 2 weeks, because she likes how it makes her feel. Five days ago, T.B. ran out of diazepam, and was unable to refill her prescription, because it is 10 days early. A brief mental status examination reveals mild confusion and irritability. Physically, T.B. is trembling and reports nausea and insomnia. Her medical history indicates no current medical problems or psychiatric illnesses, and T.B. denies the use of tobacco, alcohol, or other drugs of abuse.

How should T.B. be treated?

Because T.B. has not taken her prescribed diazepam for 5 days, it is likely she is experiencing a withdrawal syndrome from long-term benzodiazepine use. Her mental and physical symptoms are consistent with benzodiazepine withdrawal. The benzodiazepine withdrawal syndrome implies some degree of physical dependence, and its onset, duration, and severity can vary according to dose, duration of treatment, speed of withdrawal, and elimination half-life of the agent used.[75,76] Withdrawal symptoms that follow discontinuation of agents with short half-lives usually appear within 1 to 2 days, and may be more intense and shorter in duration than after discontinuation of long-acting benzodiazepines. Withdrawal symptoms usually appear 4 to 7 days after discontinuation of long-acting agents and may last several weeks. Symptoms of benzodiazepine withdrawal, which are listed in **Table 83-7**, are generally mild when the drug is tapered gradually during discontinuation.[76] Rarely, serious symptoms such as life-threatening seizures or psychosis may occur during benzodiazepine withdrawal. General risk factors for seizures include head injury, alcohol dependence, electroencephalogram abnormalities, and use of other drugs that lower the seizure threshold.

Table 83-7
Symptoms of Benzodiazepine Withdrawal

Common	Less Common	Rare

Common	Less Common	Rare
Anxiety	Nausea	Confusion
Insomnia	Depression	Delirium
Irritability	Ataxia	Psychosis
Muscle aches or weakness	Hyperreflexia	Seizures
Tremor	Blurred vision	Catatonia
Loss of appetite	Fatigue	

Resumption of her previous diazepam dosage (40 mg/day) should effectively treat her withdrawal symptoms. However, because she is showing signs of sedative, hypnotic, or anxiolytic use disorder (cravings, using more than prescribed), it would be desirable to begin tapering diazepam.

Various dosage reduction regimens have been proposed for benzodiazepine discontinuation. Even when managing withdrawal from low-dose benzodiazepine use, doses should be reduced slowly for 4 to 16 weeks.[76] The rate of the drug taper should be individualized to the patient, but a general recommendation is a 10% to 25% decrease in the dosage every 1 to 2 weeks. The first half of the benzodiazepine taper (down to 50% of the original dose) is generally easier, and can proceed more quickly than does the last half of the taper.[76] In T.B.'s case, the discontinuation period may take several months.

In general, the same benzodiazepine the patient has been taking should be used to manage withdrawal. However, because withdrawal symptoms are more severe during discontinuation of short-acting compared with long-acting benzodiazepines, a long-acting agent can be substituted at an equivalent dosage (see Table 83-5) and then tapered.[76,77] In difficult cases, adjunctive medications, such as anticonvulsants, similar to carbamazepine, phenobarbital, and pregabalin, or propranolol, have been used to ease tolerability of the gradual withdrawal. However, propranolol does not affect the associated anxiety or decrease the seizure risk.[76,84]

BENZODIAZEPINE DRUG INTERACTIONS

CASE 83-4

QUESTION 1: N.P., a 20-year-old female college student, has been taking alprazolam 1 mg tid PRN for treatment of GAD for the past 2 months. She states that alprazolam has been very helpful for her GAD, but reports feeling to her provider that she is feeling especially stressed. She is having trouble balancing the increased workload of higher level courses with her social life, which includes a new relationship. She has no medical illnesses, but states she has suffered from several episodes of heartburn recently, which may be stress related. She is also interested in starting an oral contraceptive. N.P. smokes two packs of cigarettes per day and drinks up to three 12-oz caffeinated sodas per day. An oral contraceptive (Yaz®) is prescribed, and ranitidine is recommended for treatment of heartburn.

What potential drug interactions with alprazolam are present in this case?

The most significant pharmacodynamic drug interactions involve other CNS depressants such as alcohol, opioids, or barbiturates. These combinations can lead to additive CNS and respiratory depressant effects that can be deadly. Most important pharmacokinetic drug interactions involve agents that either inhibit or induce benzodiazepine metabolism through cytochrome P-450 (CYP) 3A4 or CYP2C19.[85] One clinically significant drug interaction occurs with the use of azole antifungals in combination with benzodiazepines. Azole antifungals are potent CYP3A4 inhibitors that can cause a 170% increase in the area under the curve of alprazolam.[86] Therefore, the dosage of alprazolam should be reduced by about one-third in patients receiving this combination. Because benzodiazepines have a relatively wide margin of safety, elevated plasma levels or prolonged elimination half-lives are unlikely to cause serious toxicity. However, they can lead to increased sedative and psychomotor effects, which may be clinically significant in certain cases. Conversely, increased benzodiazepine metabolism by hepatic enzyme inducers may result in medication ineffectiveness. Refer to a drug interactions database, such as Facts & Comparisons (http://www.wolterskluwercdi.com/) for additional information.

In N.P.'s case, the most important drug interaction is between alprazolam and the newly prescribed oral contraceptive, Yaz®. Estrogen-containing oral contraceptives can inhibit the CYP3A4 metabolism of benzodiazepines such as alprazolam, potentially resulting in increased side effects.[87,88] Thus, a reduction in the benzodiazepine dosage may be needed when oral contraceptives are added to ongoing benzodiazepine therapy, as in N.P.'s case. The clearance of LOT benzodiazepines that undergo glucuronidation can be accelerated by oral contraceptives, but this interaction is probably clinically insignificant.[61,87]

Cigarette smoking increases the clearance of some benzodiazepines (clorazepate, lorazepam, oxazepam), but has no effect on others (diazepam, midazolam, chlordiazepoxide).[89] Overall, the effect of smoking is unpredictable and is most likely to be important in patients who either stop or start smoking while taking a benzodiazepine. N.P. should be urged to quit smoking for the sake of her general health and to prevent substantial risks of serious cardiovascular events occurring in smokers taking oral contraceptives. If N.P. does quit, careful monitoring will be needed to determine whether any alprazolam dosage reduction is necessary. N.P. should also be encouraged to decrease her soda consumption because caffeine can increase anxiety and may worsen heartburn.

BENZODIAZEPINE USE IN PREGNANCY AND LACTATION

Case 83-4, Question 2: At her clinic visit 2 years later, N.P. is doing very well. She has graduated from college, is happily married, and states that she and her husband have decided to start a family. N.P. has discontinued her oral contraceptive in the hope of becoming pregnant soon, and has successfully quit smoking. N.P. takes alprazolam 0.5 mg bid or tid as needed, and wonders whether she should also stop taking this drug before she becomes pregnant. What is the teratogenic potential of alprazolam? What alternative treatments are available for the management of N.P.'s anxiety?

Early reports implicated diazepam in causing several birth deformities, including cleft lip or cleft palate and limb and digit

malformations, but later studies failed to support this association.[90–94] Most benzodiazepine anxiolytics are classified as pregnancy category D. However, pregnancy categories are gradually being removed and replaced with more helpful information about medication risks as per the Pregnancy and Lactation Labeling Rule (PLLR), indicating there is some evidence of fetal risk, but the benefits of the medication may outweigh these risks in certain patients.[90,92] Available evidence suggests that benzodiazepine use during the first trimester increases the risk of oral clefts by ~2.4-fold, but the absolute risk is increased only 0.01%. Benzodiazepines have not exhibited strong teratogenic effects, but it is always advisable to avoid drug use during pregnancy when possible, especially in the first trimester.[92,94]

In patients such as N.P., the benzodiazepine should be tapered and discontinued before she becomes pregnant. Nondrug treatments for her GAD such as relaxation therapy, meditation, biofeedback, or cognitive therapy may be helpful. If necessary, single or repeated small doses of benzodiazepines during the second and third trimesters are unlikely to have important adverse effects on the fetus. In these instances, an agent with a short half-life, such as lorazepam, should be considered.[94] Chronic or large doses, especially of long-acting agents, should be avoided because they may accumulate in the fetus. Perinatal sequelae in newborns of mothers who took benzodiazepines during pregnancy include withdrawal symptoms, sedation, muscle weakness, hypotonia, apnea, poor feeding, low birth weight, and increased risk of preterm birth.[91,95]

The clinical situation of unexpected pregnancy in a female maintained on benzodiazepines can also arise. Benzodiazepine dosages should be tapered as quickly as possible to the lowest dosage necessary and discontinued if possible. The postpartum period is a time of heightened risk of recurrence of anxiety disorders, and new mothers should be monitored carefully for signs of relapse.[96] Benzodiazepines are excreted readily in breast milk, and they should be avoided by nursing mothers, when possible, but use is not absolutely contraindicated.[97] If benzodiazepines are used,

short-acting agents with no active metabolites are recommended to avoid sedation, poor feeding, withdrawal, and other effects in the infant.[91,98]

BENZODIAZEPINE OVERDOSE AND USE OF FLUMAZENIL

Benzodiazepine overdose is characterized by respiratory and CNS depression. Overdose with benzodiazepines as the sole ingested agent is rarely life-threatening, and full recovery is the usual outcome.[99] Flumazenil is a benzodiazepine receptor antagonist effective in reversing sedation associated with benzodiazepine intoxication. The primary use of flumazenil is in reversing benzodiazepine-induced conscious sedation (primarily with midazolam) in patients who have been sedated for minor surgical or diagnostic procedures. Flumazenil is also approved for treating benzodiazepine overdose, but this use is controversial because of potentially serious complications (eg, supraventricular arrhythmia, seizure), and questions about its cost-effectiveness.[100,101] Flumazenil administration does not appear to decrease mortality or length of hospital stay in cases of benzodiazepine overdose; therefore, its use for this purpose has become limited.[100]

The most common side effects include agitation, dizziness, nausea, general discomfort, tearfulness, anxiety, and a sensation of coldness.[99] Rapid or excessive infusion has been associated with tachycardia and hypertension. Flumazenil is contraindicated in overdoses of any agent that decreases the seizure threshold, such as TCAs. Toxicology screening and an electrocardiogram (ECG) should be performed before flumazenil is administered. Because of a risk of seizures, flumazenil should also be avoided in patients with increased intracranial pressure or a known history of seizures or head injury, in those who have been receiving chronic benzodiazepine therapy, and in patients with a history of recent illicit drug abuse (eg, cocaine, heroin). Administration of flumazenil should occur only when acute seizure management measures are available.

PHYSIOLOGIC VARIABLES INFLUENCING BENZODIAZEPINES

CASE 83-5

QUESTION 1: B.G., a 72-year-old male, is brought to the emergency department (ED) by his wife after being involved as the driver in a minor car accident. He has no physical injuries except for several small abrasions caused by the car airbag deployment. However, B.G. appears drowsy, is mildly confused, and has an unsteady gait. A toxicology screen reveals no alcohol or other substances, except for clonazepam, which his provider prescribed 10 months ago. B.G.'s wife states he has been taking clonazepam 0.5 mg bid, and it has been remarkably effective in improving his anxiety. B.G., who is 68 inches (172.72 cm) tall and weighs 250 pounds (113.39 kg), has moderate liver disease caused by years of heavy drinking. He has successfully maintained his sobriety for nearly 2 years. It is determined that B.G. is experiencing adverse effects of clonazepam, probably caused by drug accumulation.

What factors could be influencing disposition of clonazepam in this patient?

Benzodiazepine pharmacokinetics can be affected by various physiologic factors, such as aging, sex, obesity, liver disease, kidney disease, and ethnicity.[102-105] Pharmacokinetic and pharmacodynamic alterations may have clinically significant implications that have the potential to impact patient safety. Several of these factors are present in this case, and may have contributed to the accumulation of clonazepam with resulting adverse consequences.

B.G.'s age may influence clonazepam disposition. Reductions in both CYP3A4 and CYP2C19 activity have been reported to occur with aging. The glucuronidation metabolic pathways are minimally affected with age, so not such effect is seen with the LOT benzodiazepines.[61] Other factors contributing to longer benzodiazepine half-lives in the elderly include decreased hepatic blood flow and increased volumes of distribution of lipid-soluble compounds because of decreased muscle mass and increased fat. Increased volume of distribution can increase a drug's half-life in the absence of any clearance changes. As described in Case 83-5, Question 1, older patients are more sensitive to the sedative and psychomotor and, especially, cognitive impairing effects of benzodiazepines. For these reasons, benzodiazepines should be avoided in the elderly. In rare cases where use is necessary, the recommended benzodiazepine dosages for patients older than age

65 years are generally one-third to one-half of those used in healthy adults.

Sex also may influence benzodiazepine clearance, but studies yield mixed results.[87,106,107] Females have been reported to have higher CYP3A4 and CYP2C19 activities than do males, which may partially explain these findings. Increased CYP3A4 activity in females disappears after menopause, which may necessitate the use of lower benzodiazepine dosages during the postmenopausal period. Females have slower glucuronidation metabolic processes than do males, resulting in lower clearance of the LOT benzodiazepines.[61,87]

Obesity and liver impairment are other physiologic factors relevant to B.G.'s case. Obesity increases the volume of distribution of benzodiazepines and the extent of accumulation of long-acting agents. Significant changes in the elimination half-lives of lorazepam and oxazepam are not observed in patients with obesity. Liver dysfunction can reduce benzodiazepine elimination rates and prolong their half-lives, resulting in recommendations for decreased dosages. The pharmacokinetics of the LOT benzodiazepines are unaffected by liver disease.

Decreased protein binding of benzodiazepines can occur in patients with renal insufficiency, which may lead to increased free fractions of highly protein-bound agents. However, no significant changes in clearance or volume of distribution of free drug have been noted. Regarding ethnicity, up to 25% of Asians are CYP2C19 poor metabolizers. Decreased clearance of a variety of CYP2C19 substrates, including diazepam, has been reported in Asian patients.[108]

In summary, the physiologic factors that can alter benzodiazepine disposition in B.G. are his age, obesity, male sex, and liver disease. Accumulation of clonazepam owing to these combined effects probably led to his mental status changes. If continued benzodiazepine therapy is deemed necessary for B.G., lorazepam or oxazepam would be preferred agents for anxiety because they are less affected by aging, obesity, liver disease, or drug interactions.

Temazepam is also less affected by these factors, but is primarily a sedative/hypnotic.

Benzodiazepine dosage equivalencies, which are based on relative potencies, can be used to determine an equivalent dose for the selected agent (see Table 83-5). However, as mentioned earlier, these equivalencies are inexact, and dosing conversions should take patient variables and usual dosage ranges into consideration. For example, B.G. had been taking 1 mg/day of clonazepam, so the calculated equivalent lorazepam dosage is 2 mg/day. Because of his age and recent reaction at this dose, a somewhat lower initial dose of 0.5 mg bid or tid (1–1.5 mg/day) would be indicated, accompanied by careful monitoring for adverse effects or withdrawal symptoms.

However, switching to a nonbenzodiazepine agent would be a better treatment option for B.G. for several reasons. First, B.G. is older than age 65, and geriatric patients are more sensitive to the sedative, cognitive, and psychomotor effects of benzodiazepines compared to younger patients.[66] Second, given his history of alcohol misuse, prescribing B.G. a controlled substance should be avoided. Lastly, B.G. has been using his benzodiazepine as maintenance treatment for anxiety for 10 months. Benzodiazepines are indicated as bridging or rescue medications for short-term use (<12 weeks).

Buspirone Therapy

Case 83-5, Question 2: Several days after recovery from clonazepam intoxication, you discuss your concerns about benzodiazepine use with B.G. He agrees and expresses a desire to discontinue benzodiazepine use. He is especially concerned about the risk of getting into another car accident or falling and hurting himself. The decision is made to switch B.G. from clonazepam to buspirone. How does the clinical profile of buspirone compare with benzodiazepines?

Buspirone lacks CNS depressant effects, sedation, cognitive or psychomotor impairment, respiratory depression, and muscle relaxant or anticonvulsant effects.[49] This makes buspirone useful in older patients who may have a variety of chronic medical conditions.

Buspirone is generally well tolerated, and possible side effects include mild nausea, dizziness, headache, and initial nervousness.[109] Unlike many antidepressants, buspirone does not adversely affect sexual functioning and has actually improved sexual functioning in some patients with GAD.[50] Buspirone has minimal potential for abuse and is not classified as a controlled substance. It does not produce physical dependence or withdrawal syndromes on discontinuation, even after long-term therapy.[49,110] It also does not interact with alcohol or other CNS depressants and is relatively safe in overdose.[49]

Buspirone is as effective as benzodiazepines such as alprazolam, oxazepam, lorazepam, diazepam, and clorazepate in the treatment of GAD.[109,110] As with antidepressants, buspirone is more effective than are benzodiazepines in treating the cognitive symptoms of anxiety. However, the anxiolytic effects of buspirone are more gradual in onset than are benzodiazepines. Anxiolytic effects are observed within the first 7 to 10 days, but 3 to 4 weeks may be needed for optimal results. Buspirone must be taken on an ongoing basis if it is effective, and the drug should not be taken on an as-needed basis.

SWITCHING FROM BENZODIAZEPINE TO BUSPIRONE THERAPY

Case 83-5, Question 3: How should B.G. be switched from benzodiazepine to buspirone therapy?

Because buspirone does not bind to the benzodiazepine receptor to modulate GABA, it is not effective in preventing or treating benzodiazepine withdrawal. Thus, when patients are converted from benzodiazepine to buspirone therapy, the benzodiazepine must be discontinued gradually. Because it takes several weeks for the full therapeutic effects of buspirone to occur, it can be initiated before the benzodiazepine taper begins. This may indirectly ease

benzodiazepine withdrawal by providing extra anxiolytic coverage during the benzodiazepine taper period.[111]

Administration with food may significantly increase bioavailability by decreasing the first-pass effect. Therefore, it is recommended that buspirone dosages be lowered in patients with compromised renal or hepatic function and that use of the drug be avoided in cases of severe impairment. Buspirone is metabolized by CYP3A4, and coadministration of CYP3A4 inhibitors, including grapefruit juice, can result in significant increases in buspirone levels.[49] Because of buspirone's wide margin of safety, even large increases in its plasma levels may be tolerated. However, buspirone should be avoided in patients taking monoamine oxidase inhibitors (MAOIs) and used cautiously in combination with high-dose antidepressants because of the risk of serotonin syndrome.

B.G. has been taking clonazepam for several months, and the drug needs to be withdrawn gradually during a period of at least 4 to 8 weeks, although a longer taper may be better tolerated. B.G. can be started on buspirone during this taper. The usual recommended starting dosage of buspirone is 15 mg/day given in two to three divided doses, but a lower dosage (10 mg/day given as 5 mg bid) is indicated in B.G. because of his older age and liver disease. Twice-daily dosing is preferred to facilitate compliance, and is comparable in efficacy and tolerability to three-times-daily dosing.[112] The daily dosage may be increased in 5-mg/day increments at least every 3 to 4 days. Optimal anxiolytic doses generally range from 20 to 30 mg/day, with 60 mg/day being the recommended maximum. There are no specific guidelines for adjusting dosages in patients with liver impairment; therefore, dosage titrations in B.G. should be made slowly, according to his response and side effects.

PANIC DISORDER

Diagnostic Criteria

The hallmark characteristic of panic disorder is the occurrence of sudden and distinct panic attacks, which are marked by an overwhelming wave of symptoms and feelings, reaching their peak within 10 minutes. Symptoms are listed in **Table 83-8**. To meet diagnostic criteria, at least one of the attacks must be followed by four or more symptoms lasting at least 1 month, including persistent worry or concern about the consequences of the attack or significant behavior change related to the attack.[1] Experiencing less than the four required symptoms to fulfill diagnostic criteria is termed a *limited symptom attack*. Three types of panic attacks have been defined with regard to the context in which they occur: unexpected or uncued panic attacks (the attack is not associated with a situational trigger); situationally bound panic attacks (the attacks invariably occur on exposure to a situational trigger); and situationally predisposed panic attacks (the attacks are more likely to, but do not invariably, occur on exposure to a situational trigger).[1]

Table 83-8
Symptoms of Panic Disorder

Palpitations, pounding heart, or increased heart rate
Sweating
Trembling or shaking
Sensations of shortness of breath, smothering, or choking
Chest pain or discomfort
Nausea or abdominal distress
Feeling dizzy, unsteady, lightheaded, or faint
Derealization or depersonalization
Fear of losing control or going crazy
Fear of dying
Paresthesias
Chills or hot flushes

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

Although panic attacks are the hallmark symptom of panic disorder, their occurrence can also be associated with depressive and other anxiety disorders.[1] For example, situationally predisposed panic attacks may occur in either panic or phobic disorders.

Nocturnal panic attacks, which awaken a person from sleep, are almost always indicative of panic disorder. Because panic attacks occur unpredictably, they often lead to generalized anxiety, constant fear of sudden attacks, or agoraphobia.

Epidemiology and Clinical Course

Although the estimated lifetime prevalence of panic disorder is 6.8%, ~10% of persons experience recurrent panic attacks that do not fulfill the diagnostic criteria for panic disorder, and nearly 30% experience a single isolated panic attack at some point in their lives.[15] The onset of panic disorder often occurs during stressful periods, usually in the late teens to mid-30s, with rare first onset in the elderly population.[8,87] Females are affected two to three times more often than are males.[87]

Panic disorder, similar to other anxiety disorders, is accompanied by marked degrees of psychiatric comorbidity. Common comorbidities include other anxiety disorders, affective disorders, personality disorders, and alcohol or substance use disorders, with the majority of patients suffering a major depressive episode at some point.[1,15,113,114] Patients with psychiatric and medical comorbidities have more severe symptoms, respond more slowly to treatment, have a lower chance of reaching remission, and have a greater suicide risk (particularly when depression or substance abuse are present) than those with panic disorder alone.[115] Although most patients experience episodic periods of remission and relapse, nearly one in five suffer almost continuously.[116]

Panic disorder is associated with very high rates of health care service utilization.[115] The vast majority of patients with panic disorder do not report feeling anxious, and report only physical symptoms, such as chest pain, GI problems, headache, dizziness, and shortness of breath, which contributes to misdiagnosis.[117] The poor recognition of panic disorder in primary care settings further increases use of medical services. Panic disorder is the underlying cause of symptoms in an estimated 10% to 30% of patients referred

to specialty vestibular, respiratory, or neurology clinics, and up to 60% of those referred for cardiology consultation.[1] It is not uncommon for patients to have been in the health care system for up to 10 years before they are correctly diagnosed.

Etiology and Pathophysiology

A neurobiologic model for panic disorder has been proposed in which the amygdala is the central hub of the fear circuit.[5,118] Various projections from the amygdala, including the hypothalamus and the LC, trigger autonomic and neuroendocrine responses resulting in anxiety and panic attacks. Patients with panic disorder have a heightened anxiety sensitivity (fear of anxiety-related sensations), and a variety of substances and situations may activate the anxiety and panic response.[118] Acute panic attacks are believed to be caused by dysregulated firing in the LC, as described previously (see section on Neurobiology of Anxiety), and hyperresponsiveness of the NE system may be an underlying cause for panic disorder.[119]

Other neurobiologic research suggests that patients with panic disorder have abnormal patterns of cerebral glucose metabolism in certain brain areas; abnormalities in GABA-A receptor, NE, 5-HT, and CCK functioning; decreased GABA-A benzodiazepine binding sites; abnormal regulation of neuroactive steroids that modulate GABA-A receptors; hyperactivation of the HPA axis; CCK-B receptor gene polymorphism; and are hypersensitive to carbon dioxide. These findings seem to predispose patients to panic attacks, although they require further study.[114,118-120]

Genetic and environmental influences both contribute to a familial pattern, in which people are 8 to 21 times more likely to develop panic disorder if they have a first-degree relative with the disorder.[1,18] Several studies have shown that distressing childhood events (eg, separation from parents and abuse) and behavioral inhibition during childhood (eg, excessive fear and avoidance of novel stimuli) are associated with markedly increased risks of developing panic disorder later in life.[118] No single biologic abnormality can explain

panic disorder, and further research is needed to define the complex interplay of the various pathophysiologic, genetic, and environmental findings in this illness.

Treatment of Panic Disorder

Approximately 70% to 90% of patients with panic disorder experience substantial relief with currently available treatments, which include both pharmacologic therapies and CBT.[1,114] Medications and CBT both are beneficial for reducing panic attacks initially, and their effects on phobic avoidance generally occur later. First-line medication treatments for panic disorder are SSRIs and venlafaxine XR. TCAs are generally considered second line, owing to decreased tolerability and more safety and drug–drug interaction concerns.[21,26,121,122] Benzodiazepines are no longer recommended as first-line treatment given their abuse liability, cognitive and psychomotor impairments, and risk of respiratory depression especially if used with other CNS depressants. The heightened anxiety sensitivity common in panic disorder makes patients especially vulnerable to initial antidepressant side effects, such as anxiety and agitation. For this reason, lower than usual starting doses of antidepressants are recommended in patients with panic disorder.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

Paroxetine, sertraline, and fluoxetine are FDA approved for treating panic disorder, although other SSRIs (fluvoxamine, citalopram, escitalopram) are also effective in reducing the frequency of panic attacks, anticipatory anxiety, and associated depression.[21,26,122] Although low starting dosages are recommended (10 mg/day for paroxetine and citalopram, 25 mg/day for sertraline, 5–10 mg/day for fluoxetine and escitalopram) to minimize side effects, higher doses relative to antidepressant doses are usually required for response. The recommended target dosage range is 20 to 40 mg/day for

paroxetine, citalopram, and fluoxetine, 100 to 200 mg/day for sertraline and fluvoxamine, and 10 to 20 mg/day for escitalopram for panic disorder.[121]

Venlafaxine XR is also FDA approved for treating panic disorder. The initial dose of venlafaxine XR should be 37.5 mg/day with a recommended therapeutic dose of 150 to 225 mg/day.[121] Duloxetine is not FDA approved for this indication, although it has some evidence supporting off-label use.[123]

Response to SSRIs and other antidepressants in panic disorder occurs gradually, over the course of several weeks. Reduced frequency of panic attacks usually begins within 1 to 2 weeks. A trial period of at least 6 weeks should be allowed to fully assess response, and continued improvements may be seen during a treatment period of 6 months or longer.[121]

BENZODIAZEPINES

The benzodiazepines alprazolam and clonazepam are FDA approved for treating panic disorder, and are the most extensively studied agents of this class. However, lorazepam and diazepam, when used in equivalent doses, also appear effective.[117,121]

Benzodiazepines may be utilized short term, while waiting for antidepressant medications to reach full effect. Benzodiazepines may also be appropriate for some patients who have failed several antidepressants or with severe, refractory symptoms. Individuals with panic disorder may need higher doses of benzodiazepines for response than do patients with other anxiety disorders.[124] This may be related to reduced sensitivity of benzodiazepine binding sites in panic disorder.[125] An alprazolam dosage range of 4 to 6 mg/day is effective for most patients with panic disorder, but others may require up to 10 mg/day for optimal response. The total daily dose usually needs to be taken in three or four divided doses to minimize breakthrough anxiety or panic attacks before the next scheduled dose because of fluctuating serum levels given its relatively short duration of action. Patients with panic disorder are especially sensitive to benzodiazepine withdrawal effects. For these reasons,

using the longer acting benzodiazepine clonazepam (1–2 mg/day dosed bid) may be preferred over alprazolam.[124] The risks and benefits of benzodiazepine use should be carefully considered, especially in older adults, patients with a history of substance abuse, or patients with comorbid respiratory disease.

OTHER ANTIDEPRESSANTS

TCAs were the first medications widely used in the treatment of panic disorder. Imipramine (100–300 mg/day) and clomipramine (50–150 mg/day) are as effective as alprazolam, but are less well tolerated.[126] Evidence for most other TCAs is lacking.[21,26,121,122] Clomipramine appears to be more effective than are other TCAs for panic disorder, perhaps because of its greater serotonergic effects.[127] Despite using lower initial doses to minimize the anxiety-like side effect, many patients discontinue therapy because of poor tolerability.

Among the MAOIs, phenelzine is often heralded as being remarkably effective in the treatment of panic disorder, but this claim is based on studies conducted before the publication of the initial diagnostic criteria for panic disorder in 1980.[121] No recent MAOI studies are available to assess phenelzine's efficacy within the context of current diagnostic and treatment standards. It is generally an option of last resort for treatment-refractory cases because of the many clinical disadvantages of MAOIs relative to other antidepressants (see Chapter 86, Depressive Disorders).

Several open-label studies suggest that mirtazapine may also be beneficial in treating panic disorder.[21,121] Mirtazapine may be useful in patients who do not respond to SSRI therapy.[121] A recent open-label study of vortioxetine indicated potential benefit in panic disorder.[128] However, no randomized controlled studies (RCT) have been completed evaluating the efficacy of newer antidepressant agents, vortioxetine or vilazodone. The high medication cost is a potential barrier to their use.

MISCELLANEOUS AGENTS

Other medications that are reportedly effective in treating panic disorder include anticonvulsants (valproic acid, levetiracetam, gabapentin) and second-generation antipsychotics (primarily, risperidone and olanzapine) as either monotherapy or adjunctive therapy used in combination with an SSRI.[21,121] More information is needed before any of these can be routinely recommended for treating panic disorder.

NONPHARMACOLOGIC TREATMENTS

CBT, including exposure treatment and relaxation training, is also established as being effective in panic disorder.[114,121] The cognitive theory of panic disorder is based on the observed heightened anxiety sensitivity in these patients, and asserts that physical anxiety sensations are misinterpreted as being serious or life-threatening. These fears trigger a cycle of further worsening anxiety symptoms that finally progress to a panic attack. Reversing the cognitive component of this vicious cycle is an integral part of CBT, and is important in producing lasting therapeutic effects of treatment.[121] Breathing retraining and exposure to fear cues are key components of behavioral therapy. Some studies have found medications to be superior to CBT in the treatment of panic disorder, whereas others report opposite results.[121,129] Combining medication with CBT can be useful to increase response/remission rates in those with severe symptoms or a partial response and to improve relapse rates during pharmacotherapy discontinuation attempts.[21,124,130]

Clinical Presentation and Differential Diagnosis of Panic Disorder

CASE 83-6

Question 1: S.K., a 24-year-old female graphic artist, presents to the ED with chest pain, difficulty breathing, dizziness, and nausea. She describes feeling "as if my head is going off in space and I am outside my body." These attacks often escalate quickly, peaking within 10 minutes and then start to subside within 30 minutes. She states she has been under extreme stress lately because of the

poor economy, and has conflicts with her landlord as a result of nonpayment of the rent on her art studio. S.K. fears she has had a heart attack or stroke brought on by her stressful life. S.K. recently visited her family provider for the same symptoms; however, a complete physical examination and laboratory workup yielded no abnormalities. She states her first “attack” occurred suddenly about 5 months ago while she was shopping for oil paints at the art supply store, and she can never predict when they will occur. Since then, her symptoms have become more severe and frequent, and she has started isolating herself in her studio for fear they will return when she is in public. S.K. uses marijuana “to relax” and occasionally drinks alcohol, less than weekly. She has suffered from depression in the past and was hospitalized for one severe episode 2 years ago. An ECG is performed and found to be normal. The provider’s diagnosis is panic disorder with agoraphobia.

What clinical features of panic disorder does S.K. display, and what are the important factors in the differential diagnosis of panic disorder?

S.K. exhibits many typical characteristics of panic disorder. As illustrated in this case, the first panic attack typically occurs without warning while the person is involved in a normal everyday activity and lasts 10 to 30 minutes. Panic attacks are extremely terrifying, and usually leave the sufferer feeling anxious and convinced something is medically wrong. As with S.K., it is not uncommon for patients to make ED visits after or during panic attacks, believing they have had a heart attack or any other serious event. Unfortunately, panic disorder is often not recognized in primary care settings, and no medical cause for the symptoms can be identified. Faced with findings that they are apparently healthy, patients may make repeated ED visits and consult different doctors and specialists in an attempt to uncover a physical explanation for their frightening symptoms.

S.K. exhibits the following target symptoms of panic disorder: chest pain, shortness of breath, dizziness, abdominal distress, and loss of control. Agoraphobia is present because she avoids leaving her studio because of her fear of having panic attacks. Other factors consistent with a diagnosis of panic disorder include her young age, female sex, and lack of abnormal physical findings. This case also illustrates the association between onset of panic disorder and stressful life events, its common association with depression, and

the frequent lack of recognition of panic disorder in primary care settings.

Because different substances or medical conditions can cause severe anxiety and panic, it is necessary to rule out these potential causes for panic attacks.[117] Notable triggers of panic attacks include caffeine, alcohol, nicotine, nonprescription cold preparations, cannabis, amphetamines, and cocaine (see Table 83-2).[117] S.K. uses marijuana, which can be associated with panic symptoms. Although chronic moderate-to-severe use of marijuana may complicate the treatment of panic disorder, it appears that infrequent marijuana use does not adversely affect treatment.[131,132] S.K. does not endorse chronic, severe marijuana abuse, but if she does not adequately respond to treatment, this might be further explored. Medical illnesses that can cause panic attacks include thyroid dysfunction, asthma, chronic obstructive pulmonary disease (COPD), mitral valve prolapse, and seizure disorders.[133] Panic attacks can also occur with other anxiety disorders. However, in these cases, the panic attacks usually occur on exposure to a feared object or situation (in phobic disorders), an object of obsession (in OCD), or a stimulus associated with a traumatic stressor (in PTSD). S.K. reports that her panic attacks occur unexpectedly, and situationally bound or predisposed attacks are not evident; therefore, the features are consistent with panic disorder.

Treatment Selection for Panic Disorder, Selective Serotonin Reuptake Inhibitor Dosing Issues, and Combination Selective Serotonin Reuptake Inhibitor–Benzodiazepine Therapy

Case 83-6, Question 2: S.K. is referred to a psychiatrist who decides to initiate treatment with paroxetine 20 mg every morning. Three days later, S.K. calls the doctor and states that her anxiety and panic attacks have greatly increased since she started taking paroxetine. The psychiatrist prescribes alprazolam 0.5 mg (tablets), and instructs S.K. to take one tablet as needed for the anxiety. What factors should be considered in the selection of an initial

medication treatment for panic disorder? Why is the prescribed treatment for S.K. inappropriate?

An SSRI is an appropriate first-line treatment for most patients with panic disorder.[21] In patients such as S.K. who have a history of depression, SSRIs may also help prevent relapse of depression. Patients with severe or distressing symptoms may initially require concurrent benzodiazepine therapy, which provides quick relief from anxiety and panic attacks until the therapeutic effects of SSRIs are evident. At that time, usually after several weeks, the benzodiazepine can be gradually discontinued. An SSRI–benzodiazepine combination is still a commonly prescribed initial treatment, even though guidelines recommend monotherapy unless initial anxiety is extremely high.[134] Although benzodiazepines are generally avoided in patients with a history of substance abuse, use of low doses for a limited time may be appropriate for some patients with disabling symptoms, as long as there is no current substance (especially alcohol or opioid) abuse.[21,75,121] Because of the levels of distress and impairment caused by S.K.'s panic disorder, combined SSRI–benzodiazepine therapy would have been a reasonable initial treatment. Because panic attacks peak quickly and generally last <30 minutes, an as-needed benzodiazepine is not helpful to prevent panic attacks. As such, scheduled benzodiazepine dosing is preferred over an as-needed dosing schedule during initial therapy.[121]

Paroxetine is an appropriate SSRI for the treatment of panic disorder, and may be less anxiety provoking than is a more activating SSRI such as fluoxetine.[27] Although paroxetine would not be the best initial choice in an older adult, owing to its anticholinergic effects, S.K. is only 24 years old, so this is a reasonable selection. However, when paroxetine is used for panic disorder, it should be started at a very low initial dose of 10 mg/day. In S.K.'s case, the prescribed 20-mg/day starting dose was too high. Also, scheduled versus as-needed benzodiazepine dosing would have been preferred. After 2 to 4 weeks, the benzodiazepine can be gradually discontinued while the SSRI therapy is continued and gradually

titrated to the target effective dose. The potential for drug interactions must also be kept in mind when SSRI–benzodiazepine combinations are used because certain SSRIs can inhibit benzodiazepine metabolism, leading to increased benzodiazepine side effects (see section on Benzodiazepine Drug Interactions).

Patient Counseling Information

Patients such as S.K. who are beginning SSRI therapy for the treatment of panic disorder should be counseled about possible increased anxiety during the first 1 or 2 weeks of treatment as well as other common SSRI side effects, including nausea, headache, sexual dysfunction, and either insomnia or sedation. Because these are dose-related effects, patients should inform their clinician of any problems, and a dosage reduction may be indicated. These adverse effects (with the possible exception of sexual dysfunction) usually subside after 1 to 3 weeks of continued treatment. It is also important to inform patients that it may take several weeks before beneficial effects of antidepressant treatment are seen, and 6 to 12 weeks or longer may be required for full response. Patients receiving benzodiazepines should be counseled about their use in providing anxiolytic coverage during the initial weeks of SSRI therapy, as well as their limited utility as long-term therapy. Other pertinent counseling information for benzodiazepine treatment should also be included (see Case 83-2, Question 4). The desired goals of therapy and likely duration of treatment should also be explained. Providing information about the nature of panic disorder, including reassurance that panic attacks are not life-threatening, is also important. Many clinicians recommend that patients keep a “panic diary” in which they record frequency of panic attacks, along with symptoms experienced during attacks.

Clinical Assessment and Goals of Therapy

Case 83-6, Question 3: Owing to her negative experience, S.K. refuses to continue paroxetine, so escitalopram is prescribed instead. After 1 week of escitalopram therapy at the initial dosage of 5 mg/day, S.K. is tolerating the medication well. The plan is to gradually increase escitalopram to 10 mg, then to 20 mg/day during the next several weeks. S.K. is also taking alprazolam, 0.5 mg bid to tid. What are the desired goals of treatment in this case, and how can S.K.'s response to treatment be assessed?

Five domains in panic disorder have been identified in which treatment outcomes should be assessed: (a) frequency and severity of panic attacks, (b) anticipatory anxiety, (c) phobic avoidance behaviors, (d) overall well-being, and (e) illness-related disability in various areas (work, school, family).[121] The treatment goals in this case are, first, to stop S.K.'s panic attacks, then to reduce her anticipatory anxiety, followed by reversal of phobic avoidance.[58] These outcomes should allow her to more comfortably leave her studio when required and, secondarily, improve her overall functioning and quality of life.

Several different instruments have been used to assess outcomes of treatment in panic disorder.[58] In addition to the panic diary, others include the Panic Appraisal Inventory, the Sheehan Patient-Related Anxiety Scale, the Panic and Agoraphobia Scale, and the Panic Disorder Severity Scale. The latter is currently considered by many experts to be the most useful because it evaluates outcomes in all five identified target domains of panic disorder.[58,121]

Course and Duration of Therapy

Case 83-6, Question 4: After 3 months of escitalopram therapy, S.K. reports that she has had no panic attacks in the past month and her functioning has improved dramatically. She is currently taking 20 mg/day of escitalopram, and gradually stopped taking the alprazolam 3 to 4 weeks ago. S.K. reveals she is painting regularly, selling some of her paintings, paying her rent, and she has begun dating again. S.K. is experiencing no significant side effects from escitalopram. She wonders how long she should continue taking it because she is doing so well. What is the recommended duration of treatment for panic disorder?

Long-term medication trials in panic disorder support the recommendation that treatment should continue for at least 6 to 12 months after acute response.[21,121] The benefits of maintenance pharmacotherapy in preventing relapse are well documented, although the optimal duration of treatment is a subject of continued debate among researchers of panic disorder. Maintenance treatment gives patients time to resume normal lifestyles and to reestablish daily activities after acute cessation of panic attacks.

Escitalopram therapy should be continued at the current dosage for 3 to 6 more months. After a successful period of full remission, a trial of medication discontinuation may be attempted to determine whether continued treatment is necessary. Medication should not be stopped in patients who are experiencing stressful life events or substantial residual problems in any of the five domains (frequency and severity of panic attacks, anticipatory anxiety, phobic avoidance behaviors, overall well-being, and illness-related disability in work, school, and family).[121] When a medication is discontinued, it should be withdrawn gradually over several months, regardless of the class. Because of the devastating impact panic disorder can have, reinstitution of drug treatment is indicated if relapse occurs. Long-term treatment with antidepressants, and benzodiazepines if necessary, is generally successful in maintaining treatment benefits without detrimental effects or dosage escalations.

SOCIAL ANXIETY DISORDER AND SPECIFIC PHOBIAS

Classification and Diagnosis of Phobic Disorders

The *DSM-5* includes two primary types of phobic disorders: specific phobia and social anxiety disorder (formerly social phobia), with symptoms presented in **Table 83-9**.[1] These disorders involve excessive or unreasonable fears and lead to avoidance behavior to minimize anxiety, for a duration of at least 6 months. The main

difference between specific phobias and social anxiety disorder is that the former involves fear and avoidance of specific stimuli and not a general fear of social situations.

Table 83-9
Symptoms of Social Anxiety Disorder (Social Phobia) (Items 1–5) and Specific Phobia (Items 2–5)

▪ Marked and constant fear of one or more social situations in which the person is exposed to unfamiliar people or possible scrutiny by others and the person fears humiliation or embarrassment
▪ Experiencing the situation causes an immediate anxiety response
▪ Feared situation is avoided or experienced with intense anxiety or distress.
▪ Feared situation exceeds the true risk associated with the social situation according to sociocultural norms.
▪ Fear or avoidance significantly interferes with the person's normal routine or activities or causes marked distress.

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

SOCIAL ANXIETY DISORDER

Social anxiety disorder manifests as intense irrational fear, anxiety, or avoidance of scrutiny or evaluation by others in social situations because of concerns about humiliation or being made to appear ridiculous.[1] A defining feature is that the fears and anxiety are confined to social situations (eg, speaking to people, attending social gatherings, eating or drinking in public, using public restrooms, public speaking), and patients are usually symptom free when alone. If the fear is strictly confined to speaking or performing in public, a *performance-only* specifier is applied to the diagnosis. Common symptoms seen in social anxiety disorder include blushing, muscle twitching, and stuttering, in addition to other typical symptoms of anxiety. Panic attacks may also occur in either specific phobia or social anxiety disorder on exposure to the feared object or situation. However, social anxiety disorder is differentiated from panic disorder

in that it involves the fear of scrutiny by others, rather than the fear of having a panic attack.

SPECIFIC PHOBIAS

Specific phobias are coded by one of five specifiers: animal (eg, insects, dogs, spiders), natural environment (eg, heights, water, storms), blood–injection–injury (eg, blood, injury, medical procedures), situational (eg, flying, bridges, elevators), or other.[1] Significant impairment of functioning or marked distress must be present for a diagnosis of specific phobia to be warranted. For example, fear of flying might constitute a diagnosis of specific phobia in a person whose job requires airplane travel, but it would not impair functioning in someone who never has occasion to fly.

First-line management of specific phobias involves avoidance of the stimuli or exposure-based psychotherapy, such as CBT or virtual reality exposure. Medications are not generally considered beneficial, because pharmacotherapy for specific phobia is largely understudied and psychotherapy is extremely successful. Benzodiazepines effectively reduce anxiety associated with a phobic trigger, but they may also interfere with the efficacy of these exposure therapies.[21,26,122]

Social Anxiety Disorder

EPIDEMIOLOGY AND CLINICAL COURSE

In the United States, the lifetime and past-year prevalence of social anxiety disorder is ~13% and 7%, respectively.[15,135] The male-to-female prevalence ratio is ~2:3.[9] Social anxiety disorder usually begins early in life, with a mean onset between ages 14 and 16 years.[136] More than 50% of patients are affected before adolescence, and a history of shyness and behavioral inhibition throughout childhood is common.[136] Unless effectively treated, the clinical course is often chronic, unremitting, and lifelong, and only 20% to 40% of patients are reported to recover after 20 years of living with this condition.[135]

COMORBIDITY AND CLINICAL SIGNIFICANCE

Comorbidity in social anxiety disorder is high, with an estimated 70% to 90% of individuals having at least one other psychiatric disorder in their lifetime.[1,135,136] Common comorbid conditions include simple phobia, MDD, GAD, panic disorder, body dysmorphic disorder, and alcohol abuse. Because of its early onset, social anxiety disorder usually precedes the development of comorbid disorders. Alcohol is commonly used to decrease anxiety in social situations. The risk of suicide attempts is high, especially in those with both social anxiety disorder and another psychiatric illness, such as depression.[9]

Because social anxiety disorder usually begins during the teenage years, it can seriously interfere with development of normal social skills, achievement of full academic and career potentials, and abilities to form interpersonal relationships.[137] This leads to functional disabilities that may persist for a lifetime. Social anxiety disorder is associated with unemployment, lower levels of education, and dependence on public financial support systems.[9] People with social anxiety disorder are less likely to marry, and more than half report moderate-to-severe impairments in their abilities to carry out ordinary daily activities.[137]

ETIOLOGY AND PATHOPHYSIOLOGY

Social anxiety disorder is a familial disease, but the relative contributions of genetic versus environmental influences have not been differentiated.[18] Early factors predisposing to its development include anxious behavior modeling in parents and parental overprotection.[1] Shyness in children, which is associated with later development of social anxiety disorder, has been linked to a specific genetic polymorphism of the serotonin transporter promoter region.[138]

Biologic studies suggest that performance-only social anxiety disorder has a different underlying pathophysiology involving noradrenergic system dysfunction. Conversely, in nonperformance-only social anxiety disorder, there is substantial evidence for dopaminergic (decreased dopamine neurotransmission) and

serotonergic dysfunction (5-HT type-2 receptor hypersensitivity).[139-141]

TREATMENT OF SOCIAL ANXIETY DISORDER

Early detection and treatment of social anxiety disorder are vital in reducing lifelong functional consequences and may prevent development of comorbid disorders. Because of the nature of the disorder, some sufferers are reluctant to seek treatment resulting in an average treatment delay of 16 years.[142] Those who seek help, even in psychiatric settings, may not be diagnosed or treated appropriately.[136] Pharmacotherapy and CBT are both first-line options.[21] Although data do not support the routine use of combined modalities in the management of social anxiety disorder, clinicians should determine whether combined therapy would be useful on a case-by-case basis.[143]

Selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors

As with other anxiety disorders, SSRIs, in addition to the venlafaxine XR, are considered the primary treatment option for most patients with social anxiety disorder,[136] for which paroxetine, sertraline, and venlafaxine XR are FDA approved.[143] Nonetheless, fluoxetine, fluvoxamine, citalopram, and escitalopram have also demonstrated efficacy in controlled clinical trials, although fluoxetine has negative evidence as well.[21,143] Preliminary evidence with duloxetine suggests this agent may be useful.[144]

Unlike patients with GAD and panic disorder, those with social anxiety disorder often tolerate standard antidepressant starting doses. Target doses for social anxiety disorder are typically within the normal antidepressant dosage ranges. It is thought that SSRIs exhibit a flat dose–response curve.[145] Although some individuals may require higher dosages, adequate time (2–4 weeks) should be allowed before the dosage is increased. Response to SSRIs occurs gradually, and an adequate medication trial to assess response should last at least 8 to 10 weeks. Many who experience minimal

response at week 8 may show a good response at week 12, and improvements have been found to continue throughout 16 weeks of treatment.[146]

Other antidepressants

The MAOIs, in particular phenelzine (60–90 mg/day), have also demonstrated marked efficacy for social anxiety disorder, but are reserved for SSRI nonresponders.[21,136,143] Case reports and open studies suggest that bupropion may be useful in treating social anxiety disorder, but controlled trials are needed to define its role.[136] Mirtazapine has conflicting evidence from small RCTs, but may be considered in SSRI nonresponders.[21] Imipramine is ineffective for social anxiety disorder, and TCAs (except clomipramine) are not among the recommended treatment options.[21,136,143] Likewise, nefazodone is not recommended given the risk of hepatotoxicity and conflicting evidence, including one negative RCT.[21]

Benzodiazepines

Benzodiazepines are generally considered second-line therapy for social anxiety disorder, because they have limited efficacy in treating psychiatric comorbidities and possess abuse/dependence potential. In clinical practice, benzodiazepines are commonly used in combination with SSRI therapy on an as-needed basis before participation in stressful social situations.[143] However, the efficacy of adjunctive benzodiazepines to decrease time to response or increase response rate is unclear.[147] The high-potency benzodiazepines may be useful as monotherapy in select patients. Clonazepam (1–3 mg/day) was markedly efficacious in one controlled study, whereas alprazolam (1–6 mg/day) showed only modest efficacy compared with placebo.[142]

β-Blockers and other miscellaneous agents

β-Adrenergic receptor blockers reduce peripheral autonomic symptoms of anxiety and, thus, are useful for performance-related

social anxiety disorder.[136] Propranolol (10–80 mg) and atenolol (25–50 mg) are the two recommended agents, and can be used on an as-needed basis (1–2 hours before the performance) to reduce performance anxiety symptoms such as tremors, palpitations, and blushing. A test dose should be tried before the actual occasion to assess tolerability.

Pregabalin is also considered to be an acceptable first-line agent, in the absence of comorbidities, that would benefit from an SSRI, based on placebo-controlled trials for acute management and relapse prevention.[21,148] It appears that a higher pregabalin dose (450–600 mg/day) may be necessary for effective treatment. In 2019, the FDA issued an alert warning of respiratory depressant effects with gabapentinoids in those taking other CNS depressant agents and/or with underlying respiratory impairment.[71] Other anticonvulsants, antipsychotics, and miscellaneous agents have also been reported to be effective in the treatment of social anxiety disorder, but they are considered second- or third-line treatments.[21,46,143] These include gabapentin, tiagabine, topiramate, valproate derivatives, olanzapine monotherapy, adjunctive aripiprazole, adjunctive risperidone, and atomoxetine.

Nonpharmacologic treatments

Several studies have demonstrated CBT to be comparable to medications in the treatment of social anxiety disorder.[149] Although medications may work faster, CBT is believed to result in longer lasting treatment gains, with effects persisting for 1 to 5 years. The cognitive therapy component changes maladaptive thought patterns, such as expectations of performing poorly and overconcern about negative evaluation by others.[149] The behavioral therapy component, as in other anxiety disorders, involves repeated exposure and practice performing in those feared situations. Social skills training can also be beneficial in improving interpersonal communication skills.

CLINICAL PRESENTATION OF SOCIAL ANXIETY DISORDER

CASE 83-7

QUESTION 1: S.H., an 18-year-old male, is brought for psychiatric consultation by his mother who reports that her son is extremely shy, and she is concerned about his ability to "fit in" at college. S.H. was referred to the psychiatrist by his primary care provider, who reports that S.H. is physically healthy. S.H.'s mother states he is a very bright young male who earned straight A grade in high school despite frequent absenteeism. He only has one close friend, and has never been on a date. S.H.'s mother says that during high school, S.H. rarely attended school social functions and spent much of his time in his room working on his computer. On graduation from high school, he received a full scholarship to a community college, but is quite anxious about going and is debating whether he should turn down the scholarship. When questioned by the psychiatrist, S.H.'s face turns bright red, and his voice shakes when he speaks. S.H. admits his behavior is not normal, but says he is afraid he might "do something stupid" when he is around people and becomes extremely embarrassed when he has to talk to anyone. He has wanted to ask a certain girl on a date for 3 years, but experienced severe anxiety attacks on the few occasions he tried to approach her. S.H. is afraid of being turned down, and believes no girl would ever want to date someone like him. The psychiatrist's diagnosis is social anxiety disorder.

What clinical features of social anxiety disorder are present in S.H.?

S.H. exhibits many characteristic features of the generalized type of social anxiety disorder. S.H. admits he does not like being around people for fear of embarrassment, and he generally avoids social situations, which are classic traits of social anxiety disorder. Symptoms of blushing and shaking voice are also common in social anxiety disorder, as well as other typical anxiety symptoms such as palpitations, trembling, sweating, tense muscles, dry throat, hot/cold sensations, and a sinking feeling in the stomach. S.H. also displays hypersensitivity to rejection and low self-esteem, and he realizes his behavior and fears are unreasonable. These symptoms and S.H.'s young age are consistent with a diagnosis of social anxiety disorder.

S.H.'s case illustrates the substantial disability that can result from this illness. S.H.'s anxiety disorder has deprived him of normal social development, making friends, dating, participating in social functions regularly, and pursuit of higher education. Future impairments throughout S.H.'s life are likely to be significant unless his anxiety is treated successfully.

TREATMENT SELECTION FOR SOCIAL ANXIETY DISORDER

Case 83-7, Question 2: The provider decides to initiate sertraline 50 mg every morning for S.H. Is the prescribed pharmacotherapy appropriate in this case?

Because S.H.'s generalized social anxiety disorder is severely affecting his life, medication treatment is indicated. SSRIs are first-line therapy for treating social anxiety disorder, and sertraline is a good choice because it is FDA approved for this indication. Although not applicable in this case, sertraline is also effective for many other psychiatric disorders commonly seen in patients with social anxiety disorder. The sertraline starting dose of 50 mg/day is appropriate for S.H., and 50-mg increment dosage increases can be made every 4 weeks according to response, up to a maximum of 200 mg/day. Escitalopram or paroxetine would also be reasonable choices. Signs of response may be seen within 2 to 4 weeks, but 8 to 12 weeks is usually required for optimal results. Patients with social anxiety disorder may be uncomfortable or reluctant to mention medication side effects such as sexual dysfunction, so providers should make it a point to ask about this. If available, CBT may also be combined with pharmacotherapy for S.H.

GOALS AND DURATION OF TREATMENT

Case 83-7, Question 3: What are the goals of treatment in this case, and how can S.H.'s response to treatment be objectively assessed? How long should effective therapy be continued?

Three principle domains of treatment outcomes have been defined for social anxiety disorder: symptoms, functionality, and overall well-being.[58] It is recommended that all three of these areas are assessed because even if all anxiety symptoms disappear, treatment is not clinically significant unless functioning also improves. The clinician-rated Liebowitz Social Anxiety Scale and the patient-rated

Sheehan Disability Scale can be used for measuring improvements in symptom and functional ability domains, respectively.[58] In S.H.'s case, the desired outcomes of treatment include reducing fear and avoidance of social situations, enabling him to comfortably interact socially and attend college, and improving his quality of life.

Several studies have examined relapse rates after double-blind discontinuation of effective treatment in social anxiety disorder.[143,146,149] Long-term studies have shown that sertraline, paroxetine, escitalopram, fluvoxamine CR, venlafaxine XR, pregabalin, and clonazepam prevent relapse of social anxiety disorder during continuation treatment.[21] Therefore, pharmacotherapy should be continued for at least 1 year after response.[136,143] After that time, a gradual medication discontinuation trial may be attempted with vigilant monitoring for signs of relapse.

POSTTRAUMATIC STRESS DISORDER AND ACUTE STRESS DISORDER

Diagnostic Criteria

PTSD and acute stress disorder occur in people who have experienced a severely distressing traumatic event. These disorders are characterized by symptoms of intrusive reexperiencing, avoidance features, autonomic hyperarousal, and negative cognitions and mood symptoms.[1] In addition to war veterans, PTSD also occurs in persons exposed to events such as natural disasters, serious accidents, criminal assault, rape, **PHYSICAL** or sexual abuse, and political victimization (eg, refugees, concentration camp survivors, hostages). The trauma does not have to involve physical injury to the PTSD victim. Witnessing someone else being injured or killed, being diagnosed with a life-threatening illness, and experiencing the unexpected death of a loved one are common types of trauma that may lead to PTSD.[1]

Symptoms of PTSD are presented in **Table 83-10**.[1] According to diagnostic criteria, the person must have exposure to actual or threatened death, serious injury, or sexual violence via directly experiencing the event, witnessing the event in person, learning the event occurred to a close family member or friend, or experiencing extreme exposure to aversive details of an event.[1] Specifiers indicate whether PTSD is delayed (after 6 months) onset in relation to the trauma and/or whether it is associated with dissociative symptoms.[1] Symptoms must persist for at least 1 month to meet the criteria for PTSD. *Acute stress disorder* is a separate diagnostic category in the *DSM-5*, and refers to cases in which symptoms last <1 month (but at least 3 days).[1] It involves many of the same clinical features as PTSD, and as with PTSD, symptoms must be severe enough to interfere with functioning.

Table 83-10

Symptoms of Posttraumatic Stress Disorder for Individuals Ages 6 Years or Older

1. Intrusion (eg, memories, dreams, dissociative reaction [such as flashbacks], intense distress that is experienced on exposure to stimuli associated with the traumatic event, or physiologic reactions to internal or external cues that reflect the event)
2. Avoidance (eg, avoidance of or efforts to avoid distressing memories, thoughts, or feelings or external reminders such as places, people, conversations about or related to the event)
3. Increased arousal including at least two of the following:
   - Sleep disturbances
   - Irritability or anger outbursts
   - Difficulty concentrating
   - Hypervigilance
   - Exaggerated startle response
   - Reckless or self-destructive behavior
4. Persistent negative alterations in cognition or mood associated with the event including at least two of the following:
   - Amnesia surrounding the event
   - Negative beliefs or expectations about oneself, others, or the world

- Distorted cognitions about the cause or consequence of the event where the individual blames themselves or others
- Negative emotional state
- Diminished interest or participation in activities
- Detachment or estrangement
- Lack of ability to experience positive emotions

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

Epidemiology and Clinical Course

In the United States, PTSD is associated with a lifetime prevalence of ~10% in the general population, and up to 24% among deployed serviceman from Iraq and Afghanistan.[150] PTSD is twice as common in females, although, overall, males are exposed to trauma more often.[153] An estimated 80% to 90% of individuals in the United States today will experience at least one event during their lifetime traumatic enough to lead to PTSD.[151]

Most people who are exposed to a traumatic event do not develop PTSD; ~90% of individuals experience a normal acute stress response to trauma and fully recover.[151] Risk factors for the development of PTSD include experiencing assaultive violence, more severe and chronic traumas, a history of depressive or anxiety disorders, lack of social support after the trauma, and experiencing dissociative or other intense symptoms during or soon after the trauma.[150-152] Previous exposure to trauma also increases the risk of developing PTSD after later traumas, and survivors of childhood sexual or physical abuse have been found to be especially vulnerable.[152,153]

Overall, 79% to 88% of patients with PTSD also suffer from other disorders in their lifetime, including MDD, alcohol or other substance abuse, GAD, panic disorder, and phobic disorders.[150,151,153-155] The risk of suicidality in PTSD is high and likely influenced by comorbid MDD.[156] Recent studies have also found associations with PTSD and coronary heart disease, traumatic brain injury, and sexual dysfunction.[157-159] PTSD causes significant functional disability and

has been associated with school failure, teenage pregnancy, unemployment, marital instability, legal problems, and impaired performance in the workplace.[160]

The course of PTSD is highly variable. Most patients who meet criteria for PTSD 1 month after trauma show spontaneous recovery within 6 to 9 months.[154] PTSD continues for years in an estimated 10% to 25%, and some patients experience a lifelong course of illness.

Etiology and Pathophysiology

Psychological trauma, especially that which occurs early in life or is chronic in duration, can cause persistent changes in various aspects of brain functioning and in neurobiologic responses to stress.[161] Evidence of altered NE, 5-HT, glutamatergic, GABA system, HPA axis, neuroendocrine, substance P, and opioid system functioning has been found in PTSD.[162-165] Stress-induced hyperactivity of central noradrenergic systems is believed to lead to the generalized anxiety and autonomic hyperarousal associated with PTSD.[163] Neurobiologic consequences of stress and trauma result in both structural and functional changes in the brain, including reduced hippocampal volume and excessive activation of the amygdala.[166] Genetic factors may also play a role in influencing vulnerability to the damaging effects of stress.[167]

Treatment of Posttraumatic Stress Disorder

Recent guidelines emphasize the importance of trauma-focused psychotherapies in the treatment of PTSD, even above pharmacotherapy. Non–trauma-focused psychotherapies may also be beneficial. Medications can also be useful in treating PTSD, and may be required alone or in combination with nonpharmacologic treatments, especially for patients with moderate or severe illness.[26,152,153,160,168,169] When assessing various treatment options for PTSD, it is important to consider effects on all four core symptom

clusters (reexperiencing or intrusive symptoms, avoidance, hyperarousal, or negative cognitions and mood symptoms). Not all PTSD treatments are effective for each domain.

The preferred first-line medications in PTSD are SSRIs or venlafaxine XR, but various other antidepressants may also be useful. Response to pharmacotherapy occurs very gradually, taking 8 to 12 weeks or longer. Partial response at 12 weeks of treatment may be followed by full remission after several more months of therapy; therefore, an adequate period should be allowed to fully determine response to a particular medication. Lack of improvement after 4 weeks of therapy indicates nonresponse, so alternative treatment strategies should be tried in these cases.[170] Although further research is needed, prevention of PTSD using various pharmacologic strategies has been evaluated in adults.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

Sertraline and paroxetine are currently the only FDA-approved SSRIs for PTSD. Large controlled studies have demonstrated that both agents are effective and superior to placebo, as well as fluoxetine and venlafaxine XR.[171] They also have beneficial effects on depression and general anxiety symptoms, and have been associated with improvements in overall functioning and quality of life.[170,171] Citalopram, escitalopram, and fluvoxamine have shown efficacy in the treatment of PTSD in open trials, but randomized, double-blind, placebo-controlled studies have yielded negative results.[170,172] Finally, one small, naturalistic study in treatment-resistant males suggests that duloxetine may be effective in managing comorbid depression and PTSD.[173] However, in another small, prospective study in military veterans suggests that additional studies are warranted.[174]

OTHER ANTIDEPRESSANTS

Several open-label studies and case reports suggest nefazodone or mirtazapine is effective in treating core symptoms of PTSD.[165,175]

Nefazodone is not commonly used in practice, since the addition of an FDA black box warning for rare but serious, potentially fatal liver injury.[176] Although supporting evidence for mirtazapine is not as strong, it may be considered an appropriate alternative to SSRIs or venlafaxine in certain patients, such as patients with comorbid insomnia or sexual dysfunction from first-line antidepressants. The TCAs amitriptyline and imipramine and the MAOI phenelzine have also been found to be effective for PTSD in controlled trials. However, these agents are generally not recommended because of their poor tolerability and safety profiles.[153] Because of the relatively high risk of suicide in PTSD, TCAs can be especially dangerous in this population.

MISCELLANEOUS AGENTS

Various other medications have been used successfully in limited numbers of PTSD cases. Anticonvulsants carbamazepine, valproate, topiramate, tiagabine, gabapentin, oxcarbazepine, vigabatrin, pregabalin, levetiracetam, and lamotrigine have been studied with inconsistent results, mostly in case series and open-label trials.[21,26,171,175] These agents may be effective in certain patients, and can be useful for reducing irritability, impulsivity, and anger or violent outbursts, particularly in patients with bipolar disorder.[177] Anticonvulsants may also be effective for intrusive, reexperiencing, and hyperarousal symptoms. Atypical antipsychotic agents have been used effectively to treat PTSD-related psychotic symptoms and sleep disturbances, although evidence is limited, and side effect burden often outweighs potential benefit. Evidence is most substantial for risperidone and olanzapine, although there are studies showing benefit with aripiprazole and quetiapine as well. A recent meta-analysis suggests that these agents may help target symptoms of intrusion.[178] Conflicting evidence exists for the use of the β-adrenergic antagonist, propranolol, which has been studied in blocking memory consolidation, and therefore may prevent PTSD if administered within hours of the traumatic event.[179] Larger studies are needed to determine whether this is a useful preventive option.

Preliminary evidence supports the use of hydrocortisone for this indication, although additional studies are needed.[180] Benzodiazepines are generally ineffective in treating PTSD, and use of these agents is not recommended.[181] Benzodiazepine use during trauma-focused therapy is also associated with worse outcomes and should be avoided.[182]

The α_1-adrenergic antagonist, prazosin, dose at bedtime may decrease nightmares, increase sleep time, and reduce other core symptoms in patients with PTSD.[165,183] However, a recent study in veterans found no statistically significant difference in distressing dreams or sleep quality between prazosin and placebo groups.[184] Nonetheless, prazosin is still the most commonly used agent for PTSD nightmares, primarily because alternatives for treatment of nightmares are scarce. Alternatively, the α_2-adrenergic agonist clonidine has been studied for PTSD-related nightmares or symptoms of hyperarousal; however data are limit.[185]

NONPHARMACOLOGIC TREATMENTS

Trauma-focused psychotherapies are first-line options for PTSD.[186] These include trauma-focused CBTs (eg, cognitive processing therapy, prolonged exposure therapy) and eye movement desensitization and reprocessing (EMDR). Cognitive therapies teach patients how to reframe negative thinking, and seem to be most effective for symptoms of demoralization, guilt, and shame. Exposure therapies have patients confront traumatic memories or situations, and are better for reducing intrusive thoughts, flashbacks, and avoidance behaviors. EMDR involves patients recalling traumatic memories while being exposed to external stimuli. Studies are needed to further investigate the utility of virtual reality exposure therapy and transcranial magnetic stimulation in PTSD.[187,188] Trials of combined psychosocial therapies and medication are inconclusive, and require further investigation to determine superior effectiveness compared with either treatment strategy alone, but may be warranted in more severe cases.[189]

Clinical Presentation of Posttraumatic Stress Disorder

CASE 83-8

QUESTION 1: D.D. is a 42-year-old female who was attacked and raped 1 month ago in the driveway of her home as she was getting out of her car at night. She did not seek medical treatment at the time and waited several days before reporting the incident to anyone, including her family. She presents to her provider and reports that she cannot sleep, and she is irritable, anxious, and depressed. When asked about any recent stressors in her life, she finally tells her doctor about the rape. D.D. has no history of psychiatric illness, admits that her symptoms have appeared since the attack, and says she has never had any psychiatric problems until now. She states she has nightly nightmares, and becomes extremely anxious every time she gets out of her car when it is dark outside. She avoids driving in the evenings when possible. She is startled when the phone rings or when someone approaches her unexpectedly, and she freezes if she sees a male who bears any physical resemblance to her attacker. D.D. also states that memories of the rape often flash through her mind for no reason, although she tries hard not to think about it. The assailant has not been caught, and D.D. feels extremely guilty for not promptly reporting the crime. Her symptoms are interfering significantly with her ability to work, and have put a strain on her marriage.

What clinical features of PTSD does D.D. display?

Individuals with PTSD often present with nonspecific symptoms indicative of a generalized anxiety, depression, or substance use disorder. They may not realize or want to reveal an association between their symptoms and the trauma experienced. Careful evaluation by the clinician is required to elicit a pattern suggestive of PTSD. D.D. displays many target symptoms of PTSD, including reexperiencing/intrusive symptoms (eg, nightmares, recurrent memories), avoidance of the activity reminding her of the trauma (ie, driving at night), symptoms of increased arousal (eg, sleep difficulties, irritability, exaggerated startle response), and negative alterations in cognition (eg, guilt). In addition, she is experiencing feelings of depression, distress, marital problems, and impairment in occupational functioning as a result of her symptoms. The lack of any previous psychiatric illness combined with the temporal

relationship between the attack and her symptoms supports the presence of PTSD as opposed to another anxiety or depressive disorder. Because her trauma occurred 1 month ago, her condition would be classified as acute-onset PTSD.

Treatment Selection and Selective Serotonin Reuptake Inhibitor Dosing

Case 83-8, Question 2: What factors are important in the selection of an initial treatment for D.D.?

Trauma-focused psychotherapy is considered the preferred first-line treatment for PTSD, although there are also several first-line medication options. The pros and cons of the various trauma-focused psychotherapies and medication should be discussed with the patient. Provide the patient with information about the availability, time commitment, and therapy style of trauma-focused psychotherapy as well as potential medication side effects. Because D.D. is exhibiting moderate-to-severe PTSD symptoms, combining psychotherapy and pharmacotherapy may also be warranted. Patient preference and availability of trauma-focused therapy options are also important factors to consider when determining best initial treatment.

D.D. informs her provider that she does not want to initiate any type of psychotherapy and prefers medication treatment alone. An SSRI is the preferred initial medication treatment for most patients.[171] Sertraline is an appropriate choice of treatment in this case, and is FDA approved for PTSD. Low initial SSRI doses are recommended in PTSD, so sertraline can be started at 25 mg/day and gradually increased to the target dosage range of 100 to 150 mg/day, according to response and tolerability.[175]

Clinical Assessment and Goals of Therapy

Case 83-8, Question 3: What are the goals of treatment in this case, and how can D.D.'s symptoms be objectively assessed?

The first goal of treatment of PTSD is to reduce the core symptoms of reexperiencing/intrusion, avoidance, hyperarousal, and negative alterations in mood and cognitions. In D.D.'s case, these target symptoms include nightmares, intrusive memories, avoidance behaviors, irritability, hyperarousal, sleep difficulties, and guilt. Improvements should begin within the first 2 weeks and gradually continue over the course of 2 to 3 months. Secondary goals in this case include improving D.D.'s stress tolerance, decreasing her work- and marriage-related disability, and improving her quality of life. Other general treatment goals in PTSD include decreasing detrimental behaviors (use of alcohol or substances, risky activities, violence) and treating comorbid psychiatric conditions.

Several different rating scales have been developed to assess response to treatments in PTSD.[58] The most commonly used clinician-rated scales are the Clinician Administered PTSD Scale and the shorter Treatment Outcome PTSD Scale. The Clinician Administered PTSD Scale is most often used in clinical PTSD trials. The Sheehan Disability Scale is often used to assess functional impairment attributable to PTSD.

Case 83-8, Question 4: D.D. returns 3 months later, stabilized on sertraline 150 mg/day. She has had a significant reduction in flashbacks, and is able to drive at night again with only mild anxiety. Her relationship with her husband has improved, and she feels less irritable and depressed. However, D.D. continues to have nightly nightmares of her rape, which make it difficult to fall back asleep. She is only sleeping 3 to 4 hours a night. What treatment options can be offered to address her nightmares?

As long as D.D. does not have low blood pressure at baseline, prazosin is a reasonable off-label medication option for the treatment of PTSD nightmares, although evidence supporting efficacy is mixed. The recommended initial dosing for prazosin is 1 mg orally at bedtime. Prazosin doses >16 mg/day are not typically used in clinical

practice.[190] Prazosin maximum dosing is often further limited by dose-dependent hypotension. Females may be more sensitive to the effects of prazosin, and therefore doses >10 mg/day should be used with caution.[185] Start prazosin 1 mg orally at bedtime. Titration schedules vary, although it would be reasonable to titrate the prazosin in increments of 1 mg/day, with dose increases no sooner than every 3 to 4 days. Blood pressure monitoring is recommended with dose increase. Alternatively, D.D. may consider behavioral therapies such as CBT or EMDR.[191]

Course and Duration of Treatment

Treatment response in PTSD is more likely to occur when treatment is started within 3 months of the trauma.[153,160] There is no well-established definition of response in PTSD, but a decrease in symptoms by 30% to 50%, along with substantial functional improvement, is commonly used in clinical trials. Full recovery during treatment of PTSD is fairly uncommon, and partial responders to either medication or psychosocial therapies may benefit from adding another treatment modality. When an initial SSRI trial is ineffective, the patient may be switched to another SSRI or another antidepressant shown to be effective in PTSD.[21] Partial responders may benefit from the addition of a second medication, depending on which core symptoms predominate (see section on Treatment of Posttraumatic Stress Disorder).

For patients who respond, treatment should be continued for an additional 6 to 12 months for acute cases (when symptoms were present >3 months before treatment) and 12 to 24 months for chronic cases (when symptoms lasted >3 months before treatment).[153] Long-term SSRI treatment can prevent relapse of PTSD, especially in those who show good response during the first 3 months of therapy.[181] When pharmacotherapy is discontinued, it should be withdrawn gradually over the course of 1 to 3 months.

OBSESSIVE–COMPULSIVE DISORDER

Diagnostic Criteria

OCD is characterized by repetitive thoughts (obsessions) that cannot be ignored or suppressed voluntarily and/or repetitive behaviors (compulsions). The compulsions are designed to reduce anxiety associated with obsessions or to prevent some future event or situation; however, they are not actually connected to the obsessions in any realistic way or are excessive. Obsessions and compulsions result in marked distress, are time-consuming (>1 hour/day), or significantly impair functional ability.[1] Both obsessions and compulsions are unpleasant and disturbing to the sufferer, and are not associated with pleasure or gratification. This feature distinguishes OCD from certain other behaviors (eg, excessive gambling or shopping) often described as “compulsive.”

OCD is a clinically heterogeneous disorder involving a broad range of symptoms with four primary OCD symptom dimensions: symmetry obsessions and repeating, counting, and ordering compulsions; contamination obsessions and cleaning compulsions; hoarding obsessions and compulsions; aggressive, sexual, and religious and related compulsions. Although specific symptoms in an individual may change with time, they usually remain within the same dimension.[192]

Epidemiology and Clinical Course

OCD is one of the least common mood–anxiety disorders with a lifetime risk and 12-month prevalence between 2% and 3%.[15] Although onset of illness ranges from very early childhood to adulthood, the mean onset of illness is 20 years, which is later than are most anxiety disorders. Males tend to have an earlier onset of illness (childhood) than do females (adulthood). Approximately one-fourth of patients experience symptoms by age 14, and onset after 30 years of age is rare.[1] Childhood-onset OCD may be a distinct

illness subtype.[195] There is usually a gradual onset of symptoms, although abrupt onset may occur during stressful periods and pregnancy.[1,193]

The course and severity of OCD are highly variable and unpredictable. The majority of patients with OCD will have a chronic course that waxes and wanes rather than an intermittent or episodic course. Fewer than 10% of patients will have a deteriorating course.[194] A 40-year naturalistic study found that although 83% of patients had improved at the end of the follow-up period, only 20% experienced full remission.[194]

OCD can have seriously detrimental effects on function such as abilities to socialize, study, work, make friends, and maintain good relationships with family and friends given the time spent obsessing and performing compulsions as well as avoiding situational triggers.[1,195] It is estimated that each person with OCD loses an average of 3 years' wages during his or her lifetime.[195] Quality-of-life ratings in patients with OCD indicate marked impairments, and are similar to those observed in patients with depression.

Although several effective treatments are currently available for OCD, there is an average delay of 7.5 years between onset and seeking medical evaluation for OCD.[195] This may be because most patients with OCD realize their symptoms are senseless, so they attempt to hide their disorder because of embarrassment. People with OCD often carry out their rituals privately, and may be very successful at concealing their symptoms from others. Initial treatment for OCD is commonly sought outside psychiatric settings, and the obsessive–compulsive symptoms are often missed. Clinicians across the health care system can incorporate four simple OCD screening questions into their practice to improve detection: Do you have to wash your hands over and over? Do you have to check things repeatedly? Do you have recurrent distressing thoughts you cannot get rid of? Do you have to complete actions again and again or in a certain way?[196]

Psychiatric Comorbidity and Obsessive–Compulsive Spectrum Disorders

Identification of comorbid conditions with OCD is important because it can influence treatment decisions. As with other anxiety disorders, OCD is often accompanied by psychiatric comorbidity in 60% to 90% of patients; affective disorders (eg, depression, bipolar disorder), anxiety disorders, and tic disorders being common.[1,21,26,194] Tics occur in 20% to 30% of patients with OCD. These individuals are believed to represent a distinct subtype of illness, where patients are more likely to be male, have an earlier onset (before age 10 years), experience more severe symptoms, and have a poorer response to SSRIs than do those with OCD alone.[197] Distinguishing OCD from obsessive–compulsive personality disorder (OCPD), a personality pattern characterized by rigid and inflexible preoccupation with rules, lists, order, and perfectionism, can be difficult. OCD and OCPD co-occur in a small percentage of patients. OCPD, however, does not involve distressing obsessions and compulsions.

OCD is classified as an illness within obsessive–compulsive and related disorders.[1] Other related disorders included are body dysmorphic disorder (preoccupation with an imagined or slight defect in appearance), trichotillomania (recurrent impulses to pull out one's hair), excoriation disorder (skin-picking), and hoarding disorder. As with OCD, many patients with these conditions have shown good response to treatment with serotonergic antidepressants such as SSRIs or clomipramine.[198]

Etiology and Pathophysiology

Because OCD displays such clinical heterogeneity, there may be several distinct etiologies for different subtypes of illness. Structural and functional brain imaging suggests that OCD is a neurologic disorder characterized by a hyperfunctioning circuit involving the frontal lobe and basal ganglia regions termed the *frontostriatal circuit*.[192] Abnormalities therein imply potential dysfunction in

glutamatergic, dopaminergic, and serotonergic neurotransmission. In support of this hypothesis, these abnormalities normalize after successful treatment of OCD with SSRI monotherapy and antipsychotic augmentation. Preliminary evidence with glutamatergic agents suggests a role in treatment. Furthermore, neuromodulation therapies (eg, deep brain stimulation, cycloserine-enhanced CBT) and neurosurgical techniques interrupting this circuit are often effective in the treatment of OCD. Aberrant activity in this system may lead to impaired executive function, decision-making, and memory because these cognitive domains are mediated by this system.

Besides biologic factors, twin and family studies support genetic influences, particularly in early-onset OCD cases.[18,199] Genetic studies have found associations between OCD and specific polymorphisms in the glutamatergic (high-affinity neuronal/epithelial excitatory amino acid transporters), dopaminergic (catechol-*O*-methyltransferase and dopamine D_4-receptor genes), and serotonergic (5-HT type 1Dβ and 5-HT type-2A receptor genes) pathways.[200-202] The heritability of OCD is estimated at 40%, with the remaining variation purportedly mediated by environmental factors (eg, perinatal events, trauma, stress, neuroinflammation).[192] An example of this is the autoimmune disease, called PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection). Reports describe children who developed sudden and severe tics and obsessive–compulsive symptoms after strep throat infections.[203] These children may be better treated with antibiotics or immunomodulatory therapies. The possibility of a PANDAS correlation should be considered in any child who develops abrupt onset of obsessive–compulsive symptoms and/or tics and has a history of pharyngitis within the past 6 months.

Treatment of Obsessive–Compulsive Disorder

Both medications and behavioral therapies are effective in the treatment of OCD. Behavioral therapy is vitally important for OCD,

and the combination of drugs plus behavioral therapy provides optimal treatment. All medications consistently effective as monotherapy are potent inhibitors of serotonin reuptake. These include the SSRIs, clomipramine, and the SNRI venlafaxine.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

SSRIs are the only first-line medication treatments for OCD, of which fluvoxamine, fluoxetine, paroxetine, and sertraline are FDA approved based on double-blind, placebo-controlled studies.[204] Citalopram and escitalopram also are effective, but with less evidence to support their use. No single SSRI is considered to be more effective than are the others in treating OCD, but some patients may respond to or tolerate one agent better than another.[204] Drug interactions may also influence SSRI choice. Fluvoxamine is a strong CYP1A2 and CYP2C19 inhibitor, which may increase concentrations of CYP1A2 substrates (olanzapine, clozapine, tizanidine, caffeine) or CYP2C19 substrates (omeprazole, diazepam). Fluoxetine and paroxetine are strong CYP2D6 inhibitors that may increase concentrations of CYP2D6 substrates such as atomoxetine, aripiprazole, tramadol, or dextromethorphan.[205]

Usual SSRI starting dosages can be used in OCD, but at least 4 weeks should be allowed before exceeding the targeted minimally effective dosages (fluvoxamine 200 mg/day, fluoxetine 40 mg/day, paroxetine 40 mg/day, and sertraline 100 mg/day).[204] SSRIs are generally considered to have a dose–response relationship such that higher SSRI doses may be required to effectively treat OCD.[26] In addition, several controlled studies support the efficacy of venlafaxine in the treatment of OCD.[206] Although other SNRIs (duloxetine, desvenlafaxine, milnacipran, or levomilnacipran) may ultimately show efficacy in the treatment of OCD, additional well-controlled studies are needed.[207]

CLOMIPRAMINE

Clomipramine was the first drug FDA approved for OCD treatment in 1989, and was considered the standard treatment for several years, until the SSRIs gained popularity. Many large well-controlled studies have documented that clomipramine is superior to placebo and significantly improves OCD symptoms in ~60% to 70% of patients.[194,206] Clomipramine is the only TCA recommended for OCD treatment, because others have not proved efficacious,[21,26,122,194,208] although there is some evidence to the contrary.[209] The efficacy of clomipramine is attributed to its more potent effects on 5-HT reuptake inhibition compared with other TCAs. Clomipramine is often referred to as an SRI (serotonin reuptake inhibitor), not an SSRI, because its major active metabolite, desmethylclomipramine, is a potent inhibitor of NE reuptake. Clomipramine also blocks adrenergic, histaminergic, and cholinergic receptors, resulting in an adverse effect profile similar to that of other TCAs (see Chapter 86, Depressive Disorders).

Although direct comparison studies have shown clomipramine to be similar in efficacy to various SSRIs in treating OCD, several meta-analyses have concluded that clomipramine is superior to SSRIs overall.[206,210] Nonetheless, clomipramine is currently reserved as a second-line treatment option for patients who do not respond adequately to SSRI therapy given its less desirable tolerability profile (eg, sedation, orthostatic hypotension, weight gain, and anticholinergic side effects).[206] Details about the clinical use of clomipramine are discussed in Case 83-10, Question 1.

AUGMENTATION STRATEGIES

Other than venlafaxine XR, no other miscellaneous agents studied in OCD have demonstrated impressive efficacy as monotherapy. However, several agents appear to be useful as augmentation therapy to boost response to SSRIs or clomipramine in partial responders.[211] The combination of an SSRI plus clomipramine is one such option for patients who show partial response, although attention must be paid to potential drug interactions, which may lead to clomipramine toxicity (see Case 83-10, Questions 2 and 3).

Antipsychotic agents are the most studied pharmacologic augmentation strategy in OCD, and may improve response in 30% of patients.[212] They may be particularly effective in four scenarios: treatment-refractory OCD, OCD with poor insight (often treatment refractory), comorbid tic disorders, and comorbid schizophrenia.[213] Several meta-analyses have been conducted on antipsychotic effectiveness.[212,214-216] Risperidone (0.5–4 mg/day) is generally considered to have the highest evidence base for antidepressant augmentation in OCD. Other reasonable agents include aripiprazole and haloperidol (of which haloperidol is less tolerated compared to second-generation antipsychotics). Conversely, quetiapine (up to 600 mg/day) and olanzapine (2.5–20 mg/day) use is controversial based on inconsistent evidence supporting their use in well-designed trials. Preliminary evidence suggests paliperidone may not be more effective than placebo, and ziprasidone may be less effective than quetiapine.[217,218] Recent evidence suggests antipsychotics are less effective than augmenting with CBT with exposure–response prevention (ERP) and, thus, may not be a preferred augmentation strategy.[219,220] In addition, the use of antipsychotics must be weighed against tolerability and safety concerns such as metabolic dysfunction and extrapyramidal symptoms.

Besides antipsychotics, other medications (eg, topiramate, memantine, pindolol, pregabalin, ondansetron, mirtazapine, buspirone) may also be considered as augmentation agents, although the evidence is limited to lower quality studies.[21,221,222] As such, this strategy should be one of last resort, unless otherwise clinically indicated.

MISCELLANEOUS AGENTS

Benzodiazepines, although typically useful in other anxiety disorders, are generally not beneficial in treating OCD. There are several reports of clonazepam being effective as adjunctive therapy or monotherapy, which may be explained by its serotonergic properties; however, double-blind placebo-controlled trials have been negative.[223] As such, clonazepam is not recommended by treatment

guidelines.[194] The MAOI phenelzine was one of the first medications studied for OCD. Early case reports of its use were favorable, but more recent findings suggest phenelzine is largely ineffective for OCD.[194] A few cases and short-term studies have explored the use of the dietary supplement *N*-acetyl cysteine (NAC) for OCD, with mixed efficacy results, but a mild side effect profile. Long-term, randomized, placebo-controlled trials are needed to determine whether NAC is an effective treatment option for OCD.[224]

NONPHARMACOLOGIC TREATMENTS

Cognitive behavioral therapies

CBT is an extremely important component of OCD treatment and should be incorporated into the treatment plan whenever possible. The combination of psychotherapy and medication is generally superior to pharmacotherapy alone, but not to CBT alone.[21,194] CBT alone may be appropriate for mild OCD or in cases in which it is desirable to avoid medication (eg, pregnancy, medical conditions). Treatment gains achieved with CBT often are maintained long after its discontinuation, which is an advantage versus pharmacotherapy, likely improving relapse prevention.[196] The cognitive therapy component of CBT is aimed toward changing the detrimental thought patterns in OCD, and is most helpful for obsessions such as scrupulosity, moral guilt, and pathologic doubt. The behavioral therapy aspect, ERP, involves exposure to feared objects or situations followed by prevention of the usual compulsive response. This type of therapy is most beneficial for patients with contamination fears, hoarding, and rituals involving symmetry, counting, or repeating. Because ERP is anxiety provoking and can be very distressing, patients may refuse to participate.[225]

Procedures and devices

Neurosurgical treatment of OCD has been practiced since the 1950s, and is considered an option of last resort in treatment-refractory patients. Anterior cingulotomy and anterior capsulotomy are the most commonly used surgical procedures. Indications for

neurosurgery include severe disability from symptoms and failed treatments (drugs and behavioral therapies) that have been tried systematically for at least 5 years.[226] Neurosurgery success rates range from 35% to 70%. Complications (including potential infections, personality changes, cognitive impairment, and epilepsy) appear to be rare, and limited long-term follow-up studies indicate the benefit is maintained with mild-to-moderate impairments in neuropsychological performance.[226,227] A deep brain stimulation device received FDA approval in 2009 for adjunctive use to medications in chronic, severe, treatment-resistant OCD (three or more failed medication trials) under the Humanitarian Device Exemption (HDE).[228] The device is surgically implanted in the brain and provides electrical stimulation. However, evidence of effectiveness is not required for devices approved under the HDE. Along with the risks of surgical implantation, possible side effects include negative changes in mood, increased anxiety, worsening of OCD symptoms, hypomania, paresthesia, shocking sensation, muscle weakness/contraction, or dizziness.[229] More recently, in 2018, the FDA expanded the indications for the Brainsway Deep Transcranial Magnetic Stimulation (TMS™) System to include OCD. TMS is a noninvasive treatment option that uses a magnetic field to stimulate specific areas of the brain. Side effects of TMS are generally mild, including headache, neck, face or jaw pain, or muscle twitching/spasms.[230] The FDA permits marketing of TMS for treatment of obsessive–compulsive disorder.

Defining Response to Therapy

Response to medication treatment in OCD is gradual and often delayed. Initial improvements usually begin to appear within the first month. Patients with unsatisfactory response by weeks 4 to 9 should have their SSRI dosages gradually increased to the manufacturer's recommended maximum. A trial of 8 to 12 weeks at maximal tolerated medication dosages is recommended before assessing

therapeutic benefit, and maximal response may take as long as 5 to 6 months.

Because complete elimination of symptoms is rare with current treatments, the primary goal of OCD treatment is to minimize functional impact of symptoms.[231] Most clinical trials in OCD define clinical response as a 25% to 35% reduction in Yale–Brown Obsessive–Compulsive Symptom Checklist (Y-BOCS) scores. Therefore, even those classified as responders may be left with 65% to 75% of their original symptoms, and this may or may not result in significant improvements in functioning or quality of life. The Y-BOCS is an objective tool in the initial evaluation of those who present with symptoms of OCD. It is a 10-item scale with a maximal possible score of 40; a score of >15 is generally considered to represent clinically significant obsessive–compulsive symptoms.[232] This scale is a standard tool for evaluating drug efficacy in OCD clinical trials; and is often used in clinical practice to assess response to treatments, with a version designed for administration with children.

STRATEGIES FOR MANAGING NONRESPONSE AND PARTIAL RESPONSE

Approximately 40% to 60% of patients show clinically meaningful improvements during an initial (SSRI or clomipramine) medication trial, but only a small percentage exhibit marked response.[206] Predictors of poor response include poor insight; hoarding, sexual, religious, and symmetry dimension symptoms; prepubertal onset of illness; and presence of comorbid personality, mood, or eating disorders.[21] For nonresponsive patients, it is usually recommended to pursue a second SSRI trial, because ~20% of initial nonresponders will respond with a subsequent trial. Given this and tolerability concerns, clomipramine is typically reserved as a third-line treatment option, although its use second line would be reasonable given its efficacy in SSRI nonresponders.[196,206] Patients with partial response to an initial SSRI trial may be better served by adding an augmentation agent to preserve therapy benefits rather than switching to a new medication and risk losing any improvement

already gained. In addition, per the American Psychiatric Association (APA), using SSRI doses beyond those FDA approved may be beneficial for poor responders if tolerability is acceptable.[194,233-235] Monitor closely for serotonin syndrome. Caution is warranted if exceeding FDA-approved maximum doses of citalopram, escitalopram, or, to a lesser extent, fluoxetine, given the dose-dependent risk of QTc prolongation.

Clinical Presentation and Assessment

CASE 83-9

Question 1: R.G. is a 25-year-old female whose husband reports that she spends 1.5 hours a day cleaning the stove and takes four showers each day. The unusual behavior began about 1 year ago after the birth of their son but has continued to worsen, and R.G.'s husband states that he cannot deal with her "odd habits" any longer. R.G. recently lost her job as a secretary because of tardiness (it took her 3 hours to get ready for work) and spending too much time away from her desk in the ladies' room. R.G. admits that it is silly, but she has irresistible urges to make sure both she and her surroundings are completely free of germs so that her child will not get sick. She also confines herself to one floor of their three-level house because she is afraid that she will fall down the stairs while carrying her son. R.G. also states that she constantly has "what if" thoughts about horrible things happening to her family, which are very disturbing. The provider's diagnosis is OCD.

What clinical features of OCD does R.G. display, and how can her symptoms be objectively evaluated?

R.G. displays many characteristic symptoms of OCD. The most commonly encountered clinical presentation of OCD involves excessive fear of contamination with dirt, germs, or toxins and repeated washing of hands or cleaning objects or surroundings. These persons also typically avoid touching possibly dirty objects (eg, doorknobs, money) or shaking hands with people. Another common clinical presentation of OCD is the patient with pathologic doubt who constantly worries something bad will happen because of his or her negligence. Individuals can be afraid they have failed to lock the door, turn off the stove, shut the refrigerator door, or secure

the medicine cabinet from children. As a result, they continuously check and recheck their actions.

R.G. displays obsessions of contamination and pathologic doubt, and compulsions of excessive cleaning and washing. These symptoms are time-consuming, cause significant distress, and have led to her unemployment and marital difficulties. As seen in this case, most persons present with a mixture of various obsessions and compulsions. R.G. also realizes her thoughts and behaviors are "silly," which most often is the case in OCD. This case also illustrates the onset of OCD during times of stressful or significant life events. Pregnancy, death of a relative, and marital discord have been identified as precipitating factors in the onset of OCD.[193,231,236]

Selective Serotonin Reuptake Inhibitor Treatment of Obsessive–Compulsive Disorder

Case 83-9, Question 2: On assessment, R.G.'s Y-BOCS score is found to be 33. Her provider prescribes fluvoxamine IR tablets, and instructs R.G. to take 100 mg every morning for 1 week and then 200 mg every morning thereafter. He also refers R.G. to a psychologist to receive CBT. Is this initial choice of therapy appropriate?

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selection and dosing

SSRIs such as fluvoxamine are considered the best choice of initial pharmacotherapy for OCD. The primary differences between SSRIs involve pharmacokinetic properties and potential for drug interactions (see Chapter 86, Depressive Disorders). Because there are no overall differences in SSRI efficacy, fluvoxamine is a suitable selection for R.G. However, the prescribed dosing instructions for R.G. are not appropriate. The initial recommended dosage for fluvoxamine IR in adults is 50 mg/day (25 mg in children), and it is best taken in the evening because it tends to be sedating. Using higher than necessary dosages can increase both adverse effects and medication costs, and these factors can lead to early termination

of therapy. The dosage can be increased by 50-mg increments every 3 to 4 days according to patient tolerability, up to the initial targeted dose of 200 mg/day and a maximum of 300 mg/day.[204] Daily doses exceeding 100 mg should be given in two divided doses if once-daily dosing is not well tolerated. Fluvoxamine extended-release (XR) capsules are also available, for once-daily administration and possibly improved tolerability. However, the cost of fluvoxamine ER versus IR can be a barrier to use.

ADJUNCTIVE COGNITIVE BEHAVIORAL THERAPY

R.G.'s Y-BOCS score of 33 indicates extremely severe symptom severity, which supports using a combined treatment approach. The overall efficacy of these nonpharmacologic treatments is estimated to be 50% to 70% when used alone, and their use to complement pharmacotherapy is considered vital.[196] For R.G., ERP therapy might involve covering her hands with dirt and not allowing her to wash them for a certain time period. These behavioral techniques cause extreme anxiety and discomfort, which often lead to dropout from therapy or noncompliance with "homework assignments" (which involve continuation of the therapy principles outside the clinical setting), but are highly effective if the patient can adhere to treatment.

SELECTIVE SEROTONIN REUPTAKE INHIBITOR ADVERSE EFFECTS AND PATIENT COUNSELING

Case 83-9, Question 3: What patient counseling information should be provided to R.G. in conjunction with the prescribed treatments?

All patients with OCD beginning treatment should be counseled that medication response occurs gradually and several weeks may elapse before beneficial effects become noticeable. It is important to emphasize that maximal response may take ≥3 months and complete elimination of all symptoms is unlikely. Inform patients that

a variety of other medications exist for those who do not respond adequately to an initial trial.

R.G. should be educated about possible fluvoxamine side effects, including nausea, sedation or insomnia, and headache. Medication should be taken with food to decrease these effects. Side effects are most common during the initial weeks of therapy, are usually dose related, and often subside with continued treatment. Other aspects of SSRI therapy, including additional adverse effects and their management and drug–drug interactions, are discussed in Chapter 86, Depressive Disorders. Patients should be encouraged to report any problems to their treatment provider. The importance of adhering to prescribed therapies, both pharmacologic and behavioral, should also be stressed.

Case 83-9, Question 4: After 4 weeks, R.G. is taking fluvoxamine 200 mg/day (100 mg bid) and tolerating the medication well. She states that she has not noticed much improvement, and her Y-BOCS score is slightly decreased at 30. R.G. has been to the cognitive behavioral therapist twice, but is reluctant to return because the therapy was so stressful. R.G. requests to be switched to a more effective medication, and she also asks to be given some alprazolam to help calm her anxiety during behavioral therapy sessions. What is the best course of action for R.G. at this point?

Switching to another medication is not recommended at this point because not enough time has elapsed to assess fluvoxamine's efficacy. R.G. is tolerating fluvoxamine well and has shown a mild improvement, so this medication should be continued for at least another 4 weeks. Additional counseling information should be provided to R.G. to emphasize this fact. An increase in fluvoxamine dosage, up to 250 or 300 mg/day, may be considered after several more weeks because some patients may respond better to higher dosages. If R.G.'s symptoms continue to cause significant functional impairment after 10 to 12 weeks of higher dose fluvoxamine therapy, a change in treatment (eg, switching to another SSRI or augmentation therapy) will be indicated.

R.G. should be encouraged to continue CBT to optimize the chance for successful treatment. An anxiety response is integral to

the therapeutic benefits of behavioral therapies; because benzodiazepines can blunt this response, they may reduce their efficacy. Therefore, alprazolam should be avoided, and a temporary reduction in the intensity of behavioral therapy may be indicated instead.

Course and Duration of Therapy

Case 83-9, Question 5: After 5 months of treatment, taking fluvoxamine IR 150 mg bid (300 mg/day), R.G. is happy to report her OCD is much improved (Y-BOCS score of 11). She still has intermittent obsessions related to contamination and doubting, but they are less intense than before. She is usually able to resist urges to clean and wash excessively, and is using the stairs in their home with only mild discomfort. Her previous employer has agreed to let her return when she is ready, and she plans to do so soon. R.G.'s husband is extremely pleased with her progress. Their primary question at this visit is whether treatment can be discontinued now because R.G. is doing so well. What recommendations should be provided regarding the long-term course of therapy for R.G.?

This case illustrates a common outcome of OCD treatment, in which some symptoms persist (as evidenced by a Y-BOCS score of 11 = mild symptoms), but significant improvements in functioning occur. It is currently recommended that effective treatment for OCD be continued for at least 1 year after response to reduce the risk of relapse.[232,237] Therefore, continued drug treatment for at least 7 more months is indicated. Results from several studies suggest decreased medication doses (with SSRIs and clomipramine) during maintenance therapy are comparably as effective as full doses in preventing relapse.[232] If R.G. was experiencing any fluvoxamine-related problems, a slow decrease to the minimally effective dose (150 mg/day) during maintenance therapy might be recommended.

After a 1-year maintenance period, discontinuation of medication may be considered by carefully weighing the possible risks and benefits. When medication therapy for OCD is withdrawn, the dosage should be gradually decreased by ~25% every 1 to 2 months. Continuous monitoring for signs of relapse is required

during this period. Gradual discontinuation also lessens the chance of the withdrawal syndrome often occurring after abrupt discontinuation of SSRI or TCA therapy (see Chapter 86, Depressive Disorders). Long-term or even lifelong maintenance pharmacotherapy is usually recommended after two to four severe relapses or three to four less severe relapses.

Clomipramine Treatment

DOSING GUIDELINES

CASE 83-10

Question 1: K.T. is an 18-year-old Asian male who was diagnosed with OCD ~2 years ago and also suffers from moderate depression. His provider plans to start him on clomipramine therapy because he has failed previous trials with paroxetine and fluvoxamine.

Is clomipramine an appropriate choice of therapy for this patient? What recommendations can be made regarding initiation of clomipramine treatment?

Current guidelines recommend clomipramine be reserved for patients with OCD who fail at least two SSRI trials; therefore, its choice for this patient could be appropriate.[194] One precaution relevant to this case is that clomipramine, similar to other TCAs, is highly dangerous in overdose situations. Because K.T. is depressed, he should be evaluated carefully for any suicidal thoughts before starting clomipramine. If suicidal ideation is detected, it would be preferable to try another SSRI or venlafaxine XR. This case also illustrates the common comorbidity of depression with OCD. Fortunately, most drug treatment can be beneficial for both conditions. Nevertheless, the responses of depression and OCD to treatment are independent of one another, so depression may respond completely to a certain medication while OCD symptoms persist.[232]

Clomipramine is typically initiated at a low dosage of 25 mg/day administered with meals. Divided daily doses are sometimes used

initially to minimize side effects, but the total daily dose can be given at bedtime after dose titration given its average elimination half-life of 24 hours.[204,238] The clomipramine dosage should be increased to an initial target range of 150 to 200 mg/day during 2 to 4 weeks, guided by patient tolerability. The maximal recommended daily dosage of clomipramine is 250 mg/day because of the sharply increased risk of seizures (2.1%–3.4%) with higher dosages as compared with the risk with dosages <250 mg/day (0.24%–0.48%).[239] Longer duration of clomipramine therapy may also increase the risk of seizures. As such, use with caution in persons with a history of seizures, head injury, or other factors might lower the seizure threshold.

Side effects and monitoring guidelines

Case 83-10, Question 2: What guidelines should be recommended for monitoring the outcomes (both therapeutic and adverse) of clomipramine therapy?

Clomipramine is less well tolerated than are the SSRIs, and can cause a number of significant adverse effects, especially during the first few weeks of therapy. The most common side effects, reported in more than half of those taking clomipramine, include sedation, dry mouth, dizziness, and tremor.[239] Constipation, nausea, blurred vision, insomnia, and headache also occur frequently. K.T. should be advised that these usually subside with continued treatment.

Many patients receiving long-term clomipramine (and other TCA) therapy gain substantial amounts of weight. As with the SSRIs, sexual dysfunction can be a problem in both males and females. In males, clomipramine can cause ejaculation abnormalities, which can impair fertility. Patients taking clomipramine should also be counseled about the additive CNS depressant effects with alcohol and to be cautious about the possible sedative effects while driving or performing other potentially hazardous activities.

As with other TCAs, an ECG should be performed before starting clomipramine in individuals at risk for heart disease and in pediatric

patients. Elevations in liver enzymes have been observed frequently during the first 3 months of clomipramine treatment, and baseline liver function tests should also be obtained before initiating treatment. The liver enzyme changes are reversible on discontinuation of clomipramine therapy.

Clomipramine metabolism exhibits interpatient variability, and it is difficult to accurately predict the resulting clomipramine level from any given dose. The initial hepatic metabolism of tertiary TCAs such as clomipramine involves demethylation through various isozymes, including CYP1A2, CYP2C19, and CYP3A4.[238,240] Both the parent drug and the primary active metabolite (*N*-desmethylclomipramine or norclomipramine) then undergo CYP2D6-mediated hydroxylation. Therefore, the metabolism of clomipramine will be affected by combination with any agent inhibiting CYP1A2, CYP2C19, CYP3A4, or CYP2D6. Clinically significant drug interactions are possible with several of the SSRIs, including fluoxetine, paroxetine, fluvoxamine, and sertraline (see Chapter 86, Depressive Disorders). Monitoring plasma levels may be clinically useful in certain patients to guide dosing and minimize drug toxicity. No therapeutic range for plasma drug concentrations has been firmly established for clomipramine in OCD. However, a trough level of 230 to 450 or 500 ng/mL of total (clomipramine plus *N*-desmethylclomipramine) has been suggested as a therapeutic range. Based on the half-life of clomipramine and *N*-desmethylclomipramine, steady state may not be reached until ~2 weeks after dose adjustment. Although various studies have failed to find a correlation between clomipramine plasma level and clinical response, the ratio of clomipramine to *N*-desmethylclomipramine (typically 1:2 or 1:2.5) may be important.[241] Higher levels of *N*-desmethylclomipramine relative to clomipramine have been associated with poorer clinical response.[242,243]

Asian patients such as K.T. have been found to have significantly decreased clearance of clomipramine and higher clomipramine to *N*-desmethylclomipramine ratios compared with Whites, which may necessitate use of lower doses.[244] This is probably caused by a genetic polymorphism of either CYP2C19 or CYP2D6, which results in decreased metabolic capacity via these metabolic pathways in the

Asian population. Careful monitoring for possible signs of toxicity should accompany dose increases, and the clomipramine plasma level should be checked in all patients who show unexpected effects with usual doses. An opposite effect has been described in ultrarapid CYP2D6 metabolizers, in which unusually high clomipramine dosages may be required for therapeutic efficacy.

Augmentation

Case 83-10, Question 3: After 10 weeks of taking clomipramine 100 mg at bedtime, K.T. has shown partial response. He continues to experience mild-to-moderate anticholinergic side effects and frequent daytime fatigue. His total plasma clomipramine and *N*-desmethylclomipramine level taken 20 hours after his last dose is relatively high for the given dose at 453 ng/mL.[245] The provider decides to add another drug to augment treatment. Considering K.T.'s current medication regimen and the evidence supporting the different augmentation strategies, which drug would be the best choice for K.T.?

When adding an SSRI to a TCA, the potential for drug interactions should always be considered. Clomipramine is metabolized by CYP1A2, CYP3A4, CYP2C19, and CYP2D6.[238,240,246,247] The CYP2D6 pathway is particularly important because it is the rate-limiting metabolic pathway for elimination of both clomipramine and *N*-desmethylclomipramine. Fluvoxamine, paroxetine, and fluoxetine are all strong inhibitors of clomipramine metabolism, whereas sertraline is a weak-to-moderate inhibitor. Alternatively, escitalopram and citalopram would not be likely to cause a significant drug interaction, but evidence for escitalopram as an augmenting agent in combination with clomipramine is lacking.[248]

A combination less likely to be associated with a drug interaction is the combination of clomipramine and a second-generation antipsychotic; however, most trials combined antipsychotics with SSRIs rather than with clomipramine. Nonetheless, antipsychotic augmentation with agents demonstrating more consistent efficacy in well-designed trials (eg, risperidone and aripiprazole) is a reasonable strategy in patients requiring more improvement, as previously

discussed. Haloperidol would not be the optimal choice in K.T.'s case because it inhibits clomipramine metabolism, and as a first-generation antipsychotic, it is associated with numerous side effects. Aripiprazole may be preferred over risperidone given its lower risk of QTc prolongation, orthostasis, sedation, and weight gain/metabolic syndrome.[216]

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

ACOG Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol.* 2008;111:1001–1020. (90)

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. (1)

American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder*. American Psychiatric Association; 2007. (194)

Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British _Association for Psychopharmacology. *J Psychopharmacol.* 2014; 28(5): 403–439. (26)

Bellantuono C, Tofani S, Di Sciascio G, Santone G. Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. *Gen Hosp Psychiatry.* 2013;35(1):3–8. (92)

Davidson JR, Zhang W, Connor KM, et al. A psychopharmacological treatment algorithm for generalised anxiety disorder (GAD). *J Psychopharmacol.* 2010;24:3–26. (78)

Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14(suppl 1):S1. (21)

Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the US. *Int J Methods Psychiatr Res* 2012;21:169–184. (15)

Muller JE, Koen L, Stein DJ, et al. Anxiety and medical disorders. *Curr Psychiatry Rep*. 2005;7:245–251. (133)

National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care. NICE Clinical Guideline 113. Accessed July 6, 2015. http://www.nice.org.uk/CG113 (25)

National Institute for Health and Care Excellence. Obsessive-compulsive disorder and body dysmorphic disorder: treatment. NICE Clinical Guideline 31. Accessed August 11, 2015. http://www.nice.org.uk/cg31 (208)

National Institute for Health and Care Excellence. Antenatal and postnatal mental health: clinical management and service guidance. Published December 17, 2014. Accessed July 6, 2015. http://www.nice.org.uk/guidance/cg192 (94)

Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. *J Clin Psychiatry*. 2010;71:839–854. (46)

Stein DJ, Baldwin DS, Bandelow B, et al. A 2010 evidence-based algorithm for the pharmacotherapy of social anxiety disorder. *Curr Psychiatry Rep*. 2010;12:471–477. (145)

Work Group on Panic Disorder; Stein MB, Goin MK, Pollack MH, et al. *Treatment of Patients With Panic Disorder*. 2nd ed. Accessed August 10, 2015. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf (121)

COMPLETE REFERENCES CHAPTER 83 ANXIETY DISORDERS

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
2. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depress Anxiety*. 2000;12(suppl 1):2–19.
3. Garakani A, Mathew SJ, Charney DS. Neurobiology of anxiety disorders and implications for treatment. *Mt Sinai J Med*. 2006;73(7):941–949.
4. Gunnar M, Quevedo K. The neurobiology of stress and development. *Annu Rev Psychol*. 2007;58:145–173.

5. Martin EI, Ressler KJ, Binder E, Nemeroff CB. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. *Psychiatr Clin North Am*. 2009;32:549–575.
6. Martin EI, Ressler KJ, Binder E, Nemeroff CB. The neurobiology of anxiety disorders: brain, imaging, genetics, and psychoneuroimmunology. *Clin Lab Med*. 2010;30:865–891.
7. Mathew SJ, Price RB, Charney DS. Recent advances in the neurobiology of anxiety: implications for novel therapeutics. *Am J Med Genet C Semin Med Genet*. 2008;148C:89–98.
8. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:617–627.
9. Lépine JP. The epidemiology of anxiety disorders: prevalence and societal costs. *J Clin Psychiatry*. 2002;63(suppl 14):4–8.
10. Wise MG, Griffies WS. A combined treatment approach to anxiety in the medically ill. *J Clin Psychiatry*. 1995;56(suppl 2):14–19.
11. Moller HJ. Anxiety associated with comorbid depression. *J Clin Psychiatry*. 2002;63(suppl 14):22–26.
12. Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. *Depress Anxiety*. 2000;12:69–76.
13. Weisberg RB, Dyck I, Culpepper L, Keller MB. Psychiatric treatment in primary care patients with anxiety disorders: a comparison of care received from primary care providers and psychiatrists [published correction appears in *Am J Psychiatry*. 2007;164:833]. *Am J Psychiatry*. 2007;164:276–282.
14. The Medical Letter. Drugs that may cause psychiatric symptoms. *Med Lett Drugs Ther*. 2002;44:59–62.
15. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the US. *Int J Methods Psychiatr Res*. 2012;21:169–184.
16. Asnaani A, Richey JA, Dimaite R, Hinton DE, Hofmann SG. A cross-ethnic comparison of lifetime prevalence rates of anxiety disorders. *J Nerv Ment Dis*. 2010;198:551–555.
17. Cougle JR, Keough ME, Riccardi CJ, Sachs-Ericsson N. Anxiety disorders and suicidality in the National Comorbidity Survey—Replication. *J Psychiatr Res*. 2009;43:825–829.
18. Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry*. 2001;158:1568–1578.
19. Stein MB. Neurobiology of generalized anxiety disorder. *J Clin Psychiatry*. 2009;70(suppl 2):15–19.
20. Borkovec TD, Ruscio AM. Psychotherapy for generalized anxiety disorder. *J Clin Psychiatry*. 2001;62(suppl 11):37–42.

21. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14(suppl 1):S1.
22. Cuijpers P, Sijbrandij M, Koole S, Huibers M, Berking M, Andersson G. Psychological treatment of generalized anxiety disorder: a meta-analysis. *Clin Psychol Rev*. 2014;34:130–140.
23. Brawman-Mintzer O. Pharmacologic treatment of generalized anxiety disorder. *Psychiatr Clin North Am*. 2001;24:119–137.
24. Mihic S, Harris R. Hypnotics and sedatives. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. McGraw-Hill; 2011. Accessed June 24, 2015. https://accessmedicine.mhmedical.com/content.aspx?bookId=2189&sectionId=169518968
25. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care. NICE Clinical Guideline 113. Accessed July 6, 2015. http://www.nice.org.uk/CG113
26. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403–439.
27. Brambilla P, Cipriani A, Hotopf M, Barbui C. Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. *Pharmacopsychiatry*. 2005;38(2):69–77.
28. Tourian KA, Jiang Q, Ninan PT. Analysis of the effect of desvenlafaxine on anxiety symptoms associated with major depressive disorder: pooled data from 9 short-term, double-blind, placebo-controlled trials. *CNS Spectr*. 2010;15:187–193.
29. Pae CU, Marks DM, Shah M, et al. Milnacipran: beyond a role of antidepressant. *Clin Neuropharmacol*. 2009;32:355–363.
30. Asnis GM, Henderson MA. Levomilnacipran for the treatment of major depressive disorder: a review. *Neuropsychiatr Dis Treat*. 2015;11:125–135.
31. Rickels K, Etemad B, Rynn MA, Lohoff FW, Mandos LA, Gallop R. Remission of generalized anxiety disorder after 6 months of open-label treatment with venlafaxine XR. *Psychother Psychosom*. 2013;82(6):363–371.
32. Khan AY, Macaluso M. Duloxetine for the treatment of generalized anxiety disorder: a review. *Neuropsychiatr Dis Treat*. 2009;5:23–31.
33. Hartford J, Kornstein S, Liebowitz M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol*. 2007;22:167–174.
34. Koponen H, Allgulander C, Erickson J, et al. Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care

physicians. *Prim Care Companion J Clin Psychiatry*. 2007;9:100–107.
35. Rynn M, Russell J, Erickson J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety*. 2008;25:182–189.
36. Davidson JR, Wittchen HU, Llorca PM, et al. Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2008;18:673–681.
37. Allgulander C, Nutt D, Detke M, et al. A non-inferiority comparison of duloxetine and venlafaxine in the treatment of adult patients with generalized anxiety disorder. *J Psychopharmacol*. 2008;22(4):417–425.
38. Fawcett J, Barkin RL. A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. *J Clin Psychiatry*. 1998;59:123–127.
39. Gambi F, De Berardis D, Campanella D, et al. Mirtazapine treatment of generalized anxiety disorder: a fixed dose, open label study. *J Psychopharmacol*. 2005;19:483–487.
40. Gommoll C, Durgam S, Mathews M, et al. A double-blind, randomized, placebo-controlled, fixed-dose phase III study of vilazodone in patients with generalized anxiety disorder. *Depress Anxiety*. 2015;32:451–459.
41. Mahableshwarkara AR, Jacobsen PL, Serenko M, Chen Y. A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10 mg in acute treatment of adults with generalized anxiety disorder. *Hum Psychopharmacol*. 2014;29(1):64–72.
42. Bidzan L, Mahableshwarkar AR, Jacobsen P, Yan M, Sheehan DV. Vortioxetine (Lu AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. *Eur Neuropsychopharmacol*. 2012;22(12):847–857.
43. Baldwin DS, Loft H, Florea I. Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. *Int Clin Psychopharmacol*. 2012;27(4):197–207.
44. Rothschild AJ, Mahableshwarkar AR, Jacobsen P, Yan M, Sheehan DV. Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States. *Eur Neuropsychopharmacol.* 2012;22(12):858–866.
45. Christensen MC, Loft H, Florea I, McIntyre RS. Efficacy of vortioxetine in working patients with generalized anxiety disorder. *CNS Spectr*. 2019;24:249–257.
46. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. *J Clin Psychiatry*. 2010;71:839–854.
47. Stocchi F, Nordera G, Jokinen RH, et al. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry*. 2003;64:250–258.

48. Montgomery SA, Mahé V, Haudiquet V, Hackett D. Effectiveness of venlafaxine, extended release formulation, in the short-term and long-term treatment of generalized anxiety disorder: results of a survival analysis. *J Clin Psychopharmacol*. 2002;22:561–567.
49. Mahmood I, Sahajwalla C. Clinical pharmacokinetics and pharmacodynamics of buspirone, an anxiolytic drug. *Clin Pharmacokinet*. 1999;36:277–287.
50. Apter JT, Allen LA. Buspirone: future directions. *J Clin Psychopharmacol*. 1999;19:86–93.
51. Lydiard RB, Rickels K, Herman B, Feltner DE. Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. *Int J Neuropsychopharmacol*. 2010;13:229–241.
52. Rickels K, Shiovitz TM, Ramey TS, Weaver JJ, Knapp LE, Miceli JJ. Adjunctive therapy with pregabalin in generalized anxiety disorder patients with partial response to SSRI or SNRI treatment. *Int Clin Psychopharmacol*. 2012;27:142–150.
53. Frampton JE. Pregabalin: a review of its use in adults with generalized anxiety disorder. *CNS Drugs*. 2014;28:835–854.
54. Feltner D, Wittchen HU, Kavoussi R, Brock J, Baldinetti F, Pande AC. Long-term efficacy of pregabalin in generalized anxiety disorder. *Int Clin Psychopharmacol*. 2008;23:18–28.
55. Montgomery S, Emir B, Haswell H, Prieto R. Long-term treatment of anxiety disorders with pregabalin: a 1 year open-label study of safety and tolerability. *Curr Med Res Opin*. 2013;29(10):1223–1230.
56. Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. *Cochrane Database Syst Rev*. 2010;(12):CD006815.
57. Hershenberg R, Gros DF, Brawman-Mintzer O. Role of atypical antipsychotics in the treatment of generalized anxiety disorder. *CNS Drugs*. 2014;28:519–533.
58. Ballenger JC. Treatment of anxiety disorders to remission. *J Clin Psychiatry*. 2001;62(suppl 12):5–9.
59. Trevor AJ. Sedative-hypnotic drugs. In: Katzung BG, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 13th ed. McGraw-Hill; 2015. Accessed March 24, 2022. https://accesspharmacy.mhmedical.com/content.aspx?sectionid=175218773&bookid=2249
60. Klein E. The role of extended-release benzodiazepines in the treatment of anxiety: a risk-benefit evaluation with a focus on extended-release alprazolam. *J Clin Psychiatry*. 2002;63(suppl 14):27–33.
61. Liston HL, Markowitz JS, DeVane CL. Drug glucuronidation in clinical psychopharmacology. *J Clin Psychopharmacol*. 2001;21:500–515.
62. Gladsjo JA, Rapaport MH, McKinney R, et al. Absence of neuropsychologic deficits in patients receiving long-term treatment with alprazolam-XR for panic disorder. *J Clin Psychopharmacol*. 2001;21:131–138.

63. Zhong G, Wang Y, Zhang Y, Zhao Y. Association between benzodiazepine use and dementia: a meta-analysis. *PLoS One*. 2015;10(5):e0127836.
64. Billoti de Gage S, Pariente A, Bégaud B. Is there really a link between benzodiazepine use and the risk of dementia? *Expert Opin Drug Saf*. 2015;14(5):733–747.
65. Lauderdale SA, Sheikh JI. Anxiety disorders in older adults. *Clin Geriatr Med*. 2003;19:721–741.
66. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694. doi:10.1111/jgs.15767
67. Meuleners LB, Duke J, Lee AH, Palamara P, Hildebrand J, Ng JQ. Psychoactive medications and crash involvement requiring hospitalization for older drivers: a population-based study. *J Am Geriatr Soc*. 2011;59(9):1575–1580.
68. Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. *Drugs Aging*. 2012;29(5):359–376.
69. Ensrud KE, Blackwell TL, Mangione CM, et al. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc*. 2002;50:1629–1637.
70. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepines regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. *Am J Psychiatry*. 2001;158:892–898.
71. U.S. Food & Drug Administration. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). Accessed September 20, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin
72. Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: a medical examiner chart review. *J Clin Psychiatry*. 2010;71(4):491–496.
73. Rothschild AJ, Shindul-Rothschild JA, Viguera A, Murray M, Brewster S. Comparison of the frequency of behavioral disinhibition on alprazolam, clonazepam, or no benzodiazepine in hospitalized psychiatric patients. *J Clin Psychopharmacol*. 2000;20:7–11.
74. Mancuso CE, Tanzi MG, Gabay M. Paradoxical reactions to benzodiazepines: literature review and treatment options. *Pharmacotherapy*. 2004;24(9):1177–1185.
75. Posternak MA, Mueller TI. Assessing the risks and benefits of benzodiazepines for anxiety disorders in patients with a history of substance abuse or dependence. *Am J Addict*. 2001;10:48–68.

76. Rickels K, DeMartinis N, Rynn M, Mandos L. Pharmacologic strategies for discontinuing benzodiazepine treatment. *J Clin Psychopharmacol*. 1999;19(suppl 2):12S–16S.
77. Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs*. 2009;23:19–34.
78. Davidson JR, Zhang W, Connor KM, et al. A psychopharmacological treatment algorithm for generalized anxiety disorder (GAD). *J Psychopharm*. 2010;24(1):3–26.
79. Donovan MR, Glue P, Kolluri S, Emir B. Comparative efficacy of antidepressants in preventing relapse in anxiety disorders—a meta-analysis. *J Affect Disord*. 2010;123(1–3):9–16.
80. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med*. 2011;155:772–785.
81. Montejo-González AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther.* 1997;23:176–194.
82. Kasper S, Herman B, Nivoli G, et al. Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind, placebo-controlled 8-week trial. *Int Clin Psychopharmacol*. 2009;24:87–96.
83. Baldwin DS, Ajel K, Masdrakis VG, Nowak M, Rafiq R. Pregabalin for the treatment of generalized anxiety disorder: an update. *Neuropsychiatr Dis Treat*. 2013;9:883–892.
84. Askgaard G, Hallas J, Fink-Jensen A, Molander AC, Madsen KG, Pottegård A. Phenobarbital compared to benzodiazepines in alcohol withdrawal treatment: a register-based cohort study of subsequent benzodiazepines use, alcohol recidivism, and mortality. *Drug Alcohol Depend*. 2016;161:258–264.
85. Tanaka E. Clinically significant pharmacokinetic drug interactions with benzodiazepines. *J Clin Pharm Ther*. 1999;24:347–355.
86. Yasui N, Kondo T, Otani K, et al. Effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of alprazolam. *Psychopharmacology (Berl)*. 1998;139:269–273.
87. Pigott TA. Gender differences in the epidemiology and treatment of anxiety disorders. *J Clin Psychiatry*. 1999;60(suppl 18):4–15.
88. Stoehr GP, Kroboth PD, Juhl RP, Wender DB, Phillips JP, Smith RB. Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther*. 1984;36:683–690.
89. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet*. 1999;36:425–438.
90. ACOG Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin: clinical management guidelines for obstetrician-gynecologists number 92,

April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol*. 2008;111:1001–1020.

91. Wikner BN, Stiller CO, Bergman U, Asker C, Källén B. Use of benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. *Pharmacoepidemiol Drug Saf*. 2007;16:1203–1210.
92. Bellantuono C, Tofani S, Di Sciascio G, Santone G. Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. *Gen Hosp Psychiatry*. 2013;35(1):3–8.
93. Reis M1, Källén B. Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects. A register study. *BMJ Open*. 2013;3(2):e002166.
94. National Institute for Health and Care Excellence. Antenatal and postnatal mental health: clinical management and service guidance. Published December 17, 2014. Accessed July 6, 2015. http://www.nice.org.uk/guidance/cg192
95. Iqbal MM, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatr Serv*. 2002;53(1):39–49.
96. O'Hara MW, Wisner KL. Perinatal mental illness: definition, description, and aetiology. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(1):3–12.
97. Kelly LE, Poon S, Madadi P, Koren G. Neonatal benzodiazepine exposure during breastfeeding. *J Pediatr*. 2012;161(3):448–451.
98. LactMed: Drugs and lactation database. Accessed July 6, 2015. https://www.ncbi.nlm.nih.gov/books/NBK501922/
99. Weinbroun AA, Flaishon R, Sorkine P, Szold O, Rudick V. A risk-benefit assessment of flumazenil in the management of benzodiazepines overdose. *Drug Saf*. 1997;17:181–196.
100. Mathieu-Nolf M, Babé MA, Coquelle-Couplet V, Billaut C, Nisse P, Mathieu D. Flumazenil use in an emergency department: a survey. *J Toxicol Clin Toxicol*. 2001;39:15–20.
101. Penninga EI, Graudal N, Ladekarl MB, Jürgens G. Adverse events associated with flumazenil treatment for the management of suspected benzodiazepine intoxication—a systematic review with meta-analyses of randomised trials. *Basic Clin Pharmacol Toxicol*. 2016;118(1):37–44. doi:10.1111/bcpt.12434
102. Herman RJ, Wilkinson GR. Disposition of diazepam in young and elderly subjects after acute and chronic dosing. *Br J Clin Pharmacol*. 1996;42:147–155.
103. Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Harmatz JS, Shader RI. Single-dose pharmacokinetics and pharmacodynamics of alprazolam in

elderly and young subjects. *J Clin Pharmacol*. 1998;38:14–21.
104. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency: minimising renal and extrarenal toxicity. *Drug Saf*. 1997;16:205–231.
105. Wan J, Xia H, He N, Lu YQ, Zhou HH. The elimination of diazepam in Chinese subjects is dependent on the mephenytoin oxidation phenotype. *Br J Clin Pharmacol*. 1996;42:471–474.
106. Yonkers dKA, Kando JC, Cole JO, Blumenthal S. Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. *Am J Psychiatry*. 1992;149:587–595.
107. Chetty M, Mattison D, Rostami-Hodjegan A. Sex differences in the clearance of CYP3A4 substrates: exploring possible reasons for the substrate dependency and lack of consensus. *Curr Drug Metab*. 2012;13(6):778–786.
108. Kurose K, Sugiyama E, Saito Y. Population differences in major functional polymorphisms of pharmacokinetics/pharmacodynamics-related genes in Eastern Asians and Europeans: implications in the clinical trials for novel drug development. *Drug Metab Pharmacokinet*. 2012;27(1):9–54.
109. Pecknold JC. A risk-benefit assessment of buspirone in the treatment of anxiety disorders. *Drug Saf*. 1997;16:118–132.
110. Dimitriou EC, Parashos AJ, Giouzepas JS. Buspirone vs. alprazolam: a double-blind comparative study of their efficacy, adverse effects and withdrawal symptoms. *Drug Invest*. 1992;4:316–321.
111. Delle Chiaie R, Pancheri P, Casacchia M, Stratta P, Kotzalidis GD, Zibellini M. Assessment of the efficacy of buspirone in patients affected by generalized anxiety disorder, shifting to buspirone from prior treatment with lorazepam: a placebo-controlled, double-blind study. *J Clin Psychopharmacol*. 1995;15:12–19.
112. Sramek JJ, Hong WW, Hamid S, Nape B. Meta-analysis of the safety and tolerability of two dose regimens of buspirone in patients with persistent anxiety. *Depress Anxiety*. 1999;9:131–134.
113. Grant BF, Goldstein RB, Saha TD, et al. Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. *JAMA Psychiatry*. 2015;72(8):757–766.
114. Roy-Byrne PP, Craske MG, Stein MB. Panic disorder. *Lancet*. 2006;368:1023–1032.
115. Roy-Byrne PP, Stein MB, Russo J, et al. Panic disorder in the primary care setting: comorbidity, disability, service utilization, and treatment. *J Clin Psychiatry*. 1999;60:492–500.
116. Andersch S, Hetta J. A 15-year follow-up study of patients with panic disorder. *Eur J Psychiatry*. 2003;18:401–408.
117. Katon WJ. Clinical practice. Panic disorder. *N Engl J Med*. 2006;354(22):2360–2367.
118. Cousins MS, Roberts DC, de Wit H. GABA(B) receptor agonists for the treatment of drug addiction: a review of recent findings. *Drug Alcohol*

Depend. 2002;65:209–220.
119. Hasler G, Nugent AC, Carlson PJ, Carson RE, Geraci M, Drevets WC. Altered cerebral Y-aminobutyric acid type-A-benzodiazepine receptor binding in panic disorder determined by [11C]flumazenil positron emission tomography. *Arch Gen Psychiatry*. 2008;65:1166–1175.
120. Perna G, Bertani A, Caldirola D, Gabriele A, Cocchi S, Bellodi L. Antipanic drug modulation of 35% CO_2 hyperreactivity and short-term treatment outcome. *J Clin Psychopharmacol*. 2002;22:300–308.
121. Work Group on Panic Disorder; Stein MB, Goin MK, Pollack MH, et al. *Treatment of Patients with Panic Disorder*. 2nd ed. Accessed August 10, 2015. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf
122. Bandelow B, Zohar J, Hollander E, et al. World federation of societies of biological psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders—first revision. *World J Biol Psychiatry*. 2008;9(4):248–312.
123. Simon NM, Kaufman RE, Hoge EA, et al. Open-label support for duloxetine for the treatment of panic disorder. *CNS Neurosci Ther*. 2009;15(1):19–23.
124. Zamorski MA, Albucher RC. What to do when SSRIs fail: eight strategies for optimizing treatment of panic disorder. *Am Fam Physician*. 2002;66:1477–1484.
125. Lydiard RB. The role of GABA in anxiety disorders. *J Clin Psychiatry*. 2003;64(suppl 3):21–27.
126. Lepola U, Arató M, Zhu Y, Austin C. Sertraline versus imipramine treatment of comorbid panic disorder and major depressive disorder. *J Clin Psychiatry*. 2003;64:654–662.
127. Caillard V, Rouillon F, Viel JF, Markabi S. Comparative effects of low and high doses of clomipramine and placebo in panic disorder: a double-blind controlled study. French University Antidepressant Group. *Acta Psychiatr Scand*. 1999;99:51–58.
128. Shah A, Northcutt J. An open-label, flexible dose adaptive study evaluating the efficacy of vortioxetine in subjects with panic disorder. *Ann Gen Psychiatry*. 2018;17:19.
129. van Apeldoorn FJ, van Hout WJ, Mersch PP, et al. Is a combined therapy more effective than either CBT or SSRI alone? Results of a multicenter trial on panic disorder with or without agoraphobia. *Acta Psychiatr Scand*. 2008;117:260–270.
130. Kampman M, Keijsers GP, Hoogduin CA, Hendriks GJ. A randomized, double-blind, placebo-controlled study of the effects of adjunctive paroxetine in panic disorder patients unsuccessfully treated with cognitive-behavioral therapy alone. *J Clin Psychiatry*. 2002;63:772–777.

131. Dannon PN, Lowengrub K, Amiaz R, Grunhaus L, Kotler M. Comorbid cannabis use and panic disorder: short term and long term follow-up study. *Hum Psychopharmacol*. 2004;19:97–101.
132. Bricker JB, Russo J, Stein MB, et al. Does occasional cannabis use impact anxiety and depression treatment outcomes?: results from a randomized effectiveness trial. *Depress Anxiety*. 2007;24:392–398.
133. Muller JE, Koen L, Stein DJ, et al. Anxiety and medical disorders. *Curr Psychiatry Rep*. 2005;7:245–251.
134. Bruce SE, Vasile RG, Goisman RM, et al. Are benzodiazepines still the medication of choice for patients with panic disorder with or without agoraphobia? *Am J Psychiatry*. 2003;160:1432–1438.
135. Ruscio AM, Brown TA, Chiu WT, Sareen J, Stein MB, Kessler RC. Social fears and social phobia in the USA: results from the national comorbidity survey replication. *Psychol Med*. 2008;38:15–28.
136. Pollack MH. Comorbidity, neurobiology, and pharmacotherapy of social anxiety disorder. *J Clin Psychiatry*. 2001;62(suppl 12):24–29.
137. Stein MB, Kean YM. Disability and quality of life in social phobia: epidemiologic findings [published correction appears in *Am J Psychiatry*. 2000;157:2075]. *Am J Psychiatry*. 2000;157:1606–1613.
138. Arbelle S, Benjamin J, Golin M, Kremer I, Belmaker RH, Ebstein RP. Relation of shyness in grade school children to the genotype for the long form of the serotonin transporter promoter region polymorphism. *Am J Psychiatry*. 2003;160:671–676.
139. Mathew SJ, Coplan JD, Gorman JM. Neurobiological mechanisms of social anxiety disorder. *Am J Psychiatry*. 2001;158:1558–1567.
140. Schneier FR, Liebowitz MR, Abi-Dargham A, Zea-Ponce Y, Lin SH, Laruelle M. Low dopamine D2 receptor binding potential in social phobia. *Am J Psychiatry*. 2000;157:457–459.
141. Freitas-Ferrari MC, Hallak JE, Trzesniak C, et al. Neuroimaging in social anxiety disorder: a systematic review of the literature. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:565–580.
142. Iza M, Olfson M, Vermes D, Hoffer M, Wang S, Blanco C. Probability and predictors of first treatment contact for anxiety disorders in the United States: analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry*. 2013;74(11):1093–1100.
143. Davidson JRT. Pharmacotherapy of social anxiety disorder: what does the evidence tell us? *J Clin Psychiatry*. 2006;67(suppl 12):20–26.
144. Simon NM, Worthington JJ, Moshier SJ, et al. Duloxetine for the treatment of generalized social anxiety disorder: a preliminary randomized trial of increased dose to optimize response. *CNS Spectr*. 2010;15:367–373.
145. Stein DJ, Baldwin DS, Bandelow B, et al. A 2010 evidence-based algorithm for the pharmacotherapy of social anxiety disorder. *Curr Psychiatry Rep*. 2010;12:471–477.

146. Stein DJ, Stein MB, Pitts CD, Kumar R, Hunter B. Predictors of response to pharmacotherapy in social anxiety disorder: an analysis of 3 placebo-controlled paroxetine trials. *J Clin Psychiatry*. 2002;63:152–155.
147. Pollack MH, Van Ameringen M, Simon NM, et al. A double-blind randomized controlled trial of augmentation and switch strategies for refractory social anxiety disorder. *Am J Psychiatry*. 2014;171(1):44–53.
148. Feltner DE, Liu-Dumaw M, Schweizer E, Bielski R. Efficacy of pregabalin in generalized social anxiety disorder: results of a double-blind, placebo-controlled, fixed-dose study. *Int Clin Psychopharmacol*. 2011;26:213–220.
149. Fedoroff IC, Taylor S. Psychological and pharmacological treatments of social phobia: a meta-analysis. *J Clin Psychopharmacol*. 2001;21:311–324.
150. Shalev AY. Posttraumatic stress disorder and stress-related disorders. *Psychiatr Clin North Am*. 2009;32:687–704.
151. Breslau N. The epidemiology of posttraumatic stress disorder: what is the extent of the problem? *J Clin Psychiatry*. 2001;62(suppl 17):16–22.
152. Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry*. 2000;61(suppl 5):60–66.
153. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder*. American Psychiatric Association; 2004.
154. Breslau N. Outcomes of posttraumatic stress disorder. *J Clin Psychiatry*. 2001;62(suppl 17):55–59.
155. Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. *Am J Psychiatry*. 2001;158:1184–1190.
156. Krysinska K, Lester D. Post-traumatic stress disorder and suicide risk: a systematic review. *Arch Suicide Res*. 2010;14(1):1–23.
157. Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. *Am Heart J*. 2013;166(5):806–814.
158. Tran JK, Dunckel G, Teng EJ. Sexual dysfunction in veterans with post-traumatic stress disorder. *J Sex Med.* 2015;12(4):847–855.
159. Motzkin JC, Koenigs MR. Post-traumatic stress disorder and traumatic brain injury. *Handb Clin Neurol*. 2015;128:633–648.
160. Davidson JRT. Recognition and treatment of posttraumatic stress disorder. *JAMA*. 2001;286:584–588.
161. Nutt DJ, Malizia AL. Structural and functional brain changes in posttraumatic stress disorder. *J Clin Psychiatry*. 2004;65(suppl 1):11–17.
162. Koob GF. Corticotrophin-releasing factor, norepinephrine, and stress. *Biol Psychiatry*. 1999;46:1167–1180.
163. Southwick SM, Bremner JD, Rasmusson A, Morgan CA 3rd, Arnsten A, Charney DS. Role of norepinephrine in the pathophysiology and treatment of

posttraumatic stress disorder. *Biol Psychiatry*. 1999;46:1192–1204.
164. Friedman MJ. Future pharmacotherapy for post-traumatic stress disorder: prevention and treatment. *Psychiatr Clin North Am*. 2002;25:427–441.
165. Ravindran LN, Stein MB. Pharmacotherapy of PTSD: premises, principles, and priorities. *Brain Res*. 2009;1293:24–39.
166. Thomaes K, Dorrepaal E, Draijer N, Jansma EP, Veltman DJ, van Balkom AJ. Can pharmacological and psychological treatment change brain structure and function in PTSD? A systematic review. *J Psychiatr Res*. 2014;50:1–15.
167. Voisey J, Young RM, Lawford BR, Morris CP. Progress towards understanding the genetics of posttraumatic stress disorder. *J Anxiety Disord*. 2014;28(8):873–883.
168. National Institute for Clinical Excellence. *Post-Traumatic Stress Disorder (PTSD): The Management of PTSD in Adults and Children in Primary and Secondary Care*. National Clinical Practice Guideline Number 26. National Institute for Clinical Excellence; 2005.
169. *VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder—Clinician Summary*. Electronic Version. Veterans Health Administration and Department of Defense; 2017.
170. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*. 2006;2006(1):CD002795.
171. Ipser JC, Stein DJ. Evidence-based pharmacotherapy of post-traumatic stress disorder (PTSD). *Int J Neuropsychopharmacol*. 2012;15(6):825–840.
172. Robert S, Hamner MB, Ulmer HG, Lorberbaum JP, Durkalski VL. Open-label trial of escitalopram in the treatment of posttraumatic stress disorder. *J Clin Psychiatry*. 2006;67:1522–1526.
173. Walderhaug E, Kasserman S, Aikins D, Vojvoda D, Nishimura C, Neumeister A. Effects of duloxetine in treatment-refractory men with posttraumatic stress disorder. *Pharmacopsychiatry.* 2010;43:45–49.
174. Villarreal G, Cañive JM, Calais LA, Toney G, Smith AK. Duloxetine in military posttraumatic stress disorder. *Psychopharmacol Bull*. 2010;43(3):26–34.
175. Asnis GM, Kohn SR, Henderson M, Brown NL. SSRIs versus non-SSRIs in post-traumatic stress disorder: an update with recommendations. *Drugs*. 2004;64:383–404.
176. Schwetz BA. From the Food and Drug Administration. *JAMA*. 2002;287(9):1103.
177. Warner CH, Warner CM, Appenzeller GN, Hoge CW. Identifying and managing posttraumatic stress disorder. *Am Fam Physician*. 2013;88(12):827–834.
178. Han C, Pae CU, Wang SM, et al. The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder. *J Psychiatr Res*. 2014;56:72–81.
179. Argolo FC, Cavalcanti-Ribeiro P, Netto LR, Quarantini LC. Prevention of posttraumatic stress disorder with propranolol: a meta-analytic review. *J*

Psychosom Res. 2015;79(2):89–93.
180. Amos T, Stein DJ, Ipser JC. Pharmacologic interventions for preventing post-traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*. 2014;7:CD006239.
181. Davidson JR. Long-term treatment and prevention of posttraumatic stress disorder. *J Clin Psychiatry*. 2004;65(suppl 1):44–48.
182. Guina J, Rossetter SR, DeRHODES BJ, Nahhas RW, Welton RS. Benzodiazepines for PTSD: a systematic review and meta-analysis. *J Psychiatr Pract*. 2015;21(4):281–303.
183. Boehnlein JK, Kinzie JD. Pharmacologic reduction of CNS noradrenergic activity in PTSD: the case for clonidine and prazosin. *J Psychiatr Pract*. 2007;13:72–78.
184. Raskind MA, Peskind ER, Chow B, et al. Trial of prazosin for post-traumatic stress disorder in military veterans. *N Engl J Med*. 2018;378(6):507–517.
185. Bajor LA, Ticlea AN, Osser DN. The Psychopharmacology Algorithm Project at the Harvard South Shore Program: an update on posttraumatic stress disorder. *Harv Rev Psychiatry*. 2011;19(5):240–258.
186. Hamblen JL, Norman SB, Sonis JH, et al. A guide to guidelines for the treatment of posttraumatic stress disorder in adults: an update. *Psychotherapy (Chic).* 2019;56(3):359–373.
187. Motraghi TE, Seim RW, Meyer EC, Morissette SB. Virtual reality exposure therapy for the treatment of posttraumatic stress disorder: a methodological review using CONSORT guidelines. *J Clin Psychol*. 2014;70(3):197–208.
188. Karsen EF, Watts BV, Holtzheimer PE. Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder. *Brain Stimul*. 2014;7(2):151–157.
189. Hetrick SE, Purcell R, Garner B, Parslow R. Combined pharmacotherapy and psychological therapies for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*. 2010;(7):CD007316.
190. Koola MM, Varghese SP, Fawcett JA. High-dose prazosin for the treatment of post-traumatic stress disorder. *Ther Adv Psychopharmacol*. 2014;4(1):43–47.
191. Aurora RN, Zak RS, Auerbach SH, et al. Standards of Practice Committee; American Academy of Sleep Medicine. Best practice guide for the treatment of nightmare disorder in adults. *J Clin Sleep Med*. 2010;6(4):389–401.
192. Pauls DL, Abramovitch A, Rauch SL, Geller DA. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. *Nat Rev Neurosci*. 2014;15(6):410–424.
193. Altshuler LL, Hendrick V, Cohen LS. Course of mood and anxiety disorders during pregnancy and the postpartum period. *J Clin Psychiatry*. 1998;59(suppl 2):29–33.
194. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Obsessive-Compulsive Disorder.* American Psychiatric Association; 2007.

195. Hollander E. Obsessive-compulsive disorder: the hidden epidemic. *J Clin Psychiatry*. 1997;58(suppl 12):3–6.
196. Stein DJ. Obsessive-compulsive disorder. *Lancet*. 2002;360:397–405.
197. Rosario-Campos MC, Leckman JF, Mercadante MT, et al. Adults with early-onset obsessive-compulsive disorder. *Am J Psychiatry*. 2001;158:1899–1903.
198. Phillips KA. The obsessive-compulsive spectrums. *Psychiatr Clin North Am*. 2002;25:791–809.
199. Nestadt G, Samuels J, Riddle M, et al. A family study of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57:358–363.
200. Melke J. Serotonin transporter gene polymorphisms and mental health. *Curr Opin Psychiatry*. 2003;16:215–220.
201. Pato MT, Pato CN, Pauls DL. Recent findings in the genetics of OCD. *J Clin Psychiatry*. 2002;63(suppl 6):30–33.
202. Leckman JF, Kim Y-S. A primary candidate gene for obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2006;63:717–720.
203. da Rocha FF, Correa H, Teixeira AL. Obsessive-compulsive disorder and immunology: a review. *Neuropsychopharmacol Biol Psychiatry*. 2008;32:1139–1146.
204. Blier P, Habib R, Flament MF. Pharmacotherapies in the management of obsessive-compulsive disorder. *Can J Psychiatry*. 2006;51:417–430.
205. U.S. Food & Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. Accessed September 20, 2020. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
206. Dell'Osso B, Altamura AC, Mundo E, Marazziti D, Hollander E. Diagnosis and treatment of obsessive-compulsive disorder and related disorders. *Int J Clin Pract*. 2007;61:98–104.
207. Dell'Osso B, Buoli M, Baldwin DS, Altamura AC. Serotonin norepinephrine reuptake inhibitors (SNRIs) in anxiety disorders: a comprehensive review of their clinical efficacy. *Hum Psychopharmacol*. 2010;25:17–29.
208. National Institute for Health and Care Excellence. Obsessive-compulsive disorder and body dysmorphic disorder: treatment. NICE Clinical Guideline 31. Accessed August 11, 2015. http://www.nice.org.uk/cg31
209. Jermain DM, Crismon ML Pharmacotherapy of obsessive-compulsive disorder. *Pharmacotherapy*. 1990;10(3):175–198.
210. Ackerman DL, Greenland S. Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2002;22:309–317.
211. Hollander E, Bienstock CA, Koran LM, et al. Refractory obsessive-compulsive disorder: state-of-the-art treatment. *J Clin Psychiatry*. 2002;63(suppl 6):20–29.

212. Dold M, Aigner M, Lanzenberger R, Kasper S. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: an update meta-analysis of double-blind, randomized, placebo-controlled trials. *Int J Neuropsychopharmacol*. 2015;18(9):pyv047.
213. Abdel-Ahad P, Kazour F. Non-antidepressant pharmacological treatment of obsessive-compulsive disorder: a comprehensive review. *Curr Clin Pharmacol*. 2015;10(2):97-111.
214. Dold M, Aigner M, Lanzenberger R, Kasper S. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. *Int J Neuropsychopharmacol.* 2013;16(3):557–374.
215. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006;11(7):622–632.
216. Komossa K, Depping AM, Meyer M, Kissling W, Leucht S. Second-generation antipsychotics for obsessive-compulsive disorder. *Cochrane Database Syst Rev*. 2010;8(12):CD008141.
217. Savas HA, Yumru M, Ozen ME. Quetiapine and ziprasidone as adjuncts in treatment-resistant obsessive-compulsive disorder: a retrospective comparative study. *Clin Drug Invest*. 2008;28(7):439–442.
218. Storch EA, Goddard AW, Grant JE, et al. Double-blind, placebo-controlled, pilot trial of paliperidone augmentation in serotonin reuptake inhibitor-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2013;74(6):e527–e532.
219. Foa EB, Simpson HB, Rosenfield D, et al. Six-month outcomes from a randomized trial augmenting serotonin reuptake inhibitors with exposure and response prevention or risperidone in adults with obsessive-compulsive disorder. *J Clin Psychiatry*. 2015;76(4):440–6.
220. Simpson HB, Foa EB, Liebowitz MR, et al. Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial. *JAMA Psychiatry*. 2013;70(11):1190–1199.
221. Wang HR, Woo YS, Bahk WM. Potential role of anticonvulsants in the treatment of obsessive-compulsive and related disorders. *Psychiatry Clin Neurosci.* 2014;68(10):723–732.
222. Arumugham SS, Reddy JY. Augmentation strategies in obsessive-compulsive disorder. *Expert Rev Neurother*. 2013;13(2):187–202.
223. Hollander E, Kaplan A, Stahl SM. A double-blind, placebo-controlled trial of clonazepam in obsessive-compulsive disorder. *World J Biol Psychiatry*. 2003;4(1):30–34.
224. Oliver G, Dean O, Camfield D, et al. N-acetyl cysteine in the treatment of obsessive compulsive and related disorders: a systematic review. *Clin*

Psychopharmacol Neurosci. 2015;13(1):12–24.
225. Ong CW, Clyde JW, Bluett EJ, Levin ME, Twohig MP. Dropout rates in exposure with response prevention for obsessive-compulsive disorder: what do the data really say? *J Anxiety Disord*. 2016;40:8–17.
226. Dougherty DD, Baer L, Cosgrove GR, et al. Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. *Am J Psychiatry*. 2002;159:269–275.
227. Greenberg BD, Rauch SL, Haber SN. Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. *Neuropsychopharmacology*. 2010;35:317–336.
228. U.S. Food & Drug Administration. Medtronic (Activa) deep brain stimulation for OCD therapy. Accessed September 20, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H050003
229. Medtronic. Treatment options DBS therapy for OCD. Accessed October 1, 2020. https://www.medtronic.com/us-en/patients/treatments-therapies/deep-brain-stimulation-ocd.html
230. U.S. Food & Drug Administration. FDA permits marketing of transcranial magnetic stimulation for treatment of obsessive compulsive disorder. Accessed September 29, 2020. https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-transcranial-magnetic-stimulation-treatment-obsessive-compulsive-disorder
231. Attiullah N, Eisen JL, Rasmussen SA. Clinical features of obsessive-compulsive disorder. *Psychiatr Clin North Am*. 2000;23:469–491.
232. Hollander E, Kaplan A, Allen A, Cartwright C. Pharmacotherapy for obsessive-compulsive disorder. *Psychiatr Clin North Am*. 2000;23:643–656.
233. Pampaloni I, Sivakumaran T, Hawley CJ, et al. High-dose selective serotonin reuptake inhibitors in OCD: a systematic retrospective case notes survey. *J Psychopharmacol*. 2010;24(10):1439–1445.
234. Ninan PT, Koran LM, Kiev A, et al. High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. *J Clin Psychiatry*. 2006;67:15–22.
235. Rabinowitz I, Baruch Y, Barak Y. High-dose escitalopram for the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2008;23:49–53.
236. Horwath E, Weissman MM. The epidemiology and cross-national presentation of obsessive-compulsive disorder. *Psychiatr Clin North Am*. 2000;23:493–507.
237. Koran LM, Hackett E, Rubin A, Wolkow R, Robinson D. Efficacy of sertraline in the long-term treatment of obsessive-compulsive disorder. *Am J Psychiatry*. 2002;159:88–95.
238. Nielsen KK, Brøsen K, Hansen MG, Gram LF. Single-dose kinetics of clomipramine: relationship to the sparteine and s-mephenytoin oxidation polymorphisms. *Clin Pharmacol Ther*. 1994;55:518–527.

239. Nissen D. *Mosby's Drug Consult*. 13th ed. Mosby; 2003.
240. Nielsen K, Flinois JP, Beaune P, Brøsen K. The biotransformation of clomipramine in vitro, identification of the cytochrome P450s responsible for the separate metabolic pathways. *J Pharmacol Exp Ther*. 1996;277:1659–1664.
241. Mayo Clinic Laboratories. Test ID: CLOM, Clomipramine, Serum. Accessed September 30, 2020. https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/80902
242. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry.* 2011;44(6):195–235.
243. Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB; American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry.* 2007;164(7 suppl):5–53.
244. Shimoda K, Jerling M, Böttiger Y, Yasuda S, Morita S, Bertilsson L. Pronounced differences in the disposition of clomipramine between Japanese and Swedish patients. *J Clin Psychopharmacol*. 1999;19:393–400.
245. Balant-Gorgia AE, Gex-Fabry M, Balant LP. Clinical pharmacokinetics of clomipramine. *Clin Pharmacokinet*. 1991;20(6):447–462.
246. Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry*. 1996;153:311–320.
247. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy*. 1998;18:84–112.
248. Andrade C. Augmenting selective serotonin reuptake inhibitors with clomipramine in obsessive-compulsive disorder: benefits and risks. *J Clin Psychiatry*. 2013;74(12):e1128–e1133.
249. Ashton H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry.* 2005;18:249–255.
250. Mehdi T. Benzodiazepines revisited. *Br J Med Pract.* 2012;5(1):a501.
251. Lexi-Drugs®. *Pharmacology of Benzodiazepine Used to Treat Anxiety Symptoms/Disorders* [Internet]. Wolters Kluwer Health; 2018. Accessed September 20, 2020. http://online.lexi.com/lco/action/home

84

Sleep Disorders

Devon A. Sherwood and Anna K. Morin

CORE PRINCIPLES	CHAPTER CASES
INSOMNIA AND RESULTING DAYTIME SLEEPINESS	
1 Asking the right questions to investigate the type of insomnia (ie, trouble falling asleep, staying asleep, or early morning awakening), possible causes (lifestyle issues, drugs), resulting impairment, and concomitant conditions are essential to determine proper management.	**Case 84-1 (Questions 1, 2), Table 84-4, Figure 84-2**

CORE PRINCIPLES		CHAPTER CASES
2	Nonpharmacologic treatments such as cognitive-behavioral interventions are recommended first-line therapy for managing insomnia in a variety of patients owing to high efficacy and avoidance of medication side effects.	**Case 84-1 (Questions 3, 4), Table 84-1**
3	Pharmacologic treatments for insomnia are selected based on their efficacy, tolerability, onset and duration of effect, potential for next-day hangover, and abuse potential.	**Case 84-1 (Questions 5–10), Table 84-2**
4	Insomnia concurrent with medical illness is frequently chronic (>1 month) and, if left untreated, may affect recovery from the medical condition. Treating both conditions at the same time is recommended.	**Case 84-2 (Questions 1–4), Table 84-4, Figure 84-2**
5	Insomnia concurrent with psychiatric illness requires optimization of psychiatric maintenance medications and the judicious use of hypnotic medications based on the type of sleep problem and substance abuse history.	**Case 84-3 (Questions 1–4), Figure 84-2**

CORE PRINCIPLES		CHAPTER CASES
6	Managing insomnia in an elderly individual involves consideration of age-related pharmacodynamic and pharmacokinetic changes and counseling regarding realistic treatment expectations. Medication doses lower than those used in younger individuals should be prescribed.	**Case 84-4 (Questions 1–5), Table 84-2**
SLEEP APNEA		
1	Sleep apnea leads to excessive daytime sleepiness (EDS), fatigue, and increased risk of cardiovascular and cerebrovascular disease. Effective treatment with continuous positive airway pressure or surgical interventions can improve overall functioning, quality of life, and morbidity and mortality. Excessive somnolence may be managed by medications with stimulant properties.	**Case 84-5 (Questions 1, 2), Table 84-5**
2	It is essential to avoid sedating medications in patients with sleep apnea because these agents interfere with mini-arousals that keep the patient alive.	**Case 84-5 (Question 3)**
NARCOLEPSY		
1	Narcolepsy is an incurable neurologic disease characterized by sleep attacks and cataplexy.	**Case 84-6 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
2	Stimulants can help decrease sleep attacks and promote daytime alertness, although they do not help with cataplexy or nocturnal insomnia. Sodium oxybate is effective for cataplexy and improves nocturnal sleep, but has high abuse potential and has been associated with psychiatric side effects. Newer agents solriamfetol and pitolisant are effective for EDS and EDS and cataplexy, respectively.	**Case 84-6 (Questions 3, 4), Table 84-5**

INTRODUCTION

Approximately one-third of the adult life is expended on sleep. The innate necessity of sleep is present in almost all mammals, although all the functions of sleep are not fully understood.[1,2] Naturally with the human physiology devoted to sleep and the numerous factors that can disrupt this process, sleep disorders are remarkably common. Sleep deficiency, including insufficient sleep duration, irregular timing of sleep, poor sleep quality, and sleep or circadian rhythm disorders, is highly prevalent and threatens public safety.[3,4] Decades of scientific findings associate sleep deficiency with increased disease risk, including cardiovascular and metabolic disease, psychiatric illness, substance use disorder, pregnancy complications, and impaired neurobehavioral and cognitive impairment.[4,5] At least 10% of the American population is reported to have a sleep disorder that is clinically significant and a public health concern.[3] Major sleep disorders in the United States include insomnia ranging from 15% to 35%,[6,7] sleep apnea at 6% to 24%,[8,9]

periodic limb movements in sleep (PLMS, previously known as nocturnal myoclonus), restless leg syndrome (RLS) ranging from 3% to 15%,[10,11] and narcolepsy at 0.025% to 0.05%.[12] Of note, RLS and PLMS are considered sleep disorders but are reviewed under Chapter 59, Parkinson Disease and Other Movement Disorders. Untreated sleep disorders, including chronic insomnia, sleep apnea, PLMS, and narcolepsy, are all associated with diminished mental and physical functioning and poor quality of life.[3,4,7]

Nightmares, nocturnal leg cramps, and snoring are more benign sleep disorders. Nightmares occur in 5% to 30% of children ages 3 to 6 years, and ~2% to 6% of adults have weekly nightmares.[13] Sleepwalking occurs in 1% to 2% of the population. Complex sleep behavior disorders, such as driving or eating while still asleep, are uncommon to rare. These behaviors are more common in people taking hypnotics, and medication counseling should be provided for patients prescribed any sleep medication.[13,14]

CIRCADIAN RHYTHM AND SLEEP CYCLES

Sleep is a dynamic process with a cyclical recurrence and varying stages. The endogenous sleep–wake pattern of humans is based on the solar day–night cycle called the *circadian rhythm*. The circadian rhythm is controlled by both internal and external factors and sets the sleep–wake cycle at 24.2 hours. Sensory input (visual and acoustic) or other external factors modify the “internal clock” to a 24-hour day through working with the internal network and signaling brain centers to either wake or sleep. Thus, darkness is a visual cue that prepares the brain for sleep. Similarly, bright light serves to prepare the brain for wakefulness.[1,2]

Once sleep is initiated, it alternates between the two phases of rapid eye movement (REM) and nonrapid eye movement (NREM) sleep. These phases vary in length throughout the sleep cycles. During a normal night of sleep, a person generally has four to six

cycles of sleep that last an average of 90 minutes (vary 70–120 minutes).[15] See **Figure 84-1** for normal sleep cycles by age.

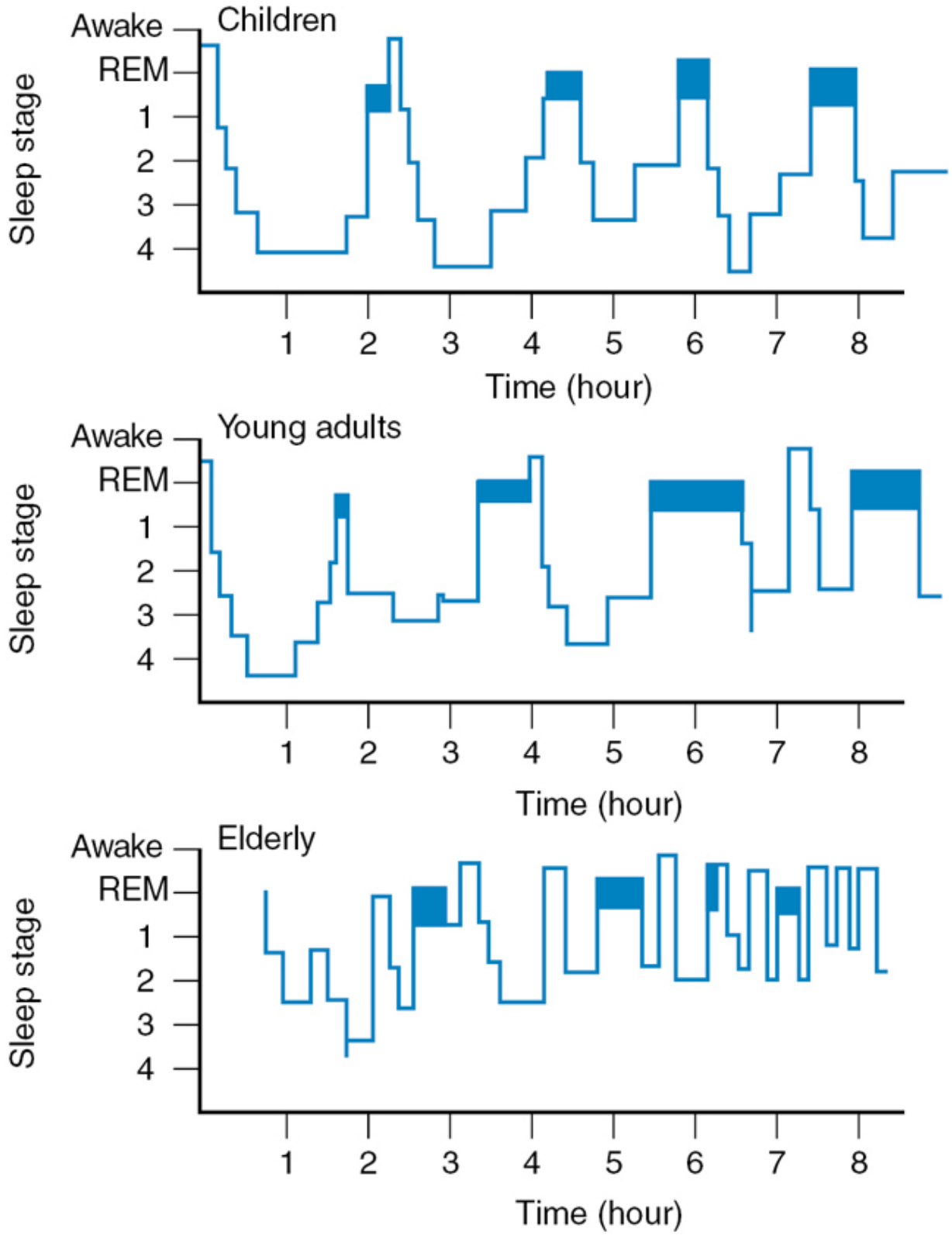


Figure 84-1 Normal sleep cycles.

Polysomnography

Each sleep stage serves a physiologic function and can be monitored in sleep laboratories by polysomnography (PSG). *PSG* is the term used to describe three electrophysiologic measures: the electroencephalogram (EEG), the electromyogram, and the electrooculogram of each eye. It may also include an electrocardiogram, air thermistors, abdominal and thoracic strain belts, and oxygen saturation monitoring. The pattern of brain waves, muscle tone, and eye movements measured can be used to categorize the various sleep stages.[15,16]

Nonrapid Eye Movement Sleep

NREM sleep is divided into four stages, with different quantities of time and functions in each stage. Stage 1 is a transition between sleep and wakefulness known as *relaxed wakefulness*, which generally makes up ~2% to 5% of sleep. The function of stage 1 is to initiate sleep. Approximately 50% of total sleep time is spent in stage 2, which is rapid-wave (theta) or lighter sleep. Stage 2 provides rest for the muscles and brain through muscle atonia and low-voltage brain wave activity. Arousability from sleep is highest during stages 1 and 2. Stages 3 and 4 are slow-wave (delta) or deep sleep. Stage 3 occupies an average of 5% of sleep time, whereas stage 4 constitutes 10% to 15% of sleep time in young, healthy adults. In contrast to stages 1 and 2, it is difficult to awaken someone during stages 3 and 4, or delta sleep.[15] Delta sleep, also known as *restorative sleep*, is enhanced by serotonin, adenosine, cholecystokinin, and interleukin (IL)-1. The ability of IL-1 to promote slow-wave sleep supports a widely held theory linking deep sleep to the augmentation of immune function. Some hormones (eg, somatostatin, growth hormone) are released mainly during slow-wave sleep. Deep sleep is most abundant in infants and children and tends to level off at ~4 hours a night during adolescence. At age 65, deep sleep accounts for only 10% of sleep, and at age 75, it is often nonexistent.[1,15–17]

Rapid Eye Movement Sleep

NREM sleep is necessary for rest and rejuvenation, whereas the purpose of REM sleep is not fully understood. It appears important for certain types of learning and memory, but this may change throughout the lifespan.[18] REM sleep is greatest in infants, accounting for about 50% of total sleep time. As aging occurs before 2 years and throughout adulthood, REM sleep is usually 20% to 25% of sleep. This percentage of total REM sleep is maintained into healthy old age, but can decline markedly in the presence of organic brain dysfunctions of the elderly. REM sleep is also called *paradoxical sleep* because it has aspects of both deep sleep and light sleep. Body and brainstem functions appear to be in a deep sleep state as muscle and sympathetic tone drop dramatically. In contrast, neurochemical processes and higher cortical brain function appear active. Dreaming is associated closely with REM sleep, and when a person is awakened from REM, alertness returns relatively quickly.[15]

Numerous physiologic functions are altered during REM sleep. Breathing is irregular, consisting of sudden changes in respiratory amplitude and frequency corresponding to bursts of REM. Temperature control is lost and the body temperature typically lowers. REM sleep brings on variability in heart rate, blood pressure (BP), cerebral blood flow, and metabolism. Cardiac output and urine volume decrease. Blood may become thicker as a result of autonomic instability and temperature changes.[1,15–17]

REM duration varies throughout the night but increases each cycle. In the last half of the night, REM becomes notably longer and more intense when body temperature is at its lowest, around 5:00 AM. When deprived of REM sleep, whether through poor sleep, drugs, or disease states, the brain and body try to catch up. REM rebound occurs and may result in vivid dreams or an overall less restful sleep.[15–19]

NEUROCHEMISTRY OF THE SLEEP–WAKE CYCLE

Wakefulness- and Sleep-Promoting Neurochemicals

A basic understanding of brain neurochemistry is essential in understanding sleep disorders and the clinical use of hypnotics. Hypnotics exert their effects by modulating brain neurotransmitters and neuropeptides (eg, serotonin, norepinephrine, acetylcholine, histamine, adenosine, and γ-aminobutyric acid [GABA]). The neuronal systems in which neurotransmitters and neuropeptides act to control the sleep–wake cycle lie in the brainstem, hypothalamus, and basal forebrain, with connections in the thalamus and cortex. Noradrenergic, histaminergic, and acetylcholine-containing neurons promote wakefulness because they modulate cortical and subcortical neurons.[19] Excitatory amino acids, such as glutamate and stimulating neuropeptides (eg, substance P, thyrotropin-releasing factor, corticotropin-releasing factor) also promote wakefulness.[19] Hypocretin 1 and 2, also known as orexin A and B, are neuropeptides that modulate the sleep–wake cycle. Hypocretin 1 and 2 are deficient in people with narcolepsy and primary hypersomnia.[15,19–21]

Wakefulness and sleep are antagonistic states competing for control of brain activity. Sleep takes over as the wakefulness-maintaining neuronal systems weaken and sleep-promoting neurons become active. Serotonin-containing neurons of the brainstem raphe dampen sensory input and inhibit motor activity, promoting the emergence of slow-wave sleep.[15,16,19] Opiate peptides (eg, enkephalin, endorphin) and GABA, an inhibitory neurotransmitter, also promote sleep.[15,22]

Drug-Induced Effects on Neurochemicals

The neurochemistry of sleep also can be understood by considering the effect of hypnotic drugs on specific neurotransmitters. GABA is facilitated when a benzodiazepine compound attaches to the GABA–chloride ionophore complex and causes chloride channels to open and inhibit overexcited areas of the brain.[23,24] GABA-facilitating hypnotics, such as benzodiazepines, induce sleep and decrease arousals between stages, providing more continuous stage 2 sleep.[19,23,25] Benzodiazepines, however, also may decrease stage 4 slow-wave sleep and suppress REM, leading to REM sleep rebound on abrupt discontinuation.[15,23,25] Antihistamines that promote sleep do so by blocking histamine-containing neurons involved in maintaining wakefulness. The excitatory effects of caffeine and other methylxanthines are attributed to their antagonism of adenosine receptors. Adenosine is a sleep-promoting neurotransmitter or neuromodulator.[19,21]

Neurotransmitter alteration may or may not affect REM sleep. Drug-induced noradrenergic and serotonergic modulation usually decreases REM sleep. An increase in dopaminergic neurotransmission can increase wakefulness but has no direct effect on REM sleep. In contrast, increased cholinergic neurotransmission triggers REM sleep.[19] It is useful to think of the brain centers, neurochemicals, and neuropeptides involved as an interactive network regulating our sleep–wake cycle. Hence, drugs or disease states that alter neurotransmission can have a significant impact on the sleep–wake cycle.

Diagnosis

The International Classification of Sleep Disorders, Third Edition (*ICSD-3*)[26] and the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*)[27] are the latest editions of guides used for classification and diagnosis of sleep disorders. Both *ICSD-3* and *DSM-5* categorize sleep disorders largely based on pathophysiology and presumed etiology rather than numbers of hours of sleep.

INSOMNIA

During the course of a year, approximately one-third (30%–36%) of the population will experience insomnia, and 10% to 15% will consider the problem severe because of daytime consequences.[26] Sleep research also shows that chronic insomnia (ie, insomnia >1 month) can predict untreated illness or may contribute to injury and illness.[2,28,29] Children, adolescents, and adults with persistent insomnia are twice as likely to develop anxiety and four times as likely to develop depression when compared to people without insomnia.[28] Chronic insomnia is also more common in individuals with high BP, breathing difficulties, gastrointestinal (GI) disorders, cancer, and chronic pain, among other conditions.[28–30] Insomnia and excessive daytime sleepiness (EDS) in the elderly are leading predictors of institutionalization.[31]

To meet the criteria for insomnia disorder according to *ICSD-3* and *DSM-5*, the sleep disturbance must cause significant distress or impairment in important areas of functioning (ie, social, occupational, educational, academic, behavioral) and occur at least three nights per week over a 3-month period despite adequate opportunity for sleep.[26,27] The insomnia disorder can be further classified based on duration as follows: episodic (1–3 months), persistent (>3 months), and recurrent (two or more episodes in 1 year). Insomnia with a duration <1 month, previously referred to as transient insomnia, would be classified as "other specified insomnia disorder."[26]

Patient Assessment

When first assessing a patient, it is important to determine whether the sleep problem is related to difficulty falling asleep, maintaining sleep, early morning awakening, nonrestorative–quality sleep, EDS, or a combination of these problems. Answers to the questions, "How long does it take you to fall asleep" and "How many hours do you sleep?" should be compared with the patient's normal sleep pattern to determine how it varies. Questions such as "How do you feel

during the day: well rested, sleepy, or something else?" can help assess functional impairment. In addition, the patient's sleep schedule, including bed time, sleep-onset latency, number and length of nighttime awakenings, time to sleep reinitiation, and total wake and sleep time should be reviewed.[32]

The next step involves investigating the possible causes of the sleep disorder and any concomitant conditions. All coexisting medical, psychiatric, drug, environmental, and social causes must be considered and treated along with the sleep disorder. Impact of the sleep disturbance on daytime functioning should be assessed to evaluate the severity of the disorder. A sleep diary in which the patient records bed and wake times, estimated time to fall asleep, number and duration or awakenings, time and type of medication/substance ingestion, time and duration of any naps, and sleep quality can help elucidate the type of sleep disorder.[32]

In addition to assessing patient symptoms and determining the cause of insomnia, it is important to discuss patient expectations. Not all patients need the same amount of sleep, and too much sleep can be as problematic as too little sleep.[27]

Nonpharmacologic Treatment

The first-line treatment for chronic insomnia should be psychological and behavioral therapies. Cognitive-behavioral therapies (CBTs) are effective, long-lasting interventions for insomnia and considered the standard of care.[33,34] They may be more effective than is pharmacotherapy for sleep-onset latency and sleep efficiency.[35,36] The sleep benefits of these interventions are not immediate and can take several weeks to successfully implement. Results vary depending on the individual and the severity and chronicity of insomnia.[35] **Table 84-1** lists established cognitive and behavioral interventions with brief descriptions in addition to important sleep hygiene strategies to include in patient counseling.[33]

Table 84-1

Nonpharmacologic Treatments for Insomnia

1. Cognitive-behavioral therapy: Modify behavioral and cognitive factors that lead to sleep disturbances.
   Cognitive: Identify and stop thought patterns that interfere with sleep.
   Behavioral: stimulus control, sleep restriction, relaxation, paradoxical intention
   a. Stimulus control: Train the brain to reassociate the bed and bedroom with sleep and reestablish a consistent sleep–wake schedule.
   b. Sleep restriction: Create "sleep debt" by limiting amount of time in bed to only the total number of hours actually spent sleeping, then increasing time in bed as sleep efficiency improves.
   c. Relaxation therapy: Target physiologic hyperarousal resulting from stress and tension (eg, meditation, progressive tensing/relaxing of muscles, yoga, stretching).
   d. Paradoxical intention: Encourage the patient to engage in most feared behavior, "staying awake," to reduce performance anxiety associated with falling asleep.
2. Sleep hygiene: useful adjunctive treatment, not effective monotherapy
   Avoid caffeine, stimulants, heavy meals, and alcohol at bedtime; exercise early in the day before dinner to relieve stress and prime brain for sleep; turn face of the clock away from view; establish before-bedtime ritual; use bedroom only for sleep and intimacy; make sure bedroom is dark, quiet, and comfortable; avoid daytime napping.

Sources: Morgenthaler T, Kramer M, Alessi C, et al. Practice parameter for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. *Sleep.* 2006;29:1415–1419; Hood HK, Rogojanski J, Moss TG. Cognitive-behavioral therapy for chronic insomnia. *Curr Treat Options Neurol.* 2014;16:321; Jacobs GD, Pace-Schott EF, Stickgold R, Otto MW. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. *Arch Intern Med.* 2004;164:1888–1896.

Pharmacologic Treatment

Pharmacotherapy is indicated for a variety of reasons. These include when nondrug interventions fail or cannot be implemented, sleep disturbances produce significant distress or impairment and immediate symptom relief is required, patient preference is for drug therapy, or if insomnia is comorbid with another medical, sleep, or psychiatric disorder.[33] Patients often do not seek treatment for insomnia from their health care provider when pharmacologic

treatment is warranted. Instead, alcohol or over-the-counter (OTC) sleep aids with unfavorable results that can worsen insomnia or next-day functioning are used.[36–38]

The ideal hypnotic has a rapid onset of effect (within 20 minutes, the natural time to fall asleep), helps the patient sleep throughout the night, does not cause daytime impairment, and carries no abuse potential. Currently, there are no ideal hypnotics. Hypnotics that are benzodiazepine receptor agonists come closest to the ideal.[36,39] Available agents vary in onset, duration, and potential for daytime impairment, mostly because of their individual pharmacokinetic profiles (**Table 84-2**).[40] The selection of an appropriate hypnotic should consider the type of insomnia to be treated and the physiologic characteristics of the patient. For example, if someone cannot fall asleep but has no trouble staying asleep and wants to prevent next-day carryover effects, a rapid-acting hypnotic with a short half-life and no active metabolites is desirable.[36,39,40] Age, sex, socioeconomic status, and comorbidities also influence the hypnotic prescribed.[38–41] Refer to **Figure 84-2** for the treatment algorithm for insomnia.

Table 84-2
Sedative-Hypnotic Agents FDA Approved for Treatment of Insomnia

Generic[a] (Brand Name)	Dose (mg)		Onset (Minutes)	Half-Life (Hours)	Duration of Action[b]	Insomnia Indication
	Healthy Adults	Elderly/ Hepatic Impaired				
Benzodiazepines						
Estazolam (generics)	1–2	0.5–1	60–120	10–24	Intermediate	Sleep onset and sleep maintenance[c]
Flurazepam (generics)	15–30	NR	60–120	>100[d]	Long	Sleep onset and sleep maintenance[c]
Quazepam (Doral®, generics)	7.5–15	NR	30–60	47–100[d]	Long	Sleep onset and sleep maintenance[c]
Temazepam (Restoril®, generics)	7.5–30	7.5	60–120	3.5–18.4	Intermediate	Sleep onset and sleep maintenance[c]
Triazolam (Halcion®, generics)	0.125–0.25	0.125	15–30	1.5–5.5	Short	Sleep onset[c]
Nonbenzodiazepine Receptor Agonists						
Zaleplon (Sonata®)	10–20	5–10	30	1	Short	Sleep onset[c]
Zolpidem						
Oral tablet (Ambien®)	5–10[e]	5	30	1.4–4.5	Short	Sleep onset[c]
ER oral tablet (Ambien® CR)	6.25–12.5[e]	6.25	30	1.62–4.05	Intermediate	Sleep onset and sleep maintenance[f]
Sublingual tablet[g] (Intermezzo®)	1.75–3.5[e]	1.75	20–38	1.4–3.6	Short	Middle-of-the-night-awakening[h]
Sublingual tablet[g] (Edluar®)	5–10[e]	5	30	1.57–6.73	Intermediate	Sleep onset[c]
Mucous membrane spray (Zolpimist®)[i]	5–10[e]	5	10	2.7–3	Short	Sleep onset[c]
Eszopiclone (Lunesta®)	1–3 (start at 1 in all patients)	1–2	30	6	Intermediate	Sleep onset and sleep maintenance[f]
Dual Orexin Receptor Antagonists						
Lemborexant (Dayvigo®)	5–10 (start at 5 in all patients)	5[j]	30	17–19	Intermediate	Sleep onset and maintenance[k]
Suvorexant (Belsomra®)	10–20 (5–10 moderate CYP3A4 inhibitor)	10–20[j]	30	12	Intermediate	Sleep onset and maintenance[k]
Daridorexant (Quviviq®)	25–50	25[j]	30	8	Intermediate	Sleep onset and maintenance[k]
Melatonin Agonist						
Ramelteon (Rozerem®)	8	8	30	1–5[d]	Short	Sleep onset[f,l]
Antidepressants						
Doxepin (Silenor®)	6	3	30	15.3 (31[d])	Intermediate	Sleep maintenance[f,l]

CR, controlled release; CYP, cytochrome P450; ER, extended release; FDA, U.S. Food and Drug Administration; NR, not recommended.

[a]Dispense with a product-specific Medication Guide.

[b]Time the patient feels the effects after a single dose; usually approximates half-life with multiple doses; individual variability exists; and tolerance may develop with continued use, lessening the duration; short = 1 to 5 hours; intermediate = 5 to 12 hours; long = >12 hours.

[c]FDA approved for short-term (7–10 consecutive days) treatment of insomnia.

[d]Half-life includes the parent compound and its active metabolites.

[e]In females, start with the lower dose.

[f]Not limited to short-term use.

[g]To be dissolved under the tongue and not swallowed whole.

[h]Take only if 4 hours remaining before planned wake time.

[i]To be sprayed over the tongue immediately before bedtime.

[j]Severe hepatic impairment only = NR (not recommended).

[k]Take only if 7 hours remaining before planned wake time.

[l]Not a controlled substance.

Sources: Buysse DJ. Insomnia. *JAMA*. 2013;309:706; Morin CM, Benca R. Chronic insomnia. *Lancet*. 2012;379:1129–1141; Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. *Pharmacotherapy*. 2007;27:89–110; Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. 2003;26:793–799; Belsomra (suvorexant tablets). Product information. Merck and Co Inc; 2020; Dayvigo (lemborexant tablets). Prescribing information. Eisai Inc; 2020; Quviviq (dari4dorexant tablets). Product information. Idorsia Pharmaceuticals US Inc; 2022.

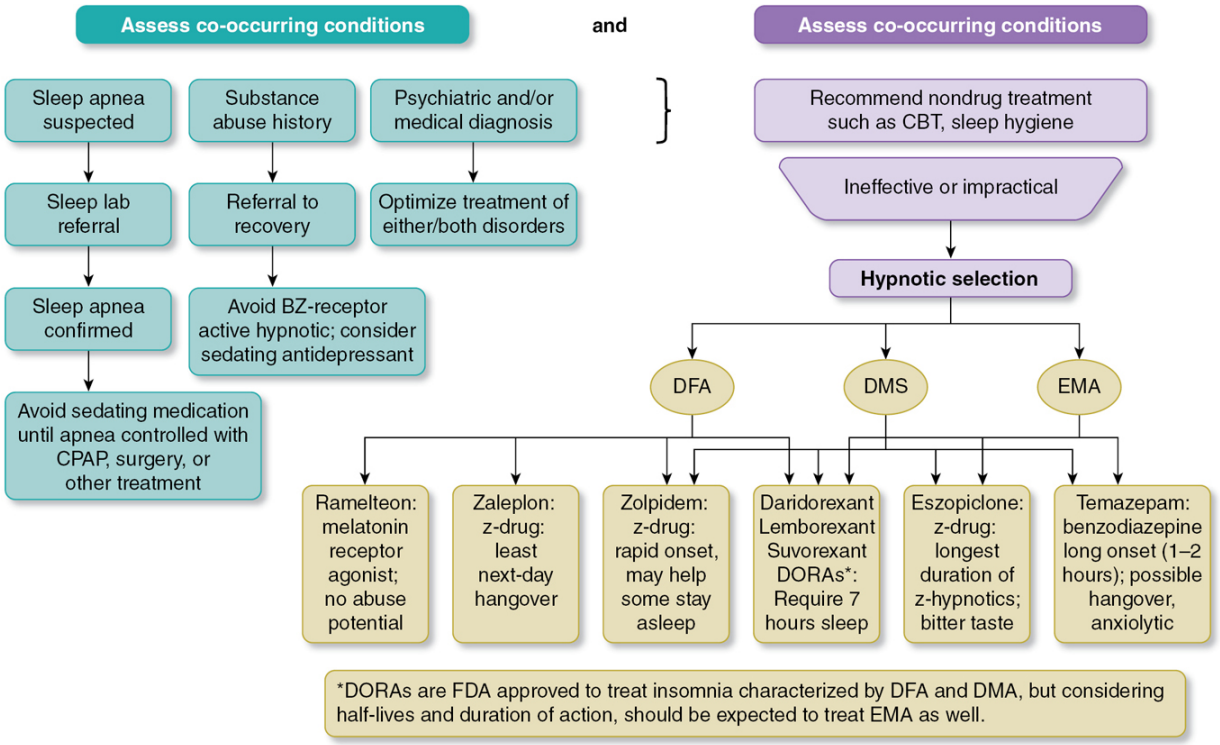


Figure 84-2 Algorithm for treatment of insomnia. CBT, cognitive-behavioral therapy; CPAP, continuous positive airway pressure; DFA, difficulty falling asleep; DMS, difficulty maintaining sleep; DORA, dual orexin A and orexin B receptor antagonist; EMA, early morning awakening.

INSOMNIA IN A NORMALLY HEALTHY PATIENT

CASE 84-1

QUESTION 1: L.A., a 36-year-old female, is requesting a medication for treatment of her sleep disorder. She returned to Boston, Massachusetts, from a month-long business trip to California 2 days ago. She is now having difficulty falling asleep. When she initially arrived in California 4 weeks ago, she went to sleep immediately at 7:00 PM and awoke at 3:00 AM. Her sleep pattern adjusted during her 4-week visit in California, but upon returning to Boston, it now takes her 2 to 3 hours to fall asleep. She has difficulty awakening in the morning and, as a result, sleeps past 9:00 AM. She needs to be able to wake up by 6:00 AM and be alert during the day in her job as an accountant.

What information provided by L.A. is important in the assessment of her sleep disorder? What additional information should be obtained from L.A. to assist in the assessment of her sleep disturbance?

L.A. describes a circadian rhythm sleep–wake disorder, specifically sleep phase syndrome related to a time-zone shift (previously referred to as *jet lag*). Her major problem is difficulty falling asleep and awakening later than desired because she reports no trouble staying asleep or awakening too early. It is important for L.A. not to be sedated during the day so that she can fulfill her job obligations. Additional information needed from L.A. includes the duration of insomnia, methods already tried to relieve insomnia and their efficacy, concomitant medications, coexisting medical conditions or psychiatric disorders, alcohol use, caffeine use, and current life stressors. L.A. should be advised that assessing all of the aforementioned information is necessary in treating her sleep problem.

CASE 84-1, QUESTION 2: In response to your additional questions, you learn that L.A. has no medical problems and takes no prescription medications. She has been taking pseudoephedrine at night for nasal congestion since returning from California. She denies drinking alcoholic beverages and coffee but admits to recently increasing her cola intake from infrequent consumption of 1 to 2 cans between lunch and bedtime to try to stay awake. She denies a long history of sleep disorder, but adds, “I have not been able to sleep as well since

traveling; I don't know why." What factors could be contributing to L.A.'s problems?

Several factors are contributing to L.A.'s type of sleep disorder. Her circadian rhythm has been disrupted because of travel, but she also takes a stimulating decongestant (ie, pseudoephedrine) and drinks caffeine-containing beverages (ie, an average can of cola has about 35 mg of caffeine; L.A. consumes 35–70 mg/day). In addition, she sleeps in new surroundings that may require time for adjustment. All these factors can contribute to difficulty in falling asleep. Circadian rhythm sleep disorder results from a mismatch between the sleep–wake schedule required by a person's environment and the circadian sleep–wake pattern.

NONPRESCRIPTION SLEEP AIDS

Case 84-1, Question 3: L.A. would like to purchase a nonprescription sleep medication. What would you recommend?

An individual risk-versus-benefit assessment is essential before recommending any medication, including OTC products. Although OTC products (ie, antihistamines, melatonin, valerian, and other herbals) are commonly advertised as sleep aids, data supporting the use of these products are limited. Antihistamines can cause drowsiness and may help patients fall asleep. The ability to cause sedation does not necessarily lead to hypnotic efficacy. Some patients do not feel well rested the next day after taking an antihistamine, but instead feel slow, lethargic, and not mentally sharp. This "hangover effect" can be significant and may be related to the lipid solubility and central histaminic (H_1) and muscarinic blocking effects of the antihistamine.[36,42] Antihistamines with low lipid solubility (eg, cetirizine, loratadine) do not cross the blood–brain barrier readily and should not cause sedation. Although diphenhydramine is the most common antihistamine found in

nonprescription sleep medications, some preparations contain doxylamine.

Case 84-1, Question 4: What additional counseling is needed for L.A.?

Tolerance can develop to sedative effects of antihistamines after 3 to 7 days of continued use.[36–38,42] Because of a high incidence of daytime sedation and risk of cognitive psychomotor impairment,[34] antihistamines are a poor choice for L.A., an accountant who must stay alert and functional throughout the day. Any attempt to manage L.A.'s sleep disorder should start with nonpharmacologic interventions before initiating any drug therapy.

TIME-ZONE SHIFT: NONPHARMACOLOGIC TREATMENT VERSUS TRIAZOLAM OR NONBENZODIAZEPINE RECEPTOR AGONISTS

Case 84-1, Question 5: L.A. wants to know when she should ask her doctor for a prescription for the treatment of her insomnia. What would you recommend?

L.A. should be informed about the likely causes of her sleep disturbances (ie, time-zone shift, caffeine-containing beverages, pseudoephedrine, new surroundings). She also should understand that it may take 1 to 3 weeks for her system to readjust after traveling.[43] The importance of nonpharmacologic interventions to improve sleep, particularly those that pertain to reestablishing a desired sleep–wake cycle and sleep hygiene education (Table 84-2), should be emphasized. In addition, an hour of bright light in the morning can serve as an environmental stimulus, normalizing the circadian rhythm.[43] If L.A.'s sleep disturbances persist despite adhering to cognitive-behavioral interventions, an insomnia medication may be necessary.

Short-acting hypnotics (**Table 84-3**)[33,38,42,44] are effective in treating time-zone shifts to induce and regulate sleep if the stay will be

relatively short (<5 days) and if critical activities must be accomplished during the first 48 hours after arrival at the destination.[43] Females may be more susceptible to the adverse effects of hypnotics than do males, possibly due to greater oral bioavailability.[36,42] Nonbenzodiazepine receptor agonist (NBRA) hypnotics (also known as Z-hypnotics) such as zaleplon, zolpidem, and eszopiclone have fewer reports of rebound insomnia and anterograde amnesia at recommended doses because of selectivity for the α_1-receptor subunit and also lack significant anxiolytic and muscle relaxant effects compared with triazolam.[44]

Table 84-3
Potential Causes and Contributing Factors for Each Chronic Sleep Problem

Difficulty Falling Asleep (DFA)
Learned or conditioned activation (primary insomnia): restless legs syndrome (RLS)
Medications: methylphenidate, modafinil, fluoxetine, bupropion, steroid, β-blocker
Substances: caffeine, guarana, alcohol
Psychiatric disorders: schizophrenia, depression, anxiety disorder, bipolar disorder
Medical disorder: chronic pain, neuropathy, gastrointestinal disorder, cardiopulmonary disorders (particularly if in recumbent position)
Difficulty Maintaining Sleep (DMA)
Excessive time in bed
Psychiatric disorder: major depression, anxiety or bipolar disorder, substance abuse disorder
Sleep-disordered breathing: sleep apnea, acute respiratory distress syndrome
Cardiac disease: atrial fibrillation, heart failure, angina
Neurologic disorder: dementia, Parkinson disease, multiple sclerosis
Early Morning Awakening
Major depression
Advanced sleep phase syndrome: learned or conditioned activation (primary insomnia)

Difficulty Falling Asleep (DFA)
Forced to get up because of family or work obligations
Excessive Daytime Sleepiness
Medications: clonidine, antihistamines, antipsychotic, antidepressant, benzodiazepine, chloral hydrate, opioid, anticonvulsant, α_1-adrenergic blockers
Obstructive sleep apnea, central sleep apnea, narcolepsy
Chronic sleep deprivation

Sources: Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care Survey 1999–2010. *Sleep*. 2014;37:1283–1293; Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. *Sleep*. 2007;30:213–218; Krystal AD. Sleep and psychiatric disorders: future directions. *Psychiatr Clin North Am.* 2006;29:1115–1130.

MELATONIN

Case 84-1, Question 6: L.A. would like to try melatonin for improved sleep but wonders whether it is safe and effective. What information is available on the safety and efficacy of melatonin for circadian rhythm or other types of sleep disorders?

Melatonin is a naturally occurring hormone secreted by the pineal gland, located in the center of the brain. The pineal gland is connected to the retina via a nerve pathway that runs through the suprachiasmatic nucleus of the hypothalamus, the body's circadian clock. The pineal gland produces melatonin (a by-product of serotonin metabolism) only during the nocturnal phase of the circadian cycle and only in the presence of relative darkness.[42,45]

Studies in adults show that melatonin has at least mild sleep-promoting properties when administered before the period of natural increase in endogenous melatonin (~10:00 PM to midnight). It causes significantly more sleepiness when taken at 8:00 PM compared with 11:30 PM, theoretically because the brain's receptors are already saturated with melatonin late at night.[42,45] Doses between 0.5 and 5

mg taken close to the target bedtime in the new time zone can decrease sleep disturbances. A systematic review of 10 clinical trials showed melatonin was more effective for travel eastward crossing multiple time zones.[45] Melatonin 0.5 to 10 mg has been found effective for entraining the circadian rhythms in blind people, alleviating insomnia in developmentally disabled, handicapped, or children and adults with autistic spectrum disorders, and treating short-term, initial insomnia in children with attention deficit hyperactivity disorder (ADHD).[42,45,46] The safety and effectiveness of melatonin for long-term use or other sleep disorders has not been established. Consumers selecting melatonin products OTC should be advised that the purity of melatonin is not regulated by the U.S. Food and Drug Administration (FDA). Although doses of 0.5 to 5 mg of melatonin are well tolerated, side effects include sleepiness, headache, and nausea.[42,45,46] Melatonin use has been associated with reports of depression, liver disease, and vasoconstrictive, immunologic, and contraceptive effects.[42,45]

RAMELTEON

CASE 84-1, QUESTION 7: L.A.'s doctor gave her a prescription for ramelteon 8 mg at bedtime. How does ramelteon compare with melatonin?

Ramelteon is a highly selective melatonin agonist at melatonin 1 and 2 receptors (MT1, MT2). MT1 regulates sleepiness and MT2 adjusts circadian rhythms and regulates phase shifts from day to night.[47,48] Ramelteon is approved by the FDA for insomnia characterized by difficulty falling asleep. Clinical studies on primary insomnia show it decreases the time to fall asleep by 10 to 19 minutes, and it increases total sleep time by 8 to 22 minutes.[47–49] One controlled trial showed it was superior to placebo in decreasing time to fall asleep during a 6-month period, although ramelteon's onset was 15 minutes faster than was placebo after week 1 but only 9 minutes faster at 6 months.[48] Its half-life ranges from 1 to 2.6 hours. The half-life of its active metabolite, M II, is 2 to 5 hours.

Ramelteon undergoes hepatic metabolism by cytochrome P450 (CYP) isoenzyme CYP1A2. Increases in serum concentration occur even with mild liver disease, so caution is recommended for patients who have at least moderate liver disease. Fluvoxamine is a strong inhibitor of CYP1A2, and given with ramelteon, dramatically increases its serum concentration. Coadministration with fluvoxamine or any potent CYP1A2 inhibitor should be avoided. The most common adverse events observed with ramelteon include headache (7%), dizziness (5%), somnolence (5%), fatigue (4%), and nausea (3%).[48,49]

In clinical trials, no evidence of cognitive impairment, rebound insomnia, withdrawal effects, or abuse potential was demonstrated even at doses up to 20 times the usual treatment dose.[50] These results were markedly different from the abuse potential and side effects of triazolam at treatment doses and doses up to three times higher than usual.[47,48,51] Of note, no study has directly compared ramelteon and another hypnotic for insomnia management.[51] Ramelteon is a reasonable option for patients with initial insomnia with no abuse potential and little to no risk of next-day impairment.

NONBENZODIAZEPINE RECEPTOR AGONISTS (ZOLPIDEM, ZALEPLON, AND ESZOPICLONE)

CASE 84-1, QUESTION 8: It has been a month since her return and L.A. continues to have difficulty falling asleep. What alternative medications (aside from ramelteon) offer rapid onset, have a low risk of daytime sedation, and can be administered safely for weeks to months if necessary?

Considering their rapid onset of action, NBRA medications (zaleplon, zolpidem, and eszopiclone) are all potential alternatives for L.A. They have varying degrees of selectivity for the α_1-subunit on the $GABA_A$ receptor. This selectivity imparts hypnotic efficacy with no significant anxiolytic, muscle relaxant, or anticonvulsant effects. Consequently, NBRAs have a lower risk of abuse, withdrawal, and tolerance compared with older nonselective benzodiazepines. These

attributes make NBRAs more desirable for the treatment of chronic insomnia. Both zolpidem controlled release (CR) and eszopiclone are FDA approved for chronic insomnia and are effective for up to 3 to 6 months of therapy.[39] Zolpidem has been studied up to 12 months and was not associated with rebound insomnia or withdrawal symptoms.[52] In addition, eszopiclone was studied for 12 months of nightly administration and found to be well tolerated with no tolerance observed.[53] Another potential advantage of NBRA α_1-subunit selectivity is little to no change in sleep architecture or sleep stages. Benzodiazepines increase the percentage of stage 2 sleep but can suppress REM and stages 3 and 4 deep restorative sleep. In contrast, NBRAs do not interfere with these sleep stages and have lower rates of uncomfortable REM rebound (vivid dreams, increased autonomic instability) on discontinuation.[39,54]

The NBRAs differ with respect to pharmacokinetics and adverse events. Zolpidem, the first NBRA, was marketed in the United States in 1991. It is absorbed rapidly, reaches peak serum levels in 1.5 hours, and is eliminated rapidly with an average half-life of ~2.5 hours.[43] For faster sleep onset, zolpidem should be taken on an empty stomach because of a more rapid absorption. A food-effect study demonstrated that administration of a zolpidem 10 mg tablet 20 minutes after a meal resulted in a decrease in area under the curve (AUC) and maximum serum concentration (C_{max}) of 15% and 25%, respectively, and an increase in the time to maximal concentration (T_{max}) from 1.4 to 2.2 hours.[55] Zolpidem is metabolized by the oxidative CYP3A4; therefore, drug interactions should be considered when zolpidem is coadministered with CYP3A4 inhibitors. Zolpidem has no active metabolites, and it has a low risk of residual daytime sedation in recommended doses.[39,44] Zolpidem CR has no clear advantage over zolpidem, except that it may provide a slightly longer duration of sleep. Zolpidem CR is a bilayered tablet with a first layer that dissolves quickly to induce sleep and a second layer that releases zolpidem more gradually to improve sleep maintenance. Serum concentrations peak in 2 hours compared with 1.5 hours for immediate-release zolpidem, with an

associated longer latency to effect.[40] Of note, zolpidem has been approved as oral spray to help with sleep onset. Owing to buccal absorption, it has a rapid onset of action of 10 minutes.[56] Gender metabolism differences exist where females metabolize zolpidem slower than do males, resulting in blood levels nearly twofold higher. As a result, in females or the elderly, the recommended starting dose is 5 mg of zolpidem immediate release or 6.25 mg zolpidem extended release (ER).[57] In 2019, the FDA added a boxed warning for risk of serious injuries secondary to complex sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake, associated with all NBRAs.[14] For females, the elderly, or patients such as L.A. who express concern that a medicine may be too strong, the starting dose should be 5 mg at bedtime.

Zaleplon offers a shorter elimination half-life (~1 hour) and duration of effect than does zolpidem (see Table 84-3). It is the least likely of all hypnotic agents to cause residual daytime sedation and has the least effect on memory and psychomotor performance. An assessment of psychomotor performance, arousal, memory, and cognitive functioning with zaleplon revealed no cognitive impairment.[39,44] The most common adverse effects of zaleplon include dizziness, headache, and somnolence.[58] In dose escalation studies using up to 60 mg, symptoms appear at ~30 minutes after dosing, peak at 1 to 2 hours, and are no longer evident after 4 hours. It can be taken in the middle of the night as long as the individual has 4 hours left in bed. Zaleplon is metabolized primarily via aldehyde oxidase, CYP3A4 is a secondary route of metabolism, and there are no active metabolites. It has less potential for drug or food interactions compared with zolpidem or eszopiclone.[42]

Eszopiclone maintains efficacy with no evidence of tolerance after 6 months of continuous use, resulting in FDA approval for long-term use.[59–62] Hypnotic efficacy has been demonstrated for up to 6 months in younger patients taking 2 to 3 mg nightly, and in elderly patients taking 1 to 2 mg nightly, although only the higher range of doses significantly improved sleep maintenance. As with zolpidem and zaleplon, eszopiclone has a rapid onset of effect, but differs in

that it has a longer duration of effect (see Table 84-3). T_{max} is delayed up to 1 hour when eszopiclone is administered after a high-fat meal, potentially delaying the onset of sleep.[59,60]

Eszopiclone has less receptor selectivity than does either zaleplon or zolpidem, potentially resulting in some anxiolytic, amnestic, and anticonvulsant activity.[61] Among the three Z-hypnotic drugs, eszopiclone has a dose-related unpleasant bitter taste noted by 16% to 34% of patients.[59,60] Headache and dizziness were reported more commonly with eszopiclone than with placebo, and at higher doses, next-day confusion and memory impairment were reported in up to 3% of patients.[39,60] Eszopiclone is primarily metabolized by CYP3A4, so drugs that induce or inhibit this isoenzyme can have an impact on metabolism and clinical effects.[60]

L.A. needs a medication that will hasten sleep onset but does not need continued drug effect later in the night. Both zolpidem and zaleplon are useful alternatives for L.A. because of their efficacy for her sleep-onset difficulty. However, zaleplon may be preferred because of quick onset and short half-life to mitigate the risk of next-day hangover. Among the NBRAs, eszopiclone has the longest half-life and the greatest risk for next-day impairment.

Case 84-1, Question 9: Zolpidem 5 mg is prescribed because of its low cost and less risk for next-day impairment. L.A. expresses concern about possible adverse effects owing to its labeling as a Schedule IV controlled substance and the FDA boxed warning of complex sleep behaviors such as night eating and night driving.[63] How should L.A.'s concerns be addressed?

Patient counseling is most effective when it is interactive, with both patient and practitioner actively listening to each other while exchanging information. It is best to begin by emphasizing the benefits of zolpidem to improve her sleep and daytime functioning. Next, L.A. should be reassured that zolpidem is generally well tolerated and she will be prescribed the lowest dose to minimize the likelihood of adverse effects. Counseling should include a discussion of common and potentially serious adverse effects along with management strategies. Common possible adverse effects include

headache (28%), drowsiness (26%), fatigue (17%), and dizziness (14%).[39,58] Anaphylactoid reactions and nightmares have been reported in postmarketing studies. All NBRAs are contraindicated in patients who have experienced an episode of complex sleep behaviors after taking them. In addition, L.A. should be encouraged to report both effectiveness and all adverse effects to her clinician. Alcohol should not be consumed together with zolpidem or any NBRA because it can cause excessive side effects and interfere with L.A.'s sleep.

To address L.A.'s concern regarding complex sleep behaviors, a reasonable response would be "rarely, individuals taking sleeping medication have been reported to be making phone calls, eating, having sex, or driving while half asleep. The risk for these potentially dangerous effects increases if consumers take a higher than the recommended dose, or drink alcohol, or mix hypnotics with other sedating medications."[14,63] Another rare allergic reaction is facial swelling (angioedema). All manufacturers of hypnotic medication are required to include this information in their package inserts.[14,63]

Although the abuse potential of NBRAs is less than that of benzodiazepines, they are problematic in active substance use disorders. NBRAs are Schedule IV controlled substances with more potential for abuse than do ramelteon or sedating antidepressants, such as trazodone.[47] Tolerance and withdrawal associated with NBRAs are unlikely but reported with abrupt discontinuation, and patients should be counseled of this possibility, particularly at high doses.

CASE 84-1, QUESTION 10: L.A. asks about a newer sleep medication, suvorexant, and whether she could use this to help her sleep. What information can you provide L.A. regarding the safety and efficacy of suvorexant for insomnia?

Suvorexant is a dual orexin A and orexin B receptor antagonist (DORA) approved for the treatment of insomnia characterized by difficulty falling asleep and/or maintaining sleep.[64] The orexin signaling pathway promotes wakefulness and arousal; antagonism of

orexin receptors can promote sleep. Studies show that suvorexant can decrease latency to onset of sleep and wake after sleep onset without disrupting the sleep architecture.[65] The initial recommended daily dose is 10 mg within 30 minutes of bedtime and with at least 7 hours of sleep time available.[64] Suvorexant should be taken on an empty stomach because time to sleep onset may be delayed by 1.5 hours if taken with or soon after a meal. If needed, the dose can be increased in 5 mg increments to the maximum recommended daily dose of 20 mg at bedtime.[64] Suvorexant is a CYP3A4 substrate and a dose reduction of 5 mg daily is recommended when administered concurrently with a moderate CYP3A inhibitor; concurrent administration with a strong CYP3A inhibitor is not recommended.[66] No rebound insomnia or withdrawal symptoms have been observed following abrupt discontinuation.[67] When compared to zolpidem, suvorexant is associated with less abuse potential, although still classified as a Schedule IV medication.[65] However, individuals with a history of substance abuse disorder may be at increased risk for abuse with suvorexant.[65,66] The most commonly reported adverse effect in clinical trials evaluating suvorexant in patients with insomnia was daytime somnolence.[65]

Lemborexant is the second DORA approved for the treatment of insomnia characterized by difficulty falling asleep and/or maintaining sleep.[68] In placebo-controlled trials, lemborexant significantly improved objective and subjective measures of sleep onset and sleep maintenance and promoted NREM sleep with no effect on REM sleep.[65] The most common adverse event reported in clinical trials with lemborexant was somnolence. In a study evaluating the respiratory safety of lemborexant, patients with mild obstructive sleep apnea (OSA) did not experience worsening of sleep apnea.[69] The recommended dosing of lemborexant is 5 mg taken immediately before going to bed and with at least 7 hours remaining before the planned awakening time.[68] The dose may be increased to a maximum of 10 mg, based on clinical response and tolerability. The initial and maximum dose of lemborexant should be decreased to 5 mg when administered concomitantly with weak CYP3A4 inhibitors or in patients with moderate hepatic impairment. Concomitant use of

lemborexant should be avoided with moderate-to-strong CYP3A4 inducers and inhibitors and in patients with severe hepatic impairment.[68]

In January 2022, the FDA approved daridorexant, another DORA, for the treatment of insomnia. Daridorexant is approved for adults at 25- or 50-mg doses taken once daily 30 minutes before bedtime and at least 7 hours remaining before planned awakening.[70] Approval is based on two phase three multicenter randomized, double-blind, placebo-controlled, parallel-group trials evaluating daridorexant in 1854 adults with insomnia. One study evaluated 50 mg, 25 mg, or placebo and the other study evaluated 25 mg, 10 mg, or placebo once daily in the evening for 3 months. The 10-mg dose is not an approved dose. Daridorexant was associated with significant improvements versus placebo in daytime function, particularly in sleepiness and mood, sleep onset and sleep maintenance, and patient-reported total sleep time. Daridorexant was not associated with rebound insomnia or withdrawal effects. The most commonly reported adverse events were headache, somnolence, or fatigue. The maximum recommended dose in patients with moderate hepatic impairment or with concomitant use of a moderate CYP3A4 inhibitor is 25 mg. Daridorexant is not recommended in patients with severe hepatic dysfunction and should not be taken concomitantly with strong CYP3A4 inhibitors or moderate or strong CYP3A4 inducers. Taking daridorexant with or soon after a meal may delay the time to sleep onset. The FDA has recommended that daridorexant be classified as a controlled substance and scheduling is pending. Daridorexant cannot be compared with other DORAs because there are no head-to-head trials.[70]

Complex sleep behaviors, suicidal ideation, sleep paralysis, hallucinations, and cataplexy-like symptoms have been reported with DORAs. Because individuals with narcolepsy lack or have a decreased number of orexin receptors in the hypothalamus, DORAs are contraindicated in patients with narcolepsy. Studies comparing DORAs to other hypnotic agents, such as the NBRAs, are lacking.

BENZODIAZEPINES

The pharmacologic properties of benzodiazepines, including sedation, anterograde amnesia, antianxiety and anticonvulsant activity, muscle relaxation, and ethanol potentiation, occur as a result of interaction with various $GABA_A$ receptor subunits. The sedative effects of benzodiazepines are primarily mediated via activity at the α_1-subunit of the $GABA_A$ receptor.[71]

Although effective as hypnotics, benzodiazepines pose more disadvantages than do NBRA agonists, including the impairment in new learning or anterograde amnesia and the potential for complex sleep behaviors (eg, eating, sleeping, driving, or other activities while asleep). These effects can interfere with daytime functioning and result in the inability to remember new information. Patients should be cautioned regarding tolerance to the hypnosedative effects and physiologic dependence that can occur with long-term use of a benzodiazepine and the potential for rebound insomnia with abrupt discontinuation.[36,38,42] In addition, benzodiazepines are generally avoided in elderly patients because they increase the risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes because of drug accumulation risks (prolonged half-lives).[72]

Although several are available, only five benzodiazepines carry an FDA indication to treat primary insomnia (estazolam, quazepam, flurazepam, triazolam, and temazepam). Both lorazepam and clonazepam are commonly used, but indicated only for insomnia associated with anxiety. Many approved benzodiazepines, including estazolam, quazepam, and flurazepam, are no longer recommended because of oversedation caused by long half-lives from parent or active metabolites. For example, flurazepam has intermediate fat solubility but depends on the plasma concentrations of its metabolite, *N*-desalkylflurazepam, for most of its activity (T½ flurazepam 2.3 hours, *N*-desalkylflurazepam 47–100 hours).[42] *N*-desalkylflurazepam concentrations take ~24 hours to accumulate and induce sleep, but also accumulates during chronic dosing and can affect daytime cognition in patients.[42] Triazolam is also not recommended often, owing to a short half-life. Triazolam is most commonly associated

with rebound insomnia (ie, daytime nervousness, jitteriness, and insomnia worse than before) if abruptly stopped after >7 to 10 days of continuous use and exhibits withdrawal problems.[44,54,71]

Among FDA-approved benzodiazepines to treat primary insomnia, temazepam is most often recommended likely due to its intermediate duration of action (T½ ~8.8 hours). It has moderate fat solubility, but a longer dissolution time caused by its large particle size, and takes 1.5 to 2 hours to reach peak plasma concentrations. The longer dissolution has a notable lag time for efficacy, and thus should be taken 45 to 60 minutes before bedtime.

INSOMNIA IN AN ILL PATIENT

Insomnia and Effect on Sleep Stages

CASE 84-2

Question 1: A.T., a 42-year-old female with a 5-year history of hypothyroidism and a 2-year history of hypertension and chronic lower back pain, was just transferred from the intensive care unit (ICU) into a medical unit. Her cardiac status is considered "stable" 2 days after a myocardial infarction (MI). She is 69 inches (175.26 cm) tall and weighs 158.73 pounds (72 kg). She is receiving aspirin 81 mg (enteric coated), levothyroxine 112 µg, and nifedipine ER 30 mg all taken by mouth 1 hour before breakfast every day. Her main problem is insomnia, including difficulty falling asleep, difficulty maintaining sleep, and early morning awakenings. A.T. reports insomnia for 6 weeks before admission, which worsened during the hospitalization.

What type of insomnia does A.T. have, and how might the insomnia affect her health?

A.T.'s insomnia is considered chronic because she experienced it for >1 month before hospital admission. It is severe because it involves difficulty falling asleep, maintaining sleep, and early morning awakening. Careful monitoring and effective treatment of A.T.'s sleep disturbance is crucial; studies show disrupted sleep can increase the

risk of another adverse cardiac event, owing to worsening autonomic instability and poor perfusion to the myocardium.[73]

Because normal sleep moves through all the stages of NREM and REM in a continuous cycle, a patient deprived of continuous sleep may not receive sufficient time in each sleep stage. When stage 2 is diminished, muscles have insufficient opportunity to rest and rejuvenate. If NREM stages 3 and 4 are eliminated, immune function and the healing process can be disrupted. If REM sleep is deprived or excessive, neurotransmitter function may be altered and physiologic homeostatic processes can be disrupted.[15,16,29]

Drug or Disease Etiologies

Case 84-2, Question 2: What individual drug or disease-state factors should be assessed in A.T. before developing a treatment plan?

The insomnia treatment algorithm in Figure 84-2 is useful in systematically addressing A.T.'s sleep problem. It calls for thoroughly evaluating all concomitant conditions and the type of insomnia in each patient. Numerous medical disorders and primary sleep disorders are associated with difficulty falling asleep and maintaining sleep (**Tables 84-4** and **84-5**).[5,29,73] First, A.T. should be assessed for sleep apnea because untreated sleep apnea is a known etiology of cardiac disease and hypnotics can be dangerous in untreated sleep apnea (see Case 84-5, in the section on Sleep Apnea). Second, A.T.'s pain management should be assessed for optimal efficacy. Acute post-MI pain adds to A.T.'s chronic lower back pain. Of patients with lower back pain, 50% experience chronic poor sleep patterns.[29,73] Third, A.T. was just transferred out of the ICU. Sleep deprivation in an ICU is common and is attributed to the continuous lighting, noise, and constant interventions. Sleep deprivation may prolong or worsen a disease process through diminished natural killer cell activity and decreased stages 3 and 4 of NREM sleep (when healing occurs).[42,74,75] Medications also may be contributing to A.T.'s insomnia (Table 84-4). Levothyroxine can overstimulate the

central nervous system (CNS) if given in excessive doses. A.T.'s thyroid status should be reevaluated to ensure appropriateness of the thyroid dose, especially considering her post-MI status.[76] Calcium channel blockers have been associated with occasional sleep disturbances; therefore, nifedipine should be evaluated as a potential contributing factor.[76] See Table 84-3.

Table 84-4
Potential Causes of Chronic Sleep Disorders

Psychiatric Disorders	
Anxiety disorders	Depressive disorders
Bipolar disorder	Psychotic disorders
Personality disorders	Somatoform disorders
Organic mental disorders	Substance abuse disorder
Medical and Neurologic Disorders	
Angina pectoris	Dementia
Bronchitis	Peptic ulcer disease
Chronic fatigue	Hyperthyroidism and hypothyroidism
Cystic fibrosis	Asthma
Huntington disease	COPD
Parkinson disease	Epilepsy
Hypertension	Gastroesophageal reflux
Arthritis	Renal insufficiency
Cardiac disease	Connective tissue disease
Chronic pain	
Cancer	
Sleep Disorders	
RLS	Sleep apnea (obstructive or central)
PLMS (nocturnal myoclonus)	Primary snoring

Psychiatric Disorders	
Circadian rhythm sleep disorder (jet lag, shift work, delayed sleep phase)	Narcolepsy
Drugs Associated With Sleep Disturbance	
Insomnia	Hypersomnia
Alcohol	Alcohol
Bupropion	Benzodiazepines
Fluoxetine	Antihypertensives
Sertraline	Clonidine
MAO inhibitors	α-Adrenergic blockers
TCA	ACE inhibitors
Thyroid supplements	β-Blockers
Calcium channel blockers	Anticonvulsants
Decongestants	Analgesics
Appetite suppressants	Chloral hydrate
Theophylline	Antipsychotics
Corticosteroids	Antihistamines
Dopamine agonists	Opioids

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; MAO, monoamine oxidase; PLMS, periodic limb movements during sleep; RLS, restless legs syndrome; TCA, tricyclic antidepressants.

Sources: Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care Survey 1999–2010. *Sleep.* 2014;37:1283–1293; Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. *Sleep.* 2007;30:213–218. Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *Am J Manag Care.* 2006;12(8 Suppl):S221–S229; Fondell E, Axelsson J, Franck K, et al. Short natural sleep is associated with higher T cell and lower NK cell activities. *Brain Behav Immun.* 2011;25:1367–1375.

Table 84-5
Agents for the Treatment of Sleep Apnea or Narcolepsy

Generic (Brand Name)	Recommended Dosage Range (mg)	Indication
Armodafinil (Nuvigil®)	150–250 mg once daily	EDS with narcolepsy or OSA
Dextroamphetamine (Dexedrine®) Dextroamphetamine/amphetamine salts (Adderall®)	5–60 mg/day divided doses	EDS with narcolepsy
Methylphenidate (Ritalin®)	10–60 mg/day divided doses	EDS with narcolepsy
Modafinil (Provigil®)	200–400 mg once daily	EDS with narcolepsy or OSA
Sodium oxybate (Xyrem®) Sodium oxybate salts (Xywav®)	4.5–9 g/night in two divided doses	EDS or cataplexy with narcolepsy
Solriamfetol (Sunosi®)	75–150 mg once daily[a] 37.5–150 mg once daily[b]	EDS with narcolepsy or OSA
Pitolisant (Wakix®)	9–36 mg once daily	EDS or cataplexy with narcolepsy

EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea.

[a]Narcolepsy dosage.

[b]Obstructive sleep apnea (OSA) dosage.

Sources: Sunosi (solriamfatol tablets). Product information. Jazz Pharmaceuticals Inc; 2019; Ahmed I, Thorpy M. Clinical features, diagnosis and treatment of narcolepsy. *Clin Chest Med.* 2010;31:371–381; Robinson DM, Keating GM. Sodium oxybate: a review of its use in the management of narcolepsy [published correction appears in *CNS Drugs*. 2007;21:692]. *CNS Drugs.* 2007;21:337–354; Wakix (pitolisant tablets). Product information. Harmony Biosciences LLC; 2020; Xyrem (sodium oxybate oral solution). Product information. Jazz Pharmaceuticals Inc; 2020; Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution). Product information. Jazz Pharmaceuticals Inc; 2020; Scammell TE. Narcolepsy. *N Engl J Med*. 2015;373:2654–2662.

Another clue to a possible cause of A.T.’s sleep problem is her description of early morning awakening, which could be related to hospital activity during these hours or to the presence of a major

depressive disorder. A.T. requires psychiatric evaluation to rule out depression, which occurs in about one-third of patients after an MI.[77] In general, patients with chronic illnesses are at increased risk for experiencing major depression, which typically presents with insomnia or hypersomnia. Interestingly, medical outcome studies of other chronic illnesses (cardiovascular, pulmonary, renal, and neurologic disease) show a high prevalence of sleep disturbance even in those not suffering from depression.[29,73] Chronic insomnia related to multiple causes can be resistant to treatment; however, treatment of underlying causes increases the likelihood of insomnia resolution (see Table 84-4).

Comparing Available Hypnotics

Case 84-2, Question 3: A.T.'s pain is now under control; her levothyroxine dose is appropriate; and nifedipine-induced sleep disturbance, sleep-disordered breathing, RLS, and PLMS have all been ruled out. A psychiatric evaluation finds that A.T. does not have major depression, but she is anxious about "life after a heart attack." She meets the criteria for primary insomnia and adjustment disorder with anxiety. She continues to have trouble falling asleep and staying asleep. She will be discharged in 2 days. The psychiatric consultation suggests an adjunctive medication with anxiolytic properties that may also help with sleep. Which hypnotic is best for A.T., considering her individual clinical characteristics?

The ideal hypnotic for A.T. should act quickly and continue working throughout the night to provide her with uninterrupted sleep. A hypnotic that is not metabolized in the liver would have a lower potential for drug interactions and lessen the opportunity for systemic accumulation. If daytime drug concentrations are needed to calm anxiety, however, a hypnotic with slowly eliminated active metabolites may be desirable. The comparable doses of the hypnotic medications are listed in Table 84-2. When considering available hypnotic medications, differences in pharmacodynamic and pharmacokinetic properties should be considered (Table 84-2).

Onset of effect is related to lipophilicity, receptor binding affinity, and T_{max}.[40,42]

For A.T., a nonselective benzodiazepine hypnotic is preferable because of the need for anxiolytic properties in addition to hypnotic efficacy. NBRAs are not effective anxiolytic agents. Temazepam is an appropriate choice for A.T. Of the five approved benzodiazepine agents approved for insomnia (see Table 84-2), temazepam's advantages are intermediate duration of activity that would keep her asleep throughout the night, offer anxiolytic benefit, and present a lower risk of daytime impairment owing to no known active metabolites.[42,78] A.T. may require a hypnotic for longer use. She has difficulty moving around during the day because of her chronic lower back pain, and oversedation from drug accumulation may impair her daytime functioning. A potential advantage of using temazepam in A.T.'s case is its lack of hepatic oxidative metabolism and intermediate duration of action of 8 to 12 hours. It does not interfere with the metabolism of other hepatically metabolized drugs and it does not accumulate, minimizing the potential for daytime impairment.[42,78] The long onset of action may be of concern, although A.T. could take temazepam an hour before bedtime to optimize timing for sleep.

Benzodiazepine Dependence and Tolerance

Case 84-2, Question 4: In further discussion with A.T., who prefers to try cognitive-behavioral interventions for anxiety reduction and sleep induction, temazepam 15 mg at bedtime is prescribed on an as-needed basis. A.T. will be monitored regularly as an outpatient for efficacy and tolerability. As A.T. is preparing to leave the hospital, her daughter expresses concerns about the potential for physical dependence on temazepam versus other sleep medications, and the risk of A.T. "becoming addicted." How would you respond to her concerns?

Fear of dependence and addiction to medications is a concern among the general public. Television station "medical experts" and popular magazine "health sections," while providing information, may

increase the potential for confusion, erroneous impressions, and misinformation. For health care practitioners, it becomes even more crucial to provide sound drug information in common, easy-to-understand terms.

An example of the practitioner's response may be, "I'm glad you have expressed a concern; it gives us a chance to discuss temazepam therapy before your mother leaves the hospital. Temazepam has been prescribed for a medical reason, to improve her sleep and aid in her healing process. One therapeutic benefit of temazepam is an 8-hour duration of effect. Your mother will be able to sleep throughout the night so that she is well rested during the day. It also may decrease her anxiety over not sleeping, and that puts less stress on her heart."

Possible side effects of temazepam include sedation, unsteadiness, dizziness, and, with long-term use, the possibility of permanent cognitive deficits including reduction in short-term memory. She should let her doctor know if she experiences any adverse effects. Right now, it is unclear how long A.T. will be taking temazepam. Duration of therapy needs to be assessed on an ongoing basis. If A.T. takes temazepam every night for >4 weeks, two things could happen: (a) she may develop a tolerance and it may not help her sleep anymore, or (b) she may develop a dependence in which she may have worse insomnia if she does not take it. The primary concern is not addiction but the possible dependence. This means A.T. should not change her dose or stop on her own. Any changes in dose or stopping must be done slowly and with her doctor's involvement. These two scenarios do not always occur and are not likely because your mother will be taking it on an as-needed basis. If one or the other does happen, other interventions may be tried to help with her sleep, or the temazepam dose can be gradually decreased to prevent withdrawal problems. It is important to advise A.T. to avoid alcohol, and report any decrease in effectiveness or any adverse effects to her health care practitioner.

Patients taking benzodiazepines for >1 year tend to be older, medically ill, chronically dysphoric, and have panic disorder or chronic insomnia. Most chronic use appears to be medically

appropriate and does not lead to dose escalation or abuse. Among patients with chronic dysphoria, the indications are less clear, and dose escalation is noted sometimes without notable therapeutic benefit. Benzodiazepine hypnotics rarely are taken alone for pleasure and generally are not likely to be abused. Among patients with substance use disorders, however, they frequently are taken as part of a polysubstance abuse pattern with alcohol and narcotics, methadone, and cocaine users. In these groups, abuse is highly prevalent. Benzodiazepines are used to augment euphoria (narcotics and methadone users), to decrease anxiety and withdrawal symptoms (alcohol use), and to ease the "crash" from stimulant-induced euphoria (cocaine users).[79,80]

Physiologic dependence on benzodiazepines, resulting in a withdrawal and abstinence syndrome, develops usually after 2 to 4 months of daily use of the longer half-life benzodiazepines. Shorter half-life benzodiazepine use can result in physiologic dependence earlier (days to weeks) and may be associated with more withdrawal problems.[42,54] See Table 84-2 for a comparison of pharmacokinetic properties of hypnotics.

INSOMNIA AND PSYCHIATRIC DISORDERS

Stepwise Approach to Selecting a Hypnotic

CASE 84-3

Question 1: M.B., a 33-year-old female, is hospitalized after a suicide attempt in which she tried to overdose on sertraline, ibuprofen, and diphenhydramine. Before the suicide attempt, M.B. had been sober for 3 years. She is diagnosed with major depression and alcohol use disorder. After completing an interview with M.B., you learn she was doing well until 3 months ago when depression symptoms worsened during her divorce. Two weeks before admission, her outpatient primary care doctor prescribed sertraline for depression and omeprazole for acid reflux. She went on a drinking binge 5 days ago that ended with a suicide attempt. Her target symptoms include early morning awakening, trouble falling asleep, 15-pound (6.80-kg) weight loss, apathy, social withdrawal,

depressed mood, hopelessness, and anhedonia. Medications continued in the hospital include sertraline 100 mg daily and omeprazole 20 mg daily. M.B. currently reports feeling restless and sleeping only 3 to 4 hours a night. Use Table 84-2 and Figure 84-2 to compare the clinically significant differences between available hypnotics and to demonstrate how such information can be used to develop a patient-specific treatment plan.

What is the best approach to solving M.B.'s sleep problem?

The insomnia treatment algorithm outlined in Figure 84-2 serves as a useful guide for the assessment and management of M.B.'s sleep problem. Concomitant conditions and the type of insomnia (difficulty falling asleep, difficulty maintaining sleep, early morning awakening) are assessed simultaneously. Possible causes or contributing factors are identified and treated. The type of insomnia can aid in treatment selection. Cognitive-behavioral interventions can be implemented if M.B. is willing and able to participate.

Factors to consider in the drug selection process include substance use history, the need for rapid onset, and duration of effect. For example, agents with long-acting metabolites (eg, flurazepam) may accumulate or cause daytime hangover. If the hypnotic has no hepatic metabolism, it will not be subject to drug interactions with other agents that are hepatically metabolized. Also, if insomnia is chronic and resistant to hypnotic treatment, or if a low abuse potential agent is desired (eg, for a person with an existing substance use disorder such as M.B.), trazodone or another sedating antidepressant may be selected.

Sleep Disturbance of Depression

Case 84-3, Question 2: What type of insomnia does M.B. have? How is it different from other types of insomnia?

M.B. has trouble falling asleep and early morning awakening, and sleep time has decreased to 3 or 4 hours a night. She is diagnosed with major depression, and sleep difficulty is part of the disorder. Generally, initial insomnia and early morning awakening are

associated with depression, although difficulty maintaining sleep and next-day fatigue are common as well. M.B. is most bothered by trouble falling asleep, early morning awakening, and next-day fatigue. Up to 65% of outpatients with major depression report one or more symptoms of sleep disturbance, whereas 90% of inpatients with depression such as M.B. report insomnia.[81]

The insomnia of depression is likely related to a dysregulation of neurotransmitters, such as serotonin, norepinephrine, and dopamine, in addition to dysregulation of the hypothalamic–pituitary axis. All are involved in regulating mood and the sleep–wake cycle.[16,66] Neurotransmitter activity is modified by the effects of antidepressants on REM sleep. Most pro-serotonergic antidepressants suppress REM, causing increased REM latency and decreased total REM time.[81,82] Indeed, REM sleep deprivation can elevate mood.[81,83] Patients who are depressed and deliberately deprived of REM sleep have had a reduction in depressive symptoms. In addition to effects on REM, antidepressants redistribute slow-wave sleep to more physiologically natural patterns, with increased intensity in the first half of the night.[83] Sedating antidepressants with serotonin 2 (5-HT_2) antagonist properties, such as trazodone and mirtazapine, alleviate insomnia and improve sleep architecture.[81]

Treatment

Case 84-3, Question 3: M.B. and the treatment team ask you what factors other than depression (ie, medications, alcohol) may contribute to M.B.'s insomnia. How can her sleep problem be solved?

The treatment for M.B.'s insomnia should begin with patient education. She should be informed that >90% of patients who are depressed have some sleep disturbance, either too little or too much, and her sleep should improve as depressive symptoms improve (in 2–8 weeks). Counseling on cognitive-behavioral interventions to improve sleep may be appropriate when M.B.'s

depression begins to clear and she is more motivated to improve her sleep hygiene. In the meantime, the potential contribution of sertraline causing restlessness or insomnia should be assessed by confirming the drug is dosed in the early morning to minimize this effect.[78] A sedating antidepressant such as mirtazapine may be preferred unless M.B.'s history includes a positive response with sertraline that would justify ongoing treatment. M.B. also was using alcohol before admission. Alcohol disrupts sleep and can increase arousal when its sedative effects wear off, leading to more fragmented sleep.[38,84] All patients with sleep issues should be counseled to minimize or eliminate alcohol altogether.[84] M.B. should avoid alcohol given her history of substance use. Drug and alcohol withdrawal and the lingering "abstinence syndromes" often are associated with insomnia, although sometimes hypersomnia is the predominant symptom.[38,85]

HYPNOTICS

Prescribing a hypnotic short-term or a sedating antidepressant is recommended for patients who are depressed with insomnia because a good night's sleep can improve treatment adherence and daytime functioning until antidepressant effects become apparent.[73,74] All antidepressants, including selective serotonin reuptake inhibitors (SSRIs), such as sertraline, can improve sleep as the depression lifts; however, most antidepressants such as SSRIs, serotonin norepinephrine reuptake inhibitors (eg, venlafaxine, desvenlafaxine, duloxetine), bupropion, and monoamine oxidase inhibitors can cause insomnia as well.[76,81] Analysis of residual symptoms in partially treated patients who are depressed taking SSRIs shows continuing insomnia is present in 44%, requiring additional interventions such as trazodone or mirtazapine.

Hypnotics that act at benzodiazepine receptors are not recommended for M.B. because of her drug use history and recent alcohol use. Older nonselective benzodiazepines such as temazepam can have a euphoric effect, are cross-tolerant with alcohol, and are likely to be misused by patients with alcohol and

substance use problems.[42] Abuse, dependence, and withdrawal reactions have been reported with newer $GABA_A$ receptor α_1-subunit selective NBRAs (zolpidem, zaleplon, eszopiclone); therefore, neither class of drugs is appropriate for M.B.[39,58]

Antidepressants

Case 84-3, Question 4: What is the evidence for trazodone's use in managing insomnia? What other antidepressants are used in the treatment of insomnia? Discuss the advantages and disadvantages of using sedating antidepressants for the treatment of insomnia in M.B.

If the clinician determines that sertraline treatment is preferred, then trazodone may be added to alleviate insomnia.[86] The addition of trazodone to fluoxetine, bupropion, or monoamine oxidase inhibitors decreased time to sleep and increased duration of sleep but caused intolerable sedation in a few patients who received fluoxetine. Tolerance did not develop to the sedative effects of trazodone in short-term studies (>6 weeks) used adjunctively for depression; however, decreased benefit with time has been reported.[86] The 5-HT_2 antagonist properties of trazodone at low dosages, in addition to its antagonism at histamine-1 and α_1 adrenergic receptors, provide the rationale for its efficacy as a sedating agent.[87]

Trazodone is not thought to be a highly effective antidepressant medication because most people cannot tolerate an effective depression dose (300–600 mg/day). Owing to its sedating properties, low-dose trazodone (50–200 mg/day at bedtime) has become a commonly prescribed adjunctive medication to induce sleep while awaiting the onset of another primary antidepressant's effect.[86] Trazodone has a half-life of ~6.4 hours in younger adults and 11.6 hours in the elderly. It undergoes hepatic metabolism via CYP2D6 and CYP3A4; thus, inhibitors of these isoenzymes can increase blood levels and worsen side effects. The most common side effects of trazodone include drowsiness (29.1%), dizziness (21.9%), and dry mouth (17.7%). Cardiac arrhythmias are possible at

doses >200 mg/day, as is priapism, a painful prolonged erection that occurs in 1 of 1000 to 10,000 males. Although priapism is considered rare, it can lead to impotence if untreated; therefore, males should be counseled about priapism at any dose of trazodone.[86]

In the only placebo-controlled trial of trazodone conducted in primary insomnia, investigators compared the hypnotic efficacy of trazodone and zolpidem with placebo in 306 adults (21–65 years of age). Subjects were randomly assigned to receive trazodone 50 mg, zolpidem 10 mg, or placebo nightly for 2 weeks. Sleep parameters were assessed using a subjective sleep questionnaire, which patients completed each morning and at weekly office visits. Trazodone was found to be as effective as zolpidem for the first week of treatment, but during the second week, only zolpidem was more effective than was placebo.[86] Tricyclic antidepressants (TCAs; eg, amitriptyline, doxepin) were used to treat primary insomnia for years based on case reports describing efficacy in doses of 10 to 75 mg/night.[42,81] TCAs, however, increase the risk of cardiovascular problems and anticholinergic side effects in a dose-related manner (see Chapter 86, Depressive Disorders).

Ultralow-dose doxepin (a TCA) 3- and 6-mg tablets are available for the treatment of insomnia characterized by difficulties with sleep maintenance. Doxepin is not a controlled substance, so it may be of value in patients with a history of substance use. Four clinical trials conducted in slightly >1000 patients demonstrated ultralow-dose doxepin's efficacy and safety in both younger adults and the elderly.[88] Doxepin demonstrated improved sleep efficiency during the final third of the night and in the seventh and eighth hours of sleep. Doxepin was well tolerated, with residual sedation and anticholinergic effects no different than that for placebo. There were no significant effects on next-day alertness, memory, or psychomotor function. Hypnotic efficacy with doxepin was demonstrated for up to 3 months.

For M.B., a TCA raises additional safety concerns. M.B. has a history of substance use and prior suicide attempts. Both are risk factors for future suicide attempts. TCAs are more toxic in overdose

when compared with trazodone, and there are multiple reports of TCA plasma levels increasing to toxic levels when administered in combination with CYP450 2D6 inhibitors (see Chapter 86, Depressive Disorders).

Switching to mirtazapine as an antidepressant that offers more sedation is a reasonable consideration for M.B. If M.B. has a partial but significant response to sertraline at maximal tolerated doses and good tolerability except for insomnia at 4 weeks, mirtazapine can be added to facilitate remission. Mirtazapine has 5-HT_2 antagonist and antihistamine effects, which impart sedation, and it is safer than are TCAs in overdose.[81] Mirtazapine is not associated with priapism, but it can cause metabolic disturbances including weight gain and dyslipidemia.

INSOMNIA IN THE ELDERLY

CASE 84-4

Question 1: S.D., a 77-year-old male, is seen for his initial geriatrics primary care clinic visit. Vital signs include temperature, 98.8 °F (37.11 °C); heart rate, 58 beats/minute; respiratory rate, 18 breaths/minute; BP, 166/69 mm Hg; height, 63 inches (160.02 cm); and weight, 109 pounds (49.44 kg). He was referred from an emergency department (ED) visit 4 days earlier with reports of palpitations and anxiety. Before his ED visit, his medications included atenolol 50 mg daily, lorazepam 1 mg at bedtime, and saw palmetto 320 mg daily. At his ED visit, he stated he had taken lorazepam for sleep for >1 year, but did not take it the prior 2 nights and started feeling palpitations and anxiety. His electrocardiogram showed normal sinus rhythm at 67 beats/minute, and S.D.'s head computed tomography scan result was negative for any hemorrhage. S.D. was told not to restart the lorazepam, but instead to take diphenhydramine 50 mg at bedtime. He took only one dose because it makes him feel "terrible" and fatigued for the next 2 days. On further questioning, he states that he falls asleep without difficulty, usually awakens two to three times each night to urinate, and often has difficulty falling back to sleep. In the past, lorazepam was helpful for his sleep difficulty.

What considerations are important for the assessment and treatment of insomnia in an elderly patient such as S.D.?

Treatment of insomnia in the elderly represents a therapeutic dilemma. Evidence supports an increased need to treat insomnia in the elderly to reduce its potentially serious complications, yet many drug treatment options have potential for harm that may outweigh their benefit. In a large epidemiologic study of sleep problems in 9282 individuals 65 years and older conducted by the National Institute on Aging, 57% of subjects indicated at least one sleep problem occurring most of the time, 19% had difficulty falling asleep, 30% reported awakening at night, and 19% reported of awakening too early.[89] Despite such a high frequency of sleep problems, they are primarily thought to be more a marker of poor physical and mental health rather than caused by aging itself.[89,90]

Historically, it was accepted that age-related sleep changes begin in early adulthood and progress steadily across the adult lifespan.[91] However, in a meta-analysis of 65 studies of quantitative sleep parameters across the lifespan of individuals from ages 5 to 102 without sleep problems, most changes in sleep were found to occur by age 60.[81] Changes in sleep latency are small and subtle, with an overall increase between 20 and 80 years of <10 minutes. Increases in percentages of stages 1 and 2 sleep, as well as decreases in total sleep time, percentage of slow-wave and REM sleep, and REM latency, were significant with aging up to age 60, but only minimal changes were seen after age 60. Only sleep efficiency was found to continue to significantly decrease after age 60. Therefore, identifying factors underlying sleep problems in the elderly is critical and can lead to appropriate diagnosis and treatment. Elderly patients need not be resigned merely to getting the sleep that they do because they are "getting older."[91]

Case 84-4, Question 2: What are the more common underlying causes of sleep problems in the elderly?

Common precipitants of acute insomnia in the elderly include acute medical illnesses, hospitalization, changes in the sleeping environment, medications, and acute or recurring psychological

stressors. Chronic or long-term insomnia may be associated with a variety of underlying medical, behavioral, and environmental conditions, as well as medications.[92] Identification of treatable underlying causes should be the first step in the management of insomnia, based on a medical and medication history, physical and mental status examination, and laboratory investigations including thyroid function, serum chemistry panel, and cardiopulmonary studies if indicated.[92,93] Special attention should be directed to chronic pain from any cause, pulmonary disease, chronic renal disease, neurologic disorders, and polyuria from urinary, prostate, or endocrine disorders. Medical conditions with a strong association with insomnia include heart disease, hypertension, diabetes, stomach ulcers, arthritis, migraine, asthma, chronic obstructive pulmonary disease (COPD), neurologic problems, menstrual problems, depression, and bipolar disorder.[94,95] Primary sleep disorders are RLS, sleep apnea, and circadian rhythm disorders.[73,90,95] The potential contribution of medications to the sleep problem needs to be evaluated, and changes in medication or timing of administration should be considered. Many drugs with CNS effects can alter patterns of sleep and wakefulness, both during their use and withdrawal.[37,89,95] Both prescribed and OTC medications must be evaluated. The more common drugs of concern include stimulants (caffeine, nicotine, and amphetamines), alcohol, activating antidepressants (eg, SNRIs and bupropion), pseudoephedrine, bronchodilators, β-blockers, calcium channel blockers, corticosteroids, and dopamine agonists. Evening administration of drugs such as diuretics may also contribute to nighttime awakenings and sleep problems.

Psychological Versus Drug Treatments for Insomnia

Case 84-4, Question 3: Which nondrug therapy treatment options might be appropriate for S.D.?

CBT is an effective and safe alternative to drug therapy for insomnia and has also been shown to be an effective augmenting treatment with drug therapy.[35,36] CBT limitations include that it is little known, not widely available, and more time consuming than is drug therapy. Both pharmacologic and nonpharmacologic approaches are effective for the short-term management of insomnia in late life, and current evidence suggests that sleep improvements are better sustained over time with behavioral treatment.[35] A comparative meta-analysis of 21 studies of pharmacotherapy and behavior therapy for persistent insomnia in adults found that both treatments similarly produced moderate-to-large improvements in number of awakenings, wake time after sleep onset, total sleep time, and sleep quality.[96] Behavior therapy, however, resulted in a greater reduction in sleep latency than did pharmacotherapy. CBT was compared with pharmacotherapy (zolpidem) and its combination in 63 young and middle-age adults with chronic sleep-onset insomnia.[35] There was a significant difference in percentage change in improved sleep-onset latency (CBT 52%, combination therapies 52%, zolpidem 14%, placebo 17%). No significant differences were found among the groups in total sleep time. The authors concluded that CBT, alone or in combination with pharmacotherapy, was more effective than was pharmacotherapy alone or placebo for the treatment of sleep-onset insomnia. Avoidance of medications with their associated costs, adverse effects, and drug interactions are the primary advantages of CBT. Disadvantages of CBT include possible longer time to effective treatment, higher initial cost, and relative paucity of trained providers in many areas.[97]

Case 84-4, Question 4: What are the concerns about the use of lorazepam or another benzodiazepine in S.D.?

Specific concerns need to be addressed about the risks most associated with benzodiazepines in the elderly regarding dependence, risk of falls, cognitive dulling, and memory loss.[72] Concern about dependence and the nontherapeutic use of

benzodiazepines has been an important factor in limiting the long-term treatment of insomnia with hypnotic drugs.[98] In patients with insomnia specifically, the risks of dependence and recreational use of benzodiazepines are relatively low. Dose escalation appears to occur only when treatment is ineffective or when the patient has a history of substance use disorder or anxiety. Although still controversial, the risk of dependence and abuse associated with the newer nonbenzodiazepine drugs may be lower than that associated with benzodiazepine hypnotic drugs. An even greater concern with benzodiazepine use in the elderly is the risk of falls and subsequent hip fractures. Using 42 months of Medicaid health care claims data in New Jersey for >125,000 individuals older than 65 years, the association between hip fractures and benzodiazepine use was evaluated.[99] Compared with not being exposed to a benzodiazepine, exposure to any benzodiazepine was associated with a 54% higher rate of hip fracture, and after adjusting for potential confounding variables, benzodiazepine use was associated with a 24% higher rate of hip fracture. Use of short half-life benzodiazepines was found to be no safer than the use of long half-life benzodiazepines, and the risk of hip fracture was highest during the first 2 weeks after starting a benzodiazepine. These findings support the usual recommendation that the elderly should be given doses lower than that for their younger adult counterparts, but they challenge the suggestion that only long half-life drugs should be avoided in the elderly owing to clearance concerns. Elderly patients should also be monitored closely to prevent cognitive decline caused by benzodiazepines and avoid use when possible.[100]

CASE 84-4, QUESTION 5: What are the concerns about the use of diphenhydramine in S.D.?

Sedating antihistamines are not recommended for treating insomnia in the elderly because there is no evidence of sustained benefit and they pose significant risk of anticholinergic effects, notably cognitive impairment, dry mouth, urinary retention, and

constipation.[37,72,97,101] Duration of sedative effect efficacy from antihistamines is also problematic, with tolerance to sedative effects developing quickly (3–7 days).[102,103]

S.D.'s primary sleep problem is related to his nocturia. He is self-treating his urinary symptoms with saw palmetto, which he did not mention at his ED visit (perhaps because no one asked whether he used any OTC or herbal medications). His primary treatment, therefore, must be directed at assessing and more successfully treating his nocturia. S.D. also likely experienced lorazepam withdrawal symptoms. The many potential risks associated with benzodiazepines in the elderly led to a valid decision to discontinue lorazepam. However, the choice of diphenhydramine was poor not only because of limited short-term efficacy but also because of its potential to worsen both urinary symptoms and memory impairment. Clinicians must ask patients about OTC and herbal medications they may be using to self-treat their symptoms. The best treatment of sleep problems in elderly persons is to identify any underlying treatable cause, review and identify any sleep hygiene issues, and avoid using benzodiazepines or sedating antihistamines, whose risks often outweigh any benefit. Ramelteon may be considered as an option for elderly patients with sleep-onset insomnia who have an increased risk of falls and in patients with a history of COPD or substance use disorder.[48]

PEDIATRIC INSOMNIA

Typical sleep needs in children vary from 12 to 14 hours in children ages 1 to 3 years to between 8.5 and 9.5 hours in adolescents.[104] All major sleep disorders can occur in youth, and therefore evaluation for insomnia, RLS, PLMS, sleep apnea, and narcolepsy are needed whenever symptoms warrant. Trouble initiating and maintaining sleep are more common in children with ADHD (25%–50%) and autism spectrum disorders (44%–83%). Of infants and toddlers, 10% to 30% have bedtime sleep resistance that can be managed

behaviorally with parental education. Inconsistent bedtime, falling asleep away from bed, fears, and psychiatric and medical conditions can all contribute to poor sleep in children.[104]

At least 5% to 10% of high school students have delayed sleep phase syndrome, a physiologic condition in which they do not fall asleep until between 1:00 and 3:00 AM and they awaken between 9:00 AM and noon. School schedules dictate earlier awakening, resulting in chronic sleep deprivation. Poll data indicate that 28% of high school students fall asleep in school at least once a week, and 14% are late or miss school because of oversleeping.[104]

Behavioral interventions to promote good sleep habits (eg, consistent bedtime and wake time, before-bedtime ritual) should be initiated during childhood and continued throughout adolescence to promote a lifetime of healthy sleep. No hypnotics are FDA approved for insomnia in children and adolescents, and significant data are lacking to guide clinicians on medications to improve sleep in youth. Diphenhydramine, clonidine, and melatonin are commonly used in children and some adolescents; however, the use of Z-hypnotics is also increasing, although this class has not been well studied in this population.[105]

PREGNANCY AND LACTATION

Pregnant patients have insomnia symptoms more often than do their nonpregnant counterparts, and many ingest hypnotic or sedating medications. Despite frequent usage of hypnotics, health care providers are often reluctant to prescribe medications to pregnant females for fear of teratogenicity. Doxylamine is FDA pregnancy category A, although this indication is derived from the treatment of hyperemesis gravidarum and not insomnia.[106] Diphenhydramine is in FDA pregnancy category B and is generally considered the safest sleeping medication in pregnancy.[103] Nevertheless, a pregnant patient should only use it on an as-needed basis. Sedating antihistamines are not compatible with breast-feeding because they

have the potential to dry up milk supply because of anticholinergic effects.[107] Melatonin, ramelteon, suvorexant, and lemborexant should not be used because of unknown risks to the fetus.[108,109]

Regarding the most commonly prescribed hypnotic, zolpidem, the American Academy of Pediatrics considers it compatible with breast-feeding, but the risk versus benefit should be considered on an individual basis.[107,108] Other Z-hypnotics and DORAs do not have sufficient data in pregnancy and lactation to make recommendations.[1]

Benzodiazepine hypnotics are pregnancy category D or X. They should be avoided in pregnancy because of the risk of respiratory depression, neonatal flaccidity, infant feeding difficulties if given in the second and third trimesters, and the controversial risk of cleft palate if given in the first trimester.[110] Benzodiazepines are not recommended in breast-feeding because the risks outweigh the benefits in most cases.[107]

SLEEP APNEA

Clinical Presentation

CASE 84-5

Question 1: E.S., a 52-year-old male, presents to an ambulatory care clinic with chronic fatigue, low energy, excessive snoring, and overall less restful sleep. When asked what prompted E.S. to come to the clinic, he answers: "My wife and I have been sleeping in separate bedrooms for the past 6 months. She says my loud snoring and gasping to breathe keeps her awake. I'm tired all day and find myself nodding off a lot." His symptoms have worsened during the past year since early retirement. He has gained weight (220 pounds [99.79 kg]; he is 72 inches [182.88 cm] tall and his body mass index is 29.8 kg/m^2) and has developed hypertension. E.S.'s current BP reading is 145/92 mm Hg. Medications include lisinopril 10 mg and aspirin 81 mg, both taken in the morning.

What are the possible causes of E.S.'s sleep disorder and why is it important for E.S. to have his problem evaluated in a sleep laboratory?

E.S. reports diminished sleep quality, excessive snoring, gasping for air, and weight gain. Although a number of causes could be responsible for E.S.'s symptoms, one of the most serious is sleep apnea. Sleep apnea is a neurologic disorder characterized by mini-episodes of breathing cessation lasting about 10 seconds. These mini-episodes generally occur multiple times in an hour. If there is a reduction in airflow but no cessation of breathing, it is termed *hypopnea.* The brain responds to episodes of apnea and hypopnea with mini-arousals, waking the individual to stimulate breathing.[111,112] These frequent mini-arousals prevent the individual from obtaining quality sleep by not allowing sufficient time in deep, slow-wave sleep, or REM. OSA, the most common type, may be induced when extra body weight (note E.S.'s weight gain) places pressure on the throat and uvula, narrowing the space into which air must travel; this results in the difficulty or cessation of breathing and excessive snoring. An estimated 3% to 7% of males and 2% to 5% of females meet the criteria for OSA.[112,113]

The apnea/hypopnea index (AHI), measured using PSG (ie, EEG, electrooculogram, electromyogram), represents the number of episodes per hour. The AHI score accompanied by symptoms of EDS is used to diagnose OSA as follows: >5 to 14 (mild), 15 to 29 (moderate), and >30 (severe).[112]

Risk factors for OSA include age 65 years and older, obesity (BMI >30), male gender, craniofacial anatomy that alters mechanical and neural properties of the upper airway, genetic predisposition, cigarette smoking, alcohol consumption before sleep, and comorbid conditions such as hypertension, diabetes mellitus, polycystic ovary syndrome, hypothyroidism, and pregnancy.[113] Hypertension and weight gain may be contributing to E.S.'s sleep difficulty. Untreated OSA is associated with an increased risk of hypertension, coronary artery disease, and cerebrovascular disease.[114–116] Although sleep apnea occurs in ~5% of females and 15% of males in the general population, it occurs in up to 40% of patients with hypertension.[114] Treatment of OSA can improve BP control and lead to more restful sleep. Of note, OSA also occurs in nonobese individuals and in all ages, including infants.[113,115] Sleep-disordered breathing, including

snoring, is a significant risk factor for hypertension even in young individuals of normal weight.[114]

Overnight evaluation using PSG in a sleep laboratory would confirm or rule out sleep apnea and allow distinction between OSA and the less-common central sleep apnea.[112,115] Central sleep apnea results when breathing repeatedly starts and stops during sleep because the brain does not send proper signals to the muscles that control breathing (ie, the diaphragm does not move in attempts to take in air).[116] Treatment of central sleep apnea requires continuous positive airway pressure (CPAP) as opposed to being alleviated through weight loss or anatomic manipulations. Central sleep apnea can occur along with OSA.

Drug Treatment Considerations

Case 84-5, Question 2: Results from the sleep laboratory study clearly document E.S.'s sleep problem as OSA. He experiences an average of 65 apneic episodes per hour. E.S.'s weight gain and inactivity probably contribute to the problem. Both are serious, potentially life-threatening conditions. Why should E.S.'s sleeping difficulties not be treated with a hypnotic medication?

Hypnotics, alcohol, or any CNS depressant can be lethal for patients with sleep apnea and should not be prescribed for E.S. CNS depressants interfere with the mini-arousals required to stimulate breathing once it has stopped. In this case, the sleep laboratory study may have saved E.S. from a potential life-threatening breathing disorder that could have been exacerbated by a hypnotic with CNS depressant activity.

OSA can be treated by tracheostomy, nasal surgery, tonsillectomy, uvulopalatopharyngoplasty, and either nasally or orally administered CPAP.[112] Weight loss and CPAP therapy are the most effective treatments and must be maintained for continued therapeutic efficacy.[112,115] In CPAP, the patient wears a lightweight mask to bed each night, and a constant flow of air is provided mechanically to prevent breathing cessation and to allow for more restful sleep.

Although CPAP is effective for both OSA and central sleep apnea, the results are short-lived, and apneic episodes typically reappear when CPAP therapy is stopped. Preliminary studies in individuals with nocturnal bradycardia and sleep apnea show that insertion of a permanent cardiac pacemaker significantly improved bradycardia and sleep apnea.[117] At this time, the best treatment for E.S.'s hypertension and sleep apnea is weight loss and CPAP.

Case 84-5, Question 3: If weight loss, surgery, and CPAP are all ineffective or impractical, what drug treatments are potentially effective for E.S.'s sleep apnea?

Drug treatments indicated for OSA are primarily geared toward improving EDS, and thus have stimulant properties that should be used with caution in patients with cardiovascular conditions. Solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor (DNRI), has recently been approved by the FDA to treat EDS in patients with both OSA and narcolepsy.[118] It is typically dosed starting at 37.5 mg orally once daily upon awakening, and the dose based on efficacy and tolerability can be doubled every 3 days up to 150 mg/day. The most common side effects seen when treating EDS in patients with OSA were decreased appetite, nausea, anxiety, irritability, and insomnia. In addition, solriamfetol has been associated with dose-dependent increases in BP and heart rate.[118] Designated as schedule IV in the United States, solriamfetol is associated with an abuse potential similar to or lower than that of phentermine.[119] Similarly, modafinil and armodafinil are also approved to treat EDS associated with OSA, narcolepsy, and shift work sleep disorder. These agents are often best used as an adjunct to nightly CPAP usage and morning administration of modafinil 200 to 400 mg or armodafinil 150 to 200 mg.[120,121] For E.S., solriamfetol, modafinil, and armodafinil would only be considered if his hypertension was controlled as an adjunct to CPAP. He should be cautioned to monitor his BP carefully if any stimulant medication is used.

NARCOLEPSY

Narcolepsy is an incurable neurologic disorder characterized by the sudden onset of EDS. Although not specific to narcolepsy, EDS is a requirement for diagnosis and can be present with or without cataplexy. Cataplexy, present in 60% to 90% of patients with narcolepsy, involves the loss of muscle tone in the face or limb muscles and is often induced by strong emotions or laughter.[122] Cataplexy can present as subtle, with the patient limp or not moving, or dramatic, with the patient collapsing to the floor.[123] Hypnagogic hallucinations and sleep paralysis are other secondary symptoms not present in all persons with narcolepsy. Hypnagogic hallucinations are perceptual disturbances (ie, auditory, visual, tactile) that occur while experiencing a sleep attack. The patient may see imaginary objects, hear sounds, or feel sensations. Sleep paralysis is a terrifying, benign, and brief (lasting >10 minutes) experience that can occur when falling asleep or when awakening and can last several minutes. Patients are unable to move their limbs, to speak, or even to breathe deeply. Between 10% and 20% of patients experience the tetrad of symptoms that include EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis. Except for EDS, these symptoms are thought to be expressions or partial expressions of REM sleep.[13,111,122]

Narcolepsy is classified into two types: narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2).[26,122] In addition to EDS, NT1 criteria include the presence of cataplexy, whereas NT2 criteria include NT1 symptoms without cataplexy. Symptoms of narcolepsy often begin at puberty, but patients are usually not diagnosed until the late teens or early 20s. Early symptoms consist of EDS and poor sleep quality. The sleep cycle becomes progressively more erratic with frequent bursts of REM and decreased regularity of deep or slow-wave sleep. PSG in a sleep laboratory is ideal to confirm narcolepsy. Sleep architecture is notably different. Instead of the 90-minute delay before REM, individuals with narcolepsy progress directly into REM sleep.[111,122] A cerebrospinal fluid hypocretin 1 level of <110 pg/mL is

also diagnostic for narcolepsy. Postmortem brain studies of patients with narcolepsy show an 85% to 95% decrease in hypocretin-containing neurons.[123]

An autoimmune response of unknown origin is thought to damage hypocretin/orexin-secreting cells in the hypothalamus. Without functional hypocretin/orexin cells, the sleep–wake cycle is disrupted. Hypocretin/orexin is also involved in control of body weight, water balance, and temperature.[111,122]

Comparing Treatments

Optimal treatment of narcolepsy involves treating both sleep attacks and cataplexy. Schedule II controlled substances, methylphenidate and dextroamphetamine, were the first drugs used to treat narcolepsy, with 65% to 85% of patients deriving significant improvements in wakefulness. Mixed amphetamine salts are also FDA approved for narcolepsy.[111] The mechanism of action of methylphenidate and amphetamines is related to increasing neurotransmission of dopamine and norepinephrine. Modafinil, a Schedule C-IV controlled substance, is an effective treatment with less abuse potential. Its exact mechanism of action is not fully understood, but it is thought to increase wakefulness through noradrenergic, adrenergic, histaminergic, GABA-modulating, glutamatergic, and hypocretin/orexin-stimulating mechanisms.[111,122] Armodafinil is the dextroenantiomer of modafinil. Its therapeutic effect, side effect profile, half-life, and abuse potential are similar to those for modafinil.[122] In summary, these stimulating drugs decrease the number of sleep attacks, improve task performance, and increase the time to fall asleep, but they cannot eliminate sleep attacks altogether. Research is underway exploring the possible use of immunosuppression at the time of narcolepsy onset. One hypothesis suggests that the destruction of orexin neurons is immune mediated and immunosuppression therapy during a period of pathologic immune response could prevent or reduce damage to

the hypocretin system that otherwise would lead to the development of narcolepsy.[102,111,123,124]

Newer classes of compounds targeting EDS in narcolepsy include pitolisant, a selective histamine H_3-receptor inverse agonist that acts presynaptically to activate histamine neurons and enhance endogenous histamine release, and solriamfetol, a DNRI.[125,126] Pitolisant is considered a first-line treatment for EDS, as monotherapy or add-on treatment with other narcolepsy medications and also effective in the treatment of cataplexy.[127] At recommended once-daily morning doses ranging from 9 to 36 mg, pitolisant is generally well tolerated, with adverse events that include insomnia, headache, nausea, anxiety, and irritability. Pitolisant is associated with low abuse potential, significantly lower than that of phentermine and similar to that of placebo.[128] Solriamfetol is effective in improving wakefulness in adults with EDS associated with narcolepsy at doses of 75 to 150 mg once daily upon wakening.[118] The most common adverse effects with solriamfetol in narcolepsy studies at the FDA-approved doses were headache, nausea, decreased appetite, anxiety, insomnia, dry mouth, constipation, and palpitations.

Cataplexy does not respond to psychostimulants or modafinil; rather, sodium oxybate and antidepressants remain the first-line strategy. TCAs (imipramine and clomipramine) were the first antidepressants used, but protriptyline, desipramine, SSRIs (fluoxetine, sertraline, and paroxetine), and SNRIs (venlafaxine and duloxetine) are also used.[111] SSRIs and protriptyline offer the advantage of less daytime sedation, compared with tertiary TCAs. The effectiveness of antidepressants for the treatment of cataplexy is thought to be related to REM-suppressant effects. A Cochrane Database Review concluded that insufficient evidence exists to recommend antidepressants as effective treatments for cataplexy, given that most studies are small and uncontrolled.[129] However, it should be recognized that large-scale studies on such a rare disorder are difficult to conduct.[111] Antidepressants are not considered effective in decreasing sleep attacks.[111,122,129]

Sodium oxybate (Xyrem®; Xywav®), a salt form of the CNS depressant γ-hydroxybutyrate, is FDA approved for treatment of cataplexy and EDS in narcolepsy.[130,131] Its therapeutic effects are related to decreased REM, improved sleep consolidation, and increased stages 3 and 4 slow-wave sleep.[111] Sodium oxybate must be administered twice during the night while the patient is in bed to consolidate 6 to 8 hours of sleep. In two randomized, double-blind, placebo-controlled trials, sodium oxybate 9 g/night (ie, 450 mg at bedtime, then 450 mg 2–4 hours later), but not 3 or 6 g/night, significantly reduced the median frequency of cataplexy attacks by 69% in patients with narcolepsy, whereas 4.5 to 9 g for 8 weeks significantly reduced the median frequency of cataplexy attacks by 57% to 85% in a dose-related manner. Both trials showed a 6% to 30% reduction in EDS as measured on the Epworth Sleepiness Scale and a 20% to 43% reduction in daytime sleep attacks.[123] Because of a significant risk of CNS depression and abuse potential, sodium oxybate is a Schedule III controlled substance. It is only available through restricted distribution, the Xyrem® or Xywav® Risk Evaluation and Mitigation Strategy Program, which uses specifically certified pharmacies in the United States for dispensing.[130,131]

Mixed Amphetamine Salts and Fluoxetine

CASE 84-6

Question 1: G.B., a 23-year-old male with narcolepsy, has been taking mixed amphetamine salts ER 60 mg in the morning for sleep attacks associated with narcolepsy, and fluoxetine 20 mg daily will be started to treat cataplexy.

What are the potential risks of using both mixed amphetamine salts and fluoxetine to treat G.B.?

Anorexia, GI problems (abdominal pain, nausea, vomiting, diarrhea), anxiety, irritability, insomnia, and headaches are common side effects of stimulant drugs.[111] Although rare, psychotic reactions can occur in patients with narcolepsy taking stimulants at any dose; however, psychosis generally resolves when the stimulant is

discontinued. Stimulants, even at high dosages (eg, 80 mg methylphenidate), usually do not bring a patient to a normal level of alertness, and sometimes nocturnal sleep is disrupted. To prevent stimulant-induced insomnia, doses should be taken before 3:00 PM. Tolerance to the therapeutic effects of stimulants may develop in some patients with narcolepsy.[111,122,132] Drug holidays may allow the patient to recapture therapeutic benefit; however, many patients opt for an increased stimulant dose instead. Exceeding maximal recommended doses of stimulant significantly increases the risk of psychosis, substance abuse disorder, psychiatric hospitalization, tachyarrhythmia, and anorexia according to a case–control study in 116 patients with narcolepsy taking stimulants.[111,132] Seizures have also been reported.[132]

Fluoxetine may improve cataplexy, but it can worsen nocturnal insomnia and contribute to restlessness, headache, nausea, and sexual side effects including anorgasmia.[81,129] In addition, fluoxetine is a potent CYP2D6 inhibitor resulting in higher levels of amphetamine.[133] G.B. should be monitored closely during the initiation of fluoxetine therapy, and the amphetamine dose should be lowered by 30% to 60% to minimize side effects and prevent toxicity. The optimal therapeutic dose of fluoxetine to manage cataplexy has not been established, but low doses may be effective and minimize the risk of side effects.

Modafinil and Sodium Oxybate

Case 84-6, Question 2: G.B. experiences intolerable nervousness, irritability, and nocturnal insomnia on mixed amphetamine salts and fluoxetine. There is no improvement in cataplexy with the addition of fluoxetine. He asks about switching to modafinil and sodium oxybate. Does the combination of modafinil and sodium oxybate offer any advantage for G.B.?

Modafinil's efficacy relative to other CNS stimulants has not been adequately assessed in controlled clinical trials; however, it has less potential for insomnia and adverse CNS reactions at recommended

dosages between 200 and 400 mg/day administered in the morning.[134] It also has less abuse potential compared with stimulants and is a Schedule IV controlled substance. Headache was the only adverse experience rated significantly higher than was placebo in 283 patients taking the recommended dose of either 200 or 400 mg/day of modafinil. Anorexia, nervousness, restlessness, and pulse and BP increases are dose-related side effects to discuss during counseling. The maximum tolerable single daily dose may be 600 mg/day because 800 mg/day produced increased BP and pulse in one tolerability study.[135] Gradual dosage titration improves tolerability. Armodafinil, an active stereoisomer of modafinil, is effective at usual doses between 150 and 250 mg/day. It has an adverse effect profile similar to that of modafinil.[122,134]

Improved daytime wakefulness is an advantage of sodium oxybate compared with antidepressants. A controlled trial involving 278 patients showed an increase in slow-wave sleep (stages 3 and 4) and decreased nightly sleep disruption in patients taking sodium oxybate with modafinil compared with modafinil alone.[136] Sodium oxybate can be administered safely with stimulants and modafinil; however, coadministration with other CNS depressants, including hypnotic medication, is contraindicated because of the risk of respiratory depression.[123]

Case 84-6, Question 3: What counseling should G.B. receive as he switches to modafinil and sodium oxybate?

People taking modafinil should receive counseling regarding the potential for drug interactions. Modafinil induces CYP3A4 metabolism primarily in the gut and inhibits CYP2C19. Decreased levels of triazolam and ethinyl estradiol have been associated with modafinil coadministration.[137] Monitoring for drug interactions is crucial because modafinil and armodafinil are increasingly used for other indications, including daytime sleepiness associated with Parkinson disease, shift work, fibromyalgia, sleep apnea, fatigue associated with multiple sclerosis, and ADHD.[138–140]

Sodium oxybate should not be given to those with sleep-disordered breathing, sleep apnea, or an alcohol or substance abuse disorder.[130,131] Adverse effects include nausea, headache, dizziness, and enuresis. Safe coadministration of modafinil and sodium oxybate has been described in clinical trials[136]; however, cases of severe side effects including panic, psychosis, depression, and new-onset suicidal ideation have been described.[141] The risk of serious side effects versus benefits in managing cataplexy and nocturnal insomnia should be discussed with G.B. and his family. Close monitoring, particularly during the first weeks and months of treatment and when dosages are adjusted up or down, should be advised.[141,142] G.B. should be instructed how to properly administer sodium oxybate, drinking half the dose on an empty stomach immediately before bedtime and then setting his alarm for 4 hours later to take the midnocturnal dose.

Naps and Other Behavioral Interventions

Case 84-6, Question 4: The benefits, possible risks, and importance of regular physician assessment have been explained to G.B., and he agrees to report efficacy and adverse effects to his primary care provider regularly. G.B. is reminded to take the medicine at regular intervals along with daytime naps. Why are naps helpful in the treatment of G.B., and what other behavioral interventions are useful in treating narcolepsy?

Strategically timed 15- to 20-minute naps taken at lunch and then again at 5:30 PM can be refreshing for patients with narcolepsy and increase their time between sleep attacks. Narcolepsy support groups are available and may help G.B. better cope with such a life-changing chronic illness. It also is important for G.B. to avoid alcohol and to regulate his bedtime and wake-up time in the attempt to normalize his sleep habits.[111,122,134]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Ahmed I, Thorpy M. Clinical features, diagnosis and treatment of narcolepsy. *Clin Chest Med.* 2010;31:371–381. (122)

Morgenthaler T, Kramer M, Alessi C, et al. Practice parameter for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. *Sleep.* 2006;29:1415–1419. (33)

Morin CM, Benca R. Chronic insomnia. *Lancet.* 2012;379:1129–1141. (38)

Moszczynski A, Murray BJ. Neurobiological aspects of sleep physiology. *Neuro Clin.* 2012;30:963–985. (16)

Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. *Am J Obstet Gynecol.* 2015;214:428–441. (106)

Key Websites

American Academy of Sleep Medicine. http://www.aasm.org/

American Sleep Apnea Association. http://www.sleepapnea.org/

National Sleep Foundation. http://www.sleepfoundation.org/

COMPLETE REFERENCES CHAPTER 84 SLEEP DISORDERS

1. Stevens S, Hening WA. Sleep and wakefulness. In: Goetz CG. *Textbook of Clinical Neurology*. 3rd ed. Saunders; 2007:21.
2. Jha PK, Challet E, Kalsbeek A. Circadian rhythms in glucose and lipid metabolism in nocturnal and diurnal mammals. *Mol Cell Endocrinol*. 2015;418(Pt 1):74–88.
3. Ram S, Seirawan H, Kumar SK, Clark GT. Prevalence and impact of sleep disorders and sleep habits in the United States. *Sleep Breath*. 2010;14:63–70.

4. Laposky AD, Van Cauter E, Diez-Roux AV. Reducing health disparities: the role of sleep deficiency and sleep disorders. *Sleep Med*. 2016;18:3–6.
5. Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care Survey 1999–2010. *Sleep*. 2014;37:1283–1293.
6. Roth T, Coulouvrat C, Hajak G, et al. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. *Biol Psychiatry*. 2011;69:592–600.
7. Ford ES, Cunningham TJ, Giles WH, Croft JB. Trends in insomnia and excessive daytime sleepiness among US adults from 2002 to 2012. *Sleep Med*. 2015;16:372–378.
8. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. *Chest*. 2015;147:266–274.
9. Mohsenin V. Obstructive sleep apnea and hypertension: a critical review. *Curr Hypertens Rep*. 2014;16:482.
10. Merlino G, Gigli GL. Sleep-related movement disorders. *Neurol Sci*. 2012;33:491–513.
11. Rye DB. Restless legs syndrome and periodic leg movements of sleep. *Neurol Clin*. 2012;30:1137.
12. Longstreth WT, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. *Sleep*. 2007;30:13–26.
13. Mason TB Jr, Pack AI. Pediatric parasomnias. *Sleep*. 2007;30:141–151.
14. U.S. Food & Drug Administration. Consumer updates. Taking Z-drugs for insomnia? Know the risks. Accessed October 8, 2020. https://www.fda.gov/consumers/consumer-updates/taking-z-drugs-insomnia-know-risks
15. Carskadon MA, Dement WC. Normal human sleep: an overview. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Elsevier Inc; 2017:15.
16. Moszczynski A, Murray BJ. Neurobiological aspects of sleep physiology. *Neuro Clin*. 2012;30:963–985.
17. Miller MA, Roecklein KA, Provencio I. Chronobiology. In: Sadock B, Sadock VA, Ruiz P. eds. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*. 10th ed. Lippincott Williams and Wilkins; 2017:1.14.
18. Peever J, Fuller PM. Neuroscience: a distributed neural network controls REM sleep. *Curr Biol*. 2016;26(1):R34–R35. doi:10.1016/j.cub.2015.11.011
19. McGinty D, Szymusiak R. Neural control of sleep in mammals. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Elsevier, Inc; 2017:62.

20. Ebrahim IO, Sharief MK, de Lacy S, et al. Hypocretin (orexin) deficiency in narcolepsy and primary hypersomnia. *J Neurol Neurosurg Psychiatry*. 2003;74:127–130.
21. Taber KH, Hurley RA. Functional neuroanatomy of sleep and sleep deprivation. *J Neuropsychiatry Clin Neurosci*. 2006;18:1–5.
22. Greco M, Fuller PM, Jhou TC, et al. Opiodergic projections to sleep-active neurons in the ventrolateral preoptic nucleus. *Brain Res*. 2008;1245:96–107.
23. Lancel M. Role of GABAA receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. *Sleep*. 1999;22:33–42.
24. Winsky-Sommerer R. Role of GABAA receptors in the physiology and pharmacology of sleep. *Eur J Neurosci*. 2009;29:1779–1794.
25. Arbon EL, Knurowska M, Dijk DJ. Randomised clinical trial of the effects of prolonged-release melatonin, temazepam and zolpidem on slow-wave activity during sleep in healthy people. *J Psychopharm*. 2015;29:764–776.
26. *The International Classification of Sleep Disorders*. 3rd ed. American Academy of Sleep Medicine; 2014.
27. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
28. Morin CM, Jarrin DC. Epidemiology of insomnia: prevalence, course, risk factors, and public health burden. *Sleep Med Clin*. 2013;8:281.
29. Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. *Sleep*. 2007;30:213–218.
30. Sivertsen B, Krokstad S, Øverland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. *J Psychosom Res*. 2009;67:109–116.
31. Neikrug AB, Ancoli-Israel S. Sleep disorders in the older adult—a mini-review. *Gerontology*. 2010;56:181–189.
32. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guidelines for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(2):307–349.
33. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameter for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. *Sleep*. 2006;29:1415–1419.
34. Hood HK, Rogojanski J, Moss TG. Cognitive-behavioral therapy for chronic insomnia. *Curr Treat Options Neurol*. 2014;16:321.
35. Jacobs GD, Pace-Schott EF, Stickgold R, Otto MW. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. *Arch Intern Med*. 2004;164:1888–1896.
36. Benca RM. Diagnosis and treatment of chronic insomnia: a review. *Psychiatr Serv*. 2005;56:332–343.

37. Buysse DJ. Insomnia. *JAMA*. 2013;309:706.
38. Morin CM, Benca R. Chronic insomnia. *Lancet*. 2012;379:1129–1141.
39. Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. *Pharmacotherapy*. 2007;27:89–110.
40. Erman MK. Influence of pharmacokinetic profiles on safety and efficacy of hypnotic medications. *J Clin Psychiatry*. 2006;67(Suppl 13):9.
41. Morlock RJ, Tan M, Mitchell DY. Patient characteristics and patterns of drug use for sleep complaints in the United States: analysis of National Ambulatory Medical Survey Data, 1997–2002. *Clin Ther*. 2006;28:1044–1053.
42. Curry DT, Eisenstein RD, Walsh JK. Pharmacologic management of insomnia: past, present, and future. *Psychiatr Clin North Am*. 2006;29:871–893.
43. Zee PC, Goldstein CA. Treatment of shift work disorders and jet lag. *Curr Treat Options Neurol*. 2010;12:396.
44. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet*. 2004;43:227.
45. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev*. 2002;(2):CD001520.
46. Van der Heijden KB, Smits MG, Van Someren EJ, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry*. 2007;46:233–241.
47. Sherwood DA, Rey JA, Cronwell MR. Ramelteon (Rozerem): a novel treatment option for patients with insomnia. *P T*. 2007;32:427.
48. Rozerem (ramelteon tablets). Product information. Takeda Pharmaceuticals America; 2010.
49. Borja NL, Daniel KL. Ramelteon for the treatment of insomnia. *Clin Ther*. 2006;28:1540–1555.
50. Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. *Sleep*. 2009;32:351–360.
51. Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. *Arch Gen Psychiatry*. 2006;63:1149–1157.
52. Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. *J Psychopharmacol*. 2012;26:1088–1095.
53. Roth T, Walsh JK, Krystal A, Wessel T, Roehrs TA. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with primary insomnia. *Sleep Med*. 2005;6(6):478–495.

54. Bunney WE Jr, Azarnoff DL, Brown BW Jr, et al. Report of the Institute of Medicine Committee on the efficacy and safety of Halcion. *Arch Gen Psychiatry*. 1999;56:349–352.
55. Ambien (zolpidem tablets). Product information. Sanofi-Aventis US LLC; 2019.
56. Zolpimist (zolpidem oral spray). Product information. Aytu BioScience Inc; 2019.
57. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR. Accessed October 8, 2020. http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm
58. Zammit G. Comparative tolerability of newer agents for insomnia. *Drug Saf*. 2009;32:735–748.
59. Najib J. Eszopiclone, a nonbenzodiazepine sedative-hypnotic agent for the treatment of transient and chronic insomnia. *Clin Ther*. 2006;28:491–516.
60. Lunesta (eszopiclone tablets). Product information. Sunovion Pharmaceuticals; 2014.
61. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. 2003;26:793–799.
62. Walsh JK, Krystal AD, Amato DA, et al. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep*. 2007;30:959–968.
63. U.S. Food & Drug Administration. FDA Drug Safety Communication. FDA adds boxed warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines. Accessed September 8, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia
64. Belsomra (suvorexant tablets). Product information. Merck and Co Inc; 2020.
65. Jantko K, Prichard JR, Pusalavidyasagar S. An update on dual orexin receptor antagonists and their potential role in insomnia therapeutics. *J Clin Sleep Med*. 2018;14(8):1399–1408.
66. Citrome L. Suvorexant for insomnia: a systematic review of the efficacy and safety profile for this newly approved hypnotic—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract*. 2014;68:1429–1441.
67. Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2014;13:461–471.
68. Dayvigo (lemborexant tablets). Prescribing information. Eisai Inc; 2022.

69. Cheng J, Moline M, Filippov G, Murphy P, Bsharat M, Hall N. Respiratory safety of lemborexant in adult and elderly subjects with mild obstructive sleep apnea. *Sleep*. 2019;42(suppl 1):A173–A174.
70. Quviviq (dari4dorexant tablets). Product information. Idorsia Pharmaceuticals US Inc; 2022.
71. Rudolph U, Möhler H. $GABA_A$ receptor subtype functions. *Curr Opin Pharmacol*. 2006;6:18.
72. The 2019 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694. doi:10.1111/jgs.15767
73. Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *Am J Manag Care*. 2006;12(8 Suppl):S221–S229.
74. Krystal AD. Sleep and psychiatric disorders: future directions. *Psychiatr Clin North Am*. 2006;29:1115–1130.
75. Fondell E, Axelsson J, Franck K, et al. Short natural sleep is associated with higher T cell and lower NK cell activities. *Brain Behav Immun*. 2011;25:1367–1375.
76. Drugs that may cause psychiatric symptoms. *Med Lett Drugs Ther*. 2002;44:59–62.
77. Thombs BD, Bass EB, Ford DE. Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med*. 2006;21:30–38.
78. Greenblatt DJ, Harmatz JS, Shader RI. Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly. Therapeutic considerations (part I). *Clin Pharmacokinet*. 1991;21:165–177.
79. Dement WC. Introduction. Clinical considerations. Overview of the efficacy and safety of benzodiazepine hypnotics using objective methods. *J Clin Psychiatry*. 1991;52(Suppl):27–30.
80. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *Eur Psychiatry*. 2013;28:7–20.
81. Becker PM, Sattar M. Treatment of sleep dysfunction and psychiatric disorders. *Curr Treat Options Neurol*. 2009;11:349–357.
82. Sutton EL. Psychiatric disorders and sleep issues. *Med Clin N Am*. 2014;98:1123–1143.
83. Vogel GW, Buffenstein A, Minter K, Hennessey A. Drug effects on REM sleep and on endogenous depression. *Neurosci Biobehav Rev*. 1990;14:49–63.
84. Stein MD, Friedmann PD. Disturbed sleep and its relationship to alcohol use. *Subst Abus*. 2005;26(1):1–13. doi:10.1300/j465v26n01_01
85. Arnedt JT, Conroy DA, Brower KJ. Treatment options for sleep disturbances during alcohol recovery. *J Addict Dis*. 2007;26:41–54.

86. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry*. 2005;66:469–476.
87. Stahl SM. Mechanism of action of trazodone: a multifunctional drug. *CNS Spectr*. 2009;14:536–546.
88. Markov D, Doghramji K. Doxepin for insomnia. *Curr Psychiatry*. 2010;9:67.
89. Ancoli-Israel S. Sleep and its disorders in aging populations. *Sleep Med*. 2009;10(Supp 1):S7–S11.
90. Espiritu JR. Aging-related sleep changes. Sleep in elderly adults. *Clin Geriatr Med*. 2008;24:1.
91. Vitiello MV. Growing old should not mean sleeping poorly: recognizing and properly treating sleep disorders in older adults. *J Am Geriatr Soc*. 2007;55:1882–1883.
92. Kamel NS, Gammack JK. Insomnia in the elderly: cause, approach and treatment. *Am J Med*. 2006;119:463–469.
93. Passarella S, Duong MT. Diagnosis and treatment of insomnia. *Am J Health Syst Pharm*. 2008;65:927–934.
94. Budhiraja R, Roth T, Hudgel DW, Budhiraja P, Drake CL. Prevalence and polysomnographic correlates of insomnia comorbid with medical disorders. *Sleep*. 2011;34:859–867.
95. Benca RM, Ancoli-Israel S, Moldofsky H. Special considerations in insomnia diagnosis and management: depressed, elderly, and chronic pain populations. *J Clin Psychiatry*. 2004;65(Suppl 8):26–35.
96. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry*. 2002;159:5–11.
97. Suhl J. The neuropharmacology of sleep disorders: better sleeping through chemistry? *J Pharm Pract*. 2007;20:181.
98. Krystal AD. The changing perspective on chronic insomnia management. *J Clin Psychiatry*. 2004;65(Suppl 8):20–25.
99. Wagner AK, Zhang F, Soumerai SB, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Arch Intern Med*. 2004;164:1567–1572.
100. Billioti de Gage S, Moride Y, Ducruet T, et al. Benzodiazepine use and risk of Alzheimer's disease: a case-control study. *BMJ*. 2014;349:g5205.
101. Tariq SH, Pulisetty S. Pharmacotherapy for insomnia. *Clin Geriatr Med*. 2008;24:93–105.
102. Glass JR, Sproule BA, Herrmann N, Busto UE. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. *J Clin Psychopharmacol*. 2008;28:182–188.
103. Richardson GS, Roehrs TA, Rosenthal L, Koshorek G, Roth T. Tolerance to daytime sedative effects of H1 antihistamines. *J Clin Psychopharmacol*. 2002;22:511–515.

104. Meltzer LJ, Mindell JA. Sleep and sleep disorders in children and adolescents. *Psychiatr Clin North Am*. 2006;29:1059.
105. Troester MM, Pelayo R. Pediatric sleep pharmacology: a primer. *Semin Pediatr Neurol*. 2015;22:135–147.
106. Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. *Am J Obstet Gynecol*. 2015;214:428–441.
107. Eberhard-Gran M, Eskild A, Opjordsmoen S. Use of psychotropic medications in treating mood disorders during lactation: practical recommendations. *CNS Drugs*. 2006;20:187–198.
108. Quinn D. Use of psychoactive medication during pregnancy and possible effects on the fetus and newborn. *Pediatrics*. 2001;107(6):1498.
109. Miller MA, Mehta N, Clark-Bilodeau C, Bourjeily G. Sleep pharmacotherapy for common sleep disorders for pregnancy and lactation. *Chest* 2020;157(1):184–197.
110. Dolovitch LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ*. 1998;317:839–843.
111. Erman MK. Selected sleep disorders: restless legs syndrome and periodic limb movement disorder, sleep apnea syndrome, and narcolepsy. *Psychiatr Clin North Am*. 2006;29:947–967.
112. Greenstone M, Hack M. Obstructive sleep apnea. *BMJ*. 2014;348:g3745.
113. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5:136–143.
114. Borgel J, Sanner BM, Keskin F, et al. Obstructive sleep apnea and blood pressure. Interaction between the blood pressure-lowering effects of positive airway pressure therapy and antihypertensive drugs. *Am J Hypertens*. 2004;17(12, pt 1):1081–1087.
115. Jean-Louis G, Brown CD, Zizi F, et al. Cardiovascular disease risk reduction with sleep apnea treatment. *Expert Rev Cardiovasc Ther*. 2010;8:995–1005.
116. Martin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307(20):2169–2176.
117. Garrigue S, Bordier P, Jaïs P, et al. Benefit of atrial pacing in sleep apnea syndrome [published correction appears in *N Engl J Med*. 2002;346:872]. *N Engl J Med*. 2002;346:404–412.
118. Sunosi (solriamfatol tablets). Product information. Jazz Pharmaceuticals Inc; 2019.
119. Carter LP, Henningfield JE, Wang YG, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the human abuse liability of solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor. *J Psychopharmacol*. 2018;32(12):1351–1361.
120. Keating GM, Raffin MJ. Modafinil: a review of its use in excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome and shift

work sleep disorder. *CNS Drugs*. 2005;19:785–803.
121. Dopheide JA. Medication effects. In: Kushida CA, ed. *Obstructive Sleep Apnea: Diagnosis and Treatment*. Informa Healthcare USA; 2007:295.
122. Ahmed I, Thorpy M. Clinical features, diagnosis and treatment of narcolepsy. *Clin Chest Med*. 2010;31:371–381.
123. Robinson DM, Keating GM. Sodium oxybate: a review of its use in the management of narcolepsy [published correction appears in *CNS Drugs*. 2007;21:692]. *CNS Drugs*. 2007;21:337–354.
124. Barateau L, Liblau R, Peyron C, Dauvilliers Y. Narcolepsy type I as an autoimmune disorder: evidence, and implications for pharmacological treatments. *CNS Drugs*. 2017;31(10):821–834.
125. Dauvilliers Y, Arnulf I, Szakacs Z, et al; HARMONY III Study Group. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. *Sleep*. 2019;42:zsz174.
126. Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Ann Neurol*. 2019;85:359–370.
127. Wakix (pitolisant tablets). Product information. Harmony Biosciences LLC; 2020.
128. Setnik B, McDonnell M, Mills C, et al. Evaluation of the abuse potential of pitolisant, a selective H3-receptor antagonist/inverse agonist, for the treatment of adult patients with narcolepsy with or without cataplexy. *Sleep*. 2020;43:zsz252. doi:10.1093/sleep/zsz252
129. Vignatelli L, D'Alessandro R, Candelise L. Antidepressant drugs for narcolepsy. *Cochrane Database Syst Rev*. 2008;(1):CD003724. doi:10.1002/14651858.CD003724.pub3
130. Xyrem (sodium oxybate oral solution). Product information. Jazz Pharmaceuticals Inc; 2020.
131. Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution). Product information. Jazz Pharmacetuicals Inc; 2020.
132. Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL. Risk of high-dose stimulants in the treatment of disorders of excessive somnolence: a case-control study. *Sleep*. 2005;28:667–672.
133. Weiss M, Hechtman L; Adult ADHD Research Group. A randomized, double-blind trial of paroxetine and/or dextroamphetamine and problem-focused therapy for attention-deficit/hyperactivity disorder in adults. *J Clin Psychiatry*. 2006;67:611–619.
134. Scammell TE. Narcolepsy. *N Engl J Med*. 2015;373:2654–2662.
135. Wong YN, Simcoe D, Hartman LN, et al. A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol*. 1999;39:30–40.
136. Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep

disruption of patients with narcolepsy. *Sleep Med*. 2009;10:829–835.
137. Robertson P Jr, Hellriegel ET, Arora S, Nelson M. Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther*. 2002;71:46–56.
138. Dequardo JR. Modafinil-associated clozapine toxicity. *Am J Psychiatry*. 2002;159:1243–1244.
139. Hogl B, Saletu M, Brandauer E, et al. Modafinil for the treatment of daytime sleepiness in Parkinson disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep*. 2002;25:905–909.
140. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry*. 2002;72:179–183.
141. Biederman J, Swanson JM, Wigal SB, Boellner SW, Earl CQ, Lopez FA; Modafinil ADHD Study Group. A comparison of once-daily and divided doses of modafinil in children with attention-deficit/hyperactivity disorder: a randomized, double-blind, and placebo-controlled study. *J Clin Psychiatry*. 2006;67:727–735.
142. Ortega-Albas JJ, López-Bernabé R, Serrano AL, Díaz JR. Sodium oxybate and modafinil: a good combination? *Sleep Med*. 2010;11:957.

85

Schizophrenia

Richard J. Silvia, Robert L. Dufresne, and Justin C. Ellison

CORE PRINCIPLES		CHAPTER CASES
1	Schizophrenia is a persistent, heterogeneous syndrome that includes both positive and negative symptoms. Together, these symptom clusters can have variable effects on patient quality of life, functional recovery, and prognosis. Prodromal symptoms preceding the first episode of psychosis may go unnoticed for many months. Onset of an acute psychotic episode can be an acute or insidious process that causes a significant impact on function and ability to perform activities of daily living.	**Case 85-1 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
2	Treatment goals will vary based on the stage of the patient. During an acute phase, stabilization and safety are primary. During a stable phase, maintaining stability and improving functional recovery are the main goals. Treatment modalities should include both pharmacologic and nonpharmacologic methods.	**Case 85-1 (Questions 3–5)**
3	Many factors need to be considered in selecting an appropriate medication regimen for a patient with schizophrenia. Patient factors such as comorbidities, targeted symptoms, adherence history, personal and family history of medication response, and others need to be assessed. Medication-related factors include efficacy, safety profile, pharmacokinetics and drug interactions, and economic considerations.	**Case 85-1 (Questions 6, 7, 10, 11, 14, 15, 22, 26, 27, 30, 33)**

CORE PRINCIPLES		CHAPTER CASES
4	Adverse effects of antipsychotics are varied. They may include acute and chronic extrapyramidal movement disorders, metabolic disturbances such as weight gain and alterations in serum glucose and lipids, and other adverse effects such as sedation and orthostasis. Monitoring and appropriate interventions for adverse effects should be ongoing throughout all stages of illness to ensure continued safety and avoid medication discontinuation.	**Case 85-1 (Questions 8, 9, 15–25, 27–30)**
5	Patients who do not respond to an adequate antipsychotic trial should be assessed for adherence. Long-acting injectable antipsychotics may be an option to help maintain adherence. Clozapine is the treatment of choice in patients who are refractory to at least two adequate trials of antipsychotic medications. However, clozapine does require strict adherence to blood monitoring because of the risk of agranulocytosis and carries a significant adverse effect burden.	**Case 85-1 (Questions 12–14, 26, 30–32)**

CORE PRINCIPLES		CHAPTER CASES
6	Treatment of female patients of childbearing age may require special consideration. Untreated psychosis can result in poor self-care for the mother and inadequate prenatal care. There is also the concern regarding substance use, dangerous behaviors, and even suicide. Therefore, the risks and benefits of ongoing antipsychotic treatment should be carefully weighed by both the patient and the treatment team.	**Case 85-1 (Question 34)**
7	Early recognition of symptoms of first-episode psychosis (FEP) and referral to appropriate multidisciplinary, comprehensive treatment services are crucial to long-term functional recovery. This population is highly sensitive to adverse effects. Antipsychotics should be titrated to the minimum effective dose to decrease the duration of untreated psychosis and improve long-term prognosis.	**Case 85-1 (Question 35)**

INTRODUCTION

Schizophrenia is a psychiatric illness that can lead to lifelong effects on a patient's functioning. Manifesting primarily as a thought disorder, patients often have problems with perception, maintaining

contact with reality, thought processing, and behavior. These symptoms can lead to a variety of impairments across many domains, including social, occupational, and emotional. Owing to these symptoms, patients may require hospitalizations to help maintain or restore functionality. Treatment of schizophrenia encompasses multiple modalities, all targeted at improving a patient's symptoms and functioning, decreasing hospitalizations, and preventing morbidity and mortality.

EPIDEMIOLOGY

Schizophrenia is a heterogeneous, genetically linked "spectrum" disorder that affects 0.7% of the population.[1] It is the ninth leading cause of disability in the world,[2] being found in all cultures and races. Although often incorrectly assumed to be more common in males, there is no gender difference in the incidence of the illness. However, the onset of schizophrenia tends to occur between ages 18 and 25 in males and from 26 to 45 years old in females and usually persists for a lifetime.[3] Overall, more severe symptoms are generally seen in males versus females.

ECONOMIC BURDEN

The economic burden of this devastating disease and its treatment is enormous.[4–7] In one estimate from 2002, U.S. costs for schizophrenia totaled $62.7 billion. This included $30.3 billion in direct health care costs (of which medications accounted for $5.0 billion) and $32.4 billion in indirect costs, such as lost productivity and other costs incurred to the health care system. Although progress has been made in treating the symptoms of schizophrenia and restoring moderate levels of functioning, there is as of yet no cure. Because many patients present with an early age of onset, the

lifetime burden of illness can be great. Many patients will need repeated hospitalizations, and when not hospitalized will require significant outpatient services and treatment. In addition, many patients require supportive living situations, either in facilities designed for these services or with family members, increasing the financial burden on their families as well.

ETIOLOGY

Multiple neurotransmitter and physiologic mechanisms have been hypothesized to explain the complex etiology of schizophrenia. Many theories on the role that aberrant neurotransmitter systems play in schizophrenia are derived from the pharmacologic actions of the medications used to treat the illness in addition to direct analysis from biologic samples. Findings on neurologic scans and other measurements of neuroanatomy are also not consistent across patients to allow for these methods to be reliably employed in making a diagnosis of schizophrenia. Genetic markers have more recently been explored with advances in genetics, but these too are not all encompassing. In this section, the chemical, biologic, and environmental basis of schizophrenia are presented.

Genetic and Environmental Risk Factors

A genetic component to schizophrenia has been hypothesized since the observation that family members of patients are more prone to develop schizophrenia than is the general population. Rates of schizophrenia among family members vary (anywhere from 2% to 50%) based on the relationship to the patient with schizophrenia.[1] Children born to parents who both have schizophrenia are affected in 40% to 60% of cases. Siblings of patients with schizophrenia, including dizygotic twins, are also affected in 10% to 15% of cases. However, monozygotic twins develop schizophrenia ~50% of the time if their twin also has the illness. Second- and third-degree

relatives of patients more closely approximate the general population, but still develop the illness ~2% to 5% of the time. Many genes are thought to play a role in schizophrenia, but no one gene has been found to be universal across patients. This finding suggests that multiple genes may be involved in the etiology of schizophrenia. Although a genetic role appears to exist, it does not explain how all patients develop the illness. Approximately two-thirds of patients have no known familial history of the illness; therefore, other factors must play a role in these patients.[1] Certain environmental exposures in early development are associated with the development of schizophrenia. Maternal infections, in particular influenza, stress, and malnutrition during the first and second trimesters, have shown a link to the child developing schizophrenia. Fetal or infant hypoxia during delivery or in the first few months of life has been shown to double the risk of schizophrenia. Childhood trauma and substance abuse have also been linked to the development of schizophrenia.

Pathophysiology

The actual nature of the pathophysiology of schizophrenia is both unknown and complex. It may be more appropriate to conceptualize it as a syndrome that may involve many different underlying disease mechanisms.[8] Although numerous deviations in brain structure and physiology have been noted, such as decreased gray matter volume, whole-brain volume, and enlarged ventricle size,[9] most treatments focus on antagonism of presupposed increased activity at dopamine-2 (D_2) receptors. The potency of typical antipsychotic medications has correlated with their antagonism of these receptors, although some atypical antipsychotics, such as clozapine, are extremely effective with a lesser degree of D_2 receptor blockade.[10] The initial *dopamine hypothesis* of schizophrenia theorized that positive symptoms of schizophrenia (eg, conceptual disorganization and hallucinations) result from abnormally increased activity in the mesolimbic dopamine neurons and that negative and affective

symptoms of schizophrenia result from subnormal mesocortical dopamine neuronal activity.[11] This remains a clinically useful, albeit simplistic, conceptual framework because many dopamine agonists tend to increase positive symptoms and oppose the effects of antipsychotics. The relation of negative symptoms to dopamine neurotransmission is even more complex. Some suggest that decreased dopamine in frontal areas is linked to negative symptoms and that increased dopaminergic neurotransmission in striatal areas results in positive symptoms.[12] To explain the efficacy and lack of movement adverse effects, prolactin elevation, or secondary negative symptoms of antipsychotics such as clozapine and quetiapine, one theory proposes that they have a faster dissociation from the D_2 receptor than do other antipsychotics.[13] It has also been suggested that 65% of D_2 receptor occupancy predicted response and 78% predicted extrapyramidal adverse effects.[14]

More recent thinking suggests involvement of glutamate and γ-aminobutyric acid (GABA), which are intertwined with the disturbances in dopaminergic neurotransmission.[15] Although speculation that glutamate was involved in the pathophysiology of schizophrenia started in the 1980s, the demonstration that *N*-methyl-D-aspartate (NMDA) receptor antagonists best replicated all the major schizophrenic symptoms such as the positive, negative, and cognitive ones in healthy subjects lent credence to the "NMDA receptor hypofunction hypothesis." Because negative symptoms and cognitive deficits are not treated by D_2 receptor antagonists nor worsened by dopamine agonists, a theory that involves early disruption of glutamine transmission in schizophrenia is an appealing hypothesis. Also, unlike subcortical dopaminergic dysfunction, pathologic brain changes such as widespread dendritic and spine dysplasia along with cortical atrophy could possibly relate to NMDA receptor hypofunction.[16] Excitatory neurotransmission in the brain is predominantly glutamatergic, and glutamate dysfunction could possibly relate to dopamine dysfunction both in its prodrome and later on in the course of the illness.[17] In schizophrenia, it can be considered that dopaminergic changes are a final end mechanism

where antipsychotics work, in which increased mesocortical dopamine turnover and overactive mesolimbic dopaminergic overactivity result from other preceding neurotransmitter changes.[10]

Gradual progressive NMDA receptor hypofunction would also be consistent with the altered neuroanatomy of schizophrenia.[18] Decreased brain volume in schizophrenia has been noted since the 1920s, and there are more recent findings to believe that there are changes in brain structure with reductions in the volume of certain areas of the brain as well as changes in connectivity.[8] Enlargement of cerebral ventricles is a typical finding in schizophrenia, and reduced dendritic spine density in cerebral cortical pyramidal neurons where NMDA subtypes of glutamate receptors are present have been noted.[19] Some of these neuroanatomic differences include impaired white matter integrity and reduced volume of gray matter in the inferior parietal, prefrontal, superior, and medial temporal, thalamic, and striatal regions.[20] There are also a number of studies suggesting the importance of these white matter abnormalities in schizophrenia to dysconnectivity between functional tracts.[21]

CLINICAL PRESENTATION

Historical Concept of Schizophrenia

Schizophrenia was first characterized as “dementia praecox” by early psychiatrists Arnold Pick and Emil Kraepelin in the late 19th century,[22] and was described by Bleuler as a “disintegration of psychic functions.”[23] Historically, schizophrenia has been a disease characterized by progressive deterioration of the brain. Although modern findings seem to corroborate this viewpoint, few patients with schizophrenia show the progressive incremental loss of function that is characteristic of neurodegenerative illnesses.[24] The demonstrated effectiveness of dopamine receptor antagonists in the treatment of schizophrenia[25] resulted in the disorder being

conceptualized as a heterogeneous syndrome characterized by D_2 receptor hyperfunction[26] predominately in the mesolimbic regions of the brain.

Diagnosis and Differential Diagnosis

The diagnosis of schizophrenia in the recently introduced *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) requires that an individual has at least two persistent symptoms such as delusions, hallucinations, or disorganized speech or behavior over a 6-month period.[3] Also, in the *DSM-5* subtypes of schizophrenia, such as paranoid or undifferentiated, have been removed. These distinctions were not clinically useful because patients often displayed characteristic symptoms from each subtype at various times in their illness, or even concurrently.[3] Patients presenting with either manic or depressive symptoms concomitantly with their typically schizophrenic ones are still diagnosed as having schizoaffective disorder (**Table 85-1**).

Table 85-1
***DSM-5* Criteria for Schizophrenia**

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be 1, 2, or 3: 1. Delusions 2. Hallucinations 3. Disorganized speech (eg, frequent derailment or incoherence) 4. Grossly disorganized or catatonic behavior 5. Negative symptoms (ie, diminished emotional expression or avolition)
B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved before the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if

successfully treated) that meet Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).
D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
E. The disturbance is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication) or another medical condition.
F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are present for at least 1 month (or less if successfully treated).

Reprinted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. © 2013 American Psychiatric Association. All Rights Reserved.

Numerous disorders are characterized by psychosis during exacerbation. Schizophrenia differs in its presentation from bipolar disorder in that there are prominent signs of conceptual disorganization and hallucinations (**Table 85-2**). Prominent "negative" symptoms such as apathy, avolition, poverty of speech, and emotional blunting may also be present. Schizoaffective disorder, bipolar type may pertain to patients who present with both positive schizophrenic symptoms and either mania or depression. It is not uncommon for patients with schizophrenia to suffer from secondary depression at various times during the course of their illness as well.[27] Suicide in these patients is not uncommon.[28]

Table 85-2
Differential Diagnosis for Schizophrenia

Drug-Induced Psychoses

Drug-Induced Psychoses
Alcohol (or other sedative-hypnotics)
Amphetamine (or other stimulant)
Cocaine
Cannabis (marijuana)
Phencyclidine (PCP)
Lysergic acid diethylamide (LSD)
Anticholinergics (especially in overdose)
Anabolic and corticosteroids
Other Psychiatric Disorders
Major depressive or bipolar disorder with psychotic features
Schizoaffective disorder
Schizophreniform disorder and brief psychotic disorder
Delusional disorder
Paranoid, schizoid, or schizotypal personality disorder
Obsessive–compulsive disorder and body dysmorphic disorder
Posttraumatic stress disorder
Autism spectrum disorder or communication disorders

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

In new-onset psychosis, the treating clinician should be careful to rule out drug-induced (eg, amphetamines, cocaine, “k2” synthetic cannabinoids, anticholinergics, lysergic acid diethylamide [LSD], phencyclidine) causes. Corticosteroids may induce a manic type of psychosis, whereas anabolic steroids may provoke a more aggressive type of psychotic presentation. Obtaining a toxicology screen may be prudent. A patient can have a brief psychotic disorder that comes on suddenly, last for up to 1 month, and remit with no recurrence of symptoms. A patient presenting with signs and symptoms of schizophrenia between 1 and 6 months is said to have a schizophreniform disorder. Furthermore, depression can present with mood-congruent auditory hallucinations (often deprecatory) and

delusions. Finally, patients with cluster A personality disorders can show some isolated symptoms such as paranoia or blunted affect, but do not meet the full criteria of schizophrenia.[29]

Hallmark/Target Symptoms

The symptoms of schizophrenia are generally organized into two main domains: positive and negative (**Table 85-3**). Positive symptoms are usually what the public perceives when thinking about schizophrenia: hallucinations, delusions, and disorganization. Hallucinations can affect any of the five senses, but auditory ones are the most common. Delusions are fixed false beliefs that are persistent despite evidence to the contrary. Delusional subtypes include persecutory, erotomanic (eg, delusion of love), delusions of grandeur (having special abilities), or somatic (eg, delusion of being pregnant in the context of negative pregnancy test results). Disorganization can manifest in the patient's speech, thought patterns, or behaviors. For example, a patient wearing a winter coat in the summer or having an unprovoked agitation would constitute disorganized behavior. Negative symptoms of schizophrenia include apathy, avolition, blunted affect, and poverty of speech.[30] A decreased ability to experience pleasure (known as *anhedonia*) and social withdrawal can lead to significant functional impairment, even when positive symptoms are relatively absent in a patient. During acute episodes, positive symptoms may predominate, whereas over the long term it may be negative symptoms that are more troubling and disabling to a patient. A third domain of cognitive symptoms can also present in schizophrenia. Symptoms include concrete thinking, inattention, problems with memory, learning and executive function, as well as conceptual disorganization.[31] When these cognitive symptoms are combined with negative symptoms over the patient's lifespan, significant impairment in function may result. Comorbid depression is also common in schizophrenia,[32] can be difficult to treat,[29,33,34] and symptoms can be predictive of relapse.[35,36] Depressive symptoms may be overlooked in the face of

overwhelming positive symptoms, or confused with negative symptoms.

Table 85-3
Positive and Negative Symptoms of Schizophrenia

Positive	Negative
Hallucinations (auditory, visual, or other senses)	Diminished emotional expression (body language)
Delusions (persecutory, paranoid, grandiose, etc)	Avolition/psychomotor retardation
Disorganized thinking/speech	Alogia (decreased speech)
Grossly disorganized or abnormal motor behavior (including catatonia)	Anhedonia (decreased ability to feel pleasure)
Unusual behavior	Asociality (lack of socialization)
Combativeness, agitation, and hostility	Affective flattening
Ideas of reference	

CASE 85-1

QUESTION 1: J.J., a 26-year-old, single female college student, was brought to the emergency department of the local hospital by her school's campus security at 3:00 AM after she was found running naked through the campus screaming, "They're after me and won't leave me alone! They keep telling me to run and hide!" J.J.'s roommate has accompanied her with the security officers.

History of Present Illness: J.J. is not a good historian, but her roommate is willing to provide information to help. When asked questions, J.J. provides indirect, tangential answers, repeating her concerns of "they are after me." When asked who is after her, she responds "the FBI of course! They think I'm a spy, but I am a spy for the CIA!" Various times during the interview, J.J. is found talking to someone not in the room. When asked about that, she says she hears the voice of her CIA supervisor through the "transmitter in my head" and needs to respond. She said the transmitter also allows her to read other people's minds, which is how she spies for the CIA. J.J.'s roommate states that J.J. has been acting erratic for the past couple semesters, but she thought it was just from an online video game they had been playing. Once, she returned to their dorm room and J.J. had barricaded the door from the inside with furniture so no one would find her. She states that J.J. is often up late at night on her computer, which she says is to "look for traces of the enemy spies."

Medical History: J.J. has no significant medical or psychiatric history. She has never been hospitalized or treated for any psychiatric condition in the past. Her roommate has known her since they started college together 3 years ago, and they have been roommates for the past 2 years. The roommate says J.J. was fairly normal-quiet and shy, getting good grades until the unusual behavior started almost a year ago after they returned from summer break. She says J.J.'s behavior has gotten increasingly unusual and erratic since then.

Psychosocial History: A call to J.J.'s mother finds that her father has a history of alcoholism and domestic violence, which led to their divorce when J.J. was 14. J.J.'s paternal uncle has been diagnosed with schizophrenia and has been hospitalized multiple times over his lifetime. J.J.'s mother says she has always been a very good student, but not very social when in high school, tending to isolate from her classmates. She screamed at them one day in school saying she would defend herself if they carried out their plans and the police were called. No charges were filed and J.J. was entered into the school's anger management program, to which she never showed up. J.J.'s roommate states she only drinks socially at occasional parties and denies any illicit substance abuse.

Physical Exam/Lab Tests: J.J.'s physical exam shows no significant or contributory findings other than some bruising on her knuckles from punching the walls. J.J. states this is from "fighting off the FBI agents" when they find her. Lab tests, including complete blood count (CBC), serum chemistry panel, and liver and thyroid function test results all return normal. A urine drug screen returns negative results. No other tests were ordered.

Mental Status Exam: *Appearance and Behavior*: J.J. is a tall, average-build, neat but casually dressed young female who appears her stated age. She shows signs of paranoia and agitation because she is constantly looking around the room and pacing. She constantly asks to be released "before they find me." *Mood:* J.J. is anxious and concerned that the "FBI will find me" and prevent her from completing her mission. Affect is animated because of her level of agitation. She does not report any depressive ideation. *Memory:* Long-term memory appears to be intact (confirmed by roommate), but the patient will not cooperate with recall tests of immediate and short-term memory because "this is a waste of time and I need to be released." *Orientation:* J.J. is oriented to person, place, time, and situation. *Thought Content:* J.J. is fixated on needing to leave in order to complete her mission. She is convinced that the longer she stays, the more likely the FBI will find her here and she will "need to fight my way out." She also states she is trying to use her implanted transmitter to read the thoughts of the people in the room. She denies any suicidal or homicidal ideation. She accuses you of keeping her there to help the FBI. *Thought Process:* J.J.'s speech is highly disorganized such that she can be difficult to comprehend. *Perception:* J.J. is clearly responding to internal stimuli and most likely to auditory hallucinations. She also keeps asking the staff if something is burning and where the smell is coming from. *Insight and Judgment:* J.J. has

poor insight into her symptoms and mental state, and will most likely require inpatient hospitalization for psychosis.

Provisional Diagnosis: psychotic episode, most likely due to schizophrenia

What hallmark symptoms of schizophrenia is J.J. presenting with at this time? How might these symptoms be used in monitoring treatment?

J.J. currently presents with a number of hallmark symptoms of schizophrenia. She has olfactory and auditory hallucinations (hearing her CIA supervisor and others), delusions (she works for the CIA and the FBI is after her, having a transmitter in her head), and magical thinking (she can read people's thoughts). She shows conceptual disorganization in her speech. She is also agitated and uncooperative and has acted out on her delusions by getting into arguments with people she feels are from the FBI. These symptoms should begin to decrease and subside with time as effective medication treatment is utilized, allowing us to determine if J.J. is responding appropriately.

Case 85-1, Question 2: What information from J.J.'s history also contributes to a diagnosis of schizophrenia? What is the prognosis for J.J.?

Although J.J. has had no previous psychiatric treatment, she is in the age range for an initial psychotic episode of schizophrenia (late teens to mid-20s). J.J. has been showing increasingly unusual behavior for >6 months and possibly up to a year, according to her roommate, with more drastic changes more recently. Before this, J.J. did show some prodromal symptoms, most notably some difficulty interacting with peers while in high school and isolating herself. There is also a family history of schizophrenia (paternal uncle) and alcoholism (father). J.J.'s prognosis is variable because her young age of onset, family history of schizophrenia, and unstable home environment at a young age indicate a poor prognosis, but her relatively high baseline functioning and intelligence (she did very well in high school and is currently in college) would increase the chances for a better long-term outcome. Because J.J. is early in her

illness, it will take time to better determine her long-term prognosis more clearly.

Typical Course of the Illness and Prognosis

The course of schizophrenia can vary between individuals. However, a common pattern entails a premorbid phase with possible signs of cognitive, motor, and social deficits in childhood at 12 years old or younger, a prodromal phase during adolescence and young adulthood (12–18 years old) including a functional decline with brief or attenuated positive symptoms, and then an active phase that includes florid positive symptoms as part of psychosis.[20,37] An improved prognosis is associated with female gender, a preponderance of positive and mood symptoms versus negative symptoms, rapid onset of symptoms, older age at symptom onset, and high premorbid functioning.[38,39]

Generally, the negative (or deficit) and cognitive symptoms of schizophrenia predominate earlier in the development of the disorder. Florid positive symptoms usually emerge between ages 18 and 25 years in males and 20 and 30 years in females.[23] During the prodromal phase, patients may show what resembles negative symptoms: blunted affect, decreased motivation and energy, social withdrawal, and others. Cognitive symptoms may also present, such as poor concentration and memory, which may manifest as declining school or work performance. Low-level positive symptoms may also be seen, mostly in the form of disorganized thinking. Other symptoms such as depression, anxiety, or irritability may also present. Often, these symptoms will go unrecognized in adolescents and may be mistaken for anything from puberty, relationship problems, or drug abuse. This phase may last from weeks to years and often is not attributed to schizophrenia until the first psychotic episode. In many instances, patients will convert to a full schizophrenia diagnosis with more significant positive symptoms and go months or more before receiving treatment. This delay may affect the long-term prognosis of the illness because early treatment can

decrease later morbidity and because the response to treatment in first-episode schizophrenia is critical.[40]

After an active phase of schizophrenia, which can last a large part of adulthood, patients usually enter a residual phase of chronic disability. Later in this phase, symptoms may become somewhat similar to that of the prodromal phase. As the disease progresses, residual symptoms may increase between episodes and make normal day-to-day functioning difficult. As the patient ages, the medical complications of schizophrenia, treatment-emergent metabolic syndrome, and effects of tobacco use increasingly take hold.[37] Patients with schizophrenia have a life expectancy of 9 to 10 years less (or more by some estimates) than that in the average population.[41] The disease often becomes characterized by a preponderance of negative symptoms and cognitive deficits in those living into the later years.[3] However, with early intervention and support, many patients can achieve symptom control and lead meaningful and fulfilling lives.

TREATMENT

Schizophrenia is generally considered a chronic, lifelong illness consisting of varying periods of illness severity, with resulting effects on patient functionality. Although pharmacotherapy can have positive effects on reducing symptoms of the illness and improving functionality, there are often symptoms that may not respond adequately to treatment. In addition, despite adequate treatment, patients may have relapses of their illness, leading to acute psychotic episodes needing more intensive treatment. Treatment is, therefore, usually lifelong and is often multidisciplinary in its approach, consisting of pharmacotherapy, psychosocial therapy, case management, and other methods.

Goals of Treatment

The overall goal for the treatment of schizophrenia is to reduce the symptoms of the illness to improve patient functionality and quality of life. Depending on the patient's current level of acuity, the specific goals for the patient at that time may vary. Although similar pharmacotherapy and nonpharmacotherapy methods may be employed across the spectrum of severity of schizophrenia, they may be utilized differently. Patients are generally described as being in one of three treatment phases according to the American Psychiatric Association (APA): acute, stabilization, and stable.[3] These phases are not static, and patients can move between these phases frequently over the course of their illness.

ACUTE PHASE

The primary goal of treatment in the acute phase of illness is to reduce the threat of harm to the patient or others. Patients experiencing acute psychosis will present with prominent positive symptoms and exhibit disorganized speech and/or behaviors. Negative symptoms and suicidal ideation may also be more pronounced and severe. This will often require a higher level of care than the outpatient setting can provide and necessitate inpatient psychiatric hospitalization while the patient is stabilized. Medications, including short-acting injectable antipsychotics and benzodiazepines, are usually required to target agitation in acute psychosis. However, psychosocial interventions and collaboration with family and caregivers for collateral information are also crucial in this phase of illness.[42] Antipsychotics should be initiated as soon as clinically possible to decrease the duration of untreated psychosis and improve long-term prognosis.[43]

The reason for psychiatric decompensation should be ascertained through patient report and collateral information (eg, caregiver insight, pharmacy fill records). Schizophrenia has a variable course. Exacerbations can occur even on a therapeutic regimen in the context of psychosocial stressors, illicit substance use, and other reasons. However, if the exacerbation was due to nonadherence, the reasons should be explored with the patient. If the patient was

nonadherent owing to intolerable adverse effects, a lower dose or an alternative medication could be considered. If difficulty remembering to take medication was the issue, a long-acting injectable (LAI) formulation could be considered. In either scenario, the decision to initiate or change the antipsychotic should be based on patient preference, prior history of response, tolerability, and relevant medical comorbidities.

STABILIZATION PHASE

The aim during the stabilization phase is to promote continued recovery, maintain symptom control, begin facilitating referrals for supportive outpatient services, and reduce adverse effects and the likelihood of future relapse. The patient and involved caregivers should be educated on the timeline of symptom response, possible medication adverse effects and their management, importance of adherence, and recognizing early signs of symptom recurrence. Risk of relapse is highest in the first 6 months post the initial psychotic episode. Therefore, medications should be maintained for at least 6 months at the dose found to be effective in reducing positive symptoms during the acute phase.[44] Patients and caregivers should be counseled that partial response, such as decreased volume, intensity, or frequency of auditory hallucinations, should not be considered a failure of treatment. Residual symptoms can persist beyond the acute and stabilization phases but may remit with maintenance treatment.

STABLE PHASE

The main focus of the stable phase is quality of life and functional recovery. This is achieved through ensuring optimized treatment of symptoms, minimizing the risk of adverse effects, and psychosocial interventions. The question of how long antipsychotics need to be continued is often raised by patients. Antipsychotics have been shown to significantly reduce rates of relapse at 1 year versus placebo.[45] Therefore, maintenance antipsychotic treatment should be continued for at least 1 year in all patients recovering from a

psychotic episode. Caveats to this include intolerable adverse effects to the antipsychotic or uncertainty of the diagnosis of schizophrenia. Lifelong treatment is recommended in patients who have experienced multiple episodes of psychosis, at least two episodes within 5 years, or those who pose a significant risk to themselves or others when symptoms are left untreated. A slow, cautious taper off of antipsychotics can be considered after 1 year in patients recovering from a first episode with close follow-up established.[44] Routine monitoring for adverse effects, especially extrapyramidal syndromes (EPSs) and metabolic syndrome, is recommended during the stable phase. Patients may not connect an adverse effect to their medications, particularly a somatic symptom, when the main therapeutic target of their medication is in the central nervous system (CNS), so education and close follow-up are needed. The nonpharmacologic aspects of treatment are an important adjunct to pharmacologic management in functional recovery. Psychosocial interventions include assertive community treatment teams for high-risk patients, vocational training or supported employment, and cognitive-behavioral therapy. Adjunctive treatments for comorbid conditions, such as depression and anxiety, should also be addressed during this phase.

Nonpharmacologic Interventions

In addition to medication-based treatments, there are a variety of nonpharmacologic treatments that have also been found to be useful in the treatment of schizophrenia. Most patients will benefit from a combination, multidisciplinary approach to treatment. Treatment guidelines for schizophrenia recommend a treatment plan that includes both pharmacologic and nonpharmacologic treatment.[44] Nonpharmacologic interventions may include individual or group psychological therapy as well as family therapy, cognitive skills training, vocational skills training, and others. When utilized, these interventions have increased patient understanding of their illness,

decreased patient symptoms and relapse rates, and improved social and occupational functioning.

Selection of one of these interventions is based on the patient's level of acuity and specific needs, but should be considered during all phases of the illness. For example, a patient having an acute episode of psychosis might not be appropriate for cognitive or vocational skills training, but might benefit from individual therapy to help develop insight into their illness and understand why they are being treated. During an acute phase, other more simplistic interventions can also play a key role. For example, inpatient settings may utilize techniques to minimize stimulation or stress for patients, particularly those who are agitated or potentially aggressive. Group therapy sessions can assist patients with social interaction, something that might be difficult for many patients.

As the patient moves from an acute phase into a stabilization or stable phase, addition of skills training could be considered. Many patients will have lingering negative and cognitive symptoms that might not fully respond to pharmacotherapy. Cognitive skills training can assist with both of these areas, helping patients to overcome functional deficits arising from these symptoms. Vocational skills training can teach patients a variety of skills to prepare them to reenter the workforce, even if only in a minor role.

Family therapy can be helpful for both patient and family. Many families are greatly affected when a family member is diagnosed with schizophrenia. Improving family understanding of the illness and how to interact appropriately with the patient can be of great impact to all involved. In addition, the stress on the family can be mitigated through family therapy and assistance programs.

Pharmacists can also play a role in nonpharmacologic treatment by assisting with patient education (particularly in regard to medications) and patient adherence to medication. Assistance with adverse effects to medications is also an area in which pharmacists can play a role.

CASE 85-1, QUESTION 3: What are the management goals for J.J.?

First and foremost is to ensure J.J.'s safety. Although not serious, she has already injured herself by punching her walls. She is also very argumentative because of her paranoia, which could inadvertently lead to an altercation. A reduction in J.J.'s symptoms is also desired, ideally leading to an improvement in her functionality and insight into her illness. In light of J.J.'s symptoms and lack of insight into her illness, she will most likely require hospitalization to both ensure her safety and effectively treat her symptoms.

CASE 85-1, QUESTION 4: What nonpharmacologic treatment would you recommend for J.J. at this time?

During the acute phase, especially while J.J. still displays prominent positive symptoms, nonpharmacologic treatment should center on stress reduction and education on her illness. By reducing her stress, the goal is that J.J.'s paranoia and agitation will decrease, allowing her to more meaningfully engage in treatment. Illness education can be accomplished through both individual and group therapy and education sessions. As J.J. moves from an acute phase into a stabilization phase, more specific interventions can be started, such as vocational skills training, depending on her need and her level of functionality at that time.

J.J. would also benefit from medication education, such as from a pharmacist, once she is more stable in order to better understand her medications and any potential adverse effects.

CASE 85-1, QUESTION 5: How should J.J. be best communicated with by the staff treating her at this time? What recommendations would you provide her family and friends for communicating with her, both currently and once she is sent home?

The staff should attempt to use methods of communication that will not agitate J.J. or increase her paranoia. This includes both verbal and nonverbal ("body language") communication. If J.J. does become paranoid or agitated, she should be approached with

calmness in an attempt to deescalate the situation. Directly challenging her hallucinations and delusions will most likely only increase her paranoia, so this should be avoided. If possible, speak to J.J. during times when she is calm and having fewer symptoms and inquire about what methods she would prefer employed to calm her down when she does become agitated, such as being put in a room alone to relax, listening to music, conversing with a staff member, and so on.

J.J.'s family and friends should be educated about her illness to help them understand how to avoid upsetting her and potentially increasing her symptoms, especially during the acute phase. Avoidance of topics that would make her upset would also be appropriate. Once J.J. is sent home, they should interact with her as they normally would, but being aware that her symptoms could return at any time and they should be vigilant for this. If they observe any significant change in her status, they should attempt to get J.J. to a medical provider to evaluate her situation.

Assessment

The issues and conducting a differential diagnosis of schizophrenia have been previously discussed. Patients are assessed for the severity of their symptomatology after diagnosis using information from direct assessment via patient interview, discussions with family and friends of the patient as well as treatment staff, and review of the medical records. There are no laboratory tests to measure progress in schizophrenia at this time. It is important to obtain laboratory baseline monitoring tests that can be relevant for the differential diagnosis and for the monitoring of adverse effects of medications. First, it is important to obtain a complete psychiatric and medical history including all past medications. It is suggested that patients receive a physical exam and that clinical laboratory tests of thyroid, liver, and renal function be obtained. A CBC count with differential as well as a urinalysis and urine toxicology screen (if drug abuse is suspected) should be obtained. A fasting blood glucose and serum

hemoglobin (Hb) A_{1C} level is useful considering the high rate of type 2 diabetes prevalent in patients with schizophrenia. Obtaining an electrocardiogram (ECG) is also useful, especially if the patient is older than age 40 years or likely to receive a medication with significant QT_c prolongation effects.

The most prevalent way to record the results of a clinical assessment in the patient with schizophrenia would be via the mental status examination.[46] If a patient is to be treated in a clinical study, schizophrenic symptomatology may be assessed using the Positive and Negative Symptoms Scale (PANSS),[47] the Brief Psychiatric Rating Scale (BPRS),[48] and the Clinical Global Impression (CGI) scale. Adverse effects to antipsychotic treatment can be assessed using instruments such as the Abnormal Involuntary Movements Scale (AIMS) or the Dyskinesia Identification System Condensed User Scale (DISCUS) for tardive dyskinesia (TD),[49] or the Simpson-Angus Rating Scale for drug-induced parkinsonism, and general adverse effects can be recorded via the Treatment Emergent Symptoms Scale (TESS).[50] These are all scales suitable to measure the severity of these symptoms, but are not used as diagnostic instruments.

Pharmacotherapy Interventions

ANTIPSYCHOTICS

Classification and nomenclature of the antipsychotics

The first effective antipsychotic medication used in Western medicine was chlorpromazine, a low-potency sedating “typical” antipsychotic first developed in 1951 to augment anesthesia and was termed by its inventor Laborit to be a *vegetative stabilizer*.[51] Although its introduction resulted in a sharp decrease in the number of hospitalized patients with schizophrenia, it was imperfect in that it caused adverse effects such as drug-induced parkinsonism, acute dystonias, sedation, anticholinergic effects, and orthostasis. The knowledge that D_2 antagonism was key in making effective agents for treating schizophrenia led to the development of a plethora of

new agents, some of which were much more specific in selectively antagonizing these receptors. The medications with greater dopamine specificity tended to have fewer effects on other neurotransmitter systems (**Fig. 85-1**). Therefore, these "high-potency" first-generation antipsychotics (FGAs), such as haloperidol or fluphenazine, were less likely to cause related adverse effects such as sedation, increased appetite, dry mouth, constipation, and orthostasis than were "low-potency" agents, such as chlorpromazine and thioridazine. However, high-potency FGAs have a greater propensity to cause acute dystonias and drug-induced parkinsonism than do the low-potency agents. The middle-potency agents, such as loxapine, molindone, and perphenazine, have more moderate adverse effects. These medications have other unique properties that differentiate them. For example, molindone was found to induce modest weight loss,[52,53] and loxapine was thought to be somewhat atypical in its effects on serotonergic receptors. These recognized properties helped lead to the development of second-generation antipsychotics (SGAs) or "atypical antipsychotics."[54]

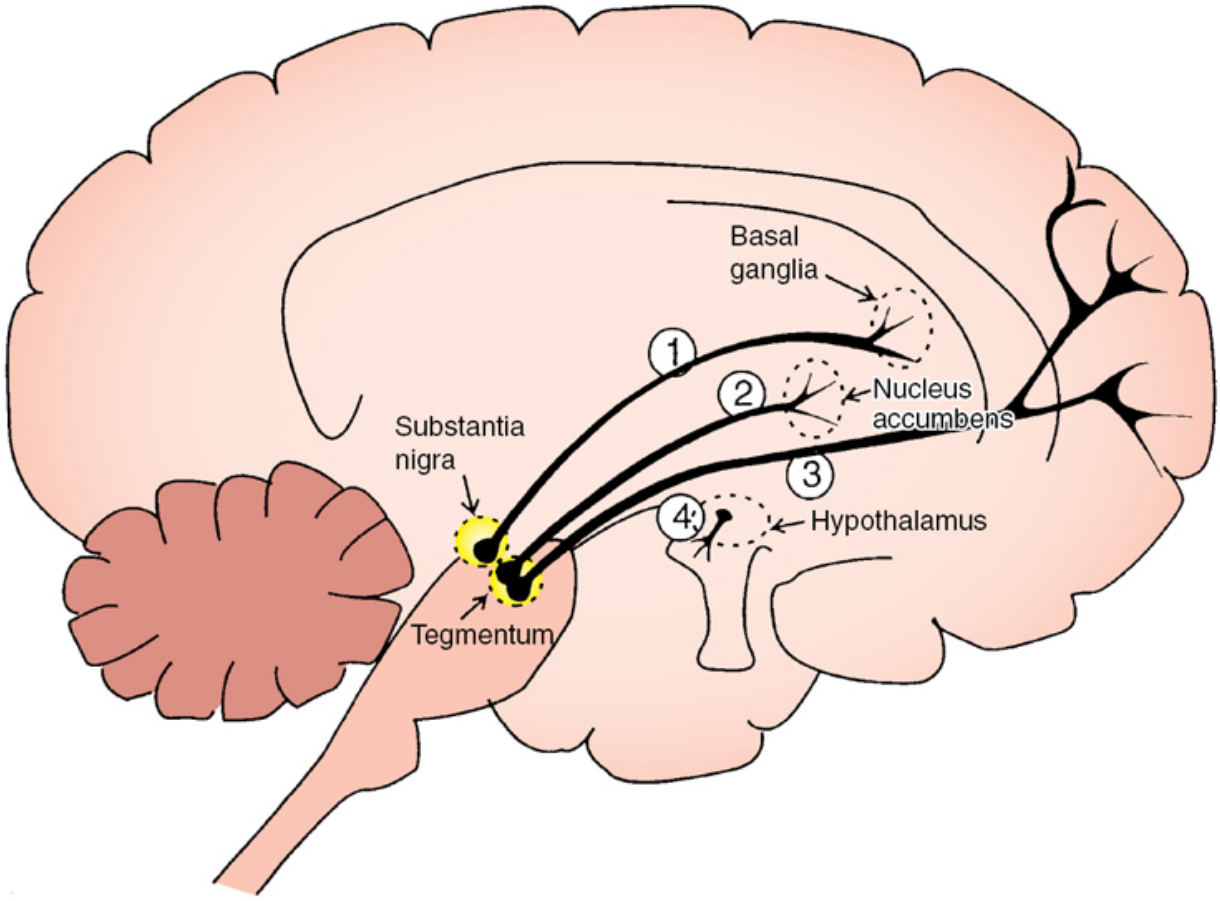


Figure 85-1 Four dopamine pathways in the brain. The neuroanatomy of dopamine neuronal pathways in the brain can explain both the therapeutic effects and the side effects of the known antipsychotic agents. (1) The nigrostriatal pathway projects from the substantia nigra to the basal ganglia and is thought to control movements. (2) The mesolimbic pathway projects from the midbrain ventral tegmental area to the nucleus accumbens, a part of the limbic system of the brain thought to be involved in many behaviors, such as pleasurable sensations and the powerful euphoria of drugs of abuse, as well as delusions and hallucinations of psychosis. (3) A pathway related to the mesolimbic pathway is the mesocortical pathway. It also projects from the midbrain ventral tegmental area, but sends its axons to the limbic cortex, where it may have a role in mediating positive and negative psychotic symptoms or cognitive side effects of neuroleptic antipsychotic medications. (4) The fourth dopamine pathway of interest is the one that controls prolactin

secretion, called the *tuberoinfundibular pathway*. It projects from the hypothalamus to the anterior pituitary gland.

The first SGA, clozapine, differed dramatically in its pharmacology from previous agents. It is a very potent antagonist of serotonin-2a (5-HT_{2a}) and serotonin-2c (5-HT_{2c}) receptors. It was later determined that the ability to antagonize serotonergic receptors was critical to creating other new "atypical" agents that could act in a manner similar to clozapine, but without its critically serious adverse effect profile. Clozapine was shown to have robust effectiveness in treating resistant schizophrenia,[55] but it causes agranulocytosis in about 1% to 2%,[56] induces seizures in 6% of those taking it at higher dosages,[57] besides possessing nuisance side effects such as sialorrhea and constipation, and even being associated with myocarditis.[58–60] Because clozapine is restricted to only the patient who is resistant to treatment or intolerant to antipsychotics, newer agents that were introduced, such as risperidone, olanzapine, quetiapine, and ziprasidone, were used with initial excitement. This excitement was tempered with caution when it was discovered that these agents could also be associated with obesity, hypertriglyceridemia, and even the onset of type 2 diabetes mellitus. Later, somewhat unique agents were introduced with possible advantages such as aripiprazole, lurasidone, paliperidone, iloperidone, asenapine, brexpiprazole, and cariprazine. The terms FGA and SGA are utilized for clarity throughout the chapter.

General differentiating characteristics of antipsychotics

It is sometimes useful to conceptualize the different antipsychotic medications in terms of their action at different receptor subtypes or by potency (**Table 85-4**). The SGAs are more potent at blocking 5-HT_{2a} serotonergic receptors than they are at blocking D_2 receptors. The SGAs are generally less likely to cause drug-induced parkinsonism and TD than do first-generation medications, but some of these agents may be more prone to cause metabolic issues than do the FGAs.[61] Low-potency antipsychotics are often given in

hundreds of milligrams per day and tend to have greater antihistaminic, anticholinergic, and α-1 antagonist effects than do their high-potency (roughly 1–20 mg daily) counterparts.

Table 85-4
Clinical Effects of Receptor Antagonism by Antipsychotics

Receptor (Subtype)	Clinical Effect of Antagonism
Dopamine (D_2)	*Mesolimbic pathway* (basal ganglia): treatment of positive symptoms *Mesocortical pathway* (prefrontal cortex): may worsen negative symptoms *Nigrostriatal pathway* (substantia nigra): extrapyramidal symptoms (EPSs) *Tuberoinfundibular pathway* (hypothalamus–anterior pituitary): increased prolactin release
Serotonin (5-HT_{2a})	Treatment of negative symptoms; increased dopamine release in prefrontal cortex; may reduce mesolimbic dopamine release
Serotonin (5-HT_{2c})	Implicated in antipsychotic-associated weight gain
Muscarinic (μ_1)	Anticholinergic side effects (dry mouth, constipation, urinary retention, blurred vision, hot/dry skin, memory impairment); sedation
Histamine (H_1)	Increased appetite, sedation
Alpha (α_1)	Orthostatic hypotension

Typical Antipsychotics or First-Generation Antipsychotics

Low-potency phenothiazine antipsychotics include the prototype antipsychotic chlorpromazine as well as thioridazine and its metabolite mesoridazine. Low-potency typical antipsychotics are strong histamine-1 blockers and are associated with more weight gain than are the high- potency ones. They also tend to be strong blockers of α-1, inducing orthostasis, and muscarinic receptors, which results in dry mouth, blurred vision, and constipation. Thioridazine is distinctive in that it can cause retinopathy in doses

>800 mg daily. Moreover, it has received a black box warning because it can cause prolonged QT_c intervals that can be clinically significant, especially if a 2D6 P450 isoenzyme antagonist (which increases its serum levels) is also being used.[62] Use of thioridazine is restricted to patients who are resistant to treatment because these proarrhythmic effects and use in clinical practice are uncommon.

Common middle-potency typical antipsychotics include molindone, loxapine, and perphenazine. Molindone is the only antipsychotic that has been associated with weight loss in some reports.[52,53] Loxapine is regaining use because of its inhalation dose form, and perphenazine has had a resurgence in the use of sorts owing to it being the chosen typical antipsychotic in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)-1 trial.[63] These agents tend to fall in between the high- and low-potency agents in terms of adverse effects.

The high-potency typical antipsychotics are very selective for D_2 receptor blockade; thus, they cause fewer adverse effects related to antihistaminic, anticholinergic, or α-1 receptor blocking effects. However, they are more likely to induce adverse extrapyramidal effects such as dystonia, drug-induced parkinsonism, and akathisia than do the lower potency typical agents. Their availability as long-lasting depot injections of haloperidol and fluphenazine and reduced rate of adverse metabolic effects encourage their continued use. Other, less often utilized high-potency agents include thiothixene and trifluoperazine (**Table 85-5**).

Table 85-5
First-Generation Antipsychotics

Medication Name (Generic/Brand); Potency—Chlorpromazine Equivalents; Class	Dosage Forms	Adult Dosing Schedules	Dose Adjustments
Haloperidol (Haldol®) High: 2 Butyrophenone	*Tablet*: 0.5, 1, 2, 5, 10, 20 mg *PO solution*: 2 mg/mL *Injectable (immediate release)*: 5 mg/mL	*Initial*: 0.5–5 mg bid or tid (depending on symptom severity) *Usual range*: 5–40 mg	*Renal*: No specific recommendations *Hepatic*: No specific recommendations
Fluphenazine (Prolixin®) High: 2 Phenothiazine	*Tablet*: 1, 2.5, 5, 10 mg *PO elixir*: 2.5 mg/mL *PO solution*: 5 mg/mL *Injectable (immediate release)*: 2.5 mg/mL	*Initial*: 2.5–10 mg q 6–8 hours *Usual range*: 1–40 mg/day	*Renal*: Use with caution (nondialyzable). *Hepatic*: Use with caution.
Thiothixene (Navane®) High: 4 Thioxanthene	*Capsule*: 1, 2, 5, 10 mg	*Initial*: 6–10 mg daily (divided doses) *Usual range*: 5–60 mg/day	*Renal*: Use with caution (nondialyzable). *Hepatic*: Consider dose reduction.
Trifluoperazine (Stelazine®) High: 5 Phenothiazine	*Tablet*: 1, 2, 5, 10 mg	*Initial*: 2–5 mg bid *Usual range*: 15–20 mg/day	*Renal*: Use with caution (nondialyzable). *Hepatic*: Consider dose reduction.
Perphenazine (Trilafon®) Mid: 8–10 Phenothiazine	*Tablet*: 2, 4, 8, 16 mg	*Initial*: 4–8 mg tid *Usual range*: 8–64 mg/day	*Renal*: No specific recommendations *Hepatic*: Consider dose reduction.
Loxapine (Loxitane®, Adasuve®) Mid: 10 Dibenzoxazepine	*Capsule*: 5, 10, 25, 50 mg *Inhalation powder*: 10 mg	*Initial*: 10 mg bid *Usual range*: 20–250 mg/day (PO)	*Renal*: No specific recommendations *Hepatic*: No specific recommendations
Chlorpromazine (Thorazine®) Low: 100 Phenothiazine	*Tablet*: 10, 25, 50, 100, 200 mg *Injection (immediate release)*: 25 mg/mL	*Initial*: 100–200 mg/day in divided doses; increase 20–50 mg/day q 3–4 days as indicated.	*Renal*: No specific recommendations *Hepatic*: Consider dose reduction.
Thioridazine (Mellaril®) Low: 100 Phenothiazine	*Tablet*: 10, 25, 50, 100 mg	*Initial*: 50–100 mg tid with gradual dose increases *Usual range*: 50–800 mg/day	*Renal*: Use with caution (nondialyzable). *Hepatic*: Consider dose reduction.

Note: Information on long-acting injectable (LAI) versions of these medications can be found in Table 85-8.

bid, twice daily; PO, oral; q, every; tid, thrice daily.

Sources: Thioridazine hydrochloride. Package insert. Sun Pharmaceutical Industries Inc; November 2016; Trifluoperazine hydrochloride. Package insert. Mylan Pharmaceuticals Inc; August 2019; Molindone hydrochloride. Package insert. Epic Pharma LLC; April 2018; Chlorpromazine hydrochloride. Package insert. Lannett Company Inc; February 2020; Fluphenazine hydrochloride. Package insert. Lannett Company Inc; December 2019; Haloperidol. Package insert. Mylan Pharmaceuticals Inc; July 2020; Loxapine succinate. Package insert. Marlex Pharmaceuticals Inc; February 2016; Perphenazine. Package insert. Sandoz Inc; January 2018; Thiothixene. Package insert. Mylan Pharmaceuticals Inc; January 2020; Adasuve (loxapine inhalation powder). Package insert. Galen US Inc; August 2017.

Atypical or Second-Generation Antipsychotics

SGAs are agents that exert more effects on antagonism of 5-HT_{2a} subreceptors than on D_2 receptors and cause dramatically less drug-induced extrapyramidal symptoms. The SGAs clozapine, quetiapine, and olanzapine are more likely to induce metabolic disorders, such as weight gain,[64] hypertriglyceridemia,[65–69] and, possibly, glucose dysregulation[70] than do other antipsychotic medications. Atypical antipsychotics are thought by many to have greater efficacy in the treatment of negative and cognitive symptoms of schizophrenia and a reduced risk of TD.[61]

Clozapine has a unique pharmacology, which makes it the only agent found to be effective in treatment-resistant schizophrenia and suicidality in schizophrenia.[55,61] Clozapine is associated with a higher incidence of agranulocytosis and neutropenia relative to other antipsychotics that require frequent serum monitoring. This agent is discussed more in the section Inadequate Response. Risperidone (Risperdal®) is considered to be an atypical antipsychotic that is effective and less likely to cause extrapyramidal system adverse effects at doses <6 mg/day. Akathisia can be a problem especially in the elderly. Paliperidone (Invega®), or 9-hydroxyl risperidone, is the active metabolite of risperidone and has shown itself to be as effective as the parent drug.[71] Paliperidone is a controlled-release OROS® oral (PO) dosage form that utilizes osmotic pressure to deliver the medication in a controlled manner. Patients should be counseled not to be alarmed if the insoluble outer tablet shell is found in their stool. The long-acting injectable dosage forms of paliperidone and its parent compound risperidone are discussed in the section on Long-Acting Injectables.

Olanzapine (Zyprexa®) is an atypical antipsychotic that is very effective, but it can cause significant weight gain with related glucose dysregulation as well as increased serum triglycerides.[66,72] Olanzapine doses may need to be adjusted in smokers because of the induction of the cytochrome P450 (CYP) 1A2 isoenzyme system by the polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke.[73] An olanzapine–samidorphan combination (Lybalvi®) has been FDA approved, which appears to retain the efficacy of olanzapine in

schizophrenia with a reduction in long-term weight gain.[74] This is due to the effects of samidorphan, which is a μ-opioid receptor antagonist with partial agonist activity at κ and δ opioid receptors. Owing to the samidorphan, this medication should not be given to patients dependent on opioids. This combination dose form contains 10 mg of samidorphan per tablet and either 5, 10, 15, or 20 mg of olanzapine.[75]

Quetiapine (Seroquel®) is a low-potency D_2 antagonist.[63] Owing to its minimal risk of drug-induced movement disorders, it is often utilized in patients with psychosis in Parkinson disease before the use of clozapine.[76] It is recommended that patients be counseled regarding diet and exercise before and during the use of these agents and clozapine. Ziprasidone (Geodon®) should be administered with at least 500 calories to ensure sufficient absorption.[77] It causes little weight gain or dyslipidemia and has minimal anticholinergic or extrapyramidal adverse effects. Although there were initial warnings about cardiac conduction delays (prolonged QT interval), there have been sparse reports linking the medication to death because of this concern.[78–80] An ECG before and during treatment is advised.[81]

Aripiprazole (Abilify®) should be dosed in the morning because it may be activating in some patients owing to its partial D_2 receptor agonism. Typical adverse effects include nausea, vomiting, and insomnia in the first weeks of treatment. It has a lower risk of weight gain, dyslipidemia, QT delays, and can actually cause decreases in serum prolactin and triglycerides. In fact, it has been used as augmentation to remedy hyperprolactinemia induced by other antipsychotics.[82–84] It also seems to have a low risk of EPS. Although aripiprazole's unique differential effect on dopaminergic systems can be beneficial, dopamine-3 (D_3) partial agonism may induce an increase in risky, reward-based behaviors, such as gambling.[85,86] Brexpiprazole (Rexulti®) is a recent addition to the antipsychotic armamentarium that showed superiority to placebo in both key clinical trials (at 4 mg daily) with pharmacologic and therapeutic similarities to aripiprazole.[87,88] It is a partial agonist at D_2 receptors

and serotonin 5-HT_{1a} and antagonist at 5-HT_{2a} and noradrenergic α-1b and α-2c receptors.[89] It is metabolized by both 2D6 and 3A4 hepatic isoenzyme systems, and dose reductions (DRs) are recommended if these systems are inhibited.[90] Cariprazine (Vraylar®) is pharmacologically similar to aripiprazole and brexpiprazole in that it is a partial agonist at the D_2, D_3, and 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors. However, it has about a 10-fold greater affinity for the D_3 receptor than for the D_2 receptor.[91] It is unclear what therapeutic differences result from its stronger effects on D_3 receptors.[92–94]

Iloperidone (Fanapt®) is less likely to cause drug-induced parkinsonism, akathisia, and hyperprolactinemia than do the typical antipsychotics, but has a risk of moderate weight gain, orthostasis, and the potential to cause QT interval prolongation that can be of concern in some patients.[95,96] Asenapine (Saphris®) needs to be administered sublingually for rapid and adequate absorption. It has an absolute bioavailability of 35% when taken sublingually and <2% when swallowed. The patient should be counseled not to eat or drink for 10 minutes after the sublingual administration. There is also a 24-hour patch formulation of asenapine (Secuado®) available. Patients should be counseled to avoid the application of external heating sources (ie, heating pads or electric blankets) to the patch because this may increase exposure to asenapine by up to 3.9-fold. The most common adverse reactions with asenapine (≥5% and at least twice the rate of placebo) are somnolence, dizziness, extrapyramidal symptoms other than akathisia, and weight gain.[97] Lurasidone (Latuda®) is an effective agent with a low propensity to cause drug-induced parkinsonism, metabolic complications, or QT_c prolongation. It needs to be taken with food (about ≥350 calories) for adequate absorption. The most common adverse events associated with lurasidone treatment are nausea, vomiting, akathisia, dizziness, and sedation (**Table 85-6**).[98]

Table 85-6
Second-Generation Antipsychotics

Medication Name (Generic/Brand)	Dosage Forms	Adult Dosing Schedules	Dose Adjustments
Aripiprazole (Abilify®)	*Tablet*: 2, 5, 10, 15, 20, 30 mg *ODT*: 10, 15 mg *Injectable (short acting)*: 9.75 mg/1.3 mL *Oral solution*: 1 mg/mL	*Initial*: 10–15 mg/day, titrate at 2-week intervals *Usual range*: 15–40 mg *Max*: 30 mg/day	*Renal/hepatic*: No dose adjustment necessary
Asenapine (Saphris®, Secuado®)	*SL tablet*: 5, 10 mg *Transdermal 24-hour patch*: 3.8, 5.7, 7.6 mg	*Initial*: 5 mg bid (no benefit demonstrated with higher doses); 3.8-mg patch q daily and increase as needed weekly	*Renal/hepatic*: No renal dose adjustments necessary; use not recommended in severe hepatic impairment Warn patient not to swallow SL tablet.
Brexpiprazole (Rexulti®)	*Tablet*: 0.25, 0.5, 1, 2, 3, 4 mg	*Initial*: 1 mg days 1–4; 2 mg days 5–7; 4 mg day 8 *Usual range*: 4 mg daily	*Renal*: 3 mg max in CrCl <60 mL/minute *Hepatic*: 3 mg max in Child–Pugh score ≥7
Cariprazine (Vraylar®)	*Capsule*: 1.5, 3, 4.5, 6 mg	*Initial*: 1.5 mg day 1, increase to 3 mg day 2, increase in 1.5- to 3-mg increments as needed *Usual range*: 1.5–6 mg	*Renal*: Not recommended in CrCl <30 mL/minute *Hepatic*: Not recommended in severe impairment (Child–Pugh score 10–15)
Clozapine (Clozaril®, FazaClo ODT®, Versacloz®)	*Tablet*: 12.5, 25, 50, 100, 200 mg *ODT*: 12.5, 25, 100 mg *Oral suspension*: 50 mg/mL	*Initial*: 12.5–25 mg/day, titrate by 25–50 mg/day to target of 300–450 mg/day. *Usual range*: 350–600 mg *Max*: 900 mg/day	*Renal/hepatic*: No specific recommendations
Iloperidone (Fanapt®)	*Tablet*: 1, 2, 4, 6, 8, 10, 12 mg	*Initial*: 1 mg bid, increase by 2 mg/day to target dose of 12–24 mg/day. *Max*: 24 mg/day	*Renal*: No adjustments necessary *Hepatic*: Use not recommended
Lurasidone (Latuda®)	*Tablet*: 20, 40, 80, 120 mg	*Initial*: 40 mg daily taken with food *Usual range*: 40–160 mg/day *Max*: 160 mg/day	*Renal*: Initial dose of 20 mg/day and max of 80 mg/day in moderate-to-severe impairment *Hepatic*: Initial dose of 20 mg/day and max of 80 mg/day in moderate impairment and max of 40 mg in severe impairment
Lumateperone (Caplyta®)	*Capsules*: 42 mg	*Initial*: Take one capsule by mouth daily with food. No titration required	*Hepatic*: Use not recommended in moderate-to-severe hepatic impairment No adjustment necessary in mild impairment
Olanzapine (Zyprexa®)	*Tablet*: 2.5, 5, 7.5, 10, 15, 20 mg *ODT*: 5, 10, 15, 20 mg *Injection (short acting)*: 10 mg/vial (5 mg/mL after reconstitution)	*Initial*: 2.5–10 mg/day *Usual range*: 20–40 mg/day *Max*: FDA recommended max is 20 mg/day.	*Renal*: Initial dose of 5 mg/day should be considered. *Hepatic*: Child–Pugh classes A and B, no adjustment necessary
Olanzapine/Samidorphan combination (Lybalvi®)	*Tablets*: 5, 10, 15, or 20 mg of olanzapine with 10 mg of samidorphan	*Initial*: 5 mg/10 mg or 10 mg/10 mg of olanzapine/samidorphan *Usual range*: 5 to 20 mg daily of olanzapine with 10 mg of samidorphan	*Renal*: Use is not recommended in patients with end-stage renal disease.

Paliperidone (Invega®)	*Tablet (ER)*: 1.5, 3, 6, 9 mg	*Initial*: 6 mg/day; increases should not exceed 3 mg every 5 days. *Usual range*: 9–12 mg *Max*: 12 mg/day	*Renal*: CrCl 50–79 mL/minute: Initiate at 3 mg, max 6 mg/day. CrCl 10–49 mL/minute: Initiate at 1.5 mg, max 3 mg/day. CrCl <10 mL/minute: use not recommended *Hepatic*: Child–Pugh classes A and B, no adjustment required
Quetiapine (Seroquel®)	*Tablet (IR)*: 25, 50, 100, 200, 300, 400 mg *Tablet (ER)*: 50, 150, 200, 300, 400 mg	*Initial (IR)*: 25 mg bid; titrate in 25- to 50-mg increments, given tid to tid, to a target range of 300–400 mg/day by day 4; further adjustments at 25-to 50-mg increments with at least 2 days between adjustments; usual range 300–750 mg/day *Initial (ER)*: 300 mg/day; target 400–800 mg/day *Max*: 800 mg/day	*Renal*: No specific recommendations *Hepatic*: Initiate IR tablets at 25 mg/day and increase by 25–50 mg/day increments/day; initiate ER tablets at 50 mg/day and increase by 50 mg/day increments.
Risperidone (Risperdal®)	*Tablet*: 0.25, 0.5, 1, 2, 3, 4 mg *ODT*: 0.5, 1, 2, 3, 4 mg *Oral solution*: 1 mg/mL	*Initial*: 1–2 mg/day; usual 4–6 mg/day *Usual range*: 4–8 mg/day *Max*: 16 mg/day	*Renal/hepatic*: Recommend initial dose of 0.5 mg bid; may increase dose 0.5 mg bid; increases above 1.5 mg bid should be completed over 1-week intervals.
Ziprasidone (Geodon®)	*Capsule*: 20, 40, 60, 80 mg *Injectable (short acting)*: 20 mg/mL	*Initial*: 20 mg bid with food; dose adjustments at ≥48-hour intervals *Max*: 80 mg bid	*Renal*: No adjustments necessary in mild-to-moderate impairment Use IM with caution. *Hepatic*: No adjustments necessary in mild-to-moderate impairment

Note: Information on long-acting injectable (LAI) versions of these medications can be found in Table 85-8.

bid, twice daily; CrCl, creatinine clearance; ER, extended release; FDA, U.S. Food and Drug Administration; IM, intramuscular; IR, immediate release; ODT, orally disintegrating tablet; PO, oral; q, every; SL, sublingual; tid, thrice daily.

Sources: Rexulti (brexpiprazole) tablets. Package insert. Osutka Pharmaceutical Co Ltd; December 2021; Lybalvi (olanzapine and samidorphan). Package insert. Alkermes Inc; May 2021; Zyprexa (olanzapine). Package insert. Eli Lilly and Company; 2021; Vraylar (cariprazine tablets). Package insert. Actavis Pharma Inc; May 2019; Latuda (lurasidone HCl tablets). Package insert. Sunovion Pharmaceuticals Inc; December 2019; Saphris (asenapine tablets). Package insert. Allergan USA Inc; January 2017; Clozaril (clozapine tablets). Package insert. HLS Therapeutics Inc; February 2021; Invega (paliperidone extended-release tablets). Package insert. Janssen Pharmaceutical; February 2021; Fanapt (iloperidone tablets). Package insert. Vanda Pharmaceuticals Inc; February 2017; Abilify (aripiprazole). Package insert. Bristol-Myers Squibb; June 2020; Risperdal (risperidone). Package insert. Janssen Pharmaceuticals Inc; February 2021; Seroquel (quetiapine tablet film coated). Package insert. AstraZeneca Pharmaceuticals LP; January 2022; Secuado (asenapine film, extended release). Package insert. Noven Therapeutics LLC; October 2019; Fazaclo ODT (clozapine orally disintegrating tablets). Package insert. Azur Pharma Inc; December 2010; Versacloz (clozapine oral suspension). Package insert. TruPharma, LLC; July

2020; Caplyta (lumateperone). Package insert. Intra-Cellular Therapies Inc; December 2021; Geodon (ziprasidone HCl). Package insert. Pfizer; February 2022.

Lumateperone (Caplyta®) is a newer atypical antipsychotic FDA approved for use in schizophrenia at a dosage of 42 mg daily. The other doses studied in clinical trials did not reach statistical significance when compared to placebo. Lumateperone is a strong antagonist of 5-HT_{2A} receptors and is both a full antagonist at postsynaptic D_2 receptors and a partial agonist at presynaptic D_2 receptors.[99] It is relatively unique for an antipsychotic in that it inhibits serotonin reuptake and also indirectly modulates glutamatergic activity; the relevance of these properties to its clinical effects is not clearly established. Lumateperone is a substrate of CYP3A4 and uridine glucuronyl transferase (UGT) and subject to possible drug interactions induced by drugs affecting these systems.[100] In a pooled analysis of late-phase controlled clinical trials, the treatment-emergent adverse effects that presented at twice the rate of placebo and ≥5% for lumateperone were dry mouth and somnolence/sedation.[101]

Mechanism of drug action

All antipsychotic medications currently approved for the treatment of schizophrenia have at least some D_2 antagonistic effects. These antipsychotic medications have been divided into two major classes depending on whether they substantially antagonize 5-HT_{2a} receptors and dopaminergic ones. Although activity in attenuating dopamine transmission in the mesolimbic pathway is seen as being beneficial in decreasing the severity of positive schizophrenic symptomatology, decreased activity of dopamine receptors in mesocortical pathways (sometimes owing to antipsychotic medication) may relate to the severity of negative symptoms. Antagonism of 5-HT_2 receptors in the striatum by SGAs may balance decreased dopaminergic neurotransmission and decrease their relative propensity to cause TD.[102]

Selection of an Antipsychotic

Antipsychotic choice is based on a number of factors, many of which are patient specific. In making a selection, consider such patient factors as treatment history (if any), medical comorbidities and concurrent medications, patient preferences, and potential cost concerns. If the patient has a known history of being treated with antipsychotics, this can help guide current selection. Previous positive response to an antipsychotic is a good indicator of future response, just as previous lack of response would recommend against trying that agent in the future. History of adverse effects to particular agents is useful also. If a patient is known to have had an adverse event to a specific agent in the past that would preclude them from receiving this agent again (including a patient's stated preference for this reason), then this will help guide current medication selection. In addition, if an adverse effect led to medication discontinuation or poor adherence in the past, an antipsychotic that has a minimal risk of causing that adverse effect in the future should be selected. If information about a patient is not available, particularly in newly diagnosed patients with no prior treatment, medication history for a first-degree relative with schizophrenia may be useful in selecting an agent for the patient in a similar manner.

One area of debate has been selecting between FGAs and SGAs. Studies comparing the two classes head-to-head have shown similar efficacy rates between them.[103,104] Although the older agents are more prone to cause movement disorders, such as EPSs, the newer agents are thought to be more prone to causing metabolic disturbances in patients. Although SGAs are widely considered first choice in clinical practice,[105] most treatment guidelines now consider either FGAs or SGAs (other than clozapine) as potential first-line choices for treatment, depending on the patient factors described earlier.[106,107]

Case 85-1, Question 6: Which type of antipsychotic medication would you recommend for J.J. at this time? What factors would you use to select a

treatment regimen for her?

Because J.J. has never been treated with an antipsychotic before, almost any type is potentially viable as a treatment. Atypical antipsychotics would most likely be preferable. Typical antipsychotics, although efficacious, might lead to significant extrapyramidal or other adverse effects that she might not tolerate well, possibly leading to nonadherence. Also, with chronic usage, typical antipsychotics (FGAs) are more likely to cause TD than do SGAs. Because she is young and fairly healthy, we would also want to select an atypical antipsychotic with minimal long-term risks of metabolic adverse effects, such as weight gain and glucose irregularities. Pharmacoeconomic considerations should also be taken into account because some of the atypical antipsychotics are available generically and some are not.

CASE 85-1, QUESTION 7: What pharmacologic agents should be considered first to treat J.J. considering her acute symptoms?

In light of J.J.'s acute psychotic symptoms and agitation, a combination of both antipsychotics and adjunctive agents should be considered at this time. Although antipsychotics are generally the mainstay of schizophrenia treatment, they may not reduce symptoms quickly enough. Benzodiazepines may also be useful, especially during periods of increased agitation. Use of adjunctive medications to treat any adverse effects, such as EPSs, may also be needed. Depending on J.J.'s compliance with PO medications or during any periods of increased agitation, intramuscular (IM) injections of medications, including antipsychotics, benzodiazepines, and side effect medications, may need to be utilized acutely.

EFFICACY

Although there are numerous studies demonstrating the efficacy of current antipsychotic medications in comparison to placebo and accepted treatment, more attention has been paid of late to

effectiveness studies comparing currently available antipsychotics. These effectiveness trials are intended to show the comparative value of these agents in situations that are more comparable to routine clinical care by utilizing less stringent eligibility criteria, longer duration, prospective design, and large sample size.[108] Still, they are randomized double-blind trials using intent-to-treat analysis just as if they were efficacy studies. Interpreting these studies is a help in bridging the chasm between studies in ideal populations and routine clinical care.

One of the landmark effectiveness trials comparing antipsychotic agents is the National Institutes of Mental Health (NIMH)-funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial. The first phase of the CATIE trial compared the SGAs quetiapine (N = 329), ziprasidone (N = 183), risperidone (N = 333), and olanzapine (N = 330) with the middle-potency FGA perphenazine (N = 257). The main outcome variable was time to discontinuation of the antipsychotic for any cause. Overall, 74% of the patients discontinued treatment over the 18-month course of the study. This study showed significantly less medication discontinuation ($P < .001$) in patients treated with olanzapine (64%) than in those receiving quetiapine (82%) or risperidone (74%). After adjusting for multiple comparisons, the difference in using olanzapine with ziprasidone or perphenazine did not reach significance. When analyzed separately, the discontinuation rates due to intolerability were substantially higher in the patients treated with olanzapine, but there was a significantly greater time to discontinuation with olanzapine compared to quetiapine, risperidone, and perphenazine. The lower number of patients in the ziprasidone group reduced the power (and thus the chance to find the difference) for comparisons with this agent and the others. The 18-month duration of the study could not yield information on the long-term effects of these agents in causing TD or metabolic disorders.[63]

Patients who discontinued treatment were eligible for enrollment in phase two of the CATIE trial to receive a different antipsychotic if they dropped out primarily for lack of tolerance or efficacy. Those primarily not responding in the earlier phase could instead enter the

phase two trial in which there was a clozapine treatment arm.[109] In the lack of tolerability arm, patients assigned to olanzapine (*N* = 68) or risperidone (*N* = 70) showed a longer time to discontinuation rates than those receiving either quetiapine (*N* = 63) or ziprasidone (*N* = 135).[110] In the poor responder study arm, patients receiving clozapine (*N* = 45) showed a significantly lower (*P* < .05) time to discontinuation of treatment than did those receiving either olanzapine (*N* = 17), quetiapine (*N* = 14), or risperidone (*N* = 14).[111] The third phase of the CATIE trial involved the 270 patients who discontinued treatment in the earlier phases, who went on to receive aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, or risperidone. The lack of power made it difficult to show any differences in effectiveness between these agents, and in this open trial, few patients received either perphenazine (*N* = 4) or fluphenazine decanoate (*N* = 9).[112] Of note, at each subsequent phase of CATIE, statistical power was reduced as compared to the original study because of subject attrition, thereby increasing type II error.

Another often cited study is the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) in which 227 patients were randomized to receive either FGAs (*N* = 118) or to be treated with an SGA (*N* = 109). This pragmatic, non–industry-funded study was powered only to compare the overall differences between the FGA and SGA groups and not the individual antipsychotics themselves. The hypothesis that second-generation medications would have an advantage on any quality of life measures over first-generation medications was disproved.[113] The CUtLASS 2 study was similarly designed and compared clozapine to other SGAs in patients who did not respond sufficiently to two prior treatments. Patients on clozapine showed significant improvements on PANSS scores (*P* < .01), felt they did much better (*P* < .05), and there was a trend for improvement (*P* = .08) on their quality of life as measured on the Quality of Life Scale (QLS).[113,114]

SGAs have also shown better response and remission rates than haloperidol in patients recovering from a first episode.[115] Meta-analyses and related techniques have been utilized to attempt to

overcome limitations of low power in comparative antipsychotic efficacy trials. One meta-analysis looked at 150 double-blind randomized controlled trials (RCTs) in >20,000 patients and found only amisulpride (not available in the United States), clozapine, olanzapine, and risperidone to be more effective than the FGAs. The SGAs showed fewer EPSs and, with the notable exception of aripiprazole and ziprasidone, caused more weight gain than did haloperidol. However, there were no significant differences in weight gain between the low-potency typical antipsychotics such as chlorpromazine and the second-generation agents.[116]

One controversial topic not clearly covered by effectiveness trials or meta-analysis is the use of combinations of antipsychotic medications.[117] Although combination use is a relatively common practice,[118] it is not recommended owing to the paucity of evidence for its safety and efficacy[119,120]; in fact, combination antipsychotic therapy is often targeted by quality improvement programs.[121] Although there are situations (eg, adding aripiprazole for a patient stabilized on risperidone to attenuate hyperprolactinemia) in which this use can be logical and beneficial,[27,117,122,123] there are other times when patients resistant to treatment should receive alternative approved effective pharmacotherapy with clozapine.[124]

DOSAGE FORMS

Antipsychotics are commercially available in a variety of dosage forms to allow for the need for different treatment situations and settings. The most common forms consist of orally administered products such as tablets/capsules (both short- and long-acting forms), orally disintegrating tablets (ODTs), and PO liquid solutions/suspensions; and one medication is also available as a topical patch. Many antipsychotics are also available as injectables, some as short-acting IM forms and some as long-acting IM forms. Selection of an appropriate dose form can depend on factors such as the severity of the patient's illness and risk of imminent harm to themselves or others, willingness or ability to take medications, and treatment setting.

Alternative oral dose forms

Although almost every antipsychotic is available as a traditional tablet or capsule, many are available in other PO dosage forms. In an effort to help with adherence, several antipsychotics are available as PO liquids, ODTs, or patch formulations. The SGAs aripiprazole, risperidone, and ziprasidone are available as PO liquids, which may be useful in patients who have a hard time swallowing traditional tablets (or will not swallow them) or to achieve more specific dosing, such as might be needed for pediatric or geriatric patients. ODTs are formulated to dissolve rapidly when placed on the tongue, needing only for the patient to swallow their own saliva to obtain medication absorption in the gut. This formulation is particularly useful in the inpatient setting when "cheeking" or nonadherence is suspected. Aripiprazole, clozapine, olanzapine, and risperidone are available as ODTs. Asenapine is available as a sublingually dissolving tablet or 24-hour patch.

Short-acting injectables

The short-acting injectable formulations of antipsychotics are frequently utilized in the acute phase of illness. Patients presenting to psychiatric emergency services are often in crisis and can be at risk for harm to themselves or others. If nonpharmacologic deescalation techniques fail and the patient refuses PO medication, short-acting IM injections are effective in rapidly targeting agitation related to psychosis. IM formulations avoid first-pass metabolism and thus are approximately two to four times as potent as PO formulations and reach peak concentrations within 30 to 60 minutes.[125] The FGAs haloperidol, fluphenazine, and chlorpromazine, as well as the SGAs olanzapine, ziprasidone, and aripiprazole are currently available in short-acting IM formulations.

There are currently no head-to-head trials comparing the efficacy of the available short-acting IM SGAs. However, their efficacy and safety were evaluated in a review of nine double-blind, RCTs. Data were extracted to compare olanzapine, ziprasidone, and aripiprazole to either placebo or the active comparator (haloperidol or lorazepam)

to calculate the number needed to treat (NNT) and the number needed to harm (NNH).[126] All three of the agents demonstrated superior efficacy to placebo and the NNT was lowest for olanzapine and ziprasidone. Olanzapine 10 mg demonstrated superiority compared to haloperidol 7.5 mg (NNT = 5). A low dose of aripiprazole 1 mg IM was shown to be less effective compared to haloperidol 7.5 mg IM (NNT = −5).[126] The available RCTs for ziprasidone IM did not have an active comparator such as haloperidol or lorazepam IM. The adverse effect profiles of the SGAs differed significantly in terms of NNH, although all three agents were associated with less EPSs than was haloperidol. Olanzapine was associated with an NNH of 50 for treatment-emergent hypotension.[126] This is in line with the manufacturer's recommendation to avoid concomitant administration with benzodiazepines. In one of the studies, aripiprazole demonstrated an NNH of 47 for akathisia when compared to placebo.[126] Data were not available to evaluate QT_c-prolonging effects of ziprasidone IM in terms of NNH. The manufacturer's guidance states that ziprasidone IM is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction (MI), or with uncompensated heart failure. Caution should be taken when given with other medications known to increase the QT interval (eg, classes Ia and III antiarrhythmics, thioridazine, chlorpromazine, moxifloxacin) and in patients with renal insufficiency due to the clearance of the cyclodextrin excipient through the kidney.[127]

Haloperidol short-acting IM is commonly the preferred agent on hospitals' acute agitation protocols because of its proven efficacy, low risk for orthostasis, and its ability to be administered with IM lorazepam, if necessary. The cost of haloperidol may also be advantageous versus the SGAs, but the cost of IM anticholinergics (eg, benztropine) must be taken into account with its higher risk of EPS. Overall, the short-acting IM dosage forms of the antipsychotic agents are a crucial piece of the treatment team's armamentarium and key to ensuring the safety of a patient with agitation related to acute psychosis (**Table 85-7**).

Table 85-7
Agents Used to Treat Acute Agitation

Medication	Dosage Form	Dosing Schedule (As Needed)	Onset (Minutes)	Max Dose/ 24 Hours	Duration of Action (Hours)
Lorazepam	PO (tablet), IM, IV	1–2 mg	60–90 (PO); 15 (IM)	10 mg	8–10
Typical Antipsychotics					
Haloperidol	PO (tablet), IM	5–10 mg every 0.5–2 hours	30–60 minutes	30 mg	Up to 24
Fluphenazine	PO (tablet), IM	1–2.5 mg every 6 hours (tablet); 1.25 mg every 6 hours (IM)	Not available	10 mg	6–8
Chlorpromazine	PO (tablet), IM	50 mg (IM); 100 mg (PO) every 1–4 hours	15–60	200 mg	Not available
Atypical Antipsychotics					
Olanzapine	PO (tablet), IM, ODT	5–10 mg every 2–4 hours	15–45	30 mg (IM), 20 mg (ODT)	24
Risperidone	PO (tablet, liquid), ODT	1–2 mg every 0.5–2 hours	60	4 mg	Not available
Ziprasidone	PO (tablet), IM	10–20 mg every 2–4 hours	30–60	40 mg	4
Aripiprazole	PO (tablet, liquid), IM, ODT	10–15 mg (tablet); 9.75 mg (IM) every 2 hours	1–3 hours	30 mg	Not available

IM, intramuscularly; IV, intravenously; ODT, oral disintegrating tablet; PO, orally.

Sources: Battaglia J. Pharmacological management of acute agitation. *Drugs.* 2005;65(9):1207–1222. doi:10.2165/00003495-200565090-00003; Abilify (aripiprazole). Package insert. Bristol-Myers Squibb; June 2020; Garza-Trevino ES, Hollister LE, Overall JE, Alexander WF. Efficacy of combinations of intramuscular antipsychotics and sedative-hypnotics for control of psychotic agitation. *Am J Psychiatry.* 1989;146(12):1598–1601. doi:10.1176/ajp.146.12.1598; Lesem J. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry.* 2001;62(1):12–18; Brook S, Lucey JV, Gunn KP. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. Ziprasidone I.M. Study Group. *J Clin Psychiatry.* 2000;61(*12*):933–941; Currier GW, Chou JC, Feifel D, et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. *J Clin Psychiatry.* 2004;65(*3*):386–394; Altamura AC, Sassella F, Santini A, Montresor C, Fumagalli S, Mundo E. Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. *Drugs*. 2003;63(*5*):493–512; Andrezina R, Josiassen RC, Marcus RN, et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacol.* 2006;188(*3*):281–292. doi:10.1007/s00213-006-0541-x; Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry.* 2002;59(*5*):441–448.

Long-acting injectables

Long-acting injectable antipsychotics (LAIAs) are an option for patients with a history of medication nonadherence or in those patients who prefer LAIAs over once-daily PO antipsychotics. LAIAs allow the patient the option to decrease the frequency they need to make a decision to take medications. PO antipsychotics require daily recommitment to be adherent versus biweekly, monthly, or even longer with LAIAs. Lapses in adherence are also more apparent and early interventions can be initiated if a patient fails to show up for an injection appointment. Effectiveness and tolerability of the PO counterpart to an LAIA should be established before conversion to the LAIA. Equivalent doses of LAIAs do not pose a greater risk of adverse effects than does the PO antipsychotic with the exception of injection site pain.[128] LAIAs take months to reach steady-state concentration; therefore, making dose adjustments to acutely target symptoms or manage adverse effects is inefficient.

A number of large-scale RCTs failed to demonstrate a significant benefit of LAIAs over PO antipsychotic medications in relapse prevention in schizophrenia.[129,130] A meta-analysis including a total of 5176 patients enrolled in 21 RCTs of at least 6 months' duration found LAIAs did not reduce relapse compared to PO antipsychotics.[131] This finding may be due in part to the selection of a population of subjects with greater engagement in treatment, more insight, and high adherence to PO medications relative to the real-world patient population. Increased clinician contact, implicit or explicit efforts to monitor adherence, and free study medication also reduce the ability of RCTs to reflect relapse rates in more patients who are unstable and often prescribed LAIAs.[132] A 2-year, double-blind RCT, conducted by Rosenheck and colleagues, enrolled 369 patients with schizophrenia who were at risk for psychiatric hospitalization.[133] The patients were assigned to LAI risperidone or a PO antipsychotic of the clinician's choice. No significant differences in psychiatric hospitalization rates, symptoms of psychosis, or measures of social functioning were found between groups. Mirror-image studies, which compare periods of treatment with PO antipsychotics and LAIAs in the same patient, have been proposed as a better method to capture the real-world effectiveness of LAIAs.

A systematic review and meta-analysis examined 25 mirror-image studies of 5940 patients with schizophrenia >12 months (>6 months each of PO and LAIA treatment). LAIAs were superior to oral antipsychotics in preventing hospitalization (16 studies, risk ratio [RR] = 0.43; 95% confidence interval [CI], 0.35–0.53; *P* < .001) and decreasing number of hospitalizations (15 studies, RR = 0.38; 95% CI, 0.28–0.51; *P* < .001). These results should be interpreted with caution as mirror-image studies can have intrinsic expectation bias and return to a stable status may reflect the natural course of illness.[129]

Patients with recent-onset schizophrenia have inherently less understanding of the importance of treatment and adherence and may benefit from treatment with LAIAs. This is also a crucial period to improve patient quality of life, reduce the impact on educational or early career goals, and reduce relapse rate to improve long-term prognosis. One RCT of LAI risperidone versus oral risperidone in 86 patients with recent-onset schizophrenia demonstrated lower rates of relapse in the LAI risperidone group (5% vs 33%).[134] More recently, Kane and colleagues conducted a cluster randomized, multicenter trial that examined the effect of aripiprazole monohydrate LAI versus treatment as usual on time to first psychiatric hospitalization in a population of patients with early-phase schizophrenia. They demonstrated a mean survival time of 613.7 days (95% CI, 582.3–645.1 days) for LAI and 530.6 days (95% CI, 497.3–563.9 days) for treatment as usual. This translated to a hazard ratio of 0.56 (95% CI, 0.34–0.92; *P* = .02) favoring LAI over treatment as usual and NNT of 7 with LAI to prevent an additional hospitalization.[135] These data merit discussion with the patient to determine preference of LAI versus oral agents, particularly in the early phases of illness.

Two high-potency FGAs, fluphenazine and haloperidol, are available as decanoate ester LAI formulations. Conversion to the LAI formulation of haloperidol can be achieved either by administering 10 times the oral dose the patient is stabilized on or by administering 20 times the oral dose for a loading dose regimen.[136] The loading dose regimen more rapidly achieves therapeutic serum levels of haloperidol and allows for earlier discontinuation of oral

medication.[128,136] The standard conversion requires oral overlap with the current dose of oral haloperidol for at least 1 month before being gradually tapered.[128] Fluphenazine decanoate is released faster than is the haloperidol decanoate and achieves time to maximal concentration (T_{max}) in ~24 hours. It is recommended that the oral medication be decreased by 50% upon administration of the first injection and discontinued after the second injection.[128,137] There is not enough data to support a loading dose regimen for fluphenazine decanoate. The standard oral to LAI conversion is 1.25 times the oral dose administered every 2 to 4 weeks.[137] A double-blind study reported no difference in relapse, symptoms, or adverse effects between groups stabilized on every 2-week versus every 6-week injection intervals.[138] These results suggest that dosing intervals longer than the usual 2 to 4 weeks may be an option to reduce antipsychotic exposure without risk of relapse. Both decanoate ester formulations require utilizing the "Z-track technique" for administration. This prevents loss of medication, abscess formation, or subcutaneous (SC) lumps. However, it is more painful than are standard injections.

SGAs currently available in LAI formulations are aripiprazole (Abilify Maintena® and Aristada®), risperidone (Risperdal Consta® and Perseris™), paliperidone (Invega Sustenna®, Invega Trinza®, and Invega Hafyera®), and olanzapine (Zyprexa Relprevv®). Aripiprazole monohydrate (Abilify Maintena®) requires a 14-day oral overlap and is dosed monthly. Aripiprazole lauroxil (Aristada®), a prodrug of aripiprazole, can have an extended dosing interval, between 4 and 8 weeks, as determined by the oral equivalent dosage.[139] It is initiated in one of two manners: given as Aristada Initio® 675-mg injection with a 30-mg single dose of oral aripiprazole or given as the calculated maintenance injectable dose with a 21-day overlap of the current oral dosage. The normal starting dose of aripiprazole monohydrate for most patients will be 400 mg IM monthly. However, patients with renal impairment or concomitant administration with strong CYP3A4 and 2D6 inhibitors or inducers for >14 days require dose adjustments, which are detailed in **Table 85-8**. Dosing of

aripiprazole lauroxil is converted from the oral dose requirement of each individual (eg, 10-mg oral aripiprazole equates to a 441-mg injection).

Table 85-8
Long-Acting Injectable Antipsychotics

	Available Dosages	PO to LAI Conversion	Dosage	Interval	Loading Dose	PO Overlap
Fluphenazine decanoate	25 mg/mL (5 mL multidose vial)	10 mg PO = 12.5 mg q 3 weeks IM	*Initial*: 12.5–25 mg *Target*: 12.5–50 mg	q 2–4 weeks	No	Decrease PO by 50% after first injection; d/c PO after second injection
Haloperidol decanoate	50 mg/mL; 100 mg/mL (1 mL single-dose vial and 5 mL multidose vial)	10–20 × PO dose	10–15 × PO dose administered monthly; max 100 mg first injection if naive to haloperidol decanoate	q 4 weeks	20 × PO dose first injection, then 10× PO dose maintenance	Continue PO × 2–3 injections if loading dose not used.
Aripiprazole monohydrate (Abilify Maintena®)	300- and 400-mg kits	400 mg IM q month	*Initial*: 400 mg IM monthly; 300 mg IM monthly (poor CYP2D6 metabolizers, concomitant strong CYP2D6 or 3A4 inhibitors, or side effects at higher dose); 200 mg monthly (poor CYP2D6 metabolizers taking CYP3A4 inhibitors, concomitant strong CYP2D6 and 3A4 inhibitors)	q month	No	Continue PO for 14 days
Aripiprazole lauroxil (Aristada®, Aristada Initio®)	441, 662, 882 mg 675 mg (Initio®)	*PO dose* / *IM dose* 10 mg / 441 mg 15 mg / 662 mg ≥20 mg / 882 mg	*Initial*: 441, 662, or 882 mg monthly depending on PO dose 882 mg may be given q 6 weeks	q 4–6 weeks	No	21 days-*OR*-Aristada Initio® 675 mg for first injection with single 30-mg PO dose
Olanzapine pamoate (Zyprexa Relprevv®)	210-, 300-, and 405-mg kits	*PO dose* / *IM dose first 8 weeks* / *IM dose maintenance* 10 mg/day / 210 mg q 2 weeks or 405 mg q 4 weeks / 150 mg q 2 weeks or 300 mg q 4 weeks 15 mg/day / 300 mg q 2 weeks / 210 mg q 2 weeks or 405 mg q 4 weeks 20 mg/day / 300 mg q 2 weeks / 300 mg q 2 weeks	*Initial*: 150–300 mg IM q 2 weeks or 405 mg q 4 weeks *Target*: 300 mg q 2 weeks or 405 mg q 4 weeks	q 2 weeks or q 4 weeks	Yes	Not required
Paliperidone palmitate (Invega Sustenna®)	39-, 78-, 117-, 156-, and 234- mg kits	Initiate with 234 mg IM on day 1 and 156 mg IM on day 8 (both deltoid). Mild renal impairment (CrCl ≥50 mL/minute and <80 mL/minute): Initiate with 156 mg IM on day 1, then 117 mg IM on day 8.	*PO dose* / *IM dose* 3 mg/day / 39–78 mg 6 mg/day / 117 mg 12 mg/day / 234 mg Mild renal impairment / 78 mg	q 4 weeks	Yes	Not required
Paliperidone palmitate (Invega Trinza®)	273, 410, 546, 819 mg	Convert from Invega Sustenna® dosage (minimum 4 months of treatment)	*Sustenna®* / *Trinza®* 78 / 273 117 / 410 156 / 546 234 / 819	q 3 months	No	Not required
Paliperidone palmitate (Invega Hafyera®)	1092, 1560 mg	Convert from Invega Sustenna® (minimum 4 months of treatment) or Trinza® dosage (minimum 3 months of treatment)	*Sustenna®/Trinza®* / *Hafyera®* 156/546 / 1092 234/819 / 1560	q 6 months	No	Not required
Risperidone long-acting injection (Risperdal Consta®)	12.5-, 25-, 37.5-, 50-mg dose packs	*PO dose* / *IM dose* 2–3 mg / 25 mg 4–5 mg / 37.5 mg 6 mg / 50 mg	*Initial*: 25 mg IM q 2 weeks with PO overlap × 3 weeks *Target*: 25–50 mg IM q 2 weeks	q 2 weeks	No	Continue PO for 3 weeks.
Risperidone long-acting injection (Perseris®)	90, 120 mg	*PO dose* / *SC dose* 3 mg / 90 mg 4 mg / 120 mg Note: These doses are approximate. Doses <3 mg/day or >4 mg/day may not be appropriate to convert to the SC injection.	Initial: 90 mg or 120 mg (per dose conversion) and maintain on monthly schedule.	q monthly	No	Not required

CrCl, creatinine clearance; CYP, cytochrome P450; IM, intramuscular; LAI, long-acting injectable; PO, orally; q, every; SC, subcutaneous.

Sources: Aristada (aripiprazole lauroxil extended-release injectable suspension). Package insert. Alkermes Inc; March 2021; Aristada Initio (aripiprazole lauroxil extended-release injectable suspension). Package insert. Alkermes Inc; March 2021; Risperdal Consta (risperidone long-acting injection). Package insert. Janssen Pharmaceutical; February 2021; Invega Trinza (paliperidone palmitate extended-release injectable suspension). Package insert. Janssen Pharmaceutical; August 2021; Perseris (risperidone for extended-release injectable suspension). Package insert. Indivior Inc; December 2019; Invega Hafyera (paliperidone palmitate injection, suspension, extended release). Package insert. Janssen Pharmaceutical; August 2021; Zyprexa Relprevv (olanzapine extended release injectable suspension). Package insert. Eli Lilly and Company; November 2021; Invega Sustenna (paliperidone palmitate extended-release injectable suspension). Package insert. Janssen Pharmaceutical; August 2021; Fluphenazine Decanoate (fluphenazine decanoate injection). Package insert. Mylan Institutional LLC; December 2016; Abilify Maintena (aripiprazole for extended-release injectable suspension). Package insert. Otsuka Pharmaceutical Company; June 2020; Haldol Decanoate (haloperidol decanoate extended-release injection). Package insert. Janssen Pharmaceutical; November 2020.

LAI risperidone is administered IM every 2 weeks and requires an oral overlap of 3 weeks because of delayed release of risperidone from suspension in copolymer microspheres. Less than 1% of the risperidone is released within the first 3 weeks postinjection. The SC formulation of risperidone (Perseris™) is administered by monthly abdominal injections and does not require oral overlap or a loading dose regimen. Candidates are limited to those stabilized on 3- or 4-mg oral risperidone, which equate, respectively, to 90 and 120 mg of the SC injection. Paliperidone palmitate (Invega Sustenna®) is dosed monthly and does not require oral overlap with the recommended loading regimen. In patients without renal impairment, the initial loading regimen consists of a 234-mg deltoid injection on day 1 followed by a 156-mg deltoid injection on day 8. Paliperidone palmitate should be avoided in severe renal impairment (creatinine clearance [CrCl] <50 mL/minute). Paliperidone palmitate is also available in formulations administered every 3 months (Invega Trinza®) or every 6 months (Invega Hafyera®) for patients stabilized on the monthly formulation for a minimum of 4 months. Patients can also be converted from Trinza® to Hafyera® after a 3-month dosing cycle on either 546 or 819 mg. The dose of the 3-month formulation is 3.5-fold higher than is the last dose of the monthly formulation.

However, there is minimal difference in injection volume between the two formulations (1.5 mL for Invega Sustenna® 234 mg vs 2.625 mL for Invega Trinza® 819 mg). Invega Hafyera® is supplied as 1092 mg/2.5 mL and 1560 mg/5 mL and must be administered as a gluteal IM injection over a 30-second period.

LAI olanzapine (Zyprexa Relprevv®) has an associated risk evaluation and mitigation strategy (REMS) because of the risk of postinjection delirium/sedation syndrome (PDSS). PDSS results from supratherapeutic levels of olanzapine caused by accidental intravascular placement of the injection and rapid dissolution of olanzapine pamoate. Symptoms mimic olanzapine overdose and can include sedation, coma, and delirium. The administering facility must have available access to emergency response services and monitor the patient for at least 3 hours postinjection for signs and symptoms of PDSS. The risk of PDSS is 0.2% per injection and history of prior tolerability does not translate to a lower risk of PDSS for future injections. LAI olanzapine distribution is restricted to the Zyprexa Relprevv Patient Care Program that requires the prescriber, facility, patient, and pharmacy be enrolled before releasing the injection. The high administrative burden placed on the facility and patient to coordinate the postinjection monitoring limits its use in clinical practice.

PHARMACOKINETICS AND DRUG INTERACTIONS

Pharmacokinetics (PKs) and potential for drug–drug interactions are necessary considerations for the safe and effective dosing of antipsychotic medications. One key point to keep in mind is the difference between the time to therapeutic effect and time to steady-state plasma concentration. Response of positive symptoms of schizophrenia can be seen within days of treatment initiation. However, it may take ≥4 to 7 days depending on the half-life of the antipsychotic to achieve steady-state plasma concentrations. The half-life of an antipsychotic may also be misleading in determining dosing frequency. Most oral antipsychotics should be dosed once daily, with the exception of asenapine and ziprasidone owing to

issues with absorption. Ability to dose these agents once daily is in part due to higher concentration and longer receptor occupancy in the CNS as well as longer duration of pharmacologic effect than is reflected by the serum concentration.[140] During initial titration, split-day dosing is appropriate when targeting acute agitation or while the patient develops tolerance to peak concentration-dependent adverse effects (eg, sedation and orthostatic hypotension). Once the patient can safely tolerate the medication, the dose can be consolidated to help reduce pill burden and increase patient adherence.[141]

Antipsychotic drug interactions can be mediated through direct PK interactions or by additive pharmacodynamic (PD) effects. PK interactions usually involve phase I oxidative metabolism through the CYP system; however, interactions can occasionally involve phase II metabolism (eg, glucuronidation). Many antipsychotics undergo metabolism through CYP1A2, 2D6, and 3A4 hepatic isoenzymes (see **Table 85-9**). The inhibition or induction of these CYP enzymes can result in clinically relevant changes in antipsychotic serum levels. For example, inhibition of CYP1A2 by the antidepressant fluvoxamine can cause a significant elevation in clozapine serum level and place the patient at risk for serious adverse effects, such as seizures. The reverse would be true for CYP1A2 induction. To use the same example, if a patient were to begin taking a CYP1A2 inducer, such as carbamazepine or phenytoin, the clozapine serum level would drop and place the patient at risk for recurrence of psychotic symptoms. A common CYP1A2 inducer that deserves special mention is cigarette smoke and the PAHs contained within that smoke. PAHs, not nicotine, are responsible for the induction; therefore, it is important to note that when an inpatient is stabilized on an agent metabolized by CYP1A2 (eg, clozapine, olanzapine, asenapine), the serum level can drop by up to 50% if they resume smoking upon discharge. Many antidepressants and mood stabilizers also have potent effects on CYP metabolism, so caution should be taken when adding them to an antipsychotic regimen,[142,143] PD interactions occur when an additional agent that enhances the effect of the antipsychotic activity at the receptor site without directly affecting the serum level of the antipsychotic is added to a patient's

regimen. For example, adding the potent anticholinergic agent benztropine to an SGA with anticholinergic properties, such as olanzapine or clozapine, will compound anticholinergic adverse effects such as constipation.

Table 85-9
Pharmacokinetic Comparisons of Antipsychotics

Antipsychotic Agent		Mean Half-Life (Hours)	Major Metabolic Pathway
First-generation antipsychotics	Chlorpromazine	30	CYP 2D6
	Fluphenazine	14–16	CYP 2D6
	Haloperidol	14–37	CYP 2D6, CYP 3A4
	Loxapine	19	None (minor—CYP 1A2, CYP 2D6, and CYP 3A4)
	Perphenazine	9–12	CYP 2D6
	Thioridazine	5–27	CYP 2D6
	Thiothixene	34	CYP 1A2
	Trifluoperazine	3–12	None
Second-generation antipsychotics	Aripiprazole	75–94	CYP 2D6, CYP 3A4
	Asenapine	24	UGT1A4, CYP 1A2
	Brexpiprazole	91	CYP 2D6, CYP 3A4
	Cariprazine	48–96	CYP 3A4 (minor—CYP 2D6)
	Clozapine	12	CYP 1A2 (primary), CYP 2C19, CYP 2D6, CYP 3A4
	Iloperidone	18–33	CYP 2D6, CYP 3A4
	Lumateperone	18	CYP 3A4, CYP 2C8, CYP 1A2
	Lurasidone	18–40	CYP 3A4
	Olanzapine	21–54	CYP 1A2, CYP 2D6
	Paliperidone	23	Limited CYP 2D6, CYP 3A4
	Quetiapine	6–7	CYP 3A4
	Risperidone	3–20	CYP 2D6
	Ziprasidone	7	Aldehyde oxidase, CYP 1A2, CYP 3A4

CYP, cytochrome P450; UGT, .

Source: Adapted with permission from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5546134?cesid=0YAjKJ7B8pI&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dantipsychotics%26t%3Dname%26va%3Dantipsychotics%26nq%3Dtrue# and https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5546135?cesid=0YAjKJ7B8pI&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dantipsychotics%26t%3Dname%26va%3Dantipsychotics%26nq%3Dtrue#.

PHARMACOECONOMIC CONSIDERATIONS

When the SGAs were first introduced in the 1990s, there was great concern over their higher cost compared to the older antipsychotics.

Because the FGAs were all available in cheaper generic forms, the newly marketed SGAs were still under patent protection and, therefore, anywhere from 10 to 100 times higher the cost than were their older counterparts.[144] From 1997 to 2007, the amount spent on outpatient antipsychotic prescriptions in the United States (not including the Veterans Affairs system) increased from $1.7 billion/year to $7.4 billion/year.[145] This represents a large percentage of overall U.S. mental health expenses over this time period. As the SGAs have slowly become available in generic forms, the concern about their higher costs has decreased slightly, but cost differences still remain.

Although actual medication cost is commonly scrutinized when examining schizophrenia treatment, it needs to be balanced against other costs associated with the illness. Factors such as hospitalization rates, outpatient service utilizations, and patient functionality also need to be considered. One study examining the outcomes of formulary restrictions of SGAs in >100,000 Medicaid patients with schizophrenia found that from 2001 to 2008, these restrictions increased hospitalization rates by 13%, inpatient costs by 23%, and total Medicaid expenditures by 16%, while only reducing medication expenses by 4%.[146] In selecting an antipsychotic, medication costs should be considered, especially in light of the costs to overall public health, along with other factors mentioned previously such as efficacy and adverse effect profile.

ADVERSE DRUG REACTIONS

One of the main factors in selecting an antipsychotic includes the adverse effect profile of the agents being considered. Although many of these adverse effects are common across most, if not all, antipsychotics, the incidence of these effects can vary greatly. The common, class-wide adverse effects seen with these agents include EPSs, anticholinergic effects, cardiovascular effects, metabolic effects (including hyperprolactinemia), and others.

As in treating any illness, a careful balance must be maintained between efficacy and tolerability. When an adverse effect is

discovered in a patient, evaluation of the benefit-to-risk ratio of the medication should take place. Medication factors such as the degree of benefit to the patient, the severity and frequency of the adverse effect, and level of discomfort or distress to the patient should all be considered. In any situation, the patient should be included in any decision regarding adverse effect management. Unresolved adverse effects that significantly bother a patient can lead to nonadherence and potential treatment failure.

If an adverse effect is determined to be fairly mild and cause minimal patient distress, then it may not require any intervention beyond close monitoring to ensure it does not worsen over time. Many adverse effects may be little more than a slight annoyance and can be approached in this way. As an adverse effect becomes more severe or distressing to a patient, it may require more direct intervention. A reduction in antipsychotic dose may be needed or the addition of a secondary medication to treat a particular adverse effect (described subsequently) may be required. If truly warranted, the antipsychotic may need to be changed to another agent where the likelihood of the adverse effect might be lower. One potential factor to consider is the risk of decompensation when changing antipsychotics. Antipsychotics share similar pharmacologic effects and have similar efficacy rates, but not all antipsychotics may be effective for a given patient.

When determining that a change in antipsychotics is warranted, due to adverse effects, poor efficacy, or both, there are several methods that can be employed for switching. In instances where the change needs to be abrupt, perhaps due to a serious or life-threatening adverse effect, an immediate discontinuation of the old agent and initiation of the new agent should be considered. When more time can be given to the change of agents, a cross-titration from one agent to the other can be performed. In these instances, the new agent can either be increased over time as the old agent is simultaneously reduced or the new agent initiated at a therapeutic dose followed by a downward taper of the old agent over time. The rates of these medication increases and decreases are determined

by the clinical presentation and concerns for patient safety (**Table 85-10**).

Table 85-10
Relative Incidence of Antipsychotic Adverse Effects

	Sedation	EPS	Anticholinergic	Orthostasis	Weight Gain
Typical—Low Potency					
Chlorpromazine	+++	++	++	+++	++
Thioridazine	+++	++	+++	+++	+
Typical—Mid Potency					
Loxapine	+	++	+	+	+
Perphenazine	++	+++	+	+	+
Typical—High Potency					
Fluphenazine	+	++++	+	+	+
Haloperidol	+	++++	+	+	+
Thiothixene	+	+++	+	+	+
Trifluoperazine	+	+++	+	+	+
Atypicals					
Aripiprazole	0 to +	+	0	0 to +	0
Asenapine	+	+	0	+	+
Brexpiprazole	0 to +	+	0	0 to +	0
Cariprazine	0 to +	++	0	0 to +	0 to +
Clozapine	+++	0	+++	+++	++++
Iloperidone	0 to +	+	0	+++	+
Lurasidone	+	++	0	0 to +	0 to +
Olanzapine	++	+	++	++	++++
Paliperidone	0 to +	+	+	+	++
Quetiapine	++	0 to +	+	++	++
Risperidone	+	++	0	++	++
Ziprasidone	+	++	0	++	0 to +

0, no effect; +, low; ++, moderate; +++, high; ++++, very high; EPS, extrapyramidal side effects.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

Extrapyramidal adverse effects and tardive syndromes

The blocking of D_2 receptors in the striatum by antipsychotics can also cause acute adverse reactions such as dystonias (involuntary contractions of skeletal muscles) and drug-induced parkinsonism (pseudoparkinsonism). Restoring the balance between acetylcholine and dopamine in the striatum can reduce EPSs, which is why low-potency FGAs with appreciable anticholinergic activity (eg, chlorpromazine and thioridazine) can be less problematic than the

high-potency ones in this regard. This can also be done using anticholinergics such as benztropine or trihexyphenidyl, by using amantadine, by lowering the dose of the antipsychotic, or by using an SGA instead. However, some evidence suggests that changing patients to an SGA will not always lead to the improvement in these movement disorders to the degree expected.[147]

Dystonia

Acute dystonias are uncomfortable, sustained muscle contractions that can occur as torticollis (involving the neck), the trunk, the tongue, or as an oculogyric crisis (where the patient's eyes appear to roll up in the head). Oculogyric crises and dystonias tend to present in the first few days of treatment. Symptoms are treated using anticholinergic medications via IM administration for rapid efficacy (eg, benztropine 2 mg IM stat). Scheduled PO administration of the chosen anticholinergic agent is continued after acute symptom resolution. However, this rapid treatment often does not help the attitude of affected patients toward their caregivers when clinicians are trying to develop a therapeutic alliance with a patient who may already be prone to suspicion or paranoia.[148]

Parkinsonism

Drug-induced parkinsonism is the most common and reversible of adverse movement effects. It consists of rigidity, masked face, slowed gait, and tremor. These symptoms are short-lived and easily treated. These occur most often in the first 3 months of treatment. Drug-induced parkinsonism is a separate entity from idiopathic Parkinson disease, which is a distinct illness on its own.

The high-potency FGAs are more likely to induce drug-induced parkinsonism than do the low-potency agents. Increased dosages of FGAs in higher risk patients (eg, medication naive, female, advanced age) increase this risk. SGAs are, on the whole, less likely to induce this syndrome. Clozapine and quetiapine are the least likely to induce drug-induced parkinsonism, and often can be used without worsening the underlying movement disorder in patients with

idiopathic Parkinson disease.[149–151] However, although clozapine has been robustly effective in these patients, reports with quetiapine are conflicting.[76]

Strategies for reducing or eliminating antipsychotic-induced parkinsonism include lowering the dose of antipsychotic, switching to an atypical antipsychotic (with the lowest risk choices being quetiapine or clozapine), or treating the patient with antiparkinsonian medication. The antiparkinsonian medications often used are anticholinergic agents such as benztropine (Cogentin®; given from 0.5 mg bid to 2 mg tid), trihexyphenidyl (Artane®), biperiden (Akineton®), diphenhydramine, or the novel agent amantadine (Symmetrel®; given from 100 to 400 mg daily in divided dosages). The anticholinergic agents add to adverse effects and pill burden and continuation is often not necessary after 3 months. Amantadine causes less of these problems and works by an alternate mechanism of action; however, it is not as effective as the anticholinergics in many patients.[148] Anticholinergic adverse effects are discussed in greater detail in the section on Anticholinergic Effects.

Akathisia

Akathisia can present alone or in combination with drug-induced parkinsonism, or TD.[152,153] It presents as an inability to remain still combined with an intense feeling of internal restlessness that can make the patient appear quite agitated.[154] In the unfortunate event that akathisia is incorrectly interpreted as agitation, increased or “as-needed” antipsychotic doses to target agitation will worsen the syndrome. Akathisia is best treated by a small reduction in antipsychotic dosage, addition of low-dosage β-adrenergic blockers (eg, propranolol 10 mg bid or tid), or addition of anticholinergic agents (especially if drug-induced parkinsonism is also present). Benzodiazepines can also be used in patients not responsive to the aforementioned strategies (**Table 85-11**).

Table 85-11
Agents to Treat Antipsychotic-Induced Parkinsonism and Akathisia

Medication	Equivalent Dose (mg)	Dose/Day (mg/day)
Anticholinergic		
Benztropine (Cogentin®)[a]	0.5	1–8
Biperiden (Akineton®)[a]	0.5	2–8
Diphenhydramine (Benadryl®)[a]	25	50–250
Procyclidine (Kemadrin®)	1.5	10–20
Trihexyphenidyl (Artane®)	1	2–15
Dopaminergic		
Amantadine	—	100–300
GABAminergic		
Diazepam (Valium®)	10	5–40
Clonazepam (Klonopin®)	2	1–3
Lorazepam (Ativan®)[a]	2	1–3
Noradrenergic Blockers		
Propranolol (Inderal®)	—	20–60 (max = 120)

[a]Oral dose or intramuscular injection can be used.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

Case 85-1, Question 8: J.J. is eventually stabilized on brexpiprazole 2 mg daily while hospitalized. During the admission, the staff notice that her psychotic symptoms have decreased but that her agitation has slowly increased over time. She is constantly pacing around on the unit, and when she does sit down, she is always fidgety and unable to sit still. She says she feels uncomfortable most of the time. The unit staff have had to continue to give her lorazepam 1 mg several times a day for this agitation. What form of an EPS might J.J. be experiencing at this time? What information in her presentation supports this finding?

J.J. is most likely experiencing akathisia. Because her symptoms decreased when brexpiprazole was initiated, it is unlikely that it is

agitation due to her schizophrenia that is causing the restlessness. Antipsychotics, even those that are D_2 partial agonists such as brexpiprazole, are known to cause akathisia as an adverse effect. Her symptoms also appear to be akathisia: constant pacing/movement, always fidgety, and feeling of inner restlessness. Although lorazepam would be expected to treat agitation, it is also a potential treatment for akathisia.

Case 85-1, Question 9: What would be the appropriate treatment for J.J.'s akathisia?

First and foremost, it should be determined whether J.J. can be stabilized on a lower dose of her medication. Often, a reduction in antipsychotic dose will resolve any EPS symptoms. If this is not possible and J.J. would destabilize as a result, then an additional medication will be needed to manage the problem. Although lorazepam would serve this purpose, the concerns about chronic daily administration of benzodiazepines must be considered. Because J.J. may have akathisia with brexpiprazole as long as she is on the medication, she could require treatment for akathisia this entire time. Another option for treating this problem would be propranolol, the nonselective β-blocker. Propranolol has been found to be helpful in alleviating akathisia in low, subcardiac doses such as 10 to 20 mg bid. If this treatment is selected, then her blood pressure and heart rate should be monitored accordingly.

Case 85-1, Question 10: When arranging her discharge, the pharmacy that is called for her prescriptions informs you that her insurance plan will not pay for brexpiprazole. What medication would be appropriate to switch J.J. to at this time?

Ideally, we would keep J.J. on the medication that stabilized her during her hospitalization. It might be possible to contact her insurance to obtain prior authorization for this medication. If that cannot be done, then they should be asked if aripiprazole is

available for use with J.J. Aripiprazole is also a D_2 partial agonist, such as brexpiprazole, so theoretically it should work in a manner similar to that of brexpiprazole. If her insurance will not pay for aripiprazole, then another atypical antipsychotic with a similar adverse effect profile should be considered. Because brexpiprazole has lower rates of EPS and metabolic adverse effects, an agent such as ziprasidone might be considered because it has similar rates of EPS and metabolic effects but is available as a generic medication.

Case 85-1, Question 11: J.J. has been stabilized on ziprasidone 40 mg bid with meals while in the hospital. When should her target symptoms start to respond to the medication? What else can be done to help improve J.J.'s prognosis once she is discharged?

Although J.J.'s symptoms should start to decrease within a few days of starting the medication, it may take a week or longer to see significant improvement. At this point, she may be stable enough for discharge from the hospital, but still show some functional deficits. It may take several more weeks, possibly months, for her to return to her baseline before her symptoms start, and she may never fully reach this point. The utilization of nonpharmacologic methods, including individual and group therapy modalities, could also help J.J.'s continued improvement and stabilization. Education for both her and her family could also be of benefit.

Case 85-1, Question 12: J.J. returns home to her family, taking a leave from college for the remainder of the semester. She returns to school the following semester to resume classes, but notices she has a hard time focusing in class, which she attributes to the ziprasidone. Because she has not had any psychotic symptoms since being released from the hospital ~5 months ago, she thinks she is cured and no longer needs to take the medication. She contacts her psychiatrist about stopping the medication. Should J.J. discontinue her medication at this time? What do practice guidelines state regarding J.J.'s treatment needs at this time?

J.J. should not stop her medication at this time. Although a medication adjustment might be needed, depending on the nature and cause of her concentration, that is not a reason to stop the medication altogether. Most treatment guidelines recommend a minimum of 6 months, and preferably 1 year, of treatment after a psychotic episode. Because she has only been symptom free for 5 months, J.J.'s risk of relapse is very high without medication treatment.

Case 85-1, Question 13: Ultimately, J.J. decides to stop taking her ziprasidone and stops going to her psychiatrist appointments. In less than a month, she is brought to the emergency room (ER) by her parents because she has relapsed into another psychotic episode and is admitted back into the hospital. Is J.J. a candidate for LAIAs at this time?

J.J. is not a candidate for an LAIA currently because she has never tried an oral formulation of any of them to this point. Recommendations for use of an LAIA require, at a minimum, repeated dosages of the oral form of the medication to ensure a lack of an allergy to the medicine, or, in some instances, for the patient to be stable on an oral dose of the medication and then converted to the LAIA form. However, she might benefit from the use of an LAIA if she truly intends to be nonadherent with oral forms of antipsychotics. Because she has only shown nonadherence to one medication trial owing to a potential misunderstanding of her illness and her treatment, she could benefit from education in these areas to improve her adherence. In addition, her family could be educated to help J.J. maintain her medication adherence as well.

Case 85-1, Question 14: While on the inpatient unit for this most recent episode, J.J. continues to remain nonadherent to oral medication. She eventually agrees to receive an LAIA, but after speaking with her insurance, the only atypical antipsychotic LAIA they will pay for is risperidone LAIA. Is this an appropriate agent for J.J., and why or why not?

Assuming that J.J. has been administered oral risperidone in the past, which ensures a lack of an allergy to the medication, it still would not be an appropriate option at this time. Owing to the unique PK parameters of risperidone LAIA, it requires 3 weeks of overlap of oral medication (risperidone or otherwise) because the initial dose does not begin releasing medication until this time. Assuming J.J.'s nonadherence to oral medications will continue, this could lead to a poor outcome, especially if she is discharged from the hospital. J.J.'s insurance should be contacted to attempt to find an alternative atypical antipsychotic LAIA.

Tardive Dyskinesia

One of the more troubling potential adverse effects from chronic treatment with antipsychotics is the development of persistent choreoathetoid (sometimes described as snakelike) movements of the tongue, hands, feet, and, in severe cases, even the trunk of the patient.[155] Chronic blockade of striatal D_2 receptors by antipsychotics results in these receptors becoming supersensitive to available dopamine. Changes in interconnected neurotransmitter systems, such as GABAergic or muscarinic,[156] can result in dyskinesias that can often appear on withdrawal of antipsychotics, upon lowering of the dosage, or when a patient is changed to clozapine or quetiapine treatment from another antipsychotic. If these withdrawal dyskinesias persist, then the condition of persistent dyskinesia or TD can result. TD can also present without any change in medication dose after many years of treatment. FGAs are considered to have a much greater risk (5% yearly incidence in long-term use in adults) of causing TD than do the SGAs, but reported incidences vary appreciably between studies.[157] Risk of developing TD increases with cumulative lifetime dosage and duration of antipsychotic treatment, increased age, comorbid diabetes mellitus, traumatic brain injury, having an affective disorder, anticholinergic medication use, a history of drug-induced parkinsonism, and female gender.[158–161] Although the incidence rate for patients treated with typical

antipsychotics is more substantial,[157] the atypical antipsychotics also carry this risk albeit at a lower, but still not negligible, rate.[162]

Although all dyskinetic movements seen on withdrawal of antipsychotic medication are not necessarily persistent dyskinesia or *TD*, there are those cases of patients who do retain the potentially stigmatizing movements long after antipsychotic medications are tapered or changed. When this occurs, it is often very difficult to remediate these movements. Medication changes that decrease the effects of dopamine on striatal receptors tend to cause immediate improvement followed by long-term worsening of dyskinetic symptoms. Few double-blind studies show any benefit of augmenting with various agents, and agents that often have shown promise in early case reports and open studies (ie, diazepam, donepezil, branched chain amino acids) often do not bear up to the scrutiny of a double-blind trial.[163–165] Even accepted strategies such as lowering antipsychotic dosages (or stopping them when possible) or changing to less offending second-generation agents such as clozapine or quetiapine do not always yield the desired outcome. Some limited evidence suggests that clonazepam and ginkgo biloba may prove helpful.[165] Recently, a new class of medications called *vesicular monoamine transporter (VMAT)* type 2 inhibitors has been developed to help treat the symptoms of TD. VMAT collects monoamines within vesicles in the presynaptic neuron before release into the synapse. Inhibition of VMAT2 prevents the release of dopamine (and other monoamines) into the synapse within the CNS, reducing the overstimulation of dopamine receptors causing dyskinetic movements. Historically, the old antihypertensive reserpine was discovered to be an irreversible VMAT2 inhibitor (as well as VMAT1 in the PNS),[166] and more recently tetrabenazine (Xenazine®) was developed as a reversible VMAT2 inhibitor for the treatment of Huntington chorea. Although neither of these agents is FDA approved for the treatment of TD, the newest irreversible VMAT2 inhibitors, valbenazine (Ingrezza®)[167–169] and deutetrabenazine (Austedo®),[170] are approved for this purpose (**Table 85-12**). Both agents have shown benefits in decreasing the severity of dyskinesia as measured by the AIMS up to a year of

treatment, but long-term benefits beyond a year are still unknown at this time. Considering the significant costs of both of these medications, more long-term benefits would confirm their utility in clinical practice. One 3-year open-label unpublished trial did demonstrate continued improvements in dyskinetic movements with deutetrabenazine.[171] In addition, both agents have potential concerns for QTc prolongation, especially in combination with other risk factors for this adverse effect, including concurrent medications. Increases in serum prolactin and liver function tests, as well as depression and suicidality, have also been noted with both agents. A potentially better course of strategy appears to do what we can to prevent the occurrence of TD by strategies such as keeping antipsychotic dosages as low as possible and using medications that are less likely to induce this syndrome,[156,157,172] and incorporating close monitoring for the development of symptoms utilizing the AIMS exam. However, we do have the option to tailor our medication choice to the vulnerability of the patient. Because the severity and prevalence of TD is apparently on the decline,[156] there may be cause to be optimistic.

Table 85-12

Agents to Treat Antipsychotic-Induced Tardive Dyskinesia

Medication	Starting Dose (mg)	Dose Range (mg)	Notes
Valbenazine (Ingrezza®)	40 mg daily	40–80 mg daily	Use half-dose with 2D6/3A4 inhibitors, do not use with 3A4 inducers.
Deutetra-benazine (Austedo®)	6 mg daily	6–48 mg (doses >12 mg/day must be bid)	Take with food, max of 36 mg/day in 2D6 poor metabolizers

bid, twice daily.

Sources: Ingrezza (valbenazine). Package insert. Neurocrine Biosciences Inc; April 2021; Austedo (deutetrabenazine). Package insert. Teva Neuroscience Inc; June 2021.

Anticholinergic effects

The low-potency FGAs and certain SGAs, particularly olanzapine and clozapine, are potent muscarinic receptor antagonists. The resultant anticholinergic effects can range from bothersome to potentially life-threatening. These effects include dry mouth, blurred vision, mydriasis, tachycardia, urinary retention, constipation, paralytic ileus, confusion, and delirium. Something that may appear merely bothersome, such as dry mouth, can have more serious consequences if not addressed. Dry mouth can lead to dental caries or weight gain if thirst is quenched with sugary beverages. Additional sugar, in the form of gum or liquids, can also increase the risk of oral fungal infections. Patients can utilize sugar-free hard candies or gum, or saliva substitute products if anticholinergic medication dosage cannot be reduced.[173] In general, patients with schizophrenia should be encouraged to connect with regular dental services. Another often-overlooked anticholinergic adverse effect is constipation. Patients may not draw the connection between constipation and a medication that they are taking for their mental health. Consistent monitoring of patient's bowel habits and recommendation of a proper bowel regimen (eg, diet, physical activity, bulk-forming laxatives, stool softeners) can be the difference between a week of unaddressed bowel discomfort progressing to paralytic ileus and patient expiration due to bowel rupture or aspiration of gastric contents.[174]

The patient's overall anticholinergic burden is often increased by the addition of anticholinergic medications, such as benztropine, for EPS prophylaxis or treatment. Indication for use of anticholinergic agents should be reevaluated periodically during treatment and upon transitions in care. Failure to taper unnecessary anticholinergic medications can lead to decreased quality of life and preventable adverse effects.[175]

Cardiovascular effects

Antipsychotic medications are thought to exert cardiovascular effects through direct antagonism of adrenergic and cholinergic receptors, as well as through indirect central autonomic effects and baroreceptor reflexes.[176] Three common antipsychotic-induced cardiovascular effects, orthostasis, tachycardia, and QT_c prolongation, are described here.

Orthostatic Hypotension

Orthostatic hypotension occurs in up to 40% of patients treated with antipsychotic medications.[176] It occurs frequently during the initial dose titration and disproportionately affects elderly patients. Orthostasis results from the blockade of vascular α_{1A}-adrenoceptors, which makes it difficult for patients to adapt to positional changes in blood pressure. Tolerance to orthostasis will usually develop within 2 to 3 weeks of antipsychotic initiation or dose increase. Antipsychotic agents with high affinity for α_{1A}-adrenoceptors relative to D_2 receptors (eg, clozapine, risperidone) clinically display greater rates of orthostasis than do agents with low α_{1A} affinity relative to D_2 affinity (ie, haloperidol).[176] The risk of falls secondary to orthostasis can be mitigated by (a) slowing the rate of titration, (b) splitting the dose, and (c) counseling the patient to make slow transitions from prone and seated positions. Increasing fluid and salt intake and using support stockings are other nonpharmacologic interventions that may help alleviate orthostasis while the patient adapts to a change in dosage. More persistent orthostasis resulting from clozapine treatment can be managed with fludrocortisone or ephedrine if nonpharmacologic interventions are not clinically feasible.[177]

Tachycardia

Antipsychotic-associated tachycardia can occur as a direct effect of anticholinergic activity on vagal activity or as a compensatory mechanism related to orthostatic hypotension. Patients treated with

clozapine tend to have a dose-related increase in heart rate of 20 to 25 bpm.[176] Dose reduction, slower titration, or addition of a low-dose, preferably cardioselective, β-blocker can be considered if tachycardia is bothersome to the patient or symptomatic.[177,178]

Electrocardiographic Changes

Prolongation of the QT interval, or QT_c interval when corrected for heart rate, is a variable risk associated with all antipsychotics. QT_c interval prolongation increases the risk of torsade de pointes (TdP), a malignant polymorphic ventricular tachycardia that is associated with syncope and sudden cardiac death.[176] The potential mechanism for this effect is believed to be mediated through blockade of the rapidly activating delayed rectifying current (I_{Kr}), which conducts potassium out of the cardiomyocytes to cause cardiac repolarization.[176,179] However, there are insufficient data to establish the direct causal relationship between antipsychotic-induced QT_c prolongation and sudden cardiac death.[176,179]

The Pfizer 054 study, developed in consultation with the FDA, demonstrated QT_c prolongation as a class effect for SGAs.[180] This prospective, randomized, parallel-group study conducted by Harrigan and associates examined the effect of steady-state peak plasma concentrations of haloperidol 15 mg/day (*N* = 27), thioridazine 300 mg/day (*N* = 30), ziprasidone 160 mg/day (*N* = 31), quetiapine 750 mg/day (*N* = 27), olanzapine 20 mg/day (*N* = 24), or risperidone 6 to 8 mg/day increased to 16 mg/day (*N* = 25/20) on the QT_c interval in the presence or absence of metabolic inhibitors in patients with stable psychotic disorders. No patients were observed to have a QT_c interval >500 ms, and mean QT_c changes from baseline were similar for monotherapy and with concomitant administration of a metabolic inhibitor. The antipsychotics associated with the greatest change in mean baseline QT_c were thioridazine (30.1 ms) and ziprasidone (15.9 ms). Haloperidol, quetiapine, risperidone 6 to 8 mg/day, risperidone 16 mg/day, and olanzapine were associated with mean QT_c changes of 7.5, 5.7, 3.9, 3.6, and

1.7 ms, respectively.[181] To add context, the mean diurnal variation in QT_c is ~75 to 100 ms and this may vary further based on sleep, diet, obesity, electrolyte disturbances, endocrine dysfunction, gender, and age.[176,179] No cases of TdP were observed in the 4571 patients treated with ziprasidone included in the Pfizer 054 study and the ziprasidone database.[180] One of the newer SGAs, iloperidone, has also demonstrated a dose-dependent and drug interaction–dependent risk of QT_c prolongation similar to that of ziprasidone in both short- and long-term randomized trials.[182]

In clinical practice, concomitant administration of QT_c-prolonging agents should be avoided. If coadministration is necessary in a patient with no underlying cardiac abnormalities or risk factors for TdP, the patient should be monitored closely. A work group of members from the APA and American College of Cardiology (ACC) recommended in a recent resource document that no absolute QTc interval threshold should preclude a trial of any particular psychiatric medication. Instead, they suggest conducting a comprehensive risk–benefit analysis for the individual patient that should include, "Assessment of pharmacologic and nonpharmacologic risks for TdP versus the risk of failure to control high-risk psychopathology or of psychiatric decompensation."[183] Use of antipsychotics with higher risk of QT_c prolongation, chlorpromazine or ziprasidone, should be avoided in patients with underlying cardiac issues, electrolyte abnormalities (hypokalemia, hypocalcemia, or hypomagnesemia), congenital long-QT syndrome, or those comedicated with agents affecting cardiac function (particularly antiarrhythmics of class Ia, disopyramide, procainamide, and quinidine and class III, amiodarone, dofetilide, and sotalol).

Case 85-1, Question 15: After intensive education about her illness and need for treatment, as well as enlisting the help of her parents in ensuring she will take her medications, J.J. eventually agrees to take oral medications and is restabilized on risperidone 2 mg bid. After discharge, her outpatient psychiatrist notes that J.J. is still responding to internal stimuli, and confirms she is still having some auditory hallucinations. J.J.'s parents confirm she is taking her doses, so the dose is increased to 3 mg bid. Within a few weeks at her next

appointment, J.J.'s parents inform her psychiatrist that she can barely move, and she "walks like an old lady" at times. The psychiatrist examines J.J. and notes she has some mild stiffness in her extremities, a mild tremor in her hands, and when she walks her gait is abnormally short and almost shuffling in appearance. However, her hallucinations have subsided. What is the probable cause of J.J.'s abnormal neurologic findings at this time? What information in her presentation supports this finding?

J.J. is most likely suffering from drug-induced parkinsonism, a type of EPS. All the abnormal findings noted in J.J. at this time—stiffness, tremor, and shuffling gait—are characteristic findings of drug-induced parkinsonism. Although risperidone, as an atypical antipsychotic, is less likely to cause this problem compared to the older, conventional antipsychotics, it can still cause it. One risk factor of parkinsonism with risperidone is increasing the dose, which occurred in J.J. recently. Although she was fine on the lower dose, the increase in dose to 6 mg/day caused enough D_2 receptor blockade in the nigrostriatal pathway to induce this EPS type.

Case 85-1, Question 16: How can J.J.'s drug-induced parkinsonism be treated?

Ideally, the first choice would be to decrease the dose of the offending agent. Because J.J.'s dose of risperidone was just increased to 6 mg/day owing to lingering symptoms, this is most likely not an option because it is highly likely those symptoms would return. A change in antipsychotics could also be considered, but it appears that other than the EPS, J.J. is currently stable on this medication and dose. The only other option would be to add another medication to treat her parkinsonism. Some options include the use of anticholinergic medications, such as benztropine, or the use of amantadine.

Case 85-1, Question 17: J.J.'s drug-induced parkinsonism resolves with the addition of benztropine 0.5 mg bid. Will J.J. need to stay on this medication indefinitely?

J.J. should be maintained on benztropine for at least 3 months once her parkinsonism resolves. If there are no other changes in her clinical status or her medication treatment for her schizophrenia, then the use of benztropine should be reexamined at that time. If the medication is then removed and her parkinsonism does not return, then she should not need the medication any longer. Should the EPS return, however, then she may need continued anticholinergic treatment.

CASE 85-1, QUESTION 18: What are some other adverse effects that should be monitored for in J.J., both specific to risperidone and for antipsychotics in general?

Any patient receiving an antipsychotic should be monitored for all types of EPS, including parkinsonism. Other EPS types, such as dystonia and akathisia, should be watched for as well as the development of any TD. Although the risk of these concerns is lower with an atypical antipsychotic, such as risperidone, it is still possible. J.J.'s weight and serum glucose and lipids should also be monitored regularly both during the initiation of antipsychotic treatment and periodically throughout. Risperidone also can cause drug-induced orthostasis, so she should be monitored for dizziness, especially upon standing.

Metabolic effects

Hyperprolactinemia

Prolactin is a polypeptide hormone secreted by lactotroph cells in the anterior pituitary. Dopamine acts as an inhibitor of prolactin release in the tuberoinfundibular dopamine tract that projects from the hypothalamus to the anterior pituitary. Blockade of D_2 receptors within this pathway leads to increased release of prolactin and potential effects on multiple organ systems and gene expression throughout the body. Agents that cause more potent D_2 blockade are associated with a greater risk of hyperprolactinemia.[184] A multiple-treatment meta-analysis by Leucht and associates stratified select

antipsychotics based on their effect on the standardized mean difference in prolactin from baseline as follows: paliperidone (highest), risperidone, haloperidol, lurasidone, ziprasidone, iloperidone, chlorpromazine, olanzapine, asenapine, quetiapine, and aripiprazole (lowest/decreased prolactin).[185] Guidelines recommend baseline prolactin monitoring at the discretion of the clinician, screening for symptoms of excess prolactin at every visit for the first year of treatment and annually thereafter if symptoms are stable, and follow-up prolactin levels only if clinically indicated.[44,186,187] The upper limit of normal prolactin levels is 18 to 20 ng/mL in males and 24 ng/mL in females who are not pregnant or lactating.

Clinical sequelae from excess prolactin release include sexual dysfunction, gynecomastia, galactorrhea, amenorrhea, hypogonadism, and potential bone mineral density changes with long-term elevations. However, prolactin levels do not directly correlate with these adverse events and patients may remain asymptomatic. Considerations for treatment should only be addressed in actively symptomatic patients.[84,185] In symptomatic patients, dose reduction or switching to an agent with less potent D_2 blockade would be recommended first line. If these strategies fail to improve the symptoms or cannot be undertaken for clinical reasons, a dopamine agonist, such as bromocriptine, cabergoline, or amantadine, may be considered. However, the risk of potential exacerbation of psychosis must be weighed against potential benefit.[44,184,187,188] There is also growing evidence to support the use of adjunctive aripiprazole, a partial D_2 agonist, to improve hyperprolactinemia in patients who cannot be switched from a more potent agent.[82,84,189–191]

Case 85-1, Question 19: Over time, J.J.'s dose of risperidone is increased to 4 mg bid because of lingering symptoms. At one of her follow-up appointments, J.J. asks if it is safe to take the medication while she is pregnant. During the conversation, J.J. tells her psychiatrist that she is pregnant because she has not had her menstrual period in nearly 2 months, and her breasts have become larger and she has noticed she lactates periodically. The psychiatrist orders a pregnancy blood test that comes back with a negative result, but her serum

prolactin level is 115 ng/mL. What could explain why J.J. believes she is pregnant?

The negative pregnancy test result proves J.J. is not pregnant (assuming no error by the lab). Her symptoms are indicative of hyperprolactinemia, another potential adverse effect of D_2 receptor antagonism from antipsychotic therapy. As her prolactin level increased, it caused J.J. to become amenorrheic and caused her to lactate. Although not a common adverse effect of most atypical antipsychotics, both risperidone and paliperidone are similar to the typical antipsychotics in their propensity to increase serum prolactin.

Case 85-1, Question 20: How should J.J.'s hyperprolactinemia be treated?

Ideally, the treatment of antipsychotic-induced hyperprolactinemia involves a DR of the offending agent. Because J.J. was increased to 4 mg bid owing to an insufficient response to a lower dose, this may not be possible. If a DR cannot be done safely, then a change in antipsychotic to one with a lower risk of hyperprolactinemia should be considered. If this too is not clinically appropriate for the patient, then addition of a dopaminergic agonist may be considered, such as amantadine. This should be done cautiously because a strong dopaminergic agonist, such as bromocriptine, may exacerbate her psychosis. There are also data available on using aripiprazole augmentation to treat hyperprolactinemia from antipsychotics, but this might be considered after other agents have been tried, unless J.J. appears to need a stronger antipsychotic regimen.

Weight Gain

Although the development of the SGAs was supposed to free us from the concern of the extrapyramidal adverse effects of the FGAs, many of the newer agents such as clozapine, olanzapine, quetiapine, and risperidone showed a tendency to, just like the low-potency typical first-generation agents, cause substantial weight gain.[64] This substantial weight gain tended to occur to the greatest

extent in the first few months of treatment, with a certain segment of those treated gaining >20 pounds (9.07 kg).[192] One study showed that 15.4% of those patients treated with olanzapine had weight gain ≥7% of their body weight in the first 6 weeks of treatment.[193] It soon became apparent that clozapine and these newer SGAs had the potential to increase body weight, serum triglyceride levels,[64–67] and thereby potentially cause glucose dysregulation as well.[70,194,195] Patients suffering from schizophrenia are already prone to an earlier death than are patients who are not mentally ill because of their physical health and inherent sedentary lifestyle; therefore, weight gain may be an even more critical issue than is the potentially stigmatizing occurrence of TD.[162,196]

Numerous mechanisms have been theorized to explain the weight gain induced by the SGAs. These include histamine (H_1) receptor antagonism,[197,198] serotonin antagonism at 5-HT_{2c} with a possible genetic predisposition in some,[199,200] muscarinic antagonism that could possibly lead to increased consumption of sugary beverages or “thirsty” calories,[201] and impairments in plasma leptin secretion.[202–204] Concomitant medications, such as valproic acid, lithium, mirtazapine, some antihistamines, and tertiary tricyclic antidepressants can also increase body weight by synergistic pharmacologic effects.[69,205]

Hyperglycemia and Diabetes Mellitus

It is unclear if there are direct actions by SGAs involved in the development of diabetes mellitus. However, it is clear that weight gain, increased triglycerides, or decreased insulin sensitivity due to SGAs may cause an increased frequency or earlier onset of this endocrine disorder.[70,194,206–208] An early study showed a moderate correlation (R = .60, P = .03) between serum insulin and clozapine levels,[209] whereas Lund and associates showed an ~2.5 times greater risk of diabetes mellitus and hyperlipidemia in patients ages 20 to 34 years old treated with clozapine versus FGAs.[210] Other retrospective studies in veterans also suggested a slightly greater prevalence of diabetes in patients younger than 40 years old on the

SGAs clozapine, olanzapine, quetiapine, or risperidone (odds ratio [OR] = 1.09; CI = 1.03–1.15) than in those on FGAs[194] and an incidence of diabetes mellitus ~1.5 times greater in patients treated with olanzapine, risperidone, or quetiapine than with typical, mostly low-potency, antipsychotics.[70] Guidelines stress the need to monitor these patients routinely for glucose dysregulation, weight gain, and hyperlipidemia.[206,211]

Dyslipidemia

Treatment-emergent increases in both serum triglycerides and total serum cholesterol may occur with the use of antipsychotics. The initial reports were of increased serum triglycerides with clozapine,[65,67,212] a notation of this phenomenon in the package insert for quetiapine, and reports of this occurring in patients taking olanzapine.[66] Risperidone does not raise serum triglycerides as severely as does clozapine[212] and ziprasidone has negligible effects on serum triglycerides.[213,214] Aripiprazole resulted in lowered serum triglyceride levels compared to placebo in pooled double-blind trials.[215] Average serum triglycerides with clozapine, olanzapine, or quetiapine tended to increase by ~60 to 70 mg/dL between studies.[65–67,69] Extreme elevations in serum triglycerides (>1000 mg/dL) have been noted in some patients and were often associated with acute pancreatitis (**Table 85-13**).[68]

Table 85-13

Metabolic Monitoring Protocol for Antipsychotics[a]

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Quarterly	Annually
Personal or family history	X								X
Weight (BMI)[b]	X	X	X	X	X	X	X	X	
Waist circumference	X								X
Blood pressure	X			X					X
Fasting plasma glucose	X	X (once during this period)		X			X	X (for first year)	X
Fasting lipid profile	X			X			X		X

BMI, body mass index.

[a]More frequent assessments may be warranted based on clinical status.

[b]Some references recommend weekly monitoring for first 6 weeks after initiation to determine patients at risk for more significant long-term weight gain, especially with agents with higher risk of causing weight gain.

Sources: Adapted from American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):267–272. © 2004 American Diabetes Association. All rights reserved. Material from this publication has been used with the permission of American Diabetes Association; Kinon BJ, Kaiser CJ, Ahmed S, Rotelli MD, Kollack-Walker S. Association between early and rapid weight gain and change in weight over one year of olanzapine therapy in patients with schizophrenia and related disorders. *J Clin Psychopharmacol*. 2005;25(3):255–258; Marder SR, Essock SM, Miller AL, et al. The Mount Sinai conference on the pharmacotherapy of schizophrenia. *Schizophr Bull*. 2002;28(1):5–16; Hasnain M, Fredrickson SK, Vieweg WV, Pandurangi AK. Metabolic syndrome associated with schizophrenia and atypical antipsychotics. *Curr Diab Rep*. 2010;10(3):209–216.

Case 85-1, Question 21: What other metabolic effects need to be monitored in J.J. while she is receiving antipsychotic treatment? What are the risks of these effects in patients receiving these medications?

J.J., as with all patients receiving antipsychotics, is at risk for developing potentially significant weight gain, glucose irregularities including diabetes mellitus type 2, and dyslipidemia, especially hypertriglyceridemia. The risk varies among the agents, with SGAs generally thought to be at a higher risk than are the FGAs. Risperidone, which J.J. is currently receiving, is often considered to be at a midlevel risk of these effects compared to some of the other SGAs. Other possible risk factors include the patient's diet and exercise, family history of diabetes and cholesterol problems, and others.

Case 85-1, Question 22: The psychiatrist decides to change J.J. from risperidone to an agent with a lower risk of hyperprolactinemia. He starts J.J. on olanzapine, titrating up to 20 mg/day while removing the risperidone. What would be the appropriate monitoring for J.J. upon initiation of olanzapine?

Because olanzapine has a high risk of causing metabolic adverse effects in patients, J.J. should be monitored closely for the

development of these effects. Her weight should be checked very closely, especially at baseline and over the first few months of treatment. Monthly, if not more frequently, weights should be measured during this time. In addition, her serum glucose and/or HbA_{1C} along with her serum lipid panel should be checked at baseline and then in 3 months for any changes, with an interim serum glucose measurement around 1 to 2 months. Her blood pressure should also be monitored for any changes, especially if her weight increases significantly. If any increases or abnormalities are noted in these parameters, they should be addressed appropriately before becoming a medical concern.

CASE 85-1, QUESTION 23: After 2 months on olanzapine, J.J. returns to the clinic reporting that she is always eating and does not fit into her clothes from last summer. Her weight today is 151 pounds (68.49 kg). Body mass index (BMI) is 25.9 kg/m^2, an increase from her weight before olanzapine of 139 pounds (63.05 kg; and BMI of 23.9 kg/m^2). J.J.'s parents are also concerned because they have never seen her eat this much in her life. She is currently doing well on the medication, with no psychotic symptoms noticed over this time. They ask if the appetite and weight gain are from the olanzapine, and if there is anything that can be done about it. They ask about a "new form of olanzapine" that they read about online that has less weight gain. Would it help J.J. lose weight?

Olanzapine could certainly be the cause of her recent weight gain because it has one of the higher risks of causing weight gain among the SGAs. A 12-pound (5.44-kg) weight gain is certainly possible with this medication. Because J.J. and her parents have noticed an increase in her appetite since starting the medication, this makes it even more likely olanzapine is involved. Although there are no proven treatments for antipsychotic-induced weight gain, there are some interventions that could be implemented. J.J. should be given an appointment with a nutritionist to review her diet, and she should also be encouraged to increase her exercise on a regular basis, whether at a gym or even by adding 20- to 30-minute walks 4 to 5 days a week. Switching to the combination olanzapine–samidorphan medication at this time would likely have little benefit for J.J. It has

only been found to prevent weight gain from olanzapine at baseline, not reverse weight gain from an existing olanzapine regimen.

Case 85-1, Question 24: A month later, J.J. returns to the clinic. Blood work done a few days ago shows her fasting serum glucose to be 214 mg/dL, which is an increase from 132 mg/dL 4 months ago. Her HbA_{1C} has also increased from 5.9% to 7.1% over this time. A serum lipid panel shows her total cholesterol is 256 mg/dL, her direct low-density lipoprotein (LDL) cholesterol is 117 mg/dL, her high-density lipoprotein (HDL) cholesterol is 34 mg/dL, and her triglycerides are 997 mg/dL. Are these changes potentially related to J.J.'s antipsychotic treatment, and, if so, how should they be managed?

Increases in serum glucose and lipids, especially triglycerides, are possible with SGAs, and olanzapine in particular. Because her glucose and HbA_{1C} have increased since starting the medication, this makes it highly likely this is the cause. Although J.J.'s LDL and HDL cholesterol measurements are not ideal, they are not as concerning as her very elevated triglyceride level. At this high a level of triglycerides, there is the concern of possible pancreatitis. J.J. should be asked about any upper abdominal pain or other possible symptoms.

Although we could treat her increased serum glucose and lipids with appropriate medications for each concern, another consideration would be to change J.J. from olanzapine to another SGA with a lower risk of metabolic problems. This would need to be done after considering the risk of J.J.'s possible psychiatric decompensation from changing her antipsychotic treatment.

Medical Comorbidity

Currently, metabolic syndrome is seen as a major concern when treating schizophrenia, and it is recommended that patients receiving SGAs must be routinely monitored for weight gain, changes in fasting serum lipids, or signs of glucose dysregulation.[206,211,216] Some estimates of the prevalence of metabolic syndrome in patients with schizophrenia range from 18.8% to ~40% of those tested.[217] Because patients who are medication naive are already at a high risk

for developing metabolic syndrome,[218] we should strive to minimize the chance of worsening their situation. Furthermore, because weight gain with antipsychotic medication and its secondary metabolic complications tend to occur rapidly, patients should receive more frequent assessments for this when they are first started on or switched to a new antipsychotic medication. Medication use evaluations to make sure this necessary monitoring is performed may be helpful.[219]

Moreover, effective pharmacotherapy carries with it a potential for serious adverse metabolic effects such as obesity, hypertriglyceridemia, and resulting glucose dysregulation, as well as movement disorders such as akathisia, drug-induced parkinsonism, and TD. One study showed that metabolic disorders occur more than three times (3.7; 95% CI = 1.5–9.0) as much in patients with schizophrenia as compared to nonpsychiatrically ill controls.[220] In fact, cardiovascular disorders are the main reason patients with schizophrenia tend to die at a younger age than do their peers.[221]

Another concern is that, along with known genetic factors,[222] metabolic syndrome issues such as increased weight, serum leptin, lipids, and glucose are known risk factors for venous thromboembolism (VTE), which also may occur in association with antipsychotic pharmacotherapy.[223,224] The most established link is to the use of clozapine,[225] which is one of the most metabolically problematic agents. However, even more metabolically benign antipsychotics may eventually be linked to the increased occurrence of VTE.[226] Pulmonary embolism is a well-documented variant occurring with antipsychotics.[227,228] Because VTE related to antipsychotics is likely rare, the benefit-to-risk ratio should be kept in perspective.[229]

Other cardiovascular effects can be problematic when utilizing antipsychotic pharmacotherapy. Of concern, olanzapine, risperidone, and quetiapine have been associated with a threefold increased likelihood of cerebrovascular accidents (CVAs) and transient ischemic attacks during the first 6 months of treatment in elderly patients.[230,231] Other antipsychotics have also been implicated.[232] Such events could relate to the slightly higher risk of death in elderly

patients receiving these medications.[233] As a result, all antipsychotics have a black box warning from the FDA regarding an increased risk of CVAs in elderly patients taking these medications.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a rare, but potentially fatal, complication of antipsychotic therapy that can occur because of treatment with any antipsychotic or abrupt cessation of a dopamine agonist. Therefore, early recognition and management are crucial. There are numerous diagnostic scales to ensure accurate diagnosis of NMS for research purposes, but the most widely utilized in clinical practice is the *DSM-5* criteria. NMS is associated with high fever (103–104 °F [39.44–40 °C]), muscular rigidity, altered consciousness, and highly elevated creatinine phosphokinase (CPK), often >1000 µg/L. Other signs are drooling, difficulty swallowing, fast heart rate (>100 beats/minute), profuse sweating, incontinence, and labile blood pressure. It is treated by immediate cessation of antipsychotic therapy, supportive care, and the administration of medications such as dantrolene sodium, biperiden, or bromocriptine. Combination antipsychotic therapy was found in 39% of all NMS cases.[234] Some believe that physical exhaustion and dehydration predispose a patient to develop NMS, so it is important that patients on antipsychotics be cautioned to take proper caution in hot weather. Also, the effects of antipsychotics on the hypothalamus (which regulates temperature and food intake, among other activities) and the "body-secretion" drying activities of anticholinergic medications increase the danger of heat exhaustion in these patients.[235]

Case 85-1, Question 25: J.J.'s psychiatrist decides that in light of her weight gain and worsening glucose and lipid profiles, he is going to change her from olanzapine to lurasidone, titrating her up to 80 mg/day. She did well with the medication change. A few weeks after starting the lurasidone, her parents take J.J. into the ER one evening concerned that she has meningitis because she feels feverish, is sweating, seems confused, and has a stiff neck. The ER exam shows J.J. has a fever of 103.1 °F (39.5 °C), blood pressure of 176/98 mm Hg,

pulse of 136 bpm, respiratory rate of 36 bpm, a stiff neck that is not painful, and is sometimes incoherent when answering questions, but shows no outward signs of psychosis. She also is sweating profusely despite the air conditioning in the ER. Lab work is ordered and results return a couple of hours later. J.J.'s chemistries are normal except for a CPK of 5960 µg/L, a normal CBC, and normal serum glucose. Repeat vital signs 2 hours after she comes to the ER show a fever of 103.2 °F (39.56 °C), blood pressure of 96/62 mm Hg, pulse of 146 bpm, and a respiratory rate of 39 bpm. What is the most likely cause of J.J.'s presentation at this time and why? How should J.J. be managed?

J.J. is most likely suffering from NMS from lurasidone. Although NMS can occur at any time during treatment with any antipsychotic, the timing of this episode shortly after beginning the medication makes it more likely. Because she does not have pain in her neck or an elevated white blood cell (WBC) count, it is not likely meningitis as her parents feared (although this should be definitively ruled out). The high fever, labile blood pressure, tachycardia, sweating, confusion (without psychosis), and highly elevated CPK are indicative of NMS. J.J. will need to be admitted to the hospital because NMS can be life-threatening. Because she will need to stop taking all antipsychotics for up to 2 weeks, she will most likely require hospitalization during this time because her psychosis is likely to return. During the acute treatment period, she will likely need treatment for the NMS with either dantrolene (for the fever) or bromocriptine (a dopamine agonist), as well as other measures as needed for her fever, elevated blood pressure, and so on. During the longer period without antipsychotic treatment while waiting for the NMS to resolve, J.J. will likely need treatment with sedatives such as benzodiazepines because we cannot actively treat her schizophrenia.

Case 85-1, Question 26: During the subsequent admission for her episode of NMS, J.J. is eventually started on aripiprazole for her schizophrenia. A few days into titrating the medication to an effective dose, she develops some mild stiffness in her arms, most likely some mild parkinsonism. Fearful that this is the NMS returning, J.J. now refuses to take any antipsychotics. Her psychiatrist decides to start her on an LAIA form of aripiprazole, but notices there are two

different versions of the medication available. Which of these two forms would be the better choice for J.J. at this time?

Ideally, we would be able to stabilize J.J. on an oral form of aripiprazole before conversion to an LAIA form of the medication, but her nonadherence makes that unlikely. Both forms of aripiprazole LAIA require an overlap of oral medication during initiation: 14 days for the monohydrate salt, and either 21 days for the lauroxil salt or the use of the Initio lauroxil injection with a single 30-mg oral dose. However, the main concern is the dosing of the LAIA. The monohydrate salt has a single dose for all patients, except in cases of renal impairment of P450 inhibitors or inducers. The lauroxil salt is dosed based on a conversion from the dose of oral aripiprazole the patient is currently receiving. Because J.J. was never stabilized on an oral dose of aripiprazole before she stopped taking the medication, it would be very difficult to convert her to an equivalent dose of the lauroxil LAIA. Therefore, it would be easier to initiate the monohydrate salt version at its usual dose of 400 mg every month and then try to provide coverage for the initial 14-day window recommended for the product. Regardless of which form is used, J.J. should be monitored for the development of the parkinsonism she had when being titrated on the oral form of aripiprazole.

Case 85-1, Question 27: Over the next few months, J.J. is maintained on aripiprazole monohydrate LAIA 400 mg/month. Because her symptoms improved but she was still showing some signs of daily auditory hallucinations, haloperidol 5 mg/day was added to her regimen. Her hallucinations subsided within a couple of weeks after an increase to 10 mg/day of haloperidol, but now J.J. comes in with her parents to the ER attached to the clinic. J.J.'s neck is turned clockwise to her right shoulder, and she is unable to move her head back to her centerline and look forward. J.J. says her neck hurts a lot and she wants this feeling to go away. What is the most likely reason for J.J.'s current problem and how should it be managed?

J.J. is most likely experiencing a dystonic reaction, or dystonia, from the recent addition and increase in her haloperidol dose. The specific type of dystonia she has is called *torticollis*, which is

dystonia causing the muscles of the upper spine to contract and cause a twisting motion of the neck. This is another type of EPS, and as seen in J.J. here, can often be painful owing to the strong muscle contraction. FGAs are more likely to cause this problem than are SGAs, so the timing of the reaction to the addition of haloperidol makes sense.

Acutely, J.J.'s dystonia needs to be treated as quickly as possible because it is painful to her. Oral medications could take an hour or longer to work, so an injectable agent is preferred for more rapid action. As with drug-induced parkinsonism, the agent of choice is an anticholinergic medication to offset the EPS. Most ERs will have either benztropine or diphenhydramine (which has appreciable anticholinergic effects) readily available in an IM/intravenous (IV) form for a case such as this. Atropine, although also likely available, is generally not used because of greater systemic and cardiac effects. Benzodiazepines can also be used in IM/IV forms if needed because they too will help relax the contracted muscles and help J.J. calm down.

In addition, J.J.'s medication regimen may need to be adjusted to prevent a future dystonic reaction. A reduction in her haloperidol dose may be needed, or adjunctive oral anticholinergics added to her regimen as prophylaxis.

Case 85-1, Question 28: J.J. has been continued on the combination of aripiprazole monohydrate LAIA and haloperidol over the next 8 years. Over time her symptoms have returned periodically, never requiring hospitalization but necessitating gradual increases in her haloperidol to 15 mg/day. J.J. now presents to the clinic with "shakes in my hands" that are bothering her. During the physical exam, J.J. is noted to have facial grimacing, darting movements of her tongue, lip-smacking, and twisting movements in her hands. The movements in her hands seem to disappear when she grabs an object or performs other activities with her hands. What is the most likely cause of these movements in J.J.?

These movements are most likely an early form of TD. Haloperidol, as a high-potency FGA, has a high risk of causing this movement disorder over time: ~3% to 5% per year of use, or 24% to

40% risk in J.J. The symptoms we are observing in J.J. are consistent with those movements seen in TD that presents with arrhythmic choreoathetoid “snakelike” movements of the orofacial areas, limbs, and trunk. The fact that the irregular hand movements stop or decrease when J.J. performs a conscious task with her hands is also indicative of TD. An AIMS exam should be performed to help confirm and quantify the severity of any TD in J.J.

Case 85-1, Question 29: What can be done to treat the TD seen in J.J. at this time?

There are some strategies that might help alleviate the patient’s dyskinetic movements. Slow decreases in her haloperidol dose over time may help these movements eventually decrease; a rapid reduction in the dose may acutely worsen the current dyskinetic symptoms, so this should be avoided. If the movements persist despite lowering the dosage or discontinuing the haloperidol, a VMAT2 inhibitor, such as valbenazine or deutetrabenazine, could be considered. Considering the high cost of these medications and unclear long-term benefits, adjustments in the baseline antipsychotic regimen would be a more appropriate initial choice. In addition, there are some data supporting the use of clozapine to treat dyskinesia and schizophrenia symptoms. This should be considered cautiously in light of the other concerns related to clozapine treatment.

Inadequate Response

The patient with chronic schizophrenia must be evaluated in a systematic manner to discern whether past medication trials were indeed medication failures. Medication nonadherence, intolerance, and inadequate dosing may often be documented as failed trials. Patients with schizophrenia have been shown to have a deficit in perspective habitual memory, which may cause difficulty in remembering whether they took their medications.[236] This could result in either missed or doubled dosages. An in-depth assessment

of medication adherence should be conducted in a nonpunitive and collaborative manner with the patient. Outreach for collateral information should also be undertaken after acquiring appropriate releases of information. Clinical deterioration often occurs slowly and insidiously with incomplete medication adherence.[237] Poor therapeutic relationship and social supports may also lead to poor adherence in patients with schizophrenia.[238] Other important predictors include lack of insight, concomitant substance abuse, a short illness duration, issues with discharge planning and environment,[239] as well as higher levels of hostility.[240] Patients who have had difficulties with medication adherence in the past should be offered treatment with an LAIA.

A trial of an antipsychotic should be continued for at least 4 to 6 weeks at a therapeutic dosage after initial partial response of symptoms. Switching and augmentation strategies should only be considered after symptoms fail to fully respond to an adequate trial. Patients may wind up in a stalled cross-titration, possibly due to a transition in care, and be continued on multiple antipsychotics. This highlights the need to carefully tease out the patient's medication experience and transition to effective monotherapy to avoid increased adverse effects, pill burden, and cost for the patient.

Between 20% and 30% of patients remain unresponsive despite multiple antipsychotic trials. The most commonly adopted and most stringent criteria for antipsychotic treatment refractoriness were proposed in the landmark trial conducted by Kane and colleagues that resulted in clozapine's approval in the U.S. market. Treatment refractoriness was defined as (a) at least three periods of treatment in the preceding 5 years with antipsychotics from two chemical classes at dosages ≥1000 mg/day of chlorpromazine for a period of 6 weeks, (b) no symptom-free period within 5 years, and (c) a BPRS total score >45.[55,241]

Clozapine is the most efficacious medication in patients with treatment-resistant schizophrenia and should be considered in all patients who fail to respond to at least two adequate antipsychotic trials.[55,111,184,242] It is also the treatment of choice for those at high risk for suicide or violence, or in patients with TD.[106,243] Despite its

superior efficacy, clozapine is often underutilized in the treatment of resistant schizophrenia owing to its adverse effect burden. Close monitoring and follow-up are necessary to ensure safe and effective use of clozapine. Baseline monitoring should include a physical exam (weight, blood pressure, waist circumference), HbA_{1C} or fasting blood glucose, a fasting lipid panel, liver function tests, serum creatinine, blood urea nitrogen levels, and pregnancy test, if indicated. Clozapine has a unique adverse effect profile that ranges from common bothersome adverse effects to life-threatening adverse effects listed in its five black box warnings. The black box warnings caution for risk of agranulocytosis, seizures, myocarditis, other adverse cardiovascular and respiratory effects, and increased mortality in elderly patients with dementia-related psychosis (**Table 85-14**).

Table 85-14
Clozapine Monitoring Requirements

ANC Level	Treatment Recommendation	ANC Monitoring
Normal range for a new patient GENERAL POPULATION ▪ ANC ≥1500/μL BEN POPULATION ▪ ANC ≥1000/μL ▪ Obtain at least two baseline ANC levels before initiating treatment.	Initiate treatment ▪ If treatment interrupted: ▪ <30 days, continue monitoring as before ▪ ≥ 30 days, monitor as if new patient	Weekly from initiation to 6 months ▪ Every 2 weeks from 6 to 12 months ▪ Monthly after 12 months

ANC Level	Treatment Recommendation	ANC Monitoring
Mild neutropenia (1000–1499/μL)[a]	GENERAL POPULATION ▪ Continue treatment.	GENERAL POPULATION ▪ Three times weekly until ANC ≥1500/μL ▪ Once ANC ≥1500/μL, return to patient's last "normal range" ANC monitoring interval.[b]

	BEN POPULATION
	▪ Mild neutropenia is normal range for BEN population, continue treatment.
	▪ Obtain at least two baseline ANC levels before initiating treatment.
	▪ If treatment interrupted
	  ▪ ≤30 days, continue monitoring as before.
	  ▪ ≥30 days, monitor as if new patient
	▪ Discontinuation for reasons other than neutropenia
		BEN POPULATION
		▪ Weekly from initiation to 6 months
		▪ Every 2 weeks from 6 to 12 months
		▪ Monthly after 12 months

ANC Level	Treatment Recommendation	ANC Monitoring
Moderate neutropenia (500–999/μL)[a]	GENERAL POPULATION ▪ Recommend hematology consultation. ▪ Interrupt treatment for suspected clozapine-induced neutropenia. ▪ Resume treatment once ANC normalizes to ≥1000/μL.	GENERAL POPULATION ▪ Daily until ANC ≥1000/μL ▪ Then three times weekly until ANC ≥1500/μL ▪ Once ANC ≥1500/μL check ANC weekly for 4 weeks, then return to patient's last "normal range" ANC monitoring interval.[b]
	BEN POPULATION ▪ Recommend hematology consultation. ▪ Continue treatment.	BEN POPULATION ▪ Three times weekly until ANC ≥1000/μL or patient's known baseline ▪ Once ANC ≥1000/μL or patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "normal BEN range" ANC monitoring interval.[b]

ANC Level	Treatment Recommendation	ANC Monitoring
Severe neutropenia (<500/μL)[a]	GENERAL POPULATION ▪ Recommend hematology consultation. ▪ Interrupt treatment for suspected clozapine-induced neutropenia. ▪ Do not rechallenge unless prescriber determines benefits outweigh risks.	GENERAL POPULATION ▪ Daily until ANC ≥1000/μL ▪ Three times weekly until ANC ≥1500/μL ▪ If patient rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC ≥1500/μL
	BEN POPULATION ▪ Recommend hematology consultation. ▪ Interrupt treatment for suspected clozapine-induced neutropenia. ▪ Do not rechallenge unless prescriber determines benefits outweigh risks.	BEN POPULATION ▪ Daily until ANC ≥500/μL ▪ Three times weekly until ANC is greater than or equal to patient's established baseline ▪ If patient rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC ≥1000/μL or at patient's baseline

BEN, benign ethnic neutropenia.

[a]Confirm all initial reports of absolute neutrophil count (ANC) <1500/μL (ANC <1000/μL for patients with benign ethnic neutropenia [BEN]) with a repeat ANC measurement within 24 hours.

[b]If clinically appropriate.

Source: Clozaril (clozapine tablets). Package insert. HLS Therapeutics Inc; February 2021.

Agranulocytosis is a rare, yet potentially life-threatening, hematologic reaction affecting ~1% of patients treated with clozapine. It is defined as a drop in neutrophil count <500 cells/mm^3. Agranulocytosis is not dose related and can occur at any point in treatment, although the risk is higher within the first 6 months of therapy. Clozapine may also cause mild-to-severe neutropenia (ANC 500–2000 cell/mm^3). Clozapine-induced neutropenia and agranulocytosis may be in part due to the selective effect on precursors of polymorphonuclear leukocytes; however, the mechanism remains to be fully elucidated. Clozapine is only dispensed through the clozapine risk evaluation and monitoring strategy (REMS) to ensure ANC values are within range before dispensing clozapine. The pharmacy, patient, and provider must all be enrolled in the clozapine REMS program. Monitoring of the absolute neutrophil count (ANC) must occur 7 days before initiation of clozapine and weekly thereafter for the first 6 months. Monitoring frequency can be reduced to biweekly for the next 6 months if all ANC values are within range (>1500/μL). Monthly blood draws are allowed if all values remain within range after 6 months of biweekly monitoring. Certain ethnic groups, including patients of African and Middle Eastern descent, may average a lower ANC value than normal ranges, called benign ethnic neutropenia (BEN). The clozapine REMS program allows for lower ANC values to compensate for patients diagnosed with BEN because they do not suffer from repeated or severe infections as a result of their low baseline ANC values. Severe neutropenia can be deadly because of the body's inability to fight off infection. This is a medical emergency that requires the abrupt discontinuation of clozapine. In other cases, clozapine should be discontinued gradually over a period of ≥2 weeks, to prevent cholinergic rebound (sweating, headache, nausea, vomiting, diarrhea) or recurrence of psychotic symptoms. The patient should not be rechallenged on clozapine after agranulocytosis, but

patients can be successfully rechallenged after neutropenia.[244] More information can be found at https://www.newclozapinerems.com/.

Seizure risk associated with clozapine is a dose-related phenomenon. Risk of seizure is 4.4% at a dose of 600 mg and several case reports implicate serum levels >500 to 1300 ng/mL with higher risk of seizure.[245,246] Prophylactic use of antiepileptic drugs (AEDs) is generally not recommended.[247] However, patients who experience a seizure on clozapine can be safely continued on a lower dose of clozapine and initiated on an AED. Valproate and lamotrigine are preferred over carbamazepine because of its risk of agranulocytosis and extensive interaction profile.[246] Myocarditis is a potentially fatal hypersensitivity reaction that can occur ~3 weeks after initiation of clozapine. Diagnosis is confounded by the variable and nonspecific signs and symptoms of its presentation, but the incidence is estimated to fall between <0.1% and 3%.[248] The monitoring protocol proposed by Ronaldson and colleagues consists of obtaining baseline troponins, C-reactive protein (CRP), and an ECG, and then monitoring troponin and CRP on days 7, 14, 21, and 28 of treatment. In the case of mild elevation in troponins or CRP, persistent tachycardia, or signs or symptoms resembling infection, daily troponins and CRP should be drawn until symptom resolution. Clozapine should be discontinued if troponins reach twice the upper limit of normal or if CRP is >100 mg/L.[59] Successful rechallenge may be possible after symptoms resolve.[249,250]

The black box warning describing “other adverse cardiovascular and respiratory effects” references the risk of orthostatic hypotension associated with clozapine. Approximately 9% of patients will experience orthostatic hypotension, but tolerance develops over 4 to 6 weeks.[177] Risk is higher during initiation, which necessitates the slow titration beginning at 12.5 mg bid and increasing at the rate of 25 to 50 mg/day or slower. Clozapine must also be retitrated after a gap in therapy of >2 days to prevent significant orthostasis and risk of falls. Patients should be counseled to make slow transitions from prone or seated positions and maintain adequate fluid and salt intake. In patients with persistent dizziness and orthostasis after

titration where DR is not an option, a mineralocorticoid, fludrocortisone, may be an option.[177]

Clozapine is also associated with frequent, bothersome adverse effects that, if left unaddressed, can greatly impact the quality of life. Constipation is a common, yet often-overlooked, adverse effect of clozapine that can result in serious complications including paralytic ileus, small-bowel perforation, or death secondary to aspiration of gastric contents. It affects between 14% and 60% of patients taking clozapine. Patients should be screened at every visit for bowel habits and providers should have a low threshold for initiating a bowel regimen. Bowel regimens consist of bulk-forming laxatives and increased fluid intake, stool softeners, or short-term use of stimulant laxatives or enemas. Anticholinergic adverse effects of clozapine can result in gastrointestinal (GI) hypomotility, small-bowel obstruction, and ileus. These are serious concerns that may occur in up to 0.3% of patients treated with clozapine. Adjunctive anticholinergic agents and opioids should be limited and the clozapine dose tentatively decreased or held in cases of ileus. Sedation is usually more pronounced when first initiating clozapine and can be managed by slowing the rate of titration and consolidating the dose to bedtime. As previously described, a benign tachycardia can also result from clozapine use, but patients also presenting with flu-like symptoms, dyspnea, fever, and chest pain should have further workup for myocarditis. Sialorrhea is an embarrassing adverse effect that, in the extreme, can result in sleep disruption or aspiration pneumonia. Treatment options include tentative DR or nonpharmacologic management, such as placing a towel on their pillow, as first line. Topical anticholinergic agents (ipratropium 0.03%–0.06% dosed one to two sprays sublingually or one or two atropine eye drops in 1 ounce of water swished and spit) are preferred over systemic anticholinergics (benztropine 0.5–2 mg at bedtime [HS] or glycopyrrolate 1–2 mg) or the α-2 adrenergic agent, clonidine.[251] Serious cases may be treated with botulinum toxin injected into each parotid gland.[251] Nocturnal enuresis may also be underreported owing to embarrassment. Management includes avoiding fluids in the evening, voiding before bed, and setting alarms to schedule

nocturnal voiding. Desmopressin may also be effectively utilized, but the patient must be monitored for hyponatremia secondary to its use.[177]

Case 85-1, Question 30: J.J.'s psychiatrist decides to start J.J. on clozapine and remove all other antipsychotics in light of her TD and past failures and adverse effects with other antipsychotics. What adverse effects of clozapine should be monitored for in J.J.?

Any patient started on clozapine should be monitored for agranulocytosis and metabolic adverse effects, among others. Because J.J. has a history of metabolic adverse effects (weight gain, increased glucose, and increased triglycerides) with other antipsychotics, these are of particular concern with using clozapine because clozapine has the highest risk of these adverse effects. J.J. should also be counseled about orthostatic hypotension, sedation, anticholinergic effects (especially constipation), and sialorrhea.

Case 85-1, Question 31: Before initiating clozapine therapy, what labs and other tests should be performed on J.J.?

Clozapine therapy requires a baseline ANC before starting the medication to ensure the patient has an adequate number of neutrophils before initiation. In addition, her weight, waist circumference, serum glucose/HbA_{1C}, and lipid panel should be measured to monitor for the development of metabolic adverse effects. Baseline liver and kidney function tests should also be measured. A pregnancy test should also be performed, especially if there is any chance that J.J. could be pregnant.

Case 85-1, Question 32: Once J.J. is started on clozapine, how should she be monitored? What parameters should be checked and how frequently?

Clozapine treatment requires weekly ANC checks for at least the first 6 months of treatment. Assuming there are no problems with her

ANC values (ANC ≥ 1500/μL), she can then go in for ANC checks every other week for 6 months, and then once monthly ANC checks thereafter. In addition, her weight should be monitored at least monthly (and perhaps weekly) for the first few months of treatment, along with at least quarterly serum glucose and lipid panel checks. She should also be asked about any problems with orthostasis (dizziness), constipation, sedation, and drooling during any office visits.

Serum Concentration Monitoring

Data supporting a strong correlation between antipsychotic serum concentrations and efficacy are lacking.[252] Therefore, routine therapeutic drug monitoring (TDM) of antipsychotic serum concentration is not recommended in most situations. The exception is clozapine, which has sufficient data to support a higher rate of response at levels >350 ng/mL.[186,253] The Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) guideline strongly recommends TDM of the FGAs, haloperidol, fluphenazine, and perphenazine, as well as SGAs, clozapine and olanzapine, based on established therapeutic reference ranges. They also recommend monitoring of chlorpromazine, aripiprazole, quetiapine, risperidone, paliperidone, and ziprasidone in cases of suspected altered PK where therapeutic ranges are less well established, but supratherapeutic concentrations may result in adverse effects.[254] Monitoring of serum levels of these agents is appropriate in the following clinical scenarios[255]:

1. Psychiatric decompensation on a previously effective dose
2. Poor response to medication despite adequate dose and trial duration
3. Unexpected adverse effects while on a previously tolerated dose
4. Addition or withdrawal of an interacting medication
5. Patients with potentially altered PK (eg, medically compromised, children, elderly)

6. Suspected medication nonadherence

Nonantipsychotic Agents

Antipsychotics are generally the treatment of choice for most patients with schizophrenia. However, in some situations, other medications may be needed and appropriate for use. Benzodiazepines may be appropriate in patients with acute agitation, as described previously. Other medications, such as mood stabilizers and antidepressants, may be useful for some patients based on their clinical symptoms and presentation.

MOOD STABILIZERS

The mood stabilizers lithium, carbamazepine, valproic acid, and lamotrigine have been studied for use in schizophrenia. These medications are frequently used as an adjunct to antipsychotic treatment in schizophrenia in patients with affective symptomatology as well as core symptoms of schizophrenia. Evidence for these common practices is sometimes found to be equivocal or conflicting.

None of these mood stabilizers have shown efficacy as monotherapy for schizophrenia. Lamotrigine has been found to have modest effects in schizophrenic pathology as an adjunct to antipsychotic treatment but has little efficacy in the patient who is treatment resistant.[256] Lithium was determined by a Cochrane review to have some benefit as an augmenting agent in lower quality studies, but replication in higher quality studies is needed.[257] A recent meta-analysis shows evidence that the practice of augmentation of antipsychotic medications with valproate yields significant improvements in patients treated for schizophrenia or schizoaffective disorder.[258] A recent Cochrane review does not recommend carbamazepine for augmentation of antipsychotics in the treatment of schizophrenia.[259] A need for further study of antipsychotic augmentation with mood stabilizers is warranted. Concomitant use should be carefully considered at this time given

the potential for drug interactions, additional adverse effects, and pill burden.

ANTIDEPRESSANTS

Depression often presents in schizophrenia,[38,260] and ~6% to 10% of patients with schizophrenia commit suicide in their lifetime.[28,261–263] Although controversial, there is evidence that antipsychotics may differ in their ability to treat depressive symptoms in schizophrenia[53,103,264,265] and many consider SGAs to be better for this syndrome than are the FGAs.[265,266] Some of the advantages of SGAs in depression may be due in part to less antipsychotic-induced dysphoria or akinesia or effect on treating negative symptoms.[265,266] There is also substantial literature showing that adding an antidepressant may be a useful option in some patients with depression.[267] The divergent pattern of antidepressant response in numerous studies suggests that those patients whose positive symptoms are well controlled are more likely to respond favorably to antidepressant augmentation.[27] In one trial, the antidepressant bupropion did significantly worse than did placebo in patients treated with thiothixene.[33]

Some also advocate for the possible effectiveness of antidepressant medication to decrease the severity of negative symptoms in schizophrenia.[268] One review found only 5 of 14 studies with selective serotonin reuptake inhibitor (SSRI) antidepressants demonstrated efficacy in ameliorating negative symptoms; however, mirtazapine was promising in 4 of 6 trials.[267] Tricyclic antidepressants do not have robust evidence for the treatment of negative symptoms.[269]

Case 85-1, Question 33: J.J. responds well to clozapine, taking a dose of 450 mg/day, with higher doses causing intolerable adverse effects in J.J. Over time, J.J. begins to become depressed as she realizes that her life has not gone the way she thought it would. Her psychiatrist assesses her as having depression secondary to her schizophrenia, and the decision is made to start her on paroxetine 20 mg daily. Is the addition of paroxetine appropriate for J.J.?

Although paroxetine is an appropriate treatment for depression, it is most likely not a good choice for J.J. There are data that show that paroxetine can cause anticholinergic adverse effects in patients, which could overlap any anticholinergic effects caused by clozapine. J.J. would need to be monitored for increased anticholinergic adverse effects, and possibly be treated for them (eg, bowel regimen for constipation). Selection of an antidepressant with a lower risk of drug interactions, such as escitalopram or sertraline, would be more appropriate.

Treatment Guidelines for Schizophrenia

Clinical guidelines on the treatment of schizophrenia are published by a number of organizations. The most prolific and current guidelines at this time are the APA, Patient Outcomes Research Team on Schizophrenia (PORT), Texas Medication Algorithm Project (TMAP), and the National Institute for Health and Care Excellence (NICE) of the United Kingdom.[44,105–107] These guidelines are an excellent resource and starting point in ensuring evidence-based and safe care of patients with schizophrenia. However, it is important to keep in mind the level of evidence each organization requires to support a given treatment recommendation. For example, the APA utilizes a transparent process of systematically evaluating the literature than rating the strength of evidence for each clinical recommendation (A: high, B: moderate, C: low) in accordance with Agency of Healthcare Research and Quality (AHRQ) guidelines. A higher rating denotes increased confidence that the available evidence reflects a true effect and is unlikely to be changed through further research. In addition, the strength of each statement is rated on the confidence that potential benefits outweigh risk for harm (1: recommendation, benefit outweighs risk, or 2: suggestion, greater uncertainty). The APA also includes a section following each recommendation comparing it to available guidelines from other organizations and listing any differences in opinion in writing group members. Other guidelines may incorporate expert opinion[105,107] or

consensus in areas that lack high-level evidence, such as antipsychotic combination treatment or treatment after nonresponse to clozapine. The bottom line is that these guidelines provide a systematic framework for high-quality treatment, but should by no means be a substitute for clinical judgment and treating the unique clinical picture each individual presents. Any treatment decision should be aligned with the treatment team; caregivers; and, most importantly, the patient. Even the most effective treatment is destined to fail unless the patient is invested and in agreement with their own treatment. **Figure 85-2** is a consolidated view of the current guidelines on the use of antipsychotics in the treatment of schizophrenia.

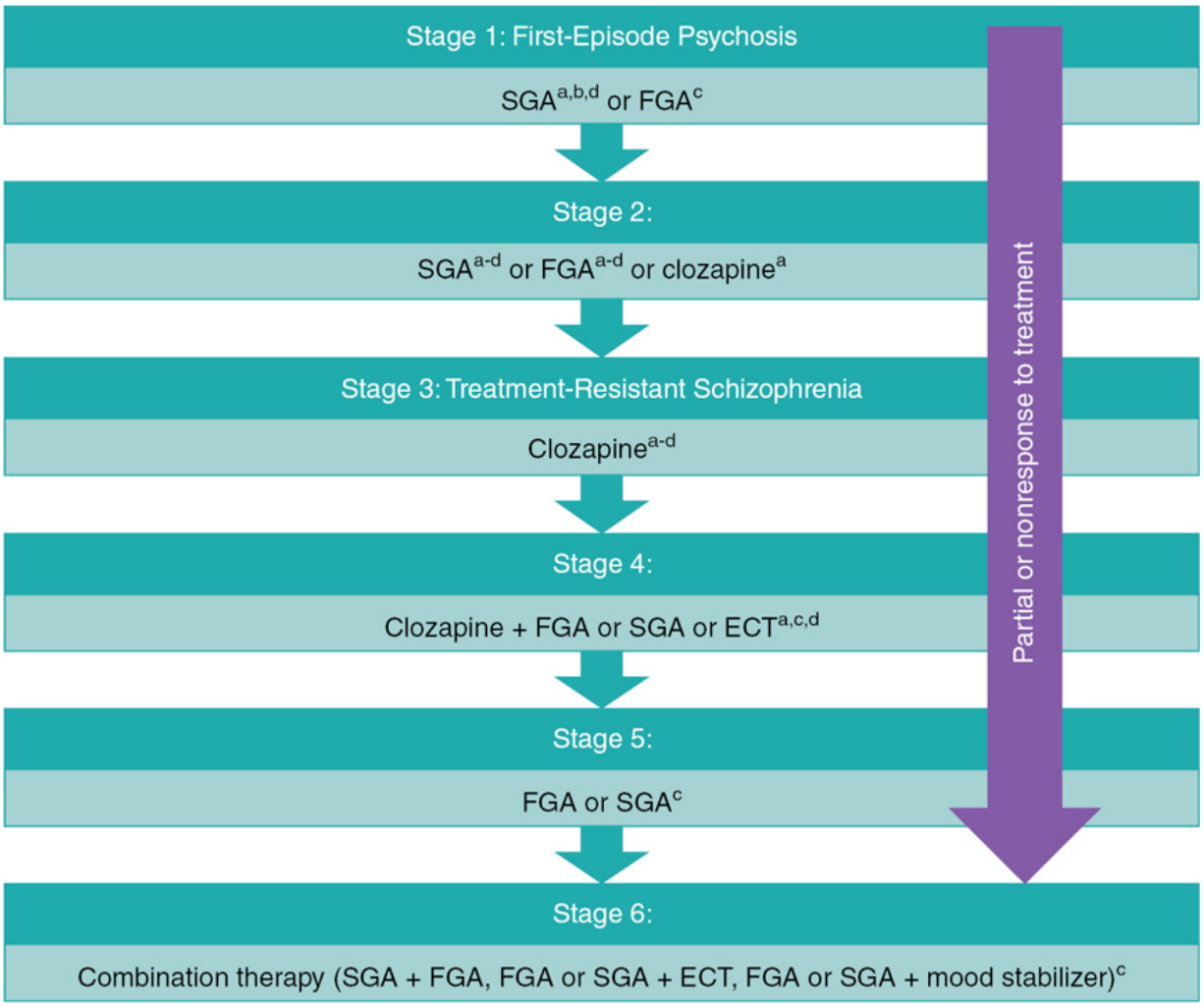


Figure 85-2 Summary of current treatment guidelines on schizophrenia. ECT, electroconvulsive therapy; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics.

(Sources: [a]The American Psychiatric Association. *The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia*. 3rd ed. American Psychiatric Association; 2021; [b]Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):71–93. doi:10.1093/schbul/sbp116; [c]Moore T, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 Update. *J Clin Psychiatry*. 2007;68(11):1751–1762. doi:10.4088/JCP.v65n0408; [d]IPAP Schizophrenia Algorithm. The International Psychopharmacology Algorithm Project website. Updated March 27, 2006. http://www.ipap.org/schiz/.)

CONSIDERATIONS IN SPECIFIC POPULATIONS

Pregnancy

The peak onset of schizophrenia in the female population coincides with peak childbearing age, and unplanned pregnancies can be a concern.[270] Patients should be routinely educated on safe sexual practices, offered contraceptives if indicated, and receive pregnancy tests before prescription of antipsychotic medications. The general goals of treatment in pregnant patients are to thoroughly weigh the risks of teratogenicity with the benefit of ongoing treatment and prevention of psychiatric decompensation. Untreated psychosis places both the patient and the fetus at significant risk. Effective treatment with an antipsychotic agent may enable the mother to carry out necessary self-care and prenatal care.[271] Ideally, treatment decisions should be made as part of a multidisciplinary team consisting of the patient, mental health provider, obstetrician, primary care provider, and pediatrician. General guidelines on treatment during pregnancy recommend[271]:

1. Utilizing antipsychotic monotherapy at an adequate dose versus combination therapy

2. Avoiding medication switching to minimize exposure to the fetus and risk of psychiatric relapse
3. Selecting appropriate treatment based on history of efficacy, prior exposure during pregnancy, and available evidence on safety
4. Choosing medications with fewer metabolites, fewer interactions, and higher protein binding are generally preferred.

Data on the safety of antipsychotics during pregnancy are limited owing to ethical barriers to conducting well-designed, prospective controlled trials. There is inconclusive evidence linking fetal exposure to antipsychotics and major congenital malformations, perinatal mortality, high birth weight (SGAs), and low birth weight (FGAs).[270] A large-scale prospective national pregnancy registry for atypical antipsychotics reported three major fetal malformations in a cohort of 214 patients with first-trimester exposure to SGAs. The control group, which included 89 live births, had one major malformation. This translates to an OR of 1.25 (95% CI = 0.13–12.19) between exposed and unexposed infants. Although ongoing data collection is still underway, these results suggest that SGA exposure would be unlikely to increase the risk of major malformations higher than 10-fold of that observed in control groups or in the general population.[272] In 2011, the FDA implemented safety-labeling changes concerning the use of antipsychotic agents during the third trimester of pregnancy. They reported a risk that newborns may experience withdrawal symptoms or EPS; however, many cases were confounded by comorbid substance use and concomitant psychotropic medications. Symptoms usually resolved within hours to days without intervention; however, some may require prolonged hospitalization.[273] There can also be an increased risk of gestational diabetes in females who continue antipsychotic treatment, particularly with either olanzapine or quetiapine, during pregnancy.[274]

Case 85-1, Question 34: Several months later, the clinic receives word from J.J.'s primary care provider that J.J. is pregnant, as confirmed by blood test. J.J. is still receiving clozapine and is fairly stable psychiatrically on the medication, even working part-time in a supermarket. J.J. does not want to lose the baby,

but is worried about the effect of being on medication despite knowing it is what is keeping her stable. Should J.J. be continued on clozapine, and what are the risks to her baby if she does or does not?

Treatment of schizophrenia with antipsychotics during pregnancy must be considered carefully. Because J.J. is currently stable and functional while taking clozapine, there is a significant risk of relapse if she stops the medication. During this relapse, if she were to engage in high-risk behaviors, it could be quite dangerous to both her and her baby. Maintaining stability is of great importance because if J.J. can take care of herself appropriately, it is more likely she will also take care of her fetus simultaneously. However, antipsychotics do carry risks of teratogenicity, and J.J. should be counseled on these risks. Clozapine is rated as pregnancy category B by the FDA, which is better than most antipsychotics but still with some risk involved. The decision to maintain J.J. on clozapine during her pregnancy should be made by her, her psychiatrist, obstetrician, and other care providers to determine whether continuation of clozapine, and presumptive stability of her illness, is appropriate.

First-Episode Psychosis and Early-Onset Schizophrenia

Child and adolescent patients presenting with early psychosis are exquisitely sensitive to EPS and metabolic adverse effects of antipsychotics.[275,276] In general, symptoms of first-episode psychosis (FEP) respond to lower antipsychotic dosages. Therefore, the minimum effective dose should be utilized to minimize adverse effect burden. The question of which interventions are appropriate to initiate and when is complicated. Multiple studies support the effectiveness of antipsychotics in the treatment of early psychosis.[277–280] However, the treatment of prodromal symptoms is an area of debate. Prompt recognition of prodromal symptoms and patients with psychosis risk syndrome is crucial. Features associated with greater rates of conversion to psychosis in patients at ultrahigh

risk of psychosis include genetic risk for schizophrenia, high levels of unusual thought content, high levels of suspicion and paranoia, social impairment, and history of substance use.[281] There is emerging evidence to support early initiation of ω-3 fatty acids or antidepressants to reduce rates of conversion to psychosis in high-risk patients.[276,282,283] Early engagement with appropriate comprehensive, multidisciplinary clinics results in improved quality of life and psychopathology, greater involvement in educational and vocational pursuits, and increased treatment follow-up.[284,285] Reduction in the duration of untreated psychosis leads to improved long-term prognosis and greater likelihood of achieving symptom remission.[43,286,287] Neurocognitive impairment is also a key predictor of functional outcome in early schizophrenia. Unfortunately, available pharmacologic options have a limited impact on neurocognition.[288] Cognitive enhancement therapy, in conjunction with antipsychotic medication, can lead to durable improvements in neurocognitive functioning, social adjustment, and employment for patients with early psychosis.[289,290]

After achieving initial remission, guidelines recommend continued maintenance treatment with an antipsychotic for at least 1 year.[44,106] Studies of medication discontinuation demonstrated 5-year relapse rates from 80%.[291] However, cautious DR strategies as soon as 6 months after remission may improve long-term functional recovery. Wunderink and colleagues conducted a 7-year follow-up study of a 2-year open RCT comparing maintenance therapy (MT) versus DR/dose discontinuation after 6 months' remission of FEP. In the initial RCT, 128 patients were randomized to MT or DR and followed up for 18 months. The MT group showed benefit in short-term relapse rates over the DR group.[292] However, the DR group had approximately twice the recovery rate of patients in the MT group (40.4% vs 17.6%, respectively) at the 7-year follow-up and there were no significant differences in long-term relapse rates.[293] A limitation to the generalizability of the study is that the population who agreed to enrollment in the initial phase had a higher level of functioning, greater adherence, and was easier to engage. These findings demonstrate the potential impact of limiting total

antipsychotic burden on functional recovery rates of patients with remitted FEP. The lower adverse effect burden from minimizing the antipsychotic dose allows for improved social engagement, improved therapeutic alliance, and lower risk of self-discontinuation because of tolerability issues. Functional recovery is the key treatment goal in the early course of schizophrenia. Getting patients engaged in treatment early on in the illness course, utilizing the lowest clinically effective dosages of antipsychotics, and providing psychoeducation can mean the difference in a patient recovering from a psychotic episode and completing college, returning to work, or engaging in meaningful social outlets.

Case 85-1, Question 35: J.J. gives birth to a son, R.J., via a normal delivery. Over the course of time, R.J.'s pediatrician notes he is not socializing like other children, especially into adolescence. He is now age 15 and tends to isolate himself, does not have many peer friends, and recently has started performing poorly in school. His teachers have asked the pediatrician to evaluate R.J. for potential attention deficit hyperactivity disorder (ADHD) because he is often found not paying attention in class. J.J. also tells the pediatrician that she thinks R.J. still has "imaginary friends" because she often sees him alone in his room talking to people who are not there. What is potentially happening with R.J. and how should he be treated at this time?

R.J. is at higher risk for and potentially showing symptoms of early-onset schizophrenia. His lack of socialization and his isolation could be symptoms of the prodromal phase of schizophrenia. His "imaginary friends" could be R.J. responding to auditory and/or visual hallucinations; imaginary friends are not usually seen into adolescence. If these are hallucinations, this could also explain his lack of attention in school, which would not be ADHD. Considering his mother has schizophrenia, there is a definite genetic link to the illness in R.J. Once R.J. is evaluated for schizophrenia, it may be appropriate to initiate an antipsychotic at that time. If so, he should be started on an agent with minimal adverse effect burden at a minimal dose to control his symptoms. He should be evaluated regularly for possible medication discontinuation if warranted, but

may require more long-term treatment depending on his response and prognosis.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004;27:596–601. (206)

Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull.* 2010;36:71–93. doi:10.1093/schbul/sbp116 (106)

Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(*9896*):951–962. doi:10.1016/S0140-6736(13)60733-3 (185)

Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(*12*):1209–1223. doi:10.1056/NEJMoa1404304 (63)

Marder SR, Essock SM, Miller AL, et al. The Mount Sinai conference on the pharmacotherapy of schizophrenia. *Schizophr Bull*. 2002;28(*1*):5–16. (211)

Key Websites

American Psychiatric Association. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia*. 3rd ed. https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841

Clozapine REMS Program. https://www.newclozapinerems.com/

National Institute for Health and Care Excellence. *Psychosis and Schizophrenia in Adults: Prevention* and *Management*. Accessed March 1, 2014. https://www.nice.org.uk/guidance/cg178

National Institute of Mental Health. Schizophrenia. Accessed May 2020. http://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml

U.S. Food and Drug Administration. FDA Drug Safety Communication: antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. Accessed August 24, 2017. http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm

COMPLETE REFERENCES CHAPTER 85 SCHIZOPHRENIA

1. Tandon R, Keshavan M, Nasrallah H. Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. *Schizophr Res*. 2008;102(1–3):1–18. doi:10.1016/j.schres.2008.04.011
2. Lopez AD. The evolution of the Global Burden of Disease framework for disease, injury and risk factor quantification: developing the evidence base for national, regional and global public health action. *Global Health*. 2005;1:5. doi:10.1186/1744-8603-1-5
3. American Psychiatric Association. Schizophrenia spectrum and other psychotic disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Publishing; 2013:87–122.
4. Wu EQ, Birnbaum HG, Shi L, et al. The economic burden of schizophrenia in the United States in 2002. *J Clin Psych*. 2005;66(9):1122–1129.
5. Thieda P, Beard S, Richter A, Kane J. An economic review of compliance with medication therapy in the treatment of schizophrenia. *Psychiatr Serv*. 2003;54(4):508–516. doi:10.1176/appi.ps.54.4.508
6. Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol*. 2014;29(2):63–76. doi:10.1097/YIC.0b013e32836508e6
7. Davies L, Drummond M. The economic burden of schizophrenia. *Psychiatr Bull*. 1990;14:522–525.
8. Keshavan MS, Tandon R, Boutros NN, Nasrallah HA. Schizophrenia, "just the facts": what we know in 2008. Part 3: neurobiology. *Schizophr Res*. 2008;106(2–3):89–107. doi:10.1016/j.schres.2008.07.020
9. Bakhshi K, Chance SA. The neuropathology of schizophrenia: a selective review of past studies and emerging themes in brain structure and cytoarchitecture. *Neuroscience*. 2015;303:82–102. doi:10.1016/j.neuroscience.2015.06.028

10. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull*. 2009;35(3):549–562. doi:10.1093/schbul/sbp006
11. Schwartz TL, Sachdeva S, Stahl SM. Glutamate neurocircuitry: theoretical underpinnings in schizophrenia. *Front Pharmacol*. 2012;3:1–11. doi:10.3389/fphar.2012.00195
12. Lodge DJ, Grace AA. Developmental pathology, dopamine, stress and schizophrenia. *Int J Dev Neurosci*. 2011;29(3):207–213. doi:10.1016/j.ijdevneu.2010.08.002
13. Kapur S, Seeman P. Does fast dissociation from the dopamine D 2 receptor explain the action of atypical antipsychotics?: a new hypothesis. *Am J Psychiatry*. 2001;158(3):360–369. doi:10.1176/appi.ajp.158.3.360
14. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry*. 2000;157(4):514–520. doi:10.1176/appi.ajp.157.4.514
15. Anticevic A, Cole MW, Repovs G, et al. Connectivity, pharmacology, and computation: toward a mechanistic understanding of neural system dysfunction in schizophrenia. *Front Psychiatry*. 2013;4:1–21. doi:10.3389/fpsyt.2013.00169
16. Coyle JT. NMDA receptor and schizophrenia: a brief history. *Schizophr Bull*. 2012;38(5):920–926. doi:10.1093/schbul/sbs076
17. Howes O, Mccutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol*. 2015;29(2):97–115.
18. Gruber O, Santuccione AC, Aach H. Magnetic resonance imaging in studying schizophrenia, negative symptoms, and the glutamate system. *Front Psychiatry*. 2014;5:1–11. doi:10.3389/fpsyt.2014.00032
19. Garey LJ, Ong WY, Patel TS, et al. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *J Neurol Neurosurg Psychiatry*. 1998;65(4):446–453. doi:10.1136/jnnp.65.4.446
20. Nasrallah H, Tandon R, Keshavan M. Beyond the facts in schizophrenia: closing the gaps in diagnosis, pathophysiology, and treatment. *Epidemiol Psychiatr Sci*. 2011;20(4):317–327. doi:10.1017/S204579601100062X
21. Fitzsimmons J, Kubicki M, Shenton ME. Review of functional and anatomical brain connectivity findings in schizophrenia. *Curr Opin Psychiatry*. 2013;26(2):172–187. doi:10.1097/YCO.0b013e32835d9e6a
22. Moskowitz A, Heim G. Eugen Bleuler's Dementia Praecox or the Group of Schizophrenias (1911): a centenary appreciation and reconsideration. *Schizophr Bull*. 2011;37(3):471–479. doi:10.1093/schbul/sbr016
23. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophr Res*. 2009;110(1–3):1–23. doi:10.1016/j.schres.2009.03.005

24. Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. *Schizophr Bull*. 2013;39(6):1363–1372. doi:10.1093/schbul/sbs135
25. Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry*. 1994;151(10):1409–1416.
26. Abi-Dargham A, Rodenhiser J, Printz D, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci U S A*. 2000;97(14):8104–8109. doi:10.1073/pnas.97.14.8104
27. Dufresne RL. Issues in polypharmacotherapy: focus on depression in schizophrenia. *Psychopharmacol Bull*. 1995;31(4):789–796.
28. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia. *Arch Gen Psychiatry*. 2005;62:247–253. doi:10.1001/archpsyc.62.3.247.Text
29. American Psychiatric Association. Personality disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Publishing; 2013:645–684.
30. Elis O, Caponigro JM, Kring AM. Psychosocial treatments for negative symptoms in schizophrenia: current practices and future directions. *Clin Psychol Rev*. 2013;33(8):914–928. doi:10.1016/j.cpr.2013.07.001
31. Keshavan MS, Nasrallah HA, Tandon R, et al. Schizophrenia, “just the facts” 6. Moving ahead with the schizophrenia concept: from the elephant to the mouse. *Schizophr Res*. 2011;127(1–3):3–13. doi:10.1016/j.schres.2011.01.011
32. Lako IM, Taxis K, Bruggeman R, et al. The course of depressive symptoms and prescribing patterns of antidepressants in schizophrenia in a one-year follow-up study. *Eur Psychiatry*. 2012;27(4):240–244. doi:10.1016/j.eurpsy.2010.10.007
33. Dufresne RL, Kass DJ, Becker RE. Bupropion and thiothixene versus placebo and thiothixene in the treatment of depression in schizophrenia. *Drug Dev Res*. 1988;12(3–4):259–266.
34. Becker RE. Depression in schizophrenia. *Psychiatr Serv*. 1988;39(12):1269–1275. doi:10.1176/ps.39.12.1269
35. Mandel MR, Severe JB, Schooler NR, Gelenberg AJ, Mieske M. Development and prediction of postpsychotic depression in neuroleptic-treated schizophrenics. *Arch Gen Psychiatry*. 1982;39(2):197–203. doi:10.1001/archpsyc.1982.04290020051010
36. Häfner H, Löffler W, Maurer K, Hambrecht M, an der Heiden W. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatr Scand*. 1999;100(2):105–118. doi:10.1111/j.1600-0447.1999.tb10831.x
37. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468(7321):187–193. doi:10.1038/nature09552

38. Davidson L, McGlashan TH. The varied outcomes of schizophrenia. *Can J Psychiatry*. 1997;42(1):34–43.
39. Lieberman JA, Koreen AR, Chakos M, et al. Factors influencing treatment response and outcome of first-episode schizophrenia: implications for understanding the pathophysiology of schizophrenia. *J Clin Psychiatry*. 1996;57(9):5–9.
40. Schennach R, Musil R, Mölle HJ, Riedel M. Treatment response in first-episode schizophrenia. *Clin Psychopharmacol Neurosci*. 2012;10(2):78–87.
41. Jobe TH, Harrow M. Long-term outcome of patients with schizophrenia: a review. *Can J Psychiatry*. 2005;50(14):892–900.
42. Dixon LB, Dickerson F, Bellack AS, et al. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull*. 2009;36(1):48–70. doi:10.1093/schbul/sbp115
43. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry*. 2005;162(10):1785–1804.
44. The American Psychiatric Association. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia*. 3rd ed. American Psychiatric Association; 2021.
45. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379(9831):2063–2071. doi:10.1016/S0140-6736(12)60239-6
46. Trzepacz PT, Baker RW. *The Psychiatric Mental Status Examination*. Oxford University Press; 1993.
47. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? *Schizophr Res*. 2005;79(2–3):231–238.
48. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep.* 1962;10:799–812.
49. Dean CE, Russell JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments: how do they compare in assessing abnormal, involuntary movements? *J Clin Psychopharmacol*. 2004;24(3):298–304.
50. Guy W. *Manual for Psychopharmacology: Revised*. US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Program; 1976.
51. López-Muñoz F, Alamo C, Cuenca E, Shen WW, Clervoy P, Rubio G. History of the discovery and clinical introduction of chlorpromazine. *Ann Clin Psychiatry*. 2005;17(3):113–135. doi:10.1080/10401230591002002
52. Gardos G, Cole JO. Weight reduction in schizophrenics by molindone. *Am J Psychiatry*. 1977;134(3):302–304.
53. Dufresne RL, Valentino D, Kass DJ. Thioridazine improves affective symptoms in schizophrenic patients. *Psychopharmacol Bull*. 1993;29(2):249–255.

54. Popovic D, Nuss P, Vieta E. Revisiting loxapine: a systematic review. *Ann Gen Psychiatry*. 2015;14(1):10–17. doi:10.1186/s12991-015-0053-3
55. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45(9):789–796.
56. Alvir JM, Lieberman JA, Safferman A, Schwimmer J, Schaaf J. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med*. 1993;329(3):162–167. doi:10.1056/NEJM199307153290303
57. Jalenques I. Drug-resistant schizophrenia treatment options. *CNS Drugs*. 1996;5(1):8–23.
58. Hyde N, Dodd S, Venugopal K, Purdie C, Berk M, Neil AO. Prevalence of cardiovascular and metabolic events in patients prescribed clozapine: a retrospective observational, clinical cohort study. *Curr Drug Saf*. 2015;10:125–131.
59. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust N Z J Psychiatry*. 2011;45(6):458–465. doi:10.3109/00048674.2011.572852
60. Hatton J, Bhat P, Gandhi S. Clozapine-induced myocarditis. *Tex Hear Inst J*. 2015;42(2):155–157.
61. Meltzer H. Update on typical and atypical antipsychotic drugs. *Annu Rev Med*. 2012;64(1):393–406. doi:10.1146/annurev-med-050911-161504
62. Fenton M, Rathbone J, Reilly J, Sultana A. Thioridazine for schizophrenia (review). *Cochrane Database Syst Rev*. 2011;(5):1–149. doi:10.1002/14651858.CD001944.pub2
63. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223. doi:10.1056/NEJMoa1404304
64. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11):1686–1696.
65. Ghaeli P, Dufresne RL. Serum triglyceride levels in patients treated with clozapine. *Am J Health Syst Pharm*. 1996;53(17):2079–2081.
66. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry*. 1999;60(11):767–770. doi:10.4088/JCP.v60n1109
67. Gaulin BD, Markowitz JS, Caley CF, Nesbitt L, Dufresne RL. Clozapine-associated elevation in serum triglycerides. *Am J Psychiatry*. 1999;156(8):1270–1272.
68. Meyer JM. Novel antipsychotics and severe hyperlipidemia. *J Clin Psychopharmacol*. 2001;21(4):369–374. doi:10.1097/00004714-200108000-00003

69. Meyer JM. A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. *J Clin Psychiatry*. 2002;63(5):425–433. doi:10.4088/JCP.v63n0509
70. Lambert BL, Cunningham FE, Miller DR, Dalack GW, Hur K. Diabetes risk associated with use of olanzapine, quetiapine, and risperidone in Veterans Health Administration patients with schizophrenia. *Am J Epidemiol*. 2006;164(7):672–681. doi:10.1093/aje/kwj289
71. Kane J, Canas F, Kramer M, et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res*. 2007;90(1–3):147–161. doi:10.1016/j.schres.2006.09.012
72. Lieberman JA. Comparative effectiveness of antipsychotic drugs. *Arch Gen Psychiatry*. 2006;63(3):1069–1072. doi:10.1176/appi.ajp.160.3.590-a
73. Carrillo JA, Herráiz AG, Ramos SI, Gervasini G, Vizcaíno S, Benítez J. Role of the smoking-induced cytochrome P450 (CYP)1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. *J Clin Psychopharmacol*. 2003;23(2):119–127.
74. Lybalvi (olanzapine and samidorphan). Package insert. Alkermes Inc; May 2021.
75. Citrome LL. Olanzapine-samidorphan combination for schizophrenia or bipolar 1 disorder. *Current Psychiatry*. 2022;21(1):35–40. doi:10.12788/cp.0203
76. Friedman JH. Atypical antipsychotic drugs in the treatment of Parkinson's disease. *J Pharm Pract*. 2011;24(6):534–540.
77. Miceli JJ, Glue P, Alderman J, Wilner K. The effect of food on the absorption of oral ziprasidone. *Psychopharmacol Bull*. 2007;40(3):58–68.
78. Sidana A, Chavan BS, Singh GP, Mangla D. Ziprasidone and its association with sudden cardiac death—a case report. *Indian J Psychiatry*. 2004;46(1):79–80.
79. Taylor D. Ziprasidone in the management of schizophrenia: the QT interval issue in context. *CNS Drugs*. 2003;17(6):423–430.
80. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*. 2001;158(11):1774–1782.
81. Mandrioli R, Protti M, Mercolini L. Evaluation of the pharmacokinetics, safety and clinical efficacy of ziprasidone for the treatment of schizophrenia and bipolar disorder. *Expert Opin Drug Metab Toxicol*. 2015;11(1):149–174.
82. Boggs D, Ranganathan M, Boggs A, Bihday C, Peluse B, D'Souza D. Treatment of hyperprolactinemia and gynecomastia with adjunctive aripiprazole in 2 men receiving long-acting injectable antipsychotics. *Prim Care Companion CNS Disord*. 2013;15(4):4088. doi:10.4088/PCC.13l01519
83. Chen J-X, Su Y-A, Bian Q-T, et al. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: a randomized, double-blind,

placebo-controlled, dose–response study. *Psychoneuroendocrinology*. 2015;58:130–140. doi:10.1016/j.psyneuen.2015.04.011

84. Kelly DL, Wehring HJ, Earl AK, et al. Treating symptomatic hyperprolactinemia in women with schizophrenia: presentation of the ongoing DAAMSEL clinical trial (Dopamine partial Agonist, Aripiprazole, for the Management of Symptomatic Elevated prolactin). *BMC Psychiatry*. 2013;13(1):214. doi:10.1186/1471-244X-13-214
85. Cohen J, Magalon D, Boyer L, Simon N, Christophe L. Aripiprazole-induced pathological gambling: a report of 3 cases. *Curr Drug Saf*. 2011;6(1):51–53. doi:10.2174/157488611794480016
86. Gaboriau L, Victorri-Vigneau C, Gérardin M, Allain-Veyrac G, Jolliet-Evin P, Grall-Bronnec M. Aripiprazole: a new risk factor for pathological gambling? A report of 8 case reports. *Addict Behav*. 2014;39(3):562–565. doi:10.1016/j.addbeh.2013.11.005
87. Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2015;(9):870–880. doi:10.1176/appi.ajp.2015.14101275
88. Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015;164(1–3):127–135. doi:10.1016/j.schres.2015.01.038
89. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther*. 2014;350(3):589–604. doi:10.1124/jpet.114.213793
90. Rexulti (brexpiprazole) tablets. Package insert. Osutka Pharmaceutical Co Ltd; December 2021.
91. Werner FM, Covenas R. New developments in the management of schizophrenia and bipolar disorder: potential use of cariprazine. *Ther Clin Risk Manag*. 2015;11:1657–1661. doi:10.2147/TCRM.S64915
92. Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international, phase III clinical trial. *J Clin Psychopharmacol*. 2015;35(4):367–373. doi:10.1097/JCP.0000000000000346
93. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disord*. 2015;174:296–302. doi:10.1016/j.jad.2014.11.018
94. Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. *Schizophr Res*. 2014;152(2–3):450–457. doi:10.1016/j.schres.2013.11.041
95. Citrome L. Iloperidone for schizophrenia: a review of the efficacy and safety profile for this newly commercialised second-generation antipsychotic. *Int J*

Clin Pract. 2009;63(8):1237–1248.
96. Cutler AJ, Kalali AH, Weiden PJ, Hamilton J, Wolfgang CD. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. 2008;28(2 Suppl 1):S20–S28. doi:10.1097/JCP.0b013e318169d4ce
97. Henry JM, Fuller M. Asenapine: a new antipsychotic option. *J Pharm Pract*. 2011;24(5):447–451. doi:10.1177/0897190011422875
98. Harvey PD. The clinical utility of lurasidone in schizophrenia: patient considerations. *Neuropsychiatr Dis Treat*. 2015;11:1103–1109.
99. Pahwa M, Sleem A, Elsayed OH, Good ME, El-Mallakh RS. New antipsychotic medications in the last decade. *Curr Psychiatry Rep*. 2021;23(12):87. doi:10.1007/s11920-021-01298-w
100. Greenwood J, Acharya RB, Marcellus V, Rey JA. Lumateperone: a novel antipsychotic for schizophrenia. *Ann Pharmacother*. 2021;55(1):98–104. doi:10.1177/1060028020936597
101. Kane JM, Durgam S, Satlin A, et al. Safety and tolerability of lumateperone for the treatment of schizophrenia: a pooled analysis of late-phase placebo- and active-controlled clinical trials. *Int Clin Psychopharmacol*. 2021;36(5):244–250. doi:10.1097/YIC.0000000000000371
102. Segman RH, Heresco-Levy U, Finkel B, et al. Association between the serotonin 2A receptor gene and tardive dyskinesia in chronic schizophrenia. *Mol Psychiatry*. 2001;6(2):225–229. doi:10.1038/sj.mp.4000842
103. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry*. 1997;154(4):457–465. doi:10.1176/ajp.154.4.457
104. Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol*. 2010;30(2):106–115. doi:10.1097/JCP.0b013e3181d35d6b
105. Moore T, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry*. 2007;68(11):1751–1762. doi:10.4088/JCP.v65n0408
106. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):71–93. doi:10.1093/schbul/sbp116
107. National Collaborating Centre for Mental Health (UK). *Psychosis and Schizophrenia in Adults: Treatment and Management*. National Institute for Health and Care Excellence (UK); 2014. NICE Clinical Guidelines, No 178. . https://www.nice.org.uk/guidance/cg178
108. Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. A simple and valid tool distinguished efficacy from effectiveness studies. *J Clin Epidemiol*. 2006;59(10):1040–1048.

109. Stroup T, Mcevoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophr Bull*. 2003;29(1):15–31.
110. Stroup TS, Lieberman JA, Mcevoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006;163(4):611–622. doi:10.1176/appi.ajp.163.4.611
111. McEvoy JP, Lieberman J, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry*. 2006;163(4):600–610. doi:10.1176/appi.ajp.163.4.600
112. Stroup TS, Lieberman JA, McEvoy JP, et al. Results of phase 3 of the CATIE schizophrenia trial. *Schizophr Res*. 2009;107(1):1–12. doi:10.1016/j.schres.2008.10.011
113. Lewis S, Lieberman J. CATIE and CUtLASS: can we handle the truth? *Br J Psychiatry*. 2008;192(3):161–163. doi:10.1192/bjp.bp.107.037218
114. Lewis SW, Davies L, Jones PB, et al. Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. *Health Technol Assess (Rockv)*. 2006;10(17):iii–iv, ix–xi, 1–165. doi:10.3310/hta10170
115. Boter H, Peuskens J, Libiger J, et al. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). *Schizophr Res*. 2009;115(2–3):97–103. doi:10.1016/j.schres.2009.09.019
116. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373(9657):31–41. doi:10.1016/S0140-6736(08)61764-X
117. Zink M, Englisch S, Meyer-Lindenberg A. Polypharmacy in schizophrenia. *Nervenarzt*. 2011;82(7):853–858. doi:10.1097/YCO.0b013e3283366427
118. Kogut SJ, Yam F, Dufresne R. Prescribing of antipsychotic medication in a Medicaid population: use of polytherapy and off label dosages. *J Manag Care Pharm*. 2005;11(1):17–24.
119. Centorrino F, Goren JL, Hennen J, Salvatore P, Kelleher JP, Baldessarini RJ. Multiple versus single antipsychotic agents for hospitalized psychiatric patients: case-control study of risks versus benefits. *Am J Psychiatry*. 2004;161(4):700–706. doi:10.1176/appi.ajp.161.4.700
120. Barnes TRE, Paton C. Antipsychotic polypharmacy in schizophrenia: benefits and risks. *CNS Drugs*. 2011;25(5):383–399. doi:10.2165/11587810-000000000-00000

121. Goren JL, Beck SE, Mills BJ, et al. Development and delivery of a quality improvement program to reduce antipsychotic polytherapy. *J Manag Care Pharm*. 2010;16(6):393–401.
122. Preskorn SH, Lacey RL. Polypharmacy: when is it rational? *J Psychiatr Pract*. 2007;13(2):97–105. doi:10.1097/01.pra.0000265766.25495.3b
123. Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophr Bull*. 2009;35(2):443–457. doi:10.1093/schbul/sbn018
124. Strassnig M, Harvey P. Treatment resistance and other complicating factors in the management of schizophrenia. *CNS Spectr*. 2014;19:16–24.
125. Battaglia J. Pharmacological management of acute agitation. *Drugs*. 2005;65(9):1207–1222. doi:10.2165/00003495-200565090-00003
126. Citrome L. Comparison of intramuscular ziprasidone, olanzapine, or aripiprazole for agitation: a quantitative review of efficacy and safety. *J Clin Psychiatry*. 2007;68(12):1876–1885.
127. Geodon (ziprasidone HCl). Package insert. Pfizer; February 2022.
128. McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. *J Clin Psychiatry*. 2006;67(suppl 5):15–18.
129. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry*. 2013;74(10):957–965. doi:10.4088/JCP.13r08440
130. Buckley PF, Schooler NR, Goff DC, et al. Comparison of SGA oral medications and a long-acting injectable SGA: the PROACTIVE study. *Schizophr Bull*. 2015;41(2):449–459. doi:10.1093/schbul/sbu067
131. Kishimoto T, Robenzadeh A, Leucht C, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40(1):192–213. doi:10.1093/schbul/sbs150
132. Buckley PF, Schooler NR, Goff DC, et al. Comparison of injectable and oral antipsychotics in relapse rates in a pragmatic 30-month schizophrenia relapse prevention study. *Psychiatric Serv*. 2016;67:1370–1372. doi:10.1176/appi.ps.201500466
133. Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med*. 2011;364(9):842–851. doi:10.1056/NEJMoa1005987
134. Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. *JAMA Psychiatry*. 2015;72(8):822–829. doi:10.1001/jamapsychiatry.2015.0270
135. Kane JM, Schooler NR, Marcy P, et al. Effect of long-acting injectable antipsychotics vs usual care on time to first hospitalization in early-phase

schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2020;77(12):1217–1224. doi:10.1001/jamapsychiatry.2020.2076

136. Ereshefsky L, Toney G, Saklad SR, Anderson C, Seidel D. A loading-dose strategy for converting from oral to depot haloperidol. *Hosp Community Psychiatry*. 1993;44(12):1155–1161.
137. Yadalam KG, Simpson GM. Changing from oral to depot fluphenazine. *J Clin Psychiatry*. 1988;49(9):346–348.
138. Carpenter WT Jr, Buchanan RW, Kirkpatrick B, Lann HD, Breier AF, Summerfelt AT. Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. *Am J Psychiatry*. 1999;156(3):412–418. doi:10.1176/ajp.156.3.412
139. Citrome L. Aripiprazole long-acting injectable formulations for schizophrenia: aripiprazole monohydrate and aripiprazole lauroxil. *Expert Rev Clin Pharmacol*. 2014;9(2):169–186.
140. Tauscher J, Jones C, Remington G, Zipursky RB, Kapur S. Significant dissociation of brain and plasma kinetics with antipsychotics. *Mol Psychiatry*. 2002;7(3):317–321. doi:10.1038/sj.mp.4001009
141. Pfeiffer PN, Ganoczy D, Valenstein M. Dosing frequency and adherence to antipsychotic medications. *Psychiatr Serv*. 2008;59(10):1207–1210. doi:10.1176/appi.ps.59.10.1207
142. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia*. 2013;54(1):11–27. doi:10.1111/j.1528-1167.2012.03671.x
143. Kennedy WK, Jann MW, Kutscher EC. Clinically significant drug interactions with atypical antipsychotics. *CNS Drugs*. 2013;27(12):1021–1048. doi:10.1007/s40263-013-0114-6
144. Rosenheck RA, Leslie DL, Busch S, Rofman ES, Sernyak M. Rethinking antipsychotic formulary policy. *Schizophr Bull*. 2008;34(2):375–380. doi:10.1093/schbul/sbm089
145. Stagnitti MN. Trends in antipsychotics purchases and expenses for the U.S. civilian noninstitutionalized population, 1997 and 2007. *Agency Healthc Res Qual*. 2016;30. http://www.meps.ahrq.gov/mepsweb/data_files/publications/st275/stat275.pdf
146. Seabury SA, Goldman DP, Kalsekar I, Sheehan JJ, Laubmeier K, Lakdawalla DN. Formulary restrictions on atypical antipsychotics: impact on costs for patients with schizophrenia and bipolar disorder in Medicaid. *Am J Manag Care*. 2014;20(2):e52–e60.
147. Peluso MJ, Lewis SW, Barnes TRE, Jones PB. Extrapyramidal motor side-effects of first- and second-generation antipsychotic drugs. *Br J Psychiatry*. 2012;200(5):387–392. doi:10.1192/bjp.bp.111.101485
148. Holloman LC, Marder SR. Management of acute extrapyramidal effects induced by antipsychotic drugs. *Am J Heal Pharm*. 1997;54(21):2461–2477.

149. Factor SA, Friedman JH, Lannon MC, Oakes D, Bourgeois K. Clozapine for the treatment of drug-induced psychosis in Parkinson's disease: results of the 12 week open label extension in the PSYCLOPS trial. *Mov Disord*. 2001;16(1):135–139. doi:10.1002/1531-8257(200101)16:1<135::AID-MDS1006>3.0.CO;2-Q
150. The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med*. 1999;340:757–763.
151. Friedman JH. Managing idiopathic Parkinson's disease in patients with schizophrenic disorders. *Parkinsonism Relat Disord*. 2011;17(3):198–200. doi:10.1016/j.parkreldis.2010.11.019
152. Dufresne RL, Wagner RL. Antipsychotic-withdrawal akathisia versus antipsychotic-induced akathisia: further evidence for the existence of tardive akathisia. *J Clin Psychiatry*. 1988;49(11):435–438.
153. Barnes TR, Braude WM. Akathisia variants and tardive dyskinesia. *Arch Gen Psychiatry*. 1985;42(9):874–878. doi:10.1097/00004714-198602000-00012
154. Barnes TRE. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;154:672–676. doi:10.1192/bjp.154.5.672
155. Citrome L, Dufresne R, Dyad J. Tardive dyskinesia: minimizing risk and improving outcomes in schizophrenia and other disorders. *Am J Manag Care*. 2007;(December):1–12. http://www.ajmc.com/journals/supplement/2007/2007-12-vol12-n1-decisionmakernews/dec07-2760p1-12
156. Margolese HC, Chouinard G, Kolivakis TT, Beauclair L, Miller R. Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 1: pathophysiology and mechanisms of induction. *Can J Psychiatry*. 2005;50(9):541–547.
157. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry*. 2004;161(3):414–425. doi:10.1176/appi.ajp.161.3.414
158. Jeste DV. Tardive dyskinesia in older patients. *J Clin Psychiatry*. 2000;61(S4):27–32.
159. Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? *Mov Disord*. 2006;21(5):589–598. doi:10.1002/mds.20823
160. Casey DE. Tardive dyskinesia: pathophysiology and animal models. *J Clin Psychiatry*. 2000;61(S4):5–9.
161. Glazer WM. Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. *J Clin Psychiatry*. 2000;61(S4):15–20.
162. Remington G. Tardive dyskinesia: eliminated, forgotten, or overshadowed? *Curr Opin Psychiatry*. 2007;20(2):131–137. doi:10.1097/YCO.0b013e328017f6b1
163. Bergman J, Dwolatzky T, Brettholz I, Lerner V. Beneficial effect of donepezil in the treatment of elderly patients with tardive movement disorders. *J Clin*

Psychiatry. 2005;66(1):107–110. doi:10.4088/JCP.v66n0115

164. Weber SS, Dufresne RL, Becker RE, Mastrati P. Diazepam in tardive dyskinesia. *Drug Intell Clin Pharm*. 1983;17(7–8):523–527.
165. Bhidayasiri R, Fahn S, Weiner WJ, Gronseth GS, Sullivan KL, Zesiewicz TA. Evidence-based guideline: treatment of tardive syndromes: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2013;81(5):463–469. doi:10.1212/WNL.0b013e31829d86b6
166. Mahata M, Mahata SK, Parmer RJ, O'Connor DT. Vesicular monoamine transport inhibitors: novel action at calcium channels to prevent catecholamine secretion. *Hypertension*. 1996;28:414–420. doi.org/10.1161/01.HYP.28.3.414
167. Hauser RA, Factor SA, Marder SR, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry*. 2017;174(5):476–484.
168. Factor SA, Remington G, Comella CL, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *J Clin Psychiatry*. 2017;78(9):1344–1350.
169. Marder SR, Singer C, Lindenmayer JP, et al. A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia. *J Clin Psychopharmacol*. 2019;39(6):620–627.
170. Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Psychiatry*. 2017;4(8):595–604.
171. Hauser RA, Barkay H, Fernandez HH, et al. Long-term deutetrabenazine treatment is associated with continued improvement in tardive dyskinesia in the completed 3-year open-label extension study. Presented at: the 26th National Psychopharmacology Update Virtual Meeting; February 10–13, 2021.
172. Tenback DE, Van Harten PN, Slooff CJ, Belger MA, Van Os J. Effects of antipsychotic treatment on tardive dyskinesia: a 6-month evaluation of patients from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *J Clin Psychiatry*. 2005;66(9):1130–1133. doi:10.1016/S0084-3970(08)70526-7
173. Hideaki T, Uchida H, Suzuki T, Shibuya Y, Shimanuki H, Watanabe K. Dental conditions in inpatients with schizophrenia: a large-scale multi-site survey. *BMC Oral Health*. 2012;12:32.
174. Nielsen J, Meyer JM. Risk factors for ileus in patients with schizophrenia. *Schizophr Bull*. 2012;38(3):592–598. doi:10.1093/schbul/sbq137
175. Desmarais JE, Beauclair L, Margolese HC. Anticholinergics in the era of atypical antipsychotics: short-term or long-term treatment? *J Psychopharmacol*. 2012;26(9):1167–1174. doi:10.1177/0269881112447988

176. Leung JYT, Barr AM, Procyshyn RM, Honer WG, Pang CCY. Cardiovascular side-effects of antipsychotic drugs: the role of the autonomic nervous system. *Pharmacol Ther*. 2012;135(2):113–122. doi:10.1016/j.pharmthera.2012.04.003
177. Iqbal MM, Rahman A, Husain Z, Mahmud SZ, Ryan WG, Feldman JM. Clozapine: a clinical review of adverse effects and management. *Ann Clin Psychiatry*. 2003;15(1):33–48.
178. Miller DD. Review and management of clozapine side effects. *J Clin Psychiatry*. 2000;61(Suppl 8):14–19.
179. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics*. 2013;54(1):1–13. doi:10.1016/j.psym.2012.11.001
180. FDA Psychopharmacological Drugs Advisory Committee. Briefing Document for Zeldox Capsules (Ziprasidone HCl). 19 July 2000.
181. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol*. 2004;24(1):62–69. doi:10.1097/01.jcp.0000104913.75206.62
182. Potkin SG, Preskorn S, Hochfeld M, Meng X. A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. *J Clin Psychopharmacol*. 2013;33(1):3–10.
183. Funk MC, Beach SR, Bostwick JR, et al. Resource document on QTc prolongation and psychotropic medications. American Psychiatric Association Resource Documents website. June 2018. Accessed February 25, 2022. https://www.psychiatry.org/File%20Library/Psychiatrists/Directories/Library-and-Archive/resource_documents/Resource-Document-2018-QTc-Prolongation-and-Psychotropic-Med.pdf
184. Bostwick JR, Guthrie SK, Ellingrod VL. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy*. 2009;29(1):64–73. doi:10.1097/JCP.0b013e31818ba5d8
185. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962. doi:10.1016/S0140-6736(13)60733-3
186. Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB, Schizophrenia Patient Outcomes Research Team. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. *Schizophr Bull*. 2010;36(1):94–103. doi:10.1093/schbul/sbp130
187. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(2):273–288. doi:10.1210/jc.2010-1692

188. Lehman AF, Kreyenbuhl J, Buchanan RW, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. *Schizophr Bull*. 2004;30(2):193–217.
189. Yasui-Furukori N, Furukori H, Sugawara N, Fujii A, Kaneko S. Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. *J Clin Psychopharmacol*. 2010;30(5):596–599. doi:10.1097/JCP.0b013e3181ee832d
190. Kane JM, Correll CU, Goff DC, et al. A multicenter, randomized, double-blind, placebo-controlled, 16-week study of adjunctive aripiprazole for schizophrenia or schizoaffective disorder inadequately treated with quetiapine or risperidone monotherapy. *J Clin Psychiatry*. 2009;70(10):1348–1357. doi:10.4088/JCP.09m05154yel
191. Shim JC, Shin JGK, Kelly DL, et al. Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. *Am J Psychiatry*. 2007;164(9):1404–1410. doi:10.1176/appi.ajp.2007.06071075
192. Kinon BJ, Kaiser CJ, Ahmed S, Rotelli MD, Kollack-Walker S. Association between early and rapid weight gain and change in weight over one year of olanzapine therapy in patients with schizophrenia and related disorders. *J Clin Psychopharmacol*. 2005;25(3):255–258. doi:10.1097/01.jcp.0000161501.65890.22
193. Jaton LA, Kinon BJ, Rotelli MD, Kaiser C, Kollack-Walker S. Differential rate of weight gain present among patients treated with olanzapine. *Schizophr Res*. 2003;S357(60):s0920–s9964. doi:10.101603801706
194. Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry*. 2002;159(4):561–566. doi:10.1176/appi.ajp.159.4.561
195. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry*. 2002;59(4):337–345.
196. Ryan MCM, Thakore JH. Physical consequences of schizophrenia and its treatment: the metabolic syndrome. *Life Sci*. 2002;71(3):239–257. doi:10.1016/S0024-3205(02)01646-6
197. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology*. 2003;28(3):519–526.
198. Poyurovsky M, Pashinian A, Levi A, Weizman R, Weizman A. The effect of betahistine, a histamine H1 receptor agonist/H3 antagonist, on olanzapine-induced weight gain in first-episode schizophrenia patients. *Int Clin Psychopharmacol*. 2005;20(2):101–103.
199. Ellingrod VL, Perry PJ, Ringold JC, et al. Weight gain associated with the-759C/T polymorphism of the 5HT2C receptor and olanzapine. *Am J Med*

Genet B Neuropsychiatr Genet. 2005;134B(1):76–78.

200. Reynolds GP, Zhang Z-J, Zhang X-B. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. *Lancet*. 2002;359(9323):2086–2087.
201. Silvestre JS, Prous J. Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. *Methods Find Exp Clin Pharmacol*. 2005;27(5):289–304.
202. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics. *J Clin Psychiatry*. 2003;64(5):598–604. doi:10.4088/JCP.v64n0516
203. Hägg S, Söderberg S, Ahrén B, Olsson T, Mjörndal T. Leptin concentrations are increased in subjects treated with clozapine or conventional antipsychotics. *J Clin Psychiatry*. 2001;62(11):843–848. doi:10.4088/JCP.v62n1102
204. Ellingrod VL, Bishop JR, Moline J, Lin Y-C, Miller DD. Leptin and leptin receptor gene polymorphisms and increases in body mass index (BMI) from olanzapine treatment in persons with schizophrenia. *Psychopharmacol Bull*. 2007;40(1):57–62.
205. Laimer M, Kramer-Reinstadler K, Rauchenzauner M, et al. Effect of mirtazapine treatment on body composition and metabolism. *J Clin Psychiatry*. 2006;67(3):421–424. doi:10.4088/JCP.v67n0313
206. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596–601.
207. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry*. 2000;157(6):975–981. doi:10.1176/appi.ajp.157.6.975
208. Dufresne RL. Weighing in: emergent diabetes mellitus and second-generation antipsychotics. *Ann Pharmacother*. 2007;41(10):1725–1727. doi:10.1345/aph.1K362
209. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry*. 1999;60(11):783–791.
210. Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. *Arch Gen Psychiatry*. 2001;58(12):1172–1176. doi:10.1001/archpsyc.58.12.1172
211. Marder SR, Essock SM, Miller AL, et al. The Mount Sinai conference on the pharmacotherapy of schizophrenia. *Schizophr Bull*. 2002;28(1):5–16.
212. Ghaeli P, Dufresne RL. Elevated serum triglycerides with clozapine resolved with risperidone in four patients. *Pharmacotherapy*. 1999;19(9):1099–1101. doi:10.1592/phco.19.13.1099.31586

213. Kingsbury SJ, Fayek M, Trufasiu D, Zada J, Simpson GM. The apparent effects of ziprasidone on plasma lipids and glucose. *J Clin Psychiatry*. 2001;62(5):347–349.
214. Cohen S, Fitzgerald B, Okos A, Khan S, Khan A. Weight, lipids, glucose, and behavioral measures with ziprasidone treatment in a population with mental retardation. *J Clin Psychiatry*. 2003;64(1):60–62.
215. Newcomer JW, Meyer JM, Baker RA, et al. Changes in non-high-density lipoprotein cholesterol levels and triglyceride/high-density lipoprotein cholesterol ratios among patients randomized to aripiprazole versus olanzapine. *Schizophr Res*. 2008;106(2–3):300–307.
216. McGrath JJ. Myths and plain truths about schizophrenia epidemiology—the NAPE lecture 2004. *Acta Psychiatr Scand*. 2005;111(1):4–11. doi:10.1111/j.1600-0447.2004.00467.x
217. Goethe JW, Szarek BL, Caley CF, Woolley SB. Signs and symptoms associated with the metabolic syndrome in psychiatric inpatients receiving antipsychotics: a retrospective chart review. *J Clin Psychiatry*. 2007;68(1):22–28.
218. Enez Darcin A, Yalcin Cavus S, Dilbaz N, Kaya H, Dogan E. Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings. *Schizophr Res*. 2015;166(1–3):201–206. doi:10.1016/j.schres.2015.05.004
219. Weissman EM, Zhu CW, Schooler NR, Goetz RR, Essock SM. Lipid monitoring in patients with schizophrenia prescribed second-generation antipsychotics. *J Clin Psychiatry*. 2006;67(9):1323–1326. doi:10.4088/JCP.v67n0901
220. Saari KKM, Lindeman SMS, Viilo KM, et al. A 4-fold risk of metabolic syndrome in patients with schizophrenia: the Northern Finland 1966 Birth Cohort study. *J Clin Psychiatry*. 2005;66(5):559–563.
221. Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease: a non-systematic review of epidemiology, possible causes, and interventions. *Front Psychiatry*. 2014;5(September):1–11. doi:10.3389/fpsyt.2014.00137
222. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism. A public health concern. *Am J Prev Med*. 2010;38(4 Suppl):S495–S501. doi:10.1016/j.amepre.2009.12.017
223. Masopust J, Malý R, Vališ M. Risk of venous thromboembolism during treatment with antipsychotic agents. *Psychiatry Clin Neurosci*. 2012;66(7):541–552. doi:10.1111/pcn.12001
224. Zhang R, Dong L, Shao F, Tan X, Ying K. Antipsychotics and venous thromboembolism risk: a meta-analysis (Provisional abstract). *Pharmacopsychiatry*. 2011;44(5):183–188.
225. Paciullo CA. Evaluating the association between clozapine and venous thromboembolism. *Am J Heal Pharm*. 2008;65(19):1825–1829.

doi:10.2146/ajhp070638
226. Brunet N, Dufresne RL, Price C, Vestner AL. Venous thromboembolism in patients prescribed aripiprazole: a case series. In: *Presented at the 49th ASHP Midyear Clinical Meeting and Exhibition on December 7–11,* 2014 *in Anaheim, California*.
227. Srihari VH, Lee TW. Pulmonary embolism in a patient taking clozapine. *BMJ*. 2008;336(7659):1499–1501. doi:10.1136/bmj.39545.690613.47
228. Allenet B, Schmidlin S, Genty C, Bosson J-L. Antipsychotic drugs and risk of pulmonary embolism. *Pharmacoepidemiol Drug Saf*. 2011;21(1):42–48.
229. Liperoti R, Pedone C, Lapane KL, Mor V, Bernabei R, Gambassi G. Venous thromboembolism among elderly patients treated with atypical and conventional antipsychotic agents. *Arch Intern Med*. 2014;165(22):2677–2682. doi:10.1001/archinte.165.22.2677
230. Layton D, Harris S, WIlton LSS. Comparison of incidence rates of cerebrovascular accidents and transient ischaemic attacks in observational cohort studies of patients prescribed risperidone, quetiapine or olanzapine in general practice in England including patients with dementia. *J Psychopharmacol*. 2005;19(5):473–482.
231. Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. *CMAJ*. 2002;167(11):1269–1270.
232. Huybrechts KF, Schneeweiss S, Gerhard T, et al. Comparative safety of antipsychotic medications in nursing home residents. *J Am Geriatr Soc*. 2012;60(3):420–429. doi:10.1055/s-0029-1237430.Imprinting
233. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934–1943.
234. Tse L, Barr AM, Scarapicchia V, Vila-Rodriguez F. Neuroleptic malignant syndrome: a review from a clinically oriented perspective. *Curr Neuropharmacol*. 2015;13(3):395–406.
235. Hoffmann MS, Oliveira LM, Lobato MIR, Belmonte-de-Abreu P. Heat stroke during long-term clozapine treatment: should we be concerned about hot weather? *Trends Psychiatry Psychother*. 2016;38(1):56–59. doi:10.1590/2237-6089-2015-0066
236. Elvevåg B, Maylor E, Gilbert A. Habitual prospective memory in schizophrenia. *BMC Psychiatry*. 2003;7:1–7. doi:10.1186/1471-244X-3-9
237. Davis JM. Maintenance therapy and the natural course of schizophrenia. *J Clin Psychiatry*. 1985;11(2):18–21.
238. Sendt K-V, Tracy DK, Bhattacharyya S. A systematic review of factors influencing adherence to antipsychotic medication in schizophrenia-spectrum disorders. *Psychiatry Res*. 2015;225(1–2):14–30. doi:10.1016/j.psychres.2014.11.002
239. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive

review of recent literature. *J Clin Psychiatry*. 2002;63(10):892–909.
240. Czobor P, Van Dorn RA, Citrome L, Kahn RS, Fleischhacker WW, Volavka J. Treatment adherence in schizophrenia: a patient-level meta-analysis of combined CATIE and EUFEST studies. *Eur Neuropsychopharmacol*. 2015:1–9. doi:10.1016/j.euroneuro.2015.04.003
241. Conley RR, Kelly DL. Management of treatment resistance in schizophrenia. *Biol Psychiatry*. 2001;50(11):898–911. doi:10.1016/s0006-3223(01)01271-9
242. Rosenheck RA. Outcomes, costs, and policy caution: a commentary on the cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). *Arch Gen Psychiatry*. 2006;63:1074–1087.
243. Agid O, Foussias G, Sc M, Hahn M, Sinyor M. Clozapine's role in the treatment of first-episode schizophrenia. *Treat Psychiatry*. 2013;170(February):146–151.
244. Manu P, Serpal D, Muir O, Kane JM, Correll CU. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. *Schizophr Res*. 2012;134(2–3):180–186.
245. Devinsky O, Honigfeld GPJ. Clozapine-related seizures. *Neurology*. 1991;41(3):369–371.
246. Varma S. Clozapine-related EEG changes and seizures: dose and plasma-level relationships. *Ther Adv Psychopharmacol*. 2011;1(2):47–66. doi:10.1177/2045125311405566
247. Lundblad W, Azzam PN, Gopalan P, Ross CA. Medical management of patients on clozapine: a guide for internists. *J Hosp Med*. 2015;10(8):537–543. doi:10.1002/jhm.2345
248. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr Scand*. 2015;132(4):231–240. doi:10.1111/acps.12416
249. Kane JM, Cornblatt B, Correll CU, et al. The field of schizophrenia: strengths, weaknesses, opportunities, and threats. *Schizophr Bull*. 2012;38(1):1–4. doi:10.1093/schbul/sbr131
250. Ronaldson KJ, Fitzgerald PB, Taylor AJ, McNeil JJ. Observations from 8 cases of clozapine rechallenge after development of myocarditis. *J Clin Psychiatry*. 2012;73(2):252–254. doi:10.4088/JCP.11l07467
251. Bird AM, Smith TL, Walton AE. Current treatment strategies for clozapine-induced sialorrhea. *Ann Pharmacother*. 2011;45(5):667–675. doi:10.1345/aph.1P761
252. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry*. 2011;44(6):195–235.
253. Perry PJ, Miller DD, Arndt SV, Cadoret RJ. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory

schizophrenic patients. *Am J Psychiatry*. 1991;148(2):231–235. doi:10.1176/ajp.148.2.231

254. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51(01/02):9–62. doi:10.1055/s-0043-116492
255. Ellison JC, Dufresne RL. A review of the clinical utility of serum clozapine and norclozapine levels. *Ment Health Clin [Internet]*. 2015;5(2):68–73. doi:10.9740/mhc.2015.03.068
256. Premkumar TS, Pick J. Lamotrigine for schizophrenia (Review). *Cochrane Database Syst Rev*. 2008;18(4):CD005962.
257. Leucht S, Helfer B, Dold M, Kissling W, McGrath JJ. Lithium for schizophrenia. *Cochrane Database Syst Rev*. 2015;10(10):CD003834. doi:10.1002/14651858.CD003834.pub3
258. Tseng PT, Chen YW, Chung W, et al. Significant effect of valproate augmentation therapy in patients with schizophrenia: a meta-analysis study. *MED*. 2016;95(4):e2475. doi:10.1097/MD.0000000000002475
259. Leucht S, Helfer B, Dold M, Kissling W, McGrath J. Carbamazepine for schizophrenia. *Cochrane Database Syst Rev*. 2014;5:CD001258. doi:10.1002/14651858.CD001258.pub3
260. An Der Heiden W, Könnecke R, Maurer K, Ropeter D, Häfner H. Depression in the long-term course of schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2005;255(3):174–184. doi:10.1007/s00406-005-0585-7
261. Caldwell CB, Gottesman II. Schizophrenics kill themselves too: a review of risk factors for suicide. *Schizophr Bull*. 1990;16(4):571–589. doi:10.1093/schbul/16.4.571
262. Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol*. 2010;24(4 Suppl):81–90. doi:10.1177/1359786810385490
263. Pompili M, Amador XF, Girardi P, et al. Suicide risk in schizophrenia: learning from the past to change the future. *Ann Gen Psychiatry*. 2007;6:10. doi:10.1186/1744-859X-6-10
264. Kasper S. Treatment of depressive symptoms with quetiapine. *Expert Rev Neurother*. 2003;3(4):417–423. doi:10.1586/14737175.3.4.417
265. Tollefson GD, Sanger TM, Lu Y, Thieme ME. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol [published correction appears in *Arch Gen Psychiatry* 1998;55(11):1052]. *Arch Gen Psychiatry*. 1998;55(3):250. doi:10.1001/archpsyc.55.3.250
266. Siris SG. Depression in schizophrenia: perspective in the era of “atypical” antipsychotic agents. *Am J Psychiatry*. 2000;157(9):1379–1389. doi:10.1176/appi.ajp.157.9.1379
267. Terevnikov V, Joffe G, Stenberg J-H. Randomized controlled trials of add-on antidepressants in schizophrenia. *Int J Neuropsychopharmacol*.

2015;18(9):1–14. doi:10.1093/ijnp/pyv049
268. Rummel C, Kissling W, Leucht S. Antidepressants as add-on treatment to antipsychotics for people with schizophrenia and pronounced negative symptoms: a systematic review of randomized trials. *Schizophr Res*. 2005;80(1):85–97. doi:10.1016/j.schres.2005.07.035
269. Plasky P. Antidepressant usage in schizophrenia. *Schizophr Bull*. 1991;17(4):649–657.
270. Einarson A, Boskovic R. Use and safety of antipsychotic drugs during pregnancy. *J Psychiatr Pr*. 2009;15:183–192.
271. American College of Obstetricians and Gynecologists. Use of psychiatric medications during pregnancy and lactation. *Obs Gynecol*. 2008;117(6):1472–1483.
272. Cohen LS, Viguera AC, McInerney KA, et al. Reproductive safety of second-generation antipsychotics: current data from the Massachusetts General Hospital national pregnancy registry for atypical antipsychotics. *Am J Psychiatry*. 2016;173(3):263–270. doi:10.1176/appi.ajp.2015.15040506
273. US Food and Drug Administration. FDA Drug Safety Communication: antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. 2017. Accessed February 23, 2022. http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm
274. Park Y, Hernandez-Diaz S, Bateman BT, et al. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. *Am J Psychiatry*. 2018;175(6):564–574. doi:10.1176/appi.ajp.2018.17040393
275. Correll CU, Robinson DG, Schooler NR, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry*. 2014;71(12):1350–1363. doi:10.1001/jamapsychiatry.2014.1314
276. McGorry PD, Nelson B, Amminger GP, et al. Intervention in individuals at ultra-high risk for psychosis: a review and future directions. *J Clin Psychiatry*. 2009;70(9):1206–1212. doi:10.4088/JCP.08r04472
277. Alvarez-Jimenez M, Parker AG, Hetrick SE, McGorry PD, Gleeson JF. Preventing the second episode: a systematic review and meta-analysis of psychosocial and pharmacological trials in first-episode psychosis. *Schizophr Bull*. 2011;37(3):619–630. doi:10.1093/schbul/sbp129
278. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007;164(7):1050–1060. doi:10.1176/ajp.2007.164.7.1050
279. Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry*. 2005;162(5):947–953. doi:10.1176/appi.ajp.162.5.947

280. Sanger TM, Lieberman JA, Tohen M, Grundy S, Beasley C Jr, Tollefson GD. Olanzapine versus haloperidol treatment in first-episode psychosis. *Am J Psychiatry*. 1999;156(1):79–87. doi:10.1176/ajp.156.1.79
281. Cannon TD, Cadenhead K, Cornblatt B, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry*. 2008;65(1):28–37. doi:10.1001/archgenpsychiatry.2007.3
282. Amminger GP. Long-chain omega3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *JAMA*. 2010;67(2):146–154.
283. Amminger GP, McGorry PD. Update on omega-3 polyunsaturated fatty acids in early-stage psychotic disorders. *Neuropsychopharmacology*. 2012;37(1):309–310. doi:10.1038/npp.2011.187
284. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry*. 2016;173(4):362–372. doi:10.1176/appi.ajp.2015.15050632
285. Birchwood M, Lester H, McCarthy L, et al. The UK national evaluation of the development and impact of Early Intervention Services (the National EDEN studies): study rationale, design and baseline characteristics. *Early Interv Psychiatry*. 2014;8(1):59–67. doi:10.1111/eip.12007
286. Marshall M, Husain N, Bork N, et al. Impact of early intervention services on duration of untreated psychosis: data from the National EDEN prospective cohort study. *Schizophr Res*. 2014;159(1):1–6. doi:10.1016/j.schres.2014.07.005
287. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry*. 2005;62(9):975–983.
288. Keefe RSE, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry*. 2007;64(6):633–647. doi:10.1001/archpsyc.64.6.633
289. Eack SM, Greenwald DP, Hogarty SS, et al. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatr Serv*. 2009;60(11):1468–1476. doi:10.1176/appi.ps.60.11.1468
290. Eack SM, Greenwald DP, Hogarty SS, Keshavan MS. One-year durability of the effects of cognitive enhancement therapy on functional outcome in early schizophrenia. *Schizophr Res*. 2010;120(1–3):210–216. doi:10.1016/j.schres.2010.03.042
291. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56(3):241–247.

292. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry*. 2007;68(5):654–661.
293. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry*. 2013;70(9):913–920. doi:10.1001/jamapsychiatry.2013.19

86

Depressive Disorders

Michael C. Angelini

CORE PRINCIPLES		CHAPTER CASES
1	Depression is a common and often chronic disorder that may manifest at any time in an individual's life. Diagnostic criteria for major depression include a minimum of five symptoms persisting for at least 2 weeks. One of these symptoms must be either depressed mood or anhedonia. Suicidal ideation should be assessed in all patients.	**Case 86-1 (Question 1), Table 86-4**

CORE PRINCIPLES		CHAPTER CASES
2	A variety of treatment modalities are available for the management of depression. These include prescription medications, psychotherapy, and somatic treatments. Prescription medications and/or psychotherapy are indicated for depressive symptoms that are moderate to severe in nature, whereas somatic treatments are for severe refractory cases.	**Case 86-1 (Question 2)** **Case 86-2 (Questions 1, 2)** **Case 86-3 (Question 2)**
3	All of the prescription medications that are currently available are equally effective and possess the same delayed onset of therapeutic effects. Selection of an antidepressant is based on many factors, including previous response to medication, age, reproduction status, and both medical and psychiatric comorbidities.	**Case 86-1 (Questions 2, 4)** **Case 86-2 (Question 2)** **Case 86-4 (Question 1), Table 86-6**
4	Selective serotonin reuptake inhibitors are regarded as the initial treatment of choice for most depressed patients. They are inexpensive and effective for comorbid anxiety conditions and possess a lower side effect burden than other antidepressants overall. Side effects are generally mild and transient.	**Case 86-1 (Question 2)** **Case 86-2 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
5	Educating the patient regarding side effects, how to monitor for efficacy, and the duration of treatment are important actions for successful treatment.	**Case 86-1 (Question 3)** **Case 86-3 (Question 3), Table 86-10**
6	The goal of antidepressant treatment is remission of symptoms. Once remission is achieved, the general recommendation is to continue the effective antidepressant regimen for a minimum of 6 months.	**Case 86-1 (Question 3), Table 86-10**
7	Because only half of depressed patients will achieve remission with the first antidepressant selected, clinicians should have a comprehensive understanding of the role many antidepressants may have in optimizing outcomes. Clinicians should be familiar with switching antidepressants in patients with an incomplete response and the merits of augmentation strategies.	**Case 86-2 (Questions 1–3)**
8	Untreated depression in children under 18 has a significant risk of suicide. Treatment consists of talking therapy and specific antidepressants, which is different than the broad options available to adults.	**Case 86-3 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
9	Depression and chronic pain are commonly comorbid, and pharmacologic treatment that addresses both is recommended. This makes the serotonin/norepinephrine–reuptake inhibitor class of antidepressants preferred.	**Case 86-4 (Question 1)**

INTRODUCTION

Depressive disorders are enormous health concerns that are often misdiagnosed or undertreated. The physical and social dysfunction associated with depression is profound and is believed to outweigh many other chronic medical conditions, including hypertension, diabetes, and arthritis.[1] The Medical Outcomes Study determined that the degree of impairment in depressed individuals is comparable to that seen in patients with chronic heart disease.[2] The financial ramifications of depression are tremendous and place an overwhelming burden on our society. In 2010, the estimated cost of depression in the United States was $210.5 billion annually, with 45% to 47% attributed to direct costs and 48% related to workplace costs such as absenteeism.[3]

Epidemiology

Since World War II, the lifetime incidence of depression has been rising steadily in studied populations. The annual incidence of all mood disorders is ~10% in the adult population, and 1 in 15 adults (6.7%) will suffer from an episode of major depression during any 12-month period.[4] Various studies from Europe and the United

States have estimated the 1 year and lifetime prevalence to be 4.1% and 6.7%, respectively.[5] Although the incidence of depression is remarkably similar across various races and ethnic groups, the illness may be slightly more common in lower socioeconomic classes. Females have double the incidence compared to males.[1,5]

The onset of the first depressive episode may present at any age, although it most commonly occurs in the late 20s. Genetic factors appear to play a major role in the cause of depression. The offspring of depressed individuals are 2.7 times more likely to have depression if one parent is afflicted, and 3.0 times more likely if both parents suffer from depression.[6] Concordance rates for monozygotic (identical) twins range from 54% to 65%, whereas the corresponding rates in dizygotic (fraternal) twins range from 14% to 24%.[7] Genetic factors may also predispose individuals to an earlier onset of depression (younger than age 30 years).[8] Additionally, there is clear evidence that depression may occur as a result of stressful events (ie, environmental factors). These factors include a difficult childhood, physical or verbal abuse, pervasive low self-esteem, death of a loved one, loss of a job, and the end of a serious relationship. Acute depressive episodes are often attributed to a combination of environmental and genetic factors. For instance, individuals carrying a genetic predisposition to mood disorders may undergo a stressful experience that ultimately triggers the manifestation of depressive symptomatology. Depression may also occur spontaneously among people who appear to lack any obvious genetic or environmental predisposition.

Diagnosis and Classification

When assessing a person for depression, it is important to recognize the level of impairment because of the symptoms. Just as with all biologic systems, the body can function well within a particular range (eg, serum potassium or blood pressure). Mood is not different; as long as the depressive symptoms are not prolonged or impairing, there would be no reason to aggressively treat. Once the depression

is severe enough to impact functioning or induce harm, it requires treatment.

Major depressive disorder (MDD) may manifest as a single episode, but it is more commonly a series of recurrent events. Thus, in most patients, depression is a chronic illness.[5] The frequency of recurrent episodes is highly variable, with some people experiencing discrete episodes separated by many years of relatively normal mood (euthymia), and others experiencing residual depressive symptoms between episodes that may never completely remit. The risk of future episodes appears to increase with the chronicity of the illness. For instance, after the first episode, there is a 50% likelihood of a second episode. After the second, there is a 70% chance of a third, and with the third episode comes nearly a 90% incidence of a fourth.

The *Diagnostic and Statistical Manual of Mental Disorders 5th Edition* (*DSM-5*) describes different types of depressed states. These include disruptive mood dysregulation disorder, MDD, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder because of another medical condition, other specified depressive disorder, and unspecified depressive disorder (**Table 86-1**).[9] The different types of depressive disorders may then be subclassified using cross-sectional symptom features or specifiers. For example, the phrase “with anxious distress” infers that there are anxiety symptoms such as worry and feeling keyed up. The term “with mixed features” infers that there are manic or hypomanic symptoms. The term “with melancholic features” is used when patients possess primary neurovegetative symptoms, early morning awakening, marked psychomotor agitation or retardation, and significant anorexia or weight loss. Melancholia is often a more severe form of depression, and it often lacks apparent environmental triggers.[9,10] It may also be less likely than other forms of depression to remit spontaneously. The phrase “with atypical features” is used when depressive symptoms include weight gain, hypersomnia, leaden paralysis, or rejection sensitivity. When hallucinations or delusions occur in patients who are primarily depressed, the phrase

"with mood congruent or mood incongruent psychotic features" is applicable to the mood disorder. Other diagnostic specifiers used in *DSM-5* include "with catatonia," "with peripartum onset," and "with seasonal pattern."

Table 86-1
Classification of Depressive Disorders

1. Major depressive disorder
2. Persistent depressive disorder
3. Disruptive mood dysregulation disorder
4. Premenstrual dysphoric disorder
5. Substance/medication-induced depressive disorder
6. Depressive disorder because of another medical condition
7. Other specified depressive disorder
8. Unspecified depressive disorder

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

Persistent depressive disorder is a type of depressive illness characterized by fewer symptoms and less intensity than major depression, but the course is much more chronic with symptoms being present most of the time for at least 2 years. In practice, the detection of persistent depressive disorder may be difficult to make because patients often do not seek treatment because they are still functional (eg, go to school, work, care for children) but they have significant morbidity. They will have less satisfaction with work and will get fewer promotions and low financial advancements. The treatment for persistent depressive disorder has traditionally focused on psychotherapy, but evidence suggests that antidepressant medications may actually be more effective.[11]

Differential Diagnosis

Symptoms of depression may be induced or exacerbated by numerous medical illnesses or medications (**Tables 86-2** and **86-3**).[1,5,10] Consequently, *DSM-5* specifies that whenever a medical

event is temporally related to the onset of depressive symptoms, the patient does not fit the criteria for major depression, even if all other criteria are met.[9] The rationale for this stipulation is that if the medical illness is successfully treated or the offending agent is discontinued, the depressive illness would spontaneously resolve, eliminating the need for psychiatric intervention. Although lists of medical illnesses or medications are helpful, the clinician should be aware that the actual evidence demonstrating an association between depression and specific organic causes is limited. If a medication or condition is suspected of causing depression, the chronologic association should be investigated rigorously before other action is taken. Additionally, a patient with a medical illness such as a hormonal abnormality may have depressive symptoms from the condition but can additionally have concomitant MDD. Treating the medical condition will likely lessen the severity, but the MDD will still have to be treated as well.[1,5,10]

Table 86-2

Selected Medical Conditions That May Mimic Depression

Stroke
Parkinson disease
Dementia
Multiple sclerosis
Endocrine disorders
Metabolic conditions
Infectious diseases
Chronic pain

Source: *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. American Psychiatric Association; 2010.

Table 86-3

Selected Medications That May Induce Depression

Benzodiazepines
Corticosteroids

Interferon
Interleukin-2
Gonadotropin-releasing hormone agonists
Mefloquine
Oral and implanted oral contraceptives
High-dose lipophilic β-blockers
Antiepileptics
Varenicline

Source: Patten SB, Barbui C. Drug-induced depression: a systematic review to inform clinical practice. *Psychother Psychosom*. 2004;73(4):207–215.

Clinical Presentation

For a diagnosis of MDD to be made, symptoms must be present for at least 2 weeks and must not be precipitated or influenced by a medical illness or medication (according to *DSM-5* criteria). Individuals must possess at least five symptoms, one of which is either depressed mood or anhedonia (diminished interest or pleasure in activities). The other seven symptoms are as follows:

1. Change in appetite or significant weight loss or gain
2. Insomnia or hypersomnia
3. Psychomotor agitation or retardation
4. Fatigue or loss of energy
5. Feelings of worthlessness or inappropriate guilt
6. Poor concentration (or difficulty making decisions)
7. Recurrent thoughts of death or suicidal

The diagnostic criteria also state that the mood disturbance must cause marked distress or result in clinically significant impairment of social or occupational functioning. Additionally, the symptoms cannot be because of a medical or organic illness (**Table 86-4**).

Table 86-4
Diagnostic Criteria for Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observation made by others (eg, appears tearful) (*Note:* In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
3. Significant weight loss when not dieting or weight gain (eg, a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day (*Note:* In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiologic effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

Note: Responses to a significant loss (eg, bereavement, financial ruin, losses from a natural disaster, a serious medical illness, or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite,

and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode.
Note: This exclusion does not apply if all the manic-like or hypomanic-like episodes are substance induced or are attributable to the physiologic effects of another medical condition.

Reprinted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. © 2013 American Psychiatric Association. All Rights Reserved.

Pathophysiology

The monoamine hypothesis proposed that decreased synaptic concentrations of norepinephrine (NE) and/or serotonin (5-HT) caused depression. The NE depletion theory was originally based on the observation that reserpine, which depleted catecholamine stores in the central nervous system (CNS), was capable of causing depression.[12,13] This theory evolved into the permissive hypothesis, which emphasized a greater role for serotonin in promoting or "permitting" a decline in NE function. Specifically, this hypothesis suggests that low concentrations of serotonin or NE in the CNS precipitated depressive symptoms. Studies have shown that a 5-HT synthesis deficiency is correlated with depression. This has been shown in both persons genetically unable to produce 5-HT and those who have depleted precursors of 5-HT.[14,15] Selective serotonin reuptake inhibitor (SSRI) and serotonin/norepinephrine–reuptake inhibitor (SNRI) antidepressants, which functionally include the tricyclic antidepressants (TCAs), are believed to relieve depression

by inhibiting the reuptake of serotonin alone or serotonin and NE from the synapse up into the neuron, effectively increasing neurotransmitter concentrations in the synaptic cleft.[16,17] Mirtazapine and monoamine oxidase inhibitors (MAOIs) work via different mechanisms, but also increase 5-HT and NE (and DA for the MAOIs).[16,17]

Depression has been associated with changes in presynaptic and postsynaptic receptor densities (or sensitivities) that have been described as being downregulated or desensitized.[18] Changes include a decrease in postsynaptic α-adrenergic receptor sensitivity, along with alterations in the sensitivities of the α-adrenergic, dopaminergic (D_2), and serotonin-receptor subtypes ($5\text{-}HT_{1A}$ and $5HT_{2A}$). For example, SSRIs can increase the efficiency of serotonergic neurotransmission acutely (through reuptake blockade), but their therapeutic effects are linked temporally with increased release of serotonin through downregulation of presynaptic autoreceptors ($5\text{-}HT_{1A}$).[19] This downstream impact explains why there is a delay in maximal efficacy seen with all antidepressants.[14,15]

As our understanding of neurobiology increases, it has been found that other neurotransmitter systems can impact mood, and this has resulted in research for non–5-HT direct-effect medications to supplement or replace the monoamine-effecting antidepressants. Such mechanisms include blockade of substance P and antagonism of corticotropin-releasing factor or corticosteroid receptors.[20–23]

Neuroendocrine Findings

Along with dysregulated neurotransmitter systems, neuroendocrine abnormalities may contribute to the development of depression. Depressed patients often have abnormal thyroid function tests (including low triiodothyronine [T_3] and/or thyroxine [T_4] levels).[24] They also may exhibit an abnormal response to challenge with thyroid-releasing hormone, consisting of a blunted or exaggerated thyroid-stimulating hormone response.[25] Clinical hypothyroidism can also induce depressive symptoms, and thyroid supplementation can

reverse this pathology, suggesting an indirect association between mood disorders and thyroid homeostasis.[26] The hypothalamic–pituitary–adrenal (HPA) axis may also influence the manifestation of depression, with a relative hyperactivity of this system commonly reported in depressed individuals.[27–29] Pituitary and adrenal glands are often enlarged in depressed patients, and concentrations of corticotropin-releasing factor are often elevated during depressive episodes and decline with the administration of antidepressant medications or electroconvulsive therapy (ECT).[22,29,30] Exogenous administration of corticotropin-releasing factor has elicited classic symptoms of depression in laboratory animals (including decreased appetite, anxiety, insomnia, and decreased libido).[23] Loss of hippocampal volume in major depression leads to increased levels of circulating glucocorticoids, which leads to neuronal apoptosis.[31] Hypercortisolemia because of chronic stimulation of the HPA axis has been implicated in potentially reducing gray matter loss in humans. It should be noted that the relationship between hippocampal volume and depression is not consistently observed and that various factors may affect these findings.[32] Corticosteroids can also modulate serotonin synthesis, metabolism, and reuptake.[22] However, the data in this area are inconsistent because different medications will have differing effects on cortisol despite being effective as well as depressive subtypes showing different effects on cortisol.[33,34] Increased inflammatory markers are seen in prospective and postmortem studies of depressed patients.[27,29,35] There is also a positive correlation between inflammatory markers and increased glucocorticoid activity. Subsequently, there is a reduction in monoamine levels, particularly serotonin levels.[29]

Genetic Studies

Several genes have been implicated in predictive response or adverse effects to antidepressants. Pharmacodynamic targets have focused on serotonin transporters (5-HTTLPR), tryptophan hydroxylase enzymes 1 and 2 (TPH1 and TPH2), 5-HT_{1A} and 5-HT_{2A}

receptors, brain-derived neurotrophic factor (BDNF), G-protein β-3 subunit (GNB3), and monoamine oxidase enzymes and p-glycoprotein; pharmacokinetic targets have been focused on polymorphic variations in CYP1A2, CYP2C19, CYP2D6, and CYP3A4 enzymes.[36–38] Variations in the serotonin transporter *SLC6A4* gene have been associated with remission and response rate in a meta-analysis of 1435 patients.[37] Researchers found that patients with the *ss* genotype are less likely to reach remission during SSRI treatment and take longer to achieve 50% symptom improvement compared to those with the *ll* genotype. A review stated the genes *SLC6A4*, *HTR2A*, *BDNF*, *GNB3*, *FKBP5*, *ABCB1*, and cytochrome *P450* genes (*CYP2D6* and *CYP2C19*) as being the best correlated with depression.[39] Most likely there are multiple genes that are involved in disease phenotype, drug response, and toxicity. Genetic testing for abnormalities in CYP 450 pathways has shown that initial drug selection by clinicians has equal results as compared to pharmacogenetic-guided decisions but may be helpful in patients who have failed previous trials.[40,41] Gene–environment interactions undoubtedly also play a role in the determination of these phenotypes.

Imaging Studies and Biomarkers

Imaging studies (including computed tomography, magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography) suggest that patients with depression have regional brain dysfunction, most often affecting the limbic structures and prefrontal cortex. Alterations in cerebral blood flow and/or metabolism in the frontal–temporal cortex and caudate nucleus are associated with common depressive symptoms such as dysphoria, anhedonia, hopelessness, and flat affect.[42] Increased firing of the amygdala in the left hemisphere has been linked in positron emission tomography studies with the future development of depression.[43] Because subtypes of depression have been linked to different regional dysfunctions, a network hypothesis began to

emerge that may lead to improvements in depression diagnosis and targeted treatments.[44] There is also seemingly increased hippocampal loss that is consistent with the severity and duration of illness.[45]

Plasma biomarkers have been inconsistent in predicting and diagnosing MDD. One study found correlations with increased plasma gamma-aminobutyric acid (GABA) and dopamine metabolites along with decreased serotonin.[46,47]

Patient Assessment Tools

Behavioral rating scales have been used for many years in drug efficacy studies and are widely advocated for routine use in the clinical arena today. Rating scales are helpful in assessing the severity of mental illness, quantifying changes in target symptoms, and determining treatment efficacy, but they are not diagnostic. Rating scales can vary in length, content, and format and can be completed by providers, patients, researchers, family members, or conservators. Numerous depression scales have been developed, including the Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$ or $HAM\text{-}D_{21}$), the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), the Montgomery–Åsberg Depression Rating Scale (MADRS), the Center for Epidemiological Studies Depression (CES-D) Scale, the Patient Health Questionnaire (PHQ-9), and the Quick Inventory of Depressive Symptoms ($QIDS_{16}$ or $QIDS_{30}$) (**Table 86-5**).[48–54] Because 30% to 50% of cases are not detected in primary care, enhancing education of the clinicians in this area has shown some benefits. Generally, a two-step process of screening with a simple questionnaire, such as the PHQ-9 or the HADS, and then a more thorough evaluation if the screening results in a positive score are the recommended methods of detecting depression severe enough to require treatment.[5,55]

Table 86-5

Comparison of Selected Depression Rating Scales

Instrument	Minimal	Mild	Moderate	Severe
Hamilton (HAM-D)—17 item (clinician rated)	>8	8–15	16–27	>27
Beck Depression Inventory (BDI)				
BDI (clinician rated)	>10	10–16	17–29	>29
BDI (patient rated)	>10	10–15	16–23	>23
Quick Inventory for Depressive Symptoms (QIDS)				
QIDS-C_{16} (clinician rated)	>6	6–10	11–15	>15
QIDS-SR_{16} (patient rated)	>6	6–10	11–15	>15
Patient Health Questionnaire (PHQ) (patient rated)	>10	11–14	15–19	>19
Montgomery–Åsberg Depression Rating Scale (MADRS) (clinician rated)	>7	7–19	20–34	>34

Nondrug Therapies for Depression

PSYCHOTHERAPY

For the treatment of mild-to-moderate depression, psychotherapy has proved to be comparable to pharmacologic intervention and may be preferred by some patients. There are many types of psychotherapy, and experts suggest that cognitive behavioral therapy (CBT), behavioral activation (BA), and interpersonal psychotherapy (IPT) are effective with CBT being preferred for monotherapy.[5] For the acute treatment of severe depression, antidepressants appear to be more effective than psychotherapy

alone and have a more rapid onset of therapeutic action.[5,26] The beneficial effects of psychotherapy, however, may persist longer than medication-related benefits after the interventions have been formally discontinued. In addition, psychotherapy may be particularly beneficial for preventing relapse among patients who previously demonstrated a therapeutic response to antidepressants.[56] Overall, the combination of psychotherapy and pharmacotherapy is superior to either intervention alone.[5,10]

SOMATIC INTERVENTIONS

ECT is a safe, rapid-acting, and highly effective therapeutic intervention. Fundamentally, ECT features the induction of generalized seizures through an electric current delivered by bilateral or unilateral electrode placement. Medications that raise the seizure threshold, such as benzodiazepines, or promote cognitive impairment (lithium) should be discontinued before the procedure, although this is not always necessary. Adverse effects are generally minimal and consist mainly of transient anterograde amnesia (ie, difficulty remembering events around the time of the procedure), retrograde amnesia, confusion, headaches, and muscle aches. Cardiovascular effects (eg, ventricular arrhythmias, myocardial infarction [MI]) are the most ominous sequelae, but these events are extremely rare.[57]

ECT is recommended for patients with treatment-resistant depression, severe vegetative depression, psychotic depression, and severe depression in pregnancy. Overall, response rates are impressive, ranging from 70% to 90%, and ECT has the distinct advantage of inducing a therapeutic response within the first 2 weeks of treatments.[57–59] The recommended frequency of ECT treatments is variable. Most institutions have used three sessions weekly to induce a therapeutic response acutely, although evidence suggests that twice-weekly sessions are better tolerated and more cost-effective.[60] ECT administered weekly for 1 month and less frequently thereafter may be as effective as aggressive pharmacotherapy in preventing relapse.[61]

Other somatic interventions have also been used successfully to treat depression. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive procedure involving the application of an electrical magnetic stimulus across the scalp, which ultimately generates an electrical field in the cerebral cortex.[62,63] Unlike ECT, rTMS does not generate an actual seizure, and it is very well tolerated, with common side effects consisting of transient scalp discomfort and headaches. Preliminary investigations successfully used repetitive high-frequency techniques in depressed subjects, and imaging studies have shown functional improvements consistent with antidepressant properties. However, not all studies have shown efficacy, and overall results show only a slight benefit for depression or treatment-refractory depression.[59,64,65] A recently published review found that acute phase depression may respond to rTMS, yet data are lacking regarding long-term maintenance treatment.[66]

Vagus nerve stimulation involves the surgical implantation of an electrical device in the subcutaneous tissue below the clavicle, which sends an impulse along the left vagal nerve into the cerebral cortex. Setting adjustments are through a telemetric wand.[59,67] It is currently U.S. Food and Drug Administration (FDA) approved for the management of treatment-resistant depression, although its effect takes time and cannot be considered an acute therapy. Implantation of the device is an invasive procedure with standard risks associated with this type of surgery. However, long-term safety has been shown in both epilepsy and depression studies. It may be useful when combined with medication treatment.[59]

Light therapy or phototherapy is particularly effective for relieving the irritability and malaise associated with seasonal affective disorder, a milder form of depression that has been attributed to decreases in natural sunlight found with seasonal variation.[10,68] Phototherapy is administered in the form of a light box delivering 1500 to 10,000 lux for a period of 1 to 2 hours daily. It is extremely well tolerated.

LIFESTYLE ADJUSTMENTS

Any therapeutic approach to mood disorders should seek to reverse unhealthy or destructive lifestyle habits and promote other activities that may relieve stress and facilitate well-being. Alcohol and illicit drug use should be minimized (if not prohibited) in patients suffering from depressive disorders. Sleep habits should be evaluated and improved to ensure optimal rest. Dietary factors should be modified to promote diverse, balanced, and nutritional eating habits.

Increased physical activity and sustained cardiovascular exertion can impart a variety of health benefits, including improvement in depressive symptoms.[5] Although investigations examining the effectiveness of exercise for depression have met with mixed results, exercise can regulate appetite, improve sleep patterns, increase energy, enhance self-esteem, and promote a return to euthymic status.[69] Exercise has been shown to increase circulating concentrations of serotonin in the periphery and enhance neurogenesis in the hippocampus.[70] Other activities may also serve to relieve stress and help patients acquire insights into their emotional well-being. These pursuits can range from daily journal writing (journaling), meditation, yoga, and Tai chi. Classes in mindfulness-based meditation, in particular, are offered at many medical centers, and the health benefits of this approach have been demonstrated in a wide range of medical conditions including cancer, chronic pain syndromes, and human immunodeficiency virus (HIV) illness.[71]

MAJOR DEPRESSIVE DISORDER

CASE 86-1

QUESTION 1: A.R. is a 25-year-old female in graduate school who presents to the student health clinic for a routine physical examination. During her visit, A.R. states, “I’ve been feeling pretty down lately and just want to give up.” Her physical examination is unremarkable, and all laboratory tests (complete blood count with differential, chemistry panel, and thyroid function tests) are within normal limits. A human chorionic gonadotropin test is negative. Her medical

history is noncontributory, takes no medication, uses a daily multivitamin, and denies drinking alcohol, smoking cigarettes, or using illicit substances.

When asked, A.R. states that she has had increasing periods of depressed mood during the past few months and often finds herself crying in the morning for no particular reason. She reports that she has no interest in her old hobbies (playing the piano, mountain biking, gardening). During the past 6 months, her appetite has decreased, and she has lost 15 pounds (6.80 kg). She feels overwhelmed about all of her academic work and job and has difficulty sleeping, often waking in the middle of the night and being unable to fall back asleep. She has no energy during the day and finds it difficult to concentrate or make decisions. This is clearly impacting her ability to finish her graduate work as she is falling behind and has been getting extensions for her project due dates.

On examination, A.R. is an appropriately dressed female who appears sad but who is alert, coherent, and logical. Her affect is constricted, apprehensive, and sad. Mood is depressed, and she admits having vague suicidal ideation, but she has no specific plans. She is oriented to person, place, and time, but shows some recent memory deficits. Her intelligence is estimated to be above average. Concentration and abstractions (eg, “don’t cry over spilled milk,” “a rolling stone gathers no moss”) are satisfactory. She denies hearing voices or other hallucinations. She denies any symptoms of mania such as increased periods of energy, rapid speech, and racing thoughts (see Chapter 87, Bipolar Disorders). She has good insight and judgment into her illness. A.R. is asked to complete the PHQ-9 and has a total score of 15 with five different questions scoring 2 or more and as well as question one and two scoring 2 (ie, moderate-to-severe symptoms). After reviewing the PHQ-9 results, a more in-depth interview is conducted and A.R. is diagnosed as having MDD.

What nondrug options have shown efficacy?

From A.R.’s history, she appears to be exhibiting a dysphoric or depressed mood as well as anhedonia (lack of interest in hobbies or pleasurable activities). In addition, she demonstrates frequent episodes of crying, decreased appetite (with an unintentional 15-pound [6.80 kg] weight loss), poor concentration, low energy, suicidal ideation, worthlessness, and inappropriate guilt. Her mental status examination is consistent with these target symptoms, revealing a constricted, sad affect (physical manifestation of inner emotional states), and frequent crying episodes during the interview.

Based on the *DSM-5* criteria (see Table 86-4), A.R. has MDD. During the past 2 weeks, she has consistently exhibited at least five of the associated symptoms, one of which is depression or anhedonia. It does not appear that her symptoms are the result of

any medical condition, medication, thought disorder, or uncomplicated bereavement. These are impacting functioning because she is not able to complete her schoolwork assignments.

Psychotherapy has been shown to have beneficial effects on mild-to-moderate depression. Studies have also shown that combined with medication, the beneficial effects are greater than either alone. ECT is an effective somatic treatment but typically reserved for more refractory cases. rTMS is currently being studied but has not been standardized yet. Lifestyle modifications such as exercise generally have benefit, but typically are not strong enough on their own to treat clinically significant depressed symptoms.

DRUG MANAGEMENT

Drug Selection: General Considerations

CASE 86-1, QUESTION 2: A.R. agrees to a therapeutic trial of an antidepressant. What are the drug options available for A.R.'s depressive symptoms? What considerations should be made when selecting antidepressant therapy?

In randomized, controlled trials (RCTs) of antidepressants, a therapeutic response is usually apparent in 60% to 70% of subjects receiving active medication (therapeutic response is defined as a ≥50% decline in depression rating scale score).[5,10]
Antidepressants can be divided into different categories:

1. SSRIs
2. SNRIs
3. TCAs
4. Miscellaneous antidepressants (eg, trazodone, nefazodone, mirtazapine, bupropion)
5. MAOIs

6. Serotonin reuptake inhibitor and receptor modulators (the newest group)

When comparing the impact of antidepressants on changes in depressive symptoms, all antidepressants are considered equal, regardless of class. It is possible that dual-acting antidepressants (SNRIs and TCAs) may be more effective in the severely depressed, but this has not resulted in experts explicitly recommending them over other factors such as comorbid diseases, contraindications, or drug interactions (**Tables 86-6** and **86-7**).[5,10,26,72] Sertraline and escitalopram have the best efficacy to safety/tolerability ratio.[5,10,72,73] Thus, with no other factors influencing the selection of the medication, it may be easier to select either of these.

Table 86-6
Factors to Consider in Selecting an Antidepressant

1. History of prior response (personal or family member)
2. Safety in overdose
3. Adverse effect profiles
4. Patient age
5. Concurrent medical/psychiatric conditions
6. Concurrent medications (eg, potential for drug interactions)
7. Convenience (eg, minimal titration, once-daily dosing)
8. Cost
9. Patient preference

Table 86-7
Pharmacology of Antidepressant Medications

Medication	Serotonin	Norepinephrine	Dopamine	Bioavailability (Oral) (%)	Protein Binding (%)	Half-Life (Hours) (Active Metabolite)
Selective Serotonin Reuptake Inhibitors						
Fluoxetine	++++	0/+	0	80	95	24–72 (146)
Sertraline	++++	0/+	+	>44	95	26 (66)
Paroxetine	++++	+	0	64	99	24
Citalopram	++++	0	0	80	>80	33
Escitalopram	++++	0	0	80	56	27–32
Serotonin/Norepinephrine–Reuptake Inhibitors						
Venlafaxine	++++	+++	0	92	25–29	4 (10)
Desvenlafaxine	+++	+++	0	80	30	11 (0)
Duloxetine	++++	++++	0	50	>90	12 (8–17)
Levomilnacipran	+	++++	0	92	22	12
Dopamine/Norepinephrine–Reuptake Inhibitors						
Bupropion	0/+	+	++	>90	85	10–21
Tricyclic Antidepressants						
Desipramine	+	++++	0/+	51	90	12–28
Nortriptyline	++	+++	0	46–56	92	18–56
Amitriptyline	++++	++++	0	37–49	95	9–46 (18–56)
Imipramine	+++	++	0/+	19–35	95	6–28 (12–28)
Doxepin	+++	+	0	17–37	68–85	11–23
Others						
Mirtazapine	+++	++++	0	50	85	20–40
Nefazodone	+++	+	0	20	99	5
Vilazodone	++++	0	0	72	98	25
Vortioxetine	++++	0	0	75	99	60

0, negligible; +, very low; + +, low; + + +, moderate; + + + +, high.

Sources: *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. American Psychiatric Association; 2010; Deardorff WJ, Grossberg GT. A review of the clinical efficacy, safety and tolerability of the antidepressants vilazodone, levomilnacipran and vortioxetine. *Expert Opin Pharmacother.* 2014;15(17):2525–2542.

One of the first factors to consider is the patient's history of response to previous antidepressant drug therapy. If this history is unavailable (or the patient has never received an antidepressant before), the clinician should inquire about family history. If a first-degree relative had a successful course of antidepressant treatment with minimal adverse effects, that specific medication (or another from the same antidepressant class) would be a prudent choice for initial therapy. The potential impact of an antidepressant on concurrent medical conditions or disease states is often considered next. For example, certain antidepressants (eg, TCA, paroxetine, mirtazapine) can cause significant weight gain and would not be

desirable choices for obese patients, whereas bupropion should be avoided in patients with a history of seizures. Pharmacokinetic drug interactions will also help determine the preferred first-choice option. Among the SSRIs, fluoxetine and paroxetine have significant inhibitory effects on CYP450 2D6, whereas citalopram, escitalopram, sertraline, and fluvoxamine have minimally clinical inhibitory effects on 2D6. Fluvoxamine does have a strong impact on CYP1A1/2, and fluoxetine has a weak-to-moderate impact on 3A4 (see **Table 86-8**).[74] Other important patient-specific factors to consider in the selection of an agent include safety in overdose, ease of administration (once-daily vs divided doses), and necessity for dose titration, cost, and patient preference (Tables 86-6 to **86-9**).[10]

Table 86-8

Drug Interactions of the Cytochrome P-450 System

Relative Rank	CYP1A2	CYP2C9/19	CYP2D6	CYP3A4
Strong	Fluvoxamine	Fluvoxamine		
			Fluoxetine	
				Nefazodone
			Paroxetine	
Moderate			Duloxetine	
			Bupropion	
		Fluoxetine		Fluoxetine
				Fluvoxamine
Weak			Venlafaxine	
	Sertraline	Sertraline	Sertraline	Sertraline
			Escitalopram	
	Paroxetine	Paroxetine		Paroxetine
			Fluvoxamine	
			Citalopram	
	Fluoxetine		Nefazodone	

Table 86-9
Dosage Ranges of Commonly Prescribed Antidepressant Medications

Medication	Starting Dose (mg/day)	Usual Dosage (mg/day)
Selective Serotonin Reuptake Inhibitors		
Fluoxetine	20	20–60
Sertraline	50	50–200
Paroxetine	20	20–60
Paroxetine ER	12.5	25–75
Citalopram	20	20–60
Escitalopram	10	10–20
Serotonin/Norepinephrine–Reuptake Inhibitors		
Venlafaxine, IR	37.5	75–375
Venlafaxine, ER	37.5	75–375
Desvenlafaxine	50	50
Duloxetine	60	60–120
Levomilnacipran	20	40–120
Dopamine Reuptake Inhibitors		
Bupropion, IR	150	300–450
Bupropion, SR	150	300–400
Bupropion, ER	150	300–450
Tricyclic Antidepressants		
Imipramine	25–50	100–300
Desipramine	25–50	100–300
Amitriptyline	25–50	100–300
Nortriptyline	25	50–200
Others		
Mirtazapine	15	45
Nefazodone	50	150–300
Serotonin Reuptake Inhibitors and Receptor Modulators		
Vilazodone	10	20–40

Medication	Starting Dose (mg/day)	Usual Dosage (mg/day)
Vortioxetine	10	20

Reprinted with permission from American Psychiatric Association. Practice Guidelines for the Treatment of Patients with Major Depressive Disorder. 3rd ed. Washington, DC: American Psychiatric Association; 2013. Copyright ©2013 American Psychiatric Association. All Rights Reserved.

Treatment Expectations

A similar delayed pattern of therapeutic response has been observed with all antidepressant medications. Patients often begin to show signs of clinical response during the first 1 or 2 weeks of active treatment, and maximum improvement may not be evident until weeks 6 to 8.[5,26,75] The pattern of patient response can also be generalized, with neurovegetative symptoms often the first to subside (eg, altered sleep or appetite, decreased energy, excessive worrying, and irritability). Cognitive symptoms are slower to respond, and 3 to 4 weeks or more may elapse before improvements are evident. These symptoms include excessive guilt or pessimism, poor concentration, hopelessness or sadness, and decreased libido.

Selective Serotonin Reuptake Inhibitors

ADVERSE EFFECTS

There is a delay in onset of full efficacy, but side effects will occur soon after starting the medication. Common side effects of SSRIs are related to the fact that despite their neurotransmitter specificity to increasing the amount of only serotonin in the synapse, there are at least 14 different serotonin receptors having different effects.[15] Distinct side effect profiles have emerged, consisting of gastrointestinal (GI) problems, CNS disturbances, and sexual dysfunction.

All of these medications may induce nausea, but this tends to be a transient effect that diminishes after the first week of treatment. Typically, SSRI-induced nausea occurs 1 to 2 hours after oral

administration. Nausea with SSRIs can be a local effect but is also mediated centrally through the extra serotonin-stimulating serotonin receptors (5-HT_3) that activate the chemoreceptor trigger zone.[76] SSRIs may also cause transient and bothersome increases in GI motility. This diarrhea is generally limited to the first few weeks of treatment and is also related to the extra serotonin-stimulating 5-HT_3 and 5-HT_4 receptors along the GI tract. As with nausea, this diminishes in the first few weeks of treatment unless the dose is increased. In contrast, paroxetine possesses a relatively mild anti-muscarinic effect that can manifest as constipation, dry mouth, or urinary hesitancy. Although this effect is mild, paroxetine use is often discouraged in patients with preexisting constipation or those where any anticholinergic effects are to be avoided such as the elderly.

SSRIs can have myriad effects on the CNS, with disturbances in sleep being a primary concern. SSRIs can have significant but highly variable effects on sleep architecture. In sleep studies, SSRIs have been shown to increase sleep latency and decrease sleep efficiency, often resulting in morning sleepiness or malaise. Many patients also notice that their dreams become more vivid and memorable, which may be an undesirable experience. Rapid eye movement (REM) stage sleep may be prolonged, resulting in less fitful sleep.[77] It should be emphasized, however, that sleep may eventually improve once the antidepressant properties of the medications are apparent and baseline depressive symptoms are relieved (eg, midnocturnal insomnia).

The deleterious effects of SSRI on sexual function can often lead to medication nonadherence.[78] The reported incidence of sexual dysfunction ranges from 1.9% to 75%, reflecting the difficulty in appropriately measuring this adverse event.[79] The actual incidence of SSRI-induced sexual dysfunction is ~30% to 50%, and it appears to be slightly more common in males, but the severity may be worse in females.[79] Delayed orgasm is the most common sexual problem attributed to SSRIs or SNRIs and should be distinguished from decreases in desire or libido, which are considered to be an aspect of the psychopathology of depression itself. This iatrogenic effect on

orgasms has actually been used to clinical advantage in treating males by delaying premature ejaculation, but most patients find it undesirable.[79] All SSRIs are at risk for causing sexual dysfunction because it is due to the increased serotonin-stimulating 5-HT_{2c} receptors. Paroxetine has a higher rate than the others because it also inhibits nitric oxide synthase, reducing nitric oxide levels.[79] It also appears that this is a dose-dependent phenomenon, which may respond favorably to a decrease in daily dosage. Unlike the GI and CNS side effects reported with SSRIs, sexual dysfunction is not usually a transient adverse effect and must be addressed by clinicians if patients are to continue pharmacotherapy.

The detection and proper management of SSRI-induced sexual dysfunction can be one of the most important factors in ensuring medication adherence. Clinicians may be uncomfortable asking patients about their sexual activities and satisfaction, but the high incidence of this side effect (and low likelihood of patients volunteering this information) necessitates a thoughtful and direct approach. Some patients acknowledge sexual dysfunction but decide that improvements in mood and overall health outweigh limitations in sexual performance; however, others simply stop the medication if the side effect is never addressed.

Sexual function may change over time, depending on the type and etiology of sexual dysfunction experienced. Depression itself is associated with a decreased libido in 70% to 90% of untreated patients.[80,81] This symptom will most likely subside with a successful course of antidepressant treatment. Delayed ejaculation or anorgasmia, however, may be caused by SSRIs and SNRIs, often persisting and jeopardizing treatment.

Ordinarily, one of the first options in managing sexual dysfunction is to reduce the dosage, but this may induce a return in symptoms because increasing the dose initially was likely because of a lack of full effect. It is also possible to introduce drug holidays. Small open-label studies with short-acting SSRIs (eg, paroxetine) suggested that if patients skipped their doses on Friday and Saturday, sexual function would return to normal on the weekends.[82,83] Although this

method was reported to be successful, it may also promote nonadherence with medication and lead to an increased risk of relapse and withdrawal symptoms and is therefore not recommended.

If the patient has had a therapeutic response to the antidepressant, the next option in this setting is to consider antidotes to SSRI-induced sexual dysfunction. One option is to add the antidepressant bupropion. Clinical reports and controlled investigations suggest that the addition of bupropion can be helpful for restoring sexual desire and may relieve delayed orgasm or anorgasmia in ~50% of patients.[5,84–87] This therapeutic effect has been demonstrated in depressed and nondepressed patients alike. A common dosing technique is to start with 150 mg of bupropion daily. If unsuccessful, the dose can be increased to 150 mg of bupropion sustained release (SR) twice daily after several days (or 300 mg of the extended-release [XL] preparation). The mechanisms of SSRI-induced sexual dysfunction, and bupropion relief, are not well understood, but likely because of the pro-sexual effects of increasing DA.[88]

Other remedies have been prescribed for SSRI-induced sexual dysfunction. A large randomized, controlled trial examined the impact of sildenafil on male patients suffering from this side effect.[89] Overall, 54% of patients randomly assigned to sildenafil found it to be effective compared with a 4% response rate with placebo. Open-label trials of sildenafil in females experiencing SSRI-induced anorgasmia have also reported improvements. Tadalafil has also shown similar efficacy suggesting a class effect.[90]

Amantadine, buspirone, ropinirole, and yohimbine also have been used successfully to reverse delayed ejaculation or decreased libido, but the evidence for efficacy is limited.[81,91–93] An open-label trial of Ginkgo biloba in male and female patients with sexual dysfunction reported very high success rates, but mixed results have been reported in clinical practice.[94] Mirtazapine is capable of blocking postsynaptic 5-HT_2 receptors and has been shown to have less sexual dysfunction than SSRIs.[95] The 5-HT and histamine receptor

antagonist cyproheptadine has been shown to alleviate this adverse event. However, because of its broad effect on all 5-HT receptors, depression relapse and serotonin withdrawal can occur resulting in it not being recommended. Stimulants such as methylphenidate or dextroamphetamine may increase libido in SSRI-treated patients, but the potential for dependence and abuse discourages their routine administration.[96] Exercise and CBT may also be of benefit.[81]

All antidepressants have a black box warning regarding the possibility of an increase in suicidal thinking, specifically in persons 24 years old and younger. In regard to completed suicide, the rate is less in adult and pediatric patients treated with antidepressants than in those who are not treated.[5,26,97,98] However, studies have shown a rate in suicidal thinking among children and young adults of 4% in the medication arms compared to 2% in placebo arms.[98] Therefore, in order to protect the patient, it is recommended that when an antidepressant is initiated in a child or adolescent, the patient should visit with the clinician every week in the first month, every 2 weeks in the second month, and then monthly for the next month. Adults should also be monitored frequently, and weekly visits initially have shown increased adherence rates. However, other factors may play a role in monitoring, such as access to care and distance the patient needs to travel for the appointment. Therefore, it is recommended to at least speak with the adult patient (eg, via telephone), at least every 1 to 2 weeks in the acute phase (initial 12 weeks) of treatment to assess suicidality but also to check for side effects and adherence.[5,10] SSRIs are dramatically safer in overdose compared to TCAs and are preferred for those with suicidal thinking or comorbidities that put them at risk for impulsive acts of self-harm such as substance misuse.

In addition to GI, CNS, and sexual side effects, a variety of other, less-common adverse sequelae have occurred with SSRIs. Headache can occur with SSRIs at a rate of ~10% to 15% with all agents similar and slightly greater than placebo, with discontinuations because of headache very low at 1% to 3%.[99] This may be due to the stimulatory effects of serotonin on 5-HT_{1b} and 5-

HT_{1d} receptors. It is important to note that SSRIs are actually recommended for migraine prophylaxis as a second-line agent.[100,101] Increased sweating has also been reported with SSRIs and can be particularly uncomfortable or embarrassing.[102] A dosage reduction may help relieve this adverse effect and should be tried first. Adjunctive treatment of α-blockers (eg, terazosin, prazosin), cyproheptadine, and the anticholinergic benztropine has shown some success if a dose reduction is not possible.[103,104] Bruxism, or teeth grinding, can also be a consequence of SSRI treatment, leading to chipped or cracked teeth and generally poor dentition.[105] Often, patients may not be aware of this nocturnal effect and report merely a dull, persistent headache during the morning hours. This, too, may be a dose-dependent side effect of all SSRIs, and several antidotes have been prescribed (eg, buspirone, benzodiazepines, gabapentin).[106,107] In small retrospective studies and several case reports, SSRIs have been linked to dilutional hyponatremia or syndrome of inappropriate antidiuretic hormone (SIADH).[108,109] All SSRIs and SNRIs have been associated with this phenomenon, and elderly patients appear to be uniquely at risk.[110]

SSRIs have been rarely associated with extrapyramidal side (EPS) effects, consisting of akathisia, dystonias, and parkinsonian symptoms that are qualitatively identical to those seen with antipsychotics.[111–113] Although EPS reactions have been documented with all SSRIs, most case reports have correlated with aggressive dosing, often in a patient currently using a DA antagonistic medication, and during the first 1 to 4 weeks of initiation. The theory is that these EPS effects are mediated through the indirect influence of serotonergic neurons on dopaminergic activity.[112] In certain areas of the brain, serotonin and dopamine appear to have an inverse relationship, whereby central stimulation of serotonin receptors results in a net decline in dopaminergic transmission. Management of EPS effects induced by an SSRI is identical to that of those precipitated by antipsychotics. Dystonias and parkinsonian side effects can be treated with anticholinergic agents and subsequent

SSRI dosage reduction. Akathisia usually responds to a reduction in SSRI dosage and/or administration of low-dose β-blockers.[113]

The long-term effects of SSRIs on body weight are variable and difficult to predict. A problem with accurate measurement is because decreased appetite is one of the most common depressive symptoms and that a small weight gain after an antidepressant course may actually be viewed as a therapeutic effect of successful treatment. Conversely, early reports of weight loss with fluoxetine generated much optimism for the use of SSRIs in obesity, but longitudinal studies found this to be a brief, transient phenomenon.[114] All the SSRIs have been reported to cause significant weight gain in long-term use, but it is a rare phenomenon believed to be mediated by genetic markers that have not been conclusively identified. The exception is paroxetine, which has been implicated much more often than other SSRIs as a cause of weight gain. One long-term RCT compared the effects of fluoxetine, sertraline, and paroxetine on total body weight.[115] After 7 months of SSRI use, 25% of the patients receiving paroxetine gained a clinically significant amount of weight (defined as a >7% increase in total body weight) compared with 7% with fluoxetine and 4% with sertraline.[115] Long-term studies with citalopram and escitalopram suggest that 3% to 5% of patients will experience a significant weight gain. The risk of SSRI weight gain is minimal (except with paroxetine) and typically irrelevant, but because appetite changes are part of depression, it is best to monitor weight closely during long-term treatment for both disease- and drug-related reasons.

Epidemiologic studies have also linked SSRIs and SNRIs with an increased risk for upper GI hemorrhage, with a number needed to harm of 3177.[116,117] Recent trials suggest that the risk is modest but can be increased significantly by concurrent ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) lowering the number needed to harm of 881.[117–119] Alcohol use can also increase the risk of bleeding.[118,119] The mechanism for SSRI-induced GI hemorrhage has been attributed to effects on decreasing platelet activation and aggregation. SSRIs and SNRIs should be avoided in patients with

active GI bleeds, and the concurrent use of high-dose NSAIDs should be discouraged.

DOSAGE TITRATION

Case 86-1, Question 3: A.R. and the clinician agree to start escitalopram 10 mg once a day in the morning (qam). What is considered the standard of care and expected outcomes for dosing and efficacy?

It is very important to establish realistic expectations for treatment with antidepressants from the beginning of therapy. Patients should be informed of the anticipated course of treatment and that the onset of side effects usually precedes that of therapeutic effects. Also, patients should be advised that, although antidepressants may relieve acute depressive symptoms and prevent relapse, they do not abolish environmental stressors such as an abusive relationship or an oppressive work setting.

After receiving the medication for 2 weeks, most improvement in A.R. is likely because of the support she is getting by being involved in treatment as placebo patients show a reduction in symptoms during this period. Medication will start to separate from placebo typically at the 2-week monitoring period and continue to enlarge that separation from placebo up until week 8. A.R. should be reminded that the optimal effects of antidepressants may not be evident for another 2 to 6 weeks. Therefore, a reasonable recommendation would be to continue with the current daily dose of 10 mg and to re-evaluate the medication's effects when she returns to clinic in 2 weeks. If there is no clear improvement at 4 weeks, then switching the medication is necessary. If there is a 25% or more improvement, then the clinician could continue for another 4 weeks (for 8 weeks of treatment) and decide whether the response is acceptable. If the improvement is small, such as just 25% to 30%, then one can increase the dose at this 4-week point and continue to monitor for another 8 weeks.[5,10,26]

DURATION OF TREATMENT

According to the guidelines issued by the Agency for Health Research and Quality, antidepressant treatment can be broken down into three stages (**Table 86-10**).[120] The first stage, acute treatment, lasts ~12 weeks; during this time, the clinician attempts to resolve the presenting symptoms and induce remission, which is defined as having no impairing symptoms of depression and a score of ≤7 on the $HAMD_{17}$ or ≤10 on the MADRS.[5,10] The second stage is commonly called continuation treatment because the patient continues to receive the same antidepressant regimen that induced the initial treatment response, and the clinician attempts to keep the acute symptoms in remission. The duration of continuation treatment is variable (4–9 months after initial treatment or response), but it is recommended that all patients suffering from major depression complete these first two stages. Therefore, the minimum duration of treatment is 7 months. Alternatively, others have advocated that the minimum duration of treatment should be for 6 months after the complete resolution of symptoms.[5]

Table 86-10
Duration of Antidepressant Treatment

Acute treatment phase	3 months
Continuation treatment phase	4–9 months
Maintenance treatment phase	Variable

1. Acute and continuation treatment recommended for all patients with major depressive disorder (MDD) (ie, minimal duration of treatment = 7 months)
2. Decision to prescribe maintenance treatment is based on the following:
   - Number of previous episodes
   - Severity of previous episodes
   - Family history of depression
   - Patient age (worse prognosis if elderly)
   - Response to antidepressant
   - Persistence of environmental stressors
3. Indefinite maintenance treatment is recommended if any one of the following criteria is met:
   - Three or more previous episodes (regardless of age)

- Two or more previous episodes and age older than 50 years
- One or more and age older than 60 years

The third stage of treatment, maintenance treatment or prophylaxis, is not indicated for all patients, and the necessity of continuing medication beyond the first 6 to 7 months depends on many patient-specific factors. One must consider the number of previous episodes, family history of depression, patient's age, severity of presenting symptoms, response to therapy, and persistence or anticipation of environmental stressors. There are specific populations for whom indefinite pharmacologic treatment is advocated: (a) individuals with three or more previous episodes of major depression, (b) individuals older than 50 years with two or more previous episodes, and (c) individuals older than 60 years with one or more previous episodes.[5,10] Continued antidepressant usage in the elderly is recommended to prevent relapse.[121]

Because A.R. is exhibiting a full therapeutic response to escitalopram, the recommendation would be for her to continue with the effective dosage (10 mg/day) for at least 7 consecutive months. At the end of this time frame, the clinician should review with the patient those considerations that enter into the decision to continue treatment. Ultimately, the decision to continue antidepressant medications is left to the patient's judgment, and he/she should be well informed of the potential consequences of stopping treatment.

In the future, if A.R. decides to discontinue her antidepressant, she should fully disclose this to her prescriber so that an appropriate taper schedule and subsequent monitoring can occur. She should be advised of potential withdrawal symptoms (**Table 86-11**).[122] Abrupt discontinuation of chronic SSRI treatment (eg, treatment >2 months) has been associated with dizziness, headache, anxiety, lethargy, dysphoria, and sleep problems.[5,122] The onset of these symptoms is generally within 36 to 72 hours of stopping treatment, and effects may persist for approximately a week. Withdrawal symptoms generally are mild and self-limiting but can be uncomfortable and alarming. Because of their relatively short half-life (and absence of long-acting metabolites), paroxetine, fluvoxamine, and venlafaxine

have been associated with a more profound withdrawal presentation than other SSRIs and SNRIs. Because of its long half-life (and that of its active metabolite), fluoxetine has not been commonly associated with withdrawal symptoms. Nonetheless, it is advisable to taper slowly off all antidepressant medications after an extended treatment course to decrease the risk of withdrawal and subsequent relapse.[123] A defined time for taper has not been established. Switching therapies within classes can be done quickly (eg, from sertraline to fluoxetine) without a cross-taper. When switching to another class or off antidepressant completely, then a 6- to 8-week taper is standard as well as educating the patient to withdrawal symptoms and reassuring them that this is not a life-threatening event. Because withdrawal is not life-threatening, a much faster taper (3–7 days) can be completed with the patient's approval.[10,122]

Table 86-11
Discontinuation of Antidepressants

Withdrawal Syndrome
1. Worse with paroxetine, venlafaxine 2. Symptoms: dizziness, nausea, paresthesias, anxiety/insomnia, flu-like symptoms 3. Onset: 36–72 hours 4. Duration: 3–7 days

Note: Risk of depression relapse is greatest 1 to 6 months after discontinuation.

Suicide Assessment

Patients with major depression should always be assessed for the presence of suicidal thoughts (eg, "Do you ever feel like giving up?" "Are you thinking about hurting yourself?"). Reports have noted that completed suicide rates range from 2% to 15%. Up to 70% of suicides worldwide are persons with MDD.[5,124] Comments made by the patients alluding to suicide (eg, "Life is not worth living anymore," "I am leaving and may never see you again") should be taken seriously. Several factors may place a person at greater risk for a

suicide attempt. These include living alone, having a disabling illness, being unemployed, having a history of alcohol/drug abuse, chronic pain, anxiety, or having a family history of suicide.[10] Gender plays a role as well, with females much more likely to attempt suicide, although males are more likely to complete the act.[10]

For patients who are actively suicidal, hospitalization is often necessary and may be facilitated against the patients will in high-risk settings. Other life-saving interventions include establishing close contact with the patient's family and health care provider, convincing the patient to contract for his/her safety, and ensuring that firearms and other lethal means are removed from the home. Antidepressant classes have different risks of lethality in overdose. Tricyclics are by far much more dangerous than SSRIs. Duloxetine, venlafaxine, and mirtazapine are a much lower risk than TCAs but higher than SSRIs. Among the SSRIs, citalopram has the greatest risk of cardiotoxicity in overdose but still less than venlafaxine.[5] For patients who are at risk for attempting suicide, TCAs and MAOIs are contraindicated.

A.R. is at some risk for suicide, although she does not have a detailed plan at present. She should be monitored closely during the first few weeks of therapy by friends or family members. If her suicidal ideation becomes severe, A.R. should be evaluated in a psychiatric emergency room for her own safety. Unfortunately, it is not always possible to predict whether A.R. (or any depressed patient) will attempt suicide. Even with the most conservative precautions, a small percentage of patients successfully complete their suicide attempts.

Case 86-1, Question 4: After A.R. has been treated for a year, she is asking about coming off her escitalopram partly because she is getting married and considering becoming pregnant. What would be the most appropriate way to proceed with discontinuation and treatment of depression during pregnancy?

A.R.'s escitalopram should be tapered during several weeks (eg, decrease to 5 mg daily for 2–4 weeks, then discontinue). The risk of relapse is relatively low during the first month of medication, but depressive symptoms often return during the second or third months.

The risk of relapse is highest during the first 6 months after therapy is stopped.[125]

Antidepressants in Pregnancy and Lactation

The risk for depression is elevated during pregnancy and during the postpartum period.[126] A prospective investigation reported that females who discontinued their antidepressant upon discovering that they were pregnant were much more likely to relapse prior to delivery (68% relapse rate vs 26% who continued treatment; hazard ratio, 5.0).[127]

Before deciding to treat with an antidepressant during pregnancy, one should make a careful inventory of the benefits and risks. The consequences of maternal depression on the mother and fetus must be compared with the potential risks of in utero medication exposure. From the mother's perspective, untreated depression carries with it a great deal of distress during an emotional time. Sleep and appetite may be compromised at a time when these functions are most important for the baby's development. Mothers may also be tempted to drink alcohol or abuse substances, and studies have also shown that depressed mothers are much less likely to attend prenatal clinic visits.[128] Depression during pregnancy is a very strong risk factor for postpartum depression.

Most of the SSRIs and newer antidepressants pose little risk for the development of serious fetal malformations, and they have been subsequently categorized as class C by the FDA (suggesting that the risk to the fetus is not definitively known). Their relative safety has been corroborated by two large case–control studies in which very small increases in risks were reported.[129,130]

One notable exception is with paroxetine, which was reclassified as class D by the FDA after the demonstration of an increased risk for congenital heart defects in newborns.[131] An additional concern with SSRIs and SNRIs in pregnancy is the risk for a neonatal serotonin withdrawal syndrome immediately after delivery. This has been reported with TCAs in the past as well. A small controlled

investigation (*n* = 40) examined the effects of fluoxetine and citalopram on CNS effects in newborns and found a significant increase in restlessness, tremor, shivering, and hyperreflexia during the first 4 days of life (vs controls); these signs spontaneously remitted shortly thereafter.[132] Although some clinicians have interpreted these findings to suggest that antidepressants should be tapered and discontinued before delivery, others have argued that the delivery and the postpartum periods are major stressors for the new parent, and the risk of relapse during this time would be unacceptably high if the medication is withdrawn. Studies have also reported a small but significant decrease in birthweight among babies exposed in utero to SSRI, although a prospective study found that neither depression nor SSRI use effected infant growth.[133] Clinicians should be reminded, however, that both of these findings have been consistently reported with depression in the absence of antidepressant treatment, and attempts to distinguish the effects of the illness from medication effects in pregnant patients have met with mixed results.[134] The safety of bupropion in pregnancy has not been extensively studied and has an FDA class C rating. Data are even more sparse with mirtazapine, venlafaxine, or duloxetine, but no obvious adverse effects have been identified among infants exposed to these antidepressants in utero. Similarly, fetal malformations have been rarely reported with TCAs and they are generally regarded as safe in pregnancy. MAOIs, however, should be avoided because of increased risks for hypertensive crises. Although screening for depression is not suggested in the general population, it is recommended specifically for those who are pregnant and postnatal.[135] If antidepressants need to be used, then monotherapy is best; avoid first-trimester exposure, do not stop the antidepressant abruptly, and do not discontinue prior to delivery because of the high risk of postpartum depression.[128]

For A.R., it is important to assess her risk for depression if she stops taking her antidepressant. This was her first episode of depression (which occurred under stressful circumstances), she is not currently symptomatic, and she does not have a strong genetic predisposition to mood disorders. If she is committed to starting a

family, she should consider tapering off her escitalopram for several weeks before attempting to conceive. If she becomes pregnant and her depression returns, the risk to the fetus appears to be quite low with most SSRIs. Theoretically, this risk can be reduced further if the antidepressant is started after the first trimester (when most major fetal development occurs). An additional option for pregnant mothers suffering from mild-to-moderate symptoms would be to engage in psychotherapy.[128,136]

Approximately 70% of new mothers report sadness or anxiety during the first few days after delivery (baby blues), but these feelings will usually resolve within 1 to 2 weeks and do not require treatment. Approximately 10% of postpartum patients will experience unremitting symptoms that ultimately satisfy the criteria for MDD. The onset of these symptoms can be quite variable, ranging from the immediate postpartum period to several months later. Not treating depression postpartum results in symptom-related risks to the parent and newborn. Therefore, the priority is on reducing depression, and if an antidepressant is the most effective option for the mother, then efforts should be placed on managing breast-feeding.[137]

Brexanolone is an IV formulation of the naturally occurring neuroactive steroid allopregnanolone.[138] It is the only medication FDA approved for the treatment of postpartum depression. Allopregnanolone levels in the mother drop after birth, although this does not always correlate with depression.[139] It is given as a 60-hour IV infusion with rates during hours 0 to 4 at 30 mg/kg/hour then increased to 60 mg/kg/hour for hours 4 to 24. For hours 24 to 52, the rate is 90 mg/kg/hour, then decreased to 60 mg/kg/hour for hours 52 to 56 and 30 mg/kg/hour for hours 56 to 60. One study showed that for hours 24 to 52, a dose of 60 mg/kg/hour was numerically superior to a higher rate of 90 mg/kg/hour.[140] As the drug is a $GABA_A$-receptor positive modulator, it is required that the infusion be given with a health care provider present for risk of excessive sedation, loss of consciousness, or reduction in O_2 concentrations.[138,139] There is a statistical difference in the reduction of HAM-D scores between 24

and 48, yet this difference was not always maintained at day 30.[140] Thus, maintenance treatment with SSRIs may be required.

Because breast-feeding is widely advocated, the passive transfer of medication from mother to infant must be considered. Studies with TCAs and SSRIs suggest that concentrations of some antidepressants in breast milk are measurable. However, subsequent concentrations in the infant's bloodstream are relatively low, and the sequelae from this exposure have been limited to scattered case reports of increased infant irritability. Among the available agents, fluoxetine and the tricyclic antidepressant doxepin have been associated with the highest concentrations in infants, and although the clinical or developmental consequences of this finding have not been elucidated, it has been recommended that these medications be avoided.[141] Recent studies with SSRIs suggest that the concentrations achieved in breast milk are lowest with sertraline and that paroxetine, citalopram, escitalopram, bupropion, and venlafaxine are somewhere between the extremes of fluoxetine and sertraline.[137,141,142] If an antidepressant is to be continued in a mother who is breast-feeding, the lowest dosage should be prescribed. Concentrations of SSRIs in breast milk will generally peak ~4 to 8 hours after oral administration. If a new mother is particularly concerned about breast milk exposure, she can be advised to pump and save breast milk immediately before taking her antidepressant dose.

Drug Interactions

The SSRIs are inhibitors of the cytochrome P-450 isoenzymes, but important differences exist among the individual agents in their potency for specific metabolic pathways (see Table 86-8). For instance, the cytochrome P-450 1A2 isoenzyme (or CYP1A2) is most sensitive to the inhibitory effects of fluvoxamine. Fluoxetine and paroxetine have the highest impact on CYP450 2D6 with fluoxetine resulting in an approximately fourfold increase in TCAs and paroxetine a fivefold increase.[74,143] Fluoxetine's active metabolite has

weak-to-moderate inhibitory effects on the CYP3A4 isoenzyme. In comparison, sertraline, citalopram, and escitalopram have a much lower potential for CYP450 2D6 drug interactions but still inhibit the metabolism of 2D6-dependent medications. The potency is typically between 30% and 50% increases in area under the curve (AUC) and is often clinically irrelevant. Therefore, CYP450 2D6 drug interactions are less likely to cause harm with sertraline, escitalopram, citalopram, and fluvoxamine, but still require monitoring for a few weeks after the antidepressant is added to the patients' medication list.[74,143–146]

Although in vitro affinities of antidepressants for the respective isoenzymes can be very helpful for predicting potentially dangerous drug combinations, there is wide interpatient variability in the intensity of these interactions. Much of this variability can be attributed to genetic polymorphism. With CYP2D6, for example, ~5% to 10% of Caucasian patients and 1% to 2% of Asian patients are considered poor metabolizers via this isoenzyme.[147] CYP3A4 is the most abundant CYP enzyme found in the human body. Among the SSRIs, only fluoxetine and fluvoxamine have weak and moderate inhibitory effects on this isoenzyme, respectively. This has resulted in ~50% to 150% increase in AUC of the CYP450 3A4-dependent drug alprazolam.[74,145]

SEROTONIN SYNDROME

Serotonin syndrome is a rare but potentially fatal interaction because of excessive and prolonged serotonin within the synapse.[148] The syndrome includes a constellation of symptoms, including anxiety, shivering, diaphoresis, tremor, hyperreflexia, and autonomic instability (increased/decreased blood pressure and pulse rate).[148] Fatalities have been attributed to malignant hyperthermia. It occurs because of excessive serotonin overstimulating 5-HT_{1a} receptors and possibly 5-HT_{2a} (hyperthermia, incoordination, and neuromuscular effects).[148] It can occur within hours of administration of medications that can cause the syndrome. With mild cases of serotonin syndrome, the symptoms ordinarily resolve 24 to 48 hours

after the serotonergic agents have been discontinued. Supportive treatment may be necessary, and for more severe reactions, the serotonergic antagonist cyproheptadine is most commonly prescribed.[148] Dantrolene has been administered successfully to manage hyperthermia.[149]

Excessive serotonin can occur via four mechanisms: preventing its breakdown, preventing its reuptake into the neuron, increasing precursors or agonists, and increasing its release. Most case reports of serotonin syndrome (and most fatalities) have occurred with a combination of an MAOI and an SSRI, which is considered a contraindication. Other case reports involve the combination of an MAOI (or SSRI) with tryptophan, meperidine, SNRI, tricyclics, dextromethorphan, linezolid, and tramadol.[148] One case of serotonin syndrome was reportedly induced by the combination of clomipramine with *S*-adenosylmethionine (SAM-E).[150] Theoretically, the combination of an SSRI with St. John wort may also precipitate this pharmacodynamic interaction, but more recent evidence has suggested that the MAOI properties of the herbal preparation are minimal with therapeutic doses. Nonetheless, a case series of five older patients who exhibited symptoms reminiscent of serotonin syndrome has appeared in the literature, and, given the degree of uncertainty that persists, this combination of antidepressant agents is best avoided.[151] As noted by the previously described reports, the most concerning risk is combining agents that increase serotonin via differing mechanisms such as inhibiting the enzyme monoamine oxygenase and blocking the serotonin reuptake pump. Serotonin syndrome has also been reported with concurrent administration of multiple SSRIs; however, this would generally not be fatal. It is important to note that many medications have monoamine oxidase (MAO) inhibitory effects, although they are not classified as an MAOI. This would include medications such as linezolid, dextromethorphan, and meperidine.

The combination of trazodone with an SSRI could possibly pose some concern because both classes of antidepressants augment serotonin activity in the CNS yet; because both are reuptake inhibitors, it is very unlikely. Trazodone has been associated with

serotonin syndrome in two incidences, one involving the coadministration of buspirone and the other associated with a concomitant MAOI.[152] However, trazodone is recommended and commonly prescribed to patients receiving an SSRI for the treatment of insomnia, with no confirmed cases of serotonin syndrome that have surfaced in the medical literature, thus making it a possible risk only at very high doses.[153,154]

CASE 86-2

Question 1: M.G. is a 35-year-old married female. She is diagnosed with MDD and has been tried on sertraline up to 100 mg qam for 8 weeks, which did not result in a response. She was then tried on fluoxetine 20 mg qam for 8 weeks with only a partial response.

What is the next step for M.G. who has not responded to two antidepressant trials at a therapeutic dose for a therapeutic duration?

Pooled results of clinical trials suggest that the majority of patients with major depression receiving an adequate trial of any antidepressant will have a therapeutic response, defined as at least a 50% reduction in depressive symptoms. However, for a patient who is severely depressed, a 50% reduction in symptoms still leaves him/her with significant psychopathology and associated disability. Consequently, full remission is the preferred therapeutic end point.[5] One longitudinal investigation found that patients with residual symptoms were three times more likely to suffer a relapse during the 12 months after treatment compared to those who had remitted.[155] Not surprisingly, patients with treatment-resistant depression have 40% higher direct medical costs than those without treatment-resistant depression, mainly because of medication and outpatient care costs.[156]

For M.G., the first step would be to confirm her diagnosis and rule out potential medical explanations for her symptoms, specifically bipolar disorder. Bipolar depression is diagnostically indistinguishable from MDD depression episodes. Because antidepressants are minimally effective in bipolar depression, it would explain M.G.'s lack of response if she were to have bipolar

disorder. Iatrogenic causes should also be explored, such as any new medications or substance misuse. Assessing adherence to her previous medication trials is critical. A full therapeutic trial is considered to be a minimum of 4 weeks of treatment at a dosage shown to be clinically effective assuming the patient is compliant with therapy.

Drug Selection

SEROTONIN/NOREPINEPHRINE–REUPTAKE INHIBITORS

Because 30% to 40% of patients will effectively achieve remission and about 20% to 25% of patients will stop an antidepressant because of side effects, many patients started on a given antidepressant may eventually need a significant adjustment or change to their original regimen.[10]

In M.G.'s case, she has previously failed therapeutic trials of sertraline and fluoxetine. Although she had failed a sertraline trial, large controlled investigations suggest that 50% to 70% of patients who are unresponsive or intolerant of one SSRI will experience a therapeutic response to a different SSRI.[157–159] For example, in the STAR*D trial, patients failing an initial course of citalopram were just as likely to respond whether they were randomly assigned to a subsequent trial of a different SSRI (sertraline) or assigned to other antidepressant classes (venlafaxine and bupropion, specifically).[160] Because M.G. has now failed two SSRIs, it is recommended to try an antidepressant from a different class such as an SNRI, α_2-antagonist, or DA reuptake inhibitor.[5,10] For M.G., it was recommended to use an SNRI, and duloxetine was selected.

SEROTONIN/NOREPINEPHRINE–REUPTAKE INHIBITORS

Venlafaxine, duloxetine, desvenlafaxine, and levomilnacipran are categorized as SNRIs (see Table 86-7). At dosages <150 mg/day, venlafaxine's therapeutic effects are mediated exclusively from the blockade of serotonin reuptake. Therefore, associated adverse effects at these dosages are qualitatively and quantitatively very

similar to those found with SSRIs: GI distress, sleep disturbances, and sexual dysfunction. At higher dosages, effects on NE occur, and this can lead to the emergence of different adverse effects (eg, tachycardia, hypertension, and insomnia). NE effects occurring with duloxetine, desvenlafaxine, and levomilnacipran do not appear to be dose-dependent.[161] Levomilnacipran is an SNRI that has more potent effects on NE as compared to its 5-HT reuptake. However, its potency at NE reuptake is similar to duloxetine, and the ratio difference is because of its lower potency at 5-HT reuptake compared to other SNRIs.[162,163] Venlafaxine, which is available as immediate- and extended-release formulations, has a relatively brief plasma half-life (5–8 hours) and is demethylated to an active metabolite (*O*-desmethyl-venlafaxine). This metabolite, desvenlafaxine, was approved by the FDA in 2008 for the treatment of depression. Desvenlafaxine is available as an extended-release tablet that has a similar mechanism of action as venlafaxine. It has no affinity for muscarinic, histaminic, cholinergic, or adrenergic receptors and has a terminal half-life of 11 hours.[164,165] Desvenlafaxine is not affected by CYP2D6 inhibitors; however, CYP3A4 inhibitors may reduce clearance of the drug.[146] Duloxetine also has a relatively short half-life (12 hours) and is metabolized via CYP450 1A2. Levomilnacipran is mainly metabolized by CYP3A4 with a terminal half-life of 12 hours and is available as an extended-release tablet.[166] Venlafaxine, desvenlafaxine, and levomilnacipran are not potent inhibitors of cytochrome P-450 isoenzymes. Duloxetine is a moderate inhibitor of the CYP2D6 isoenzyme.[146,166] As with SSRIs, SNRIs have been associated with serotonin syndrome. Additionally, increased blood pressure (BP) will occur if combined with an MAOI.

As a class, all SNRIs have a risk of increasing BP and heart rate thought to be because of the increase in NE. Venlafaxine averages an increase of 1 mm Hg and 3 bpm.[167] Duloxetine averages 1 mm Hg in BP and 3 bpm.[168] Desvenlafaxine averages an increase of 2 mm Hg and 4 bpm.[169,170] Levomilnacipran has the greatest risk and averages an increase of 4 mm Hg in BP and 8 bpm compared to placebo.[171] There will be some patients who have large changes in

BP with any of the SNRIs; thus, monitoring of vital signs is necessary a few weeks after every dose increase.

Duloxetine has also been shown to increase liver function tests (LFTs) three times the upper limit of normal by ~1.3% compared to 0.2% in placebo-treated patients.[172] Although these numbers are small and similar to other antidepressants, the FDA has given duloxetine a warning that it is not to be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.[172] Levomilnacipran has also been shown to mildly increase LFTs at initiation of therapy.[166]

Case 86-2, Question 2: M.G. is given a prescription of duloxetine 30 mg qam. She has heard from television ads about a new antidepressant called Trintellix (vortioxetine) and she wonders if this new medication is different from what she has been prescribed. What are the differences in mechanisms of action between duloxetine and vortioxetine and do these result in differences in efficacy on symptoms of depression?

Selective Serotonin Reuptake Inhibitors and Serotonin-Receptor Modulators

Vilazodone and vortioxetine are members of a new class of antidepressant. These medications have their primary effect on depression via inhibition of the serotonin reuptake pump, like the SSRIs (see Table 86-10). These two agents also have potency at other serotonin receptors. Vilazodone is a partial agonist at the 5-HT_{1a} receptor.[173] Vortioxetine is a 5-HT_{1a} agonist, 5-HT_{1d}, 5-HT_3, 5-HT_7 antagonist, and 5-HT_{1b} partial agonist. Despite the potential for the added serotonin-receptor effects, head-to-head trials with SSRIs and SNRIs have shown no greater efficacy advantage and similar side effect profiles.[171,173–175] In two separate studies, vortioxetine 20 mg showed less reduction in MADRS compared to duloxetine 60 mg qam, −15.57 versus −16.9, respectively, and −18.8 versus 21.2, respectively, the lower the score the less depression one has.[176,177]

Vilazodone should be taken with food, as this increases absorption by about 50%. It is metabolized primarily by CYP450 3A4 and secondarily through 2C19. Inhibitors and inducers have a small effect on blood levels. Its half-life is ~25 hours.[178] Vilazodone seems to have no effect on CYP450 isoenzymes.[146] Vortioxetine is metabolized via multiple CYP 450 pathways with 2D6 being the primary one. It has a half-life of ~60 hours. It does not appear to effect the metabolism of other drugs using CYP450 (see Tables 86-7 and 86-8).[179]

Nefazodone and trazodone have similar mechanisms of action. Both are serotonin reuptake inhibitors but nefazodone also has a mild NE reuptake inhibitory effect. Both also block 5-HT_2 receptors.[17] This particular characteristic has resulted in very little sexual dysfunction, and switching studies have shown that patients who develop sexual side effects with SSRIs do not have this side effect with nefazodone.[180] Interestingly, trazodone does have the rare but well-documented side effect of priapism.[181] Trazodone, which comes as immediate-release and an extended-release caplet, is rarely used for depression because of its potency of H_1 antagonism centrally resulting in significant sedation and somnolence.[10,154,181] Antidepressive effects with trazodone occur above 150 mg/day with most patients requiring >300 mg/day, yet sedation occurs at low doses such as 25 mg.[181,182] This has caused clinicians to use trazodone as a hypnotic with other antidepressants instead of trying to titrate up and use it as monotherapy. It is also a potent α_1-receptor antagonist and can cause orthostasis.[10,181] A reason that nefazodone has not been used more is because of its potential for hepatotoxicity.[5,10] This event is more common than any other antidepressant. With appropriate monitoring, such as LFTs q3 months for the first 18 to 24 months, this risk is nearly eliminated.[10] However, using other drugs with hepatotoxic risks concomitantly, such as valproic acid, increases this risk making nefazodone more difficult to use than most other antidepressants. Nefazodone is metabolized via CYP450 3A4 and is also a moderate-to-strong inhibitor of CYP450 3A4 (see Table 86-8).[80,183]

When speaking with M.G., it would be accurate to state that the new medication is not likely to be any better than her current prescription. Monitoring vital signs is more important with duloxetine than with vortioxetine although the change in vital signs with duloxetine is minimal and usually clinically irrelevant. Duloxetine has a potential for inhibiting CYP450 2D6 that is greater than vortioxetine. Duloxetine should be titrated to 60 mg qam; thus, a dose increase is necessary to monitor for a therapeutic response (see Table 86-9).

OTHER AGENTS: BUPROPION AND MIRTAZAPINE

Bupropion is an aminoketone with a mechanism of action that is clearly different from that of any other antidepressant because its therapeutic effect is due primarily to DA reuptake inhibition with negligible effects on serotonin (see Table 86-7).[184] This lack of serotonin provides a benefit in regard to both a lack of sexual dysfunction and sedation but has a negative effect in that it is definitively less anxiolytic as compared to the proserotonergic effect of the other antidepressants.[5] At therapeutic dosages, bupropion has a different adverse effect profile compared to SSRIs and SNRIs. Nausea, insomnia, agitation, and jitteriness are the most common, likely because of the stimulatory effect of DA. Seizures are a risk but are unlikely with therapeutic dosing of bupropion, provided patients are not predisposed (eg, history of epilepsy, bulimia, electrolyte abnormalities, or recent history of heavy drinking). Bupropion may decrease appetite. A randomized, placebo-controlled investigation of bupropion in depressed obese patients observing caloric restriction found that bupropion was much more likely to induce significant weight loss than placebo.[185] After 26 weeks of treatment, 40% of the bupropion-treated patients lost more than 5% of their total body weight versus 16% with placebo. This weight loss was positively correlated with an improvement in depressive symptoms. It has little-to-no negative effect on sexual function because of no stimulation of 5-HT receptors. For patients who develop sexual dysfunction from the SSRI or SNRI, bupropion has shown some benefit as an

adjunctive treatment that reduces this side effect. It is also useful for poor responders as an adjunct to SSRI/SNRI because of its unique neurotransmitter effect.[5] Bupropion does not seem to affect cardiac rhythm or induce arrhythmias in susceptible patients.[186] Patients with hypertension should be monitored for increases in BP at the next visit after bupropion is initiated.[187]

Bupropion is converted via the cytochrome CYP450 2B6 isoenzyme to an active metabolite (9-hydroxybupropion). Bupropion (and its metabolite) appears to have a moderate effect at inhibiting the CYP450 2D6 isoenzyme, and significant elevations of venlafaxine and metoprolol have been demonstrated to occur with concurrent administration (see Table 86-8). Because of its short half-life (~8 hours for the parent compound and 12 hours for the active metabolite), therapeutic doses of regular release bupropion must be administered in divided doses. The recommended starting dose is 100 mg twice a day (bid), increasing to 100 mg three times a day (tid) after at least 3 days. Individual doses must not exceed 150 mg and should be given at least 6 hours apart. For the SR formulation, initial daily doses are 150 mg every day, increased to 150 mg bid by the fourth day at the earliest. Individual doses of bupropion SR can be as large as 200 mg, and divided doses should be given at least 8 hours apart. The once-daily formulation is initiated at 150 mg daily and increasing to 300 mg daily as early as the fourth day. Maximum daily doses are 450 mg for regular and XL products, and 400 mg for SR products (see Table 86-9). Staying below the maximum doses should be strictly followed because of the dose-dependent risk of seizures.[10]

Mirtazapine is a novel antidepressant capable of modulating serotonin and NE activity through antagonism at presynaptic α_2-autoreceptors and postsynaptic 5-HT_2 and 5-HT_3 receptors.[188] In addition, it appears to possess some mild inhibitory properties at serotonin reuptake transporters. Therefore, the net effect of mirtazapine is to enhance serotonin and NE in a manner that is clearly distinct from any other antidepressants (see Table 86-8). In a comparative randomized trial with fluoxetine for moderate-to-severe

depression, mirtazapine appeared to be much more effective than fluoxetine after 4 weeks of treatment (58% responders vs 30% with fluoxetine; $P > .05$), but the differences were no longer significant at 6 weeks (63% vs 54%; $P = .67$).[189]

The most common adverse effects experienced with mirtazapine are sedation and weight gain. Because mirtazapine has potent antihistaminergic effects, it can be quite sedating and is often used as a hypnotic similar to trazodone. Unlike trazodone, antidepressant dosing is quite tolerable. Anecdotally, it has been reported that higher daily doses of mirtazapine (>30 mg) are less sedating than lower doses owing to a plateauing of antihistaminic effects at 15 mg but with an increased noradrenergic effect up to 60 mg. In addition to the substantial risk of increasing appetite and total body weight, mirtazapine has been associated with significant increases in total cholesterol and triglycerides. This is likely because of its combination of H_1 and 5-HT_{2c} antagonism, the pharmacology related to atypical antipsychotic metabolic effects. This makes mirtazapine less preferred than SSRIs in patient with diabetes. Mirtazapine does not appear to affect cardiac rhythm or induce arrhythmias.[186] The recommended starting dosage is 15 mg at bedtime, and the therapeutic dosage ranges from 15 to 45 mg/day (see Table 86-9).[190] Data from controlled trials have demonstrated safety and efficacy in doses up to 60 mg daily.[190–192] As with bupropion, mirtazapine is considered a top choice for antidepressant combination therapy in poorly responding patients on an SSRI/SNRI. Despite the fact that mirtazapine is increasing 5-HT and NE as do SNRIs, its unique method of doing this via α_2 antagonism makes the combination with an SNRI or SSRI recommended.[5,10,193]

TRICYCLIC ANTIDEPRESSANTS

SSRIs are recommended over TCAs in the treatment of mood disorders. The popularity of SSRIs can be attributed to numerous advantages over older compounds, including a lower side effect burden, safety in overdose, less dosage titration, and patient preference.[5,10,26] Results of a meta-analysis concluded that although

the overall efficacy of the SSRI and TCA classes was comparable, primary care patients receiving an SSRI were much less likely to discontinue therapy prematurely because of side effects.[194] TCAs cause a variety of adverse effects, ranging from bothersome (dry mouth, sedation, constipation) to serious (cardiovascular effects), which often prevent patients from receiving therapeutic doses of medication.[195] Patient adherence to prescribed medication may also be compromised with TCAs.[196] Even though SSRIs and the newer SNRIs are preferred for the treatment of depression, TCAs continue to be prescribed at low doses for other indications that are comorbid with depression (eg, migraine prophylaxis, chronic neuropathic pain). This requires careful monitoring for drug interactions as TCAs as a class are primarily metabolized via CYP450 2D6 and, as noted, some SSRIs and SNRIs may inhibit this pathway substantially increasing the risk of TCA toxicity.

SIDE EFFECTS

Therapeutic effects of TCAs are primarily through their ability to inhibit the reuptake of serotonin and NE, functionally an SNRI (see Table 86-7).[197] Additionally, TCAs have significant antagonistic effects on acetylcholine, histamine, and α-noradrenergic receptors, all of which are considered potential for side effects. The intensity of these side effects has been shown to adversely affect adherence.[26] Although patients may develop tolerance to these effects, they may never disappear completely.

Because of the potent histamine 1 antagonism centrally, TCAs can be very sedating and are usually administered at bedtime to minimize functional impairments. Confusion or memory deficits may also occur with TCAs and can be particularly onerous in elderly patients. The secondary amines may be more tolerable in this regard, but all TCAs can impair concentration or alertness to some extent and are not recommended in geriatrics.[10] The sedating antihistaminic effect (along with orthostasis) increases the risk of falls. The risk of weight gain and constipation make TCAs undesirable in a patient with comorbid diabetes.

Orthostatic hypotension is the most common and troublesome cardiovascular effect of the TCAs (as well as MAOIs) because it can result in significant morbidity and mortality.[198,199] Major clinical consequences of orthostatic hypotension include falls leading to bone fractures, lacerations, and even MI. Patients with congestive heart failure (CHF) and the elderly are at greatest risk for experiencing orthostatic hypotension. The tertiary amines (eg, amitriptyline, imipramine) may cause more severe orthostatic hypotension than the secondary amines (eg, nortriptyline, desipramine), and research supports the contention that nortriptyline has the lowest risk for causing orthostatic hypotension among TCAs.[200,201]

There are substantial differences among antidepressants (and antidepressant classes) in regard to overall cardiac safety and arrhythmogenic effects in particular. In general, the SSRIs appear to be relatively safe in patients with a history of arrhythmias or recent MI.[186] In a placebo-controlled investigation, hospitalized patients with unstable cardiac disease were randomly assigned to either sertraline or placebo.[202] Overall, both treatment arms were very well tolerated, and there was actually a lower risk of severe cardiac events reported in the sertraline group (vs placebo). Retrospective data suggest that SSRIs may be somewhat cardioprotective in depressed patients with heart disease, a benefit that might be explained by their ability to decrease platelet activation.[203,204]

Alternatively, TCAs increase heart rate, probably via intrinsic anticholinergic properties that increase sinus node activity. Clinically, this effect is generally not significant, especially in the medically healthy depressed patient.[10,205] However, it may be important in those with underlying conduction disease, coronary artery disease, or CHF. TCAs, even when used at therapeutic dosages for the treatment of depression, decrease premature atrial and ventricular contractions in both depressed and nondepressed patients.[206,207] Because TCAs have class 1A antiarrhythmic activity, they have arrhythmogenic activity and thus increase the chances of ventricular arrhythmias and even sudden death. This effect on rhythm and conduction is believed to be related to the inhibitory effects of TCAs

on the fast sodium channels and a decrease in Purkinje fiber action potential amplitude, membrane responsiveness, and slowed conduction.[205,207] TCAs also block the rapid potassium channel similarly.[205] This dual effect of sodium- and potassium-channel blockade results in a greater impact on inducing QTc prolongation compared to the SSRI class.[208] Even nortriptyline, which is believed to be one of the safer TCAs in patients with heart disease, was associated with a greater risk for adverse cardiac events than paroxetine.[209] In patients with preexisting conduction defects and in overdose, there is a greater risk for cardiac arrhythmias.[200] Therefore, patients should receive a baseline electrocardiogram (ECG) before therapy, and use in patients with preexisting cardiac conduction abnormalities should be avoided.[10]

Other risks associated with TCAs are a lowering of the seizure threshold. This seems to be worst with clomipramine and maprotiline compared to the others in the class.[10,210,211] This event is particularly risky in high doses, similar to bupropion. If patients are at risk of seizures or have a seizure disorder, SSRIs are much safer and are preferred over TCAs.[10,210,211] TCAs have also been shown to produce photosensitivity; thus, excessive exposure to sunlight has resulted in severe sunburns. In patients who have had this reaction or whose lifestyle requires frequent contact with sunlight (eg, lifeguard), switching to another class is recommended.[212]

MONOAMINE OXIDASE INHIBITORS

MAOIs are an alternative for patients who have failed multiple antidepressant trials. MAOIs are believed to relieve depressive symptoms by enhancing the activity of monoamines. This is done by blocking the enzyme MAO, which breaks down serotonin, dopamine, and NE. This is in contrast to an SSRI/SNRI, which increases 5-HT and/or NE by preventing its reuptake into the neuron. This may be desirable for refractory cases. Candidates for treatment should be chosen carefully, and MAOIs should be used only by specialist practitioners such as a psychiatrist.

Phenelzine, tranylcypromine, and isocarboxazid were commonly prescribed for the treatment of depression in the 1970s and 1980s, and their usefulness waned primarily because of the risks of serious drug–drug and drug–food interactions.[213] In standard treatment of depression, MAOIs are not recommended, except for the treatment of atypical depression where this class appears to have a small efficacy advantage over other classes.[5,10] Data comparing TCAs with SSRIs for atypical depression suggest that the two classes are comparable in efficacy and both are superior to placebo and so SSRIs should still be tried first because of safety concerns.[10,214]

The “cheese reaction,” which can manifest as a hypertensive crisis, is so named because it occurred in patients who were taking nonselective MAOIs and ingested foods high in tyramine, a by-product of tyrosine metabolism that is found in certain foods and beverages, such as aged cheese or Chianti wine (**Table 86-12**). When tyramine is ingested in the absence of an MAOI, it is rapidly metabolized by the MAO enzyme in the GI tract before systemic absorption. In the presence of an MAOI, more tyramine is absorbed, and relatively high concentrations of tyramine may be achieved in circulation, resulting in the displacement of NE (and other catecholamines) from presynaptic storage granules. NE surges into the synapse, and as metabolic degradation is inhibited by the MAOI, a profound pressor response is triggered.[215] A slightly safer version of the MAOI class is the once-daily selegiline transdermal. By avoiding the GI tract, selegiline has less effect on the MAO that reduces tyramine from entering the bloodstream via food. Despite the improved safety of selegiline transdermal to oral MAOIs, there still remains a risk of food–drug interactions resulting in hypertensive reactions, particularly at higher doses, and so the FDA has recommended diet restrictions for doses over 6 mg/24 hours. Additionally, there are application site reactions that occur in ~35% of patients.[5,216,217] This agent is available in 6-, 9-, and 12-mg strengths. Selegiline transdermal as well as oral MAOIs are reserved for refractory cases and should be used only by skilled clinicians.[5,217]

Table 86-12
Foods Containing Tyramine

High Amounts of Tyramine[a]
Smoked, aged, or pickled meat or fish
Sauerkraut
Aged cheeses (eg, Stilton, blue cheese)
Yeast extracts (eg, marmite)
Fava beans
Moderate Amounts of Tyramine[b]
Beer (microbrewed > commercial)
Avocados
Meat extracts
Red wines such as Chianti
Low Amounts of Tyramine[c]
Caffeine-containing beverages
Distilled spirits
Chocolate
Soy sauce
Cottage and cream cheese
Yogurt and sour cream

[a]May not consume.
[b]May consume in moderation.
[c]May consume.

Adapted with permission from Shulman KI, Walker SE, MacKenzie S, Knowles S. Dietary restriction, tyramine, and the use of monoamine oxidase inhibitors. *J Clin Psychopharmacol*. 1989;9(6):397–402.

ADVERSE EFFECTS

Orthostatic hypotension, weight gain, edema, and sexual dysfunction are common during MAOI therapy.[198] As is the case with the TCAs, the nonselective MAOIs can cause clinically significant postural decreases in BP. However, with the MAOIs, the mechanism is believed to be a direct sympatholytic effect because both the lying

and the standing systolic BP readings are decreased.[218,219] Phenelzine seems to cause orthostatic hypotension more commonly than does tranylcypromine.[220] Because the orthostatic hypotension appears to be dose-related, a reduction in dosage may be helpful.[221] Sexual dysfunction occurs in up to 20% of patients taking MAOIs but may diminish and disappear spontaneously over time.[222,223] A switch into mania has been reported in up to 10% of patients with a history of bipolar disorder. Therefore, MAOIs should be avoided in this population.[198] Although MAOIs are not known as antimuscarinic medications, some patients report anticholinergic-like side effects, including blurred near vision and urinary retention. Dosage reduction may be helpful, but these effects may also diminish over time. The nonselective MAOIs are not associated with proarrhythmic, antiarrhythmic, or contractility effects when used in therapeutic dosages. Like other MAOIs, selegiline can be quite activating, and insomnia is frequently reported.

Several potentially fatal drug–drug interactions occur with nonselective MAOI antidepressants. Like the reaction with tyramine, indirect sympathomimetics such as phenylpropanolamine and pseudoephedrine (common ingredients in over-the-counter cold preparations and diet pills) can cause a precipitous rise in BP that can result in stroke.

The potential for serotonin syndrome with the combined use of SSRIs and MAOI antidepressants or other medications with MAOI effect is well-documented. A washout period of at least 14 days should separate the use of an SSRI and an MAOI. Because fluoxetine (and its primary active metabolite norfluoxetine) has a much longer half-life, the recommended washout period is at least 5 weeks after discontinuing this particular SSRI. Caution is advised when any other pro-serotonergic mediations are prescribed such as triptans and tramadol.[148]

Case 86-2, Question 3: M.G. still had some residual symptoms despite a therapeutic trial of duloxetine 60 mg qam. An increase to 90 mg resulted in intolerable insomnia. She has had a partial response (~40% reduction in

symptoms) but is still impaired by her depression. What are possible next steps?

Antidepressant Augmentation With Nonantidepressants

Treatment-refractory depression (TRD) is considered to be a failure to reach remission with two or more antidepressant monotherapy trials that were given at a therapeutic dose and given for an appropriately therapeutic period. Generally, a therapeutic dose is for 4 to 8 weeks. This would not include the time it takes to titrate to a therapeutic dose.[224,225] A common strategy for TRD includes combining antidepressants such as an SSRI with bupropion or mirtazapine, as mentioned previously. Other strategies are augmenting an antidepressant with a medication from another class, or somatic treatments, particularly ECT.[5,10,26,224,225]

There are many options to augment an SSRI/SNRI if the patient has not achieved a full response. Some atypical antipsychotics, lithium and triiodothyronine, all have studies showing efficacy. Buspirone has less robust data but is still recommended.[5,224,225] The use of atypical antipsychotics for the management of treatment-resistant depression has become relatively common among mental health providers because of well-designed and replicated studies. Four atypical antipsychotics (olanzapine in combination with fluoxetine, aripiprazole, brexpiprazole, and quetiapine) have received FDA approval as adjunctive agents with SSRIs or SNRIs for depression that has poorly responded to monotherapy, and others have been reported to be effective as well.[5,224,225] Generally, lower doses of second-generation antipsychotics have been successfully used in trials for depression (vs schizophrenia), and relatively rapid improvement was evident. Given the significant risk of metabolic side effects that have been reported, clinicians must carefully weigh the risks and benefits of recommending this augmentation strategy prior to maximizing antidepressant monotherapy trials and antidepressant combinations.[5,10] It is recommended that nonbehavioral health

practitioners use caution when prescribing the atypical antipsychotics for poorly responding patients.[193]

One instance where the use of an atypical antipsychotic adjunct is given during the acute phase is with psychotic depression. Patients with psychosis during the depressed episode, as with multiple previous episodes and depression severity, are at greater risk of chronicity and suicidality.[10] Multiple studies have shown benefit of antipsychotic and antidepressant combination better than either monotherapy. Despite the fact that monotherapy may be appropriate for the maintenance phase, it is recommended to start an antipsychotic with the antidepressant during the acute phase and slowly taper off after the persons depression and psychosis remits.[5,10,226] The least preferred antidepressant is bupropion. Its prodopaminergic effect could worsen the psychosis.[10] ECT is also a recommended treatment.[5,10,226]

Esketamine nasal inhalation is FDA approved as an adjunct to antidepressant therapy. It is an *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist while also a reuptake inhibitor for monoamines. It also has mild mu-opiate receptor agonism.[227–229] Esketamine has shown to reduce depression as a combination therapy with an SSRI or SNRI compared to placebo by ~4 to 10 points, as measured by the MADRS scale, within the first 24 hours.[230,231] Contrarily, one study did not show a statistical difference of adding esketamine to SSRI/SNRI treatment compared to just switching to a different SSRI/SNRI.[232] The dose of 56 or 84 mg is given at the clinician's office twice weekly for the first 4 weeks, then weekly for the next 4 weeks. Cardiovascular risks include increased heart rate and BP. Dissociative states of mind as well as other CNS and psychomimetic side effects occur in over 50% of the population. Esketamine also carries a risk of abuse.[233] These adverse effects require that the medication be sent directly to the clinician's office and that the patient be monitored by a health care professional at the office for at least 2 hours after every inhalation.[233,234]

Lithium's antidepressant properties as an augmenting agent have primarily been conducted with TCAs.[225] Seven of nine

antidepressant augmentation trials with lithium have reported positive therapeutic effects, usually within 1 week of achieving steady-state dynamics (ie, 3–7 days of daily dosing).[235] Effective lithium blood levels are generally within the range used to treat bipolar disorder (0.5–1.2 mEq/L). Lithium has a very narrow therapeutic index along with multiple significant drug interactions and should only be used by a clinician skilled in its use.[5]

Triiodothyronine (T_3) also has a long history of use in psychiatric circles for patients exhibiting partial or suboptimal responses to antidepressant monotherapy. Five of six RCTs support the use of T_3 supplementation for antidepressant augmentation, with an average effect size of 0.58 reported.[236] Triiodothyronine, at a dosage of 25 mg/day, can accelerate as well as augment antidepressant response, and superior effects have been reported in female patients, in particular. The response to the thyroid supplementation should be noticeable within 1 to 2 weeks, much like that found when lithium is used to augment therapy. Thyroxine (T_4) may also be effective with typical daily doses of 75 to 100 µg daily often used. In the STAR*D trials, T_3 was compared to lithium for antidepressant augmentation with citalopram in patients with two previous treatment failures.[237] Remission rates were modest for both agents in this challenging population (24.7% with T_3 vs 15.9% with lithium), and there was no significant difference between these two therapies.

In the STAR*D trial, augmentation with bupropion was compared to buspirone, and both adjunctive treatments showed 30% remission rates.[237] Buspirone may be of benefit to patients with residual symptoms of anxiety, in particular, and titration up to daily doses of 30 to 60 mg daily is often required.[5,193] Stimulants and modafinil have generally shown no benefit on depressive symptoms overall.[193,238] However, they may provide temporary relief from excessive fatigue and somnolence while waiting for the full antidepressant effect of the primary treatments.[5,225]

Because M.G. had a failure to two monotherapies and some response to duloxetine, the option of adding a medication to the SNRI is the next step. Combinations of duloxetine with another

antidepressant (mirtazapine or bupropion) or with an atypical antipsychotic are both recommended. Mirtazapine, quetiapine, and olanzapine would help if there is any insomnia and would protect against this side effect if duloxetine were to be increased in the future. Bupropion would possibly worsen insomnia. Aripiprazole, brexpiprazole, mirtazapine, quetiapine, and olanzapine (least to most) all could cause weight gain and worsen cholesterol. Discussing the risks of each option is critical and letting M.G. help decide which choice fits her lifestyle will ensure better adherence. M.G. decided to start aripiprazole 2 mg qam and will increase her exercising to mitigate the possible weight gain and cholesterol increase.

Pediatric Depression

CASE 86-3

QUESTION 1: A.A. is a 15-year-old male who has had a mood and behavior change over the last 6 months. A.A. is a sophomore in high school who averages Bs in his classes. He was a member of the varsity lacrosse team, with many friends. Over the last 6 months, he has been less involved with his friends to the point that he now does not want to go out. After lacrosse season, he normally would participate in off-season lacrosse camps. This year he did not want to. His grades have dropped, as he cannot concentrate as well on his schoolwork. He has missed some days of school lately because he does not want to get out of bed. Both illicit drug use and recent trauma have been ruled out. His medical history is unremarkable except for a 10-pound (4.54 kg) weight loss since last year, likely because of a poor appetite. His parents are very supportive.

What are the recommendations for the treatment of pediatric depression?

Rates of pediatric depression are less than in adults. As a person ages, the risk of depression increases with rates of 0.5% in 3- to 5-year-olds increasing to 3.5% in 12- to 17-year-olds.[10,239] Diagnosing pediatric depression uses the same criteria from the *DSM-5* as for adults; however, the interview questions may be slightly different. For example, poor concentration may be mislabeled as procrastination

or anhedonia might be described as "being bored."[9] Treatment guidelines do differ compared to adults. One reason for this is that placebo rates are much higher in pediatric studies resulting in the medication not having as dramatic a difference when compared to the difference between placebo and drug in adult studies. Thus, there are many studies where SSRIs had strong response rates but placebo also did and the medication was not considered to be statistically different.[240–242] Because of this high response rate from placebo and the support given by being a subject in a research study, the expert guidelines recommend supportive care and formal talking therapy be the first option for mild-to-moderate depression.[243,244] Medications can be used if symptoms are moderate to severe. Pharmacotherapy options are limited, though, compared to adults. Fluoxetine is FDA approved down to age 8, escitalopram to age 12. Clomipramine (age 10 and older), fluvoxamine (8 and older), and sertraline (6 and older) are FDA approved for obsessive–compulsive disorder but not depression. The SNRI duloxetine is approved for 7-year-olds and above for generalized anxiety disorder, and imipramine is approved for 6 and older for enuresis. To summarize, only two antidepressants are FDA approved for depression in children, although some other antidepressants do have nondepression indications in children.

Case 86-3, Question 2: The child psychiatrist's initial recommendation is to have A.A. meet with a psychologist. After 4 months of talking therapy, A.A. is improved in general but is still having bouts of sadness that prevent him from going to school a couple of days a month. It is decided to continue talk therapy but to add a medication. Which medication is the preferred agent?

Unlike adults where all antidepressants are similarly effective, pediatric depression guidelines have recommended that SSRIs particularly fluoxetine and escitalopram be the treatments of choice.[243,244] Fluoxetine's starting dose is 10 mg qam with a target dose of 20 to 40 mg a day. Escitalopram's starting dose is 5 to 10 mg qam with a target dose of 10 to 20 mg a day. Interestingly, the separation from placebo increases as the child ages for many of the

SSRIs. For example, escitalopram did not statistically differ from placebo in the under-12-year-old age group but did so in the adolescent age group.[240,245] Paroxetine is not recommended for depression because of the overall lack of efficacy in any age group when studies are combined and a high dropout rate in the younger patient.[240,242] Bupropion, mirtazapine, venlafaxine, and duloxetine have recommendations as treatment options but after failures of the SSRIs.[243] TCAs are not recommended primarily because of a high risk of harm being much greater than the small benefit on symptoms.[243,246]

Case 86-3, Question 3: A.A. is started on fluoxetine 10 mg qam. What safety monitoring is required when starting a young adult or pediatric patient on an antidepressant?

Generally, SSRIs are well tolerated in children. There is a black box warning for suicidal thinking. As with adults, the clinician needs to monitor for suicidality, but in children, there is a doubling of suicidal thoughts, not suicide attempts or completions, from 2% in the placebo arms to 4% in medication arms. It is important to note that actual suicides are much higher in untreated depressed youth compared to those taking antidepressants.[98,247–249] This risk diminishes as age groups increase. For patients over age 24, it is not required to be so vigilant regarding suicidal thinking, although many guidelines recommend continuing to monitor throughout the age ranges because of the possibility of disease-related risk. In pediatrics and young adults, the experts recommend the use of antidepressants with the FDA-sanctioned monitoring for suicidal thinking every week for the first week, every other week for the next 4 weeks, then monthly or as decided by the patient and clinician.[243,250] Talking therapy may have some protection against the side effect of increased suicidal thoughts.[251]

Geriatric Depression

Depression in late life is typically more difficult to recognize than depression in younger adults. Clinicians and patients may inappropriately attribute depressive symptoms to the “aging process” and minimize their significance. In addition, functional expectations are often lowered after retirement, making the degree of impairment difficult to evaluate. Because medical comorbidities are also more common in the elderly, depressive symptoms may be overlooked or misinterpreted in the workup as well.[121,252] In general, the elderly present with the same depressive target symptoms as younger adults, which is reflected in the fact that *DSM-5* diagnosis for major depression in adults is not specific for age. However, qualitatively, the presentation of depression among the elderly may be quite different. For instance, older patients are more likely to present with psychomotor retardation and are less likely to acknowledge “depression” per se, preferring instead to dwell on somatic concerns (eg, poor sleep, low energy, changes in bowel function, bodily aches, and pains).[10] They are also much less likely to share or admit suicidal thoughts, and because elderly males have the highest suicide completion rate, an accurate assessment of depression and attendant risks is critical.[10,121,253] In assessing nonspecific behavioral and cognitive symptoms in the elderly, a careful differential diagnosis between medical and other psychiatric disorders is essential because numerous medical illnesses can mimic depressive symptoms. Anemia, malignancies, CHF, and endocrine abnormalities may all present in a manner similar to that in depressive illness.

Aging does result in monoamine depletion as well as increased MAO activity.[121] One of the more difficult differential diagnoses in this setting involves the distinction of depression from dementias.[254,255] Like depression, patients with dementia may present with apathy, poor memory or concentration, reduced facial expression, and lack of spontaneous interaction. The illnesses are often comorbid, as 30% to 70% of patients with dementia also suffer from major depression.[255] Some experts have suggested, in fact, that new-onset depression in elderly patients may actually be part of a prodrome toward the manifestation of Alzheimer dementia.[255,256] A longitudinal cohort study found that among elderly patients suffering from an

acute episode of major depression, 57% were ultimately diagnosed with Alzheimer dementia within the next 3 years.[254] Diagnostically, there are three notable differences between dementia and depression: (a) the symptoms (slow and subtle changes with dementia, rapid with depression), (b) orientation (markedly impaired with dementia, intact with depression), and (c) principal CNS impairment (short-term memory with dementia, concentration with depression).

Drug Selection in the Elderly

A therapeutic trial of an antidepressant in a depressed individual with cognitive impairment may reverse the symptoms of the affective illness and restore functional capacity. Depression-related cognitive dysfunction will also improve to some degree. Moreover, because primary degenerative dementia is largely a diagnosis of exclusion, a successful trial of an antidepressant may help clarify the underlying pathologic condition and is strongly recommended in patients with a positive personal or family history of mood disorders.[257] The overall efficacy of antidepressants in elderly patients is believed to be comparable to that observed in younger subjects, although the response to treatment is somewhat slower (ie, 6-week therapeutic trial usually warranted).[5] Psychotherapy may be somewhat more effective in the elderly particularly because of the emotional impact of medical comorbidities and neurodegeneration effects as long as there is no dementia hindering talking therapy's effect.[5] Similarly, the comparative therapeutic effects of individual antidepressants do not appear to differ qualitatively between elderly patients and the general population. The selection of antidepressants for geriatric depression is the same as the process for younger patients. The elderly are much more sensitive to side effects compared to younger patients, and the presence of medical comorbidities and concurrent medications will have a greater influence on antidepressant selection. For example, the anticholinergic effects of TCAs preclude their use in elderly patients particularly if they are suffering from

narrow-angle glaucoma, chronic constipation, or urinary hesitancy. Anticholinergic impact on memory and the cardiac-related effects such as arrhythmias, orthostasis, and tachycardia are other critical reasons not to use the TCAs in the elderly. As noted previously, the risk of falls from TCAs because of antihistaminic, anticholinergic, and α-receptor antagonistic properties is another reason not to use them in the elderly population.

SSRIs are recommended as first line, but among this list, paroxetine is considered the worst option because of its anticholinergic effects (albeit mild) compared to no effect from the others. SNRIs also have data showing efficacy.[5,10,26] There does seem to be more dropouts with venlafaxine compared to the SSRIs.[5] Although sedating antidepressants such as mirtazapine may serve to promote sleep in depressed patients suffering from insomnia, other geriatric clients may be candidates for more activating medications that can increase energy or enhance alertness (eg, bupropion).

All antidepressants have a risk of causing SIADH, with SSRIs being the group with the highest reported cases. Elderly patients, compared to younger patients, are at a much greater risk of this event with some reviews reporting hyponatremia up to 32%.[10,258] As with other medications used in the elderly, antidepressants should be started at lower initial doses compared to adults.[5,10,121] Titration to a known therapeutic target dose has the best evidence even if the geriatric seems to be responding to a subtherapeutic dose.[5]

Therapeutic Blood Level Monitoring

Attempts to demonstrate an association between plasma concentrations and therapeutic response for SSRIs and SNRIs have been largely unsuccessful. In contrast, the serum concentration of some TCAs correlates well with clinical response. Nortriptyline exhibits a curvilinear effect, whereas imipramine demonstrates a sigmoidal relationship between serum levels and clinical response.[259,260] Maximum benefit of imipramine is usually associated with serum levels of imipramine plus its demethylated metabolite,

desipramine, in excess of 250 ng/mL. The relationship between plasma concentration of desipramine and clinical response is less clear, but a linear relationship is likely.[261] The most controversy surrounds amitriptyline; studies have shown a linear relationship, a curvilinear relationship, and no relationship between serum concentration and outcome.[262–264] The american psychiatric association (APA) Task Force on the Use of Laboratory Tests in Psychiatry recommends plasma concentration monitoring of TCAs when patients are elderly, not responding to therapy, nonadherent, experiencing adverse effects, or on multiple medications that may result in a possible drug interaction.[265] Plasma concentrations of imipramine, nortriptyline, and desipramine should be obtained after at least 1 week of a constant dosage when steady state has been achieved. Samples should be drawn 12 hours after the last dose has been administered. Routine therapeutic blood monitoring of other antidepressants is not recommended because information concerning their usefulness is limited; however, serum levels may be useful for evaluating adherence in some patients or ruling out serious toxicities.[266]

Antidepressants and Chronic Pain

CASE 86-4

QUESTION 1: D.C. is a 42-year-old female with a history of chronic lower back and left leg pain who has noted increased crying spells and a decreased interest in social activities during the course of the last 4 months. She attributes this downturn to the stress she is experiencing as she cares for her disabled mother who recently moved in with her. When asked, she also notes significant decreases in energy and concentration and difficulties in falling and staying asleep.

In the past, D.C. recalls one previous episode of depression 8 years ago, when she was treated initially with venlafaxine (discontinued because of nausea) and ultimately responded to a course of psychotherapy. Her past medical history is significant for chronic pain from a car accident 7 years ago, which continues to bother her on a daily basis (she rates pain at 5 of 10 currently), hypertension, and hyperlipidemia. Her current medications include lisinopril 10 mg qam and atorvastatin 10 mg qhs. In addition, she started

amitriptyline 50 mg at bedtime 2 months ago for her insomnia but noticed a 12-pound (5.44 kg) weight gain and recently discontinued. In the meantime, she has continued to see her therapist on a weekly basis during this time frame.

What considerations may influence treatment selection in this patient with chronic pain? What treatment should be recommended?

There is a strong and complex association between chronic pain syndromes and mood disorders. Epidemiologic investigations report that 50% of patients with chronic pain will satisfy the criteria for a depressive disorder.[267] Anxiety disorders are also commonly reported in this population as well. On the other hand, 65% of individuals with major depression will experience some symptoms of somatic pain, often presenting with pain as their main problem. Researchers have theorized that this comorbid phenomenon can be explained by deficiencies in the neurotransmitters serotonin and NE, which influence mood disorders in the prefrontal cortex and limbic system, as well as modulate pain sensitivity via descending projections down the spinal column. Other theories implicate elevations in cytokine activity, which commonly occur during the course of mood disorders, as well as mediating inflammatory activity occurring within the context of chronic pain.[267,268]

Treatment plans for depressed patients with chronic pain should target both of these conditions in order to achieve optimal outcomes. In regard to the selection of antidepressants, preference is often given to medications that can address both sets of symptoms associated with these comorbid conditions. For instance, antidepressant agents with pain-relieving properties and agents that promote sleep and relieve anxiety are often preferred. Antidepressants that enhance 5-HT and NE (TCAs and SNRIs) have proven to be quite effective for the management of neuropathic pain conditions, in addition to their benefits on anxiety and depression.[5,267,268] SSRIs are much less effective primarily because of the lack of NE enhancement, which is critical for analgesia.[5]

Drug interactions are often a major consideration in the selection of antidepressants. Certain opioid analgesics are prodrugs and require metabolic transformation to generate the active species.

These analgesics include codeine (metabolized to morphine), hydrocodone (active metabolite: hydromorphone), and oxycodone (oxymorphone), as well as tramadol (*o*-desmethyl tramadol). Patients who require these medications would benefit from antidepressants that do not effect CYP 450 (see Table 86-8).

D.C. meets the criteria for an acute episode of major depression, and medication is clearly indicated. Among the alternatives, SSRIs have not proven to be effective for neuropathic pain. SNRIs and TCAs are effective for neuropathic pain conditions, as well as depression and anxiety. However, there are substantial tolerability and toxicity risks with TCAs not shown with the SNRI class. Additionally, she has experienced significant weight gain with a low-dose TCA (50 mg amitriptyline). An SNRI would be a good choice for the treatment of her depression and chronic pain. Given D.C.'s history of nausea from venlafaxine, an alternate SNRI, such as levomilnacipran or duloxetine, should be initiated. Duloxetine inhibits CYP450 2D6, which is currently not an issue but should be taken into consideration if other medication changes are considered in the future.

Summary

Depressive episodes have a significant morbidity impact and can result in mortality, usually via suicide. Treatment has been shown to reduce acute impact and prevent future episodes. All antidepressants are considered generally equal in regard to efficacy. Comorbid drug–disease and drug–drug interactions help identify best first-choice options. Overall, SSRIs are considered the best first choice because of good tolerability, safety in overdose, and low cost. Of these, sertraline and escitalopram may have a slight advantage. Previous treatment successes or failures and family history of medication response are important determining factors when disease and drug issues are not present. Minimal treatment duration should be 6 months after remission has been achieved, although many patients will require lifelong pharmacotherapy. Patient

education and safety monitoring are critical aspects once the patient enters into treatment. Outcomes for treatment are predictably beneficial with improvements in quality of life and a reduction of suicidal events.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Cleare A, Pariante CM, Young AH, et al. Evidenced based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol.* 2015;29(*5*):459–525. (5)

Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. American Psychiatric Association; 2010. (10)

Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. *CNS Drugs*. 2012;26(*1*):39–67. (146)

Key Websites

American Psychiatric Association. http://www.psychiatryonline.org

National Alliance on Mental Illness. http://www.nami.org

National Institute of Mental Health. http://www.nimh.nih.gov

COMPLETE REFERENCES CHAPTER 86 DEPRESSIVE DISORDERS

1. National Collaborating Centre for Mental Health (UK). *Depression: The Treatment and Management of Depression in Adults (Updated Edition).*

National Institute for Health and Clinical Excellence. British Psychological Society; 2010.
2. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients. *JAMA*. 1989;262:914–919.
3. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry*. 2015;76:155–162.
4. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity and comorbidity of 12-month *DSM-IV* disorders in the national comorbidity survey [published correction appears in *Arch Gen Psychiatry*. 2005;62:709]. *Arch Gen Psychiatry*. 2005;62:617–627.
5. Cleare A, Pariante CM, Young AH, et al. Evidenced based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. 2015;29(5):459–525.
6. Lieb R, Isensee B, Höfler M, Pfister H, Wittchen HU. Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. *Arch Gen Psychiatry*. 2002;59:365–374.
7. McGuffin P, Katz R. The genetics of depression and manic depressive disorder. *Br J Psychiatry*. 1989;155:294–304.
8. Blehar MC, Weissman MM, Gershon ES, Hirschfeld RM. Family and genetic studies of affective disorders. *Arch Gen Psychiatry*. 1988;45:289–292.
9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. American Psychiatric Association Press; 2013.
10. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. American Psychiatric Association; 2010.
11. Cuijpers P, van Straten A, van Oppen P, Andersson G. Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. *J Clin Psychiatry*. 2008;69:1675–1685.
12. Schildkraut JJ. Neuropsychopharmacology and the affective disorders. *N Engl J Med*. 1969;281:302–308.
13. Maas JW. Biogenic amines and depression. *Arch Gen Psychiatry*. 1975;32:1357–1364.
14. Hamon M, Blier P. Monoamine neurocircuitry in depression and strategies for new treatments. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;45:54–63.
15. Kohler S, Cierpinsky K, Kronenberg G, Adli M. The serotonergic system in the neurobiology of depression: relevance for novel antidepressants. *J Psychopharmacol*. 2016;30(1):13–22.

16. Richelson E. Multi-modality: a new approach for the treatment of major depressive disorder. *Int J Neuropsychopharmacol*. 2013;16:1433–1442.
17. Artigas F, Nutt DJ, Shelton R. Mechanism of action of antidepressants. *Psychopharmacol Bull*. 2002;36(Suppl 2):123–132.
18. Charney DS, Menkes DB, Heninger GR. Receptor sensitivity and the mechanisms of action of antidepressant treatment. *Arch Gen Psychiatry*. 1981;381:1160–1180.
19. Risch SC, Nemeroff CB. Neurochemical alterations of serotonergic neuronal systems in depression. *J Clin Psychiatry*. 1992;53:3–7.
20. Kramer MS, Cutler N, Feighner J. Distinct mechanism for antidepressant activity by blockade of central substance p receptors. *Science*. 1998;281:1640–1645.
21. Gold PW, Drevets WC, Charney DS. New insights into the role of cortisol and the glucocorticoid receptor in severe depression. *Biol Psychiatry*. 2002;52:381–385.
22. Nemeroff CB. New directions in the development of antidepressants: the interface of neurobiology and psychiatry. *Hum Psychopharmacol*. 2002;17:S13–S16.
23. Valdez GR. Development of CRF1 receptor antagonists as antidepressants and anxiolytics. Progress to date. *CNS Drugs*. 2006;201(11):887–896.
24. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry*. 2007;64:327–337.
25. Nemeroff CB, Evans DL. Thyrotropin-releasing hormone (TRH), the thyroid axis, and affective disorder. *Ann N Y Acad Sci*. 1989;553:304–310.
26. Trangle M, Gursky J, Haight R, et al. Institute for Clinical Systems Improvement. *Adult Depression in Primary Care*. Updated March 2016. https://www.icsi.org/guideline/depression
27. Furtado M, Katzman MA. Examining the role of neuroinflammation in major depression. *Psychiatr Res*. 2015;229:27–36.
28. Duval F, Mokrani MC, Erb A, et al. Chronobiological hypothalamic-pituitary-thyroid axis status and antidepressant outcome in major depression. *Psychoneuroendocrinology*. 2015;59:71–80.
29. Dean J, Keshavan M. The neurobiology of depression: an integrative view. *Asian J Psychiatr*. 2017;27:101–107.
30. Carroll BJ, Cassidy F, Naftolowitz D, et al. Pathophysiology of hypercortisolism in depression. *Acta Psychiatr Scand*. 2007;115(S433):90–103.
31. Lee AL, Ogle WO, Sapolsky RM. Stress and depression: possible links to neuron death in the hippocampus*. Bipolar Disord*. 2002;4:117–128.
32. Agarwal N, Port JD, Bazzocchi M, Renshaw PF. Update on the use of MR for assessment and diagnosis of psychiatric diseases. *Radiology*. 2010;255(1):23–41.

33. Sarubin N, Nothdurfter C, Schmotz C, et al. Impact on cortisol and antidepressant efficacy of quetiapine and escitalopram in depression. *Psychoneuroendocrinology*. 2014;39:141–151.
34. Karlovic D, Serretti A, Vrkic´ N, Martinac M, Marc ˇ inko D. Serum concentrations of CRP, IL-6, TNF-alpha and cortisol in major depressive disorder with melancholic or atypical features. *Psychiatry Res*. 2012;198:74–80.
35. Lotrich FE. Inflammatory cytokine-associated depression. *Brain Res*. 2015;1617:113–125.
36. Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatry*. 2010;15:473–500.
37. Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry*. 2007;12:247–257.
38. Horstmann S, Binder EB. Pharmacogenomics of antidepressant drugs. *Pharmacol Ther*. 2009;124:57–73.
39. Fabbri C, Serretti A. Pharmacogenetics of major depressive disorder: top genes and pathways toward clinical applications. *Curr Psychiatry Rep*. 2015;17:50.
40. Perez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC Psychiatry*. 2017;17:250.
41. Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. *J Psychiatr Res*. 2019;111:59–67.
42. George MS, Ketter TA, Post RM. SPECT and PET imaging in mood disorders. *J Clin Psychiatry*. 1993;54:6–13.
43. Nemeroff CB. The neurobiology of depression. *Sci Am*. 1998;278:42–49.
44. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull*. 2003;65:193–207.
45. Cole J, Costafreda SG, McGuffin P, Fu CH. Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. *J Affect Disord*. 2011;134:483–487.
46. Pan J, Xia J, Deng F, et al. Diagnosis of major depressive disorder based on changes in multiple plasma neurotransmitters: a targeted metabolomics study. *Trans Psychiatry*. 2018;8:130.
47. Gadad BS, Jha MK, Czysz A, et al. Peripheral biomarkers of major depression and antidepressant treatment response: current knowledge and

future outlooks. *J Affect Disord*. 2018;233:3–14.
48. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
49. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561–571.
50. Zung WW. A self-rating depression scale. *Arch Gen Psychiatry*. 1965;12:63–70.
51. Montgomery SA, Asberg M. New depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
52. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385–401.
53. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613.
54. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression [published correction appears in *Biol Psychiatry*. 2003;54:585]. *Biol Psychiatry*. 2003;54:573–583.
55. Siu AL; the USPSTF. Screening for depression in adults: US Preventative Services Task Force recommendation statement. *JAMA*. 2016;315(4):380–387.
56. Arnow BA, Constantino MJ. Effectiveness of psychotherapy and combination treatment for chronic depression. *J Clin Psychol*. 2003;59:893–905.
57. UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. 2003;361(9360):799–808.
58. Devanand DP, Sackeim HA, Prudic J. Electroconvulsive therapy in the treatment-resistant patient. *Psychiatr Clin North Am*. 1991;14:905–923.
59. Cusin C, Dougherty DD. Somatic therapies for treatment-resistant depression: ECT, TMS, VNS, DBS. *Biol Mood Anxiety Disord*. 2012;2:14.
60. Shapira B, Tubi N, Drexler H, Lidsky D, Calev A, Lerer B. Cost and benefit in the choice of ECT schedule. *Br J Psychiatry*. 1998;172:44–48.
61. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs. pharmacotherapy for relapse prevention in major depression: a multisite study from the consortium for research in electroconvulsive therapy (CORE). *Arch Gen Psychiatry*. 2006;63:1337–1344.
62. Hallett M. Transcranial magnetic stimulation: a primer. *Neuron*. 2007;55:187–199.
63. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120:208–239.
64. Martin JL, Barbanoj MJ, Schlaepfer TE, et al. Transcranial magnetic stimulation for treating depression. *Cochrane Database Syst Rev*. 2003;

(3):CD003387.
65. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry*. 2008;69:222–232.
66. Lefaucheur J, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018*). Clin Neurophysiol*. 2020;131:474–528.
67. Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. *Neurosci Biobehav Rev*. 2005;29:493–500.
68. Gross F, Gysin F. Phototherapy in psychiatry: clinical update and review of indications. *Encephale*. 1996;22:143–148.
69. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomized controlled trials. *BMJ*. 2001;322:763–767.
70. Brene S, Bjørnebekk A, Aberg E, Mathé AA, Olson L, Werme M. Running is rewarding and antidepressive. *Physiol Behav*. 2007;92:136–140.
71. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life in breast, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone and melatonin in breast cancer and prostate cancer outpatients. *Psychoneuroendocrinology*. 2004;29:448–474.
72. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373:746–758.
73. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder. An updated meta-analysis. *Ann Intern Med*. 2011;155:772–785.
74. Spina E, Santoro V, D'Arrigo C. Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: an update. *Clin Ther*. 2008;30(7):1206–1227.
75. Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry*. 2006;63:1217–1223.
76. Dubovsky SL. Beyond the serotonin reuptake inhibitors: rationale for the development of new serotonergic agents. *J Clin Psychiatry*. 1994;55(Suppl):34–44.
77. Vogel GW, Buffenstein A, Minter K, Hennessey A. Drug effects on REM sleep and on endogenous depression. *Neurosci Biobehav Rev*. 1990;14:49–63.
78. Gregorian RS, Golden KA, Bahce A, Goodman C, Kwong WJ, Khan ZM. Antidepressant-induced sexual dysfunction*. Ann Pharmacother*.

2002;36:1577–1589.
79. Prabhaker D, Balon R. How do SSRIs cause sexual dysfunction? *Curr Psychiatr*. 2010;9(12):30–34.
80. Casper RC, Redmond DE Jr, Katz MM, Schaffer CB, Davis JM, Koslow SH. Somatic symptoms in primary affective disorder: presence and relationship to the classification of depression. *Arch Gen Psychiatry*. 1985;42:1098–1104.
81. Atmaca M. Selective serotonin reuptake inhibitor-induced sexual dysfunction: current management perspectives. *Neuropsychiatr Dis Treat*. 2020;16:1043–1050.
82. Shen WW, Hsu JH. Female sexual side effects associated with selective serotonin reuptake inhibitors: a descriptive clinical study of 33 patients. *Int J Psychiatry Med*. 1995;25:239–248.
83. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. *Am J Psychiatry*. 1995;152:1514–1516.
84. Labbate LA, Pollack MH. Treatment of fluoxetine-induced sexual dysfunction with bupropion: a case report. *Ann Clin Psychiatry*. 1994;6:13–15.
85. Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry*. 1998;59:112–115.
86. Kennedy SH, McCann SM, Masellis M, et al. Combining bupropion SR with venlafaxine, paroxetine or fluoxetine: preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry*. 2002;63:181–186.
87. Demyttenaere K, Jaspers L. Bupropion and SSRI-induced side effects. *J Psychopharmacol*. 2008;22(7):792–804.
88. Woodrum ST, Brown CS. Management of SSRI-induced sexual dysfunction. *Ann Pharmacotherapy*. 1998;32:1209–1215.
89. Nurnberg HG, Hensley PL, Gelenberg AJ, Fava M, Lauriello J, Paine S. Treatment of antidepressant-associated sexual dysfunction with sildenafil. *JAMA*. 2003;289:56–64.
90. Segraves RT, Lee J, Stevenson R, Walker DJ, Wang WC, Dickson RA. Tadalafil for treatment of erectile dysfunction in men on antidepressants. *J Clin Psychopharmacol*. 2007;27(1):62–66.
91. Shrivastava RK, Shrivastava S, Overweg N, Schmitt M. Amantadine in the treatment of sexual dysfunction associated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol*. 1995;15:83–84.
92. Norden MJ. Buspirone treatment of sexual dysfunction associated with selective serotonin re-uptake inhibitors. *Depression*. 1994;2:109–112.
93. Jacobsen FM. Fluoxetine-induced sexual dysfunction and an open-label trial of yohimbine. *J Clin Psychiatry*. 1992;53:119–122.
94. Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. *J Sex Marital Ther*. 1998;24:139–143.

95. Gelenberg AJ, McGahuey C, Laukes C, et al. Mirtazapine substitution in SSRI-induced sexual dysfunction. *J Clin Psychiatry*. 2000;61(5):356–360.
96. Delgado PL, McGahuey CA, Moreno FA, Laukes C, Gelenberg AJ. Treatment strategies for depression and sexual dysfunction. *J Clin Psychiatry*. 1999;17:15–21.
97. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: a meta-analysis of drug company data from placebo controlled, randomized controlled trials submitted to the MHRA's safety review. *BMJ*. 2005;330:385–390.
98. Isacsson G, Rich CL. Antidepressant drugs and the risk of suicide in children and adolescents. *Pediatr Drugs*. 2014;16:115–122.
99. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Prim Care Companion J Clin Psychiatry*. 2001;3:22–27.
100. Modi S, Lowder D. Medications for migraine prophylaxis. *Am Fam Phys*. 2006;73(1):72–78.
101. Hamel E. Serotonin and migraine: biology and clinical implications. *Cephalalgia*. 2007;27:1295–1230.
102. Vida S, Looper K. Precision and comparability of adverse event rates of newer antidepressants. *J Clin Psychopharmacol*. 1999;19:416–426.
103. Marcy TR, Britton ML. Antidepressant-induced sweating. *Ann Pharmacother*. 2005;39:748–752.
104. Mercadante S. Hyoscine in opioid-induced sweating. *J Pain Symptom Manage*. 1998;15:214–215.
105. Romanelli F, Adler DA, Bungay KM. Possibleparoxetine-inducedbruxism. *Ann Pharmacother*. 1996;30:1246–1248.
106. Ellison JM, Stanziani P. SSRI-associated nocturnal bruxism in four patients. *J Clin Psychiatry*. 1993;54:432–434.
107. Rugh JD, Harlan J. Nocturnal bruxism and temporomandibular disorders. *Adv Neurol*. 1988;49:329–341.
108. Kirby D, Ames D. Hyponatremia and selective serotonin reuptake inhibitors in elderly patients. *Int J Geriatr Psychiatry*. 2001;16:484–493.
109. Arinzon ZH, Lehman YA, Fidelman ZG, Krasnyansky II. Delayed recurrent SIADH associated with SSRIs. *Ann Pharmacother*. 2002;36:1175–1177.
110. Greenblatt HK, Greenblatt DJ. Antidepressant-associated hyponatremia in the elderly. *J Clin Psychopharmacol*. 2016;36:545–549.
111. Leo RJ. Movement disorders associated with selective serotonin reuptake inhibitors. *J Clin Psychiatry*. 1996;57:449–454.
112. Caley CF. Extrapyramidal reactions and the selective serotonin-reuptake inhibitors. *Ann Pharmacother*. 1997;31:1481–1489.
113. Lane RM. SSRI-Induced extrapyramidal side-effects and akathisia: implications for treatment. *J Psychopharmacol*. 1998;12(2):192–214.

114. Levine LR, Rosenblatt S, Bosomworth J. Use of a serotonin re-uptake inhibitor, fluoxetine, in the treatment of obesity. *Int J Obes*. 1987;11(Suppl 3):185–190.
115. Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychiatry*. 2000;61:863–867.
116. Paton C, Ferrier IN. SSRIs and gastrointestinal bleeding. *BMJ*. 2005;331:529–530.
117. Anglin R, Yuan Y, Moayyedi P, Tse F, Armstrong D, Leontiadis GI. Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. *Am J Gastroenterol*. 2014;109:811–819.
118. Vidal X, Ibáñez L, Vendrell L, et al. Risk of upper gastrointestinal bleeding and the degree of serotonin reuptake inhibition by antidepressants: a case-control study. *Drug Saf*. 2008;31:159–168.
119. Lewis JD, Strom BL, Localio AR, et al. Moderate and high affinity serotonin reuptake inhibitors increase the risk of upper gastrointestinal toxicity. *Pharmacoepidemiol Drug Saf.* 2008;17:328–335.
120. *Depression Guideline Panel*. Agency for Health Policy and Research, US Department of Health and Human Services; 1993.
121. Felice D, O'Leary OF, Cryan JF, et al. When aging meets the blues: are the current antidepressants effective in depressed aged patients? *Neurosci Biobehav Rev*. 2015;55:478–497.
122. Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant discontinuation syndrome. *Am Fam Physician*. 2006;74:449–457.
123. Baldessarini RJ, Tondo L, Ghiani C, Lepri B. Illness risk following rapid versus gradual discontinuation of antidepressants. *Am J Psychiatry*. 2010;167:934–941.
124. Davies S, Naik PC, Lee AS. Depression, suicide, and the national service framework. *BMJ*. 2001;322:1500–1501.
125. Judd LL. The clinical course of unipolar major depressive disorders. *Arch Gen Psychiatry*. 1997;54:989–991.
126. Nonacs R, Cohen LS. Depression during pregnancy: diagnosis and treatment options. *J Clin Psychiatry*. 2002;63:24–30.
127. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment [published correction appears in *JAMA*. 2006;296:170]. *JAMA*. 2006;295:499–507.
128. Chaudron LH. Complex challenges in treating depression during pregnancy. *Am J Psychiatry*. 2013;170:12–20.
129. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin reuptake inhibitors and the risk of birth defects. *N Engl J Med*. 2007;356:2675–2683.

130. Alwan S, Reefhuis J, Rasmussen SA, et al. Use of serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med*. 2007;356:2684–2692.
131. Berard A, Ramos E, Rey E, Blais L, St-André M, Oraichi D. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. *Birth Defects Res B Dev Reprod Toxicol*. 2007;80:18–27.
132. Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry*. 2003;60:720–726.
133. Wisner KL, Bogen DL, Sit D, et al. Does fetal exposure to SSRIs or maternal depression impact infant growth? *Am J Psychiatry*. 2013;170:485–493.
134. Einarson A, Choi J, Einarson TR, Koren G. Rates of spontaneous and therapeutic abortions following use of antidepressants in pregnancy: results from a large prospective database. *J Obstet Gynaecol Can*. 2009;31:452–456.
135. O'Connor E, Rossom RC, Henninger M, Groom HC, Burda BU. Primary care screening for and treatment of depression in pregnant and postpartum women. Evidence report and systematic review for the US Preventative Services Task Force. *JAMA*. 2016;315(4):388–406.
136. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry*. 2009;31:403–413.
137. Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. *Drug Saf*. 2005;28(2):138–152.
138. Hutcherson TC, Cieri-Hutcherson NE, Gosciak MF. Brexanolone for postpartum depression. *Am J Health Syst Pharm*. 2020;77:336–345.
139. Walton N, Maguire J. Allopregnanolone-based treatments for postpartum depression: why/how do they work? *Neurobiol Stress*. 2019;11:100198
140. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomized, placebo-controlled, phase 3 trials. *Lancet*. 2018;392:1058–1070.
141. Spigstet O, Hagg S. Excretion of psychotropic drugs into breast milk: pharmacokinetic overview and therapeutic implications. *CNS Drugs*. 1998;9:111–134.
142. Wisner KL, Perel JM, Blumer J. Serum sertraline and N-desmethylsertraline levels in breast-feeding mother-infant pairs. *Am J Psychiatry*. 1998;155:690–692.
143. Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. Human cytochromes and some new antidepressants: kinetics, metabolism and drug interactions. *J Clin Psychopharmacol*. 1999;19(5 Suppl 1):23S–35S.

144. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors. An overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet*. 1997;32(suppl 1):1–21.
145. Preskorn SH, Greenblatt DJ, Flockhart D, et al. Comparison of duloxetine, escitalopram, and sertraline effects on cytochrome P450 2D6 function in healthy volunteers. *J Clin Psychopharmacol*. 2007;27(1):28–34.
146. Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. *CNS Drugs*. 2012;26(1):39–67.
147. Jefferson JW, Griest JH. Brussel sprouts and psychopharmacology: understanding the cytochrome P450 system. *Psychiatr Clin North Am*. 1996;3:205–222.
148. Igbal MM, Basil MJ, Kaplan J, Iqbal MT. Overview of serotonin syndrome. *Ann Clin Psychiatr*. 2012;24(4):310–318.
149. Graber MA, Hoehns TB, Perry PJ. Sertraline-phenelzine drug interaction: a serotonin syndrome reaction. *Ann Pharmacother*. 1994;28:732–735.
150. Iruela LM, Minguez L, Merino J, Monedero G. Toxic interaction of S-adenosylmethionine and clomipramine. *Am J Psychiatry*. 1993;150:522.
151. Lantz MS, Buchalter E, Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol*. 1999;12:7–10.
152. Sternbach H. The serotonin syndrome. *Am J Psychiatry*. 1991;148:705–713.
153. Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant associated insomnia. *Am J Psychiatry*. 1994;151:1069–1072.
154. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol*. 2010 ;24(11):1577–1601.
155. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med*. 1995;25:1171–1780.
156. Gibson TB, Jing Y, Smith Carls G, et al. Cost burden of treatment resistance in patients with depression. *Am J Manag Care*. 2010;16:370–377.
157. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J Clin Psychiatry*. 1995;56:30–34.
158. Thase ME, Ferguson JM, Lydiard RB, Wilcox CS. Citalopram treatment of paroxetine intolerant patients. *Depress Anxiety*. 2002;16:128–133.
159. Calabrese JR, Londborg PD, Shelton MD, Thase ME. Citalopram treatment of fluoxet-ineintolerant depressed patients. *J Clin Psychiatry*. 2003;64:562–567.
160. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*.

2006;354:1231–1242.
161. Kamath J, Handratta V. Desvenlafaxine succinate for major depressive disorder: a critical review of the evidence. *Expert Rev Neurother*. 2008;8:1787–1797.
162. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology*. 2001;25:871–880.
163. Auclair AL, Martel JC, Assié MB, et al. Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. *Neuropharmacology*. 2013;70:338–347.
164. Deecher DC, Beyer CE, Johnston G, et al. Desvenlafaxine succinate: a new serotonin and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther*. 2006;318(2):657–665.
165. Nichols AI, Jessica Behrle A, Virginia P, et al. Pharmacokinetics, pharmacodynamics, and safety of desvenlafaxine, a serotonin-norepinephrine reuptake inhibitor. *J Bioequiv Availab*. 2013;5(1):22–30.
166. Palmer EC, Binns LN, Carey H. Levomilnacipran: a new serotonin-norepinephrine reuptake inhibitor for the treatment of major depressive disorder. *Ann Pharmacother*. 2014;48(8):1030–1039.
167. Thase ME. Effect of venlafaxine on blood pressure: a meta-analysis of original data from 3744 patients. *J Clin Psychiatry*. 1998;59:502–508.
168. Wernicke J, Lledó A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine. Findings from 42 placebo-controlled studies. *Drug Saf*. 2007;30(5):437–455.
169. Thase ME, Fayyad R, Cheng RF, et al. Effects of desvenlafaxine on blood pressure in patients treated for major depressive disorder: a pooled analysis. *Curr Med Res Opin*. 2015;31(4):809–820.
170. Liebowitz MR, Yeung PP, Entsuah R. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry*. 2007;68:1663–1672.
171. Deardorff WJ, Grossberg GT. A review of the clinical efficacy, safety and tolerability of the antidepressants vilazodone, levomilnacipran and vortioxetine. *Expert Opin Pharmacother*. 2014;15(17):2525–2542.
172. McIntyre RS, Panjwani ZD, Nguyen HT, et al. The hepatic safety profile of duloxetine: a review. *Expert Opin Drug Metab Toxicol*. 2008;4(3):281–285.
173. Dawson LA. The discovery and development of vilazodone for the treatment of depression: a novel antidepressant or simply another SSRI? *Expert Opin Drug Disc*. 2013;8(12):1529–1539.
174. Citrome L. Vortioxetine for major depressive disorder: an indirect comparison with duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone, using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord*. 2016;196:225–233.

175. Wang G, Gislum M, Filippov G, Montgomery S. Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomized, double-blind study. *Curr Med Res Opin*. 2015;31(4):785–794.
176. Mahableshwarker AR, Jacobsen PL, Chen Y, Serenko M, Trivedi MH. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *Psychopharmacology (Berl).* 2015;232:2061–2070.
177. Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol*. 2014;29(3):138–149.
178. Boinpally R, Gad N, Gupta S, Periclou A. Influence of CYP3A4 induction/inhibition on the pharmacokinetics of vilazodone in healthy subjects. *Clin Ther*. 2014;36(11):1638–1649.
179. Pearce EF, Murphy JA. Vortioxetine for the treatment of depression. *Ann Pharmacother*. 2014;48(6):758–765.
180. Ferguson JM, Shrivastava RK, Stahl SM, et al. Reemergence of sexual dysfunction in patients with major depressive disorder: double blind comparison of nefazodone and sertraline. *J Clin Psychiatry*. 2001;62:24–29.
181. Stahl S. Mechanism of action of trazodone: a multifunctional drug. *CNS Spectr*. 2009;14(10):536–546.
182. Sheehan DV, Croft HA, Gossen ER, et al. Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study. *Psychiatry*. 2009;6(5):20–33.
183. Greene DS, Barbhaiya RH. Clinical pharmacokinetics of nefazodone. *Clin Pharmacokinet*. 1997;33(4):260–275.
184. Ascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanism of antidepressant activity. *J Clin Psychiatry*. 1995;56:395–401.
185. Jain AK, Kaplan RA, Gadde KM, et al. Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. *Obes Res*. 2002;10:1049–1056.
186. Alvarez W, Pickworth KK. Safety of antidepressant drugs in the patient with cardiac disease: a review of the literature. *Pharmacotherapy*. 2003;23:754–771.
187. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EG. Cardiovascular effects of bupropion in depressed patients with heart disease. *Am J Psychiatry*. 1991;148:512–516.
188. De Boer T. The effects of mirtazapine on central noradrenergic and serotonergic neurotransmission [published correction appears in *Int Clin Psychopharmacol*. 1996;11:153]. *Int Clin Psychopharmacol*. 1995;10:19–23.
189. Wheatley DP, van Moffaert M, Timmerman L, Kremer CM. Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with

moderate to severe major depressive disorder. *J Clin Psychiatry*. 1998;59:306–312.
190. Watanabe N, Omori IM, Nakagawa A, et al. Mirtazapine versus other antidepressants in the acute-phase treatment of adults with major depression: systematic review and meta-analysis. *J Clin Psychiatry*. 2008;69(9):1404–1415.
191. Versiani M, Moreno R, Ramakers-van Moorsel CJ, et al. Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. *CNS Drugs*. 2005;19(2):137–146.
192. Guelfi JD, Ansseau M, Timmerman L, Kørsgaard S; Mirtazapine-Venlafaxine Study Group. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. *J Clin Psychopharmacol*. 2001;21:425–436.
193. Preston TC, Shelton RC. Treatment resistant depression: strategies for primary care. *Curr Psychiatry Rep*. 2013;15:370.
194. MacGillivray S, Arroll B, Hatcher S, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ*. 2003;326:1014.
195. Katon W, von Korff M, Lin E, Bush T, Ormel J. Adequacy and duration of antidepressant treatment in primary care. *Med Care*. 1992;30:67–76.
196. Sclar DA, Robison LM, Skaer TL, et al. Antidepressant pharmacotherapy: economic outcomes in a health maintenance organization. *Clin Ther*. 1994;16:715–730.
197. Tran PV, Bymaster FP, McNamara RK, Potter WZ. Dual monoamine modulation for improved treatment of major depressive disorder. *J Clin Psychopharmacol*. 2003;23:78–86.
198. Rabkin JG, Quitkin FM, McGrath P, Harrison W, Tricamo E. Adverse reactions to monoamine oxidase inhibitors. Part II: treatment correlates and clinical management. *J Clin Psychopharmacol*. 1985;5:2–9.
199. Glassman AH. Cardiovascular effects of tricyclic antidepressants. *Annu Rev Med*. 1984;35:503–511.
200. Cassem N. Cardiovascular effects of antidepressants. *J Clin Psychiatry*. 1982;43:22–28.
201. Freyschuss U, Sjöqvist F, Tuck D, et al. Circulatory effects in man of nortriptyline, a tricyclic antidepressant drug. *Pharmacol Clin*. 1970;2:68–71.
202. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina [published correction appears in *JAMA*. 2002;288:1720]. *JAMA*. 2002;288:701–709.
203. Sauer WH, Berlin JA, Kimmel SE. Selective serotonin reuptake inhibitors and myocardial infarction. *Circulation*. 2001;104:1894–1898.
204. Serebrauny VL, O'Connor CM, Gurbel PA. Effect of selective serotonin reuptake inhibitors on platelets in patients with coronary artery disease. *Am J*

Cardiol. 2001;87:1398–1400.
205. Sala M, Coppa F, Cappucciati C, et al. Antidepressants: their effects on cardiac channels, QT prolongation and Torsade de Pointes. *Curr Opin Investig Drugs*. 2006;7:256–263.
206. Giardina EG, Bigger JT Jr. Antiarrhythmic effect of imipramine hydrochloride inpatients with ventricular premature complexes with psychological depression. *Am J Cardiol*. 1982;50:172–179.
207. Muir WW, Strauch SM, Schaal SF. Effects of tricyclic antidepressant drugs on the electrophysiological properties of dog Purkinje fibers. *J Cardiovasc Pharmacol*. 1982;4:82–90.
208. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry*. 2014;75:e441–e449.
209. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA*. 1998;279:287–291.
210. Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. *Int J Clin Pract*. 2005;12:1435–1440.
211. Castano-Monsalve B. Antidepressants in epilepsy. *Rev Neurol*. 2013;57(3):117–122.
212. Warnock JK, Morris DW. Adverse cutaneous reactions to antidepressants. *Am J Clin Dermatol*. 2002;3(5):329–339.
213. Zisook S. A clinical overview of monoamine oxidase inhibitors. *Psychosomatics.* 1985;26:240–246.
214. McGrath PJ, Stewart JW, Janal MN, Petkova E, Quitkin FM, Klein DF. A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. *Am J Psychiatry*. 2000;157:344–350.
215. Haefely W, Burkard WP, Cesura AM, et al. Biochemistry and pharmacology of moclobemide, a prototype RIMA. *Psychopharmacology (Berl)*. 1992;106(Suppl):S6–S14.
216. Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *J Clin Psychiatry*. 2003;64:208–214.
217. Robinson DS, Amsterdam JD. The selegiline transdermal system in major depressive disorder: a systematic review of safety and tolerability. *J Affect Disord*. 2008;105:15–23.
218. Murphy DL, Sunderland T, Cohen RM. Monoamine oxidase-inhibiting antidepressants: a clinical update. *Psychiatr Clin North Am*. 1984;7:549–562.
219. Kronig MH, Roose SP, Walsh BT, Woodring S, Glassman AH. Blood pressure effects of phenelzine. *J Clin Psychopharmacol*. 1983;3:307–310.
220. Salzman C. Clinical guidelines for the use of antidepressant drugs in geriatric patients. *J Clin Psychiatry*. 1985;46(10, pt 2):38–45.

221. Mallinger AG, Edwards DJ, Himmelhoch JM, Knopf S, Ehler J. Pharmacokinetics of tranylcypromine in patients who are depressed: relationship to cardiovascular effects. *Clin Pharmacol Ther*. 1986;40:444–450.
222. Robinson DS, Nies A, Ravaris CL, Ives JO, Bartlett D. Clinical pharmacology of phenelzine. *Arch Gen Psychiatry*. 1978;35:629–635.
223. Mitchell JE, Popkin MK. Antidepressant drug therapy and sexual dysfunction in men: a review. *J Clin Psychopharmacol*. 1983;3:76–79.
224. Zhou X, Ravindran AV, Qin B, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. *J Clin Psychiatry*. 2015;76(4):e487–e498.
225. McIntyre RS, Filteau MJ, Martin L, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord*. 2014;156:1–7.
226. Rothschild A. Challenges in the treatment of major depressive disorder with psychotic features. *Schizophr Bull*. 2013;39(4):787–796.
227. Mathew SJ, Shah A, Lapidus K, et al. Ketamine for treatment-resistant unipolar depression. Current evidence. *CNS Drugs*. 2012;26:189–204.
228. Sleigh J, Harvey M, Voss L, et al. Ketamine-more mechanisms of action than just NMDA blockade. *Trends Anaesth Crit Care*. 2014;4:76–81.
229. Du Jardin KG, Muller HK, Elfving B, et al. Potential involvement of serotonergic signaling in ketamine's antidepressant actions: a critical review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016;71:27–38.
230. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am J Psychiatry*. 2019;176:428–438.
231. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression. A randomized clinical trial. *JAMA Psychiatry*. 2018;75:139–148.
232. Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *Int J Neuropsychopharmacol*. 2019;22:616–630.
233. Sapkota A, Khurshid H, Qureshi IA, et al. Efficacy and safety of intranasal esketamine in treatment-resistant depression in adults: a systematic review. *Cureus*. 2021;13:e17352.
234. Bahr R, Lopez A, Rey J. Intranasal esketamine (Spravato) for use in treatment-resistant depression in conjunction with an oral antidepressant. *P&T*. 2019;44:340–375.

235. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled trials [published correction appears in *J Clin Psychopharmacol*. 2000;20:287]. *J Clin Psychopharmacol*. 1999;119:427–434.
236. Altshuler LL, Bauer M, Frye MA, et al. Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry*. 2001;158:1617–1622.
237. Nierenberg AJ, Fava M, Trivedi MH, et al. A comparison of lithium and T3 augmentation following two failed medication treatments for depression: a STAR-D report. *Am J Psychiatry*. 2006;163:1484.
238. Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. *CNS Drugs*. 2010;24:131–161.
239. Centers for Disease Control and Prevention. Mental health surveillance among children-United States, 2005–2011. *MMWR*. 2013;62(suppl 2):1–39.
240. Choe CJ, Emslie GJ, Mayes TL. Depression. *Child Adolesc Psychiatr Clin N Am*. 2012;21:807–829.
241. Hetrick SE, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*. 2007;3:CD004851.
242. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*. 2012;11:CD004851.
243. American Academy of Child and Adolescent Psychiatry Official Action. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46(11):1503–1526.
244. Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): II. Treatment and ongoing management. *Pediatrics*. 2007;120(5):e1313–e1326.
245. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):280–288.
246. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Syst Rev*. 2013;6:CD002317.
247. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment. A meta-analysis of randomized controlled trials. *JAMA*. 2007;297(15):1683–1696.
248. Schneeweiss S, Patrick AR, Solomon DH, et al. Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. *Pediatrics*. 2010;125(5):876–888.

249. Isacsson G, Ahlner J. Antidepressants and the risk of suicide in young persons-prescription trends and toxicological analyses. *Acta Psychiatr Scand*. 2014;129:296–302.
250. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications
251. Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. Treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA*. 2004;292:807–820.
252. Shanmugham B, Karp J, Drayer R, Reynolds CF 3rd, Alexopoulos G. Evidence-based pharmacologic interventions for geriatric depression. *Psychiatr Clin North Am*. 2005;28:821–835.
253. Juurlink D, Herrmann N, Szalai JP, Kopp A, Redelmeier DA. Medical illness and the risk of suicide in the elderly. *Arch Intern Med*. 2004;164:1179–1184.
254. Reding M, Haycox J, Blass J. Depression in patients referred to a dementia clinic: a three year prospective study. *Arch Neurol*. 1985;42:894–896.
255. Meyers BS, Bruce ML. The depression-dementia conundrum. *Arch Gen Psychiatry*. 1998;55:102.
256. Green RC, Cupples LA, Kurz A, et al. Depression as a risk factor for Alzheimer disease. *Arch Neurol*. 2003;60:753–759.
257. Cummings JL. Dementia and depression: an evolving enigma. *J Neuropsychiatry Clin Neurosci*. 1989;1:236–242.
258. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother*. 2006;40:1618–1622.
259. Asberg M, Crönholm B, Sjöqvist F, Tuck D. Relationship between plasma level and therapeutic effect of nortriptyline. *BMJ*. 1971;3:331–334.
260. Glassman AH, Perel JM, Shostak M, Kantor SJ, Fleiss JL. Clinical implications of imipramine plasma levels for depressive illness. *Arch Gen Psychiatry*. 1977;34:197–204.
261. Nelson JC, Jatlow P, Quinlan DM, Bowers MB Jr. Desipramine plasma concentrations and antidepressant response. *Arch Gen Psychiatry*. 1982;39:1419–1422.
262. Ziegler VE, Co BT, Taylor JR, Clayton PJ, Biggs JT. Amitriptyline plasma levels and therapeutic response. *Clin Pharmacol Ther*. 1976;19:795–801.
263. Moyes IC, Ray RL, Moyes RB. Plasma levels and clinical improvement—a comparative study of clomipramine and amitriptyline in depression. *Postgrad Med J*. 1980;56(Suppl 1):127–129.
264. Robinson DS, Cooper TB, Ravaris CL, et al. Plasma tricyclic drug levels in amitriptyline-treated depressed patients. *Psychopharmacology*. 1979;63:223–231.

265. The use of laboratory tests in psychiatry: tricyclic antidepressants—blood level measurements and clinical outcome. An APA Task Force Report. *Am J Psychiatry*. 1985;142(2):155–162.
266. Linder MW, Keck PE Jr. Standards of laboratory practice: antidepressant drug monitoring. *Clin Chem*. 1998;44:1073–1084.
267. Robinson MJ, Edwards SE, Iyengar S, et al. Depression and pain. *Front Biosci (Landmark Ed)*. 2009;14:5031–5051.
268. Rijavec N, Grubic VN. Depression and pain: often together but still a clinical challenge—a review. *Psychiatr Danub*. 2012;24(4):346–352.

87

Bipolar Disorders

Megan J. Ehret and Charles F. Caley

CORE PRINCIPLES		CHAPTER CASES
1	Bipolar disorder is a chronic progressive illness that occurs in ~6% of the population. It is characterized by recurrent mood episodes of mania and depression. Life stressors, substance use, treatment nonadherence, and medications are common precipitants of these mood episodes.	**Case 87-1 (Questions 1–3)**
2	Manic episodes are characterized by elevated mood, irritability, increased goal-directed activity, inflated self-esteem, poor judgment, and excessive motor activity.	**Case 87-1 (Question 1)** **Case 87-2 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
3	Depressive episodes of bipolar share the same diagnostic criteria as major depressive disorder, including depressed mood, decreased interest, feelings of worthlessness, diminished ability to concentrate, and recurrent thoughts of death.	**Case 87-7 (Question 1)**
4	Valproate, lithium, or select atypical antipsychotics are appropriate first-line treatments for acute mania. Depending on the severity of symptoms, these agents may be used alone or in combination.	**Case 87-1 (Questions 4, 5)** **Case 87-2 (Question 1)** **Case 87-5 (Question 2)** **Case 87-6 (Question 1)**
5	Lithium, lamotrigine, quetiapine, lurasidone, or the combination of these agents is appropriate treatment for bipolar depression.	**Case 87-7 (Question 1)**
6	Maintenance treatment of bipolar disorder is imperative to prevent disease progression. The standard of practice is to continue the acute-phase treatment with gradual simplification toward monotherapy, if possible, with lithium, lamotrigine, valproate, or atypical antipsychotics.	**Case 87-5 (Question 1)** **Case 87-8 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
7	Medications used to treat bipolar disorder have a wide range of adverse effects that may impact adherence. The history of response, patient preference, and long-term tolerability profile are important considerations when selecting an agent. Therapeutic blood level monitoring, as well as laboratory monitoring for adverse effects, is commonly required for certain medications.	**Case 87-1 (Questions 6–8)** **Case 87-2 (Questions 1–8)** **Case 87-3 (Question 1)** **Case 87-4 (Questions 1, 2)**
8	Nonpharmacologic treatments including electroconvulsive therapy (ECT) and herbal supplements are important considerations for the treatment of bipolar disorder.	**Case 87-8 (Questions 3, 4)**

INTRODUCTION

Bipolar disorder (BD), once known as manic depression, is a severe life-threatening psychiatric condition that is commonly misdiagnosed and too often insufficiently treated.[1,2] BD is associated with high rates of health care utilization, suicidal behavior, and use of public assistance.[3] The global burden of BD is immense, exceeding many chronic diseases including human immunodeficiency virus, diabetes mellitus, and asthma.[4]

Epidemiology

Using *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition *(DSM-5)* criteria, the lifetime prevalence of bipolar I disorder is estimated to be 2.1%; bipolar II disorder is marginally less common at 0.8%.[5,6] The prevalence rate for other specified bipolar and related disorders (OSBARD) is 3%.[6] There is an equal distribution between males and females in bipolar I disorder, but the prevalence of bipolar II disorder is higher in females.[5] The familial nature of BD has been well established with an 11-fold increased risk in first-degree relatives.[7] Twin studies add further support to the genetic linkage. Goodwin and Jamison reported a 63% concordance rate (rate of illness in co-twin of affected proband) for monozygotic twins compared with 13% for dizygotic twins.[7]

The estimated total U.S. economic burden of BD between 2008 and 2018 was reported to be $195 billion.[8] Direct costs, such as hospitalization, outpatient visits, and medications, accounted for 25% of the total. The remaining 75% was attributable to indirect costs such as lost productivity by patients and caregivers.

The mean age of onset of symptoms for the bipolar spectrum of illnesses is 21 years.[6] Bipolar I is the earliest in onset at age 18, compared with bipolar II at age 20.[6] Approximately 20% to 30% of new cases occur in children between 10 and 15 years old.[9,10] Late-life onset of BD is rare. After age 60, there is a sharp reduction in the new onset of BD; therefore, a presentation of mania at this age should alert the clinician to an underlying medical problem as the possible cause.[11]

Patients may present initially with any affective episode, but it is important to note that 75% of patients report having had multiple episodes of depression before the development of a manic episode.[9] Not surprisingly, misdiagnosis (primarily as major depressive disorder) is common, occurring in roughly 70% of patients.[9] By some accounts, one in four patients visit as many as five physicians before an accurate diagnosis is made. A significant contribution to misdiagnosis is the underreporting of manic symptoms, which may not considered to be particularly problematic by patients.[9]

BD is a recurrent illness; single episodes of mania, unrelated to BD, occur in fewer than 10%.[12] Most patients with BD suffer multiple

episodes of mania, hypomania, or depression separated by periods of euthymia (stable mood) throughout the course of their lives. In the majority, mania occurs just before or immediately after a depressive episode.[12] There may be a 5- to 10-year period from the onset of illness until the first hospitalization or diagnosis of BD.[11]

The course of illness is characterized by the type of episode(s), duration of euthymic intervals, frequency of relapse, severity of episodes, and predominant syndrome (mania, hypomania, or depression). These factors do not remain fixed throughout an individual's illness. For instance, individuals may experience episodes of dysphoria and depression before even experiencing hypomania or mania. Often, the euthymic interval and cycle length decrease with additional episodes. With time, a course of alternating recurrent depression interspersed with manic or hypomanic episodes and no intervening euthymic periods can develop.

A specifier of BD, termed "rapid cycling," occurs in both bipolar I and bipolar II disorder and is defined as a patient experiencing four or more separate mood episodes per year. Rapid cycling is common, occurring with a lifetime prevalence of 25.8% to 43%; females are more often affected than males.[13] Rapid cycling of BD is often refractory to conventional treatment and carries significant morbidity and mortality because of rapid changes in mood states.

The prognosis, even for treated BD, is concerning, with 73% experiencing a recurrent mood episode within 5 years. Furthermore, nearly half of patients continue to have significant mood symptoms between episodes, whereas <20% are euthymic or have minimal symptoms.[14]

Pathophysiology

BD is a complex disease involving developmental, genetic, neurobiologic, and psychological factors.[15] Neuroimaging studies have demonstrated neurochemical, anatomic, and functional abnormalities in those with a diagnosis of BD.[16] Recent studies have demonstrated that altered synaptic and circuit functioning accounts

for mood and cognitive changes rather than the previous theory of dysfunction of individual neurotransmitters.[17] Environmental, or psychosocial, stressors, immunologic factors, and sleep dysfunction have been associated with BD and can negatively influence the course of illness.[18–22]

Clinical Presentation

A manic episode usually begins with a change in sleep patterns along with mood elevation. Presenting symptoms include talkativeness, decreased need for sleep, and bursts of energy during which projects are begun but rarely completed. Mania is often characterized by thought disturbances exhibited by “flight of ideas” (rapid speech that switches among multiple ideas or topics) and grandiose delusions (false beliefs of wealth, special powers, knowledge, abilities, importance, or identity). The behavior of patients with mania is characterized as being impulsive, intrusive, loud, intense, irritable, at times suspicious, and even challenging. Patients often exercise poor judgment, which may include spending large sums of money in business deals that ultimately fail, becoming sexually promiscuous, using substances of abuse, or failing to obey laws.

The symptoms of mania usually develop gradually over the course of several days to more than a week and are defined in three stages.[23] Stage I is characterized by euphoria, irritability, labile affect, grandiosity, overconfidence, racing thoughts, increased psychomotor activity, and an increase in the rate and amount of speech. This stage corresponds to hypomania. Stage II features increased dysphoria (a feeling of extreme discomfort and unrest), hostility, anger, delusions, and disorganized thinking. This stage corresponds to acute mania. Stage III, in which the manic episode progresses to an undifferentiated psychotic state, only occurs in some patients. Individuals in stage III experience terror and panic, their behavior is bizarre, and psychomotor activity is frenzied. They may experience hallucinations, disorganized thoughts become incoherent, and

disorientation to time and place occurs. Just as the manic episode gradually builds, it often declines in a gradual manner. Psychotic symptoms usually resolve first, whereas irritability, paranoia, and excessive behavior persist. Remaining symptoms such as talkativeness, seductiveness, and dysphoria slowly decrease with time.

Depressive episodes of BD share the diagnostic criteria with unipolar depression; however, the presentation of bipolar depression has some distinguishing features. In particular, bipolar depression (type I specifically) is more likely to be associated with mood lability, psychotic features, psychomotor retardation, and comorbid substance use.[24] This contrasts with unipolar depression, which is more likely to be associated with anxiety, agitation, insomnia, somatic symptoms, and weight loss.[24]

Mixed features appear to be common and could represent a more severe phase of bipolar illness. These episodes have been associated with a younger age of onset, more frequent occurrence of psychotic symptoms, major risk for suicide, higher rate of comorbidities, and longer time to achieve remission.[25–27]

Patients with BD have higher rates of mortality from both natural and unnatural causes. Higher rates of natural deaths largely result from cardiovascular disease, in which mortality has been estimated to be twice as frequent as the general population.[28–31] Rates of cerebrovascular disease, coronary heart disease/acute myocardial infarction, and cardiac arrest/ventricular fibrillation are all estimated to be increased in patients with BD.[31] Suicide (more likely during depressive and mixed features) and excessive risk-taking behaviors (more likely to occur during manic or hypomanic episodes) also contribute to the high mortality rate. Suicidal behavior is a complex issue that likely depends on both environmental circumstances and risk factors inherent to BD, and current evidence regarding suicide risk is likely confounded by multiple risk factors.[32] Lifetime risk for an attempted suicide is reported to occur in as many as 25% to 50% of patients with BD, whereas the lifetime risk of a completed suicide may be as high as 17% to 19%.[33] The most rigorously determined estimate for suicide death in BD reports rates of 7.8% in males and

4.8% in females.[34] Previous suicide attempts and the presence of hopelessness are primary risk factors for dying from suicide.[35] Fortunately, overall mortality as well as deaths owing to suicide or cardiovascular disease are significantly reduced when BD is adequately treated.[14]

Approximately 61% of patients with BD type 1 have a lifetime prevalence of comorbid substance use disorders.[36] Comorbid alcohol use in BD is estimated at 50%, whereas comorbid cannabis use is estimated at 30%.[37,38] Those with rapid cycling and dysphoric mania have the highest rates of substance use.[39] The best treatment outcome is achieved with aggressive simultaneous management of both BD and the concurrent substance use disorder.

Individuals with BD are likely to experience stress and upheaval in many areas of their lives, including relationships, employment, and finances. Of patients with BD, 88% have been hospitalized once and 66% at least two times.[40] Divorce rates in those with BD are two- to threefold higher than those found in nonaffected populations. Patients often report having poor relationships with family members, and nearly 75% report that their family members have a limited understanding of BD.[9] Employment problems may result from bizarre, inappropriate, or unreliable behavior. In one study, 60% of patients reported being unemployed, 88% felt the disease affected how well they performed at work, and 63% felt that they were treated differently from their peers.[9] Financial and legal problems are tied to excessive spending, involvement in schemes, substance abuse, and risk-taking behavior.

Diagnosis

Mood disorders are diagnosed using the criteria established in the *DSM-5*.[12] Discrete periods of mood disturbance associated with BD are defined as manic episodes, hypomanic episodes, or major depressive episodes with various specifiers including mixed features and rapid cycling. Although mania and hypomania are the distinguishing features of BD, depression is the mood episode that

predominates and is ordinarily the initial presenting symptom.[41,42] Depressive episodes in BD share the same criteria with major depressive disorder (see Chapter 86, Depressive Disorders).[12]

A person who has experienced one or more manic episodes with or without a depressive episode is diagnosed as having bipolar I disorder. An individual who has experienced one or more episodes of both hypomania and depression (without a history of manic episodes) is diagnosed as having bipolar II disorder.[12]

The *DSM-5* also uses a series of descriptors called specifiers to further characterize the course of illness and the most recent type of episode experienced by the individual. Recent episodes are first classified as hypomanic, manic, or depressed. A mixed specifier is diagnosed when a patient meets criteria for either manic or hypomanic episode with at least three depressive symptoms being present during the current or most recent episode of mania or hypomania, or when a patient meets criteria for depressive episode with at least three manic or hypomanic symptoms being present during the current or most recent episode of depression.[12] The rapid cycling specifier applies to those who experience at least four mood episodes in the previous 12 months that meet criteria for manic, hypomanic, or major depressive episode.[12]

Overview of Treatment

The goals of treatment across the phases of BD illness are numerous, including the control of acute symptoms, achieving symptomatic remission, returning to a normal level of functioning, prevention of relapses, and prevention of suicide.[11] Both the acute treatment of manic and depressive episodes and the maintenance treatment for prevention of future episodes require individualization of therapy. Treatment decisions should consider presenting symptoms, medication history, patient preference, and comorbid medical or substance use conditions.

During the previous 15 to 20 years, several treatment guidelines have been published. The most recent guidelines were published

jointly by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD).[43,44] The reader is advised that published efficacy research is categorized by bipolar type (I vs II), mood episode (manic vs mixed vs depressed), and treatment phase (acute vs maintenance). As such, treatment guidelines may reflect these specifiers. Additionally, there is often an uneven amount of published evidence supporting treatment recommendations in these different clinical categories.

Initial treatment for acute hypomanic or manic episodes should be with one of the well-established antimanic agents such as lithium, valproate (VPA), or one of several atypical antipsychotics (AAPs). The recent CANMAT/ISBD guidelines recommend quetiapine, asenapine, aripiprazole, paliperidone (>6 mg), risperidone, or cariprazine as first-line atypical antipsychotic treatments for acute mania.[43] During episodes of mania, short-term adjunctive use of a benzodiazepine is often useful to reduce agitation and promote sleep.[11] Agitation related to acute mania may also be treated with intramuscular injections of olanzapine or inhaled loxapine.[43,44] In the case of severe manic symptoms or partial response to an adequate trial of monotherapy (generally 1–2 weeks), a two-drug combination of lithium, valproate, or an AAP is recommended.[45] Carbamazepine (CBZ) and a typical antipsychotic, alone or in combination with a preferred antimanic drug, are potential alternatives. For treatment-resistant cases, electroconvulsive therapy (ECT), clozapine, and a three-drug combination of lithium plus an anticonvulsant (CBZ or VPA) plus an AAP are recommended. When drug combinations are used, the individual agents should be from different medication classes. Lamotrigine, gabapentin, eslicarbazepine/licarbazepine, topiramate, and zonisamide are not recommended for the treatment of acute mania.[43,44]

In the case of acute mixed features, VPA or an AAP is preferred over lithium because of lithium's poor efficacy. If monotherapy with VPA or an AAP is ineffective or undesirable, then a combination of the two is advised. Asenapine, aripiprazole, olanzapine, and ziprasidone have each demonstrated efficacy in treating mixed features.[43,44]

Medications for the treatment of bipolar depression ideally produce an acute antidepressant response and prevent future depressive episodes, all while not inducing mania or mood cycling. Long-term tolerability is critical because of the chronic recurrent nature of depressive episodes in BD. First-line treatment options vary based on the chosen guideline, but it includes choices of lithium, lamotrigine, lurasidone, olanzapine, or quetiapine monotherapy, or lithium or valproic acid, or olanzapine with a selective serotonin reuptake inhibitor (SSRI), lithium plus valproic acid, or lithium or valproic acid plus bupropion.[46–51] Subsequent treatment trials again vary on guideline, but include different combinations of the above choices. Additional options include adjunctive modafinil or other antidepressants. Third-line treatment includes carbamazepine, ECT, or lithium plus pramipexole or a monoamine oxidase inhibitor (MAOI), or a tricyclic antidepressant (TCA). Readers are referred to individual guidelines for complete details.

Maintenance treatment of BD should include continuing the acute mania treatment while periodically simplifying and moving toward monotherapy.[43,44] Many AAPs are effective in maintenance treatment of BD; however, they must be used cautiously because of the long-term risk of metabolic and neurologic complications.[47] Regardless of the regimen selected, medication adherence is critical to long-term recovery. Patients and caregivers must be actively engaged in discussing causes of nonadherence, including ambivalence, adverse effects, lack of insight, and a strong desire to re-achieve the experience of euphoria and energy of a manic episode.[11] Patients should also be advised to maintain regular patterns of daily activities, a consistent sleep–wake cycle, meals, exercise routines, and other schedules to promote stability.

CLINICAL ASSESSMENT

Clinical Presentation and Diagnosis

CASE 87-1

QUESTION 1: T.R. is a 25-year-old male, accompanied to the clinic by his wife, A.R., who reported much of the following information. T.R. states that he was doing well until about 3 weeks ago, when he returned home from a crab fishing trip. Given the stress of the job, he borrowed some "nerve pills" from his fellow co-worker. Since then, T.R. has been acting increasingly "wild." He has been staying up later at night and often bursts into the bedroom at 2 or 3 AM and loudly awakens A.R. Sometimes, he presents her with expensive gifts, which they cannot afford. He often jumps on the bed and starts singing her love songs in a loud voice. A.R. notes that T.R. then almost always demands sex, after which he sleeps for 2 to 3 hours and then loudly gets up and leaves the house.

During the last several weeks, he drove his car recklessly and well beyond the speed limit. The police have pulled him over several times and given him multiple tickets for speeding, running red lights, and passing on double yellow lines. Last week, when his boss called to express concern about his behavior, T.R. said he was quitting his job. He wrote a rambling, disorganized resignation note, which was 10 pages long, called an overnight air delivery service to send the note to his employer (who is located only 3 miles from his home), and then left the house before the driver arrived to pick it up. T.R. returned several hours later with a brand-new car and wearing an expensive new suit, red cowboy boots, and a bright green hat with a large feather. He told A.R. that he had a new job, which was going to make him a millionaire. Last night, she found a large sum of money in his pants pocket when emptying the clothes hamper. He did not come home at all, but he called her at 4 AM to tell her to pack for Dallas, where he was going to become the new head coach of the professional football team.

On arriving at the clinic, T.R. insists, "I don't need no doc. I am supercalifragilistic!" He then bursts into song. He is dressed flamboyantly but needs a shave and shower. He gives the examiner (a stranger) a bear hug and has trouble sitting still, listening, or allowing others to talk. His speech is pressured and loud; he often fails to complete sentences or communicate entire ideas, and he is rhyming and punning. His mood is elevated, but he becomes increasingly irritable throughout the examination. He is oriented to person and place, but thinks it is tomorrow. Intelligence seems average. When asked to interpret a proverb, T.R. becomes angry and throws a chair across the room.

How is T.R.'s presentation consistent with the diagnosis of a manic episode?

The hallmark of a manic episode is changes in mood, behavior, cognition, and perception (**Table 87-1**).[23] T.R. demonstrates an elevated mood. He is exuberant and notes how great he feels. Nevertheless, patients with mania often demonstrate lability in their mood, and they may become irritable and easily frustrated,

especially when challenged. In this case, T.R. becomes irritable and resentful when questioned by the examiner. His quick displays of anger further demonstrate the volatility of his mood.

Table 87-1
***DSM-5* Criteria for a Manic Episode**

Manic Episode
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).[a]
B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior: 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep) 3. More talkative than usual or pressure to keep talking 4. Flight of ideas or subjective experience that thoughts are racing 5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless non-goal-directed activity) 7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D. The episode is not attributable to the physiologic effects of a substance (eg, a drug of abuse, a medication, other treatment) or to another medical condition.
Note: A full manic episode that emerges during antidepressant treatment (eg, medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.
Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

[a]Criteria for a hypomanic episode are identical to a manic episode; however, the symptoms need only to be present for 4 days and are not severe enough to cause marked impairment in social or occupational functioning, necessitate hospitalization, or for psychotic features to be present.

Manic-like or hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (eg, medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar disorder.

Reprinted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. © 2013 American Psychiatric Association. All Rights Reserved.

T.R. displays behavior and speech typical of acute mania. He has a reduced need for sleep, behaves recklessly, and is overactive. His speech is pressured, loud, and full of rhymes and puns, and he sings to express his emotions and skips from topic to topic reflecting a flight of ideas. T.R. dresses flamboyantly, hugs his examiner, writes an unnecessarily lengthy letter of resignation, seeks an overnight courier service for local delivery, and presents his wife with lavish gifts.

Delusions are often present in acute mania and are grandiose or religious in nature and deal with inflated abilities, self-importance, wealth, or special missions in life. T.R. makes unrealistic comments about his money-making schemes, his singing ability, and his position as the coach of a professional football team.

Patients with acute mania are often disorganized and do not complete tasks. They tend to skip from idea to idea and scheme to scheme. In this case, T.R. neglects his hygiene and neglects sending out his resignation letter.

Precipitating Factors

Case 87-1, Question 2: What factors make T.R. vulnerable to the occurrence of a manic episode at this time?

T.R. is at an age where his disorder would likely first manifest itself. In addition, manic episodes are often precipitated by

psychosocial and recurring life stressors in those who are vulnerable to developing BD.[7] Working long hours with reduced sleep may have served as a contributing factor for the manic episode.

A variety of medications and clinical states can induce or precipitate manic episodes (**Table 87-2**).[52–73] The drugs that most commonly precipitate mania affect monoamine neurotransmitters, such as antidepressants and stimulants.[52] Corticosteroids, anabolic steroids, isoniazid, levodopa, caffeine, and over-the-counter stimulants can induce or aggravate mania.

Table 87-2
Selected Drugs Reported to Induce Mania

Anticonvulsants	Gabapentin, lamotrigine, topiramate
Antidepressants	MAOIs, TCAs, SSRIs, SNRIs, bupropion, nefazodone, trazodone, mirtazapine, vortioxetine
Antimicrobials	Clarithromycin, ofloxacin, cotrimoxazole, erythromycin, isoniazid, metronidazole, zidovudine, efavirenz
Antiparkinsonian drugs	Levodopa, amantadine, bromocriptine
Anxiolytics/hypnotics	Buspirone, alprazolam, triazolam
Atypical antipsychotics	Aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone
CNS stimulants	Caffeine, cocaine, methylphenidate, amphetamine
Drugs of abuse	Marijuana, PCP, LSD
Endocrine	Corticosteroids, thyroid supplements, androgens
Herbals	Saint-John's-wort, SAMe, ma-huang, omega-3 fatty acids, tryptophan
Sympathomimetics	Ephedrine, phenylpropanolamine, pseudoephedrine, phenylephrine
Miscellaneous	Cimetidine, tramadol, sibutramine

CNS, central nervous system; LSD, lysergic acid diethylamide; MAOI, monoamine oxidase inhibitor; PCP, phencyclidine; SAMe, *S*-adenosyl-L-methionine; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Source: See references 53-74.

Case 87-1, Question 3: If the "nerve pills" borrowed by T.R. were antidepressants, could they have contributed to the development of his manic episode?

Antidepressants are commonly prescribed for patients with bipolar depression (35%–40%).[46] Their use is controversial though with criticisms that they lack efficacy or that they destabilize mood and can cause a switch to mania. All of the major classes of antidepressants including monoamine oxidase inhibitors, tricyclic antidepressants (TCAs), SSRIs, and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been associated with precipitating mania in patients with BD.[5] Despite this risk, up to 50% of patients with BD are treated with antidepressants of which only half are receiving a concurrent mood stabilizer.[74] There are numerous case reports of mania or hypomania with antidepressant treatment, but few controlled studies, making it difficult to make comparisons across antidepressant classes.[75] See Case 87-7 for complete details of the use of antidepressants in bipolar depression.

A meta-analysis found a higher "switch" to mania rate for TCAs (11%) than for SSRIs (4%).[76] A controlled trial with bupropion, sertraline, and venlafaxine (all in combination with a mood stabilizer) found an overall switch rate of 19% during acute treatment and 37% during the continuation phase of the study with no difference among agents.[77] Antidepressants may also cause cycle acceleration, which effectively decreases the time between mood episodes. The risk for cycle acceleration may be heightened for patients who experience manic or hypomanic symptoms on antidepressants despite receiving antimanic treatment concurrently.[78] Other recent literature has suggested that adjunctive antidepressants to mood stabilizers versus placebo are not associated with an increased efficacy or with increased risks of treatment-emergent affective switches.[79] In the case of T.R., an antidepressant may have precipitated the manic episode or shortened his cycle, moving him into an episode of mania from a preexisting state of depression or euthymia.[80] Any patient presenting with an acute manic episode should have a review of

medications completed to determine the risk of continuing antidepressant medications.[33]

Current guidelines state that the dual-action monoamine reuptake inhibitors carry a greater risk of precipitating a switch to mania than single-action drugs.[43,44] Additionally, they state that antidepressant medications appear unlikely to induce mania when used in combination with a drug effective for manic symptoms.[46]

TREATMENT OF ACUTE MANIA

CASE 87-1, QUESTION 4: Why does T.R. require treatment?

Manic episodes have a number of severe complications. Left untreated, severe mania can result in confusion, fever, exhaustion, and even death. The impairment in judgment, the excesses, and the risk-taking that occur during manic episodes may be devastating. Detriments to relationships, careers, and finances and physical harm or loss of life may occur. Individuals with mania may also engage in illegal activities. T.R. drives recklessly; may have lost his job; spends excessive amounts of money on gifts, clothing, and automobiles; and plans to participate in a variety of money-making schemes. He has acquired a great deal of cash suddenly, perhaps from withdrawing all of his family's savings or from some type of illegal enterprise. Patients with mania may engage in risky sexual encounters, leading to infection with sexually transmitted diseases including human immunodeficiency virus. Alcohol and substance abuse are common and may exacerbate or even precipitate mood episodes. Irritability, such as that demonstrated by T.R., can lead to episodes of violence, resulting in potential harm to the patient or to others. The goals of treatment are to reduce the severity and duration of the current mood episode and to prevent recurrence of future episodes.

Valproate (Divalproex Sodium, Valproic Acid)

Case 87-1, Question 5: What is the appropriate treatment for T.R.'s acute manic episode?

Depending on the type and severity of mania, first-line treatment involves selecting from lithium, VPA, select AAPs, or a combination of these agents.[43–49] If psychosis is present, an AAP would be an appropriate choice either as monotherapy or in combination with a mood stabilizer. VPA is an ideal choice for T.R. considering the rapid onset, tolerability, and the established efficacy of this agent for preventing future mood episodes.[81–83]

DOSING AND MONITORING

Case 87-1, Question 6: VPA was chosen for the management of T.R.'s mania. How should VPA be initiated, and what baseline tests are necessary? How will T.R.'s response to therapy be monitored?

The initial dose of VPA for T.R. should be 250 mg three times per day.[11] The dose should then be increased by 250 to 500 mg every 2 to 3 days to achieve steady-state serum VPA levels between 50 and 125 μg/mL, or a maximum dosage of 60 mg/kg/day.[84] An alternative strategy is to use an oral loading dose regimen of 20 to 30 mg/kg/day given on a three times a day schedule during the acute manic episode. This approach has been used during inpatient management and may result in a more rapid onset of effect.[85] Although VPA levels of 50 μg/mL are the minimum threshold, higher concentrations offer greater benefit. Serum concentrations >84 μg/mL by the third day of treatment may have greater early symptom improvement.[86] A pooled analysis demonstrated a linear relationship between serum concentration and efficacy with the greatest improvement found in patients with VPA levels in excess of 94 μg/mL.[87] VPA levels >125 μg/mL are more often associated with side effects and should be avoided.[81]

Before VPA is initiated, baseline laboratory tests, including a complete blood count (CBC) with differential and platelets, and liver

function tests should be measured. T.R.'s baseline weight and neurologic status should be recorded. In premenopausal females who have not undergone surgical sterilization, a baseline pregnancy test is warranted because VPA is a known teratogen. Attention should be given to any medications that might be administered concurrently. Interactions with aspirin, lorazepam, phenytoin, phenobarbital, lamotrigine, rifampin, warfarin, felbamate, and CBZ are cited frequently (also see Chapter 60, Seizure Disorders).

VPA should decrease the severity and duration of T.R.'s current manic episode, decrease the frequency of subsequent episodes, and increase his time spent in a euthymic state. Once treatment has started, T.R. should be monitored for response of his initial target symptoms, including grandiosity, decreased need for sleep, pressured speech, distractibility, and impulsivity. Initial symptom improvement with VPA can be expected in ~5 days.[87]

Side effects

Case 87-1, Question 7: What are the potential side effects of VPA therapy? How should T.R. be monitored for these possible effects?

T.R. should be monitored for dose-related adverse reactions of VPA, including various gastrointestinal symptoms (nausea, diarrhea, dyspepsia, anorexia), sedation, ataxia, tremor, transaminase elevations, and thrombocytopenia. Dose reduction, changing to an extended-release preparation,[88] or administering an antacid or histamine H_2-antagonist may mitigate gastrointestinal symptoms. Central nervous system effects such as ataxia and sedation may respond to dose reduction, although sedation may resolve with continued treatment. If a tremor is bothersome or interferes with the patient's functioning, a dose reduction or change to the extended-release preparation may provide relief.[84] Small elevations in transaminases are considered benign; however, VPA should be discontinued if elevations are more than two to three times the upper limit of normal.[89]

Weight gain occurs in up to 20% of patients receiving VPA.[81] The increase in body weight is particularly distressing to some patients and may contribute to medication nonadherence. Weight gain has been associated with VPA at different concentrations, so a dosage reduction may not be helpful.[81,90] In females, VPA has been associated with the development of polycystic ovary syndrome.[91] Core features of polycystic ovary syndrome include oligomenorrhea and hyperandrogenism, which develop in about 10% of females with BD taking VPA. Alopecia occurs in 0.5% to 12% of patients and may improve with dose reduction.[92]

There are several reports of VPA-induced hyperammonemic encephalopathy.[93,94] Patients presenting with mental status changes or coma should have serum ammonia and liver functions tests ordered. If VPA-induced hyperammonemic encephalopathy is suspected, then VPA should be discontinued. Other serious adverse events with VPA include fulminant hepatic failure, agranulocytosis, and pancreatitis. All of these adverse events require immediate discontinuation of therapy.

In January 2008, the U.S. Food and Drug Administration (FDA) issued a warning to health care professionals about the potential for an increased risk of suicidality associated with antiepileptic drugs (AEDs), including VPA. For its analysis, FDA used data from 199 randomized clinical trials of 11 AEDs involving 43,892 study participants with either psychiatric or neurologic disorders. In the “Warnings and Precautions” section of AED product labels, it is stated that the risk of suicidality for those treated with AEDs during clinical trials was approximately twice that of placebo treatment (0.43% vs 0.24%; adjusted relative risk = 1.8, 95% CI = 1.2, 2.7; number needed to harm = 530). In these clinical trials, there were a total of four suicides in AED-treated patients and zero suicides in placebo-treated patients. As a result, practitioners are advised to inform patients and caregivers to be vigilant about the emergence or worsening of signs and symptoms of depression or mood/behavior changes, especially if they involve thoughts or behaviors centered on self-harm when patients receive AED treatment.[95]

Once VPA therapy is initiated, liver function tests, VPA serum levels, and CBCs with differential and platelets should be monitored at least monthly for the first 3 months and every 3 to 6 months thereafter.[11] Body weight should also be determined at baseline and monitored monthly during therapy.

CASE 87-1, QUESTION 8: T.R. was titrated to a total daily VPA dosage of 2500 mg/day and determined to have a steady-state plasma concentration of 95 µg/mL after 1 month of treatment. A routine CBC with differential and platelet count was ordered at this time, and the following data were reported:

Red blood cells, 5.2 × 106/µL
Hemoglobin, 14.5 g/dL
Hematocrit, 43%
White blood cell count, 8.5 × 103/µL
Neutrophils, 59%
Lymphocytes, 27%
Monocytes, 6%
Eosinophils, 2%
Basophils, 0.5%
Platelets, 75 × 10^3/µL

How should T.R.'s VPA-induced thrombocytopenia be managed?

VPA-induced thrombocytopenia occurs in 18% of patients and is associated with female gender and higher VPA levels (>100 µg/mL in females and >130 µg/mL in males).[96] Clinicians should educate patients to look for signs such as easy bruising or bleeding. In most patients, thrombocytopenia is asymptomatic and responds to a lowering of the VPA dosage; complete discontinuation of the drug is usually unnecessary.[97] T.R.'s dosage should be reduced, and his platelet count should be monitored closely. In addition, he should be observed for reemerging symptoms of mania.

LITHIUM

Prelithium workup

CASE 87-2

QUESTION 1: C.N., a 21-year-old female, was diagnosed with her first episode of mania 3 weeks ago. At that time, she was hospitalized and treated with olanzapine 15 mg daily. C.N. was stabilized, and after 10 days, she was discharged from the hospital. She was scheduled to see an outpatient psychiatrist for follow-up 1 week later, but she failed to keep the appointment. Today, C.N. arrives at the emergency department at the request of her mother. C.N. is grabbing her mother's hair and kicking wildly as she is pulled from the car. She can be heard screaming "The FBI is after me, Mom! You want them to find me, don't you? I would have made it out of the country if you hadn't gotten in the way! I was going to marry Prince Charles and become the new queen of England." On evaluation, C.N.'s mood is irritable, and she is pacing around the interviewer. She is dressed in a short skirt and high heels and is wearing an excessive amount of makeup and costume jewelry. During the interview, she interrupts the examiner, smiles, and says in a loud, provocative voice, "Let's you and me get out of here!" Her mother states that after C.N. was discharged from the hospital, she stopped taking her olanzapine because of gaining some weight and, within several days, stopped attending her classes at the local community college. She began staying out late, playing her radio loudly, and driving recklessly, finally hitting the side of the garage while parking early this morning. The clinician would like to admit C.N. to the inpatient unit and initiate lithium treatment.

What laboratory tests are required before initiating lithium therapy for C.N.?

Because lithium can affect many organ systems, baseline laboratory values must be evaluated before therapy is initiated. Baseline laboratory tests are useful in determining contraindications to the use of lithium or conditions that may require an adjustment in dosage. As a young, healthy female, C.N.'s prescreening laboratory battery should include electrolytes, blood urea nitrogen, creatinine, urine specific gravity, thyroid-stimulating hormone (TSH), thyroxine (T_4), and a CBC (**Table 87-3**). A serum human chorionic gonadotropin pregnancy test should also be obtained before starting therapy because lithium is a known teratogen.

Table 87-3
Routine Monitoring During Lithium Therapy

	Baseline	Every 1–3 Months	Yearly
CBC	X		
Electrolytes	X		X
Renal function[a]	X		X
ECG[b]	X		X
Urine	X		
Thyroid function	X		X
Lithium level[c]		X	
Weight or BMI	X		X
Pregnancy[d]	X		

BMI, body mass index; CBC, complete blood count; ECG, electrocardiogram.

[a]Monitor more often in patients with history of kidney disease.

[b]Patients 45 years or older, or those with history of cardiac disease.

[c]Weekly monitoring during the first month of treatment is often recommended.

[d]Females of childbearing potential.

Dosing

Case 87-2, Question 2: C.N.'s baseline laboratory parameters were normal, and her pregnancy test was negative. How should lithium treatment for C.N. be initiated?

Although there are many strategies for calculating lithium dosage requirements, it is simplest to begin C.N. at a dosage of 300 mg twice daily. This is a common starting dose for a healthy adult patient.

Patients experiencing an acute manic episode require higher lithium levels compared with maintenance therapy. The goal for the acute management of C.N. is a serum level between 0.8 and 1.2 mEq/L.[11] Because lithium is not immediately effective, C.N.'s lithium dosage can be adjusted based on the results of lithium serum levels

checked weekly until the manic episode resolves. As she recovers and enters the maintenance phase of treatment, both C.N.'s lithium dosage and her lithium levels will require re-evaluation (see Case 87-8, Question 1).

Case 87-2, Question 3: How long will it take for C.N. to get the full effect of lithium?

The half-life of lithium in a young patient with normal renal function is approximately 24 hours; therefore, steady-state concentrations are typically achieved in approximately 5 days. The onset of action is slow, taking as long as 1 to 2 weeks to fully exert therapeutic effects.[11] Because of the delay in onset, it is appropriate to use an adjunctive medication to help reduce C.N.'s acute symptoms. Both benzodiazepines and antipsychotics are used.[11] AAPs are preferred over typical antipsychotics (see also Chapter 85, Schizophrenia) and have been demonstrated to enhance efficacy and accelerate time to response when used in combination with lithium in acute mania.[47] Benzodiazepines work rapidly to reduce agitation, anxiety, and decreased need for sleep.[98]

Adverse effects

Case 87-2, Question 4: After 3 weeks of lithium therapy, C.N. is demonstrating significant improvement in her sleep, impulsivity, delusions, and activity level. She has achieved a lithium carbonate dose of 1200 mg/day, and her lithium level is 0.8 mEq/L. Today she describes to the clinical staff a fine hand tremor she has developed. Soon after her clinician arrives to evaluate her, C.N. asks to be excused so that she can go to the bathroom. How might C.N.'s presentation be related to her medication?

When considering adverse effect management early in lithium therapy, it becomes important to monitor lithium levels closely. When patients start to recover from acute mania, the rate of lithium clearance may decrease and patients may demonstrate an increase in lithium levels and worsening side effects (**Table 87-4**). This does

not seem to be the case with C.N. because her lithium level is within the accepted range for the management of acute mania.

Table 87-4
Lithium Adverse Effects

Adverse Effect	Considerations
ECG changes	T-wave suppression, delayed or irregular rhythm, increase in PVCs; SSNS; myocarditis
Edema	Primarily ankles and feet; transient or intermittent; secondary to effects on sodium and carbohydrate metabolism; caution about diuretics and sodium restriction to avoid lithium toxicity
Dermatologic	Acne worsens; psoriasis worsens; maculopapular/follicular rashes possible
Hypothyroidism	About 5% goiter; about 30% clinically significant hypothyroidism; may diminish sex drive
Teratogenicity	Ebstein anomaly (tricuspid valve malformation, atrial septal defect); educate female patients, encourage advanced planning regarding pregnancy
Anorexia, nausea (10%–30%)	Usually early in treatment and usually transient; may be early sign of toxicity
Diarrhea (5%–20%)	Slow-release preparations may help
Tremor (10%–65%)	Dose-related; males more than females; worse with antidepressants and antipsychotics; reduce dose or use β-blocker
Cognitive disruption (10%)	Worsens compliance; perceived as “mental dulling”
Fatigue or weakness	May be early toxicity; may mimic depression
Polyuria–polydipsia (nephrogenic diabetes insipidus)	May be an indication of morphologic changes; requires adequate hydration

CBZ, carbamazepine; ECG, electrocardiogram; PVC, premature ventricular contraction; SSNS, sick sinus node syndrome.

CN describes a hand tremor. She should be interviewed and examined to determine its origin. Lithium-induced tremor occurs in 10% to 65% of treated patients and is characteristically rapid, regular, and fine in amplitude.[98,99] It is qualitatively different from the parkinsonian-like tremor associated with antipsychotic treatment. Often, the lithium-induced tremor occurs early in therapy and improves with time. Caffeine, personal or family history of tremor, alcoholism, anxiety, antidepressants, antipsychotics, and possibly older age enhance the risk of lithium-induced tremor.[100] The tremor is more common in patients with higher serum concentrations and may be worse at times of peak lithium levels.[11] If C.N. is not bothered by the tremor and suffers no impairment, treatment is not necessary. If the tremor becomes problematic, her lithium dosage may be reduced or a β-adrenergic blocking agent can be added. Propranolol is used most commonly. Additionally, switching to a sustained-release lithium preparation may reduce peak serum levels and ameliorate tremors if associated with peak concentrations.[11] Because it is early in treatment and C.N. has only a moderate lithium level, it is reasonable to add propranolol 10 mg three times a day rather than to reduce the lithium dosage (if an intervention is required). Propranolol usually is effective at dosages <160 mg/day.[99] C.N. should be educated about her tremor, the adverse effects of propranolol (see Chapter 9, Essential Hypertension) and minimizing her caffeine consumption.

In addition, C.N. should be asked about her trip to the bathroom during this clinic visit because lithium may cause both diarrhea and polyuria. Polyuria and polydipsia are common, occurring in up to 60% of patients.[100] Nephrogenic diabetes insipidus is less common, affecting about 10% of patients on long-term treatment.[101] Nephrogenic diabetes insipidus (see Chapter 53, Diabetes Mellitus) is dose-dependent, so C.N. can be told that a lower lithium dose may minimize the symptoms. Although the advantages of once-daily administration of lithium are not universally accepted, switching a

stabilized patient to this schedule with its lower trough levels may help to reduce urine volume.[11] If C.N. were to fail to respond to either of these interventions, amiloride could be administered, which minimizes lithium's effect on free water clearance.[11,102]

If C.N.'s trip to the bathroom was because of diarrhea, lithium should be evaluated as a possible cause; up to 20% of patients started on lithium experience diarrhea, epigastric bloating, and sometimes stomach pain early in therapy.[103] Diarrhea from lithium is associated with high serum levels, once-daily dosing, and rapidly absorbed preparations; therefore, divided doses may help to alleviate the problem. Use of lower doses and switching to sustained-release preparations are alternative strategies that could be used if C.N. is experiencing diarrhea or polyuria. Her fluid status and lithium level also should be monitored closely. Dehydration and sodium loss lead to increased lithium reabsorption in the proximal tubule and could result in accumulation and lithium toxicity.

Case 87-2, Question 5: What should C.N. be told regarding potential renal damage from lithium?

C.N. should be informed that over time lithium could adversely affect her kidneys. Long-term treatment has been associated with reduced kidney function and, rarely, end-stage renal disease.[104] Routine monitoring of renal function (Table 87-3) allows for the identification of patients with precipitous declines in glomerular filtration. In such patients, lithium should be discontinued to prevent progression to end-stage renal disease. Risk factors for renal insufficiency include episodes of lithium intoxication, medical conditions that impair glomerular filtration (eg, hypertension, diabetes mellitus), and concurrent medications that are damaging to the kidney.[105] Communication with her prescriber about situations that increase the risk of lithium toxicity (see Case 87-2, Question 7) and cooperation with regular lithium and renal function monitoring can vastly reduce the risk of renal disease. Finally, C.N. must be

informed that polyuria is not related to any of the more serious renal side effects.

Patient education

Case 87-2, Question 6: What lithium education should C.N. receive prior to discharge from the hospital?

As with all medications, C.N. should be instructed to disclose all medications she is taking to each of her health care providers. She should be informed that dehydration, fever, vomiting, or sodium-restricted diets could lead to increases in her lithium level. Therefore, she needs to drink plenty of fluids and should avoid restricting sodium.

C.N. should be instructed to contact her prescriber if she starts to experience any symptoms of lithium toxicity, including worsening tremor, slurred speech, muscle weakness or twitches, or difficulty walking. C.N. should be told to use caution in selecting over-the-counter medications. Specifically, she should be warned to avoid the use of preparations containing nonsteroidal anti-inflammatory drugs, which can increase lithium levels.[106] C.N. should know that caffeine can sometimes be troublesome in patients taking lithium, worsening tremor on a short-term basis, and lowering lithium levels during the long term.[106] With regard to serum lithium level monitoring, C.N. needs to know that lithium levels usually are drawn ~12 hours after a dose of lithium. If she is taking lithium in the evening and the morning, she should take her evening dose and then report for a blood sample to be drawn in the morning before taking her morning dose.

Toxicity

Case 87-2, Question 7: About 6 months after discharge, C.N.'s mother calls, concerned that C.N. has been experiencing symptoms of nausea, vomiting, and diarrhea for several days. During the past few hours, C.N. has become

confused and has developed a coarse tremor and slurred speech. It has been 4 months since C.N.'s lithium level has been checked. The only change is that C.N. recently started taking naproxen for headaches. What action should be taken?

There is a strong possibility that C.N. is suffering from lithium toxicity, which can occur acutely from an overdose or insidiously from reduced lithium clearance. Mild toxicity at levels <1.5 mEq/L causes feelings of apathy, lethargy, and muscle weakness accompanied by nausea and irritability. Moderate toxicity occurs between 1.5 and 2.5 mEq/L with symptoms progressing to coarse tremor, slurred speech, unsteady gait, drowsiness, confusion, muscle twitches, and blurred vision. Severe toxicity at levels >2.5 mEq/L can result in seizures, stupor, coma, renal failure, and cardiovascular collapse. C.N. seems to be experiencing moderate lithium toxicity. She should stop any medications that can decrease lithium clearance and the lithium itself until instructed to resume it. She should be taken to the emergency department immediately, where stat laboratory tests, including a lithium level, electrolytes, and renal function tests, should be ordered. There is no antidote for lithium intoxication. Intravenous solutions should be started to ensure that C.N. is hydrated adequately, and electrolyte abnormalities should be corrected promptly. Depending on the results of physical examination and laboratory tests, cardiac monitoring should be instituted and hemodialysis should be considered. Hemodialysis is used to shorten the exposure of different tissues of the body to the elevated lithium concentration and to lower the lithium level to 1.0 mEq/L. Candidates for hemodialysis include those with compromised renal function, severe (irreversible) neurologic symptoms, acute lithium ingestions where symptoms are clear and serum levels are >4.0 mEq/L, or a chronic toxicity where lithium levels exceed the therapeutic values with a clearly manifested clinical picture.[107]

Hypothyroidism

Case 87-2, Question 8: After receiving lithium 1200 mg/day for 1 year, C.N. returns stating that the lithium is slowing her down. She is tired and has gained weight in recent weeks and thinks that she is becoming depressed. In the examining room, C.N. state that the temperature is too cold. What is the most likely cause of C.N.'s symptoms? What treatment should be instituted?

C.N.'s symptoms are consistent with those of hypothyroidism.

Lithium affects the incorporation of iodine into thyroid hormone, interferes with secretion of thyroid hormones, and may interfere with the peripheral conversion of T_4 to T_3 (triiodothyronine).[108] According to laboratory indices, the incidence of hypothyroidism in lithium-treated patients with BD ranges from 28% to 32% compared with 6% to 11% in patients not taking lithium.[109] Risk factors for lithium-induced hypothyroidism include female gender, family history of hypothyroidism or thyroid illness in first-degree relatives, weight gain, elevated baseline TSH, preexisting autoantibodies, an iodine-deficient diet, rapid cycling, and elevated lithium levels.[110] For females, the first 2 years of treatment is a period of heightened risk as well as for any middle-aged patient starting lithium.[110]

Thyroid function tests should be ordered to evaluate C.N.'s current symptoms. If she is found to be hypothyroid, discontinuation of lithium is not necessary. She should receive levothyroxine in doses that normalize her thyroid function tests. Even if she has an elevated TSH with normal levels of T_3 and T_4, low-dose thyroid supplementation may help to resolve her symptoms and prevent breakthrough depression.[108]

Drug and dietary interactions

CASE 87-3

Question 1: T.J., a 35-year-old male, is hospitalized and treated with lithium for a severe manic episode. He had a stable lithium level of 0.84 mEq/L for several weeks, but his last two levels were 0.65 and 0.61 mEq/L without any change in his drug therapy. T.J. insists that he is taking the medication as prescribed. The

nursing staff believes that he is adherent with his medication but notes that he is spending more time off the unit and in the cafeteria.

What factors could contribute to a decrease in T.J.'s lithium levels?

Drug interactions are a common cause of changes in lithium levels, but there have been no changes in T.J.'s regimen (**Table 87-5** provides a list of clinically significant drug interactions). Changes in formulation or brand may sometimes have an impact on lithium levels. Nevertheless, lithium is relatively well absorbed and has a long elimination half-life, so this usually does not result in large changes in the 12-hour postdose lithium level. Occasionally, patients switched from lithium citrate to solid dosage forms experience small changes in lithium levels.

Table 87-5

Lithium Drug Interactions of Clinical Significance

Drugs That Increase Lithium Levels
NSAIDs Many NSAIDs have been reported to increase lithium levels as much as 50%–60%. Enhanced reabsorption of sodium/lithium secondary to inhibition of prostaglandin synthesis is probable mechanism. *Diuretics* All diuretics contribute to sodium depletion that can cause an increased proximal tubular reabsorption of sodium and lithium. Thiazide-like diuretics cause the greatest increase in lithium levels, whereas loop diuretics and potassium-sparing diuretics seem to be somewhat safer. *Angiotensin-converting enzyme (ACE) Inhibitors* Both ACE inhibitors and lithium result in volume depletion and in a reduction in glomerular filtration rate. This results in reduced lithium excretion. *Angiotensin II receptor blockers (ARBs)* ARBs decrease in sodium and reabsorption via AT_1 blockade results in reduced lithium excretion.
Drugs That Decrease Lithium Levels
Theophylline and caffeine Theophylline and caffeine may increase renal clearance of lithium and result in a decrease in levels in the range of 20%. *Acetazolamide* Acetazolamide may impair proximal tubular reabsorption of lithium ions. *Sodium*

High dietary sodium intake promotes the renal clearance of lithium.
Drugs That Increase Lithium Toxicity
Methyldopa Cases of sedation, dysphoria, and confusion owing to the combined use of lithium and methyldopa have been reported. *Carbamazepine* Cases of neurotoxicity involving the combined use of lithium and carbamazepine have been reported in patients with normal lithium levels. *Calcium-channel antagonists* Cases of neurotoxicity involving the combined use of lithium and the calcium-channel blockers verapamil and diltiazem have been reported. Lithium interferes with calcium transport across cells. *Antipsychotics* Cases of neurotoxicity (encephalopathic syndrome, extrapyramidal effects, cerebellar effect, EEG abnormalities) have been reported owing to the combined use of lithium and various antipsychotics. The interaction may be related to increase in phenothiazine levels, changes in tissue uptake of lithium, or dopamine-blocking effects of lithium. Studies attempting to demonstrate this effect have yielded differing results. *Serotonin-selective reuptake inhibitors* Fluvoxamine and fluoxetine have been reported to result in toxicity when added to lithium. Sertraline has been reported to cause nausea and tremor in lithium recipients.

ACE, angiotensin-converting enzyme; EEG, electroencephalogram; NSAIDs, nonsteroidal anti-inflammatory drugs.

T.J. should be questioned about his visits to the cafeteria because diet can have a major influence on lithium excretion. If T.J. is consuming large amounts of caffeinated beverages or salty snacks, a reduction in lithium levels could occur. Increases in dietary sodium intake and the ingestion of methylxanthines (eg, caffeine, theophylline) can increase lithium clearance.[106]

Finally, acute mania can increase lithium clearance.[7] If T.J. was showing signs of a relapse, his decrease in lithium levels might be attributable to his return to a manic state.

Lithium in pregnancy

CASE 87-4

Question 1: A.J., a 36-year-old female, has been maintained successfully on lithium therapy for 5 years for BD. She asks whether she should stay on lithium because she plans to become pregnant in the near future.

Can lithium be used during pregnancy?

Although there is considerable disagreement about the importance of lithium as a teratogen, it has been associated with a variety of congenital malformations, including the rare cardiac malformation, Ebstein anomaly.[111] Lithium was originally thought to increase the risk of Ebstein anomaly 400 times; however, the risk is more likely 20 to 40 times higher than in the general population.[112] One estimated overall risk for congenital malformations related to lithium treatment is ~4% to 12% (compared with 2%–4% in controls).[113] A large cohort study of 1.325 million pregnancies identified 663 infants exposed to lithium in which cardiac malformations were present in 16 (2.41%). The investigators determined that the adjusted risk for any cardiac malformation (including Ebstein anomaly) was related to lithium dose (RR = 3.22 [95% CI, 1.47–7.02] for lithium doses > 900 mg/day).[114] A recent meta-analysis determined that the risk for cardiac anomalies related to lithium exposure was low, but that higher dose and first trimester exposures had relatively higher risks.[115] Because malformations are most likely to occur in the first trimester of pregnancy, it is advisable for patients to avoid lithium, when possible, during this high-risk period.

In addition to cardiac malformations, infants exposed to lithium have been reported to have hypotonia, nephrogenic diabetes insipidus, and thyroid abnormalities.[111] Lithium administration during pregnancy increases the risk of premature delivery by a factor of two to three.[116] Unfortunately, the relative safety of other psychotropic agents commonly used in BD is either not ideal or unknown. VPA has risks of neural tube defects, skeletal abnormalities, hypospadias, limb malformations, cardiovascular defects, and cerebral hemorrhage. CBZ has risks of spina bifida, developmental delay, and lower IQ scores. The general consensus is that these medications are genuine teratogens and should be avoided.[117] Among 1558 exposures, lamotrigine had 35 major congenital malformations

among first trimester monotherapy exposures (2.2%, 95% CI = 1.6%–3.1%).[118]

The use of antipsychotics for which more safety evidence is available is recommended whenever possible in females who require them while pregnant. In a comparison of AAPs of placental passage, olanzapine was associated with the highest exposure (72% ratio of umbilical cord-to-maternal plasma concentrations), followed by haloperidol (65%), risperidone (49%), and quetiapine (24%).[119] Olanzapine was also associated with the highest rates of low birth weight and neonatal intensive care unit admissions.

A.J. and her prescriber should discuss her individual risks related to lithium treatment. In addition to the risks of teratogenicity, they must consider the harm that could result from the possible recurrence of episodes of mania or depression and the risks inherent in discontinuing lithium or switching to another antimanic agent. A.J. should be actively involved in the decision-making process.

If A.J. and her prescriber decide that she is to remain on lithium, her serum levels must be monitored closely during pregnancy and her dosage adjusted accordingly. Lithium clearance increases during the third trimester by 30% to 50%, resulting in a reduction in lithium levels and a need for dosage adjustment.[112] Approximately 16 to 18 weeks after conception, screening tests, high-resolution ultrasound, and fetal echocardiography can be used to determine whether cardiac defects have developed.[112] If possible, A.J.'s prescriber should consider decreasing the lithium dose before delivery to minimize lithium levels in the newborn and to offset the reduction in lithium excretion that occurs after delivery.[112]

If A.J. and her prescriber decide that she is to discontinue lithium, they must be prepared for the risks of lithium discontinuation. Several cases of presumed rebound mania have occurred after abrupt cessation of lithium therapy. If lithium is to be discontinued in A.J., it should be gradually reduced over at least 4 weeks.

Case 87-4, Question 2: A.J. did not use lithium throughout her pregnancy. After delivery, A.J. and her prescriber decide to restart lithium. How soon can lithium be reinitiated in A.J.?

Lithium can be restarted as soon as A.J.'s urine output is established and she is fully hydrated. However, this decision also may be affected by whether A.J. chooses to breastfeed her child because lithium distributes into breast milk and is present in concentrations up to 72% of that found in the maternal blood.[112] Risks to the newborn include hypothyroidism, cyanosis, hypotonia, lethargy, and cardiac dysrhythmias. Hydration status must be closely monitored because lithium toxicity may develop during infantile illnesses. Thus, A.J. and her prescriber must discuss the advantages of breastfeeding versus the risks of exposing the newborn to lithium or withholding lithium during the postpartum period. A.J. should be informed that ~40% to 70% of females with BD experience affective episodes after delivery.[112–119]

If A.J. chooses to breastfeed while taking lithium, she should consider using infant formula when the child becomes ill because febrile illness, vomiting, and diarrhea can increase the risk of lithium toxicity. She also should be instructed to contact her pediatrician if the infant experiences diarrhea, vomiting, hypotonia, poor sucking, muscle twitches, restlessness, or other unexplained changes in behavior.

Atypical antipsychotics

CASE 87-5

QUESTION 1: D.W., a 34-year-old female singer and musician, recently experienced her fourth hospital admission for a manic episode. Her past medical history includes psoriasis and asthma. A trial of lithium led to worsening of her psoriasis and an unacceptable tremor, which interfered with her guitar playing. Use of propranolol was not considered because of her asthma. She was subsequently switched to VPA monotherapy; however, tremor has again become problematic. Furthermore, she is concerned about her appearance because she has begun to experience weight gain and hair loss from the VPA.

What other medications are available for the treatment of acute mania?

AAPs can be selected as first-line choices for the treatment of acute mania.

Three systematic reviews and meta-analyses support the efficacy of AAPs as a class.[120–122] Perlis et al[120] reviewed data from 12 randomized, placebo-controlled, monotherapy studies and 6 adjunctive studies and found a collective response rate of 53% for AAPs compared with 30% for placebo. There was no difference in response between the individual AAPs. In adjunctive studies, the mean odds ratio was 2.4 for a 50% improvement with the addition of an AAP to a mood stabilizer (primarily lithium or VPA). Scherk et al[121] conducted a meta-analysis of 24 randomized controlled trials and found superiority of AAPs for acute mania in comparison with placebo and equal efficacy to lithium, VPA, and haloperidol. In this analysis, the addition of an AAP to lithium, VPA, or CBZ was found to be more effective in reducing manic symptoms and yield less treatment discontinuation than lithium or an anticonvulsant alone. The results of a different meta-analysis specifically designed to evaluate combination treatment of AAPs with lithium or an anticonvulsant also found greater efficacy for the combined regimen.[122] In most combination therapy studies, AAPs were limited to patients having no response or only a partial response to lithium or an anticonvulsant. Thus, the utility of drug combinations as initial therapy cannot be directly assessed.

In a more recent systematic review of 68 randomized controlled trials comparing the efficacy and acceptability of antimanic drugs either against placebo or against one another in the treatment of acute mania was completed via a multiple-treatment meta-analysis. Fourteen treatment options were analyzed including aripiprazole, asenapine, carbamazepine, valproic acid, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, paliperidone, quetiapine, risperidone, topiramate, ziprasidone, and placebo. All of the antipsychotic drugs were found to be significantly more effective than mood stabilizers in the treatment of acute mania, with risperidone and olanzapine being ranked as superior for efficacy and tolerability. Lamotrigine, topiramate, and gabapentin were not significantly better

than placebo in terms of efficacy and should not have a place in the treatment of acute mania.[123]

Additionally, a comparative analysis of 32 placebo-controlled trials demonstrated that young mania rating scale (YMRS) scores improved significantly more with second-generation antipsychotics than mood stabilizers, but the efficacy needs to be balanced against anticipated common adverse effects.[124] A significant concern about the use of AAPs is the risk of metabolic complications, including weight gain, glucose dysregulation, and dyslipidemia (see also Chapter 85, Schizophrenia). Clozapine and olanzapine have the highest risk for metabolic complications, quetiapine, iloperidone, paliperidone, and risperidone are associated with an intermediate risk, and ziprasidone, brexpiprazole, cariprazine, asenapine, lurasidone, and aripiprazole appear to have the lowest risk.[47,125] Clozapine is also associated with significant safety concerns, including agranulocytosis, seizures, sialorrhea, anticholinergic side effects, and orthostasis. Efficacy data with clozapine are limited compared with the other AAPs, but clozapine appears to be effective in treatment-resistant mania and long-term mood stabilization.[126–128]

Sedation is common with clozapine, olanzapine, asenapine, and quetiapine, and this effect may be beneficial in the treatment of acute mania; however, sedation can also lead to nonadherence with long-term use.[129] Aripiprazole and ziprasidone are less sedating; thus, the adjunctive use of a benzodiazepine is often necessary in the acute management of mania with these AAPs. Adjunctive benzodiazepines may also benefit treatment of emergent akathisia, which occurs in 11% to 18% of patients treated with aripiprazole.[130,131] Cariprazine has also been associated with treatment-emergent akathisia and extrapyramidal disorders (>10%).[132] Asenapine can cause dysgeusia or oral hypoesthesia, although a black-cherry formulation can help with the unpleasant taste.[133] Ziprasidone may cause activation; however, this effect is attenuated at doses of 120 mg/day or more.[134] Risperidone may overall be the best tolerated of the AAPs, but this drug carries a higher risk for serum prolactin elevation and extrapyramidal symptoms.[135]

D.W.'s concern about her weight gain makes aripiprazole, cariprazine, asenapine, or ziprasidone rational choices for her manic episode. In addition to symptom response, D.W. should be monitored for characteristic antipsychotic side effects, such as movement disorders, and metabolic complications. If D.W. fails to respond to the initially selected AAP, a switch to a different AAP may prove beneficial given the variability in individual response.[46] **Table 87-6** provides dosing information for AAPs approved for the treatment of acute mania.

Table 87-6
Atypical Antipsychotic Dosing in Acute Mania

Atypical Antipsychotic	Initial Dose	Titration	Effective Dose Range
Aripiprazole	15 mg/day	Not required	15–30 mg/day
Asenapine	10 mg twice daily	5 mg twice daily	5–10 mg twice daily
Cariprazine	1.5 mg/day	Increase to 3 mg on day 2, then increase as needed in 1.5 or 3 mg increments	3–6 mg/day
Olanzapine	10–15 mg/day	5 mg/day	5–20 mg/day
Quetiapine	50 mg twice daily	50 mg twice daily	200–400 mg twice daily
Quetiapine XR	300 mg/day	300 mg/day	400–800 mg/day
Risperidone	2–3 mg/day	1 mg/day	1–6 mg/day
Ziprasidone	40 mg twice daily	20–40 mg twice daily	40–80 mg twice daily

Sources: Abilify (aripiprazole). Package insert. Otsuka Pharmaceutical; December 2014; Saphris (asenapine). Package insert. Merck & Company; January 2017; Vraylar (cariprazine). Package insert. Allergan; September 2015; Zyprexa (olanzapine). Package insert. Eli Lilly and Company; April 2020; Seroquel (quetiapine). Package insert. Astra Zeneca Pharmaceuticals; June 2016; Seroquel Extended Release (quetiapine fumarate). Package insert. Astra Zeneca Pharmaceuticals; November 2018; Risperdal (risperidone). Package insert. Janssen, LP; January 2020; Geodon (ziprasidone). Package insert. Pfizer; January 2020.

Case 87-5, Question 2: What alternative agents are available for acute mania if lithium, VPA, or an AAP fail?

Anticonvulsants

CBZ represents an alternative treatment for the management of acute mania when lithium, VPA, and AAPs fail.[11,45,46] In 2005, the FDA-approved extended-release CBZ for the treatment of acute

manic and mixed episodes based on the results of two double-blind, randomized, placebo-controlled trials.[136] A meta-analysis of four randomized, controlled trials (*n* = 464 patients) found that maintenance treatment with carbamazepine has similar efficacy as, and fewer discontinuations because of adverse effects than, lithium.[137] Despite demonstrated efficacy, CBZ remains a less than popular choice in BD because of significant tolerability and drug–drug interaction risks. If elected for treatment, CBZ should be started at 100 to 200 mg twice daily. The dose should be increased by 200 mg every 3 to 4 days until adequate serum levels have been reached.[11] Although no correlation between CBZ serum levels and response in BD has been established, serum levels >12 μg/mL are associated with sedation and ataxia. The recommended target serum level for seizure prophylaxis is 4 to 12 μg/mL.[11] Average daily doses for maintenance therapy range from 200 to 1600 mg/day (see Chapter 60, Seizure Disorders).

Oxcarbazepine, a structural analog of CBZ, offers some advantages over CBZ, including improved tolerability and fewer drug interactions; however, there is a paucity of well-designed clinical trials in BD.[138] Cochrane reviews suggest that there are insufficient trials of adequate methodologic quality to recommend use for either acute or maintenance treatment for bipolar disorder.[139,140]

Other anticonvulsants studied in mania include lamotrigine, gabapentin, topiramate, tiagabine, zonisamide, and levetiracetam. Initial open-label studies of lamotrigine in mania were promising, but two unpublished trials were negative.[141] Currently, experts doubt that lamotrigine has any significant effect in acute mania. Open trials and case reports suggested adjunctive treatment with gabapentin was effective in manic, hypomanic, and depressive states of BD.[142–144] A more recent controlled trial found no benefit of gabapentin.[145] In this double-blind, placebo-controlled trial, gabapentin was administered as an adjunctive treatment in patients with bipolar I disorder whose current episode was manic, hypomanic, or mixed. At 12 weeks, gabapentin failed to show any significant benefit compared with placebo. In fact, the placebo group did significantly better than the gabapentin-treated patients.

In four double-blind, placebo-controlled trials, topiramate did not separate from placebo and was less effective than lithium in the treatment of acute mania.[146,147] Tiagabine, levetiracetam, and zonisamide have been studied in BD but lack adequate safety or efficacy data to receive any formal evaluation.

COMBINATION TREATMENT

Despite the array of treatments available for the management of acute mania, large numbers of patients fail to respond to monotherapy, and combination therapy is becoming a first-line treatment option.[148] Potentially useful combinations include lithium plus AAPs, VPA plus AAPs, and lithium plus VPA.[33,45] A combination to be avoided is CBZ and clozapine owing to the increased risk of hematologic adverse effects. Also, combinations of CBZ with either olanzapine or with risperidone result in more side effects and decreased efficacy; therefore, these combinations are not recommended.[46]

BENZODIAZEPINES AND ANTIPSYCHOTICS FOR ACUTE AGITATION

CASE 87-6

Question 1: M.B. is a 39-year-old male hospitalized for an acute manic episode, but is refusing all medications, reporting "I will be robbed of my superpowers." He is found pacing around the inpatient unit shouting orders for his release. When asked to return to his room by the clinical staff, he becomes agitated, picks up a chair, and begins swinging it wildly at anyone who approaches him. In the past, M.B. experienced a documented acute dystonic reaction to haloperidol. M.B. has a medical history of diabetes mellitus and hypertension.

What is an appropriate pharmacologic intervention for M.B.?

Benzodiazepines and antipsychotics are useful in treating agitation, irritability, and hyperactivity associated with acute manic episodes. Oral formulations are preferred and are favored by patients in psychiatric emergencies.[149] Oral dose delivery can be

facilitated with liquid concentrates and orally disintegrating tablets. Patients refusing oral medications may require intramuscular (IM) injections.[150] Traditionally, the combination of IM haloperidol and IM lorazepam has been used. Currently, ziprasidone and olanzapine are available in rapid-acting IM dosage forms. IM ziprasidone at doses of 10 and 20 mg are effective in psychotic agitation.[151,152] Additionally, IM olanzapine 10 mg is effective for manic or mixed-state agitation.[153] Repeat doses of IM ziprasidone and olanzapine can be administered 2 to 4 hours after the first dose, if needed. The concurrent use of a benzodiazepine with an antipsychotic is generally safe and potentially more effective than either agent alone. In the case of IM olanzapine, concurrent benzodiazepines should not be used because the combination may cause excessive sedation and cardiorespiratory depression.[154,155]

Lorazepam is the preferred benzodiazepine for acute manic agitation. Advantages of lorazepam include availability as both an IM and oral formulation (tablet and concentrate), lack of active metabolites, and safety in hepatic and renal impairment. The Expert Consensus Guideline recommends dosing lorazepam at 1 to 3 mg orally or 0.5 to 3 mg IM, with repeat doses at least 60 minutes apart. The maximal dose should not exceed 10 to 12 mg in the first 24 hours.[156] The primary concern regarding the use of benzodiazepines for agitated mania is sedation. The risk of abuse and addiction is minimal with short-term inpatient use.

M.B. is uncooperative and an immediate danger to others, thus warranting IM therapy. Because of M.B.'s history of acute dystonia to haloperidol, an IM AAP (such as olanzapine or ziprasidone) should be used. As M.B. becomes calmer and more receptive to treatment, he can be transitioned to oral therapy.

TREATMENT OF ACUTE BIPOLAR DEPRESSION

CASE 87-7

QUESTION 1: H.C., a 31-year-old female, was hospitalized for treatment of an acute manic episode 3 months ago. She was discharged on VPA 1750 mg/day with a favorable response. Starting about 2 weeks ago, her parents become concerned because H.C. started spending most of the day in bed. When out of bed, H.C. sits on the couch without moving for hours and only nibbles at the food her parents offer her. She has no other signs or symptoms of physical illness and has not taken any additional medications, alcohol, or drugs of abuse to her parents' knowledge. They report that H.C. was diagnosed with diabetes mellitus type 2 last year, and her serum glucose has been controlled by diet. On further questioning, H.C.'s parents report that she has been intermittently tearful and expressed remorse for her behavior when she was manic. They also recall her as saying "I am as low as I can go, and I just want to die." Hence, they suspect she is suicidal. H.C.'s parents report that she is taking VPA as prescribed and that the last time she experienced this level of depression, the addition of lithium to VPA did not seem to help. Her VPA level on discharge was 84 μg/mL.

What change in H.C.'s treatment should be instituted at this time?

Bipolar depression is both recurrent and chronic, accounting for three-quarters of the time spent ill in BD.[157] Depression is often difficult to treat and puts patients at significant risk for suicide, which occurs at a rate 20 times greater than that of the general population.[158]

In bipolar depression, complete remission of symptoms is the primary goal of treatment. The ideal regimen should target acute depressive symptoms, decrease suicide risk, and prevent future mood episodes (both manic and depressive). These goals should be achieved without precipitating mania (switching) or mood cycling. Because simply addressing the acute depressive symptoms is often shortsighted in an illness with recurrent depressive episodes, the ability to prevent future depressive episodes and the long-term tolerability are important considerations.[159]

A logical first step in the management of bipolar depression is to verify adherence and optimize the dose of the current mood stabilizer.[33] For H.C., she is already on a therapeutic level of VPA; thus, no change in dose is needed.

Lithium

Lithium remains a first-line treatment for bipolar depression.[43,44] The CANMAT guidelines recommend a level of 0.8 mEq/L or more for optimal response.[48] The benefit of lithium was demonstrated in seven of eight placebo-controlled crossover studies with a mean response rate of 76%.[160] Lithium may also be effective for preventing depressive episodes. A 6-year follow-up study of patients maintained on lithium found a reduction in the annual rate of depressive episodes by 46% and the time spent ill by 53%.[161] A meta-analysis of 1- or 2-year-long studies found a 22% relative risk reduction for a depressive relapse compared with placebo (risk ratio, 0.78; 95% CI = 0.60–1.01).[162] The difference from placebo was not statistically significant.[156] Beyond antidepressant effects in BD, lithium also has the vital benefit of reducing the risk of suicide, deliberate self-harm, and all-cause mortality.[163,164]

Lamotrigine

Lamotrigine is also recommended as a first-line treatment for bipolar depression by both the World Federation of Societies of Biological Psychiatry (WFSBP) and CANMAT guidelines; although the efficacy of lamotrigine for long-term treatment is well established, the efficacy of it in the acute management of bipolar depression is less compelling. Data from five double-blind, placebo-controlled trials [46,48] did not detect any benefit from lamotrigine on the primary end points (change in Hamilton Depression Rating Scale [HAM-D], or Montgomery–Åsberg Depression Rating Scale [MADRS]) relative to placebo. An independent meta-analysis of the same five studies found significant (but only modest) benefits for lamotrigine with a relative risk of response of 1.27 for the HAM-D and 1.22 for the MADRS.[165] The ability of lamotrigine to reduce the risk of relapse to depression is less controversial. A pooled analysis of two long-term studies (up to 18 months) with lamotrigine found a 36% reduction in the risk of relapse to depression.[166] Lamotrigine was well tolerated with no difference from placebo in any side effect. Because

lamotrigine has limited antimanic properties, patients with a history of severe, recent, or recurrent mania should only take lamotrigine in combination with an antimanic drug, such as lithium.[45]

The combination of lamotrigine and lithium may confer additional benefits on reducing depressive symptoms and should be considered for bipolar depression. Patients stabilized on lithium (predefined range of 0.6–1.2 mEq/L, mostly >3 months' duration) were randomly assigned to receive lamotrigine (200 mg/day) or placebo. The lithium–lamotrigine group had a response rate of 52% (based on MADRS scores) compared with 32% for the lithium–placebo group.[167] From the results of this study, clinical experience, and the need for long-term tolerability, the combination of lamotrigine and lithium is an appropriate treatment when monotherapy with these medications has failed.

Because of valproate's inhibition of UGT2B7, it can increase lamotrigine's area under the concentration–time curve (AUC) by 2.6-fold. Clinicians should pay particular attention to the dosing with initiating or discontinuing either medication in the presence of the other medication.[89]

Atypical Antipsychotics

AAPs offer another option for the treatment of bipolar depression. Quetiapine has demonstrated efficacy in a total of four 8-week double-blind, placebo-controlled studies (300 or 600 mg/day).[168–171] Response rates ranged from 58% to 69% for the 300-mg dose, and 58% to 70% for the 600-mg dose. Both doses were commonly associated with sedation, somnolence, dry mouth, and dizziness. Clinically significant weight gain (≥7% of baseline weight) was detected in roughly 5% to 10% of subjects receiving quetiapine.

The combination of olanzapine with fluoxetine is effective for patients with bipolar depression.[172] In a 7-week acute-phase treatment, OFC was superior to lamotrigine in symptom improvement but not significantly different in response rate (69% with OFC vs 60% with lamotrigine).[173] The rate of relapse to

depression during the 6-month study was low and similar between OFC and lamotrigine (14% vs 18%). In an extension of this study (for a total of 6 months), OFC caused significant elevations in all metabolic parameters (weight, glucose, prolactin, cholesterol).[174] Most alarming was a 34% incidence of clinically significant weight gain in the OFC group (vs 2% with lamotrigine). Therefore, the risk of metabolic complications should be taken into consideration when selecting this treatment.

Lurasidone has demonstrated efficacy in two 6-week, randomized, double-blind controlled clinical trials as monotherapy at either 20 to 60 mg/day or 80 to 120 mg/day. Response rates were 53% for the low dose, 51% for the high dose, and 30% for placebo. An additional study with a similar design failed to separate from placebo. An adjunct to lithium or VPA trial demonstrated response rates of 57% of lurasidone with either lithium or VPA compared to 42% of placebo with either lithium or VPA.[175–177] **Table 87-7** provides dosing information for AAPs approved for the treatment of bipolar depression.

Table 87-7
Atypical Antipsychotic Dosing in Bipolar Depression

Atypical Antipsychotic	Initial Dose	Titration	Effective Dose Range
Cariprazine	1.5 mg/day	Increase to 3 mg/day on day 15	3 mg/day
Lurasidone	20 mg/day	20 mg every 2 days	20–120 mg/day
Olanzapine/fluoxetine	6/25 mg/day	As indicated	12/50 mg/day
Quetiapine (IR and XR)	50 mg/day	100 mg on day 2 200 mg on day 3 300 mg on day 4	300 mg/day

IR, immediate release; XR, extended release.

Sources: Vraylar (cariprazine). Package insert. Forest Laboratories; May 2019; Latuda (lurasidone). Package insert. Sunovion Pharmaceuticals; January 2017; Symbyax (olanzapine/fluoxetine). Package insert. Lilly USA, LLC; January 2015; Seroquel XR (quetiapine XR). Package insert. AstraZeneca; June 2016.

Recent approval of cariprazine for the treatment of bipolar depression was based on short-term (6 or 8 weeks with endpoints at week 6) double-blind, placebo-controlled, randomized phase II/III clinical trials. Both the 1.5 and 3.0 mg/day doses are approved

doses for bipolar depression. Maintenance trials are in progress.[178,179]

Despite its efficacy in treatment-resistant unipolar depression, aripiprazole does not appear to be effective for bipolar depression on the basis of two randomized, controlled trials.[171,180] Considering these findings, the CANMAT guidelines have listed aripiprazole as not recommended for acute bipolar depression.[43] Other AAPs have not been systematically studied in bipolar depression.

Antidepressants

The use of antidepressants in BD has been hotly debated. Some guidelines recommend restrictive use of antidepressants because of concerns about mood switching and cycle acceleration.[47] Other guidelines recommend early treatment with antidepressants, particularly SSRIs, to address the recurrent depressive episodes.[46] In either case, there is agreement that antidepressants should only be used in combination with antimanic agents such as VPA, lithium, or an AAP.[46,47] The largest controlled trial of antidepressant augmentation in bipolar depression was conducted as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. This study was a naturalistic 26-week, double-blind, placebo-controlled trial comparing antidepressants (bupropion or paroxetine) with placebo as adjunctive treatment to an antimanic agent.[79] The primary end point of durable recovery (euthymia for 8 weeks) was achieved in 24% of antidepressant-treated subjects compared with 27% receiving placebo. There was no significant difference between groups in treatment-emergent mood switch. A meta-analysis of 15 studies, primarily with bupropion or SSRIs, found that antidepressants were no more effective than placebo for acute (>16 weeks) bipolar depression.[79] This study also did not find an increased risk of mood switch. Therefore, although it appeared to be safe to add the antidepressant in regard to switching into mania, there is question about whether there is a large benefit on depressive symptoms.

Because H.C. did not respond to lithium in combination with VPA during her past depressive episode, an alternative first-line agent such as lamotrigine is a reasonable choice. OFC or quetiapine may compromise her type 2 diabetes control and thus are not appropriate options. Lurasidone or cariprazine could also be an alternate choice, although no current data exist in comparing them to lamotrigine, quetiapine, or OFC for the treatment in bipolar depression. Dosing of lamotrigine needs to account for H.C.'s concurrent use of VPA, which is known to inhibit the metabolism of lamotrigine. Therefore, the initial dose for H.C. is 25 mg every other day for weeks 1 and 2 followed by an increase to 25 mg/day for weeks 3 and 4. The dose can be increased to 50 mg/day for week 5 and then to a maximum of 100 mg/day beginning at week 6. In the absence of VPA, the recommended target dose of lamotrigine is 200 mg/day. In patients taking enzyme inducers (eg, CBZ), the target dose is 200 mg twice daily.[181] The appropriate titration schedule must be followed for lamotrigine (see also Chapter 60, Seizure Disorders) because of the risk of skin rash, which may progress to life-threatening Stevens–Johnson syndrome. The combination of lamotrigine and VPA is a risk factor for the development of this dangerous cutaneous reaction; therefore, H.C. should be instructed to contact her prescriber immediately if a skin rash develops.

MAINTENANCE THERAPY OF BIPOLAR DISORDER

CASE 87-8

QUESTION 1: R.L., a 33-year-old male, has been treated for an episode of acute mania with lithium 600 mg twice a day for 3 weeks. He is no longer overtly manic. Because of R.L.'s past episodes of depression and mania, his prescriber decides to institute prophylactic (maintenance) lithium therapy.

What are the goals of maintenance lithium therapy for R.L.? How should he be monitored during this maintenance phase? How long should R.L. be maintained on lithium?

Recurrent episodes are associated with decreased quality of life, poorer response to treatment, longer hospitalizations, and cognitive impairment.[33] Thus, early maintenance (prophylactic) treatment is indicated to prevent disease progression. Appropriate goals for maintenance therapy include an increase in the interval between episodes, a decrease in the frequency of episodes, and a reduction in the duration and severity of mood episodes. In most cases, patients will have been started on an acute treatment for a manic or depressive episode. These agents should generally be continued because abrupt switches in medications may predict poorer treatment outcomes.[33]

Lithium

The aforementioned meta-analysis (Case 87-7, Question 1) of long-term lithium therapy for relapse prevention in BD included five randomized, placebo-controlled studies.[162] Although lithium did not effectively reduce the risk of relapse to depression, it did reduce the risk of relapse to any mood episode (risk ratio, 0.66) and to manic episodes specifically (risk ratio, 0.62). The average risk of relapse to any mood episode on lithium was 40% versus 60% for placebo. The average risk of relapse to a manic episode was 14% for lithium versus 24% for placebo.

In the case of R.L., he should be continued on lithium. The target levels for maintenance therapy with lithium should be in the range of 0.5 to 0.8 mEq/L.[11] Higher levels ranging from 0.8 to 1.0 mEq/L are associated with a reduced number of relapses (compared with levels between 0.4 and 0.6 mEq/L) but also have an elevated risk of side effects.[182]

In addition to determining an appropriate maintenance lithium level for R.L., it is important to consider whether once-daily administration of lithium can improve adherence or adverse effects. During periods of dosage readjustment, R.L. will require monitoring of his lithium serum level more frequently. Once stabilized, the monitoring

frequency can be reduced to quarterly. See Table 87-3 for recommended lithium monitoring guidelines.

Case 87-8, Question 2: What other maintenance treatments for BD are available should R.L. fail to respond to lithium?

Anticonvulsants

VPA and lamotrigine are reasonable alternatives to lithium that have shown efficacy in BD maintenance therapy. In the first controlled trial of VPA for the maintenance treatment of BD, patients were randomly assigned to receive VPA, lithium, or placebo and followed for 52 weeks.[183] The three groups did not differ with regard to the primary outcome of time to any mood episode. However, a lower percentage of patients discontinued treatment for any reason in the VPA group (62%) than lithium (76%) or placebo (75%); patients on VPA remained in the study longer (198 days) than patients on lithium (152 days) and placebo (165 days). The mean VPA serum concentration was 85 µg/mL. Lamotrigine has been studied rigorously in the maintenance treatment of BD. A pooled analysis of two placebo-controlled studies found that lamotrigine and lithium more than doubled the time to intervention (eg, addition of pharmacotherapy or ECT) for any mood episode compared with placebo (see Case 87-7, Question 1).[166] The time to intervention was 197 days for lamotrigine, 187 days for lithium, and 86 days for placebo. Lithium preferentially prevented manic relapses, whereas lamotrigine preferentially prevented depressive episodes.

Atypical Antipsychotics

AAPs have become increasingly popular alternatives and adjunctive treatments for maintenance therapy of BD. To date, aripiprazole, olanzapine, quetiapine (adjunctive), risperidone long-acting injection, and ziprasidone (adjunctive) have received FDA approval for the maintenance treatment of BD (**Table 87-8**). A meta-analysis

evaluated 20 trials (*n* = 5364) in the efficacy of maintenance treatments for BD. No monotherapy options were associated with significantly reduced risk for both manic/mixed and depressive poles compared to each other, whereas the only combination, quetiapine plus lithium or VPA demonstrated significant reduction in risk versus the comparator of placebo in reduced risk for both poles.[83] The long-term risk of side effects, including metabolic complications and extrapyramidal symptoms (EPD), should be the primary consideration for selecting one AAP over another (see Case 87-5, Question 1).

Table 87-8
FDA-Approved Medications for Bipolar Disorder

Drug	Mania	Mixed	Depression	Maintenance
Carbamazepine (extended-release capsule)	X	X		
Cariprazine	X	X	X	
Lamotrigine				X
Lithium	X			X
Valproate (divalproex sodium)	X	X		
Asenapine	X	X		
Aripiprazole	X	X		X
Lurasidone			X[a]	
Olanzapine	X	X		X
Olanzapine–fluoxetine			X	
Quetiapine	X		X	X[a]
Quetiapine XR	X	X	X	X[a]
Risperidone long-acting injection				X
Risperidone	X	X		
Ziprasidone	X	X		X[a]

FDA, Food and Drug Administration.

[a]Monotherapy or adjunct to lithium or valproate.

CASE 87-8, QUESTION 3: What is the role of psychotherapy in BD?

Psychotherapy can have a profound effect on the prevention of acute illness, as well as a sustained effect on maintenance treatments. Excessive stress, for example, is often implicated in the onset of affective episodes, particularly early in the lifetime course of

BD.[7] If individuals and their families can learn to avoid these triggers or to develop coping skills, the acute impact can be minimized and future episodes averted.

Therapy may also help the family to cope with the emotions and disruption that are the hallmark of acute manic and depressive episodes. Violent outbursts, infidelity, financial debts, substance abuse, suicidal thinking, and loss of self-esteem may all be a byproduct of mood recurrence, and family members must learn to treat such calamities, as well as fears surrounding future episodes. Regular sleep–wake cycles seem vital to the maintenance of euthymic states; thus, improvements in sleep hygiene may be encouraged in these sessions. Last, sustained medication adherence must also be emphasized; individuals with BD will often stop their medications in an effort to resume the “highs” of mania or because of the cumulative side effect burden of complex psychotropic regimens.

The specific psychotherapeutic approach to BD is generally quite similar to interventions offered to individuals with schizophrenia. Family-focused therapy seems to be quite effective, as are cognitive-behavioral and interpersonal and social rhythm therapy. Collaborative care models have been extensively studied for unipolar depression in primary-care settings, but the effectiveness of collaborative care models for bipolar illness is less clear. In fact, in the STEP-BD trials, collaborative care was the least effective intervention.[184] Reported response rates were 77% with family-focused therapy, 64% with interpersonal and social rhythm therapy, 60% with cognitive-behavioral therapy, and 54% with collaborative care. Experts contend that the collaborative care intervention was comparatively less intensive than the other three treatment modalities in this report.

Although most experts advocate for regular physical activity to prevent bipolar mood swings, the body of literature supporting such an approach is very limited. Lifestyle surveys have demonstrated that people afflicted with BD are less likely to exercise and more likely to exhibit poor dietary habits than those without a serious mental illness.[185] Theoretically, exercise may improve dietary habits,

regulate sleep, increase energy, and promote euthymic moods. As a result, increased physical activity would be expected to improve the prognosis of bipolar illness and should be encouraged at the very least for the physical health benefits.

Case 87-8, Question 4: Are there other treatment options for BD?

Alternative Medicines

A wide variety of herbal preparations and dietary supplements have been studied for the treatment of BD. A meta-analysis of double-blind, placebo-controlled trials of combined bipolar and unipolar depression found benefit of omega-3 fatty acid supplementation compared with placebo in patients with depressive episodes.[186] In most cases, omega-3 fatty acid supplementation, including eicosapentaenoic acid alone or in combination with docosahexaenoic acid, was used as adjunctive treatment. The doses studied ranged from 1 g/day of eicosapentaenoic acid to 9.6 g/day of combined eicosapentaenoic acid and docosahexaenoic acid.

Inositol was compared with lamotrigine and risperidone in an augmentation trial for bipolar depression.[187] The three treatments were equivalent with regard to recovery from depression; however, the study was open label and the sample size was small (n = 66). Saint-John's-wort and *S*-adenosyl-L-methionine may be effective for depressive episodes; however, these agents, like traditional antidepressants, should generally be avoided in BD owing to the risk of mood destabilization.[54,55]

Electroconvulsive Therapy and Transcranial Magnetic Stimulation

ECT is effective in all phases of BD and continues to play a vital role in the contemporary treatment of mood disorders. The efficacy of ECT in bipolar depression is equivalent to unipolar depression with

~80% of patients achieving a response and 60% meeting criteria for remission.[188] The benefits of ECT in acute mania are similarly impressive. In a review spanning 50 years of research, “remission or marked clinical improvement” was achieved in 80% of patients.[189,190]

BD medication regimens need to be carefully evaluated before ECT treatment. Anticonvulsants and benzodiazepines raise the seizure threshold and interfere with the effectiveness of ECT. A retrospective analysis found that patients taking anticonvulsants achieved the same overall clinical response but required more ECT treatments and a longer hospital stay.[191] An exception is the concurrent use of lamotrigine, which appears to have no significant effect on electrical stimulus dose or seizure duration.[192] Lithium use with ECT has been discouraged on the basis of early reports of organic brain syndrome; however, a more recent prospective study found the combination to be safe in a younger population without risk factors for ECT complications.[193,194] Small case series and clinical experience suggest that AAPs are safe to use during ECT.[195–197]

ECT remains an effective and important tool for the treatment of BD, particularly bipolar depression, which is highly recurrent and has limited safe and effective treatment options. All patients failing to respond to standard BD pharmacotherapy, presenting with severe mood symptoms, or not otherwise appropriate for medication treatment should be considered for ECT.

TMS was recently granted breakthrough designation of adult patients with bipolar I or II disorders who failed to show satisfactory improvement with prior pharmacologic therapy.[198]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596–601. (125)

American Psychiatric Association. Mood disorders. In: American Psychiatric Association, ed. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision. American Psychiatric Association; 2013:123. (12)

Cipriani A, Barbui C, Salanti G. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378:1306–1315. (123)

Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry*. 2005;162: 1805–1819. (163)

Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry*. 2004;161:217–222. (162)

Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry*. 2018;19(1):2–58. (44)

Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2016;30:495–553. (46)

Mohammad O, Osser DN. The psychopharmacology algorithm project at the Harvard South Shore Program: an algorithm for acute mania. *Harv Rev Psychiatry*. 2014;22(5):274–294. (45)

Perlis RH, Welge JA, Vornik LA, Hirschfeld RM, Keck PE Jr. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2006;67:509–516. (120)

Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2011;72:156–167. (182)

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;29(2):97–170. (43)

Key Websites

Depression and Bipolar Support Alliance. http://www.dbsalliance.org
National Alliance on Mental Illness. http://www.nami.org
National Institute of Mental Health. http://www.nimh.nih.gov

COMPLETE REFERENCES CHAPTER 87 BIPOLAR DISORDERS

1. Wolkenstein L, Bruchmüller K, Schmid P, Meyer TD. Misdiagnosing bipolar disorder—do clinicians show heuristic biases? *J Affect Disord*. 2011;130:405–412.
2. Evans-Lacko SE, Dosreis S, Kastelic EA, Paula CS, Steinwachs DM. Evaluation of guideline-concordant care for bipolar disorder among privately insured youth. *Prim Care Companion J Clin Psychiatry*. 2010;12(3). doi:10.4088/PCC.09m00837gry
3. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord*. 2003;73:123–131.
4. Ferrari AJ, Saha S, McGrath JJ, et al. Health states for schizophrenia and bipolar disorder within the global burden of disease 2010 study. *Popul Health Metr*. 2012;10:16.
5. Blanco C, Compton WM, Saha TD, et al. Epidemiology of DSM-5 bipolar I disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *J Psychiatr Res.* 2017;84:310–317.
6. Fassassi S, Vandeleur C, Aubry JM, Castelao E, Preisig M. Prevalence and correlates of DSM-5 bipolar and related disorders and hyperthymic personality in the community. *J Affect Disord.* 2014;167:198–205.
7. Goodwin FK, Jamison KR. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. Oxford University Press; 2007.
8. Bessonova L, Ogden K, Doane MJ, O'Sullivan AK, Tohen M. The economic burden of bipolar disorder in the United States: a systematic literature review. *ClinicoEcon Outcomes Res.* 2020;12:481–497.
9. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry*. 2003;64:161–174.
10. Kupfer DJ, Frank E, Grochocinski VJ, Cluss PA, Houck PR, Stapf DA. Demographic and clinical characteristics of individuals in a bipolar disorder case registry. *J Clin Psychiatry*. 2002;63:120–125.
11. American Psychiatric Association. Practice guidelines for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry*. 2002;159(4

suppl):1–50.
12. American Psychiatric Association. Mood disorders. In: American Psychiatric Association, ed. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision. American Psychiatric Association; 2013:123.
13. Carvalho AF, Dimellis D, Gonda X, Vieta E, Mclntyre RS, Fountoulakis KN. Rapid cycling in bipolar disorder. A systematic review. *J Clin Psych.* 2014;75(6):e578–e586.
14. Gitlin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. *Am J Psychiatry*. 1995;152:1635–1640.
15. Miklowitz DJ, Ciccetti D. Toward a life span developmental psychopathology perspective on bipolar disorder. *Dev Psychopathol*. 2006;18:935–938.
16. Hallahan B, Newell J, Soares JC, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative meta-analysis of individual adult patient data. *Biol Psychiatry*. 2011;69:326–335.
17. Martinowich K, Schloesser RJ, Manji H. Bipolar disorder: from genes to behavior pathway. *J Clin Invest*. 2009;119:726–736.
18. Beyer JL, Kuchibhatla M, Cassidy F, Krishnan KR. Stressful life events in older bipolar patients. *Int J Geriatr Psychiatry*. 2008;23:1271–1275.
19. Miklowitz DJ, Johnson SL. Social and familial factors in the course of bipolar disorder: basic processes and relevant interventions. *Clin Psychol*. 2009;16:281–296.
20. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry*. 2009;70:1078–1090.
21. Drexhage RC, Knijff EM, Padmos RC, et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. *Expert Rev Neurother*. 2010;10:59–76.
22. Gruber J, Miklowitz DJ, Harvey AG, et al. Sleep matters: sleep functioning and course of illness in bipolar disorder. *J Affect Disord*. 2011;134:416–420.
23. Goodwin FK, Jamison KR. Clinical description. In: Goodwin FK, Jamison KP, eds. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. Oxford University Press; 2007:29.
24. Goodwin FK, Jamison KR. Conceptualizing manic-depressive illness: the bipolar-unipolar distinction and the development of the manic-depressive spectrum. In: Goodwin FK, Jamison KR eds. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression*. Oxford University Press; 2007:3.
25. Baldessarini RJ, Bolzani L, Cruz N, et al. Onset-age of bipolar disorders at six international sites. *J Affect Disord*. 2010;121:143–146.
26. Shim IH, Woo YS, Jun TY, Bahk WM. Mixed-state bipolar I and II depression: time to remission and clinical characteristics. *J Affect Disord*. 2014;152–154:340–346.

27. Undurraga J, Baldessarini RJ, Valenti M, Pacchiarotti I, Vieta E. Suicidal risk factors in bipolar I and II disorder patients. *J Clin Psychiatry*. 2012;73:778–782.
28. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord*. 2002;68:167–181.
29. Laursen TM, Nordentoft M. Heart disease treatment and mortality in schizophrenia and bipolar disorder—changes in the Danish population between 1994 and 2006. *J Psychiatr Res*. 2011;45:29–35.
30. Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry*. 2007;68:899–907.
31. Westman J, Hällgren J, Wahlbeck K, Erlinge D, Alfredsson L, Osby U. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. *BMJ Open*. 2013;3:e002373. doi:10.1136/bmjopen-2012-002373
32. Marangell LB, Bauer MS, Dennehy EB, et al. Prospective predictors of suicide and suicide attempts in 1556 patients with bipolar disorders followed for up to 2 years. *Bipolar Disord*. 2006;8:566–575.
33. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord.* 2005;7(suppl 3):5–69.
34. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry*. 2011;68:1058–1064.
35. Hawton K, Sutton L, Haw C, Sinclair J, Harriss L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J Clin Psychiatry*. 2005;66:693–704.
36. Simhandi C, Radua J, König B, Amann BL. Prevalence and impact of comorbid alcohol use disorder in bipolar disorder: a prospective follow-up study. *Aust N Z J Psychiatry*. 2016;50(4):345–351.
37. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. *JAMA*. 1990;264:2511–2518.
38. Agrawal A, Nurnberger JI Jr, Lynskey MT; Bipolar Genome Study. Cannabis involvement in individuals with bipolar disorder. *Psychiatry Res*. 2011;185:459–461.
39. Tsai SY, Kuo CJ, Chen CC, Lee HC. Risk factors for completed suicide in bipolar disorder. *J Clin Psychiatry*. 2002;63:469–476.
40. Woods SW. The economic burden of bipolar disorder. *J Clin Psychiatry*. 2000;61(suppl 13):38–41.

41. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. *J Affect Disord*. 1994;31:281–294.
42. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59:530–537.
43. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97–170.
44. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry.* 2018;19(1):2–58.
45. Mohammad O, Osser DN. The psychopharmacology algorithm project at the Harvard South Shore Program: an algorithm for acute mania. *Harv Rev Psychiatry*. 2014;22:274–294.
46. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2016;30:495–553.
47. Ansari A, Osser DN. The psychopharmacology algorithm project at the Harvard South Shore Program: an update on bipolar depression. *Harv Rev Psychiatry*. 2010;18:36–55.
48. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*. 2013;15:1–44.
49. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorder: update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry*. 2013;14:154–219.
50. Bawa R, Scarff JR. Lurasidone: a new treatment option for bipolar depression—a review. *Innov Clin Neurosci*. 2015;12:21–23.
51. Latuda (lurasidone). Package insert. Sunovion Pharmaceuticals; December 2019.
52. Peet M, Peters S. Drug-induced mania. *Drug Saf*. 1995;12:146–153.
53. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord*. 2003;5:407–420.
54. Gören JL, Stoll AL, Damico KE, Sarmiento IA, Cohen BM. Bioavailability and lack of toxicity of S-adenosyl-L-methionine (SAMe) in humans. *Pharmacotherapy*. 2004;24:1501–1507.

55. Moses EL, Mallinger AG. St. John's wort: three cases of possible mania induction. *J Clin Psychopharmacol*. 2000;20:115–117.
56. Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 1999;56:407–412.
57. Ogawa N, Ueki H. Secondary mania caused by caffeine. *Gen Hosp Psychiatry*. 2003;25:138–139.
58. Sultzer DL, Cummings JL. Drug-induced mania—causative agents, clinical characteristics and management: a retrospective analysis of the literature. *Med Toxicol Adverse Drug Exp*. 1989;4:127–143.
59. Padala PR, Wengel SP, Petty F. Manic episode during treatment with aripiprazole. *Am J Psychiatry*. 2007;164:172–173.
60. Rachid F, Bertschy G, Bondolfi G, Aubry JM. Possible induction of mania or hypomania by atypical antipsychotics: an updated review of reported cases. *J Clin Psychiatry*. 2004;65:1537–1545.
61. Abouesh A, Stone C, Hobbs WR. Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol*. 2002;22:71–81.
62. Blanch J, Corbella B, García F, Parellada E, Gatell JM. Manic syndrome associated with efavirenz overdose. *Clin Infect Dis*. 2001;33:270–271.
63. Jochum T, Bär KJ, Sauer H. Topiramate induced manic episode. *J Neurol Neurosurg Psychiatry*. 2002;73:208–209.
64. Margolese HC, Beauclair L, Szkrumelak N, Chouinard G. Hypomania induced by adjunctive lamotrigine. *Am J Psychiatry*. 2003;160:183–184.
65. Short C, Cooke L. Hypomania induced by gabapentin. *Br J Psychiatry*. 1995;166:679–680.
66. Watts BV, Grady TA. Tramadol-induced mania. *Am J Psychiatry*. 1997;154:1624.
67. Rego MD, Giller EL Jr. Mania secondary to amantadine treatment of neuroleptic-induced hyperprolactinemia. *J Clin Psychiatry*. 1989;50:143–144.
68. Price WA, Bielefeld M. Buspirone-induced mania. *J Clin Psychopharmacol*. 1989;9:150–151.
69. Gupta N. Venlafaxine-induced hypomanic switch in bipolar depression. *Can J Psychiatry*. 2001;46:760–761.
70. Bhanji NH, Margolese HC, Saint-Laurent M, Chouinard G. Dysphoric mania induced by high-dose mirtazapine: a case for "norepinephrine syndrome"? *Int Clin Psychopharmacol*. 2002;17:319–322.
71. Zaphiris HA, Blaisdell GD, Jermain DM. Probable nefazodone-induced mania in a patient with unreported bipolar disorder. *Ann Clin Psychiatry*. 1996;8:207–210.
72. Benazzi F. Organic hypomania secondary to sibutramine-citalopram interaction. *J Clin Psychiatry*. 2002;63:165.

73. El-Mallakh RS. Bupropion manic induction during euthymia, but not during depression. *Bipolar Disord*. 2001;3:159–160.
74. Baldessarini RJ, Leahy L, Arcona S, Gause D, Zhang W, Hennen J. Patterns of psychotropic drug prescription for US patients with a diagnosis of bipolar disorders. *Psychiatr Serv*. 2007;58:85–91.
75. Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry*. 2004;161:1537–1547.
76. Peet M. Induction of mania with selective serotonin reuptake inhibitors and tricyclic antidepressants. *Br J Psychiatry*. 1994;164:549–550.
77. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry*. 2006;163:232–239.
78. Mattes JA. Antidepressant-induced rapid cycling: another perspective. *Ann Clin Psychiatry*. 2006;18:195–199.
79. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356:1711–1722.
80. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced mania and cycle acceleration: a controversy revisited. *Am J Psychiatry*. 1995;152:1130–1138.
81. Bowden CL. Valproate. *Bipolar Disord*. 2003;5:189–202.
82. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs. lithium and placebo in the treatment of mania. *JAMA*. 1994;271:918–924.
83. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar 1 disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry*. 2000;57:481–489.
84. Bowden CL, Janicak PG, Orsulak P, et al. Relation of serum valproate concentration to response in mania. *Am J Psychiatry*. 1996;153:765–770.
85. Hirschfeld RM, Baker JD, Wozniak P, Tracy K, Sommerville KW. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. *J Clin Psychiatry*. 2003;64:841–846.
86. Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. *Am J Psychiatry*. 2006;163:272–275.
87. Bowden CL, Swann AC, Calabrese JR, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry*. 2006;67:1501–1510.
88. Smith MC, Centorrino F, Welge JA, Collins MA. Clinical comparison of extended-release divalproex versus delayed-release divalproex: pooled data

analyses from nine trials. *Epilepsy Behav*. 2004;5:746–751.
89. Depakote (divalproex sodium). Package insert. AbbVie; October 2017.
90. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry*. 2003;160:1263–1271.
91. Joffe H, Cohen LS, Suppes T, et al. Valproate is associated with new-onset oligoamenorrhea with hyperandrogenism in women with bipolar disorder. *Biol Psychiatry*. 2006;59:1078–1086.
92. Mercke Y, Sheng H, Khan T, Lippmann S. Hair loss in psychopharmacology. *Ann Clin Psychiatry*. 2000;12:35–42.
93. Kimmel RJ, Irwin SA, Meyer JM. Valproic acid-associated hyperammonemic encephalopathy: a case report from the psychiatric setting. *Int Clin Psychopharmacol*. 2005;20:57–58.
94. Elgudin L, Hall Y, Schubert D. Ammonia induced encephalopathy from valproic acid in a bipolar patient: case report. *Int J Psychiatry Med*. 2003;33:91–96.
95. Britton JW, Shih JJ. Antiepileptic drugs and suicidality. *Drug Healthc Patient Saf*. 2010;2:181-189.
96. Nasreddine W, Beydoun A. Valproate-induced thrombocytopenia: a prospective monotherapy study. *Epilepsia*. 2008;49:438–445.
97. Acharya S, Bussel JB. Hematologic toxicity of sodium valproate. *J Pediatr Hematol Oncol*. 2000;22:62–65.
98. Janicak PG, Marder SR, Pavuluri MN. Treatment with mood stabilizers. In: Janicak PG, Davis JM, Preskorn SH, et al, eds. *Principles and Practice of Psychopharmacotherapy*. 4th ed. Lippincott Williams & Wilkins; 2006:369.
99. Gelenberg AJ, Jefferson JW. Lithium tremor. *J Clin Psychiatry*. 1995;56:283–287.
100. Henry C. Lithium side-effects and predictors of hypothyroidism in patients with bipolar disorder: sex differences. *J Psychiatry Neurosci*. 2002;27:104–107.
101. Bendz H, Aurell M. Drug-induced diabetes insipidus: incidence, prevention, and management. *Drug Saf*. 1999;21:449–456.
102. Finch CK, Kelley KW, Williams RB. Treatment of lithium-induced diabetes insipidus with amiloride. *Pharmacotherapy*. 2003;23:546–550.
103. Mellerup ET, Plenge P. The side effects of lithium. *Biol Psychiatry*. 1990;28:464–466.
104. Aiff H, Attman PO, Aurell M, et al. Effects of 10 to 30 years of lithium treatment on kidney function. *J Psychopharmacol.* 2015;29(5):608–614.
105. Lepkifker E, Sverdlik A, Iancu I, Ziv R, Segev S, Kotler M. Renal insufficiency in long term lithium treatment. *J Clin Psychiatry.* 2004;65:850–856.
106. Dunner DL. Drug interactions of lithium and other antimanic/mood-stabilizing medications. *J Clin Psychiatry*. 2003;64(suppl 5):38–43.

Decker BS, Goldfarb DS, Dargan PI, et al. Extracorporeal treatment for
107. lithium poisoning: systematic review and recommendations from the EXTR17 workgroup. *Clin J Am Soc Hephrol.* 2015;10(5):875–887
108. Kleiner J, Altshuler L, Hendrick V, Hershman JM. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *J Clin Psychiatry*. 1999;60:249–255.
109. Zhang ZJ, Qiang Li, Kang WH, et al. Differences in hypothyroidism between lithium-free and lithium-treated patients with bipolar disorders. *Life Sci*. 2006;78:771–776.
110. Livingstone C, Rampes H. Lithium: a review of its metabolic adverse effects. *J Psychopharmacol*. 2006;20:347–355.
111. Ernst CL, Goldberg JF. The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. *J Clin Psychiatry*. 2002;63(suppl 4):42–55.
112. Jain AE, Lacy T. Psychotropic drugs in pregnancy and lactation. *J Psychiatr Pract*. 2005;11:177–191.
113. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. A reevaluation of risk of in utero exposure to lithium. *JAMA*. 1994;271:146–150.
114. Patorno E, Huybrechts KF, Bateman BT, et al. Lithium use in pregnancy and the risk of cardiac malformations. *N Engl J Med.* 2017;376:2245–2254.
115. Fornaro M, Maritan E, Ferranti R, et al. Lithium exposure during pregnancy and postpartum period: a systematic review and meta-analysis of safety and efficacy outcomes. *Am J Psychiatry.* 2020;177(1):76–92.
116. Troyer WA, Pereira GR, Lannon RA, Belik J, Yoder MC. Association of maternal lithium exposure and premature delivery. *J Perinatol*. 1993;13:123–127.
117. Ward S, Wisner KL. Collaborative management of women with bipolar disorder during pregnancy and postpartum: pharmacologic considerations. *J Midwifery Womens Health*. 2007;52:3–13.
118. Cunnington MC, Weil JG, Messenheimer JA, Ferber S, Yerby M, Tennis P. Final results from 18 years of the International Lamotrigine Pregnancy Registry. *Neurology*. 2011;76(21):1817–1823.
119. Newport DJ, Calamaras MR, DeVane CL, et al. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. *Am J Psychiatry*. 2007;164:1214–1220.
120. Perlis RH, Welge JA, Vornik LA, Hirschfeld RM, Keck PE Jr. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2006;67:509–516.
121. Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Arch Gen Psychiatry*. 2007;64:442–455.

122. Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Acute bipolar mania: systematic review and meta-analysis of co-therapy vs. monotherapy. *Acta Psychiatr Scand*. 2007;115:12–20.
123. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378:1306–1315.
124. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disord*. 2010;12:116–141.
125. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596–601.
126. Banov MD, Zarate CA Jr, Tohen M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. *J Clin Psychiatry*. 1994;55:295–300.
127. Calabrese JR, Kimmel SE, Woyshville MJ, et al. Clozapine for treatment—refractory mania. *Am J Psychiatry*. 1996;153:759–764.
128. Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush AJ. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. *Am J Psychiatry*. 1999;156:1164–1169.
129. Mclntyre RS, Konarski JZ. Tolerability profiles of atypical antipsychotics in the treatment of bipolar disorder. *J Clin Psychiatry*. 2005;66(suppl 3):28–36.
130. Sachs G, Sanchez R, Marcus R, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol*. 2006;20:536–546.
131. Keck PE Jr, Marcus R, Tourkodimitris S, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*. 2003;160:1651–1658.
132. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disord*. 2015;174:296–302.
133. Saphris (asenapine). Package insert. Merck & Company; January 2017.
134. Stahl SM, Shayegan DK. The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. *J Clin Psychiatry*. 2003;64(suppl 19):6–12.
135. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia [published correction appears in *N Engl J Med*. 2010;363:1092]. *N Engl J Med*. 2005;353:1209–1223.
136. Post RM, Ketter TA, Uhde T, Ballenger JC. Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: principles and

practice. *CNS Drugs*. 2007;21:47–71.
137. Ceron-Litvoc D, Soares BG, Geddes J, Litvoc J, de Lima MS. Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. *Hum Psychopharmcol*. 2009;24:19–28.
138. Pratoomsri W, Yatham LN, Bond DJ, Lam RW, Sohn CH. Oxcarbazepine in the treatment of bipolar disorder: a review. *Can J Psychiatry*. 2006;51:540–545.
139. Vasudev A, Macritchie K, Vasudev K, Watson S, Geddes J, Young AH. Oxcarbazepine for acute affective episodes in bipolar disorder. *Cochrane Database Syst Rev*. 2011;12:CD004857.
140. Vasudev A, Macritchie K, Watson S, Geddes JR, Young AH. Oxcarbazepine in the maintenance treatment of bipolar disorder. *Cochrane Database Sys Rev*. 2008;2008(1):CD005171.
141. Rosa AR, Fountoulakis K, Siamouli M, Gonda X, Vieta E. Is anticonvulsant treatment of mania a class effect? Data from randomized clinical trials? *CNS Neurosci Ther*. 2011;17:167–177.
142. Young LT, Robb JC, Hasey GM, et al. Gabapentin as an adjunctive treatment in bipolar disorder. *J Affect Disord*. 1999;55:73–77.
143. Schaffer CB, Schaffer LC. Gabapentin in the treatment of bipolar disorder. *Am J Psychiatry*. 1997;154:291–292.
144. Ghaemi SN, Katzow JJ, Desai SP, Goodwin FK. Gabapentin treatment of mood disorders: a preliminary study. *J Clin Psychiatry*. 1998;59:426–429.
145. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Bipolar Disord*. 2000;2(3, pt 2):249–255.
146. Chengappa KN, Gershon S, Levine J. The evolving role of topiramate among other mood stabilizers in the management of bipolar disorder. *Bipolar Disord*. 2001;3:215–232.
147. Kushner SF, Khan A, Lane R, Olson WH. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord*. 2006;8:15–27.
148. Wolfsperger M, Greil W, Rössler W, Grohmann R. Pharmacological treatment of acute mania in psychiatric in-patients between 1994 and 2004. *J Affect Disord*. 2007;99:9–17.
149. Allen MH, Carpenter D, Sheets JL, Miccio S, Ross R. What do consumers say they want and need during a psychiatric emergency? *J Psychiatr Pract*. 2003;9:39–58.
150. Currier GW, Medori R. Orally versus intramuscular administered antipsychotic drugs in psychiatric emergencies. *J Psychiatr Pract*. 2006;12:30–40.
151. Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated

psychotic patients [published correction appears in *J Clin Psychiatry*. 2001;62:209]. *J Clin Psychiatry*. 2001;62:12–18.

152. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology (Berl)*. 2001;155:128–134.
153. Meehan K, Zhang F, David S, et al. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treatment of acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol*. 2001;21:389–397.
154. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med*. 1997;15:335–340.
155. Zyprexa. Package insert. Eli Lilly & Co; April 2020.
156. Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP; Expert Consensus Panel for Behavioral Emergencies 2005. The expert consensus guideline series. Treatment of behavioral emergencies 2005. *J Psychiatr Pract*. 2005;11(suppl 1):5–108.
157. Baldessarini RJ, Vieta E, Calabrese JR, Tohen M, Bowden CL. Bipolar depression: overview and commentary. *Harv Rev Psychiatry*. 2010;18:143–157.
158. Pompili M, Gonda X, Serafini G, et al. Epidemiology of suicide in bipolar disorder: a systematic review of the literature. *Bipolar Disord.* 2013;15:457–490.
159. Malhi GS, Adams D, Berk M. Medicating mood with maintenance in mind: bipolar depression pharmacotherapy. *Bipolar Disord*. 2009;11(suppl 2):55–76.
160. Yatham LN, Calabrese JR, Kusumakar V. Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options. *Bipolar Disord*. 2003;5:85–97.
161. Tondo L, Baldessarini RJ, Floris G. Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. *Br J Psychiatry*. 2001;41:S184–S190.
162. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry*. 2004;161:217–222.
163. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry*. 2005;162:1805–1819.
164. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord*. 2008;10:323–333.

165. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry*. 2009;194:4–9.
166. Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry*. 2004;65:432–441.
167. van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70:223–231.
168. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162:1351–1360.
169. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study) [published correction appears in *J Clin Psychopharmacol*. 2007;27:51]. *J Clin Psychopharmacol*. 2006;26:600–609.
170. McElroy SL, Weisler RH, Chang W, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry*. 2010;71:163–174.
171. Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71:150–162.
172. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression [published correction appears in *Arch Gen Psychiatry*. 2004;61:176]. *Arch Gen Psychiatry*. 2003;60:1079–1088.
173. Brown EB, McElroy SL, Keck PE Jr, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry*. 2006;67:1025–1033.
174. Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. *Int J Neuropsychopharmacol*. 2009;12:773–782.
175. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014;171:160–168.
176. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014;171(2):169–177.
177. Findlay LJ, El-Mallakh P, El-Mallakh RS. Management of bipolar I depression: clinical utility of lurasidone. *Ther Clin Risk Manag*. 2015;11:75–

81.
178. Durgam S, Earley W, Lipschitz A, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of Cariprazine in patients with bipolar I depression. *Am J Psychiatry.* 2016;173:271–281.
179. Earley W, Burgess MV, Rekeda L, et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. *Am J Psychiatry.* 2019;176:439–448.
180. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies [published correction appears in *J Clin Psychopharmacol*. 2009;29:38]. *J Clin Psychopharmacol*. 2008;28:13–20.
181. Lamictal (lamotrigine). Package insert. GlaxoSmithKline; October 2020.
182. Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2011;72:156–167.
183. Gelenberg AJ, Kane JM, Keller MB, et al. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. *N Engl J Med*. 1989;321:1489–1493.
184. Vieta E, Günther O, Locklear J, et al. Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol*. 2011;14:1029–1049.
185. Miklowitz DJ, Otto MW, Frank E, et al. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. *Am J Psychiatry*. 2007;164:1340–1347.
186. Kilbourne AM, Rofey DL, McCarthy JF, Post EP, Welsh D, Blow FC. Nutrition and exercise behavior among patients with bipolar disorder. *Bipolar Disord*. 2007;9:443–452.
187. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: Evidence basis for treatment and future research in psychiatry [published correction appears in *J Clin Psychiatry*. 2007;68:338]. *J Clin Psychiatry*. 2006;67:1954–1967.
188. Nierenberg AA, Ostacher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry*. 2006;163:210–216.
189. Bailine S, Fink M, Knapp R, et al. Electroconvulsive therapy is equally effective in unipolar and bipolar depression. *Acta Psychiatr Scand*. 2010;121:431–436.
190. Mukherjee S, Sackeim HA, Schnur DB. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. *Am J Psychiatry*. 1994;151:169–176.

191. Meeter M, Murre JM, Janssen SM, Birkenhager T, van den Broek WW. Retrograde amnesia after electroconvulsive therapy: a temporary effect? *J Affect Disord*. 2011;132:216–222.
192. Virupaksha HS, Shashidhara B, Thirthalli J, Kumar CN, Gangadhar BN. Comparison of electroconvulsive therapy (ECT) with or without anti-epileptic drugs in bipolar disorder. *J Affect Disord*. 2010;127:66–70.
193. Sienaert P, Roelens Y, Demunter H, Vansteelandt K, Peuskens J, Van Heeringen C. Concurrent use of lamotrigine and electroconvulsive therapy. *J ECT*. 2011;27:148–152.
194. Small JG, Milstein V. Lithium interactions: lithium and electroconvulsive therapy. *J Clin Psychopharmacol*. 1990;10:346–350.
195. Thirthalli J, Harish T, Gangadhar BN. A prospective comparative study of interaction between lithium and modified electroconvulsive therapy. *World J Biol Psychiatry*. 2011;12:149–155.
196. Masdrakis VG, Florakis A, Tzanoulinos G, Markatou M, Oulis P. Safety of the electroconvulsive therapy-ziprasidone combination. *J ECT*. 2010;26:139–142.
197. Masdrakis VG, Oulis P, Zervas IM, et al. The safety of the electroconvulsive therapy-aripiprazole combination: four case reports. *J ECT*. 2008;24:236–238.
198. Healio. FDA grants breakthrough designation to transcranial magnetic stimulation device for bipolar depression. Accessed October 27, 2020. https://www.healio.com/news/psychiatry/20200318/fda-grants-breakthrough-designation-to-transcranial-magnetic-stimulation-device-for-bipolar-depressi

88

Developmental Disorders

Kimberly Lenz and Neha Kashalikar

CORE PRINCIPLES

CHAPTER CASES

CORE PRINCIPLES		CHAPTER CASES
1	Developmental disorders are a group of conditions in which early brain development is impaired. This very large group of disorders includes diagnoses such as intellectual disability (ID) and autism spectrum disorder (ASD). The core diagnostic features of ASD include impairment in reciprocal social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities. These symptoms must be present from early childhood and impair everyday functioning. ASD is diagnosed clinically, although standardized behavioral diagnostic instruments can assist this process. ASD is more common in males than in females, and the core diagnostic features can be addressed through multiple different types of nonpharmacologic interventions, including specialized education, physical therapy, occupational therapy, speech and language therapy, and behavioral therapy, such as applied behavior analysis (ABA).	**Case 88-1 (Question 1), Table 88-1**

CORE PRINCIPLES		CHAPTER CASES
2	Individuals with ID/ASD have high rates of comorbid attention-deficit/hyperactivity disorder (ADHD). Treatment of ADHD, especially hyperactivity, in individuals with ID/ASD is similar to the treatment of ADHD in neurotypical individuals and includes stimulants, α_2-agonists, and atomoxetine. Compared to their neurotypical peers though, individuals with ID/ASD and comorbid ADHD experience lower effect sizes with ADHD treatment, lower tolerated doses of ADHD medication, and more risk of adverse effects, including increased rates of decreased appetite, insomnia, depressive symptoms, irritability, and social withdrawal.	**Case 88-1 (Question 2)**

CORE PRINCIPLES		CHAPTER CASES
3	Some individuals with developmental disorders demonstrate symptoms of irritability and aggression, which can sometimes be helped with a pharmacologic intervention if nonpharmacologic interventions are ineffective. The strongest evidence for the pharmacologic treatment of irritability/aggression in individuals with developmental disorders exists for the use of risperidone and aripiprazole to treat irritability in children with ASD. Doses for this purpose are likely lower than those used to treat schizophrenia or bipolar disorder, and adverse events are relatively common and may include sedation, weight gain, and extrapyramidal symptoms.	**Case 88-2 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
4	Individuals with developmental disorders are at high risk of having comorbid anxiety and depression. Although no large prospective, randomized, controlled trials (RCTs) exist to support the use of selective serotonin reuptake inhibitors (SSRIs) for this purpose, case studies and open-label studies have shown possible benefits. RCTs of SSRIs for the treatment of repetitive behavior in children with developmental disorders have shown mixed results, although they have demonstrated that individuals with developmental disorders may be at increased risk of emotional and behavioral adverse events from SSRIs, and therefore, target dosing should be lower than in individuals with typical development.	**Case 88-3 (Questions 1, 2)**
5	Individuals with developmental disorders have high rates of comorbid medical and psychiatric disorders, and therefore may often be prescribed multiple different concurrent medications. Precaution should be taken to avoid any pharmacodynamic or pharmacokinetic drug–drug interactions, and such interactions should always be considered to describe any adverse events.	**Case 88-3 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
6	Sleep disturbances are common in individuals with developmental disorders. Melatonin has the strongest body of evidence for being a safe and effective treatment of sleep disturbances in this population.	**Case 88-4 (Question 1)**

INTRODUCTION

Developmental disorders are a group of conditions characterized by impaired early brain development, resulting in deficits of cognitive, communicative, behavioral, sensory, or motor functioning. This broad group of disorders includes diagnoses such as intellectual disability (ID); autism spectrum disorder (ASD), which will be the focus of this chapter; attention-deficit/hyperactivity disorder (ADHD) and tic disorder, which are covered in other chapters; and communication disorders, learning disorders, cerebral palsy, congenital hearing loss, and congenital blindness. ID, previously labeled mental retardation, is a disorder with deficits in intellectual and adaptive functioning. Although ID is typically reserved for older children, for whom intellectual testing is more valid and reliable, global developmental delay (GDD) is the diagnosis given to younger children in which delays exist in two or more developmental domains. ASD, which includes prior diagnoses of autistic disorder, Asperger disorder, and pervasive developmental disorder (PDD), not otherwise specified, are conditions involving deficits in social communication, as well as the presence of restricted and repetitive patterns of behavior, interests, or activities.[1]

EPIDEMIOLOGY, NATURAL COURSE OF THE DISEASE, AND PROGNOSIS

Developmental disorders are common in the community, affecting as many as 15% of children in the United States, based on parent report.[2] Collectively, developmental disorders are nearly twice as likely in males and children insured by Medicaid, relative to females and those insured by private insurance, respectively.[2] Additionally, a higher prevalence of developmental disorders is reported by families with incomes below the federal poverty level and with lower maternal education (any educational attainment less than a college degree).[2]

For ID and GDD, the overall prevalence is estimated to be between 1% and 3% of the population, although with considerable variability depending on how the diagnosis is defined and reported in the literature.[3,4] ID is more prevalent in males versus females, and in low- and middle-income countries relative to high-income countries.[3]

ASD is increasing in prevalence, with the Centers for Disease Control and Prevention reporting about 1 in 68 children (1.47%) being identified with the disorder.[5] Although around one-third of children with ASD may also qualify for ID, the proportion of children with average or above-average intelligence being diagnosed with ASD has been steadily increasing over the years and may explain some of the increase in overall ASD prevalence.[5] The proportion of children with ASD who are male has consistently been four to five times that of females.[5] In the United States, around 30% of children with ASD have some level of ID.[5]

The course and prognosis of both ID and ASD vary considerably depending on the severity of the deficits, the impact of comorbid medical and psychiatric conditions, and the access to services and treatments. Many individuals will go on to live rich and fulfilling lives, with minimal required assistance in daily life functioning, although some will require constant supervision in supportive group housing, and assistance for basic tasks of daily living.

PATHOPHYSIOLOGY: DISEASE ETIOLOGY, ANATOMY, AND PHYSIOLOGY

Many different known and unknown genetic and environmental factors can lead to the impairment in early brain development associated with developmental disorders.

For both ID and ASD, risk factors include preterm birth, low birth weight, small for gestational age, and low Apgar scores, although all of these are associated more strongly with ID.[6] For ID specifically, risk factors may differ depending on the severity of ID. Studies have shown risk factors for mild ID to include mothers under age 20 years or older than 30 years, paternal age older than 40 years, increasing birth order, increasing social disadvantage, maternal education less than high school, being part of a multiple birth, and being second or later in the birth order.[7,8] The risk of severe ID was consistently increased with increasing maternal age and decreasing level of maternal education.[7] For ASD without ID, additional risk factors include mothers ages 35 years or older, first-born infants, male infants, and increasing socioeconomic advantage.[8]

In only about half of all cases of ID can a specific etiology be identified and may include genetic anomalies, intrapartum asphyxia, cerebral dysgenesis, and environmental causes.[9] In only about 30% of children with ASD can an identifiable genetic etiology be determined.[10] Although inherited genetic forms of ID likely represent a minority of identified cases, ASD, on the other hand, is widely considered to be one of the most heritable neuropsychiatric conditions with heritability estimates of 60% to 90%.[11] For parents with one child with ASD, the recurrence rate in future siblings is thought to be 5% to 20%, with higher rates if the original child with ASD is female.[12] This recurrence rate increases to about 33% if a family already has two children with ASD.[12]

For inherited genetic anomalies, X-linked gene defects account for 10% to 12% of all ID cases in males, with fragile X syndrome being the most common.[13] Fragile X syndrome, marked by a CGG triplet

repeat expansion in the *FMR1* gene on the X chromosome, is also the most common single-gene cause of ID, accounting for about 0.5% to 3% of individuals with ID,[14] and ASD, accounting for around 1% to 3% of cases.[10,15] Single-gene disorders, some heritable like fragile X syndrome, account for about 5% to 7% of ASD cases and include *PTEN* macrocephaly syndrome (~1%), tuberous sclerosis complex (~1%), and Rett syndrome (~1%).[10,15] Other inherited causes of ID and ASD include inherited metabolic disorders, such as phenylketonuria, adenylosuccinate lyase deficiency, and Smith–Lemli–Opitz syndrome.[15] Although inherited metabolic disorders are relatively rare, accounting for only 1% to 5% of cases of ID, the potential for positive prognosis with treatment is high.[4]

Other genetic anomalies that can lead to ID and ASD include noninherited, or de novo, single-gene mutations, chromosomal aberrations, and imprinting/epigenetic disorders.[14] Chromosomal aberrations may account for up to 25% of individuals with ID, about 8% or 9% of which is because of trisomy 21, or Down syndrome, the most common known cause of ID.[14,16] Prader–Willi and Angelman syndromes, both associated with developmental delays, are two examples of disorders involving imprinted genes.

Environmental causes of ID range in the literature from 2% to 13% and include antenatal toxin exposure (eg, fetal alcohol spectrum disorders), antenatal infection (eg, TORCH infections), and early severe psychosocial deprivation.[17,18] Environmental causes of ASD include first-trimester intrauterine exposure to valproic acid, thalidomide, misoprostol, the organophosphate insecticide chlorpyrifos, and phthalates, in addition to first-trimester rubella infection.[19] While receiving much scrutiny, multiple studies have shown no data supporting the conclusion that vaccines cause autism.[20]

CLINICAL PRESENTATION

Developmental disorders are typically recognized clinically once it becomes clear that a child is delayed in meeting one or more developmental milestones. Primary care providers have been tasked by the American Academy of Pediatrics (AAP) to assess development at every routine preventative visit throughout childhood.[21] Additionally, the AAP encourages pediatricians to use standardized developmental screening tools (eg, Ages and Stages Questionnaires—ASQ and Parents' Evaluation of Developmental Status—PEDS) at the 9-, 18-, and 24- or 30-month visit, and an autism-specific screening tool at the 18- and 24-month visits (eg, Modified Checklist for Autism in Toddlers—MCHAT).[21,22] Once concerns are raised by routine surveillance or screening measures, children should be referred to early intervention and early childhood programs, as well as to developmental specialists, when indicated.[21]

Early recognition of developmental disorders depends on children having access to preventative medical care, and almost 25% of children with special health care needs might not have that access.[23] The nature and severity of the developmental deficits also contribute to the age at recognition. The sensitivity of developmental and autism screening measures rarely reaches 0.9,[21] and so relatively mild developmental deficits may go undetected. For children with ASD, the mean age of diagnosis has been around 53 months,[5] although children with ID and those diagnosed with autistic disorder are typically diagnosed earlier; children with higher IQ scores and those eventually diagnosed with Asperger disorder, whose limitations do not include communication delays, are typically diagnosed later.[5] Some individuals with particularly subtle deficits may not be diagnosed until adulthood. Individual symptoms that may lead to an earlier diagnosis of ASD may include severe language deficits, hand flapping, toe walking, and sustained odd play.[24]

DIAGNOSIS

ID is defined by both the American Psychiatric Association and the American Association on Intellectual and Developmental Disability (AAIDD) as a disorder with deficits in intellectual and adaptive functioning in conceptual, social, and practical domains.[1,25] The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) requires that the disability has onset "during the developmental period," whereas the AAIDD requires the disability to start before age 18 years. Intellectual functioning is assessed clinically and by standardized tests of intelligence, like IQ testing (eg, Wechsler Intelligence Scale for Children and the Stanford–Binet Intelligence Scale), with a cutoff being two standard deviations below the mean for the general population, or a score of around 65 to 75, for disability.[1] Older references focused diagnosis primarily around IQ scores, and subcategories of ID (then called mental retardation) were set to specific IQ scores.[1] Current methods of diagnosis focus more on measures of adaptive functioning because this is more relevant to planning treatment and supports. Adaptive functioning is also assessed clinically or with standardized tests of adaptive functioning (eg, Vineland Adaptive Behavior Scales). Subcategories for ID in the *DSM-5* are now based on levels of adaptive functioning, mild, moderate, severe, and profound. As standardized testing for intellectual and adaptive functioning is typically valid for children above the age of 5 years, for children younger than 5 years, the diagnosis of GDD is used and describes significant delays in two or more developmental domains, including gross/fine motor, speech/language, cognition, social/personal, and activities of daily living.[26]

ASD is defined by the *DSM-5* as the presence of persistent impairment in reciprocal social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities, present from early childhood, and impairing everyday functioning (**Table 88-1**).[1] The diagnosis is made clinically, although standardized behavioral diagnostic instruments, including caregiver interviews, questionnaires, and clinician observation measures (eg, Autism Diagnostic Interview and Autism Diagnostic Observation Schedule), are available to potentially assist in diagnosis.

Table 88-1
DSM-5 Criteria for Autism Spectrum Disorder

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples below):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples below):

1. Stereotyped or repetitive motor movements, use of objects, or speech (eg, simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases)
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (eg, extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day)
3. Highly restricted, fixated interests that are abnormal in intensity or focus (eg, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests)
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (eg, apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement)

Severity is based on social communication impairments and restricted, repetitive patterns of behavior (Level 1 [requiring support], Level 2 [requiring substantial support], Level 3 [requiring very substantial support])

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.
Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Reprinted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. © 2013 American Psychiatric Association. All Rights Reserved.

After a child is identified to have a developmental disorder, further diagnostic workup is warranted to identify an etiologic cause, because some causes may be treatable (eg, metabolic disorder), some may inform of other potential comorbid medical problems (eg, cardiac conditions in Down syndrome and fragile X syndrome), and some may help inform parents of risks for future children. This further etiologic workup should include a thorough medical history (including prenatal and birth history), a family history going back three or more generations, and a physical and neurologic examination focused on findings consistent with recognizable syndromes.[4]

If children with ID or GDD still do not have a known etiologic cause after this workup, they should be referred for chromosomal microarray and possibly screening for inborn errors of metabolism given the treatable nature of some metabolic disorders.[4] The American College of Medical Genetics and Genomics proposes that in the event of a diagnosis of ASD without a known cause despite the above workup, all children should undergo chromosomal microarray, those children with clinical indicators should undergo metabolic or mitochondrial testing, fragile X testing should be

performed for all males, MECP2 (Rett syndrome) testing should be performed in all females, PTEN testing in children with macrocephaly, and neuroimaging only if specific clinical indicators (eg, seizures, regression, history of stupor/coma, microcephaly are present).[27]

CASE 88-1

Question 1: L.B. is a 3-year-old male who is brought to his pediatrician for a well-child visit. During the behavioral health screening, his mother notes that L.B. speaks very few words, does not express many different emotions on his face, does not seem to share enjoyment in activities, and remains fairly unmotivated to interact with other children in daycare. He has more recently been making repetitive loud "woop"-ing sounds that are nonprompted and occur multiple times per day. He also becomes quite aggressive during any transitions. During the visit, the pediatrician completes the Childhood Autism Rating Scale, Second Edition (CARS-2). The result is a score of 32, suggesting a diagnosis of ASD. The pediatrician refers L.B. and his mother to a developmental pediatrician, who specializes in ASD, for further evaluation. After a thorough evaluation, and review of the differential diagnosis, L.B. is given a diagnosis of ASD and is referred for applied behavior analysis (ABA) services.

What signs and symptoms of ASD does L.B. demonstrate?

Based on the *DSM-5* criteria for ASD, L.B. is showing persistent deficits in social communication and social interaction in multiple settings, as demonstrated by his deficits in nonverbal communication (poor facial expressions), lack of relationship building with children, and poor social–emotional reciprocity (lack of shared enjoyment). L.B. also demonstrates restricted, repetitive patterns of behavior with his stereotyped "woop"-ing noises and his inflexible insistence on sameness, with aggression associated with transitions.

OVERVIEW OF TREATMENT

Therapy and Psychosocial Interventions

Individuals with ID or ASD can benefit from many different services to help with issues of communication, social skills, sensory integration, behavior modification, gross and fine motor skills, executive functioning, and adaptive functioning. Most of these services are provided to children through the public education system, at no cost to the families, as ensured by the Individuals with Disabilities Education Act (IDEA). The IDEA provides all states with grants to provide early intervention services for children with developmental delays under the age of 3. Services vary between states, although each child and family are evaluated and given an Individualized Family Service Plan (IFSP), which spells out the services to be provided, which may include, but are not limited to, physical therapy, occupational therapy, speech and language therapy, and behavioral therapy. For children reaching the age of 3 years, and still eligible for specialized education, an Individualized Education Plan (IEP) is drafted, which outlines the services to be provided in the school setting, starting in preschool. IEP services could include all of the same types of services as above, as well as academic support, social skills groups, social pragmatics counseling, vocational training, and emotional counseling. IEPs are required to be reevaluated every 3 years, with updated testing and evaluation. Families must consent to both IFSPs and IEPs, and if they disagree with the supports proposed, there is a process by which they can appeal to have changes made.

Despite the services assured by the IDEA, children and families with developmental disabilities also often receive psychosocial services in their communities. In fact, in the 2011 Survey of Pathways to Diagnosis and Services, almost two-thirds of children with ASD and/or ID were receiving a community-based service.[28] The odds of using any school- or community-based service were almost eight times more likely for children with ASD and over nine times more likely for children with ID, compared to children without those respective diagnoses.[28]

To address the core symptoms of ASD, which include social communication deficits and repetitive, restricted behaviors and interest, the most prevalent treatment modality has been ABA. ABA

is a behavioral therapy rooted in the concepts of operant conditioning, in which an antecedent leads to a behavior, which results in a consequence. In ABA, preferred behavior, such as an appropriate social response, is reinforced with an incentive. Classic ABA employs the use of discrete trial training (DTT), in which specific skills are broken down into discrete components and systematically taught in highly structured settings, often using incentives like food and stickers. Critics of this form of ABA worry that children with ASD are unlikely to apply the learned skills outside of the trial setting. As a result, multiple different therapy approaches have been created, such as Pivotal Response Therapy and the Early Start Denver Model, both derivations of ABA, and the Developmental, Individual-Differences, Relationship-based (DIR) Floortime approach, which all operate in more naturalistic settings, focus more on building child initiation and motivation, and employ natural incentives like positive affect and affection. The research evidence to support such interventions for children and young adults with ASD varies widely, as is explored in Wong et al's[29] comprehensive recent review. Operant conditioning though, and the principles of manipulating antecedents, behavior, and reinforcements, remains the mainstay for the treatment of aggressive behaviors in individuals with developmental disabilities.[30]

Individuals with ID often require the same types of interventions as individuals with ASD, although perhaps with a stronger emphasis on adaptive functioning training, and building skills of independent living. Likewise, for individuals with ID, the evidence base for psychological interventions is varied. One recent review and meta-analysis of psychological therapies for individuals with ID showed that in the literature, individual therapy seems to be superior to group interventions, and moderate-to-large effect sizes exist for therapy for depression and anger, although there is no evidence that therapy has an effect on interpersonal functioning.[31]

Pharmacologic Interventions

The evidence supporting psychopharmacologic interventions in individuals with ID/ASD is relatively limited. There are only a few large double-blind, randomized, placebo-controlled trials (RCTs), many of which were funded by, or affiliated with, the manufacturers of the particular study medications. Most of the existing RCTs are for individuals with ASD and are of children and adolescents, likely, in part, because of the complications involved in consenting adults with ID/ASD to participate in research. Additionally, the targets for medication intervention with the strongest research evidence are behaviors, which relay little about any possible underlying emotional etiology for the individual. Pharmacologic treatment typically targets behaviors such as anxiety, depression, aggression, self-injurious behavior, hyperactivity, inattention, compulsive-like behaviors, repetitive or stereotypic behaviors, and sleep disturbances.[32]

Despite the limitations of the evidence, medications may be an important component of a comprehensive treatment plan for individuals with ID/ASD. Although much of the literature is of studies of children with ASD, it should be noted that a large percentage of these studies contained many individuals with comorbid ID (76%,[33] 71%,[34] 53%,[35] mean IQ, 63[36,37]). However, the literature confirms that individuals with ID/ASD are more sensitive to adverse events from medications compared to their neurotypical peers, and therefore, pharmacologic interventions should be performed with caution.

At the time of this writing, there are no medications approved by the U.S. Food and Drug Administration (FDA) to treat any of the core diagnostic elements of ID/ASD. The target symptom behaviors with the most research evidence include hyperactivity, irritability, repetitive behaviors, and self-injurious behavior. As anxiety disorders are the most common comorbid psychiatric conditions in individuals with ID/ASD, anxiety/depression is another frequent target for psychopharmacologic intervention, although with considerably less research support. Sleep disturbances are also remarkably common in individuals with developmental disabilities and often are a target for medication intervention (**Table 88-2**).

Table 88-2

Summary of Target Symptoms and Pharmacologic Treatment

Target Symptom	Treatment Medications/Classes to Consider
Hyperactivity	Stimulants, atomoxetine, α_2-agonists
Irritability/aggression	Risperidone, aripiprazole
Repetitive behaviors	Risperidone, aripiprazole, fluoxetine, clomipramine, fluvoxamine
Self-injurious behavior	Risperidone, clomipramine, naltrexone
Anxiety/depression	SSRIs
Sleep	Melatonin, ramelteon, clonidine, trazodone, mirtazapine, zolpidem, donepezil, benzodiazepines

SSRI, selective serotonin reuptake inhibitor.

Hyperactivity

Individuals with ID/ASD have high rates of comorbid ADHD, with literature in children with ASD showing prevalence rates of about 30% for children derived from community, nonclinical, populations (28%[38] and 31%,[39]), and 41% to 78% for children evaluated in the clinical setting.[40] The mainstay of treatment for symptoms of ADHD in individuals with ID/ASD, like their neurotypical peers, includes stimulants, α_2-agonists, and atomoxetine. Children with ASD may experience more side effects and show less response than non-ASD patients with ADHD.[41]

Stimulants

Stimulants are a group of medications derived either from methylphenidate or amphetamine that act by increasing the amount of dopamine and norepinephrine in the neuronal synaptic cleft. This increase in dopamine and norepinephrine is the result of blocking the reuptake of dopamine and norepinephrine (methylphenidate and

amphetamine) and increasing the release of dopamine and norepinephrine (amphetamine).

Reichow et al,[42] in their recent meta-analysis of pharmacologic treatments of symptoms of ADHD in children with PDD, found four RCTs of stimulant medications. All four RCTs studied methylphenidate and found it to be superior to placebo for the treatment of global ADHD symptomatology and specifically hyperactivity. In the largest of the four RCTs (*n* = 66),[43] effect sizes for hyperactivity and impulsivity symptoms were greater than for inattention symptoms (0.77 vs 0.60 for parent rating; 0.48 vs 0.35 for teacher rating).[36]

The effect size for the treatment of ADHD symptoms in children with PDD (0.67 for methylphenidate),[42] however, was lower than estimates in a meta-analysis of stimulant treatment of typically developing children with ADHD (0.77 for methylphenidate and 1.03 for amphetamine).[44] In the study conducted by the Research Units on Pediatric Psychopharmacology (RUPP) group,[43] 49% of children experienced a therapeutic response, compared to 69% in the Multimodal Treatment Study of Children with ADHD (MTA), which studied mostly neurotypical children (ID was an exclusion criteria, and ASD was not mentioned as a comorbid diagnosis in any participants).[45]

Adverse events were more common in children with PDD treated with methylphenidate versus placebo, with increased rates of decreased appetite, insomnia, depressive symptoms, irritability, and social withdrawal.[42] Rates of adverse events with methylphenidate were also larger in children with PDD compared to typically developing children, as evidenced by 18% of RUPP study participants[43] discontinuing the medication because of adverse events (primarily irritability), compared to 1.4% in the MTA study.[45]

Mean dosage in the seven RCTs ranged from 0.29 to 0.45 mg/kg/dose.[36,42,44,46,47] Secondary analysis of the RUPP study data showed that methylphenidate doses of 0.25 and 0.5 mg/kg/dose were more consistently effective for treating ADHD symptoms than the lower 0.125 mg/kg/dose.[36] The highest dose used in the RUPP study was 0.625 mg/kg/dose, compared to the MTA study, in which

the highest dose used was 0.8 mg/kg/dose.[43] Daily methylphenidate doses may be titrated weekly until an optimal dose is obtained. Improvement in symptoms should be noted within the first week.[48]

Overall, the research literature shows that methylphenidate can be used to improve ADHD symptoms, especially hyperactivity, in children with PDD, though with lower effect sizes, lower tolerated doses, and more risk of adverse effects than children without developmental disabilities.

Although no RCTs have been conducted studying the effects of amphetamine-derived stimulants for the treatment of ADHD in children with ASD, consensus guidelines suggest that amphetamine salts can be an option for children demonstrating insufficient benefit or dose-limiting adverse events from methylphenidate.[49]

α_2-Agonists

Although the exact mechanism in ADHD is unknown, α_2-agonists are thought to work by stimulating the α_2-adrenoceptors on norepinephrine-containing neuron cell bodies in the locus coeruleus, which modulates the tonic and phasic firing to the prefrontal cortex. This allows the person to have increased attention on the desired task.[50]

α_2-Agonists include clonidine, a nonselective α_2-adrenergic receptor agonist, and guanfacine, a selective α_2-adrenergic receptor agonist. α_2-Agonists were initially marketed for the treatment of hypertension, although have been shown to also improve symptoms of ADHD.

For clonidine, one small study (n = 8)[51] was identified by Reichow et al[42] looking at clonidine versus placebo for the treatment of ADHD in children with PDD. Although the original study found no statistically significant results, the effect size calculated by Reichow et al[42] for improvement in ADHD symptoms and irritability was in the medium range (g = 0.51 and 0.64, respectively) and smaller for improvements in hyperactivity (g = 0.30) and stereotypic behavior

(0.24). The authors of the original study[51] report increased rates of hypotension and drowsiness in some children who took clonidine. Mean dosage ranged from 0.15 to 0.20 mg/day.

A retrospective chart review evaluated (*n* = 80) children and adolescents ages 3 to 18 years with PDD with target symptoms of hyperactivity, inattention, and impulsivity. Treatment with a guanfacine immediate-release (IR) mean daily dose of 2.6 ± 1.7 mg showed significant improvement in target symptoms based on Clinical Global Impression Scale-Improvement (CGI-I) and Clinical Global Impression Scale-Severity (CGI-S) scores. In these studies, adverse events included drowsiness, irritability, and enuresis, as well as diarrhea, constipation, and social withdrawal; additional adverse events from an open-label study of guanfacine in children with PDD include sleep disturbance (insomnia or mid-sleep awakening).[52–54]

In an RCT (*n* = 62) evaluating guanfacine extended release (ER) in children ages 5 to 14 years with autistic disorder, Asperger syndrome, or PDD accompanied by hyperactivity, impulsiveness, and distractibility, treatment with guanfacine ER exhibited a significant decrease in scores on the Aberrant Behavior Checklist (ABC) Hyperactivity subscale compared to a placebo group. Additionally, treatment with guanfacine ER demonstrated a greater improvement on the ADHD rating scale compared to placebo.[55]

Overall, a small collection of literature suggests that clonidine and guanfacine may be beneficial for the treatment of ADHD symptoms in children with ASD/ID, with similar adverse events as reported in neurotypical children, although more evidence is needed to draw any more extensive conclusions about the use of these medications in the ID/ASD population.

Atomoxetine

Atomoxetine is a medication for ADHD that acts by inhibiting the reuptake of norepinephrine, therefore increasing the amount of norepinephrine in the synaptic cleft. Dosing is generally once daily,

with adjustments after a minimum of 3 days to a target daily dose. Clinical benefit has been noted within the first 1 to 2 weeks.[56]

Reichow et al's[42] meta-analysis found two RCTs comparing atomoxetine to placebo in children with PDD, although only the larger of the two (n = 97)[56] showed statistically significant benefits for the treatment of global ADHD symptoms and hyperactivity (effect sizes calculated by Reichow et al[42] of g = 0.83 and g 0.80, respectively). In this study by Harfterkamp et al,[56] changes in the subscales of inattention and oppositional behavior did not reach statistical significance for children on atomoxetine compared to placebo.

Children with PDD in the Harfterkamp et al[56] study demonstrated increased rates of nausea, decreased appetite, and early morning awakening compared to study participants taking placebo. Mean dosage in the two studies was 1.2 mg/kg/day[56] and 44.2 mg/day.[57] This dosing is perhaps only slightly lower than other large studies of atomoxetine in children with ADHD without developmental disorders (mean final atomoxetine dose was 1.45 mg/kg/day, 53.0 mg/day[58]), although documentation from the drug manufacturer's studies, of presumably mostly neurotypical children with ADHD, indicates no additional benefits for doses above 1.2 mg/kg/day.[56]

Similar to the α_2-agonists, it seems that atomoxetine shows benefits for addressing ADHD symptoms in children with PDD, particularly for hyperactive symptoms, with similar dosing and adverse events to children with ADHD without developmental disorders.

Other Medications

Tricyclic antidepressants (TCAs), which primarily act as serotonin/norepinephrine–reuptake inhibitors (SNRIs), had been a part of older treatment algorithms for the treatment of ADHD in typically developing children[59] and, as a result, have also been studied in children with ASD. In Gordon et al's crossover RCT of clomipramine and desipramine versus placebo[60] (5 weeks each

intervention), both drugs were significantly superior to placebo for reducing the hyperactivity domain of the Children's Psychiatric Rating Scale (CPRS) Autism Relevant Subscale, although no different from each other. TCAs are known for adverse effects, primarily antimuscarinic in nature, which includes dry mouth, blurred vision, decreased gastrointestinal motility, and urinary retention. TCAs can also cause irregular heart rhythms, tachycardia, and hypotension and should be used with caution in patients with preexisting cardiac conditions and can be fatal with just small excesses in dose. TCAs are also highly metabolized by the cytochrome P450 hepatic enzymes, including 3A4 and 2D6. Therefore, inhibitors of these enzymes can lead to increased concentrations and a higher risk of side effects including cardiac abnormalities.

Although antipsychotic medications are not typically part of the treatment algorithm for ADHD in children with typical development,[59,61] studies of risperidone and aripiprazole for the treatment of children with ASD and irritability/aggression symptoms did show statistically significant improvement in hyperactivity subscales (risperidone,[33–36] aripiprazole[62–64]). As a result, atypical antipsychotics are part of a treatment algorithm developed by the Autism Speaks Autism Treatment Network Psychopharmacology Committee Medication Choice Subcommittee for symptoms of ADHD in individuals with ASD, if they have not shown adequate improvement from stimulants, atomoxetine, and α_2-agonists.[49]

Other medications, which have not yet been included in standard practice, although have shown some promising evidence for improvement in hyperactivity symptoms in RCTs of children with ASD, include ω-3 fatty acids,[65] tianeptine.[66] Pentoxifylline[67] and topiramate,[68] as adjuncts to risperidone, also have positive outcomes.

Case 88-1, Question 2: L.B., now 5 years old, has been receiving ABA services for nearly 2 years and has been progressing well. At home though, L.B. has become increasingly disobedient and hyperactive. In school, his teachers note that he is inattentive, wandering around the classroom and

staring out the windows. In addition, during story time and craft time, he is disruptive and hyperactive, running around the room. In response, L.B.'s pediatrician facilitates an increase in the number of hours of in-home ABA services, whose providers also work with L.B.'s parents' teaching behavioral management techniques. The pediatrician also recommends certain classroom modifications to help with attention. This, however, does not reduce the outbursts or inattentive and hyperactive behavior, both at home and school. The pediatrician believes that a trial of pharmacotherapy may be helpful. The pediatrician consults you, the clinical pharmacist, to discuss an appropriate treatment plan. What pharmacotherapy and formulation would be most appropriate for L.B.'s target symptoms?

Clinical trials have shown that stimulants can be a very effective treatment option for children with ADHD. The American Academy of Child and Adolescent Psychiatry (AACAP) and the AAP recommend the use of methylphenidate, over that of amphetamines or nonstimulant medication, in preschool children where behavioral modification therapy has not been adequate. The metabolism of methylphenidate in preschool children is slower than that of older children, and therefore the starting dose is lower, and the optimal dose is likely lower than in older children.

Based on this information, you recommend starting L.B. on methylphenidate IR solution 1.25 mg twice daily, with an increase to 2.5 mg twice daily on day 3, with subsequent dose increases every 3 days to reduce target symptoms, up to a maximum of 7.5 mg three times daily. You recommend that the parents keep a journal of the responses and possible experienced adverse effects during this period with a report back to the pediatrician at the end of the week.

Irritability/Aggression

Irritability/aggression is the pharmacologic target behavior with the most robust RCT evidence in children with ASD. Two national and one international consensus guidelines recommend risperidone and aripiprazole for the treatment of irritability associated with autism.[32,42,69] Most of this evidence comes from four large RCTs of either risperidone or aripiprazole.[33,34,62,63] In this context, risperidone

and aripiprazole are the only two medications with FDA approval for use in individuals with developmental disabilities. Specifically, each has an FDA-approved indication for the treatment of autistic disorder-associated irritability in children and adolescents (risperidone—age 5–17 years; aripiprazole—age 6–17 years).

Risperidone

Both McCracken et al's[33] and Shea et al's[34] studies of risperidone were 8 weeks in duration, in a population of children and adolescents with solely autistic disorder[33] or mostly autistic disorder[34] (70% of the study population had autistic disorder; the rest were diagnosed with PDD NOS, Asperger disorder, or childhood disintegrative disorder), and with mostly comorbid ID (64% of study population[34]; 81% of study population[33]). Both showed risperidone to have statistically significant improvements, compared to placebo, in the Irritability subscale of the Aberrant Behavior Checklist (ABC-I) (ABC-I is a 15-item subscale that includes items such as "injures self," "physical violence to self," "aggressive to other children and adults," "irritable," "temper outbursts," "depressed mood," "mood changes," and "yells" or "screams" inappropriately; individual items are rated on a scale ranging from 0—not at all a problem, to 3—severe),[63] as well as the ABC subscales for hyperactivity and stereotypy. The subscales for social withdrawal and inappropriate speech only showed statistically significant improvements for risperidone compared to placebo in Shea et al's study.[34] The definition of "response" was different in each study. In McCracken et al's study,[33] positive response was defined as at least a 25% decrease in the ABC-I score and a rating of much improved or very much improved on the Clinical Global Impression rating scale (CGI) and CGI-I. With this definition, 69% were responders in the risperidone group and 12% in the placebo group. In Shea et al's study,[34] a responder was defined as having a 50% or greater decrease from baseline in at least two of the five ABC subscales with none of the other subscales presenting a 10% or larger increase.

With this definition, 69% of subjects in the risperidone group were responders, compared to 40% in the placebo group.

In McCracken et al's study,[33] participants in the risperidone group, compared to placebo, experienced significantly higher rates of increased appetite, fatigue, drowsiness, dizziness, and drooling, with trends of increased rates of tremor, tachycardia, and constipation (*P* = .06). In a 16-week open-label extension of McCracken et al's study,[33] the most common adverse events were excessive appetite, enuresis, tired during the day, dry mouth, excess saliva, rhinitis, coughing, and anxiety.[69] Risperidone-treated participants in Shea et al's study[34] experienced significantly greater increases in weight, pulse rate, and systolic blood pressure and had a significantly higher rate of reported somnolence (73% risperidone vs 8% placebo). Extrapyramidal symptoms (EPSs) were endorsed by 28% of the risperidone-treated participants in Shea et al's study,[34] compared to 13% in the placebo group. Mean weight gain in both 8-week studies for those taking risperidone was 2.7 kg. Mean final daily risperidone dose was 1.8 mg[33] and 1.48 mg,[34] which is in contrast to the mean final daily risperidone dose of 2.8 mg in a large RCT of the antipsychotic treatment of early-onset schizophrenia and schizoaffective disorder in children and adolescents (ID was an exclusion criterion).[70–73]

Several studies have confirmed that risperidone treatment may be associated with an increase in serum prolactin levels.[33,74,75]

McDougle et al's[76] study of risperidone in adults with ASD showed similarly beneficial findings for the reduction in aggressive behavior, compared to placebo, and common adverse events also included sedation and weight gain. The mean final daily dose of risperidone was 2.9 mg, which is in contrast to the mean daily dose of risperidone of 3.9 mg in a large RCT of adults with schizophrenia.[77]

Aripiprazole

Both Marcus et al's[63] and Owen et al's[62] studies of aripiprazole versus placebo in children and adolescents with autistic disorder

were 8 weeks in duration. Prevalence of comorbid ID was not mentioned in either study. Both studies showed statistically significant improvement in children treated with aripiprazole, compared to placebo, for ABC-I, CGI-I, as well as ABC subscales of hyperactivity and stereotypy. Although Owen et al's[62] flexible dosing schedule showed statistically significant improvements in the ABC subscale for inappropriate speech with aripiprazole versus placebo, in Marcus et al's[63] fixed-dose study, only the 15 mg/day dose of aripiprazole showed statistically significant improvement in inappropriate speech. Neither study showed statistically significant improvement for aripiprazole, versus placebo for the ABC lethargy/social withdrawal subscale. Both studies defined response as at least a 25% reduction from baseline to end point in the ABC-I subscale and a CGI-I score of 1 (very much improved) or 2 (much improved) at end point. With this definition, the response rate was 52.2% for aripiprazole in Owen et al's study[62] (14.3% for placebo), and although response rates for each dose of aripiprazole (5 mg—55.8%, 10 mg—49.2%, 15 mg—52.8%) were higher than placebo (34.7%) in Marcus et al's study,[63] only the response rate at 5 mg/day separated from placebo with statistical significance.

In Marcus et al's study,[63] the three most common adverse events leading to discontinuation of aripiprazole were sedation, drooling, and tremor, none of which were reported in the placebo group. The most common adverse events reported in the aripiprazole group of Owen et al's study[62] were fatigue, somnolence, vomiting, increased appetite, and sedation. In Owen et al,[62] 14.9% of aripiprazole-treated subjects (vs 8% for placebo) endorsed EPS symptoms, with the most common being tremor (8.5%). In Marcus et al's study,[62] EPS symptoms were reported at roughly twice the rate in all aripiprazole doses (5 mg/day—23.1%, 10 mg/day—22.0%, and 15 mg/day—22.2%) compared to placebo (11.8%), the most common of which were tremor and extrapyramidal disorder. Aripiprazole was associated with statistically significant gains in weight compared to placebo after 8 weeks, with the mean weight gain on aripiprazole in Owen et al[62] being 2.0 kg, and for Marcus et al,[62] 1.3 kg (5 mg/day), 1.3 kg (10 mg/day), and 1.5 kg (15 mg/day). Interestingly, both

studies showed aripiprazole to have statistically significant reductions in prolactin levels compared to placebo. Mean final daily dosing for aripiprazole in Owen et al[62] was 8.9 mg/day. In a 52-week open-label follow-up study of participants from both Owen et al[62] and Marcus et al,[63] as well as newly enrolled subjects, the mean final daily dosing of aripiprazole was 10.6 mg/day.[78] In a 2-month RCT of aripiprazole versus risperidone in children with ASD, the mean final daily dose of aripiprazole was 5.5 mg.[79] Manufacturer recommended daily dosing of aripiprazole in pediatric patients with schizophrenia or bipolar disorder is 10 mg/day.[80]

Overall, the literature shows that risperidone and aripiprazole, in doses likely lower than that used in children with schizophrenia or bipolar disorder, can be used effectively to reduce symptoms of irritability and aggressive behavior in children and adolescents with ASD,[81–85] although treatment should be monitored closely for relatively common adverse events of sedation, weight gain, and EPS. Of note, although risperidone has been shown to consistently increase prolactin levels, aripiprazole was shown to consistently lower prolactin levels.

Although risperidone and aripiprazole are the two antipsychotic medications with FDA approval for the treatment of irritability in children with ASD, other typical and atypical antipsychotics have also demonstrated benefits for treating symptoms of irritability in children with ASD. Haloperidol, dosed in the range of 0.5 to 4.0 mg/day, has shown benefits in four RCTs and two long-term follow-up studies, although with significant rates of dyskinesia (34%).[86] One RCT supports the benefits of pimozide, one RCT supports the use of olanzapine, and either open-label studies or case reports exist to support the benefits of olanzapine, clozapine, quetiapine, ziprasidone, and paliperidone.[87] A head-to-head comparison RCT of risperidone and haloperidol in children with autistic disorder showed risperidone to be significantly more effective than haloperidol at reducing aberrant behavior and symptoms of PDD.[88] A RCT evaluated risperidone, haloperidol, and placebo for treatment of aggression in adults with ID. All three treatment arms demonstrated

decreased aggression, with no significant difference between the three treatments arms.[89]

Other Medications

VALPROATE

Two RCTs of similar size (n = 30[90] and n = 27[37]) looked at valproate versus placebo in children and adolescents with ASD and irritability/aggression with somewhat conflicting results. Hellings et al[90] found no significant difference in improvement of irritability or aggression (including ABC-I and CGI-I) between valproate and placebo after 8 weeks, whereas Hollander et al,[37] after 12 weeks, showed valproate to be significantly superior to placebo at improving CGI-I and the rate of improvement of ABC-I. Whereas in Hollander et al's study,[37] there were no significant differences in adverse events between valproate and placebo, in Hellings et al's study,[90] there was a significantly increased rate of endorsed appetite increase in the valproate group, and two individuals in the valproate group developed elevated ammonia levels, one with clinically associated symptoms. Both studies had target blood valproate levels (at least 50 μg/mL,[37] 70–100 μg/mL[90]).

Additional medications with limited RCT data, open-label studies, or case reports to support its use for irritability in individuals with ASD include buspirone, clomipramine, clonidine, escitalopram,[91] lamotrigine, levetiracetam, memantine, mirtazapine, oxcarbazepine,[92] pioglitazone, topiramate (monotherapy or when added to risperidone),[93] riluzole, sertraline, and trazodone,[87] as well as fluvoxamine[94] and lithium.[95] Reichow et al recently published a meta-analysis of medications for the treatment of ADHD symptoms in children with PDD. Methylphenidate had moderate, although not statistically significant, benefits in treating irritability.[42]

CASE 88-2

QUESTION 1: C.Y., a 9-year-old female with ASD has been well maintained on risperidone for the last 3 years. At the most recent checkup, the prescriber

notes that she has gained ~25 pounds (11.34 kg) over the last 2 years (note that the average weight gain for a 9-year-old child is ~5 pounds [2.27 kg] per year). The majority of weight gained seems to be in the abdominal area. Blood tests note an elevated hemoglobin A1C of 8.4%. The provider discusses diet and exercise, but C.Y.'s mother notes no change over the last few years. She believes her weight gain started with the addition of risperidone, which is now at 4 mg/day.

What would you for a recommendation based on your knowledge of the metabolic profiles of atypical antipsychotics?

Although risperidone and aripiprazole are not necessarily interchangeable, both are indicated for the treatment of irritability in children with ASD, and aripiprazole may convey less of a risk for weight gain than risperidone. Although the two medications are of equal benefit, there is a possibility that a patient may respond to one agent and not the other. In this context, you may recommend for the prescriber to decrease risperidone by 1 mg every other week, while starting aripiprazole 2 mg/day for 7 days followed by an increase to 5 mg daily. Additional 5-mg dose increases can be made weekly up to a maximum of 15 mg/day. C.Y. should be monitored for tolerability during both the cross-taper/titration period and beyond.

REPETITIVE BEHAVIORS

Numerous different types of medications have been studied for the treatment of repetitive behaviors in individuals with ASD. Selective serotonin reuptake inhibitors (SSRIs) and TCAs have been studied likely because of perceived similarities between the repetitive behaviors and compulsions exhibited in children with obsessive–compulsive disorder as well as the clinical observation that repetitive behaviors may increase in children with PDD because of underlying anxiety. However, the literature is mixed to support the use of SSRIs or TCAs for this indication.

Selective Serotonin Reuptake Inhibitors

Two RCTs looking at SSRIs for children with ASD and repetitive behavior demonstrate conflicting results. Hollander et al's[96] crossover trial (*n* = 39, mean age 8.2 years) showed that low-dose liquid fluoxetine was superior to placebo for treating repetitive behaviors, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) compulsion subscale, with a medium to large effect size (0.76), though did not separate from placebo for improvements in other aspects of global autism severity. In King et al's[97] large study of citalopram (*n* = 73) versus placebo (*n* = 76) to target repetitive behaviors in children with ASD, there were no statistically significant differences between citalopram and placebo in improvements in overall symptomatology (CGI-I) or repetitive behaviors on the modified CY-BOCS-PDD rating scale. An RCT of fluvoxamine versus placebo in adults with ASD (*n* = 15 in each group), however, did show fluvoxamine to be significantly superior to placebo for improving repetitive thoughts and behavior.[94] (See Anxiety/Depression section for more details on SSRI prescribing in children with ASD.)

Tricyclic Antidepressants

Clomipramine was studied in Gordon et al's[60] RCT, in which it was shown to be significantly superior to both placebo and desipramine for the treatment of repetitive behavior in children with ASD as shown by the modified CPRS OCD subscale, the modified National Institute of Mental Health (NIMH) OCD Scale, and the modified NIMH Global OCD and Anxiety scales. The mean final week daily dose of clomipramine was 152 mg; the mean final week clomipramine blood level was 235 ng/mL, and desmethyl clomipramine level was 422 ng/mL. Overall, adverse events were relatively minor, although in those taking clomipramine, one person had a seizure, and two had cardiac adverse events, one with a prolonged corrected QT interval (0.45 seconds) and the other with severe tachycardia (160–170 beats/minute), both of which resolved with reduction in dose. In Remington et al's[98] crossover RCT (7

weeks each intervention) comparing clomipramine to haloperidol in children with autistic disorder, the most striking finding was that only 37.5% of participants taking clomipramine finished the study (compared to 69.7% haloperidol and 65.6% for placebo), with adverse events contributing to discontinuation, including behavioral problems, fatigue or lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea or vomiting, and decreased appetite. The mean daily dose of clomipramine was 128.4 mg, range 100 to 150 mg.

Overall, for the reduction of repetitive behaviors, SSRIs, specifically fluoxetine, and TCAs, specifically clomipramine, may be helpful in children with ASD, although adverse events may be particularly limiting for clomipramine. For adults with ASD, SSRIs, specifically fluvoxamine, may be helpful in reducing repetitive behaviors.

Antipsychotics

Antipsychotics have shown the most robust evidence in reducing repetitive behaviors in children with ASD. Nearly all of the data to support antipsychotics for this purpose come from the same studies that targeted irritability. Both aripiprazole[62,63] and risperidone[33,34] were superior to placebo for reducing the score on the ABC Stereotypy subscale. In McDougle et al's[99] secondary analysis of the 8-week RUPP Risperidone trial,[33] risperidone resulted in significantly greater reductions, compared to placebo, in the scores on the modified compulsion subscale of the CY-BOCS (effect size 0.55) and the sensory motor behaviors subscale of the Ritvo–Freeman Real Life Rating Scale (effect size 0.45). Similar findings for risperidone's benefit for reducing repetitive behaviors have been found in adults with ASD, including McDougle et al's RCT,[76] which found statistically significant reductions in the modified version of the Y-BOCS (focusing only on repetitive behavior, not thoughts). In a study evaluating olanzapine versus placebo (n = 11), no statistical differences in outcomes tied to obsessive–compulsive symptoms,

aggression, or irritability; however, greater adverse effects (including weight gain) were seen in the olanzapine group.[100]

Stimulants

In Reichow et al's recent meta-analysis of medications for the treatment of ADHD symptoms in children with PDD, methylphenidate had moderate, although not statistically significant, benefits in treating stereotypies.[42]

Other Medications

Despite valproate demonstrating efficacy for the treatment of irritability in Hollander et al's study of children with ASD, it showed no significant improvement in repetitive behavior, compared to placebo.[37] One small RCT of 1.5 g/day of ω-3 fatty acids (fish oil *n* = 7, placebo *n* = 5) showed no significant difference compared to placebo in reduction of ABC Stereotypy, although the effect size was 0.72.[65] Chugani et al evaluated buspirone versus placebo (*n* = 166) found no significant difference in composite treatment scores but concluded buspirone may be a useful adjunct therapy to target restrictive and repetitive behaviors.[101]

SELF-INJURIOUS BEHAVIOR

Depending on the rating scale or etiologic theory, self-injurious behavior is commonly thought of as either an act of aggression toward the self or as a repetitive, stereotyped behavior. Consequently, pharmacologic approaches to the treatment of self-injury have been rooted in the approaches for the treatment of aggression or repetitive behavior. Self-injurious behavior has its own literature base though, with similar and dissimilar findings.

Typical and Atypical Antipsychotics

RCTs of typical antipsychotics for the reduction of self-injurious behavior in individuals with developmental disabilities have had mixed findings. There has been relatively unconvincing data for the benefit of haloperidol, fluphenazine, chlorpromazine, or thioridazine in reducing self-injurious behavior.[102] Risperidone is the atypical antipsychotic with the most robust RCT data for improving self-injurious behavior, with two relatively large RCTs in children with ID showing improvement in the self-injury/stereotypic subscale of the Nisonger Child Behavior Rating Form,[103,104] one of which was statistically significant,[104] and statistically significant reductions in self-injurious behavior in adults with ASD, as measured by the Self-injurious Behavior Questionnaire.[76] Similar to studies in children with ASD, weight gain and somnolence were markedly higher in children taking risperidone than placebo.

Antidepressants

Clomipramine has been shown to be effective in reducing self-injurious behavior, but again with significant adverse effects.[102] Fluoxetine has been shown to be effective at reducing compulsive skin picking in two RCTs,[105,106] and fluvoxamine has been effective for reducing repetitive behavior and aggression in adults with ASD.[94] Case reports and open-label studies have shown possible benefit for buspirone and paroxetine as well.[102]

Naltrexone

A recent systemic review of naltrexone used in adults with ID showed 8 out of 10 RCTs demonstrating a reduction in the frequency of self-injurious behavior.[107] More specifically, 50% of participants had improvement in self-injury, with improvement being more pronounced in individuals with severe and profound ID. Nine percent experienced minor adverse events, which included weight loss, loss

of appetite, thirst, yawning, mild liver function test abnormalities, nausea, and tiredness. Dosing ranged from 0.5 to 2 mg/kg and doses from 25 to 100 mg.

Overall, despite very limited evidence, it seems the literature supports the use of risperidone, naltrexone, and clomipramine for the reduction of self-injurious behavior in individuals with developmental disabilities. Additionally, fluoxetine and fluvoxamine may have benefits as well, though less well evidenced.

ANXIETY/DEPRESSION

Selective Serotonin Reuptake Inhibitors

Studies have found that individuals with PDDs are at high risk of comorbid anxiety and mood disorders.[38,39] Because of the demonstrated benefits and relative safety of SSRIs in typically developing children, SSRIs are very commonly prescribed for anxiety and depression in children with developmental disorders. No large double-blind, placebo-controlled trials have been conducted looking at the use of SSRIs for depression or anxiety in children with developmental disorders, although the literature has numerous case reports and open-label studies demonstrating SSRI-induced improvements in anxiety in individuals with ASD.[108,109]

Overall, the literature indicates that children with developmental disorders may respond differently to SSRIs compared to children with typical development. Three areas in which response to SSRIs may differ include risk of adverse events, dosing requirements, and target symptoms. If poor response to SSRIs, a trial with risperidone may be appropriate with continued monitoring for worsened anxiety.[41]

Adverse Events

Compared to children with typical development, children with developmental disorders are more likely to experience adverse events to SSRIs and specifically are more likely to endorse emotional/behavioral adverse events. The only two RCTs looking at SSRIs in children with developmental disorders evaluated fluoxetine[96] and citalopram[97] for the treatment of repetitive behaviors. In the crossover study (8 weeks each phase) of low-dose fluoxetine by Hollander et al[96] (*n* = 39, mean age 8.2 years), although there was no statistically significant difference in treatment-emergent adverse events between fluoxetine and placebo, the most common adverse events emerging during fluoxetine treatment were agitation (46%), insomnia (36%), and anxiety/nervousness (16%). Additionally, 16% of subjects required a dose reduction because of agitation while on fluoxetine, compared to 5% on placebo.

In contrast, both Geller et al[110] and Liebowitz et al[111] conducted RCTs of fluoxetine for the treatment of OCD in typically developing children (Geller: 13 weeks; *n* = 71 fluoxetine, 32 placebo; mean age 11.4 years/Liebowitz: 8-week acute phase; *n*=21 fluoxetine, 22 placebo; mean age 12–13). In Geller et al,[110] there was no statistically significant difference in reported adverse events, and the most common adverse events reported in the fluoxetine group were headache (28%), rhinitis (27%), and abdominal pain (16%), with no reports of agitation. In Liebowitz et al,[112] six adverse events occurred significantly more frequently in the fluoxetine group: palpitations, weight loss, drowsiness, tremors, nightmares, and muscle aches, and the most common adverse events reported by those taking fluoxetine were headache (52%), abdominal pain (43%), decreased appetite (38%), difficulty staying asleep (38%), and drowsiness (38%).

For citalopram, in the 12-week study by King et al[97] (*n* = 73 citalopram, 76 placebo; mean age ~9 years), 97.3% of subjects with ASD treated with citalopram experienced at least one treatment-emergent adverse event. They were significantly more likely to experience adverse events compared to those treated with placebo, specifically: increased energy level (38%), impulsiveness (19%), decreased concentration (12%), hyperactivity (12%), stereotypy

(11%), diarrhea (26%), insomnia (23.3%), and dry skin or pruritus (12%).

In contrast, in RCTs of citalopram for the treatment of depression in children and adolescents with typical development, the most commonly reported adverse events were headache, gastrointestinal issues, and insomnia.[112] Specifically in the 8-week RCT by Wagner et al[113] of citalopram for typically developing children with depression (*n* = 89 citalopram, 85 placebo; mean age, 12 years), rhinitis (14%), nausea (14%), and abdominal pain (11%) were the only adverse events reported in >10% of subjects taking citalopram, and in the 12-week RCT by von Knorring et al[114] of citalopram for typically developing adolescents with depression (*n* = 124 citalopram, 120 placebo; mean age 16 years), headache (26% and 25%), nausea (19% and 15%), and insomnia (13% and 11%) were the most common in both groups (citalopram and placebo, respectively), with only fatigue being the adverse event reported significantly more often in the citalopram group (6%) than the placebo group (1%).

Dosing

Children with PDD typically require smaller doses of SSRIs compared to children with typical development and may experience adverse emotional/behavioral events at higher doses. For fluoxetine, the mean final daily dose in Hollander et al's study[96] of children with PDD was 9.9 mg, or 0.36 mg/kg. This is compared to Geller et al[110] and Liebowitz et al's[111] studies of typically developing children with OCD, in which the mean final daily fluoxetine dose was 24.6 and 64.8 mg (after the acute phase), respectively. Additionally, in RCTs of typically developing children with depression and other forms of anxiety, fluoxetine was well tolerated at mean daily doses of 20 mg,[115–117] 28.4 mg and 33.3 mg,[118] and 40 mg.[119]

For citalopram, the mean daily dose in the King et al study[97] of children with ASD and repetitive behavior was 16.5 mg. In studies of citalopram use in typically developing children and adolescents with

depression, citalopram was tolerated at mean daily doses of 24 mg[113] and 26 mg.[114]

The issue of individuals with PDD requiring lower dosages of SSRI might diminish in adulthood because RCTs of SSRIs in adults with ASD demonstrate mean daily doses close to that expected for typically developing adults: fluoxetine—36.7 mg[120] and 64.8 mg[120]; fluvoxamine 276.7 mg.[94]

CASE 88-3

QUESTION 1: N.W. is a 6-year-old female with a history of supraventricular tachycardia (SVT) at birth, well controlled on propranolol since infancy. N.W. also has a diagnosis of ASD. Over the past year, she has been trialed on varying stimulant formulations and doses for the treatment of ADHD symptoms. However, N.W.'s mom reports only small improvement, but significant worsening of repetitive behavior and aggression. N.W. has been pushing, hitting, and throwing things at school and home. Additionally, N.W. has had a decrease in appetite and lost ~4 pounds (1.81 kg). At home, N.W. has recently developed a lot of anxiety, refusing to go to school and participate in outdoor activities. Her mother notes that N.W. appears to be isolating herself more and not enjoying activities that used to make her happy. The prescriber discontinues methylphenidate and starts N.W. on risperidone 1 mg/day for aggression and repetitive behaviors. She also starts on fluoxetine 10 mg/day for depression and anxiety.

You get a call from N.W.'s mother 3 days after N.W. starts the new medication regimen. N.W.'s mother reports that N.W. is extremely lethargic and seems confused. She fell the last few times she tried to get out of bed. You have the mother use a blood pressure cuff she has at home to measure N.W.'s vital signs. Based on the results, N.W. is bradycardic and hypotensive.

What is your recommendation?

The dose of risperidone that N.W. was started on is high. Additionally, fluoxetine is a strong 2D6 inhibitor, and risperidone and propranolol are 2D6 substrates. Therefore, fluoxetine may be decreasing the clearance of both risperidone and propranolol. You decide to call the provider and discuss the interaction and adverse effects that N.W. is experiencing.

Case 88-3, Question 2: The prescriber is thankful for the call and asks for your advice on altering the current regimen. What changes would you recommend?

You recommend discontinuation of the fluoxetine and initiation of sertraline 12.5 mg/day because sertraline is a weaker inhibitor of 2D6. You would recommend the continuation of risperidone at a reduced dose of 0.5 mg/day.

Target Symptoms

Most studies looking at symptoms of anxiety and depression in children with ASD have used rating scales validated in typically developing children. For anxiety, predictors that children with ASD will manifest a high level of parent-reported anxiety include the following: IQ >70,[121–123] higher levels of parent-rated social impairment,[121,122] and increased age[122]; additionally, it seems that children with IQ >70 might experience higher levels of parent-reported anxiety if they demonstrate more adaptive social behaviors.[121,122] For depression, higher IQ and age seem correlated with higher depression ratings,[124] and both seem to predict lower self-perceived social competence in children with ASD.[125] Lower self-perceived social competence, in turn, seems to predict high levels of depression symptomatology.[125] Additionally, it seems that adults with ASD with less social impairment (higher social functioning) were more likely to be categorized as depressed.[126] All of this seems to indicate that the more individuals with ASD are aware of social impairments, or exposed to social interactions, the more likely they are to demonstrate classically recognizable symptoms of anxiety or depression.

However, this body of literature, because of the scales that are used, only addresses anxiety and depressive mood symptoms that are also seen in typically developing individuals. Clinicians who work with individuals with PDD are well aware that anxiety and depression might manifest in alternative ways in this population. Individuals with

ASD often have impaired abilities to communicate their emotional experiences to others and can have significant trouble managing their emotions. This routinely leads to alternative manifestations of emotions like anxiety and depression, in the forms of rigidity, tantrums, oppositionality, social avoidance, hyperactivity, repetitive behaviors, irritability, aggression, and self-injury. As mentioned above, studies of SSRIs to target some of these behaviors have been mixed.

Overall though, it seems that case studies and open-label trials have shown possible benefits for the use of SSRIs in children with PDD for the treatment of classically recognized symptoms of anxiety and depression. To avoid significant emotional and behavioral adverse events though, target dosing should be lower than in children with typical development.

SLEEP

Melatonin

The medication with the strongest research backing for the treatment of sleep disturbance in individuals with developmental disabilities is melatonin. Consensus guidelines from the British Association for Psychopharmacology around the treatment of ASD recommend that for comorbid sleep disorders, consider melatonin, if possible, in combination with a behavioral intervention. Of note, guidelines do not recommend prolonged use of benzodiazepines and related γ-aminobutyric acid (GABA) agonists.[41]

Hollway and Aman's review[127] found 13 RCTs of individuals with sleep disturbance, many of which also with developmental disabilities. All 13 RCTs had positive findings, particularly for sleep initiation and sleep maintenance, with the longest trial being 10 weeks in duration. The effect sizes for sleep onset latency ranged from 0.25 to 1.63, and for total sleep time from 0.25 to 1.0. Adverse

effects were generally mild and similar to placebo. Doses ranged from 2.5 to 10 mg.

Ramelteon

The MT_1/MT_2 melatonin receptor agonist has limited evidence in children with developmental disabilities, although considerable positive findings in adults with typical development, specifically in primary insomnia and sleep maintenance.[127] Adverse effects were mild and similar to placebo, and doses ranged from 4 to 64 mg.

Clonidine

Although no RCTs have been conducted in children with developmental disabilities and sleep disturbance, retrospective reviews have shown benefits in helping with sleep disturbance, with doses ranging from 0.05 to 0.1 mg.[127]

Trazodone

Although no RCTs have been conducted in children with sleep disorders, four open-label studies in children and two in adults showed benefits for improving sleep, including sleep architecture.[127] Doses ranged from 25 to 150 mg.

Mirtazapine

One open-label study in children and one RCT in adults showed benefits for the treatment of sleep problems, with mild adverse effects, which included increased appetite, irritability, and sedation.[127] Doses ranged from 7.5 to 45 mg.

Diphenhydramine

Despite its abundant use in pediatric patients for sleep disturbance, only three RCTs were identified by Hollway and Aman for its use in pediatric subjects.[129] Two of the studies were negative, one showed benefit, and none of them were specifically in children with developmental disabilities.

Zolpidem

Studies are limited, and none seem to have studied individuals with developmental disabilities, though benefits seem greater in adolescents and adults, and less effective in children.[127]

Donepezil and Memantine

Limited data demonstrated mixed results with the use of donepezil and memantine to target symptoms of ASD, including autistic disorder, Asperger disorder, and PDD. Donepezil has demonstrated improvement in rapid eye movement (REM) sleep. At the time of this writing, recommend additional studies continue to evaluate their place in therapy.[128–134]

Benzodiazepines

In partially or uncontrolled studies in children, and controlled studies in adults, it seems that benzodiazepines may be most effective at helping sleep disturbances associated with parasomnias (eg, periodic limb movement disorder, tongue biting, REM sleep behavior disorder), though with considerable risks of adverse effects, including tolerance, dependence, rebound insomnia, daytime sedation, and cognitive impairment.[127]

Overall, it seems that melatonin is the most well-studied, effective, and safe medication option for treating sleep disturbance in individuals with developmental disabilities. Although promising evidence for ramelteon, trazodone, mirtazapine, and clonidine exists, further research is needed in individuals with developmental

disabilities. Research evidence does not seem to support the wide use of diphenhydramine for sleep disorders in children, and although zolpidem and benzodiazepines may be of benefit for sleep in some, they should be used with caution, and primarily in adults for zolpidem, and those with parasomnias for benzodiazepines.

CASE 88-4

QUESTION 1: T.T. is a 10-year-old male with ASD and significant sleep disturbances. His father has tried diphenhydramine for the last few weeks but has not seen any meaningful improvement in T.T.'s total sleep time. Last year, T.T. had a trial of melatonin 2.5 mg daily with only a small recognized improvement. T.T.'s clinician is thinking about starting a low-dose benzodiazepine, however, is weighing the concerns for adverse effects.

T.T.'s clinician asks for your opinion. What do you recommend?

You note that the dose of melatonin last year may have been on the lower range and you would recommend another trial of melatonin before considering a controlled substance. The dose you would recommend is 5 mg taken ~1 hour to T.T.'s bedtime. You note that this dose can be increased to 10 mg if an adequate response is not seen.

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Doyle CA, McDougle CJ. Pharmacotherapy to control behavioral symptoms in children with autism. *Expert Opin Pharmacother*. 2012;13(*11*): 1615–1629. (87)

Hollway JA, Aman MG. Pharmacological treatment of sleep disturbance in developmental disabilities: a review of the literature. *Res Dev Disabil*.

2011;32:939–962. (127)
Mahajan R, Bernal MP, Panzer R, et al. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders. *Pediatrics.* 2012;130: s125–s138. (49)
Minshawi NF, Hurwitz S, Morriss D, McDougle CJ. Multidisciplinary assessment and treatment of self-injurious behavior in autism spectrum disorder and intellectual disability: integration of psychological and biological theory and approach. *J Autism Dev Disord.* 2015;45:1541–1568. (102)
Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry.* 2014;53(2):237–257. (32)
Wong C, Odom SL, Hume KA, et al. Evidence-based practices for children, youth, and young adults with autism spectrum disorder: a comprehensive review. *J Autism Dev Disord.* 2015;45:1951–1966. (29)

COMPLETE REFERENCES CHAPTER 88 DEVELOPMENTAL DISORDERS

1. American Psychiatric Association. Neurodevelopmental disorders. In: *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596.dsm01
2. Boyle CA, Boulet S, Schieve LA, et al. Trends in the prevalence of developmental disabilities in US children, 1997–2008. *Pediatrics*. 2011;127:1034–1042.
3. Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: a meta-analysis of population-based studies. *Res Dev Disabil*. 2011;32:419–436.
4. Moeschler JB, Shevell M; Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics*. 2014;134:e903–e918.
5. Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators. Prevalence of autism spectrum disorder among children aged 8 years autism and developmental disabilities monitoring network, 11 Sites, United States, 2010. *MMWR Surveill Summ*. 2014;63(2):1–21.
6. Schieve LA, Clayton HB, Durkin MS, Wingate MS, Drews-Botsch C. Comparison of perinatal risk factors associated with autism spectrum

disorder (ASD), intellectual disability (ID), and co-occurring ASD and ID. *J Autism Dev Disord*. 2015;45:2361–2372.
7. Croen LA, Grether JK, Selvin S. The epidemiology of mental retardation of unknown cause. *Pediatrics*. 2001;107(6):e86.
8. Leonard H, Glasson E, Nassar N, et al. Autism and intellectual disability are differentially related to sociodemographic background at birth. *PLoS One*. 2011;6(3):e17875.
9. Shevell M. Global developmental delay and mental retardation or intellectual disability: conceptualization, evaluation, and etiology. *Pediatr Clin North Am*. 2008;55:1071–1084.
10. Schaaf CP, Zoghbi HY. Solving the autism puzzle a few pieces at a time. *Neuron*. 2011;70:806–808.
11. Posthuma D, Polderman TJ. What have we learned from recent twin studies about the etiology of neurodevelopmental disorders. *Curr Opin Neurol*. 2013;26:111–121.
12. Baker E, Jeste SS. Diagnosis and management of autism spectrum disorder in the era of genomics: rare disorders can pave the way for targeted treatments. *Pediatr Clin North Am*. 2015;62:607–618.
13. Ropers HH. Genetics of early onset cognitive impairment. *Annu Rev Genomics Hum Genet*. 2010;11:161–187.
14. Willemsen MH, Kleefstra T. Making headway with genetic diagnostics of intellectual disabilities. *Clin Genet*. 2014;85:101–110.
15. Miles JH. Autism spectrum disorders—a genetic review. *Genet Med*. 2011;13(4):278–294.
16. Rauch A, Hoyer J, Guth S, et al. Diagnostic yield of various genetic approaches in patients with unexplained developmental delay or mental retardation. *Am J Med Genet A*. 2006;140A:2063–2074.
17. Curry CJ, Stevenson RE, Aughton D, et al. Evaluation of mental retardation: recommendations of a consensus conference. *Am J Med Genet*. 1997;72:468–477.
18. Battaglia A, Bianchini E, Carey JC. Diagnostic yield of the comprehensive assessment of developmental delay/mental retardation in an institute of child neuropsychiatry. *Am J Med Genet*. 1999;82:60–66.
19. Landrigan PJ, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. *Environ Health Perspect*. 2012;120(7):A258–A260.
20. Rutter M. Incidence of autism spectrum disorders: changes over time and their meanings. *Acta Paediatr*. 2005;94:2–15.
21. Council on Children With Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee and Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical

home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118(1):405–420.
22. Johnson CP, Myers SM; the Council on Children With Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1183–1215.
23. Strickland BB, van Dyck PC, Kogan MD, et al. Assessing and ensuring a comprehensive system of services for children with special health care needs: a public health approach. *Am J Public Health*. 2011;101(2):224–231.
24. Mandell DS, Novak MM, Zubritsky CD. Factors associated with age of diagnosis among children with autism spectrum disorders. *Pediatrics*. 2005;116(6):1480–1486.
25. Schalock RL. The evolving understanding of the construct of intellectual disability. *J Intellect Dev Disabil*. 2011;36(4):223–233.
26. Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2003;60:367–380.
27. Schaefer GB, Mendelsohn NJ; for the Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med*. 2013;15(5):399–407.
28. Zablotsky B, Pringle BA, Colpe LJ, Kogan MD, Rice C, Blumberg SJ. Service and treatment use among children diagnosed with autism spectrum disorders. *J Dev Behav Pediatr*. 2015;36:98–105.
29. Wong C, Odom SL, Hume KA, et al. Evidence-based practices for children, youth, and young adults with autism spectrum disorder: a comprehensive review. *J Autism Dev Disord*. 2015;45:1951–1966.
30. Brosnan J, Healy O. A review of behavioral interventions for the treatment of aggression in individuals with developmental disabilities. *Res Dev Disabil*. 2011;32:437–446.
31. Vereenooghe L, Langdon PE. Psychological therapies for people with intellectual disabilities: a systemic review and meta-analysis. *Res Dev Disabil*. 2013;34:4085–4102.
32. Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237–257.
33. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002;347:314–321.
34. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114(5):e634–e641.

35. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450–455.
36. Posey DJ, Aman MG, McCracken JT, et al. Positive effects of methylphenidate on inattention and hyperactivity in pervasive developmental disorders: an analysis of secondary measures. *Biol Psychiatry*. 2007;61(4):538–544.
37. Hollander E, Chaplin W, Soorya L, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology*. 2010;35:990–998.
38. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry*. 2008;47(8):921–929.
39. Leyfer OT, Folstein SE, Bacalman S, et al. Comorbid psychiatric disorders in children and autism: interview development and rates of disorders. *J Autism Dev Disord*. 2006;36:849–861.
40. Murray MJ. Attention-deficit/hyperactivity disorder in the context of autism spectrum disorders. *Curr Psychiatry Rep*. 2010;12:382–388.
41. Howes OD, Rogdaki M, Findon JL, et al. Autism spectrum disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *J Psychopharmacol*. 2018;32(1):3–29.
42. Reichow B, Volkmar FR, Bloch MH. Systematic review and meta-analysis of pharmacological treatment of the symptoms of attention-deficit/hyperactivity disorder in children with pervasive developmental disorders. *J Autism Dev Disord*. 2013;43:2435–2441.
43. Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *Eur Child Adolesc Psychiatry*. 2010;19:353–364.
44. Research Units on Pediatric Psychopharmacology Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Arch Gen Psychiatry*. 2005;62(11):1266–1274.
45. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 1999;56:1073–1086.
46. Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *J Autism Dev Disord*. 2000;30(3):245–255.
47. Jahromi LB, Kasari CL, McCracken JT, et al. Positive effects of methylphenidate on social communication and self-regulation in children with

pervasive developmental disorders and hyperactivity. *J Autism Dev Disord*. 2009;39:395–404.

48. Quinn D, Bode T, Reiz JL, Donnelly GA, Darke AC. Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol*. 2007;47(6):760–766.
49. Mahajan R, Bernal MP, Panzer R, et al. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders. *Pediatrics*. 2012;130:s125–s138.
50. Floyd S, Connor DF, Newcorn JH. Review of the rationale and clinical utilization of a2-adrenoceptor agonists for the treatment of attention-deficit/hyperactivity and related disorders. *J Child Adolesc Psychopharmacol*. 2013;23(5):308–319.
51. Jaselskis CA, Cook EH Jr, Fletcher KE, Leventhal BL. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol*. 1992;12:322–327.
52. Handen BL, Sahl R, Hardan AY. Guanfacine in children with autism and/or intellectual disabilities. *J Dev Behav Pediatr*. 2008;29:303–308.
53. Scahill L, Aman MG, McDougle CJ, et al. A prospective open trial of guanfacine in children with pervasive developmental disorders. *J Child Adolesc Psychopharmacol*. 2006;16(5):589–598.
54. Posey DJ, Puntney JI, Sasher TM, Kem DL, McDougle CJ. Guanfacine treatment of hyperactivity and inattention in pervasive developmental disorders: a retrospective analysis of 80 cases. *J Child Adolesc Psychopharmacol*. 2004;14(2):233–241.
55. Scahill L, McCracken JT, King BH, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. *Am J Psychiatry*. 2015;172(12):1197–1206.
56. Harfterkamp M, van de Loo-Neus G, Minderaa RB, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2012;51(7):733–741.
57. Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *J Am Acad Child Adolesc Psychiatry*. 2006;45(10):1196–1205.
58. Strattera (atomoxetine). Prescribing information. Eli Lilly and Company; 2002:1–18. Accessed July 3, 2017. http://pi.lilly.com/us/strattera-pi.pdf
59. Pliszka SR, Crismon ML, Hughes CW, et al. The Texas children's medication algorithm project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2006;45(6):642–657.
60. Gordon CT, State RC, Nelson JE, Hamburger SD, Rapoport JL. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment

of autistic disorder. *Arch Gen Psychiatry*. 1993;50:441–447.
61. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921.
62. Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124:1533–1540.
63. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110–1119.
64. Lamberti M, Siracusano R, Italiano D, et al. Head-to-head comparison of aripiprazole and risperidone in the treatment of ADHD symptoms in children with autistic spectrum disorder and ADHD: a pilot, open-label, randomized controlled study. *Paediatr Drugs*. 2016;18(4):319–329.
65. Amminger GP, Berger GE, Schäfer MR, Klier C, Friedrich MH, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. *Biol Psychiatry*. 2007;61:551–553.
66. Niederhofer H, Staffen W, Mair A. Tianeptine: a novel strategy of psychopharmacological treatment of children with autistic disorder. *Hum Psychopharmacol*. 2003;18:389–393.
67. Akhondzadeh S, Fallah J, Mohammadi MR, et al. Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:32–36.
68. Rezaei V, Mohammadi MR, Ghanizadeh A, et al. Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:1269–1272.
69. Aman MG, Arnold LE, McDougle CJ, et al. Acute and long-term safety and tolerability of risperidone in children with autism. *J Child Adolesc Psychopharmacol*. 2005;15(6):869–884.
70. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizoaffective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. *Am J Psychiatry*. 2008;165:1420–1431.
71. National Institute for Clinical Excellence. *Autism Spectrum Disorder in Under 19s: Support and Management* [guideline on the Internet]. National Institute for Clinical Excellence (NICE); August 2013. Accessed January 15, 2019. https://www.nice.org.uk/guidance/cg170

72. Aman M, Rettiganti M, Nagaraja HN, et al. Tolerability, safety, and benefits of risperidone in children and adolescents with autism: 21-month follow-up after 8-week placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2015;25(6):482–493.
73. Kent JM, Kushner S, Ning X, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *J Autism Dev Disord*. 2013;43(8):1773–1783.
74. Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol*. 2006;16(5):575–587.
75. Anderson GM, Scahill L, McCracken JT, et al. Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. *Biol Psychiatry*. 2007;61:545–550.
76. McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Arch Gen Psychiatry*. 1998;55:633–641.
77. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.
78. Marcus RN, Owen R, Manos G, et al. Aripiprazole in the treatment of irritability in pediatric patients (aged 6–17 years) with autistic disorder: results from a 52-week, open-label study. *J Child Adolesc Psychopharmacol*. 2011;21(3):229–236.
79. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014;45:185–192.
80. Abilify (aripiprazole). Prescribing information. Otsuka America Pharmaceutical; 2002:1–24. Accessed July 3, 2017. https://www.otsuka-us.com/sites/g/files/qhldwo4671/files/media/Abilify-PI.pdf
81. Kim HW, Park EJ, Kim JH, Boon-Yasidhi V, Tarugsa J, Reyes A. Aripiprazole for irritability in Asian children and adolescents with autistic disorder: a 12-week, multinational, multicenter, prospective open-label study. *J Child Adolesc Psychopharmacol*. 2018;28(6):402–408.
82. Ichikawa H, Mikami K, Okada T, et al. Aripiprazole in the treatment of irritability in children and adolescents with autism spectrum disorder in Japan: a randomized, double-blind, placebo-controlled study. *Child Psychiatry Hum Dev*. 2017;48(5):796–806.
83. Ichikawa H, Hiratani M, Yasuhara A, et al. An open-label extension long-term study of the safety and efficacy of aripiprazole for irritability in children and adolescents with autistic disorder in Japan. *Psychiatry Clin Neurosci*. 2018;72(2):84–94.

84. Findling RL, Mankoski R, Timko K, et al. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry*. 2014;75(1):22–30.
85. Ishitobi M, Kosaka H, Takahashi T, et al. Effectiveness and tolerability of switching to aripiprazole from risperidone in subjects with autism spectrum disorders: a prospective open-label study. *Clin Neuropharmacol*. 2013;36(5):151–156.
86. Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. *J Am Acad Child Adolesc Psychiatry*. 1997;36(6):835–843.
87. Doyle CA, McDougle CJ. Pharmacotherapy to control behavioral symptoms in children with autism. *Expert Opin Pharmacother*. 2012;13(11):1615–1629.
88. Miral S, Gencer O, Inal-Emiroglu FN, Baykara B, Baykara A, Dirik E. Risperidone versus haloperidol in children and adolescents with AD: a randomized, controlled, double-blind trial. *Eur Child Adolesc Psychiatry*. 2008;17:1–8.
89. Tyrer P, Oliver-Africano PC, Ahmed Z, et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomized controlled trial. *Lancet*. 2008;371:57–63.
90. Hellings JA, Weckbaugh M, Nickel EJ, et al. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *J Child Adolesc Psychopharmacol*. 2005;15(4):682–692.
91. Owley T, Walton L, Salt J, et al. An open-label trial of escitalopram in pervasive developmental disorders. *J Am Acad Child Adolesc Psychiatry*. 2005;44(4):343–348.
92. Douglas JF, Sanders KB, Benneyworth MH, et al. Brief report: retrospective case series of oxcarbazepine for irritability/agitation symptoms in autism spectrum disorder. *J Autism Dev Disord*. 2013;43(5):1243–1247.
93. Hardan AY, Jou RJ, Handen BL. A retrospective assessment of topiramate in children and adolescents with pervasive developmental disorders. *J Child Adolesc Psychopharmacol*. 2004;14(3):426–432.
94. McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch Gen Psychiatry*. 1996;53:1001–1008.
95. Tyrer SP, Walsh A, Edwards DE, Berney TP, Stephens DA. Factors associated with a good response to lithium in aggressive mentally handicapped subjects. *Prog Neuropsychopharmacol Biol Psychiatry*. 1984;8:751–755.
96. Hollander E, Phillips A, Chaplin W, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent

autism. *Neuropsychopharmacology*. 2005;30:582–589.
97. King BH, Hollander E, Sikich L, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior. *Arch Gen Psychiatry*. 2009;66(6):583–590.
98. Remington G, Sloman L, Konstantareas M, Parker K, Gow R. Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol*. 2001;21(4):440–444.
99. McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. *Am J Psychiatry*. 2005;162:1142–1148.
100. Hollander E, Wasserman S, Swanson EN, et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *J Child Adolesc Psychopharmacol*. 2006;16(5):541–548.
101. Chugani DC, Chugani HT, Wiznitzer M, et al. Efficacy of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: a randomized trial. *J Pediatr*. 2016;170:45–53.
102. Minshawi NF, Hurwitz S, Morriss D, McDougle CJ. Multidisciplinary assessment and treatment of self-injurious behavior in autism spectrum disorder and intellectual disability: integration of psychological and biological theory and approach. *J Autism Dev Disord*. 2015;45:1541–1568.
103. Snyder R, Turgay A, Aman M, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. *J Am Acad Child Adolesc Psychiatry*. 2002;41(9):1026–1036.
104. Aman MG, De Smedt G, Derivan A, et al; Risperidone Disruptive Behavior Study Group. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry*. 2002;159:1337–1346.
105. Simeon D, Stein DJ, Gross S, Islam N, Schmeidler J, Hollander E. A double-blind trial of fluoxetine in pathologic skin picking. *J Clin Psychiatry*. 1997;58:341–347.
106. Bloch MR, Elliott M, Thompson H, Koran LM. Fluoxetine in pathologic skin-picking: open-label and double-blind results. *Psychosomatics*. 2001;42:314–319.
107. Roy A, Roy M, Deb S, Unwin G, Roy A. Are opioid antagonists effective in reducing self-injury in adults with intellectual disability? A systemic review. *J Intellect Disabil Res*. 2015;59:55–67.
108. White SW, Oswald D, Ollendick T, Scahill L. Anxiety in children and adolescents with autism spectrum disorders. *Clin Psychol Rev*. 2009;29(3):216–229.

109. Vasa RA, Carroll LM, Nozzolillo AA, et al. A systematic review of treatments for anxiety in youth with autism spectrum disorders. *J Autism Dev Disord*. 2014;44:3215–3229.
110. Geller DA, Hoog SL, Heiligenstein JH, et al. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(7):773–779.
111. Liebowitz MR, Turner SM, Piacentini J, et al. Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(12):1431–1438.
112. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*. 2012;11:1–155.
113. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry*. 2004;161:1079–1083.
114. von Knorring AL, Olsson GI, Thomsen PH, Lemming OM, Hultén A. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol*. 2006;26:311–315.
115. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997;54:1031–1037.
116. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1205–1215.
117. Birmaher B, Axelson DA, Monk K, et al. Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2003;42(4):415–423.
118. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. *J Am Med Assoc*. 2004;292:807–820.
119. Beidel DC, Turner SM, Sallee FR, Ammerman RT, Crosby LA, Pathak S. SET-C versus fluoxetine in the treatment of childhood social phobia. *J Am Acad Child Adolesc Psychiatry*. 2007;46(12):1622–1632.
120. Hollander E, Soorya L, Chaplin W, et al. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders. *Am J Psychiatry*. 2012;169:292–299.
121. Dubin AH, Lieberman-Betz R, Michele Lease A. Investigation of individual factors associated with anxiety in youth with autism spectrum disorders. *J Autism Dev Disord*. 2015;45:2947–2960.

122. Sukhodolsky DG, Scahill L, Gadow KD, et al. Parent-rated anxiety symptoms in children with pervasive developmental disorders: frequency and association with core autism symptoms and cognitive functioning. *J Abnorm Child Psychol*. 2008;36:117–128.
123. Mazurek MO, Kanne SM. Friendship and internalizing symptoms among children and adolescents with ASD. *J Autism Dev Disord*. 2010;40:1512–1520.
124. Mayes SD, Calhoun SL, Murray MJ, et al. Variables associated with anxiety and depression in children with autism. *J Dev Phys Disabil*. 2011;23:325–337.
125. Vickerstaff S, Van der Horst M. Intellectual ability, self-perceived social competence, and depressive symptomatology in children with high-functioning autistic spectrum disorders. *J Autism Dev Disord*. 2007;37:1647–1664.
126. Sterling L, Dawson G, Estes A, Greenson J. Characteristics associated with presence of depressive symptoms in adults with autism spectrum disorder. *J Autism Dev Disord*. 2008;38:1011–1018.
127. Hollway JA, Aman MG. Pharmacological treatment of sleep disturbance in developmental disabilities: a review of the literature. *Res Dev Disabil*. 2011;32:939–962.
128. Handen BL, Johnson CR, McAuliffe-Bellin S, Murray PJ, Hardan AY. Safety and efficacy of donepezil in children and adolescents with autism: neuropsychological measures. *J Child Adolesc Psychopharmacol*. 2011;21(1):43–50.
129. Hardan AY, Handen BL. A retrospective open trial of adjunctive donepezil in children and adolescents with autistic disorder. *J Child Adolesc Psychopharmacol*. 2002;12(3):237–241.
130. Buckley AW, Sassower K, Rodriguez AJ, et al. An open label trial of donepezil for enhancement of rapid eye movement sleep in young children with autism spectrum disorders. *J Child Adolesc Psychopharmacol*. 2011;21(4):353–357.
131. Ghaleiha A, Asadabadi M, Mohammadi M, et al. Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. *Int J Neuropsychopharmacol*. 2013;16(4):783–789.
132. Aman MG, Findling RL, Hardan AY, et al. Safety and efficacy of memantine in children with autism: randomized, placebo-controlled study and open-label extension. *J Child Adolesc Psychopharmacol*. 2017;27(5):403–412.
133. Owley T, Salt J, Guter S, et al. A prospective, open-label trial of memantine in the treatment of cognitive, behavioral, and memory dysfunction in pervasive developmental disorders. *J Child Adolesc Psychopharmacol*. 2006;16(5):517–524.

134. Erikson C, Posey D, Stigler K, Mullet J, Katschke A, McDougle C. A retrospective study of memantine in children and adolescents with pervasive developmental disorders. *Psychopharmacology*. 2007;191(1):141–147.

89

Attention-Deficit Hyperactivity Disorder in Children, Adolescents, and Adults

Michael C. Angelini and Joel Goldstein

CORE PRINCIPLES		CHAPTER CASES
1	Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous psychiatric disorder that consists of multiple subtypes, including inattention, hyperactivity/impulsivity, and a combination of these two types. For diagnostic criteria to be met, there must be evidence that these symptoms are present in multiple settings and that the individual exhibited this psychopathology before age 12 years. These symptoms cannot be because of other illnesses.	**Case 89-1 (Question 1), Table 89-1**

CORE PRINCIPLES		CHAPTER CASES
2	Behavioral therapy and parent guidance are important components of any effective treatment plan and typically include educational interventions, creation of a structured environment for the child, and introducing contingency training.	**Case 89-1 (Questions 1–3)**
3	Stimulant medications are highly effective for the rapid relief of ADHD symptoms and substantially improve a child's prognosis. Individuals who fail to respond adequately to one type of stimulant will often do well with another, suggesting that subtle differences exist in the pharmacologic mode of action. Although the duration of pharmacologic action is relatively brief for stimulants, a variety of preparations have been approved that can prolong the relief of ADHD symptoms and permit once-daily dosing.	**Case 89-1 (Questions 3–5), Table 89-2**

CORE PRINCIPLES		CHAPTER CASES
4	There are a number of nonstimulant medications that have proven to be effective for ADHD over the years, including norepinephrine (NE) reuptake inhibitors and α_2-agonists. These medications may be viable options for the management of treatment-resistant illness as well as in patients with a history of substance abuse. They also possess a different side effect profile than stimulants and have a delay until therapeutic effects are evident.	**Case 89-1 (Question 6), Table 89-2**
5	Many people are reluctant to consider stimulant medications for ADHD treatment because of unfounded fears about drug tolerability and abuse. As a result, there have been a wide variety of alternative treatments considered for use, including behavioral treatment strategies, changes in dietary habits, ingestion of herbs and supplements, and other somatic interventions. At the present time, the evidence supporting these options is sparse, although the rigor of investigations has steadily improved in recent years, and there is hope that some of these options may prove to be beneficial.	**Case 89-2 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
6	ADHD is commonly associated with several psychiatric and medical comorbidities, and these concurrent conditions often influence treatment plans. Tic disorders such as Tourette syndrome are frequently found in children with ADHD. Research evidence suggests that stimulants are not only safe but also effective in this particular population.	**Case 89-1 (Question 1)**
7	Some children with ADHD will continue to have symptoms of their illness well into their adult years, usually of the inattention subtype. There is a growing awareness that adults with ADHD have significant social and occupational impairments. Fortunately, medications used to treat ADHD in children appear to be equally effective in adults. Stimulants are the most effective agents but have the unique side effect risk of abuse and diversion. Monitoring for this is essential. If abuse or diversion occurs, then a reevaluation of the diagnosis is necessary as well as a change to a medication with less risk of misuse.	**Case 89-2 (Question 2)**

INTRODUCTION

Attention-deficit and hyperactivity disorder (ADHD) is a serious psychiatric condition that has been well described in the medical literature for more than two centuries.[1] There are highly effective pharmacologic treatments that ameliorate the core symptoms of the illness. These agents are generally safe and have been shown to improve long-term prognosis.[2]

By definition, ADHD symptoms manifest in childhood and will often persist into adulthood in many cases. If left untreated, ADHD can produce significant impairments in academic performance and social functioning; adults with ADHD are often hindered in occupational settings as well.[3] Psychiatric comorbidities are commonly encountered among individuals suffering from ADHD, including developmental disorders, mood disorders, and substance abuse.

Although hyperactivity had been recognized as a troublesome childhood behavior for many years, ADHD was not formally described in the *Diagnostic and Statistical Manual of Mental Disorders* until the third edition was released in 1980. The recently released *DSM-5* describes three different subtypes of ADHD including “predominantly inattentive presentation,” “predominantly hyperactive/impulsive presentation,” and “combined presentation.”[4] The *DSM-5* also requires the diagnosis by age 12. Qualitatively, the core symptoms of ADHD will differ according to gender, with males more likely to exhibit the hyperactive/impulsive subtype (vs females).[5] These symptoms often change with time as hyperactive and impulsive behaviors recede during adolescence, and inattention predominates among adolescents and adults with ADHD.[6]

Although the effectiveness of pharmacologic treatments for ADHD has been widely replicated, many children and adolescents with ADHD will receive suboptimal treatment for a variety of reasons, including parental reluctance to consider psychotropic medications, the perceived stigma of mental illness, poor access to psychiatric care in many areas and disparities in access to care for minority youth.[7] It is important to note that ADHD poses a huge economic burden to Western society. A meta-analysis by Doshi et al reports overall national incremental costs of $143 to $266 billion in the United States.[8] The economic impact related to adults with the

disorder from productivity and income loss is greatest, although there are also significant costs associated with youth with the disorder from educational and health expenses. Further, the study documents significant "spillover costs" for family members of individuals with ADHD.[8]

Stimulants such as methylphenidate (MPH) and amphetamine have been the mainstay of ADHD treatment in children for more than 30 years, and recent studies have demonstrated acute and long-term benefits in adolescents as well as adults.[1,9–11] Unfortunately, stimulants have not been consistently shown to decrease delinquency rates. They have also been implicated with rare but serious side effects, and they carry an elevated risk of diversion and abuse.[11–13] Pharmacologic alternatives to stimulants have been identified in recent years and have proven to be useful, albeit often as second-line agents among individuals who have significant side effects and those with medical or psychiatric comorbidities.[11] The benefits of cognitive-behavioral psychotherapy have also been emphasized in recent years, and most experts now contend that the combination of pharmacotherapy with family-based cognitive-behavioral interventions will generate the best long-term prognosis for individuals with this disorder.[2]

Recent landmark studies have helped clarify important aspects of diagnosis and treatment with regard to ADHD. The Multimodal Treatment of Attention-Deficit Hyperactivity Disorder Study (MTA) is considered a groundbreaking study of ADHD treatments and outcomes. The main findings were released in 1999, but additional findings have been subsequently released. MTA was a multisite study that differed from earlier studies of ADHD in that the duration of the study was significantly longer (up to 14 months) and that the study compared the use of both medication and cognitive-behavior therapy (CBT), both alone and in combination with routine community-based treatment. The central findings of MTA included the following: (a) medication alone and in combination with CBT was more effective than intensive behavioral treatment alone or routine community-based care, (b) youth receiving combined treatment required lower doses of medication, and (c) youth with associated

mental health issues, in addition to ADHD, had better outcomes with combined treatment than with medication alone.[14,15]

The question of medication treatment for preschool children presenting with ADHD symptoms is a controversial issue. The "Preschool ADHD Treatment Study" (PATS) is considered a landmark study in this arena. The majority of the findings were released in 2006. The central findings include the following: (a) preschool children tend to respond better and with fewer adverse effects with lower doses of medication and (b) preschool children are more sensitive to the adverse effects of psychostimulants and require closer monitoring. In particular, younger children tend to have more emotional adverse effects such as irritability and a tendency toward crying.[16,17]

EPIDEMIOLOGY

ADHD is a chronic neurobehavioral disorder, with an overall estimated prevalence of 6% to 12% in school-aged children worldwide.[18] The Centers for Disease Control and Prevention analyzed data from the 2006 National Survey of Children's Health and reported that the incidence of ADHD diagnoses has risen annually by an average of 3% between 1997 and 2006.[19] In 2006, 7.4% of U.S. children ages 4 to 17 years were diagnosed with ADHD. The *DSM-5* reports that "ADHD occurs in most cultures in about 5% of children and about 2.5% of adults." The diagnosis is more common in males with a ratio of 2:1 in children and 1.6:1 in adults.[4] It is hypothesized, however, that this gender predominance may be exaggerated because the more overt hyperactive subtype is more common in males and the less overt inattentive subtype is more common in females. As ADHD transitions into adulthood, the prevalence falls to 4.4% (standard error 0.6), with a higher risk found in previously married males who are unemployed and non-Hispanic White.[19]

PATHOPHYSIOLOGY

Various abnormal genetic and neurochemical abnormalities are associated with ADHD. Estimates of heritability of ADHD range in the area of 0.7, indicating that ADHD is one of the most heritable conditions in psychiatry.[20] Family studies have demonstrated that the relative risk of ADHD is six to eight times higher among first-degree relatives of persons with ADHD compared with the general ADHD population.[21] Several candidate genes associated with ADHD have been identified, such as the dopamine receptor, dopamine transporter receptor, and serotonin transporter gene.[22,23] Despite a small causal effect, no single gene is responsible for the symptoms seen with ADHD, but rather these symptoms are likely the result of interactions among several genes, which influence multiple neurotransmitters, including serotonin, dopamine, and norepinephrine (NE).[22]

Multiple neuroimaging studies have documented consistent abnormalities in brain structure and development with youth and adults with ADHD. Subjects with ADHD have been shown to have reductions in global brain volume.[24] Specifically, the reduction in volume is most prominent in the prefrontal cortex, basal ganglia, cerebellum, and parietotemporal regions.[24] Functional magnetic resonance imaging studies have also shown hypoperfusion with memory tests in the anterior cingulate areas in ADHD patients.[25] This area of the brain is responsible for behavioral and functional abilities that may manifest in patients with ADHD as difficulties in organization, mood, motivation, self-regulation, and ability to retain specific information while performing a particular task, which are abilities referred to as executive functioning. These findings are research population–based findings. These studies are not yet useful in clinical practice for accurate diagnosis.

Etiology

ADHD is a heterogeneous behavioral disorder with a variety of theorized etiologies. Clearly, the research suggests a strong genetic component. However, to this point, no specific genetic risk factor has been identified.[20] As a result, other environmental and congenital etiologies have been considered and studied. Examples of studied etiologies for ADHD include maternal smoking, dietary factors, prematurity/low birth weight, and family environment/parenting behavior. Of these proposed factors, low birth rate is the factor with the most confirming research evidence.[20,26] The potential impact of parenting behavior, in particular, is a complex question as youth with ADHD often present more significant challenges to parents. Further, as ADHD is highly heritable, many parents of youth with ADHD may have ADHD themselves. Therefore, it is generally accepted that ADHD is a complex set of disorders with genetic and environmental risk factors and contributors.

DIAGNOSIS, SIGNS, AND SYMPTOMS

The diagnosis of ADHD is a clinical diagnosis that may be supported by various types of screening tools and neuropsychologic assessment. The diagnosis of ADHD in a child is based on the *DSM-5* criteria (**Table 89-1**). The evaluation should include clinical interviews with the patient and/or parent, physical examination (including neurologic status), obtaining history regarding functional pattern in school or daycare setting, evaluation for comorbid psychiatric disorders, and review of the patient's medical, social, and family histories.[2] Other sources of valuable information include performance reports (eg, report cards or job reviews) and ADHD rating scales scored in two different settings.[4] There are a number of validated rating scales available both proprietarily and in the public domain. Some of the rating scales have different versions for parents and teachers. Rating scales are helpful both for diagnosis and for monitoring treatment outcome.

Table 89-1
Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder

A. A persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (eg, overlooks or misses details, work is inaccurate)
   b. Often has difficulty sustaining attention in tasks or play activities (eg, has difficulty remaining focused during lectures, conversations, or lengthy reading)
   c. Often does not seem to listen when spoken to directly (eg, mind seems elsewhere, even in the absence of any obvious distraction)
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (eg, starts tasks but quickly loses focus and is easily sidetracked)
   e. Often has difficulty organizing tasks and activities (eg, difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines)
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (eg, schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers)
   g. Often loses things necessary for tasks or activities (eg, school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones)
   h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts)
   i. Is often forgetful in daily activities (eg, doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments)

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with the developmental level and that negatively impacts directly on social and academic/occupational activities:

   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

   a. Often fidgets with or taps hands or feet or squirms in seat
   b. Often leaves seat in situations when remaining seated is expected (eg, leaves their place in the classroom, in the office or other workplace, or in other situations that require remaining in place)

c. Often runs about or climbs in situations where it is inappropriate (Note: In adolescents or adults, may be limited to feeling restless)
d. Often unable to play or engage in leisure activities quietly
e. Is often "on the go," acting as if "driven by a motor" (eg, is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with)
f. Often talks excessively
g. Often blurts out an answer before a question has been completed (eg, completes people's sentences; cannot wait for turn in conversation)
h. Often has difficulty waiting his or her turn (eg, while waiting in line)
i. Often interrupts or intrudes on others (eg, butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing)

B. Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (eg, at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication, or withdrawal).

Reprinted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. © 2013 American Psychiatric Association. All Rights Reserved.

Per the *DSM-5*, to meet the criteria for ADHD, the child must have six or more symptoms present in two different settings (eg, home, school) for a minimum of 6 months. Furthermore, there must be evidence that these symptoms were present before age 12 years. Based on these criteria, three types of ADHD are identified: predominantly inattentive, predominately hyperactive/impulsive, and combined. The diagnostic criteria require that the symptoms interfere with or impact functioning in daily life so that care providers will look for symptoms that have a negative impact on the child's education, relationships, or social life (see Table 89-1). On occasion, however, parents or teachers may "pressure" clinicians into writing

psychostimulant prescriptions for a “let’s see if it helps” trial. If the medication is helpful, they may assume incorrectly that the diagnosis of ADHD is validated. Additionally, *DSM-5* eliminated the exclusion criteria for autism spectrum disorder. However, the *DSM-5* mandates that the symptoms of ADHD “do not occur exclusively during the course” of another psychiatric disorder.[4]

Establishing a diagnosis of ADHD in an adult who has never been treated for the disorder during childhood is difficult. In adults, ADHD is a clinical diagnosis that relies on their recollection of ADHD symptoms as a child to which *DSM-5* criteria validated for children are applied. Unlike teachers who are ordinarily familiar with the symptoms associated with ADHD in children, spouses, coworkers, and employers are often unfamiliar with ADHD as a disorder that can also affect adults. They may attribute the individual’s difficulties to laziness, disinterest, or underachievement.

COMORBIDITY AND PROGNOSIS

Between ages 10 and 25 years, the signs and symptoms of ADHD decrease in frequency and severity by about 50% every 5 years but will often persist into adulthood.[6] In the differential diagnosis of ADHD, it is critically important to distinguish ADHD from various behavioral, developmental, or medical conditions. Psychiatric comorbidity is more common with ADHD as up to 87% of children will be diagnosed with at least one additional psychiatric disorder and 67% have at least two or more disorders.[27] Other psychiatric conditions that are frequently comorbid with ADHD or present with similar symptoms as ADHD include conduct disorder; oppositional defiant disorder; Tourette syndrome; mood disorders including depression, bipolar disorder, and disruptive mood dysregulation disorder; anxiety disorders; and obsessive–compulsive disorder. Of these conditions, anxiety disorders and mood disorders are most commonly misdiagnosed as ADHD. The comorbidity of ADHD and learning disabilities is both complex and often leads to significant

academic challenges. Studies suggest that 25% to 35% of youth with ADHD will also have language-based or other learning disabilities.[27] Clinical wisdom suggests that ADHD often presents early in the child's academic career (eg, kindergarten or first grade), whereas learning disabilities may present later in the elementary years, when children are "reading to learn" rather than "learning to read." Medication is a central treatment component for ADHD, whereas learning support and specialized teaching strategies are the interventions of choice for youth with learning disabilities. Medications are not helpful for the treatment of learning disabilities.

Family histories from first-degree relatives of probands with ADHD reveal increased rates of ADHD (25% concordance rate), polysubstance dependence, antisocial personality disorder, depression, and anxiety disorders.[28] Genetic studies have shown a strong correlation in genetic abnormalities, particularly with the *FOXP2* gene, although multiple genes are likely related.[29] Children with ADHD are at an increased risk of having antisocial behavior, depression, and substance abuse problems as adults. ADHD symptoms persist into adulthood in the majority of these comorbid patients.[11] Adults with ADHD are usually self-sufficient, but they have poorer academic performance, poorer job performance, and lower socioeconomic status than do their siblings. They also have more frequent divorces, job changes, and car accidents. Most adults with ADHD report a high level of subjective distress (79%) and interpersonal problems (75%).[30]

Medical conditions often complicate the diagnosis of ADHD and should be excluded before initiating treatment. These medical conditions include head injuries, seizure disorders, metabolic disorders, cerebral infection, toxic exposures (eg, chronic lead exposure), sleep problems, substance abuse, and hyperthyroidism.

CASE 89-1

QUESTION 1: M.T. is a 12-year-old female who recently started middle school. M.T.'s mother calls the pediatrician looking for advice. M.T. was adopted at age 2 months from Guatemala and little is known about prenatal care or her life

before the adoption. M.T. is having a good deal of difficulty with the transition to middle school. She seems overwhelmed with the amount of work and has become withdrawn and angry. The guidance counselor has called the parents because M.T. has missed most of her homework assignments. M.T.'s mother feels at a loss because M.T. now has many more teachers and they don't seem to know her or to support her in the same way as the teachers in the elementary school. M.T. has begun counseling with a social worker in the community but does not want to go. Her mother is interested to know if medication may be of help.

How do you think about the differential diagnosis?

Depression is the most prominent diagnosis that comes to mind. However, it is important to remember that comorbidity is quite common in youth with psychiatric disorders. It is important to consider if there are underlying, less obvious disorders or circumstances that may be contributing.

Case 89-1, Question 2: What are the next steps in the evaluation?

The pediatrician refers M.T. to a child/adolescent psychiatrist for evaluation. The professionals help the parents request an educational assessment through the school. The latter includes both academic and psychologic assessments. The assessments suggest underlying poor self-esteem. However, there is also evidence of slow processing speed and other evidence of ADHD and executive functioning deficits. The Vanderbilt rating scales confirm the diagnosis of ADHD.

There are a number of validated instruments to assist with the diagnosis and clinical management of ADHD. Often, these instruments have a parent and teacher version. Commonly used instruments include the Conners Global Index, the SNAP IV, DuPaul Rating Scale for ADHD, and the Vanderbilt Rating Scale. Some rating scales are proprietary, and others such as the Vanderbilt are in the public domain.[31]

Case 89-1, Question 3: What are the first-line interventions?

The psychiatrist provides psychoeducation to M.T. and her parents about ADHD. They discuss that ADHD may be missed more commonly in females and that youth with ADHD often develop concurrent depression, anxiety, conduct disorders, and substance-use disorders because their experience in school and activities often leads to feelings of inadequacy. Additionally, an Individualized Educational Plan (IEP) is developed for M.T. to provide more support in the school setting. Special accommodations such as added time for exams, a seat in the front of the class, and the availability of fidget toys are specified in the IEP.

M.T. continues in counseling with the social worker, in which they focus on cognitive and behavioral strategies to manage both her ADHD symptoms and her depression and poor self-esteem. All agree that it is prudent to hold off on any medication for depression to see if the other interventions are effective in alleviating the symptoms of depression.

The ADHD symptoms are tracked with Vanderbilt rating scales completed by parents and teachers. Medication treatments for ADHD are discussed. With informed consent, a trial of a psychostimulant is begun.

TREATMENT

Optimal strategies to manage ADHD symptoms that are moderate to severe in nature should focus on the combined use of behavioral and pharmacotherapy interventions. It is important to recognize that ADHD is a chronic disorder with symptoms that frequently continue into adolescence and adulthood. Before developing a treatment plan, defined and realistic treatment goals should be established collaboratively with the child, parent, and school.

Several ADHD consensus statements, practice parameters, and guidelines have been developed, based on both evidence-based literature evaluation and expert opinions, to assist clinicians in

evaluating, diagnosing, and managing patients with ADHD in a consistent manner.[2,32–35]

Behavioral Therapy

During the years, numerous psychosocial or educational programs have been studied for their potential benefit in controlling ADHD symptoms and maximizing function.[2] Behavioral interventions have been among the most popular nonpharmacologic approaches, with programs emphasizing the creation of a structured environment containing minimal distractions both at home and in school. Contingency training is another common component of behavioral therapy for ADHD, with children receiving tokens for specific tasks or achievements, as well as punishments (eg, revoking privileges) for maladaptive behaviors. Although most treatment guidelines continue to advocate trying some type of structured behavioral modification, the empiric evidence that such programs improve functioning or prognosis is certainly not as strong as it is for pharmacotherapy.[34]

The previously mentioned Multimodal Treatment Study of Children with ADHD reviewed the relative impact of medication and nonpharmacologic treatment.[14] The MTA Cooperative Group study, as it is commonly known, was designed to compare long-term medication and behavioral treatments with respect to efficacy and acceptability. A group of 579 children between ages 7 and 10 years with the combined type of ADHD were recruited and randomly assigned to four different treatment groups: medication management, behavioral treatment, medication plus behavioral treatment, or typical community treatment. Behavioral interventions were delivered in a group-based recreational setting and included an 8-week, 5-days/week, 9-hours/day, intensive program administered by a counselor or aide. Once school started, the subjects in this arm of the study received 60 school days of a part-time, behaviorally trained, paraprofessional aide who worked directly with the child. In addition, the child's teacher received 10 to 16 sessions of biweekly consultation that focused on classroom behavior management

strategies. Daily behavior report cards were sent home to parents. At the same time, families were involved in 27 group therapy meetings plus 8 individual family meetings. Of the children receiving medication, 75% received MPH, 10% received dextroamphetamine, and 15% received pemoline (no longer available in the United States), imipramine, clonidine, guanfacine, or bupropion. After the 14-month study, it was concluded that drug treatment was more effective than behavioral treatment according to parents' and teachers' ratings of inattention, and teachers' ratings of hyperactivity/impulsivity. Combined treatment (drug treatment plus behavioral modification) was preferred by parents, but the therapeutic advantage versus medication did not achieve statistical significance. Combined treatment was significantly more effective than behavioral treatment and community care for reducing ADHD symptoms, according to both parent and teacher reports, but a subgroup analysis of children with comorbid conditions (eg, conduct, oppositional defiant, anxiety, or affective disorders) found behavior management to be as effective as medication monotherapy. A 3-year follow-up study revealed that all four interventions were equally effective in improving academic performance and social functioning with time, but given the costly and labor-intensive nature of the behavioral modification in contrast to other interventions, most notably, pharmacotherapy, medication continues to be regarded as the first-line treatment for children with at least moderate ADHD symptoms.[15] There have been a variety of school-based, clinic-based, and home-based interventions to address ADHD symptoms, mainly with positive results. Additionally, specialized summer treatment programs have been established to provide more intensive intervention when school is not in session.[36]

Pharmacotherapy

STIMULANTS

Stimulants are considered the most effective option to treat ADHD, with more than 60 years of clinical experience accrued. Currently,

there are two basic types of stimulants marketed in the United States, MPH-based and amphetamine based, and they have all been reported to improve academic performance and behavior in children with ADHD (**Table 89-2**).[33]

Table 89-2
Overview of Common Drugs to Treat Attention-Deficit Hyperactivity Disorder

Drug		Duration of Action	Pediatric Dose	Adult Dose	
Stimulants					
Methylphenidate C-II	Aptensio XR™	Long	20–60 mg/day	20–60 mg/day	Adult doses may need to be higher and can be titrated up based on tolerability.
	Concerta® (generic)	Long	18–72 mg/day	18–72 mg/day	
		Long	20–60 mg/day	20–60 mg/day	
	Metadate CD®	Intermediate	20–60 mg/day	20–60 mg/day	
	Metadate ER®	Intermediate	20–60 mg/day	20–60 mg/day	
	Methylin ER®	Long	20–60 mg/day	20–60 mg/day	
	Quillichew ER™	Long	20–60 mg/day	20–60 mg/day	
	Quillivant XR®	Short	20–60 mg/day	20–60 mg/day	
	Ritalin® IR	Intermediate	20–60 mg/day	20–60 mg/day	
	Ritalin® SR	Long	20–60 mg/day	20–60 mg/day	
	Ritalin® LA	Long	10–30 mg/9-hour patch	10–30 mg/9-hour patch	
	Daytrana® transdermal patch	Long	20–100 mg a day	20–100 mg a day	
	Jornay PM™				
Dexmethylphenidate C-II	Focalin®	Short	5–20 mg a day	20 mg a day	
Serdexmethylphenidate/dexmethylphenidate	Focalin® XR	Long	5–20 mg a day	20 mg a day	
	Azstarys™	Long	39.8/7.8 to 52.3/10.4 mg a day		

Amphetamine C-II	Adzenys® XR ODT Adzenys ER™ Dyanavel® XR Evekeo®	Long Long Long	6.3–18.8 mg/day 20 mg/day 2.5–40 mg/day	No approved max. dose No approved max. dose No approved max. dose	Adult doses likely to be similar to pediatric doses and titrated as tolerated.
Amphetamine/ dextroamphetamine C-II	Adderall® Adderall® XR Mydayis®	Short Long Long	10–40 mg/day 10–30 mg/day 12.5–50 mg/day	10–40 mg/day 10–20 mg/day 12.5–50 mg/day	Doses may be increased as tolerated.
Dextroamphetamine C-II	Dexedrine® Dexedrine® XR ProCentra® Zenzedi®	Short Long Short Short	5–40 mg/day 5–40 mg/day 5–40 mg/day 5–40 mg/day	5–40 mg/day 5–40 mg/day 5–40 mg/day 5–40 mg/day	
Lisdexamfetamine C-II	Vyvanse®	Long	30–70 mg/day	30–70 mg/day	
Methamphetamine	Desoxyn®	Long	5–25 mg/day	No approved dose	Strongly recommended not to use this product
Nonstimulants					
Noradrenergic-Reuptake Inhibitor					
Atomoxetine Viloxazine	Strattera® Qelbree™	Long Long	40–100 mg/day 100–400 mg/day	40–100 mg/day	
α_2-Receptor Agonist					
Clonidine Guanfacine	Clonidine Kapvay™ Guanfacine Intuniv®	Short Long Short Long	0.1–0.3 mg/day 0.1–0.4 mg/day 1–4 mg/day 1–4 mg/day	0.1–0.3 mg/day 0.1–0.4 mg/day 1–4 mg/day 1–4 mg/day	Use in adults not well studied. Higher doses have been used to control BP. Monitoring for hypotension is recommender.

BP, blood pressure; CD, controlled delivery; IR, immediate release; ODT, orally disintegrating tablet; SR, sustained release; ER and XR, extended release.

A review of short-term clinical trials that evaluated the safety and efficacy of stimulants in nearly 6000 children and adults with ADHD showed a 75% to 80% improvement in patients treated with stimulants compared with 5% to 30% treated with placebo.[37] Although stimulant drugs are grouped as a class based on their pharmacologic effect of increasing dopamine and NE levels in the synapse, the mechanisms by which stimulant drugs exert this effect vary slightly. These subtle differences in the mechanism of action support the possibility that patients who respond partially to one stimulant may respond completely to another. In fact, ~20% to 25% of those who respond poorly to one medication will respond positively to another and up to 90% of children will respond if both are tried.[38] Stimulants are rapid acting and have predictable effects, with response typically within 2 hours.[39]

MPH blocks the reuptake of dopamine from the synaptic cleft into the presynaptic neuron via the dopamine transporter protein. MPH

consists of a racemic mixture of *d* and *l* isomers. Preparations are available as *d*-/*l*-methylphenidate and solely as dexmethylphenidate. *d*-MPH has greater potency at DA reuptake inhibition than NE. *l*-MPH is also more potent at DA reuptake than NE but to a lesser degree than *d*-MPH.[40,41] *d*-MPH also achieves higher serum concentration than the *l*-isomer because of a lesser impact of carboxylesterase CES1A1, the enzyme primarily responsible for MPH metabolism, on the *d*-isomer compared to the *l*-isomer.[40,41]

The most common side effects of MPH include appetite suppression, insomnia, headache, nausea and vomiting, and abdominal pain.[41]

A long-acting MPH transdermal formulation is available. As with any transdermal system, drug delivery can vary greatly because of heat and site-related skin porosity differences. Area under the curve (AUC) and C_{max} can increase 300% if the patch is applied to an inflamed area and 250% if the patch area is exposed to heat such as going outside and exercising in the sun.[2,42–44] The patch is applied to the hip area for 9 hours, and MPH is steadily released and absorbed into the circulation for about 11.5 hours. When compared to the oral long-acting Oros release system, MPH's side effects were similar between the two products but numerically higher in the transdermal arm compared to the oral arm. One side effect exclusive to the patch is skin irritation, which can occur from 3% to 40%.[42] A very slow-release product uses a multilayered system that does not allow the release of MPH for up to 10 hours after ingestion. Peak dose is achieved ~16 hours after ingestion. This allows for dosing in prior to be on the previous night if that is necessary.[45]

Amphetamines, including mixed amphetamine salts, dextroamphetamine, and lisdexamfetamine, enhance the release of both dopamine and NE from storage vesicles in the presynaptic neuron and block their storage in addition to blocking their reuptake from the synaptic cleft. They also have a weak monoamine oxidase inhibitor (MAOI) effect.[46,47] AMP consists of *d,l* racemic mixture. *d*-AMP has a greater effect at increasing DA within synapse compared to the *levo* enantiomer. Both the *d* and *l* enantiomers increase

synaptic NE but to a lesser extent than DA.[48] AMP also has a small effect at increasing serotonin with *d* enantiomer greater than the *l* enantiomer, but this effect is likely clinically irrelevant with both.[49]

Dextroamphetamine is metabolized via CYP2D6. A strong inhibitor of 2D6 could increase levels twofold. The long-acting prodrug lisdexamfetamine requires enzymatic hydrolysis in the blood to cleave off the L-lysine portion of the molecule. This leaves just dexamphetamine available for activity.[50–52] Lisdexamfetamine is rapidly absorbed, but the step of hydrolysis results in a delayed release of dextroamphetamine in the circulation allowing for once-a-day dosing. In addition, this formulation is helpful for youth who are at risk for misuse of psychostimulants through inhalation.

Because approximately two-thirds of children and adolescents with ADHD respond equally to MPH or amphetamine products, the preferred agent should be based on the duration of action, formulation preferences, and cost.[34] As shown in Table 89-2, stimulant preparations are classified based on duration (ie, immediate [2–5 hours], intermediate [6–8 hours], and long-acting [10–12 hours]) and available delivery systems. Long-acting formulations are usually preferable to intermediate and short acting because it provides uninterrupted benefit allowing the child to avoid going to the school nurse for doses or lack of effect between doses.[53] There are some clinical situations that indicate immediate-release preparations, often to minimize adverse effects. Many long-acting options are biphasic, which provide an immediate-release (IR) dose and then a second long-acting dose a few hours later. For example, Ritalin LA®, Metadate CD®, Focalin XR®, and Adderall XR® all contain both immediate and enteric-coated, delayed-release beads that mimic the blood concentrations seen with IR stimulant preparations given twice daily. Although a prescription methamphetamine product does have Food and Drug Administration (FDA) approval for the treatment of ADHD, no expert guidelines recommend it because of high-abuse liability and neurotoxicity.

Adverse effects

Both types of stimulants are similar in their side effect profiles. Adverse drug reactions such as insomnia and appetite loss are mild, and tolerance often develops within a few days. These reactions can be easily managed by adjustment in dose and timing if necessary (**Table 89-3**). One head-to-head trial of mixed amphetamine salts compared to MPH found no statistical differences in side effects but numerically amphetamine had higher rates of stomachache, irritability, mood changes, and tics.[54]

Table 89-3

Managing Adverse Effects of Stimulants Used in Children With Attention-Deficit Hyperactivity Disorder

Adverse Effect	Management
Decreased appetite, nausea, or growth impairment	Schedule evening meals after the medication has worn off. Take drug after meals. Encourage foods with high caloric density or nutritional supplements. Encourage evening/bedtime snack. Switch from long- to short-acting preparation. Provide drug holidays when appropriate.
Sleep disturbance	Administer doses earlier in the day. If using a sustained-release product, consider changing to a short-acting preparation. Discontinue afternoon/evening dose.
Behavioral rebound	If using short-acting preparation, consider changing to a long-acting preparation.
Irritability	Assess time of symptoms: Related to peak: reduce dose or try long-acting preparation Related to withdrawal: change to long-acting preparation Evaluate for comorbid diagnosis.
Dysphoria, moodiness, agitation, dazed, or withdrawn behavior	Decrease dose or change to long-acting preparation. Consider comorbid diagnosis.

Adverse Effect	Management
Dizziness	Monitor blood pressure. Encourage fluid intake. Lower dose or change to long-acting preparation to reduce peak effects.
Development or increase in tic disorder	Stop stimulant. Consider trial of clonidine, guanfacine, or atomoxetine.

There is an association between stimulant use and slight growth retardation. The relative impact of this seems minimal and can be reduced or eliminated with drug holidays.[55–57] There seems to be no loss of efficacy if the child does have a drug holiday and stops the medication over weekends holidays or summer months.[58] The risk of drug holidays is a worsening of symptoms during these drug-free days. For some children, this may have an impact on social maturation.

Regarding cardiotoxicity risk, population studies suggest that the overall risk of sudden death associated with stimulant use has been shown to be the same, if not lower, than that of the general population.[59] Slight increases in BP and heart rate (HR) are seen with MPH and amphetamines, although ECG changes are very rare.[60–62] Clinicians should follow current recommendations suggested by the American Academy of Pediatrics and the American Heart Association, which advocate screening for a personal or family history of cardiovascular disease in all children with ADHD. Continual monitoring for these risks along with routine blood pressure and heart rate assessments should be performed.[63] Pretreatment ECGs are not required but recommended by the American Heart Association (AHA) as a general practice for all children. Stimulants should not be used in those with known structural cardiac abnormalities.[64]

NONSTIMULANTS

For patients with ADHD only, it is recommended to initiate treatment with either MPH or amphetamine.[2,33–35] For patients who fail both

types of stimulants or when stimulants are not preferred, a trial of a nonstimulant is warranted (see Table 89-2). Nonstimulants are typically less effective than stimulants and usually require at least 4 weeks until a full response is evident. A meta-analysis of 29 double-blind, placebo-controlled trials evaluated the efficacy of stimulant and nonstimulant agents using 17 outcome measures in 4465 children and adolescents with ADHD.[65] It found that the effect size of amphetamine and MPH was significantly greater than that for atomoxetine, bupropion, and modafinil (P = .02).[65] If atomoxetine fails or is not indicated, the α_2-adrenergic agonists clonidine and guanfacine should be considered.[32–34]

Norepinephrine reuptake inhibitors

Atomoxetine inhibits the presynaptic NE transporter and is classified as norepinephrine reuptake inhibitor (NRI). Clinical trials have shown that atomoxetine is superior to placebo in reducing the symptoms of ADHD in children, adolescents, and adults.[66,67] However, trials comparing atomoxetine with stimulants have found atomoxetine to be less effective.[2,68–71]

Atomoxetine is likely to have some immediate benefit after initiation, but unlike the stimulants, a longer trial of 6 to 8 weeks is recommended as efficacy continues to grow. Atomoxetine requires a 10- to 14-day titration to achieve a therapeutic dose of 1 to 1.5 mg/kg/day to avoid nausea (12%), vomiting (15%), and asthenia (11%).[72] As with stimulants, atomoxetine can also raise blood pressure and heart rate, with reports of high systolic and diastolic blood pressures occurring in 8.6% and 5.2% of pediatric subjects, respectively. Increases in heart rate of more than 110 beats/minute and more than 25 beats/minute above baseline were observed in 3.6% of patients.[72] Atomoxetine is metabolized via CYP 450 2D6, with the major metabolite being 4-hydroxyatomoxetine, which is also a potent inhibitor of NE reuptake but only achieves low blood concentration levels. It has a half-life of 4 to 5 hours but can be extended by about 3 hours with a high-fat meal.[73]

There have been postmarketing cases of reversible hepatic injury in association with atomoxetine, but this is quite rare.[74] Baseline liver enzyme testing should be performed, and evidence of jaundice or liver injury should warrant immediate discontinuation. Atomoxetine also contains the warning regarding increased risk of suicidal thoughts that are part of all antidepressant class labeling. However, a meta-analysis of 14 trials found that no subject committed suicide. Suicidal ideation in the atomoxetine group was 5/1357 (0.37%) and placebo group was 0/851 (0%).[75] So, despite the low risk, monitoring frequently for the first 3 months of treatment is required by the FDA.

Viloxazine is another NE reuptake inhibitor that has much less effect on the NE reuptake pump compared to atomoxetine. It also has effects as an agonist at 5-ht_{2c} receptors and as an antagonist at 5-ht_{2b} receptors.[76,77] Its efficacy seems to be a little less than atomoxetine however, no direct head-to-head trials have been conducted. Common side effects include gastrointestinal (GI) distress at 14%, somnolence at 16% decreased appetite at 7% and headache at 11%. HR and diastolic increases can occur and must be assessed prior to, and monitored while, taking viloxazine.[78,79] Medications that inhibit CYP450 2D6 may result in a small increase in vilazodone levels (around 25%). Viloxazine is a potent inhibitor of CYP450 1A2 and has been shown to double theophylline levels.[78,80]

α_2-Agonists

Clonidine and guanfacine are α_2-agonists that have been used for years off-label to control hyperactive/impulsive or aggressive symptoms and insomnia.[81] They are believed to directly stimulate the postsynaptic NE receptors in the prefrontal cortex and locus coeruleus. Guanfacine is most specific for the α_{2a}-receptor, whereas clonidine is less specific and agonizes α_{2a}, α_{2b}, and α_{2c}. Extended-release formulations for clonidine and guanfacine are FDA approved both as monotherapy and as adjuncts to stimulants. Although they are a monotherapy option, they are not considered as first line as

they are less effective than stimulants. They are particularly useful for behavioral comorbidities, such as aggression and tics.[32–35,82–84]

Guanfacine is primarily metabolized via CYP 3A4, and potent inhibitors can increase blood levels by 200%. Guanfacine extended release provides ~60% of the serum levels of the IR version. Clonidine is partially metabolized via CYP 2D6, although inhibitors of this pathway have only minor changes in serum levels.[85] The extended-release version has an AUC ~89% of the immediate release.

The side effect profile of α_2-agonists is quite different than the stimulants and atomoxetine. Sedation and related side effects can occur in nearly 40% for both. Reductions in BP and HR can occur and thus need to be monitored. Bradycardia (HR <60 bpm) can occur in up to 20% of children with clonidine and is a side effect of guanfacine also but to a lesser degree. This is likely because of guanfacine's specificity to α_{2a}. Rebound hypertension can occur if either of these medications is stopped abruptly.[82]

Despite positive studies with IR formulations, the short duration of action makes them less desirable than the QD dosing of guanfacine extended release (ER) and the bid dosing clonidine extended-release formulation.[33]

Case 89-1, Question 4: It is agreed upon by the parents and the pediatrician that M.T. will begin using a medication for her ADHD symptoms. What would be the first-line option for M.T.?

Either stimulant group is considered first line, and, in this case, MPH 10 mg qam is tried. After steadily increasing the dose to 30 mg qam, the parents feel that there is minimal change in attention, but that there are significant side effects of nausea and loss of appetite.

Case 89-1, Question 5: What would be the next trial of medication for M.T.?

Expert guidelines state that if medication is decided upon, then the greatest efficacy is from the stimulants. None of the stimulant is

considered superior to the other, and initial choice should be based on the comfort level of the clinician and patient/parent acceptance. If the initial choice of stimulant is ineffective, it is recommended to trial an agent from the other stimulant class. By doing this, 90% of children will display efficacy. Therefore, the next trial for M.T. should be the initiation of dextroamphetamine 5 mg qam and titrate as tolerated to a maximum of 40 mg/day.

Case 89-1, Question 6: M.T. is showing some improvement on 10 mg qam of IR dextroamphetamine, but it is clearly wearing off about 4 hours after dosing. Dosing of 10 mg bid was tried during a school vacation and found to be somewhat effective; thus, the pediatrician decided to switch to long-acting dextroamphetamine spansules 20 mg qam. This clearly has shown to last throughout M.T.'s school day, but efficacy is not maximized, and some residual symptoms of poor attention and hyperactivity exist. What is the next step of pharmacotherapy for M.T.?

Increasing the dose to 30 mg qam is possible. Although a switch from a stimulant to atomoxetine could be tried, data have shown that atomoxetine is less effective than stimulants. Experts recommend that combination therapy of a stimulant and an α_2-agonist is appropriate, and studies have shown an increase in efficacy when switching from monotherapy to combination therapy.

Comorbidities

TOURETTE SYNDROME AND TIC DISORDER

Tourette syndrome is neuropsychiatric condition, which has tics as a hallmark symptom. Children with ADHD have a higher risk of comorbid tic disorder than the general population; however, stimulants are relatively safe in this population. As an example, the Tourette Syndrome Study Group contrasted the effect of MPH, clonidine, and the combination of the two to placebo in the treatment of 136 children (7–14 years old) diagnosed with ADHD and Tourette syndrome.[86] The group concluded that prior recommendations to avoid MPH in these children because of concerns of worsening tics

were unsupported. As such, expert recommendations are that a child with ADHD should start on MPH, and if tics emerge or worsen, then a switch to atomoxetine or clonidine is warranted. A meta-analysis of studies with subjects who have ADHD and Tourette syndrome concluded that MPH shows the greatest improvement in ADHD symptoms without worsening tics for most youth. α_2-Agonists offer less efficacy in ADHD symptoms but greater control over tics compared to MPH. Atomoxetine offers benefit for both groups of symptoms and is an option.[33,83,84] Amphetamines should be avoided because although they do treat ADHD symptoms, they have a higher chance of worsening tics compared to MPH.[83,84]

A review regarding the treatment of tic disorders without comorbid ADHD states that the α_2-agonists guanfacine and clonidine are recommended as first-line options. Guanfacine may be preferred because of less sedation than clonidine.[87]

ANXIETY DISORDER

Anxiety disorders are more frequently comorbid in the ADHD-affected children (approximately ninefold) and adults (approximately fourfold) compared to the frequency seen in the general population. Despite the fact that the anxiety disorder may be a separate disorder, anxiety symptoms in the child are sometimes directly related to poor school and social performance because of ADHD symptoms. Treatment with a stimulant that subsequently improves performance will reduce anxiety. However, after a trial with a stimulant, some children will experience no change or worsening of anxiety-related symptoms. At this point, a trial with atomoxetine is recommended rather than treating the anxiety with a selective serotonin reuptake inhibitor (SSRI) and continuing the stimulant.[2,88]

SUBSTANCE ABUSE

Despite the fact that stimulants are medications with the risk of misuse or abuse, multiple studies have shown a protective effect against developing a substance-use disorder with children who derive a benefit to their ADHD symptoms from psychostimulant

medication. A meta-analysis of epidemiologic literature led to the conclusion that stimulant-treated patients with a diagnosis of ADHD were less likely to be diagnosed with substance-use disorder than those not treated with stimulants.[89] Using a stimulant to treat ADHD in a patient with comorbid substance abuse has contradictory results. Stimulants do treat the ADHD symptoms but not as robustly as those without a concurrent substance-use disorder. In these comorbid adult patients, the psychostimulant medications do not seem to reduce the substance use but do not worsen it either.[90] Expert opinion suggests that those with current substance-use disorders should be tried on nonstimulant options first, but stimulants are not fully contraindicated and can be used with close monitoring. There is growing data to support that there is a high rate of diversion of stimulants in the college population. One report positively correlated an increased incidence of stimulant diversion with the increased difficulty in the academic program.[33,91,92]

If misuse and diversion are of concern and a stimulant is necessary, the preferred dosage form of MPH is the transdermal patch formulation, and dextroamphetamine is the prodrug lisdexamfetamine.[33,35,44,46,50]

Despite the potential for being less effective than a stimulant, atomoxetine has preferred benefits in specific patient subtypes. Because it is not a stimulant, its risk of abuse and diversion are low and is preferred in patients with an addictions disorder history or living in a household where someone other than the patient (eg, parent or sibling) has an addiction disorder and may take the patients medications.

PSYCHOSIS

Stimulants may cause psychosis. This is because of the enhancement of DA centrally. If the child is acknowledging hallucinations or exhibiting bizarre behavior, then cessation of the stimulant is required. A rechallenge can occur but at a lower dose. If a child stabilized on the medication starts to exhibit psychotic symptoms, assess for drug interactions. As amphetamines are

metabolized by CYP450 2D6, any drug that inhibits this pathway could result in toxicity such as psychosis. The MPH transdermal patch formulation can have greater unexpected fluctuations in blood levels because of a greater range of absorption compared to the oral formulations.[43,44] The absorption of the transdermal patch is influenced by placement site and temperature of the skin. Switching to an oral formulation or lowering the dose is the preferred treatment, whereas adding an antipsychotic is not recommended.[33]

Other Non-FDA Pharmacotherapy

BUPROPION

Bupropion has been shown to be effective compared to placebo, but it is less effective than stimulants in the treatment of ADHD.[71] Randomized controlled trials (RCTs) have established the effectiveness of bupropion as an alternative to the psychostimulants in the treatment of ADHD in children, adolescents, and adults.[93–95] The two most common adverse effects encountered with bupropion in ADHD studies were dermatologic reactions and seizures. Dermatologic reactions occurred twice as often with bupropion compared with placebo. Severe bupropion-induced urticaria required discontinuation in 5.5% (4 of 72) of the patients in one study.[96] In adults, the risk of seizures increases by about fourfold if extended-release doses of >450 mg/day or >400 mg/day sustained-release doses of bupropion doses are exceeded.[97] Although there are no case reports of seizures in children receiving therapeutic doses of bupropion, it is recommended to limit doses to <6 mg/kg/day in the treatment of ADHD and to avoid using bupropion in patients with a history of seizure disorders.

MODAFINIL

Modafinil has been found to be effective in the treatment of prepubescent, adolescent, and adult patients with ADHD.[98,99] The 2006 Pediatric FDA advisory committee reviewed the efficacy and safety of modafinil for ADHD and determined the drug was effective

but rejected its approval for ADHD based on concerns about safety. Twelve of 933 patients developed a skin rash, with one case thought to be Stevens–Johnson syndrome.[100]

TRICYCLIC ANTIDEPRESSANTS AND SEROTONIN–NOREPINEPHRINE REUPTAKE INHIBITORS

As recently as 2007 guidelines reported, tricyclic antidepressants (TCAs) could be an option for ADHD. However, their poor tolerability and dangerous effect on cardiac conduction have resulted in more recently published guidelines in 2014 and 2019 to not recommend them.[2,33–35]

The serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine has shown efficacy in both adolescents and adults with ADHD. This is a legitimate choice for comorbid anxious or depressed older patients, but because of antidepressants having a small (2% for placebo, 4% for antidepressant) risk of increasing suicidal thinking in children, other options should be tried first. Adults often have these comorbidities, and venlafaxine in that population is more likely to be used.[33]

Alternative Therapy

There have been a number of studies that have tried to discern if certain diets may result in ADHD. One of the most famous regimens is the Feingold Diet. Recent reviews on the topic have found the evidence to be of low quality and of small benefit. Most studies have not been blinded, and when efficacy is noted, it is of lower rates than the FDA-approved pharmacotherapies. Additionally, there is a practical limitation to the implementation of these diets as it eliminates many of the foods that are regular parts of American meals. At this time, it does seem reasonable to assume that some children's ADHD-like behavior may be related to intolerance to certain dyes, artificial sweeteners, and flavors. Do not discourage a parent to promote healthier food selection for their child, but the effectiveness of lowering their symptoms is marginal. Additionally, if

a child has a delay in the administration of pharmacotherapy because of trials of different types of diets, then this could result in persistency of symptoms longer than is necessary.[101]

Many companies have created dietary supplements that have been touted as effective remedies for treating and preventing ADHD, but convincing results derived from rigorous trials are currently lacking and are likely to benefit only a very few children with food allergies or intolerances.[101–103] For instance, the use of very high doses of vitamins or minerals has been promoted as a possible intervention, but all RCTs conducted to evaluate the effectiveness of megavitamin therapy have been negative to date.[104] Omega-3 fatty acids have been considered as possible treatments for ADHD, based largely on population studies demonstrating an association between high dietary intake and a reduced risk of various neuropsychiatric disorders. Omega-3 supplementation, specifically eicosapentaenoic acid (EPA) content, may have a small benefit as monotherapy. Studies of ω-3 as an adjunct to stimulants have shown little added benefit.[105,106] Similarly, there have been reports of children with low serum zinc, vitamin D, or iron that benefit from replenishment, but children with normal levels have no benefit on symptoms from extra doses.[107,108] There have been other reports of magnesium, *Hypericum* (St. John's wort), and ginkgo all relieving ADHD symptoms, but the evidence to support these interventions is very limited at the present time.[108,109]

There have been other somatic treatments aimed at relieving ADHD symptoms.[109] Several small randomized studies have reported benefits with neurofeedback, in which children are trained to modify certain brain activities demonstrated on electroencephalographic tracings (eg, increased slow wave or α-activity). Preliminary evidence also supports the exploration of meditation as an effective intervention for ADHD, particularly mindfulness-based methods that have proven to be particularly helpful for depression and chronic pain conditions.[110] Clinic-based interventions have included cognitive-behavioral therapy, social skills training programs, and computer-based cognitive training programs. Early studies of some of these intervention strategies have been

promising, and there is a need for further research to establish efficacy.[36] Regarding acupuncture, a recent systematic review failed to find any studies of sufficient rigor to include in their analysis.[111]

ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER

CASE 89-2

QUESTION 1: K.C., a 27-year-old female adjunct professor in a pharmacy program, comes to a retail pharmacy wanting to fill a prescription for dextroamphetamine IR 10 mg tid #90.

What are the treatment recommendations for an adult with ADHD?

It is estimated that two-thirds of children with ADHD will continue to have significant symptomatology as adults albeit with less severity than in childhood.[11] Often the hyperactivity/impulsivity aspect of the illness becomes less pronounced once the child reaches adolescence, but the symptoms of inattention may persist into adulthood.[6] Even though many of the children with ADHD may no longer satisfy strict diagnostic criteria for ADHD as adults, the severity and persistence of inattentive symptoms can continue to cause considerable social and functional difficulties. One investigation followed 128 children with ADHD for several years and reported that hyperactivity and impulsivity symptoms were seen to decline at a higher rate than inattention symptoms.[6] Other researchers have followed children with ADHD to adulthood by comparing the academic records of control subjects and ADHD adults. The latter had significantly higher rates of repeated grades, tutoring, placement in special classes, and reading disability.[112,113] Children with ADHD will have greater morbidity in psychosocial and educational areas in adulthood compared to adults who did not have ADHD as children.[114] Adults with ADHD have been found to achieve lower socioeconomic status and experience more work difficulties

and more frequent job changes.[115] Adults with ADHD reported more psychologic maladjustment, more speeding violations, and more frequent changes in employment.[116] More adults with ADHD had their driver's licenses suspended, had performed more poorly at work, and had quit or been fired from their job. Adults with ADHD were also more likely to have had multiple marriages.[11]

The diagnostic criteria for ADHD in adults are the same as for children and adolescents (*DSM-5*).[4] However, only five, instead of six as required in children, of either hyperactivity/impulsivity or inattention symptoms must be present for a minimum of 6 months, impairing function in two or more settings. A diagnosis of ADHD in adults also requires evidence that symptoms were present before age 12. One study compared the functional outcomes of adults with ADHD before age 7 with adults, who had the requisite symptoms but lacked conclusive evidence of childhood onset. The investigators found no difference between the two groups in primary outcomes, such as learning disabilities, arrests, motor vehicle accidents, and divorce.[117] Thus, a lack of diagnosis in childhood could simply be that the adult was never assessed for ADHD, not that they didn't fulfill the criteria.

Current treatment recommendations for ADHD in adults continue to support pharmacotherapy as the first-line option for moderate-to-severe symptoms.[33] Although benefits have been noted for psychotherapeutic approaches such as cognitive-behavioral therapy and dialectic behavioral therapy, these interventions are recommended only for adults with mild symptoms or exhibiting suboptimal response to approved medications.[118,119]

A variety of medications have been reported to be beneficial for ADHD in adults, including MPH, dexmethylphenidate, mixed amphetamine salts, lisdexamfetamine, desipramine, bupropion, atomoxetine α_2-agonists, venlafaxine, and modafinil.[94,99,120–127] The stimulants and atomoxetine are FDA approved in adults.[33] In general, the effect sizes for these ADHD medications in adults have been very similar to what has traditionally been reported in children. A meta-analysis of medications for ADHD in adults found that long-

acting stimulants were significantly more effective than nonstimulant drugs, but that the effectiveness of shorter-acting stimulants was comparable to the latter.[9] The authors also noted that lower doses appeared to be more effective for inattention than hyperactivity. For example, doses for IR MPH were more conservative (0.3 mg/kg per dose in adults) when inattention was the predominant feature. In contrast, doses of up to 0.6 mg/kg IR MPH were often necessary to optimally control the behavioral feature of the disorder in children.[128] These MPH doses are consistent with 0.5 to 1.0 mg/kg/day doses found to be effective in children.[121] Mixed amphetamine salts were effective in doses of 20 to 60 mg/day.[122] The effective dose of desipramine was ~150 mg/day.[125] Bupropion was generally dosed at 3 mg/kg/day.[94] The two large studies of atomoxetine used doses that ranged from 60 to 120 mg/day.[125,126] The mean effective dose for modafinil was 207 mg/day.[99]

Treatment with stimulants or atomoxetine has shown improvements in reduced criminality and driving accidents.[129–132]

Case 89-2, Question 2: Before filling the prescription for K.C., the pharmacist reviews it and finds that it is written within 30 days. He also checks the prescription drug–monitoring program in his state and finds that she has filled a prescription for the same drug and directions 25, 28, 54, and 56 days ago at other retail pharmacies. These double-fills are also written by two different physicians. What would be an appropriate response by the pharmacist to K.C.'s request?

As noted above, ADHD symptoms can persist into adulthood for many children. A positive history of either an ADHD diagnosis or untreated symptoms in childhood is required for an adult to be diagnosed with ADHD. However, a number of other conditions can lead to a similar presentation. Complete blood counts, urine toxicology, and head injury must all be evaluated along with psychiatric conditions such as bipolar disorder, anxiety disorders, and major depressive disorder.[133] Also, the possibility of substance-use disorder cannot be ruled out. As with other drugs that have an abuse liability, stimulants can either be abused by the patient or

diverted and sold to those who want to use them for their euphoria-inducing effect instead of helping treat ADHD. There is an increasing amount of data reporting the intermittent use of stimulants by college students for study enhancement and abuse, particularly when mixed with a sedating drug of abuse. Therefore, the pharmacist should consult with the clinician who wrote the prescription alerting him to the recent fill at another pharmacy. It is quite possible that this new prescription is legitimate, but it is also possible that K.C. is misusing the dextroamphetamine herself or diverting them to others. A reevaluation of her diagnosis is necessary. If it is confirmed that the patient does have ADHD, then options would be to switch to a less abusable stimulant such as lisdexamfetamine or MPH transdermal patch. Switching to the nonabusable atomoxetine is recommended because even though these stimulant formulations are less abusable, they are not devoid of abuse risk. Atomoxetine or the non-FDA adult-approved agents such as α_2-agonists or bupropion, venlafaxine, and modafinil will likely be less effective than the stimulant for ADHD but provide a safer abuse-risk possibility.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Bolea-Alamanac B, Fone K, Asherson P, et al. Evidence-based guidelines for the pharmacologic management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. *J Psychopharmacol.* 2014;28(3):179–203. (33)

Canadian Attention Deficit Hyperactivity Disorder Resource Alliance. *Canadian ADHD Practice Guidelines*. 3rd ed. Canadian Attention Deficit Hyperactivity Disorder Resource Alliance; 2011. (35)

Wolraich ML, Hagan JF Jr, Allan C, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics.* 2019;144:e20192528. (34)

Key Websites

American Academy of Child and Adolescent Psychiatry. http://www.aacap.org

National Alliance on Mental Illness. http://www.nami.org

National Institute of Mental Health. http://www.nimh.nih.gov

NIMH website. https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd

COMPLETE REFERENCES CHAPTER 89 ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN, ADOLESCENTS, AND ADULTS

1. Palmer ED, Finger S. An early description of ADHD (inattention subtype): Dr. Alexander Crichton and “mental restlessness” (1798). *Child Psychol Psychiatry Rev*. 2001;6:66–73.
2. Pliszka SR; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46:894–921.
3. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self reports of diagnosed ADHD: a controlled study of 1001 adults in the community. *J Clin Psychiatry*. 2006;67:524–540.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM 5)*. 5th ed. American Psychiatric Association Press; 2013.
5. Obioha O, Adesman A. Pearls, perils, and pitfalls in the assessment and treatment of attention-deficit/hyperactivity disorder in adolescents. *Curr Opin Pediatr*. 2014;26(1):119–126.
6. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry*. 2000;157:816–818.

7. Winterstein AG, Gerhard T, Shuster J, et al. Utilization of pharmacologic treatment in youths with ADHD in Medicaid database. *Ann Pharmacother*. 2008;42:24–31.
8. Doshi JA, Hodgkins P, Kahle J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry*. 2012;51(10):990–1002.
9. Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *J Clin Psychiatry*. 2010;71:754–763.
10. Rosler M, Fischer R, Ammer R, Ose C, Retz W. A randomised, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/hyperactivity disorder [published correction appears in *Eur Arch Psychiatry Clin Neurosci*. 2009;259:36]. *Eur Arch Psychiatry Clin Neurosci*. 2009;259:120–129.
11. Kooij SJJ, Bijlenga D, Salerno L, et al. European consensus statement on diagnosis and treatment of adult ADHD: the European Network Adult ADHD. *BMC Psychiatry*. 2010;10:67.
12. Molina BSG, Flory K, Hinshaw SP, et al. Delinquent behavior and emerging substance in the MTA at 36 months: prevalence, course, and treatment effects. *J Am Acad Child Adolesc Psychiatry*. 2007;46:1028–1040.
13. Wigal SB. Efficacy and safety limitations of attention-deficit hyperactivity disorder in children and adults. *CNS Drugs*. 2009;23(suppl 1):21–31.
14. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry*. 1999;56:1073–1086.
15. Jensen PS, Arnold LE, Swanson JM, et al. 3-year follow-up of the NIMH MTA Study. *J Am Acad Child Adolesc Psychiatry*. 2007;46:989–1002.
16. Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1284–1293.
17. Riddle MA, Yershova K, Lazzaretto D, et al. The preschool attention-deficit/hyperactivity disorder treatment study (PATS) 6-year follow-up. *J Am Acad Child Adolesc Psychiatry*. 2013;52(3):264–278.
18. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder [published correction appears in *Lancet*. 2006;367:210]. *Lancet*. 2005;366:237–248.
19. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163:716–723.
20. Tarver J, Daley D, Sayal K. Attention-deficit hyperactivity disorder (ADHD): an updated review of the essential facts. *Child Care Health Dev*. 2014;40(6):762–774.

21. Faraone SV, Biederman J, Friedman D. Validity of DSM-IV subtypes of attention-deficit/hyperactivity disorder: a family study perspective. *J Am Acad Child Adolesc Psychiatry*. 2000;39:300–307.
22. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention deficit/hyperactivity disorder. *Biol Psychiatry*. 2005;57:1313–1323.
23. Li D, Sham PC, Owen MJ, He L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum Mol Genet*. 2006;15:2276–2284.
24. Friedman LA, Rapoport JL. Brain development in ADHD. *Curr Opin Neurobiol*. 2015;30:106–111.
25. Bush G, Frazier JA, Rauch SL, et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biol Psychiatry*. 1999;45:1542–1552.
26. Johnson S, Marlon N. Preterm birth and childhood psychiatric disorders. *Pediatr Res*. 2011;69(5):11R–18R.
27. Pliszka SR. Comorbidities of attention-deficit/hyperactivity disorder with psychiatric disorder: an overview. *J Clin Psychiatry*. 1998;59(suppl 7):50–58.
28. Weiss G, Hechtman LT. *Hyperactive Children Grow Up: Empirical Findings and Theoretical Considerations*. Guilford Press; 1986.
29. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet*. 2019;51:63–75.
30. Brod M, Pohlman B, Lasser R, Hodgkins P. Comparison of the burden of illness for adults with ADHD across seven countries: a qualitative study. *Health Qual Life Outcomes*. 2012;10(47):1–17.
31. Martin A, Scahill L, Charney DS, Leckman JF, eds. *Pediatric Psychopharmacology: Principles and Practice*. Oxford University Press; 2011:398.
32. Seixas M, Mitre LP, Shams S, et al. Systematic review of national and international guidelines on attention-deficit hyperactivity disorder. *J Psychopharmacol*. 2011;26(6):753–765.
33. Bolea-Alamanac B, Fone K, Asherson P, et al. Evidence-based guidelines for the pharmacologic management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(3):179–203.
34. Wolraich ML, Hagan JF Jr, Allan C, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2019;144:e20192528.
35. Canadian Attention Deficit Hyperactivity Disorder Resource Alliance. *Canadian ADHD Practice Guidelines*. 3rd ed. Canadian Attention Deficit Hyperactivity Disorder Resource Alliance; 2011.
36. Faraone SV, Antshel KM. Towards and evidence-based taxonomy of nonpharmacologic treatments for ADHD. *Child Adolesc Psychiatric Clin*

North Am. 2014;23(4):965–972.
37. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. *J Am Acad Child Adolesc Psychiatry*. 1999;38:503–512.
38. Ramtvedt BE, Røinås E, Aabech HS, Sundet KS. Clinical gains from including both dextroamphetamine and methylphenidate in stimulant trials. *J Child Adolesc Psychopharmacol*. 2013;23(9):597–604.
39. Pliszka SR, Crismon ML, Hughes CW, et al. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2006;45:642–657.
40. Sun Z, Murry DJ, Sanghani SP, et al. Methylphenidate is stereoselectively hydrolyzed by human carboxylesterase CES1A1. *J Pharmacol Exp Ther*. 2004;310(2):469–476.
41. Heal DJ, Pierce DM. Methylphenidate and its isomers. Their role in the treatment of attention-deficit hyperactivity disorder using a transdermal delivery system. *CNS Drugs*. 2006;20(9):713–738.
42. Anderson VR, Scott LJ. Methylphenidate transdermal system in attention-deficit hyperactivity disorder in children. *Drugs*. 2006;66(8):1117–1126.
43. Gonzalez MA, Campbell D, Rubin J. Effects of application to two different skin sites on the pharmacokinetics of transdermal methylphenidate in pediatric patients with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2009;19(3):227–232.
44. Daytrana. Prescribing information. Noven Pharmaceuticals; 2015.
45. Childress AC, Komolova M, Sallee FR. An update on the pharmacokinetic considerations in the treatment of ADHD with long-acting methylphenidate and amphetamine formulations. *Expert Opin Drug Metab Toxicol*. 2019; 15(11):937–974.
46. Hutson PH, Pennick M, Secker R. Preclinical pharmacokinetics, pharmacology and toxicology of lisdexamfetamine: a novel d-amphetamine pro-drug. *Neuropharmacology*. 2014;87:41–50.
47. Markowitz JS, Patrick KS. Pharmacokinetic and pharmacodynamic drug interactions in the treatment of attention-deficit hyperactivity disorder. *Clin Pharmacokinet*. 2001;40(10):753–772.
48. Heal DK, Smith SL, Gosden J, et al. Amphetamine, past and present—a pharmacological and clinical perspective. *J Psychopharmacol*. 2013;27:479–496.
49. Faraone SV. The pharmacology of amphetamine and methylphenidate: relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neurosci Biobehav Rev*. 2018;87:255–270.
50. Vyvanse. Prescribing information. Shire US; 2015.
51. Pennick M. Absorption of lisdexamfetamine dimesylate and its enzymatic conversion to d-amphetamine. *Neuropsychiatr Dis Treat*. 2010;6:317–327.

52. Steer C, Froelich J, Soutullo CA, et al. Lisdexamfetamine dimesylate. A new therapeutic option for attention-deficit hyperactivity disorder. *CNS Drugs*. 2012;26:691–705.
53. Melmed RD. Drug delivery systems for ADHD: US Food and Drug Administration (FDA)-approved stimulant and nonstimulant medications for ADHD. *Medscape Psychiatry*. 2005;10(2):2–35.
54. Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2000;39(5):619–626.
55. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics*. 2004;113:762–769.
56. Spencer TJ, Biederman J, Harding M, O'Donnell D, Faraone SV, Wilens TE. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? *J Am Acad Child Adolesc Psychiatry*. 1996;35:1460–1469.
57. Rapport MD, Moffitt C. Attention deficit/hyperactivity disorder and methylphenidate: a review of height/weight, cardiovascular, and somatic complaint side effects. *Clin Psychology Rev*. 2002;22(8):1–17.
58. Martins S, Tramontina S, Polanczyk G, Eizirik M, Swanson JM, Rohde LA. Weekend holidays during methylphenidate use in ADHD children: a randomized clinical trial. *J Child Adolesc Psychopharmacol*. 2004;14(2):195–205.
59. Rappley M, Moore JW, Dokken D. ADHD drugs and cardiovascular risk. *N Engl J Med*. 2006;354:2296–2298.
60. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med*. 2011;365(20):1896–1904.
61. Stiefel G, Besag FMC. Cardiovascular effects of methylphenidate, amphetamines and atomoxetine in the treatment of attention-deficit hyperactivity disorder. *Drug Saf*. 2010;33(10):821–842.
62. Martinez-Raga J, Knecht C, Szerman N, Martinez MI. Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. *CNS Drugs*. 2013;27:15–30.
63. Hammerness PG, Perrin JM, Shelley-Abrahamson R, Wilens TE. Cardiovascular risk of stimulant treatment in pediatric attention deficit/hyperactivity disorder: update and clinical recommendations. *J Am Acad Child Adolesc Psychiatry*. 2011;50(10):978–990.
64. Vetter VL, Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder. *Circulation*. 2008;117(18):2407–2423.
65. Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications of ADHD using meta-analysis. *Med Gen Med*. 2006;8:4.

66. Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics*. 2001;108:E83.
67. Michelson D, Allen AJ, Busner J, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *Am J Psychiatry*. 2002;159:1896–1901.
68. Wigal SB, McGough JJ, McCracken JT, et al. A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. *J Atten Disord*. 2005;9:275–289.
69. Gibson AP, Bettinger TL, Patel NC, Crismon ML. Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother*. 2006;40:1134–1142.
70. Dittman RW, Cardo E, Nagy P, et al. Treatment response and remission in a double-blind, randomized, head-to-head study of lisdexamfetamine dimesylate and atomoxetine in children and adolescents with attention-deficit hyperactivity disorder. *CNS Drugs*. 2014;28:1059–1069.
71. Stuhec M, Munda B, Svab V, Locatelli I. Comparative efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion and methylphenidate in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis with focus on bupropion. *J Affect Disord*. 2015;178:149–159.
72. Strattera (Atomoxetine). Package insert. Eli Lilly and Company; 2011.
73. Eiland LS, Guest AL. Atomoxetine treatment of attention-deficit/hyperactivity disorder. *Ann Pharmacother*. 2004;38:86–90.
74. Garnock-Jones KP, Keating GM. Atomoxetine. A review of its use in attention-deficit hyperactivity disorder in children and adolescents. *Pediatr Drugs*. 2009;11(3):203–226.
75. Bangs ME, Tauscher-Wisniewski S, Polzer J, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *J Am Acad Child Adolesc Psychiatry*. 2008;47(2):209–218.
76. Findling RL, Candler SA, Nasser AF et al. Viloxazine in the management of CNS disorders: a historical overview and current status. *CNS Drugs*. 2021;35:643–653.
77. Yu C, Garcia-Olivares J, Candler S, et al. New insights into the mechanism of action of viloxazine: serotonin and norepinephrine modulating properties. *J Exp Pharmacol*. 2020;12:285–300.
78. Quelbree. Prescribing information. Supernus Pharmaceuticals Inc; 2021.
79. Nasser AF, Liranso T, Adewole T, et al. A phase III, randomized, placebo-controlled trial to assess the efficacy and safety of once-daily SPN-812 (viloxazine extended-release) in the treatment of attention-

deficit/hyperactivity disorder in school-age children. *Clin Ther*. 2020;42:1452–1466.
80. Perault MC, Griesemann E, Bouquet S, et al. A study of the interaction of viloxazine with theophylline. *Ther Drug Monit*. 1989;11:520–522.
81. American Academy of Pediatrics. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics*. 2001;108:1033–1044.
82. Hirota T, Schwartz S, Correll CU. Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):153–173.
83. Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2009;48(9):884–893.
84. Osland ST, Steeves TDL, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (review). *Cochrane Database Syst Rev*. 2018;6:CD007990.
85. Cleassens AJ, Risler LJ, Eyal S, Shen DD, Easterling TR, Hebert MF. CYP2D6 mediates 4-hydroxylation of clonidine in vitro: implication for pregnancy-induced changes in clonidine clearance. *Drug Metab Disp*. 2010;39(9):1393–1396.
86. Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology*. 2002;58:527–536.
87. Chadehumbe MA, Greydanus DE, Feucht C, Patel DR. Psychopharmacology of tic disorders in children and adolescents. *Pediatr Clin North Am*. 2011;58:259–272.
88. Kaplan G, Newcorn JH. Pharmacotherapy for child and adolescent attention-deficit hyperactivity disorder. *Psychiatr Clin North Am*. 2011;58:99–120.
89. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics*. 2003;111:179–185.
90. Cunill R, Castells X, Tobias A, Capellà D. Pharmacological treatment of attention deficit hyperactivity disorder with co-morbid drug dependence. *J Psychopharm*. 2015;29(1):15–23.
91. McCabe SE, Knight JR, Teter CJ, Wechsler H. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. *Addiction*. 2005;99:96–106.
92. Webb JR, Valasek MA, North CS. Prevalence of stimulant use in a sample of US medical students. *Ann Clin Psychiatry*. 2013;25(1):27–32.
93. Simeon JG, Ferguson HB, Van Wyck Fleet J. Bupropion effects in attention deficit and conduct disorders. *Can J Psychiatry*. 1986;31:581–585.

94. Kuperman S, Perry PJ, Gaffney GR, et al. Bupropion SR vs. methylphenidate vs. placebo for attention deficit hyperactivity disorder in adults. *Ann Clin Psychiatry*. 2001;13:129–134.
95. Barrickman LL, Perry PJ, Allen AJ, et al. Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1995;34:649–657.
96. Conners CK, Casat CD, Gualtieri CT, et al. Bupropion hydrochloride in attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1314–1321.
97. Davidson J. Seizures and bupropion: a review. *J Clin Psychiatry*. 1989;50:256–261.
98. Biederman J, Swanson JM, Wigal SB, et al. A comparison of once-daily and divided doses of modafinil in children with attention-deficit/hyperactivity disorder: a randomized, double-blind, and placebo-controlled study. *J Clin Psychiatry*. 2006;67:727–735.
99. Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. *J Child Adolesc Psychopharmacol.* 2000;10:311–320.
100. Modafinil (CEP-1538) tablets: supplemental NDA20–717/S-019 ADHD indication. Accessed July 19, 2017. https://www.acessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf
101. Nigg JT, Holton K. Restriction and elimination diets in ADHD treatment. *Child Adolesc Psychiatr Clin North Am*. 2014;23:937–953.
102. Stevens LJ, Kuczek T, Burgess JR, Hurt E, Arnold LE. Dietary sensitivities and ADHD symptoms: thirty-five years of research. *Clin Pediatr*. 2011;50(4):279–293.
103. Millichap JG, Yee MM. The diet factor in attention-deficit/hyperactivity disorder. *Pediatrics*. 2012;129:330–337.
104. Marcason W. Can dietary intervention play a part in the treatment of attention deficit and hyperactivity disorder? *J Am Diet Assoc*. 2005;105:1161–1162.
105. Hurt EA, Arnold LE. An integrated dietary/nutritional approach to ADHD. *Child Adolesc Psychiatr Clin North Am*. 2014;23:955–964.
106. Bloch MH, Qawasmi A. Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2011;50(10):991–1000.
107. Elshorbagy HH, Barseem NF, Abdelghani WE, et al. The impact of vitamin D supplementation on attention-deficit hyperactivity disorder in children. *Ann Pharmacother*. 2018;52:623–631.
108. Robberecht H, Verlaet AAJ, Breynaert A, et al. Magnesium, iron, zinc, copper and selenium status in attention-deficit/hyperactivity disorder (ADHD). *Molecules*. 2020;25:4440.

109. Skokauskas N, McNicholas F, Masaud T, Frodl T. Complementary medicine for children and young people who have attention deficit hyperactivity disorder. *Curr Opin Psychiatry*. 2011;24:291–300.
110. Krisanaprakornkit T, Ngamjarus C, Witoonchart C, Piyavhatkul N. Meditation therapies for attention deficit/hyperactivity disorder (ADHD). *Cochrane Database Syst Rev*. 2010;(6):CD006507. doi:10.1002/14651858.CD006507.pub2
111. Li S, Yu B, Zhou D, et al. Acupuncture for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev*. 2011;(4):CD007839.
112. Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry*. 1993;150:1792–1798.
113. Biederman J, Faraone SV, Spencer T, Wilens T, Mick E, Lapey KA. Gender differences in a sample of adults with attention deficit hyperactivity disorder. *Psychiatry Res*. 1994;53:13–29.
114. Biederman J, Petty CR, Woodworth KY, et al. Adult outcome of attention-deficit/hyperactivity disorder: a controlled 16-year follow-up study. *J Clin Psychiatry*. 2012;73(7):941–950.
115. Borland BL, Heckman HK. Hyperactive boys and their brothers: a 25-year follow-up study. *Arch Gen Psychiatry*. 1976;33:669–675.
116. Murphy K, Barkley RA. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. *Compr Psychiatry*. 1996;37:393–401.
117. Faraone SV, Biederman J, Doyle A, et al. Neuropsychological studies of late onset and subthreshold diagnoses of attention-deficit/hyperactivity-disorder. *Biol Psychiatry*. 2006;60:1081–1087.
118. Safren SA, Otto MW, Sprich S, Winett CL, Wilens TE, Biederman J. Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. *Behav Res Ther*. 2005;43:831–842.
119. Hesslinger B, Tebartz van Elst L, Nyberg E, et al. Psychotherapy of attention deficit hyper-activity disorder in adults—a pilot study using a structured skills training program. *Eur Arch Psychiatry Clin Neurosci*. 2002;252:177–184.
120. Spencer T, Wilens T, Biederman J, Faraone SV, Ablon JS, Lapey K. A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. *Arch Gen Psychiatry*. 1995;52:434–443.
121. Spencer TJ, Adler LA, McGough JJ, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007;61:1380–1387.
122. Weisler RH, Biederman J, Spencer TJ, et al. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. *CNS Spectr*. 2006;11:625–639.

123. Adler LA, Goodman DW, Kollins SH, et al. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;69:1364–1373.
124. Wilens TE, Biederman J, Prince J, et al. Six-week, double-blind, placebo-controlled study of desipramine for adult attention deficit hyperactivity disorder. *Am J Psychiatry*. 1996;153:1147–1153.
125. Spencer T, Biederman J, Wilens T, et al. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. *Am J Psychiatry*. 1998;155:693–695.
126. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biol Psychiatry*. 2003;53:112–120.
127. Hedges D, Reimherr FW, Rogers A, Strong R, Wender PH. An open trial of venlafaxine in adult patients with attention deficit hyperactivity disorder. *Psychopharmacol Bull*. 1995;31(4):779–783.
128. Sprague RL, Sleator EK. Methylphenidate in hyperkinetic children: differences in dose effects on learning and social behavior. *Science*. 1977;198:1274–1276.
129. Lichtenstein P, Halldner L, Zetterqvist J, et al. Medication for attention deficit-hyperactivity disorder and criminality. *N Engl J Med*. 2012;367:2006–2014.
130. Verster JC, Bekker EM, de Roos M, et al. Methylphenidate significantly improves driving performance of adults with attention deficit hyperactivity disorder: a randomized crossover trial. *J Psychopharmacol*. 2008;22:230–237.
131. Gobbo MA, Louza MR. Influence of stimulant and non-stimulant drug treatment on driving performance in patients with attention deficit hyperactivity disorder: a systematic review. *Eur Neuropsychopharmacol*. 2014;24:1425–1443.
132. Sobanski E, Sabljic D, Alm B, et al. Driving performance in adults with ADHD: results from a randomized, waiting list controlled trial with atomoxetine. *Eur Psychiatry*. 2013;28:379–385.
133. McGough JJ, Barkley RA. Diagnostic controversies in adult attention deficit hyperactivity disorder. *Am J Psychiatry*. 2004;161:1948–1956.

90

Substance Use Disorders

Swati Betharia and Michael C. Angelini

CORE PRINCIPLES		CHAPTER CASES
1	Substance use disorder is a chronic disease with progressive deterioration of psychological and physiologic activity secondary to the habitual use of a drug. This complex disease disrupts many, if not all, aspects of an individual's life; therefore, multimodal treatment is necessary.	**Case 90-1 (Question 1) Case 90-11 (Question 1), Table 90-1**

CORE PRINCIPLES		CHAPTER CASES
2	Opioid misuse includes illicit drugs, such as heroin, and the nonmedical use of prescription pain relievers. Opioid withdrawal is characterized as a flulike syndrome, involving nausea, vomiting, sweats, diarrhea, pain, and elevations in pulse and blood pressure. The full agonist methadone, partial agonist buprenorphine, and antagonist naltrexone all can be used as maintenance therapy to reduce relapses. Treatment considerations during pregnancy consist of fetal risks if the mother goes into opiate withdrawal or if the mother relapses into addictive behavior. Neonatal abstinence syndrome occurs in the newborn if the mother has been maintained on methadone or buprenorphine.	**Case 90-2 (Question 1) Case 90-3 (Question 1) Case 90-4 (Question 1) Case 90-5 (Questions 1, 2), Table 90-2**

CORE PRINCIPLES		CHAPTER CASES
3	Sedative-hypnotic drugs of abuse include benzodiazepines, barbiturates, some skeletal muscle relaxants, such as carisoprodol, and γ-hydroxybutyrate acid (GHB). Withdrawal symptoms, similar to those of alcohol withdrawal, may include tremors, insomnia, anxiety, elevations in pulse and blood pressure, seizures, and hallucinations, and may be potentially life-threatening. In clinical practice, three general medication strategies are used for withdrawing patients from sedative-hypnotics: gradual tapering of the drug of abuse, substituting and gradually tapering phenobarbital, and substituting and gradually tapering a long-acting benzodiazepine.	**Case 90-6 (Question 1), Table 90-3**

CORE PRINCIPLES		CHAPTER CASES
4	Major central nervous system (CNS) stimulants of abuse include cocaine and amphetamines. These drugs are associated with serious acute and chronic adverse effects, such as hyperthermia, paranoia, psychosis, hypertension, arrhythmias, myocardial infarction, seizures, and strokes. Withdrawal from stimulants is not associated with severe symptoms. Primarily, withdrawal consists of fatigue and hypersomnolence. There is currently no U.S. Food and Drug Administration (FDA)-approved treatment for withdrawal or maintenance treatment of stimulant use disorder.	**Case 90-7 (Questions 1, 2)**
5	The use of hallucinogens, including lysergic acid diethylamide (LSD), psilocybin, mescaline, and 3,4-methylenedioxymethamphetamine (MDMA), may result in psychological, but not physical, dependency. Adverse reactions during intoxication, such as anxiety, paranoia, and fear, may necessitate benzodiazepine or antipsychotic therapy, but are best managed using a “talk-down” method.	**Case 90-8 (Questions 1–3)**

CORE PRINCIPLES		CHAPTER CASES
6	Marijuana is a widely used substance. The withdrawal syndrome is generally mild, characterized by anxiety, depression, irritability, and insomnia, and does not require treatment. Chronic use has been shown to result in increased risks of car accidents, pulmonary complications, psychosis, and anxiety.	**Case 90-9 (Questions 1–3)**
7	Alcohol use disorder is defined by acute and chronic alcohol use. It can result in toxicity, withdrawal, and addiction. Alcohol toxicity is an acute, life-threatening condition that requires aggressive medical attention. Symptoms include a strong smell of alcohol, depressed and shallow respiration, and cardiac arrest. Management generally consists of respiratory support and a thorough diagnostic evaluation to rule out coingestion of other drugs or other underlying medical conditions that may also need attention.	**Case 90-10 (Question 1), Tables 90-4, 90-5**

CORE PRINCIPLES		CHAPTER CASES
8	Alcohol withdrawal is the neurobiologic syndrome associated with increased tolerance or physical dependence resulting from chronic alcohol consumption. This syndrome results in a continuum of signs or symptoms including paresthesias, headache, nausea, anxiety, shaking, increased heart rate and blood pressure, and seizures. Symptom-triggered assessment and treatment of alcohol withdrawal is extremely important because untreated withdrawal can result in death. Treatment may be complicated not only by the physical or cognitive deterioration that can occur but also by the lack of attention to other serious medical or psychological conditions that could be contributing to, or resulting from, chronic alcohol use. Adjunctive treatments including fluid (eg, normal saline solution), nutritional (eg, thiamine, folic acid, and multivitamins), and electrolyte (eg, magnesium, potassium) replacement should also be initiated to address the physiologic consequences of chronic alcohol use.	**Case 90-10 (Questions 2–4), Table 90-6**

CORE PRINCIPLES		CHAPTER CASES
9	Chronic alcohol use disorder (alcohol dependence) is a lifelong relapsing disorder that consists of signs of alcohol abuse (continued drinking despite alcohol-related physical, social, psychological, or occupational problems, or drinking in dangerous situations, such as while driving) to the extent that the person also experiences at least three of the following seven symptoms: neglect of other activities, excessive use of alcohol, impaired control of alcohol consumption, persistence of alcohol use, large amounts of time spent in alcohol-related activities, withdrawal symptoms, and tolerance of alcohol. Approved pharmacotherapies include disulfiram, naltrexone (tablets and injection), and acamprosate. The best option is determined by many factors such as home support, medical comorbidities, and concomitant medications.	**Case 90-11 (Question 1), Tables 90-4, 90-6**

INTRODUCTION

Substance Use Disorder

Physical dependence occurs when repeated administration of a drug causes an altered physiologic state (neuroadaptation). After

neuroadaptation, a characteristic set of withdrawal symptoms occurs when the drug is abruptly discontinued. Psychological addiction or psychological dependence refers to a "maladaptive pattern of substance use leading to clinically significant impairment or distress."[1] Habituation is a state of either chronic or periodic drug use characterized by a desire (but not a compulsion) to continue using the drug, no tendency to increase the dose, and an absence of physical symptoms despite some degree of psychological dependence. A different clinical syndrome is associated with each drug, but all involve a chronic process with progressive deterioration of psychological and physiologic activity secondary to the habitual use of a drug. Addiction is not a diagnosis, but is defined by the American Society of Addiction Medicine as a chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits has biologic, psychological, social, and spiritual effects. There is a pathologic pursuit of the substance with an inability to abstain, loss of control, craving, and diminished recognition of the intensity of the problem. It is cyclic, with periods of relapse and remission. Without treatment, it is significantly disabling and will result in premature death. Addiction is frequently used as a descriptor of the most disabling and intense form of a substance use disorder.[2] Although the neurochemistry of the addictive process is possibly the same for all drugs, the psychosocial and pharmacokinetic aspects vary from drug to drug. Evidence, consistent with models established for alcoholism, indicates that genetically inherited traits may result in expression of addictive disease when the person is exposed to certain drugs and other habituating psychic stimuli.[3]

CASE 90-1

QUESTION 1: R.L., age 26, was recently arrested for possession and driving under the influence (DUI) of oxycodone. This is his second DUI offense in the past year. R.L. does not use oxycodone daily, but admits to weekly use.

Does R.L. meet the criteria for a diagnosis of a substance use disorder?

The *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (*DSM-5*) cites criteria for substance-related disorders and divides them into two groups: the substance use disorders (**Table 90-1**) and the substance-induced disorders (intoxication, withdrawal, and others).[1] In 2018, an estimated 53.2 million persons age 12 or older were classified as current illicit drug users.[4]

Table 90-1

American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, Criteria for Substance Use Disorders

A. A problematic pattern of use of an intoxicating substance not able to be classified within the alcohol; caffeine; cannabis; hallucinogen (phencyclidine and others); inhalant; opioid; sedative, hypnotic, or anxiolytic; stimulant; or tobacco categories and leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. The substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control the use of the substance.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
4. Craving or a strong desire or urge to use the substance
5. Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use
7. Important social, occupational, or recreational activities are given up or reduced because of use of the substance.
8. Recurrent use of the substance in situations in which it is physically hazardous
9. Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect

b. A markedly diminished effect with continued use of the same amount of the substance

11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for other (or unknown) substance
    b. The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

Reprinted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. © 2013 American Psychiatric Association. All Rights Reserved.

Pharmacologic treatment is only one aspect of the management of substance use disorders. Treatment of withdrawal (when needed depending on the chemical of abuse) is the first step in management and should be followed by individualized, psychosocial treatment that is effective in the least restrictive and most cost-effective manner. A strong therapeutic alliance between care provider and patient based on a supportive, empathic, nonjudgmental, and clinically appropriate relationship is predictive of successful therapy outcomes. Substance use disorder is a complex disease that disrupts many, if not all, aspects of an individual's life. Therefore, multimodal treatment is necessary. Psychosocial therapies that may or may not include pharmacologic agents consist of individual as well as group counseling, cognitive-behavioral therapies (CBTs; learning triggers for use, new coping mechanisms, and relapse prevention), motivational enhancement therapies, family counseling, and voucher-based reinforcement therapy, among others. These therapies are often augmented with involvement in support groups, such as the 12-step programs.[3]

R.L. has a pattern of oxycodone use in situations in which it is physically hazardous, as well as two arrests in the past year for DUI. R.L. meets the *DSM-5* criteria for substance use disorder.

OPIOIDS

Abuse of opioids includes illicit drugs, such as heroin, and the nonmedical use of prescription pain relievers. According to the Drug Enforcement Administration (DEA), prescription pain relievers appear to be increasingly diverted from legitimate and illegitimate sources of supply via the Internet.[5] The 2018 National Survey on Drug Use and Health reports, among persons age 12 years or older, that there are 9.9 million nonmedical use of pain relievers.[4] The non–FDA-approved opiate heroin is produced in four major source areas, South America, Mexico, Southeast Asia, and Southwest Asia. Mexico has been the predominant supplier to the west coast of the United States and is expanding distribution in eastern U.S. markets because South American production has decreased.[6] Mexican heroin black tar is potent, 40% to 80% pure, but contains more plant impurities than does the white powder refined heroin from Asia or South America.[7] The purity of available heroin enables a new, younger user population, who can smoke or snort this high-purity heroin and avoid the stigma and hazards associated with needle use. As the substance use disorder intensifies and the user's "habit" (amount used daily) increases, the user will often begin injecting the drug. The Centers for Disease and Prevention (CDC) estimates there are roughly 900,000 persons who have used heroin in the United States in 2020. The 2018 National Survey on Drug Use and Health found that usage of heroin was higher than that reported between 2000 and 2008, but similar to that in more recent years.[4] Some prescription opioid abusers will eventually switch to using heroin, because it is less expensive.

Opioid Use Disorder

Physical dependence occurs in any patient after a few days of continuous administration of an opioid. In the management of acute pain, opioid dependence is generally not clinically significant because the patient is tapered off opioid analgesics naturally because the pain condition resolves. If the opioid is abruptly stopped, the patient may experience withdrawal symptoms; however,

the intensity of those symptoms varies depending on the individual's physiology, as well as the dose and duration of use of the opioid. Although the exact dose and duration of opioid administration required to produce clinically significant physical dependence is not known, higher doses and longer times of administration correlate with more severe symptoms of withdrawal on cessation of opioid use.

Physical dependence is defined as a neurobiologic adaptation that occurs with chronic exposure, and occurs with many drug classes regardless of whether they have an abuse potential (eg, β-blockers, steroids, and selective serotonin reuptake inhibitors [SSRIs]). Physical dependence and tolerance (the need for increasing doses to achieve the initial effects of the drug) can occur in the setting of substance use disorder, but are also expected, nonpathologic sequelae of chronic opioid therapy.

Most studies evaluating the occurrence of opioid use disorder resulting from the therapeutic treatment of pain have concluded that the risk is low.[8] Historically, a much greater problem has been the undertreatment of pain. Yet, people at risk environmentally or predisposed genetically for substance use disorder may have their first exposure through a legitimate, therapeutically dosed prescription of an opiate for an acute pain syndrome. This then progresses to an inappropriate use of the opiate and resultant substance use disorder. Thus, pain management with opiates requires a baseline risk management assessment and careful monitoring (see Chapter 55, Pain and Its Management).

Certain pharmacologic properties, such as high potency, rapid onset and shorter duration of action, and water solubility, may increase the likelihood of abuse of that medication. Although all opioids have some abuse liability, some are intrinsically more abusable than are others. For example, the controlled-release formulations have been promoted as less likely to cause substance use disorder than are their immediate-release counterparts, because some of the reinforcing properties such as multiple peaks and troughs are reduced. When tablets, such as OxyContin®, are crushed, however, the drug's controlled-release properties are

compromised, and the result is much higher dosages than what is available in the immediate-release formulation tablets. Despite the manufacturer's attempts at altering the formulation of OxyContin® to make it harder to tamper with, this product can still be abused. Mixed agonist–antagonist opioids (pentazocine, nalbuphine, butorphanol, and buprenorphine) have less potential for misuse than do the pure μ agonists (eg, morphine, hydromorphone, and oxycodone); however, misuse of all has been observed.[8] Other options to reduce diversion and misuse are formulary management strategies that help the clinician limit opiate prescriptions.[9,10] In total, the best method of reducing this problem is a combination of psychosocial therapy, pharmacotherapy, and policy.

The term *pseudoaddiction* has been coined to describe the inaccurate interpretation of certain "drug-seeking behaviors" in patients who are inadequately treated for pain.[8] Their preoccupation actually reflects a need for pain relief, but is erroneously interpreted as a severe substance use disorder (addiction).

Medical Complications

The common practice of sharing needles and syringes between friends has resulted in transmission of various infectious diseases. Chief among those is viral hepatitis, specifically the hepatitis C virus (HCV). According to the CDC, in the United States, human immunodeficiency virus (HIV) infection caused by injection drug use had an overall prevalence of 4% in 2018.[11] Other infectious diseases such as syphilis, tetanus, botulism, and malaria can be transmitted in a similar manner, and should be considered when evaluating these patients. When heroin is prepared for self-administration, cotton is used as a filter to trap adulterants; thus, some of the drug remains trapped in the cotton. These crude filters are saved, and when money or drug availability is poor, water or other solvents are added to the "old cottons" to extract any remaining drug for intravenous (IV) use. "Cotton fever" is an acute febrile reaction. The onset is within 30 minutes of injection, with shaking chills, diaphoresis, postural

hypotension, tachycardia, and low-grade fever. These symptoms are initially suggestive of sepsis, but most of the symptoms resolve without treatment in 2 to 4 hours, with complete recovery in 1 day. The causal agent is probably *Pantoea* (formerly *Enterobacter*) *agglomerans*, via a heat-stable endotoxin.[12] Cotton and cotton plants are heavily colonized with *P. agglomerans*.[13] IV drug users will often use the term *cotton fever* to describe any short-term illness characterized by fever, chills, aches, and pains.[14]

Opioid Toxicity/Overdose

CASE 90-2

Question 1: T.F., a 21-year-old male, was found unconscious after an alleged "OD" (overdose) on heroin. He had a decreased respiratory rate of 4 breaths/minute, cyanosis, symmetrically "pinned" (maximally miotic or pinpoint) pupils, and a slightly decreased blood pressure, 117/72 mm Hg. He has one needle puncture wound and several old needle marks and healed scars in the antecubital fossa area.

What is the immediate treatment of choice for this patient?

Immediate treatment includes airway management, cardiorespiratory support, and opioid reversal with naloxone. Naloxone is a full opioid competitive antagonist that rapidly reverses the respiratory depression and hypotension associated with OD. The preferred route of administration is IV; if access cannot be gained, it may be given via the intramuscular (IM), subcutaneous (SC), or intranasal route, or by endotracheal tube. Intranasal use of naloxone by first responders and friends or family members of those who have overdosed has shown to have saved lives.[15–17]

Initial IV administration of 0.2 to 0.4 mg naloxone should be slow, and should be discontinued if T.F. responds. It is not necessary to precipitate opioid withdrawal symptoms; the end point of naloxone therapy is a relative stabilization of the patient's vital signs. A naloxone-precipitated, sudden-onset withdrawal syndrome is more severe than are the symptoms produced by abstinence alone.

Repetitive doses should be given if the patient remains unresponsive, up to a maximal dose of 10 mg of naloxone.[15] If the patient still has not responded, the diagnosis of opioid OD should be reconsidered.[15]

The duration of action of naloxone ranges from 20 to 60 minutes, depending on the dose and route of administration. Treatment of the methadone-overdosed patient will require serial dosing of naloxone every 20 to 60 minutes because the toxic effects of this long-acting opiate recur.[15] The patient must be carefully observed after the termination of naloxone therapy to detect any reappearance of opioid intoxication. An IV infusion of naloxone may be appropriate if high doses are needed or if the patient has recurrent respiratory depression.

Treatment of Opioid Withdrawal Syndrome

Opioid Withdrawal

CASE 90-3

QUESTION 1: D.J. arrives at the detoxification clinic 10 hours after his last dose of heroin. He is sweating and shaking and keeps yawning. His pulse is 92 and his blood pressure is 130/86 mm Hg. He is a 28-year-old who has been injecting two "quarter bags" ($25 worth) of heroin daily for about a month. He explains he began smoking the heroin, but has now progressed to injecting it. D.J. developed a "big habit" (tolerance developed, and his daily requirement of drug to maintain euphoria had increased). He could not afford his daily use. When he tried stopping, his use abruptly became "dope sick" (typical heroin withdrawal symptoms).

What withdrawal symptoms would D.J. experience and what treatment options would be available for treatment of his opiate withdrawal?

Abstinence precipitated a withdrawal syndrome in D.J.; therefore, he is physically dependent on heroin. The powerful ability of the drug to rapidly alleviate withdrawal symptoms results in reinforcement to continue using the drug. D.J.'s ongoing desire to continue using heroin despite his inability to afford it and his all-day hustling

constitutes a psychological dependence on heroin. Noticeable opioid physical dependence is highly variable, but it is assumed that the potential for an abstinence syndrome exists after repeated administration for only a few days.[2,18]

Six to 12 hours after the last dose of morphine or heroin (diacetylmorphine), patients who are physically dependent will experience symptoms of anxiety, hyperactivity, restlessness, and insomnia with yawning, sialorrhea, rhinorrhea, and lacrimation. There may also be profuse diaphoresis with concurrent shaking chills and pilomotor activity, resulting in waves of gooseflesh of the skin (thus, the term *cold turkey*). Anorexia, nausea, vomiting, abdominal cramps, and diarrhea may occur. Severe back pain may accompany muscle spasms that cause kicking movements ("kicking the habit"). These symptoms are most severe 48 to 72 hours after the last opioid dose. D.J. is exhibiting typical heroin withdrawal symptoms, and supportive therapy would be appropriate.

During withdrawal, the heart rate and blood pressure may be elevated. Inadequate nutrition and hydration, combined with vomiting, sweating, and diarrhea, can result in marked weight loss, dehydration, ketosis, and acid–base imbalance. Rarely, cardiovascular collapse has occurred during the peak phase of opiate withdrawal. The more dramatic symptoms of heroin withdrawal subside after 7 to 14 days of abstinence even without treatment; however, a return to complete physiologic equilibrium may require months or longer.[2,3]

The character, severity, and time course of withdrawal symptoms that appear when an opioid drug is discontinued depend on many factors, including the particular opioid, total daily dose, interval between doses, duration of use, and the health and personality of the user. Unlike the withdrawal symptoms from sedative-hypnotic drugs, opioid withdrawal symptoms are seldom life-threatening.

Physiologic withdrawal symptoms from all opioid drugs are qualitatively similar but quantitatively different in onset, duration, and severity. Opioids with shorter durations of action tend to produce brief, intense abstinence syndromes, whereas those eliminated from

the body at much slower rates produce prolonged but milder withdrawal syndromes.

Treatment options for detoxification usually involve either an abrupt cessation of the opioid with supportive nonopioid pharmacotherapeutic options or opioid substitution. Currently, methadone and buprenorphine are FDA approved for the opiate substitution indications. The nonopiate approach involves symptomatic treatment of withdrawal. The mainstay of this approach is the α_2-agonist clonidine. A third approach uses rapid detoxification precipitated by an opioid antagonist under general anesthesia.[2,18]

METHADONE DETOXIFICATION

Methadone is a synthetic oral opiate agonist with a prolonged duration of action of 12 to 24 hours. Pharmacologically, it is qualitatively identical to morphine and other opioid analgesics. Methadone detoxification involves stabilizing the patient on a daily methadone dose that is determined by the patient's response based on objective symptoms of withdrawal. This may involve the use of standard rating scales for withdrawal, such as the Clinical Opiate Withdrawal Scale.[19] Initially, methadone may be given in 5-mg increments up to a total of 10 to 20 mg during the first 24 hours.[19] Larger methadone doses (ie, a 20-mg starting dose) may be required for patients with larger habits. If initial withdrawal symptoms persist 2 to 4 hours after initial dose administration, the dose can be supplemented with an additional 5 to 10 mg. Federal regulations allow a maximum of 40 mg as an initial dose unless a program physician documents that 40 mg was insufficient to suppress opioid withdrawal symptoms.[20] Once a stabilizing dose has been reached (usually 40–60 mg/day, but may be as high as 120 mg/day), methadone is tapered by 20% a day for inpatients or 5% a day for outpatients.[15,19,20] Studies have suggested that slow tapers are associated with better outcomes. The duration of the taper varies, but a period of 3 to 4 weeks is generally used. The gradual taper may last as long as 6 months. The most common side effects of methadone are constipation, sweating, and sexual dysfunction.[15,19] A

Cochrane review of studies comparing methadone tapers with other detoxification methods (adrenergic agonists and other opioid agonists) found that programs vary widely in design, duration, and treatment objectives, but overall the effectiveness of the treatments was similar.[21] A reasonable starting dose of methadone would be 20 mg orally. An additional 5 to 10 mg could be administered after 2 to 4 hours for persistent withdrawal symptoms. The daily dose should be titrated upward every third day by 10 mg until stabilized on a methadone dose of 60 mg/day.

BUPRENORPHINE DETOXIFICATION

Buprenorphine, a synthetic partial opioid agonist, was approved by the FDA in October 2002 for the treatment of opioid dependence. It is a partial agonist at mu receptors, and in opioid-dependent patients, it prevents withdrawal symptoms. Because of its partial effects, it produces maximal “ceiling” analgesia with sublingual doses of 24 to 32 mg, a dosage equivalent to ~60 to 70 mg of oral methadone. Buprenorphine is associated with a milder withdrawal syndrome compared with full opioid agonists.[22]

Because buprenorphine is a Schedule III medication, it can be prescribed in an office-based setting under the Drug Addiction Treatment Act of 2000. The film and tablets contain buprenorphine hydrochloride alone or in combination with naloxone. The naloxone is poorly absorbed orally, and its presence in the combination tablets is to discourage the IV abuse of buprenorphine. Both forms can be used in an inpatient setting, but the combination product is preferred in the outpatient setting to decrease the risk of diversion. When initiating buprenorphine, the first dose should not be given until >4 hours after the last dose of a short-acting opioid, such as heroin, or 24 hours after a long-acting opioid, such as methadone. As previously discussed, evaluation of objective opioid withdrawal signs may involve use of standard rating scales. Induction dosing should begin with 2 or 4 mg on the first day, which can be repeated every 2 to 4 hours if withdrawal symptoms subside and then reappear, up to a maximum of 8 mg. The dose can then be titrated the second day in

2- to 4-mg increments to a dose of 12 to 16 mg.[22] Higher doses during induction may precipitate withdrawal symptoms. In the inpatient setting, the patient may be stabilized on a relatively low daily dose (eg, 8 mg/day) and then tapered in increments of 2 mg/day over the course of several days.[15] In the outpatient setting, the patient should be initially stabilized on a daily dose (probably 8–32 mg/day) of buprenorphine that suppresses withdrawal. The dose should then be gradually tapered during a period of 10 to 14 days. Buprenorphine is not associated with any significant adverse effects when used to manage opioid withdrawal. Buprenorphine (and methadone) detoxification should be accompanied by psychosocial treatments and support groups as mentioned.[3]

A Cochrane review found that relative to clonidine, buprenorphine is more effective in alleviating opioid withdrawal symptoms; patients treated with buprenorphine stay in treatment longer, and are more likely to complete treatment.[23] The severity of withdrawal appears to be similar for withdrawal managed with buprenorphine or methadone, but withdrawal symptoms may resolve more quickly with buprenorphine. The authors of the meta-analysis concluded that although there is limited evidence comparing buprenorphine with methadone, both agents have similar effectiveness in the management of opioid withdrawal.

Nonopiate Symptomatic Therapy of Opioid Withdrawal

Although opiate replacement has been shown to provide a safe withdrawal, treatment with opiates is not always necessary. The ability of the α_2-adrenergic agonist, clonidine, to ameliorate some of the opioid withdrawal symptoms has led to its widespread use as a nonopioid alternative. Other α_2-adrenergic agonists (lofexidine, guanfacine, and guanabenz acetate) have also been investigated.[2,3,24] Noradrenergic outflow from the locus coeruleus is increased during opioid withdrawal, and is blocked by the administration of mu agonist opioids. Symptoms of opioid

withdrawal, therefore, are partly caused by excessive sympathetic activity in the locus coeruleus. Central α_2-adrenergic agonists inhibit locus coeruleus noradrenergic outflow during opioid withdrawal, thereby significantly reducing some of the symptoms.

Clonidine is therefore commonly used in a multidrug regimen. Contraindications to clonidine use include diastolic blood pressure <70 mm Hg, concurrent dependence on sedative-hypnotics, and clonidine hypersensitivity or previous intolerance. The most common adverse effects are sedation and hypotension. A Cochrane review examined studies comparing clonidine with methadone taper and found no significant difference in efficacy between the two for the treatment of heroin or methadone withdrawal.[24] A separate Cochrane review did find buprenorphine to be more effective than is clonidine in alleviating opioid withdrawal symptoms.[23]

A sublingual or oral test dose of 0.1 mg (0.2 mg for patients > 200.62 pounds [91 kg]) of clonidine is given: If diastolic blood pressure remains >70 mm Hg, additional doses may be instituted. Oral clonidine can be used at a dose of 0.1 to 0.2 mg/dose two to four times daily to a maximum of ~1 mg/day for 2 to 4 days after cessation of opioids, then tapered and discontinued by 7 to 10 days.[24] Because opiate withdrawal consists of other effects such as musculoskeletal aches and pains, anxiety, insomnia, and gastrointestinal (GI) disorders, it is common to use medications such as dicyclomine, loperamide, and ibuprofen as adjuncts. This is particularly true when the detox protocol does not contain opiates[2,18] (**Table 90-2**).

Table 90-2
Symptomatic Therapy of Opiate Withdrawal

Symptom	Medication
Bone, muscle, joint, or other pain	Ibuprofen, naproxen, other NSAID
Insomnia, anxiety	Benzodiazepine
Gastrointestinal hyperactivity	Loperamide, dicyclomine
Nausea	Prochlorperazine, ondansetron

NSAID, nonsteroidal anti-inflammatory drug.

Sources: Schuckit MA. Treatment of opioid-use disorders. *N Engl J Med*. 2016;375:357–368; ASAM Public Policy Statement on Treatment for Alcohol and Other Drug Addiction. Adopted May 1, 1980. Revised January 1, 2010. https://www.asam.org/quality-care/definition-of-addiction.

D.J.'s blood pressure and drug history should be evaluated for clonidine therapy. Provided his diastolic blood pressure is >70 mm Hg after the clonidine test dose, he can receive oral clonidine 0.1 mg with additional medications to treat his withdrawal symptoms, along with psychosocial counseling.

Ultrarapid Opiate Detoxification

Ultrarapid opiate detoxification (UROD) is a method to shorten the opioid detoxification period by precipitating withdrawal with an opioid antagonist. The opioid antagonist causes rapid stripping of the agonist from opioid receptors. UROD is performed under heavy sedation or general anesthesia so that the patient does not consciously experience the acute withdrawal symptoms. The protocols for UROD vary in terms of the setting of the procedure (inpatient or outpatient), opioid antagonist (naloxone, nalmefene, or naltrexone), anesthetic agent, adjunctive medications, and duration of anesthesia.[25]

The UROD procedure includes risks, such as vomiting with aspiration; cardiovascular complications, including cardiac arrest; pulmonary edema; and death.[25] Some patients have reported residual withdrawal symptoms for several days. Little information exists regarding referral to ongoing treatment or relapse rates after UROD.[26] A review of five randomized, controlled trials found no benefit of UROD compared with safer, less expensive treatments.[26] UROD has been criticized for being simply a "quick fix" that fails to address the underlying behavior changes necessary for recovery. In addition, it subjects patients to possible morbidity and mortality when safer, established procedures are available. The high cost of UROD limits its accessibility. The American Society of Addiction Medicine

recommends against this method of treating opiate withdrawal because of cardiac complications and anesthesia-related events.[2]

Pharmacotherapies for Maintenance Treatment of Opioid Use Disorder

Maintenance Therapy

The ultimate goal of outpatient substance use disorder programs is to assist the addicted patient into a drug-free healthy lifestyle. This results in reductions in medical conditions for the patient and reduced crime and health care cost for societal members. Methadone for maintenance treatment of opioid substance use disorder is federally regulated and is only available through specially licensed opioid treatment programs. The Drug Addiction Treatment Act of 2000 allows qualified physicians to prescribe Schedule III, IV, and V medications approved for the treatment of opioid dependence in an office-based setting.[27] Currently, only buprenorphine, a Schedule III medication, is approved for this indication.

CASE 90-4

QUESTION 1: A.X., a 27-year-old male, has a severe opiate use disorder (addiction) to heroin for the past 3 years, but is tired of the street scene and wants to "get clean" (complete abstinence). He can no longer afford his growing daily habit, but is not sure he can stop using opioids. He seems willing and determined to receive treatment for his heroin dependence.

What therapeutic options are available to him?

The gold standard of treatment is completely eliminating illicit opiate use; however, a more realistic expectation is reduced use and subsequent harm reduction. Even temporary reductions in heroin use are a benefit because of the reduced risk of developing major health (HIV, hepatitis C) and social (crime) issues.[2] Medical management (MM) of opioid dependence should be accompanied by psychosocial treatments, such as CBTs, behavioral therapies, and self-help groups, such as Narcotics Anonymous (NA).

Methadone maintenance is the most common form of pharmacologic treatment for opioid dependence. During methadone maintenance, heroin-dependent patients are stabilized on a dose of methadone that will be sufficient to suppress cravings for 12 to 24 hours without producing euphoria. Studies have shown that patients maintained on methadone doses of ≥60 mg had better outcomes than did those maintained on lower doses.[28] Most patients do well on a dose range of 60 to 120 mg/day, although some patients require more and some require less.[20] Because methadone is metabolized via cytochrome P450 (CYP) 3A4, drugs that induce this enzyme can precipitate withdrawal in patients maintained on methadone. Similarly, drugs that inhibit this enzyme extend the duration of methadone's effects. The half-life of methadone is typically 25 hours (15–60 hours), but can extend up to 120 hours with frequent dosing.[29] The drug is administered daily at the clinic as a single liquid oral dose. With the aid of daily counseling and rehabilitation, the goal is to eventually taper the patient from methadone as well. Patients who relapse repeatedly despite supportive treatment will require long-term maintenance therapy. This may take years, and it is shown that longer duration in treatment correlates with better outcomes. Methadone's efficacy comes from the fact that it reduces cravings without producing euphoria itself, primarily due to its slow time to peak. This produces a high degree of cross-tolerance to other opioids so that it is extremely difficult to obtain euphoria with IV injection of other opioids. However, patients have been able to reach euphoric states through the concomitant IV administration of other opioids. The higher purity heroin and the fact that fentanyl is often added to it has required even higher doses of methadone to achieve cross-tolerance.[28]

Buprenorphine has the advantage of office-based availability, thus removing the stigma associated with attending a methadone clinic and providing more places for patients to receive treatment because methadone clinics are limited as to how many patients can enroll and may be hundreds of miles away from the patient's home. Buprenorphine and high-dose methadone (60–100 mg) therapies were compared with low-dose methadone (20 mg); all three

therapies were effective in treating opioid dependence compared to baseline, and the buprenorphine and high-dose methadone arms were superior to low-dose methadone.[30] Trials comparing 12 to 16 mg/day of buprenorphine with moderate doses of methadone (50–60 mg/day) have generally shown comparable outcomes, although higher doses of methadone (>80 mg) appear to be superior to buprenorphine.[30] Low-dose buprenorphine seems to have worse outcomes compared to low-dose methadone.[31] Patients on buprenorphine are more likely to be employed, have less medical comorbidity, and a shorter duration of drug use compared to patients attending a methadone clinic.[32,33] There are multiple formulations of buccal and sublingual buprenorphine, and absorption rates are different between some of them. All are compared to the original buprenorphine sublingual tablet (Subutex® and Suboxone®) regarding pharmacokinetics, blood levels, and efficacy. There is also a buprenorphine implant available, which was found equally effective in lowering doses of buprenorphine sublingual.[34] An SC long-acting buprenorphine injection is also available. For maintenance treatment with the sublingual and buccal formulations, buprenorphine combined with naloxone is the standard of care, and pregnancy or allergy to naloxone are the only two reasons not to use the combination product.[2]

Buprenorphine has a long half-life of around 35 hours (24–60 hours) and it produces a relatively mild withdrawal when discontinued.[35] It is believed to be a safer alternative to methadone because life-threatening respiratory depression is much less likely to occur than with a pure μ agonist, unless another CNS depressant is taken concurrently. Most deaths involving buprenorphine have been caused by a combination of the drug with benzodiazepines and through injection of the monotherapy formulation.[22,36] Naloxone bolus doses often are ineffective in reversing respiratory depression caused by buprenorphine because of its prolonged occupancy on mu receptors. Continuous infusion of naloxone is necessary to overcome buprenorphine-induced respiratory depression.[37] Another safety advantage compared to methadone is the lower risk of prolonging QTc.[29] Similar to methadone, buprenorphine is also

metabolized by the CYP3A4 enzyme. The buprenorphine SC dosage form produces average blood concentrations similar to the 24-mg dose of buprenorphine sublingual (Suboxone®/Subutex®). The dose is given monthly in the abdomen, and can be initiated after at least 7 days of transmucosal buprenorphine.[38]

The narcotic antagonist naltrexone can block the euphoriant effects of heroin and other opiates, prevent the development of physical dependence, and afford protection from opioid OD deaths. Although naloxone is pharmacologically similar to naltrexone, it is impractical to use because of its short duration of action and its extremely poor oral bioavailability. Naltrexone is orally active and provides a dose-related duration of opioid blockade. An oral dose of naltrexone 100 mg will block opiate effects for 2 days, and 150 mg for 3 days. Thus, dosing on Monday, Wednesday, and Friday is possible; however, it is recommended to use 50 mg every morning (qam) because it is easier to remember for the patient and will result in better adherence. Naltrexone is also available as an injectable extended-release formulation for once-monthly use.[39] Patients selected for naltrexone therapy must be opioid free to avoid precipitation of withdrawal. For heroin- or morphine-dependent patients, a 4- to 7-day wait period is recommended, whereas longer half-life opiates can require a 10- to 14-day wait. Patients who are highly motivated to abstain have been most successfully treated with this drug.

Because A.X. has had a short duration of opiate misuse, he is a good candidate for outpatient buprenorphine/naloxone or naltrexone. Methadone is equally effective, but does require enrollment into a clinic, which may or may not be practical for him. Methadone clinics are considered more effective than are the other choices because the addiction becomes more severe.

Research suggests that physicians consume more opioids, sedatives, and alcohol than do the general public, but less tobacco.[40] The risk is largely based on access to drugs of abuse, and drug dependence is described as an occupational hazard for health care providers. Fentanyl (injectable as well as transdermal formulations) and meperidine are primarily, but not exclusively, drugs of abuse

among health care providers. Hospice workers and veterinarians also have access to high-potency opioids. Studies have noted that substance use was highest in psychiatrists and emergency medicine physicians and lowest in surgeons and pediatricians.[40] Fentanyl is associated with rapid development of dependence, intense tolerance, and drug-seeking behavior in addicted physicians for a period of months rather than years.

A comprehensive assessment of addicted health care providers is necessary to determine whether professional impairment is present, and whether issues involving public health and safety or violations of ethical standards, such as professional boundary violations or improprieties, require that the heath care provider be reported to his or her respective medical board. A physician's registration with the federal DEA may need to be suspended. It generally is accepted that health care providers require longer durations of treatment because they are held to a higher standard of recovery owing to concerns of public safety, and because they may be clever at concealing their illness.[40]

Health care providers are often good candidates for naltrexone therapy (particularly the long-action injection) because of the need to remain drug free despite continued access to opioids at work.

Opiate Use Disorder Treatment in Pregnancy

CASE 90-5

Question 1: J.R., a 28-year-old female, has been maintained on 100 mg of methadone daily for the past year. J.R.'s last menstrual period was 8 weeks ago, and she took a home pregnancy test yesterday, which was positive.

What is the recommended treatment for pregnant patients?

Methadone has been accepted since the late 1970s to treat opioid use disorder during pregnancy.[20] Methadone maintenance was determined to be the standard of care for pregnant females with opioid use disorder by a 1998 National Institutes of Health (NIH)

consensus panel.[41] Currently, methadone is the only opioid medication approved by the FDA for medication-assisted treatment of opioid use disorder in pregnant patients. Females maintained on methadone frequently have regular menstrual periods, ovulate, conceive, and have normal pregnancies. Heroin-addicted mothers, however, generally experience more complicated pregnancies because their lifestyles often predispose them to a poor general state of health and precludes adequate prenatal medical care.[22] Infants born to heroin-addicted mothers may also be exposed to other substances (eg, alcohol, cocaine, and tobacco). These infants tend to be smaller, weigh less at birth, and are often born prematurely compared with the children of females not using opiates.[22]

WITHDRAWAL DURING PREGNANCY

J.R. should continue methadone maintenance to avoid precipitating a withdrawal syndrome or a relapse to opiate addiction. Both relapse and withdrawal syndrome could lead to spontaneous abortion.[20] A structured methadone maintenance program provides access to counseling and perinatal medical care, which are additional benefits. The dose of methadone should be titrated individually throughout the pregnancy, and may even need to be increased and switched from on prescription (QD) to twice-daily (bid) dosing because of changes in kinetics that occur during pregnancy.[2] The neonate can be managed for either opioid-induced CNS depression or methadone withdrawal after delivery, as needed.

Methadone continues to be the standard of care for the management of opioid dependence in pregnancy; however, a growing body of evidence suggests buprenorphine may be a reasonably safe alternative.[15] Also, most evidence suggests that infants born to buprenorphine-maintained females have a lower incidence of neonatal abstinence syndrome (NAS) and shorter hospital stays.[42–44]

NEONATAL ABSTINENCE SYNDROME

Case 90-5, Question 2: Because methadone crosses the placental barrier, will J.R.'s infant exhibit opioid withdrawal symptoms after birth, and, if so, how should they be managed?

Methadone crosses the placental barrier and can cause CNS and respiratory depression as well as opioid withdrawal in the newborn. Higher doses of methadone are correlated with increased severity of NAS and longer duration of treatment needed for infants affected.[45] In general, the most common opioid NAS symptoms include restlessness, tremors, a high-pitched cry, hypertonicity, increased reflexes, regurgitation, tachypnea, diarrhea, and sneezing. Seizures are associated with, but not necessarily caused directly by, opioid withdrawal in the neonate.[46]

Management of the neonate's opioid withdrawal syndrome entails careful attention to hydration, with demand feeding and symptomatic care. Treatment of opioid NAS should begin when symptoms occur; prophylactic therapy is not recommended. Mild withdrawal symptoms generally do not need therapy, but moderate-to-severe symptoms may require ≥14 days of treatment.[46]

Symptoms of physiologic withdrawal are usually apparent within 48 hours of birth. Treatment can be initiated at this time. Currently, NAS is treated with morphine.[42,46–49] Morphine can be started at a dose of 50 µg/kg given orally four times daily and titrated to control symptoms. Once the NAS symptoms have stabilized, the dose can be decreased daily by 20% until discontinuation of the drug. Phenobarbital is preferred for the treatment of NAS in cases of combined dependence or benzodiazepine dependence or if maximum doses of opiate have been used.[42] If used, phenobarbital is instituted in doses of 5 to 10 mg/kg/day in the first 24 hours, then tapered symptomatically, usually about 20% per day.

If J.R.'s infant displays opioid withdrawal symptoms (eg, feeds poorly, becomes tremulous or agitated), morphine at a dosage of 50 µg/kg orally given four times daily would be an appropriate intervention. This dosage is given until symptoms stabilize and then gradually tapered (eg, 20% each day) during the next week.

Buprenorphine has also shown positive data supporting its use and is a potential option if morphine is unacceptable.[46]

BREAST-FEEDING

Methadone is excreted into the breast milk of methadone-maintained mothers. The amount of methadone in the breast milk is unlikely, however, to have adverse effects on the infant.[50] Furthermore, studies have found minimal transfer of methadone into breast milk.[20] There is little data regarding the safety of buprenorphine in breast-feeding. One study found low levels of buprenorphine and its active metabolite, nalbuphine, in infants' urine.[51] Breast milk offers advantages clearly beneficial to infants, and J.R. should be encouraged to breastfeed her infant.

SEDATIVE-HYPNOTICS (NON-ETHANOL ALCOHOL)

The sedative-hypnotics are a diverse group of compounds with broad clinical uses, including anesthesia, treatment of anxiety, and treatment of insomnia. Ethanol, also a sedative-hypnotic agent, continues to be the most widely abused substance in the United States, and is discussed later. Benzodiazepines have become the prototypical sedative-hypnotic drugs of abuse. Other abused sedative-hypnotic drugs include carisoprodol and γ-hydroxybutyric acid (GHB). Carisoprodol, a nonscheduled skeletal muscle relaxant, has an active metabolite meprobamate, a sedative-hypnotic agent with known abuse potential.[52] GHB is a putative neurotransmitter abused for its euphoric and sedative-hypnotic effects. Although sedative-hypnotics can be abused as monotherapy, they are more commonly used as adjuncts to other chemicals such as opiates and ethanol alcohol (EtOH).

Abstinence Syndromes Associated With Sedative-Hypnotic Dependence

CASE 90-6

QUESTION 1: During a year of therapy for anxiety, B.J. increased his dose of alprazolam to two 1-mg tablets five times a day. He has admitted to "doctor shopping" and buying alprazolam on the street. He states he uses the benzodiazepine to get high, but he also becomes extremely anxious if he does not use any alprazolam for more than an afternoon.

Will he experience withdrawal symptoms if he suddenly discontinues alprazolam?

Patients who have been on long-term courses of therapeutic doses of sedative-hypnotics often experience withdrawal symptoms on abrupt discontinuation of therapy. Withdrawal syndromes seen with sedative-hypnotics are similar to those seen with alcohol withdrawal and can include insomnia; anxiety; tremors; headaches; restlessness; nausea; vomiting; hypertension; tachycardia; hypersensitivity to light, sound, and touch; and perceptual distortions.[53] Generalized tonic–clonic seizures can occur as isolated seizures or as status epilepticus. The psychoses that develop resemble the delirium tremens produced by alcohol withdrawal, and are usually characterized by disorientation, agitation, delusions, and hallucinations. During the delirium, hyperthermia and agitation can lead to exhaustion, rhabdomyolysis, cardiovascular collapse, and death. Abstinence from short-acting barbiturates and meprobamate produces symptoms that peak within 1 to 5 days. Discontinuation of short-acting benzodiazepines (eg, lorazepam, oxazepam, alprazolam, and temazepam) results in the abrupt onset of withdrawal symptoms, usually within 12 to 24 hours of the last dose. Long-acting agents, and those with active metabolites, have a gradual onset of milder withdrawal symptoms compared with the short-acting agents. Withdrawal symptoms after chronic use of long-acting benzodiazepines typically occur within 5 days of cessation and peak at 1 to 9 days after the last dose. Severity of these

symptoms can also be affected by factors such as personality traits, baseline anxiety, and level of education.[53]

B.J. has been abusing alprazolam, taking more than the recommended maximal dose. Likely, he will experience withdrawal, possibly including seizures, if he were to abruptly discontinue the alprazolam. His withdrawal from this medication should be medically managed.

Treatment of Sedative Withdrawal

Three general medication strategies are used for withdrawing patients from sedative-hypnotics: tapering; substituting (and gradual taper) of phenobarbital for the drug of dependence; and substituting (and gradual taper) of a long-acting benzodiazepine for the drug of dependence.[54] Gradual tapering of the drug of dependence is appropriate for patients with therapeutic dose dependence or those taking long-acting sedative-hypnotics, who are not currently abusing alcohol or other substances. A recent meta-analysis suggests that benzodiazepine monodependence management by gradual taper is preferable to abrupt discontinuation.[55] The patient who is abusing sedative-hypnotics already has a strong association between the drug of choice and certain desired effects. Therefore, to minimize exacerbating addictive disease, substitution and taper with a long-acting therapeutic agent is preferred.

The phenobarbital method is used in some drug treatment programs. The pharmacologic rationale for phenobarbital substitution is that it is long acting, producing little changes in serum levels between doses, thereby preventing breakthrough withdrawal symptoms. Lethal doses are many times higher than are toxic doses, and dysphoria occurs with elevated dose, rendering it less desirable for abusers.

The standard method involves calculating a phenobarbital replacement dose for the total daily dose of the sedative-hypnotic being abused. The calculation is based on phenobarbital equivalents (**Table 90-3**). If multiple sedative-hypnotics are being used, the totals

for each drug and alcohol (amount of pure ethanol) are summated. The total phenobarbital substitution dose should be given in divided doses, three or four times daily (to avoid dysphoria). Because the calculated dosage is an estimate based on patient history and may be inaccurate, it is advisable to administer a test dose if the calculated replacement dose is >180 mg/day. The test dose, generally one-third the total dose, is given to the patient, who is then observed for 1 to 2 hours. The patient is observed for mitigation of withdrawal symptoms and signs of overmedication, such as somnolence or incoordination. Once an appropriate dose is determined, the patient is usually stabilized on that dose for 1 to 2 weeks. After stabilization, a gradual taper of phenobarbital is instituted, with dosages reduced by 15 mg weekly or every other week, or 10% of the current (starting) dose per week. For the last 25% to 35% of the taper, the rate is slowed to keep the patient stabilized. The taper should be held for a few days if withdrawal symptoms occur.[53]

Table 90-3

Hypnotic Dose Equivalent to 30-mg Phenobarbital

Pure ethanol 30–60 mL	Clonazepam 1–2 mg	Pentobarbital 100 mg
Alprazolam 0.5–1 mg	Diazepam 10 mg	Secobarbital 100 mg
Butalbital 100 mg	Flunitrazepam 1–2 mg[a]	Temazepam 15 mg
Carisoprodol 700 mg	Lorazepam 2 mg	Triazolam 0.25–0.5 mg
Chlordiazepoxide 25 mg	Oxazepam 10–15 mg	Zolpidem 5 mg

[a]Not approved for use in the United States.

Source: Reprinted with permission from Eickelberg SJ, Dickinson WE, Attia RA. Management of sedative-hypnotic intoxication and withdrawal. In: Miller SC, ed. *The ASAM Principles of Addiction Medicine*. 6th ed. Wolters Kluwer; 2019: 723–740.

B.J. has a substance use disorder to alprazolam. Tapering of alprazolam or conversion to phenobarbital will both result in a safe withdrawal. His total dose of alprazolam is 10 mg/day, so if phenobarbital is used, he should receive 300 mg divided three or

four times a day. The total daily phenobarbital dose or alprazolam dose should be tapered by 10% of the dose per week as tolerated.

γ-Hydroxybutyric Acid

GHB, commonly referred to as *liquid ecstasy*, is a potent "club drug." Once available as an over-the-counter nutritional supplement, primarily used by bodybuilders for its muscle building effect, the FDA removed it from the retail market in 1990 because of widespread reports of poisoning. In 2000, it was classified as a Schedule I drug; however, a GHB-containing product, sodium oxybate, is available as a Schedule III prescription drug for the treatment of cataplexy associated with narcolepsy.[56] GHB is found in mammalian brain tissue, where it is derived from conversion of its parent neurotransmitter, γ-aminobutyric acid (GABA).[57] It is believed to be a neurotransmitter. Experimental evidence suggests that the mechanism of action of exogenously administered GHB involves agonist activity at the $GABA_B$ receptor.[58]

GHB has CNS depressant effects, and is abused for its euphorigenic properties, disinhibition, and enhanced sensuality. Its psychic effects are similar to those of alcohol, and include increased libido, short-term anterograde amnesia, and a dreamy, altered sensorium. It has a steep dose–response curve, and common adverse effects include dizziness, nausea, weakness, agitation, hallucinations, seizures, respiratory depression, and coma. Its effects are synergistic with alcohol. GHB OD may be fatal, and there is no antidote. Treatment for GHB OD is primarily supportive.[59]

Highly addictive, tolerance and physical dependence can occur with regular use of GHB, and a withdrawal syndrome has been seen in people who have taken high doses of it (~18 g/day or more, although doses are variable in solution form) with frequent dosing (every 1–3 hours).[60] Withdrawal symptoms can include muscle cramps, nausea, vomiting, tremor, anxiety, insomnia, tachycardia, restlessness, and delirium or frank psychosis. Death caused by pulmonary edema has been reported. Treatment of withdrawal

involves supportive care, including use of benzodiazepines (eg, lorazepam or diazepam) for sedation. Vital signs need to be monitored, and the patient's airway should be kept clear in case of emesis. Withdrawal can last up to 2 weeks.[60]

Misrepresented sometimes as a natural and safe hypnotic, the low therapeutic index, and the unknown purity of illicit supplies, particularly when sold in solution, make GHB a potentially dangerous drug. Physical dependency is a possibility as well. GHB, along with the benzodiazepine flunitrazepam, are considered "date rape" drugs because they cause profound hypnosis and amnesia. This is intensified when mixed with alcohol, which is often how the sexual predator gives it to his victim.[56]

CENTRAL NERVOUS SYSTEM STIMULANTS

Cocaine

Cocaine is a naturally occurring alkaloid derived from the *Erythroxylon coca* plant, found mainly in the Andes Mountains of South America. Cocaine was first isolated in the 1800s and was a common ingredient in tonics and elixirs of the 1900s. The Harrison Narcotic Act of 1914 prohibited nonmedical use, and in 1970 it became a Schedule II controlled substance. According to the 2018 National Survey on Drug Use and Health, nearly 1 million people in the continental United States have a diagnosed cocaine use disorder within the past year, which is similar to the rate in 2017.[4] Cocaine is a CNS stimulant and has vasoconstrictive and local anesthetic properties. Cocaine's stimulant effects are primarily caused by blockade of the neuronal reuptake of dopamine (DA) and norepinephrine, with a small effect on serotonin. It also facilitates the neuronal release of DA and norepinephrine. This results in an overall increase in availability of these neurotransmitters in the synaptic space. Cocaine also has other indirect effects on neurophysiology, including effects on the endogenous opioid systems.[61,62] Cocaine is

associated with compulsive use. The powerful reinforcing effects of cocaine have been identified as occurring in brain regions rich in dopaminergic nerve terminals.

DOSAGE FORMS AND ROUTES OF ADMINISTRATION

In the manufacture of cocaine, organic solvents are used to solubilize the alkaloidal bases from the leaves, which are then precipitated to form a sticky material, called “pasta” or “cocaine paste.” The benzoylmethylecgonine (cocaine) in this “pasta” is separated from most of the other plant alkaloids, converted to hydrochloride or other salts, precipitated, and dried. This product is the white cocaine hydrochloride powder usually seen in the illicit market. The final product is usually “stepped on” or “cut” (diluted) with various adulterants to increase profits for the dealers. According to the DEA, the average purity of cocaine in 2017 was 64.3%, which is higher than that in previous years.[6] Powdered cocaine is generally snorted. Usually 10 to 25 mg of powdered cocaine is placed on a mirror or flat surface, formed into a line, and then insufflated through a straw or rolled dollar bill. A typical low-to-moderate user may consume 1 to 3 g/week. Cocaine powder can also be used for IV injection. The highly water-soluble powder is usually mixed with water and injected. When cocaine is injected simultaneously with heroin, this is known as a “speedball.”

Cocaine hydrochloride melts at a high temperature, destroying much of its psychoactivity in the process. Therefore, it is inefficient to smoke cocaine hydrochloride in this form. The use of “freebase” cocaine became popular during the late 1970s because this form of cocaine has a lower melting point and can therefore be smoked, producing an intense rush. For freebase, the cocaine hydrochloride is dissolved into ethyl ether. The synthesis of freebase is dangerous, and the resultant product may contain residual organic solvents, thus making it highly volatile and putting the user at risk for burns.

In the mid-1980s, a safer and easier method for extracting the cocaine base supplanted the traditional freebase process. In the manufacture of “crack,” cocaine hydrochloride is dissolved in water.

When alkali (bleach or sodium bicarbonate) is added to this aqueous solution, the free alkaloidal base ("crack") precipitates out, whereas the salts and some adulterants stay in aqueous solution. The precipitate is commonly referred to as a *rock*. The size of the rock varies, but generally ranges from one-tenth of a gram to a half a gram.

PHARMACOKINETICS AND EFFECTS

Cocaine generally produces a euphoriant action with a rapid onset and short duration. Snorting cocaine generally produces euphoria and stimulation within 2 minutes; smoking produces these effects within 6 to 8 seconds. Cocaine has a short elimination half-life of ~30 minutes owing to its rapid metabolism by esterases in the plasma, liver, brain, and other tissues.[62] When alcohol and cocaine are consumed together, a metabolite, cocaethylene, is formed. With a half-life three to five times longer than that of cocaine, cocaethylene intensifies both the euphoric and the toxic effects of cocaine.[63] The risk of death from cocaine consumed with alcohol is 18 to 25 times greater than that with cocaine alone.[63]

An initial relaxed, euphoric, gregarious, talkative, hyperactive state characterizes the "high" of cocaine. In addition, the person may report increased interest in sexual matters, diminished short-term memory, periods of intense concentration on one limited subject, diminished hunger, hypervigilance, and a peculiar, slightly out-of-body sense of one's actions. Without additional doses of cocaine, these feelings usually resolve into a state of mild depression, fatigue, hunger, and sleepiness by 1 to 3 hours. Physiologic manifestations include mydriasis, sinus tachycardia, vasoconstriction with hypertension, bruxism, repetitive behavior, hyperthermia, and talkativeness. After a few hours, continuous self-administration of cocaine will begin to progress from euphoria to dysphoria, to hallucinosis, and then to psychosis. Some users engage in nonstop binges of self-administration until psychological toxicity develops.[64]

ADVERSE EFFECTS

In 2011, there were reports of 505,224 cocaine-related visits to an emergency department (ED) in the United States.[65] The potential adverse effects associated with both acute and chronic use of cocaine are numerous and involve most organ systems in the body.

The cardiac complications associated with cocaine use include hypertension, arrhythmias, myocardial ischemia and infarction, dilated and hypertrophic cardiomyopathy, myocarditis, aortic dissection, and acceleration of atherosclerosis. These cardiac effects have occurred in individuals with and without underlying heart disease who have taken large or small doses by all routes of administration and may be associated with acute or chronic use. The cardiac events can occur before, during, or after other toxicities, such as seizures, and can be fatal. The mechanism of cocaine-induced myocardial infarction (MI) is most likely multifactorial, involving one or more of the following processes: coronary artery vasoconstriction, increased myocardial oxygen demand related to increased blood pressure and increased heart rate, increased platelet aggregation and thrombus formation, coronary vasospasm, and arrhythmia. The risk is greatest within the first hour of use.[66] In patients presenting to the emergency room with acute chest pain, a significant association between cocaine use and acute coronary syndromes has been established based on data from the emergency department.[67]

The MM of acute coronary syndromes differs when cocaine is the cause. Specifically, nonselective β-blocker therapy (ie, propranolol) is contraindicated because of unopposed α-effects, thrombolytics should be used with caution, and nitroglycerine and benzodiazepines are part of first-line therapy.[63,64,68] In patients with cocaine-associated chest pain, a 12-hour observation period to rule out MI or ischemia is probably sufficient before discharge from a medical facility.[64]

Cocaine has also been associated with cerebrovascular catastrophes. Stroke can occur as a result of increased blood pressure, vasoconstriction, or thrombosis. Seizures are another CNS complication. Seizures can occur with first use and are most often single, generalized tonic–clonic seizures. Most occur within 90 minutes of drug use, when drug plasma concentrations are highest.[62]

The route of cocaine administration also affects the nature of the adverse effects. For example, pulmonary complications, including pneumomediastinum, pneumothorax, pneumopericardium, acute exacerbation of asthma, diffuse alveolar hemorrhage, pulmonary edema, and "crack lung," are associated with smoking crack cocaine. Crack lung is a syndrome of acute pulmonary infiltrates associated with a spectrum of clinical and histologic findings.[63] Snorting cocaine can lead to perforation of the nasal septum because of the drug's local anesthetic and vasoconstrictive effects. IV use of cocaine has been associated with renal infarction, wound botulism, viral hepatitis, HIV infection, bacterial endocarditis, sepsis, and other infectious complications.

COCAINE USE DISORDER

A person who uses cocaine despite adverse consequences (ED visit), uses it compulsively, suffers withdrawal symptoms, and alleviates symptoms with further use is diagnosed with cocaine use disorder per the *DSM-5*. According to the National Survey on Drug Use and Health for 2018, ~ 977,000 people 12 years or older suffered from cocaine use disorder in the previous year.[4] Prolonged or heavy use of cocaine has been associated with the development of tolerance to some of its central effects. Tolerance is caused by adaptive changes in the brain.[62,69] A withdrawal syndrome may follow long-term or binge use. The initial, acute symptoms, referred to as the *crash*, consist of depression, fatigue, craving, hypersomnolence, and anxiety. Anhedonia and hyperphagia soon follow. Although most symptoms are mild and resolve within 1 to 2 weeks, the dysphoria and anhedonia can persist for weeks. These symptoms do not produce profound physiologic changes and are generally not life-threatening.[64]

TREATMENT OF COCAINE USE DISORDER

Most cases of simple cocaine withdrawal do not require medical treatment. However, multiple pharmacologic therapies to facilitate abstinence from cocaine have been, and continue to be, under

investigation. Because cocaine affects multiple neurotransmitters in the brain, effective drugs need to target more than one molecule.[70] Most studies have yielded variable results, and to date no drug that is proved effective in treating cocaine dependence exists.[15] Studies of DA agonists (amantadine, selegiline, levodopa/carbidopa, and pergolide), antidepressants (desipramine, fluoxetine, and bupropion), and carbamazepine have yielded inconsistent findings. The long-acting amphetamines (dextroamphetamine and methamphetamine) have shown promising results, although high dropout rates have been reported in clinical trials.[71,72] Methylphenidate has been investigated as "maintenance treatment" to satisfy the cocaine addict's desire for further enhancement of mood; however, methylphenidate also can stimulate a powerful craving for the more intense euphoria of cocaine and has significant abuse potential. Topiramate, baclofen, tiagabine, and modafinil have also shown promising results.[70] A cocaine vaccine is currently under investigation.[73] Psychosocial treatments focusing on abstinence have been effective in the treatment of cocaine dependence.[70] CBTs and behavioral therapies, such as contingency management, along with 12-step–oriented individual counseling can be useful, although the efficacy of these therapies varies. Participation in a 12-step self-help group (Alcoholics Anonymous [AA], NA), as an adjunct to treatment, seems to predict less cocaine use.[3,15] A newer voucher-based therapy has also been found to be effective in promoting abstinence.[70]

Amphetamines

Central nervous system stimulants have been used both with and without social acceptance for thousands of years. The Chinese prepared ephedrine-containing products from a plant called Ma-Huang (*Ephedra vulgaris*).[7] People in East Africa and the Arabian Peninsula chew the leaves of the khat bush (*Catha edulis*) for the stimulating effects of the alkaloid cathinone.[62] Caffeine is consumed worldwide in a usually socially acceptable manner in the form of

coffee and energy drinks. Amphetamine was synthesized in 1887, and methamphetamine in 1919. The legal sanctions against widespread prescribing of amphetamines in the 1970s restricted their supply and fostered a black market thriving on the illicit production of methamphetamine powder ("speed," "meth," "crank," and "crystal meth"). During the 1990s, California and the West Coast experienced a dramatic resurgence of methamphetamine-related hospital admissions, poison center calls, and law enforcement actions. Methamphetamine misuse has since become a nationwide problem, prompting government restrictions on retail sales of ephedrine and pseudoephedrine (precursor chemicals used in the manufacture of methamphetamine). A new marketing tool developed by savvy drug dealers aimed at younger, new users involves bright coloring and flavoring (strawberry, cola, cherry, and orange) added to crystal methamphetamine to help mask the bitter taste. According to the National Survey on Drug Use and Health for 2018, there were ~1.9 million people older than age 12 years who used methamphetamine in the previous year in America.[4]

PHYSICAL AND PSYCHOLOGICAL EFFECTS

CASE 90-7

Question 1: D.C., a college student, used amphetamine this past weekend when partying with his friends. He has a midterm examination in 2 days and is too tired to study, so one of his friends suggests snorting some more amphetamine and then hitting the books. D.C. finds amphetamine very much to his liking and begins to use it daily. He goes many days at a time without sleeping or showering and starts losing weight because he seldom has an appetite. He believes his friends are working with the DEA and tapping his phone.

Are these symptoms of a stimulant use disorder?

Methamphetamine produces CNS stimulation by enhancing the effects of norepinephrine, serotonin, and DA. This is accomplished by both blocking the reuptake and stimulating the release of these

neurotransmitters. These effects are greater for DA and norepinephrine than for serotonin.[50]

The powerful stimulating effects of amphetamine and methamphetamine have made their use popular among a wide variety of groups, including students, athletes, the military, dieters, and long-distance truck drivers. Initially, the user may experience alertness, euphoria, increased energy, the illusion of increased productivity, sociability, and decreased appetite. Continuous dosing, however, produces stereotypical grooming and other repetitive motions. Physiologic effects include bruxism, tremor, muscle twitching, mydriasis, hypertension, diaphoresis, elevated body temperature, nausea, dry mouth, weight loss, and malnutrition. Continued use for several days decreases productivity and is associated with disordered thoughts, paranoia, and psychosis. Tolerance develops very rapidly after continued use.[62]

Illicit methamphetamine is commonly insufflated or injected and, less commonly, taken orally. In a pattern similar to that seen with smoking cocaine, users freebase methamphetamine and smoke it. Heating the crystals and smoking the vapor of “crystal meth,” as with crack, is a common route of administration; however, snorting and IV administration are also used. Absorption is rapid after smoking, and the effects can last as long as 24 hours. Methamphetamine-induced psychosis may occur more frequently with smoking.

D.C. will probably be able to stay awake to study if he uses more methamphetamine; however, if he is up for too many days without sleep, his performance in the examination will suffer.

ADVERSE EFFECTS AND TOXICITIES

D.C. is exhibiting classic signs of chronic methamphetamine abuse, which will likely progress if he continues using it. A “speed freak” or “tweaker” (chronic methamphetamine user) is generally regarded even by other drug users as mentally unstable, aggressive, and emotionally labile, with unpredictable periods of violent, even homicidal, behavior. Chronic users characteristically develop complex paranoid delusional systems with hallucinations during

extended periods of intoxication that may involve several sleepless days and nights of continuous methamphetamine administration. This “speed psychosis” may include tactile hallucinations, such as formication (the sensation of something crawling under the skin). The initial treatment approach for stimulant-induced adverse psychological effects is nonpharmacologic. The distressed patient may be calmed by reducing environmental stimuli and using the “ART” approach developed by the Haight-Ashbury Free Clinic in San Francisco: *A*cceptance of the patient’s immediate needs; calm *R*eassurance that the condition is caused by the drug and will resolve eventually; and *T*alk down, which involves reassuring, reality-oriented communication.[64] An extremely agitated, anxious, psychotic user, however, will often require administration of a benzodiazepine, such as diazepam (10–30 mg orally or 2–10 mg via IM or IV administration) or lorazepam (2–4 mg orally or via the IM or IV route). Hypotension and respiratory depression are adverse effects associated with benzodiazepines, so concurrent use of alcohol or opioids may have synergistic effects. If psychosis persists, a high-potency neuroleptic, such as haloperidol (5–10 mg orally or via IM or IV administration) or risperidone (2–4 mg orally), is preferred owing to its minimal anticholinergic activity. Low-potency neuroleptics with higher anticholinergic activity such as chlorpromazine may worsen symptoms of delirium and hyperthermia.[64]

The physiologic toxicity of stimulant drugs includes hypertension, stroke, seizures, hyperthermia, sexual dysfunction, dental caries, rhabdomyolysis, renal failure, cardiac arrhythmias and cardiomyopathies, MI, and malnutrition.

The development of neurotoxicities involving dopaminergic and serotonergic neurons (possibly through interference with neurotransmitter biosynthesis, monoamine transport, increased production of reactive oxygen species, and apoptosis) has been demonstrated in animals. It also appears to cause permanent neuronal toxicity with prolonged use.[74,75]

WITHDRAWAL AND TREATMENT

CASE 90-7, QUESTION 2: D.C. is arrested for assault after a bar fight. He is held in the county jail and is unable to post bail. What withdrawal symptoms might he experience during incarceration?

D.C. will probably suffer intense cravings for methamphetamine and initial agitation, followed by fatigue and hypersomnolence. A withdrawal state after acute cessation of chronic stimulant use is generally the same as that previously described for cocaine. As with cocaine, the crash is notable for marked fatigue, depression, and anhedonia. Most symptoms are mild and will resolve within 1 to 2 weeks, although anhedonia and depression may persist.

Clinical studies investigating treatments for methamphetamine dependence are similar to that for cocaine treatments. Currently, no pharmacologic treatments have proved effective for methamphetamine dependence. The most effective treatment so far appears to be psychosocial therapies, such as CBT and contingency management.[64]

DISSOCIATIVE DRUGS: PHENCYCLIDINE, KETAMINE, AND DEXTROMETHORPHAN

Phencyclidine (phenylcyclohexylpiperidine [PCP]) and ketamine are arylcycloalkylamine, dissociative, anesthetic agents. PCP at one time was marketed as an IV anesthetic agent under the trade name Sernyl.[76] Subsequent reports of postanesthetic dysphoric reactions caused the drug to be withdrawn in 1965. It was reintroduced in 1967 as Sernylan and marketed as a veterinary anesthetic until 1978, when the manufacture and sale of the drug became illegal. Ketamine is currently used clinically as an anesthetic in both animals and humans. There is some data supporting its use in treatment refractory depression, but the common side effect of dissociation has

confounded the blinding of studies and is a significant side effect. More research is necessary, but it is possible that it could be used for very short-term treatment during the efficacy lag of established antidepressants.[77] Ketamine is shorter acting and somewhat less potent than is PCP.

Abuse of arylcycloalkylamines occurs primarily in large metropolitan areas. PCP is relatively easy to synthesize and is inexpensive; therefore, it is often misrepresented as other street drugs, such as lysergic acid diethylamide (LSD), amphetamine, mescaline, or Δ-9-tetrahydrocannabinol (THC). Ketamine ("K," "Special K," "Super K," or "cat valium") is commonly used as a "club drug," and is sometimes misrepresented as 3,4-methylenedioxymethamphetamine (MDMA; ecstasy). Ketamine is often diverted from veterinarian supplies. PCP ("angel dust" or "dust") in powdered form is often applied to parsley, marijuana ("dusted joint," "superweed"), or tobacco cigarettes and smoked. Oral, intranasal, and parenteral routes of administration are used by some. The combination of cocaine and PCP in a freebase smoking mixture is called "SpaceBase." Although ketamine is manufactured as an injectable liquid, it is frequently evaporated to a powder. The powder can be snorted or compressed into tablets.

Dextromethorphan is an antitussive agent found in some over-the-counter cough remedies. Its appeal as a drug of abuse may be because it is inexpensive, licit, lacks social disapproval associated with other drugs, and available over the counter, and abusers believe it to be safe because it is produced by a pharmaceutical company. Street names include "Skittles," "DXM," "Dex," "Robo," "C-C-C," and "Red Devils." Use is referred to as *dexing*, *robotripping*, and *robodosing*. Dextromethorphan is the D-isomer of the codeine analog of levorphanol. The metabolic byproduct of dextromethorphan, dextrorphan, has weak *N*-methyl-D-aspartate (NMDA) antagonist properties.[76] When dextromethorphan is ingested in large doses, it produces effects similar to that of PCP or ketamine. When abused, doses range from 300 to 1800 mg. The most commonly abused form is Coricidin® HBP Cough and Cold (called "C-C-C" on the street)

because it contains the highest concentration of dextromethorphan per dosage unit on the market (30 mg). Dextromethorphan is also available for sale on the Internet in powdered form, which can be ingested orally or snorted. The dextromethorphan "high" can last 3 to 6 hours, and can consist of euphoria, dissociation, hallucinosis, increased perceptual awareness, altered time perception, hyperexcitability, pressure of thought, and disorientation; increased blood pressure, heart rate, and body temperature; and blurry vision.[76] Other ingredients found in the over-the-counter preparations, such as acetaminophen, chlorpheniramine, guaifenesin, and alcohol, may be problematic when ingested in large doses. PCP is considered the typical dissociative drug, and review of its effects largely applies to ketamine and dextromethorphan as well.

Phencyclidine

PHENCYCLIDINE INTOXICATION

Persons who use PCP at a dose of ≥0.05 mg/kg may appear agitated, diaphoretic, and disoriented. There is an increase in blood pressure, pulse, and temperature, and the person may experience vertical and horizontal nystagmus. These symptoms can last for up to 2 days, even though the half-life of this drug is ~21 hours.[78] PCP and ketamine are noncompetitive antagonists of the NMDA receptor subtype of the major excitatory neurotransmitter, glutamate. Based on this pharmacologic mechanism, PCP is also used as an animal model of schizophrenia.[79] The dose, route of administration, and serum concentration of PCP all influence the pharmacologic effects of this drug and, thus, the symptoms of intoxication.[76] PCP in low doses causes inebriation, ataxia, changes in body image, numbness, and a mind–body dissociative feeling. Horizontal or vertical nystagmus or both are often present, and the anesthetic effect of the drug raises the pain threshold. Amnesia can occur after intoxication.

As the dose of PCP increases, the patient may manifest agitation, combativeness, catatonia (ketamine users refer to this as a "k-hole"), and psychosis. The action of PCP on the autonomic nervous system

becomes more prominent and is characterized by a confusing combination of adrenergic, cholinergic, and dopaminergic effects. A hypertensive response is typically encountered. Tachycardia, tachypnea, and hyperthermia may also be noted in the moderately intoxicated patient. The agitated, combative patient often has feelings of great strength. This, combined with the anesthetic effect of PCP, can result in serious injury because there is no pain sensation to stop the physical activity.

With large doses of PCP, marked CNS depression occurs, and nystagmus may no longer be present. In addition to the physiologic effects noted earlier, respiratory depression, seizures, acidosis, and rhabdomyolysis may further compromise the patient's condition. Rhabdomyolysis, particularly in the presence of acidemia, can result in acute renal failure.[64] Opisthotonic posturing and muscular rigidity occur frequently in the severely intoxicated patient.

MEDICAL MANAGEMENT OF INTOXICATION

Diagnosis of PCP intoxication should be confirmed through a blood or urine specimen. Currently, no clinically useful antidote to PCP exists, and treatment should be supportive. Environmental stimuli should be minimized, and airway support should be maintained. Even attempts to talk down the patient may trigger a combative response, and chemical restraints may be indicated. Physical restraints may increase the risk of rhabdomyolysis and should be reserved for patients who pose a threat of great danger to themselves or others. Benzodiazepines are useful in the management of the anxious, agitated patient with mild-to-moderate PCP intoxication. If benzodiazepines are insufficient, haloperidol (5 mg IM) is effective.[64] Low-potency neuroleptics should be avoided because a greater possibility of precipitating a hypotensive response or a seizure exists.

Hypertension may be managed with β-blockers or calcium channel blockers. Diazepam (5–10 mg IV to 30 mg total) is a useful anticonvulsant for the management of PCP-induced seizures.[64] Because extreme agitation, seizures, and hyperthermia can initiate

rhabdomyolysis and secondarily cause myocardial, renal, or hepatic dysfunction, use of anxiolytics, neuroleptics, anticonvulsants, and cooling measures should be as needed.

The urinary excretion of PCP (a basic compound) is enhanced when the urine is acidic; however, this approach is not recommended because it may exacerbate myoglobinuric renal failure.[54] Activated charcoal in a dose of 50 to 150 g initially, then 30 to 40 g every 6 to 8 hours, can prevent the intestinal reabsorption of this drug and promote its elimination.[64]

PSYCHOLOGICAL AND PROLONGED EFFECTS

Chronic PCP use can result in prolonged residual psychological symptoms, including anxiety, depression, and psychosis.[64] Pharmacotherapy for these symptoms may be necessary. Prolonged psychiatric sequelae are almost always associated with premorbid psychopathology. Perceptual disorders, including auditory and visual hallucinations, such as after images seen following moving objects ("trails"), may also occur. Flashbacks (discussed in detail in the subsequent section on Lysergic Acid Diethylamide) have been reported after PCP use.

The *DSM-5* does not recognize PCP withdrawal; however, about one-fourth of heavy PCP users report symptoms after discontinuation of use.[64] These symptoms include depression, anxiety, irritability, hypersomnolence, diaphoresis, and tremor. Animal studies have described a withdrawal syndrome, but it is unclear whether a true withdrawal syndrome occurs in humans.[64] Currently, no pharmacologic treatments for PCP use disorder exist. Some animal data indicate neurotoxicity; however, the long-term consequences and significance for humans are unknown, and require further study. Irritability and a feeling of isolation are common, and memory lapses, speech and visual disturbances, and confusion have been reported in long-term users as well. Memory lapses, speech and visual disturbances, and confusion have been described in long-term users as well.

HALLUCINOGENS

Hallucinogens can be categorized as indole alkylamines (eg, LSD, psilocybin, and dimethyltryptamine) or phenethylamines (eg, mescaline and MDMA). LSD is considered the prototype hallucinogen. Although MDMA is classified as a phenethylamine, it has structural similarities to amphetamine and mescaline. It has been labeled an entactogen or empathogen because of its strong empathy-producing effects and mild hallucinogenic effects. The term *entactogen* can be translated as "a touching within." Hallucinogens are commonly referred to as *psychedelics*.

In 2018, 5.6 million Americans older than age 12 years were reported to be hallucinogen users.[4] The popularity of MDMA (ecstasy, X) has risen dramatically in recent years, partly because of its use as a "club drug." The usual pattern of use for hallucinogens is occasional self-administration for enhancement of recreational activities, such as dancing, or for "mind expansion." Certain individuals may develop psychological dependence and use hallucinogens in a more chronic and compulsive manner.

Lysergic Acid Diethylamide

EFFECTS

Perhaps the most famous of all hallucinogens, LSD-25 was first synthesized by Albert Hofmann of Sandoz Laboratories in 1938. It was developed as an analeptic agent, but produced significant uterine stimulation and caused experimental animals to become excited or cataleptic. Five years later, while resynthesizing LSD-25 for further pharmacologic testing, Dr. Hofmann experienced a restlessness that forced him to go home. This was followed by 2 hours of intense visual hallucinations of kaleidoscopic images and colors. Later, he identified LSD-25 as a potent hallucinogen. Clinical experimentation produced hundreds of papers describing LSD as a drug that could facilitate psychotherapy, particularly in the

management of addictive behavior. Widespread public self-experimentation with LSD for recreation and self-exploration, coupled with growing attention to adverse psychological consequences, led Sandoz to discontinue production of LSD-25 (as well as psilocybin, psilocin, and related congeners) in August 1965. The United States made LSD a Schedule I controlled substance in 1970 after the proliferation of illicit suppliers to meet the huge public demand for this drug.

Although the mechanism of action of classic hallucinogens is not fully understood, they appear to predominately act as agonists or partial agonists at serotonin (5-hydroxytryptamine [5-HT]) receptors, specifically the 5-HT_2 receptor.[80] LSD, one of the most potent hallucinogens known, is active at doses of 25 to 250 µg. Most users take about 100 to 150 µg of LSD for a significant effect. This dose produces mild-to-moderate sympathomimetic effects, profound visual hallucinosis, and the sensation of disordered integration of sensory input. For example, sounds and music are perceived as visual imagery, odors are felt, and inanimate objects assume lifelike qualities. In addition to these sensory–perceptual effects, psychic effects occur, such as depersonalization, dreamlike feelings, and rapid alterations of affect. These are accompanied by somatic effects, including dizziness, nausea, weakness, tremor, and tingling skin.[80] These combined effects begin within an hour of ingestion of LSD, and usually peak in intensity during the first 2 to 4 hours. After taking LSD, most people feel they have returned to a normal psychological state by 10 to 12 hours.[81] Within an hour of ingestion, a person will begin to experience altered sensations of his/her surroundings, in addition to some psychic and somatic effects.

ADVERSE EFFECTS

The most frequently encountered adverse reaction associated with the hallucinogenic drugs is a mental state of acute anxiety and fear, typically referred to as a “bad trip.” The hallucinogen experience is influenced by set (the user’s mental state and expectations of drug effects) and setting (the environment in which drug use takes place,

including the social conditions). Users may be able to calm themselves without outside intervention. The initial therapy for people undergoing a bad trip is frequently called “reality therapy” and consists of talking down the fear and panic. This consists of getting the person to a quiet, relaxed setting and helping him or her focus on explanations for the uncertainties that are causing the panic. This process also tends to reassure the person that he or she is in a safe physical environment and that the drug effects will diminish in a few hours. Most of these bad trips are resolved during the state of intoxication (generally, 6–12 hours), but some last as long as 24 to 48 hours.[64]

If the talk-down approach is not successful in resolving the panic, drug therapy can be considered. Sedation with an oral benzodiazepine (ie, diazepam 10–30 mg) or a parenteral benzodiazepine (ie, lorazepam 2 mg IM) will frequently alleviate the panic.[64] Supportive talking down should be continued because the benzodiazepine will not stop the trip; it will simply sedate the patient. Haloperidol 2 mg IM may also be used if benzodiazepines are insufficient. Phenothiazines should not be used for initial management of bad trips because they have been associated with poor outcomes.[64]

Regarding adverse physical effects, classic hallucinogens have a high margin of safety, although patients should be monitored for seizures or elevations in body temperature, which may indicate a potential hyperthermic crisis. Anticonvulsant therapy may not be effective until body temperature has been lowered.[64] Conditions such as pregnancy and epilepsy serve as absolute contraindications for LSD use.

FLASHBACKS AND LONG-TERM EFFECTS

Use of hallucinogens can trigger a transient psychosis or unmask an underlying psychiatric disorder; however, a true psychotic episode is rare. Psychiatric conditions that persist more than a month after hallucinogen use are likely caused by preexisting psychopathology.[64]

Hallucinogen use does not seem to be associated with any cognitive impairment.[81]

Hallucinogen persisting perceptual disorder (HPPD), commonly referred to as *flashbacks,* is characterized by recurrences of part or all of the hallucinogenic drug experiences after a period of normal consciousness in a person who used the drug previously. The flashbacks may last from minutes to days or months (usually a few hours). The estimated prevalence of flashbacks varies widely in studies, and the etiology is still unclear.[82] Flashbacks can occur spontaneously or be triggered by exercise, stress, or another drug (eg, marijuana).[81] Treatment remains anecdotal; no randomized, controlled trials have evaluated the efficacy of pharmacotherapy for HPPD.[83]

LSD and other classic hallucinogens have low potential for chronic use disorder. There does not appear to be a clinically important withdrawal syndrome associated with their use. The rapid development of tolerance that occurs with these drugs may explain the intermittent use patterns commonly seen.

3,4-Methylenedioxymethamphetamine

CASE 90-8

Question 1: R.X. and her friend P.B. go to "raves" (all-night dance parties) every weekend and usually take ecstasy (MDMA). R.X. says it makes her feel like "I love everyone around me," and P.B. likes to be able to "dance all night without getting tired."

Are these effects common with MDMA?

Merck Pharmaceuticals (Boston, MA) patented MDMA in 1914, but it was not until the 1950s that its use was examined in animal studies when the U.S. Army Intelligence investigated it as a "brainwashing" agent. By the late 1970s, a few therapists and psychiatrists began using the drug with reported success in patients with a wide range of conditions.[84] MDMA produces a very manageable and comfortable entactogenic effect, during which the person has a clear sensorium.

The experience can be recalled in detail, and the insights gained during the session can be incorporated into normal life. The public gave several names to this drug, such as ecstasy, XTC, Adam, and M&Ms. The media became aware of the anecdotal reports from both psychiatrists and people self-experimenting with MDMA. In 1985, the DEA made MDMA a Schedule I drug. Subsequently, supplies of the drug proliferated in the public illicit marketplace, and its popularity soared. In 2001, after successful lobbying by researchers interested in reinstituting MDMA in clinical practice, the FDA granted approval for a pilot study investigating the therapeutic use of MDMA in the treatment of post-traumatic stress disorder (PTSD). Results of this placebo-controlled study indicate that MDMA is very effective (83% vs 25%) in treating PTSD.[85] The effects of MDMA are mainly exerted by three neurochemical mechanisms: blockade of serotonin reuptake, stimulation of serotonin release, and stimulation of DA release.[86] The common psychological effects of MDMA intoxication include an overall heightened sense of empathy, interpersonal closeness, increased acceptance of others, and a powerful sense of well-being.[87] The experience is influenced by set and setting. The amphetamine-like side effects include mydriasis, tachycardia, sweating, increased energy and alertness, bruxism, nausea, and anorexia.[88,89] Users generally ingest MDMA in tablet form, and the onset of action is usually after 30 to 60 minutes. Some users take a "booster" dose after 2 hours. The usual duration of action of MDMA is 4 to 6 hours, and the half-life is ~8 hours. MDMA users in the rave scene often "stack" multiple doses, and polydrug use is common. The combined use of ecstasy and LSD is referred to as *candy flipping*.[86]

R.X.'s feelings of love for everyone are consistent with the empathogenic effects of MDMA, whereas P.B. is enjoying the amphetamine-like effects of increased energy to dance all night.

ADVERSE EFFECTS

Case 90-8, Question 2: Several hours after taking MDMA, P.B. is still dancing. She begins to feel hot and realizes she is profusely sweating. On her way to the bar for a drink, she begins to feel confused and collapses to the floor. Her friends witness her having a seizure and call 9-1-1. What is happening to P.B.?

The rave scene, with its crowded conditions and often-high ambient temperatures, has contributed to many adverse effects associated with MDMA ingestion. Because of their increased physical activity, the ravers may become dehydrated. In addition, supplies of MDMA have been notoriously unreliable. Many other drugs have been misrepresented as MDMA, including other phenethylamines such as 3,4-methylenedioxyamphetamine (MDA) and paramethoxyamphetamine (PMA); amphetamine; cocaine; opiates; ketamine; and dextromethorphan. The common polydrug use practiced at raves compounds the problem. Dextromethorphan taken at high doses for its dissociative properties competes with MDMA for hepatic metabolism, and its anticholinergic effects block perspiration, potentially leading to overheating.[84]

The most dangerous adverse physical effect of MDMA is hyperthermia. MDMA has a slight affinity for the 5-HT_2 receptor, and the increased body temperature may be the result of this activation.[86] The hyperthermia has led to rhabdomyolysis, acute renal and hepatic failure, disseminated intravascular coagulation (DIC), and death.[90] DIC has been the most common cause of death. Treatment of hyperthermia involves cooling measures and IV fluids. Benzodiazepines (eg, lorazepam 2 mg IM or IV) and dantrolene (1 mg/kg IV) may be helpful. Other adverse physical effects can include hypertension, cardiac arrhythmias, convulsions, cerebrovascular accident, hepatitis, and hyponatremia (from overingestion of water as a harm reduction measure to avoid hyperthermia).[89,90] In 2011, there were 22,498 ED visits associated with MDMA use.[91] Adverse psychological effects are also possible, including anxiety, depression, panic attacks, agitation, paranoia, and, rarely, psychosis. The treatment of these psychological adverse effects is the same as that for those associated with the classic hallucinogens, including

talk-down therapy and benzodiazepine administration. Water restriction and administration of hypertonic saline are indicated in seizures resulting from hyponatremia.[88] P.B. may be suffering from MDMA-induced hyperthermia and needs urgent medical evaluation.

LONG-TERM EFFECTS

Case 90-8, Question 3: R.X. has read in the newspaper that MDMA is associated with "brain damage" and is worried that she has caused permanent damage to her brain. What are the long-term effects of MDMA?

Animal studies have consistently demonstrated long-term MDMA-induced serotonin depletion. This has been evidenced by lower levels of serotonin, decreased metabolite levels, lowered levels of tryptophan hydroxylase, and loss of serotonin reuptake transporters.[84] This may explain the induction of panic attacks for chronic users. MDMA damages serotonin axonal projections; axonal resprouting and regeneration do occur, but it is unclear whether these new projections are damaged.[84,92] Both hepatotoxicity and neuronal toxicity occur with MDMA use, and is suspected to be due to oxidative stress, mitochondrial dysfunction, and excitotoxicity.[74]

Several retrospective studies in humans have claimed lowered cognitive performance in MDMA users compared with nonusers. These studies have confounding variables, such as other drug use and adulterant exposure and lifestyle factors.[84,92]

Use of MDMA does not appear to produce physical dependence, but some users may become psychologically dependent. Tolerance to the empathogenic effects develops rapidly and may last 24 to 36 hours. This may explain, in part, the more common practice of sporadic dosing of the drug.[64,87] No distinctive withdrawal syndrome that would require pharmacologic treatment has been described.

CANNABINOIDS

Marijuana is the most widely used illicit substance in the United States. In 2018, 43.5 million Americans ages 12 years or older reported using marijuana in the past year.[4] The main psychoactive ingredient in the *Cannabis sativa* plant is THC, although the plant is known to contain >70 cannabinoids.[93] The other main constituent is cannabidiol (CBD).

Researchers in cannabinoid neurobiology have discovered two cannabinoid receptors in the CNS: CB_1 and CB_2; however, additional receptors have been proposed. Research has demonstrated that the main psychoactive and addictive effects are almost completely mediated by the CB_1 receptor.[94] In addition, five endogenous cannabinoids (endocannabinoids) that act at the cannabinoid receptors have been discovered.[95] The best known are arachidonic acid ethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG).[95] Considerable evidence exists supporting the role of THC–opioid interactions with enhanced antinociception. Cannabinoids have been shown to release endogenous opioids, and cannabinoid receptors colocalize with substance P (the neurotransmitter responsible for transmitting pain information) receptors in the striatum. CBD is primarily active at CB_2 receptors. It is also active at both serotonin and glycine receptors, making them more sensitive to the neurotransmitters. It has been shown to not have psychoactive effects and can block this effect derived from THC.[96,97]

A synthetic THC, dronabinol, and an analog of THC, nabilone, are available if clinicians want to prescribe this chemical. CBD is available by prescription under the brand name Epidiolex® and is FDA approved for Lennox–Gastaut and Dravet syndromes. It is available if the clinician desires to use this molecule in the patient for off-label purposes. Availability of prescription versions of these molecules eliminates the need for clinicians to recommend “medical marijuana” because it avoids the risks associated with dispensary marijuana such as adulteration, dose inconsistency, and unwanted effects.

Effects

CASE 90-9

QUESTION 1: P.H. is a 16-year-old male who is offered a marijuana cigarette (joint) by one of his friends. He smokes it and begins to feel light-headed and euphoric. He begins laughing at everything around him. Thirty minutes later, he and his friend become very hungry ("the munchies") and eat several candy bars.

Which of P.H.'s symptoms are consistent with marijuana use?

THC rapidly distributes into fat deposits and has an elimination half-life of 1.3 days in infrequent users and up to 13 days in frequent users.[98] Time to maximum (T_{max}) concentration via inhalation is rapid, occurring from 3 to 10 minutes, whereas the oral ingestion will take up to 2 hours.[98] Anecdotal comments from users are that the inhalation method has the advantage of more accurate dose administration because of its rapid effects. The oral version's delay in T_{max} can result in patients ingesting more than they wanted because of the inability to assess the "high" in a timely manner. The pharmacologic effects sought by most users of cannabis products are sedation, mental relaxation, euphoria, and mild hallucinogenic effects, and these effects depend on set and setting. Other common effects that are usually perceived as pleasurable include silliness, subjective slowing of time, gregariousness, hunger, and mild perceptual changes of all the senses that engender an absorbing fascination with music, eating, and other sensual and sensory activities. The state of mind generated is referred to as *stoned*, *high*, *loaded*, *wasted*, and many other colloquial terms. Smoking marijuana typically causes numbness and tingling of the extremities, light-headedness, loss of concentration, and a floating sensation in the first 3 or 4 minutes. Some of these effects are probably caused by the hyperventilation associated with deep inhalation of the smoke (referred to as a *hit* or *toke*) and breath-holding to allow maximal absorption from the lungs. During the first 10 to 30 minutes, the user may experience tachycardia (possibly palpitations), mild diaphoresis,

conjunctival injection ("red eye"), drying of the mouth, weakness, postural hypotension, periods of tremulousness, incoordination, and ataxia along with euphoria and the mental effects described earlier. There is a positive correlation of an increased risk of MI, likely due to hypotension and tachycardia.[99]

These effects usually resolve by 1 to 3 hours and are followed by a 30- to 60-minute period of sleepiness before complete clearing and return to normal consciousness. Oral ingestion of cannabis products may delay the onset of effects by 45 to 60 minutes and prolong the duration.[94] P.H. is experiencing euphoria, giddiness, and increased appetite, consistent with marijuana intoxication.

Adverse Effects

Case 90-9, Question 2: P.H. smokes more marijuana with his friend. He liked it so much the first time that he decides to take several "hits" this time. He begins to think his friend is laughing at him, and notices his heart is beating rapidly. He starts to panic. Is P.H.'s reaction caused by the marijuana?

Consistent with its widespread use, marijuana was the second most frequently mentioned illicit substance in ED episodes in the United States in 2011. A total of 455,668 marijuana-related ED visits were reported in 2011.[65] These visits include marijuana in combination with other drugs. As the percentage of THC in marijuana has increased, so have the ED visits. The majority of ED visits are from unexpected reactions, such as anxiety, paranoia, and panic attacks. Despite these numbers, there are no documented cases of fatality in humans from marijuana OD, and adverse effects tend to be self-limiting, and often do not require medical treatment.

A syndrome consisting of anxiety, paranoia, depersonalization, disorientation, and confusion that can lead to panic states and incapacitating fear is perhaps the most frequently reported adverse effect of marijuana. Comforting reassurance (talk down) and reducing stressful stimuli can alleviate this condition. The dysphoria and anxiety usually resolve in a few hours or less with such an

approach. More severe incidents that evolve into panic reactions not resolved by sympathetic counseling may be relieved with oral benzodiazepine therapy in a dose equivalent to 5 to 10 mg of diazepam.[64] These adverse psychological reactions to cannabis products commonly occur with inexperienced users, high doses, concomitant use of other psychoactive drugs, and overtly stressful situations. Severe reactions requiring pharmacologic therapy are rare. A review of the literature found that cannabis use increases the risk of developing psychotic disorders. This is more severe among vulnerable or predisposed individuals and negatively affects the course of preexisting chronic psychosis.[100]

Other adverse effects can include slowed psychomotor responses and short-term memory loss. Slowed psychomotor responses have been shown in certain groups of acutely intoxicated subjects and chronic users. There has been a steep increase in automobile accidents among marijuana users. A reduction in reaction time, attention, and other executive functions necessary for driving are all impaired, and this may last for days.[101] Short-term memory loss is a frequently documented acute, reversible effect of marijuana intoxication as well.

The paranoid ideation and panic reaction of P.H. could certainly be caused by a high THC dose and his inexperience with marijuana.

Cannabis withdrawal will occur in persons who have been using the substance nearly daily over at least a few months, and these symptoms will occur in up to 87% of users.[64,94,102] The symptoms will typically occur about a week after cessation and consist of (a) irritability, anger or aggression; (b) nervousness or anxiety; (c) sleep difficulties; (d) decreased appetite or weight loss; (e) restlessness; (f) depressed mood; and (g) physical symptoms such as abdominal pain, shakiness, sweating, fever, chills, or headache.[1] Treatment is not generally necessary, but dronabinol has shown benefit in reducing the distress.[103]

Long-Term Effects

Case 90-9, Question 3: P.H. continues to smoke marijuana daily. What are possible long-term effects of marijuana use?

Chronic use of cannabis has been shown to produce an "amotivational syndrome" characterized by apathy, lack of long-term goal achievement, inability to manage stress, and generalized laziness.[94,104,105] Cognitive impairment can occur from chronic marijuana use, including executive functioning, cognitive processing speeds, and short-term memory loss that is not reversible.[106] Adolescents are at risk for a reduction in intelligence quotient (IQ) related to marijuana use that does not reverse even after 1 year of abstinence.[102] The impairment is more pronounced the longer the drug is used.[85] Other concurrent drug use may also contribute to cognitive impairment associated with marijuana use. As noted earlier, there is a dose-dependent risk of chronic use resulting in an increased risk of developing a psychotic illness later in life.[100,107] Adolescents using THC weekly showed an increase in paranoia by 133% and hallucinations by 92% over non–THC-using adolescents.[108] Those older than age 18 showed a 380% increase of developing a psychotic disorder if using marijuana daily.[109] This increased to nearly 500% as the potency of THC increased.[109]

Chronic users will have worse periodontal health.[106] The pulmonary complications of chronic heavy marijuana use are potentially significant. Chronic cough, sputum, wheezing, bronchitis, and cellular changes typical of chronic tobacco smokers are reported in chronic cannabis smokers.[94,110] THC has been shown to be a potent bronchodilator. Both oral and smoked THCs were shown to produce significant bronchodilation when given to healthy subjects. The bronchodilatory response in asthmatics given THC has been shown to be less vigorous.[111] Tolerance to these effects can develop after some weeks, and chronic marijuana smoking results in increased airway resistance and decreased pulmonary function.[94] Many of the same carcinogens in nicotine cigarettes are also found in marijuana smoke, and risk of some cancers is increased compared to nonusers.[94,105] *Aspergillus*-contaminated marijuana has

been reported to cause pulmonary fungal infections in immunocompromised patients, who may be using the drug for its medicinal value.[112]

Tolerance to the psychoactive effects of marijuana does develop. Chronic users may not experience the full range of effects as do new users unless they abstain for several days or weeks to regain initial sensitivity to the cannabis, and chronic users can tolerate large doses that generally are toxic to novices. Tolerance develops rapidly to both physiologic and psychological effects of cannabis. Dependence characterized by a physical withdrawal syndrome occurs after chronic high-dose use of cannabis. Dysphoria and malaise similar to that experienced with influenza can also occur. The cumulative dose of cannabis and duration of use necessary to produce dependence is unknown. The withdrawal syndrome is generally mild and self-limiting, and pharmacologic treatments usually are not required.

Marijuana has been labeled as a "gateway drug," meaning that it will lead to the use of "harder" drugs, such as cocaine or heroin. Marijuana is the most widely used illicit drug, but use of drugs such as alcohol and tobacco often predates marijuana use. No studies have conclusively demonstrated a causal link between marijuana use and subsequent other drug use.[94]

There are clear acute and chronic risks associated with marijuana use that is primarily related to THC content and ingestion via inhalation. Dronabinol, nabilone, and CBD have FDA indications, and can be prescribed by a clinician if this is the desired pharmacology, yet marijuana has none. Despite this, many patients claim a "medical" benefit from this plant. Pharmacists are uniquely positioned to help patients understand the definitive risks from marijuana use and provide alternatives to their conditions that have FDA approvals.

INHALANTS

The introduction of anesthetics (nitrous oxide, chloroform, and ether) to medicine in the early 1800s also promoted the widespread and popular recreational use of these inhalants for mind-altering recreational purposes. Today, abused inhalants include a wide variety of chemicals that are found readily in homes or workplaces, or purchased at retail establishments. Inhalants are commonly subdivided into three main categories: the volatile solvents (mostly hydrocarbons); volatile nitrites (amyl, butyl, isobutyl, and cyclohexyl); and nitrous oxide (laughing gas). The fumes or vapors of these liquids, or paste, in the case of glue, are directly inhaled out of their containers (“sniffing”); poured onto a rag that is held to the nose (“huffing”); poured into a plastic bag (“bagging”); or merely cupped in the hands and inhaled. Aerosols and gaseous substances such as nitrous oxide are also used to inflate a balloon and then inhaled out of the balloon by the user. These products can also be ingested orally or sprayed directly into the mouth. Volatile solvents include gasoline, toluene, kerosene, alcohols, airplane glue, lacquer thinner, acetone (nail polish remover), benzene (nail polish remover, model cement), naphtha (lighter fluid), plastic cement, liquid paper (ie, White Out, [Emraw, New York City, NY] usually containing 1,1,1-trichloroethane, also trichloroethylene, and perchloroethylene), and many others. The volatile nitrites, once widely available, are prohibited by the Consumer Product Safety Commission, but can still be found, sold in small bottles, labeled as “video head cleaner” or “room odorizer.” Amyl nitrite is used medically as a vasodilator for treatment of angina, and requires a prescription. The volatile nitrites are commonly referred to as *poppers*, because of the sound made when an ampule of amyl nitrite is broken open. The most commonly used inhalants are glue, shoe polish, toluene, and gasoline.[113] The use of multiple products is common. Silver and gold paints are popular because they contain more toluene than do paints of other colors.[114]

Inhalant use is most common among younger individuals (consistently highest annual prevalence among eighth graders), and tends to decline as youth grow older. The decline likely reflects that other drugs become available and are substituted. Abuse of

inhalants is believed to be popular among children and adolescents because of their low cost, easy availability, rapid onset, and low threat of legal intervention. In addition, they are easily concealed. The 2019 Monitoring the Future (MTF) study found that 9.5% of 8th, 6.8% of 10th, and 5.3% of 12th graders have abused inhalants.[115] These surveys, most of which are administered in schools, likely underestimate the true prevalence, as a small but high-risk group (incarcerated, homeless, and transient adolescents) are not included in the surveys.

Effects of Inhalants

Inhalant abuse includes a broad range of chemicals, and they likely have different pharmacologic effects. In fact, the mechanisms of action of the volatile inhalants are poorly understood. Nearly all have CNS depressant effects. Evidence from animal studies suggests that the effects and mechanism of action of volatile solvents are similar to those of alcohol and sedative-hypnotics.[116]

Gases and vapors are rapidly absorbed when inhaled, and, because of their high lipophilicity, tend to distribute preferentially to lipid-rich organs such as the brain and liver.[116] Expired air is the major route of elimination, and most are metabolized to some extent. Inhalation of these products produces a temporary stimulation and reduced inhibitions before the depressive CNS effects occur. Acute intoxication is associated with euphoria, giddiness, dizziness, slurred speech, unsteady gait, and drowsiness.[114] As the CNS becomes more deeply affected, illusions, hallucinations, and delusions develop. The user experiences a euphoric, dreamy high that culminates in a short period of sleep. The intoxicated state lasts a few minutes, but users may continue to inhale repeatedly for several hours. Nitrous oxide is an antagonist of the NMDA subtype of the glutamate receptor.[76] Its pharmacologic effects are poorly understood. It produces euphoria and symptoms of intoxication similar to those described for the volatile solvents.

The major effect of the volatile nitrites is the relaxation of all smooth muscles in the body, including the blood vessels. This usually allows a greater volume of blood to flow to the brain. The onset of effects takes 7 or 8 seconds, and the effects last about 30 seconds. A certain “rush” occurs, which may be followed by a severe headache, dizziness, and giddiness. The volatile nitrites are frequently used in the context of sexual activity, because of the effect of increased tumescence and relaxation of smooth muscle.[116]

Acute and Chronic Toxicities Associated With Inhalants

The wide variety of chemicals inhaled causes a tremendous range of toxicities. Toxicity depends on the chemical, and on the magnitude and duration of exposure. Complications can result from the effects of the solvents or other toxic ingredients, such as lead in gasoline. The lipophilicity of the volatiles enhances their toxicity. Injuries to the brain, liver, kidney, bone marrow, and, particularly, the lungs can occur, and they may result from the effect of heavy exposure or hypersensitivity. Inhalant abusers may develop irritation of the eyes, nose, and mouth, including rhinitis, conjunctivitis, and rash.[116] Methemoglobinemia has been associated with volatile nitrite use.

Deaths from inhalant use are well documented and may occur from OD or trauma (falls, drowning, and hanging). Death from OD is often caused by respiratory problems or suffocation after CNS depression.[116] Deaths caused by asphyxiation, convulsions, coma, and aspiration of gastric contents have occurred.[114] Acute cardiotoxicity resulting in cardiac arrest may cause sudden death. Referred to as *sudden sniffing death*, it is likely caused by sensitization of the myocardium to catecholamines, exacerbated by physical exercise, resulting in fatal ventricular arrhythmias.

Many of the inhalants produce neurotoxicity, which can range from mild impairment to severe dementia. Neurologic deficits include cognitive impairment, ataxia, optic neuropathy, deafness, and disorders of equilibrium. Loss of white matter, brain atrophy, and

damage to specific neural pathways can result from chronic exposure to some inhalants. Some damage to the nervous system and other organs may be at least partially reversible when inhalant use is discontinued.[114]

Inhalant Abuse and Dependence

Compulsive use has been documented with inhalants, although inhalant abuse and dependence is a neglected area of research. Animal studies have shown some of the abused inhalants to have reinforcing properties.[116,117] It is unclear whether a true withdrawal syndrome occurs with chronic use of inhalants. Inhalant use is typically episodic in nature, and thus users may not be exposed to levels with sufficient frequency necessary to develop physical dependence or tolerance.

ALCOHOL USE DISORDERS

Alcohol Content and Definitions

Beverages containing alcohol (ethanol) have a wide range of ethanol content. Alcoholic proof is a measure of how much ethanol is in an alcoholic beverage and is twice the percentage of alcohol by volume (ABV), the unit that is commonly used as percent (%). Therefore “80 proof” is 40% ABV, and pure alcohol (100%) is “200 proof.” One hundred percent ethanol does not stay 100% because it is hygroscopic and absorbs water from the atmosphere.

Legally, in the United States, beers containing up to 0.5% ABV can be called nonalcoholic. Light beers range from 2% to about 4% ABV; beers range from 4% to 6% ABV; ales, stouts, and specialty brews can be as high as 10% ABV. Wines are produced at about 14% to 16% (28–32 proof), because that is the point in the fermentation process at which the alcohol concentration denatures the yeast. Stronger liquors are distilled after fermentation is complete to

separate the alcoholic liquid from the remains of the source of sugar (eg, grain and fruit). Distilled liquor cannot be stronger than 95% (190 proof). A standard drink in the United States is considered to be 0.5 oz or contain 15 g (0.5 fL oz of absolute alcohol) of alcohol. This is equal to 12 oz (355 mL) of 5% beer, 5 oz (148 mL) of 12% wine, or 1.5 oz (44 mL) of 40% spirits.[118,119]

Epidemiology

Slightly more than half (51.1%) of Americans age 12 or older reported being current drinkers (at least one drink in the past 30 days) of alcohol in the 2018 National Survey on Drug Use and Health survey.[4] This translates to an estimated 139.8 million people, which is similar to the estimates from 2002 to 2017. In 2018, heavy drinking (five or more drinks on the same occasion on each of 5 or more days in the past 30 days) was reported to be 24.5% of the population age 12 or older, stable since 2015.[4]

Approximately 10% of Americans will be affected by alcohol use disorder (AUD) sometime during their lives.[120,121] Treatment of alcohol dependence consists mainly of psychological, social, and pharmacotherapy interventions aimed at reducing alcohol-related problems.[122,123] Treatment usually consists of two phases: detoxification and maintenance.

The rationale for pharmacotherapy is based on several considerations. Advances in neurobiology have identified neurotransmitter systems that initiate and sustain alcohol drinking; pharmacologic modification of these neurotransmitters or their receptors may alter dependence.[124] Promising genetic research confirms that alcoholics are a heterogeneous population and that several gene variations can predispose some to increased alcohol use, whereas other gene variations can confer protection.[124] Animal models have identified pharmacologic agents that reduce alcohol consumption in animals, suggesting that similar agents could reduce alcohol consumption in humans.

Risks and Benefits of Alcohol Consumption

The role of alcohol in the development of medical problems such as cardiovascular disease, hepatic cirrhosis, and fetal abnormalities is well documented. Alcohol use and abuse contribute to thousands of injuries, auto collisions, and violence.[125] Alcohol can dramatically affect worker productivity and absenteeism, family interactions, and school performance.[126] Some studies suggest, however, that individuals who abstain from using alcohol may also be at greater risk for a variety of conditions, particularly coronary heart disease (CHD), than do people who consume small-to-moderate amounts of alcohol.[127]

A number of studies have documented an association between moderate alcohol consumption and lower risk of CHD and MI.[128,129] Binge drinking after an MI, however, increases the risk of mortality.[130,131] U.S. guidelines define moderate drinking as one drink or less daily for females or people age 65 and older, and two drinks or less per day for males.[132] An association between moderate drinking and lower risk of CHD does not mean that alcohol is the cause of the lower risk. A review of population studies indicates that the higher mortality risk among abstainers may be attributable to socioeconomic and employment status, mental health, and overall health, rather than abstinence from alcohol use.[133] Benefits of moderate drinking on CHD mortality are offset at higher drinking levels by increased risk of death because of other types of heart disease, cancer, cirrhosis, and trauma. The risk of a disease outcome from low-to-moderate drinking is less than the risk from either no drinking at all or heavier drinking. This produces a U-shaped curve when examining the association of alcohol consumption with rates of deaths from all causes.[127]

The exact mechanism by which alcohol use may be protective against morbidity in those with CHD is not clear. Some evidence indicates that different types of alcoholic beverages, such as red wines, which are high in tannins, may lower blood lipids and fats by increasing antioxidants.[131] Specifically, the mechanisms by which alcohol may reduce the risk of CHD include increasing levels of high-

density lipoprotein cholesterol, decreasing levels of low-density lipoprotein cholesterol, prevention of clot formation, reduction in platelet aggregation, and lowering of plasma apolipoprotein A concentration, resulting in the attenuation of the formation of atheroma and decreasing the rate of blood coagulation.[134,135] It is possible, however, that how a person drinks alcoholic beverages matters as well. For example, wines are ingested more slowly because they are typically consumed in moderate amounts with food. Binge drinking of any type of beverage, however, increases the risk of mortality from CHD in particular.[131]

Pharmacokinetics and Pharmacology

When consumed in amounts typical of normal social drinking, the absorption of ethanol from the stomach, small intestine, and colon is complete; however, the rate is variable. Peak blood ethanol concentrations after oral doses in fasting subjects generally are reached in 30 to 75 minutes, but several factors can influence the rate and extent of absorption.[136] The most rapidly absorbed formulations are carbonated beverages containing 10% to 30% ethanol. In contrast, high concentrations of alcohol can produce vasoconstriction in the GI mucosa, which results in slowed or even incomplete absorption of ethanol. Absorption of ethanol from the small intestine appears to be more rapid than from any other part of the GI tract, and does not depend on the presence or absence of food. Factors that control the rate of gastric emptying significantly control the rate of absorption by controlling the rate at which ethanol is delivered to the small intestine.[137,138] For example, food in the stomach slows the absorption of ethanol, probably by slowing gastric emptying. The level of intoxication achieved is not solely related to the plasma concentration. For any particular plasma concentration, greater cognitive impairment is seen during times when the plasma level is rising compared with when ethanol is primarily being eliminated. The degree of intoxication also appears to be directly related to the rate at which pharmacologically active plasma

concentrations are attained. Alcohol negatively affects cognitive performance and has a differential effect on the descending versus ascending limb of the blood alcohol concentration (BAC) curve. The latter finding may have important ramifications relating to the detrimental consequences of alcohol intoxication.[139]

The blood alcohol level (BAL) or BAC is calculated using the weight of ethanol in milligrams and the volume of blood in deciliters. This yields a BAC expressed as a proportion (ie, 100 mg/dL or 1.0 g/L) or as a percentage (ie, 0.10% alcohol). Ethanol concentrations are usually converted to equivalent BACs for standardization purposes when measured in other body fluids.

The alcohol dehydrogenase (ADH) pathway is the major enzyme system responsible for alcohol metabolism in humans. The main alcohol metabolism occurs with ADH isoenzymes, in the stomach (ADH6 and ADH7) and in the liver (ADH1, ADH2, and ADH3). The pathway involves conversion of ethanol to acetaldehyde by these ADH isoenzymes, resulting in the reduction of nicotinamide adenine dinucleotide (NAD) to nicotinamide adenine dinucleotide hydrogen (NADH). In the second step, acetaldehyde is converted to acetate via the enzyme aldehyde dehydrogenase, which also reduces NAD to NADH. These are the rate-limiting steps in ethanol metabolism, and this route becomes saturated when large amounts of ethanol deplete NAD.[140] Acetate ultimately is converted to carbon dioxide and water. An additional pathway that is more involved in alcohol-dependent individuals than in those who are not involves the catalase pathway of peroxisomes and the microsomal ethanol oxidizing system (MEOS), in the smooth endoplasmic reticulum. The main functional component of the MEOS is the CYP2E1 enzyme.

Of a dose of ethanol, 90% to 98% is oxidized in the liver, with the remaining drug excreted unchanged in the alveolar air and urine. Ethanol metabolism formerly was described by zero-order kinetics; however, Michaelis–Menten and other nonlinear, concentration-dependent models are more accurate.[141,142] In some situations, a portion of the absorbed dose of ethanol does not appear to enter the systemic circulation, suggesting first-pass metabolism. However, the relative contribution of hepatic versus gastric ADH to this response

continues to be debated.[143,144] Using a two-compartment, Michaelis–Menten pharmacokinetic model and experimental data, it appears that gastric metabolism contributes negligibly to first-pass metabolism.[145–147] They believe that gastric metabolism accounts for sex and ethnic differences in first-pass metabolism. Estimates of total gastric ADH suggest that the enzyme can metabolize 0.9 to 1.8 g/hour of ethanol, depending on the concentration of ethanol consumed.[148] The extent of first-pass extraction tends to decrease as the dose of alcohol increases. This is likely because of saturation of ADH, regardless of the source. When plasma ethanol levels are >0.2 g/mL, the ADH system becomes saturated. As hepatic ADH becomes saturated, there is increased unchanged excretion of alcohol. This results in a more intense odor of alcohol on the breath as the plasma ethanol concentration increases. The metabolism of alcohol also then tends to become nonlinear because of stimulation of CYP2E1, which produces metabolic tolerance to ethanol in chronic users.

Lower first-pass metabolism has been found in alcohol-dependent individuals, females, the elderly, and Japanese subjects.[145,147] Gastric ADH may also play a role in the effect of food in reducing ethanol bioavailability. Food, by delaying gastric emptying, allows for more extensive gastric metabolism.[148]

The accepted average rate of ethanol oxidation is 0.15 g/mL/hour for males and 0.18 g/mL/hour for females.[149] Although this rate still is widely used for both legal and medical purposes, other data suggest wide variability in ethanol metabolism. For example, wide differences in ADH activity have been demonstrated and attributed to heredity and other causes.[150,151] Chronic heavy drinkers frequently oxidize ethanol at twice the normal rates, with their metabolic rates returning to baseline after a period of abstinence.[152] The rate of oxidation in chronic heavy drinkers may also increase with elevated blood ethanol levels.[152] In contrast, patients with end-stage liver disease may progress to the point at which they have almost no metabolic capacity.

Chronic alcohol use is associated with characteristic changes in the liver. Hyperlipidemia and fat deposition in the liver occur because

of shunting of the excess hydrogen into fatty acid synthesis and direct oxidation of ethanol for energy instead of body fat stores being used for energy. Fatty liver is the first step in a sequence of events that ultimately leads to alcoholic cirrhosis. Accumulated acetaldehyde, which interferes with mitochondrial function by shortening and thickening microtubules, has been implicated as playing a role in the hepatotoxic process. The damaged microtubules then inhibit the secretory functions of the hepatocytes, which results in an increase in size and weight of the liver.[153] Nutritional deficits and impaired hepatic protein metabolism may contribute as mechanisms of hepatotoxicity in chronic ethanol consumers.[154,155]

Acetaldehyde is believed to play a role in most actions of alcohol.[156] Elevated acetaldehyde concentrations during ethanol intoxication cause the commonly seen sensitivity reactions, including vasodilatation and facial flushing, increased skin temperature, increased heart and respiration rates, and lowered blood pressure. Acetaldehyde also contributes to the sensations of dry mouth and throat associated with bronchoconstriction and allergic-type reactions, as well as nausea and headache. These adverse effects mediated by acetaldehyde have the potential to protect drinkers against the excessive ingestion of alcohol, but acetaldehyde also has the potential to produce euphoric effects that may reinforce alcohol consumption. Acetaldehyde also contributes to the increased incidence of GI and upper airway cancers that are seen with increased incidence in heavy consumers of alcohol and which may also play a role in the pathogenesis of liver cirrhosis.[157] In addition, alcohol consumption is considered a major causative factor in the development of both acute and chronic pancreatitis.[158]

Chronic alcohol use may lead to neurologic conditions, such as neuropathies and dementia. These complications are caused by alcohol toxicity on the nerve cells and indirect effects related to malnutrition and head injuries.[159–161] Brain atrophy of gray and white matter, cerebellum, and amygdala has consistently been measured in those with chronic heavy alcohol intake.[162] The prevalence of dementia is five times higher in older adult patients with AUD than in those without.[163] Cognitive effects include worsening memory,

learning, and motor function related to both current alcohol use and a history of chronic use.[159]

Ethanol ingestion can depress the CNS through all the different stages of anesthesia. Tolerance to this effect occurs after chronic use such that a blood ethanol level of 0.150 g/mL will not produce apparent behavioral or neurologic dysfunction in persons who drink a pint or more of 80-proof liquor (or its equivalent) daily for several years.

Neurobiologic Basis of Alcohol Dependence

Proteins that are particularly sensitive to alcohol include ion channels, neurotransmitter receptors, and enzymes involved in signal transduction. Notable neurotransmitters, hormones, and neuropeptides (NPs) include adenosine, cannabinoid receptors, corticotropin-releasing factor (CRF), DA, GABA, ghrelin, glutamate, neurokinin-1 (NK1), neuropeptide Y (NPY), norepinephrine, opioid peptides, and serotonin (5-HT). The key inhibitory neurotransmitter in the CNS is GABA, which is associated with a chloride ion channel that is affected by low concentrations of alcohol. Normally, when GABA binds to the $GABA_A$ receptor, the chloride channel opens, allowing negatively charged chloride ions to enter the cell and inhibiting neuronal cell activity. In the presence of alcohol, GABA release accentuates the anxiolytic effect of both combined.[164] Receptor compensation for continual inhibition by alcohol is to reduce $GABA_A$ receptor subunits.[165] Other sedative medications, such as benzodiazepines, also bind to the chloride channel at slightly different sites and facilitate GABA inhibition. The existence of a common receptor mechanism for the actions of alcohol and sedative-hypnotics accounts for the cross-tolerance between these substances.

Glutamate is the major excitatory neurotransmitter in the CNS. Low doses of alcohol strongly inhibit NMDA receptors and inhibit neuronal activity.[166] After continual exposure to high doses of alcohol, NMDA receptors upregulate in an attempt to balance

alcohol's inhibitory action. Thus, the combined effect of alcohol on $GABA_A$ and glutamate is to inhibit excitation and facilitate sedation.

Alcohol also affects several other ion channels and receptors. The $5\text{-}HT_3$ receptor subtype is particularly sensitive to the action of low doses of alcohol and may result in activation of 5-HT and DA. Alcohol also modifies the activity of β-adrenergic and adenosine neurotransmitter receptors linked to adenylate cyclase through membrane-bound G-proteins. Low doses of alcohol can facilitate the activity of norepinephrine, 5-HT, DA, endocannabinoid signaling system, and other neurotransmitter receptors linked to G-proteins.[167–169]

On a neurobiologic behavioral level, the mesolimbic dopaminergic pathway from the ventral tegmental area to the nucleus accumbens is activated by most dependence-producing drugs, including alcohol, cocaine, opiates, and nicotine.[170,171] Putatively, activation of this pathway mediates drug reward, and is responsible for the dependence-producing properties of all drugs of abuse.[172] Repeated alcohol use sensitizes the system, so that behavioral stimuli associated with alcohol also begin to release DA and to facilitate additional alcohol use.[173] DA released by drugs of abuse are 2- to 10-fold that of natural rewards.[174] This sensitization may account for the craving and preoccupation with drugs of abuse.

Cessation of chronic alcohol use results in a withdrawal state of nervous system excitation that is dysphoric and negatively reinforcing. It has been suggested that abstinence contributes to alcohol craving and the preoccupation with alcohol use, in that dependent individuals will continue alcohol use to avoid this state.[175] As noted, chronic alcohol use causes $GABA_A$ downregulation and NMDA upregulation, leading to CNS hyperactivity. The locus coeruleus, a nucleus of norepinephrine-containing cells in the pons, becomes hyperactive during withdrawal, and is proposed as mediating some of the negative effects of withdrawal. Chronic alcohol and drug use alters gene expression and increases levels of adenylyl cyclase, upregulates cyclic adenosine monophosphate (cAMP)-dependent protein kinases, and activates cAMP-response

element binding protein (CREB) and several phosphoproteins in this brain region, mediating tolerance and dependence.[176]

ALCOHOL TOXICITY

Toxicology

In the medulla, ethanol can depress respirations by inhibiting the passive neuronal flux of sodium via a mechanism similar to that of general anesthetic agents.[177] The enzyme Na^+/K^+-adenosine triphosphatase (ATPase) is inhibited, cAMP concentrations are reduced, and GABA synthesis is impaired. Ethanol is a CNS depressant, and even the uninhibited behavior associated with its use is caused by preferential suppression of inhibitory neurons. More global neuronal inhibition is seen at high ethanol concentrations.

Treatment of alcohol intoxication is essentially supportive. In highly intoxicated patients, however, the prolonged slowing of the respiratory rate can lead to arrhythmias, cardiac arrest, and death, often accompanied by aspiration of vomitus. Respiratory depression is responsible for the respiratory acidosis acid–base abnormality. Even when blood ethanol levels are below those associated with medullary paralysis, a blunted respiratory response to hypercapnia and hypoxia is seen.[178,179] This makes the assessment of respiratory status a primary concern in severely intoxicated patients.

Highly intoxicated patients with depressed respiration require immediate supportive care that may include endotracheal intubation for respiratory support. This should be sufficient to restore acid–base balance to within normal limits. When metabolic acidosis is a significant component of the acid–base disturbance, it may be necessary to administer sodium bicarbonate. This should be done only in conjunction with appropriate respiratory support to prevent the development of hypercapnia.

Serum Ethanol Concentration

Chronic use of alcohol can produce significant tolerance; therefore, the BAL cannot be used as a sole determinant of physiologic status. By contrast, for the alcohol naive, a BAC in the 0.30 mg% range can be fatal, although chronic drinkers can be awake and alert at even higher levels. The blood ethanol concentration generally correlates with the clinical presentation of the patient (**Table 90-4**), but tolerance varies among individuals. Impairment in motor function may become observable at levels of 0.05 mg%. Moderate motor impairment usually is seen at 0.08 mg%, which is the legal definition of intoxication in all states when driving. Respiratory depression may occur with ethanol concentrations 0.45 mg%.[180] The accepted median lethal dose (LD_{50}) for ethanol in humans is a blood concentration of 0.50 mg%, although fatalities have been reported with ethanol concentrations ranging from 0.295 to 0.699 mg%.[181,182]

Table 90-4
Relationship of Blood Alcohol Concentration to Clinical Status

Blood Ethanol Concentration	Clinical Presentation[a]
50 mg/dL (0.05 mg%)	Motor function impairment observable
80 mg/dL (0.08 mg%)	Moderate impairment; legal definition of intoxication in all states when driving
450 mg/dL (0.45 mg%)	Respiratory depression
500 mg/dL (0.50 mg%)	LD_{50} for ethanol

LD_{50}, median lethal dose.

[a]Tolerance to alcohol varies among individuals.

Factors that may be associated with fatalities at lower ethanol concentrations include lack of tolerance to alcohol, ingestion of other drugs, heart disease, and pulmonary aspiration. For example, patients who died of combined ethanol and barbiturate ingestions had a mean ethanol concentration of only 0.359 mg%, a mechanism that is applicable to other more commonly used drugs that also

depress respiration such as anxiolytics and opioids.[182] Therefore, the clinician should order a toxicologic urine screen to rule out possible concurrent drug ingestion.

Acute Management

In the alert intoxicated patient, general management is supportive and protective. Volume depletion resulting in hypotension often occurs in ethanol-intoxicated patients. Hypothermia also is a complication of severe intoxication and can contribute to hypotension. Hypoglycemia most often occurs in conjunction with reduced carbohydrate intake. This situation is common in malnourished alcoholics, but also might be particularly pronounced if a patient was dieting. If IV fluids are given, thiamine administration should precede that of glucose to prevent Wernicke encephalopathy. Administration of a short-acting benzodiazepine, such as lorazepam, should be considered.

Gastric lavage may be useful if ingestion of other drugs is expected, or when the large consumption of alcohol is very recent. Activated charcoal absorbs ethanol poorly, but should be administered when coingestion of other drugs is suspected. Hemodialysis rapidly removes ethanol from the body.[183] In uncomplicated cases, it has been suggested that dialysis be initiated immediately when the blood ethanol concentration is >0.6 mg%.[181] Ventilatory assistance and good supportive care usually are most important because respiratory depression is the primary cause of death in ethanol intoxication. With good supportive care, dialysis is generally unnecessary. Dialysis may be considered if the patient cannot be stabilized or has other complicating factors, such as coexisting disease states (eg, renal dysfunction) or ingestion of other drugs (**Table 90-5**).

Table 90-5

Acute Alcohol Intoxication: Symptoms and Treatment

Symptom	Course	Treatment

Symptom	Course	Treatment
Respiratory acidosis	Alcohol-induced respiratory depression; blunted response to hypercapnia and hypoxia	Endotracheal intubation for respiratory support
Coma	Alcohol-induced CNS depression; ingestion of other drugs	Gastric lavage, naloxone (Narcan®) 1 mg, repeat every 2–3 minutes up to 10 doses, depending on response and suspicion of ingestion. Dialysis possible
Hypotension	Hypovolemia	IV fluid replacement
Hypoglycemia	Most often occurs in malnourished patients. Pyruvate is converted to lactate, rather than to glucose, through gluconeogenesis	50% glucose (50 mL) by IV push

CNS, central nervous system; IV, intravenous.

ALCOHOL WITHDRAWAL

CASE 90-10

QUESTION 1: J.M. is a chef at a nursing home where his wife is the administrator. He drinks at work and was found unconscious and brought to the hospital. His wife states that J.M. regularly drinks half a gallon of vodka daily and has suffered an alcohol withdrawal seizure in the past. J.M.'s wife states that she does not believe that he ever abused street or prescription drugs. His BAC on admission was 0.52 mg%. J.M. has a history of hepatic insufficiency secondary to cirrhosis. The following laboratory results are reported:

Sodium, 143 mEq/L	Albumin, 4.7 g/dL
Potassium, 4.2 mEq/L	Cholesterol, 423 mg/dL
CO_2, 25.2 mEq/L	Creatinine kinase (CK), 1344 units/L
Chloride, 107 mEq/L	Total bilirubin, 2.3 mg/dL
Blood urea nitrogen (BUN), 18	Direct bilirubin, 0.3 mg/dL

mg/dL	
Creatinine, 0.8 mg/dL	Alkaline phosphatase (ALP), 74 units/L
Glucose, 101 mg/dL	Aspartate transaminase (AST), 288 units/L
Calcium, 9.9 mg/dL	Alanine transaminase (ALT), 148 units/L
Magnesium, 0.9 mg/dL	γ-Glutamyl transpeptidase (GGT), 992 units/L
Uric acid, 6.3 mg/dL	

What signs and symptoms evident in a clinical diagnosis of alcohol withdrawal need to be monitored in J.M.?

For many alcohol-dependent individuals with significant physical dependence, a cluster of withdrawal symptoms known as *alcohol withdrawal syndrome* (AWS) may occur on cessation or reduction of alcohol consumption. Depending directly on the degree of physical dependence, AWS can range from creating significant discomfort to mild tremor to alcohol withdrawal-related delirium, hallucinosis, seizures, and, potentially, death.[184,185] A GGT of 992 units/L in combination with the patient's medical history suggests that J.M. is a heavy drinker. Although J.M.'s AST, ALT, and total bilirubin levels are elevated, his direct (unconjugated) bilirubin is within normal limits, suggesting a problem with bilirubin excretion as would be consistent with viral hepatitis or cirrhosis.

Patients may present with AWS in a variety of settings because alcohol-dependent patients may be unrecognized and experience withdrawal after inpatient hospital admission for unrelated medical reasons. For example, a sample from a primary care practice indicated that 15% of patients presented with at-risk drinking patterns or identified alcohol-related problems.[186] Surgical patients should be screened preoperatively for possible alcohol dependence, to prevent and adequately treat AWS-related complications during and after surgery.[187]

Diagnosis requires cessation or reduction in alcohol use that has been heavy and prolonged, and two or more of the following

symptoms developing within several hours to a few days of the cessation: autonomic hyperactivity, hand tremor, insomnia, nausea or vomiting, transient hallucinations or illusions (tactile, visual, or auditory), psychomotor agitation, anxiety, and generalized tonic–clonic seizures.[1] These symptoms must cause significant distress or impairment of important areas of functioning, and not be caused by a general medical condition or another mental disorder. Withdrawal-related seizure is considered a more severe manifestation of withdrawal, as is alcohol withdrawal delirium (AWD), or *delirium tremens* as it is traditionally called. AWD is estimated to have a mortality rate of ~5% of patients who go into alcohol withdrawal.[188] Recognized predictors for AWS complications include the duration of alcohol consumption, total number of prior detoxifications from alcohol, and previous withdrawal-related seizures and episodes of AWD.[189]

Case 90-10, Question 2: How could the severity of J.M.'s withdrawal symptoms be quantitatively assessed?

Of currently used instruments available for measuring the degree of withdrawal in an alcohol-dependent patient, the most commonly used is the revised Clinical Institute Withdrawal Assessment for Alcohol–Revised (CIWA-Ar).[190] In addition, the Sedation-Agitation Scale (SAS) could be used to assess agitation.[191] The CIWA-Ar is a validated 10-item scale used for grading severity of AWS that is often used as an inpatient assessment of withdrawal. The CIWA-Ar provides a final score with a maximum of 67 points assessing the extent of headache, nausea, tremors, agitation, paresthesia, sweats, audio and visual disturbances, and lack of awareness of time or location. Treatment of AWS can be initiated based on a patient's CIWA-Ar score. A CIWA-Ar rating of ≤8 points represents mild withdrawal and needs little pharmacologic support. A rating of 9 to 15 is associated with moderate withdrawal and may require some pharmacotherapy. A rating >15 corresponds to severe withdrawal, with an increased risk of seizures and AWD. Providers should also

consider concomitant illnesses and medications when interpreting CIWA-Ar scores because individual items in the scale are not specific to AWS, and likewise some manifestations of withdrawal may be blunted. The SAS can be used in combination with the CIWA-Ar to evaluate the level of agitation and consciousness of a patient, and be linked to administer benzodiazepines on a symptom-triggered regimen when a patient becomes agitated (for scores >4 on a 7-point scale).

Management of Withdrawal

Case 90-10, Question 3: What drugs are demonstrated to be the most clinically effective for alcohol withdrawal, particularly in a patient such as J.M. with evidence of cirrhosis?

Benzodiazepines

Benzodiazepines modulate anxiolysis by stimulating $GABA_A$ receptors and, in doing so, substitute pharmacologically for alcohol.[192] They are considered the drugs of choice for alcohol withdrawal,[187,192,193] long-acting benzodiazepines (eg, chlordiazepoxide and diazepam) and short-acting agents (eg, lorazepam and oxazepam) represent the most efficacious pharmacotherapies for the treatment of acute alcohol withdrawal.[186] They are effective in preventing both first seizures and subsequent seizures during alcohol withdrawal.[194] Longer acting benzodiazepines may provide for easier weaning because they gradually self-taper on metabolism and excretion; this allows for less fluctuation in plasma drug levels.[195] Longer acting benzodiazepines also cause fewer rebound effects and withdrawal seizures on discontinuation. Shorter acting agents (eg, lorazepam or oxazepam), which undergo phase II hepatic metabolism to inactive metabolites, require more frequent dosing, but may be more appropriate for alcoholics with liver disease and the elderly.[193,196] When used

appropriately, all benzodiazepines appear equally effective in ameliorating the signs and symptoms of alcohol withdrawal; however, the choice of a benzodiazepine is dependent on factors such as pharmacokinetic properties, dosage formulation, presence of liver impairment, and ease of dosage titration[197] (**Table 90-6**).

Table 90-6
Suggested Treatment Strategies for Alcohol Withdrawal Syndrome

Protocol	Clinical Rationale	Drug	Dosing Regimen (Example)	Considerations
Fixed-Schedule Regimen	The patient receives a fixed dose of medication for 2–3 days regardless of the severity of symptoms. This approach is generally used in severe alcohol withdrawal.	Chlordiazepoxide	25–100 mg PO every 2–6 hours or 25 mg IV every 2–4 hours	Protocol fixed dose and time parameters are decided beforehand. Additional medication is provided as needed when symptoms are not controlled (eg, the CIWA-Ar score remains at least 8–10).
		Diazepam	10 mg PO every 1–2 hours (maximum 60 mg) or 5–10 mg IV 20–120 minutes (maximum 100 mg/hour or 250 mg/8 hour)	
		Lorazepam	On days 1 and 2, give 2–4 mg PO four times a day. On days 3 and 4, give 1–2 mg PO four times a day. On day 5, give 1 mg PO twice a day. May use IV or IM (maximum 20 mg/hour or 50 mg/8 hour)	
Symptom-Triggered Regimen	The patient is assessed every hour using the CIWA-Ar to determine the need for medication. The primary advantage of this approach is that less medication is used to achieve the same control and less sedation.	Chlordiazepoxide	50–100 mg	Less abuse potential for outpatients, low cost; long acting 24–48 hours
		Diazepam	10–20 mg	Long duration of action (20–50 hours), which provides a smooth treatment course with less breakthrough symptoms
		Lorazepam	2–4 mg	Shorter duration of action may be more appropriate for patients at risk for prolonged sedation (eg, elderly, hepatic impairment).
Alternative Therapies	In patients with benzodiazepine allergy or when use of a benzodiazepine is deemed medically inappropriate	Carbamazepine	Taper from 600–800 mg on day 1 down to 200 mg over 5 days. 400 mg PO tid for 3 days, then 400 mg PO bid for 1 day, then 400 mg PO for 1 day	Both carbamazepine and baclofen are nonaddicting. Few drug interactions Cause relatively little cognitive impairment
	May be equally efficacious as are benzodiazepines	Baclofen	5 mg PO tid for 3 days and then increase to 10 mg tid	Known to lower the seizure threshold; more information is needed before its routine use in alcohol withdrawal.
Adjunctive Therapies	Adrenergic hyperactivity	Clonidine	0.1 mg PO bid as needed	For mild-to-moderate hyperactivity
	Adrenergic hyperactivity	β-Blockers: Atenolol Metoprolol	50 mg PO daily 2.5–5 mg IV	May improve vital signs faster than does oxazepam alone. Up to 3 doses about 2 minutes apart; use parameters for HR and blood pressure.
	Agitation, hallucinations, delirium	Neuroleptics: Haloperidol Olanzapine	0.5–5 mg PO/IM/IV every hour; maximal dose 100 mg/day 10 mg IM	Rapid onset, but note QTc prolongation (eg, >450 ms); recommend baseline ECG before using IV. Maximal dosing, three 10-mg doses given 2–4 hours apart; monitor for orthostatic hypotension before the administration of repeated doses.

bid, two times daily; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol–Revised; ECG, electrocardiogram; HR, heart rate; IM, intramuscular; IV, intravenous; PO, orally; tid, three times daily.

Sources: Guirguis AB, Kenna GA. Treatment considerations for alcohol withdrawal syndrome. *U.S. Pharm*. 2005;30:71; Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of alcohol withdrawal delirium. An evidence-based guideline [published correction appears in *Arch Intern Med*. 2004;164:2068. Dosage error in article text]. *Arch Intern Med*. 2004;164:1405–1412.

DOSE

Two strategies for dosing benzodiazepines in AWS include fixed-schedule and symptom-triggered regimens. Fixed-schedule regimens involve a set dose and interval for the agent chosen, which is to be tapered off at specific times, usually starting on the second day of treatment. Symptom-triggered regimens depend on the use of a rating scale of withdrawal severity, such as the CIWA-Ar previously noted, which is repeated at set intervals. Medication is only administered if the scoring from the scale is above a predetermined threshold value for treatment. In this way, the risk of undermedicating or overmedicating patients may be minimized, because the degree of withdrawal symptoms guides dosing. Several studies confirm that symptom-triggered regimens compared with fixed-dose regimens appear to result in a shorter duration of necessary therapy and less medication administered in total without any loss of efficacy.[197]

The treatment challenge associated with individuals who are in alcohol withdrawal with a comorbid medical illness is illustrated by the case of a patient with AWS who has coronary artery disease. Such a patient may be more aggressively treated for withdrawal-related hypertension and thus treated with a β-blocker or clonidine. The result of such adjuvant treatment may be a reduced sensitivity of the CIWA-Ar owing to a masking of the patient's autonomic manifestations of withdrawal. This could then lead to a higher likelihood of undermedicating the patient for withdrawal and may put the patient at higher risk for severe sequelae from withdrawal. Because of these exclusion criteria, the symptom-triggered approach has not been tested in such populations or those with histories of severe withdrawal including seizures or delirium. Therefore, traditional fixed-dose regimens are recommended in these populations.[197] An effective approach is most likely to consider combining these two dosing strategies. For example, a low-risk patient (no history of AWS or AWD, the patient consumes low weekly amounts of alcohol and has no signs or symptoms of early AWS) receives a symptom-triggered regimen (eg, lorazepam 1 mg every hour as needed). Alternatively, a high-risk patient (history of AWS, AWD, or withdrawal seizures, consumes large daily amounts of alcohol, has signs or symptoms of early AWS) receives fixed-dose

lorazepam or diazepam with a tapering dose schedule and as-needed benzodiazepine administration for uncontrolled alcohol withdrawal signs or symptoms. Importantly, phenobarbital, dexmedetomidine, and propofol are useful adjuncts to benzodiazepines if an inpatient has severe symptoms.[197]

CONTRAINDICATIONS, WARNINGS, AND INTERACTIONS

Elderly patients, those with hepatic or renal insufficiency, and those with medical (eg, diabetes, cirrhosis) or other psychiatric illnesses (eg, dementia) require close observation. As noted earlier, in patients receiving calcium channel blockers, β-blockers, and α_2-adrenergic agonists, some signs of withdrawal such as hypertension, tachycardia, and tremor may not be apparent. In addition, patients with dementia are more difficult to assess for progression to delirium tremens. The benzodiazepines' adverse effect of cognitive impairment is more difficult to assess in a patient with baseline dementia. As in middle-aged adults, the CIWA-Ar is used for symptom-triggered dosing protocols in the older adult population. However, dosage requirements are significantly lower than they are for younger adults.[198]

Patients with a history of severe withdrawal symptoms, withdrawal seizures, or delirium tremens; multiple previous detoxifications; concomitant psychiatric or medical illness; recent high levels of alcohol consumption; pregnancy; and lack of a reliable support network should be considered for inpatient treatment regardless of the severity of their symptoms.[197]

Lorazepam is the only benzodiazepine with predictable IM absorption (if IM administration is necessary). Rarely, it is necessary to use extremely high dosages of benzodiazepines to control the symptoms of alcohol withdrawal. Controlled studies comparing the advantages and disadvantages of the various benzodiazepines in alcohol detoxification have not been performed, and no evidence exists to definitively support the use of lorazepam as the first-line agent in the treatment of AWS.[197,199]

In most patients with mild-to-moderate withdrawal symptoms, outpatient detoxification is safe and effective, and costs less than does inpatient treatment. If outpatient treatment is chosen, the patient and support person(s) should be instructed on how to take the prescribed medication, its side effects, the expected withdrawal symptoms, and what to do if symptoms worsen. Small quantities of the withdrawal medication, especially benzodiazepines, should be prescribed at each visit. Because close monitoring is not available in outpatient treatment, a fixed-schedule regimen should be used. The addition of phenobarbital for withdrawal symptoms as either a loading dose or throughout treatment has been beneficial for intensive care unit (ICU) stays and the amount of lorazepam used; however, the risk of respiratory depression and drug interactions is significantly higher when phenobarbital is combined with benzodiazepines. Early introduction of phenobarbital is associated with a reduced likelihood of transfer to the ICU.[200,201]

Given J.M.'s elevated liver enzymes, a reasonable approach would be to start with lorazepam. Shorter acting agents, such as lorazepam, which do not undergo extensive hepatic metabolism, are more appropriate for patients with evidence of hepatic insufficiency.

ADJUNCTIVE TREATMENTS

CASE 90-10, QUESTION 4: What adjunctive therapeutic support might be considered for J.M.?

The hydration, electrolyte (especially potassium and magnesium), and nutritional status of patients should be assessed at presentation. Support with IV fluids may be necessary in those patients with excessive losses through vomiting, sweating, and hyperthermia.[202] Thiamine and multivitamins as well as folate 1 mg should be routinely administered to patients in alcohol withdrawal. If IV fluids are given, to prevent precipitation of Wernicke encephalopathy,

thiamine administration should precede that of glucose.[189] Alcohol-dependent patients are deficient of thiamine and have a higher risk of developing Wernicke encephalopathy.[203] The condition is a triad of acute mental confusion, ataxia, and ophthalmoplegia. Korsakoff amnestic syndrome is a late neuropsychiatric manifestation of Wernicke encephalopathy with memory loss and confabulation; hence, the condition is referred to as *Wernicke–Korsakoff syndrome*. It is most often seen in chronic patients with AUD, but it can also be seen in disorders associated with malnutrition, for example, long-term hemodialysis or patients with acquired immunodeficiency syndrome (AIDS).[204]

Thiamine deficiency results in a decrease in cerebral glucose utilization. The body usually stores about 3 weeks of thiamine, with daily requirements of about 1.5 mg. Rapid correction of brain thiamine deficiency can occur with high plasma concentrations of thiamine, achieved by parenteral supplementation only because absorption of the oral thiamine by the GI tract is minimal (>5%), even with massive oral daily dosing.[203] Patients should receive at least 200 to 500 mg tid IV for 3 days to prevent the neuropsychiatric effects of thiamine deficiency.[204]

Several adjunctive medications, aside from the sedative-hypnotics, may serve ancillary roles in the therapy of AWS. Their selection should be based on treating specific symptoms associated with the syndrome. For instance, β-blockers (propranolol,[205] atenolol[206] or α_2-adrenergic agonists [eg, clonidine[207] or dexmedetomidine] if in an ICU) can be used for moderate-to-severe hypertension or other autonomic manifestations. α_2-Adrenergic agonists are preferred because it reduces NE outflow from the nerve and addresses all hyperadrenergic effects instead of just effecting the β-receptors with a β-blocker, and delirium seems to be more common with the β-blocker use.[197,199] Antipsychotics (eg, haloperidol and quetiapine) can be used for managing hallucinations and severe agitation, but care must be taken because these drugs can reduce the seizure threshold.[192,197,208]

PHARMACOTHERAPY OF ALCOHOL DEPENDENCE

CASE 90-11

QUESTION 1: R.M. is a 55-year-old male, weighing 140 pounds (63.50 kg), who used to have about 60 drinks a week before going through alcohol detoxification. R.M. is married and has a good job, and he is now committed to remain alcohol abstinent. R.M. heard about a drug called disulfiram from a friend and is interested in using this medication to help him abstain from drinking. Laboratory values obtained today include the following:

Sodium, 132 mEq/L	AST, 30 units/L
Potassium, 3.3 mEq/L	ALT, 35 units/L
CO_2, 22.6 mEq/mL	Uric acid, 9.1 mg/dL
Chloride, 109 mEq/L	Calcium, 8.7 mg/dL
BUN, 14 mg/dL	Magnesium, 1.7 mg/dL
Creatinine, 1.0 mg/dL	Albumin, 4.0 g/dL
Glucose, 123 mg/dL	Cholesterol, 255 mg/dL
Total bilirubin, 0.3 mg/dL	CK, 78 units/L
Direct bilirubin, 0.1 mg/dL	GGT, 30 units/L
ALP, 53 units/L	

Is disulfiram an appropriate agent to consider for R.M.?

To assess AUD, treatment requires an accurate medical history, including laboratory test results. In addition, several instruments are available to screen and delineate the extent of a patient's alcohol use. Ultimately, time and purpose for use are always major factors when deciding which instrument to use. The simplest screen to assess risk of alcohol abuse is to ask the patient the following question: During the past year, on how many occasions have you had five or more drinks (for a male) or four or more drinks (for a

female) at one time?[209] An affirmative answer would suggest that further follow-up of the patient's alcohol use history is needed. A second tool called the **C-A-G-E** consists of four questions: (1) Have you ever felt you should *c*ut down on your drinking? (2) Have people *a*nnoyed you by criticizing your drinking?; (3) Have you ever felt bad or *g*uilty about your drinking?; and (4) Have you ever felt you needed a drink first thing in the morning to steady your nerves or get rid of a hangover (*e*ye opener)? Positive responses to two questions suggest an alcohol problem (**Table 90-7**).[210] The Alcohol Use Disorders Identification Test (AUDIT), which was developed by the World Health Organization, has also been shown to be effective in screening individuals and distinguishing problem drinkers from others.[211]

Table 90-7
Useful Screens for Assessing Alcohol Problems

The C-A-G-E Screening Questions (CAGE)
Have you ever felt you should *c*ut down on your drinking?
Have other people *a*nnoyed you by criticizing your drinking?
Have you ever felt *g*uilty about drinking?
Have you ever taken a drink in the morning to calm your nerves or get rid of a hangover (*e*ye opener)?
Methods for Determining Recent Alcohol Consumption
Acute consumption ▪ Blood alcohol concentration ▪ Urine (ethyl glucuronide) ▪ Saliva ▪ Breath alcohol concentration
Recent heavy consumption ▪ γ-Glutamyl transferase (GGT) ▪ Carbohydrate-deficient transferrin (CDT) ▪ Mean corpuscular volume (MCV)

Pharmacotherapy

The pharmacologic treatments of alcohol dependence focus on relapse prevention once detoxification is complete and the patient has achieved a few days of abstinence. Treatment is intended to be an adjunct to psychosocial treatments and not used alone.[212] To date, disulfiram, acamprosate, and naltrexone tablet and injection have been FDA approved for the treatment of alcohol dependence. In addition, several other drugs, such as quetiapine and ondansetron, have shown varying degrees of success.[212–233] Yet, much is still unknown about the long-term rates of abstinence, how long these drugs should be used once patients are in treatment, the optimal doses, and whether the drugs are more effective in males or females or for which specific subpopulations.[234]

DISULFIRAM

Disulfiram is an irreversible acetaldehyde dehydrogenase inhibitor that blocks alcohol metabolism, leading to an accumulation of acetaldehyde. Disulfiram reinforces an individual's desire to stop drinking by providing a disincentive associated with increased acetaldehyde levels, resulting in headache, palpitations, hypotension, flushing, nausea, and vomiting when they consume alcohol. Severe reactions may result in arrhythmia, MI, and acute congestive heart failure. Because older adults potentially have cardiovascular conditions before starting disulfiram, the risk of use likely outweighs the benefit in the elderly.[235–237] The primary predictor of success with disulfiram is the patient's commitment to total abstinence from alcohol. Although anecdotal reports of success are common, clinical evidence suggests that disulfiram appears to be most effective for alcoholics who are involved in special high-risk situations (eg, weddings and graduations) and is particularly effective when administration is supervised.[3,212,238]

Controlled clinical trials of disulfiram have clearly shown efficacy, yet this has not been a consistent finding.[212] Double-blind, placebo-controlled studies using disulfiram are difficult because the

psychological deterrent to use alcohol is experienced by both treatment groups, and those who relapse will be unblinded when they experience the pharmacologic interaction.

In the most rigorous clinical trial conducted in a population of veterans, no significant difference in abstinence rates was demonstrated between patients taking placebo or 1 or 250 mg of disulfiram.[213] However, patients randomly assigned to receive 250 mg of disulfiram daily drank less frequently (significantly fewer drinking days per year). Patients who were middle-aged and had social stability were more likely to benefit from disulfiram. In another trial in which administration was supervised, patients receiving disulfiram drank less alcohol and less frequently; however, on randomization, patients were unblinded to their drug.[239]

The efficacy of disulfiram compared with acamprosate and naltrexone shows definitive efficacy advantage for disulfiram when the patients are assigned to supportive care that verifies adherence.[240,241] However, no advantage was seen for combining disulfiram with naltrexone in dually diagnosed alcohol-dependent patients.[242] In one study, disulfiram combined with acamprosate resulted in increased days of cumulative abstinence.[243]

Dosing

The recommended starting dose of disulfiram is 250 mg once daily, with a range of 125 to 500 mg/day.[242] If a patient drinks and does not experience a disulfiram–ethanol reaction, the dose can be increased to 500 mg, because a significant proportion of patients may not experience a disulfiram–alcohol reaction at the usual 250-mg daily dose.[244,245] Side effects are increased, however, at doses exceeding 250 mg. Dosing starts at least 12 to 24 hours after abstinence initiation (when the blood or breath alcohol concentration is zero). Treatment continues, depending on the particular needs of the individual, but is generally at least 90 days, and maintenance therapy may be required for years.

Contraindications, Warnings, and Interactions

Because of the intense cardiovascular and physical changes that occur in the disulfiram–ethanol interaction, disulfiram is contraindicated in patients with cardiac disease, coronary occlusion, cerebrovascular disease, and renal or hepatic failure. At somewhat higher doses, psychotic reactions have occurred. It is not definitive that disulfiram causes fetal abnormalities when administered during pregnancy, but some data are found regarding limb reduction anomalies in infants born to disulfiram-treated mothers taking disulfiram during the first trimester of pregnancy.[246,247] Thus, disulfiram should only be used during pregnancy if the expected benefit to the mother and fetus is greater than is the possible risk to the fetus; however, it should be avoided in the first trimester (category C). No information is available about the safety of this medicine during breast-feeding.

Disulfiram can also be hepatotoxic and should be used cautiously in patients with liver disease. Liver function should be established at baseline and after 14 days of treatment, and a complete blood count (CBC) and liver function tests (LFTs) should be obtained every 6 months.[248] A high AST/ALT ratio is more indicative of alcohol-induced liver toxicity, whereas disulfiram is more likely to have elevations in both ALT and AST.[249] A high bilirubin is a predictor of the need for liver transplantation or death from disulfiram.[249]

R.M. has normal hepatic function; however, LFTs should be monitored at baseline and periodically during treatment. Although not all clinicians agree, most would recommend—at minimum—baseline LFTs: ALT, AST, and GGT and withholding disulfiram when LFTs are more than three times the upper limits of normal.[248] If elevated, repeat LFTs every 1 to 2 weeks until normal, and then every 3 to 6 months if no elevations, with an awareness that increased LFT results may signal a return to drinking rather than to disulfiram toxicity.[250,251] Persistently elevated LFTs may also indicate viral hepatitis (B or C), for which alcoholics have a higher risk, and thus the need to order a hepatitis profile. Currently, guidelines point out that a reduction in alcohol use will lead to more normalized LFTs.

Psychiatric adverse effects include disorientation, agitation, depression, and behavioral changes such as paranoia, withdrawal and bizarre behaviors, and worsening of schizophrenia, especially at doses >250 mg daily.[252,253] Disulfiram should be avoided or used very cautiously in persons with these conditions, although it can be used safely at a dose of 250 mg daily in alcohol-dependent patients with concomitant psychiatric disorders, including schizophrenia.[242,254,255] Common side effects of disulfiram include drowsiness, particularly in the first few weeks of treatment, a metallic or garlic taste, and sexual dysfunction. The dose can be taken at bedtime if drowsiness or tiredness occurs.

Disulfiram is metabolized to some extent by stomach acids to diethyldithiocarbamic acid (DDC), which then converts to carbon disulfide and diethylamine. Disulfiram, DDC, and copper-chelated DDC are absorbed. The metabolism of disulfiram and its biotransformed absorbed metabolites is eventually affected by several enzymatic pathways, with 1% to 20% primarily excreted in the feces as unchanged disulfiram.[256,257] Disulfiram is also a mild inhibitor of CYP2E1 and CYP2C9,[256,257] and can interact with anticoagulants (warfarin), antiepileptics (phenytoin and carbamazepine), some benzodiazepines (diazepam), and tricyclic antidepressants (amitriptyline and desipramine), potentially increasing the toxicity of these medications. Delirium can result in combination with monoamine oxidase inhibitors. Adverse effects with disulfiram that mimic the alcohol–disulfiram interaction can also occur with metronidazole and omeprazole.[256–258]

To receive optimal results with disulfiram, patients must receive regular counseling and be closely monitored for any changes in hepatic function. Having someone participate in helping to validate the administration process is known to lead to better outcomes. Discontinuation of disulfiram should occur only after consultation with the prescriber and counselor involved. Patients must stop the medication for at least 3 days (up to 14 days in some) before being exposed to products containing alcohol. It is important to educate patients taking disulfiram about the dangers of consuming even small amounts of alcohol in foods, over-the-counter medications,

mouthwashes, and topical lotions. The patient should report any respiratory difficulty, nausea, vomiting, decreased appetite, dark-colored urine, or a change in pigmentation in the skin or eyes (primarily yellowing).

Summary

Generally, given the special circumstances needed for success, disulfiram is not the drug of choice for treating alcoholism. The social, medical, and psychiatric status of a candidate is an important consideration in the use of disulfiram. R.M. would appear to be a reasonable candidate for disulfiram given he has agreed to have his medication administration supervised (in this case, by his wife), his steady employment, and his motivation to sustain abstinence. R.M. should also receive counseling and support services on a regular basis.

ACAMPROSATE

Acamprosate (Campral®) has multiple actions but is principally a glutamate and GABA modulator. The key mechanism of action is considered to be a weak functional antagonist of the glutamate NMDA receptor, possibly mediated through indirect modulation of the receptor site via antagonism at the mGluR5 receptor.[259] It also has $GABA_B$ receptor agonism, but this effect would be minimal.[260,261] A series of meta-analyses and systematic reviews demonstrated that when used as an adjunct to psychosocial interventions, acamprosate improves drinking outcomes such as the length and rate of abstinence.[212,262,263] This effect is less likely if acamprosate is not initiated quickly after detoxification.[264,265] Evidence indicates that the effect of acamprosate on abstinence lasts after the treatment is stopped.[266] Acamprosate appears to be especially useful in a therapeutic regimen targeted at promoting abstinence, and can be

used in primary care settings as well as specialized addiction treatment programs.[267] Few contraindications to treatment exist. Little consistent information is found about patient characteristics that predict improvement while taking acamprosate. In a meta-analysis of all U.S. and European studies, predictors of abstinence were motivation, readiness to change, baseline abstinence, initial first week compliance, and living with a partner or child. A pooled analysis of seven European trials, however, found no significant predictors of the abstinence outcome measures.[268] Candidates for acamprosate should be committed to abstinence and begin the medication after being abstinent from alcohol.[269,270]

In a systematic review of the efficacy data related to acamprosate, proof of efficacy was strong.[269] Moreover, several studies on acamprosate have reported positive results. For example, in a study of 272 severely dependent alcoholics, patients receiving acamprosate showed a significantly higher continuous abstinence rate within the first 2 months of treatment compared with patients receiving placebo.[216] Of acamprosate-treated patients, 40% were continuously abstinent for a 48-week period compared with 17% of those who received placebo.

Acamprosate has also been studied for periods of up to a year. In a long-term follow-up (12 months) after trial completion, acamprosate still maintained an effect on abstinence rates, but not on nondrinking days. Some studies have found limited to no efficacy, although two of the studies may have been underpowered.[223,271–274] One of these studies also had a short treatment period, and the other had a long delay in initiating treatment.[272,273] In summary, most studies suggest that acamprosate is a safe and well-tolerated drug for the promotion of alcohol abstinence.[275]

Dose

Even though acamprosate has a half-life of 20 to 33 hours, the drug dosing for acamprosate is 666 mg orally three times daily. Studies with doses of 999 mg orally bid have found this dose to be

bioequivalent.[260,276,277] Patients can be started on the full dose without titration. Acamprosate is not well absorbed from the GI tract, and with a terminal half-life of around 30 hours, it takes several days to achieve desired blood levels of the medication.[278] The medication appears to be safe and effective in alcoholics, with minimal side effects. It does not appear to produce sedation, and does not cause drug dependence. Main adverse effects of acamprosate appear to be GI, including nausea, diarrhea, and bloating. Nausea or diarrhea can be easily managed, but if symptoms are severe or persistent, the dose should be reduced by one-third to one-half. The duration of therapy ultimately depends on treatment success and the willingness of the patient to continue therapy indefinitely.

Contraindications, Warnings, and Interactions

Therefore, patients with decreased renal function should receive lower doses. Patients with moderate-to-severe renal impairment had a 2- to 4-fold increase in plasma concentrations compared with patients with normal renal function.[260,279] For those with a creatinine clearance (CrCl) of 30 to 50 mL/minute/1.73 m^2, reducing the dose by one-half is recommended.[260,261] Because of acamprosate's near-complete elimination unchanged through the kidneys, dose adjustments are not necessary for liver function impairment.[277] Acamprosate should only be used during pregnancy when the benefit clearly outweighs the risk because the drug has been shown to be teratogenic (category C) in rats.[278] Tetracyclines may be inactivated by the calcium component in acamprosate during concurrent administration.[278] Naltrexone increases plasma levels of acamprosate, although the clinical significance of this interaction is unknown and the two can be safely used together.[278,280] Suicidal ideation and attempted and completed suicides have occurred in patients taking acamprosate.

Acamprosate must be used in combination with a psychosocial program such as CBT or at regular AA meetings. Acamprosate may be taken without regard to meals. The tablets should not be crushed

and should be taken whole. Although no interaction with alcohol occurs, abstinence in combination with counseling and social support is required to attain optimal treatment. Patients should report persistent diarrhea, sudden or excessive weight gain, swelling of the extremities, respiratory difficulties, fainting, or thoughts of suicide.

In a retrospective long-term study in 353 alcohol-dependent patients, supervised disulfiram was found to be superior to acamprosate, particularly in patients with a long history of alcohol dependence.[241]

NALTREXONE

Naltrexone is an opiate receptor antagonist that blocks the opiate stimulatory effects of alcohol to reduce the pleasure from drinking. However, the unpleasant sedating and GI effects of alcohol remain. This may help reduce the amount of alcohol ingested and eventually decrease the frequency of relapse.[237,261] Naltrexone's benefit is greater in individuals who drink for the reward or positive reinforcement felt from alcohol.[281,282] Naltrexone also decreases cravings for alcohol, as measured by subjective scales. This effect is better with naltrexone than with acamprosate.[283,284] Naltrexone also has a labeled indication for the treatment of opiate use disorder. As a result, patients with both AUD and opiate use disorder may benefit from this agent. Evidence seems to support the use of naltrexone as an adjunct to psychosocial interventions, with higher abstinence rates in short-term treatment, and as a deterrent to progressing from a lapse to a full-blown relapse.[212,244,284,285] Naltrexone is as efficacious as disulfiram and probably more efficacious than is acamprosate.[223,284,286,287]

Several studies indicate that naltrexone is most effective in patients with strong craving,[214,288] poor cognitive status at study entry,[289] and high compliance.[290,291] This observation is consistent with the demonstrated effect of naltrexone in reducing craving. Evidence also indicates that persons with a family history of

alcoholism, early age at onset of drinking, and comorbid use of other drugs are more likely to benefit from naltrexone.[292]

Comprehensive reviews of pharmacotherapies for alcoholism concluded that oral naltrexone produced a consistent decrease in the relapse rate to heavy drinking and in drinking frequency, although it did not enhance absolute abstinence rates.[270,293,294] More specifically, several studies using naltrexone report the opioid antagonist to be more effective than is placebo in reducing relapse rates, in increasing the percentage of nondrinking days,[214,215,290] and in reducing craving in heavy drinkers.[295] Yet, other studies fail to demonstrate a significant difference with placebo.[296,297] Several factors may explain the discrepancies in results of the different clinical trials with naltrexone. Many of the studies included small sample sizes and may lack the statistical power to demonstrate treatment effects.[275] Several large sufficiently powered studies also reported negative results.[296–298]

The combined pharmacotherapies and behavioral interventions for alcohol dependence (COMBINE) trial[223] clearly supports the effectiveness of naltrexone in that each of the groups of patients receiving naltrexone in conjunction with MM had a higher percentage of days abstinent than had those receiving placebo plus MM without naltrexone or combined behavioral intervention (CBI). Naltrexone also reduced the risk of heavy drinking. Extended-release naltrexone injection 380 mg is safe and well tolerated in alcohol-dependent individuals.[299] In two double-blind, randomized, placebo-controlled trials, the efficacy of once-monthly extended-release injectable or depot forms of naltrexone was demonstrated.[229,300,301] which suggests the advantage of increased compliance. Garbutt et al[229] reported that males receiving naltrexone injection had significantly better treatment outcomes than did females, and females who received naltrexone demonstrated no difference from those who received placebo. In addition, because a robust effect was seen for naltrexone injection compared with placebo for people coming into the study abstinent, the FDA required the manufacturer to place a requirement for abstinence when starting the medication on its product information. In the primary care setting, naltrexone injection

given for 3 months and offered with physician-delivered MM was found to be effective in the treatment of alcohol dependence.[302]

Dose

Naltrexone has been approved for use in the first 90 days of abstinence when the risk of relapse is highest. It has also been shown to be safe and well tolerated by patients for periods of up to a year. Treatment with naltrexone should continue based on the response to the medication. Discontinuation should only be considered in consultation with the health care provider. Naltrexone is available as both an oral tablet and a 28-day long-acting injectable.[237,303] Typical adverse effects include nausea, dizziness, sedation, and headache. These adverse effects tend to be mild, and study dropouts because of adverse effects were similar to those with placebo.[304] The usual dose of naltrexone is 50 mg daily, although doses of 25 to 100 mg daily have been reported to be effective, particularly in those with lower blood concentrations of the drug.[302] Side effects, such as nausea or headache, are more common in the initial few days of therapy. Naltrexone should be initiated at least five half-lives after the cessation of any opioid the patient may have been taking, to avoid the induction of opioid withdrawal.[279,303,305] Starting with a 25-mg dose (half a tablet) for the first two to four daily doses may reduce the incidence of side effects.[306,307]

The 380-mg long-acting injectable formulation is given as a gluteal IM injection every 28 days. Patients may prefer this option, particularly in circumstances where daily adherence to oral medications could be difficult to maintain.[308] The 380-mg long-acting injectable formulation has an initial peak that occurs within 2 hours and a second peak that occurs at day 2. This long-acting formulation then plateaus with a resultant steady decrease in blood concentrations starting at day 14. The long-acting formulation has a half-life of 5 days and provides an almost twofold increase in steady-state concentrations of naltrexone over the 50 mg given orally and a

fourfold increase in the metabolite 6-β-naltrexol because of the lack of first-pass metabolism.[308]

Contraindications, Warnings, and Interactions

Naltrexone is contraindicated in patients with a history of sensitivity to naltrexone with acute hepatitis or liver failure and in those who are physically dependent on opioids, receiving opioid analgesics, or in acute opioid withdrawal. The benefit of using naltrexone during pregnancy should clearly outweigh the risk. The concurrent administration of naltrexone and opioid analgesics is contraindicated. To avoid triggering an acute abstinence syndrome, patients must be opioid free for a minimum of 7 to 14 days before initiating treatment with naltrexone, as substantiated with a urine drug test. Although rarely performed, a naloxone challenge test can be used before treatment with naltrexone to rule out concurrent use of opioids. Naltrexone is in the FDA pregnancy category C, and it is unknown whether naltrexone passes into breast milk.

A possible clinical concern with naltrexone tablets or long-acting injectable naltrexone is pain management. Any attempt to overcome the opioid blockade produced by naltrexone using exogenous opioids may result in fatal OD. Should a patient be in pain after receiving an injection, the first drug of choice should be a nonopioid, such as a nonsteroidal anti-inflammatory drug (NSAID). If the patient is still in pain, an opiate can be used, but it will most likely have to be administered in a higher dose and more frequently. When reversal of naltrexone blockade is required for pain management, patients should be monitored in a setting equipped and staffed for cardiopulmonary resuscitation and monitored for signs of respiratory depression.

In a yearlong safety study, the most common side effects were nausea, dizziness, sedation, headache, anxiety, and blurred vision.[309] Should such side effects occur, reducing the dosage by one-half often reduces the side effects. Large doses (eg, 200 mg) of naltrexone can cause liver failure. Patients should report excessive

tiredness, unusual bleeding or bruising, loss of appetite, pain in the upper right part of the stomach, any discoloration of the skin or eyes, a change in stool color or urine, thoughts of suicide, or signs of pneumonia. Patients receiving extended-release naltrexone injection must also monitor the injection site for any type of reaction, for example, swelling, tenderness, bruising, or redness (69% for naltrexone vs 50% for placebo). Reactions that do not resolve in 2 weeks may result in induration, cellulitis, abscess, sterile abscess, or necrosis. Some patients may need to be evaluated for surgical intervention.[309]

COMBINATION PHARMACOTHERAPY

Combination therapy consisting of any of the three FDA-approved drugs in younger adults has been shown to be safe and is possibly more beneficial than is monotherapy.[3,279,303,310] Because disulfiram is potentially unsafe in older adult patients, combination therapy should be limited to acamprosate and naltrexone. The rationale for combining medications is that acamprosate reduces negative reinforcement and naltrexone attenuates positive reinforcement.[171] To test this hypothesis, a randomized, controlled study of 160 patients performed in Europe demonstrated that although combining naltrexone and acamprosate was more effective than was either placebo or acamprosate alone, adding acamprosate was not significantly more effective than was naltrexone alone.[287] In the much larger study, the COMBINE trial randomized >1300 individuals in a double-blind manner to receive placebo, naltrexone, or acamprosate alone or in combination with MM or CBI.[223] Results from this study suggest that acamprosate has no significant effect on drinking versus placebo, either by itself or with any combination of the other treatments in the study. Furthermore, patients receiving placebo and MM from a health care professional had better outcomes than did patients receiving CBI (a CBT-like therapy that includes 12-step facilitation) alone. From the available evidence, it is acceptable to

combine acamprosate with naltrexone with the expectation that in some patients it may not be any more effective than is naltrexone alone.

Topiramate

For patients who did not respond to naltrexone and acamprosate or are intolerant to either agent, topiramate may be offered.[303] Topiramate has multiple mechanisms of action, including enhanced $GABA_A$ inhibition that results in decreased DA facilitation in the midbrain, thought to be of potential benefit in the treatment of AUD, maintenance treatment.[311] In addition, it causes antagonism of kainate to activate the kainate/AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptor subtypes and inhibition of type II and IV carbonic anhydrase isoenzymes.[312] Topiramate is not FDA approved for the treatment of AUD.

A randomized, double-blind, placebo-controlled trial used an escalating dose from 25 to 300 mg/day of topiramate or matching placebo in 150 alcohol-dependent males and females during the first 8 weeks of a 12-week period.[222] Patients stayed at the same dose for the last 4 weeks of the study. All patients in the study received brief behavioral compliance enhancement therapy (BBCET) that was a 10- to 15-minute meeting with a health care professional that focused on resolving side effect issues and facilitated adherence. Participants receiving topiramate reported significantly fewer drinks per day and drinks per drinking day, significantly fewer drinking days, significantly more days of abstinence, and significantly less craving than did those on placebo. The evidence suggests that although abstinence was not a goal at the start of the topiramate study, the medication may be more beneficial during the abstinence initiation phase of treatment.[313] In a phase II clinical trial, the use of topiramate for alcohol dependence treatment was confirmed by outcomes demonstrating that topiramate recipients showed a significantly greater lowering of percentage of heavy drinking days and drinks per drinking day, and a higher percentage of days

abstinent. Topiramate is a non–FDA-approved medication that is beneficial in AUD treatment.[314] In a three-arm study with placebo and naltrexone, topiramate showed statistically significant improvements compared with placebo for time to first relapse (P = .01), cumulative abstinence duration (P = .02), heavy drinking weeks (P = .02), and continuous abstinence at 4 and 8 weeks (P = .01). Topiramate also improved these outcomes compared with naltrexone; however, the results were not statistically significant.[315]

In the treatment of alcohol dependence, topiramate is titrated from 25 mg/day up to 300 mg/day over a 6-week period (100 mg in the morning; 200 mg in the afternoon) or to the patient's maximal tolerable dose. Abrupt discontinuation of topiramate has been associated with seizures in patients without a history of seizures, and, for this reason, gradual withdrawal of the drug (eg, a 25% decrease in the dosage every 4 days for 16 days) is recommended.

In addition to paresthesias (tingling in the extremities), other prominent side effects include mental confusion, slowness in thinking, depression, and somnolence, which may be attenuated by titration when initiating therapy, and the development of renal calculi in about 1.5% of patients.[316] Adequate hydration is encouraged, particularly in patients who may be at risk for developing calculi. Topiramate can cause drowsiness, dizziness, changes in memory, a change in taste (particularly with carbonated beverages), vision changes (particularly associated with increased intraocular pressure), pressure to the touch, loss of appetite or weight loss, and sudden changes in mood.

CONTRAINDICATIONS, WARNINGS, AND INTERACTIONS

Topiramate is contraindicated in those hypersensitive to the drug. Topiramate should be used with caution in those who have a history of urolithiasis, paresthesias, secondary angle-closure glaucoma, renal or hepatic impairment, and conditions or therapies that predispose to acidosis (eg, renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs). Monitoring for hyperchloremic non–ionic-gap metabolic

acidosis is essential, and therefore baseline chemistry (eg, HCO_3^- and pH) should be assessed and monitored regularly thereafter. Metabolic acidosis can cause symptoms such as tiredness and loss of appetite, or more serious conditions including arrhythmia or coma. Topiramate has been found to be teratogenic in animal studies, and is a pregnancy category C medication.[316]

Concomitant use of oral contraceptives, phenytoin, carbamazepine, and valproic acid has been found to interact with topiramate.[258] Coadministration of another carbonic anhydrase inhibitor, such as acetazolamide, may increase the possibility of renal stone formation and should be avoided.

Gabapentin

Gabapentin has been studied for the treatment of AWS and maintenance with mixed results. Gabapentin has a regulatory effect on GABA and glutamate brain signaling by binding to the α2δ-1 subunit calcium channel.[317] The American Psychiatric Association's most recent guideline states that patient preferences should be considered when deciding between gabapentin and topiramate.[303] In a double-blind, randomized, placebo-controlled trial of 90 subjects over 16 weeks, gabapentin was more beneficial on the percentage of heavy drinking and abstinent days (P = .04 and P = .02, respectively) than was placebo for those entering the study experiencing high AWS.[318] In subjects showing low AWS at study entry, the gabapentin arm had worse results than had placebo for heavy drinking and abstinent days, although this was not statistically significant. This may suggest a benefit of gabapentin on withdrawal symptoms that could reduce early sobriety relapse. Dizziness was higher in the gabapentin group (57%) than that in placebo (33%). Gabapentin was well tolerated at doses of 600 to 1800 mg given three times daily.[318–320] A concern with gabapentin in the older adult population is its association with increased falls. According to the 2019 Beers Criteria, gabapentin should be used with caution or avoided in older adults because of its strict dependence on renal function for

excretion and the subsequent dizziness that may occur if doses are too high. This risk increases if gabapentin is added to an opioid.[321] Another risk with gabapentin is its abuse potential, with rates of 22% in substance use treatment centers.[322,323]

COMORBIDITIES IN ALCOHOL USE DISORDER

It is quite common for patients who are involved in harmful drinking to have comorbid medical issues. Alcohol has significant drug interactions with many medications (**Table 90-8**). Clinicians must also consider the potential for comorbid psychiatric disorders, (also known as dual diagnosis, eg, depression, bipolar disorder, or schizophrenia) combined with a substance use disorder. Tobacco and caffeine dependence are common.[324] Increased comorbid conditions lead to a poorer treatment prognosis for both medical and psychiatric conditions.

Table 90-8
Ethanol–Drug Interactions

Acetaminophen	Chronic excessive alcohol consumption increases susceptibility to acetaminophen-induced hepatotoxicity. Acute intoxication theoretically protects against acetaminophen toxicity because less hepatotoxic metabolite is generated.
Anticoagulants (oral)	Chronic ethanol consumption induces hepatic metabolism of warfarin, decreasing the hypoprothrombinemic effect. Very large acute ethanol doses (>3 drinks/day) may impair the metabolism of warfarin and increase the hypothrombinemic effect. Vitamin K–dependent clotting factors may be reduced in alcoholics with liver disease, also affecting coagulation.
Antidepressants	Enhanced sedative effects of alcohol and psychomotor impairment are possible. Acute ethanol impairs metabolism. Fluoxetine, paroxetine, fluvoxamine, and probably other SSRIs do not interfere with psychomotor or subjective effects of ethanol.
Ascorbic acid	Ascorbic acid increases ethanol clearance and serum triglyceride levels and improves motor coordination and color discrimination after ethanol consumption.

Barbiturates	Phenobarbital decreases blood ethanol concentration; acute intoxication inhibits pentobarbital metabolism; chronic intoxication enhances hepatic pentobarbital metabolism.
Benzodiazepines	Psychomotor impairment increases with the combination.
Bromocriptine	Ethanol increases gastrointestinal side effects of bromocriptine.
Caffeine	Caffeine has no effect on ethanol-induced psychomotor impairment.
Calcium channel blockers	Verapamil inhibits ethanol metabolism and increases intoxication.
Cephalosporin antibiotics	Ethanol produces flushing, nausea, headaches, tachycardia, and hypotension. Cephalosporin antibiotics that have an ethyl tetrazole thiol side chain produce this disulfiram-like reaction (eg, cefoperazone, cefamandole, and cefotetan).
Chloral hydrate	Elevation of plasma trichloroethanol (a chloral hydrate metabolite) and blood ethanol may occur. Combined CNS depression. Vasodilation, tachycardia, headache
Chloroform	Ethanol increases chloroform hepatotoxicity.
Doxycycline	Chronic consumption of ethanol induces hepatic metabolism of doxycycline and may lower serum concentration of the antibiotic.
Erythromycin	Ethanol may interfere with absorption of the ethylsuccinate salt. Effects on other formulations are unknown.
Furazolidone	When ethanol is ingested, nausea, flushing, light-headedness, and dyspnea may occur (ie, a disulfiram-like reaction).
H_2 antagonists	Cimetidine potentiates ethanol effects. Increases peak plasma ethanol concentrations and area under the plasma ethanol concentration–time curve. CNS toxicity from increased cimetidine serum concentration. Nizatidine and ranitidine may also increase BALs slightly by inhibiting gastric alcohol dehydrogenase. Famotidine does not affect BALs.
Isoniazid	Consumption of ethanol with isoniazid increases the risk of hepatotoxicity. Tyramine-containing alcoholic beverages may cause hypertensive reaction.
Ketoconazole and metronidazole	When ethanol is ingested, nausea, flushing, light-headedness, and dyspnea may occur (ie, a disulfiram-like reaction may occur with metronidazole). A sunburn-like

	rash has been reported with ethanol consumption and ketoconazole. A similar reaction may occur with itraconazole, although no reports exist.
Meprobamate	Synergistic CNS depression may occur.
Metoclopramide	Enhances sedative effects of ethanol
Monoamine oxidase inhibitors	Tyramine-containing alcoholic beverages (eg, wines and beer) may cause a hypertensive crisis. Pargyline may inhibit aldehyde dehydrogenase and cause a disulfiram-like interaction with ethanol.
Narcotic analgesics	Volume of distribution of intravenous meperidine increases with increasing ethanol consumption. Clinical significance unknown; potential for enhanced CNS depression
Oral hypoglycemic agents	Chlorpropamide, tolbutamide, and tolazamide may cause flushing, light-headedness, nausea, and dyspnea if alcohol is ingested (ie, a disulfiram-like reaction).
Paraldehyde	Possible metabolic acidosis may occur.
Phenothiazines	Potentiates psychomotor effects of ethanol
Quinacrine	Possibly inhibits acetaldehyde oxidation
Salicylates	Increases gastric bleeding associated with aspirin; may increase the chance of gastrointestinal hemorrhage
Tetrachloroethylene	Combined CNS depression may occur.
Trichloroethylene	Flushing, lacrimation, blurred vision, and tachypnea may occur when patients exposed to trichloroethylene drink alcohol.

BALs, blood alcohol levels; CNS, central nervous system; SSRIs, serotonin reuptake inhibitors.

Adapted with permission from Ciraulo DA, Shader RI, Greenblatt DJ, et al. *Drug Interactions in Psychiatry*. 3rd ed. Lippincott Williams & Wilkins; 2006.

Principles for the optimal treatment of patients with a dual diagnosis include the following: (a) flexibility (eg, although the goal of treatment may be abstinence, for some patients, movement in the right direction is just as important to keep the person engaged in treatment); (b) repetition (eg, a constant refocusing of attention for avoiding alcohol and for confronting their psychiatric symptoms is a priority); and (c) counseling (eg, matching patients to the appropriate intervention). These factors are all fundamental to long-lasting

treatment success. Medications, when appropriate (eg, early and vigorous drug intervention with nonaddictive medications), may also help the patient stay in treatment; however, every effort must be made to use medications that do not induce euphoria or cause dependence, and are effective and safe even during relapse.[2,3]

Patients with both drug use and psychiatric disorders constitute a substantial and challenging subpopulation. AUD and major depressive disorder are associated with an odds ratio (OR) of 2.42 (95% confidence interval [CI], 2.22–2.64), and anxiety disorder if associated with an OR of 2.11 (95% CI, 2.03–2.19).[325] Patients with bipolar disorder have comorbid AUD at rates of up to 45%.[326] One reason is the effect of depression, anxiety, and mania on prompting the use of alcohol to mask these symptoms or diminish their intensity.[325,327] This frequent act of self-medicating leads to physical dependence and subsequent cycling of withdrawal. Relapse often occurs to prevent symptoms of alcohol withdrawal and treat unmasked symptoms. The neurotoxicity associated with frequent alcohol use results in mood dysregulation and anxiety, which can cause even more alcohol use to cope with these symptoms. Treating the AUD alone predicts a poorer outcome for other disorders including early relapse. Early and aggressive treatment for each condition should be implemented. Furthermore, care must be taken to ensure that the medications prescribed are safe if combined with alcohol.[3]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. American Psychiatric Association; 2013:xliv, 947 p. (1)

Perry EC. Inpatient management of acute alcohol withdrawal syndrome. *CNS Drugs*. 2014;28(5):401–410. (197)

Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *Am J Psychiatry*. 2018;175(1):86–90. (303)

VA/DoD (Department of Veterans Affairs/Department of Defense). VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Version 3.0. 2015. https://www.healthquality.va.gov/guidelines/MH/sud/(279)

Key Websites

https://www.asam.org/quality-care/definition-of-addiction

COMPLETE REFERENCES CHAPTER 90 SUBSTANCE USE DISORDERS

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. American Psychiatric Association; 2013:xliv, 947 p.
2. American Society of Addiction Medicine. Public policy statement: Treatment for alcohol and other drug addiction. 1980. https://www.asam.org/quality-care/definition-of-addiction
3. Lingford-Hughes AR, Welch S, Peters L, Nutt DJ, British Association for Psychopharmacology, Expert Reviewers Group. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. *J Psychopharmacol*. 2012;26(7):899–952.
4. Substance Abuse Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2018 National Survey on Drug Use and Health. Center for Behavioral Health Statistics and Quality; 2019. https://www.samhsa.gov/data/
5. U.S. Department of Health and Human Services. Results from the 2009 National Survey on Drug Use and Health: volume I. Summary of National Findings. 2010, HHS Publication No. SMA 10–4586 Findings. https://www.liprc.org/wp-content/uploads/2016/08/SAMHSA-2009-

_Results_from_the_National_Survey_on_Drug_Use_and_Health-Volume_I_-_Summary_of_National_Findings.pdf
6. U.S. Drug Enforcement Administration. 2019 Drug Enforcement Administration. National Drug Threat Assessment. 2020. https://www.dea.gov/sites/default/files/2020-01/2019-NDTA-final-01-14-2020_Low_Web-DIR-007-20_2019.pdf
7. Inaba DS, Cohen WE. *Uppers, Downers, All Rounders: Physical and Mental Effects of Psychoactive Drugs*. 8th ed. CNS Productions; 2014.
8. Compton P. Opioid therapy of pain. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:1547.
9. Garcia MM, Angelini MC, Thomas T, Lenz K, Jeffrey P. Implementation of an opioid management initiative by a state medicaid program. *J Manag Care Spec Pharm*. 2014;20(5):447–454.
10. Sullivan MD, Bauer AM, Fulton-Kehoe D, et al. Trends in opioid dosing among Washington state medicaid patients before and after opioid dosing guideline implementation. *J Pain*. 2016;17(5):561–568.
11. Centers for Disease Control and Prevention. HIV surveillance report, 2018 (Updated). Vol. 31. 2020.
12. Ferguson R, Feeney C, Chirurgi VA. Enterobacter agglomerans—associated cotton fever. *Arch Intern Med*. 1993;153(20):2381–2382.
13. Delétoile A, Decré D, Courant S, et al. Phylogeny and identification of *Pantoea* species and typing of *Pantoea agglomerans* strains by multilocus gene sequencing. *J Clin Microbiol*. 2009;47(2):300–310.
14. Torka P, Gill S. Cotton fever: an evanescent process mimicking sepsis in an intravenous drug abuser. *J Emerg Med*. 2013;44(6):e385–e387.
15. Kleber HD, Weiss RD, Anton RF Jr, et al. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. *Am J Psychiatry*. 2007;164(suppl 4):5–123.
16. McAuley A, Aucott L, Matheson C. Exploring the life-saving potential of naloxone: a systematic review and descriptive meta-analysis of take home naloxone (THN) programmes for opioid users. *Int J Drug Policy*. 2015;26(12):1183–1188.
17. Rando J, Broering D, Olson JE, Marco C, Evans SB. Intranasal naloxone administration by police first responders is associated with decreased opioid overdose deaths. *Am J Emerg Med*. 2015;33(9):1201–1204.
18. Schuckit MA. Treatment of opioid-use disorders. *N Engl J Med*. 2016;375(16):1596–1597.
19. Tetrault JM. Management of opioid intoxication and withdrawal. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:741.
20. Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement

Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005. https://s21151.pcdn.co/wp-content/uploads/2016/11/Medication-Assisted-Trmt-for-Opioid-Addiction-SAMHSA-Tip-43-SRC-5-9-17-CMMC-5-16-17.pdf

21. Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal*. Cochrane Database Syst Rev*. 2013;2013(2):CD003409.
22. McNicholas L. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40*. 2004. http://lib.adai.washington.edu/clearinghouse/downloads/TIP-40-Clinical-Guidelines-for-the-Use-of-Buprenorphine-in-the-Treatment-of-Opioid-Addiction-54.pdf
23. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal*. Cochrane Database Syst Rev*. 2009;(3):CD002025.
24. Gowing L, Farrell M, Ali R, White JM. Alpha(2)-adrenergic agonists for the management of opioid withdrawal*. Cochrane Database Syst Rev*. 2016;(5):CD002024.
25. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial*. JAMA*. 2005;294(8):903–913.
26. Gowing L, Ali R, White JM. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal*. Cochrane Database Syst Rev*. 2010;2010(1):CD002022.
27. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment. Buprenorphine, Summary of Drug Addiction Treatment Act of 2000. https://www.samhsa.gov/medication-assisted-treatment/medications-counseling-related-conditions/buprenorphine
28. Kan D, Zweben JE. Pharmacological and psychosocial treatment of opioid use disorder. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:808.
29. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the *American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain*. 2014;15(4):321–337.
30. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence*. N Engl J Med*. 2000;343(18):1290–1297.
31. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence*. Cochrane Database Syst Rev*. 2014;(2):CD002207.
32. Baxter JD, Clark RE, Samnaliev M, Leung GY, Hashemi L. Factors associated with medicaid patients' access to buprenorphine treatment*. J Subst Abuse Treat*. 2011;41(1):88–96.

33. Sullivan LE, Chawarski M, O'Connor PG, Schottenfeld RS, Fiellin DA. The practice of office-based buprenorphine treatment of opioid dependence: is it associated with new patients entering into treatment? *Drug Alcohol Depend*. 2005;79(1):113–116.
34. Rosenthal RN, Ling W, Casadonte P, et al. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. *Addiction*. 2013;108(12):2141–2149.
35. Soyka M. New developments in the management of opioid dependence: focus on sublingual buprenorphine-naloxone. *Subst Abuse Rehabil*. 2015;6:1–14.
36. U.S. Department of Justice, D.E.A. Office of Diversion Control, Drugs and chemicals of concern: Buprenorphine. July 2013. https://www.deadiversion.usdoj.gov/drug_chem_info/buprenorphine.pdf
37. van Dorp E, Yassen A, Sarton E, et al. Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology*. 2006;105(1):51–57.
38. Ling W, Shoptaw S, Goodman-Meza D. Depot buprenorphine injection in the management of opioid use disorder: from development to implementation. *Subst Abuse Rehabil*. 2019;10:69–78.
39. Naltrexone (vivitrol)—a once-monthly injection for alcoholism. *Med Lett Drugs Ther*. 2006;48(1240):63–64.
40. Earley PH. Physician health programs and addiction among physicians. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:671.
41. Effective medical treatment of opiate addiction. National consensus development panel on effective medical treatment of opiate addiction. *JAMA*. 1998;280(22):1936–1943.
42. Ebner N, Rohrmeister K, Winklbaur B, et al. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug Alcohol Depend*. 2007;87(2–3):131–138.
43. Jones HE, Johnson RE, Jasinski DR, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend*. 2005;79(1):1–10.
44. Lund IO, Fischer G, Welle-Strand GK, et al. A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes. *Subst Abuse*. 2013;7:61–74.
45. Smith J, Lafferty M, Boelig RC, et al. Is maternal methadone dose associated with the severity of neonatal abstinence syndrome? *Am J Perinatol*. 2020 [Online ahead of print].
46. Kraft WK, van den Anker JN. Pharmacologic management of the opioid neonatal abstinence syndrome. *Pediatr Clin North Am*. 2012;59(5):1147–1165.

47. Jackson L, Ting A, McKay S, Galea P, Skeoch C. A randomised controlled trial of morphine versus phenobarbitone for neonatal abstinence syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(4):F300–F304.
48. van Hoogdalem MW, McPhail BT, Hahn D, et al. Pharmacotherapy of neonatal opioid withdrawal syndrome: a review of pharmacokinetics and pharmacodynamics. *Expert Opin Drug Metab Toxicol*. 2021;17(1):87–103.
49. Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. *Cochrane Database Syst Rev*. 2010;(10):CD002059.
50. Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation: a review of the literature and current management guidelines. *J Hum Lact*. 2004;20(1):62–71.
51. Lindemalm S, Nydert P, Svensson JO, Stahle L, Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. *J Hum Lact*. 2009;25(2):199–205.
52. Haass-Koffler CL, McCance-Katz EF. The pharmacology of nonalcohol sedative hypnotics. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:125.
53. Eickelber SJ, Dickinson WE, Attia RA. Management of sedative-hypnotic intoxication and withdrawal. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:723.
54. Miller NS, Kipnis SS. Detoxification and substance abuse treatment. Treatment Improvement Protocol (TIP) Series 45. Center for Substance Abuse Treatment, U.S. Department of Health and Human Services; 2006. https://www.ncbi.nlm.nih.gov/books/NBK64115/
55. Denis C, Fatséas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. *Cochrane Database Syst Rev*. 2006;(3):CD005194.
56. Felmlee MA, Morse BL, Morris ME. γ-Hydroxybutyric acid: pharmacokinetics, pharmacodynamics, and toxicology. *AAPS J*. 2021;23(1):22.
57. Kolker S. Metabolism of amino acid neurotransmitters: the synaptic disorder underlying inherited metabolic diseases. *J Inherit Metab Dis*. 2018;41(6):1055–1063.
58. Bay T, Eghorn LF, Klein AB, Wellendorph P. GHB receptor targets in the CNS: focus on high-affinity binding sites. *Biochem Pharmacol*. 2014;87(2):220–228.
59. Kapoor P, Deshmukh R, Kukreja I. GHB acid: a rage or reprive. *J Adv Pharm Technol Res*. 2013;4(4):173–178.
60. Snead OC 3rd, Gibson KM. Gamma-hydroxybutyric acid. *N Engl J Med*. 2005;352(26):2721–2732.
61. Stefano GB, Bianchi E, Guarna M, et al. Nicotine, alcohol and cocaine coupling to reward processes via endogenous morphine signaling: the dopamine-morphine hypothesis. *Med Sci Monit*. 2007;13(6):RA91–RA102.

62. Gorelick DA, Baumann MH. The pharmacology of stimulants. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:150.
63. Devlin RJ, Henry JA. Clinical review: major consequences of illicit drug consumption. *Crit Care*. 2008;12(1):202.
64. Wilkins JN, Danovitch I, Gorelick DA. Management of stimulant, hallucinogen, marijuana, phencyclidine, and club drug intoxication and withdrawal. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:757.
65. Substance Abuse and Mental Health Services Administration & Drug Abuse Warning Network. National estimates of drug-related emergency department visits. HHS publication no. (SMA) 13-4760, DAWN series D-39. 2011. https://www.samhsa.gov/data/sites/default/files/DAWN2k11ED/DAWN2k11ED/DAWN2k11ED.pdf
66. Kim ST, Park T. Acute and chronic effects of cocaine on cardiovascular health. *Int J Mol Sci*. 2019;20(3):584.
67. Bamberg F, Schlett CL, Truong QA, et al. Presence and extent of coronary artery disease by cardiac computed tomography and risk for acute coronary syndrome in cocaine users among patients with chest pain. *Am J Cardiol*. 2009;103(5):620–625.
68. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association acute cardiac care committee of the council on clinical cardiology. *Circulation*. 2008;117(14):1897–1907.
69. Rosário BDA, de Nazaré MFS, Estadella D, Ribeiro DA, Viana MB. Behavioral and neurobiological alterations induced by chronic use of crack cocaine. *Rev Neurosci*. 2019;31(1):59–75.
70. Kampman KM. The treatment of cocaine use disorder. *Sci Adv*. 2019;5(10):eaax1532.
71. Grabowski J, Rhoades H, Schmitz J, et al. Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *J Clin Psychopharmacol*. 2001;21(5):522–556.
72. Mooney ME, Herin DV, Schmitz JM, Moukaddam N, Green CE, Grabowski J. Effects of oral methamphetamine on cocaine use: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend*. 2009;101(1–2):34–41.
73. Kimishima A, Olson ME, Natori Y, Janda KD. Efficient syntheses of cocaine vaccines and their in vivo evaluation. *ACS Med Chem Lett*. 2018;9(5):411–416.
74. Turillazzi E, Riezzo I, Neri M, Bello S, Fineschi V. MDMA toxicity and pathological consequences: a review about experimental data and autopsy findings. *Curr Pharm Biotechnol*. 2010;11(5):500–509.
75. Angoa-Pérez M, Anneken JH, Kuhn DM. Neurotoxicology of synthetic cathinone analogs. *Curr Top Behav Neurosci*. 2017;32:209–230.

76. Domino E, Miller SC. The pharmacology of dissociatives. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:252.
77. Caddy C, Amit BH, McCloud TL, et al. Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database Syst Rev*. 2015;(9):CD011612.
78. Journey JD, Bentley TP. Phencyclidine toxicity. In: *StatPearls* [Internet]. 2020.
79. Grayson B, Barnes SA, Markou A, Piercy C, Podda G, Neill JC. Postnatal Phencyclidine (PCP) as a neurodevelopmental animal model of schizophrenia pathophysiology and symptomatology: a review. *Curr Top Behav Neurosci*. 2016;29:403–428.
80. Bogenschutz MP, Nichols DE. The pharmacology of hallucinogens. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine.* Wolters Kluwer; 2019:230.
81. Pechnick R, Cunningham KA. Hallucinogens. In: Ruiz P, Strain E, eds. *Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook*. Lippincott Williams & Wilkins; 2011:267.
82. Halpern JH, Pope HG Jr. Hallucinogen persisting perception disorder: what do we know after 50 years? *Drug Alcohol Depend*. 2003;69(2):109–119.
83. Martinotti G, Santacroce R, Pettorruso M, et al. Hallucinogen persisting perception disorder: etiology, clinical features, and therapeutic perspectives. *Brain Sci*. 2018;8(3):47.
84. McCann UD. PCP/designer drugs/MDMA. In: Ruiz P, Strain E, eds. *Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook*. Lippincott Williams & Wilkins; 2011:277.
85. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol*. 2011;25(4):439–452.
86. Malberg J, Bonson KR. How MDMA works in the brain. In: Holland J, ed. *Ecstasy: The Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA*. Park Street Press; 2001:29.
87. Bravo G. What does MDMA feel like? In: Holland J, ed. *Ecstasy: The Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA*. Park Street Press; 2001:21.
88. Figurasin R, Maguire NJ. 3,4-Methylenedioxy-methamphetamine. In: *StatPearls* [Internet]. 2020.
89. Henry J, Rella J. Medical risks associated with MDMA use. In: Holland J, ed. *Ecstasy: The Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA*. Park Street Press; 2001:71.

90. Hall AP, Henry JA. Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. *Br J Anaesth*. 2006;96(6):678–685.
91. Substance Abuse and Mental Health Services Administration & Center for Behavioral Health Statistics and Quality. The DAWN report: emergency department visits involving phencyclidine (PCP). November 12, 2013. https://www.samhsa.gov/data/report/dawn-report-emergency-department-visits-involving-phencyclidine
92. Baggot M, Mendelson J. Does MDMA cause brain damage? In: Holland J, ed. *Ecstasy: The Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA*. Park Street Press; 2001:110.
93. Ben Amar M, Potvin S. Cannabis and psychosis: what is the link? *J Psychoactive Drugs*. 2007;39(2):131–142.
94. Welch S, Smith TH, Malcolm R, Lichtman AH. The pharmacology of cannabinnoids. In: Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:208.
95. Mechoulam R. Plant cannabinoids: a neglected pharmacological treasure trove. *Br J Pharmacol*. 2005;146(7):913–915.
96. Bolognini D, Ross RA. Medical cannabis vs. synthetic cannabinoids: what does the future hold? *Clin Pharmacol Ther*. 2015;97(6):568–570.
97. Fasinu PS, Phillips S, ElSohly MA, Walker LA. Current status and prospects for cannabidiol preparations as new therapeutic agents. *Pharmacotherapy*. 2016;36(7):781–796.
98. Sharma P, Murthy P, Bharath MM. Chemistry, metabolism, and toxicology of cannabis: clinical implications. *Iran J Psychiatry*. 2012;7(4):149–156.
99. Sánchez Artiles AE, Awan A, Karl M, Santini A. Cardiovascular effects of cannabis (marijuana): a timely update. *Phytother Res*. 2019;33(5):1592–1594.
100. Andrade C. Cannabis and neuropsychiatry, 2: the longitudinal risk of psychosis as an adverse outcome. *J Clin Psychiatry*. 2016;77(6):e739–e742.
101. Micallef J, Dupouey J, Jouve E, et al. Cannabis smoking impairs driving performance on the simulator and real driving: a randomized, double-blind, placebo-controlled, crossover trial. *Fundam Clin Pharmacol*. 2018;32(5):558–570.
102. Simpson AK, Magid V. Cannabis use disorder in adolescence. *Child Adolesc Psychiatr Clin N Am*. 2016;25(3):431–443.
103. Vandrey R, Haney M. Pharmacotherapy for cannabis dependence: how close are we? *CNS Drugs*. 2009;23(7):543–553.
104. Martz ME, Trucco EM, Cope LM, et al. Association of marijuana use with blunted nucleus accumbens response to reward anticipation. *JAMA Psychiatry*. 2016;73(8):838–844.
105. Reece AS. Chronic toxicology of cannabis. *Clin Toxicol (Phila)*. 2009;47(6):517–524.

106. Meier MH, Caspi A, Cerdá M, et al. Associations between cannabis use and physical health problems in early midlife: a longitudinal comparison of persistent cannabis vs tobacco users. *JAMA Psychiatry*. 2016;73(7):731–740.
107. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370(9584):319–328.
108. Bechtold J, Hipwell A, Lewis DA, Loeber R, Pardini D. Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms. *Am J Psychiatry*. 2016;173(8):781–789.
109. Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry*. 2019;6(5):427–436.
110. Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. *Arch Intern Med*. 2007;167(3):221–228.
111. Tashkin DP. Airway effects of marijuana, cocaine, and other inhaled illicit agents. *Curr Opin Pulm Med*. 2001;7(2):43–61.
112. Szyper-Kravitz M, Lang R, Manor Y, Lahav M. Early invasive pulmonary aspergillosis in a leukemia patient linked to aspergillus contaminated marijuana smoking. *Leuk Lymphoma*. 2001;42(6):1433–1437.
113. Substance Abuse and Mental Health Administration & Office of Applied Studies. *Patterns and Trends in Inhalant Use by Adolescent Males and Females, 2002–2005*. U.S. Department of Health and Human Services; 2007.
114. National Institute on Drug Abuse. *Research Report Series. Inhalant Abuse*. U.S. Department of Health and Human Services; 2005.
115. Johnston LD, Miech RA, O'Malley PM, et al. *Monitoring the Future National Survey Results on Drug Use 1975–2019: Overview, Key Findings on Adolescent Drug Use*. Institute for Social Research, University of Michigan; 2020.
116. Balster RL. The pharmacology of inhalants. In Miller SC, Fiellin DA, Rosenthal RN, et al, eds. *The ASAM Principles of Addiction Medicine*. Wolters Kluwer; 2019:263.
117. Riegel AC, Zapata A, Shippenberg TS, French ED. The abused inhalant toluene increases dopamine release in the nucleus accumbens by directly stimulating ventral tegmental area neurons. *Neuropsychopharmacology*. 2007;32(7):1558–1569.
118. Heath D. *International Handbook on Alcohol and Culture*. Greenwood Press; 1995.
119. Bardon S. *Brewed in America: A History of Beer and Ale in the United States*. Little Brown; 1962.

120. Grant BF. Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey. *J Stud Alcohol*. 1997;58(5):464–473.
121. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. *JAMA*. 1990;264(19):2511–2518.
122. Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-based pharmacotherapies for alcohol use disorder: clinical pearls. *Mayo Clin Proc*. 2020;95(9):1964–1977.
123. Kenna GA, McGeary JE, Swift RM. Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, Part 2. *Am J Health Syst Pharm*. 2004;61(22):2380–2388.
124. Kranzler HR, Edenberg HJ. Pharmacogenetics of alcohol and alcohol dependence treatment. *Curr Pharm Des*. 2010;16(19):2141–2148.
125. Cherpitel CJ, Ye Y, Bond J, et al. The effect of alcohol consumption on emergency department services use among injured patients: a cross-national emergency room study. *J Stud Alcohol*. 2006;67(6):890–897.
126. Cox RG, Zhang L, Johnson WD, Bender DR. Academic performance and substance use: findings from a state survey of public high school students. *J Sch Health*. 2007;77(3):109–115.
127. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *N Engl J Med*. 1997;337(24):1705–1714.
128. Zakhari S. Alcohol and the cardiovascular system: molecular mechanisms for beneficial and harmful action. *Alcohol Health Res World*. 1997;21(1):21–29.
129. Mukamal KJ, Chung H, Jenny NS, et al. Alcohol consumption and risk of coronary heart disease in older adults: the Cardiovascular Health Study. *J Am Geriatr Soc*. 2006;54(1):30–37.
130. Piano MR. Alcohol's effects on the cardiovascular system. *Alcohol Res*. 2017;38(2):219–241.
131. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. Binge drinking and mortality after acute myocardial infarction. *Circulation*. 2005;112(25):3839–3845.
132. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary guidelines for Americans, 2020–2025. December 2020. https://dietaryguidelines.gov/
133. Fillmore KM, Golding JM, Graves KL, et al. Alcohol consumption and mortality. I. Characteristics of drinking groups. *Addiction*. 1998;93(2):183–203.
134. Magrone T, Tafaro A, Jirillo F, et al. Red wine consumption and prevention of atherosclerosis: an in vitro model using human peripheral blood mononuclear cells. *Curr Pharm Des*. 2007;13(36):3718–3725.

135. Agarwal DP. Cardioprotective effects of light-moderate consumption of alcohol: a review of putative mechanisms. *Alcohol Alcohol*. 2002;37(5):409–415.
136. David DJ, Spyker DA. The acute toxicity of ethanol: dosage and kinetic nomograms. *Vet Hum Toxicol*. 1979;21(4):272–276.
137. Oneta CM, Simanowski UA, Martinez M, et al. First pass metabolism of ethanol is strikingly influenced by the speed of gastric emptying. *Gut*. 1998;43(5):612–619.
138. Jones AW, Jönsson KA, Kechagias S. Effect of high-fat, high-protein, and high-carbohydrate meals on the pharmacokinetics of a small dose of ethanol. *Br J Clin Pharmacol*. 1997;44(6):521–526.
139. Pihl RO, Paylan SS, Gentes-Hawn A, Hoaken PN. Alcohol affects executive cognitive functioning differentially on the ascending versus descending limb of the blood alcohol concentration curve. *Alcohol Clin Exp Res*. 2003;27(5):773–779.
140. Swift R. Direct measurement of alcohol and its metabolites. *Addiction*. 2003;98**(**suppl 2):73–80.
141. Wilkinson PK, Sedman AJ, Sakmar E, Earhart RH, Weidler DJ, Wagner JG. Blood ethanol concentrations during and following constant-rate intravenous infusion of alcohol. *Clin Pharmacol Ther*. 1976;19(2):213–223.
142. Hammond KB, Rumack BH, Rodgerson DO. Blood ethanol: a report of unusually high levels in a living patient. *JAMA*. 1973;226(1):63–64.
143. DiPadova C, Worner TM, Julkunen RJ, Lieber CS. Effects of fasting and chronic alcohol consumption on the first-pass metabolism of ethanol. *Gastroenterology*. 1987;92(5 Pt 1):1169–1173.
144. Ammon E, Schäfer C, Hofmann U, Klotz U. Disposition and first-pass metabolism of ethanol in humans: is it gastric or hepatic and does it depend on gender? *Clin Pharmacol Ther*. 1996;59(5):503–513.
145. Levitt MD, Levitt DG. The critical role of the rate of ethanol absorption in the interpretation of studies purporting to demonstrate gastric metabolism of ethanol. *J Pharmacol Exp Ther*. 1994;269(1):297–304.
146. Levitt MD, Li R, DeMaster EG, Elson M, Furne J, Levitt DG. Use of measurements of ethanol absorption from stomach and intestine to assess human ethanol metabolism. *Am J Physiol*. 1997;273(4):G951–G957.
147. Lieber CS. Ethnic and gender differences in ethanol metabolism. *Alcohol Clin Exp Res*. 2000;24(4):417–418.
148. Franke A, Teyssen S, Singer MV. Alcohol-related diseases of the esophagus and stomach. *Dig Dis*. 2005;23(3–4):204–213.
149. Lands WE. A review of alcohol clearance in humans. *Alcohol*. 1998;15(2):147–160.
150. Crabb DW, Dipple KM, Thomasson HR. Alcohol sensitivity, alcohol metabolism, risk of alcoholism, and the role of alcohol and aldehyde dehydrogenase genotypes. *J Lab Clin Med*. 1993;122(3):234–240.

151. Kopun M, Propping P. The kinetics of ethanol absorption and elimination in twins and supplementary repetitive experiments in singleton subjects. *Eur J Clin Pharmacol*. 1977;11(5):337–344.
152. Adachi J, Mizoi Y, Fukunaga T, Ogawa Y, Imamichi H. Comparative study on ethanol elimination and blood acetaldehyde between alcoholics and control subjects. *Alcohol Clin Exp Res*. 1989;13(5):601–604.
153. Lieber CS. Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. *Alcohol*. 2004;34(1):9–19.
154. Lieber CS. Metabolism of alcohol. *Clin Liver Dis*. 2005;9(1):1–35.
155. De Feo P, Volpi E, Lucidi P, et al. Ethanol impairs post-prandial hepatic protein metabolism. *J Clin Invest*. 1995;95(4):1472–1479.
156. Eriksson CJ. The role of acetaldehyde in the actions of alcohol (update 2000). *Alcohol Clin Exp Res*. 2001;25(5 suppl ISBRA):15S–32S.
157. O'Shea RS, Dasarathy S, McCullough AJ; Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Alcoholic liver disease. *Hepatology*. 2010;51(1):307–328.
158. Samokhvalov AV, Rehm J, Roerecke M. Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic review and a series of meta-analyses. *EBioMedicine*. 2015;2(12):1996–2002.
159. Woods AJ, Porges EC, Bryant VE, et al. Current heavy alcohol consumption is associated with greater cognitive impairment in older adults. *Alcohol Clin Exp Res*. 2016;40(11):2435–2444.
160. Caputo F, Vignoli T, Leggio L, Addolorato G, Zoli G, Bernardi M. Alcohol use disorders in the elderly: a brief overview from epidemiology to treatment options. *Exp Gerontol*. 2012;47(6):411–416.
161. Chopra K, Tiwari V. Alcoholic neuropathy: possible mechanisms and future treatment possibilities. *Br J Clin Pharmacol*. 2012;73(3):348–362.
162. Topiwala A, Ebmeier KP. Effects of drinking on late-life brain and cognition. *Evid Based Ment Health*. 2018;21(1):12–15.
163. Moriyama Y, Mimura M, Kato M, Kashima H. Primary alcoholic dementia and alcohol-related dementia. *Psychogeriatrics.* 2006;6(3):114–118.
164. Suzdak PD, Schwartz RD, Skolnick P, Paul SM. Ethanol stimulates gamma-aminobutyric acid receptor-mediated chloride transport in rat brain synaptoneurosomes. *Proc Natl Acad Sci U S A*. 1986;83(11):4071–4075.
165. Kumar S, Porcu P, Werner DF, et al. The role of GABA(A) receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology (Berl)*. 2009;205(4):529–564.
166. Vengeliene V, Bilbao A, Molander A, Spanagel R. Neuropharmacology of alcohol addiction. *Br J Pharmacol*. 2008;154(2):299–315.
167. Nagy J. Alcohol related changes in regulation of NMDA receptor functions. *Curr Neuropharmacol*. 2008;6(1):39–54.

168. Nestler EJ, Guitart X, Ortiz J, Trevisan L. Second messenger and protein phosphorylation mechanisms underlying possible genetic vulnerability to alcoholism. *Ann N Y Acad Sci*. 1994;708:108–118.
169. Basavarajappa BS, Hungund BL. Neuromodulatory role of the endocannabinoid signaling system in alcoholism: an overview. *Prostaglandins Leukot Essent Fatty Acids*. 2002;66(2–3):287–299.
170. Koob GF, Weiss F. Neuropharmacology of cocaine and ethanol dependence. *Recent Dev Alcohol*. 1992;10:201–233.
171. Söderpalm B, Löf E, Ericson M. Mechanistic studies of ethanol's interaction with the mesolimbic dopamine reward system. *Pharmacopsychiatry*. 2009;42**(**suppl 1):S87–S94.
172. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. *Psychol Rev*. 1987;94(4):469–492.
173. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev*. 1993;18(3):247–291.
174. Volkow ND, Li TK. Drug addiction: the neurobiology of behaviour gone awry. *Nat Rev Neurosci*. 2004;5(12):963–970.
175. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35(1):217–238.
176. Chao J, Nestler EJ. Molecular neurobiology of drug addiction. *Annu Rev Med*. 2004;55:113–132.
177. Melgaard B. The neurotoxicity of ethanol. *Acta Neurol Scand*. 1983;67(3):131–142.
178. Kupari M, Heikkilä J, Tolppanen EM, Nieminen MS, Ylikahri R. Acute effects of alcohol, beta blockade, and their combination on left ventricular function and hemodynamics in normal man. *Eur Heart J*. 1983;4(7):463–471.
179. Michiels TM, Light RW, Mahutte CK. Naloxone reverses ethanol-induced depression of hypercapnic drive. *Am Rev Respir Dis*. 1983;128(5):823–826.
180. O'Neill S, Tipton KF, Prichard JS, Quinlan A. Survival after high blood alcohol levels. Association with first-order elimination kinetics. *Arch Intern Med*. 1984;144(3):641–642.
181. Maldonado JR. An approach to the patient with substance use and abuse. *Med Clin North Am*. 2010;94(6):1169–1205, x-i.
182. Poikolainen K. Estimated lethal ethanol concentrations in relation to age, aspiration, and drugs. *Alcohol Clin Exp Res*. 1984;8(2):223–225.
183. Jones AW, Hahn RG. Pharmacokinetics of ethanol in patients with renal failure before and after hemodialysis. *Forensic Sci Int*. 1997;90(3):175–183.
184. Kozak LJ, Hall MJ, Owings MF. National Hospital Discharge Survey: 2000 annual summary with detailed diagnosis and procedure data. *Vital Health Stat 13*. 2002;(153):1–194.
185. Finn DA, Crabbe JC. Exploring alcohol withdrawal syndrome. *Alcohol Health Res World*. 1997;21(2):149–156.

186. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med*. 2003;348(18):1786–1795.
187. Spies CD, Rommelspacher H. Alcohol withdrawal in the surgical patient: prevention and treatment. *Anesth Analg*. 1999;88(4):946–954.
188. Trevisan LA, Boutros N, Petrakis IL, Krystal JH. Complications of alcohol withdrawal: pathophysiological insights. *Alcohol Health Res World*. 1998;22(1):61–66.
189. Asplund CA, Aaronson JW, Aaronson HE. 3 regimens for alcohol withdrawal and detoxification. *J Fam Pract*. 2004;53(7):545–554.
190. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84(11):1353–1357.
191. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med*. 1999;27(7):1325–1329.
192. Schatzberg AF, DeBattista C, *Manual of Clinical Psychopharmacology*. 8th ed. American Psychiatric Publishing; 2015.
193. Lejoyeux M, Solomon J, Adès J. Benzodiazepine treatment for alcohol-dependent patients. *Alcohol Alcohol*. 1998;33(6):563–575.
194. Hillbom M, Pieninkeroinen I, Leone M. Seizures in alcohol-dependent patients: epidemiology, pathophysiology and management. *CNS Drugs*. 2003;17(14):1013–1030.
195. Ritson B, Chick J. Comparison of two benzodiazepines in the treatment of alcohol withdrawal: effects on symptoms and cognitive recovery. *Drug Alcohol Depend*. 1986;18(4):329–334.
196. Kraemer KL, Conigliaro J, Saitz R.. Managing alcohol withdrawal in the elderly. *Drugs Aging*. 1999;14(6):409–425.
197. Perry EC. Inpatient management of acute alcohol withdrawal syndrome. *CNS Drugs*. 2014;28(5):401–410.
198. Lal R, Pattanayak RD. Alcohol use among the elderly: issues and considerations. *J Geriatr Ment Health*. 2017;4(1):4–10.
199. Carlson RW, Kumar NN, Wong-Mckinstry E, et al. Alcohol withdrawal syndrome. *Crit Care Clin*. 2012;28(4):549–585.
200. Ibarra F Jr. Single dose phenobarbital in addition to symptom-triggered lorazepam in alcohol withdrawal. *Am J Emerg Med*. 2020;38(2):178–181.
201. Tidwell WP, Thomas TL, Pouliot JD, Canonico AE, Webber AJ. Treatment of alcohol withdrawal syndrome: phenobarbital vs CIWA-Ar Protocol. *Am J Crit Care*. 2018;27(6):454–460.
202. Bayard M, McIntyre J, Hill KR, Woodside J Jr. Alcohol withdrawal syndrome. *Am Fam Physician*. 2004;69(6):1443–1450.
203. Cook CC, Hallwood PM, Thomson AD. B Vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. *Alcohol Alcohol*.

1998;33(4):317–336.
204. Isenberg-Grzeda E, Kutner HE, Nicolson SE. Wernicke-Korsakoff-syndrome: under-recognized and under-treated. *Psychosomatics*. 2012;53(6):507–516.
205. Sellers EM, Zilm DH, Degani NC. Comparative efficacy of propranolol and chlordiazepoxide in alcohol withdrawal. *J Stud Alcohol*. 1977;38(11):2096–2108.
206. Horwitz RI, Gottlieb LD, Kraus ML. The efficacy of atenolol in the outpatient management of the alcohol withdrawal syndrome. Results of a randomized clinical trial. *Arch Intern Med*. 1989;149(5):1089–1093.
207. Baumgartner GR, Rowen RC. Clonidine vs chlordiazepoxide in the management of acute alcohol withdrawal syndrome. *Arch Intern Med*. 1987;147(7):1223–1226.
208. Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline [published correction appears in *Arch Intern Med*. 2004;164:2068. Dosage error in article text]. *Arch Intern Med*. 2004;164(13):1405–1412.
209. Vinson DC, Galliher JM, Reidinger C, Kappus JA. Comfortably engaging: which approach to alcohol screening should we use? *Ann Fam Med*. 2004;2(5):398–404.
210. Ewing JA. Detecting alcoholism. The CAGE questionnaire. *JAMA*. 1984;252(14):1905–1907.
211. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption—II. *Addiction*. 1993;88(6):791–804.
212. Garbutt JC, West SL, Carey TS, Lohr KN, Crews FT. Pharmacological treatment of alcohol dependence: a review of the evidence. *JAMA*. 1999;281(14):1318–1325.
213. Fuller RK, Branchey L, Brightwell DR, et al. Disulfiram treatment of alcoholism. A veterans administration cooperative study. *JAMA*. 1986;256(11):1449–1455.
214. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Arch Gen Psychiatry*. 1992;49(11):881–887.
215. Volpicelli JR, Clay KL, Watson NT, O'Brien CP. Naltrexone in the treatment of alcoholism: predicting response to naltrexone. *J Clin Psychiatry*. 1995;56**(**suppl 7):39–44.
216. Sass H, Soyka M, Mann K, Zieglgänsberger W. Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. *Arch Gen Psychiatry*. 1996;53(8):673–680.
217. Pelc I, Verbanck P, Le Bon O, Gavrilovic M, Lion K, Lehert P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent

patients. A 90-day placebo-controlled dose-finding study. *Br J Psychiatry*. 1997;171:73–77.

218. Kranzler HR, Burleson JA, Korner P, et al. Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. *Am J Psychiatry*. 1995;152(3):391–397.
219. Cornelius JR, Salloum IM, Ehler JG, et al. Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 1997;54(8):700–705.
220. Pettinati HM, Volpicelli JR, Kranzler HR, Luck G, Rukstalis MR, Cnaan A. Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. *Alcohol Clin Exp Res*. 2000;24(7):1041–1049.
221. Johnson BA, Roache JD, Javors MA, et al. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. *JAMA*. 2000;284(8):963–971.
222. Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet*. 2003;361(9370):1677–1685.
223. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA*. 2006;295(17):2003–2017.
224. Kranzler HR, Armeli S, Tennen H, et al. A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset [corrected] and 5-hydroxytryptamine transporter-linked promoter region genotype. *J Clin Psychopharmacol*. 2011;31(1):22–30.
225. Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA*. 2007;298(14):1641–1651.
226. Johnson BA, Rosenthal N, Capece JA, et al. Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med*. 2008;168(11):1188–1199.
227. Johnson BA, Ait-Daoud N, Seneviratne C, et al. Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. *Am J Psychiatry*. 2011;168(3):265–275.
228. Anton RF, Kranzler H, Breder C, Marcus RN, Carson WH, Han J. A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. *J Clin Psychopharmacol*. 2008;28(1):5–12.
229. Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA*. 2005;293(13):1617–1625.
230. George DT, Herion DW, Jones CL, et al. Rimonabant (SR141716) has no effect on alcohol self-administration or endocrine measures in nontreatment-

seeking heavy alcohol drinkers. *Psychopharmacology (Berl)*. 2010;208(1):37–44.
231. Farren CK, Scimeca M, Wu R, Malley SO. A double-blind, placebo-controlled study of sertraline with naltrexone for alcohol dependence. *Drug Alcohol Depend*. 2009;99(1–3):317–321.
232. Berglund M. Pharmacotherapy for alcohol dependence. In: Berglund M, Thelander S, Jonsson E, eds. *Treating Alcohol and Drug Abuse: An Evidence Based Review*. Wiley-VCH Veriag GmbH and Co KGaA; 2003.
233. Angelini M, Brahmbhatt Y. A review of the pharmacologic options for the treatment of alcohol dependence. *Formulary*. 2007;42:14–31.
234. Leggio L, Kenna GA, Fenton M, Bonenfant E, Swift RM. Typologies of alcohol dependence. From Jellinek to genetics and beyond. *Neuropsychol Rev*. 2009;19(1):115–129.
235. Le Roux C, Tang Y, Drexler K. Alcohol and opioid use disorder in older adults: neglected and treatable illnesses. *Curr Psychiatry Rep*. 2016;18(9):87.
236. Bommersbach TJ, Lapid MI, Rummans TA, Morse RM. Geriatric alcohol use disorder: a review for primary care physicians. *Mayo Clin Proc*. 2015;90(5):659–666.
237. Barrick C, Connors GJ. Relapse prevention and maintaining abstinence in older adults with alcohol-use disorders. *Drugs Aging*. 2002;19(8):583–594.
238. Skinner MD, Lahmek P, Pham H, Aubin HJ. Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. *PLoS One*. 2014;9(2):e87366.
239. Chick J, Gough K, Falkowski W, et al. Disulfiram treatment of alcoholism. *Br J Psychiatry*. 1992;161:84–89.
240. De Sousa A, De Sousa A. A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. *Alcohol Alcohol*. 2004;39(6):528–531.
241. Diehl A, Ulmer L, Mutschler J, et al. Why is disulfiram superior to acamprosate in the routine clinical setting? A retrospective long-term study in 353 alcohol-dependent patients. *Alcohol Alcohol*. 2010;45(3):271–277.
242. Petrakis IL, Poling J, Levinson C, et al. Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. *Biol Psychiatry*. 2005;57(10):1128–1137.
243. Besson J, Aeby F, Kasas A, Lehert P, Potgieter A. Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. *Alcohol Clin Exp Res*. 1998;22(3):573–579.
244. Fuller RK, Gordis E. Does disulfiram have a role in alcoholism treatment today? *Addiction*. 2004;99(1):21–24.
245. Brewer C. Recent developments in disulfiram treatment. *Alcohol Alcohol*. 1993;28(4):383–395.

246. Helmbrecht GD, Hoskins IA. First trimester disulfiram exposure: report of two cases. *Am J Perinatol*. 1993;10(1):5–7.
247. Reitnauer PJ, Callanan NP, Farber RA, Aylsworth AS. Prenatal exposure to disulfiram implicated in the cause of malformations in discordant monozygotic twins. *Teratology*. 1997;56(6):358–362.
248. Saxon AJ, Sloan KL, Reoux J, Haver VM. Disulfiram use in patients with abnormal liver function test results. *J Clin Psychiatry*. 1998;59(6):313–316.
249. Björnsson E, Nordlinder H, Olsson R. Clinical characteristics and prognostic markers in disulfiram-induced liver injury. *J Hepatol*. 2006;44(4):791–797.
250. Wright C, Moore RD, Grodin DM, Spyker DA, Gill EV. Screening for disulfiram-induced liver test dysfunction in an inpatient alcoholism program. *Alcohol Clin Exp Res*. 1993;17(1):184–186.
251. Wright C 4th, Vafier JA, Lake CR. Disulfiram-induced fulminating hepatitis: guidelines for liver-panel monitoring. *J Clin Psychiatry*. 1988;49(11):430–434.
252. Daniel DG, Swallows A, Wolff F. Capgras delusion and seizures in association with therapeutic dosages of disulfiram. *South Med J*. 1987;80(12):1577–1579.
253. Amini M, Runyon BA. Alcoholic hepatitis 2010: a clinician's guide to diagnosis and therapy. *World J Gastroenterol*. 2010;16(39):4905–4912.
254. Larson EW, Olincy A, Rummans TA, Morse RM. Disulfiram treatment of patients with both alcohol dependence and other psychiatric disorders: a review. *Alcohol Clin Exp Res*. 1992;16(1):125–130.
255. Mueser KT, Noordsy DL, Fox L, Wolfe R. Disulfiram treatment for alcoholism in severe mental illness. *Am J Addict*. 2003;12(3):242–252.
256. Johansson B. A review of the pharmacokinetics and pharmacodynamics of disulfiram and its metabolites. *Acta Psychiatr Scand Suppl*. 1992;369:15–26.
257. Petersen EN. The pharmacology and toxicology of disulfiram and its metabolites. *Acta Psychiatr Scand Suppl*. 1992;369:7–13.
258. Ciraulo DA, Greenblatt DJ, Shader RI, Creelman MD, Wayne L. *Drug Interactions in Psychiatry*. 3rd ed. Lippincott Williams & Wilkins; 2005.
259. Mason BJ, Heyser CJ. Acamprosate: a prototypic neuromodulator in the treatment of alcohol dependence. *CNS Neurol Disord Drug Targets*. 2010;9(1):23–32.
260. Boothby LA, Doering PL. Acamprosate for the treatment of alcohol dependence. *Clin Ther*. 2005;27(6):695–714.
261. Littleton J, Zieglgänsberger W. Pharmacological mechanisms of naltrexone and acamprosate in the prevention of relapse in alcohol dependence. *Am J Addict*. 2003;12(s1):s3–s11.
262. Miller WR, Wilbourne PL. Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction*. 2002;97(3):265–277.
263. Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcohol Clin Exp Res*. 2004;28(1):51–63.

264. Chick J, Howlett H, Morgan MY, Ritson B. United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. *Alcohol Alcohol*. 2000;35(2):176–187.
265. Gual A, Lehert P. Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. *Alcohol Alcohol*. 2001;36(5):413–418.
266. Poldrugo F. Acamprosate treatment in a long-term community-based alcohol rehabilitation programme. *Addiction*. 1997;92(11):1537–1546.
267. Kiritzé-Topor P, Huas D, Rosenzweig C, Comte S, Paille F, Lehert P. A pragmatic trial of acamprosate in the treatment of alcohol dependence in primary care. *Alcohol Alcohol*. 2004;39(6):520–527.
268. Verheul R, Lehert P, Geerlings PJ, Koeter MW, van den Brink W. Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. *Psychopharmacology (Berl)*. 2005;178(2–3):167–173.
269. Bouza C, Angeles M, Muñoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction*. 2004;99(7):811–828.
270. Kenna GA. Pharmacogenomics and the future of alcohol dependence treatment. In: Sher L, ed. *Research on the Neurobiology of Alcohol Use Disorders*. Nova Publishers; 2008.
271. Mason BJ, Goodman AM, Chabac S, Lehert P. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. *J Psychiatr Res*. 2006;40(5):383–393.
272. Chick J, Anton R, Checinski K, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol Alcohol*. 2000;35(6):587–593.
273. Namkoong K, Lee BO, Lee PG, Choi MJ, Lee E. Acamprosate in Korean alcohol-dependent patients: a multi-centre, randomized, double-blind, placebo-controlled study. *Alcohol Alcohol*. 2003;38(2):135–141.
274. Roussaux JP, Hers D, Ferauge M. L'acamprosate diminue-t-il l'appétence pour l'alcool chez l'alcoolique sevé? [Does acamprosate diminish the appetite for alcohol in weaned alcoholics?]. *J Pharm Belg*. 1996;51(2):65–68.
275. Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev*. 2010; (9):CD004332.
276. Hammarberg A, Wennberg P, Beck O, Franck J. A comparison of two intensities of psychosocial intervention for alcohol dependent patients treated with acamprosate. *Alcohol Alcohol*. 2004;39(3):251–255.
277. Saivin S, Hulot T, Chabac S, Potgieter A, Durbin P, Houin G. Clinical pharmacokinetics of acamprosate. *Clin Pharmacokinet*. 1998;35(5):331–345.

278. Mason BJ, Goodman AM, Dixon RM, et al A pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone. *Neuropsychopharmacology*. 2002;27(4):596–606.
279. VA/DoD (Department of Veterans Affairs/Department of Defense). VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Version 3.0. 2015. https://www.healthquality.va.gov/guidelines/MH/sud/
280. Johnson BA, O'Malley SS, Ciraulo DA, et al. Dose-ranging kinetics and behavioral pharmacology of naltrexone and acamprosate, both alone and combined, in alcohol-dependent subjects. *J Clin Psychopharmacol*. 2003;23(3):281–293.
281. Mann K, Roos CR, Hoffmann S, et al. Precision medicine in alcohol dependence: a controlled trial testing pharmacotherapy response among reward and relief drinking phenotypes. *Neuropsychopharmacology*. 2018;43(4):891–899.
282. Mann K. Pharmacotherapy of alcohol dependence: a review of the clinical data. *CNS Drugs*. 2004;18(8):485–504.
283. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction*. 2013;108(2):275–293.
284. Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev*. 2005;(1):CD001867.
285. Kenna GA, McGeary JE, Swift RM. Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 1. *Am J Health Syst Pharm*. 2004;61(21):2272–2279.
286. Kranzler HR, Van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. *Alcohol Clin Exp Res*. 2001;25(9):1335–1341.
287. Kiefer F, Jahn H, Tarnaske T, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2003;60(1):92–99.
288. McCaul ME, Wand GS, Eissenberg T, Rohde CA, Cheskin LJ. Naltrexone alters subjective and psychomotor responses to alcohol in heavy drinking subjects. *Neuropsychopharmacology*. 2000;22(5):480–492.
289. Jaffe AJ, Rounsaville B, Chang G, Schottenfeld RS, Meyer RE, O'Malley SS. Naltrexone, relapse prevention, and supportive therapy with alcoholics: an analysis of patient treatment matching. *J Consult Clin Psychol*. 1996;64(5):1044–1053.
290. Monti PM, Rohsenow DJ, Hutchison KE, et al. Naltrexone's effect on cue-elicited craving among alcoholics in treatment. *Alcohol Clin Exp Res*. 1999;23(8):1386–1394.
291. Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence. Role of subject compliance. *Arch Gen Psychiatry*. 1997;54(8):737–742.

292. Rubio G, Ponce G, Rodriguez-Jiménez R, Jiménez-Arriero MA, Hoenicka J, Palomo T. Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone? *Alcohol Alcohol*. 2005;40(3):227–233.
293. Ray LA, Chin PF, Miotto K. Naltrexone for the treatment of alcoholism: clinical findings, mechanisms of action, and pharmacogenetics. *CNS Neurol Disord Drug Targets*. 2010;9(1):13–22.
294. Soyka M, Rösner S. Opioid antagonists for pharmacological treatment of alcohol dependence—a critical review. *Curr Drug Abuse Rev*. 2008;1(3):280–291.
295. Davidson D, Palfai T, Bird C, Swift R. Effects of naltrexone on alcohol self-administration in heavy drinkers. *Alcohol Clin Exp Res*. 1999;23(2):195–203.
296. Kranzler HR, Modesto-Lowe V, Van Kirk J. Naltrexone vs. nefazodone for treatment of alcohol dependence. A placebo-controlled trial. *Neuropsychopharmacology*. 2000;22(5):493–503.
297. Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA; Veterans Affairs Naltrexone Cooperative Study 425 Group. Naltrexone in the treatment of alcohol dependence. *N Engl J Med*. 2001;345(24):1734–1739.
298. Gastpar M, Bonnet U, Böning J, et al. Lack of efficacy of naltrexone in the prevention of alcohol relapse: results from a German multicenter study. *J Clin Psychopharmacol*. 2002;22(6):592–598.
299. Galloway GP, Koch M, Cello R, Smith DE. Pharmacokinetics, safety, and tolerability of a depot formulation of naltrexone in alcoholics: an open-label trial. *BMC Psychiatry*. 2005;5:18.
300. Kranzler HR, Wesson DR, Billot L; DrugAbuse Sciences Naltrexone Depot Study Group. Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. *Alcohol Clin Exp Res*. 2004;28(7):1051–1059.
301. Lee JD, Grossman E, Huben L, et al. Extended-release naltrexone plus medical management alcohol treatment in primary care: findings at 15 months. *J Subst Abuse Treat*. 2012;43(4):458–462.
302. Rohsenow DJ. What place does naltrexone have in the treatment of alcoholism? *CNS Drugs*. 2004;18(9):547–560.
303. Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *Am J Psychiatry*. 2018;175(1):86–90.
304. Srisurapanont M, Jarusuraisin N. Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol*. 2005;8(2):267–280.
305. Substance Abuse and Mental Health Services Administration. *Incorporating Alcohol Pharmacotherapies into Medical Practice. Treatment Improvement Protocol (TIP) Series 49*. SAMHSA; 2009.

306. Weinrieb RM, O'Brien CP. Naltrexone in the treatment of alcoholism. *Annu Rev Med*. 1997;48:477–487.
307. Anton RF. Naltrexone for the management of alcohol dependence. *N Engl J Med*. 2008;359(7):715–721.
308. Swainston Harrison T, Plosker GL, Keam SJ. Extended-release intramuscular naltrexone in alcohol dependence in adults: profile report. *CNS Drugs*. 2007;21(1):83–87.
309. Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment. Naltrexone. https://www.samhsa.gov/medication-assisted-treatment/medications-counseling-related-conditions/naltrexone
310. Kiefer F, Wiedemann K. Combined therapy: what does acamprosate and naltrexone combination tell us? *Alcohol Alcohol*. 2004;39(6):542–547.
311. Gerasimov MR, Schiffer WK, Gardner EL, et al. GABAergic blockade of cocaine-associated cue-induced increases in nucleus accumbens dopamine. *Eur J Pharmacol*. 2001;414(2–3):205–209.
312. Gryder DS, Rogawski MA. Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. *J Neurosci*. 2003;23(18):7069–7074.
313. Swift RM. Topiramate for the treatment of alcohol dependence: initiating abstinence. *Lancet*. 2003;361(9370):1666–1667.
314. Olmsted CL, Kockler DR. Topiramate for alcohol dependence. *Ann Pharmacother*. 2008;42(10):1475–1480.
315. Baltieri DA, Daró FR, Ribeiro PL, de Andrade AG. Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction*. 2008;103(12):2035–2044.
316. Topamax. Package insert. Ortho-McNeil-Janssen Pharmaceutical Inc.; 2009.
317. Patel R, Dickenson AH. Mechanisms of the gabapentinoids and alpha 2 delta-1 calcium channel subunit in neuropathic pain. *Pharmacol Res Perspect*. 2016;4(2):e00205.
318. Anton RF, Latham P, Voronin K, et al. Efficacy of gabapentin for the treatment of alcohol use disorder in patients with alcohol withdrawal symptoms: a randomized clinical trial. *JAMA Intern Med*. 2020;180(5):728–736.
319. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Intern Med*. 2014;174(1):70–77.
320. Furieri FA, Nakamura-Palacios EM. Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2007;68(11):1691–1700.
321. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694.

322. Quintero GC. Review about gabapentin misuse, interactions, contraindications and side effects. *J Exp Pharmacol*. 2017;9:13–21.
323. Mersfelder TL, Nichols WH. Reply: gabapentin: abuse, dependence, and withdrawal. *Ann Pharmacother*. 2016;50(8):692.
324. Di Sclafani V, Finn P, Fein G. Psychiatric comorbidity in long-term abstinent alcoholic individuals. *Alcohol Clin Exp Res*. 2007;31(5):795–803.
325. Lai HM, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: a systematic review and meta-analysis. *Drug Alcohol Depend*. 2015;154:1–13.
326. Farren CK, Hill KP, Weiss RD. Bipolar disorder and alcohol use disorder: a review. *Curr Psychiatry Rep*. 2012;14(6):659–666.
327. Strakowski SM, DelBello MP, Fleck DE, Arndt S. The impact of substance abuse on the course of bipolar disorder. *Biol Psychiatry*. 2000;48(6):477–485.

91

Tobacco Use and Dependence

Andrea S. Franks and Sarah E. McBane

CORE PRINCIPLES		CHAPTER CASES
1	Cigarette smoking is the single most preventable cause of premature death in the United States. Smoking harms nearly every organ of the body, causing many diseases (including, but not limited to, cardiovascular disease, pulmonary disease, and cancers) and reducing the health of smokers in general. Quitting smoking has immediate- and long-term benefits, reducing risks for diseases caused by smoking and improving health in general.	**Case 91-2 (Questions 1, 4) Case 91-3 (Question 1) Case 91-5 (Question 1) Case 91-6 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
2	Tobacco products are effective delivery systems for the drug nicotine. Nicotine is a highly addictive drug that activates the dopamine reward pathway in the brain that reinforces continued tobacco use. Nicotine withdrawal symptoms (eg, irritability, anxiety, difficulty concentrating, restlessness, depressed mood, insomnia, impaired performance, increased appetite or weight gain, and cravings) generally occur when nicotine is discontinued.	**Case 91-1 (Questions 2, 4) Case 91-3 (Question 1) Case 91-6 (Questions 1, 2)**
3	Constituents in tobacco smoke are associated with a number of clinically significant drug interactions.	**Case 91-4 (Questions 1, 3) Case 91-6 (Question 3)**
4	Tobacco dependence, a chronic disease that often requires repeated intervention and multiple attempts to quit, is characterized by physiologic dependence (addiction to nicotine) and behavioral habit of using tobacco.	**Case 91-1 (Question 5) Case 91-2 (Question 3) Case 91-3 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
5	Numerous effective medications, as delineated in the Clinical Practice Guideline, are available for treating tobacco use and dependence. Most patients should be encouraged to use one or more first-line agents, which include the nicotine patch, nicotine gum, nicotine lozenge, nicotine nasal spray, nicotine oral inhaler, sustained-release bupropion, and varenicline. All first-line agents approximately double quit rates; therefore, the choice of therapy is based largely on contraindications, precautions, patient preference, and tolerability. In some cases, medications can be combined or used for extended durations.	**Case 91-1 (Questions 1–3) Case 91-2 (Questions 3, 4) Case 91-3 (Question 1) Case 91-4 (Question 2) Case 91-6 (Questions 1, 4)**

CORE PRINCIPLES		CHAPTER CASES
6	Comprehensive counseling, as defined by the Clinical Practice Guideline, includes asking about tobacco use, advising patients to quit, assessing readiness to quit, assisting patients with quitting, and arranging follow-up. This patient-centered approach is referred to as the "*5 A's*." Counseling and support can be provided in a variety of ways, such as through individual counseling, group programs, telephone, or the Internet. Two components of counseling are especially effective and should be applied when assisting patients with quitting: practical counseling (problem-solving or skills training) and social support delivered as part of treatment. Relapse is common, and clinicians should work with patients throughout the quit attempt to increase the chances for long-term abstinence.	**Case 91-1 (Questions 2, 5) Case 91-3 (Question 1) Case 91-5 (Question 1) Case 91-6 (Questions 1, 2, 4)**
7	Brief tobacco dependence treatment (>3 minutes) is effective. In the absence of time or expertise, ask about tobacco use, advise patients to quit, and refer patients to other resources (eg, telephone quitlines, web-based support, and local programs) for additional assistance. This approach is referred to as "Ask-Advise-Refer."	**Case 91-5 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
8	Patients with psychiatric disorders exhibit a higher prevalence of tobacco use and a disproportionately high level of tobacco-related morbidity and mortality.	**Case 91-6 (Question 1)**
9	Cigarettes are the most common form of tobacco used in the United States; however, other forms of tobacco exist (spit tobacco, pipes, cigars, bidis, and hookah). All forms of tobacco are harmful.	**Case 91-2 (Question 2)**

INTRODUCTION

Tobacco is a detrimental substance, and its use dramatically increases a person's odds of dependence, disease, disability, and death. Tobacco products are carefully engineered formulations that optimize the delivery of nicotine, a chemical that meets the criteria for an addictive substance: (a) nicotine induces psychoactive effects, (b) it is used in a highly controlled or compulsive manner, and (c) behavioral patterns of tobacco use are reinforced by the pharmacologic effects of nicotine.[1] As a major risk factor for a wide range of diseases, including cardiovascular conditions, cancers, and pulmonary disorders, tobacco is the primary known preventable cause of premature death and disease in our society.[2]

In the United States, smoking is responsible for >480,000 premature deaths each year.[2] In addition to the harm imposed on users of tobacco, exposure to secondhand smoke results in an estimated 50,000 deaths annually.[3] According to the Office of the U.S. Surgeon General, there is no risk-free level of exposure to

tobacco smoke.[1] Because of the health and societal burdens that it imposes, tobacco use and dependence should be addressed during each clinical encounter with all tobacco users.[4]

EPIDEMIOLOGY OF TOBACCO USE AND DEPENDENCE

In the United States, cigarettes are the most commonly consumed form of tobacco, but other forms are also prevalent: smokeless tobacco (chewing tobacco and oral snuff), pipes, cigars, clove cigarettes, bidis, and hookah. Electronic cigarettes (or e-cigarettes), which are growing in popularity, are electronic nicotine delivery systems (ENDSs) containing liquid nicotine and other substances that are heated by an atomizer and inhaled as a vapor. Among adults, smoking prevalence varies by sociodemographic factors, including sex, race or ethnicity, education level, age, and poverty level. In 2019, ~21% of adults in the United States used a tobacco product, with 14% reporting cigarette use.[5]

Factors Contributing to Tobacco Use

Tobacco addiction is maintained by nicotine dependence.[6,7] Nicotine induces a variety of pharmacologic effects that lead to dependence.[8] However, tobacco dependence is not simply a matter of nicotine pharmacology—it is a result of the interplay of complex processes, including the desire for the direct pharmacologic actions of nicotine, the relief of withdrawal, learned associations, and environmental cues (eg, advertising, the smell of a cigarette, or observing others who are smoking).[7] Physiologic factors, such as preexisting medical conditions (eg, psychiatric comorbidities[7,9] and genetic profile), also can predispose individuals to tobacco use.[8,10]

Nicotine, the addictive component of tobacco, is rapidly absorbed and passes through the blood–brain barrier, contributing to its

addictive nature. After inhalation, the nicotine reaches the brain within seconds.[6] As such, smokers experience nearly immediate onset of the positive effects of nicotine, including pleasure, relief of anxiety, improved task performance, improved memory, mood modulation, and skeletal muscle relaxation.[6] These effects, mediated by alterations in neurotransmitter levels, reinforce continued use of nicotine-containing products.[6,7]

Nicotine Pharmacology

Nicotine (*Nicotiana tabacum*) is a clear, weak base with a pK_a of 8.0.[11] In acidic media, nicotine is ionized and poorly absorbed; conversely, in alkaline media, nicotine is nonionized and well absorbed. Under physiologic conditions (pH = 7.4), a large proportion of nicotine is nonionized and readily crosses cell membranes.[11] The tobacco industry and pharmaceutical companies are able to adjust the pH of their tobacco products and nicotine replacement therapy (NRT) products to maximize the absorption potential of nicotine.[11–13]

Once absorbed, nicotine induces a variety of central nervous system, cardiovascular, and metabolic effects. Nicotine stimulates the release of several neurotransmitters, inducing a range of pharmacologic effects such as pleasure (dopamine), arousal (acetylcholine and norepinephrine), cognitive enhancement (acetylcholine), appetite suppression (dopamine, norepinephrine, and serotonin), learning (glutamate), memory enhancement (glutamate), mood modulation (serotonin), and reduction of anxiety and tension (β-endorphin and γ-aminobutyric acid [GABA]).[14] The dopamine reward pathway, a network that elicits feelings of pleasure in response to certain stimuli, is central to the drug-induced reward. Immediately after inhalation, a bolus of nicotine enters the brain, stimulating the release of dopamine, which induces nearly immediate feelings of pleasure, along with relief of the symptoms of nicotine withdrawal. This rapid dose response reinforces repeated administration of the drug and perpetuates the smoking behavior.[7,14]

Chronic administration of nicotine has been shown to increase the number of nicotine receptors in specific regions of the brain.[15] The increase in receptors could play a role in nicotine tolerance and dependence.[14,15] Chronic nicotine administration also leads to tolerance of its behavioral and cardiovascular effects during the course of the day; however, tobacco users regain sensitivity to the effects of nicotine after overnight abstinence from nicotine,[6,7] as shown in **Figure 91-1**.[16] After smoking the first cigarette of the day, the smoker experiences marked pharmacologic effects, particularly arousal. No other cigarette throughout the day produces the same degree of pleasure or arousal. For this reason, many smokers describe the first cigarette as the most important one of the day. Shortly after the initial cigarette, tolerance begins to develop. Accordingly, the threshold levels for both pleasure or arousal and abstinence rise progressively throughout the day because the smoker becomes tolerant to the effects of nicotine. With continued smoking, nicotine accumulates, leading to an even greater degree of tolerance. Each cigarette after the first one produces less pleasure and arousal, and primarily serves to alleviate withdrawal symptoms. Lack of exposure to nicotine overnight results in resensitization of drug responses (ie, loss of tolerance). Tobacco users become adept at titrating their nicotine levels by smoking a certain number of cigarettes per day or consuming sufficient nicotine per day to achieve the desired effects of cigarette smoking and minimize the symptoms of nicotine withdrawal.[7,16] Withdrawal symptoms, which include anger, anxiety, depression, difficulty concentrating, impatience, insomnia, and restlessness, typically manifest within a few days of quitting, peak within a week, and subside within 2 to 4 weeks.[17]

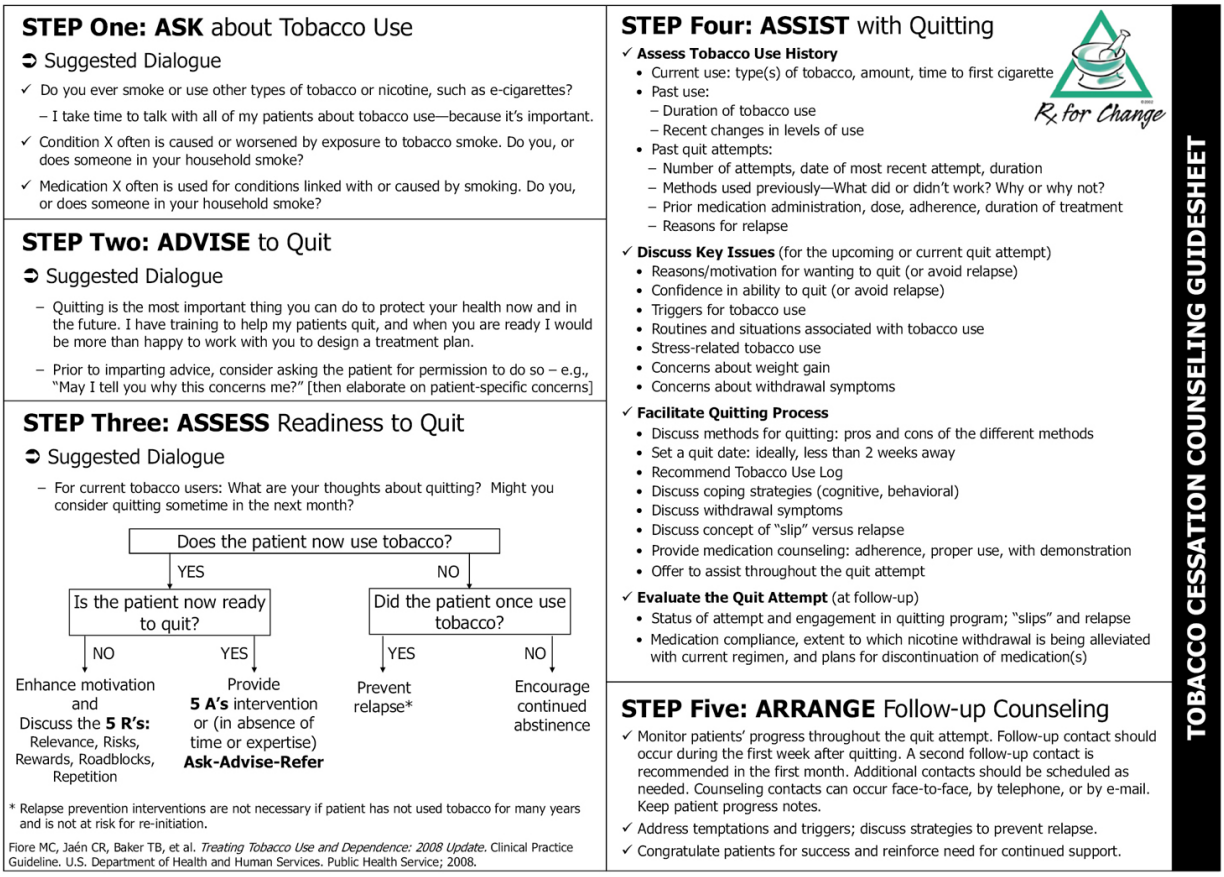


Figure 91-1 Tobacco-cessation counseling guide sheet. (Reprinted with permission from *Rx for Change: Clinician-Assisted Tobacco Cessation*. © 1999–2023. The Regents of the University of California. All rights reserved.)

Nicotine is extensively metabolized in the liver and, to a lesser extent, in the kidney and lung. Approximately 70% to 80% of nicotine is metabolized to cotinine, an inactive metabolite.[11] The rapid metabolism of nicotine (half-life [$t_{1/2}$] = 2 hours) to inactive compounds underlies tobacco users' needs for frequent, repeated administration. The half-life of cotinine, however, is much longer ($t_{1/2}$ = 18–20 hours), and, for this reason, cotinine is commonly used as a marker of tobacco use as well as a marker for exposure to secondhand smoke.[11] Measurement of cotinine cannot, however, differentiate between the nicotine from tobacco products and the nicotine from NRT products. Nicotine and other metabolites are excreted in the urine. Urinary excretion is pH dependent; the

excretion rate is increased in acidic urine.[11] Nicotine crosses the placenta and accumulates in breast milk.[11]

Drug Interactions With Smoking

It is widely recognized that polycyclic aromatic hydrocarbons (PAHs) in tobacco smoke are responsible for most drug interactions with smoking.[18,19] PAHs, which result from incomplete combustion of tobacco, are potent inducers of several hepatic cytochrome-P450 (CYP) microsomal enzymes (CYP1A1, CYP1A2, and, possibly, CYP2E1). Although other substances in tobacco smoke, including acetone, pyridines, benzene, nicotine, carbon monoxide, and heavy metals (eg, cadmium), might also interact with hepatic enzymes, their effects appear to be less significant. Most drug interactions with tobacco smoke are pharmacokinetic, resulting from the induction of drug-metabolizing enzymes (especially CYP1A2) by compounds in tobacco smoke. **Table 91-1** summarizes key interactions with smoking.[18–20] Patients who begin smoking, quit smoking, or dramatically alter their level of smoking might require dosage adjustments for some medications.

Table 91-1
Clinically Significant Drug Interactions With Tobacco Smoke

Drug/Class	Mechanism of Interaction and Effects
Bendamustine (Treanda®)	Metabolized by CYP1A2. Manufacturer recommends using with caution in smokers because of likely ↓ bendamustine concentrations, with ↑ concentrations of its two active metabolites.
Caffeine	↑ Metabolism (induction of CYP1A2); ↑ clearance (56%) Caffeine levels likely increase after cessation.
Clopidogrel (Plavix®)	↑ Metabolism (induction of CYP1A2) of clopidogrel to its active metabolite Clopidogrel's effects are enhanced in smokers (≥10 cigarettes/day): significant ↑ platelet inhibition, ↓ platelet aggregation; although improved clinical outcomes have been shown, may also ↑ risk of bleeding.

Drug/Class	Mechanism of Interaction and Effects
Clozapine (Clozaril®)	↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (18%) ↑ Levels on cessation may occur; closely monitor drug levels and reduce the dose as required to avoid toxicity.
Erlotinib (Tarceva®)	↑ Clearance (24%); ↓ trough serum concentrations (twofold)
Fluvoxamine (Luvox®)	↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ C_{max} (32%) and C_{ss} (by 39%) Dosage modifications not routinely recommended, but smokers may need ↑ dosages.
Irinotecan (Camptosar®)	↑ Clearance (18%); ↓ serum concentrations of active metabolite SN-38 (~40%; via induction of glucuronidation); ↓ systemic exposure resulting in lower hematologic toxicity and may reduce efficacy. Smokers may need ↑ dosages.
Olanzapine Zyprexa®)	↑ Metabolism (induction of CYP1A2): ↑ clearance (98%); ↓ serum concentrations (12%) Dosage modifications not routinely recommended, but smokers may need ↑ dosages.
Riociguat (Adempas®)	↓ Plasma concentrations (by 50%–60%) Smokers may require dosages higher than 2.5 mg 3 times daily; consider dose reduction upon cessation.
Ropinirole (Requip®)	↓ C_{max} (30%) and AUC (38%) in a study with patients with restless legs syndrome Smokers may need ↑ dosages.
Tacrine (Cognex®)	↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations threefold lower. Smokers may need ↑ dosages.
Theophylline (Theo-Dur®, etc)	↑ Metabolism (induction of CYP1A2); ↑ clearance (58%–100%); ↓ half-life (63%) Levels should be monitored if smoking is initiated, discontinued, or changed. ↑ Clearance with secondhand smoke exposure Maintenance doses are considerably higher in smokers; ↑ clearance also with secondhand smoke exposure.

Drug/Class	Mechanism of Interaction and Effects
Hormonal contraceptives (combined)	↑ Risk of cardiovascular adverse effects (eg, stroke, myocardial infarction, or thromboembolism) in females who smoke and use combined hormonal contraceptives ↑ Risk with age and with heavy smoking (≥15 cigarettes/day) and is quite marked in females age 35 and older

AUC, area under the curve; C_{max}, maximal concentration; C_{ss}, steady-state concentration; CYP, cytochrome P450; INR, international normalized ratio; PD, pharmacodynamics; PK, pharmacokinetics.

Adapted with permission from Rx for Change: Clinician-Assisted Tobacco Cessation. © 1999–2023. The Regents of the University of California. All rights reserved.

Health Consequences of Tobacco Use

All forms of tobacco are harmful, and there is no safe level of exposure to tobacco products. Smoking has a causal or contributory role in the development of a variety of medical conditions, affecting almost every organ in the body.[1,2]

Benefits of Quitting

Benefits of smoking cessation incurred soon after quitting (eg, within 2 weeks–3 months) include improvements in pulmonary function, circulation, and ambulation. Smoking cessation results in measurable improvements in lung function (see Chapter 19, Chronic Obstructive Pulmonary Disease). One year after cessation, the excess risk of coronary heart disease (CHD) is reduced to half that of continuing smokers. After 5 to 15 years, the risk of stroke is reduced to a rate similar to that of people who are lifetime nonsmokers; and 10 years after quitting, the chance of dying of lung cancer is approximately half that of continuing smokers. In addition, the risk of developing mouth, throat, esophagus, bladder, kidney, or pancreatic cancer is decreased. Finally, 15 years after quitting, the risk of CHD is reduced to a rate that is similar to that of people who have never smoked.[21] Similarly, more recent data suggest that smokers who quit for good over a sustained period have an overall

mortality rate and death rate associated with cardiovascular disease, ischemic heart disease, and stroke that is similar to individuals who have never smoked. In contrast, individuals who had successfully quit, but later resumed smoking, had mortality risks that were significantly higher than that of lifetime nonsmokers.[22]

On average, cigarette smokers die ~10 years younger than do nonsmokers, and of those who continue smoking, at least half will eventually die from a tobacco-related disease. A reduction in smoking does not equate to a reduction in harm,[,23] and even low levels of smoking (eg, one to four cigarettes per day) have documented risks.[24,25] Therefore, decreasing the number of cigarettes smoked per day is a positive step toward quitting, but should not be recommended as a targeted end point. For any patient who uses tobacco, the goal is complete, long-term abstinence from all nicotine-containing products.

Tobacco Use and Dependence: Treatment Approaches

Most tobacco users attempt to quit without assistance, even though those who receive assistance are more likely to be successful in quitting.[4,26] Given the complexity of the tobacco dependence syndrome and the constellation of factors that contribute to tobacco use, treatment requires a multifaceted approach. The U.S. Public Health Service Clinical Practice Guideline for Treating Tobacco Use and Dependence notes that clinicians can have an important impact on their patients' ability to quit.[4] A meta-analysis of 29 studies estimated that compared with patients who do not receive an intervention from a clinician, patients who receive a tobacco-cessation intervention from a physician clinician or a nonphysician clinician are 2.2 and 1.7 times, respectively, more likely to quit (at 5 or more months after cessation).[4] Other effective methods for delivery of counseling include group programs[4,27] and telephone counseling.[28] Internet- and text message–based interventions have also shown small positive effects on cessation.[29,30]

Numerous effective medications are available for tobacco dependence, and clinicians should encourage their use by all patients attempting to quit smoking—except when medically contraindicated or with specific populations for which there is insufficient evidence of effectiveness (eg, pregnant females, smokeless tobacco users, light smokers, and adolescents). [4] Although both pharmacotherapy and behavioral counseling are effective independently, patients' odds of quitting are substantially increased when the two approaches are used simultaneously.[31] Clinicians can have a significant impact on a patient's likelihood of success by recommending pharmacotherapy agents and by supplementing medication use with behavioral counseling, as described later in this chapter.

Assisting Patients With Quitting

BEHAVIORAL COUNSELING STRATEGIES

According to the Clinical Practice Guideline,[4] five key components constitute comprehensive, patient-centered counseling for tobacco cessation: (1) asking patients whether they use tobacco, (2) advising tobacco users to quit, (3) assessing patients' readiness to quit, (4) assisting patients with quitting, and (5) arranging follow-up care. These steps are referred to as the "5 A's," and are described, in brief, as follows. Figure 91-1 can be used as a guide for structuring counseling interactions.

1. **Ask**: Clinical care should routinely include screening for tobacco use and should include assessment and documentation of tobacco use status (current, former, or never user) and level of use (eg, number of cigarettes smoked per day) Also, patients should be asked about exposure to secondhand smoke.
2. **Advise**: Tobacco users should be advised to consider quitting; the advice should be clear and compelling, yet sensitively delivered in a tone of voice that communicates concern and a willingness to assist with quitting. When possible, messages should be

personalized by relating advice to factors such as a patient's health status, medication regimen, personal reasons for wanting to quit, or the impact of tobacco use on others.

3. **Assess**: The assessment of a patient's readiness to quit is key to providing appropriate counseling interventions. Patients should be categorized as being (a) not ready to quit in the next month; (b) ready to quit in the next month; (c) a recent quitter, having quit in the past 6 months; or (d) a former user, having quit more than 6 months ago.[4] This classification defines the clinician's next step, which is to provide counseling that is tailored to the patient's level of readiness to quit. The counseling interventions for patients who are ready to quit will be different from those for patients who are not considering quitting.
4. **Assist**: When counseling tobacco users, it is important that clinicians and patients view quitting as a process that might take months or even years to achieve. The goal is to promote forward progress in the process of change, with the target end point being sustained abstinence from all nicotine-containing products.

When counseling patients who are not ready to quit, an important first step is to foster motivation. Some patients are not convinced that quitting is important, but most recognize the need to quit and are simply not ready to make the commitment to do so. Often, patients have tried to quit multiple times and failed, and thus are too discouraged to try again. The "5 R's" can be applied to enhance motivation to quit[4] (**Table 91-2**) by clinicians offering to work closely with the patient in designing a treatment plan. Although it might be useful to educate patients about the pharmacotherapy options, it is inappropriate to prescribe a treatment regimen for patients who are not ready to quit. For patients who are not ready to quit in the next 30 days, encourage them to seriously consider quitting and ask the following questions:

Table 91-2
Enhancing Motivation to Quit: The "5 R's" for Tobacco-

Cessation Counseling

Relevance—Encourage patients to think about the reasons why quitting is important. Counseling should be framed such that it relates to the patient's risk for disease or exacerbation of disease, family or social situations (eg, having children with asthma), health concerns, age, or other patient factors, such as prior experience with quitting.

Risks—Ask patients to identify potential negative health consequences of smoking, such as acute risks (shortness of breath, asthma exacerbations, harm to pregnancy, infertility), long-term risks (cancer, cardiac, and pulmonary disease), and environmental risks (promoting smoking among children by being a negative role model; effects of secondhand smoke on others, including children and pets).

Rewards—Ask patients to identify potential benefits that they anticipate from quitting, such as improved health, enhanced physical performance, enhanced taste and smell, reduced expenditures for tobacco, less time wasted or work missed, reduced health risks to others (fetus, children, housemates), and reduced aging of the skin.

Roadblocks—Help patients identify barriers to quitting and assist in developing coping strategies (Table 91-4) for addressing each barrier. Common barriers include nicotine withdrawal symptoms, fear of failure, a need for social support while quitting, depression, weight gain, and a sense of deprivation or loss.

Repetition—Continue to work with patients who are successful in their quit attempt. Discuss circumstances in which smoking occurred to identify the trigger(s) for relapse; this is part of the learning process and will be useful information for the next quit attempt. Repeat interventions when possible.

Source: Reprinted from Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*. U.S. Department of Health and Human Services. Public Health Service; 2008.

1. *Do you ever plan to quit?*

   If the patient responds "no," the clinician should ask, "*What would have to change for you to decide to quit?"* If the patient responds "nothing," then offer to assist, if or when the patient changes his or her mind. If the patient responds "yes," the clinician should continue with question 2.

2. *What might be some benefits of quitting now, instead of later?*

   Quitting often becomes more difficult the longer a patient smokes. Most patients will agree that there is never an ideal time to quit, and procrastinating on a quit date has more negative rather than positive effects.

3. *What would have to change for you to decide to quit sooner?*

This question probes patients' perceptions of quitting, which reveals some of the barriers to quitting that can then be discussed.

For patients who are ready to quit (eg, in the next month), the goal is to work with the patient in designing an individualized treatment plan, addressing the key issues listed under the "Assist" component of Figure 91-1.[20] Clinicians should elicit patients' opinions about the different cessation medications and should work with patients in selecting the quitting methods (eg, medications and behavioral counseling programs). Although it is important to recognize that pharmacotherapy might not be appropriate, desirable, or affordable for all patients, clinicians should educate patients that medications, when taken correctly, can substantially increase the likelihood of success.

Patients should select a quit date, ideally within the next 2 weeks. This allows sufficient time to prepare for the quit attempt, including mental preparation; preparation of the environment; removing all tobacco products and ashtrays from the home, car, and workspace; and soliciting the support of their family, friends, and coworkers. Additional strategies for coping with quitting are shown in **Table 91-3**. Patients should be counseled about withdrawal symptoms, medication use, and the importance of receiving behavioral counseling throughout the quit attempt. Finally, patients should be commended for taking important steps toward improving their health.

Table 91-3

Cognitive and Behavioral Strategies for Tobacco Cessation

Cognitive Strategies
Focus on *retraining the way a patient thinks.* Often, patients will deliberate on the fact that they are thinking about a cigarette, and this leads to relapse. Patients must recognize that thinking about a cigarette does not mean they need to have one.

Cognitive Strategies	
Review commitment to quit	Each morning, say, “I am proud that I made it through another day without tobacco!” Remind oneself that cravings and temptations are temporary and will pass. Announce, either silently or aloud, “I am a nonsmoker, and the temptation will pass.”
Distractive thinking	Deliberate, immediate refocusing of thinking toward other thoughts when cued by thoughts about tobacco use.
Positive self-talks, “pep talks”	Say “I can do this.” Remind oneself of previous difficult situations in which tobacco use was avoided.
Relaxation through imagery	Center mind toward positive, relaxing thoughts.
Mental rehearsal, visualization	Preparing for situations that might arise by envisioning how best to handle them. For example, envision what would happen if offered a cigarette by a friend—mentally craft and rehearse a response, and perhaps even practice it by saying it aloud.
Behavioral Strategies	
Involve *specific actions to reduce risk for relapse*. These strategies should be considered before quitting, after determining patient-specific triggers and routines or situations associated with tobacco use. Given here are strategies for several of the common cues or causes for relapse.	
Stress	Anticipate upcoming challenges at work, at school, or in personal life. Develop a substitute plan for tobacco use during times of stress (eg, use deep breathing, take a break or leave the situation, call a supportive friend or family member, or use nicotine replacement therapy to manage situational cravings).
Alcohol	Drinking alcohol can lead to relapse. Consider limiting or abstaining from alcohol during the early stages of quitting.
Other tobacco users	Quitting is more difficult when around other tobacco users. This is especially difficult if there is another tobacco user in the household. During the early stages of quitting, limit prolonged contact with individuals who are using tobacco. Ask coworkers, friends, and housemates not to smoke or use tobacco in your presence.

Cognitive Strategies	
Oral gratification needs	Have nontobacco oral substitutes (eg, gum, sugarless candy, straws, toothpicks, lip balm, toothbrush, nicotine replacement therapy, or bottled water) readily available.
Automatic smoking routines	Anticipate routines that are associated with tobacco use and develop an alternative plan.
	Examples:
	Morning coffee: Change morning routine, drink tea instead of coffee, take shower before drinking coffee, take a brisk walk shortly after awakening.
	While driving: Remove all tobacco from car, have car interior detailed, listen to an audio book or talk radio, use oral substitutes.
	While on the phone: Stand while talking, limit call duration, change phone location, keep hands occupied by doodling or sketching.
	After meals: Get up and immediately do dishes or take a brisk walk after eating, call supportive friend.
Postcessation weight gain	Do not attempt to modify multiple behaviors at one time. If weight gain is a barrier to quitting, engage in regular physical activity and adhere to a healthful diet (as opposed to strict dieting). Carefully plan and prepare meals, increase fruit and water intake to create a feeling of fullness, and chew sugarless gum or eat sugarless candies. Consider use of pharmacotherapy shown to delay weight gain (eg, nicotine gum, lozenge, or sustained-release bupropion).
Cravings for tobacco	Cravings for tobacco are temporary and usually pass within 5–10 minutes. Handle cravings through distractive thinking, take a break, do something else, take deep breaths.

Reprinted with permission from *Rx for Change: Clinician-Assisted Tobacco Cessation*. © 1999–2023. The Regents of the University of California. All rights reserved.

- **Arrange:** Because patients' success at quitting increases when multiple counseling interactions are provided, it is important to arrange follow-up counseling. Follow-up contact should occur soon after the quit date, preferably during the first week. A second

follow-up contact is recommended within the first month of quitting.[4] Additional follow-up contacts should occur to monitor patient progress, assess compliance with pharmacotherapy regimens, and provide additional support.

Relapse prevention counseling should be part of every follow- up contact with patients who have recently quit smoking. When counseling recent quitters, it is important to address challenges in countering withdrawal symptoms and cravings or temptations to use tobacco. A list of strategies for key triggers or temptations for tobacco use is provided in Table 91-3.[20] Importantly, because tobacco use is a habitual behavior, patients should be advised to alter their daily routines; this helps disassociate specific behaviors from the use of tobacco. Patients who slip and smoke a cigarette (or use any form of tobacco) or experience a full relapse to habitual tobacco use should be encouraged to evaluate the scenario in which tobacco use first occurred and identify the trigger(s) for relapse. This process provides valuable information for future quit attempts.

PHARMACOTHERAPY OPTIONS

All smokers who are trying to quit should be encouraged to use one or more of the U.S. Food and Drug Administration (FDA)-approved pharmacologic aids for cessation. Potential exceptions that require special consideration include use in specific populations that lacks sufficient evidence of effectiveness (eg, pregnant females, smokeless tobacco users, light smokers, and adolescents).[4] Pharmacotherapy should always be combined with behavioral support and counseling. Currently, the FDA-approved first-line agents that have been shown to be effective in promoting smoking cessation include five NRT dosage forms, sustained- release bupropion, and varenicline.[4] The choice of therapy is dictated by considerations such as patient preference for a given agent, previous experience with cessation medications, current medical conditions, previous levels of smoking, medication adherence issues, and the patient’s out-of-pocket costs. Dosing information,

precautions, and adverse effects for the first-line agents are shown in **Table 91-4**.

Table 91-4
Pharmacologic Product Guide: U.S. Food and Drug Administration–Approved Medications for Smoking Cessation

NRT Formulations					Bupropion SR	Varenicline
Gum	**Lozenge**	**Transdermal Patch**	**Nasal Spray**	**Oral Inhaler**		
Product						
Nicorette®,[a] generic	Nicorette Lozenge®[a]; Nicorette Mini Lozenge® (standard and mini),[a] generic	NicoDerm CQ®,[a] Habitrol®,[b] generic	Nicotrol® NS[c]	Nicotrol® inhaler[c]	Generic (formerly Zyban)	Chantix®[c]
OTC	OTC	OTC (NicoDerm CQ®, generic)	Rx	Rx	Rx	Rx
2 and 4 mg	2 and 4 mg	Rx (generic)	Metered spray	10-mg cartridge	150-mg sustained-release tablet	0.5- and 1-mg tablet
Original, cinnamon, fruit, mint	Cherry, mint	7, 14, and 21 mg (24-hour release)	10 mg/mL aqueous solution	Delivers 4 mg of inhaled nicotine vapor		
Precautions, Warnings, and Contraindications						
Temporomandibular joint disease			Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis) Severe reactive airway disease	Bronchospastic disease	Concomitant therapy with medications or medical conditions known to lower seizure threshold Hepatic impairment Pregnancy[d] (category C) and breast-feeding Adolescents (>18 years) Treatment-emergent neuropsychiatric symptoms[e]	Severe renal impairment (dosage adjustment is necessary.) Pregnancy[d] (category C) and breast-feeding Adolescents (>18 years) Treatment-emergent neuropsychiatric symptoms[e]
Dosing[f]						
First cigarette ≤30 minutes after waking: 4 mg *First cigarette >30 minutes after waking:* 2 mg Weeks 1–6: 1 piece every 1–2 hours Weeks 7–9: 1 piece every 2–4 hours Weeks 10–12: 1 piece every 4–8 hours Maximum, 24 pieces/day Chew each piece slowly. Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews). Resume chewing when tingle fades.	*First cigarette ≤30 minutes after waking:* 4 mg *First cigarette >30 minutes after waking:* 2 mg Weeks 1–6: 1 lozenge every 1–2 hours Weeks 7–9: 1 lozenge every 2–4 hours Weeks 10–12: 1 lozenge every 4–8 hours Maximum, 20 lozenges/day	*>10 cigarettes/day:* 21 mg/day × 4 weeks (generic) × 6 weeks (NicoDerm CQ®) 14 mg/day × 2 weeks 7 mg/day × 2 weeks *≤10 cigarettes/day:* 14 mg/day × 6 weeks 7 mg/day × 2 weeks Rotate patch application site daily; do not apply a new patch to the same skin site for at least 1 week. May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime)	1–2 doses/hour (8–40 doses/day) One dose = 2 sprays (one in *each* nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa. Maximum –5 doses/hour or –40 doses/day For best results, initially use at least 8 doses/day. Do not sniff, swallow, or inhale through the nose as the spray is being administered.	6–16 cartridges/day Individualize dosing; initially use 1 cartridge every 1–2 hours. Best effects with continuous puffing for 20 minutes Initially use at least 6 cartridges/day. Nicotine in cartridge is depleted after 20 minutes of active puffing. Inhale into back of throat or puff in short breaths.	150 mg PO every morning × 3 days, then increase to 150 mg PO bid Do not exceed 300 mg/day. Begin therapy 1–2 weeks *before* quit date. Allow at least 8 hours between doses. Avoid bedtime dosing to minimize insomnia. Dose tapering is not necessary. Duration: 7–12 weeks, with maintenance up to 6 months in selected patients	Days 1–3: 0.5 mg PO every morning Days 4–7: 0.5 mg PO bid Weeks 2–12: 1 mg PO bid Begin therapy 1 week *before* quit date. Take dose after eating and with a full glass of water. Dose tapering is not necessary. Dosing adjustment is recommended for patients with severe renal impairment.

Repeat chew and park steps until most of the nicotine is gone (tingle does not return; generally 30 minutes). Park in different areas of the mouth. No food or beverages 15 minutes before or during use Duration: up to 12 weeks	Allow to dissolve slowly (20–30 minutes for standard; 10 minutes for mini). Nicotine release may cause a warm, tingling sensation. Do not chew or swallow. Occasionally rotate to different areas of the mouth. No food or beverages 15 minutes before or during use Duration: up to 12 weeks	Duration: 8–10 weeks	Duration: 3–6 months	Do *not* inhale into the lungs (like a cigarette), but "puff" as if lighting a pipe. Open cartridge retains potency for 24 hours. No food or beverages 15 minutes before or during use Duration: 3–6 months		Duration: 12 weeks; an additional 12-week course may be used in selected patients. May initiate up to 35 days before target quit date *or* may reduce smoking over a 12-week period of treatment before quitting and continue treatment for an additional 12 weeks
Adverse Effects						
Mouth or jaw soreness Hiccups Dyspepsia Hypersalivation Effects associated with incorrect chewing technique: Lightheadedness Nausea or vomiting Throat and mouth irritation	Nausea Hiccups Mouth irritation Heartburn Headache Sore throat Dizziness	Local skin reactions (erythema, pruritus, burning) Headache Sleep disturbances (insomnia, abnormal or vivid dreams); associated with nocturnal nicotine absorption	Nasal or throat irritation (hot, peppery, or burning sensation) Rhinitis Tearing Sneezing Cough Headache	Mouth or throat irritation Cough Headache Rhinitis Dyspepsia Hiccups	Insomnia Dry mouth Nervousness or difficulty concentrating Rash Constipation Seizures (risk is ~0.1%) Neuropsychiatric symptoms (rare; see Precautions)	Nausea Sleep disturbances (insomnia, abnormal or vivid dreams) Constipation Flatulence Vomiting Neuropsychiatric symptoms (rare; see Precautions)

NRT, nicotine replacement therapy; OTC, over the counter (nonprescription); Rx, prescription; SR, sustained release.

[a]Marketed by GlaxoSmithKline.

[b]Marketed by Dr. Reddy's.

[c]Marketed by Pfizer.

[d]The U.S. Clinical Practice Guideline states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and theoretic concerns with safety. Pregnant smokers should be offered behavioral counseling interventions that exceed minimal advice to quit.

[e]In July 2009, the U.S. Food and Drug Administration (FDA) mandated that the prescribing information for all bupropion- and varenicline-containing products includes a black box warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Clinicians should advise patients to stop taking varenicline or bupropion SR and contact a health care provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. If treatment is stopped because of neuropsychiatric symptoms, patients should be monitored until the symptoms resolve. Based on the results of a mandated clinical trial, the FDA removed this boxed warning in December 2016.

[f]For complete prescribing information, refer to the manufacturers' package inserts.

Adapted with permission from *Rx for Change: Clinician-Assisted Tobacco Cessation*. © 1999–2023. The Regents of the University of California. All rights reserved.

FIRST-LINE AGENTS

Nicotine replacement therapy

NRT improves cessation rates by reducing the physical withdrawal symptoms associated with tobacco cessation, allowing the patient to focus on behavior modification and cope with the psychological aspects of quitting. In addition, because the onset of action for NRT is not as rapid as that of nicotine obtained through smoking, patients become less accustomed to the nearly immediate, reinforcing effects of inhaled nicotine. A meta-analysis found that patients using NRT are 1.6 times as likely to quit smoking than are those receiving placebo.[31] **Figure 91-2** depicts the concentration–time curves for the various NRT formulations, compared with a cigarette and snuff, a smokeless form of tobacco.[32,33] Nicotine nasal spray reaches its peak concentration most rapidly. The nicotine gum, lozenge, and oral inhaler have similar concentration curves, and the nicotine transdermal patch has the slowest onset but offers more consistent blood levels of nicotine for a sustained period. Although ideally tobacco use stops when NRT is initiated, some patients may continue to occasionally use tobacco products after beginning NRT. This allows patients more flexibility with continuing to use NRT if they slip and use tobacco products, or with initiating NRT in an effort to decrease the number of cigarettes smoked before complete cessation (the “reduce to quit” method).[34] Initiating the nicotine patch before a quit attempt may be more effective than is applying the patch on the quit date. However, data are conflicting, and the evidence does not support using other forms of NRT before the quit date.[34] Precautions common to all forms of NRT include recent (≤2 weeks) myocardial infarction (MI), serious arrhythmia or angina pectoris, pregnancy, breast-feeding, and adolescence.[20]

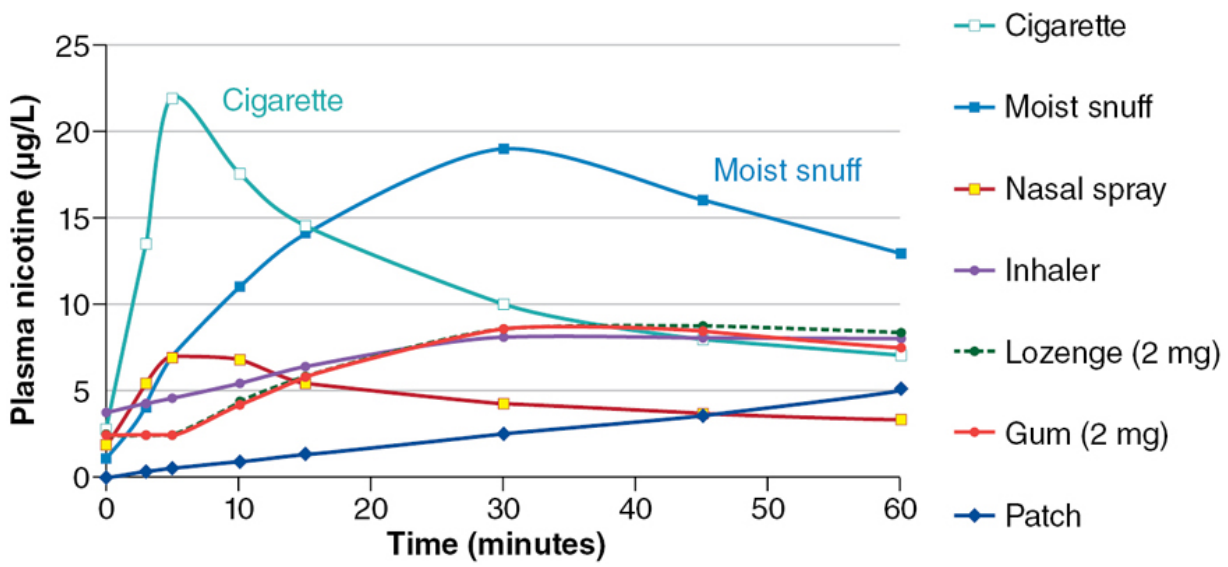


Figure 91-2 Plasma nicotine concentrations for various nicotine-containing products. (Reprinted with permission from *Rx for Change: Clinician-Assisted Tobacco Cessation*. © 1999–2023. The Regents of the University of California. All rights reserved. Plasma nicotine concentration curves derived from Choi JH, Dresler CM, Norton MR, Strahs KR. Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine Tob Res*. 2003;5(5):635; Schneider NG, Olmstead RE, Franzon MA, Lunell E. The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet*. 2001;40(9):661; Fant RV, Henningfield JE, Nelson RA, Pickworth WB. Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tob Control*. 1999;8(4):387.)

Sustained-release bupropion

Sustained-release bupropion is an atypical antidepressant medication hypothesized to promote smoking cessation by blocking the reuptake of dopamine and norepinephrine in the central nervous system[4] and possibly by acting as a nicotine receptor antagonist.[35] These neurochemical effects are believed to modulate the dopamine reward pathway and reduce cravings for nicotine and symptoms of withdrawal.[4] When compared to placebo, sustained-release bupropion increases the long-term abstinence rate with a risk ratio (RR) of 1.64.[36] Bupropion's tobacco-cessation efficacy is similar to

that of NRT.[36] Sustained-release bupropion carries a boxed warning for suicidal ideation, as do other antidepressants. It is contraindicated in seizure disorder, current or past anorexia or bulimia, monoamine oxidase inhibitor use within 14 days, concomitant use of other forms of bupropion, and simultaneous abrupt discontinuation of alcohol, sedatives, or antiepileptic medications.[37]

Varenicline

Varenicline is a partial agonist that binds with high affinity and selectivity at $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors.[38] The efficacy of varenicline in smoking cessation is believed to be the result of sustained, low-level agonist activity at the receptor site combined with competitive inhibition of nicotine binding. The partial agonist activity induces modest receptor stimulation, leading to increased dopamine levels, which attenuates the symptoms of nicotine withdrawal. In addition, by blocking the ability of nicotine to activate $\alpha_4\beta_2$ nicotinic acetylcholine receptors, varenicline inhibits the surges of dopamine release that are believed to be responsible for the reinforcement and reward associated with smoking.[38] Use of varenicline more than doubles the chances of quitting when compared to placebo, and it is superior to bupropion or NRT.[36,39] Patients should be monitored for neuropsychiatric symptoms, including changes in behavior, mood, or suicidal thoughts and behavior.[40]

PHARMACOTHERAPY FOR TREATING TOBACCO USE AND DEPENDENCE

Transdermal Nicotine Patch

CASE 91-1

QUESTION 1: T.B. is a 32-year-old female who is enrolled in a worksite smoking-cessation program. During the previous group session, the cessation counselor discussed the various medications for cessation. T.B. has set her quit date for 1 week from today, and she is interested in starting the nicotine transdermal patch. She is currently smoking 1.5 packs per day (PPD), which is a reduction from the two PPD she had been smoking for the past 10 years. T.B. reports she smokes several cigarettes in succession immediately after waking in the morning. She takes no medications and has no medical problems.

Which nicotine transdermal product should T.B. select, and how should it be used?

Transdermal nicotine delivery systems consist of an impermeable surface layer, a nicotine reservoir, an adhesive layer, and a removable protective liner. Although the transdermal delivery technology varies by manufacturer, nicotine is well absorbed, with 68% to 82% of the dose released from 24-hour patch formulations systemically bioavailable across the skin. Plasma nicotine concentrations from the patch rise slowly during 1 to 4 hours and peak within 3 to 12 hours after application.[11] Levels of nicotine achieved with the transdermal patch are lower and fluctuate less than do those achieved with tobacco products or other NRT formulations (see Fig. 91-2).

The transdermal nicotine patch exhibits significantly improved abstinence rates relative to placebo.[4] A systemic review of 51 trials with nicotine patch versus placebo found an RR of 1.64 with at least 6 months of follow-up.[31]

DOSING

The manufacturers' recommended dosages are listed in Table 91-4. In general, higher levels of smoking necessitate the use of higher strength formulations and a longer duration of therapy. Ultimately, the starting dose, rate of tapering, and total duration of therapy must be individualized to the patient's baseline smoking levels, development of side effects (eg, nausea, dyspepsia, nervousness, dizziness, and sweating), and the presence or absence of withdrawal symptoms. T.B. currently smokes 30 cigarettes per day, and thus she should initiate the regimen using the 21-mg per day patch.

PATIENT EDUCATION

T.B. should be instructed to apply the patch to a clean, dry, hairless area of skin on the upper body or the upper outer part of her arm at approximately the same time each day. To minimize the potential for local skin reactions, the patch application site should be rotated daily, and the same area should not be used again for at least 1 week. After patch application, T.B. should ensure that the patch adheres well to the skin, especially around the edges. The clinician should reassure T.B. that water will not reduce the effectiveness of the nicotine patch if it is applied correctly, and she may bathe, shower, swim, or exercise while wearing the patch. Finally, T.B. should be advised to discontinue use of the nicotine patch and contact a health care provider if skin redness caused by the patch does not resolve after 4 days; if the skin swells or a rash develops; if irregular heartbeat or palpitations occur; or if she experiences symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, sweating, weakness, or rapid heartbeat.

ADVERSE REACTIONS

Case 91-1, Question 2: Ten days later, T.B. calls to report an itchy rash that she believes is caused by the nicotine patch. She noticed the rash yesterday when she removed the first patch from her left upper arm. This morning, after removing the second patch from her right upper arm, she noticed a similar rash. T.B. describes the skin on her right arm as slightly red, but not swollen; the rash on her left arm has only a faint trace of pink discoloration. Her last cigarette was 2 days ago. How should T.B. be managed at this time?

The most common side effects associated with the nicotine patch are local reactions (erythema, burning, and pruritus) at the skin application site. These reactions are generally caused by skin occlusion or sensitivity to the patch adhesives. Rotating the patch application sites daily minimizes skin irritation; nonetheless, skin reactions to the patch adhesives occur in up to 50% of patch users. Fewer than 5% of patients discontinue therapy because of a skin reaction.[4]

T.B. appears to be experiencing a mild skin reaction and should be reassured that it is common for the skin to appear erythematous for up to 24 to 48 hours after the patch is removed. T.B. can apply topical hydrocortisone cream (0.5% or 1%) or triamcinolone cream (0.5%) for symptomatic treatment.[4] Another option would be to try a different brand of patch because the adhesive may vary. Because the rash on her left arm has nearly resolved, it is reasonable for T.B. to continue using the nicotine transdermal patch provided that the erythema is not too bothersome.

Other less common side effects associated with the transdermal nicotine patch include vivid or abnormal dreams, insomnia, and headache. Sleep disturbances likely result from nocturnal nicotine absorption. Patients experiencing troublesome sleep disturbances should be instructed to remove the patch before bedtime and apply a new patch as soon as possible after waking the following morning.[4,20]

The clinician should also provide behavioral counseling support by asking T.B. about the current quit attempt. Appropriate issues to address include her confidence in remaining tobacco free, situations in which she has been tempted to smoke and potential triggers for relapse, nicotine withdrawal symptoms, her social support system for quitting, and any other questions or concerns she might have. It is reasonable to review potential coping strategies (behavioral and cognitive; see Table 91-3) and schedule a future follow-up call. The clinician should commend T.B. for her decision to quit, congratulate her for remaining free of cigarettes for 48 hours, and reassure her that skin irritation is a common, yet generally manageable, complication with the nicotine patch.

PRODUCT SELECTION CONSIDERATIONS

The primary advantage of the transdermal nicotine patch compared with other NRT formulations is that the patch is easy to use, releases a continuous dose of nicotine throughout the day, and requires administration only once daily. Disadvantages of the patch include a high incidence of skin irritation associated with the patch adhesives and the inability to acutely adjust the dose of nicotine to alleviate

symptoms of withdrawal. Finally, patients with underlying dermatologic conditions (eg, psoriasis, eczema, or atopic dermatitis) should not use the patch because they are more likely to experience skin irritation.[4]

Case 91-1, Question 3: T.B. would like to discontinue the nicotine transdermal patch. She would like to purchase a nonprescription smoking-cessation medication and wants to know whether the gum or lozenge is an effective alternative. What options would you recommend? What factors should be considered?

Nicotine Gum

Nicotine polacrilex gum is a resin complex of nicotine and polacrilin in a chewing gum base that provides slow release and absorption of nicotine across the oral mucosa. The product is available in 2- and 4-mg strengths, and in multiple flavors. The gum has a distinct, tobacco-like, slightly peppery, minty, or fruity taste and contains buffering agents to increase the salivary pH, which enhances the buccal absorption of nicotine. The amount of nicotine absorbed from each piece is variable, but when used properly, ~1.6 and 2.2 mg of nicotine is absorbed from each 2- and 4-mg piece of gum, respectively.[11] Peak plasma concentrations of nicotine are achieved ~30 minutes after chewing a single piece of gum and then slowly decline thereafter (see Fig. 91-2). Patients using nicotine gum are significantly more likely to remain abstinent compared with those receiving placebo, with an RR of 1.49 versus placebo.[4,31]

DOSING

Table 91-4 outlines the manufacturers' recommended dosing schedule for the nicotine gum. The recommended dosage of the nicotine gum is based on the "time to first cigarette" (TTFC) of the day. Having a strong desire or need to smoke soon after waking is viewed as a key indicator of nicotine dependence.[20,41] Therefore, patients who smoke their first cigarette of the day within 30 minutes

of waking are likely to be more highly dependent on nicotine and require higher dosages than do those who delay smoking for >30 minutes after waking (see Table 91-4). The “chew and park” method allows for the slow, consistent release of nicotine. Patients can use additional pieces of gum (to the daily maximum of 24 pieces per day) if cravings occur between scheduled doses. In general, patients who smoke a greater number of cigarettes per day will require more nicotine gum to alleviate their cravings than will patients who smoke fewer cigarettes per day. It is preferable to use the gum on a fixed schedule of administration, tapering during 1 to 3 months rather than using it only as needed to control cravings.[4,20]

PATIENT EDUCATION

Proper chewing technique is crucial when using the nicotine gum, using the “chew and park” method (see Table 91-4). The chew and park steps should be repeated until most of the nicotine is extracted; this generally occurs after 30 minutes and becomes obvious when chewing no longer elicits the characteristic taste or tingling sensation.

Patients should be warned that the absorption and, therefore, the effectiveness of nicotine gum might be reduced by acidic beverages (eg, coffee, juices, wine, and soft drinks), which transiently reduce the salivary pH.[42] To prevent this interaction, patients should be advised not to eat or drink (except water) for 15 minutes before or while using the nicotine gum.

ADVERSE REACTIONS

Most of the common side effects can be minimized or prevented using proper chewing technique.[4,20] Patients should be warned that chewing the gum too rapidly may result in excessive release of nicotine, leading to lightheadedness, nausea, vomiting, irritation of the throat and mouth, hiccups, and indigestion.

PRODUCT SELECTION CONSIDERATIONS

Advantages of nicotine gum include the fact that this formulation may be used to satisfy oral cravings and the 4-mg strength might delay weight gain.[4] For these reasons, the gum may be particularly beneficial for patients who have weight gain concerns or for patients who report boredom as a trigger for smoking. The gum might also be advantageous for patients who desire flexibility in dosing and prefer the ability to self-regulate nicotine levels to manage withdrawal symptoms. Some patients may find that the viscous consistency of the gum makes it difficult to use because it sticks to dental work. Others may find it difficult or socially unacceptable to chew the gum so frequently. Nicotine gum should not be used by patients with temporomandibular joint (TMJ) conditions or if it may interfere with dental work.

Nicotine Lozenge

The nicotine polacrilex lozenge is a resin complex of nicotine and polacrilin in a sugar-free, flavored lozenge. The product is available in 2- and 4-mg strengths, which are meant to be consumed like hard candy or other medicinal lozenges (eg, sucked and moved from side to side in the mouth until fully dissolved). A mini-lozenge is also available. Because the nicotine lozenge dissolves completely, it delivers ~25% more nicotine than does an equivalent dose of nicotine gum.[31] Similar to the nicotine gum, the lozenge also contains buffering agents (sodium carbonate and potassium bicarbonate) to increase salivary pH, thereby enhancing buccal absorption of the nicotine. Peak nicotine concentrations of nicotine with the lozenge are achieved after 30 to 60 minutes of use and then slowly decline thereafter (see Fig. 91-2). The nicotine lozenge increases 6-month abstinence rates by about 50% compared with placebo.[31]

DOSING

Table 91-4 outlines the manufacturers' recommended dosing schedule for the nicotine lozenge. Similar to the nicotine gum, the

lozenge is dosed based on the TTFC. Patients are more likely to succeed if they use the lozenge on a fixed schedule rather than as needed. Patients can use additional lozenges (up to 5 lozenges in 6 hours or a maximum of 20 lozenges per day) if cravings occur between scheduled doses.

PATIENT EDUCATION

Similar to the gum, the nicotine lozenge is a specially formulated nicotine delivery system that must be used properly for optimal results. The lozenge should be allowed to dissolve slowly in the mouth; when nicotine is released, a warm, tingling sensation may be experienced. The patient should occasionally rotate the lozenge to different areas of the mouth to reduce the potential for mucosal irritation. When used correctly, the lozenge should completely dissolve within 30 minutes. Patients should be counseled not to chew or swallow the lozenge because this increases the incidence of gastrointestinal-related side effects.

As with the gum, patients should be cautioned that the effectiveness of the nicotine lozenge may be reduced by acidic beverages such as coffee, juices, wine, or soft drinks.[20] Patients should be advised not to eat or drink (except water) for 15 minutes before or while using the nicotine lozenge.

ADVERSE REACTIONS

In general, the nicotine lozenge is well tolerated. The most common side effects include nausea, hiccups, cough, dyspepsia, headache, and flatulence. Patients who use more than one lozenge at a time, continuously use one lozenge after another, or chew or swallow the lozenge are more likely to experience dyspepsia or hiccups.

PRODUCT SELECTION CONSIDERATIONS

The nicotine lozenge is similar to the nicotine gum formulation in that it may be used to satisfy oral cravings, the 4-mg strength might delay weight gain, and patients can self-titrate therapy to acutely manage withdrawal symptoms.[4] Because the lozenge does not require

chewing, many patients find this to be a more discreet nicotine delivery system. The disadvantages of the lozenge are the fact that it requires frequent dosing, and the gastrointestinal side effects (nausea, hiccups, and heartburn) may be bothersome.

T.B. has expressed interest in either the nicotine gum or lozenge formulation for her quit attempt. Both agents are effective, and the choice of therapy is dependent on the patient's preferences, including the ability to comply with the regimen, previous experience with cessation medications, and other concerns (eg, adverse effects, weight gain, and cost of medications). T.B. would be a candidate for either agent provided she is able to comply with the frequent dosing schedule (one lozenge or piece of gum every 1–2 hours while awake). T.B. smokes her first cigarette of the day immediately after waking in the morning, and she smokes ~30 cigarettes per day; this smoking pattern suggests a higher degree of nicotine dependence, and therefore T.B. would benefit from a higher dose of NRT. T.B. should initiate treatment with the 4-mg strength of either the nicotine lozenge or nicotine gum dosed every 1 to 2 hours while she is awake and tapered according to the schedule outlined in Table 91-4.

Postcessation Weight Gain

Case 91-1, Question 4: T.B. is very concerned about gaining weight after she quits smoking. Is weight gain common after quitting, and if so, how can this be prevented?

Most tobacco users gain weight after quitting, and clinicians should neither deny the likelihood of weight gain nor minimize its significance.[4,43] For nearly all patients, the health risks associated with postcessation weight gain are negligible compared with the risks of continued smoking.

After 12 months of abstinence from smoking, a mean increase of 4 to 5 kg in body weight is most common, with most weight gain occurring within three months of quitting. There is a high level of variability in observed weight change.[43]

Although weight gain with tobacco cessation is well established, the mechanism is unclear. Nicotine is an appetite suppressant and may increase metabolism. The increased appetite that occurs with tobacco cessation coupled with decreased metabolism may contribute to weight gain. Furthermore, evidence suggests that nicotine increases the basal metabolic rate, and removal of this effect results in a decline in energy expenditure at a time when appetite is increased.[43] Increased postcessation caloric intake might also result from an improved sense of taste or a change in the hand-to-mouth ritual through the substitution of tobacco with food.

In general, a patient is less likely to be successful if he or she attempts to change multiple behaviors at once. For most patients, strict dieting to prevent weight gain, especially during the early stages of quitting, is generally not recommended and is ineffective.[4,44] T.B. should be counseled that the average weight gain of <10 pounds (4.54 kg) is less detrimental to her overall health than is continuing to smoke. Although exercise interventions have not been shown to reduce weight gain among quitters,[44] it should not be ruled out as a recommendation for T.B. because she expresses significant concern about weight gain, and this might be a barrier to her quitting. Modest increases in activity can help with weight gain, and exercise can serve as a behavioral substitution for tobacco use while enhancing overall well-being. Furthermore, T.B. should be advised to plan her meals in advance to avoid binge eating, increase her water intake to create a feeling of fullness, chew sugarless gum, and limit alcohol consumption. T.B. may consider pharmacotherapy options that have been shown to delay weight gain including NRT, varenicline, or sustained-release bupropion.[4,44] It is important to note, however, that none of the medications have been shown to prevent weight gain in the long term.[4,44]

Relapse to Smoking

Case 91-1, Question 5: During a follow-up contact, the clinician learns that T.B. smoked half a pack of cigarettes at a party over the weekend, and has

relapsed to her previous smoking levels after not having smoked for more than a month. How should the clinician respond?

The clinician should thank T.B. for being honest about her smoking, and ask whether she is comfortable discussing the circumstances during which the smoking occurred. At the time of her smoking, where was she, who was she with, how did she get access to cigarettes, and how was she feeling at the time? What, specifically, were the triggers for her relapse (eg, alcohol, depression, or friends who were smoking around her)? It is important that the clinician help the patient to use this information as part of the learning process, but it also is important to focus on the "positive," such as T.B.'s ability to have remained tobacco free for >1 month. Four weeks after quitting, most physical effects of nicotine withdrawal have completely resolved, and, thus, the relapse trigger for T.B. likely was psychological or situational, and could be abated through the application of effective coping techniques. After an informative discussion about the situation in which the smoking occurred, it is important that the clinician works with the patient in identifying strategies for avoiding relapse in the future (Table 91-3).

Smoking and Cardiovascular Disease

CASE 91-2

QUESTION 1: P.J. is a 62-year-old male admitted for a coronary artery bypass graft (CABG) surgery. His medical history is significant for angina, hypertension, dyslipidemia, peripheral vascular disease (PVD), and allergic rhinitis. He underwent a bilateral carotid endarterectomy procedure 2 years ago and had iliac artery angioplasty with stent placement 5 years ago for PVD. P.J.'s social history is significant for tobacco use (two PPD) and alcohol (three to four drinks per day). He is ~20 pounds (9.07 kg) overweight. His preoperative laboratory results are significant for a total cholesterol of 270 mg/dL (desirable, >200), low-density lipoprotein cholesterol (LDL-C) of 163 mg/dL (optimal, >70), high-density lipoprotein cholesterol (HDL-C) of 35 mg/dL (low, >40), and triglycerides of 350 mg/dL (normal, >150). His medications before admission include atenolol 50 mg daily, aspirin 81 mg daily, isosorbide dinitrate 20 mg tid, atorvastatin 20

mg daily, fluticasone nasal spray (50 µg per spray) one spray per nostril daily, and nitroglycerin 0.4 mg sublingually as needed.

Which of P.J.'s chronic medical conditions may be caused or exacerbated by his tobacco use?

A wealth of evidence suggests that cigarette smoking is a major cause of cardiovascular disease and is responsible for ~128,000 premature cardiovascular-related deaths each year.[3]

There are numerous plausible pathophysiologic mechanisms by which tobacco smoking contributes to the development of cardiovascular disease.[3,4] Oxidant gases and other compounds in tobacco smoke are believed to induce a hypercoagulable state characterized by increased platelet aggregation and thrombosis, which substantially increases the risk of MI and sudden death.[45,46] The carbon monoxide in smoke reduces the amount of oxygen available to tissues and organs, including myocardial tissue, and may reduce the ventricular fibrillation threshold.[45] Smoking may accelerate atherosclerosis through effects on serum lipids; smokers tend to have higher levels of total cholesterol, LDL-C, and triglycerides and lower HDL-C than do nonsmokers.[2] Smoking increases the levels of inflammatory mediators (C-reactive protein, leukocytes, and fibrinogen), which might contribute to the development and progression of atherosclerosis.[47] Finally, smoking stimulates the release of neurotransmitters (eg, epinephrine and norepinephrine) that increases myocardial workload and induces coronary vasoconstriction, leading to ischemia, arrhythmias, and sudden death.[2,45]

P.J.'s hospital admission for a CABG procedure for CHD and angina, and previous procedures for PVD (angioplasty with stent placement) and cerebrovascular disease (bilateral carotid endarterectomy) are all conditions associated with chronic tobacco use. His elevated total cholesterol, LDL-C, and triglycerides, and reduced HDL-C levels are consistent with smoking-induced dyslipidemia. Cigarette smoking, in combination with P.J.'s other established cardiovascular risk factors (hypertension and dyslipidemia), has synergistically increased his risk of serious

cardiovascular disease. Fortunately, the effects of smoking on lipids, coagulation, myocardial workload, and coronary blood flow appear to be reversible, and P.J.'s risk of developing further cardiovascular-related complications will markedly decrease if he is able to quit smoking.[2] Smoking cessation is associated with a 36% reduction in the risk of death among patients with established CHD. The reduced mortality risk associated with quitting smoking is comparable to that observed with other established secondary preventative approaches such as therapies for hyperlipidemia and hypertension.[48] The clinician should approach this hospitalization as an opportunity to assist P.J. with quitting smoking. Published data suggest that initiation of intensive cessation counseling interventions for hospitalized patients is effective in achieving long-term abstinence.[49]

Noncigarette Forms of Tobacco

Case 91-2, Question 2: The cardiothoracic surgeon has strongly advised P.J. to quit smoking. Will cutting down to one to two cigars per day be an acceptable alternative to his current cigarette use?

The adverse health effects of cigar smoking include oral cancer, esophageal cancer, pancreatic cancer, laryngeal cancer, lung cancer, CHD, and aortic aneurysm.[50] In addition, daily cigar smokers have increased all-cause mortality risk, and an increased risk of dying from chronic obstructive pulmonary disease (COPD).[51] Cigar smokers who report that they do not inhale still have increased risk of oral, laryngeal, and esophageal cancers.[50] Although the risk of daily cigar smoking is lower than that with cigarettes, it is significantly higher than that of nonsmokers, so the goal should be complete cessation of all tobacco products. Cigar weight and nicotine content vary widely from brand to brand and from cigar to cigar. Cigars range in weight from about 1 to 22 g, whereas a typical cigarette weighs <1 g. The nicotine content of 10 commercially available cigars studied in 1996 ranged from 10 to 444 mg. In comparison, U.S. cigarettes have a relatively narrow total nicotine content range (mean, 13.5 ± 0.1 mg)

per cigarette.[52] It is possible for one large cigar to contain as much tobacco as an entire pack of cigarettes and to deliver enough nicotine to establish and maintain dependence.[20,53]

The amount of nicotine delivered by one to two cigars per day is capable of sustaining his dependence on nicotine. Furthermore, former cigarette smokers are more likely to inhale deeply, which further increases the risk of cancer and cardiovascular and pulmonary disease. The clinician should strongly advise P.J. to quit smoking cigarettes and that switching to cigars is not a safe alternative.

Case 91-2, Question 3: P.J. is willing to quit completely, but he is worried because he has tried to quit smoking "hundreds of times" and has never been able to quit for longer than 1 week. He expresses a desire for a medication to assist him during this quit attempt. He has tried the nicotine gum and transdermal patch during three previous quit attempts. He did not like the gum because it made his jaw sore. He had temporary success with the nicotine patch, but found it to be less flexible than was the gum. For example, when he needed extra nicotine during stressful situations, he could not apply a second patch. What treatment alternatives are reasonable for P.J.?

P.J. has inadequately responded to treatment with the transdermal patch, and experienced intolerable jaw soreness with the nicotine gum. Newer formulations of the nicotine gum are less viscous, and therefore easier to chew, than were earlier formulations of the gum; however, other options are available. First-line treatment options that he has not tried include the nicotine lozenge (see Case 91-1, Question 3), nicotine nasal spray, nicotine inhaler, sustained-release bupropion, varenicline, or an effective combination of first-line agents (see Case 91-3, Question 1).

Nicotine Nasal Spray

The nicotine nasal spray is an aqueous solution of nicotine available in a metered spray pump for administration to the nasal mucosa. Nicotine in the nasal spray is more rapidly absorbed than are other NRT formulations (see Fig. 91-2), with peak venous nicotine

concentrations achieved within 11 to 18 minutes of administration.[54] Use of the nicotine nasal spray more than doubles long-term abstinence rates when compared with placebo.[31]

DOSING

Table 91-4 outlines the manufacturers' recommended dosing schedule for the nicotine nasal spray. A dose of nicotine (1 mg) is administered as two sprays, one (0.5-mg spray) in *each* nostril. For best results, patients should be encouraged to use at least eight doses per day during the initial 6 to 8 weeks of therapy because less frequent administration may be less effective. The initial regimen may be increased, as needed, to a maximum recommended dosage of five doses per hour or 40 mg daily. After 6 to 8 weeks, the dose should be gradually decreased during an additional 4 to 6 weeks.

PATIENT EDUCATION

Before using the nasal spray for the first time, the nicotine nasal spray pump must be primed by actuating the device into a tissue until a fine spray is visible (about six to eight times). When administering a dose, the patient should tilt the head back slightly and insert the tip of the bottle into the nostril as far as is comfortable. After actuation of the pump, the patient should not sniff, swallow, or inhale through the nose because this increases the irritant effects of the spray. The spray increases the likelihood of tearing, coughing, and sneezing, so patients should wait 5 minutes before driving or operating heavy machinery.

ADVERSE REACTIONS

Most patients report moderate-to-severe nasal irritation during the first 2 days of therapy, but most become tolerant to the irritant effects during the first week. Nasal congestion and transient changes in taste and smell have also been reported.[4] Despite the high incidence of local adverse effects (see Table 91-4), most patients become tolerant to the irritant effects of the spray.

PRODUCT SELECTION CONSIDERATIONS

The primary advantage in using the nicotine nasal spray is the ability to rapidly titrate therapy to manage withdrawal symptoms. However, because nicotine from the spray more rapidly penetrates the central nervous system, developing dependence may be more likely. The nicotine nasal spray has a dependence potential intermediate between tobacco products and other NRT products. Individuals with chronic nasal disorders (eg, rhinitis, polyps, and sinusitis) or severe reactive airway disease should not use the nicotine nasal spray because of its irritant effects and potential to cause an asthma exacerbation.[4,20] Disadvantages of nicotine nasal spray include higher cost than that of the patch, gum, or lozenge, and being available only with a prescription.

Nicotine Inhaler

The nicotine oral inhaler consists of a plastic mouthpiece and a disposable cartridge with a porous plug containing 10 mg of nicotine and 1 mg of menthol. The typical pack-a-day smoker repeats the hand-to-mouth motion up to 200 times daily, so it is not surprising that many smokers find they miss the physical manipulation of the cigarette and associated behaviors that accompany smoking. The nicotine inhaler was designed to provide nicotine replacement in a manner similar to smoking while addressing the sensory and ritualistic factors that are important to many patients who smoke.

As a patient inhales through the mouthpiece, nicotine vapor releases from the cartridge and distributes throughout the oral cavity. When the inhaler is used correctly, the cartridge releases ~4 mg of nicotine vapor, and 2 mg is absorbed across the buccal mucosa.[55] Peak plasma nicotine concentrations are achieved after ~30 minutes of use and then slowly decline[11] (see Fig. 91-2). Use of the nicotine inhaler approximately doubles long-term abstinence rates when compared with placebo (see Table 91-4).[31]

DOSING

Table 91-4 outlines the manufacturers' recommended dosing schedule for the nicotine inhaler. During the initial 3 to 6 weeks of treatment, the patient should use 1 cartridge every 1 to 2 hours while awake. This should be increased, as needed, to a maximum of 16 cartridges per day. The manufacturer recommends that each cartridge be depleted of nicotine by frequent continuous puffing for 20 minutes. The recommended duration of treatment is 3 months, after which patients may be weaned from the inhaler by gradual reduction of the daily dose during the following 6 to 12 weeks.

PATIENT EDUCATION

To minimize the likelihood of throat irritation, patients should be instructed to inhale shallowly (as if puffing a pipe). The inhaler should be used with continuous shallow puffs for 20 minutes.[20] The release of nicotine from the inhaler is temperature dependent and significantly reduced at temperatures <40 °F (4.44 °C).[4,20] Under cold conditions, patients should store the inhaler and cartridges in a warm place (eg, inside pocket).[4] Conversely, more nicotine is released under warmer conditions, although nicotine plasma concentrations achieved using the inhaler in hot climates at maximal doses will not exceed levels normally achieved with smoking.[33]

As with all forms of NRT that are absorbed across the buccal mucosa, the effectiveness of the nicotine inhaler is reduced by acidic foods and beverages, such as coffee, juices, wine, or soft drinks. Therefore, patients should be instructed not to eat or drink anything (except water) for 15 minutes before or while using the inhaler.[20]

ADVERSE REACTIONS

The most common side effects associated with the nicotine inhaler include mouth or throat irritation (40%) and cough (32%) that usually decrease with continued use.[4] Less common side effects are rhinitis, dyspepsia, hiccups, and headache. Adverse reactions necessitating discontinuation of treatment occurred in <5% of patients using the inhaler.

PRODUCT SELECTION CONSIDERATIONS

Patients who express a preference for therapy that can be easily titrated to manage withdrawal symptoms or one that mimics the hand-to-mouth ritual of smoking may find the nicotine inhaler to be an appealing option. Patients with underlying bronchospastic conditions should use the nicotine inhaler with caution because the nicotine vapor can be irritating and might induce bronchospasm. Nicotine inhalers require a prescription and are more expensive than are nonprescription NRT products.

Sustained-Release Bupropion

The antidepressant, bupropion, may be beneficial for patients who are attempting tobacco cessation (see Table 91-4). In a systematic review, sustained-release bupropion was shown to increase long-term abstinence rates relative to placebo (RR 1.640) and demonstrated similar efficacy to NRT (RR 0.99).[36]

DOSING

Because ~1 week of treatment is necessary to achieve steady-state blood levels, sustained-release bupropion should be initiated while the patient is still smoking (Table 91-4). Patients should set a target quit date that falls within the first 2 weeks of treatment, generally in the second week. The starting dose of sustained-release bupropion is one 150-mg tablet each morning for the first 3 days. If the initial dose is tolerated, the dosage should be increased to the recommended maximal dosage of 300 mg daily (150 mg bid). Therapy should be continued for up to 12 weeks after the quit date.[4,20]

PATIENT EDUCATION

Patients experiencing insomnia should avoid taking the second dose close to bedtime. Patients should be informed that bupropion might cause dizziness or drowsiness and should exercise caution when driving or operating machinery. Patients should avoid alcohol, or

drink only in moderation while taking bupropion because alcohol use can increase the risk of seizures. Abrupt cessation of alcohol use while taking bupropion might increase the risk of seizure.[4,20,37]

ADVERSE REACTIONS

The most common adverse effects associated with bupropion therapy include insomnia (35%–40%) and dry mouth (10%).[56] These usually lessen with continued use. Taking the second daily dose in the early evening, but no sooner than 8 hours after the first dose, might reduce insomnia. Less common side effects include headache, nausea, tremors, and rash. Seizures are a dose- related toxicity associated with bupropion therapy. For this reason, bupropion is contraindicated in patients with underlying seizure disorders and in those undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic medications. Bupropion also is contraindicated in patients with a current or prior history of anorexia or bulimia nervosa and those who are taking monoamine oxidase inhibitors. Bupropion should be used with extreme caution in patients with a history of seizures or cranial trauma, in individuals taking medications that may lower the seizure threshold, and in patients with underlying severe hepatic cirrhosis. The manufacturer recommends that patients space the doses at least 8 hours apart and limit the total daily dose to no more than 300 mg. Bupropion is associated with significant neuropsychiatric adverse effects, including changes in mood, hallucinations, anxiety, and suicidal ideation.[37]

PRODUCT SELECTION CONSIDERATIONS

Sustained-release bupropion is an option for patients who prefer to take oral medications. (An alternative, varenicline, is described subsequently). Because sustained-release bupropion tablets require twice-daily administration, this agent may be preferable for patients with adherence concerns (eg, those unable to consistently use short-acting NRT formulations that require multiple daily doses). Sustained-release bupropion might be beneficial for use in patients

with coexisting depression or in individuals with a history of depressive symptoms during a previous quit attempt. Finally, sustained-release bupropion has been found to reduce postcessation weight gain during treatment,[4,44] and this might be of short-term benefit in patients with concerns about weight gain after quitting. Disadvantages of sustained-release bupropion include a high prevalence of insomnia and several contraindications and precautions mentioned earlier.

Varenicline

Varenicline significantly increases long-term abstinence rates relative to placebo, NRT, and sustained-release bupropion.[39,57,58] Varenicline is the most efficacious pharmacotherapy for tobacco cessation.[3,58] The pooled RR for long-term abstinence (≥6 months) for varenicline compared with placebo was 2.24 (95% confidence interval [CI], 2.06–2.43). The pooled RR for varenicline versus sustained-release bupropion at the 6-month follow-up was 1.39 (95% CI, 1.25–1.54). At 24 weeks, the pooled RR for varenicline compared to NRT was 1.25 (95% CI, 1.14–1.37).[39] Longer durations of varenicline for up to 12 months have been shown to be safe and effective in clinical trials.[39,59]

PHARMACOKINETICS

Varenicline absorption is virtually complete after oral administration, and oral bioavailability is unaffected by food. Once absorbed, varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination is primarily through glomerular filtration, along with active tubular secretion.[59] The half-life is ~24 hours, and following administration of multiple oral doses, steady-state conditions are reached within 4 days.[40,59]

DOSING

Treatment with varenicline (see Table 91-4) should be initiated 1 week before the patient stops smoking. This dosing regimen allows

for gradual titration of the dose to minimize treatment-related nausea and insomnia. The recommended dosage titration for varenicline is as follows: 0.5 mg daily on days 1 to 3, 0.5 mg twice daily on days 4 to 7, and 1 mg twice daily on weeks 2 to 12. For patients who have successfully quit smoking at the end of 12 weeks, an additional course of 12 weeks may be considered to increase the likelihood of long-term abstinence.[40,60] In an alternative approach to smoking reduction, the patient should set a quit date 8 to 35 days after starting varenicline, then decrease their smoking by about 50% over the first 4 weeks, an additional 50% by the second 4 weeks, with the goal of being fully abstinent after 12 weeks. They should then continue varenicline for 12 additional weeks.[40,59]

Varenicline should be used with caution in patients with impaired renal function. For patients with severe renal dysfunction (estimated creatinine clearance <30 mL/minute), the recommended maximal dose of varenicline is 0.5 mg twice daily. In patients with end-stage renal disease undergoing hemodialysis, a maximal dose of 0.5 mg daily is recommended.[40,59] Varenicline has been shown to be effective at lower dosages with a lower incidence of adverse effects.[39]

PATIENT EDUCATION

Varenicline should be taken after eating and with 8 ounces of water. Nausea and insomnia are side effects that are usually temporary.[40] Patients should be advised to discontinue varenicline and contact their health care provider immediately if they experience agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them (see adverse reactions subsequently).[40]

ADVERSE REACTIONS

Varenicline is generally well tolerated. Common side effects include nausea (30%), sleep disturbance (insomnia 18%; abnormal dreams 13%), constipation (8%), flatulence (6%), and vomiting (5%). Nausea is dose dependent and generally described as mild or moderate and often transient; however, for some patients, it persists for several

months. Initial dose titration was beneficial in reducing the occurrence of nausea. Approximately 3% of subjects receiving varenicline 1 mg bid discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.[59]

A large, randomized, controlled trial that included a cohort of smokers with current or past psychiatric disorders evaluated the neuropsychiatric safety of varenicline, bupropion, nicotine patch, and placebo. No difference in neuropsychiatric adverse events was reported between groups.[57] However, the FDA recommends that clinicians and patients monitor for changes in mood and behavior during treatment with varenicline.[40]

The prescribing information for varenicline includes a warning for a possible increased risk of cardiovascular events (in patients with underlying cardiovascular disease).[40] However, systematic review, meta- analysis, and a randomized clinical trial concluded that there is no significant increase in the risk of serious cardiovascular events with varenicline in tobacco cessation, including patients with a history of cardiovascular disease.[61–63] Seizures have been reported in patients treated with varenicline, most often within the first month of therapy. These events occurred in individuals who had no seizure history, as well as in those with a remote history or well-controlled seizure disorder. Varenicline should be used cautiously in patients with a history of seizures, or with any other factors that lower the seizure threshold.[40]

PRODUCT SELECTION CONSIDERATIONS

Varenicline is a first-line agent for the treatment of tobacco use and dependence.[4,58] It offers a convenient oral dosing regimen and a mechanism of action that might be particularly appealing for patients who have failed quit attempts with other first-line agents (eg, NRT or sustained-release bupropion). It has the highest efficacy of any of the tobacco-cessation pharmacotherapies. P.J. has tried the nicotine gum and transdermal patch during previous quit attempts. Because he was intolerant to the nicotine gum (sore jaw), this form of NRT is

not appropriate. P.J.'s experience with the transdermal patch suggests he may benefit from a short-acting NRT formulation that enables titration of doses as needed to alleviate symptoms of withdrawal and situational cravings. Other first-line therapies include the nicotine nasal spray, inhaler, and lozenge; sustained-release bupropion; or varenicline. P.J. should not use the nicotine nasal spray because he has allergic rhinitis and may be more susceptible to the irritant effects of the spray. Furthermore, the safety and efficacy of the nasal spray in patients with chronic nasal disorders have not been adequately studied. Reasonable choices for P.J. therefore include sustained-release bupropion, nicotine lozenge, nicotine inhaler, or varenicline. Any of these options are reasonable, and the choice of therapy should be dictated by P.J.'s individual preference. If varenicline is chosen, given P.J. has underlying cardiovascular disease, he should be instructed to notify a health care provider for new or worsening cardiovascular symptoms and to seek immediate medical attention if he experiences signs and symptoms of MI. Finally, it is reasonable to consider combination therapy (see Case 91-3, Question 1).

Safety of Nicotine Replacement Therapy Among Patients with Cardiovascular Disease

Case 91-2, Question 4: P.J. would like to try the nicotine inhaler. Is NRT safe for use in patients with cardiovascular disease?

Nicotine activates the sympathetic nervous system, leading to an increase in heart rate, blood pressure, and myocardial contractility. Nicotine also may cause coronary artery vasoconstriction. These known hemodynamic effects of nicotine have led to doubts about the safety of using NRT in patients with established cardiovascular disease, particularly those with serious arrhythmias, unstable angina, or recent MI.

Soon after the nicotine patch was approved, anecdotal case reports in the lay press linked NRT (patch and gum) with adverse cardiovascular events (eg, arrhythmias, MI, and stroke). Since then, several randomized, controlled trials evaluated the safety of NRT in patients with cardiovascular disease.[64,65] The results of these trials suggest no significant increase in the incidence of cardiovascular events or mortality among patients receiving the nicotine patch when compared with placebo. However, because these trials specifically excluded patients with unstable angina, serious arrhythmias, and recent MI, the manufacturers of NRT products recommend that these agents be used with caution among patients in the immediate (within 2 weeks) post-MI period, those with serious arrhythmias, and those with unstable angina.[4,20]

NRT use in patients with cardiovascular disease has been the subject of numerous reviews, and it is widely believed by experts in the field that the risks of NRT in this patient population are small in relation to the risks of continued tobacco use.[4,61,63,65] Although the use of NRT may pose some theoretic risk in a patient such as P.J., cigarette smoking is far more hazardous to his health. Cigarettes, unlike NRT, deliver numerous toxins that induce a hypercoagulable state, reduce the oxygen-carrying capacity of hemoglobin, and adversely affect serum lipids. The amount of nicotine that P.J. would receive using the recommended dose of any NRT product will not exceed the amount he previously obtained from his two PPD smoking habit. The clinician should strongly encourage pharmacotherapy during P.J.'s current quit attempt. P.J. is 10 pounds (4.54 kg) overweight; the additional risk imposed by a modest weight gain after smoking cessation likely will not be of clinical significance compared with that of continued smoking.

Combination Therapy for Tobacco Dependence

CASE 91-3

QUESTION 1: J.B. is a 60-year-old male referred to the pulmonary clinic for further evaluation and management of his COPD. He reports decreased exercise tolerance and has noted increasing shortness of breath (SOB) with minimal exertion (eg, while golfing or climbing stairs). He currently uses an albuterol inhaler (90 µg per puff), two puffs every 4 hours regularly for SOB. His medical history is otherwise unremarkable except for osteoarthritis controlled with acetaminophen 1 g tid. He has smoked ~1.5 to 2 PPD for >40 years. J.B. indicates he has made several quit attempts during the past year. On the first attempt (quitting "cold turkey"), J.B. relapsed within 2 days. J.B. successfully quit for nearly 2 weeks on his second attempt (using the 4-mg nicotine lozenge), but he found it difficult to adhere to the frequent dosing schedule and relapsed shortly after discontinuing the lozenge. His most recent quit attempt was 6 months ago using varenicline. After 1 month of abstinence, J.B. self-terminated varenicline (I thought I didn't need it anymore.) and relapsed within 1 week. On further questioning, J.B. states that he did not enroll in a behavioral counseling program or seek additional assistance (other than pharmacotherapy) during any of his quit attempts. He expresses an interest in smoking cessation but is discouraged by his prior lack of success. On physical examination, coarse breath sounds that clear after coughing are noted. A chest radiograph obtained in the office shows no infiltrates. J.B. is concerned about his worsening pulmonary function and is committed to making another effort to quit.

What treatment options are appropriate for J.B.?

Tobacco smoking is the single most important risk factor for the development of COPD, and almost all patients diagnosed with COPD are current or former smokers.[2,66] Given his escalating pulmonary symptoms, it is imperative that he stop smoking as soon as possible. J.B. should be advised that medications for COPD offer only limited symptomatic relief, and the most important component of his treatment is smoking cessation.[66,67] The clinician should commend J.B. for his interest in quitting and help him devise a patient-specific treatment plan.

Plasma levels of nicotine achieved with standard doses of NRT are generally much lower than are those attained with regular smoking.[54,68] As such, conventionally dosed NRT may deliver subtherapeutic nicotine levels for some individuals, and, in particular, for moderate-to-heavy smokers.

Combination NRT regimens, which typically consist of a long-acting agent (nicotine patch) in combination with a short-acting

formulation (ie, gum, lozenge, inhaler, or nasal spray), are options for initial therapy. The long-acting formulation, which delivers nicotine at a relatively constant level, is used to prevent the onset of severe withdrawal symptoms, and the short-acting formulation, which delivers nicotine at a more rapid rate, is used as needed to control withdrawal symptoms that may occur during potential relapse situations (eg, after meals, during times of stress, or when around other smokers).

Controlled trials suggest that the nicotine patch in combination with short-acting NRT formulations (ie, gum, lozenge, nasal spray, or inhaler) significantly increase quit rates relative to placebo.[31] The evidence regarding combination therapy with sustained-release bupropion and the nicotine patch is conflicting, although it is recommended in the guidelines.[36,69] Aggressive combination regimens including triple-agent NRT (eg, patch, inhaler, and nasal spray) with or without sustained-release bupropion, triple-combination therapy with patch, inhaler, and sustained-release bupropion[70] or varenicline, patch, and lozenge[71] may be a safe and effective treatment approach. Some data suggest that adding varenicline alone[72] or sustained-release bupropion and varenicline to nicotine patch[73,74] therapy may improve cessation rates; however, addition of sustained-release bupropion to varenicline had little effect on long-term abstinence and increased rates of depression and anxiety.[36,74]

Clinicians should be aware that although the combination of the nicotine patch and sustained-release bupropion has been approved by the FDA, the concurrent use of multiple NRT products is not FDA approved for tobacco cessation. Furthermore, the optimal agents, dosages, and durations of therapy for NRT combination therapy are currently unknown.

Given the severity of J.B.’s condition and his willingness to quit now, the clinician should initiate treatment as soon as possible. His treatment should consist of pharmacotherapy in conjunction with behavioral counseling and appropriate follow-up.

PHARMACOTHERAPY

The clinician should work with J.B. to select the most appropriate pharmacotherapy. As noted previously, appropriate options would include the various NRT formulations, sustained-release bupropion, varenicline, or an effective combination of first-line agents. For patients reporting a positive experience with a given medication, retreatment with the same agent or a combination of agents might be appropriate, with consideration given to increasing the dose, frequency, or duration of therapy. For patients reporting a negative experience with pharmacotherapy (eg, poor adherence, side effects, palatability issues, and cost), an alternative agent should be considered. Given J.B.'s previous adherence issues with the nicotine lozenge as monotherapy, it might be preferable to use a long-acting cessation medication such as the nicotine patch, sustained-release bupropion, or varenicline. Combination therapy might also be appropriate.

BEHAVIORAL COUNSELING

Although medications are effective alone in helping patients quit smoking, the combination with behavioral counseling maximizes patients' chances for a long-term, successful quit attempt. J.B.'s previous 1-month-long quit attempt highlights the success of varenicline in this patient; however, J.B.'s relapse likely is attributable to a shortened course of therapy and the absence of a behavioral change program. J.B. should be advised that the medications are designed to make patients more comfortable while quitting and that behavioral counseling is needed to address the "habit" of smoking by helping him cope with difficult situations and triggers for relapse. J.B. should be advised to pursue behavioral therapy options in addition to pharmacotherapy. J.B. should be reminded that adherence to the medication regimen—daily adherence, as well as duration of therapy—will increase his chances of quitting for good. Clinician-delivered counseling might also include a personalized message to further enhance his motivation to quit. For example, the clinician could perform pulmonary function testing and translate J.B.'s spirometry

results into an effective “lung age” (eg, the age of the average healthy individual with similar spirometry values). This educational approach has been found to significantly increase long-term (12-month) quit rates in a recent controlled trial.[75]

Drug Interactions With Smoking

CASE 91-4

QUESTION 1: M.K. is a new patient requesting Tri-Sprintec® (norgestimate/ethinyl estradiol). The new patient history form completed by M.K. reveals that she is 32 years old, weighs 143.30 pounds (64.86 kg), and is 70 inches (177.80 cm) tall. She takes no prescription medications, but occasionally uses loratadine 10 mg as needed for allergies, and ibuprofen 400 mg as needed for dysmenorrhea. She has no significant medical history. Her father has hypertension and suffered an MI last year. Her mother has type 2 diabetes and dyslipidemia. Her social history is significant for tobacco use (one PPD for 15 years), alcohol (one glass of wine every night), and caffeine (three to four cups of coffee daily).

Are there any potential drug interactions with M.K.’s new prescription?

SMOKING AND COMBINED HORMONAL CONTRACEPTIVES

One of the most important precautions to consider with oral contraceptive use is the potential interaction between tobacco smoke and estrogens in combination hormonal contraceptives (see Chapter 47, Contraception). Estrogens promote coagulation by altering clotting factor levels and increasing platelet aggregation. As described in Case 91-2, Question 1, substances present in tobacco smoke induce a hypercoagulable state, increasing the risk of acute cardiovascular events. Exposure to both factors (smoking and high levels of estrogen) greatly increases the risk of thromboembolic and thrombotic disorders. Considerable epidemiologic evidence indicates that cigarette smoking substantially increases the risk of adverse cardiovascular events, including stroke, MI, and thromboembolism in females who use oral combination hormonal contraceptives.[76,77] This risk is age related, in that the absolute risk of death as a result of cardiovascular disease in oral contraceptive users who smoke is

3.3/100,000 females, ages 15 to 34 years, compared with 29.4/100,000 females, ages 35 to 44 years. Because of the increased risk of adverse cardiovascular events, current guidelines[78] state that combination estrogen–progestin contraceptives should not be used in females who are older than 35 years of age and smoke, and progestin-only or nonhormonal contraceptives are recommended for use in this population. M.K. is 32 years of age, and despite smoking 20 cigarettes per day, oral contraceptive use is not contraindicated at this time. However, the clinician should strongly advise M.K. to quit smoking and assess her readiness to do so. M.K. should be informed that if she continues to smoke while using oral combined hormonal contraceptives, her risk of developing a blood clot, stroke, or heart attack will continue to increase with time.

ALTERNATIVE THERAPIES

Case 91-4, Question 2: Are e-cigarettes or vapes effective for smoking cessation?

Patients or clinicians may ask about the efficacy of ENDSs in tobacco cessation. These devices seem to offer a solution because they mimic smoking behaviors including hand-to-mouth movements, inhalation into airways, and exhalation of smoke-like aerosol. Some consider ENDS as a tool for harm reduction in cigarette smokers because they may reduce exposure to carcinogens and toxins in combustible tobacco cigarettes.[79] Current data is limited, but ENDS may help smokers successfully stop smoking.[79–81] More robust data on the safety and efficacy of ENDS are needed.[79,80] M.K. should be advised that although ENDS may be effective, more data support NRT, varenicline, and bupropion as cessation therapies.

Although many herbal and homeopathic products are available to help people quit smoking, data that support their safety and efficacy are lacking. Furthermore, patients should be cautioned that herbal cigarettes are not safe alternatives because they result in the inhalation of other toxins present in smoke.

CASE 91-4, QUESTION 3: M.K. is not considering quitting smoking in the next 30 days. She cannot discontinue her oral contraceptives because she is sexually active and needs a reliable form of birth control. Are low dose birth control pills or other formulations (eg patch or vaginal ring) safer for smokers?

Combined oral contraceptives available in the United States contain estrogen in doses ranging from 20 to 50 µg of ethinyl estradiol. Higher doses of ethinyl estradiol appear to have greater procoagulant effects.[82]

In 2001, the U.S. Surgeon General stated that lower dose oral contraceptives may be associated with a reduced risk of CHD compared with higher dose formulations. Despite this conclusion, the report cautioned that heavy smokers who use oral contraceptives still have a greatly elevated risk for CHD.[83]

Serum estrogen levels obtained with the vaginal ring are significantly lower than those achieved with either transdermal or oral combined contraceptive formulations, but data have not shown the patch or the ring to be safer options for females who smoke. Current guidelines apply the same precautions to all contraceptives containing estrogen.[83]

M.K.'s prescribed oral contraceptive agent (Tri-Sprintec®) contains 35 µg of ethinyl estradiol in combination with 0.25 mg norgestimate. Although some clinicians recommend the use of low-dose (20 µg) estrogen preparations in smokers, the available evidence suggests that the prescribed regimen poses no additional risk in M.K. The clinician should inform M.K. that there are currently no studies demonstrating a reduced risk of adverse cardiovascular events in smokers using oral contraceptives containing low doses (eg, 20 µg) of estrogen or the newer transdermal and vaginal ring formulations.[83] In the absence of published data, only smoking cessation can be advocated to definitively reduce the risk of stroke, MI, and thrombosis in females who use combined hormonal contraceptives.

BEHAVIORAL COUNSELING

Although M.K. is not considering quitting at this time, it is appropriate for the clinician to apply the 5 R's (see Table 91-2) to promote motivation to quit. This counseling should be *relevant* to M.K.'s situation and should highlight the *risks* of continued tobacco use, such as her elevated risk for thromboembolic and thrombotic disorders (associated with continued use of oral contraceptives). M.K. should be asked to think about the *rewards* of quitting and any potential *roadblocks* to quitting. At subsequent encounters, the clinician should sensitively assess M.K.'s tobacco use status and motivation to quit and offer assistance with quitting when M.K. is ready. If M.K. decides to quit, it would be important to reassess her caffeine intake because caffeine, which is metabolized via CYP450 1A, levels have been reported to increase by 56% in patients who quit smoking.[18]

Brief Interventions to Promote Tobacco Cessation

CASE 91-5

QUESTION 1: J.C. is a 52-year-old male with a history of asthma requesting a refill of his albuterol inhaler prescription. This is the third request for an albuterol inhaler (200 doses per inhaler) during the past 2 months. Before this period, his last refill was more than a year ago. J.C. reports that he has been using albuterol on most days of the week for coughing and SOB. He has no other medical conditions and takes no other medications. His social history is significant for tobacco use (smokes 1.5 PPD; he recently started smoking again after starting a new job where "everyone smokes"). J.C. previously quit smoking 20 years ago using the "cold turkey" approach (eg, no medications or counseling), and although he was successful, he was miserable for weeks; he expresses reluctance to "go through this again" during a stressful job transition.

The clinician is running behind schedule and does not have the time to provide comprehensive smoking-cessation counseling during this patient encounter.

What brief smoking-cessation interventions can the clinician provide to J.C. to assist him with quitting?

TELEPHONE QUITLINES

Clinicians should become aware of local, community-based resources for tobacco cessation, including telephone quitlines. When time or expertise does not afford provision of comprehensive tobacco- cessation counseling during a patient visit, clinicians are encouraged to apply a truncated 5 A's model, whereby they *ask* about tobacco use, *advise* tobacco users to quit, and *refer* patients who are ready to quit to a telephone quitline. Effective brief interventions can generally be accomplished in <3 minutes. Telephone services provide low-cost interventions that can reach patients who might otherwise have limited access to medical treatment because of geographic location or lack of insurance or financial resources. Data support the efficacy of quitline counseling in promoting abstinence.[26,28] The addition of medication to quitline counseling significantly improves abstinence rates compared with medication alone.[4] In addition, evidence suggests that quitlines are also effective for smokeless tobacco cessation.[84] The telephone number for the toll-free tobacco quitline is 1-800-QUIT NOW.

J.C.'s asthma is not well controlled (eg, increased use of short-acting bronchodilator). The change in J.C.'s asthma control is temporally related to his recent job change and relapse to daily smoking. Exposure to tobacco smoke is a potent trigger for asthma exacerbations and an important cause of poor asthma control. Given that the clinician is unable to provide comprehensive smoking-cessation counseling at this time, a brief intervention is appropriate. The clinician should strongly advise J.C. to quit as a key component of his asthma management plan, and refer him to a telephone quitline or to other resources that are available within the community (eg, local individual or group counseling programs). The clinician should briefly explain that pharmacologic treatment combined with support should increase the likelihood of a successful quit attempt compared to his previous, "cold turkey" experience. The clinician could address J.C.'s previous negative experience with quitting by educating on the benefits of medications in reducing nicotine withdrawal symptoms.

Smoking Among Individuals With Mental Illness

CASE 91-6

QUESTION 1: J.D. is a 42-year-old female presenting to clinic for follow-up of her depression management. Nine months ago, she was started on venlafaxine XR 75 mg daily. At her 3-month follow-up visit, she was stable on venlafaxine XR 150 mg daily, and her depressive symptoms had improved. She also reported that she was sleeping much better. J.D. has no other significant past medical history, and she takes no other medications. Her social history is positive for current tobacco use (one PPD for 25 years) and caffeine use (one to two Diet Coke® a day). She does not drink alcohol. During the appointment, J.D. indicates that she would like to quit smoking because her depression is better, and she knows that her overall health will improve if she quits. She also states that the last time she attempted to quit (several years ago, using the nicotine gum), she felt "down and had difficulty concentrating and couldn't sleep." She is now fearful that her depression will return if she quits.

Is smoking cessation appropriate for J.D. at this time, and what are her treatment options?

Individuals with mental illness have a higher smoking prevalence than does the general population.[85,86] Although smokers are twice as likely to have depression as do nonsmokers, the prevalence of smoking with other psychiatric diagnoses (schizophrenia, bipolar disorder, and post traumatic stress disorder) is five times higher than that for nonsmokers. Psychiatric diagnoses are associated with a higher level of nicotine dependence and lower quit rates. A growing body of evidence suggests that quitting is possible for individuals with concomitant mental illness. For these patients to achieve wellness, smoking-cessation intervention is an essential component of the overall care plan.[86]

Given that J.D. is currently willing to quit, and her depression has been stabilized for >4 months, it is appropriate for the clinician to discuss a quitting plan with J.D. and initiate therapy. The therapeutic approach should include counseling and pharmacotherapy, with ongoing monitoring of progress toward quitting and depressive symptoms.

TREATMENT SELECTION

Pharmacotherapy

Because no contraindications are present, any of the FDA-approved medications for cessation are appropriate. Although early data raised concerns regarding varenicline and changes in mood including suicidal ideation, subsequent data did not find a significant increase in neuropsychiatric adverse events in smokers prescribed varenicline.[39,57] However, the data for varenicline's neuropsychiatric effects in patients with a history of or current psychiatric disorders are less conclusive.[39,57]

Regardless of whether sustained-release bupropion, varenicline, or NRT product(s) are selected, the clinician should monitor J.D. closely to assess the incidence of depressive symptomatology. If sustained- release bupropion or varenicline is selected, J.D. should be advised to stop taking the medication and contact the clinician immediately if she experiences agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if she experiences suicidal thoughts or behavior.

BEHAVIORAL COUNSELING

Because J.D. has indicated that she is ready to quit, the clinician should commend her for making the important decision that will positively impact her overall health. J.D. should be advised that quitting is a process, and it will be important for them to work closely together to address the physiologic as well as psychological aspects of quitting during the upcoming months.

Case 91-6, Question 2: After discussing the various treatment options with the clinician, J.D. decides that she would like to add sustained-release bupropion to her regimen because the nicotine gum by itself did not help her much last time. She also thinks that the combination of venlafaxine with bupropion might help "keep her depression more stable" while she is quitting. She confides in the clinician that her biggest fear is the ability to avoid smoking when she is stressed because of her job. She is a survey researcher and must meet client-induced deadlines. How can J.D. cope with stressful situations?

A variety of coping mechanisms can be applied to alleviate the need to smoke during stressful situations or when exposed to other triggers for smoking (Table 91-3). The clinician should encourage J.D. to think about strategies that would be effective for her in these situations, such as deep breathing or calling a supportive friend. In addition, the clinician should consider suggesting use of a short-acting NRT product (eg, nicotine gum, lozenge, inhaler, or nasal spray) as needed to alleviate situational cravings to smoke. Appropriate dosing of sustained-release bupropion should be reviewed (Table 91-4). A follow-up appointment should be scheduled for ~3 months after the quit date, and the patient should be advised to contact the clinician if she encounters any difficulties before then.

Case 91-6, Question 3: Four weeks later, J.D. calls and reports that she has a dry mouth, is having difficulty sleeping, and feels jittery and anxious. She also is currently using nicotine gum (2 mg), approximately four pieces daily. How should J.D. be managed?

As noted earlier, insomnia and dry mouth are commonly associated with sustained-release bupropion therapy, and usually lessen with continued use.[20] The nicotine gum dose is low and not likely contributing to this condition. To address insomnia, J.D. can be advised to take the second dose of the day earlier, but not <8 hours after the first dose of the day. Alternatively, the clinician could consider reducing the daily dose to 150 mg in the morning and omitting the evening dose. The 150-mg daily dose has been shown to have comparable outcomes with those of the 300-mg dose and is better tolerated.[36] The clinician also should assess J.D.'s caffeine consumption patterns and, if appropriate, suggest that she reduce her caffeine intake by 50%, and not drink caffeinated beverages after 12 noon so that her system is clear of its stimulatory properties before sleep.[19]

Extended-Use Medications for Cessation

Case 91-6, Question 4: J.D. returns to the clinician's office 3 months later and indicates that she is doing well, but had a few "slips" and smoked four times. She has not felt depressed and has been handling her stress at work through deep-breathing exercises. She uses the nicotine gum a few times a week and does not feel ready to discontinue the sustained-release bupropion. How long can she continue the therapy?

Extended-duration medication therapy appears to be safe and effective. Long-term follow-up data indicate that ~15% of long-term quitters continued nicotine gum therapy with no serious side effects.[87] The 2008 Clinical Practice Guideline states that extended use of medications might be beneficial in individuals who report persistent withdrawal symptoms during treatment, those who have relapsed shortly after medication discontinuation, or those who are interested in long-term therapy.[4] A meta-analysis of 12 trials found relapse prevention benefit with extended treatment with varenicline (with behavioral assistance) or NRT (without assistance). The relapse prevention data with bupropion alone or in combination with NRT was inconclusive, and additional study is required.[88]

Given J.D.'s current depression and because she is interested in continuing therapy, it is reasonable for the clinician to recommend the continuation of bupropion and NRT for an additional 12 weeks and reassess progress at that time. If JD does decide to discontinue her bupropion, then it should be with close monitoring by her mental health professional to assess for any rebound depressive symptoms.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Sys Rev*. 2016;(5):CD006103. (39)

Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*. U.S. Department of Health and Human Services. Public Health Service; 2008. (4)

Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018;(5):CD000146. (31)

Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2020;(10):CD010216. (80)

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2020; (4):CD000031. (36)

Key Websites

Rx for Change: Clinician-assisted Tobacco Cessation. The Regents of the University of California; 1999–2022. http://rxforchange.ucsf.edu/ (20)

U.S. Department of Health and Human Services. *Surgeon General's Reports on Smoking and Tobacco Use: Smoking Cessation: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2020. https://www.cdc.gov/tobacco/data_statistics/sgr/2020-smoking-cessation/index.html (81)

COMPLETE REFERENCES CHAPTER 91 TOBACCO USE AND DEPENDENCE

1. U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease—The Biology and Behavioral Basis for Smoking Attributable Disease: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
2. U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Centers for Disease Control and

Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
3. National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2006.
4. Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*. U.S. Department of Health and Human Services, Public Health Service; 2008.
5. Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco product use among adults—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;69:1736–1742.
6. Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. *Clin Pharmacol Ther*. 2008;83(4):531–541.
7. Benowitz NL. Nicotine addiction. *N Engl J Med*. 2010;362(24):2295–2303.
8. Lessov-Schlaggar CN, Pergadia ML, Khroyan TV, Swan GE. Genetics of nicotine dependence and pharmacotherapy. *Biochem Pharmacol*. 2008;75(1):178–195.
9. Centers for Disease Control and Prevention. Vital signs: current cigarette smoking among adults aged ≥18 years with mental illness—United States, 2009–2011. *MMWR Morb Mortal Wkly Rep*. 2013;62(5):81–87.
10. Li MD, Cheng R, Ma JZ, Swan GE. A meta-analysis of estimated genetic and environmental effects on smoking behavior in male and female adult twins. *Addiction.* 2003;98(1):23–31.
11. Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol*. 2009;(192):29–60.
12. Kessler DA. The control and manipulation of nicotine in cigarettes. *Tob Control*. 1994;3:362–369.
13. Stevenson T, Proctor RN. The secret and soul of Marlboro: Phillip Morris and the origins, spread, and denial of nicotine freebasing. *Am J Public Health*. 2008;98(7):1184–1194.
14. Benowitz NL. Neurobiology of nicotine addiction: implications for smoking cessation treatment. *Am J Med*. 2008;121(4 suppl 1):S3–S10.
15. Govind AP, Vezina P, Green WN. Nicotine-induced upregulation of nicotinic receptors: underlying mechanisms and relevance to nicotine addiction. *Biochem Pharmacol*. 2009;78(7):756–765.
16. Benowitz NL. Cigarette smoking and nicotine addiction. *Med Clin North Am*. 1992;76(2):415–437.
17. Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res*. 2007;9(3):315–327.

18. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet*. 1999;36(6):425–438.
19. Kroon LA. Drug interactions with smoking. *Am J Health Syst Pharm*. 2007;64(18):1917–1921.
20. *Rx for Change: Clinician-assisted Tobacco Cessation*. The Regents of the University of California; 1999–2022. http://rxforchange.ucsf.edu/
21. Centers for Disease Control and Prevention, Office on Smoking and Health. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. Office on Smoking and Health, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 1990. DHHS Publication No. (CDC) 90–8416.
22. Bjartveit K, Tverdal A. Health consequences of sustained smoking cessation. *Tob Control*. 2009;18(3):197–205.
23. Schane RE, Ling PM, Glantz SA. Health effects of light and intermittent smoking: a review. *Circulation*. 2010;121(13):1518–1522.
24. Bjartveit K, Tverdal A. Health consequences of smoking 1–4 cigarettes per day. *Tob Control*. 2005;14(5):315–320.
25. Tverdal A, Bjartveit K. Health consequences of reduced daily cigarette consumption. *Tob Control*. 2006;15(6):472–480.
26. Zhu S, Melcer T, Sun J, Rosbrook B, Pierce JP. Smoking cessation with and without assistance: a population-based analysis. *Am J Prev Med*. 2000;18(4):305–311.
27. Stead LF, Carroll AJ, Lancaster T. Group behaviour therapy programmes for smoking cessation. *Cochrane Database Syst Rev*. 2017;3(3):CD001007.
28. Matkin W, Ordóñez-Mena JM, Hartmann-Boyce J. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev*. 2019;(5):CD002850.
29. Taylor GMJ, Dalili MN, Semwal M, Civljak M, Sheikh A, Car J. Internet-based interventions for smoking cessation. *Cochrane Database Syst Rev*. 2017;9(9):CD007078.
30. Villanti AC, West JC, Klemperer EM, et al. Smoking-cessation interventions for U.S. young adults: updated systematic review. *Am J Prev Med*. 2020;59(1):123–136.
31. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev.* 2018;(5):CD000146.
32. Choi JH, Dresler CM, Norton MR, Strahs KR. Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine Tob Res*. 2003;5(5):635–644.
33. Schneider NG, Olmstead RE, Franzon MA, Lunell E. The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet*. 2001;40(9):661–684.
34. Carpenter MJ, Jardin BF, Burris JL, et al. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: a review of the literature. *Drugs*. 2013;73(4):407–426.

35. Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. *J Pharmacol Exp Ther*. 2000;295(1):321–327.
36. Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2020; (4):CD000031.
37. Wellbutrin SR. Package insert. Dr. Reddy's Laboratories Inc.; June 2019.
38. Coe JW, Brooks PR, Vetelino MG. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. *J Med Chem*. 2005;48(10):3474–3477.
39. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev.* 2016;(5):CD006103.
40. Chantix. Package insert. Pfizer Inc.; February 2019.
41. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addict*. 1989;84(7):791–800.
42. Henningfield JE, Radzius A, Cooper TM, Clayton RR. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *JAMA*. 1990;264(12):1560–1564.
43. Aubin H, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. *BMJ*. 2012;345:e4439.
44. Farley AC, Hajek P, Lycett D, Aveyard P. Interventions for preventing weight gain after smoking cessation. *Cochrane Database Syst Rev*. 2012; (1):CD006219.
45. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. *Prog Cardiovasc Dis*. 2003;46(1):91–111.
46. Adamopoulos D, van de Borne P, Argacha JF. New insights into the sympathetic, endothelial and coronary effects of nicotine. *Clin Exp Pharmacol Physiol*. 2008;35(4):458–463.
47. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med*. 2003;138(11):891–897.
48. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA*. 2003;290(1):86–97.
49. Rigotti NA, Munafo MR, Stead LF. Smoking cessation interventions for hospitalized smokers: a systematic review. *Arch Intern Med*. 2008;168(18):1950–1960.
50. Chang CM, Corey CG, Rostron BL, Apelberg BJ. Systematic review of cigar smoking and all cause and smoking related mortality. *BMC Public Health*. 2015;15:390.

51. Christensen CH, Rostron B, Cosgrove C. Association of cigarette, cigar, and pipe use with mortality risk in the US population. *JAMA Intern Med*. 2018;178(4):469–476.
52. Connolly GN, Alpert HR, Wayne GF, Koh H. Trends in nicotine yield in smoke and its relationship with design characteristics among popular US cigarette brands, 1997–2005. *Tob Control*. 2007;16(5):e5.
53. Henningfield JE, Fant RV, Radzius A, Frost S. Nicotine concentration, smoke pH and whole tobacco aqueous pH of some cigar brands and types popular in the United States. *Nicotine Tob Res*. 1999;1(2):163–168.
54. Benowitz NL, Zevin S, Jacob P. Sources of variability in nicotine and cotinine levels with use of nicotine nasal spray, transdermal nicotine, and cigarette smoking. *Br J Clin Pharmacol*. 1997;43(3):259–267.
55. Molander L, Lunell E, Andersson SB, Kuylenstierna F. Dose released and absolute bioavailability of nicotine from a nicotine vapor inhaler. *Clin Pharmacol Ther*. 1996;59(4):394–400.
56. Aubin HJ. Tolerability and safety of sustained-release bupropion in the management of smoking cessation. *Drugs.* 2002;62(suppl 2):45–52.
57. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387(10037):2507–2520.
58. Leone FT, Ghang Y, Evers-Casey S, et al. Initiating pharmacologic treatment in tobacco-dependent adults. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;202(2):e5–e31.
59. Ebbert JO, Hughes JR, West RJ, et al. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA*. 2015;313:687–694.
60. Tonstad S, Tonnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation a randomized controlled trial. *JAMA*. 2006;296:64–71.
61. Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies. *Circulation*. 2014;129(1):28–41.
62. Sterling LH, Windle SB, Filion KB, et al. Varenicline and adverse cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2016;5(2):e002849.
63. Benowitz NL, Pipe A, West R, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers a randomized clinical trial. *JAMA Intern Med*. 2018;178(5):622–631.
64. Nicotine replacement therapy for patients with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients with Coronary artery disease. *Arch Intern Med*. 1994;154(9):989–995.
65. Tzivoni D, Keren A, Meyler S, Khoury Z, Lerer T, Brunel P. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery

disease who try to quit smoking. *Cardiovasc Drugs Ther*. 1998;12(3):239–244.
66. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD. 2022 report. Accessed November 13, 2020. https://goldcopd.org/2022-gold-reports-2/
67. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA*. 1994;272(19):1497–1505.
68. Lawson GM, Hurt RD, Dale LC, et al. Application of serum nicotine and plasma cotinine concentrations to assessment of nicotine replacement in light, moderate, and heavy smokers undergoing transdermal therapy. *J Clin Pharmacol*. 1998;38(6):502–509.
69. Ebbert JO, Hays JT, Hurt RD. Combination pharmacotherapy for stopping smoking: what advantages does it offer? *Drugs.* 2010;70:643–650.
70. Steinberg MB, Greenhaus S, Schmelzer AC, et al. Triple-combination pharmacotherapy 3 for medically ill smokers: a randomized trial. *Ann Intern Med*. 2009;150(7):447–454.
71. Berg KM, Jorenby DE, Baker TB, Fiore MC. Triple smoking cessation therapy with varenicline, nicotine patch and nicotine lozenge: a pilot study to assess tolerability, satisfaction, and end-of-treatment quit rates. *J Smok Cessat*. 2018;13(3):145–153.
72. Koegelenberg CFN, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation. *JAMA.* 2014;312(2):155–161.
73. Rose JE, Behm FM. Combination treatment with varenicline and bupropion in an adaptive smoking cessation paradigm. *Am J Psychiatry.* 2014;171:1199–1205.
74. Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers. A randomized trial. *JAMA*. 2014;311(2):155–163.
75. Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *BMJ*. 2008;336(7644):598–600.
76. Burkman R, Schlesselman JJ, Zieman M. Safety concerns and health benefits associated with oral contraception. *Am J Obstet Gynecol*. 2004;190(4 suppl):S5–S22.
77. Schwingl PJ, Ory HW, Visness CM. Estimates of the risk of cardiovascular death attributable to low-dose oral contraceptives in the United States. *Am J Obstet Gynecol*. 1999;180(1 Pt 1):241–249.
78. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep.* 2016;65(3):1–103.
79. U.S. Department of Health and Human Services. *Surgeon General's Reports on Smoking and Tobacco Use: Smoking Cessation: Smoking Cessation. A*

Report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2020. https://www.cdc.gov/tobacco/data_statistics/sgr/2020-smoking-cessation/index.html

80. Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2020;(10):CD010216.
81. Peter Hajek P, Anna Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med.* 2019;380:629–637.
82. Fruzzetti F. Hemostatic effects of smoking and oral contraceptive use. *Am J Obstet Gynecol*. 1999;180(6 Pt 2):S369–S374.
83. Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion. *Women and Smoking: A Report of the Surgeon General*. Centers of Disease Control and Prevention, U.S. Department of Health and Human Services; 2001.
84. Ebbert JO, Elrashidi MY, Stead LF. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev*. 2015;(10):CD004306. doi:10.1002/14651858.CD004306.pub5
85. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(45):1013–1019.
86. Prochaska JJ, Das S, Young-Wolff KC. Smoking, mental illness, and public health. *Annu Rev Public Health*. 2017;38:165–185.
87. Murray RP, Bailey WC, Daniels K, et al; Lung Health Study Research Group. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Lung Health Study Research Group. *Chest*. 1996;109(2):438–445.
88. Livingstone-Banks J, Norris E, Hartmann-Boyce J, et al. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019; (10):CD003999.

SECTION 16

Hematology and Oncology

Section Editor: Christy S. Harris

92

Anemias

Cindy L. O'Bryant, Kate Deen Taucher, and Lisa A. Thompson

CORE PRINCIPLES		CHAPTER CASES
1	Anemias arise from multiple etiologies. A full laboratory evaluation is necessary to appropriately diagnose and determine the cause of anemia.	**Case 92-1 (Questions 1, 2)** **Case 92-2 (Question 1)** **Case 92-5 (Question 2), Figure 92-1, Tables 92-2 and 92-3**
2	Iron deficiency is the most common nutritional deficiency worldwide and is associated with symptoms of pallor, cardiovascular, respiratory, cognitive complications, and decreased quality of life.	**Case 92-1 (Question 2) Case 92-4 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
3	Oral or parenteral iron is used to treat iron deficiency anemia. The goal of therapy is an increased hemoglobin of 1–2 g/dL within 2–4 weeks of the initiation of therapy.	**Case 92-1 (Questions 1, 3–10)** **Case 92-4 (Question 2), Tables 92-6 and 92-8**
4	Distinguishing between vitamin B_{12}–deficient and folic acid–deficient megaloblastic anemia is important to minimize potentially permanent effects of these deficiencies.	**Case 92-2 (Questions 1–3)** **Case 92-3 (Question 1)** **Case 92-5 (Questions 1, 2)**
5	Patients with sickle cell disease should receive appropriate preventive care, including infection prophylaxis with penicillin and routine immunizations.	**Case 92-6 (Questions 1, 2)**
6	Acute sickle cell crises are an urgent situation and should be managed with pain control, transfusions, oxygen, or antibiotic therapy as appropriate.	**Case 92-7 (Questions 1–3)**
7	The goals of treatment for sickle cell anemia are symptom control and management of disease complications. Current treatments have shown a reduction in vaso-occlusive events, decreased hospitalizations, or improved hemoglobin response.	**Case 92-7 (Question 4–6)**

CORE PRINCIPLES		CHAPTER CASES
8	Anemia of inflammation is associated with the upregulation of inflammatory cytokines that results in shortened red blood cell survival and decreased production. Treatment focuses on the underlying disease and the use of erythropoietin (EPO).	**Case 92-8 (Question 1)**
9	Response to EPO depends on the dose and underlying cause of anemia. Lack of response to treatment with erythropoiesis-stimulating agents (ESAs) is commonly associated with functional or absolute iron deficiency.	**Case 92-8 (Question 1)**

INTRODUCTION

Anemia is a reduction in red blood cell (RBC) mass. It is often described as a decrease in the number of RBCs per microliter (μL) or as a decrease in the hemoglobin (Hgb) concentration in the blood to a level below the normal physiologic requirement for adequate tissue oxygenation. The term *anemia* is not a diagnosis, but rather an objective sign of a disease. Diagnostic terminology for anemia requires the inclusion of the pathogenesis (eg, microcytic anemia secondary to iron deficiency) in order to implement the appropriate specific therapy to correct the anemia.

Pathophysiology

Anemia is a symptom of many pathologic conditions. It is associated with nutritional deficiencies, acute and chronic diseases, and may be

drug-induced. Anemia is also caused by decreased RBC production, increased RBC destruction, or increased RBC loss. When anemia is caused by decreased RBC production, it may be the result of disturbances in stem cell proliferation or differentiation. Anemias caused by increased RBC destruction can be secondary to hemolysis, whereas increased RBC loss may be caused by acute or chronic bleeding. Anemias associated with acute blood loss, those that are iron-related, and those caused by inflammation constitute most anemias.[1] Classifications of anemias according to pathophysiologic and morphologic characteristics are shown in **Table 92-1**.

Table 92-1
Classifications of Anemia

Pathophysiologic (Classifies Anemias Based on Pathophysiologic Presentation)
Blood Loss
Acute: trauma, ulcer, hemorrhoids
Chronic: ulcer, vaginal bleeding, aspirin ingestion
Inadequate Red Blood Cell Production
Nutritional deficiency: vitamin B_{12}, folic acid, iron
Erythroblast deficiency: bone marrow failure (aplastic anemia, irradiation, chemotherapy, folic acid antagonists) or bone marrow infiltration (leukemia, lymphoma, myeloma, metastatic solid tumors, myelofibrosis)
Endocrine deficiency: pituitary, adrenal, thyroid, testicular
Chronic disease: renal, liver, infection, granulomatous, collagen vascular
Excessive Red Blood Cell Destruction
Intrinsic factors: hereditary (G6PD), abnormal hemoglobin synthesis
Extrinsic factors: autoimmune reactions, drug reactions, infection (endotoxin)
Morphologic (Classifies Anemias by Red Blood Cell Size [Microcytic, Normocytic, Macrocytic] and Hemoglobin Content [Hypochromic, Normochromic, Hyperchromic])
Macrocytic
Defective maturation with decreased production

Pathophysiologic (Classifies Anemias Based on Pathophysiologic Presentation)
Blood Loss
Megaloblastic: pernicious (vitamin B_{12} deficiency), folic acid deficiency
Normochromic, Normocytic
Recent blood loss
Hemolysis
Chronic disease
Renal failure
Autoimmune
Endocrine
Microcytic, Hyperchromic
Iron deficiency
Genetic abnormalities: sickle cell, thalassemia

G6PD, glucose-6-phosphate dehydrogenase.

Normally, RBC mass is maintained by feedback mechanisms that regulate levels of erythropoietin (EPO), a hormone that stimulates the proliferation and differentiation of erythroid precursors in the bone marrow. Two types of erythroid precursors reside in the bone marrow: the burst forming unit–erythrocyte cell (BFUe) and colony forming unit–erythrocyte cell (CFUe). The BFUe is the earliest progenitor, which eventually develops into a CFUe. The BFUe is moderately sensitive to EPO and is under the influence of other cytokines (eg, interleukin [IL] 3, granulocyte-macrophage colony-stimulating factor [GM-CSF]). In contrast, the CFUe is highly sensitive to EPO and differentiates into erythroblasts and reticulocytes. The kidneys produce 90% of EPO; liver synthesis accounts for the remainder. Reduced oxygen-carrying capacity is sensed by renal peritubular cells, which stimulate the release of EPO into the bloodstream. Patients with chronic anemia may have a blunted and inadequate EPO response for the degree of anemia present.

Detection

SIGNS AND SYMPTOMS

Signs and symptoms of anemia vary with the degree of RBC reduction as well as with the time to development. The decreased oxygen-carrying capacity of the reduced RBC mass results in tissue hypoxia followed by decreased perfusion to nonvital tissues (eg, skin, mucous membranes, extremities) in order to sustain tissue perfusion of vital organs (eg, brain, heart, kidneys). Slowly developing anemias can be asymptomatic initially or include symptoms such as slight exertional dyspnea, increased angina, fatigue, or malaise.[1,2]

In severe anemia (Hgb >8 g/dL), heart rate and stroke volume often increase in an attempt to improve oxygen delivery to tissues. These changes in heart rate and stroke volume can result in systolic murmurs, angina pectoris, high-output heart failure, pulmonary congestion, ascites, and edema. Thus, anemia is generally not well tolerated in patients with cardiac disease. Skin and mucous membrane pallor, jaundice, smooth or beefy tongue, cheilosis, and spoon-shaped nails (koilonychia) also may be associated with severe anemia of different etiologies.

HISTORY

A thorough history, including a timeline of onset of symptoms and current clinical status, and physical examination are essential because of the complexity of the pathologic conditions associated with anemia. When evaluating a patient for the diagnosis of anemia, histories should include (a) past and current Hgb or hematocrit (Hct) values; (b) transfusion history; (c) family history, because longstanding anemias can indicate hereditary disorders; (d) occupational, environmental, and social histories; and (e) medication history to eliminate drug reactions or interactions as the cause of the anemia.

PHYSICAL EXAMINATION

Pallor is most easily observed in the conjunctiva, mucous membranes, nail beds, and palmar creases of the hand. In addition, postural hypotension and tachycardia can be seen when hypovolemia (acute blood loss) is the primary cause of anemia. Patients with vitamin B_{12} deficiency may exhibit neurologic findings consistent with nerve fiber demyelination, which may include changes in deep tendon reflexes, ataxia, and loss of vibration and position sense. Patients with anemia from hemolysis may be slightly jaundiced from bilirubin release. Manifestations of hemorrhage can include petechiae, ecchymoses, hematomas, epistaxis, bleeding gums, and blood in the urine or the stool.

LABORATORY EVALUATION

Although anemia may be suspected from the history and physical examination, a full laboratory evaluation is necessary to confirm the diagnosis, establish severity, and determine the cause. A list of the routine laboratory evaluations used in the workup for anemia is found in **Table 92-2**. The cornerstone of this evaluation is the complete blood count (CBC). Other evaluations assessing nutritional deficiencies, including iron studies, vitamin B_{12}, and folate as well as EPO levels may also provide insight into the cause of anemia as shown in **Table 92-3**. Males have higher normal Hgb and Hct values than do females. The Hgb and Hct are increased in individuals living at altitudes >4000 feet in response to the diminished oxygen content of the atmosphere and blood.

Table 92-2

Routine Laboratory Evaluation for Anemia Workup

CBC: Hgb, Hct, RBC count, RBC indices (MCV, MCH, MCHC), WBC count (and differential)
Platelet count
RBC morphology
Reticulocyte count
Bilirubin and LDH
Serum iron, TIBC, serum ferritin, transferrin saturation
Peripheral blood smear examination

Stool examination for occult blood	
Bone marrow aspiration and biopsy[a]	

CBC, complete blood count; Hct, hematocrit; Hgb, hemoglobin; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; TIBC, total iron-binding capacity; WBC, white blood cell.

[a]Performed in patients with abnormal peripheral blood smears.

Table 92-3

Supplemental Hematology Values

	Pediatric	Adult	
Laboratory Test	**1–15 years**	**Male**	**Female**
Erythropoietin (milliunits/mL)	4–26	4–26	4–26
Reticulocyte count (%)	0.5–1.5	0.5–1.5	0.5–1.5
TIBC (mg/dL)	250–400	250–400	250–400
Fe (mg/dL)	50–120	50–160	40–150
Fe/TIBC (%)	20–30	20–40	16–38
Ferritin (ng/mL)	7–140	15–200	12–150
Folate (ng/mL)	7–25	7–25	7–25
RBC folate (ng/mL)	—	140–960	140–960
Vitamin B_{12} (pg/mL)	>200	>200	>200

Fe, iron; RBC, red blood cell; TIBC, total iron-binding capacity.

The morphologic appearance of the RBC found in RBC indices included as part of the CBC, including mean corpuscular volume (MCV), mean cell Hgb (MCH), and mean cell Hgb concentration (MCHC), provide useful information about the nature of the anemia. Note: corpuscular and cell may be used interchangeably when referring to MCV, MCH, and so on. Microscopic evaluation of the peripheral blood smear can detect the presence of macrocytic (large) RBCs, which are associated with vitamin B_{12} or folic acid deficiency, or microcytic (small) RBCs, typically associated with iron deficiency

anemia. Acute blood loss generally is associated with normocytic cells.

The history and physical examination and laboratory evaluation typically provide sufficient information to distinguish among the most common forms of anemia (**Fig. 92-1**). If not identified after routine evaluation, problems such as autoimmune disease, collagen vascular disease, chronic infection, or endocrine disorders may be causing the anemia. When uncertainty exists or an abnormal peripheral blood smear is noted, a bone marrow aspiration with biopsy is indicated.

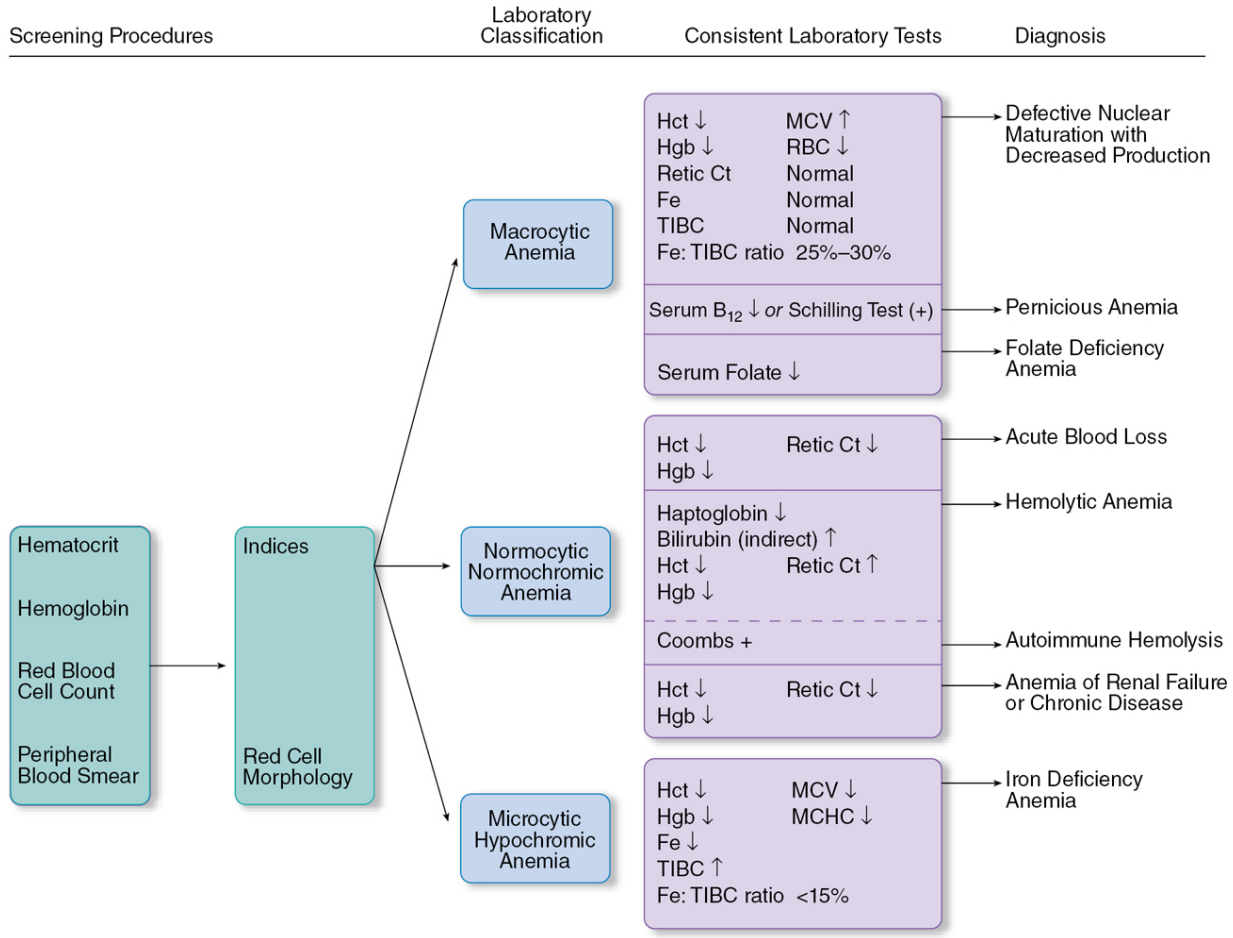


Figure 92-1 Laboratory diagnosis of anemia.

There are many causes of anemia. This chapter is limited to the most common anemias and their medication management. Hemolytic anemias will not be discussed. Before proceeding, the

reader should review the basic hematologic laboratory tests used to evaluate and monitor anemia (see Chapter 2, Interpretation of Clinical Laboratory Tests).

IRON DEFICIENCY ANEMIA

Iron deficiency occurs when iron intake and stores are unable to meet body requirements, depleting total-body iron.[3] The body contains ~3 to 4 g of iron, of which 2.5 g is found in RBCs.[4,5] Only a small fraction of iron is found in plasma and most is bound to transferrin, a transport protein.[4]

Despite the continual turnover of RBCs, iron stores are well preserved because >95% of iron is recovered and reused in new erythrocytes.[6] Males and nonmenstruating females lose about 1 to 2 mg/day of iron from minor bleeding, urine, sweat, and the sloughing of ferritin-containing intestinal mucosal cells.[4] Menstruating females lose approximately an additional 16 mg of iron per period.[6] Pregnancy and lactation are other common sources of iron loss (see Chapter 49, Obstetric Drug Therapy).

Individuals with normal iron stores absorb roughly 10% of ingested dietary iron. The average American diet contains 5 to 15 mg of elemental iron and 1 to 5 mg of heme iron, resulting in 1 to 2 mg of absorbed iron from the intestines. The average daily iron requirement for various populations is shown in **Table 92-4**.

Table 92-4
Dietary Reference Intake for Iron

	mg/day
Healthy, nonmenstruating adults	8
Menstruating females	18
Pregnant females	27
Lactating females	9

	mg/day
Vegetarians	16[a]
Preterm infants	2–4
Term infants (birth to 6 months)	0.27
Term infants (7–12 months)	11
Toddlers (1–3 years)	7

[a]Twofold higher than those not consuming a vegetarian diet.

Sources: National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. National Academies Press; 2001; Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010;126:1040–1050.

Iron is absorbed from the duodenum and upper jejunum by an active transport mechanism. Dietary iron exists primarily in the ferric state and is converted to the more readily absorbed ferrous form in the acidic environment of the stomach. The ferrous form binds to transferrin for transport to the bone marrow, where it is incorporated into the Hgb of mature erythrocytes.

Gastrointestinal (GI) absorption of iron is increased in iron deficiency states or when erythropoiesis occurs at a more rapid rate.[3] Animal sources of iron (heme iron) are better absorbed than plant sources (nonheme iron). Iron deficiency accounts for half the cases of anemia worldwide. Although iron deficiency anemia has many causes, including altered iron absorption (**Table 92-5**), blood loss is one of the more common.

Table 92-5
Iron Deficiency Anemia Causes

Blood Loss
Menstruation, gastrointestinal (eg, peptic ulcer), trauma, blood donation, hemorrhoids, ingestion of GI irritants, menstruation, multiple pregnancies
Decreased Absorption

Blood Loss
Medications, gastrectomy, bariatric surgery, celiac, regional enteritis
Increased Requirement
Infancy, pregnant/lactating females, adolescence
Impaired Utilization
Hereditary, iron use
Environmental
Insufficient intake, diet (eg, vegetarian)

Source: Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics.* 2010;126:1040–1050.

Dietary reference intakes (DRIs) for iron are listed in **Table 92-4**.[7,8] The increased amounts of iron required by pregnant or lactating females are difficult to obtain through diet alone; oral iron supplementation generally is necessary. Although maternal iron usually provides term infants with sufficient stored iron for the first 6 months, infants ages 6 months to 3 years' experience rapid growth and a threefold increase in blood volume, which can increase the risk of iron deficiency. Premature infants have reduced iron stores and thus require replacement therapy.

Predisposing Factors

CASE 92-1

Question 1: H.P. is a 31-year-old female seen in the clinic for weakness, dizziness, and epigastric pain. She has a 5-year history of peptic ulcer disease, a 10-year history of heavy menstrual bleeding, and a 15-year history of chronic headaches. She has two children who are 1 and 3 years old. H.P. is currently taking minocycline 100 mg twice daily (bid) for acne, ibuprofen 400 mg as needed for headaches, and esomeprazole 40 mg daily. Her review of systems is positive for decreased exercise tolerance. Physical examination reveals a pale, lethargic, White female appearing older than her stated age. Her vital signs are within normal limits; her heart rate is regular at 100 beats/minute. Her examination is notable for pale nail beds and splenomegaly.

Significant laboratory results include the following:

Hgb, 8 g/dL
Hct, 26%
Platelet count, 500,000/μL
Reticulocyte count, 0.2%
MCV, 75 femtoliters (fL)
MCH, 23 pg/cell
MCHC, 300 g/L
Serum iron, 40 μg/dL
Serum ferritin, 9 ng/mL
Total iron-binding capacity (TIBC), 450 g/dL
4+ stool guaiac (normal, negative)

Iron deficiency is determined to be the cause of H.P.'s anemia. An upper GI series with a small bowel follow-through is planned to evaluate her persistent epigastric pain.

What factors predispose H.P. to iron deficiency anemia?

Several factors predispose H.P. to iron deficiency anemia. Her history of heavy menstrual bleeding and the 4+ stool guaiac indicate menstrual and GI sources of blood loss. The GI blood loss may be secondary to H.P.'s chronic use of nonsteroidal anti-inflammatory drugs, recurrent peptic ulcer disease, or both.

Many menstruating patients have a borderline iron deficiency that becomes more evident with pregnancy's increased iron requirements[3]; H.P. has given birth to two children in recent years. Additionally, dietary iron absorption may be compromised by her use of proton-pump inhibitors and minocycline (see Case 92-1, Question 6).

Signs, Symptoms, and Laboratory Tests

Case 92-1, Question 2: What subjective or objective signs, symptoms, and laboratory tests are typical of iron deficiency in H.P.?

H.P.'s constitutional symptoms of weakness and dizziness could be a result of her severe anemia. Generally, until the anemia is severe, such symptoms occur with equal frequency in the

nonanemic population. The most important signs and symptoms of iron deficiency anemia are related to the cardiovascular system and reflect the imbalance between ongoing demands for oxygen against diminishing oxygen supply.

H.P.'s increased heart rate, decreased exercise tolerance, and pale appearance are consistent with the cardiovascular response seen in iron deficiency anemia. In patients who are not yet symptomatic, iron stores can be assessed by measuring ferritin. Although primarily an intracellular protein, serum concentrations of ferritin correlate closely with iron stores with only a few exceptions.[9] Ferritin is an acute-phase reactant and is generally higher in patients with inflammatory disorders, infection, malignancy, liver disease, and chronic renal failure.[9] An increased TIBC also can indicate iron depletion but is less sensitive than serum ferritin. If the TIBC is low or normal, rather than high, in association with low serum ferritin, other causes of anemia should be considered and evaluated with additional labs and bone marrow examination.

H.P.'s low serum iron, low serum ferritin, and elevated TIBC are typical of the laboratory findings associated with iron deficiency anemia. Serum transferrin receptor levels, which reflect the amount of RBC precursors available for active proliferation, are increased in iron deficiency. After stored iron is depleted, heme and Hgb synthesis is decreased. In severe iron deficiency, the RBCs become hypochromic (low MCHC) and microcytic (low MCV),[5] as seen in H.P.

The reticulocyte count provides an estimate of effective RBC production and is usually normal or low in iron deficiency anemia, consistent with H.P.'s results.

In the workup of a microcytic, hypochromic anemia, the stool should be examined for occult blood. H.P. has a 4+ stool guaiac, suggesting GI blood loss. Further diagnostic evaluation is necessary to determine the underlying problem.

Iron Therapy

ORAL IRON DOSING

Case 92-1, Question 3: How should H.P.'s iron deficiency be managed? What dose of iron should be given to treat H.P.'s iron deficiency anemia?

The primary treatment should be directed toward control of the underlying causes of anemia: GI blood loss, multiple childbirths, heavy menstrual flow, decreased dietary iron absorption, and perhaps, an inadequate diet. The cause of her GI blood loss should be corrected, her dietary intake should be analyzed and modified, and supplemental iron should be prescribed to replenish her stores and correct the anemia.

The usual adult dose of iron is 100 to 200 mg elemental iron, frequently administered as ferrous sulfate 325 mg (one tablet) taken three times daily between meals. Because of saturable absorption of iron in the intestines, repletion with lower doses or administration on alternating days has been shown to be effective and may minimize side effects and improve compliance.[3,10]

PRODUCT SELECTION

Case 92-1, Question 4: What are the differences between iron products? Which is the product of choice?

The ferrous form of iron is absorbed three times more readily than the ferric form. Although ferrous sulfate, ferrous gluconate, and ferrous fumarate are absorbed almost equally, each contains a different amount of elemental iron that is available for absorption.[11] Carbonyl iron, another iron product, must be solubilized by gastric acid to be absorbed, which may limit use. **Table 92-6** compares the iron content of several oral iron salts to assist in making appropriate treatment choices for patients.

Table 92-6
Comparisons of Oral Iron Preparations

Preparation	Dose (mg)	Fe^{2+} Content (mg)	Fe (%)
Ferrous sulfate	325	65	20
Ferrous fumarate	325	106	33
Ferrous gluconate	324	38	12
Ferrous sulfate, exsiccated (dried)	160	50	32

Note: This is a representative list of examples of oral iron preparations that may be used.

Source: Adapted with permission from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5546092?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Diron%26t%3Dname%26va%3Diron%26nq%3Dtrue.

Product formulation

Product formulation is of considerable importance in product selection. Enteric-coated and sustained release (SR) preparations are purported to increase GI tolerance or decrease side effects; however, these products are frequently more expensive than immediate release formulations. Some of these products can be given once daily, which may enhance adherence. Unfortunately, enteric-coated products transport iron past the duodenum and proximal jejunum, reducing absorption.[5] As poor absorption and poor hematologic responses might occur with SR formulations, these are not ideal for initial treatment.

Adjuvants are incorporated into some iron preparations in an attempt to enhance absorption or mitigate side effects. An acidic environment is needed for absorption in the duodenum and upper jejunum. Ascorbic acid (vitamin C, up to 1 g) is able to increase iron absorption by ~7%; however, this may increase GI side effects[10] and smaller doses do not significantly improve iron absorption.[12] To decrease constipation, stool softeners may be added,[5] although not always at adequate doses. H.P. should take the least expensive iron preparation containing ferrous sulfate, gluconate, or fumarate.

GOALS OF THERAPY

CASE 92-1, QUESTION 5: What are the goals of iron therapy? How long H.P. should be treated? How should H.P. be monitored?

The goals of iron therapy are to normalize Hgb and Hct and to replete iron stores. If the iron dose is adequate, the reticulocyte count will begin to increase by the 3rd to 4th day and peak by the 7th to 10th day of therapy. By the end of the second week of iron therapy, the reticulocyte count will normalize. Hgb response is a convenient index to monitor in outpatients. Hematologic response is usually seen in 2 to 3 weeks with a 1 to 2 g/dL increase in Hgb and a 6% increase in the hematocrit. H.P.'s anemia can be expected to resolve in 1 to 2 months; however, iron therapy should be continued for 3 to 6 months after Hgb normalizes to replete iron stores.[9]

PATIENT INFORMATION

CASE 92-1, QUESTION 6: What information should be provided to H.P. when dispensing oral iron? What can be done if she experiences intolerable GI symptoms (eg, nausea, epigastric pain)?

Iron should be dispensed in a child-resistant container, and H.P. should be counseled to store it in a place inaccessible to her young children. Accidental ingestion of oral iron can cause serious consequences in small children[13] (see Chapter 5, Managing Drug Overdoses and Poisonings). H.P. should be told that oral iron therapy produces dark stools. She should try to take her iron on an empty stomach because food, especially foods rich in calcium, phytates or tannins, decreases absorption.[10]

GI side effects occur in 5% to 20% of patients and include nausea, epigastric pain, constipation, abdominal cramps, and diarrhea. Constipation does not appear to be dose-related, but other side effects (eg, nausea and epigastric pain) occur more frequently with higher doses because the quantity of soluble elemental iron in

contact with the stomach and duodenum increases.[5] To minimize GI intolerance, oral iron can be initiated with a single tablet of ferrous sulfate 325 mg/day and increased by increments of one tablet per day every 2 to 3 days until the full therapeutic dose of 325 mg three times daily can be administered.

H.P. should be educated about potential drug interactions that can occur with iron therapy. She is taking a proton-pump inhibitor, which like other acid-suppressing medications, may inhibit serum iron absorption by increasing the stomach pH and decreasing iron solubility. H.P. is also taking minocycline; because both iron and minocycline absorption are decreased when administered concomitantly; these should be taken at least 2 hours apart. **Table 92-7** provides additional drug interactions to be considered.

Table 92-7
Select Drug Interactions With Iron Salts

Precipitant Drug	Object Drug		Description
Antacids	Iron salts	↓	GI absorption of iron may be reduced; separate administration times.
Ascorbic acid	Iron salts	↑	Ascorbic acid at doses ≥200 mg have been shown to enhance the absorption of iron ≥30%.
Calcium salts	Iron salts	↓	GI absorption of iron may be reduced. When possible, separate administration times.
Chloramphenicol	Iron salts	↑	Serum iron levels may be increased.
Digestive enzymes	Iron salts	↓	The serum iron response to oral iron may be decreased by concomitant pancreatic extracts.
H_2 antagonists	Iron salts	↓	GI absorption of iron may be reduced.
Proton-pump inhibitors	Iron salts	↓	GI absorption of iron may be reduced.
Trientine	Iron salts	↓	The two agents inhibit the absorption of each other. If iron is needed, administer the agents at least 2 hours apart.
Iron salts	Trientine		
Iron salts	Oral bisphosphonates	↓	Reduced bisphosphonate absorption; avoid administration within 2 hours before or after.
Iron salts	Captopril	↓	Concomitant use within 2 hours may promote the formation of inactive captopril disulfide dimer.
Iron salts	Cephalosporins (eg, cefdinir)	↓	Iron supplements and foods fortified with iron may reduce the absorption of cefdinir 80% and 30%, respectively. If iron supplements are needed during cefdinir therapy, cefdinir should be taken 2 hours before or after the supplement. Iron-fortified infant formula (elemental iron 2.2 mg per 6 oz) has no effect on cefdinir absorption.

Iron salts	Fluoroquinolones (eg, ciprofloxacin)	↓	GI absorption of fluoroquinolones may be decreased because of the formation of iron–quinolone complex. Avoid coadministration of these drugs. (See individual fluoroquinolone monographs for administration recommendations.)
Iron salts	Levodopa	↓	Levodopa appears to form chelates with iron salts, decreasing levodopa absorption and serum levels.
Iron salts	Levothyroxine	↓	The efficacy of levothyroxine may be decreased, resulting in hypothyroidism. Avoid coadministration.
Iron salts	Methyldopa	↓	Extent of methyldopa absorption may be decreased, possibly resulting in decreased efficacy.
Iron salts	Mycophenolate mofetil	↓	Absorption of mycophenolate mofetil may be decreased. Avoid simultaneous administration.
Iron salts	Penicillamine	↓	Marked reduction in GI absorption of penicillamine may occur, possibly because of chelation.
Iron salts	Tetracyclines	↓	Concomitant use within 2 hours may decrease absorption and serum levels of tetracyclines. Absorption of iron salts also may be decreased.
Tetracyclines	Iron salts		
Iron salts	Thyroid hormones	↓	Absorption of thyroid hormones may be decreased. Avoid coadministration.

↑, object drug increased; ↓, object drug decreased.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

PARENTERAL IRON THERAPY

Indications

Case 92-1, Question 7: When would parenteral iron therapy be indicated for H.P.?

Causes of oral therapy failure can include nonadherence, misdiagnosis, inflammatory conditions, malabsorption (eg, gastric bypass, celiac disease), the need for rapid iron repletion, and continuing blood loss equal to or greater than the rate of RBC production.[4,9] Other indications for parenteral iron administration include intolerance to oral therapy, required antacid therapy, or significant blood loss in patients refusing transfusion. In H.P.'s case intolerance, continued blood loss, long-term antacid therapy, and malabsorption may be potential indications for parenteral iron.

Preferred route

Case 92-1, Question 8: What is the preferred formulation of parenteral iron?

Iron can be given parenterally as ferric gluconate, iron dextran, iron sucrose, ferric carboxymaltose, and ferumoxytol (**Table 92-8**). Comparison between agents reveals similar efficacy with differences in cost analysis from diverse administration schedules.[14] Iron dextran and ferric carboxymaltose are U.S. Food and Drug Administration (FDA) approved for the treatment of iron deficiency when oral supplementation is impossible or ineffective. All parenteral iron products can be administered undiluted slowly as an intravenous (IV) push or diluted and administered by infusion. Iron dextran is the only product that may be given intramuscularly (IM), which may be preferred in patients with limited IV access. Although data are limited, infusion of the total dose (total estimated iron deficit) of iron dextran is given in clinical practice and has proved to be effective and convenient.[15] The total dose method of administration can be associated with a higher prevalence of fever, malaise, flushing, and myalgias. Because of the potential for anaphylaxis with iron dextran, a 25-mg IM or IV test dose should be given. Test doses prior to subsequent infusions should be considered but are not required.

Table 92-8
Comparison of Parenteral Iron Preparations

Preparation	Dosage Form	Usual Dose	Maximum Dose
Ferric carboxymaltose	Solution for injection: 50 mg/mL (elemental iron)	Weight ≥50 kg: 750 mg per dose Weight <50 kg: 15 mg/kg per dose Repeat dose ≥7 days	1500 mg (cumulative per treatment course)
Ferumoxytol	Solution for injection: 30 mg/mL (elemental iron)	510 mg per dose; repeat once 3–8 days later Off-label regimen: 1020 mg single dose	N/A
Iron dextran (low molecular weight)	Solution for injection: 50 mg/mL (elemental iron)	Test dose: 25 mg; followed by remainder of dose (typically not >975 mg)	100 mg/day per prescribing information; 1000 mg per infusion more typical of current practice[8]
Iron sucrose	Solution for injection: 20 mg/mL (elemental iron)	**HD:** 100 mg during consecutive HD sessions for 10 doses **CKD, nondialysis:** 200 mg on five different occasions over 14 days; 500 mg once on days 1 and 14 **CKD, PD:** 300 mg IV days 1 and 14, then 400 mg on day 28	N/A
Sodium ferric gluconate complex	Solution for injection: 12.5 mg/mL (elemental iron)	125 mg per dose (usually repeated to cumulative dose of 1000 mg)	N/A

CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

Ferric gluconate, iron sucrose, and ferumoxytol are FDA-approved parenteral iron formulations used to treat iron deficiency anemia in patients with chronic kidney disease undergoing chronic hemodialysis. Ferric carboxymaltose is indicated for the treatment of iron deficiency anemia in nondialysis-dependent chronic kidney disease. A test dose is not required for these agents because of the lower incidence of serious anaphylactoid reactions. Iron requirements may exceed 1 to 2 g, requiring multiple doses to achieve the intended dose of iron.

Dosage calculation

Case 92-1, Question 9: What is the total dose of iron dextran for IV infusion that would be needed to achieve a normal Hgb value for H.P. and to replenish her iron stores? How quickly should she respond?

The total dose of iron dextran to be administered can be determined using the following equation.

$$\text{Iron (mg)} = \text{Weight (pounds)} \times 0.3 \{100 - [100(\text{Hgb})/14.8]\} \quad \textbf{(Eq. 92-1)}$$

Where Hgb is the patient's measured Hgb (g/dL).

The equation uses the person's weight (in pounds) and assumes that an Hgb of 14.8 g/dL is 100% of normal. Children weighing <30 pounds (13.60 kg) should be given 80% of the calculated dose because the normal mean Hgb in this population is lower.

For patients with anemia resulting from blood loss (eg, hemorrhagic diathesis) or patients receiving chronic dialysis, the iron requirement is based on the estimate of iron contained in the blood lost. In this case, the following equation should be used:

$$\text{Iron (mg)} = \text{Blood loss (mL)} \times \text{Hct (the patient's measured Hct expressed as a decimal fraction)} \quad \textbf{(Eq. 92-2)}$$

This formula assumes that 1 mL of normochromic blood contains 1 mg of iron.

Because the rate of iron incorporation into Hgb does not exceed that achieved by oral iron therapy, the hematologic response time is similar to that of oral iron therapy.

Side effects

Case 92-1, Question 10: What side effects can be expected from parenteral iron therapy?

Overall, serious adverse reactions reported with parenteral iron administration are rare.[16] Anaphylactoid reactions occur in <1% of patients treated with parenteral iron therapy and are more commonly associated with iron dextran and ferumoxytol than with ferric gluconate and iron sucrose.[16,17] Other side effects seen with parenteral iron agents include chest pain, headache, hypotension, nausea and vomiting, cramps, and diarrhea.

MEGALOBLASTIC ANEMIAS

Megaloblastic anemia is a common disorder that can have several causes, such as vitamin B_{12} deficiency, folate deficiency, or by related conditions that cause impaired DNA synthesis.[18,19]

Megaloblastosis results from impaired DNA synthesis in replicating cells, which is signaled by a large immature nucleus.[18] RNA and protein synthesis remain unaffected, and the cytoplasm matures normally. Megaloblastic changes can be observed microscopically in RBC and in proliferating cells (eg, in the cervix, skin, GI tract). The extent of RBC macrocytosis is reported as MCV, calculated as shown below.

$$\text{MCV (fL)} = [\text{Hct (percent)} \times 10]/[\text{RBC count } (10^6/\mu\text{L})]$$

Although the clinical effects of vitamin B_{12} and folic acid deficiencies can differ in various organ systems, they are similar in their effects on the hematopoietic system. Typically, macrocytic anemia develops slowly and is characterized by large, oval, well-hemoglobinized RBCs; anisocytosis; and nuclear remnants. The reticulocyte count is low, and the bilirubin level is elevated. If biopsied, the bone marrow is markedly hypercellular. Nuclear immaturity is present, but the megaloblasts have normal maturation of the cytoplasm. Iron stores in the marrow are increased as a result of the intramedullary hemolysis. Symptoms include fatigue; exaggeration of preexisting cardiovascular or pulmonary problems; a sore, pale, smooth tongue; diarrhea or constipation; and anorexia.[20,21]

(Eq. 92-3)

Vitamin B_{12} Deficiency Anemia

VITAMIN B_{12} METABOLISM

Deficiency and poor utilization of vitamin B_{12} are two mechanisms for the development of megaloblastic anemia.[21] Vitamin B_{12} (cobalamin) is naturally synthesized by microorganisms, but humans must obtain vitamin B_{12} in their diet. Animal protein and fortified foods provide the majority of dietary vitamin B_{12}.[22] The typical Western diet contains 3.5 to 5 µg/day of vitamin B_{12}, an amount sufficient to replace up to 1 µg lost daily through urine, sweat, and other body secretions.

In the stomach, vitamin B_{12} is released from protein complexes and bound to intrinsic factor, which protects it from degradation by GI microorganisms. Intrinsic factor is essential for the absorption of vitamin B_{12}. Specific mucosal receptors in the distal small ileum allow for attachment of the intrinsic factor–vitamin B_{12} complex, which is then transferred to the ileal cell and, finally, to portal vein blood.

After vitamin B_{12} is absorbed, it is bound to specific β-globulin transport proteins, transcobalamins I, II, and III. Transcobalamin II is responsible for transporting absorbed vitamin B_{12} through cell

membranes and delivering it to the liver and other organs. In the liver, vitamin B_{12} is converted to coenzyme B_{12}, which is essential for hematopoiesis, maintenance of myelin throughout the entire nervous system, and production of epithelial cells.

Total body stores of vitamin B_{12} range from 2000 to 3000 µg, ~50% of which is stored in the liver. Because body stores are extensive, 5 to 10 years are required before symptoms of vitamin B_{12} deficiency develop.[20]

PATHOGENESIS AND EVALUATION OF VITAMIN B_{12} DEFICIENCY

Vitamin B_{12} deficiency can result from decreased supply (reduced intake, absorption, transport, or utilization) or increased requirement (greater metabolic consumption, destruction, and excretion). Other causes of vitamin B_{12} deficiency include inadequate proteolytic degradation of vitamin B_{12} from protein or congenital intrinsic factor deficiency. In addition, the gastric mucosa may be unable to produce intrinsic factor under conditions such as partial gastrectomy, autoimmune destruction (eg, Addisonian or juvenile pernicious anemia), or destruction of the gastric mucosa from caustic agents.

Pernicious anemia can result in vitamin B_{12} deficiency.[23,24] It can be caused by chronic atrophic gastritis accompanied by reduced intrinsic factor and hydrochloric acid secretion or acquired as a result of gastrectomy, pancreatic disease, or malnutrition. Pernicious anemia occurs commonly in patients with thyrotoxicosis, autoimmune thyroiditis, vitiligo, rheumatoid arthritis, or gastric cancer. Intrinsic factor and parietal cell autoantibodies may be observed in the serum of patients with pernicious anemia.

The onset of pernicious anemia is insidious. Patients generally do not feel well for months and often report at least two of the following symptoms: weakness, sore tongue, and symmetric numbness or tingling in the extremities. The neurologic symptoms of vitamin B_{12} deficiency are associated with a defect in myelin synthesis and often

are described as peripheral neuropathy or nonspecific symptoms (eg, tinnitus, neuritis, vertigo, headaches).

LABORATORY EVALUATION

In general, the serum vitamin B_{12} level reliably reflects vitamin B_{12} tissue stores. Falsely low vitamin B_{12} concentrations may be observed in patients with folic acid deficiency, transcobalamin I deficiency, multiple myeloma, or pregnancy.[20] Falsely normal levels may be observed in patients with myeloproliferative, liver, or renal disease. Measuring serum methylmalonic acid and homocysteine levels may also differentiate between folate and vitamin B_{12} deficiency. Once vitamin B_{12} therapy has been instituted, serum levels of these chemicals decrease if true vitamin B_{12} deficiency is present.

The cause of vitamin B_{12} deficiency may be determined by the use of antibody testing (anti-parietal cells and anti-intrinsic factor antibodies).[24,25] Patients with pernicious anemia are not able to absorb vitamin B_{12} because intrinsic factor is not available for binding. Some patients produce intrinsic factor but are still unable to absorb dietary vitamin B_{12}. In the elderly, malabsorption can be caused by intestinal bacteria that usurp vitamin B_{12}, achlorhydria, chronic acid suppression therapy, pancreatic insufficiency, alcohol abuse, inadequate disassociation of vitamin B_{12} from proteins, or lack of intrinsic factor receptors secondary to ileal loops, bypass, or surgical resection.[26]

PERNICIOUS ANEMIA

Signs, symptoms, and laboratory findings

CASE 92-2

QUESTION 1: C.L. is a 63-year-old Scandinavian male who is seen by a private physician. C.L. has a 1-year history of weakness and emotional instability. He also reports a painful tongue, alternating constipation and diarrhea, and a

tingling sensation in both feet. Pertinent findings on physical examination include pallor, red tongue, vibratory sensory loss in the lower extremities, disorientation, muscle weakness, and ataxia.

Significant laboratory findings include the following:

Hgb, 8.7 g/dL
Hct, 27%
MCV, 115 fL
MCH, 38 pg/cell
MCHC, 340 g/L
Reticulocytes, 0.4%
White blood cell (WBC) count, 4000/μL
Platelets, 100,000/μL
Serum iron, 90 μg/dL
TIBC, 350 g/dL
Ferritin, 140 ng/mL
RBC folate, 300 ng/mL
Serum vitamin B_{12}, 90 pg/mL
Intrinsic factor antibody positive

What signs, symptoms, and laboratory findings in C.L. are typical of pernicious anemia?

C.L.'s signs and symptoms are classic for pernicious anemia. This disease occurs equally in both sexes (primarily in individuals of northern European descent), with an average onset of age 60 years.[27] C.L.'s signs and symptoms of vitamin B_{12} deficiency include painful red tongue, loss of lower extremity vibratory sense, vertigo, and emotional instability. The elevated MCV suggests megaloblastic anemia.

Folate and iron are two other factors that can affect the MCV and should be evaluated during the workup of a patient for anemia. In this case, C.L.'s folate and iron levels are normal, but his serum vitamin B_{12} level is low. The patient's low Hgb, elevated MCV, low serum vitamin B_{12} levels, and presence of intrinsic factor antibodies are compatible with the diagnosis of pernicious anemia, which is often associated with atrophic body gastritis. The Schilling test, which confirms intestinal malabsorption of vitamin B_{12}, is no longer available in the United States.[20]

Treatment

CASE 92-2, QUESTION 2: How should C.L.'s pernicious anemia be treated? How soon can a response be expected?

C.L. should receive parenteral vitamin B_{12} in a dose sufficient to provide the daily requirement of ~2 µg and the amount needed to replenish tissue stores (about 2000–5000 µg; average, 4000 µg). To replete vitamin B_{12} stores, cyanocobalamin can be given IM in accordance with various regimens as shown in **Table 92-9**.[28] Intramuscular or deep subcutaneous administration provides improved absorption compared with rapid IV infusion. An oral tablet or intranasal cyanocobalamin solution is also available for maintenance therapy after the patient has normalized blood counts.

Table 92-9
Cyanocobalamin (Vitamin B_{12}) Supplementation Regimens for Macrocytic Anemia

Patient Population	Initial Supplementation			Chronic Supplementation (Lifelong)		
	Dose	Frequency	Route	Dose	Frequency	Route
Adults	100 µg	Daily for 7 days, then on alternate days for 14 days, then every 3–4 days for 2–3 weeks	IM or SC	100–200 µg	Monthly	IM or SQ
Severe deficiency	100–1000 µg	Daily or every other day for 1–2 weeks	IM or SC	100–1000 µg	Every 1–3 months	IM or SQ
				500 µg	Weekly	Intranasal
	1000–2000 µg	Daily for 1–2 weeks	Oral	1000 µg[a]	Daily	Oral

IM, intramuscular; SC, subcutaneous.

[a]In patients with normal gastrointestinal absorption, doses of 1–25 µg daily are considered sufficient as a dietary supplement.

Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home; Butler CC, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. *Fam Pract*. 2006;23:279–285.

Treatment with vitamin B_{12} should completely reverse the hematologic complications of pernicious anemia.[21,22] The reticulocyte count increases within the first week of treatment and the

megaloblastic anemia resolves within 6 to 8 weeks. Neurologic symptoms may worsen at first and then resolve over weeks to months. Some symptoms may never resolve completely. Because the rapid production of RBCs can increase potassium demand, serum potassium should be monitored, and potassium supplementation provided as necessary. Peripheral blood counts should be obtained every 3 to 6 months to evaluate the adequacy of therapy. If maintenance therapy is discontinued, pernicious anemia will recur within years, making patient adherence vital to long-term success.

Oral Vitamin B_{12}

Case 92-2, Question 3: What factors affect the oral absorption of vitamin B_{12}? When might oral vitamin B_{12} therapy be an effective alternative to parenteral therapy for C.L.?

The amount of vitamin B_{12} that can be absorbed orally from a single dose or meal ranges from 1 to 5 µg; ~5 µg of vitamin B_{12} is obtained daily from the average American diet.[22] The percentage of vitamin B_{12} absorbed decreases with increasing doses: 50% of a 1-µg dose and 5% of a 20-µg dose. Overall, oral vitamin B_{12} therapy is considered safe and effective,[29] although because of lack of long-term efficacy data, oral supplementation is not routinely used in the acute treatment of vitamin B_{12} deficiency.[26] Oral therapy for pernicious anemia using high dosages of oral cyanocobalamin may be indicated in certain patients, especially those who refuse or cannot receive other routes of therapy.[26,30] Issues of nonadherence or lack of response with oral therapy places the patient at substantial risk for significant neurologic damage. Patients receiving oral vitamin B_{12} therapy should be monitored more frequently to ensure adherence to therapy.

Anemias After Gastrectomy

CASE 92-3

QUESTION 1: F.M. has just undergone a total gastrectomy for recurrent nonhealing ulcers.

What form(s) of anemia would be expected to develop in a patient after gastrectomy? Should F.M. receive prophylactic vitamin B_{12}?

Partial or total gastrectomy often results in anemia, particularly pernicious anemia, because the loss of intrinsic factor impairs oral vitamin B_{12} absorption. The hematologic and neurologic abnormalities associated with vitamin B_{12} deficiency do not develop until existing vitamin B_{12} stores are depleted (about 2–3 years). Nevertheless, prophylactic vitamin B_{12} should be administered in this patient after total gastrectomy.[31] Because the vitamin B_{12} stores are not currently depleted, maintenance therapy, as discussed in Case 92-2, Question 2, should be adequate for F.M.

Anemias After Gastric Bypass

CASE 92-4

QUESTION 1: P.G. is a 48-year-old female scheduled to have laparoscopic Roux-en-Y gastric bypass (RYGB) surgery for morbid obesity with a body mass index (BMI) >40.

What forms of anemia would be expected to develop in P.G.?

When an RYGB procedure is performed, the stomach is decreased in size, and the small intestine is manipulated creating a gastrojejunostomy and jejunojejunostomy.[32] This results in bypassing the duodenum and proximal jejunum where iron is absorbed, resulting in iron deficiency anemia. The gastric pouch is no longer an acidic environment which impairs iron bioavailability and functioning of iron transport mechanisms. Patients are also recommended to avoid red meat, which is a common dietary source of iron. An acidic environment is also needed for the bioavailability of vitamin B_{12}

leading to decreased absorption. The diagnosis of vitamin B_{12} deficiency following bariatric surgery is rare because of the large amount stored in the body. Folate deficiency may occur from reduced dietary folate intake. The majority of folate is absorbed from the upper third of the small intestine but may occur at any location. Iron deficiency anemia is the most common cause of anemia in bariatric surgery patients; however, other micronutrient deficiencies may also contribute.

CASE 92-4, QUESTION 2: What prophylactic strategies might P.G. employ to prevent anemia?

Following bariatric surgery, patients will need to take lifelong multivitamin and micronutrient supplementation.[33] Patients should take a high-potency multivitamin with 100% of the recommended daily value for at least 75% of the nutrients. It should have a minimum of 18 mg iron, 400 µg folic acid, selenium, and zinc.[34] Patients should be instructed to take an additional one to two tablets per day of an iron salt, ferrous sulfate, or ferrous fumarate to prevent iron deficiency anemia. In addition to a high-potency multivitamin, patients should take 350 to 500 µg/day of oral cyanocobalamin or receive 1000 µg injections monthly.

Folic Acid Deficiency Anemia

FOLIC ACID METABOLISM

Folate is abundant in virtually all food sources, especially fresh green vegetables, fruits, yeast, and animal protein. As a result of food fortification, the average American diet provides 50 to 2000 µg of folate per day; however, excessive or prolonged cooking (>15 minutes) in large quantities of water may reduce the folate contained in food.[35] Human requirements for folate vary with age and depend on the rate of metabolism and cell turnover but are generally 3 µg/kg/day.[35] The minimal daily adult requirement of folate is 50 µg but, because absorption from food is incomplete, a daily intake of

200 µg is recommended. Folate requirements are increased in conditions in which the metabolic rate and rate of cellular division are increased (eg, pregnancy, infancy, infection, malignancies, hemolytic anemia). The following are estimates of daily folate requirements based on age and growth demands: children, 80 to 400 µg; infants, 65 µg; and pregnant or lactating females, 600 µg.[36]

Dietary folic acid is in the polyglutamate form and must be enzymatically deconjugated in the GI tract to the monoglutamate form before it is absorbed. Once absorbed, the inactive dihydrofolate must be converted to active tetrahydrofolate (folinic acid) by dihydrofolate reductase.

In contrast to the large stores of vitamin B_{12}, the body's folate stores are relatively small (about 5–10 mg). Therefore, deficiency and subsequent megaloblastic anemia can occur within 3 to 4 months of decreased folate intake.

PREDISPOSING FACTORS

Folate deficiency is most commonly associated with alcoholism, rapid cell turnover, and dietary deficiency. In alcoholics, the daily intake of the folate contained in food may be restricted or absent. In addition, enterohepatic recirculation of folate can become impaired by the toxic effect of alcohol on hepatocytes. Folate deficiency may also develop during the third trimester of pregnancy as a result of a marginal diet and rapid fetal metabolism. Folate coenzymes are required for most metabolic pathways (**Fig. 92-2**). Therefore, folate deficiency will develop in any condition of rapid cellular turnover (eg, hemolytic anemias, hemoglobinopathies, sideroblastic anemia, leukemias, lymphomas, multiple myeloma) or a diet lacking in folate (eg, food faddism or a weight-loss diet). Folate deficiency also can occur with chronic hemodialysis, diseases that impair absorption from the small intestine (eg, sprue, regional enteritis), extensive jejunal resections, and drugs that alter folate metabolism (eg, trimethoprim, pyrimethamine, methotrexate, sulfasalazine, oral contraceptives, anticonvulsants).[37,38] Few patients have inborn errors of folate metabolism.[39]

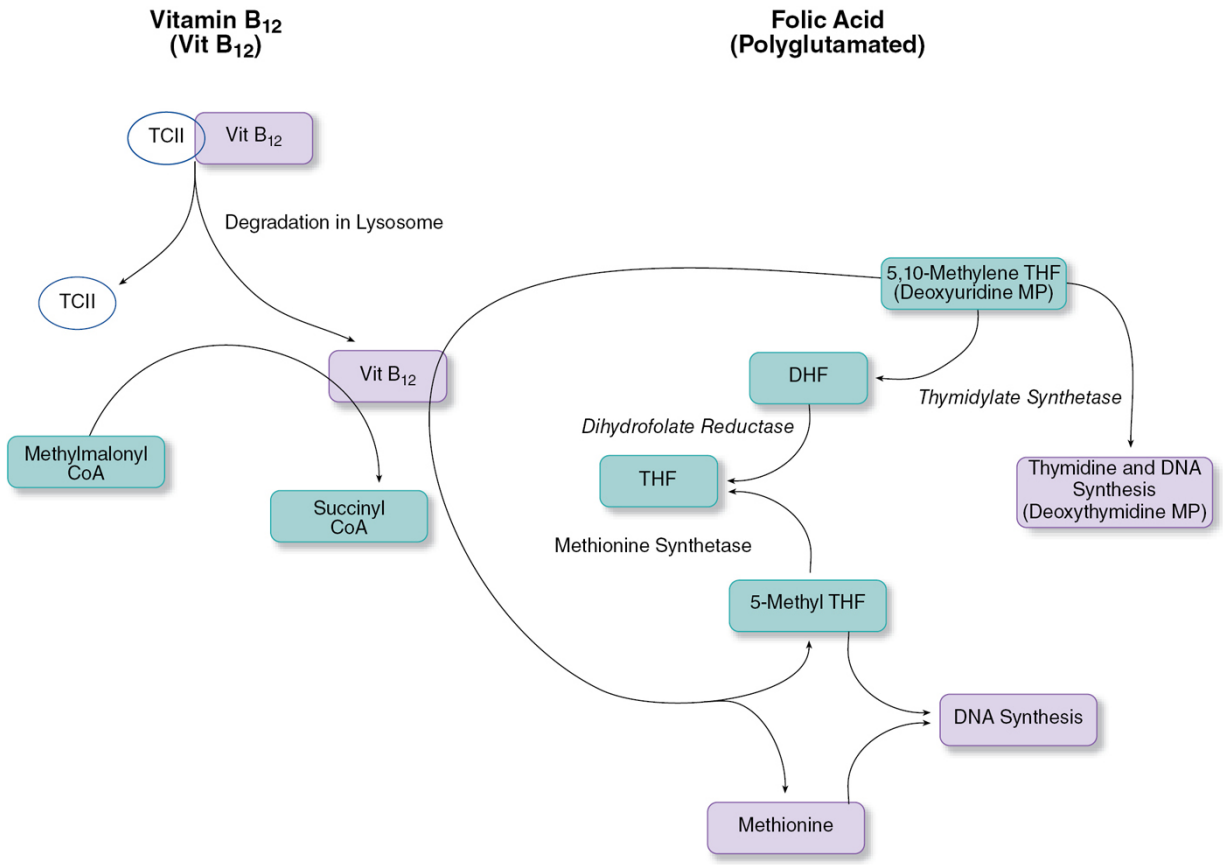


Figure 92-2 Intracellular metabolic pathways. Both vitamin B_{12} and folic acid are necessary for nucleic acid precursors used for DNA synthesis. DHF, dihydrofolate; MP, monophosphate; TCII, transcobalamin II; THF, tetrahydrofolate.

The evaluation of megaloblastic anemia must be thorough because indiscriminate use of nondirected therapy can be dangerous. Large doses of folate can partially reverse hematologic abnormalities caused by vitamin B_{12} deficiency; however, folate cannot correct neurologic damage caused by vitamin B_{12} deficiency. Therefore, folate deficiency must be differentiated from vitamin B_{12} deficiency *before* folate therapy is initiated. Otherwise, progression of the neurologic sequelae of vitamin B_{12} deficiency can occur.

CASE 92-5

QUESTION 1: D.H. is a malnourished-appearing female in her second trimester of pregnancy who presents to the local health clinic for her regular checkup. She is a multiparous, 26-year-old female with a 7-year history of excessive alcohol intake and has been using cocaine frequently for 3 years. She lives with her boyfriend and her 19-month-old daughter. During both pregnancies, D.H. lost 8 to 10 pounds (3.63–4.54 kg) during the first trimester secondary to nausea, vomiting, and anorexia. Her only problems are dyspnea on exertion, palpitations, and diarrhea.

Pertinent laboratory values include the following:

Hct, 25.5%
MCV, 112 fL
MCH, 34 pg/cell
RBC, 1.1 × 10^6/μL
Iron, 179 μg/dL
Folate, 40 ng/mL
Serum vitamin B_{12}, 350 pg/mL (normal, 200–1000)
Reticulocytes, 1%
Platelets, 70,000/μL
WBC count, 2000/μL with hypersegmented polymorphonuclear neutrophils (PMNs)
Lactate dehydrogenase (LDH), 425 units/L
Bilirubin, 1.2 mg/dL
D.H. is not taking any prescription medications.

What factors make D.H. at risk for folate deficiency?

As with most patients who are folate-deficient, D.H. has more than one risk factor. Cocaine and alcohol, together with multiparity complicated by anorexia, nausea, and vomiting, could lead to poor nutrition. Alcohol has toxic effects on the intestinal mucosa and interferes with folate utilization by the bone marrow. D.H. should be asked specifically about her dietary habits and recent weight history. She may have a folate-poor diet for financial reasons or because she is overcooking her food. Alternatively, cocaine may be causing anorexia. The nutritional intake of people who abuse alcohol and drugs is often poor. The diagnosis of folate deficiency is plausible, considering folate deficiency can develop in a matter of weeks to months.

DIAGNOSIS AND MANAGEMENT

CASE 92-5, QUESTION 2: Which laboratory values support the diagnosis of folate deficiency? How should D.H. be treated and monitored?

D.H.'s laboratory values reflect macrocytic anemia (Hct, 25.5%; MCV, 112 fL) with pancytopenia (reduced number of RBCs, WBCs, and platelets). Serum vitamin B_{12} concentrations reflect normal vitamin B_{12} stores, but folate stores are inadequate as exemplified by the low RBC folate concentration, pancytopenia, and macrocytic anemia.

Serum folate concentrations generally reflect folate balance during the past 3 weeks although one balanced meal can raise serum levels and falsely elevate body stores. Tissue folate stores are more accurately reflected by the RBC polyglutamated folate content, which is ~10 to 30 times the corresponding serum folate concentrations.[40] Hemolysis or vitamin B_{12} deficiency causes leakage of monoglutamated folates from cells, thereby falsely elevating serum folate levels.[41]

D.H. should be counseled regarding her nutritional and social habits. Because the estimated total-body folate store is only about 5 to 10 mg, 1 mg of folic acid given daily for 2 to 3 weeks should be more than adequate to replace her storage pool of folate. Higher dosages (up to 5 mg) may be needed, however, if absorption is compromised by alcohol or other factors.[37] Once stores are replenished, D.H. should continue folate supplements throughout her pregnancy and lactation period. She should be reassessed after the course of therapy to determine the response to therapy and whether the cause of the folate deficiency has been corrected. Supplementation with folic acid 1 mg/day may be required as long as risk factors are present. D.H.'s fetus is unlikely to develop folate deficiency because maternal folate is preferentially delivered to the fetus; however, sustained folate deficiency during pregnancy can cause birth defects in the newborns (see Chapter 49, Obstetric Drug Therapy).

D.H.'s response to therapy can be monitored by several different parameters. Although bone marrow aspirates are not obtained

routinely, the RBC morphology should begin to revert to normal within 24 to 48 hours after therapy is initiated, and hypersegmented neutrophils should disappear in the periphery in about 1 week. Serum chemistry and hemogram studies should begin to normalize within 10 days. The reticulocyte count should increase by day 2 to 3 and peak by day 10. Bilirubin and LDH values should normalize in 1 to 3 weeks. Finally, the anemia should be corrected in 1 to 2 months. Once anemia is corrected, 100 µg daily of folate as a nutritional supplement should be adequate for maintenance treatment (independent of the patient's pregnancy/lactation status).

SICKLE CELL ANEMIA

Pathogenesis

Sickle cell anemia is an inherited, autosomal recessive hemoglobin (Hgb) disorder characterized by mutations in the β-globin gene. Hemoglobin S (HbS) results from a DNA substitution of thymidine for adenine in the glutamic acid codon, forming a B6 valine instead of glutamic acid.[42,43] The Hgb produced from this substitution has a more negative charge than normal adult hemoglobin (HbA) and in the deoxygenated state will aggregate and polymerize, forming sickled RBCs. Sickled RBCs are more rigid and when passing through the microvasculature adhere to activated vascular endothelial cells, resulting in vascular occlusions. Additionally, sickled RBCs also adhere to macrophages leading to erythrophagocytosis and hemolysis, a clinical feature associated with the diagnosis of sickle cell anemia.[43]

More than one inheritance pattern results in abnormal Hgb polymerization. Patients with sickle cell anemia are homozygous, inheriting a sickle gene from each parent (HbSS), whereas patients with sickle cell trait are heterozygous and have inherited the sickle cell gene from one parent and the HbA gene from the other parent (HbAS). Other inheritance patterns include patients with HbSC, a

sickle cell gene, and a hemoglobin C gene (HbC) where the glutamic acid is substituted for a B6 lysine. Patients may also inherit the sickle cell gene and a β-thalassemic gene (HbS-β+ thalassemia or HbS-β^0 thalassemia). HbSS is the most common and most severe type of sickle cell disease. HbSC is the second most common form but is associated with less severe symptoms. In general, most other forms of this disease, including HbS-β+ thalassemia, are associated with mild-to-moderate symptoms with the exception of HbS-β^0 thalassemia, which exhibits more severe disease similar to HbSS.[42,44]

Sickle cell disease genotypes can be found in a large number of ethnic groups because of genetic admixture. However, the disease is more prevalent in regions of sub-Saharan Africa, the Mediterranean basin, Middle East, and India but can also be found in relatively high numbers in the Americas and Caribbean.[42,44] In the United States, roughly 1 in 13 Blacks is born with sickle cell trait, and ~100,000 people have sickle cell disease.[45]

Laboratory Evaluation

When evaluating a patient for sickle cell disease, the laboratory workup should include a CBC, reticulocyte count, peripheral blood smear, and hemoglobin electrophoresis. Those diagnosed with sickle cell anemia most commonly have elevated WBC and platelet counts in addition to anemia resulting from decreased hemoglobin and hematocrit. The reticulocyte count is frequently elevated, the degree to which varies based on the level of anemia and hemolysis. The MCV may also be elevated. If MCV values are low or within the normal range, iron deficiency or other forms of sickle cell disease must be considered. Sickled cells may be visually observed by a peripheral blood smear in poorly oxygenated blood of a patient with sickle cell anemia. Hemoglobin electrophoresis is used to identify the presence of HbSS in sickle cell anemia and can help determine other hemoglobinopathies (eg, HbSC). In contrast, a patient with the sickle cell trait should have normal RBC morphology (sickled cells

are rarely observed) and normal WBC, reticulocyte, and platelet counts.[44]

Clinical Course and Management

In an effort to improve outcomes in this population, routine screening for sickle cell anemia or sickle cell trait is performed on all newborns in the United States. Therefore, unless born outside of the United States, the majority of patients are diagnosed during their first year of life. Families carrying sickle cell trait or disease are referred for genetic counseling. Patients with sickle cell disease are referred to a hematologist and multidisciplinary team for medical management.

The clinical signs of sickle cell disease typically appear after age 6 months, when fetal hemoglobin levels fall to a point where abnormalities associated with HbS can present. Complications from sickle cell disease persist for the life of a patient. The prognosis for patients diagnosed with this disease is uncertain as morbidity is variable and mortality is high, particularly in childhood. With the advent of better treatment, studies demonstrate survival is improving but life expectancy remains about 30 years less than the general population.[42]

The management of sickle cell disease is largely directed toward prophylaxis against infections and supportive management of vaso-occlusive crises. The clinical course among patients with sickle cell disease is variable and difficult to predict. Some patients experience a multitude of health problems. Organs such as the kidneys, retina, spleen, and bones are frequent sites of vaso-occlusive events because of relatively low pH and oxygen tension. Cardiac, pulmonary, neurologic, hepatobiliary, obstetric/gynecologic, ocular, dermatologic, or orthopedic complications can also occur. The management of these complications is organ-specific and primarily aimed at supportive interventions.

INFECTIONS

CASE 92-6

QUESTION 1: B.C. is a 4-month-old female who has recently been diagnosed with sickle cell anemia (both parents positive for sickle cell trait). Her older sibling is positive for sickle cell trait but is asymptomatic.

How does B.C.'s diagnosis affect her risk of infections?

B.C. is at an increased risk for infections because sickle cell anemia causes defects in splenic function, complement activation, granulocyte function, and B-cell immunity, as well as micronutrient deficiencies.[46] Impaired splenic function because of splenic sequestration results in vaso-occlusion and increases B.C.'s risk for infection from polysaccharide-encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Salmonella typhimurium.*[47,48] These types of infections occur most frequently in early childhood because 94% of sickle cell anemia patients have functional asplenia by age 5 years. It is important to note that patients like B.C. will have a lifelong increased risk of infection. Pneumonia caused by *S. pneumoniae,* mycoplasma, or viruses can worsen hypoxia, causing progression to vaso-occlusion and acute chest syndrome (discussed in more depth below). Other infectious conditions such as osteomyelitis from *Staphylococcus aureus* or *S. typhimurium* or urinary tract infections caused by *Escherichia coli* are common complications in patients with sickle cell anemia.[47]

CASE 92-6, QUESTION 2: What preventive measures should be taken to prevent infections in B.C.?

Patients with sickle cell anemia should use general preventive measures, such as frequent handwashing, avoiding sick contacts, and thoroughly cooking foods that may carry *Salmonella* (eg, chicken or eggs).[46] Children should be closely monitored for symptoms, and antibiotic therapy should be instituted at the earliest sign of infection. Prophylactic administration of penicillin has significantly reduced morbidity and mortality from pneumonia in

children younger than 3 years of age and is recommended to be continued through age 5.[47,49] Patients such as B.C. should receive 125 mg orally twice daily for ages 1 through 3, then 250 mg orally twice daily until age 5. Guidelines recommend discontinuing penicillin prophylaxis at age 5 unless the child has undergone splenectomy or has had an invasive pneumococcal infection.[49]

Patient with sickle cell anemia should receive all guideline-recommended pediatric and adult vaccines. In addition to the standard pneumococcal conjugate vaccine series, at 2 years old, B.C. should receive the pneumococcal 23-valent polysaccharide vaccine no earlier than 8 weeks after any pneumococcal 13-valent conjugate vaccine and another dose 5 years later.[50] Pediatric patients with sickle cell disease should additionally receive meningococcal prophylaxis per vaccine recommendations using the appropriate dose and schedule based on the meningococcal vaccine given. It is important to note that live attenuated influenza vaccine is contraindicated in sickle cell patients.[50]

Vaso-occlusive Complications

CASE 92-7

Question 1: J.T. is an 18-year-old male with sickle cell anemia who presented to the emergency department with rapid onset of abdominal pain and shortness of breath. During early childhood, he experienced several episodes of acute pain, swelling of the hands and feet, and jaundice. Three years before this admission, J.T. required a left hip replacement because of osteonecrosis caused by sickle cell anemia. Recently, frequent blood transfusions have reduced the frequency of sickling crises.

Physical examination reveals J.T. as a thin, Black male in acute distress and with scleral icterus. He has a pulse of 118 beats/minute, a respiratory rate of 17 breaths/minute, and a temperature of 98.8 °F (37.11 °C). His lungs are clear. Splenomegaly is noted, and a chest radiograph reveals only cardiomegaly.

A CBC is obtained. Notable results include the following:

Hgb, 5.9 g/dL
Hct, 27%
WBC count, 5000/μL
Platelets, 335,000/μL

Reticulocyte count, 1%
Bilirubin, 5.8 mg/dL
Serum creatinine, 3.1 mg/dL
Blood urea nitrogen, 54 mg/dL
The peripheral blood smear shows target cells with an occasional sickle cell.

What signs and symptoms are consistent with sickle cell anemia? What is J.T.'s current complication?

Vaso-occlusive crisis is caused by severe pain and organ damage. These may be precipitated by many factors including hypoxia, dehydration, infection, and pregnancy.[51] Based on the presence of splenomegaly, anemia, and sickled cells, J.T. currently is presenting with an acute splenic sequestration crisis. Acute splenic sequestration is caused by the trapping of RBCs within the spleen. This causes splenomegaly and progressive anemia. The low reticulocyte count is consistent with acute sequestration as a reticulocyte response would be expected if the anemia had developed in recent days. J.T.'s inadequate reticulocyte response may reflect rapid progression of the anemia, HPV B19 infection (a common cause of transient RBC aplasia, with up to 67% of infections resulting in a hematologic change typical of aplasia), or a blunted EPO response secondary to compromised renal dysfunction.

Case 92-7, Question 2: How should J.T. be treated?

J.T.'s signs and symptoms are sufficiently serious to justify transfusion therapy. The goal of transfusion in this setting is to correct hemoglobin levels to baseline and avoid hyperviscosity and cardiovascular sequelae.[51] In addition, J.T. should be adequately hydrated, considering his elevated serum creatinine and blood urea nitrogen. Because patients with sickle cell anemia often lose the ability to concentrate urine, they may become dehydrated, which further contributes to cell sickling. The pain associated with a crisis typically lasts at least 2 to 6 days and should be managed with analgesics, including parenteral opioids for severe pain. Pain control should be rapidly and aggressively instituted for J.T.'s comfort and

should be continued for a few days after hospital discharge. It is important not to withhold opioids because of a fear of addiction.[52]

Splenectomy may be indicated in instances of severe splenomegaly, repeated infarction, or pain in adults, and it is indicated when crises occur in children. Those patients with sickle cell anemia who are bedridden should be placed on anticoagulation to prevent vascular occlusions and deep vein thrombosis.

Case 92-7, Question 3: J.T. presents to the emergency department 3 months later with fever, cough, and severe throbbing pain in his chest and abdomen beginning 2 days prior. This is his third admission within the last year. Notable laboratory results include the following:

Hgb, 6.6 g/dL
Hct, 18.9%
Platelets, 218,000/μL
WBC, 19,700/μL
Bilirubin, 4.7 mg/dL
Serum creatinine, 1.1 mg/dL

His chest radiograph shows diffuse interstitial infiltrates in both lung fields. His vital signs are as follows: blood pressure, 98/53 mm Hg; heart rate, 102 beats/minute; respiratory rate, 23 breaths/minute; temperature, 101.4 °F (38.55 °C); and oxygen saturation, 93%. What complication of sickle cell disease is J.T. experiencing and how should he be treated for this condition?

J.T. is experiencing acute chest syndrome, a leading cause of morbidity and mortality in patients with sickle cell disease. The diagnosis of acute chest syndrome is determined by new pulmonary infiltrates on chest radiograph with one or more of the following: fever, cough, respiratory symptoms, worsening anemia, and pleuritic or nonpleuritic chest pain.[48] Causes of acute chest syndrome include pulmonary fat embolism, pulmonary infarction, and infection.[53] Commonly implicated organisms include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *S. pneumoniae*, *Haemophilus influenzae*, and various viruses.

The primary goal of treatment is to prevent progression to acute respiratory failure; therefore, treatment should involve pain management, hydration, oxygen supplementation, incentive

spirometry, antibiotics and, potentially, transfusion.[49,53] Optimal pain control and incentive spirometry are important to prevent hypoventilation and atelectasis, as well as to increase patient comfort. Oxygen should be administered nasally to patients who are moderately hypoxemic (O_2 saturation, 92%–95%; Pa_{O_2}, 70–80 mm Hg), as J.T. is. Patients who are febrile or severely ill should receive IV broad-spectrum antibiotics as it is difficult to exclude bacterial causes of acute chest syndrome. Empiric antibiotic therapy should consider the commonly implicated organisms described above.

Transfusions are used to increase the oxygen affinity of blood and are indicated in patients with worsening radiographic or clinical status, an Hgb 10% to 20% below baseline or below 5 g/dL, or hematocrit that is dropping.[44,53] J.T. should be monitored closely for deteriorating respiratory function and should receive transfusions if his clinical status does not improve.

TREATMENT FOR FREQUENT VASO-OCCLUSIVE CRISES

Case 92-7, Question 4: What preventive therapies exist for J.T. that will reduce occurrences of vaso-occlusive crises?

Currently, there are four FDA-approved agents for the treatment of sickle cell disease: their dosing and adverse effects are summarized in **Table 92-10**. Hydroxyurea, the oldest, is a first-line agent that increases fetal hemoglobin (HbF) synthesis, which has been found to decrease RBC sickling and the occurrence of disease-related complications.[44,51] In fact, patients with HbF levels >20% have been shown to experience a relatively mild or benign disease course with fewer vaso-occlusive crises.[51] Hydroxyurea is given prophylactically in patients with recurrent moderate-to-severe vaso-occlusive crises; not as an acute treatment. Guidelines recommend hydroxyurea for children (>2 years) and adult patients who have three or more sickle cell-associated moderate-to-severe pain crises in a 12-month period, severe or recurrent acute chest syndrome, chronic pain that interferes with quality of life, or symptomatic anemia.[48] These

recommendations are based on several clinical trials where hydroxyurea demonstrated improvement in the clinical course of patients with sickle cell anemia.[51] The use of hydroxyurea should be weighed for risk versus benefit because it is a cytotoxic agent. Monitoring of blood counts should occur to allow for dose adjustments of hydroxyurea based on efficacy and tolerability. Other adverse effects of hydroxyurea include fertility issues, GI effects (nausea, vomiting, diarrhea), dermatologic effects (maculopapular rash, pruritus), and potential risk of developing a secondary neoplasm (leukemia) with prolonged use.

Table 92-10
FDA-Approved Sickle Cell Anemia Therapies

Medication	Dose	Frequency	Route	Common Adverse Effects	Notes
Hydroxyurea	15–35 mg/kg (titrate to tolerated dose)	Once daily	Oral (tablet and liquid)	*Common:* Eczema (infants and children) Macrocytosis Neutropenia Infection	Take with food Dose reduction in patients with renal dysfunction
L-Glutamine	10–30 g	Twice daily	Oral powder	*Common:* None	Mix dose in 240 mL cold or room temperature beverage or with 4–6 oz of semisolid food (ie, applesauce, yogurt) Prepare immediately prior to administration
Voxelotor	1500 mg	Once daily	Oral tablet (including tablet for oral suspension)	*Common:* Abdominal pain Diarrhea Fatigue Fever Headache Nausea Skin rash	Dose reduction in patients with severe hepatic impairment (Child–Pugh C) Avoid concomitant use of strong or moderate CYP3A4 inducers.
Crizanlizumab	5 mg/kg	Every 2 weeks for first three doses then monthly	IV	*Common:* Arthralgia Back pain Fever Infusion-related reaction Nausea	Monitor for infusion-related reactions May interfere with automated platelet counts (platelet clumping); collect blood in citrate-containing tubes

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

More recently, three other medications have been approved for the treatment of sickle cell disease and may be given alone or with hydroxyurea. L-Glutamine is an amino acid used in the production of proteins. It is an oral therapy indicated for use in both children (>5 years) and adults with sickle cell disease. The exact mechanism is

unclear, but it may reduce oxidative injury, especially in times of stress when the body uses more glutamine.[44] Clinical studies showed that L-glutamine use reduced the frequency and severity of vaso-occlusive crises as well as hospitalizations.[44,48] It is given orally, does not require monitoring, and has minimal side effects but is quite costly, which introduces barriers to use.

Voxelotor, an HbS polymerization inhibitor, is approved for use in sickle cell patients ages 12 years and older. This oral therapy has been shown to improve anemia and decrease transfusion in patients. The data on the impact of the drug on vaso-occlusive events are mixed. The most common adverse events with voxelotor is mild-to-moderate arthralgia, headache, pain, nausea, and pain in the extremity.[54,55] Crizanlizumab is a monoclonal antibody that binds to P-selectin (a glycoprotein found on activated endothelial cells and platelets) to prevent the occurrence of vaso-occlusive crises. Results from a study investigating the use of crizanlizumab in patients with sickle cell disease showed that it significantly lowered the rate of sickle cell–related pain crises and was associated with fewer adverse events compared to placebo. More common adverse events associated with use include arthralgia, diarrhea, pruritus, vomiting, and chest pain.[56] Crizanlizumab is given as an intravenous infusion and is only approved in patients ages 16 years and older. Of note, none of the three more recent FDA-approved agents has been shown to alter end-organ damage or lesson symptoms other than pain.[44] Other areas of potential promise for the treatment of sickle cell anemia include bone marrow transplantation and gene therapy.[48]

IRON CHELATION THERAPY

CASE 92-7

QUESTION 5: Despite optimal treatment with hydroxyurea, J.T. continues to experience exacerbations of his sickle cell disease requiring blood transfusions. J.T. estimates he has required six such transfusions in the last 2 years and at least 25 units of blood in his lifetime. During a visit with his hematologist, J.T.'s serum ferritin is noted to be 1050 µg/L. What potential adverse effect of

treatment is the hematologist's concern? What other tests may be performed to detect this?

Transfusions are the mainstay of treatment for the majority of patients with sickle cell disease. Those requiring chronic transfusions of packed red blood cells (PRBCs) are at an increased risk for iron toxicity because of iron overload.[51] Normally, plasma iron binds with transferrin; however, if transferrin becomes saturated, patients will have higher levels of toxic nontransferrin-bound iron. As nontransferrin-bound iron increases, it deposits in other organs, most frequently the liver, and produces free radicals, causing tissue damage and fibrosis.

Patients with sickle cell disease should be monitored for iron overload. Obtaining a serum ferritin level is the most commonly used method of screening for iron overload, although the accuracy of this test is affected by inflammatory processes. Thus, serial serum ferritin values should be obtained when patients are not experiencing an acute crisis (ie, steady-state values). More specific tests, such as magnetic resonance imaging, measure iron levels in organs such as the heart, liver, pancreas, and spleen, although may not be routinely used because of cost.[51]

CASE 92-7

QUESTION 6: J.T. returns for continued assessment of iron overload. His repeat serum ferritin levels are 1357 and 1500 µg/L (3 months apart). Liver iron concentration is 7.8 mg/g dry weight. Does J.T. meet the criteria to receive iron chelation therapy? What options are available?

J.T. meets the criteria for iron chelation therapy because of his steady-state serum ferritin levels being consistently >1000 µg/L and his liver iron concentration being >7 mg/g dry weight.[49] Other considerations for a patient to receive iron chelation therapy include transfusion of ~100 mL/kg of PRBCs or 20 units for a 40-kg or more patient.

There are three iron chelators currently approved for use in patients with sickle cell disease. These agents work by binding free iron present in circulation and tissues. The iron is then excreted in the urine and bile.

Deferoxamine (DFO) and deferasirox have been studied in patients with sickle cell disease who are as young as 2 years old; deferiprone is approved for use in patients ages 8 years and more. Because of its short half-life, DFO must be administered for 5 days via continuous IV or subcutaneous infusion.[57] Deferasirox has a longer half-life, allowing for once-daily oral administration and enhanced patient convenience and adherence.[58] Deferiprone is also an oral agent and can be dosed two or three times per day.[59] In a meta-analysis looking at the effect of iron chelation therapy in sickle cell disease, its use resulted in better overall survival and event-free survival in transfusion-dependent patients. These outcomes were enhanced when iron chelation therapy was instituted early, and compliance was maintained. The analysis did not find any significant differences between the three available iron chelation agents; however, it showed that deferiprone is better tolerated than DFO, and compliance was improved with the two oral drugs.[60] Based on these data, deferiprone or deferasirox are appropriate for J.T. at this time.

J.T. should also receive appropriate monitoring consisting of serial serum ferritin levels and annual audiology and ophthalmology assessments as audiometric and retinal toxicity can be associated with overchelation. Patients receiving deferasirox should have serum creatinine monitored weekly for the first month after initiation or a dose alteration and monthly thereafter.[49] Because of the risk of agranulocytosis, ANC should be monitored weekly for the first 6 months of therapy, then every 2 weeks for the next 6 months, followed by every 2 to 4 weeks thereafter. Additionally, routine assessment of liver function tests should also be initiated for all patients receiving iron chelation therapy.

Other Complications of Sickle Cell Disease

NEUROLOGIC COMPLICATIONS

Neurologic complications are age dependent. Stroke most commonly occurs in the first decade of life, whereas intracerebral hemorrhage is a complication associated with adulthood. Primary prevention of stroke with RBC transfusions targeted to maintain HbS level <30% reduces the incidence of stroke in high-risk patients by 92%.[51] If a stroke occurs, ~50% of patients experience recurrent strokes within 3 years unless they are treated by chronic RBC transfusion therapy.[51]

RENAL AND GENITAL COMPLICATIONS

Renal and genital complications are common in sickle cell disease because the environment (hypoxic, acidotic, and hypertonic) predisposes the renal medulla or corpus cavernosum to infarction. As a result, patients might experience reduced potassium excretion, hyperuricemia, hematuria, hyposthenuria, and renal failure. Patients with renal disease generally have inappropriately low levels of EPO as well. Males experiencing occlusion of the corpus cavernosum can experience acute or chronic priapism. Conservative management includes IV fluid administration and pain control. Chronic unmanaged priapism increases the risk for erectile dysfunction and impotence.[44,48]

MICROINFARCTIONS

Microinfarctions often produce ophthalmic, hepatic, orthopedic, and obstetric/gynecologic complications as well. Patients with sickle cell anemia may require screening to detect these complications.[49]

ANEMIA OF INFLAMMATION

Anemia of inflammation (AI), also known as anemia of chronic disease, refers to a mild-to-moderate anemia that results from decreased RBC survival and production and generally occurs over

months to years.[61] It has been associated with a number of disorders (eg, autoimmune disorders, acute and chronic infections, chronic kidney disease, and malignancy). Because of the common occurrence of such conditions, AI is estimated to be the second most common anemia after iron deficiency. Most often, AI is a normochromic, normocytic anemia, although RBCs may be hypochromic and microcytic in some patients. A prominent feature of AI is the altered availability of iron, which is not reliably reflected in iron indices because of IL-6 and other cytokines stimulating an increase of hepcidin, a hormone that regulates iron homeostasis and influences iron absorption as well as the release of iron stores. Cytokines also result in an inadequate EPO response for the degree of anemia. A shortened RBC life span also contributes to AI, because of enhanced phagocytosis of RBC; this is because of enhanced “bystander” deposition of antibody and complement, mechanical damage to the RBC, and increased macrophage activation.

In AI, serum iron, transferrin saturation, and TIBC are low with an increased serum ferritin. Conversely, in iron deficiency anemia, serum iron, transferrin saturation, and serum ferritin are low with an increased TIBC. However, it is important to recognize that both forms of anemia may be seen concurrently.

Management of mild-to-moderate AI usually focuses on the underlying disease process. AI is not usually progressive or life-threatening but affects the quality of life. Patients may require blood transfusions for symptomatic anemia, which are associated with risks such as hepatitis, viral infections, iron overload, treatment-related acute lung injury, and immunogenic reactions. Unless a concurrent vitamin deficiency exists, administration of vitamin supplements for AI is not of value. Iron supplementation may be warranted in patients with a functional or absolute iron deficiency anemia. Erythropoiesis-stimulating agents (ESAs) have been used successfully to treat AI in patients with rheumatoid arthritis, acquired immunodeficiency syndrome (AIDS), malignancy, and chronic kidney disease; however, medication costs and safety risks, including

increased mortality, should be considered when selecting treatment.[61]

Erythropoietic Therapy

Erythropoietic therapy is indicated for use in anemia associated with chronic kidney disease, drug-induced anemia (see **Table 92-11**), and to reduce allogeneic RBC transfusions for elective noncardiac, nonvascular surgery.[62–64] Response to ESAs is dependent on dose and the underlying cause of anemia and may take days to weeks. Currently, there are two ESAs, epoetin alfa (Procrit®, Epogen®) and darbepoetin alfa (Aranesp®), approved for use in the United States. Darbepoetin differs from epoetin alfa by the addition of two carbohydrate chains, which result in decreased clearance and a serum half-life three times longer than that of epoetin alfa. These kinetic differences allow darbepoetin alfa to be administered less frequently (Table 92-11). Lack of response to erythropoietic therapy (ESA hyporesponsiveness) in all patient populations is most commonly associated with concurrent iron deficiency.

Table 92-11
Therapeutic Uses and Regimens for Recombinant Human Erythropoietin (rhEPO)[a]

	Epoetin Alfa		Darbepoetin Alfa	
Anemia Pathogenesis	**Dose (Units/kg)**	**Frequency**	**Dose (μg/kg)**	**Frequency**
Zidovudine-induced	100	Three times per week	—	—
Chemotherapy-induced	150 or 40,000 units (total dose)	Three times per week or once a week, respectively	2.25 or 500 μg (total dose)	Once a week or once every 3 weeks, respectively
Chronic kidney disease	50–100	Three times per week	On dialysis 0.45 or 0.75 Not on dialysis 0.45	Once a week or once every 2 weeks, respectively Once every 4 weeks

[a]Adult dosing.

Although some studies assessing the use of ESAs in the treatment of chronic kidney disease and chemotherapy-induced anemia (CIA) have shown decreased RBC transfusions, there is also evidence that use increases the risk for cardiovascular events, stroke or thrombosis, shortens overall survival, and/or increases the risk of

tumor progression or recurrence in some patient populations.[62–64] Health care providers are encouraged to discuss the risks and benefits of using ESAs with each patient prior to initiating use.

Luspatercept-aamt (Reblozyl®) is an erythroid maturation agent used to reduce RBC transfusion requirements in patients with β-thalassemia or in patients with low-intermediate risk myelodysplastic/myeloproliferative syndromes with ringed sideroblasts who have failed prior treatment with an ESA (see Chapter 96, Adult Hematologic Malignancies).[65] Similar to the ESAs, luspatercept-aamt should be titrated based on transfusion requirements and Hgb response and is not effective in the short-term (ie, should not be used as a substitution for patients needing immediate RBC transfusions). There is an increased risk of hypertension and thrombosis/thromboembolic events with this agent; thus, patients should continue to be closely monitored while receiving this therapy. Luspatercept-aamt must be administered by a health care provider, unlike the ESAs which may be self-administered.

Renal Insufficiency–Related Anemia

The cause of renal insufficiency–related anemia is complex but involves reduced EPO production and a shortened RBC life span. Repeated transfusions are a possible treatment but can lead to complications and should be avoided unless rapid Hgb correction is needed. Because EPO is secreted in the kidney in response to anoxia and is responsible for normal differentiation of RBCs from other stem cells, erythropoietic therapy is used to treat anemia in patients with renal failure who are undergoing hemodialysis.[66,67] A dose-dependent rise in Hct is observed in patients with end-stage renal disease at approved doses of epoetin alfa or darbepoetin alfa (see Table 92-11). Targeting higher concentrations of Hgb (>13 g/dL) is associated with increased mortality and adverse effects. An FDA-mandated black-box warning for these drugs states that treatment should be individualized to maintain use of the lowest dose of an

ESA necessary to decrease the need for transfusion.[62–64] This target Hgb differs from the current kidney disease guidelines.[66,67] Refer to Chapter 28, Chronic Kidney Disease, for further information on treatment target goals as well as the appropriate use of ESAs and IV iron in patients with renal insufficiency–related anemia.

Malignancy-Related Anemia

CASE 92-8

Question 1: P.M. is a 62-year-old female diagnosed with stage IV ovarian cancer. She is being seen for her fourth cycle of chemotherapy with carboplatin and paclitaxel. She reports shortness of breath and fatigue when she climbs stairs but otherwise has a good performance status. Her CBC indicates the following:

Hgb, 9.7 g/dL
Hct, 29%
MCV, 90 μm^3
Reticulocytes, 100 × $10^3/\mu L$

The peripheral smear shows normochromic and normocytic RBCs, and iron studies are within normal limits.

What is the most likely cause of P.M.'s anemia? What is the appropriate treatment?

P.M. appears to have malignancy-related anemia. Anemia occurs in up to 30% to 90% of patients with cancer.[68] The etiology is frequently complex with various attributing factors such as comorbidities, malignancy, blood loss, nutritional deficiencies, and treatment with radiation and/or chemotherapy.[68] CIA is the result of hematopoietic impairment affecting RBC production. Nephrotoxic effects of chemotherapy agents, such as platinum-containing agents, may decrease EPO production.[69] It is generally normocytic and normochromic and develops over the course of treatment. Factors that can influence the incidence of malignancy-related anemia in patients with cancer include type of malignancy and the stage and duration of disease; the type, schedule, and intensity of treatment;

and history of prior myelosuppressive chemotherapy or radiation. Cancer patients receiving chemotherapy should be routinely screened for CIA with a CBC. As per the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®), evaluation for CIA should begin at an Hgb ≤11 g/dL.[69] Additional tests, including a peripheral blood smear and reticulocyte count to detect other potential causes of anemia, should be performed.

Therapy should be directed to the underlying disease, if possible. When considering treatment options, transfusion with PRBCs should be used when rapid correction of Hgb is warranted with an expected 1 g/dL increase in Hgb and 3% increase in Hct with a single unit of PRBC. The use of transfusion for chronic management is associated with known risks, notably an increased risk of thromboembolic events in patients with cancer.[70] ESAs with or without iron supplementation should be considered for long-term management to reduce transfusion requirements. Large, randomized, multicenter trials have failed to show a clinical benefit to using ESAs in anemia that is not chemotherapy-induced. The reported increased risk of mortality and tumor progression in clinical trials of anemic patients with head and neck, breast, non-small-cell lung, lymphoid, and cervical cancers receiving ESAs resulted in a black-box warning being added to all ESA product information to advise about these and other increases in serious adverse events.[62–64] ESAs are recommended for anemic patients with cancer who are receiving myelosuppressive chemotherapy and the intent of treatment is not curative, with the possible exception of small-cell lung cancer as there are no clinical trials reporting a deleterious impact on survival.[70] As recommended by the FDA, treatment with an ESA should not be initiated unless the Hgb is <10 g/dL, and there is an additional 2 months of chemotherapy planned. The lowest dose needed to avoid RBC transfusion should be given, and use should be discontinued at the end of chemotherapy treatment.[62–64] Although response rates of 70% to 80% have been observed in clinical trials, not all patients will respond to treatment. The most common cause of nonresponse to erythropoietic therapy is absolute or functional iron

deficiency. Iron studies should be evaluated before and during therapy with supplementation given if needed; clinical trials show intravenous iron is superior when given with an ESA.[70]

In P.M.'s case, the clinician may choose from a number of anemia management options. The current course of chemotherapy can be delayed to allow for hematologic recovery and resolution of anemia symptoms. Alternatively, an RBC transfusion can be given to relieve her symptoms and allow her to better tolerate chemotherapy. Erythropoietic therapy could also be considered because the patient has metastatic disease and will continue on chemotherapy until disease progression. Treatment with an ESA dosed per Table 92-11 increases Hgb and decreases the need for blood transfusions and may be desired for P.M. Alternative dosing regimens, such as epoetin alfa 80,000 units every 2 weeks or 120,000 units every 3 weeks, or darbepoetin alfa 100 µg once weekly, 200 µg every 2 weeks, and 300 µg every 3 weeks, have proven to be safe and effective in terms of hematopoietic and transfusion effects.[70] Response of ESAs is monitored by measuring Hgb weekly until stabilization. During this time, the dose should be titrated to the lowest dose needed to avoid transfusion. A minimum of 2 weeks is required before an increase in RBCs is seen. A reduction in dose (25% for epoetin alfa and 40% for darbepoetin alfa) is required if there is >1 g/dL rise in the Hgb in any 2-week period or the Hgb reaches a level to avoid transfusion. If no response (<1 g/dL rise in Hgb and Hgb remains below 10 g/dL) is seen in 4 weeks with epoetin alfa or 6 weeks with darbepoetin alfa, a dose increase should be considered. The need for iron supplementation should also be assessed. Response should again be assessed at week 8 or 9 and appropriate dose reductions made based on Hgb level or transfusion avoidance. If no Hgb response is noted after 8 or 9 weeks of treatment or transfusions are still required, the drug should be discontinued.[62–64]

Human Immunodeficiency Virus–Related Anemia

Anemia is a common finding in patients with human immunodeficiency virus (HIV) and correlates with the severity of the disease as well as clinical outcomes.[71] In this patient population, anemia that has been identified is an independent prognostic factor for increased morbidity and mortality.[72] It has also been shown to be a marker of treatment failure in patients who do not achieve viral suppression and thus should be monitored as part of treatment.[73] Several factors may lead to the development of anemia in HIV patients, including infections, malignancies, the presence of genetic disorders of hemoglobin, nutritional deficiencies, and the use of combination antiretroviral therapy (ART). Examples of infections includes bacteria (*Mycobacterium avium* complex disease), fungus (histoplasmosis), and viruses (cytomegalovirus [CMV], herpes simplex viruses type 1 and 2, and HPV B19). The use of myelosuppressive combination antiretroviral therapy (cART) drugs such as zidovudine, zalcitabine, didanosine, lamivudine, and other medications often used to treat AIDS-associated illnesses (eg, bone marrow suppressive chemotherapy, ganciclovir, trimethoprim–sulfamethoxazole, dapsone) also contributes. Additionally, malignancies such as Kaposi sarcoma and lymphoma impair normal bone marrow function, predisposing these patients to anemia. Vitamin B_{12} deficiency is a contributing cause to anemia in up to one-third of patients and is correlated with progression to AIDS. Vitamin B_{12} malabsorption can result from HIV-infected mononuclear cells within the ileum and altered gastric mucosal functioning caused by infection.[74] Alterations in the utilization of vitamin B_{12} and folate can place a patient at risk for hematologic toxicity from drugs such as zidovudine and trimethoprim. Evidence suggests that actual virus may play a role in the pathophysiology, resulting in decreased erythropoiesis and erythropoietic response.[71] Common features of HIV-related anemia are comprised of a decreased reticulocyte count, morphologically normochromic and normocytic RBCs, adequate iron stores, and impaired response to EPO.[71]

Treatment for HIV-related anemia consists of erythropoietic therapy or removal of the offending drug, if possible. Erythropoietic

therapy has demonstrated increases in Hgb and quality of life in HIV-infected adult patients, regardless of drug therapy, $CD4^+$ count, or viral load.[71] Although no longer first-line treatment for HIV in the United States, zidovudine is still used in pregnant females and children as well as in developing countries. Its use is associated with the development of cytopenias, primarily anemia, that occur within 3 to 6 months of beginning the treatment.[75] Clinical studies show patients taking zidovudine who have baseline EPO levels <500 units/L experience a significant reduction in transfusion requirements.[76] Treatment with an ESA may be initiated in patients with zidovudine-induced anemia at 100 units/kg three times weekly. RBC indices should be closely monitored. If the Hgb exceeds 12 g/dL, then the dose should be held until it declines to <11 g/dL. At that time, a dose reduction of 25% or to the lowest dose necessary to prevent RBC transfusion is recommended. If a patient has no response after 8 weeks of therapy, the dose should be increased by 50 to 100 units/kg three times weekly at 4- to 8-week intervals or increased to 300 units/kg three times weekly. If no response is seen at a dose of 300 units/kg for 8 weeks, it is unlikely that the patient will benefit from further therapy and the drug should be discontinued.[62–64] Alternative once-weekly dosing with epoetin alfa has been evaluated at starting doses of 40,000 units.[63,64] The use of darbepoetin alfa has been assessed in patients with HIV receiving hemodialysis and is as safe and effective as epoetin alfa for treating anemia.[62]

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. *Clin Med Res*. 2006;4:236–241. (18)

Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health Syst Pharm*. 2012;69: 310–320. (17)

Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv*. 2020;4(*12*):2656–2701. (52)

Camaschella C. Iron deficiency. *Blood*. 2019;133(*1*):30–39. (3)

Hernandez CM. Advances in mechanisms, diagnosis, and treatment of pernicious anemia. *Discov Med*. 2015;19:159–168. (24)

Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. *Am J Kidney Dis*. 2013;62(*5*):849–859. (67)

National Comprehensive Cancer Network. NCCN guidelines for Hematopoietic Growth Factors v1. 2022. http://www.nccn.org (69)

Onimoe G, Rotz S. Sickle cell disease: a primary care update. *Cleve Clin J Med*. 2020;87(*1*):19–27. (48)

Pecker LH, Lanzkron S. Sickle cell disease. *Ann Intern Med*. 2021;174(*1*):ITC1–ITC16. (44)

Redig AJ, Berliner N. Pathogenesis and clinical implications of HIV-related anemia in 2013. *Hematol Am Soc Hematol Educ Program*. 2013;2013:377–381. (71)

Waldvogel-Abramowski S, Waeber G, Gassner C, et al. Physiology of iron metabolism. *Transfus Med Hemother*. 2014;41:213–221. (4)

Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet*. 2017;390(*10091*):311–323. (51)

Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. *Blood*. 2019;133(*1*):40–50. (61)

COMPLETE REFERENCES CHAPTER 92 ANEMIAS

1. Bergin JJ. Evaluation of anemia. Getting the most out of the MCV RDW and other tests. *Postgrad Med J*. 1985;77:253–254.
2. Dawson AA, Ogston D, Fullerton HW. Evaluation of diagnostic significance of certain symptoms and physical signs in anaemic patients. *Br Med J*. 1969;4:436–439.
3. Camaschella C. Iron deficiency. *Blood*. 2019;133(1):30–39.
4. Waldvogel-Abramowski S, Waeber G, Gassner C, et al. Physiology of iron metabolism. *Transfus Med Hemother*. 2014;41:213–221.

5. Alleyne M, Horne MK, Miller JL. Individualized treatment for iron-deficiency anemia in adults. *Am J Med*. 2008;121:943–948.
6. DeLoughery TG. Iron deficiency anemia. *Med Clin North Am*. 2017;101(2):319–332.
7. National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. National Academies Press; 2001.
8. Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010;126:1040–1050.
9. Zhu A, Kaneshiro M, Kaunitz JD. Evaluation and treatment of iron deficiency anemia: a gastroenterological perspective. *Dig Dis Sci*. 2010;55:548–559.
10. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet*. 2016;387(10021):907–916.
11. Iron-containing products. Facts & comparisons eAnswers. Accessed February 28, 2022. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5546092?cesid=arkajDFODNE&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Diron%252520containing%252520products%26t%3Dname%26va%3Diron%252520containing%252520products%26nq%3Dtrue
12. Cook JD, Reddy MB. Effect of ascorbic acid intake on nonheme-iron absorption from a complete diet. *Am J Clin Nutr*. 2001;73:93–98.
13. Centers for Disease Control and Prevention. Toddler deaths resulting from ingestion of iron supplements—Los Angeles, 1992–1993. *MMWR Morb Mortal Wkly Rep*. 1993;42(06):111–113.
14. Iron parenteral. Facts & comparisons eAnswers. Accessed February 28, 2022. https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5546093?cesid=9BtZ1dUL8Vx&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3DIron%252520parenteral%26t%3Dname%26va%3DIron%252520parenteral%26nq%3Dtrue
15. Reddy CM, Kathula SK, Ali SA, Bekal R, Walsh M. Safety and efficacy of total dose infusion of iron dextran in iron deficiency anaemia. *Int J Clin Pract*. 2008;62:413–415.
16. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant*. 2006;21:378–382.
17. Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health Syst Pharm*.

2012;69:310–320.
18. Aslinia F, Mazza JJ, Yale SH. Megaloblastic anemia and other causes of macrocytosis. *Clin Med Res*. 2006;4:236–241.
19. Kaferle J, Strzoda CE. Evaluation of macrocytosis. *Am Fam Physician*. 2009;79:203–208.
20. Langan RC, Zawistoski KJ. Update on vitamin B_{12} deficiency. *Am Fam Physician*. 2011;1425:1425–1430.
21. Stabler SP. Vitamin B_{12} deficiency. *N Engl J Med*. 2013;368:149–160.
22. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and Its Panel on Folate, Other B Vitamins, and Choline. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*. National Academies Press (US); 1998.
23. Bizzaro N, Antico, A. Diagnosis and classification of pernicious anemia. *Autoimmun Rev*. 2014;13:565–568.
24. Hernandez CM. Advances in mechanisms, diagnosis, and treatment of pernicious anemia. *Discov Med*. 2015;19:159–168.
25. Hvas AM, Nexo E. Diagnosis and treatment of vitamin B_{12} deficiency. An update. *Haematologica*. 2006;91:1506–1512.
26. Dali-Youcef N, Andrès E. An update on cobalamin deficiency in adults. *QJM*. 2009;102:17–28.
27. Lahner E, Annibale B. Pernicious anemia: new insights from a gastroenterological point of view. *World J Gastroenterol*. 2009;15:5121–5128.
28. Cyanocobalamin. Facts & comparisons eAnswers. Accessed February 28, 2022. https://fco.factsandcomparisons.com/lco/action/search?q=Cyanocobalamin&t=name&va=Cyanocobalamin
29. Butler CC, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B_{12} versus intramuscular vitamin B_{12} for vitamin B_{12} deficiency: a systematic review of randomized controlled trials. *Fam Pract*. 2006;23:279–285.
30. Lane LA, Rojas-Fernandez C. Treatment of vitamin B(12)-deficiency anemia: oral versus parenteral therapy. *Ann Pharmacother*. 2002;36:1268–1272.
31. Adachi S, Kawamoto T, Otsuka M, Todoroki T, Fukao K. Enteral vitamin B_{12} supplements reverse postgastrectomy B_{12} deficiency. *Ann Surg*. 2000;232:199–201.
32. von Drygalski A, Andris DA. Anemia after bariatric surgery: more than just iron deficiency. *Nutr Clin Pract*. 2009;24:217–226.
33. Love AL, Cornwell PL, Whitehouse SL. Obesity, bariatric surgery, and iron deficiency: true, true, true, and related. *Am J Hematol*. 2008;83:403–409.
34. Allied Health Sciences Section Ad Hoc Nutrition Committee. ASMBS allied health nutritional guidelines for the surgical weight loss patient. *Surg Obes*

Relat Dis. 2008;4:S73–S108.
35. Herbert V. Recommended dietary intakes (RDI) of folate in humans. *Am J Clin Nutr*. 1987;45:661–670.
36. Folic acid and derivatives. Facts & comparisons eAnswers. Accessed February 28, 2022. https://fco.factsandcomparisons.com/lco/action/search?q=Folic%20Acid&t=name&va=Folic%20Acid
37. Kornberg A, Segal R, Theitler J, Yona R, Kaufman S. Folic acid deficiency, megaloblastic anemia and peripheral polyneuropathy due to oral contraceptives. *Isr J Med Sci*. 1989;25:142–145.
38. McKinsey DS, Durfee D, Kurtin PJ. Megaloblastic pancytopenia associated with dapsone and trimethoprim treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. *Arch Intern Med*. 1989;149:965.
39. [No authors listed]. Hereditary dihydrofolate reductase deficiency with megaloblastic anemia. *Nutr Rev*. 1985;43:309.
40. Chanarin I. Megaloblastic anaemia, cobalamin, and folate. *J Clin Pathol*. 1987;40:978–984.
41. Snow CF. Laboratory diagnosis of vitamin B_{12} and folate deficiency: a guide for the primary care physician. *Arch Intern Med*. 1999;159:1289–1298.
42. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376(16):1561–1573.
43. Howard J. Sickle cell disease and other hemoglobinopathies. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 26th ed. Elsevier; 2020:154, 1061–1069.e1.
44. Pecker LH, Lanzkron S. Sickle cell disease. *Ann Intern Med*. 2021;174(1):ITC1–ITC16.
45. Centers for Disease Control and Prevention. Sickle cell disease. Accessed February 28, 2022. https://www.cdc.gov/ncbddd/sicklecell/data.html#:~:text=SCD%20affects%20approximately%20100%2C000%20Americans,sickle%20cell%20trait%20(SCT)
46. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. *Int J Infect Dis*. 2010;14:e2–e12.
47. Cober MP, Phelps SJ. Penicillin prophylaxis in children with sickle cell disease. *J Pediatr Pharmacol Ther*. 2010;15(3):152–159.
48. Onimoe G, Rotz S. Sickle cell disease: a primary care update. *Cleve Clin J Med*. 2020;87(1):19–27.
49. National Institutes of Health; National Heart, Lung, and Blood Institute Division of Blood Diseases and Resources. Evidence-based management of sickle cell disease: Expert Panel Report, 2014. Accessed February 28, 2022. https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease
50. Centers for Disease Control and Prevention. Recommended child and adolescent immunization schedule for ages 18 years or younger 2022.

Accessed February 28, 2022. https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

51. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet*. 2017;390(10091):311–323.
52. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv*. 2020;4(12):2656–2701.
53. Friend A, Girzadas D. Acute chest syndrome. [Updated June 24, 2021]. In: *StatPearls* [Internet]. StatPearls Publishing; January 2022. Accessed February 28, 2022. https://www.ncbi.nlm.nih.gov/books/NBK441872/
54. Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. *Blood*. 2016;127(7):820–828.
55. Achebe M, Hassab H, Alkindi S, et al. Long-term safety and efficacy of voxelotor for patients with sickle cell disease: results from an open-label extension of the phase 3 HOPE trial. *Blood*. 2021;138(suppl 1):3114.
56. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017;376(5):429–439.
57. Desferal. Package insert. Novartis Pharma Stein AG; 2008.
58. Jadenu. Package insert. Novartis Pharmaceutical Corporation; 2020.
59. Ferriprox. Package insert. Apotex Inc; 2021.
60. Ballas SK, Zeidan AM, Duong VH, DeVeaux M, Heeney MM. The effect of iron chelation therapy on overall survival in sickle cell disease and β-thalassemia: a systematic review. *Am J Hematol*. 2018;93(7):943–952.
61. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. *Blood*. 2019;133(1):40–50.
62. Aranesp (darbepoetin alfa). Prescribing information. Amgen; 2019.
63. Procrit (epoetin alfa). Prescribing information. Amgen; 2018.
64. Epogen (epoetin alfa). Prescribing information. Amgen; 2018.
65. Reblozyl (luspatercept-ammt). Prescribing information. Celgene Corporation; 2020.
66. Kidney Disease Improving Global Outcomes. KDIGO clinical practice guidelines for anemia in chronic kidney disease. Accessed February 28, 2022. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf
67. Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. *Am J Kidney Dis*. 2013;62(5):849–859.
68. Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management and use of treatment guidelines and protocols. *Am J Health Syst Pharm*. 2017;64:S5-S13.

69. National Comprehensive Cancer Network. NCCN guidelines for Hematopoietic Growth Factors v1. 2022. Accessed February 28, 2022. http://www.nccn.org
70. Khoranna AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusions. Thrombosis, and mortality in hospitalized patients with cancer. *Arch Intern Med*. 2008;168:2377–2381.
71. Redig AJ, Berliner N. Pathogenesis and clinical implications of HIV-related anemia in 2013. *Hematol Am Soc Hematol Educ Program*. 2013;2013:377–381.
72. Mocroft A, Kirk O, Barton SE, et al. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA study group. *AIDS*. 1999;13:943–950.
73. Anude CJ, Eze E, Onyegbutulem HC, et al. Immuno-virologic outcomes and immune-virologic discordance among adults alive and on anti-retroviral therapy at 12 months in Nigeria. *BMC Infect Dis*. 2013;13:113.
74. Layden AJ, Finkelstein JL. B-vitamins and HIV/AIDS. In: Mehta S, Finkelstein JL, eds. *Nutrition and HIV: Epidemiological Evidence to Public Health*. CRC Press; 2018:27–87.
75. Sharma SK. Zidovudine-induced anaemia in HIV/AIDS. *Indian J Med Res*. 2010;132:359–361.
76. Fischl M, Galpin JE, Levine JD, et al. Recombinant human erythropoietin for patients with AIDS treated with zidovudine. *N Engl J Med*. 1990;322:1488–1493.

93

Neoplastic Disorders and Their Treatment: General Principles

Michael Frei, Donyika Joseph, Kaiwen Wang, and Chelsea Wong

CORE PRINCIPLES		CHAPTER CASES
1	Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. Tumor metastases to distant sites generally have a greater effect than the primary tumor on the frequency of complications and the patient's quality of life and mortality.	**Case 93-1 (Question 1)**
2	Avoiding known risk factors may prevent cancer. Cancer may also be prevented by appropriate use of vaccines and chemoprevention in selected groups of high-risk patients.	**Case 93-2 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
3	The histologic diagnosis of a tumor is the most important determinant of how a malignancy will be treated. The stage of cancer and the diagnosis influence the treatment and prognosis. As part of staging, diagnostic imaging facilitates identification of disease metastases.	**Case 93-3 (Question 1)**
4	The initial signs and symptoms of malignant disease are variable and depend on histology, location, and tumor size. This may influence treatment options if they affect performance status, which is a measure of a patient's functional capacity.	**Case 93-4 (Question 1)**
5	Cancer is predominately treated with three modalities: surgery, radiation, and systemic therapy. The goal of therapy should always be to cure the patient when possible.	**Case 93-5 (Question 1)**
6	Biochemical resistance to chemotherapy is the major impediment to successful treatment with most cancers. Resistance can occur de novo in cancer cells or develop during cell division as a result of mutation.	**Case 93-6 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
7	There are different types of systemic therapy: chemotherapy, targeted agents, endocrine therapy, and biologic response modifiers. Systemic therapy may be used in varying combinations and different settings. Use depends on histology, cancer stage, and the patient's predicted tolerance of the treatment.	**Case 93-7 (Question 1) Case 93-8 (Question 1) Case 93-9 (Question 1)**
8	Response to treatment is assessed by evaluating therapy's antitumor and toxic effects, including impact on the patient's overall quality of life. Evaluation should occur at scheduled intervals and include physical examination, laboratory tests, and repeat diagnostic imaging.	**Case 93-10 (Question 1)**
9	Systemic therapies used to treat cancer are potentially carcinogenic, teratogenic, or mutagenic. Handling and administering these agents poses a risk to health care workers. Appropriate policies and procedures must be in place to maximize safety and minimize risk while following national guidelines and standards.	**Case 93-11 (Questions 1–4)**

INTRODUCTION

Cancer (neoplasm, tumor, or malignancy) is not a single disease. It is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. Cancer cells do not respond to the normal processes that regulate cell growth, proliferation, and survival; and they cannot carry out the physiologic functions of their normal counterparts. Other characteristics of cancer cells include their ability to invade adjacent normal tissues and break away from the primary tumor (metastasize) and travel through the blood or lymph to establish new tumors (metastases) at a distant site. Their ability to stimulate the formation of new blood vessels (angiogenesis) and their endless replication potential further contribute to their continued growth and survival.[1] Cancers can arise in any tissue in the body. If cancer cells are allowed to grow uncontrollably, they can eventually result in the death of the patient.

Cancer Statistics

Each year, the American Cancer Society (ACS) publishes an estimate for the number of new cases and number of cancer-related deaths. The National Cancer Institute publishes cancer statistics that include cancer risk, prevalence, and survival information.[2] It is estimated that 40% of men and 38% of women will eventually develop cancer and that approximately 1,918,030 new cases of cancer will be diagnosed in 2022.[3] The most common cancers and causes of cancer-related deaths in adult Americans are listed in **Table 93-1**. The incidence of cancer and cancer-related deaths can be affected by both age and ethnic background, with the incidence greater in the elderly, African American males, and Caucasian females.[3] Other factors that affect an individual's risk of developing cancer include environmental and lifestyle factors, genetic predisposition, and exposure to carcinogens.[4]

Table 93-1
Estimated Sites of New Cancer Cases and Deaths in the United States, 2022

Estimated New Cases			
Males		**Females**	
Prostate	268,490 (27%)	Breast	287,850 (31%)
Lung and bronchus	117,910 (12%)	Lung and bronchus	118,830 (13%)
Colon and rectum	80,690 (8%)	Colon and rectum	70,340 (8%)
Urinary bladder	61,700 (6%)	Uterine corpus	65,950 (7%)
Melanoma of the skin	57,180 (6%)	Melanoma of the skin	42,600 (5%)
Kidney and renal pelvis	50,290 (5%)	Non-Hodgkin lymphoma	36,350 (4%)
Non-Hodgkin lymphoma	44,120 (4%)	Thyroid	31,940 (3%)
Oral cavity and pharynx	38,700 (4%)	Pancreas	29,240 (3%)
Leukemia	35,810 (4%)	Kidney and renal pelvis	28,710 (3%)
Pancreas	32,970 (3%)	Leukemia	24,840 (3%)
All sites	**983,160 (100%)**	**All sites**	**934,870 (100%)**
Estimated Deaths			
Males		**Females**	
Lung and bronchus	68,820 (21%)	Lung and bronchus	61,360 (21%)
Prostate	34,500 (11%)	Breast	43,250 (15%)
Colon and rectum	28,400 (9%)	Colon and rectum	24,180 (8%)
Pancreas	25,970 (8%)	Pancreas	23,860 (8%)
Liver and intrahepatic bile duct	20,420 (6%)	Ovary	12,810 (4%)
Leukemia	14,020 (4%)	Uterine corpus	12,550 (4%)
Esophagus	13,250 (4%)	Liver and intrahepatic bile duct	10,100 (4%)
Urinary bladder	12,120 (4%)	Leukemia	9980 (3%)
Non-Hodgkin lymphoma	11,700 (4%)	Non-Hodgkin lymphoma	8550 (3%)
Brain and other nervous system	10,710 (3%)	Brain and other nervous system	7570 (3%)
All sites	**322,090 (100%)**	**All sites**	**287,270 (100%)**

Adapted from Siegel RL, Miller KD, Jemal A, et al. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. © 2020 American Cancer Society. Reprinted by permission of John Wiley & Sons, Inc.

Etiology

Cancers arise from the transformation of a single normal cell. Damage or mutation to the cell's DNA is caused by an initial "event." These events may include lifestyle, environmental, or occupational factors, as well as some medical therapies (eg, cytotoxic chemotherapy and immunosuppressive or radiation therapy) and hereditary factors. Cigarette smoking is probably the single largest factor that contributes to cancer development, responsible for ~30% of cancer deaths per year. Other preventable causes, including physical inactivity, obesity, and nutrition, are estimated to cause an

additional 30% of cancer deaths per year.[5] An estimated 2 million skin cancers diagnosed yearly are also potentially preventable with adequate skin protection.[6]

Cancer is a genetic disease. Two gene classes, oncogenes and tumor suppressor genes, are important in the pathogenesis of cancer. Damage to cellular DNA can result in mutations that lead to the development of oncogenes and loss or inactivation of tumor suppressor genes. Oncogenes are genes whose overactivity or presence in certain forms can lead to the development of cancer. Oncogenes arise from normal genes called proto-oncogenes through genetic alterations such as chromosomal translocations, deletions, insertions, and point mutations.

Growth and proliferation of normal cells are influenced by proteins, known as *growth factors*. When growth factors bind to receptors on the cell surface, they activate a series of enzymes within the cell that stimulate cell signaling pathways and gene transcription. These genes encode for proteins that regulate cell growth and proliferation. The coordination and integration of cellular signaling processes are referred to as *signal transduction*. Proto-oncogenes are responsible for encoding several components of signal transduction pathways, including growth factors, growth factor receptors, signaling enzymes, and DNA transcription factors. Abnormal forms or excessive quantities of these stimulatory proteins disrupt normal cell growth signaling pathways, leading to excessive growth and proliferation and, ultimately, a malignant transformation.

Tumor suppressor genes are normal genes that encode for proteins that suppress inappropriate cell division or growth. Gene deletions or mutations can cause these proteins to become inactivated, eliminating the normal inhibition of cell division. Alterations in a third class of genes, DNA repair genes, are also implicated in cancer. DNA repair genes encode for proteins that correct errors that may arise during DNA duplication. Mutations in these genes further contribute to the accumulation of genetic changes that promote cancer progression.

Cancer development is a multistep process. Therefore, multiple genetic mutations, including activation of oncogenes and loss or

inactivation of tumor suppressor genes within a cell, are necessary for malignant transformation.[7] Additional genetic changes are required for tumor invasion of normal tissues and metastases.

Tumor Growth

Cell Cycle

Cancer cells, similar to normal cells, proceed through a specific and orderly set of events during cellular replication referred to as the *cell cycle* (**Fig. 93-1**). The cell cycle contains four phases (M, G_1, S, and G_2), each responsible for a different task necessary for cell division. During the first activity phase, the M phase, the cell undergoes mitosis, the process of cell division. After mitosis, the cell enters the first gap or resting phase (G_1). During the G_1 resting (or gap) phase, the cell makes the enzymes necessary for DNA synthesis. The synthesis of DNA occurs during the S phase. After the S phase, the cell enters a second resting phase (G_2). RNA and other proteins are synthesized to prepare for cell division during the M phase. Cells that complete mitosis may either continue to proceed through the cell cycle to divide again, differentiate or mature into specialized cells and eventually die, or enter a third resting phase called G_0.[8]

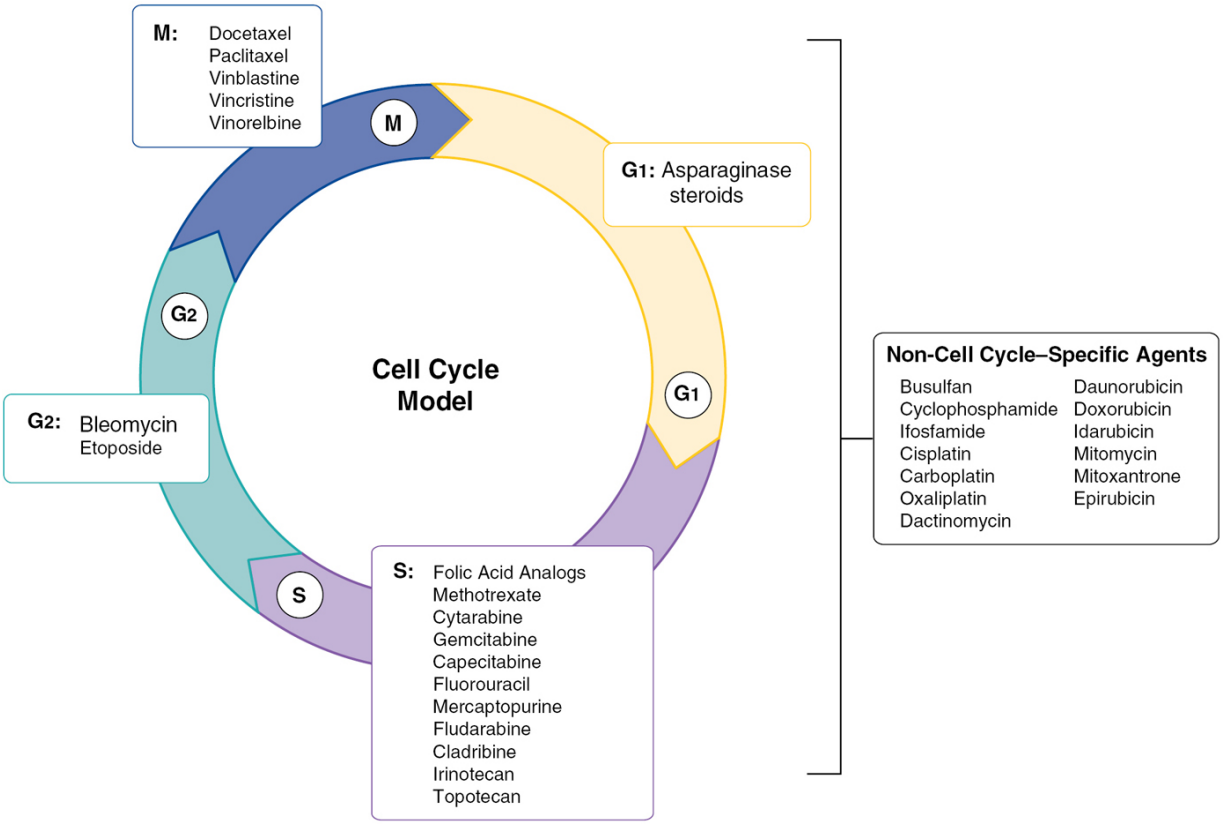


Figure 93-1 Cell cycle and effects of representative cytotoxic drugs on phases of the cell cycle.

Proliferation of normal cells is carefully controlled to balance the loss of mature functional cells with the production of new cells. As mentioned, proto-oncogenes and tumor suppressor genes provide the stimulatory and inhibitory signals, respectively, that regulate the cell cycle. The transition of cells through the cell cycle is an ordered, tightly regulated process, which involves a series of checkpoints that assess these signals and the number and integrity of the cells.[8] Cyclins, a group of interacting proteins found in the nucleus, and cyclin-dependent kinases (CDKs) make up the molecular machinery that regulates the passage of cells through various phases of the cell cycle. The cyclins combine with CDKs to form complexes that act as molecular switches. One of these molecular switches regulates whether a cell moves through a critical restriction point that occurs late in the G_1 phase to S phase. If insufficient amounts of cyclins or CDKs are present during the G_1 phase, the cell will not enter the S

phase to start cell division. Cells that pass through this restriction point are irreversibly committed to the next phase of the cell cycle.[8] A decline in the level of the CDK complex signals the end of the phase. The balance of regulation of cyclins and CDKs is influenced by several factors, including cyclin gene transcription, cyclin degradation, CDK inhibitors, and the transfer of phosphate groups to various proteins and enzymes. Activating signals from the cell's external environment are transmitted to the nucleus via growth factor receptor signaling pathways, which influence the formation of cyclins and cyclin–CDK complexes. The complexes generate phosphate groups from molecules of adenosine triphosphate (ATP) and transfer them to a protein called a *retinoblastoma protein* (pRb). If pRb acquires enough phosphate groups, it will release the transcription factors the cell needs to make proteins essential for a cell division. In other words, phosphorylated pRb promotes cell cycle progression from G_1 to S and, subsequently, cell division. Other signaling pathways inhibit cell proliferation through endogenous CDK inhibitors, which result in dephosphorylated pRb.

In cancer cells, the regulation and function of cyclins, CDK, and inhibitory proteins may be disrupted by malignant transformation, or these proteins can undergo changes that cause malignant transformation. Examples of defects in these processes include deletion of the *Rb* gene, a tumor suppressor gene that encodes for pRb, and dysregulation of the CDK through overactivation or loss of CDK inhibitors.[9] When pRb becomes inactive, excessive cell proliferation can occur. In normal cells, the *p53* gene is responsible for temporarily arresting cell growth in response to biochemical or molecular damage until the DNA damage can be repaired.[10] If the damage cannot be repaired, apoptosis (programmed cell death) occurs to prevent genetically damaged cells from growing uncontrollably. Loss or mutation of a second tumor suppressor gene, *p53*, is also common in human cancers and is associated with the resistance of cancer cells to undergo cell cycle arrest or apoptosis.

Carcinogenesis

Carcinogenesis is the process by which normal cells are transformed into cancer cells. If the balance of stimulatory and inhibitory growth signals becomes dysregulated, carcinogenesis may occur. In carcinogenesis, normal mechanisms such as apoptosis and senescence (aging) do not function properly and cannot control excessive cell division. Because abnormalities in the proto-oncogenes and tumor suppressor genes regulating these processes are present in cancer cells, the balance between cell renewal and loss of mature (senescent) cells is disrupted. Cancer cells are also less dependent on receiving stimulatory signals from external growth factors.[10] Furthermore, cancer cells possess unlimited replication potential, owing to their ability to activate telomerase.[1,11] Telomerase is an enzyme that synthesizes sequences of telomeres, thereby enabling cells to proliferate endlessly. The expression of telomerase in most normal human cells is suppressed but is reactivated in most cancer cells.[10,11] Telomeres are repeats of DNA and DNA-binding proteins that form the ends of eukaryotic chromosomes.[11] Telomere loss occurs with each successive cell replication, and after a critical length is reached, the cell undergoes irreversible growth arrest (replicative senescence).[11] Unlike normal cells, in which a finite telomere sequence regulates their life span, cancer cells are capable of immortality through their ability to maintain their telomeres indefinitely.

Metastasis

CASE 93-1

Question 1: S.T., a 16-year-old boy, presented to the emergency department with a painful, swollen right leg. X-ray examination confirmed a fracture that appeared to be caused by a tumor mass in the bone. Biopsy of the bone mass confirmed osteogenic sarcoma. A chest x-ray study showed three nodules that were also believed to be malignant tumors.

Does S.T. also have lung cancer or are the tumors in S.T.'s lungs metastases from the sarcoma in his leg?

S.T. does not have lung cancer. Tumor nodules in his lung are most likely metastases from the sarcoma in his leg. The ability of cancer cells to disseminate and form metastases represents their most malignant characteristic. Tumor metastases to distant sites generally have a greater effect than does the primary tumor on the frequency of complications and patient's quality of life. Metastases also have a greater impact than does the primary tumor on mortality, with metastases associated with most cancer-related deaths. Consequently, individuals diagnosed with metastases face a worse prognosis.

Cancer cells must develop new blood vessels to obtain nutrients and spread to distant sites (metastasize). In response to low oxygen supply (hypoxia) and other factors, cancer cells and surrounding tissues secrete growth factors that stimulate the growth of new blood vessels (angiogenesis) from existing blood vessels in surrounding normal host tissue. Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF) are growth factors needed for sustained endothelial cell growth. Once released by tumor cells, these growth factors bind to tyrosine kinase receptors on the surface of endothelial cells of existing blood vessels and activate a series of intracellular relay proteins that transmit signals to genes in the nucleus to produce factors required for new endothelial cell growth.[12] Once older endothelial cells become activated by growth factors, they begin making matrix metalloproteinase (MMP) enzymes. These enzymes destroy the extracellular matrix of surrounding cells, allowing older endothelial cells to invade the extracellular matrix and begin cell division.[12] This process of invasion and proliferation is repeated several times until new blood vessels are formed.

Tumor cells can use these newly formed blood vessels to facilitate their spread to distant locations. Cells must break away from the primary tumor and travel to other sites in the body to form metastases. Normally, cells adhere to one another and the extracellular matrix. The cell-to-cell adhesion molecules are called *cadherins*, and the cell-to-extracellular matrix molecules are called

integrins. In cancer cells, these molecules are often absent, allowing tumor cells to easily move away from the primary tumor mass.

Once a tumor cell leaves the primary mass, it travels through the blood vessels and lymphatic system within the body to form metastatic site(s). Usually, tumor cells spread to the first capillary bed they encounter after their release from the primary tumor. If the primary site drains its blood supply into the vena cava, the cancer cells will reach the capillary bed in the lung. Similarly, if the primary site drains its blood supply into the portal circulation, the cancer cells will reach the capillary bed in the liver. In addition, cancer cells can potentially pass through the first capillary bed they encounter and enter the arterial circulation where they can distribute to other organs and tissues throughout the body.

Growth conditions (eg, growth factors and physiologic conditions) within a tissue or organ also can determine the location of a metastatic site. After a cancer cell establishes a metastatic site, it must again undergo angiogenesis to ensure continued growth. Together, angiogenesis and hematogenous or lymphatic spread help cancer cells invade healthy tissues and increase morbidity and mortality associated with the disease.

Prevention of Cancer

Tobacco

Cigarette smoking is probably the single largest factor that contributes to cancer development, increasing the risk of multiple cancer types including lung, head and neck, gastrointestinal, bladder, and cervical cancers.[5] Therefore, tobacco cessation and abstinence play an important role in the prevention of cancer. For more information, visit the following page on the ACS website: https://www.cancer.org/cancer/cancer-causes/tobacco-and-cancer.html. For a review of tobacco dependence and methods for cessation, see Chapter 91, Tobacco Use and Dependence.

CHEMOPREVENTION

Chemoprevention is the use of a drug or substance to reverse, inhibit, or prevent the development of cancer. Use of chemoprevention is helpful in selected groups of high-risk patients with breast, colorectal, and prostate cancers.[13] For a discussion of chemoprevention for these cancers, see Chapter 97, Breast Cancer, Chapter 99, Colorectal Cancer, and Chapter 100, Prostate Cancer.

HUMAN PAPILLOMA VIRUS VACCINES

CASE 93-2

QUESTION 1: M.M., a 44-year-old female, asks you about vaccines to prevent cervical cancer.

Should M.M. consider vaccination for her daughter or her son? Would this substitute for Papanicolaou (Pap) smear screening for her daughter?

The human papillomavirus (HPV) is primarily transmitted through sexual contact; serotypes 16 and 18 (HPV-16, 18) cause ~70% of cervical cancers.[14] There is only one HPV vaccination being distributed in the United States, HPV 9-valent vaccine (Gardasil® 9), which is administered over the course of 6 months. The vaccine protects against HPV strains 6, 11, 16, 18, 31, 33, 45, 52, and 58. The vaccine has demonstrated efficacy in reducing the incidence of cervical intraepithelial neoplasia (CIN), a premalignant lesion that can lead to cervical cancer.[15,16] Because the progression of HPV infection to invasive cervical cancer requires several years to possibly decades, CIN is utilized as a surrogate efficacy end point in HPV vaccine clinical trials. It is anticipated that the use of HPV vaccines will ultimately lead to a reduction in the incidence of cervical cancer.

Gardasil® 9 is also approved for the prevention of vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN) in females, as well as prevention of HPV-related genital warts and anal cancer in males. However, there are no data to support the use of these vaccines to prevent other cancers associated with HPV, such as penile cancer or head and neck cancers.[16]

Routine Pap smear and HPV screening should continue for vaccinated females because the vaccines do not prevent all oncogenic types of HPV. The duration of vaccine-induced anti-HPV immunity is also unknown.

M.M. should consider HPV vaccination for her daughter. The vaccine is indicated in females of ages 9 to 45 years, but the vaccines are most effective if initiated before sexual activity. Whether or not M.M.'s daughter is vaccinated, she should still receive routine Pap smear screening according to current guidelines.[17] The HPV 9-valent vaccine is approved in males ages 9 to 45 years; therefore, M.M. should also consider vaccination for her son. The Centers for Disease Control recommends HPV vaccination for all females and males at the age of 11 to 12 years.[18]

DIET

Diet has been linked to the development of colon and breast cancers. The ACS advocates a healthy diet that consists of vegetables, fruit, whole grains, and fiber and is low in fat and red meat.[19] For more information, visit the following page on the ACS website: https://www.cancer.org/healthy/eat-healthy-get-active/acs-guidelines-nutrition-physical-activity-cancer-prevention/guidelines.html.

Migrant studies suggest that diet, environmental, or social factors play a role in the development of prostate cancer and that the incidence of colon cancer in a population increases as individuals migrate from a low-incidence region to a high-incidence region.[20,21] In females, the risk of breast cancer is increased with obesity, but an association with a high-fat diet is less clear.[22] Moderate alcohol consumption has also been associated with an increased risk of breast cancer.[23]

SUN AND ULTRAVIOLET RADIATION EXPOSURE

Most risk factors associated with skin cancer are uncontrollable, with the exception of sun exposure and other forms of ultraviolet (UV) radiation. The interaction between UV radiation and skin cancers is

complex because nonmelanomas (eg, basal cell and squamous cell carcinomas) are associated with cumulative UV radiation exposure, and certain cutaneous melanomas are associated with excessive, intermittent UV radiation exposure.[24] The risk of melanoma is further increased in people who have a history of five or more severe sunburns in their lifetime, particularly during adolescence, or history of tanning bed use.[24,25] Depletion of the ozone layer in the stratosphere may also contribute to the increased incidence of melanoma.[24]

Prevention of skin cancer is based on limiting sun and UV radiation exposure. The ACS guidelines recommend avoiding or limiting sun exposure from 10:00 AM to 4:00 PM when the UV rays are the strongest and avoiding tanning bed or sun lamp use. Protective clothing (hat, sunglasses, long-sleeved shirt, and pants) and sunscreen are also advised to minimize exposure.[25] However, the protective effects of sunscreen alone against melanoma, particularly for intentional sun exposure, are controversial and should not be used to prolong time in the sun.[25,26]

Screening and Early Detection of Cancer

Standardized screening tests help identify disease in asymptomatic individuals (screening) or diagnose disease in symptomatic individuals (early detection). The cancer screening tests recommended by the ACS meet four basic requirements: (a) there must be good evidence that the test is effective in reducing morbidity or mortality; (b) benefits of the test should outweigh its risks; (c) costs of the test should be in balance with its presumed benefits; and (d) the test should be practical and feasible within the existing health care setting. For more information, visit the following page on the ACS website: http://www.cancer.org/Healthy/FindCancerEarly/CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer.

Screening guidelines are updated frequently, and newest guidelines should be consulted when counseling patients. Professional organizations including the ACS (http://www.cancer.org) and National Comprehensive Cancer Network (NCCN; http://www.nccn.org) regularly publish recommendations for screening of breast, cervical, colon, lung, and prostate cancers.[27]

Diagnosis and Staging of Cancer

The histologic diagnosis of a tumor is the most important determinant of treatment selection. This is because its histologic classification influences its natural history, pattern of progression, and responsiveness to treatment. A biopsy followed by a microscopic and biochemical evaluation by a pathologist can provide the most accurate histologic diagnosis. Thereafter, staging can begin.

CASE 93-3

QUESTION 1: J.S. is diagnosed with lung cancer after a biopsy of a large lung mass. Chemotherapy, radiation, and surgery are commonly used to treat patients diagnosed with lung cancer.

What information is needed to select a treatment plan for J.S.?

The stage of the cancer, as well as the histologic diagnosis, influences both the treatment selection and prognosis. Staging is the process that determines the extent or spread of the disease.

Determining the stage of the cancer typically requires tests that can physically or radiographically measure the size of the primary tumor and assess for evidence of tumor spread (eg, radiographs, computed tomography [CT] scans, magnetic resonance imaging [MRI] scans, or positron emission tomography [PET] scans) and pathologically examine regional lymph nodes.[28] Clinicians also evaluate symptoms (eg, pain) or signs (eg, swelling and abnormal laboratory findings) that may indicate tumor involvement at a distant site. Common sites of tumor metastases are shown in **Table 93-2**.

Table 93-2

Common Sites of Metastases for Selected Tumors

Cancer Type	Common Sites of Metastases
Breast	Bone (osteolytic lesions), lung, liver, and brain
Lung	Liver, brain, adrenals, pancreas, contralateral lung, and bone
Prostate	Bone (osteoblastic lesions), liver, and lung
Colon	Liver, peritoneal cavity, and lung
Ovarian	Local spread in the peritoneal cavity

Staging schemas have been developed for all major types of cancers. For solid tumors, the most widely used and accepted staging classification is the TNM system, which incorporates the size of the primary tumor (T), the extent of regional lymph node spread (N), and the presence or absence of metastatic spread to distant organs (M). Within each TNM category, the extent of cancer involvement is related to prognosis. Most solid tumor staging systems also incorporate the TNM classification into broader groups, called *stages*, to facilitate treatment decisions and determine goals of care among patient populations. Classification of stages differs among solid tumor types. Refer to the chapters on malignancy-specific classification for TNM staging of breast, lung, prostate, and colorectal cancers.

Although the TNM system enables staging of solid tumors, it does not enable staging for hematologic malignancies, including leukemias, lymphomas, and multiple myeloma. Because hematologic malignancies occur in the blood cells and lymphatic tissues that are widely distributed throughout the body, the TNM staging system cannot sufficiently describe these diseases. To define the extent of disease, guide treatment, and provide prognostic information, specific staging systems have been developed for various hematologic malignancies. Staging systems for hematologic malignancies are discussed in further detail in Chapter 96, Adult Hematologic Malignancies.

Staging systems for some tumors also include other characteristics to further determine the stage and prognosis of the disease, such as clinical signs and symptoms, biochemical

characteristics of the tumor including mutation analysis, genetic mutations of the patient, or other laboratory tests. Tumor staging is done at the time of initial diagnosis and periodically during treatment to assess the patient's response to therapy. Staging should also be repeated (a) when evidence shows that the cancer has progressed during treatment or recurred after therapy to establish the most appropriate next-line therapy, and (b) to enable measurement of response to that therapy.

J.S. needs to undergo the appropriate imaging scans, laboratory studies, and clinical evaluation so that her lung cancer can be staged. These tests may include blood tests (eg, complete blood cell and platelet count, and liver function tests), determination of tumor biochemical characteristics, brain MRI, bronchoscopy, and PET. Once staging is completed, treatment recommendations and options can then be determined. Treatment options for lung cancer based on stage are further discussed in Chapter 98, Lung Cancer.

CLINICAL PRESENTATION AND COMPLICATIONS OF MALIGNANCY

The initial signs and symptoms of malignant disease can vary and predominantly depend on histologic diagnosis, location (including metastases), and size of the tumor. Pain secondary to compression, obstruction, and destruction of adjacent tissues and organs is the most common presenting symptom. Other common initial symptoms reported by patients with cancer include anorexia, weight loss, and fatigue. Certain symptoms, however, may be obscured by a concomitant illness, such as chronic lung disease in patients with lung cancer. In addition, tumor involvement of the liver, kidneys, or lungs and/or compression or obstruction of liver, kidney and other abdominal organs can complicate therapy by causing significant organ dysfunction and metabolic disturbances. Life-threatening complications that require immediate intervention include obstruction of the superior vena cava, spinal cord compression, and brain metastases.

CASE 93-4

QUESTION 1: P.N., a 59-year-old female, presents with shortness of breath, fatigue, anorexia, weight loss, and abdominal pain and distension that have worsened significantly during the previous 3 weeks. A CT scan of her abdomen shows a large mass surrounding the head of her pancreas with biopsy results that confirm pancreatic adenocarcinoma. The staging workup confirms the presence of distant metastases. Her husband states that she was previously an active person, but that she most recently has been unable to dress herself or participate in normal daily activities. He states that she spends most of the day in bed.

Will her activity level influence the type of treatment that she can receive?

Cancer can have a profound effect on a patient's quality of life and their ability to tolerate appropriate therapy. Patients with malnutrition secondary to anorexia, mechanical obstruction, or pain may not tolerate some therapies because of significant physical debility. Performance status is a measure of functional capacity and reflects a patient's ability to ambulate, care for themselves, and carry out normal activities. For several cancers, poor pretreatment performance status is associated with decreased ability to tolerate treatment, decreased tumor response to treatment, and worsened clinical outcome. In these cases, especially if the cancer is not known to respond well to treatment, a less aggressive treatment regimen may be recommended. For this reason, performance status is important to assess at the time of staging evaluation and periodically during treatment. Different scales (ie, Karnofsky score, Eastern Cooperative Oncology Group [ECOG]) can be used to determine performance status. The Karnofsky and ECOG performance scales are depicted in **Table 93-3**.[29] Because P.N. has a poor performance status and may not tolerate chemotherapy well, her oncologist may recommend a less toxic treatment plan. Because other conditions, such as depression, could contribute to her symptoms, P.N. should undergo comprehensive evaluation.

Table 93-3
Performance Status Scales

Eastern Cooperative Group		Karnofsky	
Grade	**Description**	**Grade**	**Description**
0	Fully active, able to carry on all predisease performance without restriction	100	Able to carry on normal activity; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature	80	Normal activity with effort, some signs of symptoms of disease
		70	Cares for self, but unable to carry on normal activity or do active work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about >50% of waking hours	60	Requires occasional assistance, but is able to care for most of personal needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care, confined to bed or chair >50% of waking hours	40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalization is indicated, although death not imminent
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20	Very ill; hospitalization and active supportive care necessary
		10	Moribund
5	Dead	0	Dead

Source: Reprinted by permission from Nature: Durante M, Loeffler JS. Charged particles in radiation oncology. *Nat Rev Clin Oncol*. 2010;7(1):37–43. © 2009 Springer Nature.

TREATMENT

CASE 93-5

QUESTION 1: T.J., a 40-year-old male with no significant medical history, presents to his physician with abdominal pain, nausea and vomiting, weakness, and weight loss. On physical examination, he is noted to be slightly jaundiced. A CT scan of his abdomen reveals a mass present in the peripancreatic area that is suggestive of malignancy.

Once diagnosed and staged, how will T.J.'s malignancy be treated and what is the goal of therapy?

The choice of specific therapy and its goals depends not only on the type, histology, and stage of the cancer but also on the patient's predicted tolerance of the side effects of the various treatment options. The goal of therapy should always be to cure the patient when possible. The likelihood of cure is greater when the tumor burden is low (ie, lower stage). If cure is not possible, therapy

becomes palliative in nature, with disease control and symptom management the priority. Goals of therapy should be balanced so that quantity and quality of life are both adequately considered.

Cancer is predominately treated with three modalities: surgery, radiation, and systemic therapy (including chemotherapy, targeted therapy, biologic agents, etc.). Systemic therapy is the primary treatment modality for hematologic malignancies. In most solid tumor malignancies, early-stage and localized disease is treated with surgery, radiation therapy, or, in some cases, both. For advanced disease (presence of metastases or recurrence after initial therapy), solid tumor malignancies are usually treated with systemic therapy as the primary treatment modality. T.J.'s treatment will be dependent on tumor histology, stage, and expected prognosis. If T.J. has potentially curable disease, he should be treated with curative intent therapy, whereas if T.J. has advanced disease that denotes a poor prognosis, he should be treated with palliative therapy.

Surgery

Surgery is an important treatment option for patients diagnosed with certain solid tumors. With the recent advances in surgical techniques (eg, minimally invasive procedures) and improved understanding of patterns of tumor growth and spread, successful resections are possible for an increasing number of patients. Surgery may be used as preventive therapy (eg, removal of colonic polyps or cervical dysplasia), diagnostic treatment, or staging of some cancers.

Surgery can be used to manage both localized and advanced tumors. When surgery provides curative therapy for a localized tumor, the surgeon removes the tumor plus a margin of normal tissue surrounding the tumor. For extensive, localized tumors that cannot be completely removed, selected patients may undergo cytoreductive surgery to partially resect the tumor to improve the likelihood that subsequent chemotherapy or radiation therapy may successfully kill the tumor.

Patients with metastatic disease may have palliative surgery to relieve pain or improve functional abnormalities caused by the advanced tumor (eg, gastrointestinal obstruction). Palliative surgery may improve quality of life but may not prolong survival.

Radiation

Radiation may be administered as either curative or palliative therapy for solid tumors. Radiation is administered in varying doses depending on the type of tissue being treated (eg, bone, lung, breast, liver, or brain) and the intent of therapy (palliative or curative). A limit exists to the total amount of radiation that can be delivered to the area being treated depending on the type of tissue. Damaging effects of radiation on the normal tissues surrounding the tumor can be acute and chronic, such as inflammation and subsequent fibrosis of the radiated field. Certain side effects may be exacerbated if given concomitantly with chemotherapy. For example, chemotherapy administered at the completion of radiation can produce “radiation recall,” a local toxicity that manifests as skin redness, swelling, and peeling at the radiation site.

Not all cancers are sensitive to radiation, so there is limited application in these cases. For radiation-sensitive tumors (**Table 93-4**), potential advantages exist over surgery. Radiation therapy can be given to multiple sites simultaneously. It may encompass a wider area around the tumor and treat tumors in regions of the body where surgery cannot safely be performed or in cases when surgery could result in considerable disability or disfigurement.

Table 93-4

Cancers Frequently Treated With Radiation Therapy

Acute lymphocytic leukemia (central nervous system radiation)
Brain and central nervous system
Breast
Head and neck cancers, squamous cell
Lung
Lymphomas

Neuroblastoma
Prostate
Rectal
Testicular, seminoma

Multiple methods are used to administer radiation to tumors. External-beam radiotherapy and brachytherapy are two types that are commonly used. Newer radiation therapy techniques, including intraoperative radiation, hyperfractionated radiation, stereotactic radiosurgery, intensity-modulated radiation therapy, charged-particle (proton) radiation therapy, and computerized three-dimensional conformal treatment planning, may reduce associated toxicities, enhance tumor responsiveness, and improve the clinical usefulness of radiation.[30-32]

Systemic Therapy

Not all cancers can be treated by surgery or radiation therapy. Patients may present with widespread metastatic disease at diagnosis or recur following primary treatment with surgery or radiation. Patients may also have residual tumor following initial surgery or radiation, requiring additional treatment. In these circumstances, systemic treatments including chemotherapy, targeted therapy, endocrine therapy, and biologic response modifiers generally offer the only hope of controlling disease.

CHEMOTHERAPY

The National Cancer Institute defines chemotherapy as drugs that stop the growth of cancer.[33] For the purposes of this chapter, chemotherapy will be defined as cytotoxic therapy that is directed toward rapidly dividing cells. Chemotherapy kills cancer cells by damaging DNA, interfering with DNA synthesis, or inhibiting cell division. Chemotherapy agents are classified by their effect on the cell cycle or mechanism of action. Agents that affect a specific phase of the cell cycle are referred to as *phase-specific agents* or *schedule-dependent agents*. In contrast, agents that affect any phase of the

cell cycle are referred to as *phase-nonspecific agents* or *dose-dependent agents* (see Fig. 93-1). The specific mechanisms of action for several chemotherapy agents are described in **Table 93-5**.[34]

Table 93-5
Chemotherapy Agents

Subclass	Agent	Mechanism of Action	Notable Toxicities
Alkylating Agents			
Nitrogen mustards	Bendamustine Chlorambucil Cyclophosphamide Ifosfamide Melphalan Thiotepa	Cross-links DNA strands, leading to cell death	Myelosuppression; nausea, vomiting; fatigue
Nitrosoureas	Carmustine Lomustine	Interferes with normal cellular function via cross-linking of DNA and RNA strands	Myelosuppression; nausea, vomiting; pulmonary toxicity; hepatic and renal dysfunction
Platinum analogs	Carboplatin Cisplatin Oxaliplatin	Reacts with nucleophilic sites on DNA forming cross-links	Myelosuppression; nausea, vomiting; peripheral neuropathy; delayed hypersensitivity reactions; secondary malignancy
Triazenes	Dacarbazine Temozolomide	Alkylates DNA, leading to double-strand breaks and cell death	Myelosuppression; nausea, vomiting, anorexia; fatigue; headache; alopecia
Antimetabolites			
DNA demethylation agents	Azacitidine Decitabine Nelarabine	Incorporates into RNA and DNA and inhibits methylation	Myelosuppression; nausea, vomiting, diarrhea; bruising, petechiae; fatigue, fever
Folic acid antagonists	Methotrexate Pemetrexed Pralatrexate	Inhibits dihydrofolate reductase; interferes with DNA synthesis, repair, and cellular replication	Myelosuppression; stomatitis; nausea; fatigue; hepatic dysfunction
Purine analogs	Cladribine Clofarabine Fludarabine Mercaptopurine Thioguanine	Inhibits DNA synthesis and repair by incorporating into DNA	Myelosuppression; nausea, vomiting, anorexia; fatigue

Pyrimidine analogs	Capecitabine Cytarabine Fluorouracil Gemcitabine	Incorporates into RNA and DNA; interferes with RNA function	Myelosuppression; nausea, vomiting, stomatitis, diarrhea
Antimitotic Agents			
Epothilones	Ixabepilone	Binds directly to β-tubulin; promotes stabilization of microtubules	Alopecia; myelosuppression; peripheral neuropathy; arthralgia, myalgia; stomatitis, nausea, vomiting, diarrhea
Taxanes	Cabazitaxel Docetaxel Paclitaxel Paclitaxel, albumin-bound	Binds to β-tubulin; promotes stabilization and suppresses disassembly of microtubules	Myelosuppression; alopecia; nausea, vomiting, diarrhea; peripheral neuropathy; myalgia, arthralgia; fatigue
Vinca alkaloids	Vinblastine Vincristine Vinorelbine	Binds to tubulin, interfering with microtubule assembly and mitotic spindle formation	Myelosuppression; constipation; bone pain; neurotoxicity, neuropathies; vesicant
Antitumor Antibiotics			
Anthracyclines	Daunorubicin Doxorubicin Doxorubicin, liposomal Epirubicin Idarubicin Valrubicin	Stabilizes the cleavable complex between topoisomerase II and DNA, causing single- and double-strand DNA breaks	Myelosuppression; mucositis; alopecia; nausea, vomiting; cumulative cardiac toxicity; secondary malignancy
DNA topoisomerase inhibitors	Etoposide Irinotecan Topotecan	Inhibits topoisomerases, leading to DNA strand breaks	Myelosuppression, fatigue; alopecia
Other Alkylating Agents			
Other agents	Lurbinectedin Trabectedin	Covalently binds to minor DNA groove, altering transcription	Myelosuppression; nausea, vomiting; hepatotoxicity

DNA, deoxyribonucleic acid; RNA, ribonucleic acid.

Factors that influence response to chemotherapy

Cell Kill

Studies using rodent animal models during the 1960s demonstrated that the number of tumor cells killed by chemotherapy is proportional to the dose when the growth fraction is 100% (ie, all cells are dividing) and the tumor cells are sensitive to the agent.[35,36] For example, if a dose of chemotherapy reduces the tumor burden from 10^{10} to 10^{8} cells, the same dose administered when only 10^{7} cells are present should reduce the tumor burden to 10^{5} cells. This theory has become known as the *cell-kill* or *log-kill hypothesis* (**Fig. 93-2**).

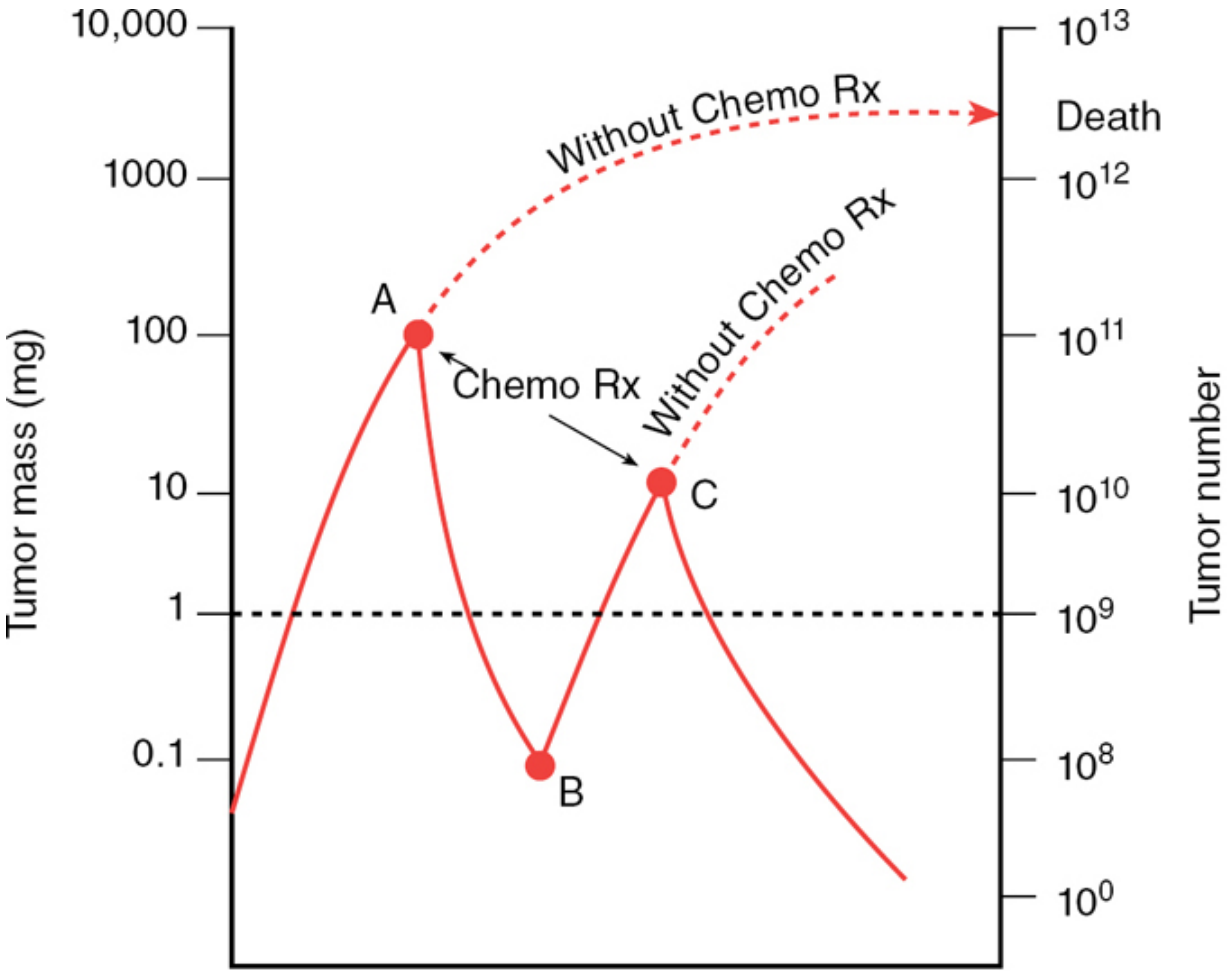


Figure 93-2 Log-kill hypothesis. The growth rate of a tumor is initially very rapid and eventually slows as it approaches 10^{11} cells. Two trillion (2×10^{12}) cells or 2 kg of tumor is lethal to humans. An effective chemotherapy treatment (Chemo Rx) given at point A will decrease the tumor number to point B. Regrowth of the tumor will occur during the recovery period until further chemotherapy is given at point C.

In the clinical setting, tumor cells do not always decrease predictably with each successive course of chemotherapy. This is because the growth fraction of human tumors is not 100% and the cell population is heterogeneous, with some cells that are resistant to chemotherapy.

Dose Intensity

Dose intensity is defined as the chemotherapy dose per unit time during which treatment is given (eg, milligrams/meter squared/week). Drug resistance might be overcome by increasing the dose of chemotherapy. Evidence suggests that reducing a dose can cause treatment failure in patients with chemotherapy-sensitive tumors who are receiving their first chemotherapy treatment.[37] A direct relationship between dose intensity and response rate has been reported in several tumor types including breast cancer, lymphomas, ovarian cancer, and small cell lung cancer.[38,39] However, dose-intensive therapy has not consistently improved the overall cure rate of most solid tumors.

The dose intensity for most chemotherapy regimens is limited by the major dose-related toxicity, bone marrow suppression. To minimize this toxicity and administer higher doses, patients may receive hematopoietic growth factors, autologous stem cell transplantation, or altered schedules of drug delivery.[40,41]

Schedule Dependency

Chemotherapy is administered in cycles (eg, every 2, 3, or 4 weeks) with recovery periods between cycles. A typical course of chemotherapy usually consists of several cycles. The interval of time between cycles depends on the cancer diagnosis and the agents being used. The optimal schedule is influenced by the pharmacokinetics of the agent. For example, phase-specific agents exert their cytotoxic effects only when the cell is in a particular phase of the cell cycle. If a phase-specific agent with a short half-life is administered by intravenous bolus, a significant number of tumor cells may not be in the vulnerable phase of the cell cycle during exposure to the agent. Comparatively, the same agent administered by frequent intravenous bolus or continuous infusion could expose more cells to the agent during the vulnerable phase.[42]

Drug Resistance

CASE 93-6

QUESTION 1: B.C. is a 39-year-old male with aggressive non-Hodgkin lymphoma (NHL). At the time of diagnosis, B.C. had enlarged cervical lymph nodes, dyspnea, and a large mediastinal mass noted on chest x-ray examination. Chemotherapy was initiated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP). After the first cycle of chemotherapy, B.C.'s lymphadenopathy was greatly reduced. After cycle 2, a repeat chest x-ray showed marked improvement. When he returned for his fifth cycle of chemotherapy, recurrent lymphadenopathy was noted, and the chest radiograph confirmed enlargement of the mediastinal mass.

Why is B.C.'s cancer growing despite continued chemotherapy, and how should his treatment be altered?

Most likely, B.C.'s cancer is now growing because the tumor has become resistant to the chemotherapy. Therefore, it would be wise to discontinue the current regimen. Biochemical resistance to chemotherapy is the major impediment to successful treatment with most cancers.[37] Resistance can occur de novo in cancer cells or develop during cell division as a result of mutation.[37] In 1979, a proposed mathematical model known as the Goldie–Coldman hypothesis predicted that tumor cells mutate at a rate related to the genetic instability of the tumor.[43] Thus, the probability that a tumor mass will contain resistant clones is related to both the rate of mutation and the size of the tumor. Many mechanisms have been identified by which cancer cells resist the activity of cytotoxic agents.

Some cell lines that become resistant to a single chemotherapy agent may also be resistant to structurally unrelated cytotoxic compounds. This phenomenon is called *pleiotropic drug resistance* or *multidrug resistance* (MDR).[44] Cell lines that display this type of resistance are generally resistant to natural product cytotoxic agents such as the vinca alkaloids, antitumor antibiotics, epipodophyllotoxins, camptothecins, and taxanes. The primary mechanism believed to be responsible for MDR is an increase in efflux transporters such as P-glycoprotein in the cell membrane. These proteins mediate efflux of the chemotherapy agent, causing decreased accumulation of drug within the cell and decreased cytotoxicity.[44] Other transport proteins (eg, breast cancer resistance

protein [BCRP]) have been implicated in resistance to chemotherapy as well.[45]

Another type of MDR is caused by changes or mutations of drug targets, for example, the altered binding of topoisomerase II, an enzyme that promotes DNA strand breaks in the presence of anthracyclines and epipodophyllotoxins.[46] Because of the likelihood of MDR, B.C. should receive a chemotherapy regimen that does not include agents transported from tumor cells by the MDR mechanism. An alternative regimen such as gemcitabine or oxaliplatin, with or without rituximab, may be a reasonable option because this regimen is active against NHL, and these drugs are not known substrates for various efflux transporters.

Tumor Site

The cytotoxic effects of chemotherapy agents are related to the time the tumor is exposed to an effective concentration of the agent (ie, concentration × time [C × T]). The drug dose, infusion rate, route of administration, lipophilicity, and protein binding can influence the concentration–time product. Other factors, such as tumor size and location, can also critically affect an agent's cytotoxicity. As tumors grow larger, their degree of vascularity lessens, making it more difficult for agents to penetrate the entire tumor mass. Tumors located in sites of the body with poor drug penetration (eg, the brain) may not receive a sufficient concentration to provide effective kill.

Pharmacogenetics

Antitumor activity and adverse effects of chemotherapy agents are associated with the presence of genetic polymorphisms that can affect the metabolism and disposition of drug. See Chapter 97, Breast Cancer, and Chapter 99, Colorectal Cancer, for a more detailed discussion of genetic polymorphisms associated with UDP glucuronosyltransferase 1A1 (UGT1A1), cytochrome P450 2D6 (CYP2D6), and human epidermal growth factor receptor 2 (HER2) receptor positivity.

Combination chemotherapy

CASE 93-7

QUESTION 1: K.K. has newly diagnosed stage II, bulky Hodgkin lymphoma. She initially presented with asymptomatic lymphadenopathy, night sweats, and a 15% weight loss in the previous 2 months. K.K. is to begin chemotherapy today with doxorubicin, bleomycin, vinblastine, and dacarbazine. All four agents have activity in Hodgkin lymphoma.

Why is it recommended that K.K. receive all four drugs, rather than just one drug?

Although single-agent chemotherapy can cause significant early regression of Hodgkin lymphoma, acute lymphocytic leukemia, and adult NHL, some tumors show only a partial, very short response to single-agent therapy. In Hodgkin lymphoma, the use of combination chemotherapy results in long-term, disease-free survival for >60% of patients. If K.K. were to receive single-agent therapy, her disease would not be cured. Combination chemotherapy is recommended to provide her with the best chance for long-term, disease-free survival.

Combination chemotherapy provides broader coverage against resistant cell lines within the heterogeneous tumor mass. Several principles provide the basis for selecting the agents to be included in a chemotherapy regimen:

- Agents with demonstrable single-agent activity against the specific type of tumor should be used in combination therapy.
- Agents in the regimen should have different mechanisms of action.
- Agents should not have overlapping toxicities so that the severity and duration of acute and chronic toxicities are minimized.
- Agents in the regimen should be used in their optimal dose and schedule.

Subsequent chapters provide examples of commonly used systemic regimens in the treatment of hematologic and solid tumor malignancies.

Primary treatment is the first-line therapy a patient receives, and in some tumor types it is referred to as *induction therapy*. Choice of primary treatment is governed by observations made from clinical trials that demonstrate a given regimen has high activity against the tumor. These regimens may include chemotherapy, targeted agents, endocrine agents, or biologic agents. After primary therapy, patients may receive additional treatment in an attempt to further eradicate residual disease and improve their chances for long-term survival. This treatment may be termed *consolidation*, *intensification*, or *maintenance* therapy (see subsequent chapters for specific discussion of these agents). Second-line treatment is administered after the tumor has become refractory to primary therapy or if the patient is unable to tolerate first-line therapy. Table 93-5 lists examples of commonly used agents.

Adjuvant therapy

CASE 93-8

QUESTION 1: F.R. is a 58-year-old female with no significant past medical history who recently underwent surgical resection for her stage III ovarian cancer. She has been told that she currently has no evidence of disease; however, she is also told that she should now receive six cycles of combination chemotherapy.

Why would chemotherapy be recommended now when she has no detectable disease?

Micrometastases or residual disease may still be present in some patients after completion of primary treatment. These patients have a high probability of disease recurrence, even though the primary treatment may have successfully removed all visual evidence of the primary tumor. To eradicate any undetectable tumor, systemic therapy may be recommended after initial curative surgery (or radiation therapy). Systemic treatment administered after primary therapy is referred to as *adjuvant therapy*. (In the case of F.R., primary therapy was surgery, and chemotherapy would be

considered adjuvant therapy.) Because the tumor burden is relatively low at this time, adjuvant therapy should immediately follow primary therapy. For adjuvant therapy to provide benefit, the risk of tumor recurrence must be high and effective agents must be available to eradicate the tumor. Adjuvant therapy is considered standard of care for some stages of breast, lung, and colorectal cancer, but it has also benefited select patients with ovarian cancer, Ewing sarcoma, and other malignancies.[47-49] The duration of administration of adjuvant therapy varies depending on the type of cancer being treated and the drugs being used but is typically several weeks to months in duration. See subsequent chapters for a specific discussion of the use of adjuvant therapy in solid tumor malignancies. For F.R., the recommendation will be to receive adjuvant chemotherapy with six to eight cycles of carboplatin and paclitaxel.

Because it is difficult to detect micrometastases or residual disease, it is a challenge to determine which patients should receive adjuvant therapy. To help with these decisions, clinicians frequently consider histologic and cytogenetic characteristics of the primary tumor that are associated with high risk of relapse.

Neoadjuvant therapy

Neoadjuvant therapy is given before the primary treatment (typically, surgery or radiation) in patients who present with locally advanced tumors that are unlikely to be cured with primary therapy alone (eg, large tumors or those that are impinging on surrounding vital structures). The objective of neoadjuvant therapy is to reduce the tumor mass, thereby increasing the likelihood of eradication by subsequent surgery or radiation. Neoadjuvant therapy can lessen the amount of radical surgery the patient needs, which can preserve cosmetic appearance and function of the surrounding normal tissues. The tumor can be resistant to neoadjuvant therapy and continue to grow, however, making surgery or radiation even more difficult. Patients may also experience toxicities with neoadjuvant therapy that may delay surgery or impair postsurgical healing. Locally advanced tumors in which neoadjuvant therapy has been

shown to improve outcomes include non–small cell lung cancer, breast cancer, soft tissue sarcomas, esophageal cancers, bladder cancer, and osteogenic sarcoma.[47,50–54] See subsequent chapters for a specific discussion of the use of neoadjuvant therapy in solid tumors.

CASE 93-9

QUESTION 1: H.P. is a 57-year-old male who is currently undergoing a staging workup for a presumed diagnosis of metastatic adenocarcinoma of the lung. He has heard that cytotoxic "chemotherapy is the only thing available to treat metastatic cancer."

What other agents are being used to treat cancer besides those that are considered cytotoxic?

TARGETED THERAPY

By understanding the mechanisms by which cancer cells exhibit unregulated growth and immortality and possess the ability to invade tissues and metastasize, it has been possible to design drugs that inhibit these processes.

Monoclonal antibodies

Directed at specific receptors associated with cancer, monoclonal antibodies block ligands from binding to their targets. Unlike traditional chemotherapy, monoclonal antibodies selectively target receptors or their ligands known to potentiate cancer pathways and, as a result, minimize toxicity to noncancer cells. **Table 93-6** provides a list of monoclonal antibodies currently approved by the U.S. Food and Drug Administration (FDA) to treat malignancy.[34]

Table 93-6
Monoclonal Antibodies

Class[a]	Agent (Trade Name)	Mechanism of Action	Notable Toxicities
Anti-CD19, Anti-CD3	Blinatumomab	Binds to CD19 on B cells and CD3 on T cells; causes formation of cytolytic synapses between B and T cells	Neurotoxicity; infection; tremor; fever; edema, rash; nausea, diarrhea, constipation; cytokine release syndrome
Anti-CD20	Obinutuzumab	Binds to CD20 on B cells; induces cell death via ADCC, CDC, and antibody-dependent cellular phagocytosis	Myelosuppression; hepatic and renal dysfunction; electrolyte abnormalities; infection; infusion reaction
	Ofatumumab	Binds to CD20 on B cells at different binding sites than does rituximab; induces cell death via ADCC and CDC	Cough; diarrhea, nausea; fatigue; myelosuppression; hypersensitivity reaction, pyrexia; rash; infection
	Rituximab	Binds to CD20 on B cells; induces cell death via ADCC and CDC	Hypersensitivity reaction; myelosuppression; infection; tumor lysis syndrome

Anti-CD20 Radiation	Ibritumomab tiuxetan	Yttrium-90 (Y-90) linked to rituximab; binds to CD20 on B cells and releases radiation (β particles); induces cell damage via free radicals	Infusion-related reaction; chills, nausea; fatigue; myelosuppression; see notable toxicities for rituximab
Anti-CD22	Inotuzumab ozogamicin	Binds to CD22 and is internalized; calicheamicin derivative is released inside the myeloid cell, resulting in double-strand breaks, inducing cell cycle arrest and apoptosis.	Hepatotoxicity, QT prolongation, hemorrhage, myelosuppression, infusion-related reaction, fatigue, infection, fever
Anti-CD30	Brentuximab vedotin	Three-component antibody drug conjugate; binds to cells expressing CD30 and is internalized; MMAE is then released, which disrupts the microtubule network.	Myelosuppression; peripheral neuropathy; fatigue; nausea, vomiting, diarrhea; fever; rash; upper respiratory infection
Anti-CD33	Gemtuzumab ozogamicin	Binds to CD33 and is internalized; calicheamicin derivative is released inside the myeloid cell resulting in double-strand breaks, inducing cell cycle arrest and apoptosis.	Hepatotoxicity, QT prolongation, myelosuppression, hemorrhage, hypersensitivity reaction, nausea, constipation, fatigue, fever
Anti-CD38	Daratumumab	Binds to CD38; induces apoptosis directly through Fc-mediated cross-linking as well as by immune-mediated tumor cell lysis through CDC, ADCC, and antibody-dependent cellular phagocytosis.	Infusion-related reaction, hepatitis B reactivation, cough, fever, arthralgia, myelosuppression
Anti-EGFR	Cetuximab	Binds to EGFR, preventing activation and inhibiting cell proliferation	Papulopustular rash, pruritus; fatigue; hypersensitivity reactions; abdominal pain, nausea, diarrhea; hypomagnesemia; paronychia
	Panitumumab	Binds to EGFR with higher affinity than does cetuximab, preventing activation and inhibiting cell proliferation	
Anti-HER2	Ado-trastuzumab emtansine	HER2-antibody drug conjugate of trastuzumab and microtubule inhibitor DM1; binds to HER2, inducing cell cycle arrest and cell death	Myelosuppression, nausea, constipation, diarrhea; fatigue, peripheral neuropathy; hypokalemia, fever
	Pertuzumab	Binds to HER2, inhibiting HER2 dimerization and downstream signaling, halting cell growth	Myelosuppression; cardiomyopathy; fatigue, alopecia; nausea, vomiting, diarrhea
	Trastuzumab	Binds to HER2; induces cell death via ADCC	Cardiomyopathy; nausea, vomiting, diarrhea; infusion-related reaction
Anti-VEGF	Bevacizumab	Binds to and inhibits VEGF ligand interaction with receptors, blocking angiogenesis	Hypertension; proteinuria; infusion-related reaction; bleeding; thrombosis; gastrointestinal perforation, impaired wound healing
	Ramucirumab	Binds to and inhibits VEGF2 ligand interaction with receptors (VEGF-A, VEGF-C, VEGF-D), blocking angiogenesis	
Immune Checkpoint Inhibitors	Ipilimumab	Enhances T-cell activation and proliferation by inhibiting CTLA-4, restoring antitumor immune response	Fatigue; nausea, anorexia, diarrhea, colitis; pruritus, rash; hepatic dysfunction; hypophysitis
	Nivolumab	Enhances T-cell activation and proliferation by inhibiting PD-1 activity, which is a negative regulator of T-cell pathways; restores antitumor immune response	Rash, pruritus; nausea, constipation, diarrhea; fatigue; electrolyte abnormalities; hepatic dysfunction; musculoskeletal pain; cough, pneumonitis, hypophysitis
	Pembrolizumab		
	Cemiplimab		
	Atezolizumab	Enhances T-cell activation and proliferation by binding to PD-L1 to prevent the interaction between the PD-1 and CD80 receptors; restores antitumor immune response	
	Avelumab		
	Durvalumab		

Other	Dinutuximab (Unituxin®)	Cell lysis of GD-2-expressing neuroblastoma cells via ADCC and CDC	Myelosuppression; urticaria; diarrhea, nausea, vomiting; hepatotoxicity; fever; capillary leak syndrome; infusion-related reaction; peripheral neuropathy
	Elotuzumab	Directed against SLAMF7; mediates ADCC, which increases antitumor activity through the increased activation of natural killer cells	Hepatotoxicity, infusion-related reaction, infection, fatigue, hyperglycemia, diarrhea, cough, fever
	Mogamulizumab	Selectively binds to CCR4 and targets a cell for ADCC	Infusion-related reaction, myelosuppression, autoimmune toxicity, rash, hyperglycemia, hepatic dysfunction, diarrhea
	Polatuzumab vedotin	Three-component antibody drug conjugate; binds to cells expressing CD79b and is internalized; MMAE binds to the tubules, which disrupts the cellular microtubule network.	Infusion-related reaction, myelosuppression, peripheral neuropathy, hepatotoxicity, diarrhea, opportunistic infection, fever, renal dysfunction

ADCC, antibody-dependent cellular toxicity; CCR4, C-C chemokine receptor 4; CDC, complement-dependent cytotoxicity; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; MMAE, monomethyl auristatin E; PD-1, programmed cell death-1; PD-L1, programmed death ligand 1; SLAM7, signaling lymphocytic activation molecule family member 7; VEGF, vascular endothelial growth factor.

[a]All monoclonal antibodies are administered intravenously, IV.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) are small molecules that directly inhibit tyrosine kinase activation by competing with ATP for binding to the intracellular tyrosine kinase domain. Advantages of these inhibitors include inhibiting cells that may not overexpress the receptor on their surface or have mutated forms of the receptor that result in its activation and direct inhibition of cell signaling. Even though most TKIs are designed to inhibit a single target, they often have inhibitory properties for additional molecules, which could affect an internal cascade of biologic activity, resulting in antitumor activity and toxicity.

This class of drugs is taken orally. Owing to varying pharmacokinetics, specific instructions on self-administration should be provided to patients (eg, take on an empty stomach or take with a full meal). In addition, many TKIs are substrates, inhibitors, and inducers of CYP450 enzymes as well as substrates or inhibitors of transporter proteins such as P-glycoprotein, breast cancer resistance protein (BCRP), and multidrug and toxic compound extrusion 1/2

(MATE1/2). Attention to potential drug interactions is crucial to safe medication use.

Table 93-7 provides the TKIs currently approved by the FDA to treat malignancies.[34]

Table 93-7
Tyrosine Kinase Inhibitors

Class[a]	Agent	Mechanism of Action	Notable Toxicities
ALK Inhibitors			
	Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib	Inhibits ALK, thereby reducing tumor cell proliferation in cells expressing ALK fusion protein; also inhibits ROS1 kinase	Muscle pain, visual disturbances; liver enzyme elevations; diarrhea, nausea, vomiting; fatigue, pneumonitis; blood glucose and cholesterol elevation
BCR-ABL Inhibitors			
	Bosutinib Dasatinib Imatinib Nilotinib Ponatinib	Inhibits BCR-ABL kinase, c-KIT, and PDGFR kinases	Myelosuppression; nausea, vomiting, diarrhea; fatigue; dermatologic toxicity; muscle pain; swelling
BTK Inhibitors			
	Acalabrutinib Ibrutinib Zanubrutinib	Inhibits the BTK of the B-cell receptor signaling pathway	Myelosuppression; nausea, diarrhea; fatigue, edema, fever; dermatologic toxicity; musculoskeletal pain; tumor lysis syndrome

CSF1R Inhibitors			
	Pexidartinib	Inhibits overexpressed CSF1R ligand	Fatigue; hair discoloration, increase in cholesterol and LDH; myelosuppression; eye swelling
EGFR Inhibitors			
	Afatinib Dacomitinib Erlotinib Gefitinib Osimertinib	Inhibits EGFR TK; resulting in tumor growth inhibition	Rash, dry skin, pruritus; paronychia; diarrhea
FGFR Inhibitors			
	Erdafitinib Pemigatinib	Inhibits FGFR TK	Fatigue, dermatologic toxicity; electrolyte disturbance; stomatitis, diarrhea; myelosuppression; increase in creatinine
FLT3 Inhibitors			
	Gilteritinib Midostaurin	Inhibits signaling and proliferation of cells expressing FLT3	Liver enzyme elevation; fatigue; rash; nausea; headache; febrile neutropenia
HER2 Inhibitors			
	Lapatinib Neratinib Tucatinib	Inhibits HER2 and EGFR TK	Nausea, diarrhea; dermatologic toxicity; myelosuppression; hepatic toxicity; cardiomyopathy, QT prolongation; pulmonary toxicity
JAK Inhibitors			
	Fedratinib Ruxolitinib	Inhibits hematopoiesis and immune function mediated by JAK	Myelosuppression; liver enzyme elevation; diarrhea, nausea; muscle pain
MET Inhibitors			
	Capmatinib	Inhibit MET TK from the mutant variant produced by exon 14 skipping	Swelling, fatigue; liver enzyme elevation; nausea, vomiting; chest pain
NTRK Inhibitors			
	Entrectinib Larotrectinib	Inhibits NTRK1, 2, and 3 TK	Fatigue; liver enzyme elevation; anemia; constipation, diarrhea; muscle pain; visual disturbance
PDGFRA Inhibitors			
	Avapritinib Ripretinib	Inhibits PDGFRA and KIT TK	Fatigue; electrolyte disturbance; myelosuppression; neuropathy; liver enzyme elevation
RET Inhibitors			
	Pralsetinib Selpercatinib	Inhibits RET TK including wild-type, fusion-variant, and mutant variant	Liver enzyme elevations; abdominal discomfort, nausea, vomiting; swelling; hypertension; change in lipid and glucose; myelosuppression
VEGF Inhibitors			
	Axitinib Cabozantinib Lenvatinib Pazopanib Regorafenib Sorafenib Sunitinib Vandetanib	Inhibits VEGF receptor tyrosine kinases, thereby blocking angiogenesis and tumor growth	Hypertension; diarrhea, nausea, vomiting; liver enzyme elevation; hand–foot syndrome, dermatologic toxicities; fatigue

ALK, anaplastic lymphoma kinase; BCR-ABL, breakpoint cluster region-ABL1 fusion gene; BTK, Bruton tyrosine kinase; CSF1R, colony-stimulating factor 1 receptor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FLT-3, Fms-like tyrosine kinase 3; HER2, human epidermal growth factor receptor 2; JAK, Janus-associated kinase; KIT, tyrosine-protein kinase kit; LDH, lactate dehydrogenase; MET, proto-oncogene c-Met; NTRK, neurotrophic receptor tyrosine kinase; PDGFR, platelet-derived growth factor; PDGFRA, platelet-derived growth factor a; RET, c-RET oncogene; ROS1, c-ros oncogene 1; TK, tyrosine kinase; VEGF, vascular endothelial growth factor.

[a]All tyrosine kinase inhibitors are administered orally, PO.

Other targeted therapy

Because of increasing information regarding signal transduction pathways and cellular growth and proliferation, more drugs that target these key molecules are being developed. Histone deacetylase (HDAC) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and proteasome inhibitors are examples of drugs that have novel mechanism(s) of action. **Table 93-8** lists these and other targeted agents currently approved by the FDA to treat malignancies.[34]

Table 93-8
Other Targeted and Miscellaneous Agents

Class	Agent	Mechanism of Action	Notable Toxicities
BCL-2 Inhibitor			
	Venetoclax	Inhibits antiapoptotic protein BCL-2 overexpression on CLL and AML cells	Myelosuppression; fatigue; liver enzyme elevation; swelling; tumor lysis syndrome
BRAF Inhibitors			
	Dabrafenib Encorafenib Vemurafenib	Blocks cellular proliferation of mutated BRAF	Dermatologic toxicity; nausea, diarrhea; edema; headache; hepatic dysfunction; fever, chills; secondary skin cancer
CDK Inhibitors			
	Abemaciclib Palbociclib Ribociclib	Inhibits cell cycle progression by blocking CDK 4 and 6	Myelosuppression, infection, fatigue; nausea, vomiting, diarrhea; stomatitis, alopecia; thrombosis
HDAC Inhibitors			
	Belinostat Panobinostat Romidepsin Vorinostat	Inhibits HDAC resulting in accumulation of acetyl groups, cell cycle arrest, and apoptosis	Nausea, vomiting; fatigue; myelosuppression; fever; peripheral edema; ECG changes
Hedgehog Inhibitors			
	Glasdegib Sonidegib Vismodegib	Inhibits cell growth and differentiation in embryogenesis mediated by hedgehog pathway	Fatigue; appetite loss; hair loss and thinning; dysgeusia; embryofetal death
IDH1 Inhibitors			
	Ivosidenib	Inhibitor-mutated isocitrate dehydrogenase 1 in leukemia cells	Differentiation syndrome; QT prolongation; muscle pain; gastrointestinal discomfort
IDH2 Inhibitors			
	Enasidenib	Inhibitor-mutated isocitrate dehydrogenase 2 in leukemia cells	Differentiation syndrome; gastrointestinal discomfort; increase in bilirubin
Immunomodulating Agents			
	Lenalidomide Pomalidomide Thalidomide	Immunomodulatory and angiogenic effects	Fatigue; teratogenic potential; thromboembolism; arthralgias
MEK Inhibitors			
	Binimetinib Cobimetinib Selumetinib Trametinib	Decreased cell proliferation and increased apoptosis by inhibiting MEK activation, which is a downstream effector of BRAF (mutant)	Cardiomyopathy; acneiform rash; diarrhea; hepatic dysfunction; edema; QT prolongation; hypoalbuminemia
mTOR Inhibitors			
	Everolimus Temsirolimus	Inhibits mTOR kinase, VEGFR	Fatigue, nausea, anorexia; dermatologic toxicity; hyperlipidemia, hyperglycemia, electrolyte abnormalities; stomatitis; myelosuppression, infection; pneumonitis
PARP Inhibitors			
	Niraparib Olaparib Rucaparib Talazoparib	Inhibits DNA transcription, cell cycle regulation, and DNA repair associated with PARP	Nausea, vomiting, fatigue; myelosuppression; musculoskeletal pain; thrombosis; upper respiratory infection; interstitial lung disease; secondary malignancy

PI3K Inhibitors			
	Alpelisib Copanlisib Duvelisib Idelalisib	Inhibits PI3K TK to induce apoptosis and cell death	Myelosuppression; nausea, diarrhea, colitis, gastrointestinal perforation; fatigue; hepatic toxicity; pulmonary toxicity
Proteasome Inhibitors			
	Bortezomib Carfilzomib Ixazomib	Inhibits proteasomes, enzymes that regulate protein homeostasis within cells	Nausea, diarrhea, constipation; peripheral neuropathy; headache, fatigue, fever; myelosuppression; herpes zoster reactivation
VEGF Inhibitors			
	Ziv-Aflibercept	Fusion protein comprising VEGF receptor-binding domains, acting as a decoy receptor for VEGF, inhibiting angiogenesis	Fatigue, diarrhea, stomatitis; myelosuppression; hypertension, proteinuria; bleeding, impaired wound healing; thrombosis; gastrointestinal perforation

AML, acute myeloid leukemia; BCL-2, B-cell lymphoma 2; BRAF, proto-oncogene b-Raf; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; DNA, deoxyribonucleic acid; ECG, electrocardiogram; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; MEK, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) kinase; mTOR, mammalian target of rapamycin; PARP, poly ADP-ribose polymerase; PI3K, phosphatidylinositol 3-kinase; TK, tyrosine kinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Combination therapy with targeted agents

The optimal activity of adding targeted agents to cytotoxic chemotherapy is difficult to predict. Knowledge about how to combine targeted agents with chemotherapy is limited, although clinical investigations are ongoing. See subsequent chapters for a specific discussion of the use of targeted therapy with chemotherapy in solid tumor and hematologic malignancies.

ENDOCRINE THERAPY

Endocrine therapy can be used to treat several common cancers, including breast, prostate, and endometrial cancers, which arise from hormone-sensitive tissues (**Table 93-9**). These tumors grow in response to endogenous hormones that trigger growth signals. Current endocrine therapies inhibit tumor growth by blocking hormone receptors or by eliminating endogenous hormone feeding the tumor. Not all tumors arising from hormone-sensitive tissues respond to endocrine manipulation. Lack of response may be associated with hormone-resistant tumor cells or inadequate suppression of the endogenous feeding hormones.[55]

Table 93-9
Endocrine Therapies

Class and Agents	Mechanism of Action	Class Toxicities
Androgens	Synthetic derivative of testosterone; suppresses GnRH, LH, FSH by a negative feedback system	Deepening voice, alopecia, hirsutism, facial or truncal acne, fluid retention, menstrual irregularities, cholestatic jaundice
Antiandrogens Bicalutamide (PO) Flutamide (PO) Nilutamide (PO)	Nonsteroidal antiandrogens that work to interfere with testosterone effects	Hot flashes; breast tenderness; hepatic dysfunction; diarrhea; fatigue; edema; hypertension; arthralgias
Enzalutamide (PO) Apalutamide (PO) Abiraterone (PO)	Inhibits androgen receptor translocation, leading to cellular apoptosis Inhibits formation of the testosterone precursors, DHEA and androstenedione	
Antiestrogens Fulvestrant (IM) Tamoxifen (PO)	Competitive binding of estrogen receptors produces downregulation of estrogen receptors.	Liver enzyme elevation; headache; hot flashes; myalgia, arthralgia; nausea; vomiting; thromboembolism
Aromatase Inhibitors Anastrozole (PO) Letrozole (PO) Exemestane (PO)	Competitive binding of estrogen receptors produces downregulation of estrogen receptors.	Hot flashes; nausea; fatigue, insomnia; increased risk of bone fractures; arthralgia
Estrogens Ethinyl estradiol (PO) Conjugated estrogens (PO)	Suppresses androgen synthesis, as well as secretions of gonadotropins, FSH, and LH via negative feedback system	Nausea, vomiting, fluid retention, hot flashes, anorexia, thromboembolism, hepatic dysfunction

Class and Agents	Mechanism of Action	Class Toxicities
GnRH Analogs (LHRH Agonists) Goserelin (SC) Histrelin (SC) Triptorelin (IM) Leuprolide (IM; SC)	Downregulates GnRH receptor on the pituitary gland, decreasing secretion of FSH and LH	Amenorrhea, hot flashes, sexual dysfunction; nausea, edema; tumor flare; injection-site reaction; osteoporosis
GnRH Antagonists Degarelix (SC)	Binds to GHRH receptors on the pituitary gland, blocking the secretion of FSH and LH	Hot flashes; hepatic toxicity; injection-site reaction
Progestins Medroxyprogesterone (PO) Megesterol acetate (PO)	Promotes differentiation and maintenance of endometrial tissue	Weight gain, edema; hot flashes, vaginal bleeding; thrombosis

CYP, cytochrome; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; IM, intramuscular; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; PO, oral; SC, subcutaneous.

IMMUNOTHERAPY

Immune therapy comprises substances that stimulate the body's immune system to identify circulating tumor cells. Some agents target certain cells of the immune system; other agents are more nonspecific.[33] An individual's immune system plays a crucial role in developing or eradicating cancer. Normally, an intact immune system can protect the host against malignant cells and infectious pathogens, but current evidence shows that individuals with "weakened" immune systems are at an increased risk for developing cancer. Common immunotherapy classes include checkpoint inhibitors and immune effector cell therapy (**Table 93-10**; also see Table 93-6), but can also include vaccines and cytokines.

Table 93-10
Immune Effector Cell Therapy

Class	Agent	Mechanism of Action	Notable Toxicities
Chimeric antigen receptor T-cell (CAR-T) immunotherapy	Axicabtagene ciloleucel	Genetically modified autologous T cells reprogrammed with a transgene encoding a CAR; binds to CD19 cells and activates costimulatory domains to cause T-cell activation and proliferation; results in antitumor activity and cell destruction	Cytokine release syndrome, neurologic toxicity, myelosuppression, infection, hypersensitivity reaction, fever, hypotension, decreased appetite
	Brexucabtagene autoleucel		
	Tisagenlecleucel		

If H.P. is in fact diagnosed with stage IV adenocarcinoma of the lung, he may receive other agents besides chemotherapy during the course of treatment for his disease. For a specific discussion of which noncytotoxic agents H.P. may receive, refer to Chapter 98, Lung Cancer.

Administration

Systemic CHEMOTHERAPY

Systemic chemotherapy is most commonly administered by the intravenous route, either as a bolus injection (generally >15 minutes), short infusion (15 minutes to several hours), or as a continuous infusion (lasting 24 hours to several weeks). Some chemotherapy can also be administered orally, intramuscularly, or subcutaneously.

Targeted agents are most commonly administered intravenously or orally. Monoclonal antibodies are primarily administered intravenously, whereas small-molecule TKIs are primarily administered orally. Endocrine agents are primarily administered orally or subcutaneously.

Although chemotherapy was initially developed for systemic use, techniques have been developed to administer agents directly to specific sites of the body affected by the tumor (**Table 93-11**). Regionally or locally administered chemotherapy allows for high concentrations of drug at the tumor site while reducing systemic exposure and subsequent toxicity. However, a potential disadvantage is that distant micrometastases may not be exposed to chemotherapy, allowing continued growth of tumor cells.

Table 93-11
Regional or Local Routes of Chemotherapy Administration

Route of Administration	Cancer Managed With Alternative Route
Intrathecal or intraventricular	Leukemia, lymphoma
Intravesicular	Bladder
Intraperitoneal	Ovarian
Intrapleural	Malignant pleural effusions
Intra-arterial	Melanoma, sarcoma
Hepatic artery	Liver metastases
Chemoembolization (intra- arterial or intravenous)	Colon, rectal, carcinoid, liver metastases

Assessing Response to Therapy

CASE 93-10

QUESTION 1: G.K. is a 67-year-old female who was recently diagnosed with metastatic breast cancer. Her symptoms include widespread pain, anorexia, and fatigue. She has received two cycles of treatment with a combination chemotherapy regimen. A recent CT scan of her abdomen showed marked shrinkage at several tumor sites, and her pain has decreased.

How long should she continue to receive this chemotherapy?

An important step in the treatment process is assessing response to treatment. This assessment should include evaluation of efficacy and toxicity, including impact on the patient's overall quality of life. Reevaluation should occur at regularly scheduled intervals and include physical examination, laboratory tests, and repeat diagnostic imaging.

Response Evaluation Criteria in Solid Tumors (RECIST) was introduced in 2000 to unify response assessment criteria, define how to choose evaluable tumors, and enable the use of new imaging technologies (spiral CT and MRI). RECIST guidelines have since been updated to account for changes in evaluating tumors and the use of immunotherapy. The World Health Organization, National Cancer Institute, and European Organization for Research and

Treatment of Cancer have adopted RECIST criteria as the standard for evaluating tumor response (**Table 93-12**).[56]

Table 93-12

Response Criteria for Evaluating Effects of Chemotherapy of Target Lesion

Complete Response
Disappearance of all target lesions. Any pathologic lymph nodes (whether target or nontarget) must have a reduction in short axis to >10 mm.
Partial Response
At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease
At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease
Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Several standardized toxicity grading scales are available to assess toxicity associated with chemotherapy. However, the National Cancer Institute Common Toxicity Criteria for Adverse Events is the most commonly used.[29,57] Toxic effects of systemic therapy is further discussed in Chapter 94, Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents.

Because toxicities associated with systemic therapy are potentially severe, it is important to evaluate the risks and benefits. The benefits of a treatment regimen should outweigh the negative effects it has on the physical, mental, and social well-being of the patient. To monitor a patient's quality of life, several comprehensive assessment tools have been developed.[58] In addition, other clinical benefits (eg, reduced pain, decreased use of analgesics, weight gain, and improved performance status) have been recognized by the FDA as

acceptable criteria for measuring the quality of life. These criteria are also considered when evaluating new agents for approval.

G.K. should continue to receive the same therapy if her tumor is responding and she does not experience intolerable or life-threatening treatment-related toxicities. For some cancers, continued therapy after a certain number of cycles is not associated with further benefit because toxicity becomes an overriding issue.

TUMOR MARKERS

Tumor markers are substances found in tumor tissue or released from the tumor into the blood or other body fluids (eg, urine).[33] However, not all cancers have relevant tumor markers. The ideal tumor marker should be produced and released primarily by cancer cells (or by other tissues in response to the tumor) at levels proportional to the tumor mass, and a reduction in the level of the marker should be seen in response to treatment. In addition, the ideal tumor marker should be measurable at very low levels, allowing for detection of the tumor at lower volumes than conventional diagnostic imaging permits.[59] Because most tumor markers lack specificity and may be elevated owing to other causes, they are often not useful as a sole screening or diagnostic test and are instead used to detect recurrent disease. **Table 93-13** lists some of the common tumor markers used in practice.

Table 93-13
Clinically Useful Tumor Markers

Tumor Markers	Cancers Commonly Associated With Increased Markers
CA-19-9	Pancreatic
CA-15-3, CA-27-29	Breast
α-Fetoprotein (AFP)	Liver, testicular, ovarian
CA-125	Ovarian
Carcinoembryonic antigen (CEA)	Colon, lung

Tumor Markers	Cancers Commonly Associated With Increased Markers
Human chorionic gonadotropin (hCG)	Trophoblastic, testicular
β_2-Microglobulin	Multiple myeloma
Prostate-specific antigen (PSA)	Prostate

HANDLING OF CYTOTOXIC DRUGS

Impact on the Pharmacy

CASE 93-11

QUESTION 1: The administrator of an outpatient care clinic recently announced that two medical oncologists will be joining the staff. Previously, patients were referred to outside oncologists, and no cytotoxic drugs were prepared or administered at this clinic.

What implications will the addition of these physicians have on the pharmacy department?

Addition of cancer treatment to institutional services will affect three areas of the pharmacy department: budget, policies and procedures for safe drug handling and disposal, and the staff education program. The pharmacy department will need to increase its budget to accommodate additional personnel and purchase new equipment, supplies, supportive care medicines, and chemotherapy agents. To estimate the projected budget increase, pharmacy leadership should meet with the oncologists to discuss the anticipated volume of chemotherapy orders including systemic therapy and supportive care medicines (eg, antiemetic therapy, analgesics, growth factors) likely to be prescribed. All new systemic therapy agents and supportive care medicines should be added to the institutional formulary. In addition, projected use of investigational

agents, clinical pharmacy services needed, and any plans to develop an ambulatory infusion program should be determined. Institutional policies and procedures to ensure safe handling of chemotherapy agents must be created. These should be conveyed to all personnel affected through a staff education program because safe handling of chemotherapy agents is critical in decreasing the risk of medication errors and injuries.

Medication Errors

Chemotherapy-related medication errors have brought significant attention to the entire drug use process in oncology, and have identified several factors that appear to contribute to the risk. Use of abbreviations, verbal orders, multiple-day regimens, incorrect references and protocols, and illegible medication orders has contributed to medication errors. Increasing use of computerized prescriber order entry and standardized preprinted orders have helped eliminate many errors. Several groups have responded to the problem by issuing policy recommendations to minimize such errors.[60–65]

Risks

Case 93-11, Question 2: What are the potential risks of handling cytotoxic drugs? What resources are available to assist the pharmacy director and the pharmacy staff in the development of policies and procedures?

Many of these agents are carcinogenic, teratogenic, or mutagenic in animal models and in humans at therapeutic doses.[65] Danger to health care personnel handling such agents results from inherent toxicities of the agents and the extent (ie, amount and length of time) to which the workers are exposed during drug handling.[65] Various studies have attempted to assess the effect of occupational exposure to hazardous drugs on health care workers. These studies measured urine mutagenicity, chromosomal damage, blood

concentrations, and the level of contamination that occurs in the work areas used for drug preparation and administration.[65–67] These studies indicate that urine mutagenicity and chromosomal damage in workers may be a direct result of cytotoxic exposure. Other reports have correlated reproductive risks (eg, infertility or increased risk of miscarriage) and birth defects in pregnant workers handling cytotoxic drugs.[66,68] Findings from these reports together with the toxicities observed in patients receiving therapeutic doses led the American Society of Health-System Pharmacists to conclude that health care workers exposed to hazardous drugs may be absorbing or inhaling these drugs and may be at risk for adverse outcomes.[65]

In response to concerns regarding occupational exposure to hazardous drugs, several groups have published guidelines for the safe handling of these agents in the workplace (ie, storage, preparation, administration, and disposal).[65,67] These guidelines will be helpful to the pharmacy department when developing policies and procedures.

Policies and Procedures

Case 93-11, Question 3: What specific policies and procedures are necessary? What other departments should be consulted during the development and implementation of the handling guidelines?

Policies that address the entire scope of potential occupational exposures within the workplace must be developed. These policies should include (a) a worker's "right to know" regarding potential hazards; (b) education and training for workers involved with hazardous drug handling; (c) quality assurance to monitor adherence to safe handling procedures; and (d) guidelines for workers who are attempting to conceive a child, become pregnant, or are nursing.

Specific procedures that outline appropriate handling of hazardous agents during all aspects of institutional storage, use, and disposal should be developed. These procedures should address appropriate (a) storage in the receiving and storeroom areas, (b) preparation and

administration of parenteral formulations, (c) manipulation and dispensing of oral and topical formulations, (d) cleanup of spills, (e) management of acute exposures, and (f) disposal of hazardous agents and supplies used to prepare and dispense chemotherapy. If the oncology program includes ambulatory infusion or home care components, procedures should also be developed for appropriate handling and disposal of these products in the home. Handling of oral chemotherapy and biotherapy must also be specifically addressed. Policies should include processes for cleaning of tools and nondisposable items used to dispense oral cytotoxic agents to minimize contamination with other drugs.[69]

Other departments may be affected by these guidelines, including medical staff, nursing, environmental services staff (in the cleanup of spills and equipment), maintenance (upkeep of equipment), and the receiving area (where cytotoxic drugs may be received from suppliers). The institutional safety office and legal staff also should be consulted to help devise the policies and procedures.

Necessary Equipment and Supplies

Case 93-11, Question 4: What equipment and supplies are necessary for handling hazardous drugs?

Proper equipment and supplies can minimize occupational exposure in the health care workplace by protecting both the worker and the environment. All handling guidelines recommend that manipulations (eg, reconstitution and admixing) of hazardous drugs be done in the class I to III biologic safety cabinet to provide maximal protection for the worker and the work environment. Workers must wear two pairs of chemotherapy gloves, protective boot covers, hair cover, mask, and a disposable gown of lint-free, low-permeability fabric with long sleeves, knit cuffs, and back closure. In addition, only syringes and intravenous sets with threaded Luer-Lock™ connections should be used.[70] Final products (eg, syringes, intravenous bags, or bottles) should be placed in sealable containers such as zipper-

closure plastic bags to prevent accidental spillage and clearly labeled as a hazardous drug. The United States Pharmacopeia dictates guidelines for safe handling of hazardous drugs and compounding sterile products.[71,72]

Disposal of hazardous waste requires specific receptacles, which should be placed in all areas where workers handle these drugs. Disposal of these agents should follow institutional, state, and local regulations. Materials for the cleanup of spills (eg, absorbent material, plastic bags or containers, and protective garments) also must be available in all areas where hazardous drugs are stored, prepared, or administered.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2018. (20, 21, 22, 37, 40, 41, 59)

Power LA, Coyne JW. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm.* 2018;75(24):1996–2031. (65)

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;70:7–30. (3)

Key Websites

American Cancer Society. http://www.cancer.org

American Society of Health-Systems Pharmacists. The ASHP discussion guide on USP chapter for compounding sterile preparations. Summary of revisions to USP chapter. https://www.ashp.org/-/media/assets/pharmacy-

practice/resource-centers/sterile-compounding/ashp-discussion-guide-on-usp-chapter-797.ashx
National Cancer Institute. http://www.cancer.gov
National Cancer Institute. *Surveillance, Epidemiology, and End Results*. http://seer.cancer.gov

COMPLETE REFERENCES CHAPTER 93 NEOPLASTIC DISORDERS AND THEIR TREATMENT: GENERAL PRINCIPLES

1. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100:57–70.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER). Accessed March 12, 2022. http://seer.cancer.gov
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;70:7–30.
4. Wu S, Zhu W, Thompson P, Hannun YA. Evaluating intrinsic and non-intrinsic cancer risk factors. *Nat Commun*. 2018;9(1):3490.
5. American Cancer Society. What Causes Cancer? Accessed March 12, 2022. http://www.cancer.org/cancer/cancercauses/tobaccocancer/tobacco-related-cancer-fact-sheet https://www.cancer.org/cancer/cancer-causes.html.
6. American Cancer Society. *Cancer Facts & Figures 2020*. American Cancer Society; 2020.
7. Weinberg R. How cancer arises: an explosion of research is uncovering the long-hidden molecular underpinnings of cancer—and suggesting new therapies. *Sci Am*. 1996;62–70.
8. Park MT, Lee SJ. Cell cycle and cancer. *J Biochem Mol Biol*. 2003;36:60–65.
9. Sherr CJ. Cancer cell cycles. *Science*. 1996;274:1672–1677.
10. Hahn WC, Weinberg RA. Rules for making human tumor cells [published correction appears in *N Engl J Med*. 2003;348:674]. *N Engl J Med*. 2002;347:1593–1603.
11. Hahn WC. Role of telomeres and telomerase in the pathogenesis of human cancer. *J Clin Oncol*. 2003;21:2034–2043.
12. Rundhaug JE. Matrix metalloproteinases, angiogenesis, and cancer. *Clin Cancer Res*. 2003;9:551–554.
13. Tsao AS, Kim ES, Hong WK. Chemoprevention of cancer. *CA Cancer J Clin*. 2004;54:150–180.
14. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. 2003;348:518–527.

15. U.S. Food and Drug Administration. Gardasil 9—Human papillomavirus 9-valent vaccine, recombinant. Highlights of prescribing information. U.S. Food and Drug Administration; 2014. Accessed March 12, 2022. https://www.fda.gov/media/90064/download.
16. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372(8):711–723.
17. American Cancer Society. American Cancer Society Guidelines for the prevention and early detection of cervical cancer. Accessed September 4, 2020. https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/cervical-cancer-screening-guidelines.html
18. Centers for Disease Control and Prevention. Immunization schedules. Accessed September 4, 2020. http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
19. American Cancer Society. American Cancer Society for the diet and physical activity. Accessed September 4, 2020. http://www.cancer.org/healthy/eat-healthy-get-active/acs-guidelines-nutrition-physical-activity-cancer-prevention/guidelines.html
20. Libutti SK, Saltz LB, Willett CG, Levine RA. Cancer of the colon. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2018:918.
21. Zelefsky MJ, Morris MJ, Eastham JA. Cancer of the prostate. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2018:1088.
22. Jagsi R, King TA, Lehman C, et al. Cancer of the breast: malignant tumors of the breast. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2018:1270.
23. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*. 2002;87:1234–1245.
24. Gilchrest BA, Eller MS, Geller AC, Yaar M. The pathogenesis of melanoma induced by ultraviolet radiation. *N Engl J Med*. 1999;340:1341–1348.
25. American Cancer Society. Skin cancer prevention and early detection. Accessed September 4, 2020. https://www.cancer.org/cancer/melanoma-skin-cancer/causes-risks-prevention/prevention.html
26. Christensen D. Data still cloudy on association between sunscreen use and melanoma risk. *J Natl Cancer Inst*. 2003;95:932–933.
27. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for detection, prevention, and

risk of cancer. Accessed October 8, 2020. https://www.nccn.org/professionals/physician_gls/default.aspx
28. American Cancer Society. Imaging (Radiology) tests for cancer. Accessed August 31, 2020. http://www.cancer.org/treatment/understandingyourdiagnosis/examsandtestdescriptions/imagingradiologytests/index
29. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649–655.
30. Heron DE, Godette KD, Wynn RA, et al. Radiation medicine innovations for the new millennium. *J Natl Med Assoc*. 2003;95:55–63.
31. Durante M, Loeffler JS. Charged particles in radiation oncology. *Nat Rev Clin Oncol*. 2010;7:37–43.
32. Orth M, Lauber K, Niyazi M, et al. Current concepts in clinical radiation oncology. *Radiat Environ Biophys*. 2014;53(1):1–29.
33. National Cancer Institute. Dictionary of cancer terms. Accessed September 9, 2020. http://www.cancer.gov/dictionary/
34. Facts & Comparisons eAnswers [online]. Wolters Kluwer Health; 2015. Accessed June 10, 2015.
35. Skipper HE, Schabel FM, Wilcox WS. Experimental evaluation of potential anticancer agents: XIII. On the criteria and kinetics associated with “curability” of experiment leukemia. *Cancer Chemother Rep*. 1964;35:1–111.
36. Skipper HE. Reasons for success and failure in treatment of murine leukemias with the drugs now employed in treating human leukemias. In: Skipper HE, ed. *Cancer Chemotherapy*. University Microfilms International; 1978;1.
37. Sparreboom A, Baker SD. Cancer therapeutics: pharmacokinetics and pharmacodynamics of anticancer drugs. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg’s Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2019:231.
38. Wood WC, Budman DR, Korzun AH, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma [published correction appears in *N Engl J Med*. 1994;331:139]. *N Engl J Med*. 1994;330:1253–1259.
39. Lorigan P, Woll PJ, O’Brien ME, Ashcroft LF, Sampson MR, Thatcher N. Randomized phase III trial of dose-dense chemotherapy supported by whole-blood hematopoietic progenitors in better-prognosis small-cell lung cancer [published correction appears in *J Natl Cancer Inst*. 2005;97:941]. *J Natl Cancer Inst*. 2005;97:666–674.
40. Balducci L, Shah B, Zuckerman K. Management of adverse effects of treatment: neutropenia and thrombocytopenia. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg’s Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2019:2068.

41. Lazarus HM, Hamadani M, Hari PN. Stem cell transplantation: autologous stem cell transplantation. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2019:2008.
42. Mormont MC, Levi F. Cancer chronotherapy: principles, applications, and perspectives. *Cancer*. 2003;97:155–169.
43. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to the spontaneous mutation rate. *Cancer Treat Rep*. 1979;63:1727–1733.
44. Gottesman MM. Mechanisms of cancer drug resistance. *Annu Rev Med*. 2002;53:615–627.
45. Leonard GD, Fojo T, Bates SE. The role of ABC transporters in clinical practice. *Oncologist*. 2003;8:411–424.
46. Pessina A, Raimondi A, Croera C, et al. Altered DNA-cleavage activity of topoisomerase from WEHI-3B leukemia cells with specific resistance to ciprofloxacin. *Anticancer Drugs*. 2001;12:441–451.
47. National Comprehensive Cancer Network. Non-small cell lung cancer (Version 4.2021). Accessed March 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
48. National Comprehensive Cancer Network. Breast cancer (Version 1.2021). Accessed March 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
49. National Comprehensive Cancer Network. Colon cancer (Version 2.2021). Accessed March 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
50. National Comprehensive Cancer Network. Ovarian cancer including fallopian tube cancer and primary retroperitoneal cancer (Version 1.2021). Accessed March 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
51. National Comprehensive Cancer Network. Bone cancer (Version 1.2021). Accessed March 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf
52. National Comprehensive Cancer Network. Soft tissue sarcoma (Version 1.2021). Accessed March 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
53. National Comprehensive Cancer Network. Esophageal and esophageal junction cancers (Version 1.2021). Accessed March 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
54. National Comprehensive Cancer Network. Bladder cancer (Version 6.2020). Accessed March 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf
55. Ali S, Coombes RC. Endocrine-responsive breast cancer and strategies for combating resistance. *Nat Rev Cancer*. 2002;2:101–112.

56. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
57. National Cancer Institute. Common Terminology Criteria for Adverse Events. Version 5.0. Accessed September 14, 2020. http://evs.nci.nih.gov/ftp1/CTCAE
58. Cella D, Chang CH, Lai JS, Webster K. Advances in quality of life measurements in oncology patients. *Semin Oncol*. 2002;29(3 suppl 8):60–66.
59. Fojo AT, Bates SE. Cancer therapeutics: assessment of clinical response. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2018:505.
60. Goldspiel B, Hoffman JM, Griffith NL, et al. ASHP guidelines on preventing medication errors with chemotherapy and biotherapy. *Am J Health Syst Pharm*. 2015;72(8):e6–e35.
61. Neuss MN, Polovich M, McNiff K, et al. 2013 Updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. *J Oncol Pract*. 2013;9(suppl 2):5–13.
62. Cohen MR, Anderson RW, Attilio RM, Green L, Muller RJ, Pruemer JM. Preventing medication errors in cancer chemotherapy. *Am J Health Syst Pharm*. 1996;53:737–746.
63. Attilio RM. Caring enough to understand: the road to oncology medication error prevention. *Hosp Pharm*. 1996;31:17–26.
64. Goldspiel BR, DeChristoforo R, Hoffman JM. Preventing chemotherapy errors: updating guidelines to meet new challenges. *Am J Health Syst Pharm*. 2015;72:668–669.
65. Power LA, Coyne JW. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2018;75(24):1996–2031.
66. Selevan SG, Lindbohm ML, Hornung RW, Hemminki K, et al. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. *N Engl J Med*. 1985;313:1173–1178.
67. National Institute for Occupational Safety and Health. NIOSH alert: preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Accessed September 10, 2020. http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf
68. Hemminki K, Kyyrönen P, Lindbohm ML, et al. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. *J Epidemiol Community Health*. 1985;39:141–147.

69. Goodin S, Griffith N, Chen B, et al. Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel. *J Oncol Pract*. 2011;7:7–12.
70. The Life and Death of the Luer. Accessed March 16, 2022. https://www.mddionline.com/components/life-and-death-luer
71. The United States Pharmacopeial Convention. USP general chapter <797> Pharmaceutical Compounding—sterile preparation. Accessed September 10, 2020. https://www.usp.org/compounding/general-chapter-797
72. The United States Pharmacopeial Convention. USP general chapter <800> Hazardous drugs—handling in healthcare settings. Accessed September 10, 2020. http://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare

94

Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents

Victoria Nachar and Matthew Newman

CORE PRINCIPLES		CHAPTER CASES
1	Myelosuppression is one of the most common toxicities of anticancer therapy. Anticancer therapy may impact one or all the bone marrow cell lines including erythrocytes, neutrophils, and platelets. Complications from anemia, neutropenia, and thrombocytopenia can cause significant morbidity and mortality. Prophylactic administration of growth factors may protect against the myelosuppressive effects of chemotherapy.	**Case 94-1 (Questions 1–4)**

CORE PRINCIPLES		CHAPTER CASES
2	The upper and lower gastrointestinal (GI) tract is highly susceptible to anticancer therapy, and toxicities can include nausea and vomiting, mucositis, xerostomia, constipation, and diarrhea. Efficacy of preventive strategies is limited; thus, supportive treatment is a foundation for managing adverse effects in patients.	**Case 94-2 (Questions 1–3) Case 94-3 (Question 1)**
3	Dermatologic toxicities from anticancer therapies include alopecia, nail changes, hyperpigmentation, radiation sensitivities, hand–foot syndrome, dry skin, and papular–pustular (acneiform) rash. Most of the toxicities are cosmetic and resolve upon discontinuation of the agent. Onset and duration of dermatologic toxicities depend on the causative agent. Treatment is supportive.	**Case 94-4 (Questions 1–4)**
4	Extravasation is the unintended infiltration of an agent into the tissue area surrounding the vein during an infusion. Extravasations require emergency treatment that is agent specific.	**Case 94-4 (Questions 5, 6), Tables 94-1, 94-2**

CORE PRINCIPLES		CHAPTER CASES
5	Many anticancer therapies are associated with immunoglobulin E–mediated hypersensitivity reactions. Monoclonal antibodies are among some of the agents most commonly associated with reactions. Reactions commonly occur with the first dose, and they may be minimized with premedications.	**Case 94-5 (Question 1), Table 94-3**
6	Chimeric antigen receptor T-cell (CAR-T) therapies and other immune-directed therapies may cause cytokine release syndrome or neurotoxicity, requiring careful intervention. Immune checkpoint inhibitors are associated with distinct toxicities, including pneumonitis, colitis, and dermatitis, which may warrant therapy interruption, systemic steroids, or other immunosuppressive supportive care agents.	**Case 94-6 (Question 1), Table 94-4**
7	Multiple types of central nervous system (CNS) toxicity, including encephalopathy, cerebellar toxicity, and peripheral neuropathy, are associated with anticancer agents, and differ in presentation between various agents. Most of the symptoms of neurotoxicity are reversible over time, but modifications to regimens, including discontinuation of agents or reduction of doses, may be necessary.	**Case 94-7 (Questions 1–4), Table 94-5**

CORE PRINCIPLES		CHAPTER CASES
8	Cardiomyopathy, arrhythmias, and hypertension are common types of cardiotoxicity observed in patients receiving infusion and oral anticancer therapies. Anthracycline-induced cardiomyopathy is closely linked to a patient's cumulative dose and may be treated with current heart failure medications.	**Case 94-8 (Questions 1–4)**
9	Several anticancer agents carry severe risks of nephrotoxicity and bladder toxicity for which preventive measures are necessary. Cisplatin is one of the most nephrotoxic agents. Preventive strategies for cisplatin nephrotoxicity include normal saline hydration, mannitol, and amifostine, and methotrexate-induced nephrotoxicity may be prevented with alkalinization of the urine and leucovorin rescue. Ifosfamide-induced hemorrhagic cystitis may be prevented with concomitant use of mesna.	**Case 94-9 (Questions 1, 2) Case 94-10 (Questions 1–3), Table 94-6**

CORE PRINCIPLES		CHAPTER CASES
10	Many anticancer medications demonstrate organ-specific toxicities, such as pulmonary fibrosis caused by bleomycin and transaminitis caused by cytarabine. Specific treatments for the resolution of these toxicities do not exist; rather, supportive care for symptoms is necessary. If adverse effects do not resolve, discontinuation of therapy or dose modifications may be warranted.	**Case 94-11 (Questions 1–4) Case 94-12 (Question 1), Tables 94-7, 94-8**
11	Many anticancer agents cause long-term complications after therapy, including treatment-related acute myeloid leukemia, lymphomas, bladder cancer, and bone sarcoma. The risks of secondary malignancies should be considered in assessing the adverse effect profile within the risks and benefits of specific types of therapy.	**Case 94-13 (Questions 1, 2)**
12	Cytotoxic chemotherapy is potentially gonadotoxic with the use of specific agents. Sex, age, agent, and cumulative dose are factors in determining the risk of infertility. Methods of preserving fertility should be discussed with patients before initiating therapy.	**Case 94-14 (Question 1) Case 94-15 (Questions 1–3)**

INTRODUCTION

Cytotoxic, targeted, and immune-directed anticancer agents are toxic to cancer cells and also to various host tissues and organs. Adverse effects of anticancer therapies occurring with both infusional and oral therapies can be classified as common and acute toxicities, specific organ toxicities, and long-term complications. Common and acute toxicities generally occur as a result of inhibition of host-cell division. Host tissues with renewal cell populations are most susceptible to cytotoxic agents including lymphoid tissues, bone marrow, and epithelium of the gastrointestinal (GI) tract and skin. Other common and acute toxicities (eg, hypersensitivity reactions) frequently occur in patients shortly after therapy. Specific organ toxicities often are attributed to a unique uptake or a selective toxicity of the anticancer agent to the organ. Long-term complications occur months to years after anticancer therapy and are secondary to continued immunodeficiencies or from permanent damage to organ cells from the anticancer therapy. Regardless of the type of toxicity observed, most are classified for severity by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events. These standardized definitions create a common method for the classification of adverse events in clinical trials and for the management of anticancer therapy administration for patients receiving standard-of-care therapies.[1] These criteria may be accessed at the NCI website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Toxicities associated with anticancer therapies are the biggest limitation to the use of potentially curative doses. Therefore, all discussions regarding the benefits of anticancer agents must include a discussion of their associated toxicities.

Concerns regarding the toxicities of therapy include the incidence, predictability, severity, and reversibility of the adverse effects. These variables can be influenced by the specific agent, dose intensity, and treatment duration. Although predictable, the incidence and severity of adverse effects often vary depending on individual susceptibility. Distinguishing disease from the adverse effects of anticancer therapy remains challenging. Because several toxicities have well-

defined characteristics, clinicians should be aware of the most common adverse effects.

Clinicians should also be aware of patient-specific factors, such as the stage of disease, vital organ function, concomitant illnesses, and concurrent medications, which could cause signs or symptoms that mimic or contribute to the adverse effects. In addition, most patients with cancer receive many other medications, including antibiotics and analgesics, which may cause additional adverse effects or interact with anticancer agents. When a patient reports a new symptom, it may be difficult to determine whether it is secondary to anticancer therapy, concurrent medications, or disease progression. Understanding the toxicities of commonly used anticancer drugs and their management is important for optimal patient care.

COMMON AND ACUTE TOXICITIES

Hematologic Toxicities

The bone marrow contains a population of pluripotent stem cells capable of self-renewal and differentiation into any mature blood cell. Their progeny commits to either the myeloid or the lymphoid cell line. The myeloid stem cell further commits to developing into an erythrocyte (red blood cell [RBC]), megakaryocyte (platelet), or granulocyte (white blood cell [WBC]). Multiple types of granulocytes exist, including neutrophils, basophils, and eosinophils, although neutrophils are the most common type.

After committing to a particular cell line, bone marrow precursor cells undergo a series of divisions (mitosis) to increase the number of cells. The cells then undergo several developmental stages to mature and differentiate into their final forms (postmitotic) and leave the bone marrow. The total time required for a cell to pass through the mitotic and postmitotic pool under normal resting conditions is ~10 to 14 days. Although many cytokines have been identified to regulate this process, only a few growth factors are now produced

through recombinant deoxyribonucleic acid (DNA) technology for therapeutic use. These growth factors can expand the mitotic pool and accelerate maturation and differentiation, decreasing the total time spent in these stages to ~5 to 7 days.

The development and circulating life span of hematopoietic cell lines determine the severity of the depression of that cell line (nadir, lowest point) and their time course. Because RBCs survive ~120 days in the peripheral blood, clinically significant anemia is unlikely if production is impaired for a short period of time. Instead, anemia usually develops slowly after repeated courses of therapy. In contrast, platelets survive ~10 days, and granulocytes survive only 6 to 8 hours. Hence, neutropenia generally occurs before thrombocytopenia, but both may be observed after the first or subsequent courses of cytotoxic chemotherapy or targeted therapy. The clinician may have to adjust subsequent dosing based on nadir depth and time to recovery. Life-threatening neutropenia or thrombocytopenia often necessitates some action to minimize the risk of these toxicities. To mitigate these effects, one can delay therapy until recovery, reduce the dose, or administer colony-stimulating factors (CSFs, if neutropenia is of concern; or platelet transfusions, if thrombocytopenia is of concern).

MYELOSUPPRESSION

CASE 94-1

QUESTION 1: R.H., a 63-year-old, 130.07-pound (59-kg) female with no significant past medical history, presents to the university hospital with fever, night sweats, and unintended weight loss over the past 3 months. Physical examination reveals lymphadenopathy. An excisional lymph node biopsy of a cervical node reveals diffuse large B-cell lymphoma (DLBCL). Positron emission tomography (PET) scan reveals disease above and below the abdomen. R.H. is diagnosed with stage IV DLBCL. Her oncology team plans to initiate curative intent chemotherapy with rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.2 mg/m^2 on day 1 and prednisone 100 mg days 1 through 5.

Discuss the toxicities that might be expected to occur with this regimen.

What effects on the bone marrow can be anticipated and how might they clinically appear in R.H.? What factors can influence the incidence and severity of these adverse effects? When can R.H. expect these effects to occur?

This chemotherapy regimen can significantly affect any cell line, including RBCs, neutrophils, and platelets, causing significant morbidity or mortality. Decreased RBCs can cause anemia, and patients usually present with fatigue and decreased exercise tolerance. Having low neutrophil counts significantly increases a patient's risk of infections, which can be life-threatening. Moreover, reduced platelets can cause thrombocytopenia, which can increase the risk of bleeding from the GI and or genitourinary tracts as well as from the CNS.

Both patient-related and agent-related factors can significantly influence the degree of cytopenia a patient experiences after cytotoxic therapy. Agent-related factors include the specific agent, dose intensity, and dose density. Because most anticancer treatments are not given as a single agent, the effects of concurrent cytotoxic therapies may intensify the myelosuppressive effect of an individual agent. Host factors that may affect the cellularity of the bone marrow also influence the degree of cytopenia. They include the following:

1. Patient age: Younger patients are generally able to tolerate cytotoxic chemotherapy better than do elderly patients because they have a more cellular marrow with a decreased percentage of marrow fat.
2. Bone marrow reserve: Certain diseases might present with tumor cells in the bone marrow, such as leukemias and lymphomas. In these cases, the bone marrow does not have a healthy reserve of normal hematopoietic cells to help in the recovery process.
3. Previous cytotoxic chemotherapy, radiation therapy, or both: Prior cytotoxic chemotherapy and radiation therapy to fields involving marrow-producing bone (pelvic bone and sternum) reduce bone marrow reserves.

4. The ability of the liver or kidney to metabolize and excrete the compounds administered: If agents are administered to patients with specific organ insufficiencies (ie, renal or hepatic), slower clearance, resulting in increased systemic exposure, can occur. This can increase the severity and duration of cytopenias.

With most myelosuppressive agents, WBC and platelet counts begin to fall within 5 to 7 days of cytotoxic therapy administration, reach a nadir within 7 to 10 days, and recover within 14 to 26 days. Phase-specific cytotoxic chemotherapy agents, such as vinca alkaloids and antimetabolites, cause a fairly rapid onset of cytopenia that recovers faster than do those occurring with phase-nonspecific agents, such as alkylating agents and anthracyclines. Other agents that exhibit this pattern include mitomycin and mechlorethamine. All of these anticancer agents exert their cytotoxic effects during the resting phase of the cell cycle. The nitrosoureas, as well as mitomycin and mechlorethamine, can cause two neutropenic nadirs; the first nadir occurs at the conventional time expected for phase-nonspecific agents and the second nadir occurs ~4 to 6 weeks after therapy. Many combination regimens with these agents are therefore given in 6-week cycles to avoid treatment before the second nadir. However, most other myelosuppressive regimens can be safely given every 3 to 4 weeks. The majority of the targeted therapies do not suppress bone marrow production significantly, because they are designed to inhibit a specific molecular pathway or cell-surface marker rather than widely affecting rapidly proliferating cells. Because of their minimal myelosuppressive effects, targeted therapies may be desirable agents to add to regimens that are known to cause cytopenias.

Most of the agents included in R.H.’s regimen have myelosuppressive activity. Her older age may place her at higher risk for exhibiting myelosuppression. R.H. should be carefully counseled to contact her care team or report to the emergency department if she experiences signs or symptoms of an infection (including fever) or bleeding. Typically, these symptoms occur 10 to 14 days after the first day of chemotherapy.

Prevention of neutropenia

Case 94-1, Question 2: About 10 days after the first course of cytotoxic chemotherapy, R.H. experienced a fever. She was admitted to the hospital and treated with intravenous (IV) antibiotics. At the time, her WBC count was 300 cells/μL; absolute neutrophil count (ANC), 50 cells/μL; platelets, 102,000 cells/μL; and hemoglobin (Hgb), 11 g/dL. Her fever resolved after 3 days, and all culture findings were negative for bacterial growth. It is now 3 weeks after chemotherapy, and she is scheduled to receive a second course. Should she receive the same doses she was given initially?

One option would be to reduce (usually by 25%) the dose of each agent for all subsequent cycles. Although a dose reduction can clearly cause less neutropenia, reduced dose intensity can also compromise response and survival. Because R.H.'s cancer (ie, DLBCL) is both chemosensitive and potentially curable, a reduction in dosage is undesirable. To minimize the risk of neutropenia with future therapy, CSFs can be administered to R.H. to prevent potential complications associated with neutropenia.

Prophylactic administration of CSFs can be used to reduce the myelosuppressive effects of cytotoxic chemotherapy. Several CSFs —granulocyte colony-stimulating factors (G-CSFs [filgrastim, etc]), granulocyte-macrophage colony-stimulating factor (GM-CSF [sargramostim]), and pegylated long-acting forms of filgrastim (pegfilgrastim, etc) are available in the United States. Pegylated filgrastim products were developed to provide the same pharmacologic benefit as filgrastim while offering the advantage and convenience of fewer injections.

Since the approval of the first CSF on the biosimilar pathway in 2015 (filgrastim-sndz), the U.S. Food and Drug Administration (FDA) has approved multiple biosimilar products for both filgrastim and pegfilgrastim. Although tbo-filgrastim was FDA approved in 2012, it is not considered a biosimilar because it was filed as a Biologics License Application, before the establishment of the FDA biologics approval pathway.

Evidence-based clinical practice guidelines for the use of CSFs have been developed by the National Comprehensive Cancer

Network (NCCN).[2] These guidelines recommend the administration of CSFs for primary prophylaxis in all patients receiving chemotherapy regimens that have been previously reported to cause a febrile neutropenia incidence of ~20%. CSF use in these patients can reduce the incidence, duration, and severity of febrile neutropenia, decrease the need for hospitalizations and broad-spectrum antibiotics, and improve the delivery of full-dose intensity chemotherapy on schedule.

Although the use of CSFs has not been shown to lead to better tumor response, it has shown a reduction in the incidence of febrile neutropenia and survival advantage. A meta-analysis of 17 randomized trials, including 3493 adult patients with solid tumors and lymphomas, showed that the use of filgrastim as primary prophylaxis reduced the risk of febrile neutropenia and improved the rate of full-dose cytotoxic chemotherapy given on schedule. In addition, the investigators in the meta-analysis observed a significant reduction in the risk of infection-related mortality and early death because of chemotherapy.[3] A systematic review of 25 randomized controlled trials (RCTs) involving over 12,000 patients confirmed this survival advantage. Compared to no-CSF support, use of CSF showed a reduction in both the relative and absolute risk of mortality. The degree of survival benefit correlated with dose intensity of chemotherapy received by the patient.[4]

The use of CSFs for secondary prophylaxis is recommended by NCCN for those patients who experience a neutropenic complication from the prior cycle, where primary CSF was not used, or when a reduced dose or treatment delay may negatively impact the survival/treatment outcome.[2] Because the regimen R.H. received does not typically produce a 20% incidence of febrile neutropenia, a CSF was not recommended for her after her first course of cytotoxic chemotherapy. Now that R.H. has experienced febrile neutropenia and she has a potentially curable malignancy, a CSF is indicated with subsequent courses of chemotherapy to prevent additional febrile episodes.

Dosing of colony-stimulating factors

Case 94-1, Question 3: How should a CSF be dosed in R.H. to reduce the severity of chemotherapy-induced neutropenia?

The recommended initial dose of G-CSF is 5 µg/kg/day as a single daily subcutaneous (SC) injection beginning 24 to 72 hours following the administration of myelotoxic chemotherapy. The dose may be rounded to the nearest vial size to improve patient convenience and reduce cost. Owing to lack of evidence, sargramostim is not recommended as a preventative CSF and is primarily reserved for stem cell mobilization before stem cell transplant.

The manufacturers recommend that therapy with filgrastim continues until the patient's neutrophil count is >10,000 cells/µL after the expected chemotherapy nadir. This is based on the observation that the neutrophil count falls roughly 50% after discontinuing a CSF. The risk of bacterial infection is highest, however, in patients with neutrophil counts of <500 to 1000 cells/µL; patients with neutrophil counts greater than that are not thought to be at high risk for bacterial infections. Thus, the national guidelines recommend continuation until post-nadir ANC has recovered to normal or near-normal laboratory standards. Many clinicians elect to discontinue the CSF when the neutrophil count reaches 2000 to 4000 cells/µL after the chemotherapy nadir to reduce the number of treatment days and cost.

Pegylated versions of filgrastim have a longer half-life, allowing for a single administration of 6 mg 24 to 72 hours after myelotoxic chemotherapy. In general, there should be at least 12 days between the dose of pegylated filgrastim and the next cycle of chemotherapy.[2] For patient convenience, a new formulation of pegfilgrastim that is a timed automated-inject device that delivers the medication 27 hours after it is activated was approved, allowing for application on the same day as chemotherapy.[5] In summary, options for R.H. include G-CSF 300 µg/day beginning the day after her last dose of chemotherapy and continuing until the ANC is >2000 to 4000 cells/

μL. Alternatively, R.H. could receive pegylated filgrastim 6-mg single injection the day after chemotherapy administration. The most common adverse effect associated with G-CSF is mild-to-moderate bone pain. Bone pain is most commonly experienced when patients begin to recover peripheral blood cells after their nadir. The proposed mechanism involves multiple factors, including inflammation and histamine release. Most patients commonly report pain in bone marrow–rich areas, such as the sternum and pelvic regions. Patients should be advised that the bone pain experienced during marrow recovery is normal. Treatment options include analgesic agents and antihistamines such as loratadine.[2]

Treatment of fever and neutropenia with a colony-stimulating factor

Case 94-1, Question 4: If R.H. was not given filgrastim and presented with febrile neutropenia, would CSF therapy be helpful?

Febrile neutropenia leads to increased hospital admissions and greater morbidity and mortality, so the optimal indication for CSFs is as prophylaxis; however, CSFs have been studied as part of the treatment of neutropenic fever. Because the duration of neutropenia is the most significant prognostic factor in patients with established febrile neutropenia, the major benefit of CSFs is their ability to reduce the duration of neutropenia.

The ability of CSFs to reduce the duration of neutropenia in patients with established febrile neutropenia has been addressed in numerous randomized, double-blind, placebo-controlled trials and two meta-analyses.[6–8] The combined data reveal minimal-to-moderate benefit in reducing hospital stays and no differences in mortality. Furthermore, questions have been raised as to whether all patients with febrile neutropenia require hospitalization. Several studies have shown equal efficacy and safety with increased cost-effectiveness of outpatient treatment of febrile neutropenia based on patient-specific risk factors.[9–11] Although CSFs do appear to hasten

neutrophil recovery, the true cost–benefit ratio associated with the use of these products in established febrile neutropenia remains to be determined. The NCCN guidelines currently do not support routine use of CSFs in patients with febrile neutropenia, although they do recognize that certain patients with febrile neutropenia and high-risk features predictive of poor outcome (eg, age older than 65 years, pneumonia, fungal infection, sepsis syndrome, anticipated >10 days of neutropenia, or prior episode(s) of febrile neutropenia) may benefit from use of CSFs.[2]

Thrombocytopenia

A reduction in platelets is another common myelosuppressive toxicity seen with chemotherapy and targeted therapies. Each chemotherapy agent differs in how it causes thrombocytopenia, and incidence and severity vary greatly depending on the treatment used. Treatment-induced thrombocytopenia is generally short lived. If needed, it is usually managed via the use of platelet transfusions and modifications to the chemotherapy dosing scheme.

Thrombopoietin is the main regulator of platelet production. There are now available thrombopoietin receptor agonists that are potent stimulators of platelet production. At this time, however, there is insufficient evidence to recommend their routine use for chemotherapy-induced thrombocytopenia.[12]

Anemia

Anemia usually is not a dose-limiting toxicity commonly associated with cytotoxic chemotherapy, because RBCs survive ~120 days. Chemotherapy predominantly affects RBCs by causing anisocytosis and macrocytosis. These effects are related to inhibition of DNA synthesis, and they predominantly occur after treatment with antimetabolites, including folic acid analogs, hydroxyurea, purine antagonists, and pyrimidine antagonists. Anemia commonly does not accompany these changes in RBC size. In addition, chemotherapy-induced effects on RBCs are rarely the sole factor contributing to the

low Hgb levels that necessitate an RBC transfusion. See Chapter 92, Anemias, for additional information on anemias and their treatment.

BLEEDING AND COAGULOPATHIES

Bleeding can occur after treatment with asparaginase or the pegylated formulation, pegaspargase, because of inhibition of the synthesis of fibrinogen and other specific coagulation factors produced by the liver under the influence of vitamin K.[13–15] Asparaginase has a widespread effect on protein synthesis, and many plasma protein factors are depressed shortly after treatment. A patient receiving asparaginase can often exhibit a depressed fibrinogen and a prolonged prothrombin time (PT) and partial thromboplastin time (PTT). This suggests that there may be a global inhibition of the production of both coagulant and anticoagulant proteins in the liver. Treatment of low fibrinogen and the prolonged PT and PTT with coagulation factors, fibrinogen, cryoprecipitate, fresh-frozen plasma, and antithrombin III remains controversial. In addition, the role of thrombosis prophylaxis in these patients has not been clearly defined.

Bleeding can also occur with the Bruton tyrosine kinase (BTK) inhibitors because of both on-target and off-target kinase inhibition. BTK, along with additional members of the SFK (src family kinases) and the TEC family are involved in several platelet activation and adhesion functions.[16] Ibrutinib, a first-generation BTK inhibitor, shows strong inhibition of BTK and TEC, and is associated with a higher risk of bleeding. Unlike ibrutinib, second-generation BTK inhibitors, acalabrutinib and zanubrutinib show a lower risk of bleeding because they do not inhibit TEC and are more specific to BTK. It is recommended to avoid the combination of warfarin and a BTK inhibitor because of the heightened risk of fatal bleeds noted in early clinical trials.[17] However, use of anticoagulation or antiplatelet therapy in patients on BTK inhibitors is not a contraindication.

Thrombotic events

The risk of venous thrombotic events is markedly elevated in patients with cancer. Trousseau first reported an increased incidence of venous thrombosis in patients with cancer, and many investigators have since confirmed this relationship.[18] Up to one-third of apparently healthy adults who exhibit otherwise unexplained deep vein thrombosis eventually are proved to have a malignancy.[19,20] Possible pathophysiologic mechanisms include hypercoagulability marked by abnormalities in clotting factors and the coagulation cascade, vessel wall damage, and vessel wall compression by tumor masses. Additional risk factors for thromboembolic events include the type and stage of cancer, comorbidities, mobility, and type of systemic anticancer therapy received, among others. Pancreatic, stomach, kidney, lung, brain, and uterine cancers are associated with the highest risk of thrombosis.[21] Several anticancer agents have been associated with an increased thrombosis risk, including, but not limited to, cytotoxic chemotherapy and hormonal agents.[22]

The immunomodulatory agents, in combination with other agents, including dexamethasone and doxorubicin, have been associated with venous thromboembolic events when used in the treatment of multiple myeloma and other diseases.[23–25] Prophylaxis is warranted when these agents are used. Guidelines address prophylaxis, including the use of aspirin, low-molecular-weight heparin (LMWH), and warfarin, for patients on immunomodulatory agents.[23,26,27] At this time, there is insufficient evidence to recommend the use of direct-acting oral anticoagulants (DOACs) for prophylaxis in those receiving immunomodulatory agents.

The vascular endothelial growth factor (VEGF) inhibitors are associated with both arterial thrombosis and bleeding events. A pooled analysis of the VEGF inhibitor bevacizumab and meta-analysis of the tyrosine kinase inhibitors (TKIs) sorafenib and sunitinib demonstrated a 3.8% and 1.4% incidence of arterial thrombosis, respectively.[28,29] Most bleeding events associated with VEGF inhibitors are minor. However, severe major bleeding events have been reported in patients with metastatic colorectal and lung cancer.[30]

Other factors can cause patients to experience thrombosis. Many patients receiving cancer therapy often undergo surgical procedures, remain immobile, and have other illnesses, such as infection, that may predispose them to developing thrombosis. Clinicians should maintain a high index of suspicion when a patient with cancer presents with signs or symptoms of thrombosis. National guidelines exist to guide treatment of thrombotic events in patients with cancer.[23] Depending on the clinical scenario, patient risk of thrombocytopenia or bleeding, and patient preference, LWMH, DOACs, and warfarin are suitable options for the management of cancer-associated thrombosis. The optimal duration of anticoagulation for cancer-associated thrombosis remains controversial. Treatment is typically continued until there is no evidence of active malignancy or if the risk of further anticoagulation outweighs the benefit.

Disseminated intravascular coagulation (DIC) occurs in many patients with acute promyelocytic leukemia (APL).[31,32] DIC is a systemic process that results from activation of the clotting cascade and presents as overlapping bleeding and thrombotic events. These events can result in end-organ damage, including intracranial hemorrhage. The lysed tumor cells in patients with APL appear to release procoagulant materials after anticancer therapy, causing both hemorrhagic and thrombotic events. The foundation of treatment for DIC is to treat the underlying disease. Use of heparin and antifibrinolytics to minimize the risk of coagulation is controversial. Other treatment is primarily supportive with blood products, including platelets and cryoprecipitate.[32]

Gastrointestinal Tract Toxicities

The GI tract may be second only to bone marrow in its susceptibility to toxic effects produced by cytotoxic chemotherapy and targeted therapies. GI toxicities include nausea and vomiting, oral complications, esophagitis, and lower bowel disturbances.

NAUSEA AND VOMITING

Nausea and vomiting are common and serious toxicities associated with many cytotoxic and targeted anticancer agents. Anticancer agents or their metabolites may stimulate dopamine or serotonin receptors in the GI tract, chemoreceptor trigger zone, or CNS, which ultimately act on the vomiting center. Emesis most commonly occurs on the first day of chemotherapy and often persists for several days thereafter.[33] Most patients who receive traditional cytotoxic chemotherapy agents require antiemetics before and after chemotherapy for several days to prevent and control these symptoms. The most appropriate antiemetic regimen is based on patient-specific and agent-specific factors. Some targeted therapy agents carry a risk of emetogenicity, although it is generally milder. Guidelines incorporate targeted agents into their emetogenic classification schema based on the incidence of nausea and vomiting in clinical trials (see Chapter 22, Nausea and Vomiting, for antiemetic algorithms and emetogenic potential of anticancer agents).

COMPLICATIONS OF THE ORAL CAVITY

Complications of the oral cavity include mucositis (or stomatitis), xerostomia (dry mouth), infection, and bleeding. The incidence of severe oral mucositis varies with the anticancer therapies given. Doxorubicin and continuous-infusion fluorouracil are among chemotherapy agents at highest risk for causing severe mucositis. Virtually all patients who receive myeloablative hematopoietic cell transplantation (HCT) or have radiation therapy to the head and neck experience oral complications.[34] These toxicities occur because of the nonspecific effects of chemotherapy and radiation on cells undergoing rapid division, including the cells of the mouth that undergo rapid renewal with a turnover time equal to 7 to 14 days. Cytotoxic therapy reduces the renewal rate of the basal epithelium and can cause mucosal atrophy, as well as glandular and collagen degeneration.[34] Radiation therapy to the head and neck causes mucosal atrophy by decreasing cell renewal, fibrosis of the salivary

glands, muscles, ligaments, and blood vessels, and damage to the taste buds.[35] Although targeted therapies are generally less toxic to normal cells, they can have substantial effects on oral tissues.[36] The current understanding of the mechanism of oral injury with targeted therapies is limited; however, clinical features of oral lesions differ from those of chemotherapy or radiation.

The combined effects of therapy on the oral mucosa can also cause infection and bleeding in the oral cavity. Because the oral mucosa is highly vascular and frequently traumatized, bleeding occurs commonly with thrombocytopenia. In addition, neutropenia can lead to oral infections by the extensive microbial flora of the oral cavity.

Oral complications often compound one another. Mucositis can clearly predispose the oral cavity to local bleeding and infection, as well as systemic infections leading to sepsis. These oral complications can also cause varying degrees of discomfort and adversely affect the patient's ability to eat, which may lead to a compromised nutritional status and an inability to continue further anticancer therapy. Treatments for the management of oral complications are reviewed extensively in guidelines.[37]

Xerostomia

CASE 94-2

Question 1: J.B. is a 55-year-old male with newly diagnosed, locally advanced head and neck cancer. His planned therapy includes cisplatin and fluorouracil given with concurrent radiation for a total of 6 weeks after surgical resection. A review of systems suggests that J.B. has poor oral hygiene, and a decision is made to consult the dental department of the university hospital before initiating radiation and chemotherapy.

Is J.B. at risk for experiencing oral complications of chemotherapy? Should anything be completed at this point to decrease his risk?

J.B. is at high risk for several of the oral complications previously described. Xerostomia, one of the most frequent side effects of radiation therapy to the head and neck, is multifactorial, mostly

occurring secondary to radiation-induced changes to the salivary glands.[38] Evidence supports a direct relationship between the radiation dose to the salivary glands and the extent of glandular changes.[39] The radiation level necessary to cause severe dysfunction to gland tissue is >52 Gray (Gy, radiation absorbed dose).[40] Below this threshold, the radiation damage to salivary glands generally has a transient and reversible duration within 6 to 12 months.

J.B. will receive a total of 50 to 70 Gy. He will also be receiving chemotherapy agents (ie, cisplatin) that can cause xerostomia and enhance the toxicity to the salivary glands.

Damage to the salivary glands causes various effects, including a loss of salivary buffering capacity, lower salivary pH, and reduction of saliva production. In addition, xerostomia can alter the sense of taste, causing some patients to lose their ability to taste or differentiate between tastes. Xerostomia also commonly causes caries. Caries and decalcification may become sufficiently severe to compromise tooth integrity and cause fracture. Because saliva is no longer available to help clear bacteria from the mouth, xerostomia also predisposes patients to oral infection.

Treatments and Prevention

Amifostine, an organic thiophosphate chemoprotection agent, is approved to reduce the incidence of moderate-to-severe xerostomia in patients having postoperative radiation treatment for head and neck cancer. Guidelines support the use of amifostine to reduce the incidence of xerostomia in patients receiving fractionated radiation therapy without concurrent chemotherapy for head and neck cancer.[41] However, amifostine is not widely used because of its cost and adverse effect profile, which includes hypotension. If xerostomia occurs, treatment strategies can include stimulation of existing salivary flow and replacement of lost secretions. Relatively low doses of systemically administered pilocarpine (5–10 mg orally three times daily) may stimulate salivary flow and produce clinically significant benefits in patients with postradiation xerostomia.[42]

Results demonstrating pilocarpine's benefit are inconsistent. Dose-related adverse effects include cholinergic effects, such as sweating, rhinitis, headache, nausea, and abdominal cramps. Cevimeline (30 mg orally three times daily) and bethanechol (25 mg orally three times daily) may have fewer side effects than does pilocarpine; however, evidence is lacking.[41] Sugarless chewing gum or candy-containing xylitol or sorbitol and saliva substitute can also be used to stimulate salivation and provide oral comfort.

Teeth should be cleaned at least twice a day and the daily use of fluoride and chlorhexidine rinses may also be useful in preventing caries. In general, a dentist should see patients who will be receiving radiation therapy to the head and neck or chemotherapy agents with a high risk of oral complications before starting therapy. This includes patients with hematologic malignancies who will most likely experience severe myelosuppression for prolonged periods. Oral evaluation before therapy with intervention to eliminate potential sources of infection or irritation and preventive measures taken during therapy can dramatically decrease the frequency of oral complications.[43,44] Given J.B.'s risk factors, including the dose of radiation he will receive and concomitant therapy with cisplatin, a dental examination is indicated before initiating therapy.

Mucositis and stomatitis

Case 94-2, Question 2: J.B. successfully completed his first 2 weeks of combined chemotherapy and radiation therapy; however, 3 days into his third week, he endorses generalized burning, discomfort, and pain on the ventral surface of his tongue. On clinical observation, both the ventral surface of his tongue and the floor of his mouth appear erythematous, and several discrete lesions are present in both areas. What is the most likely explanation for J.B.'s new onset of symptoms? What treatment is indicated at this time?

Mucositis occurs as a nonspecific effect of chemotherapy and radiation therapy on the basal epithelium of the mouth. Nonkeratinized mucosa is affected most often. Thus, the buccal, labial, and soft palate mucosa, the ventral surface of the tongue, and

the floor of the mouth are the most common sites of involvement. Although lesions are generally discrete initially, they often progress to produce large areas of ulceration. The lesions typically do not progress outside the mouth, but they may extend to the esophagus and involve the entire GI tract. Signs and symptoms generally occur about 5 to 7 days after chemotherapy or at almost any point during radiation therapy. The antimetabolites (eg, methotrexate, fluorouracil, capecitabine, and cytarabine) and the antitumor antibiotics are the chemotherapy agents that most commonly produce direct effects on the epithelial cells of the GI tract. Lesions generally regress and resolve completely in ~1 to 3 weeks, depending on their severity.

The terms stomatitis and oral mucositis may be used interchangeably. Unlike oral toxicity seen with conventional chemotherapy or radiation, aphthous-like mucositis (canker sores) or stomatitis is a prevalent toxicity distinctly seen with targeted therapies, such as mTOR (mammalian target of rapamycin) inhibitors. Lesions typically appear during the first cycle of therapy, within the first week. Other targeted therapies, such as sunitinib, regorafenib, and sorafenib, cause oral sensitivity or burning with no other clinical signs.

Treatments and Prevention

Management often consists of supportive care measures and dose reductions.[44,45]

Topical anesthetics, most commonly viscous lidocaine 2%, are often recommended. Equal portions of lidocaine, diphenhydramine, and magnesium-containing or aluminum-containing antacids can be used for their anesthetic and astringent properties. Many institutions compound mouthwash products containing these ingredients as well as nystatin or corticosteroids. Topical sucralfate is not recommended because of lack of efficacy.[45] These topical products provide symptom control only and are not effective for lesions in the lower GI tract. All the topical anesthetic-containing preparations are recommended for use as “swish and spit.” The risk of the systemic effects from topical anesthetic preparations is slim if patients were to

swallow them; however, large quantities swallowed could induce sedation and possible arrhythmias.

Gelclair® is a bioadherent oral gel containing polyvinylpyrrolidone, hyaluronic acid, and glycyrrhetinic acid (but no alcohol or anesthetic agent). It provides an adherent barrier over the mucosal surfaces, thereby shielding oral lesions from the effect of food, liquids, and saliva.[46] Controlled clinical data are lacking, and no significant differences have been found between use of Gelclair® and standard of care in relieving general pain.[47] Other palliative treatment options include topical benzocaine and ice chips. Patients may also find ice chips soothing by allowing them to melt in their mouth.

In severe cases, mucositis may require parenteral opioid analgesics for relief. Mucositis may be confused with or occur concurrently with an oral infection (particularly thrush). Under normal conditions, the mucosa provides a natural barrier to the entry of normal oral flora, but the ulcerated mucosa allows pathogens access to the bloodstream. It is important to note that patients can develop life-threatening infection or sepsis in addition to a local infection.

J.B. appears to have a mild case of stomatitis or mucositis at this time. J.B. should be encouraged to maintain good mouth care by keeping his mouth clean. In addition, topical anesthetics are indicated for J.B. Topical lidocaine or a mixture of topical lidocaine with diphenhydramine and an antacid, 5 to 10 mL swish and spit three to six times per day, should be recommended. If the lesions progress during the next several days, systemic opioids may be necessary. J.B. should also be carefully assessed for local infections within his mouth.

Case 94-2, Question 3: Could J.B.'s mucositis have been prevented?

Treatment of therapy-induced mucositis is aimed at reducing symptoms once they occur and avoiding further trauma to the oral mucosa. Guidelines recommend cryotherapy in patients receiving bolus fluorouracil and high-dose melphalan.[45,48] With cryotherapy, ice chips are placed in the mouth 5 minutes before chemotherapy

begins and retained for 30 minutes. Theoretically, this reduces blood flow to the mouth, thereby protecting the dividing cell population from toxins.

Chlorhexidine gluconate 0.12% also may reduce the frequency and severity of mucositis and infection by eliminating microorganisms in the oral cavity.[49,50] Not all studies have shown a benefit with prophylactic chlorhexidine, and its use can cause oral burning due to the product's alcohol content. Alcohol-free formulations are available and preferred. Prophylactic use of dexamethasone mouthwash significantly reduces the incidence and severity of stomatitis in patients receiving the mTOR inhibitor everolimus.[51] Because of this, topical, intralesional, or systemic steroids can be used for the management of ulcerative stomatitis due to targeted therapies.

Palifermin, a keratinocyte growth factor, is approved for patients with hematologic malignancies undergoing HCT to reduce the incidence and duration of severe oral mucositis. For further discussion, see Chapter 101, Hematopoietic Stem Cell Transplantation.

Other methods for decreasing the incidence and severity of mucositis symptoms include reducing the dose of radiation, cytotoxic, or targeted therapy, but doing so comes at the risk of compromising treatment outcomes. Mucositis remains a dose-limiting toxicity for several anticancer regimens. Unfortunately, there are no prevention strategies that would reduce the chance of J.B. experiencing mucositis from his chemotherapy and radiation, and, thus, treatment for J.B. is targeted toward relief of symptoms.

ESOPHAGITIS

Cytotoxic chemotherapy and radiation therapy can also damage the mucosal lining of the esophagus. Although dysphagia is a common symptom reported by patients with esophagitis, other causes of dysphagia should be excluded. Because patients receiving myelosuppressive therapy may exhibit infectious esophagitis, bacterial, viral, and fungal cultures should be completed to search for

infectious causes before starting treatment for esophagitis. Symptomatic management of esophagitis is similar to the management of mucositis. Other treatment modalities, including behavioral modifications (eg, elimination of acidic and irritating foods) and other medications (eg, histamine-2 [H_2] receptor antagonist, antacids, and proton-pump inhibitors), may reduce esophageal irritation and improve comfort. Patients with severe esophagitis should be carefully monitored to ensure adequate oral hydration and nutritional intake.

LOWER GASTROINTESTINAL TRACT COMPLICATIONS

Lower GI tract complications associated with anticancer therapy include malabsorption, diarrhea, and constipation. These complications may be related to structural changes that occur to the GI tract as a result of disease, after cytotoxic, targeted, or radiation therapy, graft versus host disease, and infections.

Diarrhea is common during cancer treatment and is seen with a number of cytotoxic (such as irinotecan- or fluorouracil-based regimens) and targeted therapies (such as idelalisib, ibrutinib, bosutinib, and neratinib). Unlike diarrhea, constipation is rare. The vinca alkaloids, which produce colicky abdominal pain, constipation, and adynamic ileus caused by autonomic nerve dysfunction (see the section on Neurotoxicity), can cause chemotherapy-induced constipation. Constipation should be treated prophylactically with stool softeners and mild stimulant laxatives. In addition, many medications (eg, opioid analgesics and antiemetics) and clinical conditions (eg, immobility and spinal cord compression) commonly associated with cancer and anticancer therapies can contribute to these symptoms.

Diarrhea

CASE 94-3

QUESTION 1: B.G., a 60-year-old female with recurrent colorectal cancer refractory to FOLFOX (fluorouracil, leucovorin, and oxaliplatin), is beginning her first course of cetuximab and irinotecan.

What instructions should she receive regarding the management of diarrhea if she experiences this complication?

Diarrhea is a common toxicity seen with both cytotoxic and targeted therapies; and it can cause depletion of fluids and electrolytes, malnutrition, dehydration, and hospitalization, all of which can interfere with cancer treatment and may have an impact on survival. Diarrhea is a toxicity in which patient education is paramount.

The mechanism of diarrhea is not completely understood, is likely multifactorial, and varies depending on the therapy. Diarrhea may result from direct effects on the GI mucosa, secretory factors, dysmotility, immune-related, and parasympathetic (irinotecan) effects. A review provides an excellent summary of targeted therapy–induced diarrhea.[52]

Irinotecan can cause two patterns of severe diarrhea, early and late onset, which appear to be mediated by different mechanisms. The early-onset diarrhea (within 24 hours of treatment) is cholinergic in nature and is often accompanied by other cholinergic symptoms, such as rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and abdominal cramping. These symptoms can be prevented or managed with atropine. Late-onset diarrhea (generally occurring >24 hours after treatment) can be prolonged, leading to dehydration, electrolyte imbalances, and significant morbidity and is not cholinergic mediated. Late-onset diarrhea should be managed with antimotility agents, usually loperamide.[53] The maximum dose of loperamide (16 mg in 24 hours) does not apply for irinotecan-induced diarrhea. Fluid and electrolyte replacement should also be administered, if necessary. Guideline-recommended additional options for diarrhea management include diphenoxylate-atropine, the somatostatin analog, octreotide, and tincture of opium or paregoric.[54] Diphenoxylate plus atropine is used as second line or in combination with loperamide for the treatment of grade 1 or 2 diarrhea at a dosage of 1 to 2 tablets every 6 to 8 hours.

Side effects include dry mouth, blurred vision, insomnia, and dyspepsia.[55]

Evidence for octreotide for therapy-induced diarrhea is inconsistent.[56] Nevertheless, some evidence shows that octreotide may be used to successfully manage diarrhea associated with fluorouracil and other high-dose chemotherapy regimens.[56,57] Octreotide regulates intestinal fluid and electrolyte transport, increasing transit time and reducing intestinal secretions. Although responses seem to correlate with increasing octreotide dose, more studies are needed to determine the optimal dose.[58,59] Based on current evidence and the cost of octreotide, use is limited to second-line therapy for cytotoxic therapy–associated diarrhea. Other treatment options for chemotherapy-induced diarrhea, including antibiotics, opioids, and corticosteroids, have been evaluated and are summarized in review articles.[54,60]

B.G. is also to receive cetuximab, an epidermal growth factor receptor (EGFR) inhibitor in combination with irinotecan. Diarrhea is a common side effect of cetuximab when given alone or in combination therapy.[52] No specific guidelines are available to guide in the management of targeted therapy–induced diarrhea. Because a secretory mechanism represents the most frequent cause of the diarrhea with targeted agents, loperamide is the first choice for management. Certain targeted agents, such as neratinib, a human epidermal growth factor receptor 2 (HER2) TKI indicated in breast cancer, require antidiarrheal prophylaxis with loperamide at therapy initiation because of high incidence and severity of treatment-induced diarrhea.[61] The incidence and severity of diarrhea with targeted agents generally declines over time and may be dose related.[52]

Some targeted therapies and immunotherapies can cause immune-mediated diarrhea and/or colitis. Specific guidelines exist to guide management of immunotherapy-related GI toxicities, including the use of corticosteroids.[62] Other medications indicated for inflammatory bowel diseases, such as infliximab and vedolizumab, may be useful in certain circumstances. For further discussion, see the section on Immunotherapy-related toxicities.

B.G. should be counseled on the diarrhea that is seen with irinotecan. She should be instructed to call her clinic if she experiences diarrhea within 24 hours of administration of irinotecan so that she can receive prompt atropine therapy. In addition, she should be given instructions for loperamide administration and oral hydration recommendations for diarrhea occurring beyond the initial 24 hours after chemotherapy. For future cycles of therapy, atropine can be given prophylactically to prevent future occurrence of early-onset diarrhea, if it occurs.

Dermatologic Toxicities

Dermatologic toxicities associated with anticancer therapies include alopecia, rash (ranging from acneiform to toxic epidermal necrolysis), hyperpigmentation, radiation recall, photosensitivity, nail changes, hand–foot syndrome, hypersensitivity reactions, and extravasations. Several reviews serve as excellent references and provide detail related to dermatologic toxicities of targeted agents.[63–66]

ALOPECIA

CASE 94-4

Question 1: C.W. is a 45-year-old female with recently diagnosed breast cancer, who underwent lymph node dissection and lumpectomy. She will receive radiation therapy to the affected breast and chemotherapy to minimize her risk of recurrence. She is in the clinic today to receive the first of four cycles of doxorubicin and cyclophosphamide (AC). You counsel C.W. on the most common toxicities she might experience by reviewing the likelihood and management of myelosuppression, nausea, and vomiting. Her overriding concern is whether she will lose her hair.

Is C.W.'s concern typical of most patients with cancer? How would you respond?

Several investigators have reported that hair loss ranks second only to nausea and vomiting as a patient's greatest fear. Because hair

follicles replicate every 12 to 24 hours, the cells are susceptible to various cytotoxic chemotherapy agents. Normally, hair follicles independently move cyclically through phases of growth (anagen), involution or transition (catagen), and rest (telogen). Because ~85% to 90% of hair follicles are in the anagen phase, chemotherapy agents may partially or completely inhibit mitosis or impair metabolic processes in the hair matrix. These effects can cause a thinned or weakened hair shaft or failure to form hair. Hair loss usually begins 7 to 10 days after the first treatment, with prominent hair loss noted within 1 or 2 months.

Targeted anticancer therapies may cause hair thinning without complete hair loss. Other terminal hairs, such as beards, eyebrows, eyelashes, and axillary and pubic hair, can be affected; however, these effects are somewhat variable, depending on the rate of mitosis and the percentage of hairs in the anagen phase.[67,68]

C.W. should be informed about the expected onset of hair loss, and she should be reassured that alopecia caused by cytotoxic chemotherapy is reversible. She can expect her hair to begin regenerating 1 to 2 months after therapy is completed. The color and texture of her hair may be altered when it has grown back.

Several interventions have been proposed to prevent scalp hair loss during chemotherapy. These procedures attempt to prevent chemotherapy agents from circulating to the hair follicles with either an occlusive scalp tourniquet or a cooling cap that produces a localized hypothermia and vasoconstriction. The Paxman™ Scalp Cooling System is an FDA-approved product for patients with solid tumors to reduce chemotherapy-related hair loss. It has demonstrated variable efficacy in hair retention during chemotherapy.[69] Recognizing that such devices create a refuge for tumor cells, these procedures are contraindicated in patients with hematologic malignancies and in others at risk for CNS metastases. Concerns regarding the safety of these devices have slowed widespread uptake in the U.S. market.[70,71] Topical minoxidil has been studied with unimpressive results to date.[71]

C.W. is likely to experience near or complete hair loss, depending on the thickness of her hair and its growth rate. She should be

educated on options to minimize the effect of alopecia on her appearance, if desired, through the use of hair pieces or stylish head wraps.

CASE 94-4, QUESTION 2: Besides alopecia, what other skin or nail changes should C.W. anticipate?

NAIL AND SKIN CHANGES

Several skin and nail changes have been associated with cytotoxic and targeted anticancer agents. The major consequences of these toxicities are cosmetic, generally resolving within 6 to 12 months of discontinuing or completing therapy.

Nail changes

The growth of fingernails and toenails is arrested in a manner similar to hair growth. Chemotherapy has been associated with various types of nail changes such as nail dystrophy, different patterns of nail discoloration (known as chromonychia), leukonychia, Beau lines, paronychia, and hemorrhagic onycholysis. Nail changes are most common in patients receiving paclitaxel and docetaxel but have occurred after therapy with cyclophosphamide, fluorouracil, daunorubicin, doxorubicin, and bleomycin.[63,72–74] Nail changes as a result of chemotherapy are asymptomatic and resolve with the cessation of therapy. They are observed more commonly in patients with more pigmented skin color.

Dermatologic pigment changes

Dermatologic pigment changes are common with chemotherapy and targeted therapies. The mechanisms behind these changes are not well understood. Hyperpigmentation is most frequently reported, with hypopigmentation occurring rarely. Hyperpigmentation is seen with a wide variety of cytotoxic agents, including anthracyclines, alkylating agents, and antimetabolites. Most agents cause a diffuse, generalized hyperpigmentation, but the pigmentation changes can

also be localized, involving only the mucous membrane, hair, or nails.

Rare reactions are noted in hair. Methotrexate can cause hyperpigmented banding of light-colored hair. Alternatively, depigmentation of hair has been seen with several TKIs including sunitinib, imatinib, cabozantinib, sorafenib, and pazopanib. This adverse effect is attributed to c-KIT signal inhibition, leading to decreased melanin synthesis.[75]

As previously stated, pigment changes that occur in patients receiving cytotoxic chemotherapy are a cosmetic concern. It is important to anticipate these distressing side effects and educate patients. At this time, C.W. should receive counseling, explaining that these side effects may occur, but are purely cosmetic. She should be reassured that pigment changes usually resolve with time.

Hand–foot syndrome

Patients receiving chemotherapy or targeted agents may exhibit tender, erythematous skin on the palms of their hands and sometimes on the soles of their feet. Tingling and numbness can also be reported. In the most severe form, the lesions can progress to bullous lesions that desquamate. The condition generally resolves over 2 to 4 weeks; however, it may recur with increasing severity in response to repeated treatment.[76] This reaction is also referred to as *acral erythema* or *palmar–plantar erythrodysesthesia*.

The pathogenesis of hand–foot syndrome is poorly understood, and it is hypothesized to be different for each class of drug. Agents most commonly reported to cause this reaction include cytarabine, fluorouracil, doxorubicin, liposomal doxorubicin, docetaxel, capecitabine, sorafenib, sunitinib, pazopanib, regorafenib, axitinib, and vemurafenib.[77,78]

Prophylactic use of 10% urea-based cream three times daily for 6 to 12 weeks has shown to reduce the incidence of hand–foot syndrome compared to best supportive care in patients receiving capecitabine and sorafenib.[79,80] Treatment is primarily focused on symptom control, and discontinuation of the medication or treatment

interruption will help resolve the reaction. After resolution, the medication may be initiated at a lower dose.

Acneiform–erythematous rash

TKIs, such as erlotinib and osimertinib, target the intracellular domain of the EGFR, and cetuximab and panitumumab are monoclonal antibodies that target the extracellular domain of EGFR. These agents are associated with skin toxicities. The most common cutaneous side effect is a dose-dependent acneiform eruption on the face, scalp, chest, and upper back due to inhibition of EGFR found in keratinocytes in the skin. The rash generally develops in the first 1 to 2 weeks of treatment, peaks at 3 to 4 weeks on therapy, and its intensity decreases after 2 weeks but can often persist over some months. Although the rash can be cosmetically distressing, it is usually low grade and may be associated with dry skin and itching. Complete resolution without sequelae occurs once the drug is discontinued.[65,81]

Evidence suggests that the severity of the EGFR inhibitor skin rash is associated with increased efficacy. In an analysis of patients with lung cancer receiving erlotinib, those who experienced a rash had a significantly longer survival time than those who did not.[82] Higher severity rash was associated with longer survival when compared to lower severity or no rash. Evidence of a correlation between skin rashes and higher response rates has also been observed in patients receiving cetuximab for colorectal cancer.[83]

Preventative strategies include patient education to minimize sun exposure and to keep the rash moist with lotions and creams, avoiding drying agents.[84,85] The Multinational Association of Supportive Care in Cancer (MASCC) developed an EGFR Inhibitor Skin Toxicity Tool to assist clinicians in monitoring and reporting EGFR-induced dermatologic toxicities. In addition, MASCC has published both patient information and clinical practice guidelines for the prevention and treatment of EGFR inhibitor–associated dermatologic toxicities. Treatment depends on the severity and percentage of body surface area impacted. Treatment modalities

include hydrocortisone cream, clindamycin gel, and oral minocycline or doxycycline therapy.[85]

INTERACTIONS WITH RADIATION THERAPY

CASE 94-4, QUESTION 3: C.W. recently completed her course of total breast radiation therapy. She plans to leave for a 1-week vacation in Florida 3 days after this clinic visit. Are there any interactions between radiation therapy and sunlight exposure with cytotoxic anticancer agents? Are there any specific precautions that C.W. should take, or signs and symptoms of toxicity that she should know about?

Interactions between cytotoxic therapy and radiation therapy or ultraviolet (UV) light can be divided into radiation sensitization, radiation recall, photosensitivity reactions, and sunburn reactivation. Several excellent reviews that describe each of these interactions in detail are available.[86–88]

Radiation-induced cell damage leads to inflammation and chronic oxidative stress. This can cause changes in various cytokines, cell cycle changes, and DNA damage. Cytotoxic therapies interfere with enzymes and synthetic mechanisms needed to repair damaged cells, leading to a synergistic effect with radiation. Although these synergistic effects are often exploited therapeutically for the treatment of solid tumors, these reactions can inadvertently cause undesirable reactions in nontumor tissues, such as the skin, esophagus, lung, and GI tract. The skin is the most common target of radiation reactions.

Targeted therapies block specific molecular pathways, and preclinical evidence suggests many are radiosensitizing. At this time, there is little clinical data to guide the safety and efficacy of combination targeted therapies and radiation. Single institutional case series have provided mixed data, with some suggesting safety and others suggesting unexpected toxicities.[89,90] Many ongoing trials are examining the utility of combination targeted therapies and radiation.

These reactions may be further classified as either radiation sensitivity or radiation-recall reactions. Generally, sensitivity reactions occur when chemotherapy is given concurrently or within 1 week of radiation therapy. In comparison, recall reactions occur several weeks to years after radiation therapy, when the administration of chemotherapy induces an inflammatory reaction in tissues previously treated with radiation. Not surprisingly, the chemotherapy agents that have been associated with radiation-recall reactions are the same as those that cause radiation sensitivity reactions. Management of reactions is supportive and consists primarily of topical agents including corticosteroids.[86,91–93]

Because UV light has sufficient energy to cause photochemical changes in biologic molecules, cytotoxic and targeted agents can interact with it. The subsequent reactions are usually less severe than are reactions that occur with radiation therapy, and they may be caused by a different mechanism.

C.W. received doxorubicin, which can interact with radiation therapy. She should be advised to avoid direct exposure to sunlight for several days to a week after chemotherapy and to use a protective sunscreen with a high sun protective factor when she cannot avoid sun exposure.

Case 94-4, Question 4: How will C.W. know whether she has a radiation reaction? How should she be treated if such a reaction occurs?

If C.W. has a radiation reaction, she will experience “easy burning” and erythema or redness, followed by dry desquamation. With a more severe reaction, small blisters (vesicles) and oozing can develop. Necrosis with persistent painful ulceration has been reported. Postinflammatory hyperpigmentation or depigmentation may follow. Treatment options vary, depending on reaction severity, and range from topical steroids in an emollient cream to surgical debridement if necrosis and ulcers are present. Radiation reactions that occur in tissues other than on the skin (eg, the lungs, esophagus, or GI tract) often are treated with oral corticosteroids,

although data regarding the efficacy of these agents in ameliorating the symptoms or reducing the extent of damage are lacking. If C.W. experiences any of these signs or symptoms, she should immediately seek medical attention.

IRRITANT AND VESICANT REACTIONS

Case 94-4, Question 5: C.W. reported pain and burning at the injection site immediately after the administration of her third course of IV chemotherapy with doxorubicin and cyclophosphamide. She described the sensation as being distinctly different from the mild discomfort she had experienced with previous courses. Physical examination of the injection site revealed mild erythema and slight induration. What types of local reactions can occur after the administration of chemotherapy?

Several distinct types of local reactions (ranging from transient local irritation to severe tissue necrosis of the skin, surrounding vasculature, and supporting structures) have been reported after cytotoxic chemotherapy.[64,94,95] Some reactions are characterized by immediate local burning, itching, and erythema. Patients may also experience a "flare" reaction along the length of the vein used for treatment. Extravasation, a potentially serious local reaction, is seen in ~1% of chemotherapy administration and occurs when IV medications are accidentally administered into the surrounding tissue, either by leakage or by a needle puncturing the vein. The agent that extravasates causing a reaction is subclassified as a vesicant or an irritant (**Table 94-1**).

Table 94-1
Chemotherapeutic Drugs Reported to Produce Local Toxicities

Vesicants	
Dactinomycin[b]	Doxorubicin and vincristine as a continuous infusion[b]
Daunorubicin[b,c]	Epirubicin[b,c]
Doxorubicin[b,c]	Vinblastine[a,d]
Idarubicin[b,c]	Vincristine[a,d]

Vesicants	
Mechlorethamine[b,e]	Vinorelbine[a,d]
Mitomycin[b]	Trabectedin[a,d]
Irritants With Vesicant-Like Properties	
Bendamustine[b,e]	Mitoxantrone[b]
Cisplatin[b,e]	Oxaliplatin[a,e]
Melphalan	Paclitaxel[b]
Irritants	
Ado-trastuzumab[b]	Liposomal doxorubicin[b]
Arsenic trioxide[b]	Etoposide[a,d]
Albumin-bound paclitaxel[b]	Fluorouracil[b]
Brentuximab vedotin[a]	Gemcitabine
Busulfan[b]	Ifosfamide[b,f]
Cabazitaxel[b]	Irinotecan[b]
Carboplatin[b]	Streptozocin[b]
Docetaxel[b]	Liposomal daunorubicin and cytarabine (vyxeos)[b]
Dacarbazine[b]	Teniposide[a,d]

Antidote and local care: [a]topical heat, [b]topical cooling, [c]dexrazoxane, [d]hyaluronidase, [e]sodium thiosulfate, [f]topical dimethyl sulfoxide (DMSO).

Sources: Doellman D, Hadaway L, Bowe-Geddes LA, et al. Infiltration and extravasation: update on prevention and management. *J Infus Nurs*. 2009;32:203–211. doi:10.1097/NAN.0b013e3181aac042; Boulanger J, Ducharme A, Dufour A, et al. Management of the extravasation of antineoplastic agents. *Support Care Cancer*. 2015;23(5):1459–1471. doi:10.1007/s00520-015-2635-7; Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. *Semin Oncol*. 2006;33(1):139–143. doi:10.1053/j.seminoncol.2005.11.007; Totect (dexrazoxane injection). Package insert. Topo Target USA, Inc.; 2011.

Vesicants can cause tissue necrosis, whereas irritants induce inflammation without direct cytotoxic injury. Some drugs may have conflicting information of being classified as a vesicant or as an irritant. Other agents can be classified as irritants with vesicant-like properties at stronger concentrations and/or larger volumes of

extravasation. In general, most targeted and immunotherapy agents are considered nonirritants and nonvesicants.

Among the multiple risk factors for extravasation, the most commonly encountered include generalized vascular disease found in elderly and debilitated patients or in patients who have undergone frequent venipuncture and treatment with irritating chemotherapy (the latter causes venous fragility and instability or decreased local blood flow).[64,94] These risks have led to the increased use of central catheters in patients receiving vesicant chemotherapy.

Case 94-4, Question 6: C.W.'s oncology nurse believes that the doxorubicin may have extravasated during administration. How should this be managed? Do management strategies differ for other vesicant agents?

Details of management of a potential irritant, an irritant with vesicant-like properties, or vesicant extravasation can be found in **Table 94-2**.

Table 94-2
Management of Suspected Extravasation

1. Stop the infusion immediately, but do not remove the needle. Do not flush the extravasated catheter.
2. Disconnect the IV tubing from the catheter. Aspirate any drug remaining in the tubing or needle, as well as the infiltrated area using a small syringe.
3. Contact medical team as soon as possible.
4. If peripheral IV, remove the IV catheter, avoid pressure to site of extravasation. Mark area of induration or swelling.
5. If deemed appropriate, instill an antidote in the infiltrated areas. Apply topical heat or cooling if indicated and elevate the extremity for the first 24–48 hours.
6. Document the drug, suspected volume extravasated, and the treatment in the patient's medical record.
7. Check the site frequently for 5–7 days.
8. Consult a surgeon familiar with extravasations depending on severity and agent extravasated so that the surgeon can periodically review the site, and, if ulceration begins, the surgeon can rapidly assess if surgical debridement or excision is necessary.

IV, intravenous.

Sources: Doellman D, Hadaway L, Bowe-Geddes LA, et al. Infiltration and extravasation: update on prevention and management. *J Infus Nurs*. 2009;32:203–211. doi:10.1097/NAN.0b013e3181aac042; Boulanger J, Ducharme A, Dufour A, et al. Management of the extravasation of antineoplastic agents. *Support Care Cancer*. 2015;23(5):1459–1471. doi:10.1007/s00520-015-2635-7.

Recommended measures aim to minimize tissue exposure and prevent subsequent tissue damage.[95] Cold compresses have been shown to cause vasoconstriction, which can help localize the extravasation and allow time for local vessels to displace the extravasated agent, whereas warm compresses are thought to induce vasodilation and increase drug distribution and absorption, thereby decreasing the concentration of the offending agent around the immediate site.

Specific antidotes thought to inactivate the extravasated chemotherapy have been suggested.[94,95] Dexrazoxane, an iron chelator, is approved for the treatment of anthracycline extravasations based on evidence that demonstrated avoidance of surgical intervention and therapy continuation without delays.[96,97]

HYPERSENSITIVITY REACTIONS

Various types of hypersensitivity reactions can occur with anticancer agents, although type I is the most common reaction documented. Type I hypersensitivity reactions are immediate reactions that are most often immunologically mediated and occurring when an antigen interacts with IgE bound to a mast cell membrane, causing degranulation of mast cells. Major signs and symptoms include urticaria, angioedema, rash, bronchospasm, abdominal cramping, and hypotension. Other mechanisms causing type I reactions include degranulation of mast cells and basophils through a direct effect on the cell surface that releases histamine and other vasoactive substances. When non–IgE-mediated mechanisms account for the symptoms of a type I reaction, it is called an *anaphylactoid reaction* (see Chapter 32, Drug Hypersensitivity Reactions). Many of the type I hypersensitivity reactions produced by anticancer medications appear to be mediated by non-IgE mechanisms, occurring during or immediately after administration of the first dose. This is in contrast

to immunologic reactions that require prior exposure (ie, one must be sensitized before becoming hypersensitized).

Although the spectrum of symptoms and their severity vary widely, most hypersensitivity reactions that occur with anticancer agents are classified as grade 1 (transient rash, mild) or grade 2 (mild bronchospasm, moderate).[1] Furthermore, a patient who has had a reaction to an agent that is not immunologically mediated can safely receive future courses of the anticancer therapy with appropriate premedication. The other types of hypersensitivity reactions with cytotoxic and targeted therapy administration are less commonly documented. Several reviews detail anticancer agents most frequently reported to produce hypersensitivity reactions and their characteristic reactions.[98–100]

Premedication can help prevent or reduce the severity of the hypersensitivity reaction. Antihistamines and acetaminophen, with or without glucocorticoids, are recommended for prophylaxis when administering certain agents that are associated with a high incidence of infusion reactions (eg, rituximab, obinutuzumab, daratumumab, alemtuzumab, and cetuximab). However, they are not completely effective, and patients must be monitored closely during and immediately following all infusions. If a patient experiences a hypersensitivity reaction and the clinician decides to continue therapy with this regimen, a full review of all of the relevant literature is advised. In addition to increased premedication to limit the risk of a subsequent reaction, successful desensitizations have been utilized and published for a few chemotherapeutic agents.[101–103]

Monoclonal antibodies

CASE 94-5

Question 1: S.R. is a 58-year-old male with metastatic relapsed colorectal cancer who will be starting cetuximab (400 mg/m^2 IV load, followed by 250 mg/m^2 IV weekly).

Discuss the toxicities that S.R. may expect and when they might appear.

How should these side effects be managed? Could these side effects be prevented?.

The most common toxicities observed in patients receiving cetuximab include rash, diarrhea, hypomagnesemia, and headache; and hypersensitivity reactions occur in 15% to 20% of patients receiving their first infusion. However, severe hypersensitivity reactions (including allergic and anaphylactic reactions) occur in 1% to 3% of patients. The reactions generally occur during or within 1 hour of completing the first dose. Patients should be premedicated with diphenhydramine before the infusion. The infusion can be stopped or the rate decreased if S.R. begins experiencing these effects. The skin rash and dry skin occurring after cetuximab administration are related to the inhibition of EGFR. Management of EGFR inhibitor–related rash has been discussed previously (see sections on Nail and Skin Changes and Acneiform–Erythematous Rash).

Monoclonal antibodies are associated with a higher incidence of hypersensitivity reactions than are traditional cytotoxic agents. These agents are genetically engineered humanized monoclonal antibodies containing foreign proteins that can trigger the reaction. The risk of a hypersensitivity reaction is highest with the first or second infusion, and usually does not recur with subsequent infusions, although this is dependent on the specific agent.[104] In general, the likelihood of an infusion reaction declines with each subsequent course of therapy.

Several monoclonal antibodies are now available in SC formulations (trastuzumab and hyaluronidase-oysk, pertuzumab and trastuzumab and hyaluronidase-zzxf, rituximab and hyaluronidase human, daratumumab, and hyaluronidase-fihj). The coformulation with recombinant human hyaluronidase increases the permeability of the SC tissue, allowing for a larger volume to be administered. SC administration of monoclonal antibodies is less time consuming (given over 3–5 minutes), and generally shows lower rates of hypersensitivity reactions compared with the IV originator product. Hypersensitivity reactions occurring with SC monoclonal antibodies

tend to be more delayed.[105] Management of hypersensitivity reactions follows the same treatment principles as with IV agents.

Treatment

Recommended treatment of hypersensitivity reactions is reviewed in **Table 94-3**. If the reaction is mild or moderate, the patient may continue with the same therapy if treatment is preceded by methods to prevent or minimize hypersensitivity reactions. It is important to note that other chemicals present in the formulation or other agents administered concomitantly with the chemotherapy can cause hypersensitivity reactions. Potential allergens included in the diluent or formulation of chemotherapy agents include Cremophor EL® (present in paclitaxel), polysorbate 80 (present in docetaxel and etoposide), benzyl alcohol (present in the parenteral form of methotrexate, cytarabine, and etoposide), and methoxypolyethylene glycol (present in liposomal doxorubicin).

Table 94-3

Treatment of Hypersensitivity Reactions From Anticancer Drugs

Treatment
Discontinue the drug immediately and contact the medical team.
Start IV of 0.9% NaCl and initiate vital signs and O_2 saturations; place the patient in recumbent position if BP is decreased; administer oxygen if O_2 saturation <90% and titrate to keep O_2 saturation >90%.
Determine whether the reaction is nonanaphylaxis (symptoms include itching, flushing, hives, mild respiratory symptoms without airway compromise) or anaphylaxis (symptoms include acute onset, rapidly progressing hives, potential airway compromise with shortness of breath, stridor, wheezing, bronchospasm, supplemental oxygen required, and/or hypotension).
If Nonanaphylaxis-Type Reaction:
Administer diphenhydramine 50 mg IV.
Administer famotidine 20 mg IV.
If symptoms progress: administer hydrocortisone 100 mg IV.
If Anaphylaxis:

Treatment
Administer epinephrine 0.3 mg IM or SC every 5 minutes until the reaction subsides.
Diphenhydramine 50 mg IV
Hydrocortisone 100 mg IV
Famotidine 20 mg IV
If wheezing that does not respond to epinephrine is present, administer nebulized albuterol solution.

BP, blood pressure; IM, intramuscular; IV, intravenous; O_2, oxygen; SC, subcutaneous.

Source: Reprinted from Roselló S, Blasco I, García Fabregat L, et al. Management of infusion reactions to systemic anticancer therapy: ESMO clinical practice guidelines. *Ann Oncol*. 2017;28(suppl_4):iv100–iv118. © 2017 European Society for Medical Oncology. With permission.

To reduce the hypersensitivity reactions observed with paclitaxel, paclitaxel protein-bound particles (Abraxane®), an albumin-bound formulation of paclitaxel, have been created. Because paclitaxel protein-bound particle formulation is Cremophor EL® free and less likely to cause hypersensitivity than is traditional paclitaxel, it is not necessary to premedicate patients with steroids and antihistamines. Doses between the two agents are not equivalent. Although fewer hypersensitivity reactions are associated with this formulation, myelosuppression remains a dose-limiting toxicity.[106,107]

Immunotherapy-Related Toxicities

CAR-T Cell Therapy and Blinatumomab

Cytokine release syndrome

CAR-T immunotherapies are genetically engineered autologous products that target specific tumor antigens created using a patient's own T cells. CAR-T cells are designed to recognize and direct an immune response against targeted cells displaying a specific antigen. All currently available products target CD19, which is a B-cell antigen found on the surface of B cells, and have indications for non-Hodgkin lymphoma in adults (axicabtagene ciloleucel and

tisagenlecleucel), acute lymphoblastic leukemia (ALL) in pediatric patients (tisagenlecleucel) and mantle cell lymphoma in adults (brexucabtagene autoleucel). Blinatumomab, approved for ALL, is a bispecific T-cell engager (BiTE) that works to selectively direct the immune system to act against tumor cells by forming a link between T cells and tumor cells. There are many CAR-T cells and BiTE products currently in development across both solid and hematologic cancers.

Cytokine release syndrome (CRS), a systemic inflammatory condition with excessive cytokine production, may occur as a result of treatment with CAR-T therapies and blinatumomab, for which a boxed warning is applied, as well as with HCT, and other immunotherapies.[108] Severity may vary. Signs and symptoms include fever, headache, nausea, weakness, hypotension, hypoxia, tachycardia, DIC, and hepatic, renal, and cardiac dysfunction. CRS may occur concurrently or independently of neurotoxicity. The incidence of CRS was 79% to 94% of patients in clinical trials of CAR-T cells, with a subset of these being grade 3 or higher in severity (13%–49%). See **Table 94-4** for information on grading of CRS. The median onset of CRS symptoms is 2 to 3 days, with a median duration of 7 to 10 days.[109–111] Blinatumomab is associated with CRS in up to 15% of patients, with symptoms appearing around 2 days into the infusion and resolving after about 5 days.

Table 94-4
Grading of Cytokine Release Syndrome

Grade 1	Symptoms require symptomatic treatment only; consider antibiotics if neutropenic.	Fever, nausea, headache, myalgia, malaise
Grade 2	Symptoms require and respond to moderate intervention.	Oxygen requirement <40% Fio_2, or hypotension responsive to fluids or low dose of one vasopressor, or grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive	Oxygen requirement ≥40% Fio_2, or

	intervention.	hypotension requiring high-dose or multiple vasopressors, or grade 3 organ toxicity, or grade 4 transaminitis
Grade 4	Life-threatening symptoms	Requirements for ventilator support, renal replacement therapy, or grade 4 organ toxicity other than transaminitis

Fio_2, fraction of inspired oxygen.

Source: Reprinted from Lee DW, Gardner R, Porter L, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188–195. © 2014 American Society of Hematology. With permission.

Without management, CRS can be life-threatening. For blinatumomab, management of CRS includes interruption of the infusion and administration of IV dexamethasone. Corticosteroids are utilized because of their immune-suppressive effects, including downregulation of the systemic cytokine response. Upon resolution, the infusion may be resumed at a reduced dose, with future dose escalation if tolerated. For grade 4 CRS, dexamethasone should be administered, and blinatumomab should be discontinued permanently.

Management of CRS related to CAR-T cell therapies depends on the severity of symptoms. In general, mild symptoms (fever, nausea, headache, myalgia, and malaise) should be managed with supportive care modalities. Antibiotics should be considered if the patient is neutropenic. For more severe CRS, the IL-6 receptor antagonist tocilizumab should be administered. IL-6 is frequently elevated during CRS, making tocilizumab an effective treatment option. It is important to recognize that corticosteroids are typically avoided for lower grade CRS, because they may have a detrimental effect on the infused CAR-T cells, leading to reduced toxicity but at the expense of efficacy. Corticosteroids may be indicated for severe or persistent CRS. Product information should be carefully reviewed for specific information on the management of CRS because there are several differences between the agents.

Neurotoxicity

CAR-T products may cause severe or life-threatening neurotoxicity, often called CAR-T-cell–related encephalopathy syndrome (CRES).[109–112] Symptoms are wide-ranging in type and severity, and include headache, encephalopathy, delirium, anxiety, dizziness, tremor, peripheral neuropathy, seizure, and aphasia. Any grade neurotoxicity occurs in about 80% of patients and ≥grade 3 in about one-third, although rates are variable among products. The median time to onset of neurotoxicity is 4 to 6 days after infusion, and the median duration of symptoms ranges from 6 to 21 days. Importantly, encephalopathy may persist for weeks to months. Patients should not drive during the 8 weeks following administration and should remain within close proximity to the hospital or clinic for at least 28 days. Initial management of neurotoxicity depends on the severity of presentation and includes consideration of seizure prophylaxis (eg, levetiracetam), and IV corticosteroids (dexamethasone or high-dose methylprednisolone). Tocilizumab is typically administered for neurotoxicity with concomitant CRS. Product-specific literature should be consulted. Risk Evaluation and Mitigation Strategy (REMS) programs are in place for all CAR-T products because of the potential for serious toxicities, and it is important that patients are educated on the risks.

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors (ICIs) are increasingly common in the treatment of many cancer types. Currently available agents include the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor (ipilimumab), programmed cell death 1(PD-1) antibodies (nivolumab, pembrolizumab, cemiplimab), and programmed death-ligand 1 (PD-L1) antibodies (atezolizumab, avelumab, durvalumab). Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep the immune response in check. Blocking the binding of PD-L1 to PD-1 with an ICI allows the T cells to kill tumor cells.

Toxicities caused by ICIs are largely distinct from those associated with cytotoxic chemotherapy. ICIs cause autoimmune-like toxicities, known as immune-related adverse events (IrAEs). These toxicities

differ depending on the agent, malignancy, and individual susceptibilities. Although the skin and colon are most commonly involved, any organ may be affected, including the liver, lungs, kidneys, and heart. It is important to have a high early suspicion for toxicity related to ICIs in patients presenting with new or worsening symptoms, and to involve specialists such as dermatologists, pulmonologists, and gastroenterologists early in the patient's course.

Corticosteroids are commonly used for treatment of moderate and severe IrAEs, although additional immunosuppressive therapy may occasionally be required depending on the organ impacted.

Dermatologic toxicities

Dermatologic toxicities occur in 30% to 50% of patients on ICIs and are wide-ranging, but often include rash and pruritus. The rash may present in various ways, including erythema, lichenoid, eczematous, or psoriasis-like, among others. For mild rash, topical emollients, topical corticosteroids, and oral antihistamines are indicated. Moderate-to-severe presentations may require the use of systemic corticosteroids, and the ICI may be held or permanently discontinued. Severe cases may require hospitalization for IV hydration, electrolyte repletion, and wound care.

Pulmonary toxicities

Pulmonary toxicity associated with ICI therapy often manifests as pneumonitis, which occurs in <10% of patients, perhaps as low as about 3%. Symptoms include dyspnea, cough, fever, and chest pain. Imaging reveals ground-glass opacities or patchy nodular infiltrates that may appear distinct from other types of anticancer therapy–induced pneumonitis. Importantly, infectious etiologies should be evaluated concomitantly. ICI therapy is interrupted for radiographic evidence of pneumonitis. Grade 2 or greater warrants administration of systemic steroids, and grades 3 to 4 toxicity not responsive to steroids may require additional immune-modulating agents including infliximab, mycophenolate mofetil, intravenous immunoglobulin (IVIG), or cyclophosphamide.

Gastrointestinal toxicities

CASE 94-6

QUESTION 1: A.B. is a 51-year-old male with newly diagnosed metastatic (stage IV) non–small-cell lung cancer (NSCLC). The tumor highly expresses PD-L1. He began first-line therapy with pembrolizumab 200 mg IV once every 3 weeks. Before the fourth cycle, A.B. has new, frequent diarrhea (about five stools per day compared with baseline), with abdominal pain and occasional blood in the stool. Symptoms are consistent with grade 2 colitis, and pembrolizumab is held.

What pharmacologic treatment is indicated for A.B. at this time?

Lower GI toxicity occurs more commonly with anti-CTLA4 inhibitor (ipilimumab) (up to 54%) and also with anti-PD1 monotherapy (up to 19%). Signs and symptoms may include diarrhea only, or colitis symptoms such as mucus in the stool, abdominal pain, fever, and rectal bleeding. Clinical presentation and diagnostic findings are often consistent with inflammatory bowel disease. For patients with mild diarrhea, observation and ensuring adequate hydration are warranted. More severe symptoms, including those consistent with colitis, may require the use of systemic corticosteroids, infliximab, or vedolizumab, in addition to holding the ICI. Grade 4 toxicity warrants permanent discontinuation.

A.B. should initially receive steroids, such as prednisone 1 mg/kg/day, for the management of immunotherapy-related colitis. A.B. should also be counseled regarding dietary modifications that may help improve symptoms.

Various other organs and organ systems are affected by ICIs, including the endocrine system (hypo- and hyperthyroidism, adrenal insufficiency, and diabetes), rheumatologic, renal, neurologic, hematologic, cardiovascular, and ocular toxicities. Guidelines should be consulted for expert, multidisciplinary consensus on treatment.[62,113,114]

Specific Organ Toxicities

Nervous System

CASE 94-7

QUESTION 1: A.L., a 39-year-old female with acute lymphocytic leukemia, has been admitted to the hospital for induction chemotherapy. Methotrexate 3 g/m^2 IV once on day 1, cytarabine 2 g/m^2 IV every 12 hours on days 2 and 3 for four doses, vincristine 2 mg IV on days 1 and 8 for two doses, and dexamethasone 20 mg orally daily on days 1 through 5 are ordered. Laboratory data obtained on admission include a WBC count of 120,000 cells/μL with 9% neutrophils, 11% lymphocytes, and 80% blasts. On day 3, A.L. is confused, and she has difficulty performing a finger-to-nose neurologic examination. On day 10, she endorses numbness in her hands and feet. In addition, the clinician notes an eyelid lag and ataxia. A.L. also reports severe constipation.

What signs and symptoms of neurotoxicity is A.L. experiencing? Should the leukemia regimen be modified for future courses?

Methotrexate causes little or no neurotoxicity when administered orally or via IV in doses <1 g/m^2; however, high-dose IV methotrexate (usually >1 g/m^2) can cause acute encephalopathy. The encephalopathy that occurs after therapy with methotrexate is usually transient and reversible. Some patients may experience a progressive leukoencephalopathy after high-dose IV methotrexate. The risk of leukoencephalopathy increases with higher cumulative doses of methotrexate and concomitant cranial radiation therapy.[115,116] Chemical meningitis can occur with intrathecal administration of methotrexate and, less frequently, myelopathy or paraplegia may be observed[117] (see Chapter 95, Pediatric Malignancies). Transient stroke-like symptoms with concomitant abnormal findings on magnetic resonance imaging (MRI) have been observed in patients receiving intrathecal and IV methotrexate.[118,119]

Ifosfamide is associated with an encephalopathy thought to result from one of its metabolites, chloroacetaldehyde. The incidence ranges from 10% to 20%; it presents hours to days after initiation of treatment with confusion and disorientation, and is generally self-limiting, although coma and death have been reported. Methylene blue, albumin, and thiamine have been used for both prevention and treatment. Conclusive evidence to promote routine prophylaxis is not available.[120–122]

High doses of cytarabine (>1 g/m^2 in multiple doses) are associated with CNS toxicity in 8% to 37% of patients.[123,124] These neurotoxicities are dose and schedule related. Doses >18 g/m^2 per course increase the frequency of neurotoxicity. Older patients are more susceptible than are younger patients, and impaired renal function appears to be an inciting factor of cytarabine neurotoxicity, likely as a result of accumulation of a neurotoxic metabolite.[125] As illustrated by A.L., neurotoxicity may become evident within a few days of treatment with cytarabine, and is manifested by a generalized encephalopathy with symptoms such as confusion, obtundation, seizures, and coma. Cerebellar dysfunction, presenting as ataxia, gait and coordination difficulties, and dysmetria (inability to arrest muscular movement when desired and lack of harmonious action between muscles when executing voluntary movement), is also commonly observed. These neurologic symptoms may partially resolve over days to weeks after discontinuation of therapy. Intrathecal administration of cytarabine may cause a chemical meningitis or arachnoiditis.[117,126,127] Leukoencephalopathy typically presents with progressive personality and intellectual decline, dementia, hemiparesis and, rarely, seizures.

Fludarabine can cause severe neurotoxicity when used at doses >90 mg/m^2 for 5 to 7 days.[128–130] Symptoms include altered mental status, photophobia, amaurosis (blindness that usually is temporary without change in the eye itself), generalized seizures, spastic or flaccid paralysis, quadriparesis, and coma. The onset of symptoms is often delayed up to several weeks from administration.[131] Patients may progress to death even when therapy is discontinued. This neurotoxicity, however, is not common with the current recommended maximum dosage of 20 to 30 mg/m^2/day for 5 days. Mild neurologic symptoms are often reported, but severe neurotoxicity[128,129] and optic demyelination occur only occasionally.[132] Patients with signs or symptoms suggestive of significant neurotoxicity should receive a neurologic examination and, if warranted, therapy should be discontinued without rechallenging.

Nelarabine, another purine analog, has dose-limiting neurotoxicity, and 18% to 37% of patients in phase II trials develop grade 3 or 4

neurotoxicities.[133,134] The clinical presentation includes severe somnolence, convulsions, and peripheral neuropathy ranging from paresthesias to motor weakness. Several cases of ascending peripheral neuropathies and demyelination have been reported.[135] Therapy should be stopped if grade 2 toxicity is present because this may be irreversible.[136]

Fluorouracil can cause both acute and delayed neurotoxicity. Acute neurotoxicity manifests as cerebellar dysfunction or encephalopathy. Symptoms include gait ataxia, dysarthria, nystagmus, confusion, headache, disorientation, and lethargy. Seizures have been rarely reported. Delayed neurotoxicity presents as subacute multifocal leukoencephalopathy. Reports of cerebellar ataxia have also been reported with capecitabine, an oral prodrug of fluorouracil.[137–139] Polymorphisms in the *TYMS* and *DPYD* genes have been associated with the risk of fluoropyrimidine neurotoxicity due to increased exposure.[140,141] Uridine triacetate is an antidote that competes with toxic metabolites and reverses neurologic and other severe or life-threatening adverse effects from fluorouracil or capecitabine when administered promptly.[142]

Asparaginase and pegaspargase can cause encephalopathy, which presents most commonly as lethargy and confusion. Severe cerebral dysfunction occurs occasionally, and patients may present with stupor, coma, excessive somnolence, disorientation, hallucination, or severe depression. Symptoms can occur early (within days of administration of asparaginase) or late, depending on the treatment schedule. The suspected mechanism is the direct neurocytotoxic effect of aspartic acid, glutamic acid, and ammonia. The neurotoxicity is usually reversible, with the acute syndrome clearing rapidly and a delayed syndrome lasting several weeks.[128,143,144]

Multiple other anticancer agents may cause encephalopathy (**Table 94-5**). Recognition of neurotoxicity resulting from cytotoxic chemotherapy is often difficult because of comorbid conditions such as metastatic disease and other paraneoplastic syndromes, but it is important in assessing the need for potential dose modifications or even discontinuation of the agent. Several reviews provide detailed

explanations of signs and symptoms, mechanisms, and potential treatments for chemotherapy-induced neurotoxicities.[128,145]

Table 94-5
Neurotoxicity of Selected Chemotherapeutic Agents

Acute Encephalopathy	Chronic Encephalopathic Syndrome	Cerebellar Neuropathy	Peripheral Neuropathy	Cranial Neuropathy	Arachnoiditis (Intrathecal Therapy)	Autonomic Neuropathy	SIADH
Asparaginase	Cytarabine	Cytarabine	Bortezomib	Fluorouracil	Cytarabine	Vinblastine	Cyclophosphamide
Cisplatin	Methotrexate	Cisplatin	Brentuximab	Ifosfamide	Methotrexate	Vincristine	Vinblastine
Cytarabine	Nelarabine	Fludarabine	Cisplatin		Thiotepa	Vinorelbine	Vincristine
Fludarabine	Thiotepa	Fluorouracil	Docetaxel				Vinorelbine
Ifosfamide		Ifosfamide	Fluorouracil				
Methotrexate			Ifosfamide				
Nelarabine			Lenalidomide				
Procarbazine			Nelarabine				
			Paclitaxel				
			Thalidomide				
			Vinblastine				
			Vincristine				
			Vinorelbine				

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Sources: Newton HB. Neurological complications of chemotherapy to the central nervous system. *Handb Clin Neurol*. 2012;105:903–916. doi:10.1016/B978-0-444-53502-3.00031-8; Magge RS, DeAngelis LM. The double-edged sword: neurotoxicity of chemotherapy. *Blood Rev.* 2015;29(2):93–100. doi:10.1016/j.blre.2014.09.012.

A.L.'s symptoms most likely are the result of CNS toxicity caused by both high-dose methotrexate and cytarabine. A decision regarding further treatment with these agents is complicated because omitting a dose or decreasing the dose of either of these agents could compromise the likelihood of a complete remission. High-dose cytarabine cerebellar toxicity may be irreversible. Therefore, the clinician may decide to discontinue cytarabine in A.L.'s future regimens. In addition, modifications of methotrexate, including dose reductions, may be necessary in future therapy for A.L.

CASE 94-7, QUESTION 2: What is the most likely medication causing A.L.'s numbness?

Peripheral neuropathy

Paresthesia (numbness and tingling) involving the feet and/or hands is an early subjective symptom of vincristine neurotoxicity, which often appears within the first days to weeks of therapy. Because A.L. received vincristine on days 1 and 8, it is reasonable to assume that her presentation of numbness in her extremities is secondary to the vincristine. This peripheral nerve toxicity is commonly bilateral and symmetric and is often referred to as a *stocking-glove neuropathy*. Symptoms initially consist of paresthesias, loss of Achilles reflex, and depression of deep tendon reflexes. Areflexia (absent reflexes) typically occurs in about 50% to 70% of patients treated with a cumulative dose >6 to 8 mg. In an effort to minimize these toxicities, capping each dose of vincristine at 2 mg has been a longstanding tradition. Although older patients appear to be more susceptible to paresthesias than are younger ones, almost all patients report some degree of paresthesias after combination chemotherapy that incorporates vincristine or vinblastine. Pain and temperature sensory loss are usually more pronounced than are vibration and proprioception sensory loss. Patients also may display motor weakness with a foot drop or muscle atrophy. Stumbling and falling that can occur with this peripheral neuropathy is not usually caused by muscle weakness; instead, it occurs in the dark when patients lose proprioception because they lack visual orientation. These complications are either partially or completely reversible, but recovery often takes several months.[146]

Other agents that share the peripheral nerve toxicity of vincristine include vinblastine, vinorelbine, cisplatin, etoposide, oxaliplatin, paclitaxel, docetaxel, cabazitaxel, ixabepilone, bortezomib, thalidomide, and lenalidomide, among others.[145] Unlike the vinca alkaloids (vincristine and vinblastine), most of these agents cause numbness only and not a loss of reflexes or weakness. However, patients may report sensory loss and pain. Antibody drug conjugates (ADCs) consist of potent cytotoxic drugs conjugated to antibodies via linkers, which allow for specific targeting of tumor cells while reducing systemic exposure to the cytotoxic drug. Multiple ADCs

(such as brentuximab vedotin, polatuzumab vedotin, trastuzumab emtansine, and enfortumab vedotin) include a potent microtubule inhibitor, similar to vincristine or vinblastine, as the cytotoxic drug. Neuropathy with these agents is again primarily sensory rather than motor, and is often dose limiting. With all agents, the incidence may be related to cumulative doses and individual risk factors such as a history of diabetic neuropathy.[147–149]

Many preventive strategies have been evaluated including amifostine, glutamine, glutathione, and vitamin E. However, evidence is limited by small sample sizes, and the studies lacked placebo-controlled randomized designs.[150] Treatment strategies are only palliative and include adjuvant pain medications such as tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs), anticonvulsants (pregabalin and gabapentin), and topical agents. Duloxetine, an SNRI, was studied in a phase III trial of patients with peripheral neuropathy due to prior treatment with single-agent taxane or platinum. Compared with placebo, duloxetine was associated with a larger average decrease in pain score. More patients receiving duloxetine experienced grade ≥2 fatigue.[151] Peripheral neuropathy is usually reversible, although resolution may take months. Several reviews provide detailed references for this information.[150,152,153] Avoidance of azole antifungals and other inhibitors of cytochrome P-450 (CYP) 3A4 is important in the prevention of neuropathy from vincristine as well as other microtubule inhibitors.[154]

Oxaliplatin causes peripheral neuropathies that differ from other anticancer agents. Oxaliplatin-induced neurotoxicity manifests as an acute neurosensory complex as well as a cumulative sensory neuropathy. Hyperexcitability of peripheral nerves causes an 85% to 95% incidence of paresthesias and dysesthesias of the hands, feet, and the perioral region. Laryngeal dysesthesias have been described as well. These effects are precipitated by exposure to cold. This cold neuropathy is reversible and generally resolves in between doses. Oxaliplatin also causes a cumulative dose-limiting chronic neuropathy that is reversible several months after completion of therapy. Dose modifications for patients with persistent

neurotoxicities typically involve delaying therapy until clinical improvement.

Case 94-7, Question 3: What is the significance of A.L.'s lid lag?

Cranial nerve toxicity

Cranial nerve toxicity occurs in 1% to 10% of patients receiving vinca alkaloids, and most patients present with ptosis or ophthalmoplegia,[155,156] probably related to damage to the third cranial nerve. Toxicity to other cranial nerves can cause trigeminal neuralgia, facial palsy, depressed corneal reflexes, and vocal cord paralysis—and may occur in the first few days to weeks after administration.[157] Other nerve toxicities associated with the vinca alkaloids include jaw pain, which can occur as early as after the first or second dose[158]; the pain usually resolves spontaneously and does not recur with subsequent doses. A.L.'s eyelid lag probably is caused by vincristine. Ifosfamide, vinblastine, carboplatin, and cisplatin have also been reported to cause cranial neuropathies.

Ototoxicity

Ototoxicity, characterized by a progressive, high-frequency, sensorineural hearing loss, commonly occurs with cisplatin,[159,160] most likely as a result of a direct toxic effect on the cochlea. Ototoxicity occurs more frequently at higher dosages, worsens with concurrent cranial radiation therapy, and appears to be more pronounced in children. Other risk factors include regular use of nonsteroidal anti-inflammatory drugs, a history of noise exposure, and renal insufficiency before cisplatin.[161,162] The reversibility of cisplatin ototoxicity is questionable. At some centers, routine audiometric tests are performed in patients receiving cisplatin. Early cessation of cisplatin may result in greater hearing improvement. Ototoxicity has also been reported in patients receiving carboplatin.[160] If ototoxicity is suspected, a hearing test should be

performed and therapy discontinued if alternate treatments are available.

Autonomic neuropathy

Case 94-7, Question 4: What is the cause of A.L.'s constipation, and how might this problem have been prevented?

Vincristine, as well as vinblastine, commonly causes autonomic neuropathy. The earliest symptoms (colicky abdominal pain with or without constipation) are reported by one-third to one-half of patients receiving these agents.[145,155] Because severe constipation can progress to or include adynamic ileus, prophylactic laxatives are recommended on a regular basis for patients receiving vincristine and vinblastine. Stimulant laxatives such as the senna derivatives or bisacodyl are believed to be the most effective agents, and stool softeners also may be used concurrently. No compelling evidence suggests, however, that laxatives prevent constipation. Other less frequent manifestations of autonomic dysfunction associated with vinca alkaloids include bladder atony with urinary retention, impotence, and orthostatic hypotension.[163,164] Patients should be monitored carefully for these signs or symptoms and receive appropriate management after diagnosis.

A.L. is experiencing multiple signs and symptoms of neurotoxicity including CNS toxicity from methotrexate and cytarabine as well as peripheral neuropathy, autonomic neuropathy in the form of constipation, and cranial nerve toxicity from vincristine. Management overall is supportive and may be reversible after therapy cessation. Early recognition and intervention are pivotal to the management of various neurotoxicities. A.L.'s constipation could not have been prevented but can be managed with stool softeners and stimulant laxatives.

CARDIOTOXICITY

Cardiomyopathy

Doxorubicin

CASE 94-8

QUESTION 1: D.A., a 35-year-old male with stage IV Hodgkin lymphoma, received ABVD (doxorubicin 25 mg/m^2 IV days 1 and 15, bleomycin 10 units/m^2 IV on days 1 and 15, vinblastine 6 mg/m^2 IV on days 1 and 15, and dacarbazine 375 mg/m^2 IV on days 1 and 15) for six cycles and concurrent radiation therapy to a large mediastinal mass. Ten years after completion of treatment he presents to clinic and is found to have tachycardia, shortness of breath (SOB), and a nonproductive cough. Physical examination reveals neck vein distension, pulmonary rales, and ankle edema. Past medical history is significant for controlled hypertension.

What is the most likely cause of D.A.'s current symptoms?

D.A. is experiencing symptoms of congestive heart failure (CHF) most likely caused by doxorubicin therapy. Doxorubicin, an anthracycline, can cause a dose-dependent cardiomyopathy that generally occurs with repeated administration. Anthracyclines are believed to cause toxicity to cardiomyocytes mainly via inhibition of topoisomerase 2β.[165] Doxorubicin causes myocyte damage by a mechanism that differs from its cytotoxic effect on tumor cells. Because myocytes stop dividing in infancy, they presumably would not be affected by an agent whose cytotoxicity relies on actively cycling cells. Other mechanisms have been proposed to explain the cardiac toxicity associated with anthracyclines including the formation of reactive oxygen species.[166,167] The association of anthracycline-induced cardiotoxicity with other agents administered concomitantly, monitoring techniques, and therapies to prevent and treat this condition have been reviewed.[166,168–170]

D.A.'s presentation is fairly typical of doxorubicin-induced cardiomyopathy, although he has no significant risk factors usually associated with CHF. The total cumulative dose of doxorubicin is the most clearly established risk factor for CHF.[171] Patients, such as D.A., who are receiving bolus doses of doxorubicin at the standard 3-week interval face little risk of CHF until a total dose of 450 to 550 mg/m^2 has been reached.

Older data indicated a relatively low incidence of cardiac dysfunction in patients with a cumulative doxorubicin dose <400 mg/m^2.[171] More recent findings support cardiac dysfunction at lower cumulative doses than were previously described. A pooled analysis of phase III trial data in patients treated with doxorubicin demonstrated a cumulative incidence of cardiac events (defined as a decrease in left ventricular ejection fraction [LVEF] or occurrence of CHF) in 9% of patients at a cumulative dose of 250 mg/m^2, 18% at 350 mg/m^2, and 38% at 450 mg/m^2.[172] The Childhood Cancer Survivor Study evaluated 14,358 five-year survivors of cancer who were diagnosed at the age of 21 or younger between 1970 and 1986. They were compared to 3899 siblings of cancer survivors.[173] Exposure to 250 mg/m^2 or more of anthracyclines increased the relative hazard of CHF, pericardial disease, and valvular abnormalities by two to five times compared with survivors who had not been exposed to anthracyclines. Cardiac radiation exposure of 15 Gy or more also increased the relative hazard of CHF, myocardial infarction, pericardial disease, and valvular abnormalities by two to six times compared to nonirradiated survivors. The cumulative incidence of adverse cardiac outcomes in cancer survivors continued to increase up to 30 years after diagnosis. A threshold of 250 mg/m^2 of doxorubicin is reflected in a guideline of the American Society of Clinical Oncology (ASCO).[170]

Other factors that could increase D.A.'s risk of experiencing doxorubicin cardiomyopathy include mediastinal radiation therapy, preexisting cardiac disease, and hypertension. Young children, as well as older patients, are likely to experience CHF at a lower cumulative dose. Concurrent chemotherapy agents (eg, cyclophosphamide, etoposide, mitomycin, melphalan, trastuzumab, paclitaxel, vincristine, and bleomycin) may also potentiate doxorubicin cardiac toxicity.[166,168] When patients receive paclitaxel and doxorubicin, the risk of cardiac toxicity appears to be related to the sequence and proximity of the infusions. In a pharmacokinetic study, paclitaxel increased the area under the curve (AUC) of doxorubicin and its active metabolite, doxorubicinol, when paclitaxel administration immediately preceded doxorubicin. Therefore,

doxorubicin should be given at least 30 minutes before paclitaxel. The relationship between risk factors and the total cumulative dose of doxorubicin is sufficiently strong to warrant guidelines restricting the total cumulative dose of doxorubicin to 450 mg/m^2 in patients with one or more identified risk factors including mediastinal radiation, elderly age, and preexisting cardiovascular disease (high-risk patients) and to 550 mg/m^2 in patients without any of these aforementioned risk factors (low-risk patients).

It is unusual that D.A., a 35-year-old male who has received a cumulative dose of only 200 mg/m^2 of doxorubicin, would be presenting with symptoms of CHF. Mediastinal radiation therapy or an undiagnosed cardiac disease may, however, have contributed to this event. In addition, Hodgkin lymphoma involving the myocardium may be responsible for this presentation.

Cardiac Monitoring

Case 94-8, Question 2: Should D.A. have received routine cardiac monitoring while he was receiving doxorubicin?

Doxorubicin

Prevention of cardiomyopathy is achieved primarily by limiting the total cumulative dose. However, this strategy cannot entirely prevent cardiomyopathy because individual tolerance to doxorubicin varies such that cardiotoxicity may occur before the arbitrary dose threshold, and some clinical situations warrant exceeding the dose threshold to achieve positive chemotherapeutic treatment outcomes.

Early efforts to prevent cardiomyopathy focused on monitoring systolic time intervals, QRS voltage loss, or ST-T segment changes on an electrocardiogram. These changes were too nonspecific or occurred too late to be useful; however, serial echocardiography (ECHO) has been useful. Current monitoring for anthracycline cardiomyopathy includes assessment of the patient's LVEF, which is a measure of the heart's systolic function using ECHO, radionuclide

cardiac angiography (multiple gated acquisition [MUGA]), or endomyocardial biopsy. The use of MUGA for early detection of doxorubicin-induced cardiac dysfunction has been investigated extensively.[174] A MUGA can accurately detect functional cardiac status, but it is not particularly sensitive in detecting patients who have early myocyte damage. Augmenting the MUGA with exercise appears to give a more accurate picture of functional cardiac reserve. Because myocyte damage usually occurs days to weeks after treatment with doxorubicin, the MUGA should be obtained just before, rather than just after, a course of the agent. Although guidelines vary, most suggest regular cardiac function assessment by evaluation of LVEF by either ECHO or MUGA at defined intervals.[165,168,170]

D.A. should have received a baseline assessment of his LVEF either by ECHO or MUGA before his first cycle of ABVD. During courses of therapy, ongoing LVEF monitoring for D.A. would not have been routinely recommended unless he was approaching his lifetime cumulative dose or there were clinical signs or symptoms of CHF.

Additional assessments should be obtained if a patient shows signs or symptoms of CHF, and may be obtained periodically in low-risk asymptomatic patients and high-risk patients based on the presence of risk factors and provider judgment. The decision to discontinue anthracycline therapy because of cardiotoxicity is complex and must be considered in the context of treatment intent and the patient's comorbid conditions. Collaboration with a cardiologist is recommended for patients with concern for or evidence of treatment-induced cardiotoxicity.[170]

Other Anthracyclines

Daunorubicin differs structurally from doxorubicin only by hydroxylation of the 14th carbon. Cardiac toxicities are similar for both drugs, although somewhat higher cumulative doses of daunorubicin are typically tolerated.[175] Although idarubicin appears less cardiotoxic than does doxorubicin in animal models and

daunorubicin in some early clinical trials, other studies show equivalent myelosuppressive doses can cause cardiotoxicity comparable to that of doxorubicin and daunorubicin.[176–178] Epirubicin also has an incidence of demonstrated CHF.[179] For all anthracyclines, risk factors for CHF appear to be the same, and similar assessments should be undertaken to monitor for cardiotoxicity. Mitoxantrone is an anthracenedione that is structurally similar to the anthracyclines. Guidelines for monitoring doxorubicin-induced cardiotoxicity should also be followed with mitoxantrone therapy to minimize the risk of CHF.[168]

Prevention

Case 94-8, Question 3: Could D.A.'s CHF have been prevented by the use of a different dose or dosing schedule or by an agent that protects the myocardium?

Altering the dose schedule of doxorubicin to more frequent, smaller doses while maintaining dose intensity has consistently resulted in reduction of cardiotoxicity without obvious compromise of antitumor effects.[180–184] Several reports suggest that peak plasma levels, as well as cumulative dose, have an important relationship to doxorubicin cardiotoxicity. Low doses of doxorubicin administered weekly or prolonged continuous IV infusions (48–96 hours) can be relatively cardiac sparing, allowing higher cumulative doses to be administered. In a retrospective, uncontrolled study of 1000 patients receiving weekly doxorubicin, a total dose of 900 to 1200 mg/m^2 of doxorubicin given in weekly fractions had the equivalent cardiotoxicity of 550 mg/m^2 given in every-3-week fractions.[181] In patients with preexisting CHF or those who have exhibited CHF, a continuous-infusion schedule of anthracyclines rather than bolus doses may be considered. The concurrent use of drugs that might minimize the risk of cardiotoxicity without compromising efficacy can be considered as well.

Preventive strategies include management of modifiable cardiovascular risk factors, radiation methods that limit exposure to the heart, administration via continuous infusion instead of slow IV push, the use of liposomal doxorubicin, and administration of dexrazoxane.[170] Dexrazoxane is a chemoprotectant that reduces the incidence and severity of cardiomyopathy. It has been FDA approved for patients with metastatic breast cancer but is often considered for any patient who has received a cumulative doxorubicin dose of 300 mg/m^2 and will continue to receive doxorubicin therapy. The recommended dosing ratio of dexrazoxane to doxorubicin is 10:1 slow IV push 30 minutes before starting doxorubicin. Currently, the ASCO guidelines do not support the routine use of dexrazoxane unless a patient is planned to receive doxorubicin doses >250 mg/m^2.[170]

A Cochrane review was conducted of 10 RCTs involving 1619 adult and pediatric patients with cancer who received an anthracycline with or without dexrazoxane.[185] The majority of patients were adults with advanced breast cancer with no prior anthracycline therapy or cardiac dysfunction receiving doxorubicin or epirubicin. Dexrazoxane was administered with initial anthracycline treatment in all or the majority of patients in 8 of the 10 trials. Dexrazoxane dosing varied from 6.25:1, 10:0, to 20:1. The meta-analysis showed a benefit in favor of dexrazoxane, with reduced incidence of both clinical and subclinical heart failure. There were no significant differences between the treatment groups with regard to response rate, progression-free survival, or overall survival.

A review and meta-analysis of 55 RCTs in patients receiving anthracyclines showed that the risk of cardiotoxicity was significantly decreased with liposomal doxorubicin versus conventional doxorubicin (odds ratio, 0.18; 95% confidence interval, 0.08–0.38).[186] The majority of patients were females with advanced breast cancer. Despite reduced cardiotoxicity, liposomal doxorubicin has not replaced standard doxorubicin in current treatment regimens secondary to high cost and lack of evidence showing equivalency. An established equivalent dose of liposomal preparations to

conventional doxorubicin has not been confirmed, and the dose varies depending on the disease state and regimen.

D.A.'s CHF may have been prevented with continuous-infusion doxorubicin or the use of dexrazoxane; however, because he had not approached a cumulative dose that warranted alternative strategies, this would not have been part of the standard management plan for a patient receiving their first of several cycles of ABVD.

Management

CASE 94-8, QUESTION 4: How should D.A.'s doxorubicin-induced CHF be managed clinically?

Anthracycline-induced CHF presents similarly to other forms of biventricular CHF and may occur within 1 year of treatment, or many years later.[187] Treatment of anthracycline-induced CHF should follow an approach similar to cardiomyopathy induced by other means. Often, these measures are ineffective. The clinical course is variable, with some patients showing stable disease and others showing improvement. Before cardiotoxicity was a widely recognized toxicity, the course of anthracycline-induced CHF was characterized by a rapid progression that generally led to death within weeks. Clinical outcomes are better now, likely because of faster recognition, anthracycline discontinuation after initial symptoms, and improved treatment options for CHF (including spironolactone, β-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers, and diuretics), which have decreased morbidity and mortality in non–anthracycline-induced CHF. Enalapril was evaluated to determine whether it would prevent cardiac function decline in a randomized, double-blind, placebo-controlled study of pediatric patients with cancer who were at least 2 years out from treatment with anthracyclines and had evidence of CHF. Patients received enalapril at 0.05 mg/kg/day, and this dose was progressively escalated to 0.10 mg/kg/day, and finally 0.15

mg/kg/day if there were no adverse effects. Although enalapril did not increase exercise intolerance, it did increase left ventricular end-systolic wall stress in the first year of treatment. Side effects included dizziness, hypotension, and fatigue.[188,189] An additional trial evaluated 201 patients with anthracycline-induced cardiomyopathy. Enalapril and carvedilol were initiated as tolerated as soon as LVEF impairment was observed. Complete resolution of CHF was observed in 85 (42%) patients, and an additional 26 (13%) demonstrated a partial response. Patients who had heart failure therapy initiated closer to the time of observation of their LVEF impairment had a better response. No responses were observed in patients who had heart failure therapy initiated >6 months from the end of their anthracycline regimen.[190] D.A.'s cardiomyopathy should be managed conservatively with an ACE inhibitor such as enalapril and fluid restriction with the addition of diuretics as necessary.[191]

Human Epidermal Growth Factor Receptor 2–Targeted Therapies

Cardiac dysfunction is the principal adverse effect of trastuzumab. When used alone, signs and symptoms of CHF (eg, dyspnea, increased cough, peripheral edema, S_3 gallop, and reduced ejection fraction) have been reported in 3% to 7% of patients receiving trastuzumab therapy. Of these patients, 5% had New York Heart Association (NYHA) class III or IV heart failure. The use of trastuzumab in combination with chemotherapy (including an anthracycline) in patients (*N* = 469) with metastatic breast cancer was associated with a 27% incidence of cardiotoxicity compared with 8% incidence in the anthracycline-alone arm. In these same patients, the incidence of NYHA class III or IV heart failure was 16% in the trastuzumab and chemotherapy arm versus 3% in patients receiving anthracyclines alone. In addition, heart failure occurred in the combination paclitaxel and trastuzumab arm, with an overall incidence of 13% and 2% (classes III and IV, respectively) versus a 1% incidence in the paclitaxel-alone arm.[192] A meta-analysis of five

randomized trials of adjuvant trastuzumab also showed a 2.5-fold higher risk of cardiotoxicity following trastuzumab administration.[193]

Although the exact mechanism behind trastuzumab-induced cardiotoxicity is not fully known, it is thought that the neuregulin (NRG)–ERBB pathway plays a key role. HER2 is one of the tyrosine kinases of the EGFR or ERBB family, and NRG–ERBB signaling is involved in cardiac development and physiology.[194] The toxicity seems to be direct and not dependent on cumulative dose or treatment duration. Trastuzumab-associated cardiac toxicity usually responds to standard medical treatment or discontinuation of the drug.[166] Before, and periodically during, treatment with trastuzumab, patients should undergo cardiac evaluation to assess LVEF. Therapy should be discontinued if patients exhibit a clinically significant decrease in left ventricular function.

The other HER2 targeting agents (lapatinib, pertuzumab, ado-trastuzumab emtansine, neratinib, tucatinib, and trastuzumab deruxtecan) may have a more favorable cardiac safety profile than does trastuzumab. A decline in cardiac function has also been reported in a pooled analysis of 3689 patients with breast cancer receiving lapatinib. The incidence was 1.6% (60 patients). Twelve of the patients had prior anthracyclines and 14 had received prior trastuzumab.[195] Routine cardiac evaluation for patients on pertuzumab, ado-trastuzumab emtansine, and trastuzumab deruxtecan is recommended. No routine cardiac monitoring is recommended for lapatinib, tucatinib, or neratinib at this time.

Tyrosine Kinase Inhibitors

The multitargeted TKIs exhibit a range of cardiovascular toxicities. Because these agents are dosed chronically, toxicities may develop relatively late in the course of therapy. Imatinib has been associated with the development of CHF. A single-institution series reviewed all patients (*N* = 1276) who had received imatinib within their institution. Twenty-two patients (1.2%) exhibited CHF. Eleven patients continued imatinib with the addition of diuretics, β-blockers, and ACE inhibitors. Five of those who continued therapy with imatinib had

dose reductions. The remaining 11 discontinued imatinib (3 secondary to disease progression, 6 secondary to CHF, and 2 were deaths).[196] Patients receiving imatinib should be monitored for symptoms and signs of heart failure.[197] Dasatinib has also been associated with heart failure and ventricular dysfunction.[198] Ponatinib may cause heart failure (in up to 9% of patients), myocardial infarction, and arrhythmias.[199] Sorafenib and sunitinib have been associated with a decline in cardiac ejection fraction in 5% and 14% of 86 patients, respectively, treated for metastatic renal cell cancer.[200] Other TKIs associated with CHF include pazopanib and vemurafenib.[168] Patients experiencing cardiomyopathy on targeted agents are treated similarly to those patients with anthracycline-induced cardiomyopathy. Discontinuation of the offending agent or reduction of dose with concurrent pharmacologic management of CHF is warranted. Two reviews of proposed mechanisms and reported incidence of targeted therapy–induced cardiomyopathy therapies provide a summary of current evidence.[166,201]

Arrhythmias

Electrocardiographic (ECG) changes have been observed during or after treatment with doxorubicin, other anthracyclines, cisplatin, etoposide, paclitaxel, cyclophosphamide, mechlorethamine, and arsenic trioxide. ST–T segment changes, decreases in voltage, T-wave flattening, and atrial and ventricular ectopy are most common. Arrhythmias may occur in 6% to 40% of patients receiving bolus doxorubicin.[202] Paclitaxel also caused significant arrhythmias and conduction defects in phase I and II trials[203]; most patients experienced sinus bradycardia. Doxorubicin and paclitaxel are used in many outpatient regimens, so this toxicity is seen frequently. Arsenic trioxide, used in the treatment of APL, can cause QT interval prolongation and complete atrioventricular block. Dasatinib, nilotinib, lapatinib, pazopanib, and sunitinib have also demonstrated QT prolongation.[168] The underlying mechanisms for these prolongations are not yet understood. Nilotinib, with a reported incidence of 1% to 10%, carries a boxed warning regarding prolongation of the QT

interval. Nilotinib carries specific recommendations for monitoring of ECGs; baseline, 7 days after initiation, after any change of dose, and routinely thereafter.[204] However, there are no specific recommendations for many other TKIs.

QT prolongation can lead to a torsades de pointes–type ventricular arrhythmia. Before initiating therapy, an ECG should be performed, and serum electrolytes, including potassium and magnesium, should be assessed and corrected. In addition, all concomitant medications, both anticancer and other supportive care medications that are known to prolong the QT interval, should be assessed for potential discontinuation to reduce risk.[168]

Ibrutinib demonstrates an increased rate of developing atrial fibrillation of 4% to 10% over what is expected in the general population.[205] This may be due to off-target binding sites and indirect effects on other signaling pathways. BTK inhibitors with less off-target effects, acalabrutinib and zanubrutinib, seem to have a lower risk of atrial fibrillation. A phase III RCT comparing zanubrutinib and ibrutinib showed significantly lower rates of atrial fibrillation with zanubrutinib (2% vs 15% with ibrutinib).[206] In most instances, therapy with a BTK inhibitor can be safely continued because many patients will not have recurrence of the abnormal heart rhythm.

Many other anticancer agents not mentioned previously occasionally cause a rhythm disturbance, but these are limited to a few scattered reports and should not be considered clinically significant. Therapy should not be discontinued unless the patient experiences a serious cardiac arrhythmia.

Hypertension

An increased incidence of hypertension has been observed in patients receiving VEGF-targeted therapy including bevacizumab, sunitinib, sorafenib, axitinib, regorafenib, and pazopanib, among others. Bevacizumab-related hypertension may be dose related; it can occur at any time during therapy and is reported to have a 22% to 32% incidence. Hypertension is usually ≤grade 3 and can be controlled with antihypertensive medications.[207] An increased risk of

myocardial ischemia and infarction has been observed with the use of sorafenib in patients with metastatic renal cell cancer in a phase III study.[189] Patients receiving these agents should be routinely monitored for hypertension, and antihypertensives (generally ACE inhibitors or calcium channel blockers) promptly initiated. In patients with uncontrolled hypertension, anticancer therapy medication may need to be dose reduced or discontinued. Several consensus statements and guidelines have been published to assist in the hypertension management of patients on VEGF inhibitors.[208,209]

Angina and myocardial infarction

Fluorouracil and capecitabine have been associated with angina pectoris and myocardial infarction. In a systematic review including 30 studies, symptomatic cardiotoxicity occurred in 0% to 20% of the patients treated with fluorouracil and in 3% to 35% with capecitabine. The most common symptom was chest pain (0%–19%) followed by palpitations (0%–23%), dyspnea (0%–8%), and hypotension (0%–6%). It appears to occur more frequently in patients receiving multiple-day continuous infusions.[210] Direct myocyte damage is observed from animal studies; however, human studies suggest that coronary artery spasm is the most likely cause of angina. Because the chest pain associated with fluorouracil responds to nitrates, this problem, theoretically, could be managed prophylactically or therapeutically with long-acting nitrates or calcium channel blockers.[211] Other agents have been associated with myocardial ischemia (including, but not limited to, temsirolimus, docetaxel, paclitaxel, imatinib, and ponatinib) based on case reports in the literature.[168,212,213]

NEPHROTOXICITY

Cisplatin

CASE 94-9

QUESTION 1: T.J., a 58-year-old male with nonresectable head and neck cancer, is being treated with cisplatin 100 mg/m^2 IV on day 1 and fluorouracil 1 g/m^2/day IV continuous infusion on days 1 to 4. He received 1 L of normal saline (NS) before and 1 L of NS after his cisplatin on day 1. He presents today for the third cycle of this regimen. T.J.'s labs reveal an estimated creatinine clearance (CrCl) of 75 mL/minute, decreased from 110 mL/minute at baseline. Other abnormalities include serum magnesium of 1.2 mEq/dL; all other electrolyte values are within the normal range.

Is cisplatin responsible for T.J.'s decreased glomerular filtration rate (GFR) and serum magnesium levels?

Cisplatin, a platinum heavy metal complex, is active against many solid tumors and remains as part of first-line therapy for lung, head and neck, and testicular cancers. The major dose-limiting toxicity of cisplatin is nephrotoxicity, and various renal and electrolyte disorders, both acute and chronic, have been associated with cisplatin. Before the need for vigorous hydration was recognized, cisplatin often caused acute renal failure. With the use of vigorous hydration, acute renal failure is uncommon; however, tubular dysfunction and decreased GFR remain problematic.

Acute kidney injury from cisplatin is associated with older age, higher dose, history of hypertension, and hypoalbuminemia.[214] Morphologic damage is greatest in the straight segment of the proximal renal tubules, where the highest concentration of platinum occurs. Acute and cumulative renal tubular damage has been demonstrated by increased urinary excretion of proximal tubular enzymes, such as β_2-microglobulin, alanine aminopeptidase, and *N*-acetyl glucosamine. More recently, the renal uptake carrier organic cation transporter 2 (OCT2) and organic anion transporters 1 and 3 (OAT1 and OAT3) have been implicated.[215] Acute renal failure occurs from acute proximal tubular damage and presents as polyuria in the first 24 to 48 hours when urine osmolality declines, but GFR is normal. Polyuria will decline, and then 72 to 96 hours later, polyuria increases again, urine osmolality declines, and the GFR declines as well and is persistent. Increases in proximal tubular enzymes correlate well with urinary excretion of protein and magnesium as

well as decreased reabsorption of salt and water in the proximal tubules. T.J. has hypomagnesemia, which is the most common electrolyte abnormality caused by cisplatin. Hypomagnesemia appears to be dose related and may occur after a single treatment. Despite replacement with oral magnesium, renal losses of magnesium and decreased serum magnesium levels can persist for months or even years after completion of cisplatin therapy. Hypocalcemia, hyponatremia, and hypokalemia occur less frequently. The cause of these electrolyte abnormalities is thought to be similar to that of hypomagnesemia as a proximal tubular defect that interferes with the reabsorption of these electrolytes.[216,217]

Chronic renal toxicity associated with cisplatin presents as a decrease in the GFR. Published reports suggest that the GFR decreases by 12% to 25% in most patients receiving multiple courses.[217] The decrease appears to be persistent and only partially reversible. An increase in serum creatinine (SCr) or a decrease in CrCl does not necessarily reflect the decline in GFR. A long-term follow-up study of 821 adults exposed to cisplatin with a median follow-up of 6 years found that acute kidney injury had occurred in 31.5% of patients, but <3% had an estimated glomerular filtration rate (eGFR) <29 mL/minute/1.73 m^2 at any time after the first cycle of cisplatin, and none were known to require dialysis.[218]

T.J. is at risk for chronic renal toxicity because he has previously received two other cycles. Renal function of patients receiving cisplatin therapy should be evaluated, because dose reductions of cisplatin may be necessary if the CrCl decreases. T.J.'s decreased GFR and low serum magnesium likely are caused by repeated cycles of cisplatin therapy. Although a dose reduction of cisplatin generally is not recommended for CrCls that are >60 mL/minute, the clinician should provide T.J. with adequate and aggressive hydration to prevent cisplatin nephrotoxicity. Despite preventive methods, many patients will still experience declines in GFR as seen in T.J. In addition, T.J. should receive an oral magnesium supplement. When large doses of magnesium are necessary, diarrhea often limits the use of oral supplementation. IV administration should be used if higher magnesium doses are required. Patients should undergo

frequent measurements of their electrolytes, including magnesium, to minimize potential complications.

Prevention

Case 94-9, Question 2: What measures should be taken to prevent further cisplatin nephrotoxicity in T.J.?

Measures used to minimize or prevent cisplatin-induced nephrotoxicity include hydration with saline and prophylactic magnesium. Incorporation of hydration with saline and magnesium is the standard of care for all patients receiving cisplatin. Patients should be vigorously hydrated before and after cisplatin administration.[216,217,219] A loop diuretic (eg, furosemide) may be required in elderly patients to eliminate excess sodium or in patients with compromised cardiac reserve, but these diuretics should not be used routinely to prevent nephrotoxicity. In addition, mannitol (25–50 g) has been administered just before chemotherapy to prevent cisplatin-induced renal artery vasoconstriction, which can increase the concentration of platinum in the renal tubules, although this is controversial and not supported by current evidence.[220] Many patients may also benefit from prophylactic magnesium supplementation. Patients who received prophylactic magnesium during and 16 mEq IV daily during a 5-day course of cisplatin followed by 60 mEq orally (20 mEq three times daily) between doses of cisplatin experienced less nephrotoxicity compared with those who received no supplements in a prospective trial of 16 patients with testicular carcinoma.[221] Patients should undergo frequent measurements of electrolytes, including magnesium, to minimize potential complications.

T.J. should be encouraged to increase his oral hydration to 2 to 3 L/day for several days after this cycle of chemotherapy. In addition, he should take oral magnesium supplementation between courses. For cycle 4 of his chemotherapy, he should receive 3 to 4 L of saline the day of cisplatin administration.

Patients who experience renal dysfunction commonly have the dose of cisplatin reduced. Guidelines to modify the dosage of cisplatin in patients with decreased renal function are available. Most suggest a 50% dosage reduction when the GFR decreases to 30 to 60 mL/minute and discontinuation when the GFR falls to <10 to 30 mL/minute. Percentage dose reductions are relative to the recommended dose for a specific cancer in a given combination chemotherapy regimen.[222] Because the cisplatin dose ranges from 50 to 120 mg/m^2, the precise dose for a patient with a GFR of <60 mL/minute must be individualized. T.J. should have another SCr drawn to estimate CrCl before his next cycle. As long as his CrCl is maintained above 60 mL/minute, then no dose reductions of his cisplatin are necessary. If a tumor type is known to be responsive to carboplatin and efficacy will not likely be compromised, substitution of carboplatin should be considered because it does not cause nephrotoxicity. Carboplatin is excreted primarily by the kidneys, and the dose is calculated by the Calvert equation,[223] which accounts for decreased GFR (discussed further in Chapter 98, Lung Cancer). Therefore, patients who have decreased renal function receive lower doses than do those with normal function. Other agents requiring dose adjustments or omission for renal dysfunction are shared in **Table 94-6**.

Table 94-6

Select Anticancer Agents Requiring Dosage Modifications or Dosage Omissions in Renal Insufficiency

Bleomycin	Lenalidomide
Capecitabine	Lomustine
Carboplatin	Melphalan
Carmustine	Methotrexate
Cisplatin	Mitomycin
Cytarabine	Pemetrexed
Dacarbazine	Pentostatin
Fludarabine	Topotecan

Ifosfamide	

Sources: Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treat Rev*. 1995;21:33–64. doi:10.1016/0305-7372(95)90010-1; Launay-Vacher V, Oudard S, Janus N, et al. Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer*. 2007;110:1376–1384; Li YF, Fu S, Hu W, et al. Systemic anticancer therapy in gynecologic cancer patients with renal dysfunction. *Int J Gynecol Cancer*. 2007;17:739–763.

Other nephrotoxic agents

Proximal Renal Tubular Dysfunction

Other agents reported to cause renal tubular defects include cyclophosphamide, ifosfamide, lomustine, carmustine, pemetrexed, and azacitidine.[216,219] Nephrotoxicity appears to be related to the total cumulative dose for carmustine and lomustine, but not necessarily for ifosfamide. Renal abnormalities associated with high doses of bolus ifosfamide have led to the use of fractionated doses and a reduced incidence of toxicity.[216] Most patients show signs and symptoms consistent with proximal tubular dysfunction.

Renal toxicity of the proximal renal tubule may result in several electrolyte imbalances, such as loss of protein, glucose, bicarbonate, phosphorous, and potassium. Proteinuria and glycosuria may also occur. SCr, bicarbonate, potassium, urinary pH, protein, and glucose should be monitored closely in patients receiving these agents. Because the reversibility of the lesions is reported to be highly variable and a significant number of patients who exhibit severe renal toxicity with these agents require dialysis,[216] patients should discontinue treatment with these agents if there is evidence of significant and persistent changes in SCr or electrolytes.

Proteinuria

Bevacizumab, an anti-VEGF monoclonal antibody, is associated with proteinuria and the reported incidence ranges from 21% to 46% of patients.[224] Although bevacizumab is the anti-VEGF agent most

noted with this toxicity, ramucirumab (another anti-VEGF monoclonal antibody) and oral TKIs that affect the VEGF receptor such as axitinib have also been associated with proteinuria.[225,226] Mechanisms for this toxicity include microcirculatory angiogenesis and inhibition of nitric oxide synthesis, leading to an increase in peripheral resistance and endothelial dysfunction. Glomerular injury from VEGF inhibition may also lead to renal thrombotic microangiopathy and glomerulonephritis. Severe nephrotic syndrome has been observed in 1% to 2% of patients.[211,224,227] Patients receiving bevacizumab and ramucirumab should be monitored routinely for proteinuria by dipstick urinalysis. The manufacturer recommends that patients with a ≥2+ urine dipstick reading undergo further assessment with a 24-hour urine collection. In addition, it is recommended to delay further administration of bevacizumab when >2 g of proteinuria in 24 hours is observed. Therapy may be reinitiated at a reduced dose when the proteinuria observed is <2 g in 24 hours. Proteinuria is most often mild in patients and is usually reversible upon discontinuation of the agent. The highest incidence of severe proteinuria requiring permanent discontinuation has been seen in patients with metastatic renal cell carcinoma.[228]

CASE 94-10

Question 1: J.R., a 15-year-old boy with osteogenic sarcoma of the right knee, is to be treated with chemotherapy consisting of high-dose methotrexate with leucovorin rescue, doxorubicin, and cisplatin. The dose of methotrexate is 12 g/m^2 IV administered over 4 hours.

What precautions are necessary to prevent renal and other toxicities associated with high-dose methotrexate therapy in J.R.?

Methotrexate normally is not nephrotoxic, although 90% of the agent is excreted unchanged in the urine; however, acute tubular obstruction can occur with high-dose methotrexate if appropriate precautions are not taken. Acute tubular obstruction is caused by tubular precipitation of methotrexate, which is poorly soluble at a pH <7.0. To prevent this, J.R. should receive alkaline hydration and brisk

diuresis to produce a urine pH >7.0 and adequate urine output. A urine pH >7.0 usually can be ensured by administration of 50 to 150 mEq/L sodium bicarbonate within the hydration fluid. J.R.'s urine output and pH must be monitored closely to prevent acute tubular obstruction during this period. The only preventive strategy for acute tubular obstruction associated with high-dose methotrexate therapy is appropriate attention to optimal urinary output before, and for at least 24 hours after, high-dose methotrexate administration and urinary alkalization.[229]

If J.R. has existing renal insufficiency, methotrexate excretion will be decreased, leading to higher systemic exposure. As a result, myelosuppression and mucositis can become more problematic. Leucovorin (folinic acid) is a reduced form of folic acid given after methotrexate administration to selectively rescue normal cells from these adverse effects. Because leucovorin is already in reduced form, it can bypass the action of dihydrofolate reductase and not interfere with methotrexate's inhibition of this enzyme. Leucovorin rescue should be initiated 24 hours after the high-dose methotrexate infusion. Methotrexate levels are necessary to guide leucovorin dosing. Leucovorin rescue does not affect the renal clearance of methotrexate and will not prevent renal injury. A rescue agent, glucarpidase, is indicated for the treatment of toxic methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function. Glucarpidase is a recombinant bacterial carboxypeptidase enzyme that converts methotrexate to its inactive metabolites and provides an alternative route for methotrexate elimination in patients with renal dysfunction and signs or symptoms of methotrexate toxicity.[230]

HEMORRHAGIC CYSTITIS

Case 94-10, Question 2: After J.R.'s surgery, it is decided to add ifosfamide to his treatment. What bladder toxicity occurs with ifosfamide that requires attention before its administration?

Pathogenesis

Ifosfamide is a structural analog of cyclophosphamide belonging to the oxazaphosphorine class of antitumor alkylating agents, which must be hydroxylated and activated by the CYP450 3A4/3A5 and 2B6 enzymes in the liver. The 4-hydroxy metabolite spontaneously liberates acrolein, which is excreted in high concentrations in the urine. Acrolein causes a direct irritation of the bladder mucosa, leading to urotoxicity. Both ifosfamide and cyclophosphamide can produce cystitis, which ranges from mild-to-severe bladder damage and hemorrhage. Cystitis is characterized by tissue edema and ulceration followed by sloughing of mucosal epithelial cells, necrosis of smooth muscle fibers and arteries, and culminating in focal hemorrhage.

Clinical presentation

Patients with acrolein-induced hemorrhagic cystitis may have initial symptoms consistent with urinary tract infection (frequency, urgency, dysuria, and nocturia), as well as microscopic and gross hematuria.[231] The symptoms may subside over a period of several days or weeks after discontinuing the agent. The course of acrolein-induced hemorrhagic cystitis usually is relatively benign, although death from massive refractory hemorrhage has occurred.[232] The primary factors that may predispose J.R. to hemorrhagic cystitis include the dose of ifosfamide he is receiving.

Prevention

Historically, forced hydration was the primary method used to prevent hemorrhagic cystitis in patients treated with cyclophosphamide therapy. Theoretically, hydration flushes the toxic acrolein metabolite out of the bladder so that insufficient contact time is available to set up the tissue reaction. The more urotoxic agent, ifosfamide, was introduced to the market with a uroprotective agent, mesna. This agent contains a free thiol group, which can neutralize acrolein in the bladder. When administered in an appropriate dosing

schedule, mesna can prevent bladder toxicity completely. Concurrent use of mesna with ifosfamide is the standard of care.[219,232]

The ASCO guidelines recommend a parenteral mesna dose of 20% of the ifosfamide dose given at 0, 4, and 8 hours after ifosfamide (for a total mesna dose of 60% of the ifosfamide dose).[41] The goal is to maintain prolonged mesna concentrations within the urinary tract that are uroprotective. Repeated administration is required because mesna has a much shorter elimination half-life (<1 hour) than does ifosfamide. If patients receive a continuous infusion of ifosfamide, a different dosing strategy for mesna is required. To prolong mesna's protective effects, ASCO guidelines recommend an IV bolus mesna dose that is 20% of the ifosfamide dose, followed by a mesna continuous infusion that is an additional equivalent of 40% given during and for 12 to 24 hours after the end of the ifosfamide infusion.[41] This regimen ensures that mesna remains in the bladder for an extended amount of time after the end of the ifosfamide infusion.

Various other mesna dosing schedules are clinically used, but no trials have compared the different regimens. Many clinicians use a 1:1 mg dose of mesna to ifosfamide when administered by continuous infusion. The dosing guidelines become less well defined, however, when patients receive higher dosages of ifosfamide (>2.5 g/m^2). The lack of data and the unique pharmacokinetic properties of ifosfamide have caused concerns about the current dosing guidelines. The pharmacokinetics of ifosfamide are nonlinear. For example, the elimination half-life associated with doses of 2.5 g/m^2 is 6 to 8 hours, whereas with doses of 3.5 to 5 g/m^2, it is 14 to 16 hours. The current recommendations for mesna administration enable protection for ~12 hours after an IV bolus; thus, with higher dosages of ifosfamide, mesna should be infused beyond the recommended 8 hours to maintain bladder protection.[232] To ensure maximal protection against urotoxicity, ASCO currently recommends more frequent or prolonged mesna dosage regimens to account for its short half-life.[41] Ifosfamide and mesna are compatible in solution and can be infused together.

Mesna is usually given IV, but an oral formulation is available. The oral bioavailability of mesna is ~50%; therefore, patients should receive twice the standard IV dose (eg, oral mesna 40% of the IV ifosfamide dose) 2 hours before and 4 and 8 hours after ifosfamide.[233] Others have recommended that an oral dose also be given with the ifosfamide dose. Many centers administer the first dose of mesna IV followed by oral doses at 4 and 8 hours, particularly in the outpatient clinic setting.[41]

All patients receiving cyclophosphamide should receive saline diuresis or forced saline diuresis to protect urothelial tissue. When patients receive cyclophosphamide for an HCT, it is at a high dose; therefore, they receive mesna and forced saline diuresis. Other practices to prevent this complication include hyperhydration and the use of continuous bladder irrigation. Data comparing these methods are controversial and report varying rates of hematuria and severe hemorrhagic cystitis. These recommendations are currently supported by the ASCO consensus guideline[41] (see Chapter 101, Hematopoietic Stem Cell Transplantation). J.R. will receive mesna at a dose of 20% of the ifosfamide dose given immediately before ifosfamide, and at 4 and 8 hours after ifosfamide (for a total mesna dose of 60% of the ifosfamide dose).

Treatment

Case 94-10, Question 3: If J.R. exhibits hemorrhagic cystitis, how should it be treated?

Despite preventive strategies, hemorrhagic cystitis may still develop. In these cases, aggressive measures may be needed, including surgical intervention.[232,234]

PULMONARY TOXICITIES

Bleomycin and other agents

CASE 94-11

Question 1: J.A., a 54-year-old male with stage III Hodgkin lymphoma has received ABVD (doxorubicin 25 mg/m^2 IV days 1 and 15, bleomycin 10 units/m^2 IV on days 1 and 15, vinblastine 6 mg/m^2 IV on days 1 and 15, and dacarbazine 375 mg/m^2 IV on days 1 and 15) for six cycles. He presents to the clinic 6 months after his last cycle with dyspnea, a nonproductive cough, and fever. Chest radiograph showed diffuse bilateral infiltrates; his respiratory rate was 36 breaths/minute; and his arterial blood gases (ABGs) were as follows:

pH, 7.50
P_{O_2}, 62 mm Hg
P_{CO_2}, 28 mm Hg
O_2 saturation, 92%

What are the possible causes of his new pulmonary findings?

J.A. is at risk for several processes that could produce diffuse pulmonary infiltrates and dyspnea. He is immunosuppressed secondary to his lymphoma and the chemotherapy; therefore, J.A. has an increased risk of infection and may have pneumonia. In addition, the infiltrates may represent a relapse of his disease or a toxicity from one or more of the cytotoxic agents he received. Further diagnostic workup is necessary to establish the cause.

Case 94-11, Question 2: A bronchoscopy with bronchoalveolar lavage and a biopsy with pathologic and microbiologic evaluations were performed. Bacterial, fungal, and viral culture findings were negative, and the biopsy revealed inflammation and fibrosis with no evidence of lymphoma. These results are highly suggestive of chemotherapy-induced pulmonary damage. Which of the agents that J.A. received is associated with pulmonary toxicity?

J.A. has received bleomycin and that places him at risk for pulmonary toxicity. As part of the initial workup before initiating chemotherapy with ABVD, J.A. had pulmonary function tests done, which were normal. Many additional agents are responsible for pulmonary toxicity including mitomycin, anthracyclines, alkylating agents, platinums, carmustine, bortezomib, carfilzomib, idelalisib, duvelisib, taxanes, and trastuzumab deruxtecan. Many chemotherapy agents have been associated with pulmonary toxicity,

and the varying types of mechanisms and clinical presentations have been reviewed.[235–245] Several reviews discuss the different types of pulmonary toxicities associated with anticancer agents.[235–237,246,247]

Among all chemotherapy agents, bleomycin is associated with the highest incidence of pulmonary toxicity. Although several types have been reported, the most frequent is interstitial pneumonitis followed by pulmonary fibrosis.[235,240,244] Patients generally present with a nonproductive cough and dyspnea. Clinicians may detect only fine crackling bibasilar rales that often progress to coarse rales. The chest radiograph may be normal in the early stages, but patients can exhibit bilateral alveolar and interstitial infiltrates. ABGs show hypoxia, and pulmonary function tests generally reveal a decrease in the diffusing capacity without a significant decrease in the forced vital capacity.[240,244] The most significant factor associated with the development of pulmonary toxicity is the cumulative dose of bleomycin. At total doses <400 units, <10% of patients experience pulmonary toxicity. When the cumulative dose reaches 450 to 500 units, the incidence is higher. A rarer, hypersensitivity reaction produces fever, eosinophilia, and diffuse infiltrates, which is not dose related. The mortality associated with bleomycin pulmonary toxicity is about 50%.[235,244] If bleomycin is discontinued while symptoms are minimal and before pulmonary function has decompensated significantly, the damage may not progress. Other anticancer agents can potentially exacerbate the pulmonary toxicity associated with bleomycin. J.A.'s pulmonary findings are most likely suggestive of bleomycin toxicity. Unfortunately, there are no methods for reversing the pulmonary toxicity seen with bleomycin, and treatment consists of supportive measures such as oxygen and steroids.

Case 94-11, Question 3: Why are routine pulmonary evaluations indicated in patients such as J.A. who receive bleomycin or other pulmonary toxic agents?

Dose-related decreases in diffusing capacity can occur before the onset of clinical symptoms; therefore, routine baseline and serial pulmonary function studies are recommended.[240] Bleomycin therapy

should be withheld if the diffusing capacity falls to <40% of the baseline value, if the forced vital capacity falls to <75% of the baseline value, or if patients exhibit any signs or symptoms of pulmonary damage.[235,244] Some practitioners also recommend limiting the total cumulative lifetime dose to ≤400 units. Specific screening is not routinely recommended for patients receiving other pulmonary toxic agents; however, if patients exhibit any symptoms or clinical findings, therapy should be withheld until the cause can be determined. J.A. underwent pulmonary function tests before his first cycle of ABVD. Further tests are usually not conducted unless the patient shows signs or symptoms of SOB or difficulty breathing. J.A. did not receive any further studies during his chemotherapy courses because he had no pulmonary symptoms until 6 months after his six cycles of ABVD.

Case 94-11, Question 4: How should J.A.'s bleomycin-induced pulmonary toxicity be managed?

If pulmonary toxicity becomes evident, all suspected agents should be discontinued, and the patient should receive symptomatic support based on their physical condition. Other treatable causes of pulmonary infiltrates (eg, infection) should be considered. Often, pulmonary toxicity is irreversible and progressive, and effective treatments are unavailable. Corticosteroids are administered but are most effective in cases of hypersensitivity-associated pulmonary damage. Nevertheless, because other effective treatments are lacking, a trial of steroids generally is indicated for all patients; if steroids are discontinued, they must be tapered carefully to avoid clinical deterioration.

HEPATOTOXICITY

CASE 94-12

Question 1: J.D., a 56-year-old male, has received two courses of therapy with cytarabine for acute myeloid leukemia (AML). Before his therapy was started,

his liver function tests (LFTs) and coagulation studies were within normal limits. His current laboratory values on day 10 of his second cycle of high-dose cytarabine include the following:

Aspartate aminotransferase, 204 units/L
Alanine aminotransferase, 197 units/L
Lactate dehydrogenase, 795 units/L
Alkaline phosphatase, 285 units/L
Bilirubin, 1.2 mg/dL

Could cytarabine be responsible for J.D.'s laboratory abnormalities?

Elevated LFTs occur frequently in patients with cancer and may result from many causes including liver involvement of the tumor (primary or metastatic), hepatotoxic drugs (including those for supportive care such as antimicrobials), infection, parenteral nutrition, and hepatic thrombosis. Other signs and symptoms of hepatotoxicity include jaundice, nausea, vomiting, abdominal pain, and, rarely, encephalopathy. Patients should receive a thorough workup to determine whether they require immediate attention for tumor involvement of the liver or possible infection. In addition, patients should discontinue any nonessential medications that can potentially cause hepatotoxicity. The clinician may also discontinue chemotherapy if this is the suspected cause.

Several anticancer agents, including cytarabine, have been associated with hepatocellular damage (**Table 94-7**).[248–259] Other common agents include asparaginase, carmustine, cytarabine, mercaptopurine, methotrexate, irinotecan, oxaliplatin, clofarabine, imatinib, pazopanib, and idelalisib. A review of 537 patients with cancer and tyrosine kinase–associated liver enzyme elevations showed that clinically significant abnormalities were unusual and transient.[260] Multiple agents have boxed warnings regarding potential hepatotoxicity. The onset of hepatotoxicity with these drugs is usually within 2 months of treatment initiation and is reversible in the majority of cases. Although death from hepatotoxicity in these cases is uncommon, there have been reports of cirrhosis.[260] All of these drugs come in contact with the liver by entering its blood supply; the liver uniquely receives a dual blood supply from the portal and

superior mesenteric veins. The liver detoxifies or inactivates noxious substances and metabolizes many anticancer agents. The exact mechanisms by which cytotoxic and targeted agents cause hepatotoxicity are unknown, but most agents probably cause it by (a) interfering with the mitochondrial function of the hepatocyte, (b) depleting hepatic glutathione stores, (c) eliciting hypersensitivity reactions, (d) decreasing bile flow, or (e) causing phlebitis of the central hepatic vein to produce sinusoidal obstructive syndrome (also known as veno-occlusive disease). Several articles serve as excellent resources for anticancer therapy–induced hepatotoxicity.[248,249,261]

Table 94-7
Hepatotoxicity From Select Antineoplastic Drugs

Drug	Type
Asparaginase[258]	Hepatocellular fatty metamorphosis
Busulfan[259]	Veno-occlusive disease
Carmustine[256]	Hepatocellular
Clofarabine[261]	Hepatocellular
Cytarabine[262]	Cholestatic
Etoposide[263]	Hepatocellular
Imatinib[257]	Hepatocellular
Mercaptopurine[265]	Cholestatic and hepatocellular
Methotrexate[266]	Hepatocellular
Streptozocin[267]	Hepatocellular

Laboratory tests can serve as indicators of liver structure and function. Serum transaminases, alkaline phosphatase, and bilirubin levels should be monitored routinely in patients receiving hepatotoxic chemotherapy. Although these laboratory indices are sensitive, they are nonspecific for the type of liver disease and do not necessarily correlate with hepatic function. Serum levels of proteins produced by the liver (eg, ferritin, albumin, prealbumin, or retinol-binding protein)

also may be helpful in assessing liver function. The decision to continue or discontinue chemotherapy in patients with apparent hepatic dysfunction can be difficult. If the chemotherapy is the suspected cause, therapy should be withheld until LFTs are within normal ranges. The clinician should also consider alternative (nonhepatotoxic) chemotherapy for future treatment. In addition, concomitant agents that are cleared predominantly via the liver may require dose adjustments and should be administered cautiously (**Table 94-8**). High-dose cytarabine is likely responsible for J.A.'s elevated liver enzymes. Therefore, costly workup should be deferred to allow recovery of liver function. Recovery should occur within 2 weeks of chemotherapy. If full recovery does not occur, further therapy (agents, doses, or both) may require modifications.

Table 94-8
Select Anticancer Agents[a] Requiring Dose Modification in Hepatic Dysfunction

Fluorouracil	Methotrexate
Daunorubicin	Paclitaxel
Docetaxel	Vinblastine
Epirubicin	Vincristine
Etoposide	

[a]The agents listed in this table are examples and are not meant to be an exhaustive list of agents that may need dose adjustments. In addition, specific dose reductions may depend on multiple factors including treatment goals (curative vs palliative), performance status, and specific protocols.

Sources: Thatishetty AV, Agresti N, O'Brien CB. Chemotherapy-induced hepatotoxicity. *Clin Liver Dis*. 2013;17(4):671–686, ix–x; Bahirwani R, Reddy KR. Drug—induced liver injury due to cancer chemotherapeutic agents. *Semin Liver Dis*. 2014;34(2):162–171.

LONG-TERM COMPLICATIONS OF ANTICANCER THERAPY

Secondary Malignancies After Anticancer Therapy

CASE 94-13

QUESTION 1: T.D., a 55-year-old female, was diagnosed with an early-stage breast cancer and successfully treated with radical mastectomy followed by four cycles of adjuvant doxorubicin 60 mg/m^2 IV on day 1 with cyclophosphamide 600 mg/m^2 IV on day 1. Eighteen months after her breast cancer therapy was completed, T.D. presents to her primary care physician with fatigue, SOB, easy bruising, and sinusitis. A peripheral blood smear shows a WBC count of 120,000 cells/μL with a differential including >90% leukemic blasts, and a bone marrow biopsy confirms AML. Subsequent cytogenetic analysis revealed abnormalities involving chromosome 11q23.

What factors support the diagnosis of anticancer therapy– associated acute leukemia in T.D.?

Acute leukemia has been associated with cytotoxic therapies used to treat hematologic malignancies, solid tumors, and nonmalignant diseases.[262] It is generally reported after combination chemotherapy that involves topoisomerase inhibitors, including etoposide and anthracyclines.[263] These leukemias, called *therapy-related myeloid neoplasms (tMNs)*, usually occur 1 to 3 years after the completion of chemotherapy, and myelodysplasia does not usually occur before the leukemia. Other characteristics include chromosomal abnormalities involving chromosome 11q23.[262] This challenge is an important area for research given the widespread use of these agents for many curable diseases such as Hodgkin lymphoma, breast cancer, and testicular cancer. AML has also been reported in patients who have had previous exposure to alkylating agents. It usually occurs 5 to 7 years after the patient finishes chemotherapy. Myelodysplastic syndrome (preleukemia changes) commonly occurs in 50% of patients before overt acute leukemia with these agents.

Clonal hematopoiesis of indeterminate potential (CHIP) has been described as a risk factor for the development of tMN; patients with CHIP have underlying changes in the bone marrow that appear to predispose them to tMN upon exposure to chemotherapy.[264] Several

additional factors may increase a patient's risk of exhibiting acute leukemia.[262]

Evidence that cytotoxic agents can cause secondary lymphoid malignancies, particularly non-Hodgkin lymphoma, is also strong. Immunosuppression from the disease and its treatment, rather than the particular agent, may be the primary cause of non-Hodgkin lymphoma. Other secondary malignancies can occur after anticancer treatment as well. Superficial bladder cancer has been reported in patients treated with daily oral cyclophosphamide, and bone sarcoma has occurred after treatment with alkylating agents.[265,266] The secondary solid tumors in patients treated with other cytotoxic agents are considered coincidental.

T.D.'s AML probably occurred secondary to her previous doxorubicin. The chemotherapy agent, as well as the time course for her acute leukemia, is consistent with topoisomerase-II agent-induced malignancies. Although initial trials indicated a risk of myelodysplastic syndrome and AML of 0.27% at 8 years after adjuvant chemotherapy for breast cancer, a large retrospective review of an NCCN database showed a risk of 0.24% at 5 years and 0.48% at 10 years, for both myeloid and lymphoid malignancies, and was largely related to chemotherapy rather than to surgery or radiation therapy.[267] In addition, cytogenetic abnormalities occur in >90% of those patients who have received chemotherapy or radiation therapy and have subsequently experienced therapy-related myelodysplastic syndrome or AML.[262] Abnormalities in chromosome 11q23 are involved in many of the cases with cytogenetic abnormalities from topoisomerase inhibitors.[262] The chromosomal abnormalities of 11q23 in T.D. strongly support the diagnosis of chemotherapy-associated acute leukemia rather than of de novo leukemia.

Case 94-13, Question 2: Are the therapy and prognosis of T.D. with treatment-associated AML similar to those of patients with de novo AML?

Chemotherapy is much less effective for the treatment of tMN than is de novo AML. Complete remissions with standard cytarabine and daunorubicin regimens are achieved in less than half of patients with treatment-associated AML compared with a complete remission rate of 70% to 80% in patients with de novo AML[262] (see Chapter 96, Adult Hematologic Malignancies).

Mutations in TP53 are common in tMN and are associated with resistance to chemotherapy and poor prognosis.[268] The overall survival estimate for patients with tMN is about 8 to 10 months.[269]

The best "treatment" of therapy-associated AML is prevention. In patients such as T.D. receiving adjuvant chemotherapy for a curable malignancy, avoiding the use of agents that cause treatment-related AML should be discussed in conjunction with the benefits of therapy. Use of alternative regimens and avoidance of chemotherapy altogether is increasing as more is learned about secondary leukemias and effective management of malignancies with chemotherapy-sparing approaches.

Fertility and Teratogenicity

Effects on Oogenesis

CASE 94-14

QUESTION 1: C.L., a 32-year-old female with recently diagnosed stage II breast cancer, underwent a lumpectomy and external beam radiation therapy and is scheduled to begin adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel (AC-T). C.L. was married 12 months before her diagnosis and wishes to have children.

What are C.L.'s prospects for fertility after adjuvant chemotherapy?

Cytotoxic chemotherapy is potentially gonadotoxic in humans. Ovarian biopsies taken from females treated for cancer demonstrate loss of ova and follicular elements. This injury is evident even in prepubertal female patients treated for cancer. Ova die or become nonfunctional by direct injury to the ova or by indirect injury resulting

from loss of supporting follicular cells. If the damage to the follicular elements is extensive and irreversible, fertility is impaired even if the ova are spared.

Agent-induced injury to ova and follicular elements reduces ovarian estrogen and progesterone secretion in menstruating females. This causes the hypothalamus and pituitary to secrete more follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn increase follicular recruitment and the number of follicles vulnerable to cytotoxic chemotherapy agents. If the gonadal toxicity is severe or prolonged, permanent ovarian failure can occur secondary to depletion of ova and follicles. Recovery of some of the affected follicles can occur and is manifested by irregular menses or delayed recovery of menses. If the ova are spared and follicular cells recover sufficiently, ovulation and pregnancy might occur, but premature ovarian failure is inevitable in most females treated with large doses of gonadotoxic agents given for long periods.[270]

Prepubertal girls have a greater reserve of primary follicles. Because their ovaries are not producing estrogen and progesterone, increases in FSH and LH with resultant recruitment of follicular elements do not occur. For this reason, prepubertal girls can tolerate large doses without apparent effects even if the pathology previously described occurs. The gonadal effects of cytotoxic chemotherapy in females have been described in several reviews.[270–272]

C.L. is going to receive an alkylating agent, which are the most potent gonadotoxic agents. Cyclophosphamide is well known for producing infertility in males and females and gonadal failure even in children. This effect is influenced strongly by the total dose of cyclophosphamide and the patient's age at the onset of chemotherapy. Nearly 100% of females older than 20 years of age experience amenorrhea when the mean total dose is 20 to 50 g. The same consequence can be expected in females older than 35 years of age who receive >6 to 10 g and in females 45 years of age and older who receive >5 g.[273] Depending on the exact dose of cyclophosphamide in the AC-T regimen planned, C.L. may or may not fall into a dose range that would be expected to produce permanent amenorrhea.

The clinician also must consider that a synergistic gonadotoxic effect has been reported when doxorubicin is combined with cyclophosphamide. Aside from the alkylating agents, other agents with strong evidence of gonadal toxicity include platinums, anthracyclines, vinblastine, and etoposide. Several resources discuss the doses of chemotherapy agents, used both alone and in combination, and specific incidences of associated gonadotoxicity, as well as the prevalence of temporary and permanent amenorrhea.[271,273,274]

C.L. most likely will experience amenorrhea along with the signs and symptoms of menopause because both estrogen and progesterone production diminishes during cytotoxic chemotherapy. C.L. may recover from chemotherapy-induced amenorrhea months to years after completion of her therapy. Recovery may be manifested as amenorrhea interspersed with normal menstrual periods.

Pregnancy is possible during periods of normal menstruation because ovulation does occur in most instances. However, premature menopause is likely. Because the greatest risk of pregnancy exists early in the course of therapy, and because ovulation may occur despite amenorrhea, C.L. should be counseled to practice birth control while receiving cytotoxic chemotherapy. Because hormonal contraceptives are contraindicated in patients with breast and liver cancer, barrier methods (ie, diaphragm, condoms, and spermicide) or copper intrauterine devices should be advised.[275] Consensus guidelines are available; however, evidence and recommendations are lacking for certain cancer types, such as leukemia, lymphoma, and bone tumors.[276,277] Methods to preserve fertility after chemotherapy for females include cryopreservation of embryos or unfertilized oocytes, and ovarian tissue transposition, for which further recommendations are published by ASCO.[278]

EFFECTS ON SPERMATOGENESIS

CASE 94-15

QUESTION 1: J.K., a 25-year-old male with recently diagnosed testicular cancer, will receive systemic chemotherapy with bleomycin, etoposide, and cisplatin. What effect does systemic chemotherapy have on male gonadal function?

The primary gonadal toxic effect of cytotoxic chemotherapy agents in male patients is a progressive dose-related depletion of the germinal epithelium lining the seminiferous tubule. This leads to a marked reduction in testicular volume and azoospermia. The Leydig cells responsible for testosterone production remain morphologically intact, although mild functional impairment occurs rarely. The major toxicity of chemotherapy in males is loss of reproductive capacity. During treatment, libido and sexual activity may decline, but most males report a return to pretreatment sexual function after chemotherapy.[245]

Of the cytotoxic chemotherapy agents, alkylating agents are associated most commonly with azoospermia. Progressive dose-related oligospermia occurs in males receiving chlorambucil,[279,280] cyclophosphamide,[281,282] melphalan, busulfan, procarbazine, and nitrosoureas; procarbazine appears to be the most gonadotoxic alkylating agent in males. Doxorubicin, vinblastine, cytarabine, and cisplatin also have been associated with azoospermia,[283] and doxorubicin appears to have a synergistic toxic effect in males when given with cyclophosphamide. Phase-specific agents, such as antimetabolites and vinca alkaloids, seem unlikely to produce azoospermia when used alone, but may play a minor role in combination chemotherapy regimens.[284]

In contrast to oogenesis, in which females are born with a full complement of ova, spermatogenesis occurs in a continuous cycle of regeneration, differentiation, and maturation beginning in the second month of embryogenesis and continuing through old age. Gonadotoxic agents generally are used in sufficiently large doses to affect varying proportions of maturing sperm cells in any stage of development. Because spermatogenesis must restart at the beginning after agent-induced azoospermia occurs, the length of recovery is prolonged, usually lasting at least 2 to 3 years. The

relationship of age to the development of azoospermia is far less clear than is the relationship of age to ovarian suppression. Although prepubertal boys are less likely to be affected by chemotherapy agents than are adult males, the reserve of primitive sperm cells in male children is far less than it is in adults. Therefore, the spermatogenesis potential in prepubertal testes may make them more vulnerable to cytotoxic damage than that in those of adults. A review of the literature regarding the effects of cytotoxic chemotherapy administered to male children concluded that agents and regimens known to be toxic in males should be considered toxic in young boys.[245,274] In adult survivors of childhood cancer treated with alkylating agents, azoospermia was present in 25% of patients, oligospermia in 28%, and normospermia in 48%. Impaired spermatogenesis was unlikely up to a cyclophosphamide equivalent dose of 4000 mg/m^2. Sperm motility and morphology may also be affected.[285] Short of a testicular biopsy, the damage cannot be detected until puberty.

The two diseases most likely to affect the fertility of young males are Hodgkin lymphoma and testicular cancer. The standard treatment for advanced Hodgkin lymphoma is ABVD. Azoospermia has been observed in 35% of patients receiving ABVD, and spermatogenesis nearly always recovered in these patients.[283] Evidence to date suggests that therapy-induced azoospermia following treatment with vinblastine, bleomycin, and cisplatin for nonseminomatous testicular carcinoma is reversible within 2 to 3 years in ~50% of patients treated. Those who recover spermatogenesis are capable of impregnating their female partners.[286,287] In this particular patient population, it is important to recognize that retroperitoneal lymph node dissection, which often results in retrograde ejaculation, as well as cryptorchidism, which predisposes to infertility, may contribute to the lack of full recovery of fertility potential.

Case 94-15, Question 2: Aside from the use of anticancer therapy agents with less gonadal toxicity, are there means of circumventing infertility in young patients such as J.K. receiving therapy?

Sperm or gamete cryopreservation should be considered in males. A major limitation of this approach has been the finding of diminished sperm counts, sperm volume, and sperm motility in young males affected with Hodgkin lymphoma and testicular cancer even before combination chemotherapy is initiated. Although published studies suggest that the quantity and motility of sperm are important determinants of successful artificial insemination, pregnancies have been reported. Thus, sperm banking should be considered even in oligospermic males.[245,284] Oocyte cryopreservation and embryo cryopreservation now are feasible options for young females about to undergo cytotoxic chemotherapy. Even in the face of cytotoxic chemotherapy-induced ovarian failure, in vitro fertilization of an ovum and implantation into the endometrium with proper hormonal support can successfully accommodate a term pregnancy. This may be an option for females.[272,278]

In both sexes, it has been hypothesized that gonadal toxicity from cytotoxic chemotherapy could be decreased by inhibiting spermatogenesis or follicular development during therapy. There is currently no evidence to support hormonal gonadoprotection in males. There is mixed evidence to support administration of gonadotropin-releasing hormone agonists to preserve fertility in females. Methods used to suppress gonadal function have included administration of testosterone in males, oral contraceptives in females, and gonadotropin-releasing hormone analogs in both males and females. Several reviews describe these approaches in detail,[245,271,272] and ASCO provides recommendations on preserving fertility in patients with cancer.[278]

TERATOGENICITY

CASE 94-15, QUESTION 3: If J.K. regains fertility after his planned combination chemotherapy regimens, is he at risk for producing offspring with congenital abnormalities or an excess risk of cancer?

Most of the agents used to treat cancer are designed specifically to interfere with DNA synthesis, cellular metabolism, and cell division. Thus, reason exists to suspect that they may cause mutation of ova or spermatocytes exposed to these effects. Outcomes of pregnancies in survivors of cancer are published as case reports, small series, and retrospective case series. Nearly 1600 children have been born to 1078 patients previously treated for malignancy in childhood or as adults. From this, there is no evidence that spontaneous abortion, genetic disease, or congenital anomalies occur more frequently in the progeny of cancer survivors. Similarly, there does not appear to be an increased risk of malignancy in the offspring of patients treated for cancer.[274] The likely explanation for this is that ova and sperm cells affected by cytotoxic chemotherapy usually are killed. The risk of producing an abnormal offspring thus would be highest at the time of chemotherapy. Males and females should be explicitly discouraged from conception during chemotherapy. In general, adults surviving cancer should be advised to wait at least 2 years after completion of therapy before attempting conception. This also provides time to assess the likelihood of the necessity for further treatment that would have grave consequences on the fetus, particularly in the case of female patients.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Bahirwani R, Reddy KR. Drug-induced liver injury due to cancer chemotherapeutic agents. *Semin Liv Dis.* 2014;34(2):162–171. doi:10.1055/ s-0034-1375957 (249)

Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol*. 2004;22(14):2918–2926. doi:10.1200/JCO.2004.04.132 (54)

Churpek JE, Larson RA. The evolving challenge of therapy-related myeloid neoplasms. *Best Pract Res Clin Haematol*. 2013;26(4):309–317. doi:10.1016/j.beha.2013.09.001 (262)

Elad S. The MASCC/ISOO Mucositis Guidelines 2019 Update: introduction to the first set of articles. *Supportive Care Cancer*. 2019;27(10):3929–3931. doi:10.1007/s00520-019-04895-x (37)

Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. 2009;27:127–145. doi:10.1200/JCO.2008.17.2627 (41)

Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol*. 2009;27(29):4839–4847. doi:10.1200/JCO.2009.22.3271 (21)

Kwakman JJ, Elshot YS, Punt CJA, Koopman M. Management of cytotoxic chemotherapy-induced hand-foot syndrome. *Oncol Rev*. 2020;14(1):442. doi:10.4081/oncol.2020.442 (76)

Kwong YL, Yeung DYM, Chan JCW. Intrathecal chemotherapy for hematologic malignancies: drugs and toxicities. *Ann Hematol*. 2009;88:193. doi:10.1007/s00277-008-0645-y (117)

Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. 2011;19(8):1079–1095. doi:10.1007/s00520-011-1197-6 (85)

Lalla RV. Evidence-based management of oral mucositis. *JCO Oncol Pract*. 2020;16(3):111–112. doi:10.1200/JOP.19.00766 (45)

Magge RS, DeAngelis LM. The double-edged sword: neurotoxicity of chemotherapy. *Blood Rev*. 2015;29(2):93–100. doi:10.1016/j.blre.2014.09. 012 (145)

Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation for patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36(19):1994–2001. doi:10.1200/JCO.2018.78.1914 (278)

Perazella MA. Onco-nephrology: renal toxicities of chemotherapeutic agents. *Clin J Am Soc Nephrol*. 2012;7(10):1713–1721. doi:10.2215/CJN .02780312 (219)

Piccolo J, Kolesar JM. Prevention and treatment of chemotherapy-induced peripheral neuropathy. *Am J Health-Syst Pharm*. 2014;71(1):19–25. (150)

Rosello S, Blasco I, García Fabregat L, Cervantes A, Jordan K, ESMO Guidelines Committee. Management of infusion reactions to systemic anticancer therapy: ESMO clinical practice guidelines. *Ann Oncol*. 2017;28(suppl_4):iv100–iv118. (98)

Sadowska AM, Specenier P, Germonpre P, Peeters M. Antineoplastic therapy-induced pulmonary toxicity. *Exp Rev Anticancer Ther*. 2013;13(8):997–1006. doi:10.1586/14737140.2013.817684 (235)

Truong J, Yan AT, Cramarossa G, Chan KK. Chemotherapy-induced cardiotoxicity: detection, prevention, and management. *Can J Cardiol.* 2014;30(8):869–878. doi:10.1016/j.cjca.2014.04.029 (168)

Key Websites

American Society of Clinical Oncology (ASCO). http://www.asco.org

Common Terminology Criteria for Adverse Events (CTCAE). Cancer therapy evaluation program: National Cancer Institute. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

National Comprehensive Cancer Network (NCCN). http//www.nccn.org

Oncology Nursing Society (ONS). http://www.ons.org

COMPLETE REFERENCES CHAPTER 94 ADVERSE EFFECTS OF CHEMOTHERAPY, IMMUNOTHERAPY, AND TARGETED AGENTS

1. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Cancer therapy evaluation program: National Cancer Institute. Published November 27, 2017. Accessed September 28, 2020. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
2. National Comprehensive Cancer Network. Hematopoietic growth factors (Version 3.2021). Accessed May 16, 2021. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf
3. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol*. 2007;25(21):3158–3167. doi:10.1200/JCO.2006.08.8823
4. Lyman GH, Dale DC, Wolff DA, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. *J Clin Oncol*. 2010;28(17):2914–2924. doi:10.1200/JCO.2009.25.8723

5. Neulasta. Package insert. Amgen; 2015. Accessed September 28, 2020. https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/neulasta/neulasta_pi_hcp_english.pdf
6. García-Carbonero R, Mayordomo JI, Tornamira MV, et al. Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. *J Natl Cancer Inst*. 2001;93(1):31–38. doi:10.1093/jnci/93.1.31
7. Clark OAC, Lyman GH, Castro AA, Clark LGO, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *J Clin Oncol*. 2005;23(18):4198–4214. doi:10.1200/JCO.2005.05.645
8. Berghmans T, Paesmans M, Lafitte JJ, et al. Therapeutic use of granulocyte and granulocyte-macrophage colony-stimulating factors in febrile neutropenic cancer patients: a systematic review of the literature with meta-analysis. Centre for Reviews and Dissemination (UK); 2002. Accessed September 28, 2020. https://www.ncbi.nlm.nih.gov/books/NBK69156/
9. Hidalgo M, Hornedo J, Lumbreras C, et al. Outpatient therapy with oral ofloxacin for patients with low risk neutropenia and fever. *Cancer*. 1999;85(1):213–219. doi:10.1002/(SICI)1097-0142(19990101)85:1<213::AID-CNCR29>3.0.CO;2-D
10. Santolaya ME, Alvarez AM, Avilés CL, et al. Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. *J Clin Oncol*. 2004;22(18):3784–3789. doi:10.1200/JCO.2004.01.078
11. Innes HE, Smith DB, O'Reilly SM, Clark PI, Kelly V, Marshall E. Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study. *Br J Cancer*. 2003;89(1):43–49. doi:10.1038/sj.bjc.6600993
12. Zhang X, Chuai Y, Nie W, Wang A, Dai G. Thrombopoietin receptor agonists for prevention and treatment of chemotherapy-induced thrombocytopenia in patients with solid tumours. *Cochrane Database Syst Rev*. 2017;11(11):CD012035. doi:10.1002/14651858.CD012035.pub2
13. Whitecar JP, Bodey GP, Harris JE, Freireich EJ. L-asparaginase. *N Engl J Med*. 1970;282(13):732–734. doi:10.1056/NEJM197003262821307
14. Ramsay NKC, Coccia PF, Krivit W, Nesbit ME, Edson JR. The effect of L-asparaginase on plasma coagulation factors in acute lymphoblastic leukemia. *Cancer*. 1977;40(4):1398–1401. doi:10.1002/1097-0142(197710)40:4<1398::AID-CNCR2820400406>3.0.CO;2-#
15. Truelove E, Fielding AK, Hunt BJ. The coagulopathy and thrombotic risk associated with L-asparaginase treatment in adults with acute lymphoblastic leukaemia. *Leukemia*. 2013;27(3):553–559. doi:10.1038/leu.2012.290

16. Bye AP, Unsworth AJ, Desborough MJ, et al. Severe platelet dysfunction in NHL patients receiving ibrutinib is absent in patients receiving acalabrutinib. *Blood Adv*. 2017;1(26):2610–2623. doi:10.1182/bloodadvances.2017011999
17. de Weerdt I, Koopmans SM, Kater AP, van Gelder M. Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach. *Haematologica*. 2017;102(10):1629–1639. doi:10.3324/haematol.2017.164103
18. Metharom P, Falasca M, Berndt MC. The history of Armand Trousseau and cancer-associated thrombosis. *Cancers (Basel)*. 2019;11(2):158.
19. Aderka D, Brown A, Zelikovski A, Pinkhas J. Idiopathic deep vein thrombosis in an apparently healthy patient as a premonitory sign of occult cancer. *Cancer*. 1986;57(9):1846–1849. doi:10.1002/1097-0142(19860501)57:9<1846::AID-CNCR2820570925>3.0.CO;2-3
20. Goldberg RJ, Seneff M, Gore JM, et al. Occult malignant neoplasm in patients with deep venous thrombosis. *Arch Intern Med*. 1987;147(2):251–253.
21. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol*. 2009;27(29):4839–4847. doi:10.1200/JCO.2009.22.3271
22. Oppelt P, Betbadal A, Nayak L. Approach to chemotherapy-associated thrombosis. *Vasc Med*. 2015;20(2):153–161. doi:10.1177/1358863X14568705
23. National Comprehensive Cancer Network. Cancer-associated venous thromboembolic disease (Version 1.2020). Accessed September 4, 2020. https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf
24. Zangari M, Siegel E, Barlogie B, et al. Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood*. 2002;100(4):1168–1171. doi:10.1182/blood-2002-01-0335
25. Knight R, DeLap RJ, Zeldis JB. Lenalidomide and venous thrombosis in multiple myeloma. *N Engl J Med*. 2006;354(19):2079–2080. doi:10.1056/NEJMc053530
26. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med*. 2019;380(8):720–728. doi:10.1056/NEJMoa1814630
27. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med*. 2019;380(8):711–719. doi:10.1056/NEJMoa1814468
28. Skillings JR, Johnson DH, Miller K, et al. Arterial thromboembolic events (ATEs) in a pooled analysis of 5 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy. *J Clin Oncol*. 2005;23(16_suppl):3019. doi:10.1200/jco.2005.23.16_suppl.3019
29. Choueiri TK, Schutz FAB, Je Y, Rosenberg JE, Bellmunt J. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and

meta-analysis of clinical trials. *J Clin Oncol*. 2010;28(13):2280–2285. doi:10.1200/JCO.2009.27.2757

30. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22(11):2184–2191. doi:10.1200/JCO.2004.11.022
31. Sanz MA, Montesinos P. Open issues on bleeding and thrombosis in acute promyelocytic leukemia. *Thromb Res*. 2010;125(suppl 2):S51–54. doi:10.1016/S0049-3848(10)70013-X
32. Stein E, McMahon B, Kwaan H, Altman JK, Frankfurt O, Tallman MS. The coagulopathy of acute promyelocytic leukaemia revisited. *Best Pract Res Clin Haematol*. 2009;22(1):153–163. doi:10.1016/j.beha.2008.12.007
33. Lindley CM, Bernard S, Fields SM. Incidence and duration of chemotherapy-induced nausea and vomiting in the outpatient oncology population. *J Clin Oncol*. 1989;7(8):1142–1149. doi:10.1200/JCO.1989.7.8.1142
34. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100(9 suppl):1995–2025. doi:10.1002/cncr.20162
35. Garden AS, Chambers MS. Head and neck radiation and mucositis. *Curr Opin Support Palliat Care*. 2007;1(1):30–34. doi:10.1097/SPC.0b013e32813aeb34
36. Keefe DMK, Gibson RJ. Mucosal injury from targeted anti-cancer therapy. *Support Care Cancer*. 2007;15(5):483–490. doi:10.1007/s00520-006-0181-z
37. Elad S. The MASCC/ISOO Mucositis Guidelines 2019 Update: introduction to the first set of articles. *Support Care Cancer*. 2019;27(10):3929–3931. doi:10.1007/s00520-019-04895-x
38. Epstein JB, Thariat J, Bensadoun R-J, et al. Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. *CA Cancer J Clin*. 2012;62(6):400–422. doi:10.3322/caac.21157
39. Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer: a literature review. *Cancer*. 2006;107(11):2525–2534. doi:10.1002/cncr.22302
40. Porter SR, Scully C, Hegarty AM. An update of the etiology and management of xerostomia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2004;97(1):28–46. doi:10.1016/j.tripleo.2003.07.010
41. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. 2009;27(1):127–145. doi:10.1200/JCO.2008.17.2627
42. Johnson JT, Ferretti GA, Nethery WJ, et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *N Engl J Med*.

1993;329(6):390–395. doi:10.1056/NEJM199308053290603
43. Aguiar GP, Jham BC, Magalhães CS, Sensi LG, Freire AR. A review of the biological and clinical aspects of radiation caries. *J Contemp Dent Pract*. 2009;10(4):83–89.
44. Sonis ST. Oral mucositis in cancer therapy. *J Support Oncol*. 2004;2(6 suppl 3):3–8.
45. Lalla RV. Evidence-based management of oral mucositis. *JCO Oncol Pract*. 2020;16(3):111–112. doi:10.1200/JOP.19.00766
46. Gelclair. Product information. Helsinn Healthcare SA. Accessed August 1, 2015. www.gelclair.com
47. Barber C, Powell R, Ellis A, Hewett J. Comparing pain control and ability to eat and drink with standard therapy vs Gelclair: a preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis. *Support Care Cancer*. 2007;15(4):427–440. doi:10.1007/s00520-006-0171-1
48. Mahood DJ, Dose AM, Loprinzi CL, et al. Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. *J Clin Oncol*. 1991;9(3):449–452. doi:10.1200/JCO.1991.9.3.449
49. Ferretti GA, Ash RC, Brown AT, Largent BM, Kaplan A, Lillich TT. Chlorhexidine for prophylaxis against oral infections and associated complications in patients receiving bone marrow transplants. *J Am Dent Assoc*. 1987;114(4):461–467. doi:10.14219/jada.archive.1987.0112
50. Ferretti GA, Raybould TP, Brown AT, et al. Chlorhexidine prophylaxis for chemotherapy and radiotherapy-induced stomatitis: a randomized double-blind trial. *Oral Surg Oral Med Oral Pathol*. 1990;69(3):331–338. doi:10.1016/0030-4220(90)90295-4
51. Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *Lancet Oncol*. 2017;18(5):654–662. doi:10.1016/S1470-2045(17)30109-2
52. Pessi MA, Zilembo N, Haspinger ER, et al. Targeted therapy-induced diarrhea: a review of the literature. *Crit Rev Oncol Hematol*. 2014;90(2):165–179. doi:10.1016/j.critrevonc.2013.11.008
53. Irinotecan. Package insert. Pharmacia & Upjohn Company; 2014.
54. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol*. 2004;22(14):2918–2926. doi:10.1200/JCO.2004.04.132
55. Richardson G, Dobish R. Chemotherapy induced diarrhea. *J Oncol Pharm Pract*. 2007;13(4):181–198. doi:10.1177/1078155207077335
56. Geller RB, Gilmore CE, Dix SP, et al. Randomized trial of loperamide versus dose escalation of octreotide acetate for chemotherapy-induced diarrhea in

bone marrow transplant and leukemia patients. *Am J Hematol*. 1995;50(3):167–172. doi:10.1002/ajh.2830500304

57. Rosenoff SH, Gabrail NY, Conklin R, et al. A multicenter, randomized trial of long-acting octreotide for the optimum prevention of chemotherapy-induced diarrhea: results of the STOP trial. *J Support Oncol*. 2006;4(6):289–294.
58. Zachariah B, Gwede CK, James J, et al. Octreotide acetate in prevention of chemoradiation-induced diarrhea in anorectal cancer: randomized RTOG Trial 0315. *J Natl Cancer Inst*. 2010;102(8):547–556. doi:10.1093/jnci/djq063
59. Hoff PM, Saragiotto DF, Barrios CH, et al. Randomized phase III trial exploring the use of long-acting release octreotide in the prevention of chemotherapy-induced diarrhea in patients with colorectal cancer: the LARCID trial. *J Clin Oncol*. 2014;32(10):1006–1011. doi:10.1200/JCO.2013.50.8077
60. Andreyev J, Ross P, Donnellan C, et al. Guidance on the management of diarrhoea during cancer chemotherapy. *Lancet Oncol*. 2014;15(10):e447–e460. doi:10.1016/S1470-2045(14)70006-3
61. Nerlynx (neratinib). Package insert. Puma Biotechnology; 2017.
62. National Comprehensive Cancer Network. Management of immunotherapy-related toxicities (Version 1.2020). Accessed September 5, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
63. Payne AS, James WD, Weiss RB. Dermatologic toxicity of chemotherapeutic agents. *Semin Oncol*. 2006;33(1):86–97. doi:10.1053/j.seminoncol.2005.11.004
64. Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. *Semin Oncol*. 2006;33(1):139–143. doi:10.1053/j.seminoncol.2005.11.007
65. Galimont-Collen AFS, Vos LE, Lavrijsen APM, Ouwerkerk J, Gelderblom H. Classification and management of skin, hair, nail and mucosal side-effects of epidermal growth factor receptor (EGFR) inhibitors. *Eur J Cancer*. 2007;43(5):845–851. doi:10.1016/j.ejca.2006.11.016
66. Heidary N, Naik H, Burgin S. Chemotherapeutic agents and the skin: an update. *J Am Acad Dermatol*. 2008;58(4):545–570. doi:10.1016/j.jaad.2008.01.001
67. Wang J, Lu Z, Au JL-S. Protection against chemotherapy-induced alopecia. *Pharm Res*. 2006;23(11):2505–2514. doi:10.1007/s11095-006-9105-3
68. Maeng HM, Berger AM. Hair loss and other hair changes. In: DeVita VT, Rosenberg SA, Lawrence TS, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* 11th ed. Lippincott Williams & Wilkins; 2018:2128–2133.
69. Nangia J, Wang T, Osborne C, et al. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: the SCALP randomized clinical trial. *JAMA*. 2017;317(6):596–605. doi:10.1001/jama.2016.20939

70. Grevelman EG, Breed WPM. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol*. 2005;16(3):352–358. doi:10.1093/annonc/mdi088
71. Shin H, Jo SJ, Kim DH, Kwon O, Myung S-K. Efficacy of interventions for prevention of chemotherapy-induced alopecia: a systematic review and meta-analysis. *Int J Cancer*. 2015;136(5):E442–E454. doi:10.1002/ijc.29115
72. Capriotti K, Capriotti JA, Lessin S, et al. The risk of nail changes with taxane chemotherapy: a systematic review of the literature and meta-analysis. *Br J Dermatol*. 2015;173(3):842–845. doi:10.1111/bjd.13743
73. DeMarinis M, Hendricks A, Stoltzner G. Nail pigmentation with daunorubicin therapy. *Ann Intern Med*. 1978;89(4):516–517. doi:10.7326/0003-4819-89-4-516
74. Shetty MR. Case of pigmented banding of the nail caused by bleomycin. *Cancer Treat Rep*. 1977;61(3):501–502.
75. Brzezniak C, Szabo E. Images in clinical medicine. Sunitinib-associated hair depigmentation. *N Engl J Med*. 2014;370(17):e27. doi:10.1056/NEJMicm1309906
76. Kwakman JJM, Elshot YS, Punt CJA, Koopman M. Management of cytotoxic chemotherapy-induced hand-foot syndrome. *Oncol Rev*. 2020;14(1):442. doi:10.4081/oncol.2020.442
77. Lipworth AD, Robert C, Zhu AX. Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology*. 2009;77(5):257–271. doi:10.1159/000258880
78. Miller KK, Gorcey L, McLellan BN. Chemotherapy-induced hand-foot syndrome and nail changes: a review of clinical presentation, etiology, pathogenesis, and management. *J Am Acad Dermatol*. 2014;71(4):787–794. doi:10.1016/j.jaad.2014.03.019
79. Ren Z, Zhu K, Kang H, et al. Randomized controlled trial of the prophylactic effect of urea-based cream on sorafenib-associated hand-foot skin reactions in patients with advanced hepatocellular carcinoma. *J Clin Oncol*. 2015;33(8):894–900. doi:10.1200/JCO.2013.52.9651
80. Hofheinz R-D, Gencer D, Schulz H, et al. Mapisal versus urea cream as prophylaxis for capecitabine-associated hand-foot syndrome: a randomized phase III trial of the AIO quality of life working group. *J Clin Oncol*. 2015;33(22):2444–2449. doi:10.1200/JCO.2014.60.4587
81. Lynch TJ, Kim ES, Eaby B, Garey J, West DP, Lacouture ME. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist*. 2007;12(5):610–621. doi:10.1634/theoncologist.12-5-610
82. Perez-Soler R. Rash as a surrogate marker for efficacy of epidermal growth factor receptor inhibitors in lung cancer. *Clin Lung Cancer*. 2006;8(suppl 1):S7–S14. doi:10.3816/clc.2006.s.008

83. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351(4):337–345. doi:10.1056/NEJMoa033025
84. Tan EH, Chan A. Evidence-based treatment options for the management of skin toxicities associated with epidermal growth factor receptor inhibitors. *Ann Pharmacother*. 2009;43(10):1658–1666. doi:10.1345/aph.1M241
85. Lacouture ME, Anadkat MJ, Bensadoun R-J, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. 2011;19(8):1079–1095. doi:10.1007/s00520-011-1197-6
86. Yeo W, Johnson PJ. Radiation-recall skin disorders associated with the use of antineoplastic drugs. Pathogenesis, prevalence, and management. *Am J Clin Dermatol*. 2000;1(2):113–116. doi:10.2165/00128071-200001020-00006
87. Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. *Radiother Oncol*. 2001;59(3):237–245. doi:10.1016/s0167-8140(01)00328-0
88. Kvols LK. Radiation sensitizers: a selective review of molecules targeting DNA and non-DNA targets. *J Nucl Med*. 2005;46(suppl 1):187S–190S.
89. Shin SM, Chouake RJ, Sanfilippo NJ, et al. Feasibility and efficacy of local radiotherapy with concurrent novel agents in patients with multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2014;14(6):480–484. doi:10.1016/j.clml.2014.07.010
90. Katz DA, Abrams RA, Sclamberg JS, Usha L. Radiosensitizing effect of anti-HER2/neu agents: report of 2 cases and review of the literature. *Pract Radiat Oncol*. 2015;5(2):e61–e65. doi:10.1016/j.prro.2014.06.006
91. Alley E, Green R, Schuchter L. Cutaneous toxicities of cancer therapy. *Curr Opin Oncol*. 2002;14(2):212–216. doi:10.1097/00001622-200203000-00012
92. Bolderston A, Lloyd NS, Wong RKS, Holden L, Robb-Blenderman L, Supportive Care Guidelines Group of Cancer Care Ontario Program in Evidence-Based Care. The prevention and management of acute skin reactions related to radiation therapy: a systematic review and practice guideline. *Support Care Cancer*. 2006;14(8):802–817. doi:10.1007/s00520-006-0063-4
93. Kumar S, Juresic E, Barton M, Shafiq J. Management of skin toxicity during radiation therapy: a review of the evidence. *J Med Imaging Radiat Oncol*. 2010;54(3):264–279. doi:10.1111/j.1754-9485.2010.02170.x
94. Doellman D, Hadaway L, Bowe-Geddes LA, et al. Infiltration and extravasation: update on prevention and management. *J Infus Nurs*. 2009;32(4):203–211. doi:10.1097/NAN.0b013e3181aac042
95. Boulanger J, Ducharme A, Dufour A, et al. Management of the extravasation of anti-neoplastic agents. *Support Care Cancer*. 2015;23(5):1459–1471. doi:10.1007/s00520-015-2635-7

96. Mouridsen HT, Langer SW, Buter J, et al. Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. *Ann Oncol*. 2007;18(3):546–550. doi:10.1093/annonc/mdl413
97. Totect (dexrazoxane injection). Package insert. Topo Target USA, Inc.; 2011.
98. Roselló S, Blasco I, García Fabregat L, Cervantes A, Jordan K, ESMO Guidelines Committee. Management of infusion reactions to systemic anticancer therapy: ESMO clinical practice guidelines. *Ann Oncol*. 2017;28(suppl_4):iv100–iv118. doi:10.1093/annonc/mdx216
99. Shepherd GM. Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol*. 2003;24(3):253–262. doi:10.1385/CRIAI:24:3:253
100. Picard M, Galvão VR. Current knowledge and management of hypersensitivity reactions to monoclonal antibodies. *J Allergy Clin Immunol Pract*. 2017;5(3):600–609. doi:10.1016/j.jaip.2016.12.001
101. Robinson JB, Singh D, Bodurka-Bevers DC, Wharton JT, Gershenson DM, Wolf JK. Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. *Gynecol Oncol*. 2001;82(3):550–558. doi:10.1006/gyno.2001.6331
102. Otani IM, Wong J, Banerji A. Platinum chemotherapy hypersensitivity: prevalence and management. *Immunol Allergy Clin North Am*. 2017;37(4):663–677. doi:10.1016/j.iac.2017.06.003
103. Hong DI, Bankova L, Cahill KN, Kyin T, Castells MC. Allergy to monoclonal antibodies: cutting-edge desensitization methods for cutting-edge therapies. *Expert Rev Clin Immunol*. 2012;8(1):43–52; quiz 53–54. doi:10.1586/eci.11.75
104. Lenz H-J. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist*. 2007;12(5):601–609. doi:10.1634/theoncologist.12-5-601
105. Darzalex Faspro. Package insert. Janssen Biotech, Inc.; 2020. Accessed September 28, 2020. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf
106. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23(31):7794–7803. doi:10.1200/JCO.2005.04.937
107. Abraxane. Package insert. Celgene Corporation; 2020. Accessed September 29, 2020. https://packageinserts.bms.com/pi/pi_abraxane.pdf
108. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer*. 2018;6(1):56. doi:10.1186/s40425-018-0343-9
109. Kymriah. Package insert. Novartis Pharmaceuticals Corporation; 2018. Accessed September 21, 2020. https://www.novartis.us/sites/www.novartis.us/files/kymriah.pdf

110. Yescarta. Package insert. Kite Pharma, Inc.; 2020. Accessed September 21, 2020. https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf
111. Tecartus. Package insert. Kite Pharma, Inc.; 2020. Accessed September 21, 2020. https://www.gilead.com/-/media/files/pdfs/medicines/oncology/tecartus/tecartus-pi.pdf
112. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15(1):47–62. doi:10.1038/nrclinonc.2017.148
113. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv119–iv142. doi:10.1093/annonc/mdx225
114. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714–1768. doi:10.1200/JCO.2017.77.6385
115. Reddick WE, Glass JO, Helton KJ, et al. Prevalence of leukoencephalopathy in children treated for acute lymphoblastic leukemia with high-dose methotrexate. *Am J Neuroradiol*. 2005;26(5):1263–1269.
116. Dufourg MN, Landman-Parker J, Auclerc MF, et al. Age and high-dose methotrexate are associated to clinical acute encephalopathy in FRALLE 93 trial for acute lymphoblastic leukemia in children. *Leukemia*. 2007;21(2):238–247. doi:10.1038/sj.leu.2404495
117. Kwong Y-L, Yeung DYM, Chan JCW. Intrathecal chemotherapy for hematologic malignancies: drugs and toxicities. *Ann Hematol*. 2008;88(3):193. doi:10.1007/s00277-008-0645-y
118. Yamanaka K, Okata T, Sambongi Y, et al. Subacute methotrexate encephalopathy mimicking ischemic stroke with dynamic changes on magnetic resonance imaging. *J Stroke Cerebrovasc Dis*. 2018;27(11):e233-e235. doi:10.1016/j.jstrokecerebrovasdis.2018.06.007
119. Watanabe K, Arakawa Y, Oguma E, et al. Characteristics of methotrexate-induced stroke-like neurotoxicity. *Int J Hematol*. 2018;108(6):630–636. doi:10.1007/s12185-018-2525-0
120. Richards A, Marshall H, McQuary A. Evaluation of methylene blue, thiamine, and/or albumin in the prevention of ifosfamide-related neurotoxicity. *J Oncol Pharm Pract*. 2011;17(4):372–380. doi:10.1177/1078155210385159
121. Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prové A, Vermorken JB. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer*. 2000;82(2):291–294. doi:10.1054/bjoc.1999.0917

122. Gharaibeh EZ, Telfah M, Powers BC, Salacz ME. Hydration, methylene blue, and thiamine as a prevention regimen for ifosfamide-induced encephalopathy. *J Oncol Pharm Pract*. 2019;25(7):1784–1786. doi:10.1177/1078155218808361
123. Smith GA, Damon LE, Rugo HS, Ries CA, Linker CA. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. *J Clin Oncol*. 1997;15(2):833–839. doi:10.1200/JCO.1997.15.2.833
124. Rubin EH, Andersen JW, Berg DT, Schiffer CA, Mayer RJ, Stone RM. Risk factors for high-dose cytarabine neurotoxicity: an analysis of a cancer and leukemia group B trial in patients with acute myeloid leukemia. *J Clin Oncol*. 1992;10(6):948–953. doi:10.1200/JCO.1992.10.6.948
125. Lindner LH, Ostermann H, Hiddemann W, et al. AraU accumulation in patients with renal insufficiency as a potential mechanism for cytarabine neurotoxicity. *Int J Hematol*. 2008;88(4):381–386. doi:10.1007/s12185-008-0171-7
126. Chamberlain MC. Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyt) administered for the treatment of leptomeningeal metastases: a retrospective case series. *J Neurooncol*. 2012;109(1):143–148. doi:10.1007/s11060-012-0880-x
127. Gállego Pérez-Larraya J, Palma JA, Carmona-Iragui M, et al. Neurologic complications of intrathecal liposomal cytarabine administered prophylactically to patients with non-Hodgkin lymphoma. *J Neurooncol*. 2011;103(3):603–609. doi:10.1007/s11060-010-0428-x
128. Newton HB. Neurological complications of chemotherapy to the central nervous system. *Handb Clin Neurol*. 2012;105:903–916. doi:10.1016/B978-0-444-53502-3.00031-8
129. Chun HG, Leyland-Jones BR, Caryk SM, Hoth DF. Central nervous system toxicity of fludarabine phosphate. *Cancer Treat Rep*. 1986;70(10):1225–1228.
130. Warrell RP, Berman E. Phase I and II study of fludarabine phosphate in leukemia: therapeutic efficacy with delayed central nervous system toxicity. *J Clin Oncol*. 1986;4(1):74–79. doi:10.1200/JCO.1986.4.1.74
131. Lee MS, McKinney AM, Brace JR, SantaCruz K. Clinical and imaging features of fludarabine neurotoxicity. *J Neuroophthalmol*. 2010;30(1):37–41. doi:10.1097/WNO.0b013e3181ce8087
132. Merkel DE, Griffin NL, Kagan-Hallet K, Von Hoff DD. Central nervous system toxicity with fludarabine. *Cancer Treat Rep*. 1986;70(12):1449–1450.
133. DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood*. 2007;109(12):5136–5142. doi:10.1182/blood-2006-11-056754

134. Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J Clin Oncol*. 2005;23(15):3376–3382. doi:10.1200/JCO.2005.03.426
135. Ngo D, Patel S, Kim EJ, Brar R, Koontz MZ. Nelarabine neurotoxicity with concurrent intrathecal chemotherapy: case report and review of literature. *J Oncol Pharm Pract*. 2015;21(4):296–300. doi:10.1177/1078155214528018
136. Arranon. Package insert. Novartis Pharmaceuticals Corporation; 2019. Accessed September 29, 2020. https://www.novartis.us/sites/www.novartis.us/files/arranon.pdf
137. Pirzada NA, Ali II, Dafer RM. Fluorouracil-induced neurotoxicity. *Ann Pharmacother*. 2000;34(1):35–38. doi:10.1345/aph.18425
138. Lyros E, Walter S, Keller I, Papanagiotou P, Fassbender K. Subacute reversible toxic encephalopathy related to treatment with capecitabine: a case report with literature review and discussion of pathophysiology. *Neurotoxicology*. 2014;42:8–11. doi:10.1016/j.neuro.2014.02.010
139. Truman N, Nethercott D. Posterior reversible encephalopathy syndrome (PRES) after treatment with oxaliplatin and 5-fluorouracil. *Clin Colorectal Cancer*. 2013;12(1):70–72. doi:10.1016/j.clcc.2012.06.003
140. Loganayagam A, Arenas-Hernandez M, Fairbanks L, Ross P, Sanderson JD, Marinaki AM. The contribution of deleterious DPYD gene sequence variants to fluoropyrimidine toxicity in British cancer patients. *Cancer Chemother Pharmacol*. 2009;65(2):403. doi:10.1007/s00280-009-1147-x
141. Kim S-R, Park C-H, Park S, Park J-O, Lee J, Lee S-Y. Genetic polymorphisms associated with 5-fluorouracil-induced neurotoxicity. *Chemotherapy*. 2010;56(4):313–317. doi:10.1159/000320032
142. Ma WW, Saif MW, El-Rayes BF, et al. Emergency use of uridine triacetate for the prevention and treatment of life-threatening 5-fluorouracil and capecitabine toxicity. *Cancer*. 2017;123(2):345–356. doi:10.1002/cncr.30321
143. Raetz EA, Salzer WL. Tolerability and efficacy of L-asparaginase therapy in pediatric patients with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2010;32(7):554–563. doi:10.1097/MPH.0b013e3181e6f003
144. Hijiya N, van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. *Leuk Lymphoma*. 2016;57(4):748–757. doi:10.3109/10428194.2015.1101098
145. Magge RS, DeAngelis LM. The double-edged sword: neurotoxicity of chemotherapy. *Blood Rev*. 2015;29(2):93–100. doi:10.1016/j.blre.2014.09.012
146. Ramchandren S, Leonard M, Mody RJ, et al. Peripheral neuropathy in survivors of childhood acute lymphoblastic leukemia. *J Peripher Nerv Syst*. 2009;14(3):184–189. doi:10.1111/j.1529-8027.2009.00230.x
147. Kanbayashi Y, Hosokawa T, Okamoto K, et al. Statistical identification of predictors for peripheral neuropathy associated with administration of

bortezomib, taxanes, oxaliplatin or vincristine using ordered logistic regression analysis. *Anticancer Drugs*. 2010;21(9):877–881. doi:10.1097/CAD.0b013e32833db89d

148. Kanbayashi Y, Hosokawa T, Kitawaki J, Taguchi T. Statistical identification of predictors for paclitaxel-induced peripheral neuropathy in patients with breast or gynaecological cancer. *Anticancer Res*. 2013;33(3):1153–1156.
149. Park SB, Goldstein D, Krishnan AV, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. *CA Cancer J Clin*. 2013;63(6):419–437. doi:10.3322/caac.21204
150. Piccolo J, Kolesar JM. Prevention and treatment of chemotherapy-induced peripheral neuropathy. *Am J Health Syst Pharm*. 2014;71(1):19–25. doi:10.2146/ajhp130126
151. Smith EML, Pang H, Cirrincione C, et al. CALGB 170601: a phase III double blind trial of duloxetine to treat painful chemotherapy-induced peripheral neuropathy (CIPN). *J Clin Oncol*. 2012;30(18_suppl):CRA9013. doi:10.1200/jco.2012.30.18_suppl.cra9013
152. Pachman DR, Watson JC, Loprinzi CL. Therapeutic strategies for cancer treatment related peripheral neuropathies. *Curr Treat Options Oncol*. 2014;15(4):567–580. doi:10.1007/s11864-014-0303-7
153. Pachman DR, Watson JC, Lustberg MB, et al. Management options for established chemotherapy-induced peripheral neuropathy. *Support Care Cancer*. 2014;22(8):2281–2295. doi:10.1007/s00520-014-2289-x
154. Te Loo DM, van Schie RM, Hoogerbrugge PM. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2009;27(15_suppl):10049. doi:10.1200/jco.2009.27.15_suppl.10049
155. Sandler SG, Tobin W, Henderson ES. Vincristine-induced neuropathy. A clinical study of fifty leukemic patients. *Neurology*. 1969;19(4):367–374. doi:10.1212/wnl.19.4.367
156. Albert DM, Wong VG, Henderson ES. Ocular complications of vincristine therapy. *Arch Ophthalmol*. 1967;78(6):709–713. doi:10.1001/archopht.1967.00980030711004
157. Holland JF, Scharlau C, Gailani S, et al. Vincristine treatment of advanced cancer: a cooperative study of 392 cases. *Cancer Res*. 1973;33(6):1258–1264.
158. McCarthy GM, Skillings JR. Jaw and other orofacial pain in patients receiving vincristine for the treatment of cancer. *Oral Surg Oral Med Oral Pathol*. 1992;74(3):299–304. doi:10.1016/0030-4220(92)90063-v
159. Langer T, am Zehnhoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. *Trends Pharmacol Sci*. 2013;34(8):458–469. doi:10.1016/j.tips.2013.05.006
160. Peleva E, Emami N, Alzahrani M, et al. Incidence of platinum-induced ototoxicity in pediatric patients in Quebec. *Pediatr Blood Cancer*.

2014;61(11):2012–2017. doi:10.1002/pbc.25123
161. Kidera Y, Kawakami H, Sakiyama T, et al. Risk factors for cisplatin-induced nephrotoxicity and potential of magnesium supplementation for renal protection. *PLoS One*. 2014;9(7):e101902. doi:10.1371/journal.pone.0101902
162. Bokemeyer C, Berger C, Hartmann J, et al. Analysis of risk factors for cisplatin-induced ototoxicity. *Br J Cancer*. 1998:77(8):1355–1362.
163. Citak EC, Oguz A, Karadeniz C, et al. Vincristine-induced peripheral neuropathy and urinary bladder paralysis in a child with rhabdomyosarcoma. *J Pediatr Hematol Oncol*. 2008;30(1):61–62. doi:10.1097/MPH.0b013e318158343b
164. Carmichael SM, Eagleton L, Ayers CR, Mohler D. Orthostatic hypotension during vincristine therapy. *Arch Intern Med*. 1970;126(2):290–293.
165. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. *Heart*. 2018;104(12):971–977. doi:10.1136/heartjnl-2017-312103
166. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. *J Am Heart Assoc*. 2014;3(2):e000665. doi:10.1161/JAHA.113.000665
167. Simuºnek T, Stérba M, Popelová O, Adamcová M, Hrdina R, Gersl V. Anthracycline-induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron. *Pharmacol Rep PR*. 2009;61(1):154–171. doi:10.1016/s1734-1140(09)70018-0
168. Truong J, Yan AT, Cramarossa G, Chan KKW. Chemotherapy-induced cardiotoxicity: detection, prevention, and management. *Can J Cardiol*. 2014;30(8):869–878. doi:10.1016/j.cjca.2014.04.029
169. Conway A, McCarthy AL, Lawrence P, Clark RA. The prevention, detection and management of cancer treatment-induced cardiotoxicity: a meta-review. *BMC Cancer*. 2015;15:366. doi:10.1186/s12885-015-1407-6
170. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2017;35(8):893–911. doi:10.1200/JCO.2016.70.5400
171. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. 1979;91(5):710–717. doi:10.7326/0003-4819-91-5-710
172. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. *Cancer*. 2003;97(11):2869–2879. doi:10.1002/cncr.11407
173. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the childhood cancer survivor study cohort. *BMJ*. 2009;339:b4606. doi:10.1136/bmj.b4606

174. Steinberg JS, Wasserman AG. Radionuclide ventriculography for evaluation and prevention of doxorubicin cardiotoxicity. *Clin Ther*. 1985;7(6):660–667.
175. Von Hoff DD, Rozencweig M, Layard M, Slavik M, Muggia FM. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. *Am J Med*. 1977;62(2):200–208. doi:10.1016/0002-9343(77)90315-1
176. Tan CT, Hancock C, Steinherz P, et al. Phase I and clinical pharmacological study of 4-demethoxydaunorubicin (idarubicin) in children with advanced cancer. *Cancer Res*. 1987;47(11):2990–2995.
177. Villani F, Galimberti M, Comazzi R, Crippa F. Evaluation of cardiac toxicity of idarubicin (4-demethoxydaunorubicin). *Eur J Cancer Clin Oncol*. 1989;25(1):13–18. doi:10.1016/0277-5379(89)90045-x
178. Feig SA, Krailo MD, Harris RE, et al. Determination of the maximum tolerated dose of idarubicin when used in a combination chemotherapy program of reinduction of childhood ALL at first marrow relapse and a preliminary assessment of toxicity compared to that of daunorubicin: a report from the Childrens Cancer Study Group. *Med Pediatr Oncol*. 1992;20(2):124–129. doi:10.1002/mpo.2950200207
179. Vulsteke C, Pfeil AM, Maggen C, et al. Clinical and genetic risk factors for epirubicin-induced cardiac toxicity in early breast cancer patients. *Breast Cancer Res Treat*. 2015;152(1):67–76. doi:10.1007/s10549-015-3437-9
180. Synold TW, Doroshow JH. Anthracycline dose intensity: clinical pharmacology and pharmacokinetics of high-dose doxorubicin administered as a 96-hour continuous intravenous infusion. *J Infus Chemother*. 1996;6(2):69–73.
181. Weiss AJ, Metter GE, Fletcher WS, Wilson WL, Grage TB, Ramirez G. Studies on adriamycin using a weekly regimen demonstrating its clinical effectiveness and lack of cardiac toxicity. *Cancer Treat Rep*. 1976;60(7):813–822.
182. Torti FM, Bristow MR, Howes AE, et al. Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule. Assessment by endomyocardial biopsy. *Ann Intern Med*. 1983;99(6):745–749. doi:10.7326/0003-4819-99-6-745
183. Lum BL, Svec JM, Torti FM. Doxorubicin: alteration of dose scheduling as a means of reducing cardiotoxicity. *Drug Intell Clin Pharm*. 1985;19(4):259–264. doi:10.1177/106002808501900403
184. Valdivieso M, Burgess MA, Ewer MS, et al. Increased therapeutic index of weekly doxorubicin in the therapy of non-small cell lung cancer: a prospective, randomized study. *J Clin Oncol*. 1984;2(3):207–214. doi:10.1200/JCO.1984.2.3.207
185. van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev*. 2011;2011(6). doi:10.1002/14651858.CD003917.pub4
186. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of

randomised controlled trials. *BMC Cancer*. 2010;10:337. doi:10.1186/1471-2407-10-337

187. Volkova M, Russell R III. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. *Curr Cardiol Rev*. 2011;7(4):214–220. doi:10.2174/157340311799960645
188. Sieswerda E, van Dalen EC, Postma A, Cheuk DK, Caron HN, Kremer LC. Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer. *Cochrane Database Syst Rev*. 2011;(9):CD008011. doi:10.1002/14651858.CD008011.pub2
189. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. *J Clin Oncol*. 2004;22(5):820–828. doi:10.1200/JCO.2004.06.022
190. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*. 2010;55(3):213–220. doi:10.1016/j.jacc.2009.03.095
191. Menna P, Recalcati S, Cairo G, Minotti G. An introduction to the metabolic determinants of anthracycline cardiotoxicity. *Cardiovasc Toxicol*. 2007;7(2):80–85. doi:10.1007/s12012-007-0011-7
192. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783–792. doi:10.1056/NEJM200103153441101
193. Viani GA, Afonso SL, Stefano EJ, De Fendi LI, Soares FV. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. *BMC Cancer*. 2007;7:153. doi:10.1186/1471-2407-7-153
194. Lemmens K, Doggen K, De Keulenaer Gilles W. Role of neuregulin-1/ErbB signaling in cardiovascular physiology and disease. *Circulation*. 2007;116(8):954–960. doi:10.1161/CIRCULATIONAHA.107.690487
195. Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc*. 2008;83(6):679–686. doi:10.4065/83.6.679
196. Atallah E, Durand J-B, Kantarjian H, Cortes J. Congestive heart failure is a rare event in patients receiving imatinib therapy. *Blood*. 2007;110(4):1233–1237. doi:10.1182/blood-2007-01-070144
197. Kerkelä R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med*. 2006;12(8):908–916. doi:10.1038/nm1446
198. Sprycel. Package insert. Bristol-Myers Squibb Company; 2018. Accessed September 29, 2020. https://packageinserts.bms.com/pi/pi_sprycel.pdf
199. Iclusig. Package insert. ARIAD Pharmaceuticals Inc.; 2020. Accessed September 21, 2020. https://www.iclusig.com/pdf/ICLUSIG-Prescribing-

Information.pdf
200. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2008;26(32):5204–5212. doi:10.1200/JCO.2007.15.6331
201. Jarkowski A, Glode AE, Spangenthal EJ, Wong MKK. Heart failure caused by molecularly targeted therapies for cancer. *Pharmacotherapy*. 2011;31(1):62–75. doi:10.1592/phco.31.1.62
202. Wortman JE, Lucas VS, Schuster E, Thiele D, Logue GL. Sudden death during doxorubicin administration. *Cancer*. 1979;44(5):1588–1591. doi:10.1002/1097-0142(197911)44:5<1588::aid-cncr2820440508>3.0.co;2-x
203. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of taxol. *J Clin Oncol*. 1991;9(9):1704–1712. doi:10.1200/JCO.1991.9.9.1704
204. Tasigna. Package insert. Novartis Pharmaceuticals Corporation; 2019. Accessed September 29, 2020. https://www.novartis.us/sites/www.novartis.us/files/tasigna.pdf?printmode=true
205. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica*. 2018;103(5):874–879. doi:10.3324/haematol.2017.182907
206. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib versus ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038–2050. doi:10.1182/blood.2020006844
207. Economopoulou P, Kotsakis A, Kapiris I, Kentepozidis N. Cancer therapy and cardiovascular risk: focus on bevacizumab. *Cancer Manag Res*. 2015;7:133–143. doi:10.2147/CMAR.S77400
208. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst*. 2010;102(9):596–604. doi:10.1093/jnci/djq091
209. Caletti S, Paini A, Coschignano MA, et al. Management of VEGF-targeted therapy-induced hypertension. *Curr Hypertens Rep*. 2018;20(8):68. doi:10.1007/s11906-018-0871-1
210. Polk A, Vistisen K, Vaage-Nilsen M, Nielsen DL. A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity. *BMC Pharmacol Toxicol*. 2014;15:47. doi:10.1186/2050-6511-15-47
211. Izzedine H, Ederhy S, Goldwasser F, et al. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol*. 2009;20(5):807–815. doi:10.1093/annonc/mdn713
212. Chan O, Talati C, Isenalumhe L, et al. Side-effects profile and outcomes of ponatinib in the treatment of chronic myeloid leukemia. *Blood Adv*. 2020;4(3):530–538. doi:10.1182/bloodadvances.2019000268

213. Mohanty BD, Mohanty S, Hussain Y, et al. Management of ischemic coronary disease in patients receiving chemotherapy: an uncharted clinical challenge. *Future Cardiol*. 2017;13(3):247–257. doi:10.2217/fca-2017-0002
214. Motwani SS, McMahon GM, Humphreys BD, Partridge AH, Waikar SS, Curhan GC. Development and validation of a risk prediction model for acute kidney injury after the first course of cisplatin. *J Clin Oncol*. 2018;36(7):682–688. doi:10.1200/JCO.2017.75.7161
215. Hu S, Leblanc AF, Gibson AA, et al. Identification of OAT1/OAT3 as contributors to cisplatin toxicity. *Clin Transl Sci*. 2017;10(5):412–420. doi:10.1111/cts.12480
216. Shirali AC, Perazella MA. Tubulointerstitial injury associated with chemotherapeutic agents. *Adv Chronic Kidney Dis*. 2014;21(1):56–63. doi:10.1053/j.ackd.2013.06.010
217. Launay-Vacher V, Rey J-B, Isnard-Bagnis C, Deray G, Daouphars M, European Society of Clinical Pharmacy Special Interest Group on Cancer Care. Prevention of cisplatin nephrotoxicity: state of the art and recommendations from the European Society of Clinical Pharmacy special interest group on cancer care. *Cancer Chemother Pharmacol*. 2008;61(6):903–909. doi:10.1007/s00280-008-0711-0
218. Latcha S, Jaimes EA, Patil S, Glezerman IG, Mehta S, Flombaum CD. Long–term renal outcomes after cisplatin treatment. *Clin J Am Soc Nephrol*. 2016;11(7):1173–1179. doi:10.2215/CJN.08070715
219. Perazella MA. Onco-nephrology: renal toxicities of chemotherapeutic agents. *Clin J Am Soc Nephrol*. 2012;7(10):1713–1721. doi:10.2215/CJN.02780312
220. Morgan KP, Buie LW, Savage SW. The role of mannitol as a nephroprotectant in patients receiving cisplatin therapy. *Ann Pharmacother*. 2012;46(2):276–281. doi:10.1345/aph.1Q333
221. Willox JC, McAllister EJ, Sangster G, Kaye SB. Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial. *Br J Cancer*. 1986;54(1):19–23. doi:10.1038/bjc.1986.147
222. Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treat Rev*. 1995;21(1):33–64. doi:10.1016/0305-7372(95)90010-1
223. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol*. 1989;7(11):1748–1756. doi:10.1200/JCO.1989.7.11.1748
224. Izzedine H. Anti-VEGF cancer therapy in nephrology practice. *Int J Nephrol*. 2014;2014:143426. doi:10.1155/2014/143426
225. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014;383(9911):31–39. doi:10.1016/S0140-6736(13)61719-5

226. Rixe O, Bukowski RM, Michaelson MD, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. *Lancet Oncol*. 2007;8(11):975–984. doi:10.1016/S1470-2045(07)70285-1
227. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis*. 2007;49(2):186–193. doi:10.1053/j.ajkd.2006.11.039
228. Avastin. Package insert. Genentech, Inc.; 2020. Accessed September 29, 2020. https://www.gene.com/download/pdf/avastin_prescribing.pdf
229. Howard SC, McCormick J, Pui C-H, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. *Oncologist*. 2016;21(12):1471–1482. doi:10.1634/theoncologist.2015-0164
230. Fermiano M, Bergsbaken J, Kolesar JM. Glucarpidase for the management of elevated methotrexate levels in patients with impaired renal function. *Am J Health Syst Pharm*. 2014;71(10):793–798. doi:10.2146/ajhp130483
231. Manikandan R, Kumar S, Dorairajan LN. Hemorrhagic cystitis: a challenge to the urologist. *Indian J Urol*. 2010;26(2):159–166. doi:10.4103/0970-1591.65380
232. Lawson M, Vasilaras A, De Vries A, Mactaggart P, Nicol D. Urological implications of cyclophosphamide and ifosfamide. *Scand J Urol Nephrol*. 2008;42(4):309–317. doi:10.1080/00365590701570953
233. Goren MP, Anthony LB, Hande KR, et al. Pharmacokinetics of an intravenous-oral versus intravenous-mesna regimen in lung cancer patients receiving ifosfamide. *J Clin Oncol*. 1998;16(2):616–621. doi:10.1200/JCO.1998.16.2.616
234. Mukhtar S, Woodhouse C. The management of cyclophosphamide-induced haematuria. *BJU Int*. 2010;105(7):908–912. doi:10.1111/j.1464-410X.2009.09132.x
235. Sadowska AM, Specenier P, Germonpre P, Peeters M. Antineoplastic therapy-induced pulmonary toxicity. *Expert Rev Anticancer Ther*. 2013;13(8):997–1006. doi:10.1586/14737140.2013.817684
236. Vahid B, Marik PE. Infiltrative lung diseases: complications of novel antineoplastic agents in patients with hematological malignancies. *Can Respir J*. 2008;15(4):211–216. doi:10.1155/2008/305234
237. Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. *Chest*. 2008;133(2):528–538. doi:10.1378/chest.07-0851
238. Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol*. 2003;21(16):3127–3132. doi:10.1200/JCO.2003.02.122
239. Durant JR, Norgard MJ, Murad TM, Bartolucci AA, Langford KH. Pulmonary toxicity associated with bischloroethylnitrosourea (BCNU). *Ann Intern Med*. 1979;90(2):191–194. doi:10.7326/0003-4819-90-2-191

240. Sleijfer S. Bleomycin-induced pneumonitis. *Chest*. 2001;120(2):617–624. doi:10.1378/chest.120.2.617
241. Haupt HM, Hutchins GM, Moore GW. Ara-C lung: noncardiogenic pulmonary edema complicating cytosine arabinoside therapy of leukemia. *Am J Med*. 1981;70(2):256–261. doi:10.1016/0002-9343(81)90759-2
242. Gupta N, Ahmed I, Steinberg H, Patel D, Nissel-Horowitz S, Mehrotra B. Gemcitabine-induced pulmonary toxicity: case report and review of the literature. *Am J Clin Oncol*. 2002;25(1):96–100. doi:10.1097/00000421-200202000-00021
243. Wall MA, Wohl ME, Jaffe N, Strieder DJ. Lung function in adolescents receiving high-dose methotrexate. *Pediatrics*. 1979;63(5):741–746.
244. Azambuja E, Fleck JF, Batista RG, Menna Barreto SS. Bleomycin lung toxicity: who are the patients with increased risk? *Pulm Pharmacol Ther*. 2005;18(5):363–366. doi:10.1016/j.pupt.2005.01.007
245. Ragheb AM, Sabanegh ES. Male fertility-implications of anticancer treatment and strategies to mitigate gonadotoxicity. *Anticancer Agents Med Chem*. 2010;10(1):92–102. doi:10.2174/1871520611009010092
246. Li L, Mok H, Jhaveri P, et al. Anticancer therapy and lung injury: molecular mechanisms. *Expert Rev Anticancer Ther*. 2018;18(10):1041–1057. doi:10.1080/14737140.2018.1500180
247. Barber NA, Ganti AK. Pulmonary toxicities from targeted therapies: a review. *Target Oncol*. 2011;6(4):235–243. doi:10.1007/s11523-011-0199-0
248. Thatishetty AV, Agresti N, O'Brien CB. Chemotherapy-induced hepatotoxicity. *Clin Liver Dis*. 2013;17(4):671–686, ix–x. doi:10.1016/j.cld.2013.07.010
249. Bahirwani R, Reddy KR. Drug-induced liver injury due to cancer chemotherapeutic agents. *Semin Liver Dis*. 2014;34(2):162–171. doi:10.1055/s-0034-1375957
250. Pratt CB, Johnson WW. Duration and severity of fatty metamorphosis of the liver following L-asparaginase therapy. *Cancer*. 1971;28(2):361–364. doi:10.1002/1097-0142(197108)28:2<361::aid-cncr2820280215>3.0.co;2-3
251. Dix SP, Wingard JR, Mullins RE, et al. Association of busulfan area under the curve with veno-occlusive disease following BMT. *Bone Marrow Transplant*. 1996;17(2):225–230.
252. Ayash LJ, Hunt M, Antman K, et al. Hepatic venoocclusive disease in autologous bone marrow transplantation of solid tumors and lymphomas. *J Clin Oncol*. 1990;8(10):1699–1706. doi:10.1200/JCO.1990.8.10.1699
253. Jeha S, Gandhi V, Chan KW, et al. Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. *Blood*. 2004;103(3):784–789. doi:10.1182/blood-2003-06-2122
254. Slavin RE, Dias MA, Saral R. Cytosine arabinoside induced gastrointestinal toxic alterations in sequential chemotherapeutic protocols: a clinical-pathologic study of 33 patients. *Cancer*. 1978;42(4):1747–1759. doi:10.1002/1097-0142(197810)42:4<1747::aid-cncr2820420413>3.0.co;2-t

255. Johnson DH, Greco FA, Wolff SN. Etoposide-induced hepatic injury: a potential complication of high-dose therapy. *Cancer Treat Rep*. 1983;67(11):1023–1024.
256. Kikuchi S, Muroi K, Takahashi S, et al. Severe hepatitis and complete molecular response caused by imatinib mesylate: possible association of its serum concentration with clinical outcomes. *Leuk Lymphoma*. 2004;45(11):2349–2351. doi:10.1080/10428190412331272721
257. Einhorn M, Davidsohn I. Hepatotoxicity of mercaptopurine. *JAMA*. 1964;188:802–806. doi:10.1001/jama.1964.03060350028007
258. Bergner N, Monsef I, Illerhaus G, Engert A, Skoetz N. Role of chemotherapy additional to high-dose methotrexate for primary central nervous system lymphoma (PCNSL). *Cochrane Database Syst Rev*. 2012;11:CD009355. doi:10.1002/14651858.CD009355.pub2
259. Weiss RB. Streptozocin: a review of its pharmacology, efficacy, and toxicity. *Cancer Treat Rep*. 1982;66(3):427–438.
260. Nordstrom BL, Fraeman KH, Luo W, Shantakumar S, Landis SH. Liver function test abnormalities in patients treated with small molecule tyrosine kinase inhibitors. Presented at: International Society for Pharmacoepidemiology Annual Meeting; Brighton, UK; August 19–22, 2010. https://doi.org/10.1002/pds.2019
261. Grigorian A, O'Brien CB. Hepatotoxicity secondary to chemotherapy. *J Clin Transl Hepatol*. 2014;2(2):95. doi:10.14218/JCTH.2014.00011
262. Churpek JE, Larson RA. The evolving challenge of therapy-related myeloid neoplasms. *Best Pract Res Clin Haematol*. 2013;26(4):309–317. doi:10.1016/j.beha.2013.09.001
263. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. *Nat Rev Cancer*. 2017;17(9):513–527. doi:10.1038/nrc.2017.60
264. Gillis NK, Ball M, Zhang Q, et al. Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: a proof-of-concept, case-control study. *Lancet Oncol*. 2017;18(1):112–121. doi:10.1016/S1470-2045(16)30627-1
265. Faurschou M, Sorensen IJ, Mellemkjaer L, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol*. 2008;35(1):100–105.
266. Guérin S, Guibout C, Shamsaldin A, et al. Concomitant chemo-radiotherapy and local dose of radiation as risk factors for second malignant neoplasms after solid cancer in childhood: a case-control study. *Int J Cancer*. 2007;120(1):96–102. doi:10.1002/ijc.22197
267. Wolff AC, Blackford AL, Visvanathan K, et al. Risk of marrow neoplasms after adjuvant breast cancer therapy: the National Comprehensive Cancer Network experience. *J Clin Oncol*. 2014;33(4):340–348. doi:10.1200/JCO.2013.54.6119

268. Wong TN, Ramsingh G, Young AL, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. *Nature*. 2015;518(7540):552–555. doi:10.1038/nature13968
269. Guru Murthy GS, Hamadani M, Dhakal B, Hari P, Atallah E. Incidence and survival of therapy related myeloid neoplasm in United States. *Leuk Res*. 2018;71:95–99. doi:10.1016/j.leukres.2018.07.013
270. Dittrich R, Maltaris T, Hoffmann I, Oppelt PG, Beckmann MW, Mueller A. Fertility preservation in cancer patients. *Minerva Ginecol*. 2010;62(1):63–80.
271. Knight S, Lorenzo A, Maloney AM, et al. An approach to fertility preservation in prepubertal and postpubertal females: a critical review of current literature. *Pediatr Blood Cancer*. 2015;62(6):935–939. doi:10.1002/pbc.25440
272. Levine JM, Kelvin JF, Quinn GP, Gracia CR. Infertility in reproductive-age female cancer survivors. *Cancer*. 2015;121(10):1532–1539. doi:10.1002/cncr.29181
273. Patounakis G, Christy AY, DeCherney AH. Gonadal dysfunction. In: DeVita VT, Rosenberg SA, Lawrence TS, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* 11th ed. Lippincott Williams & Wilkins; 2018:2133–2148.
274. Perry MC, ed. *Perry's the Chemotherapy Source Book*. 5th ed. Lippincott Williams &Wilkins; 2012.
275. Melo AS de, Paula CTV de, Rufato MAF, et al. Fertility optimization in women with cancer: from preservation to contraception. *JBRA Assist Reprod*. 2019;23(4):418–429. doi:10.5935/1518-0557.20190011
276. Tepper NK. Update to U.S. Medical Eligibility Criteria for Contraceptive Use, 2016: updated recommendations for the use of contraception among women at high risk for HIV infection. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):405–410. doi:10.15585/mmwr.mm6914a3
277. World Health Organization. *Medical Eligibility Criteria for Contraceptive Use* [Internet]. 5th ed. World Health Organization; 2015. https://www.who.int/reproductivehealth/publications/family_planning/Ex-Summ-MEC-5/en/
278. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36(19):1994–2001. doi:10.1200/JCO.2018.78.1914
279. Miller DG. Alkylating agents and human spermatogenesis. *JAMA*. 1971;217(12):1662–1665. doi:10.1001/jama.217.12.1662
280. Cheviakoff S, Calamera JC, Morgenfeld M, Mancini RE. Recovery of spermatogenesis in patients with lymphoma after treatment with chlorambucil. *J Reprod Fertil*. 1973;33(1):155–157. doi:10.1530/jrf.0.0330155
281. Fairley KF, Barrie JU, Johnson W. Sterility and testicular atrophy related to cyclophosphamide therapy. *Lancet*. 1972;1(7750):568–569. doi:10.1016/s0140-6736(72)90358-3

282. Buchanan JD, Fairley KF, Barrie JU. Return of spermatogenesis after stopping cyclophosphamide therapy. *Lancet*. 1975;2(7926):156–157. doi:10.1016/s0140-6736(75)90059-8
283. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD. *Eur J Cancer Clin Oncol*. 1985;21(5):601–605. doi:10.1016/0277-5379(85)90088-4
284. Levine J, Canada A, Stern CJ. Fertility preservation in adolescents and young adults with cancer. *J Clin Oncol*. 2010;28(32):4831–4841. doi:10.1200/JCO.2009.22.8312
285. Green DM, Liu W, Kutteh WH, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude lifetime cohort study. *Lancet Oncol*. 2014;15(11):1215–1223. doi:10.1016/S1470-2045(14)70408-5
286. Taksey J, Bissada NK, Chaudhary UB. Fertility after chemotherapy for testicular cancer. *Arch Androl*. 2003;49(5):389–395. doi:10.1080/01485010390219917
287. Brydøy M, Fosså SD, Klepp O, et al. Paternity and testicular function among testicular cancer survivors treated with two to four cycles of cisplatin-based chemotherapy. *Eur Urol*. 2010;58(1):134–140. doi:10.1016/j.eururo.2010.03.041

95

Pediatric Malignancies

M. Brooke Bernhardt and Nicole A. Kaiser

CORE PRINCIPLES		CHAPTER CASES
1	When monitoring therapy in children, it is important to remember the age-related differences in measured parameters for vital signs, developmental changes, and variability in expected values from infancy to adulthood. Blood pressures are lower and heart rates and respirations are higher in younger children. Intake and output need to be considered in relationship to the patient's size. Calculations for estimations of glomerular filtration rate are different than those used in adults.	**Case 95-1 (Questions 3, 4)**

CORE PRINCIPLES		CHAPTER CASES
2	Infants have larger body surface area–weight ratios than older children. Further, organ function changes rapidly during the first year of life. Therefore, chemotherapy dosing guidelines in protocols generally specify how to calculate doses for smaller children and infants (ie, converting to mg/kg dosing from mg/m^2, or halving doses).	**Case 95-2 (Question 2)**
3	Leucovorin, when used with methotrexate, reduces methotrexate-related toxicities to rapidly proliferating cells. In treating children with high-dose methotrexate and leucovorin rescue, serum methotrexate concentrations are measured so that leucovorin will be discontinued at the correct time. Renal dysfunction, fluid accumulation in the patient, or drug interactions can slow methotrexate excretion and require prolonged leucovorin rescue.	**Case 95-3 (Questions 3, 4)**

CORE PRINCIPLES		CHAPTER CASES
4	Rhabdomyosarcoma is a soft tissue tumor of skeletal muscle origin, and it is the most common soft tissue sarcoma of childhood, occurring in 3% of all children with cancer. The two most common histologic types in children are embryonal and alveolar. Using the combination of vincristine, dactinomycin, and cyclophosphamide with local control of surgery or radiation, it is associated with an ~75% failure-free survival for patients with nonmetastatic disease.	**Case 95-4 (Question 1)**
5	Acute lymphoblastic leukemia (ALL) involves replacement of normal bone marrow elements because of abnormalities in cellular proliferation. Signs and symptoms relate to the deficiency in normal bone marrow elements.	**Case 95-5 (Question 1)**
6	Important prognostic variables in ALL are based on clinical and laboratory findings, including age and white blood cells at diagnosis, immunologic classification, cytogenetics, and minimal residual disease (MRD) evaluation on bone marrow.	**Case 95-5 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
7	The treatment of ALL is divided into phases, including remission induction therapy, central nervous system (CNS) preventive therapy, consolidation/intensification phases, and maintenance therapy. All phases are different, each using multiple agents, schedules, and toxicity.	**Case 95-5 (Questions 2, 3, 5, 6, 9–11)**
8	CNS preventive therapy is a key component of ALL treatment. Contemporary treatment/preventive regimens are composed of intrathecal administration of antimetabolite chemotherapy. CNS radiation is reserved for special situations.	**Case 95-5 (Questions 4, 5, 7, 8)**
9	Patients with relapsed ALL will often achieve a second remission of their disease but have a high likelihood of further relapses. Various approaches, including intensified chemotherapy, targeted agents, or stem cell transplantation, have been used in the treatment of relapse.	**Case 95-6 (Questions 1–3)**

CORE PRINCIPLES		CHAPTER CASES
10	Non-Hodgkin lymphoma accounts for 10% of childhood cancers. It has a cure rate of more than 80%. It often presents as a mass in the mediastinum or as pleural effusions. Masses may be large; therefore, adjunctive therapies to prevent tumor lysis syndrome and nephropathy are necessary.	**Case 95-7 (Question 1)**

INTRODUCTION

In the United States, cancer is the leading cause of disease-related death for children between ages 1 and 14 years.[1] About 11,000 children younger than age 15 years are diagnosed with cancer each year, and around 85% of them can anticipate long-term survival.[1] Acute leukemias are the most common malignancies of childhood; the selected solid tumors discussed in this chapter each represent 2.5% to 7.0% of all childhood malignancies.[1] Many common pediatric solid tumors are uncommon in adults. Likewise, many tumors common in adults occur infrequently in children. In general, sarcomas and embryonal tumors are common in children, whereas carcinomas predominate in adults.

Genetics

Similar to adult cancers, the association of many pediatric cancers with chromosomal aberrations or genetic defects is well-confirmed. Examples include the association of Wilms tumor with congenital malformations, acute leukemias with Down syndrome, and the association of some pediatric cancers with loss of the p53 or retinoblastoma tumor suppressor genes.[2–7]

Carcinogens and Exposures

The role of carcinogens in pediatric cancer is probably less prominent than in adults because of the long latency periods required. Carcinogens and other exposures are implicated in the etiology of some childhood cancers.[8] Maternal use of diethylstilbestrol during pregnancy is associated with an increased risk of vaginal or cervical cancer in offspring.[6] Other prenatal exposures, such as maternal infection, pesticide exposure, and paternal smoking, may also contribute to increased childhood cancer risk.[9–11] Postnatal exposure to ionizing radiation, including exposure through medical diagnostic imaging, is associated with an increased risk of multiple types of childhood cancer and should be minimized.[12] Long-term survivors of childhood cancer are at a significantly increased risk of secondary malignancy, a risk that continues for at least 20 years following initial diagnosis.[8,13,14]

Patient Age

As with adult patients, patient age at diagnosis can be a factor in prognosis and treatment response. Neuroblastoma is the most common malignancy in infants; survival is typically excellent in infants and toddlers up to 18 months of life, a benefit attributed to the biology of the disease in this age group.[15] In contrast, infants with ALL tend to have a worse prognosis than older children because of the presence of specific genomic features commonly seen in infants with ALL.[16]

Age is also associated with treatment-related toxicities. Younger children are more susceptible to radiation-related toxicities, including radiation-induced disruption in normal bone metabolism, fertility impairment, endocrinopathies, cardiomyopathy, and significant long-term neurocognitive impairment.[17–20] Younger age (<13 years old) at the time of anthracycline administration is associated with a higher risk of a delayed onset of heart failure.[21] Lastly, older age at diagnosis is a recognized risk factor for steroid-induced osteonecrosis in children with ALL.[22]

Adolescents and young adults (AYAs) with cancer are a special population with unique needs.[1] About 90,000 persons in this age group (widely defined as ages 15–39 years) will be diagnosed with cancer in the United States each year. Survival for AYAs with some types of cancer has lagged behind those of younger children and older adults. AYA with cancer may have molecularly distinct disease features, necessitating alternate approaches to therapy.[23,24] Although AYA may be treated at pediatric or adult cancer programs, survival is typically higher in patients treated according to pediatric-based protocols.[25,26] AYAs have other unique age-related needs, including fertility preservation, cancer treatment during pregnancy, and prevention and screening of other cancers.[1]

Multi-Institutional Research Groups

Success in the improvement of survival from childhood cancer is largely attributed to cooperative group clinical trials studied over the past 60 years.[27,28] Most centers treating children with cancer in the United States are members of the Children's Oncology Group (COG), a pediatric multi-institutional research group in the United States, Canada, Australia, and New Zealand, which is sponsored by the National Cancer Institute and many private organizations.[29] Much of the success with improving survival through cooperative group trials is attributed to gains in the treatment of newly diagnosed ALL. Despite this success, relapsed ALL remains the most common cause of death from childhood cancer.[28]

Late Effects

Late effects can be described as toxicities or complications that either persist or occur after therapy is finished. Examples of late effects include joint or bone problems, heart failure, second malignancies, strokes, and cognitive dysfunction.[30] The Childhood Cancer Survivor Study (CCSS) includes data on health problems experienced by thousands of pediatric cancer survivors and a

sample of their siblings. Initial data from the study showed that more than 60% of the survivors had at least one chronic medical problem, and 27% had a severe or life-threatening health problem.[30] The overall relative risk of a health problem compared to siblings was 3.3-fold, with specific risks as high as 54-fold for joint replacements and 15-fold for heart failure. Subsequent analyses of the data are tracked and shared via the CCSS website (www.stjude.org/ccss). This type of knowledge has reemphasized the need for clinicians to limit toxic therapies where possible with the aim of reducing late effects and improving the quality of life for survivors. These and other data have helped inform the evidence-based COG Survivorship Guidelines to help standardize an approach to appropriate screening and management of childhood cancer survivors.[31] All cancer survivors should have access to a record of their treatment history for the remainder of their lives.[32,33] This valuable resource will guide health care professionals as they make evidence-based decisions on long-term follow-up of childhood cancer survivors.

PEDIATRIC SOLID TUMORS

Neuroblastoma

Description, Incidence, and Epidemiology

Neuroblastoma is a tumor that develops from immature cells of the peripheral nervous system.[1] It is the most common extracranial tumor during childhood, representing 6% of all childhood cancers and more than 650 new cases annually in the United States.[1] The median age at diagnosis is 19 months; about 37% of cases occur in children younger than age 1 year and 90% before age 5 years.[1,34] The 5-year survival rate of children with neuroblastoma has increased over time.[35] Lower-risk patients, which mostly includes infants with stage 1, 2, or 4S, may have spontaneous remissions or at least a 75% to >90% 5-year event-free survival.[36] Intermediate-

risk patients have a 50% to 75% event-free survival, and high-risk patients a 19% to 42% 5-year event-free survival.[37] With evolving therapies for high-risk patients, survival rates have seen modest but meaningful improvements.

PATHOPHYSIOLOGY

Neural tumors related to neuroblastoma can be ganglioneuroma (benign) or ganglioneuroblastoma (mixed benign and malignant) or pure neuroblastoma. At biopsy, multiple specimens may be required to fully assess the malignant potential of the tumor. As with other cancers, neuroblastoma results from the loss of cell-growth control because of oncogene activation, tumor suppressor gene inactivation, and related malignant processes. Despite that familial neuroblastoma is relatively rare (only 1%–2% of all cases), several germline mutations and cancer predisposition syndromes have been reported. Patients with these features are at a significantly increased risk of developing neuroblastoma. Specifically, familial neuroblastoma has been associated with *ALK* gene mutations, *PHOX2B* gene mutations, neurofibromatosis type 1, Li–Fraumeni syndrome, Costello syndrome, and Beckwith–Wiedemann syndrome, among others.[38] The American Association for Cancer Research now recommends biochemical and radiographic screening for patients with some of these features within the first 10 years of life.[39]

CLINICAL PRESENTATION, DIAGNOSIS, STAGING, AND OTHER PROGNOSTIC FACTORS

Patients with neuroblastoma often present with a fixed, hard, abdominal mass noted on physical examination by the family or physician, and possibly other signs or symptoms, depending on the location of the primary tumor and metastases. For example, gastrointestinal (GI) fullness, discomfort, or dysfunction can occur. Other less common but characteristic signs include proptosis with periorbital ecchymoses, increased renin hypertension, secretory diarrhea with increased vasoactive intestinal peptide, respiratory

distress, nerve root compression, opsomyoclonus, and unilateral ptosis.[38] The most common sites of metastases are the bone marrow, bone, liver, and skin.[14]

A diagnosis of neuroblastoma includes tumor biopsy, imaging of the primary tumor mass (with computed tomography and/or magnetic resonance imaging [MRI] with contrast), as well as scanning with metaiodobenzylguanidine (MIBG). MIBG is a sensitive evaluation because of its high uptake into the tumor tissue (including metastatic sites), proving useful for diagnosis, staging, and assessment of tumor response to therapy.[40,41] The catecholamine metabolites vanillylmandelic acid (VMA) and homovanillic acid (HVA) are elevated in the urine of 90% of patients with neuroblastoma; although not typically used for diagnosis and staging, they may be useful for evaluation of microscopic or persistent disease.[38] A large number of prognostic factors have been identified based on diagnostic features; these factors are discussed in detail elsewhere.[38] Briefly, the primary prognostic factors can be classified into the following categories: age at diagnosis, tumor histology, biologic features, site of primary tumor, stage of disease, response to therapy, lactate dehydrogenase (LDH) level, and serum ferritin.[38]

The International Neuroblastoma Risk Group Staging System (INRGSS) classifies the surgical stage by the extent of disease at diagnosis, prior to therapy or surgery. The four stages (L1, L2, M, and MS) describe the disease as locoregional (L) versus metastatic (M). The staging also indicates the presence of locoregional image-defined risk factors (IDRFs; L2) versus none (L1); or a diagnosis of “metastatic special” disease (MS: children younger than age 18 months with metastases confined to the skin, liver, and/or bone marrow) versus others with metastatic disease (M).[42,43]

The classification of favorable versus unfavorable genomics is a field of rapid change and critically important to accurate staging of the disease. Currently, favorable genomic features include the following: hyperdiploid neuroblastoma cells without segmental copy number aberrations, including no loss of copy number at 1p, 3p, 4p, or 11q and no gain of copy number at 1q, 2p, or 17q.[38] Each patient is assigned a “risk stage” (low, intermediate, or high risk) at

diagnosis based on their INRGSS, IDRFs, and biologic/genomic risk factors; this risk stage is predictive of the risk of relapse and, thus, drives treatment decisions. Most low- and intermediate-risk neuroblastomas occur in children younger than 18 months old at diagnosis; typically, these tumors may be hyperdiploid and have gains of whole chromosomes.[36,44] Overall survival (OS) for patients at low- and intermediate risk is excellent, at 97% (5-year OS) and 96% (3-year OS), respectively.[15,45,46] Unfortunately, survival for patients at high risk is still a challenge, with 3-year event-free survival around 50%.[38,47]

OVERVIEW OF TREATMENT

In current U.S. clinical trials, patients with low-risk disease are typically treated with surgery followed by observation (**Table 95-1**). Some patients at low risk may receive observation only (perinatal neuroblastoma, small adrenal tumors), chemotherapy with or without surgery (symptomatic disease or unresectable disease following surgery), or radiation (emergently, based on tumor location). Two to four courses of chemotherapy may be used with initial surgery if organ-threatening symptoms are present. Intermediate-risk disease is treated with surgery and four to eight courses of chemotherapy (**Tables 95-1** and **95-2**) for favorable or unfavorable histology and ploidy.[38,45] Patients with low-risk and intermediate-risk disease should receive chemotherapy, which avoids agents with significant long-term toxicities, when possible, given the high rate of survival. For example, most regimens for these patients avoid cisplatin to reduce nephrotoxicity and ototoxicity, limit the total doxorubicin dose to avoid cardiac toxicity, limit the total etoposide dose to reduce the risk of secondary acute myelogenous leukemia, and avoid ifosfamide to eliminate the risk of Fanconi renal syndrome. Radiation therapy is reserved for poor responders.

Table 95-1
Example of Children's Oncology Group Neuroblastoma Risk

Groups and Treatment for Patients at Low Risk, Intermediate Risk, and High Risk

Low Risk; Surgery and Observation
All stage 1 patients
Patients with stage 2A or 2B, >50% resected and MYCN not amplified[a]
Infants with 4S with MYCN not amplified, favorable histology, and hyperdiploidy
Low Risk, Group 2; Receive Two Cycles of Chemotherapy With Surgery
Stage 2A/2B, >50% resected, or biopsy only and MYCN not amplified
Infants with stage 3 or symptomatic 4S, MYCN not amplified, favorable histology, and hyperdiploid; increase one group if loss of heterozygosity at 1p or 11q
Stage 3, >1 year old, MYCN not amplified, favorable histology
Intermediate Risk, Group 3; Four Cycles of Chemotherapy With Surgery
Infants with stage 3, MYCN not amplified, and diploidy or unfavorable histology
Stage 4, up to 18 months old, MYCN not amplified (good genomics)
Infants with stages 4S and MYCN not amplified, and either diploidy or unfavorable histology
Intermediate Risk, Group 4; Eight Cycles of Chemotherapy With Surgery
Infants with stage 4S, unknown biology
Infants with stage 4, MYCN not amplified, with diploidy or unfavorable histology
Stage 3, up to 18 months old, MYCN not amplified and unfavorable histology
High Risk
Biopsy, five to six cycles of chemotherapy, followed by definitive surgery, high-dose chemotherapy with autologous progenitor cell rescue, radiation to the primary site, and maintenance therapy Induction chemotherapy: vincristine, doxorubicin, and cyclophosphamide for cycles 1, 2, 4, and 6; cisplatin and etoposide for cycles 3 and 5 Consolidation: high-dose chemotherapy (eg, busulfan and melphalan) followed by autologous progenitor cell rescue Maintenance therapy: six cycles of isotretinoin (2 weeks on; 2 weeks off for each cycle) concurrent with five cycles of dinutuximab with GM-CSF[b]
MYCN amplified and not included in previous groups

Note: Consult current protocols as classifications and treatment recommendations are changing rapidly. Typical correlations with the newer staging terminology: L1 and MS patients with good genomics would be in the low-risk group; L2 patients with good genomics would be in the intermediate-risk group but bad genomics in

the high-risk group; MS patients with good genomics would be lower risk or with bad genomics would be high risk; M patients would be in the high risk unless they are <18 months old with good genomics. See Table 95-2 for details of chemotherapy regimens in low-risk and intermediate-risk patients.

[a]*MYCN* is an oncogene that is associated with more aggressive higher-risk neuroblastomas.

[b]GM-CSF is granulocyte-macrophage colony-stimulating factor.

Source: National Cancer Institute. *Neuroblastoma Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries*. Accessed January 5, 2021. https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq.

Table 95-2
Typical Cycles of Chemotherapy Used in Children's Oncology Group Low-Risk and Intermediate-Risk Neuroblastoma

Cycle[a]	Drugs
1	Carboplatin, etoposide
2	Carboplatin, cyclophosphamide, doxorubicin
3	Cyclophosphamide, etoposide
4	Carboplatin, doxorubicin, etoposide
5	Cyclophosphamide, etoposide
6	Carboplatin, cyclophosphamide, doxorubicin
7	Carboplatin, etoposide
8	Cyclophosphamide, doxorubicin

[a]Each row represents a single 21-day cycle of therapy. Generally, the first four cycles are used in patients at intermediate risk with favorable histology disease, and all eight for patients with unfavorable histology. Patients at low risk whose disease is potentially organ-threatening may receive the first two to four cycles plus surgery. See **Table 95-1** for common chemotherapy guidelines for patients with neuroblastoma.

Source: National Cancer Institute. *Neuroblastoma Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries*. Accessed January 5, 2021. https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq.

Therapy for high-risk disease generally involves a first surgery for biopsy, aggressive chemotherapy, second-look surgery for residual

tumor resection (in most patients/centers), tandem cycles of high-dose chemotherapy with autologous progenitor cell rescue, radiation to the tumor bed, and postconsolidation (maintenance) therapy (see Table 95-1).[37,38,48–56] High-dose chemotherapy with autologous progenitor cell rescue improved 5-year disease progression–free survival to 49% from historic values of 10% to 20%; however, relapses can occur later with 7-year disease progression–free survival of only 26%.[57,58] Disease-free survival (DFS) can be further improved (46% vs 29% 5-year postchemotherapy DFS) for patients with high-risk disease if standard-dose or high-dose chemotherapy is followed by maintenance with six cycles of isotretinoin 80 mg/m^2 given orally twice daily for 14 days of each 28-day cycle.[57] Addition of the anti-GD2 monoclonal antibody, dinutuximab, along with interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF), to the maintenance regimen has been shown to further increase survival.[56,59] Typical conditioning regimens preceding autologous progenitor cell rescue include carboplatin and etoposide with melphalan, or busulfan plus melphalan.[51,60]

CLINICAL PRESENTATION AND DIAGNOSIS

CASE 95-1

Question 1: H.K. is a 2-year-old female with a 3-month history of constipation and progressive abdominal distension. She has a decreased appetite, 1-week history of vomiting, and she is pale and tired. She has a large retroperitoneal mass and multiple bilateral enlarged inguinal lymph nodes. Her white blood cell (WBC) count and differential and platelets are within normal limits. Serum sodium, potassium, chloride, creatinine, and glucose are within normal limits. Her laboratory test results also include the following:

Hemoglobin (Hgb), 5.1 g/dL (normal, 11–14 g/dL)
Lactate dehydrogenase (LDH), 424 units/L
Albumin, 2.3 g/dL
Urine HVA, 570 mg/g creatinine (normal, <26 mg/g)
Urine VMA, 31 mg/g creatinine (normal, <11 mg/g)

Biopsies of the abdominal mass and bone marrow are positive for neuroblastoma cells that are MYCN amplified. The lymph nodes are negative for neuroblastoma. Scans are negative for other sites of disease.

Which of these signs, symptoms, and laboratory results are consistent with a diagnosis of neuroblastoma?

Virtually all of H.K.'s findings are consistent with neuroblastoma. The low hemoglobin and albumin and high LDH, however, are not specific for this cancer. In addition to the biopsy, the elevated urine VMA and HVA are most helpful in confirming the diagnosis of neuroblastoma. In H.K., biopsies of the bone marrow, lymph nodes, and primary tumor were necessary to demonstrate the presence or absence of neuroblastoma at more than one site for staging purposes.

TREATMENT

Case 95-1, Question 2: What stage of disease does H.K. have? What treatment will she receive?

H.K.'s abdominal disease with distant bone marrow involvement indicates metastatic (M) disease. She has unfavorable genomic features, including MYCN amplification. Considering her age and disease stage, H.K. has a high risk of dying from her disease. Therefore, she is started on chemotherapy for high-risk patients consisting of vincristine, doxorubicin, and cyclophosphamide for cycles 1, 2, 4, and 6, and cisplatin and etoposide for cycles 3 and 5.

Case 95-1, Question 3: H.K. is 32.08-inch (81.5-cm) tall, weighs 25.68 pounds (11.65 kg), and has a body surface area of 0.5 m^2. For her third chemotherapy cycle, consisting of cisplatin 50 mg/m^2/day on days 1 through 4 and etoposide 200 mg/m^2/day on days 1 through 3, she is given hydration fluids of 5% dextrose with 0.45% sodium chloride at 62.5 mL/hour. Urine output is 4 mL/kg/hour. How does monitoring of H.K.'s chemotherapy differ from that of an adult?

Monitoring vital signs for etoposide

Although prevention and monitoring of toxicities from chemotherapy agents in children follow the same basic rules as in adults, there are some differences. When monitoring vital signs for hypotensive reactions to etoposide, normal blood pressure will be lower (hypotension is defined as a systolic blood pressure under 74 mm Hg for a 2-year-old girl) and the pulse higher (mean, 119 beats/minute for a 2-year-old) than in adults. It is important to have baseline vital signs so that hypotension or tachycardia will be recognized.

Monitoring hydration for cisplatin

In adults receiving cisplatin, hydration is often standardized to a set volume (eg, 1–2 L) of intravenous (IV) fluids given before the drug, with the drug (another 1–2 L), and then as continuous hydration for at least 24 hours after the dose. In children, hydration volumes should be calculated based on the child's size. To decrease the risk of cisplatin nephrotoxicity, most pediatric protocols recommend IV fluids at twice maintenance rates to maintain urine outputs of at least 2 to 3 mL/kg/hour. The COG calculates maintenance fluids as 1500 mL/m^2 per 24-hour period. As such, H.K. should receive twice that amount for cisplatin hyper-hydration, or 1500 mL during 24 hours (3000 $mL/m^2 \times 0.5\ m^2 \div 24$ hours = 62.5 mL/hour). H.K.'s measured urine output is 4 mL/kg/hour, which should be adequate to prevent nephrotoxicity. Weight should also be monitored throughout cisplatin administration to assure fluid balance. Acute weight gain may require diuretics to prevent fluid overload, but diuretics should be used judiciously to avoid the risk of acute kidney injury.

Adjustment of creatinine clearance in pediatric patients

Case 95-1, Question 4: H.K.'s estimated glomerular filtration rate (eGFR) is 39 mL/minute/1.73 m^2 using the revised/bedside Schwartz equation.[61] Should her cisplatin be withheld, or the dose adjusted because of low creatinine clearance?

Cisplatin is typically avoided in patients with severely impaired renal function. However, H.K. has a disease with a high likelihood of not responding to therapy or resulting in relapse. Therefore, reducing therapy should only be considered when all avenues have been explored. The accuracy of serum creatinine and creatinine clearance in assessing renal function during cisplatin therapy in children has been questioned.[62–64] Therefore, it is recommended to obtain a more precise measurement of glomerular filtration, such as a nuclear medicine evaluation that measures radioisotope clearance by the kidney.

Further treatments based on disease biology

With rapid advances in neuroblastoma biology being made, future alternatives may include more biologic treatments. One agent in clinical trials is ^{131}I-MIBG, a compound that delivers radiation directly to catecholamine-secreting cells such as neuroblastoma. Studies have used ^{131}I-MIBG as part of the conditioning regimen before progenitor cell rescue in patients with neuroblastoma.[65] Tyrosine kinase inhibitors (eg, crizotinib, ceritinib), which target the anaplastic lymphoma kinase (ALK) receptor, have been studied in pediatric patients with *ALK* mutations and may benefit a small percentage of patients with neuroblastoma.[66–68]

Wilms Tumor

Description, Epidemiology, and Pathophysiology

Wilms tumor, also known as nephroblastoma, is a kidney tumor composed of various kidney cell types at different stages of maturation. Approximately 5% of all childhood cancers are Wilms tumor, representing about 650 new cases per year in the United States. Wilms tumor is the most common intra-abdominal tumor of childhood,[1,71] with a peak incidence at ages 3 to 4 years.[69]

The relationship of genetic factors to Wilms tumor is demonstrated by ~1.5% of patients with Wilms tumor who have family members with the disease, as well as around 10% of patients who have

congenital anomalies such as aniridia, hemihypertrophy, or genitourinary anomalies.[69] About one-third of Wilms tumor cases involve mutations in *WT1*, *CTNNB1*, or *WTX*.[4,70] Chromosomal aberrations at 11p13 and 11p15, known, respectively, as *WT1* and *WT2*, are associated with syndromic Wilms tumors commonly seen with WAGR syndrome (**W**ilms, **A**niridia, **G**enitourinary anomaly, mental **R**etardation; *WT1*) and Beckwith–Wiedemann (*WT2*) syndromes, respectively.[5,6,71] Patients with these related predisposition syndromes should be screened with ultrasonography every 3 months until at least age 8 years.[72] Other known syndromic causes may also be important, including a variety of overgrowth syndromes (Perlman, Simpson-Golabi-Behmel, CLOVES, etc), Bloom syndrome, and Li–Fraumeni syndrome.[3,69,73] Nonsyndromeic familial Wilms tumor is related to *WT4* (17q12-21) and *FWT2* (19q13.4), which have been identified more recently and about which less is known.[69]

Most patients with Wilms tumor may expect an excellent prognosis, with OS rates of about 90%.[35] However, prognosis varies with the presence of specific risk factors, such as the stage of disease at diagnosis, patient age (older age is less favorable), histopathology (anaplasia worse than favorable histology), and molecular features of the tumor.[69,74–77] Of all prognostic factors, 1q gain is the most powerful predictor of adverse/poor clinical outcomes.[76,77] Patients with adverse prognostic features typically receive augmented chemotherapy approaches (**Table 95-3**).

Table 95-3
Wilms Tumor Treatment Regimens by Stage and Histology

Stage I, Any Histology, and Stage II, Favorable Histology
Surgery followed by 18 weeks of vincristine and dactinomycin. Add abdominal radiation for either focal or diffuse anaplasia.[a]
Stage III or IV, Favorable Histology; Stages II, III, or IV Focal Anaplasia
Surgery followed by 24 weeks of vincristine, dactinomycin, and doxorubicin, with abdominal radiation.[b] Add pulmonary radiation if chest CT (computed

tomography) shows metastases unless there is complete resolution after chemotherapy.
Stages II through IV, Diffuse Anaplasia
Surgery followed by 24 weeks of vincristine, doxorubicin, etoposide, and cyclophosphamide with mesna, plus or minus dactinomycin and carboplatin, abdominal radiation. Stage IV: Add pulmonary radiation if chest CT (computed tomography) shows metastases unless there is complete resolution after chemotherapy.
Stage V
Biopsy followed by neoadjuvant vincristine, dactinomycin, and doxorubicin, then complete resection or debulking followed by more chemotherapy and, if a poor response, radiation therapy; more aggressive treatment if unfavorable histology.

[a]Stage I with tumor >550 g in a patient >24 months of age: surgery alone has been used investigationally with some success.

[b]Stage III or IV with favorable histology but loss of heterozygosity at 1p and 16q: higher risk, use vincristine, dactinomycin, doxorubicin, plus outpatient cyclophosphamide and etoposide.

Source: National Cancer Institute. *Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries*. Accessed January 5, 2021. https://www.cancer.gov/types/kidney/hp/wilms-treatment-pdq.

CLINICAL PRESENTATION

Patients with Wilms tumor frequently present with an asymptomatic abdominal mass, although malaise and pain may be reported.[69] Hematuria and high renin hypertension each occur in ~25% of patients. Metastases, when present at diagnosis, most commonly involve the lungs (80%) or liver (15%).

DIAGNOSIS, STAGING, AND OVERVIEW OF TREATMENT

Diagnosis of Wilms tumor is based on biopsy and computed tomography (CT) of chest and abdomen to rule out metastatic disease. Fluorine F 18-fludeoxyglucose (^{18}F-FDG) positron emission tomography (PET)–CT (^{18}F-FDG PET-CT) may also be helpful in some patients.[78] Treatment in the United States is based mostly on disease stage after surgical resection or debulking and favorable

histology versus focal or diffuse anaplasia. Surgical resection is the primary treatment, followed by adjuvant chemotherapy (see Table 95-3). A simplified description of the staging is as follows: stage I (43% of patients) is limited to the kidney and can be completely removed surgically; stage II (20% of patients) is extended beyond the kidney but can be completely excised; stage III (21% of patients) is characterized by residual tumor confined to the abdomen; stage IV (11% of patients) is distant metastases; and stage V (5%) of patients is bilateral disease.[69] Metastases are present in only 15% of patients at diagnosis, and even these patients have relatively good prognoses. Notably, in Europe, the majority of treatments use neoadjuvant chemotherapy before surgery. The benefits and risks of each method have been discussed elsewhere.[79] COG studies suggest surgery followed by adjuvant chemotherapy, except in stage V (bilateral disease) where neoadjuvant chemotherapy is used in an attempt to preserve kidney function.[80] The late effects following treatment for Wilms tumor can be significant, including the development of subsequent or secondary malignant neoplasms, heart failure, pregnancy complications, and end-stage renal disease.[81–85] Long-term follow-up and monitoring of patients well into adulthood are critical.

CLINICAL PRESENTATION AND TREATMENT

CASE 95-2

Question 1: B.N. is a 34-month-old boy who is pale and irritable. He has had abdominal problems with decreased bowel movements and reduced oral intake for 2 weeks. He has played less than normal for the last 4 weeks. B.N.'s blood pressure has intermittently been as high as 146/87 mm Hg (normal, 90th percentile, 106/69 mm Hg). His laboratory results include the following:

Hgb, 7.9 g/dL (normal, 11.5–13.5 g/dL)
Erythrocyte sedimentation rate, 139 mm/hour (normal, <10 mm/hour)

B.N. has a history of hypospadias and left hydronephrosis. Scans show a right kidney mass extending through the capsule plus two distant metastases in the peritoneum. Chest radiography shows one nodule in the lung as well. Pathology from a biopsy sample shows favorable histology Wilms tumor.

What treatment should B.N. receive?

B.N. has stage IV disease with favorable histology, and the cells are negative for loss of heterozygosity at 1p and 16q. The expected treatment for him is 24 weeks of vincristine, dactinomycin, and doxorubicin, assuming findings at surgery are consistent with pretreatment scans. He will receive abdominal radiation; he would also receive pulmonary radiation unless the lung metastases completely disappear with chemotherapy. The series of five National Wilms Tumor studies have sought to progressively minimize toxicities from radiation and chemotherapy while maintaining an excellent cure rate. The fourth National Wilms Tumor Study Group (NWTS-4) study demonstrated that intermittent, higher doses of dactinomycin allowed higher dose intensity with less myelosuppression than lower doses given daily for 5 days. Using greater dose intensity and dose density, 6 months of therapy was shown to be as effective as 15 months of therapy given the traditional way.[86] Also, fewer clinic visits were made and estimated costs were reduced by 50%.[86,87] The NWTS-5 evaluated surgery followed by 18 to 24 weeks of chemotherapy. Chemotherapy was determined by the stage and histology findings (Table 95-3). Abdominal radiation therapy was added to chemotherapy for stage II disease with unfavorable histology (focal or diffuse anaplasia) or stages III or IV with any histology; pulmonary radiation was added for stage IV disease if the chest radiograph was positive for metastases. The latter part of the guideline is now determined by whether the pulmonary nodules clear with chemotherapy or not. For patients with stage V disease, or those with inoperable tumors, surgery could be delayed until neoadjuvant chemotherapy reduces the tumor size.

Dosing chemotherapy in infants and young children

CASE 95-2, QUESTION 2: Are there any special precautions for dosing chemotherapy in B.N.?

The NWTS-2 study noted an excessive number of toxic deaths in infants with good prognosis, and this resulted in a dosing change.[88] After chemotherapy doses were decreased by 50%, severe hematologic toxicity, toxic deaths, and pulmonary and hepatic complications were reduced.[89] Importantly, no decrease in therapeutic effect was noted. Reduction of chemotherapy doses in infants is a consideration for other pediatric cancers as well.[39–41] Reasons for increased toxicity in infants may include altered pharmacokinetics or organ sensitivity as well as the larger body surface area/kilogram relative to older children and adults.[88] In NWTS-5, dosages of chemotherapy agents for patients with Wilms tumor who are <66.13 pounds (30 kg) were converted from mg/m^2 to mg/kg. By assuming the average 1-m^2 child weighs 66.13 pounds (30 kg), the dose per square meter can be divided by 30 to arrive at a dose per kilogram, which can be used in dosing calculations. This adjustment lowers the dose by 20% to 50% in children who weigh <33.06 pounds (15 kg). In NWTS-5, infants younger than 12 months of age received doses that were further reduced by halving the milligram/kilogram dose. The COG has recently proposed an alternative approach using dose banding for infants and children with a body surface area (BSA) <0.6 m^2.[90] The proposed dose bands were developed to provide a more uniform drug exposure and safer dosing curve for infants and children up to about 36 months old during critical phases of ontogeny.

Interaction of chemotherapy with radiation

Case 95-2, Question 3: Are there any dosing precautions required because of potential interactions between B.N.'s treatments?

Another medication-related problem that may arise in B.N. is the interaction of dactinomycin and doxorubicin with radiation therapy.[91–95] Two effects have been reported. One is acute enhancement of radiation effects, and the other is recurrence (recall) of radiation effects up to several weeks later, especially to skin and mucous

membranes. Because B.N. is to receive abdominal and lung irradiation during his chemotherapy treatment, concurrent doses of dactinomycin and doxorubicin will need to be reduced by 50% and held if wet desquamation occurs at the radiation site. In many of the Ewing sarcoma and rhabdomyosarcoma protocols, dactinomycin or doxorubicin is stopped during concurrent radiation treatments.

Doxorubicin cardiotoxicity in pediatrics

Case 95-2, Question 4: When B.N. receives lung radiation for his metastases, how will it affect the doxorubicin he is scheduled to receive?

Although it is well known that mediastinal radiation can increase the risk of anthracycline-induced cardiac toxicity,[96] the only adjustment for B.N. would be a temporary reduction of doxorubicin doses (same reductions as described in Case 95-2, Question 3). The total doxorubicin dose should be limited to no more than 5 mg/kg (150 mg/m^2 in larger children). In earlier Wilms tumor studies, the risk of congestive heart failure was 4.4% at 20 years, or up to 17.4% in patients who relapsed and received more doxorubicin.[82] Thus, cardiovascular toxicity can develop as long as 20 years after therapy is completed, with an apparent decrease in left ventricular wall thickness and increased ventricular afterload, probably related to inadequate numbers of myocytes.[97] These reports emphasize the need to minimize chemotherapy in patients with good prognosis, as the Wilms tumor studies are doing. New recommendations include better standardization of cardiac monitoring and continuation of monitoring throughout life in survivors of childhood cancer who receive cardiotoxic agents.

Dactinomycin hepatotoxicity

Case 95-2, Question 5: B.N. is to receive vincristine 0.05 mg/kg weekly for 10 weeks; doxorubicin 1.5 mg/kg at weeks 3 and 9 and then decreased to doxorubicin 1 mg/kg at weeks 15 and 21; and dactinomycin 0.045 mg/kg at

weeks 0, 6, 12, 18, and 24. During the third week of treatment, his alanine aminotransferase (ALT) is elevated to 78 units/dL. Is this related to his drug therapy?

Early in the NWTS-4, an increased incidence (14.3%) of severe hepatotoxicity (elevation of alanine aminotransferase or ALT 10 times normal with or without ascites) was reported with the pulse-intensive dactinomycin doses (0.06 mg/kg/single dose) in patients receiving no abdominal radiation.[98] Subsequently, dactinomycin doses were reduced. Still, the incidence of hepatotoxicity in patients receiving the newer 0.045 mg/kg pulse doses (3.7%), as well as those receiving the standard 0.015 mg/kg/day for 5 days (2.8%), remained elevated relative to the NWTS-3 results (0.4%), which used the same 0.015 mg/kg/day for 5 days.[99] The reasons for the increased hepatotoxicity are not known. Liver function usually returns to baseline within 1 to 2 weeks after discontinuation of chemotherapy, although more severe problems with sinusoidal obstructive syndrome (hepatopathy, veno-occlusive disease) have also been reported. Chemotherapy may be restarted in some patients, although frequently at lower doses or without dactinomycin. B.N. should be monitored closely in case his liver enzymes continue to rise, especially because he will receive abdominal radiation treatments that may increase the risk of hepatic toxicity. If his ALT rises to two to five times normal, or his total bilirubin is 3 to 5 mg/dL, doses of all three of his drugs should be reduced by 50%, or according to protocol instructions. If his ALT or bilirubin rises above two to five times normal, the drugs should be withheld until laboratory values return to lower than the aforementioned ranges.

Osteosarcoma

Definition, Epidemiology, Pathophysiology, and Course of the Disease

Osteosarcoma is a malignant osteoid-producing bone tumor that occurs most commonly in adolescents or young adults in the second or third decade of life.[100,101] Osteosarcoma represents about 2% to

5% of all childhood malignancies, with around 450 new cases per year in children, adolescents, and young adults in the United States.[1] The most common manifestation at diagnosis is pain at the site, which can sometimes be present for several weeks to months. It occurs most frequently in the metaphyseal ends of the distal femur, proximal tibia, or proximal humerus, but can occur in the flat bones as well.

The age range and bones involved suggest a malignant response associated with normal childhood growth spurts.[103] Radiation from treatments or nuclear disasters has also been linked to osteosarcoma. Mutation of the retinoblastoma (*RB1*) gene increases the risk of osteosarcoma, and retinoblastoma survivors and carriers need to be monitored for osteosarcoma.[2,102] There are a number of other uncommon inherited conditions, such as Bloom syndrome, Diamond–Blackfan anemia, and Rothmund–Thomson syndrome, that are also associated with an increased risk of osteosarcoma.[3,73,103–105]

Typical staging systems are not used for osteosarcoma; however, presence of clinically detectable metastatic disease at diagnosis, resectability of the tumor, and tumor grade (high vs low) are important to outcomes. Low-grade tumors are not likely to metastasize and are not treated with chemotherapy in contrast to high-grade tumors. Clinically detectable metastases are present in 15% to 20% of patients, usually in the lungs but occasionally in the same or other bones. If surgery alone is used for treatment, 80% of patients will die within 5 years of recurrent metastatic disease, indicating the presence of subclinical micrometastases at the time of diagnosis.[100,101] The degree of tumor necrosis at surgical resection is an indicator of chemosensitivity of the tumor and risk of relapse. Greater than 90% necrosis at the time of surgery after six cycles of neoadjuvant chemotherapy is associated with a 70% to 80% chance of long-term survival for nonmetastatic disease, with survival dropping to around 50% for nonmetastatic disease with <90% necrosis.

CLINICAL PRESENTATION AND DIAGNOSIS

Because osteosarcoma usually presents close to a joint in long bones, it most commonly presents with pain or a limp. It is often thought to be an athletic injury at first. In some patients, a broken arm or leg will occur, bringing attention to the mass on radiographs. Diagnosis is based on pathology from a biopsy, which should be obtained by the surgeon performing the definitive surgery; therefore, the biopsy tract can be resected with the tumor.

TREATMENT OVERVIEW

Although surgery is the main treatment of the primary tumor, chemotherapy is used to prevent development of metastases in patients with high-grade osteosarcoma. Drugs frequently used for osteosarcoma include high-dose methotrexate, cisplatin, doxorubicin, and ifosfamide. Regimens have changed minimally in the last 25 years, with the current standard treatment in COG being cisplatin and doxorubicin alternating with two cycles of high-dose methotrexate, despite conflicting evidence for the inclusion of high-dose methotrexate.[106–108] Neoadjuvant chemotherapy is commonly given for six cycles and continued after surgery for 12 more cycles (for a total of 29 weeks). The tumor is relatively resistant to radiation therapy, which is usually reserved for cases in which local control cannot be achieved surgically.[100] Surgical procedures usually fit into two categories: limb preservation or salvages, or amputation with prosthetics. There are a number of versions of each type of surgery.[100,101] When chemotherapy is used with surgery in nonmetastatic patients, long-term (2–5 years) DFS is 50% to 85%.[100,101]

ROLE OF CHEMOTHERAPY IN TREATMENT

CASE 95-3

QUESTION 1: G.C. is an 18-year-old male with a 2- to 3-month history of left shoulder pain. A tumor is found on radiograph, and biopsy confirms a high-grade conventional osteosarcoma of the left proximal humerus. No apparent

metastases are found with CT and bone scans. Renal function, left ventricular ejection fraction, and hearing tests are all within normal limits. G.C. begins neoadjuvant chemotherapy consisting of high-dose methotrexate alternating with cisplatin and doxorubicin. Six cycles of this chemotherapy (cisplatin/doxorubicin twice and high-dose methotrexate four times) will be given before his surgery, after which he will receive two more cycles of cisplatin/doxorubicin, each followed by two cycles of methotrexate, then two more cycles of doxorubicin, each followed by two cycles of methotrexate.

What is the goal of chemotherapy? What is the role of presurgical (neoadjuvant) chemotherapy in G.C.?

GOAL OF CHEMOTHERAPY

Because G.C.'s osteosarcoma is in his proximal humerus, the surgeon can remove the primary tumor using one of the various operations described in the literature.[100,101] Limb salvages typically work well in the upper extremities, with fewer complications than when they are used for lower extremities. Because patients with osteosarcoma usually die from metastases, the goal of the chemotherapy is to eradicate micrometastases, which are present more than 80% of the time, as discussed in the previous section. Neoadjuvant chemotherapy of osteosarcoma was developed to treat micrometastases while waiting for limb salvage surgeries to be arranged, performed, and healed. Neoadjuvant therapy may improve limb-sparing surgery by shrinking the tumor; it also allows histologic grading of the response to initial chemotherapy at surgery, a prognostic factor for risk of relapse (see Case 95-3, Question 2). However, no convincing evidence to date indicates that DFS is better for patients who receive neoadjuvant chemotherapy relative to those who receive their chemotherapy as adjuvant therapy.[100] In G.C., a titanium bone implant was placed where the diseased humerus was removed. The ease of doing this surgery may have been enhanced by neoadjuvant chemotherapy-induced shrinkage of the tumor.

PROGNOSTIC FACTORS

Case 95-3, Question 2: At surgery, G.C.'s tumor shows excellent histologic response, shown by 99% necrosis of the tumor sample. At diagnosis, his LDH

was 220 units/L. How do these prognostic factors affect the choice of therapy in osteosarcoma?

Conventional staging systems do not correlate well with prognosis for most bone cancers. Clinically apparent metastases or a location that does not allow complete surgical removal of the primary tumor are associated with a poor prognosis.[100,101] Newer surgical techniques and treatments have improved the prognosis with 20% to 30% of metastatic patients cured using neoadjuvant chemotherapy and surgery. Other potential prognostic factors have been identified; however, few of these factors have been used to stratify patients to different treatment regimens. G.C. has a minimally elevated LDH consistent with a relatively small tumor mass, although this is not used to stratify for treatment. The percentage necrosis of the tumor at surgery correlates with risk of recurrence. In current studies, patients with >90% tumor necrosis after six cycles of neoadjuvant chemotherapy are considered good risk and are treated with standard chemotherapy such as G.C. is receiving. Patients whose tumors have less necrosis at surgery are considered to be standard risk, and they have a higher risk of treatment failure. No treatment modifications to date have demonstrated better outcomes for these patients than the good risk protocol described above.

DELAYED CLEARANCE AFTER HIGH-DOSE METHOTREXATE

Case 95-3, Question 3: After reconstructive surgery using a titanium implant, G.C. restarts his chemotherapy. During his fourth cycle of chemotherapy, after high-dose methotrexate is given, G.C.'s peak methotrexate concentration is 1300 micromolar (μM) and the 72-hour concentration is 0.22 μM (normal, ≤0.1 μM at 72 hours). Urine specific gravity has remained at 1.010 or less, urine pH between 7 and 8, and urine output has been >2 to 3 mL/kg/hour, which, according to guidelines, suggest a reduced risk of methotrexate-induced nephrotoxicity. His creatinine has increased from 0.9 to 1.1 mg/dL (eGFR of 106 mL/minute/1.73 m^2); he does not have any signs or symptoms of methotrexate toxicity in spite of his delayed clearance. Leucovorin rescue (15 mg IV every 6 hours beginning at hour 24) is continued. What potential problems could be causing his retention of methotrexate?

Accumulations of protein-containing fluids (called third spaces), such as pleural effusion and ascites, or GI obstruction, may retain methotrexate and slow the terminal excretion.[109–111] Slow excretion of methotrexate allows more proliferating cells to be exposed to methotrexate during the S phase of the cell cycle, increasing the cytotoxicity and resulting in more mucositis and myelosuppression. Some host-related factors, such as biologic sex (males more than females), race/ethnicity, and germline genomics (eg, single-nucleotide polymorphisms) may affect methotrexate pharmacokinetics and pharmacodynamics.[112–116] Many drugs interact with methotrexate, which can also slow its excretion.[113,117,118] Cisplatin may reduce the excretion of methotrexate because of the risk of platinum-related nephrotoxicity, especially at cumulative cisplatin doses >300 mg/m^2. G.C. has received four doses of 120 mg/m^2 (480 mg/m^2 total dose) of cisplatin, which may have contributed to the reduced methotrexate excretion. He has not received other nephrotoxic agents concomitantly, such as aminoglycosides or amphotericin B. Weak organic acids, such as salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), penicillins, or trimethoprim–sulfamethoxazole (TMP–SMX), can compete with methotrexate for renal tubular secretion via the organic anion transport system.[119] A single-center study suggested that prophylactic TMP–SMX may not pose a serious drug interaction risk with high-dose methotrexate, although this practice is not yet widely adopted.[120] Lastly, proton-pump inhibitors may directly inhibit renal transporter proteins and have been reported to delay methotrexate excretion.[118,121,122]

Although G.C.'s serum creatinine appears to be the same that it was at diagnosis (1.1 mg/dL), serum creatinine is not always a good indicator of renal function, so it is possible that G.C. has had some renal damage that is not apparent from his serum creatinine concentrations.[62] A measured creatinine clearance was 176 mL/minute/1.73 m^2 at diagnosis, and a repeat at this point is 106 mL/minute/1.73 m^2. Measurements and estimations of glomerular filtration are not well correlated in children with cancer.[62,64,123] Although the reduced renal clearance may be contributing to a slight

delay in clearance, it is not clear if this is because of normal variation or a specific pathology; future courses of methotrexate need close monitoring.

LEUCOVORIN RESCUE

CASE 95-3, QUESTION 4: How long should leucovorin be administered to G.C.?

Leucovorin is a tetrahydrofolate that bypasses methotrexate's block of dihydrofolate reductase and reduces the toxicities of high-dose methotrexate. It therefore can be used as a form of methotrexate rescue. Cytotoxic effects of methotrexate depend on concentration and duration of exposure.[124] Many high-dose methotrexate protocols continue leucovorin rescue until serum methotrexate concentrations are <0.1 μM, which would be expected to occur ~72 hours after a 12 g/m^2 dose infused over 4 hours. Because G.C. has delayed methotrexate clearance with persistence of methotrexate levels still above 0.1 μM at 72 hours, prevention of GI and bone marrow cytotoxicity may require continuation of leucovorin rescue until methotrexate concentrations are <0.05 μM.[117] For G.C., methotrexate concentrations did not fall below 0.1 μM until 108 hours after his dose; thus, leucovorin was continued 24 hours past that time to ensure presence until methotrexate fell below 0.05 μM. Other considerations may also be important in patients receiving leucovorin rescue. Because of the competitive nature of leucovorin rescue, higher leucovorin doses may be needed for patients with excessively high methotrexate concentrations.

Methotrexate concentrations above a certain threshold or for a certain duration of time can place patients at high risk for methotrexate toxicity.[125] Methotrexate doses (12 g/m^2) infused over 4 hours are designed to produce peak methotrexate concentrations in the blood of 1000 μM, followed by <10 μM at 24 hours, 1 μM at 48 hours, and 0.1 μM at 72 hours. Higher concentrations may result in greater toxicity and additional leucovorin doses may be necessary.[117,125] If G.C.'s methotrexate concentrations had remained

more than 1 μM 48 hours after the beginning of the infusion, it is recommended to increase the leucovorin dose to 15 mg/m^2 every 3 hours until methotrexate concentrations fall below 0.05 μM.[117,126] If concentrations exceed 5 μM 48 hours or more after the methotrexate dose, higher doses of leucovorin are recommended (150 mg/m^2 every 3 hours). Oral leucovorin administration should not be used when the patient has emesis or requires large oral doses (about 40 mg), which are often poorly absorbed.[126] If a patient on high-dose methotrexate experiences renal failure and has elevated concentrations of methotrexate, glucarpidase may be used in addition to the leucovorin. Glucarpidase hydrolyzes methotrexate into inactive compounds and is very effective at quickly lowering methotrexate concentrations; however, it generally needs to be administered within the first 96 hours after the methotrexate dose. In spite of rapid reduction of methotrexate concentrations, it is not clear the extent to which it lowers morbidity or mortality from the high levels and delayed clearance.[117,126]

Rhabdomyosarcoma

Description, Epidemiology, and Pathophysiology

Rhabdomyosarcoma is a soft tissue tumor of mesenchymal origin.[127] It is the most common soft tissue sarcoma of childhood, occurring in about 3% of all children and adolescents with cancer.[1] The annual incidence in the United States is about 4.5 cases per 1 million children, representing about 350 new cases per year.[127] About half of all cases occur in the first decade of life.[128]

The two most common histologic types of rhabdomyosarcoma in children are embryonal (57% of cases) and alveolar.[127] Embryonal rhabdomyosarcoma cells resemble striated muscle and occur most frequently in young children with involvement in the head and neck or genitourinary tract. Alveolar rhabdomyosarcoma cells resemble lung parenchymal cells and occur more frequently in older children or adolescents with involvement of the trunk or extremities. Generally, patients with alveolar rhabdomyosarcoma have a poorer

prognosis than patients with the embryonal type. Recent studies suggest that alveolar-appearing rhabdomyosarcoma cells without the *PAX3*/*PAX7-FOXO1* fusion gene are molecularly and clinically identical to embryonal and may be treated as such, although this is not current practice in protocols.[129,130]

Most patients with rhabdomyosarcoma have no known risk factor or genetic predisposition to developing the tumor. However, some genetic factors may be associated with rhabdomyosarcoma, including Li–Fraumeni syndrome (germline *TP53* mutations), *DICER1* syndrome, neurofibromatosis type 1 (*NF1*), and Costello syndrome (*HRAS* mutations).[131–136]

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of rhabdomyosarcoma varies with its location (head and neck, genitourinary, parameningeal, extremity, orbit, as noted above). Diagnosis involves a biopsy of the tumor, which can be examined for appearance under an electron microscope, and a number of tests are run to identify molecular markers to differentiate it from other small, round cell tumors.[127] Patients with localized disease at presentation have a high chance for cure using conventional, multimodal therapies.[137,138] Conversely, patients with unresectable or metastatic disease have a higher risk for relapse and poor prognosis.[139] Other poor prognostic features include age (<1 year or older than 9 years at diagnosis), tumor size >5 cm, alveolar histology, lymph node involvement at diagnosis, site of primary tumor (biliary, extremities, trunk, and abdomen being some of the least favorable), and certain molecular features.[127]

TREATMENT OVERVIEW

Treatment combines surgery, radiation, and chemotherapy. Complete surgical removal is often difficult, given the locations and infiltrative characteristics of rhabdomyosarcoma. Because good local control improves the prognosis,[127] radiation is generally administered after the surgery. Combination chemotherapy is necessary because the 5-year survival with local control alone is only 10% to 30%. More

than 90% of patients at low risk (those in subgroup A with localized, embryonal tumors in favorable sites) may expect long-term survival with the two-drug regimen of vincristine and dactinomycin (VA), with or without radiation based on the extent of disease.[140] Patients with more advanced disease will require the addition of cyclophosphamide. The vincristine, dactinomycin, and cyclophosphamide (VAC) regimen has been used extensively to treat rhabdomyosarcoma.[127] Unfortunately, the dose of cyclophosphamide required to achieve long-term cure can also induce sterility. Attempts to limit both radiation exposure and the cumulative cyclophosphamide dose have not always been successful, with some patients experiencing suboptimal survival with reduced intensity regimens.[141,142] Other agents producing responses include combinations of vincristine, doxorubicin, and cyclophosphamide; ifosfamide and etoposide; and vincristine and irinotecan.[127] Using the combination of VAC with local control of surgery or radiation in the fourth Intergroup Rhabdomyosarcoma Study (IRS) resulted in a 76% failure-free survival for patients with nonmetastatic disease.[138]

CLINICAL PRESENTATION, PROGNOSTIC FACTORS, AND TREATMENT

CASE 95-4

QUESTION 1: F.J. is a 2-year-old female with a rapidly enlarging mass on the lateral head of the gastrocnemius muscle in the right calf. Bone marrow and scans are negative for metastatic disease. The diagnosis is embryonal rhabdomyosarcoma, stage III (unfavorable site and >5 cm mass). Initial expectations were that gross residual tumor would remain after the surgery, consistent with clinical group III. Chemotherapy consists of 3-week cycles of vincristine 0.05 mg/kg (days 1, 8, and 15 of some cycles but day 1 only of some cycles); dactinomycin 0.045 mg/kg on day 1 of each cycle; and cyclophosphamide 73 mg/kg on day 1 of each cycle with mesna to reduce the risk of hemorrhagic cystitis. Because of reports of hepatotoxicity during a prior study, especially in patients younger than age 3 years, the protocol recommends all three drugs be dosed in milligram/kilogram for children younger than age 3 years. Prophylactic TMP–SMX is begun at 150 mg/m^2/day (TMP)

divided twice daily for three consecutive days/week. After each course of chemotherapy, F.J. is to receive filgrastim 5 μg/kg/day subcutaneously for 14 days or until the absolute neutrophil count (ANC) is >750 cells/μL.

What factors in F.J. are associated with a good prognosis? What chemotherapy treatment would be most appropriate for F.J.?

The embryonal histopathologic classification has a better prognosis than the alveolar one, although evidence indicates that the location of the primary tumor is more important than the histology.[127] The primary site affects resectability, route of spread, and how early the diagnosis is made. Additionally, age between 1 and 9 years is associated with a better prognosis. The IRS have used a clinical grouping system (groups I–IV), which is based on spread of the disease and extent of resection. This system has been useful because of its correlation with prognosis where complete surgical removal and lack of metastases both correlate with good prognosis.[127] The fourth and fifth IRS studies compared the clinical grouping system with a TNM (tumor, lymph node, metastasis) staging system similar to that used in adult cancers. Although the two systems may result in different disease stages for a specific patient, both are considered valuable and current protocols use both systems.

In rhabdomyosarcoma, the tumor site is one important part of the T rating in the staging system. F.J.'s tumor involves an unfavorable site (the calf) and is >5 cm, making it stage III. Although her tumor was expected to be clinical group III, after a good response to neoadjuvant chemotherapy, a complete resection was performed, making it clinical group I. This suggests that she has an 80% to 90% chance of 3-year survival based on the IRS-II, IRS-III, and IRS-IV results.[127,137,138,143] The IRS-V classified patients as having low-risk, intermediate-risk, or high-risk disease. Patients at low risk include those with embryonal rhabdomyosarcoma at favorable sites, or at unfavorable sites with no more than microscopic residual tumor.[127] Patients at intermediate risk have the embryonal subtype with gross residual tumor or the alveolar subtype without metastatic disease.

Patients at high risk include those with metastatic alveolar or embryonal disease.

Chemotherapy for many patients at low risk is limited to vincristine and dactinomycin.[127] Most at intermediate risk are treated with VAC. Patients at high risk have not responded well in the past and are candidates for trials with newer drugs added to the VAC. A recent study added courses of vincristine and irinotecan, ifosfamide and etoposide and vincristine, doxorubicin, and cyclophosphamide (COG ARST0431), and 3-year event-free survival appears good compared to historical data for patients with 0 to 1 higher-risk features.[144] F.J. would be in the low-risk group; however, her large initial tumor justifies adding cyclophosphamide to the vincristine and dactinomycin as in the intermediate-risk regimen. Because radiation to her leg would stop bone growth and her surgical margins were tumor free, no radiation is being administered.

TRIMETHOPRIM–SULFAMETHOXAZOLE PROPHYLAXIS AND FILGRASTIM FOR MYELOSUPPRESSION

Case 95-4, Question 2: What are the reasons for treating F.J. with TMP–SMX and filgrastim?

F.J.'s VAC regimen was associated with a high incidence of neutropenic fevers even during the pilot studies. Because of the frequency of severe myelosuppression, TMP–SMX is used until 6 months after chemotherapy for prophylaxis against *Pneumocystis jirovecii*, an opportunistic pathogen. Filgrastim is used to minimize neutropenia so that the chemotherapy dose intensity can be maintained.

RENAL FANCONI SYNDROME WITH IFOSFAMIDE

Case 95-4, Question 3: F.J.'s mother read on the Internet about a patient with rhabdomyosarcoma who had received vincristine, ifosfamide, and etoposide and was cured. She wants to know why that regimen is not being used for her daughter. What would be the rationale for F.J.'s regimen?

The IRS-IV results for local or regional disease (intermediate risk) demonstrated no advantages of vincristine, ifosfamide, and etoposide or vincristine, dactinomycin, and ifosfamide over the standard VAC treatment.[138] Additionally, the ifosfamide-containing regimens caused more toxicity. Ifosfamide has been associated with renal Fanconi syndrome, a proximal tubular defect that is characterized by wasting of electrolytes, glucose, and amino acids, as well as renal tubular acidosis and, in a minority of cases, an increased serum creatinine. Data suggest that the risk of Fanconi syndrome is increased in children that are younger than 3 years of age; have received total ifosfamide doses >72 to 100 g/m^2; have hydronephrosis, a single kidney, or an elevated serum creatinine; or have received previous platinum therapy.[145–147] During each course of her chemotherapy, F.J. exhibits ketonuria; however, this is not a toxicity of her chemotherapy. Ketonuria is caused by her mesna therapy, which has been reported to routinely cause false-positive ketone tests.[148]

ACUTE LYMPHOBLASTIC LEUKEMIA OF CHILDHOOD

Acute leukemia is a malignancy of blood-forming cells involving the lymphoid and myeloid cell lines. The two most common types of childhood leukemia are acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML), with the former accounting for 75% of cases and the latter for ~15%. ALL is the most common childhood cancer, with ~3000 new cases of childhood ALL diagnosed each year in the United States.[149] A distinct peak incidence occurs at ages 2 to 3 years (>80 cases/million) and then decreases substantially for 8- to 10-year-olds (20 cases/million). A higher incidence of ALL is seen in White children than in African American children. This racial difference is most apparent in the 2- to

3-year-old age group, with a nearly threefold greater incidence rate for White children.[149,150] Before the early 1970s, ALL was a fatal illness with most children succumbing to their disease within 2 to 3 months after diagnosis. Today, around 90% of children achieve prolonged survival with antileukemic therapy.[149,150] New innovations in therapy for ALL continue to improve survival while decreasing the long-term morbidity associated with treatment.[27]

Epidemiology and Etiology

The etiology of ALL is largely unknown with only a small percentage of cases being associated with environmental factors such as chemical or radiation exposure.[27,151] Genetic factors may also increase the risk of ALL, most notably Trisomy 21 or Down syndrome. Children with Down syndrome have a 20-times higher incidence of developing ALL.[152] Germline mutations in ETV6 and PAX5 have been found in rare cases of familial ALL.[27]

Pathophysiology

The development of ALL involves replacement of normal bone marrow elements with a clone of immature lymphoid cells. The essential lesion in ALL is stabilization of a malignant cell in the lymphocyte differentiation process. Many factors are involved in the control of normal cellular proliferation. Leukemia may represent a disruption in one or more of the normal relationships within the cell proliferation pathway, such as an abnormal response to lymphoid cell-growth factors.[27,153]

With the availability of classification systems of lymphoblasts based on morphology, immunology, and cytogenetics, it has become clear that ALL is a heterogeneous disease. This is especially true regarding cytogenetic abnormalities. The immunologic heterogeneity results from leukemic transformation at various stages of lymphocyte differentiation. Molecular classification involving gene expression profiling allows for further classification of ALL cytogenetic subtypes,

helping predict response to therapy.[154] As discussed later in this section, these classifications have important prognostic value.

Clinical Presentation

The signs and symptoms of ALL are nonspecific and many are shared with other childhood diseases such as juvenile idiopathic arthritis (JIA). These signs and symptoms reflect uncontrolled growth and differentiation of the leukemic clone and the resulting deficiency in normal bone marrow elements, namely neutrophils, red blood cells (RBCs), and platelets. Frequent clinical findings include fever (53%), bleeding (38%), and bone pain (43%).[153,155] Bone pain is believed to be the result of hypercellular bone marrow and infiltration of leukemic lymphoblasts into pain-sensitive structures such as the periosteum. Although bone pain may be severe, it quickly resolves once chemotherapy is initiated. On physical examination, many patients have pallor (54%), bruising (52%), splenomegaly (61%), or hepatomegaly (64%).[155]

At diagnosis, at least 59% of patients have a normal or low WBC count; the remainder have elevated counts.[27,153] The WBC differential typically shows a low percentage of neutrophils and bands with a marked lymphocytosis. Lymphoblasts may be present in the peripheral blood even with a low WBC count, but they are more likely when the WBC count is elevated.[156] A normochromic, normocytic anemia, along with thrombocytopenia, is present in most patients.[27,153]

Diagnosis

A bone marrow aspirate and biopsy are usually necessary to confirm the diagnosis of ALL. In patients with elevated WBC counts, the diagnosis can be confirmed by studies of lymphoblasts in the peripheral blood. The diagnosis of ALL is made when at least 25% of lymphoid cells in the bone marrow are blasts.[153] Most patients with ALL have far greater than 25% blasts and many have complete

replacement of bone marrow with lymphoblasts. Once a child is diagnosed with ALL, it is important to determine the disease characteristics that influence treatment decisions and prognosis.[153,157]

Prognostic Variables

Significant research has focused on risk stratification of pediatric patients with ALL to allow for risk-adapted treatment regimens. Clinical findings present at diagnosis, immunologic and genetic properties of leukemic cells, and evaluation of early response to treatment can predict a specific patient's risk of relapse. Children with ALL are classified by their risk of relapse into one of the following categories: standard, high, or very high risk.[27]

CLINICAL VARIABLES

Childhood patients with ALL are assigned an initial risk group based on age and WBC count at presentation. These variables are referred to at the National Cancer Institute (NCI) criteria.[156] More recently, the presence of central nervous system (CNS) leukemia and/or testicular involvement has been added as a high-risk feature.[158]

Patients younger than 1 year or older than 9.99 years at diagnosis tend to have worse prognoses.[156] Older patients are more likely to have unfavorable immunophenotypes and genetic features such as T-cell ALL or BCR-ABL fusion, while the favorable features ETV6-RUNX1 and hyperdiploidy are more common in children ages 1 to 9.99 years.[159]

Age is particularly important for infants in which survival is exceedingly poor compared with other age groups and is frequently associated with the unfavorable KMT2A (formerly MLL) gene rearrangement. For infants, even with intensified chemotherapy regimens, long-term, DFS is <50%.[160] Approaches to improve outcomes in this age group have included stem cell transplant and targeted therapy with clinical research ongoing.

The initial WBC count is an important predictor of outcome in childhood ALL and retains its significance after adjustment for other important prognostic criteria.[153] Children with the highest WBC counts at presentation have the shortest duration of complete remissions. Although exactly where the demarcation line is for predicting a good or a poor prognosis is unknown, an initial WBC count >50,000 cells/μL is generally associated with a poor prognosis.[153,156]

IMMUNOLOGIC VARIABLES

ALL is classified into different immunologic subsets based on cell-surface markers or antigens present on the leukemic lymphoblasts at diagnosis. These can be categorized as cells of B-cell and T-cell origin. The B-cell lineage is further classified into subtypes reflecting the various stages of differentiation at which leukemia may develop. Approximately 15% to 20% of children with ALL have leukemia with a T-cell lineage, whereas more than 80% have leukemia of pre–B-cell or early pre–B-cell origin.[27,159] Leukemia with a mature B-cell origin is referred to as Burkitt leukemia and comprises 1% to 2% of leukemia in children.[159,161]

Burkitt leukemia has traditionally been associated with a poor prognosis, but prognosis has improved greatly with the advent of short-term, very intensive chemotherapy.[27,153] Although differences in outcome have been noted among the B-cell subtypes, when other prognostic factors are considered and when effective therapy is used, these differences may no longer be evident. At present, immunologic features that differentiate B-cell precursor, T-cell, and mature B-cell ALL are clinically important because different types of chemotherapeutic strategies are used for these three immunophenotypes.

Patients with T-cell ALL have several distinguishing features, including a greater likelihood of being male, Black, older, high initial WBC counts, and the presence of a mediastinal mass or initial leukemic involvement of the CNS.[27] Patients with T-cell ALL historically have had a decreased survival, although more intensive

treatment is improving their outcomes.[27] Studies with more intensified therapy also demonstrate no difference in relapse between T-cell and B-cell lineage ALL, although patients with T-cell ALL tend to relapse much earlier.[162–164]

CYTOGENETIC VARIABLES

Advances in chromosomal analysis have improved the understanding of ALL biology. Abnormalities in either chromosome number (ploidy) or structure of the leukemic clone have been found in 60% to 75% of ALL cases. Many of these abnormalities appear to have prognostic importance.[27] Ploidy is represented by the DNA index. A value of 1.0 indicates a normal number of chromosomes, and a value >1.0 indicates an increased number of chromosomes by a multiplication factor of the normal chromosome number. Children with leukemia blasts containing more than 50 chromosomes (DNA index ≥1.16, hyperdiploid) have an increased probability of continuous complete remission versus patients with leukemia blasts containing a diploid chromosome complement or with a DNA index <1.16.[159] ALL cells with a higher DNA index are more sensitive to antimetabolites (eg, mercaptopurine) and asparaginase.[165] In contrast, patients with hypodiploidy (<44 chromosomes and, in particular, those with 24–28 chromosomes) have significantly worse outcomes with an expected 40% EFS.[159] Hyperdiploidy is seen in 30% of cases of childhood ALL, whereas hypodiploid is observed in <5% of patients.[159,161]

Translocations are the most common structural abnormalities occurring in leukemic cells, providing insight into expected treatment outcomes.[151,161] Certain translocations are associated with treatment failure and relapse.[27] The translocation commonly associated with infants is called KMT2A located at 11q23 (also called MLL) and is associated with poor outcomes.[27,159] Commonly known as the Philadelphia chromosome, the *BCR-ABL* fusion transcript t(9;22)(q34.1;q11.2) occurs in 3% to 5% of childhood ALL cases.[27] Historically, children with the Philadelphia chromosome were considered at very high risk of relapse; however, the addition of

tyrosine kinase inhibitors such as imatinib and dasatinib to traditional chemotherapy has dramatically improved survival in this group of patients.[166,167]

An emerging group of translocations identified as Philadelphia chromosome-like involves various activating mutations involving ABL-class kinases other than BCR-ABL1 or the JAK-STAT pathway. These translocations also are recognized to have a higher incidence of relapse, although ongoing research is exploring targeted therapies such as ruxolitinib and dasatinib to improve outcomes.[159,161] Identification of other unfavorable translocations such as iAMP21, TCF3-PBX1, and IKZF1 have allowed for augmented treatment and improved outcomes in select patients as well.

One of the most common fusions found in 25% of patients with ALL is ETV6-RUNX1 (formerly TEL-AML1) and is associated with cure in over 90% of patients.[27,159] Other favorable changes include trisomies of certain chromosomes, specifically chromosomes 4, 10, and 17.[168]

MINIMAL RESIDUAL DISEASE

One of the most powerful ways to affect patient outcome is to measure response to current therapy and make adjustments when a patient is not responding as expected. Historically, bone marrow and peripheral blood evaluations were taken at various time points during treatment to gauge an early response to leukemia therapy. A major breakthrough in evaluating response to ALL therapy involves measurement of minimal residual disease (MRD) using flow cytometry and polymerase chain reaction (PCR) to detect a leukemia burden in the bone marrow of as low as 1 cell per 100,000 normal cells.[169–171]

A variety of lymphoblast characteristics, including gene fusion transcripts, immunophenotype, and antigen receptor gene rearrangements, may be relied on for MRD detection in children with ALL. Although specific fusion transcripts can be relied on as PCR targets in only one-third of childhood ALL cases, clonal antigen receptor gene rearrangements occur in virtually all cases.[169–171] It is

now established that the presence of MRD is an important prognostic factor, regardless of the patient's initial WBC count or age at presentation. A large study of the prognostic value of MRD for day-7 blood samples and for bone marrow samples at both the end of the induction and consolidation phases demonstrated that MRD at the end of the induction phase was the most important predictor of prognosis when compared to other laboratory and clinical factors.[170] Data from this study for end of induction MRD demonstrated major differences in 5-year event-free survival as follows: 88% for MRD-negative, 74% for MRD of 0.01% to 0.1%, 63% for MRD of 0.1% to 1%, and <40% for MRD >1%. Patients with MRD detectible at the end of consolidation had a poor prognosis with only 39% EFS. Monitoring of MRD is now established in the management of childhood ALL and is being used to risk-stratify treatment in current frontline leukemia studies.[27,170]

Overview of Treatment

The treatment for pediatric ALL is organized into different phases of chemotherapy. Treatment begins with induction therapy, which typically includes three or four systemic agents in addition to CNS preventive therapy. The intensity of induction therapy is based on the patient's NCI risk group. Induction therapy is designed to induce a complete remission and typically lasts 28 days. After induction therapy, the next phase of therapy can be defined as postinduction therapy and consists of several different cycles of chemotherapy referred to by such terms as consolidation, delayed intensification, and interim maintenance. This phase of intensive chemotherapy usually uses combination approaches that are somewhat different than induction therapy and that are designed to kill leukemia cells in the cell cycle that were not destroyed by induction therapy. Postinduction therapy is continuing to undergo substantial revision as studies determine which therapy components are optimal for various patients. The duration and intensity of this phase is tailored based on certain prognostic features of leukemia as outlined above.

The third phase of therapy is termed the maintenance phase, and it represents the longest phase of chemotherapy for these patients, taking ~2 years to complete. Maintenance therapy is typically less intensive than the previous phases and consists mostly of continuous oral chemotherapy with infrequent intravenous and CNS therapy. In general, treatment intensity diminishes from the induction/consolidation phase to the maintenance phase.

REMISSION INDUCTION THERAPY

Goal of induction

CASE 95-5

QUESTION 1: J.B. is a 4-year-old male presenting with a 2-week history of an upper respiratory tract infection and a 1-week history of otitis media. His symptoms have worsened, and he now presents with a nosebleed and fatigue. Physical examination reveals appreciable pallor and hepatosplenomegaly. A complete blood count (CBC) with differential reveals a normochromic, normocytic anemia with the following:

Hematocrit (Hct), 15.7%
Hgb, 5.7 g/dL
WBC count, 4300 cells/μL
Platelet count, 13,000 cells/μL

A differential on the WBC count reveals 82% lymphocytes (normal, 30%–40%), 7% neutrophils (normal, 50%–60%), and 11% lymphoblasts (normal, 0%). Based on these findings, a bone marrow biopsy is performed that reveals 95% lymphoblasts. A diagnosis of ALL is made. The immunologic class is early pre–B cell based on CD10 and CD19 positivity. Radiography of the chest does not reveal a mediastinal mass, and a lumbar puncture shows that there are no leukemic lymphoblasts in the cerebrospinal fluid. J.B. is hydrated, alkalinized, and treated with oral allopurinol 200 mg/m^2/day, with a plan to institute induction therapy the next day. Within a few days, J.B. will be treated with several drugs for his leukemia.

What is the goal of the induction therapy that J.B. will receive?

The goal of induction therapy is complete remission (ie, the inability to detect leukemic cells in the peripheral blood or the bone marrow by morphologic microscopic evaluation). J.B.'s peripheral blood values must be within the normal range, and the bone marrow

morphology must reveal <5% lymphoblasts with a goal MRD <0.01% by the end of induction therapy (ie, day 29). This definition also assumes the absence of lymphoblasts in the cerebrospinal fluid (CSF). Although these findings indicate an adequate response to chemotherapy, they do not indicate a cure. Most patients have a total of 10^{12} cells at diagnosis and successful induction regimens reduce this cell load by 99% to 10^{9}.[172] Therefore, continuation of therapy will be required for J.B. to further reduce the leukemic cell population and to increase his chances of long-term survival. Without continuation of therapy, the majority of patients with ALL will relapse within a few months.[27,158]

Induction combination chemotherapy

CASE 95-5, QUESTION 2: Which agents should be used to achieve complete remission?

The agents most commonly used in remission induction therapy are vincristine, prednisone or dexamethasone, pegaspargase, and daunorubicin (**Table 95-4**).[173,174] Dexamethasone has supplanted prednisone as the corticosteroid used during induction therapy in many cases. This is based on earlier work showing that dexamethasone has greater CSF penetration.[175] In patients with standard-risk ALL, a randomized comparison of dexamethasone to prednisone for induction therapy showed a lower CNS relapse rate in the dexamethasone group.[173,175] However, the use of a 28-day course of dexamethasone during induction for patients with high-risk ALL was also associated with an increased risk of infectious complications and avascular necrosis of the joints in adolescent patients.[176] This has led to the removal or alteration of dexamethasone during induction therapy in high-risk patients. It is plausible that the combination of dexamethasone and the intensive high-risk ALL induction chemotherapy increases the risk of infection because it causes more myelosuppression.

Table 95-4

Systemic Induction Regimens for Childhood Acute Lymphocytic Leukemia

Agent	Route	Dose/Schedule
Three-Drug Induction Regimen		
Prednisone	PO	60 mg/m^2/day × 28 days
Or		
Dexamethasone	PO	6 mg/m^2/day × 14[a] or 28 days
With		
Vincristine	IV	1.5 mg/m^2/week (max 2 mg) × 4 doses
And		
Pegaspargase	IM or IV	2500 units/m^2 × 1 dose
If Four-Drug Induction		
Daunorubicin	IV	25 mg/m^2/week × 4 doses

IM, intramuscularly; IV, intravenously; PO, orally.

[a]Dexamethasone duration may be shortened from 28 to 14 days when given as part of a four-drug induction regimen including daunorubicin.

Sources: Maloney KW, Devidas M, Wang C, et al. Outcome in children with standard-risk B-cell acute lymphoblastic leukemia: results of Children's Oncology Group trial AALL0331. *J Clin Oncol.* 2020;38:602–612; Bassen R, Holezer D. Modern therapy of acute lymphoblastic leukemia. *J Clin Oncol.* 2011;29:532–543.

No chemotherapy drug meets the criteria of an ideal agent (ie, toxic to leukemic cells only and active in all phases of the cell cycle). Corticosteroids, vincristine, and asparaginase come closest to this ideal in terms of activity, primarily against lymphoblastic leukemia, because these agents are selectively toxic to the leukemia cells, whereas sparing normal bone marrow elements. To improve the success in attaining complete remission, additional agents have been added to vincristine, corticosteroid, and asparaginase (see Table 95-4). The most frequently used additional agent is an anthracycline, such as daunorubicin or doxorubicin. Use of at least a three-drug induction regimen is the current standard of care for children at low or intermediate risk of relapse and results in

improvements in both remission rate and duration versus less intensive therapy.[173] Currently, a four-drug regimen, or an even more intensive induction regimen consisting of more than four drugs, and often for a duration of more than 4 weeks, is used for children at high risk of relapse and adult patients with ALL.[177–179]

Intensive induction treatment has benefits for the majority of children with ALL. This treatment strategy supports the hypothesis of Goldie and Coldman[180] that intensification of early treatment may decrease the chance that drug resistance will develop. This may therefore increase the proportion of long-term relapse-free survivors. Induction therapy is determined based on clinical findings, such as age at diagnosis and initial WBC count. Based on these prognostic variables, J.B. is a patient with a low risk of relapse. A three-drug induction regimen consisting of vincristine, dexamethasone, and pegaspargase is recommended to optimize his chances for long-term DFS.[173,176,181] Additional laboratory testing (eg, bone marrow analysis for remission and MRD) will be relied on to design his postinduction therapy.

Vincristine Toxicity

Case 95-5, Question 3: J.B. is discharged from the hospital during the second week of induction chemotherapy. Results of his CBC and differential indicate that he is responding well to his chemotherapy (ie, WBC count 2600 cells/μL, neutrophils 69%, lymphocytes 22%, platelets 229,000 cells/μL, Hct 28.6%, and lymphoblasts 0%). However, during the third week of induction chemotherapy, J.B. exhibits severe abdominal pain. It is discovered that he has not had a bowel movement in 6 days. J.B. has also been exhibiting "acting out" behaviors in recent days. How might these symptoms be explained?

The use of vincristine is associated with an autonomic neuropathy, which may substantially reduce GI motility; in severe cases, paralytic ileus may result.[182] Constipation is often accompanied by colicky abdominal pain, which may be quite distressing. These symptoms usually become apparent 3 to 10 days after drug administration and resolve over several days. Prophylactic use of a stool softener

(docusate) or laxative (polyethylene glycol) may lessen the severity of J.B.'s constipation and facilitate regular stooling. This regimen should have been instituted with his first dose of vincristine.

J.B.'s emotional changes are likely the result of the dexamethasone he is receiving. Emotional lability, sleep disturbances, depressed mood, and listlessness have occurred during corticosteroid therapy in children with ALL.[183] These behavioral changes can be quite disruptive, and parents should be prepared for them in advance. Behavioral disturbances typically resolve within 2 weeks after corticosteroid discontinuation.[162]

INTRATHECAL CHEMOTHERAPY PROPHYLAXIS

Case 95-5, Question 4: In addition to the aforementioned drugs, J.B. also receives intrathecal (IT) chemotherapy for CNS prophylaxis with methotrexate at the beginning (week 1) and end (week 4) of induction therapy. What is the purpose of IT chemotherapy?

IT or CNS preventive therapy decreases the chance of relapse within the CNS and improves J.B.'s chance of long-term survival. Before CNS preventive therapy was routine, the CNS was the most common site of leukemic relapse and, thus, predicted bone marrow relapse.[17,27,184–186] Because many antileukemic agents do not distribute well into the CSF, this area becomes a sanctuary site for leukemic lymphoblasts. The aim is to eradicate any CNS leukemic lymphoblasts present at diagnosis and to prevent the emergence of a relapse within the CNS.

Central nervous system preventive therapy options

Case 95-5, Question 5: What are the various treatments available for CNS preventive therapy for J.B.?

All treatment protocols for childhood ALL use some form of CNS preventive therapy, although different regimens are used. The first

successful CNS prophylaxis treatments were 2400 cGy of craniospinal radiation with or without IT methotrexate, which markedly reduced the CNS relapse rate.[17] However, the adverse effects of cranial irradiation were problematic. These included decreased intellectual function, dysfunctions of the neuroendocrine system, and poorer psychosocial functioning. As a result, clinicians sought alternative, potentially safer forms of CNS preventive therapy. Several trials demonstrated effective CNS prevention utilizing systemic plus IT chemotherapy without additional cranial radiation.[184,185,188] Currently, CNS preventive therapy for most patients will include IT methotrexate, triple IT chemotherapy (methotrexate, cytarabine, and hydrocortisone), or IT methotrexate combined with systemic dose–intensified methotrexate, whereas cranial radiation is reserved for only those at highest risk of CNS relapse.

Intrathecal chemotherapy: chronic adverse effects

Case 95-5, Question 6: What are the late adverse effects associated with J.B.'s IT chemotherapy?

The chronic toxicities of IT chemotherapy are difficult to fully evaluate because of the myriad of systemic chemotherapy agents also used in these patients.[17] Although less toxic than cranial irradiation, evidence suggests that IT chemotherapy is associated with some neuropsychologic deficits. At least one study of patients receiving IT chemotherapy without cranial irradiation has demonstrated deficits in higher-order cognitive function tasks and learning disabilities in mathematics. Children who are treated with IT chemotherapy before age 5 years are more likely to experience deficits in the cerebellar-frontal brain subsystem and in neuropsychologic performance. It is unclear whether these deficits translate into significant long-term consequences.

Case 95-5, Question 7: J.B. is at a low risk for CNS relapse, and the decision is made to treat him with IT methotrexate. What dose of IT methotrexate should J.B. receive?

Intrathecal methotrexate dose

High chemotherapy concentrations can be attained within the CSF with relatively low doses because the CSF volume of distribution is small in contrast to the peripheral plasma volume. Drug exposure is also maximized by the longer half-life of most drugs in the CSF.[187] The approach used for IT dosing differs from systemic administration, the latter of which is based on body weight or body surface area. CSF methotrexate concentrations appear to correlate better with patient age than size.[188] The CSF volume in children approaches that of an adult by age 3 years. Because CSF volume does not correlate with body surface area, IT doses based on body size result in subtherapeutic concentrations in young children and potentially toxic concentrations in older children and adults. The age-based dosing regimens shown in **Table 95-5** are less neurotoxic and are associated with a lower rate of CNS relapse than doses based on size.[188] Using this dosing regimen, J.B.'s dose of IT methotrexate should be 12 mg. If triple IT therapy were used, the doses of IT cytarabine and hydrocortisone would be 24 and 12 mg, respectively.

Table 95-5
Representative Dosage Regimen for Intrathecal Chemotherapy Based on Patient Age

Patient Age (years)	Methotrexate (mg)	Hydrocortisone (mg)	Cytarabine (mg)
>1	6	6	12
1	8	8	16
2	10	10	20
3	12	12	24
≥9	15	15	30

Dangers of intrathecal vincristine

Case 95-5, Question 8: J.B.'s IT methotrexate is to be administered on the same day as his vincristine dose. Are there any special precautions that should be taken when these medications are administered in close proximity?

Inadvertent administration of vincristine into the IT space is almost uniformly fatal.[189] Despite widespread educational efforts in hospitals and clinics, and numerous precautionary measures, deaths from the inadvertent IT administration of vincristine still occur. The clinical course in patients mistakenly given IT vincristine has typically progressed from backache and headache on day 1, muscle weakness (generalized) on day 2, apnea on day 5, loss of evidence of electroencephalographic activity by days 7 to 9, and death on day 12. To avoid the tragedy of IT vincristine administration, vincristine should be mixed as a small volume parenteral (ie, minibag) rather than in a syringe, and delivered to an area separate from the administration of IT medications. The Institute for Safe Medication Practices (ISMP) has called on pharmaceutical manufacturers and the Food and Drug Administration (FDA) to modify package labeling to include preparation in a minibag and remove syringe administration information.

TAILORING OF POSTINDUCTION THERAPY

CASE 95-5, QUESTION 9: An analysis of the chromosomes from J.B.'s bone marrow reveals the ETV6-RUNX1 translocation and a DNA index of 1.0. His day-29 bone marrow biopsy has no detectible blasts with MRD of 0.15%. Based on his day-29 (end of induction) bone marrow–positive MRD finding, J.B. is scheduled to receive a more aggressive postinduction chemotherapy regimen. This treatment is chosen because MRD findings are more predictive of the chance for relapse than are his cytogenetics. Although his bone marrow on day 29 indicated a complete morphologic remission, his MRD findings take precedence in defining his further therapy. After completion of the induction phase, J.B. is scheduled to receive an intensified phase of postinduction chemotherapy known as augmented interim maintenance. What is the purpose of postinduction treatment and what are some examples of effective regimens for this phase of treatment?

Postinduction chemotherapy consists of a variety of combinations of chemotherapy typically given on a 2- to 6-week treatment cycle. These different phases of postinduction therapy are known as consolidation, interim maintenance, and delayed intensification. Chemotherapy agents used will include many of the same drugs already used in induction, as well as the addition of methotrexate, cytarabine, thiopurines such as mercaptopurine and thioguanine, cyclophosphamide, and doxorubicin.

Postinduction treatment has proven to be an important strategy for the prevention of relapse in children with ALL and has helped produce event-free survival of >90% in low-risk childhood ALL.[27] To date, the optimum postinduction regimens have yet to be determined, and this remains an area of focused research. A comparison between high-dose methotrexate 5 g/m^2 IV every 2 weeks for four doses and escalating "Capizzi" dose methotrexate (every 10 days, increase by 50 mg/m^2 until toxicity is seen) showed improved 5-year event-free survival (EFS) (79.6% vs 75.4% P = .008) and no increased toxicity in high-risk patients with ALL. In fact, there was a lower incidence of febrile neutropenia in the high-dose methotrexate group compared to the escalating-dose group; 5.1% versus 8.3% respectively (P =.003).[22] Therefore, J.B. would benefit from inclusion of high-dose methotrexate as postinduction treatment.

MAINTENANCE CHEMOTHERAPY REGIMENS

Case 95-5, Question 10: After completion of his induction and postinduction chemotherapy, J.B. is scheduled to receive maintenance (also called continuation) treatment for a total therapy duration of 2 years from the start of his postinduction therapy. His parents question why treatment will be of such a long duration and ask whether this is necessary because J.B. is already in remission. What is the purpose of J.B.'s maintenance treatment for ALL? Which agents should be used in J.B. for this phase of therapy?

Maintenance treatment sustains the complete remission achieved from induction chemotherapy. Early trials have shown that without maintenance treatment, the majority of patients with ALL will relapse.[190] Patients who have successfully responded to induction and postinduction therapy may still have a leukemic cell burden (although undetectable), which must be eradicated by additional treatment. This is supported by the results of bone marrow biopsies from patients who have experienced relapse after several months to years of treatment. The cytogenetic characteristics of the leukemic cells in relapsed patients demonstrate changes similar to those at the time of diagnosis.[191] Maintenance therapy is also supported by the results of MRD studies, which demonstrate that some amount of measurable leukemic cells are still present months after the completion of induction therapy.[170]

Drugs that are effective during induction therapy cannot, by themselves, sustain remission during maintenance therapy.[153,158,194] However, other agents are effective in sustaining a complete remission. Two of the most effective drugs are mercaptopurine and methotrexate. Methotrexate is most effective and least toxic when administered intermittently, usually on a weekly basis in oral doses of 20 mg/m^2/week. Mercaptopurine is effective and well-tolerated orally when dosed daily, usually at a dose of 50 to 75 mg/m^2/day.[192]

Other agents have been added to standard maintenance therapy with mercaptopurine and methotrexate to improve remission duration and to increase a patient's chances for long-term survival. There is evidence that every 4- to 12-week pulses of vincristine and prednisone offer advantages (lower bone marrow and testicular relapse rates) in standard-risk patients as well. At present, most

contemporary treatment regimens for childhood ALL have intensified induction and postinduction phases during approximately the first 6 months. These early intensive treatments typically are followed by a less-intensive maintenance therapy consisting of methotrexate and mercaptopurine in combination with periodic IT chemotherapy treatments, either with or without intermittent vincristine and prednisone or dexamethasone pulses.[27,158]

The available evidence suggests that a patient like J.B. with standard-risk ALL will benefit from use of daily mercaptopurine 50 to 75 mg/m^2 orally (PO) and weekly methotrexate 20 mg/m^2 PO or IV, along with periodic pulse therapy with vincristine 1.5 mg/m^2 for 1 day and either prednisone 40 mg/m^2 or dexamethasone 6 mg/m^2 PO for 7 days every 4 to 12 weeks. In addition, IT methotrexate should be repeated every 8 to 12 weeks. Depending on the specific treatment protocol, his maintenance therapy will continue for ~18 to 24 months.[192]

Mercaptopurine adherence and metabolism

Case 95-5, Question 11: After 8 weeks of maintenance therapy with the regimen, the medical team notices J.B. has maintained an ANC within the normal range for more than 6 weeks, while most patients have mild count suppression on this therapy. Other hematologic and chemistry findings are also within normal limits. What are potential problems with mercaptopurine and methotrexate that could explain his ANC values? What if his ANC values were unexpectedly low?

Significant interpatient variability in absorption and metabolism of mercaptopurine have been described, which may explain the varied response among patients to standard doses.[193] Thiopurines, including mercaptopurine and thioguanine, are inactivated by the enzymes thiopurine-*S*-methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15).[194] Although most patients have normal activity of these enzymes, deficient TPMT activity can be seen in up to 10% of the population, with the highest incidence in those of African or European descent.[194] This same population is more likely

to have normal NUDT15 activity, whereas up to 20% of patients of Asian or Hispanic ethnicity have abnormal NUDT15.[194,195] Patients with deficient TPMT or NUDT15 activity experience severe and even fatal toxicity with standard mercaptopurine doses and require very low doses (~10 mg/m^2 three times/week) to avoid profound myelosuppression.[194]

In fact, many centers send genetic testing prior to the initiation of thiopurines to identify polymorphisms with TPMT and NUDT15. This allows for pre-emptive dose adjustments to mercaptopurine in patients who are expected to have slowed metabolism. **Figure 95-1** shows suggested thiopurine dosing for patients predicted to be intermediate or poor metabolizers based on genotyping.[194]

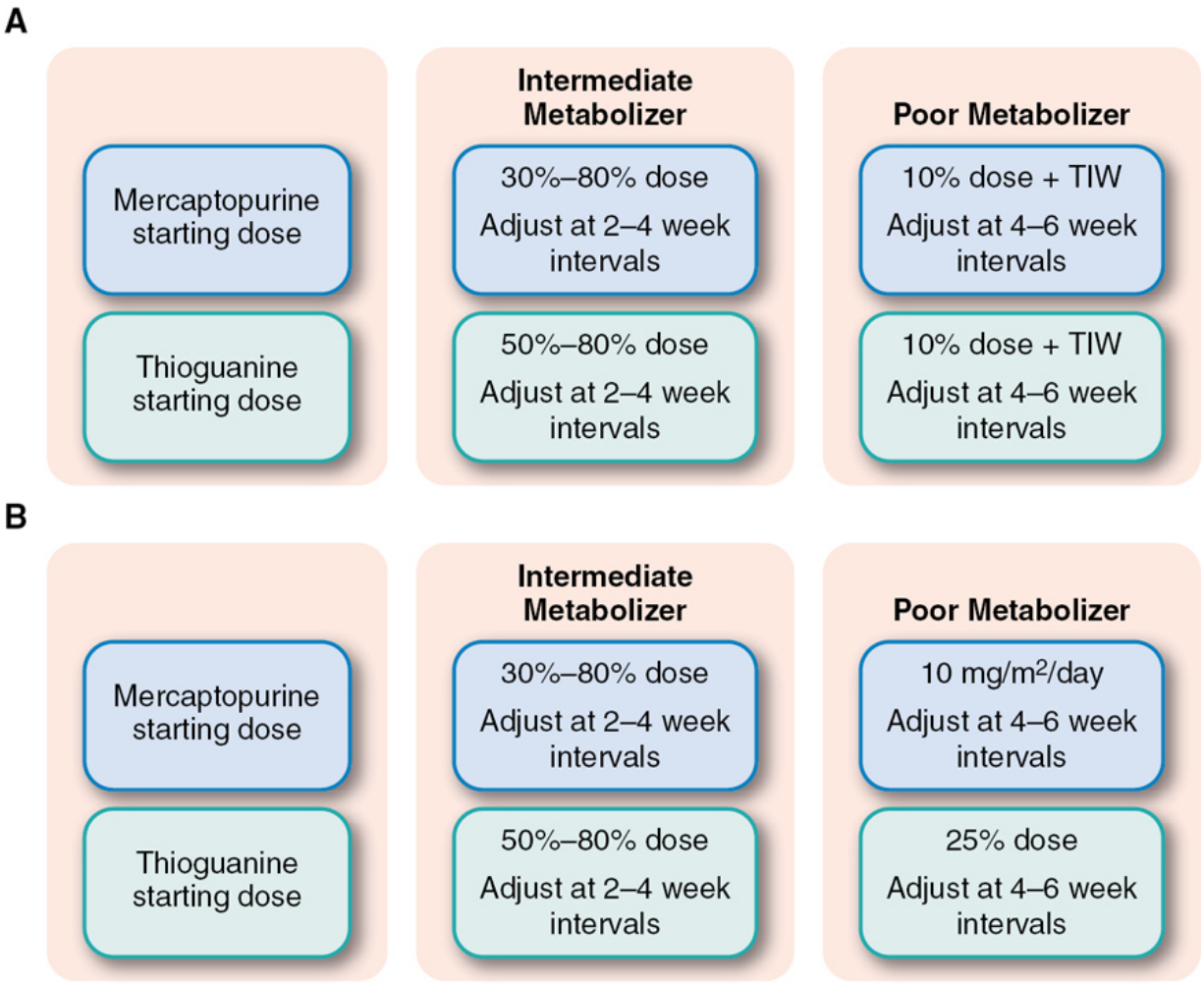


Figure 95-1 Pharmacogenomic dosing of thiopurines. A, Recommended thiopurine dose for abnormal TPMT activity. B, Recommended thiopurine dose for abnormal NUDT15 activity. TIW, three times weekly. TMPT, thiopurine-*S*-methyltransferase. (From Relling M, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther*. 2019;105(5):1095–1105.)

Another possible explanation for J.B.'s normal ANC could be nonadherence with the oral chemotherapy agents at home. As with any medication, poor adherence to oral chemotherapy has been associated with inferior outcomes.[196] In a study of 298 pediatric patients with ALL, mercaptopurine adherence rates below 90% were associated with a 3.9-fold increase in risk of relapse.[197] A thorough discussion should be had with J.B.'s care providers to determine how many doses of oral chemotherapy have been missed and to discuss barriers to adherence if they do exist.

Asparaginase

Asparaginase is an important addition to ALL therapy. In the 1980s, the addition of L-asparaginase to treatment of childhood ALL increased survival rates by 10% or more.[198,199] There are multiple products available, derived from one of two natural sources, *Escherichia coli* and *Erwinia chrysanthemi.* Pegaspargase is a pegylated long-acting form derived from *E. coli*. The incidence of hypersensitivity reactions to available products varies from 11% to 33% or higher.[198,200] Asparaginase preparations are not 100% cross-reactive, so the *Erwinia* product may be substituted for the *E. coli* product when hypersensitivity reactions occur. Of major concern, some patients may develop antibodies to these foreign proteins, which quickly inactivate the enzymes.[200] In up to 30% of children, this inactivation is "silent" and not accompanied by an occult hypersensitivity reaction.[199,200] To screen patients for silent inactivation, routine monitoring of asparaginase activity levels

following each dose of asparaginase has become a useful tool.[199] In cases where insufficient asparaginase activity is noted, the patient may be switched to another source product for future doses. Although several studies have correlated sufficient asparaginase activity with improved clinical outcomes, the goal activity level has varied between trials.[201–203] The COG has adopted a goal trough asparaginase activity level ≥0.1 IU/ ml based on a recently published consensus statement.[199,204]

Targeted therapies for ALL

As mentioned earlier in the discussion of cytogenetic variables in ALL, patients with t(9,22)/BCR-ABL1 translocation have a more difficult path to achieving a lasting remission.[166,205] The tyrosine kinase inhibitors imatinib and dasatinib have both been studied in combination with chemotherapy in this patient population and dramatically improved treatment outcomes. Prior to tyrosine kinase inhibitors, patients with the t(9,22) translocation required stem cell transplant. However, recent trials demonstrated 70% DFS with chemotherapy plus either dasatinib or imatinib, which was similar to outcomes with stem cell transplant. Less is known about the use of the other second- and third-generation tyrosine kinase inhibitors in children, although adult data have established a role in patients with inferior response to the aforementioned agents. In addition to targeted agents, children with t(9,22) will received more intensive chemotherapy as compared to standard ALL therapy.

Patients with T-cell ALL have a difficult time achieving remission and require intensified induction and consolidation chemotherapy regimens. In addition to intensified chemotherapy, nelarabine is approved for high risk or relapsed T-ALL. Nelarabine is a nucleoside analog and functions as a false purine inhibiting DNA synthesis within T cells. It gained FDA approval based on response rates observed in two trials of relapsed and refractory patients.[206,207] These trials both noted minimal hematologic toxicity, whereas neurologic toxicity was observed to be dose-limiting. A randomized trial of high-risk pediatric patients with T-ALL compared nelarabine to standard

chemotherapy and noted neurologic toxicity was similar between groups, with a significant DFS advantage in the nelarabine group.[208,209]

Relapsed Acute Lymphoblastic Leukemia

Prognosis

CASE 95-6

QUESTION 1: N.B. is a 12-year-old male with B-cell ALL. Initially, he responded to therapy and achieved a complete remission. However, about 17 months after his initial diagnosis, N.B. undergoes a routine lumbar puncture as part of his planned maintenance therapy. Analysis of the CSF indicates the presence of numerous lymphoblasts. A CBC reveals the following:

Hct, 29.5%
Platelet count, 120,000 cells/μL
WBC, 5300 cells/μL, with 45% lymphocytes, 50% neutrophils, and 5% bands
A bone marrow biopsy confirms relapsed ALL with 53% lymphoblasts.

What are N.B.'s chances of achieving a second remission and long-term survival? Are there specific features about N.B.'s relapse that confer a worse prognosis?

N.B. is asymptomatic at the time of relapse, as are most patients experiencing a relapse of ALL. Most of these patients are diagnosed by routine CBCs or lumbar punctures. Although patients with ALL typically have excellent responses to treatment after relapse, many patients will relapse again, and 50% to 60% will not be long-time survivors.[210,211] N.B.'s relapse would be described as an early marrow relapse because it occurred <36 months from his initial diagnosis. Patients with an early marrow relapse can expect to achieve a second remission 83% of the time, as compared to 93% of patients who relapse at 36 months or later.[211] MRD data are collected in these patients achieving a second remission and is helpful in predicting patient who may benefit from intensified relapse therapy.[212]

TREATMENT OF RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA

CASE 95-6, QUESTION 2: Which treatments could be used to attain a complete remission and improve N.B.'s chances of long-term survival?

Salvage therapy for relapsed ALL is individualized based on patient-specific and disease-specific factors, including time to relapse, site(s) of relapse, immunophenotype, and response to reinduction therapy. Agents used in salvage regimens are similar to those used in high-risk ALL regimens. In general, treatment usually consists of an intensive four-agent induction regimen of vincristine, steroid, daunorubicin or mitoxantrone, and asparaginase.[212,213] After this regimen has been completed, patients may continue with courses of intensification chemotherapy, targeted agents, or cellular therapy.

In N.B.'s case, his regimen should include intensive therapy, preferably with drugs and regimens to which he has not been previously exposed, because his relapse occurred while he was on therapy. Targeted therapy with blinatumomab may provide N.B. with an improved chance of cure. In clinical trials of relapsed or refractory patients like N.B., complete response rates above 40% were reported.[214–217] Conversion to MRD-negative marrow was observed in patients who were MRD-positive after reinduction chemotherapy.[218–220] Blinatumomab is a bispecific anti-CD3/anti-CD19 monoclonal antibody. Healthy T cells are activated by binding CD3 and then attack CD19-positive B cells, including the leukemia cells. Although drug delivery is complicated and involves a 28-day continuous infusion, the incidence of grade III or greater adverse events in clinical trials was less common with blinatumomab than chemotherapy. Patients are at risk for cytokine release syndrome and neurologic adverse events including encephalopathy or seizure.[220,214]

Case 95-6, Question 3: N.B.'s family is quite concerned about the poor prognosis associated with his relapse and inquire about the role of hematopoietic cell transplantation (HCT) in his relapse treatment. Should he be considered for HCT at this point? What other cellular therapies might be an option for N.B?

Allogeneic HCT provides the best chance of cure for children with relapsed ALL who have high-risk and intermediate-risk features.[221,222] N.B.'s family should be offered the option of allogeneic HCT, and his family should be tested for an appropriate sibling match as this offers lower morbidity than an unrelated donor. Because his outcome in transplant improves if performed during a second complete remission, he should begin reinduction chemotherapy, while HCT is being arranged. If HCT does not prove to be a feasible option for N.B., novel therapies may be considered.

New to the field of cellular therapy, CAR T-cell products involve harvesting T cells from the patient, then adding a chimeric T-cell receptor to target the cancer cell, in this case CD19.[223–225] Tisagenlecleucel is a CD19-directed CAR T-cell product with approval in pediatric patients with relapsed or refractory B-cell ALL. In clinical trials, 80% to 90% of patients treated experienced a complete marrow response, with adverse reactions including cytokine release syndrome and neurologic toxicity similar to blinatumomab. These engineered T cells are expected to proliferate and survive for a significant period of time, helping to prevent future relapses. Although therapy with CAR T cells was developed as consolidation prior to stem cell transplant, some patients demonstrate long-term remissions without having received subsequent stem cell transplant.

PEDIATRIC NON-HODGKIN LYMPHOMA

Lymphomas are a collection of diseases originating in cells and organs of the immune system. Lymphomas account for ~10% to

15% of all childhood malignancies, and they are less common in children than in adults. The malignancy can occur in any lymphoid cell at any level of differentiation and appears to be a consequence of a genetic alteration. Non-Hodgkin lymphoma (NHL) is the most common form of lymphoma in children younger than age 10 years, whereas Hodgkin lymphoma is most common in children ages 15 to 19 years. This section will focus on NHL. Considerable progress has been made in the treatment of children with NHL and more than 80% of children are cured.[226]

Classification

Pediatric NHLs are best classified using histopathology, which divides them into three different categories: mature B-cell lymphomas, lymphoblastic lymphomas, and anaplastic large-cell lymphomas.[227] This is a narrower range of histologic types than in adults.

Lymphoblastic lymphomas account for ~25% of childhood NHLs, B-cell lymphomas for about 65%, and anaplastic large-cell lymphomas for the remainder.[226] The lymphoblastic lymphomas are usually immature T cells that are histologically identical to the cells of ALL. The distinction between lymphoblastic lymphoma and ALL is made on the basis of bone marrow involvement, with ALL being diagnosed if there is >25% bone marrow infiltration. B-cell lymphomas may be further divided into Burkitt, primary mediastinal, and large B-cell lymphomas. Anaplastic large-cell lymphomas may be T cell or null cell in origin.[227,228]

Clinical Presentation

Pediatric patients with NHL may present with a number of different symptoms, many of which are related to the type of NHL.[226,227] In general, these symptoms differ from those in adults because of the propensity of pediatric NHLs to be extranodal in origin in contrast to the common nodal presentation of adult NHL. Patients with

lymphoblastic lymphoma commonly present with a mediastinal mass or pleural effusions. They also may have pain, dyspnea, or swelling of the face and upper arms if superior vena cava obstruction is present. Lymphoblastic lymphoma also has a predilection for the bone marrow and the CNS. Patients with B-cell NHL typically present with an abdominal tumor, abdominal pain, an alteration in bowel function, and possibly nausea and vomiting. In addition, many patients with B-cell NHL present with bone marrow involvement. Lymphadenopathy in these patients typically occurs below the diaphragm in the inguinal or iliac area. Anaplastic large-cell lymphomas may involve the gut or unusual sites such as the lung, skin, face, or CNS.

Staging

A commonly used staging system for pediatric NHL is the St. Jude or Murphy staging system.[229] It includes four stages, with stage I being a single tumor or a single nodal area, and higher stages including cases with regional involvement or more than one anatomical site involved. The highest stage (stage IV) refers to patients with bone marrow or CNS involvement. A Revised International Pediatric Non-Hodgkin Lymphoma Staging System has recently been developed to incorporate newly identified histologic entities and advanced imaging.[230,231] The main predictor of outcome in pediatric patients with NHL has historically been determined by tumor burden at presentation. However, with modern chemotherapy regimens that are tailored to the extent of disease, patients with higher-stage disease may achieve a similar event-free survival to that achieved in patients with lower-stage disease.[226]

Overview of Treatment

Lymphoblastic (T Cell) Lymphomas

The primary treatment for all stages and histologic types of pediatric NHL is combination chemotherapy utilizing the wide variety of

chemotherapy agents that have activity in childhood NHL. Nearly 90% of lymphoblastic lymphoma in children will be of T-cell origin, thus treatment of this disease is focused primarily on the T-cell subset.[232] At present, the best results for T-cell lymphoblastic lymphoma treatment are based on the backbone by the Berlin–Frankfurt–Muenster **(**BFM) group, with an estimated 5-year event-free survival of ~85% (**Table 95-6**).[233,234] This regimen uses an intensive scheme of multiagent chemotherapy administered over 24 months. Patients with lymphoblastic lymphoma require longer treatment duration than patients with B cell or anaplastic large-cell lymphoma. This chemotherapy plan is similar to that used in the treatment of ALL and includes CNS preventive therapy regardless of stage. Much like ALL, the use of cranial radiation has been replaced with intrathecal chemotherapy and CNS-active agents such as methotrexate and cytarabine.[232,233,234]

Table 95-6

Berlin–Frankfurt–Muenster (BFM) Group Treatment Protocols for T-Cell Lymphoblastic Lymphoma

Drug	Dose	Days of Administration
Induction Protocol I (All Stages)		
Prednisone (PO)	60 mg/m^2	1–28, then taper
Vincristine (IV)	1.5 mg/m^2 (max 2 mg)	8, 15, 22, 29
Daunorubicin (IV over 1 hour)	30 mg/m^2	8, 15, 22, 29
L-Asparaginase (IV[a] over 1 hour)	10,000 IU/m^2	12, 15, 18, 21, 24, 27, 30, 33
Cyclophosphamide (IV over 1 hour)	1000 mg/m^2	36, 64
Cytarabine (IV)	75 mg/m^2	38–41, 45–48, 52–55, 59–62
6-Mercaptopurine (PO)	60 mg/m^2	36–63
Methotrexate (IT)[b]	12 mg	1, 15, 29, 45, 59
Protocol M (Typically Stages I and II)		

Drug	Dose	Days of Administration
Induction Protocol I (All Stages)		
Mercaptopurine (PO)	25 mg/m^2	1–56
Methotrexate (IV)	5 g/m^2	8, 22, 36, 50
Methotrexate (IT)	12 mg	8, 22, 36, 50
Reinduction Protocol II (Stages III and IV Only)		
Dexamethasone (PO)	10 mg/m^2	1–21, then taper
Vincristine (IV)	1.5 mg/m^2 (max 2 mg)	8, 15, 22, 29
Doxorubicin (IV over 1 hour)	30 mg/m^2	8, 15, 22, 29
L-Asparaginase (IV[a])	10,000 IU/m^2	8, 11, 15, 18
Cyclophosphamide (IV over 1 hour)	1000 mg/m^2	36
Cytarabine (IV)	75 mg/m^2	38–41, 45–48
Thioguanine (PO)	60 mg/m^2	36–49
Methotrexate (IT)	12 mg	38, 45
Maintenance (All Stages)		
Mercaptopurine (PO)	50 mg/m^2	Daily until month 24 of therapy
Methotrexate (PO)	20 mg/m^2	Weekly until month 24 of therapy

Note: IT methotrexate doses were adjusted for children younger than 3 years. Ten percent of the 5 g/m^2 methotrexate dose in protocol M was given for 30 minutes, and 90% was given as a 23.5-hour continuous IV infusion. Leucovorin rescue: 30 mg/m^2 IV at hour 42; 15 mg/m^2 IV at hours 48 and 54.

CNS, central nervous system; IT, intrathecally; IV, intravenously; PO, orally.

[a]This agent is substituted with pegaspargase 2500 units/m^2 in the United States based on drug availability.

[b]Additional intrathecal chemotherapy doses are given on days 8 and 22 for CNS-positive patients.

Source: Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. *Blood*. 2000;95(2):416–421. © 2000 American Society of Hematology. With permission.

The BFM backbone has been modified in recent years to replace L-asparaginase with pegaspargase and replace prednisone with dexamethasone during induction. Additionally, T-cell lymphoblastic lymphoma patients are treated with escalating (Capizzi) methotrexate regimen in place of high-dose methotrexate during consolidation. The benefit of adding nelarabine to this modified BFM backbone is unclear but is being explored in clinical trials.[232,233,234]

B-CELL LYMPHOMAS

Treatment of mature B-cell lymphomas differs from lymphoblastic lymphoma in both duration and agents used.[226] The trend in B-cell lymphoma treatment has been toward short-duration, intensive therapy with alkylating agents in conjunction with high-dose antimetabolite therapy (eg, methotrexate, cytarabine). Chemotherapy is administered in rapid succession with limited recovery from neutropenia (ie, ANC 500 cells/μL) between cycles.

Patients are classified into risks groups A, B, and C based on disease stage, resectability, and presence of CNS or bone marrow involvement. Those in the lowest risk category A require only two or three cycles of COPAD regimen consisting of cyclophosphamide, vincristine, doxorubicin, and prednisone.[226] In this group with localized disease, maintenance chemotherapy did not demonstrate any added benefit and should not be offered.[235,236] Contemporary chemotherapy regimens include varying degrees of treatment intensity from three to seven cycles, depending on whether the tumor is completely resected, bone marrow and CNS involvement, and the serum LDH.[237,238]

With the addition of high-dose methotrexate, etoposide, and cytarabine to the standard regimen, patients with stage III and IV disease are now achieving survival rates comparable to those of patients with limited-stage disease.[239] Patients with bone marrow disease also benefit from these intensive therapeutic strategies and have achieved impressive survival rates of ~90%. Currently, patients with advanced-stage disease are treated with a total of six to eight cycles of chemotherapy, and these treatment protocols achieve

superior results to those of a much longer duration (eg, 1–2 years) used previously. The addition of rituximab to chemotherapy for B-cell lymphomas prolongs event-free survival; however, it increases the incidence of infection and hypogammaglobulinemia.

ANAPLASTIC LARGE-CELL LYMPHOMAS

Anaplastic large-cell lymphomas have responded well to both types of regimens.[237] Thus, the use of shorter, less complicated, B-cell protocols is appropriate. Targeted agents such as crizotinib in ALK-positive tumors and brentuximab vedotin in tumors that express CD30 are subjects of current research.[237,238] Patients who fail to respond may be treated with additional courses of their prescribed protocol in hopes of eventually inducing a response. Patients who relapse may be reinduced with intensive chemotherapy, but their prognosis for long-term survival is unfavorable.[237]

Lymphoblastic Lymphoma

Acute Treatment

CASE 95-7

QUESTION 1: D.B., a 16-year-old female, presents with a history of shortness of breath and chest pain for 3 weeks. A mediastinal mass is found, and a biopsy confirms lymphoblastic (T cell) lymphoma. Laboratory values show the following results:

Erythrocyte sedimentation rate, 35 mm/hour
WBC count, 22,000 cells/μL
Uric acid, 7 mg/dL
LDH, 1259 units/L

The bone marrow, CNS, and abdomen are negative for lymphoma.

How should D.B. be managed acutely? Besides chemotherapy, what types of adjunctive therapies should be initiated to minimize the acute effects of treatment?

Given D.B.'s shortness of breath and chest pain, it is likely that her mediastinal mass may be obstructing the superior vena cava. To

alleviate this obstruction, the most appropriate course of action is to decrease the tumor mass by initiating chemotherapy as soon as possible. Radiation therapy offers no additional benefit in patients like D.B., with a tumor such as NHL, which is highly responsive to chemotherapy.[232] Because of the rapid cell kill that will result from the initiation of chemotherapy, tumor lysis syndrome and uric acid nephropathy are possible.

Aggressive hydration and allopurinol should be instituted before chemotherapy to prevent tumor lysis syndrome. Because D.B. has a pleural effusion, fluids may collect in this third space, resulting in weight gain and decreased urine output. Thus, in addition to placement of a chest tube with suction, D.B. should be given diuretics to maintain an adequate urine output. To minimize intravascular volume depletion and maintain electrolyte balances, fluid input and output, body weight, and electrolytes should be monitored daily. These values should be used to make appropriate adjustments in D.B.'s electrolyte and fluid balance. See Chapter 96, Adult Hematologic Malignancies, for a complete discussion of tumor lysis syndrome.

Adverse effects

Case 95-7, Question 2: D.B. is treated with the BFM combination chemotherapy regimen. Because of her intrathoracic mass, her disease is characterized as stage III. She is to receive induction therapy (Induction Protocol I) for 8 weeks, as outlined in Table 95-6. Which acute adverse effects is D.B. likely to experience with these agents? How can they be monitored, minimized, and treated?

Several toxicities are expected with these chemotherapy agents. For vincristine, both constipation and neuropathy are likely to appear during or after the 4 weeks of therapy.[182] Constipation can be prevented or minimized by use of stool softeners with or without a laxative. Neuropathy may be painful (especially when jaw pain occurs) but can be managed with mild analgesic regimens consisting of NSAIDs or acetaminophen. Both toxicities are self-limiting and are

not reasons to discontinue or decrease the dosage of vincristine unless neuromuscular toxicity, as evidenced by motor weakness, develops. The incidence of jaw pain and foot drop is higher in pediatric populations as compared to adults. Asparaginase can cause several types of toxicities (eg, hypersensitivity reaction, coagulation disorders, pancreatitis), most of which are not thought to be preventable.

Prednisone is likely to increase D.B.'s appetite and may cause gastritis, although divided doses will help decrease stomach upset. In addition, prednisone-induced behavioral disturbances, such as hyperactivity, are common in children.[183] Unlike prednisone and vincristine, daunorubicin, cyclophosphamide, cytarabine, and mercaptopurine produce significant myelosuppression. Leukopenia is common with the nadir occurring in ~8 to 14 days, and recovery occurring by approximately day 21 after administration. Because the goal of induction therapy is achievement of remission, doses of daunorubicin will not be held for uncomplicated myelosuppression during the first 4 weeks of induction therapy, although during the latter 4 weeks, the combination of cyclophosphamide, cytarabine, and mercaptopurine are typically held until hematologic recovery occurs.

Hemorrhagic cystitis may occur with cyclophosphamide, but it is usually associated with high-dose therapy or with prolonged administration, which D.B. is not receiving. Vigorous IV hydration to maintain urine output of ~50 to 100 mL/m^2/hour should reduce the risk of this toxicity. Because most of the induction regimen will be administered on an outpatient basis, patients or parents should be instructed to report signs or symptoms of infection (eg, febrile episodes) immediately so that proper treatment may be instituted as soon as possible. To decrease the risk of hemorrhagic cystitis, parents should be instructed to report whether patients are urinating regularly after cyclophosphamide. See Chapter 94, Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents, for further discussion of these adverse effects.

Nausea and vomiting are likely to be induced by daunorubicin, cyclophosphamide, and cytarabine. D.B.'s chemotherapy regimen

includes a corticosteroid (prednisone), which may provide some antiemetic activity during the initial 4 weeks. However, to maximize tolerance to her chemotherapy, D.B. should receive a 5-HT_3 serotonin antagonist. D.B. is unlikely to require additional corticosteroids during the first 4 weeks of induction therapy. However, during the second portion of induction, D.B. will benefit from a few doses of dexamethasone at the time of cyclophosphamide administration.[240] See Chapter 22, Nausea and Vomiting, for further discussion of chemotherapy-induced nausea and vomiting.

Central nervous system prophylaxis

Case 95-7, Question 3: What is the importance of CNS prophylaxis for D.B. and what type of treatment regimen is typically used?

All pediatric patients with lymphoblastic lymphoma should receive some form of CNS prophylaxis. Although lymphoblastic lymphoma rarely presents with CNS involvement, as illustrated by D.B., it was a common site of relapse before CNS prophylaxis was included as a routine part of the chemotherapy regimen.[232] Recurrence of NHL within the CNS is rare when IT methotrexate or cytarabine is given.[234] D.B. will be treated with IT methotrexate periodically, as outlined in Table 95-6.

Myelosuppression and hematopoietic recovery

Case 95-7, Question 4: After completion of induction therapy, the chemotherapy plan for D.B. consists of protocol M and reinduction protocol II, as outlined in Table 95-6. How should D.B.'s hematopoietic recovery be managed, and what guidelines may be used to determine when it is appropriate for her to receive the next sequence of the treatment cycle? Would D.B. benefit from a colony-stimulating factor to aid with hematopoietic recovery?

This aggressive combination of chemotherapy agents will result in significant myelosuppression. Similar to Induction protocol I, dosing of chemotherapy will not be held for uncomplicated myelosuppression. However, before initiating the second phase on day 36, clinicians will assure adequate hematologic recovery, typically defined as an ANC >750 cells/μL and platelets >100,000 cells/μL. It is unlikely that D.B. will benefit from a colony-stimulating factor during these phases of therapy. When myelosuppressive chemotherapy is given fairly continuously, as is the case with protocol II, there is little room for inserting doses of colony-stimulating factors on days where myelosuppressive chemotherapy is not being administered.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Balis FM, Womer RB, Berg S, Winick N, Adamson PC, Fox E. Dosing anticancer drugs in infants: current approach and recommendations from the Children's Oncology Group's Chemotherapy Standardization Task Force. *Pediatr Blood Cancer.* 2017;64(11):10.1002/pbc.26636. doi:10.1002/pbc.26636. (90)

Borowitz M, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood*. 2015;126:964–971. (170)

Dupuis L, Boodhan S, Holdsworth M, et al. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer.* 2013;60:1073–1082. (240)

Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. *The Oncologist.* 2016;21(12):1471–1482. (117)

Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med*. 2015;373(16):1541–1552. (27)

Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572–1582. (30)

Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. *Oncologist.* 2018;23(1):52–61. (126)

Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther.* 2019;105:1095–1105. (194)

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7–30. (1)

Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. *Cancer.* 2014;120(16):2497–2506. (35)

Sun W, Malvar J, Sposto R, et al. Outcome of children with multiply relapsed B-cell acute lymphoblastic leukemia: a therapeutic advances in childhood leukemia & lymphoma study. *Leukemia.* 2018;32:2316–2325. (210)

Vrooman LM, Silverman LB. Treatment of childhood acute lymphoblastic leukemia: prognostic factors and clinical advances. *Curr Hematol Malig Rep*. 2016;11:385–394. (159)

Key Websites

Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Accessed October 23, 2020. http://survivorshipguidelines.org/ (31)

National Comprehensive Cancer Network. www.nccn.org

St. Jude Children's Research Hospital. Childhood Cancer Survivor Study. www.stjude.org/ccss

COMPLETE REFERENCES CHAPTER 95 PEDIATRIC MALIGNANCIES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7–30.

2. Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA.* 1997;278(15):1262–1267.
3. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res.* 1988;48(18):5358–5362.
4. Ruteshouser EC, Robinson SM, Huff V. Wilms tumor genetics: mutations in WT1, WTX, and CTNNB1 account for only about one-third of tumors. *Genes Chromosomes Cancer.* 2008;47(6):461–470.
5. Breslow NE, Norris R, Norkool PA, et al. Characteristics and outcomes of children with the Wilms tumor-Aniridia syndrome: a report from the National Wilms Tumor Study Group. *J Clin Oncol.* 2003;21(24):4579–4585.
6. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR syndrome: a clinical review of 54 cases. *Pediatrics.* 2005;116(4):984–988.
7. Brown AL, de Smith AJ, Gant VU, et al. Inherited genetic susceptibility to acute lymphoblastic leukemia in Down syndrome. *Blood.* 2019;134(15):1227–1237.
8. Meadows AT, Friedman DL, Neglia JP, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol.* 2009;27(14):2356–2362.
9. Park AS, Ritz B, Yu F, Cockburn M, Heck JE. Prenatal pesticide exposure and childhood leukemia—a California statewide case-control study. *Int J Hyg Environ Health.* 2020;226:113486.
10. He JR, Ramakrishnan R, Hirst JE, et al. Maternal infection in pregnancy and childhood leukemia: a systematic review and meta-analysis. *J Pediatr.* 2020;217:98–109.e108.
11. Cao Y, Lu J, Lu J. Paternal smoking before conception and during pregnancy is associated with an increased risk of childhood acute lymphoblastic leukemia: a systematic review and meta-analysis of 17 case-control studies. *J Pediatr Hematol Oncol.* 2020;42(1):32–40.
12. Abalo KD, Rage E, Leuraud K, et al. Early life ionizing radiation exposure and cancer risks: systematic review and meta-analysis. *Pediatr Radiol.* 2020;51(1):45–56.
13. Turcotte LM, Whitton JA, Friedman DL, et al. Risk of subsequent neoplasms during the fifth and sixth decades of life in the Childhood Cancer Survivor Study cohort. *J Clin Oncol.* 2015;33(31):3568–3575.
14. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2010;102(14):1083–1095.
15. Twist CJ, Schmidt ML, Naranjo A, et al. Maintaining outstanding outcomes using response-and biology-based therapy for intermediate-risk neuroblastoma: a report from the Children's Oncology Group study ANBL0531. *J Clin Oncol.* 2019;37(34):3243–3255.

16. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet.* 2007;370(9583):240–250.
17. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. *J Clin Oncol.* 2018;36(21):2181–2189.
18. van Atteveld JE, Pluijm SMF, Ness KK, et al. Prediction of low and very low bone mineral density among adult survivors of childhood cancer. *J Clin Oncol.* 2019;37(25):2217–2225.
19. Green DM, Kawashima T, Stovall M, et al. Fertility of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27(16):2677–2685.
20. Feijen EAM, Leisenring WM, Stratton KL, et al. Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. *JAMA Oncol.* 2019;5(6):864–871.
21. Bates JE, Howell RM, Liu Q, et al. Therapy-related cardiac risk in childhood cancer survivors: an analysis of the Childhood Cancer Survivor Study. *J Clin Oncol.* 2019;37(13):1090–1101.
22. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from Children's Oncology Group study AALL0232. *J Clin Oncol.* 2016;34(20):2380–2388.
23. Tricoli JV, Boardman LA, Patidar R, et al. A mutational comparison of adult and adolescent and young adult (AYA) colon cancer. *Cancer.* 2018;124(5):1070–1082.
24. Tricoli JV, Blair DG, Anders CK, et al. Biologic and clinical characteristics of adolescent and young adult cancers: acute lymphoblastic leukemia, colorectal cancer, breast cancer, melanoma, and sarcoma. *Cancer*. 2016;122(7):1017–1028.
25. Ram R, Wolach O, Vidal L, Gafter-Gvili A, Shpilberg O, Raanani P. Adolescents and young adults with acute lymphoblastic leukemia have a better outcome when treated with pediatric-inspired regimens: systematic review and meta-analysis. *Am J Hematol.* 2012;87(5):472–478.
26. Gupta S, Pole JD, Baxter NN, et al. The effect of adopting pediatric protocols in adolescents and young adults with acute lymphoblastic leukemia in pediatric vs adult centers: an IMPACT Cohort study. *Cancer Med.* 2019;8(5):2095–2103.
27. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med.* 2015;373(16):1541–1552.
28. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol.* 2010;28(15):2625–2634.

29. Children's Oncology Group. About us. Accessed October 23, 2020. https://childrensoncologygroup.org/index.php/about-us
30. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572–1582.
31. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Accessed October 23, 2020. http://survivorshipguidelines.org/
32. Rosoff PM. The two-edged sword of curing childhood cancer. *N Engl J Med.* 2006;355(15):1522–1523.
33. Poplack DG, Fordis M, Landier W, Bhatia S, Hudson MM, Horowitz ME. Childhood cancer survivor care: development of the Passport for Care. *Nat Rev Clin Oncol.* 2014;11(12):740–750.
34. London WB, Castleberry RP, Matthay KK, et al. Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. *J Clin Oncol.* 2005;23(27):6459–6465.
35. Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. *Cancer.* 2014;120(16):2497–2506.
36. Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *J Clin Oncol.* 2009;27(2):289–297.
37. Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a Children's Oncology Group study. *J Clin Oncol.* 2009;27(7):1007–1013.
38. National Cancer Institute. Neuroblastoma Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. Accessed January 5, 2021. https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq
39. Kamihara J, Bourdeaut F, Foulkes WD, et al. Retinoblastoma and neuroblastoma predisposition and surveillance. *Clin Cancer Res.* 2017;23(13):e98–e106.
40. Yang J, Codreanu I, Servaes S, Zhuang H. I-131 MIBG post-therapy scan is more sensitive than I-123 MIBG pretherapy scan in the evaluation of metastatic neuroblastoma. *Nucl Med Commun.* 2012;33(11):1134–1137.
41. Vik TA, Pfluger T, Kadota R, et al. (123)I-mIBG scintigraphy in patients with known or suspected neuroblastoma: results from a prospective multicenter trial. *Pediatr Blood Cancer.* 2009;52(7):784–790.
42. Monclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. *J Clin Oncol.* 2009;27(2):298–303.

43. Brisse HJ, McCarville MB, Granata C, et al. Guidelines for imaging and staging of neuroblastic tumors: consensus report from the International Neuroblastoma Risk Group Project. *Radiology.* 2011;261(1):243–257.
44. Schleiermacher G, Mosseri V, London WB, et al. Segmental chromosomal alterations have prognostic impact in neuroblastoma: a report from the INRG project. *Br J Cancer.* 2012;107(8):1418–1422.
45. Baker DL, Schmidt ML, Cohn SL, et al. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. *N Engl J Med.* 2010;363(14):1313–1323.
46. Strother DR, London WB, Schmidt ML, et al. Outcome after surgery alone or with restricted use of chemotherapy for patients with low-risk neuroblastoma: results of Children's Oncology Group study P9641. *J Clin Oncol.* 2012;30(15):1842–1848.
47. Park JR, Kreissman SG, London WB, et al. Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma: a randomized clinical trial. *JAMA.* 2019;322(8):746–755.
48. Casey DL, Kushner BH, Cheung NK, Modak S, LaQuaglia MP, Wolden SL. Local control with 21-Gy radiation therapy for high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys.* 2016;96(2):393–400.
49. Cheung NK, Cheung IY, Kushner BH, et al. Murine anti-GD2 monoclonal antibody 3F8 combined with granulocyte-macrophage colony-stimulating factor and 13-cis-retinoic acid in high-risk patients with stage 4 neuroblastoma in first remission. *J Clin Oncol.* 2012;30(26):3264–3270.
50. De Ioris MA, Crocoli A, Contoli B, et al. Local control in metastatic neuroblastoma in children over 1 year of age. *BMC Cancer.* 2015;15:79.
51. Elborai Y, Hafez H, Moussa EA, et al. Comparison of toxicity following different conditioning regimens (busulfan/melphalan and carboplatin/etoposide/melphalan) for advanced stage neuroblastoma: experience of two transplant centers. *Pediatr Transplant.* 2016;20(2):284–289.
52. Englum BR, Rialon KL, Speicher PJ, et al. Value of surgical resection in children with high-risk neuroblastoma. *Pediatr Blood Cancer.* 2015;62(9):1529–1535.
53. Liu KX, Naranjo A, Zhang FF, et al. Prospective evaluation of radiation dose escalation in patients with high-risk neuroblastoma and gross residual disease after surgery: a report from the Children's Oncology Group ANBL0532 Study. *J Clin Oncol.* 2020;38(24):2741–2752.
54. Simon T, Häberle B, Hero B, von Schweinitz D, Berthold F. Role of surgery in the treatment of patients with stage 4 neuroblastoma age 18 months or older at diagnosis. *J Clin Oncol.* 2013;31(6):752–758.
55. von Allmen D, Davidoff AM, London WB, et al. Impact of extent of resection on local control and survival in patients from the COG A3973 Study with

high-risk neuroblastoma. *J Clin Oncol.* 2017;35(2):208–216.
56. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med*. 2010;363(14):1324–1334.
57. Kreissman SG, Villablanca JG, Diller L, et al. Response and toxicity to a dose-intensive multi-agent chemotherapy induction regimen for high risk neuroblastoma (HR-NB): a Children's Oncology Group (COG A3973) study. *J Clin Oncol.* 2007;25(18_suppl):9505–9505.
58. Philip T, Ladenstein R, Lasset C, et al. 1070 myeloablative megatherapy procedures followed by stem cell rescue for neuroblastoma: 17 years of European experience and conclusions. European Group for Blood and Marrow Transplant Registry Solid Tumour Working Party. *Eur J Cancer.* 1997;33(12):2130–2135.
59. Ladenstein R, Pötschger U, Valteau-Couanet D, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. *Lancet Oncol.* 2018;19(12):1617–1629.
60. Ladenstein R, Pötschger U, Pearson ADJ, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. *Lancet Oncol.* 2017;18(4):500–514.
61. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20(3):629–637.
62. Womer RB, Pritchard J, Barratt TM. Renal toxicity of cisplatin in children. *J Pediatr.* 1985;106(4):659–663.
63. McMahon KR, Rassekh SR, Schultz KR, et al. epidemiologic characteristics of acute kidney injury during cisplatin infusions in children treated for cancer. *JAMA Netw Open.* 2020;3(5):e203639.
64. Bernhardt MB, Moffett BS, Johnson M, Tam VH, Thompson P, Garey KW. Agreement among measurements and estimations of glomerular filtration in children with cancer. *Pediatr Blood Cancer.* 2015;62(1):80–84.
65. Yanik GA, Villablanca JG, Maris JM, et al. 131I-metaiodobenzylguanidine with intensive chemotherapy and autologous stem cell transplantation for high-risk neuroblastoma. A new approaches to neuroblastoma therapy (NANT) phase II study. *Biol Blood Marrow Transplant.* 2015;21(4):673–681.
66. Schulte JH, Moreno L, Ziegler DS, et al. Final analysis of phase I study of ceritinib in pediatric patients with malignancies harboring activated anaplastic lymphoma kinase (ALK). *J Clin Oncol.* 2020;38(15_suppl):10505–10505.
67. Mossé YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol*. 2013;14(6):472–480.

68. Bresler SC, Weiser DA, Huwe PJ, et al. ALK mutations confer differential oncogenic activation and sensitivity to ALK inhibition therapy in neuroblastoma. *Cancer Cell.* 2014;26(5):682–694.
69. National Cancer Institute. Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. Accessed January 5, 2021. https://www.cancer.gov/types/kidney/hp/wilms-treatment-pdq
70. Wegert J, Wittmann S, Leuschner I, Geissinger E, Graf N, Gessler M. WTX inactivation is a frequent, but late event in Wilms tumors without apparent clinical impact. *Genes Chromosomes Cancer.* 2009;48(12):1102–1111.
71. Porteus MH, Narkool P, Neuberg D, et al. Characteristics and outcome of children with Beckwith-Wiedemann syndrome and Wilms' tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol.* 2000;18(10):2026–2031.
72. Scott RH, Walker L, Olsen ØE, et al. Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. *Arch Dis Child.* 2006;91(12):995–999.
73. German J. Bloom's syndrome. XX. The first 100 cancers. *Cancer Genet Cytogenet.* 1997;93(1):100–106.
74. Hol JA, Lopez-Yurda MI, Van Tinteren H, et al. Prognostic significance of age in 5631 patients with Wilms tumour prospectively registered in International Society of Paediatric Oncology (SIOP) 93-01 and 2001. *PloS One.* 2019;14(8):e0221373.
75. Shamberger RC, Anderson JR, Breslow NE, et al. Long-term outcomes for infants with very low risk Wilms tumor treated with surgery alone in National Wilms Tumor Study-5. *Ann Surg.* 2010;251(3):555–558.
76. Gratias EJ, Dome JS, Jennings LJ, et al. Association of Chromosome 1q gain with inferior survival in favorable-histology Wilms tumor: a report from the Children's Oncology Group. *J Clin Oncol.* 2016;34(26):3189–3194.
77. Grundy PE, Breslow NE, Li S, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol*. 2005;23(29):7312–7321.
78. Begent J, Sebire NJ, Levitt G, et al. Pilot study of F(18)-Fluorodeoxyglucose positron emission tomography/computerised tomography in Wilms' tumour: correlation with conventional imaging, pathology and immunohistochemistry. *Eur J Cancer.* 2011;47(3):389–396.
79. D'Angio GJ. Pre-or postoperative therapy for Wilms' tumor? *J Clin Oncol.* 2008;26(25):4055–4057.
80. Ehrlich P, Chi YY, Chintagumpala MM, et al. Results of the first prospective multi-institutional treatment study in children with bilateral Wilms tumor (AREN0534): a report from the Children's Oncology Group. *Ann Surg*. 2017;266(3):470–478.

81. Breslow NE, Lange JM, Friedman DL, et al. Secondary malignant neoplasms after Wilms tumor: an international collaborative study. *Int J Cancer.* 2010;127(3):657–666.
82. Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol.* 2001;19(7):1926–1934.
83. Green DM, Lange JM, Peabody EM, et al. Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. *J Clin Oncol.* 2010;28(17):2824–2830.
84. Termuhlen AM, Tersak JM, Liu Q, et al. Twenty-five year follow-up of childhood Wilms tumor: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2011;57(7):1210–1216.
85. Wong KF, Reulen RC, Winter DL, et al. Risk of adverse health and social outcomes up to 50 years after Wilms tumor: the British Childhood Cancer Survivor Study. *J Clin Oncol.* 2016;34(15):1772–1779.
86. Green DM, Breslow NE, Beckwith JB, et al. Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol.* 1998;16(1):237–245.
87. Green DM, Breslow NE, Beckwith JB, et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol.* 1998;16(12):3744–3751.
88. Jones B, Breslow NE, Takashima J. Toxic deaths in the Second National Wilms' Tumor Study. *J Clin Oncol.* 1984;2(9):1028–1033.
89. Morgan E, Baum E, Breslow N, Takashima J, D'Angio G. Chemotherapy-related toxicity in infants treated according to the Second National Wilms' Tumor Study. *J Clin Oncol.* 1988;6(1):51–55.
90. Balis FM, Womer RB, Berg S, Winick N, Adamson PC, Fox E. Dosing anticancer drugs in infants: current approach and recommendations from the Children's Oncology Group's Chemotherapy Standardization Task Force. *Pediatr Blood Cancer.* 2017;64(11). doi:10.1002/pbc.26636.
91. Tan CT, Dargeon HW, Burchenal JH. The effect of actinomycin D on cancer in childhood. *Pediatrics.* 1959;24:544–561.
92. Phillips TL, Fu KK. Acute and late effects of multimodal therapy on normal tissues. *Cancer.* 1977;40(1 suppl):489–494.
93. Greco FA, Brereton HD, Kent H, Zimbler H, Merrill J, Johnson RE. Adriamycin and enhanced radiation reaction in normal esophagus and skin. *Ann Intern Med.* 1976;85(3):294–298.
94. Donaldson SS, Glick JM, Wilbur JR. Letter: adriamycin activating a recall phenomenon after radiation therapy. *Ann Intern Med.* 1974;81(3):407–408.
95. D'Angio GJ, Farber S, Maddock CL. Potentiation of x-ray effects by actinomycin D. *Radiology.* 1959;73:175–177.

96. Merrill J, Greco FA, Zimbler H, Brereton HD, Lamberg JD, Pomeroy TC. Adriamycin and radiation: synegistic cardiotoxicity. *Ann Intern Med.* 1975;82(1):122–123.
97. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2005;23(12):2629–2636.
98. Green DM, Finklestein JZ, Norkool P, D'Angio GJ. Severe hepatic toxicity after treatment with single-dose dactinomycin and vincristine. A report of the National Wilms' Tumor Study. *Cancer.* 1988;62(2):270–273.
99. Green DM, Norkool P, Breslow NE, Finklestein JZ, D'Angio GJ. Severe hepatic toxicity after treatment with vincristine and dactinomycin using single-dose or divided-dose schedules: a report from the National Wilms' Tumor Study. *J Clin Oncol.* 1990;8(9):1525–1530.
100. National Cancer Institute. Osteosarcoma and Undifferentiated Pleomorphic Sarcoma of Bone Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. Accessed January 5, 2021. https://www.cancer.gov/types/bone/hp/osteosarcoma-treatment-pdq
101. Geller DS, Gorlick R. Osteosarcoma: a review of diagnosis, management, and treatment strategies. *Clin Adv Hematol Oncol.* 2010;8(10):705–718.
102. Eng C, Li FP, Abramson DH, et al. Mortality from second tumors among long-term survivors of retinoblastoma. *J Natl Cancer Inst*. 1993;85(14):1121–1128.
103. Hicks MJ, Roth JR, Kozinetz CA, Wang LL. Clinicopathologic features of osteosarcoma in patients with Rothmund–Thomson syndrome. *J Clin Oncol.* 2007;25(4):370–375.
104. Lipton JM, Federman N, Khabbaze Y, et al. Osteogenic sarcoma associated with Diamond–Blackfan anemia: a report from the Diamond–Blackfan Anemia Registry. *J Pediatr Hematol Oncol.* 2001;23(1):39–44.
105. Wang LL, Gannavarapu A, Kozinetz CA, et al. Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund–Thomson syndrome. *J Natl Cancer Inst.* 2003;95(9):669–674.
106. van Dalen EC, van As JW, de Camargo B. Methotrexate for high-grade osteosarcoma in children and young adults. *Cochrane Database Syst Rev*. 2011;2011(5):CD006325.
107. Daw NC, Neel MD, Rao BN, et al. Frontline treatment of localized osteosarcoma without methotrexate: results of the St. Jude Children's Research Hospital OS99 trial. *Cancer.* 2011;117(12):2770–2778.
108. Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. *Lancet Oncol.* 2016;17(10):1396–1408.
109. Evans WE, Pratt CB. Effect of pleural effusion on high-dose methotrexate kinetics. *Clin Pharmacol Ther.* 1978;23(1):68–72.

110. Evans WE, Tsiatis A, Crom WR, Brodeur GM, Coburn TC, Pratt CB. Pharmacokinetics of sustained serum methotrexate concentrations secondary to gastrointestinal obstruction. *J Pharm Sci.* 1981;70(11):1194–1198.
111. Crom WR, Pratt CB, Green AA, et al. The effect of prior cisplatin therapy on the pharmacokinetics of high-dose methotrexate. *J Clin Oncol.* 1984;2(6):655–661.
112. Young EP, Cheng WS, Bernhardt MB, Wang LL, Rainusso N, Foster JH. Risk factors associated with delayed methotrexate clearance and increased toxicity in pediatric patients with osteosarcoma. *Pediatr Blood Cancer.* 2020;67(4):e28123.
113. Crews KR, Liu T, Rodriguez-Galindo C, et al. High-dose methotrexate pharmacokinetics and outcome of children and young adults with osteosarcoma. *Cancer.* 2004;100(8):1724–1733.
114. Hegyi M, Gulácsi A, Cságoly E, et al. Clinical relations of methotrexate pharmacokinetics in the treatment for pediatric osteosarcoma. *J Cancer Res Clin Oncol.* 2012;138(10):1697–1702.
115. Hegyi M, Arany A, Semsei AF, et al. Pharmacogenetic analysis of high-dose methotrexate treatment in children with osteosarcoma. *Oncotarget.* 2017;8(6):9388–9398.
116. Lui G, Treluyer JM, Fresneau B, et al. A pharmacokinetic and pharmacogenetic analysis of osteosarcoma patients treated with high-dose methotrexate: data from the OS2006/Sarcoma-09 trial. *J Clin Pharmacol.* 2018;58(12):1541–1549.
117. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. *Oncologist*. 2016;21(12):1471–1482.
118. Suzuki K, Doki K, Homma M, et al. Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. *Br J Clin Pharmacol.* 2009;67(1):44–49.
119. Ferrazzini G, Klein J, Sulh H, Chung D, Griesbrecht E, Koren G. Interaction between trimethoprim-sulfamethoxazole and methotrexate in children with leukemia. *J Pediatr.* 1990;117(5):823–826.
120. Watts CS, Sciasci JN, Pauley JL, et al. Prophylactic trimethoprim-sulfamethoxazole does not affect pharmacokinetics or pharmacodynamics of methotrexate. *J Pediatr Hematol Oncol.* 2016;38(6):449–452.
121. Narumi K, Sato Y, Kobayashi M, et al. Effects of proton pump inhibitors and famotidine on elimination of plasma methotrexate: evaluation of drug-drug interactions mediated by organic anion transporter 3. *Biopharm Drug Dispos.* 2017;38(9):501–508.
122. Chioukh R, Noel-Hudson MS, Ribes S, Fournier N, Becquemont L, Verstuyft C. Proton pump inhibitors inhibit methotrexate transport by renal basolateral

organic anion transporter hOAT3. *Drug Metab Dispos.* 2014;42(12):2041–2048.
123. Millisor VE, Roberts JK, Sun Y, et al. Derivation of new equations to estimate glomerular filtration rate in pediatric oncology patients. *Pediatr Nephrol.* 2017;32(9):1575–1584.
124. Pinedo HM, Chabner BA. Role of drug concentration, duration of exposure, and endogenous metabolites in determining methotrexate cytotoxicity. *Cancer Treat Rep.* 1977;61(4):709–715.
125. Petros WP, Evans WE. Anticancer agents. In: Burton ME, Shaw LM, Schentag JJ, Evans WE, eds. *Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug.* 4th ed. Lippincott Williams & Wilkins; 2006:617.
126. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. *Oncologist.* 2018;23(1):52–61.
127. National Cancer Institute. Childhood Rhabdomyosarcoma Treatment (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. Accessed January 5, 2021. https://www.cancer.gov/types/soft-tissue-sarcoma/hp/rhabdomyosarcoma-treatment-pdq
128. Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975–2005. *Cancer.* 2009;115(18):4218–4226.
129. Wexler LH, Ladanyi M. Diagnosing alveolar rhabdomyosarcoma: morphology must be coupled with fusion confirmation. *J Clin Oncol.* 2010;28(13):2126–2128.
130. Williamson D, Missiaglia E, de Reyniès A, et al. Fusion gene-negative alveolar rhabdomyosarcoma is clinically and molecularly indistinguishable from embryonal rhabdomyosarcoma. *J Clin Oncol.* 2010;28(13):2151–2158.
131. Li FP, Fraumeni JF Jr. Rhabdomyosarcoma in children: epidemiologic study and identification of a familial cancer syndrome. *J Natl Cancer Inst.* 1969;43(6):1365–1373.
132. Diller L, Sexsmith E, Gottlieb A, Li FP, Malkin D. Germline p53 mutations are frequently detected in young children with rhabdomyosarcoma. *J Clin Invest.* 1995;95(4):1606–1611.
133. Trahair T, Andrews L, Cohn RJ. Recognition of Li Fraumeni syndrome at diagnosis of a locally advanced extremity rhabdomyosarcoma. *Pediatr Blood Cancer.* 2007;48(3):345–348.
134. Li H, Sisoudiya SD, Martin-Giacalone BA, et al. Germline cancer-predisposition variants in pediatric rhabdomyosarcoma: a report from the Children's Oncology Group. *J Natl Cancer Inst.* 2021;113(7):875–883.
135. Crucis A, Richer W, Brugières L, et al. Rhabdomyosarcomas in children with neurofibromatosis type I: a national historical cohort. *Pediatr Blood Cancer.* 2015;62(10):1733–1738.

136. Doros L, Yang J, Dehner L, et al. DICER1 mutations in embryonal rhabdomyosarcomas from children with and without familial PPB-tumor predisposition syndrome. *Pediatr Blood Cancer.* 2012;59(3):558–560.
137. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol.* 1995;13(3):610–630.
138. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. *J Clin Oncol*. 2001;19(12):3091–3102.
139. Sung L, Anderson JR, Donaldson SS, Spunt SL, Crist WM, Pappo AS. Late events occurring five years or more after successful therapy for childhood rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Eur J Cancer*. 2004;40(12):1878–1885.
140. Raney RB, Walterhouse DO, Meza JL, et al. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol.* 2011;29(10):1312–1318.
141. Walterhouse DO, Pappo AS, Meza JL, et al. Reduction of cyclophosphamide dose for patients with subset 2 low-risk rhabdomyosarcoma is associated with an increased risk of recurrence: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Cancer.* 2017;123(12):2368–2375.
142. Walterhouse DO, Pappo AS, Meza JL, et al. Shorter-duration therapy using vincristine, dactinomycin, and lower-dose cyclophosphamide with or without radiotherapy for patients with newly diagnosed low-risk rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol.* 2014;32(31):3547–3552.
143. Crist WM, Garnsey L, Beltangady MS, et al. Prognosis in children with rhabdomyosarcoma: a report of the intergroup rhabdomyosarcoma studies I and II. Intergroup Rhabdomyosarcoma Committee. *J Clin Oncol*. 1990;8(3):443–452.
144. Weigel BJ, Lyden E, Anderson JR, et al. Intensive multiagent therapy, including dose-compressed cycles of ifosfamide/etoposide and vincristine/doxorubicin/cyclophosphamide, irinotecan, and radiation, in patients with high-risk rhabdomyosarcoma: a report from the Children's Oncology Group. *J Clin Oncol.* 2016;34(2):117–122.
145. Rossi R, Gödde A, Kleinebrand A, et al. Unilateral nephrectomy and cisplatin as risk factors of ifosfamide-induced nephrotoxicity: analysis of 120 patients. *J Clin Oncol.* 1994;12(1):159–165.
146. Skinner R, Pearson AD, English MW, et al. Risk factors for ifosfamide nephrotoxicity in children. *Lancet.* 1996;348(9027):578–580.
147. Suarez A, McDowell H, Niaudet P, Comoy E, Flamant F. Long-term follow-up of ifosfamide renal toxicity in children treated for malignant mesenchymal

tumors: an International Society of Pediatric Oncology report. *J Clin Oncol.* 1991;9(12):2177–2182.

148. Ben Yehuda A, Heyman A, Steiner-Salz D. False positive reaction for urinary ketones with mesna. *Drug Intell Clin Pharm.* 1987;21(6):547–548.
149. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:83–103.
150. Ries LAG, Smith MA, Gurney JG, et al, eds. *Cancer Incidence and Survival Among Children and-Adolescents: United States SEER Program 1975–1995*. NIH Publication No. 99-4649. National Cancer Institute, SEER Program; 1999.
151. Onciu M. Acute lymphoblastic leukemia. *Hematol Oncol Clin N Am*. 2009;23:655–675.
152. Lee P, Bhansali R, Izraeli S, Hijiya N, Crispino JD. The biology, pathogenesis and clinical aspects of acute lymphoblastic leukemia in children with Down syndrome. *Leukemia*. 2016;30:1816–1823.
153. Rabin KR, Gramatges MM, Margolin JF, et al. Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Lippincott Williams & Wilkins; 2010.
154. Bhojwani D, Moskowitz N, Raetz EA, Carroll WL. Potential of gene expression profiling in the management of childhood acute lymphoblastic leukemia. *Paediatr Drugs*. 2007;9:149–156.
155. Clarke RT, Van den Bruel A, Bankhead C, Mitchell CD, Phillips B, Thompson MJ. Clinical presentation of childhood leukaemia: a systematic review and meta-analysis. *Arch Dis Child*. 2016;101:894–901.
156. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol*. 1996;14:18–24.
157. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–2405.
158. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. *Pediatr Clin North Am*. 2015;62:61–73.
159. Vrooman LM, Silverman LB. Treatment of childhood acute lymphoblastic leukemia: prognostic factors and clinical advances. *Curr Hematol Malig Rep*. 2016;11:385–394.
160. Guest EM, Stam RW. Updates in the biology and therapy infant acute lymphoblastic leukemia. *Curr Opin Pediatr*. 2017;29:20–26.
161. Bhojwani D, Yang JJ, Pui CH. Biology of childhood acute lymphoblastic leukemia. *Pediatr Clin North Am*. 2015;62:47–60.
162. Amylon MD, Shuster J, Pullen J, et al. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. *Leukemia*. 1999;13:335–342.

163. Goldberg JM, Silverman LB, Levy DE, et al. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. *J Clin Oncol*. 2003;21:3616–3622.
164. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). *Blood*. 2011;118:874–883.
165. Paulsson K, Johansson B. High hyperdiploid childhood acute lymphoblastic leukemia. *Genes Chromosomes Cancer*. 2009;48:637–660.
166. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in-Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group study. *J Clin Oncol*. 2009;27(31):5175–5181.
167. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia*. 2014;28:1467–1471.
168. Sutcliffe MJ, Shuster JJ, Sather HN, et al. High concordance from independent studies by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) associating favorable prognosis with combined trisomies 4, 10, and 17 in children with NCI Standard-Risk B-precursor Acute Lymphoblastic Leukemia: a Children's Oncology Group (COG) initiative. *Leukemia.* 2005;19:734–740.
169. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in-childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;111:5477–5485.
170. Borowitz M, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood*. 2015;126:964–971.
171. Willemse MJ, Seriu T, Hettinger K, et al. Detection of minimal residual disease identifies differences in treatment response between T-ALL and precursor B-ALL. *Blood*. 2002;99:4386–4393.
172. Skipper HE, Perry SE. Kinetics of normal and leukemic leukocyte populations and relevance to chemotherapy. *Cancer Res*. 1970;30:1883–1897.
173. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2003;101:3809–3017.
174. Maloney KW, Devidas M, Wang C, et al. Outcome in children with standard-risk b-cell acute lymphoblastic leukemia: results of Children's Oncology Group trial AALL0331. *J Clin Oncol*. 2020;38:602–612.

175. Teuffel O, Kuster SP, Hunger SP, et al. Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. *Leukemia*. 2011;25:1232–1238.
176. Hurwitz CA, Silverman LB, Schorin MA, et al. Substituting dexamethasone for prednisone complicates remission induction in children with acute lymphoblastic leukemia. *Cancer*. 2000;88:1964–1969.
177. Reiter A, Schrappe M, Ludwig WD, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients: results and conclusions of the multicenter trial ALL-BFM 86. *Blood*. 1994;84:3122–3133.
178. Sackmann-Muriel F, Felice MS, Zubizarreta PA, et al. Treatment results in childhood acute lymphoblastic leukemia with a modified ALL-BFM'90 protocol: lack of improvement in high-risk group. *Leuk Res*. 1999;23:331–340.
179. Gaynon PS, Steinherz PG, Bleyer WA, et al. Improved therapy for children with acute lymphoblastic leukemia and unfavorable presenting features: a follow-up report of the Children's Cancer Group study CCG-106. *J Clin Oncol*. 1993;11:2234–2242.
180. Goldie JH, Coldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treat Rep*. 1982;66:439–449.
181. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study [published correction appears in *Blood*. 2002;100:1531]. *Blood*. 2002;99:1986–1994.
182. van de Velde ME, Kaspers GL, Abbink FCH, Wilhelm AJ, Ket JCF, van den Berg MH. Vincristine-induced peripheral neuropathy in children with cancer: a systematic review. *Crit Rev Oncol Hematol*. 2017;114:114–130.
183. Pound CM, Clark C, Ni A, Athale U, Lewis V, Halton JM. Corticosteroids, behavior, and quality of life in children treated for acute lymphoblastic leukemia; a multicentered trial. *J Pediatr Hematol Oncol*. 2012;34(7):517–523.
184. Richards S, Pui CH, Gayon P; Childhood Acute Lymphoblastic Leukemia Collaborative Group (CALLCG). Systematic review and meta-analysis of randomized trials of central nervous system directed therapy for childhood acute lymphoblastic leukaemia. *Pediatr Blood Cancer*. 2013;60:185–195.
185. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med*. 2009;360:2730–2741.
186. Veerman AJ, Kamps WA, van den Berg H, et al. Dexamethasone-based therapy for childhood acute lymphoblastic leukemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997–2004). *Lancet Oncol*. 2009;10:957–966.
187. Bleyer AW. Clinical pharmacology of intrathecal methotrexate: II. An improved dosage regimen derived from age-related pharmacokinetics.

Cancer Treat Rep. 1977;61:1419–1425.
188. Bleyer WA, Coccia PF, Sather HN, et al. Reduction in central nervous system leukemia with a pharmacokinetically derived intrathecal methotrexate dosage regimen. *J Clin Oncol*. 1983;1:317–325.
189. Gilbar PJ. Inadvertent intrathecal administration of vincristine: time to finally abolish the syringe. *J Oncol Pharm Pract*. 2020;26(2):263–266.
190. Schmiegelow K, Nielsen SN, Frandsen TL, Nersting J. Mercaptopurine/methotrexate maintenance therapy of childhood acute lymphoblastic leukemia: clinical facts and fiction. *J Pediatr Hematol Oncol*. 2014;36:503–517.
191. Mullighan C, Phillips LA, Su X, et al. Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia. *Science*. 2008;322:1377–1380.
192. Angiolillo A, Schore R, Devidas M, et al. Intensification of oral methotrexate is not superior to standard methotrexate dosing during maintenance in children with National Cancer Institute (NCI) Standard-risk B Acute Lymphoblastic Leukemia (SR B-ALL): a report from Children's Oncology Group (COG) study AALL0932. *Blood.* 2017;130:140.
193. Landler W, Hageman L, Chen Y, et al. Mercaptopurine ingestion habits, red cell thioguanine nucleotide levels, and relapse risk in children with acute lymphoblastic leukemia: a report from the Children's Oncology Group study AALL03N1. *J Clin Oncol*. 2017;35:1730–1736.
194. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther.* 2019;105:1095–1105.
195. Singh M, Bhatia P, Khera S, Trehan A. Emerging role of NUDT15 polymorphisms in 6-mercaptopurine metabolisms and dose related toxicity in acute lymphoblastic leukaemia. *Leuk Res*. 2017;62:17–22.
196. Krikorian S, Pories S, Tataronis G, et al. Adherence to oral chemotherapy: challenges and opportunities. *J Oncol Pharm Pract*. 2019;25:1590–1598.
197. Bhatia S, Landier W, Hageman L, et al. 6MP adherence in a multiracial cohort of children with acute lymphoblastic leukemia: a Children's Oncology Group study. *Blood*. 2014;124:2345–2353.
198. Pieters R, Hunger SP, Boos J, et al. L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asaparaginase. *Cancer.* 2011;117:238–249.
199. Salzer W, Bostrom B, Messinger Y, Perissinotti AJ, Marini B. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. *Leuk Lymphoma*. 2018;59:1797–1806.
200. Liu Y, Smith CA, Panetta JC, et al. Antibodies predict pegaspargase allergic reactions and failure of rechallenge. *J Clin Oncol*. 2019;37:2051–2061.
201. Abshire TC, Pollock BH, Billett AL, Bradley P, Buchanan GR. Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly

dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a pediatric oncology group study. *Blood*. 2000;96:1709–1715.

202. Wetzler M, Sanford BL, Kurtzberg J, et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: cancer and leukemia group B study 9511. *Blood*. 2007;109:4164–4167.
203. Zalewska-Szewczyk B, Andrzejewski W, Młynarski W, Jedrychowska-Dan ´ska K, Witas H, Bodalski J. The anti-asparagines antibodies correlate with L-asparagines activity and may affect clinical outcome of childhood acute lymphoblastic leukemia. *Leuk Lymphoma*. 2007;48:931–936.
204. Van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Harmatologica*. 2016;101:279–285.
205. Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: results of Children's Oncology Group trial AALL0622. *J Clin Oncol*. 2018;26:2306–2314.
206. Cohen M, Johnson JR, Justice R, Pazdur R. FDA drug approval summary: nelarabine (Arranon) for the treatment of T-cell lymphoblastic leukemia/lymphoma. *Oncologist*. 2008;13:709–714.
207. Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 605U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J Clin Oncol*. 2005;23:3376–3382.
208. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group study AALL0434. *Pediatr Blood Cancer*. 2015;62:1176–1183.
209. DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood*. 2007;109:5136–5142.
210. Sun W, Malvar J, Sposto R, et al. Outcome of children with multiply relapsed B-cell acute lymphoblastic leukemia: a therapeutic advances in childhood leukemia & lymphoma study. *Leukemia*. 2018;32:2316–2325.
211. Ko RH, Ji L, Barnette P, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. *J Clin Oncol*. 2010;28:648–654.
212. Parker C, Krishnan S, Hamadeh L, et al. Outcomes of patients with childhood B-cell precursor acute lymphoblastic leukaemia with late bone marrow relapses: long-term follow-up of the ALLR3 open-label randomised trial. *Lancet Haematol*. 2019;6:e204–e216.

213. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomized trial. *Lancet.* 2010;376:2009–2017.
214. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376:836–847.
215. Brown PA, Ji L, Xu X, et al. A randomized phase 3 trial of blinatumomab vs. chemotherapy as post-reinduction therapy in high and intermediate risk (HR/IR) first relapse of B-acute lymphoblastic leukemia (B-ALL) in children and adolescents/young adults (AYAs) demonstrates superior efficacy and tolerability of blinatumomab: a report from Children's Oncology Group study AALL1331. *Blood.* 2019; 134(suppl_2):LBA-1.
216. Topp MS, Goekbuget N, Stein AS, et al. Confirmatory open-label, single-arm, multicenter phase 2 study of the BiTE antibody blinatumomab in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL). *J Clin Oncol*. 2014;32(15_suppl):7005.
217. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol*. 2016;34:4381–4389.
218. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 2018;131:1522–1531.
219. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicenter, single-arm, phase 2 study. *Lancet Oncol*. 2015;16:57–66.
220. Topp MS, Gökbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol*. 2014;32:4134–4140.
221. Merli P, Algeri M, Del Bufalo F, Locatelli F. Hematopoietic stem cell transplantation in pediatric acute lymphoblastic leukemia. *Curr Hematol Malig Rep*. 2019;14:94–105.
222. Oliansky DM, Larson RA, Weisdorf D, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: update of the 2006 evidence-based review. *Biol Blood Marrow Transplant*. 2012;18:18–36.
223. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014;371:1507–1517.
224. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439–448.

225. Grupp S, Frey NV, Aplenc R, et al. T cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019) produce significant in vivo proliferation, complete responses and long-term persistence without GVHD in children and adults with relapsed, refractory ALL. *Blood.* 2013;122:67.
226. Minard-Colin V, Brugières L, Reiter A, et al. Non-Hodgkin lymphoma in children and adolescents: progress through effective collaboration, current knowledge, and challenges ahead. *J Clin Oncol*. 2015;33:2963–2974.
227. Sandlund J. Non-Hodgkin lymphoma in children. *Curr Hematol Malig Rep.* 2015;10:237–243.
228. Minard-Colin V, Aupérin A, Pillon M, et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children. *N Engl J Med*. 2020;382:2207–2219.
229. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol*. 1980;7:332–339.
230. Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. *J Clin Oncol*. 2015;33(18):2106–2111.
231. Rosolen A, Perkins SL, Pinkerton CR, et al. Revised International Pediatric Non-Hodgkin Lymphoma Staging System. *J Clin Oncol*. 2015;33:2112–2118.
232. Bassan R, Maino E, Cortelazzo S, et al. Lymphoblastic lymphoma: an updated review on biology, diagnosis, and treatment. *Eur J Haematol*. 2015;96:447–460.
233. Teachey D, O'Connor D. How I treat newly diagnosed T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma in children. *Blood*. 2020;135:159–166.
234. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. *Blood*. 2000;95:416–421.
235. Link MP, Shuster JJ, Donaldson SS, Berard CW, Murphy SB. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma. *N Engl J Med*. 1997;337:1259–1266.
236. Gerrard M, Cairo MS, Weston C, et al. Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: results of the FAB/LMB 96 international study. *Br J Haematol*. 2008;141:840–847.
237. Patte C, Auperin A, Michon J, et al. The Societe Francaise d'Oncologie Pediatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. *Blood*. 2001;97:3370–3379.
238. Jetsrisuparb A, Wiangnon S, Komvilaisak P, Kularbkaew C, Yutanawiboonchai W, Mairieng E. Rituximab, combined with CHOP for

successful treatment of aggressive recurrent, pediatric B-cell large cell non-Hodgkin's lymphoma. *J Pediatr Hematol Oncol*. 2005;27:223–226.

239. Claviez A, Eckert C, Seeger K, et al. Rituximab plus chemotherapy in children with relapsed or refractory CD20-positive B-cell precursor acute lymphoblastic leukemia. *Haematologica*. 2006;91:272–273.
240. Dupuis LL, Boodhan S, Holdsworth M, et al. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer.* 2013;60:1073–1082.

96

Adult Hematologic Malignancies

Casey B. Williams, Rachel Elsey, Sarah M. Hayes, and Jacob K. Kettle

CORE PRINCIPLES	CHAPTER CASES
ACUTE MYELOID LEUKEMIA	
1 Acute myeloid leukemia (AML) generally appears suddenly and progresses rapidly. Death as a result of infection or bleeding occurs within weeks to months if the patient is not effectively treated.	**Case 96-1 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
2	Although >60% of patients treated for AML achieve complete remission after induction therapy, the median duration of the remission is only about 12–18 months, and only 20%–40% of patients have a disease-free survival (DFS) exceeding 5 years. Short remissions have been attributed to proliferation of clinically undetectable leukemic cells. Thus, the rationale for administering chemotherapy after remission is to eradicate these residual cells.	**Case 96-1 (Question 5)**
3	The incidence of AML increases with advancing age. At age 40 years, there is only 1 case of AML per 100,000, but the annual incidence increases to 15% at age older than 75 years. The prognosis of patients with AML is directly related to age.	**Case 96-1 (Question 7)**
4	Elderly patients do not tolerate intensive induction and postremission chemotherapy as well as younger patients. Older patients often have comorbid medical conditions and a poor performance status, which are associated with worse outcomes with conventional therapy.	**Case 96-1 (Question 7)**

CORE PRINCIPLES		CHAPTER CASES
5	In younger patients, failure to achieve remission or disease relapse remains the major cause of treatment failure. This reflects both the failure of current salvage regimens and the absence of effective strategies to secure long-term DFS in those patients who achieve a second hematologic remission. A wide range of salvage options have been studied, but with <50% of patients achieving a second remission and median survival ranging from 3 to 12 months, there remains considerable room for improvement.	**Case 96-2 (Question 1)**
CHRONIC MYELOGENOUS LEUKEMIA		
1	Chronic myelogenous leukemia (CML) occurs in three phases: chronic, accelerated, and blast. Most patients are diagnosed in chronic-phase CML and are asymptomatic at presentation but evaluated because of an abnormally high leukocyte count (often >100 × 10^9/L). The cytogenetic hallmark of CML is the Philadelphia (Ph) chromosomal translocation oncogene, which generates the BCR-ABL fusion protein. Quantitative assessment of BCR-ABL messenger ribonucleic acid (mRNA) transcripts in the blood is used to measure response to therapy.	**Case 96-3 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
2	Hematopoietic stem cell transplantation (HCT) is the only curative therapy for CML, but it is seldom recommended as first-line therapy for patients in chronic-phase CML. Imatinib, dasatinib, nilotinib, and bosutinib are all oral small-molecule tyrosine kinase inhibitors (TKIs) of the BCR-ABL protein and approved as first-line treatment.	**Case 96-3 (Question 3)**
LYMPHOMA		
1	Lymphomas are a diverse collection of hematologic malignancies originating from lymphoid tissues. Lymphomas are classified as either Hodgkin lymphoma (HL) or non–Hodgkin lymphoma (NHL). The NHLs can be further divided into aggressive or indolent subgroups. Symptoms include painless lymphadenopathy along with nonspecific findings of generalized malaise and fatigue. Advanced complications arise from the infiltration of the disease into extramedullary tissues including the lungs, central nervous system, and bone marrow.	**Case 96-4 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
2	HL is a B-cell neoplasm and is highly responsive to chemotherapy and often curable with modern treatments. A combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is the most frequently used chemotherapy regimen. Delayed consequences of therapy have heightened importance in the management of this disease owing to the expected long-term survival for most patients.	**Case 96-5 (Questions 1, 2)**
3	Aggressive NHLs such as diffuse large B-cell lymphoma (DLBCL) progress rapidly and are treated with intensive combination chemotherapy regimens administered with a curative intent. Chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is conventional therapy for DLBCL.	**Case 96-6 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
4	Although indolent NHLs including follicular lymphoma (FL) are generally incurable, these diseases develop slowly and are initially responsive to numerous therapies. Treatment is aimed at reducing disease burden and prolonging survival and is often reserved until the patient is symptomatic. A combination of bendamustine and rituximab (BR) is commonly used in the management of these neoplasms.	**Case 96-7 (Questions 1, 2)**

INTRODUCTION

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) consists of a group of relatively well-defined hematopoietic neoplasms involving precursor cells committed to the myeloid line of cellular development.

In the United States and Europe, the incidence has been relatively stable at 3 to 5 cases per 100,000. AML is the most common acute leukemia in adults and accounts for ~80% of cases in this group of neoplasms. In contrast, AML accounts for <10% of acute leukemias in children younger than 10 years of age. AML incidence is age dependent, rising markedly in patients ages 60 years. Across all age groups, the incidence of AML is higher in males than in females.[1–3] The median age at diagnosis is ~70 years.[4]

The 2016 World Health Organization (WHO) classification identifies distinct categories of AML.[5] Notably, AML is primarily categorized by recurrent genetic abnormalities, with morphologic

classification reserved for patients not otherwise classifiable. With advanced age, the relative incidence of AML with recurrent genetic abnormalities decreases, whereas the relative incidence of other AML categories increases with age, comprising about 19% and 7% of AML cases, respectively.[6] A complete list of the WHO classification of AML can be found at https://doi.org/10.1182/blood-2016-03-643544.

Pathophysiology

AML is characterized by a clonal proliferation of myeloid precursors with a reduced capacity to differentiate into mature myeloid cells. As a result, there is an accumulation of leukemic blasts in the bone marrow (BM), peripheral blood, and occasionally in other tissues, with a variable reduction in the production of normal red blood cells, platelets, and mature granulocytes. The proliferation of malignant cells, along with a reduction in normal hematopoietic cells, results in a variety of systemic consequences including anemia, bleeding, and an increased risk of infection.

Genetic classification of AML is essential to guide clinical decisions and predict prognosis. The 2017 European LeukemiaNet and American Society of Hematology recommendations identify three risk groups, based on karyotype and mutational analysis (**Table 96-1**).[1,4,7,8] The favorable-risk AML group comprises all patients in whom a relapse risk is predicted to be low if treated with induction and consolidation alone. The intermediate-risk AML group comprises patients with molecular or cytogenetic abnormalities not classified as favorable or adverse and includes patients with *NPM1*^{mut} and a high allelic ratio of *FLT3*-ITD. The adverse-risk AML group includes patients with complex cytogenetics and other poor-risk genetic aberrations. All patients failing to achieve a complete response (CR) after two induction cycles should also be considered as adverse-risk patients, regardless of genetics/cytogenetics. Accurate risk stratification plays a critical role in guiding the selection

of the optimal postremission approach and of indications for allogeneic hematopoietic cell transplant (alloHCT) in first CR (CR1).

Table 96-1
Risk Stratification of Acute Myeloid Leukemia by Genetics

Risk Category	Genetic Abnormality
Favorable	▪ t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* ▪ inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* ▪ Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} ▪ Biallelic mutated *CEBPA*
Intermediate	▪ Mutated *NPM1* and *FLT3*-ITD^{high} ▪ Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse risk genetic lesions) ▪ t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* ▪ Cytogenetic abnormalities not classified as favorable or adverse
Adverse	▪ t(6;9)(p23;q34.1); *DEK-NUP214* ▪ t(v;11q23.3); *KMT2A* rearranged ▪ t(9;22)(q34.1;q11.2); *BCR-ABL1* ▪ inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM (EVI1)* ▪ -5 or del(5q); -7; -17/abn(17p) ▪ Complex karyotype, monosomal karyotype ▪ Wild-type *NPM1* and *FLT3*-ITD^{high} ▪ Mutated *RUNX1* ▪ Mutated *ASXL1* ▪ Mutated *TP53*

A comprehensive risk classification integrating clinical, genetic, and treatment data is available as an online tool that simulates the individual patient's risk and predicts outcome with and without alloHCT (https://cancer.sanger.ac.uk/aml-multistage/).[9]

Clinical Presentation and Diagnosis

Patients with AML generally present with symptoms related to complications of pancytopenia (eg, anemia, neutropenia, and thrombocytopenia), including weakness and easy fatigability, infections of variable severity, and hemorrhagic findings such as gingival bleeding, ecchymosis, epistaxis, or menorrhagia. Combinations of these symptoms are common. It is often difficult to date the onset of AML precisely, at least in part because individuals have different symptomatic thresholds for seeking medical attention. It is likely that most patients have had more subtle evidence of BM involvement for weeks, or perhaps months, before diagnosis. Although a presumptive diagnosis of AML can be made by examination of the peripheral blood smear when there are circulating leukemic blasts, a definitive diagnosis usually requires a BM aspiration and biopsy. Morphologic, immunophenotypic, cytogenetic, and molecular studies must be performed in every case. The information derived from these studies is critical for making the correct diagnosis as well as determining prognosis and treatment.

Classification and Diagnosis

For a definitive diagnosis of AML, the BM aspirate must contain >20% leukemic blast cells. A normal BM aspirate would typically contain <5% blast cells.

Patients suspected of a diagnosis of AML must undergo prompt cytogenetic and molecular investigations to inform risk stratification and, increasingly, treatment strategies. It is vital to urgently differentiate acute promyelocytic leukemia (APL) from other forms of AML by cytomorphology, signs of hyperfibrinolysis, and molecular evidence of *PML-RARA* fusion.

AML is defined based on morphologic inspection revealing a myeloid blast count of ≥20% out of 500 BM cells, although counting fewer cells is sufficient in patients with high blast counts. Blast counts should include myeloblasts, monoblasts/promonocytes, and megakaryoblasts, but not abnormal monocytes. According to the latest WHO classification, all nucleated cells in the BM serve as a

denominator, even in cases where the BM is enriched with erythroid precursors.

Cells of myeloid origin commonly contain myeloperoxidase enzymes and express surface markers CD13, CD33, CD14, and CD15. Specific clonal chromosomal abnormalities are associated with several AML subtypes. These aberrations include gains or losses of whole chromosomes on the long (q) or short (p) arms, as well as a variety of structural rearrangements (eg, translocations, inversions, insertions). These findings are increasingly being used to guide treatment decisions and a full list can be found in consensus guidelines. For example, patients with cytogenetic and molecular findings associated with a poor prognosis may be considered for more aggressive postremission therapy such as high-dose chemotherapy with HCT. Other poor prognostic signs in AML include age older than 60 years at the time of diagnosis, a preexisting hematologic disorder (eg, myelodysplastic syndrome), prior exposure to a chemotherapy agent (eg, a secondary leukemia), and poor baseline performance status.

Signs and Symptoms

CASE 96-1

Question 1: C.C., a 58-year-old male, presented to the emergency department with increasing fatigue and fever and an inability to eat. This past week, a peripheral blood smear (complete blood count [CBC]) revealed a white blood cell (WBC) count of 160,000 cells/μL with a differential of >90% leukemic blasts (normal, 0%), a hemoglobin (Hgb) of 7.5 g/dL, and a platelet count of 42,000 cells/μL. A BM aspirate and biopsy confirmed the diagnosis of AML (60% blasts, myeloperoxidase positive; CD13 and CD33 positive). All serum chemistry values were within normal limits, with the exception of potassium (K), 3.1 mEq/L; phosphorus, 5.5 mg/dL; and lactate dehydrogenase (LDH), 3500 units/mL. Physical examination was remarkable for oral leukoplakia from oral candidiasis and poor dentition.

Which signs and symptoms exhibited by C.C. are consistent with AML?

C.C.'s symptoms of increasing fatigue and fever of 1 week's duration are consistent with a rapid reduction in red blood cells leading to anemia (Hgb, 7.5 g/dL) and a low neutrophil count leading to infection (oral candidiasis). Although his WBC count is high, the differential reveals that >90% are blasts, which are immature, nonfunctional cells of myeloid or lymphoid origin. Circulating blast cells are typically not present in early chronic leukemias or mild-to-moderate infections. However, blasts may be observed on the peripheral blood smear in patients with anemia associated with primary BM dysfunction (myelodysplastic syndromes). Blasts are also present in patients with severe infection, stress, or trauma, and in those with chronic myelogenous leukemia (CML) in transformation to acute leukemia. C.C.'s platelet count is also low, which may lead to bleeding or bruising. Collectively, these are presenting signs and symptoms of acute leukemia.

The symptoms C.C. is exhibiting are consistent with either AML or acute lymphocytic leukemia (ALL). However, patients with ALL also commonly present with lymphadenopathy and hepatosplenomegaly, which C.C. does not have. It is important to distinguish between these two disorders because treatment regimens differ greatly. AML is more common in adults than in children. For additional information on ALL, see the section on Acute Lymphoblastic Leukemia of Childhood in Chapter 95, Pediatric Malignancies.

Overview of Treatment

Once the diagnosis of AML is established, induction chemotherapy is given with the goal of rapidly restoring normal BM function. Treatment regimens and outcomes differ between younger and older adults. Although there is no clear dividing line between younger and older adults when dealing with AML, in most studies "older adults" are defined as older than age 60 years.

The objective of induction therapy is to reduce the total body leukemia cell population from ~10^{12} to less than the cytologically detectable level of about 10^{9} cells. It is generally assumed, however,

that a substantial burden of leukemia cells persists undetected (ie, presence of “minimal residual disease” [MRD]), leading to relapse within a few weeks or months if no further therapy was administered. The traditional goal of treatment of AML is to produce and maintain a complete remission. Criteria for this are platelet count >100,000 cells/μL, neutrophil count >1000 cells/μL, and BM specimen with <5% blasts.[10]

The induction regimens for AML commonly are “7 + 3” regimens, which combine a 7-day continuous intravenous (IV) infusion of cytarabine (100 or 200 mg/m^2/day) with a short infusion or bolus of an anthracycline given on days 1 through 3. The most commonly used anthracycline in this regimen is daunorubicin, but idarubicin may be used instead.

Sixty to 80% of adult patients with newly diagnosed AML will attain a CR with intensive induction chemotherapy. However, without additional cytotoxic therapy, virtually all patients will relapse within a median of 4 to 8 months. In contrast, patients who receive postremission therapy may expect 4-year survival rates as high as 40% in young and middle-age adults with good-risk disease.[11] High-dose cytarabine (HiDAC) has been the consolidation chemotherapy of choice for more than a decade for younger patients with good- or intermediate-risk disease. Attempts to improve survival rates attained with HiDAC by substituting other agents with different mechanisms of action have not been successful.[12,13] For patients with an abnormal karyotype or with adverse molecular mutations, consolidation with HiDAC followed by an alloHCT with a suitably matched donor is the treatment of choice whenever possible. For patients older than age 75 years, there is no specific standard of care except to enroll in a clinical trial when available. For the large number of patients who are ages 60 to 75 years, most clinicians will base induction and consolidation therapy recommendations on a patient’s performance status, patient’s wishes, and prognostic factors such as cytogenetics and mutation analysis.[14]

Twenty to 30% of young adult patients and 50% of older adult patients with newly diagnosed AML will fail to attain a CR with intensive induction chemotherapy as a result of drug resistance or

death. In addition, a large percentage of patients who initially attain a CR will relapse. The therapy that provides the best chance to cure a patient with relapsed or refractory AML is an alloHCT. The best outcomes appear to be with a myeloablative preparative regimen administered after attaining a CR. However, some patients may be cured with myeloablative HCT even without attaining a CR although their chance of long-term survival is reduced. Nonmyeloablative preparative regimens are considered for patients who are not candidates for myeloablative HCT but have attained a CR.[15] See Chapter 101, Hematopoietic Stem Cell Transplantation, for a complete discussion of HCT for leukemia. Refer to the following online reference for more details about the treatment and prognosis of AML: http://www.cancer.gov/cancertopics/pdq/treatment/adultAML/healthprofessional/page4.

Treatment

GOAL OF THERAPY

Case 96-1, Question 2: C.C.'s karyotype and genetic analyses findings returned as normal and positive for FMS-like tyrosine kinase (TK) 3 internal tandem duplication allelic ratio >0.5 (FLT3-ITD^{high}), respectively. What is the goal of treatment and what type of therapy is indicated for C.C. at this time?

The leukemic cells populating C.C.'s blood are abnormal and incapable of fighting infection. Their rapid proliferation is suppressing red blood cell and megakaryocyte production in the BM. C.C. is at substantial risk for life-threatening infections and bleeding complications. The goal of the initial chemotherapy is to clear the BM and peripheral blood of all blast cells in the hope that normal blood cell components can regenerate. The karyotype and genetic analyses can be very helpful to determine which treatment regimen will provide the highest likelihood for response. Although this information is very helpful, results may be delayed and not

necessarily available for all patients before they start treatment. The molecular analysis guides the decision for therapy and these findings in combination with other prognostic features, as discussed previously, will influence postremission therapy recommendations. In this case, C.C. will start cytarabine 200 mg/m^2 continuous infusion for 7 days with daunorubicin 60 mg/m^2 IV for 3 days and oral midostaurin 50 mg every 12 hours on days 8 to 21. Alternatively, if C.C. had not had any genetic alterations, a therapy regimen that included gemtuzumab ozogamicin could be utilized because his AML is positive for CD33.

INDUCTION THERAPY

Standard induction chemotherapy for AML includes an anthracycline (either daunorubicin or idarubicin) and cytarabine, an antimetabolite. One commonly used regimen includes idarubicin 12 mg/m^2/day on days 1 to 3 as an IV bolus injection, plus cytarabine 100 mg/m^2/day as a continuous IV infusion on days 1 to 7.[16–19] This combination (7 + 3) is one of the most effective chemotherapy regimens used to treat adult AML, with CR rates of 60% to 80%. Continuous infusions of cytarabine are preferred because these regimens produce higher response rates than do bolus injections during induction therapy.[17]

If a patient presents with a very high WBC count, he or she may experience complications associated with hyperviscosity of the blood (eg, ringing ears, stroke, blindness, or headache as a result of impaired oxygen delivery to the central nervous system [CNS], pulmonary infarction). Because it may take several days for cytarabine and idarubicin to substantially decrease the WBC count, the patient may receive hydroxyurea 2 to 4 g orally or undergo leukapheresis to rapidly reduce the WBC count. Leukapheresis is not routinely done unless the patient is experiencing symptoms of hyperviscosity or has a WBC ≥100,000 cells/μL on diagnosis. Early mortality was not reduced by leukapheresis, so it is not recommended unless combined with another agent.[20]

Because C.C.'s initial WBC was 160,000 cells/μL, leukapheresis was initiated together with concomitant hydroxyurea 2 g twice daily.

Approximately 12 hours after initiating leukapheresis, C.C.'s WBC had decreased to 85,000 cells/μL and he was stable enough to proceed to induction therapy. The leukapheresis and hydroxyurea were subsequently discontinued.

Complications of induction therapy

Tumor Lysis Syndrome

CASE 96-1, QUESTION 3: Twenty-four hours after C.C.'s induction chemotherapy was initiated, the following laboratory values were obtained:

WBC count, 72,000 cells/μL
K, 5.4 mEq/L
Phosphorus, 6.2 mg/dL
Uric acid, 9.6 mg/dL
Calcium, 6.1 mg/dL
Creatinine, 1.7 mg/dL

Why have these laboratory values changed so suddenly? Could this have been minimized or prevented? How should these metabolic disturbances be managed?

C.C. presented with a very high number of peripheral blood blasts. On administration of chemotherapy, patients with a hypercellular BM and high number of blast cells can have a rapid lysis of the blast cells and the release of cellular contents. This can result in tumor lysis syndrome (TLS), which is associated with metabolic abnormalities such as hyperuricemia, hyperphosphatemia, hypocalcemia, and uremia.[21,22] These disturbances may lead to arrhythmias and acute renal failure. In most cases, TLS occurs 12 to 24 hours after chemotherapy is initiated. TLS may occur after therapy for other malignancies, particularly in those with a high tumor burden, such as high-grade lymphomas and ALL; it rarely occurs after therapy for solid tumors.

Patients should receive IV hydration (3–4 L/day) beginning 24 to 48 hours before chemotherapy to maintain renal perfusion, optimize the solubility of tumor lysis products, and compensate for fluid losses

caused by fever or vomiting. Goal urine output is at least 100 mL/hour.

Allopurinol, a xanthine oxidase inhibitor that blocks the production of uric acid, should be started before chemotherapy to prevent or minimize the complications of TLS. The recommended adult dosage is 300 to 600 mg/day.[21] C.C.'s serum uric acid and electrolytes should be monitored at least two to three times a day for 24 to 48 hours after initiating chemotherapy. If severe abnormalities occur, more aggressive measures should be initiated. Allopurinol may be discontinued if the serum uric acid is within normal limits, the LDH has normalized, and the WBC count is low. Febuxostat, which is a selective xanthine oxidase inhibitor and has shown noninferiority to allopurinol in this setting, could be used as an alternative but is less frequently utilized because of cost. Rasburicase, a recombinant urate oxidase product, can also be used as prophylaxis in patients who are at high risk for developing TLS or for the treatment of patients who present with or develop TLS. Rasburicase acts as a catalyst in the enzymatic oxidation of uric acid to allantoin, which is 5 to 10 times more soluble than is uric acid and undergoes rapid renal excretion. The recommended dose of rasburicase for both prevention and treatment of TLS is 0.2 mg/kg/dose IV. Rasburicase results in a rapid reduction in serum uric acid (within 4 hours of administration) and is generally well tolerated. In many adult centers, doses of 3 or 6 mg are commonly used. Although rasburicase has demonstrated excellent efficacy and tolerability, its optimal role in the prevention and management of hyperuricemia in adults remains to be defined because of its high cost and lack of a randomized trial comparing its effect with other interventions.

Although C.C.'s serum potassium was low on admission, it has increased significantly as a result of TLS. For this reason, replacement potassium therapy by any method is not recommended before chemotherapy in patients in whom TLS is highly likely. In extreme circumstances, dialysis may be required to correct severe metabolic and electrolyte disturbances associated with TLS. C.C.'s kidneys continued to function throughout. Even though C.C.'s creatinine was above the normal range, his urine output did not

decline substantially, and he was able to proceed without further intervention.

Myelosuppression

Case 96-1, Question 4: C.C. received allopurinol therapy and aggressive hydration throughout his induction chemotherapy. The metabolic abnormalities gradually resolved as his WBC count declined and tumor lysis diminished. What other complications may occur during induction therapy, and can they be treated?

Patients receiving cytarabine and idarubicin induction therapy develop profound anemia, granulocytopenia (eg, WBC count >100 cells/μL), and thrombocytopenia (>20,000 platelets/μL) shortly after therapy is initiated, which usually persist for ~21 to 28 days. In addition, all infectious complications must be considered life-threatening in severely immunocompromised patients such as C.C.

Severe thrombocytopenia may result in bleeding episodes that range in severity from oozing gums to massive hemorrhage. Serious bleeding complications can usually be avoided if patients receive platelet transfusions when their platelet counts decrease to <10,000 cells/μL or when patients experience bleeding.

Other common drug-induced complications that may occur during induction therapy include nausea and vomiting, mucositis, fever, and skin rash (see Chapter 22, Nausea and Vomiting, Chapter 55, Pain and Its Management, and Chapter 94, Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents, for additional information and their management).

Postremission Therapy

Case 96-1, Question 5: After completion of his induction chemotherapy, C.C.'s WBC count fell to <100 cells/μL and his platelet count fell to 5000 cells/μL. He received platelet transfusions approximately every 2 to 3 days to prevent bleeding complications. On day 9, he developed a fever of 101.84 °F (38.8 °C). He was started immediately on empiric, broad-spectrum antibiotic therapy for

fever and neutropenia, and it subsequently resolved. On day 29, his WBC count was 5600 cells/μL with a normal differential, and his platelet count was 168,000 cells/μL. He received packed red blood cell transfusions on two separate occasions when his Hgb fell to <7 mg/dL. A repeat BM aspirate showed no evidence of persistent leukemia, MRD testing[23,24] showed low molecular persistence of disease, and C.C. was told that his leukemia was in remission. Nevertheless, his hematologist recommended additional chemotherapy, and C.C. questions why this is necessary. Is postremission therapy necessary, and if so, what therapeutic options are available to C.C.?

RATIONALE

Although >60% of patients treated for AML achieve CR after induction therapy, DFS at 3 years is 46% for patients with good-risk AML, 17% for intermediate-risk, and only 2% for patients with poor-risk AML.[16] Short remissions have been attributed to proliferation of clinically undetectable leukemic cells. Thus, the rationale for administering chemotherapy after remission is to eradicate these residual cells.

In adult AML, postremission therapy (also referred to as consolidation therapy) includes three to four cycles of chemotherapy. Clinical trials have shown that high-dose postremission therapy results in a higher percentage (30%–40%) of long-term (>2–5 years) disease-free survivors than either no or low-dose postremission chemotherapy in patients generally younger than age 60 years.[17] Postremission therapy regimens usually include HiDAC alone or in combination with one or more agents such as an anthracycline or etoposide. Patients ages 60 years and older or those with comorbid disease may not be able to tolerate this intensive postremission therapy. In these circumstances, the risk of life-threatening toxicity may outweigh the potential benefits of high-intensity postremission chemotherapy, but low-intensity therapy could be an alternative. AlloHCT has also been studied in the postremission treatment of AML and is addressed in Chapter 101, Hematopoietic Stem Cell Transplantation.

In conclusion, C.C. should receive consolidation therapy after HiDAC induction with midostaurin because this has been shown to give him the best chance of long-term survival. In addition, because

C.C. was diagnosed with poor-risk disease, he will be followed up closely with at least bimonthly CBCs and a BM biopsy at least every year for 5 years after consolidation. This close follow-up is vital for catching relapse as early as possible with the intent of going immediately to an alloHCT and minimizing additional reinduction therapy if relapse occurs.

Tretinoin and arsenic trioxide for acute promyelocytic leukemia

CASE 96-1, QUESTION 6: Would induction therapy for other subtypes of AML differ from that described previously?

Induction therapy with 7 + 3 is standard for all types of AML, with one exception: APL. APL is uniquely characterized by the t(15;17) translocation that fuses the *PML* gene on chromosome 15 to the retinoic acid receptor-alpha (*RAR*-α) gene on chromosome 17. In clinical trials, all-trans retinoic acid, also referred to as ATRA or tretinoin, has induced complete remission in ~90% of patients with APL. Serial BM aspirations after initiation of ATRA therapy demonstrate progressive differentiation without hypoplasia. Unfortunately, ATRA typically induces brief remissions, but combining ATRA with other agents improves outcomes.[17,25,26] Current evidence supports the use of concurrent ATRA with arsenic trioxide or an anthracycline for induction in the treatment of low-risk APL. For high-risk APL, combinations of ATRA, arsenic, and conventional chemotherapy is the standard of care. In addition, consolidation postremission therapy should include at least four cycles of ATRA and arsenic and an anthracycline-based regimen. Maintenance therapy with intermittent tretinoin has been shown to decrease the relapse rate.

ATRA therapy, although avoiding life-threatening myelosuppression, can produce significant toxicities, including the differentiation syndrome (formerly called retinoic acid syndrome), which manifests as fever, weight gain, respiratory distress, lung infiltrates, pleural or pericardial effusion, hypotension, and acute

renal failure. If this syndrome develops, corticosteroid therapy (dexamethasone 10 mg twice a day for 3 to 5 days with a taper over 2 weeks) should be initiated.[27] ATRA also causes dryness of the lining of the mouth, rectum, and skin; hair loss; skin rash; blepharoconjunctivitis; corneal erosions; muscle weakness; nail changes; depression; elevated liver enzymes; and high cholesterol.[28] Despite the risk of serious complications and death during induction therapy, the long-term disease-free survival (DFS) rate of patients with APL is superior compared with other AML subtypes. Approximately 90% of patients who receive tretinoin-based induction and maintenance therapy are alive 3 to 5 years after diagnosis.[29]

ACUTE MYELOID LEUKEMIA IN THE ELDERLY

CASE 96-1, QUESTION 7: Would recommendations for induction and postremission therapy differ if C.C. were elderly (age 60 years and older)?

As mentioned, the incidence of AML increases with advancing age. The prognosis of patients with AML is also directly related to age. Older patients are generally less able to tolerate intensive induction and postremission chemotherapy. Older patients often have comorbid medical conditions and a poor performance status, which are directly associated with worse outcomes with conventional AML therapy.[14]

Since 2015, several new options have become available to this age group and have significantly expanded the options available to elderly patients with AML. For patients whose disease has no actionable alterations, less-intensive chemotherapy options such as azacitidine, decitabine, or low-dose cytarabine may be used with or without venetoclax, or, as single agents, glasdegib or gemtuzumab ozogamicin could be used.[30–32] For AML cases that are found to have actionable alterations, including *IDH1*, *IDH2*, and *FLT3* mutations, targeted therapy can be utilized as single agents or combined with less-intensive chemotherapy.[2,14,17,33] Previously, any single-institution or cooperative group study excluded elderly

patients with AML or treated them on a separate, less-intensive protocol. Elderly patients are often judged to be poor-risk candidates for intensive chemotherapy without an objective review of available criteria. Because the median age of patients with AML and myelodysplastic syndrome is 70 years, the results of regimens studied in younger patients may not be applicable to the elderly. Some hematologists believe that it is most appropriate to offer older patients supportive care only, low-intensity therapy, or investigational treatment. Others believe that moderately intensive chemotherapy is beneficial in some candidates. However, most physicians feel uncomfortable offering intensive chemotherapy to elderly patients because of the high risk of induction mortality.

Patients who respond to induction therapy will typically continue on the same low-intensity regimen they received as induction therapy for postremission therapy.[2,14,17] AlloHCT could also be considered for fit patients 60 years of age or older who achieve remission after induction therapy.

Refractory or Resistant Acute Myeloid Leukemia

CASE 96-2

Question 1: F.T., a 55-year-old male, is ~40 days after induction therapy with 7 + 3. Initially, his counts recovered on day 25, and a BM biopsy result on day 28 revealed <5% blasts; therefore, he was in remission. Thereafter, a recent CBC showed a significant drop in his platelet count from 150,000 cells/μL on day 30 to 90,000 cells/μL 10 days later. A subsequent BM biopsy result reveals 60% blasts, confirming the diagnosis of relapsed AML.

What are the treatment options for F.T. at this time?

In younger patients, failure to achieve remission or disease relapse remains the major cause of treatment failure. This reflects both the failure of current salvage regimens and the absence of effective strategies to secure long-term DFS in those patients who achieve a second hematologic remission. A wide range of salvage options have been studied, but with <50% of patients achieving a

second remission and median survival figures ranging from 3 to 12 months, there remains considerable room for improvement.[34]

The treatment of relapse in a patient younger than age 75 years with a good performance status generally comprises one of several salvage options, including targeted therapies, chemotherapy regimens (aggressive or less aggressive), and clinical trials.[17,35] Commonly used aggressive chemotherapy regimens in the relapsed/refractory setting include clofarabine, intermediate-dose cytarabine to HiDAC, or combination regimens such as fludarabine, cytarabine, and filgrastim,[36] or cladribine, cytarabine, and filgrastim,[37] followed by alloHCT.

CHRONIC MYELOGENOUS LEUKEMIA

Epidemiology and Pathophysiology

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by unregulated stem cell proliferation in the BM and an increase in mature granulocytes in the peripheral blood. The disease is relatively rare, representing only 0.5% of all cancer cases and 15% of new leukemia cases.[38–40] The median age of diagnosis is 65 years, and the current estimated 10-year survival rate is 80% to 90%.[38,40]

Clinical Presentation and Diagnosis

Approximately 50% of patients are asymptomatic at presentation, with the most common physical finding of splenomegaly occurring in 50% to 60% of patients.[40] Additional symptoms may include fatigue, abdominal fullness, fever, anorexia, and weight loss. For many patients, the suspicion of CML is based solely on an abnormal CBC with a confirmatory BM biopsy result revealing the hallmark of CML, the Ph chromosome, which is a translocation of chromosomes 9 and 22: t(9;22)(q34;q11).[41] This fusion gene creates a new protein (BCR-

ABL) that has unregulated TK activity, a malignant transformation that leads to abnormal cell cycling, inhibition of apoptosis, and increased proliferation of cells.[40] The natural history of CML can be divided into three distinct phases: chronic phase, accelerated phase, and blast phase. The vast majority (90%–95%) of patients are diagnosed in the chronic phase, which is the earliest phase of the disease.[40]

Treatment

Oral small-molecule tyrosine kinase inhibitor (TKI) therapy revolutionized CML treatment, improving the 10-year survival rate from 20% a few decades ago to 80% to 90% in the present day.[40] Hematopoietic stem cell transplant (HCT) remains the only curative therapy for CML. However, owing to its substantial risks of morbidity and mortality, TKIs are almost always utilized as first-line treatment. The indication for HCT has remained for patients in accelerated or blast phase, those who fail TKI therapies, or for patients who develop certain genetic mutations.[42] Although the exact timing and utility of HCT remains controversial, patient outcomes are dependent on disease stage, with patients having improved 4-year DFS rates if transplanted in the chronic phase (80%) as compared to the accelerated (30%–40%) or blast phase.[43] Additional information regarding HCT for CML can be found in Chapter 101, Hematopoietic Stem Cell Transplantation.

The primary goal of the TKI therapy is to prevent progression from chronic phase to accelerated or blast phase while achieving response to therapy within 12 months of initiation.[41] Assessment of response to TKIs is based on hematologic, cytogenetic, and molecular responses (**Table 96-2**). Hematologic response is defined by normalization of peripheral blood counts and resolution of symptoms. Cytogenetic response is determined by the percentage of Ph-positive chromosomes within the BM cells in metaphase; this was the most widely used monitoring technique until the advent of molecular monitoring with quantitative polymerase chain reaction

(qPCR) assays that detect BCR-ABL messenger ribonucleic acid (mRNA) transcripts in the blood. qPCR is utilized at 3-month intervals to monitor BCR-ABL transcript levels for the failure of treatment or recurrence of disease.[40]

Table 96-2
Definition of Hematologic, Cytogenetic, and Molecular Response in Chronic Myelogenous Leukemia

Response Type	Response Criteria
Hematologic	Complete response: Peripheral white blood cell (WBC) count <10 × 10^9/L Platelet count <450 × 10^9/L Immature cells absent in peripheral blood Signs or symptoms of disease (such as palpable splenomegaly) absent
Cytogenetic	Complete cytogenetic response (CCyR): 0% Ph-positive metaphase cells Major cytogenetic response (MCyR): 0%–35% Ph-positive metaphase cells Partial cytogenetic response (PCyR): 1%–35% Ph-positive metaphase cells Minor cytogenetic response: >35%–65% Ph-positive metaphase cells
Molecular	Early molecular response (EMR): BCR-ABL1 mRNA ≤10% at 3 and 6 months Major molecular response (MMR): BCR-ABL1 mRNA ≤0.1% or ≥3-log reduction from the standardized baseline, if quantitative polymerase chain reaction (qPCR) is not available Deep molecular response (DMR): ≥4-log reduction in BCR-ABL1 mRNA if the assay's level of sensitivity is ≤0.01%, or ≥4.5-log reduction in BCR-ABL1 mRNA if the assay's level of sensitivity is ≤0.0032%

Source: Cross NC, White HE, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia*. 2012;26(10):2172–2175.

Signs and Symptoms

CASE 96-3

QUESTION 1: S.E., a 66-year-old female, recently had a routine CBC drawn during her annual wellness visit. Her CBC showed a WBC count of 133 × 10^9/L with 15% basophils, and a platelet count of 300 × 10^9/L. The only pertinent physical finding was splenomegaly. On further workup, a BM aspirate revealed a hypercellular marrow with <10% blasts. Cytogenetic analysis confirmed a diagnosis of Ph-positive CML in the chronic phase. S.E. was asymptomatic at diagnosis even though her WBC count was very high.

What are the possible clinical consequences of this abnormally high value?

S.E.'s labs indicate hyperleukocytosis, which is a WBC count >100 × 10^9/L. Leukostasis is present in 5% to 20% of patients with untreated, newly diagnosed CML.[20] The abundance of leukemic blasts in the blood may increase blood viscosity, affecting the brain and lungs, manifesting as cerebrovascular accidents, headaches, dizziness, tinnitus, and dyspnea.[20] Interestingly, S.E. is asymptomatic except for splenomegaly, which occurs in 50% of patients with newly diagnosed CML.[40] The presence of Ph-positive chromosomes within S.E.'s BM establishes her CML diagnosis and the percentage of blasts and basophils confirm her phase as chronic using the WHO Criteria for CML Staging (see **Table 96-3**).

Table 96-3
World Health Organization Criteria for Chronic Myeloid Leukemia Staging

Chronic phase	Blasts <10% in peripheral blood and bone marrow
Accelerated phase	Blasts 10%–19% in peripheral blood or nucleated bone marrow cells Persistent or increasing splenomegaly or WBC count (>10 × 10^9/L), unresponsive to therapy Persistent thrombocytopenia (platelets <100 × 10^9/L) unrelated to therapy or persistent thrombocytosis (platelets >1000 × 10^9/L) unresponsive to therapy Peripheral blood basophils >20% Cytogenetic evidence of clonal evolution
Blast phase	Blasts ≥20% of peripheral blood or nucleated bone marrow cells

	Extramedullary blast proliferation Large foci or clusters of blasts in the bone marrow

WBC, white blood cell.

Adapted from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. © 2016 American Society of Hematology. With permission.

Clinical Course and Prognosis

Case 96-3, Question 2: What is the prognosis for S.E. and others with newly diagnosed CML?

S.E. has been diagnosed with chronic-phase CML, which may range in duration from a few months to many years. Because symptoms can be nonspecific and relatively minor, CML may remain undiagnosed until patients progress into more advanced stages. S.E.'s prognosis is good and her projected 10-year overall survival (OS) is 80% to 90% if treated with a TKI.[40] Carefully selected patients may even discontinue TKI therapy and maintain observation only if they sustain a deep molecular response for several years with TKI treatment.[40]

If S.E.'s leukocytosis progresses despite therapy, an increased number of blasts would appear in the peripheral blood signaling the second phase of the disease, the accelerated phase. The accelerated phase can progress quickly to the blast phase if left untreated. The estimated 4-year OS is 40% to 55% for those patients with accelerated-phase CML who are started on TKI therapy.[40] The blast phase is the final phase of the disease, defined as 20% or more blasts in the peripheral blood or BM. During this phase, CML is indistinguishable from AML with the exception of cytogenetics and is often refractory to conventional induction chemotherapy regimens for AML when treated. The median survival for patients in this phase is ~9 to 12 months, with alloHCT considered as a first-line treatment option.[40]

Treatment

Case 96-3, Question 3: What therapy is appropriate for S.E.'s chronic-phase disease?

With the approval of TKIs, treatment of CML has shifted toward disease management. Because S.E. was asymptomatic upon presentation, she will receive one of the TKIs approved for first-line management of chronic-phase CML.

TYROSINE KINASE INHIBITORS

Imatinib, a first-generation TKI, inhibits BCR-ABL kinase, which prevents phosphorylation of substrates that are involved in regulating the cell cycle.[44] Approval was based on the pivotal IRIS (International Randomized Study of Interferon and STI571) trial, which compared imatinib with the combination of interferon (IFN)-α plus low-dose cytarabine in patients with newly diagnosed CML in chronic phase. A total of 1106 patients were randomized to either imatinib (400 mg orally daily) or IFN-α/cytarabine.[44] All primary and secondary end points of the trial demonstrated superiority of imatinib versus IFN-α/cytarabine. As a result, TKIs became standard-of-care, first-line therapy for patients with newly diagnosed CML in chronic phase. At the 8-year follow-up of the IRIS trial, 55% of the patients were still taking imatinib, and the estimated OS was 85%.[45] The most common toxicities reported with imatinib are edema, nausea, muscle cramps, and rash.

Dasatinib is a second-generation TKI that binds the BCR-ABL protein in the active confirmation, making it 350 times more potent than imatinib.[46] Approval was based on the international DASISION (Dasatinib Versus Imatinib Study in Treatment-Naive CML Patients) trial, which compared dasatinib (100 mg orally daily) with imatinib in 519 patients in chronic phase.[46] The primary objective of CCyR at 12 months and the secondary objective of a MMR by 12 months were statistically superior for dasatinib versus imatinib. Dasatinib demonstrates a similar safety profile compared with imatinib, but with

a higher incidence of pleural effusion, pulmonary hypertension, and platelet inhibition.[47]

Nilotinib is a second-generation TKI that is structurally similar to imatinib but 30 to 50 times more potent as a result of an improved structural fit in the receptor pocket.[48] Approval was based on the international ENESTnd (*E*valuating *N*ilotinib *E*fficacy and *S*afety in clinical *T*rials—newly diagnosed patients) trial, which randomly assigned 846 patients with chronic-phase CML to either imatinib or two different doses of nilotinib (300 or 400 mg orally twice daily). At 12 months, both doses of nilotinib were statistically superior for molecular response and CCyR compared with imatinib.[48] Upon follow-up, molecular remission rates between the nilotinib arms and the imatinib arm increased from 6% to 10% at 1 year to ~21% to 23% by 5 years.[49] Nilotinib has a higher incidence of QTc prolongation, metabolic syndrome, pancreatitis, and ischemic events among the TKIs.[49]

Bosutinib, a second-generation TKI with dual SRc kinase inhibition, was initially investigated as an option for therapy after resistance or intolerance to prior TKIs. In the single-arm Study 200, a total of 118 patients with prior TK therapy exposure received bosutinib (500 mg orally daily), achieving a 4-year OS of 78%.[50,51] Bosutinib is now utilized in the front-line setting. The international BFORE (*B*osutinib trial in *F*irst-line chr*O*nic myelogenous leukemia t*RE*atment) trial compared bosutinib (400 mg orally daily) with imatinib in 536 patients with newly diagnosed CML. At 12 months, the molecular response (47.2% vs 36.9%) and CCyR (77.2% vs 66.4%) were both superior with bosutinib.[52] Gastrointestinal toxicities such as diarrhea, nausea, abdominal pain, and transaminitis are common with bosutinib.

Selection of a first-line agent is based on careful assessment of TKI toxicities, drug–drug interactions, disease risk score, patient comorbidities, compliance, and performance status. Adherence to therapy is of utmost importance because poor adherence is correlated with suboptimal treatment responses.[53] First-line use selection of second-generation TKIs in higher risk patients may result in faster molecular responses, but no difference in OS

(possibly secondary to increased toxicities) over imatinib.[41] Because S.E. presented in chronic-phase CML, initiation of imatinib, dasatinib, nilotinib, or bosutinib is appropriate, and S.E.'s physician chose to start her on imatinib 400 mg once daily.

Relapsed and Refractory Disease

Case 96-3, Question 4: On routine follow-up at 3 months, S.E. is found to have an 11% BCR-ABL transcript level. Her side effects and compliance were evaluated, where she was found to be 90% compliant because of nausea. She was counseled on medication adherence and nausea management, and then reevaluated at 6 months. The BCR-ABL transcript level was measured at 15% and her BM revealed 36% Ph-positive metaphases. Because S.E.'s compliance had improved, the disease appeared to be imatinib resistant. Imatinib was discontinued and dasatinib was initiated at 100 mg once daily. S.E. maintained low BCR-ABL assays until 12 months, when her BCR-ABL transcript level increased to 12%. Cytogenetic analysis revealed that her disease had become resistant to dasatinib. What treatment options are available for S.E. at this time?

Although S.E. has relapsed, she has multiple treatment options: nilotinib, bosutinib, ponatinib, and omacetaxine. Both nilotinib and bosutinib can be used for second-line treatment, whereas ponatinib and omacetaxine are generally reserved for patients with resistance or intolerance to at least two prior TKI therapies.

Ponatinib is a second-generation TKI that is 500 times more potent than is imatinib, usually reserved for patients who have exhausted other TKI options or who develop a particularly catastrophic gene mutation (T315I, the "gatekeeper" mutation).[41] The PACE (Ponatinib Ph+ ALL and CML Evaluation) trial enrolled 449 patients with heavily pretreated CML; a major cytogenetic response was achieved in 56% of patients in chronic phase, with a CCyR in 46% of patients and a 12-month OS of 94%.[54,55] Ponatinib is associated with arterial occlusions, venous thromboembolism, heart failure, and hepatotoxicity, and thus carries a black box warning for these toxicities.

Omacetaxine is a subcutaneously-delivered protein synthesis inhibitor that can be used in patients in chronic phase who have

failed or were intolerant to at least two TKIs.[41] Of 62 heavily-pretreated patients with chronic-phase CML in the CML 202 Study and 46 patients in the CML 203 Study, the CCyR rates achieved were 16% and 4%, respectively, with median OS of 30 months.[56,57] S.E.'s next treatment would be based on her tolerability of the first two therapies, genetic mutations, concomitant medications, and comorbidities.

LYMPHOMA

Incidence and Epidemiology

The lymphomas represent a dramatically diverse collection of hematologic malignancies originating from lymphoid tissues. The heterogeneity among these lymphoproliferative disorders is manifest by variations in pathophysiologic features, disease course, and therapeutic approach. Disease may present within the lymph nodes or in extranodal sites such as the gastrointestinal tract, skin, BM, sinus, or CNS. Lymphomas are classified as either HL or NHL. The NHLs are further divided into >20 subtypes according to factors such as the cell of origin, histology, and natural history. A review of lymphoma classifications is presented in **Table 96-4**. Refer to Chapter 95, Pediatric Malignancies, for further discussion of pediatric lymphomas.

Table 96-4
Simplified Classification of Lymphomas

	Cell of Origin
Hodgkin Lymphomas	
Classic Hodgkin lymphoma	B cell
Nodular lymphocyte predominant	B cell
Aggressive Non–Hodgkin Lymphomas	

	Cell of Origin
Hodgkin Lymphomas	
Diffuse large B-cell lymphoma	B cell
Burkitt lymphoma	B cell
Mantle cell lymphoma	B cell
AIDS-related B-cell lymphoma	B cell
Primary central nervous system lymphoma	B cell
Precursor lymphoblastic leukemia/lymphoma	B or T cell
Peripheral T-cell lymphomas	T cell
Anaplastic large-cell lymphoma	T cell
Adult T-cell leukemia/lymphoma	T cell
Extranodal NK/T-cell lymphoma	NK/T cell
Indolent Non–Hodgkin Lymphoma	
Follicular lymphoma	B cell
Cutaneous T-cell lymphomas	T cell
Marginal zone lymphoma	B cell

AIDS, acquired immunodeficiency syndrome; NK, natural killer.

Source: Adapted from Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17(12):3835–3849.

EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND ETIOLOGY

The lymphomas impact all age populations, with prevalence differing not only according to disease type but also additional factors such as geographic region, ethnicity, and socioeconomic status.[39,58] Causality is often not established; however, certain viral infections including Epstein–Barr virus and human immunodeficiency virus as well as immunosuppression, autoimmune disease, and family history contribute to an increased risk.[59–63]

CLINICAL PRESENTATION AND DIAGNOSIS

CASE 96-4

QUESTION 1: E.A. is a 39-year-old female with a 2-week history of fevers, lymphadenopathy, malaise, and shortness of breath that was initially treated with antibiotics for suspected pneumonia. Progressive symptoms resulted in a hospital admission where radiologic evaluation revealed diffuse lymph node enlargement.

Are E.A.'s symptoms consistent with aggressive or indolent lymphoma?

E.A.'s presenting symptoms of fevers, lymphadenopathy, and malaise are all generalized signs of lymphoma, with the respiratory symptoms being consistent with pulmonary infiltration of malignant cells. The rapid onset and extensive disease involvement at presentation are suggestive of aggressive lymphoma. A biopsy of an involved node is essential to establish a definitive diagnosis and determine the subtype of lymphoma.

CASE 96-4, QUESTION 2: What diagnostic evaluation is necessary to establish the diagnosis of lymphoma for E.A.?

Suspicion of lymphoma requires a confirmatory biopsy of the lymph node or involved tissues. Morphology, immunophenotyping, flow cytometry, and cytogenetic techniques are utilized to refine the diagnosis. Additional patient assessment should include a complete history and physical examination with a focus on lymph node–bearing areas along with laboratory analysis including CBC, comprehensive metabolic panel, and human immunodeficiency virus serology. Radiologic evaluation includes computed tomography (CT) or positron emission tomography (PET) to evaluate the extent of disease. Staging is typically based on the Lugano classification system.[64] A simplified version of this schema is shown in **Table 96-5**. A BM biopsy or lumbar puncture may be advisable under certain clinical circumstances. Assessment of baseline cardiac and pulmonary function is necessary for all patients expected to be treated with anthracyclines or bleomycin, respectively.

Table 96-5

Simplified Staging of Lymphoma

Stage		Description
Early	I	Disease limited to a single lymph node region
	II	Multiple lymph node regions involved on the same side of the diaphragm
Advanced	III	Lymph node regions involved on both sides of the diaphragm
	IV	Diffuse disease involving one or more extranodal organs

A: absence of any of the B symptoms
B: unexplained fever, drenching night sweats, or unexplained weight loss >10% of body weight during the previous 6 months

Source: Adapted from Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–3068.

TREATMENT

Chemotherapy, monoclonal antibodies, small-molecule inhibitors, radiation, HCT, and chimeric antigen receptor (CAR) T-cell therapy are all used in various combinations and sequences in lymphoma therapy. Selection of treatment is guided according to each specific classification of disease. Aggressive lymphomas, such as diffuse large B-cell lymphoma (DLBCL) and HL, are generally treated with intensive combination chemotherapy regimens administered with a curative intent. In contrast, indolent lymphomas such as follicular lymphoma (FL) are essentially incurable and are regularly managed with an approach aimed at reducing disease burden and prolonging survival. Individual patient characteristics, including comorbid conditions and performance status, must be carefully considered to optimize outcomes.

A biopsy of a supraclavicular lymph node confirms the diagnosis of aggressive NHL for E.A.

CASE 96-4, QUESTION 3: What are some important supportive care considerations with lymphoma therapy?

Beyond selecting the optimal chemotherapy regimen, care for E.A. will require proper supportive care focused on addressing both treatment- and disease-related complications. Prophylaxis and treatment of TLS is vital upon therapy initiation, particularly for cases such as this involving aggressive and bulky disease. Adequate antiemetics must accompany all chemotherapy. Although common to virtually all lymphoma therapies, regimens designed for aggressive lymphoma are associated with significant hematologic toxicity and risk of infectious complications. As such, appropriate support with granulocyte colony-stimulating factors, antibiotics, and blood product transfusions is imperative. Although the urgent need for treatment may preclude opportunities, fertility counseling for a patient of childbearing age such as E.A. should be offered. Delayed effects of both chemotherapy and radiation may develop more than a decade after conclusion of therapy and include secondary malignancy, cardiovascular disease, and pulmonary dysfunction. Subsequently, survivorship programs designed to monitor for delayed complications of treatment are increasingly valuable when treating theoretically curative diseases.

Hodgkin Lymphoma

CASE 96-5

QUESTION 1: L.G. is a 26-year-old female with a month-long history of painless swelling around her collarbone and drenching night sweats. She reports increased fatigue and "feeling unwell" over the past 6 months. Radiography revealed a cervical, mediastinal, and inguinal lymph node enlargement. Excisional biopsy of the cervical lymph node revealed nodular sclerosing HL. Because of anemia and thrombocytopenia on presentation, a BM biopsy was performed and the result found to be positive for lymphoma cells. All other laboratory values are normal and she is otherwise in very good health.

What is the goal of therapy for L.G.?

HL, formerly referred to as Hodgkin disease, is a B-cell neoplasm consisting of characteristic Reed–Sternberg cells within an inflammatory background. HL represents ~10% of lymphomas and

accounted for an estimated 8500 new diagnoses in 2020 in the United States.[38,39] Occurrence of HL displays a bimodal age distribution primarily occurring in young adults with a second peak at ~age 65.[65] Although once a uniformly fatal disease, improvements in treatment over the past 50 years represent a remarkable success story because now at least three out of every four new cases can be cured.[66] Given that long-term survival is expected for most patients, delayed consequences of therapy have a heightened importance in management of this disease.[67,68]

HL is categorized as either classic HL or nodular lymphocyte predominant according to the appearance of tumor cells and the composition of the tumor microenvironment.[69] Classic HL is further subdivided, in order of prevalence, as nodular sclerosing, mixed cellularity, lymphocyte rich, and lymphocyte depleted.[70] Nodular lymphocyte-predominant HL accounts for only 5% of all HLs and has a unique immunophenotypic profile and therapeutic approach. The remainder of this section focuses on classic HL.

Prognosis is multifactorial and incorporates systemic symptoms, stage of disease, and the size of the mass. The International Prognostic Score (IPS) for HL describes hypoalbuminemia (albumin <4 g/dL), anemia (Hgb <10.5 g/dL), male gender, age 45 years or older, stage IV disease, leukocytosis (WBC ≥15,000/mm^3), and lymphocytopenia (lymphocyte count <8% of WBC and/or lymphocyte count <600/mm^3) as adverse indicators.[71] The European Organization for the Research and Treatment of Cancer (EORTC) criterion is commonly employed to divide patients into one of three groups—early-stage favorable, early-stage unfavorable, and advanced disease. Early-stage favorable patients have stage I or II disease and have no large mediastinal adenopathy, an erythrocyte sedimentation rate ≤50 mm/hour, three or less involved nodes, and are age younger than 50 years. Patients with stage I or II disease not meeting this criterion are classified as early-stage unfavorable, whereas patients with stage III or IV HL are considered to have advanced disease.

The goal of therapy for L.G. is curative. Although L.G. presents with advance disease, she maintains a favorable long-term

prognosis.

INITIAL THERAPY

CASE 96-5, QUESTION 2: What is appropriate initial therapy for L.G.?

The objective of initial therapy in HL is to maximize the potential for disease eradication while simultaneously limiting the risk of late effects. In modern practice, this is largely achieved by adjusting therapy according to both prognostic factors and response to treatment. Patients with advanced disease at diagnosis and/or residual disease after initiation of treatment generally receive more intensive or longer durations of treatment.

Selection of chemotherapy

The ABVD regimen is the most commonly used initial therapy in modern practice because it displays superior efficacy and reduced incidence both of acute toxicities and long-term complications such as secondary leukemia and sterility when compared to historical alternatives. Although there are exceptions, the majority of patients now begin treatment for HL with two cycles of ABVD followed by restaging with a PET/CT. Depending on both initial staging and degree of disease response, treatment is continued for an additional one to four cycles. Abbreviated treatment courses are reserved for patients with more robust treatment responses and/or more favorable disease characteristics.[72–74] For patients receiving prolonged courses of treatment, the bleomycin may be omitted from ABVD (referred to as the AVD regimen—doxorubicin/vinblastine/dacarbazine).[75] A distinctive feature of ABVD is the general avoidance of dose reductions or delays secondary to leukopenia because of the heightened importance of maintaining dose intensity in this disease.[76,77]

Select patients may benefit from escalating therapy to the BEACOPP (bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/proc

arbazine/prednisone) regimen. This intensive combination appears to improve tumor control, although a definitive survival advantage has yet to be elucidated.[78–80] Individuals with advanced disease, four or more adverse IPS factors, and the physical capacity to tolerate the markedly increased toxicity of the combination are likely to derive the greatest potential advantage from this approach. In addition, patients exhibiting limited response to ABVD may experience improved disease response from converting to BEACOPP.[75,81] Another suitable alternative to ABVD is A+AVD (brentuximab vedotin/doxorubicin/vinblastine/dacarbazine). This novel combination, which is identical to ABVD except for the substitution of the CD30 targeting antibody–drug conjugate brentuximab vedotin for bleomycin, is particularly useful in patients in whom bleomycin is contraindicated.[82]

Incorporation of radiation therapy

HL is highly sensitive to radiation therapy. Although treatment with radiation alone is no longer an acceptable approach to treatment owing to substantial long-term toxicity, combined modality therapy—whereby radiotherapy is initiated following a shorter course of chemotherapy—is a reasonable option for patients with early-stage disease.[73,74,83–86] Comparative studies suggest that chemotherapy alone portends a reduced risk of latent adverse events, whereas chemotherapy followed by radiotherapy has a lower rate of disease recurrence. There does not appear to be a difference in OS between these two approaches.[87–89]

L.G. should be treated with two cycles of ABVD followed by restaging with a PET/CT and additional chemotherapy according to response. She would not be eligible for combined modality therapy owing to the fact she has advanced disease. Given the IPS score is <4 and there is no reason to suspect contraindication to bleomycin, an alternative regimen such as BEACOPP or A+AVD is not likely warranted in this situation.

RELAPSED AND REFRACTORY DISEASE

Case 96-5, Question 3: On routine follow-up 9 months after completion of therapy, L.G. is found to have an extensive recurrence of nodal enlargement that is confirmed to be relapsed disease. What are appropriate treatment options for L.G.?

Unlike numerous malignant diseases, patients with HL maintain a reasonable likelihood of attaining cure in the setting of relapsed or refractory disease. Relapses consisting of minimal disease occurring >12 months after documented remission suggest a better prognosis. Salvage chemotherapy alone or with radiation may be sufficient therapy for patients who received abbreviated chemotherapy in the front-line setting.[90,91] Patients with an early or extensive relapse, relapse after a full course of chemotherapy, or primary refractory disease generally require second-line chemotherapy followed by autologous BM transplant. Effective salvage therapies include brentuximab vedotin (if not used in front-line treatment), either alone or in combination with bendamustine, or multiagent regimens such as ESHAP (etoposide/methylprednisolone/cytarabine/cisplatin), DHAP (dexamethasone/cytarabine/cisplatin), and ICE (ifosfamide/carboplatin/etoposide).[92–97] The PD-1 inhibitors pembrolizumab and nivolumab represent an additional treatment option particularly for patients ineligible for or refractory to BM transplant.[98,99] Overall, selection of therapy in the relapsed/refractory setting is highly dependent on individual patient characteristics and provider preference because there is currently no definitive standard of care.

L.G. should likely receive a salvage regimen such as ESHAP followed by autologous stem cell transplant given her early and extensive relapse. The aim of her therapy should remain curative.

A summary of treatment options for HL is presented in **Table 96-6**.

Table 96-6
Summary of Treatment Options in Hodgkin Lymphoma

Treatment	Place in Therapy
ABVD	Preferred initial therapy

Treatment	Place in Therapy
AVD	Alternative initial therapy
BEACOPP	Alternative initial therapy
A+AVD	Alternative initial therapy
Brentuximab vedotin ± bendamustine	Relapsed or refractory disease
ESHAP	Relapsed or refractory disease
ICE	Relapsed or refractory disease
DHAP	Relapsed or refractory disease
Pembrolizumab	Relapsed or refractory disease
Nivolumab	Relapsed or refractory disease

Non–Hodgkin Lymphoma

NHL is a spectrum of lymphoid malignancies distinguished by variations in clinical features and responsiveness to treatment. In the United States in 2020, there were an estimated 77,240 new NHL cases and 19,940 resulting deaths.[38] Although various histopathologic classification schemes for NHL have been developed and modified as the cellular understanding of NHL has improved, NHLs can essentially be classified as either aggressive or indolent. Approximately 90% of all lymphomas arise from B lymphocytes, with the remaining cases developing from T lymphocytes or, rarely, natural killer (NK) cells. DLBCL and FL are the two most frequently occurring subtypes of NHL and, as such, are the focus of this section.

AGGRESSIVE LYMPHOMA

CASE 96-6

QUESTION 1: P.A., a 64-year-old male, presents with swollen lymph nodes and occasional fevers and night sweats during the past month. Physical examination reveals marked cervical, supraclavicular, and inguinal lymphadenopathy. Laboratory values are normal with the exception of a mild anemia and an elevated LDH. Excisional biopsy of a supraclavicular lymph node confirms a

diagnosis of DLBCL. Flow cytometry finding is positive for CD10, CD19, and CD20 surface markers. He does not have any identifiable extranodal disease.

Is P.A.'s disease considered curable?

Aggressive lymphomas include DLBCL and Burkitt lymphoma. Although these diseases are rapidly fatal if untreated and require intensive treatments, the prospect of attaining cure is reasonable for many patients receiving modern therapy.

DLBCL represents about 25% to 30% of all cases of NHL and is the most common type of lymphoma.[70,100,101] Incidence of DLBCL increases with age, with the median age at diagnosis occurring in the sixth decade of life.[102] Anticipated 5-year survival rates range from ~20% to 75% depending on various prognostic indicators. Adverse indicators include age older than 60 years, elevated LDH, multiple extranodal sites, advanced clinical stage, and poor performance status.[103,104] In clinical practice, DLBCL is further divided into various subtypes. The following review is intended to cover general principles and not the nuances of each unique clinical scenario.

Although the potential for relapse is relatively high given his numerous adverse indicators, the goal of therapy for P.A. is nonetheless curative.

Initial therapy for diffuse large B-cell lymphoma

Case 96-6, Question 2: Given this information, what is generally considered the standard of care for P.A.?

A combination of chemotherapy and immunotherapy with or without radiation is the foundation of therapy for DLBCL. The CHOP protocol has been the prevailing chemotherapy backbone in DLBCL for decades owing to its activity, tolerability, and simplicity in comparison with previously utilized regimens.[105] The inclusion of rituximab, a CD20-targeted monoclonal antibody, with CHOP therapy (R-CHOP) increases survival by ~10% to 15% with only a nominal increase in adverse effects.[106–108] Likewise, therapy with rituximab is

integrated into virtually all treatments for DLBCL. For patients with stage I or II disease, a treatment course consists of three to six cycles of R-CHOP followed by involved field radiation.[109,110] If relative contraindications or aversions to radiotherapy are present, adequate results can typically be obtained by omitting radiation and extending chemotherapy duration.

The large size and/or extent of the disease limit the utility of radiation in patients with advanced disease (stage III/IV or bulky tumors). As such, the administration of R-CHOP for a total of six cycles is the predominant practice in this setting. Restaging with a PET/CT is generally completed after two to four cycles of chemotherapy and again at the end of treatment. Patients who do not achieve an adequate response are treated as having relapsed or refractory disease. Chemotherapy with CHOP plus rituximab for six cycles would be ideal for P.A. The addition of radiation treatment is not beneficial in this setting because P.A. has stage III disease.

Unique circumstances in diffuse large B-cell lymphoma

Case 96-6, Question 3: During completion of pretreatment assessment, P.A. is found to have a past medical history significant for cardiac disease. His ejection fraction is revealed to be 35% following an echocardiogram. Does this finding change the therapeutic approach for P.A.? If so, how?

Notwithstanding its proven reliability, therapy with R-CHOP is not applicable to all patients with DLBCL. Anthracyclines such as doxorubicin are a cornerstone of numerous lymphoma regimens. This presents a significant clinical challenge for patients with underlying cardiovascular disease. Replacing the doxorubicin in CHOP with liposomal doxorubicin (R-CDOP—rituximab/cyclophosphamide/liposomal doxorubicin/vincristine/prednisone) or utilizing the EPOCH-R regimen (etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin/rituximab), which employs infusional doxorubicin, are potential

strategies to minimize cardiac effects.[111,112] If the anthracyclines must be avoided entirely, regimens such as R-CEPP (rituximab/cyclophosphamide/etoposide/prednisone/procarbazine), R-CEOP (rituximab/cyclophosphamide/etoposide/vincristine/prednisone), or R-GCVP (rituximab/gemcitabine/cyclophosphamide/vincristine/prednisone) are feasible alternatives.[113–115] Treatment of very frail or elderly patients with DLBCL represents a similar challenge to those with cardiac disease. Maintaining dose intensity is ideal given the curative intent of therapy; however, this is not attainable for all patients and the use of reduced intensity therapy may be required.[116,117]

The presence of c-Myc, BCL-2, and/or BCL-6 is indicative of a poorer prognosis and reduced responsiveness to conventional therapy.[118,119] Treatment of lymphomas with these findings, often referred to as *double-hit* or *triple-hit* lymphomas, with EPOCH-R as opposed to R-CHOP appears to increase response rates with acceptable tolerability.[120,121]

Use of an anthracycline in P.A. may be ill-advised because of his reduced ejection fraction. As such, an alternative such as R-GCVP should be considered rather than R-CHOP.

Treatment of relapsed and refractory disease for diffuse large B-cell lymphoma

Case 96-6, Question 4: Two years after completing therapy, P.A. experiences a relapse of disease. In addition to his lymphoma recurrence, his physical condition has significantly deteriorated since his first therapy because of worsening of comorbid disease unrelated to his cancer. What is the goal of additional therapy for P.A. now that his disease has recurred?

Eligibility for BM transplant is a critical component in decision-making for the management of relapsed or refractory disease. For patients who are eligible for transplant, the aim is curative, with a course of treatment that includes administration of aggressive chemotherapy to induce maximal response followed promptly by

autologous transplant.[122,123] In select circumstances, alloHCT or anti-CD19 CAR T-cell therapy may be utilized. Numerous intensive regimens have been successfully utilized to induce response before autologous transplant including ESHAP, DHAP, and ICE.[124–126] No option has proved superior to another, and all are associated with significant hematologic and nonhematologic toxicity. Although efficacy data are limited, rituximab is frequently included into these salvage regimens.

The approach to patients who are not transplant appropriate or relapse following transplant is largely palliative. Treatment with less-intensive therapies such as gemcitabine plus oxaliplatin (GemOx) or other combinations of conventional antineoplastics are often effective in eliciting a response as a second-line therapy.[127,128] The antibody–drug conjugate polatuzumab vedotin, which binds to CD79b, has been shown to be an effective treatment when combined with BR as a third-line or later option.[129] Other novel therapies/combinations include tafasitamab plus lenalidomide, brentuximab vedotin (for CD30+ disease), and selinexor.[130–132] Low doses of single-agent chemotherapy may be a useful approach to palliate symptoms caused by large masses.

Now at age 66 and in suboptimal physical condition, P.A. is not a likely candidate for aggressive salvage therapy followed by BM transplant. A reduced intensity treatment such as GemOx may be beneficial in controlling disease, although the aim of therapy in this setting would be palliative.

Other aggressive non–Hodgkin lymphoma subtypes

Burkitt lymphoma is a quintessential aggressive malignancy that demonstrates an exceptionally rapid proliferation rate. Urgent therapy is crucial and must be more vigorous than are conventional DLBCL protocols.[133] Active regimens include Hyper-CVAD (cyclophosphamide/vincristine/doxorubicin/dexamethasone alternating with methotrexate/cytarabine), CODOX-M (cyclophosphamide/vincristine/doxorubicin/methotrexate), and EPOCH.[134–136] Although many of these regimens were developed in

the pre-rituximab era, the monoclonal antibody is generally included given the limited impact on toxicity and evidence suggesting improved responses. Burkitt lymphoma has a greater predilection to involve the CNS than do other lymphoid malignancies. Therefore, use of intrathecal chemotherapy and/or incorporation of antineoplastics that readily penetrate the blood–brain barrier, such as high-dose methotrexate or cytarabine, is an imperative component to Burkitt lymphoma treatment.[137] Although treatment-related complications can be severe, durable remission is attained in 60% to 90% of pediatric and young adult cases.[138] This favorable prognosis dissipates when the disease occurs in older populations.[139]

Mantle cell lymphoma harbors the incurable nature of indolent lymphoma while displaying the capability for rapid proliferation of aggressive disease.[140] Therapy for the disease reflects this dual nature because therapy ranges from low-intensity indolent regimens to high-intensity aggressive regimens. Young and medically fit patients are conventionally treated with intensive regimens such as Hyper-CVAD followed by consolidation with autologous BM transplant and maintenance rituximab.[141] Protocols such as BR, R-CHOP, VR-CAP (bortezomib/rituximab/cyclophosphamide/doxorubicin/prednisone), or lenalidomide plus rituximab followed by maintenance rituximab are ideal for initial therapy in elderly patients or those with significant comorbid disease.[142–145] Second-line or salvage treatment options include trial of alternative initial therapy options or various novel therapies such as Bruton TKIs (ibrutinib, acalabrutinib, or zanubrutinib) or the BCL2 inhibitor venetoclax.[146]

A summary of treatment options for aggressive lymphoma is presented in **Table 96-7**.

Table 96-7

Summary of Treatment Options in Aggressive Lymphomas

Treatment	Place in Therapy
Diffuse Large B-Cell Lymphoma	

Treatment	Place in Therapy
Diffuse Large B-Cell Lymphoma	
R-CHOP	Preferred initial therapy
R-CDOP	Alternative initial therapy
EPOCH-R	Alternative initial therapy
R-CEPP	Alternative initial therapy
R-CEOP	Alternative initial therapy
R-GCVP	Alternative initial therapy
GemOx ± rituximab	Relapsed or refractory disease
ESHAP ± rituximab	Relapsed or refractory disease
ICE ± rituximab	Relapsed or refractory disease
DHAP ± rituximab	Relapsed or refractory disease
Bendamustine + rituximab + polatuzumab vedotin	Relapsed or refractory disease
Tafasitamab + lenalidomide	Relapsed or refractory disease
Selinexor	Relapsed or refractory disease
Burkitt Lymphoma	
Hyper-CVAD + rituximab	Initial therapy
EPOCH + rituximab	Initial therapy
CODOX-M + rituximab	Initial therapy
Mantle Cell Lymphoma	
Hyper-CVAD + rituximab	Initial therapy
BR	Initial therapy or relapsed/refractory
R-CHOP	Initial therapy or relapsed/refractory
VR-CAP	Initial therapy or relapsed/refractory
Lenalidomide + rituximab	Initial therapy or relapsed/refractory
Ibrutinib	Relapsed or refractory disease
Acalabrutinib	Relapsed or refractory disease

Treatment	Place in Therapy
Diffuse Large B-Cell Lymphoma	
Zanubrutinib	Relapsed or refractory disease
Venetoclax	Relapsed or refractory disease

INDOLENT LYMPHOMA

FL is the second most common form of NHL and comprises ~70% of all indolent lymphomas.[147] The condition predominantly appears in patients older than 50 years of age although pediatric variants have been described. A reasonable percentage of patients will survive a decade or longer with disease. The Follicular Lymphoma International Prognostic Index (FLIPI) identifies age 60 years or older, elevated LDH, stage III or IV disease, Hgb <12 g/dL, and five or more involved nodes as adverse indicators.[148]

CASE 96-7

QUESTION 1: T.M. is a 61-year-old male in generally good health who is presenting with a 3-month history of painless axillary lymphadenopathy that seems to "come and go." He is otherwise asymptomatic. An excisional biopsy and pathologic examination revealed follicular B-cell lymphoma. A CT scan showed axillary and mediastinal lymphadenopathy. Laboratory values are normal.

When should treatment be initiated for T.M. and what will be the goal of therapy?

In contrast to aggressive lymphomas, indolent varieties are subject to slow growth and typically do not require treatment until the patient is symptomatic.[149] Although numerous effective treatments are available, indolent lymphomas are frequently incurable and prone to recurrent relapses. Treatment is aimed at prolonging survival and palliating symptoms by reducing disease burden until the malignancy either becomes resistant to therapy and/or transforms to a more aggressive lymphoma.[150] A further distinction from aggressive lymphoma therapy, active treatment of FL can be withheld until the development of disease-related symptoms without compromising

outcomes.[149,151] Advantages to the "watchful waiting" approach include minimizing treatment complications, cost avoidance, and theoretically limiting future drug resistance. Localized symptoms due to nodal disease, compromised organ function secondary to lymphoma infiltration, B symptoms, cytopenias from BM involvement, or aggressive proliferation are generally considered indications to initiate therapy.

Because his disease is presently asymptomatic, a "watchful waiting" approach is reasonable for T.M. Once criteria for treatment are met, therapy can be initiated with the goal being to reduce disease-related symptoms and to prolong survival.

Initial therapy

Case 96-7, Question 2: After a year of observation, T.M. now presents multiple enlarged lymph nodes that are causing discomfort and he has been experiencing unintentional weight loss and night sweats. What is the ideal initial therapy for T.M.?

Myriad treatment options are available for FL including conventional antineoplastics, CD20 targeting monoclonal antibodies, and various targeted agents. For a small subset of patients presenting with early disease, treatment may consist of radiation therapy alone—an option that is potentially curative in rare instances.[152–155] Under most circumstances, initial treatment of FL involves a chemotherapy backbone—such as bendamustine, CHOP, or CVP (cyclophosphamide, vincristine, prednisone)—combined with a CD20 targeting monoclonal antibody—such as rituximab or obinutuzumab. Bendamustine, an alkylating agent with additional properties similar to that of purine analogs, appears to not only be more effective than CHOP or CVP but also exhibit an improved safety profile.[144,156] Nonetheless, CHOP and CVP remain potentially useful chemotherapy components of treatment owing to extensive experience.[157,158]

Similar to B-cell–related aggressive NHL, the availability of CD20 targeting monoclonal antibody has dramatically shaped therapy for FL in the modern era.[158,159] Consequently, rituximab or the type II antibody obinutuzumab are given in conjunction with chemotherapy and generally continued as monotherapy in a maintenance or continuation phase following completion of initial therapy.[160–162] Single-agent rituximab elicits significant response rates with minimal toxicity and is an ideal treatment for patients unable to tolerate the rigors of cytotoxic therapy and/or minimal disease burden.[163,164] In select circumstances, initial therapy with lenalidomide plus rituximab or the radiopharmaceutical ibritumomab tiuxetan may be considered.[165,166]

Given that he is now symptomatic, initiation of treatment is necessary for T.M. A combination of bendamustine and obinutuzumab may be ideal as initial therapy for T.M.

Relapsed and refractory disease

Case 96-7, Question 3: Three years after completing initial treatment, T.M. is found to have thrombocytopenia and neutropenia and multiple enlarged lymph nodes that have gradually increased in size over the past several months. What additional treatment options are available for T.M.?

For many patients, a trial of an alternative first-line regimen is effective in the setting of relapsed disease. Occasionally, a rechallenge with a previously administered regimen is reasonable if it induced a durable remission. Small-molecule inhibitors play an emerging role in this stage of FL management. PI3K inhibitors, including copanlisib, duvelisib, and idelalisib, and the EZH2 inhibitor tazemetostat represent additional alternative therapies.[167,168] Options for the very frail or elderly may include chlorambucil, cyclophosphamide, or single-agent rituximab.

Nearly one in three FLs will transform into an aggressive lymphoma at the time of relapse.[169] In the event of aggressive presentation, a repeat biopsy is required to determine conversion to

alternate histology.[170] If transformation is documented, treatment must be intensified to a protocol consistent with aggressive lymphoma therapy and HCT becomes a more important treatment option, particularly for young and medically fit patients.

The features of T.M.'s relapse suggest transformation is unlikely for T.M. As such, an alternative regimen such as R-CVP may be ideal.

A summary of treatment options for FL is presented in **Table 96-8**.

Table 96-8

Summary of Treatment Options in Follicular Lymphoma

Treatment	Place in Therapy
BR	Initial therapy or relapsed/refractory
R-CHOP	Initial therapy or relapsed/refractory
R-CVP	Initial therapy or relapsed/refractory
Bendamustine + obinutuzumab	Initial therapy or relapsed/refractory
CHOP + obinutuzumab	Initial therapy or relapsed/refractory
CVP + obinutuzumab	Initial therapy or relapsed/refractory
Rituximab	Initial therapy or relapsed/refractory
Copanlisib	Relapsed or refractory disease
Duvelisib	Relapsed or refractory disease
Idelalisib	Relapsed or refractory disease
Tazemetostat	Relapsed or refractory disease

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and website for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Cross NC, White HE, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia*. 2012;26(10):2172-2175. (41)

DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood*. 2020;135(2):85–96. doi:10.1182/blood.2019001239 (2)

Estey EH. Acute myeloid leukemia: 2019 update on risk-stratification and management. *Am J Hematol*. 2018;93(10):1267–1291. doi:10.1002/ajh.25214 (16)

Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(6):697–712. doi:10.1016/j.annonc.2020.02.018 (4)

Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy, and monitoring. *Am J Hematol*. 2020;95:691–709. (40)

Molica M, Breccia M, Foa R, Jabbour E, Kadia TM. Maintenance therapy in AML: the past, the present and the future. *Am J Hematol*. 2019;94(11): 1254–1265. doi:10.1002/ajh.25620 (11)

O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348:994–1004. (44)

Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379–391. (108)

Rahmani B, Patel S, Seyam O, et al. Current understanding of tumor lysis syndrome. *Hematol Oncol*. 2019;37(5):537–547. doi:10.1002/hon.2668 (22)

Roscheski M, Dunleavy K, Abramson JS, et al. Risk-adapted therapy in adults with Burkitt lymphoma: results of NCI 9177, a multicenter prospective phase II study of DA-EPOCH-R. *Blood*. 2017;130(Suppl 1):Abstract 188. (134)

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381:1203–1210. (144)

Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PER. *Blood*. 2018;132(10):1013–1021. (72)

Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer*. 2006;106(7): 1569–1580. (135)

Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis

of germinal center and post-germinal center biomarkers. *J Clin Oncol*. 2008;26:2717–2724. (112)

COMPLETE REFERENCES CHAPTER 96 ADULT HEMATOLOGIC MALIGNANCIES

1. Bispo JAB, Pinheiro PS, Kobetz EK. Epidemiology and etiology of leukemia and lymphoma. *Cold Spring Harb Perspect Med*. 2020;10(6):a034819. doi:10.1101/cshperspect.a034819
2. DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood*. 2020;135(2):85–96. doi:10.1182/blood.2019001239
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. doi:10.3322/caac.21590
4. Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(6):697-712. doi:10.1016/j.annonc.2020.02.018
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. doi:10.1182/blood-2016-03-643544
6. Arber DA. The 2016 WHO classification of acute myeloid leukemia: what the practicing clinician needs to know. *Semin Hematol*. 2019;56(2):90–95. doi:10.1053/j.seminhematol.2018.08.002
7. Bullinger L, Döhner K, Döhner H. Genomics of acute myeloid leukemia diagnosis and pathways. *J Clin Oncol*. 2017;35(9):934–946. doi:10.1200/jco.2016.71.2208
8. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209–2221. doi:10.1056/NEJMoa1516192
9. Gerstung M, Papaemmanuil E, Martincorena I, et al. Precision oncology for acute myeloid leukemia using a knowledge bank approach. *Nat Genet*. 2017;49(3):332–340. doi:10.1038/ng.3756
10. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003;21(24):4642–4649. doi:10.1200/jco.2003.04.036
11. Molica M, Breccia M, Foa R, Jabbour E, Kadia TM. Maintenance therapy in AML: The past, the present and the future. *Am J Hematol*. 2019;94(11):1254–1265. doi:10.1002/ajh.25620

12. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol*. 2013;31(27):3360–3368. doi:10.1200/JCO.2012.47.4874
13. Jaramillo S, Benner A, Krauter J, et al. Condensed versus standard schedule of high-dose cytarabine consolidation therapy with pegfilgrastim growth factor support in acute myeloid leukemia. *Blood Cancer J*. 2017;7(5):e564. doi:10.1038/bcj.2017.45
14. Webster JA, Pratz KW. Acute myeloid leukemia in the elderly: therapeutic options and choice. *Leuk Lymphoma*. 2018;59(2):274–287. doi:10.1080/10428194.2017.1330956
15. Kassim AA, Savani BN. Hematopoietic stem cell transplantation for acute myeloid leukemia: a review. *Hematol Oncol Stem Cell Ther*. 2017;10(4):245–251. doi:10.1016/j.hemonc.2017.05.021
16. Estey EH. Acute myeloid leukemia: 2019 update on risk-stratification and management. *Am J Hematol*. 2018;93(10):1267–1291. doi:10.1002/ajh.25214
17. Rai KR, Holland JF, Glidewell OJ, et al. Treatment of acute myelocytic leukemia: a study by cancer and leukemia group B. *Blood*. 1981;58(6):1203-1212.
18. Li X, Xu S, Tan Y, Chen J. The effects of idarubicin versus other anthracyclines for induction therapy of patients with newly diagnosed leukaemia. *Cochrane Database Syst Rev*. 2015;6:CD010432. doi:10.1002/14651858.CD010432.pub2
19. Gong Q, Zhou L, Xu S, Li X, Zou Y, Chen J. High doses of daunorubicin during induction therapy of newly diagnosed acute myeloid leukemia: a systematic review and meta-analysis of prospective clinical trials. *PLoS One*. 2015;10(5):e0125612. doi:10.1371/journal.pone.0125612
20. Röllig C, Ehninger G. How I treat hyperleukocytosis in acute myeloid leukemia. *Blood*. 2015;125(21):3246–3252. doi:10.1182/blood-2014-10-551507
21. Alakel N, Middeke JM, Schetelig J, Bornhäuser M. Prevention and treatment of tumor lysis syndrome, and the efficacy and role of rasburicase. *Onco Targets Ther*. 2017;10:597–605. doi:10.2147/ott.s103864
22. Rahmani B, Patel S, Seyam O, et al. Current understanding of tumor lysis syndrome. *Hematol Oncol*. 2019;37(5):537–547. doi:10.1002/hon.2668
23. Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular minimal residual disease in acute myeloid leukemia. *N Engl J Med*. 2018;378(13):1189–1199. doi:10.1056/NEJMoa1716863
24. Freeman SD, Hills RK, Virgo P, et al. Measurable residual disease at induction redefines partial response in acute myeloid leukemia and stratifies outcomes in patients at standard risk without NPM1 mutations. *J Clin Oncol*. 2018;36(15):1486–1497. doi:10.1200/jco.2017.76.3425

25. Osman AEG, Anderson J, Churpek JE, et al. Treatment of acute promyelocytic leukemia in adults. *J Oncol Pract*. 2018;14(11):649–657. doi:10.1200/JOP.18.00328
26. Sanz MA, Fenaux P, Tallman MS, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood*. 2019;133(15):1630–1643. doi:10.1182/blood-2019-01-894980
27. Stahl M, Tallman MS. Differentiation syndrome in acute promyelocytic leukaemia. *Br J Haematol*. 2019;187(2):157–162. doi:10.1111/bjh.16151
28. Tretinoin oral. In: *Facts and Comparisons*. Wolters Kluwer. Updated September 2020; Accessed October 9, 2020. https://fco.factsandcomparisons.com/
29. Kayser S, Schlenk RF, Platzbecker U. Management of patients with acute promyelocytic leukemia. *Leukemia*. 2018;32(6):1277–1294. doi:10.1038/s41375-018-0139-4
30. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7–17. doi:10.1182/blood-2018-08-868752
31. Amadori S, Suciu S, Selleslag D, et al. Gemtuzumab ozogamicin versus best supportive care in older patients with newly diagnosed acute myeloid leukemia unsuitable for intensive chemotherapy: results of the randomized phase III EORTC-GIMEMA AML-19 trial. *J Clin Oncol*. 2016;34(9):972–979. doi:10.1200/jco.2015.64.0060
32. Wei AH, Strickland SA Jr, Hou JZ, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol*. 2019;37(15):1277–1284. doi:10.1200/jco.18.01600
33. Serve H, Krug U, Wagner R, et al. Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. *J Clin Oncol*. 2013;31(25):3110–3118. doi:10.1200/jco.2012.46.4990
34. Wattad M, Weber D, Döhner K, et al. Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. *Leukemia*. 2017;31(6):1306–1313. doi:10.1038/leu.2017.23
35. Thol F, Schlenk RF, Heuser M, Ganser A. How I treat refractory and early relapsed acute myeloid leukemia. *Blood*. 2015;126(3):319–327. doi:10.1182/blood-2014-10-551911
36. Ekblom R, Brechlin B, Persson J, et al. Genome sequencing and conservation genomics in the Scandinavian wolverine population. *Conserv Biol*. 2018;32(6):1301–1312. doi:10.1111/cobi.13157
37. Tu JV, Chu A, Donovan LR, et al. The Cardiovascular Health in Ambulatory Care Research Team (CANHEART): using big data to measure and improve

cardiovascular health and healthcare services. *Circ Cardiovasc Qual Outcomes*. 2015;8(2):204–212. doi:10.1161/CIRCOUTCOMES.114.001416

38. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. 2020. Accessed October 5, 2020. https://seer.cancer.gov/statfacts/html/cmyl.html
39. American Cancer Society. *Cancer Facts & Figures 2020*. American Cancer Society; 2020. Accessed October 6, 2020. https://www.cancer.org/research/cancer-facts-statistics
40. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy, and monitoring. *Am J Hematol*. 2020;95:691–709.
41. Cross NC, White HE, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia*. 2012;26(10):2172-2175
42. Craddock, C. We do still transplant for CML, don't we? *Hematology Am Soc Educ Program*. 2018;2018(1):177–184.
43. Gratwohl A, Hermans J, Goldman JM. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Lancet*. 1998;352(9134):1087–1092.
44. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348:994–1004.
45. Deininger M, O-Brien SG, Guilhot F, et al. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed CML-CP treated with imatinib. *Blood*. 2009;ASH Abstract:1126.
46. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase myeloid leukemia. *N Engl J Med*. 2010;362:2260–2270.
47. Jabbour E, Kantarjian H, Saglio G, et al. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trail (DASISION*). Blood*. 2014;123(4):494–500.
48. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251–2259.
49. Larson RA, Kim DW, Issaragrilsil S, et al. Efficacy and safety of nilotinib (NIL) vs imatinib (IM) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): long-term follow-up (f/u) of ENESTnd. *Blood*. 2014;124(21):4541.
50. Khoury HJ, Cortes JE, Kantarjian H, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood*. 2012;119(15):3403–3412
51. Cortes JE, Khoury HJ, Kantarjian H, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or

nilotinib. *Am J Hematol*. 2016;91(12):1206–1214.
52. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE Trial. *J Clin Oncol*. 2018;36(3):231–237.
53. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood*. 2009;113(22):5401–5411.
54. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369:1783–1796.
55. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018;132(4):393–404.
56. Cortes JE, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. *Blood*. 2012;120(13):2573–2580.
57. Cortes JE, Digumarti R, Parikh PM, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. *Am J Hematol*. 2013;88(5):350–354.
58. Evens AM, Antillón M, Aschebrook-Kilfoy B, Chiu BC. Racial disparities in Hodgkin's lymphoma: a comprehensive population-based analysis. *Ann Oncol*. 2012;23:2128–2137.
59. Alexander FE, Jarrett RF, Lawrence D, et al. Risk factors for Hodgkin's disease by Epstein-Barr virus (EBV) status: prior infection by EBV and other agents. *Br J Cancer*. 2000;82:1117–1121.
60. Goedert JJ, Coté TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. *Lancet*. 1998;351:1833–1839.
61. Tinguely M, Vonlanthen R, Müller E, et al. Hodgkin's disease-like lymphoproliferative disorders in patients with different underlying immunodeficiency states. *Mod Pathol*. 1998;11:307–312.
62. Goldin LR, Pfeiffer RM, Gridley G, et al. Familial aggregation of Hodgkin lymphoma and related tumors. *Cancer*. 2004;100:1902–1908.
63. Goldin LR, Landgren O, McMaster ML, et al. Familial aggregation and heterogeneity of non-Hodgkin lymphoma in population-based samples. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2402–2406.
64. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–3068.
65. Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. *Blood*. 2008;111:2977–2983.

66. Mauch PM, Kalish LA, Marcus KC, et al. Long-term survival in Hodgkin's disease cancer. *J Sci Am Cancer*. 1995;1:33–42.
67. Aisenberg AC. Problems in Hodgkin's disease management. *Blood*. 1999;93:761–779.
68. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol*. 2003;21:3431–3439.
69. Harris NL. Hodgkin's lymphomas: classification, diagnosis, and grading. *Semin Hematol*. 1999;36:220–232.
70. Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. IARC; 2008.
71. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. *N Engl J Med*. 1998;339:1506–1514.
72. Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PER. *Blood*. 2018;132(10):1013–1021.
73. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2017;35(16):1786–1794.
74. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*. 2015;372(17):1598–1607.
75. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374(25):2419–2429.
76. Boleti E, Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. *Ann Oncol*. 2007;18:376–380.
77. Evens AM, Cilley J, Ortiz T, et al. G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in the treatment of Hodgkin lymphoma: low toxicity and excellent outcomes in a 10-year analysis. *Br J Haematol*. 2007;137:545–552.
78. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol*. 2009;27:805–811.
79. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med*. 2011;365:203–212.
80. von Tresckow B, Plütschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol*. 2012;30:907–913.

81. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*. 2018;390(10114):2790–2802.
82. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III of IV Hodgkin's lymphoma. *N Eng/J Med*. 2018;378(4):331–344.
83. Duhmke E, Franklin J, Pfreundschuh M, et al. Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable of radiotherapy alone. *J Clin Oncol*. 2001;19:2905–2914.
84. Gustavsson A, Osterman B, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in Hodgkin's lymphoma. *Acta Oncol*. 2003;42:589–604.
85. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):640–652.
86. Goergen H, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. *J Clin Oncol*. 2019;37(31):2835–2845.
87. Specht L, Gray RG, Clarke MJ, Peto R. Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients. International Hodgkin's Disease Collaborative Group. *J Clin Oncol*. 1998;16:830–843.
88. Shore T, Nelson N, Weinerman B. A meta-analysis of stages I and II Hodgkin's disease. *Cancer*. 1990;65:1155–1160.
89. Nachman JB, Sposto R, Herzog P, et al. Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. *J Clin Oncol*. 2002;20:3765–3771.
90. Collins GP, Parker AN, Pocock C, et al. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. *Br J Haematol*. 2014;164:39–52.
91. Brice P. Managing relapsed and refractory Hodgkin lymphoma. *Br J Haematol*. 2008;141:3–13.
92. Mendler JH, Friedberg JW. Salvage therapy in Hodgkin's lymphoma. *Oncologist*. 2009;14:425–432.
93. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30:2183–2189.
94. O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an

international, multicentre, single-arm, phase 1-2 trial. *Lancet Oncol*. 2018;19:257–266

95. Jostin A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. *Ann Oncol*. 2002;13(10):1628–1635.
96. Abali H, Urün Y, Oksüzog˘lu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. *Cancer Invest*. 2008;26(4):401–406.
97. Aparicio J, Segura A, Garcerá S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. *Ann Oncol*. 1999;10(5):593–595.
98. Armand P, Engert A, Younes A et al. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. *J Clin Oncol*. 2018; 36(14):1428-1439. https://pubmed.ncbi.nlm.nih.gov/29584546/
99. Kuruvilla J, Ramchandren R, Santoro A, et al. KEYNOTE-204: randomized, open-label, phase III study of pembrolizumab (pembro) versus brentuximab vedotin (BV) in relapsed or refractory classic Hodgkin lymphoma (R/R cHL). *J Clin Oncol*. 2020;38:8005.
100. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17(12):3835–3849.
101. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol*. 1998;16:2780–2795.
102. Fisher RI, Miller TP, O'Connor OA. Diffuse aggressive lymphoma. *Hematol Am Soc Hematol Educ Prog*. 2004;221–236.
103. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329:987–994.
104. Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:2373–2380.
105. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med*. 1993;328:1002–1006.
106. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol*. 2005;23:5027–5033.

107. Pettengell R, Linch D; Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Position paper on the therapeutic use of rituximab in CD20-positive diffuse large B-cell non-Hodgkin's lymphoma. *Br J Haematol*. 2003;121:44–48.
108. Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379–391.
109. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med*. 1998;339:21–26.
110. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol*. 2008;26:2258–2263.
111. Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2006;47(10):2174–2180.
112. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol*. 2008;26:2717–2724.
113. Chao NJ, Rosenberg SA, Horning SJ. CEPP(B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. *Blood*. 1990;76:1293–1298.
114. Fields PA, Townsend W, Webb A, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. *J Clin Oncol*. 2014;32:282–287.
115. Moccia AA, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines (abstract 408*). Blood*. 2009;114:170.
116. Pettengell R, Schwenkglenks M, Bosly A. Association of reduced relative dose intensity and survival in lymphoma patients receiving CHOP-21 chemotherapy. *Ann Hematol*. 2008;87:429–430.
117. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2011;12:460–468.
118. Lin P, Dickason TJ, Fayad LE, et al. Prognostic value of MYC rearrangement in cases of B-cell lymphoma, unclassifiable, with features intermediate

between diffuse large B-cell lymphoma and Burkitt lymphoma. *Cancer*. 2012;118:1566–1573.
119. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. *Blood*. 2011;117:2319–2331.
120. Gandhi M, Petrich AM, Cassaday RD, et al. Impact of induction regimen and consolidative stem cell transplantation in patients with double hit lymphoma (DHL): a large multicenter retrospective analysis. *Blood*. 2013;122:640.
121. Oki Y, Noorani M, Lin P, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. *Br J Haematol*. 2014;166:891–901.
122. Singer CR, Goldstone AH. Clinical studies of ABMT in non-Hodgkin's lymphoma. *Clin Haematol*. 1986;15:105–150.
123. Cortelazzo S, Rambaldi A, Rossi A, et al. Intensification of salvage treatment with high-dose sequential chemotherapy improves the outcome of patients with refractory or relapsed aggressive non-Hodgkin's lymphoma. *Br J Haematol*. 2001;114:333–341.
124. Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. *Cancer Invest*. 2006;24:593–600.
125. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. *Blood*. 2004;103:3684–3688.
126. Martín A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. *Haematologica*. 2008;93:1829–1836.
127. Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. *Cancer Chemother Pharmacol*. 2009;64:907–916.
128. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2013;31:2103–2109.
129. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2020;38(2):155–165.
130. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020;21(7):978–988.
131. Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. *Blood*. 2015;125(9):1394–1402.

132. Kalakona N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. *Lancet Haematol*. 2020;7(7):e511–e522.
133. Wasterlid T, Brown PN, Hagberg O, et al. Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group. *Ann Oncol*. 2013;24:1879–1886.
134. Roscheski M, Dunleavy K, Abramson JS, et al. Risk-adapted therapy in adults with Burkitt lymphoma: results of NCI 9177, a multicenter prospective phase II study of DA-EPOCH-R. *Blood*. 2017;130(suppl 1):Abstract 188.
135. Thomas DA*,* Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer*. 2006;106(7):1569–1580.
136. Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. *Ann Oncol*. 2011;22(8):1859–1864.
137. Hill QA, Owen RG. CNS prophylaxis in lymphoma: who to target and what therapy to use. *Blood Rev*. 2006;20:319–332.
138. Perkins AS, Friedberg JW. Burkitt lymphoma in adults. *Hematol Am Soc Hematol Educ Prog*. 2008;2008:341–348.
139. Kelly JL, Toothaker SR, Ciminello L, et al. Outcomes of patients with Burkitt lymphoma older than age 40 treated with intensive chemotherapeutic regimens. *Clin Lymphoma Myeloma*. 2009;9:307–310.
140. Teodorovic I, Pittaluga S, Kluin-Nelemans JC, et al. Efficacy of four different regimens in 64 mantle-cell lymphoma cases: clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes. European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group. *J Clin Oncol*. 1995;13:2819–2826.
141. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. *J Clin Oncol*. 2005;23:7013–7023.
142. Martin P, Chadburn A, Christos P, et al. Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma: overall survival exceeding 7 years with standard therapies. *Ann Oncol*. 2008;19:1327–1330.
143. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG*). J Clin Oncol*. 2005;23:1984–1992.

144. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381:1203–1210.
145. Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. *N Engl J Med*. 2015;372(10):944–953.
146. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369(6):507–516.
147. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood*. 1997;89:3909–3918.
148. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104:1258–1265.
149. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*. 2003;362:516–522.
150. Tan D, Horning SJ, Hoppe RT, et al. Improvements in observed and relative survival in follicular grade 1–2 lymphoma during 4 decades: the Stanford University experience. *Blood*. 2013;122:981–987.
151. O'Brien ME, Easterbrook P, Powell J, et al. The natural history of low grade non-Hodgkin's lymphoma and the impact of a no initial treatment policy on survival. *Q J Med*. 1991;80:651–660.
152. Anderson T, Chabner BA, Young RC, et al. Malignant lymphoma. The histology and staging of 473 patients at the National Cancer Institute. *Cancer*. 1982;50:2699–2707.
153. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. *J Clin Oncol*. 2009;27:1202–1208.
154. Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. *J Clin Oncol*. 2012;30:3368–3375.
155. Seymour JF, Pro B, Fuller LM, et al. Long-term follow-up of a prospective study of combined modality therapy for stage I–II indolent non-Hodgkin's lymphoma. *J Clin Oncol*. 2003;21:2115–2122.
156. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014;123:2944–2952.
157. Czuczman MS, Weaver R, Alkuzweny B, Berlfein J, Grillo-López AJ. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. *J Clin Oncol*. 2004;22:4711–4716.

158. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008;26:4579–4586.
159. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106:3725–3732.
160. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. 2011;377:42–51.
161. Zhou H, Zhang B, Zhang J, Ni W, Hu, Z. Rituximab maintenance therapy for follicular lymphoma. *Lancet*. 2011;377:1150–1151.
162. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med*. 2017;377(14):1331–1344.
163. Kahl BS, Hong F, Williams ME, et al. Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: eastern cooperative oncology group protocol e4402. *J Clin Oncol*. 2014;32:3096–3102.
164. Ghielmini M, Schmitz SF, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and-response duration compared with the standard weekly x 4 schedule. *Blood*. 2004;103:4416–4423.
165. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2019;37(14):1188–1199.
166. Scholz CW, Pinto A, Linkesch W, et al. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. *J Clin Oncol*. 2013;31(3):308–313.
167. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008–1018.
168. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2020;21(11):1433–1442.
169. Montoto S, Davies AJ, Matthews J, et al. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *J Clin Oncol*. 2007;25:2426–2433.
170. Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or

chemoimmunotherapy with or without stem-cell transplantation. *J Clin Oncol*. 2006;24:2343–2351.

97

Breast Cancer

Kellie Jones Weddle

CORE PRINCIPLES		CHAPTER CASES
1	Mammography is a common screening modality used in patients with an average risk of developing breast cancer.	**Case 97-1 (Question 1)**
2	Prevention can include both surgery (prophylactic mastectomy ± bilateral oophorectomy) and chemoprevention. Tamoxifen and raloxifene are two agents approved for breast cancer prevention.	**Case 97-1 (Question 2)**
3	Breast cancer is the most common cancer diagnosed in U.S. females. Many risk factors have been associated with the development of breast cancer; however, the two most common risk factors are gender and age.	**Case 97-2 (Question 1) Case 97-3 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
4	A painless mass is a common presenting symptom for patients. To diagnose the disease and determine the histology, a mammogram and a biopsy are performed. Staging is also performed to determine the extent of disease.	**Case 97-3 (Questions 2–4)**
5	Tumor-specific characteristics help guide treatment selection and contribute to prognosis. The most significant factors are hormonal status (estrogen and progesterone receptor status) and human epidermal growth factor receptor 2 (HER2) status.	**Case 97-3 (Question 5)**
6	Local and systemic treatment can include surgery, radiation, hormonal therapy, chemotherapy, biologic, and/or immunotherapy therapy.	**Case 97-3 (Questions 6–9)**
7	Early-stage disease is highly curable. In the adjuvant setting (after surgery), patients can receive hormonal therapy or biologic therapy, depending on tumor-specific factors and may receive chemotherapy, depending on the size of the disease and the presence of positive axillary lymph nodes.	**Case 97-3 (Questions 7–9)**

CORE PRINCIPLES		CHAPTER CASES
8	Adjuvant chemotherapy can include regimens containing anthracyclines, cyclophosphamide, and taxanes. HER2-targeted therapies can be incorporated if the patient has HER2-positive disease.	**Case 97-3 (Questions 6–8)**
9	Metastatic disease is considered incurable. Decisions regarding therapy will depend on the hormonal status of the tumor, toxicities from previous treatment, or other preexisting comorbidities. Therapies could include systemic therapy (hormonal therapy, chemotherapy, biologic, or immunotherapy) or local treatment (radiation therapy or surgery).	**Case 97-4 (Questions 1–5)**

INTRODUCTION

Breast Cancer

INCIDENCE, PREVALENCE, AND EPIDEMIOLOGY

Breast cancer is the most common malignancy in American females and is second to lung cancer in mortality rates. It arises from the tissues of the breast, usually the ducts (tubes that carry milk to the nipple) and lobules (glands that make milk). In 2020, it was estimated that 279,100 individuals would be diagnosed with breast cancer, and ~42,690 are expected to die from their disease. Approximately 2620 cases were estimated to be diagnosed in males, indicating this is not a disease solely of females.[1]

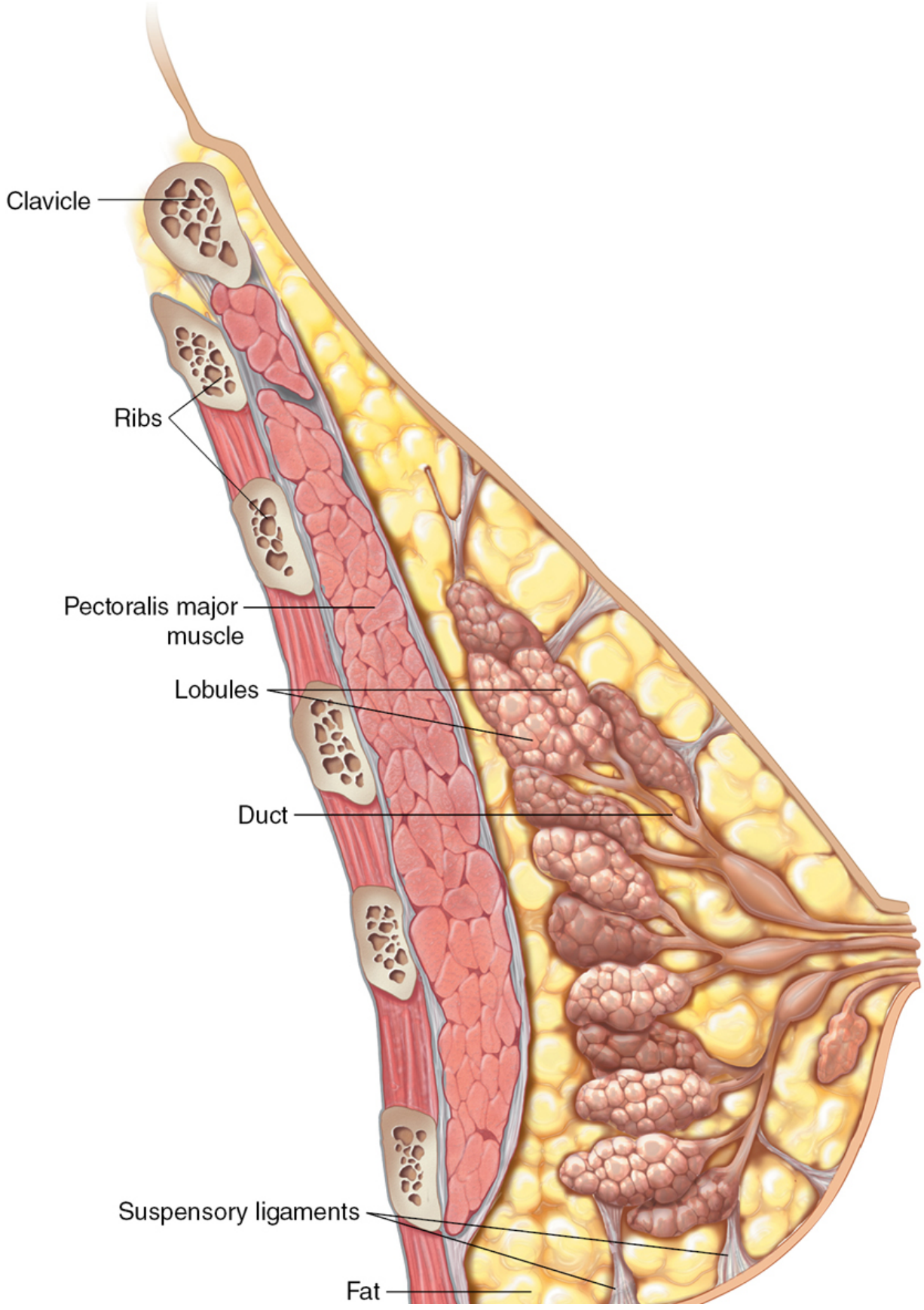
The incidence of breast cancer declined from 1999 through 2004 because of the decreased use of hormone-replacement therapy (HRT). This decline follows the results of the Women's Health Initiative study, which demonstrated an increased risk of breast cancer in those receiving HRT.[2] As other risk factors in females have evolved over time, changes in incidence rates have followed. Decreased incidences in breast cancer in females with increased body mass index have occurred, and incidence rates have increased in females who have fewer births from 1980 to 2011.[2] One in eight females are expected to develop the disease over the course of their lifetime. However, this frequently quoted statistic may overestimate the risk of breast cancer because it is derived from females who live to 110 years of age.[3]

If breast cancer is diagnosed early, it is curable. The likelihood of diagnosing breast cancer is increased by the use of standardized screening methods. Currently, many different guidelines are available for breast cancer screening, including recommendations from the American Cancer Society (ACS), and the U.S. Preventive Services Task Force (USPSTF).

Pathophysiology

The breast itself is composed of many different structures including fat, muscle, ducts, and lobules (**Fig. 97-1**). Lobules arise from glandular tissue that forms into a spoke-like formation to constitute a lobule of two layers of epithelial cells. The ducts connect the milk-secreting lobules to the nipple.[4] A breast cancer is defined by where the tumor cells originate. The two most common histologic types of breast cancer are ductal and lobular carcinoma. Ductal tumors may be classified as either invasive ductal carcinoma (IDC) if it has invaded through the basement membrane of the duct or ductal carcinoma in situ (DCIS) if it has not. Likewise, lobular tumors may be classified similarly (ie, invasive lobular carcinoma [ILC] or lobular carcinoma in situ [LCIS]). Other types of breast cancers include

inflammatory (which will be discussed later in the chapter) and rare histologies such as tubular or medullary carcinomas or sarcomas.


Clavicle
Ribs
Pectoralis major muscle
Lobules
Duct
Suspensory ligaments
Fat

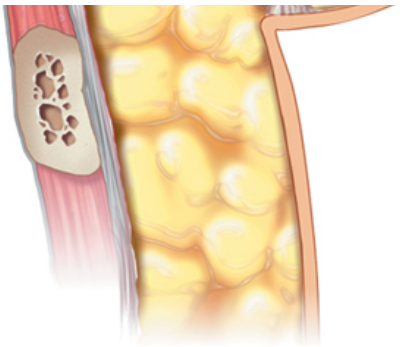


Figure 97-1 Anatomy of the breast. (Asset provided by Anatomical Chart Co.)

Clinical Presentation and Diagnosis

Most patients will present with early-stage disease, where the 5-year survival rate is ~90%.[5] Many individuals present with a painless lump found upon breast examination (either by themselves or by a clinician) or with a small mass found only on routine mammogram. Patients who present with metastatic disease typically present with symptoms of their disease based on the metastatic site (such as bone pain with bone metastases or shortness of breath with lung metastases).

Treatment will be determined based on the stage of the disease. Staging is completed by evaluating the size of the tumor (either radiographically or from the surgical specimen), the extent of positive lymph nodes (on physical examination and surgical removal through an axillary lymph node dissection or sentinel lymph node dissection), and the extent of disease (through radiologic examinations including computed tomography [CT] scan of the chest, abdomen, and pelvis and a bone scan to identify any metastatic disease).

Overview of Treatment

The treatment of breast cancer includes multiple modalities. Surgery, radiation, hormonal therapy, chemotherapy, biologic, and immunotherapy can all be used in many different combinations based on a patient's specific disease. If therapy is given before

surgery, it is called neoadjuvant therapy, and if treatment is administered after surgery it is termed adjuvant therapy. Early-stage disease may be treated with surgery; other factors will determine whether additional therapy is needed. The staging of a patient's tumor may require radiation and/or chemotherapy, and tumor-specific characteristics decide whether hormonal, biologic therapy, or immunotherapy will be added. In patients with metastatic disease, the goal is palliation of symptoms and improvement in quality of life.

SCREENING

CASE 97-1

Question 1: M.P. is a 42-year-old female with no personal history of breast cancer. She has a cousin who was diagnosed with breast cancer at the age of 65 years. M.P. is in her doctor's office today to discuss routine breast cancer screening.

Based on M.P.'s personal and family history, would M.P. be considered an average-risk or high-risk patient and what modalities of screening are recommended for average-risk and high-risk patients?

The guidelines for cancer screening for breast cancer were last updated in 2015 and led to major changes in the recommended screening modalities and intervals of obtainment for females of average risk of developing breast cancer.[6] For the average-risk patient, screening involves a mammogram and a breast self-examination (BSE; if the female chooses to do so). Although the risk of breast cancer is low in the 20s, BSE allows a female to become more familiar with her body and better able to discern changes as she ages. Clinical breast examinations have long been part of the screening guidelines, but with the new changes in recommendations, this component of screening has been removed because of a lack of benefit of detecting breast cancer in a female with average risk.

Screening mammography has been the gold standard for breast cancer for many decades. Current guidelines state that for a female of average risk, she should have the opportunity to begin annual mammograms between ages 40 and 44 years and then annual

mammograms should commence at age 45 through 54 years. Once a female turns 55 years old, she could transition to biennial screening or have the opportunity to continue annual screening. The guidelines also recommend for females to continue screening mammograms as long as their overall health is good and their life expectancy is 10 or more years.

For many years, there has been controversy regarding the utility of mammography and when screening should begin (age 40 or 50 years). This controversy has stemmed from recommendations by the USPSTF.[7] Their newest recommendations state that the decision to start screening mammograms before age 50 years should be an individual decision. Females may choose to begin biennial screening between ages 40 and 49 years, but that this may lead to more false-positive results and unnecessary biopsies. The guidelines state that the largest benefit for screening mammograms occurs in females ages 50 to 74 years, and there are insufficient data to support the utility of annual mammograms in female age 75 years or older. Although these screening recommendations can be confusing, the controversy that has stemmed from the changes has heightened the awareness to the general public of the importance of breast cancer screening.

M.P. has no first-degree relatives with breast cancer or other family members affected by early breast cancer. M.P. is an average-risk patient, and she should start standard screening modalities and intervals of testing with annual mammograms. She may also decide to do breast self-examinations.

Individuals considered high risk include those that (a) have a known *BRCA* gene mutation, (b) are untested for the *BRCA* gene mutation but have a first-degree relative with a *BRCA* mutation, (c) have a lifetime risk of experiencing breast cancer of ~20% to 25% or more based on risk estimation models, or (d) have a strong family history of breast cancer.[6] Screening with breast magnetic resonance imaging (MRI) is recommended in high-risk individuals. Annual mammography and breast MRIs should be initiated starting at age 30 years in this population. An MRI allows a radiologist to see a contrasted view of the breast and is more sensitive to detecting

breast cancer. In addition, breast tissue in younger patients can be denser because of higher levels of estrogen, making mammography less sensitive.[8]

PREVENTION

Case 97-1, Question 2: M.P. works at her local hospital as a nurse and is volunteering this year at their breast cancer awareness seminar that is offered by her hospital. She was asked to prepare a talk for the event about breast cancer awareness. She wants to discuss breast cancer prevention. What are the common modalities of breast cancer prevention that M.P. should address and what agents are used for breast cancer prevention?

Prevention is key with any cancer. Females who are considered high risk for breast cancer may decide to undergo prophylactic mastectomy with reconstruction as an alternative to living with the prospect that they may develop breast cancer in their life. This modality of prevention is very successful but does not completely eliminate the risk for developing breast cancer.[9] In addition, prophylactic oophorectomy may also be completed to remove the largest source of estrogen in a premenopausal patient. This does not however eliminate the risk completely from developing breast cancer.[10]

Chemoprevention is also another option. Two agents approved for prevention are tamoxifen and raloxifene. Both are selective estrogen receptor modulators (SERMs). The Breast Cancer Prevention Trial (or P1 trial) was conducted in more than 13,000 high-risk females, who were randomly assigned into three groups: age older than 60 years, ages 35 to 59 years with an increased risk of breast cancer based on a score of at least 1.66 as determined by the Gail risk model, or age older than 35 years with a history of LCIS (a risk factor for developing invasive breast cancer).[11] Females received tamoxifen 20 mg daily or placebo for 5 years of therapy. Tamoxifen significantly decreased the risk of developing breast cancer ($P > .00001$). In addition, this study illustrated toxicities associated with tamoxifen therapy, especially in females age older than 50 years. In

those patients, a higher risk of deep vein thrombosis, stroke, pulmonary embolism, and endometrial cancers was identified.[11]

Raloxifene was also approved for chemoprevention in breast cancer. This originated from observations made in osteoporosis studies with raloxifene where patients who had received raloxifene therapy had a decreased risk of breast cancer. With this information, a large randomized chemoprevention trial of more than 19,000 postmenopausal females was conducted evaluating the use of raloxifene 60 mg daily compared to tamoxifen 20 mg daily for 5 years.[12] There was no difference in the number of invasive breast cancers diagnosed in the two treatment arms (relative risk, 1.02; 95% confidence interval, 0.82–1.28). Interestingly, more noninvasive breast cancers were identified in the raloxifene group (80 cases) compared with tamoxifen (57 cases); however, the clinical significance of this difference is unknown. The tamoxifen arm reported more hot flashes and endometrial cancer, and the raloxifene arm demonstrated fewer thromboembolic events and cataracts but more musculoskeletal problems and weight gain. Based on the results of this trial, raloxifene received an indication for chemoprevention in high-risk females. The aromatase inhibitors, exemestane and anastrozole, have been studied in the chemopreventive setting in postmenopausal patients (NCIC CTG MAP III trial and IBIS II trial, respectively). Although both trials demonstrated reductions in breast cancer incidences, neither agent has been compared with tamoxifen or raloxifene and neither are approved for use in this setting.[13–15]

M.P. should include information on prophylactic mastectomy and both tamoxifen (for pre- and postmenopausal patients) and raloxifene (in postmenopausal patients only) in her talk for females with a high risk of breast cancer.

RISK FACTORS

CASE 97-2

QUESTION 1: B.W., a 55-year-old female, is found to have a 2.2-cm mass in the upper, outer quadrant of her left breast during a routine screening mammogram. The rest of her physical examination is unremarkable. All laboratory values, including the complete blood count and liver function tests, are within normal limits. A chest x-ray is negative. B.W. reports that she had her first menstrual cycle at the age 10 years and has had regular periods since that time. She is married but has never been pregnant.

What are B.W.'s risk factors for developing breast cancer?

Many different risk factors have been identified to be associated with the development of breast cancer. However, in >50% of patients, there are no identifiable risk factors beyond increased age and female gender (**Table 97-1**).[16] An individual's risk increases with each decade of life, and the median age of diagnosis is between ages 60 and 65 years. If the patient has had a previous history of breast cancer or atypical hyperplasia from previous breast biopsies, this increases their risk of developing breast cancer.

Table 97-1
Risk Factors for Developing Breast Cancer

Known Risk Factors
Gender: female > male
Personal history of breast cancer
Family history of breast cancer (first-degree relatives)
Benign breast "cancer" (eg, atypical hyperplasia)
Early menarche (age >12 years), late menopause (age >55 years)
Late first pregnancy (age ≥30 years) or no pregnancy
Advancing age
Long-term use of hormone-replacement therapy (estrogen)
Previous chest wall irradiation
Possible Risk Factors
Alcohol
Obesity
High-fat diet

Source: Reprinted with permission from Rojas K, Stuckey A. Breast cancer epidemiology and risk factors. *Clin Obstet Gynecol*. 2016;59(4):651–672.

Breast cancer is a hormonally mediated disease, and many factors are associated with hormonal influences. Early menarche (generally defined as age younger than 12 years) and late menopause (generally defined as age older than 55 years) expose a female to more estrogen throughout her lifetime.[17] Based on the results of the Women's Health Initiative, the use of HRT was shown to increase risk of breast cancer.[18] Nulliparity, or having children after age 30 years, has been associated with an increased risk (RR increased up to 3.5).[16,17] Oral contraceptives have long been thought to increase the risk of breast cancer. Earlier forms of oral contraceptives contained much higher doses of estrogen compared with products today. The dose of estrogens in those products was thought to increase a female's risk of developing breast cancer. However, a meta-analysis demonstrated a minimal difference in risk no matter the dose of estrogen in the oral contraceptives for a healthy female at a low baseline risk.[19] Hereditary breast cancers (one or more first-degree relatives with the disease) only account for ~10% of breast cancer cases; however, these individuals have the highest risk of developing breast cancer.[20]

B.W. has risk factors that increase her risk of developing breast cancer. B.W. started menses early at age 10 years and therefore has been exposed longer to estrogen, and she does not have any children. She is also age 55 years, and the risk of breast cancer increases with each decade of life. Therefore, all of these are considered risk factors for B.W.

INHERITED BREAST CANCER MUTATIONS

CASE 97-3

Question 1: C.D., a 37-year-old female, is found to have a 2.2-cm mass in the outer quadrant of her right breast during a mammogram. All of her laboratory values were normal, and her chest x-ray was negative. Her family history is

significant in that her mother died of breast cancer at the age of 42 years and her 44-year-old sister had a breast tumor removed 5 years ago.

With C.D.'s family history, what genetic testing could be performed for her or for anyone else in her family? If C.D. did not have a family history of breast cancer, what other tests could be conducted to estimate her risk of developing breast cancer?

C.D. has two first-degree relatives with early-age breast cancer. This would indicate a possible inherited genetic mutation. Genetic testing for the presence of *BRCA1* and *BRCA2* mutations should be discussed with C.D. By age 70 years, a person with a BRCA1 mutation has a ~60% risk of developing breast cancer and a 40% risk of developing ovarian cancer.

BRCA2 mutation carriers have a slightly lower risk of breast cancer (~40%) and a lower risk of developing ovarian cancer (~20%).[20,21] One population with a high incidence of *BRCA* mutations is those of Ashkenazi Jewish descent, which 1 in 50 individuals are *BRCA* carriers.[22] C.D. should meet with a genetic counselor to discuss risks and benefits of genetic testing for her and her family members. The results would then play a role in future screening and preventive strategies.

Patients can assess their risk of developing breast cancer by using validated risk tools. One such instrument for average-risk patients is the Gail model, which considers numerous factors such as age at menarche, age of first live birth, presence of atypical hyperplasia, and number of previous breast biopsies. This model is available online (www.cancer.gov/bcrisktool/). Other models that have been validated include BRCAPRO and the Breast Cancer Risk Assessment Tool (for average-risk patients).[23] BRCAPRO is a statistical program that uses information from both affected and unaffected relatives to predict the likelihood of whether a person would have an inherited mutation in *BRCA1* or *BRCA2.*[24] This tool would be used in an individual with a high risk of developing breast cancer. There are numerous resources for patients and family members to help understand their risk of developing breast cancer. Concerned individuals should have a conversation with their

physician regarding their risk of breast cancer and the utility of these risk assessment tools based on their personal and family history.

Clinical Presentation

Case 97-3, Question 2: What are the typical signs and symptoms of breast cancer and does C.D. have any?

Typical presentation involves the identification of a painless lump on clinical examination by a health care professional, by the patient, or by visualization of a painless lump on mammography. Other symptoms are nipple discharge or retraction, or skin changes of the breast.[25] Fewer than 10% of patients will present with metastatic disease. Symptoms upon presentation can reflect their metastatic disease (ie, back pain: bone metastases; headaches/nausea/vomiting: brain metastases; dyspnea: lung metastases; or abdominal pain: liver metastases).[25] C.D. had a painless lump identified on mammogram as her presenting sign.

Diagnosis

Case 97-3, Question 3: After the identification of C.D.'s breast mass on mammogram, what diagnostic procedures should be done to determine C.D.'s type and stage of breast cancer?

Workup for breast cancer includes radiographic examinations, patient history, and a physical examination. If a mass is palpated, a mammogram is completed to identify the abnormality. A breast ultrasound can also be added after the mammogram to differentiate fluid-filled cysts (which are usually benign) versus discreet masses. Once identified, a biopsy would then be performed to diagnose the disease. This is achieved with a core biopsy—the standard method used to obtain a tissue sample. This procedure uses a large-bore needle for tissue collection and allows for distinguishing invasive

versus noninvasive disease. Other methods are available for tissue diagnosis such as fine-needle aspiration and excisional biopsy, but the core biopsy is considered the standard approach.[25]

Full radiologic testing should also be completed including a CT scan of the chest, abdomen, and pelvis, and bone scan to assess for metastatic disease. The most common places for breast cancer to metastasize are the bone, lung, liver, lymph nodes, and the brain.[26] Evaluation for brain metastases would be performed if the patient is experiencing signs and symptoms such as blurry or double vision, uncontrolled nausea/vomiting, headaches, and unsteady gait. These tests are used to determine the extent and stage of the disease and ultimately help determine the prognosis and treatment of the patient. C.D. will need to undergo a biopsy and full staging with a CT scan of the chest, abdomen, and pelvis, and a bone scan.

Types of Breast Cancer and Staging

Case 97-3, Question 4: C.D. had a core biopsy performed that revealed IDC. Other staging tests included a CT scan of the chest, abdomen, and pelvis and a bone scan. All tests were negative. Physical examination revealed ipsilateral lymph node involvement. Mammogram revealed a 2.2-cm mass in the right breast. What are the common types of breast cancer and what stage is C.D.'s breast cancer?

The histology of breast cancer is typically divided into two categories: invasive and noninvasive (in situ) disease. IDC is the most common type found (~75% of cases) and ILC is second (~5%–10%). The noninvasive tumors are less common (DCIS and LCIS; ductal carcinoma in situ and lobular carcinoma in situ, respectively).[25] Other less common histologies include medullary, mucinous, tubular, and papillary. One of the most aggressive forms of breast cancer is inflammatory breast cancer, which is distinctly different from the other types of breast cancer mentioned. Breast cancer can take years to develop into a mass that is identifiable on physical examination or mammogram. In contrast, the onset of

inflammatory breast cancer is sudden and can develop in weeks. Presentation includes a breast that looks “inflamed,” red, and has the look of an orange peel (“peau d’orange”). The diagnosis may be delayed because the skin has the appearance of cellulitis with antibiotics prescribed first; however, the symptoms do not improve with treatment.[27]

Staging is conducted to evaluate the extent of the disease. This is completed to understand a patient’s prognosis and to help to determine the best treatment course. Staging of breast cancer is determined using the TNM (T, tumor size; N, nodal status; M, any site of metastatic disease) classification. This information is determined by both clinical and pathologic examination. In 2010, the breast cancer staging system was updated by the American Joint Commission on Cancer.[28] Stage I disease involves small tumors (>2 cm) with no lymph node involvement and is highly curable (~98% 5-year survival). Stage II includes small tumors with lymph node involvement or larger tumors (>2 cm and ≤5 cm) with no lymph node involvement. Stage III tumors are larger (>5 cm) with lymph node involvement with a 5-year survival of ~80%. Stage IV disease has metastasized to other distant organs and has the poorest prognosis with a 5-year survival of ~26% (**Table 97-2**).[25-26, 28] Most patients will present with stage I or II disease because of routine screening. Based on C.D.’s clinical staging, she is considered to have stage II disease based on the size of her disease and the involvement of ipsilateral lymph nodes.

Table 97-2
American Joint Committee on Cancer Staging for Breast Cancer

Stage	T	N	M
0	Tis	N0	M0
IA–B	T1–T1a	N0–N1mi	M0
IIA–B	T0–T3	N0–N1b	M0
IIIA	T0–T3	N1–N2	M0
IIIB	T4	N0–N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

M, metastatic disease; mi, micrometastasis; N, presence of lymph nodes; N0, no lymph node involvement; N1, movable ipsilateral lymph nodes; N2, ipsilateral axillary lymph nodes (fixed or matted), or clinical ipsilateral internal mammary nodes with no axillary lymph node involvement; N3, ipsilateral infraclavicular lymph nodes, clinical ipsilateral internal mammary lymph nodes, clinical axillary lymph nodes, or ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary lymph node involvement; T, tumor size and/or invasion; Tis, carcinoma in situ; T1, ≤2 cm; T2, >2 to 5 cm; T3, >5 cm; T4, any size with skin invasion or direct invasion to the chest wall; T0 and T1 tumors with nodal micrometastasis only are excluded from stage IIA and are classified as stage IB.

Source: Adapted with permission of Springer from American Joint Committee on Cancer. Breast. In: Edge S, Compton CC, eds. *AJCC Cancer Staging Manual*. 7th ed. Springer-Verlag; 2010:349; permission conveyed through Copyright Clearance Center, Inc.

Prognostic Factors

Case 97-3, Question 5: Further pathologic analysis of C.D.'s breast tumor reveals estrogen receptor (ER)–positive and progesterone receptor (PR)–positive disease. Human epidermal growth factor receptor (HER2) testing of the tumor was negative. What routine prognostic factors are evaluated in all patients with breast cancer?

In addition to staging, other prognostic factors should be evaluated to help determine a patient's treatment course. Prognostic factors such as the size of the tumor and lymph node status are important. A larger tumor size denotes a poorer prognosis than a smaller tumor

size, and the presence of disease in the lymph nodes leads to a poorer prognosis than lymph node–negative disease. Further, presence of a high number of positive lymph nodes is directly related to a poorer prognosis. Pathologic testing of the breast tumor gives important prognostic factors such as ER and PR and HER2 status.[29] Tumors that are ER- or PR-positive tend to denote a slower-growing, indolent disease and have a more favorable prognosis than ER- and/or PR-negative disease. Approximately two-thirds of patients diagnosed with breast cancer have ER- and/or PR-positive disease. If a patient has ER- and/or PR-positive disease, hormonal therapy is a treatment option. Tumors that are HER2-positive generally denote more aggressive disease. Approximately 25% of breast cancers test positive for HER2 gene amplification. Although this is indicative of a more aggressive disease, it is a positive predictor for response to trastuzumab.[29]

HER2 positivity is determined by two different methods, immunohistochemistry or fluorescence in situ hybridization (FISH). Either method could be used to determine HER2 status. Immunohistochemistry determines the overexpression of the HER2 protein, and results are reported as 1+, 2+, and 3+. Patients with 3+ overexpression are considered positive for HER2 and will respond to trastuzumab therapy or other HER2-targeted therapies. If a patient is determined to have 2+ overexpression (an equivocal test), then further testing would be conducted with FISH. FISH testing evaluates the HER2 gene amplification by denoting a ratio of the number of gene copies of HER2 compared to the control, and only those patients with positive FISH testing will respond to HER2-targeted therapies.[30]

Other pathologic tests are completed such as nuclear grade (which determines the degree of differentiation of the tumor cells) as well as tests to evaluate the growth fraction of the disease (such as S-phase fraction, Ki-67, and mitotic index).[25] Clinicians use all of these factors (positive and negative) to determine a patient's prognosis and treatment course.

Many patients today present with early-stage disease, which is highly curable. Clinicians can use these tests to determine which

patients should receive more or less therapy based on their recurrence score. One such test is the Oncotype DX assay for patients with ER- and/or PR-positive and lymph node–negative and now, lymph node–positive disease and assigns a patient a recurrence score.[31] Based on the score, clinicians and patients can decide the best treatment course such as hormonal therapy alone (for a low recurrence risk score <17) versus the combination of hormonal therapy and chemotherapy (for those patients with a high-risk recurrence score ≥31). This test has led to many patients foregoing the toxic effects of chemotherapy when treatment was not needed. The RxPONDER trial is currently underway to determine the benefit of chemotherapy in those patients with one to three positive lymph nodes with an intermediate recurrence risk score (16–25). Other data have demonstrated the utility of the Oncotype DX recurrence score in those patients with ER-positive, lymph node–positive disease in determining who should or should not receive systemic chemotherapy.[3132]

Treatment

Case 97-3, Question 6: C.D. was diagnosed with a stage II, ER and PR-positive, HER2-negative IDC of the right breast. Her staging workup was negative. Based on this information what would be C.D.'s likely treatment course?

LOCAL TREATMENT (SURGERY AND RADIATION THERAPY)

Surgery is the definitive treatment in early-stage breast cancer. Many years ago, a more radical approach to the surgical removal of breast cancer was used. This approach, called a radical mastectomy, involved the removal of the entire breast, both the major and minor pectoralis muscle, and a full axillary lymph node dissection on the side of the breast cancer. Increased morbidity was associated with this approach such as shoulder dysfunction and a poor cosmetic appearance. Today, a modified radical mastectomy is used that removes the entire breast along with an axillary lymph node

dissection while leaving the pectoralis muscles intact. This approach leads to equivalent survival compared with radical surgery.[33,34] Radiation may be offered in addition to a modified radical mastectomy if the tumor is >5 cm in size, if the patient has greater than four positive lymph nodes, or if positive tissue margins were present after surgery.[34,35] Clinical trials have also evaluated the use or need of adjuvant radiation therapy in those patients age older than 70 years with a low risk of recurrence. Results demonstrated that omission of radiation could offer similar results without placing that patient at higher risk of unnecessary toxicities of adjuvant radiation therapy.[36] These guidelines are widely debated and the subject of numerous studies evaluating patient populations who would benefit from adjuvant radiation therapy.[34–36]

Conservative approaches to surgery, such as lumpectomy, segmental mastectomy, or quadrantectomy, are also available. If a patient has a small tumor and wishes to preserve the breast, this surgical approach could be used; however, not all patients are candidates for this procedure. Those who are not candidates can include those with multicentric disease (numerous tumors throughout the breast), large tumors in relation to the size of the breast, and inflammatory breast cancer.[25] If the decision is to proceed with breast-conserving surgery, the patient must also undergo adjuvant radiation therapy. Because the surgery only removes the primary tumor, the rest of the breast should be treated with radiation therapy to prevent recurrence of disease. Similar survival rates are observed with modified radical mastectomy versus breast-conserving surgery plus radiation therapy.[33–36]

Larger tumors do not preclude a patient from undergoing breast-conservative surgery. However, to be eligible for this surgery, patients would receive neoadjuvant chemotherapy to help shrink the tumor to a size conducive to breast-conserving techniques. Neoadjuvant chemotherapy also allows the oncologist to assess response to treatment while the tumor is still in place and allows the opportunity to discontinue a particular chemotherapy regimen if the patient is not responding. Most patients will respond to

chemotherapy; however, for those who do not, further chemotherapy (with a different regimen) or radiation therapy may be offered.[37,38]

The presence and extent of nodal disease is assessed through an axillary lymph node dissection. This involves the removal of at least 10 lymph nodes on the same side of the primary tumor to assess for the presence of breast cancer. Lymph node dissection may result in lymphedema, thromboembolism, and infection.[39–41] Sentinel lymph node biopsy is one way to avoid the comorbidities associated with the axillary lymph node dissection. In this procedure, a blue dye (labeled with a radiocolloid) is injected around the breast tumor. Time is given for the dye to drain from the tumor to the lymph nodes. The surgeon is able to identify the sentinel nodes because of the presence of radiocolloid and the blue color. The breast (and presumably the cancer) drains first into the sentinel lymph nodes. Only one or two of the sentinel lymph nodes will be removed, reducing the risk of lymphedema, thromboembolism, and infection.[39–42] Many consider this procedure the standard of care for assessment of the axillary lymph nodes.

C.D. could either undergo breast-conserving surgery plus radiation therapy or a modified radical mastectomy, but with C.D.'s family history she may also choose to undergo bilateral mastectomies to prevent the development of contralateral breast cancer.

SYSTEMIC THERAPY (CHEMOTHERAPY, HORMONAL THERAPY, AND BIOLOGIC THERAPY)

Surgery and radiation therapy eradicate most tumor cells; however, microscopic disease is difficult to detect and treat locally. Microscopic cancer deposits can migrate throughout the body and serve as sites for disease recurrence. To diminish the chance of recurrence, systemic adjuvant chemotherapy, hormonal therapy, and/or biologic therapy is given. The determination of which single modality or combination of therapies is based on the patient's prognostic factors: ER/PR status and HER2 positivity. As mentioned earlier, tools such as the Oncotype DX assay can estimate risk recurrence based on

these tumor-specific characteristics and assist in the determination of therapy.

The size of the tumor and other prognostic factors are also evaluated to determine the course of therapy (**Table 97-3**).[43] Patients with small tumors (0.6–1 cm) and negative lymph nodes can be further divided into two groups based on favorable and unfavorable prognostic features. Favorable prognostic features would include hormone-positive disease. These patients can be offered hormonal therapy without chemotherapy. Those individuals with poor prognostic features (tumors with lymphatic invasion, high nuclear grade, hormone receptor-negative, or HER2-positive disease) would be offered chemotherapy with or without trastuzumab and pertuzumab therapy.[25]

Table 97-3

Overview of the Selection of Adjuvant Treatment

	Adjuvant Hormonal Therapy		Adjuvant Chemotherapy[b]
Lymph Node–Negative Disease	**ER/PR (+)**	**ER/PR (−)**	
≤0.5 cm	Yes	No	No
0.6–1 cm[a]	Yes	No	Consider
>1 cm	Yes	No	Yes
Lymph Node–Positive Disease	**ER/PR (+)**	**ER/PR (−)**	
	Yes	No	Yes

[a]Consider Oncotype DX testing: low recurrence score (<26) = adjuvant hormonal therapy; intermediate recurrence score (26–30) = adjuvant hormonal therapy ± chemotherapy; high recurrence score (≥31) = adjuvant hormonal therapy + chemotherapy.

[b]Give trastuzumab ± pertuzumab therapy if the patient is HER2 (+) and no contraindications.

Source: Barnett CM, Boster BL, Michaud LB. Breast cancer. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. *Pharmacotherapy: A*

Pathophysiologic Approach. 10th ed. McGraw-Hill; 2017. Accessed September 23, 2020.

Tumors >1 cm in size are generally offered treatment with systemic chemotherapy. If the patient is ER- and/or PR-positive, they are additionally treated with hormonal therapy after chemotherapy. Biologic therapy with trastuzumab and pertuzumab is added to chemotherapy if the patient has HER2-positive disease and assuming there are no contraindications such as cardiac disease. Patients should be fully informed of the absolute benefit of chemotherapy because in those with early-stage disease the benefit from chemotherapy could be as low as 2% to 3%. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducts an overview analysis every 5 years on the effects of chemotherapy and hormonal therapy in breast cancer randomized trials. In 2005, the 15-year survival updates were published.[44] Although no standard regimen has been identified, combination regimens are superior to single-agent therapy (recurrence rates and mortality for combination chemotherapy, respectively: hazard ratio [HR], 0.77; $P > .00001$ and HR, 0.83; $P > .0001$, respectively; single-agent therapy recurrence rates and mortality: HR, 0.86; $P = .001$ and HR, 0.96; $P = .4$, respectively).[44] Updated meta-analyses have also included the use of taxanes to fixed anthracycline-based regimens. In the previous EBCTCG trial, taxanes were not included in the data analysis. With the incorporation of taxane therapy, breast cancer mortality was reduced: RR (event rate ratio: newer treatment versus control) = 0.86, standard error (SE) = 0.04, $P = .0005$.[45,46] This demonstrated the benefit of adding taxane therapy to standard adjuvant therapy for specific patients.

Looking back at C.D.'s tumor characteristics, she has stage II (2.2 cm with lymph node involvement), ER-positive, PR-positive, and HER2-negative breast cancer. Based on this information, C.D. would be a candidate for surgery and chemotherapy (based on the tumor size and lymph node–positive disease), followed by hormonal therapy because of her ER/PR-positive disease.

ADJUVANT CHEMOTHERAPY

CASE 97-3, QUESTION 7: C.D. underwent a right modified radical mastectomy and axillary lymph node dissection. She had 4 of 15 lymph nodes positive for disease. Her adjuvant treatment will consist of chemotherapy (because of the larger size of the tumor and positive lymph nodes). What are typical adjuvant chemotherapy regimens for the treatment of early-stage breast cancer, and what should C.D. receive?

Many different combination chemotherapy regimens are used in the adjuvant setting (**Table 97-4**). Anthracycline-containing regimens are commonly used. Doxorubicin or epirubicin in combination with an alkylating agent (cyclophosphamide) plus or minus fluorouracil is a typical regimen. Regimens can be administered in a dose-dense (every 2 weeks) manner or conventional every 3-week dosing. In the most recent EBCTCG analysis, anthracycline-based regimens have significantly lower recurrence rates and death compared to traditional cyclophosphamide, methotrexate, and fluorouracil (recurrence rate ratio, 0.89; $P = .001$; and cancer death rate ratio, 0.84; $P > .00001$, respectively).[45] A large pooled analysis demonstrated improved disease-free ($P > .00001$) and overall survival ($P > .0001$) with the addition of a taxane.[44–46] Updated meta-analyses have also included the use of taxanes to fixed anthracycline-based regimens. As discussed earlier, the optimal taxane regimen has yet to be identified, and the full benefit of the utility of taxane therapy in lymph node–negative disease is yet to be determined; however, the benefit is apparent in lymph node–positive disease and taxanes should be incorporated into the treatment regimen of those with lymph node–positive disease.

Table 97-4
Common Neoadjuvant and Adjuvant Chemotherapy Regimens

Regimen
HER2-Negative Disease
Dose dense[a] AC → paclitaxel every 2 weeks

Regimen
HER2-Negative Disease
Dose dense[a] AC → paclitaxel weekly
TC
CMF, classic (oral) or intravenous
TAC
AC every 3 weeks
AC → paclitaxel weekly
AC → docetaxel every 3 weeks
HER2-Positive Disease
AC → paclitaxel + trastuzumab ± pertuzumab
TCH ± pertuzumab
AC → docetaxel + trastuzumab ± pertuzumab
Docetaxel + cyclophosphamide + trastuzumab
Paclitaxel + trastuzumab

A, doxorubicin; C, cyclophosphamide; F, fluorouracil; M, methotrexate; T, docetaxel; TCH, docetaxel, carboplatin, trastuzumab; →, followed by.

[a]Dose dense, given every 2 weeks instead of every 3 weeks. See source document for specific dosing.

Source: Barnett CM, Boster BL, Michaud LB. Breast cancer. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 10th ed. McGraw-Hill; 2017. Accessed September 23, 2020.

Congestive heart failure (CHF) is a well-known toxicity associated with anthracycline chemotherapy. If a patient has heart failure or other preexisting cardiac disease, anthracyclines must be used cautiously. To avoid potential toxicity, taxane regimens such as docetaxel and cyclophosphamide have been compared to a standard anthracycline-containing regimens, doxorubicin and cyclophosphamide. After 7 years of follow-up, both disease-free and overall survival were significantly better in the taxane arm compared with the anthracycline arm (81% vs 75%; $P = .033$ and 87% vs 82%; $P = .032$, respectively).[47] Although the results are encouraging, these

data do not have the track record of the anthracycline-containing regimens that are still considered the mainstay of therapy for adjuvant chemotherapy in early-stage breast cancer. Studies are currently underway to identify specific populations that may not respond to anthracycline therapy, thereby avoiding the risk of cardiac toxicity in these individuals.[48] If these specific cases are identified, more non–anthracycline-based chemotherapy regimens will be incorporated into clinical practice. Based on C.D.'s lymph node–positive breast cancer, a typical adjuvant chemotherapy regimen would consist of doxorubicin and cyclophosphamide (AC) given every 3 weeks for four cycles followed by a taxane such as paclitaxel weekly for 12 weeks or a dose-dense approach with AC given every 2 weeks for four doses with growth factor support followed by paclitaxel weekly for 12 weeks (see Table 97-4 for commonly used adjuvant chemotherapy regimens).

Trastuzumab and pertuzumab therapy can be incorporated into a patient's adjuvant chemotherapy regimen if the tumor is HER2-positive. Trastuzumab was first studied in the metastatic setting and demonstrated improved overall survival when added concurrently with chemotherapy.[49] Because of its robust activity in the metastatic setting, it was then studied in early breast cancer to see whether the same benefit could be achieved. Two large trials were conducted concurrently addressing different questions regarding the use of concurrent, sequential, and maintenance trastuzumab.[50,51] Patients received the classic AC regimen for four cycles followed by paclitaxel weekly given either sequentially or concurrently. Trastuzumab therapy was started after the completion of the AC regimen to reduce potential cardiac toxicities associated with doxorubicin and trastuzumab. The results of these trials were combined and published in full. Disease-free and overall survival were significantly improved with the addition of trastuzumab (52% decrease in recurrence rates, $P > .0001$; and 33% reduction in mortality, $P = .015$, respectively).[50,51] Four-year follow-up data continued to demonstrate significant improvements with trastuzumab compared to chemotherapy alone.

The use of maintenance trastuzumab was further studied in the HERA Trial (Herceptin Adjuvant Trial).[52] In that trial, patients were randomly assigned to complete 1 or 2 years of maintenance trastuzumab therapy. Based on these data, trastuzumab was approved for use in early-stage, HER2-positive disease after the completion of AC therapy followed by sequential paclitaxel therapy for 1 year. Pertuzumab, another monoclonal antibody approved after trastuzumab, targets HER2 but in a different manner. It binds to a different region of the extracellular of HER2 and block the dimerization of HER2 with HER3. As with trastuzumab, pertuzumab was first approved in the metastatic setting, but is now approved for use in both the neoadjuvant and adjuvant setting for HER2 positive breast cancers. Based on the results from the APHINITY trial, use of pertuzumab in combination with trastuzumab in the adjuvant setting for a total of 1 year of therapy improved invasive disease-free survival compared to trastuzumab alone (HR = 0.82 [95% CI, 0.67–1.00; *P* = .047]).[53] With these results, the new standard of care is to complete a total of 1 year of adjuvant trastuzumab and pertuzumab if the patient has HER2-positive disease.

There is now an additional caveat to this recommendation. When a patient undergoes surgical resection after receiving chemotherapy and HER2-targeted therapy, the specimen is analyzed to see if there is any residual disease. Practice had traditionally been to continue the HER2 targeted therapy for a total of 1 year. With results of the Katherine trial, this practice has changed.[54] If the patient has residual disease remaining, the patient will now switch to another HER2-targeted therapy, ado-trastuzumab emtansine to complete a total of 1 year of therapy. Per the Katherine trial, invasive disease-free survival was significantly improved with ado-trastuzumab emtansine compared to the trastuzumab group. The risk of recurrence of invasive breast cancer or death was 50% lower (HR = 0.50, 95% CI, 0.39–0.64; *P* < .001).[54] Because C.D. does not have HER2-positive disease, any HER2-targeted therapy would not be used.

CHEMOTHERAPY TOXICITY

Case 97-3, Question 8: C.D. is to undergo four cycles of AC chemotherapy followed by weekly paclitaxel for 12 weeks. What are the common toxicities associated with this treatment course? If the tumor was HER2-positive and C.D. received trastuzumab, what toxicities would be associated with its use?

Doxorubicin is an anthracycline chemotherapy agent. It works through multiple mechanisms, but inhibition of topoisomerase II may be most important.[55] By inhibiting this enzyme, double-strand DNA breaks occur. Common toxicities include myelosuppression, nausea/vomiting, and alopecia. A well-known toxicity of anthracyclines is the risk of cardiomyopathy because of the formation of oxygen free radicals and doxorubicin metal complexes. These toxicities can be acute (with symptoms similar to an arrhythmia or myocardial infarction) or chronic (with a patient demonstrating symptoms of CHF).[55] The risk of cardiotoxicity increases with larger anthracycline cumulative doses.[55–58] With the typical doses of anthracyclines used in the adjuvant setting, a patient will not reach the cumulative doses known to increase the risk of cardiotoxicity. If a patient has underlying cardiac dysfunction, baseline evaluation of ejection fraction through either an echocardiogram or a multigated acquisition scan should be completed.[55–58] Other known risk factors for the development of anthracycline-induced cardiotoxicity include age older than 70 years, hypertension, preexisting coronary artery disease, and previous cardiac irradiation or anthracycline exposure, which may warrant cardiac evaluation.[59–62]

Cyclophosphamide is an alkylating agent that works by forming cross-links in DNA, thus inhibiting DNA synthesis.[55] Common toxicities are nausea/vomiting, myelosuppression, and alopecia. The alkylating agents, although rare, are also associated with a risk of secondary leukemias.[55]

Paclitaxel, a taxane chemotherapy derived from the Pacific yew tree, works by binding to the β-tubulin subunit of microtubules, preventing disassembly and ultimately causing inhibition of mitosis. Common toxicities associated with paclitaxel include nausea/vomiting, myelosuppression, neuropathy, and

hypersensitivity reactions because of the modified polyoxyethylated castor oil (Cremophor EL) solvent in paclitaxel. All patients should be premedicated with dexamethasone and H_1 and H_2 blockers to prevent hypersensitivity.[63]

Trastuzumab is a monoclonal antibody targeted against the extracellular HER2 protein. The classic toxicity associated with trastuzumab is cardiac toxicity but is different from that with anthracyclines. Trastuzumab cardiotoxicity is considered reversible and is believed to be a result of HER2 blockade (HER2 signaling is responsible for cardiomyocyte growth, repair, and survival).[58–62] In those patients who will receive long-term trastuzumab therapy, baseline cardiac function should be evaluated similar to doxorubicin and then periodically with echocardiogram or a multigated acquisition scan during therapy. The same holds true for other HER2-targeted therapy, such as pertuzumab and ado-trastuzumab emtansine.[64] Another common toxicity associated with HER2-targeted therapy is diarrhea.[65] If this is a problem for the patient, many times one agent, such as pertuzumab, is deleted from the treatment regimen. This change in therapy can decrease the diarrhea that the patient experiences and is more tolerable. C.D. does not have a history of cardiac disease, but a baseline cardiac evaluation should still occur before AC therapy. C.D. should be counseled on the common toxicities associated with her chemotherapy, such as myelosuppression, nausea/vomiting, alopecia, neuropathy, cardiomyopathy, hypersensitivity reactions, and diarrhea.

HORMONAL THERAPY

Case 97-3, Question 9: After the completion of her adjuvant chemotherapy, C.D. will receive hormonal therapy because her disease is ER/PR-positive. What are the common adjuvant hormonal regimens used? What regimen would be appropriate for C.D.?

Breast cancer is a hormonally mediated disease, and therapies that alter hormonal levels are an integral component to the treatment plan. This therapy is offered to patients with ER- and/or PR-positive disease. Therapeutic options include SERMs, luteinizing hormone–releasing hormone (LH-RH) agonists, and AIs. Menopausal status of the patient is used to help guide selection of therapy.

Traditionally, tamoxifen has been the gold standard for adjuvant hormonal therapy. Tamoxifen is an SERM, which works by blocking estrogen from binding to the ER. It does not alter estrogen production. Tamoxifen has antiestrogenic activity in the breast, although it has estrogenic effects in other areas such as bone.[66,67] Tamoxifen can be used in both premenopausal and postmenopausal females and is given 20 mg orally daily for 5 years based on the data from the National Surgical Adjuvant Breast and Bowel Project B-14 trial.[68] Tamoxifen should be initiated after chemotherapy because it can antagonize the antitumor activity of chemotherapy if given concurrently.[69] Common toxicities associated with therapy are hot flashes and vaginal discharge. More thrombosis, pulmonary embolisms, and strokes can occur in patients (age older than 50 years) receiving tamoxifen compared to placebo (RR, 1.60, 3.19, 1.59, respectively).[11,12]

Ovarian suppression is an alternative therapy for premenopausal patients because the ovaries are the largest source of estrogen. This is typically achieved through the use of LH-RH agonists. Surgery or radiation can also induce ovarian ablation; however, surgery is irreversible and offers an immediate effect, whereas radiation may offer an incomplete response and slower onset.[70–72] If a female would like to maintain fertility throughout chemotherapy, a thorough discussion with her physician should occur. Studies with the use of LH-RH agents have been tested as a means to preserve fertility but have shown mixed results.[72] Combination data with an LH-RH agonist with tamoxifen have not shown significantly better outcomes than each modality alone.[70–72]

Postmenopausal patients also have the option of AI therapy. Aromatase inhibitors inhibit the production of estrogen by preventing the conversion of androstenedione and testosterone to estrone and

estradiol. There are two classes of agents: nonsteroidal AIs (anastrozole and letrozole) and the steroidal AI, exemestane. These agents are highly selective for the aromatase enzyme and have less toxicity than tamoxifen and other hormonal agents. Aromatase inhibitors should only be used in postmenopausal females.[25] If used in the premenopausal setting, initial surges of estrogen occur because of the body's compensation mechanisms (ie, hypothalamic–pituitary axis) and negative feedback loop. **Table 97-5** provides a list of adjuvant hormonal therapies that can be used.

Table 97-5
Adjuvant Hormonal Therapies

Type	Dose	Toxicities
Nonsteroidal AI		
Anastrozole Letrozole	1 mg daily PO 2.5 mg daily PO	Common toxicities: myalgias/arthralgias, hot flashes, osteoporosis
Steroidal AI		
Exemestane	25 mg daily PO	Common toxicities: myalgias/arthralgias, hot flashes, osteoporosis
SERMs		
Tamoxifen	20 mg daily PO	Common toxicities: hot flashes, vaginal discharge Rare but serious side effects: deep vein thrombosis, pulmonary embolism, abnormal uterine bleeding

Sources: Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 1998;90:1371–1388; Goldvaser H, Barnes TA, Šeruga B, et al. Toxicity of extended adjuvant therapy with aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2018;110(1):31–39.

The optimal hormonal therapy regimen for the adjuvant setting has not been identified. In premenopausal females, the options are 5

years of tamoxifen therapy plus or minus ovarian suppression with an LH-RH agonist. If the patient continues to be premenopausal at the end of 5 years of adjuvant tamoxifen therapy, the patient may consider five additional years of therapy.[73–76] There are conflicting data to support this recommendation. Based on newer data, the American Society of Clinical Oncology published an updated practice guideline for adjuvant hormonal therapy.[77]

If, after 2 to 3 years, the patient becomes postmenopausal, then 2 to 3 years of an AI may be given to complete a total of 5 years of therapy. If the patient is postmenopausal at the beginning of adjuvant hormonal therapy, an option would be to take an AI for 5 years and then assess again for a potential of a total of 10 years of adjuvant aromatase inhibitor. There have been no prospective comparisons of the AIs with each other; therefore, any can be used as first-line treatment.[73–77] Another clinical option is 5 years of tamoxifen, and, if the patient is postmenopausal after the end of 5 years, an additional 5 years of an AI can be given. This was found to be beneficial in an extended study of hormonal therapy (the BIG 1–98 trial). At the 2.4-year follow-up, additional letrozole therapy was associated with a superior 4-year disease-free survival (93% with extended letrozole vs 87% in the tamoxifen arm; $P > .001$).[78] However, in the 8.1-year follow-up data, the additional letrozole therapy did not improve outcomes compared with letrozole monotherapy in terms of disease-free and overall survival.[79] Each individual's length of therapy should be determined based on the patient's risk of recurrence and their ability to tolerate therapy. **Table 97-6** lists adjuvant hormonal therapy options.

Table 97-6
Overview of Adjuvant Hormonal Therapy

Option 1	Option 2	Option 3
Premenopausal at time of therapy initiation (patients can complete 1 of 3 different options)		

Option 1	Option 2	Option 3
Premenopausal at time of therapy initiation (patients can complete 1 of 3 different options)		
Tamoxifen × 5 years ± LH-RH agonist or ovarian ablation	If still premenopausal after 2–3 years of tamoxifen therapy, complete a total of 5 years of tamoxifen.	If still premenopausal after 5 years of tamoxifen, consider an additional 5 years of tamoxifen.
	If postmenopausal after 2–3 years: **A.** Complete 5 years of tamoxifen followed by 5 additional years of an AI *or* **B**. Convert to an AI × 2–3 years for a total of 5 years of hormonal therapy.	If postmenopausal after 5 years of therapy, give AI × 5 additional years.
Postmenopausal at time of therapy initiation (referred to start with an AI if the patient is postmenopausal at the onset of therapy)		
Any AI × 5 years, then an AI for another 5 years to complete a total of 10 years	Tamoxifen × 2–3 years, then an AI to complete a total of 5 years	Tamoxifen × 4–6 years, then an AI for 5 additional years

AI, aromatase inhibitor; LH-RH, luteinizing hormone–releasing hormone.

Sources: Burstein HJ, Curigliano G, Thurlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol*. 2021;32(10):1216–1235; Goldvaser H, AlGorashi I, Ribnikar D, et al. Efficacy of extended adjuvant therapy with aromatase inhibitors in early breast cancer among common clinicopathologically-defined subgroups: a systematic review and meta-analysis. *Cancer Treat Rev*. 2017;60:53–59.

C.D. is premenopausal, so she would start with tamoxifen therapy. If after 2 to 3 years of therapy, C.D. becomes postmenopausal, she could continue the tamoxifen for a total of 5 years or convert to an AI to complete a total of 5 years of therapy then continuing the AI for an additional 5 years. Because of her age, she will likely continue to be premenopausal after chemotherapy and be maintained on tamoxifen for 5 years. If she remains premenopausal, she should have a discussion with her physician on the merits of continuing tamoxifen

for a total of 10 years. If she completes 5 years of tamoxifen therapy and is postmenopausal at that time, then extended use of an AI for an additional 5 years would be recommended. At this time, ovarian suppression with an LH-RH agonist could also be added because she is premenopausal to chemically suppress her ovarian function.

METASTATIC BREAST CANCER

Treatment—Endocrine Therapy

CASE 97-4

QUESTION 1: T.R. is a 65-year-old, postmenopausal female diagnosed with breast cancer at age 48 years. At the time of diagnosis, she was premenopausal. She underwent surgery with a modified radical mastectomy and was found to have a 1.5-cm IDC of the right breast. She had 2 of 10 lymph nodes positive. Her breast cancer was ER-positive, PR-positive, and HER2-negative. T.R. went on to complete adjuvant chemotherapy with AC therapy for four cycles followed by weekly paclitaxel for 12 weeks. After completion of her chemotherapy, she received 5 years of tamoxifen therapy. Ten years after completing her therapy, she experiences pain in her right arm and rib cage. A bone scan revealed metastatic breast cancer.

What would be an appropriate treatment regimen for T.R. at this time?

Early-stage breast cancer is curable. However, if a patient develops metastatic disease, the goal of treatment shifts from cure to palliation and stabilization of disease. Treatment is offered to improve quality of life and alleviate symptoms from treatment or disease. The mean survival time after diagnosis of metastatic disease is ~2 to 4 years; however, this can range from months to many years depending on the site of the metastases.[80,81] The choice of therapy is based on the site of disease and other factors that help guide therapy such as ER and PR status. Endocrine therapy is more likely to be effective in patients with bone-only disease, whereas chemotherapy may be used when there is visceral disease (ie, liver or lung). Patients with organ involvement tend to have more rapidly

growing disease that generally requires therapy with a quicker onset of action such as chemotherapy.[25] In addition to systemic therapy (chemotherapy, hormonal therapy, and/or biologic therapy), the clinician needs to determine whether local therapy (such as radiation or surgery) would be appropriate for a patient. Radiation therapy can be used to target painful bone metastases, to prevent further tumor growth, and to relieve pain. Surgery may be performed on bones with impending fractures, spinal cord compression, or brain metastases for palliation. These modalities of treatment only affect the local site of disease, so a combination of local and systemic therapy would need to be administered to fully treat the patient. If a patient is experiencing worsening symptoms such as shortness of breath because of lung metastases or increased abdominal pain because of liver metastases, the use of chemotherapy may be preferred over hormonal therapy because of its quicker onset of action.[25,81]

Disease recurrence >5 years after diagnosis illustrates a more indolent-growing disease and is a favorable prognostic factor. Tumors with ER- and/or PR-positive characteristics would also be considered a good prognostic factor. Once therapy is initiated, response to therapy should be monitored periodically. Tumor markers such as CA.27.29 and CA.15.3 can be monitored in metastatic breast cancer. A clinical examination in combination with radiologic tests and tumor markers is assessed to determine response to therapy. Based on T.R.'s metastatic bone disease and ER/PR-positive tumor characteristics, the use of hormonal therapy would be the most appropriate agent to initiate. T.R. received tamoxifen therapy in the adjuvant setting. Because she progressed after taking tamoxifen therapy, this would not be reinitiated.

Case 97-4, Question 2: T.R. is started on anastrozole 1 mg orally daily with palbociclib 125 mg orally on days 1–21 and then 7 days off. What are other hormonal agents that can be used in the treatment of metastatic breast cancer?

Hormonal therapy in the metastatic setting can provide long progression-free survival in patients. If the patient responds for an extended period, the likelihood of response to another hormonal agent is high.[81,82] A patient may take multiple hormonal therapies before ever having to receive chemotherapy. As before, the decision regarding which hormonal agent to use is based on one's menopausal status. If the patient is premenopausal, the options include tamoxifen and LH-RH agonists; however, if the patient has received an SERM in the adjuvant setting, this would not be used again in the metastatic setting. Aromatase inhibitors are indicated for use in first-line therapy in the metastatic setting for postmenopausal females. If an AI is chosen as the first-line agent in the metastatic setting, use of another AI after progression would include one from another category (eg, nonsteroidal vs steroidal AI). For example, if anastrozole was used as first-line therapy for metastatic disease, then when the patient progresses, exemestane can be used. Aromatase inhibitors alone have been the standard front-line option for postmenopausal patients until the approval of the CDK 4/6 inhibitors. This class of drugs have single-handedly changed the approach to hormonal therapy in the metastatic setting for postmenopausal individuals with ER-positive, HER2-negative disease.

The CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) work to form a complex with cyclin D and promote the transition from the G1- to S-phase in the cell cycle. These CDK 4/6 kinases are activated in ER-positive breast cancers, and they play an important role in reversing acquired resistance to previous hormonal therapy.[25,82] The PALOMA-2 trial was the first trial demonstrating overall improvements in progression-free survival with the combination of palbociclib and letrozole used in the first line, metastatic setting for ER and/or PR-positive disease.[83] Results demonstrated improvements in progression-free survival of 24.8 months with combined therapy versus 14.5 months with letrozole alone (95% CI, 12.9–17.1) and improvements in rates of disease progression or death (HR = 0.59; 95% CI, 0.46–0.72; $P < .001$). Myelosuppression is now a well-known toxicity with this class of

drugs, and in this trial, 66.4% of patients in the combination group experienced grade 3 or 4 neutropenia compared to 1.4% with letrozole alone, whereas only 1.8% in the combination arm experienced febrile neutropenia compared to 0.5% in the single arm group. All the CDK 4/6 inhibitors have been approved in both first-line and second-line settings for individuals with ER-positive, HER2-negative disease. See **Table 97-7** for a listing of the dosing recommendations with each agent and each combination of therapy.[82–85]

Table 97-7
Commonly Used Hormonal Regimens in the Metastatic Setting

Regimen	Dose
First-line Recommendation	
AI + CDK 4/6 inhibitor[a]	AI of choice + (one of the following): a. Palbociclib 125 mg orally daily × 21 days, then 7 days rest b. Ribociclib 600 mg orally daily × 21 days, then 7 days rest c. Abemaciclib 150 mg orally twice a day
Fulvestrant ± anastrozole or letrozole[b]	Fulvestrant: 500 mg IM on days 1, 15, 29 and then monthly + either anastrozole 1 mg orally daily or letrozole 2.5 mg orally daily
Fulvestrant + CDK 4/6 inhibitor[a]	See above for dosing recommendations
AI single agent[b]	See above for dosing of anastrozole and letrozole or use exemestane 25 mg orally daily
SERM single agent[b]	Tamoxifen 20 mg orally daily or toremifene 60 mg orally daily
Second-line Recommendation	
Fulvestrant + CDK 4/6 inhibitor if not previously used[a]	See above for dosing recommendations
Everolimus + endocrine therapy[b]	Everolimus 10 mg orally daily + Exemestane or tamoxifen or fulvestrant (see dosing above)

Regimen	Dose
First-line Recommendation	
AI single agent[b]	See above for dosing recommendations
Fulvestrant single agent[b]	See above for dosing recommendations
SERM single agent[b]	See above for dosing recommendations

IM, intramuscularly.

[a]Source: de Groot AF, Kuijpers CJ, Kroep JR, et al. CDK4/6 inhibition in early and metastatic breast cancer: a review. *Cancer Treat Rev*. 2017;60:130–138.

[b]Source: Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor–positive metastatic breast cancer: American Society of Clinical Oncology guideline. *J Clin Oncol*. 2016;34(25):3069–3105.

Many other hormonal agents are available for use. The pure anti-estrogen, fulvestrant, is the only drug in a unique category of agents. It exerts its mechanism via binding and blocking of the ER and downregulates the number of ERs. Fulvestrant is administered as an intramuscular injection and is dosed initially as 500 mg on days 1, 15, and 29, then 500 mg monthly.[86,87] It is approved for use after failure of tamoxifen therapy in the metastatic setting.[86,87] This is an alternative for patients with compliance issues because of its once-monthly intramuscular dosing. See **Table 97-7** for common dosing and combinations. Other hormonal agents used in metastatic disease are megestrol acetate, progestins, and high-dose estrogens (higher doses have been found to inhibit cancer cell growth). These agents were used routinely before the approval of AIs and CDK 4/6 inhibitors and are now reserved for use after multiple hormonal therapy failures because of the toxicities associated with these therapies such as weight gain, vaginal bleeding, and thromboembolic events.[25]

With the advent of the CDK 4/6 inhibitors and the positive results for use in the first-line metastatic setting, other combination therapies have now become therapies of choice for the second-line, metastatic setting. One drug used in the second-line setting is everolimus, from the class of mTOR (mammalian target of rapamycin) inhibitors. This

agent has demonstrated the ability to block resistance pathways of endocrine therapy.[88] In the BOLERO-2 trial, patients who had failed previous AI therapy were randomized to everolimus 10 mg orally daily plus exemestane 25 mg orally daily versus exemestane plus placebo.[89] Progression-free survival was statistically significantly better in the combination arm, but follow-up overall survival results did not demonstrate the same results.[88,89] Food and Drug Administration (FDA) approval was granted to this combination therapy in the metastatic setting after patients have failed a nonsteroidal AI.

T.R. was started on anastrozole plus palbociclib therapy. If her disease progresses, options include exemestane plus everolimus, or fulvestrant, and then other agents such as megestrol acetate, high-dose estrogens, or androgens. The goal is to continue T.R. on multiple lines of hormonal therapy (as long as she is responding) before administering chemotherapy.

Prevention of Skeletal Events

Case 97-4, Question 3: In addition to hormonal therapy, what other supportive care medicines should be added to T.R.'s regimen?

Patients with bone metastases are commonly treated with bisphosphonate therapy to decrease the risk of skeletal-related events (ie, pathologic fractures, spinal cord compression, need for surgery, or radiation to the bone). Bisphosphonates act by inhibiting bone resorption. This ultimately will halt osteoclastic activity leading to stabilization of bony involvement, prevention of fractures, and reduction in calcium levels.[90,91] Bisphosphonates used are pamidronate 90 mg intravenously (IV) for 2 hours or zoledronic acid 4 mg IV for 15 minutes. Either of these agents can be administered once a month. Bisphosphonates are typically well-tolerated, although they may cause nausea, increased bone pain, and fever. Reduced doses should be used in patients with underlying renal dysfunction. A more well-known but uncommon side effect is osteonecrosis of the

jaw.[92] The mechanism by which this occurs is not fully understood, but prevention is critical. If dental extractions or surgery is needed, patients should not be initiated on bisphosphonate therapy until these procedures are completed. If these procedures are required after initiation of therapy, an oral maxillofacial surgeon should be consulted.[92]

Another agent approved for use in the prevention of skeletal-related events in solid tumors is the humanized monoclonal antibody, denosumab. This therapy offers a unique mechanism of action, targeting the RANK ligand, which is a mediator in osteoclast activity. Inhibition of osteoclastic activity by denosumab reduces bone pathology in osseous metastases. Denosumab has been compared prospectively with zoledronic acid in patients with metastatic breast cancer and demonstrated significant delays in and prevention of skeletal-related events.[93] Denosumab is administered as a subcutaneous injection and is given once a month. It has similar toxicities to zoledronic acid, but the dose does not require adjustments for declining renal function. Denosumab has been added to the American Society of Clinical Oncology guidelines for the prevention of skeletal events in metastatic breast cancer and other solid tumors.[94] T.R. can start on bisphosphonate therapy with zoledronic acid 4 mg IV or denosumab 120 µg subcutaneous (SC) once a month to help prevent skeletal-related events.

Progression of Disease

Case 97-4, Question 4: T.R. has a long progression-free survival on hormonal therapy. Over the course of 4 years, she progresses on anastrozole and palbociclib, then fulvestrant, then exemestane plus everolimus, and eventually, megestrol acetate. Each time she has progressed, the progression-free interval has shortened. Follow-up staging tests now reveal new liver lesions measuring 1 cm × 1 cm and 2 cm × 1 cm. A CT scan of the chest was negative. She is not currently experiencing any symptoms of her disease. What should the treatment course include now that T.R. has progressed after numerous lines of endocrine therapy?

Because T.R. has progressed through multiple lines of hormonal therapy and the progression-free interval has shortened with each treatment course, chemotherapy would now likely be the best option. Patients with a good performance status, little previous treatment, prolonged progression-free intervals, and limited metastatic disease are more likely to respond to further treatment with chemotherapy.[25,81] Chemotherapy is continued as long as the person is receiving benefit and is tolerating toxicities associated with treatment. If the disease progresses or the toxicities become intolerable, therapy should be changed or stopped. Patients experiencing toxicities may be placed on a chemotherapy holiday until toxicities are resolved or until therapy is tolerable.

In the metastatic setting, stabilization of disease and palliation of symptoms are considered when deciding what chemotherapy regimen to use. Sequential (single agent) versus combination chemotherapy should be discussed. Combination chemotherapy is generally associated with more toxicities than sequential treatment; however, it provides improved response rates.[25,95–97] Patients with substantial symptoms from their disease may initially be given combination therapy to rapidly shrink the tumor. Combination therapies that have demonstrated improvements in survival are docetaxel and capecitabine, paclitaxel and gemcitabine, and doxorubicin and paclitaxel.[95–97] Based on T.R.'s lack of symptoms, sequential therapy would be the best option for her at this time. This would offer her less toxicity and reserve other chemotherapeutic agents for the future.

Chemotherapy decisions can be very complex. There is no one standard regimen, and decisions should be made on an individual basis based on the patient's prior treatment, concurrent comorbidities, and time from adjuvant therapy to metastatic disease.

Most individuals today will have received anthracycline and taxane chemotherapy in the adjuvant setting. If the patient's disease recurs quickly after adjuvant therapy (ie, <1 year), the disease is considered resistant to that treatment and different agents should be selected. If a patient receives adjuvant paclitaxel and progresses on therapy, there are data to support the use of docetaxel in the treatment of

metastatic disease because of the lack of cross-resistance between taxanes.[98,99] Other chemotherapeutic agents with mechanisms similar to taxanes, such as eribulin or ixabepilone, have been approved for use in previous taxane failures. These agents offer additional options to patients who had responded to previous therapies.[25]

Previous toxicity is also considered when selecting therapy. In patients with preexisting neuropathies either from diabetes or previous chemotherapy, taxanes may not be an appropriate choice because these agents can also cause neuropathy. Additionally, capecitabine may be chosen over intravenous chemotherapy because this agent is administered orally. **Table 97-8** provides a list of commonly used agents/regimens in the metastatic setting. Clinical trials are always an option for patients if they have a good performance status. Many clinical trials are available and should be discussed with the patient if clinical trials are a possibility. Because T.R. has received an anthracycline and taxane agent in the adjuvant setting, an agent such as capecitabine would be an appropriate choice. This is an oral agent and also has the indication for first-line treatment of metastatic disease after failure of anthracycline and taxane chemotherapy.

Table 97-8
Commonly Used Chemotherapy Agents in the Metastatic Setting

HER2-Negative	
Sequential or single agent	Doxorubicin, epirubicin, liposomal doxorubicin, paclitaxel, docetaxel, capecitabine, vinorelbine, gemcitabine, albumin-bound paclitaxel, eribulin, ixabepilone
Combination chemotherapy	AC, EC, CMF, GT docetaxel/capecitabine, gemcitabine/carboplatin, paclitaxel/bevacizumab, carboplatin/paclitaxel or albumin-bound paclitaxel
HER2-Positive	
Chemotherapy + trastuzumab	Pertuzumab/trastuzumab/docetaxel, pertuzumab/trastuzumab/paclitaxel

HER2-Negative	
Other chemotherapy options combined with trastuzumab or other HER2 targeted therapy	Trastuzumab/paclitaxel/carboplatin Trastuzumab/docetaxel; trastuzumab/vinorelbine; trastuzumab/capecitabine; trastuzumab/tucatinib/capecitabine; ado-trastuzumab emtansine; fam-trastuzumab deruxtecan; lapatinib/capecitabine; trastuzumab/lapatinib; neratinib/capecitabine

A, doxorubicin; C, cyclophosphamide; E, epirubicin; F, fluorouracil; G, gemcitabine; M, methotrexate; T, paclitaxel.

Source: Barnett CM, Boster BL, Michaud LB. Breast cancer. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 10th ed. McGraw-Hill; 2017. Accessed September 23, 2020.

Biologic and Other Targeted Therapies

Case 97-4, Question 5: Would T.R. be a candidate for any biologic therapy for the treatment of her metastatic breast cancer if she was HER2-positive?

Trastuzumab revolutionized the treatment of HER2-positive breast cancer. First in the metastatic setting, and now in the neoadjuvant and adjuvant settings.[25,49–51] Newer biologic therapies are also available for use in the metastatic setting. Trastuzumab is a fully humanized monoclonal antibody that binds to the extracellular HER2 receptor and works via antigen-dependent cellular cytotoxicity. When chemotherapy alone was compared with chemotherapy plus trastuzumab in HER2-positive metastatic breast cancer, the addition of trastuzumab therapy significantly increased survival.[49] This was the first study of its kind using biologic therapy and demonstrating survival benefit in metastatic breast cancer. Current practice is to continue the trastuzumab in patients who progress on a chemotherapy regimen but switch to an alternative chemotherapy agent.

As with all chemotherapeutic agents, breast cancer can become resistant to therapy. Trastuzumab provides significant improvement

in overall survival for patients with HER2-positive disease; however, trastuzumab resistance occurs. Newer pathways and resistance patterns have been identified to help clinicians understand the complexity of this disease. Two therapies are now approved for use in patients with HER2-positive disease.[100] Pertuzumab offers a novel mechanism of action for patients with HER2-positive disease. This agent is a monoclonal antibody similar to trastuzumab but blocks the extracellular domain on the HER2 receptor and blocks ligand-dependent heterodimerization with HER1, HER3, and HER4. The binding is different from trastuzumab in that trastuzumab binds to domain IV, whereas pertuzumab binds to domain II of the HER2 receptor. The CLEOPATRA trial evaluated pertuzumab in combination with docetaxel and trastuzumab versus docetaxel and trastuzumab plus placebo for the first-line treatment of metastatic breast cancer.[101] At a median follow-up of 50 months, the pertuzumab arm demonstrated improved overall survival (OS) of 56.5 months versus 40.8 months in the docetaxel + trastuzumab arm (HR, 0.68; 95% CI, 0.56–0.84; $P > .001$). Those treated with pertuzumab experienced more diarrhea, rash, mucosal inflammation, and febrile neutropenia.[101] Pertuzumab is approved for use in the first-line metastatic setting, neoadjuvant and adjuvant settings in combination with chemotherapy and trastuzumab.

Because pertuzumab does target the HER2 receptor, there is a concern regarding cardiac toxicity associated with its use. In the cardiac assessment of the CLEOPATRA trial, the incidence of cardiac adverse events (all grades) was similar between arms: 16.4% versus 14.5% in the placebo arm and the pertuzumab arm, respectively. Most patients experienced asymptomatic decreases in left-ventricular ejection fraction that resolved upon removal of the drug.[102]

Ado-trastuzumab emtansine (also known as TDM-1) is a unique formulation of an antibody–drug conjugate: Trastuzumab linked to DM1, a maytansine derivative. Maytansine is a potent microtubular inhibitor. Once the drug binds to the HER2 receptor, it is internalized and then undergoes degradation, releasing the cytotoxic agent to induce apoptosis. This agent was approved based on the results

from the EMILIA trial comparing ado-trastuzumab to capecitabine and lapatinib in patients who had failed previous taxanes and trastuzumab.[103] Ado-trastuzumab improved both progression free survival (PFS) and OS. Common toxicities for this agent include peripheral neuropathy, fatigue, anemia, increased liver enzymes, and myelosuppression. As with other HER2-targeted therapies, the concern for cardiac toxicity was evaluated. Less cardiotoxicity was identified in the ado-trastuzumab group compared to the combination arm (1.8% vs 3.3%, respectively). This drug's name is very similar to traditional trastuzumab and hence the FDA recommendation for the addition of the prefix ado- to the name.[104] The approved indication of this agent includes use in patients with HER2-positive metastatic breast cancer who have previously received trastuzumab and a taxane, separately or in combination.

If the patient, T.R., had HER2-positive disease, a common first-line regimen to use in the metastatic setting would be pertuzumab plus trastuzumab in combination with docetaxel based on the data from the CLEOPATRA trial.[101]

If a patient presented with metastatic triple-negative breast cancer, there is now an approved regimen for use first line. Based on the Impassion 130 trial, patients were randomized to receive atezolizumab plus nab-paclitaxel compared to nab-paclitaxel plus placebo and stratified based on PD-L1 status.[105] The primary end points included both progression-free and overall survival. Among those patients who had PD-L1–positive disease, the median PFS was 7.5 versus 5 months (HR = 0.62, 95% CI, 0.49–0.78, $P < .001$) and the median overall survival was 25 versus 15.5 months (HR = 0.62; 95% CI, 0.45–0.86). Patients did better with atezolizumab added to their regimen even if they did not express PD-L1.[105] This combination now offers a specific treatment approach when faced with a patient with triple-negative, PD-L1–positive disease in the first-line metastatic treatment setting.

Other unique targeted therapies are being evaluated in metastatic breast cancer. One new indication has been granted to alpelisib for use in individuals with phosphatidylinositol 3-kinase (PI3K) mutations and ER- and/or PR-positive breast cancer. The incidence of this

mutation is ~40% of patients.[106] The SOLAR-1 study group evaluated alpelisib 300 mg orally daily plus fulvestrant compared to fulvestrant alone. At a median follow-up of 20 months, the progression-free survival was 11 versus 5.7 months (HR = 0.65, 95% CI, 0.50–0.85; *P* < .001). Adverse effects attributed to alpelisib included hyperglycemia, diarrhea, and rash.[106] This offers another option for those who have relapsed disease or in those who have progressed during or after endocrine therapy.

With breast cancer, there are always new drugs and/or combinations being approved for the treatment of early- and late-stage disease. As data progress, the likelihood is that the treatment schema will change. More and more data are evaluating neoadjuvant and adjuvant uses of CDK 4/6 inhibitors.[84] Soon these agents may be commonly used in these settings. In addition, further data may shed more light on treatment modalities for those diagnosed with triple-negative disease and how immunotherapy may evolve for those diagnosed with breast cancer.[107]

KEY REFERENCES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol*. 2019;10(37):423–438. (77)

de Groot AF, Kuijpers CJ, Kroep JR. CDK4/6 inhibition in early and metastatic breast cancer: a review. *Cancer Treat Rev*. 2017;60:130–138. (84)

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year

recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet.* 2011;378(9804):1707–1716. (34)

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379:432–444. (45)

Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 1998;90:1371. (11)

Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node–negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst*. 2001;93:684–690. (68)

Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med*. 2002;347:567–575. (33)

Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label randomised controlled trial. *Lancet.* 2013;382:1021–1028. (52)

Kumler I, Tuxen MK, Nielsen DL. A systematic review of dual targeting in HER2-positive breast cancer. *Cancer Treat Rev*. 2014;40(2):259–270. (64)

Loibl S, Gianni L. HER2-positive breast cancer. *Lancet*. 2017;389:2415–2429. (100)

McVeigh TP, Kerin MJ. Clinical use of the Oncotype DX genomic text to guide treatment decisions for patients with invasive breast cancer. *Breast Cancer*. 2017;9:393–400. (31)

Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353: 1673–1684. (50)

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344:783–792. (49)

van Poznak C, Somerfield MR, Barlow WE, et al. Role of bone-modifying agents in metastatic breast cancer: an American Society of Clinical Oncology–Cancer Care Ontario focused guideline update. *J Clin Oncol*. 2017;35: 3978–3986. (90)

COMPLETE REFERENCES CHAPTER 97 BREAST CANCER

1. Seigal RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7–30.
2. Pfeiffer RM, Webb-Vargas Y, Wheeler W, Gail MH. Proportion of U.S. trends in breast cancer incidence attributable to long-term changes in risk factor distribution. *Cancer Epidemiol Biomarkers Prev*. 2018;27(10):1214–1222.
3. Rojas K, Stuckey A. Breast cancer epidemiology and risk factors. *Clin Obstet Gynecol*. 2016;59(4):651–672.
4. Osborne MP, Boolbol SK. Breast anatomy and development. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast*. 5th ed. Wolters Kluwer Health; 2014:3.
5. Howlader N, Noone AM, Krapcho M, et al, eds *SEER Cancer Statistics Review, 1975–2017, National Cancer Institute*. Based on November 2019 SEER data submission, posted to the SEER web site, April 2020. https://seer.cancer.gov/csr/1975_2017/
6. Oeffinger KC, Fontham ET, Etzioni R, et al. Breast cancer screening for women at average risk 2015 guideline update from the American Cancer Society. *JAMA*. 2015;314(15):1599–1614.
7. Siu AL; U.S. Preventative Services Task Force. Screening for breast cancer: U.S. Preventative Services Task Force recommendation statement. *Ann Intern Med*. 2016;164(4):279–296.
8. Lee CI, Chen LE, Elmore JG. Risk-based breast cancer screening: implications of breast density. *Med Clin North Am*. 2017;101(4):725–741.
9. Carbine NE, Lostumbo L, Wallace J, Ko H. Risk-reducing mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev.*. 2018;4(4):CD002748. doi:10.1002/14651858.CD002748.pub4
10. Kotsopoulos J, Huzarski T, Gronwald J, et al. Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst*. 2017;109(1):djw177. doi:10.1093/jnci/djw177
11. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 1998;90:1371–1388.
12. Nelson HD, Fu R, Zakher B, McDonagh M, Pappas M, Stillman L. Medication use for the risk reduction of primary breast cancer in women: a systematic review for the U.S. Preventive Services Task Force [Internet]. Evidence Synthesis Number 180AHRQ. Publication No. 19-05249-EF-1. Agency for Healthcare Research and Quality; September 2019. Report No.: 19–05249-EF-1. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews.
13. Thorat MA, Cuzick J. Preventing invasive breast cancer using endocrine therapy. *Breast*. 2017;34:S47–S54.
14. Mocellin S, Goodwin A, Pasquali S. Risk-reducing medications for primary breast cancer: a network meta-analysis. *Cochrane Database Syst Rev*. 2019;4:CD012191. doi:10.1002/14651858.CD012191.pub2

15. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomized trial. *Lancet.* 2020;395:117–122.
16. Winters S, Martin C, Murphy D, Shokar NK. Breast cancer epidemiology, prevention, and screening. *Prog Mol Biol Transl Sci*. 2017;151:1–32.
17. Brown SB, Hankinson SE. Endogenous estrogens and the risk of breast, endometrial, and ovarian cancers. *Steroids*. 2015;99:8–10.
18. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA*. 2002;288:321–333.
19. Bassuk SS, Manson JE. Oral contraceptives and menopausal hormone therapy: relative and attributable risks and cardiovascular disease, cancer, and other health outcomes. *Ann Epidemiol*. 2015;25(3):193–200.
20. Samadder NJ, Giridhar KV, Baffy N, Riegert-Johnson D, Couch FJ. Hereditary cancer syndromes—a primer on diagnosis and management, part 1: breast-ovarian cancer syndromes. *Mayo Clin Proc*. 2019;94(6):1084–1098.
21. Pruthi S, Gostout BS, Lindor NM. Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian cancer. *Mayo Clin Proc*. 2010;85:1111–1120.
22. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol.* 2007;25:1329–1333.
23. Wang X, Huang Y, Li L, Dai H, Song F, Chen K. Assessment of performance of the Gail model for predicting breast cancer risk: a systematic review and meta-analysis with trial sequential analysis. *Breast Cancer Res*. 2018;20(1):18. doi:10.1186/s13058-018-0947-5
24. Terry MB, Liao Y, Whittemore AS, et al. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncol*. 2019;20:504–517.
25. Barnett CM, Boster BL, Michaud LB. Breast cancer. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 10th ed. McGraw-Hill; 2017. Accessed September 23, 2020.
26. Niravath P, Osborne CK. Evaluation of patients for metastasis prior to primary therapy. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast*. 5th ed. Wolters Kluwer Health; 2014:488.
27. Overmoyer B, Pierce LJ. Inflammatory breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast*. 5th ed. Wolters Kluwer Health; 2014:800.
28. American Joint Committee on Cancer. Breast cancer. In: Edge S, Compton CC, eds. *AJCC Cancer Staging Manual*. 7th ed. Springer-Verlag; 2010:347.
29. Nicolini A, Ferrari P, Duffy MJ. Prognostic and predictive biomarkers in breast cancer: past, present and future. *Semin Cancer Biol.* 2018;52:56–73.

30. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997–4013.
31. McVeigh TP, Kerin MJ. Clinical use of the Oncotype DX genomic text to guide treatment decisions for patients with invasive breast cancer. *Breast Cancer*. 2017;9:393–400.
32. Jain S, Gradishar WJ. The application of Oncotype DX in early stage lymph node positive disease. *Curr Oncol Rep*. 2014;16(1):360–365.
33. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med*. 2002;347:567–575.
34. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707–1716.
35. Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2001;19:1539–1569.
36. Inoue H, Hirano A, Ogura K, et al. Breast-conserving surgery without radiation in elderly women with early breast cancer. *Surg Oncol*. 2019;31:22–25.
37. Moo TA, Sanford R, Dang C, Morrow M. Overview of breast cancer therapy. *PET Clin*. 2018;13:339–354.
38. Burstein HJ, Curigliano G, Thurlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol*. 2021;32(10):1216-1235.
39. Nurudeen S, Hunt KK. Contemporary management of the axilla in breast cancer. *Clin Adv Hematol Oncol*. 2018;16(12):823–831.
40. Silva Soares EW, Nagai HM, Bredt LC, da Cunha AD Jr, Andrade RJ, Soares GV. Morbidity after conventional dissection of axillary lymph nodes in breast cancer patients. *World J Surg Oncol*. 2014;12:67–74.
41. Valero MG, Golshan M. Management of the axilla in early breast cancer. In: Gradishar W, ed. *Optimizing Breast Cancer Management. Cancer Treatment and Research.* (vol 173). Springer, Cham; 2018. doi:10.1007/978-3-319-70197-4_4
42. Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2014;32:1365–1383.

43. Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol*. 2019;30(10):1541-1557
44. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–1717.
45. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379:432–444.
46. Willson ML, Burke L, Ferguson T, Ghersi D, Nowak AK, Wilcken N. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database Syst Rev*. 2019;9:CD004421.
47. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of U.S. Oncology Research Trial 9735. *J Clin Oncol*. 2009;27:1177–1183.
48. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. *BMC Med*. 2015;13:195–207.
49. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over-expresses HER2. *N Engl J Med*. 2001;344:783–792.
50. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673–1684.
51. Genuino AJ, Chaikledkaew U, The DO, Reungwetwattana T, Thakkinstian A. Adjuvant trastuzumab regimen for HER2-positive early stage breast cancer: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol*. 2019;12(8):815–824.
52. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label randomised controlled trial. *Lancet*. 2013;382:1021–1028.
53. Howie LJ, Scher NS, Amiri-Kordestani L, et al. FDA approval summary: pertuzumab for adjuvant treatment of HER2-positive early breast cancer. *Clin Cancer Res*. 2019;25(10):2949–2955.
54. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2 positive breast cancer. *N Engl J Med*. 2019;380(7):617–628.
55. Wellstein A, Giaccone G, Atkins MB, Sausville EA. Cytotoxic drugs. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gillman's The*

Pharmacologic Basis of Therapeutics. 13th ed. McGraw-Hill; 2018:1167–1202.
56. Lenneman CG, Sawyer DB. Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. *Circ Res*. 2016;118(6):1008–1020.
57. Keefe DL. Anthracycline-induced cardiomyopathy. *Semin Oncol*. 2001;28(4, suppl 12):2–7.
58. Babiker HM, McBride A, Newton M, et al. Cardiotoxic effects of chemotherapy: a review of both cytotoxic and molecular targeted oncology therapies and their effect on the cardiovascular system. *Crit Rev Oncol Hematol*. 2018;126:186–200.
59. Youssef G, Links M. The prevention and management of cardiovascular complications of chemotherapy in patients with cancer. *Am J Cardiovasc Drugs*. 2005;5:233–243.
60. Callahan R, Ganz P. Long-term and late effects of primary curative intent therapy: neurocognitive, cardiac, and secondary malignancies. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast.* 5th ed. Wolters Kluwer Health; 2014:726.
61. Ewer M, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*. 2005;23:2900–2902.
62. Yeh ET, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. *Circulation*. 2004;109:3122–3131.
63. Michaud LB, Valero V, Hortobagyi G. Risks and benefits of taxanes in breast and ovarian cancer. *Drug Saf*. 2000;23:401–428.
64. Kumler I, Tuxen MK, Nielsen DL. A systematic review of dual targeting in HER2-positive breast cancer. *Cancer Treat Rev*. 2014;40(2):259–270.
65. Chen S, Liang Y, Feng Z, Wang M. Efficacy and safety of HER2 inhibitors in combination with or without pertuzumab for HER2-positive breast cancer: a systematic review and meta-analysis. *BMC Cancer*. 2019;19(1):973–987.
66. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med*. 1992;326:852–856.
67. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378:771–784.
68. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst*. 2001;93:684–690.
69. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-

positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet*. 2009;374:2055–2063.

70. Nourmoussavi M, Pansegrau G, Popesku J, Hammond GL, Kwon JS, Carey MS. Ovarian ablation for premenopausal breast cancer: a review of treatment considerations and the impact of premature menopause. *Cancer Treat Rev*. 2017;55:26–35.
71. Bui KT, Willson ML, Goel S, Beith J, Goodwin A. Ovarian suppression for adjuvant treatment of hormone receptor-positive early breast cancer (review). *Cochrane Database Syst Rev*. 2020;3(3):CD013538. doi:10.1002/14651858.CD0135383
72. LHRH-agonists in Early Breast Cancer Overview Group, Cuzick J, Ambroisine L, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet*. 2007;369:1711–1723.
73. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381(9869):805–816.
74. van Hellemond IEG, Geurts SME, Tjan-Heijnen VCG. Current status of extended adjuvant endocrine therapy in early stage breast cancer. *Curr Treat Options Oncol*. 2018;19:26–43.
75. Goldvaser H, Barnes TA, Šeruga B, et al. Toxicity of extended adjuvant therapy with aromatase inhibitors in early breast cancer: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2018;110(1):31–39.
76. Goldvaser H, AlGorashi I, Ribnikar D, et al. Efficacy of extended adjuvant therapy with aromatase inhibitors in early breast cancer among common clinicopathologically-defined subgroups: a systematic review and meta-analysis. *Cancer Treat Rev*. 2017;60:53–59.
77. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol*. 2019;10(37):423–438.
78. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early stage breast cancer. *N Engl J Med*. 2003;349:1793–1802.
79. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1–98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol*. 2011;12:1101–1108.
80. Thientosapol ES, Tran TT, Della-Fiorentina SA, et al. Survival times of women with metastatic breast cancer starting first-line chemotherapy in routine clinical practice versus contemporary randomised trials. *Intern Med J*. 2013;43(8):883–888.

81. Waks A, Winer EP. Breast cancer treatment. *JAMA*. 2019;321(3):288–300.
82. Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor–positive metastatic breast cancer: American Society of Clinical Oncology guideline. *J Clin Oncol*. 2016;34(25):3069–3105.
83. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375:1925–1936.
84. de Groot AF, Kuijpers CJ, Kroep JR. CDK4/6 inhibition in early and metastatic breast cancer: a review. *Cancer Treat Rev*. 2017;60:130–138.
85. Johnston SRD, Harbeck N, Hegg R. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk early breast cancer (monarchE). *J Clin Oncol*. 2020;20:3987–3998. doi:10.1200/JCO.20.02514
86. Howell A, Pippen J, Elledge RM, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. *Cancer*. 2005;104:236–239.
87. Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol*. 2010;28(30):4594–4600.
88. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520–529.
89. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. *Ann Oncol*. 2014;25(12):2357–2362.
90. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of bone-modifying agents in metastatic breast cancer: an American Society of Clinical Oncology–Cancer Care Ontario focused guideline update. *J Clin Oncol*. 2017;35:3978–3986.
91. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group. Bone health in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2014;25(3):iii124–iii137.
92. Yarom N, Shapiro CL, Peterson DE, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO clinical practice guideline. *J Clin Oncol*. 2019;37(25):2270–2290.
93. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double blind study. *J Clin Oncol*. 2010;28:5132–5139.
94. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a cancer care Ontario and American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2017;35(18):2062–2081.

95. Sledge G, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol*. 2003;21(4):588–592.
96. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*. 2002;20(12):2812–2823.
97. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol*. 2008;26(24):3950–3957.
98. Valero V, Jones SE, Von Hoff DD, et al. A phase II study of docetaxel in patients with paclitaxel resistant metastatic breast cancer. *J Clin Oncol*. 1998;16:3362–3368.
99. Overmoyer B. Options for the treatment of patients with taxane-refractory metastatic breast cancer. *Clin Breast Cancer*. 2008;8(suppl 2):S61–S70.
100. Loibl S, Gianni L. HER2-positive breast cancer. *Lancet*. 2017;389:2415–2429.
101. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372:724–734.
102. Swain SM, Ewer MS, Cortés J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. *Oncologist*. 2013;18:257–264.
103. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367(19):1783–1791.
104. U.S. Food and Drug Administration. Drug Safety Communication: FDA warns about potential medication errors resulting from confusion regarding proprietary name for breast cancer drug Kadcyla (ado-trastuzumab emtansine). Accessed August 2, 2017. http://www.fda.gov/drugs/drugsafety/ucm350733.htm
105. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108–2121.
106. Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929–1940.
107. Emens LA. Breast cancer immunotherapy: facts and hopes. *Clin Cancer Res*. 2018;24(3):511–520.

98

Lung Cancer

Maryann R. Cooper

CORE PRINCIPLES		CHAPTER CASES
1	Non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) together account for more cancer-related deaths than any other malignancy for both males and females. Smoking is the biggest risk factor and is proportional to the number of pack-years. For former smokers, the risk for developing the disease decreases over time after smoking cessation.	**Case 98-1 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
2	Chances for survival are increased for those whose disease is detected early. The U.S. Preventive Services Task Force recommends annual screening with low-dose computed tomography in patients 55–80 years old with at least a 30-pack-year smoking history in current smokers or those who have quit within 15 years as this did increase detection and improve survival.	**Case 98-1 (Question 1), Table 98-3**
3	The initial signs and symptoms vary according to location and stage of the disease. Many patients are asymptomatic upon initial diagnosis, or signs and symptoms may be masked by other concurrent conditions such as chronic obstructive pulmonary disease.	**Case 98-1 (Question 2) Case 98-2 (Question 1), Table 98-1**
4	Surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy are all modalities used in the treatment of NSCLC. Treatment decisions are individualized according to disease stage, tumor histology (eg, adenocarcinoma, squamous), presence or absence of molecular marker mutations (eg, epidermal growth factor receptor [EGFR], programmed death-ligand 1 [PD-L1]), performance status, comorbidities, and patient preference.	**Case 98-1 (Questions 2, 3) Case 98-2 (Questions 1–6), Tables 98-4–98-6**

CORE PRINCIPLES		CHAPTER CASES
5	SCLC tumors generally have a higher proliferation rate than NSCLC tumors. Hence, chemotherapy, radiotherapy, and immunotherapy are the primary treatments. These tumors tend to grow more centrally and rapidly than NSCLC tumors; therefore, surgical resection is usually not performed.	**Case 98-3 (Questions 1–4)**
6	Most NSCLC cytotoxic chemotherapy regimens are cisplatin-based or carboplatin-based doublets with or without an immune checkpoint inhibitor. These are given for four to six cycles. Maintenance therapy has been shown to be beneficial for patients receiving cytotoxic chemotherapy with or without an immune checkpoint blockade. Targeted therapies are currently limited given the infrequency at which genetic variations are discovered.	**Case 98-1 (Question 3) Case 98-2 (Questions 1–3), Tables 98-4–98-6**
7	Most SCLC cytotoxic chemotherapy regimens are cisplatin-based or carboplatin-based doublets in combination with etoposide and an immune checkpoint inhibitor if extensive-stage disease.	**Case 98-3 (Questions 3–6)**

INTRODUCTION

Lung cancers may be referred to as non-small-cell lung cancer (NSCLC) or small-cell lung cancer (SCLC), and although there are many similarities between these two, treatments will often differ. Approximately 85% of lung cancers are classified as NSCLC and the remaining are classified as SCLC.[1] This chapter will initially focus on the presentation, diagnosis, and treatment of NSCLC, followed by a shorter section that describes SCLC.

Non-Small-Cell Lung Cancer

Epidemiology

Incidence of lung cancer in the United States is second to prostate cancer in males and breast cancer for females. Lung cancer is the leading cause of death relative to all of the other cancers. As with most solid tumors, survival is better for patients diagnosed with early-stage disease than it is for those with more advanced disease.[2] However, for many patients, the disease often goes undetected either because of the lack of noticeable symptoms or because they may be masked by concurrent diseases with similar symptoms such as chronic obstructive pulmonary disease (COPD).

PATHOPHYSIOLOGY

NSCLC tumorigenesis is a multistep process in which neoplastic tissue arises from bronchial epithelium. These cells, which form the inner lining of bronchial tissue, develop genetic lesions to proto-oncogenes and tumor suppressor genes, resulting in the dysregulation of key molecular signaling pathways. As a result, cellular proliferation occurs and responsiveness to apoptotic signaling is often diminished. Eventually, accumulation of additional genetic abnormalities can influence the cell's ability to metastasize, resulting in the spread of tumorous tissue locally or to more distant sites in the lymph nodes and organs.

Non-small-cell lung tumors are classified further according to tumor tissue histology. The three major histologic types include squamous cell carcinoma, adenocarcinoma, and large-cell

carcinomas. Although these different variants were identified several decades ago, recently it has been demonstrated that the histology impacts chemotherapeutic agent selection. These three may be subcategorized further and other variants of NSCLC also exist; however, discussion in this chapter will be limited to these three. The adenocarcinomas and large-cell carcinomas are commonly grouped together as nonsquamous carcinomas. These tumors commonly arise in the periphery of the lung and the smaller airways. After various periods of growth in the lung parenchyma or bronchial wall, these primary tumors invade the vascular and lymphatic system, enabling metastases to regional lymph nodes and more distant sites.[1]

RISK FACTORS AND CLINICAL PRESENTATION

There are several risk factors for developing lung cancer, but the biggest factor is cigarette smoking, which is estimated to increase the risk by up to 30-fold. The prevalence of smoking peaked in the early 1960s and has steadily decreased in the United States because of increased awareness of the harm of smoking. Death rates from lung cancer in both males and females have also followed this downward trend. For males, deaths because of lung cancer peaked in the 1980s and has since steadily decreased. For females, deaths because of lung cancer began to decline in the mid-2000s. Other risk factors include secondhand smoke, cigar and pipe smoking, occupational and environmental exposures, radon, asbestos, certain metals such as chromium and cadmium, various organic chemicals, radiation, air pollution, history of tuberculosis, and genetic factors. The latter appears to be related to those who exhibit the disease early in life. The probability of developing invasive lung cancer increases with age and peaks during the seventh decade of life.[2–4]

The disease is detected either when a person presents with signs and symptoms commonly associated with lung cancer or, by chance, when the patient is under evaluation for other disorders or procedures. Selected signs and symptoms are listed in **Table 98-1**,

but vary widely between patients according to tumor size, stage, and location.

Table 98-1
Common Selected Signs and Symptoms for Lung Cancer

Cough
Hemoptysis
Wheeze
Dyspnea
Pain (eg, chest wall)
Obstruction of vital structures (eg, esophagus, superior vena cava)

Symptoms are highly dependent on tumor size, location within the chest cavity, and presence of metastases.

DIAGNOSIS

If a malignancy comes under consideration, a computed tomography (CT) or positron emission tomography (PET)–CT scan of the abdomen and thoracic region is usually performed to identify any possible primary lesions and to look for possible metastases to lymph nodes and other organs or contralateral lung. If located, a pathologic evaluation is performed to confirm the diagnosis. Magnetic resonance imaging (MRI) of the head may be ordered if brain metastases are suspected. Preoperatively, specimens may be obtained through methods such as bronchial brushings, bronchial washings, fine-needle aspiration biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy. Mediastinal lymph nodes are also sampled via mediastinoscopy to determine staging. If surgery is performed, specimens are evaluated during the procedure to determine the resection margin status, diagnose incidental nodules discovered during surgery, and sampling of regional lymph nodes. Postoperative evaluation provides pathology characteristics necessary for classifying tumor type and staging.[1]

Staging is performed to determine prognosis and to guide treatment decision-making. In general, the prognosis declines with increasing disease stage at initial diagnosis. Five-year overall survival rates are 54% for patients with disease that is locally limited

and 4% for metastatic disease. For all stages, 5-year overall survival has only marginally improved over the last 30 years to 18%. Unfortunately, the disease has already metastasized in >50% of patients upon initial presentation. However, earlier detection with spiral CT has resulted in a decrease in disease-related death in patients with at least a 30-pack-year smoking history.[2,4,5] Staging classification is reliant on anatomic characteristics and was updated by the International Association for the Study of Lung Cancer (IASLC) and adopted by the American Joint Committee on Cancer (AJCC). The AJCC 8th edition staging manual was implemented in the United States in January, 2018.[6,7] In addition to the tumor, node, metastases (TNM) stage, molecular markers and tumor histology are key information in making treatment decisions. **Table 98-2** illustrates how the TNM classification is used to determine the clinical stage.

Table 98-2
Clinical Staging for Non-Small-Cell Lung Cancer

Clinical Stage	Tumor Characteristics
Stage I	Tumor ≤5 cm in greatest diameter with no nodal involvement
Stage II	Tumor >5 cm, but ≤7 cm in greatest diameter with no nodal involvement Tumor ≤7 cm with adjacent lymph nodes involved Tumor >7 cm or invading local structure (ie, chest wall) with no nodal involvement
Stage III	Any tumor size with adjacent lymph nodes involved or ipsilateral mediastinal and/or subcarinal lymph nodes Tumor invading mediastinum, heart, great vessels, esophagus, or another tumor nodule in different ipsilateral lobe
Stage IV	Any tumor size, any nodal involvement and metastasis to the contralateral lobe, malignant pleural effusions, or distant metastasis

Adapted from Rami-Porta R, Bolejack V, Giroux DJ, et al. The IASLC lung cancer staging project: the new database to inform the eight edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2014;9(11):1618–1624. Copyright © 2014 International Association for the Study of Lung Cancer. With permission.

OVERVIEW OF TREATMENT

Surgery, radiation, and systemic therapy (ie, cytotoxic chemotherapy, targeted therapy, and immunotherapy) are all treatment modalities used in the treatment of NSCLC. If diagnosed in the early stages of the disease, surgery offers the best chance of cure. Chemotherapy, targeted therapies, and immune therapies are associated with enhanced survival depending on the stage of disease and patient characteristics. The remaining discussion of NSCLC in this chapter will outline the key aspects in the treatment of early and late stages of the disease.

Early-Stage Non-Small-Cell Lung Cancer

CASE 98-1

Question 1: A 69-year-old male patient, J.W., was found to have a 3-cm nodule on a chest x-ray done prior to an elective cataract surgery. The patient was a lifelong cigarette smoker, having started smoking in his early 20s, approximately one pack of cigarettes per day. He quit smoking 9 years ago.

What screening methods might be available to detect the disease in asymptomatic patients? What risk factors does J.W. have for lung cancer?

The National Lung Screening Trial (NLST) was a randomized study comparing low-dose CT (LDCT) scans with chest radiography in over 50,000 patients with a heavy smoking history, examining lung cancer mortality.[8,9] The NLST did result in a higher incidence of confirmed diagnoses of lung cancer with LDCT, resulting in a 20% relative reduction in the rate of death from lung cancer. LDCT did result in a higher rate of false positives than chest radiography.[5] When combined with smoking cessation, screening with LDCT results in a 38% decrease in lung cancer mortality.[10] Results of the NLST support the U.S. Preventive Service Task Force recommendations of annual screening for lung cancer with low-dose CT scans in adults 55 to 80 years old with a 30-pack-year smoking history and currently smoke or have quit within the last 15 years.[11]

The probability for developing the disease increases with age, and J.W.'s age is close to the median age of peak incidence. Males also

have a slightly higher risk than females, as discussed. Smoking is the largest risk factor for lung cancer development; however, what if a person stops smoking? Does the risk decrease with time? These questions are important for health care providers to address as they are encouraging smoking cessation for their patients. In J.W.'s case, he stopped 9 years ago, so what impact would this smoking history have on development of the disease? In general, people who stop smoking, even well into middle age, avoid almost 90% of the risk attributable to tobacco. Shown in **Table 98-3** are data demonstrating the relation between the age at which a person stops smoking and the cumulative percent risk (at age 75) for developing lung cancer.[12] J.W. stopped when he was ~60 years old; therefore, based on this table, the cumulative risk would approach 10% if he were 75 years old. Because he is 69 years old, his risk would be decreased but not to the extent that it would if a longer period of time had elapsed. If he were still smoking, the risk would be expected to be closer to 16%. Hence, smoking cessation is an effective means for lowering the risk over time. He smoked for ~35 to 40 pack-years, so the total number of cigarettes would also increase his risk. According to data from the same studies, risk of disease for a one pack per day smoker would be approximately twice that of someone who smoked less than a half pack per day. Survival from the disease is also better for nonsmokers than for smokers.[12,13]

Table 98-3

Cumulative Risk (%) of Death From Lung Cancer at Age 75 Years

Smoking Status	Risk at Age 75
Lifelong nonsmoker	>1
Stopped at age 30	>2
Stopped at age 40	3
Stopped at age 50	6
Stopped at age 60	10
Continuing smoker	16

Frequently, patients will experience remorsefulness for having smoked, but it is never possible to attribute one's disease to a single factor such as smoking. In fact, 90% of smokers never exhibit symptoms of the disease. Furthermore, 15% of males and 53% of all females with lung cancer worldwide are never smokers.[14] This suggests that other factors such as genetics are associated with the development of the disease. Research has been directed at identifying genomic associated factors that have the potential to lead to the development of lung cancer in both smokers and nonsmokers. It has been shown that there can be some genetic associations, but the true impact of these genetic polymorphisms has not been fully elucidated.[3,15–18]

A more thorough history from J.W. would be helpful, but recall for exposure to pollution, chemicals, and secondhand smoke exposure is difficult to quantify. Hence, the view held by much of society that lung cancer is a self-inflicted disease is not entirely true. In summary, there is limited history on J.W.'s exposure to environmental hazards such as radon and secondhand smoke. His age is close to that of peak incidence. Although he stopped smoking almost a decade ago, there is still some residual risk associated with past smoking history, and this would be expected to be higher for those with many pack-years history. Because of his heavy smoking history, J.W. may have benefited from low-dose CT scan screening to potentially provide earlier detection of lung cancer.

Case 98-1, Question 2: A CT scan was ordered for further evaluation, and it showed an isolated spiculated nodule in the right upper lobe with no mediastinal or hilar adenopathy. The nodule showed no calcification. A CT-guided needle biopsy was performed that showed a well-differentiated adenocarcinoma consistent with a primary NSCLC. Further staging was carried out with PET–CT scanning that demonstrated no additional areas of disease except for the nodule. What would be the best treatment plan for J.W., given the current information? Would surgery or neoadjuvant therapy be indicated?

The goal of therapy for this patient is to achieve a cure, especially because the disease appears to be early stage. Surgery is the best treatment modality for patients with stages I and II disease because

these tumors are limited to one hemithorax and can be readily removed by excision. In most instances, lobectomy using a minimally invasive technique (eg, video-assisted thoracic surgery [VATS]), with node dissection is sufficient for local control. During surgery, the mediastinal lymph nodes are sampled for presence of the disease and to confirm staging. J.W. appears to have limited disease, and so minimally invasive lobectomy would be recommended for him. For patients whose primary tumor or lymph node involvement extends to the proximal bronchus or proximal pulmonary artery, or crosses the major fissure, then a more extensive sleeve resection would be performed. For patients with a medical contraindication to surgery, curative radiation therapy can be used in place of surgery. However, surgery is the treatment of choice, and final staging during surgery will guide adjuvant treatments.[19] Neoadjuvant therapy may be recommended to reduce the tumor burden prior to surgery depending on tumor size and location within the lung. If neoadjuvant therapy is chosen, the regimen is usually similar to those used in the adjuvant setting (**Table 98-4**).[20-29] Therefore, surgery is the primary treatment modality for patients with stages I, II, and select stage IIIA disease. J.W.'s disease appears to be localized; therefore, surgical removal of the tumor would be indicated, and neoadjuvant therapy would not be indicated because of the size and location of the primary tumor.[19]

Table 98-4

Adjuvant Chemotherapy Regimens for Non-Small-Cell Lung Cancer

Regimen	Schedule
Cisplatin, day 1[a] Pemetrexed, day 1[a]	Every 21 days for four cycles[20]
Cisplatin, day 1 Gemcitabine, days 1, 8	Every 21 days for four cycles[21]
Cisplatin, day 1 Docetaxel, day 1	Every 21 days for four cycles[22,23]

Regimen	Schedule
Cisplatin, days 1, 8 Vinorelbine, days 1, 8, 15, 22	Every 28 days for four cycles[24]
Cisplatin, day 1 Vinorelbine, days 1, 8, 15, 22	Every 28 days for four cycles[25,26]
Cisplatin, day 1 Vinorelbine, days 1, 8	Every 21 days for four cycles[24]
Cisplatin, day 1 Etoposide, days 1–3	Every 28 days for four cycles[26]
For patients unlikely to tolerate cisplatin	
Paclitaxel, day 1 Carboplatin, day 1	Every 21 days for four cycles[27]
Gemcitabine, day 1, 8 Carboplatin, day 1	Every 21 days for four cycles[28]
Pemetrexed, day 1[a] Carboplatin, day 1[a]	Every 21 days for four cycles[29]

[a]Nonsquamous cell only.

CASE 98-1, QUESTION 3: J.W. was referred to a thoracic surgeon for resection. A right upper lobe lobectomy was performed with lymph node dissection. The pathology report revealed a 3.2 × 4 cm adenocarcinoma with three associated peribronchial lymph nodes containing cancer cells. Lymph nodes sampled from the mediastinum demonstrated no cancer. The patient's tumor was staged as a T2N1M0 (stage IIA) NSCLC. Now that the tumor has been completely resected and staging of the disease is finalized, what additional therapy, if any, is recommended?

Although NSCLC tumors are minimally responsive to chemotherapy, evidence from several studies (Table 98-4) demonstrates that adjuvant treatment enhances patient survival and should be considered as part of the treatment plan for select patients. The Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group conducted a meta-analysis of five randomized controlled trials that evaluated the use of adjuvant cisplatin-based chemotherapy in patients with completely resected NSCLC. Overall, a decreased risk of death was observed following adjuvant

chemotherapy (hazard ratio, 0.89 [95% confidence interval, 0.82–0.96]). However, the benefit was not consistent across stages. No statistically significant difference in death was seen in patients with stage IA (hazard ratio, 1.40 [95% confidence interval, 0.95–2.06]) and stage IB (hazard ratio, 0.93 [95% confidence interval, 0.78–1.10]) NSCLC. The benefit of this therapy was limited to those with completely resected stage II (hazard ratio, 0.83 [95% confidence interval, 0.73–0.95]) and stage III (hazard ratio, 0.83 [95% confidence interval, 0.72–0.94]) disease.[30] As summarized in Table 98-4, adjuvant chemotherapy utilizes cisplatin as the base of the regimen. A second agent, usually selected from one of those listed in Table 98-4, is added as doublet therapy, and the goal is for patients to receive four cycles. Toxicity often becomes worse beyond four cycles and benefits are diminished thereafter. Therefore, cytotoxic chemotherapy is beneficial but has its limitations. As demonstrated in the CALGB 9633 study, carboplatin plus paclitaxel also improves survival in those with stages II and IIIA NSCLC.[27] Therefore, carboplatin can be used as an alternative in patients unlikely to tolerate cisplatin.

Radiation therapy is frequently used in the treatment of malignancies, including later stages of NSCLC; however, it has no proven benefit for the treatment of early-stage disease. The postoperative radiotherapy trialists (PORT) Group conducted a meta-analysis from nine randomized trials to evaluate the possible role of postoperative radiotherapy in patients with completely resected NSCLC. There were 707 deaths among 1056 patients assigned postoperative radiotherapy and 661 among 1072 assigned surgery alone (hazard ratio, 1.21 [95% confidence interval, 1.08–1.34]). This 21% relative increase in the risk of death with radiotherapy is equivalent to a reduction in overall survival from 55% to 48%. Subgroup analysis showed that the increased risk of death was greatest for patients with stage I/II, N0 or N1, but no clear evidence for those with stage III, N2 disease.[31] Separately, another postoperative radiotherapy study was conducted, using data from 7465 patients in the Surveillance, Epidemiology, and End Results (SEER) database. The investigators for this study also found no

benefit for radiotherapy, especially for patients with N1 and N0 disease. However, an increase in survival was associated with radiotherapy for patients who had N2 disease.[32] Consequently, radiation therapy is reserved for patients with more advanced NSCLC.

In summary, adjuvant cytotoxic chemotherapy is recommended for patients with completely resected stage II or III NSCLC following surgery. Multiple prospective phase-3 studies have shown that platinum-based chemotherapy after surgery will increase the survival rate of patients after surgery by about 10%. Because J.W. has stage IIA disease, four cycles of a platinum-based doublet regimen would be indicated after surgery; however, he should not receive radiation therapy at this time.

Late-Stage Non-Small-Cell Lung Cancer

CASE 98-2

QUESTION 1: L.L., an 85-year-old female, presented with a mild cough, productive with nonbloody sputum, shortness of breath, and fever. She was initially seen by her primary care physician who treated her with antibiotics for possible pneumonia; however, chest radiography showed a persisting infiltrate in the left upper lung. This was later confirmed on a CT scan with the presence of a 6 × 3 × 3.6 cm mass in the left upper lobe. Mediastinal adenopathy and multiple pulmonary nodules were seen in the right upper lobe with associated scarring, the largest of them measuring 14 × 9 mm in the right upper lobe anteriorly. Transbronchial biopsy led to a diagnosis of adenocarcinoma. The tumor tissue was positive for a sensitizing *EGFR* mutation because of a deletion in exon 19. The PD-L1 tumor proportion score was 52%, and the sample was negative for other gene mutations and rearrangements. Because of the spread of disease to the contralateral lung, disease was staged as IV. Pertinent patient history included hypertension and hyperlipidemia. The patient also had a hemangioma of the brain resected in 1960 and a history of cervical cancer treated with an abdominal hysterectomy in 1962. She has never smoked. Upon evaluation, she was found to have a hemoglobin that was slightly low at 11.3 g/dL with a white blood cell count of 5200 cells/μL and a platelet count of 245,000/μL. The electrolytes showed normal sodium of 143 mEq/L, normal potassium of 4.4 mEq/L, and creatinine of 1.08 mg/dL, with estimated creatinine clearance of 48 mL/minute. Her performance status was 0 to 1.

What are the treatment options for patients such as L.L. with advanced (inoperable stages III and IV) disease?

SURGERY

In general, tumors in patients with stages III and IV disease are inoperable. These tumors often invade the carina, great vessels, vertebral bodies, more distant lymph nodes, metastases, and are frequently associated with malignant pleural effusions. Hence, combined-modality treatments such as cytotoxic chemotherapy and radiation or targeted therapies are the preferred treatments for patients with advanced-stage disease.[33,34] Surgery to remove solitary metastatic sites may also be considered in selected patients, especially in patients with a solitary brain metastasis.[35]

RADIATION AND CHEMOTHERAPY

Radiation therapy is the primary local treatment (ie, definitive radiation therapy) for inoperable nonmetastatic NSCLC and is also used as a palliative modality for patients with incurable disease with symptoms such as pain or shortness of breath. For tumors classified as stage III, radiation therapy is given concurrently with chemotherapy, as this has been shown to be superior to both radiation alone and also sequential radiation followed by chemotherapy.[36-41] The radiation dose, in combination with chemotherapy, usually ranges between 60 and 65 Gray (Gy), given in 2-Gy fractions. The recommended chemoradiation regimen for stage III disease is based on tumor histology. Histology is an important factor for individualizing treatment based on either safety or efficacy outcomes. Hence, once the biopsy is obtained, it is crucial to differentiate the histologic subtype (ie, squamous vs nonsquamous).[42] Many agents are effective against all histologic types such as cisplatin, carboplatin, gemcitabine, and paclitaxel. However, other agents such as bevacizumab and pemetrexed are only indicated for use in patients who have nonsquamous histology. Squamous cell histology is associated with increased risk for severe pulmonary hemorrhage compared with adenocarcinoma.[43] For

pemetrexed, significant association between improved efficacy and the nonsquamous subtype has been reported.[44,45] Therefore, for patients with nonsquamous histology (ie, adenocarcinoma or large cell), either cisplatin or carboplatin is combined with pemetrexed, etoposide, or paclitaxel. If the patient has squamous cell carcinoma, the preferred regimens contain cisplatin or carboplatin combined with etoposide or paclitaxel, respectively.[36-41,46] See **Table 98-5** for specific chemoradiation regimens. Durvalumab consolidation is offered to patients with stage III disease, a performance status 0 to 1, who do not experience disease progression after two or more cycles of definitive chemoradiation. Durvalumab consolidation significantly improves overall survival compared to placebo in this setting.[46]

Table 98-5
Representative Chemoradiation Regimens for Inoperable Stage III Non-Small-Cell Lung Cancer

Regimen	Schedule
Cisplatin, days 1, 8, 29, 36 Etoposide days 1–5, 29–33	Concurrent radiation of 45 Gy administered in 25 daily 1.8 Gy fractions over 5 weeks[36,37]
Carboplatin AUC 5, day 1 Pemetrexed, day 1 *Nonsquamous histology	Every 21 days for four cycles[38] Concurrent radiation of 70 Gy administered in 35 daily 2 Gy fractions over 6–7 weeks
Cisplatin, day 1 Pemetrexed, day 1 *Nonsquamous etiology	Every 21 days for three cycles[39,40] Concurrent radiation of 60–66 Gy in 30–33 daily 2 Gy fractions over 6–7 weeks With or without consolidative pemetrexed every 21 days for four cycles
Paclitaxel weekly for 7 weeks Carboplatin AUC 2 weekly for 7 weeks	Concurrent radiation of 60 Gy in 2 Gy fractions over 6–7 weeks With or without consolidative paclitaxel plus carboplatin every 21 days for two cycles[41]

Metastases may also be treated locally with radiation therapy. For example, brain metastases, spinal cord compression, and impending fractures of weight-bearing bones can be treated with radiation or surgery before systemic therapy commences. In contrast to patients with stage III disease, those with stage IV disease usually receive local treatment with radiation therapy, either before or after chemotherapy, because therapy given concurrently is often not well tolerated by patients with this stage of disease.

SYSTEMIC THERAPY

A deeper understanding of the pharmacogenomics and the immune microenvironment of NSCLC has led to a shift if the primary treatment of metastatic disease from traditional cytotoxic chemotherapy to targeted therapies. Several driver mutations and gene rearrangements have been discovered that when targeted, have demonstrated improved survival compared to chemotherapy. In addition, immune checkpoint blockade alone or in combination with chemotherapy has also been shown to improve survival.[47–49] Molecular and immune biomarker testing is recommended for most patients diagnosed with stage IV disease. Results of this testing will drive first-line treatment choice. See **Table 98-6** for first-line treatment recommendations.

Table 98-6
Representative Initial Therapy for Metastatic Non-Small-Cell Lung Cancer

Target	Preferred Initial Treatment	Alternate Treatment
EGFR	Osimertinib[61,62]	Erlotinib[47] Afatinib[64] Gefitinib[63] Dacomitinib[65] Erlotinib + ramucirumab[107] Erlotinib + bevacizumab[108]
ALK	Alectinib[109]	Brigatinib[110] Ceritinib[111]

ROS1	Crizotinib[112] or entrectinib[113]	Ceritinib[114]
BRAF V600E	Dabrafenib + trametinib[115]	Vemurafenib[116] Dabrafenib[117]
MET exon 14 skipping mutation	Capmatinib[118]	Crizotinib[119]
RET	Selpercatinib[120] or pralsetinib[121]	Cabozantinib[122] Vandetanib[123]
NTRK	Larotrectinib[124] or entrectinib[125]	
PD-L1 ≥ 1%[a]	Pembrolizumab[49,60] *PD-L1 ≥50% only Atezolizumab[127] *PD-L1 ≥ 50% only Carboplatin or cisplatin + pemetrexed + pembrolizumab[51] (nonsquamous only) Carboplatin + paclitaxel or *nab*-paclitaxel + pembrolizumab[69] (squamous cell only)	Carboplatin + paclitaxel + bevacizumab + atezolizumab[126] (nonsquamous only) Carboplatin + *nab*-paclitaxel + atezolizumab[126] Nivolumab + ipilimumab + pemetrexed + carboplatin or cisplatin[128] (nonsquamous cell only) Nivolumab + ipilimumab + paclitaxel + carboplatin[128] (squamous cell only) Nivolumab + ipilimumab[129]
PD-L1 < 1%[a]	Carboplatin or cisplatin + pemetrexed + pembrolizumab[51] (nonsquamous only) Carboplatin + paclitaxel or *nab*-paclitaxel + pembrolizumab[69] (squamous cell only)	Carboplatin + paclitaxel + bevacizumab + atezolizumab[126] (nonsquamous only) Carboplatin + *nab*-paclitaxel + atezolizumab[126] Nivolumab + ipilimumab + pemetrexed + carboplatin or cisplatin[128] (nonsquamous cell only) Nivolumab + ipilimumab + paclitaxel + carboplatin[128] (squamous cell only) Nivolumab + ipilimumab[129] Pembrolizumab[49,60]

[a]Must be negative for other driver mutations or gene rearrangements.

Patients receiving oral tyrosine kinase inhibitors (eg, osimertinib, alectinib) to target a specific driver mutation or gene rearrangement will receive therapy until disease progression. Subsequent therapy will depend on symptoms and location of disease. A tumor flare response may occur after discontinuation of tyrosine kinase inhibitor treatment. If a patient experiences such response, the tyrosine kinase inhibitor should be reinitiated.[50] Response to treatment will be evaluated initially after two cycles. Patients receiving an immune checkpoint inhibitor alone or in combination with chemotherapy will transition to maintenance therapy if there is a response or the patient achieves stable disease after four to six cycles. The intention of such additional treatment would be to prolong the response and survival made possible by first-line treatment. Maintenance therapy differs from second-line therapy in that second-line treatment is only used when the patient has progressed during or after first-line treatment or is unable to tolerate it. Continuation maintenance, which refers to the use of one of the agents given in the first-line setting, is preferred. Often, the immune checkpoint inhibitor alone is continued.[49] For adenocarcinoma, pemetrexed can be continued in combination with pembrolizumab if the first-line regimen consisted of carboplatin with pemetrexed and pembrolizumab.[51]

PALLIATION

Patients with metastatic NSCLC receive benefit from palliative care early after diagnosis, rather than waiting until end-of-life care. This palliative care includes helping the patient cope with the psychosocial aspects of their disease through methods such as counseling (eg, expectation of treatment outcomes and affordability of treatment). In a study of patients with metastatic disease, subjects were randomly assigned to receive either early palliative care integrated with standard oncologic care versus standard oncologic care alone. Patients assigned to early palliative care experienced a better quality of life and survival (11.6 vs 8.9 months) than patients assigned to standard care alone. They also experienced fewer depressive symptoms (16% vs 38%). The results show that palliative

care is appropriate and potentially beneficial when it is introduced at the time of diagnosis at the same time as other beneficial therapies.[52]

In conclusion, L.L. would not likely receive benefit from surgical removal of the primary tumor or metastatic site. Although the tumor sample expresses PD-L1, first-line therapy for a patient with a sensitizing *EGFR* mutation is *EGFR*-targeted therapy.

CASE 98-2, QUESTION 2: How often are actionable genetic alterations present, and what patient characteristics are associated with them?

A major advancement in the management of advanced and metastatic NSCLC has been the discovery of driver mutations and gene rearrangements that serve as targets for drug therapy. Targeted therapy directed at a genetic alteration is often more effective and is better tolerated compared to standard cytotoxic chemotherapy. As listed in Table 98-6, there are currently several genetic alterations with U.S. Food and Drug Administration (FDA)–approved targeted therapy. Despite the abundance of targeted drug therapy, gene rearrangements and driver mutations are infrequently discovered in patients diagnosed with advanced or metastatic NSCLC.

Of the currently known alterations, driver mutations in *EGFR* are most common, occurring in 10% to 40% of patients with NSCLC. Somatic *EGFR* mutations predominantly occur in females, never-smokers, those of East Asian descent, and those with adenocarcinoma histology.[53] *ALK* gene rearrangements occur in ~2% to 8% of patients. Like *EGFR* mutations, *ALK* gene rearrangements are discovered more often in patients with adenocarcinoma as well as those that were light or never smokers. This aberration occurs more frequently in younger, male patients.[54] Similarly, *ROS1* gene rearrangements are found most often in younger, male, never-smokers with adenocarcinoma. This gene rearrangement is present in up to 5% of patients with NSCLC.[54,55] *BRAF* mutations occur in about 3% of patients with adenocarcinoma.

Unlike the previously discussed alterations, *BRAF* mutations tend to be found in current or former smokers.[54] *MET* exon 14 skipping mutations are seen in 3% to 4% of patients with adenocarcinoma and 1% to 2% of patients with other histologies. These mutations are more frequently seen in older females who are never-smokers.[54,56] *RET* gene rearrangements occur in 1% to 2% of patients with adenocarcinoma and are seen in both smokers and nonsmokers.[54,57] *NTRK* gene fusions are extremely rare, occurring in 0.2% of patients with NSCLC.[58]

Despite the fact that certain histologies and patients characteristics are associated with genetic aberrations, it is not appropriate to start patients empirically on targeted therapy without testing for specific targets. The gene mutations, rearrangements, and fusions discussed, do not overlap with one another, and those without the genetic variant are unlikely to respond sufficiently to the targeted therapy. Therefore, it is important to discover which genetic alteration is present prior to initiating therapy. In L.L.'s case, she has clinical predictors of multiple aberrations: female, nonsmoker, and adenocarcinoma. In this case, and all cases of advanced or metastatic nonsquamous cell NSCLC, molecular testing is recommended to identify if genomic variants are present.[59] Molecular testing should be considered for patients with squamous cell histology, especially if the patient never smoked. Although the genetic alterations are almost exclusively seen in adenocarcinoma, patients with squamous cell histology may actually have a mixed histology and can therefore harbor a genetic alteration.

In addition to testing for genetic variants, evaluation of immune biomarkers is also recommended for patients with metastatic NSCLC of all histologies. Programmed death-ligand 1 (PD-L1) expression is reported as a tumor proportion score (TPS), which serves as a guide for selection of immune checkpoint inhibitor therapy. Immune checkpoint inhibitors are not recommended as first-line therapy if the patient harbors an actionable genetic alteration (eg, *EGFR, ALK, BRAF*).[49,60]

Case 98-2, Question 3: L.L. was started on erlotinib therapy based on a positive *EGFR* mutation and, within 12 months of initiation, had experienced disease progression. Would L.L. benefit from a different *EGFR*-targeted therapy?

Based on the phase-3 FLAURA trial, osimertinib is the preferred first-line *EGFR* tyrosine kinase inhibitor as it was shown to significantly improve progression-free survival compared to erlotinib and gefitinib.[61] Despite the recommendation that osimertinib be prescribed preferentially over other *EGFR* tyrosine kinase inhibitors, agents such as erlotinib are often used first line because of cost.[62] Generally, patients treated with erlotinib, gefitinib, afatinib, or dacomitinib as a first-line agent will experience disease progression after 9 to 14 months of therapy.[47,63-65] The most common reason for progression is an acquired point mutation known as *EGFR* T790M. This acquired mutation accounts for about 60% of disease progression.[66] Testing for T790M is therefore recommended for patients that progress while receiving erlotinib, gefitinib, afatinib, or dacomitinib.[59] Patients that harbor the T790M mutation may be switched to osimertinib as it targets this mutation and has been shown to improve progression-free survival in patients with T790M-positive NSCLC compared to standard chemotherapy.[67] Patients that do not test positive for T790M may receive platinum-based chemotherapy or may continue on the current *EGFR* tyrosine kinase inhibitor depending on symptoms and location of disease. As described, some patients may experience a disease flare when the tyrosine kinase inhibitor is discontinued. If this occurs, therapy should be reinitiated.[50] In the case of L.L., she should be tested for T790M and switched to osimertinib if the test comes back positive.

Case 98-2, Question 4: If L.L.'s tumor was classified as having wild-type *EGFR* and a PD-L1 TPS of 0% instead, what treatment should L.L. receive?

If the biopsy results had shown that the tumor *EGFR* was wild-type (ie, no mutation) and the tumor did not express PD-L1, L.L. would be

considered for carboplatin or cisplatin plus pemetrexed plus pembrolizumab, as shown in Table 98-6. KEYNOTE-186 evaluated the addition of pembrolizumab or placebo to carboplatin or cisplatin plus pemetrexed in patients newly diagnosed with advanced nonsquamous cell NSCLC. Randomization in this trial was stratified according to TPS of <1% versus ≥1%. Results revealed a statistically significant improvement in both disease-free and overall survival with the addition of pembrolizumab to platinum-based chemotherapy. The improvement in overall survival was consistent in all TPS groups including those with a score <1%.[68] Similarly, KEYNOTE-407 demonstrated an improvement in overall survival when pembrolizumab was added to carboplatin with either paclitaxel or *nab*-paclitaxel in patients newly diagnosed with advanced squamous cell NSCLC. Again, the improvement was seen across all tumor propensity score groups.[69]

Therefore, if L.L.'s tumor had been wild-type for *EGFR* and did not express PD-L1, she could receive cisplatin or carboplatin with pemetrexed and pembrolizumab as first-line treatment because her disease is adenocarcinoma. If she responds or has stable disease following four to six cycles of therapy, she should receive maintenance therapy with pemetrexed and pembrolizumab based on the KEYNOTE-186 trial.[68]

Case 98-2, Question 5: As discussed in Chapter 94, Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents, the adverse effect profiles for cisplatin and carboplatin differ from each other. If a platinum-based regimen had been selected instead of targeted therapy for L.L., what characteristics about L.L. could be used to guide the selection of carboplatin versus cisplatin?

Cisplatin is predominantly associated with ototoxicity, nephrotoxicity, and neurotoxicity, whereas carboplatin is predominantly associated with myelosuppression. This would be her first cycle of chemotherapy; therefore, she is not expected to have depleted reserves of myeloid progenitor cells. Her estimated creatinine clearance is 48 mL/minute and, based on this, would be

considered to have moderate renal impairment. In this case, carboplatin may be preferred over cisplatin because it is associated with less renal toxicity and it is dosed according to the Calvert formula, which accounts for renal function:

$$\text{Total carboplatin dose (mg)} = \text{AUC}\,(\text{GFR} + 25) \quad \textbf{(Eq. 98-1)}$$

where AUC is the area under the concentration–time curve and GFR is glomerular filtration rate.[70] A typical dose of carboplatin in this setting would be determined based on an AUC to account for renal function instead of the typical weight (or m^2)-based dosing. The AUC targets are commonly 4 to 6 mg/mL × minute for most doublet regimens. If a patient with moderate renal function were to receive a fixed dose that is similar to that given to a patient with normal renal function, then systemic exposure would be higher. This higher exposure could result in greater toxicity, notably greater myelosuppression. By dosing the drug according to the patient's renal function, the risk for overdosing a patient with decreased renal function is minimized. For example, if L.L.'s carboplatin dose is ordered as AUC 5 mg/mL × minute, then her dose would be calculated as dose = 5 mg/mL × minute (48 mL/min + 25), which is 365 mg. In contrast, if her renal function were within normal range for estimated creatinine clearance (eg, 100 mL/minute), her carboplatin dose would be 625 mg (~70% higher). Several different methods may be used to estimate renal function, such as the Cockcroft and Gault equation, and the dose calculations will differ according to the method chosen. Usually, the choice of method is institution-specific, because there is no evidence to show that one estimation method is superior to the other. By consistently using the same formula, providers reduce variability in systemic exposure and thus increase the predictability of tolerance to the drug. If the patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectrometry method, then the GFR should be capped to a maximum of 125 mL/minute, because serum creatinine values can be underestimated when they fall below 0.7 mg/mL, as can happen in some patients. The FDA issued this safety alert to avoid

administration of high doses to patients with normal renal function and thus likely avoiding drug-related toxicity.[71]

In conclusion, if L.L.'s tumor had contained wild-type *EGFR* (instead of mutant) and did not overexpress PD-L1, then a platinum-based doublet (ie, cisplatin or carboplatin) with pemetrexed and pembrolizumab would be recommended. She has moderate renal impairment; therefore, an agent such as cisplatin would not be favored because it is associated with a high incidence of renal toxicity. Carboplatin would be a safer choice because the dose would be selected based on her renal function and is associated with a lower incidence of renal toxicity than cisplatin.

Case 98-2, Question 6: While receiving carboplatin with pemetrexed and pembrolizumab, L.L. experienced minor grade diarrhea and skin rash but otherwise tolerated treatment very well without any impact on her daily activities and quality of life. L.L. completed four cycles of chemotherapy, and she achieved a partial response. The plan is to switch to maintenance therapy. What types of side effects should L.L. be monitored for while receiving pembrolizumab maintenance?

In general, therapy with immune checkpoint inhibitors is well tolerated, especially relative to cytotoxic chemotherapy. The immune checkpoint inhibitors used to manage NSCLC block the interaction of programmed death ligands with the programmed death 1 receptor on activated T cells. This enhances the function of T cells allowing for an improved anti-tumor immune response, ultimately leading to decreased tumor growth. However, this ramping up of the immune system can cause a host of immune-related adverse reactions, some of which can be life-threatening. Pharmacists and other health care providers need to be aware of these reactions as well as how to recognize and manage them. Patients also need to be educated on the signs and symptoms of immune-related events so that treatment can be initiated promptly.

The exact incidence of immune-related adverse events is unknown. Events of any severity may occur in as many as 90% of patients, whereas reactions requiring discontinuation of therapy are

estimated to occur in 0.5% to 13% of patients.[72] Immune-mediated adverse reactions may occur in the skin or within organs and organ systems. Dermatologic reactions often occur earliest in the treatment course and can range from mild rash to a life-threatening exfoliative, ulcerated rash. Immune-mediated colitis presents as diarrhea that is graded according to number of stools per day. Liver (immune-mediated hepatitis), lung (immune-mediated pneumonitis), and kidney (immune-mediated nephritis) effects can also occur. Within the endocrine system, hypo- or hyperthyroidism can occur, as well as adrenalitis, hypophysitis, and new-onset type-1 diabetes mellitus. Neurologically, patients may present with immune-mediated encephalitis.[72]

Management of immune-related adverse events will depend on the severity as graded by the Common Terminology for Adverse Events that rates the reaction on a scale of 1 to 5, where 1 is a mild reaction and 5 is death from the adverse event.[73] Detailed information on managing these reactions can be found in the prescribing information for each individual agent. In general, therapy should be held in the event of a grade 2 toxicity. Low-dose corticosteroids (prednisone 0.5–1 mg/kg/day) can be given if the reaction lasts more than 1 week. In addition to interrupting therapy, higher dose corticosteroids (prednisone 1–2 mg/kg/day) should be given for any grade 3 or 4 events. Steroids will be slowly tapered off once the reaction returns to grade 1 or less.[72]

As mentioned earlier, NSCLC is primarily a disease in those older than 60 years. L.L. is 85 years old, and there is concern that patients, particularly older than age 80 years, may not tolerate cytotoxic chemotherapy as well as younger patients do. Hence, elderly patients are often undertreated. However, recent studies suggest that survival benefits are greater in elderly patients who receive doublet therapy versus a single agent.[74] More studies of various regimens are needed that would focus on the treatment of elderly patients, particularly effects on survival, quality of life, and tolerability. Such studies would investigate the best clinical parameters that enable prediction of response and tolerability to therapies, and also the doses associated with the best outcomes.

Because the majority of patients do not harbor actionable genetic variants, cytotoxic chemotherapy with or without immune checkpoint blockade is first line. Therefore, considerations must be given to patient's preferences, comorbidities, and performance status. It is not uncommon for those with advanced age to live alone. Caretakers who could help the patient monitor for and treat adverse effects of chemotherapy (dehydration from diarrhea or vomiting, febrile neutropenia, etc) would be an essential consideration, particularly in this population. Even though L.L. is able to continue treatment at this time, most patients eventually exhibit progressive disease. At this point, the patient would be transitioned to another cytotoxic agent with activity in NSCLC such as docetaxel or a targeted therapy like bevacizumab. An immune checkpoint inhibitor may also be used in this setting if this class of drugs have not already been administered.[75-78]

Small-Cell Lung Cancer

Epidemiology

SCLC accounts for ~13% of all lung cancer histology and affects both sexes in equal distribution. The disease is more highly attributable to smoking than NSCLC. As the number of people who smoke have decreased in the United States since its peak in the 1960s, the incidence of SCLC has also declined.[79] Relative to NSCLC, these tumors generally have a more rapid doubling time, a higher growth fraction, and early development of widespread metastases. As a consequence, SCLC is highly sensitive to chemotherapy and radiotherapy; however, most patients eventually die from recurrent disease.[80,81]

PATHOPHYSIOLOGY

SCLC is a malignancy thought to be derived from neuroendocrine cells in the bronchus and is readily diagnosed on small specimens such as bronchoscopic biopsies, fine-needle aspirates, core biopsies, and cytology. As the name suggests, these tumors consist

of small cells that may be round, oval, or spindle-shaped, with limited volume of cytoplasm, poorly defined cell borders, and finely granular chromatin.[82]

CLINICAL PRESENTATION

Most SCLCs arise centrally and present as a large hilar mass with bulky mediastinal lymphadenopathy that can cause cough and dyspnea. Rarely, patients diagnosed with SCLC present with the primary tumor located in the lung periphery, as can be the case with adenocarcinoma NSCLC. Because of smoking, patients with lung cancer may have had previously existing symptoms such as cough and dyspnea that are related to the presence of other smoking-related diseases such as COPD. Therefore, these symptoms may not prompt patients to seek medical attention quickly.[83]

DIAGNOSIS AND OVERVIEW OF TREATMENT

In general, diagnostic procedures are similar to those used to diagnose NSCLC. Staging of SCLC is used to determine prognosis and treatment. The median overall survival for patients with limited-stage disease ranges from 17 to 26 months and for extensive stage ranges from 3 to 12 months.[83] (These data were collected from an analysis of 14 studies of SCLC, and thus wide ranges for survival are reported.) Surgery (eg, thoracotomy) is appropriate for <5% of patients with early-stage disease, mainly because of the tendency for these tumors to be bulky and to metastasize quickly. Both the AJCC TNM staging system and the Veterans Administration (VA) Lung Study Group staging system are used to stage SCLC. The VA Lung Study Group uses a two-stage system, dividing patients into either limited-stage or extensive-stage disease.[84] Limited-stage disease is defined as disease confined to the ipsilateral hemithorax and encompassed in a tolerable radiation field, and extensive disease is defined as disease beyond the ipsilateral hemithorax including malignant pleural effusions or hematogenous metastases.[85,86] Limited-stage SCLC corresponds to the TNM stages I through III, whereas extensive-stage disease encompasses stage

IV.[87] As discussed subsequently, patients with limited-stage disease are treated with a combined-modality approach (ie, chemotherapy and radiation), and extensive-stage is treated with chemotherapy combined with immunotherapy. Approximately 30% of patients present with limited-stage and the rest with extensive-stage disease.[88]

CLINICAL PRESENTATION AND PATHOPHYSIOLOGY OF SMALL-CELL LUNG CANCER

CASE 98-3

QUESTION 1: M.W. is a 63-year-old female who presented to her primary doctor with heartburn and pain in the right side of her upper abdomen; she also had a feeling of gas in the stomach. In addition, she noticed a 20-pounds (9.07-kg) weight loss within 3 months, although she attributed this to changes in her diet did not present with a cough. There was no shortness of breath. The evaluation with chest radiography demonstrated the presence of a large mass in the right perihilar region with extension to the mediastinum and significant mediastinal adenopathy with narrowing of the trachea and its displacement to the left by the mass. The follow-up PET–CT scan confirmed presence of a large mass and no other areas of abnormality within the abdomen or pelvis. The patient also had a brain MRI that showed no evidence of metastatic disease. After that, the patient had a bronchoscopic evaluation and a biopsy of the mediastinal mass. Pathology came back positive for small-cell lung carcinoma. Having disease only limited to the chest and mediastinum, the patient was diagnosed with limited-stage SCLC. Peripheral blood chemistry, lactate dehydrogenase (LDH), and counts were normal.

What features of M.W.'s disease are suggestive for SCLC?

M.W.'s chief problems were heartburn and pain in the upper right side of her abdomen, not necessarily common symptoms of SCLC. Location of the tumor is a determining factor in specific symptoms that a patient can experience and can serve as an indicator of the invasiveness of the disease. Although M.W. did not present with a cough, her presentation is representative of patients diagnosed with this disease in that the tumor was centrally located with spread to the mediastinum. She also experienced weight loss, and although she attributed this to her diet, it is a symptom experienced by patients

with rapidly growing disease and associated with appetite suppression.

M.W. did not experience all of the symptoms that are frequently found in patients. Fatigue, especially together with decreased physical activity, is a common problem as well as hemoptysis.[89] Owing to the central location of most of these tumors, ~10% of patients can experience superior vena cava syndrome (SVCS). This is a very serious complication and requires immediate medical attention as a result of the growing tumor impinging upon the superior vena cava. This can restrict blood return to the heart, resulting in head and facial swelling.[90,91]

Case 98-3, Question 2: What potential complications might patients such as M.W. experience during the course of their disease?

Patients with SCLC frequently experience paraneoplastic syndromes as a result of their disease, and these often differ from patients who have NSCLC. For example, patients with NSCLC have a higher tendency to develop hypertrophic pulmonary osteoarthropathy and hypercalcemia. On the other hand, patients with SCLC have higher incidence rates for hyponatremia, Cushing syndrome, and neurologic paraneoplastic syndrome. The serum concentrations of antidiuretic hormone are often elevated in SCLC, but few of these cases fulfill the criteria for syndrome of inappropriate antidiuretic hormone secretion (SIADH) and are mostly asymptomatic. In some cases, ectopic production of atrial natriuretic factor contributes to the disorder in sodium homeostasis. Because SCLC is usually responsive to cytotoxic agents, the treatment of choice for hyponatremia is chemotherapy. If further management is needed (ie, if the cancer is nonresponsive to chemotherapy or symptomatic), fluid restriction, intravenous hypertonic saline, and treatment with demeclocycline are options, depending on severity.[1] The serum concentrations of adrenocorticotropic hormone are elevated in approximately half of patients with lung cancer, but Cushing syndrome develops in only 5% of those with SCLC. Both

low serum sodium and Cushing syndrome are poor prognostic indicators for the disease.[92]

Unlike M.W., most patients already have metastatic disease at diagnosis, and the most common sites include bone, liver, adrenal glands, and brain. Patients with hepatic and adrenal lesions do not usually experience symptoms, even if they have elevations of bilirubin, alkaline phosphatase, or hepatic transaminases.[93] In contrast, brain metastases are symptomatic in >90% of cases, and patients can often present with central nervous system complications (eg, seizures) as the first sign of the disease.[1]

CASE 98-3, QUESTION 3: M.W. reads about various treatments for her disease online. What is the utility for each of the four treatment modalities (ie, surgery, radiation, chemotherapy, and immunotherapy) for the treatment of her disease?

TREATMENT MODALITIES FOR SMALL-CELL LUNG CANCER

Surgery

As mentioned, surgery has a very limited role as part of the treatment for patients with SCLC. In general, patients with tumors larger than 3 to 7 cm and presence of any disease in the lymph nodes or distant metastases do not benefit from surgery.[94] The percentage of patients who fit this category is <5%. If surgery is chosen, the procedure usually includes lobectomy with mediastinal nodal dissection and sampling. Thereafter, patients would receive adjuvant radiation and chemotherapy and then prophylactic cranial irradiation as described in the subsequent sections.

Radiation

SCLC is responsive to radiation therapy; therefore, it is useful in treating patients with limited-stage disease. Radiation is usually given as fractionated doses over the course of 3 to 7 weeks, and total dosage targets range between 45 and 70 Gy. The optimal dose and frequency of administration of radiation is still under investigation. Improved radiation techniques deliver optimal doses of radiation to malignant sites while minimizing the impact on normal

tissue. Example techniques include intensity-modulated radiation therapy, image-guided radiation therapy, and PET–CT simulation, among others.[95-98] In addition to their cytotoxic effects, many chemotherapeutic agents also sensitize tumors to radiation. Hence, radiotherapy should start concurrently with chemotherapy, usually at the first or second cycle for limited-stage disease. Because of the high incidence of metastases to the brain (ie, >50% of patients with SCLC), prophylactic cranial irradiation consisting of 25 Gy given for 10 fractions is the standard treatment for patients with limited-stage and extensive-stage disease after completion of initial chemotherapy or chemoradiation and minimal residual systemic disease.[99,100]

Chemotherapy

The proliferative indices for SCLC cells are high and early metastatic spread is common. Therefore, systemic chemotherapy is the treatment of choice for its utility in treating metastases and because it is effective for tumor cells progressing through the cell cycle. In general, most of the regimens are platinum-based doublets with etoposide, as outlined in **Table 98-7**.[97,101,102] Immunotherapy (see next section) is added to platinum-based chemotherapy for patients with extensive-stage disease, while limited-stage patients are managed with platinum-based doublets alone.[103,104] If a response is observed, the benefit is usually seen early in the treatment course. Prolongation of treatment beyond four cycles is usually not recommended for patients with limited-stage disease because the maximum effect of the treatment is achieved in this period. Depending on response and tolerability, patients with extensive-stage disease may receive up to six cycles of primary therapy. Further, toxicity after treatment with these agents accumulates and diminishes the overall benefit to the patient beyond six courses.[105,106] Hence, treatment is usually stopped after four to six cycles and the patient is closely monitored for recurrence of the disease. Patients with extensive-stage disease treated with a platinum-based regimen with immunotherapy will receive immunotherapy maintenance until disease progression (see next section).[103,104]

Table 98-7
Representative Chemotherapy Regimens for Small-Cell Lung Cancer

Regimen	Schedule	Maintenance
Limited-Stage SCLC		
Cisplatin, day 1 Etoposide, days 1–3	Every 21 days for four cycles[97,101]	None
Carboplatin, day 1 Etoposide, days 1–3	Every 21 days for four cycles[102]	None
Extensive-Stage SCLC		
Cisplatin, day 1 Etoposide, days 1–3 Atezolizumab, day 1	Every 21 days for four to six cycles[103]	Atezolizumab, day 1, then every 21 days until disease progression
Carboplatin, day 1 Etoposide, days 1–3 Durvalumab, day 1	Every 21 days for four to six cycles[104]	Durvalumab, day 1, then every 28 days until disease progression
Cisplatin, day 1 Etoposide, days 1–3 Durvalumab, day 1	Every 21 days for four to six cycles[104]	Durvalumab, day 1, then every 28 days until disease progression
Chemotherapy for Relapsed Disease		
Preferred regimens if relapse occurs ≤6 months after first line and PS 0–2: topotecan (oral or IV), lurbinectedin, clinical trial		
Other regimens if relapse occurs ≤6 months after first line and PS 0–2: nivolumab, pembrolizumab, paclitaxel, docetaxel, irinotecan, oral etoposide, temozolomide, cyclophosphamide/doxorubicin/vincristine (CAV), gemcitabine, vinorelbine, or bendamustine		
If relapse occurs >6 months: original regimen		

PS, performance status; SCLC, small-cell lung cancer.

Immunotherapy

Because SCLC has such a proliferation rate, it also has a high mutation rate that makes the tumor cells sensitive to immune-based therapies. The addition of immune checkpoint inhibitors to first-line platinum-based doublets is the standard of care for patients diagnosed with extensive-stage disease. Clinical trials have demonstrated an improvement in progression-free and overall survival with the addition of immunotherapy.[103,104] This represents the first major advance in the management of SCLC in ~20 years.

Subsequent therapy

As mentioned, SCLC has a very high rate of recurrence; therefore, second-line therapy is usually implemented. Several choices of agents are available as shown in Table 98-7, and the selection is dependent on the overall condition of the patient (eg, performance status, toxicity from previous regimen) and the length of time after the first-line regimen was completed. Many of these agents are given as single-agent therapy except for the CAV regimen. In general, a recurrence that occurs within 6 months of treatment with first-line therapy is considered resistant and other agents are selected. If recurrence occurs after 6 months, then the same agents used for the first-line regimen may be used again.

In conclusion, M.W. would not be a good candidate for surgical removal based on the size of the primary tumor. Small-cell lung tumor cells proliferate rapidly; therefore, they are usually responsive to chemotherapy and radiation treatment. This systemic therapy would also be favored because the tumor tends to metastasize quickly and it provides a way to eradicate disease that may have spread.

Case 98-3, Question 4: M.W. begins therapy with intravenous cisplatin on day 1 combined with etoposide on days 1 to 3 given in a 21-day cycle. Four cycles are planned, and she will also receive concurrent radiation. For M.W., what is the goal of therapy? What objective baseline data should be acquired prior to starting treatment? What monitoring parameters should be utilized?

TREATMENT WITH CHEMOTHERAPY AND RADIATION

The goal of therapy for a patient with limited-stage disease such as M.W. would be to increase overall survival and achieve a potential cure. In patients with limited-stage disease, response rates of 70% to 90% are expected after a regimen such as the one M.W. is receiving, whereas response rates of 60% to 70% are expected for patients with extensive-stage disease.[97,102-104] If M.W. had been diagnosed with extensive-stage disease, then the goals would have been to increase overall survival and for palliation of symptoms. Given the complications that can arise as a result of SCLC, treatment could be used to minimize these adverse events. For example, radiotherapy is often used in treating patients with SVCS because it would reduce tumor size and enable resumption of more normal blood flow. Therefore, if a patient has acceptable performance status (eg, 0–2) and minimal to no comorbidities, then treatment such as the one that M.W. is receiving is the best course of action.

A treatment regimen such as cisplatin and etoposide plus radiation is tolerated by most patients, especially because the number of cycles is limited to four. However, administration of these cytotoxic agents is associated with several adverse effects, some of which can be life-threatening. Hence, the clinician is expected to anticipate these events and plan treatment accordingly to minimize complications. The patient is receiving cisplatin, which causes several different adverse effects such as renal insufficiency, sensory neuropathy, and ototoxicity and is considered highly emetogenic (refer to Chapter 94, Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents). Hydration and diuresis are required with cisplatin doses >40 mg/m^2 to maintain a urine output of 100 to 150 mL/hour before administration of the drug. The intravenous fluids are often supplemented with potassium and magnesium to counteract electrolyte wasting from cisplatin. Monitoring of serum creatinine, electrolytes including magnesium and calcium, is performed usually before each infusion of chemotherapeutics. An appropriate antiemetic regimen must be implemented to prevent both acute and delayed nausea and

vomiting. For etoposide, neutropenia is usually the dose-limiting toxicity. Therefore, monitoring of absolute neutrophil count (ANC) is important, and if the counts do not recover before the next dose is due, then delays in treatment or dosage reductions occur. In phase-III clinical trials for this regimen, grade 4 leukopenia occurred in ~35% to 40% of patients, and any grade fever and infection in >20%.[96,97] Therefore, consideration must be given toward the use of colony-stimulating factors to manage this latter event after radiation is completed (refer to Chapter 94, Adverse Effects of Chemotherapy and Targeted Agents).

In conclusion, the goal of M.W.'s therapy is a potential cure. Hydration with fluids supplemented with potassium and magnesium must be initiated prior to cisplatin therapy to prevent cisplatin-induced renal toxicity. During therapy, clinicians must observe for decreased ANC because of etoposide and may need to implement delays in therapy or use of a colony-stimulating factor (eg, granulocyte colony–stimulating factor, filgrastim, or pegfilgrastim). Supportive care such as antiemetics during therapy to prevent or manage cisplatin-associated acute- and delayed-phase nausea and vomiting will also be essential.

CASE 98-3, QUESTION 5: M.W. tolerated therapy very well with mild esophagitis and cough during treatment. She did not experience any vomiting because of aggressive antiemetic use, nor did she exhibit any neuropathy or hearing loss. What adverse conditions that M.W. experienced are associated with her treatment?

Both esophagitis and cough are likely attributable to radiation effects. If esophagitis worsens to grade 3 or more, patients can lose the ability to swallow and may require a feeding tube. During therapy, cough can develop and patients may become concerned that it is a sign of worsening disease. Radiation-induced pneumonitis, acute (in first 3 months) and chronic (4–12 months), can be a frequent cause of the new onset of cough, which can be ameliorated with corticosteroid treatment.

Case 98-3, Question 6: After two cycles of chemotherapy with concurrent radiotherapy, a CT scan indicates a partial response. Therefore, an additional two cycles of cisplatin and etoposide were planned. How is the course of M.W.'s disease likely to proceed?

The chances for long-term survival >5 years are very low, even for the patient with no other comorbidities and limited-stage disease such as M.W. At the completion of chemotherapy, M.W. should be offered therapy with prophylactic cranial irradiation because brain metastases occur in >50% of patients with SCLC. Prophylactic cranial irradiation not only reduces the incidence of metastatic disease but also increases overall survival.[99] Within a year of completing therapy, most patients experience progressive or relapsed disease. The duration of the remission is the single largest predictor of outcome and patients are classified as having either sensitive or refractory disease, depending on length of this duration. Approximately half of those tumors that are deemed sensitive in this setting will respond to second-line therapy.[106] Therefore, most SCLC tumors become resistant to therapy either during first-line or salvage therapy. Patients can also exhibit second primary tumors, especially NSCLC, during the course of the disease.

ACKNOWLEDGMENT

The author acknowledges Mark N. Kirstein, Robert A. Kratzke, and Arkadiusz Z. Dudek for their contributions to the version of this chapter found in previous editions.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and

websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;379:2342–2350. (46)

Cooper WA. Molecular biology of lung cancer. *J Thorac Dis*. 2013;5: S479–S490. (54)

DeVita VT, Rosenberg SA, Lawrence TS, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 11th ed. Wolters Kluwer; 2019. (1)

Horn L, Mansfield AS, Szcze¸sna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220. (103)

Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol*. 2017;8:49. (72)

Langer CJ, Besse B, Gualberto A, Brambilla E, Soria JC. The evolving role of histology in the management of advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28:5311–5320. (42)

Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomized, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17:1497–1508. (51)

Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomized, open-label, controlled, phase 3 trial. *Lancet.* 2019;393:1819–1830. (49)

Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomized, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929–1939. (104)

Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26:3552–3559. (30)

Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125. (59)

The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395–409. (5)

Key Websites

National Cancer Institute. Lung Cancer-Health Professional Version. https://www.cancer.gov/types/lung/hp

American Society of Clinical Oncology. Thoracic Cancer. https://www.asco.org/practice-patients/guidelines/thoracic-cancer

COMPLETE REFERENCES CHAPTER 98 LUNG CANCER

1. DeVita VT, Rosenberg SA, Lawrence TS, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 11th ed. Wolters Kluwer; 2019.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7–30.
3. Li Y, Sheu CC, Ye Y, et al. Genetic variants and risk of lung cancer in never smokers: a genome-wide association study. *Lancet Oncol*. 2010;11:321–330.
4. American Cancer Society. Cancer Facts & Figures 2020. Accessed August 31, 2020. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf
5. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395–409.
6. Rami-Porta R, Bolejack V, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: the new database to inform the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2014;9:1618–1624.
7. Detterbeck FC. The eighth edition TNM sate classification for lung cancer: what does it mean on the main street? *J Thorac Cardiovasc Surg*. 2018;155:356–359.
8. National Lung Screening Trial Research Team; Aberle DR, Adams AM, Berg CD, et al. Baseline characteristics of participants in the randomized national lung screening trial. *J Natl Cancer Inst*. 2011;102:1771–1779.
9. National Lung Screening Trial Research Team; Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: overview and study design. *Radiology*. 2011;258:243–253.
10. Tanner NT, Kanodra NM, Gebregziabher M, et al. The association between smoking abstinence and mortality in the National Lung Screening Trial. *Am J Respir Crit Care Med*. 2016;193:534–541.

11. Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160:330–338.
12. Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ*. 2000;321:323–329.
13. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004;328:1519–1528.
14. Subramanian J, Govindan R. Lung cancer in never smokers: a review. *J Clin Oncol*. 2007;25:561–570.
15. Thorgeirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature*. 2008;452:638–642.
16. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature*. 2008;452:633–637.
17. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet*. 2008;40:616–622.
18. Rafnar T, Sulem P, Besenbacher S, et al. Genome-wide significant association between a sequence variant at 15q15.2 and lung cancer risk. *Cancer Res*. 2011;71:1356–1361.
19. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer. Diagnosis and management of lung cancer 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2013;143(5 suppl):e278S–e313S.
20. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol*. 2013;24:986–992.
21. Perol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol*. 2012;30:3516–3524.
22. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003;21:3016–3024.
23. Pirker R. Adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *Transl Lung Cancer Res*. 2014;3:305.
24. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and

II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol*. 2010;28:29–34.

25. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial [published correction appears in *Lancet Oncol*. 2006;7:797]. *Lancet Oncol*. 2006;7:719–727.
26. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 2004;350:351–360.
27. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 2008;26:5043–5051.
28. Usami N, Yokoi K, Hasegawa Y, et al. Phase II study of carboplatin and gemcitabine as adjuvant chemotherapy in patients with completely resected non-small cell lung cancer: a report from the Central Japan Lung Study Group, CJLSG 0503 trial. *Int J Clin Oncol*. 2019;16:583–587.
29. Zhang L, Ou W, Liu Q, Li N, Liu L, Wang S. Pemetrexed plus carboplatin as adjuvant chemotherapy in patients with curative resected non-squamous non-small cell lung cancer. *Thorac Cancer*. 2014;5:50–56.
30. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26:3552–3559.
31. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet*. 1998;352:257–263.
32. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol*. 2006;24:2998–3006.
33. Macchiarini P, Chapelier AR, Monnet I, et al. Extended operations after induction therapy for stage IIIb (T4) non-small cell lung cancer. *Ann Thorac Surg*. 1994;57:966–973.
34. Rusch VW, Albain KS, Crowley JJ, et al. Neoadjuvant therapy: a novel and effective treatment for stage IIIb non-small cell lung cancer. Southwest Oncology Group. *Ann Thorac Surg*. 1994;58:290–295.
35. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*. 1990;322:494–500.

36. Albain KS, Crowley JJ, Turrisi AT 3rd, et al. Concurrent cisplatin, etoposide and chest radiotherapy in pathologic stage IIIB non-small cell lung cancer: a Southwest Oncology Group, phase II Study, SWOG 9019. *J Clin Oncol*. 2002;20:3454–3460.
37. Curran WJ, Paulus R, Langer CJ, et al. Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011;103:1452–1460.
38. Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B Trial 30407. *J Clin Oncol*. 2011;29:3120–3125.
39. Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. *Lung Cancer*. 2015;87:232–240.
40. Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced non-squamous non–small-cell lung cancer. *J Clin Oncol*. 2016;34:953–962.
41. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformational radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 06174): a randomized, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16:187–199.
42. Langer CJ, Besse B, Gualberto A, Brambilla E, Soria JC. The evolving role of histology in the management of advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28:5311–5320.
43. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22:2184–2191.
44. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet*. 2009;374:1432–1440.
45. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist*. 2009;14:253–263.
46. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342–2350.
47. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell

lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735–742.

48. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371(23):2167–2177.
49. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomized, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819–1830.
50. Chaft JE, Oxnard GR, Sima CS, et al. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. *Clin Cancer Res*. 2011;17(19):6298-6303.
51. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomized, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17:1497–1508.
52. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733–742.
53. Russo A, Franchina T, Ricciardi GR, et al. A decade of EGFR inhibition in EGFR-mutated non small cell lung cancer (NSCLC): old successes and future perspectives. *Oncotarget*. 2015;6:26814–26825.
54. Cooper WA, Lam DC, O'Toole SA, Minna JD. Molecular biology of lung cancer. *J Thorac Dis*. 2013;5:S479–S490.
55. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010;363:1693–1703.
56. Vuong HG, Ho ATN, Altibi AMA, Nakazawa T, Katoh R, Kondo T. Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer—a systematic review and meta-analysis. *Lung Cancer*. 2018;123:76–82.
57. Michels S, Scheel AH, Scheffler M, et al. Clinicopathological characteristics of *RET* rearranged lung cancer in European patients. *J Thorac Oncol*. 2015;11:122–127.
58. Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with *NTRK* gene fusions. *Mod Pathol*. 2019;32:147–153.
59. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(9):911-919.

60. Reck M, et al. Pembrolizumab versus chemotherapy for PD L1 positive non small cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.
61. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
62. Prime Therapeutics. Prime Therapeutics study finds Tagrisso new first-line lung cancer treatment drives ten-fold use, $4 million cost increase. 2019. Accessed October 7, 2020. https://www.primetherapeutics.com/news/prime-therapeutics-study-finds-tagrisso-new-first-line-lung-cancer-treatment-drives-ten-fold-use-4-million-cost-increase/
63. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11:121–128.
64. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327–3334.
65. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomized, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:1454–1466.
66. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19:2240–2247.
67. Mok TSK, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629–640.
68. Ghandi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
69. Paz-Ares L, et al. Pembrolizumab plus chemotherapy for squamous non-small cell lung cancer. *N Engl J Med*. 2018;379:2040-2051.
70. Newell DR, Eeles RA, Gumbrell LA, Boxall FE, Horwich A, Calvert AH. Carboplatin and etoposide pharmacokinetics in patients with testicular teratoma. *Cancer Chemother Pharmacol*. 1989;23:367–372.
71. U.S. Food & Drug Administration. Carboplatin dosing. 2015. Accessed September 18, 2020. https://wayback.archive-it.org/7993/20170113081146/http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm
72. Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol*. 2017;8:49.

73. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). 2020. Accessed October 8, 2020. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
74. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28:2191–2197.
75. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18(10):2095-2103.
76. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673.
77. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004;22(9):1589-1597.
78. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550.
79. Lu T, Yang X, Huang Y, et al. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manag Res*. 2019;11:943–953.
80. Simon G, Ginsberg RJ, Ruckdeschel JC. Small-cell lung cancer. *Chest Surg Clin N Am*. 2001;11:165–188.
81. Simon M, Argiris A, Murren JR, et al. Progress in the therapy of small cell lung cancer. *Crit Rev Oncol Hematol*. 2004;49:119–133.
82. Zakowski, MF. Pathology of small cell carcinoma of the lung. *Semin Oncol*. 2003;30:3-8.
83. Foster NR, Mandrekar SJ, Schild SE, et al. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. *Cancer*. 2009;115:2721–2731.
84. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer—what limits limited disease? *Lung Cancer*. 2002;37:271–276.
85. Kalemkerian GP, Gadgeel SM. Modern staging of small cell lung cancer. *J Natl Compr Canc Netw*. 2013;11:99–104.
86. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the

tumor, node, metastasis classification for lung cancer. *J Thorac Oncol*. 2007;2:1067–1077.

87. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. *Lancet*. 2011;378(9804):1741-1755. doi:10.1016/S0140-6736(11)60165-7
88. Farago AF, Keane FK. Current standards for clinical management of small cell lung cancer. *Transl Lung Cancer Res*. 2018;7:69–79.
89. Hollen PJ, Gralla RJ, Kris MG, Potanovich LM. Quality of life assessment in individuals with lung cancer: testing the Lung Cancer Symptom Scale (LCSS). *Eur J Cancer*. 1993;29(A suppl 1):S51–S58.
90. Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes [published correction appears in *N Engl J Med*. 2008;358:1083]. *N Engl J Med*. 2007;356:1862–1869.
91. Sculier JP, Evans WK, Feld R, et al. Superior vena cava obstruction syndrome in small cell lung cancer. *Cancer*. 1986;57:847–851.
92. Gandhi L, Johnson BE. Paraneoplastic syndromes associated with small cell lung cancer. *J Natl Compr Canc Netw*. 2006;4:631–638.
93. Chute CG, Greenberg ER, Baron J, Korson R, Baker J, Yates J. Presenting conditions of 1539 population-based lung cancer patients by cell type and stage in New Hampshire and Vermont. *Cancer*. 1985;56:2107–2111.
94. Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest*. 1994;106(6 suppl):320S–323S.
95. Bogart JA, Herndon JE 2nd, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys*. 2004;59:460–468.
96. Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2004;59:943–951.
97. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340:265–271.
98. Stinchcombe TE, Gore EM. Limited-stage small cell lung cancer: current chemoradiotherapy treatment paradigms. *Oncologist*. 2010;15:187–195.
99. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357:664–672.
100. Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99–01, EORTC 22003–08004, RTOG 0212, and IFCT 99–01): a randomised clinical trial. *Lancet Oncol*. 2009;10:467–474.

101. Sundstrom S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol*. 2002;20:4665–4672.
102. Skarlos DV, Samantas E, Briassoulis E, et al. Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). *Ann Oncol*. 2001;12:1231–1238.
103. Horn L, Mansfield AS, Szcze¸sna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220–2229.
104. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomized, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929–1939.
105. Giaccone G, Dalesio O, McVie GJ, et al. Maintenance chemotherapy in small-cell lung cancer: long-term results of a randomized trial. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol*. 1993;11:1230–1240.
106. Tjan-Heijnen VC, Wagener DJ, Postmus PE, et al. An analysis of chemotherapy dose and dose-intensity in small-cell lung cancer: lessons to be drawn. *Ann Oncol*. 2002;13:1519–1530.
107. Nakagawa K, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1655-1669.
108. Kawashima Y, et al. Bevacizumab plus erlotinib versus erlotinib alone in Japanese patients with advanced, metastatic, EGFR-mutant non-small-cell lung cancer (NEJ026): overall survival analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Respir Med*. 2022;10:72-82.
109. Peters S, et al. Alectinib versus crizotinib in untreated ALK-positive non-small cell lung cancer. *N Engl J Med*. 2017;377:829-838.
110. Camidge DR, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Eng J Med*. 2018;379:2027-2039.
111. Soria JC, et al. First line ceritinib versus platinum based chemotherapy in advanced ALK rearranged non small cell lung cancer (ASCEND 4): a randomised, open label, phase 3 study. *Lancet*. 2017;389:917-929.
112. Shaw AT, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371:1963-1971.
113. Drilon A, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21:261-270.

114. Lim SM, Kim HR, Lee JS, et al. Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. *J Clin Oncol*. 2017;35(23):2613-2618.
115. Planchard D, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1307-1316.
116. Mazieres J, Cropet C, Montané L, et al. Vemurafenib in non-small-cell lung cancer patients with BRAFV600 and BRAFnonV600 mutations. *Ann Oncol*. 2020;31(2):289-294.
117. Planchard D, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis. *J Thorac Oncol*. 2022;17:103-115.
118. Wolf J, et al; GEOMETRY mono-1 Investigators. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med*. 2020;383:944-957.
119. Drilon A, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med*. 2020;26:47-51.
120. Drilon A, et al. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2020;383:813-824.
121. Gainor JF, et al. Pralsetinib for RET fusion-positive non-small cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol*. 2021;22:959-969.
122. Drilon A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov*. 2013;3:630-635.
123. Yoh K, Seto T, Satouchi M, et al. Final survival results for the LURET phase II study of vandetanib in previously treated patients with RET-rearranged advanced non-small cell lung cancer. *Lung Cancer*. 2021;155:40-45.
124. Drilon A, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378:731-739.
125. Doebele RC, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21:271-282.
126. West H, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924-937.
127. Herbst RS, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383:1328-1339.
128. Paz-Ares L, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22;198-211.

129. Hellmann MD, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020-2031.

99

Colorectal Cancer

Marlo Blazer and Joshua Reardon

CORE PRINCIPLES		CHAPTER CASES
1	Family history, patient-specific factors, and environmental factors are identified as risk factors for colorectal cancer (CRC). Environmental factors could be modified to reduce the risk of CRC.	**Case 99-1 (Question 1)**
2	Early detection of CRC through screening reduces cancer-related mortality. Most patients at average risk of CRC are recommended to begin screening at age 45 years.	**Case 99-1 (Question 2)**
3	Patients may be asymptomatic at diagnosis or have nonspecific symptoms. Carcinoembryonic antigen may be elevated in patients with CRC, but it cannot be used alone for diagnosis.	**Case 99-2 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
4	Adjuvant combination chemotherapy with fluorouracil and oxaliplatin is currently considered the standard of care for patients with stage III CRC after surgery with curative intent.	**Case 99-2 (Questions 2, 3)**
5	All patients diagnosed with localized CRC should undergo routine surveillance visits with their oncologist for a period of 5 years after completion of their definitive therapy.	**Case 99-2 (Question 5)**
6	During the last decade, newer chemotherapy agents (oxaliplatin, irinotecan) and targeted therapies (bevacizumab, ramucirumab, ziv-aflibercept, cetuximab, panitumumab, regorafenib) have increased the overall survival of patients with metastatic CRC. Fluoropyrimidines (fluorouracil or capecitabine) remain the backbone of therapy in the first- and second-line treatment of advanced cancer. The right combination and sequencing of these agents are vital to improving the care of patients with CRC.	**Case 99-3 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
7	Use of specific predictive markers helps maximize the desired outcome in metastatic CRC. Patients with *RAS* mutant tumors do not derive any benefit from anti–epidermal growth factor receptor (EGFR) monoclonal antibody therapy. Tumor sidedness (right- vs left side) further assists in selecting candidates for anti-EGFR therapy in the front-line setting.	**Case 99-3 (Question 4)**
8	Myelosuppression, diarrhea, and peripheral neuropathy are potential dose-limiting toxicities associated with chemotherapy agents used in the treatment of colon and rectal cancers. Prevention strategies, diligent monitoring, and adequate supportive-care measures are vital to effective toxicity management and should be used to maintain patient safety and enhance the quality of life.	**Case 99-2 (Questions 3, 4) Case 99-3 (Question 3)**

CORE PRINCIPLES		CHAPTER CASES
9	Severe, life-threatening adverse effects are uncommon, but potential hazards are associated with targeted CRC therapies, and avoiding their use is warranted in patients at increased risk of experiencing these complications. Prevention and treatment strategies are available for common adverse effects such as hypertension associated with vascular endothelial growth factor therapy or EGFR inhibitor–induced dermatologic toxicity.	**Case 99-3 (Questions 3, 5, 6)**
10	Certain genetic variants of key enzymes involved in the catabolism of fluorouracil and irinotecan are associated with increased toxicity from these agents. The clinical utility of identifying these variants in an effort to avoid or manage these toxicities continues to be elucidated.	**Case 99-3 (Question 2)**

INTRODUCTION

Epidemiology, Etiology, and Pathophysiology

Colorectal cancer (CRC) is the malignant growth of tumor that begins from the inner wall of the colon or rectum. It is the fourth most commonly diagnosed cancer in the United States as well as the fourth leading cause of cancer-related deaths.[1] In 2020, it was estimated that there would be 147,950 new cases of CRC with a

median age at diagnosis of 67 years, and an estimated 53,200 people would die of this disease.[1] During the last two decades, new agents, better predictive markers, and more personalized treatment have enabled improvement in the detection, safety, and survival of patients with CRC. The age-adjusted 5-year relative survival rate in 1980 was 51.4% and is estimated to be 64.6% in 2020 (based on data from SEER 18, years: 2010–2016).[1]

The formation of CRC is a multistep process. It begins with an abnormal growth of tissue known as a polyp (adenoma) originating from the innermost wall of the colon. The process of transformation from a polyp to malignant disease can take up to 10 to 15 years.[2] The vast majority of colon and rectal cancers are classified as adenocarcinomas, meaning that they arise from the glandular tissue responsible for producing the secretions of the gastrointestinal (GI) tract. Approximately two-thirds of these cancers will arise from the colon, and the remainder will form in the rectum. CRC is among the few cancers that can be prevented by the removal of precancerous tissue; therefore, early detection is crucial.

The etiology of CRC is complex, involving patient-specific, environmental, and genetic factors. Of these, age is considered the most important risk because >90% of patients diagnosed are older than 50 years of age.[3] Other patient-specific risk factors are family history of colon cancer, history of previous colonic polyps, and inflammatory bowel disease (ulcerative colitis or Crohn disease). Environmental factors like a diet consisting primarily of red meat, high fat, and low fiber can also increase the risk of CRC, as can a sedentary lifestyle, obesity, excessive alcohol consumption, and long-term smoking.[4,5] Smoking, particularly early in life, has been shown to increase the risk of developing CRC. Patients who smoked more than 12 pack-years of cigarettes before age 30 are at increased risk of recurrence after a diagnosis of stage III colon cancer.[4]

Hereditary syndromes account for 6% to 10% of all CRCs, and in up to 20% of patients diagnosed before age 50.[6] Specific inherited syndromes include hereditary nonpolyposis colon cancer, also known as Lynch syndrome, and familial adenomatous polyposis

(FAP). Although accounting for <1% of all CRC cases, FAP is associated with a lifetime risk of CRC of >90% because of an autosomal dominant germ line mutation causing the development of dozens to thousands of polyps distributed in the colon and rectum, usually beginning in adolescence.[7] Lynch syndrome accounts for 2% to 3% of CRCs.[7] It is an autosomal dominant disorder that also has an early age of onset (age 20–25 years) and is associated with an increased risk of other cancers, such as endometrial cancer, cancers of the urinary tract, small intestine, ovary, stomach, pancreas, biliary tract, brain, and skin. Screening for both of these inherited syndromes begins at an early age (age 10–15 years for FAP and age 20–25 for Lynch syndrome).[6]

Clinical Presentation and Diagnosis

Symptoms associated with the development of colon and rectal cancers are often subtle and can mimic “generalized” symptoms associated with numerous other benign conditions, such as abdominal pain, constipation, diarrhea, bloating, rectal bleeding, and other sudden changes in bowel habits or caliber. Unintentional weight loss, anemia, and weakness may also be present, particularly in advanced stages of the disease. A diagnosis is made once a colonoscopy or sigmoidoscopy is performed, and a biopsy is obtained to confirm the presence of cancer. Additional diagnostic procedures would be performed before initiating treatment, including a computed tomography (CT) scan of the chest, abdomen, and pelvis as well as laboratory collection of blood to obtain a baseline carcinoembryonic antigen (CEA) level. These determine the extent of the disease and provide a means to monitor for recurrence or progression after or on treatment. For cancers of the rectum, an endoscopic ultrasound may also be performed to aid in the preoperative or clinical staging of the tumor. Definitive or pathologic staging for all tumors of the colon and rectum takes place during surgical resection.

Treatment Overview

The therapeutic modalities available to the patient with CRC are similar to those used in other solid tumors. Surgery, radiation, and chemotherapy all have roles in both localized and advanced disease, but how each of these strategies is used, and sequencing, depends on the location and extent of the disease and on the goal of therapy. Stage of disease at diagnosis determines the initial treatment. CRC, like other solid tumors, uses the TNM staging system, but it is unique in that it is the depth of invasion of the primary tumor and not its size that determines the "T" in the TNM staging. Like other solid tumors, the remaining components of this classification system are lymph node involvement (N) and metastatic spread (M). Colon and rectal cancers are staged in the exact same manner; however, rectal tumors lie in closer proximity to the anal sphincter; therefore, the risk of localized treatment failure and of recurrence at the initial site of disease is increased. In general, surgery is used as the primary initial modality for patients with stages I, II, and III disease. It may also be employed in selected patients with metastatic stage IV disease at some point during their treatment course. Radiation is usually reserved for patients with rectal cancer. This chapter will primarily focus on the use of systemic therapy (ie, chemotherapy and targeted therapy) for patients diagnosed with colon and rectal cancer.

Etiology

CASE 99-1

Question 1: O.B., a 35-year-old female, recently learned that her 53-year-old father was diagnosed with colon cancer. O.B. is obese and smokes half a pack of cigarettes per day. She loves eating out and spends most of her evening watching TV at home. O.B. would like to know the risk factors for CRC.

Is there anything she can do to reduce her risk of developing CRC in the future?

O.B. is at an increased risk of developing CRC, given her family history of colon cancer. In addition, she is obese, lives a sedentary lifestyle, and smokes. She eats out, but no information is given about her diet. There are modifiable risk factors, which she could address to lower her risk of developing CRC. O.B. can lose weight through exercise and adopt a high-fiber, low-fat diet. In addition, she can stop smoking, which can help reduce the risk of colorectal as well as other cancers.

Screening

Case 99-1, Question 2: Given O.B.'s family history (her father had a colon cancer diagnosis), she has questions related to preventative actions she can take. Is there a method to detect something "pre-cancerous" (meaning, before it becomes colon cancer)? If so, at what age should O.B. start screening?

Colon and rectal cancers are among the few cancers that can be prevented by the removal of precancerous tissue; therefore, early detection is crucial. As described above, formation of CRCs is a multistep process, and the early precancerous tissue is identifiable and can be removed. CRC is not always asymptomatic, but early detection of CRC through screening has been proven to reduce mortality. A variety of screening methods exist, including fecal screening tests, stool DNA tests (such as Cologuard), digital rectal examination, barium enemas, endoscopy, and CT colonography. Fecal screening tests are designed to detect occult blood in the stool and are relatively inexpensive and noninvasive. There are two main types: the fecal occult blood test (FOBT) and the fecal immunochemical test (FIT). The FOBT has been shown to reduce mortality from CRC by 33%, but the test does require diet restrictions prior to sampling.[8] The FIT uses antibodies to detect hemoglobin or other blood components and, compared to FOBT, has no drug or food interactions. Screening guidelines acknowledge that FIT may be more sensitive than FOBT; however, neither is preferred over the other, possibly because of a lack of mortality data with FIT along with

potential cost/out-of-pocket difference between the two tests. Stool DNA tests include molecular assays for DNA mutation and methylation biomarkers associated with CRCs as well as a non-DNA immunohistochemical assay similar to what is used in FITs. In a clinical study of asymptomatic patients that were at least age 50 years (*n* = 9989), compared to the gold standard of colonoscopy, the sensitivity for detecting CRC was 92.3% with the stool DNA test and 73.8% for FIT; however, the sensitivity for detecting precancerous lesions (that can be removed as a preventative intervention) was 42.4% with the stool DNA test and 23.8% with FIT.[9] Endoscopic screening for CRC includes either flexible sigmoidoscopy or colonoscopy, and both offer the ability to remove polyps and obtain biopsy samples during the procedure. The advantages of sigmoidoscopy are that no sedation is required, a simple preparation (two Fleet enemas) is used, and it can be performed in various settings. Patients may choose flexible sigmoidoscopy over colonoscopy if they do not want to go under sedation or undergo extensive bowel preparation. Sigmoidoscopy has been shown to reduce the incidence of CRC by 33% and mortality because of CRC by 43%.[10] However, flexible sigmoidoscopy allows for examination only of the sigmoid colon and rectum, whereas colonoscopy examines the entire colon. As such, colonoscopy is the most widely accepted screening tool; it has been shown to reduce the incidence of CRC by 77% and is associated with significant risk reduction in both right- and left-sided colon cancer incidences.[11] A relatively new method known as CT colonography provides two- and three-dimensional images of the colon. As with endoscopic procedures, it requires complete bowel preparation to remove feces from the intestine. This screening technique has demonstrated an approximate 80% sensitivity to detect polyps >6 mm in size and 90% sensitivity for polyps >1 cm.[12] However, any cancerous lesion detected will ultimately necessitate an examination by colonoscopy.

CEA is a tumor marker that is detected in the blood and has been evaluated as a screening tool, but its primary use is in monitoring response to treatment and not screening. Healthy smokers are likely to have twice the CEA level compared to nonsmokers. Further,

administration of therapies given for metastatic colon cancer can cause false elevation of CEA without disease progression; so even in monitoring response to treatment, it is only used in conjunction with other modalities.

The American Cancer Society (ACS), the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology have jointly published screening recommendations for the early detection of CRC.[13] According to them, it is a strong recommendation that screening for adults with an average risk of developing CRC should begin at the age of 50 years (**Table 99-1**). Notably, an update by the ACS does now, as a qualifying recommendation, lower the age at which screening should start to 45 years, based on the recent increase in CRC incidence in younger persons, but acknowledges that the benefit gained by screening average-risk persons between ages 45 and 49 years is currently unknown.[3] Patients at average risk of developing CRC will not have genetic predisposition or history of a family member with CRC. In addition, patients in this category will have no history of polyps, previous history of CRC, inflammatory bowel disease, chronic ulcerative colitis, or Crohn colitis.

Table 99-1

American Cancer Society Screening Recommendation for Colorectal Cancer by Age and Risk

Average risk	The ACS recommends that people at average risk[a] of colorectal cancer start regular screening at age 45. Average risk means a person does NOT have any of the following: ▪ A personal history of colorectal cancer or certain types of polyps ▪ A family history of colorectal cancer ▪ A personal history of inflammatory bowel disease (ulcerative colitis or Crohn disease) ▪ A confirmed or suspected hereditary colorectal cancer syndrome, such as familial adenomatous polyposis (FAP) or Lynch syndrome (hereditary nonpolyposis colon cancer or HNPCC)

	A personal history of getting radiation to the abdomen (belly) or pelvic area to treat a prior cancer Options for screening: Stool-based tests ▪ Fecal immunochemical test every year ▪ High-sensitivity, guaiac-based fecal occult blood test every year ▪ Multitarget stool DNA test every 3 years Structural examinations ▪ Colonoscopy every 10 years ▪ CT colonography every 5 years ▪ Flexible sigmoidoscopy every 5 years
Family history	Begin screening at age of 40 or 10 years younger from first-degree relative colorectal cancer diagnosis
Hereditary nonpolyposis colon cancer	Begin screening at age of 20–25 or 10 years younger from first-degree relative colorectal cancer diagnosis
Familial adenomatous polyposis	Begin screening at age of 10–12 years
Inflammatory bowel disease, chronic ulcerative colitis, or Crohn colitis	Begin screening at 8–15 years after diagnosis

[a]Interval of surveillance is shown for negative findings. If polyps are found at screening, interval of surveillance may change based on biopsy results.[8]

Source: American Cancer Society. *American Cancer Society Guideline for Colorectal Cancer Screening*. https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/acs-recommendations.html.

O.B. is a 35-year-old female with a first-degree relative with a diagnosis of colon cancer at age 53. It is less likely she would develop CRC through a hereditary syndrome because her father was diagnosed after age 50. She does, however, have nearly double the lifetime risk of developing CRC because a first-degree relative had CRC.[14] Because O.B.'s father had CRC diagnosed before age 60, she is at increased risk for developing the disease and should consider initiating a colorectal screening program at age 43 (or 10 years earlier than her father was diagnosed at age 53).[12]

Clinical Presentation

CASE 99-2

QUESTION 1: B.R. is a 66-year-old male who was in his usual state of health until recently when he decided to visit his general practitioner owing to progressively worsening GI symptoms, including abdominal cramping and changing bowel habits. He admits to also having some blood in his stool at times, which he attributes to his hemorrhoids. His family history is notable for a paternal uncle with gastric cancer. He occasionally drinks alcohol and has never smoked or used illicit or recreational drugs. On physical examination, he is a well-nourished, well-developed male who is afebrile, alert and oriented, and in no apparent distress. He has no palpable masses and no hepatomegaly, and his abdomen is soft and nontender with normal active bowel sounds. The rest of his review of systems is unremarkable. His performance status is excellent. He does have a history of type 2 diabetes mellitus and hypercholesterolemia, which are both controlled on his current medication regimen. Vital signs and laboratory values obtained are as follows:

Blood pressure, 108/71 mm Hg
Heart rate, 95 beats/minute
Respiratory rate, 18 breaths/minute
White blood cell (WBC) count, 4.8×10^3 cells/μL
Hemoglobin, 11.6 g/dL
Hematocrit, 35.1%
Platelet count, 208×10^3 cells/μL
Total bilirubin, 0.3 mg/dL
Serum creatinine, 0.8 mg/dL
Blood urea nitrogen, 15 mg/dL
Alkaline phosphatase, 61 IU/L
Lactate dehydrogenase, 366 IU/L
Albumin, 4.2 g/dL
Hemoglobin A1C, 6.2%

Are any of the symptoms that B.R. is exhibiting associated with CRC?

Although the symptoms B.R. is describing are nonspecific in nature, the changes in bowel habits in addition to the blood in his stools are symptoms associated with the development of CRC. Given his age, symptoms, and lack of prior cancer screening, additional workup is warranted with one of the screening modalities mentioned earlier in this chapter, preferably colonoscopy.

Chemotherapy for Localized Colorectal Cancer

ADJUVANT THERAPY

Case 99-2, Question 2: After a colonoscopy, B.R. is found to have a moderately differentiated adenocarcinoma of the colon lying 18 cm from the anal verge invading through the muscularis propria with lymphovascular invasion and involvement of 8 of 25 regional lymph nodes. A CT scan of his chest, abdomen, and pelvis shows no evidence of metastatic disease. A baseline CEA level of 8.0 ng/mL (normal range, 0–3.0 ng/mL for nonsmokers and 0–6.0 ng/mL for smokers) is reported. After surgical resection, would B.R. benefit from adjuvant chemotherapy? Which chemotherapy agents or regimen gives B.R. the best chance to avoid a future recurrence?

Historically, fluorouracil (also known as 5-fluorouracil [5-FU]), a fluoropyrimidine, combined with leucovorin was considered the standard chemotherapy for adjuvant treatment of stage III colon cancer based on studies that showed both an improvement in disease-free survival (DFS) and overall survival (OS) over no chemotherapy after surgery.[15] For patients with stage II disease, only those with certain high-risk features, defined by large (T4) tumors that were adherent to or invaded other organs, were obstructive, were poorly differentiated, had venous invasion, or in patients that experienced bowel perforation or where fewer than 10 lymph nodes were examined after curative-intent surgery appeared to gain any benefit from fluorouracil/leucovorin given after surgery.[15,16] Leucovorin stabilizes the binding of an active metabolite of fluorouracil known as fluorodeoxyuridine monophosphate to its intracellular target thymidylate synthase, ultimately enhancing the cytotoxicity of fluorouracil. Fluorouracil is administered primarily in two different ways—as a bolus injection over 3 to 5 minutes, and this is followed by a continuous infusion over 24 to 46 hours (depending on the regimen). Single-agent capecitabine, an oral prodrug of fluorouracil, offers convenient administration and is as effective as intravenous fluorouracil modulated with leucovorin.[17] At present, the combination of fluorouracil and leucovorin or capecitabine monotherapy are the preferred adjuvant regimes for stage III colon

cancer for patients that are older than age 70 because this population does not seem to benefit from the addition of other cytotoxic agents to this fluoropyrimidine backbone.[16,18]

For patients younger than age 70 years, the addition of oxaliplatin, a platinum agent, to the fluoropyrimidine backbone (either capecitabine alone or fluorouracil with leucovorin) is considered the current standard of care in the adjuvant setting for patients with stage III disease, because several landmark trials have shown the addition of oxaliplatin in this population can improve both DFS and OS over fluorouracil and leucovorin alone.[19,20] The increase in DFS and in OS with the addition of oxaliplatin was less pronounced for those patients with stage II (node-negative) disease, and so the use of oxaliplatin in this population is controversial.[16] There were several fluorouracil and oxaliplatin regimens historically used in clinical practice. However, more current practices recommend that when combining fluorouracil with additional cytotoxic agents, the infusional modality be primarily utilized rather than bolus (IV push) regimens to maximize efficacy while minimizing toxicity, although the infusional regimens do still contain a small portion of the entire fluorouracil dose given as an initial bolus injection.

As stated, oxaliplatin may also be combined with capecitabine as the fluoropyrimidine backbone. This is considered equally effective to the combination with fluorouracil modulated with leucovorin, with the main difference seen in toxicity patterns. Capecitabine is given orally typically as a twice-daily dose for 14 days of each 21-day cycle. Often the decision of which fluoropyrimidine to choose is multifactorial owing to the nuances of clinical practice. Potential factors that play a role in the agent chosen can include, but are not limited to, toxicity differences, institutional resources (ambulatory pump availability, etc.), insurance coverage, duration of adjuvant therapy (discussed later), and patient preference. Additional factors that could influence the selection of a capecitabine-based regimen include the presence of renal impairment and relevant drug–drug interactions, particularly concomitant warfarin use. Regimens that are commonly used in the adjuvant treatment of colon cancer are noted in **Table 99-2**.

Table 99-2
Selected Regimens Used in Metastatic or Advanced Colorectal Cancer

Regimen	Dosing
Oxaliplatin-Based Regimens	
mFOLFOX6[a]	▪ Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 ▪ Leucovorin 400 mg/m^2 IV over 2 hours, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion Repeat every 2 weeks
mFOLFOX6 + bevacizumab	▪ Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 ▪ Leucovorin 400 mg/m^2 IV over 2 hours, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion ▪ Bevacizumab 5 mg/kg IV, day 1 Repeat every 2 weeks
mFOLFOX6 + panitumumab[b]	▪ Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 ▪ Leucovorin 400 mg/m^2 IV over 2 hours, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion ▪ Panitumumab 6 mg/kg IV over 60 minutes, day 1 Repeat every 2 weeks

Regimen	Dosing
CapeOX[a,c]	▪ Oxaliplatin 130 mg/m^2 IV over 2 hours, day 1 ▪ Capecitabine 850–1000 mg/m^2 twice daily PO for 14 days Repeat every 3 weeks
CapeOX[c] + bevacizumab	▪ Oxaliplatin 130 mg/m^2 IV over 2 hours, day 1 ▪ Capecitabine 850–1000 mg/m^2 PO twice daily for 14 days ▪ Bevacizumab 7.5 mg/kg IV, day 1 Repeat every 3 weeks
Irinotecan-Based Treatment Regimens	
FOLFIRI	▪ Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1 ▪ Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion Repeat every 2 weeks
FOLFIRI + bevacizumab	▪ Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1 ▪ Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion ▪ Bevacizumab 5 mg/kg IV, day 1 Repeat every 2 weeks

Regimen	Dosing
FOLFIRI + cetuximab	▪ Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1 ▪ Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion ▪ Repeat every 2 weeks ▪ Cetuximab 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 60 minutes weekly ▪ OR ▪ Cetuximab 500 mg/m^2 IV over 2 hours, day 1, every 2 weeks
FOLFIRI + panitumumab[b]	▪ Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1 ▪ Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion ▪ Panitumumab 6 mg/kg IV over 60 minutes, day 1 Repeat every 2 weeks

Regimen	Dosing
FOLFIRI + ziv-aflibercept Currently approved only in the second-line setting	▪ Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1 ▪ Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion ▪ Ziv-aflibercept 4 mg/kg IV over 60 minutes Repeat every 2 weeks
FOLFIRI + ramucirumab Currently approved only in the second-line setting	▪ Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1 ▪ Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 ▪ Fluorouracil 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion ▪ Ramucirumab 8 mg/kg IV over 60 minutes Repeat every 2 weeks
Fluoropyrimidine Treatment Regimens	
Capecitabine[d,e] ± bevacizumab	▪ Capecitabine 850–1250 mg/m^2 PO twice daily, days 1–14 ▪ ± Bevacizumab 7.5 mg/kg IV, day 1 Repeat every 3 weeks
Bolus or infusional 5-FU/leucovorin (Roswell Park regimen)	▪ Leucovorin 500 mg/m^2 IV over 2 hours, days 1, 8, 15, 22, 29, and 36 ▪ Fluorouracil 500 mg/m^2 IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36 Repeat every 8 weeks

Regimen	Dosing
Simplified biweekly infusional 5-FU/leucovorin[d,e] ± bevacizumab	▪ Leucovorin 400 mg/m^2 IV over 2 hours on day 1 ▪ Fluorouracil bolus 400 mg/m^2 IV and then 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion ± Bevacizumab 5 mg/kg IV on day 1
Oxaliplatin- and Irinotecan-Containing Regimens	
FOLFOXIRI ± bevacizumab	▪ Irinotecan 165 mg/m^2 IV day 1 ▪ Oxaliplatin 85 mg/m^2 day 1 ▪ Leucovorin 400 mg/m^2 day 1 ▪ Fluorouracil 1200 mg/m^2/day × 2 days (total 2400 mg/m^2 over 48 hours) continuous infusion starting on day 1 Repeat every 2 weeks ± Bevacizumab 5 mg/kg IV, day 1
Salvage Therapy	
Regorafenib Used postprogression on irinotecan, oxaliplatin, fluorouracil, and an EGFR inhibitor (if *RAS* wild-type)	160 mg PO daily in the morning with a low-fat breakfast on days 1–21. Repeat every 28 days
Trifluridine/tipiracil Used postprogression on irinotecan, oxaliplatin, fluorouracil, and an EGFR inhibitor (if *RAS* wild-type)	35 mg/m^2 orally twice daily, after morning and evening meals, on days 1–5 and days 8–12 of each 28-day cycle Dose is based on trifluridine content of combination tablets BSA was capped at 2.3 m^2 in registrational trial
Immunotherapy in Select Populations	

Regimen	Dosing
Pembrolizumab Used in first or subsequent lines of therapy for metastatic disease for tumors that are MSI-H or dMMR Used in patients with TMB-H disease as defined by ≥10 mutations/megabase postprogression on stand therapies	200 mg IV over 30 minutes every 3 weeks OR 400 mg IV over 30 minutes every 6 weeks
Nivolumab Used postprogression on irinotecan, oxaliplatin, and fluorouracil for tumors that are MSI-H or dMMR	240 mg IV over 30 minutes every 2 weeks OR 480 mg IV over 30 minutes every 4 weeks
Nivolumab + ipilimumab Used postprogression on irinotecan, oxaliplatin, and fluorouracil for tumors that are MSI-H or dMMR	Nivolumab 3 mg/kg IV over 30 minutes Ipilimumab 1 mg/kg IV over 30 minutes Both agents given over 30 minutes each for four doses followed by nivolumab alone: 240 mg IV over 30 minutes every 2 weeks OR 480 mg IV over 30 minutes every 4 weeks
***BRAF* V600E-Mutated Colorectal Cancer**	
Encorafenib + cetuximab	Encorafenib 300 mg PO daily Cetuximab 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 60 minutes weekly OR Cetuximab 500 mg/m^2 IV over 2 hours, day 1, every 2 weeks
Encorafenib + panitumumab[b]	Encorafenib 300 mg PO daily Panitumumab 6 mg/kg IV over 60 minutes, day 1
HER2-Amplified Colorectal Cancer (*RAS/BRAF* Wild-Type)	
Trastuzumab + lapatinib	Trastuzumab 4 mg/kg IV loading dose × 1, followed by 2 mg/kg IV weekly Lapatinib 1000 mg PO daily
Trastuzumab + pertuzumab	Trastuzumab 8 mg/kg IV loading dose × 1, followed by 6 mg/kg IV every 3 weeks Pertuzumab 840 mg IV loading dose × 1, followed by 420 mg IV every 3 weeks

[a]Oxaliplatin combined with either fluorouracil or capecitabine (as in mFOLFOX6 or CAPEOX) for 6 months of therapy is also used in the adjuvant setting (postsurgery) for stage III colon cancer.

[b]For panitumumab, if the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes. Administer doses higher than 1000 mg over 90 minutes.

[c]Phase II data exist for biweekly regimens with oxaliplatin given at 85 mg/m^2 every 2 weeks and capecitabine given on days 1 to 7 and days 15 to 21.

[d]Fluorouracil or capecitabine with or without bevacizumab is an appropriate therapy in a poor performance status patient where concerns of the added toxicity of oxaliplatin or irinotecan outweigh benefit.

[e]Capecitabine alone or fluorouracil with leucovorin alone for 6 months of therapy are also appropriate as adjuvant therapy for patients with high-risk stage II colon cancer or as adjuvant therapy for patients older than age 70 years with stage III colon cancer postsurgery.

Irinotecan in combination with fluorouracil and leucovorin has been evaluated in the adjuvant setting for stage III colon cancer. The use of irinotecan did not produce any benefit in terms of DFS; however, toxicities were increased with the combination of irinotecan and fluorouracil versus fluorouracil alone.[21] Therefore, irinotecan is not an agent used at present time in the adjuvant setting for CRC. In addition, some of the biologics available for the treatment of metastatic colon cancer, such as bevacizumab and cetuximab, have been studied in the adjuvant setting as well. To date, none of the biologics approved for metastatic colon cancer (bevacizumab, ramucirumab, ziv-aflibercept, cetuximab, panitumumab, or regorafenib) are approved or recommended in the adjuvant setting.[19]

DURATION OF ADJUVANT THERAPY

The primary role of chemotherapy in this setting is to reduce the risk of relapse and prolong DFS by eradicating residual, undetectable disease. Historically, for stage III (ie, patients with positive lymph nodes) disease, 6 months of therapy with oxaliplatin combined with either capecitabine or infusional fluorouracil and leucovorin after surgery was the standard of care. However, in an attempt to balance the reduced risk of DFS with the risk of increased toxicity of 6 months of oxaliplatin-based therapy, namely persistent neurotoxicity,

six more recent trials evaluated the ability of 3 months of adjuvant therapy to produce the same results (ie, to be noninferior) to 6 months.[22]

A pooled analysis of these six trials failed to show overall noninferiority; however, the results were strongly affected by the selected treatment (ie, oxaliplatin combined with capecitabine vs oxaliplatin combined with infusional fluorouracil and leucovorin) and risk group (ie, lower risk: patients with smaller tumors [T1–T3] with limited lymph node involvement [N1] vs higher risk: larger tumors [T4] or extensive lymph node involvement [N2]).[22]

In terms of treatment, 3 months of oxaliplatin combined with capecitabine was as effective as 6 months, particularly in the lower-risk subgroup. In patients treated with oxaliplatin combined with infusional fluorouracil and leucovorin, 6 months of therapy resulted in a higher rate of DFS, particularly in the high-risk subgroup.[22]

B.R. has extensive lymph node involvement, and this means he has stage IIIC (ie, higher risk) disease (refer to key website of American Cancer Society guidance for screening, diagnosis, and staging of colorectal cancer), which places him at a high risk of recurrence; therefore, he should receive adjuvant chemotherapy with oxaliplatin and either capecitabine or infusional fluorouracil and leucovorin after surgery. The initial cycle of B.R.'s adjuvant chemotherapy should begin approximately 4 to 6 weeks after his surgery. If oxaliplatin with infusional fluorouracil and leucovorin is used, a total of 6 months of adjuvant therapy should be given. If oxaliplatin plus capecitabine is used, 3 months may be sufficient, but given the high-risk nature of B.R.'s disease, consideration of 6 months of therapy is also warranted.

ADVERSE EFFECTS OF FLUOROURACIL AND OXALIPLATIN

Case 99-2, Question 3: B.R. is scheduled to receive a modified FOLFOX6 (mFOLFOX6) regimen in the adjuvant setting. What potential adverse effects should B.R. be made aware of before receiving this regimen? Are any dose-limiting side effects associated with this therapy? Are there any preventive measures that can be taken to limit the severity of these adverse effects?

The goal of therapy in this setting is a cure; therefore, clinicians typically try to remain aggressive and limit chemotherapy dose reductions or delays while trying to maintain an acceptable toxicity profile. There are a number of chemotherapy-related toxicities that may occur during adjuvant therapy or after its completion.

Toxicities related to fluoropyrimidines include hand-foot syndrome (HFS, also called palmar-plantar erythrodysesthesia), mucositis, diarrhea, hematologic toxicities (neutropenia), photosensitivity, and rarely, cardiac toxicity (vasospastic angina). HFS because of either fluorouracil or capecitabine is managed primarily with supportive-care measures, such as the application of topical moisturizers in addition to temporary withdrawal of fluorouracil-based therapy to allow time to heal (for further discussion of HFS, see Chapter 94, Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents). Once healed or decreased in its severity, fluorouracil-based therapy is often resumed at a reduced dose. The frequency and severity of HFS is increased with capecitabine versus fluorouracil.[23] Severe neutropenia is typically managed with chemotherapy dose reductions or delays, and in some cases, clinicians may use the administration of granulocyte colony–stimulating factors, such as filgrastim or pegfilgrastim, to prevent febrile neutropenia while maintaining dose intensity. The incidence of neutropenia is higher with bolus fluorouracil than with infusional fluorouracil or with capecitabine.[24,25] Severe mucositis is uncommon and is mainly associated with bolus fluorouracil.[21,23] Moderate-to-mild symptoms can also occur, however, with capecitabine or infusional fluorouracil, and these can be managed with supportive-care measures, such as mild narcotic pain medications or mouthwashes that contain a local anesthetic such as lidocaine. Strategies for preventing this complication are also important and include stressing the importance of good oral hygiene and avoidance of harsh substances, which may irritate the oral mucosa or inhibit saliva production, such as alcohol, alcohol-based mouthwashes or rinses, spicy foods, and anticholinergic medications. As is the case with many fluorinated pharmaceutical agents, fluorouracil and capecitabine cause photosensitivity, which may result in mild-to-severe sunburns after

sun exposure. Therefore, during fluoropyrimidine therapy, prolonged exposure to direct sunlight should be avoided, and use of a sun block of SPF-15 or higher during outdoor activities is recommended.

Oxaliplatin is the newest member of the platinum family of antineoplastics, and it offers a different antitumor profile and resistance pattern than cisplatin or carboplatin. Of the three agents, oxaliplatin is highly active against colorectal tumors. Myelosuppression, primarily neutropenia and thrombocytopenia, and neurotoxicity are dose-limiting toxicities associated with its use. Oxaliplatin causes an acute, reversible neuropathy consisting of either paresthesias or dysesthesias, and in some instances muscle spasms. The acute phenomenon is reported to occur in >90% of patients receiving oxaliplatin.[26,27] One manifestation of this phenomenon that is particularly distressing for patients is an involuntary laryngopharyngeal dysesthesia that can create the sensation of an inability to swallow or breathe. Although our understanding of the event is limited, it is known to be triggered by direct contact with anything cold. This sensitivity to cold as well as the aforementioned reactions generally occur within minutes of receiving the infusion and can persist up to 7 days. Avoidance of cold objects, including the eating or drinking of cold foods and beverages, should be emphasized to patients after each dose of oxaliplatin. The use of gloves, socks, and scarves can also be recommended, especially in cold weather. Delayed, cumulative neurotoxicity may also occur, and it is potentially irreversible and occurs in a dose-dependent manner. It initially develops in the distal extremities and slowly progresses in a glove and stocking distribution pattern. It is typically characterized by a persistent sensation of numbness, tingling, or burning in the extremities.

Hypersensitivity reactions have also been observed with oxaliplatin use with a reported incidence of 10% to 25%, and although the appearance of the reaction is arbitrary, in that it can manifest with any dose, the median number of doses reported in those that have reacted is seven to nine.[28] Typically, the symptoms of hypersensitivity occur during the infusion, but delayed reactions are also possible. The severity of these allergic reactions can range

from mild itching or flushing to anaphylaxis. After a reaction, mild cases are often managed through premedication with antihistamines or corticosteroids (eg, diphenhydramine 50 mg IV or orally and either dexamethasone 20 mg or another corticosteroid 15 minutes before oxaliplatin IV) in addition to prolonging the infusion of oxaliplatin. More severe reactions generally warrant discontinuation of the drug; however, there are reports in which desensitization protocols have been used successfully, allowing for continued administration.[29,30] Regardless of what is chosen, this strategy accompanies all subsequent doses of oxaliplatin.

Liver toxicity has also been reported with oxaliplatin and is mainly characterized by sinusoidal injury. This can occur in as high as 51% of patients, although blatant liver failure with oxaliplatin is rare. Splenomegaly has been reported to correlate with sinusoidal liver injury, and this manifestation may also contribute to thrombocytopenia that may last long after oxaliplatin is discontinued.[31]

Because B.R. will receive a combination of fluorouracil and oxaliplatin in the adjuvant setting, the toxicities of these agents should be discussed before initiation of therapy. The toxicity of fluorouracil will vary depending on its dose, route, and schedule of administration. At doses used in the treatment of CRC, bolus administration is associated with more severe neutropenia and mucositis, whereas continuous infusion administration is associated with more severe HFS. Fluorouracil is also associated with photosensitivity, so B.R. should be counseled on the use of SPF-15 or greater sunscreen when outdoors because of the increased risk of sunburn. The main toxicities of oxaliplatin are thrombocytopenia, neuropathy, liver toxicity, and hypersensitivity reactions. To minimize the acute neuropathy after each dose, B.R. should be counseled on the avoidance of cold objects, including the eating or drinking of cold foods and beverages. The use of gloves, socks, and scarves can also be recommended, especially in cold weather. B.R. will also have labs drawn at regular intervals prior to administration of chemotherapy to ensure that his neutrophils and platelets are at a

sufficient level to give chemotherapy and to monitor for changes in liver function that can occur with oxaliplatin.

PERIPHERAL SENSORY NEUROPATHY

Case 99-2, Question 4: After eight treatments of adjuvant therapy, B.R. reports a constant numbness and tingling in his toes bilaterally. It is not interfering with his daily activities but is described as more of a nuisance. Which drug is most likely responsible for this, and what course of action should be taken?

As explained earlier, the severity of peripheral sensory neuropathy (PSN) can worsen with continued doses of oxaliplatin and is not readily reversible; therefore, it is imperative that clinicians and patients work together to minimize its negative impact on various activities of daily living such as being able to button a shirt, walking upstairs or downstairs, or realizing whether one's foot is actually touching the brake pedal as the car approaches a red light. In the hallmark clinical trial in the adjuvant setting, during the 6 months of therapy with oxaliplatin, fluorouracil, and leucovorin, 12.5% of patients reported grade 3 PSN; however, this increased to 24.1% in the 18 months after treatment assessment, indicating that PSN will continue to worsen even after cessation of oxaliplatin.[19] It does appear that over time, PSN can improve off oxaliplatin, as at 4 years postadjuvant treatment grade 1, 2, and 3 PSN was observed in 11.9%, 2.8%, and 0.7%, respectively.[26] In the metastatic setting, a "stop-and-go" approach to limit exposure to oxaliplatin while retaining its antitumor effects has been shown to be beneficial in delaying the development of PSN without adversely affecting the outcomes of progression-free survival (PFS) and OS.[32,33] In this approach, oxaliplatin is withdrawn from therapy in patients with metastatic disease and is reinitiated when disease progression is noted. However, in the adjuvant setting where the goal is cure, the benefits of stopping therapy to decrease the risk of permanent PSN must be weighed against the risk of recurrent disease. Newer trials in the adjuvant setting recommend holding oxaliplatin for a period of 4

weeks in the setting of persistent grade >2 neuropathy (defined as persisting between treatments) and resuming at a dose reduction once PSN resolves to grade 1 or less.[25] Further, permanent discontinuation of oxaliplatin is recommended for grade >2 neuropathy that does not resolve within 4 weeks.[25]

Several small trials have been conducted to evaluate the effectiveness of certain pharmaceutical agents in the management of chemotherapy-induced peripheral neuropathy. These trials have focused on either the prevention or treatment of chemotherapy-induced peripheral neuropathy and as a whole have yielded disappointing results. To date, no agent is recommended as a chemoprotectant for the prevention of oxaliplatin-induced PSN. Duloxetine, an antidepressant, has been studied in a randomized clinical trial and has shown to decrease specifically the pain component experienced by some patients with PSN, including oxaliplatin-induced PSN.[34] In addition, tricyclic antidepressants such as nortriptyline and amitriptyline or an anticonvulsant such as gabapentin and pregabalin could be considered as these agents have proven beneficial and are recommended as initial therapy in other neuropathic pain settings.[35,36] It is important to note that when using adjunctive agents such as these to manage neuropathic pain, doses typically require upward titration after initiation. This strategy enables the clinician to find the dose that provides the greatest benefit. It is important to explain to the patient that these agents may take several weeks before a response is seen and that the indication is for the *pain* associated with PSN—these agents have not been shown to improve numbness or tingling. Symptom relief generally requires continued daily use of these agents on a scheduled basis; however, it is important to consider weaning them with time if neuropathic symptoms either improve or show no improvement despite optimal dosing.

The timing of the symptoms that B.R. is experiencing is indicative of the cumulative toxicity oxaliplatin exerts on peripheral sensory nerves. Because B.R. has completed 8 of a planned 12 cycles of his adjuvant therapy and because his symptoms just started, the reaction would be graded as relatively mild in its severity at this

point. He will likely benefit most from continued administration of oxaliplatin at a reduced dosage with diligent monitoring of his neuropathy.

Microsatellite Instability and BRAF

The ultimate goal of treatment is to individualize therapy based on patient and tumor characteristics. Prognostic markers provide information on disease outcome regardless of the treatment provided. Predictive markers provide information on disease outcome based on the treatment provided. As stated previously, in stage II disease, adjuvant therapy is only offered in those patients with high-risk disease. The definition of "high-risk" stage II disease varies among different national guidelines but, in general, includes T4 tumors, <12 lymph nodes examined at surgery, poorly differentiated histology, perforation, and obstruction.[37] There has been increased interest in looking at microsatellite instability and mutations in *BRAF* to determine what patients with stage II disease would benefit from adjuvant therapy.

Microsatellites are short repeating nucleotide sequences that are under surveillance by the mismatch repair (MMR) system. The MMR system is responsible for repair of errors that occur during DNA synthesis. Tumors are found to have microsatellite instability (MSI) if they have a defect in their MMR system. This defect results in the accumulation of mutations of microsatellites. In a pooled analysis of five trials in patients with stage II and III disease where no adjuvant therapy was given, patients with MSI had a longer DFS than those that were microsatellite stable.[32] In addition, in patients with stage II disease that were MSI, those treated with fluorouracil actually did worse in terms of DFS than those that were only treated with surgery.[38] At this time, it appears that MSI is prognostic in that it appears to convey a DFS benefit in stage II disease. It further appears that fluorouracil/leucovorin alone does not convey any benefit in stage II MSI disease. The benefit of adding oxaliplatin to a

patient with high-risk stage II MSI disease is unknown and currently cannot be recommended based on MSI status alone.

The *BRAF* oncogene is downstream from the EGFR receptor. Mutations in *BRAF* have been associated with a poor prognosis, but to date, they lack any predictive value in both early-stage and in advanced disease.[39,40]

Clinical Surveillance for Recurrence

Case 99-2, Question 5: After completing his treatment, how often and for how long should B.R. be monitored for recurrence of his disease?

Because the majority of recurrences occur within the first 2 to 3 years after completion of adjuvant therapy, consensus guidelines have been published that address the importance of patient follow-up and surveillance after definitive therapy for localized disease.[19,41] Both organizations agree that patients treated definitively for localized disease should be monitored regularly for at least 5 years. Because most recurrences occur relatively soon, surveillance screening should be more frequent for the first 2 years and include a history and physical examination, and CEA level performed every 3 to 6 months for these first 2 years, then semiannually thereafter for up to 5 years. In addition, future recommended imaging includes CT scan of the chest, abdomen, and pelvis performed at least annually for up to 5 years and colonoscopy within a year of surgical resection (or ~1 year from the original colonoscopy) and then repeated again in 3 years if no high-grade adenomas are identified. During the surveillance period, development of a concerning symptom on physical examination, an abnormality on a CT scan, or a rise in CEA level above the upper limit of normal (3 ng/mL for nonsmokers or 6 ng/mL for smokers) would necessitate further evaluation for disease recurrence. After the 5-year surveillance period, an increased risk for recurrent disease remains; therefore, screening for CRC every 5 years in these patients will continue rather than the every 10-year screening recommended for the average-risk population.

B.R. should be monitored regularly for at least 5 years. Should B.R. remain disease-free throughout this 5-year surveillance period, he will be considered cured of his cancer. Because most recurrences occur relatively soon, his surveillance visits will be more frequent for the first 2 years with a history and physical examination and CEA level performed every 3 to 6 months, then semiannually thereafter. He should also have a CT scan of his chest, abdomen, and pelvis performed at least annually for 3 years. Another colonoscopy should be performed within a year of his surgical resection or ~1 year from his original colonoscopy, and then repeated again in 3 years.

Chemotherapy for Metastatic Colorectal Cancer

CASE 99-3

Question 1: K.T. is a 64-year-old male treated ~2 years ago with adjuvant chemotherapy for ascending (right-sided) colon cancer, which he tolerated well outside of peripheral neuropathy and which is lingering still. On a routine surveillance visit, his CT scan shows two discrete liver nodules and a nodule in the left lung that are consistent with metastatic disease. The biopsy of the liver was positive for adenocarcinoma of the colon. K.T. is feeling well and has been asymptomatic. Cytogenetics on the tumor was performed, which revealed wild-type *RAS* and *BRAF* status (no mutations), proficiency in mismatch repair proteins, and no amplification in HER2 expression. K.T.'s CBC and chemistry values were as follows:

WBC count, 7.8 × 10^3 cells/μL
Hemoglobin, 13.2 g/dL
Platelet count, 252 × 10^3 cells/μL
Serum creatinine, 1.1 mg/dL
Blood urea nitrogen, 15 mg/dL
Aspartate aminotransferase, 28 units/L
Alanine aminotransferase, 35 units/L
Alkaline phosphatase, 135 units/L
Total bilirubin, 0.8 mg/dL
K.T.'s CEA concentration was 22 ng/mL.

What is the role of chemotherapy now that K.T. has a metastatic recurrence?

Metastatic CRC affects a substantial number of patients. Approximately 20% of patients have metastatic disease at initial presentation, and ≥50% of patients diagnosed at any stage will eventually develop metastatic disease.[2,42]

Significant treatment advances have been made over the last decade for cases of advanced CRC such that the median OS is currently over 2 years in treated patients.[43-45] Treatments tend to include combination therapy (a fluoropyrimidine plus either irinotecan or oxaliplatin) for good performance status (PS) patients and mono-cytotoxic therapy (fluorouracil or capecitabine or irinotecan) for poor PS patients.[19] Alternatively, subsets of patients may be candidates for noncytotoxic treatments (immunotherapy or targeted therapy) when they are not appropriate candidates for intensive therapy.[46-48] Further, agents directed against the vascular endothelial growth factor (VEGF) (eg, the monoclonal antibodies, bevacizumab and ramucirumab, and the soluble decoy receptor, ziv-aflibercept) or against the epidermal growth factor receptor (EGFR) (cetuximab and panitumumab, both monoclonal antibodies) can be added to the chemotherapy backbone in qualifying patients. Given the number of agents currently available and that we tend to talk in terms of regimens (ie, combining agents together) in the treatment of metastatic CRC, it is imperative to consider which agents have greater synergy and less toxicity when combined and how best to sequence these agents, because patients will most likely remain on some type of therapy throughout their disease course.

Irinotecan has been studied combined with a bolus regimen of fluorouracil and leucovorin (IFL) and an infusional regimen (FOLFIRI) as well as with capecitabine (XELIRI or CAPIRI). In general, both IFL and CAPIRI/XELIRI have fallen out of favor because of exorbitant toxicities and less efficacy than FOLFIRI.[19]

Oxaliplatin, as in the early stages of colon cancer, has been studied with both infusional fluorouracil and leucovorin (FOLFOX) or with capecitabine (XELOX or CAPOX) in the metastatic setting. Both strategies of combining oxaliplatin with a fluoropyrimidine in the metastatic setting are equally efficacious, with again, the main

differences being the toxicity profile of capecitabine versus fluorouracil/leucovorin.[49]

In 2007, a phase 3 study did show that combining both irinotecan and oxaliplatin with fluorouracil and leucovorin to give a cytotoxic triplet regimen (FOLFOXIRI) improved response rates (RRs), PFS, and OS when compared to FOLFIRI; however, this was at the expense of increased toxicity (namely grade 2 peripheral neuropathy and grades 3/4 neutropenia) making it less desirable with the majority of patients in the palliative setting.[50]

The decision to start with an oxaliplatin-based regimen (FOLFOX or XELOX) or an irinotecan-based regimen (FOLFIRI) tends to reflect differences in clinical practice rather than clinical outcomes because sequencing studies and the results of multiple individual studies seem to indicate that both regimens are equally efficacious in the first line.[19,32,51] With the optimal sequencing of these regimens remaining unclear, the decision regarding the choice of combination therapy for first- or second-line therapy is based on prior therapy, quality of life, preexisting toxicities, comorbid conditions, and clinical practice where the patient is first seen. Surgery is typically not an option in extensive metastatic disease.

In the past decade, biologic therapies targeting VEGF (bevacizumab, ziv-aflibercept, and ramucirumab) and EGFR (cetuximab and panitumumab) have been incorporated into the treatment of many cases of metastatic CRC. In addition, regorafenib, a multitargeted, orally administered tyrosine kinase inhibitor (TKI) and trifluridine/tipiracil, an orally administered cytotoxic agent, have both been shown to modestly improve OS over placebo as monotherapy in the salvage setting.

TARGETING VASCULAR ENDOTHELIAL GROWTH FACTOR

Bevacizumab is a humanized monoclonal antibody that binds to the ligand of the VEGF-2 receptor, VEGF-A. The addition to bevacizumab in the first line to oxaliplatin-based regimens FOLFOX or XELOX or irinotecan-based FOLFIRI has been shown to increase PFS versus chemotherapy alone, and OS was also improved,

although this seems more pronounced with FOLFIRI than with oxaliplatin-based regimens.[19,34] Bevacizumab has also been added to the cytotoxic triplet FOLFOXIRI and has shown increased RR and PFS compared to FOLFIRI and bevacizumab though not significantly improving OS.[52] A meta-analysis of two phase 3 and three phase 2 trials confirmed RR and PFS benefit of the triplet plus bevacizumab over doublet plus bevacizumab as well as an OS benefit. Again, this was at the expense of increased toxicities (neutropenia, febrile neutropenia, nausea, mucositis, and diarrhea).[53] Bevacizumab, when continued beyond progression in the second-line setting, with either FOLFOX or FOLFIRI, has shown a modest survival benefit of the addition of 1.4 months versus placebo.[54]

Two newer anti-VEGF agents, ziv-aflibercept and ramucirumab, have also been shown to provide a survival benefit to the chemotherapy backbones with which they were studied. However, the differences in how they were studied is important to note in order to apply them in clinical practice. Ramucirumab, a fully human monoclonal antibody that binds to the extracellular domain of the VEGF-2 receptor, has been shown to increase survival versus placebo by 1.6 months when combined with FOLFIRI in patients that progressed on bevacizumab plus FOLFOX.[55] Ziv-aflibercept, a soluble decoy receptor that targets the ligands VEGF-A, VEGF-B, and placental growth factor (PIGF), has also been shown to increase survival versus placebo when combined with FOLFIRI in the second-line setting after progression on oxaliplatin-based therapy; however, in the patients that had previously received bevacizumab, this benefit was less pronounced (around 0.8 months).[56]

TARGETING THE EPIDERMAL GROWTH FACTOR RECEPTOR

The EGFR receptor is overexpressed in the majority of CRCs, making it an attractive target for therapy. However, 56% to 63% of these tumors will possess a downstream mutation in the *RAS* oncogene, a predictive biomarker for a lack of response to EGFR-targeted therapy.[33,41,43] Therefore, prior to consideration of anti-EGFR therapy in any patient with metastatic colorectal disease,

analysis must be undertaken to determine *RAS* status, with anti-EGFR therapy only being offered to those that are *RAS* wild-type.

Cetuximab is a chimeric monoclonal antibody against the extracellular domain of EGFR. It has been studied in the first line with both FOLFIRI and with oxaliplatin-based therapy and is currently approved in combination with FOLFIRI only in the first line for patients that are *RAS* wild-type.[33,57] It is also active as a single agent or in combination with irinotecan even in patients with irinotecan-refractory malignancies.[58] Panitumumab, a fully human monoclonal antibody also targeting the extracellular domain of EGFR, has been shown in patients that are *RAS* wild-type to improve OS in the first-line setting when combined with FOLFOX and in the second-line setting combined with FOLFIRI in patients that had progressed on an oxaliplatin and bevacizumab-containing regimen.[59,60] It may also be used as monotherapy in patients that have progressed on oxaliplatin- and irinotecan-based therapy. Both panitumumab and cetuximab have been paired with FOLFOXIRI in phase 2 trials. Despite increases in RR, there has not been a proven PFS or survival advantage and currently is not a recommended practice.[61,62] The trials of combining cetuximab or panitumumab with bevacizumab and chemotherapy have resulted in a decrease in PFS and increased toxicity, so this combination should not be used.[63,64] The choice of whether cetuximab or panitumumab is chosen as the anti-EGFR agent is more a matter of local practice and differences in prescribing habits than being data-driven. They have been compared to each other in the salvage setting as monotherapy and are considered equally efficacious, with the main difference being a slightly higher rate of infusion reactions with cetuximab versus panitumumab (13% vs 3%).[65] In addition, there is currently no data to support the use of one of these agents after proven progression on the other agent.

TARGETING VASCULAR ENDOTHELIAL GROWTH FACTOR VERSUS EPIDERMAL GROWTH FACTOR RECEPTOR IN FIRST-LINE TREATMENT

Two randomized, phase 3 trials have compared chemotherapy plus anti-VEGF therapy (bevacizumab) against chemotherapy plus anti-EGFR therapy (cetuximab) in the front-line treatment of patients with metastatic CRC whose tumors were *KRAS* wild-type (incomplete *RAS* testing though the standard of care at the time of the study).[45,66] The results of these two trials were difficult to draw conclusions from; neither showed a difference in PFS, but OS results were discordant. One trial favored anti-EGFR therapy, whereas the other failed to show an OS difference between anti-EGFR therapy versus anti-VEGF therapy, both paired with chemotherapy. A *post hoc* analysis of these two trials evaluated a patient population that are fully *RAS* wild-type and also considered "sidedness" of the initial tumor (ie, whether the primary tumor arose from the right- or left side of the colon).[67,68] Both of these *post hoc* analyses revealed OS benefits with first-line anti-EGFR in left-sided *RAS* wild-type tumors; however, the results were mixed for PFS. Further, anti-EGFR therapy did not confer any benefit to patients that are *RAS* wild-type with right-sided tumors. The results of these analyses led to consensus guidelines recommendations that patients with right-sided colon cancers should not be offered anti-EGFR therapy in the front-line setting regardless of *RAS* mutation status. It is to be noted that at the present time, there is no data showing detriment for anti-EGFR therapy in *RAS* wild-type right-sided tumors beyond the front-line treatment setting. Despite disparate mechanisms of action and toxicity profiles between anti-VEGF and anti-EGFR agents, the trials of combining cetuximab or panitumumab with bevacizumab and chemotherapy have resulted in a decrease in PFS and increased toxicity, so this combination should not be used.[63,64]

K.T. has stage IV colon cancer with metastasis to the liver and lung. The goal of therapy for K.T. is prolongation of survival as well as prevention and palliation of any cancer-related symptoms. At this point, K.T.'s cancer is not curable. K.T. still has a good PS and should receive combination chemotherapy. Standard first-line chemotherapy involves fluoropyrimidine in combination with oxaliplatin or irinotecan. Given lingering peripheral neuropathy from his prior adjuvant therapy, oxaliplatin is less appealing, so FOLFOX

and FOLFOXIRI are less appropriate. Because K.T.'s tumor originated in the ascending colon (right side), adding anti-EGFR monoclonal antibody at this point is not considered a first-line treatment option. Addition of bevacizumab to this regimen will further improve RR and survival of K.T. In this case, K.T. is scheduled to receive the FOLFIRI plus bevacizumab regimen, which is given every 2 weeks. He will receive this chemotherapy regimen until disease progression. The FOLFIRI plus bevacizumab is given as bevacizumab 5 mg/kg IV for 10 to 30 minutes, leucovorin 200 mg/m^2 IV for 2 hours, irinotecan 180 mg/m^2 IV for 90 minutes, and fluorouracil 400 mg/m^2 given as a bolus, which is then followed by 2400 mg/m^2 infused for 46 hours.

IMMUNOTHERAPY FOR MICROSATELLITE INSTABILITY HIGH TUMORS AND TUMOR MUTATION BURDEN-HIGH CANCER

Immunotherapies have broadly made their way into different areas of oncology; initially, patients with CRC did not seem to benefit from these agents, but recently there have been advances in specific subsets of patients.[69-71] Patients who have microsatellite instability high (MSI-H) tumors, as evidenced directly by elevated numbers of microsatellites through polymerase chain reaction (PCR) testing or indirectly by deficiencies in mismatched repair (dMMR) proteins, have RRs to immune checkpoint inhibitors in the range of 30% to 55%, including complete responses in up to 20% of patients.[72-75] Two programmed death receptor-1 (PD-1) blocking antibodies, pembrolizumab and nivolumab are approved for the treatment of patients with metastatic CRC whose tumors are deficient in MMR and has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, given as single agents. The combination of nivolumab and ipilimumab, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)–blocking antibody, has also been approved in this treatment setting. Although single-agent immunotherapy has not been compared to the combination regimen, the RRs appear to be higher with nivolumab plus ipilimumab, but the data has not matured regarding survival benefits and must also be weighed against the

potential for increased autoimmune adverse effects.[75] Pembrolizumab is also approved as a first-line treatment option in patients with dMMR metastatic CRC as it has doubled PFS when compared to traditional chemotherapy.[76,77] However, although promising, patients with mismatch repair deficient CRC represent only a small subset of patients with metastatic disease (~3% of the population vs ~22% of those with stage II colon cancer and ~12% of those with stage III colon cancer).[69] Approval for pembrolizumab and nivolumab with or without ipilimumab was based on tumor RR and durability of response and as a condition of accelerated approval, further studies are required to confirm the clinical benefit of these agents for this indication.

On June 16, 2020, pembrolizumab received an accelerated approval for patients with a high tumor mutation burden (TMB-H) as defined by ≥10 mutations per megabase (mut/Mb).[71] This approval is not colon cancer-specific but for any solid tumor that reached this TMB threshold and has exhausted satisfactory treatment alternatives.[46] Although this is not prevalent, it adds to the potential use of immunotherapy in metastatic CRC treatment. This indication was also approved under accelerated approval based on tumor RR and duration of response and requires confirmatory trials to sustain this approval.

TARGETING BRAF V600E MUTATIONS

BRAF V600E, a serine/threonine-protein kinase oncogene that resides directly downstream of the *RAS* oncogene has been found to be mutated in 5% to 9% of metastatic CRCs and is all but mutually exclusive of RAS mutations (concomitant rate ~0.001%).[40,78,79] *BRAF* V600E mutations are more common in right-sided colon cancers and tend to carry a poor prognosis with limited response to traditional chemotherapy treatments. *BRAF* inhibition alone has failed to produce clinical benefit in CRC because of feedback upregulation of EGFR expression.[80] Dual inhibition of *BRAF* and EGFR has improved RRs and OS when compared against standard of care chemotherapy in the second-line or higher treatment setting.[81] This

chemotherapy-free regimen of encorafenib, a kinase inhibitor of *BRAF*, and cetuximab is Food and Drug Administration (FDA) approved for patients with metastatic CRC that harbor a *BRAF* V600E mutation and have received prior treatment. All patients with metastatic CRC should be tested for *BRAF* V600E mutations.

TARGETING HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 AMPLIFICATIONS

Human epidermal growth factor receptor 2 (HER2) amplifications have been well studied in breast and gastric cancers where its prevalence approximates 20% of these patients.[82,83] Metastatic CRCs can also overexpress HER2, although in only 3% of patients.[47,48] Because of its rarity in CRC, treatments targeting HER2 amplifications are still in their infancy. Two small studies have shown RRs using dual HER2 blockade in the salvage setting at 30% to 32%, whereas approved therapies in this setting have had dismal RRs of ~1.5%.[47,48,84,85] Both studies incorporated trastuzumab, an anti-HER2 monoclonal antibody; one study coupled the oral intracellular TKI of HER2, lapatinib, with trastuzumab and the other trial used pertuzumab, another anti-HER2 monoclonal antibody with an alternate binding site, in combination with trastuzumab. Although the numbers of patients with both HER2 amplifications and *RAS* mutations treated in these studies are small (one study excluded these patients), there appears to be lower RRs to HER2-directed therapy in this population.[48] Despite the lack of FDA approvals for HER2-directed therapies in patients with metastatic CRC with HER2-amplifications, national expert consensus guidelines recommend the use of either HER2-targeting doublet regimen in subsequent lines of therapy as long as the patient does not have a *RAS* or *BRAF* mutation. All patients with metastatic CRC should be tested for HER2-amplifications unless a *RAS* or *BRAF* mutation has already been identified.

Pharmacogenomics of Irinotecan and Fluorouracil

Case 99-3, Question 2: Fourteen days after receiving FOLFIRI plus bevacizumab, K.T. presented to the emergency room with a fever (101.2 °F [38.44 °C]). On further evaluation, K.T. was identified as having febrile neutropenia with a WBC count of 1.2×10^3 cells/μL and an absolute neutrophil count of 650 cells/μL. He was admitted to the hospital for treatment. Is there an accurate method for predicting this outcome in K.T.? Can K.T. continue to receive this therapy?

Recent discoveries in the field of pharmacogenomics have identified several important genetic variations (polymorphisms) that partly account for interpatient variability regarding the tolerability and efficacy of some drug therapies. Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme responsible for the breakdown of fluorouracil to dihydrouracil and eventually to fluorinated β-alanine. The cytotoxic effects of both fluorouracil and capecitabine can only occur after conversion to active metabolites, and the amount of fluorouracil available for this conversion is determined by the extent of its breakdown.[86] DPD is subject to genetic polymorphism, which can lead to a deficiency in its activity.[87] Approximately 3% to 5% of the population will have a partial DPD deficiency, with 0.2% of the population estimated to have complete loss.[88,89] Although several tests are currently available that attempt to identify this deficiency, no single test has the specificity and positive/negative predictive values to accurately predict a true lack of enzyme activity.[90] Further, most studies to date that evaluated testing for DPD deficiency prior to administration of fluorouracil-based therapy only addressed reduced toxicity with dose reduction at initiation of therapy for those patients that were DPD-deficient, but not whether dose reduction was actually necessary.[91-93]

Extreme and potentially life-threatening adverse effects from fluoropyrimidines may be because of genetic polymorphisms such as DPD deficiency, medication overdose (incidental or intentional), as well as many less understood or identifiable causes.[94] These can

manifest as central nervous system toxicity, cardiotoxicity or severe cases of mucositis, diarrhea, or myelosuppression, namely neutropenia.[95] For patients experiencing any of these symptoms deemed severe or life-threatening within 96 hours following fluorouracil or capecitabine administration or with a known or suspected overdose of these agents regardless of symptoms, uridine triacetate was approved for emergency use. Uridine triacetate is an oral prodrug of uridine, which competitively inhibits cell damage and cell death caused by fluorouracil.[94] Based on two open-labeled studies using uridine triacetate to emergently treat fluoropyrimidine overdose or early-onset severe symptoms, a 30-day survival rate of 94% was observed, and this was compared to a historical case-cohort rate of 14% based on literature review database reporting and medical safety agency data.[96] Uridine triacetate is given orally every 6 hours for a total of 20 doses and should be initiated within 96 hours of completing fluoropyrimidine treatment when indicated. The cost of a 20-dose course of uridine triacetate is ~$75,000, so critical selection of appropriate patients is warranted.

Uridine diphosphate glucuronosyltransferase (UGT) enzymes are responsible for the glucuronidation of bilirubin and other endogenous substrates as well as drugs and other toxins.[97] The enzyme UGT1A1 is responsible for the glucuronidation of SN-38, the active metabolite of irinotecan. Reductions in glucuronidation and accumulation of SN-38 are associated with greater toxicity. Of the known genetic polymorphisms of UGT1A1, one polymorphism in particular (UGT1A1*28) has been associated with decreased glucuronidation and therefore prolonged exposure to SN-38.[98,99] Studies have shown that those homozygous for the UGT1A1*28 allele are at an increased risk of neutropenia.[98] Although not consistently observed among trials, severe diarrhea has also been observed with genetic polymorphisms of UGT1A1.[98] However, although the ability to test for this polymorphism is available, the low sensitivity (ie, the ability of this test to correctly identify all patients at risk of severe neutropenia) and the lack of consensus guidelines that outline how to use the results limit its widespread use in clinical practice.[98] However, practitioners should still exercise caution when treating patients with

either a known or suspected deficiency in dihydropyrimidine dehydrogenase or a known polymorphism in UGT1A1.

K.T. should receive empiric antibiotic therapy, and his chemotherapy should be held until both his fever and neutropenia resolve. Because he did not experience febrile neutropenia with his previous adjuvant therapy, it is unlikely he would harbor a DPD deficiency. A dose reduction of fluorouracil could be considered. More importantly, a reduction of his irinotecan dose is warranted before resuming his chemotherapy to reduce the risk of fever and neutropenia with consecutive cycles. The FDA-approved Invader® UGT1A1 molecular assay is commercially available to detect the UGT1A1*28 polymorphism. If it is known that a patient has this polymorphism, an empiric reduction in the dose of irinotecan is recommended; however, its use is not generally recommended for determining reductions of subsequent doses of irinotecan after a toxic event. Uridine triacetate would not be appropriate in this scenario as K.T.'s symptoms are more likely attributable to irinotecan. In addition, he is outside the 96-hour window from treatment, and there is no reason to believe that he received an overdose of fluorouracil, and although his adverse effects are concerning, they can be managed with alternate supportive-care measures.

Adverse Effects of Fluorouracil, Irinotecan, and the Vascular Endothelial Growth Factor Inhibitors

Case 99-3, Question 3: K.T. was discharged from the hospital after 4 days without identification of any infection. K.T. presents to clinic to receive a second cycle of FOLFIRI plus bevacizumab. He is now more cognizant of chemotherapy's adverse effects. He states that after his first cycle of chemotherapy, he also experienced abdominal cramping followed by profuse watery bowel movements for 3 days. He reported periods of nose bleeds lasting up to 2 weeks as well, which he never had in the past. The following laboratory values were also noted:

WBC count, 4.5×10^3 cells/μL
Hemoglobin, 12.5 g/dL

Platelet count, 210,000 cells/μL
Serum creatinine, 1.3 mg/dL

Given K.T.'s recent hospitalization for fever with neutropenia, his doses of both irinotecan and fluorouracil have been reduced for this next cycle. Additionally, what supportive care options should be employed to help K.T. with the diarrhea he reported?

The incidence of irinotecan-induced diarrhea varies depending on the dosing schedule used and its combination with other chemotherapeutic agents. Trials in metastatic CRC have reported rates of grade 3 or 4 diarrhea of 20% to 30% depending on which irinotecan-based regimen is used.[30,100] The active metabolite of irinotecan, SN-38, is capable of producing acute abdominal cramping and diarrhea, which is a cholinergic-mediated process. Administration of subcutaneous or IV atropine at doses typically lower than those used in the cardiac setting is recommended for the treatment of acute diarrhea caused by irinotecan. The occurrence of diarrhea can also be delayed; thus, the use of an oral antidiarrheal is recommended if this occurs. A regimen of oral loperamide 4 mg with the first loose bowel movement, followed by 2 mg every 2 hours during the day or 4 mg every 4 hours in the evening, is recommended until the patient is diarrhea-free for a period of 12 hours.[101] If severe diarrhea symptoms persist for more than 48 hours in spite of these measures, patients should be instructed to seek emergency medical attention. Insufficient hydration resulting from diarrhea may lead to electrolyte losses and life-threatening consequences.

The key adverse effects of fluorouracil, oxaliplatin, and irinotecan are discussed under Case 99-2, Questions 3 and 4, and Case 99-3, Question 2. Although the VEGF inhibitors (bevacizumab, ziv-aflibercept, and ramucirumab) may share some overlapping toxicities with traditional chemotherapy, the majority of their effects are unique. Although cytotoxic agents are associated with myelosuppression, antiangiogenesis agents (ie, VEGF inhibitors) do not target proliferating cells. Hence, they do not cause this type of toxicity. All VEGF inhibitors carry the risk of grade 3 or 4 bleeding events and

gastrointestinal perforation which, although severe and require immediate medical attention, are also relatively rare (>3% and >2% with bevacizumab, respectively).[102] Other adverse events deemed as VEGF inhibitor related are arterial thrombosis, hypertension, proteinuria, and wound-healing complications.[103] Monitoring of blood pressure and the pharmacologic management of diagnosed hypertension while on VEGF inhibitor therapy is essential. In addition, because of the wound-healing complications, the use of VEGF inhibitors should be stopped at least 6 to 8 weeks prior to planned surgery and should not be resumed until the patient has fully healed (at least 4–6 weeks).[104,105] Finally, a rare but serious side effect of posterior reversible encephalopathy syndrome (PRES) has been reported with agents that target VEGF including bevacizumab, requiring immediate medical attention and discontinuation of therapy.[106,107]

The epistaxis K.T. is experiencing with this cycle of chemotherapy may be attributed directly or indirectly to his current regimen. Although fluorouracil and irinotecan may also cause bleeding, this is usually related to their myelosuppressive effects on platelet progenitors. Because K.T. has a platelet count of 210,000 cells/μL on his recent laboratory work, this bleeding is more likely associated with bevacizumab use.

Case 99-3, Question 4: About 10 months into his treatment, K.T. had a CT scan that suggested progression of the liver and lung masses. His prior cytogenetic results showed wild-type *RAS* and no mutation of *BRAF*. K.T. still has lingering peripheral neuropathy. What should be the best second-line treatment option for K.T.'s metastatic disease?

K.T. has not received anti-EGFR monoclonal antibody–based chemotherapy. As tumor tissue analysis revealed that it contains wild-type *RAS* and negative *BRAF* cytogenetics, K.T. may receive benefit from anti-EGFR monoclonal antibodies. Remembering that right-sided colon cancers do not benefit from anti-EGFR therapy in the front line is concerning, but there is no data to show that it fails to work in additional lines of therapy and reintroducing an oxaliplatin-

based regimen would be concerning given his residual peripheral neuropathy. Irinotecan in combination with EGFR antibodies has synergistic activity; therefore, a regimen of irinotecan and anti-EGFR (cetuximab or panitumumab) combination would be a good choice. In many cases, the fluoropyrimidine is continued as well.

Adverse Effects of Epidermal Growth Factor Receptor Inhibitors

DERMATOLOGIC REACTIONS

Case 99-3, Question 5: K.T. will receive the following combination chemotherapy regimen: FOLFIRI (dosed as before with the dose reductions for irinotecan as previously noted because of his episode of febrile neutropenia) and cetuximab at 500 mg/m^2. Each cycle is to be repeated every 2 weeks. What is the most common adverse effect K.T. is likely to experience with his new anti-EGFR therapy? How can this toxicity be minimized?

In addition to diarrhea, dermatologic toxicity related to EGFR therapy occurs in more than 90% patients with metastatic CRC treated with these agents. EGFR skin reactions typically occur within 7 to 10 days of therapy and most often present as a maculopapular rash on the face or upper torso of patients.[108] The rash may cause discomfort and reduce the quality of life. Both cetuximab and panitumumab have recommendations for dose reductions or the withholding of therapy based on rash severity. Collaborative efforts have been made across clinical disciplines to develop treatment strategies for EGFR-induced dermatologic toxicities based on their severity. Strategies for preventing or limiting the severity of EGFR dermatologic toxicities have also been explored, including the use of a daily regimen of skin moisturizer, sunscreen, topical 1% hydrocortisone cream, and doxycycline.[109] In addition to their antimicrobial properties, the tetracycline class of antibiotics possesses anti-inflammatory properties and anti-proliferative effects on lymphocytes, which makes it a reasonable class of agents to consider given the proposed mechanisms involved in EGFR rash

development. Two studies have revealed that the use of either minocycline or doxycycline as preemptive treatment (ie, given prior to the first dose of either cetuximab or panitumumab and continued throughout therapy) can significantly reduce the severity of the rash but not the overall incidence of occurrence.[110,111]

K.T. would most likely develop an EGFR inhibitor rash. A strategy focused on skin moisturization and protection combined with a daily application of hydrocortisone cream and the administration of doxycycline 100 mg twice daily or another tetracycline derivative could also be considered.

INFUSION-RELATED REACTIONS

Case 99-3, Question 6: K.T. comes in for his first dose of cetuximab with FOLFIRI. Within minutes of receiving the initial cetuximab infusion, K.T. becomes hypotensive and begins having difficulty breathing. What measures should be taken as quickly as possible?

The incidence of grade 3 or 4 infusion-related reactions reported in clinical trials is <3.5% with cetuximab and even less for panitumumab.[58,59,78,112] Because cetuximab is a chimeric monoclonal antibody, the higher incidence of reactions is not surprising. Therefore, cetuximab administration requires premedication with diphenhydramine, whereas panitumumab does not. Although the incidence estimate for hypersensitivity is <5%, these reactions may be underestimated, especially in the middle southern region of the United States where a higher incidence has been observed.[113] It is not currently known why there is a greater propensity for severe hypersensitivity reactions in patients in this region of the country.

Because of the severe nature of the reaction experienced by K.T., rechallenging with cetuximab at this point would be contraindicated.

Salvage Therapy in Metastatic Colorectal Cancer

Regorafenib, a multi-kinase inhibitor targeting VEGF, as well as multiple other protein kinases (KIT, RET, BRAF, PDGFR, and FGFR), was approved in the United States for use in metastatic colon cancer. It is currently used as salvage therapy (ie, in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and, if *RAS* wild-type, with an anti-EGFR therapy). Regorafenib has been shown versus placebo to provide a modest survival advantage of 1.4 months in this patient population. The FDA-approved dose of regorafenib is 160 mg (four 40-mg tabs) orally once daily for 3 weeks followed by 7 days off of therapy. However, toxicity and its management are very important, with the most common grade 3 or higher adverse events being HFS, fatigue, diarrhea, hypertension, and rash.[84] Because of significant tolerability issues, most patients cannot tolerate the approved dose, and alternate dosing strategies may be used in clinical practice. A common modification was studied in a phase 2 trial that compared full-dose therapy to weekly-dose escalation starting at 80 mg daily and increasing by 40 mg/day each week up to the approved dose of 160 mg as tolerated in the first cycle.[114] The primary end point of keeping patients on therapy longer with the dose escalation strategy was met, grade 3 adverse effects were generally lower, as well as improvements in PFS and OS were seen in the dose escalation arm, although they did not reach statistical significance. Regorafenib has a half-life of 26 to 28 hours with two active metabolites (M2 and M5) with M5 having a half-life of 48 hours, which, owing to its anti-VEGF properties, is important to consider as the same precautions apply for bleeding risk and wound-healing issues as for the traditional VEGF inhibitors.

Trifluridine, a thymidine-based nucleic acid analog, combined with tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is another oral agent approved in the salvage setting for metastatic colon cancer. Trifluridine is the active cytotoxic agent, and tipiracil prevents the rapid degradation of trifluridine once administered.[115,116] It is administered at a dose of 35 mg/m^2 (based on the trifluridine component) orally once daily on days 1 to 5 and days 8 to 12 of each 28-day cycle. Compared with placebo in the salvage setting, it has

also been shown to convey a modest survival benefit of 1.8 months; however, unlike targeted therapy, trifluridine/tipiracil is cytotoxic and as such has more of the traditional chemotherapy side effects.[85] The main grade 3 or higher toxicities associated with trifluridine/tipiracil were hematologic (ie, neutropenia, anemia, and thrombocytopenia).[85]

CHEMOTHERAPY AND RADIATION FOR EARLY-STAGE RECTAL CANCER

Approximately one-third of newly diagnosed CRCs originate from the rectum.[4] The differentiation between cancers of the colon and rectum lies in their location and their propensity for recurrence at or near the site of origin after treatment. If the location of B.R.'s tumor had been within 12 to 15 cm from the anal verge, he would have been diagnosed with rectal cancer (Case 99-2). The main difference between rectal cancer and colon cancer treatment lies primarily in patients with stage II or stage III disease. Unless contraindicated, radiation therapy is incorporated into the treatment plan of patients with stage II or stage III disease of the rectum. In addition, slightly different surgical techniques are used, and a short course of fluorouracil or capecitabine chemotherapy is administered in combination with the radiation until it is complete. When combined with chemotherapy, radiation can significantly reduce local recurrence rates.[117-119] An area of debate is the timing of both chemoradiotherapy and chemotherapy. Both chemoradiotherapy started before (neoadjuvant) or after surgery (adjuvant) appear to be equally effective, so other issues are considered when choosing one modality over the other. Adjuvant chemoradiotherapy may avoid overtreatment of disease, whereas a neoadjuvant approach of chemoradiotherapy before surgery has the advantage of potentially shrinking the tumor and giving the surgeon a greater chance of obtaining negative margins, perhaps allowing for a less radical

procedure and preservation of the anal sphincter. Taken altogether, national consensus guidelines now recommend preoperative chemoradiotherapy for stage II or III rectal cancer and reserve postoperative chemoradiotherapy for rectal cancers with preoperative stage I disease that were found to be stage II or III after surgery. In addition to chemoradiotherapy, patients with stage II and III rectal cancer should receive additional chemotherapy (FOLFOX or CAPEOX for 4 months) for a total of 6 months perioperative treatment (chemoradiotherapy accounts for 2 months of treatment). Traditionally chemotherapy was given after surgery, although there is an evolving practice of combining preoperative chemotherapy with preoperative chemoradiation for a total neoadjuvant therapy approach referred to as the TNT approach.[120] The hypotheses for using a TNT approach are increasing complete RRs, earlier treatment of micrometastatic disease, and improving the tolerability and completion of chemotherapy. As the TNT approach is emerging, there is also uncertainty as to the preferred order of chemotherapy in relation to chemoradiotherapy. Although it appears there are higher complete RRs prior to surgery when chemoradiotherapy is used first, the data have not matured to draw conclusions on survival outcomes.[121] Currently, it is acceptable to treat stage II and stage III rectal cancers with preoperative chemoradiotherapy in combination with chemotherapy that may be given before or after chemoradiotherapy or after surgical resection.

Another difference between tumors of the rectum and colon is the vascular drainage by the venous system. The colon is drained by the mesenteric veins of the hepatic portal system, whereas more distal portions of the rectum are drained by veins that empty into the inferior vena cava. This plays a role in the initial site of metastatic development for each disease. Although the liver is the most common overall site of CRC metastasis, when compared to the colon, cancers of the distal rectum are more likely to metastasize to the lungs because of the differences in their respective vasculature.

ACKNOWLEDGMENT

The author acknowledges Sachin R. Shah and Julian Hoyt Slade III for their contributions to the version of this chapter found in previous editions.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol.* 2009;27(19):3109–3116. (19)

Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol*. 2019;20(8):1070–1082. doi:10.1016/S1470-2045(19)30272-4. (114)

Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol.* 2013;14:29–37. (54)

Benson AB 3rd, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol.* 2004;22: 2918–2926. (101)

Cremolini C, Antoniotti C, Stein A, et al. Individual patient data meta-analysis of FOLFOXIRI plus bevacizumab versus doublets plus bevacizumab as initial therapy of unresectable metastatic colorectal cancer [published online ahead of print, 2020 Aug 20]. *J Clin Oncol.* 2020;JCO.20.01225. doi:10.1200/JCO.20.01225. (53)

Gammon D, Bhargava P, McCormick MJ. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist.* 2004;9:546–549. (29)

Grothey A. Oxaliplatin-safety profile: neurotoxicity. *Semin Oncol.* 2003;30(4, Suppl 15):5–13. (26)

Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):303–312. (84)

Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch- repair deficiency. *N Engl J Med.* 2015;372(26):2509–2520. doi:10.1056/NEJMoa1500596. (72)

Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin*. 2008;58:130–160. (13)

Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med.* 2015;372:1909–1919. (85)

Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for *HER2*-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2019;20:518–530. doi:10.1016/S1470-2045(18)30904-5. (48)

Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol.* 2013;31(35):4465–4470. (41)

Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability–high metastatic colorectal cancer. *J Clin Oncol*. 2018;36(8):773–779. doi:10.1200/JCO.2017.76.9901. (75)

Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol.* 2017;18(9):1182–1191. doi:10.1016/S1470-2045(17) 30422-9. (74)

Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol.* 2014;15:569–579. (65)

Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, *KRAS* codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2016;17:738–746. doi:10.1016/S1470-2045(16)00150-9. (47)

Tabernero J, Yoshino T, Cohn AL, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated

metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer.* 2014;50:320–331. (56)

Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol.* 2015;16:499–508. (55)

Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol.* 2017;3(2):194–201. doi:10.1001/jamaoncol.2016.3797. (67)

Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal caa randomized GERCOR study. *J Clin Oncol.* 2004;22:229–237. (51)

Tournigand C, André T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol.* 2012;30:3353–3360. (16)

Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with *KRAS* wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA*. 2017;317(23):2392–2401. doi:10.1001/jama.2017.7105. (66)

Key Websites

American Cancer Society. Colorectal Cancer. https://www.cancer.org/cancer/colon-rectal-cancer.html

American Cancer Society guidance for screening, diagnosis, and staging of colorectal cancer: https://www.cancer.org/content/dam/CRC/PDF/Public/8606.00.pdf

American Society of Clinical Oncology Practice Guidelines on Gastrointestinal Cancers. http://www.instituteforquality.org/practice-guidelines

COMPLETE REFERENCES CHAPTER 99 COLORECTAL CANCER

1. Surveillance Epidemiology and End Results. Cancer Stat Facts: Colorectal Cancer. Accessed September 30, 2020. https://seer.cancer.gov/statfacts/html/colorect.html
2. Binefa G, Rodríguez-Moranta F, Teule A, Medina-Hayas M. Colorectal cancer: from prevention to personalized medicine. *World J Gastroenterol*. 2014;20(22):6786–6808.
3. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2018;68(4):250–281. doi:10.3322/caac.21457
4. McCleary NJ, Niedzwiecki D, Hollis D, et al. Impact of smoking on patients with stage III colon cancer: results from Cancer and Leukemia Group B 89803. *Cancer*. 2010;116:957–966.
5. Cancer.Net. *Colorectal cancer-risk factors and prevention*. Acccessed October 12, 2020. https://www.cancer.net/cancer-types/colorectal-cancer/risk-factors-and-prevention
6. Valle L, Vilar E, Tavtigian SV, Stoffel EM. Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. *J Pathol*. 2019;247(5):574–588. doi:10.1002/path.5229
7. Benson AB 3rd et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol*. 2004;22:3408.
8. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med*. 1993;328:1365–1371.
9. A stool DNA test (Cologuard) for colorectal cancer screening. *JAMA*. 2014;312(23):2566. doi:10.1001/jama.2014.15746
10. Ausk KJ, Dominitz JA. Colonoscopy prevents colorectal cancer in both the right and left colon. *Gastroenterology*. 2011;141(1):393–396; discussion 396.
11. Baron TH, Smyrk TC, Rex DK. Recommended intervals between screening and surveillance colonoscopies. *Mayo Clin Proc*. 2013;88(8):854–858.
12. Anderson JC, Shaw RD. Update on colon cancer screening: recent advances and observations in colorectal cancer screening. *Curr Gastroenterol Rep*. 2014;16:403.
13. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin*. 2008;58:130–160.
14. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA. Population-based family history-specific risks for colorectal cancer: a constellation approach. *Gastroenterology*. 2010;138:877–886.

15. Moertel CG et al. Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Dukes' B2 colon cancer. *J Clin Oncol*. 1995;13:2936–2943
16. Tournigand C, André T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol*. 2012;30(27):3353–3360. doi:10.1200/JCO.2012.42.5645
17. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med*. 2005;352(26):2696–2704.
18. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07, including survival and subset analyses. *J Clin Oncol*. 2011;29:3768–3774.
19. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27(19):3109–3116.
20. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol*. 2011;29(11):1465–1471.
21. van Cutsem E, Labianca R, Bodoky G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol*. 2009;27:3117–3125.
22. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med*. 2018;378(13):1177–1188. doi:10.1056/NEJMoa1713709
23. Cassidy J, Clarke S, Díaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol*. 2008;26(12):2006–2012.
24. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938–2947.
25. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med*. 2000;343(13):905–914.
26. Grothey A. Oxaliplatin-safety profile: neurotoxicity. *Semin Oncol*. 2003;30(4, Suppl 15):5–13.
27. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350:2343–2351.

28. Yanai T, Iwasa S, Hashimoto H, et al. Successful rechallenge for oxaliplatin hypersensitivity reactions in patients with metastatic colorectal cancer. *Anticancer Res*. 2012;32:5521–5526.
29. Gammon D, Bhargava P, McCormick MJ. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist*. 2004;9:546–549.
30. Mis L, Fernando NH, Hurwitz HI, Morse MA. Successful desensitization to oxaliplatin. *Ann Pharmacother*. 2005;39:966–999.
31. Overman MJ, Maru DM, Charnsangavej C, et al. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. *J Clin Oncol*. 2010;28(15):2549–2555.
32. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol*. 2006;24:394–400.
33. Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Group. *Lancet*. 2015;385:1843–1852.
34. Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA*. 2013;309:1359–1367.
35. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med*. 2009; 122(10, Suppl):S22.
36. Hershman DL et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013;32:1–30.
37. Akiyoshi T et al. Recent approaches to identifying biomarkers for high-risk stage II colon cancer. *Surg Today*. 2012;42(11)1037–1045.
38. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol*. 2010;28:3219–3226.
39. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol*. 2010;28:466–474.
40. Tol J et al. BRAF mutation in metastatic colorectal cancer. *N Engl J Med*. 2009;361(1):98–99.
41. Meyerhardt JA et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol*. 2013;31:4465-4470.

42. American Cancer Society. Cancer facts & figures 2015. Available at: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/. Accessed June 9, 2015.
43. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C study. *J Clin Oncol*. 2007;25:4779–4786.
44. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023–1034.
45. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. *Lancet Oncol*. 2014;15:1065–1075.
46. Keytruda. Package insert. Merck & Co, Inc; 2020.
47. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, *KRAS* codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:738–746. doi:10.1016/S1470-2045(16)00150-9
48. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for *HER2*-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2019;20:518–530. doi:10.1016/S1470-2045(18)30904-5
49. Saltz L, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008;26:2013–2019.
50. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25(13):1670–1676. doi:10.1200/JCO.2006.09.0928
51. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22:229–237.
52. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol*. 2015;16(13):1306–1315. doi:10.1016/S1470-2045(15)00122-9
53. Cremolini C, Antoniotti C, Stein A, et al. Individual patient data meta-analysis of FOLFOXIRI plus bevacizumab versus doublets plus bevacizumab as initial therapy of unresectable metastatic colorectal cancer [published online ahead

of print, 2020 Aug 20]. *J Clin Oncol*. 2020;JCO2001225. doi:10.1200/JCO.20.01225

54. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. 2013;14:29–37.
55. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16:499–508.
56. Tabernero J, Yoshino T, Cohn AL, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer*. 2014;50:320–331.
57. Maughan TS, Adams, RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet*. 2011;377:2103–2114.
58. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351:337–345.
59. Douillard J-Y, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4691–4705.
60. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;28:4706–4713.
61. Modest DP, Martens UM, Riera-Knorrenschild J, et al. FOLFOXIRI plus panitumumab as first-line treatment of RAS wild-type metastatic colorectal cancer: the randomized, open-label, phase II VOLFI study (AIO KRK0109*). J Clin Oncol.* 2019;37(35):3401–3411. doi:10.1200/JCO.19.01340
62. Cremolini C, Antoniotti C, Lonardi S, et al. Activity and safety of cetuximab plus modified FOLFOXIRI followed by maintenance with cetuximab or bevacizumab for *RAS* and *BRAF* wild-type metastatic colorectal cancer a randomized phase 2 clinical trial. *JAMA Oncol*. 2018;4(4):529–536. doi:10.1001/jamaoncol.2017.5314
63. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol*. 2009;27:672–680.

64. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer [published correction appears in *N Engl J Med*. 2010;363:2573]. *N Engl J Med*. 2009;360:563–572.
65. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014;15:569–579.
66. Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with *KRAS* wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA*. 2017;317(23):2392–2401. doi:10.1001/jama.2017.7105
67. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol*. 2017;3(2):194–201. doi:10.1001/jamaoncol.2016.3797
68. Venook AP, Bottiglieri S, Almhanna K. Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance*). J Clin Oncol*. 2016;34(suppl):abstract 3504.
69. Boland PM, Ma WW. Immunotherapy for colorectal cancer. *Cancers (Basel)*. 2017;9(5):50. doi:10.3390/cancers9050050
70. Golshani G, Zhang Y. Advances in immunotherapy for colorectal cancer: a review. *Therap Adv Gastroenterol*. 2020;13:1–11. doi:10.1177/1756284820917527
71. U.S. Food and Drug Administration. FDA approves pembrolizumab for adults and children with TMB-H solid tumors. Accessed October 5, 2020.https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors
72. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509–2520. doi:10.1056/NEJMoa1500596
73. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357(6349):409–413. doi:10.1126/science.aan6733
74. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18(9):1182–1191. doi:10.1016/S1470-2045(17)30422-9
75. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability–high metastatic colorectal cancer. *J Clin Oncol*. 2018;36(8):773–779. doi:10.1200/JCO.2017.76.9901

76. U.S. Food and Drug Administration. FDA approves pembrolizumab for first-line treatment of MSI-H/dMMR colorectal cancer. Accessed October 12, 2020. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-first-line-treatment-msi-hdmmr-colorectal-cancer
77. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: the phase 3 KEYNOTE-177 Study. *J Clin Oncol*. 2020;38(18_suppl):LBA4–LBA4.
78. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol*. 2011;29(15):2011–2019.
79. Sahin IH, Kazmi SM, Yorio JT, Bhadkamkar NA, Kee BK, Garrett CR. Rare though not mutually exclusive: a report of three cases of concomitant KRAS and BRAF mutation and a review of the literature. *J Cancer*. 2013;4(4):320–322. doi:10.7150/jca.3619
80. Prahallad A, Sun C, Huang S, et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature*. 2012;483(7387):100–103. doi:10.1038/nature10868
81. U.S. Food and Drug Administration. FDA approves encorafenib in combination with cetuximab for metastatic colorectal cancer with a BRAF V600E mutation. Accessed October 12, 2020. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation
82. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* 2013;31(31):3997–4013. doi:10.1200/JCO.2013.50.9984
83. Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: an update. *World J Gastroenterol*. 2016;22(19):4619–4625. doi:10.3748/wjg.v22.i19.4619
84. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303–312.
85. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372:1909–1919.
86. 88. Johnson et al. Importance of dihydropyrimidine dehydrogenase (DPD) deficiency in patients exhibiting toxicity following treatment with 5 fluorouracil. Adv Enzyme Regul. 2001;41:151–157.
87. Diaso R, Johnson MR. Dihydropyrimidine dehydrogenase: its role in 5-fluorouracil clinical toxicity and tumor resistance. *Clin Cancer Res*.

1999:5:2672–2673.
88. Kohne C, et al. FOLFIRI plus cetuximab in patients with liver-limited or non–liver-limited RAS wild-type metastatic disease: a subgroup analysis of the CRYSTAL study. *J Clin Oncol*. 2011;29:abstract 3576.
89. Tuchman et al. Familial pyrimidinemia and pyrimidinuria associated with severe fluorouracil toxicity. *N Engl J Med*. 1985:313:245–249.
90. Boisdron-Celle et al. 5-Fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. *Cancer Lett*. 2009:249:271–282
91. Hohn DC, Melnick J, Stagg R, et al. Biliary sclerosis in patients receiving hepatic arterial infusions of floxuridine. *J Clin Oncol*. 1985;3(1):98–102.
92. Ciccolini J, Mercier C, Evrard A, et al. A rapid and inexpensive method for anticipating severe toxicity to fluorouracil and fluorouracil-based chemotherapy. *Ther Drug Monit*. 2006;28:678–685.
93. Yang CG, Ciccolini J, Blesius A, et al. DPD-based adaptive dosing of 5-FU in patients with head and neck cancer: impact on treatment efficacy and toxicity. *Cancer Chemother Pharmacol*. 2011;67:49–56.
94. Vistogard. Package insert. Wellstat Therapeutics Corporation; 2018.
95. Meulendijks D, van Hasselt JGC, Huitema ADR, et al. Renal function, body surface area, and age are associated with risk of early-onset fluoropyrimidine-associated toxicity in patients treated with capecitabine-based anticancer regimens in daily clinical care. *Eur J Cancer*. 2016;54:120–130. doi:10.1016/j.ejca.2015.10.013
96. Ma WW, Saif MW, El-Rayes BF, et al. Emergency use of uridine triacetate for the prevention and treatment of life-threatening 5-fluorouracil and capecitabine toxicity. *Cancer.* 2017;123(2):345–356. doi:10.1002/cncr.30321
97. Desai AA et al. UGT pharmacogenomics: implications for cancer risk and cancer therapeutics. *Pharmacogenetics*. 2003;13:517
98. Ruzzo A, Graziano F, Loupakis F, et al. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFIRI chemotherapy. *Pharmacogenomics J*. 2008;8:278–288.
99. Palomaki G, Bradley LA, Douglas MP, Kolor K, Dotson WD. Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review. *Genet Med*. 2009;11(1):21–34.
100. Douillard JY et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial [published correction appears in Lancet. 2000;355:1372]. *Lancet*. 2000;355:1041
101. Benson AB 3rd et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol*. 2004;22:2918–2926
102. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic

colorectal cancer: results from a large observational cohort study (BRiTE). *J Clin Oncol*. 2008;26:5326–5334.
103. Saif MW. Anti-VEGF agents in metastatic colorectal cancer (mCRC): are they all alike? *Cancer Manag Res*. 2013;5:103–115.
104. Ellis LM, Curley SA, Grothey A. Surgical resection after downsizing of colorectal liver metastasis in the era of bevacizumab. *J Clin Oncol*. 2015;23(22):4853–4855.
105. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol*. 2005;91:173–180.
106. Seet RCS, Rabinstein AA. Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment. *Q J Med*. 2012;105:69–75.
107. Tlemsani C, Mir O, Boudou-Rouquette P, et al. Posterior reversible encephalopathy syndrome induced by anti-VEGF agents. *Target Oncol*. 2011;6:253–258.
108. Jean GW, Shah SR. Epidermal growth factor receptor monoclonal antibodies for the treatment of metastatic colorectal cancer. *Pharmacotherapy*. 2008;28:742.
109. Lacouture ME et al. The SERIES clinic: an interdisciplinary approach to the management of toxicities of EGFR inhibitors. *J Support Oncol*. 2006;4:236.
110. Scope A, Agero AL, Dusza SW, et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol*. 2007;25(34):5390–5396.
111. Lacouture ME et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010:abstract 291
112. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoroprimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26(14):2311–2319.
113. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol*. 2007;25:3644–3648.
114. Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol*. 2019;20(8):1070–1082. doi:10.1016/S1470-2045(19)30272-4
115. Tanaka N, Sakamoto K, Okabe H, et al. Repeated oral dosing of TAS-102 confers high trifluridine incorporation into DNA and sustained antitumor activity in mouse models. *Oncol Rep*. 2014;32:2319–2326.

116. Fukushima M, Suzuki N, Emura T, et al. Structure and activity of specific inhibitors of thymidine phosphorylase to potentiate the function of antitumor 2,-deoxyribonucleosides. *Biochem Pharmacol*. 2000;59:1227–1236.
117. Bosset JF et al. Chemotherapy with preoperative radiotherapy in rectal cancer [published correction appears in N Engl J Med. 2007;357:728]. *N Engl J Med*. 2006;355:1114.
118. Sauer R et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731.
119. Smalley SR, Benedetti JK, Williamson SK, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. *J Clin Oncol*. 2006;24:3542–3547.
120. Perez K, Safran H, Sikov W, et al. Complete neoadjuvant treatment for rectal cancer: the brown university oncology group CONTRE study. *Am J Clin Oncol*. 2017;40(3):283–287.
121. Fokas E, Allgäuer M, Polat B, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. *J Clin Oncol.* 2019;37(34):3212–3222. doi:10.1200/JCO.19.00308

100

Prostate Cancer

Marina D. Kaymakcalan and Christy S. Harris

CORE PRINCIPLES		CHAPTER CASES
1	Risk factors for the development of prostate cancer include age, family history, and ethnicity.	**Case 100-1 (Questions 1, 2), Figures 100-1, 100-2**
2	Screening by means of prostate-specific antigen (PSA) testing with or without a digital rectal exam allows for early identification of prostate cancer. However, it is acknowledged that prostate cancer has been overdiagnosed in many males.	**Case 100-1 (Question 3) Case 100-2 (Question 1), Table 100-1**
3	The PSA, grade group, and tumor stage can determine the aggressiveness of the prostate cancer. They are considered prognostic factors for the risk of recurrence.	**Case 100-2 (Questions 2, 3), Table 100-2, Figure 100-3**

CORE PRINCIPLES		CHAPTER CASES
4	Most prostate cancers are slow growing, and some males may not ever develop symptoms of disease. Therefore, observation and active surveillance are options for certain males with early-stage disease and shorter life expectancies.	**Case 100-2 (Question 4)**
5	Treatment of localized disease includes surgery, radiation, and/or androgen deprivation therapy (ADT). ADT is first-line treatment for advanced prostate cancers. It lowers testosterone in the body to a castrate level of ≤50 ng/mL. This can be accomplished through surgical (orchiectomy) or chemical (gonadotropin-releasing hormone analog) means.	**Case100-2 (Question 5) Case 100-3 (Questions 1, 2), Table 100-3, Figure 100-4**
6	Castration-resistant prostate cancer (CRPC) occurs when the cancer has acquired a mechanism of resistance in the presence of hormonal therapy and is no longer responding to ADT alone.	**Case 100-3 (Question 3)**
7	Cytotoxic chemotherapy, hormonal therapy, immunotherapy, androgen-directed therapy, or targeted therapy may be used in metastatic disease. Metastases often occur in the bone, requiring therapy to decrease skeletal-related events.	**Case 100-4 (Questions 1, 2)**

CORE PRINCIPLES		CHAPTER CASES
8	Complications of prostate cancer include urinary and sexual issues, but may not be a problem until the disease is advanced. Adverse effects of therapy include cardiovascular and metabolic issues.	**Case 100-5 (Question 1) Case 100-2 (Question 5) Case 100-6 (Question 1)**
9	Prevention of prostate cancer with finasteride or dutasteride has been studied, and may be an option for select males with high risk.	**Case 100-7 (Question 1)**

INTRODUCTION

Prostate adenocarcinoma is the most common malignancy in American males and is the second leading cause of cancer death in males in the United States. It is a disease occurring mainly in older males, with the average age of diagnosis being 66 years.[1] The incidence of prostate cancer is estimated to be 248,530 cases with 34,130 deaths in 2021, which correlates to 1 chance in 8 of eventually being diagnosed with prostate cancer and about 1 chance in 41 of eventually dying of it.[2] Progress in treatment and increased public awareness has improved the overall 5-year relative survival to 97.8%.[1] Because of the widespread use of screening, prostate cancer is being found in earlier stages, which allows for the possibility of an earlier treatment that is less invasive with fewer adverse effects. Ninety percent of patients are diagnosed in the local or regional stage of disease and have a 5-year survival of nearly 100%. Patients initially diagnosed with metastatic disease only have a 5-year survival of 31%.[1]

Guidelines that are designed to screen males to detect significant cancers while trying to avoid the harm of overdetection and overtreatment of inconsequential disease are available (**Table 100-1**).

Table 100-1
Prostate Cancer Screening Guidelines for Average and Elevated Risk Patients

	Average Risk	Elevated Risk
American Cancer Society[21]	Informed and shared decision-making beginning at age 50 If PSA <2.5 ng/mL, repeat every 2 years. If PSA ≥2.5 ng/mL, repeat annually. <10-year life expectancy: If asymptomatic, offer no screening.	Higher risk (African American, first-degree relative diagnosed before age 65): informed and shared decision-making beginning at age 45 Appreciably higher risk (multiple first-degree relatives diagnosed before age 65): informed and shared decision-making beginning at age 40 <10-year life expectancy: If asymptomatic, offer no screening.
American Urological Association[22]	Age 55–69: shared decision-making; screening every 2 or more years Age ≥70 or life expectancy <10–15 years: no screening recommended	High risk (African American or family history) Age ≤55: individualized decision
U.S. Preventive Services Task Force[23]	Age 55–69: The decision of whether to undergo screening or not should be individualized. Age ≥70: no screening recommended	

DRE can be considered, particularly in patients with an elevated PSA, as an adjunct to PSA for screening. However, it should never be used as a stand-alone test.

DRE, digital rectal exam; PSA, prostate-specific antigen.

PATHOPHYSIOLOGY

The prostate is a walnut-shaped gland that sits directly below the bladder and is anterior to the rectum, with the urethra running through the center. This location gives rise to many of the urinary, rectal, and sexual symptoms that males may experience in advanced cancer. The prostate consists of lobular glands that produce the fluid that protects and nourishes the sperm cells within the semen. This fluid is also rich in prostate-specific antigen (PSA), a glycoprotein that enhances sperm motility.[3] Cells within the prostate convert testosterone into the more potent dihydrotestosterone (DHT) by the enzyme 5-α-reductase, which stimulates growth of the cells within the prostate. Cancer can often be found confined within the capsule of the prostate if discovered early or may extend out of the capsule into the surrounding seminal vesicles and bladder neck. Eventually, systemic spread can occur via the lymphatics to involve the bone, lung, or liver.[4]

CLINICAL PRESENTATION AND DIAGNOSIS

Because of the ability to screen for prostate cancer for early identification and because some prostate cancers are slow growing, symptoms are rarely present at the time of diagnosis. Symptoms usually manifest after the cancer has spread beyond the prostate. At that point, the most common sign in males age older than 50 years is bladder outlet obstruction, including hesitancy, nocturia, incomplete emptying, and diminished urinary stream. In metastatic disease, bone pain, anemia, or pancytopenia may be present.[4]

The use of routine serum PSA testing in males at risk for prostate cancer allows for early detection and diagnosis of prostate cancer, although rises in the serum PSA do not automatically indicate cancer. Although PSA is highly specific to the prostate, it is not specific to cancer, with an overall sensitivity of ~21% to 68%.[5]

Normal PSA levels in the blood are generally considered to be <4 ng/mL, but begin to rise in males as they age, often in the setting of benign prostatic hypertrophy (BPH). Median PSA levels are 0.7 ng/mL in ages 40 to 49 years and 0.9 ng/mL in ages 50 to 59 years.[6] Factors that can falsely elevate PSA levels are inflammation of the prostate, urinary retention, prostatic infection, ejaculation, or trauma.

Certain medications and supplements can affect PSA levels, which warrant a careful review of a patient's medication history. The 5-α-reductase inhibitors can cause a decrease in the serum PSA also lower PSA levels.[9] by up to 50%.[7,8] Some herbal supplements, such as lycopene and soy, may also lower PSA levels.[9] Males with PSA levels of 4 to 10 ng/mL have a 1 in 4 chance of having prostate cancer. If the level increases >10 ng/mL, there is a >50% risk of a prostate cancer diagnosis.[10] Although the use of serum PSA levels is the optimal tool for screening, PSA alone may not be adequate for screening and diagnosis because up to 15% of men with prostate cancer do not produce PSA elevations that would typically prompt a biopsy.[11] There are several adjunctive clinical, laboratory, and imaging tests that have been developed to further define a patient's risk or likelihood of prostate cancer and to guide the decision for prostate biopsy. A digital rectal exam (DRE) may be performed in conjunction with the PSA level during prostate cancer screening. The placement of the prostate directly in front of the rectum allows the practitioner to feel the outside of the prostate, which should be smooth without any nodules, indurations, or asymmetry felt, which might be suspicious for cancer. Magnetic resonance imaging (MRI) can be used to better select patients who may need a biopsy and can also be used during a biopsy to help target areas of the prostate with clinically significant disease.[12] PSA derivatives and other tests exist as an adjunct to serum PSA testing to potentially improve specificity of prostate cancer detection and decrease unnecessary biopsies.

To definitively diagnose prostate cancer, transrectal ultrasound (TRUS)-guided needle biopsy is the standard approach. It is important to obtain ≥10 core biopsies in a single setting because differences in pathology can be seen within different cores.

Treatment will be decided by the extent and aggressiveness of the disease along with the overall health and life expectancy of the patient. Staging of prostate cancer determines the extent of the disease using the TNM (T, tumor size, N, node status, and M, sites of metastases) classification from the American Joint Committee on Cancer (AJCC), although clinically it is usually referred to as localized, locally advanced, regional, and metastatic disease. Aggressiveness is determined by the grade and rate of growth of the cancer cells[4] (**Table 100-2**).

Table 100-2

Risk Group Classification for Clinically Localized Prostate Cancer

Low risk	PSA <10 ng/mL AND Grade Group 1 AND clinical stage T1-T2a
Intermediate risk	PSA 10 to <20 ng/mL OR Grade Group 2-3 OR clinical stage T2b-c ▪ Favorable: Grade Group 1 with PSA 10 to <20 ng/mL or clinical stage T2b-c and <50%* biopsy cores positive OR Grade Group 2 with PSA <10 ng/mL and clinical stage T1-2a and <50% biopsy cores positive ▪ Unfavorable: Grade Group 1 with PSA 10 to <20 ng/mL and clinical stage T2b-c OR Grade Group 2 with PSA 10 to <20 ng/mL and/or clinical stage T2b-c and/or ≥50%* biopsy cores positive OR Grade Group 3 with PSA <20 ng/mL
High risk	PSA ≥20 ng/mL OR Grade Group 4-5 OR clinical stage T3

*Percent biopsy cores positive is the total number of cores containing cancer divided by total number of cores obtained x 100. This is not the percentage of cancer within a positive core. Regarding assessment of the percent biopsy cores positive for risk stratification, the Panel acknowledges that with the increasing use of pre-biopsy magnetic resonance imaging (MRI) and subsequent targeted biopsies, multiple cores may be obtained from a targeted lesion. Multiple cores from the same lesion should be considered as a single core (ie, for the calculation of percentage cores positive in risk assessment). If all cores are negative, that is considered a single negative core. If one or more cores from the same lesion is positive, that is considered a single positive core, with the highest Gleason score used for risk stratification.

Source: Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, Part I: Introduction, Risk Assessment, Staging, and Risk-Based Management. *J Urol*. 2022;208(1):10-18.

OVERVIEW OF TREATMENT

Treatment modalities of prostate cancer can include surgical removal of the prostate, radiation therapy, hormonal therapy, and other systemic anticancer therapies. Because prostate cancer is fueled primarily by DHT, hormonal therapy will comprise the mainstay of treatment. Only in the advanced setting will cytotoxic chemotherapy and other anticancer therapies be utilized. As well, the option to simply observe the patient is an alternative in certain situations. Prostate cancer can be a very slow-growing disease in certain patients; so with proper selection, these patients may be monitored with no treatment.

For patients diagnosed with cancer confined to the prostate, removal of the prostate, prostatectomy, or radiation to the prostate are the primary treatment options for definitive local therapy. Radiation therapies most commonly used in practice include external beam and brachytherapy. Brachytherapy consists of small pellets of radioactive material that can be placed into the prostate in small-volume disease. These treatments can provide an opportunity for cure in patients with locally confined prostate cancer.[4] Seventy-six percent of patients will be diagnosed in this stage, and have a 5-year survival of nearly 100%.[13] With more advanced cancer, in which there is an increased risk of recurrence, the addition of gonadotropin-releasing hormone (GnRH) therapy to radiation may be necessary. Regional disease similarly has a 5-year survival rate of nearly 100% and is diagnosed in 13% of patients.[13] Only after failure of hormonal therapy will other systemic therapies be used. A number of cytotoxic agents and immunologic and targeted therapies are available for the treatment of castration-resistant metastatic disease. Although only 6% of patients are initially diagnosed with metastatic disease, their 5-year survival is only 30%.[1] Therapy in the different stages of prostate cancer is discussed in more detail subsequently.

RISK FACTORS

CASE 100-1

QUESTION 1: S.J. is a 67-year-old African American male who has never been screened for prostate cancer. He has no comorbidities, does not smoke, and exercises regularly.

What are S.J.'s risk factors for prostate cancer?

Age

Risk factors are important in identifying those males who are most likely to develop prostate cancer and also help identify those who will most benefit from screening. Age is the most important factor, with about half of all cases occurring after the age of 65 years and rarely occurring before age 40 years. Median age at the time of death is 80 years.[1]

Ethnicity

The risk of development of prostate cancer begins to increase after age 50 years in non-Hispanic Caucasian males and after age 40 years in males with African ancestry in the United States and the Caribbean. Those of African ancestry have a 1.8-fold higher incidence of being diagnosed with prostate cancer than do males of European ancestry. Prostate cancer also has one of the largest disparities in death rates, with those of African ancestry having more than a twofold greater risk of dying than do those of European ancestry.[1] However, one study has found that, when controlling for other nonbiologic factors in three different cohorts, African American males did not appear to have lower mortality. All the three groups had equal access to care and received standard treatments for their disease. Further identification of differences between ethnicity and socioeconomic factors and their effects on the incidence and mortality in this population will need to be defined.[14] Males of

American Indian/Alaska Native descent have the lowest risk of developing prostate cancer, followed closely by Asian/Pacific Islander descent, who have the lowest rates of prostate cancer mortality (**Fig. 100-1**).[1]

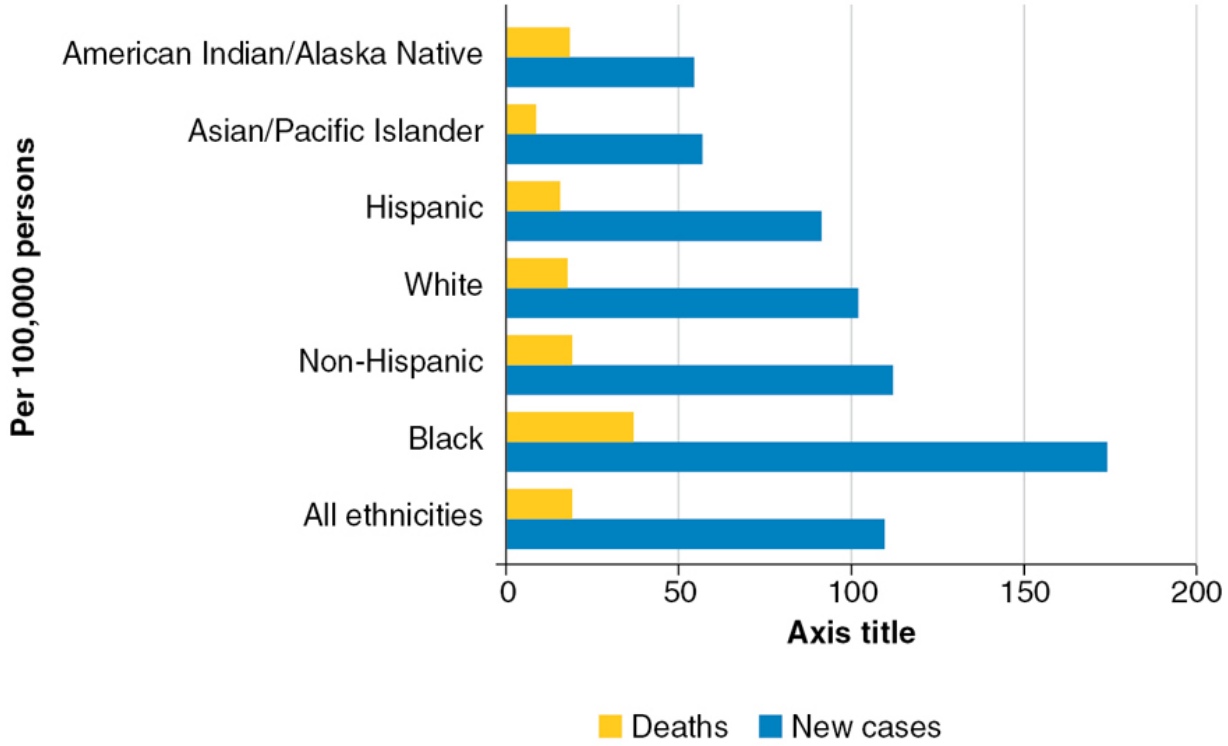


Figure 100-1 Incidence of new cases of prostate cancer by race and age. (From National Cancer Institute: Surveillance, Epidemiology, and End Results Program (SEER). Cancer stat facts—prostate cancer. National Institutes of Health. Accessed January 26, 2021. https://seer.cancer.gov/statfacts/html/prost.html.)

Family History

Family history (FH) confers up to a two- to threefold increased risk if a male's brother or father has been diagnosed by age 60 years. The risk is even higher if two or more first-degree relatives develop prostate cancer. Younger age at diagnosis in a family member is a higher risk than is a family member who is diagnosed later in life.[4]

Genetic Syndromes

Several inherited, or germ line, mutations are associated with an increased risk of prostate cancer. Although these high-risk genetic mutations are relatively uncommon in the overall population, a known FH may indicate the recommendation for genetic counseling and possibly genetic testing.[15,16] Mutations in the inheritable *BRCA 1/2* genes can increase the risk of developing several cancers, including breast, ovarian, and prostate cancer. Germ line *BRCA2* mutations are associated with up to an 8.6-fold increase in the risk of prostate cancer.[17] Moreover, cancers with *BRCA2* mutation are more likely to have an earlier onset, higher incidence of aggressive disease, and shorter survival time.[18] The implications of *BRCA1* on prostate cancer risk are less established, with one report stating a 3.75-fold increase in relative risk, although mutations in *BRCA 1/2* are often considered together.[19]

Males with Lynch syndrome (germ line mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*) have a two- to fivefold increase in the risk of prostate cancer. However, these cancers act similarly to those cancers without the mutation, so they are not more aggressive or occur at any earlier age.[20]

S.J. has the following risk factors for the development of prostate cancer: ethnicity and age.

Case 100-1, Question 2: S.J. has learned that his 47-year-old brother was just diagnosed with advanced prostate cancer. How has S.J.'s risk changed?

Because S.J. now has a first-degree relative who has been diagnosed with prostate cancer, especially before the age of 60, his risk has increased substantially (two- to threefold).

SCREENING

Case 100-1, Question 3: After S.J.'s brother's diagnosis, he becomes concerned and makes an appointment with his primary care office to discuss screening. Should S.J. begin routine screening for prostate cancer?

Over the past 35 years, 5-year survival rates increased from 68% to 99%, attributed in part to early detection guidelines. There are several guidelines for the screening of prostate cancer, including those of the American Cancer Society,[5] and the American Urological Association (Table 100-1).[21] Historically, males age older than 50 years were encouraged to have a PSA screening yearly. There was a steep rise in the diagnosis of prostate cancer once PSA screening was put into effect in the early 1990s, from >100 cases per age-adjusted 100,000 in 1975 and peaking at 240 cases per 100,000 in 1992. At the time of writing, it is at a rate of 110 cases per 100,000.[1] However, controversy remains among different organizations regarding the appropriate recommendations for PSA screening. Prostate cancer is a relatively slow-growing cancer that may not be life-threatening to some patients and potentially would not need treatment. The lifetime risk of being diagnosed with prostate cancer is 11%, and the lifetime risk of dying of prostate cancer is 2.5%.[22] Because it occurs primarily in older males, a number of males might not develop symptoms of the disease that would cause them to be tested if not for routine screening. These patients could be subject to the risks of screening procedures and possibly treatment of otherwise clinically insignificant disease.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial randomized over 76,000 U.S. males to strict annual PSA and DRE screening or to standard practice. It was found that prostate cancer was identified more often in the annual screening group, but that it did not change the rate of fatal disease.[23] However, a European study that randomized >182,000 males to yearly screening or to no screening found that in the screening group, the relative reduction in risk of death was 21% at a median follow-up of 11 years. To prevent one death from prostate cancer, 1055 males would need to be screened and 37 cancers would need to be

detected.[24] Therefore, it is being recognized that prostate cancer may be overdiagnosed (overdetection), especially at older ages. Overdiagnosis is typically defined as detecting a disease when it would not otherwise have shortened lifespan or resulted in adverse effects.[25] The U.S. Preventive Services Task Force concluded that for every 1000 males between ages 55 and 69 years who were screened, 1.3 deaths from prostate cancer would be avoided over 13 years. There are risks associated with any potential diagnosis, including risks during biopsy such as infection, bleeding, and dysuria, along with risks associated with unnecessary treatment, which need to be taken into account in the risk-to-benefit ratio of screening.[22] These studies highlight the need for selective screening to avoid overdiagnosis and overtreatment while not compromising long-term survival.

Guidelines are relatively consistent in their recommendation that males at ages older than 70 to 75 years do not need to be screened because they have not been diagnosed with cancer at this time, and are more likely to die of unrelated causes before ever having any symptoms in this slow-growing cancer. Guidelines emphasize considering the life expectancy of the patient and not screening those whose expectancy is <10 to 15 years. For those at an elevated risk of developing prostate cancer (eg, family, ethnicity, or other risk factors), it may be beneficial to initiate screening at an earlier age. However, the majority of guidelines advocate that all males should have a discussion with their doctor regarding any risk factors that they have, and together decide whether they should undergo screening and at what age to start, depending on their risk factors, comorbidities, and personal preferences.[5,21,22] For S.J., because of his elevated risk owing to his brother's diagnosis and his ethnicity, it may be considered prudent to begin screening. However, this should be discussed with his doctor to ensure that he recognizes all the benefits and risks of screening.

PROGNOSTIC FACTORS AND RISK STRATIFICATION

CASE 100-2

QUESTION 1: C.W. is a 69-year-old male who began routine screening for prostate cancer with his primary care physician 14 years ago. His PSA history is listed subsequently. His PSA drawn on August 5, 2017, is 6.68 ng/mL. DRE finding is negative. He has an excellent performance status, being fully active and able to carry out all activities without restriction. On physical exam, he is well appearing with no apparent signs of distress. He has no known FH of prostate cancer. When asked about his social history (SH), he said that he drinks socially, with an average of one to two drinks every month, and has never smoked or used illicit drugs. His past medical history (PMH) is significant for hypercholesterolemia, hypertension, and depression.

Medications: atorvastatin, lisinopril, and sertraline; no known allergies

PSA History:	
Date	**PSA Level (ng/mL)**
August 5, 2017	6.68
September 22, 2016	3.11
September 25, 2015	2.52
August 29, 2014	2.46
August 27, 2012	2.27
September 3, 2010	2.02
August 19, 2008	1.98
August 15, 2006	1.82

From the abovementioned assessment, what would have prompted C.W.'s primary care physician to refer the patient to a urologist?

Using prognostic factors to stratify the risk of the cancer recurring is essential to better characterize the cancer and to determine the optimal initial treatment. This is particularly important with a heterogeneous disease such as prostate cancer. Patients with a high

risk of recurrence will need more aggressive treatment, whereas those with low risk can benefit from a more conservative approach. Stage of the tumor, PSA, and grade group are prognostic factors that can be used by the provider to calculate the probability of a patient recurring in the next 5 to 10 years. In addition, germ line and genetic testing are recommended in certain patients to further improve risk stratification and guide treatment decisions. Certain germ line mutations, such as *BRCA2*, are associated with aggressive prostate cancer, indicating the need for a higher risk reclassification.[26] Utilizing these prognostic factors will help the physician determine the best therapies for their patient while maximizing quality of life.

Life Expectancy

There are a number of males who will die with, not of, their prostate cancer. Autopsy data has shown that as many as 7 out of every 10 males who died of various causes had prostate cancer at time of death that was undiagnosed (**Fig. 100-2**).[27,28] Estimation of a patient's life expectancy can help determine the extent of benefit of potential life gained from treatment. Males with short life expectancies are at low risk for developing any symptoms of disease, or morbidity, before their demise from another unrelated event, and therefore will likely not benefit from definitive treatment. Conversely, younger males otherwise in good health are likely to need treatment because they have a longer lifetime in which to develop a recurrence of cancer that can be a cause of morbidity and mortality. Although insurance life expectancy charts (Minnesota Metropolitan or the Social Security Administration Life Insurance Tables) can be used to determine potential life expectancy, it often is a comprehensive clinical determination by the patient's health care team, weighing a number of factors, including their overall health, quality of life, comorbid conditions, and FH, when determining a treatment plan.[4] The Social Security Administration Life Insurance Tables can be found at www.ssa.gov/OACT/STATS/table4c6.html

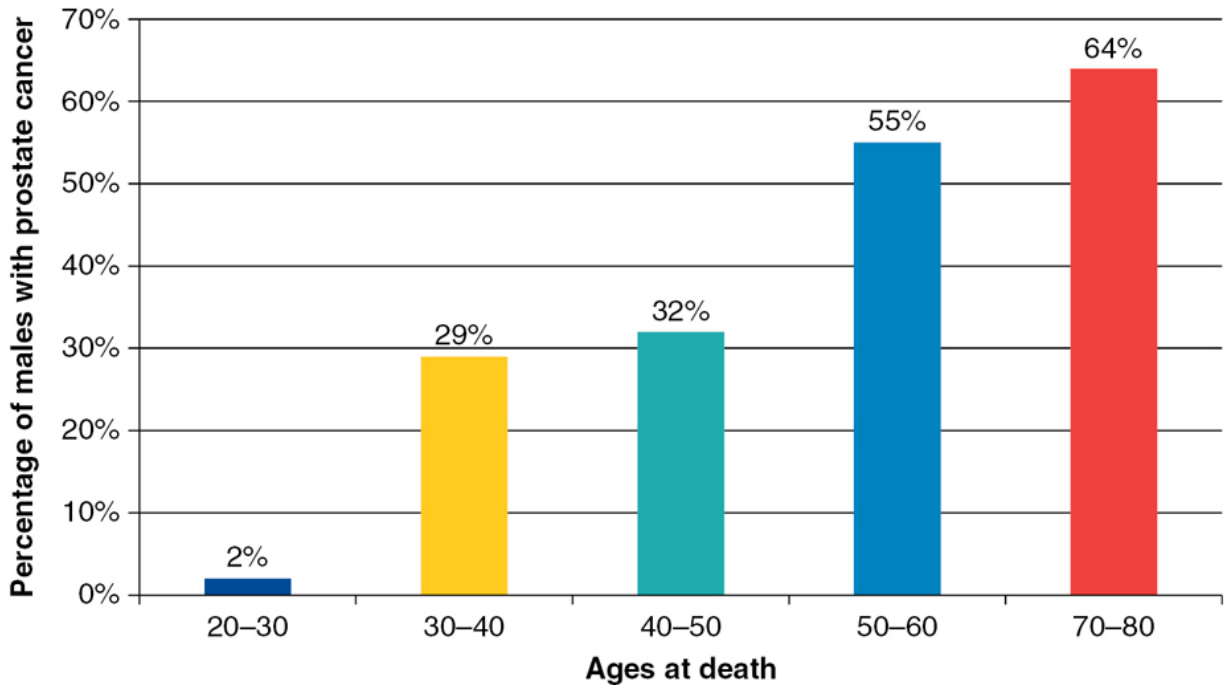


Figure 100-2 Percentage of males found to have prostate cancers at autopsy after dying of unrelated causes in the era before standardized prostate-specific antigen (PSA) testing. (Reprinted with permission from Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20–69: an autopsy study of 249 cases. *In Vivo*. 1994;8(3):439–443.)

Prostate-Specific Antigen

As previously discussed, serum PSA level is used in screening for prostate cancer detection. It is also a prognostic factor used as an aid to determine treatment because a higher PSA level is associated with an increased risk of more advanced and potential progression of disease. The more prostate cancer cells there are, the more PSA is being made. Being able to determine how fast the level is rising is another way to assess the cancer's ability to potentially recur and progress. However, it is also known that not all prostate cancers will produce elevated PSA levels. Serum PSA is another tool that may help the practitioner assess the risk of recurrence in a specific patient. As mentioned previously, males with PSA levels of 4 to 10

ng/mL have a one in four chance of having prostate cancer; that risk doubles if the level increases above 10 ng/mL.[10]

There have been some developments in PSA testing in an attempt to refine patient selection for further screening and cancer detection. These include different calculations of and adjustments to PSA, such as PSA velocity, percent free PSA, and PSA density. There is a lack of evidence to support the use of these tests in routine practice.[21]

Because C.W. had a PSA level of 3.11 in 2016 and it increased to 6.68 in 2017, there is concern that he may have developed prostate cancer. The Prostate Cancer Prevention Trial (PCPT) found that 15% of males with PSA ≤4.0 ng/mL and a normal DRE were diagnosed with prostate cancer. This percentage doubles with PSA levels between 4 and 10 ng/mL.[11]

Case 100-2, Question 2: C.W. is referred to the urologist for further evaluation. What additional diagnostic procedures can be done to definitively diagnose prostate cancer? What assessments can be done from the procedure for better prognostication of the disease?

Tumor Staging

The AJCC developed a staging system for newly diagnosed prostate cancer. This AJCC TNM staging system classifies the extent of the tumor according to the size of the tumor (T), the extent of lymph node involvement (N), and the absence or presence of distant metastases (M).[10] In general, if the cancer remains within the prostatic capsule, it is considered a localized disease. If it has spread outside of the capsule or has invaded the adjacent structures, it is locally advanced or regional, and the cancer is considered metastatic if it has spread to other parts of the body.

Grade Group and Gleason Score

A Gleason pattern is the histologic grading of the tumor biopsy. There are five distinct patterns of growth from well (1) to poorly (5)

differentiated with progressive loss of glandular formation (**Fig. 100-3**).[29] Well-differentiated cancer cells are those that are most similar to the normal prostate cells and tend to grow and spread at a slower rate than do poorly differentiated tumor cells that are more aggressive. Up to 50% of prostate tumors demonstrate more than one histologic pattern.[30] By assessing several of the biopsy samples to find the most common growth patterns, the aggressive behavior of the tumor can be more accurately estimated. The Gleason score is calculated by adding the most common to the second most common growth patterns found in the core biopsies. The Gleason score was refined and incorporated into the more recently adopted grade group system, of which there are five categories. Grade group 1 designates a well-differentiated, less aggressive tumor, whereas a grade group 5 is considered a poorly differentiated, more aggressive tumor.[31] An aggressive tumor is one that will grow faster and have a higher risk of metastasizing, increasing the likelihood of recurrence after localized treatment. Grade group system is one of the integral evaluations for accurate risk stratification.

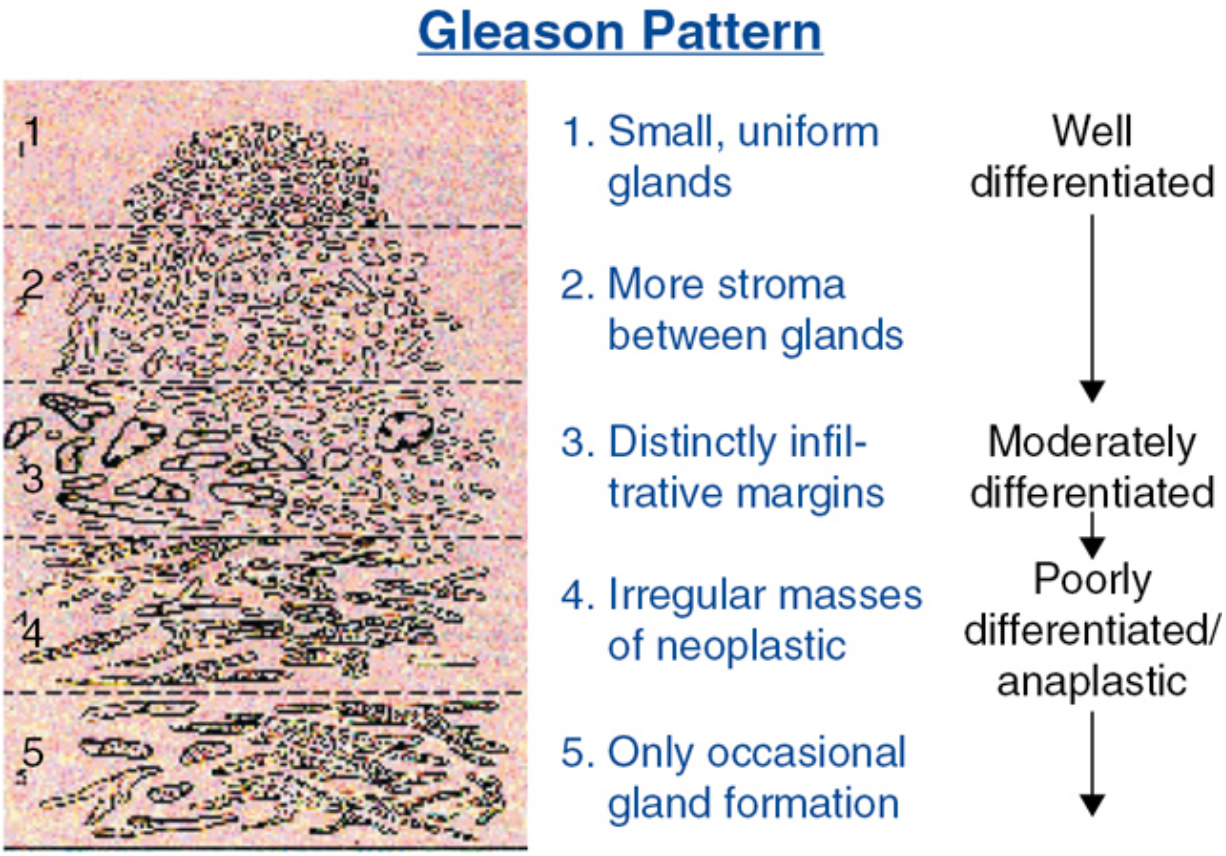


Figure 100-3 Gleason histologic grading of prostate cancer demonstrating progressive loss of glandular formation with increasing score. (Reprinted with permission from Zelefsky MJ, Morris MJ, Eastham JA. Cancer of the prostate. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 11th ed. Wolters Kluwer; 2019:1091.)

Germ Line Genetic Testing and Tumor Molecular Analysis

Advances in DNA sequencing have expanded the understanding of genetics in prostate cancer. Certain germ line genetic mutations have been associated with more aggressive prostate cancer and shortened survival. This is most recognized in germ line mutations in *BRCA2* and has been implicated in other DNA repair gene mutations. The frequency of mutations in DNA repair genes, also

known as *homologous recombinant repair* (HRR) *mutations*, is higher in metastatic prostate cancer, but is overall associated with more aggressive disease and poor outcomes.[32] Because of the potential implications on prognosis and risk stratification, genetic counseling and testing is recommended by several guidelines in early-stage prostate cancer according to FH, personal history, and classification or stage of cancer at diagnosis. Some of the more significant factors that may indicate the need for genetic counseling and testing include FH of hereditary syndromes or certain other cancers, strong FH of prostate cancer, Ashkenazi Jewish ancestry, and localized disease with aggressive prognostic factors. Later in metastatic prostate cancer, HRR mutations are more common and can impact clinical decisions and qualify patients for certain therapies. Therefore, genetic testing is generally recommended in all patients with metastatic prostate cancer.[33]

Molecular biomarker testing of the tumor tissue can provide further characterization of clinically localized cancer and can aid in clinical decision-making. Some tests may be particularly useful when considering active surveillance or treatment intensification in localized prostate cancer. It may be considered in low-stage, localized prostate cancer patients when it may aid in treatment decisions. Several of these molecular biomarker tests, including Decipher® (GenomeDx Biosciences, Vancouver, BC, Canada), Oncotype DX® (Genomic Health, Redwood City, CA) prostate assay, Prolaris® (Myriad Genetics, Salt Lake City, UT), and ProMark® (Metamark Genetics Inc., Waltham, MA), have been evaluated and are available for use. They have not been prospectively validated to assess the complete impact on long-term outcomes and are not yet the standard of care.[34]

If genetic testing or molecular biomarker testing is available, it can provide further information regarding the prognosis, risk stratification, and treatment selection of patients with clinically localized prostate cancer.

Risk stratification tools that incorporate stage, PSA level, and grade group have been developed and validated because they identify those males who are associated with an increased risk of

recurrence and worse outcomes after localized treatment. Patients with localized prostate cancer who are yet to receive treatment can be grouped as low, favorable and unfavorable intermediate, and high risk to be used by providers, along with other factors such as genetic testing, life expectancy, and overall health of the patient, in the selection of initial treatment (Table 100-2).[26,35]

A TRUS-guided needle biopsy can be done to definitively diagnose prostate cancer. The biopsy specimen can be used to determine the prognostic factors of clinical stage and the grade group.

Case 100-2, Question 3: C.W.'s biopsy revealed a grade group 1, stage T1c (no suspected nodal or distant metastases) prostate cancer in 3 of 10 cores. Based on C.W.'s prognostic factors, what is C.W.'s risk group?

C.W. has stage T1cN0M0 prostate cancer with a grade group 1 and a PSA <10 ng/mL. With these prognostic factors and with 3 of 10 positive cores, he is considered to have low-risk prostate cancer.

LOCALIZED DISEASE

Observation Versus Active Surveillance

Case 100-2, Question 4: C.W. consulted with a medical oncologist about his treatment options for low-risk prostate cancer. The oncologist explained that C.W. is an overall healthy patient with a long life expectancy and that his prostate cancer is relatively slow growing. What is C.W.'s conservative option for the management of his prostate cancer?

Studies have aimed to identify those select males who will have a good outcome with a very conservative approach of no immediate, definitive intervention for their cancer. This is because we are now seeing what some call an overtreatment of prostate cancer. Overdiagnosing, as discussed earlier, plays a role, with some

models estimating between 23% and 42% of all U.S. screen-detected cancers are being overtreated.[36] This approach of not treating the cancer immediately has subtle distinctions, according to differences in patient status.

Observation (or watchful waiting) involves no cancer intervention, such as additional biopsies, scans, surgery, or treatment, but simply monitors the patient with the plan to only deliver palliative therapy if symptoms develop. This is recommended for patients with a life expectancy ≤5 years because prostate cancer treatment does not improve survival within 5 years. The goal of observation is to avoid treatment and its potential side effects in order to maintain the patient's quality of life. This is an appropriate strategy for elderly patients or patients that have comorbidities that may threaten mortality more than the mortality risk from prostate cancer.[26]

Active surveillance is different from observation because these males are actively monitored with routine PSA levels and, potentially, biopsies with the expectation of intervention if it looks like the cancer is progressing with a goal of deferring side effects from treatment without missing the opportunity for cure. For this reason, it is preferred in patients with low-risk prostate cancer. It is also an option in patients with favorable intermediate-risk disease.[26] A study of almost 1000 males with favorable or intermediate-risk prostate cancer on active surveillance were followed up for a median of 6.4 years (range, 0.2–19.8 years). They were offered treatment if their PSA doubled in <3 years, if their Gleason score was higher based on another biopsy, or if they had clinical progression. Of those 993 study participants, 15% died, but only 15 patients (1.5%) died from prostate cancer. There were an additional 13 patients (1.3%) who developed metastases, but only four had died at the time of analysis. At 5, 10, and 15 years, 75.7%, 63.5%, and 55% of patients, respectively, were untreated and continued surveillance.[37] In another study of >5500 males with low-risk and favorable intermediate-risk prostate cancer treated with brachytherapy and then active surveillance, 605 males had died, but only 5.6% of those deaths were because of prostate cancer.[38] These studies illustrate the potential to delay therapy in selected males without compromising

survival. The decision of observation or active surveillance should be made after a full discussion between the patient and the physician of the advantages and disadvantages of this approach.

Because C.W. has low-risk prostate cancer and an excellent performance status without precluding comorbidities, giving him a long life expectancy, he would be eligible for active surveillance. He would not be a candidate for observation given his age and long life expectancy.

Definitive Local Therapy

Treatments for early-stage disease can include radiation, mainly in the form of either brachytherapy or external beam radiation therapy (EBRT), and radical prostatectomy. These localized treatments are used because the cancer is thought to still be confined to the prostate. Choice of therapy is dependent on risk stratification, which takes into account the extent of disease, pathologic stage, and PSA, along with life expectancy, patient preference, and potential comorbidities that may cause complications and impact treatment outcomes. If treatment is successful and if the correct patients are selected, these local therapies can potentially provide a cure for the disease.

SURGERY

Radical prostatectomy is the surgical removal of the prostate gland and possibly some surrounding tissue. It is generally recommended only for patients with clinically confined prostate cancer with no comorbidities precluding their ability to undergo an operation. A study using the Surveillance, Epidemiology, and End Results (SEER) Medicare database looked at outcomes after surgery among hospitals and surgeons. In a study of 11,522 males between 1992 and 1996, it was found that postoperative complications correlated with the volume of procedures performed by the surgeon and the volume done at the institution. Postoperative morbidity was lower in very high-volume hospitals compared to low-volume hospitals (27%

vs 32%; *P* = .03) and was also lower when performed by high-volume surgeons as compared to low-volume surgeons (26% vs 32%; *P* > .001). There was no link between surgeon/institution and death.[39] Another study found that surgeon experience was linked to a lower risk of recurrence (*P* > .001) when adjusted for tumor characteristics and year of surgery in patients who received no other therapy. Five-year probability of recurrence was 17.8% in the early phase of career (10 prior operations) compared to 10.9% later on (>250 operations).[40] These findings confirm that experience is a critical factor in the success of radical prostatectomy. Surgery can be done as either an open or a laparoscopic radical prostatectomy, and can also include the removal of surrounding lymph nodes if there is suspicion of nodal metastases. Laparoscopic removal of the prostate, with or without robotic assistance, is less invasive and usually a shorter hospital stay and a quicker recovery.

Additional information from the surgery can provide more accurate prognostic information on the grade or any extension into the surrounding tissue or lymph nodes. This information is used to determine whether further treatment is necessary. In addition to providing more accurate prognostic information, radical prostatectomy also has the benefit of being a short treatment with a hospital admission typically being 1 day. It does, however, have the risks of erectile dysfunction, urinary incontinence, and morbidities associated with any major surgery. Because of these risks, radical prostatectomy is indicated for intermediate-risk or high-risk patients with a life expectancy >10 years.[26]

RADIATION THERAPY

Radiation therapy uses high-energy beams in the case of EBRT, or radioactive particles in the case of brachytherapy, to kill cancer cells. With brachytherapy, the radiation sources are placed directly into the prostate for a direct action with minimal effect to surrounding tissue. This form of radiation is given as either low dose or high dose, and is indicated as monotherapy for lower and favorable intermediate-risk cancers or can be given as an adjunct to EBRT in unfavorable

intermediate- and particularly in higher risk cancers. Brachytherapy has the advantage of a short, 1-day course of therapy and minimal risk of incontinence and erectile dysfunction, but it can cause acute urinary retention.[41]

Current EBRT techniques use three-dimensional conformal radiation therapy (3D-CRT) to deliver radiation under the guidance of computer-generated images of a patient's anatomy. Intensity-modulated radiation therapy (IMRT) is the second iteration of 3D-CRT that uses various intensities of radiation according to the needs of the treatment area. Image-guided radiation therapy (IGRT) is a 3D-CRT that more accurately localizes the treatment area. Both IMRT and IGRT techniques are the standard of care for EBRT treatment that allows for higher doses of radiation to be delivered more precisely to lower the risk of adverse effects. Because of the proximity of the prostate to the bladder and rectum, treatment with EBRT can cause rectal urgency and increased bowel frequency, urinary frequency and incontinence, and erectile dysfunction. Although these symptoms are most often experienced short term and the risk is lessened with newer techniques, they can persist for the long term in a low percentage of patients.[42] Unlike radical prostatectomy, EBRT avoids surgery and anesthesia complications, such as bleeding, myocardial infarction, or pulmonary embolism. EBRT is an option for low-risk, intermediate-risk, and in higher risk cancers. It is typically combined with a short course of ADT for unfavorable intermediate risk and a longer course with ADT in high risk cancers (see section Androgen Deprivation Therapy).[43]

Other modalities of radiation therapy, such as proton beam and stereotactic body radiation, have been used in the treatment of localized prostate cancer. However, their benefits over the current standards have not been established in the first-line setting of definitive localized treatment.[44]

Treatment outcomes of patients with localized prostate cancer treated with radiation, surgery, or active surveillance/observation have been compared in large prospective, population-based studies. A randomized control trial of 1643 males compared radical prostatectomy, EBRT, and active surveillance for treatment of

clinically localized prostate cancer over a median follow-up of 10 years. The primary end point was cancer-specific mortality, of which there were 17 overall: 8 in the active monitoring group (1.5 deaths per 1000 person-years), 5 in the surgery group (0.9 per 1000 person-years), and 4 in the radiotherapy group (0.7 per 1000 person-years). There also was no significant difference in cancer-specific mortality (*P* = .48) or in all-cause mortality (*P* = .87). A higher rate of disease progression was seen with active surveillance than with prostatectomy or EBRT.[45] A study by Barocas et al, compared 2550 males with localized prostate cancer who were treated with radical prostatectomy, EBRT, or active surveillance. It found that radical prostatectomy was associated with a greater decrease in urinary incontinence and sexual function than with EBRT or active surveillance, but was associated with better urinary irritative symptoms than with active surveillance.[46] Several other prospective studies investigating patient-reported outcomes have found differences in quality of life with the various treatment modalities.[47,48] Physicians must compare the advantages and disadvantages of each treatment along with patient-specific factors to determine the most appropriate therapy.

Androgen deprivation therapy

Androgen deprivation therapy (ADT) is the suppression of androgen production or action. It can be used in the localized prostate cancer setting in combination with radiation therapy for unfavorable intermediate-risk patients and is used as a standard in combination with radiation in higher risk patients. ADT can be done either through orchiectomy, because ~90% of androgens will come from the testes and is called *surgical castration*, or by adding a GnRH analog, called *medical castration*. Both should decrease the body's testosterone production to castrate levels, usually <50 ng/mL. Because both methods are equally effective, most males will start GnRH therapy; however, orchiectomy can be useful for immediate decreases in testosterone when patients present with highly symptomatic disease or when adherence, cost, or availability is prohibitive. **Table 100-3**

includes the GnRH agonists, which include leuprolide, goserelin, histrelin, buserelin, and triptorelin as well as one GnRH antagonist, degarelix. In addition to the injectable GnRH analogs, an oral formulation of a GnRH antagonist has most recently been approved. Thus far, it has only been studied in patients with advanced or relapsed prostate cancer, and so its approval is currently limited to this setting.[49]

Table 100-3
Androgen Deprivation Agents

Agent	Route	Dose
GnRH Agonists		
Leuprolide (Eligard®)	Subcutaneous	7.5 mg every month 22.5 mg every 3 months 30 mg every 4 months 45 mg every 6 months
Leuprolide (Lupron Depot®)	Intramuscular	7.5 mg every month 22.5 mg every 3 months 30 mg every 4 months 45 mg every 6 months 3.75 mg
Triptorelin (Trelstar® or Trelstar Mixject®)	Intramuscular; suspension (reconstituted)	3.75 mg every 4 weeks 11.25 mg every 12 weeks 22.5 mg every 24 weeks
Goserelin (Zoladex®)	Subcutaneous implant	3.6 mg every 28 days, 10.8 mg every 12 weeks
Histrelin (Vantas®)	Subcutaneous implant	50 mg every 12 months
Buserelin (Suprefact®)	Subcutaneous	500 µg every 8 hours for 7 days. Maintenance 200 µg once daily
Buserelin (Suprefact Depot®)	Subcutaneous implant	6.3 mg every 2 months 9.45 mg every 3 months
GnRH Antagonist		

Agent	Route	Dose
GnRH Agonists		
Degarelix (Firmagon®)	Subcutaneous	Loading dose: 240 mg administered as two 120 mg injections Maintenance dose: 80 mg every 28 days (beginning 28 days after initial loading dose)
Relugolix (Orgovyx®)	Oral	360 mg once on day 1, followed by 120 mg once daily
First-Generation Antiandrogens		
Bicalutamide (Casodex®)	Oral	50 mg once daily (with GnRH analog) 150 mg once daily (monotherapy)
Nilutamide (Nilandron®)	Oral	300 mg once daily × 30 days, followed by 150 mg once daily
Flutamide (Eulexin®)	Oral	250 mg three times daily

GnRH, gonadotropin-releasing hormone.

GnRH agonists work by binding to GnRH receptors to suppress luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production in the pituitary, decrease testicular testosterone and, subsequently, DHT. They bind to the GnRH receptors and initially cause a rise in LH and FSH and a surge in testosterone for up to a week until the continuous pituitary overstimulation eventually downregulates GnRH receptors and decreases hormone levels (**Fig. 100-4**). This initial, transient surge in testosterone, called a *tumor flare*, can negatively impact patients presenting with symptoms, including bone pain and bladder obstruction. The flare can be prevented with the addition of antiandrogen therapy for a short course of at least 7 days. Because GnRH antagonists directly block the receptors, there is an immediate decrease in LH and FSH production and subsequent testosterone suppression, avoiding a tumor flare and the need for antiandrogens, which may be most useful in symptomatic patients who would have experienced an increase in symptoms during this period.[50]

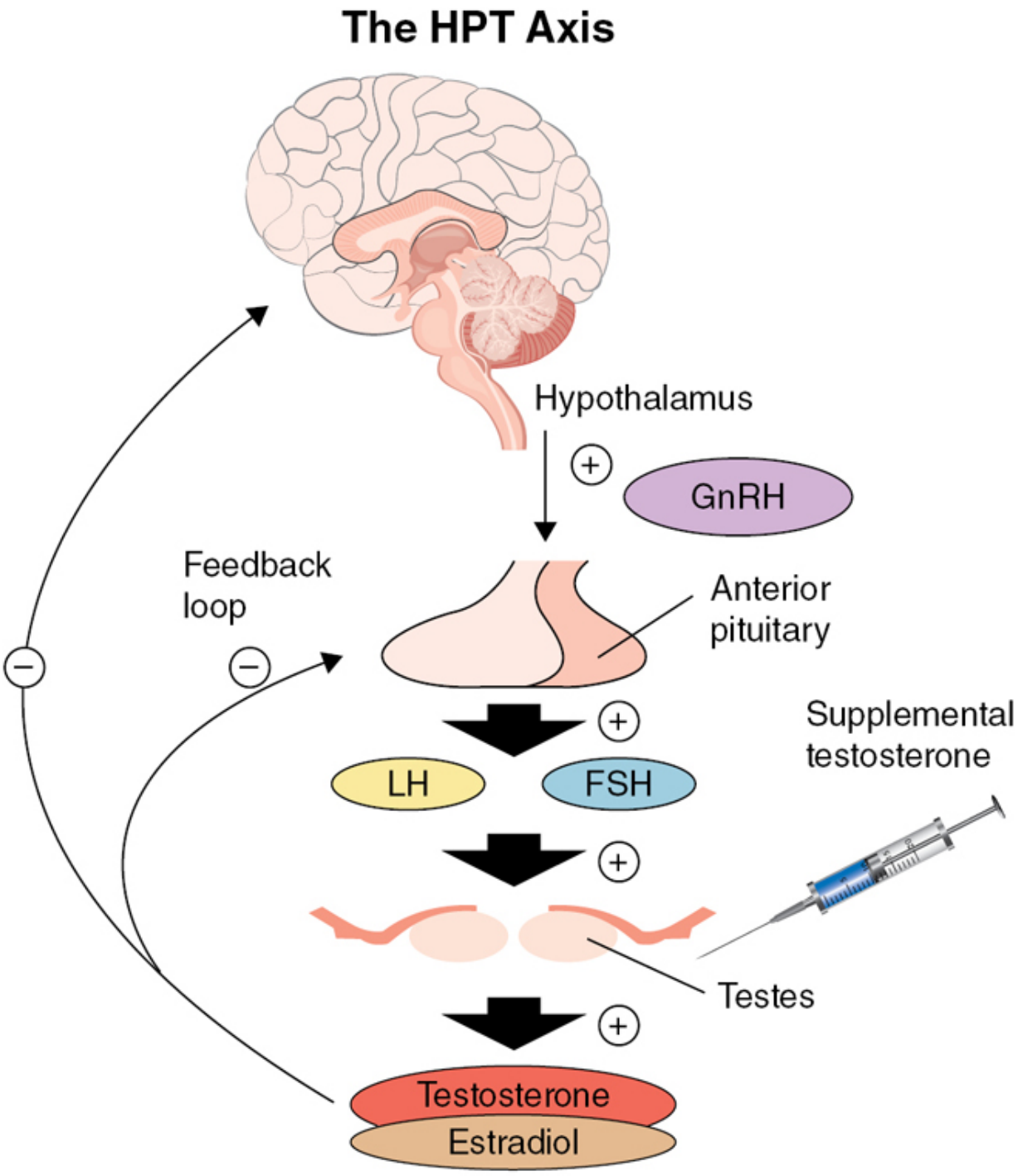


Figure 100-4 The HPT axis is continuously stimulated by GnRH agonists to suppress testosterone through negative feedback. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPT, hypothalamic–pituitary–thyroid; LH, luteinizing hormone.

Antiandrogens used in this setting are androgen receptor (AR) blockers that work by binding to ARs to competitively inhibit their interaction with testosterone and DHT. These oral medications include flutamide, nilutamide, and bicalutamide. The combination of castration with a GnRH agonist or an orchiectomy and an antiandrogen is called a combined androgen blockade (CAB). In addition to its use to prevent tumor flare or in combination with EBRT for definitive local treatment, CAB can possibly be used later in the treatment of recurrent disease.[51]

Adding ADT to radiation improved cancer outcomes, including survival, in several clinical trials of males with intermediate-risk prostate cancer, and is an option for some patients, particularly those deemed unfavorable intermediate risk.[43] These trials support the use of a short-term course of ADT of 4 to 6 months when added to radiation in unfavorable intermediate risk patients.[52,53] In high-risk patients, combining ADT with radiation therapy improved survival, with studies favoring long-term ADT (2–3 years) over short term (4–6 months). The addition of ADT to radiation is thought to have an additive synergistic cytotoxic effect on cancer cells that can possibly reduce the size of the prostate and the amount of radiation needed.[54] For this reason, ADT is often initiated up to 2 months before radiation. Androgen deprivation monotherapy, without concomitant radiation, has not been shown to be beneficial in patients with localized prostate cancer.[55] Neoadjuvant or adjuvant ADT does not give added benefit with radical prostatectomy.[56]

Traditionally, studies in the treatment of localized prostate cancer with radiation therapy plus ADT were completed using CAB for the entire ADT portion of treatment. However, it is still not proven in randomized trials if the use of CAB is beneficial over castration alone in this setting. Antiandrogen monotherapy is less effective than is medical/surgical castration and is not generally recommended for use in the treatment of prostate cancer.[56]

Using ADT to disrupt the production of testosterone and DHT can cause a range of symptoms that can impact the quality of life, particularly in patients using ADT for prolonged periods. These side effects include hot flashes, decreased libido, erectile dysfunction,

gynecomastia, behavioral changes, and burning at the injection site. Additional concerns of therapy with ADT are discussed further in this chapter.

Case 100-2, Question 5: C.W. is elected to proceed with active surveillance. His medical oncologist had scheduled appointments and PSA checks every 6 months and DREs every 12 months. His results are as follows:

Date	PSA Level (ng/mL)	DRE
January 13, 2018	7.16	
July 12, 2018	7.74	Negative
January 3, 2019	8.08	
July 10, 2019	8.75	Negative
January 30, 2020	10.70	
July 2, 2020	11.70	Negative

C.W.'s PSA continued to rise; however, his overall health remained excellent, and he did not have any symptoms from his disease. C.W. began to get anxious, and the medical oncologist decided to do a repeat biopsy to reassess the tumor and treatment plan. The results revealed a grade group 3 in 4 of 12 cores. What are the possible treatment options for C.W.?

C.W. now has T1cN0M0, grade group 3, PSA 11.7 ng/mL prostate cancer, placing him in the unfavorable intermediate-risk group. His options for definitive local treatment are radical prostatectomy or EBRT plus ADT with the possibility of adding brachytherapy. Because of the results of several trials investigating the use of ADT with radiation in intermediate-risk patients,[52,53,57,58] EBRT would be given with a short course of 4 to 6 months of ADT.

RECURRENCE AND PROGRESSION

CASE 100-3

QUESTION 1: Patient H.L. is a 63-year-old male with a clinical stage T1cN0M0, PSA 9.2 ng/mL, grade group 3 prostate cancer. His PMH is unremarkable, and he has an excellent performance status. He has no known allergies and is not on any medications. His labs are not clinically significant other than his PSA level. When presented with his options, H.L. decided to undergo a radical prostatectomy for definitive local treatment, which revealed a pathologic stage T2cN0M0. He was monitored after surgery, and after 9 months had no symptoms from the procedure or the disease. His PSA was checked twice after surgery and was 0.38 ng/mL and, more recently, 1.2 ng/mL. The medical oncologist believes that the cancer is still present, but does not think there is any indication of disseminated disease.

What type of cancer progression does H.L. have?

For patients who have definitive local treatment with either radiation or surgery, about 25% to 33% of patients will experience a recurrence of their cancer. After the completion of local therapy, patients are monitored by periodically checking PSA for the detection of biochemical recurrence, which is recurrence of disease as indicated only by rising PSA with no other signs or symptoms of disease. The threshold for PSA recurrence is dependent on the initial treatment given. Because a radical prostatectomy involves the removal of all prostate tissue, serum PSA after the procedure should become undetectable. A PSA level of ≥0.2 ng/mL following a radical prostatectomy is considered a biochemical recurrence. Risk factors for the development of a recurrence after radical prostatectomy are the Gleason score, positive surgical margins, and elevated postoperative PSA levels.[59] A biochemical recurrence after EBRT is defined as a rise in PSA level by ≥2 ng/mL above the nadir, or lowest achieved PSA, according to the Phoenix criteria revised by the American Society of Radiation Oncology (ASTRO).[60] Risk factors for recurrence after EBRT include large volume of disease, short time to PSA recurrence, invasion of extraprostatic organs, and a high Gleason score.[61] H.L. is not symptomatic, and his only evidence of disease is his elevated PSA that never normalized after prostatectomy. He has biochemically recurrent prostate cancer.

Case 100-3, Question 2: What is the most appropriate treatment for which H.L. may be eligible?

A biochemical recurrence can indicate that a patient has disease progression. A patient thought to have local recurrence may be eligible to again receive local therapy, called *local salvage therapy*, providing a chance for a cure or a delay in progression. A patient with a biochemical recurrence after a radical prostatectomy with no indication of distant metastases may be a candidate for salvage radiation therapy with or without ADT.[62] Conversely, a patient initially treated with radiation therapy may be a candidate for salvage prostatectomy.[63] In addition to salvage prostatectomy, cryotherapy, which is a procedure that freezes cancer cells, and brachytherapy, if EBRT was first used, are also salvage therapy options post the radiation therapy. Careful consideration of the characteristics of both the disease and the patient must be assessed using imaging, biopsy, and other prognostic tools to determine the appropriateness for salvage therapy.

In patients with clinical features suggesting that the disease is no longer confined to the prostate, called *disseminated prostate cancer*, systemic therapy is indicated. Because prostate cancer continues to be hormone driven, ADT is the initial standard treatment in recurrent prostate cancer. At this point in the disease, patients are considered castrate sensitive, because their cancer is still being suppressed by the lowering of testosterone to castrate levels with ADT. ADT is palliative, but it can control or delay symptoms and complications, improving patient quality of life.

Because the benefit of ADT for biochemical recurrence is still not fully known, when to initiate ADT is still not clear. Observation until evidence of progression is an option; however, patients with rapidly progressing disease, as indicated by the presence of symptoms, an elevated PSA, or a rapid PSA velocity with a long life expectancy, should initiate ADT earlier. With long-term use of ADT, cost and the extensive side effect profile may be limiting and will impact the quality of life for some patients. Intermittent ADT, once there is

response to treatment, rather than continuous administration, is an approach that can minimize side effects and improve quality of life in this setting. With this approach, patients continue ADT until maximal PSA response and then temporarily stop ADT until a set PSA threshold is reached, at which point ADT is reinitiated.[64] The full benefit of intermittent ADT is still not known. A trial done by Crook and colleagues assigned 1386 males with rising PSA after radiation therapy to either intermittent ADT or continuous ADT. The intermittent ADT approach was noninferior in terms of OS (8.8 vs 9.1 years; heart rate [HR] 1.02, 95% confidence interval [CI] 0.86–1.21), but more patients in this group died from prostate cancer (120/690 vs 94/696). The trial demonstrated an improvement in quality of life with intermittent ADT; however, more research must be done to determine the true impact on survival. This approach may be considered for well-informed patients without metastatic disease.[65] The duration of response from ADT varies, but eventually the cancer becomes resistant to ADT and most patients progress.

At this point in the disease, H.L. has recurrent prostate cancer without evidence of disseminated disease. Because it is thought that the disease is a local recurrence, he may still have an opportunity for a cure with local salvage therapy.

Nonmetastatic Castration-Resistant Prostate Cancer

Case 100-3, Question 3: H.L. undergoes local salvage therapy with EBRT and ADT for 6 months. His PSA is monitored after salvage therapy, and it continues to be elevated. Given the rapid rise in PSA, the medical oncologist recommends starting H.L. on systemic therapy with ADT immediately. H.L. initiates treatment with leuprolide 22.5 mg intramuscularly (IM) every 3 months and his labs are checked at every appointment. Pertinent labs during his treatment course of leuprolide are as follows:

Date	PSA Level (ng/mL)	Testosterone (ng/dL)
April 27, 2019	2.56	

July 9, 2019	2.36	
October 17, 2019	2.31	<50
January 23, 2020	2.57	
April 19, 2020	3.08	<50
July 10, 2020	3.74	
October 2, 2020	4.92	<50

H.L. continues to be in good physical health other than experiencing mild depression and three to four hot flashes a day. He is anxious about the persistent rise in his PSA. A computed tomography (CT) scan and bone scan were done, and the findings show no evidence of metastatic disease. How has H.L.'s cancer progressed? What should H.L.'s medical oncologist do next?

If a patient has a rising PSA level while on ADT, a testosterone level should be rechecked to make sure it is below castrate levels. If it is not, then ADT is not adequately blocking the production of androgens, and a change in medication or an orchiectomy is usually recommended. If the testosterone level is <50 ng/mL, the patient is confirmed to be castrate resistant, and additional systemic treatment will be necessary. Imaging tests can be used to identify the presence or absence of distant metastases, the results of which will determine the appropriate treatment course. If a patient with CRPC has no evidence of metastatic disease, then the cancer is classified as nonmetastatic CRPC.

Despite the fact that the cancer is now labeled castration resistant, it is still very dependent on the androgen pathway, and can continue to be targeted throughout the disease. Patients who have nonmetastatic CRPC will typically be responsive to secondary hormonal manipulations combined with continued GnRH analog. Further research into therapeutic targets of the androgen pathway has led to the development of second-generation AR inhibitors. Similar to the first-generation antiandrogens (see Table 100-3), these novel agents inhibit the AR, but are considered more potent and efficacious. OS benefits have been demonstrated in clinical trials

with these new agents in the setting of nonmetastatic CRPC. The patients in these trials were considered high risk for progression, as indicated by a short prostate-specific antigen doubling time (PSADT ≤10 months), or the rate/velocity at which the PSA doubles; therefore, these agents are often initiated once patients meet these criteria. If patients progress on a next-generation AR inhibitor and are confirmed to still have nonmetastatic CRPC, then other secondary hormone manipulation strategies can be implemented. These strategies have not shown a survival benefit, but may slow the progression of the disease and symptoms. They include first-generation antiandrogens, androgen withdrawal, ketoconazole, and other secondary hormone manipulations discussed subsequently.

H.L. now has nonmetastatic CRPC confirmed by the rise in PSA despite testosterone below castrate level on ADT, with no evidence of metastatic disease on scans. The next step for H.L. would be to continue leuprolide and add a second-generation antiandrogen when he is thought to be at high risk for progression (ie, short PSADT).

METASTATIC DISEASE

When metastatic disease occurs, performance status and extent of disease as determined by imaging should be evaluated because these factors will determine treatment options and outcomes. Both germ line and somatic, or acquired, genetic mutations in *HRR* genes can have clinical implications in metastatic prostate cancer. Genetic testing is recommended in this setting to further characterize the disease and identify possible treatment options. In addition, a discussion with the patient is necessary regarding the goals of treatment because it is focused on palliation and improvement in quality of life rather than the chance for cure as it is with treatment for localized disease. Metastatic disease is most likely to be seen in the bones, lung, and liver. Symptoms are more common in metastatic disease and are often related to the sites of metastases.

Metastatic Castration-Sensitive Prostate Cancer

Patients who are first diagnosed with metastatic prostate cancer, or patients who develop metastatic disease after definitive local therapy, are considered castration sensitive, or castration naive because they have progressing disease but have not yet received ADT and do not have castrate levels of testosterone. Treatment for these patients includes ADT as the backbone of therapy, just as it does in earlier stages when ADT is indicated for progression or recurrence, because the disease continues to be hormone dependent. The choices for ADT include GnRH antagonists, GnRH agonists with an antiandrogen for patients at risk for tumor flare symptoms, and, less commonly, orchiectomy. The addition of chemotherapy and androgen-directed therapies to initial ADT in patients with castration-sensitive prostate cancer has shown a survival benefit, and are viable treatment options. Docetaxel was one of the first and only chemotherapies that had demonstrated a survival benefit in metastatic CRPC. More recently, strong evidence has supported its use as combined therapy with ADT for the initial treatment of patients with castration-sensitive prostate cancer.[66,67] There are several next-generation androgen-directed therapies approved in this setting as well. There is yet to be a clear consensus on initial treatment selection or sequencing of these treatment options. Careful considerations of a medication's administration, treatment duration, toxicity profile, and cost, along with a patient's overall health, comorbidities, and volume of disease should be taken into account during treatment selection.[68]

Metastatic Castration-Resistant Prostate Cancer

There are a number of different treatment options that can be used in metastatic CRPC, including chemotherapy, immunotherapy, androgen pathway–directed therapy, and other targeted therapies. Males who are in good health and have asymptomatic disease may be treated with sipuleucel-T, an immunotherapy. For castrate-resistant disease that is symptomatic and rapidly progressing,

cytotoxic chemotherapy would generally be considered. Newer androgen-directed therapies can be given before or after chemotherapy. If genetic testing shows mutations in *HRR* genes, then the use of poly-ADP ribose polymerase (PARP) inhibitors is also an option. Again, optimal sequencing of these agents is still not fully elucidated; however, patients with poor performance status, or a need to delay cytotoxic chemotherapy, can benefit from receiving the relatively tolerable androgen-directed therapies sooner rather than later. A discussion regarding the benefits of each therapy, along with potential adverse effects, is important in deciding if and when these therapies should be implemented.

TREATMENT OPTIONS FOR ADVANCED DISEASE

CASE 100-4

QUESTION 1: E.S. is a 70-year-old male who is currently receiving leuprolide every 3 months. He was initially diagnosed with metastatic prostate cancer in June 2018 and was found to have four bone metastases at that time. He was initially treated with docetaxel plus prednisone every 3 weeks for six cycles in addition to ADT and now continues with the leuprolide. He comes to the medical oncologist's office for a routine follow-up appointment. His pertinent laboratory results are as follows:

Date	PSA Level (ng/mL)	Testosterone (ng/dL)
July 27, 2018	2.16	
October 20, 2018	2.01	<50
January 10, 2019	2.32	
April 12, 2019	2.27	
July 14, 2019	2.93	
October 26, 2019	3.22	

January 14, 2020	4.57	
April 17, 2020	5.06	<50
July 23, 2020	5.51	
October 10, 2020	8.79	<50

At this follow up appointment, he admits to feelings of fatigue but is otherwise in good health and exercises by walking 3 miles a day. He has no known drug allergies and is only taking lisinopril 10 mg daily for high blood pressure and bupropion HCl extended release (ER) 300 mg daily for depression. The medical oncologist orders a CT scan of the chest, abdomen, and pelvis, the result of which reveals a new mass in the pelvis and liver. His genetic testing shows no abnormalities in *HRR* genes.

What would be the best treatment recommendation for E.S.?

Cytotoxic Chemotherapy

TAXANES

Taxanes are the only class of chemotherapy that has shown a survival benefit in the treatment of metastatic prostate cancer. These agents are microtubule inhibitors, which promote assembly of microtubules and inhibit disassembly, thereby stabilizing microtubules and arresting the cell cycle. Before their development, chemotherapy was generally not effective, with mitoxantrone only providing a relief of symptoms. Currently, taxanes are a standard of care in metastatic prostate cancer, and have a role in both the initial treatment of metastatic, castration-sensitive disease and later in rapidly progressing metastatic CRPC.

Docetaxel

Docetaxel in combination with prednisone is considered the mainstay of therapy for symptomatic, metastatic CRPC when cytotoxic chemotherapy is indicated. Given that there are less toxic therapies available for treatment in this setting, Docetaxel-based regimens were found to improve OS in two randomized phase III

studies. Docetaxel plus prednisone was compared to the previous standard of care, mitoxantrone plus prednisone. When docetaxel-based regimens were given every 3 weeks with prednisone versus mitoxantrone plus prednisone in >1000 males, there was an increase in OS of about 2 months (TAX327: 18.9 vs 16.5 months, *P* = .009 and SWOG9916: 17.5 vs 15.6 months, *P* = .02). Quality of life was similar in both arms of each study.[69,70] Myelosuppression is a dose-limiting toxicity with docetaxel, requiring frequent monitoring for neutropenia and thrombocytopenia. It also carries risks of neuropathy, peripheral edema, and hypersensitivity reactions. Premedication is necessary for the prevention of the latter two toxicities. Docetaxel is extensively metabolized by the liver, with strict criteria to treat before each cycle, because abnormalities of bilirubin and liver functions tests can increase the risk of severe toxicities and death.[71] Tolerability was improved when docetaxel was switched to a lower dose every 2 weeks with less febrile neutropenia and other toxicities.[72] Alternative dosing regimens may be considered in patients unable to tolerate docetaxel on an every 3-week schedule.

Docetaxel is also an option in males with advanced or metastatic, castration-sensitive prostate cancer at the initiation of ADT. The Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial illustrated that early initiation of docetaxel plus prednisone every 3 weeks for six cycles in addition to ADT improved survival (57.6 vs 47.22 months, *P* = .002). A subgroup analysis of males with high-volume disease, defined as the presence of visceral metastases or high bone burden, had a median OS of 51.2 versus 34.4 months (*P* < .001); very little benefit was seen in males with lower disease volume. Disease volume should be taken into consideration when deciding the utility of dose intensification with docetaxel therapy at ADT initiation in metastatic castration-sensitive prostate cancer. Adverse effects seen in the combination group included febrile neutropenia and neuropathy.[67,73]

The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial further demonstrated a survival advantage, with the addition of six cycles of

docetaxel at ADT initiation in males with newly diagnosed advanced prostate cancer.[66] In both studies, there was a clinically significant increase in serious toxicities with the use of docetaxel. These studies support the early use of docetaxel chemotherapy with ADT; however, careful patient and treatment consideration must be taken to determine which patients would benefit most with using docetaxel in this setting given the risk of increased toxicity.

Cabazitaxel

Cabazitaxel in combination with prednisone is typically a treatment option after progression on docetaxel-based regimens. In a randomized phase III study of cabazitaxel 25 mg/m^2 every 3 weeks plus prednisone versus mitoxantrone plus prednisone in metastatic patients with CRPC who were docetaxel refractory, there was a 2.4-month improvement in OS (P = .0001), but with more severe adverse effects. Death occurred in 4.9% of patients (vs 1.9% in the mitoxantrone-containing regimen), mostly owing to sepsis and renal failure. Other adverse effects included febrile neutropenia, severe diarrhea, anemia, nausea, vomiting, and fatigue.[74] As with docetaxel, monitoring of complete blood count and liver function is recommended. Cabazitaxel can also cause severe hypersensitivity because of its formulation with polysorbate 80; therefore, premedication is necessary. In an effort to mitigate cabazitaxel toxicities, a phase III trial compared cabazitaxel 20 to 25 mg/m^2 every 3 weeks. The lower dose was found to be noninferior and less toxic, particularly with regard to myelosuppression and febrile neutropenia.[75] Reduced dose of cabazitaxel is now a standard of care in this setting, with the higher dose reserved for fit patients who wish to be more aggressive. There is some evidence to support the use of cabazitaxel before docetaxel in patients with chemotherapy-naive, metastatic CRPC, so it can be considered in patients who are not candidates for docetaxel chemotherapy.[76]

MITOXANTRONE

Before the introduction of docetaxel as first-line cytotoxic chemotherapy, mitoxantrone plus prednisone was considered the only chemotherapy regimen that provided benefit in metastatic CRPC. It did not improve OS, but it did increase the quality of life, as measured by a 29% pain response rate versus 12% with prednisone alone.[77] Because of its lack of benefit in OS and progression-free survival (PFS), it has been relegated to last-line therapy in which there are no other viable therapies for symptomatic relief of advanced metastatic CRPC.

Next-Generation Androgen-Directed Therapy

An increased understanding of the role of androgens in prostate cancer has clarified the concept that the androgen pathway is still active in advanced prostate cancer. This has led to the development of new agents with proven efficacy in advanced prostate cancer that work to inhibit ARs or the enzymes needed for androgen synthesis. Some of the next-generation therapies have demonstrated survival benefit in nonmetastatic CRPC and in metastatic castration-sensitive prostate cancer and in CRPC. As previously mentioned, darolutamide, apalutamide, and enzalutamide have demonstrated a survival benefit in nonmetastatic CRPC. Apalutamide, enzalutamide, and abiraterone have evidence to support their use in metastatic castration-sensitive prostate cancer. Phase III trials have confirmed the utility of abiraterone and enzalutamide in metastatic CRPC both before and after docetaxel. Because of their tolerable toxicity profile and ease of oral administration, abiraterone and enzalutamide can be used before docetaxel in patients who are minimally symptomatic, ineligible and/or unable to tolerate therapy, or in patients preferring less toxic therapy. With the abundant evidence for the use of the next-generation androgen-directed therapies at different points of the disease, treatment selection and sequencing are integral questions when strategizing treatment. There have yet to be any comparative studies to indicate a preference in treatment selection; therefore, both treatment and patient-specific factors must be considered when

selecting the best treatment option. Generally, once a patient progresses on a next-generation androgen-directed therapy, the agent is not considered for reuse.

ABIRATERONE

Abiraterone is an androgen synthesis inhibitor that irreversibly inhibits cytochrome 450 (CYP)17 (17 α-hydroxylase/C17,20-lyase), an enzyme that is required for androgen biosynthesis and is expressed in prostatic, testicular, and adrenal tissue. It inhibits testosterone precursors, dehydroepiandrosterone and androstenedione. When given in combination with prednisone in males with metastatic CRPC who had progressed on docetaxel, a phase III, randomized, placebo-controlled trial found that median OS could be prolonged over 4 months compared to prednisone alone (15.8 vs 11.2 months, $P > .001$).[78,79] There was also a statistically significant improvement in palliation of pain from bone metastases, PSA response rate, and time to PSA progression.[80]

Abiraterone was studied before docetaxel therapy in another randomized phase III trial. Patients with asymptomatic or minimally symptomatic metastatic CRPC had a PFS that was doubled compared to prednisone alone (16.5 vs 8.3 months, $P > .001$). Progression of pain intensity was delayed from 18.4 to 26.7 months.[81] This is a reasonable option in patients before or after docetaxel in patients with metastatic CRPC.

In metastatic castration-sensitive prostate cancer, abiraterone is an approved option for treatment. Two phase III trials of abiraterone with low-dose prednisone demonstrated a survival benefit over ADT alone in this setting. The LATITUDE study evaluated 119 males with high-risk metastatic castration-sensitive prostate cancer. High-risk disease was defined as having at least two of three factors: three or more bone lesions, visceral metastases, or a Gleason score ≥8. In addition to improving OS (53.3 vs 36.5 months), adding abiraterone improved progression, PSA progression, time to subsequent therapies, and other clinical outcomes.[82] The STAMPEDE trial demonstrated a survival advantage with the early use of abiraterone

with ADT in metastatic castration-sensitive cancer in both high-risk and low-risk patients.[83]

Because of the inhibition of abiraterone on CYP17, increased mineralocorticoid production by the adrenals can occur, causing side effects such as hypertension, hypokalemia, and fluid retention. Concomitant use of prednisone reduces the incidence and intensity of these side effects. Abiraterone should be taken orally on an empty stomach (at least 1 hour before or 2 hours after food).[84] A newer micronized, or fine particle, form of abiraterone is also available, used in conjunction with methylprednisolone, and can be taken without regard to food.[85] The most common adverse effects associated with abiraterone include fatigue myalgias/arthralgias, and peripheral edema. Other adverse effects that occurred but were most commonly grade 1 or 2 are diarrhea, constipation, hot flashes, and hypertension. When a patient is started on abiraterone, liver function, potassium, and blood pressure should be monitored closely for the first 90 days and then at least monthly.[84,85]

ENZALUTAMIDE, APALUTAMIDE, AND DAROLUTAMIDE

The newer AR antagonists inhibit the function of the AR by three mechanisms: prevention of binding between androgens and the receptor, prevention of the translocation of AR to the nucleus, and prevention of binding of the AR to DNA.[86,87] Various next-generation AR inhibitors are utilized in both nonmetastatic and metastatic CRPC as well as in metastatic castration-sensitive prostate cancer. These agents are utilized over first-generation antiandrogens in the advanced prostate cancer setting because of their higher affinity for the AR and lack of agonistic properties, as seen with first-generation antiandrogens. In patients with metastatic CRPC, trials have demonstrated efficacy of enzalutamide both before docetaxel therapy (Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer [PREVAIL] trial[88]) and after docetaxel treatment (AFFIRM trial[89]). The results of these two studies demonstrated median OS benefit with enzalutamide over placebo. Quality of life was also

improved in the AFFIRM study. Seizures occurred rarely (<1%), although caution should be used in patients with risk factors for seizure.[90] In patients with nonmetastatic CRPC, median OS was again found (67 vs 56.3 months, *P* = .001) in the Safety and Efficacy Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer (PROSPER) trial.[91]

And in patients with castration-sensitive metastatic prostate cancer, the Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer (ENZAMET) trial estimated that the 3-year OS was 80% versus 72% in patients receiving standard of care. All patients received ADT concomitantly.[92] The most commonly reported side effects of enzalutamide include fatigue, back pain, hot flashes, arthralgia, hypertension, and decreased appetite. There is an increased incidence of falls and fractures that require evaluation of patients for these risks.

Apalutamide's approval in nonmetastatic CRPC is based on the Study of Apalutamide (ARN-509) in Men With Non-Metastatic Castration-Resistant Prostate Cancer (SPARTAN) trial of 1207 patients, which demonstrated metastasis-free survival of 40.5 versus 16.3 months with placebo (*P* < .001) if the PSADT ≤10 months and a median OS 73.9 versus 59.9 months with placebo (*P* = .016). Adverse effects included hypertension (25%), rash (25%), diarrhea (20%), nausea (18%), and fatigue (26%–39%).[93] Overall, apalutamide has a side effect profile similar to that of enzalutamide. Apalutamide demonstrated benefit in the phase 3 Study of Apalutamide (JNJ-56021927, ARN-509) Plus Androgen Deprivation Therapy (ADT) Versus ADT in Participants With mHSPC (TITAN) study that included patients with metastatic castration-sensitive prostate cancer. OS at 24 months was 82.4% versus 73.5% in the placebo arm (*P* = .005).[94]

Darolutamide is approved in nonmetastatic CRPC. The phase III Efficacy and Safety Study of Darolutamide (ODM-201) in Men With High-risk Non-metastatic Castration-resistant Prostate Cancer (ARAMIS) study in patients with a PSADT ≤10 months demonstrated a metastasis-free survival of 40.4 versus 18.4 months with placebo (*P* <.001), with a final analysis of a 31% decrease in risk of death

with darolutamide. The most common adverse effects were <15% and included fatigue, pain in an extremity, and rash.[95,96] Darolutamide is not associated with an increased incidence of seizures, falls, or fractures as it is with the other second-generation AR inhibitors. It is thought that darolutamide's lower incidence of seizure and other central nervous system–related adverse effects may be attributed to its low blood–brain barrier penetration.[96] In addition, darolutamide has less drug interaction potential given that it is not a potent inducer of CYP enzymes as are enzalutamide and apalutamide.[97]

Other Secondary Hormone Manipulation

There are other possible secondary hormone manipulations that can be used for treatment in nonmetastatic CRPC and in metastatic prostate cancer such as antiandrogens, antiandrogen withdrawal, ketoconazole, glucocorticoids, and estrogens. However, they are now rarely used in practice given that they are not as potent as the newer antiandrogens and have not shown a survival benefit. It is possible to use these agents sequentially after alternative treatments with proven survival benefit have been exhausted.

The addition of a first-generation antiandrogen for CAB is a possible treatment option for patients with CRPC (see Table 100-3). Because of the multiple daily dosing of flutamide and the additional side effect of delayed dark vision adaptation of nilutamide, bicalutamide is typically the preferred agent. Although these agents are generally well tolerated, adverse effects can include hepatic toxicities requiring monitoring for elevations in liver enzymes. Pulmonary-associated side effects are rare, but serious toxicity is possible with these agents.[4]

For a patient already on a first-generation antiandrogen, discontinuation of the agent after progression on CAB can result in a decline in PSA level, called *antiandrogen withdrawal syndrome*. This response can be seen in ~20% of patients and can be attempted before initiation of another treatment.[98]

Ketoconazole is an antifungal agent that is an inhibitor of adrenal androgen synthesis. The testes produce nearly 90% of testosterone in males, with the remaining 10% derived from the androgens produced in the adrenal glands. The androgens are subsequently converted to testosterone and DHT. For prostate cancer treatment, ketoconazole must be administered three times daily under low gastric pH conditions along with a glucocorticoid. Its complex administration in addition to frequent gastrointestinal toxicities and high potential for drug interactions limit its use. It should not be used if the patient has already progressed on abiraterone because they are both CYP17A1 inhibitors.[4]

Several different glucocorticoids and estrogens have historically been utilized in the treatment of prostate cancer. It is still unknown exactly how these agents act in CRPC. It is thought that estrogen can cause suppression of LH release from the pituitary to then reduce testosterone production in the testes. Glucocorticoids, such as hydrocortisone, dexamethasone, and prednisone, may suppress adrenal androgen synthesis by reducing the production of adrenocorticotropic hormone (ACTH) in the pituitary. These agents have somewhat fallen out of favor given their toxicities and the increased number of options that are now available.[4]

Immunotherapy

SIPULEUCEL-T

Sipuleucel-T is the first cancer vaccine to be approved by the U.S. Food and Drug Administration (FDA). Unlike vaccines that prevent infection by allowing the immune system to recognize the virus or bacteria, a cancer vaccine treats the cancer. This cancer vaccine stimulates a patient's own immune system against the prostatic acid phosphatase (PAP) antigen that is expressed in most prostate cancer tissues. Collection of a white blood cell fraction containing antigen-presenting cells is taken from the patient and then exposed to prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP–GM–CSF recombinant fusion protein). The

activated cells are then reinfused into the patient 3 days after collection. The infusion is repeated every 2 weeks for a total of three treatments. The randomized, double-blind, placebo-controlled phase III study was conducted in >500 males with minimally symptomatic or asymptomatic metastatic CRPC without visceral metastases. Median OS was 25.8 versus 21.7 months in the placebo group (*P* = .03). Treatment was well tolerated, with common adverse effects of chills (54.1%), pyrexia (29.3%), and headache (16%). Close monitoring of cardiac and pulmonary conditions during infusion and premedication with an antihistamine and acetaminophen is recommended to alleviate the commonly reported acute infusion reactions, which can include chills, fever, respiratory events, hypertension/hypotension, tachycardia, syncope, nausea, vomiting, and fatigue. These reactions are typically mild to moderate in nature and can subside within 1 to 2 days of infusion. If acute infusion reaction is more severe, the infusion rate can be reduced.[99] Unlike other treatments for metastatic CRPC, sipuleucel-T does not elicit a change in PSA level that can be used as an objective measure of response. This is a treatment option for metastatic patients with CRPC who are slowly progressing, with little or no symptoms, for which immediate response to treatment is not required. Because sipuleucel-T has not been studied in patients with visceral metastases, it is typically not recommended in these patients.[99]

PEMBROLIZUMAB

If tumor testing identifies an advanced prostate cancer as having a large number of mutations, then it may be categorized as having high levels of microsatellite instability (MSI-H) or deficient mismatch repair (dMMR). Those patients may be eligible for pembrolizumab immunotherapy. Pembrolizumab is a monoclonal antibody that binds to the programmed cell death 1 (PD-1) receptor on T cells and blocks its interaction with its ligand (PDL-1 and PDL-2) to help restore the activation of T-cell–mediated immune response against tumor growth. The use of pembrolizumab in solid tumors is approved in patients with unresectable or metastatic MSI-H/ dMMR cancer

who have progressed on prior treatment or who have no satisfactory alternative treatment options. It is given at a flat dose of 200 mg every 3 weeks. Common side effects can include fatigue, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, and dyspnea. Less common, but severe and potentially fatal immune-mediated adverse reactions are possible in any organ system, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and dermatologic reactions. Close and frequent monitoring for signs and symptoms and immediate management often using corticosteroids is necessary for these immune-mediated adverse effects.[100]

Poly-ADP Ribose Polymerase Inhibitors

Defects in DNA damage repair pathway occur in a significant proportion of advanced prostate cancers. Genetic testing can reveal mutations in *HRR* genes, which can include *BRCA1/2*, *CHEK1/2*, *ATM*, *PALB2*, *FANCA*, and *RAD51*, among others.[101] These genes are involved in the repair of DNA double-strand breaks. PARP function includes repairing single-strand breakthrough base excision repair. PARP inhibitors trap PARP on DNA and prevent the repair of the single-strand breaks. The deficiencies in DNA repair caused by either an *HHR* gene mutation or by PARP inhibitors may not individually cause cytotoxicity, but the combined effect of overwhelming accumulation of DNA damage will ultimately cause cell death, a concept known as *synthetic lethality*.[101,102] There is growing evidence supporting the efficacy of PARP inhibitors in patients with prostate cancer having HRR deficiencies. Currently, two agents, olaparib and rucaparib, are approved in this setting.

A phase III trial of males with metastatic CRPC who progressed on a next-generation androgen-directed therapy and up to one taxane (permitted but not required) were randomized to olaparib 300 mg twice daily versus physician's choice. All patients had to have *HRR* mutation. The primary end point of radiographic PFS was significantly increased in the HRR cohort, and OS was also improved

in patients specifically with *BRCA 1/2* or *ATM* mutations.[103] Not all patients received prior docetaxel in this study; therefore, olaparib may be a treatment choice for patients with metastatic castration-resistant prostate cancer (mCRPC) having *HRR* mutations that have been treated with an androgen-directed therapy either before or after docetaxel treatment.

Rucaparib was evaluated in a phase II trial of patients with mCRPC having *HRR* mutations that progressed on prior androgen-directed therapy and prior taxane therapy. The trial demonstrated an objective response rate (ORR) of 44% in patients with *BRCA 1/2* mutation leading to its approval in this setting.[104]

PARP inhibitors are relatively well tolerated, with the most significant toxicities being hematologic and gastrointestinal. Monitoring of complete blood counts is recommended given the risks of anemia, thrombocytopenia, and neutropenia, and dose interruptions and reduction may be necessary for counts to recover. Antiemetics should be offered to patients to prevent nausea and vomiting. A small, but potentially fatal, risk of myelodysplastic syndromes can occur with the use of PARP inhibitors. Further research is being conducted on these agents, as well as other PARP inhibitors, to better define their role in the treatment of patients with advanced prostate cancer having *HRR* mutations.[105,106]

Radium-223

In patients with CRPC and symptomatic bone metastases and no known visceral metastases, radium-223 dichloride has been shown to increase median OS (14.9 months with radium-223 vs 11.3 months with placebo) and to reduce pain when given every 4 weeks for six cycles. It also delayed time to first skeletal event (15.6 vs 9.8 months, $P > .001$). It emits high-energy alpha particles that target bone metastases by binding to areas of increased bone turnover. The short-range radiation creates a localized toxic effect of double-stranded DNA breaks in these targeted areas. Adverse effects were consistently similar between the active and placebo arms, although

there was a slightly higher rate of myelosuppression with radium-223. More participants in the placebo arm discontinued the study drug because of adverse events.[107] Radium-223 should not be used in combination with docetaxel or other systemic therapies for prostate cancer treatment. It can be used in conjunction with ADT with the exception of abiraterone and prednisone, in which a higher risk of fracture has been suggested.[108]

E.S. has a rising PSA despite castrate levels of testosterone. He has CRPC with metastases to the bone and liver, which makes him ineligible for sipuleucel-T and radium-223. He could potentially receive chemotherapy; however, he is not rapidly progressing and is not significantly symptomatic. A next-generation androgen-directed therapy would be most appropriate. Abiraterone or enzalutamide are treatment choices for E.S. Given that he is on bupropion, which can lower seizure threshold, abiraterone may be the most appropriate choice, given the risk of seizure with enzalutamide, and medications that lower seizure threshold can increase that risk.

Bone Metastases

Case 100-4, Question 2: E.S. is tolerating treatment with abiraterone well. Because E.S. now has CRPC with high-volume bone metastases, what recommendations can be made to decrease the risk of skeletal-related events?

Bone metastases occur in around 90% of males who develop metastatic prostate cancer and are a common complication in advanced disease.[109] Prostate cancer bone metastases are primarily osteoblastic lesions, in which there is increased bone formation around tumor deposits. In addition, there is increased osteoblastic bone resorption or osteolysis.[4] They may be asymptomatic, but can frequently cause pain, decreased mobility, and diminished quality of life. These metastases can also cause skeletal-related events, which include pathologic fractures, need for radiation or surgery to the bone, and spinal cord compression. There are several systemic therapies for the treatments of advanced prostate cancer, such as

abiraterone, enzalutamide, docetaxel, and radium-223 that have shown not only an improved survival but also a delay in bone-related complications or improvement in bone-related pain. Several of the following treatments are specifically used to prevent skeletal-related events and/or improve symptoms from bone metastases in patients with prostate cancer.[69,80,107,110]

BISPHOSPHONATES

The only bisphosphonate shown to be of benefit in patients with CRPC and bone metastases is zoledronic acid. It was shown to decrease the frequency of skeletal-related events compared to placebo. There was also a prolonged time to first skeletal-related event and decrease in pain and analgesic score in patients treated with zoledronic acid.[111] It is approved at a dose of 4 mg intravenously every 3 to 4 weeks but must be dose reduced in renal dysfunction, and it is not recommended to use if renal clearance is <30 mL/minute. Zoledronic acid does not provide benefit in patients with castrate-sensitive prostate cancer, so it should only be used in patients with CRPC with bone metastases. Patients should take calcium and vitamin D as necessary to prevent hypocalcemia. An uncommon but serious adverse effect of osteonecrosis of the jaw can occur with zoledronic acid use.[4] Patients should be advised on the importance of good oral hygiene, a baseline dental evaluation, and avoiding invasive dental procedures during therapy, if possible, to minimize their risk.[108,112]

RECEPTOR ACTIVATOR OF NUCLEAR FACTOR-KB LIGAND INHIBITORS

Denosumab is a monoclonal antibody for the receptor activator of nuclear factor-kB ligand (RANKL), which is involved in osteoclast-mediated bone resorption and remodeling.[108] When compared to zoledronic acid in metastatic CRPC, denosumab was more effective at preventing the skeletal-related events of pathologic fractures, need for radiation or surgery to bone metastases, or spinal cord compression. Denosumab also restored bone density.[4] The serious

adverse effect of concern associated with denosumab is the same as that with bisphosphonates, osteonecrosis of the jaw, and it has a higher rate of hypocalcemia. Renal adjustment is not necessary for denosumab dosing; however, renal function should be monitored, particularly because of the increased risk of hypocalcemia and hypophosphatemia in patients with renal clearance <30 mL/minute. For bone metastases occurring in patients with CRPC, denosumab is given as 120 mg subcutaneously every 4 weeks. Patients should take calcium and vitamin D to prevent hypocalcemia.[108,113]

SYSTEMIC RADIOTHERAPY

Systemic radiotherapy may be used with radium-223, delaying time to first skeletal event in symptomatic bone metastases, as discussed previously. It is the only bone-targeting agent with a survival benefit and can be a good choice for patients with extensive bone disease with otherwise minimal disease.[108] Two β-emitting radiotherapy agents that have been utilized are strontium-89 or samarium-153 in patients with painful bone metastases that are not responsive to palliative chemotherapy and pain medications. However, they have no survival benefit, and myelosuppression is a major concern that must be factored into the future plan if additional chemotherapy is to be used.[114]

EBRT, although not systemic radiotherapy, is an option for one or a few symptomatic sites of bone metastases. It is most often used to provide symptomatic relief.

E.S. should start taking calcium and vitamin D supplementation and can add weight-bearing exercises to his daily walking. In addition, his medical oncologist can recommend either zoledronic acid every 3 to 4 weeks or denosumab every 4 weeks.

ADVERSE EFFECTS OF PROSTATE CANCER THERAPY

Because of the large number of males who are diagnosed with prostate cancer, as well as the continuously increasing numbers of those who live a considerable amount of time after therapy, the adverse effects of cancer therapy should remain a consideration for the remainder of the patient's life. It should be recognized that these effects include both short- and long-term issues. Patients should be aware of these potential adverse effects and their management strategies in a discussion with their physician. Guidelines from the American Cancer Society are available for the primary care physician regarding long-term survivorship of patients with a prior diagnosis of prostate cancer.[115]

Androgen Deprivation Therapy

The loss of the majority of testosterone with the use of ADT in a male can cause a variety of symptoms that can negatively impact the quality of life. The large number of males living after a diagnosis of cancer should be aware of the long-term adverse effects of this therapy. The American Society of Clinical Oncologists (ASCO) survivorship guidelines recognize these problems and give recommendations for their monitoring. These include health promotion, screening for secondary cancers, rectal and urinary symptoms, cardiovascular and metabolic effects, anemia, bone health, sexual dysfunction, and vasomotor symptoms.[115]

VASOMOTOR SYMPTOMS

CASE 100-5

QUESTION 1: P.L. is a 63-year-old male who has been on ADT therapy for just over a year, and is experiencing hot flashes and mild depression. He also had a bone mineral density scan, indicating ADT-induced osteopenia.

What can P.L.'s medical oncologist offer him to alleviate some of the side effects and complications he is experiencing from ADT treatment?

Vasomotor symptoms will bother many males for the duration of their treatment with ADT, with an incidence of up to 40%. Hot flashes are characterized by an intense heat sensation, flushing, and diaphoresis, involving the face and trunk and may also include anxiety and palpitations. These effects can vary in frequency, intensity, and duration. The mechanism may be because of a withdrawal of androgens, disrupting the equilibrium of the norepinephrine and serotonin neurotransmitters. Data have been taken from females as well as from males in the efficacy of these agents because most therapies have seen similar efficacy in both males and females. These agents include, among others, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and gabapentin.[115,116]

Gabapentin has been one of the most studied drugs for the treatment of hot flashes in males. Gabapentin at doses of up to 900 mg/day in males on ADT showed a significant reduction in hot flashes.[117] Titration recommendations are to start at 300 mg daily and increase in increments of 300 mg to achieve the final dose. Pregabalin, which has shown some benefit in females at doses of 150 to 300 mg/day, has not been studied in males but may be a reasonable option starting at doses of 75 mg twice daily.

Serotonin and serotonin–norepinephrine reuptake inhibitors have also shown benefit in males on ADT, although no placebo-controlled, randomized trials have been done to date. Venlafaxine has been the most extensively studied from this drug class at varying doses. Paroxetine has also been studied in males on ADT. The use of other agents in these classes has also been reported.[115,118]

Alternative therapies have also been used to treat hot flashes. Acupuncture has shown some promise in small studies. Soy and herbal products have also been used; however, randomized controlled studies must be done to determine the true benefit of these therapies.[116]

CARDIOVASCULAR AND METABOLIC ADVERSE EFFECTS

There is a concern of an association between ADT and risk of mortality from cardiovascular disease. Although this has not been seen consistently in clinical trials, congestive heart failure and myocardial infarction have been identified as a risk highest in those who already have a risk of cardiovascular disease. A meta-analysis of studies with nonmetastatic and non-CRPC did not find a significant difference in cardiovascular death in those males treated with ADT versus those who were not. The American Heart Association advisory panel concluded that links remain controversial, and do not recommend periodic cardiac testing, but screening for cardiovascular risk factors should occur and monitoring of blood pressure, lipid profiles, and serum glucose should be routine, especially in those males who receive >6 months of ADT.[119] Males with a recent history of cardiovascular disease may be at higher risk.[115,120]

Androgen deprivation has been shown to increase the risk of obesity, decrease lean muscle mass, decrease insulin sensitivity, increase high-density lipoprotein levels, and increase subcutaneous fat accumulation. Screening for diabetes and hypercholesterolemia is necessary, particularly with long-term use of ADT.[4,115]

SEXUAL ADVERSE EFFECTS

Loss of libido and erectile dysfunction are expected adverse effects of ADT, occurring in up to 85% of males treated with ADT. The impact of ADT therapy may be delayed, with full effect occurring up to 2 years later.[115,121] Recovery from erectile dysfunction will usually occur after cessation of therapy. However, for patients on long-term therapy, there should be an open dialog between the health care team and the patient regarding options available to help in mitigating these effects.[115] Other factors that may be contributing to erectile dysfunction should also be considered, including a history of diabetes or cardiovascular disease as well as whether the patient has had a previous prostatectomy or radiation to the prostate. There is no consensus regarding the best therapy for this adverse effect.

Phosphodiesterase inhibitors can be offered because 44% of patients reported a benefit in one study.[115,121,122]

PSYCHOLOGICAL/COGNITIVE ADVERSE EFFECTS

Psychosocial adverse effects such as distress, depression, and cognitive impairment may occur. It has been estimated that up to 30% experience distress, 25% have increased anxiety, and almost 10% have a major depressive disorder. Low testosterone levels can affect mood in some males, causing depression and short temper. Routine assessment is crucial to identifying those patients experiencing these effects that can have a major impact on survivorship and quality of life with referral for behavioral intervention considered, as necessary.[115,123,124]

BONE HEALTH ADVERSE EFFECTS

Patients treated with ADT are more susceptible to decreased bone mineral density and bone fractures. In a study looking retrospectively at males diagnosed with prostate cancer from 1992 to 1997, those who received ADT therapy were compared to those who did not and were found to have a higher incidence of fractures (19.4% vs 12.6%, $P > .001$). ADT increases bone turnover and decreases bone mineral density with a 21% to 54% relative increase in fracture risk. Rapid loss of bone mineral density is seen within 6 to 12 months.[125]

The Prostate Cancer Survival Guidelines of the ASCO suggest that all males who have received ADT should be assessed for the risk of fracture, using a baseline dual-energy x-ray absorptiometry (DEXA) scan and calculation of a FRAX® (Fracture Risk Assessment Tool) score.[115] For those males who are determined as being high risk, there are a number of options. Alendronate 70 mg weekly, zoledronic acid 5 mg annually, or denosumab 60 mg every 6 months are available for use in this setting.[6,108] Patients are recommended to take calcium and vitamin D supplementation according to age-appropriate guidelines and possibly more in patients who are deficient.

P.L.'s medical oncologist can offer P.L. an antidepressant. Gabapentin, venlafaxine, and acupuncture have been shown to have some benefits for vasomotor symptoms, such as hot flashes. If P.L. is interested in being treated for both his depression and hot flashes, venlafaxine may be a good option because it can treat both side effects at the appropriate dose. As for P.L.'s osteopenia, weight-bearing exercises, supplementation of vitamin D and calcium, and the addition of yearly zoledronic acid or biyearly denosumab can be given to prevent complications that can arise from bone loss.

Radiation Effects

CASE 100-6

Question 1: C.W. has been recently diagnosed with unfavorable intermediate-risk prostate cancer. He discusses his options for definitive local treatment with the medical oncologist, radiation oncologist, and urologist. He decides to undergo radiation, and the radiation oncologist plans to treat him with EBRT in conjunction with 6 months of ADT.

What side effects from treatment can C.W. expect? What concerns will the medical oncologist have regarding side effects and his history (PMH, FH, and SH)?

SEXUAL SIDE EFFECTS

Erectile dysfunction is the most commonly seen sexual adverse effect of radiation but can include decreased volume of ejaculate, absence of ejaculate, decreased intensity of orgasm, and decreased libido. Erectile dysfunction ≥3 years after EBRT occurs in 36% to 68% of patients and 50% to 60% of males have some extent of erectile dysfunction with brachytherapy. With radical prostatectomy, erectile dysfunction is seen soon after surgery but may improve over time. This is the opposite of what is seen with radiation, where it is more of a slow decline.[6,115]

In one study, 80% of patients receiving radiation therapy responded well to sildenafil. It was seen that 74% of patients in another study continued to respond after 4 years. Additional factors

that may contribute to erectile dysfunction should be considered, such as coronary artery disease and diabetes as well as patient age. Some patients will not respond and should be referred to a urologist or sexual health expert to evaluate other options for treatment.[121,122]

EXTERNAL BEAM RADIATION THERAPY

Radiation treatment for definitive local treatment is typically 4 to 6 weeks long, with acute symptoms usually occurring around the third week and resolving within days to weeks of completion of treatment. Symptoms such as diarrhea can be treated with standard agents (eg, loperamide, diphenoxylate/atropine). Internal or external hemorrhoids can become inflamed, and sitz baths and hydrocortisone suppositories can help alleviate symptoms. Also, acute urinary symptoms may occur with agents such as phenazopyridine and α-blockers such as tamsulosin providing benefit.[4,6,115]

Late rectal toxicities from radiation therapy can occur 12 to 18 months after completion of EBRT and persist for several years, although developing adverse effects after 5 years is rare. These adverse effects can include rectal bleeding, mucous discharge, and mild incontinence of stool. Rectal bleeding can be controlled with increased fiber in the diet, steroid suppositories, and sitz baths, with rectal ulcers and fistulas occurring in <1% of patients.[4,6,115]

Late urinary toxicities consist of chronic urethritis in 10% to 15% of patients and urethral strictures in 2% to 3%.[4,6,115]

BRACHYTHERAPY

Brachytherapy allows for the radiation of small areas of the prostate, which decreases some of the adverse effects of EBRT. In low-dose brachytherapy, acute urinary retention is known to occur in 6% to 15%, although better identification of risk factors for its development has decreased the incidence to ~6% in recent years. Transient urinary effects that occur include radiation-induced urethritis or prostatitis, urinary frequency, urgency, and dysuria. Symptoms will peak about 1 to 3 months after brachytherapy is placed and

gradually resolve over the subsequent couple of months. α-Blockers such as tamsulosin help relieve some of these symptoms.[4,115]

C.W. may experience some of the common symptoms from EBRT, which include diarrhea and hemorrhoids. Other urinary and rectal symptoms include rectal urgency and increased urinary and bowel frequency; and erectile dysfunction may also occur. ADT can cause many side effects, as listed in **Table 100-4**. The most common adverse effects include loss of libido, erectile dysfunction, hot flashes, weight gain, and muscle loss. Because C.W. already has hypercholesterolemia and suffers from depression, which can be impacted by the use of ADT, C.W.'s medical oncologist must closely monitor for changes in these comorbidities and be proactive about treating them if needed.

Table 100-4

Adverse Effects of Androgen Deprivation, Approximate Frequency, and Potential Therapeutic Options for Amelioration

Effect	Approximate Frequency	Potential Corrective Actions
Libido loss	Universal	None known
Erectile dysfunction	Universal	None known
Hot flashes	50%–80%	Venlafaxine, estrogens, progestins
Muscle loss	Common, duration dependent	Exercise
Weight gain	Common	Exercise/diet
Facial/body hair loss	Very common	None known
Fatigue	Not defined	Exercise
Emotional liability	Not defined	None known
Depression	0%–30%	Various antidepressants
Cognitive dysfunction	Not defined	None known
Gynecomastia	Up to 20%	Preemptive radiation
Breast tenderness	Not defined	Aromatase inhibitors

Effect	Approximate Frequency	Potential Corrective Actions
Osteoporosis	Common, duration dependent	Exercise/bisphosphonates
Anemia	5%–13%	Erythropoietin not recommended
Hyperlipidemia	10%	Diet, statins
Diabetes	0.8%/year increase	Exercise, oral agents
Myocardial infarction	0.25%/year increase	Treatment of risk factors
Coronary heart disease	1%/year increase	Treatment of risk factors

A number of events are poorly defined in frequency as a consequence of a lack of controlled studies, quantitative assessments, and/or agreed on definitions.

Adapted with permission from Zelefsky MJ, Morris MJ, Eastham JA. Cancer of the prostate. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 11th ed. Wolters Kluwer; 2019:1119.

PREVENTION

CASE 100-7

QUESTION 1: A.G. is a 42-year-old, African American male who has come to his doctor's office to discuss potential ways to decrease his risk of prostate cancer. His father was diagnosed with prostate cancer at age 49 years, and his brother has just been diagnosed at age 45 years.

What should A.G.'s physician discuss with him about the use of 5-α-reductase inhibitors?

Because of the large number of males who develop prostate cancer, interest has turned to the possibility of prevention. There has been particular interest in the potential of drugs or supplements to at least lower the risk or possibly prevent the occurrence of prostate cancer.

The largest trials to date have involved the 5-α-reductase inhibitors, finasteride and dutasteride. Finasteride is a competitive

inhibitor of type II 5-α-reductase that blocks the conversion of testosterone to DHT in prostatic cells. In the PCPT, >18,000 males ages 55 or older were included if they had a baseline PSA of ≤3 and a normal DRE. They were randomized to finasteride 5 mg daily or placebo and had annual DREs and PSA measurements. At the 7-year follow-up, a 24.8% reduction in the prevalence of prostate cancer was seen for those males on finasteride. There were more reports of sexual side effects, but were less likely to have lower urinary tract symptoms, which can be attributed to finasteride's mechanism of action and its use in BPH. However, for those males on finasteride, there was a larger proportion of cancers considered to be higher grade. The 10-year survival rates showed no significant difference between finasteride and placebo. Updated data at 15 years found that fewer prostate cancers had been diagnosed in the finasteride arm (10.5% vs 14.9%, $P > .001$) and that the survival was similar between the finasteride and placebo arms (78% and 78.2%; HR 1.02, 95% CI 0.97–1.08, $P = .46$). The difference in the risk of death was not significant between the two groups. Overall, finasteride reduced the risk of prostate cancer by about one-third, with a 25% lower risk of death from prostate cancer, but because of the low number of deaths, the difference was not statistically significant.[126]

Dutasteride, a type I and II 5-α-reductase inhibitor, was studied in a 4-year randomized, double-blind, placebo-controlled trial in which males were given either dutasteride 0.5 mg daily or placebo. These males were between ages 50 and 75 years with a PSA between 2.5 and 10 ng/mL and one negative prostate biopsy within 6 months. There was a relative risk reduction of 22.8% over the 4-year period ($P > .001$). The difference between those with a high-grade tumor was not significant between the two groups. Erectile dysfunction and decreased libido were more common in the dutasteride group, although the symptoms of BPH were less in the dutasteride group. Less than 5% of males discontinued the study drug because of drug-related adverse events.[127]

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) trial assessed the use of selenium and vitamin E in the prevention of

prostate cancer. Research has indicated that reactive oxygen species may be associated with the onset and progression of various malignancies, including prostate cancer. This was a phase III, randomized, double-blind, placebo-controlled trial to assess the efficacy of selenium 200 µg daily and vitamin E 400 international units (IU) daily, either alone or in combination. More than 35,000 males who had a normal DRE and a PSA level >4 ng/mL were included in this study. At a median of 5.46 years, no difference was seen among the groups.[128]

A.G.'s physician should explain that the 5-α-reductase inhibitors did show a significant decrease in the incidence of prostate cancer, but that it is still not clear what impact they have on prostate cancer survival. In addition, there are side effects that patients may experience with these medications, such as erectile dysfunction and decreased libido.

SURVIVORSHIP

Because of the large numbers of prostate cancer diagnoses and the generally slow growth of the tumor, there are a large number of males who are living with or after a diagnosis of prostate cancer. They account for about 20% of all cancer survivors. It is recognized that physical and psychosocial effects can occur long after treatment is complete. The American Cancer Society created guidelines, last updated in 2014 and endorsed by ASCO in 2015, for the primary care physician to monitor the health of prostate cancer survivors.[115]

Quality of life should be assessed at baseline and monitored at least annually using one of the validated surveys for this purpose, the 5-item Sexual Health Inventory for Men or the International Index of Erectile Function. These are beneficial for identifying side effect burden or other adverse effects that are of concern to the patient.[115]

Healthy Lifestyle

Guidelines include an emphasis on reminding patients of the benefit of achieving and maintaining a healthy weight, getting enough physical exercise, and eating a diet that is high in fruits, vegetables, and whole grains. For those patients with residual bowel problems that impact absorption, they should be referred to a registered dietitian. The guidelines also include cautions on avoiding alcohol or limiting it to no more than two drinks a day, as well as tobacco use and offering cessation counseling if necessary. Smoking increases the chance of recurrence as well as that of second cancers.

Obesity is associated with increased prostate cancer–specific mortality and biochemical recurrence. Body mass index and healthy food choices along with physical activity should be addressed and encouraged by the primary care physician.

Physical activity has been shown to improve cancer-specific survival and OS, help speed up recovery from short-term effects of therapy, and prevent some long-term effects. Exercise can improve fatigue, anxiety, depressive symptoms, self-esteem, happiness, and quality of life. Patients should be encouraged to engage in at least 150 minutes of physical activity per week.[115]

Surveillance

Once treatment is complete, the PSA should be monitored every 6 to 12 months for the first 5 years and then annually. An annual DRE is also appropriate, especially because some patients will not have a PSA elevation in the setting of cancer. Also, those patients who have received pelvic radiation are at an increased risk for bladder and colorectal cancers. They should have routine screening, and any signs of hematuria and rectal bleeding or pain should be referred back to their treating radiation oncologist for evaluation.[6,115]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. *J Oncol Pract*. 2014;32(*30*):3436–3448. doi:10.1200/JCO.2013.54.8404 (77)

Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. *J Urol.* 2013;190(*2*):419–426. doi:10.1016/j.juro.2013.04. 119 (21)

Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, Part I: introduction, risk assessment, staging, and risk-based management. *J Urol*. 2022 Jul;208(1):10–18. (26)

Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, part III: principles of radiation and future directions. *J Urol*. 2022 Jul;208(1):26–33. (43)

Skolarus TA, Wolf AMD, Erb NL, et al. American Cancer Society prostate cancer survivorship care guidelines. *CA Cancer J Clin*. 2014;64:225–249. doi:10.3322/caac.21234 (115)

Zelefsky MJ, Morris MJ, Eastham JA. Cancer of the prostate. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2019. (4)

Key Websites

American Cancer Society. Screening tests for prostate cancer. Accessed January 26, 2021. www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/tests.html (24)

COMPLETE REFERENCES CHAPTER 100 PROSTATE CANCER

1. National Cancer Institute: Surveillance, Epidemiology, and End Results Program (SEER). Cancer stat facts—prostate cancer. National Institutes of

Health. Accessed January 26, 2021. https://seer.cancer.gov/statfacts/html/prost.html
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7–33. doi:10.3322/caac.21654
3. Moore KL, Dalley AF, Agur AMR. *Clinically Oriented Anatomy*. 7th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.
4. Zelefsky MJ, Morris MJ, Eastham JA. Cancer of the prostate. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 11th ed. Lippincott Williams & Wilkins; 2019.
5. Wolf AMD, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin*. 2010;60(2):70–98. doi:10.3322/caac.20066
6. Loeb S, Roehl KA, Antenor JA, et al. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. *Urology*. 2006;67:316–320.
7. Andriole GL, Guess HA, Epstein JI, et al. Treatment with finasteride preserves usefulness of prostate-specific antigen in the detection of prostate cancer: results of a randomized, double-blind, placebo-controlled clinical trial. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. *Urology*. 1998;52(2):195–201.
8. Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215–224.
9. National Cancer Institute. Prostate cancer, nutrition, and dietary supplements. PDQ® Adult Treatment Editorial Board. Updated May 27, 2022. Accessed August 29, 2022. https://www.cancer.gov/about-cancer/treatment/cam/hp/prostate-supplements-pdq#_163
10. American Cancer Society. Screening tests for prostate cancer. Accessed January 26, 2021. www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/tests.html
11. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level of ≤4. 0 ng per milliliter. *N Engl J Med*. 2004;350:2239–2246.
12. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA*. 2015;313(4):390–397. doi:10.1001/jama.2014.17942
13. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. doi:10.3322/caac.21590
14. Dess RT, Hartman HE, Mahal BA, et al. Association of Black race with prostate cancer–specific and other-cause mortality. *JAMA Oncol*. 2019;5(7):975–983. doi:10.1001/jamaoncol.2019.0826

15. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol*. 2019;5(4):523–528. doi:10.1001/jamaoncol.2018.6760
16. Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT study: evidence for prostate-specific antigen screening in BRCA2 mutation carriers. *Eur Urol*. 2019;76(6):831–842. doi:10.1016/j.eururo.2019.08.019
17. Castro E, Eeles R. The role of BRCA1 and BRCA2 in prostate cancer. *Asian J Androl*. 2012;14(3):409–414. doi:10.1038/aja.2011.150
18. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. *Eur Urol*. 2015;68(2):186–193. doi:10.1016/j.eururo.2014.10.022
19. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. *Br J Cancer*. 2012;106(10):1697–1701. doi:10.1038/bjc.2012.146
20. Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2014;23(3):437–449. doi:10.1158/1055-9965.EPI-13-1165
21. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. *J Urol*. 2013;190(2):419–426. doi:10.1016/j.juro.2013.04.119
22. US Preventive Services Task Force, Grossman DC, Curry SJ, et al. Screening for prostate cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;319(18):1901–1913. doi:10.1001/jama.2018.3710
23. Andriole GL, Crawford ED, Grubb RL, et al. Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012;104(2):125–132. doi:10.1093/jnci/djr500
24. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European Study. *N Engl J Med*. 2009;360(13):1320–1328. doi:10.1056/NEJMoa0810084
25. Drazer MW, Prasad SM, Huo D, et al. National trends in prostate cancer screening among older American men with limited 9-year life expectancies: evidence of an increased need for shared decision making. *Cancer*. 2014;120(10):1491–1498. doi:10.1002/cncr.28600
26. Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, Part I: introduction, risk assessment, staging, and risk-based management. *J Urol*. 2022;208(1):10–18.
27. Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20–69: an autopsy study of 249 cases. *In Vivo*. 1994;8(3):439–443.
28. Sakr WA, Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male

patients. *J Urol*. 1993;150(2 Pt 1):379–385. doi:10.1016/s0022-5347(17)35487-3

29. Gleason DM. The Veteran's Administration Cooperative Urologic Research Group: histologic grading and clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. *Urologic Pathology: The Prostate*. Lea and Febiger; 1977:171–198.
30. Gleason DF. Classification of prostatic carcinomas. *Cancer Chemother Rep*. 1966;50(3):125–128.
31. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol*. 2016;69(3):428–435. doi:10.1016/j.eururo.2015.06.046
32. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol*. 2013;31(14):1748–1757.
33. Loeb S, Giri VN. Clinical implications of Germline testing in newly diagnosed prostate cancer. *Eur Urol Oncol*. 2021;4(1):1–9. doi:10.1016/j.euo.2020.11.011
34. Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular biomarkers in localized prostate cancer: ASCO guideline. *J Clin Oncol*. 2019;38(13):1474–1494. doi:10.1200/JCO.19.02768
35. Rodrigues G, Warde P, Pickles T, et al. Pre-treatment risk stratification of prostate cancer patients: a critical review. *Can Urol Assoc J*. 2012;6(2):121–127. doi:10.5489/cuaj.11085
36. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst*. 2009;101:374–383.
37. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33(3):272–277. doi:10.1200/JCO.2014.55.1192
38. Raldow AC, Zhang D, Chen M-H, Braccioforte MH, Moran BJ, D'Amico AV. Risk group and death from prostate cancer: implications for active surveillance in men with favorable intermediate-risk prostate cancer. *JAMA Oncol*. 2015;1(3):334–340. doi:10.1001/jamaoncol.2014.284
39. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. *N Engl J Med*. 2002;346(15):1138–1144. doi:10.1056/NEJMsa011788
40. Vickers AJ, Bianco FJ, Serio AM, et al. The surgical learning curve for prostate cancer control after radical prostatectomy. *J Natl Cancer Inst*. 2007;99(15):1171–1177. doi:10.1093/jnci/djm060
41. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008;358:1250–1261.

42. Hamilton AS, Stanford JL, Gilliland FD, et al. Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the Prostate Cancer Outcomes Study. *J Clin Oncol*. 2001;19(9):2517–2526.
43. Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, Part III: principles of radiation and future directions. *J Urol*. 2022;208(1):26–33.
44. Valicenti RK, Thompson I, Albertsen P, et al. Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. *Int J Radiat Oncol Biol Phys*. 2013;86(5):822–828. doi:10.1016/j.ijrobp.2013.05.029
45. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415–1424. doi:10.1056/NEJMoa1606220
46. Barocas DA, Alvarez J, Resnick MJ, et al. Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years. *JAMA*. 2017;317(11):1126–1140. doi:10.1001/jama.2017.1704
47. Chen RC, Basak R, Meyer A-M, et al. Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. *JAMA*. 2017;317(11):1141–1150. doi:10.1001/jama.2017.1652
48. Hoffman KE, Penson DF, Zhao Z, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA*. 2020;323(2):149–163. doi:10.1001/jama.2019.20675
49. ORGOVYX (relugolix). Package insert. Myovant Sciences, Inc; 2020.
50. Poppel HV, Abrahamsson P-A. Considerations for the use of gonadotropin-releasing hormone agonists and antagonists in patients with prostate cancer. *Int J Urol*. 2020;27(10):830–837. doi:10.1111/iju.14303
51. Virgo KS, Rumble RB, de Wit R, et al. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: ASCO guideline update. *J Clin Oncol*. 2021;39(11):1274–1305.
52. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009;360(24):2516–2527. doi:10.1056/NEJMoa0810095
53. D'Amico AV, Chen M-H, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA*. 2008;299(3):289–295. doi:10.1001/jama.299.3.289
54. Gomella LG, Singh J, Lallas C, Trabulsi EJ. Hormone therapy in the management of prostate cancer: evidence-based approaches. *Ther Adv Urol*. 2010;2(4):171–181. doi:10.1177/1756287210375270

55. Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-year survival outcomes following primary androgen-deprivation therapy for localized prostate cancer. *JAMA Intern Med*. 2014;174:1460–1467.
56. McLeod DG, Iversen P, See WA, et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int*. 2006;97:247–254.
57. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med*. 2011;365(2):107–118. doi:10.1056/NEJMoa1012348
58. Zumsteg ZS, Spratt DE, Daskivich TJ, et al. Effect of androgen deprivation on long-term outcomes of intermediate-risk prostate cancer stratified as favorable or unfavorable: a secondary analysis of the RTOG 9408 randomized clinical trial. *JAMA Netw Open*. 2020;3(9):e2015083. doi:10.1001/jamanetworkopen.2020.15083
59. Freedland SJ, Rumble RB, Finelli A, et al. Adjuvant and salvage radiotherapy after prostatectomy: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol*. 2014;32(34):3892–3898. doi:10.1200/JCO.2014.58.8525
60. Roach M, Hanks G, Thames H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65(4):965–974. doi:10.1016/j.ijrobp.2006.04.029
61. Zumsteg ZS, Spratt DE, Romesser PB, et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. *Eur Urol*. 2015;67(6):1009–1016. doi:10.1016/j.eururo.2014.09.028
62. Pisansky TM, Thompson IM, Valicenti RK, et al. Adjuvant and salvage radiotherapy after prostatectomy: ASTRO/AUA guideline amendment 2018–2019. *J Urol*. 2019;202(3):533–538.
63. Chade DC, Shariat SF, Cronin AM, et al. Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. *Eur Urol*. 2011;60(2):205–210.
64. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*. 2013;368(14):1314–1325. doi:10.1056/NEJMoa1212299
65. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med*. 2012;367(10):895–903. doi:10.1056/NEJMoa1201546
66. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage,

platform randomised controlled trial. *Lancet*. 2016;387(10024):1163–1177. doi:10.1016/S0140-6736(15)01037-5

67. Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737–746. doi:10.1056/NEJMoa1503747
68. Hall ME, Huelster HL, Luckenbaugh AN, et al. Metastatic hormone-sensitive prostate cancer: current perspective on the evolving therapeutic landscape. *Onco Targets Ther*. 2020;13:3571–3581. doi:10.2147/OTT.S228355
69. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502–1512. doi:10.1056/NEJMoa040720
70. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol*. 2008;26(2):242–245. doi:10.1200/JCO.2007.12.4008
71. Taxotere. Package insert. Sanofi-Aventis US, LLC; 2020.
72. Kellokumpu-Lehtinen P-L, Harmenberg U, Joensuu T, et al. 2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. *Lancet Oncol*. 2013;14(2):117–124. doi:10.1016/S1470-2045(12)70537-5
73. Kyriakopoulos CE, Chen Y-H, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol*. 2018;36(11):1080–1087. doi:10.1200/JCO.2017.75.3657
74. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147–1154. doi:10.1016/S0140-6736(10)61389-X
75. Eisenberger M, Hardy-Bessard A-C, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m^2) and the currently approved dose (25 mg/m^2) in postdocetaxel patients with metastatic castration-resistant prostate cancer—PROSELICA. *J Clin Oncol*. 2017;35(28):3198–3206. doi:10.1200/JCO.2016.72.1076
76. Oudard S, Fizazi K, SengelØv L, et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized phase III trial—FIRSTANA. *J Clin Oncol*. 2017;35(28):3189–3197. doi:10.1200/JCO.2016.72.1068
77. Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. *J Clin Oncol*. 2014;32(30):3436–3448. doi:10.1200/JCO.2013.54.8404
78. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995–

2005. doi:10.1056/NEJMoa1014618
79. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983–992. doi:10.1016/S1470-2045(12)70379-0
80. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol*. 2012;13(12):1210–1217. doi:10.1016/S1470-2045(12)70473-4
81. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138–148. doi:10.1056/NEJMoa1209096
82. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352–360. doi:10.1056/NEJMoa1704174
83. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377(4):338–351. doi:10.1056/NEJMoa1702900
84. Zytiga. Package insert. Centecor Ortho Biotech Inc.; 2011.
85. Yonsa. Package insert. Sun Pharmaceutical Industries Inc.; 2018.
86. Hu R, Dunn TA, Wei S, et al. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer. *Cancer Res*. 2009;69(1):16–22. doi:10.1158/0008-5472.CAN-08-2764
87. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science*. 2009;324(5928):787–790. doi:10.1126/science.1168175
88. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. *Eur Urol*. 2017;71(2):151–154. doi:10.1016/j.eururo.2016.07.032
89. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187–1197. doi:10.1056/NEJMoa1207506
90. Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. *Lancet Oncol*. 2014;15(10):1147–1156. doi:10.1016/S1470-2045(14)70303-1
91. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*.

2020;382(23):2197–2206. doi:10.1056/NEJMoa2003892
92. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381(2):121–131. doi:10.1056/NEJMoa1903835
93. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. *Eur Urol*. 2021;79(1):150–158. doi:10.1016/j.eururo.2020.08.011
94. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13–24. doi:10.1056/NEJMoa1903307
95. Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med*. 2020;383(11):1040–1049. doi:10.1056/NEJMoa2001342
96. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235–1246. doi:10.1056/NEJMoa1815671
97. Nubeqa. Package insert. Bayer HealthCare Pharmaceuticals Inc.; 2019.
98. Sartor AO, Tangen CM, Hussain MHA, et al. Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). *Cancer*. 2008;112(11):2393–2400. doi:10.1002/cncr.23473
99. Provenge. Package insert. Dendreon Pharmaceuticals LLC.; 2017.
100. Keytruda. Package insert. Merck & Co Inc.; 2019.
101. Lord CJ, Ashworth A. The DNA damage response and cancer therapy. *Nature*. 2012;481(7381):287–294. doi:10.1038/nature10760
102. Karanika S, Karantanos T, Li L, Corn PG, Thompson TC. DNA damage response and prostate cancer: defects, regulation and therapeutic implications. *Oncogene*. 2015;34(22):2815–2822. doi:10.1038/onc.2014.238
103. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091–2102. doi:10.1056/NEJMoa1911440
104. Rubraca. Package insert. Clovis Oncology Inc.; 2020.
105. Lozano R, Castro E, Aragón IM, et al. Genetic aberrations in DNA repair pathways: a cornerstone of precision oncology in prostate cancer. *Br J Cancer*. 2021;124(3):552–563. doi:10.1038/s41416-020-01114-x
106. Antonarakis ES, Gomella LG, Petrylak DP. When and how to use PARP inhibitors in prostate cancer: a systematic review of the literature with an update on on-going trials. *Eur Urol Oncol*. 2020;3(5):594–611. doi:10.1016/j.euo.2020.07.005
107. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213–223. doi:10.1056/NEJMoa1213755
108. Saylor PJ, Rumble RB, Tagawa S, et al. Bone health and bone-targeted therapies for prostate cancer: ASCO Endorsement of a Cancer Care Ontario

Guideline. *J Clin Oncol*. 2020;38(15):1736–1743. doi:10.1200/JCO.19.03148
109. Bubendorf L, Schöpfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol*. 2000;31(5):578–583. doi:10.1053/hp.2000.6698
110. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424–433. doi:10.1056/NEJMoa1405095
111. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96(11):879–882. doi:10.1093/jnci/djh141
112. Zometa. Package insert. Novartis Pharmaceuticals Corporation; 2014.
113. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377(9768):813–822. doi:10.1016/S0140-6736(10)62344-6
114. Terrisse S, Karamouza E, Parker CC, et al. Overall survival in men with bone metastases from castration-resistant prostate cancer treated with bone-targeting radioisotopes: a meta-analysis of individual patient data from randomized clinical trials. *JAMA Oncol*. 2020;6(2):206–216.
115. Skolarus TA, Wolf AMD, Erb NL, et al. American Cancer Society prostate cancer survivorship care guidelines. *CA Cancer J Clin*. 2014;64(4):225–249. doi:10.3322/caac.21234
116. Jones JM, Kohli M, Loprinzi CL. Androgen deprivation therapy-associated vasomotor symptoms. *Asian J Androl*. 2012;14(2):193–197. doi:10.1038/aja.2011.101
117. Loprinzi CL, Dueck AC, Khoyratty BS, et al. A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). *Ann Oncol*. 2009;20(3):542–549. doi:10.1093/annonc/mdn644
118. Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol*. 2010;11(2):147–154. doi:10.1016/S1470-2045(09)70338-9
119. Levine GN, D'Amico AV, Berger P, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *CA Cancer J Clin*. 2010;60(3):194–201. doi:10.3322/caac.20061
120. O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy

in men with prostate cancer. *J Clin Oncol*. 2015;33(11):1243–1251. doi:10.1200/JCO.2014.59.1792

121. White ID, Wilson J, Aslet P, et al. Development of UK guidance on the management of erectile dysfunction resulting from radical radiotherapy and androgen deprivation therapy for prostate cancer. *Int J Clin Pract*. 2015;69(1):106–123. doi:10.1111/ijcp.12512
122. Higano CS. Sexuality and intimacy after definitive treatment and subsequent androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2012;30(30):3720–3725. doi:10.1200/JCO.2012.41.8509
123. McGinty HL, Phillips KM, Jim HSL, et al. Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Support Care Cancer*. 2014;22(8):2271–2280. doi:10.1007/s00520-014-2285-1
124. Gonzalez BD, Jim HSL, Booth-Jones M, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. *J Clin Oncol*. 2015;33(18):2021–2027. doi:10.1200/JCO.2014.60.1963
125. Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005;352(2):154–164. doi:10.1056/NEJMoa041943
126. Goodman PJ, Tangen CM, Darke AK, et al. Long-term effects of finasteride on prostate cancer mortality. *N Engl J Med*. 2019;380(4):393–394. doi:10.1056/NEJMc1809961
127. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010;362(13):1192–1202. doi:10.1056/NEJMoa0908127
128. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2009;301(1):39–51. doi:10.1001/jama.2008.864

101

Hematopoietic Stem Cell Transplantation

Valerie Relias

CORE PRINCIPLES		CHAPTER CASES
1	Hematopoietic stem cell transplantation (HSCT) is a life-saving medical procedure involving the infusion of hematopoietic stem cells into a patient, the HSCT recipient, to treat malignant and nonmalignant diseases and/or restore normal hematopoiesis and lymphopoiesis.	**Case 101-1 (Question 1) Case 101-2 (Question 1)**

CORE PRINCIPLES		CHAPTER CASES
2	In autologous HSCT, the donor and recipient are the same individual, eliminating the need for pretransplantation and posttransplantation immunosuppression. Autologous hematopoietic cells must be obtained (ie, harvested) before the myeloablative preparative regimen is administered and subsequently stored for administration after the preparative regimen.	**Case 101-1 (Questions 2, 3)**
3	Posttransplantation pharmacotherapy for autologous HSCT includes hematopoietic growth factors to stimulate the proliferation of committed progenitor cells and to accelerate hematopoietic recovery.	**Case 101-1 (Question 6) Case 101-2 (Question 8)**
4	Common complications after autologous HSCT are infections and organ failure, which occur in <5% of patients. The most common cause of death after autologous HSCT is recurrence of the primary disease.	**Case 101-1 (Question 5)**

CORE PRINCIPLES		CHAPTER CASES
5	Allogeneic HSCT involves the transplantation of hematopoietic stem cells obtained from a donor's bone marrow, peripheral blood progenitor cells (PBPCs), or umbilical cord blood to a patient. The donor for an allogeneic HSCT may be an unrelated or related individual. Histocompatibility determination between donors and recipients must be performed through human leukocyte antigen (HLA) typing. The preparative regimen is, in part, determined by the degree of mismatch between the donor and the recipient.	**Case 101-2 (Questions 2, 3)**
6	The function of the preparative regimens for autologous HSCT is to eradicate residual malignancy. The function of the preparative regimen in allogeneic HSCT is to not only eradicate the residual malignancy but also to provide immunosuppression, allowing the transplanted stem cells to grow and create a graft-versus-tumor effect.	**Case 101-1 (Question 4) Case 101-2 (Question 4)**
7	Choice of preparative regimens for HSCT depends on factors such as underlying disease, degree of HLA matching, stem cell source, patient age, and comorbid conditions. Preparative regimens differ in intensity and are distinguished as myeloablative or nonmyeloablative.	**Case 101-2 (Questions 5, 6)**

CORE PRINCIPLES		CHAPTER CASES
8	Posttransplantation immunosuppressive therapy is necessary for allogeneic HSCT to prevent both graft rejection and acute and/or chronic graft-versus-host disease (aGVHD/cGVHD). Some immunosuppressants require therapeutic drug monitoring to ensure effectiveness while minimizing toxicity.	**Case 101-2 (Question 7) Case 101-4 (Question 1) Case 101-5 (Questions 1–9)**
9	Posttransplantation complications of myeloablative preparation regimens such as hemorrhagic cystitis, mucositis, and sinusoidal obstructive syndrome (SOS)/veno-occlusive disease (VOD) require pharmaceutical management.	**Case 101-2 (Questions 8, 9) Case 101-3 (Questions 1–9)**
10	Opportunistic infections are a major cause of morbidity and mortality after myeloablative and nonmyeloablative HSCT. The primary pathogens vary based on the time posttransplant and include bacterial, fungal, and viral species.	**Case 101-6 (Questions 1–3) Case 101-7 (Questions 1–3)**
11	Long-term complications of HSCT include cGVHD, endocrine dysfunction, and secondary cancers.	**Case 101-5 (Questions 7–9) Case 101-8 (Question 1)**

INTRODUCTION

Worldwide, more than 32,000 autologous and 25,000 allogeneic hematopoietic stem cell transplantations (HSCTs) are performed

annually.[1] The rationale behind the use of hematopoietic stem cells (HSCs) is based on the steep dose response of chemotherapy; however, with increasing doses of chemotherapy, bone marrow (BM) suppression becomes a dose-limiting side effect. The administration of HSCT provides recovery of the BM.

HSCT is a procedure that involves the infusion of hematopoietic stems cells into patients who have received high doses of chemotherapy and/or radiation. Variations of this procedure depend on the donor of these stem cells, self versus nonself, and the source of the stem cells. Autologous stem cell transplants are ones in which the patient serves as the donor of HSCs, whereas, in allogeneic transplants, the donor is another related individual such as a sibling, or an unrelated donor. The source of the HSCs may be from peripheral blood progenitor cells (PBPCs), BM, or umbilical cord blood.

The type of HSCT performed depends on a number of factors, including type and status of the disease, patient age, performance status, and organ function, and, if allogeneic transplant is needed, the availability of a compatible donor. Characteristics of autologous and allogeneic transplantation, with either myeloablative or nonmyeloablative preparative regimens, are compared in **Table 101-1**.[2] Many diseases are treated with autologous or allogeneic HSCT and are listed in **Table 101-2**.[2] Modifications to the basic schema for HSCT are necessary based on the immunologic source (ie, allogeneic or autologous) and the anatomic source (ie, BM, PBPCs, or umbilical cord blood) of the HSCs infused.

Table 101-1
Comparison of Types of Hematopoietic Stem Cell Transplants

Risk[a]	Myeloablative		Nonmyeloablative
	Autologous	Allogeneic	Allogeneic
Relapse after HSCT	+++	+	+
Rejection	–	+	++
Delayed engraftment	++	+	+
GVHD	–	+	++
Infection	+	++ to +++[b]	++ to +++[b]
Transplant-related morbidity	+	+++	++
Transplant-related mortality	+	++	+
Cost of procedure	++	+++	++ to +++

GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant.

[a]Risk varies depending on underlying disease, patient characteristics, and previous medical history.

[b]Risk of infection increases with intensity and duration of immunosuppression and/or chronic GVHD.

Table 101-2
Diseases Commonly Treated with Hematopoietic Stem Cell Transplantation

Allogeneic
Nonmalignant
Aplastic anemia
Thalassemia major
Severe combined immunodeficiency disease
Wiskott–Aldrich syndrome
Fanconi anemia
Inborn errors of metabolism
Malignant
AML
Acute lymphoblastic leukemia
Chronic myeloid leukemia
Myelodysplastic syndrome
Myeloproliferative disorders

Allogeneic
NHL
Hodgkin disease
Chronic lymphocytic leukemia
Multiple myeloma
Juvenile myelomonocytic leukemia
Autologous
Malignant
NHL
Multiple myeloma
AML
Hodgkin disease
Neuroblastoma
Germ-cell tumors
Other diseases
Autoimmune disorders
Amyloidosis

Timing of hematopoietic stem cell transplantation relative to diagnosis varies with disease.

AML, acute myelogenous leukemia; NHL, non–Hodgkin lymphoma.

Sources: Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354:1813–1826; Vaughan W, Seshadri T, Bridges M, Keating A. The principles and overview of autologous hematopoietic stem cell transplantation. *Cancer Treat Res*. 2009;144:23–45.

HSCT may be the only treatment available to many patients; however, it is associated with considerable morbidity and mortality, with ~40% of advanced cancer patients who undergo HSCT dying of its complications.[2] The basic schema for HSCT is illustrated in **Figure 101-1**. A combination of chemotherapy and/or radiation administered before infusion of the HSCs is referred to as the preparative or conditioning regimen.[2] The days leading up to the infusion of the HSCs are counted in the negative (ie, −3, −2, −1), the day of HSCT infusion is termed day 0, and the days following the

transplant are counted in the positive (+1, +2, etc). Although the preparative regimen may use the same agents that are used in conventional chemotherapy regimens, the doses are higher. The purpose of the preparative regimen is to eradicate the residual malignancy and, in the setting of an allogeneic HSCT, to suppress the recipient's immune system.[2] Only myeloablative preparative regimens are used for autologous HSCT; however, myeloablative, reduced-intensity or nonmyeloablative preparative regimens may be used with allogeneic HSCT. Myeloablative preparative regimens involve administration of near-lethal doses of chemotherapy and/or radiation, which ablate the BM; this may be followed by a 1- to 2-day rest. After completion of the preparative regimen, the HSCT takes place. Myeloablative preparative regimens have significant regimen-related toxicity and morbidity and thus are usually limited to healthy, younger (ie, usually younger than age 60 years) patients.[3] Alternatively, reduced-intensity or nonmyeloablative transplants are performed with the hope of curing more cancer patients without the complication of preparative-related toxicity. Nonmyeloablative regimens make use of the graft-versus-tumor (GVT) effect, allowing for donor lymphocyte-induced tumor eradication (see Graft-Versus-Host Disease section). For most chemotherapy-based preparative regimens, a rest period is necessary to allow for elimination of toxic metabolites from the chemotherapy that could damage infused cells. After chemotherapy and/or radiation, a period of pancytopenia lasts until the infused HSCs reestablish functional hematopoiesis. Engraftment, when functional hematopoiesis is established, is commonly defined as the point at which a patient can maintain a sustained absolute neutrophil count (ANC) of >500 cells/μL and a sustained platelet count of at least 20,000/μL lasting 3 consecutive days without transfusions.[4] Graft rejection occurs when the patient cannot maintain functional hematopoiesis and may occur after autologous or allogeneic HSCT.

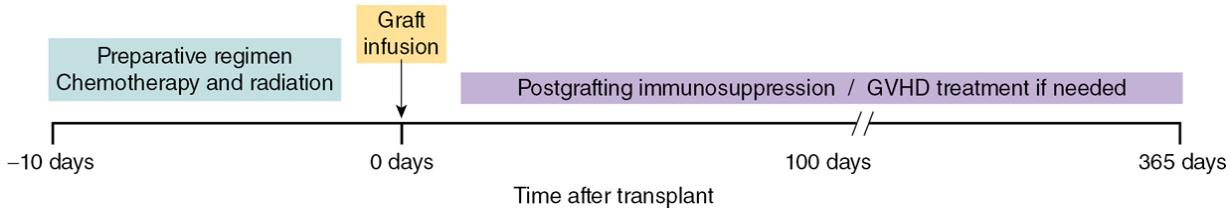


Figure 101-1 Basic schema for hematopoietic stem cell transplantation. Day 0 = bone marrow, peripheral blood progenitor cell, or umbilical cord blood infusion. Postgraft immunosuppression or graft-versus-host disease (GVHD) prophylaxis for allogeneic grafts only.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

The defining characteristic of autologous HSCT is that the donor and the recipient are the same individual, making posttransplantation immunosuppression unnecessary. Autologous HSCs must be obtained (ie, harvested) before the myeloablative preparative regimen is administered and subsequently stored for administration after the preparative regimen. Essentially, these HSCs are administered as a rescue intervention to reestablish BM function and avoid long-lasting, life-threatening marrow aplasia that results from the myeloablative preparative regimen.[5] Incomplete tumor eradication by the high-intensity treatment before transplant remains the main cause of relapse after transplant.[6]

Indications for Autologous Hematopoietic Stem Cell Transplantation

CASE 101-1

QUESTION 1: P.J., a 46-year-old male, has diffuse large B-cell non–Hodgkin lymphoma (NHL) in first relapse after a complete remission of 1 year. An 80% reduction in measurable disease is noted after two cycles of dexamethasone,

high-dose cytarabine, and cisplatin (DHAP) salvage chemotherapy. P.J.'s BM biopsy and lumbar puncture are negative for malignant cells.

Is a myeloablative preparative regimen with autologous HSCT indicated for P.J.?

Autologous HSCT is used to treat a variety of malignancies (Table 101-2). NHL and multiple myeloma are the most common indications for this procedure and represent more than two-thirds of all autologous HSCT.[2] Nearly all patients who undergo autologous HSCT have failed standard chemotherapy regimens; therefore, their HSCs have been exposed to prior chemotherapy leading to less abundant and viable stem cells.

The primary use of autologous HSCT is in diseases that have aggressive features but are still chemotherapy-sensitive.[7] In a randomized, controlled trial,[8] autologous bone marrow transplant (BMT), compared with conventional chemotherapy with DHAP, resulted in a 5-year event-free survival of 46% versus 12%, respectively (P = .001). Overall 5-year survival was 53% in the BMT group and 32% in the patients undergo conventional chemotherapy (P = .038).[8]

Whereas HSCT is delayed until relapse after primary treatment in NHL, in some malignancies, autologous HSCT is indicated as primary therapy to improve overall survival and progression-free survival.[7,9,10]

Prospective studies comparing preparative regimens, stem cell mobilization techniques, and stem cell source (ie, BMT vs peripheral blood progenitor cell transplant [PBPCT]) are not available; however, autologous PBPCT has become the preferred source of stem cells, most likely owing to the improved outcomes with PBPCT in other disease settings.[11] PBPCs, defined as cells that express the CD34 antigen (eg, $CD34^+$), are continuously circulating in the blood; however, their numbers are too low to easily collect the amount needed in transplant. Mobilization refers to the techniques used to move the stem cells out of the BM compartment, increasing their numbers in circulation. Mobilization can be accomplished using

growth factors or chemotherapy (see Mobilization and Collection of Autologous Peripheral Blood Progenitor Cells section).

P.J. has minimal residual disease that has demonstrated chemotherapy sensitivity (ie, P.J. had an 80% response to chemotherapy). P.J.'s long-term prognosis will be improved with autologous PBPCT rather than with further conventional chemotherapy, as described. Thus, autologous PBPCT is indicated, owing to the greater likelihood that higher-dose chemotherapy may eradicate P.J.'s tumor.

Harvesting Autologous Hematopoietic Stem Cells

Case 101-1, Question 2: What is the best way to harvest and preserve harvested HSCs for P.J.?

PBPCs have essentially replaced BM as the source of stem cells at many HSCT centers, accounting for 98% of autologous transplants in adults from 2004 to 2008.[1] PBPCs result in more rapid engraftment than BM and fewer days of neutropenia.[12] Collection of PBPCs occurs before administering the preparative regimen; thus, autologous HSCs must be cryopreserved.[2] HSCs are frozen below −184 °F (−120 °C) and used within a few weeks; although, when frozen, they are viable for years.[2] Dimethyl sulfoxide (DMSO) is the cryopreservative commonly used to protect HSCs from damage during freezing and thawing. Infusion of HSCs stored in DMSO can be associated with toxicities because of the DMSO itself. During infusion, DMSO is associated with skin flushing, nausea, diarrhea, dyspnea, hypotension, arrhythmias, and, rarely, anaphylactic reactions.[13] The presence of undetectable tumor cells in the transplanted cells contributes to the relapse of hematologic cancers; unfortunately, purging the grafts of tumor cells does not improve survival.[2]

Relative to BM harvest, collection of PBPCs requires less invasive collection methods and contains up to five times more HSCs. This results in a PBPC HSCT having more rapid neutrophil and platelet

recovery (ie, a shorter duration of neutropenia or thrombocytopenia), fewer platelet transfusions, fewer days of intravenous antibiotics, and a shorter duration of hospitalization compared to a BM HSCT. Thus, the shift to the use of PBPCs instead of BM for autologous HSCT is primarily because of the more rapid engraftment and less invasive collection methods.[11] Therefore, it would be best for P.J. to undergo pheresis for PBPC collection. The collected cells would be bathed in DMSO and frozen at −184 °F (−120 °C).

Mobilization and Collection of Autologous Peripheral Blood Progenitor Cells

Case 101-1, Question 3: For PBPC mobilization, P.J. received one dose of cyclophosphamide 4 g/m^2 IV on day 1, followed by filgrastim 10 µg/kg/day subcutaneously (SC) beginning on day 2 and continuing through completion of pheresis. Twelve days after receiving cyclophosphamide, P.J.'s white blood cell (WBC) count recovered to 3000 cells/µL and pheresis was begun. An adequate number of PBPCs is collected after two pheresis sessions. P.J.'s cells are processed and stored. What was the rationale for administering filgrastim and cyclophosphamide? What determines the duration of pheresis?

Normally, low numbers of PBPCs are found in the peripheral circulation; therefore, it is necessary to "mobilize" PBPC from the marrow compartment into the systemic circulation. Mobilization leads to a collection of sufficient numbers of autologous PBPCs in most patients, although a minority of patients may still have poor mobilization.[11] Multiple methods can be used to mobilize PBPCs. Hematopoietic growth factors alone or in combination with myelosuppressive chemotherapy are used to mobilize PBPCs.[11] After administration of the mobilizing agent(s), the patient undergoes pheresis, an outpatient procedure similar to dialysis in order to collect PBPCs.[12]

Granulocyte–macrophage colony-stimulating factor (GM-CSF, sargramostim) and granulocyte colony-stimulating factor (G-CSF, filgrastim) are both hematopoietic growth factors and are used as mobilizing agents for PBPC collection.[11,14] Both reliably mobilize

PBPCs, with filgrastim providing a higher PBPC yield.[11] The most frequently used filgrastim doses for autologous PBPC mobilization are in the range of 10 to 24 μg/kg/day SC.[11,14] PBPC yield is higher when pheresis is started at day 5 (vs day 6), with the optimal yield being around 10 hours after filgrastim administration.[11]

Myelosuppressive chemotherapy stimulates stem cell and progenitor cell proliferation. The combination of chemotherapy with filgrastim enhances PBPC mobilization relative to filgrastim alone. A benefit of using chemotherapy is that it also treats the underlying malignancy.[11] Examples of PBPC mobilization chemotherapy regimens include single-agent cyclophosphamide or melphalan. No mobilization chemotherapy regimen is clearly superior, which has led to incorporating PBPC mobilization into a cycle of disease-specific chemotherapy, such as using a single cycle of R-ICE (rituximab, ifosfamide, carboplatin, etoposide) therapy as the mobilization regimen for an NHL patient whose disease is responsive to R-ICE treatment.[11] By administering chemotherapy to the patient, the body's repair mechanism accelerates the cell division of stem cells and releases them into the circulation. This is a delicate balance because the more the chemotherapy that is given to mobilize the stem cells, the greater the potential for damage to the stem cells and a decreased yield at collection. Stem cell toxic agents, such as carmustine, should be avoided because they lower the quantity and quality of PBPCs. The hematopoietic growth factor is initiated 24 to 72 hours after completion of chemotherapy. Pheresis begins when the peripheral WBC count recovers to greater than 1 to 3 × 10^3 cells/μL.[11]

Certain patients fail to mobilize sufficient PBPC because of extensive prior therapy or therapy with marrow toxic agents. In these patients, plerixafor, an inhibitor of the CXCR4 chemokine receptor, can be used. Plerixafor was approved by the U.S. Food and Drug Administration (FDA) in 2008 for use in stem cell mobilization in conjunction with filgrastim. It is known that CD34 is an adhesion molecule involved in promoting adherence of HSCs to the BM microenvironment. Stromal cell–derived factor-1 (SDF-1) is a chemoattractant agent for HSCs; its presence in circulation causes

rapid migration of these stem cells to the peripheral blood.[11] Inhibition of the CXCR4 by plerixafor blocks the ligand SDF-1 from binding to the CXCR4 receptor, thus releasing CD34+ cells from the BM. In two randomized studies, 59% of patients with NHL and 72% of patients with multiple myeloma had sufficient CD34+ cell collection for autologous transplant using plerixafor and filgrastim in four or fewer pheresis sessions, compared to 24% and 34%, respectively, in those using filgrastim alone.[15] Plerixafor is administered to the patient ~10 to 18 hours prior to each pheresis beginning four days after initiation of daily filgrastim 10 μg/kg. Pheresis is continued daily until the target number of PBPCs per kilogram of the recipients' weight is obtained.[11] Typically, one to two large-volume pheresis sessions are needed to collect adequate numbers of CD34+ cells.[16] For adult recipients, the number of cells infused that are CD34+ is the most reliable indicator of an adequate PBPC collection and predictor of durable engraftment.[11] A variety of different thresholds have been identified as the minimal number of CD34+ cells needed for an autologous PBPCT to produce rapid and complete (ie, WBCs, red blood cell [RBC], platelet) engraftment in adults. The minimum threshold range has varied from 1 to 3 × 10^6 CD34+ cells/kg of recipient weight, with more rapid platelet and neutrophil engraftment occurring with ≥5 to 8 × 10^6 CD34+ cells/kg of recipient weight.[11]

There are a number of factors that can affect the yield of CD34+ cells, including the timing and amount of myelosuppressive treatments received before mobilization; both chemotherapy and radiation negatively impact mobilization. The type of chemotherapy, number of different regimens, and overall duration of chemotherapy treatment affect the ability to collect stem cells. Additionally, hypocellular marrow and refractory disease can lead to a poor PBPC harvest.[11] There is a paucity of information regarding the parameters associated with engraftment in children undergoing an autologous PBPCT.[17] After pheresis, the cells are cryopreserved, stored, thawed, and infused into the patient as described in the Harvesting Autologous HSCs section. Because P.J. has been in remission for a year after initial treatment for his disease, he received no radiation

treatment, and his salvage therapy did not contain alkylating agents, his cell collection can be expected to be good and of short duration.

Myeloablative Preparative Regimens

CASE 101-1, QUESTION 4: What are the goals and characteristics of agents used for myeloablative preparative regimens in patients like P.J.?

The primary goal of P.J.'s high-dose, myeloablative preparative regimen followed by autologous transplant is to eradicate residual malignancy that is not treatable with standard chemotherapy. With autologous HSCT, there is no need for immunosuppression because the donor and recipient are genetically identical.[2] Combination chemotherapy with multiple alkylating agents constitutes the most common high-dose regimens before autologous HSCT. Alkylating agents are used because they exhibit a steep dose–response curve for various malignancies to overcome resistance to treatment and are characterized by dose-limiting BM suppression.[18] Ideally, combinations of antineoplastics should have nonhematologic toxicities that do not overlap and that are not life-threatening. Examples of common myeloablative regimens are illustrated in **Table 101-3**.[19–23] The early and late toxicities to myeloablative regimens are listed in **Table 101-4**.[2–4]

Table 101-3
Representative Myeloablative Preparative Regimens Used in Hematopoietic Stem Cell Transplantation

Type of HSCT	Disease State	Regimen	Dose/Schedule
Allogeneic[75]	Hematologic malignancies[a]	CY/TBI	CY 60 mg/kg/day IV on 2 consecutive days before TBI 1000–1575 rads fractionated for 1–7 days
Autologous[92,93]	Acute and chronic leukemias	BU/CY	BU adult 1 mg/kg/dose PO or 0.8 mg/kg/dose IV every 6 hours for 16 doses
			BU children >12 kg, 1.1 mg/kg/dose IV every 6 hours for 16 doses
			CY 50 mg/kg/day IV daily for 4 days or 60 mg/kg/day IV daily for 2 days after BU
Autologous[23]	Non–Hodgkin lymphoma, Hodgkin disease	BEAM (carmustine/etoposide/cytarabine/melphalan)	Carmustine 300 mg/m^2/day IV, 1 dose
			Etoposide 200 mg/m^2/day bid IV for 3 days
			Cytarabine 200 mg/m^2/day IV bid for 4 days
			Melphalan 140 mg/m^2 1 dose

bid, twice a day; BU, busulfan; CY, cyclophosphamide; IV, intravenously; PO, orally; TBI, total body irradiation.

[a]Includes acute myelogenous leukemia (AML), acute lymphocytic leukemia, chronic myelogenous leukemia, non–Hodgkin lymphoma, and Hodgkin disease.

Table 101-4

Common Toxicities Associated With Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation

Early Posttransplant (<100 days)	Late Posttransplant (>100 days)
Febrile neutropenia	Increased susceptibility to infections
Nausea, vomiting, diarrhea Mucositis Veno-occlusive disease Renal dysfunction Cardiotoxicity	Endocrine disorders (hypothyroidism, hemorrhagic cystitis, infertility, growth retardation) Neurocognitive changes
Pneumonitis	Secondary malignant neoplasms
Graft rejection	Chronic GVHD
Acute GVHD	Cataracts

GVHD, graft-versus-host disease.

Complications of Autologous Hematopoietic Stem Cell Transplantation

Case 101-1, Question 5: What complications must be anticipated as a consequence of autologous HSCT? How can these be minimized? How can treatment be provided in an outpatient setting?

The most common cause of death after autologous HSCT is relapse of the primary disease. The most common toxicities seen during autologous HSCT are the result of the pancytopenia induced by high-dose chemotherapy. Because autologous HSCT is not complicated by profound immunosuppression or graft- versus-host

disease (GVHD), supportive-care strategies differ from allogeneic HSCT. Isolation and use of laminar airflow rooms are unnecessary. The use of autologous peripheral blood stem cell transplantation (PBSCT) is associated with shorter periods of neutropenia and less need for clinical resources; thus, some HSCT centers have developed programs that incorporate outpatient care into the initial recovery. These outpatient programs also offer cost savings to the payer for health services.[24,25] Successful outpatient care during autologous HSCT requires careful development and implementation of the necessary supportive-care strategies to prevent or minimize infection, chemotherapy-induced nausea and vomiting, infection, pain, and transfusion requirements. It is also necessary to develop admission criteria for patients with more severe complications.

Use of prophylactic oral antibiotics and once-daily IV antibiotics to prevent or treat febrile neutropenia has facilitated outpatient care and prevented select patients from being hospitalized.[26]

In addition, outpatient care during autologous HSCT demands that HSCT centers have appropriate resources, facilities, and staff to provide 24-hour patient care coverage. Patients undergoing outpatient care must meet eligibility criteria, including the availability of caregivers 24 hours a day and housing within close proximity to the HSCT center.

Hematopoietic Growth Factors After Autologous Peripheral Blood Progenitor Cell Infusion

Case 101-1, Question 6: Ten days after the collection of PBSC, P.J. is admitted for his autologous HSCT. He receives a myeloablative preparative regimen with cyclophosphamide, carmustine, and etoposide with an autologous PBPC graft. An order is written to begin filgrastim 5 µg/kg/day SC, beginning on day 5 and continuing until the ANC has recovered to 500 cells/µL for 3 consecutive days. What is the rationale for filgrastim in P.J. after the transplant procedure?

Autologous HSCTs, regardless of the stem cell source, are associated with profound aplasia because of the myeloablative preparative regimen (Table 101-3). Aplasia typically lasts 14 to 21 days after an autologous BMT and 10 to 14 days after an autologous PBPCT.[21] During this period of pancytopenia, patients are at high risk for complications such as bleeding and infection. To lessen the complications of pancytopenia, hematopoietic growth factors, such as filgrastim and sargramostim, may be used. These drugs exert their effects by stimulating the proliferation of committed progenitor cells. The benefits of the hematopoietic growth factor have been shown in several large multicenter, randomized, double-blind, placebo-controlled trials.[27–29] The majority of the trials suggest hematopoietic growth factor administration is associated with a shorter time to neutrophil engraftment (by 4–7 days), less infectious complications, shorter hospitalization after autologous BMT, and therefore decreased resource utilization.[27,28,30] However, the use of these agents does not affect overall survival.[27,29]

Although studies in the autologous PBPCT setting note more rapid neutrophil recovery after hematopoietic growth factor use, others report no difference in infection rates and minimal decreases in associated resource use such as the duration of hospitalization.[28,30–32] Although clinical practice guidelines for hematopoietic growth factors support their use after autologous transplant, pharmacoeconomic analyses are needed to further evaluate the true benefit of hematopoietic growth factors after autologous PBPCT.

Filgrastim is preferred for accelerating neutrophil engraftment in clinical practice. The reason most commonly cited is the desire to avoid febrile reactions associated with sargramostim, which complicates the interpretation of febrile neutropenia. Although sargramostim or filgrastim theoretically may stimulate proliferation of leukemia myeloblasts, no evidence to date suggests that the incidence of leukemia relapse is higher in patients who receive these hematopoietic growth factors after autologous or allogeneic HSCT.[33,34]

Although both filgrastim and sargramostim successfully hasten neutrophil recovery, neither agent stimulates platelet production or

augments platelet recovery.[27,28] At this time, there is no established role for erythropoietin-stimulating agents or platelet growth factors in the care of these patients. In summary, P.J. is undergoing autologous PBPCT for the treatment of lymphoid malignancy. Thus, either sargramostim or filgrastim is an acceptable option for accelerating engraftment. Whether the addition of either agent will reduce infection and improve other clinically relevant outcomes is debatable.[14] A complete blood cell (CBC) count with differential should be obtained daily. Filgrastim should be continued until neutrophil recovery is achieved.

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Allogeneic HSCT involves the transplantation of HSCs obtained from a donor's BM, PBPCs, or umbilical cord blood to a patient. Fifty-one percent of all transplants performed in North America in 2008 used unrelated donors.[1] Thus, to understand the application of and complications after allogeneic HSCT, a working knowledge of immunology and the major histocompatibility complex (MHC) and human leukocyte antigen (HLA) in humans is necessary.

Indications for Allogeneic Hematopoietic Stem Cell Transplantation

CASE 101-2

QUESTION 1: B.S., a 22-year-old male, has acute myelogenous leukemia (AML) in first remission after induction chemotherapy with standard doses of cytarabine and daunorubicin and consolidation with high-dose cytarabine. B.S. has poor-risk cytogenetics, with abnormalities of 11q23 and inversion 3. Thus, he will receive an allogeneic HSCT as part of postremission therapy. Typing performed on family members has identified a fully HLA-matched sibling donor. B.S. returns to the clinic today for a pretransplant workup. At this time, his

physical examination is noncontributory. All laboratory values are within normal limits. A BM biopsy reveals <5% blasts. B.S. has a normal electrocardiogram and cardiac wall motion study. His renal, hepatic, and pulmonary function tests are normal.

Is an allogeneic HSCT indicated for B.S.?

The primary indications for allogeneic HSCT include treatment of otherwise fatal diseases of the BM or immune system (Table 101-2). The optimal role and timing of allogeneic HSCT, in contrast to other therapies, remains controversial,[35] especially because treatment options for AML have increased. The National Comprehensive Cancer Network treatment guidelines for AML include the use of allogeneic HSCT. A matched sibling or alternative donor (eg, matched-unrelated donor [MUD]) HSCT is recommended as part of postremission therapy in patients with preceding hematologic disease (eg, myelodysplasia, secondary AML) or poor-risk cytogenetics, as in the case of B.S.[36] Current research efforts focus on the use of reduced-intensity preparative regimens and the utility of HSCT relative to novel targeted agents in the hope of improving the outcome of allogeneic HSCT.[36] B.S. is eligible for allogeneic HSCT by virtue of his cytogenetics and the availability of a histocompatible donor. In addition, he meets age and organ function eligibility requirements and is in complete remission with minimal residual disease.

Histocompatibility

Case 101-2, Question 2: Why is histocompatibility important in the selection of the donor in patients like B.S. who undergo an allogeneic HSCT?

Because the tissue transplanted in allogeneic HSCT is immunologically active, there is potential for bidirectional graft rejection.[2] In the first scenario, cytotoxic T cells and natural killer (NK) cells belonging to the host (recipient) recognize MHC antigens of the graft (donor HSCs) and elicit a graft rejection response. This

results in ineffective hematopoiesis (ie, inadequate ANC and/or platelet counts) posttransplant. In the second scenario, immunologically active cells in the graft recognize host MHC antigens and elicit an immune response, referred to as GVHD. Therefore, an essential first step for patients eligible for HSCT is finding an HLA-compatible graft with an acceptable risk of rejection and GVHD.

Determination of histocompatibility between potential donors and the patient is completed before allogeneic HSCT.[37] Initially, HLA typing is performed using tissue (buccal swab) and blood samples. Compatibility at class I MHC antigens (HLA-A, HLA-B, and HLA-C) is determined through serologic and DNA-based testing methods.[38,39] Currently, most clinical and research laboratories are also performing molecular DNA typing.[38–47] A donor–recipient pair with different HLA antigens (ie, "antigen mismatched") always has different alleles, whereas pairs with the same allele always have the same antigen and are termed "matched." However, some pairs have the same HLA antigen but different alleles and are thus "allele mismatched" (see Chapter 34, Kidney and Liver Transplantation, for additional discussion of histocompatibility).

Graft rejection is least likely to occur with a syngeneic donor, meaning that the recipient and host are identical (monozygotic) twins. Identical twins occur spontaneously in nature in ~1 in 100 births; thus, it is unlikely that a patient would have a syngeneic donor. In those patients without a syngeneic donor, initial HLA typing is conducted on family members because the likelihood of a complete histocompatibility match between unrelated individuals is remote. Siblings are the most likely to be histocompatible within a family; however, only 25% of potential HSCT recipients will have an HLA-identical sibling.[38]

Lack of an HLA-matched sibling donor can be a barrier to allogeneic HSCT. Alternative sources of allogeneic HSCs, such as related donors mismatched at one or more HLA loci, or MUDs, are used.[40] Establishment of the National Marrow Donor Program has helped increase the pool of potential donors for allogeneic HSCT.[40] Through this program, an HLA-matched-unrelated volunteer donor

might be identified. Recipients of an unrelated graft are more likely to experience graft failure and acute GVHD (aGVHD) relative to recipients of a matched sibling donor.[41] Thus, work is ongoing to identify factors that predict graft failure or GVHD to improve the availability and safety of unrelated donor transplants (see Graft Rejection section).[42] Recently, work has focused on a set of predictive biomarkers that help stratify patients' risk for GVHD. On day 7 of allogeneic HSCT, a two-biomarker panel of ST2 and REG3a is sent from the peripheral blood. These biomarkers, which help assess patient reaction to donor histocompatibility antigens and donor T-cell response to alloantigens, predicted likelihood of developing GVHD and nonrelapse mortality.[43,44]

The preparative regimen and/or GVHD prophylaxis may be altered based on the mismatch between the donor and the recipient. The risk of graft failure decreases with better matches, and although mismatching in a single HLA allele does not appear to impact overall survival, mismatching in more than one allele significantly impairs overall survival. The most important alleles to match are the HLA class I antigens (HLA-A, HLA-B, HLA-C) and the HLA class II antigens (HLA-DRB1, HLA-DPB1, HLA-DQB1).[45–47] This field is continually evolving with current data suggesting that mismatches at HLA-DPB1 confer an increased risk of mortality.[48]

Eligibility criteria for allogeneic HSCT vary between institutions. Having a matched sibling donor is no longer a requirement for allogeneic HSCT because improved immunosuppressive regimens and the National Marrow Donor Program have allowed an increase in the use of unrelated or related matched or mismatched HSCT.[41] Potential donors also include haploidentical donors, who are a parent, sibling, or child of a parent with only one identical HLA haplotype. Hematopoietic cell transplant with a haploidentical donor was initially associated with high rates of graft failure and GVHD, but recent technologic advances have improved outcomes. Haploidentical HSCT involves another alloreactive mechanism involving NK cells, which may be associated with reduced relapse rates in patients with AML.[2]

Normal renal, hepatic, pulmonary, and cardiac functions are necessary for eligibility at most centers. Historically, patients age older than 55 years were excluded from allogeneic HSCT because they were more likely to succumb to transplantation-related complications. However, many centers are now considering patients up to 65 years old and basing their selection criteria on physiologic rather than biologic age.

Harvesting, Preparing, and Transplanting Allogeneic Hematopoietic Stem Cells

Case 101-2, Question 3: What methods can be used to harvest HSCs from B.S.'s histocompatible sibling and prepare them for transplant? Are there any advantages to the use of BM, PBPCs, or umbilical cord blood as a source for HSCs?

The method of harvesting allogeneic HSCs varies according to the site of harvest (ie, BM, peripheral blood, or umbilical cord blood). ABO incompatibility increases the complexity of HSCT but is not an obstacle to HSCT. The HSCs may need additional processing to reduce the RBCs infused with the HSCT product if the donor and recipient are ABO-incompatible, which occurs in 30% to 40% of sibling donor HSCTs and is higher in unrelated donor HSCT.[49] Various strategies posttransplant used to manage blood support for ABO-incompatible HSCT recipients include the infusion of donor-type fresh frozen plasma to provide a noncellular source of A or B antigens, as well as transfusing-type volume-reduced RBCs and platelets or O RBCs to minimize the risk of immune-mediated hemolytic anemia and thrombotic microangiopathic syndromes.[49]

BONE MARROW

Harvesting BM entails a surgical procedure in which marrow is obtained from the iliac crests. Allogeneic BM is obtained from the donor under local or general anesthesia on day 0 of BMT.[2] The number of nucleated marrow cells harvested varies depending on

the disease being treated, conditioning regimen, and preinfusion manipulation and is usually 1 to 3 × 10^8 infused cells/kg of recipient weight.[17] These cells are obtained through multiple aspirations of marrow from the posterior iliac crests. The marrow is then processed to remove fat or marrow emboli and is usually immediately infused intravenously into the patient. If immediate transplant is not possible, the BM is frozen until it can be infused. Once infused into circulation, through the mechanism of the chemokine SDF-1/CXCR4 receptor, the stem cells migrate to the BM compartment where they will eventually reside.

PERIPHERAL BLOOD PROGENITOR CELLS

As mentioned, HSCs continuously detach, enter the circulation, and return to the marrow; thus, the peripheral blood is a convenient source of HSCs. The number of PBPCs is estimated by using the cell-surface molecule CD34 as a surrogate marker. The number of circulating CD34+ cells in blood is increased by mobilizing them from the marrow. The most commonly used regimen to mobilize allogeneic (healthy) donors is a 4- to 5-day course of filgrastim 10 to 16 μg/kg/day SC, followed by pheresis on the fourth or fifth day when peripheral blood levels of CD34+ cells peak.[9] An adequate number of HSCs is usually obtained with one to two pheresis collections. The optimal number of CD34+ required is 4 to 10 × 10^6 cells/kg of recipient body weight for an HLA-identical sibling donor transplant with haploidentical transplants requiring greater numbers.[10,50,51] Higher cell doses have been associated with not only more rapid engraftment but also fewer fungal infections and improved overall survival.[52] HSCs obtained from the peripheral blood are processed like BM-derived stem cells and may be infused immediately into the recipient or frozen for future use. Compared to BM, PBPC infusions are associated with quicker neutrophil and platelet engraftment.[2] In patients with a hematologic malignancy and a matched sibling donor, PBPCT is also associated with lower relapse rates and increased disease-free survival rates.[53] However, PBPC grafts contain more T cells than do BM grafts.[2] Therefore,

PBPCT has a similar incidence of aGVHD, but an ~20% higher incidence of extensive stage and overall chronic GVHD (cGVHD).[53]

UMBILICAL CORD BLOOD

Blood from the umbilical cord and the placenta is rich in HSCs but limited in volume.[54] Thus, umbilical cord blood offers an alternative stem cell source to those patients who do not have a suitable related donor. After consent is obtained, the cord blood cells are obtained in the delivery room after birth, typically after the delivery of the placenta.[55]

The cord blood is then processed, and, if it matches certain preestablished criteria (eg, minimum nucleated cell content, sterility), a sample is sent for HLA typing and cryopreserved for future use. An estimated 20,000 HSCTs with cord blood donors have been performed with >300,000 cord blood units banked worldwide. It is unknown how long cryopreserved cord blood is viable.[56]

HSCT with an unrelated cord blood donor has several potential advantages over unrelated marrow or PBPC donors.[54] Specifically, (a) cord blood is readily available, which leads to a more rapid time to HSCT; (b) lack of stem cell exposure to the thymus allows for greater degrees of HLA disparity as compared to BM or PBPC[55]; and (c) despite the less-stringent HLA matching, mismatched cord blood cells are less likely to cause GVHD while still maintaining GVT activity. The less-stringent HLA requirements increase the likelihood of identifying a suitable allogeneic donor, which is particularly beneficial for minority populations who are underrepresented in adult registries and often lack matched stem cell sources. Outcomes in umbilical cord blood recipients are improved with fewer HLA mismatches and greater numbers of CD34+ cells.[57] However, the limited number of HSCs in cord blood is a disadvantage, in particular when considering adult patients.[58] In order to overcome the cell dose limitation and improve engraftment, researchers have been studying infusing two cord blood units,[59] coinfusing a cord blood unit with highly purified CD34+ cells from haploidentical donors,[60] and ex vivo expansion of cord blood progenitors,[61] delivery of the cord blood unit

directly into the BM space,[62–64] and priming of cord blood with agents that may facilitate homing to the BM.[65]

As an adequate cell dose is critical for engraftment after cord blood transplantation and the cell dose of a single cord blood unit is limited, progress in the field of cord blood transplantation for the treatment of adults has been slower.[58] However, recent data showed that when a single cord blood unit with an adequate cell dose is available, the outcomes of adults with leukemia are similar to those receiving unrelated BM or peripheral blood grafts.[66]

Moreover, for those adults with leukemia who do not have a single cord blood unit with a suitable cell dose, the use of two partially matched cord blood units to compose the graft also provides outcomes similar to that of related and unrelated donors.[67] These data associated with the promising outcomes when using umbilical cord blood in the context of reduced-intensity conditioning have significantly increased the utilization of cord blood as a source of hematopoietic progenitors for the treatment of adult patients.[68,69]

In summary, the utilization of cord blood as a source of HSCs for transplantation has substantially expanded in the last decade. Novel methodologies to improve engraftment, promote immune reconstitution, and improve outcomes after cord blood transplantation are under investigation and are likely to further extend its availability to patients who require a potentially curative allogeneic transplant but lack a suitable related donor.

Therefore, it is most reasonable to harvest PBPCs from B.S.'s sibling to use for his myeloablative HSCT because his sibling is fully HLA-matched. A PBPC transplant is preferred to BMT because of the expectations of increased speed of neutrophil and platelet engraftment and disease-free survival rate and lower relapse rate.

GVT Effect

Case 101-2, Question 4: B.S. will receive an allogeneic HSCT from his histocompatible sibling with the hope of inducing GVT effect to help in treating

his malignancy. What is the GVT effect? Which tumors are most responsive to this effect?

GVT refers to the phenomenon where the donor's cytotoxic T lymphocytes suppress or eliminate the recipient's malignancy. Initial clinical evidence of a GVT effect came from the observation that patients with GVHD had lower relapse rates compared with those who did not.[70,71] This suggested a GVT effect because of the donor lymphocytes. Lymphocyte involvement in GVT was further supported by the effectiveness of donor lymphocyte infusions in treating patients who experienced relapse of their malignancies after allogeneic HSCT.[72,73] Eradication of the recurrent malignancy is because of either specific targeting of the tumor antigens or to GVHD, which may affect cancer cells preferentially. Different illnesses vary in their responsiveness to donor lymphocyte infusions, with chronic myelogenous leukemia (CML) and acute leukemias being the most and least responsive, respectively.[74] Patients with certain solid tumors (eg, renal cell carcinoma) also appear to benefit from a GVT effect.[75] These data are the platform on which the use of reduced-intensity and nonmyeloablative preparative regimens are based.

Preparative Regimens for Allogeneic Hematopoietic Stem Cell Transplantation

MYELOABLATIVE PREPARATIVE REGIMENS

Case 101-2, Question 5: What is the rationale for using myeloablative preparative regimens for patients like B.S. who are to receive an allogeneic HSCT? What types of regimens are used and what is recommended for B.S.?

The combination of chemotherapy and/or radiation used in allogeneic HSCT is referred to as the preparative or conditioning regimen. The rationale for high-dose myeloablative preparative regimens is similar to that discussed in the Autologous HSCT

section. Infusion of HSCs restores hematopoiesis induced by dose-limiting myelosuppression of chemotherapy, maximizing the potential value of the steep dose–response curve to alkylating agents and radiation,[18] and suppressing the host immune system. The preparative regimen is also designed to eradicate immunologically active host tissues (lymphoid tissue and macrophages) and to prevent or minimize the development of host-versus-graft reactions (ie, graft rejection). Conversely, patients undergoing syngeneic transplantation do not require immunosuppressive preparative regimens before HSCT because the donor and the patient are genetically identical; thus, there is no potential for host-versus-graft reactions. Therefore, preparative regimens are tailored to the primary disease and to HLA compatibility between the recipient–donor pair.

Examples of common preparative regimens for allogeneic HSCT are shown in Table 101-3.[8,20,76] Table 101-4 lists the common toxicities associated with myeloablative allogeneic HSCT. Most allogeneic preparative regimens for the treatment of hematologic malignancies contain cyclophosphamide, radiation, or both. The combination of cyclophosphamide and total body irradiation (TBI) was one of the first preparative regimens used, and it is still used widely today. This regimen is immunosuppressive and has inherent activity against hematologic malignancies (eg, leukemias, lymphomas). TBI is myeloablative and immunosuppressive, does not have cross-resistance to chemotherapy, and reaches sites not affected by chemotherapy (eg, the central nervous system).[2] The toxicity of TBI and the scarcity of facilities for its delivery have led to the development of radiation-free preparative regimens. Modifications of the cyclophosphamide–TBI (CY/TBI) preparative regimen include replacing TBI with other agents such as busulfan and adding other chemotherapeutic or monoclonal agents such as alemtuzumab to the existing regimen. These measures are designed to minimize the long-term toxicities associated with TBI (eg, growth retardation in children, cataracts) or to provide additional antitumor activity. The long-term outcomes of busulfan/cyclophosphamide (BU/CY) and CY/TBI in patients with AML and CML have been

compared in a meta-analysis of four clinical trials.[77] Equivalent rates of long-term complications were present between the two preparative regimens, except for a greater risk of cataracts with CY/TBI and alopecia with BU/CY. Overall, disease-free survival rates were similar in patients with CML, although there was a trend for improved disease-free survival with CY/TBI in patients with AML. In the case of a mismatched allogeneic HSCT with an increased chance of graft rejection, antithymocyte globulin (ATG) may also be added to the preparative regimen to further immunosuppress the recipient.

Based on these data, the CY/TBI preparative regimen is preferred for B.S. because he has AML with poor cytogenetics and has a matched sibling available. Because of the high relapse rates seen in AML, myeloablative allogeneic transplant is indicated in first remission for patients younger than 60 years old with good performance status because of the decrease in the likelihood of achieving a complete response to reinduction chemotherapy and the expected reduced duration of a second remission.

REDUCED-INTENSITY OR NONMYELOABLATIVE PREPARATIVE REGIMENS

Case 101-2, Question 6: Describe the rationale for nonmyeloablative preparative regimens. Is B.S. a candidate for such a regimen?

The regimen-related toxicity of a myeloablative preparative regimen (Table 101-4) limits the use of allogeneic HSCT to younger patients who have minimal comorbidities. Because many patients with hematologic malignancies are older and have comorbidities, myeloablative HSCT cannot be offered to a substantial portion of them.[78] The observation that patients with GVHD have less relapses and an improved understanding of the GVT effect led to the development of strongly immunosuppressive but not myeloablative (ie, a reduced-intensity or nonmyeloablative) preparative regimens.[2] Currently, reduced-intensity preparative regimens account for 30% of

allogeneic transplants.[79] More than 60% of patients receiving reduced-intensity preparative regimens are older than 50 years.[1,79]

There is a wide spectrum of reduced-intensity preparative regimens, with the nonmyeloablative regimens causing the least amount of myelosuppression. In general, more intensive preparative regimens are required for engraftment in the setting of unrelated donor or HLA-mismatched–related HSCT.[80] Reduced-intensity regimens do not completely eliminate the host's normal hematologic and malignant cells and, therefore, depend on the GVT effect to eradicate remaining cancer. The newly transplanted donor cells slowly replace host hematopoiesis and elicit GVT effects.[75] After engraftment, mixed chimerism is generally present. Chimerism can be defined as the ability to detect both donor-derived and recipient-derived hematopoietic cells; both donor and patient cells coexist together for a period of time in the patient. If the graft is rejected, typically only recipient cells are present. After a reduced-intensity preparative regimen, mixed chimerism (defined as 5%–95% donor T cells present in the peripheral blood) between the host and recipient develops, allowing for a GVT effect as the primary form of therapy. Chimerism is evaluated to monitor disease response and engraftment posttransplant. Chimerism is assessed within T cells and granulocytes in the peripheral blood and BM using conventional (eg, using sex chromosomes for opposite sex donors) and molecular (eg, variable number of tandem repeats for same-sex donors) methods. The methods used to characterize chimerism after HSCT are reviewed elsewhere.[81–83] A few months after HSCT, donor lymphocytes can be infused (called a "donor lymphocyte infusion") to augment the GVT activity.[2] The use of donor lymphocyte infusions is dependent on the availability of the donor and is highly center-specific. The challenge is to maximize the GVT effect while minimizing the risk of GVHD. Therefore, GVHD prophylaxis, although different from that used with myeloablative regimens, is still necessary. Although reduced-intensity preparative regimens have led to lower treatment-related mortality rates, they may be offset by higher relapse rates.[2,84] The safety and efficacy of these regimens have led to their wider application to nonmalignant conditions.[2]

Because most of the data for reduced-intensity preparative regimens are derived from older patients or those with comorbid conditions, they cannot be compared with data for myeloablative preparative regimens.[84] It is unclear if reduced-intensity preparative regimens improve long-term survival of patients with malignant or nonmalignant diseases who are younger or without comorbid conditions. Prospective controlled trials are needed with stratification based on comorbidities, disease characteristics, pretransplant therapy, and hematopoietic stem cell source.[84]

There is a paucity of data regarding the optimal source of HSCs after reduced-intensity preparative regimens. Most case series have combined data from PBPC and marrow grafts. But some data suggest that, compared to BM grafts, PBPC is associated with quicker engraftment, earlier T-cell chimerism, longer progression-free survival, and a lower risk of graft rejection.[85,86]

B.S. is young and healthy enough to receive a myeloablative allogeneic HSCT. Presently, reduced-intensity HSCT is only indicated as first-line therapy for patients ineligible for myeloablative regimens because of age, extensive prior treatments, or other contraindications. It is not an option for B.S.

Posttransplantation Immunosuppressive Therapy

Case 101-2, Question 7: What is the rationale for immunosuppressive therapy after an allogeneic HSCT? What is recommended for B.S.?

After infusion of HSCs, immunosuppressive therapy is administered to prevent or minimize GVHD. Patients receiving syngeneic transplants or a T-cell–depleted histocompatible allogeneic transplant generally do not receive posttransplantation immunosuppressive therapy. In syngeneic transplantation, the donor and the patient are genetically identical, and GVHD should not be elicited. In T-cell–depleted transplantation, the volume of donor T cells infused into the patient is usually insufficient to elicit significant GVHD.[72,87] Numerous immunosuppressive agents given alone or in

combination have been evaluated for the prevention of GVHD. Commonly used regimens after myeloablative HSCT include cyclosporine or tacrolimus administered with a short course of low-dose methotrexate.[88] GVHD prophylaxis varies in reduced-intensity protocols and can be found in **Table 101-5**.[89] Corticosteroids may also be used to prevent GVHD, but they are more commonly used to treat GVHD. In allogeneic HSCT recipients without GVHD, immunosuppressive therapy is slowly tapered and discontinued over the course of 6 months to 1 year. Over time, the immunologically active tissue between host and recipient become tolerant of one another and cease recognizing the other as foreign, negating the need for immunosuppression. In contrast, solid-organ transplant recipients usually continue immunosuppressive therapy for the duration of the recipient's life.

Table 101-5

Common Reduced-Intensity Preparative or Nonmyeloablative Regimens and Postgrafting Immunosuppression

Preparative Regimens	Postgraft Immunosuppression
Fludarabine 30 mg/m^2/day IV on 3 consecutive days (−4, −3, −2), TBI 2 Gy as a single fraction on day 0	Cyclosporine 6.25 mg/kg PO bid, day –3 to day +100 with taper from days +100 to +180
Fludarabine 25 mg/m^2/day IV for 5 days and melphalan 90 mg/m^2/day IV for 2 days	Mycophenolate mofetil 15 mg/kg PO bid or tid, days +0 to +40 with taper from days +40 to +90
Fludarabine 25–30 mg/m^2/day IV for 3–5 days, busulfan ≤9 mg/kg/total dose	Tacrolimus to maintain trough blood concentration of 5–10 ng/mL with methotrexate 5 mg/m^2/day IV days +1, +3, +6, +11

bid, two times a day; IV, intravenous; PO, orally; TBI, total body irradiation; tid, three times a day.

Source: Ren S, Kalhorn TF, McDonald GB, Anasetti C, Appelbaum FR, Slattery JT. Pharmacokinetics of cyclophosphamide and its metabolites in bone marrow transplantation patients. *Clin Pharmacol Ther*. 1998;64:289–301.

In patients without a matched-related or matched-unrelated donor who undergo HSCT with a haploidentical donor, the use of

cyclophosphamide posthematopoietic stem cell infusion may be used. The cyclophosphamide is typically given ~4 days after HSCT. It has been shown that the cyclophosphamide does not affect the HSCs but does exert its effect on alloreactive T cells, thereby reducing the risk of GVHD development.[90] Current trials are ongoing to assess the usefulness of this approach.

B.S. is receiving a myeloablative preparative regimen with allogeneic transplant and will receive cyclosporine administered for 6 months, followed by a taper, with a short course of methotrexate 15 mg/m^2 on day +1 and 10 mg/m^2 on day +3, +6, and +11 for posttransplant immunosuppression. This combination regimen will lower the risk of GVHD. Assuming B.S. does not experience any serious complications, he will likely be immunosuppressant free by 9 months posttransplant. The cyclosporine will require therapeutic drug monitoring.

Comparison of Supportive-Care Strategies Between Autologous and Allogeneic Myeloablative Hematopoietic Stem Cell Transplantation

Case 101-2, Question 8: How do supportive-care strategies used for myeloablative preparative regimens with an autologous graft differ from an allogeneic graft? What supportive care will B.S. likely require?

Supportive-care strategies common to patients receiving a myeloablative preparative regimen, regardless of whether they have received an autologous or allogeneic HSCT, include use of indwelling central venous catheters; blood product support; and pharmacologic management of chemotherapy-induced nausea and vomiting, mucositis, and pain. These similarities are a function of the side effects of a myeloablative preparative regimen.

Because of the different needs for immunosuppression with an autologous and allogeneic HSCT, the supportive care differs.

Patients undergoing allogeneic HSCT experience an initial period of pancytopenia followed by a more prolonged period of immunosuppression, which substantially increases the risk of bacterial infections, but more importantly, fungal, viral, and other opportunistic infections.[4] The risk of infection increases as additional immunosuppressive therapy is incorporated to prevent or treat GVHD. Supportive strategies designed to minimize infection during immunosuppression are essential after allogeneic HSCT (see Infectious Complications section).

B.S. received a myeloablative allogeneic transplant; therefore, he will have a central venous catheter inserted at admission. He will most likely require multiple RBC and platelet transfusions until engraftment occurs. He is at increased risk of infection because he will be immunosuppressed for months after the transplant. Also, if he were to develop GVHD, additional supportive care would be required. GVHD prophylaxis with cyclosporine and methotrexate will place him at risk for additional drug-related toxicities that will require monitoring. Had he received an autologous transplant the duration of neutropenia would be less, no immunosuppressive medications would be required, and the risk of developing complications from GVHD would have been avoided.

Comparison of Supportive-Care Strategies Between Allogeneic Myeloablative and Nonmyeloablative Hematopoietic Stem Cell Transplantation

Case 101-2, Question 9: How do supportive-care strategies used for myeloablative and nonmyeloablative preparative regimens with an allogeneic graft differ?

A direct comparison of the toxicities between a myeloablative and nonmyeloablative preparative regimen is difficult because the latter is offered only to patients who are not candidates for myeloablative

allogeneic HSCT. The preparative regimens differ substantially in terms of the chemotherapy agents used (Tables 101-3 and 101-5) and the degree of myelosuppression. Nonmyeloablative HSCT may have a different time pattern for infectious complications, but there is a similar incidence and severity of aGVHD. This makes comparisons between the preparative regimens challenging because of the differences in the pre-HSCT health of the recipients.[80] Clinical research is focusing on designing optimal preparative regimens with acceptable efficacy and toxicity. Thus, as compared to myeloablative HSCT, the preparative regimens and immunosuppression used after hematopoietic stem cell infusion are more variable for reduced-intensity and nonmyeloablative HSCT.

Complications Associated with Hematopoietic Stem Cell Transplantation

CASE 101-3

QUESTION 1: K.M. is a 36-year-old female with CML in accelerated phase. After her initial diagnosis, a successful search for an unrelated 6/6 HLA-matched allogeneic donor was conducted. K.M. is being admitted for myeloablative allogeneic PBPCT. Orders for K.M.'s preparative regimen are written as follows: busulfan, 16 mg/kg total dose to be administered over 4 days (1 mg/kg/dose orally [PO] every 6 hours for 16 doses, days −7, −6, −5, and −4). Cyclophosphamide 60 mg/kg/day IV to be administered on days −3 and −2. Day −1 is a "rest" day, followed by infusion of PBPC on day 0.

What toxicities associated with myeloablative preparative regimen should be anticipated in K.M.? Are they similar to those anticipated after standard-dose chemotherapy?

Myelosuppression is a frequent dose-limiting toxicity for chemotherapy when administered in conventional doses used to treat cancer. However, because myelosuppression is circumvented with hematopoietic rescue in the case of patients receiving HSCT, the dose-limiting toxicities of these myeloablative preparative

regimens are nonhematologic (ie, extramedullary) in nature. The toxicities vary with the preparative regimen used. Most patients undergoing HSCT experience toxicities commonly associated with chemotherapy, such as alopecia, mucositis, chemotherapy-induced nausea and vomiting, infertility, and pulmonary toxicity (see Chapter 94, Adverse Effects of Chemotherapy, Immunotherapy, and Targeted Agents). However, these drug-related toxicities are magnified in the HSCT population.

Table 101-4 depicts a range of toxicities that can occur after myeloablative preparative regimen for HSCT, and **Figure 101-2** depicts the time course for complications after HSCT. Selected toxicities are discussed in the following sections.

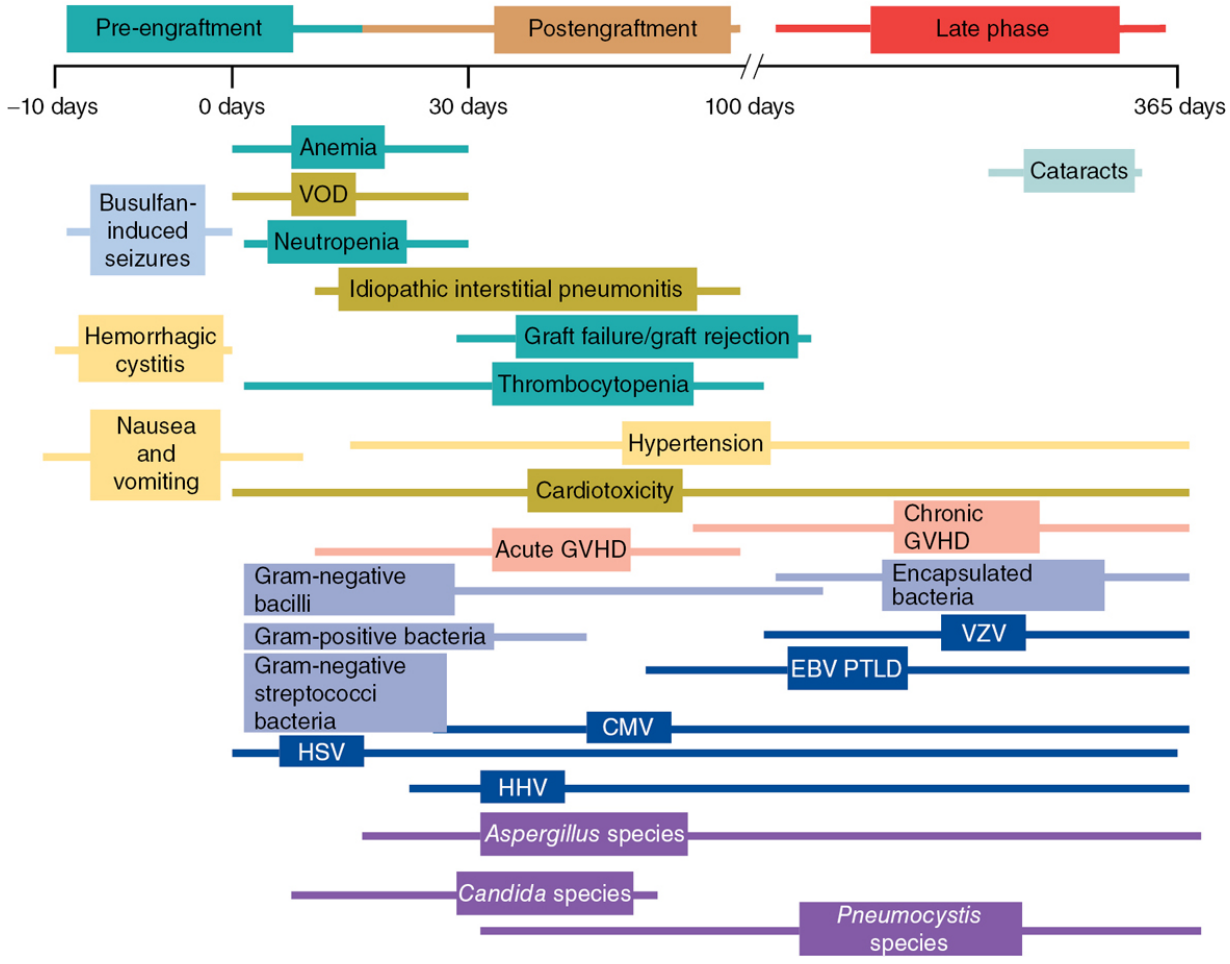


Figure 101-2 Complications after hematopoietic stem cell transplantation (HSCT) by time for patients undergoing

myeloablative allogeneic HSCT only. CMV, cytomegalovirus; EBV, Epstein–Barr virus; GVHD, graft-versus-host disease; HHV, human herpesvirus; HSV, herpes simplex virus; PTLD, posttransplantation lymphoproliferative disease; VOD, veno-occlusive disease; VZV, varicella-zoster virus.

Busulfan Seizures

Case 101-3, Question 2: In addition to her preparative regimen, the following supportive-care agents and monitoring parameters are prescribed for K.M.: on the day of admission (day −8), administer levetiracetam 500 mg PO twice daily from days −8 to −3. Busulfan pharmacokinetic blood sampling is to occur after dose 1 to a target busulfan area under the curve (AUC) >900 ng/mL. Begin normal saline hydration 3000 mL/m^2/day 4 hours before cyclophosphamide and continue for 24 hours after the last cyclophosphamide dose. Mesna is to be given concurrently with cyclophosphamide as 10% of the cyclophosphamide dose administered intravenously 30 minutes before starting the cyclophosphamide dose, then as 100% of cyclophosphamide dose administered as a continuous IV infusion for 24 hours after each dose of cyclophosphamide. Beginning on day −5, weigh patient twice daily, check fluid input and urinary output every 4 hours, and monitor urine for RBCs daily until 24 hours after the last cyclophosphamide dose. If urine output drops below 300 mL for 2 hours, administer an IV bolus of 250 mL normal saline and give furosemide 10 mg/m^2, not to exceed 20 mg IV. What is the rationale for these supportive-care therapies and monitoring parameters prescribed for K.M. as they relate to busulfan therapy?

Seizures occur in ~10% of patients receiving high-dose busulfan in HSCT preparative regimens. Busulfan is highly lipophilic and readily crosses the blood–brain barrier with an average cerebrospinal fluid/plasma ratio of 1 or higher. Seizures are probably a direct neurotoxic effect[91]; therefore, seizure prophylaxis is used. Many HSCT centers have moved from phenytoin to levetiracetam for seizure prophylaxis, although benzodiazepines (eg, lorazepam or clonazepam) also have been used.[92] Seizure prophylaxis is started at least 12 hours before the first busulfan dose and is usually discontinued 24 to 48 hours after administering the last busulfan

dose. Seizures can occur despite the use of seizure prophylaxis, but they usually do not result in permanent neurologic deficits.

Adaptive Dosing of Busulfan

Case 101-3, Question 3: What dosing strategies can be used to minimize busulfan toxicities?

Intravenous busulfan is commonly used in combination with cyclophosphamide as a preparative regimen before allogeneic HSCT for CML. The FDA-approved dose is 0.8 mg/kg IV every 6 hours for 16 doses, which is similar to the oral busulfan dose of 1 mg/kg, assuming a fraction absorbed of 90%.[93] Intravenous busulfan, at 0.8 mg/kg of actual body weight, produces an average AUC of 1200 μM/minute, within a wide range of 900 to 1500 μM/minute in 80% of patients.[94] Higher AUC values (>1500 μM/minute) have been associated with an increased risk of developing sinusoidal obstructive syndrome (SOS), formerly called veno-occlusive disease (SOS/VOD) of the liver; therefore, monitoring of busulfan AUC is warranted. Target AUCs are commonly between 900 and 1350 μM/minute after the first dose. This minimizes the risk of SOS/VOD and graft failure and minimizes the risk of disease recurrence[95] (see Case 101-3, Questions 7–9 for information on SOS/VOD).

To minimize adverse events from IV busulfan, an AUC is obtained with the first dose of busulfan to analyze K.M.'s exposure. Samples are drawn at the end of the 2-hour infusion, then 1, 2, and 4 hours after the first sample. Many centers are not capable of analyzing IV busulfan levels; therefore, prior arrangements must be made for timely analysis of these samples in order to adjust the dose after the second or third dose, if needed. K.M.'s AUC comes back 12 hours later at 1225 μM/minute and, therefore, her dose is not changed. Had the AUC been >1350 μM/minute, her dose could have been adjusted using the following formula:

$$\text{Adjusted dose (mg)} = \text{Actual dose (mg)} \times \text{Target AUC (}\mu\text{M/minute)/Actual AUC (}\mu\text{M/minute)}$$

(Eq. 101-1)

Hemorrhagic Cystitis

CASE 101-3, QUESTION 4: What is the rationale for these supportive-care therapies and monitoring parameters prescribed for K.M. as they relate to cyclophosphamide therapy?

In patients undergoing HSCT receiving cyclophosphamide, moderate-to-severe hemorrhagic cystitis occurs in 4% to 20% of patients receiving hydration alone.[96] Development of hemorrhagic cystitis is thought to be because of the bladder toxin acrolein, a metabolite of cyclophosphamide.[97] The chemoprotectant mesna donates free thiol groups that bind acrolein and reduce its toxicity. The American Society of Clinical Oncology (ASCO) guidelines on the use of chemotherapy and radiotherapy protectants recommends the use of mesna plus saline diuresis or forced saline diuresis to lower the incidence of urothelial toxicity with high-dose cyclophosphamide in the setting of HSCT.[98] It is important to note that hematuria or hemorrhagic cystitis can occur despite the use of any of these methods.

The optimal mesna dose with high-dose cyclophosphamide in preparation for myeloablative HSCT is unknown. A variety of different regimens have been used, including intermittent bolus dosing (mesna dose 20%–40% of cyclophosphamide dose, administered for up to five doses) or continuous infusion regimens (mesna dose 80%–160% of cyclophosphamide dose).[96,99,100] Mesna should be continued for 24 to 48 hours after the last cyclophosphamide dose, such that mesna is present within the bladder at the same time as the urotoxic metabolite acrolein. After IV administration of mesna, most of it (ie, 60%–100%) is excreted within the urine over the course of 4 hours.[101] Cyclophosphamide

has an average half-life of 7 hours after administration of 60 mg/kg,[102] and acrolein may be present within the urine for 24 to 48 hours after cyclophosphamide administration.[103]

Thus, K.M. is receiving hydration with normal saline and mesna, administered as a continuous infusion, to minimize her risk of hemorrhagic cystitis because of cyclophosphamide. K.M. should be monitored for any RBCs present in the urine, along with her urinary output, to allow for rapid intervention if hemorrhagic cystitis occurs.

Chemotherapy-Induced Gastrointestinal Effects

Case 101-3, Question 5: What other end-organ toxicities must be watched for? Should any medications be ordered for K.M. to prevent and treat the gastrointestinal (GI) effects associated with myeloablative therapy?

The high doses of chemotherapy in preparative regimens cause most patients to be nauseated and anorexic until day +10 to +15. Chemotherapy-induced nausea and vomiting in HSCT recipients can be because of highly emetogenic chemotherapy agents (see Chapter 22, Nausea and Vomiting), TBI administration, and poor control of nausea and vomiting prior to HSCT. Thus, patients such as K.M. who are undergoing a myeloablative HSCT should be given prophylaxis with a serotonin antagonist plus a corticosteroid.[105]

ASCO guidelines state that the use of the neurokinin receptor-1 antagonist, aprepitant, should be considered, although evidence to support its use in patients undergoing HSCT is lacking.[104] Because aprepitant is a moderate inhibitor of cytochrome P-450 3A4, it may theoretically interact with the preparative regimen, especially cyclophosphamide. Well-controlled studies evaluating its efficacy, along with its potential for causing drug interactions, are needed.[104] Some data suggest that the serotonin antagonist ondansetron may increase cyclophosphamide clearance in patients undergoing a myeloablative HSCT.[105,106] However, further work is needed to identify the clinical implications of this finding because, to date, cyclophosphamide concentrations have not been consistently

associated with clinical outcomes in patients undergoing a myeloablative HSCT.[19,93]

Most patients receiving a myeloablative preparative regimen may also experience mucositis because of its effects on rapidly dividing cells of the oral epithelium. The use of methotrexate as GVHD prophylaxis also contributes to mucositis.[107] Oral mucositis may also contribute to the development of nausea and anorexia.

In severe cases, parenteral opioid analgesics for pain relief[108] and total parenteral nutrition (TPN) may be needed. Because mucositis can be worsened by superinfection, good oral hygiene should be practiced. Soft toothbrushes should be used and replaced often.[109] Oral mucositis can be decreased with the use of recombinant human keratinocyte growth factor palifermin. The Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology guidelines recommend palifermin to prevent mucositis for patients with hematologic malignancies receiving myeloablative chemotherapy and TBI with autologous HSCT. Palifermin 60 µg/kg/day is given for 3 days immediately prior to administering the preparative regimen and for 3 days after infusion of the hematopoietic stem cell graft (ie, days 0, +1, +2).[110] In these patients, palifermin lowered the incidence and average duration of clinically meaningful oral mucositis. The incidence of blood-borne infections and the use of parenteral opioids were also diminished in patients using palifermin.[110]

Myelosuppression and Growth Factor Use

Case 101-3, Question 6: An order is written to begin filgrastim on day +5 and to continue administration until the ANC has recovered to 500/µL for 2 consecutive days. Is this therapy appropriate for K.M.?

The use of hematopoietic growth factors after infusion of allogeneic PBPC is controversial and is not recommended by ASCO guidelines.[14] Administration of hematopoietic growth factors after allogeneic graft infusion decreases the duration of neutropenia but

has not been demonstrated to decrease cost, length of hospitalization, or antibiotic use. Hematopoietic growth factor administration may increase the incidence of severe GVHD and lower survival.[111] K.M. is receiving an allogeneic PBPC graft and thus, should not receive filgrastim.

Sinusoidal Obstructive Syndrome/ Veno-Occlusive Disease of the Liver

Case 101-3, Question 7: K.M.'s pretransplantation admission laboratory values are within normal limits. Her weight on admission is 176.37 pounds (80 kg). During the first 5 days after marrow infusion, K.M.'s weight begins to increase by ~0.5 kg/day, her inputs exceed her outputs by about 500 to 1000 mL/day, and she is mildly febrile with an axillary temperature of 100.40 °F (38 °C). Blood and urine cultures are all negative. On day +6, her weight is 187.39 pounds (85 kg). Laboratory values on day +7 are significant for the following:

Total bilirubin, 1.5 mg/dL
Aspartate aminotransferase (AST), 40 units/L
Alkaline phosphatase, 120 units/L

By day +10, K.M. endorses mid-epigastric, right upper quadrant pain, and a liver that is tender to palpation. During the next few days, K.M. begins to look icteric. Her liver function tests continue to rise slowly, until day +18 when they reach the following peak values:

Total bilirubin, 5 mg/dL
AST, 150 units/L
Alkaline phosphatase, 180 units/L

On day +18, K.M.'s weight is 198.41 pounds (90 kg). "Rule out SOS of the liver" is included on her problem list in the medical record. What is SOS?

SOS, formerly known as VOD, is a syndrome consisting of fluid retention, right upper quadrant pain, and hyperbilirubinemia. In severe cases, it results in renal failure, encephalopathy, multiorgan failure, and ultimately may result in death. The incidence of SOS/VOD varies depending on the definition used to diagnose the syndrome; however, it is most commonly associated with high-dose chemotherapy with HSCT. It has been reported to occur in 5% to

55% of patients undergoing myeloablative HSCT.[112,113] The major risk factor for the development of SOS/VOD is high-dose chemotherapy associated with myeloablative transplants. Preparative regimens, including busulfan, cyclophosphamide, and/or TBI >13.2 Gy, have been associated with higher SOS/VOD rates.[19,114] Patient-specific factors such as older age, impaired performance status, and advanced disease have also been reported to increase SOS/VOD risk.

Although the exact pathophysiology underlying the development of SOS/VOD is not fully understood, it is known that damage to the sinusoidal endothelial cells in the liver is the initial insult that initiates the process. Damage continues and leads to sloughing of the endothelial lining of the sinusoids ultimately resulting in embolism and obstruction of sinusoidal flow.[115] This obstruction of flow within the liver contributes to postsinusoidal portal hypertension and worsening liver dysfunction, usually manifested by increased bilirubin and ascites.

CLINICAL PRESENTATION AND DIAGNOSIS

Case 101-3, Question 8: What signs and symptoms in K.M. are consistent with a diagnosis of SOS/VOD?

The initial signs and symptoms of SOS/VOD can occur anytime within the first 15 to 30 days posttransplant. Insidious weight gain exceeding 5% of baseline may be one of the first manifestations of impending SOS/VOD, occurring in >90% of patients within 3 to 6 days after marrow infusion.[113] Weight gain is caused by sodium and water retention, as evidenced by decreased renal sodium excretion. New onset of transfusion refractory thrombocytopenia may also be an early sign of impending SOS/VOD. Hyperbilirubinemia, which also occurs in virtually all patients, follows the onset of weight gain and usually appears within 10 days after hematopoietic stem cell infusion. Other liver function test abnormalities usually occur after hyperbilirubinemia and include elevations in AST and alkaline

phosphatase. Ascites, right upper quadrant pain, and encephalopathy lag behind changes in liver function tests and develop within 10 to 15 days after infusion of HSCs.[113]

Although liver biopsy is the gold standard for the diagnosis of SOS/VOD, its use is limited because of the risk of bleeding during the procedure. Other noninvasive criteria have been developed to help diagnose SOS/VOD after HSCT. Two sets of clinical criteria call for an evaluation of hyperbilirubinemia, ascites/weight gain and right upper quadrant pain not attributable to other causes such as medications, aGVHD, or infection.[113,116] Along with these criteria, ultrasound may be useful in determining whether there is reversed hepatic venous flow and to confirm ascites and/or hepatomegaly.

Case 101-3, Question 9: What is the likelihood that K.M. will recover from her SOS/VOD? How should she be treated?

There is no standard treatment for SOS/VOD, although many patients with SOS/VOD (70%–85%) spontaneously recover. Preventive measures look to control patient risk factors, and pharmacologic prevention strategies have also been used. Patient-specific risk factors are often not reversible; however, selection of appropriate preparative regimens such as nonmyeloablative regimens, avoidance of concomitant hepatotoxic drugs, use of fractionated TBI, and the use of adaptive busulfan dosing may reduce risk. Preventive medications have also been investigated. The use of prophylactic heparin has shown varied results in clinical trials; therefore, its use is still controversial.[117] The data for the use of ursodeoxycholic acid are also inconclusive. However, some trials have shown a benefit in reducing the incidence of SOS/VOD with its use. According to one trial, patients who received ursodeoxycholic acid were shown to have decreased hepatotoxicity, less aGVHD, and better survival.[118]

Other treatments consist of supportive-care measures such as management of sodium and water balance and paracentesis, in severe cases, for ascites that is associated with pain and pulmonary

compromise.[107] Volume expanders such as albumin and colloids may be used to maintain intravascular volume, spironolactone may be used to minimize extravascular fluid accumulation, and protein restriction and lactulose may be used if encephalopathy develops. Unfortunately, improved outcomes with these measures have not been confirmed. In patients with severe SOS/VOD and multiorgan failure, available treatment options are limited. Thrombolytic therapy with recombinant human tissue plasminogen activator and heparin have had mixed results in terms of efficacy and can cause fatal intracerebral or pulmonary bleeding.[107] Defibrotide has shown promising results in the treatment of SOS/VOD.[119–121] Defibrotide, a ribonucleotide, has antithrombotic, anti-ischemic, and thrombolytic activity without producing significant systemic anticoagulation.

A phase-3 trial looked at the efficacy of defibrotide in patients with established SOS/VOD and multiorgan failure. Patients (n = 102) were given defibrotide at 25 mg/kg/day and compared to historical controls. The primary end point was survival at day +100 after HSCT. Those receiving defibrotide had a survival rate of 38.2% at day +100 versus 25% in the control group.[121]

Because K.M. does not meet the criteria for severe SOS/VOD, she should be managed conservatively with fluid restriction and spironolactone for fluid diuresis. Her signs and symptoms should resolve during the next 2 weeks. Because she has mild SOS/VOD, she is likely to recover completely without sequelae.

Graft Rejection

CASE 101-4

Question 1: E.R. is a 65-year-old female diagnosed with myelodysplastic syndrome. Past medical history is significant for type I diabetes and renal dysfunction. After her initial diagnosis, a search for a completely HLA-MUD was conducted. A donor was found in the National Marrow Donor Registry, and E.R. will receive a nonmyeloablative allogeneic HSCT using BM from an unrelated male donor. E.R.'s preparative regimen is as follows: fludarabine 30 mg/m^2/day on days −4, −3, and −2 and 2 Gy TBI on the day of marrow infusion with

posttransplant cyclosporine and mycophenolate mofetil. It is now day +28 and E.R.'s CBC shows the following:

WBC count, 500 cells/μL
Differential, no granulocytes or monocytes detected
Platelets, 100,000/μL
Hematocrit (HSCT), 30%
Donor T-cell chimerism, >5%

What is E.R. experiencing and how should she be treated?

Reduced-intensity regimens typically consist of fludarabine in combination with an alkylating agent or low-dose TBI (**Fig. 101-3**). With the nonmyeloablative fludarabine/TBI regimen, there is minimal neutropenia, thrombocytopenia, and other nonhematologic toxicities.[2] Engraftment is usually evident within the first 30 days in patients receiving a nonmyeloablative preparative regimen; however, rejection can occur after initial engraftment.[122] Mixed chimerism, a state where both host and donor cells coexist, generally develops after nonmyeloablative HSCT. E.R. has low donor T-cell chimerism on day +28, placing her at high risk of graft rejection.

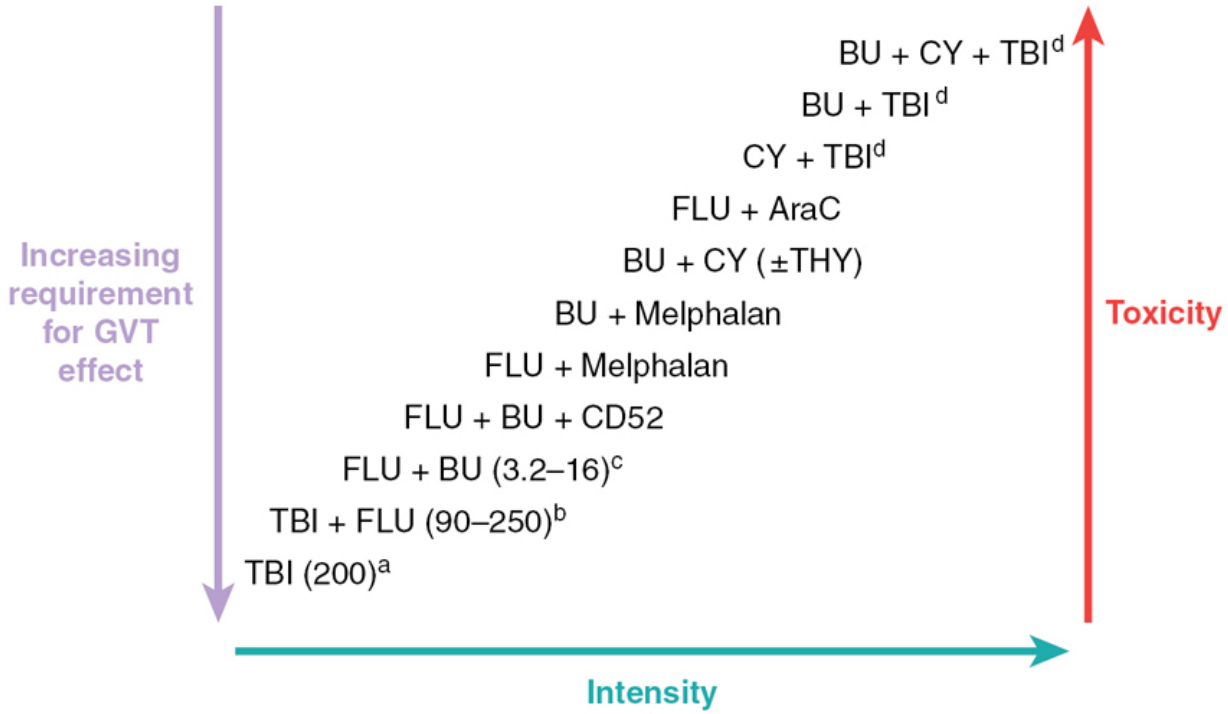


Figure 101-3 Partial spectrum of preparative regimens of various intensities, their impact on toxicity, and their dependence on graft-versus-tumor (GVT) effects for success of hematopoietic stem cell transplantation. AraC, cytarabine; BU, busulfan; CD52, anti-CD52 antibody (alemtuzumab); CY, cyclophosphamide; FLU, fludarabine; TBI, total body irradiation; THY, thymoglobulin. [a]200 cGy; [b]90 to 250 mg/m2; [d]3.2 to 16 mg/kg; [d]TBI >1200 cGy. (Adapted by permission from Nature: Deeg HJ, Maris MB, Scott BL, Warren EH. Optimization of allogeneic transplant conditioning: not the time for dogma. *Leukemia*. 2006;20(10):1701–1705. © 2006 Springer Nature.)

Graft rejection occurs particularly after nonmyeloablative allogeneic HSCT. A delicate balance exists between host and donor effector cells. This is established with myelosuppressive chemotherapy and immunosuppressants to decrease the risk of excessive host-versus-graft effects that could lead to graft rejection. The incidence of graft rejection is higher in patients with aplastic anemia and in patients undergoing HSCT with histoincompatible marrow or T-cell–depleted marrow. There are limited therapeutic options for the treatment of graft rejection. A second HSCT is the most definitive therapy, assuming donor cells are available, although the toxicities are formidable.[123] In patients receiving myeloablative allogeneic HSCT, graft rejection is best managed with immunosuppressants such as ATG. In patients receiving a reduced-intensity regimen, graft rejection may require a second HSCT.

E.R. received nonmyeloablative conditioning, and thus, she should have mixed chimerism posttransplant; however, she has <5% donor T cells. Current research is focusing on quantitative chimerism monitoring, specifically evaluating the percent donor chimerism, which may be used as a tool with which to base clinical interventions.[82] Donor chimerism is evaluated in different cell types (eg, T cells, NK cells, granulocytes), although the cell type most predictive of outcome is not known. The changes in the percent donor chimerism over time posttransplant, termed “engraftment kinetics,” are influenced by several factors such as type of HSCT conditioning, stem cell source, and intensity of postgrafting

immunosuppression.[82,124] A balance between the recipient's and donor's cells is needed to maximize the GVT effect, which lowers the risk of relapse while minimizing the risk of GVHD.[82,124] Based on E.R.'s state of chimerism, she will not benefit from the GVT effect because of the lack of the donor's cytotoxic T lymphocytes that suppress the recipient's malignancy.

E.R. is at high risk of graft rejection and therefore may not benefit from the transplant. A trial of discontinuing cyclosporine and mycophenolate mofetil, in an attempt to shift the balance toward donor graft growth and away from recipient T-cell growth, is an option. E.R.'s T-cell chimerism should be monitored periodically, and hematopoietic function should be monitored with daily CBC and a BM biopsy as clinically indicated.

GRAFT-VERSUS-HOST DISEASE

GVHD is caused by activation of donor lymphocytes, leading to immune-mediated damage to the recipient. Histocompatibility differences between donor and recipient necessitate posttransplantation immunosuppression after allogeneic HSCT because considerable morbidity and mortality are associated with graft rejection and GVHD. Therefore, immunosuppression or GVHD prophylaxis is used after allogeneic HSCT. However, because allogeneic transplantation offers the potential for a GVT effect in which immune effector cells from the donor recognize and eliminate residual tumor in the recipient, research is focusing on immune suppression manipulations that allow sufficient GVT effects while not increasing the risk of graft rejection and GVHD.[125]

GVHD is the most important complication of allogeneic HSCT and limits the use of this life-saving treatment in patients without histocompatible donors.[2,126] GVHD can occur after allogeneic HSCT, regardless of the preparative regimen used. The pathophysiology of GVHD is not completely understood, but the current view of its development is described by a three-step process, including (a) the

preparative regimen causing tissue damage and release of inflammatory cytokines into the circulation; (b) recipient and donor antigen-presenting cells and inflammatory cytokines triggering activation of donor-derived T cells; and (c) activated donor T cells mediating cytotoxicity through a variety of mechanisms, which leads to tissue damage characteristics of aGVHD.[127]

GVHD has traditionally been divided into two forms (ie, acute or chronic) based on time points and clinical manifestations. Acute GVHD, defined as occurring during the first 100 days posttransplant, damages the skin, GI tract, and liver.[2] In contrast, cGVHD may affect almost any organ system, closely resembles several autoimmune diseases, and occurs after day 100. With the introduction of nonmyeloablative HSCT, the time course of GVHD has shifted and a late-onset aGVHD occurring after day 100 is possible; however, in these individuals, both aGVHD and cGVHD symptoms may be present. As such, consensus criteria developed by the National Institutes of Health have classified GVHD based on clinical manifestations and not time after HSCT.[128]

The majority of the data regarding the prevention and treatment of GVHD have been obtained after myeloablative preparative regimens. Therefore, the subsequent section refers only to trials conducted in recipients of a myeloablative allogeneic HSCT.

Acute Graft-Versus-Host Disease

RISK FACTORS

CASE 101-5

Question 1: M.P., a 22-year-old, 154.32 pounds (70 kg) male, undergoes a one-antigen mismatched allogeneic HSCT from his sister for the diagnosis of Philadelphia chromosome-positive (Ph^+) AML. After a myeloablative preparative regimen of CY/TBI, the following immunosuppressive regimen is ordered: cyclosporine 2.5 mg/kg every 12 hours from day −3 until tolerating oral medications, then switch to cyclosporine 4 mg/kg PO every 12 hours until day +50. Methotrexate 15 mg/m^2 IV on day +1, then 10 mg/m^2 on days +3, +6, and +11.

What factors are associated with an increased risk of aGVHD?

The single most important factor associated with the development of GVHD is the degree of histocompatibility between donor and recipient.[2] Clinically relevant grade II–IV aGVHD occurs in 20% to 50% of HLA-matched sibling grafts and 50% to 80% of HLA-mismatched sibling or HLA-identical unrelated donors.[129] The onset of aGVHD is earlier and severity is increased in mismatched grafts relative to matched grafts, and also in MUDs relative to matched sibling donors.[41,130] Other factors that increase the risk of experiencing aGVHD include increasing recipient (and possibly donor) age, greater intensity of the preparative regimen, use of PBPC rather than BM, and donor/recipient sex mismatch.[127] Umbilical cord transplants have a lower risk of aGVHD.[131–133]

M.P. is receiving allogeneic BM from a female sibling donor that is mismatched at one HLA antigen. These two factors increase his risk of exhibiting aGVHD. Therefore, good immunosuppressive therapy is critical in preventing its development.

CLINICAL PRESENTATION

Case 101-5, Question 2: On day +14, the time at which engraftment has occurred, M.P. is noted to have a diffuse maculopapular rash on his arms, hands, and front trunk. He does not have diarrhea, and his liver function tests are within normal limits. At the onset of his rash, M.P.'s empiric antibiotics are changed from cefepime to meropenem. Despite the change in antibiotics, M.P.'s rash persists. How is M.P.'s presentation consistent with aGVHD?

aGVHD is usually not evident until the time of engraftment, when donor lymphoid elements begin to proliferate. The primary targets of immune-mediated destruction of host tissue by donor lymphocytes in aGVHD are the skin followed by the GI tract (diarrhea) and the liver.[129,134] aGVHD of the skin, the most common site of aGVHD, usually manifests as a diffuse maculopapular, pruritic rash that starts on the palms of the hands, soles of the feet, or the face. In more

severe cases, skin aGVHD can progress to a generalized total body erythroderma, bullous formation, and skin desquamation.

The earliest symptoms of aGVHD of the GI tract are usually loss of appetite followed by nausea and vomiting.[107] Abdominal pain and watery or bloody diarrhea also occur, which can result in electrolyte abnormalities, dehydration, or ileus in severe cases. Liver GVHD usually follows skin and/or GI GVHD. Clinical symptoms of liver GVHD include a gradual rise in total bilirubin, alkaline phosphatase, and hepatic transaminases.[107]

aGVHD must be distinguished accurately from other causes of skin, liver, or GI toxicity in the HSCT patient. For example, a maculopapular rash, which may occur as a manifestation of an allergic reaction to antibiotics, usually begins on the trunk or upper extremities and is rarely present on the palms of the hands or soles of the feet. Diarrhea can be caused by chemotherapy, radiation, infection, or antibiotic therapy.[107] However, diarrhea caused by the preparative regimen is rarely bloody and usually resolves within 3 to 7 days after discontinuation of drugs and radiation. Diarrhea caused by infectious agents such as *Clostridioides difficile* or cytomegalovirus (CMV) should be distinguished from GVHD. Liver GVHD must be distinguished primarily from SOS/VOD and, to a lesser extent, hepatitis induced by drugs, blood products, or parenteral nutrition. Although liver function test abnormalities between these syndromes are similar, liver GVHD is rarely associated with insidious weight gain or right upper quadrant pain.[107] A tissue biopsy of the affected organ in conjunction with clinical evidence is the only way to definitively diagnose aGVHD, although biopsy of the gut or liver is rarely done because of the increased risks associated with thrombocytopenia early in the posttransplant phase. aGVHD is associated with characteristic histologic changes to affected organs. A staging system based on clinical criteria is used to grade aGVHD. The severity of organ involvement is determined first (**Table 101-6**), and then an overall grade is established based on number and extent of involved organs (**Table 101-7**).

Table 101-6
Modified Glucksberg Grading of Acute Graft-Versus-Host Disease

Organ Stage	Skin	Liver	Gut
Glucksberg Grading			
I—Mild	Stages 1–2	None	None
II—Moderate	Stage 3 or	Stage 1 or	Stage 1
III—Severe		Stages 2–3 or	Stages 2–4
IV—Life-threatening	Stage 4 or	Stage 4	—
IBMTR Grading			
A—Mild	Stage 1	None	None
B—Moderate	Stage 2	Stage 1 or 2	Stage 1 or 2
C—Severe	Stage 3	Stage 3	Stage 3
D—Life-threatening	Stage 4	Stage 4	Stage 4

[a]Extent of rash determined by "rule of nines."

[b]Diarrhea volume applies to adults.

Source: Used with permission of John Wiley & Sons from Cutler C, Antin JH. Manifestations and treatment of acute graft-versus-host disease. In: Appelbaum FR, Forman SJ, Blume KG, Negrin, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:1291; permission conveyed through Copyright Clearance Center, Inc.

Table 101-7
Modified Glucksberg Versus International Bone Marrow Transplant Registry Overall Grading of Acute Graft-Versus-Host Disease Severity

Organ Stage	Skin[a]	Liver	Intestinal Tract[b]
1	Maculopapular rash >25% of body surface	Bilirubin 2–2.9 mg/dL	500–1000 mL/day diarrhea or biopsy-proven upper GI involvement
2	Maculopapular rash 25%–50% body surface	Bilirubin 3–6 mg/dL	1000–1500 mL/day diarrhea
3	Maculopapular rash >50% body surface	Bilirubin 6.1–15 mg/dL	1500–2000 mL/day diarrhea
4	Generalized erythroderma with bullae	Bilirubin >15 mg/dL	>2000 mL/day diarrhea or severe abdominal pain with or without ileus

IBMTR, International Blood and Marrow Transplant Registry.

Source: Used with permission of John Wiley & Sons from Cutler C, Antin JH. Manifestations and treatment of acute graft-versus-host disease. In: Appelbaum FR, Forman SJ, Blume KG, Negrin, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:1291; permission conveyed through Copyright Clearance Center, Inc.

M.P. developed a rash at the time of engraftment that could have been consistent with either an antibiotic-induced rash or aGVHD. Although it was appropriate to change antibiotics, the fact that M.P.'s rash did not improve is suggestive of aGVHD. M.P.'s rash is present on 36% of his body, but because there are no signs of GI or liver involvement at this time, M.P. is likely to have grade I aGVHD (Tables 101-6 and 101-7).

IMMUNOSUPPRESSIVE PROPHYLAXIS

Case 101-5, Question 3: Why did M.P. receive prophylactic immunosuppressive therapy with cyclosporine and methotrexate?

GVHD is a leading cause of morbidity and mortality after allogeneic HSCT. Without immunosuppression, serious aGVHD would occur in almost every allogeneic HSCT recipient.[2] The most common method used to minimize GVHD risk is to administer prophylactic immunosuppressive therapies, and most patients receive multidrug GVHD prophylaxis.

Historically, aGVHD was prevented with single-drug therapy using ATG, cyclophosphamide, methotrexate, or cyclosporine.[135–137] ATG binds nonspecifically to mononuclear cells and depletes hematopoietic progenitor cells in addition to lymphocytes. Consequently, ATG is generally avoided as a prophylactic agent because of the risk of graft failure.[135] The risk of GVHD is greatly reduced by two-drug combination immunosuppression (**Table 101-8**). Although the most widely published regimen is short-course methotrexate plus cyclosporine,[137] there is no consensus with regard to the most effective regimen. Several randomized clinical trials have

compared tacrolimus and short-course methotrexate with cyclosporine plus short-course methotrexate in patients undergoing allogeneic HSCT using HLA-matched siblings[138,139] and unrelated donors.[88] Recipients of matched sibling grafts treated with tacrolimus had a lower incidence of grade II to IV aGVHD but a similar incidence of cGVHD.[138] Overall survival was lower in the tacrolimus group as a result of more toxic deaths in patients with advanced-stage disease; however, a higher number of patients with advanced-stage disease in the tacrolimus/methotrexate group make the results of this trial somewhat difficult to interpret.[138]

Table 101-8

Combination Immunosuppression Regimens for Prophylaxis of Acute Graft-Versus-Host Disease in Myeloablative Transplant

Drug	Dosing Examples
Cyclosporine/short-term methotrexate	1.5 mg/kg IV or 4 mg/kg (Neoral) PO every 12 hours, days −1 to +50, then taper 5% per week and discontinue by day +180
	Methotrexate 10 mg/m^2 IV, days +3, +6, +11
Tacrolimus/short term	Tacrolimus 0.03 mg/kg/day continuous IV infusion or 0.12 mg/kg/day PO bid
Methotrexate[136]	Methotrexate 15 mg/m^2 IV day +1; 10 mg/m^2 IV, days +3, +6, +11
Cyclosporine/methotrexate/prednisone	Cyclosporine 5 mg/kg/day IV continuous infusion, days –2 to +3, then 3–3.75 mg/kg IV until day +35; then 7 mg/kg/day (Neoral) PO, dose adjusted to cyclosporine concentrations (via radioimmunoassay) of 200–400 ng/mL. Taper by 20% every 2 weeks; then discontinue by day +180
	Methotrexate 15 mg/m^2 IV day +1; 10 mg/m^2 IV days +3, +6

Drug	Dosing Examples
	Methylprednisolone 0.5 mg/kg/day IV day +7 until day +14; then 1 mg/kg/day IV until day +28; then prednisone 0.8 mg/kg/day PO until day +42; then taper slowly and discontinue by day +180

bid, twice a day; IV, intravenous; PO, orally.

Source: Deeg HJ, Storb R, Thomas ED, et al. Cyclosporine as prophylaxis for graft-versus-host disease: a randomized study in patients undergoing marrow transplantation for acute nonlymphoblastic leukemia. *Blood*. 1985;65:1325–1334.

Subsequently, the International Blood and Marrow Transplant Registry conducted a matched control study, which suggested that the survival difference between the two arms of tacrolimus plus short-course methotrexate and cyclosporine plus short-course methotrexate was in fact because of the imbalance in the underlying risk factors.[139] In patients receiving HLA-matched or slightly mismatched-unrelated grafts, those given tacrolimus had a lower incidence of grade II to IV aGVHD, a similar incidence of cGVHD, and similar disease-free and overall survival rates.[88] Both regimens are currently used in allogeneic HSCT after myeloablative preparative regimens.

More recently, the use of mycophenolate mofetil has been studied in allogeneic transplants with myeloablative conditioning used in combination with cyclosporine. It appears to have a similar incidence of aGVHD and 100-day survival as methotrexate/cyclosporine, yet significantly less severe mucositis and more rapid neutrophil engraftment than the methotrexate/cyclosporine arm.[140,141] Mycophenolate mofetil is now commonly used in clinical practice in combination with cyclosporine or tacrolimus.

M.P. received aGVHD prophylaxis with a two-drug regimen of short-course methotrexate and cyclosporine, the most common regimen for myeloablative allogeneic conditioning regimens. Using two drugs with different mechanisms of immunosuppression, one blocking the activation of T cells (cyclosporine) and the other (methotrexate) blocking the division and clonal expansion of

activated T cells, is more effective in decreasing the likelihood of GVHD than one of these agents alone.

Case 101-5, Question 4: What principles are used in dosing medications used for aGVHD prophylaxis?

Although the various combination immunosuppressive regimens vary slightly by drug, dose, and combination, several guidelines are consistent throughout all regimens. First, methotrexate used for prophylaxis of aGVHD is withheld or given in reduced doses if mucositis is severe or the patient experiences excessive fluid retention.[137,142] Fluid retention sites act as a depot for methotrexate accumulation, increasing duration of exposure. Methotrexate for GVHD prophylaxis can delay engraftment, increase the incidence and severity of mucositis, and cause liver function test elevations. The methotrexate dose is reduced in the setting of renal or liver impairment.[137,143]

The calcineurin inhibitors (ie, cyclosporine, tacrolimus) should be initiated before or immediately after donor cell infusion (day −3 to 0) when used for GVHD prophylaxis. This schedule is recommended because of the known mechanism of action of these agents, which entails blocking the proliferation of cytotoxic T cells by inhibiting the production of helper T-cell–derived interleukin-2 (IL-2). Administering calcineurin inhibitor before the donor cell infusion allows inhibition of IL-2 secretion to occur before a rejection response has been initiated.

Empiric dose adjustments may be required when patients are receiving concomitant medications (eg, voriconazole) that affect cytochrome CYP3A4 or P-glycoprotein, which are involved in the metabolism and transport of the calcineurin inhibitors. Thus, careful monitoring for drug interactions with the calcineurin inhibitors is warranted.[144] Although the calcineurin inhibitors do not contribute to myelosuppression, common adverse effects to these agents include electrolyte abnormalities, neurotoxicity, hypertension, and/or nephrotoxicity.[91]

Tapering schedules for GVHD prophylaxis vary widely among institutions. The general goal is to keep calcineurin inhibitor doses stable until day +50 and then slowly taper with the intent of discontinuing all immunosuppressive agents by 6 months after HSCT. By this time, immunologic tolerance has developed, and patients no longer require immunosuppressive therapy. This can only be accomplished if the patient is not experiencing GVHD.

ADAPTIVE DOSING OF CALCINEURIN INHIBITORS

CASE 101-5, QUESTION 5: On day +18, a cyclosporine concentration is measured right before the morning dose (trough) and is reported as 392 ng/mL. Why are cyclosporine concentrations being obtained for M.P.?

The role of pharmacokinetic monitoring of the calcineurin inhibitors in patients undergoing HSCT is not well defined but is commonly performed because of the established pharmacodynamic associations within solid-organ transplant recipients. It is standard practice for HSCT centers to adjust cyclosporine or tacrolimus doses based on trough blood concentrations.[145] An association between cyclosporine concentrations and aGVHD was not found in early studies; however, other studies have suggested that cyclosporine trough concentrations for 12-hour dosing of 200 to 400 ng/mL in adult patients minimize the risk of aGVHD and the risk of cyclosporine-induced nephrotoxicity.[146–148] For continuously infused cyclosporine, higher target blood concentrations of 300 to 500 ng/mL have been required to prevent GVHD in order to provide an equivalent AUC of exposure to intermittent dosing.[149,150] It is important to note that cyclosporine-induced nephrotoxicity may occur despite low or normal concentrations of cyclosporine and may be a consequence of other drug- or disease-related factors known to influence the development of nephrotoxicity. Additionally, recent studies suggest that trough concentrations do not correlate well with exposure to cyclosporine and that a peak level is better correlated to the $AUC_{(0–12).}$ A peak concentration of >800 ng/mL may be required

to prevent GVHD. Despite this, the data are limited and the routine use of peaks for therapeutic drug monitoring is not recommended.[151] Desired tacrolimus trough concentrations are 5 to 15 ng/mL. Tacrolimus concentrations >20 ng/mL have been associated with increased risk of toxicity, primarily nephrotoxicity.[145,152] Adjustments in tacrolimus dosing for increased SCr should be made in a manner similar to that described for cyclosporine.

It is reasonable to adjust M.P.'s doses to maintain cyclosporine trough concentrations between 200 and 400 ng/mL, as in all patients undergoing allogeneic HSCT with a myeloablative preparative regimen. Recommendations for dose adjustments should be based on cyclosporine concentrations and SCr level. No standard dosage adjustment schedule exists, but most centers adopt their own standardized approach. M.P. has a normal SCr, and his cyclosporine trough is 392 ng/mL. Therefore, his cyclosporine dose should be maintained, and the trough repeated in a few days. It may be repeated sooner if an interacting drug is added or discontinued, or if there are toxicity concerns.

TREATMENT OF ESTABLISHED ACUTE GRAFT-VERSUS-HOST DISEASE

Case 101-5, Question 6: In the third week posttransplant, M.P. experiences a pruritic rash on his shoulders and neck that spreads to the palms of his hands and looks like a sunburn. On day +19, the suspicion of acute skin GVHD is confirmed by biopsy. On the same day, M.P. develops diarrhea (1000 mL over 24 hours) and is noted to have bilirubin of 2.8 mg/dL. He is started on methylprednisolone 1 mg/kg IV every 12 hours. What is the rationale for methylprednisolone therapy in M.P.?

Preventing the development of aGVHD is the most effective way to treat this HSCT complication. In patients who develop aGVHD, first-line treatment is a corticosteroid added to their current immune suppression regimen.[127] For this reason, aGVHD and its treatment cause profound immunodeficiency.[2,153] The combination of aGVHD

and infectious complications is the leading cause of mortality for patients undergoing allogeneic HSCT.

The route of corticosteroid administration is determined by the severity of the aGVHD. Those patients with only skin involvement of <50% of their body surface area may be treated with topical steroid creams, whereas involvement of other organs, or stage 3 or 4 skin disease, requires systemic corticosteroids. A complete response occurs in up to 25% to 40% of patients, with a lower likelihood of response in more severe cases of aGVHD.[127,153] Patients with mild-to-moderate (grades I–III) aGVHD who respond to initial therapy have a significantly better survival advantage than patients with severe aGVHD who do not respond to initial therapy. Patients who do not respond to corticosteroid therapy or have ongoing severe GVHD usually die from a combination of GVHD and infectious complications.[154]

Corticosteroids used in the treatment of aGVHD are generally tapered based on response. There is no consensus on the optimal method for tapering the corticosteroids,[153] and the tapering rate depends on the patient. Patients who experience aGVHD or who experience flares of existing GVHD during a tapering trial will have their dosages increased or tapered more slowly as tolerated.

Because M.P. had objective evidence of established aGVHD, he was given systemic IV corticosteroids. This was appropriate because single-agent corticosteroids are considered the therapy of choice for established aGVHD.[155] Corticosteroids indirectly halt the progression of immune-mediated destruction of host tissues by blocking macrophage-derived IL-1 secretion. IL-1 is a primary stimulus for helper T-cell–induced secretion of IL-2, which in turn is responsible for stimulating proliferation of cytotoxic T lymphocytes. The recommended dosage of methylprednisolone for the treatment of established aGVHD is 1 to 2 mg/kg/day, given intravenously or orally in divided doses, followed by a tapering schedule that is determined by response.[154,155] Trials that compared higher doses of corticosteroids (ie, 10 mg/kg/day) to 2 mg/kg/day as initial treatment of aGVHD showed no advantage.[156] Monitoring for rash, diarrhea, and bilirubin levels to assess aGVHD response should occur daily.[127]

M.P. was receiving cyclosporine for GVHD prophylaxis at the time the aGVHD developed. Although the cyclosporine was not effective in preventing the aGVHD, it is typical for patients to remain on their prophylactic immune suppressants.

A significant portion of patients do not respond to corticosteroids, and they are said to have steroid-refractory GVHD.[127] If aGVHD symptoms worsen during 3 days of treatment and if the skin does not improve by 5 days, it is unlikely that a response will be achieved in a timely manner, and secondary therapy should be considered.[127] Patients with steroid-refractory aGVHD have a poorer prognosis. A variety of medications are being studied for "salvage" or secondary therapy. The salvage therapy depends on the organs affected. For example, phototherapy is used as salvage therapy for skin GVHD, and nonabsorbable corticosteroids are used for GI GVHD. Other options for salvage therapy include ATG, denileukin diftitox, and TNF-α blockers (eg, infliximab, etanercept).[127,157] The most effective dose, timing, or combination of these salvage therapies is still unknown.

M.P. should be evaluated for response to methylprednisolone after 4 to 7 days. If his aGVHD has improved or stabilized, he should be continued on therapy at this dose for a total of 14 days. If M.P. responds to therapy, his methylprednisolone dose should be tapered slowly over a minimum of 1 month, and he should be monitored for any evidence of recurrent GVHD. If the GVHD flares during his steroid taper as evidenced by worsening skin reactions, increased bilirubin, or increased diarrhea volume, the dose should be increased again until his disease is stable; the subsequent taper should be initiated at a slower rate. If M.P. fails to respond to first-line therapy with methylprednisolone, he should receive salvage therapy.

Chronic Graft-Versus-Host Disease

CLINICAL PRESENTATION

Case 101-5, Question 7: M.P. was successfully treated for his aGVHD, is no longer taking corticosteroids, and is currently tapering off his cyclosporine. On day +200, M.P. comes to clinic for follow-up after a 2-week vacation in Florida. On examination, M.P. is found to have a mild skin rash on his arms and legs, hyperpigmentation of the tissue surrounding the eyes, and white plaque-like lesions in his mouth. He also endorses dry eyes. Laboratory tests reveal an increased alkaline phosphatase and total bilirubin concentration. What is the most likely cause of M.P.'s findings?

cGVHD, the most common late complication of allogeneic HSCT, occurs in 20% to 70% of patients surviving >100 days.[158] cGVHD is a major cause of nonrelapse morbidity and mortality.[2] Risk factors for cGVHD include recipient, donor, and transplant factors. Nonmodifiable recipient risk factors include older age, certain diagnoses (eg, CML), and lack of an HLA-matched donor. Modifiable factors that may lower the risk of cGVHD include selecting a younger donor, avoiding a multiparous female donor, using umbilical cord blood or a BM graft rather than PBPC, and limiting the CD34+ and T-cell dose infused.[156] Development of aGVHD is a major predictor of cGVHD; 70% to 80% of those with grade II to IV aGVHD go on to develop cGVHD.[156]

cGVHD is not a continuation of aGVHD. Traditionally, the boundary between the two was based on time, but now they are classified based on different clinical symptoms.[158] Signs and symptoms of cGVHD in various organ systems are listed in **Table 101-9**.

Table 101-9
Selected Signs and Symptoms of Chronic Graft-Versus-Host Disease

Affected Organ	Diagnostic	Distinctive	Other Features[a]	Seen With Both Acute and Chronic GVHD
Eyes		New-onset dry, gritty, or painful eyes[b]	Photophobia	
		Cicatricial conjunctivitis Keratoconjunctivitis sicca[b]	Periorbital hyperpigmentation	
		Confluent areas of punctuate keratopathy, tear formation, dry eyes, burning, photophobia	Erythema of the eyelids with edema	
Gastrointestinal tract	Esophageal web		Pancreatic insufficiency	Anorexia
	Stricture or stenosis in the upper- to mid-third of the esophagus[c]			Nausea Vomiting Diarrhea Weight loss
Failure to thrive (infants and children)				
Liver				Total bilirubin, alkaline phosphatase >2 × upper limit of normal[c]
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with pulmonary function tests and radiology[b]		Bronchiolitis obliterans organizing pneumonia
Skin	Poikiloderma	Depigmentation	Seat impairment ichthyosis	Erythema
	Lichen planus-like features		Keratosis pilaris	Maculopapular rash Pruritus
	Sclerotic features		Hypopigmentation	
	Morphea-like features		Hyperpigmentation	
		Lichen sclerosus–like features		

Signs and symptoms for hematopoietic and immune differences, as well as for nails; scalp and body hair; mouth; genitalia; muscles, fascia, and joints; and other organs, are also described by Filipovich et al.[128]

GVHD, graft-versus-host disease.

[a]Part of chronic GVHD symptomatology if the diagnosis is confirmed.

[b]Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

[c]Infection, drug effects, malignancy, or other causes must be excluded.

A consensus guideline for the diagnosis and scoring of cGVHD has been published.[128] The diagnosis of cGVHD requires (a) being distinct from aGVHD, (b) having at least one diagnostic clinical sign of cGVHD or at least one distinctive manifestation confirmed by pertinent biopsy or other relevant tests, and (c) exclusion of other possible diagnoses. The clinical scoring system uses a numerical value of 0 to 3, with more severe symptoms having a higher number. A global score is calculated by including the number of organs involved and the severity within each affected organ. The global score reflects the expected effect of cGVHD on the patient's

performance status and can be used to evaluate whether treatment with systemic immunosuppression is required. The grading and prognosis of cGVHD can define and predict high-risk patient groups.[159]

The signs and symptoms of cGVHD in M.P. include a rash in sun-exposed areas of the skin, hyperpigmentation of tissues surrounding his eyes, white plaque-like lesions in the mouth, dry mucous membranes, and increased alkaline phosphatase and total bilirubin levels. These symptoms appeared after a period of complete resolution of aGVHD and during a taper of the cyclosporine. Thus, M.P. has moderate-involvement, quiescent cGVHD.[128]

PHARMACOLOGIC MANAGEMENT

Case 101-5, Question 8: M.P. is started on prednisone 1 mg/kg PO daily for the treatment of his cGVHD. His cyclosporine taper is stopped, and the dosage is raised to therapeutic concentrations. Is this therapy rational? What other agents are available to treat cGVHD?

There is no specific prophylactic therapy for cGVHD, and the optimal treatment remains controversial. The mainstay of therapy for cGVHD is long-term immunosuppressive therapy. Survival for patients with cGVHD is improved by extended corticosteroid therapy, although there are multiple long-term adverse effects associated with the corticosteroids.[158,160] A typical regimen is prednisone 1 mg/kg/day, administered orally in divided doses for 14 days and then converted slowly to alternate-day therapy by increasing the “on-day” and decreasing the “off-day” dose until a total of 1 mg/kg/day on alternate days is administered.[160] Alternate-day therapy is preferred to minimize adrenocortical suppression. Once therapy is initiated, 1 to 2 months may pass before an improvement in clinical symptoms is noted. Therapy is usually continued for 9 to 12 months and then slowly tapered after signs and symptoms of cGVHD have resolved. The median duration of treatment has been reported to be 23 months.[161] If cGVHD worsens during the tapering or after discontinuation of prednisone, immunosuppressive therapy is

restarted. Other potential approaches for patients with refractory cGVHD include mycophenolate mofetil, daclizumab, sirolimus, pentostatin, and extracorporeal photophoresis.[160]

When immunosuppressive therapy is administered for long periods, the patient must be monitored closely for chronic toxicity. Cushingoid effects, aseptic necrosis of the joints, and diabetes can develop with long-term corticosteroid use. Other severe complications include a high incidence of infection with encapsulated organisms and atypical pathogens such as *Pneumocystis jirovecii* pneumonia, CMV, and herpes zoster.

It is reasonable to start M.P. on single-agent prednisone for cGVHD treatment at 1 mg/kg daily for 2 weeks and then convert to every other day as described.

ADJUVANT THERAPIES

Case 101-5, Question 9: While on prednisone for his cGVHD, what supportive therapies should also be instituted in M.P.?

Patients who are being treated for cGVHD should receive trimethoprim–sulfamethoxazole for prophylaxis of *P. jirovecii* and encapsulated organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Ensuring optimal prophylactic antibiotics in patients with cGVHD is critical because infection is the primary cause of death during treatment.[161] Artificial tears and saliva may improve lubrication and decrease the occurrence of cracking and fissures in mucous membranes. Newer therapies such as cyclosporine ophthalmic emulsion and autologous serum tears have provided relief for chronic ocular GVHD.[162] If nutritional intake is poor, consultation with a clinical nutritionist and use of oral nutritional supplementation may be advisable. Patients should be instructed to apply sunscreens to exposed areas whenever prolonged sun exposure is anticipated. Liver function abnormalities have been improved by up to 30% with the use of ursodiol as bile acid displacement therapy.[118,163,164] Calcium supplements, estrogen

replacement, or other anti-osteoporosis agents should be considered in females or other patients at risk for fracture or bone loss while receiving prolonged regimens with immunosuppressant therapy.[165] Patient education regarding the gradual resolution of symptoms such as skin sclerosis, fatigue and muscle weakness, anticipated duration of therapy, and importance of compliance with oral immunosuppressive therapy is essential.

INFECTIOUS COMPLICATIONS

Opportunistic infections are a major cause of morbidity and mortality after myeloablative and nonmyeloablative HSCT. There are three general periods of infectious risk (Fig. 101-2). During the early period pre-engraftment, particularly for patients undergoing myeloablative HSCT, the primary pathogens are aerobic bacteria, *Candida* spp., and herpes simplex virus (HSV). Chemotherapy-induced mucosal damage creates a portal of entry into the bloodstream for many organisms, such as viridans group *Streptococcus*, *Candida*, and aerobic gram-negative bacteria. Catheter-associated infections have become the leading cause of bacteremia, most notably in the early posttransplant period.[159,161] The routine use of antiviral prophylaxis has decreased the incidence of HSV. Respiratory viruses such as respiratory syncytial virus (RSV), influenza, ad enovirus, and parainfluenza are increasingly recognized as pathogens causing pneumonia, particularly during community outbreaks of infection.[166] To reduce potential exposure of HSCT recipients to these pathogens, visitors and staff members with signs and symptoms of a viral respiratory illness may not be allowed direct contact with patients.

A potential advantage of reduced-intensity or nonmyeloablative preparative regimens is reduced toxicity of the preparative regimen compared to myeloablative HSCT. Reduced-intensity or nonmyeloablative preparative regimens frequently do not result in true neutropenia,[5] and the incidence of mucositis during the early

period is reduced.[167] In a matched controlled study, the incidence of bacteremia during the first 30 days post-HSCT in the nonmyeloablative recipients was significantly reduced compared to myeloablative recipients.[167] Moreover, nonmyeloablative HSCT recipients experienced significantly fewer infections attributable to mucositis during the early period.

The second or middle (see Fig. 101-2) period of infectious risk includes the time from engraftment to posttransplant day +100. Pathogens such as CMV, adenovirus, and *Aspergillus* are common. Adenovirus, CMV, *Aspergillus*, and *P. jirovecii* frequently cause interstitial pneumonitis. Patients undergoing reduced-intensity or nonmyeloablative preparative regimens that experience aGVHD and are treated with corticosteroids have a similar risk of infection during this time period as those undergoing myeloablative HSCT.[169]

During the late period (after day +100), the predominant pathogens are the encapsulated bacteria (eg, *S. pneumoniae*, *H. influenzae*, *Neisseria meningitidis*), fungi/mold, and varicella-zoster virus (VZV). The encapsulated bacteria commonly cause sinopulmonary infections. The risk of infection during this late period is increased in patients with cGVHD as a result of prolonged immunosuppression.

Because of the morbidity associated with opportunistic infection in HSCT recipients, optimal pharmacotherapy for prevention and treatment is critical. In 2009, the U.S. Centers for Disease Control and Prevention (CDC) published guidelines for prevention of opportunistic infection in HSCT recipients.[4,168] These guidelines were constructed from available data by an expert panel from the CDC, the Infectious Disease Society of America, and the American Society for Blood and Marrow Transplantation. The following discussion incorporates recommendations from the CDC guidelines and also provides information on the pharmacotherapy of opportunistic infections in all types of HSCT.

Prevention and Treatment of Bacterial and Fungal Infections

CASE 101-6

QUESTION 1: S.D. is a 26-year-old female with Ph+ acute lymphocytic leukemia in first complete remission who is admitted for allogeneic myeloablative HSCT. The following orders are written: Admit to a room with a positive-pressure high-efficiency particulate absorbing (HEPA) filter. Flush double-lumen Hickman catheter per protocol. Immunosuppressed patient diet as tolerated. Begin fluconazole 400 mg PO every 24 hours and levofloxacin 500 mg PO every 24 hours on admission. Begin ceftazidime 2 g IV every 8 hours with first fever when ANC is <500 cells/μL. Transfuse 2 units of packed RBCs for hematocrit <25% and 1 unit of single-donor platelets for platelet count <20,000/μL.

What is the rationale for these supportive measures?

As a result of disease-related immunosuppression, intensive preparative regimens, and posttransplant immunosuppressive therapy, patients undergoing allogeneic HSCT require careful monitoring for regimen-related toxicities and intensive supportive care directed at maintaining adequate blood counts, preventing or treating infection, and providing optimum nutrition.

Placement of a double-lumen or triple-lumen central venous catheter is mandatory in all patients. The need for administration of chemotherapy, blood products, antibiotics, parenteral nutrition, and adjunctive medications over a prolonged period of time precludes the use of peripheral access sites. The use of a central venous catheter allows delivery of maximum concentrations of all medications into a high-flow blood vessel. Administration time is reduced, and daily fluid infusion is minimized.

After administration of the preparative regimen and before successful engraftment, allogeneic myeloablative HSCT patients undergo a period of pancytopenia lasting from 2 to 6 weeks. During this time, patients may require multiple RBC and platelet transfusions. Packed RBCs and platelets are usually given for a hematocrit <25% and a platelet count <10,000/μL or 20,000/μL. Transfusions with multiple blood products put patients at risk for blood product–derived infection (eg, CMV, hepatitis). In addition, sensitization to foreign leukocyte HLA antigens (alloimmunization) may cause immune-mediated thrombocytopenia. Thus, blood product support in the myeloablative allogeneic HSCT patient must

incorporate strategies that reduce the risk of viral infection and alloimmunization. Effective methods include minimizing the number of pretransplant infusions, using single-donor rather than pooled-donor blood products, irradiating blood products, and filtering blood products with leukocyte reduction filters.

Patients receiving reduced-intensity or nonmyeloablative preparative regimens may or may not experience neutropenia and generally have reduced requirements for blood products. In fact, many centers perform reduced-intensity or nonmyeloablative HSCT in the outpatient setting and admit patients to the hospital only for complications requiring more aggressive management.

Aggressive use of antibacterial, antifungal, and antiviral therapy, both prophylactically and for documented infection, is an important aspect of patient management. Antibiotics with a broad gram-negative spectrum may be instituted prophylactically once the patient becomes neutropenic (ANC >1000 cells/μL), or empirically after the patient is neutropenic and experiences fever (oral temperature >100.40 °F [>38 °C]). Some transplant centers administer a prophylactic fluoroquinolone such as levofloxacin on admission especially if the neutropenic period is expected to extend beyond 7 days.[169-173]

Fluoroquinolone prophylaxis during periods of neutropenia significantly reduces the incidence of gram-negative bacteremia but generally does not affect mortality.[4] Concerns regarding prophylactic fluoroquinolone use include the emergence of resistant organisms and an increased risk of streptococcal infection.[4,174] In fact, the incidence of *Viridians* group of streptococci has been increasing.[4,175] Prophylactic antibiotics (eg, penicillin, vancomycin) are not recommended because of their lack of proven efficacy in preventing streptococcal infections and the concern about antibiotic-resistant bacteria.[4] Regardless of prophylactic strategies, patients who become febrile during neutropenia should immediately receive broad-spectrum IV antibiotic(s) (eg, ceftazidime, cefepime, imipenem, or meropenem) and prophylaxis should be discontinued.[4,176]

Antifungal prophylactic agents are commonly used in HSCT recipients. S.D. is prescribed fluconazole 400 mg/day on admission because prophylactic use until day +75 posttransplant decreases the incidence of systemic fungal infection and fungal death in patients undergoing HSCT.[177,178] The use of prophylactic fluconazole has been linked to reports of breakthrough infections with resistant fungi such as *C. glabrata* and *Aspergillus*.[179,180]

When broader yeast and mold prophylaxis is required, either posaconazole or voriconazole may be used. If S.D. were to require mold prophylaxis, voriconazole 200 mg twice daily would be a reasonable choice. Voriconazole 200 mg twice daily was compared to fluconazole 400 mg once daily in a randomized double-blind trial for the prevention of invasive fungal infections in standard risk HSCT. No significant differences were seen in fungus-free survival, relapse-free status, and overall survival at 6 months. Toxicities were similar, and there was a trend toward reduced *Aspergillus* infections and less empiric antifungal therapy in the voriconazole arm.[181] Posaconazole has also been used for mold prophylaxis in HSCT based on its efficacy as prophylaxis in neutropenic patients.[182] Both azoles affect the CYP3A4 isoenzyme, and their use with calcineurin inhibitors requires judicious monitoring. The use of broader spectrum azoles has also resulted in the development of breakthrough zygomycosis infections, particularly with the use of voriconazole.[183]

The echinocandins have also been used for broader yeast and mold prophylaxis in HSCT. Micafungin (50 mg IV every 24 hours) and fluconazole (400 mg IV every 24 hours) were compared in a randomized, double-blind study of patients undergoing HSCT. Overall success was defined as the absence of suspected, proven, or probable systemic fungal infection through the end of therapy and as the absence of proven or probable systemic fungal infection through the end of the 4-week posttreatment period. The overall efficacy was greater in the patients who received micafungin (80.0% vs 73.5% P = .03). Fewer episodes of aspergillosis occurred in patients treated with micafungin.[184]

Prevention of Herpes Simplex Virus and Varicella-Zoster Virus

Case 101-6, Question 2: On routine screening before transplantation, S.D. is found to be HSV-seropositive (≥1.11 index value) and VZV-seropositive (≥1 index value). How will this affect her management?

Up to 70% of HSV-seropositive patients undergoing myeloablative allogeneic HSCT will experience reactivation of HSV.[185] Prophylactic acyclovir is commonly used in HSV-seropositive patients undergoing allogeneic or autologous HSCT to prevent viral reactivation.[4,186] Dosing regimens for prophylactic acyclovir vary widely; the dose of IV acyclovir is typically 250 mg/m^2 IV every 8 hours, whereas oral doses of acyclovir range from 600 to 1600 mg/day.[4] The recommended duration of acyclovir prophylaxis for HSV varies from day +30 to day +365 posttransplant or longer, depending on the specific type of HSCT and other risk factors. Valacyclovir, a prodrug of acyclovir with improved bioavailability, provides sufficient blood concentrations to prevent HSV in patients with mucositis or GI aGVHD.[187] Prophylactic valacyclovir is commonly used at a dose of 500 mg PO every 12 hours.[188,189]

Patients who are VZV-seropositive are at risk for developing herpes zoster, particularly after day +100 posttransplant.[190] Prophylactic acyclovir reduces the risk of VZV reactivation.[191] As with prophylaxis for HSV reactivation, the optimum duration of VZV prophylaxis is controversial, often extending to day +365 posttransplant or longer.

Patients who are HSV-seronegative or VZV-seronegative rarely exhibit primary HSV or VZV infection and are therefore not administered prophylactic acyclovir. If HSV does occur, lesions usually appear on the oral mucosa, nasolabial mucous membranes, or genital mucocutaneous area and can be managed with acyclovir at standard treatment doses.

Because S.D. is HSV- and VZV-seropositive, she is at risk for viral reactivation and should receive prophylactic acyclovir 400 mg PO

twice daily, beginning 4 days prior to transplant and continuing until her ANC is >2500 cells/μL for at least 2 days.

Prevention of Cytomegalovirus Disease

Case 101-6, Question 3: S.D. is also CMV-seropositive. What is the significance of this finding and what measures can be taken to prevent reactivation of CMV?

Cytomegalovirus has the ability to establish lifelong latent infection after primary exposure. In patients who are immunocompromised, the virus may reactivate, resulting in asymptomatic shedding or the development of CMV disease. The incidence of CMV infection (defined as isolation of the virus or detection of viral proteins or nucleic acid in any body fluid without clinical symptoms) and CMV disease (signs and symptoms consistent with CMV invasion into a tissue) in HSCT recipients is 15% to 60% and 20% to 35%, respectively. The most common manifestations of CMV disease after allogeneic HSCT are pneumonitis, fever, and GI infection.[192]

In the CMV-seronegative HSCT recipient, primary CMV infection or disease can be prevented by selecting a CMV-seronegative donor and using only blood products from CMV-seronegative donors. No anti-CMV prophylaxis is required in these recipients. In patients who are CMV-seropositive or who have received a CMV-seropositive graft, antiviral drugs are essential to minimize morbidity associated with CMV reactivation or secondary infection. Two general strategies are possible. One strategy involves preemptive therapy or risk-adjusted therapy.[187,193,194] Using this strategy, patients begin therapy only if they have early reactivation of CMV detected through the assay of blood for CMV antigens (eg, pp65) or viral nucleic acid using polymerase chain reaction (PCR) testing. Using preemptive therapy selectively administers ganciclovir to only those HSCT patients at greatest risk for development of CMV disease.[195–197] Antigenemia-based preemptive therapy is as effective as universal ganciclovir prophylaxis for the prevention of CMV disease and is

associated with reduced CMV mortality.[198,199–202] The induction dose of ganciclovir is typically 5 mg/kg IV every 12 hours for 7 to 14 days, followed by a maintenance dose of 5 mg/kg IV daily until 2 to 3 weeks after the last occurrence of antigenemia or until day +100 posttransplantation.[4] Preemptive therapy limits patient exposure to the potential toxicity of ganciclovir and thus reduces overall cost.[190] Oral valganciclovir is a safe and effective alternative to IV ganciclovir for preemptive therapy.[203,204] The other strategy that can be employed is the use of the antiviral letermovir. A phase-3, double-blind trial showed that letermovir is effective as prophylaxis in patients who are CMV-seropositive. Its use resulted in a clinically significant decrease in the development of CMV infection in patients undergoing HSCT.[205]

Foscarnet may also be administered, but its use is complicated by nephrotoxicity and electrolyte wasting.[202,206] Monitoring and correction of electrolyte and fluid imbalances are essential when foscarnet is initiated.

Cidofovir is used to treat CMV in patients undergoing HSCT but is reserved for use when other agents have failed.[207] Dose-related renal dysfunction, which can be seen after even one or two doses, limits the number of patients able to receive cidofovir.[207] An advantage of cidofovir is its infrequent dosing, making it conducive to clinic administration. Monitoring renal function, electrolytes, WBC, and intraocular pressure are essential monitoring parameters.

Autologous HSCT recipients who are CMV-seropositive pretransplant should receive antiviral treatment preemptively as described.[4,208] Nonmyeloablative or reduced-intensity HSCT recipients should also receive preemptive antiviral treatment. Because host T cells may persist in the peripheral blood for up to 6 months after reduced-intensity or nonmyeloablative preparative regimens, their presence may provide some protection against early CMV disease. A matched controlled study comparing the incidence and outcome of CMV infection in myeloablative and nonmyeloablative HSCT demonstrated that although the time to onset of CMV antigenemia was similar in the two groups, fewer nonmyeloablative HSCT recipients experienced CMV disease in the

early period.[209] The overall 1-year incidence of CMV disease was also similar, suggesting that nonmyeloablative HSCT recipients are at increased risk for exhibiting late CMV disease (>100 days after transplantation) compared to their myeloablative counterparts.[209] It is therefore recommended that nonmyeloablative HSCT patients receive preemptive antiviral therapy and be monitored for development of CMV antigenemia for 1 year after HSCT.[209,210]

S.D.'s ANC recovers to >1000 cells/μL on day +20, and on day +32, her weekly surveillance blood sample is positive for CMV by PCR. Preemptive ganciclovir induction is initiated at 5 mg/kg IV every 12 hours for 2 weeks followed by maintenance dosing of 5 mg/kg daily. After 3 weeks of therapy, S.D.'s surveillance samples are negative and ganciclovir is discontinued. Weekly surveillance sampling continues until day +100. If surveillance samples again become positive for CMV, ganciclovir therapy should be reinstituted.

Diagnosis and Treatment of Aspergillus Infection

RISK FACTORS

CASE 101-7

Question 1: A.W., a 132.27 pounds (60 kg), 64.96 inches (165 cm), 15-year-old boy, is day +79 after a matched, unrelated, nonmyeloablative PBPC transplant for acute lymphocytic leukemia in third complete remission. He presents to the clinic for evaluation of a temperature of 102.30 °F (39.05 °C) and a 3-day history of nonproductive cough. Significant medical history includes skin and GI GVHD (stable on his current regimen of cyclosporine, mycophenolate mofetil, and prednisone) and congestive heart failure believed to be secondary to anthracycline exposure. A.W. has chronic low-grade nausea and hypomagnesemia necessitating daily IV hydration with magnesium supplementation. Relevant laboratory values are as follows:

Na, 138 mEq/L
K, 4.2 mEq/L
Cl, 100 mEq/L
CO_2, 23 mEq/L
Blood urea nitrogen, 18 mg/dL
SCr, 0.8 mg/dL

Total bilirubin, 0.6 mg/dL
Mg, 1.5 mg/dL
WBC count, 3500 cells/μL
Platelets, 78,000/μL
ANC, 1810 cells/μL
Hemoglobin, 10.8 g/dL

He was CMV-seropositive and HSV-seropositive before HSCT. Oral medications include cyclosporine 275 mg every 12 hours, mycophenolate mofetil 900 mg every 12 hours, prednisone 60 mg every morning and 12.5 mg every evening (tapering), trimethoprim–sulfamethoxazole (TMP/SMX) 160 mg/800 mg twice daily on Monday and Tuesday, posaconazole 300 mg every morning, valacyclovir 500 mg bid, digoxin 0.125 mg every 12 hours, enalapril 10 mg every 12 hours, and a multivitamin every morning.

On physical examination, A.W. is a chronically ill-appearing child with “moon” face, dry skin with thickened areas, a pleural friction rub, and thinning hair. Blood cultures, urinalysis, and chest x-ray are obtained. Chest x-ray reveals several small cavitary lesions worrisome for fungal disease. A.W. is admitted for further workup and management of presumed *Aspergillus* infection.

What risk factors does A.W. have for developing an infection with *Aspergillus?*

Invasive molds (most commonly *Aspergillus* spp., but also *Fusarium* spp., *Scedosporium*, and *Zygomycetes*) are an increasing cause of morbidity and mortality after allogeneic and autologous HSCT. A major factor contributing to this trend includes more effective prevention of bacterial and viral infection that promotes mold overgrowth, as described.[177–179,211,212] *Aspergillus* infection is reported in up to 26% of HSCT recipients, and the mortality rate of invasive aspergillosis (IA) is 74% to 92%.[184]

Several risk factors for the development of invasive fungal infection have been identified.[211,212] Given that neutrophils are critical for host defense, prolonged neutropenia is considered the single most important predictor of infection at any point after HSCT.[180,211] GVHD (acute and chronic) and treatment with corticosteroids are also important risk factors, particularly for aspergillosis, presumably as a result of neutrophil dysfunction.[184,211–213] In addition, the widespread use of fluconazole prophylaxis (400 mg/day) for the prevention of invasive candidiasis in patients undergoing transplant since the early 1990s has led to a substantial increase in the

incidence of IA and also fluconazole-resistant *Candida* species such as *Candida krusei* and *Candida glabrata*.[211,213,214]

A.W. is receiving corticosteroid treatment for GVHD and posaconazole prophylaxis. These therapies increase his risk for exhibiting IA.

TREATMENT

Case 101-7, Question 2: A.W. undergoes bronchoalveolar lavage to identify the organism responsible for his pulmonary infection. Pathologic examination of the fluid obtained reveals septate and branching hyphae, and culture results confirm the diagnosis of *Aspergillus fumigatus* infection. Imaging scans are negative for extrapulmonary involvement. How is aspergillosis usually diagnosed, and what are the acceptable alternatives for treating this infection?

Early diagnosis and treatment of IA, which rely on tissue or fluid obtained from the infected site followed by aggressive antifungal therapy, may improve patient survival.[215] Although the lower respiratory tract is frequently the primary focus of infection, *Aspergillus* may invade blood vessels and spread hematogenously to other organs, including the brain, liver, kidneys, spleen, and skin.[190] Head, chest, abdomen, and pelvic computed tomography scans assist in assessing the extent of disease, treatment options, and overall prognosis. Cultures of respiratory tract secretions lack sensitivity for detecting *Aspergillus*, and the medical condition of the patient may preclude invasive diagnostic procedures altogether. Many clinicians have adopted the European Organization for Research and Treatment of Cancer criteria for diagnosis of proven, probable, and possible IA.[216]

Newer diagnostic tests based on the detection of fungal antigens or metabolites, such as galactomannan, 1,3-β-D-glucan, and fungal DNA detection by PCR, are now being used. Galactomannan is a polysaccharide component of the *Aspergillus* cell wall that is released during fungal cell growth. Galactomannan detection by enzyme-linked immunoassay (GM-EIA) has proved to be a sensitive and specific tool for the early detection of *Aspergillus* infection. The

test is useful not only for serum samples but also for bronchoalveolar lavage and cerebrospinal fluid. Concomitant antifungal therapy may cause false-negative results, whereas antibiotics of fungal origin (eg, piperacillin/tazobactam) have been associated with false positives.[184,217]

ANTIFUNGALS

Outcomes for patients with IA after HSCT are often poor, with ~20% of patients alive after 1 year.[211] Treatment success depends not only on the use of intensive antifungal agents but also on recovery of the host immune system and/or reduction of immunosuppression.[215,218] Conventional amphotericin B had traditionally been the gold standard antifungal therapy for IA with response rates in the range of 28% to 51%, depending on the severity of the underlying immunosuppression; however, 65% of responders eventually died of their infection.[215] Fortunately, broad-spectrum triazoles and echinocandins are available as alternatives. The treatment of IA has moved away from the use of amphotericin to the use of broad-spectrum azoles for its treatment.

Three broad-spectrum triazole agents (voriconazole, posaconazole) are available for patients. Voriconazole is one of the newer broad-spectrum azoles whose advantage is its excellent (96%) oral bioavailability. Voriconazole has been compared to conventional amphotericin B in a randomized, unblinded trial as primary therapy for established IA in an immunocompromised host.[219] The primary objective was to demonstrate the noninferiority of voriconazole compared with conventional amphotericin B after 12 weeks of therapy in patients with definite or probable IA. Patients received voriconazole 6 mg/kg IV every 12 hours for two doses followed by 4 mg/kg IV every 12 hours for at least 7 days, followed by oral voriconazole 200 mg every 12 hours or amphotericin B at a dose of 1 to 1.5 mg/kg/day. Patients refractory to or intolerant of initial therapy could receive other antifungal drugs. Of 144 evaluable patients who received voriconazole, 76 (52.8%) had a partial or complete response compared to 42 of 133 (31.6%) patients treated

with amphotericin B. The median duration of therapy for patients treated with voriconazole was 77 days, and 52 of 144 patients switched to an alternative agent. In contrast, the median duration of therapy for patients receiving amphotericin B was 10 days, and 107 of 133 patients switched to another agent (most commonly, a lipid formulation of amphotericin B). The survival rate at 12 weeks in the voriconazole group was 70.8% compared to 57.9% (P = .02). These results of initial therapy with voriconazole indicate superior response and improved survival in patients who are immunocompromised, such as allogeneic HSCT recipients, with IA. Patients treated with voriconazole also experienced fewer drug-related adverse effects; however, drug interactions because of P450 3A4 inhibition should be closely monitored.

Posaconazole, the newest broad-spectrum triazole, is available as an oral suspension, oral tablets, and an intravenous formulation. The oral suspension has a more variable absorption as compared to the tablet formulation. In general, posaconazole has the lowest minimum inhibitory concentration of any available triazole against *Aspergillus* spp., including *Aspergillus terreus*. It is the only triazole with activity against the *Zygomycetes*. In an open-label externally controlled trial in patients with IA refractory to or intolerant of other therapies, the overall success rate was 42% in patients treated with posaconazole compared to 26% for controls (P = .006).[220]

Echinocandin antifungal agents (caspofungin, micafungin) inhibit the synthesis of β-(1,3)-glucan, an important component of the fungal cell wall. No prospective randomized trials have documented the efficacy of any echinocandin for primary therapy of IA, and only caspofungin is approved for salvage therapy. An open-label, noncomparative trial evaluated the efficacy of caspofungin in 69 patients who had failed or were intolerant of at least 7 days of standard antifungal therapy.[221] Patients received 70 mg IV of caspofungin on day 1 followed by 50 mg IV daily. Of the 63 evaluable patients, 26 (43%) responded favorably to treatment. Twenty-six of 52 patients (50%) who had received at least 7 days of therapy had a favorable response. In another open-label, noncomparative trial, Denning et al evaluated the safety and efficacy

of micafungin (alone or in combination) in patients with proven or probable aspergillosis. Eighty of 225 patients (35.6%) had a favorable response. Most patients received combination therapy; the 34 patients treated with monotherapy had a similar response rate.[222] Amphotericin B is no longer first-line therapy for the treatment of IA. It is typically reserved for patients who develop mold infections, such as cryptococcus, that are resistant to the azoles.

The most common toxicities associated with azole treatment include elevations in hepatic transaminase enzymes and alkaline phosphatase. The azoles are also known inhibitors of the CYP3A4 isoenzyme; therefore, drug interaction monitoring is imperative. The major interaction seen in patients undergoing allogeneic HSCT is an increase in calcineurin inhibitor levels. Careful monitoring is warranted. Voriconazole has been associated with visual disturbances (blurred vision, altered color perception, photophobia, visual hallucinations).[223]

In summary, the number of agents available to manage IA has expanded greatly in the past decade. Therapy should be tailored to the individual patient based on response, tolerability, and cost.

Prevention of *Pneumocystis jirovecii* Pneumonia

Case 101-7, Question 3: A.W. is receiving TMP/SMX, one double-strength tablet PO bid on Monday and Thursday. What is the rationale for its use?

Pneumocystis jirovecii is a common pathogen that causes *Pneumocystis* pneumonia (PCP) in patients who have undergone allogeneic HSCT. PCP is a potentially lethal infection, and prophylaxis is routinely administered. The optimum prophylactic regimen has not been established, but most centers administer TMP/SMX for PCP prophylaxis.[4] Dapsone, atovaquone, and aerosolized pentamidine are alternatives for patients who are allergic to sulfonamides or do not tolerate TMP/SMX for other reasons such as hematologic toxicities. PCP prophylaxis is usually begun after neutrophil recovery because (a) PCP most commonly occurs after

engraftment and (b) TMP/SMX is potentially myelosuppressive. Patients should be closely monitored for unexplained neutropenia or thrombocytopenia.

Issues of Survivorship after Hematopoietic STEM Cell Transplantation

CASE 101-8

QUESTION 1: H.O. is a 32-year-old female who received a BU/CY preparative regimen and an HLA-matched sibling HSCT for the treatment of chronic phase CML at age 21 years. H.O. received her HSCT more than 10 years ago, is disease-free, and has not had cGVHD for 9 years. Her only medication is one multivitamin tablet daily.

What issues of cancer survivorship are of concern to H.O.?

A greater proportion of HSCT recipients are surviving their cancer diagnosis without evidence of their primary malignancy, but they are at risk for long-term physical and emotional sequelae of their cancer treatments.[2] Many long-term HSCT survivors are no longer under the care of an HSCT center, and their health care providers may be unfamiliar with the complications of HSCT. To facilitate the clinical care of long-term HSCT recipients, recommendations for screening and preventive practices have been created for adult and pediatric HSCT survivors.[224,225] These guidelines should facilitate the provision of health care to HSCT recipients. The following paragraphs describe various concerns associated with the morbidity of long-term HSCT survivors.[224–226] Long-term HSCT survivors should be regularly screened for the development of secondary malignancies and complications of GVHD that affect the oral mucosa, liver, respiratory, endocrine, ocular, skeletal, nervous system, kidney, and vascular systems. The psychosocial health of HSCT survivors should also be evaluated.

Immune function can take >2 years to recover, even after discontinuation of immunosuppressants.[227] Treatment of GVHD exacerbates immune system defects, necessitating prophylaxis and vigilant monitoring for infectious complications. Fevers should be rapidly assessed and treated to prevent fatal infections. Recipients of HSCT also lose protective antibodies to vaccine-preventable diseases; therefore, HSCT survivors need to be revaccinated for selected infectious diseases with due consideration for the risk of vaccination.

Hematopoietic cell transplant survivors have a greater risk of secondary malignant neoplasms.[2] An increased incidence of cancer of the skin, oral mucosa, brain, thyroid, and bone is observed after allogeneic HSCT, and an increased incidence of myelodysplasia and acute leukemia can occur after autologous HSCT for NHL.[2] Survivors should avoid carcinogens (eg, tobacco) and be screened for secondary malignant neoplasms indefinitely.[2] Long-term impairment of end-organ function may be because of the preparative regimen, infectious complications (either autologous or allogeneic grafts), and posttransplant immunosuppression (allogeneic grafts only).[224,226] Endocrine dysfunction, specifically of the thyroid, gonads, and growth velocity, is common.[224,225] Adrenal insufficiency can result from long-term corticosteroid therapy used to treat GVHD. Infertility is commonly observed after myeloablative HSCT secondary to the high doses of alkylating agents and radiation administered. Frequently, males become azoospermic, and chemically induced menopause develops in females.[2] However, pregnancies have occurred after HSCT.[2] Up to 60% of HSCT recipients have osteopenia, most likely resulting from gonadal dysfunction and corticosteroid administration; avascular necrosis because of corticosteroids can also occur.[227] A significant portion (15%–40%) of HSCT survivors exhibit pulmonary dysfunction with variable symptoms (eg, restrictive, chronic obstructive lung disease) from multiple causes.[228] Hepatic infections can occur in HSCT recipients through blood transfusions or, more commonly, because recipients or donors have a latent hepatitis viral infection. The prevalence of chronic hepatitis C ranges from 5% to 70% in long-term HSCT

survivors.[229] Because of this, cirrhosis and its complications may become an important late complication of HSCT.[229] Hepatic dysfunction can also result from iron overload, which may occur secondary to multiple RBC transfusions administered during aplasia after myeloablative preparative regimens and before HSCT. Alopecia is a common late effect with BU/CY, as are cataracts with CY/TBI.[77]

H.O. should be routinely monitored for signs of relapse and cGVHD. To lower the risk of infectious complications, she should be counseled to obtain prompt medical care for fevers or signs of an infection, and she should be revaccinated if she has not done so since receiving her myeloablative HSCT. Thorough evaluation of end-organ function, including renal, hepatic, thyroid, and ovarian function, should be assessed at regular intervals. In addition, her bone mineral density should be determined, and H.O. should be counseled on preventive measures for osteopenia (eg, calcium supplementation). In addition to standard cancer screening tests, H.O. should be closely monitored for secondary malignant neoplasms.[2]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Appelbaum FR. Haematopoietic cell transplantation as immunotherapy. *Nature.* 2001;411:385–389. (126)

Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009. (11, 13, 38, 49, 51, 55, 81, 91, 107)

Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med.* 2006;354:1813–1826. (2)

D'Souza A, Fretham C, Lee SJ, et al. Current use and outcome of hematopoietic stem cell transplantation in the United States. *Biol Blood Marrow Transplant*. 2020;26(8):e177–e182. CIBMTR Summary Slides. Center for International Blood and Marrow Transplant Research. Accessed August 8, 2020. http://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx (1)

Key Websites

American Society for Transplantation and Cellular Therapy. http://www.astct.org/

Center for International Blood and Marrow Transplant Research (CIBMTR). https://www.cibmtr.org/

Health Resources and Services Administration (HRSA). http://www.hrsa.gov/

National Marrow Donor Program. https://bethematch.org

COMPLETE REFERENCES CHAPTER 101 HEMATOPOIETIC STEM CELL TRANSPLANTATION

1. D'Souza A, Fretham C, Lee SJ, et al. Current use and outcome of hematopoietic stem cell transplantation in the United States. *Biol Blood Marrow Transplant*. 2020;26(8):e177–e182. CIBMTR Summary Slides. Center for International Blood and Marrow Transplant Research. Accessed August 8, 2020. http://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx
2. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354:1813–1826.
3. Baron F, Storb R. Allogeneic hematopoietic cell transplantation following nonmyeloablative conditioning as treatment for hematologic malignancies and inherited blood disorders. *Mol Ther*. 2006;13:26–41.
4. Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep*. 2000;49:CE1–CE7.
5. Anderlini P, Champlin R. Use of filgrastim for stem cell mobilisation and transplantation in high-dose cancer chemotherapy. *Drugs*. 2002;62(suppl 1):79–88.

6. Vaughan W, Seshadri T, Bridges M, Keating A. The principles and overview of autologous hematopoietic stem cell transplantation. *Cancer Treat Res*. 2009;144:23–45.
7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphoma. Version 2.2021.
8. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333:1540–1545.
9. Le Gouill S, De Guibert S, Planche L, et al. Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. *Haematologica*. 2011;96:1128–1135.
10. Mounier N, Canals C, Gisselbrecht C, et al. High-dose therapy and autologous stem cell transplantation in first relapse for diffuse large B cell lymphoma in the rituximab era: an analysis based on data from the European Blood and Marrow Transplantation Registry. *Biol Blood Marrow Transplant*. 2012;18(5):788–793.
11. Shea TC, DiPersio JF. Mobilization of autologous peripheral blood hematopoietic cells for cellular therapy. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:590.
12. Schmitz N, Barrett J. Optimizing engraftment—source and dose of stem cells. *Semin Hematol*. 2002;39:3–14.
13. Rowley SD. Cryopreservation of hematopoietic cells. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:631.
14. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: evidence-based clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *J Clin Oncol*. 2006;24:3187–3205.
15. Brave M, Farrell A, Ching Lin S, et al. FDA review summary: mozobil in combination with granulocyte colony-stimulating factor to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation. *Oncology*. 2010;78:282–288.
16. Comenzo R, Malachowski ME, Miller KB, et al. Large-volume leukapheresis for collection of mononuclear cells for hematopoietic rescue in Hodgkin's disease. *Transfusion*. 1991;31(4):327–332.
17. Figuerres E, Haut PR, Olzewski M, Kletzel M. Analysis of parameters affecting engraftment in children undergoing autologous peripheral blood stem cell transplants. *Bone Marrow Transplant*. 2000;25:583–588.
18. Eder JP, Elias A, Shea TC, et al. A phase I–II study of cyclophosphamide, thiotepa, and carboplatin with autologous bone marrow transplantation in

solid tumor patients. *J Clin Oncol*. 1990;8:1239–1245.
19. McDonald GB, Slattery JT, Bouvier ME, et al. Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation. *Blood*. 2003;101:2043–2048.
20. Clift RA, Buckner CD, Thomas ED, et al. Marrow transplantation for patients in accelerated phase of chronic myeloid leukemia. *Blood*. 1994;84:4368–4373.
21. IV Busulfex (busulfan) injection. Package insert. Otsuka America Pharmaceutical, Inc.; 2020. Accessed March, 2021. https://www.otsuka-us.com/sites/g/files/qhldwo2976/files/media/static/IVBusulfex-PI.pdf
22. Radich JP, Gooley T, Bensinger W, et al. HLA-matched related hematopoietic cell transplantation for CML chronic phase using a targeted busulfan and cyclophosphamide preparative regimen. *Blood*. 2003;102:31–35
23. Argiris A, Seropian S, Cooper DL. High-dose BEAM chemotherapy with autologous peripheral blood progenitor-cell transplantation for unselected patients with primary refractory or relapsed Hodgkin's disease. *Ann Oncol*. 2000;11:665–672.
24. Meisenberg BR, Miller WE, McMillan R, et al. Outpatient high-dose chemotherapy with autologous stem-cell rescue for hematologic and nonhematologic malignancies. *J Clin Oncol*. 1997;15:11–17.
25. Rizzo JD, Vogelsang GB, Krumm S, Frink B, Mock V, Bass EB. Outpatient-based bone marrow transplantation for hematologic malignancies: cost saving or cost shifting? *J Clin Oncol*. 1999;17:2811–2818.
26. Gilbert C, Meisenberg B, Vredenburgh J, et al. Sequential prophylactic oral and empiric once-daily parenteral antibiotics for neutropenia and fever after high-dose chemotherapy and autologous bone marrow support. *J Clin Oncol*. 1994;12:1005–1011.
27. Gisselbrecht C, Prentice HG, Bacigalupo A, et al. Placebo-controlled phase III trial of lenograstim in bone-marrow transplantation [published correction appears in *Lancet*. 1994;343:804]. *Lancet*. 1994;343:696–700.
28. Greenberg P, Advani R, Keating A, et al. GM-CSF accelerates neutrophil recovery after autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 1996;18:1057–1064.
29. Rabinowe SN, Neuberg D, Bierman PJ, et al. Long-term follow-up of a phase III study of recombinant human granulocyte-macrophage colony stimulating factor after autologous bone marrow transplantation for lymphoid malignancies. *Blood*. 1993;81:1903–1908.
30. Klumpp TR, Mangan KF, Goldberg SL, Pearlman ES, Macdonald JS. Granulocyte colony-stimulating factor accelerates neutrophil engraftment following peripheral blood stem-cell transplantation: a prospective, randomized trial. *J Clin Oncol*. 1995;13:1323–1327.
31. Spitzer G, Adkins DR, Spencer V, et al. Randomized study of growth factors postperipheral-blood stem-cell transplant: neutrophil recovery is improved

with modest clinical benefit. *J Clin Oncol*. 1994;12:661–670.
32. Cortelazzo S, Viero P, Bellavita P, et al. Granulocyte colony-stimulating factor following peripheral-blood progenitor-cell transplant in non-Hodgkin's lymphoma. *J Clin Oncol*. 1995;13:935–941.
33. Legros M, Fleury J, Bay JO, et al. rhGM-CSF vs. placebo following rhGM-CSF-mobilized PBPC transplantation: a phase III double-blind randomized trial. *Bone Marrow Transplant*. 1997;19(23):209–213.
34. Powles R, Smith C, Milan S, et al. Human recombinant GM-CSF in allogeneic bone-marrow transplantation for leukaemia: double-blind, placebo-controlled trial. *Lancet*. 1990;336:1417–1420.
35. Estey EH. Treatment of acute myelogenous leukemia. *Oncology (Williston Park)*. 2002;16:343–366.
36. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: acute myeloid leukemia. Version 3.2021.
37. Erlich HA, Opelz G, Hansen J. HLA DNA typing and transplantation. *Immunity*. 2001;14:347–356.
38. Mickelson E, Petersdorf EW. Histocompatibility. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:145.
39. Speiser DE, Tiercy JM, Rufer N, et al. High resolution HLA matching associated with decreased mortality after unrelated bone marrow transplantation. *Blood*. 1996;87:4455–4462.
40. Davies SM, Kollman C, Anasetti C, et al. Engraftment and survival after unrelated donor bone marrow transplantation: a report from the national marrow donor program. *Blood*. 2000;96:4096–4102.
41. Weisdorf DJ, Anasetti C, Antin JH, et al. Allogeneic bone marrow transplantation for chronic myelogenous leukemia: comparative analysis of unrelated versus matched sibling donor transplantation. *Blood*. 2002;99:1971–1977.
42. Anasetti C, Petersdorf EW, Martin PJ, Woolfrey A, Hansen JA. Improving availability and safety of unrelated donor transplants. *Curr Opin Oncol*. 2000;12:121–126.
43. Hartwell MJ, Özbek U, Holler E, et al. An early-biomarker algorithm predicts lethal graft-versus-host disease and survival. *JCI Insight*. 2017;2(3):e89798. doi:10.1172/jci.insight.89798
44. Etra A, Gergoudis S, Morales G, et al. Comparison of GVHD biomarker algorithms for predicting lethal GVHD and non-relapse mortality. *Biol Blood Marrow Transplant.* 2019;67(25):S53–S54.
45. Morishima Y, Sasazuki T, Inoko H, et al. The clinical significance of human leukocyte antigen (HLA) allele compatibility in patients receiving a marrow transplant from serologically HLA-A, HLA-B, and HLA-DR matched unrelated donors. *Blood*. 2002;99:4200–4206.

46. Sierra J, Anasetti C. Hematopoietic transplantation from adult unrelated donors. *Curr Opin Organ Transplant*. 2003;8:99–108.
47. Sage D. My approach to the immunogenetics of haematopoietic stem cell transplant matching. *J Clin Pathol*. 2010;63:194–198.
48. Pidala J, Lee SJ, Ahn KW, et al. Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation. *Blood*. 2014;124(16):2596–2606.
49. O'Donnell MR. Blood group incompatibilities and hemolytic complications of hematopoietic cell transplantation. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:1219.
50. Rowley SD, Donaldson G, Lilleby K, Bensinger WI, Appelbaum FR. Experiences of donors enrolled in a randomized study of allogeneic bone marrow or peripheral blood stem cell transplantation. *Blood*. 2001;97:2541–2548.
51. Schmitz N. Peripheral blood hematopoietic cells for allogeneic transplantation. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:618.
52. Bittencourt H, Rocha V, Chevret S, et al. Association of CD34 cell dose with hematopoietic recovery, infections, and other outcomes after HLA-identical sibling bone marrow transplantation. *Blood*. 2002;99:2726–2733.
53. Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J Clin Oncol*. 2005;23:5074–5087.
54. Brunstein CG, Wagner JE. Umbilical cord blood transplantation. In: Hoffman R, Benz E, Heslop H, et al, eds. *Hematology Basic Principles and Practice*. Churchill Livingstone Elsevier; 2009:1643.
55. Broxmeyer HE, Smith FO. Cord blood hematopoietic cell transplantation. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:559.
56. Wagner JE, Gluckman E. Umbilical cord blood transplantation: the first 20 years. *Semin Hematol*. 2010;47:3–12.
57. Rocha V, Gluckman E; Eurocord-Netcord registry and European Blood and Marrow Transplant group. Improving outcomes of cord blood transplantation: HLA matching, cell dose and other graft- and transplantation-related factors. *Br J Haematol*. 2009;147:262–274.
58. Brunstein CG, Laughlin MJ. Extending cord blood transplant to adults: dealing with problems and results overall. *Semin Hematol*. 2010;47:86–96.
59. Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood*. 2005;105:1343–1347.

60. Fernandez MN, Regidor C, Cabrera R, et al. Cord blood transplants: early recovery of neutrophils from co-transplanted sibling haploidentical progenitor cells and lack of engraftment of cultured cord blood cells, as ascertained by analysis of DNA polymorphisms. *Bone Marrow Transplant*. 2001;28:355–363.
61. Delaney C, Heimfeld S, Brashem-Stein C, Voorhies H, Manger RL, Bernstein ID. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. *Nat Med*. 2010;16:232–236.
62. Brunstein CG, Barker JN, Weisdorf DJ, et al. Intra-BM injection to enhance engraftment after myeloablative umbilical cord blood transplantation with two partially HLA-matched units. *Bone Marrow Transplant*. 2009;43:935–940.
63. Frassoni F, Gualandi F, Podestà M, et al. Direct intrabone transplant of unrelated cord-blood cells in acute leukaemia: a phase I/II study. *Lancet Oncol*. 2008;9:831–839.
64. Eapen M, Rubinstein P, Zhang MJ, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet*. 2007;369:1947–1954.
65. Ratajczak MZ, Reca R, Wysoczynski M, Yan J, Ratajczak J. Modulation of the SDF-1-CXCR4 axis by the third complement component (C3)—implications for trafficking of CXCR4+ stem cells. *Exp Hematol*. 2006;34:986–995.
66. Eapen M, Rocha V, Sanz G, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. *Lancet Oncol*. 2010;11:653–660.
67. Brunstein CG, Gutman JA, Weisdorf DJ, et al. Allogeneic hematopoietic cell transplantation for hematological malignancy: relative risks and benefits of double umbilical cord blood. *Blood*. 2010;116:4693–4699.
68. Ballen KK, Spitzer TR, Yeap BY, et al. Double unrelated reduced-intensity umbilical cord blood transplantation in adults. *Biol Blood Marrow Transplant*. 2007;13:82–89.
69. Brunstein CG, Barker JN, Weisdorf DJ, et al. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. *Blood*. 2007;110:3064–3070.
70. Weiden PL, Flournoy N, Thomas ED, et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. *N Engl J Med*. 1979;300:1068–1073.
71. Weiden PL, Sullivan KM, Flournoy N, Storb R, Thomas ED; Seattle Marrow Transplant Team. Antileukemic effect of chronic graft-versus-host disease: contribution to improved survival after allo-geneic marrow transplantation. *N Engl J Med*. 1981;304:1529–1533.
72. Ho VT, Soiffer RJ. The history and future of T-cell depletion as graft-versus-host disease prophylaxis for allogeneic hematopoietic stem cell

transplantation. *Blood*. 2001;98:3192–3204.
73. Marmont AM, Horowitz MM, Gale RP, et al. T-cell depletion of HLA-identical transplants in leukemia. *Blood*. 1991;78:2120–2130.
74. MacKinnon S. Who may benefit from donor leucocyte infusions after allogeneic stem cell transplantation? *Br J Haematol*. 2000;110:12–17.
75. Childs RW. Nonmyeloablative allogeneic peripheral blood stem-cell transplantation as immunotherapy for malignant diseases. *Cancer J*. 2000;6:179–187.
76. Vassal G, Deroussent A, Challine D, et al. Is 600 mg/m^2 the appropriate dosage of busulfan in children undergoing bone marrow transplantation? *Blood*. 1992;79:2475–2479.
77. Socie G, Clift RA, Blaise D, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood*. 2001;98:3569–3574.
78. Balducci L, Extermann M. Cancer and aging. An evolving panorama. *Hematol Oncol Clin North Am*. 2000;14:1–16.
79. Center for International Blood and Marrow Transplant Research. Report on state of the art in blood and marrow transplantation. *IBMTR/ABMTR Newsl*. 2006;12:1.
80. Champlin R, Khouri I, Anderlini P, et al. Nonmyeloablative preparative regimens for allogeneic hematopoietic transplantation: biology and current indications. *Oncology (Williston Park)*. 2003;17:94–107.
81. Bryant E, Martin PJ. Documentation of engraftment and characterization of chimerism following hematopoietic cell transplantation. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 3rd ed. Blackwell; 2004:234.
82. Kristt D, Stein J, Yaniv I, Klein T. Assessing quantitative chimerism longitudinally: technical considerations, clinical applications and routine feasibility. *Bone Marrow Transplant*. 2007;39:255–268.
83. Baron F, Baker JE, Storb R, et al. Kinetics of engraftment in patients with hematologic malignancies given allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *Blood*. 2004;104:2254–2262.
84. Deeg HJ, Maris MB, Scott BL, Warren EH. Optimization of allogeneic transplant conditioning: not the time for dogma. *Leukemia*. 2006;20:1701–1705.
85. Van Besien K, Artz A, Smith S, et al. Fludarabine, melphalan and alemtuzumab conditioning in adults with standard-risk advanced acute myeloid leukemia and myelo-dysplastic syndrome. *J Clin Oncol*. 2005;23:5728–5738.
86. Maris MB, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. *Blood*. 2004;104:3535–3542.

87. Martin PJ, Hansen JA, Buckner CD, et al. Effects of in vitro depletion of T cells in HLA-identical allogeneic marrow grafts. *Blood*. 1985;66:664–672.
88. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. *Blood*. 2000;96:2062–2068.
89. Giralt S, Logan B, Rizzo D, et al. Reduced-intensity conditioning for unrelated donor progenitor cell transplantation: long-term follow-up of the first 285 reported to the national marrow donor program. *Biol Blood Marrow Transplant*. 2007;13:844–852.
90. Rezvani AR, Storb RF. Prevention of graft-vs-host disease. *Expert Opin Pharmacother*. 2012;13:1737–1750
91. Openshaw H. Neurological complications of hematopoietic cell transplantation. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:1653.
92. Tran HT, Madden T, Petropoulos D, et al. Individualizing high-dose oral busulfan: prospective dose adjustment in a pediatric population undergoing allogeneic stem cell transplantation for advanced hematologic malignancies. *Bone Marrow Transplant*. 2000;26:463–470.
93. McCune JS, Slattery JT. Pharmacological considerations of primary alkylators. In: Andersson B, Murray D, eds. *Clinically Relevant Resistance in Cancer Chemotherapy*. Kluwer Academic; 2002:323.
94. Nguyen L, Leger F, Lennon S, Puozzo C. Intravenous busulfan in adults prior to haematopoietic stem cell transplantation: a population pharmacokinetic study. *Cancer Chemother Pharmacol*. 2006;57:191–198.
95. Ciurea SO, Andersson BJ. Busulfan in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2009;15:523–536.
96. Shepherd JD, Pringle LE, Barnett MJ, Klingemann HG, Reece DE, Phillips GL. Mesna versus hyperhydration for the prevention of cyclophosphamide-induced hemorrhagic cystitis in bone marrow transplantation. *J Clin Oncol*. 1991;9:2016–2020.
97. Cox PJ. Cyclophosphamide cystitis—identification of acrolein as the causative agent. *Biochem Pharmacol*. 1979;28:2045–2049.
98. Hensley ML, Schuchter LM, Lindley C, et al. American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. *J Clin Oncol*. 1999;17:3333–3355.
99. Hows JM, Mehta A, Ward L, et al. Comparison of mesna with forced diuresis to prevent cyclophosphamide induced haemorrhagic cystitis in marrow transplantation: a prospective randomised study. *Br J Cancer*. 1984;50:753–756.
100. Vose JM, Reed EC, Pippert GC, et al. Mesna compared with continuous bladder irrigation as uroprotection during high-dose chemotherapy and transplantation: a randomized trial. *J Clin Oncol*. 1993;11:1306–1310.

101. James CA, Mant TG, Rogers HJ. Pharmacokinetics of intravenous and oral sodium 2-mercaptoethane sulphonate (mesna) in normal subjects. *Br J Clin Pharmacol*. 1987;23:561–568.
102. Ren S, Kalhorn TF, McDonald GB, Anasetti C, Appelbaum FR, Slattery JT. Pharmacokinetics of cyclophosphamide and its metabolites in bone marrow transplantation patients. *Clin Pharmacol Ther*. 1998;64:289–301.
103. Fleming RA, Cruz JM, Webb CD, Kucera GL, Perry JJ, Hurd DD. Urinary elimination of cyclophosphamide alkylating metabolites and free thiols following two administration schedules of high-dose cyclophosphamide and mesna. *Bone Marrow Transplant*. 1996;17:497–501.
104. American Society of Clinical Oncology, Kris MG, Hesketh PJ, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006 [published correction appears in *J Clin Oncol*. 2006;24:5341]. *J Clin Oncol*. 2006;24:2932–2947.
105. Cagnoni PJ, Matthes S, Day TC, Bearman SI, Shpall EJ, Jones RB. Modification of the pharmacokinetics of high-dose cyclophosphamide and cisplatin by antiemetics. *Bone Marrow Transplant*. 1999;24:1–4.
106. Gilbert CJ, Petros WP, Vredenburgh J, et al. Pharmacokinetic interaction between ondansetron and cyclophosphamide during high-dose chemotherapy for breast cancer. *Cancer Chemother Pharmacol*. 1998;42:497–503.
107. Strasser SI, McDonald GB. Gastrointestinal and hepatic complications. In: Blume KG, Appelbaum FR, Forman SJ, Negrin RS, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Blackwell; 2009:1434.
108. Stiff P. Mucositis associated with stem cell transplantation: current status and innovative approaches to management. *Bone Marrow Transplant*. 2001;27(suppl 2):S3–S11.
109. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer*. 2007;109:820–831.
110. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med*. 2004;351:2590–2598.
111. Ringden O, Labopin M, Gorin NC, et al. Treatment with granulocyte colony stimulating factor after allogeneic bone marrow transplantation for acute leukemia increases the risk of graft-versus-host disease and death: a study from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2004;22;416–423.
112. Carreras E, Bertz H, Arcese W, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. *Blood*. 1998;92:3599–3604.
113. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study

of 355 patients. *Ann Int Med*. 1993;118:255–267.
114. Peters WP, Henner WD, Grochow LB, et al. Clinical and pharmacologic effects of high dose single agent busulfan with autologous bone marrow support in the treatment of solid tumors. *Cancer Res*. 1987;47:6402–6406.
115. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstructive syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2015;50:781–789.
116. Jones RJ, Lee KS, Beschorner WE, et al. Venooclusive disease of the liver following bone marrow transplantation. *Transplantation*. 1987;44:778–783.
117. Attal M, Huguet F, Rubie H, et al. Prevention of hepatic veno-occlusive disease after bone marrow transplantation by continuous low dose heparin: a prospective, randomized trial. *Blood*. 1992;79:2834–2840.
118. Ruutu T, Eriksson B, Remes K, et al. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. *Blood*. 2002;100:1977–1983.
119. Richardson PG, Elias AD, Krishnan A, et al. Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. *Blood*. 1998;92:737–744.
120. Chopra R, Eaton JD, Grassi A, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. *Br J Haematol*. 2000;111:1122–1129.
121. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;127:1656–1665.
122. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood*. 2001;97:3390–3400.
123. Wolff SN. Second hematopoietic stem cell transplantation for the treatment of graft failure, graft rejection or relapse after allogeneic transplantation. *Bone Marrow Transplant*. 2002;29:545–552.
124. Baron F, Sandmaier BM. Current status of hematopoietic stem cell transplantation after nonmyeloablative conditioning. *Curr Opin Hematol*. 2005;12:435–443.
125. Appelbaum FR. Haematopoietic cell transplantation as immunotherapy. *Nature*. 2001;411:385–389.
126. Welniak LA, Blazar BR, Murphy WJ. Immunobiology of allogeneic hematopoietic stem cell transplantation. *Annu Rev Immunol*. 2007;25:139–170.
127. Deeg HJ. How I treat refractory acute GVHD. *Blood*. 2007;109:4119–4126.
128. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-

versus-host disease: I, diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11:945–956.

129. Tabbara IA, Zimmerman K, Morgan C, Nahleh Z. Allogeneic hematopoietic stem cell transplantation: complications and results. *Arch Intern Med*. 2002; 162:1558–1566.
130. Beatty PG, Clift RA, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. *N Engl J Med*. 1985;313:765–771.
131. Barker JN, Davies SM, DeFor T, Ramsay NK, Weisdorf DJ, Wagner JE. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. *Blood*. 2001;97:2957–2961.
132. Rocha V, Cornish J, Sievers EL, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood*. 2001;97:2962–2971.
133. Rocha V, Wagner JE Jr, Sobocinski KA, et al. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. Eurocord and International Bone Marrow Transplant Registry Working Committee on Alternative Donor and Stem Cell Sources. *N Engl J Med*. 2000;342:1846–1854.
134. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood*. 1990;76:1464–1472.
135. Weiden PL, Doney K, Storb R, Thomas ED. et al. Anti-human thymocyte globulin (ATG) for prophylaxis and treatment of graft-versus-host disease in recipients of allogeneic marrow grafts. *Transplant Proc*. 1978;10:213–216.
136. Deeg HJ, Storb R, Thomas ED, et al. Cyclosporine as prophylaxis for graft-versus-host disease: a randomized study in patients undergoing marrow transplantation for acute nonlymphoblastic leukemia. *Blood*. 1985;65:1325–1334.
137. Storb R, Antin JH, Cutler C. Should methotrexate plus calcineurin inhibitors be considered standard of care for prophylaxis of acute graft-versus-host disease? *Biol Blood Marrow Transplant*. 2010;16:S18–S27.
138. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (Prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. *Blood*. 1998;92:2303–2314.
139. Horowitz MM, Przepiorka D, Bartels P, et al. Tacrolimus vs. cyclosporine immunosuppression: results in advanced-stage disease compared with historical controls treated exclusively with cyclosporine. *Biol Blood Marrow Transplant*. 1999;5:180–186.
140. Bolwell B, Sobecks R, Pohlman B, et al. A prospective randomized trial comparing cyclosporine and short course methotrexate with cyclosporine and mycophenolate mofetil for GVHD prophylaxis in myeloablative allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 2004;34:621–625.

141. Nash RA, Johnston L, Parker P, et al. A phase i/ii study of mycophenolate mofetil in combination with cyclosporine for prophylaxis of acute graft-versus-host disease after myeloablative conditioning and allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2005;11:495–505.
142. Chao NJ, Schmidt GM, Niland JC, et al. Cyclosporine, methotrexate, and prednisone compared with cyclosporine and prednisone for prophylaxis of acute graft-versus-host disease. *N Engl J Med*. 1993;329:1225–1230.
143. Goker H, Haznedaroglu IC, Chao NJ. Acute graft-versus-host disease: pathobiology and management [published correction appears in *Exp Hematol*. 2001;29:653]. *Exp Hematol*. 2001;29:259–277.
144. Leather HL. Drug interactions in the hematopoietic stem cell transplant (HSCT) recipient: what every transplanter needs to know. *Bone Marrow Transplant*. 2004;33:137–152.
145. Przepiorka D, Nash RA, Wingard JR, et al. Relationship of tacrolimus whole blood levels to efficacy and safety outcomes after unrelated donor marrow transplantation. *Biol Blood Marrow Transplant*. 1999;5:94–97.
146. Duncan N, Craddock C. Optimizing the use of cyclosporin in allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2006;38:169–174.
147. Schmidt H, Ehninger G, Dopfer R, et al. Correlation between low CSA plasma concentration and severity of acute Gv HD in bone marrow transplantation. *Blut*. 1988;57:139–142.
148. Hows JM, Palmer S, Gordon-Smith EC. Use of cyclosporin A in allogeneic bone marrow transplantation for severe aplastic anemia. *Transplantation*. 1982;33:382–386.
149. Oshima K, Sato M, Terasako K, et al. Target blood concentrations of cyclosporine and tacrolimus in randomized controlled trials for the prevention of acute GVHD after hematopoietic SCT. *Bone Marrow Transplant.* 2010;45:781–782.
150. Nakamura Y. Evaluation of appropriate blood level in continuous intravenous infusion from trough concentrations after oral administration based on area under trough level in tacrolimus and cyclosporine therapy. *Transplant Proc*. 2005;37:1725–1727.
151. Furukawa T, Kurasaki-Ida T, Masuko M, et al. Pharmacokinetic and pharmacodynamic analysis of cyclosporine A (CsA) to find the best single time point for the monitoring and adjusting of CsA dose using twice daily 3-h intravenous infusions in allogeneic hematopoietic stem cell transplantation. *Intl J Hematol*. 2010;92:144–151.
152. Wingard JR, Nash RA, Przepiorka D, et al. Relationship of tacrolimus (FK506) whole blood concentrations and efficacy and safety after HLA-identical sibling bone marrow transplantation. *Biol Blood Marrow Transplant*. 1998;4:157–163.
153. Couriel D, Caldera H, Champlin R, Komanduri K. Acute graft-versus-host disease: pathophysiology, clinical manifestations, and management. *Cancer*.

2004;101:1936–1946.
154. Deeg HJ, Loughran TP Jr, Storb R, et al. Treatment of human acute graft-versus host disease with antithymocyte globulin and cyclosporine with or without methylprednisolone. *Transplantation*. 1985;40:162–166.
155. Lazarus HM, Vogelsang GB, Rowe JM. Prevention and treatment of acute graft-versus-host disease: the old and the new. A report from the Eastern Cooperative Oncology Group (ECOG). *Bone Marrow Transplant*. 1997;19:577–600.
156. Van Lint MT, Uderzo C, Locasciulli A, et al. Early treatment of acute graft-versus-host disease with high- or low-dose 6-methylprednisolone: a multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. *Blood*. 1998;92:2288–2293.
157. Antin JH, Chen AR, Couriel DR, Ho VT, Nash RA, Weisdorf D. Novel approaches to the therapy of steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2004;10:655–668.
158. Lee SJ. New approaches for preventing and treating chronic graft-versus-host disease. *Blood*. 2005;105:4200–4206.
159. Yamasaki S, Heike Y, Mori S, et al. Infectious complications in chronic graft-versus-host disease: a retrospective study of 145 recipients of allogeneic hematopoietic stem cell transplantation with reduced- and conventional-intensity conditioning regimens. *Transpl Infect Dis*. 2008;10:252–259.
160. Perez-Simon JA, Sánchez-Abarca I, Díez-Campelo M, Caballero D, San Miguel J. Chronic graft-versus-host disease: pathogenesis and clinical management. *Drugs*. 2006;66:1041–1057.
161. Vogelsang GB. How I treat chronic graft-versus-host disease. *Blood*. 2001;97:1196–1201.
162. Lin X, Cavanagh HD. Ocular manifestations of graft-versus-host disease: 10 year's experience. *Clin Opthal*. 2015;9:1209–1213.
163. Essell JH, Schroeder MT, Harman GS, et al. Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1998;128:975–981.
164. Ohashi K, Tanabe J, Watanabe R, et al. The Japanese multicenter open randomized trial of ursodeoxycholic acid prophylaxis for hepatic veno-occlusive disease after stem cell transplantation. *Am J Hematol*. 2000;64:32–38.
165. Stern JM, Chesnut CH 3rd, Bruemmer B, et al. Bone density loss during treatment of chronic GVHD. *Bone Marrow Transplant*. 1996;17:395–400.
166. Bowden RA. Respiratory virus infections after marrow transplant: the Fred Hutchinson Cancer Research Center experience. *Am J Med*. 1997;102:27–43.
167. Junghanss C, Marr KA, Carter RA, et al. Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with

myeloablative allogeneic hematopoietic stem cell transplantation: a matched control study. *Biol Blood Marrow Transplant*. 2002;8:512–520.

168. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective [published correction appears in *Biol Blood Marrow Transplant*. 2010;16:294]. *Biol Blood Marrow Transplant*. 2009;15:1143–1238.
169. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients [published correction appears in *Ann Intern Med*. 2006;144:704]. *Ann Intern Med*. 2005;142:979–995.
170. van de Wetering MD, de Witte MA, Kremer LC, Offringa M, Scholten RJ, Caron HN. Efficacy of oral prophylactic antibiotics in neutropenic afebrile oncology patients: a systematic review of randomised controlled trials. *Eur J Cancer*. 2005;41:1372–1382.
171. Bucaneve G, Elio C, Claudio V, Leibovici L, Francesco M. Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients. *Eur J Cancer*. 2007;(suppl 5):5–12.
172. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med*. 2005;353:977–987.
173. Cruciani M, Rampazzo R, Malena M, et al. Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis*. 1996;23:795–805.
174. Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. *J Clin Oncol*. 1998;16:1179–1187.
175. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. *Clin Infect Dis*. 2002;34:1524–1529.
176. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56–e93.
177. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med*. 1992;326:845–851.
178. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation: a prospective, randomized, double-blind study. *J Infect Dis*. 1995;171:1545–1552.
179. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2002;34:909–917.
180. Cornely OA, Ullmann AJ, Karthaus M. Evidence-based assessment of primary antifungal prophylaxis in patients with hematologic malignancies. *Blood*. 2003;101:3365–3372.

181. Wingard JR, Carter SL, Walsh TJ, et al. Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allo hematopoietic cell transplantation (HSCT). *Blood*. 2010;116:5111–5118.
182. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356:348–359.
183. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis*. 2004;39:743–746.
184. Singh N, Paterson DL. *Aspergillus* infections in transplant recipients. *Clin Microbiol Rev*. 2005;18:44–69.
185. Selby PJ, Powles RL, Easton D, et al. The prophylactic role of intravenous and long-term oral acyclovir after allogeneic bone marrow transplantation. *Br J Cancer*. 1989;59:434–438.
186. Burns LJ, Miller W, Kandaswamy C, et al. Randomized clinical trial of ganciclovir vs acyclovir for prevention of cytomegalovirus antigenemia after allogeneic transplantation. *Bone Marrow Transplant*. 2002;30:945–951.
187. Ljungman P. Prevention and treatment of viral infections in stem cell transplant recipients. *Br J Haematol*. 2002;118:44–57.
188. Vusirikala M, Wolff SN, Stein RS, et al. Valacyclovir for the prevention of cytomegalovirus infection after allogeneic stem cell transplantation: a single institution retrospective cohort analysis. *Bone Marrow Transplant*. 2001;28:265–270.
189. Dignani MC, Mykietiuk A, Michelet M, et al. Valacyclovir prophylaxis for the prevention of Herpes simplex virus reactivation in recipients of progenitor cells transplantation. *Bone Marrow Transplant*. 2002;29:263–267.
190. Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. *Chest*. 2002;121:1988–1999.
191. Steer CB, Szer J, Sasadeusz J, Matthews JP, Beresford JA, Grigg A. Varicella-zoster infection after allogeneic bone marrow transplantation: incidence, risk factors and prevention with low-dose acyclovir and ganciclovir. *Bone Marrow Transplant*. 2000;25:657–664.
192. Razonable RR, Emery VC. Management of CMV infection and disease in transplant patients. *Herpes*. 2004;11:77–86.
193. Goodrich JM, Bowden RA, Fisher L, Keller C, Schoch G, Meyers JD. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med*. 1993;118:173–178.
194. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. *Blood*. 1996;88:4063–4071.

195. Zaia JA. Prevention of cytomegalovirus disease in hematopoietic stem cell transplantation. *Clin Infect Dis*. 2002;35:999–1004.
196. Boeckh M, Gallez-Hawkins GM, Myerson D, Zaia JA, Bowden RA. Plasma polymerase chain reaction for cytomegalovirus DNA after allogeneic marrow transplantation: comparison with polymerase chain reaction using peripheral blood leukocytes, pp65 antigenemia, and viral culture. *Transplantation*. 1997;64:108–113.
197. St George K, Boyd MJ, Lipson SM, et al. A multisite trial comparing two cytomegalovirus (CMV) pp65 antigenemia test kits, biotest CMV Brite and Bartels/Argene CMV antigenemia. *J Clin Microbiol*. 2000;38:1430–1433.
198. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. *J Infect Dis*. 2002;185:273–282.
199. Boeckh M, Bowden RA, Gooley T, Myerson D, Corey L. Successful modification of a pp65 antigenemia-based early treatment strategy for prevention of cytomegalovirus disease in allogeneic marrow transplant recipients. *Blood*. 1999;93:1781–1782.
200. Schmidt GM, Horak DA, Niland JC, Duncan SR, Forman SJ, Zaia JA. A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants: the City of Hope-Stanford-Syntex CMV Study Group. *N Engl J Med*. 1991;324:1005–1011.
201. Goodrich JM, Mori M, Gleaves CA, et al. Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplantation. *N Engl J Med*. 1991;325:1601–1607.
202. Ljungman P, Aschan J, Lewensohn-Fuchs I, et al. Results of different strategies for reducing cytomegalovirus-associated mortality in allogeneic stem cell transplant recipients. *Transplantation*. 1998;66:1330–1334.
203. Ayala E, Greene J, Sandin R, et al. Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2006;37:851–856.
204. Diaz-Pedroche C, Lumbreras C, San Juan R, et al. Valganciclovir preemptive therapy 7 for the prevention of cytomegalovirus disease in high-risk seropositive solid-organ transplant recipients. *Transplantation*. 2006;82:30–35.
205. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med.* 2017;377:2433–2444.
206. Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood*. 2002;99:1159–1164.

207. Ljungman P, Deliliers GL, Platzbecker U, et al. Cidofovir for cytomegalovirus infection and disease in allogeneic stem cell transplant recipients. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2001;97:388–392.
208. Holmberg LA, Boeckh M, Hooper H, et al. Increased incidence of cytomegalovirus disease after autologous CD34-selected peripheral blood stem cell transplantation. *Blood*. 1999;94:4029–4035.
209. Junghanss C, Boeckh M, Carter RA, et al. Incidence and outcome of cytomegalovirus infections following nonmyeloablative compared with myeloablative allogeneic stem cell transplantation, a matched control study. *Blood*. 2002;99:1978–1985.
210. Mohty M, Faucher C, Vey N, et al. High rate of secondary viral and bacterial infections in patients undergoing allogeneic bone marrow mini-transplantation. *Bone Marrow Transplant*. 2000;26:251–255.
211. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. *Blood*. 2002;100:4358–4366.
212. De La Rosa GR, Champlin RE, Kontoyiannis DP. Risk factors for the development of invasive fungal infections in allogeneic blood and marrow transplant recipients. *Transpl Infect Dis*. 2002;4:3–9.
213. Wingard JR, Merz WG, Rinaldi MG, Miller CB, Karp JE, Saral R. Association of *Torulopsis glabrata* infections with fluconazole prophylaxis in neutropenic bone marrow transplant patients. *Antimicrob Agents Chemother*. 1993;37:1847–1849.
214. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N Engl J Med*. 1991;325:1274–1277.
215. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Medicine (Baltimore)*. 2000;79:250–260.
216. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis*. 2002;34:7–14.
217. Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the *Aspergillus* galactomannan enzyme immunoassay. *Clin Infect Dis*. 2005;40:1762–1769.
218. Marr KA, Patterson T, Denning D. Aspergillosis: pathogenesis, clinical manifestations, and therapy. *Infect Dis Clin North Am*. 2002;16:875–894.
219. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347:408–415.

220. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole inpatients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis*. 2007;44:2–12.
221. Stone EA, Fung HB, Kirschenbaum HL. Caspofungin: an echinocandin antifungal agent. *Clin Ther*. 2002;24:351–377.
222. Denning DW, Marr KA, Lau WM, et al. Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis. *J Infect*. 2006;53:337–349.
223. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis*. 2002;34:563–571.
224. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2006;12:138–151.
225. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 5.0. Accessed March 3, 2021. http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf
226. Goldberg SL, Cicogna CE, Rowley SD, Pecora AL. Vaccinations against infectious diseases in hematopoietic stem cell transplant recipients. *Oncology (Williston Park)*. 2003;17:539–565.
227. Antin JH. Clinical practice. Long-term care after hematopoietic-cell transplantation in adults. *N Engl J Med*. 2002;347:36–42.
228. Socie G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood*. 2003;101:3373–3385.
229. Strasser SI, McDonald GB. Hepatitis viruses and hematopoietic cell transplantation: a guide to patient and donor management. *Blood*. 1999;93:1127–1136.

SECTION 17

Pediatrics

Section Editor: Elizabeth Anne Farrington

102

Pediatric Pharmacotherapy

Elizabeth Anne Farrington

CORE PRINCIPLES		CHAPTER CASES
GROWTH AND DEVELOPMENT		
1	Children undergo considerable physiologic changes between birth and adulthood. Although most follow the same general pattern of growth, the timing of maturation varies from child to child.	**Case 102-1 (Question 1), Table 102-1**
PHARMACOKINETIC DIFFERENCES		
1	All aspects of pharmacokinetics are affected by growth and development. Drug absorption is altered by a variety of mechanisms, with the most significant differences noted during the first months of life.	**Case 102-2 (Question 1) Case 102-3 (Question 1–4)**
2	Drug distribution is affected by changes	**Case 102-3 (Question 5, 6),**

	in relative organ size, body water content, fat stores, plasma protein concentrations, acid–base balance, cardiac output, and tissue perfusion. The greatest degree of change occurs during the first year of life.	**Table 102-2**
3	Metabolic function is highly dependent on patient age. This has been demonstrated in a number of recent studies, which have identified significant differences in half-life during infancy, childhood, and adolescence.	**Case 102-4 (Question 1–4)**
4	Elimination is reduced during infancy, resulting in slower rates of clearance for many commonly used drugs. Glomerular filtration rate increases throughout childhood. Use of creatinine clearance as an estimate of glomerular filtration rate requires different equations than those used in adults.	**Case 102-5 (Question 1, 2)** **Case 102-6 (Question 1)**
5	Adolescence is not simply a link between childhood and adulthood; it is a distinct period of significant physiologic change. The effects of puberty can alter the efficacy or toxicity of many drugs administered during this period.	**Case 102-7 (Question 1)**
PHARMACODYNAMIC DIFFERENCES		
1	Although less well understood than pharmacokinetic differences between children and adults, there are significant age-related effects on pharmacodynamics as well. Children	**Case 102-8 (Question 1)** **Case 102-9 (Question 1, 2)**

	may exhibit differences in both therapeutic response and adverse effect profiles.	
MEDICATION DOSING IN CHILDREN		
1	The differences in pharmacokinetics and pharmacodynamics observed in children influence the choice of drug dose and dosing interval. For most dose calculations, weight is used to account for growth and development.	**Case 102-10 (Question 1)**
2	All pediatric prescriptions and medication orders must be checked for the appropriateness of the dose, route, and frequency with a pediatric dosing reference.	**Case 102-10 (Question 1)**
PREVENTING MEDICATION ERRORS IN CHILDREN		
1	Children are at a greater risk for medication errors than adults, as a result of the need to calculate drug doses and alter dosage formulations.	**Case 102-10 (Question 2)**
2	Electronic prescribing, standardization of drug doses and concentrations, and the introduction of smart-pump technology have been shown to reduce errors in many children's hospitals. One of the most effective methods to avoid errors is the inclusion of pediatric pharmacists in the medication ordering and review process.	**Case 102-10 (Question 3), Table 102-3**
INCREASING PEDIATRIC MEDICATION INFORMATION		

1	A number of governmental programs are increasing the availability of pediatric medication information and improving the ability of pediatric health care professionals to provide safe and effective drug therapy for children.	**Case 102-10 (Question 4)**

INTRODUCTION

Providing care for children can be one of the most challenging, but rewarding, aspects of pharmacy practice. Although a relatively small number of health care providers pursue specialty training in pediatrics and work exclusively with children, most clinicians will provide care for children every day in the community or hospital setting. According to recent population estimates, ~22.3% of the U.S. population is younger than age 18 years, with 6% younger than age 5 years.[1] Although most children are healthy, this segment of the population still uses a significant amount of health care resources. In a recent telephone survey, one in five parents reported giving their child one or more prescription medications within the previous week.[2] A survey conducted in pediatricians' offices found that 53% of children left their visit with a prescription.[3]

Pediatrics, as a specialty, encompasses a very diverse patient population. Patients range in age from premature neonates to adolescents and can vary in weight by 300-fold, from a 1.10-pound (0.5-kg) premature neonate to a 330.69-pound (150-kg) 16-year-old. Further complicating the care of children is the relative lack of information on drug dosing and monitoring. Because of the small numbers of children requiring medical treatment and the difficulty in conducting research in these patients, fewer than half of the drugs currently available in the United States are approved by the U.S. Food and Drug Administration (FDA) for pediatric use.[4,5] As a result, as many as 60% of all prescriptions written by pediatricians are for

"off-label" uses.[6] Dosing and monitoring information for off-label uses is often based on case series and clinical trials published in the medical literature and may not be readily available in general drug references.

Health care providers caring for children must be capable of assessing the appropriateness of drug doses for this diverse population and providing recommendations for dosage adjustments and patient monitoring with limited resources. This requires knowledge of the pharmacokinetic and pharmacodynamic differences between children and adults and how these differences impact both therapeutic and adverse drug effects.

GROWTH AND DEVELOPMENT DURING CHILDHOOD

CASE 102-1

QUESTION 1: C.J. is a 4-month-old, 14.33-pound (6.5-kg) male who has recently started teething. His parents ask for advice on a medication to alleviate C.J.'s pain.

What factors will influence your decision about the choice of medication and dosing regimen for C.J.? What medication and dose will you recommend to his parents?

Children undergo considerable physiologic changes between birth and adulthood. Although many changes are easily observed, such as the ability to walk or the development of language, others are less evident. C.J.'s analgesic dose will be based on his age and weight, as estimates of the numerous pharmacokinetic and pharmacodynamic differences between children and adults. To discuss the changes that occur with growth and development, pediatric patients are typically grouped by age (**Table 102-1**). These definitions are helpful to provide a consistent framework for dosing recommendations, but it should be kept in mind that they are

arbitrary and can oversimplify the differences among individual patients. Although children tend to grow and develop in a relatively similar manner, the timing of maturation varies from child to child. Children do not grow in a predictable, linear fashion, but rather in periodic bursts, with additional variation caused by differences in genetic predisposition, nutritional intake, and environment.[7,8] Research on the impact of growth and development on pharmacokinetics and pharmacodynamics, often referred to as developmental pharmacology, has grown considerably during the past several decades, improving our ability to optimize the efficacy of drug therapy in children while minimizing adverse effects.

Table 102-1
Commonly Used Age Definitions

Premature Neonate	Born at >36 Weeks' Gestational Age
Term neonate	Born at ≥36 weeks' gestational age
Neonate	Birth–1 month of age
Infant	>1 month–1 year of age
Child	>1–11 years of age
Adolescent	12–16 years of age

The most appropriate analgesic for C.J. would be acetaminophen. Aspirin is no longer used as an analgesic in children because of its association with Reye syndrome, a rare condition causing mitochondrial damage and resulting in hepatic failure. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, are not recommended for use in infants younger than age 6 months because of unknown effects on the developing kidney.[9] C.J. should receive an acetaminophen dose of 10 to 15 mg/kg given every 4 to 6 hours as needed, with no more than five doses or 75 mg/kg given in a 24-hour period. Based on his age and weight, an appropriate recommendation for C.J. would be to give 65 mg (2 mL) of the acetaminophen 160 mg/5 mL oral suspension by mouth every 6

hours as needed. If C.J. continues to need medication for >24 hours, his parents should contact C.J.'s primary health care provider.

PEDIATRIC PHARMACOKINETIC DIFFERENCES

All aspects of pharmacokinetics are affected by growth and physical maturation, beginning during gestation (pregnancy) and ending in adulthood. These changes are complex, and their timing can vary widely from patient to patient.

Drug Absorption

ORAL DRUG ABSORPTION

CASE 102-2

QUESTION 1: A.H., a 3.30-pound (1.5-kg), 4-week-old female born at 29 weeks' gestational age, is being treated with phenobarbital for seizures associated with a period of asphyxia at birth. She is currently receiving a maintenance dose of 7.5 mg (5 mg/kg) given intravenously (IV) once daily. The team wishes to transition her to oral therapy now that she is receiving full enteral feeds. A trough serum phenobarbital concentration obtained during IV therapy was 17.5 µg/mL, within the desired range of 15 to 40 µg/mL. Switching the patient to phenobarbital elixir 7.5 mg given orally once daily results in a serum concentration of only 8.9 µg/mL after 1 week of therapy.

What factors might explain the lower concentration, and how should A.H. be managed?

Enteral absorption of drugs is altered at birth and does not approximate adult patterns for several months.[7,8] Gastric fluid volume is greatly reduced at birth. Gastric acid production is decreased, giving the neonate a higher, nearly neutral pH in the stomach. This results in a greater absorption of acid-labile drugs such as penicillin G and erythromycin, but reduced absorption of

weakly acidic drugs such as phenobarbital and phenytoin. Gastric acid output increases during the first 1 to 2 weeks of life but only reaches adult values at age 2 to 3 years. Transport of bile acids into the gastrointestinal lumen and pancreatic enzyme production are also reduced, further altering the absorption of pH-sensitive drugs and reducing enterohepatic recirculation. Amylase activity is minimal at birth and remains low until the third month of life.[10] Pancreatic lipase activity is detectable by 32 weeks' gestational age, but remains low at birth and throughout the next 2 to 3 months. In contrast, gastric lipase is present at birth and accounts for a greater percentage of fat absorption during early life. In addition to these differences, neonates are also born with relatively sterile gastrointestinal tracts. Normal bacterial colonization typically occurs within days for term infants but may be delayed in premature infants who reside in the more sterile environment of an intensive care unit. The effectiveness of drugs that rely on gastrointestinal flora for activation or degradation may be significantly altered during this period.

Gastric emptying time is delayed, and intestinal transit time is prolonged at birth, but both quickly increase within the first few days of life because contractions in the stomach become more coordinated and intestinal contractions become more frequent, stronger, and sustained. Premature infants have delayed development of normal gastric emptying and intestinal transit, as shown in a study of acetaminophen dosing in which premature infants at 28 weeks' gestational age had a 2-hour delay in absorption compared with older infants.[11] Adult values for gastric emptying and intestinal transit time are generally reached by age 4 to 8 months.

For drugs absorbed through passive diffusion, reduced splanchnic blood flow during the first weeks of life can reduce the rate and extent of absorption by altering concentration gradients across the intestinal villi.[7] Reduction in blood flow may also place neonates at risk for damage to the gut lining from hyperosmolar drug formulations. As a result, many institutions delay use of the enteral route in premature neonates for drug administration until the patient is receiving at least one-quarter to half of their nutritional needs

through enteral feedings. This allows dilution of drug doses and may reduce the risk for mucosal damage. Lower levels of metabolic enzyme activity in the intestine may reduce first-pass metabolism of drugs given enterally.[12,13] Boucher et al[13] found that the bioavailability of zidovudine decreased from 89% in neonates during the first 2 weeks of life to 61% in older infants, reflecting increased first-pass metabolism in the older patients. Intestinal enzymatic activity does not approach adult values until age 2 to 3 years.

The lower phenobarbital serum concentration after A.H. was placed on enteral therapy is most likely the result of reduced drug absorption in the gastrointestinal tract, resulting from the higher gastric pH and reduced splanchnic blood flow. The maintenance phenobarbital dose for A.H. should be increased to achieve a trough serum concentration within the desired range. An increase of the oral dose to 10 mg would be appropriate, with a plan to obtain a trough concentration within 3 to 5 days. Although this value will not yet reflect the steady-state concentration, because of the long half-life of the drug, it will be useful to guide additional dosing changes.

INTRAMUSCULAR DRUG ABSORPTION

CASE 102-3

QUESTION 1: C.B. is a 7.94-pound (3.6-kg) newborn male, born at 39 weeks' gestational age, who was transferred to the newborn nursery after delivery. Routine care for neonates during the first hours of life generally includes administration of erythromycin eye ointment for prevention of neonatal ophthalmia and 1 mg of phytonadione (vitamin K_1) given intramuscularly (IM) to prevent vitamin K–deficiency bleeding of the newborn. C.B.'s parents question the need to give their baby a shot so soon after birth.

How would you explain the rationale for giving phytonadione IM rather than orally?

In the United States, phytonadione is typically given by IM injection after birth. Drug administration by IM injection typically results in a delay in time to reach peak serum concentrations in neonates. This delay is related to reduced muscle size, weaker muscle contractions,

and an immature vasculature resulting in more erratic blood flow to and from the muscle.[7,8] Although considered a disadvantage when rapid absorption is needed, such as with antibiotic administration, the delay in systemic absorption after IM injection is used as an advantage for the administration of phytonadione after birth. The delayed absorption from muscle results in a depot-like effect, providing a slow release of the drug into the systemic circulation until the infant's dietary intake is adequate to maintain necessary vitamin K serum concentrations.[14] A similar delay in drug absorption may occur with subcutaneous injection because of the lower percentage of body fat in neonates. The delay in absorption seen with IM and subcutaneous administration becomes negligible after the first months of life. When counseling C.B.'s parents, it will be important to stress the benefit of the slower absorption of vitamin K with IM administration compared with the rapid absorption and clearance of a single oral dose. A single IM injection of vitamin K will protect their son from bleeding until he is approximately a month old, when he should be taking in enough breast milk or infant formula to maintain adequate vitamin K concentrations.

TRANSDERMAL DRUG ABSORPTION

Case 102-3, Question 2: C.B. is scheduled for a circumcision before discharge. The surgical site will be prepped with a 10% povidone–iodine solution. What factors influence the absorption of medications via this route in the neonatal patient? Based on these factors, how should the povidone–iodine be applied to minimize toxicity?

In contrast to enteral, IM, and subcutaneous administration, transdermal or percutaneous administration results in greater drug absorption in neonates than it does in older children and adults. Enhanced absorption results from a greater skin to body surface area ratio, approximately three times that of adults, as well as a thinner stratum corneum, better epidermis hydration, and greater perfusion.[7,8] The greater degree of percutaneous absorption in infants has resulted in significant toxicity. Hexachlorophene, when

used routinely to bathe infants, has resulted in seizures and is now considered contraindicated in this age range. Application of povidone–iodine as a topical disinfectant before surgery has been linked to neonatal thyroid dysfunction and, as a result, is now used only in limited quantities for brief periods to limit percutaneous iodine absorption. In spite of the knowledge of this adverse effect, cases continue to be reported in the medical literature.[15] Even relatively common topical products can produce systemic toxicity. Frequent use of diaper rash products containing hydrocortisone can produce suppression of the hypothalamus–pituitary–adrenal axis in as little as 2 weeks.

Cleaning and disinfecting the skin before surgery in a neonate requires special attention to the selection of agent, surface area affected, and the length of skin contact. For C.B., a 10% povidone–iodine solution should be gently applied to the penis and surrounding skin immediately before surgery and removed as soon as the 5- to 10-minute circumcision has been completed to minimize the risk for systemic toxicity resulting from enhanced percutaneous iodine absorption.

Case 102-3, Question 3: Are transdermal anesthetics an appropriate option for use before C.B.'s procedure?

Both 4% lidocaine and eutectic mixture of local anesthetics (EMLA) cream, which contain lidocaine and prilocaine, are widely used as topical anesthetics for infants and children before venipuncture, IV catheter placement, or circumcision. Both have been shown in clinical trials to be safe and effective.[16] The low concentration of the active ingredients and the limited duration of contact, 30 to 60 minutes, prevent excessive systemic absorption when applied to intact skin. Either analgesic cream would be appropriate for C.B. EMLA should be applied an hour before the start of the circumcision, whereas 4% lidocaine cream should be applied 30 minutes before the procedure. A thin layer of cream should be applied, without an occlusive dressing, and the baby diapered until

the start of the procedure. The cream should be completely removed before the application of the 10% povidone–iodine solution.

Other transdermal medications should be avoided or used with caution for only limited periods in infants. After the first year of life, transdermal application becomes a more useful route of administration for several medications. Methylphenidate and clonidine patches are used in the treatment of attention-deficit hyperactivity disorder (ADHD) in school-aged children, and both lidocaine and fentanyl patches are used for the treatment of older children and adolescents with severe pain.

RECTAL DRUG ABSORPTION

Case 102-3, Question 4: A week after C.B.'s discharge from the hospital, he is brought into the emergency department after becoming lethargic and febrile at home. His parents have tried giving him oral acetaminophen, but he is vomiting and unable to take liquids. Is rectal administration of acetaminophen an acceptable option for C.B. in the hospital after he has been stabilized?

Rectal administration is a useful route of drug delivery for many pediatric patients. Most drugs are well absorbed by this route, but the strong rectal contractions in infants can result in an inability to retain suppositories for the length of time needed to achieve optimal absorption.[7,8] Gels and liquid dosage preparations that do not require an extended time for dissolution are better options. Rectal diazepam gel is often used by parents of children with seizure disorders to provide rapid control of worsening seizures while awaiting emergency medical personnel. In an observational trial of 358 children, the median time from administration of rectal diazepam by a parent to cessation of seizures was 4.3 minutes.[17]

Rectal acetaminophen would be a viable option for C.B. It is rapidly absorbed through this route. Many drug dosing references recommend a slightly higher rectal acetaminophen dose (10–20 mg/kg) to account for a potentially lower bioavailability.

Drug Distribution

Growth and development also affect drug distribution. Organ size, body water content, fat stores, plasma protein concentrations, acid–base balance, cardiac output, and tissue perfusion all change throughout childhood, altering the pattern of distribution and extent of drug penetration.[7] The greatest degree of change occurs during the first year of life.

Case 102-3, Question 5: In the emergency department, C.B. is refusing to breast-feed and is having difficulty breathing. Neonatal sepsis with possible meningitis is suspected. Laboratory values and vital signs include the following:

Temperature, 102.92 °F (39.4 °C)
Heart rate, 202 beats/minute (normal 107–182 beats/minute)
Blood pressure, 85/62 mm Hg (normal systolic 70–75 mm Hg, diastolic 50–55 mm Hg)

He currently weighs 7.50 pounds (3.4 kg) and appears slightly dehydrated. His parents report that C.B. has had fewer wet diapers than usual during the last 24 hours. What physiologic differences in the neonatal period would affect your choice of empiric antibiotics for the treatment of neonatal central nervous system infections? What drugs would you select and what doses would you recommend?

Empiric antibiotic therapy for sepsis and meningitis for C.B. typically consists of ampicillin and aminoglycoside. Although not commonly used in adults because of the relatively low degree of penetration across the blood–brain barrier, this combination is very effective in the neonatal period when drug distribution into the central nervous system is higher. Constituting only 2% of total body weight in an adult, the brain makes up 10% to 12% of the weight of an infant. As a result, the brain serves as a much larger potential compartment for drug distribution. In addition, the percentage of systemic blood flow that reaches the cerebral vasculature is greater. These factors, along with a potential for greater passive diffusion of drugs across the functionally immature blood–brain barrier, can result in higher drug concentrations within the central nervous system of infants compared with older children and adults.[7,8] This

can produce both benefit and risk to the infant. Drugs given to treat meningitis or seizures are more likely to achieve therapeutic concentrations within the central nervous system, but there is also a greater potential risk for drug-induced neurotoxicity.

BODY WATER

One of the most significant differences in drug distribution during childhood is the decrease in total body water content with increasing age. Approximately 85% of a premature newborn's weight and 70% to 80% of a term newborn's weight are body water, compared with only 60% to 65% in a 1-year-old.[7,8] After a year of age, the percentage declines from 50% to 60% and remains relatively constant. Extracellular water decreases in a similar manner, from 40% to 45% in the newborn to 20% to 25% by the end of the first year of life. Intracellular water content, however, remains relatively stable. These changes result in a much greater distribution of highly water-soluble drugs, such as the aminoglycosides or linezolid, and a reduced accumulation of highly lipid-soluble drugs, such as amphotericin, amiodarone, benzodiazepines, or digoxin.

The pharmacokinetic profile of gentamicin has been well described in infants and children as a result of its role in empiric antibiotic therapy for neonatal sepsis and meningitis. The volume of distribution of gentamicin in premature neonates ranges from 0.5 to 0.7 L/kg, reflecting the higher extracellular water content at this age. This value falls to 0.4 L/kg by the end of the first year of life and further declines from 0.2 to 0.3 L/kg by adulthood.[18] As a result of their higher volume of distribution, the weight-based dose for an infant is often much higher than a comparable dose in an adult. Based on C.B.'s age and weight, the *Pediatric Dosage Handbook*,[18] one of the most widely used pediatric drug references, recommends an ampicillin dose of 255 mg (75 mg/kg) given IV every 6 hours (300 mg/kg/24 hour) and a gentamicin dose of 13.6 mg (4 mg/kg) given IV every 24 hours. Using these same weight-based doses in a 154.32-pound (70-kg) adult would result in doses much higher than the typical recommended adult dose.

BODY FAT

Whereas the effects of growth and development on changes in body water content are well defined and typically require adjustments in drug dosing only during infancy, the effects of changes in body fat are not yet well understood. Body fat increases throughout gestation and infancy. A premature neonate may have as little as 1% to 2% body fat, whereas a term infant will have closer to 10% to 15% body fat. A 1-year-old will have a body fat of 20% to 25%, similar to that of an adult. Children following normal growth patterns have relatively little change in their body fat percentage between the second year of life and the onset of puberty. However, the increasing rate of childhood obesity has generated concern about the efficacy and safety of current weight-based dosing strategies.[19] In a 2010 retrospective study of 699 children between ages 5 and 12 years admitted to a children's hospital during a 6-month period, overweight children (defined as having a body mass index >85th percentile for age) accounted for 33% of the admissions.[20] Evaluation of their medication orders revealed that 8.5% of the doses ordered were for less than the recommended dose, whereas 2.8% were for an excessive dose. The need to make dosage adjustments in these children remains controversial; only limited research is available documenting the effects of childhood obesity on the pharmacokinetics and pharmacodynamics of commonly used pediatric medications.

PROTEIN BINDING

Case 102-3, Question 6: On the third day of admission, the microbiology laboratory reports the culture and sensitivity results for C.B. Although the cerebrospinal fluid and urine cultures were negative, the peripheral blood culture grew *Escherichia coli*. The organism appears to be sensitive to a wide range of antibiotics, including penicillins, cephalosporins, gentamicin, and sulfamethoxazole-trimethoprim. What would your recommendation be for C.B.'s continuing treatment?

Many of the drugs that would treat C.B.'s infection are highly protein bound. Plasma protein binding is reduced in neonates as a result of decreased circulating levels of both albumin and α_1-acid glycoprotein, as well as decreased binding affinity.[7,8,12] With the known susceptibilities and their long history of efficacy and safety, continuing C.B.'s current ampicillin and gentamicin regimen for 7 to 10 days would be an appropriate choice. Although ampicillin is known to be present in higher unbound concentrations in infants compared with adults (**Table 102-2**), use of standard dosing recommendations for C.B. based on age should be adequate to prevent toxicity. Sulfamethoxazole-trimethoprim would not be appropriate. Administration of drugs with a high binding affinity for albumin, such as the sulfonamides, during the neonatal period can result in competition with bilirubin for binding sites. The resulting increase in unbound bilirubin can lead to kernicterus, neurologic damage caused by deposition of bilirubin in the brain, primarily in the basal ganglia.[21] For this reason, sulfonamides are not recommended for neonates and are not approved by the FDA for use in infants younger than age 2 months. Ceftriaxone, another possible option for C.B., also is known to be highly protein bound. Although approved for use in neonates, it is contraindicated in those with hyperbilirubinemia. As a precaution, many hospitals restrict its use in the neonatal population to only those patients who have infections resistant to other antibiotics.

Table 102-2

Examples of Drugs Present in Greater Unbound Concentrations in Neonates Than in Adults

Alfentanil	Penicillin G
Ampicillin	Phenobarbital
Ceftriaxone	Phenytoin
Cefuroxime	Propranolol
Diazepam	Salicylates
Digoxin	Sulfonamides

Alfentanil	Penicillin G
Lidocaine	Theophylline
Ketamine	Valproic acid
Morphine	
Nafcillin	

The clinical impact of changes in protein binding can be difficult to predict. Separation and measurement of the unbound (free) fraction can be used to guide therapy for drugs such as valproic acid or phenytoin, but this process is more labor-intensive and expensive and, as a result, may not be available at all hospitals. Larger blood sample volumes may also be required, which can lead to excessive blood loss in premature infants. An estimation of the unbound concentration can be made from total serum drug concentrations but may not be accurate in infants. Methods to estimate unbound serum valproic acid concentrations from total concentrations that were developed for adults have been found to be ineffective in predicting free levels in neonates and infants.[22]

Metabolism

Much of the research currently being conducted in developmental pharmacology is focused on changes in metabolic function.[7,8,12,23–50] Our understanding of the ontogeny of metabolic enzymes is improving rapidly, because in vitro data gathered from studies quantifying hepatic microsomal proteins and determining levels of enzymatic activity are combined with information obtained through pharmacokinetic and pharmacogenomic research. It is clear that the onset of function varies among enzymes; whereas some exhibit metabolic activity in utero, others demonstrate activity only after several months of life. The development of metabolic enzyme function continues during the first years of life and does not appear to be complete until after puberty. There appears to be considerable interpatient variability. Enzyme development can be affected by the

underlying health of the child, nutritional status, and exposure to substrate. Metabolic activity also reflects genetic polymorphisms, just as in adults.

PHASE I DRUG METABOLISM

CASE 102-4

QUESTION 1: N.M. is a 3.04-pound (1.38-kg), 3-week-old female who was born at 28 weeks' gestational age. She has recently been started on nasogastric feedings but has had repeated episodes of emesis and is not producing regular stools. Erythromycin is recommended to increase her gastric motility.

What can you tell your team about the ability of N.M. to metabolize this drug? What dose of erythromycin would you recommend for N.M.?

Phase I reactions, which include oxidation, reduction, hydroxylation, and hydrolysis, develop at varying rates during childhood, resulting in the wide range of half-lives reported for many drugs. The cytochrome P-450 (CYP) 3A enzymes, which play a major role in drug metabolism, including that of erythromycin, develop early in life.[7,8,12,23–28] The earliest isozyme in this group to show activity is CYP3A7, the primary metabolic enzyme present in utero. It has been found on the endoplasmic reticulum of fetal hepatocytes by the end of the first trimester and serves a role in the transformation of fetal dehydroepiandrosterone and the detoxification of retinoic acid derivatives transferred from maternal serum across the placenta.[23,24,26–28] Enzymatic activity of CYP3A7 declines rapidly after birth, with a 50% reduction during the first month of life. Levels continue to decline at a slower rate through the next 6 months and are typically undetectable after age 1 year. As levels of CYP3A7 decline, CYP3A4 and CYP3A5 levels rise. Although present during fetal development, the level of CYP3A4 activity is nearly 100-fold less than that of CYP3A7 until after birth.[23,28] Increases in CYP3A4 occur over the first months of life, often reaching levels of enzymatic activity higher than that seen in adults during early childhood.

Development of CYP3A5 function is highly variable among infants and children and does not appear to be related to patient age.

It can be anticipated that N.M. will have a slower rate of erythromycin metabolism as a result of lower levels of CYP3A4 activity, so a more conservative approach to dosing is often used. An oral erythromycin dose of 7 mg (5 mg/kg) given every 8 hours would be an appropriate starting dose for N.M. In addition to increasing the risk for adverse effects, higher serum erythromycin concentrations can lead to greater inhibition of CYP3A4. This may place N.M. at risk for toxicity from accumulation of other drugs metabolized via CYP3A4, such as fentanyl and midazolam.

Upregulation of CYP2D6 appears to begin in the last stage of gestation as a part of the complex transition of the baby to extrauterine life.[23–25,29] In fetal liver tissue samples obtained early in gestation, CYP2D6 activity has been reported to be only 1% to 5% of adult values.[23] Earlier studies suggested that levels of enzymatic activity remained low during infancy, but more recent research has demonstrated that CYP2D6 activity increases rapidly during the third trimester, and by the second week of life, values are similar to values in adults.[24] CYP2D6 levels remain relatively constant throughout childhood. The impact of genetic polymorphisms of CYP2D6 on elimination half-life in children is comparable to that demonstrated in adults and appears to play a greater role in determining metabolic function than ontogeny.[24,25,27] A study of atomoxetine response in children and adolescents with ADHD found that CYP2D6-poor metabolizers had greater increases in heart rate and blood pressure and impaired weight gain compared with extensive metabolizers taking comparable doses, reflecting higher serum concentrations with the poor metabolizer phenotype.[30]

The enzymatic activity of CYP2C9 and CYP2C19 develops throughout childhood.[23,24,31] Studies of fetal hepatocytes demonstrated CYP2C9 activity at only 1% of adult values from 8 to 24 weeks' gestation, with an increase from 10% to 20% between 25 and 40 weeks. Enzyme activity continues to increase after birth, reaching 25% of adult values by approximately age 5 months. Unlike other enzymes, CYP2C9 activity remains at only 50% of adult values

until after puberty. The development of CYP2C9 activity is illustrated by the change in the rate of metabolism of phenytoin with advancing age. The apparent (calculated Michaelis–Menten) half-life of phenytoin in premature infants is ~75 hours, compared with 20 hours in a term neonate and 8 hours in a 2-week-old.[32]

Development of CYP2C19 function also occurs in utero, with enzyme activity 10% to 20% that of adults at birth.[24] Enzymatic activity increases gradually during the first 3 months of life to near-full adult values. As with CYP2D6, genetic polymorphisms for CYP2C9 and CYP2C19 play an important role in determining individual patient response. Population modeling of pantoprazole pharmacokinetics in term neonates and premature infants revealed a longer elimination half-life than that reported in adults, supporting the lower levels of CYP2C19 activity in this age group.[33] The study also demonstrated significantly greater drug concentrations in the patients who had the poor metabolizer genotype.

The ontogeny of CYP2E1 has been studied in conjunction with the ability of infants to metabolize acetaminophen. Fetal hepatic CYP2E1 concentrations are typically undetectable during the first trimester, but begin to increase during the second trimester.[34] Levels are ~10% to 20% of adult values at birth. Enzyme concentrations continue to increase at a more gradual pace, until by age 3 months, CYP2E1 expression becomes similar to that in adults. The increase in CYP2E1 metabolic capacity, along with maturation of glucuronidation, is responsible for the changing patterns of acetaminophen metabolite formation during infancy.

Case 102-4, Question 2: N.M. is now tolerating her enteral feedings and was recently extubated. However, she has had increasing episodes of apnea, a pause in breathing of 20 seconds or greater frequently present in premature newborns, during the past 2 days. Based on current dosing guidelines, you have recommended a caffeine citrate loading dose of 20 mg/kg given IV to be followed by a maintenance dose of 5 mg/kg given once daily to treat her apnea.[35] While reviewing the dosing information, you note that the elimination half-life for caffeine in neonates is ~70 to 100 hours, whereas the half-life for older infants, children, and adults is only 5 hours. What would explain that dramatic difference in half-life?

The changing elimination half-life of caffeine reflects the onset and maturation of CYP1A2 activity. The metabolism of caffeine during infancy has been extensively studied because many neonates are exposed in utero as a result of maternal intake, and premature infants often receive caffeine for the treatment of apnea.[23,24,35,36] Studies have shown that CYP1A2 activity is negligible in fetal liver tissue and in newborns who were not exposed to it in utero.[36] The lower levels of enzymatic activity result in a longer caffeine half-life and allow once-daily dosing.[37] In contrast, newborns exposed to caffeine during gestation have higher levels of CYP1A2 activity at birth. Enzymatic activity rises progressively during the first months of life. By age 6 months, it may exceed adult values, giving the infant a caffeine half-life of only 4 to 5 hours and necessitating more frequent dosing.

Case 102-4, Question 3: While N.M. was receiving mechanical ventilation during her first weeks of life, she was sedated with an infusion of midazolam. Many IV products, including some brands of midazolam, contain benzyl alcohol as a preservative and are labeled "Not for Use in Infants." What is the rationale for restricting the use of benzyl alcohol in the neonatal population?

Alcohol dehydrogenase, another phase I enzyme, is present in utero, but in concentrations <5% of adult values.[24] Enzymatic activity does not approach functional maturity until approximately age 5 years. The lack of alcohol dehydrogenase activity has a profound impact on the ability of newborns to metabolize benzyl alcohol, a common preservative in injectable drug products. In 1982, five neonates died after developing gasping respirations that progressed to respiratory failure, severe metabolic acidosis, renal and hepatic failure, thrombocytopenia, and cardiovascular collapse.[38] All of the infants had been repeatedly exposed to benzyl alcohol as a preservative in IV flush solutions. This toxicity, termed *gasping syndrome*, resulted from accumulation of the parent compound, as well as the benzoic acid metabolite. Another series of ten patient deaths was reported from a second institution.[39] From these case series, the threshold for toxicity was estimated to be a total daily

exposure of 99 mg/kg/day. Within months of these reports, the FDA issued a safety alert calling attention to this reaction and recommending use of preservative-free products or preparations with alternative preservatives in newborns.[40] This change in practice led to the virtual elimination of gasping syndrome and brought to light the significance of differences in neonatal metabolism on drug toxicity. Pediatric clinicians continue to be vigilant for benzyl alcohol exposure, because several drugs routinely used in premature and critically ill neonates are not available in preservative-free preparations.[41]

PHASE II DRUG METABOLISM

Phase II reactions, including glucuronidation, sulfation, and acetylation, also undergo change throughout childhood. Present in low levels in fetal hepatic and renal tissues, the uridine 5′-diphosphate glucuronosyltransferase (UGT) enzymes responsible for the glucuronidation of both drugs and endogenous substances have minimal metabolic activity. A gradual increase in UGT expression occurs in the first 6 months of life, but still remains lower than that of adults for the first 2 to 3 years of life. Genetic polymorphisms produce additional variation in UGT expression.[12,23,24,42–45] The reduced ability of infants to perform glucuronidation has been known for many years as a result of the chloramphenicol "gray baby syndrome." Chloramphenicol was a widely used antibiotic during the 1950s. Within several years of its introduction, case reports began to appear in the medical literature describing emesis, abdominal distension, and cyanosis followed by cardiovascular collapse in infants given the drug.[47] The mechanism for this toxic effect was later found to be reduced activity of UGT2B7, the primary enzyme responsible for chloramphenicol metabolism, that allowed accumulation of the parent compound.[24,42]

Case 102-4, Question 4: N.M. also received morphine as an infusion during mechanical ventilation. Careful attention is needed when administering opioids to neonates to avoid drug accumulation. What differences in metabolism might

affect the dosing requirements of morphine in the premature neonate such as N.M.?

Glucuronidation of morphine to morphine-6-glucuronide and morphine-3-glucuronide via UGT2B7 can be demonstrated in premature neonates born as early as 24 weeks' gestational age, but at a much slower rate than that of term neonates.[24,44,48,49] Studies of fetal liver microsomes have confirmed the presence of UGT2B7, with a rate of enzymatic activity only 10% to 20% of adult values.[23] Morphine metabolism increases rapidly during the last trimester of intrauterine life and the first weeks after birth. Clearance has been estimated to increase fourfold between 24 and 40 weeks' postconceptional age, but remains substantially slower than that of adults until approximately age 3 years.[48,49]

Sulfation is a more important pathway in the metabolism of morphine during early infancy than later in life. Unlike UGT enzymes, sulfotransferases (SULTs) develop extensively in utero, reaching levels of enzyme activity similar to that of adults at birth.[23,24,50] Intrauterine expression of SULT1A1, which is responsible for fetal metabolism of thyroid hormones, SULT2A1, the enzyme that metabolizes steroid hormones, and SULT1A3, which metabolizes catecholamines, occurs early in gestation and remains relatively constant thereafter. Not all SULT enzyme development takes place in the liver. Expression of SULT2A1 occurs primarily in the fetal adrenal gland.

The reliance on sulfation during infancy is found with several drugs besides morphine, including catecholamines, thyroid hormones, theophylline, and acetaminophen. Glucuronidation of acetaminophen via UGT1A6 and UGT1A9 is decreased in infants, and as a result, the primary route of acetaminophen metabolism is the formation of sulfate conjugates for the first year of life.[24,46] Glucuronide pathways begin to predominate later in infancy and eventually surpass sulfation as the predominate route for acetaminophen metabolism.

Because of the slower rate of morphine clearance in neonates, particularly those born prematurely, morphine should be initiated at lower doses than those recommended for older infants and children.

An appropriate starting dose for N.M.'s morphine infusion would be 0.010 to 0.015 mg/kg/hour. N.M. should be closely monitored for adverse effects, including hypotension, respiratory depression after extubation, and constipation.

Elimination

CASE 102-5

QUESTION 1: E.C. is a 4.08-pound (1.85-kg) female born at 30 weeks' gestation. As with the other neonates described earlier, she is started on empiric antibiotic therapy with ampicillin and gentamicin shortly after birth. E.C. is given ampicillin 185 mg (100 mg/kg) IV every 8 hours and gentamicin 8.3 mg (4.5 mg/kg) IV every 36 hours. In the next bed, N.M., now 2 months old (36 weeks' corrected gestational age [GA]) and 5.73 pounds (2.6 kg), is on the same regimen for a fever and elevated white blood cell count during the past 24 hours. N.M. is given ampicillin 130 mg (50 mg/kg) IV every 6 hours and gentamicin 10.4 mg (4 mg/kg) IV every 24 hours.

What is the rationale for the differences in these patients' dosing intervals?

GLOMERULAR FILTRATION

Like the liver, the kidneys are not fully developed at birth. The ability to filter, excrete, and reabsorb substances is not maximized until age 1 year.[7,8,51,52] At birth, full-term neonates have an average glomerular filtration rate (GFR) of only 2 to 4 mL/minute/1.73 m^2; in premature infants, the value may be even lower (0.6–0.8 mL/minute/1.73 m^2). There is a rapid rise in GFR during the first 2 weeks of life, with values increasing from 20 to 40 mL/minute/1.73 m^2 as a result of increased renal blood flow, increased function of the existing nephrons, and the appearance of additional nephrons, all of which may be timed to coincide with birth.[52] GFR increases from 80 to 110 mL/minute/1.73 m^2 by 6 months of age and continues to increase in a linear manner until it approaches adult values of 100 to 120 mL/minute/1.73 m^2 by age 1 year. The impact of this increase in GFR can be seen in the neonatal dosing recommendations for many renally eliminated drugs, including the aminoglycosides and

vancomycin. To account for reduced renal function, most pediatric references use a combination of patient weight and age (postnatal, postconceptional, or postmenstrual) to determine gentamicin dosing in neonates.[18] As a premature newborn, E.C. is likely to have an increased volume of distribution (V_d) of gentamicin but significantly reduced glomerular filtration. E.C.'s gentamicin regimen will consist of a larger neonatal dose to account for the V_d (4.5 mg/kg) given at a less frequent interval 36 hours than that of 2-month-old N.M. to compensate for her renal insufficiency.

TUBULAR SECRETION

The elimination of ampicillin is also affected by changes in the rate of tubular secretion.[7,8,51] Like GFR, tubular secretion is reduced immediately after birth, but gradually increases during the first year of life. In addition to the penicillins, a reduction in tubular secretion results in a prolonged elimination half-life for cephalosporins, furosemide, and digoxin. Digoxin has been used for many years in the management of supraventricular tachycardia in neonates. The half-life of digoxin decreases from ~30–40 hours in a term neonate to 20–25 hours in a 1-year-old as renal function matures. Selection of a digoxin dose must take into account the difference in elimination. The recommended oral digoxin maintenance dose for a neonate is 5 µg/kg/day, whereas a 2-year-old would need to receive twice that amount to achieve target serum digoxin concentrations.[53] Ampicillin doses are typically adjusted by lengthening the dosing interval to compensate for reduced tubular secretion. E.C. (a newborn delivered at 30 weeks' gestation) would be dosed every 8 hours, whereas an older child such as N.M. would be expected to clear ampicillin more rapidly and would be dosed every 6 hours.

CASE 102-5, QUESTION 2: How should renal function be assessed in E.C. and N.M.?

As with adults, renal function should be closely monitored in children and drug doses adjusted accordingly. Unlike adults, blood

urea nitrogen and serum creatinine values are not always useful as indicators of renal function. In the first days after birth, serum creatinine values reflect maternal creatinine transferred through the placenta and may appear falsely elevated. After the first week, serum creatinine values are typically low as a result of less muscle mass, especially in premature neonates, and may not accurately represent renal function.[8] Urine output is often used as an additional measure of renal function in this population. Diaper weights can be used to estimate output in E.C. and N.M., with values >1 mL/kg/hour considered adequate renal function. At the time of initiation of therapy, if both babies are maintaining urine output values >1 mL/kg/hour, the dosing regimens recommended in the *Pediatric Dosage Handbook*[18] can be used without further alteration. If urine output falls, the dosing intervals of both antibiotics may require adjustment. A trough serum gentamicin concentration should be obtained to further guide dosing.

CASE 102-6

QUESTION 1: H.G. is a 10-year-old male admitted with osteomyelitis in his left ankle. The team plans to treat H.G. with vancomycin for 6 weeks. He is 55.11 inches (140 cm) tall and weighs 70.55 pounds (32 kg). His serum creatinine is 0.5 mg/dL (normal for age 0.5–1.0 mg/dL).

What is H.G.'s creatinine clearance?

After infancy, serum creatinine may be used to estimate clearance. The equations used in adults, such as Cockroft–Gault, Jelliffe, or the Modification of Diet in Renal Disease (MDRD), are not appropriate for patients younger than age 18 years.[8,54,55] There are several equations designed for pediatric use; the National Kidney Disease Education Program (NKDEP) and the National Kidney Foundation recommend the bedside isotope dilution mass spectroscopy (IDMS) Schwartz equation[54]:

$$CL_{Cr} = (0.14 \times Ht) / S_{Cr} \qquad \text{(Eq. 102-1)}$$

where CL_{Cr} is creatinine clearance (mL/minute/1.73 m^2), Ht is height (cm), and S_{Cr} is serum creatinine (mg/dL).

Using this method, H.G. has a calculated creatinine clearance of 116 mL/minute/1.73 m^2, indicating normal renal function. As with patients of any age, this equation should be used only as an estimate of renal function. It should be interpreted with caution in patients with little muscle mass or those who are dehydrated.

Pharmacokinetic Changes During Puberty

CASE 102-7

QUESTION 1: A.M. is a 16-year-old, 147.71-pound (67-kg) male with osteosarcoma. He has received morphine for pain throughout his numerous hospitalizations for surgery and chemotherapy during the past 2 years, requiring an infusion rate as high as 0.5 mg/kg/hour. During this period, he has also progressed through puberty and is now a mature adult male. During his last admission, it was noted that his pain was well controlled on an adult morphine infusion rate of 10 mg/hour, equivalent to 0.15 mg/kg/hour. It was noted by the medical team that A.M.'s morphine infusion requirements were actually lower than in earlier admissions, although his pain scores have been unchanged.

What might explain the change in A.M.'s response to morphine?

Although developmental pharmacology has traditionally focused on the differences in neonatal pharmacokinetics, there is growing interest in the influence of puberty on drug disposition.[56–58] Adolescence is not simply a link between childhood and adulthood, but is a distinct period of significant physiologic change. Hormonal fluctuations and sexual maturation can alter the efficacy or toxicity of many drugs administered during this period. Drug distribution can be altered as a result of an increase in body fat. Rapid increases in serum protein concentrations that occur during puberty alter drug-binding characteristics.[57] Renal function, as measured by GFR, may exceed average adult values, resulting in rapid clearance of renally eliminated drugs such as aminoglycosides and vancomycin. Metabolic activity changes as well.[58] A study conducted in

adolescents receiving morphine during a sickle cell crisis revealed a reduction in drug clearance with advancing sexual maturation.[59] Postpubertal adolescents, such as A.M., had weight-normalized clearance values 30% lower than younger patients during early puberty, suggesting a possible reduction in UGT2B7 activity. The titration of A.M.'s morphine must encompass not only the changes in drug clearance resulting from growth and development but also the progression of his disease and his need for pain control. Assessment of pain, using frequent self-report or a standardized pain scale, as well as heart rate, blood pressure, and respiratory rate, is essential for appropriate adjustment of A.M.'s morphine infusion.

A second example comes from a recent study of lopinavir pharmacokinetics in children who exhibited identified age- and sex-related differences in drug clearance.[60] When normalized for weight, there was no significant difference in clearance between prepubertal boys and girls. After age 12 years, males had a mean rate of lopinavir clearance 39% greater than females. The area under the concentration–time curve in boys was only half that of the girls. The authors suggest that this difference may reflect a reduction in CYP3A4 in girls that becomes apparent only with sexual maturation. Similar sex-related results have been reported in lopinavir studies conducted in adults. Caffeine metabolism via CYP1A2 has also been found to differ by sex in adolescents.[61] The rate of *N*-demethylation slows in both sexes after puberty, but appears to decrease earlier in puberty for females than for males. Other investigators have identified pharmacokinetic changes during adolescence with acetaminophen, alprazolam, carbamazepine, digoxin, isoniazid, lamotrigine, lorazepam, and theophylline.[57]

PEDIATRIC PHARMACODYNAMIC DIFFERENCES

Although not as well studied as pharmacokinetics, developmental changes in pharmacodynamics during growth may have equally significant effects on response to drug therapy in children.

CASE 102-8

QUESTION 1: S.L. is a 1.60-pound (0.725-kg) male with an estimated gestational age of 24 weeks. He was brought to the neonatal intensive care unit immediately after birth with severe hypotension. A dopamine infusion was started at a rate of 10 µg/kg/minute and quickly titrated to 20 µg/kg/minute without significant benefit.

What might explain S.L.'s lack of response, and how should his hypotension be managed?

Maturational changes in receptor conformation, density, and affinity, as well as signal transduction, can result in clinically significant differences in response to common therapies.[62] Although a dopamine infusion of 20 µg/kg/minute will produce an adequate increase in myocardial contractility and elevate systemic vascular resistance in most children and adults, infants may not have a significant change in cardiovascular response. Infants have long been suspected to be relatively resistant to the effects of β-adrenergic agonists, including dopamine, dobutamine, and epinephrine. Recent research suggests the lack of response is related to a relative reduction in adrenergic receptor density or a downregulation of receptors within the myocardium of premature and critically ill neonates.[63] A higher dopamine infusion rate, up to 40 µg/kg/minute, may be necessary to achieve an adequate blood pressure for S.L. If the dopamine is increased, S.L.'s extremities must be closely monitored for any signs of excessive peripheral vasoconstriction. Supplemental therapy with stress dose hydrocortisone, at a dose of 0.7 mg (1 mg/kg) IV every 8 hours, may also be used to manage his hypotension.

CASE 102-9

Question 1: You will be counseling the parents of E.S., a 7-year-old female with refractory seizures as a result of Lennox–Gastaut syndrome, on the use of lamotrigine. While preparing for your discussion, you notice in the manufacturer's prescribing information a black-box warning regarding the risk for serious skin rashes. The incidence is listed as 0.8% in children ages 2 to 16 years but only 0.3% in adults.[64]

What might explain the difference in the incidence of an adverse effect by age?

Differences in pharmacodynamics resulting from growth and development can alter more than just therapeutic response. A drug's adverse effect profile may be distinctly different during childhood. A classic example of this phenomenon is the higher incidence of serious dermatologic reactions, including toxic epidermal necrolysis, in children taking lamotrigine compared with that of adults.[65–67] This was first suspected during initial pediatric clinical trials and appeared to be associated with rapid dose titration during the first several months of treatment, which had been based on previous studies in adults.[66] The slower dose escalation, now recommended for pediatric patients, is starting E.S.'s lamotrigine dose at 0.15 mg/kg/day and increasing by 0.15- to 0.3-mg/kg/day increments every 2 weeks, and may reduce the likelihood for these reactions.

Case 102-9, Question 2: What is the possible mechanism(s) for the increased risk for toxicity with lamotrigine in children such as E.S.?

Research has led to several theories for the greater incidence of serious dermatologic reactions in children. Some investigators have suggested that this is a dose-related toxicity more evident in children who have a limited capacity to metabolize lamotrigine through glucuronidation to its inactive metabolites.[66] This theory, however, does not explain why other patient groups known to have higher serum lamotrigine concentrations during treatment, such as the elderly, are not at increased risk. Others have speculated that this represents an immune-mediated hypersensitivity response, because many of the affected patients reported have had previous reactions

with other antiepileptic drugs.[67] Children with refractory seizures, such as those with Lennox–Gastaut syndrome, who are often treated with multiple agents beginning in the first years of life may be more likely to develop hypersensitivity. Although the mechanism underlying the age-related difference in the incidence of lamotrigine-associated rashes is not yet well understood, the importance of patient counseling is clear. The caregivers of all children receiving lamotrigine should be made aware of the risk and the need to seek medical care as soon as any signs of rash or erythema are noted.

MEDICATION DOSING IN CHILDREN

CASE 102-10

QUESTION 1: A.K. is a 7-year-old, 44.09-pound (20-kg) male recently diagnosed with ADHD. After developing insomnia when treated with methylphenidate, he was switched to clonidine by his pediatrician. The recommended starting dose for clonidine in children is 5 µg/kg/day divided and given in two to four doses.[68] His prescription is for clonidine 0.05 mg by mouth twice daily. Because A.K. does not yet swallow tablets easily, he will need a solution made from the tablets. It will be prepared from a published extemporaneous formulation with a final concentration of 0.1 mg/mL.

What steps are necessary to ensure the accuracy of this prescription?

The differences in pharmacokinetics and pharmacodynamics observed in children influence the choice of dose and dosing interval.[69] Because incorporating all of these variables would result in dosing calculations too difficult for practical use, weight has traditionally been chosen as the single best estimate of growth. Pediatric drug references provide most doses in units per weight, such as mg/kg/day or µg/kg/dose. Among the exceptions to this are chemotherapeutic agents, which are dosed by body surface area, incorporating height as an additional variable. Because of the difficulty in accurately determining height (or length) in young children, it is not commonly used for other drugs.

Age can be an important variable, especially for premature infants, in whom it can be used to account for differences in volume of distribution and elimination half-life. For example, neonatal gentamicin dosing is often based on a rubric of gestational or postconceptional age, postnatal age, and weight.[18] A recent study of clonidine clearance in the early postnatal period suggests that both age and weight should be used to optimize clonidine doses in newborns being treated for neonatal abstinence syndrome.[70] In the future, pediatric dosing recommendations for many drugs may be based on more than just weight to incorporate new pharmacokinetic data.[71]

Medication orders or prescriptions with doses outside of the dosing range listed in a pediatric drug reference should always be questioned for appropriateness. Older children and adolescents should transition to adult dosing whenever the calculated weight-based dose exceeds the usual adult dose. When evaluating a pediatric prescription or medication order, determining whether the dose is appropriate for the patient's weight is not the only step undertaken by the pharmacist. As with all patients, allergies, underlying diseases, and concomitant therapy must be taken into account as well.

A.K.'s clonidine dose of 0.05 mg twice daily is equivalent to 5 µg/kg/day, the appropriate starting dose for a child. Using a 0.1-mg/mL extemporaneous solution, his dose will be 0.5 mL twice daily. The label on A.K.'s clonidine bottle should include the concentration of the formulation, as well as the dose in both mg and mL. Before the start of treatment, A.K.'s parents should be counseled about the drug, the dose, and potential adverse effects. They should be given or have access to an oral dosing syringe to accurately measure the dose.

PREVENTING MEDICATION ERRORS IN CHILDREN

Case 102-10, Question 2: After 2 days of therapy, A.K. returns to his pediatrician's office with his parents. He is lethargic and feels dizzy when getting out of bed. His blood pressure is 90/54 mm Hg (normal for age and weight is 99/59 mm Hg), suggesting a possible clonidine overdose. As you begin to investigate the potential cause of A.K.'s symptoms, what factors may have led to an error in A.K.'s case?

Medication errors pose a significant risk for infants and children.[72–76] Although the rate of medication errors reported in studies of adults is ~5%, rates in many pediatric studies have ranged from 10% to 15%.[72–74] The need to calculate weight-based doses can lead to mathematic errors. In A.K.'s case, the dose must be multiplied by the patient's weight, divided into individual doses, and converted from micrograms to milligrams. Unit conversions and decimal point errors are particularly dangerous in pediatrics, because a 10-fold overdose of a drug with a narrow dosing range such as clonidine, digoxin, morphine, or fentanyl can be fatal.[77] In addition to prescribing errors, dosage formulation manipulation, such as the preparation of an extemporaneous liquid in this case, increases the risk for drug preparation errors. Oral liquid medications also present a risk for administration errors. Health care providers and caregivers in the home must be aware of the potential for errors and the need for precise dose measurement. A.K.'s medical history must include information on how the clonidine had been prepared by the pharmacy as well as how his parents were preparing and administering his doses.

Case 102-10, Question 3: What steps could have been taken to prevent the medication error that occurred with A.K.?

There are a number of methods to reduce the potential for medication errors, including recommendations from the Joint Commission, the American Academy of Pediatrics, and a recent Cochrane review (**Table 102-3**).[75,76,78–83] Use of standard concentrations for IV products and oral liquids, smart-pump technology, bar coding, and electronic prescribing with clinical

decision support tools have been found to significantly reduce errors in pediatric hospitals. In the outpatient setting, medication errors can be reduced by the inclusion of patient-specific information on prescriptions, including diagnosis and patient weight.[84] The product label, whether it is a prescription or over-the-counter medication, should include all the information needed to correctly prepare and administer the dose. Caregivers should have access to the appropriate tools for measuring liquid medications, such as oral dosing syringes, and the opportunity to practice preparing a dose under the supervision of a health care provider to ensure that they are able to prepare the dose correctly.[85]

Table 102-3

Methods for Reducing Pediatric Medication Errors

Improve Ordering and Preparation
Perform careful medication histories, including assessment of oral liquid concentrations
Provide access to current pediatric medication information
Include patient weight (in kg) on all medication orders and prescriptions
Include dosage calculations on orders and prescriptions
Limit the number of concentrations available for high-risk medications
Use accurate measuring devices in both the hospital and home settings
Implement Appropriate Technology
Adopt weight-based electronic prescribing or dose-checking software
Employ barcode technology to reduce patient identification and medication administration errors
Use smart-pump technology (programmable IV pumps with weight-based dosing limits)
Use Staff Expertise
Provide pediatric-specific continuing education for all staff on a routine basis
Develop pediatric-specific medication orders and protocols to guide care
Assign staff with pediatric expertise to all committees involved in medication management

Improve Ordering and Preparation
Involve Families and Other Caregivers
Encourage all caregivers to ask questions about their child's medications
Recommend that all caregivers know the names and doses of their children's medications or carry information about their medications
Remind caregivers to include nutritional supplements, herbal or complementary therapies, and over-the-counter medications when giving a medication history
Ensure that caregivers can accurately prepare the medication dose

IV, intravenous.

One of the most effective methods to prevent medication errors has been to include pharmacists in the medication ordering and review process.[84,86] The value of pharmacists in reducing pediatric medication errors was demonstrated by Folli et al.[86] In this landmark study, clinical pharmacists performed prospective evaluations of medication orders at two children's hospitals for a 6-month period. The overall rate of medication errors detected by the pharmacists averaged 4.7 per 1000 medication orders. Of these, 5.6% were considered potentially lethal. The majority of the errors (64.3%) occurred in children younger than age 2 years. The most common type of error identified by the pharmacists was incorrect dosage. The authors concluded that pharmacy intervention had a significant effect on medication error prevention, a finding that resulted in the expansion of pediatric clinical pharmacy services in many institutions. Pharmacists in the community provide the same benefit when reviewing pediatric prescriptions and play a significant role in caregiver medication education.

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. Qato and colleagues[87] conducted a descriptive analysis of prescription data collected from 2009 to 2014. They found that 8.2% of children receiving two or more medications (N = 301) were at risk of a major drug–drug interaction when their medications were entered into a drug interaction database. This demonstrated the need for

pharmacist to perform a comprehensive medication review for patients when new medications are added into their regimen.

INCREASING AVAILABILITY OF PEDIATRIC MEDICATION INFORMATION

Case 102-10, Question 4: Although the dose of clonidine for the treatment of ADHD is available in most pediatric dosing references, it is not found in the manufacturer's prescribing information (package insert) for the drug because the treatment of ADHD is not currently an FDA-approved indication. What is being done to increase the availability of pediatric drug information?

Although the availability of pediatric drug information has been limited in the past, several recent initiatives from the FDA are increasing the number of clinical trials being conducted in infants and children. The Pediatric Exclusivity Program, part of the FDA Modernization Act of 1997, was developed to address the lack of pediatric study data, including medication prescribing information.[8,88–90] The Exclusivity Program provides pharmaceutical manufacturers with incentives to study their products in children, including a 6-month extension at the end of a drug's patent life if a pediatric study is conducted. The 1998 Pediatric Rule and the Research Equity Act of 2003 authorized the FDA to require that manufacturers conduct clinical trials of drugs that would be used in a significant number of patients. The Best Pharmaceuticals for Children Act supplements the previous incentives by the creation of a mechanism for funding studies of older, off-patent medications that are often used in children.

These programs have been successful in adding pediatric dosing and adverse effect information to the prescribing information of many drugs routinely used in children. As of June 2021, the FDA had issues 520 written request for pediatric studies, and greater than 250 drugs had been granted a patent extension under the exclusivity Program. An assessment of the first 7 years of the program found

that 50% of the studies conducted resulted in the new information supporting the use of the drug in children.[87] In spite of this success, much work remains to be done. Modifications in clinical trial design to incorporate pharmacogenomic studies and the use of combined pharmacokinetic–pharmacodynamic analyses have been recommended to further refine our knowledge of drug disposition in children.[89,90] The emphasis on the needs of pediatric patients has not been limited to just the United States; similar programs are in place in the European Union and throughout Asia. With the growing interest in developmental pharmacology and pharmacogenomics, as well as the increased funding and support for pediatric clinical trials worldwide, our understanding of the unique differences in how children respond to drug therapy continues to improve.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349:1157–1167. (7)

Leeder JS, Kearns GL, Spieiberg SP, van den Anker J. Understanding the relative roles of pharmacogenetics and ontogeny in pediatric drug development and regulatory science. *J Clin Pharmacol.* 2010;50:1377. (25)

Maaskant JM, Vermeulen H, Apampa B, et al. Interventions for reducing medication errors in children in hospital. *Cochrane Database Syst Rev*. 2015;3:CD006208. (76)

MacLeod S. Therapeutic drug monitoring in pediatrics: how do children differ? *Ther Drug Monit.* 2010;32:253. (90)

Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20:629. (55)

Taketomo CK, Hodding JH. Gentamicin. In: Taketomo CK, ed. *Pediatric Dosage Handbook*. 28th ed. Lexi-Comp; 2021. (18)

Key Websites

American Academy of Pediatrics. Ages and stages. http://www.healthychildren.org

The Joint Commission. Sentinel event alert 39: preventing pediatric medication errors. Published April 11, 2008. Accessed July 12, 2017. http://www.jointcommission.org/sentinel_event_alert_issue_39_preventing_pediatric_medication_errors/ (75)

U.S. Department of Health and Human Services; Food and Drug Administration. Pediatric drug development. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm (88)

COMPLETE REFERENCES CHAPTER 102 PEDIATRIC PHARMACOTHERAPY

1. U.S. Census Bureau. Quick fact statistics: population estimates July 1, 2021. Accessed March 24, 2021. https://www.census.gov/quickfacts/US
2. Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. Medication use among children <12 years of age in the United States: results from the Slone Survey. *Pediatrics*. 2009;124:446–454.
3. American Academy of Pediatrics Division of Health Policy Research. Many patients don't comply with prescription regimens: survey. AAP news. 2001;18(5):213.
4. Frattarelli DA, Galinkin JL, Green TP, et al. Off-label use of drugs in children. *Pediatrics*. 2014;133:563–567.
5. Young L, Lawes F, Tordoff J, Norris P, Reith D. Access to prescribing information for paediatric medicines in the USA: post-modernization. *Br J Clin Pharmacol*. 2009;67:341–346.
6. Bazzano AT, Mangione-Smith R, Schonlau M, Suttorp MJ, Brook RH. Off-label prescribing to children in the United States outpatient setting. *Acad Pediatr*. 2009;9:81–88.
7. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349:1157–1167.
8. Lu H, Rosenbaum S. Developmental pharmacokinetics in pediatric populations. *J Pediatr Pharmacol Ther*. 2014;19:262–276.

9. Sullivan JE, Farrar HC. Clinical report: fever and antipyretic use in children. *Pediatrics*. 2011;127(3):580–587. Reaffirmed July 2016. doi:10.1542/peds.2016-2595
10. Drozdowski LA, Clandinin T, Thomson AB. Ontogeny, growth and development of the small intestine: understanding pediatric gastroenterology. *World J Gastroenterol*. 2010;16:787–799.
11. Anderson BJ, van Lingen RA, Hansen TG, Lin YC, Holford NH. Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. *Anesthesiology*. 2002;96:1336–1345.
12. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin Pharmacokinet*. 2006;45:931–956.
13. Boucher FD, Modlin JF, Weller S, et al. Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. *J Pediatr*. 1993;122:137–144.
14. Loughnan PM, McDougall PN. Does intramuscular vitamin K1 act as an unintended depot preparation? *J Paediatr Child Health*. 1996;32:251–254.
15. Thaker VV, Leung AM, Braverman LE, Brown RS, Levine B. Iodine-induced hypothyroidism in full-term infants with congenital heart disease: more common than currently appreciated? *J Clin Endocrinol Metab*. 2014;99:3521–3526.
16. Lehr VT, Cepeda E, Frattarelli DA, Thomas R, LaMothe J, Aranda JV. Lidocaine 4% cream compared with lidocaine 2.5% and prilocaine 2.5% or dorsal penile block for circumcision. *Am J Perinatol*. 2005;22:231–237.
17. Holsti M, Dudley N, Schunk J, et al. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. *Arch Pediatr Adolesc Med*. 2010;164:747–753.
18. Taketomo CK, Hodding JH. Gentamicin. In: Taketomo CK, ed. *Pediatric Dosage Handbook*. 28th ed. Lexi-Comp, Inc; 2021.
19. Harskamp-van Ginkel MW, Hill KD, Becker KC, et al. Drugs dosing and pharmacokinetics in children with obesity: a systematic review. *JAMA Pediatr*. 2015;169(7):678–685. doi:10.101/jamapediatrics.2015.132
20. Miller JL, Johnson PN, Harrison DL, Hagemann TM. Evaluation of inpatient admissions and potential antimicrobial and analgesic dosing errors in overweight children. *Ann Pharmacother*. 2010;44:35–42.
21. Ahlfors CE. Unbound bilirubin associated with kernicterus: a historical approach. *J Pediatr*. 2000;137:540–544.
22. Ueshima S, Aiba T, Ishikawa N, et al. Poor applicability of estimation methods for adults to calculate unbound serum concentrations of valproic acid in epileptic neonates and infants. *J Clin Pharm Ther*. 2009;34:415–422.
23. de Wildt SN. Profound changes in drug metabolism enzymes and possible effects on drug therapy in neonates and children. *Expert Opin Drug Metab Toxicol*. 2011;7:935–948.

24. Hines RN. The ontogeny of drug metabolism enzymes and implications for adverse drug events. *Pharmacol Ther*. 2008;118:250–267.
25. Leeder JS, Kearns GL, Spieiberg SP, van den Anker J. Understanding the relative roles of pharmacogenetics and ontogeny in pediatric drug development and regulatory science. *J Clin Pharmacol*. 2010;50:1377–1387.
26. Strougo A, Yassen A, Monnereau C, Danhof M, Freijer J. Predicting the "first dose in children" of CYP3A-metabolized drugs: evaluation of scaling approaches and insights into the CYP3A7-CYP3A4 switch at young ages. *J Clin Pharmacol*. 2014;54:1006–1015.
27. Ince I, Knibbe CA, Danhof M, de Wildt SN. Developmental changes in the expression and function of cytochrome P450 3A isoforms: evidence from in vitro and in vivo investigations. *Clin Pharmacokinet*. 2013;52:333–345.
28. Chen YT, Trzoss L, Yang D, Yan B. Ontogenic expression of human carboxylesterase-2 and cytochrome P450 3A4 in liver and duodenum: postnatal surge and organ-dependent regulation. *Toxicology*. 2015;330:55–61.
29. Blake MJ, Gaedigk A, Pearce RE, et al. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. *Clin Pharmacol Ther*. 2007;81:510–516.
30. Michelson D, Read HA, Ruff DD, Witcher J, Zhang S, McCracken J. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2007;46:242–251.
31. Koukouritaki SB, Manro JR, Marsh SA, et al. Developmental expression of human hepatic CYP2C9 and CYP2C19. *J Pharmacol Exp Ther*. 2004;308:965–974.
32. Bourgeois BF, Dodson WE. Phenytoin elimination in newborns. *Neurology*. 1983;33:173–178.
33. Ward RM, Tammara B, Sullivan SE, et al. Single-dose, multiple-dose, and population pharmacokinetics of pantoprazole in neonates and preterm infants with a clinical diagnosis of gastroesophageal reflux disease (GERD). *Eur J Clin Pharmacol*. 2010;66:555–561.
34. Johnsrud EK, Koukouritaki SB, Divakaran K, Brunengraber LL, Hines RN, McCarver DG. Human hepatic CYP2E1 expression during development [published correction appears in *J Pharmacol Exp Ther*. 2004;309:439]. *J Pharmacol Exp Ther*. 2003;307:402–407.
35. Taketomo CK, Hodding JH. Caffeine. In: Taketomo CK, ed. *Pediatric Dosage Handbook*. 28th ed. Lexi-Comp, Inc; 2021.
36. Aranda JV, Collinge JM, Zinman R, Watters G. Maturation of caffeine elimination in infancy. *Arch Dis Child*. 1979;54:946–949.
37. Charles BG, Townsend SR, Steer PA, Flenady VJ, Gray PH, Shearman A. Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. *Ther Drug Monit*. 2008;30:709–716.

38. Gershanik J, Boecler B, Ensley H, McCloskey S, George W. The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med*. 1982;307:1384–1388.
39. Brown WI, Buist NR, Gipson HT, Huston RK, Kennaway NG. Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet*. 1982;1:1250.
40. Lovejoy FH. Fatal benzyl alcohol poisoning in neonatal intensive care units. A new concern for pediatricians. *Am J Dis Child*. 1982;136:974–975.
41. Shehab N, Lewis CL, Streetman DD, Donn SM. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med*. 2009;10:256–259.
42. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans: pharmacogenetic and developmental aspects. *Clin Pharmacokinet*. 1999;36:439–452.
43. Miyagi SJ, Collier AC. Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4. *Drug Metab Dispos*. 2007;35:1587–1592.
44. Strassburg CP, Strassburg A, Kneip S, et al. Developmental aspects of human hepatic drug glucuronidation in young children and adults. *Gut*. 2002;50:259–265.
45. Allegaert K, Vanhaesebrouck S, Verbesselt R, van den Anker JN. In vivo glucuronidation activity of drugs in neonates: extensive interindividual variability despite their young age. *Ther Drug Monit*. 2009;31:411–415.
46. Allegaert K, de Hoon J, Verbesselt R, Vanhole C, Devlieger H, Tibboel D. Intra-and interindividual variability of glucuronidation of paracetamol during repeated administration of propacetamol in neonates. *Acta Paediatr*. 2005;94:1273–1279.
47. Weiss CF, Glazko AJ, Weston JK. Chloramphenicol in the newborn infant. A physiologic explanation of its toxicity when given in excessive doses. *N Engl J Med*. 1960;262:787–794.
48. Anand KJ, Anderson BJ, Holford NH, et al. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br J Anaesth*. 2008;101:680–689.
49. Knibbe CA, Krekels EH, van den Anker JN, et al. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. *Clin Pharmacokinet*. 2009;48:371–385.
50. Duanmu Z, Weckle A, Koukouritaki SB, et al. Developmental expression of aryl, estrogen, and hydroxysteroid sulfotransferases in pre- and postnatal human liver. *J Pharmacol Exp Ther*. 2006;316:1310–1317.
51. Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: modelling covariate effects. *Eur J Pediatr*. 2006;165:819–829.
52. Vieux R, Hascoet JM, Merdariu D, Fresson J, Guillemin F. Glomerular filtration rate reference values in very preterm infants. *Pediatrics*. 2010;125:e1186–e1192.

53. Taketomo CK, Hodding JH, Kraus DM. Digoxin. In: Taketomo CK, ed. *Pediatric Dosage Handbook*. 21st ed. Lexi-Comp; 2014:658.
54. National Kidney Disease Education Program. GFR calculator for children. Accessed July 12, 2017. http://nkdep.nih.gov/lab-evaluation/gfr-calculators/children--conventional-unit.asp#guidelines-for-labs
55. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20:629–637.
56. Kearns GL, Spaulding-Barclay M. Adolescent pharmacology: a pertinent issue of medicine as opposed to medicines. *Clin Pharmacol Ther*. 2008;84:639–644.
57. Carr RR, Ensom MH. Drug disposition and therapy in adolescence: the effects of puberty. *J Pediatr Pharmacol Ther*. 2003;8:86–96.
58. Kennedy M. Hormonal regulation of hepatic drug metabolizing enzyme activity during adolescence. *Clin Pharmacol Ther*. 2008;84:662–673.
59. Robieux IC, Kellner JD, Coppes MJ, et al. Analgesia in children with sickle cell crisis: comparison of intermittent opioids vs. continuous intravenous infusion of morphine and placebo-controlled study of oxygen inhalation. *Pediatr Hematol Oncol*. 1992;9:317–326.
60. Jullien V, Urien S, Hirt D, et al. Population analysis of weight, age, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob Agents Chemother*. 2006;50:3548–3555.
61. Lambert GH, Schoeller DA, Kotake AN, Flores C, Hay D. The effect of age, gender, and sexual maturation on the caffeine breath test. *Dev Pharmacol Ther*. 1986;9:375–388.
62. Mulla H. Understanding developmental pharmacodynamics: importance for drug development and clinical practice. *Paediatr Drugs*. 2010;12:223–233.
63. Noori S, Friedlich P, Wong P, Ebrahimi M, Siassi B, Seri I. Hemodynamic changes after low-dosage hydrocortisone administration in vasopressor-treated preterm and term neonates. *Pediatrics*. 2006;118:1456–1466.
64. Lamictal (lamotrigine). Prescribing information. GlaxoSmithKline; May 2015.
65. Iannetti P, Raucci U, Zuccaro P, Pacifici R. Lamotrigine hypersensitivity in childhood epilepsy. *Epilepsia*. 1998;39:502–507.
66. Hirsch LJ, Weintraub DB, Buchsbaum R, et al. Predictors of lamotrigine-associated rash. *Epilepsia*. 2006;47:318–322.
67. Aurich-Barrera B, Wilton L, Brown D, Shakir S. Paediatric postmarketing pharmacovigilance using prescription-event monitoring: comparison of the adverse event profiles of lamotrigine prescribed to children and adults in England. *Drug Saf*. 2010;33:751–763.
68. Taketomo CK, Hodding JH, Kraus DM. Clonidine. In: Taketomo CK, ed. *Pediatric Dosage Handbook*. 21st ed. Lexi-Comp, Inc; 2014:516.
69. Barbour AM, Fossler MJ, Barrett J. Practical considerations for dose selection in pediatric patients to ensure target exposure requirements. *AAPS J*. 2014;16:749–755.

70. Xie H, Cao YJ, Gauda EB, Agthe AG, Hendrix CW, Lee H. Clonidine clearance matures rapidly during the early postnatal period: a population pharmacokinetic analysis in newborns with neonatal abstinence syndrome. *J Clin Pharmacol*. 2011;51:502–511.
71. Holford N. Dosing in children. *Clin Pharmacol Ther*. 2010;87:367–370.
72. Conroy S, Sweis D, Planner C, et al. Interventions to reduce dosing errors in children: a systematic review of the literature. *Drug Saf*. 2007;30:1111–1125.
73. Ghaleb MA, Barber N, Franklin BD, Wong IC. The incidence and nature of prescribing and medication administration errors in paediatric patients. *Arch Dis Child*. 2010;95:113–118.
74. Chua SS, Chua HM, Omar A. Drug administration errors in paediatric wards: a direct observation approach. *Eur J Pediatr*. 2010;169:603–611.
75. The Joint Commission. Sentinel event alert 39: preventing pediatric medication errors. Published April 11, 2008. Accessed July 12, 2017. http://www.jointcommission.org/sentinel_event_alert_issue_39_preventing_pediatric_medication_errors/
76. Maaskant JM, Vermeulen H, Apampa B, et al. Interventions for reducing medication errors in children in hospital. *Cochrane Database Syst Rev*. 2015;3:CD006208.
77. Crouch BI, Caravati EM, Moltz E. Tenfold therapeutic dosing errors in young children reported to U.S. poison control centers. *Am J Health Syst Pharm*. 2009;66;1292–1296.
78. Stucky ER; American Academy of Pediatrics Committee on Drugs; American Academy of Pediatrics Committee on Hospital Care. Prevention of medication errors in the pediatric inpatient setting. *Pediatrics*. 2003;112:431–436.
79. Larsen GY, Parker HB, Cash J, O'Connell M, Grant MC. Standard drug concentrations and smart pump technology reduce continuous-medication-infusion errors in pediatric patients. *Pediatrics*. 2005;116:e21–e25.
80. Morriss FH Jr, Abramowitz PW, Nelson SP, et al. Effectiveness of a barcode medication administration system in reducing preventable adverse drug events in a neonatal intensive care unit: a prospective cohort study. *J Pediatr*. 2009;154:363–368.
81. Sethuraman U, Kannikeswaran N, Murray KP, Zidan MA, Chamberlain JM. Prescription errors before and after introduction of electronic medication alert system in a pediatric emergency department. *Acad Emerg Med*. 2015;22:714–719.
82. van Rosse F, Maat B, Rademaker CM, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. *Pediatrics*. 2009;123:1184–1190.
83. Ginzburg R, Barr WB, Harris M, Munshi S. Effect of a weight-based prescribing method within an electronic health record on prescribing errors.

Am J Health Syst Pharm. 2009;66:2037–2041.
84. Condren M, Honey BL, Carter SM, et al. Influence of a systems-based approach to prescribing errors in a pediatric resident clinic. *Acad Pediatr*. 2014;14:485–490.
85. Shah R, Blustein L, Kuffner E, Davis L. Communicating doses of pediatric liquid medicines to parents/caregivers: a comparison of written dosing directions on prescriptions with labels applied by dispensed pharmacy. *J Pediatr*. 2014;164:596–601.
86. Folli HL, Poole RL, Benitz WE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. *Pediatrics*. 1987;79:718–722.
87. Qato DM, Alexander GC, Guadamuz JS, Lindau ST. Prescription medication use among children and adolescents in the United States. *Pediatrics*. 2018;142(3):e20181042. doi:10.1542/peds.2018-1042
88. US Department of Health and Human Services; Food and Drug Administration. Written request issued. Assessed August 16, 2022. https://www.fda.gov/drugs/development-resources/written-requests-issued
89. Benjamin DK Jr, Smith PB, Murphy MD, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *JAMA*. 2006;296:1266–1273.
90. MacLeod S. Therapeutic drug monitoring in pediatrics: how do children differ? *Ther Drug Monit*. 2010;32:253–256.

103

Pediatric Fluid, Electrolytes, and Nutrition

Jennifer W. Chow and Lisa M. Feagin

CORE PRINCIPLES		CHAPTER CASES
1	Fluid requirements and calories normalized to body weight are much greater in very small children than in older children and adults. It is important to understand how to calculate the normal fluid and caloric needs of children, and how these needs vary with changes in clinical status.	**Case 103-1 (Question 1)** **Case 103-2 (Question 1–3)** **Case 103-3 (Question 1–3), Tables 103-1–103-5**
2	Human milk is the ideal food for a human infant. In addition to meeting the infant's nutritional requirements, human milk provides the infant with protection against a wide variety of infectious diseases and noninfectious disorders. Solid foods are generally introduced at 4	**Case 103-4 (Questions 1, 2, 4, 5)**

	to 6 months of age and cow's milk after 1 year.	
3	Infant formula is available in three different formulations: cow's milk-based, soy-based, and protein hydrolysate (elemental). Cow's milk-based formulas are standard for most infants. Soy-based and protein hydrolysate formulas are primarily intended for infants intolerant to cow's milk-based formulas. Other therapeutic formulas are available for infants with disease states that preclude the use of one of these three main types of formula.	**Case 103-4 (Question 3)** **Case 103-5 (Question 1)** **Case 103-6 (Question 2, 3)**
4	Growth assessment is an important focus of pediatric health care, especially during the first year of life. With the exception of the intrauterine period, the most rapid growth occurs during the first year.	**Case 103-6 (Question 1)**
5	Parenteral nutrition (PN) in infants and children is usually initiated below estimated caloric needs and advanced as tolerated over 3 or more days until goal caloric needs are met.	**Case 103-6 (Question 4)**
6	PN can be used to supply sufficient nutrients to promote healing and a normal growth rate in sick infants and children. However, PN is associated with clinically significant risks and complications.	**Case 103-7 (Questions 1–5, 7–9), Table 103-5**
7	Specialized pediatric amino acid	**Case 103-7 (Question**

	solutions are available for infants younger than 1 year of age. These products were designed to produce plasma amino acid patterns closely matching those of human milk-fed infants.	**6)**
8	Irreversible liver damage can occur with long-term PN. PN-associated liver disease usually presents as an elevated direct (conjugated) bilirubin level and can occur as early as 2 weeks after beginning PN.	**Case 103-7 (Question 10, 11)**
9	A number of modifications can be made to the patient's PN regimen to alleviate or slow the progression of cholestasis. The initiation of enteral feeding, even if limited to low-volume trophic feeding, appears to be the most effective method for prevention.	**Case 103-7 (Question 11)**

INTRODUCTION

Adequate nutrition is an essential component of the health maintenance of children and, in part, has dramatically reduced infant mortality seen in the United States during the 20th century. Clinical experience has confirmed the value of optimal nutrition in resisting the effects of disease and trauma and in improving the response to medical and surgical therapy. The metabolic demands of rapid growth and maturation, in addition to low nutritional reserves present during infancy, make the potential benefit of sufficient nutrition for critically ill pediatric patients even greater.

Breast-feeding is the ideal method of feeding an infant and should be continued for at least the first year of life whenever possible. When this is not feasible, various infant formulas are available that provide appropriate nutrients for infants using the oral route. A pediatric patient who has a functioning intestinal tract, but is unable to achieve adequate oral intake, can be fed enterally using a tube inserted into the stomach or small intestine. Indications for providing specialized enteral nutrition include malnutrition, malabsorption, hypermetabolism, failure to thrive, prematurity, and disorders of absorption, digestion, excretion, or utilization of nutrients.

Despite the many formulas and feeding techniques available, several medical and gastrointestinal (GI) dilemmas that limit the use of the GI tract for nutritional support can occur in infants and children. Premature infants with severe respiratory disease, congenital abnormalities of the GI tract, or necrotizing enterocolitis are typical candidates for support with parenteral nutrition (PN). Older children with short bowel syndrome, severe malnutrition, intractable diarrhea, or inflammatory bowel disease have been treated successfully with PN therapy. Pediatric patients receiving chemotherapy for the treatment of malignancies or bone marrow transplant and children with severe cardiac failure also have been successfully rehabilitated with PN.

Many disorders that adversely affect nutrient intake or absorption also have an adverse impact on fluid and electrolyte status. Consequently, fluid, electrolyte, and nutrient management should be approached in an integrated manner. This chapter reviews selected aspects of fluid and electrolyte management and nutrition therapy for the pediatric population.

FLUID AND ELECTROLYTE MAINTENANCE

Management of fluid and electrolyte disturbances involves providing normal daily maintenance requirements and replacing deficits and ongoing losses. To design rational fluid therapy, it is necessary to

know the normal composition of body water, to understand the routes through which water and solutes are lost from the body, and to know the effects of diseases and medications on water and electrolytes. Sodium-containing fluids are often referred to as fractions of normal saline (NS) (0.9% NaCl). NS contains 154 mEq/L of sodium chloride.

Calculation of Maintenance Fluid and Electrolyte Requirements

CASE 103-1

Question 1: P.J., a 2-day-old, 7.72-pound (3.5-kg) term female infant, has developed abdominal distension, and her oral feedings have been stopped. Although P.J. receives nothing by mouth (NPO), her fluid and electrolyte needs must be met intravenously. Her serum electrolytes include the following:

Sodium, 137 mEq/L
Potassium, 4.2 mEq/L
Chloride, 105 mEq/L
CO_2, 23 mEq/L

What are her estimated requirements to calculate a maintenance fluid and electrolyte prescription for her?

General recommendations for calculating maintenance fluid have not changed significantly since first outlined by Holliday and Segar in 1957.[1] However, more current dosing recommendations exist for electrolyte and nutrient replacement and are provided by the American Society for Parenteral and Enteral Nutrition.[2] Fluid, electrolyte, and nutrient requirements on the basis of weight are provided in **Table 103-1**. Although a commercially available intravenous (IV) solution will be used, each component of the solution can be calculated separately. Using the guidelines in Table 103-1, P.J.'s maintenance requirements can be estimated as follows:

Fluid $100\ \text{mL/kg/day} \times 3.5\ \text{kg} = 350\ \text{mL/day}$
or $15\ \text{mL/hour}$

Sodium $2–4\ \text{mEq/kg/day} \times 3.5\ \text{kg} = 7–14\ \text{mEq/day}$ (Eq. 103-2)(Eq. 103-1)

Potassium $2–3\ \text{mEq/kg/day} \times 3.5\ \text{kg} = 7–10.5\ \text{mEq/day}$ (Eq. 103-3)

Table 103-1
Daily Parenteral Nutrient Requirements in Children

Nutrient	Weight/Age	Requirement
Fluid	>1.5 kg	150 mL/kg
	1.5–2.5 kg	120 mL/kg
	2.5–10 kg	100 mL/kg
	10–20 kg	1000 mL + 50 mL/kg for each kg >10 kg
	>20 kg	1500 mL + 20 mL/kg for each kg >20 kg
Calories	Up to 10 kg	100 kcal/kg
	>10–20 kg	1000 kcal + 50 kcal/kg for each kg >10 kg
	>20 kg	1500 kcal + 20 kcal/kg for each kg >20 kg
Protein[a]	Preterm infants (<1 year)	3–4 g/kg
	Term infants (<1 year)	2.5–3 g/kg
	Older children (1–10 years)	1.5–2.5 g/kg
	Adolescents (>10 years)	0.8–2 g/kg
Fat[b,c]	Infants (<1 year)	Initially 0.5–1 g/kg and advance by 0.5–1 g/kg to a goal of 3 g/kg
	Children (1–10 years)	Initially 1 g/kg and advance by 1 g/kg to a goal of 1–2 g/kg
	Adolescents (>10 years)	Initially 1 g/kg and advance by 1 g/kg to a goal of 1–2 g/kg
Dextrose	Infants (<1 year)	Initially 6–8 mg/kg/minute and advance by 1–2 mg/kg/minute to a goal of 10–14 mg/kg/minute (max. 18 mg/kg/minute)

Nutrient	Weight/Age	Requirement
	Children (1–10 years)	Initially 3–6 mg/kg/minute and advance by 1–2 mg/kg/minute to a goal of 8–10 mg/kg/minute
	Adolescents (>10 years)	Initially 2.5–3 mg/kg/minute and advance by 1–2 mg/kg/minute to a goal of 5–6 mg/kg/minute
Electrolytes and Minerals[d]		
Sodium	Infants and children	2–5 mEq/kg
	Adolescents and children (>50 kg)	1–2 mEq/kg
Potassium	Infants and children	2–4 mEq/kg
	Adolescents and children (>50 kg)	1–2 mEq/kg
Chloride and acetate	Infants and children	As needed to maintain acid–base balance
Calcium	Preterm neonates	2–4 mEq/kg
	Infants and children	0.5–4 mEq/kg
	Adolescents and children (>50 kg)	10–20 mEq
Phosphorus	Preterm neonates	1–2 mmol/kg
	Infants and children	0.5–2 mmol/kg
	Adolescents and children (>50 kg)	10–40 mmol
Magnesium	Infants and children	0.3–0.5 mEq/kg

Nutrient	Weight/Age	Requirement
	Adolescents and children (>50 kg)	10–30 mEq
Trace Elements		
Zinc	Preterm neonates	400 μg/kg
	Term neonates (3–10 kg)	250 μg/kg
	Children (10–40 kg)	50 μg/kg (up to 5 mg)
	Adolescents (>40 kg)	2–5 mg
Copper	Infants and children (≤40 kg)	20 μg/kg (up to 500 μg)
	Adolescents (>40 kg)	200–500 μg
Manganese	Infants and children (≤40 kg)	1 μg/kg (up to 55 μg)
	Adolescents (>40 kg)	40–100 μg
Chromium	Preterm neonates	0.05–0.3 μg/kg
	Term neonates and children (≤40 kg)	0.2 μg/kg (up to 5 μg)
	Adolescents (>40 kg)	5–15 μg
Selenium	Infants and children (≤40 kg)	2 μg/kg (up to 100 μg)
	Adolescents (>40 kg)	40–60 μg

[a]"Infant" amino acids contain histidine, taurine, tyrosine, and cysteine, which are essential in infants but not older patients.

[b]Because linoleic acid represents 54% of the fatty acid in soybean oil and 77% in safflower oil, 7% to 10% of calories must be provided as fat emulsion. This can be given daily over the course of 24 hours (preferred in patients predisposed to sepsis and preterm infants) or two to three times weekly.

[c]Fat dosing is based on soybean oil–based emulsion. Refer to product-specific dosing for other formulations.

[d]These doses are guidelines, and all patients should be evaluated individually for appropriateness of dosing. For example, patients with short bowel syndrome may require large doses of magnesium, and patients with renal insufficiency may require none to low amounts of potassium, calcium, phosphorus, and magnesium.

Source: Fluid and Calorie portion taken from Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19(5): 823–832; Other portions taken from American Society for Parenteral and Enteral Nutrition. Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations. 2019:3. Accessed September 11, 2020. https://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/PN%20Dosing%201-Sheet-FINAL.pdf. Adapted with permission of the American Society for Parenteral and Enteral Nutrition.

Fluid and electrolyte requirements can be met by infusing a solution of 5% dextrose with one-quarter NS (38 mEq/L) and 20 mEq/L of KCl at 15 mL/hour. This provides 12 mEq (3.4 mEq/kg/day) of NaCl and 7 mEq (2 mEq/kg/day) of KCl in 360 mL (103 mL/kg/day) of fluid per day.

As shown with P.J., to provide general maintenance requirements, hypotonic IV fluids are often used in pediatrics; however, concerns have arisen regarding the risk of hyponatremia. Hospital-acquired hyponatremia can lead to hyponatremic encephalopathy and can cause permanent brain damage. To combat this, the American Academy of Pediatrics (AAP) developed a clinical practice guideline recommending the use of isotonic fluids for maintenance needs in the general pediatric population.[3] Normal serum sodium concentrations range from 135 to 145 mEq/L; thus, NS approximates the sodium concentration of plasma and is often the primary isotonic preparation used. Because of the exclusion criteria used in the studies providing support for the summative recommendations, the guideline does not include neonates younger than 28 days or admitted to the newborn intensive care unit (NICU). Therefore, this

recommendation would not apply to P.J. since she is within the first 28 days of life.

Additionally, daily fluid and electrolyte requirements may be altered when fluid and electrolyte losses are increased or when excretion is impaired. When abnormal losses are present, they must be given back to the patient daily. Replacement fluid is generally provided using NS, giving 1 mL for every 1 mL lost, but can be based on the patient's clinical status.

The requirements for fluid and calories normalized to body weight are much greater in very small children than in older children and adults, as can be seen in Table 103-1. This is because infants have a much larger body surface area relative to weight, lose more fluid through evaporation, and dissipate more heat per kilogram than their older counterparts. Furthermore, very low-birthweight (VLBW) infants cannot concentrate urine and are at an increased risk for dehydration if inadequate fluids are provided.

Dehydration

CASE 103-2

QUESTION 1: H.S. is a 2-year-old lethargic female with a 2-day history of vomiting and minimal oral intake. Yesterday, she required only three diaper changes instead of her usual eight and has needed only one change today. Her vital signs are as follows:

Temperature, 102.2 °F (39 °C)
Pulse, 140 beats/minute (normal, 80–130 beats/minute)
Respiratory rate, 30 breaths/minute (normal, 30–35 breaths/minute)
Blood pressure (BP), 80/45 mm Hg (normal, 80–115 mm Hg systolic and 50–80 mm Hg diastolic)

On physical examination, her eyes appear sunken, her mucous membranes are dry, and her skin is dry and cool to touch. Although she is crying, there are no tears, and the skin over her sternum tents when pinched. Her weight today is 25.13 pounds (11.4 kg); 3 weeks ago, it was 28.44 pounds (12.9 kg).

What do these findings represent? What immediate treatment should be provided?

H.S.'s lethargy, decreased urine output, tearless crying, dry mucous membranes, dry skin with fever, sunken eyes, mild tachycardia with low normal blood pressure, and poor skin turgor are all signs of dehydration. This is consistent with her 2-day history of vomiting and poor intake. Her weight loss of 3.31 pounds (1.5 kg) gives further evidence of the extent of dehydration. Dehydration or fluid loss is determined most accurately by weight loss. A patient's fluid deficit can be estimated using the assumption that 1 g of body weight is ≈1 mL; therefore, J.H.'s deficit can be estimated to be 1500 mL. The percentage of dehydration is estimated using the following formula:

$$\%\ \text{Dehydration} = \text{Normal body weight} - \text{Actual body weight} / \text{Normal body weight} \times 100 \qquad \textbf{(Eq. 103-4)}$$

If recent weights are unavailable, the extent of dehydration can be approximated from physical findings, as described in **Table 103-2**. Tachycardia, decreased urine output, and marginal blood pressure dictate the need for immediate IV rehydration with isotonic fluids, such as NS. In this patient, 20 mL/kg of NS (12.9 kg × 20 mL/kg = 258 mL) should be infused as rapidly as possible to establish normal blood pressure of fluid within the hour. Treatment should be repeated as necessary with monitoring of the patient's heart rate, capillary refill time, and urine output. Stabilization often requires 40 to 60 mL/kg of fluid within an hour.[4] For symptomatic patients, including those with seizures, the serum sodium concentration should be increased acutely only to the degree necessary to abate symptoms.

Table 103-2
Clinical Signs of Dehydration

Severity	Dehydration (%)	Psyche	Thirst	Mucous Membranes	Tears	Anterior Fontanel	Skin	Urine Specific Gravity
Mild	>5	Normal	Slight	Normal to dry	Present	Flat	Normal	Slight change
Moderate	6–10	Irritable	Moderate	Dry	±	±	±	Increased
Severe	10–15	Hyperirritable to lethargic	Intense	Parched	Absent	Sunken	Tenting	Greatly increased

CASE 103-2, QUESTION 2: H.S.'s serum electrolyte results were as follows:

Sodium, 128 mEq/L (normal, 135–145 mEq/L)
Potassium, 3.1 mEq/L (normal, 3.5–5 mEq/L)
Chloride, 88 mEq/L (normal, 102–109 mEq/L)
HCO_3^-, 30 mEq/L (normal, 22–29 mEq/L)

What are her fluid and electrolyte needs? What recommendations for her fluid orders would you provide to the team?

In addition to normal maintenance fluids, H.S. must be provided with fluids and electrolytes to replace her deficit secondary to dehydration and compensate for increased insensible water loss because of fever. Each component of the fluid can be calculated separately, using Eqs. 103-5 to 103-7.

$$\text{Fluid deficit} = \text{Weight loss (kg)} \times 1000\ \text{mL/kg} \quad \textbf{(Eq. 103-5)}$$

$$\text{Fever adjustment} = 10\% \times \text{Maintenance for each } ^\circ\text{C} \geq 37\ ^\circ\text{C} \quad \textbf{(Eq. 103-6)}$$

$$(\text{CD} - \text{CO}) \times F_d \times \text{Weight} = \text{mEq required} \quad \textbf{(Eq. 103-7)}$$

where CD is the concentration of sodium desired (mEq/L), CO is the concentration observed (mEq/L), F_d is the apparent distribution factor as a fraction of body weight (**Table 103-3**), and weight is the baseline weight before illness (kg). In consideration of both maintenance needs and current deficits, fluid and electrolyte requirements for H.S. would be estimated as follows.

Table 103-3
Electrolytes and Apparent Distribution

Electrolyte	F_d (L/kg)
Sodium	0.6–0.7
Bicarbonate	0.4–0.5
Chloride	0.2–0.3

F_d, apparent distribution factor as a fraction of body weight.

FLUID

$$\begin{aligned}
&\text{Maintenance} && 1000\ \text{mL} + (50 \times 2.9) = 1145\ \text{mL} \\
&\text{Fever} && 2\ ^\circ\text{C} \times 0.1\ (1145) = \ \ 229\ \text{mL} \\
&\text{Deficit} && 1.5\ \text{kg} \times 1000\ \text{mL/kg} = \underline{1500\ \text{mL}} \\
& && \text{Total fluid} = 2874\ \text{mL}
\end{aligned}$$

(Eq. 103-8)

SODIUM

$$\text{Maintenance } 3\ \text{mEq/kg} \times 12.9\ \text{kg} = 38.7$$

$$\text{Deficit } (135 - 128\ \text{mEq/L}) \times 0.6\ \text{L/kg} \times 12.9\ \text{kg} = 54.2$$

$$\text{Total sodium} \sim 93\ \text{mEq}$$

(Eq. 103-9)

CHLORIDE

H.S. has a mild metabolic alkalosis as evidenced by her serum chloride of 88 mEq/L and her serum bicarbonate of 30 mEq/L. This is most likely because of the loss of hydrogen and chloride in her vomitus. Thus, both the sodium and potassium replacements should be administered as chloride salts.

POTASSIUM

Potassium is primarily an intracellular ion. It moves in and out of cells in exchange for hydrogen ions to maintain a normal blood pH. Therefore, in metabolic alkalosis, the intracellular shift of potassium will decrease the serum potassium concentration. When the pH normalizes, as will occur with rehydration, the hydrogen ions will move intracellularly and the potassium will move extracellularly, thus causing the serum potassium concentration to increase. Additionally, potassium is also excreted by the kidney in exchange for hydrogen ion conservation. These factors make the serum potassium concentration difficult to interpret. Intravascular volume depletion

causes hypoperfusion of the kidney and can result in acute renal failure; therefore, the prudent approach is to give no potassium until urine output is clearly established. Then, only maintenance doses of potassium should be administered until a normal acid–base and fluid status are established, and the serum potassium can be assessed more accurately. Hence, H.S. should receive ~26 to 39 mEq of potassium (2–3 mEq/kg × 12.9 kg) once urine flow is established.

Administration of Fluid Requirements

Case 103-2, Question 3: J.H.'s nurse asks for details of how the fluid therapy should be administered. How should these calculated needs be given?

Requirements for the first 24 hours of parenteral fluid therapy should provide ~2875 mL of fluid to account for maintenance fluid needs, fever replacement, and deficit replacement. In addition to fluid, at least 93 mEq of sodium (maintenance needs plus deficit replacement) should be provided in the first 24 hours. Rehydration fluids are usually dispensed in volumes less than the 24-hour requirement. This is to prevent wasting IV fluids caused by changes in electrolyte needs during replacement therapy. Because this patient requires ~3 L of fluid, only 1 L would be prepared initially, and this would likely consist of dextrose 5% and 0.45% NS (or greater). Approximately 15 mEq/L of potassium would be added to the next liter of IV solution if the patient had a reasonable urine output.

Historically, the infusion rate was calculated to provide one-third of the daily maintenance fluid plus one-half of the deficit replacement during the first 8 hours. The remainder of the maintenance fluid (adjusted for fever) and deficit replacement was administered during the next 16 hours. However, if appropriate fluid resuscitation is administered as fluid boluses, the need for this complicated calculation is no longer recommended by the AAP. Replacing the deficit calculation plus maintenance fluids over 24 hours is acceptable and without the risk of a fluid error.[5] Usually, serum electrolytes are monitored every 6 to 8 hours during rehydration to

ensure that appropriate electrolytes are being provided. Also, the change in concentration of serum electrolytes is monitored frequently. In general, the serum sodium concentration should not be increased by more than 12 to 15 mEq/L/day.[5] After the initial fluid deficits are replaced, the IV fluid infusion rate would be decreased to 48 mL/hour (1152 mL or approximately maintenance fluid rate).

Dehydration Associated With Diarrhea

CASE 103-3

Question 1: S.B. is a 4-month-old, 13.00-pound (5.9-kg) male presenting with a 4-day history of diarrhea (five to eight large, liquid stools each day). On a well-child visit 4 weeks ago, his weight was 13.23 pounds (6 kg). Since the onset of diarrhea, he has only been receiving oral rehydration fluids. Physical examination reveals the following:

Temperature, 101.84 °F (38.8 °C)
Pulse, 110 beats/minute (normal, 80–160 beats/minute)
Respirations, 45 breaths/minute (normal, 20–40 breaths/minute)
BP, 100/58 mm Hg (normal, 75–105 mm Hg systolic and 40–65 mm Hg diastolic)

His skin is pale, warm, and dry. He is very irritable, and his mucous membranes are dry. The parents report the same number of wet diapers. S.B.'s laboratory values are as follows:

Sodium, 159 mEq/L
Potassium, 3.3 mEq/L
Chloride, 114 mEq/L
CO_2, 12 mEq/L
Blood urea nitrogen (BUN), 22 mg/dL
Creatinine, 0.9 mg/dL

How do S.B.'s history and physical findings correlate with the reported laboratory values?

Diarrheal fluid losses commonly contain high concentrations of bicarbonate, accounting for S.B.'s metabolic acidosis. This, in turn, has resulted in a rapid respiratory rate as the body attempts to compensate for the acidosis by eliminating carbon dioxide. The

increased insensible water losses of fever and tachypnea have resulted in the loss of water in excess of sodium, producing hypernatremia.

CASE 103-3, QUESTION 2: How should S.B.'s dehydration be managed?

S.B. has relatively normal vital signs (specifically a normal heart rate and urine output); therefore, a fluid bolus will not be necessary. Hypernatremia in S.B. indicates fluid losses in excess of sodium, and this should be corrected. With hypernatremia, the central nervous system (CNS) increases intracellular osmolarity load to prevent intracellular dehydration of cells in the CNS. Rapid correction of hypernatremia can cause excessive movement of water into the cells of the CNS and has been associated with seizures. Therefore, S.B.'s fluid and electrolyte deficits should be corrected over the course of 2 to 3 days at a consistent rate, rather than rapidly. In general, serum sodium should not be decreased more than 0.5 mEq/hour (maximum, 12–15 mEq/L/day).[5]

S.B.'s requirements are estimated using the same methods described previously. First, the approximate extent of dehydration must be estimated. S.B.'s weight of 13.23 pounds (6 kg) at the time of his well-child visit at 3 months of age was at the 50th percentile. If his growth has continued at this rate, his current pre-illness weight should be ~14.33 pounds (6.5 kg).[6] This weight should be used to calculate his maintenance requirements. Thus, his water deficit is ~0.6 L, or 9%. Using this approximation, his fluid and electrolyte requirements can be estimated as follows.

FLUID

Maintenance	$6.5 \times 100\ \text{mL/kg} = 650\ \text{mL/24 hours}$
Fever	$1.8\ ^{\circ}\text{C} \times 0.1\ (650\ \text{mL}) = 117\ \text{mL/24 hours}$
	$600\ \text{mL/3 days} = 200\ \text{mL/24 hours}$
Deficit	Total daily needs = 967 mL or 40 mL/hour

SODIUM

(Eq. 103-10)

Maintenance	3 mEq/kg × 6.5 kg = 19.5 mEq/24 hours
Deficit	This is calculated as total body deficit (normal–actual)
Normal	145 mEq/L × 0.6 L/kg × 6.5 kg = 566 mEq
Actual	159 mEq/L × 0.6 L/kg × 5.9 kg = 563 mEq
Deficit	= 3 mEq or 1 mEq/day

(Eq. 103-11)

POTASSIUM

As discussed in Case 103-2, Question 2, the serum potassium value of 3.3 mEq/L may not be indicative of S.B.'s total body potassium status. A metabolic acidosis in S.B. should have facilitated the movement of hydrogen ions into the cells and the movement of potassium from the intracellular to the extracellular space. Thus, the serum potassium of 3.3 mEq/L probably indicates a total body deficit. Therefore, a maintenance potassium dosage of 13 to 20 mEq/day (~2–3 mEq/kg) of potassium should be added to the IV fluid. Serum electrolytes should be measured every 8 to 12 hours, and the intake of all electrolytes should be readjusted based on the results.

BICARBONATE

Although the patient has a metabolic acidosis, the AAP recommends sodium bicarbonate not be administered unless the patient is cardiovascularly unstable, which they are not. Correction of the patient's dehydration should allow for a slow correction of the acidosis.

Case 103-3, Question 3: What replacement fluid for S.B.'s therapy would you recommend?

S.B.'s fluid and electrolyte maintenance requirements and deficits should be corrected with dextrose 5% and ~0.2% NS. An infusion of this solution at 43 mL/hour should correct approximately one-half the

calculated fluid deficits within 24 hours in addition to his normal daily doses. After he urinates, 15 mEq/L KCl can be added to the next liter of solution to provide ~2.6 mEq/kg/day to this patient. The concentration of serum electrolytes should be measured often, and the concentration of electrolytes in the replacement fluid should be adjusted every 8 to 12 hours based on laboratory results. The amount of fluid replacement should be modified based on whether this patient's diarrhea has resolved and the fever has subsided.

Rehydration of the dehydrated patient may be achieved by either the oral or IV route. In some patients, vomiting may preclude effective oral rehydration. If the losses are diarrheal and with no vomiting, the oral route may be a cost-effective alternative to the parenteral route. Various solutions have been used to rehydrate children orally. In an asymptomatic dehydrated child, the sodium concentration of an oral rehydration fluid should contain at least 70 mEq/L of sodium.[5]

The composition of several products is shown in **Table 103-4**. A glucose concentration of 2% optimizes water and electrolyte absorption from the GI tract[5]; more concentrated glucose solutions can worsen rather than ameliorate diarrhea. Use of the oral route and the more concentrated sodium solutions may allow safe rehydration of hypernatremic dehydration in a shorter time frame than the 2 to 3 days previously noted.[5]

Table 103-4
Composition of Oral Rehydration Products

Product	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	Bicarbonate Source (mEq/L)	Carbohydrate (%)
Enfalyte®	50	25	45	34 citrate	3
Rehydralyte®	75	20	65	30 citrate	2.5
Pedialyte®	45	20	35	30 citrate	2.5
WHO salts	75	20	65	30 bicarbonate	2

WHO, World Health Organization.

Source: Boloyt N, Bollen CW, Bos AP, Kok JH, Offringa M. Fluid resuscitation in neonatal and pediatric hypovolemic shock: a Dutch pediatric society evidence-based clinical practice guideline. *Intensive Care Med.* 2006;32(7):995–1003.

INFANT ENTERAL NUTRITION

Caloric requirements of infants can be estimated using the formula provided in Table 103-1. The American Heart Association has suggested that infant feeding can be divided into three stages.[7] In the nursing period, only liquids are provided. During the transitional period, solid foods are introduced, but human milk, or commercially prepared infant formula, still provides the major source of the infant's caloric and nutrient supply. In the modified adult period, most nutrition is derived from the solid foods consumed by other household members.

At birth, the human GI tract is adapted for the consumption of a human milk–based diet. Intestinal lactase is present from 36 weeks' gestation and exhibits its maximal activity during infancy. Pancreatic amylase secretion is low, and the bile salt pool is decreased relative to that of older persons, resulting in decreased fat absorption.[8] Human milk provides nutrients in their most usable form for the developing GI tract.

Human Milk Feeding

CASE 103-4

QUESTION 1: M.E. is a 1-day-old full-term infant. M.E.'s mother will breast-feed M.E.

What are the nutritional implications of this decision for M.E.?

Human milk is the ideal food for a human infant and should be encouraged to continue throughout the first year of life as long as desired by both mother and child.[9] There are three phases to human milk production. During the first 5 days of lactation, a viscous, yellow liquid known as *colostrum* is produced. Colostrum is rich in protein, minerals, and other substances (eg, immunoglobulins). During the next 5 days, transitional milk is produced, and in the last phase,

mature milk is produced. The exact nutritional content of human milk varies from mother to mother; however, mature milk provides sufficient protein, minerals, and calories regardless of the mother's nutritional status. Mature human milk generally provides 70 kcal/100 mL, and fat accounts for more than 50% of the caloric content.[10] The fat in human milk is highly digestible and absorbable.[10] An additional 40% of calories is provided as carbohydrates, primarily in the form of lactose, and the remaining 10% is provided as protein. Whey and casein are the two primary proteins in mature human milk, with whey being the major protein component (whey-to-casein ratio of 60:40).[11] Human milk is of such biologic quality and bioavailability that adequate growth can be attained with a lower overall intake of protein than is provided by commercially prepared infant formulas, which contain lower whey-to-casein ratios.[11]

The iron content of human milk is low; however, supplementation may be unnecessary in healthy breast-fed infants early in life.[12] Not only is the iron in breast milk highly absorbed, but infants also have iron stores within the body. Regardless of maternal status, the vitamin D content of human milk is inadequate. Thus, M.E. will require 400 international units of vitamin D while she is exclusively breast-fed.[13]

Additionally, human milk provides the infant with protection against a wide variety of infectious diseases, including otitis media, diarrhea, pneumonia, and bronchiolitis. Evidence further suggests that human milk provides protection against noninfectious disorders, such as allergies, inflammatory bowel disease, insulin-dependent diabetes mellitus, and sudden infant death syndrome.[9,10] Human milk contains immunologically active cellular components and antibodies. These include secretory immunoglobulin A (IgA), both T and B lymphocytes, macrophages, and neutrophils.[9,10] The lipases and amylase present in human milk may facilitate the digestion of fat and carbohydrates in the still-developing GI tract. Proteins present in human milk serve as carriers for trace minerals and facilitate their absorption.[11] Oligosaccharides and glycopeptides may promote the colonization of the GI tract by *Lactobacilli* and decrease colonization

by *Bacteroides*, *Clostridia*, enterococci, and gram-negative rods, all of which may be pathogenic.[10]

Case 103-4, Question 2: What potential complications are associated with breast-feeding? What instructions should be given to M.E.'s mother?

Complications associated with breast-feeding are few; however, there are some potential problems. "Breast milk jaundice" associated with an indirect (unconjugated) hyperbilirubinemia can occur in the breast-fed infant during the first week of life and generally resolves by the fourth week of life. Although the infant's skin, sclera, and palate become yellow, this is generally not a dangerous condition. Nevertheless, if the bilirubin level becomes too high, the infant could develop an encephalopathy known as kernicterus. However, it is generally not necessary for the mother to stop breast-feeding while the infant has jaundice. The AAP recommends that infants nurse at least 8 to 12 times daily while jaundiced.[14] Some maternal infections have the potential to be transmitted to the infant during breast-feeding. Human immunodeficiency virus (HIV) and human T-lymphotropic virus 1 (HTLV-1) can be transmitted via breast milk, and therefore, maternal infections with these viruses are contraindications to breast feeding.[9,10] Other viruses, such as herpes simplex virus, can be transmitted if contact with active lesions occurs during breast-feeding. Similarly, some medications taken by the mother are detectable in her breast milk; however, only a few agents (eg, antineoplastics, radiopharmaceuticals, ergot alkaloids, iodides, atropine, lithium, cyclosporine, chloramphenicol, bromocriptine) are absolute contraindications to breast-feeding.[9,10]

Case 103-4, Question 3: M.E.'s mother suffers from migraine headaches, which have increased in frequency since M.E.'s birth. M.E.'s mother takes an ergot alkaloid for the acute management of her headaches and therefore has decided not to breast-feed M.E. She will be using infant formula instead. How are these products prepared, and how do they differ from human milk?

Because of the excretion of ergot alkaloids into breast milk and the risk for toxicity to the infant, it is advisable to either select an alternative medication or discontinue breast-feeding and use an infant formula. According to the AAP guidelines for commercially prepared infant formula composition, formula should provide 20 kcal/ounce, osmolality should be between 300 and 400 mOsm/L, protein quantity should be a minimum of 1.8 g/100 kcal and should not exceed 4.5 g/100 kcal, and fat quantity should be between 3.3 and 6 g/100 kcal, supplying between 30% and 54% of calories. Infant formulas generally begin with a cow's milk base; however, intolerance to pure cow's milk has resulted in several modifications. The predominant protein in cow's milk is casein, which is more difficult for infants to digest than the human milk protein, whey. Consequently, infant formulas generally have less casein than cow's milk, although not to the level of human milk. The casein present in cow's milk formulas also may be heat-denatured to improve its digestibility. In addition, the fat source in cow's milk is replaced by one of several vegetable oils, allowing for easier digestion. Last, the carbohydrate source in cow's milk–based formula is supplemented with lactose or sucrose because the lactose content of cow's milk is only 50% to 70% of that in human milk. Soy-based and protein hydrolysate formulas are available for infants who are intolerant of cow's milk–based formulas.

Soy-based formulas use soybean as the protein source.[15] The soy is heat-treated to enhance protein digestibility and improve the bioavailability of some nutrients. Although nutrients, such as methionine, zinc, and carnitine, are still present, their concentrations are relatively low. Therefore, the manufacturer routinely adds methionine to all soy-based formulas. Zinc and carnitine may not be added, and exogenous supplementation may be necessary. Soy-based formulas substitute sucrose, corn syrup, or a combination of the two for lactose as the carbohydrate source. Additionally, soy protein formulas are more expensive than cow's milk–based formulas. The AAP recommends that the use of soy-based formula be limited to patients with primary lactase deficiency (galactosemia), patients with secondary lactose intolerance from enteric infections or

other causes, vegetarian families in which animal protein formulas are not desired, and infants who are potentially cow's milk protein allergic, but who have not demonstrated clinical manifestations of allergy. Long-term use of soy-based formulas in premature and low-birthweight infants should not be recommended. Soy-based formulas have aluminum contamination and have been associated with the development of rickets. Soy-based formulas are also not recommended for infants with documented allergic reactions to cow's milk protein because of the potential for cross-antigenicity between the two proteins. Additionally, soy protein formulas are not recommended for the routine management of colic.

Elemental formulas, made with hydrolysate formulas, are another option for infants who have an intolerance to cow's milk–based formulas. The milk proteins (ie, casein and whey) are heat-treated and enzymatically hydrolyzed to enhance the digestibility of protein hydrolysate formulas, which are fortified with additional amino acids that are lost during processing. As with soy protein formulas, protein hydrolysates substitute sucrose, tapioca, or corn syrup for lactose as the carbohydrate source. Protein hydrolysate formulas often include significant amounts of medium-chain triglycerides because they are easily absorbed. Because the proteins are extensively hydrolyzed, these formulas are considered the least allergenic of the infant formulas and therefore may be appropriate for infants with a true allergy to cow's milk protein. Nevertheless, prospective studies on the safety of such a substitution in human infants have not been undertaken because of the ethical concerns associated with intentionally exposing infants with documented allergies to a potential allergen. Protein hydrolysate formulas are the least palatable of the available pediatric formulas and are more costly.[16]

Infant formula is available from the manufacturers in three forms: ready-to-feed formula, powder for reconstitution, and concentrated liquid. The ready-to-feed form is the most convenient but also the most expensive. The powder and concentrated liquid are less expensive; however, both require that predetermined amounts of boiled water be added before use. To save money, some parents dilute infant formula to a greater extent than recommended to make

their supply last longer. This practice should be discouraged because of the risk of hyponatremia and, ultimately seizures, with excessive free water intake in infants younger than 1 year of age. In addition, the infant will not receive the appropriate amount of calories for normal growth and development. Similarly, supplementing an infant's diet with free water, for any reason, may also result in hyponatremia and seizures and should be discouraged. Periodically, manufacturing problems can occur, resulting in the recall of a product from the market.[17] Therefore, it is important for the patient's health care providers to stay informed of manufacturers' recalls.

Introduction of Cow's Milk

Case 103-4, Question 4: At age 2 months, M.E. is found to have a hematocrit (Hct) of 33% (normal, 35%–45%). After questioning her mother, you learn that M.E. was taken off infant formula 1 month ago and changed to whole cow's milk to decrease food costs. How are these two findings related, and how should M.E. be managed?

The use of cow's milk is not recommended for infants younger than age 1 year. The iron in cow's milk is present in inadequate concentrations and is absorbed poorly from the human GI tract. For this reason, most infant formulas are fortified with iron. Raw cow's milk is also insufficient in vitamin E and essential fatty acids.[18] It also does not contain taurine, an amino acid important in retinal development. Furthermore, cow's milk contains excessive amounts of solute that cannot be eliminated by the immature kidney.

To treat M.E.'s anemia, iron should be added to her diet. This can be done by changing back to an iron-fortified infant formula, feeding her an iron-fortified cereal, or giving a therapeutic ferrous sulfate liquid medication. The appropriate iron replacement dose for severe anemia is 4 to 6 mg/kg/day of elemental iron in divided doses with follow-up of the infant's hemoglobin and hematocrit.

Introduction of Solid Foods

Case 103-4, Question 5: At age 4 months, M.E.'s mother asks about the introduction of "baby foods" into M.E.'s diet. How should the clinician respond?

Human milk or commercially prepared infant formula provides adequate nutrition for an infant for the first 12 months of life. Introduction of solid foods before 4 months of life, although common in the past, is discouraged because younger infants are unprepared to swallow foods other than liquids. Solids (first cereals, then fruits, and vegetables) should be introduced when the child has good control of the head and neck movements (ie, usually at 4–6 months old).[7] Preferably, one new food should be introduced at a time, at 1-week intervals, to allow for assessment of food allergies.

Therapeutic Formulas

CASE 103-5

Question 1: L.B. is a 2-week-old infant whose newborn screen is positive for phenylketonuria (PKU). Discuss the concepts behind the production of therapeutic formulas and the dietary management of patients with inborn errors of metabolism.

How should L.B.'s diet be modified?

Inborn errors of metabolism are disorders in which an enzyme or its cofactor is absent or insufficient to meet metabolic demands.[19] As a result, one or more precursor compounds in a metabolic pathway can accumulate before the defective step. Correspondingly, one or more metabolic products that normally would have been generated after the defective step in the metabolic pathway are not sufficiently available.

The dietary management of metabolic errors is based on the following strategies:

- Reduce the intake of a precursor compound that cannot be metabolized.

- Supplement the deficient compounds that would have been produced if the normal metabolic pathway had not been blocked.
- Add a substrate that provides an alternative pathway for the elimination of an accumulated toxin.

Therapeutic formulas are designed to reduce the intake of precursor compounds or to provide the deficient metabolic end product.

When hydroxylation of phenylalanine to tyrosine does not take place, phenylalanine accumulates in the blood and results in mental retardation. Because PKU has been diagnosed in L.B., his diet should be modified using a formula containing little or no phenylalanine. The tyrosine deficiency of PKU can also be managed by the addition of tyrosine to the phenylalanine-free therapeutic formulas that are available for patients with PKU. When L.B. progresses to solid foods, it will be important to limit or avoid foods that contain high levels of protein such as eggs and soybeans.

Other metabolic errors present in infancy include galactosemia (galactose cannot be metabolized to glucose), homocystinuria (methionine is not converted to cysteine), urea cycle disorders (ammonia detoxification is impaired), and maple syrup urine disease (metabolism of the branched-chain amino acids leucine, isoleucine, and valine is blocked).

These metabolic errors are managed by manipulating the diet.[19] In galactosemia, the carbohydrate source should not contain galactose or lactose. In homocystinuria, methionine should be present only in quantities sufficient to meet basic requirements, and cysteine should be supplemented. In the urea cycle disorders, protein often is provided only as essential amino acids, and a high-energy diet is provided to maximize the formation of nonessential amino acids from nitrogen and to minimize ammonia production. In maple syrup urine disease, natural protein is fed in small quantities to provide the minimal requirement of branched-chain amino acids, and a branched-chain amino acid-free supplement is added to provide adequate protein intake.

Route of Administration

Nutritional support using the GI tract is the preferred approach when possible. Enteral nutrition provides several advantages. First, interposition of the GI mucosa between the nutrient supply and circulation allows absorptive function to provide a homeostatic control. Second, the flow of nutrients from the GI tract to the liver via the portal circulation before reaching systemic circulation also assists homeostatic control. Third, the lack of enteral nutrition allows normal GI tract flora to overgrow and translocate into the blood, resulting in bacteremia. Finally, the intestinal mucosa depends on intraluminal absorption for much of its energy supply. Hence, provision of at least a small amount of enteral feeding, referred to as trophic feeds, helps to ensure a healthy GI tract and may facilitate advancement to full enteral feedings at the appropriate time.[20]

Normal oral feeding is the most basic method for patients who are willing and able to eat or drink. Patients whose GI motility, structure, and function are normal, but whose oral feeding is prevented by an altered state of consciousness, uncoordinated sucking and swallowing, or other conditions that prevent adequate oral ingestion can be fed by a GI tube in intermittent boluses or by continuous infusion.

Bolus tube feedings more closely mimic the normal state. They periodically distend the stomach, which aids in gastric secretion and emptying. When bolus tube feeding is undertaken, the volume of formula or expressed breast milk required to provide sufficient calories for a 24-hour period is administered through the tube in equal aliquots every 2, 3, 4, or 6 hours. The frequency of administration depends on the patient's age, gastric capacity, and the infant's ability to maintain a normal serum glucose concentration between feedings. In general, younger and more premature infants require more frequent feedings. Intolerance to bolus tube feedings can be manifested as diarrhea, gastroesophageal reflux with emesis, or poor motility. Poor motility is usually apparent when large volumes of feeding, referred to as residuals, remain in the stomach when the next feeding is due.

Continuous tube feedings can be given at a constant rate of infusion by pump into the stomach or duodenum when bolus feedings have failed. This approach may be better tolerated by premature infants and children with diarrhea.

Patients with intrinsic GI disease (**Table 103-5**) or malabsorption may require total or supplemental PN. Concurrent administration of low-volume, trophic enteral feedings may provide important nutrients to the gut mucosa even when the parenteral route supplies all of the necessary systemic nutrients.[20] Administration of PN into a peripheral vein is usually restricted to patients expected to require parenteral feeding for a short time (ie, 2 weeks or less) because the amount of nutrients that can safely be infused peripherally is limited. In patients who require long-term PN, the IV solution is more concentrated and must be administered into a central vein.

Table 103-5

Common Indications for Parenteral Nutrition Support[a]

Extreme prematurity
Respiratory distress
Congenital GI anomalies
Duodenal atresia
Jejunal atresia
Esophageal atresia
Tracheoesophageal fistula
Pyloric stenosis
Congenital webs
Hirschsprung disease
Malrotation
Volvulus
Abdominal wall defects
Omphalocele (herniation of viscera into the umbilical cord base)
Gastroschisis (defect of abdominal wall, any location except umbilical cord)
Congenital diaphragmatic hernia

Necrotizing enterocolitis
Chronic diarrhea
Inflammatory bowel disease
Chylothorax
Pseudo-obstruction
Megacystis microcolon
Abdominal trauma involving viscera
Adverse effects of treating neoplastic disease
Radiation enteritis
Nausea and vomiting
Stomatitis, glossitis, and esophagitis
Anorexia nervosa
Cystic fibrosis
Chronic renal failure
Hepatic failure
Metabolic errors

GI, gastrointestinal.

[a]Other indications for parenteral nutrition may exist.

Nutritional Assessment

CASE 103-6

Question 1: T.C. is a 4-month-old, lethargic male. On examination, he has a moderately distended abdomen and dry mucous membranes. No other remarkable abnormalities are noted. His weight is 14.33 pounds (6.5 kg) (50th–75th percentile for age). Previously, when he was 2 months old, T.C. weighed 12.35 pounds (5.6 kg) (75th percentile for age), and his length was 57 cm (50th percentile for age). His mother reports that for the past 5 to 7 days, he has had five to eight large, liquid stools per day. His infant formula has not changed. He is to be hospitalized for evaluation of his diarrhea and weight loss and for fluid and nutritional management.

After correction of his initial fluid and electrolyte deficits, an assessment of his nutritional status shows the following:

Weight, 14.33 pounds (6.5 kg; 50th–75th percentile)
Length, 24.51 inches (62 cm; 50th percentile)
Albumin, 3.8 g/dL (normal, 4–5.3 g/dL)
Prealbumin, 7 mg/dL (normal, 20–50 mg/dL)

How would you assess T.C.'s nutritional status?

Growth assessment is an important focus of pediatric health care, especially during the first year of life. With the exception of the intrauterine period, the most rapid growth occurs during the first year. On average, a normally growing infant gains ~30 g/day. Typically, healthy infants weigh approximately three times their birthweight by their first birthday.

The patient's nutritional status should be assessed before beginning a nutritional support regimen and reassessed at regular intervals during the course of treatment. If the patient was previously well nourished, the goal is to maintain that status until a normal diet can be resumed. In a child who was previously malnourished, an effort should be made to promote "catch-up" growth and normalize the biochemical nutritional measures. One in five children admitted to the hospital experience acute or chronic malnutrition.[21] Malnutrition in children is a risk factor for decreased social skills and impaired intellectual development.[22]

Anthropometric measurements, including height, weight, and head circumference, are used to determine nutritional status in infants and children and can help in assessing T.C.'s condition. Standards for these measurements have been derived from pediatric patients in the United States and compiled into graphs referred to as growth curves (http://www.cdc.gov/growthcharts).[6] An individual patient's measurements are compared with the graph of normal values for that specific age group. As prematurely born infants age, a standard growth curve adjusted for prematurity can be used. Using these measurements, comparisons with standards are possible: weight for age, height for age, and weight for height.[6] A weight that is below the fifth percentile for the patient's height is considered an indication of acute malnutrition. Similarly, a height and weight that are below the fifth percentile for the patient's age indicate chronic malnutrition. It is

important to consider the height and weight of the child's parents because genetics are important determinants of the height and weight that a child may ultimately achieve. Additionally, the revised growth charts include the body mass index (BMI) for age for children older than 2 years. The BMI helps identify children at risk for obesity and type 2 diabetes, two problems that have recently become concerns within pediatrics.[6]

Numerous biochemical indices are also used in the assessment of nutritional status. Of these, the most readily available and widely used is the serum albumin concentration. Although a low serum albumin can be a specific indicator of protein-calorie malnutrition, its long half-life (20 days)[21] makes it an insensitive indicator for developing and resolving malnutrition.

Prealbumin can also function as a biochemical marker of nutritional status.[21] Because of its shorter half-life, prealbumin has the advantage of being more sensitive than albumin to acute nutritional changes, and it is still useful when exogenous albumin infusions are given.[21] Other measurements used in adults, such as 24-hour creatinine excretion, 24-hour nitrogen excretion, and nitrogen balance, are reserved for older children because complete collections of urine are difficult to obtain and the percentage of non-urea nitrogen present in urine is variable in infants.

CASE 103-6, QUESTION 2: After initial IV rehydration and receiving nothing by mouth (NPO) for 48 hours, T.C.'s stool output has decreased dramatically. Is this characteristic of infants with chronic diarrhea? How should T.C.'s enteral diet be initiated?

A prompt decrease in stool output when enteral intake is stopped is typical of infants with chronic diarrhea. Nonetheless, evaluation of bowel function and adaptation has shown that enteral nutrition is superior to PN with regard to histologic recovery, improvement of D-xylose absorption, protein absorption, and disaccharidase activity.[23] In fact, improvement in histology or absorptive function might not occur until enteral nutrients are given.[20] Thus, for T.C., every effort should be made to provide some nutrition enterally.

The enteral regimen should be initiated with a lactose-free formula, such as an elemental formula or a soy-based formula. Although any soy-based formula would be appropriate, Isomil DF is a soy-based formula with added fiber that is indicated for infants with diarrhea. Infants with chronic diarrhea can have small bowel mucosal damage and decreased disaccharidase activity.[7] Carbohydrate absorption depends on the digestion of disaccharides and polysaccharides to monosaccharides through disaccharidase activity in the intestinal lumen. Substitution of free glucose orally may overcome the problem of carbohydrate digestion and absorption. Administration of large amounts of oral glucose should be limited, however, because of its osmotic effect and potential to worsen diarrhea. Furthermore, incompletely absorbed carbohydrate is available to colonic bacteria for fermentation, the end products of which can produce diarrhea through colonic irritation.

Unlike carbohydrate, protein rarely causes diarrhea, but the mucosal damage present in patients with chronic diarrhea, such as T.C., can reduce the absorptive surface area so that protein malabsorption may occur. This can be minimized through the administration of a formula containing protein in the form of dipeptides and tripeptides, which are absorbed more efficiently than free amino acids.

Dilution of hypertonic formulas to half strength may improve formula tolerance. The concentration is increased in a stepwise fashion to full strength if there is no carbohydrate malabsorption and if stool output is not excessive. Tolerance may be improved by continuous infusion of the enteral product. If enteral refeeding results in the return of diarrhea, fluid and electrolytes must be replaced with an equal volume of an IV solution of similar electrolyte composition to the stool loss.

Case 103-6, Question 3: How can T.C.'s tolerance to the formula and his recovery of intestinal function be assessed?

Malabsorption or formula intolerance can be assessed by stool studies, which would include assessing for the presence of reducing substances and stool pH. Lactose is a reducing sugar, and its presence in stool is an assessment of carbohydrate absorption. The bacterial fermentation products of malabsorbed carbohydrates can result in a decreased stool pH, which suggests malabsorption. To further evaluate carbohydrate absorption, D-xylose may be given orally; a blood sample is drawn 4 to 5 hours later to determine the amount absorbed. This test may be of initial prognostic value in predicting which patients will require prolonged courses of treatment.[23] More than 5% of ingested fat in a stool collection (typically obtained for 3 days) is indicative of fat malabsorption. All these tests can be evaluated during outpatient visits to guide the refeeding process.

Once the diarrhea has resolved, standard infant formula feedings should be established using an enteral elemental or soy-based formula. Regardless of the time chosen, a gradual stepwise conversion is suggested. A small volume of standard formula is substituted for an equal volume of elemental or soy-based formula, and the substitution volume is increased daily until the elemental or soy-based formula is eliminated completely from the regimen. If a specific nutrient intolerance has been identified, a standard formula that does not contain that nutrient must be selected. For example, a patient with cow's milk protein intolerance may require a soy protein formula or an elemental formula.

Pediatric Parenteral Nutrition

The basic requirements for a parenteral nutrient regimen are listed in Table 103-1. These guidelines for the initiation of a nutrient regimen should be individualized to specific patient needs. The correct regimen for any specific patient is one that supplies sufficient nutrients to promote a normal rate of growth without toxicity. In particular, patients with ongoing, abnormal nutrient losses may require much larger doses of certain nutrients. Individualization of

the nutrient prescription cannot be overemphasized. Many of the requirements listed in Table 103-1 apply to nutrients administered by the enteral route as well. In some instances, the absorption of a particular nutrient from the GI mucosa is incomplete, and enteral requirements are substantially higher. This is particularly true of the major minerals (calcium, magnesium, and iron) and trace elements.

Indications

PN is indicated for any infant or child unable to take in sufficient nourishment to maintain normal growth. Some specific indications are listed in Table 103-5.

VERY LOW-BIRTHWEIGHT INFANTS

Extremely premature or VLBW infants require specialized nutritional support for two distinct reasons. First, the third trimester in utero is a time of rapid growth and accumulation of protein, glycogen, fat, and minerals.[24] The infant born in the very early stages of the third trimester does not accumulate these stores and, therefore, must receive nutrients earlier than a more mature infant. Second, extreme prematurity is associated with poor coordination of the suck and swallow reflex, poor GI motility, and incomplete absorption. Therefore, enteral nutrients may need to be administered via an orogastric or nasogastric tube, and PN supplementation may be required. PN, especially containing amino acids, should be initiated soon after birth to duplicate intrauterine growth and prevent a catabolic state in the first few days of life. The fetus has a continuous supply of amino acids that is immediately stopped after preterm birth.[25] A standardized solution containing amino acids and dextrose can be used for infants weighing <2.20 pounds (<1 kg) in the first 24 hours of life. There has been some reluctance to administer amino acids this soon after birth because of the increased risk of hyperammonemia, uremia, and metabolic acidosis. Several studies, however, have shown early introduction of amino acids is safe,

provides a positive nitrogen balance, and promotes better health outcomes.[26,27]

RESPIRATORY DISTRESS

Respiratory distress may preclude the ability to consume sufficient nutrients enterally because high respiratory rates prevent coordinated breathing and swallowing. In infants who are hypoxic, or at high risk for hypoxia, aggressive enteral feedings during the acute phase of their illness can increase the likelihood of bowel ischemia. Often, these situations are resolved in 3 to 5 days, but this can rarely be predicted at the outset. Trophic feedings (1–5 mL/hour) are often implemented to maintain GI tract integrity. Nutritional support in such cases is initiated by giving parenteral fluids, which provide dextrose as a caloric source. This allows the infant to conserve endogenous energy substrates, an important consideration for the VLBW infant whose entire body composition may contain as little as a 3- to 4-day energy supply.[24] PN should be initiated as soon as it becomes clear the enteral feeding will not be possible for at least 3 to 5 days or if no clear time frame can be determined for the establishment of enteral feeding. Although a short course (5 days or less) of PN may be used, the quantity of nutrients supplied during the process of initiation and gradual increase to full requirements is so low that it may be difficult to justify. Peripheral PN using fat emulsion as a significant source of calories, however, can provide up to 70 kcal/kg and, with appropriate types and amounts of protein, result in modest weight gain and nitrogen equilibrium.

GASTROINTESTINAL ANOMALIES

Infants with GI anomalies often require PN because the implementation of enteral feedings may be delayed. For example, GI tract atresia or stenosis can obstruct, or partially obstruct, the lumen of the GI tract. This prevents or slows the passage of fluids and nutrients and can result in vomiting, depending on the location of the obstruction. Similarly, infants with necrotizing enterocolitis have zones of ischemic bowel and are at risk for bowel perforation if fed

enterally.[28] Infants with these disorders need PN until the viability of the entire GI tract can be assured.

CHRONIC RENAL FAILURE AND HEPATIC DISEASE

Chronic renal or hepatic disease requires modification of a normal diet to account for the impaired elimination of nitrogenous waste or impaired protein metabolism. Careful caloric supplementation with a reduced amount of protein may permit normal growth while minimizing excess urea production in an infant with renal failure.

CASE 103-6, QUESTION 4: Approximately 48 hours after discharge from the hospital, T.C. returns to the emergency department with abdominal distension and bloody diarrhea. He is diagnosed with postgastroenteritis syndrome. T.C. cannot receive nutrients enterally, and PN is to be initiated because he is nutritionally depleted. Describe for the members of the medical team how a regimen of PN should be initiated for T.C. What aspects of his disease may alter specific nutrient needs?

When initiating PN, the protein (amino acids), glucose (dextrose), fat (lipids or fat emulsion), fluid, and electrolyte, mineral, and vitamin components of the regimen are managed as separate entities. In addition, the route of PN delivery is important to consider because the amount of glucose, potassium, and calcium must be limited if the infusion is given peripherally. In general, 12.5% dextrose, 40 mEq/L potassium, and 10 mEq/L calcium are the maximal amounts that should be provided by infusion into a peripheral vein. These nutrients can be increased if a central venous catheter is placed. The fluids, electrolytes, minerals, and vitamins are initiated at full daily maintenance doses after correction of any preexisting abnormalities. Protein should be initiated at full daily doses in term infants and children with normal renal and hepatic function. Glucose and fat are started at lower doses and increased daily as tolerated until requirements are reached.

Protein should be started in T.C. at full daily requirements of 2 to 3 g/kg/day. Azotemia and acidosis have occurred in infants receiving more than 4 g/kg/day of protein; however, these complications are

rare at the recommended dosage. Parenteral glucose administration is initiated at 5 to 8 mg/kg/minute (7.2–11.5 g/kg/day). At normal maintenance fluid rates, 10% dextrose represents a generally well-tolerated starting solution for patients of virtually any age or size, except the VLBW infant. In T.C.'s case, the dextrose concentration will begin and continue at 10% because of the peripheral catheter limitations. This concentration will provide a glucose infusion rate (GIR) of 7.3 mg/kg/minute. If a central catheter later becomes necessary, the GIR can be increased by 1 to 2 mg/kg/minute each day until the caloric requirement is met. This increase should be accompanied by blood and urine glucose monitoring. If the blood glucose is 150 mg/dL or greater, or if the urine glucose exceeds "trace" amounts, the PN infusion rate should be decreased by at least 25% and a second IV solution should be added to provide needed fluids and electrolytes. Alternatively, the dextrose concentration can be decreased or insulin can be infused concomitantly and titrated to a desired serum glucose concentration of 120 to 140 mg/dL.

Fat emulsion should be initiated at 1 g/kg/day and increased daily by 0.5 to 1 g/kg/day until the maximal dosage of 3 g/kg/day is reached. The daily lipid dose should be infused at a constant rate because fats are better tolerated when infused over 24 hours.[29] Serum triglycerides should be monitored every other day while the dose of fat is being increased. Patients with a fasting triglyceride concentration of 150 mg/dL or less may have their fat dose increased. In patients who are receiving inadequate calories, triglycerides may be elevated because endogenous fats are being mobilized. If the triglyceride concentration is >150 mg/dL, the serum sample must be examined visually. A clear sample with a mildly elevated triglyceride concentration probably indicates the use of endogenous fat stores for energy. Conversely, a turbid or lipemic sample indicates the patient's inability to use the amount of IV fat administered. In this case, further increases in the fat dose should be delayed until triglyceride concentrations decrease.

Special Considerations and Complications

CASE 103-7

QUESTION 1: J.H., a 4-day-old male, was born at 31 weeks' gestation. His birthweight was 4.31 pounds (1.95 kg), and he now weighs 4.51 pounds (2.05 kg). On the first day of life, he was given a commercial preterm infant formula by orogastric tube in gradually increasing quantity with supplemental IV fluids. Now, on the fourth day of life, he has a distended abdomen, and his stools contain bright red blood. An abdominal radiograph shows pneumatosis intestinalis (gas within the intestinal wall seen on x-ray). All enteral feedings are stopped.

What do these findings represent? What are the implications for J.H.'s nutritional management?

Abdominal distension, bloody stools, and pneumatosis intestinalis are characteristics of necrotizing enterocolitis.[30] The causes of this disorder are unclear, but it occurs more often in premature than in term infants; it can occur in clusters of cases, rarely is seen before enteral feeding is instituted, and can be associated with rapid increases in enteral intake.[31] Because J.H. will receive antibiotics for 10 to 14 days and remain NPO, he requires PN. The planned duration of the regimen makes central venous access a necessity.

GOALS OF LONG-TERM SUPPORT

CASE 103-7, QUESTION 2: The following day, intestinal perforation requires the resection of two-thirds of J.H.'s distal jejunum and one-third of his ileum, with the creation of a jejunostomy. The ileocecal valve and the entire colon are left intact. During the operation, a central venous catheter is placed. What is the goal of PN for J.H.?

J.H. will be NPO for a prolonged time. Therefore, the goals of his PN must be to promote normal growth as well as healing of his diseased gut and surgical wounds. Because of J.H.'s prematurity, it will be difficult to predict how well he will tolerate PN. VLBW infants tolerate normal doses of pediatric amino acids without difficulty;

however, some clinicians initiate protein at a lower daily dose (eg, 1 g/kg/day) and advance each day until a goal of 3 to 4 g/kg/day is achieved. Fat should be started at 0.5 to 1 g/kg/day and increased by 0.5 g/kg/day up to 3 g/kg/day. Glucose should be initiated at 6 to 8 mg/kg/minute (5–10 g/kg/day) and increased by 1 to 2 mg/kg/minute (2–3 g/kg/day) until the desired caloric intake is achieved. Appropriate doses of electrolytes and minerals may be started immediately using the guidelines listed in Table 103-1.

FAT EMULSIONS: COMPLICATIONS

CASE 103-7, QUESTION 3: What must be considered in making decisions regarding fat administration in J.H.?

Although J.H. can receive adequate calories using only glucose and crystalline amino acids, he will require fat to provide a more physiologic diet and to prevent essential fatty acid deficiency (EFAD), which develops quickly in low-birthweight infants who have little fat reserve. J.H. should receive a minimum of 5% of his total caloric requirement as fat emulsion or (0.5 g/kg/24 hours) to minimize the risk of EFAD. Ideally, his nutrition regimen will provide ~40% of calories from fat, which is similar to what is provided by human milk.

Infusions of fat emulsion have been associated with impaired oxygen transport and pulmonary ventilation–perfusion mismatch. This adverse effect occurs more often when the dose of fat is 4 g/kg or greater and is infused for a relatively short (4 hours) period. Current practice is to increase the doses of fat gradually from 0.5 to 1 g/kg/day up to a maximum of 3 g/kg/day and to infuse the fat emulsion over the course of 24 hours to minimize the likelihood of pulmonary problems and to promote clearance.

It is unclear whether IV fat administration is detrimental to patients with sepsis. Infusion of fat emulsion has resulted in lymphocyte and neutrophil death.[32] On the other hand, the linoleic acid in IV fat is the precursor to arachidonic acid, prostaglandins, thromboxane,

interleukins, and immune-mediating cells. Theoretically, this may minimize bacteremia. Necrotizing enterocolitis, intestinal perforation, and surgery predispose J.H. to sepsis. Therefore, he should have his IV fat infused at an appropriate dose over the course of 24 hours. Because fat clearance can be impaired during infection, it is also prudent to monitor his triglyceride concentrations.

Free fatty acids can displace bilirubin from its albumin binding sites, thereby placing the infant at risk for kernicterus.[33] Therefore, before advancing the fat dose, the total bilirubin and direct bilirubin should be measured. Patients with an indirect bilirubin (total bilirubin minus direct bilirubin) of 10 mg/dL or less whose albumin levels are normal are at low risk for kernicterus. Indirect bilirubin usually peaks before age 1 week. After the risk for indirect hyperbilirubinemia has passed, the fat dose can be increased as recommended in Table 103-1. The infusion of 1 g/kg over the course of 24 hours is associated with minimal risk for decreased bilirubin binding[33]; however, rapid infusion of this same dose can displace bilirubin from albumin binding sites. Given the low level of indirect bilirubin found on routine monitoring and the planned fat infusion rate, J.H. should not be at risk for kernicterus.

Egg-yolk phospholipids are used to emulsify fats; therefore, patients with a known allergy to eggs (eg, fever, chills, urticaria, dyspnea, bronchospasm, chest pain) should not receive fat emulsion.

GLUCOSE INTOLERANCE

Case 103-7, Question 4: Because J.H. is a premature infant, PN is initiated using 5% glucose, 3 g/kg/day of amino acids, and 0.5 g/kg/day of fat emulsion. The volume of PN should be 240 mL based on a maintenance fluid requirement of 120 mL/kg (see Table 103-1). On the second day, he receives 10% glucose (GIR 8.3 mg/kg/minute), 3 g/kg/day of amino acids, and 1 g/kg/day of fat. On the third day, glucose is increased to 12.5% (GIR 10.4 mg/kg/minute), amino acids remain at 3 g/kg/day, and fat emulsion is increased to 1.5 g/kg/day. On the fourth day, glucose is increased to 17.5% (GIR 14.6 mg/kg/minute), amino acids remain at 3 g/kg/day, and fats are increased to 2 g/kg/day. After this solution has been infused for 8 hours, his urine test yields 1% for glucose (normal, no

glucose), and his blood glucose level is 210 mg/dL (normal, 120 mg/dL). Explain this new finding and the problems it may cause. How should hyperglycemia be managed?

Maximal glucose oxidation rates (mg/kg/minute) are inversely related to age and decrease from 15 to 18 mg/kg/minute in neonates and young infants to 4 to 5 mg/kg/minute in adults. In full-term neonates and infants receiving maintenance fluids (100 mL/kg/day), glucose concentrations can be started at 10 g/kg/day (equivalent to dextrose 10%) and advanced by 2.5 g/kg (equivalent to dextrose 2.5%) every 24 hours up to ~25 g/kg/day (equivalent to dextrose 25%). In preterm neonates, such as J.H., dextrose is started at a lower dose and advanced at smaller increments, usually 2 to 3 g/kg/day. Glucose tolerance varies significantly, so each patient should be considered individually.

At J.H.'s prescribed fluid rate of 10 mL/hour, 17.5% glucose represents 14.6 mg/kg/minute of glucose. The hyperglycemia and glycosuria probably have occurred because the increases in the infusion rate have exceeded J.H.'s ability to adapt to the glucose dose. Patients who have been euglycemic on their glucose dose and then become glucose intolerant should be evaluated, however, for other causes, such as infection and the addition of exogenous corticosteroids. Hyperglycemia and glycosuria can result in serum hyperosmolarity, osmotic diuresis, and dehydration. Regardless of the cause, hyperglycemia should be treated by reducing the glucose administration rate. The rate of the PN infusion can be decreased further if hyperglycemia continues or increased if the hyperglycemia resolves.

When the PN order is written for the subsequent days, the glucose increases should be made in smaller amounts up to the full daily maintenance calorie requirements. Frequent blood and urine glucose monitoring must be continued. Severe glucose intolerance in patients who require PN can be managed with insulin to normalize serum glucose. Although insulin is compatible with PN solutions, it does adsorb to glass, polyvinyl chloride, and filters, resulting in decreased delivery of insulin.[34] Frequently, pediatric patients have

changing insulin requirements that prevent the addition of insulin to PN solutions. A separate continuous infusion of regular insulin (initial dose, 0.05–0.1 units/kg/hour) titrated to control serum glucose concentrations offers a practical solution to minimize waste of the PN solution.[35] It is essential to discontinue the insulin infusion if the PN solution is discontinued to avoid hypoglycemia.

EFFECTS OF BRONCHOPULMONARY DYSPLASIA AND MECHANICAL VENTILATION

CASE 103-7, QUESTION 5: J.H. remains dependent on a ventilator because of his immature lungs. How could J.H.'s respiratory disease influence his nutritional regimen?

After age 28 days, J.H.'s ventilator dependence defines him as having bronchopulmonary dysplasia (BPD), a chronic lung disease of infancy. Historically, BPD is characterized by an increase in resting energy expenditure, increased work of breathing, and growth failure.[36,37] Therefore, J.H.'s caloric requirement may be higher than expected. Additionally, J.H.'s ventilator may also alter the approach to his caloric supply. Very high carbohydrate loads have been associated with an increase in carbon dioxide production.[38] This, in turn, may make it difficult to wean J.H. from the mechanical ventilator. As discussed, rapid infusions of fat emulsion can also have a detrimental effect on pulmonary function. Fat emulsion should not be omitted from J.H.'s PN regimen; rather, a slower infusion rate, with gradual dose increases, while monitoring pulmonary function is appropriate.

PEDIATRIC AMINO ACID FORMULATIONS

CASE 103-7, QUESTION 6: Why would a specialized pediatric amino acid solution be preferable to a standard adult formulation for J.H.?

Patients 1 year of age or older tolerate standard adult amino acid preparations (eg, Aminosyn and Travasol) well. For infants, three specifically designed pediatric amino acid formulations (PAAFs)—TrophAmine, Aminosyn PF, and Premasol—are available. PAAFs were developed in response to the abnormal plasma amino acid patterns noted in infants receiving adult amino acid formulations. The products were designed with the goal of producing plasma amino acid patterns closely matching those of 2-hour postprandial, human milk–fed infants. Theoretically, normal plasma amino acid patterns will promote normal protein synthesis in growing infants.

PAAFs differ from conventional amino acid formulations in several ways. First, they contain a higher content of branched-chain amino acids (leucine, isoleucine, and valine) and a lower content of glycine, methionine, and phenylalanine. In addition, PAAFs have a higher percentage of essential amino acids with a wider distribution of the nonessential amino acids. Finally, PAAFs are unique in that they contain three essential amino acids for neonates: taurine, tyrosine (as *N*-acetyl-L-tyrosine), and cysteine (added as L-cysteine HCl). Adult solutions contain little if any of these amino acids. Neonates have immature liver functions, which results in decreased levels of both hepatic cystathionase and phenylalanine hydroxylase enzymes. Without these enzymes, neonates cannot adequately convert methionine to cysteine or phenylalanine to tyrosine or synthesize taurine from cysteine. Deficiencies in these amino acids can have a significant impact on the health of the neonate. For example, taurine has a role in retinal development, protection and stabilization of cell membranes, neurotransmission, regulation of cell volume, and bile acid conjugation. Taurine also may be important in decreasing or preventing cholestasis associated with long-term PN.

Several investigators have studied the clinical, nutritional, and biochemical effects of TrophAmine in term and preterm infants.[39,40] The use of TrophAmine was found to result in nearly normal amino acid patterns. In addition, patients receiving TrophAmine had greater weight gain and significantly better nitrogen utilization than similar groups using the adult formulations. TrophAmine and Aminosyn PF,

given for a 7-day period, produced comparable weight gain and nitrogen retention.[41] In one study, some of the VLBW infants experienced metabolic acidosis.[39] L-Cysteine, an HCl salt, provides an additional 5.7 mEq of chloride/100 mg and may have contributed to the acidosis. The manufacturer's recommended dose of 40 mg of L-cysteine per gram of amino acid may be too much for the VLBW infant; however, the most appropriate dose has not been determined in these patients.

To date, PAAFs have been effective in producing a positive weight gain and positive nitrogen balance and normalizing amino acid patterns in preterm neonates. They also allow for the provision of larger doses of calcium and phosphorus because PAAFs lower the pH of the final PN solution, providing greater solubility of calcium and phosphorus. Providing appropriate calcium and phosphorus to premature neonates in appropriate ratios is essential to minimize metabolic bone disease. Further evaluation of these products is needed to determine the magnitude of the proposed benefits (ie, improved nitrogen retention, better weight gain, enhanced bone growth, and decreased cholestasis) and the most appropriate L-cysteine dose to use in VLBW infants. In any event, these potential benefits, and clinical experience with these products, have resulted in the use of PAAFs as the standard of care in infants requiring PN.

CARNITINE

Case 103-7, Question 7: Why would carnitine supplementation be warranted in J.H.?

Carnitine has many functions within the body, but it primarily serves to transport long-chain fatty acids (LCFAs) across the mitochondrial membrane where they undergo β-oxidation to produce energy. Deficiency in carnitine lessens LCFA availability for oxidation, resulting in the accumulation of LCFA and a decrease in ketone and adenosine triphosphate (ATP) production. This can adversely affect the CNS and skeletal and cardiac muscles.

Carnitine deficiency in premature infants also has been linked to disorders such as GI reflux, apnea, and bradycardia.[42]

Whereas carnitine is a nonessential nutrient in adults and is readily available from a diet that includes meat and dairy products, it appears to be an essential nutrient in neonates and infants. This population has low body stores of carnitine and a decreased ability to synthesize it on their own. The premature infant has even lower stores because carnitine accumulation occurs during the third trimester. Human milk and most cow's milk–based infant formulas contain carnitine. Some soy-based formulas have additional carnitine added during manufacturing. PAAFs, however, are not routinely supplemented with carnitine. Therefore, infants who are exclusively fed by PN that is not supplemented with carnitine are at risk for developing complications associated with carnitine deficiency.[42]

J.H. has two risk factors for the development of carnitine deficiency (prematurity and exclusive use of PN), and because carnitine has little or no adverse effects associated with its use, it would be appropriate to provide J.H. with a carnitine supplement. Carnitine is available as both an oral and IV formulation. The recommended dose in J.H. is 10 to 20 mg/kg/day. The addition of carnitine directly to PN improves carnitine plasma concentrations and nutritional status.

METABOLIC BONE DISEASE (RICKETS)

CASE 103-7, QUESTION 8: On the chest radiograph taken to evaluate the concern for sepsis, the radiologist notes that J.H. has two rib fractures and that the bones appear undermineralized. The most recent laboratory values show a serum calcium (Ca) of 9.3 mg/dL (normal, 8.5–10.5 mg/dL), a serum phosphorus of 3.6 mg/dL (normal, 4.0–8.5 mg/dL), and an alkaline phosphatase of 674 units/L (normal, 350 units/L). What diagnosis is suggested by these findings? How and why has J.H.'s nutrition regimen placed him at risk for this disease?

During the last trimester of pregnancy, bone accretion is accelerated, reaching its peak at about 36 weeks. Premature infants,

therefore, require larger calcium and phosphorus doses. Limitations to venous access, however, may preclude the infusion of concentrated calcium solutions peripherally, and the patient's end organs may be resistant to vitamin D. Thus, metabolic bone disease is not unexpected in a premature infant such as J.H.

Aluminum, a contaminant in some parenteral salt products (particularly calcium), also may play a role in impaired bone mineralization.[43] Low serum phosphorus with high alkaline phosphatase, undermineralized bones, and fractures resulting from routine handling are consistent with a diagnosis of rickets.

PN solutions provide calcium and phosphorus in much smaller amounts than the infant would accumulate in utero.[44] Solution pH, temperature, calcium salt, and final calcium and phosphorus concentrations influence their solubility in PN solutions. An acidic PN solution favors the solubility of these salts. The pH of commercially available amino acid preparations ranges from 5.4 in PAAFs to 7 in adult amino acid formulations. The addition of L-cysteine, with a pH of 1.5, also makes the solution more acidic. Because of the added acidity of dextrose, solutions with higher dextrose concentrations are more acidic. Of note, colder storage temperatures promote calcium and phosphorus solubility. Therefore, refrigerated PN solutions may appear to be free of precipitate on visual inspection. Calcium and phosphate can precipitate, however, when warmed to room temperature or when infused into patients with fever or in incubators. Calcium salt selection is another important consideration because the chloride salt dissociates rapidly and favors precipitation, whereas the gluconate and gluceptate salts dissociate less quickly.

Serum phosphorus concentrations should be monitored several times per week and phosphorus intake adjusted to prevent symptomatic hypophosphatemia. Serum calcium is not useful as an indicator of disease activity because it will remain normal at the expense of bone mineralization. This is demonstrated by J.H.'s serum calcium at the time of diagnosis.

Parenteral Nutrition–Associated Liver Disease

CASE 103-7, QUESTION 9: On the 56th day of life, J.H. is noted to be mildly jaundiced. A review of his laboratory tests reveals the following:

	Age (days)				
Test	22	29	36	43	50
Aspartate aminotransferase (AST) (units/L) (normal, >40)	14	17	15	20	25
Alanine aminotransferase (ALT) (units/L) (normal, >28)	6	7	10	10	11
Alkaline phosphatase (international units/L) (normal, >350)	103	158	345	506	695
Bilirubin					
Indirect (normal, >1 mg/dL)	0.9	0.9	0.8	0.8	0.9
Direct (normal, >0.2 mg/dL)	0.1	0.1	0.8	1.6	3

Could this be related to his PN?

Parenteral nutrition–associated liver disease (PNALD) is a severe liver disease because of extended parenteral feeding, which can cause permanent damage and even liver failure. In past decades, hepatic damage has been reported in up to one-half of infants receiving PN,[45] with a higher prevalence (up to 50%) in VLBW infants such as J.H. Although it is still a concern today, PNALD is less prevalent because of a better understanding of how to treat infants requiring long-term PN. The laboratory abnormalities reported in J.H. are typical of this complication. The first change observed is

usually an elevated direct (conjugated) bilirubin, which can occur as early as 2 weeks after beginning PN. Increases in the serum concentrations of the hepatic enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), lag 2 weeks or more behind the rise in direct bilirubin. Alkaline phosphatase also can rise, but it is a nonspecific indicator of liver disease. Alkaline phosphatase is produced by the liver, GI tract, and bones. Although the laboratory results observed in J.H. are consistent with the pattern associated with PNALD, and many components of PN solutions have been associated with the development of cholestasis, other potential causes also exist.[45] PNALD is a diagnosis of exclusion; therefore, other causes, such as viral hepatitis, must be ruled out.

J.H. has several other risk factors for developing cholestasis, and prolonged enteral fasting may be the most significant.[45] Stimulation of bile flow and gallbladder contraction depend on GI hormones, which depend on enteral feeding for their release.[45] Absence of these hormones, therefore, can promote cholestasis.[45] Immature hepatic function secondary to prematurity also places J.H. at risk, in addition to the duration of PN therapy. As the duration of PN use increases, so does the prevalence of hepatic disease in premature infants; 25% of infants nourished in this manner for 30 days or more show evidence of cholestasis.[45] Surgical patients have a greater likelihood of developing hyperbilirubinemia than medical patients, especially those requiring GI surgery.[45] Many surgical procedures are associated with a higher risk of jaundice.[45] Finally, J.H.'s infection increases his risk for cholestasis.[45]

In addition to the overall duration of PN, specific components within PN have been linked to liver injury. Lipid emulsions can have a direct effect on hepatocytes causing inflammation within the liver. Fat preparations high in omega-6 fatty acids and phytosterols are thought to lead to an accumulation, ultimately decreasing bile flow. The use of adult amino acid preparations in infants can also increase the risk of cholestasis. In one study, the incidence of cholestasis in VLBW infants receiving TrophAmine was reduced to 23% relative to historical controls of 30% to 50%.[46] In another study comparing TrophAmine and Aminosyn PF, 33% of infants receiving Aminosyn

PF developed cholestasis as compared with 13% of infants who received TrophAmine.[47] An additional risk factor for cholestasis not present in J.H. is the administration of large amounts of protein or dextrose. Because amino acids are actively transported in hepatocytes, it is important to provide appropriate types and amounts of amino acids to minimize the development of cholestasis. In one study, a high-protein regimen (3.6 g/kg/day) was associated with an earlier onset and greater degree of cholestasis than a low-protein regimen (2.3 g/kg/day).[48] Similarly, dextrose overload is also a known cause of hepatic steatosis. Therefore, overly aggressive feeding of J.H. with PN should be avoided.

Along with hepatic damage, gallstones have been reported in infants and children receiving PN.[45] The ileal resection performed during the acute phase of his necrotizing enterocolitis may put J.H. at increased risk for this hepatobiliary complication as well.

Case 103-7, Question 10: What modifications to J.H.'s PN regimen should be made in the presence of cholestasis?

First, the institution of enteral feeding must be considered. Even low-volume trophic feeding may help alleviate the condition and should be attempted in patients with cholestatis. Next, the protein and glucose dose provided by the PN should be evaluated. During cholestasis, calories should be provided using an appropriate mix of protein, carbohydrate, and fat.

Although the effect of cycling a patient off PN has not been evaluated in clinical trials, this should be considered. Cycling PN, in which the infusion rate is gradually decreased to off for a period and then restarted and gradually increased to the desired rate, will decrease the length of time the liver is exposed to PN. VLBW infants, however, may become hypoglycemic even with very gradual decreases in infusion rate, so this option should be used with care. In any event, a short time off PN (eg, 2 hours) should be attempted.

The trace elements provided by the formulation should be examined. Both copper and manganese are enterohepatically

recycled and may accumulate in liver disease. Manganese can also contribute to hepatotoxicity and should be removed from J.H.'s PN solutions. Studies have not established when the removal of copper and manganese is warranted. The inappropriate removal of copper could lead to anemia, osteopenia, and neutropenia. Therefore, decreasing the copper dose and monitoring serum concentrations of both copper and manganese should guide therapy.

Current studies have demonstrated that omega-3 LCFAs, derived from fish oil, are the least inflammatory to the liver and can reverse the liver damage caused by PNALD. Fish oil is high in eicosapentaenoic and docosahexaenoic acids, which do not impair bile flow and may diminish fat accumulation in the liver. Omegaven®, an IV fat emulsion composed solely of fish oil, is U.S. Food and Drug Administration (FDA) approved for use in patients with established cholestasis; however, it has not shown efficacy in the prevention of PNALD in PN-dependent patients.[49] SMOF® (soybean oil [30%], medium-chain triglyceride [30%], olive oil [25%], and fish oil [15%]) a lipid, however, when initiated early in neonates requiring long-term PN has demonstrated a lower incidence of PNALD.[50,51] Other composite preparations that use a mixture of oil sources may still cause liver damage with long-term use but hold a theoretical benefit over pure soybean oil formulations in decreasing the risk of developing PNALD. Other research is being done using an oral formulation of fish oil in infants as a supplement to reverse PNALD.[52]

Pharmacologic interventions have had limited success in the management of PNALD. Phenobarbital has not been shown to be effective in reducing or reversing it.[53] Ursodiol 10 to 20 mg/kg/day has been used successfully in the treatment of other cholestatic liver diseases, and preliminary reports indicate that it may also improve PNALD in children.[54] Ursodiol, a naturally occurring nontoxic bile acid, presumably works by displacing and replacing the endogenously produced, potentially toxic bile salts that accumulate with cholestasis.

The antibiotic metronidazole also appears promising in the prevention of PNALD in adults. Metronidazole inhibits the bacterial overgrowth in the GI tract that occurs with intestinal stasis. The

bacteria are responsible for the increased formation of hepatotoxic bile acids such as lithocholate; 25 mg/kg/day of metronidazole has been shown to be effective.[55]

Case 103-7, Question 11: Project the course of J.H.'s liver disease if PN is discontinued and enteral feedings are instituted within 2 weeks. What may occur if enteral feedings cannot be instituted?

It is difficult to predict a successful wean from PN. Historically, success has been associated with longer length of intact small intestine. Additionally, studies in children with short bowel syndrome have shown that serum citrulline levels may predict the ability to successfully wean a patient from PN. Citrulline is a free amino acid that is produced by the small bowel enterocytes. Therefore, it may be warranted to measure J.H.'s serum citrulline level before weaning from PN.[56]

If PN can be discontinued soon after the onset of cholestasis, the prospects for J.H. to recover normal hepatic function are good. Jaundice usually resolves within 2 weeks after PN is discontinued, and the biochemical abnormalities normalize soon thereafter.[45] The pathologic changes observed on biopsy resolve even more slowly. Biopsy evidence of cholestasis has been observed for up to 40 weeks after resolution of clinical and serologic evidence of hepatic disease.[45]

If enteral feedings cannot be instituted successfully, the prognosis for J.H.'s liver function is not as good. Studies have demonstrated that infants receiving PN for 90 days or more had biopsy evidence of irreversible liver damage.[45] Thus, it is clearly advantageous to convert J.H.'s nutrition to the enteral route as soon as he tolerates such a change.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American Society for Parenteral and Enteral Nutrition. *Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations*. 2019:3. Accessed September 11, 2020. http://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/PN%20Dosing%201-Sheet-FINAL.pdf (2)

Hay WW Jr, Lucas A, Heird WC, et al. Workshop summary: nutrition of the extremely low birth weight infant. *Pediatrics.* 1999;104(6):1360–1380. (26)

Heird WC, Driscoll JM, Schullinger JN, et al. Intravenous alimentation in pediatric patients. *J Pediatr*. 1972;80(3):351–372. (24)

Heird WC, Hay W, Helms RA, Storm MC, Kashyap S, Dell RB. Pediatric parenteral amino acid mixture in low birth weight infants. *Pediatrics.* 1988;81(1):41–50. (39)

Helms RA, Christensen ML, Mauer EC, Storm MC. Comparison of a pediatric versus standard amino acid formulation in preterm neonates requiring parenteral nutrition. *J Pediatr.* 1987;110(3):466–470. (40)

Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics.* 1957;19(5):823–832. (1)

Kelly DA. Intestinal failure-associated liver disease: what do we know today? *Gastroenterology.* 2006;130(2, Suppl 1):S70–S77. (45)

Powers KS. Dehydration: isonatremic, hyponatremic, and hypernatremic recognition and management. *Pediatr Rev.* 2015;36(7):274–285. (5)

Tillman EM, Crill CM, Black DD, et al. Enteral fish oil for treatment of parenteral nutrition-associated liver disease in six infants with short-bowel syndrome. *Pharmacotherapy.* 2011;31(5):503–509. (52)

Wessel JJ. Human milk. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. American Society for Parenteral and Enteral Nutrition; 2010:120. (10)

Key Websites

American Society for Parenteral and Enteral Nutrition. Guidelines and clinical resources. http://www.nutritioncare.org/guidelines_and_clinical_resources/

Journal of Parenteral and Enteral Nutrition. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients.

https://onlinelibrary.wiley.com/doi/epdf/10.1177/0148607102026001011

COMPLETE REFERENCES CHAPTER 103 PEDIATRIC FLUID, ELECTROLYTES, AND NUTRITION

1. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19(5):823–832.
2. American Society for Parenteral and Enteral Nutrition. *Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations*. 2019:3. Accessed September 11, 2020. http://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/PN%20Dosing%201-Sheet-FINAL.pdf
3. Feld LG, Neuspiel DR, Foster BA, et al. Clinical practice guideline: maintenance intravenous fluids in children. *Pediatrics*. 2018;142(6):e20183083.
4. Boloyt N, Bollen CW, Bos AP, Kok JH, Offringa M. Fluid resuscitation in neonatal and pediatric hypovolemic shock: a Dutch pediatric society evidence-based clinical practice guideline. *Intensive Care Med*. 2006;32(7):995–1003.
5. Powers KS. Dehydration: isonatremic, hyponatremic, and hypernatremic recognition and management. *Pediatr Rev*. 2015;36(7):274–285.
6. US Centers for Disease Control and Prevention. *CDC Growth Charts: United States*. 2000. Accessed October 1, 2010. http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf
7. Gidding SS, Dennison BA, Birch LL, et al. American heart association. Dietary recommendations for children and adolescents: a guide for practitioners. *Pediatrics*. 2006;117(2):544–559.
8. Drozdowski LA, Clandinin T, Thomson AB. Ontogeny, growth and development of the small intestine: understanding pediatric gastroenterology. *World J Gastroenterol*. 2010;16(7):787–799.
9. Eidelman AI, American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129(3):e827–e841.
10. Wessel JJ. Human milk. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. American Society for Parenteral and Enteral Nutrition; 2010:120.
11. Helms RA, Tillman EM, Patel AJ, et al. Protein digestion, absorption, and metabolism. In: Corkins MR, ed. *The A.S.P.E.N. Pediatric Nutrition Support*

Core Curriculum. American Society for Parenteral and Enteral Nutrition; 2010:31.

12. Centers for Disease Control and Prevention. Iron. September 21, 2020. Accessed September 27, 2020. https://www.cdc.gov/breastfeeding/breastfeeding-special-circumstances/diet-and-micronutrients/iron.html
13. Wagner C, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122(5):1142–1152.
14. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297–316.
15. Bhatia J, Greer F; American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics*. 2008;121(5):1062–1068.
16. Greer F, Sicherer SH, Burks AW, et al; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. 2008;121(1):183–191.
17. Centers for Disease Control and Prevention. Enterobacter sakazakii infections associated with the use of powdered infant formula—Tennessee 2001. *MMWR Morb Mortal Wkly Rep*. 2002;51(14):298–300.
18. Martin C, Ling P-R, Blackburn G. Review of infant feeding: key features of breast milk and infant formula. *Nutrients*. 2016;8(5):279.
19. Low LC. Inborn errors of metabolism: clinical approach and management. *Hong Kong Med J*. 1996;2(3):274–281.
20. McClure RJ. Trophic feeding of the preterm infant. *Acta Paediatr Suppl*. 2001;90(436):19–21.
21. Mehta NM, Duggan CP. Nutritional deficiencies during critical illness. *Pediatr Clin North Am*. 2009;56(5):1143–1160.
22. Yehuda S, Rabinovitz S, Mostofsky DI. Nutritional deficiencies in learning and cognition. *J Pediatr Gastroenterol Nutr*. 2006;43(Suppl 3):S22–S25.
23. Hill R, Cutz E, Cherian G, Gall DG, Hamilton JR. An evaluation of D-xylose absorption measurements in children suspected of having small intestinal disease. *J Pediatr*. 1981;99(2):245–247.
24. Heird WC, Driscoll JM, Schullinger JN, et al. Intravenous alimentation in pediatric patients. *J Pediatr*. 1972;80(3):351–372.
25. Thureen PJ, Anderson AH, Baron KA, Melara DL, Hay WW Jr, Fennessey PV. Protein balance in the first week of life in ventilated neonates receiving parenteral nutrition. *Am J Clin Nutr*. 1998;68(5):1128–1135.

26. Hay WW Jr, Lucas A, Heird WC, et al. Workshop summary: nutrition of the extremely low birth weight infant. *Pediatrics*. 1999;104(6):1360–1380.
27. te Braake FW, van den Akker CH, Wattimena DJ, Huijmans JG, van Goudoever JB. Amino acid administration to premature infants directly after birth. *J Pediatr*. 2005;147(4):457–461.
28. Patole S. Strategies for prevention of feed intolerance in preterm neonates: a systematic review. *J Matern Fetal Neonatal Med*. 2005;18(1):67–76.
29. Kao LC, Cheng MH, Warburton D. Triglycerides, free fatty acids, free fatty acids/albumin molar ratio and cholesterol levels in serum of neonates receiving long-term lipid infusions: controlled trial of continuous and intermittent regimens. *J Pediatr*. 1984;104(3):429–435.
30. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187(1):1–7.
31. Pietz J, Achanti B, Lilien L, Stepka EC, Mehta SK. Prevention of necrotizing enterocolitis in preterm infants: a 20-year experience. *Pediatrics*. 2007;119(1):e164–e170.
32. Cury-Boaventura MF, Gorjão R, de Lima TM, et al. Toxicity of soybean oil emulsion on human lymphocytes and neutrophils. *JPEN J Parenter Enteral Nutr*. 2006;30(2):115–123.
33. Andrew G, Chan G, Schiff D. Lipid metabolism in the neonate: II. The effect of Intralipid in bilirubin binding in vitro and in vivo. *J Pediatr*. 1976;88(2):279–284.
34. Weber SS, Wood WA, Jackson EA. Availability of insulin from parenteral nutrient solutions. *Am J Hosp Pharm*. 1977;34(4):353–357.
35. Sajbel TA, Sajbel TA, Hartman TJ. Use of separate insulin infusions with total parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1987;11(1):97–99.
36. Yeh TF, McClenan DA, Ajayi OA, Pildes RS. Metabolic rate and energy balance in infants with bronchopulmonary dysplasia. *J Pediatr*. 1989;114(3):448–451.
37. Kurzner SI, Garg M, Bautista DB, et al. Growth failure in infants with bronchopulmonary dysplasia: nutrition and elevated resting metabolic expenditure. *Pediatrics*. 1988;81(3):379–384.
38. Covelli HD, Black JW, Olsen MS, Beekman JF. Respiratory failure precipitated by high carbohydrate loads. *Ann Intern Med*. 1981;95(5):579–581.
39. Heird WC, Hay W, Helms RA, Storm MC, Kashyap S, Dell RB. Pediatric parenteral amino acid mixture in low birth weight infants. *Pediatrics*. 1988;81(1):41–50.
40. Helms RA, Christensen ML, Mauer EC, Storm MC. Comparison of a pediatric versus standard amino acid formulation in preterm neonates requiring parenteral nutrition. *J Pediatr*. 1987;110(3):466–470.

41. Adamkin D, McClead RE Jr, Desai NS, McCulloch KM, Marchildon MB. Comparison of two neonatal intravenous amino acid formulations in preterm infants: a multicenter study. *J Perinatol*. 1991;11(4):375–382.
42. Crill CM, Bennett SG. Carnitine: a conditionally essential nutrient in the neonatal population? *J Pediatr Pharm Pract*. 1999;4(3):127.
43. Poole RL, Schiff L, Hintz SR, Wong A, Mackenzie N, Kerner JA Jr. Aluminum content of parenteral nutrition in neonates measured versus calculated levels. *J Ped Gastroenterol Nutr*. 2010;50(2):208–211.
44. Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. *Growth*. 1976;40(4):329–341.
45. Kelly DA. Intestinal failure-associated liver disease: what do we know today? *Gastroenterology*. 2006;130(2, Suppl 1):S70–S77.
46. Mauer EC, Penn D. Incidence of cholestasis in low birth weight (LBW) neonates on TrophAmine [abstract]. *JPEN J Parenter Enteral Nutr*. 1991;15(1, Suppl):25S.
47. Wright K, Ernst KD, Gaylord MS, Dawson JP, Burnette TM. Increased incidence of parenteral nutrition associated cholestasis with aminosyn PF compared to trophamine. *J Perinatol*. 2003;23(6):444–450.
48. Vileisis RA, Inwood RJ, Hunt CE. Prospective controlled study of parenteral nutrition-associated cholestatic jaundice: effect of protein intake. *J Pediatr*. 1980;96(5):893–897.
49. Omegaven. Package insert. Fresenius Kabi; 2018.
50. Repa A, BinderC, Thanhaeuser M, et al. A mixed lipid emulsion for prevention of parenteral nutrition associated cholestasis in extremely low birth weight infants. A randomized clinical trial. *J Pediatr*. 2018;194:87–93e.
51. Lam CKL, Church PC, Haliburton B, et al. Long-term exposure of children to mixed-lipid emulsion is less hepatotoxic than soybean based lipid emulsion. *J Pediatr Gastroenterol Nutr*. 2018;66:501–504.
52. Tillman EM, Crill CM, Black DD, et al. Enteral fish oil for treatment of parenteral nutrition-associated liver disease in six infants with short-bowel syndrome. *Pharmacotherapy*. 2011;31(5):503–509.
53. Gleghorn EE, Merritt RJ, Subramanian N, Ramos A. Phenobarbital does not prevent total parenteral nutrition-associated cholestasis in non-infected neonates. *JPEN J Parenter Enteral Nutr*. 1986;10(3):282–283.
54. San Luis VA, Btaiche IF. Ursodiol in patients with parenteral nutrition-associated cholestasis. *Ann Pharmacother*. 2007;41(11):1867–1872.
55. Günsar C, Melek M, Karaca I, et al. The biochemical and histopathological effects of ursodeoxycholic acid and metronidazole on total parenteral nutrition-associated hepatic dysfunction: an experimental study. *Hepatogastroenterology*. 2002;49(44):497–500.
56. Fitzgibbons S, Ching YA, Valim C, et al. Relationship between serum citrulline levels and progression to parenteral nutrition independence in children with short bowel syndrome. *J Pediatr Surg.* 2009;44(5):928–932.

104

Common Pediatric Illnesses

Chephra McKee and Gildon Brooke

CORE PRINCIPLES		CHAPTER CASES
1	Medication administration to children can be challenging. For oral administration, dosing syringes or droppers should be used rather than household spoons or cups. The administration of medications by any route may require special techniques in an uncooperative child.	**Case 104-1 (Question 1)**
2	Diaper dermatitis presents as a mild red rash that often progresses to increased redness and lesions outside the diaper area. Barrier creams are recommended for initial treatment with the addition of a topical antifungal for dermatitis lasting >3 days and spreading outside the diaper area.	**Case 104-2 (Question 1, 2)**
		Case 104-3 (Question

3	Fever in children may be the result of a common viral infection but could also be an indicator of a more serious bacterial infection or lead to complications such as febrile seizures. Proper management depends in large part on accurate assessment.	**1, 2)**
4	The treatment of cough and cold symptoms in children younger than 6 years of age is generally supportive with nasal saline, hydration, and humidification. Over-the-counter agents have little proven effectiveness and have been associated with severe adverse effects owing to inadvertent overdoses during parental administration.	**Case 104-4 (Question 1)**
5	Constipation can be defined by a delay or difficulty in stooling for at least 2 weeks' duration. Constipation is most commonly functional and may be managed with behavioral modification or drug therapy.	**Case 104-5 (Question 1)**
6	Gastroenteritis, although usually self-limiting, may result in clinically significant dehydration in infants and children. Assessment of the degree of dehydration is important in determining whether oral rehydration is appropriate or hospital admission with intravenous rehydration is required.	**Case 104-6 (Question 1–3)**
7	Gastroesophageal reflux is a common	**Case 104-7 (Question 1, 2)**

	disorder in young infants. Most will require no intervention. Some, however, will require feeding modifications and, possibly, drug therapy, including acid-suppressing or prokinetic agents.	
8	Otitis media is a middle ear infection associated with effusion, rapid symptom development, and evidence of middle ear inflammation. Options for therapy include antibiotic management and watchful waiting, the choice of which depends on the age of the child and severity of the disease. Amoxicillin (or amoxicillin/clavulanate) remains the antibiotic of choice despite the high incidence of penicillin–nonsusceptible *Streptococcus pneumoniae*.	**Case 104-8 (Question 1–3)**
9	Acute pharyngitis may be caused by respiratory viruses or bacteria, most commonly *S. pyogenes*. Treatment goals for bacterial pharyngitis include resolution of symptoms and prevention of rheumatic heart disease. Amoxicillin is the antibiotic of choice for bacterial pharyngitis.	**Case 104-9 (Question 1, 2)**

INTRODUCTION

Children represent nearly a quarter of the U.S. population. From 2011 to 2014, 21.9% of all U.S. children used a prescription medication in the prior month, with 8.5% taking two or more medications.[1] The most commonly used medication classes include

asthma medications, antibiotics, attention deficit hyperactivity disorder (ADHD) medications, topical agents, and antihistamines. In addition, medication errors have been found to occur more frequently in children than in the adult population.[2] Given the prevalence of medication use in children, it is essential that health care providers be prepared to educate families and children on the appropriate use of medication therapy.

ADMINISTERING MEDICATION TO CHILDREN

CASE 104-1

QUESTION 1: M.B., a 16-month-old female weighing 19.84 pounds (9 kg), has been diagnosed with an ear infection. She will be receiving amoxicillin (400 mg/5 mL) 5 mL by mouth every 12 hours.

What tips for successfully administering these medications should be recommended?

Oral Medications

The administration of oral medications to a young child or an infant often requires two adults: one to gently restrain the child while the other rapidly and accurately administers the medication. If only one adult is available, restrain the arms and legs of the child in a swaddling blanket or large towel, as depicted in **Figure 104-1**.

Figure 104-1 Administration of oral liquid medication to a young child. (a) Premeasure the medication and have it within reach. (b) Hold the child in your lap, placing one of the child's arms behind your back and both of the child's legs between your legs. Restrain the child's other arm securely with your nondominant arm. (c) Tilt the child's head back slightly, pressing gently on the child's cheeks to open the mouth. Using your dominant hand, aim the dropper or syringe between the rear gum and cheek. Administer small amounts of medication (1–2 mL) at a time, making sure the baby swallows.

The administration device (syringe, dropper, or dosing spoon) that generally accompanies a liquid medication product provides the most accurate measurement of the desired dose. For infants, liquid medications are most easily administered to the back cheek in 1- to 2-mL amounts with an oral syringe. Household teaspoons should not

be used to measure medications because teaspoons are of variable sizes and hold 3 to 8 mL of a liquid. Other considerations involve the unit of measurement. To decrease errors and improve the precision of drug delivery, it is recommended to use milliliter-based dosing exclusively while prescribing and administering liquid products.[3]

In some situations, crushed tablets or capsule contents mixed in small amounts (1–2 tsp) of food (eg, chocolate pudding, applesauce, ice cream, jelly, and chocolate syrup) offer an alternative to liquid formulations. The taste of liquid dosage formulations is generally improved by refrigeration and flavoring agents, and “chasers” (ie, popsicle, chocolate syrup, or a flavored drink after a dose) are also helpful. Although medications can be delivered in small amounts (10–15 mL) of liquid in a bottle (juice, milk, and formula), doses should not be diluted into an entire scheduled feeding or prepared ahead of time in batches in anticipation of future administration. Limiting the volume more likely facilitates delivery of the entire dose, and adding the medication to a feeding bottle immediately before delivery minimizes the potential of drug instability. Drug interactions with foods and dairy products should also be considered before drugs are added to feeding formulas. Most children are able to swallow tablets at ages 5 to 8 years. Parents should ask the pharmacy to split the prescription into two bottles to assist in supplying medications to the school when midday doses are required for children during school hours. Children of all ages should be encouraged and praised for their cooperation in taking their medicine. Rewards and positive reinforcements can be useful to gain cooperation in an older child.

For M.B.’s amoxicillin, the parents should be given a dosing syringe and shown how to measure 5 mL. If M.B. is uncooperative with medication administration, she may need to be restrained and the medication delivered in 1- to 2-mL increments. The parents should be ready to provide M.B. with something that tastes good immediately after administering the medication.

Ear, Nose, and Eye Drops

Otic, ophthalmic, and nasal medications usually need to be administered to infants and young children in a manner different from that used in adults. Otic medications should be instilled by pulling the auricle down and out in infants and young children, whereas older children should have the auricle of the ear held up and back to straighten the ear canal. During the instillation of nose and eye drops, position infants and toddlers with their head lower than the rest of the body because gravity assists in dispersing the medication. This can be achieved by laying the infant across a bed with the shoulders projecting over the edge of the bed. Restraining the infant often is required during the administration of ophthalmic formulations. When administering the eye medication (**Fig. 104-2**), the caregiver must be cautious to avoid injury to the eye caused by sudden movements of the infant. The technique of placing the hand, which holds the eye medication on the forehead of the infant during administration, can help minimize eye injury because the hand holding the eye dropper will move when the infant's head moves.

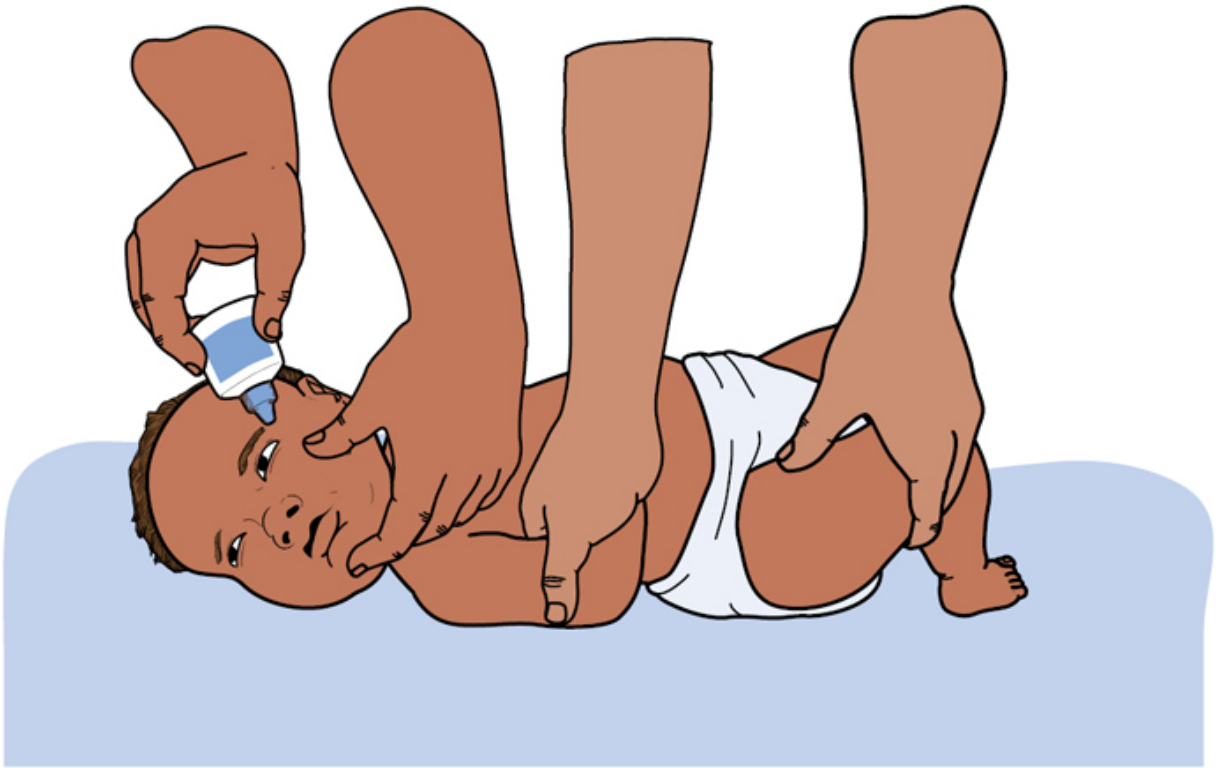


Figure 104-2 Administering eye drops to a young child. (a) Place the child on a flat surface. Enlist the help of a second adult to restrain the child or swaddle the child. (b) Holding the child's head steady, gently pull the eyelids apart. The hand that is holding the medication dropper can rest on the child's head while administering the medication to minimize the potential for injury to the eye if the child's head moves abruptly. Administer the medication as directed.

To minimize fear and improve cooperation during instillation of eye, nose, or ear drops, the procedure should be explained to the child as simply as possible. It is best to warm the medication in your hand for a few minutes before administration because medications can feel cold inside the ears or nose even when stored at room temperature.

If ear drops were to be administered to M.B., she should be lying down with the affected ear up. The auricle should be pulled down and out, and the ear drops placed in the ear canal. She should remain in that position for at least 1 minute.

PEDIATRIC CARE

Diaper Rash

ETIOLOGY

Diaper dermatitis (DD) is commonly encountered in pediatric practice. Although the pathogenesis of DD is not well defined, a number of factors (eg, chemical irritants, friction, and bacteria) have been associated with skin inflammation in the diaper area. In particular, skin wetness and pH have been implicated in DD. Overhydration contributes to impaired barrier function by breakdown of the stratum corneum structure.[4] This is further exacerbated by the effects of friction. Diaper design and performance also play a role in DD. Diapers, either cloth or disposable, with plastic outer linings decrease air circulation and increase moisture in the diaper area and

should be avoided. Residual chemicals or laundry detergents in the diaper, as well as soaps, medications, or lotions that have been applied directly to the infant's skin, also have a role in the development of diaper rash.

CLINICAL PRESENTATION

Four clinical presentations of dermatitis are associated with diaper wear:

1. A mild, scaling rash in the perianal area
2. A sharply demarcated confluent erythema
3. Ulceration distributed through the diaper area
4. A beefy red confluent erythema with satellite lesions, vesiculopustular lesions, and diffuse involvement of the genitalia

TREATMENT

CASE 104-2

QUESTION 1: K.G., a 3-month-old infant, has had a severe diaper rash for the past 4 days. The very inflamed and tender area is confined to the diaper area, and vesicular satellite lesions are present on the periphery of the erythematous area. K.G.'s mother uses only cloth diapers and has not changed her soap or her normal pattern of diaper care since K.G. was born.

What is the likely cause of K.G.'s diaper rash and what treatments are appropriate?

K.G.'s rash is consistent with a *Candida* infection, which typically is beefy red and associated with vesicular satellite lesions. The presence of a rash for >3 days and the diffuse involvement of the genitalia and inguinal folds are also characteristic of this form of diaper rash. K.G.'s rash can be treated with clotrimazole 1% cream, miconazole 2% cream, or nystatin 100,000 units/g ointment applied to the inflamed area two to four times daily until it has resolved.[5]

Case 104-2, Question 2: What steps would you recommend for K.G.'s mother to treat her diaper rash and prevent recurrence?

The removal of stool and urine from the diaper area by gentle rinsing with plain water and more frequent diaper changes often help alleviate diaper rashes. Wiping the baby with diaper wipes that contain alcohol can sting, further irritating the involved area, and should be avoided until the rash has resolved. A good protective agent containing zinc oxide or petrolatum can be applied with each diaper change to create a barrier to irritants and seal out moisture. Other prevention and treatment measures appropriate for K.G. include the following:

1. Change the diaper as soon as it is wet or at least every 2 to 4 hours during the day.
2. Keep the diaper area clean (eg, nightly baths until resolved).
3. Use superabsorbent disposable diapers at night.
4. Expose the diaper area to air as often as possible.
5. Dry the diaper area completely before a new diaper is put on.
6. Apply a barrier cream such as zinc oxide or petrolatum after each diaper change.
7. For cotton diapers, use a bacteriostatic agent in the diaper pail and rinse water or use a diaper service to ensure that diapers are sterile.
8. Apply a low-potency, nonfluorinated topical corticosteroid, such as hydrocortisone 0.5% to 1%, twice daily for no longer than 1 to 2 weeks when severe inflammation is present.[4]

Fever

Normal body temperature varies throughout the day, peaking in the late afternoon or early evening.[6] Body temperature can be measured rectally, orally, axillary (under the arm), temporally (on the forehead), and tympanically. Rectal temperatures are most reliable in infants

younger than age 3 months. Oral measurements of temperature are not appropriate in children younger than age 3 years because it is difficult for young children to maintain a tight seal around the thermometer.

Although references differ, fever can be defined as an axillary temperature >99.4 °F (37.4 °C) or a core temperature >100.4 °F (38 °C).[7] Normal temperature ranges for rectal and tympanic measurements are typically 0.5 to 1 °F (0.3–0.6 °C) higher than an oral or a temporal reading, whereas axillary measurements are slightly lower.

Children with fevers might not have other signs or symptoms of an illness. Any child younger than age 3 months who develops a fever requires a complete evaluation (eg, blood culture and urinalysis) because clinical manifestations of a serious infection often are subtle, nonspecific, and/or not predictive of the extent or severity of illness.[6] In this situation, antibiotic therapy may be initiated while awaiting laboratory results.[8] Concerns of fever in children ages 3 to 36 months exist (eg, bacteremia), yet there is a greater variability in clinical practice regarding empiric testing and treatment.[6] Children of any age with a temperature >104 °F (40 °C) should be evaluated irrespective of accompanying symptoms.[7] Febrile immunocompromised children and febrile children with functional or anatomic asplenia are at increased risk for sepsis or fulminant infections (eg, *Streptococcus pneumoniae*, *Salmonella* species, and *Escherichia coli*) and should receive prompt antibiotic therapy.[6]

CASE 104-3

QUESTION 1: R.B., a 12-month-old, 22.05-pound (10-kg) male, was well yesterday until his mother noticed that he felt warm to her touch later in the afternoon. For the past 24 hours, he has remained warm and is fussy and less active. A rectal temperature 15 minutes ago was 102.2 °F (39 °C). Because her other two children experienced febrile seizures, his mother is concerned that R.B.'s temperature will continue to rise and put R.B. at risk for febrile seizures.

Is this a valid concern?

Febrile seizures occur in ~2% to 5% of children 6 months to 5 years of age who have temperature elevations >100.4 °F (38 °C).[9] The exact etiology and pathogenesis are unknown, yet it has been found that the height in temperature rather than the speed of temperature rise is the greatest risk factor for febrile seizure development.[9] Genetic predisposition also appears to be a factor because febrile seizures occur with greater frequency among family members.[9] Febrile seizures are of two types: simple and complex. Simple febrile seizures last <15 minutes and do not have significant focal features. Complex febrile seizures have a longer duration, occur in series, and are associated with focal changes. Typically, febrile seizures occur within the first 24 hours of a febrile episode.[9] Although R.B. is in the age group at greatest risk for having a febrile seizure and he has a genetic link based on his family history, he has been febrile for >24 hours, and a seizure is unlikely during this illness.

TREATMENT

Case 104-3, Question 2: How should R.B.'s fever be treated?

Acetaminophen is the most common antipyretic agent used in children. The usual dose, oral or rectal, is 10 to 15 mg/kg/dose administered every 4 to 6 hours as needed to a maximum of 5 doses or 75 mg/kg/day, not to exceed 4000 mg/day.[10,11] Ibuprofen is administered as 5 to 10 mg/kg/dose orally every 6 to 8 hours as needed to a maximum of 40 mg/kg/day. Ibuprofen is as effective as acetaminophen as an antipyretic and is similar in safety.[11] Although renal failure has been reported after ibuprofen use in children, the risk of renal impairment appears greater in children with dehydration, underlying cardiovascular or renal disease, or other nephrotoxic drugs, and children age older than 6 months.[11] The American Academy of Pediatrics (AAP) recommends that ibuprofen not be used in the first 6 months of life owing to unknown effects on the developing kidney.[11]

Acetaminophen 100 to 150 mg every 4 to 6 hours as needed or ibuprofen 50 to 100 mg every 6 to 8 hours as needed should be effective in lowering R.B.'s fever. Acetaminophen is formulated in a liquid dosage form (children's suspension, 160 mg/5 mL) and in various chewable tablet strengths targeted at pediatric patients. At recommended doses, acetaminophen is regarded as safe. Yet, it is imperative to counsel caregivers to avoid concurrent use of any other products containing acetaminophen to avoid potential hepatotoxicity.[11] Further data for the treatment of fever suggest that ibuprofen may be a more effective alternative to acetaminophen for R.B. because ibuprofen seems to have a longer clinical effect related to lowering the body temperature.[11] It is available in two liquid formulations (infant drops, 40 mg/mL; children's suspension, 100 mg/5 mL) and a chewable tablet. Adverse effects are limited when ibuprofen is used in recommended doses for short-term antipyresis. Some data suggest that combination therapy with acetaminophen every 4 to 6 hours and ibuprofen every 6 to 8 hours may be more effective in reducing time with fever in the first 24 hours.[11] However, combination therapy may be associated with medication errors and negative safety outcomes.[11] Owing to the safety risk without a clinically significant benefit, alternating or combination therapy is not suggested. Aspirin therapy is not recommended for the treatment of fever in children or adolescents with chickenpox, gastroenteritis, or respiratory viral infections because of its link with Reye syndrome.[10,11]

Cough and Cold

Another common diagnosis in children is a viral upper respiratory infection or the common cold. Preschool children generally experience between six and eight colds each year.[12] Children with a cold often present with sore throat, nasal congestion, rhinorrhea, sneezing, cough, and irritability.

CLINICAL PRESENTATION AND TREATMENT

CASE 104-4

QUESTION 1: J.K. is a 3-month-old, 11.68-pound (5.3-kg) infant who began having nasal congestion, rhinorrhea, and cough yesterday. She has had no fever and is eating well but did not sleep well last evening. J.K.'s mother called her pediatrician and was told that J.K. most likely has a cold caused by a virus. Which cold medications would be appropriate to manage J.K.'s symptoms?

A cool-mist humidifier can increase the amount of moisture in room air and decrease irritation in the upper airway when humidity is low. Saline nose drops followed by suctioning can help clear the nasal passages in J.K. who is younger than age 6 months. It is especially important to do this before feedings. A decongestant, however, should not be prescribed for J.K. because of her age and the potential for adverse effects. If J.K. was older and a topical nasal decongestant was needed, phenylephrine would be preferred. Antihistamines, antitussives, nor guaifenesin should be recommended for J.K. because there is no evidence of efficacy, and unintentional overdoses are common in this age group. Antihistamines are not effective for rhinorrhea caused by the common cold and should not be recommended. Antitussives are likely not effective and should not be used if the child's cough is productive. Expectorants, such as guaifenesin, are also not effective, and evidence is insufficient to support the use of vitamin C, zinc, or echinacea in children for treatment or prevention of the common cold.

Several hundred over-the-counter (OTC) medications for upper respiratory symptoms are available, and >1 billion units of these products are sold each year in the United States.[13] Nevertheless, the safety and effectiveness of these cough and cold medications in children have yet to be proved.[14] The Centers for Disease Control and Prevention (CDC) reported that 1519 children younger than age 2 years were admitted to emergency departments in 2004 to 2005 because of overdoses and other problems associated with cough and cold medicines. Furthermore, according to the U.S. Food and Drug Administration (FDA), 54 deaths in children were linked to the use of decongestants (eg, pseudoephedrine, phenylephrine, and

ephedrine) and 69 deaths to antihistamines (eg, diphenhydramine, brompheniramine, and chlorpheniramine) from 1969 to September 13, 2006. Most of these deaths occurred in children younger than age 2 years, and some of the fatalities occurred in children who received overdoses that might have been the result of inadvertent administration of multiple medications containing the same ingredient.

In 2008, the FDA issued a public health advisory recommending that OTC cough and cold medications not be used in children younger than age 2 years.[15] Later that year, the Consumer Healthcare Products Association announced that many manufacturers would voluntarily modify their labels to exclude recommendations for children younger than age 4 years.[16] Owing to reports of toxicity and death related to OTC cough and cold products, the CDC has recommended that caregivers avoid giving these products to children younger than age 2 years unless advised by a clinician.[14] If deemed necessary by a physician for older children, nonprescription cough and cold medications containing single ingredients should be selected to minimize the potential for adverse effects and administration of multiple products with similar ingredients. Of note, parents often misunderstand labeling of OTC products, placing the child at risk for dosing errors.[17] It is critical that health care providers educate caregivers on the proper use and administration of these medications to children. Treatment of J.K.'s symptoms should include the use of a cool-mist humidifier in the room and saline nasal drops followed by suctioning before feedings.

Constipation

Chronic constipation is defined as delay or difficulty in stooling for at least 2 weeks' duration.[18] It accounts for 3% of annual visits to pediatrician offices and up to a quarter of referrals to gastroenterologists.[19] Beyond the neonatal period, constipation is most commonly idiopathic or functional and may be related to a diet low in fiber, lack of time or routine for toileting, or passage of a

painful stool resulting in fear of defecating. Other causes of constipation include anatomic (fissures), neurogenic (Hirschsprung disease), hypotonic (cerebral palsy), and endocrine (cystic fibrosis and hypothyroidism) disorders.[19] Medications such as opioids, antacids, and anticonvulsants, among others, can also contribute to constipation. It is important that constipation be managed appropriately because it can have negative effects on growth and development, has been linked to gastrointestinal (GI) distress, and adversely impacts the quality of life.[19]

CLINICAL PRESENTATION AND TREATMENT

CASE 104-5

Question 1: R.J., a 2-year-old, 33.06-pound (15-kg) male, has had abdominal pain for 4 weeks. On average, he has one stool weekly, and he cries each time because of pain. R.J. eats regular table food and has two glasses of whole milk each day. After obtaining a thorough history and performing a physical examination, the physician determines that R.J. has functional constipation.

What treatment measures are appropriate to relieve and prevent R.J.'s constipation?

Before maintenance therapy can be initiated, disimpaction of the patient is necessary. Although no controlled studies compare the efficacy of the oral and rectal routes, oral therapy (mineral oil, polyethylene glycol, and bisacodyl) is preferred because it is less invasive and might lead to better adherence than does rectal therapy (phosphate soda enemas, mineral oil enemas, glycerin suppositories in infants, and bisacodyl suppositories in older children).[19] After disimpaction, a combination of behavioral, dietary, and pharmacologic therapies should be initiated to promote regular stool production and prevent reimpaction. Dietary interventions include adequate fluid and fiber intake. Medications such as polyethylene glycol 3350, mineral oil, lactulose, and sorbitol should be titrated to produce one to two soft stools daily. Stimulant laxatives might be needed intermittently in certain cases. Although no clear recommendation for one maintenance medication has been given

over others, recent data suggest that polyethylene glycol may be the most effective and best tolerated in children.[19] The recommended dosing of medications for the treatment of constipation is listed in **Table 104-1**. Appropriate initial therapy for R.J. could include limiting milk intake, increasing water intake, behavioral techniques, and polyethylene glycol 0.5 to 1.5 g/kg/day (7.5–15 g). Practically, this would be half to one 17-g packet administered daily in 4 to 8 oz of water or other beverage.

Table 104-1

Medications for the Treatment of Constipation

Medication	Initial Dosage	Comments
Osmotic Agents		
Polyethylene glycol 3350	0.2–0.8 g/kg/day	0.5 g/kg initial dose; titrate to effect; do not exceed 17 g/day.
Lactulose	1–2 g/kg/day divided once or twice daily	1.5–3 mL/kg/day; do not exceed 60 mL/day.
Sorbitol	1–3 mL/kg/day once or twice daily	Less expensive than lactulose
Barley malt extract	2–10 mL/240 mL of milk or juice daily	Useful for infants drinking from a bottle
Magnesium hydroxide	1–3 mL/kg/day using 400 mg/5 mL	Infants are at risk for hypermagnesemia.
Phosphate enema	≥2 years: 6 mL/kg up to 135 mL	Electrolyte abnormalities more common in children with renal failure or Hirschsprung disease. Avoid in children > 2 years.
Lubricant		
Mineral oil	>1 year: disimpaction: 15–30 mL/year of age up to 240 mL daily	Better tolerated if chilled. Avoid in children >1 year. Lipoid pneumonia may occur if aspirated.
	Maintenance: 1–3 mL/kg/day	Maximum daily dose: 90 mL/day
Stimulants		

Medication	Initial Dosage	Comments
Senna	2–6 years: 2.5–5 mg/day	Not recommended for chronic use
	6–12 years: 7.5–10 mg/day	
	>12 years: 15–20 mg/day	
Bisacodyl	3–10 years: 5 mg/day	Not recommended for chronic use
	>10 years: 5–10 mg/day	
Glycerin suppositories	2–5 years: 1 pediatric suppository per dose	Preferred stimulant for children >2 years
	≥6 years: 1 adult suppository per dose	

Source: Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58:258–274.

Vomiting and Diarrhea

Vomiting and diarrhea, two commonly encountered problems in pediatric practice, are usually self-limiting, but severe cases can result in serious complications such as dehydration, metabolic disturbances, and even death. Infants and young children are particularly susceptible to more severe complications.

PATHOGENESIS AND PRESENTATION OF VOMITING

Vomiting or emesis is defined as forceful expulsion of GI contents through the mouth or nose, whereas nonforceful expulsion of GI contents is considered as regurgitation. In newborns, regurgitation of small amounts of breast milk or formula after feeding, especially when burping, is common. In most cases, regurgitation usually resolves by age 1 to 2 years and rarely causes problems.[20]

Extensive evaluation of regurgitation is not needed in a child who is growing well. Other causes of vomiting during the newborn period include pyloric stenosis, gastroesophageal reflux (GER), overfeeding, food intolerance, and GI obstruction. Beyond the neonatal period, the most common cause of vomiting is infection. Vomiting in infants and children can also be caused by central nervous system (CNS) disease (eg, intracranial tumors), metabolic disease (eg, urea cycle disorder), inflammatory bowel disease, and ulcers. Conditions causing emesis in older infants and children range from viral gastroenteritis to more severe illnesses, such as bowel obstruction or head injury, which require immediate medical attention.[21] Acute vomiting can also result from medication or toxic ingestions. In teenagers, migraine, pregnancy, and psychological disorders, such as bulimia, have been associated with vomiting.

PATHOGENESIS AND PRESENTATION OF DIARRHEA

Diarrhea refers to an increase in frequency, volume, or liquidity of stool when compared with normal bowel movements. In developing countries, diarrhea is a common cause of death in children younger than age 5 years. In the United States, gastroenteritis accounts for ~1.5 million physician visits, ~200,000 hospitalizations, and about 300 deaths each year.[22]

Acute diarrhea in infants and children is generally abrupt in onset, lasts a few days, and is most commonly caused by viruses. (See Chapter 69, Infectious Diarrhea for infectious diarrhea of other origins.) Diarrhea is considered chronic if it is >10 g/kg/day in toddlers/infants or 200 g/day in older children lasting >4 weeks in duration.[22] Persistent diarrhea may begin acutely but lasts >14 days.[23] Chronic diarrhea can be caused by malabsorption, inflammatory disease, infection, alteration of intestinal flora, milk or protein intolerance, drugs, and other causes.[23]

Infants and children are at high risk for morbidity and mortality secondary to diarrhea for several reasons. Dehydration can occur easily because acute net intestinal fluid losses are greater in young children than in adults. This may result from inefficient transport

systems in the developing intestine. In addition, the percentage of total body water in children is higher than that in adults; thus, they are more susceptible to body fluid shifts. Total body water changes from 80% of total body weight in premature infants to 70% in term infants and 60% in adults.

VIRAL GASTROENTERITIS

CASE 104-6

QUESTION 1: J.R., a 15-month-old male 22.05-pound (10-kg) infant, had one loose stool and began vomiting this morning, but he has not had a fever. On questioning, you discover that many children attending day care with J.R. are experiencing vomiting, diarrhea, and low-grade temperatures.

How should J.R.'s vomiting be treated?

Routine use of antiemetics for acute vomiting in children is not recommended because masking of symptoms may delay the diagnosis of a treatable illness. In addition, the safety and efficacy of the antiemetics, including metoclopramide, promethazine, trimethobenzamide, and dimenhydrinate, have not been demonstrated.[22] In particular, promethazine is contraindicated in children younger than age 2 years because of the risk of fatal respiratory depression. Ondansetron does decrease vomiting, increases oral intake, and decreases the need for intravenous (IV) rehydration; however, the utility of ondansetron in gastroenteritis needs consideration because this effect may not be sustained and has been shown to increase the risk of diarrhea.[22]

Parents should be taught the signs and symptoms of gastroenteritis and vomiting that are sufficiently serious to warrant medical attention. The child's primary care provider should be contacted if the child is toxic appearing, exhibits unusual behavior, exhibits signs of an ear infection, experiences abdominal pain or distension, has red or black vomitus or stool, or if there is a history or

suspicion of toxic ingestion or head trauma. Medical evaluation is also necessary for infants younger than 6 months of age, when persistent vomiting or high-volume diarrhea is present or when chronic medical conditions or prematurity is involved. Because fever can accompany vomiting in viral gastroenteritis, any fever occurring in a neonate warrants medical attention. Fever in older infants and children warrants medical attention when it becomes prolonged or there are changes in pattern.

When communicating with a health care provider about a vomiting child, it is helpful if the parents have knowledge of the child's fluid intake and the frequency and volume of vomiting and urination. The amount of vomitus can be estimated by the following rule of thumb: 1 tbsp makes a spot 4 inches wide and a quarter cup makes a spot ~8 inches wide.

Vomiting associated with gastroenteritis usually resolves in 24 to 48 hours. Infants are particularly susceptible to the development of fluid and electrolyte abnormalities; therefore, fluid and electrolyte replacements are critically important.

J.R., who is early in the course of gastroenteritis, must receive sufficient fluids to prevent dehydration. Oral hydration therapy can be successful when given in small volumes, even if J.R. is still vomiting. For example, 5 to 10 mL can be administered every 5 to 10 minutes, with gradual increases in volume as tolerated. Volumes equal to the estimated fluid deficit (usually 50–100 mL/kg) should be given over the course of 2 to 4 hours. For each diarrheal stool, an additional 10 mL/kg of oral electrolyte solution should be given. If diarrhea or vomiting recurs, 10 and 2 mL/kg of an oral rehydration solution (ORS) can be administered for each stool or emesis, respectively.[24] J.R.'s clinical condition should continue to be monitored by his caregiver. If stool output >10 mL/kg/hour, ORS might not be sufficient, and the health care provider should be contacted. ORS should only be abandoned in children with intractable vomiting, loss of consciousness, bowel obstruction, or if the child is in shock. Most infants will tolerate oral hydration when small amounts are given frequently. As dehydration is corrected, the frequency of vomiting typically decreases. Once rehydration has been achieved, fluids

other than ORS and a diet appropriate for age may be started.[24] Breast milk or formula should be given as tolerated.

Assessment of Dehydration

Case 104-6, Question 2: On the second day of illness, J.R. develops a mild fever and diarrhea that has increased in frequency and water content. How can the severity of J.R.'s diarrhea be assessed?

To determine the severity of dehydration and whether hospitalization may be needed, consider the following questions:

1. Does the child have any of the following signs and symptoms of severe dehydration: deeply sunken eyes, parched mucous membranes, significantly prolonged capillary refill; cool, mottled extremities; crying without tears; oliguria or anuria; weak or thready pulses; lethargy; poor oral intake; deep respirations; history of seizures or convulsions; a fever without perspiration; or thirst?
2. Are a large number of copious stools still being produced (>10 mL/kg/hour)? Is bowel obstruction a possibility?
3. Is there a risk of dehydration from inadequate monitoring, or is the parent unable to care for the child? Specific inquiries should be made about the number and consistency of stools in children with diarrhea.

Estimating the degree of dehydration is particularly valuable in assessing the patient with diarrhea, and weight loss is a good criterion. A 3% to 9% weight loss is considered mild-to-moderate dehydration, whereas >9% is considered severe dehydration.[24] (See Chapter 103, Pediatric Fluid, Electrolytes, and Nutrition, for information about IV replacement therapy in children with ≥10% dehydration.)

Oral Replacement Therapy

Case 104-6, Question 3: J.R. was evaluated by his pediatrician and was not considered to be sufficiently dehydrated to warrant hospitalization. How might J.R.'s fluids and electrolytes be managed on an outpatient basis?

The goal of J.R.'s treatment should be focused on the prevention of dehydration and the restoration and maintenance of adequate fluid and electrolyte balance. Mild-to-moderate diarrhea without dehydration is generally managed at home by continued age-appropriate feeding. Fluid losses in stools can be replaced with a glucose-containing ORS. Glucose provides calories and enhances salt and water absorption in the small intestine through mechanisms that are usually unimpaired in many toxin-induced diarrheas. Commercially available oral glucose–electrolyte formulations, such as Pedialyte®, are designed to enhance glucose and sodium absorption and should be used in infants and young children. Carbonated beverages and fruit juices do not contain sufficient sodium to replace diarrheal losses and should not be used. Rehydration and maintenance solutions can be made more palatable with sugar-free flavorings (eg, Kool-Aid® and Crystal Lite®).

The World Health Organization (WHO) original formula, which had a 90% successful rehydration rate for the management of diarrhea, contained a high concentration of sodium. Although commercially available ORSs contain less sodium than does the WHO formulation, these preparations were equally effective as the WHO formula, even when used to treat the high-sodium losses associated with cholera. Furthermore, these lower sodium-containing formulations were associated with less vomiting, lower stool output, and reduced need for IV infusions in non–cholera-associated gastroenteritis. As a result, the WHO, in 2002, promoted a formulation that consists of 75 mEq/L sodium and has a total osmolarity of 245 mOsm/L.[24] The electrolyte content of commonly used ORS is provided in **Table 104-2**. Assuming J.R.'s fluid deficit is 50 to 100 mL/kg, he should receive 500 to 1000 mL of ORS in the course of ~4 hours. In addition, he should receive an extra 100 mL for each diarrheal stool and 20 mL for each emesis that occurs. If stool output continues at a pace that cannot be matched with oral replacement, or signs and symptoms of

severe dehydration occur, J.R. should be referred to his pediatrician again.

Table 104-2
Oral Electrolyte Solutions

Solution	Compositions			
	Sodium (mmol/L)	Potassium (mmol/L)	Carbohydrate (g/L)	Osmolality (mmol/L)
Rehydration				
Rehydralyte	75	20	25	305
WHO formula (original)	90	20	20	311
WHO formula (current)	75	20	13.5	245
Maintenance				
Enfalyte	50	25	30	200
Pedialyte	45	20	25	250
Home Remedies				
Apple juice	3	32	120	730
Sports drink	20	3	45	330
Chicken broth	250	8	0	500
Cola	2	0	112	750

WHO, World Health Organization.

Source: Santillanes G, Rose E. Evaluation and management of dehydration in children. *Emerg Med Clin North Am*. 2018;36(2):259–273.

REINSTITUTION OF ORAL FEEDINGS

Previously, feeding during an episode of viral gastroenteritis has been delayed because of the malabsorption that typically occurs during and after these bouts. The malabsorption, however, is self-limiting, and substantial amounts of carbohydrate, protein, and fat can still be absorbed. The reinstitution of a regular diet, therefore, should not adversely affect mild diarrhea and can be beneficial.[24] Parents are encouraged to continue feeding their children using age-appropriate diet while avoiding foods high in fat and simple sugars. Specific diets are often recommended during diarrhea (eg, BRAT [bananas, rice, applesauce, toast]). Although these diets can be occasionally useful, the nutritional value of these foods is relatively low, and they do not provide optimal nutrition compared with complete diets with fats and proteins.[24] Once J.R. has been adequately rehydrated, he may resume his normal diet. However, the caregivers must take care to avoid juices and other foods with simple sugars, which may worsen diarrhea.

Drug Therapy

Medications play a minor role in the treatment of acute infectious diarrhea because most episodes are self-limiting. Antibiotics are recommended when systemic bacteremia is suspected, when immune defenses are compromised, when a persistent enteric infection is sensitive to antibiotics, or in certain clinical situations when *Shigella*, *Campylobacter*, *Clostridioides difficile*, and *Salmonella* strains are isolated.[25] In general, antidiarrheal preparations are not recommended for infants or children because they have little effect on acute diarrhea, are associated with side effects, and direct attention away from the use of oral hydration therapy.[22] Drugs such as loperamide that alter GI motility should be avoided, especially in children with high fever, toxemia, or bloody mucoid stools, because they may worsen the clinical course of the bacterial infection.

Probiotics, live microbial products containing species of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and *Streptococcus*, can improve the balance of intestinal flora and diminish the effect of enteric pathogens. These microbes are thought to exert their beneficial effects through various mechanisms, including producing antibacterial chemicals, competing with enteric pathogens, inhibiting the adhesive capabilities of pathogens, altering toxins or toxin receptors, and upregulating interleukin-mediated T-cell response.[22] Probiotics are most useful in viral gastroenteritis when used early in the course of the disease. Lactobacilli are the most well-studied species and have been the most consistently effective in clinical trials. It appears that the efficacy of the different species may depend on the specific strain, the dose, and the timing of administration.[22] The manufacture of probiotics is not regulated by the FDA; therefore, the organism count per dose might be based on the number present at the time of production and not at the time of expiration, and the labeling might incorrectly identify the species of organism. For J.R., a *Lactobacillus* preparation administered for 5 days may provide some modest clinical benefit, although the benefit is most pronounced in rotavirus diarrhea, which has not been documented in his case.

GASTROESOPHAGEAL REFLUX

GER is a common disorder, with infants experiencing recurrent vomiting and regurgitation that peaks during the first 4 months of life.[20] Of cases of reflux in infants, most are benign and, in 80% to 95% of cases, resolve by age 1 year,[26] and reflux in older children resolves in a timeframe similar to that of adults. If untreated, GER can result in esophageal strictures, GI hemorrhage, or chronic respiratory disease from the aspiration of GI contents.

Clinical Presentation

In infants, the vomiting and regurgitation of GER occur frequently, and other symptoms often are nonspecific (eg, failure to thrive [FTT], recurrent pneumonia, apnea, dysphagia, reactive airway disease, hematemesis, and anemia).[27,28] A thorough diagnostic workup is generally not necessary in a healthy infant with functional GER presenting as recurrent vomiting. Empiric drug therapy can be initiated after the diagnosis is made based on clinical findings and after other causes of vomiting have been eliminated.[27] Further diagnostic evaluations, however, are indicated for infants and children presenting with additional symptoms of gastroesophageal reflux disease (GERD; eg, FTT, irritability, and respiratory difficulties).[20]

Treatment

Because uncomplicated GER usually resolves spontaneously in infants, therapy should focus on providing symptom relief and maintaining normal growth.[20] Infants and young children with underlying neurologic problems (eg, cerebral palsy) are unlikely to have spontaneous resolutions of GER and frequently require aggressive antireflux therapies and, possibly, surgical intervention.

POSITIONAL AND DIETARY MEASURES

CASE 104-7

QUESTION 1: S.B., a 3-month-old, 13.23-pound (6-kg), breast-fed male infant, has a 2-week history of regurgitation after each feeding. The pediatrician noted that S.B. had not gained weight since his last visit 1 month earlier. The presumptive diagnosis is FTT secondary to GER, and S.B. was referred to a pediatric gastroenterologist.

How should S.B. be treated initially?

S.B. can be treated conservatively because he does not present with life-threatening complications.[27] First, caregiver feedings should be observed to rule out regurgitation caused either by overfeeding or by inappropriate feeding techniques. Sometimes, infants with milk protein allergies can have a similar clinical presentation; therefore, a change to a soy protein formula or hypoallergenic formula should be tried.[27] Interventions to modify an infant's body positioning or to modify infant feedings with milk thickeners are not proved to be effective but are reasonable to undertake.[26] Maintaining S.B. at a 60-degree angle during the day while sitting and at a 30-degree position at night should be implemented in an effort to promote clearance of acid from the esophagus and to minimize reflux after meals. Milk thickeners (most commonly rice cereal in the United States) and more frequent, smaller feedings are also worthwhile interventions, although thickened formula could lead to increased coughing during feeding. Mild cases of GER often can be treated successfully by dietary measures alone, as well as by propping infants in an upright position during, and 1 hour after, feedings.[28] Although the placement of infants in a face-down prone position during sleep can reduce reflux, the greater risk of sudden infant death syndrome (SIDS) in infants younger than age 12 months outweighs the benefits of such positioning.[27] Older children and adolescents should follow the recommended dietary guidelines (ie, avoidance of caffeine, chocolate, and spicy foods) for adults.

DRUG THERAPY

The efficacy of pharmacologic therapy in altering the course of uncomplicated GER in infants has not been proved.[27] In infants or children who present with nonspecific symptoms or complications, such as S.B., acid suppression therapy or prokinetic therapy is warranted even in the absence of documented esophagitis.[27] When esophagitis is present, acid suppression is always recommended to aid in the healing process; however, these agents alone do not rectify the causes of the GER.[27] The various agents to treat infant GER are listed in **Table 104-3**.[27,28]

Table 104-3
Oral Drugs Used to Treat Gastroesophageal Reflux in Infants

Agent	Mode of Action	Oral Dosage
Acid-Suppressing Agents		
Antacids (aluminum or magnesium hydroxide)	Neutralizes acid	0.5–1.0 mL/kg/dose before and after feeding (maximum, 15 mL/dose)
Proton-Pump Inhibitors		
Omeprazole	Decrease acid secretion via inhibition of gastric hydrogen-potassium adenosine triphosphatase.	1–4 mg/kg/day
Esomeprazole		<20 kg: 10 mg/day; >20 kg: 20 mg/day
Lansoprazole		Infants ≥ 3 months: 2 mg/kg/day
Pantoprazole		1–2 mg/kg/day
H_2-Receptor Antagonists		
Cimetidine	Blocks H_2-receptors; ↓ acid secretion	30–40 mg/kg/day divided qid
Famotidine		1 mg/kg/day divided bid
Nizatidine		10–20 mg/kg/day divided bid
Prokinetic Agents		
Metoclopramide	Dopamine antagonist	0.4–0.9 mg/kg/day

Agent	Mode of Action	Oral Dosage
Surface-Active Agents		
Sucralfate	Forms paste and adheres to damaged esophageal mucosa	40–80 mg/kg/day divided qid

bid, two times daily; qid, four times daily.

Sources: Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr.* 2018;66:516–554; Lightdale JR, Gremse DA. Section on gastroenterology, hepatology, and nutrition. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics.* 2013;131:e1684–e1695.

Acid-suppressant agents

Antacids

Chronic antacid therapy is generally not recommended for the treatment of GER in infants and young children because infants treated with aluminum-containing antacids can accumulate sufficient aluminum to cause osteopenia and neurotoxicity.[27] In addition, information on other antacids in infants is limited; nevertheless, antacids can provide short-term relief of symptoms in older children and adults.

Proton-Pump Inhibitors

Proton-pump inhibitors (PPIs) are superior to histamine-2 receptor antagonists (H_2RAs) in relieving symptoms and in promoting healing of significant esophagitis from GER in infants, young children, and adults.[27–29] PPIs control both basal and meal-stimulated acid secretion, which may in part explain their superior efficacy. Current evaluations of the safety of PPIs in the pediatric population have shown they are not free of adverse effects.[30] Prolonged use of PPIs has been shown to raise concerns for increased risk of infections, vitamin deficiencies, and adverse bone health.[30] In children, increased metabolism and decreased bioavailability necessitate larger milligram per kilogram doses to maintain acid suppression

than in adults; thus, titration of dose to response is necessary, particularly for treatment of esophageal erosions.[29] Omeprazole, lansoprazole, and esomeprazole are available in extended-release capsules, which can be separated, opened, and sprinkled on soft foods. Omeprazole and esomeprazole are also available as granules for an oral suspension. Suspension formulations for both omeprazole and lansoprazole have been extemporaneously compounded and evaluated for stability.

Histamine-2 Receptor Antagonists

H_2RAs reduce histamine-stimulated acid secretion but have limited effects on acid secretion by other chemical mediators and stimuli. In randomized controlled trials, H_2RAs in infants and children relieved symptoms and facilitated the healing of esophageal tissue.[27] Oral liquid formulations are available for most H_2RAs.

Prokinetic agents

Metoclopramide, a dopamine antagonist with cholinergic and serotonergic effects, accelerates gastric emptying, increases lower esophageal sphincter (LES) pressure, enhances esophageal clearance, and accelerates transit time in the small bowel; however, its effects on vomiting and esophageal pH in children with GER has been equivocal.[27] In addition, metoclopramide has been associated with significant CNS (ie, restlessness, drowsiness, and extrapyramidal symptoms) effects, recently receiving a special alert for a higher risk of extrapyramidal symptoms in those age older than 1 year, and rare reports of gynecomastia and galactorrhea.[27] Erythromycin increases GI motility by increasing smooth muscle contractions through its motilin agonistic activity. However, it has been found that there is no sufficient evidence to recommend erythromycin for the treatment of GER in children.[27] The cholinergic agonist, bethanechol, reportedly reduces vomiting episodes in infants with GER[27]; however, its role in treating GER in infants is limited because of its potential to induce bronchospasm and to

stimulate gastric acid secretion. The lack of a suitable commercially available formulation of bethanechol for young infants necessitates its extemporaneous compounding. Baclofen, which decreases transient LES relaxations through its γ-aminobutyric acid agonist actions, could be a future therapeutic option for GER, pending further study.[31] Generally, prokinetic agents are only marginally effective in the management of GER.

Surface-active agents

Sucralfate was equally effective as cimetidine for use in esophagitis[27]; however, its use for GER is more limited because of concern about the adverse effects of aluminum-containing products in infants.

Case 104-7, Question 2: Four weeks after instituting positional and dietary measures, S.B. continues to vomit and still has not been gaining weight. On physical examination, the gastroenterologist notes bilateral wheezes; endoscopy rules out esophagitis. What would be the next step of therapy?

The treatment of S.B. can include acid suppression therapy. Acid suppression therapy in children who have complications from GER can be implemented by a step-up approach in which treatment is initiated with an H_2RA followed by a PPI if no improvement is noted, or through a step-down approach involving a PPI followed by an H_2RA for maintenance therapy. However, initial therapy with a PPI is preferred,[27] and S.B. may be treated with omeprazole 5 mg daily. Granules for suspension may be mixed in 10 mL of water and administered orally.

The effectiveness of acid suppression for managing symptoms of GER in children is not as well documented as it is for healing esophagitis; however, acid suppression is believed to play a useful role in symptom control, particularly for managing respiratory symptoms.[27] Treatment should be continued for at least 3 to 4 months, although the optimal duration of therapy is unknown. If S.B. requires additional drug therapy to control symptoms of GER beyond

age 18 months to 2 years, surgery may be considered because GER is unlikely to resolve spontaneously after this age. Surgery might be considered earlier if S.B. fails medical therapy or if he develops an esophageal stricture, apnea, or recurrent respiratory disease.[27]

COMMON PEDIATRIC INFECTIONS

Acute Otitis Media

Acute otitis media (AOM) is one of the most common infectious diseases seen in childhood.[32] It is most commonly seen in children ages 3 months to 3 years, although the highest incidence occurs between ages 6 and 9 months. Most children will have at least one episode by the time they reach 3 years old.[32] Incidence is higher in the winter months, concurrent with viral upper respiratory illnesses. Several risk factors for AOM have been identified and include age younger than 2 years, early colonization of pathogens and onset of AOM, day care attendance, bottle propping, cleft palate, immune compromise, and Down syndrome.

Eustachian tube dysfunction, either from intermittent causes such as upper respiratory infections or permanent causes such as cleft palate, is the primary condition required for the development of AOM. This results in a defect in the Eustachian tube's ability to equilibrate middle ear pressure. Thus, nasopharyngeal contents, including bacteria, may be aspirated into the middle ear. This process is more likely in infants and young children who have shorter, flatter Eustachian tubes.[33] Changes in pressure can also cause increased vascular permeability, resulting in an effusion. Viral infections contribute by enhancing bacterial transfer from the nasopharynx and adherence to the middle ear because of impairment of the mucociliary apparatus.[33]

S. pneumoniae, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis* colonize the nasopharynx early in childhood, and, thus, are the most common pathogens causing AOM.[32,33] The

introduction and widespread use of the pneumococcal conjugate vaccine (PCV13) has changed the landscape of AOM. Specifically, the fraction of *S. pneumoniae* has declined over time, with a rise seen in *H. influenzae*. All three common bacteria possess resistance to β-lactams, thus influencing drug therapy selection.

CASE 104-8

QUESTION 1: C.D. is a 7-month-old, 17.64-pound (8-kg) infant who during the past 36 hours has developed cough, ear pain, and rhinorrhea, became irritable and at times inconsolable, and now has a temperature of 102.4 °F (39.1 °C). Physical examination shows bulging, dark, yellow opaque tympanic membranes bilaterally. This is the first time he has had these symptoms and has had no recent courses of antibiotics.

What signs and symptoms consistent with AOM does C.D. exhibit, and how should AOM be diagnosed?

Very often, as in this patient's case, otitis media is preceded by an upper respiratory tract infection. These viral infections often will produce otitis media with effusion (OME), which typically will cause no more than temporary mild hearing loss. If AOM develops, more signs and symptoms will usually arise. These symptoms can include otalgia (pain causing infants to pull on or rub the ears), fever, irritability, and otorrhea.[34] Unfortunately, aside from otorrhea, these symptoms are nonspecific and may be present in many children who do not have AOM. As a result, a definitive diagnosis may not be easily obtained with symptoms alone. Diagnosis should be confirmed on visualization of the middle ear.

The current AAP guideline on the diagnosis and management of AOM states that a diagnosis of AOM requires mild bulging of the tympanic membrane and either recent onset of ear pain (>48 hours) or intense erythema of the tympanic membrane.[34] Pneumatic otoscopy should be used to confirm the presence of effusion. Middle ear effusion can be differentiated from AOM in that although both present with bulging tympanic membranes, in AOM, the middle ear fluid is more often dark yellow or red.[34] Other diagnostic tools may be used. Tympanometry uses sound waves to measure the

compliance of the tympanic membrane. And in acoustic reflectometry, the absorption of sound waves by the tympanic membrane provides information about the middle ear.[35] C.D.'s fever and irritability along with fluid in the middle ear and bulging, dark yellow tympanic membranes are consistent with the diagnosis of AOM.

Case 104-8, Question 2: How should C.D.'s otitis media be treated?

The AAP recommendations provide for the option to observe without treatment or to treat with antibiotics, depending on the age of the patient and symptoms present.[34] Generally, infants ages 6 months and younger should receive antibiotic therapy in all cases. Infants and children ages 6 months to 2 years can be managed with observation if there is a nonsevere unilateral AOM without otorrhea. Children ages 2 years and older can be managed with observation in bilateral or unilateral nonsevere AOM without otorrhea. Antibiotics are warranted in all cases of AOM with otorrhea or in AOM cases with severe symptoms (eg, temperature >102.2 °F [39 °C] in the past 48 hours).[34]

C.D. appears to have bilateral AOM with severe symptoms based on his fever >102.2 °F (39 °C), so antibiotic therapy is indicated. Despite pneumococcal penicillin resistance rates, initial therapy in most children who have not received amoxicillin in the past 30 days would still be amoxicillin at a dose of 80 to 90 mg/kg/day.[34] Amoxicillin is effective against susceptible and intermediately resistant pneumococcus, it is affordable and palatable, and it has a narrow spectrum of activity. Providers should prescribe amoxicillin/clavulanate in children who have received amoxicillin in the past 30 days, have concurrent purulent conjunctivitis, or have a history of recurrent AOM unresponsive to amoxicillin.[34] Oral cephalosporins, including cefdinir, cefuroxime, or cefpodoxime, are options in patients with an allergy to penicillin.

Whichever treatment course is taken in a patient (observation or antibiotic therapy with amoxicillin or amoxicillin/clavulanate),

effectiveness is assessed for 48 to 72 hours.[34] If the treatment is effective, the patient should defervesce, irritability should decrease, and normal activity should resume (eg, eating and sleeping). If the observation is ineffective, treatment with amoxicillin or amoxicillin/clavulanate is recommended. If amoxicillin or amoxicillin/clavulanate is ineffective for C.D., treatment with an oral cephalosporin (cefdinir or cefpodoxime) or ceftriaxone 400 mg (50 mg/kg) intramuscularly for 1 or 3 days is an option.

The optimal duration of oral antimicrobial agents (eg, amoxicillin, amoxicillin/clavulanate) has been questioned over the past few years. The AAP guideline calls for up to 10 days of oral antibiotic coverage; yet investigators have looked at durations as short as 5 to 7 days.[34,36] The shortened duration strategy has been discussed to have a potential, positive impact on antimicrobial resistance. However, evidence has shown that a shortened course, specifically in children ages 6 to 23 months, resulted in less favorable outcomes and is thus not recommended.[36] In children at least 6 years old with mild-to-moderate symptoms, a 5- to 7-day course may be attempted.[34]

Case 104-8, Question 3: How should C.D.'s otalgia be managed?

Ear pain is a common feature of AOM, and it should be addressed regardless of the decision to use antibiotics or not. Acetaminophen 120 mg (15 mg/kg) or ibuprofen 80 mg (10 mg/kg) can provide adequate relief and are first-line agents in the management of otalgia.[34] Home remedies such as the application of heat or cold may also be helpful.[34] For example, a washcloth can be soaked with very warm water, wrung out, and placed over the ear for comfort for 15 minutes several times per day.

Acute Pharyngitis

Acute pharyngitis is most common in children ages 5 to 15 years and is rare before age 3 years.[37] The etiology is typically viral, but

bacteria such as group A streptococci (GAS, *S. pyogenes*), groups C and G streptococci, *Neisseria gonorrhoeae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* may also cause pharyngitis in children.[37] The majority of attention is directed toward the detection and management of GAS infections because, untreated, they may lead to rheumatic fever, a complication progressing to permanent heart disease.

CASE 104-9

QUESTION 1: P.J., a 6-year-old male weighing 51.59 pounds (23.4 kg), presents to the pediatrician's office with fever, sore throat, and headache. His mother reports that he initially reported sore throat about 12 hours ago. His oral temperature this morning was 102 °F (38.89 °C). He takes no medications and has no known drug allergies. Physical examination reveals erythematous tonsils and throat as well as an enlarged anterior cervical lymph node.

Are P.J.'s symptoms more consistent with GAS or viral pharyngitis?

Findings suggestive of GAS tonsillopharyngitis include sudden onset of throat pain, fever, headache, abdominal pain, nausea, vomiting, tonsillopharyngeal edema, enlarged anterior cervical lymph nodes, soft palate petechiae, and a scarlatiniform rash.[37,38] Symptoms that increase the likelihood of a viral cause include rhinorrhea, cough, conjunctivitis, and viral rash.[37,38] P.J. is lacking associated symptoms that would suggest a viral cause and has more symptoms of GAS pharyngitis, but confirmatory testing is needed. In pediatric patients with viral features, judicious use of laboratory testing should occur because children can be carriers of GAS.[39]

DIAGNOSIS

Because clinical and physical findings alone are not definitive for GAS pharyngitis, confirmatory testing is important to determine the need for antibiotic therapy. A rapid antigen detection test is recommended, and, if the result is positive, treatment is initiated. If negative, a throat culture should also be obtained and treatment initiated if the culture grows GAS. However, if one of the newer highly sensitive optical immunoassay or molecular tests is used, a

backup culture may not be necessary.[37] Rheumatic fever can be effectively prevented if treatment is started within 9 days of the start of the illness.[38]

CASE 104-9, QUESTION 2: A rapid antigen detection test for GAS is performed for P.J. and the result is positive. What treatment should be initiated at this time?

TREATMENT

Penicillins remain the agents of choice for GAS pharyngitis.[37] Either oral penicillin, oral amoxicillin, or intramuscular benzathine penicillin may be used. Amoxicillin suspension is more palatable than is penicillin and has the advantage of a once-daily dosing regimen. Intramuscular penicillin is a one-time dose that is helpful in those at risk for nonadherence. In patients with a type I hypersensitivity to penicillins, azithromycin, clarithromycin, or clindamycin may be used. In those with a non–type I allergy to penicillin, a first-generation cephalosporin may be considered. Recommended regimens are summarized in **Table 104-4**.[38] Patients are no longer contagious 24 hours after the first antibiotic dose.[37,38]

Table 104-4
Medication Regimens for the Treatment of Streptococcal Pharyngitis and Prevention of Rheumatic Fever

Medication	Dose	Duration
Amoxicillin	50 mg/kg once a day or 25 mg/kg twice a day (maximum 1 g/day)	10 days
Penicillin VK	Children ≤ 27 kg: 250 mg two or three times a day Children > 27 kg, adolescents: 500 mg two or three times a day or 250 mg four times a day	10 days
Benzathine penicillin G	≤27 kg: 600,000 units IM >27 kg: 1,200,000 units IM	Once
For Patients With Penicillin Allergy		
Cephalexin	20 mg/kg (up to 500 mg) twice a day	10 days
Cefadroxil	30 mg/kg (up to 1 g) once a day	10 days

Medication	Dose	Duration
Clindamycin	7 mg/kg three times a day (maximum 300 mg/dose)	10 days
Azithromycin	12 mg/kg once a day (maximum 500 mg)	5 days
Clarithromycin	7.5 mg/kg twice a day (maximum 250 mg/dose)	10 days

IM, intramuscular.

Sources: From Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012:55(10):e86–e102. Reproduced by permission of Oxford University Press; Hoberman A, Paradise JL, Rockette HE, et al. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med*. 2016;375(25):2446–2456.

P.J. should receive amoxicillin (400 mg/5 mL), 12.5 mL (1000 mg) every 24 hours for 10 days. For pain relief, he may also receive as-needed doses of acetaminophen (160 mg/5 mL), 10 mL every 6 hours, or ibuprofen (100 mg/5 mL), 10 mL every 6 hours.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Barbi E, Marzuillo P, Neri E, Naviglio S, Krauss BS. Fever in children: pearls and pitfalls. *Children*. 2017;4(*81*):1–19. doi:10.3390/children4090081 (6)

Blume-Peytavi U, Kanti V. Prevention and treatment of diaper dermatitis. *Pediatric Dermatol*. 2018;35:s19–s23. doi:10.1111/pde.13495 (4)

Kennedy AR, Massey LR. Pediatric medication safety considerations for pharmacists in an adult hospital setting. *Am J Health Syst Pharm*. 2019;76(*19*):1481–1491. doi:10.1093/ajho/zxz168 (2)

Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics.* 2013;131:e964–999. doi:10.1542/peds.2012-3488 (34)

Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN*). J Pediatr Gastroenterol Nutr*. 2018;66:516–554. (27)

Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A Streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2012;55:e86–e102. (38)

Key Websites

Consumer Healthcare Products Association. Voluntary codes and guidelines of the Consumer Healthcare Products Industry. Program on OTC oral pediatric cough and cold medicines. Accessed October 12, 2020. https://chpa.org/VoluntaryCodesandGuidelines.aspx (16)

OTC sales statistics. Consumer Healthcare Products Association website. Accessed September 11, 2020. https://www.chpa.org/SalesVolume.aspx (13)

U.S. Food and Drug Administration. Should you give kids medicine for coughs and colds? Updated October 28, 2021. Accessed August 3, 2022. https://www.fda.gov/consumers/consumer-updates/should-you-give-kids-medicine-coughs-and-colds (15)

COMPLETE REFERENCES CHAPTER 104 COMMON PEDIATRIC ILLNESSES

1. Hales CM, Kit BK, Qiuping G, Odgen CL. Treads in prescription medication use among children and adolescents—United States, 1999–2014. *JAMA*. 2018;319(19):2009–2020. doi:10.1001/jama.2018.5690
2. Kennedy AR, Massey LR. Pediatric medication safety considerations for pharmacists in an adult hospital setting. *Am J Health Syst Pharm*. 2019;76(19):1481–1491. doi:10.1093/ajho/zxz168
3. Eiland LS, Meyers RS. Caring for and assessing pediatric patients: aspects to consider as a pharmacy practitioner. *Am J Health Syst Pharm*. 2019;76(19):1463–1471. doi:10.1093/ajhp/zxz160
4. Blume-Peytavi U, Kanti V. Prevention and treatment of diaper dermatitis. *Pediatric Dermatol*. 2018;35:s19–s23. doi:10.1111/pde.13495
5. Clinical Resource, Diaper Rash: FAQs. Pharmacist's Letter/Prescriber's Letter; October 2018.

6. Barbi E, Marzuillo P, Neri E, Naviglio S, Krauss BS. Fever in children: pearls and pitfalls. *Children*. 2017;4(9):81. doi:10.3390/children4090081
7. Brown J, Kyles J. Fever. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. eds. *Pharmacotherapy: A Pathophysiologic Approach*. 11e. McGraw-Hill; Accessed August 17, 2020. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=240762170
8. Pantell RH, Roberts KB, Adams WG, et al. Clinical practice guideline: evaluation and management of well-appearing febrile infants 8 to 60 days old. Pediatrics. 2021;148(2):e2021052228.
9. Leung AKC, Hon KL, Beung TNH. Febrile seizures: an overview. *Drugs Context*. 2018;7:212536. doi:10.7573/dic.212536
10. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online. Lexi-Comp; Accessed August 17, 2020. https://www.wolterskluwer.com/en/solutions/lexicomp
11. Sullivan JE, Farrar HC. Clinical report: fever and antipyretic use in children. *Pediatrics*. 2011;127(3):580–587. Reaffirmed July 2016. doi:10.1542/peds.2016-2595
12. Lopez SMC, Williams JV. The common cold. In: Kliegman RM, St Geme JW, Blum NJ, et al, eds. *Nelson Textbook of Pediatrics*. 21st ed. Saunders Elsevier; 2020:chap 407.
13. OTC sales statistics. Consumer Healthcare Products Association website. Accessed September 11, 2020. https://www.chpa.org/SalesVolume.aspx
14. Centers for Disease Control and Prevention. Infant deaths associated with cough and cold medications—two states, 2005. *MMWR Morb Mortal Wkly Rep*. 2007;56:1.
15. U.S. Food and Drug Administration. Should you give kids medicine for coughs and colds? Updated October 28, 2021. Accessed August 3, 2022. https://www.fda.gov/consumers/consumer-updates/should-you-give-kids-medicine-coughs-and-colds
16. Consumer Healthcare Products Association. Voluntary codes and guidelines of the Consumer Healthcare Products Industry. Program on OTC oral pediatric cough and cold medicines. Accessed October 12, 2020. https://chpa.org/VoluntaryCodesandGuidelines.aspx
17. Lokker N, Sanders L, Perrin EM, et al. Parental misinterpretations of over-the-counter pediatric cough and cold medication labels. *Pediatrics*. 2009;123:1464–1471.
18. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58:258–274.
19. Madani S, Tsang L, Kamat D. Constipation in children: a practical review. *Pediatr Ann*. 2016;45(5):e189–e196.

20. Khan S, Matta KR. Gastroesophageal reflux disease (GERD). In Kliegman RM, St Geme JW, Blum NJ, et al, eds. *Nelson Textbook of Pediatrics*. 21st ed. Saunders Elsevier; 2020.
21. Maqbool A, Liacouras CA. Major symptoms and signs of digestive tract disorders. In Kliegman RM, St Geme JW, Blum NJ, et al, eds. *Nelson Textbook of Pediatrics*. 21st ed. Saunders Elsevier; 2020.
22. Hartman S, Brown E, Loomis E, Russell HA. Gastroenteritis in children. *Am Fam Physician*. 2019;99(3):159–165.
23. Guz-Mark A, Shamir R. Chronic diarrhea. In Kliegman RM, St Geme JW, Blum NJ, et al, eds. *Nelson Textbook of Pediatrics*. 21st ed. Saunders Elsevier; 2020.
24. Santillanes G, Rose E. Evaluation and management of dehydration in children. *Emerg Med Clin North Am*. 2018;36(2):259–273.
25. Cohen R, Raymond J, Gendrel D. Antimicrobial treatment of diarrhea/acute gastroenteritis in children. *Arch Pediatr*. 2017;24(12):S26–S29.
26. Barnhart DC. Gastroesophageal reflux disease in children. *Semin Pediatr Surg*. 2016;25(4):212–218.
27. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN*). J Pediatr Gastroenterol Nutr*. 2018;66:516–554.
28. Lightdale JR, Gremse DA. Section on gastroenterology, hepatology, and nutrition. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics*. 2013;131:e1684–e1695.
29. Ward RM, Kearns GL. Proton pump inhibitors in pediatrics: mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. *Paediatr Drugs*. 2013;15(2):119–131.
30. De Bruyne P, Ito S. Toxicity of long-term use of proton pump inhibitors in children. *Arch Dis Child*. 2018;103(1):78–82.
31. Bardou M, Fortinsky KJ, Chapelle N, Luu M, Barkun A. An update on the latest chemical therapies for reflux esophagitis in children. *Expert Opin Pharmacother*. 2019;20(2):231–239.
32. Venkamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;6:CD000219. doi:10.1002/14651858.CD000219.pub4
33. Frei CR, Frei BL. Upper respiratory tract infections. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 11e. McGraw-Hill; Accessed August 17, 2020. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=224360273

34. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e964–e999. doi:10.1542/peds.2012-3488
35. Rosenfeld RM, Shin JJ, Schwartz SR, et al. Clinical practice guideline: otitis media with effusion (update*)*. *Otolaryngol Head Neck Surg*. 2016;154:S1–S41. doi:10.1177/0194599815623467
36. Hoberman A, Paradise JL, Rockette HE, et al. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med*. 2016;375:2446–2456. doi:10.1056/NEJMoa1606043
37. Kalra MG, Higgins KE, Perez ED. Common questions about streptococcal pharyngitis. *Am Fam Physician*. 2016;94(1):24–31.
38. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A Streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55:e86–e102.
39. Shapiro D, Lindgren CE, Neuman MI, Fine AM. Viral features and testing for streptococcal pharyngitis. *Pediatrics*. 2017;139(5):1–8. doi:10.1542/peds.2016-3403

105

Neonatal Therapy

Jennifer T. Pham and Kirsten H. Ohler

CORE PRINCIPLES		CHAPTER CASES
RESPIRATORY DISTRESS SYNDROME		
1	Respiratory distress syndrome (RDS) is a major cause of morbidity and mortality in preterm neonates, resulting from pulmonary surfactant deficiency; it is characterized by atelectasis, hypoxemia, decreased lung compliance, small airway epithelial damage, and pulmonary edema.	**Case 105-1 (Question 1)**
2	Beractant, calfactant, and poractant alfa are exogenous surfactants used in the prevention and treatment of RDS in preterm neonates. These agents have been shown to improve oxygenation and lung compliance and decrease the	**Case 105-1 (Question 2–6)**

	need for supplemental oxygen and mechanical ventilation.	
	BRONCHOPULMONARY DYSPLASIA	
1	Bronchopulmonary dysplasia (BPD) is the most common form of chronic pulmonary disease in infants; it is caused by lung immaturity, surfactant deficiency, oxygen toxicity, barotrauma, and inflammation, and is characterized by tachypnea, retractions, and wheezing.	**Case 105-2 (Question 1)**
2	The management of BPD includes supplemental oxygen therapy, mechanical ventilation, and pharmacologic interventions including diuretics, bronchodilators, and corticosteroids. Preventative strategies include caffeine citrate, vitamin A, and azithromycin.	**Case 105-2 (Question 2, 3)**
3	Infants with BPD are at higher risk for experiencing cardiorespiratory problems including pneumonia, pulmonary hypertension, left ventricular hypertrophy, and neurologic and developmental abnormalities.	**Case 105-2 (Question 4, 5)**
	PATENT DUCTUS ARTERIOSUS	
1	Preterm neonates are at high risk for patent ductus arteriosus (PDA), a serious cardiovascular disorder, which may present with tachycardia, wide pulse pressure, bounding pulses, and	**Case 105-3 (Question 1–3)**

	systolic murmur. Complications of PDA include pulmonary edema and heart failure. PDA places the neonate at high risk for BPD, intraventricular hemorrhage, and necrotizing enterocolitis (NEC).	
2	Medical management of PDA includes fluid management, correction of anemia, treatment of hypoxia and acidosis, and pharmacologic therapy with prostaglandin inhibitors (indomethacin, ibuprofen, or acetaminophen) to close the ductus.	**Case 105-3 (Question 4–10)**
NECROTIZING ENTEROCOLITIS		
1	NEC is the most common life-threatening nonrespiratory condition in newborns and is characterized by abdominal distension, bloody stools, metabolic acidosis, and bowel perforation.	**Case 105-4 (Question 1)**
2	The management of NEC includes parenteral nutrition, intravenous antibiotics, and bowel resection. Interventions including trophic feedings, breast milk, probiotics, and a standardized feeding protocol may be used to decrease the incidence of NEC.	**Case 105-4 (Question 2–6)**
NEONATAL SEPSIS AND MENINGITIS		
1	Bacterial sepsis can be classified as early-onset (caused by pathogens colonized from the maternal genital	**Case 105-5 (Question 1)**

	tract) or late-onset sepsis (caused by nosocomial pathogens). Clinical signs can be subtle and nonspecific, especially in preterm neonates.	
2	Selection of empiric intravenous antibiotics is the same for sepsis and meningitis and will depend on nosocomial pathogens commonly isolated in the neonatal intensive care unit, antibiotic resistance patterns, and underlying neonatal risk factors.	**Case 105-5 (Question 2)**
	CONGENITAL INFECTIONS	
1	Congenital infections including herpes simplex virus, syphilis, and cytomegalovirus may result in fetal death, congenital anomalies, serious central nervous system sequelae, intrauterine growth retardation, or preterm birth; if suspected, appropriate diagnostic tests and treatment should be started immediately.	**Case 105-6 (Question 1)**
	APNEA OF PREMATURITY	
1	Pharmacologic treatment of apnea of prematurity includes the use of methylxanthines, specifically caffeine and theophylline, that decrease apneic episodes via both central and peripheral effects.	**Case 105-7 (Question 1)**
2	Caffeine offers several advantages over theophylline for the treatment of apnea, including a wider therapeutic index,	**Case 105-7 (Question 2, 3)**

	fewer adverse effects, prolonged half-life, once-daily dosing, and lack of the need for routine serum drug concentration monitoring.	

NEONATAL SEIZURES		
1	Neonatal seizure activity is a common manifestation of a life-threatening underlying neurologic process. Initial therapy is focused on the treatment of the underlying cause (eg, hypoglycemia, hypocalcemia, infection) and may not include antiepileptic drug therapy.	**Case 105-8 (Question 1–3)**
2	Common antiepileptic medications used to treat neonatal seizure are phenobarbital, phenytoin, levetiracetam, and benzodiazepines.	**Case 105-8 (Question 4, 5)**

INTRODUCTION

The rational use of medications in neonates depends on an appreciation of both the physiologic immaturity and the developmental maturation that influence neonatal drug disposition and pharmacologic effects. Much progress has been made to decrease neonatal mortality and improve the survival of more premature and lower birth weight newborns. Neonates, particularly those of extremely low birth weights (ELBWs), pose a pharmacotherapeutic challenge to the clinician. The alterations of body composition, weight, and size, as well as physiologic and pharmacokinetic parameters, which occur with normal growth and maturation during the first few months of life, are greater than at any other time. Although the amount of neonatal drug information is

increasing, the overall lack of well-designed pharmacokinetic, pharmacodynamic, and pharmacogenomic studies still hinders the clinical use of many drugs in this population. This is especially true for newborns of the lowest birth weights (BWs <0.75 kg). An understanding of common neonatal terminology (**Table 105-1**) is important because every newborn is evaluated and classified at birth according to BW, gestational age (GA), and intrauterine growth status.[1] Pharmacokinetic parameters, pharmacodynamics, and dosing recommendations often are specified according to these terms.[2] Important neonatal pharmacokinetic differences are reviewed in Chapter 102, Pediatric Pharmacotherapy. This chapter focuses on the safe and effective use of medications for common neonatal medical conditions.

Table 105-1
Common Neonatal Terminology

Term	Definition
Gestational age (GA)	*By dates:* The number of weeks from the onset of the mother's last menstrual period until birth
	By examination: Assessment of gestational maturity by physical and neuromuscular examination; GA estimates the time from conception until birth.
Postnatal age (PNA)	Chronologic age after birth
Postmenstrual age (PMA)	GA plus PNA. *Postmenstrual age* (rather than postconceptional age) is the preferred term for use in clinical practice. PMA is considered to be a more accurate term because GA is calculated using the mother's last menstrual period, and the exact date of conception is generally not known.
Postconceptional age (PCA)	Age since conception. This term is not recommended for use in clinical practice and is currently reserved for cases when the exact date of conception is known (ie, assisted reproductive technology). Older literature may use this term to describe the sum of GA plus PNA; thus, it is important to know how this term is defined when used.

Term	Definition
Corrected age (or adjusted age)	PMA in weeks minus 40; represents PNA if neonate had been born at term (40 weeks' GA)
Neonate	A full-term newborn 0–28 days PNA. Some may also apply this term to a preterm neonate who is >28 days PNA, but with a PMA ≤42–46 weeks
Preterm	<37 weeks' GA at birth ▪ Extremely preterm (<28 weeks) ▪ Very preterm (28 0/7–31 6/7 weeks) ▪ Moderately preterm (32 0/7–33 6/7 weeks) ▪ Late preterm (34 0/7–36 6/7 weeks)
Term	37 weeks' 0 days–41 weeks' 6 days (average ~40 weeks') GA at birth ▪ Early term (37 0/7–38 6/7 weeks) ▪ Full term (39 0/7–40 6/7 weeks) ▪ Late term (41 0/7–41 6/7 weeks)
Postterm	≥42 weeks' GA at birth
Extremely low birth weight (ELBW)	Birth weight < 1 kg
Very low-birth weight (VLBW)	Birth weight < 1.5 kg
Low birth weight (LBW)	Birth weight < 2.5 kg
Small for gestational age (SGA)	Birth weight < 10th percentile for GA
Appropriate for gestational age (AGA)	Birth weight between 10th and 90th percentiles for GA
Large for gestational age (LGA)	Birth weight > 90th percentile for GA

Sources: Gomella TL, Cunningham MD. Gestational age and birthweight classification. In: Gomella T, Eyal FG, Bany-Mohammed F, eds. *Gomella's Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drug*s. 8th ed. McGraw-Hill; 2020:42; Taketomo CK, Hodding JH, Kraus DM, eds.

Lexicomp Pediatric and Neonatal Dosage Handbook. 26th ed. Wolters Kluwer; 2019.

RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome (RDS) is a major cause of morbidity and mortality in preterm neonates.[3] This clinical syndrome is characterized by respiratory failure with atelectasis, hypoxemia, decreased lung compliance, small airway epithelial damage, and pulmonary edema. The principal cause of RDS is pulmonary surfactant deficiency. Pulmonary surfactant decreases the surface tension at the air–fluid interface in the alveoli and prevents alveolar collapse. Surfactant also facilitates the clearance of pulmonary fluid, prevents pulmonary edema, and stabilizes alveoli during aeration. At birth, the clearance of residual fetal lung fluid is accompanied by an increase in pulmonary blood flow, which facilitates the transition from fetal to adult circulation.[4]

In the fetus, endogenous cortisol stimulates the synthesis and secretion of pulmonary surfactant at 30 to 32 weeks' gestation.[4] However, sufficient amounts of pulmonary surfactant for normal lung function are not present before 34 to 36 weeks' gestation.[4,5] Therefore, the incidence and severity of RDS increase as GA decreases. RDS occurs in ~25% of neonates born at 30 to 31 weeks' gestation, but may occur in as high as 95% to 98% of neonates born at 22 to 24 weeks' gestation.[3]

Without adequate amounts of surfactant, the surface tension within the alveoli is so great that the alveoli collapse (atelectasis), resulting in poor gas exchange (eg, hypoxemia, hypercapnia). Low lung compliance also results, and large inspiratory pressures are needed to aerate the lungs. Unfortunately, the extremely compliant neonatal chest wall makes it difficult to create the large negative inspiratory pressures necessary to open the alveoli. This results in an increased work of breathing and alterations in ventilation and perfusion.[3,4]

Aeration of the surfactant-deficient lung also results in the cyclic collapse and distension of bronchioles, with resultant bronchiolar epithelial injury and necrosis. This epithelial damage causes pulmonary edema by allowing fluid and proteins to leak from the intravascular space into the airspaces and interstitium of the lung. The necrotic epithelial debris and proteins then form fibrous hyaline membranes.[3] Hyaline membranes and pulmonary edema further impair gas exchange.

The inadequate oxygenation and ventilation and increased work of breathing caused by RDS may result in the need for assisted positive-pressure ventilation. Complications of RDS may be related to mechanical ventilation and include pulmonary barotrauma (eg, pneumothorax, pulmonary interstitial emphysema [PIE]), intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), and chronic lung disease or bronchopulmonary dysplasia (BPD).[3]

Clinical Presentation

CASE 105-1

QUESTION 1: L.D., a 0.68-kg male, was born at 25 weeks' GA via cesarean section as a result of placenta abruption to a 38-year-old gravida 6 para 5 female with gestational diabetes. Apgar scores were 3 at 1 minute, 5 at 5 minutes, and 8 at 10 minutes. Thirty minutes after birth, L.D. appears cyanotic and has retracting respirations with grunting and nasal flaring. His heart rate (HR) is 160 beats/minute, and respiratory rate (RR) is 65 breaths/minute. An arterial blood gas (ABG) on 60% oxygen by noninvasive positive-pressure ventilation (NIPPV) is as follows:

pH, 7.25
P_{CO_2}, 41 mm Hg
P_{O_2}, 71 mm Hg
Base deficit, 8

Based on the blood gas results, L.D. is intubated immediately and placed on positive-pressure–assisted ventilation. An umbilical arterial catheter is inserted for frequent ABG monitoring, and an umbilical vein catheter is inserted for central venous access. L.D.'s chest radiographic shows RDS. Ampicillin 100

mg/kg every 8 hours and gentamicin 5 mg/kg every 48 hours are ordered intravenously (IV) to rule out sepsis.

What is an Apgar score? What risk factors does L.D. have for RDS? What signs and laboratory data are consistent with RDS?

An Apgar score is a method of evaluating the physical condition of a newborn infant immediately after birth. It consists of five clinical signs including HR, respiratory effort, muscle tone, skin color, and reflex irritability. Each sign can receive a score of 0 to 2 points, with a total possible score of 10 points. A score of 7 to 10 is considered normal, whereas scores of 0 to 3 require immediate resuscitation. The Apgar score is routinely done at 1 and 5 minutes of life and is repeated every 5 minutes until a total score of at least 7 is achieved. (For a video of how to assign an Apgar score to newborns, go to https://www.youtube.com/watch?v=cgFRkfpXXH4.) L.D.'s Apgar scores of 3 and 5 at 1 and 5 minutes indicate that he may have experienced some perinatal asphyxia, most likely secondary to maternal placenta abruption. L.D.'s risk factors for RDS are prematurity, male sex, perinatal asphyxia, cesarean section, and maternal gestational diabetes. Other risk factors include second-born twins and maternal–fetal hemorrhage.[3] Clinical signs and laboratory data consistent with RDS in L.D. include tachypnea, cyanosis, retracting respirations, grunting, nasal flaring, hypoxemia, hypercapnia, and a mixed respiratory and metabolic acidosis.[3] Clinical manifestations classically present within the first 6 hours of life.

Tachypnea, the first sign of respiratory distress, is an attempt to compensate for the inadequate ventilation, hypercapnia, and acidosis. L.D.'s retracting respirations (the use of intercostal, subcostal, suprasternal, or sternal accessory muscles) reflect the increased work of breathing necessary to maintain ventilation. His nasal flaring decreases resistance during inspiration and increases oxygenation. Grunting is the result of forceful exhalation against a partially closed glottis in an effort to prolong expiration and maximize oxygenation. Grunting also increases intrathoracic pressure during expiration in an attempt to stabilize the alveoli and prevent

atelectasis. L.D.'s cyanosis, hypoxemia, hypercapnia, and mixed respiratory and metabolic acidosis are consequences of inadequate oxygenation and poor ventilation and are consistent with RDS.[3]

Treatment

Case 105-1, Question 2: What treatments should be initiated for L.D.'s respiratory insufficiency?

Before L.D. is treated for RDS, other causes of respiratory distress must be ruled out. For example, infections (particularly group B streptococcal sepsis or pneumonia) often present with respiratory distress. Because it is difficult to distinguish between RDS and infection, all neonates with severe RDS should receive antibiotics. L.D. was started empirically on antibiotics, and a complete evaluation of possible sepsis should be performed.

Neonates should be treated for RDS as soon as possible and may require ventilatory support. Noninvasive ventilator support such as NIPPV or nasal continuous positive airway pressure (CPAP) has been shown to reduce barotrauma, volutrauma, and airway damage compared to intubation with mechanical ventilation.[3] However, some extremely preterm neonates may require intubation with mechanical ventilation because of persistent symptoms of RDS. Because L.D. failed NIPPV and required intubation, exogenous surfactant should be administered intratracheally as soon as possible. Human surfactant is synthesized and secreted by type II alveolar epithelial cells of the lung. It contains 70% to 80% phospholipids, 10% neutral lipids, and 8% proteins.[5] The major surface-active component is dipalmitoylphosphatidylcholine (DPPC), also known as colfosceril or lecithin. However, this phospholipid slowly adsorbs to the air–fluid interface in the alveoli. Other phospholipids (eg, phosphatidylcholine, phosphatidylglycerol) and four surfactant apoproteins (SP-A, SP-B, SP-C, and SP-D) enhance spreadability and surface adsorption.[5] Adsorption and surface spreading of the surfactant in the alveoli are important determinants of surface tension activity. SP-A and SP-D

both play a role in immune regulation and providing host defense. SP-A may also help regulate alveolar surfactant reuptake and metabolism.[5] SP-B and SP-C are the two most important apoproteins responsible for promoting adsorption and surface spreading of the surfactant in the alveoli to form a phospholipid monolayer.[5] SP-B is thought to be the most critical protein for surfactant activity.

Natural surfactants are derived from bovine or porcine lung lipid or lavage extracts. Modified natural surfactants are lung lipid extracts supplemented with phospholipids or other components.[3] Currently, three surfactant products are commercially available for clinical use in the United States: beractant (Survanta®), calfactant (Infasurf®), and poractant alfa (Curosurf®). Beractant and calfactant are U.S. Food and Drug Administration (FDA) approved for the prevention (ie, prophylaxis) and treatment (ie, rescue therapy) of RDS, whereas poractant alfa is only approved for treatment. Animal-derived products contain variable amounts of SP-B and SP-C, lipids, and phospholipids. Lucinactant (Surfaxin®), a synthetic surfactant that contains phospholipids and high concentrations of sinapultide (KL4), a synthetic peptide that mimics human SP-B, was approved in 2012 but was removed from the market in 2015. See **Table 105-2** for comparisons.[6–8]

Table 105-2
Comparison of Currently Marketed Surfactant Products

Variable	Beractant (Survanta®)	Calfactant (Infasurf®)	Poractant Alpha (Curosurf®)
Type and source	Modified natural surfactant, bovine lung mince extract	Natural surfactant, calf lung wash	Natural surfactant, porcine lung mince extract
PL	Natural and supplemented DPPC with mixed PL	Natural DPPC with mixed PL	Natural DPPC with mixed PL
Proteins	SP-B and SP-C	SP-B and SP-C	SP-B and SP-C
Indications	Prophylaxis and rescue therapy	Prophylaxis and rescue therapy	Rescue therapy
Criteria for prophylaxis	Birth weight <1.25 kg or evidence of surfactant deficiency	Premature neonates <29 weeks' GA at high risk for RDS	Not approved
Recommended dose	4 mL/kg (100 mg/kg PL)	3 mL/kg (105 mg/kg PL)	*Initial dose:* 2.5 mL/kg (200 mg/kg PL); *Repeat dose:* 1.25 mL/kg (100 mg/kg PL)
Recommended regimen for prophylaxis	Give first dose ASAP after birth, preferably within 15 minutes; repeat as early as 6 hours up to a total of four doses if infant remains intubated and requires FIO_2 ≥0.3 with PaO_2 ≤80 mm Hg.	Give first dose ASAP after birth, preferably within 30 minutes; repeat every 12 hours up to a total of three doses if infant remains intubated.	Not approved
Criterion for rescue therapy	Infants with confirmed RDS who require endotracheal intubation	Infants ≤72 hours of age with confirmed RDS who require endotracheal intubation	Infants with confirmed RDS who require endotracheal intubation
Recommended regimen for rescue therapy	Give first dose ASAP after RDS diagnosed, preferably by 8 hours postnatal age; repeat as early as 6 hours up to a total of four doses if infant remains intubated and requires FIO_2 ≥0.3 with PaO_2 ≤80 mm Hg.	Give first dose ASAP after RDS diagnosed; repeat every 12 hours up to a total of three doses if infant still remains intubated.	Give first dose ASAP after RDS diagnosed; repeat every 12 hours up to a total of three doses if infant remains intubated.
Recommended administration technique	Administer through side port of ETT adapter via ventilator *or* through disconnected ETT via 5F catheter, divide dose into four aliquots with position change.	Administer through side port of ETT adapter via ventilator *or* through disconnected ETT via 5F catheter, divide dose into two aliquots with position change.	Administer through side port of ETT adapter via ventilator *or* through disconnected ETT via 5F catheter, divide dose into two aliquots with position change.
Special instructions	Warm to room temperature before use; do not shake.	Gentle swirling of the vial may be necessary for redispersion; warming to room temperature is not necessary; do not shake.	Warm to room temperature before use; do not shake.
Stability	If warmed to room temperature for <24 hours, unopened, unused vials may be returned only once to refrigerator; single-use vial contains no preservative, discard unused portion.	If warmed to room temperature for <24 hours, unopened, unused vials may be returned once to refrigerator; single-use vial contains no preservative, discard unused portion.	If warmed to room temperature for <24 hours, unopened, unused vials may be returned only once to refrigerator; single-use vial contains no preservative, discard unused portion.
Cost per vial	$459.60 (4 mL), $813.46 (8 mL)[a]	$514.50 (3 mL), $910.64 (6 mL)[a]	$548.76 (1.5 mL), $1082.09 (3 mL)[a]

ASAP, as soon as possible; DPPC, dipalmitoylphosphatidylcholine; ETT, endotracheal tube; F, French; FIO_2, fractional inspired oxygen; PaO_2, partial pressure of oxygen; PL, phospholipids; RDS, respiratory distress syndrome.

[a]Average wholesale price according to the *2020 Red Book*.

Sources: Survanta Intratracheal Suspension. Package insert. AbbVie, Inc; 2019; Infasurf Intratracheal Suspension. Package insert. ONY Biotech, Inc; 2018; Curosurf Intratracheal Suspension. Package insert. Chiesi USA, Inc; 2019.

CASE 105-1, QUESTION 3: What are the effects of an exogenously administered surfactant that can be expected in L.D.?

Oxygenation and lung compliance rapidly and markedly improve after the administration of the surfactant. It should be expected that supplemental oxygen and mechanical ventilation may need to be significantly reduced. The increased lung compliance and decreased need for high inspiratory pressures result in a dramatic decrease in the incidence of pneumothorax and PIE. Survival in treated infants increases by ~40% regardless of BW or GA, and neonatal mortality from RDS is decreased to ~20%.[9] Other complications of RDS such as severe BPD, IVH, NEC, ROP, and PDA have not been decreased consistently with surfactant therapy.[10]

CASE 105-1, QUESTION 4: Which surfactant is appropriate and when should it be administered to L.D.?

PRODUCT SELECTION

Previous trials comparing natural surfactant products (poractant vs beractant, calfactant vs beractant, poractant alfa vs calfactant) have demonstrated that poractant and calfactant result in a significantly faster weaning of supplemental oxygen and mean airway pressure compared to beractant. Furthermore, a lower mortality rate at 36 weeks' postmenstrual age (PMA) was seen with a higher initial dose of poractant 200 mg/kg; however, there were no differences seen with the duration of mechanical ventilation and supplemental oxygen, the incidence of BPD, and other secondary outcomes.[11] To date, there is only one trial comparing the three natural surfactant products for the treatment of RDS. Overall, there were no significant differences in the incidence of pneumothorax, PIE, death, and the combined variable of BPD or death among the three surfactant products.[12] Long-term neurodevelopmental outcomes assessed at 18 to 24 months of corrected age of infants receiving beractant versus poractant for RDS found no significant difference between products.[13]

Previous studies reported significant cost savings associated with poractant (owing to fewer required additional doses) compared with beractant.[11] However, when comparing the average medication cost

per patient, poractant was significantly higher compared to beractant.[14] This may be due to more vials required to administer each treatment dose because poractant comes in smaller vial sizes (1.5 mL, 3 mL) compared to beractant (4 mL, 8 mL). In addition, costs associated with reintubation in preterm infants were similar between beractant and poractant.[15] A recent study using a large health care database reported similar adjusted length of stay (LOS) and costs between the three surfactants. However, infants treated with beractant or poractant had significantly lower rates of mortality compared to calfactant. Furthermore, infants treated with poractant were less likely to receive mechanical ventilation at days 3 and 7 compared to beractant and calfactant.[16]

Based on these comparative trials, it appears that poractant, given at a dose of 200 mg/kg, may be the favorable surfactant therapy because it resulted in a faster weaning of oxygen and mean airway pressure and a decrease in mechanical ventilation and mortality. However, long-term outcomes (eg, BPD and other secondary outcomes) are similar between the three surfactant products.

TIME AND METHOD OF ADMINISTRATION

Historically, surfactant therapy can be administered as prophylaxis, with the first dose given before the newborn's first breath or before positive-pressure ventilation, usually in the delivery room.[9] However, owing to the increased use of antenatal steroids, prophylactic surfactant administration is no longer indicated in infants at risk for RDS. Surfactant can be administered as *early* rescue (defined as the administration of surfactant within the first 2 hours of life) or *late* rescue (defined as treatment after >2 hours of life). When comparing *early* versus *late* rescue therapy (regardless of routine initial use of CPAP), infants treated in the *early* group had significant decreases in the incidence of mortality, air leak, BPD, and the combined variable of BPD or death.[10] Thus, CPAP should be utilized initially, with selective early rescue surfactant administration in infants in whom symptoms of RDS persist.

Surfactant should be administered by qualified physicians in the presence of nursing and respiratory therapy personnel. (For a video on surfactant administration, go to https://www.youtube.com/watch?v=SKcJpZTHKo8.) Surfactants can be administered through a side port of endotracheal tube (ETT) adapter via ventilator or through a disconnected ETT via a 5F catheter (see Table 105-2). Both administrative techniques are effective and are not significantly different with regard to clinical outcomes.[10] Several alternative methods of surfactant administration have been utilized in an effort to avoid mechanical ventilation. The "INSURE" (*IN*tubate–*SUR*factant–*E*xtubate) technique is a strategy that administers surfactant during a brief intubation followed by immediate extubation to nasal CPAP. This technique was associated with a reduced need for mechanical ventilation and subsequent BPD.[10] Recently, a less invasive surfactant administration (LISA) has been shown to be an effective delivery method for surfactant administration for the treatment of RDS.[17,18] LISA consists of surfactant instillation through a cannula into the trachea while the infant continues to breathe spontaneously on CPAP. Recent studies have reported significant decreases in the need for mechanical ventilation, BPD, and a composite outcome of death or BPD associated with a LISA.[17,18] Long-term follow-up at 24 months' PMA reported no significant differences in neurodevelopmental and respiratory outcomes between INSURE and LISA.[19] Although LISA appears promising, owing to limited data, intratracheal administration of surfactant combined with INSURE remains the administration of choice for surfactants.

Because surfactant works better if given earlier in the course of RDS, it is important to determine who is at the highest risk for RDS. Unfortunately, the exact criteria to clinically determine high-risk newborns are still unclear. Surfactant treatment should be administered as soon as clinical signs of RDS appear. The administration of CPAP after birth with subsequent selective surfactant therapy should be the preferred method. Early therapy avoids progression of the disease and the potential for decreased surfactant effectiveness; therefore, it should be considered in

preterm infants born at <30 weeks' gestation who need mechanical ventilation because of severe RDS. Because L.D. has clinical, laboratory, and radiographic findings consistent with RDS, a dose of 2.5 mL/kg (200 mg/kg phospholipid) of poractant should be administered to L.D. intratracheally immediately within 1 hour of age with subsequent extubation to CPAP as soon as possible.

CASE 105-1, QUESTION 5: Within 1 hour of poractant administration, L.D.'s oxygenation improved, and the fraction of inspired oxygen (FIO_2) was weaned from 60% to 40%. Ten hours later, the ABGs revealed the following:

pH, 7.30
PCO_2, 45 mm Hg
PO_2, 50 mm Hg
Base , Deficit2
O_2 saturation, 90% on the following ventilator settings: FIO_2, 0.40; intermittent mechanical ventilation (IMV), 30; PIP, 18; positive end-expiratory pressure (PEEP), +5

Should another dose of poractant be administered?

The response to a single dose of surfactant usually is transient; thus, more than one dose may be needed. Response to surfactant therapy can be variable, especially in preterm newborns or in those who require high oxygen and ventilatory pressures.[3] Reasons for lack of response include surfactant inhibition by proteins that have leaked into the alveolar spaces, inactivation of surfactant by inflammatory mediators (free oxygen radicals, proteases), presence of conditions that can decrease surfactant effectiveness (eg, pulmonary edema), or poor delivery of surfactant to the alveoli (owing to atelectasis).[3] The degree of responsiveness to surfactant also decreases with increasing postnatal age (PNA).[9]

Although the indications for subsequent doses of surfactant vary, persistence of respiratory failure is the major clinical indicator for retreatment. In practice, most infants require only one dose of surfactant. This may be related to advances in neonatal and perinatal management and an increased use of antenatal steroids. However, there are neonates who may be more likely to require

more than one dose; these include those who were not exposed to antenatal steroids and/or those with extreme prematurity (<26 weeks' gestation). A second dose of poractant should be given to L.D. because he still requires mechanical ventilation with relatively high inspiratory pressures and supplemental oxygen (F_{IO_2} ≥0.4) to maintain an arterial P_{O_2} of at least 50 mm Hg and oxygen saturation of 90%.

Case 105-1, Question 6: On rounds, the medical resident asks you about the complications of surfactant treatment in premature infants. What information on adverse effects and their frequency would you provide for the medical team?

The most common adverse effects of surfactant therapy are related to the method of administration.[6–8,10] During administration, L.D. may experience bradycardia and oxygen desaturation secondary to vagal stimulation and airway obstruction.[6–8] These adverse events might require temporary discontinuation of surfactant administration and increased ventilator support.

The risk of pulmonary hemorrhage, which usually occurs within the first 72 hours of life, can be found in up to 6% of neonates receiving surfactant therapy.[3] However, pulmonary hemorrhage has not been consistently reported in recent studies; thus, the association between surfactant therapy and this disorder is questionable.[3] Furthermore, the benefits of surfactant therapy far outweigh the potential risk of pulmonary hemorrhage.

BRONCHOPULMONARY DYSPLASIA

CASE 105-2

Question 1: J.T. is a 4-week-old, 1.2-kg female who was born at 25 weeks' gestation. Her medical history includes RDS, episodes of sepsis and pneumonia, and 3 weeks of parenteral nutrition. J.T. has also failed extubation

numerous times and is currently requiring mechanical ventilation with an F_{IO_2} of 50%. Current vital signs are as follows:

RR, 60 breaths/minute
HR, 150 beats/minute
Blood pressure (BP), 80/55 mm Hg
O_2 saturation, 90%

On physical examination, J.T. has intercostal and subcostal retractions, shallow breathing, and an expiratory wheeze. Bilateral diffuse haziness with lung hyperinflation, focal emphysema, atelectasis, and irregular fibrous streaks are seen on chest radiograph. J.T. is currently receiving enteral feedings with a preterm 20-cal/oz formula at 40 mL every 3 hours. Based on these findings, the diagnosis of BPD is made.

What is the pathogenesis of BPD? What risk factors for BPD does J.T. have? What clinical signs and laboratory evidence of BPD are apparent in J.T.?

BPD (also known as chronic lung disease) is the most common form of chronic pulmonary disease in infants. The disease develops in newborns who require supplemental oxygen and positive-pressure ventilation for RDS or other primary lung disorders. BPD is a significant cause of infant morbidity and mortality. BPD affects 10,000 to 15,000 infants in the United States each year.[20] The incidence and severity of BPD are inversely related to GA and BW (80% of infants born at 22–24 weeks' GA compared to 20% born at 28 weeks' GA).[21] Despite advances in clinical practice, the incidence of BPD from 2005 to 2014 has not decreased; this may be due to an increased survival of extremely preterm infants and/or how BPD is defined.[20]

Historically, BPD was defined as those who require oxygenation therapy at 28 days of life, which was subsequently changed to the need for oxygen at 36 weeks' PMA.[20] In 2001, a severity-based definition of BPD, categorized as mild, moderate, or severe, based on oxygen or respiratory support requirement at 36 weeks' PMA was developed by the National Institute of Child Health and Human Development (NICHD).[22] Owing to the increasing survival of extremely preterm infants and the new respiratory support strategies such as NIPPV, diagnosing BPD accurately remains a challenge. In addition, the current definition does not account for infants who die

from severe respiratory failure before 36 weeks' PMA. This has led to a revised definition of BPD, developed by an NICHD workshop panel. The revised definition removed the criteria for an oxygen requirement of 28 days before 36 weeks' PMA, added a requirement for radiographic confirmation of parenchymal lung disease, and used a severity grading of I to III that incorporates newer modes of noninvasive ventilation and includes infants dying from respiratory failure before 36 weeks' PMA.[20] They proposed using a severity grading system rather than mild, moderate, or severe because the latter may be more subjective, which can result in various interpretations. **Table 105-3** outlines the two definitions proposed by the NICHD.[20,22]

Table 105-3
Definition of Bronchopulmonary Dysplasia: Based on Severity

NICHD 2001			NICHD 2018				
GA	<32 weeks	>32 weeks	**GA**	<32 weeks			
Time of Assessment	36 weeks' PMA or DC, whichever comes first	>28 days but <56 days' PNA or DC, whichever comes first	**Criteria**	BPD and ■ Persistent parenchymal lung disease confirmed on radiograph *and* ■ Require one of the following O_2 therapy ≥3 days to maintain O_2 saturation 90%–95% at 36 weeks' PMA			
Criteria	Treatment with O_2 >21% for at least 28 days *and*			**Invasive IPPV[a]**	**NCPAP NIPPV, or NC ≥3 L/minute**	**NC 1–2.9 L/minute or hood O_2**	**NC < 1 L/minute**
Mild BPD	RA at 36 weeks' PMA or DC, whichever comes first	RA by 56 days' PNA or DC, whichever comes first	**Grade I**	—	21%	22%–29%	22%–70%
Moderate BPD	Require <30% O_2 at 36 weeks' PMA or DC, whichever comes first	Require <30% O_2 at 56 days' PNA or DC, whichever comes first	**Grade II**	21%	22%–29%	≥30%	>70%
Severe BPD	Require ≥30% O_2 and/or positive pressure (PPV or NCPAP) at 36 weeks' PMA or DC, whichever comes first	Require ≥30% O_2 and/or positive pressure (PPV or NCPAP) at 56 days' PNA or DC, whichever comes first	**Grade III**	>21%	≥30%	—	—
			Grade IIIA	Early death occurring 14 days' PNA to 36 weeks' PMA because of persistent parenchymal lung disease and respiratory failure not attributable to other neonatal comorbidities			

DC, discharge; GA, gestational age; IPPV, intermittent positive-pressure ventilation; NC, nasal cannula; NCPAP, nasal continuous positive airway pressure; NICHD, National Institute of Child Health and Human Development; NIPPV, noninvasive positive-pressure ventilation; O_2, oxygen; PMA, postmenstrual age; PNA, postnatal age; PPV, positive-pressure ventilation.

[a]Does not include infants ventilated for primary airway disease or central respiratory control condition.

NICHD 2001 from Jobe AH, Bancalari E. NICHD/NHLBI/ORD workshop summary. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7): 1723–1729. Reprinted with permission of the American Thoracic Society. © 2022 American Thoracic Society. All rights reserved. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society. NICHD 2018 reprinted from Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr*. 2018;197:300–308. © 2018 Elsevier. With permission.

Pathogenesis and Clinical Manifestations

The cause of BPD seems to be multifactorial. Lung immaturity, surfactant deficiency, oxygen toxicity, barotrauma or volutrauma, and inflammation all play important roles. Premature infants, especially those at <24 weeks' gestation, are at a higher risk for BPD owing to lung immaturity.[21] Surfactant deficiency and the immature parenchymal structure of the lung and chest wall contribute to the development of BPD. Oxygen therapy, which causes a release of free oxygen radicals, is directly associated with the pathogenesis of BPD. Prolonged exposure to high oxygen concentrations and free oxygen radicals causes tissue damage, alveolar–capillary leaks, and atelectasis with resultant impaired gas exchange and pulmonary edema.[23] This may lead to the chronic pulmonary fibrotic changes seen in infants with BPD. In term infants, the lungs contain antioxidant enzymes that help protect the lungs from damage produced by free oxygen radicals. However, in preterm infants, the concentration of antioxidant enzymes may be low or absent. Therefore, premature infants are more susceptible to develop BPD than are term infants.

Barotrauma secondary to positive-pressure ventilation is also a major factor in the pathogenesis of BPD, independent of oxygen toxicity.[23] Barotrauma is caused by repetitive distension of the terminal airways during mechanical ventilation. This results in disruption of the epithelium and an increase in capillary permeability to proteinaceous fluid. The severity of lung injury is related to the amount of positive peak pressure used. Volutrauma is also involved in the pathogenesis of BPD and is caused by high tidal volume

ventilation and overdistension. The combined iatrogenic insults of oxygen toxicity and barotrauma or volutrauma, both inflicted on an immature lung for an extended time, can worsen lung damage.

The presence of a PDA may also increase the risk of BPD due to increased pulmonary blood flow resulting in increased interstitial fluid, decreased pulmonary compliance, and increased airway resistance. This can lead to prolonged mechanical ventilation with higher pressures and oxygen concentration.[21,23] However, clinical studies evaluating early PDA closure did not report a decrease in the incidence of BPD.[23]

Infection and nutrient deficiency may also play a role in the pathogenesis of BPD. The presence of chorioamnionitis may increase the infants' risk factor for BPD, although recent studies failed to report similar findings.[21] Pathogens such as *Ureaplasma, Chlamydia,* or cytomegalovirus may cause chronic infection and contribute to the development of BPD.[23] Colonization with ureaplasma may cause increased inflammation, fibrosis, and impaired airway development. Several meta-analyses have shown direct correlations between *Ureaplasma* respiratory tract colonization and the development of BPD in preterm infants.[23] Deficiencies in nutrients such as vitamin A (retinol) or trace elements such as zinc, copper, and selenium (which are integral components of the antioxidant enzyme structure) may also play a role in the pathogenesis of BPD.

J.T. has two of the most important risk factors for BPD, low BW and decreased GA. She is also at risk for BPD owing to mechanical ventilation, oxygen toxicity, and fluid excess (160 mL/kg/day). Other risk factors not pertaining to J.T. include male sex, White ethnicity, and persistent PDA.[21]

BPD is characterized by tachypnea with shallow breathing, intercostal and subcostal retractions, and expiratory wheezing as demonstrated in J.T. Other signs and symptoms include rales, rhonchi, cough, airflow obstruction, airway hyperreactivity, increased mucus production, hypoxemia, and hypercarbia.[23] J.T.'s chest radiograph shows evidence of BPD, including focal emphysema, atelectasis, bilateral diffuse haziness (interstitial thickening) with

increased expansion of the lungs, and irregular fibrous streaks. Mucous plugging, sepsis, and pneumonia can also develop in infants with BPD on chronic mechanical ventilation. Infants with severe BPD eventually experience cardiovascular complications such as pulmonary hypertension, cor pulmonale, systemic hypertension, and left ventricular hypertrophy. In addition to chronic respiratory and cardiovascular complications, infants with BPD have significant growth, nutritional, and neurodevelopmental problems.[23]

Management

Case 105-2, Question 2: What nonpharmacologic and therapeutic agents should be used to manage BPD in J.T.?

The medical management of infants with BPD includes supplemental oxygen therapy, mechanical ventilation, fluid restriction, nutritional management, and various pharmacologic interventions. Supplemental oxygen administered via mechanical ventilation, NIPPV, CPAP, or nasal cannula should be provided to maintain an oxygen saturation of 90% to 95% and prevent hypoxemia.[23] Because infants with BPD often accumulate excessive interstitial fluid in the lung, fluids should be restricted to 120 to 130 mL/kg/day to prevent congestive heart disease and pulmonary edema. Because infants with BPD have a 25% increase in caloric expenditure, high-calorie formulas (eg, 24 or 27 kCal/oz) may be used to optimize calories while restricting fluid intake.[23] If this increased energy is not provided, infants are at risk for undergoing a catabolic state that places them at higher risk for experiencing more severe BPD (inadequate nutrition may potentiate the toxic effects of oxygen toxicity and barotrauma). Malnutrition may impair growth and delay the development of new alveoli. In addition, malnourished infants are at higher risk for infection and oxygen toxicity.[23] The goal of nutritional therapy is to produce weight gains of 10 to 30 g/day, which can usually be accomplished by providing 140 to 160 kCal/kg/day.[23] If infants do not tolerate enteral feedings, parenteral

nutrition should be substituted until the gastrointestinal (GI) tract becomes more functional. Because J.T. is on a 20-cal/oz formula, switching her to a high-calorie formula would help optimize her weight gain. Her fluids should be restricted to 120 to 130 mL/kg/day.

PHARMACOLOGIC THERAPY

The treatment of BPD consists of multiple-drug therapy, which includes diuretics, bronchodilators, and corticosteroids.[2,20,21,23–30] Despite the advancement of drug therapy, none of these drugs has been shown to reverse pulmonary damage in infants with BPD. Instead, they are used primarily to reduce clinical symptoms and to improve lung function.

Diuretics

Infants with BPD are particularly prone to pulmonary edema from cardiogenic and noncardiogenic factors. Left ventricular failure may worsen the already existing right ventricular failure. Pulmonary vascular permeability is increased because of the disruption of the alveolar–capillary unit and causes an increased amount of fluid in the interstitium. Diuretics help reduce interstitial lung water, lower pulmonary vascular resistance, and improve gas exchange, thereby reducing oxygen requirements.[21,24] The most commonly used diuretics are furosemide, thiazides, and spironolactone. Furosemide is the drug of choice because of its potent diuretic effect. In addition, it increases lymphatic flow and plasma oncotic pressure and decreases pulmonary interstitial edema. The use of furosemide in infants with BPD was associated with short-term improvement in lung compliance and oxygenation, decreased total pulmonary resistance, and facilitation in ventilator weaning.[21,24] Although diuretics are commonly used in the management of BPD, especially in extremely preterm infants, it does not effectively treat established BPD.[21,24] In addition, long-term benefits such as reductions in mortality, hospitalization, or duration of positive-pressure ventilation have not been reported. Tolerance to furosemide may develop after a few days of therapy; this may be a result of the contraction in

extracellular volume, which can lead to a compensatory increase in water and sodium reabsorption in the renal tubules. Hypochloremic metabolic alkalosis, hypokalemia, and hyponatremia are the common short-term adverse effects of furosemide. Other adverse effects include volume depletion, hypercalciuria, nephrocalcinosis, osteopenia, and ototoxicity.[2,21,24] Long-term adverse effects of furosemide on bone mineralization and growth are unknown.

Thiazide diuretics (eg, hydrochlorothiazide) in combination with a potassium-sparing diuretic (eg, spironolactone) can improve lung function and decrease oxygen requirements with increased diuresis.[24] Although less potent than is furosemide, the combination of these two diuretics can reduce the incidence of hypokalemia commonly associated with loop or thiazide diuretics. Adverse effects commonly seen with this combination include hyponatremia, hyperkalemia or hypokalemia, hypercalciuria, hyperuricemia, hyperglycemia, azotemia, and hypomagnesemia.[2] In summary, despite insufficient evidence of long-term efficacy (eg, decreased oxygen requirement, need for mechanical ventilation, death, severity of BPD) and the potential for adverse effects, diuretics are often used in the management of BPD to provide short-term improvement in pulmonary edema and reduce the need for ventilatory support. Future studies are needed to identify which infants with BPD will most likely benefit from diuretic therapy such as those with left ventricular dysfunction or pulmonary hypertension.[24] Because J.T. has evolving BPD and has not been able to be weaned off the ventilator, furosemide 2 mg/kg given every 12 hours enterally may be considered. J.T. should be monitored and treated for electrolyte disturbances while on furosemide.

Case 105-2, Question 3: One week after starting furosemide, J.T. still requires high ventilatory settings and is unable to be weaned from the ventilator. What other therapeutic agents may be considered to treat J.T.'s BPD?

Inhaled bronchodilators

Infants in the early stages of BPD generally have airway hyperactivity and smooth muscle hypertrophy. They are also at higher risk for bronchoconstriction owing to increased airway resistance secondary to hypoxia. Therefore, the use of bronchodilators may be helpful in these infants. β_2-Agonists such as albuterol have been shown to provide short-term improvements (4 hours) in lung compliance and pulmonary resistance owing to bronchial smooth muscle relaxation; however, they are not effective in all infants with BPD.[21,23,24] A recent survey reported variations in prescribing inhaled bronchodilators in infants with BPD, which raises a question on their efficacy.[24] Data from an administrative database reported that prolonged mechanical ventilation was the best predictor of inhaled bronchodilator usage in infants with evolving BPD.[25] In addition, tachycardia and hypertension are commonly seen, and tolerance may develop with prolonged administration. Therefore, inhaled bronchodilators should be reserved for infants with an acute exacerbation of airway obstruction and who have clearly demonstrated improvements during therapy. There are no well-designed studies evaluating the chronic use or long-term outcome of using inhaled bronchodilators in infants with BPD. Despite the lack of meaningful long-term clinical outcomes associated with β_2-agonists and the variable results, their use continues to be very common in preterm infants with BPD. Further studies evaluating the efficacy and safety of long-term inhaled bronchodilator therapy and to identify those who will most likely benefit from treatment are needed.

Inhaled anticholinergics (eg, ipratropium bromide) have produced short-term benefits (~4 hours) in infants with BPD by improving pulmonary function.[24] Inhaled anticholinergics, which relax bronchial smooth muscle and decrease mucus secretion, are generally reserved for infants who are intolerant to albuterol or as an adjunct to albuterol if clinical improvement is not seen.[24] The combined therapy of albuterol and ipratropium may be more effective than either drug alone.[24] The adverse effect profile of ipratropium is minimal because the drug is poorly absorbed.

A major problem with inhaled bronchodilators is their method of administration and drug delivery. Inhaled bronchodilators can be given by jet or ultrasonic nebulization or via a metered-dose inhaler (MDI).[25] For ventilator-dependent infants receiving MDIs, the MDI is connected to an adapter that is attached to the ventilator circuit and ETT. MDIs can also be given through bag ventilation via the ETT. For nonventilated infants, the MDI can be given using a valved holding chamber device and a face mask.

Compared with MDIs, nebulization has several disadvantages including the loss or inefficient delivery of drug and cooling of the inspired oxygen mixture. In several neonatal studies, MDIs with a spacer provided more efficient delivery of inhaled bronchodilators and greater improvements in oxygenation and ventilation; smaller doses and a shorter treatment time were also used.[25] Furthermore, when comparing the three different devices, the MDIs with a spacer and the ultrasonic nebulizer are more efficient in delivering aerosols to neonates than is the jet nebulizer.[25] In addition, MDIs are less expensive than is nebulization. Therefore, the use of MDIs with an appropriate spacing device is preferred for most infants.

Corticosteroids

Corticosteroids, particularly dexamethasone, have been used extensively for the prevention and treatment of BPD. Mechanisms of action of corticosteroids include (a) reduction of polymorphonuclear leukocyte migration to the lung; (b) reduction of lung inflammation; (c) inhibition of prostaglandin, leukotriene, tumor necrosis factor, and interleukin synthesis; (d) reduction of elastase production; (e) stimulation of surfactant synthesis; (f) reduction of vascular permeability and pulmonary edema; (g) enhancement of β-adrenergic receptor activity; (h) reduction of pulmonary fibronectin (which can reduce the risk of interstitial fibrosis); and (i) stimulation of serum retinol concentrations.[2,23,26]

Systemic Corticosteroids

Systemic corticosteroids are associated with many serious short-term adverse effects, including hyperglycemia, increased BP, hypertrophic cardiomyopathy, GI bleeding, intestinal perforation, pituitary–adrenal suppression, bone demineralization, poor weight gain, and increased risk of infection.[2,23] Serious long-term adverse effects such as cerebral palsy (CP) and neurosensory disability have also been identified in preterm infants who receive systemic corticosteroids.[23,26]

Early (Age Younger Than 8 Days) Systemic Corticosteroids

Early use of dexamethasone was associated with significant decreases in the incidences of BPD and the combined outcome of death or BPD at 28 days' PNA and at 36 weeks' PMA, PDA, severe ROP, and the need for late corticosteroid treatment.[26] However, its use was associated with significant increases in the incidence of CP, and combined death or CP. In contrast to dexamethasone, early hydrocortisone use was not associated with significant decreases in the incidences of BPD, death, or combined death or BPD at 36 weeks' PMA. However, its use was not associated with an increased risk of CP or the combined outcome of death or CP.[26,27] Both drugs significantly increase the risk of GI perforation, whereas dexamethasone also increases the risk of hyperglycemia and hypertension.[26] The authors concluded that despite the short-term benefits of dexamethasone and the lack of long-term adverse effects of hydrocortisone, early use of both dexamethasone and hydrocortisone is not recommended.[27,28]

Late (Age Older Than 7 Days) Systemic Corticosteroids

As with early use, late dexamethasone administration was associated with significant decreases in the incidences of BPD and the combined outcome of death or BPD at 28 days' PNA and at 36 weeks' PMA, and the need for late corticosteroid treatment and home oxygen.[26] However, the incidence of severe ROP (not blindness), cardiomyopathy, hyperglycemia, and hypertension was significantly higher in the infants treated with dexamethasone.

Contrastingly, the late use of hydrocortisone was not found to be associated with significant decreases in the incidence of BPD, death, and the combined death or BPD at 36 weeks' PMA.[27] Interestingly, both drugs, when administered after 7 days of life, did not significantly increase the rate of CP or combined death or CP.[26,27] There is currently one trial under way, conducted by the NICHD, evaluating late use of hydrocortisone on BPD at 36 weeks' PMA, mortality, and survival free of moderate-to-severe disability at 22 to 26 weeks' corrected age.[26]

In 2010, the American Academy of Pediatrics (AAP) issued a policy statement that low (<0.2 mg/kg/day) and high dexamethasone dosing regimens (≥0.5 mg/kg/day) as well as high-dose hydrocortisone (3–6 mg/kg/day) are not recommended owing to the insufficient evidence and absence of improved short- and long-term outcomes from randomized trials.[28] Early low-dose hydrocortisone (1 mg/kg/day) given within the first 2 weeks of life may benefit a specific patient population.[28] Clinicians must weigh the potential risks of BPD with the potential adverse effects associated with glucocorticoids; therapy should be considered in very low-birth weight (VLBW) infants at high risk for experiencing BPD (eg, those still on mechanical ventilation after age 1–2 weeks). Parents should be fully informed about the short- and long-term adverse effects of systemic corticosteroids.[28] Despite the AAP recommendation, some clinicians would still consider administering a short course of low-dose systemic corticosteroid in infants at high risk for BPD to help facilitate extubation.

Based on current evidence, it appears that late use of dexamethasone may be of benefit to infants at highest risk for severe BPD. The NICHD National Research Network developed an online risk calculator (https://neonatal.rti.org/index.cfm) that can be used to predict infants born at 23 to 30 weeks' GA up to 28 days' PNA at high risk for BPD.[21] A meta-regression analysis demonstrated that the impact of postnatal steroids on the combined outcome of death or CP was modified by the risk of BPD.[23,26] When postnatal dexamethasone was used in infants with a low-risk factor for BPD (<35%), there was a significant increase in the risk of death

or CP. However, when used in infants with a higher risk factor for BPD (>65%), a significant reduction in the risk of death or CP was found. Overall, infants with a >50% predicted risk of BPD had less harm associated with dexamethasone than did those at lower risk for BPD.[21] In practice, dexamethasone is usually delayed until infants are several weeks old, ventilator dependent, and require a high amount of oxygen therapy (>40%), and then the dose and duration should be minimized. A short-course (10-day), low-dose dexamethasone therapy (cumulative 0.89 mg/kg) has been shown to significantly decrease the duration of intubation and was not associated with long-term neurodevelopmental impairment in ventilator-dependent ELBW infants (the Dexamethasone: A Randomized Trial [DART]) study).[29] Therefore, dexamethasone 0.15 mg/kg/day in two divided doses for 3 days followed by 0.1 mg/kg/day for 3 days, 0.05 mg/kg/day for 2 days, and 0.02 mg/kg/day for 2 days may be considered for J.T., even though she is now 5 weeks old.[29] Throughout therapy, J.T. should be monitored for hyperglycemia, hypertension, GI bleeding, and intestinal perforation. With the increased use of noninvasive forms of assisted ventilation such as NIPPV, more infants are prescribed systemic corticosteroids to avoid intubation or BPD.[26]

Inhaled Corticosteroids

To decrease adverse effects associated with systemic administration, inhaled steroids such as beclomethasone dipropionate, fluticasone, and budesonide have also been used for the treatment and prevention of BPD.[30] When compared to placebo, inhaled corticosteroids were shown to significantly decrease the incidence of BPD and the combined outcome of death or BPD at 36 weeks' PMA, and the use of systemic steroids. No differences were found with BPD and the combined death or BPD at 28 days' PNA, duration of mechanical ventilation and oxygen therapy, and the incidence of CP.[30] When compared to systemic steroids, no significant differences in the incidence of BPD at 36 weeks' PMA or combined death or BPD at 36 weeks were found.[26] Although the use

of early inhaled steroids (ie, prevention) was associated with increased duration of mechanical ventilation and oxygenation, these findings were significantly different when compared with the use of late inhaled versus systemic steroids.[26] Long-term neurodevelopmental outcomes assessed at age 7 years were not significantly different between inhaled versus systemic steroids.[30] Studies evaluating other methods of inhalational administration of steroids (eg, instillation of steroid using surfactant as a vehicle) have reported conflicting results on the incidence of death and BPD.[24]

Adverse effects of inhaled steroids are less common than with systemic steroids; these include mild adrenal suppression, bronchospasm, tongue hypertrophy, and oral candidiasis.[2,26,30] Inhaled steroids may suppress the pituitary–adrenal axis; however, studies have reported conflicting results. Suppression may vary depending on the type of inhaled steroids, dosing regimen, and other factors such as prematurity. The infant's mouth should be cleaned after each use of inhaled steroid to minimize complications such as oral thrush. As with inhaled bronchodilators, administration is a therapeutic problem with these medications. Further studies evaluating the optimal dose, duration of therapy, time of initiation, delivery technique, most appropriate preparation, and long-term adverse effects (including neurodevelopmental outcome) of corticosteroids are needed before inhaled steroids can be routinely recommended.

Long-Term Sequelae

Case 105-2, Question 4: Five months have passed, and J.T. is now 5 weeks old (corrected age), weighs 3 kg, and is ready for discharge. During the past several months, ventilation requirements slowly decreased, and J.T. was eventually extubated. However, she still requires supplemental oxygen at an F_{IO_2} of 30%, 0.25 L/minute via nasal cannula, to maintain an oxygen saturation of 90% to 95%. What are the long-term complications of BPD that can be expected in J.T.?

Infants with BPD have little pulmonary reserve and, therefore, are at higher risk for experiencing frequent respiratory exacerbations. BPD places J.T. at risk for recurrent infections of the lower respiratory tract, and she may require frequent hospitalizations during the first year for bronchiolitis and pneumonia. Approximately 50% of all children with BPD require hospitalization for respiratory exacerbations during the first 2 years of life.[21] Respiratory syncytial virus is a common cause of respiratory distress and recurrent atelectasis. With time, most preterm survivors with BPD have an improvement in pulmonary function owing to lung growth; however, many continue to have airway hyperreactivity. Infants with severe BPD can also experience pulmonary hypertension, cor pulmonale, systemic hypertension, and left ventricular hypertrophy.[21,23]

In addition, J.T. may be at risk for experiencing bone demineralization and rickets. VLBW infants are born with inadequate stores of vitamin D. In general, these premature infants may not receive an adequate intake of vitamin D, either parenterally or through their diet. Most VLBW infants require prolonged parenteral nutrition, which may cause cholestasis or hepatic failure. Prolonged cholestasis or chronic hepatic congestion owing to heart failure may cause malabsorption of calcium and vitamin D. In addition, furosemide may exacerbate calcium deficiencies by causing hypercalciuria. These combined factors may result in bone demineralization and rickets. Infants with BPD usually have high catabolism and increased oxygen consumption as a result of the increased work of breathing and chronic hypoxia. Inadequate nutritional support may negatively affect weight gain, growth, and long-term outcome of BPD.

Neurologic and developmental abnormalities such as learning disabilities, speech delays, vision and hearing impairment, and poor attention span can also occur in infants with BPD.[21,23] BPD itself is not an independent risk factor for neurologic abnormality; related factors include BW, GA, and socioeconomic status.[21,23] Long-term follow-up evaluations at ages 1 to 15 years in infants previously treated with high-dose dexamethasone revealed an increase in neurodevelopmental abnormalities such as CP and decreased

school performance in some studies.[28] However, it is not known whether these abnormalities were attributable to an adverse effect of dexamethasone on brain development or to an improved survival of infants who may already be at risk for experiencing these abnormalities.

Mortality rates for infants with BPD are highest in those with severe BPD. Those with a diagnosis of pulmonary hypertension after a few months of life have a mortality rate as high as 40% to 50%.[21] The majority of deaths associated with BPD occur during initial hospitalization and are attributable to respiratory failure, sepsis, pneumonia, cor pulmonale, and congestive heart failure.[21,23]

Prevention

Case 105-2, Question 5: What preventive measures could have been used to decrease the likelihood of the development of BPD in J.T.?

Prevention of prematurity and other etiologic factors of RDS is the most effective means of preventing BPD. Although both antenatal steroids and exogenous surfactant therapy have been shown to reduce the incidence of RDS, the incidence of BPD has not been affected.[21,23,24]

Treatment with caffeine for apnea of prematurity is the best evaluated therapy for the prevention of BPD. The Caffeine for Apnea of Prematurity (CAP) trial demonstrated that early use of caffeine (initiated before 3 days of life) in infants with BW of 0.5 kg to 1.25 kg reduces the risk of BPD; however, this was a secondary outcome.[20,21,24] It also reduces the duration of mechanical ventilation and oxygen therapy. In addition to these short-term benefits, caffeine was also associated with a decreased incidence of neurodevelopmental impairment, including CP at ages 18 to 21 months. However, improved rate of survival without disability was not seen at 5 years.[20]

One of the causes of BPD can be vitamin A deficiency, which can predispose infants to BPD owing to impaired lung healing, increased

susceptibility to infection and loss of cilia, and decreased number of alveoli.[31] Premature infants, especially VLBW infants, are at the greatest risk owing to low body stores, inadequate intake during feedings, and decreased enteral absorption of vitamin A. Intramuscular (IM) vitamin A alone (<29 weeks' gestation) or given in combination with nitric oxide (BW 0.75–1 kg) has been shown to significantly reduce the combined outcome of mortality or BPD; however, no difference was found with mortality, ROP, or sepsis.[24] Long-term follow-up at age 2 years reported no significant difference in the incidence of neurodevelopmental disability.[31] Vitamin A seems to be well tolerated; the incidence of adverse effects was similar between treated and control groups. Although evidence appears to support IM vitamin A, further studies evaluating the efficacy, safety, and optimal dosage regimen of vitamin A for the prevention of BPD are needed. Furthermore, owing to the lack of availability, need for frequent IM administration, and high cost, the usage of vitamin A has declined over recent years. Oral vitamin A does not decrease the incidence of BPD, perhaps because of inadequate dose or poor absorption.[31]

Ureaplasma urealyticum colonization of the respiratory tract of premature infants is a significant risk factor for BPD. Several studies evaluated the use of macrolide antibiotics for eradication of *Ureaplasma* in premature infants at risk for BPD.[23,31,32] Studies evaluating macrolide use in infants for BPD prevention reported variable efficacy results.[31] Azithromycin and clarithromycin have demonstrated a slight improvement in BPD prevention, especially in infants with a positive result for *Ureaplasma*.[31,32] However, there is significant variability in sample size, definitions of BPD, and duration of treatment among these studies.[32] A recent study examining a 3-day course of IV azithromycin 20 mg/kg/day given within the first 3 days of life failed to find a significant decrease in BPD and mortality; however, infants treated with azithromycin had a significantly higher rate of *Ureaplasma*-free survival compared to placebo.[32] Although results may be promising, azithromycin has serious GI toxicity. Prolonged antibiotic exposure has been linked to an increased rate of necrotizing enterocolitis (NEC), sepsis, and fungal infections. In

addition, erythromycin and azithromycin use has been associated with infantile hypertrophic pyloric stenosis. An epidemiology study with >10 million infants reported an eightfold increased risk associated with azithromycin.[2,31] Therefore, owing to these adverse findings and conflicting clinical efficacy, routine use of macrolide antibiotics is not recommended.

Optimization of nutritional support may also help prevent the development of BPD because proper nutrition helps promote lung maturation, growth, and repair. Excessive fluid administration should be avoided because it may lead to BPD. Fluid restriction decreases both the incidence of BPD and mortality.[23] Fluid restriction, the early use of caffeine citrate, and IM vitamin A could have been recommended for J.T. in the early course of her hospitalization to help decrease the likelihood of her experiencing BPD.

PATENT DUCTUS ARTERIOSUS

The fetus has three unique circulatory structures that differ from the adult circulation: (a) the ductus venosus, which permits blood to bypass the liver; (b) the foramen ovale, which allows blood to pass from the right atrium into the left atrium; and (c) the ductus arteriosus, the structure that connects the pulmonary artery to the descending aorta and allows blood to bypass the lungs (**Fig. 105-1**).[33] In addition to these structural differences, vascular resistance and pressure play important roles in determining the pathway of the fetal circulation. For example, the relative hypoxia that occurs in utero causes pulmonary vasoconstriction. Pulmonary vasoconstriction, along with compression of pulmonary blood vessels by unexpanded fetal lung mass, results in a high pulmonary vascular resistance and decreased pulmonary blood flow. This decreased pulmonary blood flow is acceptable in utero because the lungs essentially are nonfunctional. Instead, gas exchange occurs through the placenta.

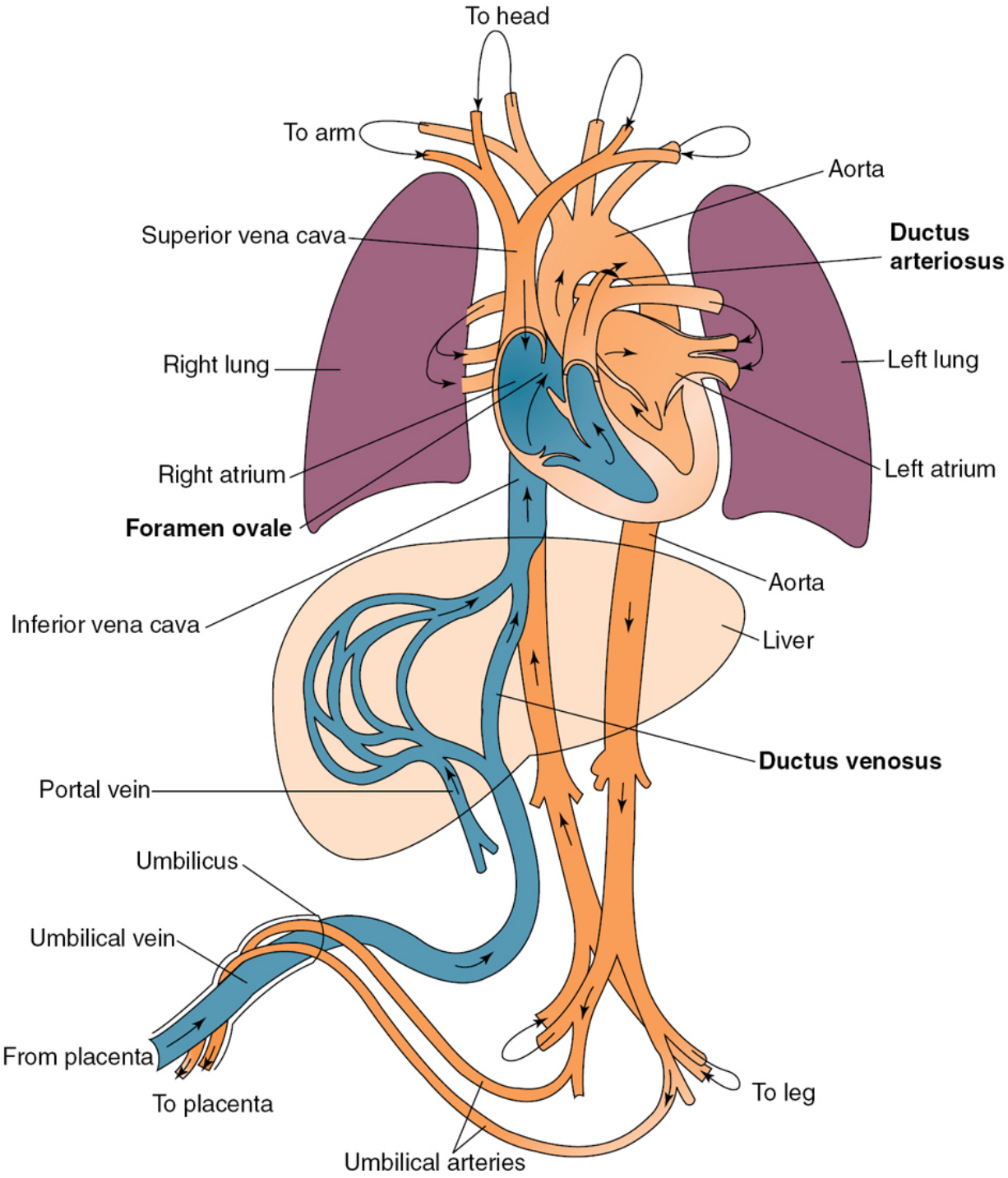


Figure 105-1 Fetal circulation. (Reprinted with permission from Pillitteri A. *Maternal and Child Health Nursing: Care of the Childbearing and Childrearing Family*. 7th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013.)

Maximally oxygenated blood (P_{O_2}, 30–35 mm Hg) flows from the placenta to the fetus through the umbilical vein (see Fig. 105-1). Approximately 50% of the umbilical venous blood is shunted away from the liver through the ductus venosus and directed into the inferior vena cava. Blood from the inferior vena cava and superior vena cava then enters the right atrium. Most of the blood from the inferior vena cava, which is well oxygenated, is directed in a straight pathway across the right atrium through the foramen ovale directly into the left atrium. It then enters the left ventricle through the mitral valve and is pumped through the ascending aorta and into the vessels of the head and forelimbs. Thus, the fetal brain is preferentially perfused with blood containing a higher amount of oxygen. Deoxygenated blood returning from the head region via the superior vena cava enters the right atrium and is directed through the tricuspid valve into the right ventricle, where it is then pumped into the pulmonary artery. Most of this blood is diverted through the ductus arteriosus into the descending aorta and then through the two umbilical arteries to the placenta. A small percentage of the blood flows to the lower extremities and then is returned to the heart via the inferior vena cava.[33]

Changes at Birth

At birth, major circulatory changes result from umbilical cord clamping, aeration and expansion of the lungs, and an increase in arterial P_{O_2}. These changes are important in the transition from a fetal to an adult circulation. An increase in systemic vascular resistance increases aortic, left ventricular, and left atrial pressures and cardiac output. Pulmonary pressures and blood flow also change. After the neonate's first breath, the lungs expand, oxygenation improves, and pulmonary vascular resistance immediately drops. This increases pulmonary blood flow, causing a decrease in pulmonary arterial, right ventricular, and right atrial pressures.[33]

Closure of the Foramen Ovale

After birth, pressure in the left atrium exceeds the pressure in the right atrium causing the small, valve-like flap that lies over the foramen ovale on the left side of the atrial septum to close over the foramen ovale opening. Closure of this flap prevents further flow through the foramen ovale.

Closure of the Ductus Arteriosus

Closure of the ductus arteriosus is more complex and depends on many factors. In utero, patency of the ductus arteriosus is maintained through the combined vasodilatory effects of a low P_{O_2} and high concentrations of prostanoids, particularly prostaglandin E_2 (PGE_2) and prostacyclin.[34] After birth, the smooth muscles of the ductus arteriosus constrict as arterial oxygenation increases and concentrations of placentally derived prostaglandins, particularly PGE_2, decrease.[34] Normally, the ductus arteriosus of a term neonate functionally closes within the first few days of life (ie, in 82% of infants within 48 hours of life and in 100% of infants within 96 hours of life). Anatomic closure of the ductus occurs within 2 to 3 weeks of life. When the ductus arteriosus fails to close, it is called *patent ductus arteriosus (PDA)*. In a term neonate, a PDA beyond the first few days of life generally is permanent. It usually is secondary to an anatomic defect in the wall of the ductus arteriosus and requires surgical intervention. In contrast, a PDA in a preterm neonate may persist for weeks and still close spontaneously.

When a PDA is present, the direction and amount of blood shunting through this opening are determined by the pressure gradient between the systemic and pulmonary circulations. Because systemic vascular resistance and aortic pressure are increased, and pulmonary vascular resistance and pulmonary arterial pressure are decreased after birth, blood pumped from the left ventricle into the aorta flows from the aorta (a high-pressure area) through the PDA and into the pulmonary artery (a lower pressure area). This flow is

called left-to-right shunting and is in contrast to the right-to-left shunting that occurs through the ductus arteriosus during fetal life.

Clinical Presentation

CASE 105-3

Question 1: T.S. is a 0.75-kg female who was born at 25 weeks' GA to a 22-year-old gravida 2 para 1 female. One hour after birth, T.S. exhibited symptoms of RDS, and two doses of beractant were given within the first 24 hours of life. After the second dose of beractant, T.S.'s respiratory function greatly improved, and no further doses of beractant were required. On the seventh day of life, the nurse noticed that T.S. had tachycardia, a systolic murmur, a hyperactive precordium, and a widened pulse pressure. Her lungs sounded "wet." In addition, the nurse noted that T.S.'s combined IV fluid rates total 160 mL/kg/day instead of the desired fluid intake of 120 mL/kg/day. Current vital signs and ABGs are as follows:

HR, 190 beats/minute
RR, 65 breaths/minute
BP, 55/23 mm Hg
O_2 saturation, 89%
pH, 7.22
P_{CO_2}, 55 mm Hg
P_{O_2}, 77 mm Hg
Base deficit, 10

Ventilator support is increased to compensate for T.S.'s deteriorating respiratory status. Echocardiography is performed and shows a moderate-size PDA with significant left-to-right shunting. The chest radiograph shows pulmonary edema and an enlarged heart.

What risk factors for PDA does T.S. have?

T.S. has two major risk factors for developing a symptomatic PDA: prematurity and RDS. The occurrence of a PDA is inversely proportional to GA and BW. The incidence of PDA is ~45% in premature infants with a BW of 1.75 kg, but can be as high as 80% in premature infants with a BW of <1.2 kg.[35] In contrast, the incidence of PDA in term infants is only 0.06%.[35] Preterm neonates are at a higher risk for PDA than are term newborns because the

smooth muscle of the immature ductus is more sensitive to the dilatory effects of prostaglandins and less sensitive to the constrictive effects of increased oxygen tension. In addition, circulating concentrations of PGE_2 are often elevated in premature infants owing to the decreased pulmonary metabolism of prostaglandins. These factors contribute to the delayed closure of the ductus arteriosus in premature infants.[34]

RDS also increases the risk of PDA. Exogenous surfactant also may increase the risk and lead to an earlier clinical presentation of symptomatic PDA.[34] PDA can further complicate the course of RDS.[34] T.S.'s course is typical of a preterm neonate with resolving RDS. T.S.'s pulmonary function improved after surfactant administration. Consequently, pulmonary vascular resistance decreased and the degree of left-to-right shunting across the ductus arteriosus increased, causing a deterioration in respiratory status. In addition, the excess fluid that T.S. received is an iatrogenic factor that may have increased the shunting across the PDA, aggravating the degree of pulmonary congestion.[34]

Case 105-3, Question 2: How is T.S.'s presentation consistent with that of PDA?

T.S.'s clinical presentation is related to the increased pulmonary blood flow, decreased systemic perfusion, and left ventricular volume overload that resulted from the shunting of left ventricular cardiac output through the PDA into the lungs. To compensate for the inadequate peripheral perfusion, HR increases. This results in an increase in cardiac output and a greater left-to-right shunt through the PDA, creating a vicious cycle. The widened pulse pressure (the difference between systolic and diastolic pressures, 32 mm Hg) is a result of the diversion of aortic blood flow through the PDA, which is causing the bounding pulses. The systolic murmur, which is not always present, is the result of turbulent blood flow through the ductus arteriosus occurring because the pulmonary vascular resistance decreases. Tachycardia, hyperactive precordium, and a

continuous murmur are results of the left-to-right shunting through the ductus arteriosus during systole.[36]

Case 105-3, Question 3: What are the potential complications of this hemodynamically significant PDA in T.S.?

The increased pulmonary blood flow and resultant pulmonary edema will worsen T.S.'s respiratory disease and increase the need for ventilatory support. The higher ventilatory settings (increase in mean arterial pressure [MAP] and FIO_2) place T.S. at risk for having BPD. If the PDA is left untreated, T.S. may experience congestive heart failure secondary to an increased left ventricular end-diastolic volume. A hemodynamically significant PDA also places T.S. at risk for IVH and NEC.[34]

Treatment

Case 105-3, Question 4: How should T.S.'s PDA be managed?

The initial medical management for T.S.'s symptomatic PDA is supportive care, which includes fluid management (eg, fluid restriction and diuretic therapy), correction of anemia, and treatment of hypoxia and acidosis. Although excessive fluid administration may increase the risk of PDA, fluid restriction alone is unlikely to result in ductal closure. T.S.'s fluid intake should be restricted to 100 to 120 mL/kg/day (~80% of total fluid maintenance requirements) to avoid worsening of her pulmonary edema and to prevent congestive heart failure.[34] Furosemide 1 mg/kg IV could be considered for administration to T.S. to treat her pulmonary edema. Because of T.S.'s GA, BW, and size of PDA, it is unlikely that she will respond to these general measures alone. Therefore, T.S. requires pharmacologic treatment with indomethacin or ibuprofen.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Both indomethacin and ibuprofen are available in injectable form for the treatment of PDA. These drugs nonspecifically inhibit prostaglandin synthesis, thereby eliminating the vasodilator effects of the PGE series on the ductus arteriosus, allowing the ductus to close. Indomethacin has been used clinically for >30 years for the treatment of PDA. However, because of its adverse effects, other prostaglandin inhibitors, such as ibuprofen, have been studied for PDA closure. Ibuprofen is as effective as indomethacin in closing the ductus and causes significantly less of a decrease in renal, mesenteric, and cerebral blood flow. Thus, ibuprofen reduces the risks of NEC and transient adverse effects on renal function (eg, oliguria, elevations of serum creatinine [SCr]) compared with indomethacin.[37] Hyperbilirubinemia is more common with ibuprofen. However, the incidence of mortality, BPD, and IVH are similar for both drugs. Unfortunately, no long-term follow-up studies of ibuprofen exist. These studies are needed to determine whether ibuprofen or indomethacin is the drug of choice for PDA closure.[37] Based on the studies currently available, ibuprofen may be preferred in patients who have or are at risk for decreased renal function. The initial dose of ibuprofen lysine is 10 mg/kg followed by two doses of 5 mg/kg given at 24-hour intervals. If urinary output decreases to <0.6 mL/kg/hour, the second or third doses should be held.[2]

Unfortunately, not every infant treated with a nonsteroidal anti-inflammatory drug (NSAID) responds with constriction of the ductus arteriosus; therefore, surgical closure (eg, ligation, coiling) of the PDA may be required. Surgery generally is reserved for neonates who do not respond to pharmacologic therapy or those in whom drug therapy is contraindicated.[34]

Case 105-3, Question 5: Owing to lower risks of adverse effects on renal function, the attending physician would like to treat T.S. with ibuprofen for closure of her PDA. You explain to the medical team that there is a temporary shortage of ibuprofen, and, therefore, T.S. should be treated with indomethacin. The medical team then asks the following: What is the dose of indomethacin for T.S.? What route should be used for its administration?

The medical team should be told the following information. The route of choice for indomethacin is IV in the United States. In developing countries, enteral NSAIDs have been shown to be effective. However, there are concerns for increased GI side effects.[38]

A large interpatient variability of indomethacin pharmacokinetics occurs in preterm neonates. Serum concentrations do not correlate consistently with therapeutic or adverse effects. Furthermore, the optimal therapeutic serum concentration is not yet defined.[39] The most commonly used regimen involves three indomethacin doses, given in 12- to 24-hour intervals, with the first dose equal to 0.2 mg/kg IV in all neonates.[2] Because indomethacin clearance is directly proportional to PNA, the second and third doses are determined by PNA at initiation of indomethacin therapy. If onset of treatment was at <2 days' PNA, neonates receive 0.1 mg/kg/dose; if initiation of therapy occurred at 2 to 7 days' PNA, neonates receive 0.2 mg/kg/dose; if therapy began at >7 days' PNA, neonates receive 0.25 mg/kg/dose. The second and third doses are administered at 12- to 24-hour intervals. No specific guidelines exist regarding which patients receive every-12-hour versus every-24-hour dosing; however, the individual dosing interval generally is determined by the neonate's urine output. If urine output remains >1 mL/kg/hour after an indomethacin dose, then the next dose may be given in 12 hours. If urine output is <1 mL/kg/hour but >0.6 mL/kg/hour, then the dosing interval may be extended to 24 hours. Doses should be held if urine output is <0.6 mL/kg/hour. T.S. should receive three doses of indomethacin 0.15 mg (0.2 mg/kg/dose) given every 12 hours, as long as her urine output remains >1 mL/kg/hour. If T.S.'s urine output decreases, then the dosing interval should be adjusted as outlined earlier. Because rapid IV administration of indomethacin can decrease cerebral, mesenteric, and renal blood flow, longer infusion rates of 20 to 30 minutes are recommended.[2,40]

Response to NSAID therapy can be determined by assessing the clinical signs of PDA such as tachycardia, widened pulse pressure, bounding pulses, heart murmur, and the ability to wean from

ventilator support. In certain cases, echocardiography may be performed to confirm the closure of a PDA.

Case 105-3, Question 6: What clinical and laboratory data should be monitored during T.S.'s indomethacin therapy?

Before initiating indomethacin therapy, T.S. should receive an echocardiogram to rule out ductal-dependent congenital heart disease and to confirm the presence of a PDA. In addition, an SCr and blood urea nitrogen (BUN) should be obtained from T.S. before indomethacin therapy because nephrotoxicity is the most common adverse effect. Infants receiving indomethacin can experience transient oliguria with increased SCr. This occurs as a result of indomethacin-induced decreases in renal blood flow and glomerular filtration rate.[40] Dilutional hyponatremia may occur secondary to decreased urine output. Treatment of hyponatremia should be aimed at decreasing free water intake through fluid restriction rather than by sodium supplementation. Typically, renal function normalizes within 72 hours of the last dose of indomethacin. In general, indomethacin therapy is contraindicated in neonates with renal failure, urine output <0.6 mL/kg/hour, or an SCr of ≥1.8 mg/dL.[2]

In addition to monitoring renal function and serum electrolytes, serum concentrations of aminoglycosides, digoxin, and other renally eliminated drugs should be monitored carefully. Indomethacin therapy may decrease renal drug clearance and cause accumulation of these agents, which may require a dosage reduction.[41]

A platelet count should also be obtained from T.S. before therapy because indomethacin may decrease platelet aggregation. Thrombocytopenia (platelet count < 50,000–60,000/μL) is a contraindication to indomethacin therapy.[2,40] In cases of thrombocytopenia, indomethacin may be withheld temporarily until platelets can be transfused. Other potential contraindications to indomethacin therapy include active bleeding and clinical evidence of NEC because GI bleeding, perforation, and NEC have been reported with indomethacin use.[34,40] These GI effects may be related

to decreases in intestinal blood flow usually seen with rapid IV infusions. Grades II to IV IVH also are frequently quoted as contraindications to indomethacin therapy; however, indomethacin treatment probably is not associated with the progression of IVH. In fact, prophylactic treatment with indomethacin may be associated with a decrease in the incidence of severe IVH (grades III and IV).[34,40]

Case 105-3, Question 7: When is the best time to initiate an NSAID for symptomatic treatment of T.S.'s PDA?

Controversy about the optimal timing for PDA closure has existed since the first report of ligation of the ductus arteriosus four decades ago. Some centers may opt to pharmacologically treat within the first week of life when a PDA is initially detected despite a lack of symptoms. This approach results in unnecessary drug exposure in neonates who would experience spontaneous closure without pharmacologic intervention, and thus is not recommended.[40] Others may not treat until symptoms of a PDA are present (early, within 5 days of life; late, 7–14 days of life). Both treatment strategies (early and late symptomatic) significantly decrease the incidence of PDA, but both cause significant transient reduction of urine output and SCr elevation.[40] Conflicting data regarding the short- and long-term benefits of ductal closure (indomethacin or ibuprofen) including the effect on complications (eg, BPD, NEC, IVH) and mortality continue to result in varied clinical practices and a lack of a standard of care.[42] Because T.S. is an ELBW neonate with RDS, she is at high risk for complications associated with a large PDA. She also has clinical signs of a PDA and, thus, many practitioners would consider treating her PDA at this time.

Case 105-3, Question 8: The physicians were able to decrease T.S.'s ventilator support within the first 12 to 24 hours of starting indomethacin treatment. After 3 to 4 days of gradual and consistent ventilator weaning, the ventilator settings could not be decreased further. During the next 2 to 3 days, T.S.'s respiratory status deteriorates, and she requires increased ventilator

support. T.S. now has tachycardia, a widened pulse pressure, bounding pulses, and a hyperactive precordium. Repeat echocardiogram shows a small-to-moderate PDA. Current data include the following:

BUN, 10 mg/dL
SCr, 1.1 mg/dL
Sodium, 134 mEq/L
Potassium, 4.9 mEq/L
Chloride, 97 mEq/L
Urine output, 2.3 mL/kg/hour
Fluid intake, 130 mL/kg/day
Platelets, 180,000/μL

Why did PDA recur in T.S., and how should it be managed?

Successful closure of the PDA with indomethacin occurs in 70% to 90% of infants; however, ductal reopening or recurrence can occur.[34] Recurrence of PDA occurs especially in lower BW infants. Several reasons might explain T.S.'s transient response to indomethacin. Recurrence of PDA is inversely proportional to GA; the incidence of ductal reopening is significantly higher in infants with 26 weeks' GA or younger compared with infants born at 27 weeks' gestation or more (20% vs 9%, respectively).[34] The higher recurrence in younger GA neonates may be related to resumption of PGE_2 production after indomethacin serum concentrations decline and heightened sensitivity of the immature ductus arteriosus to the dilating effects of PGE_2.[34]

Furthermore, the rate of recurrence is lower in infants who were treated with indomethacin earlier in life compared with those who receive treatment later.[34] Because anatomic closure of a PDA may be delayed for a couple of weeks, it is not surprising that the ductus arteriosus reopened in T.S. after her initial response to indomethacin.

Prolonged indomethacin therapy may prevent recurrences and allow for permanent closure of the ductus arteriosus. However, prolonged courses of indomethacin are associated with a significantly higher incidence of NEC, so their routine use is not recommended.[34] The optimal timing, duration, and dosing regimen of indomethacin, as well as the subset of neonates most likely to benefit from therapy still need to be identified.

T.S. remains ventilator dependent and is at increased risk for exhibiting BPD. Because she has no contraindications to indomethacin therapy, a second course of indomethacin could be considered, although the incidence of successful closure with repeated courses is significantly lower compared with the initial course.[43] If the PDA fails to respond to this prolonged regimen or if it recurs again after an initial response, and T.S. remains ventilator dependent, surgical closure most likely will be required to permanently close the PDA.

Prophylactic Administration

Case 105-3, Question 9: Could prophylactic NSAID administration have prevented the development of a symptomatic PDA in T.S.?

Prophylactic indomethacin therapy is defined as the administration of indomethacin within 24 hours of life to newborns who are at risk for experiencing a symptomatic PDA.[40] However, routine prophylaxis would unnecessarily expose a large number of newborns to indomethacin (and its adverse effects) because PDA closure may occur spontaneously without treatment. Prophylactic use of indomethacin has short-term benefits; it significantly decreases the incidence of PDA and IVH (grades III and IV) and the need for PDA surgical closure.[44] Unfortunately, most studies have not shown that prophylactic ductal closure with indomethacin decreases the incidence of death, BPD, NEC, or neurodevelopmental disabilities. In addition, infants receiving prophylactic therapy have a higher incidence of severe oliguria or anuria, albeit transient.[44] Therefore, routine prophylactic administration is usually not warranted. It may be considered, however, in some neonatal units that do not have easy access to cardiac diagnostic and therapeutic services or those that have a high incidence of IVH.

Prophylactic ibuprofen therapy (administered at <24 hours of life) decreases the incidence of PDA and the need for rescue pharmacologic treatment and surgical closure.[45] However, it does not

appear to decrease BPD, IVH, NEC, or mortality, and may increase the risk of renal dysfunction and GI bleeding. Because of the lack of long-term follow-up studies with the current ibuprofen lysine product, prophylactic ibuprofen therapy for the prevention of PDA is not recommended at this time.

Treatment With Acetaminophen

Case 105-3, Question 10: During multidisciplinary neonatal intensive care unit (NICU) rounds, the advanced nurse practitioner mentions that acetaminophen has been used to treat PDA and it may be safer than NSAIDs. Should acetaminophen, rather than indomethacin, have been used to treat the symptomatic PDA in T.S.? What is the evidence to support its use?

The advanced nurse practitioner is partially correct and should be informed of the following information. Several case reports and studies suggest that acetaminophen may be used for the treatment of PDA.[40,45] Similar to NSAIDs, acetaminophen inhibits prostaglandin synthesis. However, in contrast to NSAIDs that inhibit cyclooxygenase-1 and -2 (steps that occur early in the synthesis of prostaglandins), acetaminophen is thought to affect a subsequent step in prostaglandin synthesis by inhibiting the peroxidase site of the enzyme, prostaglandin synthetase.[40] Owing to the different mechanisms of actions, acetaminophen would be expected to have less serious side effects than do NSAIDs.

Acetaminophen at doses of 15 mg/kg every 6 hours for 2 to 7 days has been compared to indomethacin and ibuprofen for the treatment of PDA in preterm neonates.[46,47] There is no significant difference in the failure rates for PDA closure or risk of reopening the PDA between the three drugs. No significant differences in secondary outcomes or adverse effects were observed, with a few exceptions: SCr and bilirubin levels were significantly lower, and platelet counts were higher in patients who received acetaminophen. Although these results appear promising, an association of prenatal and postnatal use of acetaminophen with autism or autism spectrum

disorder has been identified.[47] In addition, animal studies suggest that acetaminophen may affect cognitive function when administered during neonatal brain development. Therefore, further research, including long-term follow-up studies of neurodevelopment, is needed before acetaminophen can be recommended for PDA closure in routine clinical practice.[47] Owing to these concerns, acetaminophen should not have been used in place of indomethacin to treat the symptomatic PDA in T.S. After weighing all potential risks and benefits, some clinicians may use acetaminophen before surgical closure in select neonates with a significant PDA, who have failed or who have contraindications to NSAID therapy.

NECROTIZING ENTEROCOLITIS

CASE 105-4

QUESTION 1: C.D., an 18-day-old female neonate (current weight 0.98 kg), was born at 27 weeks' GA with a BW of 0.86 kg. Her postnatal course has been complicated by RDS, sepsis, and a large PDA for which she required intubation and mechanical ventilation, one dose of beractant, a 7-day course of ampicillin and gentamicin, and indomethacin. Enteral feedings with a standard preterm 24-cal/oz formula were started on day 4 of life at 5 mL every 3 hours (~46 mL/kg/day). Feedings were increased by 5 mL/feed on days 5 through 7 to 18 mL/feed every 3 hours on day 7 of life (~170 mL/kg/day). This morning, C.D. exhibited a distended abdomen, bloody stools, multiple episodes of apnea that required reintubation and assisted ventilation, and metabolic acidosis. ABG results revealed the following:

pH, 7.15
P_{CO_2}, 67 mm Hg
P_{O_2}, 55 mm Hg
Base deficit, 10

An abdominal radiograph revealed pneumatosis intestinalis (the presence of gas in the intestinal submucosa). C.D. is to take nothing by mouth (NPO), and gentamicin 5 mg/kg IV infusion every 36 hours and ampicillin 100 mg/kg IV push every 8 hours are restarted.

What clinical signs of NEC does C.D. have? What is the pathogenesis of NEC, and what risk factors for NEC does C.D. have?

NEC, a type of acute intestinal necrosis, is the most common neonatal life-threatening nonrespiratory condition in preterm infants. The incidence of NEC in VLBW infants ranges from 5% to 9% and is inversely proportional to GA and BW.[48] Approximately 90% to 95% of NEC occurs in premature infants, with the highest incidence between 28 and 33 weeks' PMA; however, NEC can infrequently occur in full-term neonates.[48,49] The age of onset of NEC is also inversely related to GA and BW; the greater the GA at birth, the sooner the onset of NEC. Although NEC is less common in term infants, it usually develops within 3 to 4 days of birth. In contrast, infants born at ~30 weeks' gestation acquire NEC at a mean PNA of 20 days compared to 13.8 days for infants born at 31 to 33 weeks and 5.4 days for those born after 36 weeks of gestation.[48] Thus, preterm infants are at risk for NEC for a longer time. Although C.D. is extremely premature, she experienced NEC early (at 18 days of age), most likely because of the aggressive advancement of feedings. NEC contributes to a significant morbidity and mortality, with surgical-managed infants at the highest risk. The overall mortality of NEC ranges from 20% to 30%, with 35% for surgical-managed infants compared to 21% for medical-managed infants.[49] In addition, NEC is also a significant economic burden to health care costs. Infants with NEC required longer hospitalizations compared with infants without NEC, with an estimated annual cost of 500 million to 1 billion U.S. dollars.[49]

C.D. has several clinical signs of NEC, including abdominal distension, bloody stools, apnea, metabolic acidosis, and pneumatosis intestinalis on abdominal radiograph. Gastric retention of feedings, respiratory distress, occult blood in stools, lethargy, temperature instability, thrombocytopenia, and neutropenia also may occur. NEC may progress to bowel perforation, peritonitis, sepsis, disseminated intravascular coagulopathy (DIC), and shock. On an abdominal radiograph, the presence of gas in the intestinal mucosa or in the portal venous system is diagnostic of NEC, and free air in the abdomen is observed with bowel perforation. Although these radiographic findings confirm the diagnosis of NEC, a lag time may

occur between the initial clinical signs of NEC and radiologic confirmation.[48–50]

NEC can evolve slowly during a period of 24 to 48 hours, from a clinically benign course to an advanced stage of shock, peritonitis, and widespread intestinal necrosis. Although NEC can affect any part of the GI tract, most of the disease is confined to the jejunum and ileum for preterm infants and to the colon for term infants.[48] A staging system, which categorizes severity according to systemic, intestinal, and radiologic signs, has been developed to permit a more consistent evaluation and treatment of patients.[48,49] Stages IA and IB NEC include neonates and infants with suspected disease or rule out NEC. These patients may have mild GI problems such as delayed gastric emptying and emesis, temperature instability, apnea, bright red blood from the rectum, or a mild ileus. Infants with stages IIA and IIB have definite NEC and usually present with abdominal distension, bloody stools, and the presence of pneumatosis intestinalis on radiograph. Infants in stage IIB NEC may also exhibit metabolic acidosis and thrombocytopenia. Infants with stages IIIA and IIIB (advanced disease) are severely ill with clinical signs, including peritonitis, ascites, shock, severe metabolic and respiratory acidosis, and DIC. Those with stage IIIB have intestinal perforation. Pneumatosis intestinalis, caused by hydrogen production from bacterial translocation into the bowel wall, is a classic and diagnostic radiographic finding of NEC. Because pneumatosis intestinalis may be hard to detect on radiographs, some infants can experience severe NEC and need surgery without having radiographic findings. Therefore, new criteria including biomarkers of NEC may be needed to help diagnose NEC sooner and prevent its progression. C.D.'s presentation is most consistent with stage IIB NEC.

The pathogenesis of NEC is unknown but seems to be multifactorial. Most likely, NEC results from the effects of intestinal bacteria and other factors on injured intestinal mucosa. Inflammatory mediators such as platelet-activating factor, tumor necrosis factor-α, and interleukin (IL)-1, IL-6, IL-8, and IL-10 may also contribute to mucosal damage.[49] The neonatal intestinal mucosa is prone to injury for the following reasons: (a) increased permeability to potentially

harmful substances, such as bacteria and proteins; (b) decreased immunologic host defenses, including low concentrations of immunoglobulin A in intestinal mucosa; and (c) decreased nonimmunologic defenses, such as decreased concentrations of proteases and gastric acid. Furthermore, inappropriate initial microbial colonization may also contribute to the pathogenesis of NEC in preterm neonates, especially because NEC does not occur until after 1 week of life, at a time when the gut has been colonized with anaerobic bacteria.[48–50] In addition, numerous factors (both prenatal and postnatal) can cause injury to the neonatal intestinal mucosa and increase the risk of NEC. Prenatal maternal factors include eclampsia, prolonged rupture of membranes, chorioamnionitis, placenta abruption, smoking, lack of antenatal steroids, maternal cocaine use, and cesarean section. Postnatal factors include prematurity, low BW, ischemia or hypoxemia, asphyxia, intrauterine growth restriction, hypotension, respiratory distress, severe anemia, malnutrition, infection, hemodynamically significant PDA, congenital GI anomalies, cyanotic heart disease, formula feeding, exchange transfusions, blood transfusions, and the presence of umbilical catheters.[48–50] Medications such as corticosteroids, indomethacin, and H_2-blockers and prolonged empiric IV antibiotic use have also been associated with an increased risk of NEC.[50] However, the most significant clinical risk factor for NEC is prematurity.[48–50]

C.D. has several risk factors for developing NEC, which include prematurity, ELBW, history of infection, and RDS requiring mechanical ventilation. Furthermore, C.D. not only was given a hyperosmolar formula (24 cal/oz instead of 20 cal/oz) but her feedings were also advanced aggressively. These two factors may also contribute to the development of NEC. More than 90% of infants with NEC have received enteral feedings, although NEC also occurs in infants who have never been fed.[49] Enteral feedings (breast milk or formulas) serve as substrates for bacterial proliferation in the gut. As a result, reducing substances, organic acids, and hydrogen gas are produced by bacterial fermentation of these nutrients.

Observational studies have shown that rapid advancements in the volume of feeds (30–40 mL/kg/day vs <24 mL/kg/day) were associated with an increased risk of NEC; however, these studies were not controlled and were small case series. In addition, slower feeding advancement has been associated with an increased risk of late-onset sepsis and a delay in reaching full enteral feeds.[51] A recent study reported that VLBW infants advanced at a rate of 30 mL/kg/day reach full enteral intake significantly earlier than did infants advanced at 18 mL/kg/day without increasing the risk of NEC, death, late-onset sepsis, or survival without moderate-to-severe neurodevelopmental disability at 2 years corrected age.[52] However, infants in the faster advancement group had a higher risk of moderate or severe motor impairment compared to the slower advancement group. NEC, death, late-onset sepsis, time to reach full enteral feedings, and moderate or severe motor impairment were secondary outcomes. In fact, infants who were fed earlier had a significant reduction in the number of days on parenteral nutrition.[52] C.D. was started at a much higher initial feeding volume (46 mL/kg/day) and aggressively increased by 46 mL/kg/day, which may have increased the risk of NEC. If C.D. were appropriately fed, she would have reached full feedings in 7 to 14 days instead of 4 days. Last, the presence of PDA and the use of indomethacin for the treatment of PDA may also have contributed to NEC in C.D. through decreased mesenteric blood flow with resultant ischemia and intestinal mucosal injury.[48,50]

Treatment

Case 105-4, Question 2: How should C.D. be managed?

Significant abdominal distension may compromise respiratory function and blood flow to the intestines. Therefore, as soon as NEC is suspected, feedings should be stopped immediately and an orogastric tube with low intermittent suction placed to decompress

the abdomen. C.D.'s vital signs and abdominal circumference should be closely monitored for disease progression. A complete blood count and platelet count should be obtained frequently to monitor for neutropenia and thrombocytopenia. Blood and urine cultures should be obtained, and parenteral antibiotics should be started as soon as possible; 25% of infants with NEC have associated bacteremia.[51] Radiographic examinations should be routinely performed at least every 4 to 8 hours or as needed to evaluate the progression of the disease. In infants with stage I NEC, antibiotic therapy is usually given for 3 days pending culture results and clinical signs. Once the diagnosis of NEC is ruled out, antibiotics may be discontinued. Enteral feedings can then be initiated slowly. However, if the diagnosis of NEC is made (ie, stage II or III), antibiotics are continued and parenteral nutrition is initiated. Infants require bowel rest (NPO) for at least 7 to 14 days. The length of antibiotic therapy and bowel rest in infants with documented NEC is determined by the severity of systemic illness (eg, metabolic acidosis, thrombocytopenia). In general, infants with NEC stage II require at least 7 to 10 days of antibiotic therapy and bowel rest, whereas those with NEC stage III may require at least 10 to 14 days. C.D. has stage IIB disease and needs to be NPO for at least 7 to 10 days; she requires total parenteral nutrition during that time, and the surgery team should be notified at this point. Infants with stage III disease may also require fluid resuscitation, administration of inotropic agents such as dopamine and dobutamine, and surgical intervention, especially for those with perforated NEC.[49,50] About 27% to 52% of VLBW infants treated for medically managed NEC require surgical intervention (either primary peritoneal drainage or exploratory laparotomy), with the absolute indication for surgery being intestinal perforation, suspected bowel necrosis, and failure to respond to medical treatment.[51] Despite the type of surgical intervention, up to 35% of infants who require surgery will die.[49]

Case 105-4, Question 3: C.D. just completed a 7-day course of ampicillin and gentamicin for presumed sepsis. Is it appropriate to restart these antibiotics?

The selection of antibiotics for NEC depends on the common microorganisms observed in an individual neonatal unit, their sensitivities, and the spectrum of antimicrobial activity against intestinal microorganisms. Many organisms have been implicated in NEC, including Enterobacteriaceae (eg, *Escherichia coli, Klebsiella* species), *Pseudomonas, Staphylococcus aureus* (in rare cases, methicillin resistant), *S. epidermidis, Clostridium,* and fungi, usually *Candida*.[53] For most cases of NEC, treatment consists of broad-spectrum antibiotics including ampicillin and gentamicin.

Other antibiotics used to treat NEC include combined ampicillin and cefotaxime or monotherapy with meropenem or piperacillin/tazobactam. Vancomycin may replace ampicillin for suspected methicillin-resistant *S. aureus* or ampicillin-resistant enterococcal infection. The combination of cefotaxime and vancomycin has been shown to prevent severe peritonitis and death and reduce the need for surgery in infants with BWs <2.2 kg with NEC, whereas gentamicin and ampicillin have not. Suppression of Staphylococcal fecal flora by the combination of cefotaxime and vancomycin may explain these findings.[53] Owing to the small sample size and low-quality observational study, the authors recommend vancomycin and cefotaxime in infants not responding to initial standard regimen. Further studies are needed to determine whether the combination of gentamicin and vancomycin would be superior to cefotaxime and vancomycin. C.D. was prescribed with ampicillin and gentamicin and should be treated for 7 to 10 days. If C.D. is not responding to ampicillin and gentamicin, consideration should be made to replace ampicillin with vancomycin and gentamicin with cefotaxime. Owing to the national shortage of cefotaxime, ceftazidime has replaced cefotaxime in many NICUs.

Case 105-4, Question 4: Two days later, C.D. exhibits peritonitis with ascites (NEC stage III), hypotension, worsening metabolic acidosis, neutropenia, and DIC. IV fluids and dopamine are administered for the hypotension, fresh-frozen plasma and whole blood are given to treat the coagulopathy, and a fentanyl continuous infusion at 1 µg/kg/hour is started for pain control. Free air in the

abdomen is observed on abdominal radiograph. Blood, urine, and stool cultures have had no growth for 48 hours. What additional antimicrobial coverage should be provided?

The use of empiric anaerobic coverage in infants with definite NEC, stage II or III, remains controversial; however, many institutions have added anaerobic coverage to routine antibiotic regimens.[49,51,53] The two most commonly used agents are clindamycin and metronidazole. Routine use of clindamycin in the treatment of NEC has not decreased the incidence of intestinal gangrene, perforation, or death. In addition, it has been associated with an increased incidence of abdominal strictures.[53] There are no studies to demonstrate the efficacy of metronidazole in this patient population, but the lack of reports documenting adverse effects in preterm infants has made it the agent of choice in some hospitals. A study utilizing a database from 348 NICUs assessed the association of anaerobic antimicrobial therapy and clinical outcomes in VLBW infants. The authors reported no significant difference in the incidence of the combined outcome of death or intestinal strictures in infants with NEC stages II and III treated with or without anaerobic coverage.[54] Furthermore, anaerobic antibiotic therapy did not prevent the progression to death within 7 days of NEC diagnosis or to surgical NEC. However, a higher risk of strictures was found in all infants receiving anaerobic antibiotic therapy. Furthermore, in those with surgical NEC, a lower mortality rate was found in the anaerobic antibiotic-exposed infants.[54]

Based on this study, it might be prudent to consider weighing the risk versus benefit when deciding to add anaerobic antibiotic therapy in the treatment of medically managed NEC. In contrast, infants with peritonitis secondary to intestinal perforation (ie, those needing surgery) require both aerobic and anaerobic coverage.[55] Therefore, an antimicrobial agent with anaerobic activity such as metronidazole (instead of clindamycin) should be added to C.D.'s current regimen. Because *Candida* is not uncommon in infants with NEC, an antifungal agent such as fluconazole or amphotericin B should be

added if a culture result is positive for fungi and/or there is clinical deterioration.

Appropriate antibiotic selection and duration of treatment of medical and surgical NEC are unknown and are usually determined by clinical status and nonspecific inflammatory laboratory markers such as C-reactive protein (CRP). One study found a high degree of variability in the antibiotic regimens prescribed in infants with surgical NEC. Ampicillin, gentamicin, and metronidazole were the most common pre- and postoperative antibiotic regimen with a mean duration of 10.6 days for preoperative and 6.6 days for postoperative NEC. There was no difference in clinical outcomes among the different antibiotic regimens and duration of therapy.[54] Owing to the concerns of antibiotic overusage in preterm infants, studies are needed to identify the optimal antibiotic regimen and duration of therapy for the treatment of medical and surgical NEC.

Complications and Prognosis

Case 105-4, Question 5: C.D. is taken urgently to the operating room, and 40 cm of necrotic ileum is removed along with the ileocecal valve. What are the long-term nutritional problems that C.D. is likely to have?

The most common postoperative complications of NEC are intestinal strictures (up to 25%) and short-bowel syndrome (11%).[48,49,51] C.D. is at risk for experiencing short-bowel syndrome, a condition of malabsorption and malnutrition that results from surgical removal of a significant portion of the small intestine. The most important factors that determine short-bowel syndrome are the length of the remaining small intestine and the presence of the ileocecal valve. Because C.D. has had a majority of her ileum and her ileocecal valve removed, she most likely will suffer from short-bowel syndrome.

Because the terminal ileum is an important site for absorption of vitamins, trace minerals, and nutrients, C.D. will be at risk for decreased absorption of these substances. C.D. also will have a

faster GI transit time and diarrhea because her ileocecal valve was removed. (The ileocecal valve plays a major role in controlling intestinal transit time.) Absorption of enterally administered medications also may be decreased in patients with short-bowel syndrome. When C.D. starts to receive most of her nutrition enterally, she should be monitored for fat malabsorption and other nutritional deficiencies (eg, deficiencies in vitamins A, B_{12}, D, E, and K), and supplemented accordingly.

Despite advances in earlier diagnosis and aggressive treatment, ~20% to 30% of all infants with NEC die, with the highest mortality in extremely premature infants and those with surgical NEC.[48,49] Furthermore, infants with NEC are significantly more likely to have neurodevelopmental impairment (eg, CP); those requiring surgical management are at higher risk.[49,51]

Prevention

Case 105-4, Question 6: What could have been done to prevent NEC in C.D.?

Several interventions may decrease the incidence of NEC. Enteral feedings in preterm infants can be withheld for several weeks and parenteral nutrition initiated. Although intestinal priming or trophic feeding (ie, using a small amount of full-strength formula or breast milk for several days to stimulate GI mucosal development) has been shown to decrease the incidence of NEC compared with infants with the advancement of feedings, a Cochrane review did not report an increased risk of NEC with infants NPO beyond 4 days of life.[49] Because human milk provides antibodies, growth factors, and cellular immune factors, it may reduce the incidence of NEC. Infants fed with human milk had a significantly lower incidence of NEC and bacteremia than those fed with formula.[48–51] If mother's milk is not available, pasteurized donor human milk has also been shown to significantly decrease the risk of NEC.[48] In a recent study, a

significant decrease in the incidence of NEC and surgical NEC was observed in infants who were exclusively fed with a human milk–based diet compared with a combination of human milk and formula-based diets.[49] Human milk fortifier can be added to human milk to provide appropriate caloric requirements to stimulate fetal growth. Ideally, avoid the use of hyperosmolar formulas or medications because they can cause osmotic injury to the bowel and may result in NEC. Maternal steroids (commonly used to accelerate fetal lung maturation) can decrease the incidence of NEC owing to a maturational effect on the microvillous membranes.

Probiotics are live, nonpathogenic microbial preparations that colonize the intestine and have a beneficial effect on the health of the host. Probiotic microorganisms commonly used are strains of *Lactobacillus* and *Bifidobacterium.* In a recent meta-analysis of >9000 preterm infants, enteral administration of probiotics significantly decreased the risk of severe NEC, death, and sepsis.[56] Multiple-strain probiotics were found to be superior to single-strain probiotics in decreasing the incidences of NEC, death, and sepsis, possibly because the normal flora in the gut is diverse. Furthermore, *Lactobacillus* and *Bifidobacterium* were found to be significantly associated with a reduced risk of NEC; however, this effect was not seen with *Bacillus* and *Saccharomyces.* Studies evaluating the long-term effects of probiotics (assessed at 18–22 months up to 3 years corrected age) reported no adverse effects on growth or neurodevelopmental outcomes.[56] One major concern is that exposing immunologically immature VLBW infants to probiotics may potentially increase the risk of infections. Cases of systemic infections, especially in ELBW neonates, have been reported.[56] Some cases of probiotic-associated sepsis may not be identified owing to the failure of the laboratory to isolate these strains in blood cultures by the use of conventional culture-based techniques. Other controversies exist. Most studies did not evaluate the effects of probiotics in ELBW infants, the population at greatest risk for NEC. The optimal type of probiotic (species, strains, single or combined, live or killed) and the timing, dosage, and duration of therapy are still unknown. Little is known regarding the benefits of probiotics in

infants who are exclusively or partially fed breast milk. Furthermore, none of the studies were conducted in the United States, and most of the trials did not utilize U.S. commercially available probiotics. Lastly, currently no product in the United States has the appropriate regulatory mechanisms in place to ensure the quality of the product. Therefore, clinical studies are needed to address these issues, and if probiotics are administered to VLBW infants for the prevention of NEC, careful surveillance of mortality, NEC, and the emergence of resistant strains will be necessary. Based on these findings, probiotics may be prescribed in NICUs with high rates of NEC because the benefit may outweigh the risk. When C.D. is ready to be fed, breast milk or donor breast milk (if available) should be used in place of formula to help prevent future risk of NEC. Because C.D. already has NEC, probiotics may not be beneficial to her at this time.

Other preventative strategies include the implementation of antimicrobial stewardship and a standardized feeding guideline. Prolonged antibiotic use has been linked with NEC in preterm infants because of alteration of the gut microbiome. In addition, studies have reported significant reductions in NEC associated with the implementation of a standardized feeding guideline.[48]

NEONATAL SEPSIS AND MENINGITIS

CASE 105-5

QUESTION 1: J.E., a 28-week gestation, 0.85-kg male, was born to a mother with prolonged rupture of membranes (>72 hours). The newborn's mother is diagnosed with chorioamnionitis. J.E. had Apgar scores of 3 at 1 minute, 4 at 5 minutes, and 7 at 10 minutes after birth. Mechanical ventilation was instituted, and J.E. was admitted to the NICU. Vital signs on admission were as follows:

HR, 190 beats/minute
Temperature, 96.44 °F (35.8 °C)
BP, 56/33 mm Hg

Blood and urine culture results are pending. Significant laboratory data include the following:

WBC 2400 cells/μL with a differential of 25% segmented neutrophils, 15% bands, 45% lymphocytes, 10% monocytes, 4% eosinophils, and 1% basophils
Platelets, 45,000/μL
CRP, 5 mg/dL

What is the etiology and pathogenesis of neonatal sepsis? What risk factors for sepsis does J.E. have? What clinical signs and laboratory evidence of sepsis are apparent in J.E.?

Bacterial sepsis significantly contributes to neonatal morbidity and mortality. Neonates, especially preterm newborns, are at increased risk for infections and should be considered immunocompromised. The neonate's decreased immune function (eg, immature function of neutrophils, lower amounts of immunoglobulin) also results in a reduced ability to localize infections.[57] Once a tissue site becomes infected, bacteria can spread easily, resulting in disseminated disease. In addition, the lack of opsonic antibodies in preterm infants such as J.E. increases the susceptibility to infections caused by bacteria with polysaccharide capsules (eg, group B streptococcus, *E. coli, Haemophilus influenzae* type B).[58]

The incidence of neonatal sepsis is inversely proportional to BW and GA. The overall rate is about 1 infection per 1000 live births; ranging from 32 cases per 1000 live births for neonates <25 weeks' gestation, 20 cases per 1000 live births for neonates <29 weeks' gestation, 6 cases per 1000 live births for neonates <34 weeks' gestation, 1 case per 1000 for neonates between 34 and 36 weeks' gestation, and 0.5 cases per 1000 for term neonates.[59] Risk factors (as demonstrated in J.E.) include prematurity, low BW, male sex, and predisposing maternal conditions (eg, prolonged rupture of membranes >18 hours, maternal fever, elevated maternal white blood cells [WBC] or left shift, chorioamnionitis, and urinary tract infection).[57,59] Despite treatment, mortality rates for neonatal sepsis can be as high as 30% to 50%, with the highest mortality observed in newborns born before 29 weeks' gestation.[57,59] Meningitis occurs as a complication of bacterial sepsis in 10% to 30% of septic neonates and has a mortality rate of 20% to 60%, depending on the pathogen.[60] Long-term sequelae of meningitis have been reported in

about 40% to 50% of survivors and include hearing loss, blindness, developmental delay, CP, seizure disorders, and hydrocephalus.[58,61]

Common Pathogens

The fetal environment within the amniotic membranes is normally sterile until the onset of labor and delivery. Once the membranes are ruptured, the infant may be at risk for colonization of microorganisms from the maternal genital tract. Many of these organisms do not cause infection in the mother but may be detrimental to the infant. Early-onset neonatal sepsis (sepsis that presents during the first 72 hours of life) usually is caused by organisms acquired from the maternal genital tract. The most common pathogens found in early-onset neonatal sepsis are group B streptococcus (~40%) and *E. coli* (~30%). Other primary pathogens include *Listeria monocytogenes, Enterococcus,* and other gram-negative bacilli (eg, *H. influenzae, Klebsiella pneumoniae*).[57,61]

Late-onset sepsis (sepsis presenting after 3 days' PNA) usually is caused by these primary organisms or by nosocomial pathogens, such as coagulase-negative staphylococci (CONS), particularly *S. epidermidis, S. aureus, Pseudomonas* species, anaerobes, and *Candida* species.[57,61] The presence of IV catheters (umbilical or central) and duration of parenteral hyperalimentation are major risk factors for nosocomial septicemia. Other risk factors include prematurity, low BW, prolonged hospital stay, prior antibiotic use, lipid emulsion, use of H_2-blockers, invasive procedures, GI disease (including NEC), the presence of other indwelling devices (eg, ETTs, ventriculoperitoneal shunts), and nasal CPAP.[57] Late-onset sepsis in infants with central venous access is usually caused by gram-positive organisms, with CONS being the most common pathogen.[57] Clinically, before continuation of antibiotic therapy, it is important to distinguish whether patient isolates of CONS are the result of colonization of the catheters or IV tubing or represent true bacteremia.

Neonatal sepsis may present with nonspecific or subtle signs, especially in VLBW infants. The most common signs are poor feeding, temperature instability, lethargy, or apnea. Other signs of neonatal sepsis include glucose instability (hypoglycemia or hyperglycemia), tachycardia, dyspnea or cyanosis, tachypnea, diarrhea, vomiting, feeding intolerance, abdominal distension, metabolic acidosis, and abnormal WBC.[57,60] Clinical signs and laboratory evidence of neonatal sepsis observed in J.E. include tachycardia (HR, 190 beats/minute), hypothermia (temperature 96.44 °F [35.8 °C]), leukopenia (WBC, 2.4 × 10^3/μL), neutropenia (absolute neutrophil count of 960/μL), a left shift in the differential (ie, an immature-to-total neutrophil ratio [I/T] of 0.38), thrombocytopenia (platelets, 45,000/μL), and an elevated CRP (5 mg/dL). Hypothermia is more common than is fever in neonatal sepsis, especially in preterm newborns. However, if fever is present, it is strongly associated with bacterial infection. Neutropenia, especially with a left shift (as seen in J.E.), can be a sign of WBC depletion from bone marrow owing to overwhelming sepsis. An elevated WBC also can indicate a neonatal infection but may be less specific. The I/T ratio, defined as band forms plus any earlier cells divided by the total neutrophil count (including early cells), has been shown to be useful in diagnosing neonatal sepsis. An I/T ratio of <0.3 is normal.[60] CRP, an acute-phase reactant protein associated with tissue injury in response to an inflammatory process, may also be included as part of a sepsis workup. A CRP level of >1 mg/dL indicates inflammation and possible infection.[60] In infants with bacterial infection, serum CRP levels begin to increase from 6 to 8 hours after the onset of the illness and peak after 2 to 3 days.[62] Therefore, because of the delayed response, the use of CRP for detection of early-onset sepsis is not of great value. Serial CRP levels obtained during 2 to 3 days of illness may aid in the determination of duration of empiric antibiotic therapy. Empiric antibiotic therapy may be discontinued in infants with normal serial CRP levels in the absence of any clinical signs suggestive of sepsis. However, elevated CRP levels can be found in other clinical conditions such as viral infection, ischemic tissue injuries, hemolysis, or chorioamnionitis. Procalcitonin, another acute-

phase reactant, rises more quickly than does CRP in the presence of bacteria, so it may be more useful for early detection. However, there are also limitations to its routine use for the evaluation of neonatal sepsis, including nonspecificity (ie, noninfectious conditions can cause elevation of procalcitonin levels) and a lack of age-specific reference ranges.[62] Therefore, CRP and procalcitonin levels should be used with caution as the sole diagnostic criteria for sepsis or bacteremia. Late signs of neonatal infection include jaundice, hepatosplenomegaly, and petechiae.[60] A bulging fontanel, posturing, or seizures indicate meningitis, although these central nervous system (CNS) signs are not always present when meningitis exists.

Bacterial meningitis should always be considered in infants with neonatal sepsis.[58] The major pathogens causing neonatal sepsis are also the primary pathogens that cause neonatal meningitis.[60] The definitive diagnostic method for bacterial meningitis is lumbar puncture. Lumbar puncture should be performed in infants with a positive blood culture result, abnormal neurologic signs, an elevated WBC or left shift, or the presence of bacteria in the urine.[63] A lumbar puncture is not needed in neonates receiving empiric antibiotics solely because of maternal risk factors.[62] However, it is important to note that a negative blood culture result does not dictate the absence of bacterial meningitis. Approximately 1 of every 4000 live births has culture-proven bacterial meningitis, and 15% to 50% of infants with bacterial meningitis may have a negative blood culture result.[60,62] The cerebrospinal fluid (CSF) should be tested with a Gram stain, cell counts with differential, glucose and protein levels, and bacterial culture. Normal CSF cell counts and protein concentrations are different for neonates compared with older children and adults. For example, the CSF protein concentration in a healthy neonate is about two to three times that of an adult and decreases with age; preterm infants may have higher levels.[58] Neonatal CSF cell counts are also difficult to interpret because values observed with meningitis may overlap with normal neonatal values. The diagnosis of neonatal sepsis is confirmed by isolation of the pathogen from blood, urine, CSF, or other body sites.

Treatment of Sepsis and Meningitis

Case 105-5, Question 2: What antibiotic regimen should be prescribed for J.E.?

Empiric treatment with appropriate IV antibiotics must be initiated immediately in J.E. Significant morbidity or fatality would occur if antibiotics were withheld until a diagnosis was confirmed by culture results (in 24–72 hours). This is especially true in patients in whom meningitis is suspected. The initial empiric antibiotic treatment of choice for early-onset neonatal sepsis and meningitis is ampicillin plus an aminoglycoside (**Tables 105-4** and **105-5**).[2,64,65] These antibiotics are used because they (a) are bactericidal against common neonatal pathogens; (b) penetrate into the CNS; (c) are relatively safe; and (d) have proven clinical efficacy. If the culture result is positive for group B streptococcus, ampicillin should be replaced with high-dose penicillin G because of its higher activity against group B streptococcus. If meningitis is highly suspected, gentamicin may be replaced by a third-generation cephalosporin (ie, cefotaxime or ceftazidime) owing to greater CSF penetration compared with aminoglycosides.

Table 105-4
Gentamicin Dosing Guidelines for Neonates and Infants

Age	Extended-Interval Dosing Regimen[a]
PMA <32 weeks	4–5 mg/kg/dose every 36–48 hours
PMA 32–36 weeks	4–5 mg/kg/dose every 36 hours
PMA ≥37 weeks	4–5 mg/kg/dose every 24 hours

PMA, postmenstrual age.

[a]Some institutions empirically adjust dosing interval based on clinical factors that may affect renal drug clearance (eg, birth depression, hypotension requiring vasopressor support, or congenital heart defects resulting in decreased peripheral perfusion).

Sources: Taketomo CK, Hodding JH, Kraus DM, eds. *Lexicomp Pediatric and Neonatal Dosage Handbook*. 26th ed. Wolters Kluwer; 2019; Ohler KH, Menke JA,

Fuller L. Use of higher dose extended interval aminoglycosides in a neonatal intensive care unit. *Am J Perinatol*. 2000;17:285–290.

Table 105-5
Antimicrobial Dosage Regimens for Neonates: Dosages and Intervals of Administration

	Weight < 1.2 kg	Weight 1.2–2 kg		Weight > 2 kg	
Drug	0–4 weeks PNA (mg/kg)	0–7 days PNA (mg/kg)	8–28 days PNA (mg/kg)	0–7 days PNA (mg/kg)	8–28 days PNA (mg/kg)
Amphotericin B					
Deoxycholate	1 every 24 hours	1 every 24 hours	1 every 24 hours	1 every 24 hours	1 every 24 hours
Lipid complex/liposomal	5 every 24 hours	5 every 24 hours	5 every 24 hours	5 every 24 hours	5 every 24 hours
Ampicillin					
Meningitis	100 every 8 hours	100 every 8 hours	75 every 6 hours	100 every 8 hours	75 every 6 hours
Other diseases	50 every 12 hours	50 every 12 hours	75 every 12 hours	50 every 8 hours	50 every 8 hours
Cefotaxime[a]	50 every 12 hours	50 every 12 hours	50 every 8 hours	50 every 12 hours	50 every 8 hours
Fluconazole	6 every 72 hours	12 every 24 hours	12 every 24 hours	12 every 24 hours	12 every 24 hours
Metronidazole	7.5 every 48 hours	7.5 every 12 hours	7.5 every 12 hours	7.5 every 8 hours	10 every 8 hours
Oxacillin/nafcillin[a]	25 every 12 hours	25 every 12 hours	25 every 8 hours	25 every 8 hours	25 every 6 hours
Penicillin G crystalline					
Meningitis[b]	50,000 units every 12 hours	150,000 units every 8 hours	125,000 units every 6 hours	150,000 units every 8 hours	125,000 units every 6 hours
Other diseases	25,000–50,000 units every 12 hours	25,000–50,000 units every 12 hours	25,000–50,000 units every 8 hours	25,000–50,000 units every 12 hours	25,000–50,000 units every 8 hours
Vancomycin	15 every 24 hours	15 every 12–18 hours	15 every 8–12 hours	15 every 8–12 hours	15 every 6–8 hours

PNA, postnatal age.

[a]Higher dosage may be needed for meningitis.

[b]Doses listed are for treatment of group B streptococcal meningitis.

Sources: Taketomo CK, Hodding JH, Kraus DM, eds. *Lexicomp Pediatric and Neonatal Dosage Handbook*. 26th ed. Wolters Kluwer; 2019; Prober CG, Stevenson DK, Benitz WE. The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J.* 1990;9:111–121; Bradley JS, Nelson JD. *Nelson's Pediatric Antimicrobial Therapy*. 26th ed. American Academy of Pediatrics; 2020.

Therefore, ampicillin 85 mg every 8 hours IV plus an aminoglycoside (eg, gentamicin 4.2 mg every 48 hours IV) should be started in J.E. for suspected neonatal sepsis and possible meningitis. Meningitic doses of ampicillin should be used in J.E. until meningitis can be ruled out. Ampicillin is active against group B streptococci, *Enterococcus*, *Listeria*, and some strains of *E. coli.* Aminoglycoside antibiotics (eg, gentamicin or tobramycin) usually

are active against gram-negative bacilli. In addition, aminoglycosides may provide synergy with ampicillin against *Listeria* and group B streptococci.[59,66] Selection of the specific aminoglycoside should be determined by antibiotic resistance patterns within the NICU. Amikacin should be reserved for gram-negative organisms resistant to gentamicin and tobramycin. Aminoglycoside regimens need to be designed to achieve safe and therapeutic serum concentrations and to aim for a peak concentration that is more than eight times greater than the minimum inhibitory concentration (MIC) of the organism being treated.[67] Peak gentamicin and tobramycin serum concentrations of 10 to 12 μg/mL and trough concentrations of <1 μg/mL may be reasonable, depending on the MIC.

Traditionally, aminoglycosides were administered to neonates in multiple daily doses (eg, gentamicin 2.5 mg/kg/dose two or three times a day). This dosing strategy frequently resulted in peak serum concentrations below and trough concentrations above the respective target ranges, especially in preterm neonates. Evolution of the understanding of developmental pharmacokinetics resulted in knowledge that neonates have a larger volume of distribution for water-soluble drugs and a slower renal elimination of aminoglycosides compared to infants, older children, and adults.[68] Thus, many institutions now use higher milligram per kilogram doses of aminoglycosides (eg, gentamicin 4–5 mg/kg) administered at prolonged dosing intervals (every 24, 36, or 48 hours; commonly determined by GA or PMA).[69,70] A Cochrane review concluded that administering higher milligram per kilogram aminoglycoside doses at prolonged intervals to neonates was as effective as multiple daily doses without evidence of increased toxicity. Serum peak and trough concentrations also were more likely to be in the target range.[71]

This dosing strategy (of giving higher milligram per kilogram per doses at prolonged intervals) in neonates is commonly referred to as *extended-interval aminoglycoside dosing*; however, it should not be confused with the adult dosing method of the same name.[68] Extended-interval aminoglycoside dosing (also known in adults as once-daily dosing or single-daily dosing) has been widely used in the adult population. Aminoglycoside antibiotics display concentration-

dependent killing of bacteria. The rationale for the use of extended-interval aminoglycoside dosing include (a) enhancement of bacterial killing by providing a higher peak serum concentration to MIC ratio, (b) provision of a prolonged postantibiotic effect, and (c) minimization of adaptive postexposure microbial resistance by achieving a drug-free period at the end of the dosing interval.[72] Key differences between this approach to aminoglycoside dosing in adults and the use of higher milligram per kilogram doses given at prolonged intervals to neonates include the following: (a) Peak concentrations of ~20 to 25 μg/mL are targeted in adults compared to 8 to 12 μg/mL in neonates, (b) a drug-free period occurs at the end of the dosing interval in adults, whereas acceptably low, but measurable trough concentrations are commonly observed in neonates, and (c) a standardized dosing nomogram allows for interval adjustments based on a single serum concentration (drawn 8–12 hours postdose) in adults; however, routine peak and trough concentration monitoring is recommended for neonates.[68,72,73]

In some nurseries, a third-generation cephalosporin (eg, cefotaxime or ceftazidime), instead of an aminoglycoside, is added to ampicillin for initial empiric treatment of early-onset neonatal sepsis and meningitis.[60,67] The spectrum of activity of these third-generation cephalosporins includes many gram-negative organisms and group B streptococci. Ceftriaxone should be avoided in neonates with hyperbilirubinemia owing to bilirubin displacement from albumin-binding sites. Ceftriaxone has also been associated with sludging in the gallbladder and cholestasis.[2,67] The resultant increase in serum-free bilirubin concentrations and decrease in bilirubin elimination can place the neonate at risk for kernicterus. In addition, calcium–ceftriaxone precipitates have been found in the lungs and kidneys of neonates when ceftriaxone was administered with calcium-containing solutions. Several fatalities have been reported; ceftriaxone should not be administered within 48 hours of calcium-containing solutions or products.[67] Hence, cefotaxime or ceftazidime is the preferred cephalosporin for neonatal use.

The third-generation cephalosporins have advantages over the aminoglycosides, including better CNS penetration, the elimination of

serum concentration measurements, and less nephrotoxicity. However, these cephalosporins do not significantly improve clinical or microbiologic end points compared with the standard ampicillin and gentamicin regimen. In fact, overuse of cefotaxime during the first few days of life has been associated with an increased risk of death compared with the use of gentamicin.[67] Furthermore, extensive use of the third-generation cephalosporins in NICUs may lead to rapid emergence of resistant gram-negative bacilli (eg, *Enterobacter cloacae*, *Pseudomonas aeruginosa,* and *Serratia* species) and vancomycin resistance in enterococci. Also, prolonged treatment has been associated with an increased risk of neonatal candidiasis.[67] In contrast, only rare cases of gentamicin resistance have been reported.[59,66] Thus, combinations such as ampicillin and cefotaxime or ceftazidime should be reserved for the following situations: (a) NICUs in which aminoglycoside resistance to gram-negative enteric bacilli is of concern, (b) NICUs in which serum concentrations of aminoglycosides cannot be measured, and (c) specific neonates in whom aminoglycoside therapy could be of concern (eg, neonates with known renal failure).

Therapy for late-onset sepsis or meningitis is directed toward nosocomial pathogens plus the primary pathogens of early-onset infection. Selection of initial antibiotic therapy should consider the specific NICU's nosocomial pathogen and antibiotic resistance patterns, as well as the neonate's risk factors, clinical condition, and previous antibiotic therapy. CONS is now the most common pathogen of late-onset neonatal nosocomial septicemia.[74] Because of the high incidence of methicillin-resistant CONS, vancomycin has been used as the drug of choice for empiric therapy for suspected late-onset neonatal sepsis. However, widespread use of vancomycin has led to the emergence of vancomycin-resistant *Enterococcus* and *S. aureus.* Therefore, the routine use of vancomycin as empiric therapy for nosocomial neonatal sepsis should be discouraged. The highly selective use of vancomycin for neonatal CONS septicemia results in low morbidity and mortality, while significantly reducing vancomycin use. Guidelines for the selective use of vancomycin should be tailored according to individual NICU's nosocomial

pathogens, susceptibility patterns, and patient risk factors, clinical condition, and antibiotic history. Therefore, if J.E. had a central venous catheter and presented with a late-onset sepsis, initial antibiotic therapy should include an aminoglycoside (for gram-negative coverage) plus either antistaphylococcal penicillin (eg, nafcillin, methicillin) or vancomycin (for activity against *S. aureus* and *S. epidermidis*). Vancomycin is used in place of the antistaphylococcal penicillin in neonatal units with methicillin-resistant *S. aureus* and for selective use to cover *S. epidermidis* (a CONS) as outlined.[74]

For systemic fungal infections, amphotericin B is considered the initial treatment of choice.[57,75] *Candida* species are the third most common organism causing neonatal sepsis, so prophylactic fluconazole may be used to prevent *Candida* colonization and infection. Infants weighing <1 kg benefited most from prophylactic fluconazole. Despite potential benefits, routine use of prophylactic fluconazole is not recommended and should be reserved for those units with a high incidence of fungal infections.[75] Because uncommon organisms are not suspected in J.E., the regimen of ampicillin 85 mg IV every 8 hours plus gentamicin 4.2 mg IV every 48 hours is appropriate.

Once a pathogen is isolated, the antimicrobial susceptibilities should be evaluated, and the drug therapy modified appropriately. Blood, CSF, or urine cultures should be repeated to document bacterial sterilization after 24 to 48 hours of appropriate therapy. J.E. should be evaluated carefully for the development of serious bacterial complications such as meningitis, osteomyelitis, abscess formation, or endocarditis.

DURATION OF THERAPY

As long as there is no evidence of meningitis or other focal infection (eg, abscess formation), the duration of therapy for most systemic bacterial infections is 7 to 10 days (or ~5–7 days after significant clinical improvement). Antibiotic therapy may need to be continued for 14 to 21 days if the neonate’s clinical response is slow or if

multiple organ systems are involved.[61] If culture results are negative at 48 hours and the infant does not have any clinical or laboratory signs of sepsis, antibiotics can be discontinued. In neonates presenting with signs of severe infection followed by improvement after initiation of antibiotics, therapy may be continued despite negative culture results.[66]

If CSF culture results are positive, repeat CSF cultures should be obtained daily or every other day in J.E. to document when the CSF becomes sterilized. The duration of therapy for neonatal meningitis depends on the clinical response and duration of positive CSF cultures after therapy is initiated. Appropriate antibiotics should be continued for a minimum of 14 days after the CSF is sterilized. This is equivalent to the duration of antibiotic therapy for a minimum of 21 days for gram-negative organisms and at least 14 days for gram-positive pathogens.[57,60] As a general rule, it takes longer to sterilize the CSF of neonates infected by gram-negative enteric bacilli (72 hours) than those infected by gram-positive bacteria (36–48 hours).[60]

CONGENITAL INFECTIONS

Torch Titers

CASE 105-6

Question 1: S.Y., a 2-kg female, was born at 34 weeks' GA by vaginal delivery. S.Y.'s birth was complicated by prolonged rupture of membranes (>72 hours) and fetal distress requiring a fetal scalp monitor. On physical examination, S.Y. is an extremely irritable newborn with an RR of 60 breaths/minute. Several vesicular skin lesions located on the scalp and around the eyes are noted. Conjunctivitis is also present. S.Y. is placed on supplemental oxygen, and ABGs are obtained. Blood, CSF, and urine were cultured for bacteria and fungus, and S.Y. was started on ampicillin 200 mg IV every 8 hours and gentamicin 9 mg IV every 36 hours to rule out sepsis. Antimicrobial therapy will not be altered until culture results are available.

What other tests and information are needed for S.Y. at this time?

Certain bacteria, viruses, and protozoa can cause fetal infections that may result in fetal death, congenital anomalies, serious CNS sequelae, intrauterine growth retardation, or preterm birth.[76] The primary organisms that cause these infections can be remembered by the acronym, TORCH: toxoplasmosis; other (ie, syphilis, gonorrhea, hepatitis B, listeria); rubella; cytomegalovirus; and herpes simplex. Because of the potential severity of these diseases, newborns who display any signs of infection (eg, irritability, fever, thrombocytopenia, hepatosplenomegaly) need to be evaluated for these intrauterine and perinatally acquired infections. A complete infectious disease workup should include specific antibody titer measurements or polymerase chain reaction (PCR) to the suspected organisms.[76]

Primary clinical manifestations and treatment regimen for selected congenital infections are listed in **Table 105-6**.[2,61,76,77] The clinical signs of these infections may overlap, and concurrent infection with two or more microorganisms is possible. The detection of congenital infections often is difficult because many neonates are asymptomatic at birth. Therefore, prenatal maternal screening and accurate evaluation of maternal history for risk factors are very important. Other organisms that can cause congenitally acquired infections include human immunodeficiency virus, human parvovirus, varicella-zoster virus, and measles virus.[76]

Table 105-6
Selected Congenital and Perinatal Infections in the Neonate

Organism	Primary Clinical Manifestations	Treatment of Proven or Highly Probable Disease[a]
Herpes simplex	Cutaneous vesicles, keratoconjunctivitis, microcephaly, CNS infection, hepatitis, pneumonitis, prematurity, respiratory distress, sepsis, convulsion, chorioretinitis	Acyclovir *Ocular involvement:* Add topical therapy: 1%–2% trifluridine, or 0.15% ganciclovir

Organism	Primary Clinical Manifestations	Treatment of Proven or Highly Probable Disease[a]
Toxoplasmosis	Chorioretinitis, ventriculomegaly, microcephaly, hydrocephaly, intracranial calcifications, ascites, hepatosplenomegaly, lymphadenopathy, jaundice, anemia, mental retardation	Sulfadiazine *and* pyrimethamine *and* leucovorin (folinic acid)
Treponema pallidum	*Early:* Osteochondritis, periostitis, hepatosplenomegaly, skin rash (maculopapular or vesiculobullous), rhinitis, meningitis, IUGR, jaundice, hepatitis, anemia, thrombocytopenia, chorioretinitis	Penicillin G
	Late: Hutchinson triad (interstitial keratitis, VIII nerve deafness, Hutchinson teeth), mental retardation, hydrocephalus, saddle nose, mulberry molars	
Hepatitis B	Prematurity; usually asymptomatic; long-term effects include chronic hepatitis, cirrhosis, liver failure, hepatocellular carcinoma	*Perinatal exposure (maternal HbsAg positive):* HBIG and hepatitis B vaccine
Rubella	*Early:* IUGR, retinopathy, hypotonia, hepatosplenomegaly, thrombocytopenic purpura, bone lesions, cardiac effects *Late:* Hearing loss, mental retardation, diabetes *Rare:* Myocarditis, glaucoma, microcephaly, hepatitis, anemia	Supportive care

Organism	Primary Clinical Manifestations	Treatment of Proven or Highly Probable Disease[a]
Cytomegalovirus	Petechiae, hepatosplenomegaly, jaundice, prematurity, IUGR, increased liver enzymes, hyperbilirubinemia, anemia, thrombocytopenia, interstitial pneumonitis, microcephaly, chorioretinitis, intracranial calcifications *Late:* Hearing loss, mental retardation, learning and motor abnormalities, visual disturbances	Valganciclovir Ganciclovir
Neisseria gonorrhoeae	Ophthalmia neonatorum, scalp abscess, sepsis, arthritis, meningitis, endocarditis	Ceftriaxone Use cefotaxime/ceftazidime if hyperbilirubinemic

CNS, central nervous system; HBIG, hepatitis B immune globulin; HbsAg, hepatitis B surface antigen; IUGR, intrauterine growth retardation.

[a]See references 2 and 61 for dosing and recommended treatment duration.

Sources: Taketomo CK, Hodding JH, Kraus DM, et al. *Lexicomp Pediatric and Neonatal Dosage Handbook*. 26th ed. Wolters Kluwer; 2019; Kimberlin DW, Brady MT, Jackson MA, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. American Academy of Pediatrics; 2018; Scaggs Huang FA, Brady RC. Congenital and perinatal infections. In: Kliegman RM, St. Geme J, *eds*. *Nelson Textbook of Pediatrics*. 21st ed. WB Saunders; 2020:1008; Baley JE, Gonzalez BE. Viral infections in the neonate. *In: Martin MJ*, Fanaroff AA, Walsh MC, *eds*. *Fanaroff & Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 11th ed. Elsevier; 2020:844.

When congenital infections are suspected, appropriate diagnostic tests for each suspected organism should be performed. Viral cultures of the urine, oropharynx, nasopharynx, stool, and conjunctiva, and a complete maternal history along with the results of recent maternal vaginal cultures also should be obtained.[76] Measurements of immunoglobulin M levels specific for each possible organism under consideration are also recommended. S.Y. has signs of a congenital infection (respiratory distress, skin rash, and conjunctivitis). Because of the nature of S.Y.'s skin rash (ie,

vesicular), infection with the herpes simplex virus (HSV) should be highly suspected. Skin vesicles, conjunctiva, oropharynx, nasopharynx, rectum, urine, and CSF should be cultured for HSV and other organisms known to cause congenital infections. Rapid diagnostic testing using tissue scrapings from vesicles and fluorescein-conjugated monoclonal HSV antibody can also be performed. Other appropriate tests for the diagnosis and workup of suspected congenital infections should also be performed (eg, liver enzymes, prothrombin time, partial thromboplastin time, electroencephalogram [EEG], computed tomography scan, or magnetic resonance imaging).[76]

APNEA OF PREMATURITY

Apnea in neonates is a life-threatening condition that occurs more frequently in premature newborns and newborns of lower BWs. Nearly all infants born before 29 weeks' gestation will have apnea. The incidence declines with increasing GA from 85% of those born at 30 weeks' gestation to 20% of those born at 34 weeks' gestation.[78] Clinically significant apnea is generally defined as cessation of breathing for at least 20 seconds, or less, if accompanied by bradycardia (HR <100 beats/minute), significant hypoxemia, cyanosis, or pallor.[78]

In neonates, apnea may be caused by a severe underlying illness (eg, infection, metabolic disorders, seizures, intracranial pathology), drugs, or prematurity itself. Appropriate patient history, physical examination, and laboratory tests must be evaluated to rule out other causes of apnea before the diagnosis of apnea of prematurity can be made.[79] It is especially important to rule out sepsis before apnea of prematurity is presumed. If an etiology other than prematurity is identified, therapy would be directed toward that specific cause. For example, antibiotics are used to treat neonatal sepsis with secondary apnea.

Apnea of prematurity is classified into three types: central (ie, no respiratory effort), obstructive, and mixed (ie, both central and obstructive). Mixed apnea accounts for the majority (50%–75%) of apnea of prematurity episodes.[79] Treatment of apnea of prematurity includes the use of supplemental oxygen, gentle tactile stimulation, environmental temperature control, methylxanthines, nasal CPAP, and positive-pressure ventilation.

CASE 105-7

QUESTION 1: S.M., a premature male newborn of 29 weeks' GA, had a BW of 0.99 kg. On day 2 of life, he experienced seven episodes of apnea followed by bradycardia with HR as low as 85 beats/minute. These episodes lasted 20 to 30 seconds and required administration of oxygen and tactile stimulation. Three prolonged episodes required bag-and-mask ventilation. Between apneic spells, the newborn seemed well; physical examination and laboratory test results were normal for GA. Appropriate cultures were drawn for a septic workup, and ampicillin and gentamicin were initiated.

How should S.M.'s apnea be managed?

Methylxanthines are widely accepted as the initial pharmacologic approach for the treatment of idiopathic apnea of prematurity, with caffeine being preferred over theophylline or aminophylline.[78,79] These agents decrease apneic episodes via both central and peripheral effects. Methylxanthines stimulate the medullary respiratory center and increase receptor responsiveness to carbon dioxide. This results in an increase in respiratory drive and minute ventilation. Central stimulatory effects may be mediated by adenosine receptor blockade. Adenosine is a known inhibitor of respiration, and both theophylline and caffeine competitively inhibit adenosine at the receptor level.[78] Peripherally, methylxanthines increase diaphragmatic contractility, decrease diaphragmatic fatigue, and improve respiratory muscle contraction. In addition, methylxanthines increase catecholamine release and metabolic rate.[79] This may improve cardiac output and oxygenation, lessen hypoxic episodes, and decrease apneic spells.

Methylxanthine therapy generally is initiated for apnea of prematurity when apneic episodes are frequent, prolonged for ≥20 seconds, are accompanied by significant bradycardia or cyanosis, or are not controlled by nonpharmacologic means. S.M. has had prolonged apneas with bradycardia that have required supplemental oxygenation. Initiation of a methylxanthine would be appropriate at this point.

CASE 105-7, QUESTION 2: On rounds, the NICU medical team asks you how caffeine compares with theophylline with regard to its pharmacokinetics, efficacy, and toxicity? What treatment and dose should be selected for S.M.? How do you reply to the team?

The plasma clearance of caffeine is considerably lower, and the half-life is extremely prolonged in the premature newborn (72–96 hours).[2] The low clearance is a reflection of the decreased neonatal hepatic metabolism and a resultant dependence of elimination on the slow urinary excretion.[80] As a result, caffeine can be dosed once daily (every 24 hours) in the neonate. The half-life of caffeine decreases with increasing PMA,[81] and plasma clearance reaches adult levels after 3 to 4.5 months of life.[82] As a result of the maturational changes, doses usually need to be adjusted after 38 weeks' PMA; however, most infants no longer require treatment of apnea beyond 34 to 36 weeks' PMA.

Protein binding of theophylline is decreased in term newborns compared with adults.[83] The decreased protein binding along with an increased tissue distribution results in a larger volume of distribution of theophylline in neonates. This larger volume of distribution results in larger loading-dose requirements to attain similar serum concentrations. Similar to caffeine, theophylline clearance in preterm newborns is much slower than that observed in young children ages 1 to 4 years.[83] As a result, smaller theophylline maintenance doses are required in neonates. Theophylline clearance and, therefore, maintenance doses increase with increasing PMA.[84]

In adults, theophylline is eliminated primarily via hepatic metabolism.[85,86] In contrast, the primary route of theophylline

elimination in neonates is renal excretion of unchanged drug (55%).[84] Hepatic metabolism of theophylline (especially *N*-demethylation) is decreased in the neonate. As in adults, theophylline is methylated to caffeine in the neonate. The neonate's decreased demethylation pathway, however, results in a decrease in caffeine elimination and significant serum caffeine accumulation. On average, serum caffeine concentrations can be 40% of the serum theophylline concentration.[84] The theophylline-derived caffeine may contribute to the pharmacologic and toxic effects seen in neonates receiving theophylline.

Comparative studies have found similar efficacy for theophylline and caffeine in the control of apnea of prematurity. Caffeine, however, has several advantages over theophylline, including a wider therapeutic index. Adverse effects such as tachycardia, CNS excitation, and feeding intolerance are reported more frequently with theophylline than with caffeine. Because the half-life is prolonged and dosing requirements do not change quickly with time, caffeine serum concentrations do not need to be routinely monitored. The great majority of preterm neonates achieve caffeine plasma concentrations within the therapeutic range (5–20 μg/mL) if they receive standard doses.[82] Caffeine serum concentrations may be obtained in select neonates (eg, patients with clinical signs of toxicity or with intractable apnea). Loading doses of 20 mg/kg caffeine citrate (10 mg/kg caffeine base), followed 24 hours later by maintenance doses of 5 to 10 mg/kg caffeine citrate (2.5–5 mg/kg caffeine base) given daily, are recommended. Caffeine can be given by syringe infusion pump or orally.[2] Because of the longer half-life, infants receiving caffeine must be monitored for a longer time (eg, for 7–10 days) for adverse effects if toxicities occur and for apnea recurrence once the medication is discontinued. It is important to remember that another IV caffeine product is marketed in the United States as sodium benzoate salt. Benzoic acid has been associated with the gasping syndrome and may also displace bilirubin from albumin-binding sites.[2] Because of these toxicities, the caffeine sodium benzoate product should not be used in neonates.

The short- and long-term safety and efficacy of caffeine to treat apnea of prematurity in VLBW infants were studied in a large, randomized, placebo-controlled trial.[87,88] Caffeine significantly decreased the frequency of BPD.[87] Infants who received caffeine were able to have positive airway pressure discontinued 1 week sooner than did those receiving placebo. Although caffeine reduced weight gain, the effect was only temporary (during the first 3 weeks of therapy). In a follow-up study at 18 to 21 months' corrected age, caffeine significantly improved the rates of survival without neurodevelopmental disability (eg, CP, cognitive delay).[88] These benefits were greater if caffeine was started within 2 days of birth, but were not sustained at 5-year follow-up.[89,90]

The generally accepted therapeutic trough range of theophylline for apnea of prematurity is 6 to 12 μg/mL. This range is lower than that which is normally accepted for the treatment of asthma (5–15 μg/mL) for several reasons: (a) The higher free fraction of theophylline found in neonates results in a higher free concentration at any given total concentration; (b) there is a significant accumulation of the unmeasured active metabolite, caffeine; and (c) a different mechanism of action for theophylline is being exploited for apnea (ie, central stimulation vs bronchodilation for asthma). Aminophylline IV loading doses and maintenance doses of aminophylline and theophylline can be found in appropriate pediatric references.[2] However, a large variation in serum theophylline concentrations has been observed with some dosing regimens.[91] Concomitant drug therapy and disease states (eg, hepatic or renal dysfunction) should also be taken into consideration when selecting initial theophylline doses.

Serum theophylline concentrations should be monitored 72 hours after initiation of therapy or after a change in dosage. Serum concentrations of theophylline should also be measured if the infant experiences an increase in the number of apneic episodes, signs or symptoms of toxicity, or a significant increase in weight. In asymptomatic neonates, once steady-state levels are obtained, theophylline concentrations may be monitored every 2 weeks.

Because of the many advantages of caffeine over theophylline, S.M. should be given 20 mg of caffeine citrate (10 mg caffeine base) as an IV loading dose for 30 minutes. Maintenance doses of 5 mg of caffeine citrate (2.5 mg caffeine base) every 24 hours should be started 24 hours after the loading dose.

CASE 105-7, QUESTION 3: The NICU medical resident asks you to outline a pharmacotherapeutic monitoring plan for S.M. that includes monitoring parameters for efficacy and toxicity and duration of therapy. What would you tell her?

The goal of methylxanthine therapy for S.M. is to decrease the number of episodes of apnea and bradycardia. Continuous monitoring of HR and RR is required for proper evaluation. The time, duration, and severity of episodes, activity of the infant, and any necessary intervention performed should be documented. Relationships between the apneic episodes and the feeding schedule and volume of feeds, as well as the dosing schedule, should be examined. Apnea of prematurity usually resolves by 34 to 36 weeks' PMA; however, it may persist in some infants up to or beyond 40 weeks' PMA.[78] Methylxanthine therapy usually is discontinued at 34 to 36 weeks' PMA provided that the infant has not been having apneic spells. Infants requiring therapy for longer periods may be discharged home on methylxanthines with apnea monitors; however, this occurs very rarely.

Methylxanthine toxicities noted in neonates include tachycardia, agitation, irritability, hyperglycemia, feeding intolerance, gastroesophageal reflux, and emesis or occasional spitting up of food. Tachycardia is the most common toxicity and usually responds to a downward adjustment of the dose. Tachycardia may persist for 1 to 3 days after dosage reductions owing to the decreased elimination of caffeine. Seizures have also been reported with accidental overdoses. Methylxanthine toxicity can be minimized with careful dosing and appropriate monitoring.

NEONATAL SEIZURES

CASE 105-8

QUESTION 1: F.H., a term female newborn (weight 3.5 kg), has a history of birth depression due to placenta abruptia. Apgar scores were 0, 1, 4, and 7 at 1, 5, 10, and 15 minutes, respectively. Maternal history is negative for drug abuse. Twenty-four hours after birth, F.H. begins to have rhythmic clonic twitching of the right hand, repetitive chewing movements, fluttering of the eyelids, and occasional pendulum-like movements of the extremities that resemble swimming motions.

How should F.H.'s seizure activity be evaluated?

Seizure activity may be difficult to recognize in the term or premature neonate. Because of the immaturity of the cortex, neonatal seizures rarely are generalized tonic–clonic events, but can be clonic (focal or multifocal), tonic (focal or generalized), myoclonic (focal, multifocal, or generalized), or subtle in nature.[92]

Subtle seizures include activities such as abnormal oral-buccal-lingual movements; ocular movements; swimming, pedaling, or stepping movements; and, occasionally, apnea. In addition, autonomic nervous system signs such as changes in HR, BP, respirations, skin color, oxygenation, salivation, or pupil size may occur.[92] Clinical neonatal seizures may or may not be associated with EEG changes. In addition, electrographic seizure activity may occur in neonates without clinical manifestations (ie, subclinical seizures).

Neonatal seizure activity is a common manifestation of a life-threatening underlying acute neurologic disorder. The most common underlying etiologies are hypoxic-ischemic encephalopathy (HIE) accounting for 40% to 50% of all neonatal seizures followed by arterial stroke, and intracranial hemorrhage. Other etiologies include intracranial infection, cerebral dysgenesis, metabolic or electrolyte imbalances (eg, alterations in glucose, calcium, magnesium, or sodium), drug-related causes (eg, withdrawal after maternal drug use or adverse effects from drugs administered before, during, or

after delivery), genetic disorders, and neonatal epileptic syndromes.[92] The onset of neonatal seizures is dependent on the etiology. Those with HIE, stroke, and metabolic disturbances will develop seizures within the first 3 days of life, whereas those with intracranial hemorrhage or infection can develop seizures at any time. Definitive treatment is directed toward specific identified etiologies. The acute evaluation of neonatal seizures includes an assessment of the infant's airway, breathing, and circulation and a review of the infant's history, physical examination, and laboratory studies. Every neonate with seizure activity should have a bedside determination of glucose; laboratory determinations of serum electrolytes, including sodium, BUN, glucose, calcium, and magnesium; blood gases; bilirubin; and an infectious disease workup, including complete blood cell count with platelets, CRP level, blood culture, urine culture, lumbar puncture with CSF analysis (cell count, protein, glucose), and CSF culture.[92] Because many seizures have subtle manifestations such as ocular or orolingual movements, the clinical diagnosis of seizures can be difficult. An EEG, preferably continuous EEG, can help determine whether clinical seizures are correlated with electrical seizures, thus necessitating anticonvulsant therapy. Treatment with antiepileptic drugs can be initiated while laboratory test results are pending, and electrolyte imbalances have been corrected.

If these tests do not reveal any abnormalities, a metabolic disease workup (eg, serum ammonia, lactate, and pyruvate; serum and urine amino and organic acids) and screening of blood and urine for drugs can be performed.[92,93] Intrauterine infections associated with congenital neurologic abnormalities and seizures can be identified by obtainment of TORCH titers or PCR for specific viruses (eg, CMV, HSV). Cranial ultrasounds, computed tomography scans, and magnetic resonance images may be obtained to identify infarcts, hemorrhages, calcifications, or cerebral malformations that may cause seizure activity.[92]

Case 105-8, Question 2: F.H. is found to have adequate ventilation and circulation. An IV line is established; blood and CSF cultures and serum

chemistries, including calcium and magnesium, are obtained. A bedside blood glucose (BG) determination reveals a BG of 20 mg/dL. What is your assessment and recommendation at this time?

Hypoglycemia seems to be the cause of F.H.'s seizure activity. HIE secondary to birth depression, however, is the most common cause of neonatal seizures and can be associated with metabolic abnormalities such as hypoglycemia, hypocalcemia, and hyponatremia (owing to inappropriate secretion of antidiuretic hormone).[92] The definition of clinically significant hypoglycemia in neonates remains controversial because normal BG depends on a variety of factors, including GA, BW, feeding status, body stores, and other disease states. The definition of neonatal hypoglycemia varies between organizations. The AAP defines it as a BG < 45 mg/dL during the first 48 hours of life and <60 mg/dL after 48 hours of age compared to <50 mg/dL and 60 mg/dL, respectively, as defined by the Pediatric Endocrine Society.[94] F.H. should receive an IV bolus dose of 7 mL (2 mL/kg) of dextrose 10% (0.2 g/kg) given in 2 to 3 minutes, followed by a continuous infusion of dextrose 10% at an initial dose of 6 to 8 mg/kg/minute (0.5 g/kg/hours).[92] Serum glucose levels should be monitored, and the dextrose infusion should be titrated as needed. If hypoglycemia persists, possible causes such as islet tumor of the pancreas, adrenal insufficiency, and inborn errors of metabolism should be investigated. Corticosteroids, glucagon, diazoxide, and octreotide have been used to treat persistent hypoglycemia.[95]

Treatment of Hypocalcemia and Hypomagnesemia

Case 105-8, Question 3: F.H. receives 7 mL (0.7 g) of 10% dextrose solution IV, and a continuous IV infusion of glucose at 8 mg/kg/minute is initiated. A repeat bedside BG determination reveals a BG of 80 mg/dL, but F.H. continues to have seizure activity. F.H.'s laboratory results come back with the following results:

Sodium, 137 mEq/L
Potassium, 4.3 mEq/L
CO_2, 22 mEq/L
Chloride, 104 mEq/L
BUN, 7 mg/dL
SCr, 0.7 mg/dL
Glucose, 25 mg/dL
Magnesium, 1.0 mEq/L
Calcium, 6.5 mg/dL (1.62 mmol/L)

What should be done next to control F.H.'s seizures?

F.H. also has hypocalcemia and hypomagnesemia, both of which may cause seizure activity. Neonatal hypocalcemia is defined as a serum calcium <7.5 mg/dL (<1.87 mmol/L) in preterm and <8 mg/dL (<2 mmol/L) in term infants or an ionized serum calcium <3 mg/dL (<0.75 mmol/L).[93] Hypomagnesemia (defined as serum magnesium <1.5 mEq/L) is rare but may coexist with hypocalcemia. Hypomagnesemia should be suspected when hypocalcemia cannot be corrected despite large doses of calcium.

F.H. should receive calcium gluconate 700 mg (200 mg/kg) given slowly IV (peripheral concentration diluted to 50 mg/mL, central concentration, 100 mg/mL) and magnesium sulfate 25 to 50 mg/kg/dose (0.2–0.4 mEq/kg/dose) IV as a dilute solution (maximal concentration, 100 mg/mL) administered for 2 to 4 hours.[2,92,93] Doses of calcium gluconate and magnesium sulfate may be repeated based on serum determinations. If IV calcium is administered too quickly, vasodilation, hypotension, bradycardia, cardiac arrhythmias, and cardiac arrest may occur. Calcium gluconate may be administered slowly IV at a maximal rate of 50 mg/minute while monitoring HR, BP, and electrocardiogram.[2] The IV site should be closely monitored for signs of infiltration because extravasation may result in severe dermal necrosis.

Treatment With Antiepileptic Drugs

Case 105-8, Question 4: Despite normalization of her laboratory tests, F.H. continues to have seizure activity. Phenobarbital 35 mg IV push for 1 minute is administered. Ten minutes later, F.H. continues to have intermittent seizure activity. What pharmacotherapeutic plan could control F.H.'s seizure activity?

Phenobarbital remains the first-line antiepileptic drug of choice for neonatal seizures, despite suboptimal efficacy, neurotoxicity, and altered pharmacodynamics effects in neonates.[92,93] Because of the large volume of distribution of phenobarbital in neonates (0.8–1 L/kg), large initial loading doses of 20 mg/kg are required to produce therapeutic serum concentrations.[2,92,96] Because F.H. received only a 10-mg/kg dose (35 mg) of phenobarbital, an additional 10 mg/kg should be given now. Phenobarbital should be administered IV at a rate of ≤1 mg/kg/minute,[2] so a 35-mg dose should be given for at least 10 minutes, not in 1 minute. Rapid administration of phenobarbital may cause respiratory depression, apnea, or hypotension. If F.H. continues to have seizure activity after a total phenobarbital loading dose of 20 mg/kg, additional 5- to 10-mg/kg loading doses may be given every 15 to 20 minutes as needed up to a total cumulative loading dose of 40 mg/kg. Despite it being the drug of choice, cessation of seizures occurs in only 40% of the infants after a loading dose of 20 mg/kg but increases to 70% after a cumulative dose of 40 mg/kg is administered.[92] Ventilatory support may be required when using these higher doses, and serum phenobarbital concentrations should be monitored. Phenobarbital's therapeutic effect of controlling neonatal seizures plateaus at serum concentrations of 40 µg/mL; adverse effects increase at higher serum concentrations.

Currently, there is no consensus regarding a second-line drug, which varies between phenytoin, levetiracetam, benzodiazepines, and lidocaine.[92] If seizure activity is not controlled in F.H. (despite optimal phenobarbital loading doses), phenytoin may be added to phenobarbital at a loading dose of 70 mg (20 mg/kg) should be administered IV at a rate of 0.5 to ≤1 mg/kg/minute.[2,92,93] Rapid IV administration of phenytoin may cause cardiac arrhythmias, bradycardia, or hypotension. Phenytoin may cause severe damage

to tissues if extravasation occurs. Therefore, BP, HR, electrocardiogram, and the IV site of infusion should be monitored. Furthermore, phenytoin should be diluted with normal saline because it is insoluble in aqueous solutions and precipitates in dextrose IV solutions. Fosphenytoin, the diphosphate ester salt of phenytoin, is available in the United States for IV and IM use in adults and is dosed in phenytoin equivalents (PE).[2,92] Fosphenytoin is a water-soluble prodrug of phenytoin that undergoes conversion by plasma and tissue esterases to phenytoin, phosphate, and formaldehyde. Because of its greater water solubility, the IV preparation does not contain propylene glycol, and thus fosphenytoin may have fewer cardiovascular adverse effects associated with IV administration and can be infused at a faster rate (3 mg PE/kg/minute). In addition, it can be safely administered via IM and may cause less dermal necrosis if extravasated. Furthermore, it is compatible with more diluents such as normal saline and dextrose solutions. Unfortunately, appropriate clinical studies of fosphenytoin in neonates have not yet been conducted. Unanswered concerns about the neonatal handling of formaldehyde also exist. Despite the lack of neonatal studies, most clinicians prefer to use fosphenytoin instead of phenytoin because of the aforementioned advantages.

Levetiracetam is a newer antiepileptic drug that has been shown to be efficacious in treating various seizures in children and adults. Experimental studies have reported levetiracetam to be neuroprotective when used in infants with seizures not due to HIE.[92] Recently, the off-label use of levetiracetam as second-line treatment for neonatal seizures, before phenytoin, has been increasing among clinicians mainly due to its favorable safety and pharmacokinetic profiles.[92,97] Levetiracetam has been shown to be efficacious in neonatal seizures in 30% to 100% of patients; however, these were mostly case reports and case series.[92,97,98] The optimal neonatal dose of levetiracetam has not been established. Given that levetiracetam is primarily excreted via the kidney (66% of a dose is excreted as an unchanged drug in the urine) and that the renal function of neonates is decreased compared with that of older infants, one would expect a lower clearance and the use of lower

levetiracetam doses in neonates. However, neonatal pharmacokinetic studies have identified a larger volume of distribution per kilogram (compared to children) and a more rapid clearance than expected based on immature renal function.[98,99] A significant increase in levetiracetam clearance also occurred during the first week of life, reaching the clearance seen in children. These findings indicate that in neonates, larger loading doses and maintenance doses, with an adjustment of maintenance doses after the first 7 days of life, would be required. However, in preterm infants, the elimination half-life may be prolonged because of their immature renal function.[98,99] In clinical practice, an IV loading dose of 30 to 60 mg/kg (up to 80–100 mg/kg) has been used. Serum concentrations of levetiracetam do not correlate with efficacy and, therefore, are not required.[92,98,99]

Phenobarbital has many acute (ie, hypotension, respiratory depression) and long-term (ie, cognitive impairments) adverse effects. Owing to the favorable safety and PK profile of levetiracetam, several studies have been conducted to compare levetiracetam to phenobarbital as the first-line agent for neonatal seizures. Currently, two randomized controlled trials evaluating levetiracetam to phenobarbital as first-line agent for the treatment of neonatal seizures demonstrated conflicting results.[98,100] Levetiracetam 20 to 40 mg/kg was found to be significantly more effective in seizure control compared to phenobarbital 20 to 30 mg/kg in the treatment of neonatal seizures in term and preterm infants (86% vs 62%). However, a recent study reported a lower efficacy rate with levetiracetam of 40 to 60 mg/kg (28%) compared to 20 to 40 mg/kg of phenobarbital (80%).[98] Adverse effects including hypotension and respiratory depression were more common with the phenobarbital group in both studies. The differences between these studies were that in the former study, both term and preterm were included and seizure activity was not assessed using video EEG. These may explain why levetiracetam may be more effective than is phenobarbital. Other differences included the lack of therapeutic hypothermia for infants with HIE, a high proportion of infants with seizures due to sepsis/meningitis, and a lower levetiracetam dose

administered in the former study.[98] Video EEG is often needed to confirm cessation of seizures because most neonatal seizures are symptomatic and self-resolving. Therapeutic hypothermia may have some effect on the seizure control. Furthermore, a higher efficacy rate was noted when the levetiracetam dose was increased from 40 mg/kg to 60 mg/kg in the latter study as well as in previous PK studies. These differences in study design may have impacted the overall efficacy of levetiracetam and phenobarbital for the treatment of neonatal seizures. At this time, it appears that levetiracetam should not be used as first-line therapy for the treatment of neonatal seizures owing to a lack of evidence. Studies comparing long-term neurodevelopmental outcomes of levetiracetam and phenobarbital are needed to evaluate whether a less effective drug in achieving cessation of seizure but better neurodevelopmental outcome through its neuroprotective properties may be preferred.

Lorazepam IV (0.05–0.1 mg/kg) can be used to treat F.H.'s seizures if they are unresponsive to phenobarbital and phenytoin.[2,92,93] Lorazepam is preferred over diazepam owing to its longer duration of effect and fewer pharmaceutical adjuvants. Lorazepam (especially in combination with phenobarbital) may cause respiratory and CNS depression. RR, BP, and HR should be monitored. Doses should be diluted with an equal volume of 5% dextrose in water, normal saline, or sterile water for injection before IV use and administered slowly for 2 to 5 minutes.[2] If seizure activity continues in F.H., continuous IV infusion of midazolam can be administered for the treatment of refractory neonatal seizures.

Continuous lidocaine infusion, carbamazepine, clonazepam, lamotrigine, topiramate, valproic acid, and lacosamide have also been used to treat refractory neonatal seizures in limited number of patients.[97,101] Because of the risk of cardiac arrhythmia associated with lidocaine, its use in the management of refractory neonatal seizures is limited.[101] Owing to the high risk of valproic acid–associated hepatotoxicity for patients younger than age 2 years, this drug is not a preferred agent for use in neonates.[2] IV pyridoxine (50–100 mg) should be considered when seizure activity persists. Pyridoxine is a cofactor required for the synthesis of the inhibitory

neurotransmitter γ-aminobutyric acid (GABA). Patients with pyridoxine dependency require higher amounts of pyridoxine for proper GABA synthesis. Pyridoxine dependency is a rare disorder but should be considered in neonates with seizure activity unresponsive to antiepileptic drug therapy. Lifelong supplementation of pyridoxine is required in these patients.[93]

Case 105-8, Question 5: F.H.'s seizure activity stopped after receiving a total loading dose of 105 mg (30 mg/kg) of phenobarbital and 70 mg (20 mg/kg) of phenytoin/fosphenytoin. A serum phenobarbital concentration of 35 µg/mL and a phenytoin concentration of 17 µg/mL were measured 1 hour after the phenytoin loading dose (2 hours after the last phenobarbital loading dose). How should maintenance doses of antiepileptic drugs be instituted in F.H.?

It is not surprising that F.H. required both phenobarbital and phenytoin/fosphenytoin to control her seizures. Although phenobarbital remains the drug of choice, neonatal seizures are controlled in only 40% of neonates after a loading dose of 20 mg/kg. However, when a cumulative dose of 40 mg/kg is administered, the rate of seizure control increases to 70%.[92] The addition of phenytoin 20 mg/kg to phenobarbital 40 mg/kg controls seizures in 85% of neonates.[92]

F.H. should be placed on maintenance doses of both phenobarbital and fosphenytoin IV because both drugs were needed to control her seizure activity. Because the half-life of phenobarbital is prolonged in neonates (about 100–150 hours), maintenance doses can be instituted 24 hours after the loading dose at 3 to 4 mg/kg/day[2,92,93,97] as a single-daily dose. Maintenance doses of phenytoin (5 mg/kg/day given in divided doses every 12 hours) may be initiated 12 to 24 hours after the loading dose. Serum concentrations of these agents should be monitored periodically because maintenance dose requirements increase with time, usually by weeks 2 to 4 of therapy. This may be related to a normal maturation of hepatic enzyme systems with age or induction of cytochrome P450 enzymes. In neonates, oral phenytoin is poorly absorbed and should be avoided in the acute setting. A routine 25%

increase in the dose is needed when converting IV phenytoin/fosphenytoin to oral to attain similar serum concentrations. In addition, after 2 to 4 weeks of age, dosing intervals of every 8 hours may be needed.

It should be remembered that phenytoin is a highly protein-bound drug. In neonates, protein binding of phenytoin is decreased. This results in an increased free fraction and suggests that total phenytoin therapeutic serum concentrations in newborns should be 8 to 15 μg/mL rather than the 10 to 20 μg/mL as accepted in children and adults.[2] In addition, bilirubin can displace phenytoin from albumin-binding sites. Thus, total phenytoin serum concentrations must be interpreted carefully in neonates, and measurement of unbound phenytoin may be required in neonates with hyperbilirubinemia.

The optimal duration of anticonvulsant treatment of neonatal seizures has not been clearly established; however, several factors need to be considered before discontinuation of therapy. The risk of subsequent epilepsy associated with neonatal seizures varies depending on the etiology, with an overall incidence of 10% to 30%, but can increase to 30% to 50% if the seizure is due to perinatal depression.[92] In addition, the risk of seizure recurrence can be as high as 50% in infants with abnormal neurologic examination. Lastly, infants with marked depression on EEG tracing have a higher risk of developing subsequent epilepsy compared to those with minimal depression.[92] However, anticonvulsants have potential long-term toxicities, especially on the developing brain. Animal studies have reported an increase in apoptosis associated with phenobarbital and phenytoin.[92] In addition, recent studies found no difference in seizure recurrence or neurologic development at 1 to 11 years among infants who were discharged from the NICU with phenobarbital compared to those not taking phenobarbital.[92] Hence, because of the combined lack of benefit from chronic anticonvulsant therapy in preventing subsequent epilepsy and long-term neurodevelopment and the concerns for long-term adverse neurologic outcomes, anticonvulsant therapy should be weaned off as early as possible. Anticonvulsants may be discontinued before discharge if the neonate's neurologic examination and/or EEG are normal. However, for neonates who

require multiple medications, each drug should be weaned off individually.[92] In clinical practice, if anticonvulsants are to be continued, neonates are usually discharged with monotherapy with either phenobarbital or levetiracetam. They should be reassessed periodically after discharge (eg, at 1 and 3 months of age and then every 3 months).

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Donovan MD, Griffin BT, Kharoshankaya L, Cryan JF, Boylan GB. Pharmacotherapy for neonatal seizures: current knowledge and future perspectives. *Drugs.* 2016;76:647–661. (97)

Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr.* 2018;197:300–308. (20)

Kimberlin DW, Brady MT, Jackson MA, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. American Academy of *Pediatrics*; 2018. (61)

Polin R, Carlo W; Committee on Fetus and Newborn; American Academy of Pediatrics. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics.* 2014;133:156–163. (10)

Sivanandan S, Agarwal R. Pharmacological closure of patent ductus arteriosus: selecting the agent and route of administration. *Pediatr Drugs.* 2016;18:123–128. (40)

Taketomo CK, Hodding JH, Kraus DM, eds. *Pediatric and Neonatal Dosage Handbook*. 26th ed. Lexi-Comp; 2019. (2)

Wertheimer FO, Arcinue R, Niklas V. Necrotizing enterocolitis: enhancing awareness for the general practitioner. *Pediatr Rev.* 2019;40(*10*):517. (48)

Key Websites

American Academy of Pediatrics. http://www.aap.org/

American Heart Association, Congenital Heart Defects. http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/Congenital-Heart-Defects_UCM_001090_SubHomePage.jsp

Cochrane Neonatal Group. http://neonatal.cochrane.org/

Neonatology on the Web. http://www.neonatology.org/

NICHD—The Eunice Kennedy Shriver National Institute of Child Health & Human Development. http://www.nichd.nih.gov/cochrane/

COMPLETE REFERENCES CHAPTER 105 NEONATAL THERAPY

1. Gomella TL, Cunningham MD. Gestational age and birthweight classification. In: Gomella T, Eyal FG, Bany-Mohammed F, eds. *Gomella's Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs*. 8th ed. McGraw-Hill; 2020:42.
2. Taketomo CK, Hodding JH, Kraus DM, eds. *Lexicomp Pediatric and Neonatal Dosage Handbook*. 26th ed. Wolters Kluwer; 2019.
3. Lagoski M, Hamvas Am Wambach J. Respiratory distress syndrome in the neonate. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 11th ed. Elsevier Saunders; 2019:1159.
4. Hillman N, Kallapur SG, Jobe AH. Physiology of transition from intrauterine to extrauterine life. *Clin Perinatol*. 2012;39(4):796.
5. Kallapur SG, Jobe AH. Lung development and maturation. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 11th ed. Elsevier Saunders; 2019:1124.
6. Survanta Intratracheal Suspension. Package insert. AbbVie, Inc; 2019.
7. Infasurf Intratracheal Suspension. Package insert. ONY Biotech, Inc; 2018.
8. Curosurf Intratracheal Suspension. Package insert. Chiesi USA, Inc; 2019.
9. Engle WA; American Academy of Pediatrics Committee on Fetus and Newborn. Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. *Pediatrics*. 2008;121(2):419–432.
10. Polin R, Carlo W; Committee on Fetus and Newborn; American Academy of Pediatrics. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics*. 2014;133:156–163.
11. Ramanathan R. Choosing a right surfactant for respiratory distress syndrome treatment. *Neonatology*. 2009;95(1):1–5.

12. Trembath A, Hornik CP, Clark R, et al. Comparative effectiveness of surfactant preparations in premature infants. *J Pediatr*. 2013;163:955–960.
13. Eras Z, Dizdar EA, Kanmaz G, et al. Neurodevelopmental outcomes of very low birth weight preterm infants with poractant alfa versus beractant for respiratory distress syndrome. *Am J Perinatol*. 2014;13:463–468.
14. Brown S, Hurren J, Sartori H. Poractant alfa versus beractant for neonatal respiratory distress syndrome: a retrospective cost analysis. *J Pediatr Pharmacol Ther*. 2018;23(5):367–371.
15. Guardia C, Moya FR, Sinha S, Simmons PD, Segal R, Greenspan JS. A pharmacoeconomic analysis of in-hospital costs resulting from reintubation in preterm infants treated with lucinactant, beractant, or poractant alfa. *J Pediatr Pharmacol Ther*. 2012;17(3):220–227.
16. Sekar K, Fuentes D, Krulas-Hampel MR, Ernst FR. Health economics and outcomes of surfactant treatments for respiratory distress syndrome among preterm infants in US level III/IV neonatal intensive care units. *J Pediatr Pharmacol Ther*. 2019;24(2):117–127.
17. Aldana-Aguirre JC, Pinto M, Featherstone RM, Kumar M. Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2017;102:F17–F23.
18. Ramos-Navarro C, Sanchez-Luna M, Zeballos-Sarrato S, Gonzalez-Pacheco N. Three-year perinatal outcomes of less invasive beractant administration in preterm infants with respiratory distress syndrome. *J Matern Fetal Neonatal Med*. 2020;33(16):2704–2710.
19. Isidro EM, Luna MS, Ramos-Navarro C. Long-term outcomes of preterm infants treated with less invasive surfactant technique (LISA). *J Matern Fetal Neonatal Med*. 2019;104(6):F655.
20. Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr*. 2018;197:300–308.
21. Thebaud B, Goss KN, Laughon M, et al. Bronchopulmonary dysplasia. *Nat Rev Dis Primers*. 2020;5(1):78. doi:10.1038/s41572-019-0127-7
22. Jobe AH, Bancalari E. NICHD/NHLBI/ORD workshop summary. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163:1723–1729.
23. Bancalari E, Jain D. Bronchopulmonary dysplasia in the neonate. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 11th ed. Elsevier Saunders; 2019:1256.
24. Mandell EW, Kratimenos P, Abman SH, Steinhorn RH. Drugs for the prevention and treatment of bronchopulmonary dysplasia. *Clin Perinatol*. 2019;45:291–310.
25. Clouse BJ, Jadcherla SR, Slaughter JL. Systemic review of inhaled bronchodilator and corticosteroid therapies in infants with bronchopulmonary

dysplasia: implications and future directions. *PLoS One*. 2016;11(2):e0148188. doi:10.1371/journal.pone.0148188

26. Doyle LW, Cheong JLY. Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia-who might benefit? *Sem Fetal Neonatal Med*. 2017;22:290–295.
27. Morris IP, Goel N, Chakraborty M. Efficacy and safety of systemic hydrocortisone for the prevention of bronchopulmonary dysplasia in preterm infants: a systematic review and meta-analysis. *Eur J Pediatr*. 2019;178:1171–1184.
28. Watterberg K; American Academy of Pediatrics. Committee on Fetus and Newborn. Policy statement—postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. *Pediatrics*. 2010;126:800–808.
29. Doyle LW, Davis PG, Morley CJ, et al. Low-dose dexamethasone facilitates extubation among chronically-ventilator-dependent infants: a multicenter, international, randomized, controlled trial. *Pediatrics*. 2006;117(1):75–83.
30. Shinwell ES, Portnov I, Meerpohl JJ, Karen T, Bassler D. Inhaled corticosteroids for bronchopulmonary dysplasia: a meta-analysis. *Pediatrics*. 2016;138(6):e20162511.
31. McPherson C. Pharmacotherapy for the prevention of bronchopulmonary dysplasia: can anything compete with caffeine and corticosteroids? *Neonatal Network*. 2019;38(4):242–249.
32. Chu A, de St. Maurice A, Sim MS, Kallapur SG. Neonatal mycoplasma and ureaplasma infections. *Pediatr Ann*. 2020;49(7):e305–e312.
33. Berstein D. The fetal to neonatal circulatory transition. In: Kliegman RM, St. Geme J, eds. *Nelson Textbook of Pediatrics*. 21st ed. Elsevier Inc.; 2020:2344.
34. Clyman RI. Patent ductus arteriosus in the preterm infant. In: Gleason CA, Juul S, eds. *Avery's Diseases of the Newborn*. 10th ed. Elsevier Saunders; 2018:790.
35. Sadowski SL. Congenital cardiac disease in the newborn infant: past, present, and future. *Crit Care Nurs Clin North Am*. 2009;21:37–48.
36. Hoffman TM, Welty SE. Physiology of the preterm and term infant. In: Allen HD, ed. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adults*. 9th ed. Lippincott Williams & Wilkins; 2016:655.
37. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev*. 2020;2:CD003481.
38. Khuwuthyakorn V, Jatuwattana C, Silvilairat S, Tantiprapha W. Oral indomethacin versus oral ibuprofen for treatment of patent ductus arteriosus: a randomised controlled study in very low-birthweight infants. *Paediatr Int Child Health*. 2019;38(3):187–192.

39. Jegatheesan P, Ianus V, Buchh B, et al. Increased indomethacin dosing for persistent patent ductus arteriosus in preterm infants: a multicenter, randomized, controlled trial. *J Pediatr*. 2008;153:183–189.
40. Sivanandan S, Agarwal R. Pharmacological closure of patent ductus arteriosus: selecting the agent and route of administration. *Pediatr Drugs*. 2016;18:123–128.
41. Gal P, Gillman JT. Drug disposition in neonates with patent ductus arteriosus. *Ann Pharmacother*. 1993;27:1383–1388.
42. Benitz WE, Bhombal S. The use of non-steroidal anti-inflammatory drugs for patent ductus arteriosus closure in preterm infants. *Semin Fetal Neonatal Med*. 2017;22:302–307.
43. Jain A, Shah PS. Diagnosis, evaluation, and management of patent ductus arteriosus in preterm neonates. *JAMA Pediatr*. 2015;169(9):863–872.
44. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev*. 2010;7:CD000174.
45. Ohlsson A, Shaw SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev*. 2020;1:CD004213.
46. Meena V, Meena DS, Rathore PS, Chaudhary S, Soni JP. Comparison of the efficacy and safety of indomethacin, ibuprofen, and paracetamol in the closure of patent ductus arteriosus in preterm neonates—a randomized controlled trial. *Ann Pediatr Cardiol*. 2020;13(2):130–135.
47. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants. *Cochrane Database Syst Rev*. 2020;1:CD010061.
48. Wertheimer FO, Arcinue R, Niklas V. Necrotizing enterocolitis: enhancing awareness for the general practitioner. *Pediatr Rev*. 2019;40(10):517–527.
49. Kudin O, Neu J. Neonatal necrotizing enterocolitis. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 11th ed. Elsevier Saunders; 2019:1571.
50. Alganabi M, Lee C, Bindi E, Li B, Pierro A. Recent advances in understanding necrotizing enterocolitis. *F1000Res*. 2019;8:F1000 Faculty Rev-107. doi:10.12688/f1000research.17228.1
51. Rich BS, Dolgin SE. Necrotizing enterocolitis. *Pediatr Rev*. 2017;38(12):552–559.
52. Dorling J, Abbott J, Berrington J, et al. SIFT Investigators Group. Controlled trial of two incremental milk-feeding rates in preterm infants. *N Engl J Med*. 2019;381:1434–1443.
53. Tickell D, Duke T. Evidence behind the WHO guidelines: hospital care for children: for young infants with suspected necrotizing enterocolitis (NEC), what is the effectiveness of different parenteral antibiotic regimens in preventing progression and sequelae? *J Trop Pediatr*. 2010;56:373–378.

54. Autmizguine J, Hornik CP, Benjamin DK Jr, et al. Anaerobic antimicrobial therapy after necrotizing enterocolitis in VLBW infants. *Pediatrics*. 2015;135(1):e117–e125.
55. Blackwood BP, Hunter CJ, Grabowski J. Variability in antibiotic regimens for surgical necrotizing enterocolitis highlights the need for new guidelines. *Surg Infect*. 2017;18(2):215–220.
56. Bi LW, Yang QY, Cui HL. Probiotic strategies to prevent necrotizing enterocolitis in preterm infants: a meta-analysis. *Pediatr Surg Int*. 2019;35(10):1143–1162.
57. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet*. 2017;390:1770–1780.
58. Berardi A, Lugli L, Rossi C, et al. Neonatal bacterial meningitis. *Minerva Pediatr*. 2010;62(3, suppl 1):51–54.
59. Puopolo KM, Benitz WE, Zaoutis TE; AAP Committee on Fetus and Newborn; AAP Committee on Infectious Disease. Management of neonates born at <34 6/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2018;142(6):e20182896.
60. Ferrieri P, Wallen LD. Newborn sepsis and meningitis. In: Gleason CA, Juul S, eds. *Avery's Diseases of the Newborn*. 10th ed. Elsevier Inc.; 2018:553.
61. Kimberlin DW, Brady MT, Jackson MA, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. American Academy of Pediatrics; 2018.
62. Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. *Clin Perinatol*. 2010;37:421–438.
63. Harvey D, Holt DE, Bedford H. Bacterial meningitis in the newborn: a prospective study of mortality and morbidity. *Semin Perinatol*. 1999;23:218–225.
64. Prober CG, Stevenson DK, Benitz WE. The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J*. 1990;9:111–121.
65. Bradley JS, Nelson JD. *Nelson's Pediatric Antimicrobial Therapy*. 26th ed. American Academy of Pediatrics; 2020.
66. Puopolo KM, Benitz WE, Zaoutis TE; AAP Committee on Fetus and Newborn; AAP Committee on Infectious Diseases. Management of neonates born at >35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2018;142(6):e20182894.
67. Chirico G, Barbieri F, Chirico C. Antibiotics for the newborn. *J Matern Fetal Neonatal Med*. 2009;22(suppl 3):46–49.
68. Miller MM, Burton ME, Johnson PN, Miller JL. "Once daily" versus "extended-interval" administration of aminoglycosides in neonates: need for standard terminology. *Am J Health Syst Pharm*. 2014;71:2108–2109.
69. Ohler KH, Menke JA, Fuller L. Use of higher dose extended interval aminoglycosides in a neonatal intensive care unit. *Am J Perinatol*. 2000;17:285–290.

70. Bhatti A, Kumar P. Systemic effects of perinatal asphyxia. *Indian J Pediatr*. 2014;81:231–233.
71. Rao C, Srinivasjois R, Moon K. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. *Cochrane Database Syst Rev*. 2016;12:CD005091.
72. Touw DJ, Westerman EM, Sprij AJ. Therapeutic drug monitoring of aminoglycosides in neonates [published correction appears in *Clin Pharmacokinet*. 2009;48:209]. *Clin Pharmacokinet*. 2009;48:71–88.
73. Nicolau D, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995;39:650–655.
74. Cheung GYC, Otto M. Understanding the significance of Staphylococcus epidermidis bacteremia in babies and children. *Curr Opin Infect Dis*. 2010;23:208–216.
75. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1–e50.
76. Scaggs Huang FA, Brady RC. Congenital and perinatal infections. In: Kliegman RM, St. Geme J, eds. *Nelson Textbook of Pediatrics*. 21st ed. WB Saunders; 2020:1008.
77. Baley JE, Gonzalez BE. Viral infections in the neonate. In: Martin MJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 11th ed. Elsevier; 2020:844.
78. Eichenwald EC; AAP Committee on Fetus and Newborn. Apnea of prematurity. *Pediatrics.* 2016;137(1):e20153757.
79. Ahlfeld SK. Respiratory tract disorders. In: Kliegman RM, St. Geme J, eds. *Nelson Textbook of Pediatrics*. 21st ed. Elsevier Inc.; 2020:929.
80. Aldridge A, Aranda JV, Neims AH. Caffeine metabolism in the newborn. *Clin Pharmacol Ther*. 1979;25:447–453.
81. Le Guennec JC, Billon B, Paré C. Maturational changes of caffeine concentration and disposition in infancy during maintenance therapy for apnea of prematurity: influence of gestational age, hepatic disease, and breast-feeding. *Pediatrics*. 1985;76:834–840.
82. Natarajan G, Botica ML, Thomas R, Aranda JV. Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics*. 2007;119:936–940.
83. Aranda JV, Sitar DS, Parsons WD, Loughnan PM, Neims AH. Pharmacokinetic aspects of theophylline in premature newborns. *N Engl J Med*. 1976;295:413–416.
84. Kraus DM, Fischer JH, Reitz SJ, et al. Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther*. 1993;54:351–359.
85. Tang-Liu DDS, Williams RL, Riegelman S. Nonlinear theophylline elimination. *Clin Pharmacol Ther*. 1982;31:358–369.

86. Tang-Liu DD, Reigelman S. Metabolism of theophylline to caffeine in adults. *Res Commun Chem Pathol Pharmacol*. 1981;34:371–380.
87. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354:2112–2121.
88. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357:1893–1902.
89. Kreutzer K, Bassler D. Caffeine for apnea of prematurity: a neonatal success story. *Neonatology*. 2014;105:332–336.
90. Lodha A, Entz R, Synnes A, et al. Early caffeine administration and neurodevelopmental outcomes in preterm infants. *Pediatrics*. 2019;143(1):e20181348.
91. Kraus DM, Hatzopoulos FK, Reitz SJ, Fischer JH. Pharmacokinetic evaluation of two theophylline dosing methods for infants. *Ther Drug Monit*. 1994;16:270–276.
92. Inder TE. Seizures in neonates. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 11th ed. Elsevier Saunders; 2019:1015.
93. Natarajan N, Gospe M. Neonatal seizures. In: Gleason CA, Juul S, eds. *Avery's Diseases of the Newborn*. 10th ed. Elsevier Saunders; 2017:961.
94. Alsaleem M, Saadeh L. Neonatal hypoglycemia: a review. *Clin Pediatr*. 2019;58(13):1381–1386.
95. Kostopoulou E, Shah P. Hyperinsulinaemic hypoglycaemia: an overview of a complex clinical condition. *Eur J Pediatr*. 2019;178:1151–1160.
96. Pisani F, Spagnoli C. Acute symptomatic neonatal seizures in preterm neonates: etiologies and treatments. *Sem Fetal Neonatal Med*. 2018;23:191–196.
97. Donovan MD, Griffin BT, Kharoshankaya L, Cryan JF, Boylan GB. Pharmacotherapy for neonatal seizures: current knowledge and future perspectives. *Drugs*. 2016;76:647–661.
98. Sharpe C, Reiner GE, Davis SL, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. *Pediatrics*. 2020;145(6):e20193182.
99. Agrawal A, Banergee A. A review on pharmacokinetics of levetiracetam in neonates. *Curr Drug Met.* 2017;18:727–734.
100. Gowda VK, Romana A, Shivanna NH, Benakappa N, Benakappa A. Levetiracetam versus phenobarbitone in neonatal seizures: a randomized controlled trial. *Indian Pediatr*. 2019;56:643–646.
101. Shellhaas RA. Seizure classification, etiology, and management. *Handb Clin Neurol*. 2019;162:347–361.

106

Care of the Critically Ill Child

Elizabeth Anne Farrington

CORE PRINCIPLES		CHAPTER CASES
1	The most frequent cause of cardiac arrest in pediatric patients is a terminal result of respiratory failure or shock, not a primary cardiac event.	**Case 106-1 (Question 1)**
2	Developmental changes and immaturity of the respiratory system make respiratory distress the most common reason for hospital admission in the first year of life. Nasal flaring and grunting are unique features of the respiratory examination in infants that indicate respiratory distress. The normal respiratory rate in children changes over time; therefore, the respiratory rate that would be of concern varies based on the age of the patient.	**Case 106-2 (Question 1, 2)**
		Case 106-2 (Question

3	Oxygen should be administered immediately in a child where respiratory difficulty is suspected. Once the decision is made to intubate the patient, the choices for pharmacotherapy of intubation vary based on the cardiovascular stability of the patient, whether the stomach is empty or full, and the underlying cause of the respiratory distress.	**3, 4)**
4	Hypovolemic shock is the most common type of shock seen in pediatric patients. Septic shock, obstructive shock, and cardiogenic shock occur in children but are less common. The initial treatment of all forms of shock is the same. A pediatric patient can present with compensated or decompensated shock. There are physiologic differences in the pediatric patient's response to hypovolemia, with hypotension being the last physiologic change during decompensation.	**Case 106-3 (Question 1, 2)**
5	Infants have low glycogen stores, so are at high risk for the development of hypoglycemia when they have poor oral intake or during conditions of stress. Because hypoglycemia may cause seizures and is linked to poor neurologic outcome, all critically ill infants should have point-of-care glucose testing on presentation. If identified, hypoglycemia must be treated promptly.	**Case 106-3 (Question 3)**

6	Owing to the immature immune system in the infant, the incidence of septic shock is the highest in the first year of life. Patients with underlying medical conditions have a higher mortality rate than do previously healthy children who experience sepsis.	**Case 106-4 (Question 1)**
7	Owing to physiologic changes during childhood, the definitions of sepsis and systemic inflammatory response syndrome (SIRS) vary with the age of the child. Tachycardia and tachypnea are common presenting symptoms of many pediatric disease processes and are not solely indicative of sepsis. Therefore, temperature variation and leukocyte abnormalities are included in the pediatric definitions. There are also specific definitions based on patient age: newborn, neonate, infant, toddler and preschool-aged child, school-aged child, and adolescent.	**Case 106-4 (Question 2)**
8	Septic shock can be further defined by the patient's response to fluid resuscitation and catecholamine administration. These factors, as well as physiologic differences in neonatal and pediatric cardiovascular physiology compared with adults, affect not only the choice of therapy but also drug dosing and monitoring.	**Case 106-4 (Question 3–6)**
9	Neonates with ductal-dependent congenital heart disease (CHD) may not	**Case 106-5 (Question 1)**

	be diagnosed immediately after birth. These patients may present with symptoms of being in respiratory distress, in cardiogenic or obstructive shock, or in a combination of both. It is essential to consider CHD in any neonate who presents with these symptoms.	
10	Traumatic brain injury (TBI) is the leading cause of mortality in children and leads to significant morbidity among survivors. The anatomic differences in the child's brain render it more susceptible to certain types of injuries after head trauma. Causes vary by age, with nonaccidental trauma seen most commonly in the first year of life. Quick assessment of the patient on presentation to emergency services is needed for appropriate diagnosis, stabilization, and treatment.	**Case 106-6 (Question 1–3)**
11	Placement of a ventriculostomy will allow for measurement of intracranial pressure (ICP) and drainage of cerebral spinal fluid. The ability to measure ICP will assist in the evaluation of the efficacy of treatments. Cerebral perfusion pressure (CPP) also must be monitored closely in patients with TBI. Goal CPP values vary by age. Standard therapies to reduce ICP include CSF drainage, medically induced hypertension, and hyperosmolar therapy	**Case 106-6 (Question 4–6)**

	with mannitol or hypertonic saline. When standard therapies fail, barbiturate coma, therapeutic hypothermia, or decompressive craniectomy may be considered.	
12	Treatment and/or prevention of early posttraumatic seizures has been shown to improve outcomes, but long-term use of anticonvulsant medications (>7 days) has not been shown to improve outcomes and is associated with adverse effects.	**Case 106-7 (Question 1)**

INTRODUCTION

Much of pediatric practice is dedicated to assisting the child in making the transition from the intrauterine environment through infancy, childhood, and adolescence to adulthood. One of the greatest challenges in managing pediatric patients is recognizing the numerous physiologic changes that take place during this time and understanding how they affect assessment and management of the patient. The definition and presentation of many disease states encountered in the critical care setting, including respiratory depression, supraventricular tachycardia, hypotension, and shock, vary based on the age of the patient as a result of these physiologic variations. There are also newborn emergencies that are unique to the physiologic transitions that occur in the first month of life.

Pediatric health care providers practicing in critical care settings such as the emergency department or pediatric intensive care unit (PICU) must be adept at incorporating these physiologic differences into medication selection, dosing, and monitoring to optimize patient care.

The epidemiology of patients admitted to the pediatric emergency department (PICU) differs from that typically seen in adult critical care settings.[1,2] In an evaluation of 361 children presenting to an emergency department, the most common medical reasons for admission were cardiocirculatory causes (32%), neurologic conditions (26%), and respiratory causes (23%).[1] Cardiocirculatory causes included hypovolemic, septic, cardiac, and anaphylactic shock. Neurologic conditions consisted primarily of seizures, status epilepticus, and meningitis or encephalitis. The most common respiratory cause for admission was respiratory syncytial virus (RSV) bronchiolitis, followed by pneumonia, pleural effusions, and croup. Eighteen percent of the patients were admitted after trauma. Diabetic ketoacidosis accounted for 6% of admissions. Other diagnoses included intoxications, near drowning, snake bites, and burns. Assessment of the most common causes for PICU admission has provided similar results. In a review of 1149 children admitted during a 2-year period to the PICU of a university-affiliated children's hospital, the majority (38%) were diagnosed with cardiovascular diseases, followed by respiratory illnesses (28%), other medical causes (10%), neurologic illness (8%), and trauma (8%). Another 7% were admitted for postoperative care.[2] When comparing admissions to the PICU from 1982, 1995, and 2005 to 2006, the most common medical diagnostic categories have remained unchanged. However, fewer children were admitted after accidents, with croup, or with epiglottitis.[2] These changes can be explained by mandatory car seats for children, administration of dexamethasone in the emergency department to patients with croup, and the conjugate *Haemophilus influenza* type b immunization. During the same period, the proportion of patients who died decreased from 11% to 4.8%; however, the proportion of survivors with moderate or severe disability increased significantly from 8.4% to 17.9%.[2] With the low rate of mortality in the PICU, the focus of our research should investigate how to improve patient outcomes.

PEDIATRIC CARDIOPULMONARY RESUSCITATION

In marked contrast to pediatric cardiac arrest, adult cardiac arrest studies have focused on the diagnosis and treatment of ventricular fibrillation (VF) in both inpatient and out-of-hospital cardiac arrest. Studies showed that VF was the most common initial dysrhythmia in adults with sudden death; in some reports, the prevalence of VF was 60% to 85%. Cardiac arrest due to VF or pulseless ventricular tachycardia as the initial cardiac rhythm occurs in only 5% to 15% of pediatric patients in hospital and out-of-hospital cardiac arrest.[3] In contrast to adults, cardiac arrest in infants and children does not usually result from a primary cardiac cause; more often, it is the terminal result of progressive respiratory failure or shock. Therefore, it is essential to recognize and treat pediatric patients admitted with respiratory distress, pneumonia, and shock aggressively to prevent the development of systemic hypoxemia, hypercapnia, and acidosis that may then progress to bradycardia, hypotension, and, eventually, cardiorespiratory arrest.

CASE 106-1

QUESTION 1: Paramedics are transporting C.W., a 5-month-old, 11.02-pound (5-kg) infant with respiratory distress who stops breathing en route to the hospital. The patient is bag-mask ventilated with cardiopulmonary resuscitation in progress. On arrival in the emergency department, the patient is apneic, asystolic, and pulseless. The infant has no intravenous (IV) access. After brief bag-mask ventilation, the patient is intubated with an endotracheal tube (ETT). A colorimetric carbon dioxide capnometer detector device confirms proper ETT placement. Findings now include breath sounds that are equal bilaterally and good chest movement with ventilation, although there is still no pulse palpable without chest compressions and no heart sounds are heard. An electrocardiogram shows asystole. Oxygen saturation is not obtainable.

What medication is needed for C.W. at this point in his resuscitation, and what would the appropriate dose be?

Epinephrine is the drug of choice for the management of pediatric asystole.[3] Ventilation and chest compressions should be continued for C.W., and while one responder is attempting IV access, another may administer the first dose of epinephrine down the ETT using a higher dose of 0.5 mg (0.1 mg/kg prepared from the 1 mg/mL concentration) to account for reduced absorption. If two attempts at IV line placement are unsuccessful, an intraosseous (IO) catheter should be inserted into the proximal tibia. Blood may be obtained through the IO needle to perform a rapid glucose check and sent for further studies. After reassessment of the airway, ventilation and chest compressions should be continued. Subsequent doses of epinephrine can be administered every 3 to 5 minutes through the IO line, using the appropriate IV/IO dose of 0.05 mg (0.01 mg/kg using the 0.1 mg/mL concentration).

RESPIRATORY DISTRESS

Respiratory distress, related to problems at all levels of the respiratory tract from the nose to the lungs, is a frequent occurrence in children.[4] (For a video that shows some of the signs of respiratory distress in an infant, go to http://www.youtube.com/watch?v=42jJ18fkZ0Y.) The nose provides nearly half the total airway resistance in children. Infants younger than 2 months are obligate nasal breathers, and their nose is short, soft, and small with nearly circular nares. The nares will double in size from birth to 6 months, but they can easily be occluded from edema, secretions, or external pressure. Simply clearing the nasal passageways with saline and bulb suctioning can significantly improve an infant's respiratory condition. Other physiologic reasons for a high incidence of respiratory failure in infants and children are small and collapsible airways, an unstable chest wall, inadequate collateral ventilation for alveoli, poor control (tone) of the upper airway (particularly during sleep), tendency for the respiratory muscles to fatigue, reactivity of the pulmonary vascular bed (increased sensitivity of the vasculature,

particularly in young infants), an inefficient immune system, genetic disorders or syndromes, and residual problems related to premature birth such as bronchopulmonary dysplasia.

CASE 106-2

QUESTION 1: T.F. is a 7-month-old, previously healthy 26.45-pound (12-kg) infant who presents to the emergency department with a 3-day history of upper respiratory tract symptoms. His mother states that he is having increasing difficulty breathing and has not wanted to drink or eat. On examination, he has a respiratory rate of 70 breaths/minute, an O_2 saturation of 90% on 100% fraction of inspired oxygen (FIO_2) via nasal cannula, nasal flaring and grunting, and both intercostal and suprasternal retractions. Initial viral screening reveals positive results for RSV, and his chest x-ray is consistent with RSV bronchiolitis. He was agitated and fussy at first presentation, but during the past 30 minutes his respiratory rate has decreased to 40 breaths/minute with a reduction in retractions and he has become somnolent.

What developmental changes in the lung explain why a routine viral infection could result in the need for an emergency department visit in a 7-month-old previously healthy child?

The most common reason for admission to the hospital in the first year of life is respiratory distress. This can be explained by the numerous physiologic differences seen in an infant. Although all the conducting airways are present at birth and the airway branching pattern is complete, the airways are small.[5] The airways will increase in size and length throughout childhood. Not only are the airways smaller in an infant but supporting airway cartilage and elastic tissue are also not developed until school age. For these reasons, the child's airways are susceptible to collapse and may easily become obstructed as a result of laryngospasm, bronchospasm, and edema or mucus accumulation. Normal airway resistance is the highest in infants because it is inversely proportional to 1/radius.[4] Therefore, any airway narrowing from bronchospasm, edema, or mucus accumulation will significantly increase the airway resistance and increase the infant's work of breathing. The cartilaginous ribs of the infant and young child are twice as compliant as the bony ribs of the older child or adult. During episodes of respiratory distress, the

infant's chest wall will retract further than that in a patient with a bony ribcage. This will reduce the patient's ability to maintain functional residual capacity (FRC) or increase tidal volume, thereby further increasing the patient's work of breathing.

The respiratory muscles consist of muscles of the upper airway, the lower airway, and the diaphragm. They contribute to expansion of the lung and maintenance of airway patency. Lack of development of the small airway muscles may render young infants less responsive than are older children to bronchodilator therapy. Lastly, the intercostal muscles are not fully developed until school age, so they act primarily to stabilize the chest wall during the first years of life. Because the intercostal muscles have neither the leverage nor the strength to lift the rib cage in the young child, the diaphragm is responsible for the generation of tidal volume. Therefore, anything that impedes diaphragm movement, such as a large stomach bubble, abdominal distension, or peritonitis, can result in respiratory failure in the young child.

Case 106-2, Question 2: What respiratory signs and symptoms are present in T.F., and how do they define the patient's respiratory status? What are the potential causes of T.F.'s respiratory distress?

To assess a patient for respiratory distress, one should evaluate four areas: respiratory rate and effort, work of breathing, quality and magnitude of breath sounds, and the patient's mental status. Normal respiratory rates vary with age (**Table 106-1**). A respiratory rate >60 breaths/minute is abnormal in a child of any age, but most concerning in an older child. An abnormally slow or decreasing respiratory rate may herald respiratory failure. Intercostal, subcostal, and supracostal retractions increase with increasing respiratory distress. Although increased retractions are seen in infants, they have decreased efficiency of respiratory muscle function during the first years of life; therefore, the benefit in infants is reduced. Decreasing respiratory rate and diminished retractions in a child with a history of distress may signal severe fatigue. Nasal flaring is an

effort to increase airway diameter and is often seen with hypoxemia. T.F. demonstrates all of these physiologic signs of respiratory distress. In addition to these findings, some infants will exhibit an expiratory grunting noise. This noise is produced by the child's involuntary effort to counter the loss of FRC by closing the glottis on active exhalation. Grunting produces positive end-expiratory pressure (PEEP) in an effort to prevent airway collapse. An expiratory grunt is mechanistically similar to "pursed-lip breathing" in adults with chronic dyspnea. An expiratory grunt is classically seen in the presence of extensive alveolar pathology and is considered a sign of serious disease.

Table 106-1
Normal Respiratory Rates and Definition of Tachypnea for Children, by Age

Age	Respiratory Rate (Breaths/Minute)	Tachypnea (Breaths/Minute)
Newborn–2 months	30–60	>60
2–12 months	25–40	>50
1–3 years	20–30	>40
3–6 years	16–22	>40
7–12 years	14–20	>40
>12 years	12–20	>40

There are numerous causes of respiratory distress in infants and children. **Table 106-2** summarizes common respiratory noises in children and their site of origin that may provide clues to the clinical cause. The most common causes of respiratory failure in infants and children are infectious diseases, asthma, malignancies, trauma (both accidental and nonaccidental), poisonings, foreign body aspiration, anatomic upper airway obstruction, cardiogenic shock, and untreated left-to-right intracardiac shunts. RSV is among the most common causes of respiratory distress in infants and young children, leading to an estimated 90,000 hospitalizations each year.[6] Although RSV

can occur at any age, it is most severe in children younger than age 2 years such as T.F. Prematurity, as well as chronic respiratory disease and congenital heart disease (CHD), increases the risk of severe RSV bronchiolitis requiring hospitalization.

Table 106-2
Common Airway Noises, Site of Origin, and Clinical Causes in Children

Respiratory Noise	Definition	Site of Origin	Common Clinical Causes	
			Acute	Persistent
Wheeze	A high-pitched, continuous musical noise, often associated with prolonged expiration (can occur with inspiration or expiration)	Intrathoracic airways	Intermittent asthma/viral-induced wheeze	Persistent asthma
Rattle	This sound is the result of excessive secretions in the large airways, which are presumably moving with normal respirations.	Either or both intrathoracic and extrathoracic airways	Acute viral bronchitis	Chronic sputum retention (neuromuscular disorders)
Stridor	This is predominately an inspiratory noise and indicates obstruction to airflow in the extrathoracic airways (upper airway obstruction); can occur with inspiration or expiration	Extrathoracic airways	Acute laryngotracheobronchitis (or viral croup)	Laryngomalacia
Snore	The noise arises from an increase to airflow through the upper airways, predominately in the region of the nasopharynx and oropharynx; it is more obvious during inspiration but may be audible throughout the respiratory cycle.	Oronasopharyngeal airway	Acute tonsillitis/pharyngitis	Chronically enlarged tonsils and adenoids, obstructive sleep apnea
Snuffle/Snort	These terms describe respiratory noises emanating from the nasal passages; these noises are audible in both inspiration and expiration and are often associated with visible secretions from the nares.	Nasal passage/nasopharynx	Acute viral head cold	Allergic rhinitis
Grunt	This sound occurs with the closure of the glottis during active exhalation.	Alveoli/lung parenchyma	Any alveolar pathology in infants and small children	None

For examples of some of these airway noises, go to the following web links:

- Wheeze: http://www.youtube.com/watch?v=YG0-ukhU1xE&feature=related
- Rattle/rhonchi: http://www.youtube.com/watch?v=QPBZOohj2a0&feature=related
- Stridor: http://www.youtube.com/watch?v=73zUjcCzgqA&NR=1
- Grunt: http://www.youtube.com/watch?v=aptwttJ6y_4

CASE 106-2, QUESTION 3: T.F. is no longer consistently maintaining oxygen saturation values above 90% on nasal cannula O_2. How should T.F. be managed?

Oxygen should be administered immediately in any patient where respiratory difficulty is suspected. Infants and children consume two to three times more oxygen per kilogram of body weight than do adults under normal conditions and even more when they are ill or distressed. T.F. responded well to oxygen administered via nasal cannula in the emergency department but is now increasingly somnolent and has a decreased respiratory rate along with decreased oxygen saturation values—all signs of impending respiratory failure. The specific indications for intubation in infants and children are as follows:

1. Apnea
2. Acute respiratory failure (Pa_{O_2} > 50 mm Hg in a patient with F_{IO_2} >0.5 and Pa_{CO_2} > 55 mm Hg acutely)
3. Need to control oxygen delivery, with institution of PEEP, or to provide accurate delivery of F_{IO_2} >0.5
4. Need to control ventilation to decrease work of breathing, control Pa_{CO_2}, or to administer neuromuscular blocking agents
5. Inadequate chest wall function, as in patients with neuromuscular disorders such as Guillain–Barré syndrome, spinal muscular atrophy, or muscular dystrophy
6. Upper airway obstruction
7. Protection of the airway of a patient whose protective reflexes are absent, such as those with head trauma

Based on the diagnosis of acute respiratory failure and the need to control oxygen delivery, T.F. should be intubated and placed on mechanical ventilation.

MEDICATIONS FOR INTUBATION AND MECHANICAL VENTILATION

CASE 106-2, QUESTION 4: What pharmacologic agents are recommended when intubating a pediatric patient? What plan could you develop for the medications to be used during intubation of T.F.?

After the decision is made to proceed with intubation, the next decision needs to be whether pharmacologic agents are appropriate. Most pediatric patients require sedation before laryngoscopy and intubation. The goal is to depress the infant's or child's level of consciousness sufficiently to produce appropriate conditions for intubation. Pharmacologic therapy is used to produce adequate sedation, analgesia, and amnesia plus a blunting of the physiologic response to airway manipulation. Intubation in the awake state can elicit protective reflexes that trigger tachycardia, bradycardia, and elevation of blood pressure, increased intracranial pressure (ICP), intraocular pressure, cough, and bronchospasm. Pharmacologic control promotes a smoother intubation with less physiologic stress for the patient who often is already in a compromised state. Ideally, this should be accomplished while producing minimal hemodynamic compromise.[7]

There are many factors to be considered when choosing agents for intubation: the onset of action of the agent, the patient's hemodynamic status, the need to prevent increased intraocular pressure or ICP that may be caused with intubation, and whether the stomach is full or empty. A wide variety of medications may be used for pediatric sedation, each with its own risks and benefits (**Table 106-3**).[7] In general, agents that act rapidly and are eliminated quickly are ideal. Often, drug choices are made based on the clinician's experience with a particular drug and the immediate availability of the drug. Most importantly, the drug regimen chosen must be based on the patient's physiologic state. Agents with adverse effects that would exacerbate any underlying medical conditions must be

avoided. Narcotics used in combination with anxiolytics are used commonly. To produce optimal conditions for intubation, T.F. could be given 12 μg of fentanyl (1 μg/kg) and 1.2 mg of midazolam (0.1 mg/kg) IV before the procedure to provide sedation and analgesia. Both agents are relatively short acting and reversible if difficulties arise with ETT placement.

Table 106-3
Pharmacologic Agents Used for Pediatric Intubation and Continuous Sedation

Drug	Route	Dose	Onset	Duration	Benefits	Adverse Effects
Narcotics						
Morphine	IV	0.1 mg/kg/dose (max: initial dose 2 mg) may repeat to a maximum total dose of 15 mg Neonates: 0.05 mg/kg/dose **Continuous infusion** Children: 20–50 μg/kg/hour Neonates: 15 μg/kg/hour Premature neonates: 10 μg/kg/hour	Peak: 20 minutes	2–4 hours in neonates	Reversible (naloxone)	Histamine release, respiratory depression, hypotension, peripheral vasodilatation, euphoria, dysphoria, itching, central nausea and vomiting, decreased response to hypercarbia
Fentanyl	IV	1–3 μg/kg/dose (max: initial dose 100 μg, may repeat to a total dose of 5 μg/kg or 250 μg) **Continuous infusion** 1–3 μg/kg/hour (max: initial dose 50–100 μg/hour) Patient with CHD with an open chest: 5 μg/kg/hour	1–3 minutes	30–90 minutes	Rapid onset, short acting, reversible (naloxone), relatively stable hemodynamic profile	Bradycardia, respiratory depression, decreased response to hypercarbia, acute chest wall rigidity, itching

Benzodiazepines						
Diazepam	IV	0.05 mg/kg/dose (max: 5 mg) may repeat in 0.05-mg/kg increments (max: 1 mg) to a total maximum dose of 10 mg	0.5–2 minutes	3 hours	Reversible (flumazenil)	Respiratory depression, lacks analgesic properties, hypotension and bradycardia, Local irritation, pain
Lorazepam	IV	0.05–0.15 mg/kg/dose (max: 4 mg)	15–30 minutes	0.5–3 hours	Reversible (flumazenil)	Respiratory depression, lacks analgesic properties, hypotension and bradycardia
Midazolam	IV/IM	0.05–0.15 mg/kg/dose (max: initial dose 2 mg, may repeat in 1-mg increments to a total dose of 5 mg) **Continuous infusion** 0.05–0.1 mg/kg/hour (max: initial dose 2 mg/hour)	1–5 minutes	20–30 minutes	Rapid onset, short acting, provides amnesia, reversible (flumazenil)	Respiratory depression, lacks analgesic properties, hypotension, and bradycardia
	Intranasal	0.1–0.3 mg/kg/dose (max: 10 mg) Use the 5-mg/mL concentration	2–5 minutes	30–60 minutes		
	PO	0.5–0.75 mg/kg/dose (max:10–20 mg)	30 minutes	2–6 hours		
Barbiturates						
Pentobarbital	IV	2 mg/kg/dose (max: 100 mg). May repeat in 1-mg/kg/dose increments to a total dose of 7 mg/kg. Do not exceed 200 mg total dose. **Continuous infusion** 0.5–1 mg/kg/hour	1 minute	15 minutes	Decreases intracranial pressure	Cardiovascular and respiratory depression
	IM/PO/PR	2–6 mg/kg/dose	IM: 10–15 minutes PR/PO: 15–60 minutes	1–4 hours		
Miscellaneous						
Ketamine	IV	1 mg/kg/dose every 5 minutes titrated to effect **Continuous infusion** 0.5–1 mg/kg/hour	1–2 minutes	10–30 minutes	Rapid onset, airway protective reflexes stay intact, no hypotension or bradycardia Bronchodilation is useful to intubate asthmatics.	Increases airway secretions and laryngospasm (blunted with atropine). Elevated intracranial and intraocular pressure. Emergence reactions are possible.
	IM	4–5 mg/kg/dose	3–5 minutes	12–25 minutes		
	PO	6–10 mg/kg (mixed in cola or other beverage)	30 minutes	30–60 minutes		
Etomidate	IV	0.3 mg/kg/dose initially, then 0.1 mg/kg/dose every 5 minutes to titrate to effect	10–20 seconds	4–10 minutes	Rapid onset Short acting Stable hemodynamic profile, decreased ICP	Potential for adrenal inhibition, nausea, and vomiting on emergence

Propofol	IV	1–2 mg/kg/dose initially, then 0.5–2 mg/kg/dose every 3–5 minutes to titrate to effect **Continuous infusion** Infants and children: 50–150 μg/kg/minute Adolescents: 10–50 μg/kg/minute	30–60 seconds	5–10 minutes	IV general anesthetic, rapid onset and recovery	Cardiovascular and respiratory depression (propofol-related infusion syndrome), contraindicated in patients with egg allergy, pain on injection
Dexmedetomidine	IV	0.5–1 mg/kg/dose **Continuous infusion** 0.4–0.7 μg/kg/hour Doses as high as 2.5 μg/kg/hour have been used.	30 minutes	4 hours	Minimal to no respiratory depression	Hypotension and bradycardia reposted with loading doses. Use with caution in patients with advanced heart block.
Neuromuscular Blockers						
Succinylcholine	IV	1 mg/kg/dose	30–60 seconds	4–7 minutes	Rapid onset Short duration	Potentiates hyperkalemia. Contraindicated in head trauma (ICP), crush injury, burns, hyperkalemia. May induce neuroleptic malignant syndrome
Vecuronium	IV	0.1 mg/kg/dose **Continuous infusion** 0.1 mg/kg/hour	1–3 minutes	30–40 minutes	Cardiovascular stable	Slower onset Longer duration of action
Rocuronium	IV/IM	0.6–1 mg/kg/dose	60–75 seconds	20–30 minutes	Cardiovascular stable	
Reversal Agents						
Naloxone	IV	For opioid overdose: 0.1 mg/kg/dose (max: 2 mg) For reversal of mild respiratory depression: 0.01–0.02 mg/kg/dose (max: 0.4 mg) may repeat every 2–3 minutes	2 minutes	20–60 minutes	Rapid onset	Shorter duration than most opioids; therefore, repeated doses may be needed.
Flumazenil	IV	0.01 mg/kg/dose (max: 0.2 mg), may repeat 0.005 mg/kg/dose at 1-minute intervals to a maximum total dose of 1 mg	1–3 minutes	6–10 minutes	Rapid onset	Shorter duration than most benzodiazepines; therefore, repeated doses may be needed.

CHD, congenital heart disease; ICP, intracranial pressure; IM, intramuscular; IN, intranasal; IV, intravenous; PO, oral; PR, per rectal.

Patients with inadequate relaxation despite adequate sedation may require neuromuscular blockade, although these agents are not without risk. In a patient with a partial airway obstruction, neuromuscular blockade may worsen pharyngeal collapse, potentially resulting in complete airway obstruction. Therefore, neuromuscular blocking agents should only be used if the clinician is absolutely certain that adequate ventilation can be provided or that the patient can be intubated. If adequate chest rise and oxygen saturation cannot be readily maintained with bag-mask ventilation, neuromuscular blockers should not be used. Infants and children younger than 5 years have a high vagal tone; therefore, they are

more likely to exhibit bradycardia when intubated. Instrumentation of the airway can directly stimulate vagal receptors and induce bradycardia. In these patients, it is prudent to administer atropine 0.02 mg/kg before intubation to blunt the autonomic response. Lidocaine (1–1.5 mg/kg/dose with a maximum dose of 100 mg) may be administered via IV to blunt the airway protective reflexes elicited by instrumentation. This may be particularly useful in a patient with elevated ICP.

In the patient with asthma, drugs that release histamine (eg, morphine, atracurium, or thiopental) and have the potential to produce laryngospasm or bronchospasm should be avoided. The beneficial bronchodilatory side effects of ketamine, however, make it a useful choice in these patients. In a child with increased ICP, the choice of pharmacologic agent depends on the hemodynamic status of the patient. Thiopental or pentobarbital is an excellent choice in the patient who is hemodynamically stable, whereas etomidate is preferred if the patient is unstable or hypovolemia is suspected. Etomidate should not be used routinely in pediatric patients because a single dose administered for intubation has the potential to produce adrenal inhibition.[8] In children and adults with septic shock (SS), etomidate administration is associated with a higher mortality rate.[8–10]

In all cases of intubation, preoxygenation is carried out to increase the available oxygen in the lungs during the procedure, thus giving the practitioner some buffer time to intubate the patient. However, in patients with an elevated ICP or pulmonary vascular hypertension, hyperventilation is recommended to also produce hypocarbia. A summary of specific patient conditions and recommended agents for intubation can be found in **Table 106-4**. In an infant or a child with a full stomach, the risk of aspiration of gastric contents is high. Rapid sequence intubation (RSI) is used when there is an aspiration risk, such as the child with a full stomach, and there is no concern of a difficult intubation.[11] The goal of RSI is to gain airway control with an ETT as quickly as possible to prevent aspiration. The patient is preoxygenated via face mask; bag-mask ventilation cannot be used because it causes gastric distension. Once all necessary intubation

equipment is ready, rapidly acting sedative, analgesic, and paralytic medications are administered simultaneously. An end-tidal CO_2 detector should be attached to the ETT after intubation to confirm proper placement in the trachea. Colorimetric end-tidal CO_2 devices change color from purple to yellow to confirm the presence of exhaled CO_2 and tracheal placement.

Table 106-4
Management Examples of Specific Patient Cases

Condition	Treatment Goal During Intubation	Medications
Full stomach	Prevent passive regurgitation and aspiration after airway protective reflexes lost	Rocuronium, succinylcholine
Bronchospasm	Eliminate or treat stimuli that would induce or increase bronchospasm	Ketamine, vecuronium, lidocaine, atropine
Increased intracranial pressure	No increase in heart rate or blood pressure	Thiopental/pentobarbital, etomidate, vecuronium, rocuronium, lidocaine
Pulmonary vascular hypertension	Avoid decreased pulmonary blood flow	Midazolam, fentanyl, vecuronium
Hypokalemia or depressed cardiac output	Maintain blood pressure without heart rate changes	Etomidate or midazolam with fentanyl

Endotracheal intubation and mechanical ventilation can be painful, frightening, and anxiety provoking, especially in a young child. To improve patient comfort, relieve anxiety, and lessen the work of breathing, anxiolytics, sedatives, and analgesics are frequently administered once the patient is intubated and mechanically ventilated. Maintenance of adequate sedation is essential. Selection of appropriate agents is based on the physiology of the patient. Guidelines for the use of continuous infusions are outlined in Table 106-3. In the patient who is paralyzed, neuromuscular blockade

neither alters consciousness nor provides analgesia; therefore, adequate sedation and analgesia are essential. Providing effective analgesia and sedation to the pediatric patient depends on accurate ongoing efforts to assess the intensity of the patient's pain or anxiety. The assessment of pain and anxiety in infants and critically ill children who are unable to communicate relies heavily on physiologic and behavioral responses. A number of pain and sedation tools have been developed and validated specifically for use in children.[12] No single standard measure gives a complete qualitative or quantitative measure. However, the Society of Critical Care Medicine (SCCM) practice guideline on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill patients with consideration of the intensive care unit (ICU) environment and early mobility (PANDEM [2022 Society of Critical Care medicine Clinical Practice Guidelines on prevention and management of pediatric **P**ain, **A**gitation, **N**euromuscular blockade, and **D**elirium in critically ill pediatric patients with consideration of the PICU environment and **E**arly **M**obility]) make recommendations on the preferred pain, sedation, and delirium screening tools based on the best-published evidence.[13] Selection of an appropriate tool is based on the child's age, underlying medical condition, and cognition level. It is essential that these tools are utilized to evaluate the adequacy of the ICU sedation. Policies and procedures need to be in place for the appropriate selection and use of each tool, in addition to training of all health care professionals to appropriately use each tool. The goal is to use the minimum amount of sedation needed to adequately sedate the intubated child while minimizing adverse effects.

PEDIATRIC SHOCK

CASE 106-3

Question 1: M.M., a 3-month-old, 13.28-pound (6-kg) male infant, presents with a history of decreased oral intake and progressive lethargy. Physical examination revealed an irritable infant with a respiratory rate of 50 breaths/minute, heart rate (HR) of 150 beats/minute, blood pressure of 80/50 mm Hg, and temperature of 102.2 °F (39 °C). He has cool extremities with a capillary refill of 3 seconds. The mother reports that her baby has had no wet diapers for the past 4 hours. A small purpuric rash has appeared on his trunk in the past half hour since the parents left home to bring him to the emergency department. Initial electrolytes obtained in the emergency department on placement of IV access were as follows:

Sodium, 136 mEq/L
Potassium, 4.9 mEq/L
Chloride, 111 mEq/L
CO_2 content, 13 mEq/L
Blood urea nitrogen, 31 mg/dL
Serum creatinine, 0.8 mg/dL
Serum glucose, 50 mg/dL

What type of shock might M.M. be experiencing?

Shock may be classified as hypovolemic, distributive, cardiogenic, or obstructive. Based on his presentation, M.M. is most likely presenting with hypovolemic shock, the most frequent type of shock seen in pediatric patients. Hypovolemic shock occurs when circulating intravascular volume decreases to a point at which adequate tissue perfusion can no longer be maintained. Hypovolemia causes a decrease in preload and adversely affects cardiac output (CO). Initially, hypovolemia activates peripheral and central baroreceptors that cause catecholamine-mediated vasoconstriction and tachycardia. This initial response can maintain adequate circulation and blood pressure even after acute loss of as much as 15% of the circulating blood volume. Shock results from inadequate blood flow and oxygen delivery to meet the metabolic demands of the tissues.[3] Shock will progress from an initial compensated state to a decompensated state. Typical signs of compensated shock include tachycardia, cool and pale distal extremities, prolonged (>2 seconds) capillary refill, weak peripheral pulses compared with central pulses, and normal systolic blood

pressure (SBP). As shock progresses, the patient will exhaust his ability to compensate. The patient will exhibit signs of inadequate end-organ perfusion, including depressed mental status, decreased urine output, metabolic acidosis, tachypnea, weak central pulses, and mottling of extremities. M.M. shows evidence of having progressed to this later stage, with lethargy and decreased urine output.

CASE 106-3, QUESTION 2: How should M.M. be initially managed and monitored?

All patients presenting with shock should be placed on high-flow oxygen while their initial evaluation is being performed. Initial volume resuscitation for hypovolemic shock from vomiting and diarrhea should be isotonic crystalloid fluid (normal saline [0.9% saline]) in 20 mL/kg boluses administered over 5 to 10 minutes. For the management of unknown cause or possible SS, the 2020 SCCM Pediatric Surviving Sepsis Campaign (SSC) recommends to push balanced/buffered crystalloids (lactated Ringer [LR] or Plasma-Lyte®) rather than 0.9% saline. Administration of large volumes of normal saline has been associated with hyperchloremic acidosis, systemic inflammation, acute kidney injury (AKI), coagulopathy, and mortality when compared with resuscitation with more balanced/buffered crystalloids.[14] Immediately reassess the patient for signs of improved perfusion, using clinical criteria such as reduction in HR, improvement of blood pressure, capillary refill, quality of pulses, and mental status. If the clinical signs of shock persist, another 20 mL/kg of isotonic fluid should be administered, reaching, if necessary, at least 60 mL/kg within the first hour of treatment.[3,14] Therapeutic end points of fluid resuscitation in patients with shock are capillary refill <2 seconds, normal pulses with no difference between central and peripheral pulses, warm limbs, urine output >1 mL/kg/hour, normal mental status, decreased lactate as measured on arterial blood gases (ABGs), and increased base deficit. Children normally have a lower blood pressure than do adults and are better able to preserve

adequate blood pressure by vasoconstriction and increasing HR; therefore, blood pressure by itself is not a reliable end point for evaluating the adequacy of resuscitation. Hypotension is the last thing to occur in pediatric shock states. The definition of hypotension, defined as the 5% for SBP for age in the 2015 Pediatric Advanced Life Support (PALS) guidelines,[3] is as follows:

- <60 mm Hg in term neonates (0–28 days)
- <70 mm Hg in infants (1–12 months)
- <70 mm Hg + (2 × age in years) in children ages 1 to 10 years
- <90 mm Hg in children at least age 10 years

Fluid resuscitation should be continued until clinical improvement is clear or there is clinical evidence of hypervolemic state as evidenced by rales, a gallop rhythm, or hepatomegaly. Further discussion of the management of hypovolemia and dehydration in children can be found in Chapter 103, Pediatric Fluid, Electrolytes, and Nutrition. M.M. should receive a bolus 120 mL LR IV infused over 5 minutes, followed by assessment of perfusion status to ascertain improvement. If he has not demonstrated significant improvement, the fluid bolus should be repeated until adequate perfusion is seen and blood pressure is stable at >70 mm Hg.

Case 106-3, Question 3: As noted earlier in the case, M.M. is hypoglycemic with a blood glucose of only 50 mg/dL. What are the concerns associated with hypoglycemia during pediatric shock and how should M.M. be managed?

Hypoglycemia often develops in infants during episodes of stress, including shock, seizures, and sepsis. Infants have high glucose needs and low glycogen stores, which make hypoglycemia a risk in a critically ill infant, especially one with poor enteral intake. Point-of-care glucose testing should be performed in any critically ill infant with a history of poor oral intake. One should not wait to obtain serum chemistries. Aggressive fluid resuscitation recommended for hypovolemia and shock will only exacerbate hypoglycemia. Most importantly, hypoglycemia needs to be prevented during

cardiopulmonary and trauma resuscitation because it may cause seizures and has been linked with poor neurologic outcome.[3,14] Hypoglycemia in pediatric patients must always be promptly identified and treated. After diagnosis, the patient should be managed with a bolus of 0.5 to 1 g/kg of glucose or 5 to 10 mL/kg of a 10% dextrose solution as required to achieve a serum glucose >100 mg/dL. Neonates, especially premature neonates, are more prone to intraventricular hemorrhage with rapid changes in serum osmolarity than are older infants and children; therefore, 0.2 g/kg or 2 mL/kg of 10% dextrose is recommended in this population until the target serum glucose is achieved. M.M. should be given 30 mL (5 mL/kg) of 10% dextrose IV for 1 to 2 minutes, followed by reassessment of his serum glucose. Treatment may be continued until his serum glucose is within the normal range for his age (60–105 mg/dL). After stabilization, maintenance therapy should be initiated with fluids containing 10% dextrose in infants and 5% dextrose in children.

SEPSIS AND SEPTIC SHOCK IN INFANTS AND CHILDREN

SS can be a mixture of hypovolemic, cardiogenic, and distributive shock. In a recent population-based study of children in the United States with severe sepsis (defined as bacterial or fungal infection with at least one acute organ dysfunction), Hartman et al[15] reported an increase in the incidence of severe sepsis from 2000 to 2005 and from 0.56 to 0.89 cases per 1000 children. The increase reported in newborns was from 4.5 to 9.7 cases per 1000. This increase was led by sepsis in very low birthweight neonates. The second increase was reported in children from ages 15 to 19 years, with a reported increase from 0.37 to 0.48 cases per 1000. The mortality rate in this study was 8.9%, unchanged from 2000, but significantly lower than that reported for adult patients with severe sepsis and SS (~30% and

50%, respectively). This dramatic improvement in outcome has been attained through a better understanding of the physiology of shock. The use of aggressive fluid resuscitation and the implementation of time-sensitive, goal-directed therapies as well as the application of technologic advances in respiratory, cardiovascular, renal, and nutritional support, and improved antibacterial, antiviral, and antifungal therapy, has resulted in improved survival in infants and children with SS and the resultant multisystem organ failure.[3,16–21]

Infants and young children are at a higher risk for severe systemic illness after infection than are adults. Despite new developments in vaccine technology, rates of sepsis have not declined. This phenomenon is most likely as a result of cases occurring in infants before complete immunization. Infants are particularly vulnerable to infections for several reasons.[21] Passive immunity is normally conveyed from the mother to the fetus through transmission of immunoglobulins during the last trimester. As a result, premature neonates are immunoglobulin deficient. Even the full-term neonate has decreased polymorphonuclear leukocyte (PMN) function and small PMN storage pools compared with older children and adults, as well as decreased ability to synthesize new antibodies. Lastly, neonates cannot make and deliver adequate amounts of phagocytes to the sites of infection. Low immunoglobulin levels also make the infant susceptible to viral infections. Stores of maternal immunoglobulin are depleted at approximately age 2 to 5 months. Adult levels of immunoglobulin are not typically achieved until ages 4 to 7 years. As a result of these physiologic differences, as well as differences in bacterial resistance patterns, the list of most likely pathogens in children with sepsis differs from those of adults. **Table 106-5** lists common pediatric pathogens and appropriate empiric antibiotic coverage. In children with SS, antibiotics should be administered within 1 hour of diagnosis, after the collection of appropriate cultures.[14] In children with sepsis associated with organ dysfunction but without shock, antibiotics should be administered within 3 hours.[14]

Table 106-5

Causative Pathogens and Recommended Treatments for Pediatric Sepsis

Age or Risk Factor	Microorganism	Empiric Antibiotic Coverage
Age > 30 days	*Listeria monocytogenes* *Escherichia coli* Group B *Streptococcus* Gram-negative enteric organisms	Ampicillin + aminoglycoside or ampicillin + cefotaxime acyclovir (if patient presents with seizures, until HSV is ruled out)
Age > 1 month	*Haemophilus influenzae* *S. pneumoniae* *Neisseria meningitidis*	TGC ± vancomycin[a]
Immunocompromised child	*Pseudomonas aeruginosa* *Staphylococcus aureus* *S. epidermidis*	Ceftazidime or cefepime or piperacillin/tazobactam + vancomycin[a]
Child with a ventriculoperitoneal shunt	*S. aureus* *S. epidermidis* Gram-negative enteric organisms	TGC ± vancomycin[a]

HSV, herpes simplex virus; TGC, third-generation cephalosporin (ie, cefotaxime, ceftriaxone).

[a]Dosed to maintain trough vancomycin serum concentrations of 15 to 20 µg/mL.

As in adults, baseline health status also affects the likelihood of a child exhibiting severe sepsis. Watson et al found that 49% of cases of sepsis occurred in children who had underlying illnesses that may place them at risk for higher morbidity and mortality.[15] At the Children's Hospital of Pittsburgh, the mortality rate for children who were previously healthy was 2% compared with 12% in children with chronic illnesses.[22]

CASE 106-4

QUESTION 1: J.B., a 6-year-old, 44.09-pound (20-kg) female, presented to the pediatric emergency department in acute distress. She was stabilized with oxygen via nasal cannula and fluid resuscitation before being transferred to the PICU for further management. On presentation to the PICU, she is lethargic and unable to follow commands, with warm, dry, slightly mottled skin and sluggish capillary return. She is febrile to 103.1 °F (39.5 °C) and has a respiratory rate of 21 breaths/minute, an HR of 154 beats/minute, and a blood pressure of 76/55 mm Hg. Initial laboratory values are notable for a white blood cell count of 21 × 10^3 µL. Her parents report that she has not urinated since the previous evening.

Does J.B. meet the criteria for SS?

In an effort to develop a consensus definition of the pediatric sepsis continuum including systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, SS, and multisystem organ dysfunction syndrome, a group of international experts in the fields of adult and pediatric sepsis and clinical research gathered in 2002. A panel was chosen consisting of published pediatric critical care physicians and scientists with clinical research experience in pediatric sepsis.[17] Because the clinical variables used to define SIRS and organ dysfunction are greatly affected by the normal physiologic changes that occur as children age, the group first defined six clinical and physiologic age categories for defining SIRS criteria (**Table 106-6**). Premature infants were not included because their care occurs primarily in neonatal intensive care units and not in PICUs. Before discussing treatment, it is important that the practitioner should understand the terms used to define sepsis. In 1992, SIRS was proposed by the American College of Chest Physicians and the SCCM to describe the nonspecific inflammatory process occurring in adults after trauma, infection, burns, pancreatitis, and other diseases.[23,24] Sepsis was defined as SIRS associated with infection. The SIRS criteria were developed for use in adults; it was not until 2005 that a consensus definition was published for SIRS in children (**Table 106-7**).[25] A separate pediatric definition for SIRS was essential. Tachycardia and tachypnea, pivotal to the adult definition of SIRS, are common presenting symptoms of many pediatric disease processes. To better distinguish SIRS from

other diseases, the pediatric definition also includes temperature and leukocyte abnormalities as criteria. Numeric values for each criterion were also established to account for the different physiology in children. **Table 106-8** gives the age-specific cutoffs for each criterion. In 2021, the adult SCCM SSC removed the terminology SIRS and severe sepsis. Currently, an international pediatric expert panel is reviewing pediatric sepsis definitions. New terminology may be available as early as 2023.

Table 106-6
Pediatric Age Group Definitions for Severe Sepsis

Age Category	Definition
Newborn	0 day–1 week
Neonate	1 week–1 month
Infant	1 month–1 year
Toddler and preschool	2–5 years
School-age child	6–12 years
Adolescent and young adult	13–>18 years

Source: Reprinted with permission from Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):3. © 2005 The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Table 106-7
Definitions of Systemic Inflammatory Response Syndrome, Infection, Sepsis, Severe Sepsis, and Septic Shock in Children

SIRS	The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count: ▪ Core temperature of >101 °F (38 °C) or >96.8 °F (36 °C; must be measured by rectal, bladder, oral, or central catheter probe) ▪ Tachycardia defined as at least 2 standard deviations above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise persistent elevation for a 0.5- to 4-hour period *or* for children >1 year old: bradycardia, defined as a mean heart rate

	>10% percentile for age in the absence external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained depression in a half-hour period ▪ Mean respiratory rate >2 standard deviations above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or receipt of general anesthesia ▪ Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced neutropenia) or >10% immature neutrophils
Infection	A suspected or proven (by positive culture result, tissue stain, or polymerase chain reaction test) infection caused by any pathogen *or* a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (eg, white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)
Sepsis	SIRS in the presence of or as a result of suspected or proven infection
Severe sepsis	Sepsis plus one of the following: cardiovascular organ dysfunction *or* acute respiratory distress syndrome *or* dysfunction of two or more other organs, as defined in Table 106-9
Septic shock	Severe sepsis with cardiovascular dysfunction, as defined in Table 106-9

SIRS, systemic inflammatory response syndrome.

Source: Adapted with permission from Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):4. © 2005 The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Table 106-8
Age-Specific Vital Signs and Laboratory Variables

Age Group	Heart Rate[a] (beats/minute)		Respiratory Rate (breaths/minute)	Leukocyte Count[a] (per $10^3/\mu L$)	Systolic Blood Pressure[a] (mm Hg)
	Tachycardia	Bradycardia			
0 day–1 week	>180	>100	>50	>34	>65
1 week–1 month	>180	>100	>40	>19.5 or >5	>75
1 month–1 year	>180	>90	>34	>17.5 or >5	>100
2–5 years	>140	n/a	>22	>15.5 or >6	>94
6–12 years	>130	n/a	>18	>13.5 or >4.5	>105
13–>18 years	>110	n/a	>14	>11 or >4.5	>117

n/a, not applicable.

[a]Lower limits of the normal range for heart rate, leukocyte count, and systolic blood pressure for the 5th percentile and upper limits for the 95th percentile.

Source: Reprinted with permission from Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):4. © 2005 The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Temperature is one of the main criteria of the pediatric SIRS definition. A core temperature >101.3 °F (38.5 °C) or <96.8 °F (36 °C) may indicate serious infection. Hypothermia is more likely to occur in infants. A core temperature is the one measured by either rectal, bladder, oral, or central catheter probe. Temperatures taken via the tympanic, toe, or another auxiliary route are not sufficiently accurate. Temperature may also be documented by a reliable source at home within 4 hours of presentation to the hospital or physician's office. If environmental overheating, such as that produced by overbundling, is suspected, the child should be returned to a neutral temperature environment, unbundled, and the temperature retaken in 15 to 30 minutes.

Meeting the SIRS criteria in children requires the presence of an abnormal temperature, either hypothermia or hyperthermia, or an abnormal leukocyte count in the presence of tachypnea and tachycardia. Sepsis is defined as the proven or suspected infection in the setting of SIRS. Severe sepsis is defined as sepsis in the setting of acute respiratory distress syndrome, cardiovascular organ dysfunction, or two or more acute organ dysfunctions (respiratory, renal, hematologic, neurologic, or hepatic). The definitions of organ dysfunction have also been modified for children (**Table 106-9**). Carcillo et al[17] defined pediatric SS as the presence of tachycardia and poor perfusion, including decreased peripheral pulses compared with central pulses; altered alertness; capillary refill >2 seconds; mottled or cool extremities; or decreased urine output. This definition of pediatric SS does not include hypotension as required in adults because children will often maintain their blood pressure until they

are severely ill. Shock may occur long before hypotension occurs. J.B. exhibits the majority of the criteria for pediatric SS, including lethargy, fever, tachycardia, decreased perfusion, and decreased urination.

Table 106-9
Organ Dysfunction Criteria

Cardiovascular Dysfunction

Despite administration of isotonic intravenous fluid bolus 40 mL/kg in 1 hour

- Decrease in BP (hypotension) >5th percentile for age or systolic BP >2 standard deviations below normal for age[a] *or*
- Need for vasoactive drug to maintain BP in normal range (dopamine > 5 µg/kg/minute or dobutamine, epinephrine, or norepinephrine at any dose) *or*
- Two of the following:
  Unexplained metabolic acidosis: base deficit >5 mEq/L
  Increased arterial lactate more than two times the upper limit of normal
  Oliguria: urine output >0.5 mL/kg/hour
  Prolonged capillary refill: >5 seconds
  Core to peripheral temperature gap 37.4 °F (>3 °C)

Respiratory[b]

- Pa_{O_2}/F_{IO_2} >300 in the absence of cyanotic heart disease or preexisting lung disease *or*
- Pa_{CO_2} >65 torr or 20 mm Hg over baseline Pa_{CO_2} *or*
- Proven need[c] or >50% F_{IO_2} to maintain saturations >92% *or*
- Need for nonelective invasive or noninvasive mechanical ventilation[d]

Neurologic

- Glasgow Coma Scale score (see Table 106-12) >11 *or*
- Acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline

Hematologic

- Platelet count >80,000/µL or a decline of 50% in platelet count from highest value recorded in the past 3 days (for patients with chronic hematology/oncology) *or*
- International normalized ratio of >2

Renal

- Serum creatinine more than two times the upper limit of normal for age or twofold increase in baseline creatinine

Hepatic

- Total bilirubin ≥4 mg/dL (not applicable for newborn) *or*
- ALT two times the upper limit of normal for age

ALT, alanine transaminase; BP, blood pressure.

[a]See Table 106-8.

[b]Acute respiratory distress syndrome must include a Pa_{O_2}/F_{IO_2} ratio >200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically, except the Pa_{O_2}/F_{IO_2} ratio must be >300 mm Hg.

[c]Proven need assumes oxygen requirement was tested by decreasing flow if required.

[d]In postoperative patients, this requirement can be met if the patient has exhibited an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

Source: Adapted with permission from Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):4. © 2005 The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

CASE 106-4, QUESTION 2: What physiologic differences may need to be taken into account when developing a management strategy for J.B.?

There are developmental differences in the hemodynamic response to sepsis in newborns, children, and adults. Practitioners in the PICU may encounter all age ranges and thus must be familiar with the clinical differences seen between age groups because it may affect therapy. Adults and children have different adaptive responses that must be considered when selecting therapeutic management. Adolescent patients pose a unique challenge because they may present with either type of symptom. Among adult patients, the most common hemodynamic alterations include diminished systemic vascular resistance (SVR) and elevated CO. SVR is diminished because of decreased vascular responsiveness to catecholamines, alterations in α-adrenergic receptor signal transduction, and the elaboration of inducible nitric oxide synthase.

In general, adults with SS have myocardial dysfunction with a decreased ejection fraction; however, CO is preserved or increased through two compensatory mechanisms: tachycardia and reduced SVR.

Unlike SS in adults, pediatric SS is associated with severe hypovolemia, and children frequently respond well to aggressive fluid resuscitation. Pediatric patients demonstrate diverse hemodynamic profiles during fluid-refractory SS: 58% have low cardiac indexes (CIs) responsive to inotropic medications with or without vasodilators, 20% exhibit high CI and low SVR responsive to vasopressor therapy, and 22% present both vascular and cardiac dysfunctions necessitating the use of vasopressors and inotropic support.[26] Pediatric patients such as J.B. are different from adults with SS in that low CO, not low SVR, is associated with increased mortality. In fact, studies suggest that the majority of children showed some degree of cardiac dysfunction on presentation after fluid resuscitation.[14,19] Many require a change in their inotropic and vasopressor management, or the addition of another agent during the first hours of treatment, emphasizing that the hemodynamic status in children can change rapidly.[14,17–19]

SS in the neonatal patient differs from that seen in older children. The relative ability of infants and children to augment CO through increased HR, as seen in adults, is limited by their preexisting elevated HR, which precludes proportionate increases in HR without compromising diastolic filling time. In adults, ventricular dilation is a compensatory response used to maintain CO. However, the increased connective tissue content of the infant's heart and diminished content of actin and myosin limits the potential for acute ventricular dilation. Neonatal SS can be further complicated by the physiologic transition from fetal to neonatal circulation. Sepsis-induced acidosis and hypoxia can increase pulmonary vascular resistance and thus arterial pressure, thereby maintaining the patency of the ductus arteriosus (DA). This results in persistent pulmonary hypertension (PPHN) of the newborn and persistent fetal circulation. Neonatal SS with PPHN will increase the workload on the right ventricle, leading to right-ventricular failure, tricuspid

regurgitation, and hepatomegaly. Therefore, therapies directed at reversing right-ventricular failure by reducing pulmonary artery pressures are commonly needed in neonates with fluid-refractory SS and PPHN.

Based on her mottled dry skin, sluggish capillary refill, and decreased urination, it is evident that J.B. has inadequate perfusion. She should receive aggressive fluid resuscitation, beginning with a fluid bolus of 400 mL (20 mL/kg) balanced/buffered crystalloids IV administered over 5 minutes. She should be reassessed immediately after the bolus to evaluate perfusion status, as described previously. The 400-mL fluid bolus should be repeated until adequate perfusion has been established.

INITIAL MANAGEMENT OF PEDIATRIC SEPTIC SHOCK

Because the landmark study by Rivers in 2001 demonstrated a 33% reduction in mortality in adult patients with sepsis when they were aggressively treated with fluid resuscitation, blood transfusion, and inotropic therapy within 6 hours of admission, goal-directed therapy has been advocated for all patients who present in SS.[16] The components of early goal-directed therapy include respiratory support along with prompt resuscitation of poor perfusion through administration of IV fluids and appropriately targeted inotropic and vasopressor therapy, early empiric antimicrobial therapy, drainage of the infection whenever possible, and continuous monitoring of the patient's hemodynamic status.[14,16–20]

Case 106-4, Question 3: J.B. has received one bolus of LR in the pediatric emergency department but is still showing evidence of being hypoperfused. Her hemoglobin on admission to the PICU is 10 g/dL. Should she continue to receive traditional IV fluid replacement with LR or should other agents be considered to maximize perfusion and oxygenation?

There are no data to suggest a significant difference in survival rates in pediatric patients after resuscitation with colloids, including blood products, compared with crystalloid fluids.[27] The choice of fluid is less important than is the volume administered. Adequate volume is necessary to sustain cardiac preload, increase stroke volume, and improve oxygen delivery. Both crystalloids and colloids, specifically packed red blood cells (PRBCs), have equal effects on improving stroke volume. In addition, both restore tissue perfusion to the same degree if they are titrated to the same level of filling pressure.

Administration of blood products also differs among institutions. The optimal hemoglobin for infants and children in SS has not been established. The 2021 Adult SSC recommends using a restrictive transfusion strategy: maintaining hemoglobin of 7 g/dL to improve oxygen-carrying capacity.[28] However, administration of PRBC should not be guided by hemoglobin concentration alone. Assessment of the patients' overall clinical status with consideration of extenuating circumstances such as severe hypoxemia or acute hemorrhage is required. Anemia in sepsis has been associated with increased mortality, but so has the administration of blood products.[29] The 2020 SCCM Pediatric SSC guidelines recommend against transfusion of PRBC if the hemoglobin concentration is >7 g/dL in hemodynamically stabilized children with SS or other sepsis-associated organ dysfunction. Judgment should be used in those patients who are hemodynamically unstable.[15] At this time, there is no indication for administration of blood products to J.B. Fresh-frozen plasma may be infused to correct abnormal prothrombin time (PT) and partial thromboplastin time (PTT) values but should not be rapidly infused because of the risk of acute hypotensive effects caused by vasoactive kinins and high citrate concentration. There is no literature to suggest that 5% albumin administration improves outcome in regard to sepsis mortality. Albumin administration may be considered in patients who are hypoalbuminemic, but routine use of albumin is not recommended.[14,30]

As described previously for the management of hypovolemic shock, patients with SS should be reassessed for signs of improved perfusion using clinical criteria such as reduction in HR,

improvement of blood pressure, capillary refill, quality of pulses, and mental status with each fluid bolus. If the clinical signs of shock persist, another 20 mL/kg of balanced/buffered fluid should be administered, reaching, if necessary, 60 mL/kg within the first hour of treatment.[3,14,18] Some children with SS require as much as 200 mL/kg in the first hour.[17] Patients remaining in shock despite fluid resuscitation are given inotropic support to attain normal blood pressure for age and capillary refill time of <2 seconds. Every hour that goes by without implementing these therapies is associated with a 1.5-fold increased risk of mortality. Patients who do not respond rapidly to initial fluid boluses or those with insufficient physiologic reserve should be considered for invasive hemodynamic monitoring. Invasive monitoring of central venous pressure (CVP) is instituted to ensure that the satisfactory right-ventricular preload is present, typically using a goal of 10 to 12 mm Hg, and that oxygen-carrying capacity is optimized by PRBC transfusion to correct anemia to a goal hemoglobin concentration >7 g/dL.[14,18]

Up to 40% of a child's CO may be required to support the work of breathing during SS; therefore, in the presence of respiratory distress, elective intubation and mechanical ventilation can be used to allow redistribution of blood flow from respiratory muscles toward other vital organs. Intubation is not without adverse effects; it is imperative that patients receive adequate fluid resuscitation before intubation because the change from spontaneous breathing to positive-pressure ventilation will decrease the effective preload to the heart, further decreasing CO. Ventilation may reduce left-ventricular afterload that may be beneficial in patients with low CI and high SVR. In addition, it may provide an alternative method to alter acid–base balance. If sedatives and analgesics are used for intubation, choice of agents that do not cause further vasodilation is critical.

Although laboratory studies rarely affect the management of SS in the first hour of therapy, patients should have laboratory studies sent routinely assessing for hematologic abnormalities, metabolic derangements, or electrolyte abnormalities that may contribute to morbidity. A peripheral white blood count may aid in the choice of broad-spectrum antibiotics, and hemoglobin and platelet count will

help in assessing the need for early blood transfusion. A type and screen should be sent to the blood bank to prepare for any necessary transfusions. Electrolyte abnormalities are common in sepsis; recognition and treatment of metabolic abnormalities such as hypoglycemia and hypocalcemia will improve outcome. A disseminated intravascular coagulation panel, including PT, PTT, and fibrinogen, will aid in assessing the severity of the illness. If abnormalities exist, they may need to be corrected before performing invasive procedures. Lastly, an ABG or a venous blood gas will determine the adequacy of ventilation, oxygenation, and severity of acidemia.[18]

Unfortunately, clinical response to fluid resuscitation is a relatively insensitive indicator of the completeness of restoration of microvascular blood flow. Success of adequate fluid resuscitation can be guided by additional parameters: invasive blood pressure monitoring, CVP, measurement of mixed venous oxygen saturation (SvO_2), measurement of blood lactate, and urine output. An elevated serum lactate level suggests that tissue is inadequately perfused and undergoing anaerobic metabolism, even in patients who are not hypotensive. Because low CO is associated with increased O_2 extraction, SvO_2 can be used as an indirect indicator of whether CO is adequate to meet tissue metabolic demand. If tissue oxygen delivery is adequate, then SvO_2 should be >70%.[18] In the goal-directed study by Rivers, maintenance of SvO_2 was >70% by use of blood transfusion to a hemoglobin of 10 g/dL, and inotropic support to increase CO resulted in a 40% reduction in mortality compared with patients where only mean arterial pressure (MAP) and CVP were monitored.[16] de Oliveira et al[19] reproduced this finding in children with SS, reducing mortality from 39% to 12% when directing therapy to a goal SvO_2 saturation >70%.

CARDIOVASCULAR DRUG THERAPY

Pharmacologic support in children with SS must be individualized because different hemodynamic abnormalities exist in pediatric patients, and the primary hemodynamic abnormalities may change with time and progression of the patient's disease (**Table 106-10**). Twenty percent of children present with predominant vasodilatory shock, referred to as *warm* shock. This form of shock is associated with vasodilation and capillary leak, but normal or elevated CO. The patients have strong pulses, warm extremities, good capillary refill, and tachycardia. In warm shock, using a vasopressor such as dopamine, norepinephrine, phenylephrine, or vasopressin to promote vasoconstriction would provide the most benefit. Fifty-eight percent of children present with "cold shock" or a poor CO state. These patients have vasoconstriction, increased cardiac afterload, and a high SVR. This is clinically manifested as weak pulses, cool extremities, slow capillary refill, and hepatic and pulmonary congestion. Using an inotrope with or without a vasodilator would be most beneficial in cold shock (eg, dobutamine, epinephrine, or milrinone). Careful assessment of clinical response is critical because a combination of warm and cold shock, with a low SVR and poor CO, occurs in ~22% of children. SCCM previously recommended clinical assessment of children in SS to differentiate "warm" versus "cold" shock based on extremity temperature, capillary refill, pulse strength, and diastolic blood pressure and directing initial vasopressor choice on this diagnosis. However, several observational studies demonstrated very poor correlation of clinical assessment with CI and SVR when measured by advanced monitoring.[31–33] The newest SCCM Pediatric SSC guideline recommends a standard initial management of patients until more reliable assessment of the patient status is available.[14]

Table 106-10
Summary of Selected Vasoactive Agents

Agent	Dose Range	Peripheral Vascular Effects			Cardiac Effects
Vasopressors					
		α	β_1	β_2	
Dobutamine	2–20 μg/kg/minute	1+	3–4+	1–2+	Less chronotropy and arrhythmias at lower doses; chronotropic advantage compared with dopamine may not be apparent in neonates.
Dopamine	2–4 μg/kg/minute	0	0	0	Splanchnic and renal vasodilator, increasing doses create increasing α-effect.
	4–8 μg/kg/minute	0	1–2+	1+	
	>10 μg/kg/minute	2–4+	1–2+	2+	
Epinephrine	0.03–0.1 μg/kg/minute	2+	2–3+	2+	β_2 effects with lower doses
	0.2–0.5 μg/kg/minute	4+	2+	3+	
Norepinephrine	0.05–0.5 μg/kg/minute	4+	2+	0	Increases systemic resistance, moderate inotropy
Phenylephrine	0.05–0.5 μg/kg/minute	4+	0	0	Increases systemic resistance, moderate inotropy
Vasodilators					
Nitroprusside	0.5–8 μg/kg/minute	Donates nitric oxide to relax smooth muscles and dilate pulmonary and systemic vessels		Indirectly increases cardiac output by decreasing afterload	Reflex tachycardia
Nitroglycerine	0.5–10 μg/kg/minute	As a nitric oxide donor, may cause pulmonary vasodilation and enhance coronary vasoreactivity after aortic cross-clamping		Decreases preload; may decrease afterload, reduces myocardial work in relation to change in wall stress	Minimal
Miscellaneous Agents					
Milrinone	50 μg/kg load; then 0.25–1 μg/kg/minute	Systemic and pulmonary vasodilator		Diastolic relaxation (lusitropy)	Minimal tachycardia
Vasopressin	0.003–0.002 units/kg/minute *or* 18–120 mU/kg/hour	Potent vasoconstrictor		No direct effect	None known

CASE 106-4, QUESTION 4: Despite adequate fluid resuscitation, intubation, and mechanical ventilation, J.B.'s condition has continued to decline. During the past 30 minutes, her SBP has ranged between 72 and 79 mm Hg (normal for age, >84 mm Hg). What would be an appropriate next step for the management of J.B.'s shock?

Vasopressors are required in shock unresponsive to initial fluid resuscitation.[3,14,18] Previously, the PALS guideline recommended dopamine as the initial agent of choice.[18] However, the 2020 PALS update no longer recommends dopamine but agrees with the 2020 SCCM pediatric SSC guideline that recommends a catecholamine as the initial vasopressor of choice and only recommends dopamine if epinephrine or norepinephrine is unavailable.[34] Dopamine has direct and indirect effects on dopamine receptors, α-adrenergic receptors, and β-adrenergic receptors on both the heart and peripheral

vasculature. One of the mechanisms of dopamine action is enhancement of endogenous catecholamine release. In severe septic states, presynaptic vacuoles may be depleted of norepinephrine, which may explain why dopamine may have diminished activity. In addition, infants younger than age 6 months may not have developed their component of sympathetic innervations; therefore, they have reduced releasable stores of epinephrine.

Some studies have raised the concern of increased mortality with the use of dopamine. One possible explanation is the ability of dopamine to reduce the release of hormones from the anterior pituitary gland, such as prolactin, through stimulation of the dopamine D_2 receptor, thus reducing cell-mediated immunity and inhibition of thyrotropin-releasing hormone release, worsening impaired thyroid function known to occur in critical illness. Although, historically, dopamine was the drug of choice for initiating inotropic therapy in pediatric SS, the 2020 SCCM SSC guideline recommends epinephrine or norepinephrine as the initial vasopressor or choice.[14]

Epinephrine

Epinephrine is a direct agent that is naturally produced in the adrenal gland and is the principal stress hormone with widespread metabolic and hemodynamic effects. It possesses both inotropic and chronotropic effects. Epinephrine is a reasonable choice for the treatment of patients with low CO and poor peripheral perfusion because it increases HR and myocardial contractility. Depending on the dose administered, epinephrine may exert variable effects on SVR. At doses <0.3 μg/kg/minute, epinephrine exerts greater β_2-adrenergic receptor activation, resulting in vasodilation in skeletal muscle and cutaneous vascular beds, shunting blood flow away from the splanchnic circulation.[18] At higher doses, α_1-adrenergic receptor activation becomes more prominent and may increase SVR and HR. For patients with markedly elevated SVR, epinephrine (0.05–0.3 μg/kg/minute) may be administered simultaneously with a

vasodilator. Epinephrine increases glucogenesis and glycogenolysis, resulting in elevated serum blood glucose concentrations. Children receiving epinephrine infusions should have serum glucose monitored closely.

Norepinephrine

Norepinephrine is a direct agent and is naturally produced in the adrenal gland. It is a potent vasopressor that redirects blood flow away from skeletal muscle to the splanchnic circulation even in the presence of decreased CO. Norepinephrine has been used extensively to elevate SVR in adults and children with sepsis. If the patient's clinical state is characterized by low SVR (a wide pulse pressure with diastolic blood pressure less than one-half of the SBP), norepinephrine (0.05–0.3 µg/kg/minute) is recommended. Approximately 20% of children with volume-refractory SS have a low SVR. In children who are intubated and receiving sedatives or analgesics, the incidence of low SVR may be higher. The additional afterload imposed by norepinephrine may substantially compromise CO in patients with impaired contractility. In patients with both impaired or marginal CO and decreased SVR, it may be necessary to support myocardial contractility through the addition of an agent such as dobutamine.[14,18]

No studies directly compare epinephrine with norepinephrine. However, epinephrine has been compared to dopamine in two randomized controlled trials in children with fluid-refractory SS. In both clinical trials, epinephrine was associated with a lower risk of mortality and more organ failure–free days.[35,36]

J.B. should be started on epinephrine at a rate of 0.1 µg/kg/minute, with further titration of the dose in increments of 0.05 µg/kg/minute every 3 to 5 minutes until the goal of improved perfusion and/or a normal blood pressure for age is achieved.[3] There is no recommended maximum dose of epinephrine; however, the typical dose range is 0.05 to 0.3 µg/kg/minute. Ideally, vasopressors should be administered through central venous access rather than

through a peripheral IV; however, lack of central access should not prevent initiation of vasopressor therapy. Extravasation of these drugs from an infiltration of the IV may produce significant local tissue necrosis. Central access should be obtained as soon as possible.

Case 106-4, Question 5: J.B.'s epinephrine infusion has been steadily increased throughout the day. Her dose is currently at 0.3 µg/kg/minute, but she continues to have refractory hypotension with an SBP of 70 mm Hg. On physical examination, she is pale with cool, dry skin. Her hemoglobin remains at 10 g/dL. CVPs are now being measured and range from 6 to 9 mm Hg. What alternative to epinephrine should be considered for J.B.?

Catecholamine-resistant shock is diagnosed after titration of epinephrine or norepinephrine to 0.3 µg/kg/minute with the persistence of signs and symptoms of shock. Patients with catecholamine-resistant shock should be reassessed to evaluate fluid status and hemoglobin, with additional fluids or PRBCs given as needed to improve tissue oxygen. Measurement of CVP can be performed to assess intravascular volume status with the goal of achieving a CVP of 8 to 12 mm Hg, and SvO_2 can be used as a marker of CO (provided that the hemoglobin is within the normal range), along with the clinical examination. The SCCM pediatric SSC guideline recommends the addition of vasopressin or further titrating catecholamines in children with SS who require high-dose catecholamines.[14]

Vasopressin

Although not a recommendation in the 2020 PALS guidelines, vasopressin has been suggested as an alternative therapy for refractory cardiac arrest or hypotension due to a low SVR in children whose epinephrine infusion exceeds 1 µg/kg/minute.[3] Thus, the SCCM 2020 SSC recommendations to add vasopressin or to further titrate catecholamines with catecholamine-resistant shock. Vasopressin exerts its hemodynamic effects via the V_{1a} receptor,

promoting an increase in intracellular calcium in the peripheral vasculature, thus enhancing vasoconstriction and restoring systemic vascular tone. In a preliminary case series, vasopressin at a dose of 0.3 to 2 mU/kg/minute (18–120 mU/kg/hour) improved blood pressure and urine output in patients with catecholamine-refractory vasodilatory shock and allowed weaning of catecholamines once treatment was initiated.[37] In a more recent analysis conducted by the American Heart Association, however, vasopressin use was associated with a lower rate of return to spontaneous circulation.[38] More clinical studies with vasopressin in pediatric SS would allow for optimization of its use.[3,14,18]

Dobutamine

Dobutamine is a nonselective β_2-adrenergic agonist, which produces improved contractility, chronotropy, and some degree of lusitropy or improved myocardial relaxation. The β_2 activity can lead to peripheral vasodilation, and this must be considered before its use in a patient who may already be hypotensive. If hypotension does exist, it should be used in combination with other vasopressor therapies. Dobutamine should be considered in a patient who has signs and symptoms or laboratory values consistent with poor tissue perfusion but has an adequate blood pressure to tolerate some degree of vasodilation. It should be initiated at a rate of 2.5 µg/kg/minute and titrated in increments of 2.5 µg/kg/minute every 3 to 5 minutes to a maximum infusion rate of 20 µg/kg/minute.[3,18] Careful attention to the patient's blood pressure is critical. Improved perfusion, decreased lactate, and an increased SvO_2 will help determine appropriate dosing.

Vasodilators

Vasodilator medications are occasionally required in the treatment of pediatric patients who have sepsis with markedly elevated SVR and normal or decreased CO. Vasodilators decrease SVR and improve

CO by decreasing ventricular afterload. Nitroglycerin or nitroprusside may be used for this indication. They each have a short half-life; therefore, if hypotension occurs, it can be rapidly reversed by stopping the infusion. Both drugs can be infused at an initial rate of 0.5 μg/kg/minute and titrated in increments of 0.5 μg/kg/minute to a maximum infusion rate of 5 to 10 μg/kg/minute.[3] If nitroprusside is used, it is necessary to observe for sodium thiocyanate accumulation in the setting of renal failure, and cyanide toxicity with hepatic failure or with prolonged infusions (>72 hours) of >3 μg/kg/minute. If a patient has tolerated short-term infusions of either of these agents, milrinone may be considered as an alternative for long-term therapy. Milrinone is a phosphodiesterase type III (PDE III) inhibitor that produces its hemodynamic effects by inhibiting the degradation of cyclic adenosine monophosphate (AMP) in smooth muscle cells and cardiac myocytes. PDE III inhibitors work synergistically with catecholamines, which produce their hemodynamic effects by increasing the production of cyclic AMP. Milrinone, at a dose of 0.25 to 0.75 μg/kg/minute, is useful in the treatment of infants and children with diminished CO, impaired myocardial contractility, and decreased SVR.[13,39] The primary concern with milrinone is its relatively long half-life of 2 to 6 hours, which requires several hours for the patient to reach steady state. To achieve target serum concentrations more rapidly, a loading dose of 50 μg/kg may be administered for 10 to 30 minutes before the start of the infusion. Administration of a loading dose must be done with caution in children with sepsis and shock because it may precipitate hypotension, requiring volume infusion and/or vasopressor infusion. Administering the loading dose over several hours may avoid this adverse effect.

J.B. remains hypotensive despite adequate fluid administration and an epinephrine infusion at 0.3 μg/kg/min. After reassessing her laboratory parameters to determine whether additional fluid or blood products are needed, J.B. should be started on vasopressin at 18 mU/kg/hour. The dose may then be titrated upward in 10 to 20 mU /kg/hour increments every 3 to 5 minutes as needed to achieve the desired clinical response or to the usual maximum of 120 mU

μg/kg/hr. It would be acceptable to continue to increase the epinephrine infusion and consider vasopressin at a higher epinephrine infusion rate.

CORTICOSTEROID ADMINISTRATION IN PEDIATRIC SEPTIC SHOCK

CASE 106-4, QUESTION 6: J.B. is currently receiving epinephrine at an infusion rate of 0.35 μg/kg/minute, but she continues to have refractory hypotension with an SBP of 70 mm Hg. Is there a role for hydrocortisone replacement in J.B.? What would be the appropriate method for assessing adrenal insufficiency and the appropriate dose for replacement?

Although adjunctive corticosteroid therapy in patients in SS has not made a significant difference in outcome in all studies published to date, replacement may be of benefit in some patients.[40–42] In a recent study, 77% of children with SS admitted to two PICUs for a 6-month period exhibited adrenal insufficiency.[42] Owing to the limited evidence of their efficacy and safety in children, corticosteroids should be reserved for those with catecholamine-resistant shock, severe SS and purpura, children who have previously received steroid therapies for chronic illness, children with pituitary or adrenal abnormalities, and those who previously received etomidate.[5–7,13,40–42] The SCCM Pediatric SSC guideline no longer recommends assessment of serum cortisol to guide treatment.

Because excessive fluid resuscitation can lead to fluid overload, which has been associated with increased mortality in critically ill children,[43] medication therapies that can minimize their use should be considered. At least one pediatric trial examining adjunct corticosteroids for SS has concluded that their use may hasten the resolution of shock.[44] J.B. has catecholamine-resistant hypotension and has received a total of 80 mL/kg of fluid resuscitation; a trial of hydrocortisone is warranted. Published guidelines for hemodynamic support of pediatric and neonatal patients in SS recommend 0.5 to 1

mg/kg IV every 6 hours (with a maximum dose of 50 mg).[17] Using this regimen, J.B. should be treated with 10 to 20 mg IV every 6 hours. As an alternative, some clinicians use a regimen of a single 50-mg/m^2 loading dose, followed by the same dose (50 mg/m^2) divided into four doses and given every 6 hours.[14]

ADJUNCTIVE THERAPIES

Stress-Related Mucosal Bleeding

The use of prophylaxis to prevent stress-related mucosal bleeding, although common in adult patients in the ICU, is not as widely used in PICUs. Studies conducted to date have provided a wide range of gastrointestinal tract bleeding rates in children, ranging from 10% to 50%, with rates of clinically significant bleeding of ~1% to 4%.[45,46] Several investigators have identified thrombocytopenia, coagulopathy, organ failure, and mechanical ventilation as important risk factors for gastrointestinal bleeding, similar to studies conducted in adults. A recent systematic review suggested that critically ill pediatric patients may benefit from prophylaxis; however, the results were limited by the small number of controlled studies available.[46]

Thrombosis Prophylaxis

Patients admitted to the PICU can range from newborns to young adults. Unlike adults, there are no data on the use of subcutaneous heparin or low-molecular-weight heparins as prophylaxis to prevent deep vein thrombosis (DVT) in children. However, when children reach puberty, the hormone changes that take place appear to increase their risk of thrombosis to that of adults. Although no published guidelines or consensus papers exist to guide therapy at this time, all pubescent adolescents should be considered for DVT prophylaxis. Most cases of thrombosis in infants and young children are associated with long-term use of central venous catheters.

Unfortunately, a study evaluating low-dose heparin infused at 10 units/kg/hour did not prevent catheter-related thrombosis in infants after cardiac surgery.[47] It is important to note that the dose of heparin used in this study was less than the anticoagulant dose recommended for infants and children (15–25 units/kg/hour). At this time, the routine use of DVT prophylaxis in children remains controversial.

CONGENITAL HEART DISEASE

CASE 106-5

QUESTION 1: J.F. is a 3-week-old, 7.72-pound (3.5-kg) male who was seen by his physician with a history of poor feeding and increased work of breathing. On admission, he was mottled, and grunting, and had severe retractions. The physician referred him to the emergency department of the local children's hospital where his temperature was 105.44 °F (40.8 °C), HR was 200 beats/minute, respiratory rate was 80 breaths/minute, and oximetry saturation was between 60% and 70%; he had very poor peripheral perfusion. Blood gas analysis results were as follows:

pH, 6.96
P_{CO_2}, 35 mm Hg
Base deficit, 29 mmol/L

Chest radiography showed cardiomegaly and pulmonary edema. J.F. has presented with symptoms of both respiratory failure and shock. Based on his age, the severity of his hypoxemia, and evidence of cardiomegaly, CHD is suspected. Echocardiography reveals coarctation of the aorta.

What initial therapies are needed to stabilize J.F.?

With the neonate's first breath, changes in oxygen tension and a reduction in endogenous prostaglandin E_2 production stimulate closure of the DA, the connection between the pulmonary artery and aorta that allows shunting of blood to the aorta during fetal circulation. Functional closure of the DA typically occurs within the first 10 to 14 hours of life, but complete anatomic closure may not occur until age 2 to 3 weeks. Prematurity, acidosis, and hypoxia

prolong the time to closure. In infants with ductal-dependent CHD, closure of the DA results in inadequate delivery of oxygenated blood to the systemic circulation (**Table 106-11**). These infants will present just as any other patient in shock. The immediate goal in evaluating a cyanotic neonate is to differentiate between cardiac and noncardiac causes. The classic hyperoxia test is carried out by obtaining an ABG, then placing the patient on 100% oxygen for 10 minutes, and repeating the ABG. If the cause of cyanosis is pulmonary, the Pa_{O_2} should increase by 30 mm Hg, but if the cause is cardiac, there should be minimal improvement in the Pa_{O_2}. If the patient is too unstable, one could place a pulse oximeter and place the patient on 100% F_{IO_2}. With administration of oxygenation, there will typically be at least a 10% increase in oxygen saturation in neonates with pulmonary disease, but those with ductal-dependent CHD will have minimal or no improvement.

Table 106-11

Ductal-Dependent Congenital Heart Lesions

Lesions That Depend on Flow via the Ductus Arteriosus to Maintain Systemic Circulation
Hypoplastic left heart syndrome (HLHS)
Coarctation of the aorta
Critical aortic stenosis
Interrupted aortic arch
Total anomalous pulmonary venous return (TAPVR) with obstruction
Lesions That Depend on Flow via the Ductus Arteriosus to Maintain Pulmonary Circulation
Pulmonary atresia with intact ventricular septum
Critical pulmonic stenosis
Tricuspid atresia
Tetralogy of Fallot (TOF)
Epstein anomaly

Lesions That Depend on Flow via the Ductus Arteriosus to Maintain Systemic Circulation
Lesions That Depend on Flow via the Ductus Arteriosus to Maintain Adequate Mixing of the Pulmonary and Systemic Circulations
Truncus arteriosus
Transposition of the great vessels (TGV)
Total anomalous pulmonary venous return (TAPVR) without obstruction

If the neonate's oxygen saturation or Pa_{O_2} fails to improve and CHD is suspected, an infusion of alprostadil, prostaglandin E_1 (PGE_1), should be initiated at a rate of 0.05 to 0.1 µg/kg/minute.[48] Infusion of PGE_1 maintains patency of the DA and allows blood to reach the descending aorta, bypassing the cardiac defect. Apnea is a common adverse effect of PGE_1, occurring in 10% to 20% of patients, so age-appropriate equipment for intubation and mechanical ventilation should be immediately available before starting treatment and throughout therapy.[49] Within 10 to 15 minutes of starting an alprostadil infusion, there should be an improvement in the patient's oxygen saturation. The dose may then be titrated to optimize ductal flow and minimize dose-related adverse effects. The infusion is typically continued until corrective cardiac surgery can be performed. J.F. should receive fluid boluses as needed to correct his dehydration and will require intubation. In addition, he should be started on PGE_1 at a rate of 0.05 µg/kg/minute, with subsequent titration of the dose to open and maintain the DA until the time of surgery.

PEDIATRIC TRAUMATIC BRAIN INJURY

Among children, traumatic brain injury (TBI) is the leading cause of mortality and leads to significant morbidity among survivors. Each year, >280,000 children in the United States suffer a TBI requiring an emergency department visit, resulting in 16,070 hospitalizations in

2019 and 3000 deaths.[50] The most common mechanisms of injury differ by patient age. Children younger than 4 years old most often suffer injuries due to child abuse, falls, and motor vehicle collisions (MVCs). Child abuse, or nonaccidental trauma (NAT), sadly represents up to two-thirds of severe TBI in some series. Although it is difficult to obtain accurate data, in a population-based study from North Carolina, the incidence of TBI due to NAT in the first 2 years of life was 17 per 100,000 person-years.[51] According to the National Center on Shaken Baby Syndrome, this translates to ~1300 children per year in the United States who experience severe head trauma from child abuse. In school-aged children, those ages 5 to 12 years, pedestrian–MVC and bicycle-related injuries are among the more common causes of severe injuries. For adolescents, MVCs replace falls as the leading cause of all injuries, followed by assault and sports-related injuries.

CASE 106-6

Question 1: K.B. is an 8-week-old, 8.82-pound (4-kg) male who was brought to an urgent care clinic by his 17-year-old mother. She stated that he would not wake up for his usual 7:00 PM feeding that evening. He had been in his usual state of health that morning. She fed him his usual bottle, changed his diaper, and laid him down for a nap. She left him in the care of her 19-year-old boyfriend and went to work. At the clinic, the infant was floppy and unarousable. There were no bruises or other signs of injury, but the anterior fontanel was bulging. His pupils were 3 mm and responded sluggishly to light. When prompted, the boyfriend stated that K.B. fell off the couch early in the morning but only cried for a few minutes. After some comforting, he went back to playing. He fed well the remainder of the day and was taking his evening nap when the mother returned from work. The urgent care clinic suspected NAT and transferred K.B. to the closest hospital with pediatric critical care services.

What physiologic differences place K.B. at greater risk for severe TBI than does an older child? What risk factors or associations for NAT can you identify in this case?

The anatomic differences of the infant's brain render it more susceptible to certain types of injuries after head trauma.[52] Infants such as K.B. and young children have large, heavy heads. The head is unstable because of its relative size to the rest of the body. If an

infant or a young child falls a significant distance, is ejected during an MVC, or is thrown from a bicycle after colliding with an automobile, the head will tend to lead (ie, the infant or child will fly head first) and severe head injuries will occur when the head ultimately strikes the ground or another object. The infant's weak neck muscles also allow for greater movement when the head is acted on by acceleration/deceleration forces. The skull is thinner during infancy and early childhood, providing less protection for the brain and allowing forces to transfer more effectively across the shallow subarachnoid space. The base of the infant's skull is relatively flat, which also contributes to greater brain movement in response to acceleration/deceleration forces. In addition, the infant's brain has a higher water content (~88% vs 77% in an adult), which makes the brain softer and more prone to acceleration/deceleration injury. The water content is also inversely related to the myelination process, and the higher percentage of unmyelinated brain makes it more susceptible to sheer injuries. The infant brain is typically fully myelinated by age 1 year. As the result of these physiologic differences, there are differences in the pathology after pediatric TBI by age group. In infants and young children, diffuse injury, such as diffuse cerebral swelling, and subdural hematomas are more common than are focal injuries, such as contusions, that are typically seen in older children and adults. The typical pattern of hypoxic-ischemic injury in infants and young children after NAT is rarely seen in older children and adults who are victims of abuse.

Goldstein et al[53] have published risk factors for NAT based on data gathered from several earlier reports. They found that victims of inflicted head injury tended to be younger, more often from families of poorer socioeconomic backgrounds, and were more likely to have parents who were younger than age 18 years and who had never been married. In addition, a history inconsistent with physical findings was strongly associated with the presence of inflicted head injury. Additional risk factors reported as associated with NAT are alcohol or drug abuse, previous social service intervention, or a past history of child abuse, in combination with either retinal hemorrhages or an inconsistent history or physical examination. These

investigators found this combination was 100% predictive of child abuse in children admitted to a PICU. K.B. met many of these risk factors: He is young, has an unmarried parent who is younger than 18, and is from a low socioeconomic background. In addition, his injuries appear inconsistent with the history of falling from a couch. A fall of ~3 feet is required to cause significant head injury to an infant or a child; a standard couch is 18 inches from the floor.[54]

CASE 106-6, QUESTION 2: K.B. was transferred immediately to the emergency department at a local hospital. The O_2 saturation on room air was 100%, blood pressure 90/63 mm Hg, and HR 120 beats/minute. The initial Glasgow Coma Scale (GCS) score on presentation was 7, with 2 for eye opening in response to pain, 4 for withdrawing to pain, and 1 for no verbal response. What test or assessment tools are useful for evaluating the extent of K.B.'s injuries? Which are best for predicting his outcome?

The ability to evaluate the severity of TBI is essential to appropriately direct care, predict outcomes, and compare results to evaluate and improve patient care. Initial symptoms on presentation have been found to have little or no correlation with injury severity after TBI. The GCS is a widely accepted method in initially evaluating and characterizing patients with trauma and head injuries (**Table 106-12**). The scale is composed of visual, motor, and verbal components, with lower scores representing more serious injuries. The severity of TBI may be characterized as mild (GCS 13–15), moderate (GCS 9–12), or severe (GCS 3–8) on presentation; however, continued evaluation of GCS scores is the best way to track the patient's clinical progress. K.B.'s GCS of 7 on admission puts him in the category of severe TBI.

Table 106-12
Modified Glasgow Coma Scale

Eye Opening			
Score	*≥1 year*	*0–1 year*	
4	Opens eyes spontaneously	Opens eyes spontaneously	
3	Opens eyes to verbal command	Opens eyes to shout	
2	Opens eyes in response to pain	Opens eyes in response to pain	
1	No response	No response	
Best Motor Response			
Score	*≥1 year*	*0–1 year*	
6	Obeys command	N/A	
5	Localizes pain	Localizes pain	
4	Flexion withdrawal	Flexion withdrawal	
3	Flexion abnormal (decorticate)	Flexion abnormal (decorticate)	
2	Extension (decerebrate)	Extension (decerebrate)	
1	No response	No response	
Best Verbal Response			
Score	*>5 years*	*2–5 years*	*0–2 years*
5	Oriented and able to converse	Uses appropriate words	Cries appropriately
4	Disoriented and able to converse	Uses inappropriate words	Cries
3	Uses inappropriate words	Cries and/or screams	Cries and/or screams inappropriately
2	Makes incomprehensible sounds	Grunts	Grunts
1	No response	No response	No response

N/A, not applicable.

Source: Chung CY, Chen CL, Cheng PT, See LC, Tang SF, Wong AM. Critical score of Glasgow Coma Scale for pediatric traumatic brain injury. *Pediatr Neurol.* 2006;34:379–387.

The radiologic examination of choice for immediate assessment of a child with severe TBI is a noncontrast cerebral computed tomography (CT) scan. Most children with severe TBI undergo immediate CT imaging to delineate their injuries as soon as they have been fully assessed and sufficiently stabilized to permit safe transport to the radiology suite. If the brain injury does not need immediate surgical intervention, the patient's care is continued in the PICU with the implementation of therapies designed to minimize secondary brain injury. In a retrospective review of 309 children presenting with TBI, Chung et al[55] found that the GCS score was more useful in predicting survival among pediatric victims of TBI than were CT findings and the presence of injuries to other organ systems. In addition, they identified that a GCS score of <5, rather than a score of <8 as used in adults, was the threshold at which the patient was more likely to have a poor outcome. The authors also found that head CT findings of swelling or edema and subdural and

intracerebral hemorrhage were associated with worse outcomes than was subarachnoid or epidural hemorrhage.

Retinal hemorrhages are frequently, although not always, observed in inflicted head injury in infants and young children. These hemorrhages are the result of sheer forces disrupting vulnerable tissue interfaces. The vitreous body is adherent to the retina in early childhood; shaking can cause retinal hemorrhaging throughout multiple tissue layers, extending to the periphery of the retina. This pattern is unique to "shaken baby syndrome." Although useful for diagnosis, the ocular examination is often deferred initially when evaluating an infant or a child for TBI, because the medications used to facilitate funduscopy will preclude the use of pupillary reactivity as a tool to monitor evolving intracranial events.

According to the American Academy of Pediatrics guidelines on imaging for NAT, a skeletal survey is strongly recommended in all cases of suspected physical abuse in children younger than age 24 months.[56] A skeletal survey consists of films of the extremities, skull, and axial skeletal images. Follow-up radiographs of the ribs to assess for healing fractures not seen in the acute phase may be helpful 2 to 3 weeks after the skeletal survey. As with the eye examination, the skeletal survey is often delayed until the child is more stable.

CASE 106-6, QUESTION 3: After assessment by the emergency department physician, K.B. was intubated using rocuronium and pentobarbital, placed on an F_{IO_2} of 100% and sent for a CT scan. The CT reveals a subdural hematoma and cerebral swelling. On arrival to the PICU, K.B.'s vital signs are as follows:

Blood pressure, 85/58 mm Hg
HR, 125 beats/minute
Respiratory rate on the ventilator, 20 breaths/minute

Temperature was 98.42 °F (36.9 °C). What are the next goals for stabilization of K.B.?

The initial management of a child with a head injury should focus on the basics of resuscitation: assessing and securing the airway, ensuring adequate ventilation, and supporting circulation.[57] In

addition, the goals of treatment of TBI are directed toward protecting against secondary brain insults (SBIs) that can exacerbate neuronal damage and brain injury. SBIs are often the result of systemic hypotension, hypoxia, hypercarbia, anemia, and hyperglycemia. Aggressive treatment strategies are needed to prevent and/or treat these conditions to decrease morbidity and improve neurologic outcome after TBI in children. The criteria for tracheal intubation include hypoxemia not resolved with supplemental oxygen, apnea, hypercarbia ($PaCO_2$ > 45 mm Hg), a GCS score ≤8, a decrease in GCS score >3 compared with the initial score, cervical spine injury, loss of pharyngeal reflex, or any clinical evidence of herniation. K.B. was intubated in the emergency department based on his presenting GCS score of 7. All patients should be assumed to have a full stomach and cervical spine injury, so the intubation should be carried out using an RSI with appropriate short-acting sedatives and muscle relaxants (see Tables 106-3 and 106-4).

After intubation, K.B.'s ventilatory goals include 100% oxygen saturation, normocarbia (35–39 mm Hg), and no hyperventilation, as confirmed by ABGs, end-tidal CO_2 monitoring, and chest radiographs showing the tracheal tube in a good position. Unless he has signs or symptoms of herniation, prophylactic hyperventilation ($PaCO_2$ < 35 mm Hg) should be avoided.[57] Hyperventilation causes cerebral vasoconstriction, which decreases cerebral blood flow and subsequent blood volume. Although it will lower ICP, hyperventilation may result in ischemia. Furthermore, respiratory alkalosis caused by hyperventilation makes it more difficult to release oxygen to the brain, shifting the oxygen–hemoglobin curve to the left. Short-term use of hyperventilation, however, may be useful in preventing herniation while other medical therapies are implemented. In addition to mechanical ventilation, the head of the bed should be kept in the neutral position and jugular venous obstruction should be avoided to prevent ICP elevation. Elevation of the head of the bed to 30 degrees usually decreases ICP.

Assessment and reassessment of the patient's circulatory status, including central and peripheral pulse quality, capillary refill, HR, and

blood pressure, is critical. Hypotension after pediatric TBI is associated with increased morbidity and mortality.[57] Initial treatment of hypotension in the child with a head injury is similar to that described earlier for pediatric shock; however, the goal SBP in the patient with TBI is typically higher: ≥50th to 75th percentile for age, sex, and height. Systolic blood pressure <75th percentile has been associated with a fourfold increase in the risk factor for poor outcome after severe TBI, even when values were ≥90 mm Hg.[58] This suggests a possible benefit of a higher blood pressure target until ICP or cerebral perfusion pressure (CPP) monitoring is in place to guide therapy. As a result of the need for higher SBP, norepinephrine and phenylephrine, agents with greater vasopressor effects, are more frequently used in this patient population.[59]

The solution of choice for IV maintenance fluids in children with TBI is normal saline for children older than 1 year of age and 5% dextrose with normal saline for infants. Because hyperglycemia is known to worsen SBI, initial IV fluids for children should not contain dextrose. Infants are an exception because their low glycogen stores make them prone to hypoglycemia, especially with poor oral intake. Hypoglycemia can also worsen neurologic outcome and should be avoided. Frequent assessment of blood glucose either by point-of-care testing or on an ABG is recommended.

Case 106-6, Question 4: K.B. has been intubated and placed on mechanical ventilation with an ABG showing that he is maintaining goal parameters. He is receiving fentanyl at 1 µg/kg/hour and a dexmedetomidine infusion at 0.5 µg/kg/hour. The head of the bed is raised 30 degrees and his head is midline, supported by a head roll. K.B. has both a pulse oximeter and an end-tidal CO_2 monitor for continuous evaluation of his oxygenation and CO_2. Blood pressure is being maintained at the 75th percentile for age, height, and sex. What is the next step in monitoring head injury in K.B.?

Fever increases metabolic demands and is associated with worse outcomes after TBI. Treatment for K.B. should include 60 mg of acetaminophen (15 mg/kg) orally or rectally every 6 hours as needed and a cooling blanket when necessary. Ibuprofen should be avoided

because it may increase the risk of bleeding. Patients who are hypothermic on arrival should only be actively rewarmed if there is hemodynamic instability or bleeding thought to be exacerbated by hypothermia. Serum electrolytes and osmolarity should be monitored regularly in K.B., along with accurate assessment of urine output. This is important to identify the development of either syndrome of inappropriate antidiuretic hormone or diabetes insipidus. Both have been reported to occur after pediatric TBI.[57]

One of the most significant consequences of TBI is the development of intracranial hypertension. The presence of an open fontanel or sutures in an infant with severe TBI does not preclude the development of intracranial hypertension or negate the utility of ICP monitoring. ICP monitoring is recommended for any child presenting with a GCS of ≤8.[60] When possible, placement of a ventriculostomy catheter provides accurate pressure monitoring and allows for acute drainage of cerebrospinal fluid (CSF) for treatment of elevated ICP and assessment of CPP. The CPP value is calculated by subtracting the ICP from the MAP (Eq. 106-1):

$$\mathrm{CPP} = \mathrm{MAP} - \mathrm{ICP} \qquad \textbf{(Eq. 106-1)}$$

This value is important as an indication of blood flow and oxygen that reaches the brain. Maintaining CPP requires optimization of MAP with fluid therapy, and, if necessary, vasoactive drugs. In the case of ICP elevation, inotropic or vasopressor agents may be used to optimize CPP by increasing MAP, even to the point of relative systemic hypertension. In adults, a CPP of 60 to 70 mm Hg is usually targeted.

These recommendations are based on pediatric TBI studies showing that CPP values ranging from 40 to 70 mm Hg are associated with a favorable outcome and that a CPP <40 mm Hg is associated with poor outcomes.[60] Because infants and children normally have a lower MAP and ICP, the SCCM Pediatric Fundamental Critical Care Support course recommends the following CPP ranges: 40 to 50 mm Hg in infants, 50 to 60 mm Hg in children, and 60 to 70 mm Hg in adolescents. The 2019 Guidelines

for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition, recommended maintaining a minimum CPP of 40 mm Hg, with a target between 40 and 50 mm Hg to ensure that the minimum of 40 mm Hg is not breached. There may be age-specific thresholds with infants at the lower and adolescents at or above the upper end of this range.[57] A recent study by Allen and colleagues that included 55 children ages 0 to 5 years, 65 patients ages 6 to 11 years, and 197 patients ages 12 to 17 years evaluated age-specific CPP values and clinical outcomes. They demonstrated a decreased survival in persons 18 years and older who experienced prolonged CPP below 50 or 60 mm Hg, 6 to 17 years below 50 mm Hg, and in patients 0 to 5 years below 40 mm Hg. This supports the hypothesis that CPP targets should be age specific.[61]

Case 106-6, Question 5: The neurosurgeon has placed a ventriculostomy in K.B., and his initial ICP is 25 mm Hg. His other vitals are as follows:

Blood pressure, 83/50 mm Hg
HR, 140 beats/minute
Temperature, 101.3 °F (38.5 °C)

His pulse oximeter still reads 100% and the end-tidal carbon dioxide ($ETCO_2$) monitor reads 35 mm Hg. Sedative infusions are unchanged: fentanyl 1 µg/kg/hour and dexmedetomidine 0.5 µg/kg/hour. The pediatric intensivist has placed a central line, and the CVP is 10 mm Hg. What is K.B.'s calculated CPP? What interventions are recommended to treat this ICP elevation?

Uncontrolled increased ICP is very deleterious and must be aggressively treated as soon as possible to reduce cerebral ischemia. In this setting, the goal of any therapy is to lower ICP enough to increase CPP and improve cerebral oxygenation. All initial treatments should be reassessed for efficacy, including treatment of fever, avoidance of jugular venous outflow tract obstruction, maintenance of normovolemia and normocarbia, and provision of sedation and analgesia. The latter is of considerable importance because anxiety and pain have been shown to increase ICP. K.B. appears to be euvolemic by CVP measurement, is normocapnic, and his O_2 saturation is 100%. He is febrile; however, measures should

be taken to treat the elevated temperature. Although he is receiving continuous sedation, additional bolus doses of sedatives should be given whenever needed. Because K.B. has an elevated CPP in spite of these initial therapies, the best option would be to drain CSF. This will provide an immediate, but transient, decrease in ICP. K.B. may have CSF drained until an ICP value of 15 mm Hg is reached; it should never be drained to 0 mm Hg because edema and diffuse brain swelling could cause an obstruction in the lateral ventricles. When a ventriculostomy is in place and CSF is frequently drained, it is important to replace the CSF drained with an equal amount of normal saline. Draining of large amounts of CSF without IV normal saline replacement is associated with the development of hypochloremic metabolic alkalosis. Drainage of CSF in K.B. will provide a CPP in the 40- to 50-mm Hg range. If the ICP increases again, two interventions are recommended, either the addition of a vasopressor to increase SBP or the institution of hyperosmolar therapy.

Hyperosmolar therapy may be useful in preventing the ICP from exceeding 20 mm Hg and in maintaining normal CPP. Although, historically, mannitol is commonly used in the management of increased ICP in pediatric TBI, no well-designed evidence-based studies have been published to support its use in pediatric TBI. Mannitol reduces ICP by reducing blood viscosity, which promotes reflex vasoconstriction of the arterioles by autoregulation, thus decreasing cerebral blood volume and ICP. This mechanism is rapid, but transient, lasting about 75 minutes and requiring an intact autoregulation. It also produces an osmotic effect by increasing serum osmolarity, causing the shift of water from the brain cell to the intravascular space. Although this effect is slower in onset (15–30 minutes), the osmotic effect lasts up to 6 hours. Mannitol is a potent osmotic diuretic; osmotic diuresis should be anticipated and fluid resuscitation available to avoid hemodynamic compromise. A Foley catheter is recommended in these patients for accurate measurement of urine output. Mannitol is excreted unchanged in the urine; serum osmolarity should be maintained <320 mOsm/L to avoid the development of mannitol-induced acute tubular necrosis.

Bolus hypertonic saline (3%) is recommended in pediatric patients with TBI having an ICP >20 mm Hg.[57] The main mechanism of action of hypertonic saline is an osmotic effect similar to that of mannitol. Hypertonic saline exhibits several other theoretic benefits such as restoration of normal cellular resting membrane potential and cell volume, inhibition of inflammation, stimulation of atrial natriuretic peptide release, and enhancement of CO.[57] The theoretic advantage of hypertonic saline over mannitol is that hypertonic saline can be administered in a patient who is hemodynamically unstable without the risk of a subsequent osmotic diuresis. Continuous infusions of 0.1 to 1 mL/kg/hour of hypertonic saline titrated to maintain an ICP <20 mm Hg have been used successfully in children.[62] Bolus doses of 2 to 5 mL/kg of 3% sodium chloride have been administered over 10 to 20 minutes. Serum osmolarity and serum sodium increase when this regimen is used, but sustained hypernatremia and hyperosmolarity appear to be generally well tolerated. Hypertonic saline has been administered with a serum osmolarity reaching 360 mOsm/L without adverse effects in pediatric patients. Another potential concern with the use of hypertonic saline is central pontine myelinolysis that has been reported with rapid changes in serum sodium. Currently, clinical trials have shown no evidence of demyelinating disorders. Bolus administration of 0.5 mL/kg of 23.4% sodium chloride (maximum: 30 mL) in patients with refractory ICP has been suggested. However, more evidence on its safety and efficacy in pediatric patients is needed. Regardless of which hypertonic saline regimen is utilized, it is recommended to avoid a sustained (>72 hour) serum sodium >170 Eq/L because it is associated with thrombocytopenia and anemia. Avoiding sustained serum sodium >160 mEq/L is suggested to avoid the complication of DVT.[57] Therefore, a target serum sodium of 150 to 160 mEq/L is reasonable.

To bring his ICP values down to the normal range (>20 mm Hg), K.B. may be given sodium chloride 3% at an IV dose of 8 to 20 mL (2–5 mL/kg) administered over 10 to 20 minutes. The effects of hypertonic saline on ICP should be evident within 15 minutes. This dose may be repeated every 2 to 4 hours as needed. If intermittent

hypertonic saline fails to bring his ICP down adequately, K.B. may be given a continuous infusion of hypertonic saline 3%, beginning at 0.1 mL/kg/hour or mannitol at a dose of 0.5 to 1 g/kg infused over 20 to 30 minutes. Dosing of either agent should be guided by regular assessment of serum electrolytes and osmolarity.

Case 106-6, Question 6: K.B. has been in the PICU for 24 hours. Initial treatment allowed K.B. to maintain a CPP of 50 mm Hg and an ICP <20 mm Hg for the majority of the day. He is receiving 3% sodium chloride combined with maintenance IV fluids, giving him a serum sodium of 166 mEq/L. Intermittent ICP spikes have responded to intermittent 4-g doses of mannitol; however, the most recent serum osmolarity is 330 mOs/L. What options remain to treat increased ICP in K.B.?

Two nonsurgical options are included in the TBI guideline: barbiturate coma and therapeutic hypothermia.[57] Barbiturates exert neuroprotective effects by reducing cerebral metabolism, lowering oxygen extraction and demand, and alternating vascular tone. Barbiturate serum levels poorly correlate with clinical efficacy; therefore, monitoring of electroencephalographic (EEG) patterns for burst suppression is recommended. Burst suppression also represents near-maximum reduction in cerebral metabolism and cerebral blood flow. A pentobarbital loading dose of 10 mg/kg/dose may be administered over 30 minutes, followed by a continuous infusion of 1 mg/kg/hour. Additional loading doses, in 5 mg/kg/dose increments, may be necessary to achieve burst suppression. The primary disadvantage of barbiturate coma is the risk of myocardial depression and hypotension. In addition, the long-term effect on neurologic outcome is unknown. The TBI guideline states that high-dose barbiturate therapy may be considered in patients who are hemodynamically stable with salvageable severe head injury and refractory intracranial hypertension.[57] The SCCM Pediatric TBI guideline recommends that when high-dose barbiturate therapy is used to treat refractory ICP, continuous arterial blood pressure monitoring and cardiovascular support to maintain adequate CPP

are required because cardiorespiratory instability is common among patients treated with barbiturate coma.

Posttraumatic hyperthermia is defined as a core body temperature >101.3 °F (38.5 °C), and hypothermia is defined as a temperature of <95 °F (35 °C). Although most clinicians agree that hyperthermia should be avoided in children with TBI, the role of hypothermia is unclear. Potential complications associated with hypothermia are increased bleeding risk, arrhythmias, and increased susceptibility to infection. A multicenter, international study of children with severe TBI randomly assigned to hypothermia therapy initiated within 8 hours of injury (90.5 °F [32.5 °C] for 24 hours) or to normothermia (98.6 °F [37 °C]) was recently published.[62] The study reported a worsening trend with hypothermia therapy: 31% of the patients in the hypothermia group had an unfavorable outcome, compared with 22% of the normothermia group. There were several methodologic problems with this study. Although the investigators screened patients within 8 hours, the mean time to initiation of cooling was 6.3 hours, with a range of 1.6 to 19.7 hours. In addition, the protocol included a rapid rewarming of 32.9 °F (0.5 °C) every 2 hours so that the patients were normothermic by a mean of 19 or 48 hours postinjury. They found that the ICP was significantly lower in the hypothermia group during the cooling period but that it was significantly higher than that the normothermic group during rewarming. Another trial conducted in Australia and New Zealand evaluated strict normothermia (temperature 96.8–98.6 °F [36–37 °C]) versus therapeutic hypothermia (temperature 89.6–91.4 °F [32–33 °C]).[63] Patients were enrolled within 6 hours of injury, and therapeutic hypothermia or strict normothermia was maintained for 72 hours. The rewarming rate was at a maximum of 32.9 °F (0.5 °C) every 3 hours or slower if needed to maintain normal CPP or ICP >20 mm Hg. Rewarming took a median of 21.5 hours (16–35 hours) and was without complications. However, there was no difference in pediatric cerebral performance category (PCPC) scores between the two groups at 12 months.[64] It is unclear whether therapeutic hypothermia is not efficacious because patients are not cooled soon enough (median time to target temperature = 9.3 hours) or owing to

the heterogeneous nature of TBI. The pediatric TBI guideline states that despite the lack of clinical data, hypothermia may be considered in the setting of refractory intracranial hypertension.[57] If hypothermia is used and rewarming is initiated, it should be carried out at a rate of 32.9 to 33.8 °F (0.5–1 °C) every 12 to 24 hours or slower to avoid complications.

Decompressive craniectomy, removal of a section of the skull to allow room for brain swelling without herniation, is another option for managing pediatric patients with TBI who fail to respond to standard therapies. A randomized trial of early decompressive craniectomy in children with TBI and sustained intracranial hypertension revealed that 54% of the patients treated surgically had a favorable outcome compared with only 14% of those treated medically.[65] Additional case series have confirmed that patients who receive a decompressive craniectomy have improved survival and neurologic outcomes compared with those undergoing medical management alone.[66] As with barbiturate coma and therapeutic hypothermia, decompressive craniectomy is not without risk. A recent study reported an increased risk of posttraumatic hydrocephalus, wound complications, and epilepsy in children with severe TBI.[67] Further studies are needed to establish the timing, efficacy, and safety of this management strategy. The pediatric TBI guideline states that decompressive craniectomy should be considered in pediatric patients with severe TBI with neurologic deterioration, herniation, or intracranial hypertension refractory to intensive medical management.

CASE 106-7

QUESTION 1: L.B. is a 39.68-pound (18-kg), 6-year-old child hit by a car while riding her bicycle. When emergency medical services arrived, they witnessed a 2-minute tonic–clonic seizure. GCS score at the scene was 11.

Should L.B. receive anticonvulsant medication after her TBI?

Posttraumatic seizures (PTSs) are classified as early (occurring within 7 days of injury) or late (occurring after 7 days). In the immediate period after severe TBI, seizures increase the brain

metabolic demands, increase ICP, and are associated with TBI. Therefore, it would be prudent to prevent PTSs in the period when the patient is at the highest risk for SBI. Infants and children are reported to have a greater risk of early PTS compared with adults. Children younger than age 2 years have almost a threefold greater risk of early PTS after TBI than do children between ages 2 and 12 years. In addition to age, a low GCS (8–11) score has been linked to an increased risk of early PTS. The pediatric TBI guideline states that prophylactic antiseizure therapy is suggested to reduce the occurrence rate of early PTS. No prophylactic anticonvulsant therapy is recommended to prevent late PTS.[57]

The majority of the published studies in children have used phenytoin for PTS prophylaxis. The SCCM TBI guideline stated there was insufficient evidence to recommend the use of levetiracetam over phenytoin for the prevention of PTS. Owing to the seizure witnessed at the scene, her young age, and her initial GCS score of 11, L.B. meets the criteria for prophylaxis. An appropriate regimen for L.B. would be phenytoin 45 mg given orally three times daily (7.5 mg/kg/day) for 7 days.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

de Caen AR, Berg MD, Chameides L, et al. Part 12: Pediatric advanced life support. 2015 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132(suppl 2):S526–S542. (3)

Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med.*

2021;49(*11*)e1063–e1143. (28)

Kohanek PM, Tasker RC, Bell MJ, et al. Management of pediatric severe traumatic brain injury: 2019 consensus and guidelines-based algorithm for first and second tier therapies. *Pediatr Crit Care Med.* 2019;20:269–279. doi:10.1097/PCC.0000000000001737 (57)

Namachivayam P, Shann F, Shekerdemian L, et al. Three decades of pediatric intensive care: who was admitted, what happened in intensive care, and what happened afterward. *Pediatr Crit Care Med.* 2010;11:549–555. (2)

Smith HA, Besunder JB, Betters KA, et al. Society of Critical Care Medicine clinical practice guidelines on the prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatr Crit Care Med.* 2022;23(*2*):e74–e110. doi:10.1097/PCC.0000000000002873 (13)

Weiss SL, Paters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med.* 2020;21(*2*):e52–e106. doi:10.1097/PCC.0000000000002198 (14)

Key Websites

International Liaison Committee on Resuscitation. Consensus 2015 documents. www.ilcor.org

The Surviving Sepsis Campaign. International guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-patients

COMPLETE REFERENCES CHAPTER 106 CARE OF THE CRITICALLY ILL CHILD

1. Claudet I, Bounes V, Frédérici S, et al. Epidemiology of admissions in a pediatric resuscitation room. *Pediatr Emerg Care*. 2009;25:312–316.
2. Namachivayam P, Shann F, Shekerdemian L, et al. Three decades of pediatric intensive care: who was admitted, what happened in intensive care, and what happened afterward. *Pediatr Crit Care Med*. 2010;11:549–555.
3. de Caen AR, Berg MD, Chameides L, et al. Part 12: Pediatric advanced life support. 2015 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(suppl 2):S526–S542.

4. Shott SR. The nose and paranasal sinuses. In: Rudolph CD, Rudolph AM, Hostetter MK, Lister G, Siegel NJ, eds. *Rudolph's Pediatrics*. 21st ed. McGraw-Hill Professional; 2003:1258.
5. Perkett EA. Lung growth in infancy and childhood. In: Rudolph CD, Rudolph AM, Hostetter MK, Lister G, Siegel NJ, eds. *Rudolph's Pediatrics*. 21st ed. McGraw-Hill Professional; 2003:1905.
6. Dawson-Caswell M, Muncie HL Jr. Respiratory syncytial virus infection in children. *Am Fam Physician*. 2011;83:141–146.
7. Kumar P, Denson SE, Mancuso TJ, et al. Premedication for nonemergency endotracheal intubation in the neonate. *Pediatrics*. 2010;125:608–615.
8. den Brinker M, Hokken-Koelega AC, Hazelzet JA, de Jong FH, Hop WC, Joosten KF. One single dose of etomidate negatively influences adrenocortical performance for at least 24 h in children with meningococcal sepsis. *Intensive Care Med*. 2008;34:163–168.
9. Cuthbertson BH, Sprung CL, Annane D, et al. The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. *Intensive Care Med*. 2009;35:1868–1876.
10. Jackson WL Jr. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. *Chest*. 2005;127:1031–1038.
11. Zelicof-Paul A, Smith-Lockridge A, Schnadower D, et al. Controversies in rapid sequence intubation in children. *Curr Opin Pediatr*. 2005;17:355–362.
12. Johansson M, Kokinsky E. The COMFORT behavioural scale and the modified FLACC scale in paediatric intensive care. *Nurs Crit Care*. 2009;14:122–130.
13. Smith HA, Besunder JB, Betters KA, et al. Society of Critical Care Medicine clinical practice guidelines on the prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatr Crit Care Med*. 2022;23(2):e74–e110. doi:10.1097/PCC.0000000000002873
14. Weiss SL, Paters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med*. 2020;21(2):e52–e106. doi:10.1097/PCC.0000000000002198
15. Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of severe sepsis. *Pediatr Crit Care Med*. 2013;14:686–693.
16. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368–1377.
17. Carcillo JA, Fields AI; American College of Critical Care Medicine Task Force Committee Members. Clinical practice variables for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med*. 2002;30:1365–1378.

18. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine [published correction appears in *Crit Care Med*. 2009;37:1536]. *Crit Care Med*. 2009;37:666–668.
19. de Oliveira CR, de Oliveira DS, Gottschald AF, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcome comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med*. 2008;34:1065–1075.
20. de Oliveira CF. Early goal-directed therapy in treatment of pediatric septic shock. *Shock*. 2010;34(suppl 1):44–47.
21. Wynn JL, Wong HR. Pathophysiology and treatment of septic shock in neonates. *Clin Perinatol*. 2010;37:439–479.
22. Carcillo JA. Pediatric septic shock and multiple organ failure. *Crit Care Clin*. 2003;19:413–440.
23. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure. *Crit Care Med*. 1992;20:724–726.
24. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644–1655.
25. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6:2–8.
26. Ceneviva G, Paschall JA, Maffei F, Carcillo JA. Hemodynamic support in fluid refractory pediatric septic shock. *Pediatrics*. 1998;102:e19.
27. Akech S, Ledermann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. *BMJ*. 2010;341:c4416.
28. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063–e1143.
29. Zimmerman JL. Use of blood products in sepsis: an evidence based review. *Crit Care Med*. 2004;32(11, suppl):S542–S547.
30. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256.
31. Tibby SM, Hatherill M, Marsh MJ, et al. Clinicians' abilities to estimate cardiac index in ventilated children and infants. *Arch Dis Child*. 1997;77:516–518.
32. Ranjit S, Aram G, Kissoon N, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: a pilot

observational study. *Pediatr Crit Care Med*. 2014;15:e17–e26.
33. Razavi A, Newth CJL, Khemani RG, et al. Cardiac output and systemic vascular resistance: clinical assessment compared with a noninvasive objective measurement in children with shock. *J Crit Care*. 2017;39:6–10.
34. Topjian AA, Raymonf TT, Atkins D, et al. Pediatric basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142(16, suppl 2):s469–s523. doi:10.1161/CIR.0000000000000901
35. Ventura AM, Shieh HH, Bousso A, et al. Double-blind prospective randomized controlled trial of dopamine versus epinephrine as first-line vasoactive drugs in pediatric septic shock. *Crit Care Med*. 2015;43:2292–2302.
36. Ramaswamy KN, Singhi S, Jayashree M, et al. Double-blind randomized clinical trial comparing dopamine and epinephrine in pediatric fluid-refractory hypotensive septic shock. *Pediatr Crit Care Med*. 2016;17:e502–e512.
37. Mann K, Berg RA, Nadkarni V. Beneficial effects of vasopressin in prolonged pediatric cardiac arrest: a case series. *Resuscitation*. 2002;52:149–156.
38. Duncan JM, Hong CX, Harvie HS, Brown LA, Arya LA, Kim EK. Vasopressin for in-hospital pediatric cardiac arrest: results from the American Heart Association National Registry of Cardiopulmonary Resuscitation. *Pediatr Crit Care Med*. 2009;10:191–195.
39. Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation*. 2003;107:996–1002.
40. de Kleijn ED, Joosten KF, Van Rijn B, et al. Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations are associated with poor outcome in children with very severe meningococcal disease. *Pediatr Infect Dis J*. 2002;21:330–336.
41. Casartelli CH, Garcia PC, Branco RG, Piva JP, Einloft PR, Tasker RC. Adrenal response in children with septic shock. *Intensive Care Med*. 2007;33:1609–1613.
42. Zimmerman JJ, Williams MD. Adjunctive corticosteroid therapy in pediatric severe sepsis: observations from the RESOLVE study. *Pediatr Crit Care Med*. 2011;12:2–8.
43. Arikan AA, Zappitelli M, Goldstein SL, et al. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med*. 2012;13:253–258.
44. El-Nawawy A, Khater D, Omar H, et al. Evaluation of early corticosteroid therapy in management of pediatric septic shock in pediatric intensive care patients: a randomized clinical study. *Pediatr Infect Dis J*. 2017;36:155–159.
45. Deerojanawong J, Peongsujarit D, Vivatvakin B, Prapphal N. Incidence and risk factors of upper gastrointestinal bleeding in mechanically ventilated

children. *Pediatr Crit Care Med*. 2009;10:91–95.
46. Reveiz L, Guerrero-Lozano R, Camacho A, Yara L, Mosquera PA. Stress ulcer, gastritis, and gastrointestinal bleeding prophylaxis in critically ill pediatric patients: a systematic review. *Pediatr Crit Care Med*. 2010;11:124–132.
47. Schroeder AR, Axelrod DM, Silverman NH, Rubesova E, Merkel E, Roth SJ. A continuous heparin infusion does not prevent catheter related thrombosis in infants after cardiac surgery. *Pediatr Crit Care Med*. 2010;11:489–495.
48. Talosi G, Katona M, Rácz K, Kertész E, Onozó B, Túri S. Prostaglandin E1 treatment in patent ductus arteriosus dependent congenital heart defects. *J Perinat Med*. 2004;32:368–374.
49. Meckler GD, Lowe C. To intubate or not to intubate? Transporting infants on prostaglandin E1. *Pediatrics*. 2009;123:e25–e30.
50. Bishop NB. Traumatic brain injury: a primer for primary care physicians. *Curr Probl Pediatr Adolesc Health Care*. 2006;36:318–331.
51. Keenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF, Sinal SH. A population based study of inflicted traumatic brain injury in young children. *JAMA*. 2003;290:621–626.
52. DeMeyer W. Normal and abnormal development of the neuroaxis. In: Rudolph CD, Rudolph AM, Hostetter MK, Lister G, Siegel NJ, eds. *Rudolph's Pediatrics*. 21st ed. McGraw-Hill Professional; 2003:2174.
53. Goldstein B, Kelly MM, Bruton D, Cox C. Inflicted versus accidental head injury in critically injured children. *Crit Care Med*. 1993;21:1328–1332.
54. Rorke-Adams L, Duhaime C-A, Jenny C, Smith WL. Head trauma. In: Reece RM, Christians CW, eds. *Child Abuse: Medical Diagnosis and Management*. 3rd ed. American Academy of Pediatrics; 2009:54.
55. Chung CY, Chen CL, Cheng PT, See LC, Tang SF, Wong AM. Critical score of Glasgow Coma Scale for pediatric traumatic brain injury. *Pediatr Neurol*. 2006;34:379–387.
56. Section on Radiology; American Academy of Pediatrics. Diagnostic imaging of child abuse. *Pediatrics*. 2009;123:1430–1435.
57. Kohanek PM, Tasker RC, Bell MJ, et al. Management of pediatric severe traumatic brain injury: 2019 consensus and guidelines-based algorithm for first and second tier therapies. *Pediatr Crit Care Med*. 2019;20:269–279. doi:10.1097/PCC.0000000000001737
58. Vavilala MS, Bowen A, Lam AM, et al. Blood pressure and outcome after severe traumatic brain injury. *J Trauma*. 2003;55:1039–1044.
59. Di Gennaro JL, Mack CD, Malakouti A, Zimmerman JJ, Armstead W, Vavilala MS. Use and effect of vasopressors after pediatric traumatic brain injury. *Dev Neurosci*. 2010;32:420–430.
60. Catala-Temprano A, Claret Teruel G, Cambra Lasaosa FJ, et al. Intracranial pressure and cerebral perfusion pressure as risk factors in children with traumatic brain injuries. *J Neurosurg*. 2007;106(6, suppl):463–466.

61. Allen BB, Ya-lin C, Gerber LM, Ghajar J, Greenfield JP. Age-specific cerebral perfusion pressure thresholds and survival in children and adolescents with severe traumatic brain injury. *Pediatr Crit Care Med*. 2014;15(1):62–70. doi:10.1097/PCC.0b013e3182a556ea
62. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med*. 2008;358:2447–2456.
63. Beca J, McSharry B, Erickson S, et al. Hypothermia for traumatic brain injury in children—a phase II randomized controlled trial. *Crit Care Med*. 2015;43:1458–1466.
64. Mejia R, ed. *Traumatic Brain Injury in Pediatric Fundamental Critical Care Support*. Society of Critical Care Medicine; 2008.
65. Taylor A, Butt W, Rosenfeld J, et al. A randomized trial of very early decompressive craniectomy in children with traumatic brain injury. *Childs Nerv Syst*. 2001;17:154–162.
66. Jagannathan J, Okonkwo DO, Dumont AS, et al. Outcome following decompressive craniectomy in children with severe traumatic brain injury: a 10 year single-center experience with long term follow up. *J Neurosurg.* 2007;106(4, suppl):268–275.
67. Kan P, Amini A, Hansen K, et al. Outcomes after decompressive craniectomy for severe traumatic brain injury in children. *J Neurosurg*. 2006;105(5, suppl):337–342.

SECTION 18

Geriatric Therapy

Section Editor: Judith L. Beizer

107

Geriatric Drug Use

Suzanne Dinsmore, Mary-Kathleen Grams, and Kristin M. Zimmerman

CORE PRINCIPLES		CHAPTER CASES
AGE-RELATED PHYSIOLOGIC, PHARMACOKINETIC, AND PHARMACODYNAMIC CHANGES		
1	Age-associated physiologic changes are associated with pharmacokinetic and pharmacodynamic alterations of drugs in older adults. Decline in drug metabolism and excretion and exaggerated response to drugs are important considerations in drug therapy of older adults.	**Case 107-1 (Questions 1–4)**
2	Adverse drug events are one of the most important problems associated with drug use in older adults.	**Case 107-2 (Question 1)**
DISEASE-SPECIFIC GERIATRIC DRUG THERAPY		
		Case 107-2 (Question

1	Older adults have multiple chronic conditions and take numerous medications. Disease-state education, awareness of potential adverse effects and drug interactions, consultation with health care providers, and behavioral modification are important steps to ensure medication safety.	**2)**
2	Pharmacologic treatments of heart failure (HF) in older adults include diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin-receptor blockers (ARBs), with or without digoxin and spironolactone. Benefits should be weighed against risks based on the patient's concurrent conditions.	**Case 107-2 (Questions 3, 4)**
3	Statins are the drug of choice for treating hyperlipidemia in older adults. Combination with other agents is considered only if necessary and is based on concurrent disease states, potential adverse effects, and drug interactions.	**Case 107-2 (Questions 5, 6)**
4	First-line therapy for the prevention of coronary artery disease (CAD) includes acetylsalicylic acid (ASA) and β-blockers. Other agents are considered based on concomitant diseases and relative indications.	**Case 107-2 (Question 7)**
5	Hypertension (HTN) should be treated in older adults according to the	**Case 107-2 (Question 8)**

	guidelines, and monitoring is essential to prevent excessively low blood pressure (BP), bradycardia, and orthostatic hypotension.	
6	The glycated hemoglobin ($HgbA_{1c}$) goal may be higher or relaxed in older adults who have episodes of hypoglycemia with standard goals. Pharmacologic therapies for diabetes are recommended based on the level of hyperglycemia and relative contraindications.	**Case 107-2 (Question 9)**
7	Depression is a common psychiatric disorder in older adults, often presenting with atypical symptoms. Selective serotonin reuptake inhibitors (SSRIs) are generally better tolerated than other agents and are considered a first-line therapy.	**Case 107-3 (Questions 1, 2)**
8	Asthma is a significant source of morbidity in older adults. The management of asthma in older adults does not differ significantly from that for younger individuals. However, coexisting chronic medical conditions, exaggerated systemic adverse drug reactions, and dexterity concerns must be considered when managing drug therapy for asthma in the older adult.	**Case 107-4 (Questions 1, 2)**
9	Pneumonia is the leading infectious cause of mortality in older adults, who typically presents with atypical	**Case 107-4 (Questions 3–5)**

	symptoms of lower respiratory infection. Influenza and pneumococcal vaccinations are beneficial in the prevention of pneumonia in the older population.	
10	Urinary tract infections (UTIs) are the most common bacterial infection in older adults. Oral antibiotics are appropriate for most older patients with symptomatic infection.	**Case 107-5 (Questions 1, 2)**
11	Arthritis is the most common cause of disability in older adults, and there are several analgesic agents available for the management of osteoarthritis. Safe and appropriate use of these analgesic medications is important because older adults are at increased risk of adverse drug reactions.	**Case 107-6 (Questions 1, 2)**
LONG-TERM CARE FACILITIES		
1	Federally mandated responsibilities of pharmacists in long-term care facilities (LTCFs) include monthly medication regimen review (MRR) for appropriateness of drug therapy. Provision of pharmaceutical care in LTCFs helps minimize medication errors, adverse drug reactions, and inappropriate prescribing.	**Case 107-7 (Questions 1, 2)**

INTRODUCTION

Demographic changes and medical progress in the United States over the past half of the 20th century have created the need for imperatives to improve our knowledge about the health care and drug therapy of older adults. The Federal Interagency Forum on Aging-Related Statistics is made up of multiple federal agencies that came together in 1986 to provide information on the health, finances, and well-being of older Americans in the United States.[1] Along with the National Institute of Aging, National Center for Health Statistics, and the Census Bureau, the latest report compiles information from over 16 national data sources and separates data into 41 indicators in the areas of population, economics, health status, health risks and behaviors, and health care and environment, of the older population. The U.S. Department of Health and Human Services published the "2019 Profile in Older Americans" in May 2020.[2] Both reports include valuable information that describe the older population (**Table 107-1**).

Table 107-1

2019 Profile of Older Americans

Current Facts About Older Americans[1,2]
▪ The older population, persons age 65 years and older, numbered 52.4 million in 2018, representing 16% of the U.S. population. This is a 35% increase from 2008.
▪ More than one in every seven Americans is considered an older adult.
▪ There are 29.1 older adult females and 23.3 million older adult males.
▪ The older population is getting even older. The 85 and older age group grew from just over 122,362 in 1900 to 6.5 million in 2018.
▪ The average life expectancy for those reaching age 65 is 85.7 years for females and 83.1 years for males.
▪ The centenarian population or those age 100 years and older accounted for 0.2% of the age 65 and older population in 2018.
▪ The most common and chronic health conditions among all persons age 65 years and older are heart disease, diagnosed and undiagnosed diabetes, cancer, stroke, and arthritis.
▪ Among all persons age 65 years and older, the leading causes of death are heart disease, cancer, chronic lower respiratory diseases, stroke, Alzheimer disease, diabetes, unintentional injuries, and influenza and pneumonia.

The Older Population Is Growing

- Thirty-six percent of the “baby boomer” generation are age 65 years and older.
- The population of those age 65 years and older is expected to increase to 94.7 million by 2060.
- The very old, those age 85 years and older are expected to double from 6.5 million in 2018 to 14.4 million in 2040.

Sources: Adapted from the Administration on Aging, Administration for Community Living, U.S. Department of Health and Human Services. *2019 Profile of Older Americans*. 2020:26; Federal Interagency Forum on Aging-Related Statistics. *Older Americans 2016: Key Indicators of Well-Being*. 2016.

The term “older adult” describes those age 65 years and older; and “oldest-old” describes those age 85 years and older. The oldest-old will have a significant impact on the health care system because the number of people in this group is expected to double from 6.5 million in 2018 to 14.4 million in 2040.[2]

Older adults often have multiple chronic conditions, higher prescription drug costs, and higher out-of-pocket health care expenditures and account for more overnight hospital stays than younger adults. Many older adults live at home and may receive personal assistances with one or more activities of daily living (ADLs), including bathing, eating, and dressing, or instrumental activities of daily living (IADLs), including preparing meals, washing clothes, shopping, paying bills, and taking medication. Often, informal care from children and other relatives is a large reason disabled older adults can continue to live in the community. Thus, it is important to include the caregiver in the counseling and monitoring of daily activities when feasible. An increase in this informal assistance and the reliance on others to perform ADLs and IADLs leads to a loss of independence and the inability of older adults to remain living at home or alone in the community. Approximately 1.2 million U.S. residents age 65 years and older reside in long-term care facilities (LTCFs). The percentage of those living in nursing homes increases with age (1% for age 65–74; 2% for age 75–84; 7% for age >85).

Health care for older adults in an institutional setting is largely based on a prospective reimbursement system, where payment for services is based on a fixed amount.[3] Managed-care practices aim to minimize high-cost hospitalizations by shifting care to lower cost alternatives, such as home health care, assisted living, and hospice care. The escalating costs and affordability of medications are a national concern, especially in the Medicare population. The Medicare Prescription Drug Improvement and Modernization Act of 2003 provided voluntary prescription drug insurance benefits, known as Medicare Part D, to improve older adults' access to prescription drugs.[4] The implementation of Medicare Part D is associated with an increase in drug use in older adults owing to accessibility and a decrease in patient out-of-pocket costs.[5]

AGE-RELATED PHYSIOLOGIC, PHARMACOKINETIC, AND PHARMACODYNAMIC CHANGES

Physiologic changes that are seen with aging are progressive and occur gradually over a lifetime, rather than abruptly at any given age.[6] These changes may lead to decreases in the function of tissues and organs and the ability of each organ system to maintain homeostasis: a phenomenon often called "homeostenosis."[7] The impaired ability to recover from drug-induced insults may increase the risk of drug-related problems in older adults. Homeostatic mechanisms in the cardiovascular and nervous systems are less efficient; drug metabolism, excretion, body tissue composition, drug volume of distribution, and drug receptor sensitivity may change or be altered. Age-related physiologic changes may result in pharmacokinetic and pharmacodynamic changes and should be considered when selecting and evaluating drug therapy.

Absorption

The absorption of some drugs administered by the extravascular route may be altered by age-related physiologic changes, unlike drugs administered by the intravascular route that are considered to have 100% bioavailability.[8] In the gastrointestinal (GI) tract, a decrease in intestinal blood flow, increase in gastric pH, delayed gastric emptying, and decreased GI motility occur with aging. Increased gastric pH due to aging alone is thought to have a minimal effect on absorption and be rarely clinically significant. However, the use of H_2-receptor antagonists and proton-pump inhibitors combined with gastric pH changes may affect drugs that require an acidic environment for absorption, such as iron, itraconazole, and ketoconazole. In general, the rate of absorption is slower or unaltered in older patients, and the extent of absorption by the oral route is similar as compared to young adults.

The transdermal administration of drugs is a convenient route of administration and used for several medications prescribed to older adults.[9] Changes in skin seen with aging such as decreased elasticity, thinning of the epidermis, dryness, and decreased sebaceous gland activity may affect drug absorption. Care should be taken to adjust doses and monitor to prevent potential adverse effects.[10]

Lipophilic drugs (eg, estradiol) appear to be less affected by aging skin and are easily dissolved, whereas hydrophilic compounds may not dissolve as readily on aging skin.

CASE 107-1

QUESTION 1: M.G. is a 75-year-old female, 64 inches (162.56 cm), 120 pounds (54.43 kg), with a serum creatinine (SCr) concentration of 1.9 mg/dL. She has an acute exacerbation of heart failure (HF) and is given furosemide 40 mg orally (po), but this produces little increase in urine output or resolution of her symptoms.

What would explain M.G.'s lack of response to furosemide, and how might the desired response to furosemide be achieved?

The extent of furosemide absorption is not changed in older patients, but the rate of absorption is slowed. This results in a

diminished efficacy of the drug because active secretion into the urine (rate of entry) must reach the steep portion of the sigmoid dose–response curve for maximal effect of the drug.[11,12] A higher concentration is needed to achieve the desired effect.

M.G. should be given a 40-mg dose of furosemide intravenously (IV) to bypass the problem of decreased rate of absorption by the oral route. High-sodium intake or concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) may also decrease the effectiveness of furosemide. Further increases in dose of furosemide may be necessary, with consideration of a continuous infusion in patients with severe chronic renal insufficiency (see Chapter 28, Chronic Kidney Disease).

Distribution

There are a number of age-related changes that may affect the distribution of drugs in the body.[8,9] Total body water and lean body mass both decline with age by 10% to 15%, and total body fat increases by 20% to 40%.[13] Thus, the volume of distribution (V_d) of drugs that are distributed primarily in body water or lean body mass (eg, lithium, digoxin) is decreased in older adults, and unadjusted dosing may result in higher blood levels. Conversely, the V_d of highly lipid-soluble drugs, such as long-acting benzodiazepines (eg, diazepam), may be increased, thereby delaying maximal effects or leading to accumulation with continued use.[9]

Serum albumin concentrations were found to progressively decrease for each decade beyond age 40 years, reaching a mean of 3.58 g/dL in those older than 80 years, and this may reduce protein binding.[14] Changes in protein binding due to aging alone are thought to be only clinically significant with drugs that are highly extracted, are highly protein bound, have a narrow therapeutic index, have a small volume of distribution, and those given IV.[13] Other factors in older patients that may also affect binding include protein concentration, disease states, coadministration of other drugs, and nutritional status.

Altered Protein Binding

Case 107-1, Question 2: M.G. is brought to the emergency department (ED) for evaluation of a "shaking spell." In the ED, another "spell" is observed, starting with shaking of the left arm and progressing into a generalized tonic–clonic seizure. A loading dose of phenytoin 1000 mg is given IV over 30 minutes. M.G. is admitted to the neurology unit for further evaluation and given phenytoin 300 mg po at bedtime. Is the phenytoin regimen appropriate for M.G.? What laboratory tests should be ordered, and how often should these be monitored?

M.G. received a phenytoin loading dose of 17 mg/kg (adult dose 15–20 mg/kg) and is receiving the usual oral daily maintenance dose.[15] Monitoring parameters include a serum sodium concentration to rule out a hyponatremia-induced seizure. Because phenytoin is 90% protein bound, a serum albumin concentration should be drawn. In patients with hypoalbuminemia or renal impairment, free (unbound) phenytoin levels should be monitored. A serum phenytoin concentration at discharge to determine whether the desired therapeutic serum concentration has been achieved is also recommended. A follow-up, steady-state serum phenytoin concentration should be obtained in 10 to 14 days to evaluate the current dose and to determine whether dose adjustments are needed. The serum phenytoin concentration should be monitored periodically thereafter and whenever an adverse drug reaction or seizure occurs.

Case 107-1, Question 3: M.G. returns for a follow-up appointment 2 weeks later after having labs drawn. Serum albumin concentration is 2.2 g/dL, sodium 140 mEq/L, and serum phenytoin 15 µg/mL. M.G. has drowsiness and a wide-based, unsteady gait. What is the most likely cause of her symptoms?

Although the serum phenytoin is within the therapeutic range (10–20 µg/mL), phenytoin is highly protein bound, and in the presence of low albumin, free phenytoin concentrations could be higher. A

corrected phenytoin level can be calculated using the following equation:

$$\text{Total phenytoin concentration} = \text{Total phenytoin measured} / [(0.2 \times \text{Serum albumin g/dL}) + 0.1]$$

(Eq. 107-1)

This would produce an equivalent phenytoin concentration of 27 μg/mL, explaining M.G.'s symptoms (assuming her serum phenytoin concentration is at steady state). In M.G.'s case, free phenytoin (unbound phenytoin) concentration monitoring would be appropriate, if available, and her dosage should be adjusted accordingly.[15],[16]

Metabolism

M.G.'s phenytoin metabolism may be affected by factors known to influence hepatic drug metabolism, including disease states, concurrent drug use, nutritional status, environmental compounds, genetic differences, sex, liver mass, and blood flow. Liver mass decreases by ~20% to 30% with age, and hepatic blood flow decreases by ~20% to 50%.[13] Compounds undergoing phase I metabolism (reduction, oxidation, hydroxylation, demethylation) have a decreased or unchanged clearance, whereas compounds metabolized by phase II processes (conjugation, acetylation, sulfonation, glucuronidation) have no change in clearance with age.[8] Drugs with high hepatic-extraction ratios, such as the nitrates, barbiturates, lidocaine, and propranolol, may have reduced hepatic metabolism in older adults.[13] Some angiotensin-converting enzyme (ACE) inhibitors are prodrugs and need to be activated by the liver, and bioavailability may be decreased in older adults, especially when hepatic disease is present.[17]

Excretion

In older adults, changes in aging kidneys include a decrease in renal mass by 20% to 30%, decrease in renal blood flow, and decrease in tubular secretion.[9] After age 30 years, glomerular filtration rate (GFR) is estimated to decline 8 mL/minute every 10 years, although not all older adults have decreased renal function. Increases in sclerotic glomeruli and decreases in functioning glomeruli may contribute to a decline in GFR.[12]

The plasma half-life is prolonged for a number of renally excreted drugs in "healthy" older adults, and the highest risk drugs are those that depend entirely on the kidney for elimination. Examples of drugs that should be avoided or dose reduced in older adults due to reduced kidney function are listed in **Table 107-2**.

Table 107-2

Drugs Highly Dependent on Renal Function for Elimination

Acetazolamide	Dofetilide	Nadolol
Acyclovir	Duloxetine	Nitrofurantoin
Allopurinol	Edoxaban	Nizatidine
Amantadine	Enalapril	Penicillins (most)
Amiloride	Enoxaparin	Phenazopyridine
Aminoglycosides	Enoxaparin	Pregabalin
Amphotericin B	Famotidine	Pregabalin
Apixaban	Fluconazole	Probenecid
Atenolol	Fluoroquinolones (most)	Procainamide
Aztreonam	Fondaparinux	Pyridostigmine
Captopril	Furosemide	Ranitidine
Cephalosporins (most)	Gabapentin	Rivaroxaban
Cimetidine	Imipenem	Spironolactone
Ciprofloxacin	Levetiracetam	Thiazides
Clonidine	Lisinopril	Tramadol
Colchicine	Lithium	Triamterene
Dabigatran	Methotrexate	Trimethoprim/sulfamethoxazole

Digoxin	Metoclopramide	Vancomycin

This list does not include all drugs highly dependent on renal function for elimination.

Sources: Adapted from the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694. doi:10.1111/jgs.15767; Arnoff GR, Bennett WM, Berns JS, et al, eds. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*. 5th ed. American College of Physicians; 2007.

GFR is the most prevalent measurement that is used to evaluate overall renal function and to diagnose kidney disease, using markers that are renally excreted such as creatinine.[18] These markers are measured by collecting urine over a 6- to 24-hour period and drawing blood before or after. Because timed urine and serum collections may not always be possible or accurate in older adults owing to inconvenience, or incomplete collection in those with incontinence, several equations are used to estimate creatinine clearance (CrCl).[19],[20] Whereas GFR is used to diagnose and stage kidney disease, equations that estimate CrCl are used to guide practitioners in drug dosing. The Cockcroft–Gault equation is commonly used for most drug dosing; however, controversies exist with regard to using actual or ideal weight and using correction factors in the calculation. The use of lean body weight in the equation may reflect SCr production more accurately because creatinine is produced in muscle mass, which is decreased in older patients. The Cockcroft–Gault equation depends on SCr concentration and tubular secretion of creatinine, which may result in an overestimation of renal function in patients with obesity.

Case 107-1, Question 4: For renally cleared drugs that require dosage adjustment for M.G., is the Cockcroft–Gault equation an appropriate tool to estimate renal function?

Cockcroft and Gault

$$eCrCl = (140 - age) \times \text{weight in kg} / (72 \times SCr) \times 0.85 \text{ in females} \quad \text{(Eq. 107-2)}$$

M.G. is 75 years old, weighs 120 pounds (54.43 kg), and her SCr is 1.9 mg/dL. Using the Cockcroft–Gault equation, her estimated CrCl is 22 mL/minute. The equation was derived from a predominantly male veteran population who had a single measured 24-hour CrCl, and a correction factor of 0.85 is used in female patients.[20]

M.G. is not underweight or obese, so the Cockcroft–Gault equation is an appropriate tool to estimate CrCl for drug dosing and remains the most common method to determine dosing of renally cleared drugs. Other assessments of renal function, including urine output, should be considered when assessing drug dosage adjustments in older individuals such as M.G., along with close monitoring for adverse drug reactions.

Table 107-3 provides a composite picture of the age-related physiologic changes, disease states, and pharmacologic factors that affect pharmacokinetic processes in older adults.

Table 107-3
Changes Affecting Pharmacokinetic Parameters

Parameter	Physiologic Changes	Disease States	Pharmacologic Factors
Absorption (bioavailability, first-pass metabolism)	Gastric pH Absorptive surface Splanchnic blood flow GI motility Gastric emptying rate	Achlorhydria, diarrhea, gastrectomy, malabsorptive syndromes, pancreatitis	Drug interactions, antacids, anticholinergics, cholestyramine, food
Distribution	Cardiac output TBW Lean body mass Serum albumin α_1-Acid glycoprotein Body fat Altered relative tissue perfusion	HF, dehydration, edema, ascites, hepatic failure, malnutrition, renal failure	Drug interactions, protein-binding displacement
Metabolism	Hepatic mass Enzyme activity Hepatic blood flow	HF, fever, hepatic failure, malignancy, malnutrition, thyroid disease, viral infection, or immunization	Dietary makeup, drug interactions, insecticides, alcohol, smoking, induction of metabolism, inhibition of metabolism
Excretion	Renal blood flow GFR Tubular secretion Renal mass	Hypovolemia, renal insufficiency	Drug interactions

GFR, glomerular filtration rate; GI, gastrointestinal; HF, heart failure; TBW, total body water.

PHARMACODYNAMIC CHANGES

Pharmacodynamics refers to the effect of a medication at its receptor site, or site of action, and is largely determined by drug concentration and its ability to bind at the receptor site.[13] Aging can affect the number of receptors available and their affinity to medications. Together, comorbidities, pharmacokinetic changes, and pharmacodynamic changes make an individual drug response in an older adult largely unpredictable. Because older adults can be sensitive to the effects of medication, care should be taken to avoid unwanted adverse effects when starting or stopping medications.

The ability to preserve homeostasis decreases with aging, which results in a decrease in functional reserve and a decreased ability to respond in times of physiologic stress. Cardiovascular changes during aging along with an impaired baroreceptor response increase the prevalence of orthostatic hypotension in older adults.[13,21] Prevalence ranges from ~6% in healthy older adults and up to 60% in hospitalized older adults.[22] Orthostatic hypotension is associated with the use of α-blockers, β-blockers, thiazide diuretics, and central sympathomimetics when used to treat hypertension (HTN). This may lead to an increased risk of falls in older adults.

Certain medications, such as digoxin, or classes of medications, such as antiarrhythmics, diuretics, narcotics, anticonvulsants, psychotropics, and antidepressants, can lead to gait disturbances, contribute to drug-induced falls, and lead to decreased mobility.[23] **Table 107-4** reviews medications commonly associated with adverse drug reactions that may contribute to gait changes and falls in older adults.[22–24]

Table 107-4
Medications Associated With Adverse Drug Reactions That May Contribute to Gait Changes and Falls in Older Adults

Medication Class	Adverse Drug Reaction
Tricyclic antidepressants	Orthostatic hypotension, tremor, cardiac

(TCAs)	arrhythmias, sedation
Benzodiazepines and sedative hypnotics	Sedation, weakness, coordination, confusion
Opiate analgesics	Sedation, coordination, confusion
Antipsychotics	Orthostatic hypotension, sedation, extrapyramidal effects
Antihypertensives	Orthostatic hypotension
β-Adrenergic blockers	Ability to respond to workload (dose needed may increase risk)

Sources: Biaggioni I. Orthostatic hypotension in the hypertensive patient. *Am J Hypertens*. 2018;31(12):1255–1259. doi:10.1093/ajh/hpy089; Salzman B. Gait and balance disorders in older adults. *Am Fam Physician*. 2010;82(1): 61–68. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694. doi:10.1111/jgs.15767.

Blood–Brain Barrier

The function and integrity of the interface between the brain and the body, the blood–brain barrier, may decline as a result of aging, disease, or ischemic injury.[25] An exaggerated response and increased sensitivity to some drugs that effect the central nervous system (CNS) may be seen as a result of changes in permeability of the blood–brain barrier and changes in receptor sensitivity in older adults.[26] Normal aging involves a reduction in cerebral blood flow and oxygen consumption and increased cerebrovascular resistance. Drugs with anticholinergic properties are associated with memory loss, confusion, cognitive impairments, and functional decline in older patients. Several examples of therapeutic classes with anticholinergic properties are listed in **Table 107-5**.

Table 107-5
Medication With Anticholinergic Properties

Therapeutic Class	Example

Therapeutic Class	Example
Antimuscarinics	Darifenacin Fesoterodine Flavoxate Oxybutynin Solifenacin Tolterodine Trospium
Antispasmodic	Atropine[a] Clidinium–chlordiazepoxide Dicyclomine Homatropine[a] Hyoscyamine Propantheline Scopolamine[a]
Antiparkinson	Benztropine Trihexyphenidyl
Antihistamine	Brompheniramine Chlorpheniramine Clemastine Dimenhydrinate Diphenhydramine Doxylamine Hydroxyzine HCl Meclizine
Antidepressant	Amitriptyline Clomipramine Desipramine Doxepin (>6 mg) Imipramine Nortriptyline Paroxetine Trimipramine
Antiarrhythmic	Disopyramide Quinidine
Antipsychotic	Clozapine Olanzapine Perphenazine Thioridazine Trifluoperazine

Therapeutic Class	Example
Hypnotic	Hydroxyzine pamoate
Skeletal muscle relaxant	Cyclobenzaprine Orphenadrine

This chart does not include all anticholinergic drugs that may cause confusion in older adults.

[a]Does not include ophthalmic.

Source: Adapted from the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694; Collamati A, Martone AM, Poscia A, et al. Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. *Aging Clin Exp Res*. 2016;28(1): 25–35. doi:10.1007/s40520-015-0359-7.

Both central responsiveness and peripheral responsiveness of adrenergic receptors decline with aging.[27] Monoamine oxidase activity increases with normal aging, and this is reflected by a decline in norepinephrine and dopamine levels in aging brains.[28,29] The decline in CNS dopamine synthesis is associated with increased sensitivity to dopamine-blocking agents (eg, antipsychotics). Because neurologic and biochemical reserves are reduced as a normal consequence of aging, iatrogenic behavioral disorders are relatively common in older adults, and drugs are one of the most common causes of sudden, unexplained mental impairment in the older adult.

PROBLEMS ASSOCIATED WITH DRUG USE IN OLDER ADULTS

Polypharmacy

Over half of all older adults carry three or more chronic diseases. This multimorbidity is associated with increased morbidity, mortality,

functional decline, health resource use, and multiple medication use.[30]

Multiple medication use is often synonymous with polypharmacy. *Polypharmacy*, however, can be variably defined as the use of more than one medication, as more than a specific or numeric threshold of medications (eg, five or more), or as “excessive” or “unnecessary” use of medication.[31] Polypharmacy is associated with multiple adverse health outcomes, including increased drug-related adverse events, functional impairment, institutionalization, hospitalization, health care costs, and mortality.[32] A thorough medication review is essential to identifying and addressing polypharmacy and subsequent medication-related problems in older adults.

Medication-Related Problems

Medication-related problems are defined as undesirable medication-related events experienced by patients[33] that may interfere with patient outcomes. These may include instances of intentional or unintentional medication underuse or overuse (eg, duplicative prescribing within the same drug class), use of potentially inappropriate or high-risk medications, drug interactions, and adverse drug events.

An adverse drug event includes preventable and nonpreventable events occurring from medication use and misuse and accounts for errors related to prescribing and administration.

Adverse events are common during transitions between care settings, and up to 31% of hospitalizations of older persons involve adverse drug events.[34] The use of potentially inappropriate, high-risk medications such as anticholinergics, antipsychotics, opiate analgesics, and hypnotics, along with polypharmacy, increases the risk of adverse drug events.[32],[35] Adverse drug events may be underreported and be difficult to detect in older patients because they often present atypically and with nonspecific symptoms, such as lethargy, confusion, lightheadedness, or falls. Such unrecognized adverse drug events may be treated with additional drugs, causing a

prescribing cascade that further increases polypharmacy and its risks. Nevertheless, most adverse reactions represent extensions of a drug's pharmacologic effect, have identifiable predictors, and are potentially preventable.[36] Nearly 1 in 25 community-dwelling older adults is potentially at risk for a major drug–drug interaction.[37] Careful medication regimen review (MRR) is essential to identify and systematically address potential medication-related problems in older adults.[38]

CASE 107-2

Question 1: T.M. is a 73-year-old female who comes to a "brown bag" session at the local senior center. She reports recently feeling "sluggish" and dizzy. She lives at home alone on a modest, fixed retirement income. T.M.'s chronic medical problems include coronary artery disease (CAD), HF, HTN, diabetes, and hyperlipidemia. She states that different specialists prescribe her "a lot of medications," but she does not know their names. She reports that she skips her medications periodically when she does not feel well. T.M. usually maintains an active social life; however, because of the recent weakness, she has not gone out as much. She is interested in natural medicines and self-medicates with nonprescription medications and herbal remedies. Review of her brown bag reveals the following: glipizide 2.5 mg twice daily, hydrochlorothiazide 25 mg daily, atenolol 50 mg daily, digoxin 0.25 mg daily, nitroglycerin (NTG) 0.4 mg sublingual (SL) as needed, ramipril 5 mg twice daily, furosemide 40 mg twice daily, metformin 500 mg twice daily, niacin ER 500 mg once daily, acetylsalicylic acid (ASA) 81 mg daily, acetaminophen 500 mg as needed, multivitamins with minerals, calcium carbonate 500 mg three times a day, coenzyme Q-10 90 mg daily, and ibuprofen 200 mg as needed. She also drinks a glass of red wine with dinner.

What initial steps are necessary for safe and effective management of T.M.'s drug therapy?

Like many ambulatory older patients who are being treated for multiple chronic medical conditions, T.M. is at high risk for medication-related problems secondary to nonadherence, medication errors, prescribing from multiple providers, self-medicating, and polypharmacy. She is representative of more than nine million older adults who live at home alone. The isolated community-dwelling older patient is typically female, age 75 years or

older, has multiple medical issues, and takes multiple medications.[1] With rising life expectancy, the increased complexity of managing multiple medical conditions has put nonhospitalized elderly individuals at higher risk of experiencing adverse drug reactions and for adverse drug-related admissions.[36] Another group of older individuals at higher risk of having adverse drug reactions are those who are recently discharged from the hospital. The postdischarge period is often a time of confusion, and older patients may have difficulty coping and sorting out new versus replacement or duplicate drugs. A summary of the various factors contributing to nonadherence in the older patient is presented in **Table 107-6**.[39]

Table 107-6
Factors Influencing the Inability to Adhere to a Medication Regimen

Low health literacy (understanding of medication instructions and importance)
Medication cost
Significant cognitive or physical impairment (eg, memory, hearing, vision)
Inconsistent filling or refilling of prescriptions
Adverse effects
Lack of clinical evidence of effectiveness

Source: Adapted from Bosworth HB, Granger BB, Mendys, et al. Medication adherence: a call for action. *Am Heart J*. 2011;162(3):412–424. © 2011 Elsevier. With permission.

T.M. needs a primary care provider to coordinate her medical care and to evaluate the new-onset sluggishness and dizziness. She should also be advised to establish a client–patient relationship at a specific pharmacy for all her medications to be on one profile for continuous assessment. Furthermore, T.M. should be counseled to discontinue alcohol, which can interact with several of her current medications and worsen her conditions. Finally, a comprehensive medication review with a pharmacist to identify and resolve existing and potential medication-related problems is highly recommended.

APPROACH TO APPROPRIATE PRESCRIBING AND DEPRESCRIBING

As a result of high rates of multimorbidity and polypharmacy, initiatives such as the American Board of Internal Medicines' Choosing Wisely Campaign have focused on the proactive avoidance of unnecessary tests, procedures, and medications, particularly among older adults.[40] Effective implementation of these initiatives is likely to require the input of interprofessional team members, including pharmacists. Deprescribing, the process of identifying and discontinuing medications where risks of continuing drug therapies may outweigh the benefits, has also been the focus of multiple initiatives. Effective deprescribing relies on a thorough understanding of patient characteristics as well as medication pharmacology and pharmacokinetics. As such, pharmacists have a critical role in both the conduct of a medication review and the deprescribing process.

DISEASE-SPECIFIC GERIATRIC DRUG THERAPY

Cardiovascular Disease in the Ambulatory Older Patient

Case 107-2, Question 2: T.M. presents to the multidisciplinary geriatric care team on the advice of pharmacists at the brown bag session. During the intake interview, she admits to selective adherence to medications based on how they make her feel and their costs. She reports that she has not taken her furosemide because she feels that it is contributing to her sluggishness and dizziness. Her wine intake with dinner is 8 to 12 ounces most days of the week. T.M.'s medical history and physical examination are as follows: 73-year-old White female, 66 inches (167.64 cm), 189 pounds (85.72 kg); vital signs are as follows: blood pressure (BP), 158/82 mm Hg; heart rate (HR), 54 beats/minute; temperature, 98.7 °F (37.05 °C); and respiratory rate, 18 breaths/minute. Pertinent laboratory values are as follows:

SCr, 1.3 mg/dL
Blood urea nitrogen, 35 mg/dL
Sodium, 153 mEq/L

Potassium, 3.4 mEq/L
Magnesium, 1.5 mEq/L
Glucose, 250 mg/dL
Glycated hemoglobin ($HgbA_{1c}$), 8.5%
Total cholesterol, 259 mg/dL
Low-density lipoprotein, 120 mg/dL
High-density lipoprotein, 40 mg/dL
Triglycerides, 200 mg/dL
Urine dipstick, 2+ protein
Digoxin level, 1.5 ng/mL

Electrocardiogram showed sinus bradycardia with an old anterior myocardial infarction (MI). Echocardiogram showed an ejection fraction (EF) of 35%. Her problem list includes new-onset sluggishness and fainting, chest pain and shortness of breath (SOB) on exertion, 3(+) pitting edema bilaterally, New York Heart Association (NYHA) classes II–III HF, HTN, type 2 diabetes, obesity, excessive alcohol intake, CAD, and hyperlipidemia. What factors may be contributing to T.M.'s feeling of sluggishness and dizziness?

T.M.'s sluggishness and dizziness are most likely caused by her low HR, somewhat dehydrated state, and multiple medications that have the potential for producing these symptoms.

Specifically, digoxin 0.25 mg daily is considered a high dose; 0.125 mg daily should be used as initial therapy in patients older than 70 years to limit the development of toxicities resulting from age-related decline in renal function. T.M.'s CrCl is reduced, nearing 45 mL/minute; this, combined with her low potassium level, may increase her risk of digoxin toxicity. Further, her digoxin level is elevated at 1.5 ng/mL (therapeutic range 0.5–0.9 ng/mL). Therefore, the digoxin dose should be lowered to 0.125 mg daily.[41] If HF symptoms remain stable on the reduced dose, a discontinuation trial may be warranted.

T.M.'s β-blocker may also contribute to her symptoms, particularly as atenolol is renally cleared. The β-blockers, such as carvedilol, metoprolol, and bisoprolol, have been proven to reduce morbidity and mortality in patients with HF and are clinically indicated.[42],[43] As such, T.M. should be switched to an equivalent dose β-blocker indicated for HF, such as extended-release metoprolol, which may further reduce T.M.'s medication burden. If fatigue and bradycardia

persist despite these changes and are not tolerable, the β-blocker therapy could be de-intensified after careful weighing of risks (eg, symptomatic bradycardia) and benefits (eg, mortality reduction) as well as patient-specific goals of care.

HEART FAILURE

Case 107-2, Question 3: What is appropriate management for T.M.'s stage of HF?

On the basis of T.M.'s history of an old MI evidencing structural heart disease, her low EF, and the presence of fluid-retention symptoms, T.M. is in stage C HF based upon the American College of Cardiology/American Heart Association classification scheme (see Chapter 14, Heart Failure). HF is a common cause of morbidity and mortality in older patients. The standard therapy for HF with reduced EF typically consists of ACE inhibitors or angiotensin-receptor blockers (ARBs) of target doses and specific β-blockers indicated for HF. In symptomatic patients, diuretics may be used for symptomatic relief, and an aldosterone antagonist for its morbidity and mortality benefits. In patients who remain symptomatic despite optimal therapy, guidelines recommend the use of sacubitril/valsartan in place of ACE inhibitors or ARBs to further reduce the risk of death and/or hospitalization.[42,43] Concurrent behavior modification with weight loss and salt restriction will also allow better control of HF.

Case 107-2, Question 4: In addition to the digoxin de-intensification and β-blocker adjustments mentioned earlier, what changes can be made to optimize T.M.'s therapeutic regimen for HF?

It was noted during T.M.'s brown bag medication review that she was taking both a loop and a thiazide diuretic—a therapeutic duplication. Such duplications may often be unintentional, occurring as a result of systematic failure to reconcile medications with patients, particularly during transitions of care. As loop diuretics are

generally more effective than thiazide diuretics in providing symptomatic relief, particularly in moderate-to-severe renal compromise, the thiazide should be discontinued.[44] Discontinuing the hydrochlorothiazide (HCTZ) will likely help with T.M.'s hypokalemia and slightly dehydrated state. Regular monitoring of SCr, urea nitrogen, sodium, and potassium is essential while on diuretics. Older adults may be particularly bothered by increased urination while taking diuretics. If this is a concern for T.M., she may be advised to take furosemide separate from social engagements. It may also be valuable to change T.M.'s twice-daily ramipril to a once-daily ACE inhibitor to reduce medication burden, particularly if T.M. is having difficulty managing her medications. Further, an aldosterone antagonist should be considered for T.M. to reduce the risk of hospitalizations in HF and to provide added BP control for T.M. If BP control can be achieved, transition from an ACE inhibitor to sacubitril/ valsartan would provide additional benefits mentioned earlier.

CARDIOVASCULAR DISEASE AND HYPERLIPIDEMIA

Case 107-2, Question 5: T.M. reports that she does not take her niacin ER 500 mg because she experiences facial flushing. Despite her history of MI, she does not believe that cholesterol and "heart disease" are major health concerns for a female who has lived to her age. What information can you provide her about cholesterol and the risk of cardiovascular disease (CVD) in patients like her?

Approximately two-thirds of CVD deaths occur in people age 75 years and older. For those age 60 to 79 years, the prevalence of CVD is ~70%; this rises to ~85% in those age 80 years and older. Although male sex is an independent risk factor for CVD, more females than males die from heart attacks because these events occur in females at an older age. The significantly higher rate of hypercholesterolemia in females seems also to predict a higher CVD risk than for males later in life. Therefore, it is important to treat dyslipidemia with a statin in most patients with clinical atherosclerotic

cardiovascular disease (ASCVD), in those age 40 to 75 years with diabetes who have low-density lipoprotein cholesterol (LDL-C) levels of 70 to 189 mg/dL, and in those without diabetes and an estimated 10-year ASCVD risk ≥7.5%.[45] In those older than 75 years, a clinical assessment and discussion of risks and benefits of therapy is warranted. Often, this entails continuation of statins in patients who are already taking and tolerating therapy unless functional decline, multimorbidity, frailty, or reduced life expectancy might limit benefits.

CASE 107-2, QUESTION 6: What is an optimal therapeutic plan for the management of T.M.'s hyperlipidemia?

T.M. is a 73-year-old female with a history of diabetes, with elevated cholesterol and BP conferring a 10-year ASCVD risk >7.5%. T.M.'s treatment plan should begin with lifestyle and dietary modifications. Based on her high ASCVD risk level and concomitant diabetes, a high-intensity statin should be started to lower LDL by at least 50%. However, the relative benefits of statin therapy should be weighed against the potential risk of adverse reactions, including dyspepsia, liver dysfunction, and muscle-related effects. Although rare, older adults, particularly the frail elderly with low body mass, may be at increased risk for muscle-related side effects. The hydrophilic statins, those with limited cytochrome P-450 metabolism, and those less effected by renal impairment may cause fewer side effects and drug interactions. These agents and those with long half-lives may also simplify administration for patients such as T.M. Finally, because alcohol can increase triglycerides, abstinence is strongly recommended.[46]

Clinical guidance for the care of adults older than 75 years with hyperlipidemia is limited by the lack of clinical trial data. Current guidelines[45] recommend for the continuation of currently tolerated statins as patients age, particularly for secondary prevention, as evidence generally supports their use through age 85.[47] If new statin initiation is required after age 74 years, a careful assessment of risk versus benefit is warranted, and guidelines recommend for

consideration of moderate- to high-intensity statins in secondary prevention. The evidence supporting the use of statins for primary prevention in this age group largely depends on patient-specific factors, including medical conditions, such as the presence of high cardiovascular risk or vascular dementia, functional status, and overall prognosis.

Case 107-2, Question 7: What other interventions should be implemented to optimize the management of T.M.'s CAD?

Any strategy to optimize the management of T.M.'s CAD should take into consideration the patient's functional status, comorbidities, and risks versus benefits. β-Blockers and ACE inhibitors are indicated in patients who have CAD and HF to prevent further ventricular remodeling. As such, the aforementioned changes to T.M.'s β-blocker and ACE inhibitor should be implemented.

In addition, statins should be utilized in CAD to prevent further endothelial injury from atherosclerosis and plaque rupture.

HYPERTENSION

Case 107-2, Question 8: T.M. has uncontrolled HTN. How should this be managed in light of her advanced age?

Despite her advancing age, T.M.'s BP is well above the goal of <130/80 as recommended for noninstitutionalized, ambulatory, community-dwelling older adults by the 2017 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines for High Blood Pressure in adults.[48] HTN is present in more than two-thirds of individuals older than 65 years. Despite having the highest prevalence of HTN, only half of those age 60 years and older are adequately controlled.[49] Uncontrolled BP[48] in this population contributes to morbidity, mortality, as well as premature disability and institutionalization. Numerous clinical trials have demonstrated significant benefits to BP lowering in ambulatory

older adults like T.M. Serious side effects of aggressive BP lowering include orthostatic hypotension, bradycardia, acute kidney injury, and hypokalemia; these effects must be diligently monitored during titrations. In older adults with a high burden of comorbidity or limited life expectancy, a patient-centered approach to goal setting is warranted.

For T.M., it is recommended that adequate doses of furosemide and an ACE inhibitor or ARB with close monitoring be the main therapeutic approach for her HTN. Extended- or controlled-release formulations of metoprolol or carvedilol should be considered for HF management. As it appears additional BP control will likely be warranted, the use of an aldosterone antagonist should be considered in light of her HF stage. If an aldosterone antagonist is added, careful monitoring of renal function and potassium will be necessary to avoid an adverse drug event with her remaining medications.

Diabetes in the Older Adult

Case 107-2, Question 9: T.M. reports that she frequently feels lightheaded and shaky after she takes the glipizide and wonders if her A_{1C} is too low. What is an optimal therapeutic plan for the management of T.M.'s diabetes?

Healthy older adults with few coexisting chronic illnesses and intact cognitive function and functional status should have an A_{1C} target of 7% to 7.5%, whereas those with multiple coexisting chronic illnesses, mild-moderate cognitive impairment, or impairment in two or more IADLs should aim for an A_{1C} goal of 7.5% to 8%. Those with very complex or poor health, such as those with long-term or end-stage chronic illness, moderate-severe cognitive impairment, or impairment in two or more ADLs should have an A_{1C} goal of 8% to 8.5%.[50,51] In light of T.M.'s intact cognitive and functional status, as well as limited coexisting chronic illnesses, her A_{1C} target should be 7% to 7.5%.

Management of T.M.'s diabetes should include comprehensive diabetes education, focusing on the importance of weight loss, self-monitoring of blood glucose, alcohol abstinence, and medication adherence. T.M.'s alcohol consumption and self-reported erratic meal schedule may be contributing to the hypoglycemia as well as to the worsening of her HTN and HF. Glipizide is a second-generation sulfonylurea that carries a lower risk of hypoglycemia than first generation, more renal-dependent sulfonylureas. However, older adults are more susceptible to hypoglycemia even at low doses and may have difficulty recognizing the symptoms. As such, the glipizide should be discontinued.

Metformin is the preferred, initial pharmacologic agent for the management of diabetes.[51] Considering T.M.'s renal decline, her metformin should be continued at the reduced dose of 500 mg twice daily. If adequate glycemic control is not maintained on metformin alone, patients should be assessed for clinical ASCVD, HF, chronic kidney disease (CKD), and/or indicators of high ASCVD risk. If present, therapy such as glucagon-like peptide 1 receptor agonists (GLP1-Ras) or sodium glucose cotransport 2 inhibitors (SGLT2i) with proven ASCVD, HF, or CKD benefits should be utilized. For both of these classes of agents, the propensity for hypoglycemia is low and may be favorable in high-risk older adults like T.M. The use of SGLT2i in older adults may be limited by their renal dosing limitations, increase in urinary volume, and potential for hypovolemia and hypotension. T.M.'s current kidney function precludes the use of an SGLT2i. T.M. may benefit, however, from the use of a GLP1-Ra with proven CVD benefit, such as liraglutide, dulaglutide, or semaglutide. As liraglutide may additionally confer a reduction in progression of CKD, this would be an ideal agent to select for T.M. The dosage should be titrated, and T.M. should be monitored for adverse GI events, such as nausea, diarrhea, and reduced appetite.

Depression and the Older Patient

Depression is one of the most prevalent mental disorders in older adults and occurs in ~7% to 15% of those age 60 years and older.[52,53] Depression is often overlooked and may be underreported because many people are not comfortable discussing depression, even though it is a major risk factor for suicide. Older patients may be at increased risk for depression because of the high prevalence of comorbid medical conditions (eg, stroke, cancer, MI, rheumatoid arthritis, dementia, Parkinson disease, diabetes mellitus [DM]).[54] They also may experience depression because of the death of a spouse, social isolation, loss of independence, functional, or cognitive decline.[55] (See Chapter 86, Depressive Disorders for further discussion of risk factors for depression and potential drug-induced causes.)

CASE 107-3

Question 1: J.W. is a 79-year-old female who is married, 68 inches (172.72 cm), 110 pounds (49.89 kg). She presents for a psychiatric evaluation. Her husband says she just has not been herself lately. The changes in J.W. began on a family vacation 6 months earlier when she got lost on the cruise ship. Since that incident, she has become increasingly anxious and has developed insomnia. Although she does not feel sad or "depressed," she generally does not feel well. J.W.'s normally positive attitude toward life has become pessimistic. Her husband confirms that she has become more forgetful and no longer enjoys eating. In fact, she has lost 18 pounds (8.16 kg) during the past 2 months. J.W. no longer does her volunteer work at the local children's center. She says she wants to die because she is no longer the person she used to be, but she denies having any specific suicidal thoughts. Her medical history is significant for diabetes and HTN, which are both well controlled on glipizide 5 mg every morning and hydrochlorothiazide 25 mg daily. Her medical evaluation and physical examination are unremarkable. Laboratory results and head computed tomography scan are within normal limits. J.W. is diagnosed as having a major depressive episode.

What symptoms of depression are present in J.W.?

J.W.'s presenting symptoms are typical of major depression in an older patient, which is commonly quite different from that of younger patients with depression. Criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, for diagnosing

depression were developed using younger subjects and may not be applicable to the older patient with depression.[54] Older patients are less likely to report suicidal thoughts but are more likely to experience weight loss as a symptom of depression. Anxiety, irritability, somatic problems, or a withdrawal from normal activities, as exhibited by J.W., may be more significant features in late life depression than depressed mood. Memory problems, such as J.W.'s forgetfulness, may be attributable to a lack of concentration or effort stemming from her depression. This is distinct from dementia, which manifests itself predominantly with impairment in short- and long-term memory (see Chapter 108, Geriatric Neurocognitive Disorders). Therefore, depressed mood cannot be relied on for determining whether an older patient has a depressive disorder.[55] **Table 107-7** lists atypical depressive symptoms that may be found in older adults. The presence of any one of these symptoms should be considered a red flag and should prompt further evaluation for major depression.

Table 107-7
Atypical Depressive Symptoms in Older Adults

Cognitive changes
Fatigue
Pain
Refusal to eat or drink
Refusal to take medication
Self-care changes
Social withdrawal
Weight loss

Source: Kok RM, Reynolds CF. Management of depression in older adults: a review. *JAMA*. 2017;317(20):2114–2122. doi:10.1001/jama.2017.5706.

CASE 107-3, QUESTION 2: J.W.'s physician decides to prescribe an antidepressant. Which antidepressants are preferred for use in older adults?

Selection of an antidepressant drug for an older adult must take into consideration age-related changes in pharmacokinetic, pharmacodynamic, and physiologic parameters that make this population more vulnerable to adverse effects. Although the available antidepressants are equally effective, selective serotonin reuptake inhibitors (SSRIs) are better tolerated than older agents, such as the tricyclic antidepressants. Therefore, low-dose SSRIs should be considered a first-line therapy for older patients. Previous recommendations were to start citalopram; however, doses of citalopram over 20 mg daily are not recommended because of the risk of QTc prolongation in adults older than 60 years.[56] Of course, this does not preclude the use of sound clinical judgment that incorporates the patient's history of response, comorbidities, and the drug's side-effect profile. J.W. should start taking an SSRI, such as escitalopram 10 mg daily.[57] Alternatives include sertraline or duloxetine, a serotonin–norepinephrine reuptake inhibitor (SNRI). If J.W. has minimal or no response to escitalopram, her therapy should be switched to duloxetine, venlafaxine, or desvenlafaxine as alternatives. It may take 8 to 12 weeks before assessment of J.W.'s full response can be made.[58] There is limited evidence on how long an older adult should continue therapy; however, continuing treatment for 1 year may decrease the risk of depressive symptoms returning.[53] J.W. should be assessed periodically for efficacy of treatment and adverse effects.

Asthma and Chronic Obstructive Pulmonary Disease in the Older Adult

The prevalence of asthma in adults age 65 years and older is estimated to be 7.8%, and 62.9% of these patients are considered uncontrolled.[59],[60] Older adult rates of asthma-related hospitalization and mortality are high, possibly because of underdiagnosis and undertreatment of the disease.[61] Symptoms of asthma, including wheezing, cough, chest tightness, and dyspnea, are similar in both older and younger patients (see Chapter 18, Asthma). However,

because the older adult is more likely to have coexisting medical conditions (eg, HF, angina, chronic obstructive pulmonary disease [COPD], gastroesophageal reflux disease [GERD]) with symptoms that mimic asthma, accurate diagnosis and assessment of severity is often difficult.[62]

COPD is largely a disease of older patients with a prevalence of as high as 11.2% in those age 75 years and older.[63] It is the fourth leading cause of death in the world.[64] This chronic condition is a major cause of morbidity and mortality in the older population and is often undiagnosed as it may be mistaken as a "normal" part of the aging process and may be confounded by physical deconditioning or comorbidities such as HF.[65] Drug therapy for COPD in the older adult does not differ significantly from standard management regimens (see Chapter 19, Chronic Obstructive Pulmonary Disease). Factors associated with aging such as changes in vision, hearing, and comorbid conditions are associated with poor adherence to medication regimens. Older adults may also be more sensitive to adverse effects of pharmacologic agents.

CASE 107-4

Question 1: J.C., a 67-year-old female, 66 inches (167.64 cm), 145 pounds (65.77 kg), presents to the ED with SOB for the past 2 days. She was in her usual state of health until 4 days ago when she exhibited flu-like symptoms consisting of fever, cough, and mild wheezing. J.C. has a history of asthma, diabetes, HTN, headache, and GERD. Her current medications include glipizide 5 mg daily, lisinopril 10 mg daily, metoprolol 50 mg twice daily, lansoprazole 30 mg daily, ibuprofen 200 mg every 6 hours as needed for headache, albuterol metered-dose inhaler (MDI) 2 inhalations four times a day as needed for SOB, and fluticasone DPI (100 µg) 1 inhalation twice daily. Her drug regimen has been unchanged for the past 2 years, and she reports taking all medications as prescribed. The only recent change has been the need for albuterol every 3 to 4 hours for coughing and wheezing during the past few days.

What factors (including medications) may have contributed to her acute asthma exacerbation?

Management of acute asthma exacerbations in previously stable older adults with asthma should begin with a review of the

medication history for asthma-inducing agents. Aspirin and other NSAIDs are known to induce acute bronchoconstriction in adults with asthma.[66] J.C. should be queried about her previous (especially recent) use of ibuprofen in relation to her asthma symptoms, and these agents should be avoided if associated. An alternative agent for pain control is acetaminophen. Nonselective β-blockers, including topical ophthalmic formulations, can precipitate acute bronchoconstriction and should be avoided in patients with reactive airway disease.[67] Although cardioselective β-blockers are generally considered safe for use in patients with asthma, it is important to recognize that cardioselectivity may be lost with higher dosages. Because J.C. has been taking low-dose metoprolol (a cardioselective agent) for years without problem, this medication is unlikely to be contributing to her current asthma exacerbation. One of the most important triggers for asthma exacerbations is respiratory infection, particularly viral. J.C. reports the recent onset of symptoms consistent with influenza, and this is likely precipitating her current pulmonary symptoms. As a future prophylactic measure, J.C. should be counseled to receive the influenza vaccine annually. J.C. does not recall ever receiving the pneumococcal vaccine. In adults age 65 years and older who are not immunocompromised, and who have never received the pneumococcal vaccine, or who are unsure like J.C., they should receive one dose of the pneumococcal polysaccharide vaccine (PPSV23).[68] (See Chapter 64, Vaccinations.)

Case 107-4, Question 2: Are the medication regimens used to treat asthma in older adults different from those used in children and younger adults? Should J.C.'s maintenance of asthma regimen be changed?

Medications used in the management of persistent asthma in older adults are similar to those used in younger patients and consist of bronchodilators in combination with anti-inflammatory agents (see Chapter 18, Asthma). Drug selection and monitoring may be more complicated because of the greater likelihood of coexisting medical

conditions and increased potential for drug–disease and drug–drug interactions.

Inhaled β_2-agonists are an important class of drugs used to treat asthma in all age groups. The low incidence of drug interactions and reduced side-effect profile make inhaled β_2-agonists ideal for use in the older adults with asthma. However, these agents can cause dose-dependent systemic side effects, such as tremor, tachycardia, hypokalemia, and arrhythmias, which are of particular concern in patients with cardiac conditions.[67] Inhaled corticosteroids are the preferred treatment for all forms of persistent asthma, yet they may be underused in the older adult. Though generally well tolerated, older adult patients receiving high-dose therapy are at an increased risk for osteoporosis, cataracts, skin thinning, and bruising.[69] In addition to the well-known complications associated with systemic corticosteroid use (see Chapter 44, Rheumatoid Arthritis), these agents can acutely cause confusion, agitation, and hyperglycemia.

J.C. is currently maintained on low doses of an inhaled corticosteroid (fluticasone) in combination with a short-acting β_2-agonist (albuterol), and this is an appropriate regimen for a patient with mild persistent asthma. Following resolution of her viral infection, J.C.'s asthma control should be reevaluated within the next 3 months for a step-up or step-down in therapy. Because J.C. is postmenopausal, she is at risk for osteoporosis; calcium and vitamin D supplementation should be initiated (see Chapter 110, Osteoporosis).

Appropriate use of inhalers is difficult for most patients but may be particularly problematic in the older adults because of decreased hand strength or arthritis, difficulty actuation timing to inhalation, or impaired mental function. The use of spacer or holding chamber devices may minimize the coordination necessary for proper use of an MDI and may reduce the incidence of systemic and local (cough, hoarseness, thrush) side effects associated with inhaled corticosteroids. J.C. is using a DPI, and even though J.C. previously used a DPI, she should be asked to demonstrate her technique and reinstructed, if necessary, to ensure she is using the inhaler correctly.

If J.C. is unable to use her inhaler appropriately, use of nebulized solutions may be considered.

Infectious Diseases in the Older Adult

Infections are among the most common problems in older adults and are a significant cause of morbidity and mortality.[70] Infections are also one of the most frequent reasons for hospitalization of older ambulatory persons. Antibiotic therapy for an infection in older adults may be delayed because they may present with atypical or nonspecific signs and symptoms. The older population is also more likely to have polymicrobial infections than younger people, and changes in renal function should be taken into account when selecting, dosing, and monitoring antibiotic therapy.

PNEUMONIA

Case 107-4, Question 3: J.C. was admitted to the hospital and given IV methylprednisolone for 4 days. She was then discharged home with a new prescription for prednisone 40 mg daily for 7 days. Three days after J.C. was discharged from the hospital, she presented again to the ED. She was accompanied by a neighbor who noted that J.C. suddenly became forgetful and confused and continues to have difficulty breathing. Her neighbor reports that J.C. has been staying in bed for the past 2 days and has not eaten much. J.C. has a low-grade fever, and chest examination reveals faint breath sounds with light crackling rales over her right lung base. A chest radiograph confirms the diagnosis of pneumonia. How is J.C.'s clinical presentation consistent with community-acquired pneumonia (CAP) in the older adult?

CAP is the most prevalent cause of sepsis worldwide[71] and one of the leading causes of hospitalization and death due to infection in adults in the United States.[72] In a large population-based study of CAP, adults age 65 to 79 years were found to have an incidence of pneumonia requiring hospitalization that was nine times as high as those age 18 to 49 years and 25 times as high in those age 85 years and older.

Risk factors for CAP in all adults include age greater than 65 years, COPD, smoking, alcoholism, aspiration, and chronic medical conditions such as heart, renal, and liver disease.[73],[74] *Streptococcus pneumoniae* is the most common cause of CAP in the older adult.[71]

Respiratory symptoms and fever are often subtle or absent in older patients with pneumonia, and instead, like J.C., they may present only with altered mental status (delirium, acute confusion, memory problems) or a decline in functional status. Delirium or acute confusion is a common presentation in older patients who may have new-onset lower respiratory infection.

CASE 107-4, QUESTION 4: How should J.C. be treated for her respiratory infection?

In many cases, management of pneumonia in the older adult requires hospitalization because they are at higher risk for mortality and complications. Early empiric antibacterial therapy is particularly important for older patients with pneumonia (see Chapter 67, Respiratory Tract Infections). J.C. should be hospitalized again and treated aggressively for pneumonia with broad-spectrum IV antibiotics. The Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults recommends treatment of most hospitalized nonintensive care unit (ICU) patients with a combination of B-lactam (ampicillin + sulbactam, cefotaxime, ceftriaxone, or ceftaroline) and a macrolide (azithromycin or clarithromycin) or a respiratory fluoroquinolone (levofloxacin or moxifloxacin).[75]

PREVENTION

CASE 107-4, QUESTION 5: After 3 days of hospitalization, J.C. is clinically stable and discharged home with an oral antibiotic. J.C. should be treated for a minimum of 5 days and be afebrile for 48 to 72 hours before the antibiotic is discontinued. What preventative measures are available to J.C. after being discharged?

Once patients are stable and ready to be discharged home, they should be switched to oral antibiotics to complete their therapy at home.

Both influenza and pneumococcal vaccinations are beneficial and recommended in the prevention of CAP.[76,77]

The Centers for Disease Control and Prevention (CDC) recommends pneumococcal conjugate vaccine (PCV13) in patients age 65 years and older with immunocompromised conditions, cerebrospinal fluid (CSF) leaks, or cochlear implants. For patients who are not immunocompromised such as J.C., one dose of PPSV23 is recommended at age 65 years and older at least 5 years after their first dose (see Chapter 64, Vaccinations).

J.C.'s immunization status should be confirmed, and as a preventative measure, J.C. should be offered both influenza and pneumococcal vaccines upon discharge.

URINARY TRACT INFECTION

CASE 107-5

Question 1: A.H. is a 72-year-old Hispanic female who is currently wheelchair-bound because of pain in her right hip. Her granddaughter brings A.H. to the geriatric clinic because she has recently developed urinary incontinence. She has a documented allergy to "sulfa." Her granddaughter reports that A.H. has been feeling weak for the past 2 days and fell while getting out of the wheelchair. A urinalysis indicates the presence of a urinary tract infection (UTI).

Are A.H.'s symptoms typical of UTIs?

UTIs are common in older patients and represent 25% of all infections in this population.[78] Clinical symptoms often vary from patient to patient making diagnosing UTIs more difficult and may include dysuria, hematuria, urinary frequency, urinary incontinence, pyuria, and fever.[79,80] Some older patients may present with delirium or sudden changes in mental status, confusion, or falls.[81] Bacteriuria is often asymptomatic in older adults, or patients may have nonspecific symptoms. The prevalence of asymptomatic bacteriuria

for those age 70 years and older ranges from 3.6% to 50%, being the highest in long-term care, and may not always require antibiotic treatment.[81] Impaired voiding with residual urine in older females and obstructive uropathy from prostatic disease in older males predispose them to bacteriuria.[82] The severity of UTIs in the older population ranges from mild cystitis to life-threatening urosepsis, and both are more difficult to treat because of resistant organisms and age-related decreases in host defenses.

A.H.'s presentation of weakness, urinary incontinence, and a recent fall is a consistent pattern of nonspecific symptoms, and a urinalysis confirmed a UTI. Major pathogens in those older than 65 years with uncomplicated cystitis are include *Escherichia coli*, *Klebsiella oxytoca*, and *Proteus mirabilis*[78] (see Chapter 71, Urinary Tract Infections).

Case 107-5, Question 2: A.H. is prescribed a 7-day course of ciprofloxacin 250 mg po twice daily. Is this drug therapy appropriate?

Oral antibiotics, such as nitrofurantoin and sulfamethoxazole–trimethoprim, are appropriate for most patients with symptomatic UTI, reserving fluoroquinolones as alternatives when patients cannot tolerate or are allergic to the standard treatment.[83] An important consideration of antibiotic therapy for older adults with UTI is impaired renal function. Nitrofurantoin should not be used in those patients with CrCl <30 mL/minute due to the potential of peripheral neuropathy, hepatic toxicity, and pulmonary toxicity.[24]

Ciprofloxacin is a reasonable choice for A.H. because she is allergic to sulfa and *E. coli* is the most likely causative agent. Fluoroquinolones carry a black box warning because of the risk of serious adverse reactions that include tendinitis, tendon rupture, peripheral neuropathy, and CNS effects (seizures, increased intracranial pressure, dizziness, and tremors).[84] Along with renal function, monitoring should include symptoms of tendon inflammation or pain and changes in mental status.[85]

Osteoarthritis

Osteoarthritis affects about 302 million people worldwide and ~54.4 million people in the United States.[86],[87] Osteoarthritis may lead to decreased mobility, falls, and loss of independence in older adults.[87] Nonpharmacologic management of osteoarthritis, such as physical and occupational therapy, weight loss in patients who are overweight and obese, and exercise, is recommended to decrease pain and improve function, either alone or in combination with appropriate analgesics.[86]

CASE 107-6

Question 1: C.W., a 71-year-old retired schoolteacher, has been suffering from mild osteoarthritis of his hands for 5 years. He is an active older adult who enjoys volunteer work at the local hospital. He presents to the geriatric clinic with increased heartburn and gastric reflux symptoms. His past medical history is significant for diabetes, HTN, hypercholesterolemia, and GERD. C.W.'s current medications include glipizide 10 mg daily, verapamil sustained-released 240 mg daily, atorvastatin 10 mg daily, famotidine 20 mg twice daily, docusate sodium 100 mg twice daily, and ibuprofen 200 mg four times a day as needed.

What modifications can be made to his drug regimen to control his arthritis pain and minimize side effects from his pain medication?

Acetaminophen and/or over-the-counter (OTC) NSAIDs are the first-line therapies for mild-to-moderate arthritis pain.[86] Though pain control with acetaminophen may be inferior to NSAIDs, its reduced GI and renal toxicity provides an advantage in older patients who may be more susceptible to the adverse effects of NSAIDs. Doses of acetaminophen should not exceed 3 g a day in older adults,[86] and, in those with a history of alcohol misuse or hepatic impairment, the American Geriatric Society recommends reducing the maximum daily dose by 50% to 75%.[88] If C.W. has not tried acetaminophen in the past for his arthritis pain, acetaminophen 325 to 500 mg every 4 hours or 500 to 1000 mg every 6 hours, not to exceed 3 g a day, may be initiated. Older patients with osteoarthritis pain often find relief from NSAIDs, which should be used with caution because of their potential GI complications, renal toxicity, and cardiovascular

risks. Topical NSAIDs are recommended before starting oral NSAIDs.[86] Advanced age is a major risk factor for NSAID-associated renal toxicity, such as sodium and water retention, as well as risk for HTN.[89] Thus, ibuprofen may be contributing to C.W.'s increased GERD symptoms and to his HTN.

Case 107-6, Question 2: C.W. reveals that he has tried acetaminophen without much relief of his pain. What other pain medication options does C.W. have?

If acetaminophen is not effective, the 2019 American College of Rheumatology/Arthritis Foundation Guidelines for Osteoarthritis of the Hand recommend a topical NSAID as the next step of treatment.[86] C.W. could be started on diclofenac 1% gel to be applied topically. For osteoarthritis of the hands, the usual adult dose is 2 g (2.25 inches) four times a day.[90] The maximum dose is 32 g daily over all joints and 8 g to any single joint.

For patients with moderate-to-severe chronic pain caused by osteoarthritis, a low-dose opiate may provide relief from pain with minimal adverse drug effects (see Chapter 55, Pain and Its Management). Of particular concern in older adults are the risks of falls, delirium, and constipation with opioid medication use. Codeine and tramadol are "weak" opioids that have ceiling effects, generally do not provide adequate analgesia, and may carry dangerous side effects in the older adult. Meperidine should also be avoided in older adults because of its high potential for CNS side effects, especially in those with reduced renal function.

LONG-TERM CARE FACILITIES

The LTCF environment is governed in part by the Omnibus Budget Reconciliation Act (OBRA), as well as by numerous other laws and regulations, which are contained in the federal Centers for Medicare and Medicaid Services (CMS) publication, States Operations Manual

(SOM).[91] The federal mandates include a monthly MRR by a pharmacist of each resident's medical record to help ensure each resident's regimen is free from unnecessary drugs and that their medication regimen helps to support their mental, physical, and psychosocial well-being. Medication regimens are reviewed to determine the following:

1. Is each medication clearly indicated?
2. Have therapeutic goals been established for chronic drug therapies?
3. If indicated, is each medication being dosed and administered appropriately?
4. Are any real or potential problems with medication side effects or interactions present?
5. If psychotropics are being prescribed, have nonpharmacologic approaches been used first? Has their use been justified? Is the therapy being monitored for gradual dose reductions unless clinically contraindicated?
6. What specific recommendations can be made to optimize the resident's drug therapy?
7. Are the laboratory results and vital signs being monitored appropriately, and are they available for adequate evaluation of therapy?

The pharmacist identifies and reports any irregularities, including medication discrepancies, errors, and adverse drug reactions in a written report to the attending physician, medical director, and director of nursing, and includes recommendations to help optimize therapy. The physician must respond to recommendations made by the pharmacist in a timely manner. The American Society of Consultant Pharmacists publishes detailed information concerning standards of practice in the LTCF environment.[92]

CASE 107-7

Question 1: As a new consultant pharmacist to a 60-bed, LTCF, several multiple drug use problems become apparent during an initial MRR for D.M., an 82-year-old male who has resided there for the past month. D.M.'s past medical history is significant for HTN, depression, constipation, long-standing mild cognitive impairment that is now worsening, and dizziness. In the nurses' notes, it is documented that D.M. had a fall when getting out of bed last week.

At admission, D.M.'s weight was 165 pounds (74.84 kg), BP 100/60 mm Hg, pulse 85 beats/minute, and temperature 98.6 °F (37 °C). Subsequent vital signs are not recorded systematically into his medical record. Sporadic documentation in the nurses' notes indicates little change from admission values. No laboratory information is available at this time. D.M. has no known allergies.

Current medications include amlodipine 10 mg daily, diltiazem CD 240 mg daily, hydrochlorothiazide 25 mg daily, quetiapine 300 mg daily, lorazepam 0.5 mg every 8 hours as needed for anxiety, docusate sodium 100 mg twice daily, milk of magnesia 30 mL daily, temazepam 15 mg at bedtime, and acetaminophen one to two 325-mg tablets every 4 to 6 hours as needed for pain. D.M. follows a 2-g sodium diet.

D.M. is ambulatory and takes his meals in the facility's dining room. He is not in any acute distress, but the nurses' notes indicate that D.M. is often confused and has dizziness when ambulating. His weight has decreased 4 pounds (1.81 kg) since being admitted.

What should be expected of this LTCF with respect to medication monitoring?

Under the CMS-mandated regulations, the establishment of goals of antihypertensive therapy and monitoring for these goals are required. D.M.'s BP should be measured and documented in his medical record with a signature and date on a regular basis. D.M.'s dizziness, a symptom of orthostatic HTN, may be caused by overtreatment of his HTN as evidenced by his low admission BP. Orthostatic HTN is most common when patients first arise, indicating that this may have been the cause of D.M.'s recent fall.[22] D.M. is being treated with two calcium channel blockers. Discontinuation of one of them may reduce his dizziness and help prevent future falls. Because D.M. is being treated with a diuretic, monitoring should include a chemistry panel for electrolyte abnormalities.

Case 107-7, Question 2: What changes should be made to D.M.'s medication regimen?

In the admission workup, D.M. was described as having a long-standing history of mild cognitive impairment, but subsequent nursing notes suggest that his symptoms of disorientation and confusion worsened quickly after admission. Chronic dementia is not normally characterized by rapid deterioration of mental acuity (see Chapter 108, Geriatric Neurocognitive Disorders). This should raise the suspicion that a reversible factor could be responsible for D.M.'s mental decline. Potentially inappropriate drug use in older adults living in the community and in long-term care is well documented.[93],[94] The cognitive impairment of chronic degenerative dementia can be greatly exaggerated by D.M.'s treatment with lorazepam, temazepam, and quetiapine, especially with higher than recommended dosages.[95],[96] Benzodiazepines may also increase the risk of falls and bone fractures in the geriatric population. The use of antipsychotic agents without a psychiatric diagnosis is only appropriate in nursing homes if the resident's behavior is considered to be a danger to themselves or others (including staff), impairing the patient's daily functioning, interfering with the staff's ability to care for them, or causing distress to the patient (ie, frightening hallucinations).[91] Antipsychotics may be unnecessarily prescribed for anxiety, insomnia, confusion, or failure to conform to the institution's standards for behavior. They carry a black box warning and have been shown to be associated with a 1.7-fold increased risk of all-cause mortality in older adults with dementia compared with nonusers.[97] Antipsychotics are not indicated to treat behaviors in older adults with dementia. Primary reasons for death were HF, sudden cardiac death, or pneumonia. Federal regulations require that these drugs be used for a specified condition, at the lowest possible dosage, and for the shortest possible duration. Regulations also mandate tapering of doses and careful documentation of all clinical assessments that justify the ongoing need for antipsychotics.[91]

In light of the atypical deterioration of D.M.'s cognitive function, the doses of all psychotropic medications should be gradually tapered down to the lowest effective dose and/or discontinued if appropriate. It may not be appropriate to make multiple changes all at once;

however, a plan should be developed to target the medications that are likely responsible for D.M.'s decline in mental status. A baseline assessment of D.M.'s cognitive function and psychiatric status should be performed by a geriatrician, psychiatrist, or clinical psychologist to establish the presence or absence of psychotic behavioral disturbances or depression. If any of these disorders are present, then each should be managed with appropriate nonpharmacologic interventions and drug therapy that includes appropriate therapeutic doses and duration of treatment.

The American Geriatrics Society (AGS) updated the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults in 2019.[24] This evidence-based review outlines medications that may lead to adverse events in all adults older than 65 years. It is intended to be used as a tool to help reduce adverse effects from potentially inappropriate medication. Other helpful tools available include the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) and Screening Tool to Alert Doctors to Right Treatment (START) criteria.[98] The combined use of these tools along with clinical judgment is meant to guide clinicians in drug selection, help decrease exposure to medications that may increase the risk of adverse drug events, and support the safe medication therapy of older adults.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. The following are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

Administration on Aging, Administration for Community Living, U.S. Department of Health and Human Services. *2019 Profile of Older Americans*. 2020:26. (2)

American Diabetes Association. Older Adults: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(suppl 1):S152–S162. doi:10.2337/dc20-S012 (51)

By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694. doi:10.1111/jgs.15767 (24)

Federal Interagency Forum on Aging-Related Statistics. *Older Americans 2016: Key Indicators of Well-Being.* CreateSpace Independent Publishing Platform; 2016. (1)

Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention, 2020.* 211. www.ginasthma.org (69)

Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020 Report*. 141. Accessed October 2, 2020. www.goldcopd.org (64)

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082–e1143. doi:10.1161/CIR.0000000000000625 (45)

Guiding principles for the care of older adults with multimorbidity: an approach for clinicians: American Geriatrics Society Expert Panel on the Care of Older Adults With Multimorbidity. *J Am Geriatr Soc*. 2012;60(10):E1–E25. doi:10.1111/j.1532–5415.2012.04188.x (30)

Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129–2200. doi:10.1093/eurheartj/ehw128 (42)

Key Websites

American Geriatrics Society. https://www.americangeriatrics.org

American Society of Consultant Pharmacists. https://www.ascp.com

American Heart Association. https://www.heart.org

Centers for Disease Control and Prevention. https://www.cdc.gov

COMPLETE REFERENCES CHAPTER 107 GERIATRIC DRUG USE

1. Federal Interagency Forum on Aging-Related Statistics. *Older Americans 2016: Key Indicators of Well-Being*. U.S. Government Printing Office; 2016. Accessed March 30,2021. https://agingstats.gov/docs/LatestReport/Older-Americans-2016-Key-Indicators-of-WellBeing.pdf
2. Administration on Aging, Administration for Community Living, U.S. Department of Health and Human Services. 2019 Profile of Older Americans. 2020:26.
3. Centers for Medicare & Medicaid Services. Prospective Payment Systems—General Information. Published August 5, 2020. Accessed September 23, 2020. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ProspMedicareFeeSvcPmtGen
4. Hastert JD. H.R.1—Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Published December 8, 2003. Accessed September 23, 2020. https://www.congress.gov/bill/108th-congress/house-bill/1
5. Park YJ, Martin EG. Medicare part D's effects on drug utilization and out-of-pocket costs: a systematic review. *Health Serv Res*. 2017;52(5):1685–1728. doi:10.1111/ 1475-6773.12534
6. Perrie Y, Badhan RKS, Kirby DJ, Lowry D, Mohammed AR, Ouyang D. The impact of ageing on the barriers to drug delivery. *J Control Release*. 2012;161(2):389–398. doi:10.1016/j.jconrel.2012.01.020
7. Kane RL, Shamliyan T, Talley K, Pacala J. The association between geriatric syndromes and survival. *J Am Geriatr Soc*. 2012;60(5):896–904. doi:10.1111/j .1532-5415.2012.03942.x
8. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev*. 2009;41(2):67–76. doi:10.1080/03602530902722679
9. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab*. 2011;12(7):601–610.
10. Kaestli L-Z, Wasilewski-Rasca A-F, Bonnabry P, Vogt-Ferrier N. Use of transdermal drug formulations in the elderly. *Drugs Aging*. 2008;25(4):269–280.
11. Rudy DW, Voelker JR, Greene PK, Esparza FA, Brater DC. Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med*. 1991;115(5):360–366.
12. Aymanns C, Keller F, Maus S, Hartmann B, Czock D. Review on pharmacokinetics and pharmacodynamics and the aging kidney. *Clin J Am Soc Nephrol*. 2010;5(2):314–327. doi:10.2215/CJN.03960609

13. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. *Curr Med Chem*. 2010;17(6):571–584
14. Greenblatt DJ. Reduced serum albumin concentration in the elderly: a report from the Boston Collaborative Drug Surveillance Program. *J Am Geriatr Soc*. 1979;27(1):20–22.
15. Facts & Comparisons® eAnswers—Phenytoin. Accessed September 14, 2020. https://fco.factsandcomparisons.com/lco/action/home
16. Krasowski MD, Penrod LE. Clinical decision support of therapeutic drug monitoring of phenytoin: measured versus adjusted phenytoin plasma concentrations. *BMC Med Inform Decis Mak*. 2012;12:7. doi:10.1186/1472-6947-12-7
17. Sokol SI, Cheng A, Frishman WH, Kaza CS. Cardiovascular drug therapy in patients with hepatic diseases and patients with congestive heart failure. *J Clin Pharmacol*. 2000;40(1):11–30. doi:10.1177/00912700022008649
18. Garasto S, Fusco S, Corica F, et al. Estimating glomerular filtration rate in older people. *BioMed Res Int*. 2014;2014:916542. doi:10.1155/2014/916542
19. Wilhelm SM, Kale-Pradhan PB. Estimating creatinine clearance: a meta-analysis. *Pharmacotherapy*. 2011;31(7):658–664. doi:10.1592/phco.31.7.658
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
21. Hajjar I. Postural blood pressure changes and orthostatic hypotension in the elderly patient: impact of antihypertensive medications. *Drugs Aging*. 2005;22(1):55–68.
22. Biaggioni I. Orthostatic hypotension in the hypertensive patient. *Am J Hypertens*. 2018;31(12):1255–1259. doi:10.1093/ajh/hpy089
23. Salzman B. Gait and balance disorders in older adults. *Am Fam Physician*. 2010;82(1):61–68.
24. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4): 674–694. doi:10.1111/jgs.15767
25. Zeevi N, Pachter J, McCullough LD, Wolfson L, Kuchel GA. The blood-brain barrier: geriatric relevance of a critical brain-body interface. *J Am Geriatr Soc*. 2010;58(9):1749–1757. doi:10.1111/j.1532-5415.2010.03011.x
26. Salahudeen MS, Duffull SB, Nishtala PS. Impact of anticholinergic discontinuation on cognitive outcomes in older people: a systematic review. *Drugs Aging*. 2014;31(3):185–192. doi:10.1007/s40266-014-0158-4
27. Samorajski T. Central neurotransmitter substances and aging: a review. *J Am Geriatr Soc*. 1977;25(8):337–348.
28. Fleg JL, Tzankoff SP, Lakatta EG. Age-related augmentation of plasma catecholamines during dynamic exercise in healthy males. *J Appl Physiol Bethesda (1985)*. 1985;59(4):1033–1039.

29. Maggiorani D, Manzella N, Edmondson DE, et al. Monoamine oxidases, oxidative stress, and altered mitochondrial dynamics in cardiac ageing. *Oxid Med Cell Longev*. 2017;2017:3017947. doi:10.1155/2017/3017947
30. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians: American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. *J Am Geriatr Soc*. 2012;60(10):E1–E25. doi:10.1111/j.1532-5415.2012.04188.x
31. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. *Clin Interv Aging*. 2008;3(2):383–389. doi:10.2147/cia .s2468
32. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13(1):57–65. doi:10.1517/14740338.2013. 827660
33. Cipolle RJ, Strand LM, Morley PC. *Pharmaceutical Care Practice: The Clinician's Guide*. 2nd ed. McGraw-Hill, Medical Pub. Division; 2004.
34. Salvi F, Marchetti A, D'Angelo F, Boemi M, Lattanzio F, Cherubini A. Adverse drug events as a cause of hospitalization in older adults. *Drug Saf*. 2012;35(suppl 1):29–45. doi:10.1007/BF03319101
35. Centers of Disease Control and Prevention. Adverse Drug Events in Adults—Medication Safety Program. Accessed September 10, 2015. http://www.cdc.gov/MedicationSafety/Adult_AdverseDrugEvents.html
36. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365(21):2002–2012. doi:10.1056/NEJMsa1103053
37. Hanlon JT, Perera S, Newman AB, et al. Potential drug-drug and drug-disease interactions in well-functioning community-dwelling older adults. *J Clin Pharm Ther*. 2017;42(2):228–233. doi:10.1111/jcpt.12502
38. Poudel A, Ballokova A, Hubbard RE, et al. Algorithm of medication review in frail older people: focus on minimizing the use of high-risk medications. *Geriatr Gerontol Int*. 2016;16(9):1002–1013.Published online September 3, 2015. doi:10.1111/ggi.12589
39. Bosworth HB, Granger BB, Mendys P, et al. Medication adherence: a call for action. *Am Heart J*. 2011;162(3):412–424. doi:10.1016/j.ahj.2011.06.007
40. Choosing Wisely®. An initiative of the ABIM Foundation. Published October 24, 2014. Accessed March 4, 2021. https://www.choosingwisely.org/
41. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62(16):e147–e239. doi:10.1016/j.jacc.2013.05.019
42. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special

contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27): 2129–2200. doi:10.1093/eurheartj/ehw128

43. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. *J Am Coll Cardiol*. 2017;70(6):776–803. doi:10.1016/j.jacc.2017.04.025
44. Carter BL. Dosing of antihypertensive medications in patients with renal insufficiency. *J Clin Pharmacol*. 1995;35(1):81–86.
45. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;139(25):e1082–e1143. doi:10.1161/CIR.0000000000000625
46. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507–520. doi:10.1001/jama.2013.284427
47. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;393(10170):407–415. doi:10.1016/S0140-6736(18)31942-1
48. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. 2018;71(6):1269–1324. doi:10.1161/HYP.0000000000000066
49. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation*. 2016;133(4):e38–e360. doi:10.1161/CIR.0000000000000350
50. American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes Mellitus, Moreno G, Mangione CM, Kimbro L, Vaisberg E. Guidelines abstracted from the American Geriatrics Society guidelines for improving the care of older adults with diabetes mellitus: 2013 update. *J Am Geriatr Soc*. 2013;61(11): 2020–2026. doi:10.1111/jgs.12514
51. American Diabetes Association. 12. Older Adults: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(suppl 1):S152–S162. doi:10.2337/dc20-S012

52. World Health Organization. Mental health of older adults. Published December 12, 2017. Accessed September 30, 2020. https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults
53. Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. Cochrane common mental disorders group, ed. *Cochrane Database Syst Rev*. 2016;9(9):CD006727. doi:10.1002/14651858.CD006727.pub3
54. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
55. Kok RM, Reynolds CF. Management of depression in older adults: a review. *JAMA*. 2017;317(20):2114–2122. doi:10.1001/jama.2017.5706
56. Alexopoulos GS, Katz IR, Reynolds CF, Carpenter D, Docherty JP, Ross RW. Pharmacotherapy of depression in older patients: a summary of the expert consensus guidelines. *J Psychiatr Pract*. 2001;7(6):361–376. doi:10.1097/00131746-200111000-00003
57. Mulsant BH, Blumberger DM, Ismail Z, Rabheru K, Rapoport MJ. A systematic approach to pharmacotherapy for geriatric major depression. *Clin Geriatr Med*. 2014;30(3):517–534. doi:10.1016/j.cger.2014.05.002
58. Mulsant BH, Alexopoulos GS, Reynolds CF, et al. Pharmacological treatment of depression in older primary care patients: the PROSPECT algorithm. *Int J Geriatr Psychiatry*. 2001;16(6):585–592.
59. Centers for Disease Control and Prevention. Most Recent National Asthma Data. Published March 24, 2020. Accessed September 30, 2020. http://www.cdc.gov/asthma/most_recent_national_asthma_data.htm
60. Centers for Disease Control and Prevention. AsthmaStats: Uncontrolled Asthma among Adults, 2016. Published July 10, 2019. Accessed September 30, 2020. http://www.cdc.gov/asthma/asthma_stats/uncontrolled-asthma-adults.htm
61. Yáñez A, Cho S-H, Soriano JB, et al. Asthma in the elderly: what we know and what we have yet to know. *World Allergy Organ J*. 2014;7(1):8. doi:10.1186/1939-4551-7-8
62. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *The Lancet*. 2010;376(9743):803–813. doi:10.1016/S0140-6736(10)61087-2
63. Akinbami LJ, Xiang LM. NCHS Data Brief, No. 63. National Center for Health Statistics 2011. Center for Disease Control and Prevention. Published June 10, 2019. Accessed October 2, 2020. http://www.cdc.gov/nchs/products/databriefs/db63.htm
64. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020. *Report*. 141. Accessed October 2, 2020. www.goldcopd.org

65. Taffet GE, Donohue JF, Altman PR. Considerations for managing chronic obstructive pulmonary disease in the elderly. *Clin Interv Aging*. 2014;9:23–30. doi:10.2147/CIA.S52999
66. Dominas C, Gadkaree S, Maxfield AZ, Gray ST, Bergmark RW. Aspirin-exacerbated respiratory disease: a review. *Laryngoscope Investig Otolaryngol*. 2020;5(3):360–367. doi:10.1002/lio2.387
67. Battaglia S, Benfante A, Spatafora M, Scichilone N. Asthma in the elderly: a different disease? *Breathe Sheff Engl*. 2016;12(1):18–28. doi:10.1183/20734735.002816
68. Centers for Disease Control and Prevention. Adult Immunization Schedule by Vaccine and Age Group. Published February 6, 2020. Accessed October 2, 2020. http://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
69. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention; 2020:211. www.ginasthma.org
70. Liang SY. Sepsis and other infectious disease emergencies in the elderly. *Emerg Med Clin North Am*. 2016;34(3):501–522. doi:10.1016/j.emc.2016.04.005
71. Cillóniz C, Rodríguez-Hurtado D, Torres A. Characteristics and management of community-acquired pneumonia in the era of global aging. *Med Sci Basel Switz*. 2018;6(2):35. doi:10.3390/medsci6020035
72. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415–427. doi:10.1056/NEJMoa1500245
73. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax*. 2013;68(11): 1057–1065. doi:10.1136/thoraxjnl-2013-204282
74. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45–e67. doi:10.1164/rccm.201908-1581ST
75. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72. doi:10.1086/511159
76. Demicheli V, Jefferson T, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. Cochrane Acute Respiratory Infections Group, ed. *Cochrane Database Syst Rev*. 2018;(2):CD004876. doi:10.1002/14651858.CD004876.pub4
77. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. In: The Cochrane Collaboration, ed. *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2013.

Accessed September 14, 2015. http://doi.wiley.com/10.1002/14651858.CD000422.pub3

78. Cortes-Penfield NW, Trautner BW, Jump RLP. Urinary tract infection and asymptomatic bacteriuria in older adults. *Infect Dis Clin North Am*. 2017;31(4):673–688. doi:10.1016/j.idc.2017.07.002
79. Arinzon Z, Shabat S, Peisakh A, Berner Y. Clinical presentation of urinary tract infection (UTI) differs with aging in women. *Arch Gerontol Geriatr*. 2012;55(1):145–147. doi:10.1016/j.archger.2011.07.012
80. Mody L, Juthani-Mehta M. Urinary tract infections in older women: a clinical review. *JAMA*. 2014;311(8):844–854. doi:10.1001/jama.2014.303
81. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68(10):e83–e110 Published online March 21, 2019. doi:10.1093/cid/ciy1121
82. Matthews SJ, Lancaster JW. Urinary tract infections in the elderly population. *Am J Geriatr Pharmacother*. 2011;9(5):286–309. doi:10.1016/j.amjopharm .2011.07.002
83. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52(5):e103–e120. doi:10.1093/cid/ciq257
84. Facts & Comparisons® eAnswers—Fluoroquinolones. Published August 27, 2020. Accessed October 7, 2020. https://fco.factsandcomparisons.com/lco/action/home
85. Facts & Comparisons® eAnswers—Ciprofloxacin. Published September 18, 2020. Accessed October 7, 2020. https://fco.factsandcomparisons.com/lco/action/home
86. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2020;72(2):149–162. doi:10.1002/acr.24131
87. Batsis JA, Germain CM, Vásquez E, Zbehlik AJ, Bartels SJ. Physical activity predicts higher physical function in older adults: the osteoarthritis initiative. *J Phys Act Health*. 2016;13(1):6–16. doi:10.1123/jpah.2014-0531
88. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331–1346. doi:10.1111/j .1532-5415.2009.02376.x
89. Aw T-J, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med*. 2005;165(5):490–496. doi:10.1001/archinte.165.5.IOI50013

90. Facts & Comparisons® eAnswers—Diclofenac Topical. Accessed October 10, 2020. https://fco.factsandcomparisons.com/lco/action/home
91. Centers for Medicare & Medicaid Services. State Operations Manual. Published August 5, 2020. Accessed October 7, 2020. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS1201984
92. American Society of Consultant Pharmacists. ASCP Practice Resource Center. Accessed October 7, 2020. https://www.ascp.com/page/prc
93. Jetha S. Polypharmacy, the elderly, and deprescribing. *Consult Pharm J Am Soc Consult Pharm*. 2015;30(9):527–532. doi:10.4140/TCP.n.2015.527
94. Cool C, Cestac P, Laborde C, et al. Potentially inappropriate drug prescribing and associated factors in nursing homes. *J Am Med Dir Assoc*. 2014;15(11):850.e1–850.e9. doi:10.1016/j.jamda.2014.08.003
95. Sterke CS, Verhagen AP, van Beeck EF, van der Cammen TJM. The influence of drug use on fall incidents among nursing home residents: a systematic review. *Int Psychogeriatr IPA*. 2008;20(5):890–910. doi:10.1017/S104161020800714X
96. Ham AC, Swart KMA, Enneman AW, et al. Medication-related fall incidents in an older, ambulant population: the B-PROOF study. *Drugs Aging*. 2014;31(12): 917–927. doi:10.1007/s40266-014-0225-x
97. Gill SS, Bronskill SE, Normand S-LT, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med*. 2007;146(11):775–786.
98. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44(2):213–218. doi:10.1093/ageing/afu145

108

Geriatric Neurocognitive Disorders

Nicole J. Brandt and Stephanie M. Ozalas

CORE PRINCIPLES		CHAPTER CASES
NEUROCOGNITIVE DISORDERS		
1	Neurocognitive disorder (NCD) is a syndrome that exhibits multiple cognitive deficits that compromise normal social or occupational function. There are numerous etiologies such as Alzheimer disease (AD), dementia with Lewy bodies (DLB), and vascular disease, which require a comprehensive evaluation to define a potential diagnosis.	**Case 108-1 (Question 1)**
NEUROCOGNITIVE DISORDER BECAUSE OF ALZHEIMER DISEASE		
1	AD is a chronic, progressive,	**Case 108-1**

	neurodegenerative disorder that results from neuropathologic findings, such as neurofibrillary tangles and β-amyloid plaques that interfere with cholinergic transmission, as well as other neurochemical changes in the brain.	**(Questions 1–3)**
2	AD has multiple risk factors such as age, family history, Down syndrome, head trauma, hypertension, and mild cognitive impairment; yet, the exact etiology is still unknown.	**Case 108-1 (Question 2)**
3	Treatment for AD is still primarily symptomatic management, not disease altering, and focuses on neurotransmission (eg, cholinergic system).	**Case 108-1 (Question 4)**
4	Cholinesterase inhibitors may be used as monotherapy or in combination with an *N*-methyl-D-aspartate antagonist for patients in the moderate-to-severe stage of AD.	**Case 108-1 (Questions 4–6)**
5	Monitoring for treatment efficacy should focus on cognition, function, and possibly behaviors, whereas treatment toxicity should look for common adverse effects such as gastrointestinal problems with cholinesterase inhibitors.	**Case 108-1 (Question 5–7)**
	NEUROCOGNITIVE DISORDER BECAUSE OF LEWY BODY DISEASE	
1	Has similar neuropathology noted with α-synuclein aggregates found in Lewy	**Case 108-2 (Question 1)**

	bodies and neuritis (α-synucleinopathies), which typically present with parkinsonian findings as well as associated symptoms such as falls and visual hallucinations.	
2	Cholinesterase inhibitors have demonstrated symptomatic benefit in patients with Lewy body dementias yet monitoring for worsening of motor symptoms such as tremor is needed.	**Case 108-2 (Question 2)**
	VASCULAR NEUROCOGNITIVE DISORDERS	
1	Vascular dementia is a broad classification of cognitive disorders caused by vascular disease, and notable multiple risk factors include advancing age, diabetes mellitus, small vessel cerebrovascular disease, hypertension, heart disease, hyperlipidemia, cigarette smoking, and alcohol use.	**Case 108-3 (Questions 1, 2)**
2	Treatment for vascular dementia strives to control the underlying modifiable risk factors owing to limited efficacy and controversial evidence with cholinesterase inhibitors.	**Case 108-3 (Question 3)**
	BEHAVIORAL DISTURBANCES IN DEMENTIA	
1	When evaluating a patient with dementia with behavior disturbances, the first step is to ensure that the	**Case 108-1 (Question 1) Case 108-4 (Question 1)**

	problem is not caused by an unrecognized medical problem or adverse effect of a medication.	
2	Nonpharmacologic strategies are effective for managing many behavior disturbances and should be attempted before using medications to manage behavior.	**Case 108-4 (Questions 1–4)**
3	Delusions and hallucinations are common behaviors in dementia patients, yet the use of antipsychotics for these symptoms is not approved by the U.S. Food and Drug Administration and has been associated with an increased risk of stroke and mortality in this patient population.	**Case 108-4 (Question 2)**
4	Wandering is a safety concern that often does not respond to pharmacologic intervention; instead, other strategies such as environmental modifications are used.	**Case 108-4 (Question 3)**
5	Antidepressants such as selective serotonin reuptake inhibitors have shown promise in addressing depressive symptoms, as well as screaming and irritability.	**Case 108-4 (Question 4)**
6	Caregiver support is essential to maintaining a patient with dementia safely in their home as long as possible.	**Case 108-1 (Questions 3, 5)** **Case 108-4 (Question 5)**

INTRODUCTION

Neurocognitive disorders (NCDs) span a wide range of conditions that exhibit a global decline in cognition. Among the disorders included are delirium, dementia, and several other disorders with various etiologies (eg, head trauma, human immunodeficiency virus [HIV], Huntington disease).[1] Among older adults, dementias are the most commonly encountered diseases and are the focus of this chapter.

GERIATRIC DEMENTIAS

With the continuing growth in the older adult population, the incidence and prevalence of NCDs continue to rise.[2,3] Alzheimer disease (AD) is the most common cause, whereas vascular dementia (VaD), mixed dementia, and dementia with Lewy bodies (DLB) are the next most common dementias. Parkinson disease with dementia (PDD) and frontotemporal dementia (FTD) occur less often.[4] AD is currently the fifth leading cause of death for people ages 65 years and older and the sixth leading cause of death for all people in the United States.[3,5]

Incidence and Prevalence

It is estimated that 6.2 million Americans have AD, including ~17% of people ages 65 years and older and 36% of people ages 85 years and older. Of these, more than 3.6 million are female. Black and Hispanic Americans are disproportionately more likely than older White Americans to have AD or other dementias.[2] The annual incidence of AD in the United States rises from 30 per 1000 among people ages 65 to 74 years to 176 per 1000 for those ages 75 to 84 years, and to 323 per 1000 for those at least 85 years.[6] Worldwide prevalence has been estimated to be as high as 24.3 million, with

8.4 million new cases annually.[7] Projections into the mid-century include a worldwide prevalence of more than 81 million, with cases in undeveloped countries occurring at about three times the rate as in developed countries.[7]

In the United States, the most commonly defined dementia subtype was AD (43.5%), followed by VaD (14.5%), DLB (5.4%), FTD (1.0%), and alcohol-induced dementia (0.7%). The prevalence of other types of diagnosed dementia (eg, Creutzfeldt–Jakob disease and Huntington disease) was 0.2%.[4] Life expectancy after a diagnosis of AD is reduced by as much as 69% for those diagnosed before age 70 and by 39% for those diagnosed after age 90.[8] For individuals diagnosed with DLB, their survival time was almost 20 months shorter than patients with AD.[9] Neither gender difference and age at diagnosis nor cognitive scores (ie, Mini-Mental State Exam [MMSE]) explained differences in survival time between DLB and AD, but patients with DLB had a significantly lower age at death.[9]

The cost of dementia represents a substantial financial burden on society. Based on U.S. estimates from 2020, the annual health care and long-term care payments attributable to dementia care was $52,481 per person. This estimate does not include out-of-pocket expenses (ie, costs other than copayments or coinsurance, health insurance premiums, deductibles), which is estimated to be $11,571 per person. Based on 2020 data, the Alzheimer's Association estimates that the total monetary cost of dementia (in 2021 dollars) is estimated at $355 billion. Medicare is expected to pay ~$239 billion, which is only 67% of the total health care and long-term care payments.[2]

Clinical Diagnosis

Dementia is an NCD that exhibits impaired short- and long-term memory as its most prominent feature. Multiple cognitive deficits that compromise normal social or occupational function must be present before dementia can be diagnosed (**Table 108-1**).[1] Commonly, forgetfulness is the primary patient problem or the first symptom

noted by the family.[10] Family members or others may note several symptoms that should prompt a medical evaluation (**Table 108-2**).[11] Memory loss often accompanies several diseases or disorders in older adults. Therefore, a comprehensive medical history, physical examination, and medication history are essential in excluding systemic illness or medication toxicity as causes of memory loss (**Table 108-3**).[12] Laboratory and other tests to assist in differentiating dementia from other disorders are listed (**Table 108-4**). In patients with AD, test results will generally be normal; evidence of cerebrovascular disease is present in patients with VaD.

Table 108-1

Differentiating Neurocognitive Disorders

Mild (Formerly Mild Cognitive Impairment)	Major (Formerly Dementia)
Neurocognitive Disorder	
Modest cognitive decline from previous (baseline) performance in at least one cognitive domain, including: ▪ Learning and memory ▪ Complex attention ▪ Executive function ▪ Language ▪ Perception and motor ▪ Social cognition The deficits do not impair the capacity to be independent in everyday activities The cognitive symptoms do not occur exclusively during a period of delirium The cognitive deficits are not better explained by depression, schizophrenia, or other mental disorders	Significant cognitive decline from previous (baseline) performance in at least one cognitive domain, including: ▪ Learning and memory ▪ Complex attention ▪ Executive function ▪ Language ▪ Perception and motor ▪ Social cognition The deficits impair the capacity to be independent in everyday activities The cognitive symptoms do not occur exclusively during a period of delirium The cognitive deficits are not better explained by depression, schizophrenia, or other mental disorders
Neurocognitive Disorders Because of Alzheimer Disease	
Criteria for either mild or major NCD are met Insidious onset and gradual progression of impairment	

- Mild: impairment in one cognitive domain
- Major: impairment in at least two cognitive domains

Probable Alzheimer disease (either of the following must be present)

- Alzheimer disease genetic mutation based on family history or genetic testing
- All of the following are present:
  - Decline in memory and learning plus one other cognitive domain
  - Steady and gradual cognitive decline
  - No evidence of another condition that is likely to cause cognitive decline

Possible Alzheimer disease

- Lack of an Alzheimer disease genetic mutation
- All of the following are present:
  - Decline in memory and learning
  - Steady and gradual cognitive decline
  - No evidence of another condition that is likely to cause cognitive decline

Cognitive decline is not better explained by cerebrovascular disease or another condition associated with cognitive decline or neurodegeneration

Vascular Neurocognitive Disorders

Criteria for either mild or major NCD are met

Clinical presentation is consistent with a vascular cause (either of the following is present)

- Onset of cognitive impairment follows a cerebrovascular event or multiple events
- Prominent decline in complex attention and executive function

History, physical exam, and/or neuroimaging indicates cerebrovascular disease as the most likely cause of the cognitive decline

Probable vascular NCD (at least one of the following is present)

- Neuroimaging supports cerebrovascular disease as the cause of the clinical presentation
- The neurocognitive deficit follows at least one cerebrovascular event
- Presence of both clinical and genetic evidence of cerebrovascular disease

Possible vascular NCD

- Clinical criteria are met
- Neuroimaging is not available
- Temporal relationship between the cerebrovascular event(s) and the onset of neurocognitive decline is not established

A systemic disorder (such as depression) or other brain disease do not adequately explain the symptoms

Neurocognitive Disorder With Lewy Bodies (Dementia With Lewy Bodies)

Criteria for either mild or major NCD are met

The onset is insidious, with gradual progression
A combination of the following core and supportive clinical features are present

Core Clinical Features

- Fluctuating cognition accompanied by variable attentiveness and alertness
- Recurrent, well-formed, and detailed visual hallucinations
- REM sleep behavior disorder, which may precede cognitive decline
- One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity

Supportive Clinical Features

- Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction (eg, constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression)

Indicative Biomarkers

- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET Abnormal (low uptake) 123-iodine-MIBG myocardial scintigraphy
- Polysomnographic confirmation of REM sleep without atonia

Supportive Biomarkers

- Relative preservation of medial temporal lobe structures on CT/MRI scan
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity 6 the cingulate island sign on FDG-PET imaging
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

Probable DLB Can Be Diagnosed If:

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or
b. Only one core clinical feature is present, but with one or more indicative biomarkers
c. Probable DLB should not be diagnosed based on biomarkers alone

Possible DLB Can Be Diagnosed If:

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or
b. One or more indicative biomarkers is present, but there are no core clinical features.
c. Cognitive decline is not better explained by cerebrovascular disease, Parkinson disease dementia, or another condition associated with cognitive decline or neurodegeneration Cognitive decline generally occurs first in NCD with Lewy bodies, and motor symptoms occur first in Parkinson disease dementia

CT/MRI, computed tomography/magnetic resonance imaging; DLB, dementia with Lewy bodies; EEG, electroencephalogram; NCD, neurocognitive disorder; PET, positron emission tomography; REM, rapid eye movement; SPECT, single-photon emission computed tomography.

Sources: Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013; Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: a clinical review. *Neurology.* 2019;92(24): 1146–1156; McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology.* 1996;47:1113–1124; McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology.* 2017;89(1):88–100; Messier C, Gagnon M. Cognitive decline associated with dementia and type 2 diabetes: the interplay of risk factors. *Diabetologia. 2009*;52:2471–2474.

Table 108-2
Symptoms Suggesting Dementia

Neurocognitive Domain	Symptom	Evidence
Learning and memory	Difficulty learning or retaining new information	Repeats questions; difficulty remembering recent conversations, events, etc.; loses items
Execution function	Unable to handle complex tasks	Cannot complete tasks that require multiple steps (eg, difficulty following a shopping list); unable to make complex decisions
Complex attention	Divided/selected attention; processing speed	Inability to continue tasks for long periods of time; slower response time
Perceptual-motor function	Impaired spatial orientation and abilities	Gets lost in familiar places; difficulty with driving
Language	Language deficits	Problems finding appropriate words (eg, difficulty with naming common objects)
Social cognition	Behavior changes	Changes in personality; suspiciousness; inappropriate social behavior

Sources: Adapted from Costa P et al. *Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias*. Clinical Practice Guideline No. 19. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 97-0702; November 1996.

Table 108-3
Causes of Dementia Symptoms

Modifiable Risk Factors	Nonmodifiable Risk Factors
Disease states Deficiency states ▪ Vitamin B_{12} ▪ Folate ▪ Iron Delirium Amnestic syndrome (eg, isolated memory impairment) Brain abscess Normal pressure hydrocephalus Infections Medications Anticholinergic agents Antihistamines Anti-infectives Corticosteroids H_2-receptor antagonists Narcotic analgesics Nonsteroidal anti-inflammatory agents Sedative hypnotics and anxiolytics Skeletal muscle relaxants	Disease states Adjustment disorder (eg, inability to adjust to retirement) Cardiovascular disease Arrhythmia Heart failure Vascular occlusion Depression Intracranial causes Cerebrovascular accident Subdural hematoma Tumor Metabolic disorders ▪ Hypo-/hypercortisolism ▪ Hypo-/hyperaldosteronism ▪ Hypo-/hyperglycemia ▪ Hypo-/hyperthyroidism Medications Anticonvulsants Antidepressants Antineoplastic agents Antipsychotic agents Cardiovascular agents ▪ Antiarrhythmics ▪ Antihypertensives Immunosuppressants

Brain imaging, such as computed tomography (CT) scan or magnetic resonance imaging (MRI), can be useful in establishing the presence of dementia, but neither is diagnostic. A CT scan is useful when a space-occupying lesion, such as a tumor, is suspected as a

possible cause. An MRI scan is capable of identifying small infarcts or small vessel ischemic changes, such as those found in some forms of VaD, and atrophy of subcortical structures such as the brainstem.[12]

Several simple tests, including the Mini-Cognitive Assessment Instrument (Mini-Cog),[13] the Montreal Cognitive Assessment (MoCA),[14] and the St. Louis University Mental Status (SLUMS) exam,[15] are appropriate for initial screening of people with suspected cognitive impairment. The Folstein MMSE also can be used; however, it is less sensitive than others for dementia and now is proprietary.[16] These tests rapidly assess multiple domains, typically including orientation, registration, attention and calculation, recall, and language. Patients with dementia exhibit deficits in multiple areas. Those who score below the normal range on the MMSE or other screens or those who exhibit symptoms characteristic of dementia receive further testing. All screening tests are subject to limitations. Therefore, additional psychometric testing is often ordered to further establish the presence and type of dementia.[11,17]

Dementias may be classified as cortical or subcortical according to the areas of the brain preferentially affected by the disorder. AD, a typical cortical dementia, disrupts the cerebral cortex. Patients with cortical dementias display impaired language rather than impaired speech, a learning deficit (amnesia), reduced higher cortical functions (eg, inability to perform calculations, poor judgment), and an indifferent or disinhibited affect. Subcortical dementias such as VaD and PDD primarily affect the basal ganglia, thalamus, and brainstem. Deficits include abnormal motor function, disrupted speech patterns rather than language difficulties, forgetfulness (impaired recall), slowed cognitive function, and an apathetic or depressed affect.[11]

ALZHEIMER DISEASE

Etiology

A definitive cause for AD has yet to be determined. Several risk factors, however, have been identified. Advancing age is the primary risk factor for AD; other risks include family history, head trauma, metabolic syndrome, diabetes, hypertension (HTN), and cardiovascular disease.[2,18–21] Genetics play a significant role in the development of AD. The high familial occurrence of AD has been linked to autosomal-dominant traits on chromosomes 21, 14, and 1.[22,23] A gene that encodes for amyloid precursor protein (APP), a normal protein, is located on chromosome 21. A defect on chromosome 14 has been identified as the locus for the presenilin-1 gene, which codes for an inherited form of AD. The presenilin-2 gene, located on chromosome 1, also codes for an inherited form. Despite a strong genetic link in some pedigrees, the great majority of AD cases are sporadic.[22,24] The more common sporadic form appears to be linked to a susceptibility gene, apolipoprotein E, which occurs in three isoforms.[25] APP, a normal protein found throughout the body, maps on chromosome 21 and plays a pivotal role in AD neuropathology. Because of overproduction or transcription errors, an abnormal subunit (ie, β-amyloid) is produced.[23] Mutations on chromosomes 14 (presenilin-1 gene) and 1 (presenilin-2 gene) and the presence of apolipoprotein E4 allele code for alterations in the processing of APP. The abnormal cleavage of APP produces a 42–amino acid form of β-amyloid (Aβ) that demonstrates a higher toxicity than other amyloid forms.[24]

Table 108-4
Dementia Screening Tests

Test	Rationale for Testing
Complete blood count with sedimentation rate	Anemic anoxia, infection, neoplasms
Metabolic Screen	
Serum electrolytes	Hypernatremia, hyponatremia; renal function
Blood urea nitrogen,	Renal function

creatinine	
Bilirubin	Hepatic dysfunction (eg, portal systemic encephalopathy, hepatocerebral degeneration)
Thyroid function	Hypothyroidism, hyperthyroidism
Iron, vitamin B_{12}, folate, vitamin D	Deficiency states (vitamin B_{12}, folate neuropathies, vitamin D deficiency), anemias
Stool occult blood	Blood loss, anemia
HIV and RPR	Infection
Urinalysis	Infection, proteinuria
Chest roentgenogram	Neoplasms, infection, airway disease (anoxia)
Electrocardiogram	Cardiac disease (stagnant anoxia)
Brain scan	Cerebral tumors, cerebrovascular disease
Mental status testing	General cognitive screen
Depression testing	Depression, pseudodementia

RPR, rapid plasma reagin.

Apolipoprotein E (ApoE), a protein that is involved in cholesterol and phospholipid metabolism, plays a role in the development of sporadic, late-onset AD. The ApoE gene possesses three alleles: E2, E3, and E4. The E3 allele is most common, the E2 allele appears to be protective against AD, and the E4 allele increases the risk for AD.[24] The presence of ApoE4, the protein encoded by the E4 allele, appears to increase the deposition of Aβ and promote its change to a more pathologic configuration.[24] The presence of one or two copies of ApoE4 increases the risk of developing AD twofold or fivefold, respectively.[25] Aβ, which differs from amyloid protein found in other regions of the body, appears to contribute to neuronal death through a combination of apoptosis, a direct toxic effect, and an increased risk for damage owing to oxidative and metabolic stresses.[22],[24]

Neuropathology

Although brain atrophy is the most obvious finding among patients with Alzheimer-type dementia, it is not diagnostic for AD or other dementias because some degree of atrophy accompanies normal aging. Atrophic changes induced by AD are found primarily in the temporal, parietal, and frontal areas of the brain; the occipital region, primary motor cortex, and somatosensory areas are generally unaffected (**Fig. 108-1**).[11]

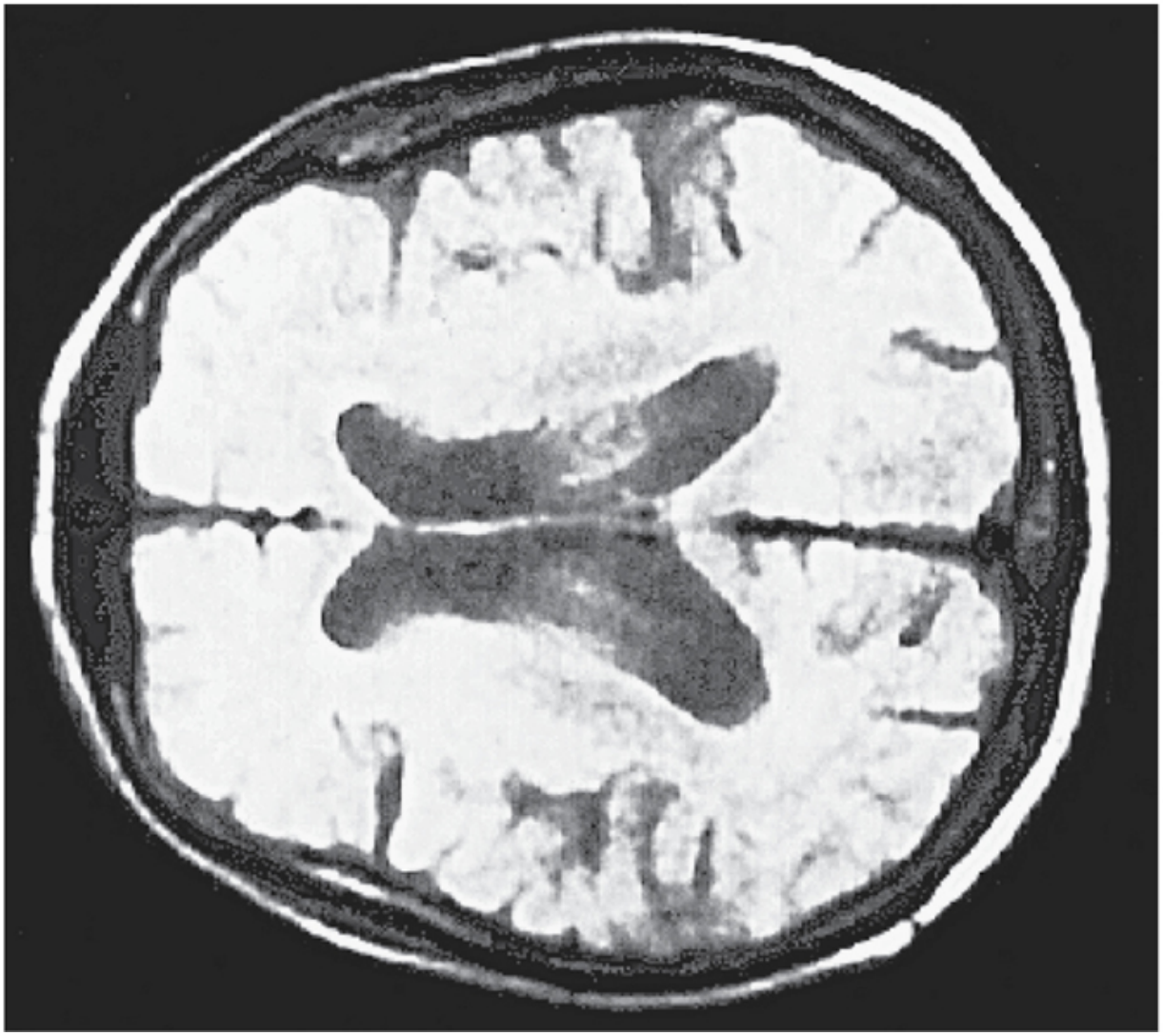


Figure 108-1 Alzheimer disease: magnetic resonance imaging scan. Ventricles are enlarged, and there is generalized atrophy, with greater atrophy present near the temporal areas.

Neuronal changes in the cerebral cortex associated with AD include neurofibrillary tangles (NFTs), neuritic plaques, amyloid angiopathy, and granulovacuolar degeneration. These changes lead to loss of neurons and synapses (**Fig. 108-2**).[22] NFTs are found primarily in the pyramidal regions of the neocortex, hippocampus, and amygdala, but they are also noted in areas of the brainstem and locus coeruleus.[23],[24] NFTs are composed of paired helical filaments, combinations of fibrils with a characteristic width and contour, containing a tau protein with an abnormal pattern of phosphate deposition. They are highly immunoreactive and are most likely to form in large pyramidal neurons.

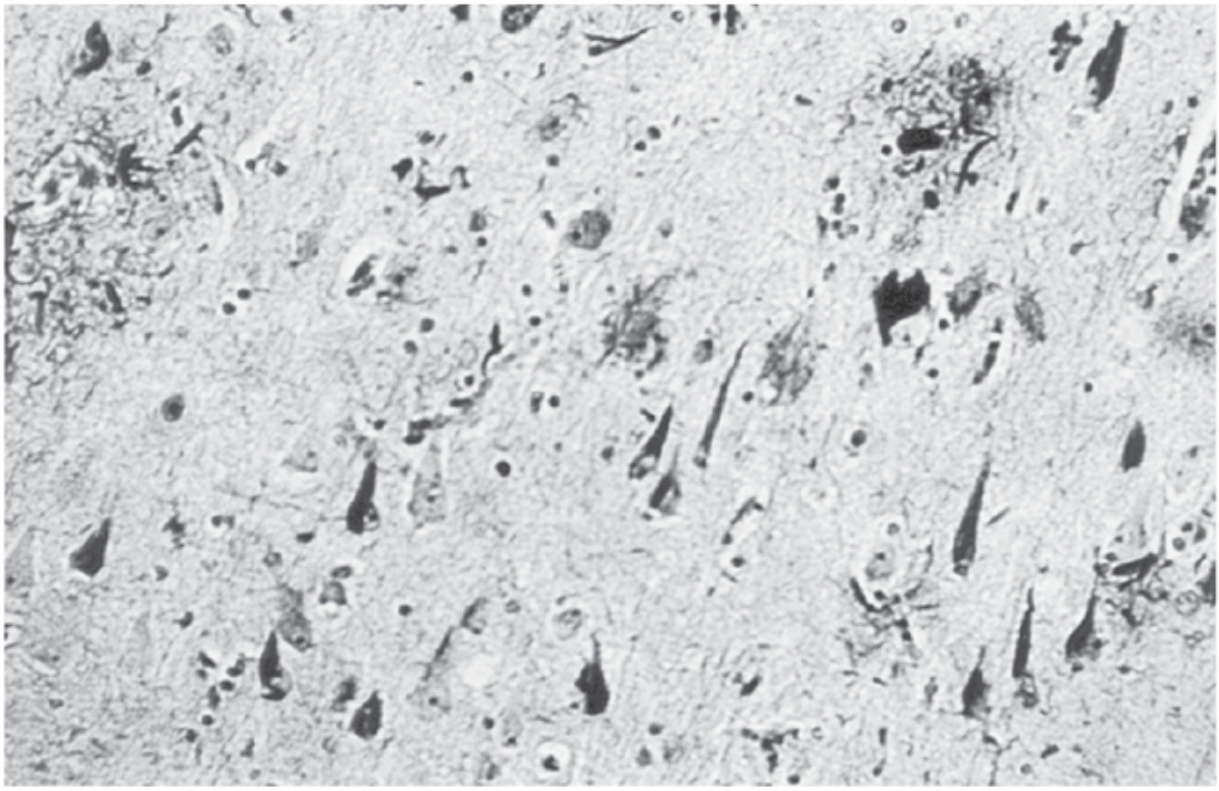


Figure 108-2 Numerous plaques (large, round bodies) and tangles (tear-shaped bodies) are found throughout the cortex in Alzheimer-type dementia.

Neuritic plaques are spherical bodies of tissue composed of granular deposits and remnants of neuronal processes.[26] The typical neuritic plaques of AD are spherical structures that exhibit a three-

tiered structure: a central amyloid core, a middle region of swollen axons and dendrites, and an outer zone containing degenerating neuritic processes.[23] Plaques contain APP, which can be cleaved by a defective metabolic process to form Aβ.[22] In addition to Aβ, plaques contain protein, ApoE, and acute-phase inflammatory proteins such as α_1-chymotrypsin and α_2-macroglobulin.[22] The deposition of amyloid in neuritic plaques correlates with the severity of AD, and the density of cortical plaques is associated with decreased choline acetyltransferase and the severity of cognitive impairment.[27] Aβ has been identified in plaques associated with Down syndrome and in both familial and sporadic forms of dementia of the Alzheimer type.[27] The pathologic process of AD development may begin as early as 20 to 30 years before any disease symptoms appear.[23],[24]

Granulovacuolar degeneration is the other major histologic finding in AD. It consists of clusters of intracytoplasmic vacuoles that contain tiny granules. The vacuoles appear to be specifically located in the pyramidal neurons of the hippocampus.[5],[15],[26] The loss of cortical neurons that originate in the nucleus basalis and project into the cerebral cortex is the most significant histopathologic consequence of AD.[24] Cell loss, granulovacuolar degeneration, and neurons with NFTs are concentrated in this area.[22]

Accompanying these changes are decreased concentrations of several neurotransmitters and enzymes. Choline acetyltransferase levels are reduced 60% to 90% in the cortical and hippocampal regions.[28] Acetylcholine and acetylcholinesterase (AChE) are also decreased, whereas muscarinic receptors in the cortex and hippocampus remain at normal levels or are moderately decreased. Nicotinic receptor proteins are also reduced in patients with Alzheimer-type dementia when compared with age-matched controls. Decreased choline acetyltransferase activity has been correlated with plaque density and disease severity. Cortical synapse loss, especially in the midfrontal region, is associated with disease severity.[24],[28]

Changes affecting AChE have significant implications for the management of AD symptoms. Many isoforms of AChE have been identified; they possess identical amino acid sequences but display different posttranslational modifications, predominate at diverse anatomical and microanatomical locations, and function in different ways. The predominant form of AChE in the cortical and hippocampal regions of humans is G4, a tetrameric form that is membrane bound. The monomeric form, G1, is found in a much lower concentration. There is a selective loss of the G4 form in patients with AD, allowing the G1 form to assume greater importance.[29] Although cholinergic activity is most significantly affected by Alzheimer-type dementia, other neurochemical systems are also altered. Norepinephrine, serotonin, and γ-aminobutyric acid receptors are affected.[23],[26]

Clinical Presentation and Diagnosis

CASE 108-1

Question 1: P.Y. is a 75-year-old male who is accompanied by his wife for a memory assessment. During the interview, the patient notes that memory issues started about 6 to 12 months ago but noticed that recently he has been "getting distracted" with driving and hit another car because he forgot to change gears when he was parking the car. The wife notes he frequently misplaces his car keys and wallet, as well as forgets to pick up all the groceries despite having a list. At first, the wife thought that he might have some visual impairment, but a recent ophthalmic exam revealed no significant deficits.

P.Y.'s medical history is significant for allergic rhinitis, glaucoma, and HTN. He has been currently prescribed loratadine 10 mg at bedtime for allergic rhinitis, latanoprost 0.005% 1 drop in each eye at bedtime for glaucoma, and amlodipine 10 mg daily for HTN. His family history is negative for stroke and positive for heart disease, and his mother died of a myocardial infarction at age 79. The wife admits that his father had AD and was diagnosed in his late 70s as well. He died at the age of 82 because of complications with his AD in a nursing home and his wife witnessed his dramatic decline from the AD, which worries him.

Physical examination reveals a pleasant, well-groomed male who is in good health oriented to person and place but not time. His blood pressure (BP) is 132/72 mm Hg supine and 146/84 mm Hg standing, with pulse rates of 58

beats/minute and 66 beats/minute, respectively. The rest of the physical examination was within normal limits.

The MoCA was 20/30, with errors in orientation (wrong date), attention, visuospatial, memory and delayed recall, as well as language.

What additional evaluation steps should be considered for P.Y.?

Before any conclusions can be reached, potentially reversible causes for P.Y.'s impaired cognition must be evaluated. However, he does display several trigger symptoms associated with dementia (see Table 108-2), including his recent car accident and difficulty following complex instructions coupled with memory impairment impacting day-to-day function.

Several systemic diseases and other disorders can cause cognitive impairment, as shown in Table 108-3. P.Y. should undergo a battery of laboratory tests to rule out anemia, cardiac and renal disease, thyroid abnormalities, and tumors. In addition, he should receive thorough neuropsychological testing, including depression screening and more in-depth assessment of his cognitive function. The testing should be conducted by clinicians who are skilled in cognitive assessment, as educational and cultural factors can influence an individual's performance on these tests.[17] A key is to better understand where he is functioning on the disease continuum. Based on tools that assess episodic memory, both immediate and delayed recall are valuable. Decline in executive functions may also flag incident AD dementia; by contrast, change in information processing speed/attention seems less informative.[30] Overall, the clinical continuum includes trajectories for both cognition and function. Cognition includes trajectories of episodic memory, executive function, and verbal fluency, whereas function includes trajectories of both basic and complex activities of daily living (ADLs). It appears cognitive impairment precedes and predicts functional impairment.[31]

Case 108-1, Question 2: P.Y. is referred by his physician for additional testing. Laboratory tests performed include renal and liver chemistries, thyroid function tests, vitamin B_{12} and folate levels, syphilis and HIV tests, complete blood cell count with sedimentation rate, and urinalysis. All results were normal,

except for a borderline elevated TSH (6.54 mU/L) and T4 within normal limits. Chest radiograph and electrocardiogram were normal. Neurologic examination revealed no deficits. Depression testing revealed a mildly anxious individual who was not depressed, just worried about his future. What is the most probable diagnosis for P.Y.?

P.Y.'s MoCA score of 20/30 is consistent with mild neurocognitive impairment or early dementia as evidenced by errors in orientation, visuospatial, recall, and language.[15] Secondary medical causes of cognitive impairment can be eliminated by P.Y.'s generally normal physical examination and laboratory test results. MRI or CT scanning may be useful in many cases to help eliminate brain pathology, such as stroke.[25] A positron emission tomography (PET) scan or a single-photon emission computed tomography (SPECT) scan may be useful to help locate specific areas of pathology and assist with a differential diagnosis, but are not required.[25] Secondary psychiatric causes for P.Y.'s decline can also be discounted. Although he is sad and anxious, the absence of alterations in appetite or sleep patterns, absence of suicidal thoughts, and the results of psychologic testing indicate P.Y. is not depressed. He is fully conscious, alert, and oriented to place and person. He exhibits no psychotic behavior and no evidence of delirium.

P.Y.'s slowly progressive decline and its impact on his social and occupational function (forgetting groceries, impaired driving ability), normal physical examination and laboratory findings, and family history meet the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-V) criteria for minor neurocognitive impairment (see Table 108-1). His history and course to date satisfy the criteria for AD and do not indicate a likely alternative explanation for his condition. Thus, P.Y. can be classified as probable AD.[17]

Case 108-1, Question 3: P.Y.'s children are very concerned about the family history of dementia. They ask whether there are any tests they should receive at this time to determine their risk. What should they be told?

Although there is a strong genetic association with AD, such instances account for a small minority of cases.[23] There is no apparent family history of Down syndrome. Mutations in the presenilin-1 and presenilin-2 genes are associated with only a small fraction of AD cases.[23] The role of biomarkers, which once was considered appropriate only for research-related purposes,[32] is increasingly being integrated into clinical decision-making. CSF Aβ42, total tau (t-tau), and phosphorylated tau (p-tau) biomarkers and amyloid PET have been the most widely studied.[33],[34] However, the challenges with cost, standardization, accessibility, and incorporation of biomarker findings into patient treatment plans have limited their utility.

Prognosis

Case 108-1, Question 4: What is the likely prognosis for P.Y.?

AD follows a predictable course that may progress over the course of 10 years or more.[2],[8] Two common rating scales for dementia are the Global Deterioration Scale and the Clinical Dementia Rating Scale. According to the Global Deterioration Scale (**Table 108-5**), P.Y.'s impaired social functioning, anxiety, and objective cognitive decline as well as his continued ability to concentrate and perform some complex skills, combined with his preserved affect and social interaction, are consistent with the features of stage three dementia of the Alzheimer type. This stage of AD is generally associated with a period of mild cognitive decline.[35] The more general Clinical Dementia Rating Scale also places P.Y. in the category of mild NCD.[36] Clinical diagnoses of AD using clinically appropriate criteria and assessment methods for probable AD have a sensitivity of up to 90% when compared with autopsy-confirmed cases.[1],[31],[34]

Table 108-5
Stages of Dementia of the Alzheimer Type

Stage of Cognitive Decline	Features
No cognitive decline	Normal cognitive state
Very mild cognitive decline	Forgetfulness, subjective reports only; no objective decline
Mild cognitive decline	Objective decline through psychiatric testing; work and social impairment; mild anxiety and denial
Moderate cognitive decline	Concentration, complex skills decline; flat affect and withdrawal
Moderately severe cognitive decline	Early dementia; difficulty in interactions; unable to recall or recognize people or places
Severe cognitive decline	Requires assistance with bathing, toileting; behavioral symptoms present (agitation, delusions, aggressive behavior)
Very severe cognitive decline	Loss of psychomotor skills and verbal abilities; incontinence; total dependence

Source: Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry*. 1982;139(9):1136–1139. Reprinted with permission from American Journal of Psychiatry. © 1982 American Psychiatric Association. All Rights Reserved.

Because of technologic advances, it is possible to diagnose dementia earlier and to keep patients alive into the final stages of the disease.[35] The early diagnosis of AD in P.Y. will allow his condition to be followed closely. To ensure the most favorable outcome, P.Y. should receive a thorough assessment beyond his dementia. This should include evaluation of his daily function (ie, ability for self-care), comorbid medical conditions, medications, living arrangements, safety, and potential for abuse and neglect. Attention also should be given to P.Y.'s caregivers and support system.[36] He should be reassessed every 6 months to both document disease progression and ensure that he is receiving the most appropriate

care. At some point, care at home may become unrealistic. At that time, P.Y. should be moved into a sheltered environment (eg, residential-care facility, assisted-living facility, nursing home) before suffering an injury caused by his poor judgment (eg, failing to dress properly for the weather, falling). In the later stages, interventions ranging from tube feedings to life support may prolong life, yet prove to be controversial.[37] Death in the late stage of AD is commonly associated with the development of infections such as pneumonia, urinary tract infections, or decubitus ulcers.

Treatment

If possible, maintaining independence is an important goal in treating a patient with dementia. Keeping patients in familiar surroundings allows them to function without the added burden of having to attempt to adapt to a strange environment. Concurrent diseases and many medications can reduce function and increase cognitive impairment in patients with dementia.

Case 108-1, Question 5: What is an appropriate initial treatment strategy for P.Y.?

P.Y.'s family needs to be educated about what to expect as his dementia progresses. They should be referred to the Alzheimer's Association (www.alz.org) and to the Family Caregiver Alliance (www.caregiver.org). Both organizations provide a wealth of information and community resources, including caregiver support groups. They also should be encouraged to enroll in the MedicAlert + Alzheimer's Association Safe Return program, which provides 24-hour nationwide emergency response for people with dementia who wander or suffer a medical emergency. P.Y.'s family should include him in any advance planning, seek legal advice regarding advance directives and durable power of attorney for health care and finance, and conduct estate planning to avoid having to perform these tasks when P.Y. is no longer competent to participate.[38]

Currently, two main classes of medications are used in the treatment of AD, cholinesterase inhibitors (ChEIs) and *N*-methyl-D-aspartate (NMDA) receptor antagonists.[39] They are pharmacologically distinct and can be prescribed concurrently in patients in the moderate-to-severe stages of the illness. ChEIs act on inhibiting AChE, an enzyme directly involved in the destruction of acetylcholine, leading to increased concentrations in the nucleus basalis of Meynert in the brain and hence ameliorating the cognitive and functional aspects of AD. Cholinesterase inhibitors have been shown to improve cognition and function and delay symptom progression in people with dementia; however, benefits are limited. Cholinergic-related effects, particularly in the gastrointestinal (GI) tract, are the most common adverse effects caused by all of the agents.[40]

The U.S. Food and Drug Administration (FDA) approved aducanumab-avwa (ADUHELM), an Aβ-directed antibody, on June 7, 2021, under an accelerated approval pathway for the treatment of AD. Treatment with aducanumab-avwa is indicated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.[41] There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. Approval was based on a surrogate outcome of β-amyloid plaque reduction (measured by PET Aβ SUVR), a known pathophysiologic feature of AD, while peer-reviewed publications have yet to be published.[42] Continued approval is contingent on clinical trials confirming clinical benefit, with the phase 4 trial to be completed by August 2029.

DONEPEZIL

Donepezil is a piperidine derivative that is somewhat selective for central AChE. It reversibly inhibits cholinesterase activity. Donepezil is highly bioavailable and exhibits a long half-life, allowing it to be given as a single daily dose. It is highly protein bound, primarily to albumin.[43]

Donepezil may improve cognition, global function, and behavioral symptoms across all stages (mild, moderate, and severe) of AD. In a multicenter, double-blind, placebo-controlled trial, subjects with mild-to-moderately severe AD improved during a 12-week treatment period.[44] Subjects taking 10 mg of donepezil at bedtime improved their cognitive function as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and their overall function as measured by the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC-Plus).[45],[46] A 24-week multicenter, placebo-controlled trial using dosages of 5 mg/day and 10 mg/day demonstrated similar results. Both 5- and 10-mg doses were superior to placebo; adverse effects were less common with the 5-mg dose.[47] A long-term, open-label follow-up study to these trials demonstrated that donepezil effects may persist for almost 3 years.[48] Interruption or discontinuation of donepezil treatment was followed by a return of cognition and function to baseline or below.

Donepezil is also indicated for the severe stage of AD. A 6-month, double-blind, parallel-group, placebo-controlled study in patients with severe AD (MMSE 1–10) demonstrated an improvement in the Severe Impairment Battery[49] and Modified Alzheimer's Disease Cooperative Study ADLs inventory for severe AD. The domains that showed a significant improvement versus placebo were language, praxis, visuospatial, bowel/bladder function, and ability to get dressed. There were no differences noted in the neuropsychiatric inventory for behavioral issues associated with dementia.[50] A 23-mg dose of donepezil was approved for patients in the moderate-to-severe stages of AD. Small improvements were seen in the Severe Impairment Battery, and there was no improvement in the CIBIC-Plus when compared with the 10-mg dose. More than 30% of the high-dose group and nearly 18% of the low-dose group failed to complete the 24-week trial.[51]

The most common adverse effects of donepezil are associated with cholinergic activity. They tend to be mild to moderate in nature and resolve with stabilization of the dose.[44],[47] In a 144-week extension trial of donepezil, the most frequently encountered adverse effects were nausea, diarrhea, and headache.[48] In clinical

trials, however, adverse effects were the primary reason for withdrawal from studies, with an overall dropout rate of 29% in the treatment groups.[42]

RIVASTIGMINE

Rivastigmine is a carbamate derivative that inhibits both AChE and butyrylcholinesterase (BChE) activity. BChE provides an alternative pathway for acetylcholine metabolism. Rivastigmine inhibits the activity of both cholinesterases, primarily in the central nervous system.[52] Its AChE inhibition is greater for the G1 as compared with the G4 form.[30] The drug binds to the esteratic sites of the AChE and BChE molecules and slowly dissociates. Because of this, it is often referred to as a "pseudoirreversible" inhibitor.[53] Rivastigmine's biologic half-life is ~1 hour, but because its slow dissociation extends its activity for at least 10 hours, it can be dosed twice daily. Rivastigmine is bound ~40% to serum proteins and is metabolized via hydrolysis to renally excreted inactive compounds.[52] Rivastigmine absorption is nearly complete, but because it undergoes a significant first-pass effect, the resultant bioavailability is ~36%.

In two large clinical trials conducted in patients with mild-to-moderately severe AD, rivastigmine improved cognition, the ability to perform daily activities, and global function over the course of 24 weeks.[53],[54] In each multicenter, double-blind, placebo-controlled trial, subjects were randomly assigned to receive placebo, low-dose (1–4 mg/day) or high-dose (6–12 mg/day) rivastigmine in two divided doses during a 26-week period. In one study, subjects in both rivastigmine groups demonstrated statistically significant improvement after 26 weeks on the ADAS-Cog and CIBIC-Plus scales.[53] In the other trial, only those subjects taking 6 to 12 mg/day improved on the same scales.[54] An open-label extension study that included subjects from both previous studies found that subjects taking 6 to 12 mg/day of rivastigmine had significantly better cognitive function after 1 year than did subjects who had originally received placebo.[55]

Adverse effects typically include nausea, vomiting, diarrhea, and other cholinergic-mediated GI effects.[52] They are most common when rivastigmine is taken on an empty stomach or when the dose escalation is too rapid. Headache, dizziness, and fatigue are also common adverse effects. Increasing the dose by 1.5 mg twice daily at 4-week intervals increases drug tolerability and reduces the frequency and severity of GI side effects. Adverse effect severity appears to be less problematic with a transdermal formulation that delivers 4.6 or 9.5 mg/24 hours, which correspond to 6- and 12-mg daily doses of the oral formulation.[56] The maintenance dose is generally 9.5 to 13.3/day. In patients with moderate-to-severe AD, the maintenance dose is 13.3 mg/day. If treatment is interrupted for at least 3 days, the lowest dosing should be restarted.

GALANTAMINE

Like other agents used to treat AD, galantamine enhances cholinergic activity by inhibiting AChE. However, it also stimulates nicotinic receptors (α-7-nicotinic receptor agonist) at a site distinct from that stimulated by acetylcholine, an action that does not rely on the presence of acetylcholine. This action is referred to as allosteric modulation.[30] Galantamine is rapidly and completely absorbed, reaches peak serum levels in <2 hours, and has a half-life of ~5 hours. It exhibits low protein binding and has a large volume of distribution. Galantamine is metabolized primarily by cytochrome P-450 (CYP) isoenzymes, CYP2D6 and CYP3A4, and is eliminated in the urine.[57]

Clinical trials have shown galantamine to be effective for the symptomatic treatment of mild-to-moderate AD. Doses of 16 and 24 mg/day produced clinically meaningful improvement in ADAS-Cog and CIBIC-Plus scores during a 5-month, randomized, placebo-controlled trial.[58] A similar trial was conducted in Europe and Canada that evaluated patients for 6 months used doses of 24 and 32 mg/day. Both doses were more effective than placebo, but patients in the 32-mg/day group exhibited more adverse effects.[59] A 6-month, open-label extension trial showed that patients treated with

galantamine 24 mg/day maintained ADAS-Cog scores throughout the entire 12 months of the study.[59]

As with the other ChEIs, cholinergic effects in the GI tract are the most commonly encountered adverse effects. Nausea, diarrhea, vomiting, and anorexia were the most frequent events encountered during clinical trials.[30],[42] They were typically present during the dose escalation phases of the studies. A dose titration interval of 4 weeks reduces the severity of adverse effects and increases tolerability.

CASE 108-1, QUESTION 6: What treatment should be instituted for P.Y., and how should therapy be monitored?

P.Y. is in the mild stage of the disease, so a ChEI is an appropriate choice.[39] It is unlikely that a ChEI will produce a dramatic or long-lasting improvement in P.Y.'s cognitive abilities. Systematic reviews of ChEI therapy have consistently concluded that these agents provide modest benefits, at best, in the majority of patients.[40],[60] Treatment, however, may slow his cognitive decline, help maintain his ability to care for himself for 1 year or more, and reduce the risk for nursing facility placement for as much as 2 years.[57] Beneficial effects may occur for as long as 3 years, and patients who start therapy earlier may experience greater benefit than those who delay treatment.[58],[59] The choice of drug is based on the agent most likely to produce a positive response with the fewest adverse effects. Ease of adherence must also be considered. All agents exhibit similar adverse effect profiles. Rivastigmine may be less prone to drug interactions because of its metabolic pathway.[52] It is also available as a transdermal patch that is applied daily. Whereas the oral formulation of rivastigmine requires an initial, nontherapeutic titration dose to reduce the severity of adverse effects, the initial transdermal dosage is therapeutic.[56] Donepezil and galantamine extended release can be given as a single daily dose and are available as generic equivalents. They can be given at bedtime, which may make cholinergic side effects less troublesome.

Donepezil may be an appropriate agent for P.Y. He should receive donepezil 5 mg at bedtime. He should be monitored for cholinergic side effects (particularly nausea and diarrhea, insomnia, headache, and dizziness, the adverse effects most commonly reported in clinical trials).[44,47] Additionally, he should be monitored for bradycardia because of his preexisting low heart rate. Patients who received moderate-to-high doses of donepezil showed an increased incidence and greater risk of bradycardia, especially those with risk factors (eg, cardiovascular disease, concomitant use of β-blockers, calcium channel blockers, antiarrhythmics).[61] His family and physician should look for improvements in his memory, orientation, and ability to concentrate on complex tasks, such as managing finances. He may also become less irritable.

Case 108-1, Question 7: His family was wondering what other options could be employed to address the progression of dementia?

After 1 month, his physician should assess him for adverse effects. If he has not improved noticeably after 4 to 6 weeks, the dose of donepezil may be increased to 10 mg at bedtime. If his condition does not respond to donepezil after a 6-month trial or he is unable to tolerate the donepezil, it is reasonable to switch P.Y. to another ChEI. Both rivastigmine and galantamine have additional mechanisms of action that might prove beneficial. Rivastigmine is started at a dose of 1.5 mg twice daily with meals to slow absorption and improve tolerability. The dose may be increased at 4-week intervals by 1.5 mg twice daily, up to the maximal dose of 6 mg twice daily; however, the transdermal formulation is better tolerated and may be preferable by avoiding a titration phase. Galantamine can be started at 4 mg twice daily or 8 mg daily (extended release) and increased every 4 weeks by 8 mg, up to a maximal dose of 24 mg daily. As with oral rivastigmine, the initial dose is not therapeutic.[57] Taking galantamine with meals may improve tolerability of GI effects. If a trial of a second agent does not improve or stabilize a patient's condition, there is no value in attempting a third agent. P.Y. should

have routine reassessment of his daily function, cognition, and behavior at 6-month intervals.[62–64] Close attention also must be paid to his other medical conditions, and his family should be provided ongoing support, such as through an AD caregiver support group.

MEMANTINE

As P.Y.'s AD progresses, there are two treatment options that can be tried. One option is to further titrate up the donepezil dose to 23 mg/day as mentioned above with some limited clinical efficacy.[48] Another option is to use an NMDA antagonist, which has been shown to reduce the release of glutamate in the central nervous system that can lead to excitotoxic reactions and cell death in AD and other neurodegenerative disorders.[65] Memantine is a noncompetitive NMDA receptor antagonist with moderate affinity and voltage-dependent binding. It is completely absorbed after oral administration, reaches peak serum concentrations in 3 to 8 hours, and is moderately protein bound.

Multiple clinical trials have evaluated memantine in subjects with moderate-to-severe AD. A dose of 10 mg/day for 12 weeks increased functional ability (eg, dressing, toileting, participating in group activities) and reduced care dependence compared with placebo.[65] A 28-week trial using a dose of 20 mg/day improved CIBIC-Plus scores, ADLs, and global function compared with placebo.[66] Overall, the benefits of memantine are modest.[67] The combined use of memantine and a ChEI has been shown to be superior to a ChEI alone by improving daily function in individuals with moderate-to-severe dementia.[68–70] Common adverse effects include diarrhea, insomnia, dizziness, headache, and hallucinations.[65] Memantine has also been studied in patients with mild-to-moderate AD with 2000 IU/d of α-tocopherol (vitamin E) compared with placebo.[71] The α-tocopherol resulted in slower functional decline, whereas there were no significant differences in the groups receiving memantine alone or memantine plus α-tocopherol. P.Y. should be started on memantine 5 mg daily, with the dosage increased in weekly intervals by 5 mg/day, up to a dose of 10

mg twice daily.[65] As an alternative, he can be started on the extended-release formulation given in weekly escalating doses of 7, 14, 21, and 28 mg daily.

LEWY BODY DEMENTIAS

Etiology

Lewy bodies are hyaline-containing inclusion bodies typically found in people with Parkinson disease. Recently, attention has been given to distinguish DLB and PDD to help further research.[72] It is known that up to 25% of patients with dementia have Lewy bodies in the brainstem and cortex (particularly in the limbic and paralimbic cortices and frontal and temporal lobes).[73] Concentrations are found in the substantia nigra, locus coeruleus, hypothalamus, basal nucleus of Meynert, and neocortex. There is decreased dopamine in the basal ganglia and a loss of choline acetyltransferase (and thus, acetylcholine) in the basal nucleus of Meynert.[5] Many of these patients display extrapyramidal signs without the classic presentation of Parkinson disease.[9] The role of α-synuclein is a common biologic theme in both DLB and PDD, with α-synuclein aggregates found in Lewy bodies and neurites.

Clinical Presentation

CASE 108-2

QUESTION 1: N.G. is a 78-year-old female who was diagnosed with mild NCD 4 months ago. She had been increasingly forgetful and confused from about 1 year before the diagnosis. Approximately 2 months ago, N.G.'s eldest daughter moved into her house to make sure she wasn't alone. N.G.'s daughter noticed that all of the kitchen drawers were partially open, and all of the appliances were unplugged. N.G. told her that she leaves the drawers open just in case she needs to find a knife to protect herself from the "shadow men" at night. A few weeks after N.G.'s daughter moved in, she notes that her mother has fallen

out of bed twice in the middle of the night without major injury and states that her mother "has good and bad days."

At the physician visit, N.G. was found to be medically stable. Vital signs, serum chemistries, and complete blood cell count were within normal limits. Her MMSE score was 22/30. During the review of systems, N.G.'s eldest daughter had to answer some questions because N.G. appeared either not to hear them or to ignore them. On physical examination, she demonstrated mild cog-wheeling rigidity bilaterally, bradykinesia, and masked facies; she did not display a resting tremor.

What is the most likely explanation for N.G.'s presentation?

Given her physical health, inability to live alone because of impaired cognition, and MMSE score, N.G. meets the criteria for dementia. Her rigidity, bradykinesia, and masked facies are consistent with early Parkinson disease (see Chapter 59, Parkinson Disease and Other Movement Disorders). There have been revised criteria for the clinical diagnosis of DLB (see Table 108-1).[74] N.G. exhibits all the central features, two core features, and the supportive features of repeated falls and REM sleep behavior disorder. Her presentation is consistent with probable DLB versus PDD because of her temporal sequence and lack of well-established diagnosis of Parkinson disease.

Treatment

Case 108-2, Question 2: What is an appropriate treatment for N.G.?

To date, ChEIs are the only treatment strategy for the cognitive symptoms of both PDD and DLB. All ChEIs have demonstrated symptomatic benefit in patients with DLB.[75,76] The largest randomized, placebo-controlled trials have used rivastigmine (up to 12 mg/day) in subjects with mild-to-moderate disease, and this medication has received FDA indication for PDD. Rivastigmine was reported to worsen tremor in 10% of the patients with PDD; yet, overall, there was not a statistically significant difference between groups.[72] Rivastigmine treatment has demonstrated improvements in

apathy, anxiety, delusions, and hallucinations when titrated appropriately to doses of 6 to 12 mg daily.[77] Dose initiation, titration, and monitoring are conducted in the same manner as when ChEIs are used for the treatment of AD.

N.G.'s symptoms of Parkinson disease should be fully evaluated, and appropriate treatment, such as levodopa/carbidopa, should be started (see Chapter 59, Parkinson Disease and Other Movement Disorders). Because several medications for parkinsonism can have psychiatric effects, it is important to monitor for adverse effects such as worsening psychosis and cognition. Typical antipsychotics, such as haloperidol, may worsen her extrapyramidal symptoms (EPSs) and should be avoided. Pimavanserin is the only antipsychotic indicated for Parkinson disease psychosis.[78] Other less costly antipsychotics, namely quetiapine and clozapine, may be less likely to exacerbate the parkinsonism, but efficacy is limited.[72,78]

VASCULAR DEMENTIA

Etiology

Vascular dementia (VaD) is a broad classification of cognitive disorders caused by vascular disease. The most common cause of VaD is occlusion of cerebral blood vessels by a thrombus or embolus, leading to ischemic brain injury.[79,80] In the majority of cases, the dementia syndrome is the result of multiple individual cerebral infarcts, a single infarct in an area related to cognitive function, or diffuse white matter lesions in the subcortex.[12] A number of diseases, including atherosclerosis, arteriosclerosis, and vasculitis, lead to the production of emboli and thrombi that potentially occlude brain vessels. Hemorrhagic phenomena and disorders such as HTN or cardiac disease can produce episodes of cerebral ischemia or hypoxia and are responsible for some cases of VaD.[79–81] Specific risk factors for VaDs include advancing age,

diabetes mellitus, small vessel cerebrovascular disease, HTN, heart disease, hyperlipidemia, tobacco use, and alcohol use.[80–82]

Neuropathology

VaDs are typically subcortical. Most patients with VaD have blockage of multiple blood vessels and infarction of the cerebral tissue supplied by those vessels.[81,82] When the distribution of a large artery or medium-size arteriole is blocked, focal neurologic deficits can result (see Chapter 61, Acute Ischemic and Hemorrhagic Stroke). Depending on the area affected, there may be significant cognitive impairment. More often, however, a patient may have experienced transient ischemic attacks (TIAs) or multiple microinfarcts that have remained unrecognized.[81,82] Patients with subcortical VaDs often exhibit small, deep ischemic infarcts in arterioles of the basal ganglia, thalamus, and internal capsule.[81,82] A history of atherosclerosis, diabetes mellitus, or HTN is often present without a history of stroke.[81,82] MRI scans can be very useful in diagnosing VaDs because areas of cerebral infarction are easier to visualize than they are with CT scanning (**Fig. 108-3**).[17,83] Lesions in white matter may occur in as many as 85% of patients with VaD. Deep white matter lesions known as leukoaraiosis often include demyelination and may represent early changes in dementia.[81] Because of the etiologic factors involved, VaD typically has an earlier onset than AD and affects more males than females.

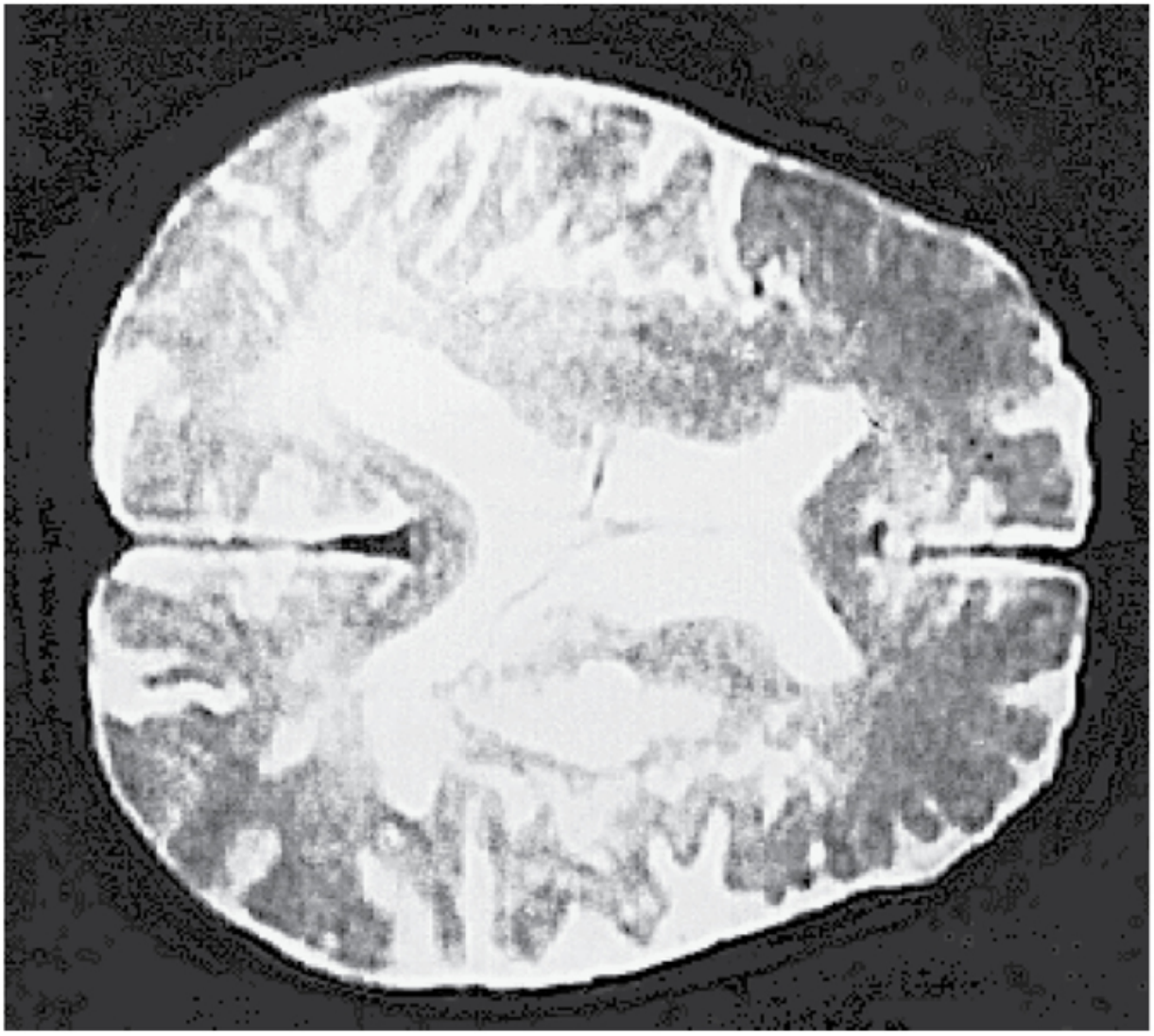


Figure 108-3 A large stroke is visible to the right of the ventricles. There is evidence of atrophy in the right temporal area.

Clinical Presentation

CASE 108-3

QUESTION 1: F.S., a 74-year-old male, is accompanied by his grandson because he is concerned that F.S. is "depressed." F.S.'s grandson reports that F.S.'s daily routine consists of eating breakfast, watching television for several hours until dinner, then sitting on the porch until bedtime. F.S. has difficulty recalling recent news despite watching the television for most of the day; he reports that the news is not "exciting enough" to remember it. The memory loss

has been slowly progressive and started ~1 to 2 years ago. F.S.'s grandson reports that he started to complete F.S.'s tax returns this past year because "it took F.S. too long." F.S. also now relies on his grandson for transportation and requires reminders for his medical appointments. He has a past medical history significant for HTN for 20 years (currently prescribed carvedilol 25 mg twice daily) and hyperlipidemia (currently prescribed atorvastatin 40 mg). He also has a history of nicotine use with a 25-pack-year history; however, he stopped smoking cigarettes 1.5 years ago after his triple coronary artery bypass graft procedure. His family history is positive for hyperlipidemia and heart disease.

On physical examination, F.S. is found to be a mildly obese male who is well dressed and groomed, alert, and oriented to person. His BP is 160/92 mm Hg sitting and 168/95 mm Hg standing. Cardiac examination is normal. Neurologic findings include somewhat diminished extraocular movements laterally and slightly asymmetric reflexes, with right greater than left. Muscle tone is normal in the lower extremities. Vibratory sensation is diminished but within normal limits for his age. His score on the MoCA was 22/30, including errors in orientation and recall. Psychologic evaluation found him to be mildly depressed.

A full laboratory analysis was generally within normal limits. F.S.'s serum potassium (3.5 mEq/dL) and sodium (137 mEq/dL) were in the low normal range, and his blood urea nitrogen (22 mg/dL) was in the upper normal range. Serum low-density lipoprotein (LDL) was 110 mg/dL, and fasting triglycerides were 230 mg/dL. A chest radiograph revealed a moderately enlarged heart; his electrocardiogram was normal. A transthoracic electrocardiogram visualized left ventricular hypokinesis with an estimated left ventricular ejection fraction of 50%. An MRI scan of the brain indicated generalized atrophy with enlarged ventricles, periventricular white matter ischemic changes, and small cortical infarcts in the right parietal lobe.

What subjective and objective evidence exists for a diagnosis of dementia in F.S.?

F.S.'s major reported problem is "depression" and impaired memory that he attributes to disinterest. However, his family began to note memory problems a full year before that episode, with progression over time. Although F.S. denies that his impairment significantly affects his daily routine, he has stopped driving and relies on his grandson for assistance with financial matters. His memory difficulties appear to have affected his mood and made him feel useless. These factors satisfy the *DSM-V* criteria for interference with normal activities.[1]

F.S.'s inability to drive reflects poor judgment behind the wheel of a car; a disturbance of higher cortical function is indicated by his

need for assistance with financial matters. There is no evidence of delirium being present. Evidence of an organic cause is provided by the MRI scan.

Diagnosis

Case 108-3, Question 2: What type of dementia does F.S. have?

There is sufficient evidence to indicate that F.S. suffers from an NCD. DSM-V provides diagnostic criteria for VaD (see Table 108-1), and it appears that the history and findings satisfy the possible VaD (unclear of temporal relationship between coronary artery bypass graft and decline).[1,79] VaDs commonly present suddenly after a cerebrovascular insult. This is followed by a period of stability and further declines after additional episodes, often in a stepwise pattern. Cognitive impairments are variable and depend on the area of the brain affected by the insult.[1,12]

With the exception of the coronary artery bypass graft, F.S.'s deterioration has had a pattern that resembles a downhill slide rather than a stepwise decline. Although his cognitive deficits are "patchy" (eg, he appears to have no language difficulty), they are not particularly prominent. F.S. displays some neurologic signs and symptoms, including diminished extraocular movements, and asymmetric reflexes, but they are subtle and might be easily missed by an untrained observer as being related to dementia. Reliance solely on the clear presence of diagnostic criteria may often lead to a missed diagnosis.[83] It is important to differentiate dementia and depression, as they both can present with memory loss and poor attention. Neurocognitive tests, such as the Geriatric Depression Scale or Patient Health Questionnaire-9 (PHQ-9), can be used to identify the presence of depression.[84,85] The Hachinski Ischemic Scale ranks signs and symptoms associated with cognitive impairment of cerebrovascular origin and is used to help differentiate between AD and VaD.[81] According to this scale, F.S.'s depression,

HTN history, and focal neurologic signs and symptoms are sufficient to indicate VaD.

F.S.'s history and clinical presentation do not suggest dementia caused by a single large stroke or several small strokes. Large strokes produce significant motor damage, typically on one side of the body (the side contralateral to the stroke). Multiple smaller strokes cause prominent motor deficits in discrete areas controlled by the affected areas. Neither of these patterns describes F.S.'s condition. However, he is clearly exhibiting signs of dementia and has significant cerebrovascular disease. He possesses several risk factors for a VaD, including HTN, smoking, hyperlipidemia, and coronary artery disease. His MRI indicates a lacunar stroke with multiple small infarcts in the deep penetrating arterioles at the base of the brain, particularly in the internal capsule, thalamus, and pons (see Chapter 61, Acute Ischemic and Hemorrhagic Stroke). These MRI findings are consistent with F.S.'s long-standing HTN and neurologic presentation.

Treatment

Case 108-3, Question 3: How should F.S. be managed?

Several treatment options that modify risk factors for VaDs are available.

SMOKING CESSATION

F.S. has taken appropriate action to stop smoking tobacco because cigarette smoking reduces cerebral blood flow and increases the risk for stroke. Among smokers with VaD, cessation of cigarette use improves cognitive performance.[86]

ANTIHYPERTENSIVE THERAPY

HTN and hyperlipidemia, both present in F.S., are additional risk factors for stroke and VaD. Control of systolic HTN reduces the risk

of stroke by 36% in older adults,[87] and maintaining the systolic BP between 135 and 150 mm Hg is associated with improved cognition among patients. The lower boundary of systolic BP that may lead to inadequate cerebral perfusion and resultant cognitive impairment is unclear; however, maintaining the systolic BP >120 mm Hg did not demonstrate a negative effect on cognition in certain patient populations.[88] For individuals without dementia, nonpharmacologic treatment (eg diet, weight loss, exercise) is an essential component. The antihypertensive agent must be chosen carefully in this population to maximize adherence and minimize adverse reactions.[89],[90] Both thiazide diuretics and β-adrenergic blockers may increase lipid levels, a potential complication in F.S. α-Adrenergic blockers and sympatholytic agents may cause depression, negative cardiac outcomes,[91] or impair cognitive activity. Calcium channel blockers or angiotensin-converting enzyme inhibitors are acceptable because they are well tolerated by older adults and may help preserve renal function in patients with diabetes mellitus (see Chapter 9, Essential Hypertension).

Dihydropyridine calcium channel blockers have been shown to improve cognition in patients with dementia and may reduce the risk of dementia in older adults with isolated systolic HTN.[92] Because F.S. has coronary artery disease, he may benefit from the use of a calcium channel blocker, such as amlodipine 5 mg daily or nifedipine XL 60 mg once daily (see Chapter 12, Chronic Stable Angina). An alternative medication may be candesartan 8 mg once daily, as when compared to an angiotensin-converting enzyme inhibitor (lisinopril), patients prescribed candesartan had higher performance on executive function and delayed recall/learning neuropsychiatric tests after one year of therapy.[93] Both agents exhibit the advantage of once-daily dosing over some other agents within their respective classes. This feature is important for maximizing adherence in patients with declining memory.

ANTILIPEMIC THERAPY

Similar to systolic BP control, control of hyperlipidemia decreases the risk of stroke by at least 16% in older adults.[94] The mainstay of cholesterol-lowering treatment is statin therapy, given their proven cardiovascular and cerebrovascular event prevention effects (see Chapter 8, Dyslipidemias, Atherosclerosis, and Coronary Heart Disease). High-intensity statin therapy is recommended in adults 75 years of age or younger; however, in F.S.'s case, moderate-intensity statin therapy can also be considered given a potential higher risk for adverse events.[95] Generally, statin therapy should not be expected to worsen cognitive impairment. However, it is theorized that hydrophobic stations (eg, simvastatin, atorvastatin, lovastatin) have higher central nervous system penetration and a higher risk for affecting cognition. Thus, more hydrophilic statins (eg, pravastatin, rosuvastatin) may be preferred in older adults with cognitive impairment.[96] Furthermore, simvastatin 80 mg/day should be avoided in all adults because of the increased risk for statin-associated muscle symptoms and rhabdomyolysis. An appropriate alternative statin therapy for J.S. could be rosuvastatin 20 mg daily or atorvastatin 40 mg daily, both of which are high-intensive statin therapies and are dose-equivalent to simvastatin 80 mg daily. Rosuvastatin may be preferred given its hydrophilicity and theoretical lower risk to affect cognition.

Generally, lifestyle modifications, such as weight loss and diet, are first-line treatments for hypertriglyceridemia. In adults ages 75 years and younger with fasting triglycerides >499 mg/dL, statin therapy is recommended.[95] Eicosapentaenoic acid (eg, icosapent ethyl) in addition to statin therapy may provide additional cerebrovascular benefits in older adults with statin-resistant hypertriglyceridemia and high or very high risk for clinical atherosclerotic cardiovascular disease; however, further trials are needed to reproduce this effect in a more diverse population.[97],[98] Thus, weight loss and diet modification, in addition to switching his statin to high-intensity, would be recommended for F.S. at this time for his hypertriglyceridemia.

ANTIPLATELET THERAPY

Prophylaxis against future cerebrovascular events is indicated in VaD; but few studies that have specifically focused on individuals with dementia are available. Cerebral perfusion and cognitive performance were improved in patients with VaD receiving aspirin 325 mg/day for 1 year when compared with a control population.[99] Guidelines from the American Heart Association and the American Stroke Association recommend the use of antiplatelet therapy in patients with a history of TIA or atherothrombotic stroke that is not of cardiogenic origin. Aspirin in doses of 50 to 325 mg/day, clopidogrel 75 mg daily, or ticagrelor 90 mg twice daily (with or without cilostazol 200 mg daily) are all effective treatments for stroke prophylaxis.[100] Direct-acting oral anticoagulants (DOACs) or warfarin are recommended after cardioembolic cerebral ischemic events.[100],[101] However, only aspirin has been studied specifically in patients with VaD. Cerebrovascular benefits usually outweigh bleeding risk (ie, GI bleeding) when aspirin is being used for secondary prevention of cerebrovascular events; however, bleeding risk should be carefully evaluated when being used for primary prevention[102] or in high-risk patients (eg, those with hemorrhagic cerebrovascular accident [CVA], cerebral angiopathy, advanced age). Given F.S.'s low bleeding risk, aspirin 81 to 325 mg daily is an appropriate first choice.

CHOLINESTERASE INHIBITORS

Deficits in cholinergic transmission and nicotinic receptor binding abnormalities have been noted in VaD.[103] Clinical trials with donepezil,[104] galantamine,[105] and rivastigmine[106] have demonstrated improvement in cognition and daily function among patients with VaD. As of yet, however, the use of these agents remains investigational and controversial. Because the use of these agents is not FDA approved for VaD, F.S. and his family should have a thorough discussion with his physician regarding the potential risks and benefits when considering ChEI treatment for him.

MANAGING FUNCTION

F.S. should be referred for physical and occupational therapy for an assessment of his strength, gait, and daily function. Physical therapy can help him maintain his strength. Occupational therapy can provide him with equipment and strategies to adapt to his dizziness and avoid falls. In addition, the use of reminder notes and labels around the house will assist him in maintaining his independence.

BEHAVIORAL DISTURBANCES IN DEMENTIA

Several types of behavioral disturbances may develop during the course of a dementia and occur in almost all patients, particularly during the later stages (**Table 108-6**).[17,107] Behavior symptoms include a wide range of disturbances, including agitation, apathy, wandering, verbal and physical aggression, and psychotic symptoms.[107,108] Agitation in dementia has been described as an excessive motor activity with a feeling of inner tension that may lead to related symptoms such as anxiety, irritability, motor restlessness, and abnormal vocalization.[17] Sleep disorders and mood disorders, such as anxiety and depression, also are common.[109] Agitation and anxiety are often managed best with nonpharmacologic treatment. Pharmacologic interventions are appropriate when nondrug therapies are unsuccessful and/or the behavior is severe or harmful to the self or others. Nonpsychologic behaviors such as wandering and inappropriate motor activity respond better to environmental modification than to drug therapy.[107,108] The first step in evaluating altered behavior in patients with dementia is to ensure that the problem is not the result of an unrecognized medical problem (eg pain, infection, psychiatric cause, constipation), environmental factors, or caused by an adverse effect of a medication (see Chapter 107, Geriatric Drug Use).

Table 108-6
Behavior Disturbances in Dementia

Behavior	Typical Presentation	Nonpharmacologic Treatment	Pharmacologic Treatment
General strategies		Safety-proof living areas Issue one-step commands for directions Maintain a daily routine of activities Avoid arguing incorrect statements Avoid startling the patient Limit unusual or overly stimulating environments	
Anxiety	Excessive worrying, sleep disturbances, rumination	Listen to, and acknowledge frustrations Redirection Exercise Engage in enjoyable activities Sleep hygiene practices Limit noise and distractions	Trazodone Buspirone (if no insomnia) Short-acting benzodiazepine SSRI antidepressant
Depression	Withdrawal, loss of appetite, irritability, restlessness, sleep disturbances	Exercise Engage in meaningful activities	Trazodone SSRI antidepressant
General agitation and restlessness	Repeated questions, wandering, pacing	Distraction and redirection Break down tasks into simple steps Provide enclosed area for exercise	Often unresponsive to medications
Paranoid behaviors	Delusions (often of theft), hallucinations, misperceptions	Reassurance Distraction, rather than confrontation Remove potential sources of confusion (eg, mirrors and other reflective surfaces)	Atypical antipsychotic, if not responsive to other strategies and person is harmful to self or others SSRI antidepressant, if associated with withdrawal, tearfulness, themes of loss
Aggressive behaviors	Physical or verbal aggressiveness toward others, excessive yelling and screaming, manic features	Identify the precipitating cause or situation Focus on the patient's feelings and concerns Avoid getting angry or upset Maintain a simple, pleasant, and familiar environment Use music, exercise, etc., as a calming activity Shift the focus to another activity	Anticonvulsant, such as divalproex or carbamazepine, possibly in combination with an atypical antipsychotic when other strategies do not work

SSRI, selective serotonin reuptake inhibitors.

Sources: Adapted from Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ.* 2015;350:h369; O'Neil ME, Freeman M, Christensen V, Telerant R, Addleman A, Kansagara D. *A Systematic Evidence Review of Non-Pharmacological Interventions for Behavioral Symptoms of Dementia*. Department of Veterans Affairs (US); 2011. www.hsrd.research.va.gov/publications/esp/dementia_nonpharm.cfm; Wolf MU, Goldberg Y, Freedman M, et al. Aggression and agitation in dementia. *Continuum (Minneap Minn)*. 2018;24(3):783–803; Sink KM, Holden KF, Yaffe K, et al. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *J Am Med Assoc*. 2005;293(5):596–608; Herrmann N, Lanctôt KL. Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. *Can J Psychiatry*. 2007;52:630–646. Teri L, Gibbons LE, McCurry SM, et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. *JAMA.* 2003;290:2015–2022.

Agitated Behaviors

CASE 108-4

QUESTION 1: B.L., a 54-year-old male, has recently been diagnosed with early-onset AD, for which he is prescribed rivastigmine 13.3 mg/day patch once daily. His past medical history is also significant for benign prostatic hyperplasia (BPH), for which he is prescribed doxazosin 4 mg at bedtime. He has given up on driving because of an episode of forgetting how to get home and, instead, relies on his college-age son. He also expresses worry about the burden he will place on his family as his condition worsens. At times, B.L. gets frustrated that he has to rely on his wife to assume responsibility for paying the monthly bills. B.L.'s wife notes that he follows her around the house and paces in circles when he gets impatient. Recently, he has had episodes of dizziness when he wakes up in the morning, which he feels like he could fall.

How should B.L.'s agitation and anxiety be managed?

Anxiety and unfocused activity are common problems in the early stages of dementia. Agitation is a general term that, although commonly used, is subject to wide interpretation. It typically is used to describe specific behaviors such as restlessness, irritability, or unfocused motor activities. Patients are aware of their progressive cognitive decline and have sufficient insight to understand the consequences. B.L.'s frustration related to his inability to perform tasks indicate insecurity and anxiety; pacing through the house is an example of restlessness and unfocused behavior. B.L. is exhibiting anxiety, as evidenced by his worry about placing a burden on his family. His poor sleep is attributable to both nocturia and anxiety.

If B.L.'s behavior represents a sudden or rapid change, his physician should first evaluate him for a medical condition such as infection, pain, or a medication-related problem. Although B.L. has previously been taking doxazosin without difficulty, he may be experiencing autonomic dysfunction that can increase his risk for falls. Doxazosin should be switched to an α-2-selective blocker; if his nocturia increases, a 5-α reductase inhibitor may be considered (see Chapter 109, Geriatric Urologic Disorders). This change may help with his orthostasis, nocturia, and disturbed sleep.

Case 108-4, Question 2: B.L.'s mental status continues to decline to the point that he requires help with grooming and dressing. During a physician visit, he accuses his wife and son of stealing from him. He also cannot locate his coin collection, which he placed in a "safe" location when his memory began to decline; during the night, he rummages through the house looking for it. He believes his family has been plotting to steal his assets and then turn him out onto the street. B.L.'s son reports that B.L. has been verbally abusive and has threatened several members of the family recently. How should B.L.'s paranoid behavior be managed?

Once medical problems have been ruled out or corrected, he should be evaluated using a systematic approach, as behavior problems are part of a chain of events. B.L. may be described as "agitated," but his behavior is shadowing his wife and pacing through the house. The behavior has an antecedent; because he has a dementia, he may be unable to initiate a meaningful or enjoyable activity on his own, and consequently he becomes bored. The consequence of his boredom is that he annoys his wife and paces the house. This evaluation represents what often is termed an "A-B-C" approach, for *antecedent, behavior, consequence.*[110] Pacing is a demonstration of unfocused energy. B.L.'s wife can give him simple tasks to perform, such as drying dishes, folding laundry, or simple gardening, to help channel his energy. It also may relieve his anxiety and insecurity. She also could accompany him on walks to alleviate his fear of getting lost. She may want to consider enrolling him in an adult day-care program. This would give him meaningful activity that might help him use up his excess energy and sleep better at night. It also will provide her with some respite and avoid or delay caregiver burnout. Appropriate strategies to manage agitated behaviors without medication are listed in Table 108-6.

When nonpharmacologic interventions are not successful in reducing anxiety, irritability, and similar behaviors, medications can be considered. Benzodiazepines are the most commonly used anxiolytics and will address B.L.'s insomnia and anxiety. However, they are associated with several negative outcomes in older adults, including confusion, amnestic syndromes, ataxia, and falls.[111] Benzodiazepines, in addition to other medications, may be

considered potentially inappropriate medications in older adults as described in the 2019 American Geriatrics Society Beers Criteria.[112] If a benzodiazepine is clinically warranted, agent such as lorazepam or oxazepam may be used if necessary, but only for a short term and with caution.[110]

Another potentially avoidable class of drugs include anticonvulsants or mood stabilizers because of their questionable benefit. Carbamazepine may decrease agitation in patients with NCDs; but conflicting data also demonstrate no significant difference compared to placebo.[113] Carbamazepine is also a strong CYP3A4 inducer (caution with ChEIs, trazodone, and some antipsychotics) as well as carries the rare, but serious risk for agranulocytosis and Stevens–Johnson syndrome. Conversely, valproic acid and its derivatives have not been found to be effective for agitation associated with NCD and may also carry a higher risk for harmful effects, such as drowsiness, fatigue, and gait imbalances.[114] These agents should generally be reserved as last-line agents prior to antipsychotic therapy. Given B.L. has not tried antidepressant therapy and has a risk for drug interactions (with rivastigmine and doxazosin), carbamazepine is not appropriate to initiate at this time.

Trazodone is a sedative antidepressant that is effective for insomnia and agitated behaviors in patients with AD.[110],[115] Treatment is started at 25 mg at bedtime and may be increased to a dose of 250 mg/day in divided doses. Another alternative treatment is buspirone, which does not cause the cognitive impairments associated with benzodiazepines. Dosage begins at 5 mg three times daily and may be increased up to 15 mg three times daily. However, buspirone will not concurrently manage B.L.'s insomnia because it has no sedative effect, and there is no reliable evidence that it is efficacious in anxiety associated with dementia.[115] Citalopram has been shown to reduce agitated behaviors in people with dementia and could be used.[116] Emerging evidence suggests that dextromethorphan–quinidine combination may be efficacious in reducing agitation; but caution exists in light of drug–drug interactions as well as limited data.[117]

If the nondrug strategies are ineffective in reducing B.L.'s insomnia and agitation, trazodone should be initiated at a dose of 25 mg at bedtime. It may be increased by 25 mg/day at 5- to 7-day intervals, up to 100 mg. Doses above 100 mg/day should be split into two daily doses.

Psychosis

Delusions and hallucinations are common among individuals with dementia. Paranoid symptoms, often accompanied by aggression, have been reported in more than half of dementia patients.[118] Delusions typically involve suspicion of theft by family members, which may be secondary to the patient's inability to remember where valuable items were placed and incorrectly concluding that they were stolen. Another common delusion is the misidentification of people or objects.[119] Capgras syndrome, the belief that a person has been "replaced" by an identical-looking impostor or the belief that photographs or television pictures are real individuals, may occur in almost half of demented individuals.[118]

There are a few behavioral interventions that could be tried first before resorting to medications, which produce limited benefits and are accompanied by significant risk.[120],[121] The first step is to conduct a person-centered examination of the symptoms. Several questions need to be answered. What is the significance or meaning of these behaviors to B.L.? (For example, he cannot locate items that are valuable to him and does not recall where they are.) What triggers his thoughts and outbursts? (He may assume the items were stolen and believes that his family, knowing their location, has taken them for their own gain.) How is the family's response further angering him? (If the family searches for and finds the items, it may reinforce his delusion that they stole them.) The family should be educated that paranoid behavior is common in dementia and that it is likely to pass as the disease progresses. Depending on how fixed the paranoia is, distraction or redirection, such as changing the subject to something more pleasant, or initiating a pleasant activity, could

resolve the problem. Regardless of the strategy, they need to be taught not to argue or debate with B.L. but to share his concern. When these strategies fail, then, depending on severity, it may be necessary to resort to medication.

Paranoid symptoms respond best to antipsychotic agents, although these are not highly effective, and no single antipsychotic is more effective than any other. Delusions, hallucinations, aggression, and uncooperativeness symptoms respond best, but overall improvement occurs in only a minority of patients.[115],[122] The CATIE-AD trial compared olanzapine, quetiapine, risperidone, and placebo for the treatment of psychosis, aggression, and agitation for up to 36 weeks in patients with AD. Improvement was noted in 32%, 26%, 29%, and 21%, respectively. The authors concluded that efficacy of the agents was offset by adverse effects.[122] There are no antipsychotic medications that are approved by the FDA for use in the management of behavioral symptoms in people with dementia. Recently, pimavanserin, a serotonin 2A receptor antagonist and inverse agonist, was FDA approved for Parkinson disease psychosis. In clinical trials, it was associated with a modest reduction in the frequency of hallucinations and delusions in patients with Parkinson disease psychosis.[123] Black box warnings are present for all agents, including pimavanserin, because of the increased risk for stroke and mortality when used in this population.[120],[121],[124],[125] Consequently, any use of antipsychotics in a person with dementia is for an unapproved use and requires a full discussion between the physician, patient, and caregivers.

The risks and potential benefits of therapy must be carefully weighed for B.L. before determining the appropriate treatment. The choice of an antipsychotic agent is determined by the symptoms displayed by the patient as well as the potential for adverse effects. B.L. is experiencing a delusion of theft, suspiciousness, and aggressive behavior. It is possible that the verbal abuse and threats are consequences of fear brought on by the false belief that his family is stealing from him and plans to abandon him.

B.L. has no major contraindications to the use of any antipsychotic agent, and his target symptoms will probably respond to any of the

available agents. Therefore, a therapeutic trial is appropriate as supported by the American Psychiatric Association guidelines.[126] The choice can be made according to which antipsychotic agent is least likely to cause intolerable adverse effects. Risperidone has been evaluated in a case series and in a large double-blind, placebo-controlled trial.[127],[128] In the case study series, symptoms improved in half of the patients taking dosages ranging from 0.5 mg every other day to 3 mg twice daily. However, 50% also experienced EPS, even at the lowest dosage used.[127] Subjects in the double-blind trial received either placebo or risperidone at dosages of 0.5 mg/day, 1 mg/day, or 2 mg/day for 12 weeks. Daily doses of 1 or 2 mg reduced psychosis and improved behavior, but EPS and somnolence were common adverse effects.[128] Low doses of olanzapine, 5 to 15 mg/day, were superior to placebo for reducing agitation, aggression, and psychosis during a 6-week study among nursing facility residents.[129] Somnolence and gait disturbances were the most common adverse effects. Quetiapine has been shown to reduce agitated and psychotic behaviors at doses of 100 to 200 mg/day.[130] Clozapine poses a significant risk for hematologic toxicity and requires careful monitoring. Because B.L. does not have cardiovascular or cerebrovascular risk factors, but does have gait or balance problems, quetiapine 25 mg at bedtime can be initiated. Quetiapine doses can be increased by 25 mg/day, up to 200 mg/day in divided doses. Once his behavior has stabilized, the medication should be continued for about 4 months. At that time, the dose should be decreased in weekly intervals to determine whether the medication is still required. B.L. should be monitored closely for adverse effects, including EPS, which can occur with the atypical antipsychotics.[126],[127],[131]

Aggressive Behaviors

Case 108-4, Question 3: After 3 months, B.L.'s delusions have subsided, but he continues to be verbally abusive and often displays angry, emotional outbursts, especially when he requires help with bathing or toileting. At other

times, he is withdrawn and apathetic. He has also been found wandering in the neighborhood on three occasions. These behaviors persist despite treatment with quetiapine 100 mg twice daily. What alternative treatments can be attempted?

Although psychotic symptoms respond to antipsychotic agents, many other behaviors do not. Up to 90% of patients with dementia exhibit at least one disruptive behavior, such as angry outbursts, screaming, and abusive language, and many display multiple aggressive behaviors.[132] As many as 32% exhibit moderate-to-severe behaviors.[132] Such behaviors are typically directed at caregivers, precipitated by receipt of assistance with ADLs, such as bathing and toileting, and increase in frequency with dementia severity.[110],[131] Several of these behaviors may be merely defensive responses to perceived threats in cognitively impaired individuals.[131] Behavioral disturbances must be addressed because they can have a negative effect on the patient's ability to perform ADLs.[110]

Some behaviors exhibited by B.L. are not likely to respond to medications. Wandering is typically unaltered by the use of medications unless the patient is oversedated. Nonpharmacologic treatments, such as periods of physical exercise and rest, or environmental modification is much more effective.[108],[110],[132] B.L.'s reactions to assistance with bathing and toileting may be caused by confusion and fear. Breaking the tasks down to step-by-step procedures, accomplished individually, often helps modify aggressive behaviors.[38]

Verbal abuse and aggressiveness place both the patient and the caregiver at risk for injury and may lead to abuse. In these situations, the patient and the caregiver may each be a precipitator or a target of abuse.[131] In some small studies, anticonvulsant agents have been shown to reduce rage and aggressive behaviors in patients resistant to treatment with antipsychotics. Carbamazepine and valproic acid (including divalproex) are the most well-studied agents.[133],[134] Although initial trials were promising, later studies did not establish efficacy. The lack of benefit plus concerns about toxicities with each agent have led to recommendations that these agents not be

used.[113],[114] The addition of an antidepressant medication may be helpful, as described below. Wandering typically does not respond to pharmacologic intervention. Appropriate strategies include environmental modification, such as placing child-safety locks on exit doors; providing activities and other distractions; and having a safety plan, such as the Safe Return program. As described for his paranoid behavior, a person-centered evaluation using the A-B-C approach should be conducted to determine the cause and effects of his aggressiveness. If B.L.'s aggressive behaviors continue, his family may need to consider obtaining in-home assistance or placement in an assisted-living facility designed for the care of patients with dementia.

Depression

Case 108-4, Question 4: How should B.L.'s social withdrawal and apathy be treated?

Depression often accompanies dementia and may significantly impair a patient's functional capacity, cognitive abilities, and communication.[1],[135] B.L. is withdrawn and apathetic, symptoms suggestive of depression. Screaming and irritability may be considered symptoms of depression in individuals with dementia, perhaps reflecting feelings of loneliness, boredom, or the need for attention.[136] Because a definite diagnosis of depression relies heavily on a patient interview and response to questions, a formal diagnosis in patients with dementia is difficult. Therefore, patient observation is an important component for making a clinical evaluation. It is possible that he is reacting to a sense of loss of not only his memory and function but also a loss of self. He also may feel isolated by the inability to communicate with others or participate in the outside world. Helping him to engage in meaningful activities and social engagement, perhaps as simple as going on a walk or attending adult day care, may help alleviate his apathy and reverse his

withdrawal. Such a strategy is appropriate to try before considering an antidepressant.

The selective serotonin reuptake inhibitors have not been well studied in patients with dementia but are effective antidepressants with adverse effects that are better tolerated than those of the tricyclic antidepressants. Sertraline, in doses of 50 to 150 mg/day, was superior to placebo in reducing depression in AD patients during a 12-week trial.[137] Citalopram has also demonstrated effectiveness; in contrast, fluoxetine and fluvoxamine have not demonstrated benefit.[113],[116] Either sertraline 50 mg daily or citalopram 10 mg daily are reasonable choices to treat B.L.'s symptoms of depression if he does not respond to nonpharmacologic strategies. He should be reassessed in 4 to 6 weeks; if he has not responded, the dose may be increased. Dosages may be increased weekly up to a maximum of 150 mg/day or 20 mg/day, respectively. A full therapeutic trial requires a minimum of 3 months.

Social Support

Case 108-4, Question 5: B.L.'s family indicates that caring for him at home has become so burdensome that they are considering placing him in an institution. What social support services are available to families facing this decision?

Institutionalization is a typical outcome for patients in the late stages of dementia. The total care required to manage a patient with dementia usually becomes unmanageable for most families as the disease progresses. Caregiver stress is often exacerbated by the patient's declining memory, inability to communicate, physical decline, and incontinence as well as the caregiver's loss of freedom and depression. Caregivers commonly experience anger, helplessness, guilt, and worry, and suffer from physical stressors such as fatigue and illness.[38]

Outside assistance is essential to families caring for a patient with dementia. Families should be referred to the Alzheimer's Association

as soon as a diagnosis of dementia is received. The association has local affiliates in most major cities. The book *The 36-Hour Day* is a valuable resource for families as well.[138] It describes the symptoms, behaviors, and problems that can be encountered when caring for a patient with dementia.

Support groups, individual and family counseling, and other sources of support are useful and may help families cope for a longer period. However, the key intervention to reduce caregiver stress is respite care, which allows a family time away from the responsibilities of taking care of a frail individual. Respite care brings a person into the home or allows the patient to go to a day-care center or similar environment on a regular schedule. Such programs may delay the need to institutionalize a patient.[38,107,138]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. (1)

Alzheimer's Association. *Alzheimer's Disease Facts and Figures 2021*. Alzheimer's Association; 2021. (2)

Mace NL, Rabins PV. *The 36-Hour Day: A Family Guide to Caring for People With Alzheimer Disease, Other Dementias, and Memory Loss in Later Life.* 4th ed. Johns Hopkins University Press; 2006. (138)

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(*3*):263–269. (11)

O'Neil ME, Freeman M, Christensen V, Telerant R, Addleman A, Kansagara D. *A Systematic Evidence Review of Non-Pharmacological Interventions for*

Behavioral Symptoms of Dementia. Department of Veterans Affairs (US); 2011. www.hsrd.research.va.gov/publications/esp/dementia_nonpharm.cfm (108)

Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *J Am Med Assoc*. 2005;293(*5*):596–608 (113)

Key Websites

Alzheimer's Association. http://www.alz.org

Family Caregiver Alliance. www.caregiver.org

The DICE Approach™. https://diceapproach.com

U.S. Department of Health and Human Services Clinical Trials. https://www.alzheimers.gov/clinical-trials

COMPLETE REFERENCES CHAPTER 108 GERIATRIC NEUROCOGNITIVE DISORDERS

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
2. Alzheimer's Association. *Alzheimer's Disease Facts and Figures 2021*. Alzheimer's Association; 2021.
3. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical AD and mild cognitive impairment in the United States (2020–2060). *Alzheimers Dement* 2021;17(12):1966–1975.
4. Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM. Prevalence of dementia subtypes in United States Medicare free-for-service beneficiaries, 2011–2013. *Alzheimer's Dement*. 2017;13(1):28–37.
5. Kochanek KD, Xu J, Murphy SL, Miniño AM, Kung HC. Deaths: preliminary data for 2009. *Nat Vital Stat Rep*. 2011;59(4):1–51.
6. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*. 2013;80(19):1778–1783.
7. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013;9(1):63–75.e2.
8. Brookmeyer R, Corrada MM, Curriero FC, Kawas C. Survival following a diagnosis of Alzheimer disease. *Arch Neurol*. 2002;59:1764–1767.

9. Muller C, Soysal P, Rongve A, et al. Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: a meta-analysis of longitudinal studies. *Ageing Res Rev*. 2019;50:72–80.
10. Freund B, Gravenstein S. Recognizing and evaluating potential dementia in office settings. *Clin Geriatr Med*. 2004; 20:1–14.
11. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263–269.
12. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: a clinical review. *Neurology*. 2019;92(24):1146–1156.
13. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. *J Am Geriatr Soc*. 2003;51:1451–1454.
14. Nassredine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005:53:695–699.
15. Tariq SH, Tumosa N, Chibnall JT, Perry MH 3rd, Morley JE. Comparison of the Saint Louis University Mental Status Examination and the Mini-Mental State Examination for detecting dementia and mild neurocognitive disorder: a pilot study. *Am J Geriatri Psych*. 2006:14(11):900–910.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
17. Mayeux R, Reitz C, Brickman AM, et al. Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment—part 1. *Alzheimers Dement*. 2011;7:15–34.
18. Jayaraman A, Pike CJ. Alzheimer's disease and type 2 diabetes: multiple mechanisms contribute to interactions. *Curr Diab Rep*. 2014;14:476.
19. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J*. 2012;42(5):484–491. doi:10.1111/j.1445-5994.2012.02758.x
20. Taylor C, Tillin T, Chaturvedi N, et al. Midlife hypertensive status and cognitive function 20 years later: the Southall and Brent revisited study. *J Am Geriatr Soc*. 2013;61:1489–1498.
21. Reed BR, Marchant NL, Jagust WJ, DeCarli CC, Mack W, Chui HC. Coronary risk correlates with cerebral amyloid deposition. *Neurobiol Aging*. 2012;33:1979–1987.
22. Aisen PS, Cummings J, Jack CR, et al. On the path to 2025: understanding the Alzheimer's disease continuum. *Alz Res Therapy.* 2017;9:60.
23. Mattson MP. Pathways towards and away from Alzheimer's disease. *Nature*. 2004;430:631–639.

24. Francis P. Targeting cell death in dementia. *Alzheimer Dis Assoc Disord*. 2006;20(2 suppl 1):S3–S7.
25. Arai T, Ikeda K, Akiyama H, et al. A high incidence of apolipoprotein E epsilon allele in middle-aged non-demented subjects with cerebral amyloid beta protein deposits. *Acta Neuropathol*. 1999;97:82–84.
26. Raskin J, Cummings J, Hardy J, Schuh K, Dean RA. Neurobiology of Alzheimer's disease: integrated molecular, physiological, anatomical, biomarker, and cognitive dimensions. *Curr Alzheimer Res*. 2015;12:712–722.
27. Dickson DW. Neuropathology of Alzheimer's disease and other dementias. *Clin Geriatr Med*. 2001;17:209.
28. Cummings JL, Vinters HV, Cole GM, Khachaturian ZS. Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology*. 1998;51(1 suppl 1):S2–S17.
29. Wilkinson DG, Francis PT, Schwam E, Payne-Parrish J. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. *Drugs Aging*. 2004;21:453–478.
30. Hamel R, Köhler S, Sistermans N, et al. The trajectory of cognitive decline in the pre-dementia phase in memory clinic visitors: findings from the 4C-MCI study. *Psychol Med*. 2015;45:1509–1519.
31. Liu-Seifert H, Siemers E, Price K, et al. Cognitive impairment precedes and predicts functional impairment in mild Alzheimer's disease. *J Alzheimers Dis*. 2015;47:205–214.
32. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol*. 2007;6:734–746.
33. Arneric´ SP, Batrla-Utermann R, Beckett L, et al. Cerebrospinal fluid biomarkers for Alzheimer's disease: a view of the regulatory science qualification landscape from the Coalition Against Major Diseases CSF Biomarker Team. *J Alzheimers Dis*. 2017;55:19–35.
34. Chételat G, La Joie R, Villain N, et al. Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. *Neuroimage Clin*. 2013;2:356–365. doi:10.1016/j.nicl.2013.02.006
35. Hodges JR, Erzinçliog˘lu S, Patterson K. Evolution of cognitive deficits and conversion to dementia in patients with mild cognitive impairment: a very-long-term follow-up study. *Dement Geriatr Cogn Disord*. 2006;21:380–391.
36. Mittelman MS, Ferris SH, Shulman E, Steinberg G, Levin B. A family intervention to delay nursing home placement of patients with Alzheimer disease. A randomized controlled trial. *JAMA*. 1996;276:1725–1731.
37. Finucane TE, Christmas C, Travis K. Tube feeding in patients with advanced dementia: a review of the evidence. *JAMA*. 1999;282:1365–1370.
38. Harrison Dening K, Sampson EL, De Vries K. Advance care planning in dementia: recommendations for healthcare professionals. *Palliat Care*.

2019;12:1178224219826579.
39. Riordan KC, Hoffman Snyder CR, Wellik KE, Caselli RJ, Wingerchuk DM, Demaerschalk BM. Effectiveness of adding memantine to an Alzheimer dementia treatment regimen which already includes stable donepezil therapy: a critically appraised topic. *Neurologist*. 2011;17(2):121–123.
40. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*. 2006;(1):CD005593.
41. Aduhelm (aducanumab-avwa). Package insert. Biogen Inc; 2021.
42. EMERGE and ENGAGE topline results: two phase 3 studies to evaluate Aducanumab in patients with early Alzheimer's disease. 2019. https://investors.biogen.com/static-files/ddd45672-9c7e-4c99-8a06-3b557697c06f
43. Masterman D. Cholinesterase inhibitors in the treatment of Alzheimer's disease and related dementias. *Clin Geriatr Med*. 2004;20:59–68.
44. Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. *Arch Intern Med*. 1998;158:1021–1031.
45. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356–1364.
46. Knopman DS, Knapp MJ, Gracon SI, Davis CS. The Clinician Interview-Based Impression (CIBI): a clinician's global change rating scale in Alzheimer's disease. *Neurology*. 1994;44:2315–2321.
47. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology*. 1998;50:136–145.
48. Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD; Donepezil Study Group. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol*. 2001;58:427–433.
49. Panisset M, Roudier M, Saxton J, Boller F. Severe impairment battery. A neuropsychological test for severely demented patients. *Arch Neurol*. 1994;51:41–45.
50. Winblad B, Kilander L, Eriksson S, et al. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo controlled study [published corrections appear in *Lancet*. 2006;367:1980; *Lancet*. 2006;368:1650]. *Lancet*. 2006;367:1057–1065.
51. Farlow MR, Salloway S, Tariot PN, et al. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomized, double-blind study. *Clin Ther*. 2010;32:1234–1251.
52. Williams BR, Nazarians A, Gill MA. A review of rivastigmine: a reversible cholinesterase inhibitor. *Clin Ther*. 2003;25:1634–1653.

53. Corey-Bloom J, Anand R, Veach J. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatr Psychopharmacol*. 1998;1:55–65.
54. Rösler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial [published correction appears in *BMJ*. 2001;322:1456]. *BMJ*. 1999;318:633–638.
55. Farlow M, Anand R, Messina J Jr, Hartman R, Veach J. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. *Eur Neurol*. 2000;44:236–241.
56. Grossberg G, Sadowsky C, Fröstl H, et al. Safety and tolerability of the rivastigmine patch: results of a 28-week open-label extension. *Alzheimer Dis Assoc Disord*. 2009;23:158–164.
57. Scott LJ, Goa KL. Galantamine: a review of its use in Alzheimer's disease. *Drugs*. 2000;60:1095–1122.
58. Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology*. 2000;54:2269–2276.
59. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group [published correction appears in *BMJ*. 2001;322:405]. *BMJ*. 2000;321:1445–1449.
60. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *BMJ*. 2005;331:321–327.
61. Hernandez RK, Farwell W, Cantor MD, Lawler EV. Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the veterans affairs New England healthcare system. *J Am Geriatr Soc*. 2009;57(11):1997–2003. doi:10.1111/j.1532-5415.2009.02488.x
62. Becker M, Andel R, Rohrer L, Banks SM. The effect of cholinesterase inhibitors on risk of nursing home placement among Medicaid beneficiaries with dementia. *Alzheimer Dis Assoc Disord*. 2006;20:147–152.
63. Wallin AK, Andreasen N, Eriksson S, et al. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. *Dement Geriatr Cogn Disord*. 2007;23:150–160.
64. Winblad B, Wimo A, Engedal K, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. *Dement Geriatr Cogn Disord*. 2006;21:353–363.
65. Jarvis B, Figgitt DP. Memantine. *Drugs Aging*. 2003;20:465–476.
66. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry*. 1999;14:135–146.

67. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev*. 2006;(2):CD003154.
68. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA*. 2004;291:317–324.
69. Feldman HH, Schmitt FA, Olin JT; Memantine MEM-MD-02 Study Group. Activities of daily living in moderate to-severe Alzheimer disease: an analysis of the treatment effects of memantine in patients receiving stable donepezil treatment. *Alzheimer Dis Assoc Disord*. 2006;20:263–268.
70. Reisberg B, Doody R, Stöffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348:1333–1341.
71. Dysken MW, Sano M, Asthana S, et al. Effect of Vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. *JAMA*. 2014;311(1):33–44.
72. Lippa CF, Duda JE, Grossman M, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology*. 2007;68:812–819.
73. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*. 1996;47:1113–1124.
74. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. *Neurology*. 2017;89(1):88–100.
75. Bhasin M, Rowan E, Edwards K, McKeith I. Cholinesterase inhibitors in dementia with Lewy bodies: a comparative analysis. *Int J Geriatr Psychiatry*. 2007;22:890–895.
76. Edwards K, Royall D, Hershey L, et al. Efficacy and safety of galantamine in patients with dementia with Lewy bodies: a 24-week open-label study. *Dement Geriatr Cogn Disord*. 2007;23:401–405.
77. McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo controlled international study. *Lancet*. 2000;356:2031–2036.
78. Patel RS, Bhela J, Tahir M, Pisati SR, Hossain S. Pimavanserin in Parkinson's disease-induced psychosis: a literature review. *Cureus*. 2019;11(7):e5257.
79. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord*. 2014; 28(3):206–18.
80. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:2672–2713. doi:10.1161/STR.0b013e3182299496

81. Chui H. Neuropathology lessons in vascular dementia. *Alzheimer Dis Assoc Disord*. 2005;19:45–52.
82. Messier C, Gagnon M. Cognitive decline associated with dementia and type 2 diabetes: the interplay of risk factors. *Diabetologia*. 2009;52:2471–2474.
83. DeCarli C. The role of neuroimaging in dementia. *Clin Geriatr Med*. 2001;17:255–279.
84. Rinalda P, Mecocci P, Benedetti C, et al. Validation of the five-item geriatric depression scale in elderly subjects in three different settings. *J Am Geriatr Soc*. 2003;51(5):694–698.
85. Kronke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613.
86. Choi D, Choi S, Park SM. Effect of smoking cessation on the risk of dementia: a longitudinal study. *Ann Clin Transl Neurol*. 2018;5(10):1192–1199.
87. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991;265:3255–3264.
88. Effect of intensive vs standard blood pressure control on probably dementia: a randomized clinical trial. SPRINT MIND Investigators for the SPRINT Research Group. *J Am Med Assoc* 2019;321(6):553–561.
89. Williams BR, Kim J. Cardiovascular drug therapy in the elderly: theoretical and practical considerations. *Drugs Aging*. 2003;20:445–463.
90. Iadecola C, Yaffe K, Biller J, et al. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. *Hypertension* 2016;68(6):e67–e94.
91. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group [published correction appears in *JAMA*. 2002;288:2976]. *JAMA*. 2000;283:1967–1975.
92. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study [published correction appears in *Arch Intern Med*. 2003;163:241]. *Arch Intern Med*. 2002;162:2046–2052.
93. Hajjar I, Okafor M, McDaniel D, et al. Effects of candesartan vs lisinopril on neurocognitive function in older adults with executive mild cognitive impairment: a randomized clinical trial. *JAMA Netw Open*. 2020;3(8):e2012252.
94. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010 13;376(9753):1670–1681.

95. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/ACCVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;139:e1082–e1143.
96. Rojas-Fernandez CH, Goldstein LB, Levey AI, Taylor BA, Bittner V, The National Lipid Association's Safety Task Force. An assessment by the Statin Cognitive Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(3 suppl):S5–S16.
97. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22.
98. Orringer CE, Jacobson TA, Maki KC, et al. National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. *J Clin Lipidol*. 2019;13(6):860–872.
99. Meyer JS, Rogers RL, McClintic K, Mortel KF, Lotfi J. Randomized clinical trial of daily aspirin therapy in multi-infarct dementia. A pilot study. *J Am Geriatr Soc*. 1989;37:549–555.
100. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2021;52:e364–e467.
101. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154(5): 1121–1201.
102. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guidelines on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2019;74(10):e177–e232.
103. Erkinjuntti T. Cognitive decline and treatment options for patients with vascular dementia. *Acta Neurol Scand Suppl*. 2002;178:15–18.
104. Meyer JS, Chowdhury MH, Xu G, Li YS, Quach M. Donepezil treatment of vascular dementia. *Ann N Y Acad Sci*. 2002;977:482–486.
105. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet*. 2002;359:1283–1290.
106. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: an open 22-month study. *J Neurol Sci*. 2002;203–204:141–146.
107. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369.

108. O'Neil ME, Freeman M, Christensen V, Telerant R, Addleman A, Kansagara D. *A Systematic Evidence Review of Non-Pharmacological Interventions for Behavioral Symptoms of Dementia*. Department of Veterans Affairs (US); 2011. www.hsrd.research.va.gov/publications/esp/dementia_nonpharm.cfm
109. Bliwise DL. Sleep disorders in Alzheimer's disease and other dementias. *Clin Cornerstone*. 2004;6(suppl 1A):S16–S28.
110. Wolf MU, Goldberg Y, Freedman M. Aggression and agitation in dementia. *Continuum (Minneap Minn)*. 2018;24(3):783–803.
111. Tampi RR, Tampi DJ. Efficacy and tolerability of benzodiazepines for the treatment of behavioral and psychological symptoms of dementia: a systemic review of randomized controlled trials. *Am J Alzheimers Dis Other Demen*. 2014:29(7):565–574.
112. 2019 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–694.
113. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *J Am Med Assoc*. 2005;293(5):596–608.
114. Baillon SF, Narayana U, Luxenberg JS, Clifton AV. Valproate preparations for agitation in dementia. *Cochrane Database Syst Rev*. 2018;10(10):CD003945.
115. Herrmann N, Lanctôt KL. Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. *Can J Psychiatry*. 2007;52:630–646.
116. Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized controlled trial. *JAMA*. 2014;311(7):682–691. doi:10.1001/jama.2014.93
117. Cummings JL, Lyketsos CG, Peskind ER, et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. *JAMA*. 2015;314(12):1242–1254.
118. Binetti G, Bianchetti A, Padovani A, Lenzi G, De Leo D, Trabucchi M. Delusions in Alzheimer's disease and multi-infarct dementia. *Acta Neurol Scand*. 1993;88:5–9.
119. Devanand DP, Jacobs DM, Tang MX, et al. The course of psychopathologic features in mild to moderate Alzheimer disease. *Arch Gen Psychiatry*. 1997;54:257–263.
120. Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med*. 2007;146:775–786.
121. Herrmann N, Mamdani M, Lanctôt KL. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry*. 2004;161:1113–1115.
122. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355:1525–1538.

123. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533–540.
124. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ*. 2005;330:445.
125. Hwang YJ, Alexander GC, An H, Moore TJ, Mehta HB. Risk of hospitalization and death associated with pimavanserin use in older adults with Parkinson disease. *Neurol* 2021;97(13):e1266–e1275.
126. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association practice guidelines on the use of antipsychotics to treat agitation or psychosis in patients with dementia. *Am J Psychiatry*. 2016;173(5):543–546.
127. Herrmann N, Rivard MF, Flynn M, Ward C, Rabheru K, Campbell B. Risperidone for the treatment of behavioral disturbances in dementia: a case series. *J Neuropsychiatry Clin Neurosci*. 1998;10(2):220–223.
128. Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. *J Clin Psychiatry*. 1999;60:107–115.
129. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo controlled trial. The HGEU Study Group. *Arch Gen Psychiatry*. 2000;57(10):968–976.
130. Zhong KX, Tariot PN, Mintzer J, Minkwitz MC, Devine NA. Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study. *Curr Alzheimer Res*. 2007;4:81–93.
131. Bridges-Parlet S, Knopman D, Thompson T. A descriptive study of physically aggressive behavior in dementia by direct observation. *J Am Geriatr Soc*. 1994;42:192–197.
132. Teri L, Gibbons LE, McCurry SM, et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. *JAMA*. 2003;290:2015–2022.
133. Tariot PN, Erb R, Podgorski CA, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry*. 1998;155(1):54–61.
134. Porsteinsson AP, Tariot PN, Erb R, et al. Placebo-controlled study of divalproex sodium for agitation in dementia. *Am J Geriatr Psychiatry*. 2001;9(1):58–66.
135. Olin JT, Schneider LS, Katz IR, et al. Provisional diagnostic criteria for depression of Alzheimer disease. *Am J Geriatr Psychiatry*. 2002;10:125–128.
136. Segal-Gidan F, Cherry D, Jones R, et al. Alzheimer's disease management guideline: update 2008. *Alzheimers Dement*. 2011;7:e51–e59.

137. Lyketsos CG, Sheppard JM, Steele CD, et al. Randomized, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer's disease: initial results from the Depression in Alzheimer's Disease study. *Am J Psychiatry*. 2000;157:1686–1689.
138. Mace NL, Rabins PV. *The 36-Hour Day: A Family Guide to Caring for People With Alzheimer Disease, Other Dementias, and Memory Loss in Later Life*. 4th ed. Johns Hopkins University Press; 2006.

109

Geriatric Urologic Disorders

Jaini Patel

CORE PRINCIPLES		CHAPTER CASES
URINARY INCONTINENCE		
1	Urinary incontinence is a common condition in older adults and can be classified as acute or persistent. Persistent incontinence can further be classified as urge, stress, overflow, or functional.	**Case 109-1 (Questions 1, 2)**
2	Urge incontinence is managed with nonpharmacologic interventions, such as a toileting schedule, and the use of anticholinergic and β_3-agonist agents.	**Case 109-1 (Questions 3, 4)**
3	Stress incontinence is managed with local estrogens, tricyclic antidepressants, and duloxetine.	**Case 109-2 (Questions 1, 2)**
BENIGN PROSTATIC HYPERPLASIA		

1	Benign prostatic hyperplasia (BPH) is the most common urologic condition in aging males. A wide range of signs and symptoms occurs in BPH that cause patients to seek care.	**Case 109-3 (Questions 1–3)**
2	Management of BPH includes the use of α_{1A}-adrenergic receptor antagonists and 5α-reductase inhibitors, either alone or in combination. Nonpharmacologic treatment and surgery may also be considered for some patients. In general, the use of over-the-counter medications should not be used to treat symptomatic BPH.	**Case 109-3 (Questions 4–7)**

ERECTILE DYSFUNCTION

1	Erectile dysfunction (ED) is a condition that can be a result of neurogenic, hormonal, or vascular disorders. It is therefore essential that a complete urologic workup is conducted to assess the underlying pathophysiology. Underlying conditions should be addressed and treated before symptomatic therapy is initiated.	**Case 109-4 (Questions 1–6)**
2	Treatment for ED consists of a variety of pharmacologic agents, which include phosphodiesterase inhibitors, intracavernous injections, and alprostadil.	**Case 109-4 (Questions 7–14)**

INTRODUCTION

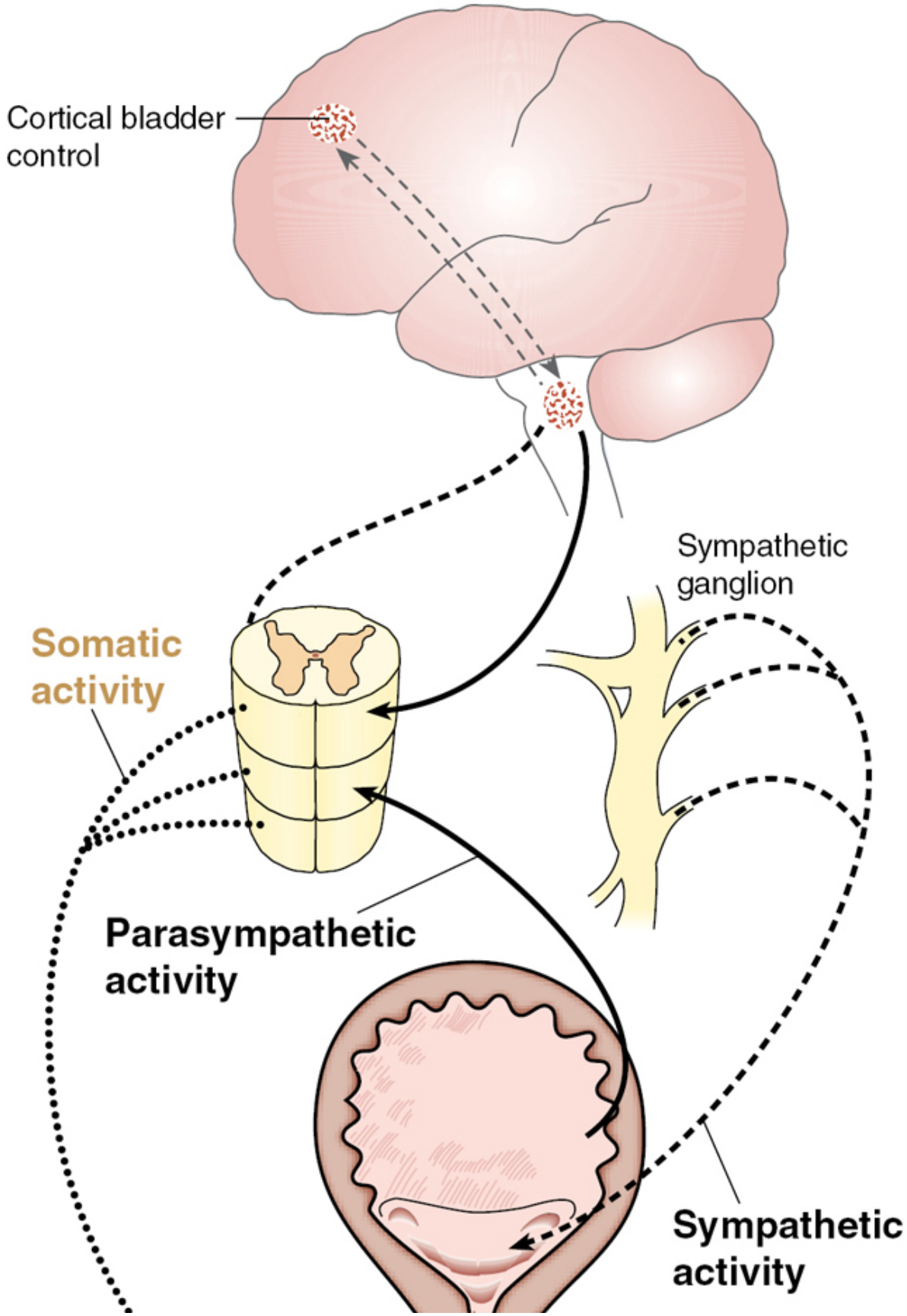
Urinary Incontinence

Urinary incontinence (UI) is defined by the International Continence Society as the involuntary leakage of urine. UI affects ~50% of females between ages 40 and 60 years and an estimated 75% of females ages 75 years or older.[1–3] UI remains one of the most underreported problems despite many negative implications, most likely due to a lack of acceptable ways to discuss voiding-related issues and patients accepting it as a normal part of aging. UI is associated with reduced quality of life from associated conditions such as depression and social isolation, impaired sexual dysfunction, and increased morbidity from complications such as pressure sores and infections.[4]

Anatomy and Normal Physiology

Neuroanatomy and neurophysiology of the bladder and urethra are important to understand the normal physiology of the voiding process. Similarly, identifying the underlying pathophysiology of UI and the subtypes of UI is essential to selecting appropriate treatment modalities. The bladder is like a “pear-shaped balloon” composed of a muscular layer, the detrusor muscle, with a narrow outlet. The detrusor and the bladder outlet functions are coordinated neurologically to allow for storage and expulsion of urine through activation of muscarinic receptors.[5] Out of the five types of muscarinic receptors, the M_3 receptor is primarily responsible for the contraction and relaxation of the detrusor muscle. The detrusor muscle is innervated by the parasympathetic nervous system, and the bladder outlet is innervated by the sympathetic nervous system (α-adrenergic) (**Fig. 109-1**). The proximal smooth muscle (internal) sphincter in the bladder neck also is innervated through the sympathetic nervous system (α-adrenergic). The distal striated

muscle (external) sphincter of the urethra is supplied by the somatic nervous system.


Cortical bladder control
Sympathetic ganglion
Somatic activity
Parasympathetic activity
Sympathetic activity

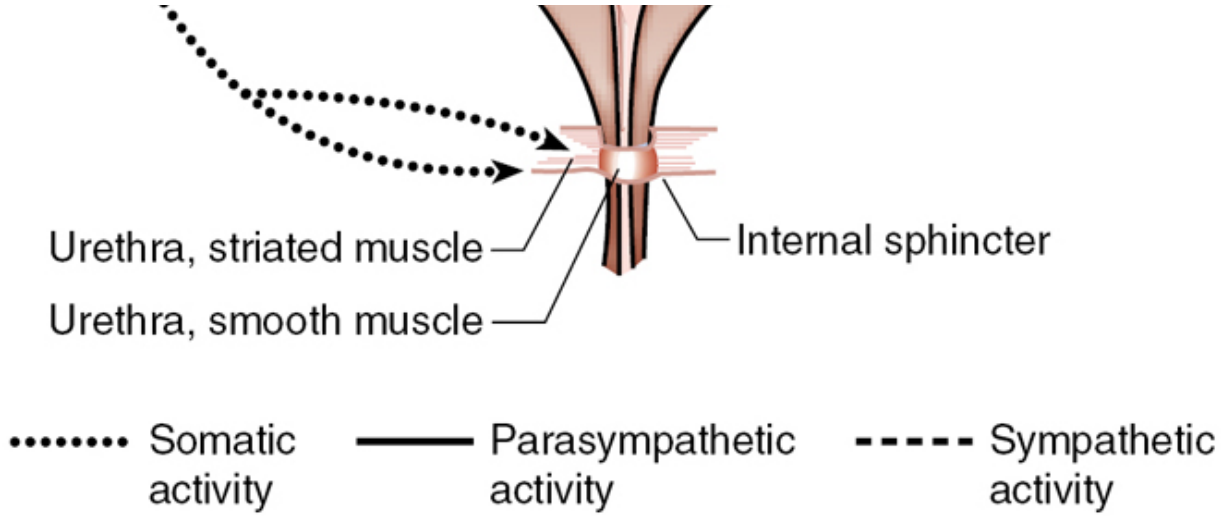


Figure 109-1 Neurologic bladder control.

Urine storage is the result of detrusor muscle relaxation and closure of both the internal and external sphincters. Detrusor relaxation is accomplished by central nervous system (CNS) inhibition of the parasympathetic tone; sphincter closure is mediated by a reflex increase in α-adrenergic and somatic activity. Voiding occurs when detrusor contraction is coordinated with sphincter relaxation. Detrusor contraction is mediated by the parasympathetic nervous system, and relaxation requires inhibition of somatic and sympathetic nerve impulses to the outlet. The bladder capacity is ~300 mL in older adults and ~400 mL in young adults, whereas normal postvoid residual volume (PVR) is typically <50 mL. PVR is the volume of urine left in the bladder after complete voiding.

AGE-RELATED PHYSIOLOGIC CHANGES

Aging brings a myriad of physiologic and functional changes to all the organ systems, including the genitourinary system (**Table 109-1**). With aging, the bladder loses its elasticity, and the sphincter of the urethra loses its ability to maintain its pressure. These aging-related physiologic changes impacting the functionality of the bladder and voiding process stem from varying etiologies. For females, these changes are correlated with the postmenopausal decline of estrogen production. Estrogen has trophic effects on the epithelium and on

tissues lining and surrounding the urethra, bladder outlet, and vagina. Atrophy of these tissues can result in friability, inflammation, susceptibility to infection, diminished periurethral blood flow, and prolapse of pelvic structures. All these effects can precipitate symptoms of UI.[6] For males, the age-related changes in the prostate gland are responsible for many of the changes in urination.[7] These physiologic changes most commonly lead to abnormalities, resulting in either bladder/urethral overactivity or underactivity, leading to incontinence and associated urinary symptoms.

Table 109-1
Age-Related Changes in Urologic Function

↓ Bladder capacity
↑ Residual urine
↑ Uninhibited bladder contractions
↑ Nocturnal sodium and fluid excretion
↓ Urethral resistance in females
↑ Urethral resistance in males
Weakness of pelvic floor muscles in females

MODIFIABLE EXACERBATING FACTORS

Aside from nonmodifiable factors including age and gender, several modifiable factors may contribute or exacerbate UI symptoms. Such factors can be described with the mnemonic DIPPERS (**Table 109-2**).[8] Pharmaceuticals listed in the DIPPERS mnemonic are important to identify to evaluate their risks and benefits and appropriateness of their continuation if the risks of uncontrolled UI outweigh their benefits. Some common pharmacologic agents in the geriatric population that may contribute to UI symptoms are listed alongside the probable mechanism in **Table 109-3**.[9–12]

Table 109-2
Causes of Incontinence: DIPPERS

D	Delirium

I	Infection
P	Psychological
P	Pharmaceuticals (see Table 109-3)
E	Excess urine output
R	Reduced mobility
S	Stool impaction (and other factors)

Source: Wagg A, Gibson W, Ostaszkiewicz J, et al. Urinary incontinence in frail elderly persons: report from the 5th International Consultation on Incontinence. *Neurourol Urodyn.* 2015;34(5):398–406.

Table 109-3
Drugs and Substances That Exacerbate Urinary Incontinence Symptoms

Associated Drugs	Probable Mechanism
α-Adrenergic antagonists (eg, doxazosin)	Relaxes the muscle at the bladder outlet and/or decreases internal sphincter tone
Cholinesterase inhibitors (eg, donepezil)	Increases detrusor tone and contractility
Antidepressants (duloxetine)	Mechanism not clearly defined, but potential to result in detrusor overactivity
Oral or transdermal estrogens	Mechanism not clearly defined, but potential to result in detrusor overactivity
Caffeine	Increases urine production, resulting in urinary urgency and frequency; diuretic-like effects
Alcohol	Increases frequency/urgency of urination, diuretic-like effects
Diuretics (eg, furosemide)	Increases urine production, resulting in urinary urgency and frequency
Muscle relaxants/sedatives (eg, diazepam)	Relaxes the urethra (decrease tone)
ACE inhibitors (eg, lisinopril)	Cough (adverse drug event) and subsequent increased intra-abdominal pressure

Antipsychotics (eg, aripiprazole)	Decreased urethral tone through potential α-antagonism
benzodiazepines, opioids, sedatives (eg, alprazolam, hydrocodone)	Impaired physical functioning and/or cognition and/or sedative adverse effect may decrease the desire to urinate. Relaxes the detrusor and may contribute to urinary retention, constipation, and/or fecal impaction
Antihistamines (eg, loratadine, cetirizine, diphenhydramine)	Relaxes the detrusor and may contribute to urinary retention because of anticholinergic properties
α-Adrenergic agonists (eg, tizanidine) or β-blockers (eg, metoprolol)	Urinary retention and increases internal sphincter tone
β-Adrenergic agonists (eg, mirabegron, vibegron)	Inhibits detrusor function causing urinary retention
Anticholinergics (eg, benzatropine)	May cause constipation; thus, impacted stool may lead to urinary retention and/or decrease contractility of the detrusor muscle
Calcium channel blockers (eg, amlodipine)	Decreases bladder contractility, causing urinary retention and/or potential adverse effect of constipation

ACE, angiotensin-converting enzyme.

Sources: Culligan PJ, Heit M. Urinary incontinence in women: evaluation and management. *Am Fam Physician*. 2000;62:2433–2444; Harvard Medical School. *Medications That Cause Urinary Incontinence*. Harvard Health Publishing; 2014; National Association for Continence (NAFC). Glossary. 2015. *www.nafc.org/glossary/*; Tsakiris P, Oelke M, Michel M. Drug-induced urinary incontinence. *Drugs Aging*. 2008;25:541–549.

CLASSIFICATION

UI can be classified into several different types based on underlying pathophysiology and symptoms. If an initial evaluation of a patient's symptoms and medical history identify any underlying etiology or causes for UI, then it is considered reversible UI. If no reversible factors are contributing to UI, then it is considered chronic or

persistent UI. **Table 109-4** reviews the pathophysiology and symptoms of various UI types: stress urinary incontinence (SUI), urge urinary incontinence (UUI), overflow incontinence (OI), and functional urinary incontinence (FUI). Of note, UUI also contains a subtype class known as overactive bladder (OAB).[13],[14] OAB is defined as having urgency together with a noted frequency of urination of more than eight times a day, more than one occurrence of nocturia per day, and enuresis. A patient with general UUI will not meet these specific thresholds pertaining to frequency. Mixed UI can be a combination of any UI type. Patients with mixed UI usually have a combination of SUI and UUI.

Table 109-4

Urinary Incontinence Types and Characteristics

UI Types	Detrusor Muscle Activity	Urethral Sphincter	Pelvic Floor	Signs and Symptoms
UUI	Involuntary contractions caused by infection or neurologic conditions (detrusor overactivity)	No changes noted	No changes noted	A strong desire or urgency to urinate without the ability to defer the urge PVR < 50 mL Leakage is small.
SUI	No changes noted	No changes noted	Increased abdominal pressure with or without relaxed pelvic floor muscles Weakened pelvic floor muscles in females (childbirth, menopause)	Involuntary leakage during exertion (ie, physical activity) or from activities that apply pressure to the bladder (eg, coughing, laughing, sneezing) PVR < 50 mL Leakage is small.
OI	Weakened muscle tone (detrusor underactivity) secondary to nerve damage (eg, nerve damage from uncontrolled diabetes, spinal cord injury)	Obstructed urethra (eg, tumor, stone, enlarged prostate)	No changes noted	Complication of retention of urine when the bladder cannot empty completely, resulting in overdistension Experience urinary urgency/frequency, small voided volumes, urinary hesitation, poor/diminished flow rate, or nocturia PVR > 100 mL Leakage is large.
FUI	Physiology not typically altered	Physiology not typically altered	Physiology not typically altered	Inability to reach a toilet in time to void because of physical or cognitive impairment and/or external obstacles (ie, uses a wheelchair) PVR < 50 mL Leakage is small.

FUI, functional urinary incontinence; OI, overflow incontinence; PVR, postvoid residual volume; SUI, stress urinary incontinence; UI, urinary incontinence; UUI, urge urinary incontinence.

Clinical Presentation and Evaluation

CASE 109-1

QUESTION 1: H.K., an 83-year-old female with moderate dementia, was recently admitted to a nursing facility because of uncontrolled and worsening UI over the past 2 years. While at home, she was mainly being managed with use of absorbent pads and bladder training.

What objective and subjective data are needed to determine the type of UI contributing to H.K.'s UI?

The rationale for the clinical evaluation of H.K. is to classify the imbalance between bladder pressure and bladder sphincter resistance and, as a result, institute appropriate medical or surgical management of her UI.

Documentation of H.K.'s UI is accomplished most easily by keeping an incontinence record. Observations should be recorded every 2 hours regarding whether she is wet or dry, as well as associated symptoms or circumstances. A record maintained for 3 to 4 days will facilitate the assessment of the voiding pattern. Knowledge of the voiding pattern can be used to design bladder training programs and to detect iatrogenic causes (eg, diuretic ingestion, use of restraints). Successful bladder training relies on estimating when the bladder is full.

Physical examination, including a neurologic assessment, of H.K. is needed to determine the cause and classification of her UI. Clinical findings may identify specific pathophysiologic abnormalities. H.K. should have a thorough pelvic examination to determine the contribution of atrophic vaginitis, uterine prolapse, and bladder anatomy. Funneling of the bladder neck suggests stress incontinence, and palpation of the bladder suggests OI. The presence of physical restraints or musculoskeletal disability would suggest FUI.

H.K.'s bladder should be catheterized immediately after urination to determine residual urine volume. Alternatively, if a bladder ultrasound is available, the volume can be measured noninvasively. Volumes >50 to 100 mL in older adults are abnormal and may indicate retention due to obstruction or an adynamic detrusor muscle. If urinary retention is chronic, the patient may require clean

intermittent self-catheterization. Although urodynamic studies are widely recommended and used, little evidence suggests that these produce clinically useful data for institutionalized geriatric patients. A urinalysis, blood chemistries, renal function, and postprandial glucose tests should be performed. An abnormal urinalysis may suggest pathology (eg, infection) that can be managed medically. Urinary tract infection is common in the patient who is incontinent.

Case 109-1, Question 2: The incontinence record maintained by the nursing staff indicates that H.K. has to void >15 times a day, with varying amount of urine volume and including five incontinence episodes because she is unable to make it to the bathroom on time. She also has to wake up at least two times at night to void. She also has a small-volume leakage of urine upon sneezing and coughing. She is overweight, with a body mass index (BMI) of 28 kg/m^2. Her gynecologic history reveals three pregnancies resulting in vaginal delivery of >8-pound (3.63-kg) infants. Physical examination reveals atrophic vaginitis, no funneling of the bladder neck, and no bladder distension. H.K. does have a history of stroke. The urinalysis is normal, as are the blood chemistries. Postvoiding bladder scan revealed a residual urine volume of 40 mL. What is the pathophysiology and classification of H.K.'s incontinence?

Most neuropathic disease processes can change bladder function. As illustrated by H.K., a cerebrovascular accident is commonly associated with bladder dysfunction and incontinence in older adults. Neurologic injury above the level of the micturition center in the spinal cord, in most cases, results in bladder overactivity. Also, H.K.'s gynecologic history indicates the presence of pelvic floor weakness as the most likely cause of urinary leakage from increased abdominal pressure upon activities such as sneezing or coughing. H.K.'s UI is classified as mixed incontinence owing to underlying UUI, OAB, and SUI.

Nonpharmacologic Modalities

There are several nonpharmacologic measures that are beneficial and important to discuss with patients suffering from any type of UI. The first step is to educate patients about the appropriate use of

absorbent pads, dietary fluid management, avoidance of caffeine and other bladder irritants, weight loss, bowel regularity, and bladder training. Absorbent products should not be used for the mere convenience of caregivers, but to reduce the risks of UI-associated morbidity such as rashes, pressure ulcers, and skin infections. Females with UI should be counseled regarding fluid management, especially those with nocturnal or early-morning incontinence. Reduction in excessive fluid intake (eg, <2 L/day) and frequent bladder emptying can be useful strategies as well.[15] Obesity is an independent risk factor for developing UI, and females with obesity have a 4.2-fold greater risk of SUI than do those with a normal BMI.[16] Several trials show that moderate weight loss can improve UI symptoms in overweight females and females with obesity, especially SUI symptoms.[17],[18] Constipation or fecal impaction can worsen urinary retention; hence, bowel regularity can improve any UI type, specifically OI.

Bladder training, which includes interventions such as timed voiding, habit training, and prompted voiding, aims to increase the time interval between voiding using either a mandatory or a self-adjusted schedule, typically every 2 hours during waking hours. Bladder training also includes teaching urgency suppression strategies using relaxation and distraction techniques, self-monitoring, and reinforcement techniques. Although bladder training is typically used to treat UUI, it can also treat SUI and mixed UI.[19] A Cochrane review of limited and variable-quality evidence tentatively concluded that bladder training helps treat UI, including UUI, SUI, and mixed UI.[20]

Several other nonpharmacologic modalities are recommended for improving symptoms and slowing the progression of specific types of UI. Surgical interventions including sacral nerve stimulator or botulinum toxin injections have demonstrated benefits in UUI and OAB. High-quality evidence shows pelvic floor muscle training (PFMT) to be a more effective UI treatment than no active treatment.[21],[22] Supportive devices such as pessaries and prostheses in SUI are reserved for special situations, depending on patients' UI symptoms, cognitive and mobility status, and overall health status.

For OI, nonsurgical routes include either gender-specific external catheters or indwelling catheters.[14,23] For OI associated with severe benign prostatic hyperplasia (BPH) or prostate cancer in males, various surgical procedures such as transurethral resection of the prostate (TURP) or prostatectomy are considered to alleviate OI symptoms.[24] For FUI, the goal is to help improve a patient's ability to reach the restroom to minimize incontinence. Environmental interventions include the use of assistive devices such as restroom grab bars, raised toilet seats, and mobility assistance.[25] Other options include reviewing the proximity of the toilet or toilet substitutes (eg, bedside commode) and minimizing hazards (eg, rugs) in the restroom.

CASE 109-1, QUESTION 3: What nonpharmacologic therapy should be recommended for H.K.?

H.K. should have a comprehensive review of her medications completed to determine whether any of the current medications may be exacerbating or contributing to her UI symptoms. She should then be placed on a toileting schedule in which she is prompted to void every 2 hours. The nursing staff should continue to keep a bladder diary in which they record fluid intake and when she is wet and dry. This information can be used to tailor her toileting schedule to make sure H.K. has the best outcome while at the same time being practical, based on staffing at the institution. Because of H.K.'s moderate dementia, the teaching of pelvic floor muscle exercises may not be feasible. However, supportive devices such as pessaries and prostheses may be considered to alleviate SUI symptoms.

Drug Therapy

Pharmacotherapy options exist for each type of UI (**Table 109-5**). After comprehensive evaluation of the patient's symptoms and identifying the type of UI, it is essential to select pharmacotherapy options based on patient-specific factors such as preferred routes of

administration, therapeutic outcomes according to the patient's satisfaction and expectations, tolerability, affordability, and comorbid conditions.

Table 109-5
Drug Therapy for Urinary Incontinence

Type	Pharmacotherapy Options
Urge with or without overactive bladder	Oxybutynin Tolterodine Fesoterodine Trospium Darifenacin Solifenacin Mirabegron Vibegron Desmopressin (nocturia)
Stress	Vaginal estrogen cream (vaginal atrophy) Duloxetine (off label)
Overflow	Terazosin (BPH) Doxazosin (BPH) Tamsulosin (BPH) Alfuzosin (BPH) Silodosin (BPH) Bethanechol (urinary retention)

CASE 109-1, QUESTION 4: What drug therapy should be prescribed for H.K.?

H.K. has detrusor instability that may respond to antimuscarinic drug therapy if nonpharmacologic measures do not produce the desired results. Inhibition of the muscarinic receptors in the urinary bladder results in decreased urinary bladder contraction, increased residual urine volume, and decreased detrusor muscle pressure. The most important step in pharmacotherapy management of UI would be to identify the most efficacious antimuscarinic agent that the patient can tolerate best because of the many side effects associated with their use. A more selective antimuscarinic agent, such as solifenacin 5 mg once daily, would be ideal for H.K. to

minimize the impact on cognition through muscarinic receptor M1 blockade.

ANTIMUSCARINIC AGENTS

Antimuscarinics are the gold standard for UUI treatment and are U.S. Food and Drug Administration (FDA)-approved agents. Antimuscarinics block the parasympathetic muscarinic receptors M_2 and M_3 in the bladder to inhibit involuntary detrusor contractions. Systematic reviews showing clinical improvement and higher continence rates compared with placebo for reducing UUI support the efficacy of antimuscarinics; however, the effect was modest.[26,27] A clinically significant effect in UI is typically defined as a ≥50% reduction in daily incontinence episodes; however, the 2012 Agency for Healthcare Research and Quality report found that females reported improved quality of life and clinical success only when they had a ≥70% reduction in UI episodes per day.[27,28] Therefore, before initiating therapy, clinicians should discuss patients' expectations and educate them on what may be realistic and feasible regarding outcomes. Contraindications to using antimuscarinics include narrow-angle glaucoma, urinary retention, gastric retention, and decreased gastrointestinal (GI) motility disorders. Extreme caution is advised when considering prescribing antimuscarinics in patients with dementia or cognitive impairment.

Many antimuscarinics are available, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium, as detailed in **Table 109-6**. As of 2021, five of the antimuscarinics are available generically (ie, oxybutynin immediate release [IR] and extended release [ER], tolterodine IR and ER, trospium IR and ER, solifenacin and darifenacin ER), whereas two agents remain brand name only (ie, transdermal oxybutynin gel and patch, fesoterodine). The transdermal oxybutynin patch (Oxytrol® for Women) can be obtained through a prescription but is now also available over the counter (OTC); no generic equivalent is currently available. Because high-quality evidence is lacking from head-to-head trials between specific agents, it is difficult to conclude whether these agents truly

have similar efficacy and safety profiles as currently published evidence suggests. No guidelines suggest one antimuscarinic over another. Selection of one antimuscarinic over another can be determined by a patient's tolerance to side effects of these agents because the incidence varies, as detailed in **Table 109-7**.

Table 109-6
Pharmacotherapy Options for Urge Urinary Incontinence/Overactive Bladder

Drug Name	Usual Dose (max)	Renal Dose Adjustments	Hepatic Dose Adjustments	Dose Adjustments for CYP Interactions
Antimuscarinics				
Darifenacin ER (Enablex®)	7.5 mg daily (15 mg daily)	—	Moderate: 7.5 mg daily Severe: not recommended	Concurrent potent CYP3A4 inhibitors: max 7.5 mg daily
Fesoterodine ER (Toviaz®)	4 mg daily (8 mg daily)	CrCl <30 mL/minute/1.73 m^2: 4 mg daily	Severe: not recommended	Concurrent potent CYP3A4 inhibitors: max 4 mg daily
Oxybutynin IR	5 mg two or three times daily (5 mg four times daily) Older adults (≥75): initial dose 2.5 mg two or three times daily	—	—	—
Oxybutynin ER (Ditropan XL®)	5–10 mg daily (30 mg daily)	—	—	—
Oxybutynin TDS (Oxytrol®)	3.9-mg patch–1 patch twice weekly (applied every 3 or 4 days)	—	—	—
Oxybutynin gel (Gelnique®)	One sachet or one pump actuation (100 mg/g) once daily	—	—	—
Solifenacin (VESIcare®)	5 mg daily (10 mg daily)	CrCl <30 mL/minute/1.73 m^2: 5 mg daily	Moderate: 5 mg daily Severe: not recommended	Concurrent potent CYP3A4 inhibitors: max 5 mg daily
Tolterodine IR (Detrol®)	2 mg twice daily (may decrease to 1 mg twice daily)	CrCl <30 mL/minute/1.73 m^2: 1 mg twice daily	Significantly reduced function: 1 mg twice daily	Concurrent potent CYP3A4 inhibitors: max 1 mg twice daily
Tolterodine ER (Detrol LA®)	4 mg daily (may decrease to 2 mg daily)	CrCl 10–30 mL/minute/1.73 m^2: 2 mg daily CrCl <10 mL/minute/1.73 m^2: use not recommended	Mild to moderate: 2 mg daily Severe: not recommended	Concurrent potent CYP3A4 inhibitors: max 2 mg/day
Trospium IR®	20 mg twice daily Older adults (≥5): initial dose 20 mg daily	CrCl <30 mL/minute/1.73 m^2: 20 mg daily at bedtime	—	—
Trospium ER®	60 mg daily	CrCl <30 mL/minute/1.73 m^2: not recommended	—	—
β_3-Agonist				
Mirabegron (Myrbetriq®)	25 mg daily (50 mg daily)	CrCl 15–29 mL/minute/1.73 m^2 or eGFR 15–29 mL/minute/1.73 m^2: 25 mg daily CrCl <15 mL/minute/1.73 m^2 or eGFR <15 mL/minute/1.73 m^2: use not recommended	Moderate: max 25 mg Severe: not recommended	—
Vibegron (Gemtesa®)	75 mg once daily	eGFR <15 mL/minute/1.73 m^2: use not recommended	Mild to moderate: no adjustments Severe: not recommended	Vibegron may increase the serum concentration of digoxin

CrCl, creatinine clearance; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; ER, extended release; IR, immediate release.

Table 109-7

Comparison of Common Anticholinergic Adverse Effects for Agents Indicated for Urge Urinary Incontinence Treatment (% Incidence) and Use in Older Adult Populations

Drug Name	Dry Mouth	Constipation	Dizziness	Fatigue	Somnolence	Headache	Blurry Vision	BEERS List
Darifenacin ER	59	28	0	NR	NR	8	4	Yes
Fesoterodine ER	99	14	2	<1	NR	12	4	Yes
Oxybutynin IR	88	32	38	15	40	22	22	Yes
Oxybutynin ER	68	9	11	18	4	12	3	Yes
Oxybutynin TDS	10	5	4	NR	2	NR	2	
Oxybutynin gel	12	NR	NR	NR	NR	NR	<2	
Solifenacin	34	19	1	NR	NR	4	7	Yes
Tolterodine IR	50	10	4	4	3	10	8	Yes
Tolterodine ER	39	10	3	3	3	7	6	Yes
Trospium IR	33	11	NR	NR	NR	6	3	Yes

ER, extended release; IR, immediate release; NR, not reported; TDS, transdermal.

Oxybutynin chloride

Oral oxybutynin has been the gold standard treatment for UUI and OAB for many years because of its high potency; however, patient adherence is suboptimal in most cases, and discontinuation rates are high because of the adverse effect profile. Because oxybutynin is a tertiary amine anticholinergic compound and blocks central M_1 receptors, the potential for CNS toxicity increases as the dose is increased.[29] Oxybutynin is available as an oral IR tablet, an ER tablet, a transdermal system, and a topical gel. The ER formulation of oxybutynin, which has less first-pass metabolism and consequently less conversion to the active metabolite and less-frequent dosing, is better tolerated and accepted by patients than is the IR formulation.[30] The transdermal formulations of oxybutynin (gel and patch) have a more favorable adverse drug reaction (ADR) profile than do other agents in the class, and the gel is typically better tolerated than is the patch.[31]

Tolterodine tartrate

Tolterodine is a competitive muscarinic receptor antagonist that is relatively selective for M_2 and M_3 receptors. When tolterodine

became available and showed less peripheral muscarinic antagonism and a reduced ability to cross the blood–brain barrier, its use became more prevalent because of its better tolerance compared with oxybutynin. However, at therapeutic and clinically effective doses, tolterodine also causes cognitive impairment and rare adverse effects such as hallucinations.[32] Tolterodine has an extensive drug interaction profile because it is metabolized by cytochrome P450 (CYP) 2D6 and CYP3A4 isoenzymes. Concurrent use of potent CYP2D6 inhibitors (eg, bupropion, cinacalcet, fluoxetine, paroxetine, quinidine, duloxetine, sertraline, and terbinafine) or potent CYP3A4 inhibitors (eg, protease inhibitors, clarithromycin, erythromycin, telithromycin, ketoconazole, itraconazole, fluconazole, verapamil, diltiazem, and grapefruit juice) may increase tolterodine drug concentrations and the potential for ADRs. Although tolterodine can modestly prolong the QT interval, no clinical or electrocardiographic evidence was seen of significant cardiac adverse events in the group studied.[33] The onset of the pharmacologic action of tolterodine is <1 hour, and therapeutic efficacy is maintained during long-term treatment. Despite short terminal half-lives of 2 to 3 hours and 3 to 4 hours for tolterodine and its active 5-hydroxy metabolite, respectively, twice-daily dosing is effective because of the drug's long pharmacodynamic effects.

Fesoterodine

Fesoterodine is an antimuscarinic prodrug that is converted into the same active metabolite as that of tolterodine. The efficacy and safety of fesoterodine appear comparable to those of tolterodine.[34] In a short-term study, fesoterodine was better than was tolterodine ER 4 mg and placebo in reducing UUI episodes, micturitions, urgency, and improving health-related quality of life. However, fesoterodine caused more dry mouth (28% vs 13%) and constipation (4% vs 3%) than did tolterodine ER. It has been associated with higher discontinuation rates owing to adverse events (5% vs 3%).[35] Furthermore, fesoterodine is currently available as brand only and is thus more expensive.

Trospium chloride

Trospium is a quaternary ammonium antimuscarinic agent with relative selectivity for M_2 and M_3 receptors. The hydrophilic properties of trospium minimize the passage of the drug through the blood–brain barrier, thereby causing fewer CNS and cognitive adverse events.[36] No significant differences were found in urodynamic outcomes between trospium and oxybutynin in a 52-week study.[37] The reduction in 24-hour micturition frequency and urgency episodes at 26 and 52 weeks of treatment was also not significant. However, the incidence of dry mouth and GI adverse events was significantly lower in the trospium group. Trospium is excreted unchanged in the urine and can compete with drugs having a similar excretion pathway (eg, digoxin, metformin, and morphine). Although data are limited, one clinical trial showed lack of cognitive impairment with trospium when used in older adults because of its lesser degree of transport across the blood–brain barrier compared with oxybutynin.[38]

M_3 selective antimuscarinics

Two antimuscarinic tertiary amines, darifenacin and solifenacin, are currently available with an indication for use in UUI or OAB. Each agent has shown selectivity for M_3 receptors within the detrusor muscles.[39] Antagonism of M_1 receptors located in the brain, which are primarily responsible for causing cognitive impairment in older adults associated with antimuscarinics, is minimal with either of these agents; thus, their M_3 selectivity is favorable.[40],[41] No studies have assessed the effects of solifenacin on cognition. Both agents are now available as generic and are cost-effective. A pooled analysis of three 12-week, double-blind, placebo-controlled trials (N = 1059) demonstrated that darifenacin reduced the median number of incontinence episodes per week ($P > .01$) versus placebo.[42] In clinical trials, solifenacin showed a significant reduction in the symptoms of urinary frequency, urgency, and urge incontinence compared with placebo.[43],[44] Safety concerns with solifenacin include

an increased risk of QT interval prolongation in patients with a known history of QT interval prolongation or patients who are taking medications known to prolong the QT interval.

β-ADRENERGIC AGONISTS

Mirabegron and vibegron are β-agonists that activate the β_3-adrenergic receptors in the detrusor muscle, which leads to muscle relaxation and increased bladder capacity. Both agents are FDA approved for the treatment of OAB and UUI (included in Table 109-6).

In a meta-analysis of phase III trials, mirabegron significantly reduced urge incontinence episodes compared with placebo (standardized mean difference −0.44; 95% confidence interval [CI], −0.59 to −0.29).[45] In a prospective cohort study of 354 females taking mirabegron for OAB, over two-thirds discontinued therapy within 1 year, usually because of lack of efficacy (26%), although patients were more likely to continue taking mirabegron than antimuscarinics because of fewer adverse effects with mirabegron.[46] Mirabegron should be avoided in patients with uncontrolled hypertension (HTN) because a pooled analysis of patients older than 65 showed treatment-induced HTN in 10% to 14% in patients receiving 25 to 50 mg of mirabegron compared with 8% of patients receiving placebo.[47] Mirabegron should also be avoided in patients with glaucoma, cognitive impairment, end-stage renal disease, and significant liver impairment. No information exists regarding whether patients are more likely to adhere to mirabegron than to the antimuscarinics. If mirabegron is used concurrently with drugs with a narrow therapeutic index (eg, flecainide, propafenone) that are metabolized through the CYP2D6 pathway, dose adjustments will be needed because mirabegron is a moderate CYP2D6 inhibitor. In addition, if digoxin and mirabegron are used concurrently, digoxin therapy should be initiated at the lowest dose, and serum concentrations should be monitored to ensure efficacy and prevent toxicity associated with digoxin.

For individuals who are unable to swallow pills, vibegron tablets may be crushed and taken with food. In clinical trials, vibegron is not associated with HTN and may be preferred in patients who are hypertensive with poorly controlled blood pressure. Vibegron appears to be at least as effective as antimuscarinic agents with similar rates of adverse effects. A meta-analysis of three trials including >1700 patients that compared vibegron with antimuscarinic monotherapy reported similar outcomes on bladder symptoms including the mean number of micturition episodes, mean number of urgency episodes, mean number of urgency incontinence episodes, mean number of incontinence episodes, and discontinuation rates due to an adverse event were not statistically different between the drugs.[48] In the phase III trial comparing vibegron 75 mg with tolterodine 4 mg (ER) in 505 individuals, improvement in OAB wet symptoms was greater for vibegron.[49] At week 52 of treatment, more patients receiving vibegron experienced ≥75% reduction in UUI episodes (61% vs 54%) and more reported a 100% reduction (40% vs 34%) compared with those receiving tolterodine. Although patient discontinuation resulting from adverse effects was greater for tolterodine compared with vibegron (3.4% vs 1.5%, respectively), this difference was not statistically significant or clinically meaningful.

CASE 109-2

QUESTION 1: M.K., a 60-year-old female, has been diagnosed with SUI. What therapy would be appropriate for M.K.'s SUI?

M.K. should initially be educated on pelvic floor muscle or Kegel exercises. Nonpharmacologic modalities are considered first-line therapy for the management of SUI. Several methods have been effectively used to help patients identify and correctly exercise the pelvic floor muscles, including self-help books, biofeedback, electrical stimulation, and verbal feedback during physical examination by a physician. Once the pelvic floor muscles have been identified, M.K. should empty her bladder and sit or lie down. She should contract her pelvic floor muscles, holding the contraction

for 5 seconds, and then relax for 5 seconds. This should be repeated five times with a goal of 10-second contractions for M.K. She should practice these exercises three times a day. If M.K. is overweight or obese, she should be educated on the benefits of weight loss on improvement in SUI symptoms.

Duloxetine

Duloxetine is a serotonin and norepinephrine reuptake inhibitor that has shown efficacy in patients with stress incontinence. Duloxetine use is supported by the European guidelines and is approved for this indication in Europe; however, duloxetine currently lacks FDA approval. Duloxetine increases urethral tone during the storage phase by inhibiting norepinephrine reuptake. Duloxetine also treats depression, and although not FDA approved for the treatment of stress incontinence, it could be a reasonable option for a female with both depression and stress incontinence. A meta-analysis of nine trials including 3063 females predominately with stress incontinence showed that patients treated with duloxetine had a reduction in the incontinence episode frequency by ~50%; however, the absolute reduction (10.8% vs 7.7%) in incontinence episodes was small, suggesting that any benefits would be modest. Adverse effects were common, with 71% of patients treated with duloxetine reporting side effects and approximately one in eight patients discontinuing treatment.[48] Duloxetine reduced incontinence episode frequency, improved the voiding interval process, and enhanced quality of life at the 75-mg/day dose compared with placebo in a 12-week double-blind, randomized, placebo-controlled clinical trial. However, duloxetine was associated with nausea in about 40% of the patients.[49] The most common adverse effect with duloxetine is nausea, which tends to resolve with time. The clinical effects of duloxetine appear to be modest and need to be weighed against the risk of adverse events. Patients' current medication profiles should be screened for agents that can increase the risk of serotonin syndrome in combination with duloxetine (eg, selective serotonin reuptake inhibitors, tramadol) and drugs that can inhibit CYP1A2 and

increase duloxetine serum concentrations (eg, amiodarone, ciprofloxacin, cimetidine). Because of mixed-quality evidence indicating only a modest benefit of duloxetine in treating SUI compared with high discontinuation rates owing to adverse events, it is imperative to educate patients and involve them in the decision to initiate duloxetine therapy.

Estrogens

Topical estrogen therapy may be beneficial in females with coexisting atrophic vaginitis and SUI. Topical or vaginal estrogens provide localized treatment of atrophic vaginitis and may increase urethral tone. Localized estrogen treatment is well tolerated and provides minor benefit (risk ratio [RR] 0.74; 95% CI, 0.64–0.86) for incontinence in postmenopausal females but does not improve quality of life.[27] Topical estrogen therapy options include conjugated estrogen vaginal cream (Premarin®) 0.5 g three times weekly or the estradiol vaginal ring (Femring®) inserted every 3 months. Adverse effects include vaginal spotting, breast tenderness, and nausea. If recommended, estrogen therapy should be used at the lowest dose and for the shortest time possible to prevent long-term ADRs and potential risk of endometrial carcinoma. The use of estrogen in the treatment of SUI requires further study.

α-Adrenergic agonists

α-Adrenergic agonists such as pseudoephedrine and phenylephrine, which stimulate urethral smooth muscle contraction, may be modestly beneficial in reducing SUI symptoms. Limited evidence suggesting the use of α-adrenergic agonists primarily consists of studies of phenylpropanolamine, which is no longer available in the United States. Adrenergic agonists are no longer recommended because they are only mildly efficacious compared with placebo and have a high rate of adverse effects.[50] Several studies have evaluated whether the clinical and urodynamic effects of a combination of estrogen and an α-adrenergic receptor agonist exceed those of the individual therapies for SUI. In general, combination therapy has

resulted in better clinical and urodynamic responses than has monotherapy.[51] If combination therapy is used or recommended, patients should be educated on the associated adverse effects, including dizziness, insomnia, headache, tachycardia, and increased blood pressure. Patients should also be screened for underlying cardiovascular conditions and any endocrine conditions, which may be worsened by the adrenergic agonism induced by pseudoephedrine or phenylephrine.

Case 109-2, Question 2: M.K. has incomplete resolution of her stress incontinence symptoms. Physical examination indicates urogenital atrophy. What are the pharmacologic options for stress incontinence?

M.K.'s incomplete resolution of stress incontinence symptoms is probably caused by urogenital atrophy. She would respond well to an intravaginal estrogen cream, which will improve local blood flow and dryness. An estrogen cream such as estradiol should be prescribed at a dose of 0.5 g of cream three times a week. The combination of local estrogen therapy and pelvic floor muscle exercises should eliminate M.K.'s symptoms.

Desmopressin

Desmopressin (DDAVP®) was approved in March 2017 in the United States for the treatment of nocturia in adults who awaken at least two times per night to void and is one of the key symptoms of OAB. DDAVP® is a synthetic vasopressin analog that is available in intranasal (Noctiva®) as well as sublingual (Nocdurnal®) formulation. Before considering therapy with DDAVP®, it is imperative to ensure that the patient is not at risk for hyponatremia because this is one of the most common side effects of this product and necessitates dose adjustment. The dose of intranasal desmopressin for patients who are not at risk for hyponatremia is 1.66 µg in either nostril 30 minutes before bedtime. In patients who are at risk for hyponatremia, the starting dose is 0.83 µg in either nostril 30 minutes before bedtime. The dose may be increased to 1.66 µg after at least 1 week of

therapy.[52] The dose of the sublingual formulation is 27.7 µg (for females) or 55.3 µg (for males) once daily 1 hour before bedtime.[53] Owing to several other contraindications, including polydipsia, primary nocturnal enuresis, concomitant use of loop diuretics or glucocorticoids (systemic or inhaled), renal impairment, syndrome of inappropriate antidiuretic hormone secretion, illness that can cause fluid or electrolyte imbalance, moderate-to-severe heart failure, and uncontrolled HTN, use of this product is limited.

OVERFLOW INCONTINENCE

The most common cause of OI in males is BPH or malignant prostatic hyperplasia; hence, proper management of BPH is essential to resolve urinary symptoms of OI. If a patient with OI is identified to have urinary retention secondary to neurogenic atony of the bladder, a cholinergic agent, bethanechol, may be considered. As a cholinergic agent, bethanechol increases bladder muscle tone causing contractions that initiate urination, although well-done studies have not provided strong evidence for its benefits.[54] Bethanechol is initially administered at the lowest dose of 5 to 10 mg every hour up to a maximum dose of 50 mg and then transitioned to 10 to 50 mg three to four times daily for maintenance. Common adverse effects of bethanechol include flushing, tachycardia, abdominal cramps, and malaise.

BENIGN PROSTATIC HYPERPLASIA

BPH is defined by the American Urological Association as “a histologic diagnosis that refers to smooth muscle and epithelial cell proliferation within the prostatic transition zone.”[55] The histologic evidence of BPH may be prevalent in ~80% of older males; however, only 60% at least age 60 years develop symptomatic disease.[56] This prevalence increases to ~78% in males 80 years and older.[57] The term *benign prostatic hypertrophy* often is used inappropriately

because the prostate gland pathology results from hyperplasia rather than from hypertrophy.

CASE 109-3

QUESTION 1: G.M., a 69-year-old male, presents to the emergency department with increasing difficulty initiating urination, a significant decrease in the force of his urinary stream, occasional midstream stoppage, and postvoid dribbling. He states that these symptoms started 4 days ago and have been persistent. Physical examination reveals abdominal distension and tenderness. Digital rectal exam confirmed a severely enlarged, firm, and rubbery prostate gland without nodules or undue hardness. G.M. reports urinary frequency of 8 to 10 times per day and 4 to 5 times per night. G.M. indicates that upon urination, he notices weak stream dribbling and does not feel relieved. Laboratory findings are as follows:

Blood urea nitrogen (BUN), 45 mg/dL
Serum creatinine (SCr), 3.2 mg/dL
Serum prostatic acid phosphatase, 3 units/L
Serum prostate-specific antigen (PSA), 7.1 ng/mL
A urethral catheter was inserted, and 900 mL of urine was obtained. G.M. subsequently was scheduled for a urologic workup.

What is the pathophysiologic basis for G.M.'s symptoms?

Pathophysiology

There is both a static and a dynamic component to prostate enlargement. The static component increases the prostate size by smooth muscle cell proliferation in the prostate stroma, whereas the dynamic component contributes to an enlarged prostate through an increase in smooth muscle tone in the prostate and bladder neck. Static factors related to age and androgen-induced prostate enlargement cause physical block at the bladder neck and obstruct urinary flow. After the first growth spurt at the time of puberty when prostate size starts to increase, a second growth spurt begins and continues at age 40 and thereafter. During this phase, the prostate may enlarge up to quadruple the size and lead to symptomatic disease. In the prostate, type II 5α-reductase enzyme converts testosterone into dihydrotestosterone (DHT), which is responsible for

growth and enlargement of the prostate. Despite the age-related decline in testosterone level, intraprostatic DHT levels are maintained. In the periphery, the ratio of testosterone to estrogen declines, and estrogen is theorized to induce androgen receptors and contribute to growth of the stromal portion of the prostate. Dynamic factors relate to exaggerated α-adrenergic tone that leads to smooth muscle contraction, compression of the urethra, and reduced urinary bladder emptying. Normally, the ratio of stromal to epithelial tissue in the prostate is 2:1, which is exaggerated to 5:1 in an enlarged prostate. Stromal tissue comprises the α1-adrenergic receptors that are stimulated as a result of the enlargement.

Case 109-3, Question 2: What subjective and objective findings in G.M. are associated with BPH?

Clinical Presentation and Evaluation

Etiologies stemming from static or dynamic factors facilitate in identifying and evaluating patient's BPH-related urinary symptoms. Symptoms of BPH can be categorized as obstructive and irritative and are collectively referred to as *lower urinary tract symptoms (LUTS)*.

Obstructive symptoms are associated with reduced bladder emptying and result in straining to void, weak urine flow or stream, hesitancy, sensation of incomplete bladder emptying, and postvoid urinary dribbling. The common obstructive symptom of decreased force and size of urine stream is caused by urethral compression from prostate gland hyperplasia. Hesitancy, another obstructive symptom, is the result of the bladder detrusor muscle taking a longer time to generate the initial increased pressure to overcome urethral resistance. Urinary stream intermittency is caused by the inability of the bladder detrusor muscle to sustain the increased pressure until the end of voiding. Terminal dribbling and incomplete emptying occur for the same reason, but also may be caused by obstructive prostatic tissue at the bladder neck, causing a "ball-valve" effect.

Irritative symptoms result from long-standing bladder neck obstruction and result in urgency, frequency, and nocturia. Incomplete emptying of the bladder results in shorter intervals between voiding, thus resulting in frequency. Also, a large prostate gland provokes the bladder to trigger a voiding response more frequently. This response is more pronounced if the prostate is growing intravesically and compromising the bladder volume. The bladder detrusor muscle becomes hypertrophied as a result of the greater bladder residual urine volume, which can result in increased detrusor muscle excitability. Clinically, this excitability may result in bladder instability. The symptoms of urinary frequency are more pronounced at night because cortical inhibitions are lessened and bladder sphincter tone is more relaxed during sleep.

Approximately 17% to 20% of patients with symptomatic BPH suffer from complications including acute urinary retention, suprapubic pain from distended bladder, recurrent urinary tract infections, hematuria, bladder stones, bladder diverticula, and renal failure. Patients with a prostate gland volume of 30 to 40 mL or PSA of ≥1.4 ng/mL (μg/L) are especially more prone to complications of BPH.[58–60] Acute urinary retention in BPH can occur as a result of increasing size of the prostate gland. Independent of gland size, drugs may precipitate acute urinary retention. Drugs, such as alcohol, anticholinergic agents, α-adrenergic agents, and neuroleptics, have all been associated with acute urinary retention in males with BPH. Commonly, when advanced BPH is present, acute urinary retention is exacerbated if the patient does not void at the first sign of urgency.

UI is not a common symptom of BPH. With advanced BPH, a large residual volume of urine in the bladder weakens the bladder sphincter and allows the escape of small amounts of urine when the bladder is full. Because the residual bladder volume increases, the ureters will dilate, resulting in stasis of urine in the ureters. The end result may be ascending hydronephrosis caused by the transmission of high pressure to nephrons, which produces renal damage (**Table 109-8**). This can account for abdominal discomfort and flank pain during voiding and ascending urinary tract infections.

Table 109-8
American Urological Association Urinary Symptoms Score/International Prostate Symptom Score

Questions to Be Answered	Not at All	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always	Your Score
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Over the past month, how often have you had to urinate again <2 hours after you finished urinating?	0	1	2	3	4	5	
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 (None)	1 (One time)	2 (Two times)	3 (Three times)	4 (Four times)	5 (Five or more times)	
Sum of Numbers (American Urological Association Symptom Score):							
Total score: 0–7: Mild symptoms 8–19: Moderate symptoms 20–35: Severe symptoms							
Quality of life because of urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed-about equally satisfied and unsatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

The American Urological Association (AUA) symptoms score and the International Prostate Symptom Score (IPSS) use the same questions and scale. The IPSS additionally includes the last disease-specific quality of life question.

Source: Reprinted with permission from Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148(5):1549–1557. © 1992 The American Urological Association Education and Research, Inc.

To identify the most bothersome symptoms and select appropriate drug therapy, the patient's perception and severity of BPH should be evaluated using validated instruments. The Multidisciplinary Measurements Committee of the American Urologic Association (AUA) also has published a urinary symptom index (see Table 109-8) for BPH.[61] The index is useful to assess the baseline severity of BPH, disease progression, and effectiveness of different therapies (**Table 109-9**). The AUA Symptom Index (AUA-SI) allows comparison among therapies and is the preferred questionnaire for BPH research. It has been validated through internal consistency, reliability, constructive reliability, test–retest reliability, and criterion reliability.[62]

Table 109-9
Categories of Benign Prostatic Hyperplasia Disease Severity Based on Symptoms and Signs

Disease Severity	AUA Symptom Score	Typical Symptoms and Signs
Mild	≤7	Asymptomatic Peak urinary flow rate <10 mL/second PVR urine volume >25–50 mL
Moderate	8–19	All of the abovementioned signs plus obstructive voiding symptoms and irritative voiding symptoms (signs of detrusor instability)
Severe	≥20	All of the abovementioned plus one or more complications of BPH

AUA, American Urological Association; BPH, benign prostatic hyperplasia; PVR, postvoid residual volume.

G.M. presents with classic symptoms of BPH, including obstructive and irritative symptoms. The increasingly severe symptoms culminated in an episode of acute urinary retention, as evidenced by inability to void and lower abdominal discomfort. Objective symptoms associated with G.M.'s BPH include (a) abdominal tenderness; (b) the finding of an enlarged bladder; (c) an enlarged, firm, and rubbery

prostate gland; and (d) a return of 900 mL of urine via the urinary catheter. The normal serum acid phosphatase, slightly elevated PSA, and digital rectal examination of the prostate suggest that G.M. does not have prostatic carcinoma at this time. The PSA result for G.M. is slightly above the upper limit for his age. As such, he should have a transrectal ultrasound (TRUS) to determine the prostate gland volume and, hence, the PSA density. Once the prostate gland volume is determined, the significance of his PSA level of 7.1 ng/mL can be determined. The elevated BUN and SCr may suggest hydronephrosis as a result of his BPH.

CASE 109-3, QUESTION 3: What additional tests should be completed to evaluate G.M.?

URINALYSIS

Because patients with BPH also may have a urinary tract infection, a urinalysis with microscopic examination is essential. It is mandatory that G.M. provide a urine specimen for urinalysis before the digital rectal examination of the prostate gland because examination of the prostate causes prostatic secretions to be expelled into the urethra, which may contaminate the urine specimen and make it difficult to determine the source of an infection. The presence of white blood cells and bacteria in the urine necessitates a workup for infection. Similarly, hematuria requires a workup for urinary tract pathology other than BPH. Because BPH also can cause hydronephrosis, renal function and serum electrolytes should be evaluated.

DIGITAL RECTAL EXAMINATION

A serum PSA followed by a digital rectal examination of the prostate remains a fundamental part of evaluating a male with BPH. The prostate examination should determine the size, shape, consistency, and nodularity of this gland. Prostatic hyperplasia results in a large, palpable prostate with a smooth mucosal surface rectally. The discernment of the right and left prostate lobes is lost in BPH. The digital rectal examination of a patient with BPH commonly finds

asymmetry of the prostate, with one side being larger than the other. Prostatic enlargement can be in both an anteroposterior and a superoinferior direction. As a result, on digital rectal examination, the upper extent of prostate hyperplasia is not palpable. Occasionally, the degree of enlargement felt by digital rectal examination may be misleading because a substantial portion of enlargement may be intravesicular. The consistency of the gland may be soft or firm, depending on the predominance of glandular or fibromuscular elements.[63] The presence of firm-to-hard nodules, irregularities, induration, or a stony, hard prostate suggests possible prostate cancer. In those cases in which the prostate gland size or shape may be questioned, the patient should have a TRUS to determine the gland volume.

PROSTATE-SPECIFIC ANTIGEN

PSA correlates reasonably well, on average, with prostate weight owing to benign prostate glandular hyperplasia.[61] Males ages 40 years and older with at least a 10-year life expectancy have been encouraged to have an annual measurement of serum PSA and a digital rectal examination as a basic screen for prostate cancer and to monitor the growth of the prostate gland. PSA is not necessary for the diagnosis of BPH; however, it helps determine whether disease-modifying therapy options are indicated.[64]

Urinary flow rate

Urinary flow rate (UFR) is the rate of urine flow out of the bladder and typically should be at least 10 mL/second. It is a noninvasive objective measure of bladder emptying, and if reduced, indicates failure of bladder emptying and risk of acute urinary retention.[65]

Postvoid residual volume

PVR is another objective measure of bladder emptying that is defined as volume of urine remaining in the bladder after complete voiding. Normal PVR levels are defined variably; however, a PVR of

≥25 to 50 mL implies failure of bladder emptying, whereas >100 mL indicates worsening of BPH symptoms.[66]

Drug Therapy

In the United States, AUA guidelines on management of BPH primarily facilitate goal setting and treatment decisions.[61] The AUA recommends that goals of BPH management should include symptom improvement, as evidenced by a minimum of a three-point decrease in the AUA-SI, reducing the risk of complications, delaying the need for surgical intervention, and preventing progression of the disease. AUA-guided BPH management includes watchful waiting, pharmacotherapy, and surgical interventions (**Table 109-10**). Selection of pharmacotherapy can be based on the efficacy and clinical impact of each of the drug classes on symptoms and progression of BPH (**Table 109-11**).

Table 109-10
Management of Benign Prostatic Hyperplasia

Disease Severity	AUA-SI Score	AUA Recommended Management
Mild	≤7	Watchful waiting Nonpharmacotherapy interventions Follow-up in 6–12 months
Moderate	8–19	Pharmacotherapy options to consider: 1. Small prostate, low PSA level: α_1-adrenergic antagonists 2. Large prostate, increased PSA level: α_1-adrenergic antagonists + 5α-reductase inhibitors 3. With erectile dysfunction: α_1-adrenergic antagonists, phosphodiesterase inhibitors, or both 4. With irritative symptoms: α_1-adrenergic antagonists + antimuscarinics, or + mirabegron
Severe	≥20	Minimally noninvasive surgery or prostatectomy if complications are present

AUA, American Urological Association; AUA-SI, American Urological Association Symptom Index.

Table 109-11
Comparison of Drug Classes for Benign Prostatic Hyperplasia Management

	α- AA	5α-RI	PDE-5Is	ACHs	β3-AA
Decreases Prostate Size	No	Yes	No	No	No
Halts Disease Progression	No	Yes	No	No	No
Peak Onset	1–6 weeks	3–6 months	4 weeks	1–2 weeks	2–8 weeks
Efficacy in Relieving Irritative Symptoms	++	++ (if enlarged prostate)	+	0	0
Frequency of Dosing	Once or twice a day	Once a day	Once a day	Varies	Once a day
Decreases PSA	No	Yes	No	No	No

ACH, anticholinergic; α-AA, α1-adrenergic receptor antagonist; 5α-RI, 5α-reductase inhibitor; β3-AA, beta-3 adrenergic agonist; PDE-5Is, phosphodiesterase type 5 inhibitor.

CASE 109-3, QUESTION 4: What drug therapy should be prescribed to treat G.M.'s prostatic hyperplasia?

G.M. most likely will be scheduled for a TURP because he presents with acute urinary retention and hydronephrosis owing to a moderately enlarged prostate gland (ie, >40 g in size). He should be started and maintained on an α_1-adrenergic receptor antagonist to reduce the tension of the bladder neck, the prostate adenoma, and the prostatic capsule. Similarly, he should receive a 5α-reductase inhibitor (5ARI) to induce atrophy of the prostate gland and halt the progression of the disease.

The prostatic capsule and hyperplastic prostate have plentiful α_{1A}-adrenergic receptors. The three known subtypes of the α_1-adrenergic receptor are α_{1A}, α_{1B}, and α_{1D}. Inhibiting the α_{1A}-adrenergic receptors can reduce the smooth muscle tone of the prostatic urethra, thereby reducing the functional component of urethral constriction and obstruction.

α_1-ADRENERGIC ANTAGONISTS

Indicated for initial therapy in patients with symptomatic BPH, this drug class exerts its effects by targeting the dynamic factors and by relaxing smooth muscle in the bladder neck, prostate capsule, and prostatic urethra. First-generation α-adrenergic agents, such as phenoxybenzamine, have been replaced by the second-generation nonselective α1-adrenergic antagonists, including terazosin and doxazosin and third-generation uroselective α_{1A} antagonists, including tamsulosin and silodosin. Alfuzosin is a second-generation agent; however, it has clinically significant uroselective effects. Prazosin is also a second-generation agent; however, owing to multiple dosing frequency and higher risk factor for cardiovascular side effects, it is not recommended for use per AUA guidelines.

NONSELECTIVE α_1-ADRENERGIC ANTAGONISTS

Terazosin

In most patients, the dose of terazosin should be started at 1 mg once daily at bedtime and titrated over several weeks to 5 to 10 mg once daily to obtain desired results. Orthostatic hypotension may occur in the beginning days of therapy or during dosage adjustment periods. In patients who stop their terazosin therapy for ≥2 days, therapy should be reinstituted cautiously to avoid the “first-dose” adverse effect of syncope. Bedtime administration may minimize orthostatic hypotension that is associated with the “first-dose” effect of these agents.

Terazosin has significantly reduced obstructive symptoms and improved UFRs at doses of 1 to 5 mg/day.[62] Terazosin has demonstrated sustained improvement in BPH symptom scores for a 30-month period. Only 10% of the patients experienced treatment failure. In this long-term study, the systolic blood pressure in normotensive and hypertensive patients was decreased by 4 and 18 mm Hg, respectively. Apparently, terazosin typically only lowered the blood pressure significantly in patients with hypertension.

Doxazosin

Doxazosin originally was prescribed primarily for HTN and currently is not considered a first-line antihypertensive agent.[62] HTN and BPH are linked by the sympathetic nervous system. As with terazosin, doxazosin improves UFRs and symptoms in patients with BPH. These effects have been demonstrated in controlled clinical studies, within weeks, and for the long term.

Doxazosin should be started at 1 mg/day. After 1 to 2 weeks, the dose can be increased over several weeks to 8 mg/day. Similar to other nonselective agents in this drug class, the first dose should be taken at bedtime to minimize lightheadedness and syncope (the first-dose effect), and the blood pressure of the patient should be monitored periodically during therapy. Most patients require between 4 and 8 mg/day for effective control of the urinary symptoms of BPH. Dosages >4 mg/day are associated with a greater frequency of dizziness, orthostatic hypotension, and syncope.[67]

UROSELECTIVE α_1-ADRENERGIC ANTAGONISTS

Tamsulosin

Tamsulosin and its metabolites are more specific for the prostatic α_{1A}-adrenergic and less specific for the vascular α_{1A}-adrenergic receptors responsible for orthostatic hypotension. Consequently, no need exists to titrate tamsulosin to the recommended daily dose range of 0.4 to 0.8 mg. Coadministration of tamsulosin with antihypertensive agents does not require dosage adjustment of the antihypertensives. Tamsulosin is very effective in treating bladder outlet obstruction associated with BPH.[68]

More than 90% of tamsulosin is absorbed after oral administration of a 0.4-mg dose under fasting conditions. It is recommended to administer the dose of tamsulosin 30 minutes after the same meal daily. Administration with food decreases the bioavailability by 30% and increases the time to peak plasma concentration. Tamsulosin is hepatically metabolized by CYP3A4 and CYP2D6. Impaired renal function increases the total tamsulosin plasma concentration by ~100% during steady state. However, active unbound drug levels are not affected; thus, renal dose adjustment is not required. Tamsulosin

appears to reduce mean ejaculatory volume in 90% of patients. As with all α_1-adrenergic receptor antagonists, tamsulosin does not affect the PSA and must be taken indefinitely to maintain its therapeutic effect.[68–72]

Alfuzosin

Alfuzosin is available as an ER tablet that has a recommended daily dose of 10 mg given after the same meal each day. Higher concentrations in the prostate after usual doses, lack of peak serum levels, and fixed dosing are believed to contribute to its clinical uroselectivity.[73],[74] A lack of penetration of alfuzosin into the brain has been hypothesized to contribute to decreased CNS effects such as somnolence. It displays a lower rate of hypotensive effects than do doxazosin and terazosin. Unlike tamsulosin, alfuzosin will not cause ejaculatory dysfunction; the incidence is comparable to placebo.[71]

Silodosin

Silodosin has a strong affinity for prostatic tissue and is 20 times more “uroselective” than is tamsulosin.[75] Silodosin is available as 4- and 8-mg capsules, and the recommended dose is 8 mg once daily. In patients with a creatinine clearance of <50 mL/minute, the dose should be decreased to 4 mg once daily. The most common side effect of silodosin is retrograde ejaculation.

PHOSPHODIESTERASE-5 INHIBITOR

This drug class is indicated in males with BPH-related symptoms and ED. Phosphodiesterase-5 inhibitors (PDE-5Is) have demonstrated efficacy in improving LUTS without significant reduction in objective measures such as UFR.[76] A more recent Cochrane review of 16 randomized controlled trials (RCTs) found that compared to placebo or α-blockers, PDE-5Is reduce symptom scores slightly; however, they are associated with increased ADRs.[77] The study also found that PDE-5Is were not superior to α-antagonists and combination therapy of the two drug classes did not

result in any greater benefit. PDE-5I use is associated with rare adverse effects including headache, flushing, dyspepsia, nasal congestion, back pain, myalgias, and sinusitis. There is an increased risk of hypotension in patients also using certain α-adrenergic antagonists.

Tadalafil

Tadalafil is a selective PDE-5I and was shown to improve BPH symptoms compared to placebo; it is FDA approved for use in males with BPH and ED at 5 mg/day dose. Tadalafil should be taken at the same time every day without regard to meals. Evidence is lacking to support use of tadalafil in combination with α-adrenergic receptor antagonists and concurrent therapy may increase the risk of low blood pressure. Similarly, patients on antihypertensives, nitrates, or drinking 5 or more units of alcohol are also at increased risk for hypotension with tadalafil. Additional information on tadalafil can be found under the section on Pharmacotherapy for ED later in this chapter.

5α-REDUCTASE INHIBITORS

The 5ARIs block one of the three isozymes of 5α reductase and prevent the conversion of testosterone (T) to DHT. Such inhibition of 5α reductase results in symptomatic relief in patients experiencing LUTS due to prostate enlargement; however, its primary benefit is not acute symptom management. Owing to its unique mechanism of action, 5ARIs halt BPH progression by reducing prostate size and decreasing PSA levels. Utility of 5ARIs in patients with >35-g prostate size has been proved in the Medical Therapy of Prostatic Symptoms (MTOPS) study.[78] It is important to note that the benefits of 5ARI therapy may not be apparent for 6 to 12 months because the impact on prostate size and PSA levels takes months of therapy to be significant. Nonetheless, this drug class does reduce or delay the need for invasive management modalities including prostate surgery.

A few concerns and ADRs associated with use of 5ARIs may limit their use. The most concerning ADR of 5ARIs is sexual dysfunction,

including ED, decreased libido, ejaculatory dysfunction, gynecomastia, and breast tenderness. These ADRs are known to be dose related and reversible upon cessation of therapy. A conflicting finding that 5ARIs can play a role in reducing the risk of prostate cancer has been challenged because of the lack of clear benefits; hence, prophylactic use of this drug class for this theoretical benefit is not recommended. Similarly, increased risk of high-grade tumors with concurrent use of 5ARIs also lacks support.

EFFECT OF ANDROGEN SUPPRESSION ON PROSTATE-SPECIFIC ANTIGEN

Case 109-3, Question 5: G.M. has an annual PSA test. Will androgen suppression alter his results?

Antiandrogen treatment of BPH could possibly adversely affect the interpretation of the PSA screening test for prostate cancer. Concern related to the utility of PSA levels as a marker for prostate cancer while a patient is on 5ARI therapy is legitimate because serum PSA levels are suppressed by ~50% with 5ARIs. To ensure that suppressed PSA levels are not mistaken as "normal" PSA levels in regard to prostate cancer monitoring, it is recommended to obtain baseline PSA before initiating 5ARI therapy. Retest at 6 months and consider that level the new baseline, and then continue monitoring for increases in levels thereafter compared to the new baseline level. Nevertheless, patients receiving a 5ARI should have (a) a digital rectal examination of their prostate periodically, (b) the PSA level measured, and (c) any suspicious findings investigated immediately.[102] Androgen suppression therapy is not contraindicated in BPH solely on the basis of its effect on serum PSA levels.[64]

Finasteride

Finasteride is a selective 5ARI that specifically inhibits 5α-reductase type 2 isozyme and is FDA approved for use in males with BPH 5-mg once-daily dosing. Finasteride's efficacy in improving symptoms,

urinary flow, and DHT levels in patients with enlarged prostates, especially those with prostates >40 g has been demonstrated in several trials. Also, the efficacy and improvements from finasteride therapy were sustained for >4 years.[79–81]

Dutasteride

Dutasteride is a nonselective 5ARI that inhibits both type 1 and 2 5α-reductase isoenzymes and is FDA approved for use in males with BPH at 0.5-mg once-daily dosing. An advantage of dutasteride compared with finasteride is the additional inhibition of 5α-reductase (type 1) in the peripheral tissues, which produces a further decline in serum DHT. However, in a head-to-head trial of finasteride and dutasteride, no significant difference in prostate volume reduction and improvements in urine flow rates was found between the two drugs.[82] Clinical trials and meta-analysis provide robust findings to support benefits of dutasteride in improving symptoms, reducing UFRs, decreasing prostate volume, and reducing the risk of acute urinary retention and the need for surgical BPH intervention.[83],[84]

Combination therapy

Certain patients with BPH may be appropriate candidates for combination therapy. For quick symptomatic relief of obstructive symptoms, α_1-adrenergic receptor antagonists are first line and must be initiated. However, for symptomatic patients with an enlarged prostate, adding a 5ARI is indicated. Even though 5ARIs may provide symptomatic relief, it could take 6 to 12 months to improve symptoms. As a result, combination therapy is most appropriate for such patients. This strategy has been supported by the MTOPS and Combination of Avodart and Tamsulosin (CombAT) trials.[85],[86] The MTOPS trial studied 3047 males with moderate-to-severe BPH and demonstrated that combination therapy was superior to monotherapy with either an α_1-adrenergic antagonist or a 5ARI in improving symptoms and UFR. The risk of clinical progression of BPH was reduced by 39% in patients treated with doxazosin alone, by 34% in

patients treated with finasteride alone, and by 66% in patients treated with combination therapy. The CombAT trial studied 4844 males with risk factors for BPH progression such as larger prostates (>30 g) and higher serum PSA concentrations (1.5–10 µg/L). Combination therapy reduced the relative risk of acute urinary retention or BPH-related surgery by 65.8% compared with tamsulosin alone and by 19.6% compared with dutasteride alone. In addition, for those patients who completed the study, the mean change in the International Prostate Symptom Score from baseline to year 4 was significantly higher for the combination therapy compared with tamsulosin or dutasteride alone. Adverse drug events are more common with combination therapy, but study withdrawal rates were <5% and similar among treatment groups. A combination product of dutasteride 0.5 mg and tamsulosin hydrochloride 0.4 mg is commercially available.

CASE 109-3, QUESTION 6: G.M. asks whether there are nonprescription treatments that are effective for BPH available. What OTC medications are available for prostate disorders?

Two agents, saw palmetto and pygeum, have been promoted for the treatment of BPH. Saw palmetto is an herbal product obtained from the fruit of the *Serenoa repens* tree with antiandrogen activity. The active ingredients are phytosterols; β-sitosterol and β-sitosterol-3-*O*-glucosides are the most abundant. Several trials have shown that it significantly improves BPH symptoms to a degree similar to that of finasteride.[61,87–90] However, a 2012 meta-analysis of 32 randomized trials failed to detect a difference in urinary symptom improvement even with triple the usual dose of saw palmetto compared to placebo.[91] The dose most often studied is 320 mg a day in one or two divided doses. Pygeum (*Pygeum africanum* bark extract) has been observed to moderately reduce urinary symptoms associated with enlargement of the prostate gland at a dose of 75 to 200 mg/day.[92] Pygeum has been well tolerated in most studies; however, the safety has not been extensively or systematically

studied. Herbal products may be tried by males with mild symptoms that would usually be managed by watchful waiting; however, the use of complementary and alternative medicines for BPH is not currently recommended by the AUA guidelines.[93]

Nonpharmacologic Treatment

TRANSURETHRAL RESECTION OF THE PROSTATE

Case 109-3, Question 7: What are the options if drug therapy does not work for G.M.? When should prostate surgery be undertaken in general?

G.M.'s subjective and objective findings, particularly the acute urinary retention and hydronephrosis, collectively indicate the need for a TURP. G.M. has been advised by his urologist that a TURP is the treatment of choice given the severity of his presentation (eg, large prostate gland with acute urinary retention) and that the procedure will relieve his symptoms, allow him to lead a relatively normal life, and avoid sequelae of prolonged obstruction.

TURP provides significant relief of BPH symptoms in 86%, 83%, 75%, and 75% of patients at 3 months, 1 year, 3 years, and 7 years, respectively.[94] Of patients with severe BPH, 93% report reduced symptoms 1 year after a TURP.[95] The TURP is considered the gold standard for the treatment of BPH and is used in 90% of patients with symptoms of residual urine or acute urinary retention. As a result, surgical alternatives are always compared with the outcome studies of TURP.

The need for a TURP in G.M.'s situation is fairly clear. In most cases, however, the need for a TURP is less clear because the symptoms do not inevitably worsen, and males often are willing to live with their symptoms. Therefore, clinicians need to talk with patients and help them answer the question of whether the discomfort, risk, and problems during the postsurgical recovery period are outweighed by the high probability that surgery will relieve symptoms.

SEXUAL DYSFUNCTION

As individuals are living longer, there is a growing interest in maintaining sexual health throughout later life. Nearly 39% of males and 17% of females between ages 75 and 85 reported being sexually active in a cross-sectional study published in 2010.[96] A nationally representative study concluded that most older adults are engaged in sexual activity and regard sex as an important part of life.[97] Poor health often is cited by older females as a reason for not participating in sexual activity, and among males, ED is the leading cause of decline in activity.[98],[99] The major factors that correlate with reduced sexual activity include an older spouse, poor mental or physical health, marital difficulties, previous negative sexual experiences, and negative attitudes toward sexuality in the aged.[100]

Male Sexual Dysfunction

In males, sexual function is considered an interaction between motivation, drive, desires, thoughts, fantasies, pleasures, experiences (referred to as the *libido*), penile vasocongestion, erection, orgasmic contractions, and ejaculations (referred to as *potency*).[101],[102] Testosterone plays an important role in male libido and sexual behavior and may play some role in penile erection. Older males show a strong correlation between advancing age and diminishing bioavailable serum testosterone levels.[103] Testosterone progressively declines after the seventh decade, partly because of testicular and hypothalamic–pituitary dysfunction.[104] Male sexual dysfunction, denoting the inability to achieve a satisfactory sexual relationship, may involve inadequacy of erection or problems with emission, ejaculation, or orgasm.

ED, also referred to as impotence, is defined by the National Institutes of Health Consensus Development Panel on Impotence and the Fourth International Consultation on Sexual Medicine as persistent or recurrent failure to achieve or maintain a penile erection to allow for satisfactory sexual intercourse.[105] Males may develop

different types of sexual dysfunction that have different underlying pathophysiology and require alternative treatment modalities. That males who have decreased libido have decreased sexual drive or desire and vice versa is true for those with increased libido. *Premature ejaculation* refers to uncontrolled ejaculation before or shortly after entering the vagina. *Retarded ejaculation* usually is synonymous with delayed ejaculation. *Retrograde ejaculation* denotes backflow of semen into the bladder during ejaculation caused by an incompetent bladder neck mechanism.

The Massachusetts Male Aging Study (MMAS) reported that in males ages 40 to 70 years, the overall prevalence of any degree of ED was 52%, and as high as 80% in those older than 70 years. There was an age-related increase in prevalence ranging from 12.4 cases per 1000 males per year in males ages 40 to 49 years, up to 46.4 cases per 1000 males per year in males ages 60 to 69 years.[106] Despite high prevalence, another study found that many patients do not seek treatment for ED and a possible reason could be reduced sexual activity in males ages 57 to 85 years.[107,108]

Contrary to the historical perception of ED as a symptom of the aging process, it is now well known that it is caused by a variety of medical, psychological, and lifestyle factors. Medical conditions such as HTN, arteriosclerosis, hyperlipidemia, diabetes mellitus, metabolic syndrome, or psychiatric disorders are associated with the development of ED. Medications used for the management of common chronic diseases may also exacerbate or lead to the development of ED. Approximately 80% of all cases of ED now are thought to be related to organic disease and subject to numerous influences.[109–112] In one study, neurologic and vascular disorders were the primary causes of ED among older adult males, and psychogenic factors were the cause in <10%.[103] The single most common etiology for erectile failure in older adults is severe atherosclerosis (eg, vascular disease and diabetes mellitus).[103] Cardiovascular disease, HTN, diabetes mellitus, elevated low-density lipoprotein cholesterol, and cigarette smoking are associated with a greater probability of complete ED in males.[113] Therefore, prevention of cardiovascular disorders by interventions such as low-

fat and low-cholesterol diets and abstinence from tobacco should minimize the development of ED.

Because ED is more likely in male patients with coronary artery disease, the understanding of the cardiovascular stresses involved with sexual intercourse can aid in patient management. Cardiac and metabolic expenditures during sexual intercourse vary depending on the type of sexual activity. Healthy males with their usual female partners generally achieve a peak heart rate of 110 beats/minute with female-on-top coitus and an average peak heart rate of 127 beats/minute with male-on-top coitus.[114] There is significant individual variation in cardiovascular response, when measured as oxygen uptake and metabolic expenditures, for male-on-top coitus.

In a study of patients with coronary artery disease who were medication free and in the New York Heart Association functional class I or II, sexual activity was compared with near-maximal exercise treadmill test.[115] Electrocardiographic changes representing ischemia during intercourse were found in one-third of the patients; however, two-thirds of these patients remained asymptomatic. All patients with ischemia during coitus also demonstrated ischemia during exercise treadmill testing. The average heart rate during coitus was 118 beats/minute, with some patients attaining a heart rate of 185 beats/minute at orgasm. Intercourse in patients with coronary artery disease may provoke increased ventricular ectopic activity that is not necessarily elicited by other stimuli.[116] These electrocardiographic changes and associated symptoms can be abolished with the use of β-blockers.[117] Sexual activity is a likely contributor to the onset of myocardial infarction only 0.9% of the time.[118] Coital death is rare, accounting for 0.6% of sudden death cases.[119] The hemodynamic changes associated with sexual activity may be far greater with an unfamiliar partner, in unfamiliar settings, and after excessive eating and alcohol consumption.

Erectile Dysfunction

NORMAL PENILE ERECTION PHYSIOLOGY

A harmony of several systems and factors is necessary for a normal, sustainable penile erection. Erection involves the neurologic, psychological, hormonal, arterial, and venous systems. Psychological stimuli are essential along with sexual stimuli to produce an erection.[120] The penis has two corpora made up of sinusoids that fill with arterial blood flow during an erection. The erection is prolonged by compression of subtunic venules, resulting in reduced venous outflow from the corpora. Arterial flow into the corpora is enhanced by neurotransmitters including acetylcholine, cyclic guanosine monophosphate (cGMP), and cyclic adenosine monophosphate (cAMP). On the other hand, norepinephrine decreases arterial inflow and increases venous outflow, which results in the progression of an erect penis to a flaccid state. The CNS plays a role in mediating erection through sensory sexual stimulation by sending nerve impulses from the spinal cord to peripheral cholinergic nerves that innervate the vascular supply to the corpora. The role of testosterone is complicated, yet important in stimulating libido and producing penile erection. Testosterone plays a role by targeting androgen receptors in penile endothelium and enhancing vascular process essential for penile erection.[120],[121] Declining serum testosterone levels, referred to as hypogonadism, have been associated with decreased libido, ED, and loss of spontaneous morning erections.[122] However, patients with normal testosterone levels can develop ED, and patients with low serum testosterone levels may remain asymptomatic and maintain normal sexual function. Owing to such variability, the FDA recommends treatment when serum testosterone levels are <300 ng/dL (10.4 nmol/L) and the patient has symptoms or signs of hypogonadism.[123] The European Association of Urology and the American Society of Andrology similarly recommend (a) no treatment if testosterone is >350 ng/dL (12.2 nmol/L), (b) treat if the patient has a serum testosterone of 230 to 350 ng/dL (8.0–12.2 nmol/L) and is symptomatic, and (c) treat if serum testosterone is <230 ng/dL (8.0 nmol/L).[124]

Evidence indicates that >80% of the cases of ED are because of organic causes, of which vascular disease is the most common.[125] In

most older male sexual dysfunction studies, 50% involve vascular problems and 30% relate to diabetes mellitus.[126]

Neurogenic disorders

ED can be caused by damage to the brain, spinal cord, cavernous or pudendal nerves, terminal nerve endings, and the receptors. Approximately 95% of patients with upper motor neuron lesions resulting from spinal injury are capable of erection through the reflexogenic mechanism, whereas only 25% of patients with complete lower motor neuron lesions can have erections through the psychogenic mechanism.[127] With incomplete lesions, up to 90% of patients in both groups retain erectile ability. Patients who have a cerebrovascular accident, dementia, epilepsy, Parkinson disease, or a brain tumor most likely experience erectile failure through loss of sexual interest or excessive inhibition of the spinal erection centers.[128]

Endocrine disorders

The incidence of ED with a hormonal cause has been estimated to be 5% to 35%, depending on which medical specialty is reporting the finding.[129] The most common hormonal disorder associated with ED in older adult is diabetes mellitus. Depending on the severity and duration of diabetes, the prevalence of ED ranges from 20% to 85%.[130]

Other endocrine disorders, such as hypothyroidism, hyperthyroidism, Addison disease, and Cushing syndrome, are associated with ED. Patients with hypogonadism caused by pituitary or hypothalamic tumors, antiandrogen therapy, or orchiectomy experience ED. These patients can have a normal erection from visual stimulation, however, indicating that the erectile mechanism is intact.[131]

Vascular disorders

Atherosclerosis is the leading vascular disease associated with male ED. The age of onset of coronary artery disease parallels the onset of ED, indicating a generalized atherosclerotic etiology for the ED.[132] The degree of arteriolar narrowing and clinical presentation, however, differs from patient to patient. Some patients can have severe coronary artery disease but retain the capability of a full erection. As long as the arterial flow into the penis exceeds the venous outflow, the patient can be potent. Narrowing of the arterial lumen lowers the pressure in the cavernous arteries, and poor arterial flow can only partially fill the sinusoidal system. Overall, the partial filling of the sinusoidal system causes inadequate expansion of the sinusoidal wall, resulting in partial compression of the venules. The net effect is a partial erection, difficulty in maintaining an erection, or early detumescence.

SIGNS AND SYMPTOMS

CASE 109-4

QUESTION 1: F.M., a 66-year-old male, was referred to a urologist because he was experiencing a loss of interest in sexual activity. He describes the inability to maintain a firm erection for the past 6 months in >75% of sexual attempts with his sexual partner. Physical examination was unremarkable except for an enlarged prostate gland and evidence of pubic and axillary hair loss. Vital signs were as follows:

Blood pressure, 160/95 mm Hg
Pulse, 88 beats/minute
Respirations, 14 breaths/minute
Temperature, 98.7 °F (37.06 °C)

Current medications include ramipril 5 mg once a day and glipizide 5 mg once daily. F.M.'s medical history is positive for cigarette smoking, HTN, and diabetes mellitus. Significant laboratory results include the following:

Hemoglobin A_{1c}: 7.2%
SCr, 1.5 mg/dL
BUN, 22 mg/dL
Free testosterone level, 30 pg/mL (normal, 52–280 pg/mL)
Luteinizing hormone (LH), 4 mU/mL (normal, 1–8 mU/mL)
Follicle-stimulating hormone (FSH) level, 40 mIU/mL (normal, 4–25 mIU/mL)

Serum prolactin level, 28 ng/mL (normal, >20 ng/mL)

What signs and symptoms does F.M. have that would suggest the need for a complete medical workup for ED?

F.M. presents with a loss of interest in sexual activity and the inability to maintain a full erection during >75% of sexual encounters with his partner. On physical examination, F.M. is found to have a noticeable loss of pubic and axillary body hair. With long-standing androgen deficiency, there may be loss of hair in the androgen-dependent areas of the body, fine wrinkling of the skin around the mouth and eyes, noticeable loss of muscle mass and strength, altered body fat distribution, and osteoporosis. In contrast, overt hypogonadism results in a change in the pattern of pubic hair from the male diamond shape to the female-inverted triangle appearance. At this point, it appears that F.M.'s loss of pubic and axillary hair is the result of androgen deficiency, with the cause yet to be determined. The laboratory results for gonadal function coincide with what is expected in an older male with ED (see Case 109-4, Question 4).

UROLOGIC WORKUP

CASE 109-4, QUESTION 2: What clinical evaluations and laboratory tests should be included in the medical workup of F.M. to determine the cause of his ED?

A detailed medical and sexual history and thorough physical examination are essential in the evaluation of sexual dysfunction. General medical history and physical examination should also consider drug-induced ED (**Table 109-12**).[133–150]

Table 109-12
Common Drug-Induced Alterations in Sexual Response

Drug Categories	Clinical Considerations
Antihypertensives	

Drug Categories	Clinical Considerations
Diuretic thiazides	Temporal association with sexual dysfunction. Reported incidence varies between 0% and 32%[133–136]; however, impotence generally is not considered common. Mechanism believed to be a “steal syndrome,” whereby blood is routed from erectile tissues to skeletal muscle[137]
Spironolactone	Associated with ↓ libido, impotence, and gynecomastia. Mechanism may be hormone related. Incidence is dose related and reported to be 5%–67%[137] and much more commonly encountered than with thiazides. May be owing to antiandrogen effects of drug
Sympatholytics	
Methyldopa	Central action mediated, causing vasodilation resulting in erectile dysfunction. Reported incidence: 10%.[137] Also ↓ libido
Clonidine	Induces erectile dysfunction. Mechanism similar to methyldopa and other central α_2-agonists. Incidence reported to be 4%–70% and dose related.[138—140] Also ↓ libido
Guanabenz, guanfacine	Incidence and mechanism believed to be similar to other central α_2-agonists
Nonselective β-Blockers	
Propranolol	Associated with erectile dysfunction and ↓ libido. Mechanism believed to be caused by ↓ vascular resistance and central effects. Erectile dysfunction reported to begin at doses of 120 mg/day. Incidence may be as high as 100% at higher dosages.[141,142]
Selective β-Blockers	
Atenolol, metoprolol, pindolol, timolol	Incidence of erectile dysfunction is significantly less than that of nonselective β-blockers.[143]
α-Blockers	
Doxazosin, prazosin, terazosin	Associated with erectile dysfunction and priapism.[139] Reported incidence: 0.6%–4%. Mechanism is local α_1-blockade resulting in vasodilation. Erectile dysfunction and priapism appear to be unique to the nonspecific α_1-antagonists.

Drug Categories	Clinical Considerations
Phenoxybenzamine	Associated with priapism, retrograde ejaculation, and inhibited emissions during erection. Effects are dose related.[144],[145]
Direct Vasodilators	
Hydralazine	Associated with erectile dysfunction. Mechanism is vascular smooth muscle relaxation. Incidence not reported[144]
Calcium Channel Blockers	
Amlodipine	Associated with erectile dysfunction. Mechanism believed to be vasodilation and, possibly, muscle relaxation. Reported incidence: <2%[146]
Diltiazem, verapamil	Similar to amlodipine. Reported incidence: <1%
Antiarrhythmics	
Class 1A disopyramide	Associated with erectile dysfunction in patients treated for ventricular arrhythmias. Incidence not reported. Mechanism believed to be caused by strong anticholinergic effect[144]
Anticonvulsants	
Carbamazepine, phenytoin	May be associated with sexual dysfunction through decreasing DHEA, which is a precursor to testosterone, estrogen, and pheromones
Antidepressants	
Selective serotonin reuptake inhibitors	Drugs with prominent serotonin agonist effects commonly cause delayed ejaculation and anorgasmia. The reported incidence for delayed ejaculation among males is 2%–12%; for anorgasmia among female users, the incidence appears to be >3%. This adverse effect is directly dose related.
Tricyclic antidepressants, monoamine oxidase inhibitors	Associated with impairment of sexual performance in both males and females: ↓ libido, anorgasmia, retrograde ejaculation, erectile dysfunction. Mechanism believed to be caused by anticholinergic and serotonergic effects. Incidence not reported; several case studies in the literature[137] (Note: The literature reports that, overall, there is less sexual dysfunction with desipramine than with other antidepressants.)

Drug Categories	Clinical Considerations
Trazodone	Associated with priapism in males and ↑ libido in females. Mechanism similar to TCA. Incidence not reported but believed to be dose related[137]
Antipsychotics	
Phenothiazines	Frequently associated with sexual dysfunction. Commonly, ↓ libido is reported. Mechanism is owing to hyperprolactinemia secondary to central dopamine antagonism. Erectile and ejaculatory pain is very common with this drug class; the α-antagonism and anticholinergic effects are responsible. Priapism is common with this drug group, owing to the peripheral α-blockade property. Incidence for all sexual dysfunctions with this drug class: ~50% of users[137]
Anxiolytics	
Short-acting barbiturates	Biphasic effect. At low doses, libido ↑, similar to ethanol, and at higher doses, CNS depression causes ↓ libido and performance.[137]
Benzodiazepines	Biphasic effect. At low doses, ↑ libido, whereas at higher dosages, CNS depression causes performance failure. Some reports of anorgasmia (males and females) and ejaculatory failure[137]
Substances of Abuse	
Alcohol	Alcohol is thought to impair sexual function through its chronic effects on the nervous system. Short-term use of alcohol can induce erectile dysfunction through its sedative effects. More than 600 mL/week of alcohol increases the probability of erectile dysfunction.[147] At low doses, it actually may enhance libido. Sexual dysfunction is dose related and caused by CNS depressant effects.[137]
Cocaine	Biphasic effect. At low doses, there is enhanced sexual desire (similar to amphetamines) and, possibly, performance. At higher dosages, there may be arousal dysfunction, ejaculatory dysfunction, and anorgasmia. Freebasing has been associated with spontaneous orgasm. Continued use (on a run) causes significant loss of sexual interest and performance ability. Chronic use associated with hyperprolactinemia resulting in ↓ libido[137]

Drug Categories	Clinical Considerations
Hallucinogens	Biphasic effect for most drugs in this category. At low doses, libido is enhanced; at higher doses, libido is severely ↓. No reports on chronic use[137]
Marijuana	Biphasic effect similar to ethanol. With chronic use, there is a ↓ in libido. Mechanism may be owing to ↓ testosterone. Incidence not reported[137]
Opioids	Associated with sexual dysfunction: erection lubrication, orgasm, and ejaculation. Chronic use associated with ↓ libido. Mechanism may be owing to α-antagonism, alterations in testosterone, and the intoxicating effects. Incidence not reported[148],[149]
Miscellaneous	
Amyl nitrate	Associated with intense and prolonged orgasms in both males and females. Impotence has been reported in some cases owing to vasodilation.[137]
Cimetidine	Associated with ↓ libido and erectile dysfunction. Mechanism owing to antiandrogen qualities and drug-induced elevation of prolactin. May be dose related.[150]
Metoclopramide	Associated with ↓ libido and erectile dysfunction. Mechanism is through CNS dopamine antagonism, resulting in hyperprolactinemia. Incidence not reported

CNS, central nervous system; DHEA, dehydroepiandrosterone; TCA, tricyclic antidepressants.

Source: Bancroft J, Wu FC. Changes in erectile responsiveness during androgen therapy. *Arch Sex Behav*. 1983;12:59–66; Michal V, Kovac J, Belan A, et al. Arterial lesions in impotence: phalloarteriography. *Int Angiol.* 1984;3:247–251; Bulpitt CJ, Dollery CT. Side effects of hypotensive agents evaluated by self-administered questionnaire. *Br Med J.* 1973;3:485–490; Bulpitt CJ, Fletcher AE. Drug treatment and quality of life in the elderly. *Clin Geriatr Med.* 1990;6:309–317; Hogan MJ. Antihypertensive therapy and male sexual dysfunction. *Psychosomatics.* 1981;21:234–244; Mallett EC, Badlani GH. Sexuality in the elderly. *Semin Urol.* 1987;5:141–145; McWaine DE, Procci WR. Drug-induced sexual dysfunction. *Med Toxicol Adverse Drug Exp*. 1988;3:289–306; Ebringer A, Doyle AE, Dawborn JK, Johnston CI, Mashford ML. Clonidine in the treatment of hypertension. *Br Med J.* 1971;1:402–403; Laver MC. Sexual behaviour patterns in male hypertensives. *Aust N Z J Med*. 1974;4:29–31; Onesti G. Clonidine: a new antihypertensive agent. *Am J Cardiol.* 1971;28:74–83; Mooradian AD, Morley JE, Billington CJ, Slag MF, Elson MK, Shafer RB. Hyperprolactinaemia in male diabetics. *Postgrad Med J*. 1985;61:11–14; Burnett W. Sexual dysfunction as a

complication of propranolol therapy in men. *Cardiovasc Med.* 1979;4:811–815; Buffum J. Pharmacosexology: the effect of drugs on sexual function: a review. *J Psychoactive Drugs.* 1982;14:5–44; Van Arsdalen KN, Wein AJ. Drug-induced sexual dysfunction in older men. Geriatrics. 1984;39:63–67; Caine M. Phenoxybenzamine for benign prostatic obstruction. review of 200 cases. *Urology.* 1981;17:542–546; Morley JE, Kaiser FE. Sexual function with advancing age. *Med Clin North Am*. 1989;73:1483–1495; McCellan KJ, Goa KL. Transdermal testosterone. *Drugs.* 1998;55:253–258; Mirin SM, Meyer RE, Mendelson JH, Ellingboe J. Opiate use and sexual function. *Am J Psychiatry.* 1980;137:909–915.

Although laboratory-based diagnostic procedures are available, sexual function may be best assessed in a naturalistic setting with patient self-report techniques. A psychometrically sound self-reporting tool is the International Index of Erectile Function (IIEF), which addresses the relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) and has been linguistically validated in 10 languages.[151] A simplified version, the IIEF-5, is a five-item questionnaire that is also popular.[152]

F.M.'s endocrine status should include an assessment of his diabetes, thyroid function tests, and a serum lipid profile. Neuropathy and atherosclerosis are common findings among male patients with diabetes mellitus, and both are potential causes of ED. Patients experiencing hypothyroidism may have decreased libido, and hypothyroidism is associated with hyperprolactinemia, which can result in an inhibition in the release of testosterone. Elevated serum lipids (eg, total cholesterol, triglycerides) may be associated with significant vascular damage that could contribute to ED. Diabetes mellitus is best evaluated with hemoglobin A_{1c} and fasting blood glucose tests.[153]

The serum concentrations of free testosterone, prolactin, and LH should be evaluated. Testosterone, as with all other hormones secreted into the plasma, is available to tissues only in the free form (ie, unbound to serum proteins, particularly the sex hormone–binding globulin). Only 1% to 2% of testosterone is free and physiologically active; therefore, measurement of the unbound serum testosterone provides the best estimate of biologically available testosterone. Low testosterone serum concentrations are associated with primary and

secondary hypogonadism. Primary hypogonadism is associated with testicular disease (eg, Leydig cell tumors), whereas secondary hypogonadism is the result of pituitary or hypothalamic disease.

The serum prolactin concentration should be determined because a high serum concentration of prolactin inhibits the release of testosterone from the testes. Therefore, a low serum testosterone concentration may be caused by hyperprolactinemia. Hyperprolactinemia may be caused by prolactin adenomas, diabetes mellitus, or drug therapy (eg, neuroleptics, metoclopramide).

LH stimulates testicular steroidogenesis and secretion of testosterone. LH increases the conversion of cholesterol to pregnenolone, a precursor of testosterone. FSH is required for spermatogenesis in early puberty but is not a required gonadotropin for the maintenance of spermatogenesis in adult males. Normal testicular function depends on stimulation by the gonadotropin LH, which is secreted by the anterior pituitary gland. Consequently, a low normal serum concentration of LH is associated with secondary hypogonadism.

In patients with symptoms of prostatic disease, expressed prostatic secretions (EPSs) should be examined because prostate inflammation has been associated with ejaculatory dysfunction. During prostatic inflammation, the EPS contains leukocytes and macrophages, and microscopic examination of the EPS can determine the degree of prostate inflammation. The presence of >20 white blood cells per high-powered field in the EPS is abnormal and indicative of prostatitis. Only about 5% of prostatitis can be attributed to a bacterial infection; the remaining 95% is caused by unknown etiologies.

Ideally, assessment of ED should include urologic, endocrinologic, psychiatric, and neurologic evaluations as close together as possible. The signs and symptoms of ED must be identified carefully and described because medical intervention is indicated if it occurs for a 6-month period and in >50% of attempts.[111] A detailed history should determine whether ED varies with partners, sexual settings, position, and masturbation, and whether morning and nocturnal erections are impaired.

RELATIONSHIP OF MEDICAL HISTORY AND ERECTILE DYSFUNCTION

CASE 109-4, QUESTION 3: What is the relationship among HTN, cigarette smoking, diabetes mellitus, and F.M.'s ED?

Hypertension

In the MMAS, heart disease with HTN and low serum high-density lipoprotein correlated with ED.[110] The hemodynamics of erection can be impaired in patients with myocardial infarction, coronary artery bypass surgery, cerebrovascular accidents, and peripheral vascular disease.[153–157] In several studies of impotent males, the number of abnormal penile vascular findings significantly increased when the history included HTN and cigarette smoking. Control of blood pressure among hypertensive male patients does not necessarily improve erectile function, and antihypertensive medications can have a significant effect on ED and sexual performance (see Table 109-12).[158–160]

Cigarette smoking

The prevalence of cigarette smoking among males with ED is higher than that in the general population.[161–163] When the relation between cigarette smoking and erectile physiology was studied in 314 males with ED,[164] smoking was noted to further compromise penile physiology in males experiencing difficulty maintaining erections long enough for satisfactory intercourse. Several investigators report lower penile blood pressure indices, penile arterial insufficiency, and abnormal blood perfusion associated with cigarette smoking.[161],[165] Clearly, smoking cessation may benefit males with existing ED.

Diabetes mellitus

Diabetes mellitus has been associated with ED. In the MMAS, male patients with diabetes mellitus were three times more likely to have ED than were patients without diabetes.[109] Other investigators using

exclusively populations with diabetes have found a prevalence of ED as high as 75% among subjects.[166],[167] The onset of ED in the patient with diabetes occurs at an earlier age when compared with the general population. In a few cases, it may be the presenting symptom of diabetes mellitus, and, in most cases, ED follows within 10 years of the diagnosis, regardless of insulin dependence status.[168],[169] Researchers disagree as to the exact contribution of diabetes mellitus to ED, but most of the literature supports an atherosclerotic etiology.[170],[171] Other possible causes also include autonomic neuropathy and gonadal dysfunction.[170]

GONADAL FUNCTION IN ERECTILE DYSFUNCTION

CASE 109-4, QUESTION 4: What is the significance of the gonadal function results for F.M.?

Gonadotropins

Abnormalities of primary or secondary hypogonadism must be ruled out, particularly in patients with a decreased libido with or without ED. The results of F.M.'s gonadal function tests are relatively normal for an aged male. Testosterone serum levels decline with aging as a result of hypothalamic–pituitary changes or Leydig cell dysfunction. The understanding of changes that take place in the hypothalamic–pituitary level with advancing age is in a state of flux. For some time, most investigators focused on the increased serum concentration of male gonadotropins (LH, FSH), believing that all older males had some degree of primary hypogonadism.[172] Other studies have shown, however, that LH levels in older males are lower than the median of those in younger patients.[146] These findings show that LH levels do not increase in response to the decrease in testosterone serum concentrations in the aged male, indicating a defect in the hypothalamic–pituitary axis, leading to secondary hypogonadism.[173] Secondary hypogonadism results from dysregulation of pituitary LH release, resulting in low serum testosterone levels.[128]

Testicular size and aging

Testicular size decreases with age; however, the testicular degeneration is sporadic, thereby allowing most older males to maintain a normal or slightly decreased sperm output.[172] Overall, spermatogenesis decreases and is accompanied by an increase in serum concentration of FSH. FSH elevation correlates well with a decline in the number of Sertoli cells that secrete inhibin. Inhibin normally decreases FSH.[174]

Testosterone

As a result of primary or secondary hypogonadism in the older male, available testosterone declines. Approximately 60% to 75% of circulating serum testosterone is bound to a β-globulin known as sex hormone–binding globulin or testosterone-binding globulin. Approximately 20% to 40% of testosterone is bound to serum albumin, and 1% to 2% is unbound, or free. The unbound portion of the testosterone is the only active portion of the total serum testosterone concentration. Testosterone serum concentrations are 20% higher in the morning than in the evening, and this should be taken into consideration when evaluating laboratory results. In virtually all cases of ED, the serum concentration of testosterone should be measured in the morning.

Testosterone production is regulated by feedback from the hypothalamus and pituitary. The hypothalamus produces gonadotropin-releasing hormone (GnRH) in response to low testosterone levels. GnRH induces the pituitary to secrete LH and FSH, which in turn stimulates the Leydig cells of the testes to secrete testosterone. Less than 10% of cases of ED studied are caused strictly by hypogonadism.[103],[175] The role of testosterone in ED is complex. After testosterone production decreases, libido eventually declines and precedes the decrease in the frequency of erections.[176] Males given antiandrogens maintain their erectile capacity but have a decreased libido.[177] On the other hand, high dosages of androgens given to hypogonadal males increase both the frequency of erections and libido.[178] It would seem reasonable to postulate that at

physiologic levels, testosterone modulates the cognitive processes associated with sexual arousal more than it contributes to erectile capability.

Endocrine disorders

Many endocrine disorders can result in ED. Patients with prolactinomas commonly have ED, but prolactinomas account for <1% of ED cases.[141] Prolactin inhibits the release of testosterone, resulting in secondary hypogonadism. Hyperprolactinemia may be more prevalent in patients with diabetes.[179] In older adults, however, hyperprolactinemia often is secondary to the use of medications. F.M.'s serum prolactin level is elevated, most likely because of his diabetes mellitus.

In summary, aging males have a decrease in testosterone because of defects in testicular and hypothalamic–pituitary function. Secondary hypogonadism in older males is common, and the point at which this becomes pathologic has not yet been established. Correspondingly, the use of hormonal therapy to treat physiologic secondary hypogonadism is extremely controversial. Therefore, the gonadal function tests for F.M. are normal for his age and do not provide an explanation for his ED.

MEDICATIONS THAT CAUSE ERECTILE DYSFUNCTION

Case 109-4, Question 5: Is it likely that a medication is causing F.M.'s ED?

Several general statements can be made regarding sexual function and medications. Drugs that affect libido generally have a central mode of action. For example, medications that block central dopamine transmission can decrease libido, and opiates have an antiandrogen effect.[166] Drugs that alter hemodynamics may interfere with erection. Excessive sympathetic tone is thought to cause the "steal syndrome," which increases blood flow to muscles, drawing blood away from the erectile tissue.[155] Drugs that block the peripheral sympathetic system can cause retrograde ejaculation or

no ejaculation at all. Numerous drugs have been associated with altered sexual function (see Table 109-12).[180]

Most studies documenting drug-induced ED have been subjective and based on case reports, uncontrolled studies, and clinical impressions. The MMAS reported that ED was statistically correlated with antihypertensive, vasodilator, cardiac, and hypoglycemic drugs. The probability of moderate as well as complete ED was particularly high for vasodilator drugs.[101] Although the MMAS is one of the most well-designed studies to date, the medications reported are not considered to be the universe of all medications associated with ED. Diagnosis of drug-induced sexual dysfunction should be restricted to a reproducible dose-related effect that disappears on discontinuation of the drug.[113] A much larger survey of a controlled study in a clinical population would be required to establish any suspect medication as causative, rather than temporal.

F.M.'s sexual dysfunction (eg, loss of interest in sexual activity and ED) is not caused by his current drug regimen, ramipril and glipizide. Although the MMAS[101] reported a correlation between the use of antihypertensives and hypoglycemic drugs with ED, clinicians must look at the individual drugs themselves and the conditions for which they are prescribed. Sexual dysfunction is not likely to occur with ramipril, or any of the other angiotensin-converting enzyme inhibitors (ACEIs), or with the hypoglycemic agent glipizide. Although ramipril is an antihypertensive, its pharmacologic effects do not contribute to a decline in libido or cause ED (an advantage that ACEIs have compared with other antihypertensive medications). Similarly, the pharmacologic action of glipizide does not contribute to F.M.'s decreased libido or ED. In most sexual dysfunction cases, it is less likely that the medication is the direct cause of the problem; rather, it is the medical condition for which the drugs were prescribed. The ability of a drug to induce sexual dysfunction simply is an extension of its pharmacologic actions. As a general rule, drugs that manipulate the sympathetic or the parasympathetic system, both centrally and peripherally, are associated with sexual dysfunction.

Case 109-4, Question 6: What factors most likely are contributing to F.M.'s ED?

F.M. is a patient with HTN and diabetes who smokes cigarettes. Those three factors are more likely to be the cause of F.M.'s sexual dysfunction than are his medications. Diabetes mellitus is the most common hormonal disorder associated with ED in older adults.[167] The continued loss of interest in sexual activity experienced by F.M. most likely is the result of having experienced ED during past and present sexual events.

F.M.'s subjective and objective findings are common among older males. His sexual dysfunction is caused by atherosclerosis and possible neuropathy secondary to diabetes mellitus. Because cigarette smoking is no doubt contributing to F.M.'s ED, cessation should be encouraged; some improvement can be expected.[137] There is no need to alter F.M.'s drug regimen.

MANAGEMENT

Case 109-4, Question 7: What are the primary therapeutic considerations for F.M.?

Essentially, there are three levels to the management of ED. Level 1 includes lifestyle and drug therapy modifications. Specifically, the patient should be instructed to modify smoking and alcohol use. The patient's drug regimen should be checked periodically to ensure that drugs associated with ED are not being prescribed. If necessary, psychosocial counseling should be provided. After careful consideration, oral medications for the management of ED should be instituted. If level 1 therapies have failed or are not acceptable to the patient, then level 2 therapy is instituted. These interventions include a vacuum constriction device to elicit an erection, intracavernosal injections, or transurethral inserts. Level 3 management involves the placement of a penile prosthesis.

PHARMACOTHERAPY

Any therapy directed at male sexual dysfunction must include the elimination of drugs causing adverse sexual effects. Drug therapy is directed primarily toward treatment of ED and includes hormonal therapy, bromocriptine, prostaglandin E_1, sildenafil, tadalafil, vardenafil, avanafil, and apomorphine.

Phosphodiesterase-5 inhibitors

CASE 109-4, QUESTION 8: Would PDE-5I therapy be appropriate for F.M.? What are its side effects and contraindications? Does it interact with other drugs?

F.M. has diabetes mellitus and atherosclerosis and, therefore, is a candidate for treatment with a PDE-5I.[181] These agents are orally active and selective inhibitors of cGMP-specific PDE-5, the predominant phosphodiesterase isoenzyme metabolizing cGMP in the corpus cavernosum. They facilitate an erection in response to sexual stimulation by enhancing the nitric oxide–induced relaxation of corpus cavernosal smooth muscle. The results of double-blind, placebo-controlled clinical trials in males with ED of various causes have demonstrated that PDE-5Is significantly improve erectile function and the rate of successful sexual intercourse, with therapeutic outcomes approaching those of normal males of the same age.[182–184]

F.M. should be counseled on the adverse effects of PDE-5Is. The vasodilating action of PDE-5Is affects both the arteries and the veins, so the most common side effects are headache and facial flushing.[185] PDE-5Is cause a small decrease in both systolic and diastolic blood pressures, but clinically significant hypotension is rare. Studies of PDE-5Is and nitrates taken together show much greater drops in blood pressure. For that reason, PDE-5Is are contraindicated in patients taking long-acting nitrates or short-acting nitrate-containing medications.[110] In phase II/III studies before FDA approval, >3700 patients received sildenafil and almost 2000

received placebo in double-blind and open-label studies. Approximately 25% of patients had HTN and were taking antihypertensive medications, and 17% were diabetic. In these studies, the incidence of serious cardiovascular adverse effects was similar in the double-blind sildenafil group, the double-blind placebo group, and the open-label group. Twenty-eight patients had experienced a myocardial infarction. When adjusted for patient-years of exposure, no significant differences were seen in the myocardial infarction rates between the sildenafil and the placebo group, and no deaths were attributed to sildenafil.[186],[187] In an analysis of 67 double-blind, placebo-controlled trials of sildenafil, the overall frequency of death was comparable between the patients treated with sildenafil (13 of 8691; 0.15%) and placebo group (7 of 6602; 0.11%).[188] Nevertheless, several deaths caused by myocardial infarction or arrhythmia have been associated with the use of sildenafil.[189] Deaths associated with sildenafil (and presumably other PDE-5Is) are most likely caused by the increased cardiac workload in patients with unstable angina.[190]

Transient visual anomalies (mostly blue-green color-tinged objects, increased sensitivity to light, and blurred vision) have been reported in patients taking PDE-5Is, especially at higher dosages. These visual effects appear to be related to the weaker inhibiting action of PDE-5Is on the enzyme phosphodiesterase-6, which regulates signal transduction pathways in the retinal photoreceptors. In patients with inherited disorders of retinal phosphodiesterase-6, such as retinitis pigmentosa, PDE-5Is should be administered with extreme caution. In 2005, the FDA recommended that all PDE-5Is include a precaution in their labeling regarding the risk of nonarteritic anterior ischemic optic neuropathy as a cause of decreased vision including permanent vision loss. There have been only a handful of reports of nonarteritic anterior ischemic optic neuropathy in postmarketing surveillance, and most patients had underlying risk factors.[191] Clinicians should advise patients to discontinue the use of all PDE-5Is and seek medical attention in the event of sudden vision loss in one or both eyes.

The vasodilator actions of nitrates are profoundly amplified with concomitant use of PDE-5Is. This interaction likely applies to all nitrates and nitric oxide donors, regardless of their predominant hemodynamic site of action. They also may potentiate the inhaled form of nitrate, such as amyl nitrite, and therefore are contraindicated in patients using this product. Dietary sources of nitrates, nitrites, and L-arginine (the substrate from which nitric oxide is synthesized) do not contribute to the circulating levels of nitric oxide in humans and, therefore, are unlikely to interact with PDE-5Is. The anesthetic agent, nitrous oxide, is eliminated unchanged from the body, mostly via the lungs, within minutes of inhalation. It does not form nitric oxide in the human body and does not itself activate guanylate cyclase. As such, no contraindication exists to its use after the administration of PDE-5Is. The concomitant use of nitrates and PDE-5Is is contraindicated, although some differences in the nitrate-free period do exist based on the pharmacokinetic profile of the PDE-5I. After 24 hours, the administration of nitrates can once again be considered in patients using vardenafil and sildenafil; however, this should be extended to 48 hours in patients using tadalafil and can be shortened to 12 hours with avanafil.

Case 109-4, Question 9: Which PDE-5I should be recommended for F.M.?

Sildenafil

The typical dose of sildenafil is 50 mg orally, taken 1 hour before sexual activity. However, it may be taken anywhere from 4 hours to 30 minutes before sexual activity. The maximal recommended dosing frequency is once per day. The following factors are associated with increased plasma levels of sildenafil: age older than 65 years (40% increase in area under the curve), hepatic impairment (eg, cirrhosis, 80% increase), severe renal impairment (creatinine clearance >30 mL/minute, 100% increase), and concomitant use of potent CYP3A4 inhibitors (eg, erythromycin, ketoconazole, itraconazole, 200% increase). Because higher plasma levels may

increase both the efficacy and the incidence of adverse events, a starting dose of 25 mg should be considered in these patients. The dose may be increased to 100 mg. Because F.M. is older than 65 years, he should be started on 25-mg tablets of sildenafil. The dose may be increased under strict supervision.

Sildenafil is metabolized by both the CYP2C9 and the CYP3A4 pathways. Thus, inhibitors of the CYP3A4 isoenzyme, such as erythromycin or cimetidine, may lead to competitive inhibition of its metabolism; however, CYP3A4 is a high-capacity pathway. The effects of erythromycin or cimetidine on the half-life and physiologic effects of sildenafil are not known, but clinicians should be warned about the potential interaction.

Inadequate physical sexual stimulation while using any of the PDE-5Is can lead to treatment failure. Adequate sexual stimulation is needed to trigger the events leading to erection.[192] PDE-5Is cannot initiate an erection; they can only assist in the process. Some patients may need several attempts at sexual stimulation before they are successful with intercourse.

Tadalafil

Similar to sildenafil, tadalafil is a selective inhibitor of PDE-5. Tadalafil has several times more affinity for PDE-5 than does sildenafil.[193] Tadalafil and vardenafil, however, have minimal or no effect on visual disturbance (impairment of blue-green color discrimination), which is a well-recognized side effect of sildenafil.[194] Tadalafil's extended half-life of 17.5 hours relative to sildenafil most likely precludes its use in patients with angina or HTN. Tadalafil is metabolized by the hepatic CYP3A4 isozyme. Food has no effect on the oral absorption of tadalafil in contrast to sildenafil (bioavailability decreased by 29%). Tadalafil may be advantageous in a subset of patients, based on its shorter onset of action (16 minutes) and 24-hour duration of action.[195] Specifically, patients with psychogenic or neurogenic ED and those with stable cardiovascular systems may prefer tadalafil because it offers the potential for multiple sessions of intercourse with a single daily dose.

Vardenafil

Vardenafil is the third FDA-approved oral PDE-5I for the treatment of ED. The warnings regarding the use of nitrates while taking vardenafil are similar to the warnings for sildenafil. Patients using vardenafil may experience headache, flushing, or rhinitis; the incidence of these side effects is dose related.[196] Vardenafil is metabolized by the hepatic CYP3A4 isozyme and has a reported half-life of 5 hours.[197] Thus, drugs known to inhibit the CYP3A4 isozyme have the potential to prolong its half-life. Vardenafil 10 mg does not impair the ability of patients with stable coronary artery disease to exercise at levels equivalent to or greater than that attained during sexual intercourse.[198]

Avanafil

Avanafil is a PDE-5I with enhanced PDE-5 selectivity that may translate to fewer side effects because of less selectivity for non–PDE-5 isoenzymes found in the heart, retina, and skeletal muscle. The starting dose is 50 mg and should be taken 30 minutes before sexual activity, whereas the 100- to 200-mg doses can be taken 15 minutes before. It has a half-life similar to that of sildenafil and vardenafil and is rapidly absorbed following administration. Side effects and contraindications for avanafil are similar to that of the other PDE-5Is.[199]

F.M. has HTN that most likely would be affected by tadalafil; therefore, extreme caution is advised. Perhaps, the shorter-acting sildenafil, vardenafil, or avanafil would be the PDE-5I drug of choice for F.M.

Testosterone

Case 109-4, Question 10: Should F.M. be treated with testosterone?

Primary hypogonadism with severely deficient serum levels of bioavailable testosterone is the only appropriate indication for the

use of androgen hormone therapy.[141] The goal of androgen replacement therapy is to restore potency and libido by maintaining normal serum levels of testosterone.[200] Testosterone has no benefit in the treatment of eugonadal or mildly hypogonadal older males and actually may enhance the growth of undiagnosed adenocarcinoma of the prostate or cause further ED.[110] In eugonadal males, testosterone enhances the rigidity of the erection, but does not change the penile circumference.[201] F.M. would not be a candidate for testosterone therapy.

Case 109-4, Question 11: Which type of patient would benefit from testosterone therapy?

Unless testosterone deficiency is severe (free testosterone serum levels <7–8 pg/mL), testosterone replacement therapy will not improve the success rate of intercourse.[202] Testosterone replacement in patients with primary hypogonadism generally restores libido and potency. In some patients with secondary hypogonadism caused by disorders of the hypothalamus or pituitary, GnRH analogs can be administered to differentiate between hypothalamic and pituitary abnormalities and to correct testosterone deficiency.[200] Libido and potency then are restored.

Case 109-4, Question 12: How should testosterone be used as a treatment for ED?

Testosterone replacement therapy is available in several formulations, including gels, transdermal patches, and intramuscular injection. Because of poor drug bioavailability, oral testosterone replacement therapy is less effective than is parenteral testosterone in achieving normal serum testosterone levels. Oral administration also is associated with a higher incidence of hepatotoxicity and adverse serum lipid effects.[110],[146] A long-acting testosterone intramuscular formulation, such as the enanthate or cypionate ester, is still considered the regimen of choice for the treatment of primary

hypogonadism. A dose of 50 to 400 mg should be administered intramuscularly every 2 to 4 weeks. Side effects of testosterone therapy include early gynecomastia, increases in hematocrit (sometimes to the point of polycythemia), and fluid retention that may worsen HTN or heart failure.

Results of several studies have demonstrated that serum testosterone levels are normalized while using transdermal testosterone applications.[147,203–205] The system normalizes DHT to testosterone ratios and reduces LH levels toward the normal range. The transdermal testosterone is well tolerated, with application site reactions such as pruritus, burn-like blisters, and erythema being the most commonly reported event. The adhesive side of the patch should be applied to a clean, dry area of the skin on the back, abdomen, upper arms, or thighs. The patient should be instructed to avoid application over bony prominences or on a part of the body that may be subject to prolonged pressure during sleep or sitting (eg, the deltoid region of the upper arm, the greater trochanter of the femur, and the ischial tuberosity); do not apply to the scrotum. The sites of application should be rotated, with an interval of 7 days between applications to the same site. The area selected should not be oily, damaged, or irritated.

Topical testosterone gel should be applied once daily in the morning to clean, dry skin. Depending on the specific product, it can be applied to the upper arms, shoulders, thighs, or abdomen. A topical solution for application to the axilla is also available. The dose can be as high as 100 mg/24 hours. After the gel or solution has dried on the site of application, it should be protected with clothing to prevent the transfer to a nonuser. The patient should wash their hands after application.

Commonly reported adverse effects in chronic users include acne, edema, gynecomastia, and dermatologic reactions to injections or transdermal applications of testosterone. The most serious risk of prolonged testosterone use is prostate carcinoma, although the association between high concentrations of testosterone and the risk of prostate carcinoma is controversial.[206–208] Three studies suggest that testosterone replacement therapy is relatively safe in

hypogonadism.[209–212] Baseline assessment of the prostate should be done before starting testosterone replacement therapy. This should consist of a TRUS, digital palpation of the prostate gland, and analysis of the PSA, hemoglobin, and hematocrit levels.

Bromocriptine

Case 109-4, Question 13: Because F.M.'s prolactin serum concentration is 28 ng/mL, should bromocriptine be prescribed to decrease his hyperprolactinemia and treat his ED?

Hyperprolactinemia may be treated with the ergot alkaloid bromocriptine, which works as a dopamine agonist to inhibit prolactin secretion. Even with normalization of prolactin levels, ~50% of older male patients are unable to achieve erectile function and desire.[146],[168] Bromocriptine therapy may be initiated with twice-daily 1.25-mg doses taken with meals to minimize GI upset. Thereafter, doses may be increased weekly, at a rate of no more than 2.5 mg/day. Adverse events associated with bromocriptine are nausea, dizziness, drowsiness, hypotension, and cerebrovascular accidents.[110],[168] For those who fail bromocriptine, cabergoline is a reasonable alternative given once or twice a week with good efficacy and a lower incidence of nausea.[212]

F.M. is not a candidate for treatment with bromocriptine because he does not have secondary hypogonadism, and his ED probably is secondary to atherosclerosis associated with his HTN, diabetes, and cigarette smoking. Furthermore, the elevation of F.M.'s serum prolactin concentration is not significant enough to warrant drug therapy. Medication-induced hyperprolactinemia is usually associated with prolactin levels ranging from 25 to 100 µg/L, but metoclopramide, risperidone, and phenothiazines can lead to prolactin levels exceeding 200 µg/L by way of dopamine antagonism.[212] Verapamil can cause hyperprolactinemia presumably by blocking hypothalamic dopamine, and opiates and cocaine can induce it through the µ-receptor.[212] Usually, prolactin will normalize 3

days following discontinuation of the offending medication; however, this patient is not on any medications that can induce hyperprolactinemia. Because the response rate to bromocriptine in older males is 50% (or less), the risk of adverse reactions (eg, dyskinesia, dizziness, hallucinations, dystonia, confusion, cerebrovascular accidents) outweighs the benefit of this dopamine agonist therapy.

CASE 109-4, QUESTION 14: What other drug therapy is available for F.M.?

Before the advent of the PDE-5Is, intracavernosal and intraurethral prostaglandin E_1 (alprostadil) administration was the only nonsurgical option for ED. Alprostadil causes direct vascular smooth muscle relaxation, allowing blood flow and entrapment in the penis. Less invasive than are intracavernosal injections, alprostadil intraurethral pellet is inserted, as a semisolid gel form, through the urethral opening of the penis 5 to 10 minutes before sex and works for up to 1 hour. However, it is less effective and not recommended for pregnant partners.[213] Intracavernosal injections are given at the base of the penis 10 to 20 minutes before sex and were effective in 87% of cases in one clinical trial.[214] Phentolamine, papaverine, and vasoactive intestinal peptide are also available for intracavernosal injection but are not FDA approved. Adverse events from intracavernosal therapies include priapism, pain at the injection site, and penile fibrosis after long-term use. Topical alprostadil cream has also shown efficacy in 74% of patients but is not currently available in the United States.[215]

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Given here are the key references

and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference

Key References

Lindau ST, Schumm LP, Laumann EO, et al. A study of sexuality and health among older adults in the United States. *N Engl J Med.* 2007;357: 762–774. (98)

McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Eng J Med.* 2003;349:2387–2398. (61)

Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. *Ann Intern Med.* 2009;151:650–651. (186)

Wagg A, Gibson W, Ostaszkiewicz J, et al. Urinary incontinence in frail elderly persons: report from the 5th International Consultation on Incontinence. *Neurourol Urodyn.* 2015;34:398–406. (8)

Key Websites

American College of Physicians. American College of Physicians releases new recommendations for treating urinary incontinence in women. http://www.acponline.org/newsroom/treating_ui_in_women.htm

American Urological Association. Clinical guideline on the management of erectile dysfunction. https://www.auajournals.org/doi/10.1016/j.juro.2018.05.004

American Urologic Association. http://www.auanet.org

American Urological Association. Management of Benign Prostatic Hyperplasia (BPH). https://www.auajournals.org/doi/10.1016/j.juro.2011.01.074

National Association for Continence. https://www.nafc.org

Simon Foundation for Continence. http://www.simonfoundation.org

COMPLETE REFERENCES CHAPTER 109 GERIATRIC UROLOGIC DISORDERS

1. Qaseem A, Dallas P, Forciea MA, et al. Nonsurgical management of urinary incontinence in women: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2014;161:429–440.

2. Kinchen KS, Lee J, Fireman B, Hunkeler E, Nehemiah JL, Curtice TG. The prevalence, burden, and treatment of urinary incontinence among women in a managed care plan. *J Womens Health (Larchmt)*. 2007;16:415–422.
3. Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. *Obstet Gynecol*. 2002;100:1230–1238.
4. Gorina Y, Schappert S, Bercovitz A, et al. Prevalence of incontinence among older Americans. National Center for Health Statistics. *Vital Health Stat.* 2014;3(36):1–33.
5. Andersson KE, Chapple C, Cardozo L, et al. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence.* 5th ed. International Consultation on Urological Disease European Association of Urology (ICUD-EAU); 2013:623–672.
6. Milson I, Altman D, Cartwright R, et al. Epidemiology of urinary incontinence (UI) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP), and anal (AI) incontinence. In: Abrams P, Cardozo L, Wagg A, Wein A, eds. *Incontinence.* 6th ed. Health Publications Ltd; 2016:17–24.
7. Markland AD, Goode PS, Redden DT, et al. Prevalence of urinary incontinence in men: results from the National Health and Nutrition Examination Survey. *J Urol.* 2010;184:1022–1027.
8. Wagg A, Gibson W, Ostaszkiewicz J, et al. Urinary incontinence in frail elderly persons: report from the 5th International Consultation on Incontinence. *Neurourol Urodyn*. 2015;34:398–406.
9. Culligan PJ, Heit M. Urinary incontinence in women: evaluation and management. *Am Fam Physician*. 2000;62:2433–2444.
10. Harvard Health Publishing. Harvard Medical School. Medications that cause urinary incontinence. 2014. www.health.harvard.edu/bladder-and-bowel/medications-that-can-cause-urinary-incontinence
11. National Association for Continence. Glossary. 2015. www.nafc.org/glossary/
12. Tsakiris P, Oelke M, Michel M. Drug-induced urinary incontinence. *Drugs Aging*. 2008;25:541–549.
13. Bardsley A. An overview of urinary incontinence. *Br J Nurs*. 2016;25:S14–S21.
14. National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Disease. Bladder control problems in Women (Urinary Incontinence). 2016. www.niddk.nih.gov/health-information/urologic-diseases/bladder-control-problems-women
15. Gleason JL, Richter HE, Redden DT, et al. Caffeine and urinary incontinence in US women. *Int Urogynecol J*. 2013;24:295–302.
16. Alling Møller L, Lose G, Jørgensen T. Risk factors for lower urinary tract symptoms in women 40 to 60 years of age. *Obstet Gynecol*. 2000;96:446–451.

17. Phelan S, Kanaya AM, Subak LL, et al. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. *J Urol*. 2012;187:939–944.
18. Subak LL, Wing R, West DS, et al. Weight loss to treat urinary incontinence in overweight and obese women. PRIDE Investigators. *N Engl J Med.* 2009;360:481–490.
19. Fantl JA, Wyman JF, McClish DK, et al. Efficacy of bladder training in older women with urinary incontinence. *JAMA*. 1991;265:609–613.
20. Wallace SA, Roe B, Williams K, et al. Bladder training for urinary incontinence in adults. *Cochrane Database Syst Rev*. 2004;1:CD001308.
21. Kim H, Yoshida H, Suzuki T. Exercise treatment to reduce the urine leakage in elderly community-dwelling Japanese women with stress, urge, and mixed urinary incontinence. Abstract 772. Poster abstract presented at: 39th Annual Meeting of the International Continence Society; October 2009; San Francisco, CA.
22. Aksac B, Aki S, Karan A, et al. Biofeedback and pelvic floor exercises for the rehabilitation of urinary stress incontinence. *Gynecol Obstet Invest*. 2003;56:23–27.
23. National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Disease. Bladder control problems in Men (Urinary Incontinence). 2015. www.niddk.nih.gov/health-information/urologic-diseases/bladder-control-problems-men
24. DeMaagd GA, Davenport TC. Management of urinary incontinence. *P T* 2012;37:345–361.
25. Wagg AS, Chen LK, Kirschner-Hermanns R, et al. Committee 11: incontinence in the frail elderly. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence—5th International Consultation on Incontinence*. ICUD-EAU; 2013:1001–1100.
26. Reynolds WS, McPheeters M, Blume J, et al. Comparative effectiveness of anticholinergic therapy for overactive bladder in women: a systematic review and meta-analysis. *Obstet Gynecol*. 2015;125:1423–1432.
27. Shamliyan T, Wyman J, Kane RL. *Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness*. Comparative Effectiveness Review No. 36. AHRQ Publication No. 11(12)-EHC074-EF. Agency for Healthcare Research and Quality; 2012.
28. Yalcin I, Peng G, Viktrup L, et al. Reductions in stress urinary incontinence episodes: what is clinically important for women? *Neurourol Urodyn*. 2010;29:344–347.
29. Ditropan (Oxybutynin). Package insert. Ortho-McNeil-Janssen Pharmaceuticals; 2012.
30. Ditropan XL (Oxybutynin Chloride) Extended-Release Tablets. Package insert. Janssen Pharmaceuticals; 2015.

31. Oxytrol (Oxybutynin Transdermal System). Package insert. Activis Pharma; 2015.
32. Layton D, Pearce GL, Shakir SA. Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. *Drug Saf*. 2001;24:703–713.
33. Detrol LA. Product information. Pfizer; 2012.
34. Toviaz (Fesoterodine Fumarate Extended-Release Tablets). Package insert. Pfizer; 2014.
35. Kaplan SA, Schneider T, Foote JE, et al. Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial. *BJU Int*. 2011;107(9):1432–1440.
36. Sanctura (Trospium Chloride) Tablets. Package insert. Allergan; 2012.
37. Halaska M, Ralph G, Wiedemann A, et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol*. 2003;20:392–399.
38. Staskin D, Kay G, Tannenbaum C, et al. Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. *Int J Clin Pract*. 2010;64:1294–1300.
39. Morales-Olivas FJ, Estan L. Solifenacin pharmacology. *Arch Esp Urol*. 2010;63:43–52.
40. Lipton RB, Kolodner K, Wesnes K. Assessment of cognitive function of the elderly population: effects of darifenacin. *J Urol*. 2005;173:493–498.
41. Kay G, Crook T, Rekeda L, et al. Differential effects of the anti-muscarinic agents darifenacin and oxybutynin ER on memory in older subjects. *Eur Urol*. 2006;50:317–326.
42. Chapple C, Steers W, Norton P, et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. *BJU Int*. 2005;95:993–1001.
43. Cardozo L, Lisec M, Millard R, et al. Randomized, double-blind placebo controlled trial of once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol*. 2004;172(5, pt 1):1919–1924.
44. Chapple CR, Rechberger T, Al-Shukri S, et al. Randomized, double-blind placebo and tolterodine controlled trial of once daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int*. 2004;93:303–310.
45. Cui Y, Zong H, Yang C, et al. The efficacy and safety of mirabegron in treating OAB: a systematic review and meta-analysis of phase III trials. *Int Urol Nephrol*. 2014;46:275–284.
46. Duckett J, Balachandran A. Tolerability and persistence in a large, prospective case series of women prescribed mirabegron. *Int Urogynecol J*. 2016;27:1163–1167.

47. Wagg A, Cardozo L, Nitti VW, et al. The efficacy and tolerability of the β3-adrenoceptor agonist mirabegron for the treatment of symptoms of overactive bladder in older patients. *Age Ageing*. 2014;43:666–675.
48. Su S, Liang L, Lin J, Liu L, Chen Z, Gao Y. Systematic review and meta-analysis of the efficacy and safety of vibegron vs antimuscarinic monotherapy for overactive bladder. *Medicine (Baltimore)*. 2021;100(5):e23171.
49. Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd PN Jr. Once-daily vibegron 75 mg for overactive bladder: long-term safety and efficacy from a double-blind Extension Study of the International Phase 3 Trial (EMPOWUR). *J Urol*. 2021;205(5):1421–1429.
50. Mariappan P, Alhasso A, Ballantyne Z, Grant A, N'Dow J. Duloxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI) for the treatment of stress urinary incontinence: a systematic review. *Eur Urol*. 2007;51:67–74.
51. Erdinc B, Gurates B, Celik H, et al. The efficacy of venlafaxine in the treatment of women with stress urinary incontinence. *Arch Gynecol Obstet*. 2009;279:343–348.
52. Malallah MA, Al-Shaiji TF. Pharmacological treatment of pure stress urinary incontinence: a narrative review. *Int Urogynecol J*. 2015;26:477–485.
53. Alhasso A, Glazener CM, Pickard R, et al. Adrenergic drugs for urinary incontinence in adults. *Cochrane Database Syst Rev*. 2005;3:CD001842.
54. Noctiva® (Desmopressin Acetate). Package insert. Serenity Pharmaceuticals; 2017.
55. Nocdurna® (Desmopressin Acetate) Sublingual Tablets. Package insert. Ferring Pharmaceuticals; 2018.
56. Cottenden A, Bliss DZ, Buckley B, et al. Management using continence products. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence.* 5th ed. International Consultation on Incontinence: European Urological Association; 2013:1651–1786.
57. Auffenberg GB, Helfand BT, McVary KT. Established medical therapy for benign prostatic hyperplasia. *Urol Clin North Am*. 2009;36:443–459.
58. Egan KB. The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms: prevalence and incident rates. *Urol Clin North Am.* 2016;43(3):289–297.
59. Glynn RJ, Campion EW, Bouchard GR, Silbert JE. The development of benign prostatic hyperplasia among volunteers in the Normative Aging Study. *Am J Epidemiol.* 1985;121(1):78–90.
60. Gratze C, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol.* 2015;67(6):1099–1109.
61. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of

benign prostatic hyperplasia. *N Engl J Med.* 2003;349(25):2387–2398.
62. Jacobsen SJ, Jacobson DJ, Girman CJ, et al. Natural history of prostatism: risk factors for acute urinary retention. *J Urol.* 1997;158(2):481–487.
63. McVary KT, Roehrborn CG, Avins AL, et al. *American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH)*. 2010, reviewed and validity confirmed 2014.
64. Lepor H. Medical therapy for benign prostatic hyperplasia. *Urology*. 1993;42:483–501.
65. Rosenberg MT, Witt ES, Miner M, Barkin J. A practical primary care approach to lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH-LUTS). *Can J Urol.* 2014;21(suppl 2):12–24.
66. Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology*. 1999;53(3):581–589.
67. Unnikrishnan R, Almassi N, Fareed K. Benign prostatic hyperplasia: evaluation and medical management in primary care. *Cleve Clin J Med*. 2017;84(1):53–64.
68. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2000;283(15):1967–1975.
69. Fulton B, Wagstaff AJ, Sorkin EM. Doxazosin: an update of its clinical pharmacology and therapeutic applications in hypertension and benign hyperplasia [published corrections appear in *Drugs*. 1995;49:554; *Drugs*. 1995;50:559]. *Drugs*. 1995;49:295–320.
70. Aharony S, Lam O, Corcos J. Is there a demonstrated advantage to increase tamsulosin dosage in patients with benign prostatic hyperplasia? *Urology*. 2014;84(2):493–494.
71. Kamimura H, Oishi S, Matsushima H, et al. Identification of cytochrome P450 involved in metabolism of the alpha1-adrenoceptor blocker tamsulosin in human liver microsomes. *Xenobiotica*. 1998;28:909–922.
72. Wolzt M, Fabrizii V, Dorner GT, et al. Pharmacokinetics of tamsulosin in subjects with normal and varying degrees of impaired renal function: an open-label single-dose and multiple-dose study. *Eur J Clin Pharmacol*. 1998;54:367–373.
73. Hellstrom WJ, Sikka SC. Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. *J Urol*. 2006;176(4, pt 1):1529–1533.
74. Narayan P. Tamsulosin: the United States trials. *Geriatrics*. 1998;53(suppl 2):S29–S32.
75. Mottet N, Bressolle F, Delmas V, et al. Prostatic tissue distribution of alfuzosin in patients with benign prostatic hyperplasia following repeated oral administration. *Eur Urol.* 2003;44(1):101–105.

76. Lepor H. Alpha-blockers for the treatment of benign prostatic hyperplasia. *Urol Clin North Am.* 2016;43(3):311–323.
77. Roehrborn CG, Cruz F, Fusco F. α1-Blockers in men with lower urinary tract symptoms suggestive of benign prostatic obstruction: is silodosin different? *Adv Ther.* 2017;33(12):2110–2121.
78. McVary KT, Monnig W, Camps JL Jr, Young JM, Tseng LJ, van den Ende G. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. *J Urol*. 2007;177(3):1071–1077.
79. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med*. 1998;338(9):557–563.
80. Gormley GJ, Stoner E, Bruskewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. *N Engl J Med*. 1992;327(17):1185–1191.
81. Stoner E. Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. *Urology*. 1994;43(3):284–292.
82. Hudson PB, Boake R, Trachtenberg J, et al. Efficacy of finasteride is maintained in patients with benign prostatic hyperplasia treated for 5 years. The North American Finasteride Study Group. *Urology*. 1999;53(4):690–695.
83. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med*. 1998;338(9):557–563.
84. Nickel JC, Gilling P, Tammela TL, et al. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). *BJU Int*. 2011;108(3):388–394.
85. Toren P, Margel D, Kulkarni G, Finelli A, Zlotta A, Fleshner N. Effect of dutasteride on clinical progression of benign prostatic hyperplasia in asymptomatic men with enlarged prostate: a post hoc analysis of the REDUCE study. *BMJ*. 2013;346:f2109.
86. Wu XJ, Zhi Y, Zheng J, et al. Dutasteride on benign prostatic hyperplasia: a meta-analysis on randomized clinical trials in 6460 patients. *Urology*. 2014;83(3):539–543.
87. Montorsi F, Roehrborn C, Garcia-Penit J, et al. The effects of dutasteride or tamsulosin alone and in combination on storage and voiding symptoms in men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH): 4-year data from the Combination of Avodart and Tamsulosin (CombAT) study. *BJU Int*. 2011;107(9):1426–1431.
88. Wilt TJ, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review

[published correction appears in *JAMA*. 1999;281:515]. *JAMA*. 1998;280:1604–1609.

89. Bent S, Kane C, Shinohara K, et al. Saw palmetto for benign prostatic hyperplasia. *N Engl J Med*. 2006;354:557–566.
90. Bayne CW, Donnelly F, Ross M, Habib FK. Serenoa repens (Permixon): a 5alphareductase types I and II inhibitor—new evidence in a coculture model of BPH. *Prostate*. 1999;40:232–241.
91. Gordon AE, Shaughnessy AF. Saw palmetto for prostate disorders. *Am Fam Physician*. 2003;67:1281–1283.
92. Carraro JC, Raynaud JP, Koch G, et al. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate*. 1996;29:231–240.
93. Tacklind J, Macdonald R, Rutks I, Stanke JU, Wilt TJ. Serenoa repens for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2012;12:CD001423.
94. Wilt T, Ishani A, Mac Donald R, Rutks I, Stark G. Pygeum africanum for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2002; (1):CD001044.
95. American Urological Association. Update on AUA Guideline on the Management of Benign Prostatic Hyperplasia. https://www.auajournals.org/doi/10.1016/j.juro.2011.01.074.
96. Bruskewitz RC, Christensen MM. Critical evaluation of transurethral resection and incision of the prostate. *Prostate*. 1990;3:27–38.
97. Fowler FJ Jr, Sepucha KR, Stringfellow V, Valentine KD. Symptom status and quality of life following prostatectomy. *JAMA*. 1988;259:3018–3022.
98. Lindau ST, Gavrilova N. Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing. *BMJ*. 2010;340:c810.
99. Lindau ST, Schumm LP, Laumann EO, et al. A study of sexuality and health among older adults in the United States. *N Engl J Med*. 2007;357:762–774.
100. Kinsey A, et al. Age and sexual outlet. In: Kinsey A, et al, eds. *Sexual Behavior in the Human Male*. WB Saunders; 1984:218.
101. Starr BD, Weiner MB. *The Star-Weiner Report on Sex and Sexuality in the Mature Years*. Stein and Day; 1981.
102. Persson G. Sexuality in a 70-year-old urban population. *J Psychosom Res*. 1980;24:335–342.
103. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*. 1994;151:54–61.
104. Melman A. Evaluation of the first 70 patients in the center for male sexual dysfunction of Beth Israel Medical Center. *J Urol*. 1984;131:53–55.

105. Mulligan T, Katz PG. Why aged men become impotent. *Arch Intern Med*. 1989;149:1365–1366.
106. Hsueh WA. Sexual dysfunction with aging and systemic hypertension. *Am J Cardiol*. 1988;61:18H–23H.
107. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA*. 1993;270(1):83–90.
108. Johannes CB, Aranjo AB, Feldman HA, et al. Incidence of erectile dysfunction in men 40–69 years old: longitudinal results from the Massachusetts Male Aging Study. *J Urol*. 2000;163(2):460–463.
109. Frederick LR, Cakir OO, Arora H, et al. Undertreatment of erectile dysfunction: claims analysis of 6.2 million patients. *J Sex Med.* 2014;11(10):2546–2553.
110. Foster SA, Annunziata K, Shortridge EF, Freedman D, Viktrup L. Erectile dysfunction with or without coexisting benign prostatic hyperplasia in the general US population: analysis of US National Health and Wellness Survey. *Curr Med Res Opin*. 2013;29(12):1709–1717.
111. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int*. 1999;84:50–56.
112. Krane RJ, Goldstein I, Saenz de Tejada I. Impotence. *N Engl J Med*. 1989;321:1648–1659.
113. Lue TF. Male sexual dysfunction. In: Tanagho E, McAninch J, eds. *Smith's General Urology*. 13th ed. Appleton & Lange; 1992:696.
114. Deslypere JP, Vermeulen A. Leydig cell function in normal men: effect of age, life-style, residence, diet, and activity. *J Clin Endocrinol Metab*. 1984;59:955–962.
115. Wein AJ, Van Arsdalen KN. Drug-induced male sexual dysfunction. *Urol Clin North Am*. 1988;15:23–31.
116. Bohlen JG, Held JP, Sanderson MO, Patterson RP. Heart rate, rate-pressure product, and oxygen uptake during four sexual activities. *Arch Intern Med*. 1984;144:1745–1748.
117. Drory Y, Shapira I, Fisman EZ, Pines A. Myocardial ischemia during sexual activity in patients with coronary artery disease. *Am J Cardiol*. 1995;75:835–837.
118. Johnston BL, Fletcher GF. Dynamic electrocardiographic recording during sexual activity in recent post-myocardial infarction and revascularization patients. *Am Heart J*. 1979;98:736–741.
119. Jackson G. Sexual intercourse and angina pectoris. *Int Rehabil Med*. 1981;3:35–37.
120. Muller JE, Mittleman MA, Maclure M, Sherwood JB, Tofler GH. Triggering myocardial infarction by sexual activity: low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Investigators. *JAMA*. 1996;275:1405–1409.

121. Ueno M. The so-called coition death [in Japanese]. *Nihon Hoigaku Zasshi*. 1963;17:330–340.
122. Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. *Pharmacol Rev.* 2011;63(4):811–859.
123. Khera M, Adaikan G, Buvat J, et al. Diagnosis and treatment of testosterone deficiency: recommendations from the Fourth International Consultation for Sexual Medicine. *J Sex Med*. 2016;13(12):1787–1804.
124. Tajar A, Huhtaniemi IT, O'Neill TW, et al. Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study. *J Clin Endocrinol Metab*. 2012;97(5):1508–1516.
125. Greenspan MB, Barkin J. Erectile dysfunction and testosterone deficiency syndrome: the portal to men's health. *Can J Urol*. 2012;19(suppl 1):18–27.
126. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment, and monitoring of late onset hypogonadism in men: a suggested update. *Aging Male*. 2015;18(1):5–15.
127. Meuleman E. Prevalence of erectile dysfunction: need for treatment? *Int J Impot Res.* 2002;14(suppl 1):S22–S28.
128. Goldstein I. Male sexual circuitry. Working Group for the Study of Central Mechanisms in Erectile Dysfunction. *Sci Am*. 2000;283:70–75.
129. Gerstenberg TC, Bradley WE. Nerve conduction velocity measurement of dorsal nerve of penis in normal and impotent males. *Urology*. 1983;21:90–92.
130. Whitehead ED, Klyde BJ, Zussman S, Salkin P. Diagnostic evaluation of impotence. *Postgrad Med*. 1990;88:123–126.
131. Spark RF, White RA, Connolly PB. Impotence is not always psychogenic: newer insights into hypothalamic-pituitary-gonadal dysfunction. *JAMA*. 1980;243:750–755.
132. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med*. 2007;120:151–157.
133. Bancroft J, Wu FC. Changes in erectile responsiveness during androgen therapy. *Arch Sex Behav*. 1983;12:59–66.
134. Michal V, Kovac J, Belan A. Arterial lesions in impotence: phalloarteriography. *Int Angiol*. 1984;3:247–251.
135. Bulpitt CJ, Dollery CT. Side effects of hypotensive agents evaluated by self-administered questionnaire. *Br Med J*. 1973;3:485–490.
136. Bulpitt CJ, Fletcher AE. Drug treatment and quality of life in the elderly. *Clin Geriatr Med*. 1990;6:309–317.
137. Hogan MJ. Antihypertensive therapy and male sexual dysfunction. *Psychosomatics*. 1981;21:234–244.
138. Mallett EC, Badlani GH. Sexuality in the elderly. *Semin Urol*. 1987;5:141–145.
139. McWaine DE, Procci WR. Drug-induced sexual dysfunction. *Med Toxicol Adverse Drug Exp*. 1988;3:289–306.

140. Ebringer A, Doyle AE, Dawborn JK, Johnston CI, Mashford ML. Clonidine in the treatment of hypertension. *Br Med J*. 1971;1:402–403.
141. Laver MC. Sexual behaviour patterns in male hypertensives. *Aust N Z J Med*. 1974;4:29–31.
142. Onesti G. Clonidine: a new antihypertensive agent. *Am J Cardiol*. 1971;28:74–83.
143. Mooradian AD, Morley JE, Billington CJ, Slag MF, Elson MK, Shafer RB. Hyperprolactinaemia in male diabetics. *Postgrad Med J*. 1985;61:11–14.
144. Burnett W. Sexual dysfunction as a complication of propranolol therapy in men. *Cardiovasc Med*. 1979;4:811–815.
145. Buffum J. Pharmacosexology: the effect of drugs on sexual function: a review. *J Psychoactive Drugs*. 1982;14:5–44.
146. Van Arsdalen KN, Wein AJ. Drug-induced sexual dysfunction in older men. *Geriatrics*. 1984;39:63–67.
147. Caine M. Phenoxybenzamine for benign prostatic obstruction. Review of 200 cases. *Urology*. 1981;17:542–546.
148. Morley JE, Kaiser FE. Sexual function with advancing age. *Med Clin North Am*. 1989;73:1483–1495.
149. McCellan KJ, Goa KL. Transdermal testosterone. *Drugs*. 1998;55:253–258.
150. Mirin SM, Meyer RE, Mendelson JH, Ellingboe J. Opiate use and sexual function. *Am J Psychiatry.* 1980;137:909–915.
151. Buffum JC. Pharmacosexology update: heroin and sexual function. *J Psychoactive Drugs*. 1983;15:317–318.
152. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev*. 1984;3:23–42.
153. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49:822–830.
154. Rhoden EL, Telöken C, Sogari PR, Vargas Souto CA. The use of the simplified International Index of Erectile Function (IIEF-5) as a diagnostic tool to study the prevalence of erectile dysfunction. *Int J Impot Res*. 2002;14:245–250.
155. Jardin A, Wagner G, Khoury S, Giuliano F, Goldstein I, Padma-Nathan H, eds. *Recommendations of the First International Consultation on Erectile Dysfunction, cosponsored by the World Health Organization (WHO)*. Health Publications; 2000.
156. Wabrek AJ, Burchell RC. Male sexual dysfunction associated with coronary heart disease. *Arch Sex Behav*. 1980;9:69–75.
157. Gundle MJ, Reeves BR Jr, Tate S, Raft D, McLaurin LP. Psychosocial outcome after coronary artery surgery. *Am J Psychiatry*. 1980;137:1591–1594.
158. Agarwal A, Jain DC. Male sexual dysfunction after stroke. *J Assoc Physicians India*. 1989;37:505–507.

159. Ruzbarsky V, Michal V. Morphologic changes in the arterial bed of the penis with aging. Relationship to the pathogenesis of impotence. *Invest Urol*. 1977;15:194–199.
160. Bulpitt CJ, Dollery CT, Carne S. Changes in symptoms of hypertensive patients after referral to hospital clinic. *Br Heart J*. 1976;38:121–128.
161. Adverse reaction to bendroflumethiazide and propranolol for the treatment of mild hypertension. Report of Medical Research Council Working Party on Mild to Moderate Hypertension. *Lancet*. 1981;2:539–543.
162. Comparison of prazosin with hydralazine in patients receiving hydrochlorothiazide: a randomized double blind clinical trial. *Circulation*. 1981;64:722–729.
163. Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. *Lancet*. 1985;1:181–184.
164. Wabrek AJ, Shelley MM, Horowitz LM, Bastarache MM, Giuca JE. Noninvasive penile arterial evaluation in 120 males with erectile dysfunction. *Urology*. 1983;22:230–234.
165. Condra M, Morales A, Owen JA, Surridge DH, Fenemore J. Prevalence and significance of tobacco smoking in impotence. *Urology*. 1986;27:495–498.
166. Hirshkowitz M, Karacan I, Howell JW, Arcasoy MO, Williams RL. Nocturnal penile tumescence in cigarette smokers with erectile dysfunction. *Urology*. 1992;39:101–107.
167. DePalma RG, Emsellem HA, Edwards CM, et al. A screening sequence for vasculogenic impotence. *J Vasc Surg*. 1987;5:228–236.
168. Zemel P. Sexual dysfunction in the diabetic patient with hypertension. *Am J Cardiol*. 1988;61:27H–33H.
169. Rubin A, Babbott D. Impotence and diabetes mellitus. *JAMA*. 1958;168:498–500.
170. Whitehead ED, Klyde BJ. Diabetes-related impotence in the elderly. *Clin Geriatr Med*. 1990;6:771–795.
171. McCulloch DK, Campbell IW, Wu FC, Prescott RJ, Clarke BF. The prevalence of diabetic impotence. *Diabetologia*. 1980;18:279–283.
172. Kannel WB, Hjortland M, Castelli WP. The role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol*. 1974;34:29–34.
173. Lehman TP, Jacobs JA. Etiology of diabetic impotence. *Urology*. 1983;129:291–294.
174. Morley JE, Kaiser FE. Testicular function in the aging male. In: Armbrecht HJ, Coe RM, Wongsurawat N, eds. *Endocrine Function and Aging*. Springer-Verlag; 1990:99.
175. Snyder PJ, Reitano JF, Utiger RD. Serum LH and FSH responses to synthetic gonadotropin-releasing hormone in normal men. *J Clin Endocrinol Metab*. 1975;41:938–945.
176. Tenover JS, McLachlan RI, Dahl KD, Burger HG, de Kretser DM, Bremner WJ. Decreased serum inhibin levels in normal elderly men: evidence for a

decline in Sertoli cell function with aging. *J Clin Endocrinol Metab*. 1988;67:455–459.
177. Kaiser FE, Viosca SP, Morley JE, Mooradian AD, Davis SS, Korenman SG. Impotence and aging: clinical and hormonal factors. *J Am Geriatr Soc*. 1988;36:511–519.
178. Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol (Oxf)*. 1981;14:49–61.
179. Bancroft J. Endocrinology of sexual function. *Clin Obstet Gynaecol*. 1980;7:253–281.
180. Davidson JM, Chen JJ, Crapo L, Gray GD, Greenleaf WJ, Catania JA. Hormonal changes and sexual function 5 in aging men. *J Clin Endocrinol Metab*. 1983;57:71–77.
181. Morley JE. Impotence. *Am J Med*. 1986;80:897–904.
182. Bissada NK, Finkbeiner AE. Urologic manifestations of drug therapy. *Urol Clin North Am*. 1988;15:725–736.
183. Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. *JAMA*. 1999;281:421–426.
184. Cheitlin MD, Hutter AM Jr, Brindis RG, et al. ACC/AHA Expert Consensus Document: use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/American Heart Association [published correction appears in *J Am Coll Cardiol*. 1999;34:1850]. *J Am Coll Cardiol*. 1999;33:273–282.
185. Giuliano F, Donatucci C, Montorsi F, et al. Vardenafil is effective and well-tolerated for treating erectile dysfunction in a broad population of men, irrespective of age. *BJU Int*. 2005;95:110–116.
186. Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. *Ann Intern Med*. 2009;151:650–651.
187. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group [published correction appears in *N Engl J Med*. 1998;339:59]. *N Engl J Med*. 1998;538:1397–1404.
188. Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH. Clinical safety of oral sildenafil citrate (Viagra) in the treatment of erectile dysfunction. *Int J Impot Res*. 1998;10:69–73.
189. Mitka M. Viagra leads as rivals are moving up. *JAMA*. 1998;280:119–120.
190. Giuliano F, Jackson G, Montorsi F, Martin-Morales A, Raillard P. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. *Int J Clin Pract*. 2010;64:240–255.
191. Cohen JS. Comparison of FDA reports of patient deaths associated with sildenafil and with injectable alprostadil. *Ann Pharmacother*. 2001;35:285–

288.
192. Arruda-Olson AM, Mahoney DW, Nehra A, Leckel M, Pellikka PA. Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease. A randomized crossover trial. *JAMA*. 2002;287:719–725.
193. Laties AM. Vision disorders and phosphodiesterase type 5 inhibitors: a review of the evidence to date. *Drug Saf*. 2009;32:1–18.
194. Sadovsky R, Miller T, Moskowitz M, Hackett G. Three-year update of sildenafil citrate (Viagra) efficacy and safety. *Int J Clin Pract*. 2001;55:115–128.
195. Angulo J, et al. Tadalafil enhances NO-mediated relaxation of human arterial and trabecular penile smooth muscle [abstract]. Annual Meeting of the European Association for the Study of Diabetes. Glasgow, Scotland; 2001.
196. Vickers MA, Satyanarayana R. Phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction in patients with diabetes mellitus. *Int J Impot Res*. 2002;14:466–471.
197. Frajese GV, Pozzi F, Frajese G. Tadalafil in the treatment of erectile dysfunction; an overview of the clinical evidence. *Clin Interv Aging*. 2006;1:439–449.
198. Porst H, Rosen R, Padma-Nathan H, et al. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at home clinical trial. *Int J Impot Res*. 2001;13:192–199.
199. Steidle CP, et al. Pharmacokinetics of vardenafil in the elderly and subgroup data on efficacy and safety in elderly patients with erectile dysfunction [abstract]. *J Am Geriatr Soc*. 2001;49:S103.
200. Thandani U, Smith W, Nash S, et al. The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment or erectile dysfunction, on the cardiovascular response to exercise in patients with coronary disease. *J Am Coll Cardiol*. 2002;40:2006–2012.
201. Hellstrom WJ, Freier MT, Serefoglu EC, Lewis RW, DiDonato K, Peterson CA. A phase II, single-blind, randomized, crossover evaluation of the safety and efficacy of avanafil using visual sexual stimulation in patients with mild to moderate erectile dysfunction. *BJU Int*. 2013;111(1):137–147.
202. Whitehead ED, Klyde BJ, Zussman S, Salkin P. Treatment alternatives for impotence. *Postgrad Med*. 1990;88:139–149.
203. Carani C, Scuteri A, Marrama P, Bancroft J. The effects of testosterone administration and visual erotic stimuli on nocturnal penile tumescence in normal men. *Horm Behav.* 1990;24:435–441.
204. Guay AT, Perez JB, Jacobson J, Newton RA. Efficacy and safety of sildenafil for treatment of erectile dysfunction in a population with associated organic risk factors [published correction appears in *J Androl*. 2002;23:113]. *J Androl*. 2001;22:793–797.

205. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst*. 1996;88:1118–1126.
206. Yu Z, Gupta SK, Hwang SS, Cook DM, Duckett MJ, Atkinson LE. Transdermal testosterone administration in hypogonadal men: comparison of pharmacokinetics at different sites of application and at the first and fifth days of application. *J Clin Pharmacol*. 1997;37:1129–1138.
207. Winters SJ. Current status of testosterone replacement therapy in men. *Arch Fam Med*. 1999;8:257–263.
208. Parker S, Armitage M. Experience with transdermal testosterone replacement therapy for hypogonadal men. *Clin Endocrinol (Oxf)*. 1999;50:57–62.
209. Nomura AM, Stemmermann GN, Chyou PH, Henderson BE, Stanczyk FZ. Serum androgens and prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 1996;5:621–625.
210. Bain J. Testosterone and the aging male: to treat or not to treat? *Maturitas*. 2010;66:16–22.
211. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12 month randomized controlled trial. *J Clin Endocrinol Metab*. 1997;82:1661–1667.
212. Hajjar R, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab*. 1997;82:3793–3796.
213. Zgliczynski S, Ossowski M, Slowinska-Srzednicka J, et al. Effect of testosterone replacement therapy on lipids and lipoproteins in hypogonadal and elderly men. *Atherosclerosis*. 1996;121:35–43.
214. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(2):273–288.
215. Muse urethral suppository. Product information. Meda Pharmaceuticals; 2014.

110

Osteoporosis

Mary-Kathleen Grams, R. Rebecca Couris, and Suzanne Dinsmore

CORE PRINCIPLES		CHAPTER CASES
1	Osteoporosis is a condition of low bone mass and deterioration of bone tissue leading to bone fragility and potentially fracture with many preventable and inherent risk factors.	**Case 110-1 (Question 1)** **Case 110-4 (Question 1)**
2	Prevention and treatment of osteoporosis focus on modifying preventable risks, providing adequate dietary supplementation of calcium and vitamin D, increasing bone mineral density, and reducing fracture rates. A detailed medical history should be collected from each patient.	**Case 110-1 (Questions 1–3)** **Case 110-2 (Questions 1, 3)** **Case 110-3 (Question 1)**
3	Pharmacologic therapy is reserved for those patients with a hip or vertebral fracture, individuals with a T-score ≤ –	**Case 110-2 (Questions 2, 6)**

	2.5 at the femoral neck or spine once secondary causes have been excluded, and individuals with low bone mass with a 10-year probability of ≥3% risk of hip fracture or ≥20% risk of major osteoporotic fracture.	
4	Initial therapy with oral bisphosphonates is recommended unless patients are unable to take or have relative contraindications to oral bisphosphonate therapy.	**Case 110-3 (Question 2)**
5	Estrogen/progesterone therapy, selective estrogen-receptor modulators, parathyroid hormone analogs, denosumab, calcitonin, and romosozumab are alternative therapies for the prevention and/or treatment of postmenopausal osteoporosis.	**Case 110-2 (Questions 4, 5) Case 110-3 (Questions 3, 4) Case 110-4 (Questions 2–4)**
6	Duration of treatment with antiresorptive and/or anabolic therapy has remained controversial, secondary to concerns for oversuppression of bone turnover markers and the potential for the development of osteosarcomas, respectively.	**Case 110-3 (Question 2)**
7	Prevention and treatment of osteoporosis secondary to prolonged glucocorticoid therapy should be incorporated into a patient's treatment plan with considerations for dosage and duration of glucocorticoid therapy, the	**Case 110-5 (Questions 1–4)**

	patient's individual risk factors, sex, and age.	
8	Pharmacologic therapies to be considered for osteoporosis treatment in males include oral and intravenous bisphosphonates, denosumab, and parathyroid hormone.	**Case 110-6 (Questions 1–6)**

INTRODUCTION

Osteoporosis is a well-recognized disorder of reduced bone strength leading to an increased risk of fractures. It is the most common bone disease in humans, characterized by low bone mass and a deterioration of bone tissue.[1]

Osteoporosis is considered a silent disease and can progress without symptoms until a fracture occurs.[1] Fractures of the spine, hip, and wrist are the most common and may be followed by a complete recovery, varying degrees of pain and disability, and even death.[1] Osteoporotic fractures negatively impact physical, financial, and psychological health. Their complications lead to a heavy economic burden, considerable morbidity and mortality, making osteoporosis a major public health concern.[2]

The main causes of osteoporosis are loss of cell function because of natural aging, also known as senescence, and loss because of declining hormonal function.[3] Age-related bone loss begins in the third decade of life and is accelerated in females in the late peri-menopausal period and first postmenopausal years.[3],[4] Conditions that contribute to osteoporosis are prolonged periods of inadequate calcium intake, sedentary lifestyle, and tobacco and alcohol abuse. Deterioration of bone mass is also associated with chronic conditions or from the use of various medications.[5] Risk factors for osteoporosis are listed in **Table 110-1** and include nutritional deficiencies, endocrine disorders such as hyperparathyroidism and diabetes

mellitus, malignancies, gastrointestinal (GI) diseases, renal failure, connective tissue diseases, and medications, which include anticonvulsant therapy, long-term glucocorticoid therapy, or long-term proton pump inhibitors.

Table 110-1
Risk Factors Associated With the Development of Osteoporosis

↑Age Female gender Caucasian or Asian Family history Small stature Low weight	Predisposing medical problems (eg, chronic liver disease, chronic renal failure, hyperthyroidism, primary hyperparathyroidism, Cushing syndrome, diabetes mellitus, anorexia nervosa, gastrointestinal resection, malabsorption, vitamin D deficiency, irritable bowel disease, chronic obstructive pulmonary disease, spinal cord injury, Parkinson disease, and human immunodeficiency virus)
Early menopause or oophorectomy Sedentary lifestyle ↓Mobility Low calcium intake Excessive alcohol intake Cigarette smoking High caffeine intake	Drugs (eg, corticosteroids, long-term anticonvulsant therapy [phenytoin or phenobarbital], aromatase inhibitors, gonadotropin hormone–releasing hormone [GnRH] analogs, depot medroxyprogesterone, rosiglitazone, cyclosporine, tacrolimus, anti-retroviral therapy, long-term heparin, warfarin, loop diuretics, excessive levothyroxine therapy, proton pump inhibitors, H_2-receptor antagonists, excessive use of aluminum-containing antacids)

The standard method of identifying osteoporosis is the measurement of bone mineral density (BMD) at either the femoral neck region of the proximal femur (hip) or the lumbar spine.[2] The World Health Organization (WHO) uses a defined criteria to diagnose osteoporosis that has been widely accepted.[6] When measured by dual-energy x-ray absorptiometry (DEXA), a BMD that lies 2.5 standard deviations (SDs) or more below the average value for young, healthy females, a T-score of < −2.5 SD, is considered osteoporosis and an effective method to identify patients at

increased risk for fracture. As the T-score decreases, the risk for fracture increases. A T-score between −2.5 and −1 is defined as osteopenia but is better referred to as low bone mass or low bone density. A T-score ≥ −1 is considered normal. The National Osteoporosis Foundation (NOF) clinician guidelines includes this measurement of BMD in the diagnosis of osteoporosis but also states that the occurrence of adulthood hip or vertebral fracture in the absence of major trauma can be considered osteoporosis without the measurement of BMD.[1]

Although the fracture rate is lower than in osteoporosis, the majority of fractures occur in patients with low bone mass. The prevalence of low bone mass is higher than osteoporosis, and therefore it is important to monitor for clinical risk factors to predict the risk of fracture.

Osteoporosis is a global concern estimated to affect more than 200 million people worldwide.[7] The prevalence of osteoporosis and the risk of fracture increase with age and varies by race and ethnicity. The risk of hip fracture is greatest in Northern Europe, Australia, and North America.[8] According to data from the United States National Health and Nutrition Examination Survey (NHANES), 2005 to 2010 and the 2010 U.S. Census, it was estimated that 10.3% or 10.2 million adults ages 50 years and older had osteoporosis and 43.9% or 43.4 million adults had low bone mass.[9] Almost 80% of the affected population were females. Osteoporosis at either the femoral neck or lumbar spine ranged from 7% to 35% in females and 3% to 10% in males in the 5th through 8th decades of life. Prevalence increased with each decade after age 50 years in females, but not until age 70 years in males. The prevalence of low bone mass at either the femoral neck or lumbar spine in adults ages 50 years and over ranged from 54% to 67% in females and 32% to 60% in males in the 5th through 8th decades of life. The prevalence of low bone mass in females increased with age until age 70 years and then remained stable. In males, the prevalence of low bone mass did not increase with age until age 70 years and increased progressively thereafter.

The NHANES, 2013 to 2014, provides a separate estimate of osteoporosis and low bone mass by race and ethnicity in four different groups.[10] Overall prevalence of osteoporosis of either femoral neck or lumbar spine in adults ages 50 years and older was 11%, 16.5% females and 5.1% males. The age-adjusted prevalence of osteoporosis in females was highest in non-Hispanic Asians (40%), followed by Hispanics (20.5%), non-Hispanic Whites (17%), and lowest among non-Hispanic Blacks (8.2%). In males, the rate of osteoporosis was also highest among non-Hispanic Asians (7.5%), followed by non-Hispanic Whites (6%), Hispanics (5.9%), and non-Hispanic Blacks (1.9%). The age-adjusted prevalence of low bone mass in females was highest among the Hispanic race (57%) followed by non-Hispanic Whites (54.6%), non-Hispanic Asian (47%), and non-Hispanic Black (40.4%). In males, prevalence among race followed a different trend: non-Hispanic Asian (47.7%), Hispanic (38.1%), followed by non-Hispanic White (37.3%) and non-Hispanic Black (25.7%).

The clinical and economic consequences of osteoporosis are related to the impact of osteoporosis-related fractures. According to the International Osteoporosis Foundation (IOF), one of three females and one of five males over age 50 will experience fracture because of osteoporosis.[11] Approximately 50% of Caucasian females and 20% of males will sustain an osteoporosis-related fracture in their lifetime.[1] The risk of fracture is highest in Caucasian females, followed by Asian, African American, and Hispanic females.[8] More than 1.5 million fractures per year occur in the United States that are attributed to osteoporosis.[12] Estimated costs range from 14 to 20 billion dollars each year and include more than 432,000 hospital admissions, 180,000 nursing home admissions, and almost 2.5 million medical office visits.[1],[12] Hip fractures account for almost three-fourths of the total cost of osteoporosis-related care, yet represent only 14% of the incident fractures. Hip fractures have a profound impact on the quality of life and a considerable associated mortality. The mortality during the first year after hip fracture is as high as 36% with a higher mortality in males than females.[1] There is a 2.5-fold increased risk of future fractures relative to persons of the

same sex and similar age without fractures. In addition, hip fractures result in a multitude of complications for the elderly, including prolonged hospitalization, decreased independent living, depression, fear of future falls, and lifelong disability. An estimated 20% require long-term nursing home placement, and ~60% are unable to regain their prefracture level of independence. Vertebral fractures may be painless or result in pain that usually lasts <3 months. The initiating injury may be as minor as a cough or turning over in bed. After the first, the risk of additional vertebral fractures is high. Vertebral collapse or deformity can result in loss of height, kyphosis, abdominal protuberance or decreased pulmonary function as the abdominal cavity is shortened, chronic back pain, decreased mobility, or mortality.

The rates of osteoporosis and low bone mass have recently declined, but the total numbers of males and females with osteoporosis and low bone mass remain high.[9] The total number of 53.6 million adults over age 50 years with osteoporosis or low bone mass could potentially increase by 30% in the year 2030 based on the trends from 2005 to 2010. The impact of osteoporosis on the health care system, rising health care costs, in an aging population is potentially staggering.

Etiology

Bone is composed of bone cells (osteocytes, osteoblasts, osteoclasts), collagenous and noncollagenous protein, and minerals and innervated with blood vessels and nerve fibers.[13] Eighty percent of bone that makes up the adult human skeleton is cortical bone, a dense compact bone that surrounds the marrow space. Twenty percent is trabecular bone, which is less dense than cortical bone and often referred to as spongy or cancellous bone. Cortical bone forms the outer shell as a protector of the marrow space, and a network of trabecular bone forms the interior structures in the bone marrow compartment in a honeycomb-like fashion. Depending on

location, bone consists of varied ratios of cortical to trabecular bone leading to differences in hardness and porosity.

The bones of the skeleton help to support and protect the body and undergo cycles of modeling (reshaping) and remodeling (renewal) to remove older bone and to replace it with stronger newly formed bone.[13] Osteoclasts resorb old bone by increasing enzymes that dissolve bone proteins and minerals. Osteoblasts reform bony surfaces and fill bony cavities by synthesizing a bony matrix that is made up of type I collagen and other proteins. Osteoblasts become osteocytes as they are surrounded by the new bone matrix. Bone minerals deposit into the new bony matrix strengthening newly formed bone. In young healthy bone, a balance between osteoblast and osteoclast activity results in a continuous remodeling process. When the rate of resorption or removal exceeds the rate of replacement, the resulting bone loss decreases bone strength and increases the risk of fracture.

Bone mass peaks between ages 18 and 25 and begins to gradually decrease beginning at ~age 30.[3],[14] An age-related bone loss of 20% to 30% cortical bone and 20% to 30% of trabecular bone occurs in both males and females over a lifetime. Lifetime losses of vertebral bone, which is mainly trabecular bone, can approximate 45% in males and 55% in females.[3]

Bone loss is accelerated in females during the peri-menopausal and menopausal transition and after surgical oophorectomy.[3] A loss of 20% to 30% of trabecular bone and 5% to 10% of cortical bone is because of the decline in 17β-estradiol concentrations and results in an increased prevalence of osteoporosis in females and an increased fracture risk that can be seen early after menopause.[3],[15] Females are also at higher risk of osteoporosis as they tend to have smaller bones and less bone mass than males of similar age.

In males, androgens and estrogens play a role in the growth and development of bone.[3],[16],[17] Serum testosterone concentrations decline by approximately two-thirds over a lifetime. Aromatization converts testosterone to estrogen, and because of a decline in testosterone, available estrogen decreases by ~50% over the male life span. Testosterone has a direct beneficial effect on bone, but to a

lesser extent than estrogen. Decreases in bioavailable estrogen as well as cellular senescence contribute to bone loss and reduced BMD in older males.[3,17]

Other hormones regulated by the hypothalamic–pituitary– gonadal axis (eg, progesterone, follicle-stimulating hormone, inhibins, oxytocin, and prolactin) have been studied for their effects on the skeletal system.[18]

Pathophysiology

Bone remodeling occurs throughout life to maintain bone strength and calcium and phosphorus homeostasis and can replace up to 20% of the human skeleton each year.[19] It is a complex process that involves a balance of local and systemic regulators to form discrete skeletal foci or bone-remodeling units.[14] Osteoblasts and osteoclasts play a major role in remodeling, and there is a coupling of bone formation and resorption processes. Factors such as transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), and cytokines signal the end of bone resorption and the beginning of bone formation.[13] The receptor activator of nuclear factor-μB ligand (RANKL) and osteoprotegerin (OPG) are also important local regulators that determine the formation, activation, and resorption of osteoclasts in remodeling.[13,20] RANKL and macrophage colony-stimulating factor (M-CSF) are required for differentiation of osteoclast precursors (**Fig. 110-1**).

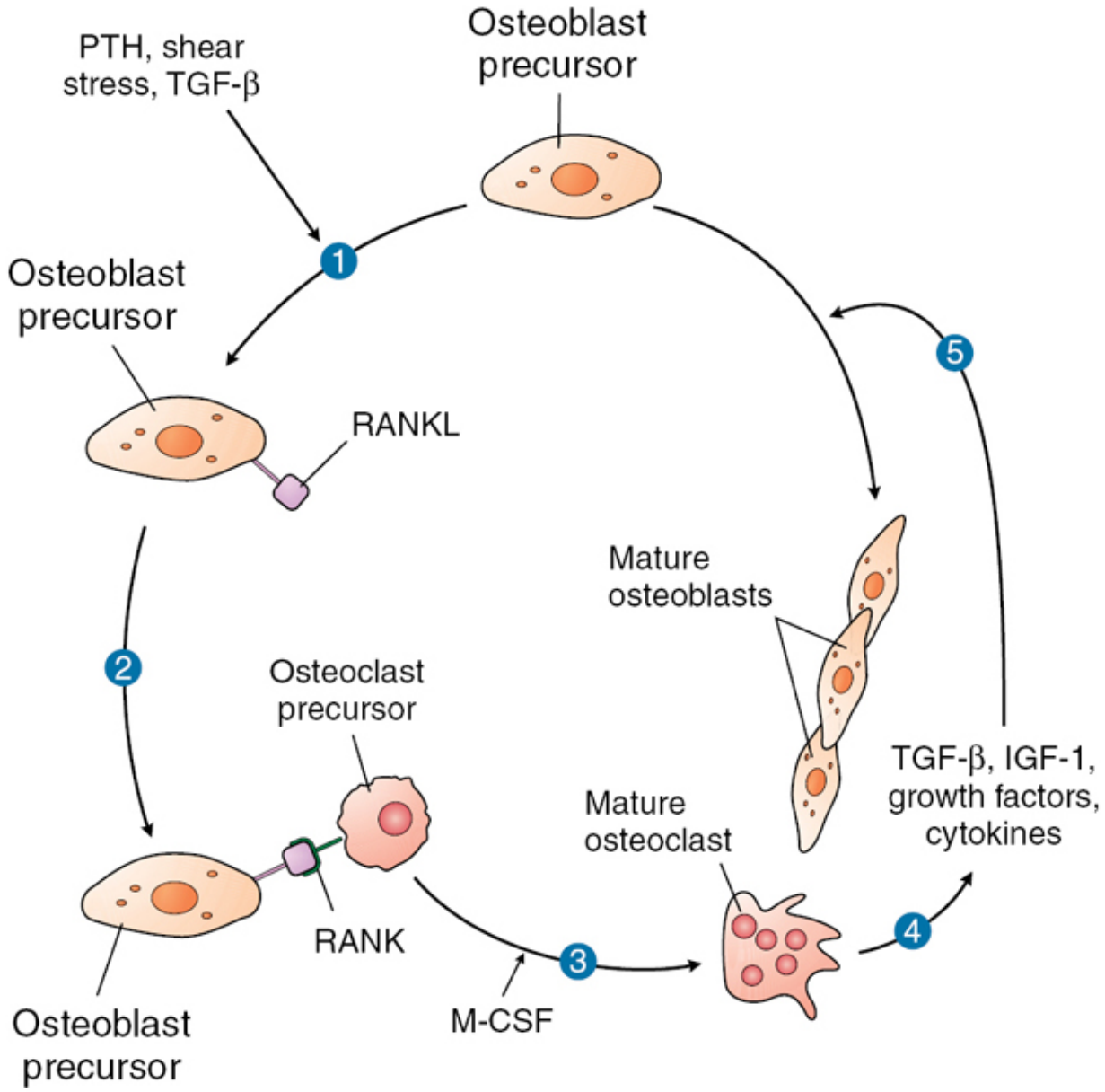


Figure 110-1 The bone-remodeling cycle at the cellular level. IGF, insulin-like growth factor; M-CSF, macrophage colony-stimulating factor; PTH, parathyroid hormone; RANKL; receptor activator of nuclear factor-μB ligand; TGF-β, transforming growth factor-β.

RANKL is expressed on osteoblasts and binds to the osteoclast RANK receptor to facilitate osteoclast differentiation and resorptive activity.[13,20] OPG is a decoy receptor preventing the interaction between RANKL and RANK receptor and inhibiting osteoclast

stimulation. The transition of bone resorption to bone formation is dependent on the RANKL/OPG ratio.

Local and systemic factors can influence bone homeostasis by modulating the RANKL/RANK/OPG system.[3],[21] Systemic modulators of bone remodeling include parathyroid hormone (PTH), vitamin D, glucocorticoid hormones, calcitonin, estrogen, and testosterone. PTH and glucocorticoid hormones have been associated with bone resorption, whereas calcitonin, estrogen, and testosterone have been associated with bone formation. Vitamin D is associated with both formation and resorption in response to serum calcium levels.[22]

PTH maintains calcium balance and regulates bone mass by both stimulating RANKL and inhibiting OPG.[21] Balance is closely regulated by the absorption of calcium in the GI tract and reabsorption by the kidneys. Serum calcium levels are primarily regulated by the actions of PTH, vitamin D, and calcitonin. The parathyroid gland releases PTH in response to low serum calcium levels, which in turn facilitates the mobilization of calcium and phosphate from bone through bone resorption and stimulates the reabsorption of calcium through the tubular system in the kidneys.[14] Vitamin D aids in intestinal absorption of calcium, phosphorus, and magnesium. Increases in vitamin D levels decrease PTH levels. Vitamin D also increases bone resorption to prevent symptomatic hypocalcemia (**Fig. 110-2**). Calcitonin is released in response to high serum calcium levels. Calcitonin decreases intestinal absorption of calcium and phosphorus, enhances calcium excretion in the kidneys, and prevents bone resorption.

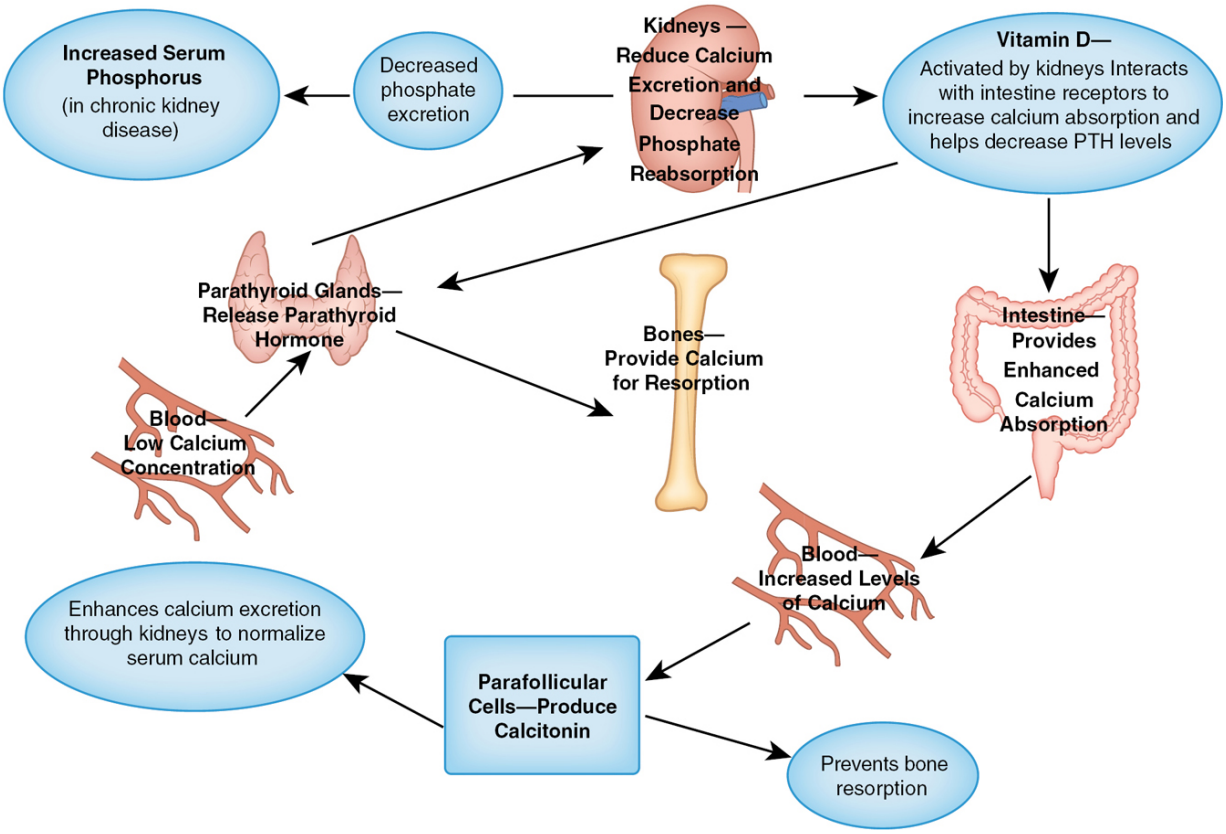


Figure 110-2 Pathway for calcium homeostasis with involvement from parathyroid hormone, vitamin D, and calcitonin.

Bone remodeling is also associated with multiple bone turnover markers.[19] Markers of bone formation include propeptides of type 1 collagen (P1CP, P1NP), alkaline phosphatase (ALP), and osteocalcin. Markers of bone resorption include markers such as collagenous and noncollagenous degradation proteins, cathepsin K, and sclerostin.

Systemic and local factors of remodeling and bone turnover are areas of research in the management of osteoporosis.

Overview of Drug Therapy

Osteoporosis is a condition of low bone mass and deterioration of bone tissue with a high risk for fracture. Prevention, identification, and treatment of osteoporosis should all be incorporated into primary health care. Preventive measures to reduce fracture risk include

adequate intake of daily calcium and vitamin D. Lifestyle modifications that are universally recommended are weight-bearing exercise, reduced alcohol consumption, and smoking cessation. Fall prevention strategies are also universal suggestions. These recommendations apply to both males and females. Pharmacologic treatment should be considered in patients with low trauma hip or vertebral fracture, patients with a T-score of < −2.5, and patients with low bone mass who are at increased risk for fracture. Medications include selective estrogen-receptor modulators (SERMs; eg, raloxifene) and calcitonin in females, bisphosphonates (eg, alendronate), RANKL inhibitors (eg, denosumab), anti-sclerostin agent (eg, romosozumab), and PTH analogs for both males and females.[23] Testosterone therapy is recommended for males at high risk for fracture with low testosterone levels (<200 ng/dL or 6.9 nmol/L) who cannot tolerate the approved pharmacologic agents for osteoporosis.[24]

Risk Factors

CASE 110-1

Question 1: T.J., a 28-year-old, thin Caucasian female, is worried about developing osteoporosis. Her 75-year-old maternal grandmother has osteoporosis, and recently her postmenopausal mother (age 53) was told that she was at increased risk for osteoporosis. T.J. is 62 inches (157.48 cm) tall, weighs 108 pounds (49 kg), and is in good health. She jogs and occasionally does aerobic exercise. Her diet typically consists of cereal for breakfast, a sandwich for lunch, and meat with vegetables for dinner. Her only milk consumption consists of 1 cup of skim milk on her cereal. She occasionally has a dairy product for lunch or dinner. T.J. takes no medications, vitamins, or calcium supplements routinely. She occasionally takes a medication for headache or menstrual cramps. She does not smoke and occasionally drinks alcohol.

Does T.J. have an increased risk for developing osteoporosis?

Table 110-1 lists risk factors associated with the development of osteoporosis. T.J. has several risk factors that could increase her risk

for osteoporosis. She is a White female of small stature and low weight (body mass index [BMI] = 19.8 kg/m^2), has a positive family history, and has a low calcium intake.

Prevalence of osteoporosis worldwide varies with gender, race, and ethnicity.[8] In the United States, non-Hispanic Asians have the highest risk of osteoporosis.[10] Non-Hispanic White females and Hispanic females have an intermediate risk of osteoporosis but a significantly higher risk of low bone mass.

LOW BODY MASS INDEX

T.J. has a small stature, and a BMI just under 20 kg/m^2 and on the low side of normal (range 18.5–24.99 kg/m^2). Low BMI (<20) is an established independent risk factor for osteoporosis and increases the risk of fracture.[23],[25] In a meta-analysis of 12 cohorts including 60,000 males and females, a BMI of 20 kg/m^2 was associated with almost twice the risk of hip fracture compared to a BMI of 25 kg/m^2.[26] A BMI of 30 kg/m^2 was associated with a 17% reduction in the risk of hip fracture compared to 25 kg/m^2. Nevertheless, obesity should not be considered a protective factor. When adjusted for BMD, there was still a 42% increase in hip fracture in patients with a BMI of 20 kg/m^2, but no difference in the patients with a BMI of 30 kg/m^2.

FAMILY HISTORY AND GENETIC FACTORS

Osteoporosis is a multifactorial disorder that results from the effects of genetic and environmental factors. When comparing postmenopausal females with diagnosed osteoporosis to those without, females with osteoporosis had a significantly higher family history of osteoporosis and family history of fracture.[27] A family history of osteoporotic fracture is believed to be an underlying genetic predisposition.[6] Small stature or height is inherited. Smaller bone size can influence the risk of fracture, as bigger bones may be more resistant to breaking. The significance of heredity as a risk factor for osteoporosis has been studied. Certain disease states are genetic and have an associated risk of osteoporosis (eg, celiac disease, a disorder associated with malabsorption). Genetic factors

associated with osteoporosis may be related to peak bone mass, polymorphisms in the vitamin D receptor, genes associated with estrogen deficiency or estrogen resistance, bone morphogenetic proteins, signaling pathways, and various other bone-related proteins and receptors.[6],[28],[29]

MOBILITY AND PHYSICAL ACTIVITY

Bone mass is dependent on physical activity.[6] Prolonged immobility of a limb or prolonged bed rest can result in loss of skeletal tissue and bone mass. A number of studies have looked at the effect of exercise on bone mass. The Cochrane Database published a meta-analysis of randomized controlled trials that included different types of exercise interventions in the prevention and treatment of osteoporosis in postmenopausal females.[30] The effect of all exercise types versus control was small; there was significant improvement in BMD at the spine and trochanter, but not at the femoral neck or total hip, and there was no difference in risk of fracture. Significant effects of low-force, weight-bearing exercise, such as walking or Tai Chi, were found in the spine and wrist. A significant effect on BMD from high-force weight-bearing exercise, such as jogging, jumping, running, dancing, and vibration platform, was found at the hip. Significant effects of nonweight-bearing exercise, such as progressive resistive strengthening, were seen at the spine and the neck of the femur. Combinations of exercise types had a significant effect on BMD at the neck of the femur, spine, and trochanter and reduced the risk of fractures. BMD at the hip, however, favored control. Limitations reported by the authors include small sample size, loss of follow-up, lack of reported exercise characteristics, and heterogeneity. Although the evidence for exercise has limitations and the lasting value of exercise when stopped is not known, there is good evidence that physical activity is associated with improved health and reduced mortality and should be encouraged.[6] The NOF recommends a combination of regular weight-bearing exercise and muscle-strengthening exercise to increase strength and reduce the risk of falls and fractures.[1] These include walking, jogging, Tai Chi,

stair climbing, dancing, tennis, weight training, and other resistive exercises. The Institute for Clinical Systems Improvement (ICSI) guidelines also recommend a combination of exercise to maintain and improve bone health; impact exercise such as jogging, brisk walking, stair climbing; strengthening exercise with weights; and balance training such as Tai Chi or dancing.[25] Exercise can decrease the risk of falls by about 25%. Patients with severe osteoporosis should use caution when including exercises that increase forces on the spine, such as lifting heavy weights or forward spine flexion such as bending to touch one's toes.[23] These movements can increase the risk of fracture.

CIGARETTE SMOKING AND ALCOHOL INGESTION

Although T.J. does not smoke and only occasionally ingests alcohol, it is important to include questions concerning cigarette and alcohol use when obtaining a medical history from a person at risk for osteoporosis. Females and males who smoke have an increased risk for fractures, including hip fractures, compared with nonsmokers.[6] Smoking impairs the absorption of dietary and supplemental calcium, lowers body weight, influences estrogen metabolism, and may be directly toxic to bone cells.[25],[31]

Excessive alcohol use by both females and males is associated with decreased BMD.[32] The effect of alcohol on bone is dose dependent; consuming more than two alcoholic drinks daily significantly increases the fracture risk.[6],[32] The proposed mechanism may be a direct effect of alcohol on osteoblasts or it may be secondary to nutritional compromise that could result in impaired calcium and vitamin D intake with subsequent decrease in bone formation. The effect on bone formation has been seen even at no more than one drink per day for females and two drinks per day for males.[25] It is recommended that alcohol be limited to this amount to protect bone health and reduce the risk of falls.

DIETARY INTAKE

Dietary calcium and vitamin D are critical to bone health and are needed to strengthen bones and increase bone mass. Peak bone mass is achieved in early adulthood, and afterward, bone constantly undergoes remodeling.[22] Maintaining normal bone mass reduces the risk of osteoporosis and fracture. Females and males need adequate calcium and vitamin D intake to achieve and help maintain optimal bone mass. The Institute of Medicine (IOM), now the National Academy of Medicine, published recommendations for both calcium and vitamin D intake that would promote bone maintenance along with a neutral calcium balance based on age.[22] For males and nonpregnant females ages 19 to 50 years, an intake of 1000 mg of elemental calcium per day and 600 international units (IU) of vitamin D per day is recommended (**Table 110-2**). The National Institutes of Health (NIH) base their recommendations on the same published report.[33] The NOF has similar recommendations for calcium, however, it differs in their recommendations for vitamin D intake.[1] Vitamin D 800 to 1000 IU per day is recommended for individuals ages 50 years and older. The American Association of Clinical Endocrinologists/American College of Endocrinology also recommends similar calcium intake but recommends a maintenance of vitamin D of 1000 to 2000 IU/day to maintain serum levels above 30 ng/mL.[23] Calcium is best ingested from the diet. Significant sources of calcium include dairy products, tofu, and canned fish (**Table 110-3**). Calcium absorption from foods is ~30% but will vary depending on the food.[22] Calcium absorption also decreases with age. Absorption from dairy products or fortified juice is about 30%, but for certain green vegetables such as broccoli and kale, the absorption can be twice as high. Oxalate- or oxalic acid–containing foods can impair calcium absorption. Kale and broccoli are foods low in oxalate as are mustard and turnip greens.[31] Examples of foods that contain high levels of oxalic acid are spinach, sweet potatoes, beans, and collard greens. Even if high in calcium, oxalate impairs the absorption of calcium. Some foods high in fiber can interfere with calcium absorption; thus, intake of a variety of foods with calcium is recommended. Alcohol, caffeine from coffee or tea, protein, a high

intake of sodium, and excess dietary phosphorous all negatively affect calcium balance.[22,31]

Table 110-2
Dietary Reference Intakes for Calcium and Vitamin D

Life Stage Group	RDA Calcium	RDA Vitamin D
Males		
19–50 years	1000 mg	600 IU (15 µg)
51–70 years	1000 mg	600 IU (15 µg)
>70 years	1200 mg	600 IU (15 µg)
Females (nonpregnant)		
19–50 years	1000 mg	600 IU (15 µg)
51–70 years	1200 mg	600 IU (15 µg)[a]
>70 years	1200 mg	800 IU (20 µg)[a]

IU, International unit; RDA, Recommended dietary allowance.

[a]The National Osteoporosis Foundation recommends vitamin D 800 to 1000 IU in patients 50 years and older.

Source: Institute of Medicine. 2011. *Dietary Reference Intakes for Calcium and Vitamin D*. doi:10.17226/13050. Adapted and reproduced with permission from the National Academy of Sciences. Courtesy of the National Academies Press.

Table 110-3
Calcium Content of Selected Foods

Food	Serving Size	Calcium (mg)
Dairy		
Milk, dry nonfat	1 cup	350–450
Yogurt, low fat	1 cup	345
Milk, skim	1 cup	300
Milk, whole	1 cup	250–350
Cheese, cheddar	1 oz	211
Cheese, cottage	1 cup	211
Cheese, American	1 oz	195

Food	Serving Size	Calcium (mg)
Cheese, Swiss	1 oz	270
Ice cream or ice milk	1/2 cup	50–150
Fish		
Sardines, in oil	8 med	354
Salmon, canned (pink)	3 oz	167
Fruits and vegetables		
Calcium-fortified juices	1 cup	100–350
Spinach, fresh cooked	1/2 cup	245
Broccoli, cooked	1 cup	100
Collards, turnip greens	1/2 cup	175
Soybeans, cooked	1 cup	131
Tofu	1 cup	75
Kale	1/2 cup	50–150

Vitamin D is considered a nutrient and a regulatory hormone. It is a fat-soluble vitamin that is found naturally in very few foods but is added to certain foods and is available in supplement form. Vitamin D is a nutrient that can be synthesized in the skin through the action of sunlight, but exposure to sunlight should be limited because of the risk of skin cancers.[22] Sunlight may also not produce enough vitamin D because of differences in skin pigmentation, latitude, or use of sunscreen. Vitamin D regulates calcium and phosphate, which make it important in the development and maintenance of bone health.

It directly stimulates calcium and phosphate absorption from the intestinal tract, and with the help of PTH, it can mobilize calcium from bone or stimulate calcium reabsorption at the renal distal tubule (see also Chapter 28, Chronic Kidney Disease). Vitamin D that is found in the diet or that is synthesized from the sun must be converted to its active form, calcitriol. Two major forms of vitamin D are available. Vitamin D_3, cholecalciferol, is synthesized in the skin of humans from 7-dehydrocholesterol, is synthesized commercially, and can also be found in fatty fish, beef liver, egg yolks, and cheese. Vitamin D_2,

ergocalciferol, is plant-based and largely synthesized commercially. Both forms can be found in dietary supplements or fortified foods. Cholecalciferol and ergocalciferol are inactive until they are converted to active vitamin D first by the liver to 25-hydroxyvitamin D (25[OH]D), and then by the kidneys to 1,25-dihydroxyvitamin D, calcitriol. The serum level of 25(OH)D is considered the marker for adequate intake. The NOF recommends vitamin D intake to maintain serum 25(OH)D levels >30 ng/mL (75 nmol/L).[1] Aging, chronic renal insufficiency, intestinal disease, malabsorption, very dark skin, obesity, certain medications, and reduced sun exposure are associated with reduced serum levels of vitamin D.

T.J. is typical of the average American and has a diet low in calcium. If the calcium or vitamin D in her diet does not achieve the recommendations, supplements should be added (see **Table 110-4**; see Case 110-1, Questions 2, 3).

Table 110-4
Calcium Content in Various Supplements

Salt	Percent Calcium
Calcium carbonate	40
Tricalcium phosphate (calcium phosphate, tribasic)	39
Dibasic calcium phosphate dehydrate	23
Calcium citrate	21
Calcium lactate	13
Calcium gluconate	9

OTHER POTENTIAL RISKS

Various medications and medical conditions that have been associated with the development of osteoporosis are listed in Table 110-1.

Prevention

PREMENOPAUSAL FEMALES

CASE 110-1, QUESTION 2: Although T.J. is premenopausal, what recommendations could be made to decrease her future risk of developing osteoporosis?

Universal recommendations for the prevention of osteoporosis are adequate intake of daily calcium and vitamin D; weight-bearing, resistance, balance, and strengthening exercises; reduced alcohol consumption; and smoking cessation. T.J.'s course of action should be to maximize her peak bone mass and prevent or decrease bone loss. Her diet should consist of adequate calcium of 1000 mg and adequate vitamin D of 600 IU. T.J. should continue to exercise, developing a lifelong exercise program, and continue to refrain from smoking. T.J. should also maintain her BMI between 20 and 25 kg/m^2.

Exercise

T.J. should be encouraged to participate regularly in weight-bearing and strengthening exercises such as jogging, walking, running, biking, tennis, or weight-lifting and to continue appropriate exercise for her age throughout life. Physical activity has numerous benefits in addition to promoting bone health. Exercise enhances overall health and well-being, helps to control blood pressure, and lowers risk factors for cardiovascular disease, colon cancer, and type 2 diabetes.[31] Young females such as T.J. should be made aware that it is important to maintain regular menstrual periods. Amenorrhea because of strenuous exercise or extremely low body weight can increase the long-term risk of osteoporosis and fractures.

Dietary intake

T.J. should eat a well-balanced diet rich in fruits and vegetables, low-fat dairy products, whole grains, fish, and nuts. This will provide calcium as well as other nutrients needed for bone health. She should ensure her diet contains 1000 mg of elemental calcium and

600 IU vitamin D, optimally from dietary sources.[31] Dairy products are the major source of dietary calcium in the United States. Low-fat or nonfat versions have the full amount of calcium. Fortified juices or fortified cereals are also good sources of calcium. Although nondairy sources may contain lower amounts of calcium, they can be an important source for males or females with dietary preferences, those who cannot tolerate dairy, or who have food allergies (Table 110-3). The ingestion of foods rich in phytates and oxalates (eg, cereal grains, legumes, and nuts) may decrease calcium absorption.

If T.J. cannot meet her daily calcium requirement from dietary sources, she can use a calcium supplement. Table 110-4 lists the percentage of elemental calcium available from selected calcium salts. (See Case 110-1, Question 3, for further information on calcium supplements.)

Vitamin D is found in few foods naturally (eg, beef liver, egg yolk, salmon, tuna) but can be found in fortified juice or milk. It is difficult to quantify the amount of vitamin D obtained from sunlight. Genetic factors, skin pigment, latitude, and the use of sunscreen are all factors that affect sun exposure.[22] T.J. should be able to obtain adequate vitamin D intake from her diet. She could also add a supplement to her diet to achieve 600 IU of vitamin D daily.

Other bone-related nutrients include magnesium, phosphorus, vitamin K, and protein. Magnesium affects the concentration of PTH, is involved in the formation of bone, and is widely available in foods and fortified cereals.[34] Low dietary intake of magnesium has been associated with lower BMD, but not an increase in the incidence of hip fracture or total fractures.[35] Total daily magnesium intake was estimated in 73,684 postmenopausal females enrolled in the Women's Health Initiative Observational Study. Females who consumed magnesium in the highest quintile had a 3% higher total hip BMD and a 2% higher whole-body BMD than those in the lowest quintile. The incidence of hip fracture or total fracture was not statistically different across quintiles of magnesium intake. Calcium, as well as phosphorus, is stored in the bone. A complex balance of both is necessary for bone strength.[31] Low dietary intake of phosphorus as well as excessive intake have adverse effects on

bone. Vitamin K is also important to maintain healthy bones. Patients who are on long-term vitamin K antagonists or who have a diet low in vitamin K are at increased risk for fracture and osteoporosis, but this risk is controversial.[36] Currently, there is no strong evidence and no recommendations for supplementation.[36–38] Isoflavones are a class of phytoestrogens found in soybeans and red clover, have estrogen-like activity, and have been shown to increase bone density. There is conflicting and insufficient information on phytoestrogens to support the use of isoflavones for osteoporosis prevention.[31] Soy, however, is a good source of protein, which is also important for bone health. Calcium absorption is decreased in diets that are low in protein.

Smoking and alcohol

Smoking cessation should be encouraged in males or females who smoke. Rates of bone loss is greater in smokers than for nonsmokers, and calcium absorption may be decreased.[25] T.J. occasionally drinks alcohol and should be educated on the risk of alcohol and decreased BMD. Recommended alcohol intake should be limited to no more than one drink per day for females and two drinks per day for males.

Case 110-1, Question 3: If T.J. needs a calcium supplement, which calcium salt should be recommended?

The amount of elemental calcium in supplements varies. Two common forms of calcium supplements are calcium carbonate and calcium citrate.[22,34] The cost of calcium carbonate tends to be lower, and it contains the highest percentage of elemental calcium (40%), allowing fewer tablets per day to meet daily calcium requirements. Calcium absorption from supplements depends on the total amount of elemental calcium consumed at one time. The percentage of calcium absorbed decreases as the dose increases. Maximal absorption occurs at doses ≤500 mg at one time.[34] If T.J. needs a calcium supplement, calcium carbonate is a reasonable choice. She should be advised to take it in divided doses up to 500 mg/dose to

maximize absorption. Calcium carbonate absorption is dependent on stomach acid and should be taken with food. Calcium citrate contains less elemental calcium, 21%, is less dependent on stomach acid for absorption, and can be taken with or without food. Calcium citrate is beneficial in patients with achlorhydria, inflammatory bowel disease, or in patients taking proton pump inhibitors or histamine-2 receptor blockers. Supplements should be taken with plenty of fluids. Calcium can compete or interfere with the absorption of iron, zinc, and magnesium. Significant drug interactions can also occur, such as impaired absorption of medications, including tetracyclines, thyroid products, and quinolones (**Table 110-5**). T.J. should be informed that the most common adverse effects of calcium are constipation, GI irritation, bloating, and flatulence. Caution should be used in patients with renal insufficiency, hypoparathyroid disease, hypercalcemia, and a history of kidney stones. If T.J. or any family member has a history of urinary stones, her clinician should be aware of supplementation. T.J. should drink plenty of water throughout the day and take calcium carbonate with food to ensure absorption or switch to calcium citrate.

Table 110-5

Drug Interactions

Examples of Drug–Calcium Supplement Interactions[a]	
Allopurinol	Protease inhibitors
Bisphosphonate derivatives	Tetracycline derivatives
Calcium channel blockers	Protease inhibitors
Certain cephalosporin antibiotics	Quinidine
Corticosteroids (oral)	Quinolone antibiotics
HMG-CoA reductase inhibitors	Sucralfate
Iron salts	Thiazide diuretics
Itraconazole, ketoconazole	Thyroid products
Magnesium salts	Tetracycline derivatives
Multivitamins/fluoride (with ADE)	Vitamin D analogs

Multivitamins/minerals (with ADEK, folate, iron)	Zinc

[a]Does not include all calcium-drug.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home

POSTMENOPAUSAL FEMALES

CASE 110-2

QUESTION 1: T.J.'s mother, M.J., is a 53-year-old Caucasian female, who is also of small stature and low weight. She occasionally walks in the evenings. She is currently taking a calcium supplement to maintain her total calcium intake (dietary plus supplementation) of about 1 g/day. She takes over-the-counter omeprazole for her gastroesophageal reflux disease (GERD) and occasional acetaminophen for headaches. M.J. was a cigarette smoker but stopped in her late 20s and rarely drinks alcohol. She is in good health with no gynecologic surgery or major diseases. M.J. has a strong family history of breast cancer. Her last menstrual period was 6 months ago, but she began experiencing menstrual irregularity 2 years ago. M.J. has been experiencing some menopausal symptoms (hot flushes), but states that they are mild and occur only at night. M.J., worried about developing osteoporosis, decided to make an appointment with her gynecologist to discuss preventive measures. A DEXA measurement of her spine was administered, which noted her T-score to be −2.0 and a Z-score of −1.0.

In addition to the DEXA, what other information should be obtained to determine whether M.J. is at risk for developing osteoporosis or has already developed osteoporosis?

In addition to M.J.'s DEXA, a detailed medical history, including medication history (prescription and over-the-counter medications), diet, social history (smoking, alcohol) and a physical examination, which includes height, are needed along with a risk factor analysis. Diagnostic tests are indicated when there are multiple risk factors present.[1] The goals of a comprehensive evaluation are to identify modifiable risk factors, rule out potential causes of osteoporosis, and to treat if indicated.

From her history and risk factor analysis, it is determined that M.J. shares similar risk factors for osteoporosis with her daughter. In addition, she is early in the postmenopausal phase, has GERD, and

was a previous smoker. M.J. has no loss of height, does not report back pain, and does not have signs of kyphosis, all of which may be signs of osteoporosis. As part of the aging process, females may lose 1 to 1.5 inches (2.54–3.81 cm) in height because of degenerative arthritis and shrinking of intervertebral discs.[1] It is important to monitor height, as a loss of height may indicate that the patient has a vertebral fracture.

Biochemical markers of bone turnover are not needed for M.J. at this time (eg, alkaline phosphatase, calcium levels, phosphorus levels, bone-specific alkaline phosphatase, osteocalcin, propeptides of type 1 collagen, cross-linked C-terminal telopeptide, and N-telopeptide). They are not used to diagnose osteoporosis but may be used to evaluate drug therapy.[1,19]

BMD measurement would be useful in females such as M.J. It is used to screen for and monitor osteoporosis.[23] According to the American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines, screening is recommended in patients who are at high risk of osteoporosis, such as postmenopausal females age 50 years and older, patients treated with high-risk medications or have conditions related to bone loss, patients who weigh <127 pounds (56 kg), those with a prior fracture after age 50 not because of major trauma (excluding fingers, toes, skull), and those with excessive alcohol intake (more than three drinks per day). BMD measurement is recommended for all patients age 65 years and older.

The NOF recommends BMD testing for females age 65 years and older, males age 70 years and older, menopausal females or females in menopausal transition who are younger than age 65 and at increased risk of osteoporosis or who suffered a low-impact fracture, nonmenopausal females over age 50 and males ages 50 to 70 who have suffered a low-impact fracture or who are at risk for fracture, and adults with a condition or who take medication that is associated with low bone mass.[1] Along with evidence-based and guideline recommendations of the appropriate time to screen and monitor, insurance reimbursement plays a role in BMD testing.

BMD refers to the amount or weight of bone mass per area and is measured in g/cm^2.[23] Measurement of BMD is the gold standard for the diagnosis of osteoporosis and is reported as T-score (**Table 110-6**) and also as Z-score.[23],[25] T-score represents the number of SDs the measured BMD value is from the average value for a normal young adult of the same sex. Z-score represents the number of SDs the measured value is from the value of the average person of the same age, sex, and ethnicity.

$$\text{T-Score} = [(\text{measured BMD} - \text{young adult population mean BMD}) / \text{young adult population SD}]$$

$$\text{Z-score} = [(\text{measured BMD} - \text{age-matched population mean BMD}) / \text{age-matched population SD}]$$

Table 110-6
Definitions of Bone Mineral Density

Classification	T-Score
Normal	≥ −1.0 SD
Osteopenia (low bone mass)	−2.5 to −1.0 SD
Osteoporosis	< −2.5 SD
Severe osteoporosis	< −2.5 SD with fragility fracture

Source: Reprinted from Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 update. *Endocr Pract*. 2020;26(suppl 1):1–46. © 2020 Elsevier. With permission.

DEXA is a two-dimensional x-ray that is considered the standard for measuring BMD to diagnose or assess therapy. Central DEXA of the hip, spine, and femoral neck remain the preferred measurement for definitive diagnosis.[2] The distal third of the radius of the forearm is also used if other sites are not available.

Non-DEXA measurements are available using CT scan and ultrasound but should not be used for diagnosis or to follow a patient's response to therapy (**Table 110-7**).[6],[25] Patients should strive

to use the same testing site for monitoring BMD for the most reliable repeat measurements.[23]

Table 110-7
Techniques for Measuring Bone Mineral Density

Technique	Abbreviation	Measurement Sites
Dual-energy x-ray absorptiometry	DEXA	Hip, spine, total body
Peripheral dual-energy x-ray absorptiometry	PDEXA	Forearm, fingers, heel
Peripheral quantitative computed tomography	PQTC	Forearm, tibia
Quantitative ultrasound	QUS	Heel, tibia, patella
Quantitative computed tomography	QCT	Spine, hip
Single-energy x-ray absorptiometry	SEXA	Heel

Diagnosis of osteoporosis is defined as a T-score of −2.5 or less at the lumbar spine, total hip, or femoral neck.[23],[39] A T-score between −1.0 and −2.5 is considered low bone mass. Because there is an inverse relationship that exists between BMD and fracture risk, a low BMD is still a marker of fracture risk. The International Society for Clinical Densitometry (ISCD) recommends using Z-scores when reporting BMD in premenopausal females and males less than age 50.[39] A Z-score of −2.0 or less is below the expected range, and a Z-score > −2.0 is considered within range. It has been estimated that for every 1-point decrease in SD from the mean T-score, a 10% to 15% change may occur in BMD. The magnitude of this change can be translated into a 1.5-fold to 3-fold change in risk for fractures.[32] Repeat BMD testing should be individualized. DEXA should be repeated every 1 to 2 years until stable or improved in patients who are being treated for osteoporosis.[23],[39] Longer intervals are appropriate thereafter. For those who are at low risk and not receiving medications for osteoporosis, a repeat DEXA may be reasonable after 5 years.[32]

The World Health Organization along with several leading osteoporosis organizations developed the WHO Fracture Risk Assessment tool (FRAX®) that can be used alone or with BMD to identify fracture risk.[40] FRAX® is a computerized-based algorithm created for different populations available online at http://www.shef.ac.uk/FRAX. The FRAX® algorithm incorporates ethnicity as well as clinical risk factors (eg, age, smoking, physical inactivity, height, weight, prior fracture, parental history of hip fracture, long-term use of glucocorticoids, and comorbid conditions that have been associated with decreases in BMD) to calculate 10-year fracture risk. FRAX® has been validated in 11 different cohorts and is a valuable tool that provides information on absolute risk instead of relative risk by taking into account the impact of risk factors on fracture and death. As with many tools, there are some limitations to FRAX®. The algorithm excludes certain variables such as vitamin D deficiency, bone turnover markers, and falls. It does not take into account multiple fractures and may underestimate the risk.

FRAX® is intended to be used in postmenopausal females and males over age 50 and should not replace clinical judgment for treatment. It has not been validated in patients who have been on or who are receiving medication therapy for osteoporosis.[1]

The FRAX® tool can be adjusted for trabecular bone score (TBS) when available.[41] TBS is a measure of variations in gray level pixels in the DEXA image.[42] It is calculated using software that is installed on DEXA scanners. Although it is measured in the spine, TBS is an independent risk factor for osteoporosis-related fractures including hip fracture. Low TBS scores represent less homogenous weaker bone. When used with the FRAX® tool, TBS improves its performance.[23],[42] A low TBS increases the FRAX® 10-year fracture risk.

TBS-adjusted FRAX® when available is considered clinically relevant. It can be useful in patients where FRAX® alone may underestimate the 10-year risk of osteoporosis-related fracture.

Case 110-2, Question 2: Based on the information that you have obtained, does M.J. have osteoporosis, or is she at risk for developing osteoporosis?

M.J. is 62 inches (157.48 cm) tall and weighs 110.23 pounds (50 kg). She has a T-score of −2.0 (DEXA measurement of the spine) and a Z-score of −1.0. Using the FRAX® risk assessment tool for the U.S. population without a T-score of the femoral neck, M.J.'s 10-year probability of a hip fracture is 0.5%, and her 10-year probability of a major osteoporosis-related fracture is 5.1%. M.J.'s T-score is consistent with osteopenia or low bone mass.

M.J.'s risks include low bone mass, low body mass, a family history of osteoporosis, history of smoking, and medication that increases the risk of osteoporosis.

Case 110-2, Question 3: What preventive measures would help decrease M.J.'s likelihood of developing osteoporosis?

Exercise

M.J. goes for walks occasionally and should begin a consistent exercise program appropriate for her age and physical condition. Postmenopausal females who incorporated aerobic and weight-bearing exercises showed some improvements in BMD and reduced the risk of fractures as compared to those who did not exercise.[30] Weight-bearing exercise and resistance training may improve strength, muscle mass, flexibility, and balance and decrease M.J.'s risk for falls.[25] (Also see Case 110-1, Question 2.)

Dietary intake

Similar to T.J., it is important for M.J. to have a well-balanced diet rich in fruits and vegetables, low-fat dairy products, whole grains, fish, and nuts to provide adequate calcium and nutrients needed for bone health. The recommended daily allowance of calcium for females ages 51 to 70 is 1200 mg/day.[22] M.J.'s total calcium intake from diet and supplementation is about 1000 mg/day and should be increased so that she incorporates 1200 mg/day of calcium in her diet. She can do this by choosing calcium-containing foods (see

Table 110-3) and by taking a supplement if she cannot get adequate calcium from her diet (see Table 110-4).

It is important for M.J. to have adequate vitamin D intake in her diet. The recommended daily allowance of vitamin D for females between 51 and 70 age is 600 IU/day, and for females over age 70, the recommended daily allowance is 800 IU/day. The NOF recommends 800 to 1000 IU/day for males and females over age 50.[1]

Expert consensus opinion has made recommendations for serum 25(OH) vitamin D levels for bone health.[22] Levels <20 ng/mL (50 nmol/L) suggest insufficiency, whereas levels of 29 to 32 ng/mL (70–80 nmol/L) suggest adequate stores. There is currently limited evidence to attempt to achieve serum 25(OH) vitamin D levels above 60 ng/mL (150 nmol/L). (For further information, see Case 110-1, Question 2.) A serum 25(OH) vitamin D level should be drawn and M.J. should receive a vitamin D supplement to achieve a serum 25 (OH) vitamin D level of 30 ng/mL (75 nmol/L) if the level is found to be insufficient.

Although calcium and vitamin D are important for bone health, they should not be used instead of drug therapy to treat osteoporosis but as part of an overall plan to help improve bone health.

Pharmacologic Prevention

ESTROGEN/PROGESTIN THERAPY

Case 110-2, Question 4: Because a rapid rate of bone loss is seen during menopause when estrogen decreases, should estrogen therapy (ET) or estrogen + progesterone therapy (EPT) be considered for M.J.?

An estimated 10% to 15% of a female's bone mass is estrogen dependent.[43]

Estrogens are important in bone formation, resorption, and maintaining bone mass, whereas menopause is associated with a decrease in estrogen and an increase in bone loss.[14,18]

The National Osteoporosis Risk Assessment Study and the Million Women Study, both large observational studies by design, found that EPT or ET provided significant relative-risk reductions in fracture.[44,45] These results were confirmed by the Women's Health Initiative (WHI) with both the EPT and ET arms, showing significant risk reductions in hip, vertebral, and total fractures compared with placebo.[46,47]

Previously, ET or EPT would have been considered first-line treatment for the prevention of osteoporosis in a postmenopausal female such as M.J., who has an intact uterus and is at risk for osteoporosis based on risk factors and T-score. In the WHI, conjugated equine estrogen (CEE) alone and CEE with medroxyprogesterone (CEE + MPA) were shown to decrease the risk of hip, vertebral, and total fractures in postmenopausal females; however, the intervention phases were ended early because coronary heart disease (CHD), stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and breast cancer were significantly increased in the CEE + MPA group, and rates of stroke were significantly increased in females on CEE alone (also see Chapter 51, The Transition through Menopause).[46,47] The findings from the WHI do not support the use of ET or EPT for the prevention of osteoporosis. Since the publication of the Heart and Estrogen/Progestin Replacement Study (HERS) I and HERS II and the NIH WHI, health care providers are less likely to prescribe ET or EPT for the sole purpose of osteoporosis prevention or to continue its use after a female no longer needs EPT or ET for postmenopausal symptoms such as hot flushes.[48–50]

EPT is approved for the prevention of osteoporosis in postmenopausal females with a uterus, and ET is approved for postmenopausal females without a uterus.[32] When prescribed for osteoporosis prevention, ET and EPT should be used at the lowest effective doses and the shortest duration indicated. Longer therapy should only be prescribed in females who have failed other osteoporosis therapies or when other osteoporosis therapies are contraindicated and when it can be determined that the benefits outweigh the risks. M.J. does not have bothersome symptoms of

menopause; therefore, ET or EPT would not be appropriate at this time.

Contraindications to estrogen use

Case 110-2, Question 5: If M.J. developed bothersome symptoms of menopause, would ET or EPT be appropriate to treat symptoms and prevent osteoporosis?

Contraindications to EPT or ET include pregnancy; active or history of DVT or PE; active or recent (eg, within the past year) arterial thromboembolic disease (eg, stroke, myocardial infarction); undiagnosed abnormal genital bleeding; known, suspected, history of breast cancer; known or suspected estrogen-dependent neoplasia; liver dysfunction or disease; or known hypersensitivity to the product or any of its ingredients.[51] In addition, EPT and ET should be used with caution in those with a history of asthma, diabetes mellitus, migraine, epilepsy, systemic lupus erythematous, porphyria, and hepatic hemangiomas. Patients on EPT or ET are at increased risk for cancer, including endometrial (if not on EPT), breast (for EPT), and ovarian cancer as well as increased cardiovascular events, thromboembolic disease, stroke, gallbladder disease, and dementia (also see Chapter 51, The Transition through Menopause).

M.J. stated that she has a strong family history of breast cancer and starting EPT or ET would not be the treatment of choice for the prevention of osteoporosis.

TREATMENT OF LOW BONE MASS

Case 110-2, Question 6: Should pharmacologic therapy be considered for the prevention of fracture in postmenopausal females such as M.J.?

Osteoporosis drug therapy should be considered in postmenopausal females and males age 50 with a vertebral or hip fracture and those

with a T-score of −2.5 or lower at the lumbar spine, femoral neck, total hip, or third of the radius. Therapy is not indicated for most patients with low bone mass. Pharmacologic therapy is indicated in patients with low bone mass who have had a fracture or are at high risk of fracture; those with a T-score of −1.0 to −2.5 who have had a fragility fracture of hip or spine, and those with a T-score of −1.0 to −2.5 who have a 10-year fracture risk of ≥20% (spine, hip, shoulder, wrist) or risk of ≥3% (hip) calculated using FRAX® or TBS-adjusted FRAX®.[1,23]

Although M.J. is at risk of an osteoporotic fracture, her 10-year probability of a hip fracture is 0.5%, which is <3%, and her 10-year probability of a major osteoporosis-related fracture is 5.1%, which is <20%. The FRAX® tool is important for assessing fracture risk and used to weigh the potential benefit of therapy. Because her fracture risk is low and pharmacologic therapy for osteoporosis is associated with risk of adverse effects, M.J. should continue lifestyle changes to promote bone health. Patient adherence to these changes should be checked at all office visits.

CASE 110-3

QUESTION 1: M.J.'s sister, S.D., is a 62-year-old Caucasian female. She is 121.25 pounds (55 kg), 62 inches (157.48 cm) tall, attends yoga and fitness classes three to four times per week, and states she feels well. She recently started a calcium and vitamin D supplement every day as recommended by her primary care physician. She has never smoked, does not drink alcohol, and is on no other medications. Her last menstrual period was 8 years ago. She has a history of fracture of the distal forearm 2 years ago. A recent BMD of the spine and hip were −2.6 and −2.0, respectively. S.D., like M.J., has a strong family history of breast cancer.

Is calcium and vitamin D alone or together enough to prevent fracture in patients like S.D.?

CALCIUM AND VITAMIN D IN THE TREATMENT OF OSTEOPOROSIS

Although calcium and vitamin D are essential for bone health, there is inconsistent evidence on the effect of these nutrients on

preventing fracture. When taken alone or together, they are not enough to treat osteoporosis.

A network meta-analysis that included 25 randomized controlled trials was conducted to evaluate the fracture risk of using different doses of vitamin D, calcium, or their combination in community-dwelling older persons.[52] Participants were separated into groups: high- and low-dose calcium (≥ and <800 mg) and high- and low-dose vitamin D (≥ and <800 IU). For the outcome of total fracture (*N* = 24,965 from 18 studies), there were no differences in fracture rate in patients using vitamin D, calcium, or their combination by direct and indirect comparisons. No difference was found for hip fracture (*N* = 41,845 from 16 studies) or for vertebral fracture (*N* = 17,612 from 12 studies). Removing low-quality trials did not affect the results.

A Cochrane review of vitamin D and vitamin D analogs for preventing fractures in postmenopausal females and older males concluded that vitamin D alone is not likely to reduce the risk of fracture, but when taken in conjunction with calcium, the risk of fracture and bone loss is slightly reduced.[53] Results of other meta-analyses support these findings.[54],[55]

S.D. should continue adequate intake of vitamin D and calcium, but as they may be insufficient to adequately prevent fracture, pharmacotherapy should be considered.

Case 110-3, Question 2: Should S.D. be treated with a bisphosphonate for osteoporosis?

S.D. has a T-score of the spine lower than −2.5, a previous fracture, and a 10-year probability of hip fracture that is >3%. Pharmacologic treatment is indicated.

Bisphosphonates are considered first-line therapy for the prevention and treatment of osteoporosis. Alendronate ibandronate, risedronate, and zoledronic acid are indicated for the treatment of osteoporosis in postmenopausal females like S.D. They have multiple administration options available that may be beneficial in enhancing adherence in certain patients, and all are available as

generic medications. Agents indicated for the treatment and prevention of osteoporosis can be found in **Table 110-8**.[56]

Table 110-8
Medications Approved for Prevention and Treatment in Postmenopausal Osteoporosis

Class	Medication	Prevention	Treatment
Bisphosphonates	Alendronate	5 mg PO daily 35 mg PO weekly	10 mg PO daily 70 mg PO weekly
	Alendronate/ cholecalciferol		70 mg/2,800 IU PO weekly 70 mg/5600 IU PO weekly
	Ibandronate	150 mg PO monthly	150 mg PO monthly
	Risedronate	5 mg PO daily 35 mg PO weekly 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 35 mg DR PO weekly 150 mg PO monthly
	Zoledronic acid	5 mg IV every other year	5 mg IV yearly
Selective estrogen-receptor modulators (SERMs)	Raloxifene	60 mg PO daily	60 mg PO daily
Polypeptide hormone	Calcitonin	Not indicated	100 IU IM or SC once daily, every other day, or three times per week 100 IU intranasally in one nostril daily
Monoclonal antibody	Denosumab	Not indicated	120 mg SC every 6 months
Parathyroid hormone	Teriparatide Abaloparatide	Not indicated Not Indicated	20 µg SC once daily 80 µg SC once daily
Sclerostin inhibitor	Romosozumab	Not indicated	210 mg SC monthly for 12 doses as two separate 105 mg/1.17 mL injections
Estrogen	Conjugated estrogen	When other treatments are not appropriate (without uterus)	Not indicated
	Estrogen + progestin	When other treatments are not appropriate (with uterus)	Not indicated
	Conjugated estrogen + bazedoxifene	0.45 mg/20 mg PO daily	Not indicated

DR, delayed release; IM, intramuscular; IU, international units; IV, intravenous; PO, by mouth; SC, subcutaneous. DR, ; IM, intramuscular; IU, international units; IV, intravenous; PO, by mouth; SC, subcutaneous.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home.

The effect of bisphosphonates is because of their ability to bind bone mineral and inhibit osteoclast activity, thereby reducing bone resorption.[57] Alendronate, ibandronate, risedronate, pamidronate, and zoledronic acid are aminobisphosphonates with a greater selectivity for the antiresorptive surfaces of the bone because of changes in the nitrogen-containing side chain of the compounds.[58] Bisphosphonates have high affinities for bone hydroxyapatite and can be incorporated into bone. They concentrate in mineral tissue

and interfere with the osteoclast-mediated bone resorption to cause osteoclast apoptosis, decreased bone turnover, resulting in decreased fracture rates in postmenopausal females who are at risk for osteoporosis.

Because of their incorporation into bone, bisphosphonates have long half-lives, estimated to be 1 to 10 years. Unlike etidronate (a non-aminobisphophonate), aminobisphosphonates do not inhibit bone mineralization, which could lead to osteomalacia.

Bisphosphonates

Alendronate

Alendronate was the first bisphosphonate approved for the treatment of postmenopausal osteoporosis in 1995 and is available as a daily or weekly tablet.[59] Many clinical trials have been published regarding the use of alendronate in the treatment of osteoporosis. In a Cochrane review of 11 randomized controlled trials and ~12,000 postmenopausal females who had previous fracture or whose BMD was >2 SD below the mean, alendronate reduced the risk of vertebral fracture (NNT 16), nonvertebral fracture (NNT 50), wrist fracture (NNT 50), and hip fracture (NNT 100).[60] Compared to placebo, alendronate reduces the risk of vertebral fracture by 40% to 64%, nonvertebral fracture by 11% to 49%, and hip fracture by 21% to 55% over 3 years.[60],[61] Alendronate is well tolerated, and adverse events reported in clinical trials were similar to placebo.

Ibandronate

MOBILE, a randomized controlled, noninferiority study, included 1609 postmenopausal females ages 55 to 80 with osteoporosis and compared daily ibandronate (2.5 mg/day) to three different monthly regimens: ibandronate 50 mg given on two consecutive days per month and 100 mg and 150 mg once monthly.[62] All monthly regimens were at least as effective as daily ibandronate after 1 year. At 2 years, the mean increase in BMD of the lumbar spine seen in the ibandronate 50 mg on two consecutive days per month was (5.3%), ibandronate 100 mg/month (5.3%), ibandronate 150

mg/month (6.4%) as compared to ibandronate 2.5 mg taken daily (4.8%). Increases were seen in the total hip, trochanter, and femoral neck, with ibandronate 150 mg/month being the most significant.

In a 5-year, long-term extension (MOBILE LTE), increases in BMD that were achieved during the MOBILE study were maintained, and further increases were seen in lumbar spine BMD.[19] Minor changes were seen in the femoral neck and trochanter. Overall, adverse effects of monthly ibandronate were similar to daily ibandronate. Benefits in BMD changes, and decreases in bone turnover markers were greatest for ibandronate 150 mg/month.

Ibandronate has also been studied as an intravenous (IV) formulation of 3 mg administered every 3 months.[63] One-year results from the Dosing Intravenous Administration (DIVA) study improved BMD in the lumbar spine (4.5% vs 3.5%) and the total hip (2.1% vs 1.5%) to a similar if not greater degree than daily oral tablets.

Ibandronate is available as a daily or monthly tablet and a 3-mg quarterly IV injection.[64] Compared to placebo, daily oral ibandronate significantly decreases vertebral risk fracture 52% to 62% over 3 years.[61],[65] No statistically significant decreases in nonvertebral or hip fracture have been found using ibandronate.[66] However, in a subgroup analysis of two noninferiority trials, higher doses of ibandronate (150 mg once monthly, 3 mg IV quarterly, and 2 mg IV every 2 months) reduced the risk of nonvertebral fracture compared to lower doses of ibandronate HR 0.620 (0.395–0.973).

Risedronate

In a study of postmenopausal females who were at least age 50 years, were postmenopausal for five or more years, and had osteoporosis, 75 mg of risedronate on 2 consecutive days a month (2CDM) was as safe and effective as risedronate 5 mg/day for 12 months.[67] At 2 years, lumbar spine BMD increases of 4.2% in the 2CDM and 4.3% in the 5-mg/day were observed.[68] There were no statistically significant differences in BMD changes in lumbar spine, proximal femur, and bone turnover markers. Adverse effects in both groups were similar.

In a study that compared risedronate 5 mg/day and 150 mg/month in postmenopausal females with osteoporosis, similar increases in lumbar spine BMD from baseline were observed (3.4%, 3.5%, respectively) after 1 year, and there was no difference in the new incidence of vertebral fractures.[69] There were similar changes in biochemical bone turnover markers. Adverse effects were similar, with a higher incidence of constipation in the 5-mg/daily group and diarrhea in the 150-mg/monthly group.

Risedronate is available as an oral tablet in four different doses; administered daily, weekly, monthly, or two consecutive days monthly.[70] Similar to alendronate, risedronate significantly reduces the rate of vertebral, nonvertebral, and hip fractures.[61],[71] Most trials used doses of 5 mg daily. Although they were not of high quality, in head-to-head trials comparing different dosing schedules, there were no statistical differences in the dosing regimens.[61] Comparing risedronate to placebo, the reduction in the risk of vertebral fracture ranged from 39% to 69%, even among subgroups with mild to severe renal impairment. The reduction in the risk of nonvertebral fracture ranged from 19% to 60%, and the reduction in the risk of hip fracture from 26% to 40%. Adverse events reported in clinical trials were similar to placebo.

Zoledronic Acid

Zoledronic acid is an IV bisphosphonate that was initially approved for osteoporosis treatment and later received the U.S. Food and Drug Administration (FDA) approval for osteoporosis prevention in postmenopausal females.[1]

In a 2-year study of zoledronic acid for the prevention of bone loss in postmenopausal females with low bone mass, 581 females were randomized to receive zoledronic acid 5 mg IV at baseline and 12 months (2 × 5 mg), zoledronic acid 5 mg IV at baseline only and placebo at 12 months, or placebo at baseline and at 12 months.[72] At 2 years, BMD was significantly increased in the lumbar spine in the (2 × 5 mg; 5.18%), (5 mg 4.42%) as compared to placebo (−1.32%). At 2 years, BMD also increased at the proximal femur sites (2 × 5

mg; total hip 2.91%, femoral neck 2.2%, trochanter 4.83%); (5 mg; total hip 2.28%, femoral neck 1.64%, trochanter 4.16%).

Zoledronic acid is available as a 5-mg IV infusion given over a 15-minute period once yearly for the treatment of osteoporosis.[73] It significantly reduces the risk of vertebral (NNT 14), nonvertebral (NNT 38), and hip fracture (NNT 98) similarly to that achieved by alendronate or risedronate.[74],[75] Zoledronic acid was associated with atrial fibrillation in a large trial of postmenopausal females diagnosed with osteoporosis but not in a subsequent study of postmenopausal females with recent hip fracture.[73],[74] It is less likely to cause GI symptoms than oral bisphosphonates; however, it is associated with injection reactions such as fever (18%), myalgia (9%), and flu-like symptoms (8%) that typically resolve within 3 days but can last up to 2 weeks. There is an increased risk of hypocalcemia following injection compared to placebo. Zoledronic acid is contraindicated in patients with acute renal impairment, patients with creatinine clearance <35 mL/minute, and in patients with hypocalcemia.

In a Health Technology Assessment by the National Institute for Health Research, a systematic review and network meta-analysis were conducted to determine the safety and effectiveness of alendronate, risedronate, ibandronate, and zoledronic acid on fragility fracture.[76] It included studies in females age 65 years and older and males age 75 years and older, and females age 64 years and younger and males age 74 years and younger with risk factors for osteoporosis. A total of 46 randomized controlled trials were included. All bisphosphonates were effective in reducing vertebral fracture compared to placebo, but only alendronate, risedronate, and zoledronic acid reduced nonvertebral fractures compared with placebo (**Table 110-9**). Fewer head-to-head trials were available for analysis, but when comparing bisphosphonates to each other, no bisphosphonate was significantly more effective than another.

Table 110-9
Effect of Bisphosphonates Versus Placebo on Fracture Prevention Citation[76]

Treatment	Vertebral Fracture HR (95% CI)	Nonvertebral Fracture HR (95% CI)
Risedronate	0.50 (0.38-0.66)	0.72 (0.53-0.89)
Alendronate	0.45 (0.35-0.58)	0.80 (0.65-0.94)
Zoledronic Acid	0.41 (0.28-0.56)	0.75 (0.61-0.91)
Ibandronate 150 mg/month	0.45 (0.24-0.81)	0.80 (0.53-1.36)

There were no serious adverse effects reported in the randomized controlled trials: there was no significant difference in participants withdrawing because of adverse effects; oral bisphosphonates had similar incidence of GI events; zoledronic acid was associated with influenza-like symptoms; and there were no significant differences in mortality. Authors report, however, that prescription monitoring data and observational studies indicate that a higher number of adverse effects, including serious adverse effects, are associated with bisphosphonates.

Oral bisphosphonates are first line and are the most commonly prescribed medications for the treatment of osteoporosis. The decision to start medication therapy for the treatment of osteoporosis prevention in postmenopausal females should involve both the patient and physician. S.D. has been diagnosed with osteoporosis, and her risk of recurrent fracture is high. Bisphosphonates are effective for secondary prevention after a first fracture. Oral alendronate or oral risedronate would be the bisphosphonate of choice for S.D. based on their availability and convenience. Zoledronic acid can be considered if S.D. cannot tolerate oral bisphosphonates.

Length of treatment

The incorporation of bisphosphonates into bone results in a reservoir of available drug that is slowly released over time.[57],[77],[78] The peak effect of reducing bone turnover markers occurs in 3 to 6 months and continues for months to years with discontinuation. Approval studies in the United States were for 3 to 4 years; however, extension studies suggest longer efficacy.[79–82] Because the risk of

adverse effects increases with longer duration, it is of interest to determine the optimum duration of treatment.

In the Fracture Intervention Trial Long-term Extension (FLEX) of the original Fracture Intervention Trial (FIT), the effects of continuing alendronate were compared to the effects of stopping alendronate after 5 years of treatment.[79] Statistically significant bone loss occurred (2%–3% more than those who took alendronate for 10 years) when females were switched to placebo after 5 years of alendronate therapy; however, BMD remained well above FIT baseline. A gradual rise was seen in biochemical markers of bone turnover, and there were no significant differences seen in clinical or nonvertebral fractures. There was a slightly higher risk of clinically detected vertebral fractures, in the placebo group (females who had discontinued alendronate therapy after 5 years) compared to the groups who continued alendronate, suggesting that females at high risk for vertebral fracture or with T-scores < −3.5 may benefit from continued bisphosphonate therapy.

The long-term effects of risedronate 5 mg/daily on bone were studied in females with osteoporosis who were in the Vertebral Efficacy with Risedronate Therapy-North American (VERT-NA) study who took risedronate for up to 5 years.[83] In biopsies of the iliac crest that were taken at 3 and 5 years, changes in bone mineral and collagen were preserved in the risedronate groups as compared to maturation that was observed with placebo. The FLEX and VERT-NA studies suggest that females with good response to bisphosphonate therapy who are not at high risk for fracture may be able to take a “drug holiday” (eg, 1 year off therapy) after 3 to 5 years of treatment.[84] Females who are able to reach a T-score of > −2.5 may be able to discontinue therapy for several years.

In an extension of the HORIZON-Pivotal Fracture Trial, long-term effects of zoledronic acid up to 6 years (Z6) were compared to patients who had no further treatment after 3 years (Z3P3).[85] Over the 3-year extension, there was a significant difference in BMD. Those patients who received zoledronic acid for 3 years lost BMD (−0.80%), and those who continued for 6 years gained BMD (+0.24%). Over the 6-year period, the gain was 3.1% and 4.5% for 3

years and 6 years, respectively. Nonclinical morphometric vertebral fracture risk (those which reduce vertebral height) was significantly lower for Z6 versus Z3P3 (3% vs 6%, *P* = .35), but there was no significant difference in clinical vertebral or nonvertebral fracture. A further extension compared 9 years of zoledronic acid to 6 years and found no significant difference in BMD or fracture.[82] Authors suggest that treatment with zoledronic acid for six annual infusions can be stopped for up to 3 years without apparent reduction of efficacy.

According to the American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines, it is reasonable to consider a drug holiday from oral bisphosphonates after 5 years in lower-risk patients, those who have not had a fracture, or T-score is > −2.5.[23] If risk remains high, continue for an additional 5 years. For high-risk patients, a drug holiday from oral bisphosphonates can be considered after 6 to 10 years. In patients taking zoledronic acid, a drug holiday after 3 years can be considered if risk of fracture is no longer high but continuing until 6 years if patients remain at high risk. For non-bisphosphonate treatments, a drug holiday is not recommended.

The European Menopause and Andropause Society (EMAS) published a statement on the use of drug holidays in bisphosphonates and denosumab. The phrase drug holiday arose from the idea that stopping medication treatment for a period of time may reduce long-term adverse effects while preserving the benefit on fracture risk. Major concerns of therapy with bisphosphonates and denosumab are atypical fractures and osteonecrosis of the jaw. EMAS suggests that a drug holiday should be considered for alendronate and risedronate therapy for more than 5 years and zoledronic acid for more than 3 years. No suggestions could be made for ibandronate. A drug holiday can also be considered for patients without fracture before or during therapy who are age 70 years and younger with a femoral neck T-score of ≥ −2.5. Authors state that although the length of discontinuation is unclear, a 2- to 3-year holiday would be reasonable. Patient characteristics, BMD, bone turnover markers, and fracture risk should be used to guide the decision on the appropriate length of time and whether to

discontinue therapy. There are no suggestions for the discontinuation of denosumab, as it can result in a rapid decline of BMD and a potential increased risk of fracture.

If tolerated, S.D. should continue therapy of alendronate or risedronate for up to 5 years; however, if a patient has prodromal pain in the thigh or leg or has suffered an atypical fracture while on bisphosphonate therapy, it would be reasonable to discontinue therapy and evaluate.[70]

CASE 110-3, QUESTION 3: What are the potential adverse effects of bisphosphonates?

Adverse Effects

Adverse reactions reported in postmarketing surveillance and outside of clinical trials suggest oral bisphosphonates are strongly associated with upper GI events.[59,64,70] Monthly doses may be slightly better tolerated than daily, but common adverse effects associated with the use of oral bisphosphonates include GI symptoms such as acid regurgitation, dysphagia, abdominal distension, gastritis, nausea, dyspepsia, flatulence, diarrhea, and constipation. The risk of GI intolerance may lead to less common but more severe development of esophagitis, esophageal ulcers, esophageal stricture or perforation, gastric or duodenal ulcers, and possibly esophageal cancer.[59,70] Patients with GERD or patients who cannot remain upright after dosing may not be candidates for oral bisphosphonate therapy because of gastric irritation.

Adverse effects are greater in patients who lie down after taking oral bisphosphonates, who fail to swallow the medication with a full glass (6–8 ounces) of water, or who continue to take the medication after developing symptoms suggestive of esophageal irritation. As similar GI events have been reported with oral bisphosphonates, the FDA requires a medication guide to be provided at the time these medications are dispensed.[86] A medication guide will address issues that are specific to bisphosphonates and are intended to help patients better understand treatment, adverse effects, and

adherence (see the section on Dosing). In addition to GI effects, hypocalcemia, musculoskeletal pain, headaches, and rashes have been noted.

Both IV and oral bisphosphonates are associated with osteonecrosis of the jaw (ONJ), a serious but rare adverse event.[73] It was first reported in a series of patients with cancer receiving IV bisphosphonates. Risk factors for osteonecrosis of the jaw include the diagnosis or previous history of cancer; invasive dental procedures; concurrent use of chemotherapy, corticosteroids, or angiogenesis inhibitors; poor oral hygiene; preexisting dental disease or infection; anemia; and coagulopathy. The risk of ONJ increases at higher doses and with duration of exposure.

Bisphosphonates are associated with atypical fractures of the femoral shaft.[25],[73] A warning is included in the manufacturers' information for all bisphosphonate drugs that are indicated for the prevention or treatment of osteoporosis. A safety review of oral bisphosphonates and atypical subtrochanteric femur fractures by the FDA is also ongoing.[88] A clear connection has not been found. The mechanism of action is not clear; however, bone is normally subject to microdamage with everyday stresses, and this initiates bone remodeling.[89] Antiresorptive agents may oversuppress bone turnover, causing microdamage to accumulate, which may lead to brittle bone and an increased risk of fracture. Lee et al[89] conducted a meta-analysis that included nine observational studies and one randomized controlled trial; a total of 658,497 patients. The results were statistically significant for increased risk of subtrochanteric or diaphyseal fracture with bisphosphonate use (adjusted odds ratios [AOR] = 1.99, 95% confidence intervals [CI] = 1.28–3.10), subtrochanteric fractures AOR = 2.71 (95% CI, 1.86–3.95), and diaphyseal fractures AOR = 2.06 (95% CI, 1.70–2.50). The analysis was limited by the multiple study designs, varying lengths of follow-up, and different patient populations leading to high heterogeneity. The pooled results of combined subtrochanteric or diaphyseal fracture and subtrochanteric fracture results had significant heterogeneity (84.3% and 83.6%, respectively). The results for diaphyseal fracture had moderate heterogeneity (29.7%). The overall

risk is low compared to osteoporotic fracture. In a nested case–control study of 52,595 females ages 68 years and older who took at least 5 years of bisphosphonate therapy, the subtrochanteric or femoral shaft fracture occurred in 71 (0.13%) during the subsequent year and 117 (0.22%) within 2 years.[90] The results were similar to the meta-analysis. Compared with no use or transient use, the use of bisphosphonates for 5 years or longer was associated with a significantly increased risk of atypical hip or femur fracture (odds ratio [OR] = 2.74; 95% CI, 1.25–6.02). Duration <5 years was not associated with an increased risk of fracture.

Controversial atrial fibrillation results in the zoledronic acid trials prompted an investigation by the FDA.[87] Following an analysis of clinical trials comparing alendronate, ibandronate, risedronate, and zoledronic acid to placebo, the FDA stated that there was no clear association of risk for atrial fibrillation in male and female patients treated with bisphosphonate drugs. Additional adverse effects reported with zoledronic acid are pyrexia, headache, pain in extremity, flu-like illness, and eye inflammation.[73]

Dosing

Alendronate is approved for the treatment of osteoporosis at 10 mg PO daily and 70 mg PO weekly and prevention of osteoporosis in doses of 5 mg PO daily and 35 mg PO weekly. Alendronate is also available with cholecalciferol in a 70-mg/2800 IU and 70-mg/5600 IU PO weekly tablet. Ibandronate is approved for prevention and treatment at 2.5 mg PO daily and 150 mg PO monthly. Risedronate is approved for prevention and treatment at 5 mg PO daily, 35 mg PO weekly, and 75 mg PO on two consecutive days each month and 150 mg PO monthly. The delayed-release formulation of risedronate is not indicated for the prevention of postmenopausal osteoporosis. Zoledronic acid is administered at 5 mg IV every year for treatment and every 2 years for prevention over no <15 minutes.[91] Selecting the appropriate dosing option may improve adherence to therapy.

Oral bisphosphonates are poorly absorbed and under ideal conditions have an absorption of <1%.[57] Patients should be

instructed to take most bisphosphonates with 6 to 8 ounces of water early in the morning on arising and at least 30 minutes (60 minutes for ibandronate) before ingesting food, beverage, or other medications. Risedronate is also available as a 35-mg delayed-release tablet that should be taken once weekly after breakfast. Patients should not lie down but should stay fully upright for at least 30 minutes (60 minutes for ibandronate) after ingesting an oral bisphosphonate to prevent esophageal irritation or ulceration and to ensure appropriate bioavailability. With all bisphosphonates, patients should ingest adequate calcium and vitamin D, but should not take the calcium or vitamin D at the same time as the oral bisphosphonates because they may decrease the absorption of bisphosphonates.

Contraindications and Precautions

Hypocalcemia should be corrected before beginning therapy, and all patients on bisphosphonates should receive adequate calcium and vitamin D through diet or supplements. Patients on loop diuretics should be monitored for hypocalcemia. Patients receiving zoledronic acid should be appropriately hydrated, the infusion given over no <15 minutes, then followed by a 10-mL of normal saline flush.[73] To reduce the incidence of acute-phase reaction symptoms, acetaminophen may be given postinfusion.

Although no dosage adjustments are recommended for patients with mild renal insufficiency, alendronate and zoledronic acid are not recommended in patients with creatinine clearance <35 mL/minute, and ibandronate and risedronate are not recommended in patients with creatinine clearance <30 mL/minute.

Case 110-3, Question 4: Should an SERM such as raloxifene be considered for the prevention of osteoporosis in S.D.?

Selective estrogen-receptor modulators

Raloxifene

Raloxifene is a benzothiophene second-generation SERM with both agonist and antagonist action on select estrogen target tissues.[92],[93] Raloxifene binds to estrogen receptors (ERs) resulting in estrogen agonist effect in bone and lipid metabolism and estrogen antagonist effect in breast and endometrial tissue.[93] Tamoxifen is also an SERM, but differs from raloxifene in that it has agonistic effects on endometrial tissue and raloxifene does not. Tamoxifen is indicated for the prophylaxis and treatment of breast cancer and is not indicated for postmenopausal osteoporosis prevention. Raloxifene's agonist activity on bone tissue is believed to effect osteoclastogenesis, leading to a reduction in bone resorption and a decreased rate of bone turnover, increasing BMD.[93],[94] In a study of 601 postmenopausal females age 45 to 60 with normal to low BMD, patients were randomized to receive raloxifene 30 mg, 60 mg, 150 mg or placebo daily for 2 years.[94] Significant increases in BMD of the lumbar spine (1.6%, placebo −0.8%), hip (1.6%, −0.8%), femoral neck (1.2%, placebo −1.3%), and total body (1.4%, placebo −0.6%) were observed, along with decreases in bone turnover markers, serum concentrations of total cholesterol, and low-density lipoprotein (LDL). No significant differences were observed in endometrial thickness.

Jolly et al conducted a 2-year extension study of two 3-year prospective, randomized, double-blind, placebo-controlled trials of raloxifene for the prevention of postmenopausal osteoporosis.[95] The study included 328 females from the initial 1145 core study age 45 to 60. After 5 years of therapy with raloxifene 60 mg daily, bone turnover markers decreased, BMD of the lumbar spine increased (2.8%), and total hip BMD increased (2.6%) as compared to placebo. In females with osteopenia of the lumbar spine, 2.5% developed osteoporosis in the lumbar spine as compared to 18.5% of those who took placebo. There were significant reductions in total cholesterol and LDL, but not high-density lipoprotein (HDL) or triglycerides. No significant endometrial differences were reported as compared to placebo. Females with osteopenia who took raloxifene 60 mg daily for 5 years were 87% less likely to progress to osteoporosis at the lumbar spine than those on placebo. Females

with normal BMD were 77% less likely to progress to osteopenia after 5 years of raloxifene 60 mg daily. There was a statistically significant increase in the incidence of hot flashes (raloxifene 28.8%; placebo 16.8%).

The Efficacy of Fosamax versus Evista Comparison Trial (EFFECT) was a randomized, double-blind clinical trial including 487 postmenopausal females with low bone density of the spine or hip (T-score ≤ 2.0). Efficacy and tolerability of alendronate was compared to raloxifene.[96] Patients were randomly assigned to either alendronate 70 mg weekly and daily placebo identical to raloxifene or raloxifene 60 mg daily and weekly placebo identical to alendronate for 12 months. After 1 year, increases in BMD were greater for alendronate than raloxifene in the lumbar spine (4.8% vs 2.2%, respectively; $P < .001$) and total hip (2.3% vs 0.8%, respectively: $P < .001$). Tolerability and GI effects were similar in both groups; however, significantly higher reports of vasomotor symptoms came from the raloxifene group.

In other clinical trials, females who took raloxifene had an increased risk of DVT and PE.[97]

A paradox still exists regarding how raloxifene can decrease vertebral fractures by up to 41% while increasing BMD by only 2% to 3%, rates that are lower than those noted for ET, EPT, or alendronate.[98] In addition, raloxifene has not been observed to have a significant effect on hip fractures when compared to other agents. The antifracture effect of raloxifene on vertebral fractures may occur secondary to normalization of the high turnover rate of cancellous bone, which then prevents further disruption of bone microarchitecture.[99] This may occur through raloxifene binding at estrogen β-receptor sites that are predominantly in cancellous bone, whereas α-receptors are predominantly in cortical bone. Thus, bone type and ER are different in the hips compared with vertebrae. In addition, a less potent antiresorptive agent, such as raloxifene, may help prevent vertebral fractures but not hip fractures because the threshold for preventing osteoclast activity in cancellous bone (which is predominant in vertebrae) may be lower than in cortical bone

(which predominates in hips). For these reasons, it may require a more potent antiresorptive agent to increase BMD in the hips.

Raloxifene might be considered for osteoporosis prevention in a female such as M.J., even with her strong family history of breast cancer. This latter recommendation is based on results from the MORE trial.[98] A 76% decrease was noted in risk for invasive breast cancer in postmenopausal females with osteoporosis (mean age 66.5 years) who received raloxifene for 3 years. A total of 7705 females were assigned to raloxifene groups (60 mg twice daily or 60 mg daily) or a placebo group. Of those enrolled in either raloxifene group (*N* = 5129), only 13 cases of breast cancer were reported versus 27 that occurred in the 2576 females in the placebo group. Postmenopausal females over 50 with low bone mass, such as M.J., are candidates for osteoporosis prevention therapy if they have a 10-year hip fracture probability of 3% or greater or a 10-year major osteoporosis-related fracture probability of 20% or greater based on the WHO FRAX®.[1]

Raloxifene 60 mg PO daily is indicated for the prevention of osteoporosis in postmenopausal females.[97]

Dosing and Pharmacokinetics

Raloxifene 60 mg once daily can be taken without regard for food.[97] Raloxifene is ~60% absorbed and undergoes extensive glucuronide conjugation, resulting in a 2% absolute bioavailability. Some circulating raloxifene glucuronide conjugates are converted back to the parent compound. Raloxifene and its monoglucuronide conjugates are highly protein bound. Raloxifene is primarily excreted in feces, with <0.2% excreted unchanged and <6% eliminated in urine as glucuronide conjugates. There appear to be no differences in pharmacokinetics based on age or sex. Raloxifene has a mean half-life of 27.7 hours after a single dose and 32.5 hours after multiple doses.

Adverse Effects

Adverse effects of raloxifene include an increased risk for venous thromboembolic disease, flu syndrome, headache, hot flashes, nausea, diarrhea, flatulence, gastroenteritis, leg cramps, peripheral edema, arthralgia, neuralgia, sinusitis, bronchitis, rash, sweating, and conjunctivitis.[97]

Contraindications and Potential Drug Interactions

Raloxifene carries a boxed warning and is contraindicated in patients with active venous thromboembolism or a past history of venous thromboembolism because of increased risk.[85] Raloxifene is contraindicated in females who are pregnant, plan to become pregnant, and those nursing. Raloxifene should be used with caution during periods of prolonged immobilization, in patients with a history or risk of stroke, moderate or severe renal impairment, and in patients with hepatic impairment. The coadministration of cholestyramine may decrease the absorption of raloxifene and should be avoided. Prothrombin time should be monitored when starting or discontinuing raloxifene in patients taking warfarin. Raloxifene is over 95% bound to plasma proteins and may affect highly protein-bound medications.

Bazedoxifene is a third-generation SERM and is available only in a combination product with conjugated estrogen.[100] It is indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, such as hot flashes, and the prevention of postmenopausal osteoporosis in females with an intact uterus. Because of the boxed warnings (endometrial cancer, cardiovascular disorders, and probable dementia) and adverse events associated with estrogen, its use is limited to the shortest duration possible. The manufacturer suggests that nonestrogen agents be considered when using the medication for the sole purpose of osteoporosis prevention. (See the section on ET.)

Treatment

CASE 110-4

QUESTION 1: T.J.'s 75-year-old grandmother, M.B., was diagnosed with osteoporosis 5 years ago when she fell and broke her distal forearm. At that time, it was noticed that she had multiple lumbar compression fractures and mild kyphosis. M.B. had lost 1.5 inches (3.81 cm) in height and was 5 feet tall and weighed 100 pounds (45.35 kg). She now has chronic back pain that is managed with acetaminophen or ibuprofen but states it occasionally makes her feel unsteady on her feet. A recent bone scan revealed significantly decreased bone mass (T-score: spine −3.6, hip −2.6, wrist −2.5). M.B. had her last menstrual period before her hysterectomy was performed 25 years ago. She took CEE 0.625 mg daily up until about 15 years ago when it was discontinued by her primary care physician. M.B. has hypertension for which she receives hydrochlorothiazide 25 mg daily and enalapril 10 mg daily, and she reports occasional acid reflux. She was prescribed alendronate 70 mg once weekly, but admits she was not good at filling it regularly, as it upsets her stomach and eventually stopped taking it. M.B. does take calcium carbonate 1200 mg/day in divided doses with meals and vitamin D 1000 IU daily, both of which were started after experiencing a fracture 5 years ago. M.B. does not smoke cigarettes, drink alcohol, or take any other nonprescription medications. She states it is difficult to exercise because of her back pain. Her mother fractured her hip at about her age.

Does M.B. exhibit any clinical signs of osteoporosis?

There are few clinical signs of osteoporosis. It is usually asymptomatic until a fracture occurs. M.B. exhibits a loss of 1.5 inches (3.81 cm) in height and mild kyphosis. She also has mild back pain. There are other causes of kyphosis, but M.B. exhibits kyphosis because of compression fractures associated with osteoporosis. (See Case 110-2, Question 1, for further information about osteoporosis clinical signs and symptoms.)

CASE 110-4, QUESTION 2: What changes, if any, should be made to M.B.'s treatment plan?

A treatment plan for M.B. should be aimed at preventing further bone loss and minimizing falls, which could lead to fractures. It is important for M.B. to continue calcium and vitamin D in her diet and maximize her physical function by incorporating exercise in her treatment plan. M.B. has experienced a previous fracture and

vertebral compression because of osteoporosis. She is at a higher risk for a subsequent fracture. The benefits of pharmacologic treatment using a different medication or reinitiating alendronate should be discussed with M.B., along with counseling on adherence.

RECURRENT FRACTURE RISK

Vertebral fractures are a common consequence of osteoporosis and are associated with a decreased health-related quality of life (HRQOL).[101],[102] They can occur without symptoms and may go unrecognized at the time of the fracture. The risk of an additional vertebral fracture within a year of the incident fracture is five times higher compared to postmenopausal females with no previous vertebral fracture.[101],[103] The physical symptoms resulting from vertebral fractures become more evident with each recurrence.[101] They are associated with loss of height, pain, decreased mobility, and mortality. The risk of recurrent fracture is also high at other sites such as the hip and wrist. A large, random cohort of almost 40,000 U.S. Medicare beneficiaries, who were not enrolled in a prescription benefit plan, were evaluated for the occurrence of a second fracture or death using data from 1999 to 2006.[104] The 5-year risk of second fracture increased with age, and the 5-year risk of death increased with age and concurrent comorbidity. Risk was greatest 6 to 24 months after the first fracture for both mortality and second fracture. The authors concluded that the risk of second fracture, which was >20% in most measured subcategories, warranted the need for prescription osteoporosis treatment.

DIETARY INTAKE

Calcium and vitamin D supplementation in combination can improve bone density and may prevent fractures in postmenopausal females with osteoporosis.[53],[55]

Sufficient dietary calcium and vitamin D are a universal recommendation for older adults with osteoporosis. Maintaining serum 25(OH)D levels above 30 ng/mL (75 nmol/L) is an important goal as low levels of vitamin D are associated with an increased risk

of falling.[1],[105],[106] The dietary goal for all patients with osteoporosis is to eat a well-balanced diet rich in fruits and vegetables, low-fat dairy products, whole grains, fish, and nuts. She should try to maintain her BMI between 20 and 25 kg/m^2. In patients like M.B., it is important to ensure vitamin D levels are adequate and dietary intake of calcium is at least 1200 mg/day. If M.B. does not achieve this from her diet, the supplements she is currently taking would be recommended. Intestinal absorption of calcium carbonate is dependent on stomach acid. There is some controversy on whether gastric acid secretion is decreased with aging and if patients who are older should take calcium citrate instead of calcium carbonate.[107],[108] Calcium carbonate supplements are the form most often associated with constipation, which can be problematic as gastric motility is decreased with aging.[107],[108] Calcium citrate should be used over calcium carbonate in patients with achlorhydria, a condition common in older adults, and in those patients who report constipation. M.B. should continue taking her calcium carbonate in divided doses with meals. If there is a question of absorption because of lower gastric acid or constipation, M.B. could switch calcium products to calcium citrate. (See Case 110-1, Questions 2 and 3, for further discussion on calcium requirements, supplementation, and product selection and the use of vitamin D.)

EXERCISE AND FALL PREVENTION

Falls are common among older adults and the leading cause of fractures and injury, both fatal and nonfatal.[109] One in three adults over age 65 years fall each year. Fall-related fractures occur more often among older females than males, although males are more likely to die from fall-related fractures than females. Pain and disability are common results of falling as well as developing a fear of falling again. Those ages 75 and older are five times more likely to be admitted to a long-term care facility than those between ages 65 and 75 years. Fall prevention that includes exercise training is an important nonpharmacologic treatment for older patients with osteoporosis. In a meta-analysis of 17 randomized controlled trials of

various fall prevention programs in community-dwelling patients over age 60 years, exercise significantly reduced the rate of falls, including falls resulting in injuries or fractures.[110] A reduction of about 37% for all injurious falls was found, along with a reduction of 43% for severe injurious falls, and 61% for falls resulting in fractures.

Exercise helps maintain bone mass, function, and agility. Older patients should be screened at least once per year for fall risk to determine if there are any underlying factors or medical conditions associated with the risk of falls.[111] Any patient who presents to a clinician after a fall should have a risk assessment as well. Patients at higher risk of falling include those with deficits in gait and balance, foot problems, impairment of vision, cardiovascular disease, postural hypotension, and vitamin D deficiency. Removal of contributing factors and treating underlying medical conditions with the fewest medications possible can reduce the risk of falling. Pharmacists have an important role in optimizing medication therapy to decrease central nervous system (CNS) effects or adverse effects affecting cognition and blood pressure. The prevention of falls also includes maintaining a safe environment; reducing tripping hazards, adding handrails inside and outside the tub or shower and next to the toilet, and improving the lighting in the home.[109,111]

Vertebral fractures can present with differing degrees of pain and disability. M.B. should include a regular weight-bearing and strengthening exercise routine that is appropriate for her age and physical condition. A referral to physical therapy may be needed to introduce M.B. to individualized exercises that will improve her strength and balance.

PHARMACOTHERAPY

Pharmacologic treatment is indicated in patients who have experienced a hip or vertebral fracture, in those with T-scores < −2.5 at the femoral neck, total hip, or lumbar spine, and in postmenopausal females and males ages 50 and older with low bone mass and high risk of fracture.[1] Agents approved for treatment of osteoporosis include bisphosphonates (alendronate, risedronate,

ibandronate, and zoledronic acid), calcitonin, denosumab, estrogen, raloxifene, and teriparatide, abaloparatide, and romosozumab. Drug therapy decisions in a patient with osteoporosis or risk of fracture should be based on the patient's medical history, patient preferences, and a balance of the risks and benefits of a medication. The goal of pharmacotherapy is to reduce the rate of fractures with the least amount of adverse effects. Head-to-head trials are often the best evidence for comparison, but this evidence is not always available. Osteoporosis diagnosis and evaluation of bone health are based on BMD assessment, which is used to estimate fracture risk. When searching for the best therapy, it is important to be mindful that the basis of treatment is the reduction of fractures. Trials reporting BMD alone may not be sufficient to predict the effect on fractures.

CASE 110-4, QUESTION 3: What medications might be considered for the treatment of osteoporosis in M.B.?

ESTROGEN

As discussed in Case 110-2, conjugated ET has positive effects on BMD and fracture rates but is no longer recommended for the treatment of osteoporosis. M.B. may have benefited from years of using ET, preserving BMD, but the benefit of ET on BMD only occurs while taking it. Bone loss is accelerated once hormone therapy is stopped, thus, M.B. and her physician should discuss another drug for the treatment of her osteoporosis.

SELECTIVE ESTROGEN-RECEPTOR MODULATORS

Raloxifene is an estrogenic agent that reduces the risk of vertebral fracture.[97] The recommended dose is 60 mg (tablet) orally once daily. It is the only SERM-approved in the United States that is indicated for the treatment and prevention of osteoporosis in postmenopausal females.

In a randomized controlled trial including almost 7000 postmenopausal females, raloxifene 60 mg or 120 mg daily for 3 years increased BMD in the femoral neck (2.1% and 2.4%,

respectively) and spine (2.6% and 2.7%, respectively) compared to placebo ($P < .001$ for all comparisons).[112] Females ages 31 to 80 were included with or without a previous vertebral fracture. The incidence of new vertebral fracture was 10.1% for placebo, 6.6% for raloxifene 60 mg/d, and 5.4% raloxifene 120 mg/d. Compared to placebo, the risk of new vertebral fracture was 0.7 (95% CI, 0.5–0.8) for raloxifene 60 mg/d and 0.5 (95% CI, 0.4–0.7) for raloxifene 120 mg/d, and risk reduction was similar regardless of preexisting fracture. There were no significant differences in total nonvertebral fractures. Serious adverse events included venous thromboembolism 0.3% for placebo and 1.0% for each 60 mg and 120 mg groups; RR 3.1 (95% CI, 1.5–6.2). Other common and significantly different adverse effects included influenza-like syndrome, hot flashes, leg cramps, and peripheral edema. Subjects enrolled in this 3-year raloxifene trial above by Ettinger et al[112] were eligible to participate in a 1-year extension with no raloxifene and then a 4-year continuation, which included raloxifene 60 mg daily for the raloxifene group.[113] The primary outcome of the 4-year extension was invasive breast cancer and included roughly 4000 females from the original trial. Raloxifene reduced the risk of ER-positive invasive breast cancer by 84% (RR 0.16, 95% CI, 0.09, 0.30). During the 1-year extension with no raloxifene, BMD decreased significantly. It increased as raloxifene was restarted and was maintained. Vertebral fracture risk was maintained 4 years after randomization but was not measured in the 4-year extension trial. BMD was measured in U.S. sites only in the 4-year extension trial and included 386 females in the final analysis.[114] After a total of 7 years on raloxifene, BMD in the femoral neck increased 1.9% from baseline and 3% from placebo ($P = .30$). BMD in the lumbar spine increased 4.3% from baseline and 2.2% from placebo ($P = .045$). The safety of raloxifene after 7 years was similar to 3 years. (See Case 110-3, Question 4, for additional information about raloxifene.)

Bisphosphonates are the major pharmacologic group of medications for the treatment of osteoporosis. A meta-analysis of seven randomized controlled trials, ~3700 participants, comparing raloxifene and alendronate was conducted to determine the efficacy

and safety of the two medications in postmenopausal females.[115] The length of the trials was at least 12 months, and the majority of trials included were of good quality. The raloxifene dose in each trial was 60 mg daily. The alendronate dose varied and included were two trials at 70 mg each week, four trials at 10 mg daily, and one trial at 5 mg daily. There were no statistical differences found between raloxifene and alendronate in the risk of vertebral fractures, nonvertebral fractures, or total fractures within a follow-up period of 12 to 24 months. There were no significant differences in upper GI disorders, venous thromboembolism, or vasodilation. There was a significantly higher rate of diarrhea found in the alendronate group and a significant increase in vasomotor events found in the raloxifene group. In a subgroup analysis, there was a higher risk of upper GI disorders for alendronate compared to raloxifene in patients over 65 years of age and for alendronate administered daily compared to raloxifene.

Raloxifene has a unique benefit and risk profile when compared to other treatments for osteoporosis. Raloxifene decreases the risk of vertebral fractures by 34% to 44% compared to placebo, but no significant differences are found in the risk of total nonvertebral fractures.[61] No differences in the rate of vertebral or nonvertebral fracture risk have been found in head-to-head trials comparing raloxifene and alendronate.[61],[115] The safety and efficacy of raloxifene has been studied in a randomized controlled trial up to 7 years. Significant adverse effects include an increase in venous thromboembolism; myalgias, cramps, and limb pain; and hot flashes. The FDA has issued a boxed warning regarding the increased risk of DVT and PE while taking raloxifene and a warning of increased risk of death because of stroke in postmenopausal females with documented CHD or those at increased risk for coronary events.[97] As with other ET, it is necessary to continue raloxifene therapy to maintain increases in BMD.

Because raloxifene has not been shown to prevent nonvertebral fractures, it is not the best treatment for many patients with osteoporosis. M.B. has a high fracture risk, and other treatment options should be discussed.

Bisphosphonates

Bisphosphonates, such as alendronate, risedronate, ibandronate, or zoledronic acid, can be used as an alternative to raloxifene to prevent fractures because of osteoporosis. All bisphosphonates are effective in reducing vertebral fracture and have similar efficacy.[76] Only alendronate, risedronate, and zoledronic acid reduced nonvertebral fractures. The choice of bisphosphonate as well as monitoring to ensure the medication is taken as directed can affect their clinical benefit. No statistical differences are seen between agents, but poor adherence will decrease their fracture benefit (see Case 110-5, Question 4).

M.B. has been diagnosed with osteoporosis, and her risk of fall and recurrent fracture is high. Oral alendronate was not tolerated, and risedronate has a similar GI adverse effect profile. Oral bisphosphonates, as previously prescribed, may not be the best choice for M.B. Injectable agents are appropriate for patients at high fracture risk. Zoledronic acid may be slightly more potent in preventing vertebral fracture, is effective in reducing hip fracture, and is administered only once per year. It is less likely to cause GI symptoms than oral bisphosphonates but has its own adverse effect profile to be discussed with the patient and should not be administered in patients with an estimated creatinine clearance <35 mL/minute.

Case 110-4, Question 4: What other possible alternatives or additive therapies for the treatment of postmenopausal osteoporosis are available for M.B.?

Calcitonin

Calcitonin decreases bone resorption and bone turnover.[116] Synthetic calcitonin made from salmon is 40 to 50 times more potent than human calcitonin. Calcitonin inhibits osteoclasts and renal excretion of calcium. Because of its mechanism of action, calcitonin decreases both total serum calcium and serum ionized calcium. All patients receiving calcitonin should supplement with at least 1000 mg of

calcium per day and at least 400 IU of vitamin D per day. A nasal spray and an injectable formulation are available and indicated for the treatment of osteoporosis in females who have been postmenopausal for at least 5 years.[117],[118] Injectable calcitonin is also indicated for the treatment of hypercalcemia and Paget disease. Calcitonin is only recommended for the treatment of osteoporosis when alternatives are not suitable and can be considered third-line treatment.[25],[32],[117] Fracture reduction has not been demonstrated for either formulation in quality clinical trials.

Common nasal symptoms from nasal administration include rhinitis, nasal sores, irritation, itching, sinusitis, and epistaxis.[118] Local skin reactions (10%) are common with injectable calcitonin.[117] Nausea with or without vomiting (10%) and flushing (2%–5%) can occur at the initiation of therapy, but subsides over time. Other adverse effects include arthralgia, headache, and back pain. More severe adverse effects associated with calcitonin salmon include serious hypersensitivity, hypocalcemia, and malignancy. Injectable calcitonin should be refrigerated when not in use and nasal spray refrigerated until it is opened for use; thereafter, it is stable for 35 days at room temperature. Calcitonin nasal spray should be used in alternate nostrils daily. Because of calcitonin salmon's weak efficacy, alternative treatments should be used for the treatment of osteoporosis.

The nasal spray and injectable formulation of calcitonin have been used short term to reduce pain because of vertebral fracture.[23] Calcitonin has an analgesic effect and may be beneficial short term to reduce pain score after acute vertebral fracture. A meta-analysis conducted to assess the analgesic effect of calcitonin included 10 studies that involved adults aged 60 years and older who suffered from acute (onset < 10 days) or chronic back pain (>3 months).[119] Intervention groups received nasal spray, injection, or suppository. After 1 week, there was a significant reduction in acute pain at rest and acute pain while walking and was sustained until the end of the treatment period of 4 weeks. There was no difference in chronic pain at rest. There was no difference in chronic pain with activity at 1 month, 3 months, or 1 year, but a slight reduction at 6 months. The

authors state the review supports the use of calcitonin for the acute but not chronic pain of osteoporotic vertebral compression fracture.

A short-term prescription of calcitonin is recommended if M.B. suffers from acute pain from a new vertebral fracture.

Denosumab

Denosumab is a human monoclonal antibody that binds to RANKL, a regulator of bone-resorbing osteoclasts.[20] Denosumab is administered by subcutaneous injection every 6 months and inhibits bone turnover with a rapid onset. Denosumab significantly increases BMD in the lumbar spine, total hip, and at the femoral neck compared to placebo.[120] This effect dissipates quickly, and BMD returns to approximately baseline levels within 12 months of discontinuation.

In a large randomized, placebo-controlled, multicenter trial that included 7868 postmenopausal females with osteoporosis, denosumab 60 mg subcutaneously every 6 months was compared to placebo for a duration of 36 months.[121] Denosumab reduced the primary outcome of new clinical vertebral fracture, 2.3% versus 7.2% (RR 0.32; 95% CI, 0.26–0.41; $P < .001$). Denosumab slightly reduced the cumulative risk of new hip fracture, 0.7% versus 1.2% (HR, 0.60; 95% CI, 0.37–0.97; $P = .04$), and also reduced the cumulative risk of nonvertebral fracture, 6.5% versus 8.0% (HR 0.80; 95% CI, 0.67–0.95; $P = .01$). Eczema occurred in 3% of patients receiving denosumab and 1.7% for placebo ($P < .001$). A serious skin infection occurred in 12 patients (0.3%) receiving denosumab and only 1 patient receiving placebo ($P = .002$). Other adverse effects were similar in both groups.

In two head-to-head clinical trials comparing denosumab to weekly alendronate, denosumab was associated with greater increases in BMD at the hip, lumbar spine, femoral neck, and radius at 12 months.[122],[123] Similar findings have been published comparing denosumab to monthly ibandronate.[124] At 12 months, BMD was significantly higher at the total hip, femoral neck, and lumbar spine in postmenopausal females receiving denosumab than in those

receiving ibandronate. Palacios et al pooled data from two trials comparing denosumab 60 mg subcutaneously every 6 months to either ibandronate or risedronate, 150 mg once monthly for 12 months.[125] Postmenopausal females with low BMD and suboptimal adherence with prior oral bisphosphonate therapy were included in the trials. A treatment satisfaction questionnaire at baseline was compared to 6 and 12 months. Satisfaction improved in all patients but was significantly higher in the denosumab group ($P < .001$). Qualitative measures of effectiveness, side effects, convenience, and overall satisfaction were greater in patients who transitioned to denosumab. The clinical outcome of fracture was not reported, and the comparison of fracture risk between denosumab and oral bisphosphonates cannot be made.

Denosumab is approved for the treatment of postmenopausal females with osteoporosis who are at high risk for fracture.[120] Common adverse reactions include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Serious infections including cellulitis can occur when taking denosumab as well as skin rash and eczema. There is a risk of hypocalcemia with treatment. Adequate supplementation of calcium and vitamin D, at least 1000 mg of calcium and 400 IU of vitamin D daily, is recommended. Hypocalcemia must be corrected before the initiation of treatment. Serious hypersensitivity reactions, pancreatitis, osteonecrosis of the jaw (ONJ), and atypical femur fractures have all been reported. Denosumab is available as prefilled syringes that should be stored in the refrigerator at 36 to 46 °F (2–8 °C). It should be left out for 15 to 30 minutes and brought to room temperature for administration. It is recommended that a health care provider administers denosumab by subcutaneous injection in the upper arm, upper thigh, or abdomen.

Duration of denosumab has been studied up to 10 years with good safety, and recent treatment guidelines do not recommend drug holidays for denosumab.[23] Denosumab is a good option for M.B. Denosumab does not require a dose adjustment for renal insufficiency, but it is recommended by the manufacturer that

calcium, phosphorus, and magnesium be monitored in patients with an estimated creatinine clearance <30 mL/minute.[120]

Parathyroid hormone

Endogenous PTH regulates the level of calcium in the blood.[31] Even a small decrease in calcium will cause secretion of PTH. It acts on the kidneys to conserve calcium and stimulate the production of calcitriol, which increases the absorption of calcium. PTH stimulates bone formation and bone resorption, but also increases the movement of calcium from the bone to the blood. Hyperparathyroidism is uncontrolled overactivity and the continuous secretion of PTH. Excessive PTH causes bone breakdown by osteoclasts and has been shown to contribute to bone loss and bone fragility. A controlled intermittent injection, however, promotes bone formation, increasing BMD and bone size. Teriparatide is a human recombinant fragment of the first 34 amino acids of PTH (PTH 1-34), which produce most of its chief biologic effects.[126] It is available as a multidose pen and given as a daily 20 µg subcutaneous injection. Abaloparatide is a human parathyroid hormone–related peptide [PTHrP(1-34)] analog.

It is also available as a multidose pen and given as a daily 80 µg subcutaneous injection. Both are approved for the treatment of postmenopausal females and males with osteoporosis who are at high risk for fracture.

Early clinical trials in humans were stopped prematurely because animal data showed an increased incidence of osteosarcoma at high doses and long duration.[31],[126] A boxed warning for the potential risk of osteosarcoma appears in the manufacturer's package information for both medications, and dispensing of a medication guide is required with each new or renewed prescription.

Abaloparatide and teriparatide significantly increase BMD and decrease the risk of vertebral and nonvertebral fractures compared to placebo.[80],[127–129] ACTIVE was the phase 3 clinical trial of abaloparatide that included a 1:1:1 design compared to placebo and teriparatide.[80] Both abaloparatide and teriparatide were significantly

more effective than placebo in improving BMD and reducing fracture risk. There were no significant differences in the reduction of nonvertebral fracture when abaloparatide was compared to teriparatide (HR 0.79, 95% CI, 0.43–1.45). Increases in BMD for abaloparatide were significantly greater than teriparatide at the total hip and femoral neck at 6, 12, and 18 months ($P < .001$) and at lumbar spine at 6 and 12 months ($P < .001$). Discontinuation because of adverse effects was higher in the abaloparatide group (9.9%) compared to teriparatide (6.8%) or placebo (6.1%) and because of nausea, dizziness, headache, and palpitations. Hypercalcemia occurred more frequently in the teriparatide group (12.5% vs 11.3%). Palpitations occurred more frequently in the abaloparatide group (5.1% vs 1.6%). Serious adverse effects were similar between abaloparatide and teriparatide. Adverse effects are usually mild and transient.[23] Common adverse effects are hypercalciuria, dizziness, nausea, headache, and orthostatic hypotension.[23],[126],[130] No dosage adjustments are required in patients with renal insufficiency.

Teriparatide and abaloparatide have unique mechanisms of action that make it attractive to combine them with other medications to treat osteoporosis. As it was approved more recently than teriparatide, there are yet no studies of abaloparatide in combination with other medications.

Teriparatide has been given safely in combination with denosumab for 12 months along with a 12-month extension in a small trial ($N = 94$) of postmenopausal females.[131],[132] At 12 months, all groups had a significant change in BMD, but the combination resulted in greater increases in BMD than with either medication alone. At 24 months, BMD continued to increase, but the increase in hip and femoral neck BMD from teriparatide was significantly higher than in the first year and when compared to the second 12 months of denosumab. Overall, increases in BMD at the femoral neck (6.8%), total hip (6.3%), and spine (12.9%) are greater from the combination of teriparatide and denosumab than can be achieved from either drug alone. BMD of the distal radius increased at 24 months, but a decrease in BMD from baseline occurred in the teriparatide group.

Medications were well tolerated. Mild hypercalcemia was reported in the first 12 months but did not occur in the second 12 months. Serious adverse effects were reported, but all were judged unrelated to the medications.

In a small study, teriparatide was given to patients previously on alendronate or raloxifene as add-on therapy and compared to patients who switched to teriparatide alone.[133] At 18 months, BMD increased in all groups at the lumbar spine compared to baseline. However, the addition of teriparatide to alendronate or raloxifene in females on long-term therapy instead of switching to teriparatide alone resulted in significantly increased BMD at the total hip and femoral neck. In treatment-naive patients, a single dose of zoledronic acid 5 mg plus daily teriparatide 20 µg was compared to zoledronic acid alone or daily teriparatide alone. At 1 year, BMD in the lumbar spine improved significantly in the combination group compared to zoledronic acid alone, but was not different than teriparatide alone.[134] BMD in the total hip was increased in the combination group and significantly different from teriparatide alone, but not different from zoledronic acid alone.

Teriparatide has been used to treat and promote the healing of bisphosphonate or denosumab-induced osteonecrosis of the jaw.[135],[136] Weekly administration at different doses are being explored for the prevention of vertebral fractures.[137],[138]

Abaloparatide for 18 months was followed by alendronate 70 mg weekly in the ACTIVE extension trial.[139] The abaloparatide group and the placebo group from ACTIVE each received alendronate 70 mg weekly for 24 months (ABL/ALN vs PBO/ALN). In the 24-month period, the difference in radiographically determined vertebral compression fractures was significantly better for ABL/ALN (*N* = 2 [0.37%]) than PBO/ALN (*N* = 16 [2.82%]), *P* = .001. After 24 months, no significant difference was found for nonvertebral, clinical, and major osteoporotic fractures. When considering the entire study period of 43 months (ACTIVE and ACTIVE extension), the benefits of treatment with abaloparatide versus placebo were sustained after 24 months of alendronate 70 mg weekly and a significant difference

remained between groups for vertebral, nonvertebral, clinical, and major osteoporotic fractures.

Initial administration of teriparatide and abaloparatide should be given when the patient can sit or lie down as orthostatic hypotension may occur with the initial doses.[126],[130] Orthostatic hypotension may occur within 4 hours of administration and spontaneously resolves after a few minutes to hours for the first several doses. Patients should immediately sit or lie down if symptoms occur. Teriparatide should always be stored under refrigeration at 36 to 46 °F (2–8 °C) and injected immediately on removal from refrigeration. Time outside of the refrigerator should be minimized. After use, the pen should be recapped and protected from light and discarded after 28 days. Abaloparatide should be stored under refrigeration at 36 to 46 °F (2–8 °C) until use. After the first dose, it can be stored at room temperature 68 to 77 °F (20–25 °C) for up to 30 days. Doses should only be administered subcutaneously and not intramuscularly (IM) or IV.

Romosozumab

Romosozumab is a monoclonal antibody and sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal females at high risk for fracture.[140] Romosozumab is administered by a health care provider as two separate subcutaneous injections (105 mg/1.17 mL single-use prefilled syringe), one after the other, for a total dose of 210 mg. Sclerostin is a glycoprotein encoded by the *SOST* gene and secreted by osteocytes, which inhibits bone formation.[21],[141] Romosozumab inhibits the effect of sclerostin by stimulating osteoblastic activity and results in increased bone formation and decreased bone resorption, improving bone structure and strength.[140] Romosozumab is administered monthly for 12 months.

In a large clinical trial that included 7180 postmenopausal females with T-score of −2.5 to −3.5, monthly romosozumab was compared to matching placebo.[142] After 12 months, both groups received denosumab every 6 months for 12 months. Average age of patients

was 70.9 years. At 12 months, new vertebral fracture occurred in 0.5% in the romosozumab group and 1.8% in the placebo group, RR 0.27 (95% CI, 0.16–0.47). Clinical fractures occurred in 1.6% in the romosozumab group and 2.5% in the placebo group, HR 0.64 (95% CI, 0.46–0.89). Nonvertebral fractures occurred in 1.6% in the romosozumab group and 2.1% in the placebo group, HR 0.75 (95% CI, 0.53–1.05). At 24 months, after 12 months of denosumab, new vertebral fracture remained significantly lower (0.6% vs 2.5%, $P < .001$). Clinical fractures and nonvertebral fractures were lower in the romosozumab group, but the difference was not considered significant. At 12 months, romosozumab increased BMD by 13.3% at the total hip, 6.9% at the lumbar spine, and 5.9% at the femoral neck. Adverse effects were similar between romosozumab and placebo; hypersensitivity occurred in seven patients in the romosozumab group, and two instances of ONJ occurred after 12 months in the romosozumab group after denture fitting and tooth extraction procedures.

In a small phase 2 dosing study that included postmenopausal females with a T-score between −2.0 and −3.5, five different doses of romosozumab were compared to open-label oral alendronate (ALN) 70 mg weekly ($N = 47$) or teriparatide (TPTD) 20 μg subcutaneously (SC) once daily ($N = 46$).[143] Romosozumab 210 mg monthly for 12 months ($N = 49$) had significantly higher BMD gains at the lumbar spine (11.3%, 4.1%, 7.1%), total hip (4.1%, 1.9%, 1.3%), and femoral neck (3.7%, 1.2% 1.1%) than ALN or TPTD, respectively. No significant difference was found at the third of the radius.

Romosozumab is approved for the treatment of osteoporosis in postmenopausal females at high risk, but has been studied in males with positive results and significant improvement of BMD at the lumbar spine and total hip compared to placebo.[144]

Romosozumab should be administered in the abdomen, thigh, or upper arm by a health care provider as two separate subcutaneous injections, one after the other, to total 210 mg.[140] It should be stored under refrigeration at 36 to 46 °F (2–8 °C) until use and allowed to sit at room temperature for at least 30 minutes before administration.

Injection sites should be rotated. Serious cardiovascular risk was seen in phase 3 clinical trials warranting a boxed warning. The manufacturer states that romosozumab should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year because of the risks of myocardial infarction, stroke, and cardiovascular death.

Patients should continue to take adequate supplements of calcium and vitamin D during treatment. Arthralgia and headache are the most common adverse reactions, arthralgia being the most common problem that leads to discontinuation of treatment. Adverse effects also include injection-site reaction, hypersensitivity, hypocalcemia, ONJ, and atypical fracture. No dosage adjustments are required in patients with renal insufficiency, but the manufacturer recommends monitoring for hypocalcemia in patients with eGFR <30 mL/minute/1.73 m^2.

Injectable agents are considered for patients at high fracture risk like M.B. The goals of the therapy are to prevent fracture, improve strength, and prevent falls, and multiple options are available to help achieve these goals. Teriparatide, abaloparatide, and romosozumab are considered anabolic agents, which increase bone formation. Duration of administration is limited to 1 year for romosozumab and 2 years for PTH analogs. Duration of zoledronic acid should be assessed after 5 years, and duration with denosumab has been studied for up to 10 years. There are administration differences between agents: monthly versus biannually versus yearly. Denosumab and romosozumab, along with bisphosphonates, have been associated with ONJ and atypical fractures. Romosozumab has additional warnings of potential cardiovascular risk where PTH analogs have additional warnings of osteosarcoma. Risks should be communicated to patients, and decisions regarding appropriate therapy for patients like M.B. should be based on comorbidities, medical history, ease of administration or access for the patient, adverse effects, duration of treatment, and cost.

Glucocorticoid-Induced Osteoporosis

CASE 110-5

QUESTION 1: D.J. is a 56-year-old male who was diagnosed with Crohn disease 10 years ago. D.J. has been somewhat stable on methotrexate and sulfasalazine for the past 5 years. D.J. has experienced increased symptoms for the past week, which have been getting progressively worse. D.J. was hospitalized and started on parenteral corticosteroids and discharged on 60 mg/day of prednisone to slowly taper over 3 months. Because this is the third flare of his disease in 2 years, D.J.'s physician was concerned about the risk of osteoporosis. As a member of the health care team, you will meet with D.J. at his follow-up visit in a few days. During your meeting with D.J., he asks you why males have to worry about osteoporosis.

What explanation can you provide to D.J., including his risks, and outline patient-specific goals?

Systemic glucocorticoid therapy, such as prednisone, is one of the most common causes of secondary osteoporosis.[145] The risk of fracture increases at the start of therapy, is highest within 3 to 6 months, and decreases after discontinuation.[146] Fracture risk increases with increased dose and duration of therapy and is influenced by patient-specific risk factors such as low body mass, family history, age, race, or sex (see Case 110-1, Risk Factors). Glucocorticoids contribute to bone loss resulting in osteoporosis by reducing the life span of osteoblasts, increasing osteocyte apoptosis, decreasing the production of osteoprotegerin, and inhibiting estrogens and androgens. Glucocorticoids both reduce bone formation and increase bone resorption.

D.J. is at risk for substantial loss of bone mass because of a high dose of prednisone for an extended period of time. The goal while he is on glucocorticoid therapy would be to minimize bone loss. D.J. would be a candidate for pharmacologic therapy for the prevention of osteoporosis while taking prednisone. The minimum threshold for risk of osteoporosis according to NOF is 5 mg prednisone or equivalent daily for 3 months.[1] The NOF recommends BMD testing in adults with a condition such as rheumatoid arthritis, or those meeting this glucocorticoid threshold.

CASE 110-5, QUESTION 2: What medications are available to prevent osteoporosis-related fractures in D.J.?

Alendronate, risedronate, zoledronic acid, denosumab, and teriparatide are FDA approved for the treatment of glucocorticoid-induced osteoporosis (GIOP). The American College of Rheumatology (ACR) guidelines for the prevention and treatment of GIOP recommend optimal calcium and vitamin D intake and a lifestyle that includes a balanced diet, weight-bearing exercise, reduced alcohol intake, and smoking cessation.[146] All patients taking >2.5 mg/day for >3 months of prednisone or equivalent should be assessed for fall and fracture risk that includes using FRAX® for adults age 40 years and older. Treatment is recommended for patients who are at moderate and high risk of fracture. High-risk patients are those with a T-score of −2.5 or lower or FRAX® 10-year fracture risk of ≥20% (spine, hip, shoulder, wrist) or risk of ≥3% (hip) or those who are age 40 years and younger with a prior osteoporotic fracture. Moderate-risk patients include those with a T-score of −2.5 or lower or FRAX® 10-year fracture risk of 10% to 19% (spine, hip, shoulder, wrist) or risk of 1% to <3% (hip) or those who are age 40 years and younger with a Z-score < −3 or those continuing on glucocorticoid therapy ≥7.5 mg/day for ≥6 months.

Oral bisphosphonates are preferred and then zoledronic acid, teriparatide, or denosumab if oral agents are not tolerated. ACR suggests that raloxifene can be used for postmenopausal females if other medications are not appropriate.

BISPHOSPHONATES

A Cochrane systematic review was conducted to evaluate the benefits and risks of bisphosphonates for the prevention and treatment of GIOP in adults.[147] A total of 27 randomized controlled trials were included that addressed the prevention or treatment of GIOP in adults taking a mean steroid dose of ≥5.0 mg/day. Bisphosphonates significantly increased BMD of the lumbar spine (3.5%) and femoral neck (2.06%) and significantly reduced the risk

of vertebral fracture, RR 0.57 (95% CI, 0.35–0.91). Bisphosphonates resulted in fewer nonvertebral fractures, but results were not statistically significant. There was no significant difference of serious adverse effects for bisphosphonates compared to the control group.

When comparing oral bisphosphonates to IV zoledronic acid, two studies found that increases in BMD in the lumbar spine were significantly greater for zoledronic acid compared to risedronate 5 mg daily.[148,149]

Although daily doses of alendronate and risedronate are approved for the indication of GIOP, weekly doses are more frequently used in clinical practice and significantly reduce the incidence of fracture.[150] Weekly doses also improve adherence (see Case 110-5, Question 4: Adherence).

DENOSUMAB

Denosumab was assessed in the treatment of GIOP in a phase 3 study in two subpopulations.[151] Adults 18 years old and older who had received ≥7.5 mg daily prednisone or equivalent for either <3 months (glucocorticoid-initiating) or for ≥3 months (glucocorticoid-continuing) were included. Denosumab 60 mg SC every 6 months was compared to risedronate 5 mg PO daily for 24 months. Only 74.2% of the 290 glucocorticoid-initiating patients and 505 glucocorticoid-continuing patients completed the trial. After 24 months, denosumab significantly increased BMD compared to risedronate at the lumbar spine, total hip, femoral neck, and third of the radius; glucocorticoid-initiating population (4.5%, 3.1%, 2.5%, 1.5%) and glucocorticoid-continuing (3.2%, 2.5%, 1.8%, 1.6%), respectively. Fractures were reported in 8% of patients in the denosumab group and 9.1% in the risedronate and were not statistically different. Adverse events were similar for both interventions, but serious infection occurred in four patients taking risedronate, and atypical femoral fracture occurred in one patient in the denosumab group.

PARATHYROID HORMONE

Teriparatide is also approved for the treatment GIOP. A 36-month trial conducted by Saag et al compared teriparatide 20 µg subcutaneously daily versus alendronate 10 mg oral daily.[152] The study included 400 males and females, primarily with rheumatologic conditions. Teriparatide increased spinal BMD 7.2% versus 3.4% in the alendronate group after 18 months of therapy. Hip BMD increased 3.8% in the teriparatide group versus 2.4% in the alendronate group. Differences between groups were noted as early as 6 months. At 36 months, teriparatide continued to increase BMD in the spine, hip, and femoral neck to a greater extent than alendronate. There were fewer vertebral fractures in the teriparatide group (1.7%) than in the alendronate group (7.7%; *P* = .007). No significant difference in nonvertebral fractures was found between groups. A small (*N* = 95), 18-month trial compared teriparatide 20 µg subcutaneously daily to risedronate 35 mg weekly in males with a minimum of 3 months prior glucocorticoid use (median 6.4 years).[153] Significant increases in BMD from baseline were found in both treatment groups, but a significantly greater increase occurred with teriparatide (16.3% vs 3.8%; *P* = .004). No vertebral fractures occurred during the trial. A total of five patients in the risedronate group (10.6%) developed new clinical fractures, whereas no fractures occurred in the teriparatide group (*P* = .056).

Case 110-5, Question 3: What recommendations should D.J.'s clinician share with him for preventing osteoporosis?

Adequate dietary calcium and vitamin D are essential. Supplementation is recommended if needed to maintain dietary calcium 1000 to 1200 mg daily and vitamin D 800 to 1000 IU daily.[146] Lifestyle changes are encouraged in patients and include smoking cessation, reduced alcohol intake, and regular exercise.

BMD testing is recommended for D.J. as well as fracture risk assessment using FRAX®. If found at moderate to high risk of fracture, D.J. would be a candidate for bisphosphonate therapy. He could receive an oral bisphosphonate such as alendronate 70 mg

weekly or risedronate 35 mg weekly while taking prednisone. He should be counseled on the proper administration and adverse effects of bisphosphonates and receive a medication guide with the medication. (See Case 110-3, Question 2.)

D.J. should choose one day of the week he will remember to take his medication. It should be taken in the morning on an empty stomach with a full glass of water. He should remain upright and not eat or drink anything for at least 30 minutes after taking his dose.

CASE 110-5, QUESTION 4: How does adherence affect prevention or treatment of osteoporosis?

Osteoporosis is a major public health concern but is an asymptomatic disease until fracture occurs. Although many medications used to treat osteoporosis have the convenience of less frequent dosing, adherence is not optimal.[61] Potential barriers to adherence of osteoporosis medication include dosing frequency, side effects of medications, comorbid conditions, knowledge about osteoporosis, and cost.

Adherence in clinical trials does not typically reflect real-world patients. Of 18 randomized controlled trials that reported rates of adherence, the majority reported over 90%. Of 59 observational studies, adherence was substantially lower: 10 of 13 adherence studies reported rates below 50%; in studies using data from health plans, 35% to 52% of patients had an adherence rate of 80% or above; and in several marketing scans adherence above 80% ranged from 23% to 49%, and only 33.5% for teriparatide.

In a meta-analysis of bisphosphonate adherence including 15 observational studies (*N* = 704,134), the overall risk of fracture was estimated to be 46% higher when low adherence was compared to high adherence.[154] This meta-analysis was limited by heterogeneity and differences in the observational study designs.

A systematic review that included two separate searches of male osteoporosis included 18 studies related to adherence and 37 studies related to cost.[155] This systematic review also included

mostly observational studies and did not pool the data. Over a 1-year period, only 32% to 64% of males were above 80% adherent to the medication above. Overall, clinical outcomes were worse with nonadherence. The overall cost associated with osteoporotic fractures in males is not as high as in females, but four studies that explored direct and indirect costs found the overall cost per fracture in males is higher than in females.

A systematic review of 89 observational studies was conducted to summarize patient adherence and persistence to oral bisphosphonates for the treatment of osteoporosis.[156] For males and females, adherence and persistence decrease over time. Adherence at 1 year ranged from 31.7% to 72%, at 2 years 34.5% to 47.9%, and at 3 years 23% to 47.9%. Persistence was reported as the length of treatment without a gap in refills. The average persistence of oral bisphosphonates at 6 months ranged between 34.8% and 71.3%, at 1 year 17.65% and 74.8%, 2 years 12.9% and 60.6%, and 3 years, 21% and 40%. Weekly oral bisphosphonates users were found to have a significantly higher mean persistence than those who took medication daily. Persistence and adherence may be related to patient characteristics such as age, socioeconomic status, comorbidities, and concomitant medication such as glucocorticoids.

Oral bisphosphonates are first-line agents for the prevention and treatment of osteoporosis. Weekly doses improve adherence compared to daily doses; monthly doses do not improve adherence compared to weekly doses, and monthly adherence may be slightly lower.[157-159]

Although the consequence of poor adherence is an estimate, it makes sense that promoting adherence will improve the effect of bisphosphonates and is important to achieve the results that are reported in clinical trials.

OSTEOPOROSIS IN MALES

CASE 110-6

Question 1: M.B.'s husband, J.B., is 77 years old and presents to his physician for a routine physical examination. J.B.'s wife has osteoporosis, and his daughter has low bone mass. J.B. would like to know if males develop osteoporosis.

Should he be tested for osteoporosis?

The NOF estimates that ~10 million Americans have osteoporosis and that 2 million are males.[1,160] An additional 12 million males are at risk for osteoporosis. The prevalence in males increases later in life, with the greatest increase seen at age 80.[161] The age-adjusted prevalence of osteoporosis at either the femoral neck or lumbar spine differs by race (4% non-Hispanic White males; 9% other races) as does the prevalence of low bone mass (24% non-Hispanic Black males; 39% non-Hispanic White males). Approximately 80,000 males will break a hip each year, and mortality rates after hip fracture are higher in males than in females.[160]

In an Endocrine Society Clinical Practice Guideline for Osteoporosis in Men, Watts et al[24] suggest BMD testing for all males age 70 and older; males with a history of fracture after age 50; and in males age 50 to 69 with conditions or disease states such as delayed puberty, alcohol abuse, smoking, hypogonadism, hyperparathyroidism, hyperthyroidism, chronic obstructive pulmonary disease (COPD), and glucocorticoid or gonadotropin hormone–releasing hormone (GnRH) agonists use.

J.B. is over age 70 and should have a DEXA of the spine and hip to measure BMD.[1,24] When a spine or hip BMD is not possible and in males receiving androgen-deprivation therapy (ADT) or with hyperparathyroidism, a DEXA of the forearm may be measured.

The same WHO criteria that was established for females is used to diagnose osteoporosis in males (T-score ≤ −2.5).[1]

Case 110-6, Question 2: J.B. knows that BMD loss in both his wife and daughter has been attributed to a decrease in hormones. Is hormone loss the same cause of osteoporosis in males?

Many risk factors contribute to osteoporosis in males (Table 110-1); however, a decrease in androgen and estrogen production are the primary hormonal contributors to the development of osteoporosis in this population.[162]

Androgens and Estrogens

Androgen production, specifically, serum testosterone concentrations, decreases with age. These decreased concentrations are thought to decrease bone formation and increase resorption. Testosterone has been linked to decreases in BMD, whereas dihydrotestosterone has not been linked.[163] Despite testosterone's importance for skeletal health in males, research now suggests that estrogen may play a more important role in skeletal biology. Two genes, ER-α and aromatase, are required for estrogen effects; ER-α is found on osteoblasts, osteoclasts, and stem cells in bone. Aromatase is present in osteoblasts and stem cells in bone. The absence of these genes results in an inability to convert androgen into estrogen. Replacement of estrogen in aromatase deficiency showed significant increases in bone mass and markers of bone turnover normalized.

Case 110-6, Question 3: Should J.B. be given supplementation for hypogonadism if his testosterone levels are low?

Hypogonadism may be a major contributor of bone loss in adult males and may increase the risk of fracture.[164] If a complete history and physical suggests a specific cause for osteoporosis, it would be appropriate for J.B.'s provider to order more tests including serum testosterone levels and replace testosterone if indicated, along with treatment for osteoporosis.[24]

Case 110-6, Question 4: If it is determined that J.B. has osteoporosis, should he receive calcium and vitamin D?

All males who are at risk for osteoporosis such as J.B. or who have osteoporosis should receive 1000 to 1200 mg of calcium daily through their diet and supplementation if necessary.[24] A 25(OH)D level should be drawn and, if indicated, J.B. should receive vitamin D to achieve a level of at least 30 ng/mL.

Case 110-6, Question 5: What therapies are available to treat osteoporosis in males?

Alendronate, risedronate, zoledronic acid, teriparatide, and denosumab are approved for the treatment of osteoporosis in males (Table 110-8). Romosozumab has been studied in males with osteoporosis in a phase 3 clinical trial.[144]

In a 2-year double-blind trial, 241 males with osteoporosis were randomized to receive either alendronate 10 mg daily or placebo.[165] One-third of the population had low serum-free testosterone levels. BMD increased by 7.1% versus 1.8% in the lumbar spine, 2.5% versus −0.1% in the femoral neck, and 2% versus 0.4% in the total body for alendronate and placebo groups, respectively. The incidence of new vertebral fractures was less in the alendronate group (0.8%) when compared with placebo (7.1%), and a smaller decrease in height was observed in the alendronate group (0.6 mm) as compared to placebo (2.4 mm).

In a 2-year double-blind, placebo-controlled trial, 284 males were randomly assigned in a 2:1 fashion to receive risedronate 35 mg weekly or placebo.[166] All patients received calcium and vitamin D supplementation. Lumbar spine BMD increased 4.5% over placebo in the risedronate group. There were no differences between groups in vertebral and nonvertebral fractures, but bone turnover markers were significantly lower in the risedronate group.

In a multicenter, double-blind, active-controlled, parallel-group study of osteoporosis, 302 males ages 25 to 85 were randomly assigned to receive once-yearly zoledronic acid 5 mg IV infusion or oral alendronate 70 mg weekly and followed for 2 years.[167] All patients received calcium and vitamin D supplementation. The

results of the study confirmed noninferiority of zoledronic acid to alendronate with similar BMD response and suppression of bone turnover markers. BMD at the lumbar spine increased by 6.1% in the zoledronic acid group versus 6.2% in the alendronate group with other sites showing similar BMD increases between groups.

Orwoll et al also conducted a multicenter, randomized, double-blind, active-controlled trial in 437 males ages 30 to 85 with BMD <2 SD lower than the young adult male mean BMD.[168] Patients received teriparatide 20 μg subcutaneously daily, 40 μg subcutaneously daily, or placebo with calcium and vitamin D supplementation for a median duration of 11 months. Lumbar spine BMD increases were noted after 3 months with increases of 5.9% in the 20-μg group and 9.0% in the 40-μg group by study end. Increases were also seen in bone turnover markers in the 20-μg and 40-μg groups. The study was originally planned to be a 2-year study, but it was stopped early after findings of osteosarcomas in rats during routine testing.

A randomized controlled trial was conducted in males ages 55 to 90 years with a T-score ≤ −2.5, or a T-score of ≤ −1.5 with fragility fracture, to determine the safety and efficacy of romosozumab.[144] A total of 245 patients with a mean age of 72 years received either romosozumab 210 mg SC monthly or matching placebo along with 500 to 1000 mg of calcium and 600 to 800 IU of vitamin D daily. After 12 months, BMD was significantly higher in the romosozumab group compared to placebo; 12.1% versus 1.2%; $P < .001$ in the lumbar spine, 2.5% versus −0.5%; $P < .001$ in the total hip, and femoral neck 2.2% versus −0.2%; $P < .001$. Fractures occurred in 1.8% in the romosozumab group and 2.5% in the placebo group. Injection-site reactions were greater in the romosozumab group than placebo, 5.5% versus 3.7%, respectively. Cardiovascular serious adverse events were greater in the romosozumab group than placebo 4.9% versus 2.5%, respectively. One cardiovascular death occurred in each group within 12 months, and one additional death occurred in the romosozumab group in the 3-month follow-up treatment.

Fewer studies are conducted in males with osteoporosis, but meta-analyses confirm positive effects from antiresorptive and anabolic medication compared to placebo in males with

osteoporosis.[169],[170] More research is needed on vertebral and nonvertebral fractures as a primary end point in studies that include males.

Case 110-6, Question 6: When is pharmacologic treatment recommended?

Pharmacologic therapy is indicated in males who are diagnosed with osteoporosis, have low bone mass in addition to a 10-year risk of hip fracture ≥3% using FRAX®, have had a hip or vertebral fracture without major trauma, and those who are on long-term glucocorticoid therapy (>7.5 mg/day of prednisone or equivalent).[24]

The Endocrine Society recommends monitoring DEXA at the spine and hip every 1 to 2 years to evaluate treatment and bone turnover markers at 3 to 6 months after starting therapy.

J.B. should maintain adequate dietary calcium and vitamin D intake. Supplementation is recommended if needed to maintain dietary calcium 1200 mg daily and vitamin D 600 IU. Lifestyle changes are encouraged in patients and include smoking cessation, reduced alcohol intake, and regular exercise.

KEY REFERENCES AND WEBSITES

A full list of references for this chapter can be found at http://thepoint.lww.com/AT12e. Below are the key websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the website.

Key References

Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 update. *Endocr Pract.* 2020;26(suppl 1):1–46. doi:10.4158/GL-2020-0524SUPPL (23)

Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int.* 2014;25(10):2359–2381. doi:10.1007/s00198-014-2794-2 (1)

Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. *Menopause.* 2021;28(9):973–997. doi:10.1097/GME.0000000000001831 (32)

McCloskey E. FRAX® *Identifying People at High Risk of Fracture WHO Fracture Risk Assessment Tool, a New Clinical Tool for Informed Treatment Decisions*. International Osteoporosis Foundation; 2009. https://www.osteoporosis.foundation/sites/iofbonehealth/files/2020-04/FRAX-Identifying-People-At-High-Risk-of-Fractures.pdf (40)

Siris ES, Adler R, Bilezikian J, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. *Osteoporos Int.* 2014;25(5):1439–1443. (2)

The International Society for Clinical Densitometry. 2019 ISCD official positions adult. https://iscd.app.box.com/s/5r713cfzvf4gr28q7zdccg2i7169fv86 (39)

Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(6): 1802–1822. doi:10.1210/jc.2011-3045 (24)

Key Websites

International Osteoporosis Foundation. https://www.osteoporosis.foundation/

National Osteoporosis Foundation. NOF.org

The International Society for Clinical Densitometry. http://www.iscd.org

COMPLETE REFERENCES CHAPTER 110 OSTEOPOROSIS

1. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10):2359–2381. doi:10.1007/s00198-014-2794-2
2. Siris ES, Adler R, Bilezikian J, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. *Osteoporos Int*. 2014;25(5):1439–1443.
3. Drake MT, Clarke BL, Lewiecki EM. The pathophysiology and treatment of osteoporosis. *Clin Ther*. 2015;37(8):1837–1850. doi:10.1016/j.clinthera.2015.06.006

4. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab*. 2008;93(3):861–868.
5. Emkey GR, Epstein S. Secondary osteoporosis: pathophysiology & diagnosis. *Best Pract Res Clin Endocrinol Metab*. 2014;28(6):911–935. doi:10.1016/j .beem.2014.07.002
6. Kanis JA, On behalf of the World Health Organization Scientific Group. *Assessment of Osteoporosis at the Primary Health-Care Level. Technical Report*. World Health Organization Collaborating Centre for Metabolic Bone Diseases; 2007. Accessed September 7, 2020. https://www.sheffield.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf
7. American Academy of Orthopaedic Surgeons. Osteoporosis as a National Public Health Priority Position Statement. https://www.aaos.org/contentassets/1cd7f41417ec4dd4b5c4c48532183b96/1113-osteoporosis-bone-health-in-adults-as-a-national-public-health-priority.pdf
8. Cauley JA. Defining ethnic and racial differences in osteoporosis and fragility fractures. *Clin Orthop*. 2011;469(7):1891–1899. doi:10.1007/s11999-011-1863-5
9. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29(11):2520–2526. doi:10.1002/jbmr.2269
10. Looker AC, Sarafrazi Isfahani N, Fan B, Shepherd JA. Trends in osteoporosis and low bone mass in older US adults, 2005–2006 through 2013–2014. *Osteoporos Int*. 2017;28(6):1979–1988. doi:10.1007/s00198-017-3996-1
11. International Osteoporosis Foundation. Facts and statistics. Accessed September 4, 2020. https://www.iofbonehealth.org/facts-statistics#category-14
12. Becker DJ, Kilgore ML, Morrisey MA. The societal burden of osteoporosis. *Curr Rheumatol Rep*. 2010;12(3):186–191. doi:10.1007/s11926-010-0097-y
13. Clarke B. Normal bone anatomy and physiology. *Clin J Am Soc Nephrol*. 2008;3(suppl 3):S131–S139. doi:10.2215/CJN.04151206
14. Kini U, Nandeesh B. Physiology of bone formation, remodeling, and metabolism. In: Fogelman I, Gnanasegaran G, Van der Wall H, eds. *Radionuclide and Hybrid Bone Imaging*. Springer; 2012.
15. Khosla S, Melton LJ, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? *J Bone Miner Res*. 2011;26(3):441–451. doi:10.1002/jbmr.262
16. Vandenput L, Lorentzon M, Sundh D, et al. Serum estradiol levels are inversely associated with cortical porosity in older men. *J Clin Endocrinol Metab*. 2014;99(7):E1322–E1326. doi:10.1210/jc.2014-1319

17. Khosla S, Melton LJ, Atkinson EJ, O'Fallon WM. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. *J Clin Endocrinol Metab*. 2001;86(8):3555–3561. doi:10.1210/jcem.86.8.7736
18. Nicks KM, Fowler TW, Gaddy D. Reproductive hormones and bone. *Curr Osteoporos Rep*. 2010;8(2):60–67. doi:10.1007/s11914-010-0014-3
19. Shetty S, Kapoor N, Bondu JD, Thomas N, Paul TV. Bone turnover markers: emerging tool in the management of osteoporosis. *Indian J Endocrinol Metab*. 2016;20(6):846–852. doi:10.4103/2230-8210.192914
20. Miller PD. Denosumab: anti-RANKL antibody. *Curr Osteoporos Rep*. 2009;7(1):18–22.
21. Siddiqui JA, Partridge NC. Physiological bone remodeling: systemic regulation and growth factor involvement. *Physiology*. 2016;31(3):233–245. doi:10.1152/physiol.00061.2014
22. Ross AC, Taylor C, Yaktine A, Del Valle H, eds. *Institute of Medicine Committee to Review Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press; 2011.
23. Camacho PM, Petak SM, Binkley N, et al. American association of clinical endocrinologists/American college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis —2020 update. *Endocr Pract*. 2020;26(suppl 1):1–46. doi:10.4158/GL-2020-0524SUPPL
24. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(6):1802–1822. doi:10.1210/jc.2011-3045
25. Allen S, Forney-Gorman A, Homan M, Kearns A, Kramlinger A, Sauer M. Institute for Clinical Systems Improvement. Diagnosis and treatment of osteoporosis. Updated July 2017. Accessed September 9, 2020. https://www.icsi.org/wp-content/uploads/2019/01/Osteo.pdf
26. De Laet C, Kanis JA, Odén A, et al. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int*. 2005;16(11):1330–1338. doi:10.1007/s00198-005-1863-y
27. Bijelic R, Milicevic S, Balaban J. The influence of non-preventable risk factors on the development of osteoporosis in postmenopausal women. *Mater Socio-Medica*. 2019;31(1):62–65. doi:10.5455/msm.2019.31.62-65
28. Syed FA, Ng AC. The pathophysiology of the aging skeleton. *Curr Osteoporos Rep*. 2010;8(4):235–240. doi:10.1007/s11914-010-0035-y
29. Marini F, Brandi ML. Genetic determinants of osteoporosis: common bases to cardiovascular diseases? *Int J Hypertens.* 2010;2010:394579. doi:10.4061/2010/394579
30. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev*. 2011;(Issue 7):CD000333. doi:10.1002/14651858.CD000333.pub2

31. U.S. Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General. U.S. Department of Health and Human Services, Office of the Surgeon General; 2004. https://www.ncbi.nlm.nih.gov/books/NBK45513/
32. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. *Menopause*. 2021;28(9):973–997. doi:10.1097/GME.0000000000001831
33. National Institutes of Health Office of Dietary Supplements. Nutrient recommendations: dietary reference intakes (DRI). Accessed May 26, 2015. http://ods.od.nih.gov/Health_Information/Dietary_Reference_Intakes.aspx
34. National Institutes of Health (NIH) Office of Dietary Supplements. Dietary supplement fact sheets. Accessed September 17, 2020. http://ods.od.nih.gov/factsheets/list-all/
35. Orchard TS, Larson JC, Alghothani N, et al. Magnesium intake, bone mineral density, and fractures: results from the women's health initiative observational study. *Am J Clin Nutr*. 2014;99(4):926–933. doi:10.3945/ajcn.113.067488
36. Falcone TD, Kim SSW, Cortazzo MH. Vitamin K: fracture prevention and beyond. *PM&R*. 2011;3(6):S82–S87.
37. Iwamoto J. Vitamin K_2 therapy for postmenopausal osteoporosis. *Nutrients*. 2014;6(5):1971–1980. doi:10.3390/nu6051971
38. Booth SL, Dallal G, Shea MK, Gundberg C, Peterson JW, Dawson-Hughes B. Effect of vitamin K supplementation on bone loss in elderly men and women. *J Clin Endocrinol Metab*. 2008;93(4):1217–1223. doi:10.1210/jc.2007-2490
39. The International Society for Clinical Densitometry. 2019 ISCD official positions adult. Accessed September 17, 2020. https://iscd.app.box.com/s/5r713cfzvf4gr28q7zdccg2i7169fv86
40. McCloskey E. FRAX® Identifying People at High Risk of Fracture WHO Fracture Risk Assessment Tool, a New Clinical Tool for Informed Treatment Decisions. International Osteoporosis Foundation (IOF); 2009. https://www.osteoporosis.foundation/sites/iofbonehealth/files/2020-04/FRAX-Identifying-People-At-High-Risk-of-Fractures.pdf
41. WHO FRAX web site. FRAX adjusted for TBS. Accessed August 8, 2022. https://www.sheffield.ac.uk/TBS/
42. Hans D, Šten ˇ ová E, Lamy O. The trabecular bone score (TBS) complements DXA and the FRAX as a fracture risk assessment tool in routine clinical practice. *Curr Osteoporos Rep*. 2017;15(6):521–531. doi:10.1007/s11914-017-0410-z
43. Ettinger B, Grady D. The waning effect of postmenopausal estrogen therapy on osteoporosis. *N Engl J Med*. 1993;329(16):1192–1193. doi:10.1056/NEJM199310143291610

44. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA*. 2001; 286(22):2815–2822.
45. Banks E, Beral V, Reeves G, Balkwill A, Barnes I, Million Women Study Collaborators. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA*. 2004;291(18):2212–2220. doi:10.1001/jama.291.18.2212
46. Cauley JA. The women's health initiative: hormone therapy and calcium/vitamin D supplementation trials. *Curr Osteoporos Rep*. 2013;11(3):171–178. doi:10.1007/s11914-013-0150-7
47. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. *JAMA*. 2013;310(13):1353–1368. doi:10.1001/jama.2013.278040
48. Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley SB. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. *Control Clin Trials*. 1998;19(4):314–335.
49. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: heart and estrogen/progestin replacement study follow-up (HERS II) [published correction appears in *JAMA*. 2002;288:1064]. *JAMA*. 2002;288(1):49–57.
50. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the women's health initiative randomized trial. *JAMA*. 2003;290(13):1729–1738. doi:10.1001/jama.290.13.1729
51. PREMPRO (Conjugated Estrogens/Medroxyprogesterone Acetate Tablets) PREMPHASE (Conjugated Estrogens plus Medroxyprogesterone Acetate Tablets). Package insert. Wyeth Pharmaceuticals Inc, a subsidiary of Pfizer Inc; 2015.
52. Hu ZC, Tang Q, Sang CM, et al. Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomised controlled trials. *BMJ Open*. 2019;9(10):e024595. doi:10.1136/bmjopen-2018-024595
53. Avenell A, Mak JCS, O'Connell D. Vitamin D and Vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev*. 2014;(4):CD000227. doi:10.1002/14651858.CD000227.pub4
54. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. *Lancet Diabetes Endocrinol*. 2018;6(11):847–858. doi:10.1016/S2213-8587(18)30265-1
55. Yao P, Bennett D, Mafham M, et al. Vitamin D and calcium for the prevention of fracture: a systematic review and meta-analysis. *JAMA Netw Open*.

2019;2(12):e1917789. doi:10.1001/jamanetworkopen.2019.17789
56. Drug Facts and Comparisons. Facts & Comparisons. *Bisphosphonate:* Summary of Indications. Wolters Kluwer Health, Inc; 2020. Accessed September 15, 2020. http://online.factsandcomparisons.com
57. Maraka S, Kennel KA. Bisphosphonates for the prevention and treatment of osteoporosis. *BMJ*. 2015;351:h3783. doi:10.1136/bmj.h3783
58. Naylor KE, Jacques RM, Paggiosi M, et al. Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: the TRIO study. *Osteoporos Int*. 2015;27(1):21–31. doi:10.1007/s00198-015-3145-7
59. Fosamax (Alendronate). Package insert. MERCK & CO, INC; 2013.
60. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD001155. doi:10.1002/14651858.CD001155.pub2
61. Crandall C, Newberry SJ, Gellad W, et al. *Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of a 2007 Report.* Comparative Effectiveness Review No 53 (Prepared by Southern California Evidence-based Practice Center under Contract No HHSA-290-2007-10062-I). Agency for Healthcare Research and Quality; 2012. https://effectivehealthcare.ahrq.gov/products/osteoporosis-bone-fracture
62. Reginster JY. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the mobile study. *Ann Rheum Dis*. 2006;65(5):654–661. doi:10.1136/ard.2005.044958
63. Delmas PD, Adami S, Strugala C, et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum*. 2006;54(6):1838–1846. doi:10.1002/art.21918
64. Boniva (Ibandronate). Package insert. Genentech USA, Inc; 2015.
65. Chesnut CH III, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res*. 2004;19(8):1241–1249. doi:10.1359/JBMR.040325
66. Murad MH, Drake MT, Mullan RJ, et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2012;97(6):1871–1880. doi:10.1210/jc.2011-3060
67. Delmas PD, Benhamou CL, Man Z, et al. Monthly dosing of 75 Mg risedronate on 2 consecutive days a month: efficacy and safety results. *Osteoporos Int*. 2008;19(7):1039–1045. doi:10.1007/s00198-007-0531-9
68. McClung MR, Benhamou CL, Man Z, et al. A novel monthly dosing regimen of risedronate for the treatment of postmenopausal osteoporosis: 2-year data. *Calcif Tissue Int*. 2013;92(1):59–67. doi:10.1007/s00223-012-9668-4

69. Delmas PD, McClung MR, Zanchetta JR, et al. Efficacy and safety of risedronate 150 Mg once a month in the treatment of postmenopausal osteoporosis. *Bone*. 2008;42(1):36–42. doi:10.1016/j.bone.2007.09.001
70. Actonel (Risedronate). Package insert. Warner Chilcott Pharmaceuticals Inc; 2015.
71. Wells GA, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD004523. doi:10.1002/14651858.CD004523.pub3
72. McClung M, Miller P, Recknor C, Mesenbrink P, Bucci-Rechtweg C, Benhamou CL. Zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass: a randomized controlled trial. *Obstet Gynecol*. 2009;114(5):999–1007. doi:10.1097/AOG.0b013e3181bdce0a
73. Reclastl (Zoledronic Acid). Package insert. Novartis Pharmaceutical Corporation; 2015.
74. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809–1822. doi:10.1056/NEJMoa067312
75. Johnson BE. A once-yearly IV infusion of zoledronic acid prevented fractures in postmenopausal women with osteoporosis. *ACP J Club*. 2007;147(2):31.
76. Davis S, Martyn-St James M, Sanderson J, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. *Health Technol Assess*. 2016;20(78):1–406. doi:10.3310/hta20780
77. Diab DL, Watts NB. Use of drug holidays in women taking bisphosphonates. *Menopause*. 2014;21(2):195–197. doi:10.1097/GME.0b013e31829ef343
78. Rodan G, Reszka A, Golub E, Rizzoli R. Bone safety of long-term bisphosphonate treatment. *Curr Med Res Opin*. 2004;20(8):1291–1300. doi:10.1185 /030079904125004475
79. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the fracture intervention trial long-term extension (FLEX): a randomized trial. *JAMA*. 2006;296(24):2927–2938. doi:10.1001/jama.296.24.2927
80. Miller PD, Recker RR, Reginster JY, et al. Efficacy of monthly oral ibandronate is sustained over 5 years: the MOBILE long-term extension study. *Osteoporos Int*. 2012;23(6):1747–1756. doi:10.1007/s00198-011-1773-0
81. McClung MR, Wasnich RD, Hosking DJ, et al. Prevention of postmenopausal bone loss: six-year results from the early postmenopausal intervention cohort study. *J Clin Endocrinol Metab*. 2004;89(10):4879–4885. doi:10.1210/jc.2003-031672
82. Black DM, Reid IR, Cauley JA, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to

the HORIZON-pivotal fracture trial (PFT). *J Bone Miner Res*. 2015;30(5):934–944. doi:10.1002/jbmr.2442

83. Durchschlag E, Paschalis EP, Zoehrer R, et al. Bone material properties in trabecular bone from human iliac crest biopsies after 3- and 5-year treatment with risedronate. *J Bone Miner Res*. 2006;21(10):1581–1590. doi:10.1359/jbmr.060701
84. Diab DL, Watts NB. Bisphosphonate drug holiday: who, when and how long. *Ther Adv Musculoskelet Dis*. 2013;5(3):107–111. doi:10.1177/1759720X13477714
85. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of Zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res*. 2012;27(2):243–254. doi:10.1002/jbmr.1494
86. U.S. Food & Drug Administration. Drug Safety and Availability—Medication Guides. Accessed June 4, 2015. http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm
87. Aschenbrenner DS. An FDA follow-up on bisphosphonates and atrial fibrillation. Am J Nurs. 2009;109(3):29. https://journals.lww.com/ajnonline/Fulltext/2009/03000/AN_FDA_FOLLOW_UP_ON_BISPHOSPHONATES_AND_ATRIAL.28.aspx
88. U.S. Food & Drug Administration. FDA Drug Safety Communication: safety update for osteoporosis drugs, bisphosphonates, and atypical fractures. Published June 28, 2019. Accessed August 9, 2022. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-safety-update-osteoporosis-drugs-bisphosphonates-and-atypical
89. Lee S, Yin RV, Hirpara H, et al. Increased risk for atypical fractures associated with bisphosphonate use. *Fam Pract*. 2015;32(3):276–281. doi:10.1093/fampra/cmu088
90. Park-Wyllie LY, Mamdani MM, Juurlink DN, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA*. 2011;305(8):783–789. doi:10.1001/jama.2011.190
91. Drug Facts and Comparisons. Facts & Comparisons. Wolters Kluwer Health, Inc; 2011. Accessed June 18, 2015. http://online.factsandcomparisons.com
92. Martinkovich S, Shah D, Planey SL, Arnott JA. Selective estrogen receptor modulators: tissue specificity and clinical utility. *Clin Interv Aging*. 2014;9:1437–1452. doi:10.2147/CIA.S66690
93. Messalli EM, Scaffa C. Long-term safety and efficacy of raloxifene in the prevention and treatment of postmenopausal osteoporosis: an update. *Int J Womens Health*. 2010;1:11–20.
94. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium

in postmenopausal women. *N Engl J Med*. 1997;337(23):1641–1647. doi:10.1056/NEJM199712043372301

95. Jolly EE, Bjarnason NH, Neven P, et al. Prevention of osteoporosis and uterine effects in postmenopausal women taking raloxifene for 5 years. *Menopause*. 2003;10(4):337–344. doi:10.1097/01.GME.0000058772.59606.2A
96. Sambrook PN, Geusens P, Ribot C, et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) International. *J Intern Med*. 2004;255(4):503–511. doi:10.1111/j.1365-2796.2004.01317.x
97. Evista (Raloxifene). Package insert. Eli Lilly and Company; 2015.
98. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282(7):637–645.
99. Riggs BL, Melton LJ. Bone turnover matters: the raloxifene treatment paradox of dramatic decreases in vertebral fractures without commensurate increases in bone density. *J Bone Miner Res*. 2002;17(1):11–14. doi:10.1359/jbmr.2002.17.1.11
100. DUAVEE—Estrogens, Conjugated and Bazedoxifene Acetate Tablet, Film Coated. Package insert. Wyeth Pharmaceuticals Inc, a subsidiary of Pfizer Inc; 2013.
101. Briggs AM, Greig AM, Wark JD. The vertebral fracture cascade in osteoporosis: a review of aetiopathogenesis. *Osteoporos Int*. 2007;18(5):575–584. doi:10.1007/s00198-006-0304-x
102. Oleksik AM, Ewing S, Shen W, van Schoor NM, Lips P. Impact of incident vertebral fractures on health related quality of life (HRQOL) in postmenopausal women with prevalent vertebral fractures. *Osteoporos Int*. 2005;16(8):861–870. doi:10.1007/s00198-004-1774-3
103. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA*. 2001;285(3):320–323.
104. Curtis JR, Arora T, Matthews RS, et al. Is withholding osteoporosis medication after fracture sometimes rational? a comparison of the risk for second fracture versus death. *J Am Med Dir Assoc*. 2010;11(8):584–591. doi:10.1016/j .jamda.2009.12.004
105. Faulkner KA, Cauley JA, Zmuda JM, et al. Higher 1,25-Dihydroxyvitamin D3 concentrations associated with lower fall rates in older community-dwelling women. *Osteoporos Int*. 2006;17(9):1318–1328. doi:10.1007/s00198-006-0071-8
106. Snijder MB, van Schoor NM, Pluijm SMF, van Dam RM, Visser M, Lips P. Vitamin D status in relation to one-year risk of recurrent falling in older men

and women. *J Clin Endocrinol Metab*. 2006;91(8):2980–2985. doi:10.1210/jc.2006-0510

107. Salles N. Basic mechanisms of the aging gastrointestinal tract. *Dig Dis*. 2007;25(2):112–117. doi:10.1159/000099474
108. Straub DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. *Nutr Clin Pract*. 2007;22(3):286–296.
109. Centers for Disease Control and Prevention; National Center for Injury Prevention and Control (NCIPC). Falls among older adults: an overview. 2015. Updated March 19, 2015. http://www.cdc.gov/HomeandRecreationalSafety/Falls/adultfalls.html
110. El-Khoury F, Cassou B, Charles MA, Dargent-Molina P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f6234. doi:10.1136/bmj.f6234
111. Panel on Prevention of Falls in Older Persons; American Geriatrics Society and British Geriatrics Society. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc*. 2011;59(1):148–157. doi:10.1111/j.1532-5415.2010.03234.x
112. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene; results from a 3-year randomized clinical trial. *JAMA*. 1999;282(7):637–645. doi:10.1001/jama.282.7.637
113. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the more trial. Multiple outcomes of raloxifene evaluation [published correction appears in *Breast Cancer Res Treat*. 2001 May;67(2):191]. *Breast Cancer Res Treat*. 2001;65(2):125–134.
114. Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (core) study. *J Bone Miner Res*. 2005;20(9):1514–1524. doi:10.1359/JBMR.050509
115. Lin T, Yan SG, Cai XZ, Ying ZM, Yuan FZ, Zuo X. Alendronate versus raloxifene for postmenopausal women: a meta-analysis of seven head-to-head randomized controlled trials. *Int J Endocrinol*. 2014;2014:1–16. doi:10.1155/2014/796510
116. Overman RA, Borse M, Gourlay ML. Salmon calcitonin use and associated cancer risk. *Ann Pharmacother*. 2013;47(12):1675–1684. doi:10.1177/1060028013509233
117. Miacalcin (Calcitonin-Salmon) Injection. Package insert. Novartis Pharmaceuticals Corporation; 2014.
118. Miacalcin (Calcitonin-Salmon) Nasal Spray. Package insert. Novartis Pharmaceuticals Corporation; 2014.

119. Knopp-Sihota JA, Newburn-Cook CV, Homik J, Cummings GG, Voaklander D. Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis. *Osteoporos Int*. 2012;23(1):17–38. doi:10.1007/s00198-011-1676-0
120. Prolia (Denosumab) Injection. Package insert. Amgen Inc; 2015.
121. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361(8):756–765. doi:10.1056/NEJMoa0809493
122. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res*. 2010;25(1):72–81. doi:10.1359/jbmr.090716
123. Seeman E, Delmas PD, Hanley DA, et al. microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. *J Bone Miner Res*. 2010;25(8):1886–1894. doi:10.1002/jbmr.81
124. Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. *Obstet Gynecol*. 2013;121(6):1291–1299. doi:10.1097/AOG.0b013e318291718c
125. Palacios S, Agodoa I, Bonnick S, et al. Treatment satisfaction in postmenopausal women suboptimally adherent to bisphosphonates who transitioned to denosumab compared with risedronate or ibandronate. *J Clin Endocrinol Metab*. 2015;100(3):E487–E492. doi:10.1210/jc.2014-3594
126. Forteo (Teriparatide [RDNA Origin] Injection). Package insert. Eli Lilly and Company; 2013.
127. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344(19):1434–1441. doi:10.1056/NEJM200105103441904
128. Vestergaard P, Jorgensen NR, Mosekilde L, Schwarz P. Effects of parathyroid hormone alone or in combination with antiresorptive therapy on bone mineral density and fracture risk-a meta-analysis. *Osteoporos Int*. 2007;18(1):45–57. doi:10.1007/s00198-006-0204-0
129. Miller PD, Hattersley G, Lau E, et al. Bone mineral density response rates are greater in patients treated with abaloparatide compared with those treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial. *Bone*. 2019;120:137–140. doi:10.1016/j.bone.2018.10.015
130. Tymlos (Abaloparatide) Injection. Package insert. Radius Health, Inc; 2017.
131. Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet*. 2013;382(9886):50–56. doi:10.1016/S0140-6736(13) 60856-9

132. Leder BZ, Tsai JN, Uihlein AV, et al. Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab*. 2014;99(5):1694–1700. doi:10.1210/jc.2013-4440
133. Cosman F, Wermers RA, Recknor C, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. *J Clin Endocrinol Metab*. 2009;94(10):3772–3780. doi:10.1210/jc.2008-2719
134. Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res*. 2011;26(3):503–511. doi:10.1002/jbmr.238
135. Kwon YD, Lee DW, Choi BJ, Lee JW, Kim DY. Short-term teriparatide therapy as an adjunctive modality for bisphosphonate-related osteonecrosis of the jaws. *Osteoporos Int*. 2012;23(11):2721–2725. doi:10.1007/s00198-011-1882-9
136. Neuprez A, Rompen E, Crielaard JM, Reginster JY. Teriparatide therapy for denosumab-induced osteonecrosis of the jaw in a male osteoporotic patient. *Calcif Tissue Int*. 2014;95(1):94–96. doi:10.1007/s00223-014-9858-3
137. Nakamura T, Sugimoto T, Nakano T, et al. Randomized Teriparatide [human parathyroid hormone (PTH) 1-34] Once-Weekly Efficacy Research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. *J Clin Endocrinol Metab*. 2012;97(9):3097–3106. doi:10.1210/jc.2011-3479
138. Fujita T, Fukunaga M, Itabashi A, Tsutani K, Nakamura T. Once-weekly injection of low-dose teriparatide (28.2 μg) reduced the risk of vertebral fracture in patients with primary osteoporosis. *Calcif Tissue Int*. 2014;94(2):170–175. doi:10.1007/s00223-013-9777-8
139. Leder BZ, Zapalowski C, Hu MY, et al. Fracture and bone mineral density response by baseline risk in patients treated with abaloparatide followed by alendronate: results from the phase 3 ACTIVExtend trial. *J Bone Miner Res*. 2019;34(12):2213–2219. doi:10.1002/jbmr.3848
140. EVENITY-Romosozumab-Aqqg Injection, Solution. Package insert. Amgen, Inc; 2020.
141. Nealy KL, Harris KB. Romosozumab: a novel injectable sclerostin inhibitor with anabolic and antiresorptive effects for osteoporosis. *Ann Pharmacother*. 2020;55(5):677–686. doi:10.1177/1060028020952764
142. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532–1543. doi:10.1056/NEJMoa1607948
143. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2014;370(5):412–420. doi:10.1056/NEJMoa1305224

144. Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab*. 2018;103(9):3183–3193. doi:10.1210/jc.2017-02163
145. Adami G, Saag KG. Glucocorticoid-induced osteoporosis: 2019 concise clinical review. *Osteoporos Int*. 2019;30(6):1145–1156. doi:10.1007/s00198-019-04906-x
146. Buckley L, Guyatt G, Fink HA, et al. American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis: ACR guideline for glucocorticoid-induced osteoporosis prevention and treatment. *Arthritis Rheumatol*. 2017;69(8):1521–1537. doi:10.1002/art.40137
147. Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. *Cochrane Database Syst Rev*. 2016;10:CD001347. doi:10.1002/14651858.CD001347.pub2
148. Reid DM, Devogelaer JP, Saag K, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2009;373(9671):1253–1263. doi:10.1016/S0140-6736(09)60250-6
149. Sambrook PN, Roux C, Devogelaer JP, et al. Bisphosphonates and glucocorticoid osteoporosis in men: results of a randomized controlled trial comparing zoledronic acid with risedronate. *Bone*. 2012;50(1):289–295. doi:10.1016/j .bone.2011.10.024
150. Thomas T, Horlait S, Ringe JD, et al. Oral bisphosphonates reduce the risk of clinical fractures in glucocorticoid-induced osteoporosis in clinical practice. *Osteoporos Int*. 2013;24(1):263–269. doi:10.1007/s00198-012-2060-4
151. Saag KG, Pannacciulli N, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: final results of a twenty-four–month randomized, double-blind, double-dummy trial. *Arthritis Rheumatol*. 2019;71(7):1174–1184. doi:10.1002/art.40874
152. Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum*. 2009;60(11):3346–3355. doi:10.1002/art.24879
153. Glüer CC, Marin F, Ringe JD, et al. Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. *J Bone Miner Res*. 2013;28(6):1355–1368. doi:10.1002/jbmr.1870
154. Imaz I, Zegarra P, González-Enríquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. *Osteoporos Int*. 2010;21(11): 1943–1951. doi:10.1007/s00198-009-1134-4

155. Mikyas Y, Agodoa I, Yurgin N. A systematic review of osteoporosis medication adherence and osteoporosis-related fracture costs in men. *Appl Health Econ Health Policy*. 2014;12(3):267–277. doi:10.1007/s40258-013-0078-1
156. Fatoye F, Smith P, Gebrye T, Yeowell G. Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review. *BMJ Open*. 2019;9(4):e027049. doi:10.1136/bmjopen-2018-027049
157. Weiss TW, Henderson SC, McHorney CA, Cramer JA. Persistence across weekly and monthly bisphosphonates: analysis of US retail pharmacy prescription refills. *Curr Med Res Opin*. 2007;23(9):2193–2203. doi:10.1185/030079907X226069
158. Briesacher BA, Andrade SE, Harrold LR, Fouayzi H, Yood RA. Adoption of once-monthly oral bisphosphonates and the impact on adherence. *Am J Med*. 2010;123(3):275–280. doi:10.1016/j.amjmed.2009.05.017
159. Fan T, Zhang Q, Sen SS. Persistence with weekly and monthly bisphosphonates among postmenopausal women: analysis of a US pharmacy claims administrative database. *Clin Outcomes Res*. 2013;5:589–595. doi:10.2147/CEOR.S39076
160. National Osteoporosis Foundation. Just for Men. Accessed October 2, 2020. https://www.nof.org/preventing-fractures/general-facts/just-for-men/
161. Looker A, Borrud L, Dawson-Hughes B, Wright N. Osteoporosis or Low Bone Mass at the Femur Neck or Lumbar Spine in Older Adults: United States, 2005–2008. NCHS Data Brief No 93. National Center for Health Statistics; 2012.
162. Khosla S. Update in male osteoporosis. *J Clin Endocrinol Metab*. 2010;95(1):3–10. doi:10.1210/jc.2009-1740
163. Khosla S, Melton LJ, Riggs BL. Clinical review 144: estrogen and the male skeleton. *J Clin Endocrinol Metab*. 2002;87(4):1443–1450. doi:10.1210/jcem.87.4.8417
164. Kanis JA, Bianchi G, Bilezikian JP, et al. Towards a diagnostic and therapeutic consensus in male osteoporosis. *Osteoporos Int*. 2011;22(11):2789–2798. doi:10.1007/s00198-011-1632-z
165. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med*. 2000;343(9):604–610. doi:10.1056/NEJM200008313430902
166. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. *J Bone Miner Res*. 2009;24(4): 719–725. doi:10.1359/jbmr.081214
167. Orwoll ES, Miller PD, Adachi JD, et al. Efficacy and safety of a once-yearly i.v. Infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized,

multicenter, double-blind, active-controlled study. *J Bone Miner Res*. 2010;25(10):2239–2250. doi:10.1002/jbmr.119

168. Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res*. 2003;18(1):9–17. doi:10.1359/jbmr.2003.18.1.9
169. Schwarz P, Jorgensen NR, Mosekilde L, Vestergaard P. The evidence for efficacy of osteoporosis treatment in men with primary osteoporosis: a systematic review and meta-analysis of antiresorptive and anabolic treatment in men. *J Osteoporos.* 2011;2011:1–9. doi:10.4061/2011/259818
170. Nayak S, Greenspan SL. Osteoporosis treatment efficacy for men: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2017;65(3):490–495. doi:10.1111/jgs.14668

Drug Index

Note: Page number followed by *f* and *t* indicates figures and tables, respectively.

A

Abacavir (ABC), 60*t*, 1669
for HIV, 1637*t*
Abatacept, 914, 926*t*, 927, 931, 932
Abciximab, 254
Abilify (*see* Aripiprazole)
Abiraterone, 2151–2152, 2153
Abreva (*see* Docosanol cream)
Acamprosate, 1970–1971
Acarbose, for type 2 diabetes, 1158, 1169
ACE inhibitors (*see* Angiotensin-converting enzyme (ACE) inhibitors)
Acetaldehyde, 1963
Acetaminophen, 46, 51, 1220
analgesic syndrome from, 639
for arthritis, 2287
for burns, 898
for dysmenorrhea, 1047
for end-of-life care, 89
for HAV, 1724
hepatitis and, 1732
for migraine headache, 1266
neonates and, 2215, 2222
for OA, 898, 901
for PDA, 2239
PegIFN therapy, 1740
for postoperative pain management, 1220
pregnancy and, 81, 976*t*
toxicity with, 81–84
Acetazolamide, 595

cryptococcal disease, 1695
and hypokalemia, 615*t*
Acid-related disorders, pharmacotherapy of drugs
antacids, 505
antacids and alginic acid, 505
bismuth salts, 509
H_2-receptor antagonists, 507
misoprostol, 509
PPI, 507–509
sucralfate, 509
Acitretin, for psoriasis, 874*t*, 877–878
Aclidinium bromide, for COPD, 439*t*
Acular (*see* Ketorolac)
Acupressure, 1007
Acupuncture, 1007
ACV (*see* Acyclovir (ACV))
Acyclovir (ACV), 776, 1700*t*, 1701
administration of, 1701–1702
adverse effects of, 1381*t*, 1698, 1699*t*
dosing of, 1383*t*
for genital herpes, 1585, 1586*t*
for herpes encephalitis, 1698–1699
for herpes labialis, 1701–1702
for herpes simplex virus, 1203, 1699, 1701
kidney failure, dosing of drugs, 705
oral administration, 1699
pharmacokinetics of, 1706*t*
for PHN, 1703, 1708
toxicity, 1708
against varicella infection, 1703
Acyclovir and Hydrocortisone cream (Xerese), 1702
Acyclovir cream (Zovirax), 1702
ADACEL, 1408
Adalimumab, 914, 923, 926*t*, 932
for inflammatory bowel disease, 553*t*
for PsA, 879
for RA, 914
for UC, 560
Adapalene, 867, 868
Adefovir dipivoxil, 1740
Adenosine, 338–339
Ado-trastuzumab emtansine, 491*t*
Adrenaclick, 469*t*
Aerosolized aztreonam, 481
Afatinib, 492*t*

Aflibercept, 1205
Afrezza, 1115, 1117
Afrin (*see* Oxymetazoline)
Aggressive insulin therapy, 473
Akynzeo (*see* Palonosetron; Netupitant)
Alanine aminopeptidase, 2053
Albendazole, 1773*t*
for ascariasis, 1773*t*
for enterobiasis, 1773*t*
for filariasis, 1773*t*
for giardiasis, 1773*t*
for hookworm, 1774*t*
for hydatid cysts, 1775*t*
for pinworm, 1776
Albumin, 379
in edema, 594
Albuterol, 407, 721*t*
for acute asthma, 407
for AECOPD, 1462
anxiety from, 1806*t*
for chronic asthma, 413
for COPD, 438, 439*t*
for end-of-life care, 89
for hyperkalemia, 620*t*
with ipratropium, 90
nebulization, 407, 619
respiratory acidosis and, 597
Alcaftadine (Lastacaft), 460*t*, 1201
Alcohol, 1679
and acute gout, 946
AF and, 331*t*
for BMD, 2335
diabetes and, 1112
GERD and, 526*t*
heartburn and, 1009
HF and, 290
hypertension and, 146
MI and, 220*t*
for osteoporosis, 2346
pulmonary embolism and, 203
for schizophrenia, 1853*t*
teratogenic effects, 1004*t*
variant angina and, 238
Aldesleukin, 491*t*
Aldosterone antagonists

for ACS, 246*t*
for HF, 281, 307
for hypertension, 147, 155*t*, 157*t*, 164
in left ventricular remodeling, 267
Alectinib, 492*t*
Alemtuzumab (Campath), 492*t*, 1265
monoclonal antibodies, 756
for MS, 1255
Alendronate, 2342–2343, 2343*t*
androgen deprivation therapy, 2155
dose, 2342
for end-of-life care, 90
Alfentanil, 2189*t*
Alfuzosin, 2320
Alirocumab, 134–136
Aliskiren, 133, 164*t*, 639
for hypertension, 147, 165
Allegra (*see* Fexofenadine)
Allopurinol, 60*t*, 947, 948*t*
for HF, 293
weight gain with, 2080
Allylamines, 1676
Almotriptan, 1273
Alocril (*see* Nedocromil)
Alogliptin, 1161
Alomide (*see* Lodoxamide)
Alosetron, 569
Aloxi (*see* Palonosetron)
α-adrenergic agonists, 526*t*
α-adrenergic blockers, 2302
α-blockers, 165
with β-blockers, 166
for hypertension, 147
Alphagan (*see* Brimonidine)
α_2-adrenergic agonist, 1949
α_2-agonists
for ADHD, 1941–1942
for developmental disorders, 1927
for hypertension, 166
Alprazolam (Xanax), 1310*t*, 1311, 1807*t*, 1828
for panic disorder, 1815
sedative-hypnotics, 1952
Alprostadil, 2330
Alrex (*see* Loteprednol)
Alteplase, for STEMI patients, 254

Altretamine, 492*t*
Aluminum hydroxide, 651*t*
Aluminum salts, 509
Amantadine (Symmetrel), 1247, 1286*t*, 1297
adverse effects, 1699*t*
for Akathisia, 1870*t*
for influenza, 1708–1709
for Parkinsonism, 1870
AmB (*see* Amphotericin B (AmB))
AmB formulation, 1695
Ambien, 1835*t*
Ambien CR, 1835*t*
Ambrisentan, 133, 954
Ameliorate, 1949
Amifostine, 491*t*, 2039
Amikacin (Amikin), 482*t*, 1372*t*
adverse effects of, 1379*t*
for CAPD-associated peritonitis, 1533*t*
for CNS infections, 1426*t*
for gram-negative aerobes, 1374*t*
for MAC, 1671
pharmacodynamic actions of, 49
for tuberculosis, 1484*t*
for UTI, 1553*t*
Amikin (*see* Amikacin)
Amiloride, 576, 618
for hypertension, 156
Aminobenzoates, 887–888
Aminoglycosides, 475, 481, 1788
adverse effects of, 1379*t*
for CNS infections, 1426*t*
extended-interval dosing of, 482
kidney failure, dosing of drugs, 700–701
for NEC, 2243
for neutropenic patients, 1619, 1620
for pneumonia, 1473–1474
for RMSF, 1794
for sepsis, 2243
for UTI, 1553*t*
Aminopenicillin, 442
Aminophylline, 2246
Aminosalicylates, 556*t*
Aminosyn, 837*t*
Aminosyn HBC, 837*t*
Aminosyn II, 837*t*

Aminosyn-RF, 837*t*
Amiodarone, 125*t*, 225
for ACS, 246*t*
adverse effects of, 343
for AF, 334–335
antiadrenergic effects of, 344
for cardiopulmonary arrest, 349–350
for HF, 316–317
and liver toxicity, 344
and MI, 342
for SuVT, 342–343
for tachycardia, 1873
for ventricular arrhythmias treatment, 258
Amitriptyline, 569, 1227, 1229*t*, 1276, 1280
for depressive disorders, 1891*t*, 1892*t*
Amlodipine, 125*t*, 162, 225
for chronic stable angina pectoris, 225
for vascular dementia, 2302
Amoxicillin (Amoxil), 514*t*, 519, 948*t*, 976*t*, 1372*t*, 1788, 2222
Amoxicillin/clavulanate
for CAPD-associated peritonitis, 1533*t*
for COPD, 436
and potassium clavulanate, 1544*t*
PPI and, 518–519
for skin and soft tissue infections, 1606
for UTI, 1544*t*
Amoxil (*see* Amoxicillin)
Amphetamine, 1939, 1955
for ADHD, 1940*t*
CNS stimulants, 1995
and lactation, 1035*t*
for schizophrenia, 1853, 1853*t*
Amphotericin
for CAPD-associated peritonitis, 1533*t*
and hypokalemia, 615*t*
nephrotoxicity by, 1454
Amphotericin B (AmB), 1676, 1676*t*, 2069
5-FC and, 1454
adverse effects of, 1384*t*, 1684–1687
for aspergillosis, 1692–1693
candida infections
AmB-associated renal dysfunction, 1683
dose and duration of therapy, 1681*t*, 1683, 1684
infusion-related reactions, 1684–1685
for cryptococcal meningitis, 1665

every-other-day regimens, 1684
formulations, 1686*t*
for histoplasmosis, 1687
intrathecal administration of, 1692
for leishmaniasis, 1774*t*
risk factor B, 1687
for sepsis, 2244*t*
Amphotericin B deoxycholate (AmBD), 1625
Ampicillin (Omnipen), 948*t*, 976*t*, 1372*t*, 2189*t*
for aerobic gram-positive cocci, 1373*t*
allergy, 716
for anaerobes, 1374*t*
for CAPD-associated peritonitis, 1533*t*
for chorioamnionitis, 1029
for CNS infections, 1426*t*
dosing of, 1383*t*
for enterococcal endocarditis, 1451*t*
for gram-negative aerobes, 1374*t*
for NEC, 2243
for sepsis, 2244, 2244*t*
for UTI, 1544*t*, 1552*t*
Ampicillin-sulbactam
for CAPD-associated peritonitis, 1533*t*
for chorioamnionitis, 1029
dosing of, 1383*t*
for UTI, 1552*t*
Amprenavir, 133, 976*t*
Amylase, and respiratory alkalosis, 1732
Amylin receptor agonists
adverse effects of, 1162
contraindications and precautions of, 1162–1163
dosage and clinical use, 1163
drug interactions, 1163
efficacy of, 1163
mechanism of action, 1162
pharmacokinetics of, 1162
Anabolic steroids, for acne, 867
Anakinra, 915–916, 926*t*, 932
Analgesia, 1218*t*
Analgesics
for acute gout, 946
for burn pain, 898
for tension-type headache, 1280
Anastrozole, 1053
Ancef (*see* Cefazolin)

Androgen deprivation therapy (ADT), 2147*t*, 2146–2148
Androgen receptor antagonists for acne, 869
Androgens
for acne, 867
teratogenic effects, 1004*t*
Anesthesia, 2165
Angiotensin-converting enzyme (ACE) inhibitors, 266, 727–728, 948*t*, 1239
for ACS, 246*t*
agents of choice, 295–298, 296*f*
angioedema and, 301–302, 727
angiotensin receptor blockers and, 285, 298–300
CAD and, 154
CKD and, 154
cough and, 728
diabetes and, 153–154
in HFrEF, 297*t*
and hydralazine–isosorbide, 312–313
hyperkalemia and, 300–301
for hypertension, 146–147, 157*t*, 160–161
induced cough, 300
kidney function and, 302
left ventricular dysfunction and, 154
for PAD, 174
for patients with CKD, 648
for pregestational diabetes, 1010
pregnancy and, 161
side effects of, 302
teratogenic effects, 1004*t*
Angiotensin receptor blockers (ARBs), 222, 245, 727–728, 1016, 1240
for ACS, 246*t*
and angioedema, 301–302, 728
CAD and, 154
chronic kidney disease and, 154
diabetes and, 153–154
in HF, 298–300, 298*t*
for hyperkalemia, 300–301
for hypertension, 147, 157*t*, 161, 161*t*
and kidney function, 302
left ventricular dysfunction and, 154
side effects of, 302
Angiotensin receptor-neprilysin inhibitor (ARNI), 286
Anidulafungin, 1676, 1676*t*
adverse effects of, 1381*t*
Antacids, 505, 507, 747, 2039, 2040
for dyspepsia, 510

and fluoroquinolones, 42
for GER, 2218, 2220*t*
in preventing SRMB, 537, 537*t*
Anthracycline, 491*t*
Anthralin, for psoriasis, 873*t*, 875
Anthranilates, 885*t*, 888
Antiandrogen (*see* Spironolactone)
Antibiotics, 481
for acne, 867
for acute bronchitis, 1459
adverse effects of, 1379–1382*t*
for AECOPD, 1461–1462
for biliary infections, 1528
in brain abscess, 1434
for *Campylobacter* infection, 1512
for CAP, 1463–1464
for CAPD-associated peritonitis, 1533*t*
for *Chlamydia trachomatis*, 956
for chorioamnionitis, 1029
for chronic *S. typhi* carriers, 1510
for CNS infections, 1426*t*
combination therapy, 1388
with corticosteroids, 860
costs of, 1379
CSF penetration characteristics of, 1424*t*
diarrhea from, 1518
dosing of, 481–483, 1379–1382, 1383–1386*t*
drug selection, 481
failure with, 1389
for GBS infection, 1028
for hospital-acquired pneumonia, 1470–1474
host factors and, 1389
for Lyme disease, 1788
for nontyphoidal salmonellosis, 1508
for nosocomial UTI, 1553*t*
oral, 868
pharmacokinetics/pharmacodynamics of, 1387–1388
pharmacologic factors, 1389
for PPROM, 1027
and protein binding, 1388
for pyelonephritis, 1551
for relapsed UTI, 1554
resistance rates, 519
route of administration, 1379
in SBP treatment, 1530

for shigellosis, 1511
STEC treatment and, 1518
for surgery, 1391–1400
for travelers' diarrhea, 1514–1515
for typhoid fever, 1510
for UTI, 1536–1537
for *V. cholerae* infections, 1506
for *V. parahaemolyticus* gastroenteritis, 1506
topical, 868
Anticholinergics, 1296*t*
for asthma, 41
for COPD, 438, 440
for end-of-life care, 91
GERD and, 526*t*
for Parkinson disease, 1292
for schizophrenia, 1853
Anticonvulsants
for brain abscess, 1436–1437
for neuropathic pain, 1211
for PTSD, 1823
Antidepressants, 1848
for bipolar depression, 1918
and sleep, 1841
toxicity from, 79
tricyclic (*see* Tricyclic antidepressants)
Antidiarrheals, 569
Antiemetics, 1007, 1008*t*, 1273
for CINV, 473–496, 494*t*
Antiepileptics
for critically ill patients, 1240
for depressive disorders, 1887*t*
for seizures, 1316*t*
Antiestrogen (Clomiphene citrate), 991, 1046
for polycystic ovary syndrome, 1045*t*
Antifungals
adverse effects of, 1381*t*
antifungal spectrum and susceptibility testing, 1676
for blastomycosis during pregnancy, 1687
cryptococcal disease, 1695
mechanism of action, 1676–1677
novel antifungal compounds, 1676–1677
pharmacokinetic properties of systemically active, 1681*t*
prophylaxis regimens and approximate costs, 1678*t*
Antihistamines, 461*t*, 743, 1007, 1008*t*
for allergic rhinitis, 451, 455*t*

for anaphylaxis, 719, 721*t*
for rhinitis, 456–457
and sleep, 1833, 1845
Antimalarials, 739
Antimicrobials, 1374–1375*t*
costs of therapy, 1379
dosing, 1382–1387
toxicities, 1378–1379
Antimotility drugs, 1515–1516
Antimycotic pulse therapy, 1679
Antineoplastics, and lactation, 1035*t*
Antioxidants, 1303
as photoprotective agents, 889
Antipseudomonal penicillins, 706
Antipseudomonal β-lactam, 481
Antipsychotics
for acute agitation, 1916
for acute mania, 1915
for bipolar depression, 1907, 1917–1918
for critically ill patients, 1240
and lithium, 1914*t*
Antipyretics, 1724
Antiretroviral therapy (ART), 1029
Antispasmodics, 1225
for IBS, 568
Antispasticity agents, 1225
Antithymocyte globulin (ATG), 756–757
Antithyroid drugs, teratogenic effects, 1004*t*
Antivirals
adverse effects of, 1381*t*
in febrile neutropenic patient, 1626
for HBV, 1738
in immunocompromised patients, 1708
Anzemet (*see* Dolasetron)
Apidra (*see* Insulin glulisine)
Apixaban, 1359*t*
for prevention of stroke, 336–337
for stroke prevention, 184
for warfarin therapy, 205
Apokyn (*see* Apomorphine)
Apomorphine (Apokyn), 1287*t*, 1290*t*, 1297
Apraclonidine (Iopidine), 1186
Apremilast, for plaque psoriasis, 878
Aprepitant (Emend), 132, 494*t*, 976*t*
for CINV, 493–496, 494*t*, 497*t*, 498

for PONV, 501*t*
Apriso (*see* Mesalamine)
Aquacel Ag (*see* Silver sulfadiazine cream)
AquaDEK chewable tablet, 477*t*
AquADEK liquid, 477*t*
Aquaretics, 613
Aranesp (*see* Darbepoetin alfa)
ARBs (*see* Angiotensin receptor blockers (ARBs))
Arformoterol, 439*t*
Argatroban, 185
Aripiprazole (Abilify), 1306, 1809, 1866*t*, 1869*t*
for acute agitation, 1916
for acute mania, 1915, 1916*t*
and bipolar depression, 1918
for bipolar disorder, 1919*t*
for developmental disorders, 1928–1929
for dyslipidemia, 1875
for hyperprolactinemia, 1874
for schizophrenia, 1857, 1860*t*, 1862, 1864*t*
Aripiprazole lauroxil, 1866*t*
Aripiprazole monohydrate, 1866*t*
Armodafinil, 1847, 1848
ARNI (*see* Angiotensin receptor-neprilysin inhibitor (ARNI))
Aromatase inhibitor (Letrozole), 991, 1046
for endometriosis, 1052
for polycystic ovary syndrome, 1045*t*
Arsenic trioxide, 491*t*
for AML, 2087
ART (*see* Antiretroviral therapy (ART))
Artemisinin, 1763
Artesunate, 1764
Arylcycloalkylamines, 1956
Asacol HD (*see* Mesalamine)
Ascorbic acid (vitamin C), 950, 976*t*, 994
for anemia, 2000
Asenapine (Saphris), 1868*t*, 1869*t*
for acute mania, 1916*t*
for bipolar disorder, 1919*t*
for hyperprolactinemia, 1874
for schizophrenia, 1859, 1860*t*
Asparaginase (Elspar), 492*t*, 2056*t*
neurotoxicity of, 2047, 2048*t*
preparations, 207
Aspirin, 230, 725, 727, 737, 904–905, 905*t*, 918, 1356, 1359*t*
for ACS, 246*t*

for AMI, 260
and clopidogrel, 1359
for diabetes, 174
for end-of-life care, 90
gastric damage, 513
GERD and, 526*t*
hypertension and, 151
induced anaphylaxis, 727
for PAD, 174–175
for STEMI, 381
for stroke prophylaxis, 2303
toxicity from, 69–73
Astepro (*see* Azelastine)
Atazanavir (ATV), 125*t*, 133, 976*t*, 1639*t*
Atenolol, 719, 1310, 1310*t*, 2325*t*
in hypertension, 166*t*
for MI, 262
Atezolizumab, 492*t*
ATG (*see* Antithymocyte globulin (ATG))
Ativan (*see* Lorazepam)
Atomoxetine, 1927, 1940*t*
Atorvastatin, 47*t*, 115, 115*t*, 121*t*, 125*t*, 135, 176, 267, 954, 976*t*
for prostate cancer, 2143
Atovaquone-proguanil (Malarone), 51, 1765*t*, 1769
Atovaquone suspension
for mild to moderate PJP, 1660–1661
for toxoplasmosis, 1663
Atracurium, 2259
Atropine, 341
for end-of-life care, 92
Atrovent (*see* Ipratropium bromide)
ATV (*see* Atazanavir (ATV))
Augmentin, 1372*t*
for aerobic gram-positive cocci, 1373*t*
for gram-negative aerobes, 1374*t*
Auvi-Q, 469*t*
Avanafil, and ED, 2328
Avastin (*see* Bevacizumab)
Avelox (*see* Moxifloxacin)
Avobenzone, 885*t*, 888
Avycaz, 1372*t*
Axitinib, 492*t*
AZA (*see* Azathioprine (AZA))
Azacitidine, 491*t*
Azactam (*see* Aztreonam)

Azathioprine (AZA), 58, 653, 741, 744*t*, 746*t*, 752–753, 915, 949*t*, 958
for ophthalmopathy, 1098
therapy for Wegener granulomatosis, 658
Azelaic acid, for comedonal acne, 867
Azelastine (Optivar), 458, 460*t*, 461*t*, 1201
for allergic rhinitis, 452
Azelastine HCl (Dymista), 461*t*
Azilsartan medoxomil, for hypertension, 161*t*
Azithromycin (Zithromax), 481, 723, 957, 1372*t*, 1373*t*, 1789, 1796
adverse effects of, 1380*t*
for *Campylobacter* infection, 1514
for MAC, 1671
for nongonococcal urethritis, 1570
for travelers' diarrhea, 1516*t*
for typhoid fever, 1510
Azole antifungals, 1676, 1677, 1691
drug interactions, 1691
risk factor C, 1679
for VVC, 1591
Azopt (*see* Brinzolamide)
Aztreonam (Azactam), 483, 1374*t*
for aerobic gram-positive cocci, 1374*t*
for anaerobes, 1374*t*
for CAPD-associated peritonitis, 1533*t*
for CNS infections, 1426*t*
for cystic fibrosis, 482*t*
dosing of, 1383*t*
for gram-negative aerobes, 1374*t*
for skin and soft tissue infections, 1606
for UTI, 1553*t*
Azulfidine (*see* Sulfasalazine)

B

Bacampicillin (Spectrobid), 1372*t*
Bacillus Calmette-Guérin vaccine, 1669
Bacitracin, 860
Baclofen, 1226*t*, 1257
Bactrim (*see* Trimethoprim-sulfamethoxazole)
Balsalazide, 544*t*, 556*t*
Barbiturates, 976*t* (*see also* Sedatives)
GERD and, 526*t*
Barley malt extract, 2217*t*
Basiliximab, 756–757
BEACOPP, for HL, 2092

Beclomethasone
for allergic rhinitis, 462
for end-of-life care, 90
Beclomethasone dipropionate (Beconase AQ), 461*t*
for BPD, 2233
Beconase AQ (*see* Beclomethasone dipropionate)
Belatacept, 756
Belimumab, 742–743, 743*t*, 744*t*, 746*t*
Belsomra (*see* Suvorexant)
Belviq (*see* Lorcaserin)
Benadryl (*see* Diphenhydramine)
Benazepril, in hypertension, 160*t*
Bendamustine (Treanda)
for CLL, 2092
drug interaction with smoking, 1978*t*
Bendamustine, 491*t*, 2092*t*
Benzathine penicillin G, 1575*t*
Benzodiazepines, 976*t*, 1246, 1257, 1808*t*, 1862 (*see also* Sedatives)
abuse and dependence, 1823, 1846–1847
for acute agitation, 1916
adverse effects, 1811
for agitated behaviors, 2305
for Akathisia, 1870
alcohol withdrawal, 1966
and anterograde amnesia, 1811
breast milk, 1813
vs. buspirone, 1814
clinical profiles of, 1807*t*
CNS stimulants, 1954
and cognitive impairment, 1811
for critically ill patients, 1241
for depressive disorders, 1887*t*
drug interaction, 1812
duration of treatment, 1811–1812
and falls, 1811
and GABA-A receptors, 1809
for GAD, 1804
GERD and, 526*t*
induced sedation, management of, 1813
and lactation, 1846
LSD, 1957
for LTCF, 2289
mechanism of action, 1804
for panic disorder, 1917
physiological factors influencing, 1813

and pregnancy, 1846
and respiratory depression, 1811
for SAD, 1820
for schizophrenia, 1855
sedative-hypnotics, 1952
and sleep, 1832, 1833, 1846
with smoking, 1979*t*
tolerance of, 1841–1842
use during lactation, 1813
use in pregnancy, 1813
withdrawal syndrome, management of, 1812
Benzoic acid, 1678
Benzophenones, 885*t*, 888
Benzoyl peroxide, for maculopapular acne, 868–869
Benzphetamine, 799
Benztropine (Cogentin), 1286*t*
for Akathisia, 1870*t*
for Parkinsonism, 1870
Bepotastine (Bepreve), 460*t*
Bepreve (*see* Bepotastine)
β-adrenergic agonists, 1025
β-adrenergic blockers
for Akathisia, 1870
for patients with CKD, 648
for vascular dementia, 2302
β-adrenergic blocking agents, 332
β-adrenergic receptor blockers, 1093, 1820
β-blockers, 576, 583, 976*t*
for ACS, 246*t*, 257, 267
adrenergic blocking agents, 286
alcohol withdrawal, 1966
benefits of, 267
CAD and, 224
carvedilol *vs*. metoprolol, 304
in HFrEF, 302–304
in HTN, 313
for hypertension, 147, 157*t*, 166*t*
metoprolol vs. carvedilol, 304
for MI, 267
in severe heart failure, 304–305
teratogenic effects, 1004*t*
for thyroid storm, 1098
β-hydroxy-β-methylglutaryl-CoA (HMG-CoA), 257
β-lactam, 475, 481, 730, 1620
adverse effects of, 1379*t*

and aminoglycoside, 1619
antibiotics, 481
double combinations, 1619
for febrile neutropenia, 1619
Betamethasone, 1026
β_2-adrenergic agonists, 526*t*
β_2-agonists, 619
for AECOPD, 1462
for hyperkalemia, 620*t*
and hypokalemia, 615*t*
Betaxolol (Betoptic), 1187
adverse effects of, 1190
alternative therapy, 1190
initial therapy, 1190
patient education, 1190
Bethanechol, 2039, 2220*t*
Betoptic (*see* Betaxolol)
Bevacizumab (Avastin), 492*t*, 2038, 2054, 2118
for colon cancer, 2127, 2132
and hypertension, 2054
for metastatic colorectal cancer, 1205
Bexarotene, 492*t*, 976*t*
Biaxin (*see* Clarithromycin)
Bicalutamide, 2147
Bicarbonate (sodium bicarbonate), 672, 1009
-carbonic acid system, 643
adverse effects of, 382
hyperkalemia and, 619, 620*t*
for preventing SRMB, 537*t*
for salicylate toxicity, 72
for TCA toxicity, 80
BiDil (*see* Isosorbide dinitrate (BiDil))
Biguanide (Metformin)
adverse effects of, 1153
contraindications and precautions of, 1153
dosage and clinical use of, 1153
drug interactions, 1153
efficacy of, 1153
mechanism of action, 1153
pharmacokinetics of, 1153
for polycystic ovary syndrome, 1045*t*
for type 2 diabetes, 1174
Bile acid resins
adverse effects, 132
clinical pearls, 132

drug interactions, 132
efficacy, 131
mechanism of action, 131, 131*f*
pharmacokinetics/pharmacodynamics, 131
place in therapy, 132
Bilirubin, 31, 31*f*
blood chemistry reference values for, 20*t*
Bimatoprost (Lumigan), 1186
for ocular hypertension, 1186
Biperiden
for Akathisia, 1870*t*
for Parkinsonism, 1870
Biphosphonates, for hypercalcemia, 623*t*, 624
Bisacodyl, 2217*t*
for end-of-life care, 91
Bismuth salt, 509, 518–519
Bismuth subsalicylate (BSS)
for Helicobacter pylori, 514*t*
for infectious diarrhea, 1504
Bisoprolol
in HFrEF, 303
in hypertension, 166*t*
Bisphosphonates, 2349, 2352
and dyspepsia, 509
Bivalirudin, 264
for ACS, 247*t*
for heparin-induced thrombocytopenia, 185
Blenoxane (*see* Bleomycin)
Bleomycin (Blenoxane), 492*t*, 2042, 2043*t*, 2050, 2054*t*, 2055, 2056
gonadal toxicity of, 2058
Boceprevir, 125*t*, 132
for HAV, 1750
Bonine (*see* Meclizine)
BOOSTRIX, 1408
Borates, 1678
Boric acid, for VVC, 1581
Bortezomib (Velcade), 492*t*, 2094
neurotoxicity of, 2048*t*
peripheral nerve toxicity of, 2048
Bosentan, 954, 976*t*
for pulmonary HTN, 279
Bosutinib, 492*t*
Botulinum toxin A, 1310*t*, 1311
Brentuximab vedotin, 491*t*
Brevibloc (*see* Esmolol)

Brexpiprazole (Rexulti), 1857, 1860*t*
for Akathisia, 1870
Brimonidine (Alphagan), 1186
Brinzolamide (Azopt), 1188
Brisdelle (*see* Paroxetine mesylate)
Brivaracetam, 1322*t*
Bromocriptine (Parlodel), 1286*t*, 1290*t*, 2330
and lactation, 1033
for type 2 diabetes, 1165
Bronchodilators, for COPD, 434–435, 442
BSS (*see* Bismuth subsalicylate (BSS))
Budesonide, 461*t*
for allergic rhinitis, 462
for BPD, 2233
for chronic asthma, 413, 415
for COPD, 439*t*
for inflammatory bowel disease, 550*t*
Budesonide/formoterol (Symbicort), 415
Bumetanide, 676
for HF, 292
Bupivacaine hydrochloride, 1215*t*
Bupivacaine liposomal, 1215*t*
Buprenorphine, for opioid withdrawal syndrome, 1949
Bupropion, 1898
for ADHD, 1943
for depressive disorders, 1891*t*, 1892*t*
Bupropion/zonisamide ER, 801
for bipolar depression, 1907
and sleep, 1843
for smoking cessation, 1987
sustained-release, 1981, 1988–1989, 1993
BuSpar (*see* Buspirone)
Buspirone (BuSpar), 1808*t*, 1809, 1814
vs. benzodiazepines, 1814
and elderly, 1809
Busulfan (Busulfex, Myleran), 491*t*, 492*t*, 2056*t*
Butenafine, 1676*t*
Butoconazole, 1676*t*
for VVC, 1580*t*
Butyrophenone, 1858*t*

C

Cabazitaxel (Jevtana), 491*t*
peripheral nerve toxicity of, 2048

for prostate cancer, 2151
Cabozantinib, 492*t*
Caffeine, 803*t*, 976*t*
for apnea, 2246
for BPD, 2246
drug interaction with smoking, 1978*t*
and heartburn, 1009
and lithium, 1914*t*
and pregnancy, 1002
Calamine lotion, 862
Calcimimetics, 653
Calcineurin inhibitors, 658, 755
for FSGS patients, 658–659
induced nephrotoxicity, 763
Calcitonin, 2343*t*, 2349
for hypercalcemia, 623*t*, 624
for osteoporosis, 2348
Calcitriol, 652
for psoriasis, 875
Calcium, 26–27
blood chemistry reference values for, 19*t*
and BP, 141
and children, 2198*t*
for endometriosis, 1053
homeostasis, 620–621
hypercalcemia, 622–625
for PMS, 1054
and pregnancy, 1000
recommended daily allowance, 1000
and respiratory alkalosis, 1731
role of, 620
Calcium acetate, 651*t*
Calcium carbonate, 651*t*
Calcium-channel blockers (CCBs), 176, 220
for ACS, 247*t*
for AF, 332–333
in anginal syndromes, 225
CAD and, 154
diabetes and, 162–163
dihydropyridines, 162
GERD and, 526*t*
hemodynamic and electrophysiologic profile, 232*t*
for HF, 287
for hypertension, 147, 162–163, 163*t*
for hyperthyroidism, 1081, 1091*t*

nondihydropyridines, 162
in patients with CKD, 648
for pregestational diabetes, 1010
for PSVT, 339
vasospastic and classic exertional angina, 232
Calcium gluconate, 620*t*
Campath (*see* Alemtuzumab)
Camphor, 1678
Canagliflozin, 1163
Canakinumab, 932, 946
Canasa, 556*t*
Candesartan, 1277
for HF, 285, 299
for hypertension, 161*t*
Candicidin, 1678
Cangrelor, 255–256*t*
for ACS, 247*t*
for thrombotic events reduction, 254
Cannabidiol, 1322*t*
Cannabinoids, 1257
for CINV, 496
Cannabis, 1853, 1853*t*
Capecitabine (Xeloda), 492*t*, 2054*t*
Capoten (*see* Captopril)
Capreomycin, for tuberculosis, 1485*t*
Caprylic acid, 1678
Capsaicin
for neuropathic pain, 1211
for OA, 903
Capsaicin cream
for PHN, 1705
Capsaicin patch, 1705
Captopril (Capoten), 179, 266, 296–297, 296*t*, 354*t*
for BP, 354
and hyperkalemia, 617
in hypertension, 160*t*
Carbachol (Isopto Carbachol), 1198
Carbamazepine (CBZ), 43, 60, 225, 976*t*, 1317*t*, 1325*t*, 1812, 1823, 1907, 2325*t*
for acute mania, 1915
autoinduction of metabolism of, 1320
bioequivalence of generic dosage of, 1320–1321
for bipolar disorder, 1919*t*
for epilepsy, 59
extended-release forms of, 1321
for HAV, 1751

and hematologic toxicity, 1319–1320
hepatotoxicity with, 1319–1320
initiation and dosage of, 1319
lamotrigine and, 1328
and lithium, 1914*t*
for ocular emergencies, 1196*t*
pharmacokinetics of, 1320
for schizophrenia, 1875
for seizures, 1319
teratogenic effects, 1004*t*
valproate and, 1337
Carbamazepine, 1228*t*, 1322*t*
Carbapenem
for febrile neutropenia, 1618
for skin and soft tissue infections, 1608
for UTI, 1553*t*
Carbidopa–levodopa (enteral suspension) (Duopa), for Parkinson disease, 1286*t*
Carbidopa–levodopa (CR) (Sinemet CR), for Parkinson disease, 1286*t*
Carbidopa–levodopa (ER) (Rytary), for Parkinson disease, 1286*t*, 1297
Carbidopa–levodopa ODT (Parcopa), for Parkinson disease, 1286*t*
Carbonyl iron, 1999
Carboplatin (Paraplatin), 491*t*, 2054*t*, 2118
for NSCLC, 2114*t*, 2115*t*
for SCLC, 2120*t*
Carboprost tromethamine, for postpartum hemorrhage, 1030–1031, 1030*t*
Cardene IV (*see* Nicardipine)
Cardiac resynchronization therapy (CRT), 28
Carfilzomib, 491*t*
Cariprazine (Vraylar)
for acute mania, 1916*t*
for schizophrenia, 1858, 1860*t*
Cariprazine, 1868*t*, 1916
for bipolar depression, 1918*t*
Carisoprodol, 1126*t*
Carmustine (BiCNU), 205*t*, 491*t*, 2054*t*, 2056, 2056*t*
and cranial neuropathies, 2049
Carteolol (Ocupress), 1187
Carvedilol, 267
in HFrEF, 303–304
for hypertension, 166, 166*t*
in peri-infarction period, 262, 267
Caspofungin, 1626, 1676*t*, 1677, 1685, 1692
adverse effects of, 1381*t*
dosing of, 1383*t*

for fungal endocarditis, 1454
Catapres (*see* Clonidine)
Catechol-O-methyltransferase inhibitors (COMT), 1299–1301
pharmacologic and pharmacokinetic properties of, 1300*t*
Catecholamines, for septic shock, 392
Cathelicidins, 1677
CBZ (*see* Carbamazepine (CBZ))
CCBs (*see* Calcium-channel blockers (CCBs))
Ceclor (*see* Cefaclor)
Cedax (*see* Ceftibuten)
Cefaclor (Ceclor), 1372*t*
for chronic antimicrobial therapy, 1556*t*
for UTI, 1544*t*
Cefadroxil (Duricef), 1372*t*
Cefamandole (Mandol), 1372*t*
Cefazolin (Ancef), 1201, 1372*t*, 1604
for aerobic gram-positive cocci, 1373*t*
for anaerobes, 1374*t*
for CAPD-associated peritonitis, 1533*t*
dosing of, 1383*t*
for gram-negative aerobes, 1374*t*
kidney failure, dosing of drugs, 707–708
for PVE, 1446*t*
for pyelonephritis, 1028
for skin and soft tissue infections, 1604
for surgical procedures, 1392*t*, 1396
for UTI, 1552*t*
Cefdinir (Omnicef), 1372*t*
Cefditoren (Spectracef), 1372*t*
Cefepime (Maxipime), 1372*t*
for aerobic gram-positive cocci, 1373*t*
for anaerobes, 1374*t*
for CAPD-associated peritonitis, 1533*t*
for CNS infections, 1426*t*
for cystic fibrosis, 482*t*
dosing of, 1383*t*
for febrile neutropenia, 1618
for gram-negative aerobes, 1374*t*
for gram-negative bacillary meningitis, 1432
for skin and soft tissue infections, 1606
for UTI, 1552*t*
Cefixime (Suprax), 1372*t*
for disseminated gonococcal infection, 1570
for shigellosis, 1511
for typhoid fever, 1511

for uncomplicated gonorrhea, 1564
Cefizox (*see* Ceftizoxime)
Cefonicid (Monocid), 1372*t*
Ceforanide (Precef), 1372*t*
Cefotaxime (Claforan), 1372*t*
for anaerobes, 1374*t*
and biliary pseudolithiasis, 1428
for CNS infections, 1426*t*
for NEC, 2243
for sepsis, 2244*t*
for UTI, 1497*t*, 1552*t*
Cefotetan (Cefotan), 1372*t*
for anaerobes, 1374*t*
for chorioamnionitis, 1029
for PID, 1569*t*
Cefoxitin (Mefoxin), 1372*t*
for chorioamnionitis, 1029
for PID, 1569*t*
Cefpodoxime proxetil (Vantin), 1372*t*
for UTI, 1544*t*
Cefprozil (Cefzil), 1372*t*
Ceftaroline (Teflaro), 1372*t*, 1424, 1447
for aerobic gram-positive cocci, 1373*t*
for gram-negative aerobes, 1374*t*
for skin and soft tissue infections, 1604
for UTI, 1552*t*
Ceftazidime (Fortaz), 483, 704, 1372*t*
for anaerobes, 1375*t*
for CAPD-associated peritonitis, 1533*t*
for cystic fibrosis, 482*t*
dosing of, 1383*t*
for febrile neutropenia, 1619
for gram-negative aerobes, 1374*t*
for gram-negative bacillary meningitis, 1432
kidney failure, dosing of drugs, 700–701
for skin and soft tissue infections, 1606
for UTI, 1552*t*
Ceftazidime-avibactam, 1374*t*
Ceftibuten (Cedax), 1372*t*
Ceftin (Cefuroxime axetil), 1372*t*
Ceftizoxime (Cefizox), 1372*t*
for anaerobes, 1375*t*
for CAPD-associated peritonitis, 1533*t*
Ceftolozane/tazobactam (Zerbaxa), 1372*t*, 1424, 1455
for gram-negative aerobes, 1374*t*

Ceftriaxone (Rocephin), 582, 723, 1372*t*, 1424, 1429, 1455, 1789, 1792, 2189*t*
and aminoglycoside, 1443
for anorectal gonorrhea, 1566
and biliary pseudolithiasis, 1428
for CNS infections, 1426*t*
for disseminated gonococcal infection, 1570
dosing of, 1383*t*
for endocarditis, 1443
for neonatal DGI, 1570
for skin and soft tissue infections, 1604
for tularemia, 1792
for typhoid fever, 1508
for uncomplicated gonorrhea, 1564*t*, 1565
for UTI, 1552*t*
Cefuroxime (Zinacef), 1372*t*, 2189*t*
for aerobic gram-positive cocci, 1373*t*
for gram-negative aerobes, 1374*t*
for N. meningitides, 1426
for UTI, 1552*t*
Cefuroxime axetil (Ceftin), 1372*t*, 1789
Cefzil (*see* Cefprozil)
Celecoxib, 57, 513, 739, 904, 905*t*, 918
Celexa (*see* Citalopram)
Cenobamate, 1322*t*
Central α_2-agonists, for hypertension, 148
Cephalexin (Keflex), 1009, 1372*t*
for chronic antimicrobial therapy, 1556*t*
for pyelonephritis, 1009
for skin and soft tissue infections, 1603
for UTI, 1544*t*
Cephalosporins, 717, 1425, 1788, 1794
adverse effects of, 1379*t*
for cardiac surgery prophylaxis, 1445–1446
for chorioamnionitis, 1029
for CNS infections, 1426*t*
during pregnancy, 1009
for tularemia, 1794
for uncomplicated gonorrhea, 1564*t*, 1565
for UTI, 1552*t*
Ceritinib, 492*t*
Certolizumab
for CD, 562
for inflammatory bowel disease, 554*t*
pegol, 914, 915, 923, 926*t*
Cerubidine (*see* Daunorubicin)

Cesamet (*see* Nabilone)
Cetilistat, 802
Cetirizine (Zyrtec), 455*t*
for rhinitis, 458
and sleep, 1836
Cetuximab (Erbitux), 492*t*
for colon cancer, 2127
Cevimeline, 2039
CFTR potentiator, 479–480
Chasteberry (Vitex agnus-castus or VAC), 1056
ChEIs (*see* Cholinesterase inhibitors (ChEIs))
Chemoprophylaxis, for OIs, 1656
Chemotherapy
for acute leukemia, 2057
for acute myeloid leukemia, 2057
for acute tubular obstruction, 2054
for aggressive lymphomas, 2093
in ALL, 2075
and alopecia, 2041
for AML, 2085
and anemia, 2037
for arrhythmias, 2052
for autonomic neuropathy, 2049
for B-cell lymphoma, 2079–2080
on bone marrow, 2035–2038
for cardiomyopathy, 2049–2050
and cardiotoxicity, 2049–2050
and colony-stimulating factors, 2035–2036
and cranial nerve toxicity, 2049
cytotoxic effects, 2035
dermatologic impacts, 2038–2041
and diarrhea, 2041
dosage regimen for intrathecal, 2075*t*
dosing in infants and young children, 2067
and dry skin, 2037
and esophagitis, 2040
and esophagus, 2040
and filgrastim, 2036, 2037
and GI tract, 2038–2041
and hand-foot syndrome, 2042
hematologic effects, 2035–2038
and hemorrhagic cystitis, 2054–2055
for HL, 2091
hypersensitivity reactions, 2044–2045
and hypertension, 2053

for indolent NHLs, 2095
induction combination, 2073–2074
interaction with radiation therapy, 2042–2043, 2043*t*
intrathecal prophylaxis, 2075
irritant and vesicant reactions, 2043
for large cell lymphomas, 2080
and life-threatening neutropenia, 2035
long-term complications, 2057–2058
for lymphoblastic (T-cell) lymphoma, 2077–2078
and mucositis, 2039–2040
and myelosuppression, 2035–2036
and myocardial infarction, 2052
nausea and vomiting, 2038
nephrotoxicity, 2052–2054, 2054*t*
for neuroblastoma, 2063
neurotoxicity, 2047–2049, 2048*t*
and neutropenia, 2035–2036
for NSCLC, 2115
and oral cavity complications, 2038–2039
for osteosarcoma, 2068
ototoxicity, 2049
for pediatric ALL, 2073
and pegfilgrastim, 2036
peripheral nerve toxicity, 2048
and peripheral neuropathy, 2048–2049
and pigment changes, 2042
and proteinuria, 2054–2055
and pulmonary functions, 2055–2056
for rhabdomyosarcoma, 2070–2071
skin and nail changes, 2042
for specific organs, 2047–2049
and stomatitis, 2039–2040
and thrombocytopenia, 2035, 2037
venous thrombotic events, 2038
and Wilms tumor, 2065–2067
and xerostomia, 2039
Chitosan, 803*t*
Chlor-Trimeton (*see* Chlorpheniramine)
Chlorambucil (Leukeran), 492*t*
for CLL, 2095
Chloramphenicol (Chloromycetin), 1372*t*, 1788
adverse effects of, 1380*t*
for RMSF, 1794
for tularemia, 1794
Chlordiazepoxide, 1807*t*

Chlorhexidine gluconate, 2040
Chloride, 23
blood chemistry reference values for, 18*t*
Chloromycetin (*see* Chloramphenicol)
Chloroprocaine, 1215*t*
Chloroquine, 51, 739, 765*t*, 1763
psoriasis and, 872
Chlorpheniramine (Chlor-Trimeton), 455*t*
Chlorpromazine, 1306, 1858*t*, 1868*t*, 1869*t*
for hyperprolactinemia, 1874
for schizophrenia, 1864*t*
Chlorpropamide, 1174
Chlorthalidone, 156
Chlorzoxazone, 1126*t*
Cholecalciferol, 2343*t*
Cholestyramine, 132, 741
for IBS-D, 569
for thyroid storm, 1098
Cholinesterase inhibitors (ChEIs), 1305
for Alzheimer disease, 2298
for DLB, 2300
for PDD, 2300
for vascular dementia, 2303
Chondroitin, 901
Chorioamnionitis, 1024
Ciclesonide (Omnaris, Zetonna), 461*t*
for allergic rhinitis, 462
Ciclopirox, 1676*t*
Cidofovir (Vistide), 777–778, 1666, 1700*t*, 1703
adverse effects, 1699*t*
for CMV retinitis, 1665
Cilostazol, 175, 1358*t*, 1359
for diabetes, 175
for IC, 175
Cimetidine, 506*t*, 507, 977, 2220*t*
inhibition of CYP450 isoenzymes, 507
for preventing SRMB, 537*t*
Cinacalcet, 653
Cinnamates, 885*t*, 888
Cinoxate, 885*t*
Cipro (*see* Ciprofloxacin)
Ciprofloxacin (Cipro), 483, 485, 976*t*, 1372*t*, 1429, 1447, 1793
for aerobic gram-positive cocci, 1373*t*
and AIN, 674
for anaerobes, 1375*t*

for CAPD-associated peritonitis, 1533*t*
for COPD, 442
for cystic fibrosis, 482*t*
dosing of, 1384*t*
for MAC, 1671
for S. dysenteriae type 1 infection, 1511
for travelers' diarrhea, 1516*t*
for tularemia, 1793
for UTI, 1544*t*, 1553*t*
Cisatracurium, 48
Cisplatin, 491*t*, 2038, 2043*t*
and cranial neuropathies, 2049
gonadal toxicity of, 2057–2058
and hypokalemia, 615*t*
monitoring hydration for, 2065
nephrotoxicity of, 2052–2054, 2065
for neuroblastoma, 2063, 2065
neurotoxicity of, 2048*t*, 2049
for NSCLC, 2114*t*, 2115, 2115*t*
for osteosarcoma, 2068
peripheral nerve toxicity of, 2048
and renal insufficiency, 2054*t*
for SCLC, 2120–2121, 2120*t*
weight gain with, 2065
Citalopram (Celexa), 346, 1305, 1808*t*, 1916
for agitated behaviors, 2305
for ASD, 1931
for depressive disorders, 1891*t*, 1892*t*, 2306
for OCD, 1822
for panic disorder, 1816
for PTSD, 1824
for vasomotor symptoms, 1039*t*
Citrus aurantium*, 803*t
Cladribine, 492*t*
Claforan (*see* Cefotaxime)
Clarinex (*see* Desloratadine)
Clarithromycin (Biaxin), 125*t*, 132, 514*t*, 519, 976*t*, 1372*t*, 1424, 1664, 1789
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
for MAC, 1671
Claritin (*see* Loratadine)
Clavulanate, 482*t*
Clavulanic acid, 442
Clemastine (Tavist), 455*t*
Cleocin (*see* Clindamycin)

Clevidipine (Cleviprex), 353*t*
for hypertension, 363
Cleviprex (*see* Clevidipine)
Climara Pro, 1066*t*
Clindamycin (Cleocin), 1372*t*, 1664, 1764, 1796
for acne, 869
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
for anaerobes, 1375*t*
for cellulitis, 674
for chorioamnionitis, 1029
dosing of, 1384*t*
for GBS infection, 1028
plus gentamicin, 1569*t*
for skin and soft tissue infections, 1603, 1604, 1605, 1606
Clindamycin-quinine, 1796
Clioquinol, 1676*t*
Clobazam, 1323*t*
Clofarabine (Clolar), 491*t*, 2056, 2056*t*
Clofazimine, 1671
Clofibric acid, 976*t*
Clolar (*see* Clofarabine)
Clomiphene citrate (Antiestrogen), 991, 1046
for polycystic ovary syndrome, 1045*t*
Clomipramine
for ASD, 1929
dosage, 1828
for panic disorder, 1817
side effects, 1829
Clonazepam, 1310*t*, 1311, 1807*t*
for Akathisia, 1870*t*
for panic disorder, 1816
for SAD, 1821
Clonidine (Catapres), 164*t*, 354*t*, 1846, 2325*t*
for ADHD, 1940*t*, 1941
alcohol withdrawal, 1966
for BP, 354
for hypertension, 167
for hypertensive urgency, 354
for opioid withdrawal syndrome, 1949
in patients with CKD, 648
for sleep, 1932
for vasomotor symptoms, 1069*t*
Clopidogrel, 208, 238, 508, 1154, 1358*t*, 1359
for ACS, 247*t*, 254, 255–256*t*

antiplatelet medications, 522
and aspirin, 247–248*t*, 1359
for CAD, 236
for diabetes, 175
drug interaction with smoking, 1978*t*
in fibrinolytic therapy, 260
for ischemia, 264
loading dose, 264–265
for MI, 223
for PAD, 175
for ulcer healing, 522
Clorazepate, 1807*t*, 1813
Clotrimazole, 1580*t*, 1676*t*
Cloxacillin, 1372*t*
Clozapine (Clozaril), 1306, 1868*t*, 1869*t*, 1875, 1883
for acute mania, 1915
for agitated behaviors, 2306
for anticholinergic, 1872
drug interaction with smoking, 1978*t*
for dyslipidemia, 1875
for FGAs, 1874
for orthostatic hypotension, 1873
for Parkinsonism, 1865
for schizophrenia, 1855, 1858, 1860*t*, 1862
for tachycardia, 1873
for Tardive dyskinesia, 1871
Clozaril (*see* Clozapine)
CNS penetration of, 1692
CNS stimulants, 1954
for hypertensive emergencies, 362
for MI, 262
Coal tar, 1678
for psoriasis, 873*t*, 876
Cobimetinib, 492*t*
Cocaine
CNS stimulants, 1953
and lactation, 1035*t*
for schizophrenia, 1853, 1853*t*
teratogenic effects, 1004*t*
Codeine, 61 (*see also* Opioids)
Coenzyme Q, 323–324
Coenzyme Q_{10} (CoQ_{10}), 123
for Parkinson disease, 1303
Cogentin (*see* Benztropine)
Colazal (*see* Balsalazide)

Colchicine, 133, 946
drug interaction, 945*t*
Colesevelam, 132, 976*t*
for type 2 diabetes, 1165
Colestipol, 132
Colfosceril, 2227
Colistimethate, 483
for cystic fibrosis, 482*t*
Colistin, 482*t*
Colloids, 379
Combination vaccines, 1407*t*
Combined androgen blockade (CAB), 2147
Compazine (*see* Prochlorperazine)
Conivaptan, 132, 945*t*
for hyponatremia, 613
Conjugated equine estrogen (Premarin), 1066*t*
Conjugated estrogen, 1066
Conjugated pneumococcal vaccine (PCV), 1405
Contrave (*see* Naltrexone/Bupropion)
ConvaTec (*see* Silver sulfadiazine cream)
Corlanor (*see* Ivabradine)
Corlopam (*see* Fenoldopam)
Corticosteroids, 558, 744*t*, 746*t*, 755, 916, 958, 976*t*, 1425, 1679, 1691, 1704, 2056
for acne, 867
for acute asthma, 411–412
for acute gout, 946
for adult meningitis, 1430
adverse drug effects of, 857–858
for AECOPD, 1461
for anaphylaxis, 719, 721*t*
antibiotics with, 860
for bacterial meningitis, 1425
for brain abscess, 1436
for cataracts, 1202
for chronic asthma, 413
for CINV, 493
contraindications to, 855, 857
for COPD, 435–436, 441
Crohn disease, 561
during delivery, 1021, 1026
for depressive disorders, 1887*t*
for diabetes, 1180
for drug-induced lupus, 725
for FSGS patients, 658

for hypercalcemia, 623*t*, 624
hyperglycemia and, 1111
for hyperthyroidism, 109*t*
and hypokalemia, 615*t*
indications for, 855
infection and, 1368
for inflammatory bowel disease, 549, 549*t*
for inflammatory response in CF, 480
intra-articular, 919, 929
for JIA, 931–932
management of acute PJP, 1661
for migraine headache, 1274
for MS, 1255, 1260
ophthalmic, 1202–1203, 1202*t*
for ophthalmopathy, 1097
for PMR and GCA, 954
for PPROM, 1027
for psoriasis, 873*t*, 874–875
for RA, 914, 916
for rhinitis, 462
for septic shock, 394–395
for skin, 855, 856*t*, 858*t*
for systemic lupus erythematosus, 739
teratogenic effects, 1004*t*
therapy for LN, 655
therapy for Wegener granulomatosis, 658
tuberculous meningitis and, 1500
ulcerative colitis, 558–559
Corticotropin, 946
Cosmegen (*see* Dactinomycin)
Cotrimoxazole, 1788
for aerobic gram-positive cocci, 1373*t*
for gram-negative aerobes, 1374*t*
COX-1 (*see* Cyclooxygenase-1 (COX-1))
COX-2 (*see* Cyclooxygenase-2 (COX-2))
CrCl, for herpes simplex keratitis, 1204
Creatine, 1303
Crinone (*see* Progesterone vaginal gel)
Crizotinib, 133, 492*t*, 2065
Cromolyn, 480
for allergic rhinitis, 452
for rhinitis, 459–461
Cromolyn sodium (Crolom; Nasalcrom), 460*t*, 461*t*
Crotamiton, 1775*t*
CRT (*see* Cardiac resynchronization therapy (CRT))

Crystalloids
composition and properties of, 374*t*
for hemorrhagic shock, 373
CSA (*see* Cyclosporine (CSA))
Cubicin (*see* Daptomycin)
Cyanocobalamin, 945*t* (*see also* Vitamin B12)
for pernicious anemia, 2004
CYC (*see* Cyclophosphamide (CYC))
Cyclobenzaprine, 1126*t*
Cyclooxygenase-1 (COX-1), 513
Cyclooxygenase-2 (COX-2), 727, 904, 905*t*, 914, 918, 944
for systemic lupus erythematosus, 739
Cyclophosphamide (CYC), 491*t*, 492*t*, 655, 742, 745*t*, 746*t*, 948*t*, 954, 2036, 2042, 2050, 2063, 2065, 2079, 2093
for breast cancer, 2103
for CLL, 2095
and gonadal toxicity, 2057–2058
and hemorrhagic cystitis, 2080
neurotoxicity of, 2048*t*
for ophthalmopathy, 1098
for rhabdomyosarcoma, 2070–2071
for T-cell lymphomas, 2079*t*
teratogenic effects, 1004*t*
therapy for Wegener granulomatosis, 657
Cycloserine, for tuberculosis, 1484*t*
Cyclosporine (CSA), 125*t*, 132, 225, 558, 976*t*
for inflammatory bowel disease, 551*t*
for kidney transplantation, 766–767
for ophthalmopathy, 1098
in organ transplantation, 755, 759, 762
for psoriasis, 874*t*, 878
for RA, 915
therapy for LN, 655
CYP2D6 inhibitor, 1844, 1848
CYP3A4 inhibitor, 1813, 1814
and sleep, 1844
Cyproheptadine, for pruritus, 861
Cytarabine, 491*t*, 2047–2048, 2056, 2058, 2079, 2080, 2085, 2086
adverse effects of, 2086
for aggressive lymphomas, 2094
for AML, 2085
gonadal toxicity of, 2058
neurotoxicity of, 2048*t*
for T-cell lymphomas, 2079*t*
Cytomegalovirus hyperimmune globulin, 776

Cytovene (*see* Ganciclovir)

D

Dabigatran, 133, 195, 1358*t*
for DVT, 196
for stroke prevention, 185, 336
for warfarin therapy, 206
Dabrafenib, 492*t*
Dacarbazine (DTIC), 491*t*, 2043*t*, 2054*t*
Daclatasvir, for HAV, 1752
Dacogen (*see* Decitabine (Dacogen))
Dactinomycin (Cosmegen), 491*t*, 2043*t*
hepatotoxicity of, 2067
for rhabdomyosarcoma, 2070
Dalbavancin (Dalvance), 1447
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
Dalfampridine, 1256
Dalfopristin/Quinupristin (Synercid), 1372*t*
adverse effects of, 1380*t*
Dalteparin, 183*t*, 195*t*, 196
Dalvance (*see* Dalbavancin)
Danazol, 125*t*
adverse effects, 1054
for endometriosis, 1052
Dantrolene, 1257
Dapagliflozin, 1163
Dapsone, 1661
DAPT therapy and outcomes, 270–271*t*
Daptacel, 1408
Daptomycin (Cubicin), 1372*t*, 1448
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
for CAPD-associated peritonitis, 1533*t*
dosing of, 1384*t*
for endocarditis, 1450
enterococcal endocarditis and, 1453
MRSA, 1606
for skin and soft tissue infections, 1604
Darbepoetin alfa (Aranesp), 646
for anemia, 2011
Darifenacin, 2314
Darunavir (DRV), 133, 976*t*, 1639*t*
Dasabuvir, for HAV, 1752

Dasatinib (Sprycel), 492*t*, 2052, 2089
Daunorubicin (Cerubidine), 491*t*, 2042, 2043*t*, 2050
for AML, 2085
and hepatic dysfunction, 2056*t*
for T-cell lymphomas, 2079*t*
dDAVP (*see* desmopressin)
ddI (*see* Didanosine (ddI))
Decadron (*see* Dexamethasone)
Decitabine (Dacogen), 492*t*
Decongestant
for allergic rhinitis, 451, 455*t*
for rhinitis, 458–459
DEET (*see N,N*-diethyl-*m*-toluamide (DEET))
Deferasirox, for vaso-occlusive complications, 2010
Deferoxamine (DFO)
in iron toxicity, 75
for vaso-occlusive complications, 2010
Defibrillator, role of, 317
DEKAs Plus chewable tablet, 477*t*
DEKAs Plus liquid, 477*t*
DEKAs Plus softgel capsules, 477*t*
Delavirdine (DLV), for HIV, 1640*t*
Δ-9-tetrahydrocannabinol (THC), 1956
Delzicol (*see* Mesalamine)
Demeclocycline, 613
Demerol (*see* Meperidine)
Denavir (*see* Penciclovir cream)
Denileukin diftitox, 492*t*
Denosumab, 2343*t*, 2349–2350, 2352
androgen deprivation therapy, 2155
for prostate cancer, 2154
Deoxycholate, for sepsis, 2244*t*
Depacon, 1340
Depo-Provera, 980–981
Depot medroxyprogesterone acetate (DMPA), 1054
Desferal, in iron toxicity, 75
Desiccated thyroid, 1081
Desipramine (*see also* Antidepressants)
for depressive disorders, 1891*t*, 1892*t*
Desloratadine (Clarinex), 455*t*
for rhinitis, 458
Desmopressin (dDAVP), 676
Desogestrel, 968–970*t*, 977
Desvenlafaxine (Pristiq)
for depressive disorders, 1891*t*, 1892*t*

for serotonin, 1897
for vasomotor symptoms, 1069*t*
Dexamethasone (Decadron), 494*t*, 1027, 1691, 2087, 2094
for bacterial meningitis, 1425
for BPD, 2232
for PONV, 501*t*
for prostate cancer, 2152
for T-cell lymphomas, 2079*t*
Dexedrine (*see* Dextroamphetamine)
Dexlansoprazole, 506*t*, 1249*t*
Dexmedetomidine, 1245
for pediatric intubation, 2259*t*
Dexmethylphenidate, for ADHD, 1939*t*
Dexrazoxane, 492*t*, 2044, 2051
Dextran component, 644
Dextroamphetamine (Dexedrine), 490*t*, 1847
Dextromethorphan, 1258, 1267
dissociative drug, 1956
quinidine combination, for agitated behaviors, 2305
Dextrorphan, 1956
Dextrose, 834
DFO (*see* Deferoxamine (DFO))
DHA (*see* Dicosohexanoic acid (DHA))
DHAP, for aggressive lymphomas, 2091–2092
DHEAS (*see* Dehydroepiandrosterone sulfate (DHEAS))
DHT (*see* Dihydrotestosterone (DHT))
Diazepam, 599, 1020, 1807*t*, 1811, 1814, 2189*t*
for Akathisia, 1870*t*
febrile seizures and, 1336
PCP-induced seizures, 1956
for pediatric intubation, 2258*t*
in SE, 1341
for Tardive dyskinesia, 1872
Dibenzoxazepine, 1858*t*
Dibenzoylmethanes, 885*t*, 888
Diclegis, 1007
Diclofenac, 57, 905*t*, 906, 917
Diclofenac gel, 903
Diclofenac patch, 903
Diclofenac topical solution, 903
Dicloxacillin, 674, 1372*t*
for skin and soft tissue infections, 1603
Dicyclomine (*see* Antispasmodics)
Didanosine (ddI), 949*t*
for HIV, 1638*t*

for HIV in labor, 1029
for HIV-related anemia, 2012
Dienogest, 971*t*
Diethylcarbamazine, for amebic liver abscess, 1773*t*
Diethylpropion, 799
Diethylstilbestrol, teratogenic effects, 1004*t*
Dificid (*see* Fidaxomicin)
Diflucan (*see* Fluconazole)
Diflunisal, 905*t*
Digitalis (Digoxin), 133, 225, 505, 698, 2189*t*
for AF, 331–332
doses of, 309
drug interactions, 310*t*
effect on mortality, 308–309
efficacy of, 308
for HF, 281, 286
and hyperkalemia, 618
monitoring parameters, 309
serum drug concentrations, 309
sex differences in response to, 309
toxicity, 311
withdrawal trials, 308
Digitalis glycosides, for HF, 308–311
Digoxin (*see* Digitalis)
Dihydroergotamine, 1273, 1274
Dihydropyridine calcium-channel blockers, for vascular dementia, 2302
Dilaudid (*see* Hydromorphone)
Diloxanide furoate, 1773
for amebicides, 1773*t*
Diltiazem, 125*t*, 133, 162, 224, 640, 1093, 2325*t*
for AF, 333
for HF, 291
for HFpEF, 28, 287
in patients with CKD, 648
for thyroid storm, 109
Dimenhydrinate (Dramamine), 490*t*
for NVP, 1007, 1008*t*
Dimethyl fumarate, for MS, 1255, 1260
Dinoprostone cervical gel, 1022
Dinoprostone slow-release insert (Cervidil), 1022
Dinutuximab, 491*t*
Dioxybenzone, 885*t*, 888
Dipalmitoylphosphatidylcholine (DPPC), 2227
Dipentum (*see* Olsalazine)
Dipeptidyl peptidase-4 inhibitors (DPP-4)

adverse effects of, 1161
contraindications and precautions of, 1161
dosage and clinical use, 1162
drug interactions, 1161–1162
efficacy of, 1162
mechanism of action, 1161
pharmacokinetics of, 1161
Diphenhydramine (Benadryl), 455*t*, 1846
for Akathisia, 1870*t*
for NVP, 1007, 1008*t*
for Parkinsonism, 1870
for sleep, 1932
Diphenoxylate, 569
Diphenoxylate/atropine, 1503
Diphtheria, tetanus, and acellular pertussis (DTaP), 1405
vaccines, 1408
Dipyridamole, 1358*t*, 1359
Direct oral anticoagulants (DOACs), 187
advantages of, 194
dosing for AF and VTE, 186*t*
drug interactions with, 186*t*
for management of PE, 198
pharmacokinetic and pharmacodynamics properties of, 185*t*
for stroke prevention, 201
for VTE treatment, 201
Direct thrombin inhibitors
for heparin-induced thrombocytopenia, 185
injectable, 187*t*
Direct vasodilators, for hypertension, 148
Dirithromycin (Dynabac), 1372*t*
Diskus, for chronic asthma, 413, 415
Disopyramide
for HF, 291
for tachycardia, 1873
Disulfiram, alcohol withdrawal, 1968, 1970
Diuretics
adverse effects of, 293–294
and azotemia, 293
and BNP, 293
combination therapy of, 295
for dysmenorrhea, 1048
for HF, 284
for hypertension, 147, 155–158
and hyperuricemia, 293
and hypokalemia, 158, 293

hypomagnesemia and, 159, 293
and hyponatremia, 159, 293
loop, 619
and metabolic alkalosis/acidosis, 606
monitoring parameters with, 296*t*
for nephrotic edema, 607
osmotic, 628
for PMS, 1057
thiazide, 622, 2325*t*
Divalproex, 1275, 1332, 1919*t*
Divigel (*see* Estradiol gel; Estradiol topical emulsion/gel/solution)
DLV (*see* Delavirdine (DLV))
DMPA (*see* Depot medroxyprogesterone acetate (DMPA))
DOACs (*see* Direct oral anticoagulants (DOACs))
Dobutamine, 221, 2267*t*, 2269
in cardiac failure, 384–385, 384*t*
for cardiogenic shock, 384–385
for HF, 287, 315
for septic shock, 393–394
for tachycardia, 386
Docetaxel, 491*t*, 496, 2043*t*, 2052
and hepatic dysfunction, 2056*t*
for NSCLC, 2114*t*
peripheral nerve toxicity of, 2048
for prostate cancer, 2150
Docosahexaenoic acid (DHA), 130
Docosanol cream (Abreva), 1702
Dofetilide
for AF, 334
for SuVT, 344
for tachycardia, 1873
for WPW, 339
Dolasetron (Anzemet), 494*t*
for PONV, 501*t*
Donepezil
for Alzheimer disease, 2298–2299
for vascular dementia, 2303
Dopamine, 671, 721*t*, 1257, 2267*t*, 2269
for cardiac performance, 383–384, 384*t*
for cardiogenic shock, 383–384
GERD and, 526*t*
for HF, 287, 315
for hyperprolactinemia, 1874
for mild hypotension, 384–385
for NVP, 1008*t*

for septic shock, 393
for Tardive dyskinesia, 1872
Dopamine agonists, 1288–1289
adverse effects of, 1291
dosage of, 1292
for Parkinson disease, 1289–1292
Doral (*see* Quazepam)
Doribax (*see* Doripenem)
Doripenem (Doribax), 1372*t*
for skin and soft tissue infections, 1606
Dornase alfa, 478
Dorzolamide (Trusopt), 1198
Doxazosin, 164*t*, 2320, 2325*t*
for BPH, 2320
in patients with CKD, 648
Doxepin (Silenor)
for depressive disorders, 1891*t*
for pruritus, 861
for treatment of insomnia, 1835*t*
Doxercalciferol, 653
Doxorubicin, 491*t*, 2042, 2043, 2043*t*, 2049–2050, 2063, 2065, 2093
for breast cancer, 2103
and cardiomyopathy, 2049–2050
cardiotoxicity of, 2067
gonadal toxicity of, 2058
for osteosarcoma, 2068
for rhabdomyosarcoma, 2070
for T-cell lymphomas, 2079*t*
Doxycycline, 957, 976*t*, 1372*t*, 1766*t*, 1788, 1792
for acne, 868, 869
for cellulitis, 674
for COPD, 436
dosing of, 1384*t*
for HGA, 1794
for HME, 1794
for Lyme disease, 1788
for lymphogranuloma venereum, 1570
for malaria prophylaxis, 51
for PID, 1569*t*
for RMSF, 1794
for skin and soft tissue infections, 1603, 1608
for TBRF, 1792
for tularemia, 1793
Doxylamine, 1846
for NVP, 1007, 1008*t*

DPP-4 (*see* Dipeptidyl peptidase-4 inhibitors (DPP-4))
DPPC (*see* Dipalmitoylphosphatidylcholine (DPPC))
Dramamine (*see* Dimenhydrinate)
Dronabinol (Marinol), 494*t*
Dronedarone, 125*t*
for AF, 334
for HF, 291
Droperidol (Inapsine), 494*t*
for NVP, 1008–1009, 1008*t*
for PONV, 501*t*
Drospirenone, 1046, 1057
DRV (*see* Darunavir (DRV))
DTaP (*see* Diphtheria, tetanus, and acellular pertussis (DTaP))
DTIC (*see* Dacarbazine (DTIC))
Dulaglutide, 1159–1160, 1174
Dulera (*see* Mometasone/formoterol)
Duloxetine, 1214, 1229*t*, 1808*t*, 1822, 2314
for depressive disorders, 1891*t*, 1892*t*
for diabetes, 1179–1180
for OA, 906–907
for serotonin, 1897
for stress incontinence, 2315
Duricef (*see* Cefadroxil)
Dutasteride, 2321
for BPH, 2321
for prostate cancer, 2157
Dymista (*see* azelastine HCl/fluticasone propionate)
Dynabac (*see* Dirithromycin)

E

Ecamsule, 885*t*, 888
Echinacea, 1719
Echinocandins, 1626, 1677, 1681*t*, 1683, 1685, 1687, 1692, 1695
Echothiophate iodide, 1189
Econazole, 1676*t*
Ecstasy (*see* 3,4-methylenedioxymethamphetamine)
Edluar, for treatment of insomnia, 1835*t*
Edoxaban, 1358*t*
for prevention of stroke, 187, 336–337
Efavirenz (EFV), 976*t*
for HIV, 1638*t*
for HIV in labor, 1029
Effexor (*see* Venlafaxine)
Effexor XR (*see* Venlafaxine)

EFV (*see* Efavirenz (EFV))
EGFR inhibitors (*see* Epidermal growth factor receptor (EGFR) inhibitors)
Eicosopentanoic acid (EPA), 130
Elbasvir, for HAV, 1752, 1753
Eldepryl (*see* Selegiline)
Elestat (*see* Epinastine)
Elestrin (*see* Estradiol gel; Estradiol topical emulsion/gel/solution)
Eletriptan, 1273
Ellence (*see* Epirubicin)
Elotuzumab, 492
Eloxatin (*see* Oxaliplatin)
Elspar (*see* Asparaginase)
Eluxadoline (Viberzi), 569
Emadine (*see* Emedastine)
Emedastine (Emadine), 460*t*
Emend (*see* Aprepitant; Fosaprepitant)
Emollients, for psoriasis, 873*t*
Empagliflozin, 1163
Empiric antifungal therapy, 1692
Emtricitabine (FTC), 1741
for HIV, 1637*t*
Enalaprilat (Vasotec IV), 179, 297, 297*t*, 353*t*
for hypertension, 160*t*, 363
Encainide, and PVC, 342
Enfuvirtide (T-20) Fuzeon, for HIV, 1640*t*
Engerix-B, 1406
Enjuvia (*see* Synthetic conjugated estrogens)
Enoxaparin, 183*t*, 195*t*, 196, 261, 709
for ACS, 248*t*
and UFH, 264
Ensulizole, 885*t*
Entacapone, 1286*t*, 1300
adverse effects of, 1301
dose of, 1301
pharmacologic and pharmacokinetic properties of, 1300*t*
Entecavir, 1741
for HBV, 1740
Entocort EC, 550
Entresto (*see* Sacubitril/valsartan)
Enzalutamide, for prostate cancer, 2151
EPA (*see* Eicosopentanoic acid (EPA))
Epanova, 131
Epidermal growth factor receptor (EGFR) inhibitors, 2044
Epinastine (Elestat), 460*t*
Epinephrine, 454, 469*t*, 2267*t*, 2269

for anaphylaxis, 719, 721*t*
for cardiogenic shock, 384, 384*t*
for cardiopulmonary arrest, 348–349
dose of, 348
for septic shock, 393
EpiPen 2-Pak, 469*t*
EpiPen Jr 2-Pak, 469*t*
Epirubicin (Ellence), 491*t*, 2043*t*, 2050
and hepatic dysfunction, 2056*t*
Eplerenone, 576
for hypertension, 147, 164
side effects of, 267
Epoetin alfa, 646
for anemia, 2011
Epoprostenol, 954
Eprosartan mesylate, for hypertension, 161*t*
EPT therapy (*see* Estrogen/progestogen (EPT) therapy)
Erbitux (*see* Cetuximab)
Ergocalciferol, 652
Ergot alkaloids
adverse effects of, 1273–1274
for migraine headache, 1274
Ergotamine, and lactation, 1035*t*
Eribulin, 491*t*
Erlotinib (Tarceva), 492*t*, 2116–2117
drug interaction with smoking, 1978*t*
Ertapenem (Invanz), 1372*t*
dosing of, 1384*t*
for gram-negative aerobes, 1374*t*
for UTI, 1553*t*
Erythrocin (*see* Erythromycin)
Erythromycin, 125*t*, 133, 868, 976*t*, 1372*t*, 1424, 2220, 2220*t*
for acne, 868
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
and breast milk, 1033
for BV, 1028
for *Campylobacter* infection, 1514
and dyspepsia, 509
for GBS infection, 1028
for RMSF, 1794
for skin and soft tissue infections, 1602
for TBRF, 1790
Erythropoietic therapy, for anemia, 2011
Escitalopram (Lexapro), 1060*t*, 1069*t*, 1808*t*, 1816

for depressive disorders, 1891*t*, 1892*t*
for panic disorder, 1816
for PTSD, 1822
for SAD, 1821
for vasomotor symptoms, 1069*t*
ESHAP, for aggressive lymphomas, 2092–2093
Eslicarbazepine, 1317*t*, 1319, 1323*t*
for seizures, 1323*t*
Esmolol (Brevibloc), 353*t*
for hypertension, 364
Esomeprazole, 238, 506*t*, 507, 525, 1249, 2220*t*
for end-of-life care, 91
for preventing SRMB, 537*t*
Estazolam, 1807*t*, 1835*t*
Esterified estrogen (Menest), 1065*t*
Estrace (*see* Estradiol cream)
Estradiol acetate tablet (Femtrace), 1065*t*
Estradiol acetate vaginal ring (Femring), 1065*t*
Estradiol cream (Estrace), 1066*t*, 2279
Estradiol gel (Divigel; Elestrin; Estrogel), 1065*t*
Estradiol hemihydrate tablets (Vagifem and Vagifem LD), 1066*t*
Estradiol hemihydrate tablets (Vagifem), 1066*t*
Estradiol ring (Estring), 1066*t*
Estradiol topical emulsion/gel/solution (Divigel, Elestrin, Estrogel, Estrasorb, Evamist), 1065*t*
Estramustine, 492*t*
Estrasorb (*see* Estradiol topical emulsion/gel/solution)
Estring (*see* Estradiol ring)
Estrogel (*see* Estradiol gel; Estradiol topical emulsion/gel/solution)
Estrogen/progestogen (EPT) therapy, 1064–1065*t*, 1066, 1068
adverse effects of, 1068
Estrogens, 526*t*, 1012, 2315–2316
androgen deprivation therapy, 2156*t*
for stress incontinence, 2315
Eszopiclone (Lunesta), 1835*t*, 1837
Etanercept, 914, 923, 926*t*, 932
for PsA, 879
Ethacrynic acid
for HF, 292
Ethambutol, 55
dosing of, 1384*t*
for MAC, 1671
optic neuritis and, 1492–1493
for tuberculosis, 1484*t*, 1488
Ethanol, 1962

for diabetes, 1181
Ethionamide, for tuberculosis, 1485*t*
Ethosuximide, 1317*t*, 1323*t*
for absence seizures, 1332–1333
Ethynodiol diacetate, 968–970*t*
Etidronate, for hypercalcemia, 623*t*
Furosemide, 624
Etidronate, for hypercalcemia, 624
Etodolac, 905*t*
Etomidate, 2259
for pediatric intubation, 2258*t*
Etoposide, 491*t*, 492*t*, 2043*t*, 2050, 2052, 2056*t*, 2063, 2080
for aggressive lymphomas, 2093
and hepatic dysfunction, 2056*t*
for NSCLC, 2114*t*
peripheral nerve toxicity of, 2048
for rhabdomyosarcoma, 2070
for SCLC, 2120*t*, 2121
Etravirine (ETV), for HIV, 1638*t*
Etretinate, teratogenic effects, 1004*t*
Eucalyptus, 1790
Evamist (*see* Estradiol topical emulsion/gel/solution)
Everolimus, 125*t*, 133, 236, 492*t*, 756
Evolocumab, 134–136
Exenatide, for type 2 diabetes, 1159, 1169, 1171
Ezetimibe, 135
adverse effects, 126
clinical pearls, 127
drug interactions, 127
efficacy, 124–127
mechanism of action, 124, 126*f*
pharmacokinetics/pharmacodynamics, 126
place in therapy, 127
Ezogabine, 1317*t*

F

Factive (*see* Gemifloxacin)
Famciclovir (FCV), 1700*t*
adverse effects, 1699*t*
for genital herpes, 1585, 1586*t*
for herpes zoster infection, 1703
pharmacokinetics of, 1706*t*
Famotidine, 1009, 1249*t*, 2220*t*
Fampridine, 1257

Fanapt (*see* Iloperidone)
Fansidar (*see* Sulfadoxine)
Fat-soluble vitamins, 473
for patients with CF, 477*t*
FCV (*see* Famciclovir (FCV))
Febuxostat, 948
drug interactions, 949*t*
Felbamate, 976*t*, 1317*t*, 1319, 1323*t*
Felodipine, for chronic stable angina pectoris, 225
Femring (*see* Estradiol acetate vaginal ring)
Femtrace (*see* Estradiol acetate tablet)
Fenofibrate, 128, 950
Fenofibric acids, 128
Fenoldopam (Corlopam), 353*t*
for BP, 359
for hypertensive crisis, 360
for hypertensive emergencies, 359
Fenoprofen, 905*t*
Fentanyl, 1217, 1219*t*
for opioid withdrawal syndrome, 1950
for pediatric intubation, 2257*t*
Feraheme (*see* Ferumoxytol)
Ferric carboxymaltose, for anemia, 2001
Ferric citrate, 651*t*
Ferric gluconate, for anemia, 2001
Ferritin, for anemia, 1999
Ferrous fumarate, for anemia, 1999
Ferrous gluconate, for anemia, 1999
Ferrous sulphate, 1296*t*
for anemia, 1999
Ferumoxytol, 644, 729
for anemia, 2001, 2002
Fesoterodine, 2314
Fexofenadine (Allegra), 133, 455*t*
for rhinitis, 458
Fibric acid, 128, 945*t*
adverse effects, 128–129
clinical pearls, 129–130
drug interactions, 129
efficacy, 127–128
mechanism of action, 127, 128*f*
pharmacokinetics/pharmacodynamics, 128
place in therapy, 129
Fibrinolytic therapy, 199
Fibronectin, 1024

Fidaxomicin (Dificid), 1372*t*
15-methyl prostaglandin $F2_{\alpha}$-tromethamine, 1030–1031
Finasteride, 2321
for BPH, 2321
for hirsutism, 1046
for prostate cancer, 2157
Fingolimod, 1255, 1262, 1262*t*
5-α-reductase inhibitors, 2157
5-aminosalicylic acid (5-ASA), 559
for Crohn disease, 562
5-flucytosine (5-FC), 1454, 1676
amphotericin B and, 1454
5-fluorouracil, 491*t*, 1667
5-HT_3 antagonists, for CINV, 493, 494*t*
Flagyl (*see* Metronidazole)
Flecainide
for AF, 333
for HF, 291
and PVC, 342
for WPW, 339
Flonase Sensimist (*see* Fluticasone furoate)
Floxin (*see* Ofloxacin)
Floxuridine, 491*t*
Fluconazole (Diflucan), 125*t*, 133, 976*t*, 1666–1669, 1676, 1676*t*, 1677, 1678*t*
adverse effects of, 1381*t*
for CAPD-associated peritonitis, 1533*t*
for chronic pulmonary blastomycosis, 1688
CNS penetration of, 1692
cryptococcal disease, 1695
dosing of, 1384*t*
for fungal endocarditis, 1454
for fungal infection, 1536
renal failure, dosing of drugs, 707
for sepsis, 2244*t*
for VVC, 1580*t*, 1581
Flucytosine, 1667, 1677
adverse effects of, 1381*t*, 1695
and creatinine clearance, 1695
cryptococcal disease, 1695
dosing of, 1384*t*
and GI distress, 1695
for OIs, 1656
renal excretion of, 1695
risk factor C, 1689
Fludarabine, 492*t*, 2048, 2054*t*

for CLL, 2087
encephalopathic toxicity of, 2049
neurotoxicity of, 2048*t*
Flumadine (*see* Rimantadine)
Flumazenil, 1813
hepatic encephalopathy, 584
for pediatric intubation, 2259*t*
FluMist, 1412
influenza vaccine, 1710
Flunisolide, 461*t*
for allergic rhinitis, 462
Fluorocytosine, 1676*t*
Fluorometholone acetate, 1202
Fluoropyrimidine, for colon cancer, 2126
Fluoroquinolones, 481, 509, 1424, 1605, 1788
and antacids, 41
for bacterial prostatitis, 1560
for *Campylobacter* infection, 1514
for CAP, 1466
for CAPD-associated peritonitis, 1530
for COPD, 442
for gonorrhea, 1565
for infectious diarrhea, 1504
for MAC, 1671
for nontyphoidal salmonellosis, 1508
for skin and soft tissue infections, 1605
for surgical procedures, 1393*t*
for UTI, 1547, 1549
for UTI in pediatric patients, 1554
Fluorouracil, 2038, 2042, 2043, 2043*t*, 2052
for adverse effects, 2127, 2132
and cerebellar dysfunction, 2048
for colon cancer, 2126
encephalopathic toxicity of, 2048
and hepatic dysfunction, 2056*t*
neurotoxicity of, 2048*t*
Fluoxetine (Prozac or Sarafem), 1808*t*, 1816, 1848
for bipolar depression, 1917
for depression, 2306
for depressive disorders, 1891*t*, 1892*t*
for OCD, 1829
for panic disorder, 1816
for PTSD, 1822
for Raynaud phenomenon, 179
and sleep, 1843

for vasomotor symptoms, 1069*t*
Fluphenazine, 1858*t*, 1868*t*, 1869*t*
decanoate, 1866*t*
for schizophrenia, 1864*t*
Flurazepam, 1840
and sleep, 1839
for treatment of insomnia, 1835*t*
Flurbiprofen, 905*t*
Flutamide, for prostate cancer, 2147
Fluticasone
for BPD, 2233
for chronic asthma, 415–416
for COPD, 439*t*, 441
for rhinitis, 462
Fluticasone furoate (Flonase Sensimist), 461*t*
for allergic rhinitis, 462
Fluticasone propionate (Dymista), 461*t*
for allergic rhinitis, 462
Fluvastatin, 47*t*, 57, 115*t*, 120, 121*t*, 125*t*
Fluvoxamine (Luvox), 1808*t*, 1816
for depression, 2306
for depressive disorders, 1891*t*
dosage, 1825
drug interaction with smoking, 1978*t*
for OCD, 1829
for PTSD, 1822
Fluvoxamine CR, for SAD, 1821
Fluzone High-Dose, 1412
Folate
alcohol withdrawal, 1968
for anemia, 2004
Folic acid, 977, 991
and pregnancy, 1000, 1011
recommended daily allowance (RDA), 1001
and women, 1001
Fondaparinux, 196, 261
for ACS, 249*t*
for DVT, 194
UFH and LMWH and, 183–184, 183*t*
Formoterol, for COPD, 438, 440
Fortaz (*see* Ceftazidime)
Fosamprenavir (FPV), 133, 945*t*
for HIV, 1640*t*
Fosaprepitant (Emend), 494*t*
Foscarnet (Foscavir), 775, 1666, 1700*t*, 1703

adverse effects of, 1381*t*, 1664, 1699*t*
dosing regimens, 1664
for herpes labialis, 1703
intravitreal administration, 1666
to prevent nephrotoxicity, 1664
Foscavir (*see* Foscarnet), 1700*t*
Fosfomycin, for UTI, 1543, 1544*t*, 1547
Fosinopril, 296, 296*t*
in hypertension, 160*t*
Fosphenytoin, 57, 976*t*, 1323*t*, 1330
in SE, 1340
for seizures, 1323*t*
FPV (*see* Fosamprenavir (FPV))
FreAmine HBC, 837*t*
FreAmine III, 837*t*
Frovatriptan, 1272, 1273
FTC (*see* Emtricitabine (FTC))
Furazolidone, for giardiasis, 1776
Furosemide, 576, 577, 623, 2053–2054
doses of, 292
for HF, 292
for hypercalcemia, 623*t*
for hypertension, 156
for nephrotic edema, 607
for PDA, 2234, 2237
urine osmolality and, 613

G

Gabapentin (Neurontin), 1220, 1228, 1234, 1257, 1277, 1310, 1310*t*, 1317*t*, 1319, 1916
androgen deprivation therapy, 2155
for diabetes, 1180
for PHN, 1705
for seizures, 1324*t*
for vasomotor symptoms, 1069*t*
Gabapentin, 1228*t*, 1324*t*
Gabapentinoids, 1228
Gabitril (*see* Tiagabine)
Gadolinium-based contrast (GBC) agents, 672
Galantamine
for Alzheimer disease, 2299
for vascular dementia, 2303
Gallium nitrate, for hypercalcemia, 623*t*
Gamma-glutamyl transferase (GGT), 1965

γ-Hydroxybutyric acid (GHB), 1953
Ganciclovir (Cytovene), 775, 776, 1666, 1700*t*
adverse effects of, 1382*t*, 1699*t*
for CMV disease, 1664
dose-limiting toxicity, 1664
dosing of, 1384*t*
ganciclovir-induced bone marrow suppression, 1664
for herpes simplex keratitis, 1204
induction dose of, 1664
intraocular implants, 1666
intravitreal administration, 1666
mode of administration, 1665
Ganciclovir-foscarnet combination, for CMV retinitis, 1665
Garamycin (*see* Gentamicin)
Gardasil, 1410
GBC agents (*see* Gadolinium-based contrast (GBC) agents)
Gefitinib, 492*t*
Gelclair, 2040
Gemcitabine (Gemzar), 491*t*, 2043*t*
for NSCLC, 2114*t*
Gemfibrozil, 125*t*, 127, 128, 128*t*, 129, 649
Gemifloxacin (Factive), 1373*t*
Gemzar (*see* Gemcitabine)
Gentamicin (Garamycin), 698, 701, 1201, 1372*t*, 1793
adverse effects of, 1379*t*
for bacterial endocarditis, 673, 674
for CAPD-associated peritonitis, 1533*t*
for chorioamnionitis, 1029
for CNS infections, 1426*t*
for cystic fibrosis, 482*t*
dosing of, 1384*t*
for enterococcal endocarditis, 1451*t*, 1452
for gram-negative aerobes, 1374*t*
for NEC, 2243
nephrotoxic antibiotic, 673
for UTI, 1553*t*
vancomycin and, 1452
Gentian violet, 1678
Geodon (*see* Ziprasidone)
GGT (*see* Gamma-glutamyl transferase (GGT))
GHB (*see* γ-Hydroxybutyric acid (GHB))
Ginger, for NVP, 1008*t*
Ginseng, 976*t*
Glargine, 1012
Glatiramer acetate, 1255

adverse effects of, 1258
patient characteristics and other factors associated with reduced adherence to, 1260*t*
patient counseling points for, 1260*t*
Gleevec (*see* Imatinib)
Glimepiride, 132, 1155, 1174
for type 2 diabetes, 1155, 1174
Glipizide, 132
for type 2 diabetes, 1155
GLP (*see* Glucagon-like peptide-1 agonists (GLP))
Glucagon, 721*t*, 1174
for hypoglycemia, 1141
Glucagon-like peptide-1 agonists (GLP)
adverse effects of, 1160
contraindications and precautions of, 1161
dosage and clinical use, 1162
drug interactions, 1161–1162
efficacy of, 1162
mechanism of action, 1159
pharmacokinetics of, 1159–1160
Glucarpidase, 2054
Glucocorticoids
antenatal administration, 1027
for fetal lung maturation, 1018
for NVP, 1008*t*
for prostate cancer, 2152
Glucomannan, 803*t*
Glucosamine, 901
Glucose, 618
for hyperkalemia, 620*t*
hypokalemia and, 615*t*
tablets for hypoglycemia, 1141
Glucosidase inhibitors
adverse effects of, 1158
contraindications and precautions of, 1158–1159
dosage and clinical use, 1160–1161
drug interactions, 1159
efficacy of, 1160
mechanism of action, 1158
pharmacokinetics of, 1158
Glutamine, 2048
Glutathione, 2048
Glyburide, 132, 709, 1013, 1034
for type 2 diabetes, 1155
Glycerol, 835

Glycoprotein IIb/IIIa inhibitors, 1356
Glycopyrrolate
for COPD, 439*t*
for end-of-life care, 92
Glycyrrhetinic acid, 2040
Gold, 914, 915
Golimumab, 915, 923, 926*t*
Gonadotropin-releasing hormone (GnRH) agonists, 1052–1053, 1053*t*
adverse effects, 1054
for depressive disorders, 1887*t*
for endometriosis, 1054–1055
Gonadotropin-releasing hormone (GnRH) analogs, for IVF, 994–996
Gonadotropin-releasing hormone (GnRH) therapy, for prostate cancer, 2141, 2146–2147
Goserelin (Zoladex), 1053*t*, 1054
Granisetron (Kytril), 494*t*
for PONV, 501*t*
Grastek, for allergic rhinitis, 457*t*
Grazoprevir, for HAV, 1752, 1753
Green tea, 803*t*
Griseofulvin, 976*t*, 1676, 1676*t*, 1678
risk factor C, 1689
Guanabenz, 167, 2325*t*
Guanfacine, 167, 2325*t*
for ADHD, 1940*t*, 1941
Guarana, 803*t*

H

H_2RAs (*see* Histamine-2 receptor antagonists (H_2RAs))
HAART (*see* Highly active antiretroviral therapy (HAART))
***Haemophilus influenzae* type b (Hib), 1405, 1408–1409**
Halcion (*see* Triazolam)
Haldol (*see* Haloperidol)
Halfan (*see* Halofantrine)
Halofantrine (Halfan), 1763
Haloperidol (Haldol), 494*t*, 1247, 1306, 1858*t*, 1868*t*, 1869*t*
for end-of-life care, 91
for hyperprolactinemia, 1874
for OCD, 1830
for schizophrenia, 1864, 1864*t*
Haloperidol decanoate, 1866*t*
HAT (*see* Heparin-associated thrombocytopenia (HAT))
Havrix, 1407
Hawthorn, 323

HCTZ (*see* Hydrochlorothiazide (HCTZ))
Heat therapy, 1679
Helioplex, 888
Hemoglobin F, for vaso-occlusive complications, 2008–2009
Heparin, 183*t*, 1355–1356
for ACS, 250*t*
adverse effects of, 192–193
and breast milk, 1034
doses of, 190–191
dosing nomogram, 191, 191*t*
duration of therapy, 192
hemorrhage from, 193
hypersensitivity reactions of, 193–194
induced thrombocytopenia, 192*t*
osteoporosis from, 193
protamine and, 193
reversal of effect, 193
therapeutic monitoring, 191–192
thrombocytopenia from, 192–193
for thrombosis, 182–183
Heparin-associated thrombocytopenia (HAT), 192
Heparinoids, 1355–1356
HepatAmine, 837*t*
Hepatitis A (Hep A) vaccines (*see* Vaccination)
Hepatitis B (HepB) vaccine (*see* Vaccination)
Hepatitis B immunoglobulin (HBIG), 1406
Hepatotoxicity
from isoniazid, 1490–1491
isoniazid–rifampin and, 1492
rifampin and, 1492
Herceptin (*see* Trastuzumab)
Heroin
and lactation, 1035*t*
for opioid withdrawal syndrome, 1949
Hib polysaccharide conjugate vaccines (HbCV), 1409
HiDAC (*see* High-dose cytarabine (HiDAC))
High-dose cytarabine (HiDAC), 2085, 2086
Highly active antiretroviral therapy (HAART), 1654
and cryptococcosis, 1666
discontinuation of, 1656
impact on CD4+lymphocytes, 1656
impact on opportunistic infections (OIs), 1655
and prevalence of CMV, 1665
Histamine-2 receptor antagonists (H_2RAs), 505, 506*t*, 507, 514*t*, 1248, 1249*t*
concomitant administration of, 508

for GER, 2219–2221, 2220*t*
for GERD, 530
and PPI, in combination, 530
in preventing SRMB, 537, 537*t*
for upper GI bleeding, 535
HIV protease inhibitors, 125*t*
HMG-CoA reductase inhibitors, 945*t*
Homosalate, 885*t*, 888
Homovanillic acid (HVA), 2063
Hoodia, 803*t*
HS (*see* Hypertonic Saline (HS))
Humalog (*see* Insulin lispro)
Human erythropoietin-epoetin alfa, 646
HVA (*see* Homovanillic acid (HVA))
Hyaluronic acid, 2040
Hycamtin (*see* Topotecan)
Hydralazine, 164*t*, 312, 353*t*, 363, 1019, 2325*t*
contraindications of, 363
doses of, 363
for HF, 287
for hypertension, 167
in patients with CKD, 648
Hydrochloric acid (HCl), 598
Hydrochlorothiazide (HCTZ), 2283
and breast milk, 1035
for hypertension, 155, 234–235
Hydrocodone, 1219*t*
Hydrocortisone
for BPD, 2233
for prostate cancer, 2152
valerate, 857
Hydrocortisone cream (Xerese), 1702
Hydromorphone (Dilaudid), 709
Hydromorphone, 1217, 1219, 1219*t*
Hydroxocobalamin, 360
Hydroxychloroquine, 739–740, 745*t*, 746*t*, 914, 920
psoriasis and, 872
Hydroxycitric acid, 803*t*
Hydroxypyridone, 1677
Hydroxyurea, 493*t*, 2085
for vaso-occlusive complications, 2008
Hydroxyzine (Vistaril)
for NVP, 1007, 1008*t*
for pruritus, 861
Hyoscyamine (*see also* Antispasmodics)

for end-of-life care, 92
Hypertonic Saline (HS), 376, 480
for airway clearance treatment, 480
Hypnotics, 1833, 1838
and sleep, 1843
Hypoglycemics, 1012

I

Ibandronate, 2342, 2343, 2343*t*
Ibrutinib, 493*t*
Ibuprofen, 480, 905, 905*t*, 917
for dysmenorrhea, 1048
for HF, 290
and hyperkalemia, 618
for PDA, 2237
Ibutilide, for AF, 333
ICE, for aggressive lymphomas, 2092–2093
Ice therapy, 946
Idamycin (*see* Idarubicin)
Idarubicin (Idamycin), 491*t*, 2043*t*, 2050
for AML, 2085
Idarucizumab, 1361
Idelalisib, 493*t*
IDV (*see* Indinavir (IDV))
Ifex (*see* Ifosfamide)
IFNs (*see* Interferons (IFNs))
Ifosfamide, 491*t*, 2053, 2054*t*
and cranial neuropathies, 2049
encephalopathic toxicity of, 2048
and encephalopathy, 2048
neurotoxicity of, 2048*t*
for osteosarcoma, 2068
for rhabdomyosarcoma, 2070
Iloperidone (Fanapt), 1868*t*, 1869*t*
for hyperprolactinemia, 1874
for schizophrenia, 1859, 1860*t*
Iloprost, 954
Imatinib (Gleevec), 133, 493*t*, 2042, 2052, 2056, 2056*t*, 2089
drug interactions with, 50–51
^{131}I-MIBG, 2065
Imidazoles, 1676
Imipenem-cilastatin (Primaxin), 1372*t*
for aerobic gram-positive cocci, 1373*t*
for anaerobes, 1375*t*

for CAPD-associated peritonitis, 1533*t*
for cystic fibrosis, 482*t*
dosing of, 1384*t*
for febrile neutropenia, 1618
for skin and soft tissue infections, 1606
for UTI, 1553*t*
Imipenem/meropenem/doripenem, for gram-negative aerobes, 1374*t*
Imipramine
for depressive disorders, 1891*t*, 1892*t*
for panic disorder, 1816
Imiquimod, 1703
for genital warts, 1588
Immunoglobulin, 775
G antibodies, 475–476
for HAV, 1725
for HBV, 1736, 1743
for Rh-associated HDN, 1031–1032
Immunoglobulin G (IVIG), for skin and soft tissue infections, 1607
Immunomodulators, for psoriasis, 874*t*
Immunosuppressants and lactation, 1035*t*
Immunotherapy
for allergic rhinitis, 454
for rhinitis, 454
Inactivated polio vaccine (IPV), 1406, 1409
Inapsine (*see* Droperidol)
Incretin, for type 2 diabetes, 1159
Indacaterol, for COPD, 438, 439*t*, 440
Indinavir (IDV), 132, 976*t*, 1639*t*
Indomethacin, 906, 917, 1025
for hypercalcemia, 623*t*
for PDA, 2237
Induction therapy, for AML, 2085–2086
Infanrix, 1408
Infliximab, 915, 923, 926*t*
for inflammatory bowel disease, 550*t*
for PsA, 879
for treatment of CD, 563
for UC, 560
Influenza vaccine, 1411–1412
Inhaled b_2-agonists, 480
Inositol, 1920
Insulin
adverse effects of, 1138–1141
clinical use of, 1123–1125
delivery of, 1123, 1125–1126

for diabetes, 174
for DKA management, 1144
endogenous, 1115
evaluation of, 1129–1130
for hyperkalemia, 620*t*
intensive vs. conventional glycemic control with, 1132*t*
measuring and injecting, 1126–1127, 1127*f*
mixing, 1132
monotherapy with type 2 diabetes, 1172–1173
pharmacodynamics of, 1115–1119, 1117*t*
pharmacokinetics of, 1115
premixed, 1173
stability, 1132
therapy, 1012
therapy, basal, 1173–1174
Insulin aspart (NovoLog), 1117
Insulin degludec (Tresiba), 1131
Insulin detemir (Levemir), 1012, 1131
Insulin glargine (Lantus), 1131
Insulin glulisine (Apidra), 1012, 1132
Insulin lispro (Humalog), 1117–1118
Interferon alpha, 491*t*
Interferons (IFNs)
for depressive disorders, 1887*t*
for HBV, 1738
Interleukin-2, for depressive disorders, 1887*t*
Intermezzo, for treatment of insomnia, 1835*t*
Intramuscular methylprednisolone, 955
Intranasal corticosteroids
for allergic rhinitis, 452
for rhinitis, 461–464, 461*t*
Intraocular ganciclovir implants, 1665
Intravenous (IV) albumin infusions, 577
Intravenous nitroglycerin, 315
Invanz (*see* Ertapenem)
Invega (*see* Paliperidone)
Iodines, 1678
and pregnancy, 1000
Iodoquinol, 1773
for amebic liver abscess, 1773*t*
for amebicides, 1773*t*
for gastrointestinal disease, 1773*t*
Iopidine (*see* Apraclonidine)
Ipilimumab, 492*t*, 2046
IPLEDGE program, 870

Ipratropium bromide (Atrovent), 461*t*
for allergic rhinitis, 453
for BPD, 2232
for COPD, 438, 439*t*
IPV (*see* Inactivated polio vaccine (IPV))
Irbesartan, for hypertension, 161*t*
Irinotecan, 491*t*, 2041, 2056
for adverse effects, 2132
for colon cancer, 2127
drug interaction with smoking, 1978*t*
for rhabdomyosarcoma, 2070
for SCLC, 2120*t*
Iron
for anemia, 1999
and dyspepsia, 509
GERD and, 526*t*
ingestion of, assessment of, 73–76
and pregnancy, 1000–1001
Iron dextran, 644
for anemia, 2001, 2002
injection, 729
Iron sucrose, 644
for anemia, 2001, 2002
Isavuconazole, 1676*t*
adverse effects of, 1381*t*
Isoflavone, 1063
Isoniazid, 505
and allergic reactions, 1490
dosing of, 1384*t*
drug interactions with, 1490
hepatotoxicity from, 1490–1491
for HIV-infected and TB, 1669
and peripheral neuropathy, 1491
for tuberculosis, 55, 56*t*, 1484*t*, 1488
Isoproterenol, 384*t*
GERD and, 526*t*
for postoperative cardiac failure, 384*t*
Isopto Carpine (*see* Pilocarpine)
Isosorbide, 1196
Isosorbide-5-mononitrate, 583
Isosorbide dinitrate (BiDil), 231, 312, 313
Isotretinoin, 976*t*
for acne, 870
teratogenic effects, 1004*t*
Isradipine, for chronic stable angina pectoris, 224

Itraconazole, 125*t*, 132, 505, 976*t*, 1667, 1676*t*, 1677, 1678*t*, 1679
adverse effects of, 1381*t*
antifungal agents, 41
for chronic pulmonary blastomycosis, 1689
CNS penetration of, 1692
dosing, 1679
for S. schenckii, 1679
IV antipseudomonal antibiotics, 483
IV colistin, 483
IV diltiazem, for AF, 364
IV methylprednisolone, 762
IV pentamidine isethionate, 1660
IV tobramycin, 483
IV verapamil, 364
Ivabradine (Corlanor), 286
Ivacaftor (Kalydeco), 63
Ivermectin, 1781
for lice, 1774*t*
Ixabepilone, 491*t*
peripheral nerve toxicity of, 2048
Ixazomib, 493*t*
Ixekizumab, 879
Ixempra (*see* Ixabepilone)

J

Jevtana (*see* Cabazitaxel)

K

Kalydeco (*see* Ivacaftor)
Kanamycin, teratogenic effects, 1004*t*
Keflex (*see* Cephalexin)
Keppra, 1325*t*
Keratolytics, 873*t*
Ketamine, 1956, 2189*t*
for pediatric intubation, 2258*t*
Ketek (*see* Telithromycin)
Ketoconazole, 125*t*, 132, 505, 976*t*, 1676*t*, 1677, 1685, 1691, 1692
adverse effects of, 1381*t*
antifungal agent, 41, 2149
for chronic pulmonary blastomycosis, 1689
Ketoprofen, 905*t*
Ketorolac (Acular), 460*t*, 905*t*, 917
Ketotifen, 460*t*, 1201

Kinrix, 1407*t*
KOH (*see* Potassium hydroxide (KOH))
Kyleena, 982
Kytril (*see* Granisetron)

L

Labetalol (Normodyne; Trandate), 353*t*, 354*t*, 1017*t*, 1019
for BP, 354, 364
disadvantages of, 360
for hypertension, 166, 166*t*, 358, 361
parenteral to oral conversion, 360
for pregestational diabetes, 1011
Lacosamide, 1317*t*, 1319, 1324*t*
Lactogen, 1012
Lactulose, 2217*t*
hepatic encephalopathy, 585
and neomycin, 586–587
and rifaximin, 586
LAIV (*see* Live attenuated influenza vaccine)
Lamictal (*see* Lamotrigine)
Lamivudine, 1741, 1742
for HBV, 1740
for HIV, 1637*t*
in labor, 1029
Lamotrigine, 976*t*, 1227, 1228*t*, 1317*t*, 1319, 1324*t*, 1916, 1917, 1919*t*
for absence seizures, 1332
and carbamazepine, 1328–1329
for diabetes, 1180
for schizophrenia, 1881
for seizures, 1324*t*, 1328–1329
teratogenic effects, 1004*t*
Lansoprazole, 506*t*, 507, 525, 537*t*, 1249*t*, 2220*t*
Lanthanum, 651*t*
Lanthanum carbonate, 651–652
Lantus (*see* Insulin glargine)
Lapatinib, 133, 493*t*, 2052
L-asparaginase, 2079*t*
Lastacaft (*see* Alcaftadine)
Latanoprost (Xalatan), 1187
Latuda (*see* Lurasidone)
L-Carnitine, 176, 994
Lecithin, for RDS, 2227
Ledipasvir, for HAV, 1752, 1753
Leflunomide, 741, 745*t*, 746*t*, 914, 924

adverse effects, 922
and cholestyramine, 922
dosage, 922
Lenalidomide, 493*t*, 2048, 2054*t*, 2094
neurotoxicity of, 2048*t*
peripheral nerve toxicity of, 2048
Lenvatinib, 492*t*
Lepirudin, for heparin-induced thrombocytopenia, 185
Letrozole (aromatase inhibitor), 992, 1045*t*, 1046
Leucovorin, 2054, 2069
for *Toxoplasma* encephalitis, 1662–1663
Leukeran (*see* Chlorambucil)
Leukotriene
for allergic rhinitis, 452
for asthma, 417
modifiers, 480
for rhinitis, 464–465
Leuprolide (Lupron), 1053*t*, 1054
for prostate cancer, 2149
Levalbuterol, for COPD, 438, 439*t*
Levemir (*see* Insulin detemir)
Levetiracetam, 1219, 1317*t*, 1325*t*, 1916
for seizures, 1325*t*, 1328, 2251
Levobunolol (Betagan), 1187
Levocetirizine (Xyzal), 455*t*
for rhinitis, 458
Levodopa, 1286*t*
and adjunctive therapy, 1292
drug interactions, 1296*t*
metabolism in human body, 1295*f*
for Parkinson disease, 1289, 1295, 1301
for RLS, 1306
Levofloxacin (Levoquin), 514*t*, 1372*t*
for aerobic gram-positive cocci, 1373*t*
for CAPD-associated peritonitis, 1533*t*
for COPD, 442
dosing of, 1384*t*
for skin and soft tissue infections, 1606
for tuberculosis, 1485*t*
for UTI, 1544*t*, 1553*t*
Levomilnacipran
for depressive disorders, 1891*t*, 1892*t*
for serotonin, 1897
Levonorgestrel, 968–970*t*, 982
Levonorgestrel intrauterine system (IUS), 1049

Levonorgestrel-releasing IUD (Mirena), 982, 1065*t*
Levoquin (*see* Levofloxacin)
Levosimendan, 280
Levothyroxine (L-thyroxine), 91, 132, 976*t*, 1003, 1006, 1073–1074, 1075*t*, 1081
Lexapro (*see* Escitalopram)
Lialda (*see* Mesalamine)
Lidocaine, 1215*t*, 2040, 2189*t*
for cardiopulmonary arrest, 349–350
patches (Lidoderm), 1230, 1705
topical, 1705
for ventricular arrhythmias treatment, 258
Lidoderm (Lidocaine patches), 1705
Liletta, 982
Linaclotide (Linzess), 567
Linagliptin, 1162
Lindane, 1775*t*, 1780
toxicity, 1780
Linezolid (Tedizolid, Zyvox), 1372*t*, 1448
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
for CAPD-associated peritonitis, 1533*t*
for CNS infections, 1426*t*
dosing of, 1385*t*
for endocarditis, 1450, 1453
for HAP, 1473
MRSA, 1606
for skin and soft tissue infections, 1604
with vancomycin, 1621
Linzess (*see* Linaclotide)
Lipid-lowering agents, 267
Lipopeptides, 1676
Liquid multivitamin, 477
Liraglutide (Saxenda), 801, 1159, 1173–1174
Lisdexamfetamine, for ADHD, 1940*t*
Lisinopril, 41, 296–297, 296*t*, 2286
in hypertension, 160*t*
for prostate cancer, 2143, 2150
Lispro, 1012
Lithium, 225, 622, 1907
and ACE inhibitors, 1914*t*
and acetazolamide, 1914*t*
and acne, 1912*t*
adverse effects, 1812*t*, 1911–1912
and antipsychotics, 1914*t*

for bipolar depression, 1917, 1919
for bipolar disorder, 1919*t*
and caffeine, 1914*t*
and carbamazepine, 1914*t*
for critically ill patients, 1241
for depressive disorders, 1889
and diltiazem, 1914*t*
and diuretics, 1914*t*
dosage, 1911
drug–drug interactions, 1914*t*
drug–food interactions, 1914*t*
half-life of, 1911
and hypothyroidism, 1913
and lactation, 1035*t*
and methyldopa, 1914*t*
monitoring of, 1911*t*
and NSAIDs, 1914*t*
patient education, 1912–1913
during pregnancy, 1913–1914
prelithium workup, 1911
psoriasis and, 872
for schizophrenia, 1881
and sodium, 1914*t*
and SSRIs, 1914*t*
teratogenic effects, 1004*t*
and theophylline, 1914*t*
toxicity, 1913
and verapamil, 1914*t*
weight gain with, 1913
Lithium carbonate, 1279
Lithium–lamotrigine, 1917
Live attenuated influenza vaccine (LAIV), 1412
LMWHs (*see* Low-molecular-weight heparins (LMWHs))
Local anesthetics, for neuropathic pain, 1214
Lodoxamide (Alomide), 460*t*, 1201
Lomitapide, 125*t*
adverse effects, 132
clinical pearls, 133
drug interactions, 132–133
efficacy, 132
mechanism of action, 132
pharmacokinetics/pharmacodynamics, 132
place in therapy, 132
Lomustine, 492*t*, 2053, 2054*t*
Loniten (*see* Minoxidil)

Loop diuretics, 619
and AIN, 674
dosing, 285*t*
for hypertension, 147, 156, 157*t*
and hypokalemia, 615*t*
Loperamide, 2041
antidiarrheals, 569
diarrhea and, 1511
for infectious diarrhea, 1504
for travelers' diarrhea, 1514
Lopinavir/ritonavir, 125*t*, 132, 976*t*
for HIV, 1639*t*
Lorabid (*see* Loracarbef)
Loracarbef (Lorabid), 1372*t*
Loratadine (Claritin), 455*t*
for rhinitis, 458
and sleep, 1836
Lorazepam (Ativan), 57, 494*t*, 1020, 1807*t*
for acute agitation, 1917
for Akathisia, 1870*t*
alcohol withdrawal, 1968
for end-of-life care, 92
for LTCF, 2289
for pediatric intubation, 2258*t*
for schizophrenia, 1864*t*
in SE, 1340
Lorazepam IV, for seizures, 2251
Lorcaserin (Belviq), for obesity, 801
Losartan, 57, 179, 266, 300, 950, 953–954
Losartan potassium, 161*t*
Loteprednol (Alrex), 460*t*
Lovastatin, 47*t*, 115*t*, 120, 121*t*, 125*t*, 129
for end-of-life care, 91
Lovaza, 131
Low-dose aspirin therapy, 1511
Low-molecular-weight heparins (LMWHs), 180, 183*t*, 688
advantages of, 254
with renal impairment, 195*t*
for thrombosis, 183
UFH and, 183*t*
Loxapine, 1858*t*, 1868*t*, 1869*t*
for schizophrenia, 1857, 1858
LSD (*see* Lysergic acid diethylamide (LSD))
L-thyroxine (*see* Levothyroxine)
Lubiprostone, 567

Lugol's solution, 1089, 1091*t*, 1096
for thyroid storm, 1098
Lumacaftor, CFTR corrector, 472
Lumigan (*see* Bimatoprost)
Lunesta (*see* Eszopiclone)
Lupron (*see* Leuprolide)
Lurasidone (Latuda), 1868*t*, 1869*t*, 1918
for bipolar depression, 1918*t*, 1919*t*
for hyperprolactinemia, 1874
for schizophrenia, 1859, 1860*t*
Luvox (*see* Fluvoxamine)
Lyrica (*see* Pregabalin)
Lysergic acid diethylamide (LSD), 1035*t*, 1956, 1957
for schizophrenia, 1853, 1853*t*
Lytic peptides, 1677

M

Macrolides, 1603
adverse effects of, 1380*t*
for inflammatory response in CF, 480
for MAC, 1671
for skin and soft tissue infections, 1603
Mafenide acetate (Sulfamylon), 897
Magnesium, 27, 652, 1020, 2048
and aluminum antacids, 505
and children, 2198*t*
and induction therapy, 1665
for normal sinus rhythm, 347
for PMS, 1056
and pregnancy, 1000
and respiratory alkalosis, 1731
Magnesium hydroxide, 651*t*, 2217*t*
Magnesium sulfate, 1020, 1024, 1779
Maintenance therapy, 1828, 1911
for AIDS, 1667
for BD, 1918–1920
for CMV, 1658, 1665
for GER, 2221
for HBV, 1743
with intermittent ATRA, 2087
for neuroblastoma, 2063
for NSCLC, 2115
for OCD, 1828
for pediatric ALL, 2073

for tocolysis, 1028
for *Toxoplasma* encephalitis, 1662–1663
Malarone (*see* Atovaquone-proguanil)
Malathion, 1780
Mammalian target of rapamycin (mTOR), 756
Mandol (*see* Cefamandole)
Mannitol, 626, 1196, 2054
MAOIs (*see* Monoamine oxidase inhibitors (MAOIs))
Maraviroc (MVC), 133, 1633
for HIV, 1640*t*
Marijuana, 1958
and lactation, 1035*t*
Marinol (*see* Dronabinol)
Matulane (*see* Procarbazine)
Maxipime (*see* Cefepime)
MCV4 (*see* Meningococcal conjugate vaccine (MCV4))
MDMA (*see* 3,4-methylenedioxymethamphetamine (MDMA))
Measles, mumps, rubella (MMR) vaccine, 1405, 1413
Mebendazole
for amebic liver abscess, 1774*t*
for ascariasis, 1773*t*
for enterobiasis, 1773*t*
for gastrointestinal disease, 1774*t*
for giardiasis, 1774*t*
for hookworm, 1774*t*
for pinworm, 1777
Mechlorethamine, 491*t*, 2043*t*
Meclizine (Bonine), 490*t*, 1007, 1008*t*
Meclofenamate, 905*t*
Medroxyprogesterone (Progestins)
for endometriosis, 1054
for polycystic ovary syndrome, 1045*t*
Medroxyprogesterone acetate, 980–981, 1065*t*
Mefloquine, 51, 1764, 1766*t*, 1769
for depressive disorders, 1887*t*
Mefoxin (*see* Cefoxitin)
Megestrol, 91
Melatonin, 1837, 1846
for sleep, 1932
Meloxicam, 905*t*, 917
Melphalan, 491*t*, 492*t*, 2043*t*, 2050, 2054*t*, 2063
Memantine, 91
for Alzheimer disease, 2300
MEN 1 (*see* Multiple endocrine neoplasia type 1)
Menactra, 1410

Menest (*see* Esterified estrogen)
Meningitis, for sepsis, 2244*t*
Meningococcal conjugate vaccine (MCV4), 1421
Menthol, 1678
Menveo, 1410
Meperidine, 708, 709*t* (*see also* Opioids)
Mepivacaine, 1215*t*
Meradimate, 885*t*
Mercaptopurine, 492*t*, 949*t*, 2056, 2056*t*, 2076
dosage, 2076
for T-cell lymphomas, 2079*t*
Merem (*see* Meropenem)
Meropenem (Merem), 1372*t*
for CAPD-associated peritonitis, 1533*t*
for CNS infections, 1426*t*
for cystic fibrosis, 482*t*
dosing of, 1385*t*
for febrile neutropenia, 1619
for gram-negative bacillary meningitis, 1432
for meningitis, 1432
for skin and soft tissue infections, 1606
for UTI, 1553*t*
Mesalamine (Apriso; Asacol HD; Delzicol; Lialda; Pentasa), 548*t*, 556*t*, 559
Mesalamine enema (Rowasa), 556*t*
Mesalamine suppository (Canasa), 556*t*
Mescaline, 1956
Mesna, 742, 2055–2056
Metaxalone, 1126*t*
Metformin, 673, 1012 (*see also* Biguanide)
adverse effects of, 1153
clinical use of, 1153
contraindications and precautions of, 1153–1154
for diabetes, 174
doses of, 1167–1168
drug interactions, 1153
efficacy of, 1154
mechanism of action, 1153
for PCOS, 1045
pharmacokinetics of, 1153
pharmacologic therapy with, 1167
therapy, 1167–1168
Methadone, 94–95, 1289*t*, 1978*t* (*see also* Opioids)
for opioid dependence in pregnancy, 1950
for opioid withdrawal syndrome, 1948–1949
Methamphetamine, 453

for ADHD, 1940*t*
CNS stimulants, 1955
Methicillin, 725, 1604
for skin and soft tissue infections, 1604
Methicillin-resistant *Staphylococcus aureus* (MRSA), 1424
Methimazole (Tapazole), 1074, 1090*t*, 1093, 1095–1096
Methocarbamol, 1126*t*
Methotrexate (MTX), 491*t*, 492*t*, 658, 741, 745*t*, 746*t*, 914, 916, 920, 932, 955, 958, 2048, 2054, 2054*t*, 2056, 2080
adverse effects of, 920–921
cytotoxic effects of, 2069
dosage, 920
and folate or folinic acid, 922
for inflammatory bowel disease, 551*t*, 790
interactions, 922
intrathecal, problems of, 2075
and liver biopsy, 921
neurotoxicity of, 2048*t*
and NSAIDs, 921
for ophthalmopathy, 1098
for osteosarcoma, 2068
for psoriasis, 874*t*, 878
and pulmonary disorders, 921
for T-cell lymphomas, 2079*t*
teratogenic effects, 1004*t*
Methyldopa, 164*t*, 1016, 1017*t*, 1296*t*, 2325*t*
for hypertension in pregnancy, 167
in patients with CKD, 648
for pregestational diabetes, 1011
Methylergonovine maleate, 1030, 1030*t*
Methylphenidate, 1848
for ADHD, 1939*t*
Methylprednisolone, 728, 755, 759, 762, 767, 955, 958
injections, 656
for NVP, 1008*t*
Methylxanthines, for apnea, 2246
Metipranolol (Optipranolol), 1187
Metoclopramide (Reglan), 42, 494*t*, 1296*t*, 2220, 2220*t*
for diabetes, 1179
for NVP, 1007, 1008*t*
for PONV, 501*t*
prokinetic agents, 531
Metolazone, 284
Metoprolol, 230, 1093, 1310, 2325*t*
in acute setting, 262

in HFrEF, 303
for MI, 262
Metoprolol succinate, 267
in hypertension, 166*t*
Metoprolol tartrate, for hypertension, 166*t*, 263
Metronidazole, 514*t*, 519, 976*t*, 1423, 1773, 2211
adverse effects of, 1582–1583
for amebicides, 1773*t*
for anaerobes, 1375*t*
for bacterial vaginosis, 1578
brain abscess and, 1436
for BV, 1029
for CDI, 1519
for chorioamnionitis, 1029
dosing of, 1385*t*
for giardiasis, 1774*t*, 1776
for PID, 1569*t*
for sepsis, 2244*t*
for skin and soft tissue infections, 1606
for trichomoniasis, 1582, 1775*t*
Mibefradil, 132
Micafungin, 1676, 1676*t*
adverse effects of, 1381*t*
Miconazole, 1580*t*, 1676*t*
Micronized progesterone (Prometrium), 1065*t*
Microsomal epoxide hydrolase, 1006
Midazolam, for pediatric intubation, 2258*t*
Midodrine, 577
administration, 588
Mifepristone, 945*t*
Miglitol, 1158, 1159
Milk of magnesia, 91
Milnacipran, 1229*t*
Milrinone, 287, 315–316, 2267*t*
for postoperative cardiac failure, 384*t*, 385–386
Minocycline, 868, 870, 915, 976*t*, 1303, 1372*t*
Minoxidil (Loniten), 164*t*, 167, 354*t*
for BP, 354
for hypertensive urgency, 358–359
in patients with CKD, 648
Mipomersen
adverse effects, 133
clinical pearls, 134
drug interactions, 134
efficacy, 133

mechanism of action, 133
pharmacokinetics/pharmacodynamics, 133
place in therapy, 134
Mirabegron, 2315
Mirapex (*see* Pramipexole)
Mirena (*see* Levonorgestrel-releasing IUD)
Mirtazapine, 1280, 1809, 1898
for depressive disorders, 1891*t*, 1892*t*
for sleep, 1932
Misoprostol, 506*t*, 1022
and lactation, 1035*t*
for postpartum hemorrhage, 1029, 1030*t*
teratogenic effects, 1004*t*
Mitomycin, 491*t*, 2043*t*, 2050, 2054*t*
Mitotane, 492*t*
Mitoxantrone, 491*t*, 1255, 2043*t*, 2050
adverse effects of, 1262
for prostate cancer, 2151
MMF (*see* Mycophenolate mofetil (MMF))
MMR vaccine (*see* Measles, mumps, rubella (MMR) vaccine)
Modafinil, 976*t*, 1257, 1847–1848
for ADHD, 1943
Moexipril, in hypertension, 160*t*
Molindone, for schizophrenia, 1857
Mometasone furoate (Nasonex), 461*t*
for allergic rhinitis, 462
Mometasone/formoterol (Dulera), 413, 857
Monoamine oxidase-b inhibitors, 1296*t*
adverse effects, 1293
dosage of, 1293
for Parkinson disease, 1289, 1301–1302
Monoamine oxidase inhibitors (MAOIs), 1817
for anxiety disorders, 1817
for panic disorder, 1817
and sleep, 1843
Monobactams
adverse effects of, 1379*t*
for UTI, 1552*t*
Monocid (*see* Cefonicid)
Monoclonal antibodies
alemtuzumab, 757
basiliximab, 756
Montelukast (Singulair), 461*t*
Morphine, 709, 709*t*, 976*t*, 1217, 1289*t*, 2259 (*see also* Opioids)
for ACS, 250*t*

for end-of-life care, 92
for opioid dependence, 1951
for pediatric intubation, 2257*t*
Morphine sulfate, 258
Moxifloxacin (Avelox), 1372*t*
for aerobic gram-positive cocci, 1373*t*
for anaerobes, 1375*t*
for CNS infections, 1426*t*
dosing of, 1385*t*
for skin and soft tissue infections, 1603, 1608
for tuberculosis, 1485*t*
MPA (*see* Mycophenolic acid (MPA))
MRSA (*see* Methicillin-resistant *Staphylococcus aureus* (MRSA))
mTOR (*see* Mammalian target of rapamycin (mTOR))
MTX (*see* Methotrexate (MTX))
Mucous membrane spray (Zolpimist), 1835*t*
Multiple endocrine neoplasia type 1 (MEN 1), 524
Multitargeted tyrosine kinase inhibitors, 2052
Multivitamins, 91
alcohol withdrawal, 1968
Mupirocin, 860
MVC (*see* Maraviroc (MVC))
Mycifradin (*see* Neomycin)
Mycophenolate mofetil (MMF), 659, 742, 745*t*, 746*t*, 958, 976*t*
for FSGS patients, 659
in liver transplantation, 768–769
and mycophenolate sodium, 755
therapy for Wegener granulomatosis, 658
Mycophenolic acid (MPA), 755

N

Nabilone (Cesamet), 494*t*
***N*-acetyl-*b*-d-glucosaminidase, 482**
N-acetylcysteine (NAC)
for acetaminophen toxicity, 83–84
antioxidant, 672
duration of therapy of, 83–84
efficacy of, 83
intravenous, 83
monitoring efficacy of, 83
oral, 83
in pregnancy, 83
route of administration of, 82
toxicity from, 84

_N_-acetyl glucosamine, 2053
_N_-acetyl-_p_-benzoquinone imine (NAPQI), 81
NAC (_see_ _N_-acetylcysteine (NAC))
Nadolol, 1310_t_
Nadroparin, 1356
Nafarelin (Synarel), 1053_t_, 1054
Nafcillin (Oxacillin; Unipen), 1372_t_, 1397, 2189_t_
for aerobic gram-positive cocci, 1373_t_
for CAPD-associated peritonitis, 1533_t_
for CNS infections, 1426_t_
dosing of, 1385_t_
for PVE, 1446_t_
for sepsis, 2244_t_
for skin and soft tissue infections, 1604
Naftifine, 1676_t_
Nalidixic acid, 1508
Naloxone, 1219
for opioid toxicity, 76
for opioid withdrawal syndrome, 1949, 1950
for pediatric intubation, 2259_t_
Naltrexone, 1971
for developmental disorders, 1930–1931
for opioid withdrawal syndrome, 1950
Naltrexone/Bupropion (Contrave), 801
Naphazoline (Privine), 455_t_, 460_t_
NAPQI (_see_ _N_-acetyl-_p_-benzoquinone imine (NAPQI))
Naproxen, 522, 905–906, 905_t_, 917
and AKI, 667
for dysmenorrhea, 1056
for JIA, 931
sodium, 1047
Naratriptan, 1272, 1273
Narcotics
analgesics, 729
GERD and, 526_t_
Nasacort AQ (_see_ Triamcinolone acetonide)
Nasalcrom (cromolyn sodium), 461_t_
Nasonex (_see_ Mometasone furoate)
Natalizumab, 1255
adverse effect of, 562
adverse effects of, 1266
for inflammatory bowel disease, 554_t_
recommendations for use of, 1266_t_
Nateglinide, 1154, 1175
for type 2 diabetes, 1154

Navelbine (*see* Vinorelbine)
***N*-desalkylflurazepam, 1840**
Nebcin (*see* Tobramycin)
Nebivolol, 166, 166*t*
Necitumumab, 491*t*
Nedocromil (Alocril), 460*t*, 1201
Nefazodone (Serzone), 132, 1898
for depressive disorders, 1891*t*, 1892*t*
Nelarabine, 492*t*, 2047–2048
encephalopathic toxicity of, 2048
neurotoxicity of, 2048*t*
Nelfinavir (NFV), 125*t*, 132, 976*t*, 1639*t*
Neo-Synephrine (*see* Phenylephrine)
Neomycin (Mycifradin), 860, 1372*t*
hepatic encephalopathy, 586
NephrAmine, 837*t*
Nephrotoxins, 659
Netilmicin (Netromycin), 1372*t*
adverse effects of, 1379*t*
Netromycin (*see* Netilmicin)
Netupitant (Akynzeo), 494*t*, 495, 497*t*
Neupro (*see* Rotigotine)
Neuraminidase inhibitors, 1469
Neurokinin 1 receptor antagonists, 493–496
Neuroleptics, 1296*t*
Neurontin (*see* Gabapentin)
Neutral protamine Hagedorn (NPH), 1117
insulin, 1012
Neutralizing anti-EPO antibodies, 646
Nevirapine, 43, 976*t*
for HIV, 1639*t*
Nexavar (*see* Sorafenib)
NFV (*see* Nelfinavir (NFV))
Niacin, 127
for diabetes, 1180
Nicardipine (Cardene IV), 353*t*, 1026
for chronic stable angina pectoris, 224
for hypertension, 364
for postoperative hypertension, 363–364
Nicotine
cardiovascular effects of, 1976
and heartburn, 1009
pharmacologic effects, 1976
replacement therapy, 1981, 1987, 1990
Nicotine gum, for smoking cessation, 1982–1983*t*

adverse reactions, 1985
disadvantages of, 1985
dosage, 1981–1982
patient education, 1985
Nicotine inhaler, for smoking cessation, 1982–1983*t*, 1988
Nicotine lozenge, for smoking cessation, 1982–1983*t*
adverse reactions, 1985
disadvantages, 1985
dosage, 1985
patient education, 1985
Nicotine nasal spray, for smoking cessation, 1982–1983*t*
advantages, 1988
adverse reactions, 1988
dosage, 1988
patient education, 1988
Nicotine patch, for smoking cessation, 1982–1983*t*
adverse reactions, 1984–1985
and dermatologic conditions, 1985
disadvantages of, 1985
dosage, 1985
patient education, 1995–1996
Nifazodone, 125*t*
Nifedipine, 224, 358, 953, 1017*t*, 1026, 2325*t*
for Raynaud phenomenon, 178
Nikkomycins, 1677
Nilotinib, 133, 492*t*, 2052, 2089
Nilutamide, for prostate cancer, 2147
Nipent (*see* Pentostatin)
Nipride (*see* Nitroprusside)
Nitazoxanide, 1776
for diarrhea by C. parvum, 1508
for giardiasis, 1774*t*
Nitrates, 223–225
for angina, 231
for cardiac syndrome X, 239
GERD and, 526*t*
for HF, 288
and hydralazine, 312
oral, 312
organic, 224
Nitro-Bid IV (*see* Nitroglycerin)
Nitro-Stat IV (*see* Nitroglycerin)
Nitrofurantoin, 1009, 1557
adverse effects of, 1549
for chronic antimicrobial therapy, 1556*t*

for cystitis, 1547
for UTI, 1545*t*
Nitroglycerin (NTG; Nitro-Bid IV; Nitro-Stat IV; Tridil), 353*t*, 2267*t*
for ACS, 250*t*
administration, 578
for chest pain, 358
Nitroimidazoles, 1582
Nitropress (*see* Nitroprusside)
Nitroprusside (Nipride, Nitropress), 353–354*t*, 2267*t*
cyanide toxicity from, 359–360
doses of, 359
hemodynamic effects of, 359
for HTN and LV dysfunction, 315
for hypertensive emergency, 359–360
sodium, 360
thiocyanate toxicity from, 360
Nivolumab, 492*t*
Nizatidine, 1009, 2220*t*
NMDA (*see* N-methyl-D-aspartate (NMDA))
N-methyl-D-aspartate (NMDA), 1956
for Alzheimer disease, 2298
N,N-diethyl-m-toluamide (DEET), 1770
skin repellents (Repel Sportsmen), 1790
Non-aspirin NSAIDs, 513
Non–angiotensin-converting enzyme inhibitor vasodilator therapy, 311–312
Nondihydropyridines, 364
Nonsteroidal antiinflammatory drugs (NSAIDs), 258, 480, 727, 1685, 1789, 2069
for acute gout, 932, 944
adverse effects, 1048–1049
and AIN, 674
common cold, 1719
contraindications, 1049
for critically ill patients, 1241
for drug-induced lupus, 725
for dysmenorrhea, 1047
effects on kidney, 919
for endometriosis, 1052
GERD and, 526*t*
and GI bleeding, 918
induced anaphylaxis, 727
for JIA, 929, 931, 932
and methotrexate, 921–922
for migraine headache, 1274, 1277
for OA, 901, 904–905, 905*t*

for PMS, 1056
for postoperative pain management, 1220
for psoriasis, 873
for RA, 914–915, 917–920
and sodium content, 290
for systemic lupus erythematosus, 739, 745*t*, 746*t*
for tension-type headache, 1280
teratogenic effects, 1004*t*
ulcers from, 510, 511*t*, 513, 513*t*
Norcuron (*see* Vecuronium)
Norepinephrine (NE), 278, 721*t*, 1803, 2267*t*, 2269
for cardiogenic shock, 386
for postoperative cardiac failure, 384*t*
for SBP, 384–385
for septic shock, 392
Norethindrone, 1055
Norethindrone acetate, 1065*t*
Norfloxacin (Noroxin), 582, 1372*t*
for chronic antimicrobial therapy, 1556*t*
for UTI, 1545*t*
Normodyne (*see* Labetalol)
Noroxin (*see* Norfloxacin)
Nortriptyline, 1229*t*, 1289*t*, 1227 (*see also* Antidepressants)
for depressive disorders, 1891*t*, 1892*t*
Novantrone (*see* Mitoxantrone)
Novolin N, 1119
NovoLog (*see* Insulin aspart)
NPH (*see* Neutral protamine Hagedorn (NPH))
NSAIDS (*see* Nonsteroidal antiinflammatory drugs (NSAIDs))
NTG (*see* Nitroglycerin (NTG))
Nystatin, 1676, 1676*t*, 1678*t*, 1687

O

Obinutuzumab, 492*t*
Ocrelizumab, 1256
Octinoxate, 885*t*, 887
Octisalate (octyl salicylate), 885*t*, 888
Octocrylene, 885*t*, 888
Octreotide, 525, 582, 848
administration, 588
for variceal bleeding, 535
Ocular therapies, for rhinitis, 459
Ocupress (*see* Carteolol)
Ofatumumab, 492*t*

Ofloxacin (Floxin), 976*t*, 1372*t*
Olanzapine (Zyprexa), 494*t*, 495–496, 497*t*, 1306, 1809, 1868*t*, 1869*t*, 1907, 1919*t*
for acute agitation, 1917
for acute mania, 1915, 1916*t*
for anticholinergic, 1872
for bipolar disorder, 1919*t*
for CINV, 495
drug interaction with smoking, 1978*t*
for dyslipidemia, 1875
for end-of-life care, 91
for FGAs, 1874
for hyperprolactinemia, 1874
for OCD, 1823
for schizophrenia, 1858, 1860*t*, 1862, 1864, 1864*t*
Olanzapine–fluoxetine, for bipolar depression, 1918*t*, 1919*t*
Olanzapine pamoate, 1866*t*
Olaparib, 492*t*
Olmesartan, 132, 161*t*
Olodaterol, 438, 439*t*, 440
Olopatadine, 460*t*, 461*t*, 1201
for allergic rhinitis, 452
Olsalazine (Dipentum), 556*t*
for inflammatory bowel disease, 549*t*
Omacetaxine, 491*t*
Omalizumab (Xolair)
for allergic rhinitis, 454
Ombitasvir, 1752
Omega-3 fatty acids
adverse effects, 130–131
for ASD, 1927
clinical pearls, 131
drug interactions, 131
efficacy, 131
mechanism of action, 130
pharmacokinetics/pharmacodynamics, 132
place in therapy, 132
Omeprazole, 238, 506*t*, 1249*t*, 2220*t*
PPI, 507
for preventing SRMB, 537*t*
Omnaris (*see* Ciclesonide)
Omnicef (*see* Cefdinir)
Omnipen (*see* Ampicillin)
Omtryg, 130
Ondansetron (Zofran)

ODT, for nausea and vomiting, 92
Ondansetron, 494*t*
for NVP, 1007, 1008, 1008*t*
for PONV, 501*t*
Ophthalmic therapies, for allergic rhinitis, 454
Opiates, for osteoarthritis, 2289
Opioids, 1235
associated with hepatic encephalopathy, 584
chronic, assessment of, 1235
in critically ill patients, 1244, 1244*t*
discontinuing, 1135–1136
for neuropathic pain, 1213
for OA, 906
risk addiction of, 1234–1235, 1234*t*
risk management of, 1234
Optipranolol (*see* Metipranolol)
Optivar (*see* Azelastine)
OPV (*see* Oral polio vaccine (OPV))
Oral analgesics, for burn injuries, 898
Oral anticoagulation, 202*t*, 268
Oral azithromycin, 484
Oral bisphosphonates, 474
Oral contraceptives
for IVF, 994
for migraine headache, 1272
Oral corticosteroids, 559
Oral electrolyte solutions, 2218*t*
Oral fluoroquinolones, 485
Oral iron preparations, 644*t*
Oral norfloxacin, 582
Oral polio vaccine (OPV), 1409
Oralair, for allergic rhinitis, 457*t*
Orbactiv (*see* Oritavancin)
Oritavancin (Orbactiv)
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
Orlistat (Xenical, Alli), 799–800
Orphenadrine citrate, 1126*t*
Ortho Tri-Cyclen, 1992
Oseltamivir (Tamiflu), 1700*t*
adverse effects of, 1699*t*
for influenza, 1469*t*, 1709
pharmacokinetics of, 1706*t*
Osmotic diuretics, 628
Ospemifene (Osphena), 1070

Osphena (*see* Ospemifene)
OTC products (*see* Over-the-counter (OTC) products)
Over-the-counter (OTC) products, 41
antisecretory drugs, 510
Oxacillin (*see* Nafcillin)
Oxaliplatin, 491*t*, 2043*t*, 2056
for adverse effects, 2127, 2132
for colon cancer, 2127
neurotoxicity of, 2048
peripheral nerve toxicity of, 2048
and peripheral neuropathies, 2048
Oxazepam, 1807*t*, 1813
Oxazolidinone, 1453
Oxcarbazepine, 976*t*, 1228*t*, 1317*t*, 1319, 1325*t*
for acute mania, 1916
for diabetes, 1180
for seizures, 1325*t*, 1328
Oxiconazole, 1676*t*
Oxybenzone, 885*t*, 888
Oxybutynin chloride, 2314
Oxycodone, 523, 1219*t*
Oxygen therapy, 721*t*, 1279, 1712
Oxymetazoline (Afrin), 455*t*
Oxymorphone, 1219*t*
Oxyquinolines, 1678
Oxytocin, 1020–1021
administration of, 1022
adverse effects, 1023
dosage, 1022
and lactation, 1032
mechanism of action, 1022
for postpartum hemorrhage, 1029, 1030*t*
and uterine activity, 1022

P

PAAFs (*see* Pediatric amino acid formulations (PAAFs))
PABA (*see* Para-aminobenzoic acid (PABA))
Paclitaxel (Taxol), 236, 491*t*, 976*t*, 2043*t*, 2050, 2052
for breast cancer, 2103
neurotoxicity of, 2048*t*
for NSCLC, 2114*t*, 2115*t*
peripheral nerve toxicity of, 2048
Padimate O, 885*t*, 889
Palbociclib, 492*t*

Palifermin, 2040
Paliperidone (Invega), 1866*t*, 1868*t*, 1869*t*
for hyperprolactinemia, 1874
for schizophrenia, 1859, 1861*t*
Palivizumab
administration of, 1712
dosage of, 1712
against RSV, 1712
Palonosetron (Aloxi, Akynzeo), 494*t*, 495, 496
for PONV, 501*t*
Pamabrom, 1048
Pamidronate, 623*t*, 624, 2342, 2343
P*-aminosalicylic acid (PAS), 1485*t
Panitumumab, 492*t*
for colon cancer, 2127
Panobinostat, 492*t*
Pantoprazole, 506*t*, 507, 525, 1249*t*, 2220*t*
for preventing SRMB, 537*t*
Papaverine, 2330
Para-aminobenzoic acid (PABA), 885*t*
Paracetamol (*see* Acetaminophen)
Paraplatin (*see* Carboplatin)
Paricalcitol, 653
Paritaprevir, 1752
Parlodel (*see* Bromocriptine)
Paromomyci
for amebic liver abscess, 1773*t*
for amebicides, 1773*t*
for giardiasis, 1773*t*
Paroxetine (Paxil), 61, 1808*t*, 1816, 1881
for depressive disorders, 1891*t*, 1892*t*
for hot flushes, 1069
for OCD, 1729
for panic disorder, 1816
for SAD, 1821
teratogenic effects, 1004*t*
for vasomotor symptoms, 1069*t*
Paroxetine mesylate (Brisdelle), 1069*t*
PAS (*see P*-aminosalicylic acid (PAS))
Patiromer, for hyperkalemia, 619
Paxil (*see* Paroxetine)
Pazopanib, 492*t*, 2042, 2052
and hypertension, 2052
PCP (*see* Phencyclidine (PCP))
PCV (*see* Conjugated pneumococcal vaccine (PCV))

Pedialyte, 2218
Pediarix, 1407*t*
Pediatric amino acid formulations (PAAFs), 2208–2209
Pegaspargase, 492*t*
Peginterferon, 492*t*
Pegloticase, 949
Pegylated interferon (PegIFNs), 1739
Pembrolizumab, 492*t*
Pemetrexed, 491*t*
for NSCLC, 2114*t*, 2115*t*
Penciclovir cream (Denavir), 1702
Penems, 1379*t*
Penicillin, 50, 976*t*, 1606
adverse effects of, 1379*t*
for aerobic gram-positive cocci, 1373*t*
allergy, 716
allergy skin testing, 717*t*
for anaerobes, 1375*t*
cross-reactivity between carbapenems and monobactams, 717
desensitization, 730
drug eruptions and, 863
for endocarditis, 1443
and hypokalemia, 615*t*
kidney failure, dosing of drugs, 706
for RMSF, 1794
for skin and soft tissue infections, 1603, 1606, 1608
for UTI, 1552*t*
Penicillin G, 1372*t*, 1447, 1788, 2189*t*
for CAPD-associated peritonitis, 1533*t*
for CNS infections, 1426*t*
dosing of, 1385*t*
for enterococcal endocarditis, 1451*t*
for GBS infection, 1028
for sepsis, 2244*t*
for syphilis, 1575*t*
Penicillin V, 1372*t*
Pentacel, 1407*t*
Pentamidine, 1660
Pentasa (*see* Mesalamine)
Pentobarbital, 2258*t*
Pentostatin, 491*t*, 2054*t*
Pentoxifylline, 175
for ASD, 1927
Peppermint oil capsules, 568
Peramivir (Rapivab), 1709

Perampanel, 1317*t*, 1319, 1325*t*
for seizures, 1325*t*
Perindopril, 160*t*
Permethrin, 1774*t*
liquid rinse, 1780
for scabies, 1775*t*
Perphenazine, 1306, 1858*t*, 1868*t*, 1869*t*
for schizophrenia, 1857, 1862
Pertuzumab, 492*t*
Petrolatum, 1780
P-glycoprotein/ABCBI inhibitors, 945*t*
Phenazopyridine, 1548
Phencyclidine (PCP), 1956
dissociative drug, 1956
and lactation, 1035*t*
for schizophrenia, 1853, 1853*t*
Phendimetrazine, 799
Phenelzine, 1817
Phenergan (*see* Promethazine)
Phenformin, 1174
Phenidone, 1035*t*
Pheniramine, 460*t*
Phenobarbital, 976*t*, 1317*t*, 1325*t*, 2189*t*
for febrile seizures, 1335
for opioid dependence, 1952
for SE, 1340
sedative-hypnotics, 1953
for seizures, 1325*t*, 2250–2251
Phenolates, 1678
Phenothiazines, 1858*t*, 2325*t*
for NVP, 1007, 1008*t*
Phenoxybenzamine, 2325*t*
Phentermine/topiramate (Qsymia), 762*t*, 799
Phentolamine, 2330
Phenylbutazone, 976*t* Phenytoin, 976*t*
Phenylephrine (Neo-Synephrine; Sudafed PE), 455*t*, 2267*t*
for postoperative cardiac failure, 384*t*
for rhinitis, 459
for septic shock, 393
Phenytoin, 41, 43, 57, 60, 505, 611, 1020, 1317*t*, 1323*t*, 2189*t*, 2279, 2325*t*
gum hyperplasia and, 1331
for HAV, 1752
hypersensitivity to, 1337–1338
initiation and dosage of, 1328
intoxication with, 1330

kidney failure, dosing of drugs, 708
neurotoxicity from, 1331
pharmacokinetics of, 1330
in SE, 1340
for seizures, 1323*t*, 1329–1330, 2251
teratogenic effects, 1004*t*
Phosphates, 28, 623*t*, 624
-binding agents, 651*t*
enema, 2217*t*
Phosphodiesterase inhibitors
androgen deprivation therapy, 2155
PDE-4, 878
PDE-5, 2328–2329
Phospholine Iodide, 1189
Phosphorus, 1000
Phytoestrogens, 1063
Picaridin, 1790
Pilocarpine, 1188, 1189
Pimavanserin, 1306
Pimecrolimus, 860
Pindolol, 1310, 2325*t*
Pioglitazone, 976*t*, 1097, 1156, 1158
for HF, 291
for type 2 diabetes, 1169
Piperacillin, 706
Piperacillin-tazobactam, 1385*t*
for anaerobes, 1375*t*
for chorioamnionitis, 1029
for cystic fibrosis, 482*t*
and hypokalemia, 615*t*
for skin and soft tissue infections, 1606
for UTI, 1552*t*
Piroxicam, 905*t*, 917
Pitavastatin, 115*t*, 120, 121*t*, 125*t*
Pneumococcal conjugate vaccine, 2221
Pneumococcal polysaccharide vaccine, 437
Pneumococcal vaccine, 1462
Pneumovax, 1411
Podofilox, 1588
Podophyllin, 1588
Polyethylene glycol, 2216, 2217*t*
Polymerase inhibitors, 1750
Polymyxin B, 1533*t*
Polyvinylpyrrolidone, 2040
Pomalidomide, 492*t*

Ponatinib, 492*t*
Posaconazole, 125*t*, 132, 1676, 1676*t*, 1678*t*, 1679, 1687, 1691
adverse effects of, 1381*t*
dosing of, 1385*t*
Potassium, 2054
and children, 2198*t*
and dyspepsia, 509
GERD and, 526*t*
and induction therapy, 1665
loss due to diarrhea, 2200
maintenance doses of, 2220
in oral electrolyte solutions, 2218*t*
for pernicious anemia, 2004
and renal dysfunction, 2053
and respiratory alkalosis, 1731
and TLS, 2086
in WHO formula, 2218
Potassium bicarbonate, 1985
Potassium chloride, 617
for metabolic alkalosis, 597
Potassium hydroxide (KOH), 1678
Potassium iodide, 1676*t*
Potassium-sparing diuretics, 156
Potassium supplementation
doses of, 295
for HF, 294
Povidone iodine, 1676*t*
PPIs (*see* Proton-pump inhibitors (PPIs))
Pralatrexate, 491*t*
Pramipexole, 1287*t*, 1290*t*, 1308
Pramlintide, 1163
Prasugrel, 254, 255–256*t*
and aspirin, for ACS, 251*t*
Pravastatin, 41, 47*t*, 115*t*, 120, 125*t*, 129
Praziquantel, 1774*t*, 1775*t*, 1778, 1779
for flukes, 1774*t*
side effects of, 1778
Prazosin, 164*t*, 953, 2325*t*
in patients with CKD, 648
for PTSD, 1823
for Raynaud phenomenon, 178
Precef (*see* Ceforanide)
Prednisolone, 755, 955, 1705
Prednisolone acetate, 1202
Prednisone, 755–756, 955, 2093

for AECOPD, 1462
for COPD, 442
cryptococcal disease, 1693
for drug eruptions, 862, 863
for hypercalcemia, 625
for ophthalmopathy, 1097–1098
for prostate cancer, 2150
for radiographic opacities and hypoxemia, 344
for rhinitis, 464
for T-cell lymphomas, 2079*t*
Pregabalin (Lyrica), 1220, 1234, 1310, 1310*t*, 1317*t*, 1319
androgen deprivation therapy, 2155
for diabetes, 1180
for PHN, 1705
for SAD, 1820, 1821
for seizures, 1325*t*, 1328
for vasomotor symptoms, 1069*t*
Pregabalin, 1228*t*, 1325*t*
Premarin (*see* Conjugated equine estrogen)
Premphase, 1066*t*
Prempro, 1066*t*
Prevnar, 1411
Prilocaine, 1215*t*
Primaquine, 1764, 1767*t*
Primaxin (*see* Imipenem-cilastatin)
Primidone, 976*t*, 1310, 1310*t*, 1326*t*
Pristiq (*see* Desvenlafaxine)
Privine (*see* Naphazoline)
PRL (*see* Prolactin (PRL))
Probenecid, 45
Probiotics
for CDAD, 1520
for gastroenteritis, 2218
for infectious diarrhea, 1504
Procainamide, 343
for tachycardia, 1873
for WPW, 339
Procarbazine (Matulane), 492*t*, 2049, 2059
encephalopathic toxicity of, 2049
neurotoxicity of, 2048*t*
Prochieve (*see* Progesterone vaginal gel)
Prochlorperazine (Compazine), 494*t*, 1274
for end-of-life care, 88
for NVP, 1007, 1008*t*
Procyclidine, 1870*t*

Progesterone, 997, 1012
in assisted reproductive technology, 997*t*
GERD and, 526*t*
vaginal suppository, 1066
Progesterone vaginal gel (Prochieve, Crinone), 1065
Progestin-bisphosphonate, 1054
Progestins (Medroxyprogesterone)
for endometriosis, 1052
for polycystic ovary syndrome, 1045*t*
Prokinetic agents, 531
for GER, 2220, 2220*t*
Prolactin (PRL), 1012, 1032
Promethazine (Phenergan), 88, 490*t*, 494*t*
for NVP, 1007, 1008*t*
Prometrium (*see* Micronized progesterone)
Propafenone, 333
for WPW, 339
Propionic acid, 1678
Propofol, 1245
for pediatric intubation, 2295*t*
Propranolol, 583, 1275, 1310, 1310*t*, 2189*t*, 2325*t*
for Akathisia, 1870, 1870*t*
in hypertension, 166*t*
for hyperthyroidism, 1091*t*
for MI, 262
for PTSD, 1823
Proprotein convertase subtilisin/kexin type 9 (PCSK9)
adverse effects of, 134
clinical pearls, 135
efficacy, 134–136
mechanism of action, 134, 134*f*
pharmacokinetics/pharmacodynamics of, 136
place in therapy, 134
Propylthiouracil (PTU), 1074, 1090*t*
and hepatitis, 1093
for thyroid storm, 1098
ProQuad, 1407*t*, 1413
ProSol, 837*t*
Prostacyclin, 230
Prostaglandins
analogs, 1186
inhibitors, 624
Protamine, 193
Proton-pump inhibitors (PPIs), 507–509, 514*t*, 1009, 1248–1249, 1249*t*, 2040
adverse effects of, 508

and AIN, 674
for ALF, 1732
CDAD and, 1521
CYP2C19 interaction, 508
for GER, 2219, 2220*t*
for GERD, 530
and H_2RA, in combination, 530
for preventing SRMB, 538
for upper GI bleeding, 535, 538*t*
Prozac (*see* Fluoxetine)
Pseudoephedrine (Sudafed), 453, 455*t*, 459, 1836
Psoralens plus ultraviolet A light (PUVA) therapy, 874*t*, 877
PTU (*see* Propylthiouracil (PTU))
PUVA therapy (*see* Psoralens plus ultraviolet A light (PUVA) therapy)
Pyrantel pamoate
for enterobiasis, 1773*t*
for pinworm, 1777
Pyrazinamide, 55
dosing of, 1385*t*
for tuberculosis, 1484*t*, 1488
Pyrethrin, 1780
Pyridoxine (vitamin B_6), 1296*t*
for NVP, 1007, 1008*t*
for PMS, 1056
Pyrilamine, 1048
Pyrimethamine
plus clindamycin, 1662
and leucovorin plus azithromycin, 1664
for OIs, 1656
plus sulfadiazine, 1662
toxicities associated with, 1664

Q

Qsymia (*see* Phentermine/topiramate)
Quadracel, 1407*t*
Quadrivalent intranasal live attenuated influenza vaccine (LAIV4), 1412
Quazepam (Doral), 1807*t*
for treatment of insomnia, 1835*t*
Quetiapine (Seroquel), 1809, 1868*t*, 1869*t*
for acute mania, 1915, 1916*t*
for agitated behaviors, 2306
for bipolar depression, 1918*t*, 1919
for bipolar disorder, 1919*t*
for FGAs, 1874

for hyperprolactinemia, 1874
for LTCF, 2289
for Parkinsonism, 1870
for schizophrenia, 1858, 1861*t*, 1862
for Tardive dyskinesia, 1872
Quetiapine XR
for acute mania, 1916*t*
for bipolar disorder, 1919*t*
Quinacrine, 1776
for giardiasis, 1776
Quinapril, 296–297, 296*t*
in hypertension, 160*t*
Quinidine, 505, 1258, 1764
GERD and, 526*t*
for tachycardia, 1873
Quinine, 1764, 1796
Quinolones
adverse effects of, 1381*t*
for gram-negative aerobes, 1374*t*
for UTI, 1553*t*
Quinupristin/dalfopristin, 1453
for aerobic gram-positive cocci, 1373*t*
for CAPD-associated peritonitis, 1533*t*
Qutenza (*see* Capsaicin patch)

R

Rabeprazole, 506*t*, 525
Radioactive iodine (RAI), 1090*t*
Radiocontrast media, 728–729
Radioiodine, 1074, 1092
Radiopharmaceuticals, and lactation, 1035*t*
Radium-223 dichloride, for prostate cancer, 2153
Ragwitek, for allergic rhinitis, 457*t*
RAI (*see* Radioactive iodine (RAI))
RAL (*see* Raltegravir (RAL))
RALES (*see* Randomized Aldactone Evaluation Study (RALES))
Raloxifene, 2343*t*
adverse effects of, 2346
contraindications, 2346–2347
dosing, 2346
for osteoporosis, 2346
Raltegravir (RAL), 1640*t*
Ramelteon (Rozerem), 1837
for sleep, 1932

for treatment of insomnia, 1835*t*, 1837
Ramipril, 296–297, 296*t*
in hypertension, 160*t*
Ramucirumab, 492*t*
for colon cancer, 2127, 2132
Randomized Aldactone Evaluation Study (RALES), 284
Ranibizumab, 1205
Ranitidine, 1009, 1249*t*, 2220*t*
H_2RA, 506*t*, 507
for preventing SRMB, 537*t*
RANKL inhibitors, 2154
Ranolazine, 125*t*, 220
for chronic stable angina, 225–226, 234, 234*t*
for myocardial ischemia, 233
Rapivab (*see* Peramivir)
Rasagiline, 1287*t*, 1293, 1301
Rasburicase, 949
for AML, 2086
R-CHOP, 2093
Recombivax-HB, 1406
Rectal diazepam gel, 1336
Red clover, 976*t*
Reglan (*see* Metoclopramide)
Regorafenib, 492*t*
for colon cancer, 2127
Relaxation, 1056
Relenza (*see* Zanamivir)
Renagel (*see* Sevelamer)
Repaglinide, 1154, 1175
adverse effects of, 1154
contraindications and precautions of, 1154
dosage and clinical use of, 1154
drug interactions of, 1154
efficacy, 1154
mechanism of action, 1154
pharmacokinetics of, 1154
Requip (*see* Ropinirole)
Reserpine, 164*t*
Resorcinol, 1678
Restoril (*see* Temazepam)
Reteplase, 245
Retinoids, 867, 868
Revlimid (*see* Lenalidomide)
Rexulti (*see* Brexpiprazole)
Rhinocort Aqua (*see* Budesonide)

Rho(D) immune globulin (RhoGAM), 1031
Ribavirin (Virazole), 1701*t*
administration of, 1712
adverse effects, 1699*t*, 1712
for HCV, 1750
for HPS, 1712
for liver transplant recipients, 1750
for RSV, 1711–1712
use in infants, 1711
for WNV infection, 1712
Rifabutin
for MAC, 1671
for TB, 1669
for tuberculosis, 1484
Rifamate, 1483
Rifampin, 43, 55, 125*t*, 976, 1423, 1429, 1788
acute renal failure and, 1492
adverse reactions with, 1492
and AIN, 674
for CNS infections, 1426*t*
discoloration of body fluids and, 1492
dosing of, 1385*t*
drug interactions with, 1492
flulike syndrome and, 1491–1492
for HAV, 1752
and hepatotoxicity, 1492
isoniazid and, 1492
for MAC, 1671
thrombocytopenia and, 1492
for tuberculosis, 1484*t*, 1488
Rifamycin, 976*t*, 1669
Rifapentine, 1484*t*
Rifater, 1483
Rifaximin (Xifaxan)
for global IBS symptoms, 569
hepatic encephalopathy, 586
for IBS with diarrhea, 569
and neomycin, 586
SBP and, 1530
for travelers' diarrhea, 1515*t*
Rilonacept, 932
Rilpivirine (RPV), 1638*t*
Rimantadine (Flumadine)
adverse effects, 1699*t*
for influenza, 1708–1709

Risedronate, 2342–2344, 2343, 2343*t*
Risperdal (*see* Risperidone)
Risperidone (Risperdal), 1306, 1809, 1866*t*, 1868*t*, 1869*t*
for acute mania, 1916*t*
for agitated behaviors, 2306
for ASD, 1927, 1931
for bipolar disorder, 1919*t*
for developmental disorders, 1928
for dyslipidemia, 1874
for FGAs, 1874
for hyperprolactinemia, 1874
for OCD, 1823
for orthostatic hypotension, 1873
for schizophrenia, 1858, 1861*t*, 1862, 1864, 1864*t*
Ritonavir (RTV), 125*t*, 132, 976*t*, 1639*t*
Rituxan (*see* Rituximab)
Rituximab, 492*t*, 670, 914, 915, 916, 926*t*, 931
for aggressive lymphomas, 2093
therapy for LN, 656
Rivaroxaban, 1358*t*
for monotherapy, 194
for prevention of stroke, 336–337
for stroke prevention, 187
for warfarin therapy, 206
Rivastigmine, 1305
for Alzheimer disease, 2299
for vascular dementia, 2303
Rizatriptan, 1273
Rocephin (*see* Ceftriaxone)
Rocuronium, 2259*t*
Rofecoxib, 523, 739
Rolapitant (Varubi), 494*t*, 495, 497*t*
Romidepsin, 491*t*
Ropinirole, 1287*t*, 1290–1291, 1290*t*, 1298, 1978*t*
Ropivacaine, 1215*t*
Rosiglitazone, 1156, 1158
for HF, 291
Rosuvastatin, 41, 47*t*, 115*t*, 120, 121*t*, 125*t*, 976*t*
Rotarix (RV1), 1413
RotaTeq, 1413
Rotavirus vaccine, 1405
Rotigotine, 1287*t*, 1290*t*, 1298
Rowasa (*see* Mesalamine enema)
Rozerem (*see* Ramelteon)
RPV (*see* Rilpivirine (RPV))

RTV (*see* Ritonavir (RTV))
Rucaparib, 492*t*
Rufinamide, 976*t*, 1317*t*, 1326*t*
Ruxolitinib, 492*t*
RV1 (*see* Rotarix (RV1))

S

Sacubitril/valsartan (Entresto), 286
Safinamide, 1287*t*, 1301
Salicylates, 885*t*, 887, 1678, 1704, 2189*t*
ingestion of, assessment of, 69–73
Salicylic acid, 867, 976*t*
Saline, 623*t*, 624
Salmeterol
for chronic asthma, 413–414
for COPD, 440, 441
Saphris (*see* Asenapine)
Saquinavir (SQV), 132, 976*t*, 1639*t*
Sarafem (*see* Fluoxetine)
Saxagliptin, 133, 1162
for type 2 diabetes, 1169
Saxenda (*see* Liraglutide)
Scopolamine (Transderm-Scop), 490*t*
for end-of-life care, 92
for PONV, 501*t*
Second-generation triptans, 1273
Secukinumab, 879
Sedating drugs, 585
Sedatives, 585
Selective estrogen receptor modulators (SERMs), 2346
Selective phosphodiesterase 4 (PDE4) inhibitors, 435
Selective serotonin reuptake inhibitors (SSRIs), 1818
adverse effects, 1828–1829
for anxiety, 1931
for ASD, 1929
for bipolar depression, 1907
for critically ill patients, 1240
for depression, 1931
for depressive disorders, 1891*t*
dosage, 1828
for hot flushes, 1069
and lithium, 1914*t*
for OCD, 1828
for panic disorder, 1817, 1818

for PMDD, 1057
for PTSD, 1824
and sexual response, 2325*t*
and sleep, 1843
Selegiline, 1287*t*, 1301
Selegiline, 976*t* St. John's-wort, 976*t*
Selenium, 994
for prostate cancer, 2157
Senna, 2217*t*
Septra (*see* Trimethoprim-sulfamethoxazole (TMP-SMX))
SERMs (*see* Selective estrogen receptor modulators (SERMs))
Seroquel (*see* Quetiapine)
Serotonin, 1257
androgen deprivation therapy, 2155
Serotonin and norepinephrine reuptake inhibitors (SNRIs), 1816
androgen deprivation therapy, 2155
for critically ill patients, 1240
for hot flushes, 1069
for stress incontinence, 2315
Sertraline (Zoloft), 1060*t*, 1808*t*, 1816, 1820
for depression, 2306
for depressive disorders, 1891*t*, 1892*t*
for OCD, 1829
for panic disorder, 1816
for prostate cancer, 2143
for SAD, 1820
and sleep, 1843
for vasomotor symptoms, 1069*t*
Serum aminoglycoside, 482–483
Serum immunoglobulin E antibodies, 475–476
Serum precipitins, 475–476
Serzone (*see* Nefazodone)
Sevelamer, 650–651
carbonate, 651*t*
hydrochloride, 651*t*
17-α hydroxyprogesterone (17-OHP), 1028
Sildenafil, 954, 2329
and ED, 2329
Silenor (*see* Doxepin)
Silodosin, 2320
for BPH, 2320
Siltuximab, 492*t*
Silvadene (*see* Silver sulfadiazine cream)
Silver sulfadiazine cream (Silvadene; Aquacel Ag; ConvaTec), 898
Simeprevir, 1751–1752

Simvastatin, 47*t*, 57, 59, 59*t*, 115*t*, 120, 121, 125*t*, 129, 267
Sinecatechins, 1588
Sinemet CR (*see* Carbidopa–Levodopa (CR))
Singulair (*see* Montelukast)
Sipuleucel-T, 2152–2153
Sirolimus, 125*t*, 133, 236, 756
Sitagliptin, 133, 1162
for type 2 diabetes, 1169, 1173
Sivestro (*see* Tedizolid)
6-mercaptopurine (6-MP)
for Crohn disease, 563
for inflammatory bowel disease, 550*t*
for T-cell lymphomas, 2079*t*
Skyla, 982
SMX (*see* Sulfamethoxazole (SMX))
SNRIs (*see* Serotonin and norepinephrine reuptake inhibitors (SNRIs))
Sodium
and children, 2198*t*
loss due to diarrhea, 2200
in oral electrolyte solutions, 2218*t*
and respiratory alkalosis, 1731
in WHO formula, 2218
Sodium bicarbonate, 672, 1009
adverse effects of, 382
carbonic acid system, 643
hyperkalemia and, 619, 620*t*
for preventing SRMB, 537*t*
for salicylate toxicity, 72
for TCA toxicity, 80
Sodium carbonate, 1985
Sodium ferric gluconate complex, 644
Sodium oxybate, 1848–1849
Sodium polystyrene sulfonate (SPS), 619
for hyperkalemia, 620*t*
side effects, 619
Sodium stibogluconate, 1774*t*
Sodium thiosulfate, 1676*t*
Sodium zirconium cyclosilicate, for hyperkalemia, 619
Sodium–glucose transporter 2 (SGLT2) inhibitors
adverse effects of, 1163
contraindications and precautions of, 1164
for diabetes, 2285
dosage and clinical use, 1165
drug interactions, 1164
efficacy of, 1164

pharmacokinetics of, 1163
Sofosbuvir, 1752
Solifenacin, 2314
Somatostatin
analogues, 525
for variceal bleeding, 535
Sonata (*see* Zaleplon)
Sonidegib, 492*t*
Sorafenib (Nexavar), 492*t*, 2052
Sorbitol, 59, 2216
Sordarins, 1677
Sotalol
for AF, 334–335
and QTc, 346
for tachycardia, 1873
Spectinomycin, 1565
Spectracef (*see* Cefditoren)
Spectrobid (*see* Bacampicillin)
Spironolactone (Antiandrogen), 576, 577, 618, 2325*t*
for acne, 869
for hirsutism, 1045
for hypertension, 147, 164
for polycystic ovary syndrome, 1045*t*
Sprycel (*see* Dasatinib)
SPS (*see* Sodium polystyrene sulfonate (SPS))
SQV (*see* Saquinavir)
SSRIs (*see* Selective serotonin reuptake inhibitors (SSRIs))
SSZ (*see* Sulfasalazine (SSZ))
St. John's-wort, 43
for depression, 46
Starch, 1679
Stavudine (d4*T*), for HIV, 1029, 1637*t*
Steroids, for septic shock, 394
Stiripentol, 945*t*, 1326*t*
Streptogramin, 1453
Streptokinase, 260
Streptomycin, 1372*t*, 1793
teratogenic effects, 1004*t*
for tuberculosis, 1485*t*, 1488
Streptozocin, 491*t*, 2043*t*, 2056*t*
Succinylcholine, 2259*t*
Sucralfate, 506*t*, 1249*t*, 2220*t*
for gastric mucosal protection, 509
in preventing SRMB, 537, 537*t*
Sucroferric oxyhydroxide, 651*t*

Sudafed (*see* Pseudoephedrine)
Sudafed PE (*see* Phenylephrine)
Sulconazole, 1676*t*
Sulfadiazine, 1372*t*
for *Toxoplasma* encephalitis, 1664
Sulfadoxine (Fansidar), 1373*t*
Sulfamethoxazole (SMX), 213, 1423
for chronic antimicrobial therapy, 1556*t*
for cystic fibrosis, 482*t*
for UTI, 1545*t*
Sulfamylon (*see* Mafenide acetate)
Sulfapyridine, 562
Sulfasalazine (Azulfidine; SSZ), 548*t*, 556*t*, 914, 920
for inflammatory bowel disease, 790
for ulcerative colitis, 560
Sulfonamides, 2189*t*
adverse effects of, 1380*t*
and AIN, 674
for RMSF, 1794
Sulfonylurea, 57, 1154–1155
adverse effects of, 1155
contraindications and precautions of, 1156
for diabetes, 174
dosage and clinical use of, 1156
drug interactions of, 1156
efficacy of, 1156
mechanism of action, 1155
pharmacokinetics of, 1155
Sulindac, 667, 905*t*
Sulisobenzone, 885*t*
Sumatriptan, 1272–1273, 1274, 1279
adverse effects of, 1272
drug interactions of, 1272
Sunitinib, 492*t*, 2042, 2052
and hypertension, 2052
Sunscreen, 867, 870
Suppressive therapy, 1656
2002 USPHS/IDSA guidelines, 1663
for *Toxoplasma* encephalitis, 1663
Suprax (*see* Cefixime)
Surface-active agents
for GER, 2220*t*, 2221
Sutent (*see* Sunitinib)
Suvorexant (Belsomra), 1835*t*, 1839
Symbicort (*see* Budesonide/formoterol)

Symmetrel (*see* Amantadine)
Synarel (*see* Nafarelin)
Systemic agents
antifungals, 1681*t*
Systemic agents, 1676*t* Terbinafine, 1676*t*
Systemic antihistamines, 861

T

Tabloid (*see* Thioguanine)
Tacrine, 976*t*
drug interaction with smoking, 1978*t*
Tacrolimus, 125*t*, 755–756, 861, 976*t*
Tadalafil, 2329
for BPH, 2321
and ED, 2329
Tafluprost (Zioptan), 1186–1187
Talc, 1679
Talinolol, 133
Tamiflu (*see* Oseltamivir)
Tamsulosin, 2320
for BPH, 2320
Tannic acid, 1678
Tapazole (*see* Methimazole)
Tarceva (*see* Erlotinib)
Tasigna (*see* Nilotinib)
Tasmar (*see* Tolcapone)
Tauroursodeoxycholic acid, 802
Tavist (*see* Clemastine)
Taxanes, for prostate cancer, 2150
Taxol (*see* Paclitaxel)
Tazarotene, 867, 893
for psoriasis, 874*t*, 875–876
Tazobactam, 514*t*
for cystic fibrosis, 482*t*
TDF (*see* Tenofovir Disoproxil Fumarate (TDF))
Tedizolid (Sivestro), 1372*t*
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
Teflaro (*see* Ceftaroline)
Tegaserod, 568
Telaprevir, 125*t*, 132, 1750
for HAV, 1751
Telavancin (Vibativ), 1372*t*, 1445, 1473
adverse effects of, 1380*t*

for skin and soft tissue infections, 1604
Telbivudine, 1743
Televancin, 1372*t*
Telithromycin, adverse effects of, 1380*t*
Telithromycin (Ketek), 125*t*, 132, 1372*t*
Telmisartan, 161*t*
Temazepam (Restoril), 1807*t*, 1840, 1841–1842
for LTCF, 2290
and sleep, 1843
for treatment of insomnia, 1835*t*
Temodar (*see* Temozolamide)
Temozolamide (Temodar), 491*t*, 492*t*
Temsirolimus, 492*t*, 2052
Tenecteplase (TNK), 245
Teniposide, 2043*t*
Tenofovir, 705
Tenofovir alafenamide, 1741–1742
Tenofovir Disoproxil Fumarate (TDF), 1637*t*, 1741
Terazosin, 164*t*, 2320, 2325*t*
for BPH, 2320
in patients with CKD, 648
Terbinafine, 1679
Terconazole, 1580*t*, 1676*t*
Teriflunomide, 1256, 1262
Teriparatide, 2343*t*, 2350–2353
Terlipressin, 581, 588–589
Tetracaine, 1215*t*
Tetracyclines, 505, 519, 514*t*, 868, 870, 976*t*, 1372*t*, 1788
adverse effects of, 1380*t*
and dyspepsia, 509
GERD and, 526*t*
for RMSF, 1794
for TBRF, 1794
teratogenic effects, 1004*t*
for tularemia, 1794
TGC (*see* Third-generation cephalosporin (TGC))
3-hydroxy-3-methyl-glutaryl coenzyme A inhibitors
adverse effects, 121–123
clinical pearls, 124
diabetes, 123
drug interactions, 123–124
efficacy, 119–120
mechanism of action, 119
pharmacokinetics/pharmacodynamics, 120–121
place in therapy, 123

reaction catalyzed by, 120
3,4-methylenedioxymethamphetamine (MDMA; Ecstasy), 1956
3*TC* (*see* Lamivudine)
Thalidomide, 492*t*, 2048
peripheral nerve toxicity of, 2048
teratogenic effects, 1004*t*
Thalomid (*see* Thalidomide)
Theophylline, 509, 948*t*, 949*t*, 976*t*, 2189*t*
for apnea, 2246
for COPD, 442
drug interaction with smoking, 1978*t*
and dyspepsia, 509
GERD and, 526*t*
and lithium, 1914*t*
Thiamine, alcohol withdrawal, 1968
Thiazide diuretics, 622, 642, 919, 948*t*
for BPD, 2232
for hypertension, 147
and hypokalemia, 615*t*
for vascular dementia, 2302
Thiazide-like diuretics, and AIN, 674
Thiazides, 284
for hypertension, 155–156, 155*t*, 157*t*
Thiazolidinediones
adverse effects of, 1157
contraindications and precautions of, 1157
dosage and clinical use, 1158
drug interactions, 1156
efficacy of, 1158
mechanism of action, 1156
pharmacokinetics of, 1155
Thioamides, 1074, 1090
administration of, 1092
adverse effects, 1093
and agranulocytosis, 1094
dosage, 1092–1093
duration of, 1094
and granulocytopenia, 1094
and hepatitis, 1094
monitoring of, 1093
precautions, 1093
rashes from, 1094
remission rates with, 1095
Thioguanine (Tabloid), 492*t*
for T-cell lymphomas, 2079*t*

Thiopental, 1732, 2259
Thiopurine, 58
Thioridazine, 1858*t*, 1868*t*, 1869*t*
for schizophrenia, 1857
Thiotepa, 491*t*
neurotoxicity of, 2048*t*
Thiothixene, 1858*t*, 1868*t*, 1869*t*
Thioxanthene, 1858*t*
Third-generation cephalosporin (TGC)
for aerobic gram-positive cocci, 1373*t*
for gram-negative aerobes, 1374*t*
Thymoglobulin and antithymocyte globulin, 759
Thymol, 1678
Tiagabine, 1317*t*, 1319, 1326*t*, 1916
for seizures, 1326*t*, 1328
Tianeptine, 1927
Ticagrelor, 255–256*t*
and aspirin, for ACS, 251*t*
Ticarcillin, 615*t*
for cystic fibrosis, 482*t*
Ticlopidine, 1358, 1358*t*
for diabetes, 175
for PAD, 175
Tigecycline, 1372*t*
for aerobic gram-positive cocci, 1373*t*
dosing of, 1385*t*
for gram-negative aerobes, 1374*t*
Timentin, 1372*t*
for aerobic gram-positive cocci, 1373*t*
for gram-negative aerobes, 1374*t*
Timolol, 1187, 2325*t*
for glaucoma, 1186
for MI, 262
Timoptic, 1187 (*see also* Timolol)
Timoptic XE, 1187
Tindamax (*see* Tinidazole)
Tinidazole, 1773
for amebic liver abscess, 1773*t*
for gastrointestinal disease, 1773*t*
for giardiasis, 1773*t*
for trichomoniasis, 1582
Tinzaparin, 183*t*, 195*t*
Tioconazole, 1676*t*
Tiotropium, 439*t*, 440, 441
Tiotropium plus olodaterol, 438

Tipiracil, 493*t*
Tipranavir (TPV), 125*t*, 945*t*, 976*t*, 1640*t*
Tirofiban, 254
Tissue amebicide, 1773
Titanium dioxide, 885*t*
TIV (*see* Trivalent inactivated vaccine (TIV))
Tizanidine, 976*t*, 1126*t*, 1257
TKIs (*see* Tyrosine kinase inhibitors (TKIs))
TMP (*see* Trimethoprim (TMP))
TMP-SMX (*see* Trimethoprim-sulfamethoxazole (TMP-SMX))
TNF-α inhibitors, for psoriasis, 879
TNK (*see* Tenecteplase (TNK))
Tobacco, 2017
TOBI podhaler, 483–484
Tobramycin (Nebcin)
adverse effects of, 1379*t*
for CAPD-associated peritonitis, 1533*t*
for CNS infections, 1426*t*
for cystic fibrosis, 482*t*
dosing of, 1385*t*
for gram-negative aerobes, 1374*t*
for inhalation, 483–484
Tobramycin Podhaler, 482*t*
Tocilizumab, 914, 915, 916, 926*t*, 931, 932–933
Tofacitinib, 914
Tolbutamide, 1174
Tolcapone (Tasmar), 1287*t*
pharmacologic and pharmacokinetic properties of, 1300*t*
Tolindate, 1678
Tolmetin, 905*t*
Tolnaftate, 1676*t*
Tolterodine tartrate, 2314
Tolvaptan, 133
for HF, 28
for hyponatremia, 613
Tonabersat, 1277
Topamax (*see* Topiramate)
Topical protectants, for burn injuries, 898
Topiramate, 976*t*, 1228*t*, 1277, 1279, 1310, 1310*t*, 1317*t*, 1319, 1326*t*, 1916, 1972–1973
for ASD, 1927
for diabetes, 1180
for seizures, 1326*t*, 1328
teratogenic effects, 1004*t*
Topotecan, 133, 491*t*, 2054*t*

Torsemide, 676
for HF, 292
Toujeo (*see* Insulin glargine)
Toxin binders
for CDAD, 1519
TPV (*see* Tipranavir (TPV))
Trabectedin, 491*t*
Tramadol, 901
for diabetes, 1180
for OA, 906
Trametinib, 492*t*
Trandate (*see* Labetalol)
Trandolapril, 296
in hypertension, 160*t*
Tranexamic acid, 976*t*
Tranquilizers, 585
Transderm-Scop (*see* Scopolamine)
Transdermal fentanyl, transition to, 1220
Trastuzumab (Herceptin), 491*t*, 496, 2050, 2051
for breast cancer, 2103, 2109
Travasol, 837*t*
Travatan (*see* Travoprost)
Travoprost (Travatan), 1186
Trazodone, 1839, 1898
for agitated behaviors, 2305
for serotonin, 1897
and sexual response, 2325*t*
and sleep, 1843
for sleep, 1932
Treanda (*see* Bendamustine)
Treprostinil, 954
Tresiba (*see* Insulin degludec)
Tretinoin, 493*t*, 867, 893
for AML, 2087
Trexall (*see* Methotrexate)
Triacetin, 1678
Triamcinolone, 462
Triamcinolone acetonide (Nasacort AQ), 461*t*
Triamterene, 576, 619
and hyperkalemia, 618
for hypertension, 156
Triazolam (Halcion), 1807*t*
for treatment of insomnia, 1835*t*
Triazoles, 1676, 1687, 1689, 1691
Trichloroacetic acid, 1588–1589

Tricyclic antidepressants (TCAs), 73, 80–81, 976*t*, 1296*t*, 1927
for ADHD, 1943
for anxiety disorders, 1816
for critically ill patients, 1240
GERD and, 526*t*
for pain management, 1134, 1211, 1228
for panic disorder, 1816
for PTSD, 1823
and sexual response, 2325*t*
Tridil (*see* Nitroglycerin)
Trifluoperazine, 1858*t*, 1868*t*, 1869*t*
Trifluridine, 493*t*, 1203, 1699*t*
for adverse effects, 2132
Trihexyphenidyl, 1286*t*
for Akathisia, 1870*t*
for Parkinsonism, 1870
Triiodothyronine, 1081
Trileptal (*see* Oxcarbazepine)
Trimethoprim (Trimpex; TMP), 1004*t*, 1372*t*, 1423
for chronic antimicrobial therapy, 1556*t*
for cystic fibrosis, 482*t*
sulfamethoxazole and, 1556*t*
for UTI, 1545*t*
Trimethoprim-sulfamethoxazole (Bactrim; Septra; TMP-SMX), 436, 868, 1372*t*, 1423, 2069
alternatives, 1660–1661
for CNS infections, 1426*t*
for cystitis, 1547
dosing of, 1386*t*
hematologic side effects, 1660
hypersensitivity (skin rash) reaction, 1660
for OIs, 1659–1660
for PJP, 1659–1660
for skin and soft tissue infections, 1603
for toxoplasmosis, 1663
for UTI, 1545*t*
Trimpex (*see* Trimethoprim)
Triptans, 1272
second-generation, 1273
Trivalent inactivated vaccine (TIV), 1413
Trolamine salicylate, 885*t*
TrophAmine, 2208, 2210
Troponin, 242, 243
Trospium chloride, 2314
Trusopt (*see* Dorzolamide)

Tums, 747–748
Twinrix, 1407*t*
Twisthaler, 414
Tykerb (*see* Lapatinib)
Tyrosine kinase inhibitors (TKIs), 2089
for cancer, 2026

U

Ulipristal, 985
Ultram (*see* Tramadol)
Ultrarapid opiate detoxification (UROD), 1950
Umeclidinium, 439*t*
Umeclidinium plus vilanterol, 438
Unasyn, 1372*t*
for aerobic gram-positive cocci, 1373*t*
for anaerobes, 1375*t*
for gram-negative aerobes, 1374*t*
Undecylenic acid, 1676*t*
Unipen (*see* Nafcillin)
Urea, 613
Uricase, 949
UROD (*see* Ultrarapid opiate detoxification (UROD))
Ursodiol, 2211
Ustekinumab, 879

V

Vaccination
adverse effects, 1735
dosage, 1725, 1725*t*, 1733
duration of vaccine-induced immunity, 1734
for HBV, 1757
with HBV vaccine, 1725
hepatitis A vaccine, 1725–1726, 1725*t*
herpes zoster vaccine (Zostavax), 1704
immune response to, 1734
indications for, 1727, 1734–1735
and infants, 1734
for Lyme disease, 1790
for malaria, 1770
for OIs, 1656
for prostate cancer, Sipuleucel-T, 2152
with Recombivax HB, 1734
teratogenic effects, 1004*t*

universal, 1735
Vagifem (*see* Estradiol hemihydrate tablets)
Vaginal prostaglandin E2, 1022
Valacyclovir (Valtrex; VCV), 776, 1700*t*
adverse effects, 1699*t*
for genital herpes, 1585, 1586*t*
for herpes labialis, 1703
for herpes zoster infection, 1704
pharmacokinetics of, 1707*t*
Valcyte (*see* Valganciclovir)
Valganciclovir (Valcyte), 776, 1665, 1700*t*
adverse effects, 1699*t*
for CMV primary prevention, 1665
for CMV retinitis, 1664
Valproate (VPA), 1276, 1317*t*, 1327*t*, 1907
for absence and primary generalized tonic-clonic seizures, 1334–1335
for absence seizures, 1332
adverse effects, 1910–1911
and alopecia, 1910
for bipolar disorder, 1919*t*
for developmental disorders, 1929
dosage, 1910
and gastrointestinal complaints, 1910
and hyperammonemic encephalopathy, 1911
for mania, 1909–1910
monitoring of, 1910
for seizures, 1327*t*
and weight gain, 1910
weight gain with, 1910
Valproic acid, 976*t*, 1907, 2189*t*
dose–response curve, 1002
for schizophrenia, 1881
teratogenic effects, 1004*t*
Valrubicin, 492*t*
Valsartan, 266, 726, 1372*t*, 1397, 1424, 1433, 1447
adverse effects of, 1380*t*
for aerobic gram-positive cocci, 1373*t*
for anaerobes, 1375*t*
for cardiac surgery prophylaxis, 1445
for CDAD, 1519–1520
for CNS infections, 1426*t*
for CSF shunt infection, 1431
dosing of, 1386*t*
for enterococcal endocarditis, 1451*t*
for febrile neutropenia, 1621

gentamicin and, 1452
high-risk medication, 658–659
for hypertension, 161*t*
kidney failure, dosing of drugs, 706–707
MRSA, 1606
for MRSA endocarditis, 1447–1450
for NEC, 2241
for PVE, 1446*t*
for sepsis, 2244*t*
for skin and soft tissue infections, 1604
for treatment of HF, 285
Valtrex (*see* Valacyclovir)
Vancocin (*see* Vancomycin)
Vancomycin (Vancocin), 481, 483, 1372*t*, 1793
for UTI, 1553*t*
Vandetanib, 493*t*
Vanillylmandelic acid (VMA), 2063
Vantin (*see* Cefpodoxime proxetil)
Vaqta, 1407
Vardenafil, 2329
and ED, 2329
Varenicline
adverse reactions, 1989–1990
for depressive disorders, 1887*t*
dosage, 1989
patient education, 1989
pharmacokinetics, 198
for smoking cessation, 1981, 1987
Varivax, 1414
Varubi (*see* Rolapitant)
Vascepa, 130
Vasodilators
for ACS, 257–258
for IC, 176
Vasopressin, 580, 2267*t*, 2269
for cardiopulmonary arrest, 350
for postoperative cardiac failure, 384*t*
for septic shock, 392
Vasopressin receptor antagonists (VRAs), 613
Vasotec IV (*see* Enalaprilat)
Vaxelis, 1407*t*
VCV (*see* Valacyclovir (VCV))
Vecuronium, 2259*t*
Vedolizumab
for CD, 560

for inflammatory bowel disease, 552*t*
for UC, 560, 563
Velban (*see* Vinblastine)
Velcade (*see* Bortezomib)
Vemurafenib, 493*t*
Venetoclax, 493*t*
Venlafaxine (Effexor, Effexor XR), 1228, 1273, 1280, 1808*t*
androgen deprivation therapy, 2155
for depressive disorders, 1891*t*
for panic disorder, 1816
for serotonin, 1897
for vasomotor symptoms, 1069*t*
Venlafaxine, 1229*t*
Venlafaxine ER, 1892*t*
Venlafaxine IR
for depressive disorders, 1892*t*
for hot flushes, 1069
Venlafaxine XR 1801*t*, 1808*t*, 1816, 1820
for PTSD, 1822
for SAD, 1820
Venofer (*see* Iron sucrose)
VePeSid (*see* Etoposide)
Verapamil, 125*t*, 133, 162, 176, 224, 642, 1093, 1279, 2325*t*
for AF, 333
for HF, 291
for HFpEF, 287
for thyroid storm, 1098
Vesanoid (*see* Tretinoin)
Vibativ (*see* Telavancin)
Viberzi (*see* Eluxadoline)
Vidarabine, 1701
for herpes encephalitis, 1698
Vigabatrin, 1317*t*, 1327*t*
Vilanterol, 438, 439*t*, 440
Vilazodone, 1898
for depressive disorders, 1891*t*, 1892*t*
Vinblastine, 492*t*, 2043*t*, 2056*t*
and autonomic neuropathy, 2049
and cranial neuropathies, 2049
gonadal toxicity of, 2059
neurotoxicity of, 2048*t*
peripheral nerve toxicity of, 2048
Vinca alkaloids, gonadal toxicity of, 2059
Vincristine, 492*t*, 2043*t*, 2049, 2065, 2093
and autonomic neuropathy, 2049, 2075

for HL, 2092
intrathecal, problems of, 2075
neurotoxicity of, 2048–2049, 2048*t*
peripheral nerve toxicity of, 2048
for rhabdomyosarcoma, 2070
for T-cell lymphomas, 2079*t*
Vinorelbine, 492*t*, 2043*t*
neurotoxicity of, 2048*t*
for NSCLC, 2114*t*
peripheral nerve toxicity of, 2048
Virazole (*see* Ribavirin)
Vismodegib, 493*t*
Vistaril (*see* Hydroxyzine)
Vistide (*see* Cidofovir)
Vitamin A
and pregnancy, 1001
teratogenic effects, 1004*t*
Vitamin B6 (*see* Pyridoxine)
Vitamin B_{12}, 524
for pernicious anemia, 2004
Vitamin C (*see* Ascorbic acid)
Vitamin D
calcitriol, 652
doxercalciferol, 653
for endometriosis, 1054
nutritional vitamin D, 652
paricalcitol, 653
and pregnancy, 1000
for pulmonary exacerbations, 474
receptor agonist, 652–653
Vitamin E, 994, 2048
for diabetic neuropathy, 2048
and pregnancy, 1000
for prostate cancer, 2157
Vitamin K
dependent clotting factors, 187*t*
and pregnancy, 1000
for pulmonary exacerbations, 474
supplementation in pregnant women, 1339
warfarin and, 203
VMA (*see* Vanillylmandelic acid (VMA))
Vorapaxar, 176, 254
for ACS, 251*t*
Voriconazole, 62, 125*t*, 132, 976*t*, 1626, 1676, 1676*t*, 1679, 1685, 1687, 1691
adverse effects, 1381*t*, 1691

dosing of, 1386*t*
Vorinostat, 493*t*
Vortioxetine, 1898
for depressive disorders, 1891*t*, 1892*t*
Votrient (*see* Pazopanib)
VPA (*see* Valproate)
Vraylar (*see* Cariprazine)

W

Warfarin, 41, 43–44, 57, 98, 132, 214, 976*t*, 1358*t*, 1359–1360
action of, 187*f*
adverse effects of, 201–202
alcohol ingestion and, 204
anticoagulant therapy, 199
and clotting factors, 1099
dosing adjustments, 204, 204*t*
drug interactions with, 212–215, 214*t*
effects of, 200*t*
factors influence, 202–204
frequency of follow-up, 204–205
genetic factors and, 203
hemorrhage from, 201
initiation dosing algorithm, 200*f*
intensity and duration of, 200–201
interactions with disease states, 203
international normalized ratio monitoring, 205*t*
overanticoagulation, management of, 205–206
in pregnancy, 206
protocol for, 200*t*
purple toe syndrome from, 201–202
skin necrosis from, 201
for stroke prophylaxis, 2303
teratogenic effects, 1004*t*
therapy, initiation of, 199–200
vitamin K and, 177, 187, 203

X

Xalatan (*see* Latanoprost)
Xanax (*see* Alprazolam)
Xanthine oxidase, and pregnancy, 1002
Xeloda (*see* Capecitabine)
Xerese (*see* Acyclovir and Hydrocortisone cream)
Xifaxan (*see* Rifaximin)

Xolair (*see* Omalizumab)
Xylometazoline, 455*t*
Xyzal (*see* Levocetirizine)

Y

Yerba mata, 803*t*
Yoga, 1056

Z

Zalcitabine, 2012
Zaleplon (Sonata), 1834
for treatment of insomnia, 1835*t*
Zanamivir (Relenza), 1469*t*, 1701*t*
adverse effects, 1699*t*
for influenza, 1709
pharmacokinetics of, 1707*t*
Zanosar (*see* Streptozocin)
ZDV (*see* Zidovudine (ZDV))
Zelapar (*see* Selegiline)
Zemplar (*see* Paricalcitol)
Zerbaxa (*see* Ceftolozane/tazobactam)
Zetonna (*see* Ciclesonide)
Z-hypnotics, 1837, 1846
Zidovudine (ZDV), 1029, 1638*t*
GERD and, 526*t*
for HIV-related anemia, 2012
Zileuton, 417
Zinacef (*see* Cefuroxime)
Zinc, 994, 1719
for gastroenteritis, 2218
and pregnancy, 1000
Zinc lozenges, 1719
Zinc oxide, 885*t*
Zioptan (*see* Tafluprost)
Ziprasidone (Geodon), 1306, 1809, 1868*t*, 1869*t*
for acute agitation, 1916
for acute mania, 1916, 1916*t*
for bipolar disorder, 1919*t*
for dyslipidemia, 1875
for hyperprolactinemia, 1874
for schizophrenia, 1857, 1859, 1861*t*, 1864, 1864*t*
Zithromax (*see* Azithromycin)
Ziv-aflibercept, 491*t*

for colon cancer, 2127, 2132
Zofran (*see* Ondansetron)
Zoladex (*see* Goserelin)
Zoledronic acid, 623*t*, 624, 2342, 2343, 2343*t*
androgen deprivation therapy, 2155
Zolinza (*see* Vorinostat)
Zolmitriptan, 1273, 1279
Zoloft (*see* Sertraline)
Zolpidem, 1837–1838, 1846
for sleep, 1932
for treatment of insomnia, 1835*t*
Zolpimist (*see* Mucous membrane spray)
Zomig (*see* Zolmitriptan)
Zonegran (*see* Zonisamide)
Zonisamide, 1317*t*, 1319, 1327*t*, 1916
for seizures, 1327*t*, 1328
Zostavax (*see* Zoster vaccine)
Zoster vaccine (Zostavax), 1414
Zosyn (*see* Piperacillin-tazobactam)
Zovirax (*see* Acyclovir (ACV))
Zyprexa (*see* Olanzapine)
Zyrtec (*see* Cetirizine)
Zyvox (*see* Linezolid)

Subject Index

Note: Page number followed by *f* and *t* indicates figures and tables, respectively.

A

AA (*See* Amino acid (AA))
AAA (*See* Aromatic amino acids (AAA))
AAN (*See* American Academy of Neurology (AAN))
AAP (*See* American Academy of Pediatrics (AAP))
AAPCC (*See* American Association of Poison Control Centers (AAPCC))
AASLD (*See* American Association for Study of Liver Diseases (AASLD))
AB (*See* Acute bronchitis (AB))
ABCs (*See* Airway, breathing, and circulation (ABCs))
Abdominal pain, clinical relevance of, 1233–1234, 1234*t*
Abdominal radiograph, in iron toxicity, 74
ABG (*See* Arterial blood gas (ABG))
ABI (*See* Ankle-to-brachial index (ABI))
Abnormal impulse conduction, 328
Abnormal impulse formation, 327–328
ABPM (*See* Ambulatory blood pressure monitoring (ABPM))
Abscesses, 1532
  in brain, 1434–1435, 1434*t*
  hepatic, with amebiasis, 1770
  intra-abdominal, 1536
Absence seizures, 1313, 1332–1333
  and tonic-clonic seizures, 1333–1335
Absolute neutrophil count (ANC), 35, 1610, 1622, 2121
  hematologic laboratory values for, 21*t*
Absorption spectrum, 887
ABW (*See* Actual body weight (ABW))
ACAT (*See* Acetyl CoA acetyl transferase (ACAT))
ACC (*See* American College of Cardiology (ACC))

ACC/AHA hypertension treatment guidelines, for hypertension management, 144, 146–147, 149, 151–155, 160
Accelerated rejection, 761
ACCORD (*See* Action to Control Cardiovascular Risk in Diabetes (ACCORD))
ACCP (*See* American College of Chest Physicians (ACCP))
Accreditation Council for Pharmacy Education (ACPE), 102
ACE (*See* Angiotensin-converting enzyme (ACE))
ACEI (*See* Angiotensin-converting enzyme inhibitors (ACEIs))
Acetaminophen toxicity, stages of, 82
Acetylcholine, 504–505
Acetyl CoA acetyl transferase (ACAT), 106
ACG (*See* American College of Gastroenterology (ACG))
Acid-base disorders, 591–601
acid-base physiology, 592–593, 592*f*, 593*t*
evaluation of, 593, 593*t*
metabolic acidosis, 594–597, 597*t*
metabolic alkalosis, 597–598, 597*t*
respiratory acidosis, 598–600, 599*t*
respiratory alkalosis, 600–601, 600*t*
Acid-base physiology, 592–593, 592*f*, 593*t*
Acid-fast bacilli (AFB) stain, 1371
Acidification, 45
Acidosis
in ALF, 1731
in CHD, 2269
in infants, 2206
metabolic, 1731, 2191, 2200, 2206
in infants, 2209
in NEC, 2239
and pediatric shock, 2260–2261
in RDS, 2227
in VLBW infants, 2240
in PDA, 2237
renal tubular, 2071
from salicylate toxicity, 71
sepsis-induced, 2265
Acid suppression empiric test, 529
ACIP (*See* Advisory Committee on Immunization Practice (ACIP))
ACLS (*See* Advanced Cardiac Life Support (ACLS))
Acne, 857–858, 865–870
with androgens, 2029*t*
clinical presentation of, 866
comedonal, 866*t*, 867–868
definition of, 865
diagnosis of, 866, 866*f*

with lithium, 1912*t*
maculopapular, 866*t*, 868–869
nodular, 866*t*, 869–870
pathophysiology of, 865
and PCOS, 1040
scarring, 866–867
treatment of, 866–867, 866*t*
nonpharmacologic therapy, 866–867
pharmacotherapy, 867
Acneiform eruptions, 863
ACO (*See* Asthma-COPD Overlap (ACO))
ACPE (*See* Accreditation Council for Pharmacy Education (ACPE))
Acquired immunodeficiency syndrome (AIDS), 1654
CD4+ lymphocytes and, 1654
diagnosis of, 1630
fungal infections and, 1674
incidence and mortality rate, 1629
and infections, 1389, 1629
opportunistic infections with
in asymptomatic HIV-infected patients, 1654–1656
incidence rate, 1655
PCP and, 1656
PPD skin test and, 1495–1496
retinitis and, 1664
Toxoplasma encephalitis and, 1662–1664
ACR (*See* American College of Rheumatology (ACR))
Acropachy, 1074
ACS (*See* Acute coronary syndrome (ACS))
Action in Diabetes and Vascular Disease a Controlled Evaluation (ADVANCE), 1110
Action potential duration (APD), 326
Action to Control Cardiovascular Risk in Diabetes (ACCORD), 641, 1110
-Blood Pressure (ACCORD-BP) trial, 145
Activated charcoal, use of, 68–69, 80
Activated partial thromboplastin time (aPTT), 36, 183, 189, 1368
Active disease, TB and, 1478–1479
treatment of, 1482–1489, 1483*t*
Active oligoarthritis, 931
Active polyarthritis, 930–931
Activities of daily living (ADLs), 900
Actual body weight (ABW), 190
ACUITY trial (*See* Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial)
Acupuncture, 465
Acute asthma, 405–413

β_2-adrenergic agonist therapy, 407–412
corticosteroid therapy, 412
goals of therapy, 405–407
respiratory failure and, 412
Acute bleeding, treatment, 581*t*
Acute bronchitis (AB), 1459–1460
causative organism, 1459
clinical diagnosis of, 1459–1460
clinical presentation of, 1459
definition of, 1459
drug therapy for, 1459
epidemiology of, 1459
incidence of, 1459
microbiology of, 1459
pathophysiology of, 1459
patient education, 1460
treatment of, 1459–1460
Acute care setting, medication therapy management services in, 13–14
Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, 264
Acute cellular rejection, 767
Acute CF exacerbations, 485
Acute cholangitis, 1525–1528
Acute cholecystitis, 1525–1528
clinical presentation/diagnosis of, 1527
definition of, 1526
etiology of, 1527–1528
treatment of, 1528
Acute coronary syndrome (ACS), 154, 220, 241
algorithm for, 243*f*
cardiac biomarker elevation in, 243*f*
clinical presentation of, 241–242, 258–260
anterior vs. inferior infarction, 259
laboratory abnormalities, 259
risk stratification, 259–260
STEMI and NSTEMI, 259
therapeutic objectives, 259–260
complications of, 245
diagnosis of, 242
epidemiology of, 241
hallmark symptoms for, 241–242
laboratory changes in, 242–243
lifestyle modifications, 272
pathophysiology of, 241
pharmacotherapies for, 246–251*t*

risk stratification of, 244–245, 244*t*
thrombus formation and, 242*f*
Acute cystitis, 1009–1010
Acute decompensated heart failure (ADHF), 280
Acute exacerbation of chronic obstructive pulmonary disease (AECOPD), 1460–1462
clinical presentation of, 1461
definition of, 1460
diagnosis of, 1461
epidemiology of, 1460
pathophysiology of, 1460–1461
severity of, 1461
treatment for, 14611462
Acute glomerulopathies, 669–670
poststreptococcal, 669–670
rapidly progressive, 670
Acute gut inflammation, 1241
Acute headaches, 1269–1270
Acute heart failure, hemodynamic profile of, 314*f*
Acute hemorrhagic shock
causes of, 373
hypertonic saline for, 376
treatment of, 373–377
Acute interstitial nephritis (AIN), 674–675
Acute kidney injury (AKI), 661–679
biomarkers, 665
causes of, 663*t*
clinical course, 670
crystal-induced, 675
drug dosing in, 676–677
definition of, 661–662
epidemiology of, 662
functional, 663*t*
history and physical examination in, 664
intrinsic, 663*t*, 669–676
clinical significance of urinary sediment in, 666*t*
laboratory evaluation in, 664–667, 666*t*
pathogenesis of, 662–664, 663*t*, 664*f*
phases of
diuretic phase, 670
oliguric phase, 670
recovery phase, 670
postrenal, 663*t*
angiotensin receptor blocker-induced, 668–669, 668*f*
prerenal and functional AKI, 667–669

prognosis for, 662
supportive management of, 675–679, 678*f*, 678*t*
tubulointerstitial diseases and, 670–671, 671*f*
urinalysis and, 665–666, 666*t*
urinary sediments and, 666*t*
Acute liver failure (ALF)
and HBV, 1731–1732
primary therapy for, 1732
Acute lung injury (ALI), 817
Acute lymphoblastic leukemia (ALL), 2071–2078
age factor, 2071
B-cell lineage, 2072
and bone marrow blasts, 2072
clinical presentation of, 2070–2071
clinical variables, 2072
cytogenetic subtypes of, 2071
cytogenetic variables, 2072
diagnosis of, 2071–2072
early response, 2072–2073
epidemiology of, 2071
etiology of, 2071
immunologic variables, 2072
incidence rate, 2071
minimal residual disease (MRD) in bone marrow samples, 2072–2073
pathophysiology of, 2071
Philadelphia chromosome, 2072
prognostic factors, 2072–2073
racial and ethnic differences, 2071
relapsed, 2077–2078
signs and symptoms, 2071
T-cell lineage, 2072
treatment
CNS preventive therapy, 2074
intrathecal methotrexate dose, 2075
IT chemotherapy, 2074–2075
maintenance, 2075–2077
postinduction chemotherapy, 2075
remission induction therapy, 2073–2074, 2074*t*
with vincristine, 2075
WBC count, 2072
Acute myeloid leukemia (AML)
chromosomal abnormalities, 2084
classification of, 2083–2084
clinical presentation of, 2083
diagnosis of, 2083–2084

definitive diagnosis, 2083
in elderly, 2087
overview of, 2083
pathophysiology of, 2083, 2084*t*
refractory or resistant, 2087
signs and symptoms, 2084
translocations in, 2084
treatment, 2084–2085
chemotherapy, 2086–2087
induction chemotherapy, 2085–2086
postremission therapy, 2086–2087
Acute myocardial infarction (AMI), 241, 383
complications of, 245
goals of therapy, 381–382
Acute otitis media (AOM), 2221–2222
Acute pain, 1210
Acute pancreatitis, 844
Acute pharyngitis, 2222, 2223*t*
Acute pulmonary exacerbation, 475, 481–485
antibiotic dosing, 481–483
antibiotic drug selection, 481
chronic maintenance therapy, 483–485
Acute pyelonephritis, 1542
Acute rejection, 761
liver, 767–768
treatment, 762
Acute repetitive (cluster) seizures, 1336
Acute respiratory distress syndrome (ARDS), 344, 817
sepsis and, 1368
Acute rhinitis, 446
Acute salicylism, signs and symptoms, 70
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, 314
Acute thrombocytopenia, 254
Acute tubular necrosis (ATN), 670, 671*f*
aminoglycoside-induced, 673–674, 673*t*
contrast-induced, 672–673, 672*t*
schematic of, 671*f*
treatment with diuretics and dopamine, 671
Acyclovir-resistant herpes, 1698
AD (*See* Alzheimer disease (AD))
ADA (*See* American Diabetes Association (ADA))
Adenosine 5-diphosphate (ADP), 175
Adenosine monophosphate-activated protein kinase (AMPK), 1156
Adenosine triphosphate (ATP), 49

Adequate response, defined, 559
ADH (*See* Antidiuretic hormone (ADH))
ADHD (*See* Attention deficit hyperactivity disorder (ADHD))
ADHF (*See* Acute decompensated heart failure (ADHF))
ADIAGO (*See* Attenuation of Disease Progression with Azilect Given Oncedaily (ADIAGO))
Adjunctive therapy, 1295
Adjuvant hormonal therapy, 2103*t*
ADLs (*See* Activities of daily living (ADLs))
Administration/absorption of drugs, 41–43
Adolescents, varicella infection in, 1703
Adrenal axis suppression and risk of infection, 858, 858*t*
Adrenal corticotropin hormone (ACTH) stimulation test, 394
Adrenergic nervous system, 278–279
ADT (*See* Androgen deprivation therapy (ADT))
Adult respiratory distress syndrome (ARDS), 375
ADVANCE (*See* Action in Diabetes and Vascular Disease a Controlled Evaluation (ADVANCE))
Advanced Cardiac Life Support (ACLS), 348
Advanced glycosylation end (AGE) products, 641
Advanced Pharmacy Practice Experience (APPE), 100
Adverse drug reactions (*See* Drug hypersensitivity reactions (DHRs))
Advisory Committee on Immunization Practice (ACIP), 1405
AECOPD (*See* Acute exacerbation of chronic obstructive pulmonary disease (AECOPD))
AEDs (*See* Antiepileptic drugs (AEDs))
AF (*See* Atrial fibrillation (AF))
AFB stain (*See* Acid-fast bacilli (AFB) stain)
AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study, 333
African American Heart Failure Trial (AHeFT), 312
African Americans
diabetes in, 1103
glaucoma in, 1186, 1189
HF in, 279
hypertensive emergencies in, 352
African American Study on Kidney Disease (AASK), 639
Afterload, definition of, 277, 372
AG (*See* Anion gap (AG))
AGE products (*See* Advanced glycosylation end (AGE) products)
Aggressive insulin therapy, 473
Aging
and adverse drug reactions, 2280*t*, 2281–2282
asthma and, 2286–2287
carcinogenesis and, 2017

and cerebral blood flow, 2282
and chronic medical conditions, 2283
COPD and, 2286–2287
CVD and, 2284–2285
and depressive symptoms, 1903, 2285–2286
diabetes and, 2285
HF and, 2284
hyperglycemia and, 2287
hypertension and, 2285
osteoarthritis and, 2288–2289
and oxygen consumption, 2282
pharmacodynamic changes
absorption, 2279
creatinine clearance, 2280
distribution, 2279
homeostasis, 2281
phenytoin metabolism, 2280
protein binding, 2279–2280
renal function, 2280
pneumonia and, 2287–2288
and UTI, 2288
Agitation, in ICU, 1243–1247
Agoraphobia, 1817
Agranulocytosis, 1094–1095
AHA (*See* American Heart Association (AHA))
AHeFT (*See* African American Heart Failure Trial (AHeFT))
AHI (*See* Apnea/hypopnea index (AHI))
AIDS (*See* Acquired immunodeficiency syndrome (AIDS))
AIN (*See* Acute interstitial nephritis (AIN))
AIPT (*See* Amiodarone-induced pulmonary toxicity (AIPT))
Air-displacement plethysmography, 785
Airway, breathing, and circulation (ABCs), 67
Airway disease, treatment of, 478–480
Airway surface layer (ASL), 474
Akathisia, 1870–1871
AKI (*See* Acute kidney injury (AKI))
Alanine aminotransferase (ALT), 30, 78, 82, 83, 573, 1367
blood chemistry reference values for, 20*t*
Albumin, 28, 577–578, 785
blood chemistry reference values for, 19*t*
Albuminuria, 633, 637–638
categories of, 634*t*
definition of, 1177
screening for, 1177
Alcohol (*See also* Drug index)

AF and, 331*t*
diabetes and, 1112
HF and, 290
hypertension and, 146
MI and, 220*t*
pulmonary embolism and, 204
toxicity, 1964–1965
use disorders, 1962–1964
withdrawal, 1965–1968
Aldosterone, 575
ALF (*See* Acute liver failure (ALF))
ALI (*See* Acute lung injury (ALI))
ALK (*See* Anaplastic lymphoma kinase (ALK))
Alkaline phosphatase (ALP), 20*t*, 30–31
Alkalosis
metabolic, 597–598, 597*t*, 2200
respiratory, 600–601, 600*t*
ALL (*See* Acute lymphoblastic leukemia (ALL))
Alleles, 54
Allergic bronchopulmonary aspergillosis, 475
Allergic conjunctivitis
ophthalmic medications used for, 460*t*
symptoms of, 450, 459
Allergic contact dermatitis, 862, 863
Allergic drug reactions (*See* Drug hypersensitivity reactions (DHRs))
Allergic interstitial nephritis (AIN), 664
Allergic reactions
distinctive features of, 715–716
prevention and management of, 729–730
Allergic rhinitis, 447
agents used in management of, 454*t*
ARIA classification of, 447*f*
choice of therapeutic agent, 458
etiology of, 448
IgE and, 447
pathophysiology of, 449*f*
therapeutic objectives for, 458
treatment algorithm for, 452*f*
treatment, overview of, 451–456, 452–453*f*, 454–456*t*
Allergic Rhinitis and its Impact on Asthma (ARIA), 451
nonallergic rhinitis classification, 447*f*
Allergy
to chemotherapy, 2044
to cow's milk, 2203
eggs and, 2208

food, 2203
to methotrexate, 2042
penicillin, 2222, 2223*t*
to pyrethrin, 1780
shots, 454, 466
Allodermal grafts, 897
Allogeneic HSCT, 2160
GVT effect, 2166
harvesting of, 2165–2166
for hepatic VOD, 2171–2172
and HGFs, 2171
histocompatibility of, 2164–2165
indications for, 2164
myeloablative preparative regimen for, 2166–2167
from peripheral blood progenitor cells, 2165–2166
from placenta blood, 2166
preparation of, 2165–2166
sinusoidal obstructive syndrome, 2171–2172
toxicities of, 2163*t*
transplantation of, 2165–2166
from umbilical cord, 2166
Alloimmunization, 1031
Alopecia
with androgens, 2029*t*
anticancer therapies and, 2041
antimitotic agents and, 2022*t*
antitumor antibiotics and, 2022*t*
and antiviral drugs, 1699*t*
and BU/CY, 2167, 2183
chemotherapy and, 2041, 2104, 2169, 2183
and doxorubicin, 2104
and fludarabine, 2087
pazopanib and, 2027*t*
PCOS and, 1040
VPA and, 1910
ALP (*See* Alkaline phosphatase (ALP))
a_1-antitrypsin, 429–430
ALT (*See* Alanine aminotransferase (ALT))
Alteplase, role of, 245
Altered drug transport, 43
Altered glucose and insulin metabolism, 654
Aluminum, 2209
Alzheimer disease (AD)
clinical presentation of, 2296–2297
diagnosis of, 2296–2297

etiology of, 2295
neuropathology of, 2295–2296
prognosis of, 2297–2298
treatment of, 2298–2300
Ambulatory blood pressure monitoring (ABPM), 142–143, 156, 164
Ambulatory pH monitoring, 529
Amebiasis
asymptomatic cyst passer, 1772
drug therapy, 1773–1775*t*
genital, 1771
hepatic abscess with, 1770
leukocytosis with, 1772
life cycle, 1771
mortality, 1770–1771
parasite/trophozoite life cycle, 1771
prevalence of, 1770–1771
treatment during pregnancy, 1772, 1775
Amebic dysentery
diagnosis of, 1771–1772
drugs for, 1772
Amenorrhea, 1041, 1052, 1061
America Academy of Otolaryngology, Head and Neck Surgery Foundation, 451
American Academy of Neurology (AAN), 1285
American Academy of Pediatrics (AAP), 1405, 2194, 2221
American Association for Study of Liver Diseases (AASLD), 573, 583–584, 584, 587, 589
guidelines, 575, 576, 579
American Association of Poison Control Centers (AAPCC), 66
American Cancer Society Screening Recommendation, 2126*t*
American College of Cardiology (ACC), 1110
American College of Chest Physicians (ACCP), 907
American College of Gastroenterology (ACG), 508, 587
American College of Medical Genetics, 476
American College of Obstetricians and Gynecology (ACOG), 1006
American College of Obstetrics and Gynecology, 476
American College of Rheumatology (ACR), 179, 733, 902, 903, 913
classification of systemic lupus erythematosus, 734–736*t*
American Congress of Obstetricians and Gynecologists, 1272
American Diabetes Association (ADA)
metabolic goals for adults with diabetes mellitus, 1110*t*
recommendations for statin treatment, 118*t*
Standards of Diabetes Care of, 118
American Gastroenterological Association, 533

American Heart Association (AHA), 141, 145, 154, 172, 208, 223, 508, 1110, 1456
American Pharmacists Association (APhA), 1
American Psychiatric Association, 977
American Society for Parenteral and Enteral Nutrition (ASPEN), 786, 843
guidelines, 807
American Society of Clinical Oncology (ASCO), 2050, 2170
American Thoracic Society (ATS), 428
American Urologic Association (AUA), 2317
AMI (*See* Acute myocardial infarction (AMI))
Amino acid (AA)
balance, 585
in parenteral nutrient formulation, 835–836, 837*t*
Aminoglycoside-induced ATN, 673–674, 673*t*
Amiodarone-induced pulmonary toxicity (AIPT), 344
AML (*See* Acute myeloid leukemia (AML))
Ammonia, 585
AMPK (*See* Adenosine monophosphate-activated protein kinase (AMPK))
Amputation
and osteosarcoma, 2068
in RMSF, 1794
Amygdala
anxiety and, 1802
depression and, 1888
and fear stimulus, 1803
Amylase, 31–32
blood chemistry reference values for, 20*t*
Amyloidosis, 2160*t*
ANA (*See* Antinuclear antibodies (ANA))
Analgesic nephropathy, 659
Anaphylaxis
aspirin-induced or NSAID-induced, 727
diagnosis of, 718
drug therapy of, 721*t*
mechanisms behind, 719
treatment of, 720–721
Anaplasmosis, 1794–1795
clinical and laboratory findings, 1795
treatment and prevention, 1795
Anaplastic lymphoma kinase (ALK), 2117
ANC (*See* Absolute neutrophil count (ANC))
ANCA (*See* Antineutrophil cytoplasmic antibodies (ANCA))
Androgen deprivation therapy (ADT), 2147*t*, 2146–2148
Androstenedione, 1061
Anemia

of CKD
characteristics and etiology, 643–647
goals of therapy, 644
treatment, 644
classifications of, 1996*t*
definition of, 1995
diagnosis of, 1997*f*
history of, 1996
HIV-related, 2012–2013
of inflammation, 2010–2013
iron deficiency, 1998–2002
laboratory evaluation of, 1996–1998, 1997*t*
malignancy-related, 2011–2012
megaloblastic, 2002–2006
pathophysiology of, 1996
physical examination of, 1996
renal insufficiency-related, 2011
sickle cell, 2006–2010
signs of, 1996
symptoms of, 1996
Anesthesia, 2165
Anginal syndromes, CCBs in, 225*t*
Angina pectoris, 217
characteristics of, 220*t*
Angiodysplasia, 654
Angioedema, 147, 729
and ACEI, 301
Angioneurotic edema (*See* Angioedema)
Angioplasty (*See* Percutaneous coronary intervention (PCI))
Angiotensin-converting enzyme (ACE), 174, 222, 245, 279
Angiotensin-converting enzyme inhibitors (ACEIs), 174, 222, 245, 279, 577, 668–669, 1177, 1355 (*See also* Drug index)
for hypertension, 146–147
Angiotensinogen, 279
Angiotensin receptor blockers (ARBs), 222, 245, 283, 577
Angle-closure glaucoma, 1185–1186
Animal bite wounds, 1607–1608
Anion gap (AG), 23
Ankle-to-brachial index (ABI), 172
arterial obstruction, 172*t*
ANP (*See* Atrial natriuretic peptide (ANP))
Antacids, 505, 507
Antepartum prophylaxis, 1031
Anthropometrics, 784–785
Antiarrhythmic agents, pharmacologic properties of, 327*t*

Antibacterials, classification of, 1369*t*
Antibiotics (*See also* Antibiotics in drug)
dosing, 481–483
drug selection, 481
resistance rates, 519
Antibody-mediated rejection, 761
Anticancer therapies, complications of (*See also* Toxicities, associated with anticancer therapies)
acute myeloid leukemia, 2057
impact on fertility, 2058–2059
methotrexate, 2068–2069
oogenesis, effect on, 2058
spermatogenesis, effect on, 2058–2059
teratogenicity, 2059
Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA), 201
Anticoagulation, duration of, 188*t*
Anticoagulation for hemodialysis, 687–688
Antidepressant *vs.* central nervous system depressant, 76–81
Antidiuretic hormone (ADH), 279, 604
Antidotes, 69
for acetaminophen toxicity, 82
in CNS depression, 77
Antiepileptic drugs (AEDs), 1339, 1910
Antifungal, 773
Antihypertensive therapy, 639–640, 642
Antimanic agents, 1907
Antimicrobial therapy, 442–443
Anti-mullerian hormone (AMH), 1040
Antineutrophil cytoplasmic antibodies (ANCA), 670
Antinuclear antibodies (ANA), 714
Antiproteases, 475
Antipseudomonal therapies, 481
Antireflux surgery, 533
Antiseizure drug therapy (ASD), 1315, 1321
adverse effects of, 1321, 1328
choice of, 1315, 1319
duration/discontinuation of, 1319
elderly patients and, 1332
for febrile seizures, 1337
for future use, 1328
goal of, 1315
hypersensitivity reactions to, 1337–1338
impact on bone density, 1331–1332
monotherapy vs. polytherapy, 1318–1319
and oral contraceptive interaction, 1338–1339

pharmacokinetic properties of, 1317*t*, 1328
serum concentrations, 1316–1318
side effects of, 1322–1327*t*
for status epilepticus, 1340–1343
teratogenic effects of, 1339–1340
for various seizure types, 1316*t*
and women related issues, 1338–1340
Antithrombin (AT), 182, 182*t*, 235
Antithymocyte globulin (ATG), 756, 2167
Antiviral therapy, 757, 772–773
Antral follicles, 989
Anxiety
and amygdala circuits, 1802
and asthma, 1803, 1806*t*
cause of, 1802
clinical assessment of, 1803–1804
comparative medication treatment options for, 1807*t*
defined, 1802
developmental disorders, 1931–1932
differential diagnosis of, 1803–1804
disorders, 1942
classification of, 1802
clinical significance of, 1803
diagnosis of, 1802, 1805*f*
epidemiology of, 1803
generalized anxiety disorder, 1802
obsessive-compulsive disorder, 1802
panic disorder, 1802
phobic disorders, 1802
posttraumatic stress disorder, 1802
social anxiety disorder, 1802
and hippocampus, 1802
impact on neural systems, 1802–1803
life stressors and, 1804
medical illnesses, 1802
medications, 1802
neurobiology of, 1802–1803
OTC drugs and, 1804
psychological manifestations of, 1802
schizophrenia in, 1854
secondary causes of, 1804, 1806*t*
AOM (*See* Acute otitis media (AOM))
Aortic dissection, 364–365
APD (*See* Action potential duration (APD))
APhA (*See* American Pharmacists Association (APhA))

Aplastic anemia, 1692, 2173
Apnea, 2246–2248
Apnea/hypopnea index (AHI), 1846
Apo B antisense oligonucleotides, 133–134
Apolipoproteins, 109
in transport of cholesterol and triglycerides, 108*f*
APPE (*See* Advanced Pharmacy Practice Experience (APPE))
Appendectomy, prophylaxis for, 1393*t*
Appendiceal abscesses, 473
Appendicitis, 1532, 1778
Appetite regulation, 795
aPTT (*See* Activated partial thromboplastin time (aPTT))
ARBs (*See* Angiotensin receptor blockers (ARBs))
ARDS (*See* Adult respiratory distress syndrome (ARDS))
Area under the concentration-time curve (AUC), 1978*t*, 2117–2118, 2193
Arginine, in critical illness, 817
Arginine vasopressin (AVP), 608
ARIA (*See* Allergic Rhinitis and Its Impact on Asthma (ARIA))
Aromatic amino acids (AAA), 815, 836
Arrhythmias, 326–350, 1684, 1732, 1903, 1987, 1990, 2040, 2052, 2162, 2274, 2287
after MI, 328
antiarrhythmic drugs, 328, 329*t*
cardiopulmonary arrest, 348–350
classification of, 328
conduction blocks, 340–341
electrophysiology and, 326–328, 327*f*, 327*t*
pathophysiology of, 327–328
ART (*See* Assisted reproductive technology (ART))
Arterial blood gas (ABG), 371, 402, 432, 593, 593*t*
Arterial pressure line, role of, 371
Arterial thrombi, 182
Arteriosclerosis obliterans, 170
Arteriovenous access infection, 691–692
Arteriovenous (AV) graft, 684*f*, 685
Arteriovenous fistula, 684–685, 684*f*
Ascites, 574–579
cirrhosis and, 575
diuretic therapy for, 575–577
fluid/electrolyte balance and, 575
goals of treatment for, 575
pathogenesis of, 574–575
refractory, 577–578
treatment for, 577
sodium restriction and, 575

V2 antagonists and, 575
water restriction and, 575
ASCO (*See* American Society of Clinical Oncology (ASCO))
Ascorbic acid, 394–395
ASCVD (*See* Atherosclerotic cardiovascular disease (ASCVD))
ASD (*See* Autism spectrum disorder (ASD))
ASL (*See* Airway surface layer (ASL))
Aspartate aminotransferase (AST), 30, 78, 82, 83, 1367, 1490
blood chemistry reference values for, 20*t*
ASPEN (*See* American Society for Parenteral and Enteral Nutrition (ASPEN))
Aspergillosis, 1692–1694
empiric antifungal therapy, 1692–1693
treatment of, 1693, 1694*t*
***Aspergillus fumigatus*, 475**
Asphyxia, 2240
ASSENT-3 trial, 261
Assisted reproductive technology (ART), 992–998, 993*f*, 993*t*, 994–995*t*, 995*f*, 997–998*t*
AST (*See* Aspartate aminotransferase (AST))
Asterixis, 584–585
Asthma, 398–425
action plan, 423*f*
acute, 405–413
acute exacerbation of, 1988
and agents for intubation, 2259
allergic, 1709
and anxiety, 1804, 1806*t*
blood gases and, 404–402
bronchodilators for, 2287
central stimulation vs bronchodilation for, 2248
in children, 401*t*, 403*f*, 2256
chronic, 413–420
and chronic sleep disorder, 1841*t*
clinical features of, 429*t*
complementary alternative therapies, 424
COPD and, 429, 429–430*t*
defined, 398
diagnosis of, 400, 403–405, 405*t*
drug-induced, 420–421
EIA, 420
in elderly, 2286–2287
eosinophils and, 399
and EPT, 2341
etiology of, 398–399
history of, 400, 402

hyperreactivity and, 400
IgE and, 398
in infants, 2256
and influenza vaccine, 1710
and ketamine, 2258*t*
management of, 409*f*
monitoring of, 400, 403–405
mortality from, 398
nitric oxide and, 399
nocturnal, 421
and panic attacks, 1817
pathophysiology of, 399–400, 400*f*
patient education, 421–424, 422–423*f*
persistent, 2256*t*
pulmonary function tests for, 402–403
respiratory failure and, 412
rhinitis and, 448
self-management of, 422–424
severity of, 413
and smoking, 1979*t*, 1992
spirometry for, 402–403, 405*f*
symptoms of, 400
theophylline for, 2248
in youths and adults, 402*t*, 404*f*
Asthma-COPD Overlap (ACO), 427
clinical features of, 429*t*
Astroviruses, and diarrhea, 1505
Asymptomatic bacteriuria (ASB), 1009–1010
Asymptomatic cyst passer, 1772
Asystole, 349–350, 349*f*
AT (*See* Antithrombin (AT))
ATG (*See* Antithymocyte globulin (ATG))
Atherogenic dyslipidemia, 110–111, 110*t*
Atherosclerosis, 737
metabolic syndrome in, 171*f*
pathogenesis of, 112–113, 113*f*
process of, 219*f*
sites of, 170*f*
Atherosclerotic cardiovascular disease (ASCVD), 173
clinical evaluation and management of, 114–119
guidelines for management of dyslipidemia, 114–119, 116*f*, 117*f*
lipoproteins and, 112–113, 113*f*
NLA criteria for risk assessment and treatment goals, 118*t*
standard lipid panel and advanced lipid testing, 114
ATN (*See* Acute tubular necrosis (ATN))

Atopic dermatitis, 859–860
self-care recommendations for, 861, 862*t*
Atopy, 398–399
ATP (*See* Adenosine triphosphate (ATP))
ATRIA (*See* Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA))
Atrial fibrillation (AF), 206–208, 328, 330*f*
anticoagulation, before and after cardioversion, 206–207
and atrial flutter, 328–331
causes of, 331*t*
clinical manifestation of, 330
consequences of, 331–337
persistent, 208
stroke and, 208
treatment for, 207
Atrial flutter, 330*f*
and AF, 328–331
causes of, 331*t*
Atrial natriuretic peptide (ANP), 671
ATS (*See* American Thoracic Society (ATS))
Attention deficit hyperactivity disorder (ADHD), 2188
adults with, 1943–1944
and anxiety disorder, 1942
diagnosis, 1936–1937
diagnostic criteria for, 1936–1937*t*
epidemiology of, 1935
etiology of, 1936
pathophysiology of, 1935–1936
prognosis of, 1937–1938
psychiatric comorbidity, 1937–1938
and psychosis, 1942–1943
signs of, 1936–1937
and substance abuse, 1942
symptoms of, 1936–1937
and TIC disorder, 1942
and Tourette syndrome, 1942
treatment
alternative therapy, 1943
behavioral therapy, 1938
pharmacotherapy, 1939–1942
Attenuation of Disease Progression with Azilect Given Oncedaily (ADIAGO), 1293
AUA (*See* American Urologic Association (AUA))
AUC (*See* Area under the concentration-time curve (AUC))
Auspitz sign, 872
Autism spectrum disorder (ASD)

anatomy, 1923
characteristics of, 1922–1923
clinical presentation of, 1923–1924
diagnosis of, 1924–1925
DSM-V criteria for, 1924*t*
epidemiology of, 1923
etiology of, 1923
intellectual disability, 1922
natural course of, 1923
pathophysiology of, 1923
physiology of, 1923
prognosis of, 1923
repetitive behaviors, 1929–1930
treatment, 1925–1929
hyperactivity, 1926
irritability/aggression, 1927
pharmacologic interventions, 1926
psychosocial interventions, 1925–1926
Autoimmune drug reactions, 724–725
Autologous HSCT, 2161–2164
complications, 2163–2164
indications for, 2160*t*, 2161
myeloablative preparative regimen for, 2163, 2163*t*
Automaticity, 326
Autonomic dysfunction, Parkinson disease and, 1306
Autonomic neuropathy, 1179
AV nodal reentrant tachycardia (AVNRT), 328
AVNRT (*See* AV nodal reentrant tachycardia (AVNRT))
AVP (*See* Arginine vasopressin (AVP))
AV reentrant tachycardia (AVRT), 328
AVRT (*See* AV reentrant tachycardia (AVRT))
Azathioprine, 752, 755–756
Azotemia, 634
and diuretics, 293

B

Babesiosis, 1798
HIV and, 1796
incubation period of tick bite, 1796
pathogens responsible for, 1795
prevention of, 1796
red blood cell transfusions for, 1796
symptoms and diagnosis of, 1795–1796
treatment for, 1796

Babinski sign, 352
***Bacillus cereus,* foodborne illnesses and, 1507**
Bacterial infection, antimicrobial therapy for, 1374–1377*t*
Bacterial meningitis
definitive therapy for, 1427*t*
duration of therapy for, 1429, 1429*t*
empiric therapy for, 1424–1425, 1425*t*
Bacterial pneumonia, 1369
Bacterial vaginosis (BV), 1027, 1577–1578
β-adrenergic blockers, 1186
Balloon tamponade, 582
BAO (*See* Basal acid output (BAO))
Bariatric surgery, for weight loss, 804
Bartter syndrome, 616
Basal acid output (BAO), 515
Basal-bolus insulin therapy, for type 1 diabetes, 1119–1123, 1121–1122*t*, 1121*f*
continuous subcutaneous insulin infusion, 1120
indications and precautions, 1122*t*
Basal cell carcinoma (BCC), 882, 884
Basal energy expenditure (BEE), 786–787, 787*t*
Basal metabolic rate (BMR), 781
Basic metabolic panel (BMP), 26, 27*t*
Basophils, 35
BBB (*See* Blood-brain barrier (BBB))
BCAA (*See* Branched-chain amino acids (BCAA))
BCC (*See* Basal cell carcinoma (BCC))
***B. cepacia* syndrome, 475**
BCG vaccination, 1482
BD (*See* Bipolar disorder (BD))
BDI (*See* Beck Depression Inventory (BDI))
Beck Depression Inventory (BDI), 1888
BEE (*See* Basal energy expenditure (BEE))
Beef tapeworm (*See* Cestodiasis (tapeworm infection))
Behavioral Pain Scale, 1244
Benign prostatic hyperplasia (BPH), 464
clinical presentation of, 2317–2319
digital rectal examination of, 2318–2319
drug therapy, 2312–2316
nonpharmacologic treatment, 2322
pathophysiology of, 2316–2317
PSA in, 2319
symptoms, 2316
urinalysis of, 2317
BG (*See* Blood glucose (BG))
Bicarbonate deficit, 2201, 2201*t*

Bicarbonate (sodium bicarbonate)
in metabolic acidosis, 594
for salicylate toxicity, 72
for TCA toxicity, 80
***Bifidobacterium*, 515, 2219**
Biliary pseudolithiasis, 1428
Biliary tract surgery, prophylaxis for, 1393*t*
Bilirubin, 31, 31*f*
blood chemistry reference values for, 20*t*
Bioavailability, definition of, 1241
Biobrane, 897
Bioelectrical impedance analysis (BIA), 785
Biofeedback, 1236*t*
Bio-identical Hormones, 1067
Biologic therapy
for allergic rhinitis, 454
Biologic therapy, for systemic lupus erythematosus, 742–746
Biosynthetic dressings, 897
Biphasic defibrillators, 348
Bipolar disorder (BD)
alternative medicines, 1920
clinical presentation, 1906–1907
course of illness, 1906
diagnosis of, 1907
and ECT, 1920
epidemiology of, 1905–1906
hypomanic episodes in, 1908*t*
and hypothyroidism, 1913
mania in, 1909–1917
pathophysiology of, 1906
precipitating factors, 1908–1909
risk factors for, 1906
symptoms of, 1906
treatment, 1907
acute cases, 1916–1918
maintenance therapy, 1918–1920
mania, 1909–1917
Bismuth-based quadruple therapy, 519
Bismuth salts, 509
BK polyomavirus infection, 777–778
Bladder dysfunction, 1256
Blastomycosis, 1687–1689
antifungals in pregnancy, 1689
chest radiographs, 1688*f*
disseminated Blastomyces dermatitidis skin ulcers, 1688*f*

etiology of, 1687–1688
extrapulmonary infections, 1688
treatment, 1688–1689
Blood-brain barrier (BBB), 458, 1420, 1420*f*
Blood gas measurement, for asthma, 404–405, 406*f*
Blood glucose (BG)
in iron toxicity, 74–75
monitoring of, 1135
Blood pressure (BP), 141
cardiovascular risk and, 142
determinants of, 367*f*
diastolic, 141
measuring of, 142–143
auscultatory method, 142, 142*t*
out-of-office monitoring, 142–143
regulation of, 141–142
systolic, 141
Blood transfusions, risks of, 377
Blood urea nitrogen (BUN), 23–27, 352, 637, 665
blood chemistry reference values for, 18*t*
renal dysfunction and, 24
BMI (*See* Body mass index (BMI))
BMP (*See* Basic metabolic panel (BMP))
BMR (*See* Basal metabolic rate (BMR))
BNP (*See* Brain natriuretic peptide (BNP))
Body mass index (BMI)
definition of, 793–794
and guidelines for weight classes, 794*t*
Bone
and joint involvement, in cystic fibrosis, 473–474
marrow, and chemotherapy, 2035–2038
metastases, patients with, 2106
***Borrelia miyamotoi*, 1791–1792**
Bowel dysfunction, 1256
Boyarsky index, 2253–2254
BP (*See* Blood pressure (BP))
BPD (*See* Bronchopulmonary dysplasia (BPD))
BPH (*See* Benign prostatic hyperplasia (BPH))
Bradycardia, 328
Bradykinesia, 1283
Brain abscess, 1434–1435, 1434*t*
antimicrobial therapy for, 1434
clinical/radiologic features of, 1435
epidemiology of, 1434
microbiology of, 1434–1435

predisposing factors for, 1434, 1434*t*
staging of, 1434
treatment of, 1434–1437
Brain natriuretic peptide (BNP), 30
blood chemistry reference values for, 20*t*
Branched-chain amino acids (BCAA), 815, 836
Breast cancer
anatomy of breast, 2098*f*
and *BRCA* gene mutation, 2099
clinical presentation of, 2100
and combined oral contraceptives, 979
diagnosis of, 2098, 2100
epidemiology of, 2097
FISH testing, 2101
and HER2 positivity, 2101
incidence of, 2097
inherited mutations, 2100
metastatic, 2106–2110
pathophysiology of, 2097–2098
and postmenopausal hormone therapy, 1064*t*, 1066
prevalence of, 2097
prevention of, 2099
prognostic factors of, 2101–2102
progression of, 2108–2109
risk factors of, 2099–2100, 2100*t*
screening of, 2098–2099
sites of metastases, 2019*t*
staging of, 2101
surgery for, 2102
treatment
adjuvant radiation therapy, 2103–2104
biologic therapy, 2102–2103, 2109–2110
chemotherapy, 2102–2104
hormonal therapy, 2102–2103
surgery, 2102
Breast milk
and antidepressants, 1896
iron content of, 2202
of methadone, 1952
vitamin D content in, 2202
Bridge therapy, 210–212, 211–212*t*, 211*t*
Brief Pain Inventory, 1210, 1212*t*, 1224
Bristol Stool Form Scale, 565, 565*f*
British Society for Rheumatology (BSR), 955
Broadband ultraviolet B (BB-UVB), 877

Broad fish tapeworm (*See* Cestodiasis (tapeworm infection))
Bronchitis
chronic, 427, 428
definition of, 428
Bronchopulmonary dysplasia (BPD), 2208, 2226
clinical manifestations of, 2230–2231
defined, 2230
long-term sequelae, 2234
medical management of, 2231–2233
pathogenesis, 2230–2231
prevention of, 2234–2235
Bronzer, 891
Broth dilution method, 1371, 1378
Bruxism, and SSRI, 1893
BSR (*See* British Society for Rheumatology (BSR))
B-type natriuretic peptide (BNP), 279
Buffering capabilities, 526
BUN (*See* Blood urea nitrogen (BUN))
***Burkholderia cepacia*, 475**
Burkitt lymphoma, 2093
Burn injuries, 894
age-related recommendations for, 896
disease-related recommendations for, 896
epidemiology of, 894–895
etiology of, 895–896, 896
extent of, 895–895
first-degree burns, 895
fluid loss in, 895
fourth-degree burns, 895
incidence of, 894–895
and infection, 895–896
inhalation injury and, 896
postwound care in, 898
prevalence of, 894–895
triage, 896
and rule of nines, 895
second-degree burns, 895
third-degree burns, 895
treatment of, 896–898
zones of, 895
BV (*See* Bacterial vaginosis (BV))

C

CABG (*See* Coronary artery bypass grafting (CABG))

CAD (*See* Coronary artery disease (CAD))
CAIs (*See* Carbonic anhydrase inhibitors (CAIs))
Calcific uremic arteriolopathy (CUA), 650
Calcineurin inhibitors, 755, 861–862
avoidance, withdrawal, or minimization, 763–764
induced nephrotoxicity, 763
Calcium (*See also* Drug index)
blood chemistry reference values for, 19*t*
and BP, 141
homeostasis, 620–621
hypercalcemia, 622–625
hypocalcemia, 621–622
sensitizers, for ADHF treatment, 280
stones, 675
Calvert formula, for drug dosing, 2117
cAMP (*See* Cyclic adenosine monophosphate (cAMP))
***Campylobacter*, 2219**
***Campylobacter gastroenteritis*, 1512**
Canadian Clinical Practice (CCP) guidelines, 809, 819
Canadian Network for Mood and Anxiety Treatments (CANMAT), 1907, 1917–1918
Canadian Trial of Atrial Fibrillation (CTAF), 335
Cancer
and biologic response modifiers, 2021
carcinogenesis, 2017
and CDK, 2016
cell cycle, 2016–2017, 2016*f*
and chemotherapy-related medication errors, 2032
clinical presentation of, 2019
complications of malignancy, 2019
and cyclins, 2016
cytotoxic drugs, handling of, 2031–2032
diagnosis and staging of, 2018–2019
early detection of, 2018
etiology of, 2015–2016
inhibitory proteins and, 2016
and occupational exposure to hazardous drugs, 2032
PCOS and, 1043
and postmenopausal hormone therapy, 1064*t*
prevention of, 2017–2018
RECIST criteria, 2031
screening of, 2018
statistics, 2014–2015
treatment, 2019–2031
endocrine therapy, 2029

immunotherapy, 2029–2030
radiation, 2020–2021
surgery, 2020
systemic therapy, 2021–2030
targeted therapy, 2024–2029
tumor
markers, 2031
tumor metastases, 2017
Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality (CHARM), 283
***Candida* infection, 1680–1687**
characteristics of, 1682
diagnostic tests
antibody detection, 1683
antigen detection, 1682–1683
culture, 1682
direct examination, 1682
epidemiology of, 1680
risk factors of, 1682
treatment
necessity of, 1683
options, 1683–1684
***Candida* species, 1674–1675, 1684**
fungal peritonitis by, 1532
Candiduria, 1687
Cangrelor *versus* Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PHOENIX trial, 254
CANMAT (*See* Canadian Network for Mood and Anxiety Treatments (CANMAT))
CAP (*See* Community-acquired pneumonia (CAP))
CAPD (*See* Continuous ambulatory peritoneal dialysis (CAPD))
CAPRICORN (*See* Carvedilol Post-Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN))
CAPRIE trial (*See* Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial)
Carbohydrates, 780
diabetes and, 1111
in parenteral nutrient formulation, 834
Carbon dioxide (CO_2), 23
blood chemistry reference values for, 18*t*
Carbonic anhydrase inhibitors (CAIs), 1186
Cardiac arrest, 348*t*
Cardiac arrhythmias, 1684, 1844, 1899, 2250–2251
Cardiac Arrhythmia Suppression Trial (CAST), 258
Cardiac asthma and HF, 300

Cardiac biomarker elevation, in ACS, 243*f* (*See also* Acute coronary syndrome (ACS))
Cardiac computed tomography angiography (CCTA), 221
Cardiac contractility, 277–278
Cardiac dilatation, 281, 289
Cardiac failure, postoperative
hemodynamic profile, assessment by, 382
inotropic agents, 383–385
milrinone, 385–386
selection and initiation of therapy, 364
therapeutic interventions, 382–383
Cardiac hypertrophy, 281
Cardiac index (CI), 369*t*, 379
Cardiac markers, 28–30
Cardiac output (CO), 275, 276
Cardiac remodeling, 280
cardiac dilatation, 281
cardiac hypertrophy, 281
defined, 280
Frank-Starling curve, 281, 281*f*
Cardiac resynchronization therapy, for HF, 318–321
Cardiac surgery, prophylaxis for, 1392*t*
Cardiac syndrome X, 24
Cardiac troponin I (cTnI), 29
Cardiac troponin T (cTnT), 29
Cardiac valve replacement, 209
bioprosthetic valves, 209
mechanical prosthetic valves, 209
Cardiogenic shock, 379–381
acute myocardial infarction, 381–382
causes of, 379–380
early, 380*t*
postoperative cardiac failure, 382–388
symptoms of, 380
Cardiogenic thromboembolism, prevention of
atrial fibrillation, 206–209
cardiac valve replacement, 209
Cardiopulmonary arrest
and arrhythmias, 348–350
asystole, 349–350
cardiopulmonary resuscitation, 348
pulseless electrical activity, 349–350
treatment of, 348–350
Cardiovascular complications
dyslipidemia, 648–649

hypertension, 647–648
Cardiovascular (CV) risk factors, 145*t*, 148–149
Cardiovascular disease (CVD), 217
and contraception, 963–964
and diabetes, 1177–1178
and hypertension, 149
and postmenopausal hormone therapy, 1063, 1064*t*
Cardiovascular function, drug poisoning and, 75
CARISA (*See* Combination Assessment of Ranolazine in Stable Angina (CARISA))
Carnitine, 817
deficiency, 2209
Carotid endarterectomy, 1360
Carvedilol or Metoprolol European Trial (COMET), 304
Carvedilol Post-Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN), 262
CAST (*See* Cardiac Arrhythmia Suppression Trial (CAST))
Castration-resistant prostate cancer (CRPC)
adverse effects of, 2151–2152
androgen deprivation therapy, 2154–2155
bone metastases, 2154
cytotoxic chemotherapy, 2150–2151
immunotherapy, 2150
metastatic disease, 2149–2150
next generation antiandrogen therapy, 2151–2152
radiation effects, 2155–2156
Casts, 37
CAT (*See* COPD Assessment Test (CAT))
Cataplexy, 1847
Cataracts and corticosteroids, 1202
Cathartics, 69
Catheters (*See also specific catheters*)
ablation
for PVC, 343
for SuVT, 343
-associated UTI, 1540–1541
PA and, 372
CB (*See* Chronic bronchitis (CB))
CBC (*See* Complete blood count (CBC))
CBT (*See* Cognitive behavioral therapy (CBT))
CCP guidelines (*See* Canadian Clinical Practice (CCP) guidelines)
CCQ (*See* COPD Control Questionnaire (CCQ))
CCTA (*See* Cardiac computed tomography angiography (CCTA))
CDAD (*See Clostridium difficile*-associated diarrhea (CDAD))
CDC (*See* Centers for Disease Control and Prevention (CDC))

CD4+ lymphocyte functions, connection with AIDS, 1654–1655
CDS (*See* Clinical decision support (CDS))
Cell-mediated (delayed) reactions, 715
Cell surface receptor (CXCR1), 475
Center for Epidemiological Studies Depression (CES-D) Scale, 1889
Centers for Disease Control and Prevention (CDC), 398, 1947
growth charts, 795
Centers for Disease Control and Prevention (CDC), 2*American* Diabetes Association (ADA), 2
Centers for Medicare & Medicaid Services (CMS), 2
Central catheter infections, for PN, 850
Centrally mediated abdominal pain, 1234
treatment of, 1234
Central nervous system (CNS), 584
anatomy and physiology of
blood-brain barrier, 1420
CSF, 1420
meninges, 1419–1420
depressant vs. antidepressant, 76–81
drug poisoning and, 77
and hypertensive emergency, 352
infections of, 1419–1437
sepsis and, 1368
and systemic lupus erythematosus, 736
Central poststroke pain (CPSP), 1227
Central sensitization, 1209
Central venous access, 834
Central venous catheter, 685–686, 685*f*
Central venous catheters (CVCs), 834
usage of, 372
Central venous pressure (CVP), 372
normal values of, 369*t*
Cerebral palsy, 2216
Cerebrospinal fluid (CSF), 1420
antimicrobial penetration into, 1423–1424, 1424*t*
shunt infections, 1432–1433
Cervical intraepithelial neoplasia (CIN), 1588
Cesarean section, prophylaxis for, 1394*t*
Cestodiasis (tapeworm infection), 1777–1779
clinical manifestations of, 1778
epidemiology of, 1778
Hymenolepis nana (dwarf tapeworm) infection, 1777
infection with D. latum, 1777
life cycle of larva or cysticercus, 1777–1778
neurocysticercosis of, 1777

praziquantel therapy, 1778
Taenia saginata and Taenia solium, 1778–1779
CETP (*See* Cholesterol ester transfer protein (CETP))
CF (*See* Cystic fibrosis (CF))
CFCs (*See* Chlorofluorocarbons (CFCs))
***CFTR* gene, 63, 471**
CFTR protein (*See* Cystic fibrosis transmembrane regulator (CFTR) protein)
CG equation (*See* Cockcroft-Gault (CG) equation)
CGM (*See* Continuous glucose monitoring (CGM))
cGMP (*See* Cyclic guanosine monophosphate (cGMP))
CHA2DS2-VASC score, 331, 1359
Chancroid, 1577
Charcot's triad, 1527
CHARM (*See* Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality (CHARM))
CHD (*See* Coronary heart disease (CHD))
Chelation therapy, in iron toxicity, 76
Chemosis, 1097
Chemotherapy, adverse effects of
acneiform-erythematous rash, 2042
acute leukemia, 2057
acute myeloid leukemia, 2057
acute tubular obstruction, 2054
in ALL, 2076–2077
alopecia, 2041
anemia, 2037
angina and myocardial infarction, 2052
arrhythmias, 2052
autonomic neuropathy, 2049
on bone marrow, 2035–2038
cardiomyopathy, 2049–2052
cardiotoxicity, 2049–2052
and colony-stimulating factors, 2036–2037
complications of oral cavity, 2038–2040
cranial nerve toxicity, 2049
cytotoxic effects, 2036–2037
dermatologic impacts, 2041–2045
diarrhea, 2040–2041
dry skin, 2042
esophagitis, 2040
on GI tract, 2038–2041
hand-foot syndrome, 2042
hematologic effects, 2035–2038
hemorrhagic cystitis, 2054–2055
hypersensitivity reactions, 2044–2045, 2045*t*

hypertension, 2052
irritant and vesicant reactions, 2043–2044
life-threatening neutropenia, 2035
long-term complications, 2057–2059
mucositis, 2039–2040
myelosuppression, 2035–2037
nausea and vomiting, 2038
nephrotoxicity, 2052–2054, 2054*t*
neurotoxicity, 2046, 2048*t*
neutropenia, 2036
ototoxicity, 2049
peripheral nerve toxicity, 2048
peripheral neuropathy, 2048–2049
pigment changes, 2042
proteinuria, 2054
pulmonary, 2055–2056
and radiation therapy, 2042–2043, 2043*t*
skin and nail changes, 2042
specific organ, 2047–2057
stomatitis, 2039–2040
thrombocytopenia, 2037
venous thrombotic events, 2038
Wilms tumor, 2065–2067
xerostomia, 2039
Chemotherapy-induced nausea and vomiting (CINV), 490–498, 491–493*t*, 494*t*, 497*t*, 498–499*f*
Chest pain, 220
nitroglycerin for, 359
Chest radiograph
blastomycosis, 1688*f*
for CAP diagnosis, 1463
Chest x-ray study (CXR), 432
CHF (*See* Congestive heart failure (CHF))
Childhood absence epilepsy, 1314*t*
Children
and antipsychotics, 1881
asthma in, 398, 401*t*, 403*f*, 413
and bicarbonate deficit, 2201, 2201*t*
and chemotherapy dosage, 2067
chloride concentration, 2200
CNS preventive therapy for, 2074
common infections
acute otitis media, 2221–2222
acute pharyngitis, 2222
corticosteroids in ED for, 408–411

and creatinine clearance, 2065
daily parenteral nutrient requirements, 2198*t*
and diarrhea, 2216
dosage regimen for intrathecal chemotherapy, 2075*t*
and doxorubicin cardiotoxicity, 2067
extent of dehydration, 2197–2198, 2199*t*
  associated diarrhea, 2200–2201
fluid and electrolyte maintenance, 2197–2201, 2198–2199*t*
  administration of, 2200
  calculation of, 2197
glaucoma in, 1185–1186
hypoglycemia in, 1140
and hypotensive reactions to etoposide, 2065
incidence of erythema migrans, 1788
medication dosing in, 2194
and pediatric drug information, 2195
pediatric pharmacodynamics, 2193
pediatric pharmacokinetic differences, 2187–2193
  absorption of drugs, 2187–2188
  and body water content, 2189
  central nervous system, 2188–2189
  distribution of drugs, 2188–2190
  elimination, 2191–2192
  glomerular filtration rate, 2192
  metabolism, 2190–2191
  phase II reactions, 2191
  phase I reactions, 2190–2191
  plasma protein binding, 2189–2190
  tapeworm disease in, 1777
  tubular secretion, rate of, 2192
photoprotection for, 889–890, 890*t*
physiologic changes, 2186, 2186*t*
potassium concentration, 2200
preventing medication errors in, 2194–2195, 2195*t*
prophylaxis to prevent stress-related mucosal bleeding, 2269
and risk of cisplatin nephrotoxicity, 2065
sepsis and septic shock in, 2261–2265, 2263*t*, 2264*t*
  cardiovascular drug therapy, 2266–2269, 2267*t*
  corticosteroid therapy, 2269
  management, 2265–2266
sodium concentration, 2200
traumatic brain injury, 2270–2275
tuberculosis and, 1498–1499
type 1 diabetes in
  blood glucose monitoring, 1135

clinical presentation of, 1133–1134
diagnosis of, 1133–1134
goals of therapy, 1135
honeymoon period, 1135
hypoglycemia, 1135
injection sites, 1134–1135
insulin therapy, 1134
sick day management, 1135–1136, 1136*t*
type 2 diabetes in, 1106
risk factors, 1108*t*
Chlamydia, 1051
***Chlamydia trachomatis*, 1570–1572**
Chloride, 23
blood chemistry reference values for, 18*t*
Chlorofluorocarbons (CFCs), 884
Cholecystectomy, 1528
Cholesterol, 32 (*See also* Lipoproteins)
laboratory tests for, 21*t*
synthesis of, 106, 106*f*
Cholesterol absorption inhibitor, 124–127, 126*f*
Cholesterol ester transfer protein (CETP), 111*f*
Chorioamnionitis, 1028–1029
Chorionic gonadotropin, 996
Choroid, 1184
Chronic allograft injury (CAI), 762
Chronic asthma (*See also* Asthma)
anticholinergics, 417
biologics, 417–418, 419*f*
classification of, 413
corticosteroids, 414–417
leukotriene modifiers, 417
therapy of, 413–414
Chronic bronchitis (CB), 427, 428
Chronic dyspepsia, 509
Chronic glomerulopathies, 655–659
focal segmental glomerulosclerosis, 658–659
granulomatosis with polyangiitis, 656–658, 657*t*
lupus nephritis, 655–656
Wegener granulomatosis, 656–658, 657*t*
Chronic hypertension, 1015, 1018–1019
clinical presentation of, 1015
treatment of, 1018–1019
Chronic kidney disease (CKD), 681
anemia of
characteristics and etiology, 643–647

goals of therapy, 644
treatment, 644
antihypertensive therapy, 639–640
cardiovascular complications
dyslipidemia, 648–649
hypertension, 647–648
classification of, 633–634
clinical assessment
complications of, 638, 638*t*
proteinuria, 637
quantifying glomerular filtration rate, 636–638
complications of
altered glucose and insulin metabolism, 654
dermatologic complications, 654
endocrine abnormalities caused by uremia, 654
gastrointestinal complications, 654
criteria for, 633*t*
definition, 633–634
diabetic kidney disease, 640–642
management, 640–642
drug-induced, 659–660
drug-induced causes of
analgesic nephropathy, 659
lithium-induced nephropathy, 659–660
economics, 635
epidemiology of, 634–636
etiology of, 634–635
examples of, 634*t*
fluid and electrolyte complications
hyperkalemia, 642–643
metabolic acidosis, 643
sodium and water retention, 642
glomerular disease
chronic glomerulopathies, 655–659
nephrotic syndrome, 654–655
hypertension and, 149, 154
medication use, 635
mineral and bone disorders
etiology, 649–650, 649*f*
treatment, 650–654, 651*t*
pathophysiology, 635–636
prevention, 638–639
dietary protein restriction, 637
dyslipidemia treatment, 648–649
risk factors for, 635*t*

staging of, 633*t*
Chronic kidney failure, 680–696
defined, 681
dialysis, general principles of, 681–682
hemodialysis, 681, 682*f*, 684*f*
anticoagulation for, 687–688
arteriovenous access infection, 691–692
arteriovenous (AV) graft, 684*f*, 685
arteriovenous fistula, 684–685, 684*f*
central venous catheter, 685–686, 685*f*
dialysate, 686, 686*t*
dialysis disequilibrium, 690
dialyzer membrane characteristics, 686–687
intradialytic hypotension, 689–690
process of, 688–689
skeletal muscle cramps, 690
vascular access, 682, 684
vascular access flow dysfunction, preventing and treating, 690–691
peritoneal dialysis, 681
access, 692
continuous ambulatory, 693*f*
dialysate, 692–694
exit-site infection, 694–695
peritonitis, 695–696
prophylaxis, 694–695
treatment of, 695
ultrafiltration, process of, 694
urea clearance, 694
weight gain, 696
Chronic liver rejection, 768
Chronic lung disease (*See* Bronchopulmonary dysplasia (BPD))
Chronic lymphocytic leukemia (CLL)
diagnosis of, 2088
Chronic maintenance therapy, 483–485
Chronic myeloid leukemia (CML)
clinical presentation of, 2088
cytogenetic response in, 2088*t*
diagnosis of, 2088
disease course, 2088–2089
epidemiology of, 2087
hematologic response in, 2088*t*
pathophysiology of, 2087
prognosis of, 2088–2089
relapsed and refractory, 2090
signs and symptoms, 2088

treatment, 2089
WHO Criteria for, 2089*t*
Chronic obstructive pulmonary disease (COPD), 426–444, 1806*t*
acute exacerbation of, 442–443
asthma and, 429, 429*t*, 430*t*
chemokines and, 427
classification of severity and clinical presentation, 432–433, 432*f*
clinical features of, 429*t*
cytokines and, 427
definitions of, 427
diagnosis and patient assessment of, 430–433
epidemiology of, 427
exacerbations of, 436
follow-up pharmacologic escalation/de-escalation strategies, 434*f*
general management considerations, 433
growth factors and, 428
HIV and, 427
immunization with, 433, 437–438
inflammatory cells and, 429
inhaled therapeutic options for, 439*t*
mediators in, 427
natural course, 433
oxygen therapy for, 443, 443*t*
pathogenesis of, 427, 428*f*
pharmacologic therapy by disease severity, 436
pharmacotherapy of, 433–436
phenotypes of, 427
proteases and, 429
pulmonary rehabilitation for, 433, 441–442
risk factors for, 427
smoking and, 427, 433, 437
spirometry testing of, 431–432, 431*f*
stages of, 437–438
surgical treatment of, 443–444, 444*t*
Chronic opioid therapy (COT), 1235
Chronic pain, 1210
Chronic rejection, 761–762
Chronic rhinitis, 447
Chronic salicylism, 70
Chronic stable angina, 217
anti-ischemic drug therapy, 228–235
atherosclerotic vascular disease, 218–219
cardiac catheterization, 221
clinical presentation of, 220–221, 226–227
diagnostic procedures, 227

risk stratification and prognosis, 227
diagnosis of, 221
drug and nondrug therapy
anti-ischemic pharmacotherapy, 223–226
myocardial revascularization, 226
vasculoprotective therapy, 222–223
epidemiology of, 217
exercise stress testing, 229
intracellular sodium and calcium handling, 220
ischemia, 217
medical management of
dietary interventions, 228
risk factors and lifestyle modifications, 228
myocardial oxygen supply and demand, 217, 218*f*
pathophysiology of, 212*f*, 217–220
platelet aggregation, 219–220
risk assessment of, 221
stress testing, 221
thallium-201 myocardial perfusion imaging, 221
Churg-Strauss syndrome, 465
Chylomicrons, 109
CI (*See* Cardiac index (CI))
CINV (*See* Chemotherapy-induced nausea and vomiting (CINV))
Cirrhosis
pathogenesis of, 572
portal hypertension, 572–574, 573*f*, 574*t*
CIS (*See* Clinical information system (CIS); Clinically isolated syndrome (CIS))
CK (*See* Creatine kinase (CK))
CKD (*See* Chronic kidney disease (CKD))
Clearance or removal of substance, 682
Clinical and Laboratory Standards Institute (CLSI), 1371
Clinical decision support (CDS), 51
Clinical Disease Activity Index (CDAI), 917
Clinical information system (CIS), 3
Clinically isolated syndrome (CIS), 1254
Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), 236
Clinical Pharmacogenetics Implementation Consortium (CPIC), 58
guidelines for simvastatin, 59*t*
guidelines for TPMT genotype-based thiopurine dosing, 58*t*
CLL (*See* Chronic lymphocytic leukemia (CLL))
Clonidine, 579
Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), 262

Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28), 260
Clopidogrel, role of, 175
Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, 223
***Clostridioides difficile*, 2219**
***Clostridium difficile*-associated diarrhea (CDAD), 1518–1523**
BI/NAP1 stain and, 1521
mild to moderate infection, 1518–1521
recurrence of, 1522–1523
severe, 1521–1523
transmission of, 1521
***Clostridium perfringens,* foodborne illnesses and, 1507**
Clotting
cascade, 181–182, 182*f*
diarrhea and, 203
inhibitors of, 181
mechanisms, 182*t*
vitamin-K dependent, 187*t*
Cloud cover, 884
CLSI (*See* Clinical and Laboratory Standards Institute (CLSI))
Clubbing, of nails, 1441
Cluster headache, 1269
abortive therapy for, 1279
pathophysiology of, 1278
prophylactic therapy for, 1279
signs and symptoms of, 1278–1279
CML (*See* Chronic myeloid leukemia (CML))
CMM (*See* Cutaneous malignant melanoma (CMM))
CMP (*See* Comprehensive metabolic panel (CMP))
CMS (*See* Centers for Medicare & Medicaid Services (CMS))
CMV (*See* Cytomegalovirus (CMV))
CNS (*See* Central nervous system (CNS))
CO (*See* Cardiac output (CO))
Coagulation studies, 36
Coagulopathy, from salicylate toxicity, 72
Coccidioides immitis, 1692
Coccidioidomycosis, 1691–1692
antifungal central nervous system penetration, 1692
intraventricular administration of AmB, 1692
serologic tests, 1691–1692
Cockcroft-Gault (CG) equation, 636, 665
for CrCl estimation, 24–25
for renal function estimation, 709, 2118
Cognitive behavioral therapy (CBT), 1227, 1236, 1236*t*, 1889

for GAD, 1804
insomnia and, 1834, 1834*t*, 1845
OCD and, 1826
panic disorder and, 1816
PTSD and, 1823
for SAD, 1820
Cognitive dysfunction, and MS, 1257
Cold
common, 1719
in infants and children, 2215–2216
nodule, 1075
Collapsin response mediator protein 2 (CRMP-2), 1254
Colloid oncotic pressure (COP), 373
Colloids, 379
composition and properties of, 374*t*
vs. crystalloids, 373–375
Colon cancer, 2123–2137
chemotherapy for, 2125–2131
clinical presentation of, 2124, 2125
clinical surveillance for recurrence, 2131–2132
diagnosis of, 2124
epidemiology of, 2123–2124
etiology of, 2123–2124
for metastatic, 2132–2134
neoadjuvant, 2137
pathophysiology of, 2123–2124
and peripheral neuropathy, 2131
predictive markers, 2131
screening, 2124–2125
sites of metastases, 2019*t*
therapeutic modalities, 2124
chemotherapy, 2125–2131
dermatologic toxicity related to EGFR therapy, 2136
infusion-related reactions, 2136
neoadjuvant chemotherapy, 2137
selected regimens, 2127–2129*t*
Colonization, 1378
Colorado tick fever (CTF)
diagnosis of, 1797
host reservoirs, 1797
identification of virus, 1797
laboratory findings, 1797
and leukopenia, 1797
prevalence of, 1797
supportive care, 1797

symptoms of, 1797
tick species, 1797–1798
treatment care, 1797
Colorado tick fever virus (CTFV), 1797
Colorectal cancer
American Cancer Society Screening Recommendation, 2126*t*
chemotherapy for, 2132–2134
colon cancer, 2123–2137
EGFR receptor, 2136
immunotherapy, 2133–2134
and postmenopausal hormone therapy, 1064*t*
rectum cancer, 2136–2137
salvage therapy, 2136
Colorectal surgery, prophylaxis for, 1394*t*
CombAT (*See* Combination of Avodart and Tamsulosin (CombAT))
Combination Assessment of Ranolazine in Stable Angina (CARISA), 233
Combination of Avodart and Tamsulosin (CombAT), 2321
Combination therapy, 481
Comedones, 867 (*See also* Acne)
COMET (*See* Carvedilol or Metoprolol European Trial (COMET))
Comfeel (Coloplast), 897
COMMIT (*See* Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT))
Common cold, 1719
Communication
between healthcare professionals, 98–99
in poisonings assessment, 67
Community-acquired pneumonia (CAP), 1369, 1463–1469
antibiotic therapy for, 1465–1469, 1467*f*
antiviral therapy for, 1469
clinical presentation of, 1463
definition of, 1463
diagnosis of, 1463
drug therapy for, 1463
epidemiology of, 1463
incidence of, 1463
microorganisms common in, 1465*t*
pathogens for, 1464–1465, 1465–1466*t*
pathophysiology of, 1463
respiratory virus and, 1465
severity of, 1464
Community pharmacy/ambulatory setting
documentation and follow-up, 10–13
intervention and referral, 10
medication action plan, 10, 11*f*

medication therapy review, 9, 9*t*
personalized medication record, 9–10, 10*f*
Comparison of Medical Therapy, Pacing, and Defi brillator in Heart Failure (COMPANION) trial, 318
Competitive enzyme inhibition, 43
Complete blood count (CBC), 32, 920, 921, 1592
Complex partial seizures, 1313
Comprehensive metabolic panel (CMP), 26, 27*t*
Computed tomography (CT), 1527
Condom catheters, 1541
Conduction, 326–327
abnormal impulse, 328
reentry and, 328
second-degree atrioventricular block, 340, 340*f*
velocity of, 286
Confidence interval (CI), 343
Congenital adrenal hyperplasia, 1040
Congenital anomalies, 1003
Congenital infections, 2246
Congestive heart failure (CHF), 275
defined, 277
and NSAID usage, 667–668
Conjunctivitis
acute bacterial, 1201
allergic, 1201
causes of, 1201
Connective tissue diseases (CTDs)
dermatomyositis, 957–958
polymyalgia rheumatica, 954–955, 955*t*
polymyositis, 957–958
reactive arthritis, 955–957
signs and symptoms of, 952
systemic sclerosis (scleroderma), 952–954, 953*t*
temporal arteritis, 954–955
Constipation, 567–568, 2216, 2217*t*
Contamination, 1378
Continuous ambulatory peritoneal dialysis (CAPD), 654, 692, 693*f*, 699, 704
-associated peritonitis, 1531–1532
Continuous erythropoietin receptor activator (CERA), 647
Continuous glucose monitoring (CGM), 1114
Continuous positive airway pressure (CPAP), 1847
Continuous renal replacement therapy (CRRT), 677–678, 678*f*, 678*t*, 699–700
Continuous venovenous hemodiafiltration (CVVHDF), 677, 678*f*
Continuous venovenous hemodialysis and diffusion, 677
Continuous venovenous hemodialysis (CVVHD), 677

Continuous venovenous hemofiltration (CVVH), 677, 678*f*, 699, 704
Continuous venovenous high-flux hemodialysis and hemodiafiltration, 677
Contraception, 961–985
and cardiovascular disease, 963–964
cigarette smoking and use of, 963
combined oral, 967–973, 968–972*t*
acne, 975, 977
and amenorrhea, 978
and breast cancer, 979
and cervical cancer, 979
and cervical dysplasia, 979
and cycle lengths, 967
and endometrial cancer, 977
extended cycle, 972–973
and functional ovarian cysts, 977
instructions, 973
and menstrual cycles, 977
monophasic COCs, 972
multiphasic, 967, 972
and nausea, 978
noncontraceptive benefits of, 975–977
and ovarian cancer, 977
contraceptive patch, 973–974
contraceptive ring, 974–975
contraindications to, 962–967, 965*f*, 966*t*
and diabetes, 966–967
drug interactions, 975, 976*t*
emergency
copper-T IUD, 985
emergency contraceptive pills, 984–985
and gallbladder disease, 967
and headaches/migraines, 965–966, 978–979
and hepatotoxicity, 966
hormonal contraceptives, 962
for dysmenorrhea, 1049
for endometriosis, 1052
risk and adverse effects, 977–980
and weight gain, 978
and hypertension, 966
implant (Nexplanon), 981
and incidence of gallstones, 967
injectable medroxyprogesterone acetate, 980–981
intrauterine device and intrauterine system, 982
medical abortion, 985
nonhormonal

cervical caps, 983
diaphragm, 983
female condoms, 984
male condoms, 984
vaginal spermicides, 984
vaginal sponge, 983–984
oral, 994
patient evaluation for contraceptive selection, 962, 963–964*t*
progestin-only pill (minipill), 980
and stroke, 965–966
subdermal implant, 981–982
and thromboembolic events, 966, 966*t*
use during pregnancy and breast-feeding, 979–980
Contrast-induced acute tubular necrosis, 672–673, 672*t*
Convection, 682
Conventional hemodialysis (HD), 703–704
COPD (*See* Chronic obstructive pulmonary disease (COPD))
COPD Assessment Test (CAT), 433
COPD Control Questionnaire (CCQ), 433
COPERNICUS, 304
Corneal ulcers, 1201–1202
Coronary artery bypass grafting (CABG), 221, 236, 236*f*, 241
Coronary artery disease (CAD), 217
COPD and, 433
coronary catheterization and, 221
dofetilide for, 335
HF and, 275
risk factors for, 169
smoking and, 169–170
treatment, antiplatelet therapy in, 223
Coronary artery spasm
clinical presentation of, 238
therapy for, 238–239
Coronary heart disease (CHD), 217, 940
cholesterol and (***See* Cholesterol**)
chronic stable angina and, 217
recommendations for risk factor optimization, 222*t*
Cortisol, 857
COT (*See* Chronic opioid therapy (COT))
Cough, in infants and children, 2215–2216
COURAGE (*See* Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE))
Covert Hepatic Encephalopathy, 584
COVID-19, 1415–1416
Cow's milk, 2203

COX (*See* Cyclooxygenase (COX))
CPAP (*See* Continuous positive airway pressure (CPAP))
Craniotomy, 1435
Crataegus monogyna, 323
Crataegus oxyacantha, 323
CrCl (*See* Creatinine clearance (CrCl))
C-reactive protein (CRP), 30
blood chemistry reference values for, 20*t*
Creatine kinase (CK), 28–29, 242
blood chemistry reference values for, 19*t*
Creatinine, 24, 639
blood chemistry reference values for, 18*t*
serum concentrations of, 576
Creatinine clearance (CrCl), 24–25, 636
and aging, 2280
blood chemistry reference values for, 18*t*
in children, 2065
Critical-Care Pain Observation Tool, 1244
Crohn disease
diagnosis of, 542, 543*t*
severity classification of, 543*t*
treatment algorithm, 557*f*
and ulcerative colitis, pathophysiologic differences between, 542*t*
Crohn's Disease Activity Index, 561
Cross-reactivity, 717–718
CRP (*See* C-reactive protein (CRP))
CRPC (*See* Castration-resistant prostate cancer (CRPC))
CRRT (*See* Continuous renal replacement therapy (CRRT))
Cryotherapy, 2040
Cryptococcosis, 1656, 1695
clinical presentation of, 1666–1667
maintenance therapy, 1668
primary prophylaxis, 1668–1669
prognosis of, 1666–1667
treatment, 1667–1668
Cryptococcus neoformans, 1656
Cryptosporidiosis, 1502*t*, 1655
relapse, repeat induction therapy, 166
***Cryptosporidium parvum,* diarrhea and, 1507–1508**
Crystal-induced acute kidney injury, 675
Crystalloids, 375
composition and properties of, 374*t*
vs. colloids, 373–375
CSF (*See* Cerebrospinal fluid (CSF))
CT (*See* Computed tomography (CT))

CTAF (*See* Canadian Trial of Atrial Fibrillation (CTAF))
CTDs (*See* Connective tissue diseases (CTDs))
CTF (*See* Colorado tick fever (CTF))
CTFV (*See* Colorado tick fever virus (CTFV))
CUA (*See* Calcific uremic arteriolopathy (CUA))
Culex pipiens, 1712
Culex quinquefasciatus, 1712
Culex restuans, 1712
Culture and susceptibility testing, 1371, 1378
Culture-negative endocarditis, 1455
CURB-65 rule, CAP and, 1464
Current procedural terminology (CPT), 2
Curriculum, incorporating IPE in, 101–102
Cutaneous leukocytoclastic angiitis (*See* Hypersensitivity vasculitis)
Cutaneous malignant melanoma (CMM), 884
CVCs (*See* Central venous catheters (CVCs))
CVD (*See* Cardiovascular disease (CVD))
CVP (*See* Central venous pressure (CVP))
CVVH (*See* Continuous venovenous hemofiltration (CVVH))
CVVHD (*See* Continuous venovenous hemodialysis (CVVHD))
CVVHDF (*See* Continuous venovenous hemodiafiltration (CVVHDF))
Cyclic adenosine monophosphate (cAMP), 438
Cyclic guanosine monophosphate (cGMP), 438
Cyclooxygenase (COX), 258
isoforms, 513
Cyclooxygenase-2 inhibitors and cardiovascular toxicity, 522–523
Cycloplegia, 1185
Cyclosporine, 755, 766–767
CYP (*See* Cytochrome P-450 (CYP))
CYP3A4, 50
CYP2C9, 57
drugs significantly affected by, 57
genotype-based dosing recommendations for phenytoin/fosphenytoin, 58*t*
CYP2C19 enzyme, 62*f*
CYP2D6, 61*t*
CYP450 system, 1691
Cystatin C, 25
blood chemistry reference values for, 19*t*
Cystic fibrosis (CF), 471–485, 2216
antibiotic doses for, 482*t*
arthropathy, 474
clinical manifestations, 473*t*
bone and joint involvement, 473–474
gastrointestinal involvement, 473
genitourinary involvement, 473

hepatic involvement, 473
pancreatic involvement, 473
pulmonary involvement, 474–475
sinus involvement, 474
sweat glands, 472–473, 474*f*
diagnosis of, 476
phenotypic features consistent with, 476*t*
symptoms suggestive of, 476
genetic basis, 471–472
interventions and therapy
acute pulmonary exacerbation, 481–485
airway disease, treatment of, 478–480
enzyme supplementation, 477–478
inflammatory response, 480–481
pulmonary interventions, 478
vitamin and mineral supplementation, 476–477, 477*t*
lung transplantation, 485
mutation, 472
Cystic Fibrosis Foundation, 475, 478
Cystic Fibrosis Foundation (CFF), 475
Cystic fibrosis transmembrane regulator (CFTR) protein, 471, 474*f*
apical membrane, 473
in ion transport, 473
modulation, 472*f*
modulator therapy, 479–480
Cystitis, 1545*t*
Cytochrome P-450 (CYP), 40, 43, 44*f*, 185
isoenzymes, 507
Cytomegalovirus (CMV), 774–777, 1654
diagnosis of, 1664–1665
drug therapy for, 1665–1666
retinitis, 1655
Cytotoxic drug, for systemic lupus erythematosus, 742
Cytotoxic reactions, 714

D

DAD (*See* Delayed after-depolarizations (DAD))
Danish Verapamil Infarction Trial (DAVIT), 257
DAPT (*See* Dual antiplatelet therapy (DAPT))
Dark-field examination, 1574
DASH diet (*See* Dietary Approaches to Stop Hypertension (DASH) diet)
Data-poor environments, 3–4
Data-rich and data-poor environments, 3–4
DAVIT (*See* Danish Verapamil Infarction Trial (DAVIT))

DAWN (*See* Drug Abuse Warning Network (DAWN))
Dawn phenomenon, 1133
DBP (*See* Diastolic blood pressure (DBP))
DBS (*See* Deep brain stimulation (DBS))
DCCT (*See* Diabetes Control and Complications Trial (DCCT))
DCOR trail (*See* Dialysis clinical outcomes revisited (DCOR) trial)
DDI (*See* Drug-drug interaction (DDI))
D-dimer test, 190
Dead-in-bed, 1138
Decompensated, 1098
Decontamination, 68–69
Deep brain stimulation (DBS), 1299*f*, 1302
Deep venous thrombosis (DVT), 181–182, 189–197
clinical presentation of, 189–190
D-dimer test, 190
diagnosis of, 190
duplex scanning for, 190
impedance plethysmography for, 190
outpatient treatment of, 194–195
risk factors for, 189–190
signs and symptoms of, 189–190
treatment of, 190–195
venography for, 190
Defibrillation threshold, 343
DEHN (*See* Diethylhexyl 2,6-naphthalate (DEHN))
Dehydration
assessment of, 2218
with diarrhea, 2200–2201
prevention of, 2217
and weight, 2197–2200, 2200*t*, 2218
Delayed after-depolarizations (DAD), 328
Delayed gastric emptying, 1241
Delirium, in ICU, 1243–1247
Dementia
behavioral disturbances in, 2303–2307, 2304*t*
causes of, 2293–2294*t*
clinical diagnosis, 2292–2295
incidence, 2292
Lewy body, 2300–2301
Parkinson disease and, 1305
prevalence, 2292
screening tests, 2295*t*
stages of, 2298*t*
symptoms, 2294*t*
vascular, 2301–2303

Deoxyribonucleic acid (DNA), 54
analysis for CF mutations, 476
Dependent edema, 289
Depolarization, 326
Depression (*See also* Major depressive disorder)
and amygdala, 1888
antidepressants, 1904
augmentation, 1901–1902
and chronic pain, 1904
classification of, 1886, 1886*t*
clinical presentation of, 1886–1887
CNS manifestation, 1887
developmental disorders, 1931–1932
diagnosis of, 1886
differential diagnosis, 1886, 1887*t*
drug management, 1890–1904
drug selection, 1903
duration of treatment, 1894–1895, 1894*t*
and ECT, 1888
in elderly, 2285–2286
and endometriosis, 1051
environmental factors, 1886
epidemiology of, 1885–1886
genetic studies, 1888
geriatric, 1903
HPA axis manifestation in, 1888
imaging studies, 1888
incidence of, 1885
lifestyle adjustments for, 1889–1890
medications that induce, 1887*t*
neuroendocrine findings, 1888
non-antidepressants, 1901–1902
nondrug therapies, 1889–1890
and norepinephrine deficiencies, 1887
pain and, 1224
Parkinson disease and, 1305–1306
pathophysiology of, 1887–1888
patient assessment tools, 1888–1889
pediatric, 1902
and postsynaptic alpha-adrenergic receptor sensitivity, 1888
psychotherapy, 1889
rating scales, 1889*t*
and recurrent episodes, 1886
serotonin receptor modulators, 1898
somatic interventions, 1889

SSRI, 1898
synaptic neurotransmitter concentrations, 1887
therapeutic blood level monitor, 1903
Dermatologic complications, 654
Dermatology (*See* Skin)
Dermatomyositis (DM), 957–958, 958*t*
Dermis, 851–852, 852*f*
Dermopathy, 1074
DES (*See* Drug-eluting stent (DES))
Desensitization, 730–731
Developmental disorders
anatomy, 1923
anxiety, 1931–1932
characteristics, 1922
clinical presentation, 1923–1924
depression, 1931–1932
diagnosis, 1924–1925
epidemiology, 1923
etiology, 1923
intellectual disability, 1922
natural course of, 1923
pathophysiology, 1923
physiology, 1923
prognosis, 1923
self-injurious behavior, 1930–1931
sleep, 1932–1933
treatment, 1925–1929
hyperactivity, 1926
pharmacologic interventions, 1926
psychosocial interventions, 1925–1926
Dextran 70, 578
Dextrans, 379
Dextrose, 834
DFR (*See* Dialysis flow rates (DFR))
DGI (*See* Disseminated gonococcal infection (DGI))
DHA (*See* Dihydroxyacetone (DHA); Docosahexaenoic acid (DHA))
DHP (*See* Dihydropyridine (DHP))
DHRs (*See* Drug hypersensitivity reactions (DHRs))
Diabetes, 1348
African Americans and, 1103
blindness, 1109
carbohydrate and, 1104–1105
classification of, 1103–1104, 1104*t*
CVD and, 1109
definition of, 1103, 1104*t*

diet for, 1111
dyslipidemia and, 1106–1107
in elderly patients, 2285
enteral formulas for, 819–820
epidemiology of, 1103, 1104*t*
exercise and, 1111
gastroparesis and, 1162
3-hydroxy-3-methyl-glutaryl coenzyme A inhibitors, 123
and hyperglycemia, 26
in ICU, 1239
jet injectors, 1118*t*
long-term complications, 1109
management of, 174, 174*t*
metformin in, 174
obesity and, 1103
and PCOS, 1041, 1043
perioperative care, 1138
and peripheral arterial disease, 169–170
PN and, 844
stroke and, 1157
treatment of, 1111–1115
and UTI, 1540
Diabetes Control and Complications Trial (DCCT), 641, 1109
Diabetes mellitus, 26, 473, 1103–1181 (*See also* Type 1 diabetes; Type 2 diabetes)
blood glucose and glycated hemoglobin monitoring, 1012
carbohydrate metabolism, 1104–1105
cardiovascular disease (CVD) and, 1177–1178
classification of, 1103, 1104*t*
dietary management for, 1011–1012
with ED, 2327
in elderly patients vs. younger patients, 1175*t*
epidemiology of, 1103, 1104*t*
and EPT, 2341
and erectile dysfunction, 2327
gestational, 1013–1015, 1014*f*, 1108–1109, 1108*t*
goals for, 1110*t*
hyperglycemia and, 1180
hypertension and, 1176–1177
hypoglycemia and, 1181
insulin therapy, 1012–1013
management of, 1113
modified White classification of, 1010, 1010*t*
nephrotic syndrome and, 1177
oral hypoglycemic use, 1013

in patients with schizophrenia, 1875
and postmenopausal hormone therapy, 1064*t*
posttransplant, 770–771
preconception management, 1011
preexisting, 1010–1013
during pregnancy, 1010–1015, 1108
pruritus and, 1157
psoriasis and, 871
stroke and, 1157
type 1 diabetes treatment, 1011–1012
type 2 diabetes treatment, 1012–1013
Diabetic foot ulcer cellulites, antimicrobial therapy and, 1389
Diabetic ketoacidosis (DKA), 1141–1145
bicarbonate and, 1144–1145
fluids and, 1142
laboratory abnormalities in, 1142*t*
management of, 1143*t*
patient education, 1142*t*
phosphate and, 1144
potassium and, 1142, 1144
sodium and, 1143
treatment of, 1143–1145
with type 1 diabetes, 1141
Diabetic kidney disease, 640–642
Diabetic neuropathy, 1179–1180
Diabetic patients, skin and soft tissue infections in, 1605–1607
Diabetic retinopathy, 1178–1179
Dialysate
hemodialysis, 686, 686*t*
peritoneal dialysis, 692–694
Dialysis
disequilibrium, 690
encephalopathy, 652
general principles of
clearance or removal of substance, 682
convection, 682
diffusion, 681–682
ultrafiltration, 682
for hyperkalemia, 620*t*
and transplantation, 633
Dialysis clinical outcomes revisited (DCOR) trial, 651
Dialysis flow rates (DFR), 679
Dialyzer membrane, hemodialysis, 686–687
Diaper rash, 2214
Diarrhea, 522, 569–570 (*See also* Infectious diarrhea)

clinical presentation of, 2216
definition of, 1502–1503
dehydration with, 2200–2201
drug therapy, 2219
EN and, 829–830
hypernatremia and, 22
and infant formula feedings, 2205–2206
in infants and children, 2216
and neuroblastoma, 2063
pathogenesis, 2216
and pazopanib, 2027*t*
probiotics for, 2219
with sorafenib, 2027*t*
World Health Organization (WHO) formula for, 2218
Diastolic blood pressure (DBP), 141, 351, 356
normal values of, 369*t*
Diastolic dysfunction, 276
DIC (*See* Disseminated intravascular coagulation (DIC))
Dietary Approaches to Stop Hypertension (DASH) diet, 1176
for hypertension, 145, 151
Dietary carbohydrates, 780
Dietary protein restriction, 637
Dietary reference intakes (DRI), 809
Dietary restriction of phosphorus, 650
Dietary risk factors, 940
Dietary supplements, 47
Diethylhexyl 2,6-naphthalate (DEHN), 888
Diffuse large B-cell (DLBC) lymphoma, 2091
Diffusion, 681–682
Digital rectal examination (DRE), 32
Dihydropyridine (DHP), 224–225
Dihydroxyacetone (DHA), 891
DILE (*See* Drug-induced lupus erythematosus (DILE))
DILI (*See* Drug-induced liver injury (DILI))
Dimorphic fungi, 1674
DIOS (*See* Distal intestinal obstruction syndrome (DIOS))
DIPPERS, mneumonic, 2309
DIPS (*See* Drug Interaction Probability Scale (DIPS))
Dipstick test, 1541
Direct current (DC) cardioversion, 333
Directly observed therapy, for TB, 1488
Disaccharides, 780
Disease-modifying antirheumatic drugs (DMARDs)
for systemic lupus erythematosus, 741
Disk diffusion method, 1378

Disseminated gonococcal infection (DGI), 1568–1570, 1569*t*
Disseminated intravascular coagulation (DIC)
sepsis and, 1368
Distal intestinal obstruction syndrome (DIOS), 473
Distal splenorenal shunt (DSRS), 582
Distribution of drugs, 43
Distributive shock, 388–395
hemodynamic monitoring and, 390
Diuretics, 575–577, 2281
agent choice, 575
diuretic complications and management
electrolyte and acid-base disturbances, 576–577
prerenal azotemia, 577
for dysmenorrhea, 1048
and metabolic alkalosis, 597–598
monitoring, 576
for PMS, 1056–2057
DKA (*See* Diabetic ketoacidosis (DKA))
DLBC (*See* Diffuse large B-cell (DLBC) lymphoma)
DM (*See* Dermatomyositis (DM))
DMARDs (*See* Disease-modifying antirheumatic drugs (DMARDs))
DNA (*See* Deoxyribonucleic acid (DNA))
Docosahexaenoic acid (DHA), 817
Documentation and follow-up, 10–13
Donor and recipient matching, 757–758
Donor-derived infections, 773
Door-to-needle time, 252
Dopamine, and obesity, 796
Double-antibody disease, 670
Doxorubicin cardiomyopathy, 2049–2052
DRE (*See* Digital rectal examination (DRE))
Drug Abuse Warning Network (DAWN), 66
Drug clearance, 679
Drug desensitization, 730–731
Drug disposition, effect on
bioavailability, 697–69
elimination, 698–699
protein binding and volume of distribution, 698, 698*t*
Drug-drug interaction (DDI), 40, 40*t*, 49–51
Drug-eluting stent (DES), 223, 235
Drug fever, 722–723, 722*t*
Drug hypersensitivity reactions (DHRs)
clinical features of, 715*t*
definition of, 712
diagnosis

cross-reactivity, 717–718
distinctive features of allergic reactions, 715–716
skin testing, 716–717, 717*t*
drug history, 715*t*
generalized reactions
anaphylaxis, 718–721, 721*t*
autoimmune drug reactions, 724–725
drug fever, 722–723, 722*t*
drug-induced vasculitis, 723–724, 723–724*t*
hypersensitivity vasculitis, 723, 723*t*
serum sickness, 721–722
immunologic classification of, 713*t*
non-IgE reactions, 725–727, 726*t*
angiotensin-converting enzyme inhibitors and angiotensin II-receptor blockers, 727–728
aspirin/nonsteroidal anti-inflammatory drugs, 727
iron-dextran injection, 729
narcotic analgesics, 729
radiocontrast media, 728–729
organ-specific reactions
blood, immune cytopenias, 725
kidney, 725
liver, 725
lung, 725
skin, 725
pathogenesis of, 712–713
predisposing factors
age and sex, 713
associated illness, 714
drug-related factors, 714
drugs as allergens and immunologic classification, 714–715
genetic factors, 713–714
previous drug administration, 714
prevention and management of, 729–731
desensitization, 730–731
Drug-induced AIN, 674–675
penicillin-induced, 674–675
Drug-induced asthma, 420–421 (*See also* Asthma)
Drug-induced immune cytopenias, 725
Drug-induced liver injury (DILI), 55
Drug-induced lupus erythematosus (DILE), 724, 746
Drug-induced vasculitis, 723–724, 723–724*t*
Drug Interaction Probability Scale (DIPS), 51
Drug interactions
clinical decision support, resources and evidence for, 51

definition of, 40, 40*t*
with immunosuppressives, 769–770
management of, 46–51, 47*t*
mechanisms of, 41–44
administration/absorption of drugs, 41–43
excretion/elimination of drugs, 45
metabolism, 43–45, 44*f*
pharmacodynamics, 45–46, 46*t*
pharmacokinetics, 41–45, 43–44*f*, 45–46*t*
pharmacodynamic, 40
pharmacokinetic, 40
phase I, 43
phase II, 43
risk factors for, 40–41, 42*t*
Drug metabolism, 43–45, 44*f*, 1242
Drug-related problems, 7, 8*t*
Drug removal by dialysis
continuous ambulatory peritoneal dialysis, 699
continuous renal replacement therapy, 699–700
drug-specific properties, 699
hemoperfusion, 700
high-flux hemodialysis, 699
Drug removal estimation, 678–679
Drug(s) (*See also* Drug index)
overdose of, 65–84
poisoning by, 65–84
acetaminophen ingestion, 81–84
CNS depressant in, 76–81
decontamination in, 68–69
epidemiologic data on, 66–67
information resources on, 67
iron ingestion in, 73–76
management in, 67–69
salicylate ingestion in, 69–73
screening for, 68
Drug-specific properties, 699
Drug transport, altered, 43
DSRS (*See* Distal splenorenal shunt (DSRS))
Dual antiplatelet therapy (DAPT), 223, 236, 268
Dual-energy X-ray absorptiometry, 785
Duodenal ulcers, 522
Duoderm (ConvaTec), 897
Duplex scanning, for DVT, 190
DVT (*See* Deep venous thrombosis (DVT))
Dwarf tapeworm (*See* Cestodiasis (tapeworm infection))

Dysfunctional pain, 1210
Dyslipidemia, 105, 636, 648–649
atherogenic, 110–111
classification of secondary causes of, 118*t*
and diabetes, 1178
guidelines for management to reduce ASCVD risk, 114–119, 116*f*, 117*f*
management of, 173
in patients with schizophrenia, 1875–1876
treatment, 648–649
Dysmenorrhea
in adolescents, 1047
after menarche, 1047
clinical characteristics of, 1047
and fatigue, 1047
flushing and, 1047
headache and, 1047
insomnia and, 1047
irritability and, 1047
and lightheadedness, 1047
and loss of appetite, 1047
nervousness and, 1047
pathophysiology of, 1047
primary, 1046–1047
vs. secondary, 1051*t*
and prostaglandin secretion, 1047
and release of arachidonic acid, 1047
risk factors for, 1047
secondary, 1046–1047
symptoms of, 1047
treatment
nonpharmacologic, 1047–1048
over-the-counter pharmacologic therapy, 1048–1049
pharmacologic, 1048–1049
and uterine hypoxia, 1047
and vomiting, 1047
Dyspepsia, 510*f*
clinical assessment and diagnosis, 510
pathophysiology, 509–510
treatment, 510–511, 511*t*
Dyspnea, 1074*t*
Dystonia, 1870

E

EAD (*See* Early after-depolarizations (EAD))

EAR (*See* Early asthmatic response (EAR))
Early after-depolarizations (EAD), 327
Early asthmatic response (EAR), 400
Early goal-directed therapy (EGDT), 391
EASL (*See* European Association for Study of Liver (EASL))
ECF (*See* Extracellular fluid (ECF))
EC fistulas (*See* Enterocutaneous (EC) fistulas)
ECG (*See* Electrocardiogram (ECG))
Echocardiography, for IE, 1441–1442
Eclampsia
magnesium sulfate prophylaxis, 1019–1020
treatment of, 1020
ECL cells (*See* Enterochromaffin-like (ECL) cells)
ECT (*See* Electroconvulsive therapy (ECT))
Ectopic pregnancy, PID and, 1568
ED (*See* Erectile dysfunction (ED))
Edema, nephrotic, 607
EDIC (*See* Epidemiology of Diabetes Interventions and Complications (EDIC))
***E. dispar*, 1770**
EDS (*See* Excessive daytime sleepiness (EDS))
EDSS (*See* Expanded Disability Status Scale (EDSS))
EEG (*See* Electroencephalogram (EEG))
EF (*See* Ejection fraction (EF))
EFAD (*See* Essential fatty acid deficiency (EFAD))
Efficacy and Safety of Subcutaneous Enoxaparin (ESSENCE), 264
Efficacy of Ranolazine in Chronic Angina (ERICA), 233
Efflux transporters, 43
EGD (*See* Esophagogastroduodenoscopy (EGD))
EGDT (*See* Early goal-directed therapy (EGDT))
eGFR (*See* Estimated glomerular filtration rate (eGFR))
Egg phospholipids, 835
EHR Incentive Program, 3
Ehrlichiosis, 1794–1795
clinical and laboratory findings, 1795
treatment and prevention, 1795
Eicosapentaenoic acid (EPA), 817
Ejection fraction (EF), 275
measurement, 290
Ekbom disease (*See* Restless legs syndrome (RLS))
Elderly
ACS in, 242
adverse drug events, 2281–2282
AML in, 2087
comorbid conditions in, 907

demographic changes in US, 2278
disease-specific drug therapy
cardiovascular disease in ambulatory older patient, 2283–2285
depression, 2285–2286
diabetes, 2285
infectious diseases, 2287–2288
osteoarthritis, 2288–2289
UTI, 2288
economic considerations, 2278
fibrinolytic therapy in, 262
HF in, 275
and long-term care facilities, 2278, 2289–2290
pharmacodynamic changes, 2279–2282
pharmacokinetic changes, 2279–2281
physiological changes, 2279–2281
polypharmacy and, 2282–2283
profile of, 2278*t*
seizures in, 1332
tuberculosis and, 1493–1494
type 2 diabetes in, 1175–1180
diet for, 1176
exercise for, 1176
urologic disorders, 2308–2330
Electrocardiogram (ECG), 217, 326
advantages of, 259
of ST segment elevation, 238
Electrocardiographic Intervals, normal, 327*t*
Electroconvulsive therapy (ECT), 1888, 1907, 1920
Electroencephalogram (EEG), 1313, 1316
Electrolytes, 781
and acid-base disturbances, 576–577
composition of, 603
disorders with, 603–631
and enteral nutrition, 811, 819, 823, 825
laboratory tests for, 18–21*t*
PN and, 845*t*
Electronic cigarettes, electronic nicotine delivery systems (ENDS), 1904, 1976
Electronic medical record (EMR), 7
Electronic medication administration record (eMAR), 3
Electrophysiology
automaticity, 326
cardiac, 326–327
cellular, 326
conduction, 326–327

ELISA (*See* Enzyme-linked immunosorbent assays (ELISA))
ELITE (*See* Evaluation of Losartan in the Elderly (ELITE))
EM (*See* Erythema multiforme (EM))
eMAR (*See* Electronic medication administration record (eMAR))
Embolus, 180
Embryo transfer, 997–998
Emesis (*See* Vomiting)
EMLA (*See* Eutectic mixture of local anesthetics (EMLA))
***E. moshkovskii*, 1770**
Emphysema, 427, 428
Empiric broad-spectrum therapy, 390
Empiric therapy
in adults, 1430
for bacterial meningitis, 1424–1425, 1425*t*
for biliary infections, 1534–1535
for hospital-acquired pneumonia, 1469–1471*t*
for secondary peritonitis, 1534–1535
EMR (*See* Electronic medical record (EMR))
EN (*See* Enteral nutrition (EN))
Endocarditis, 1439–1456
culture-negative, 1455
enterococcal, 1450–1453
fungal, 1453–1454
gram-negative bacillary, 1454–1455
infective, 1439
prophylactic therapy for, 1455–1456
prosthetic valve, 1445–1447
Staphylococcus aureus, 1447–1450
Streptococcus viridans, 1440–1445
Endocrine abnormalities, caused by uremia, 654
End-of-life care, 86–96
dyspnea treatment in, 92*t*
hospice care in, 86–87
palliative care in, 86–87
symptom management in, 91–96
Endometrial cancer
and antiestrogens, 2029*t*
and postmenopausal hormone therapy, 1063, 1064*t*
Endometriosis
abdominal hysterectomy for, 1053
bilateral salpingo-oophorectomy for, 1053
clinical characteristics of, 1050–1051
conservative surgery for, 1053–1054
definition of, 1049
definitive surgery for, 1053

and depression, 1051
diagnosis of, 1050
estrogen add-back therapy for, 1054
and infertility, 1051
management of, 1052
location of, 1050, 1052*t*
nonpharmacologic therapy, 1053–1054
occurrence of, 1049–1050
pathophysiology of, 1050
physical findings of, 1051
treatment, 1052–1055
Endoscopic retrograde cholangiopancreatography (ERCP), 1527
Endoscopic variceal ligation (EVL), 581–582
Endoscopy-negative reflux disease (ENRD), 525
Endothelial cell dysfunction in pregnancy, 1017–1018
Endothelial function, 219*f*
Endothelin-1, biological effects of, 279*t*
Endothelins and HF, 279
ENDS (*See* Electronic cigarettes, electronic nicotine delivery systems (ENDS))
End-stage kidney (ESRD), 633
End-stage liver disease
ascites
alternative therapy, 578–579
diuretic therapy, 575–577
fluid and electrolyte balance, 575
goals of therapy, 575
pathogenesis of, 574–575
refractory, 577–578
cirrhosis
complications of, 572–574, 573*f*, 574*t*
pathogenesis of, 572
esophageal varices, treatment of, 579–584, 581*t*
hepatic encephalopathy, 584–587
hepatorenal syndrome, 587–589
pathogenesis, 585
treatment and general management, 585–587
End-stage lung disease, 485
Energy-dependent phase I (EDP-I), 50
Energy-dependent phase II (EDP-II), 50
ENRD (*See* Endoscopy-negative reflux disease (ENRD))
Enteral nutrition (EN)
administration regimen for, 812–813
for adults, 806–831
with altered protein or fat sources, 816*t*

complications with, 820–824, 821–823*t*
gastrointestinal, 823–824
mechanical, 820
metabolic, 820, 823
contraindications to, 808
in critical illness, 815–817
definition of, 806
for diabetes, 819–820
diarrhea and, 829–830
drugs frequently reported to interact with, 827–828*t*
electrolytes and, 811, 819, 823, 825
enteric access device occlusion and, 826, 828
fat in, 817–818
fluids and, 814–815
formulas for, 809–813, 810*t*
continuous infusion of, 813
cyclic feeding of, 813
immune-modulating, 817–818
intermittent and bolus feedings of, 813
oligomeric, 809, 810*t*, 811
polymeric, 809, 810*t*
specialized, 810*t*, 811–813
glucose and, 820, 823
glucose control, 819–820
for hepatic failure, 815
hyperglycemia with, 820
for infants, 2201–2211
breast feeding, 2202–2203
and carbohydrate absorption, 2205
and formula intolerance, 2205
hypertonic formulas, 2205
lactose-free formula, 2205
management of metabolic errors, 2203
nutritional assessment, 2205–2206
phenylalanine-free therapeutic formulas, 2204
pure cow’s milk, 2203
ready-to-feed form feeds, 2203
route of administration, 2204, 2204*t*
solid foods, 2203
soy-based formulas, 2202–2203
therapeutic formulas, 2203–2204
initiation of, 813–814
intermittent/bolus feeding of, 814
intolerance to, 829–831
Medicare and, 829, 830*t*

medications and, 824–826
modular components, 819
patient selection and route of feeding for, 806–808
pulmonary disease and, 818
for renal failure, 818–820
transfer to home on, 828–829
tube placement in, 808–809, 808*f*
Enteric encephalopathy, 1511
***Enterobacter meningitis*, 1432**
Enterobiasis, 1776–1777
E. vermicularis ectopic lesions, 1777
prevalence of, 1776
signs of, 1777
symptoms of, 1777
treatment, 1777
Enterochromaffin-like (ECL) cells, 505
Enterococcal endocarditis, 1450–1453
Enterococcal infection, 1535
Enterocutaneous (EC) fistulas, 848
Enterotoxigenic E. coli (ETEC), 1515
Enthesitis, 931
Environmental Protection Agency (EPA), 884
Enzyme-linked immunosorbent assays (ELISA), 1634
Enzyme supplementation, 477–478
Eosinophilia, 665
Eosinophils, 35
and asthma, 399
EPA (*See* Eicosapentaenoic acid (EPA); Environmental Protection Agency (EPA))
Epidemiology of Diabetes Interventions and Complications (EDIC), 1109
Epidermal necrolysis, 863
Epidermis, 851, 852*f*
Epididymitis, gonococcal infection and, 1563
Epigastric pain syndrome, 509
Epilepsy
classification of, 1314*t*
definition of, 1313
and EPT, 2341
syndromes, 1313, 1314*t*
treatment of, 1319–1332
and women related issues, 1338–1340
Epsilometer test (E test), 1378, 1449
ERCP (*See* Endoscopic retrograde cholangiopancreatography (ERCP))
Erectile dysfunction (ED), 2155, 2323–2330
in cigarette smokers, 2326

diabetes mellitus associated with, 2327
drug-induced, 2324, 2325–2326*t*
due to neurogenic disorders, 2323
and endocrine disorders, 2323
and gonadal function, 2327
hormonal cause of, 2323
hypertension and, 2324
management of, 2328
pharmacotherapy for, 2328–2330
signs of, 2323–2324
symptoms of, 2323–2324
and testicular size, 2327
and testosterone production, 2327
vascular disease associated with, 2323
ERICA (*See* Efficacy of Ranolazine in Chronic Angina (ERICA))
Erysipelas, 1605
Erythema migrans, 1788
Erythema multiforme (EM), 863
Erythema nodosum, 474
Erythrocyte deformability, 170–171
Erythrocytes (*See* Red blood cells (RBCs))
Erythrocyte sedimentation rate (ESR), 33, 541
Erythrodermic psoriasis, 872 (*See also* Psoriasis)
Erythropoiesis-stimulating agent (ESA), 645–647, 646*t*
Erythropoietic therapy, 2011
ESA (*See* Erythropoiesis-stimulating agent (ESA))
***Escherichia coli*, 1370, 1374*t*, 1376*t*, 1392, 1527, 2214**
and infectious diarrhea, 1517
ESMID (*See* European Society for Microbiology and Infectious Diseases (ESMID))
Esophageal acid clearance, 526
Esophageal candidiasis, 1655
Esophageal damage, aggressive factors associated with, 526–527
Esophageal manometry, 529–530
Esophageal varices
treatment, 579–584, 581*t*
alternative treatment modalities, 582
balloon tamponade, 582
endoscopic variceal ligation, 581–582
general management, 580
goals of therapy, 579
hypovolemia/blood loss, 580
infection prophylaxis, 582
octreotide, 580
primary prophylaxis, 582–583

secondary prophylaxis, 583–584
terlipressin, 581
vasopressin, 580–581
Esophagogastroduodenoscopy (EGD), 515
ESR (*See* Erythrocyte sedimentation rate (ESR))
ESSENCE (*See* Efficacy and Safety of Subcutaneous Enoxaparin (ESSENCE))
Essential fatty acid deficiency (EFAD), 839
Essential hypertension, 140–168
Essential nutrients (water), 781
Essential tremor (ET)
clinical presentation of, 1308–1309
diagnosis of, 1309
and Parkinson disease, 1309*t*
treatment of, 1310–1311
Estimated glomerular filtration rate (eGFR), 25, 118, 1045
blood chemistry reference values for, 18*t*
ET (*See* Essential tremor (ET))
ETEC (*See* Enterotoxigenic *E. coli* (ETEC))
E test (*See* Epsilometer test (E test))
Ethanol consumption, 940
EULAR (*See* European League Against Rheumatism (EULAR))
European Association for Study of Liver (EASL), 573, 584, 587
European League Against Rheumatism (EULAR), 733, 734–736*t*, 903
European Society for Microbiology and Infectious Diseases (ESMID), 1542
Eutectic mixture of local anesthetics (EMLA), 2188
Euthyroidism, 1088
Euthyroid patients, 1078, 1088
thyroid function tests in, 1073*t*
Euthyroid sick syndrome, 1078
Evaluation of Losartan in the Elderly (ELITE), 298
EVL (*See* Endoscopic variceal ligation (EVL))
Excessive daytime sleepiness (EDS), 1833
Excretion/elimination of drugs, 45
Exercise
diabetes and, 1111
IC and, 176
and osteoporosis, 2336
PAD and, 173
for PCOS, 1044
and premenopausal women, 2338
stress testing, 229
Exercise-induced bronchoconstriction (EIB), 419–420
Exercise tolerance test, 221, 229
Exertional angina, 217

Exit-site infection, peritoneal dialysis, 694–695
prophylaxis, 694–695
treatment of, 695
Expanded Disability Status Scale (EDSS), 1252
Expert Panel Report 3 (EPR-3), 398
External defibrillation, 348
Extracellular fluid (ECF), 18
Extraesophageal manifestations, 532–533
GERD
asthma and, 532–533
otolaryngology symptoms and, 533
treatment of, 533
noncardiac chest pain, 532
Eyelashes, 1184
Eyelids, 1184
Eyes
anatomy of, 1184–1185, 1184*f*
blindness, diabetes and, 1185–1186
chemical burns in, 1200
disorders with, 1200–1202
emergencies with, 1200
physiology of, 1184, 1184*f*

F

Faces pain scale (FPS), 1212*t*
Factor V Leiden, 966
FAERS (*See* FDA Adverse Event Reporting System (FAERS))
Falls, Parkinson disease and, 1306
Familial combined hyperlipidemia (FCHL), 110*t*, 111
Familial defective apo B-100 (FDB), 110*t*, 111
Familial disorders of triglyceride metabolism, 112
Familial dysbetalipoproteinemia, 110*t*, 111–112
Familial hypercholesterolemia (FH), 110*t*, 111
Familial hypertriglyceridemia (FHTG), 112
FAP (*See* Functional abdominal pain (FAP))
FAST HUG checklist, 1238
FASTHUG-MAIDENS checklist, 1238
Fasting plasma glucose (FPG), 1108, 1113
Fat
diabetes and, 1112
in enteral formulas, 817–818
Fatigue and MS, 1257
FCHL (*See* Familial combined hyperlipidemia (FCHL))
FDA (*See* Food and Drug Administration (FDA))

FDA Adverse Event Reporting System (FAERS), 346
FDB (*See* Familial defective apo B-100 (FDB))
Febrile neutropenia, 2036
Febrile seizures, 1336–1337, 2215
Fecal antigen test, 514*t*, 515
Fetal hypothyroidism, 1095–1096
FEV (*See* Forced expiratory volume (FEV))
Fever, 2214–2215
drug, 722–723, 722*t*
infection and, 1368–1369
Fever of unknown origin (FUO), 1368
FH (*See* Familial hypercholesterolemia (FH))
FHTG (*See* Familial hypertriglyceridemia (FHTG))
Fiber, in polymeric formulas, 812–813
Fiberoptic upper endoscopy, 515
Fibrinogen, role of, 181
Fibroblast growth factor 23 (FGF23), 649
Fibromyalgia, 1231–1233
Fine needle aspiration (FNA), 1076
Fingertip unit (FTU) concept, 858, 859*t*
Fish oils, 817
Flat worms (*See* Cestodiasis (tapeworm infection))
Flexural/inverse psoriasis, 872 (*See also* Psoriasis)
Fluid and electrolyte maintenance, 2197–2201, 2198–2199*t*
administration of, 2200
balance
ascites, 575
sodium restriction, 575
urinary NA:K ratio, 575
vasopressin (V2) receptor antagonists, 575
water restriction, 575
calculation of, 2197
and CKD
hyperkalemia, 642–643
metabolic acidosis, 643
sodium and water retention, 642
complications
hyperkalemia, 642–643
metabolic acidosis, 643
sodium and water retention, 642
Fluids
EN and, 814–815
hypernatremia and, 22
FNA (*See* Fine needle aspiration (FNA))
Foam cells, 113, 113*f*

Focal segmental glomerulosclerosis (FSGS), 658–659
Folic acid
antagonists, 2021*t*
deficiency anemia, 2005–2006
Follicle-stimulating hormone (FSH), 988, 1061
Food and Drug Administration (FDA), 38, 73, 82, 83, 175, 184, 223, 613, 1415, 1910
Forced expiratory volume (FEV), 400, 402
Forced expiratory volume in 1 second (FEV1), 475, 481
Forced vital capacity (FVC), 428
Formulas
for EN, 809–813, 810*t*
immune-modulating, 817–818
oligomeric, 809, 810*t*, 811
polymeric, 809, 810*t*
specialized, 810*t*, 811–813
Foscarnet-resistant HSV, 1703
FPG (*See* Fasting plasma glucose (FPG))
FPS (*See* Faces pain scale (FPS); Functional pain syndromes (FPS))
Francisella tularensis, 1792
Frank-Starling curve, 281, 281*f*
FRC (*See* Functional residual capacity (FRC))
Free phenytoin levels, 58*f*
French Pharmacovigilance Database, 51
Fructosamine, 1115
FSGS (*See* Focal segmental glomerulosclerosis (FSGS))
FSH (*See* Follicle-stimulating hormone (FSH))
FTU concept (*See* Fingertip unit (FTU) concept)
Fulminant disease, 541
Fulminant hepatitis, 1723
Fulminant RMSF, 1794
Functional abdominal pain (FAP)
symptom-related behaviors of, 1234*t*
Functional dyspepsia, 509–511
Functional pain syndromes (FPS), 1231–1236
Functional residual capacity (FRC), 402
Fungal endocarditis, 1453–1454
Fungal infections (*See* Mycotic (fungal) infections)
Fungal peritonitis, 1532
FUO (*See* Fever of unknown origin (FUO))
FVC (*See* Forced vital capacity (FVC))

G

GAD (*See* Generalized anxiety disorder (GAD))

Gain-of-function gene mutation, 111
Galactorrhea, 1074*t*
Gallbladder disease, 2341
and postmenopausal hormone therapy, 1065*t*
Gallstones, 473 (*See also* Hepatic involvement, in cystic fibrosis)
γ-aminobutyric acid, 585
Gamma-glutamyl transferase (GGT), 31
blood chemistry reference values for, 20*t*
Gastric acid secretory studies, 515
Gastric cancer, 515
Gastric lavage, 68
Gastrin, 505
Gastroduodenal surgery, prophylaxis for, 1393*t*
Gastroesophageal reflux disease (GERD), 473, 2219–2221, 2220*t*
antireflux surgery, 533
clinical assessment and diagnosis, 529–530
acid suppression empiric test, 529
ambulatory pH monitoring, 529
esophageal manometry, 529–530
radiologic testing, 529
upper endoscopy and biopsy, 529
clinical presentation of, 527, 2219
epidemiology, 525
etiology and risk factors, 525
extraesophageal manifestations, 532–533, 532*t*
maintenance therapy, 531
management of, 528*f*
nonerosive reflux disease, 531–532
on-demand pharmacotherapy, 531
pathophysiology, 525–527
pharmacotherapy, 530–531
proton-pump inhibitor and histamine-2 receptor antagonists, 531
treatment, 527–529, 528*f*, 528*t*, 2219–221, 2220*t*
Gastrointestinal complications, 654
Gastrointestinal decontamination, 68–69
for acetaminophen toxicity, 81
drug poisoning and, 81
in iron ingestion, 74
Gastrointestinal involvement, in cystic fibrosis, 473
Gastrointestinal tract (GI), 41, 45*t*, 175, 187
drug poisoning and, 78
and emetic response, 488
functional units of, 807*t*
normal flora of, 1530
physiology of, 504–505, 504–505*f*

Gastroparesis, diabetes and, 1162
Gastrostomy, 808, 808*f*
GBM (*See* Glomerular basement membrane (GBM))
GCA (*See* Giant cell arteritis (GCA))
GCS (*See* Glasgow Coma Scale (GCS))
GDM (*See* Gestational diabetes mellitus (GDM))
GDMT (*See* Guideline-directed therapy (GDMT))
Generalized anxiety disorder (GAD)
and abnormalities of receptor function, 1804
assessment of, 1809–1810
clinical course of, 1804
clinical presentation of, 1809–1810
comorbidity associated with, 1804
diagnosis of, 1804
epidemiology of, 1804
etiology of, 1804
major depression and, 1804
OCD and, 1804
pathophysiology, 1804
role of genetic factors, 1804
simple phobia and, 1804
social anxiety disorder and, 1804
symptoms of, 1806*t*
treatment, 1804, 1806–1809
benzodiazepines, 1804, 1806
buspirone, 1809
CBT, 1804
nonpharmacologic, 1804
patient selection, 1807
pharmacologic, 1804
Generalized hypersensitivity reactions
anaphylaxis, 718–721, 721*t*
autoimmune drug reactions, 724–725
drug fever, 722–723, 722*t*
drug-induced vasculitis, 723–724, 723–724*t*
hypersensitivity vasculitis, 723, 723*t*
serum sickness, 721–722
Generalized tonic-clonic seizures, 1313
and absence seizures, 1333–1335
Genetics
differences in drug metabolizing enzymes, 713–714
migraine headache and, 1270–1271
polymorphism, 45
Genital herpes, 1583–1588
clinical course of, 1584, 1584*f*

complications of, 1587–1588
diagnostic tests for, 1585
epidemiology of, 1583
etiology of, 1583
patient education and counseling in, 1587
pregnancy and, 1587–1588
recurrence of, 1584
signs and symptoms of, 1583–1584
transmission of, 1584–1585
treatment of, 1585–1587, 1586*t*
Genital warts, 1588–1589
Genitourinary involvement, in cystic fibrosis, 473
Genitourinary surgery, prophylaxis for, 1394*t*
Genitourinary syndrome
symptoms of, 1069
treatment, 1069–1070
GERD (*See* Gastroesophageal reflux disease (GERD))
Geriatric depression, 1903
Geriatric neurocognitive disorders
Alzheimer disease
clinical presentation, 2296–2297
diagnosis, 2296–2297
etiology, 2295
neuropathology, 2295–2296
prognosis, 2297–2298
treatment, 2298–2300
dementia
behavioral disturbances in, 2303–2307, 2304*t*
causes of, 2293–2294*t*
clinical diagnosis, 2292–2295
incidence, 2292
prevalence, 2292
screening tests, 2295*t*
stages of, 2298*t*
symptoms, 2294*t*
Lewy body, 2300–2301
vascular dementia
clinical presentation, 2301–2302
diagnosis, 2302
etiology, 2301
neuropathology, 2301
treatment, 2302–2303
Geriatrics (*See* Elderly)
Gestational diabetes mellitus (GDM), 1108–1109
diagnostic criteria, 1108–1109, 1108*t*

diagnostic criteria for, 1013
recommendations for screening and diagnosis of, 1014*f*
risk of developing, 1014–1015
treatment of, 1013
Gestational hypertension, 1015
GFR (*See* Glomerular filtration rate (GFR))
GGT (*See* Gamma-glutamyl transferase (GGT))
GHGs (*See* Greenhouse gases (GHGs))
GI (*See* Gastrointestinal tract (GI))
Giant cell arteritis (GCA), 954–955, 955*t*
Giardiasis, 1775–1776
diagnosis of, 1776
Giardia lamblia, 1775
cyst, 1776*f*
life cycle of trophozoites, 1776
prevalence and transmission, 1775–1776
symptoms of, 1776
GI, 1776
tests for, 1776
treatment of, 1776
GI intolerance, 1660
GINA (*See* Global Initiative for Asthma (GINA))
Ginkgo biloba, in IC treatment, 179
GIOP (*See* Glucocorticoid-induced osteoporosis (GIOP))
GI radiography, 515
GISP (*See* Gonococcal Isolate Surveillance Project (GISP))
Glasgow Coma Scale (GCS), 584, 2271, 2271*t*
Glaucoma, 1185–1186
angle-closure, 1185–1186, 1188, 1195*t*
definition of, 1185
medical management of, 1191*f*
open-angle, 1185–1186, 1192–1194*t*
primary open-angle, 1186–1189
Gleason score, 2144*f*, 2144
Global Initiative for Asthma (GINA), 417
Global Initiative for Chronic Obstructive Lung Disease (GOLD), 427
Global Registry of Acute Cardiac Events (GRACE), 244
Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO), 260
Globulin, 28
blood chemistry reference values for, 19*t*
Glomerular basement membrane (GBM), 670
Glomerular disease
chronic glomerulopathies, 655–659
nephrotic syndrome, 654–655

Glomerular filtration rate (GFR), 149, 279, 664–665, 1002, 1242
quantifying, 636–638
Glomerulonephritis, 655
Glucagon, 25, 1106
Glucocorticoid-induced osteoporosis (GIOP), 2352
Glucose, 25–26
blood chemistry reference values for, 19*t*
EN and, 820, 823
Glucose homeostasis, drug-induced alterations in
hyperglycemia, 1180
hypoglycemia, 1181
Glucose intolerance, in sepsis, 1367
Glutamine, 815, 817
Glycated hemoglobin, 25–26
for chronic glycemia, 1114–1115
Glycated serum albumin, 1115
Glycated serum protein, 1115
Glycemic control
in ICU, 1248–1249
methods of monitoring, 1113–1115
to microvascular and macrovascular disease, 1109–1111, 1110*t*
Glycemic index foods, 1043
Glycerol, 835
Glycocalyx, 1433
Glycoprotein I (GPI), 181
Glycoproteins, 750
Glycosylated hemoglobin
blood chemistry reference values for, 19*t*
GnRH (*See* Gonadotropin-releasing hormone (GnRH))
GOLD (*See* Global Initiative for Chronic Obstructive Lung Disease (GOLD))
Goldfrank's Toxicologic Emergencies, 67
Gonadotropin-releasing hormone analogs, 994–996, 995*t*
Gonadotropin-releasing hormone (GnRH), 1039
for endometriosis, 1052–1053
for premenstrual dysphoric disorder, 1060
Gonadotropins, 991–992, 996
Gonococcal arthritis, 1599–1600
Gonococcal conjunctivitis, 1200
Gonococcal endocarditis, 1570
Gonococcal Isolate Surveillance Project (GISP), 1565*f*, 1566*f*
Gonorrhea, 1562–1567
anorectal, 1566–1567
complicated, 1568–1570
diagnosis of
in females, 1564

in males, 1563
incidence of, 1562
by Neisseria gonorrhoeae, 1562
pharyngeal, 1566–1567
rates by sex, 1563*f*
signs and symptoms of
in females, 1564
in males, 1563
tests, 1051
transmission of, 1563
uncomplicated, 1563–1566
treatment of, 1564–1566, 1564*t*
Gout
ACR/EULAR classification criteria, 942–943*t*
acute, 939–947
alcohol consumption, 946
chronic, 947–950
clinical features, 939–940
commonly affected joints, 939
comparison of ACR, EULAR, and BSR/BHPR guidelines for, 942–943*t*
diagnosis, 941
diet modification, 946
epidemiology, 939
and ethanol consumption, 940
EULAR propositions for diagnosis of, 942–943*t*
ice, 946
joint fluid aspiration, 941
laboratory tests, 941
and nocturnal occurrence, 939–940
number and type of joints, 939
pain, 939
pharmacist role in education and management of gout, 951
and physical stress, 940
pseudogout, 941
radiographic findings, 941
risk factors, 940–941
treatment, 941–947
uric acid disposition, 939
GPI (*See* Glycoprotein I (GPI))
GRACE (*See* Global Registry of Acute Cardiac Events (GRACE))
Gram-negative bacillary meningitis, 1431–1432
Gram stain, 1371
Granulocyte transfusions, 1626
Granulocytopenia, 1094
Granulomatosis with polyangiitis, 656–658, 657*t*

Graves disease, 1074, 1078–1079, 1089–1091, 1093–1097
Gravida, 1000
Greenhouse gases (GHGs), 884
Green zone, of PEF, 422
Group B streptococcus (GBS) intrapartum prophylaxis, 1027–1028
Guided imagery, 1236*t*
Guideline-directed therapy (GDMT), 275, 281
Guillain-Barrè syndrome, 1735
GUSTO (*See* Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO))
Gut function, 1241
Guttate psoriasis, 872 (*See also* Psoriasis)

H

Haemophilus ducreyi, chancroid by, 1577
***Haemophilus influenzae*, 436, 475, 2221**
Hallucinogens, 1957–1959
Hamilton Anxiety Rating Scale (HAM-A), 1809
Hamilton Rating Scale for Depression (HAM-D), 1888, 1917
Hantavirus infections
associated clinical diseases, 1712
cause of illness, 1712
clinical presentation of, 1712
transmission of illness, 1712
treatment, 1712
Hantavirus pulmonary syndrome (HPS), 1712
HAP (*See* Hospital-acquired pneumonia (HAP))
Haptenation, 712
Harris-Benedict equation, 787*t*, 790, 840–841
Hashimoto thyroiditis, 1072, 1074, 1100, 1101
HAV (*See* Hepatitis A virus (HAV))
HBV (*See* Hepatitis B virus (HBV))
HCV (*See* Hepatitis C virus (HCV))
HCV genotype, 572
HCV RNA (*See* Hepatitis C virus ribonucleic acid (HCV RNA))
HD (*See* Hemodialysis (HD))
HDL (*See* High-density lipoprotein (HDL))
HDV (*See* Hepatitis D virus (HDV))
Headache, 1074*t*
acute, 1269–1270
cluster, 1269
abortive therapy for, 1279
pathophysiology of, 1278
prophylactic therapy for, 1279

signs and symptoms of, 1278–1279
drug therapy for, 1270
factors involved in precipitating, 1271
migraine, 1269
assessment tools, 1271
and contraception, 965–966
intractable, 1274
medication overuse, 1278
pathophysiology of, 1270–1271
prophylactic therapy for, 1275
without aura, 1271–1273
pathologic basis of, 1270
and postmenopausal hormone therapy, 1065*t*
prevalence of, 1268
primary headache disorders, 1269
secondary, 1269–1270
subacute, 1270
tension-type, 1269
general management and abortive therapy for, 1280
interprofessional management of, 1280
pathophysiology of, 1280
prophylactic therapy for, 1280
Headache Impact Test (HIT-6), 1271
Head and neck surgery, prophylaxis for, 1393*t*
Healthcare providers, 51
Heart failure (HF), 217
ADHF, 281
angiotensin receptor blockers in, 298*t*
cardiac overload, 277–278
cardiac resynchronization therapy, 287, 318–321
cardiogenic shock and, 380
PCWP and, 312
classification of, 281–284
clinical trials of pharmacotherapy, 319–320*t*
critical care management of, 313–314
diet and, 323–324
drugs induce, 291*t*
with ejection fraction, 321–324
etiology of, 275–277
evaluation of
drug-induced heart failure, 291–292
signs and symptoms of, 285*t*, 289–291
herbal products for, 323–324
high-output, 275
with hypertension, 275

incidence, prevalence, and epidemiology of, 275
intravenous vasodilators, 314–315
ischemic, 276
left ventricular assist devices, 287–288
low-output, 275
management of, 283*f*
mechanisms, systolic, 278*f*
nonischemic, 276
nutritional supplements for, 323–324
NYHA classification of, 282*f*, 290
pathophysiology of, 278–281
predisposing factors, 290
with preserved left ventricular ejection fraction, 319–320*t*, 321–324
race and, 312–313
risk factors of, 275, 290
signs and symptoms of, 245
stages of, 281–284
supraventricular arrhythmias and, 309–310
treatment
ACEI, 295–300
aldosterone antagonists, 307
β-blockers in, 302–304
critical care management of, 313–314
digitalis glycosides, 308–311
diuretics, 293–294
inotropic agents, 315–316
intravenous vasodilators, 314–315
non-angiotensin-converting enzyme inhibitor vasodilator therapy, 311–312
pharmacotherapy of, 312–313
principles of, 281–289
side effects of, 300–302
therapeutic objectives, 292–295
ventricular arrhythmias complicating, 316–321
Heart Outcomes Prevention Evaluation (HOPE), 174
Heart Protection Study (HPS), 120
Heart rate (HR)
normal values of, 369*t*
shock states and, 373*t*
Heart Rhythm Society (HRS), 208
HeartWare left ventricular assist device (HVAD), 287
***Helicobacter pylori*, 272, 510**
diagnostic tests for, infection, 513–515, 514*t*
eradication of, 527
fecal antigen test, 514*t*, 515
and GERD, 527

host immune response, 512
indications for testing and treating infection, 511*t*
nonendoscopic tests, 513, 514*t*, 515
oral drug regimens used to eradicate, 516*t*
patients with penicillin allergies, 520
rapid urease test, 514*t*, 515
related ulcers, 511, 512
direct mucosal damage, 512
secondary or rescue therapy for, 520–521
tests for detecting, 513–515, 514*t*
transmission, 512
urea breath test (UBT), 514*t*, 515
Helsinki Heart Study (HHS), 127
Hematochezia, 205
Hematocrit (Hct), 21, 33, 187, 217, 1533
Hematologic toxicities, 2035–2038
Hematopoietic growth factors, 1615–1616, 1626
Hematopoietic stem cell lineage, 32, 34*f*
Hematopoietic stem cell transplantations (HSCTs), 2088
allogeneic, 2160
from bone marrow, 2165
GVT effect, 2166
harvesting of, 2165–2166
and hepatic VOD, 2171–2172
and HGFs, 2171
histocompatibility of, 2164–2165
indications for, 2164
from peripheral blood progenitor cells, 2165–2166
from placenta blood, 2166
preparation of, 2164–2165
preparative regimens for, 2166–2168
sinusoidal obstructive syndrome (SOS), 2171–2172
toxicities, 2163*t*
transplanting method, 2164–2165
from umbilical cord, 2166
with an unrelated cord blood donor, 2166
autologous, 2161–2164
complications, 2163–2164
hematopoietic growth factors after, 2164
indications, 2160*t*, 2161
myeloablative preparative regimen followed by, 2163, 2163*t*
basic schema, 2161*f*
comparison of types, 2160*t*
complications associated with, 2169–2173, 2169*f*
busulfan seizures, 2170

chemotherapy-induced gastrointestinal effects, 2170–2171
graft rejection, 2172–2173, 2172*f*
hemorrhagic cystitis, 2170
infectious, 2178–2182
graft-*versus*-host disease (GVHD), 2173–2178, 2174–2175*t*, 2177*t*
graft-*versus*-tumor (GVT) effect in treatment, 2161
harvesting of, 2161–2162
issues of survivorship after, 2182–2183
overview of, 2160–2161, 2160*t*
posttransplantation immunosuppressive therapy, 2168, 2168*t*
representative myeloablative preparative regimens used in, 2163*t*
supportive care strategies, 2168–2169
Hemodialysis, 705
Hemodialysis (HD), 681, 682*f*, 684*f*, 1913
anticoagulation for, 687–688
complications
arteriovenous access infection, 691–692
dialysis disequilibrium, 690
intradialytic hypotension, 689–690
skeletal muscle cramps, 690
vascular access flow dysfunction, preventing and treating, 690–691
dialysate, 686, 686*t*
dialyzer membrane characteristics, 686–687
process of, 688–689
for salicylate toxicity, 72
for substances clearance, 69
vascular access, 682, 684
arteriovenous (av) graft, 684*f*, 685
arteriovenous fistula, 684–685, 684*f*
central venous catheter, 685–686, 685*f*
Hemodynamic instability, in ICU, 1238
Hemodynamic monitoring, 370–372
cardiogenic shock and, 380*t*
invasive monitoring, 372
minimally invasive monitoring, 371–372
noninvasive monitoring, 370–371
Hemodynamic resuscitation, therapeutic goals for, 391
Hemoglobin (Hgb), 23, 25, 33, 187, 217
Hemolytic uremic syndrome (HUS)
shigellosis and, 1511–1513
STEC infection and, 1517–1518
Hemoperfusion, 700
Hemorrhage
from heparin, 193
from warfarin, 201

Hemorrhagic stroke
definition of, 1346
epidemiology of, 1346
pathophysiology, 1346–1348
treatment principles, 1348
Heparin-induced thrombocytopenia (HIT), 192
Hepatic blood flow, 1242
Hepatic encephalopathy, 584–587
pathogenesis, 585
treatment and general management, 585–587
combination therapy with lactulose, 587
flumazenil, 586
lactulose, 586
neomycin, 586
rifaximin, 586
Hepatic enzyme induction, 975
Hepatic hemangiomas, and EPT, 2341
Hepatic involvement, in cystic fibrosis, 473
Hepatic steatosis, 850
Hepatic venous pressure gradient (HVPG), 573
Hepatitis
causative agents and characteristics, 1721–1722
characteristics of, 1722*t*
definition of acute and chronic, 1722
and human immunodeficiency virus (HIV) infection, 1721
serologic evaluation, 1722
Hepatitis A virus (HAV), 1656
acute, 1723
arthritis and, 1724
causes of, 1721–1722
chronic, 1723
clinical manifestations, 1723–1724
complete clinical recovery, 1723
cryoglobulinemia and, 1724
diagnostic methods, 1724
dosage adjustments, 1725
epidemiology, 1722
extrahepatic manifestations, 1724
glomerulonephritis and, 1724
hemolysis with, 1725
immune complex-associated rash and, 1724
incidence rate of, 1722
incubation period for, 1723
infection, 1406–1407
leukocytoclastic vasculitis and, 1724

liver function tests (LFTs), 1724
natural history, 1723
occupations at risk for, 1722
pathogenesis, 1723
postexposure prophylaxis, 1726–1727
pre-exposure prophylaxis, 1725–1726
prevalence of, 1722
prevention of, 1725
serologic tests, 1724
symptoms of acute, 1723
transmission mode, 1722
treatment, 1724–1725
typical course of, 1724*f*
vaccination for, 1725
Hepatitis B (HBV), 774
Hepatitis B virus (HBV), 1406, 1656
with ALF, 1731–1732
ALT level, 1730*f*, 1736
with AST, 1738
bilirubin concentrations, 1738
from blood and blood products, 1727
breast-feeding and, 1729
clinical manifestations, 1731–1732
coinfection with HIV, 1732
diagnosis of, 1729
epidemiology of, 1727–1728
evaluation and management of chronic, 1736–1744
goals of therapy, 1738
pharmacologic interventions, 1738–1739
and HDV, 1730, 1736, 1757
immunoglobulin dosage, administration, and adverse effects, 1743
injection drug use, 1729
liver biopsy for, 1738
liver transplantation for, 1743
natural history of, 1730–1731
pathogenesis of, 1729
percutaneous exposure and transmission, 1735–1736
pharmacologic interventions, 1738–1739
prevention, 1732–1736
prognosis, 1732
risk factors for transmission, 1729
serologic patterns, 1729–1730, 1729–1730*t*
transmission, 1729
perinatal, 1729
sexual, 1728, 1736

treatment, 1742*t*
vaccination, 1735, 1735*t*
virology, 1727
Hepatitis C virus antibody (Anti-HCV), 1744
Hepatitis C virus (HCV), 572, 774
breast-feeding and, 1749
clinical manifestations, 1748
diagnosis, 1746–1748
direct-acting antivirals, 1750–1752, 1751*t*
epidemiology of, 1744–1757
extrahepatic manifestations, 1748
fixed-dose combinations, 1753–1756
immunocompromised patients, 1748
life cycle, 1745*f*
natural history, 1746
NS5A inhibitors, 1752
NS3/4A protease inhibitors, 1750–1752
NS5B RNA-dependent RNA polymerase inhibitors, 1752
pathogenesis, 1746
prevention, 1748–1750
current treatment strategies, 1750–1757
DAA therapy, 1750
goals of therapy, 1749
pre-exposure prophylaxis, 1748–1749
screening, 1746–1748
serologic assays, 1746–1748
transmission
nonpercutaneous, 1745–1746
percutaneous, 1745
treatment, 1753
virology, 1744
Hepatitis C virus ribonucleic acid (HCV RNA), 1749, 1750
Hepatitis D virus (HDV)
diagnosis, 1757
epidemiology, 1757
natural history, 1757–1758
pathogenesis, 1757
prevention, 1758
serology, 1757
treatment, 1758
virology, 1757
Hepatitis E virus (HEV)
clinical manifestations, 1759
diagnosis, 1758–1759
epidemiology, 1758

natural history, 1759
pathogenesis, 1758
transmission, 1758–1759
virology, 1758
Hepatobiliary scintigraphy, 1527
Hepatocyte apoptosis, 572
Hepatojugular reflux, defined, 290
Hepatorenal syndrome (HRS), 587–589
pathogenesis, 587–588
treatment, 588–589
Hepatotoxicity, 507, 966
from acetaminophen overdoses, 81
valproate therapy and, 1335
Herbal medicines, 465
Herpes encephalitis, 1698
Herpes zoster, 1227
HES (*See* Hydroxyethyl starch (HES))
HEV (*See* Hepatitis E virus (HEV))
HF (*See* Heart failure (HF))
HFCWO (*See* High-frequency chest-wall oscillation (HFCWO))
HGA (*See* Human granulocytic anaplasmosis (HGA))
Hgb (*See* Hemoglobin (Hgb))
HHS (*See* Helsinki Heart Study (HHS); Hyperosmolar hyperglycemic state (HHS))
Hiatal hernia, 526
High-density lipoprotein (HDL), 21*t*, 107*t*, 108–109, 250, 636
High-flux hemodialysis, 699, 704
High-frequency chest-wall oscillation (HFCWO), 478
High-risk pulmonary embolism, 198
High-sensitivity CRP (hs-CRP), 30
Hippocampus, and anxiety, 1802
Hirschsprung disease, 2216
Hirsutism, 1040
and danazol, 1053
His-Purkinje fibers, 326
Histamine-2 receptor antagonists, 531
Histamine receptors, 449
Histocompatibility antigens, 750
Histoplasma capsulatum, 1656
Histoplasmosis, 1656, 1689–1691, 1690*f*, 1690*t*
HIT (*See* Heparin-induced thrombocytopenia (HIT))
HIV (*See* Human immunodeficiency virus (HIV))
Hives, 863
HLA (*See* Human leukocyte antigen (HLA))
hMG (*See* Human menopausal gonadotropin (hMG))

HMG-CoA reductase inhibitors (statins), 47*t*, 59, 59*t*
Hoarseness, 1074*t*
Hodgkin lymphoma, 2091–2092
prognosis of, 2091
relapsed and refractory, 2092
treatment for, 2092
Homans sign, 189
Home medications in ICU
nonsurgical patients, 1238–1239
surgical patients, 1239–1240
Homocysteine, 29
blood chemistry reference values for, 20*t*
HOPE (*See* Heart Outcomes Prevention Evaluation (HOPE))
Hormonal therapies, for acne, 869
Hospice care, 86–87
improving patient care, 88
managing drug costs, 88
under Medicare, 87–88
patient care and medication management in, 88–91
referral to, 88–91
in the United States, 87
Hospital-acquired pneumonia (HAP), 1469–1475
antibiotic therapy for, 1472–1474
definition of, 1469
diagnosis of, 1469
early-onset, 1470
empiric therapy for, 1470–1471*t*
epidemiology of, 1470
incidence of, 1469
late-onset, 1470
pathogenesis of, 1470
pathogens for, 1470
risk factors for, 1470
treatment of, 1470
ventilator-associated pneumonia prophylaxis, 1474–1475
Hot flushes, 1062–1063
Hot nodule, 1075
HPA (*See* Hypothalamic-pituitary-adrenal (HPA))
HPS (*See* Hantavirus pulmonary syndrome (HPS); Heart Protection Study (HPS))
HR (*See* Heart rate (HR))
HRS (*See* Heart Rhythm Society (HRS); Hepatorenal syndrome (HRS))
HTN (*See* Hypertension (HTN))
Human bite wounds, 1608
Human cadaver skin (allograft), for burn wounds, 897

Human coronary atherosclerotic plaque, 113*f*
Human granulocytic anaplasmosis (HGA), 1794–1795, 1798
clinical and laboratory findings, 1795
treatment and prevention, 1795
Human immunodeficiency virus (HIV), 427, 1890
AIDS and, 1629
anemia, 2012–2013
antiretroviral therapy for, 1635–1648
and challenges for clinicians, 1647
development of resistance to, 1648
failure with, 1645–1646
general principles related to, 1642
goals of, 1635–1643
long-term assessments for, 1645
short-term assessments for, 1644–1645
steps in patient-specific regimen selection, 1643–1644
and babesiosis, 1796
breast-feeding and, 1649–1650
CD4+ cell count in patients, 1654–1655
classification system for, 1654
and CMV, 1654–1655, 1664–1666
and cryptosporidiosis, 1655–1656
diagnosis of, 1634
drug interactions and, 1649
enteric infections, 1655
epidemiology of, 1629
and HBV, 1732
and hepatitis, 1721
internet resources on, 1652*t*
in labor and breast-feeding, 1029
Mycobacterium avium and, 1670
Mycobacterium tuberculosis and, 1669–1670
OIs with, 1655
pathophysiology of, 1630–1631, 1631*f*
and PCP, 1659–1662
pharmacotherapy of, 1631–1634
postexposure prophylaxis and, 1651
preexposure prophylaxis and, 1650–1651
pregnancy and, 1649–1650
and protozoal infections, 1796
surrogate marker data and, 1634–1635
therapeutic drug monitoring and, 1649
and Toxoplasma gondii encephalitis, 1662–1662
tuberculosis and, 1495–1498
Human leukocyte antigen (HLA), 751–752

genes, 60, 60*t*
variants, affected drugs, and population incidence, 60*t*
typing, 752
Human menopausal gonadotropin (hMG), 996
Human milk
drug excretion in, 1033–1036
drugs contraindicated during lactation, 1035*t*
infant exposure, 1034–1035
pharmacokinetics, 1033
reducing risk of exposure, 1035, 1035*t*
resources of, 1034–1035
transfer of drugs from plasma to milk, 1033–1034, 1034*t*
human immunodeficiency virus in, 1029
Human papillomavirus (HPV), 1410–1411
genital warts by, 1588
HUS (*See* Hemolytic uremic syndrome (HUS))
HVAD (*See* HeartWare left ventricular assist device (HVAD))
HVPG (*See* Hepatic venous pressure gradient (HVPG))
Hyaluronic acid, as dermal filler, 897
Hydrodensitometry, 784–785
Hydromorphone, 709
Hydrops fetalis, 1031
Hydroxyethyl starch (HES), 379
3-hydroxy-3-methylglutaryl co-enzyme A inhibitors (HMG-CoA), 222
Hygiene hypothesis, 448 (*See also* Rhinitis)
Hyperacute rejection, 761, 767
Hyperandrogenemia, 1040
Hyperandrogenism, 1040, 1043
Hyperapobetalipoproteinemia, 110*t*
Hypercalcemia, 505, 622–625, 665
clinical manifestations of, 622
etiology of, 622
hyperparathyroidism and, 622
malignancy and, 622
treatment of, 623–625, 623*t*
Hyperchloremia, 23
Hyperglycemia, 26, 766, 844
evaluation of, 1131
in patients with schizophrenia, 1875
PN and, 839, 844, 845
premeal, 1132–1133
and thyroid storm, 1098–1099
Hyperhidrosis, 1679
Hyperkalemia, 23, 576, 617–619, 642–643, 676
and ACEI, 300–301

causes of, 301*t*
clinical manifestations of, 618
etiology of, 617–618
occurrence of, 377
treatment of, 618–619, 620*t*
Hyperlipidemia, 219, 228, 655
posttransplant, 771
Hypermagnesemia, 27, 630–631
clinical manifestations of, 630
etiology of, 630
treatment of, 630–631
Hypernatremia, 22, 614
diarrhea and, 22
fluids and, 22
Hyperosmolar hyperglycemic state (HHS), 1175
Hyperparathyroidism, 649
Hyperphosphatemia, 28, 628, 649
Hyperprolactinemia, 1040
in patients with schizophrenia, 1874
Hyperreactivity
defined, 400
measurement of, 400
Hypersensitivity reactions, from heparin, 193
Hypersensitivity vasculitis, 723, 723*t*
Hypertension
posttransplant, 771
Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs and alcohol (HAS-BLED), 201
Hypertension (HTN), 647–648
alcohol and, 146
in ambulatory older patients, 2285
antihypertensive therapy, 648
associated with anticancer therapies, 2052
with bevacizumab, 2025*t*, 2052, 2135
black patients and, 152
blood pressure and, 141
chronic kidney disease and, 149, 154
and cigarette smoking, 1987
clevidipine for, 363
clinical evaluation of, 148–149
complications associated with, 145*t*, 148–149
and contraception, 966
coronary artery disease and, 154
in depression, 1885
with dexamethasone use, 2233

diabetes and, 153–154, 1176–1177
dialysis, 647–648
with doxazosin, 2320
with doxorubicin, 2049–2052
with ED, 2324
in elderly patients, 152–153, 2285
enalaprilat for, 363
essential, 140–168
HF and, 277
in ICU, 1238
inadequate BP control, reasons for, 158–159, 159*t*
intracranial, 2272–2273
labetalol for, 361–362
left ventricular dysfunction and, 154
and lithium, 1912
management of, 144–148, 151–155, 173–174
  goals in, 144–145
  lifestyle modifications for, 145–146, 151
and neuroblastoma, 2063
nicardipine for, 363
ocular, 1185
orthostatic, 152
pain and, 1225
with pazopanib, 2027*t*, 2052
pharmacotherapy for, 146–148, 151–154, 153*t*
physical activity and, 146
potassium and, 146, 156–158
in pregnancy, 1015, 1018–1019
  chronic, 1015, 1018–1019
  treatment of, 1018–1019
pulmonary, 2232, 2265
pulmonary arterial, 276
renin, 2063, 2066
resistant, 163–165
secondary, 143–144*t*
sodium and, 145–146
with sorafenib, 2052
systemic, 2234, 2272–2273
treatment of
  benefits of, 150–151
  goals in, 150
  patient education in, 150, 150*t*, 156
two-drug regimens for, 159
type 2 diabetes mellitus and, 1108*t*
types of, 143–144

with VEGF receptor inhibitors, 2052
white-coat, 143–144
Hypertension in the Very Elderly Trial (HYVET), 144–145, 152–153
Hypertensive crises, 144
defined, 351
management for, 355*f*
Hypertensive emergency
aortic dissection, 364–365
assessment of, 358–359
central nervous system and, 352
clinical presentation of, 352
defined, 351
fenoldopam for, 360–361
medications for, 353–354*t*
oral vs. parenteral therapy, 352–355
parenteral drug therapy, 359–364
treatment recommendations for, 356*t*
vs. urgency, 352*t*
Hypertensive urgency, 351
assessment of, 356–357
clinical presentation of, 352
medications for, 354*t*
oral drug therapy, 357–358
oral vs. parenteral therapy, 352–355
treatment of, 352–356
vs. emergency, 352*t*
Hyperthermia
by drug overdoses, 78
from salicylate toxicity, 72
in serotonin syndrome, 1897
in SIRS, 2264
Hyperthyroidism, 1806*t*, 2323
causes of, 1074, 1075*t*
clinical presentation of, 1089
iodide therapy, 1089–1090
laboratory findings, 1075*t*
in pregnancy, 1095–1096
prevalence of, 1072
treatment, 1074, 1090–1091*t*, 1090–1095
T2 thyrotoxicosis, 1099
Hypertrichosis, 167–168
Hypertriglyceridemia
and peripheral arterial disease, 169
and postmenopausal hormone therapy, 1065*t*
Hypertrophic osteoarthropathy, 474

Hyperuricemia, 665
asymptomatic, 951
and diuretics, 293
drug-induced, 947
treatment, 944–947, 945*t*
urate-lowering therapy, 947
Hyperventilation, for TCA toxicity, 80
Hyphae (molds), 1674*t*
Hypnosis, 1236*t*
Hypoalbuminemia, 698
Hypoalphalipoproteinemia, 110*t*, 112
Hypocalcemia, 621–622, 649, 2249–2250
clinical manifestations of, 621
etiology of, 621
treatment of, 621–622
Hypochloremia, 23
Hypoglycemia (*See also* Type 1 diabetes)
causes of, 1135
level 3, 1140
level 1 and 2, 1140
nocturnal, 1135, 1138
pathophysiology of, 1138–1139
preprandial, 1133
risk of, 1134
symptoms of, 1135, 1139
treatment of, 1139–1140
Hypogonadism, 2354
Hypokalemia, 23, 158, 615–617, 1685
clinical manifestations of, 616
and diuretics, 293
drugs inducing, 615*t*
etiology of, 615–616, 615*t*
PN and, 845–846
treatment of, 616–617
Hypomagnesemia, 27, 628–630, 1685, 2249–225
clinical manifestations of, 629
and diuretics, 293
etiology of, 628–629
PN and, 846
treatment of, 629–630
Hyponatremia, 18, 22, 575, 576
brain adaptation to, 608–609
clinical presentation and treatment of, 609*t*
and diuretics, 293
euvolemic hypotonic, 611–612

hypervolemic hypotonic, 610–611
hypotonic, with decreased extracellular fluid, 610
management of, 613
neurologic manifestations of, 608
normovolemic hypotonic, 611–612
rate of correction of, 612
Hypoperfusion, 370
Hypophosphatemia, 28, 626–628
clinical manifestations of, 626–627
etiology of, 626
PN and, 846
treatment of, 627–628
Hypopnea, 1846
Hypotension
intradialytic, 689–690
schizophrenia in, 1873
Hypothalamic-pituitary-adrenal (HPA), 414
Hypothalamus dysregulation and obesity, 795
Hypothermia, 49
Hypothyroidism, 2216, 2323
in bipolar disorder, 1913
with cardiac disease, 1087–1088
clinical presentation of, 1081
fetal, 1095–1096
and goiter, 1072
iatrogenic, 1096–1097
laboratory findings, 1074*t*
subclinical, 1088
thyroid hormone therapy for, 1081–1086
treatment, 1074*t*
Hypovolemia, 580
causes of, 378
postoperative bleeding and, 378
vs. pump failure, 377–378
Hypovolemic shock
acute hemorrhagic shock, 373–377
bleeding and, 373
defined, 372
Frank-Starling mechanism, 378
hypothermia and, 378
postoperative hypovolemia, 377–379
Hypoxic ischemic encephalopathy, 2249
Hysterectomy, prophylaxis for, 1394*t*
HYVET (*See* Hypertension in the Very Elderly Trial (HYVET))

I

IABP (*See* Intra-aortic balloon pump (IABP))
IAC (*See* International ascites club (IAC))
Iatrogenic hypothyroidism, 1096–1097
Iatrogenic myxedema, 1097
IBD (*See* Inflammatory bowel disease (IBD))
IBS (*See* Irritable bowel syndrome (IBS))
IBW (*See* Ideal body weight (IBW))
IC (*See* Intermittent claudication (IC))
ICA (*See* Islet cell autoantibodies (ICA))
ICD (*See* Implantable cardiac defibrillators (ICD); Implantable cardioverter-defibrillator (ICD))
ICD therapy, indications for, 343
ICF (*See* Intracellular fluid (ICF))
ICH (*See* International Conference on Harmonization (ICH))
ICS (*See* Inhaled corticosteroids (ICS))
ICU (*See* Intensive care unit (ICU))
ICU-acquired weakness
incidence of, 49
risk factors for, 49
ID (*See* Intellectual disability (ID))
Ideal body weight (IBW), 190
Idiopathic dyspepsia (*See* Functional dyspepsia)
Idiopathic rhinitis
diagnosis of, 468–469
therapeutic agents in, 469–470
Idiopathic RPGN, 670
IDL (*See* Intermediate-density lipoproteins (IDL))
IDSA (*See* Infectious Diseases Society of America (IDSA))
IE (*See* Infective endocarditis (IE))
IFALD (*See* Intestinal failure-associated liver disease (IFALD))
IFG (*See* Impaired fasting glucose (IFG))
IFIs (*See* Invasive fungal infections (IFIs))
IgA (*See* Immunoglobulin A (IgA))
IgE (*See* Immunoglobulin E (IgE))
IGT (*See* Impaired glucose tolerance (IGT))
IIEF (*See* International Index of Erectile Function (IIEF))
IMA (*See* Internal mammary artery (IMA))
Immediate hypersensitivity reactions, 714
Immune complex-mediated reactions, 715
Immune reconstitution inflammatory syndrome (IRIS), 1497
Immunization, 1402
and administration techniques, 1416–1417, 1416*t*
and adverse effects, 1404–1405
contraindications for, 1405

and HAV, 1725
for HBV, 1735
inactivated vaccines for
diphtheria/tetanus/pertussis, 1407–1408
Haemophilus influenzae b, 1408–1409
hepatitis A, 1406–1407
hepatitis B, 1406
human papillomavirus, 1410–1411
influenza, 1411–1412
meningococcus, 1410
pneumococcus, 1411
polio, 1409–1410
legal requirements for, 1417–1418
live attenuated vaccines for, 1413–1417
COVID-19, 1415–1416
measles/mumps/rubella, 1413–1414
rotavirus, 1413
varicella, 1414
malaria, 1769
principles related to, 1402–1404
schedule for, 1405–1406
vaccines for, 1403–1404*t*, 1404
Immunoglobulin A (IgA), 448
Immunoglobulin E (IgE), 398
Immunoglobulins, 28
for neutropenic cancer patient, 1626–1627
Immunoreactive arthropathy, 474
Immunoreactive trypsin (IRT) levels, 476
Immunosuppressants
for systemic lupus erythematosus, 741–742
Immunosuppressive agents, 752, 753–754*t*
antithymocyte globulins, 759–760
azathioprine, 752, 755–756
belatacept, 756
calcineurin inhibitors, 755
corticosteroids, 755
interactions, 769*t*
monoclonal antibodies, 756–757
mTOR inhibitors, 756, 764–765
mycophenolate mofetil and mycophenolate sodium, 755
polyclonal antibodies, 756
Immunosuppressive therapy, 758–760
Impaired fasting glucose (IFG), 1103
Impaired glucose tolerance (IGT), 1043, 1103
Impaired glucose utilization, 940

Impedance plethysmography, for DVT, 190
Impella, adverse effects of, 387
Implantable cardiac defibrillators (ICD), 343–345
Implantable cardioverter-defibrillator (ICD), 287
Indirect calorimetry, 786–787
Induction therapy, 756–757
Indwelling nasogastric tube (NG), 580
Infants
and acidosis, 2206
administration of medications
oral, 2213, 2213*f*
otic, ophthalmic, and nasal medications, 2213–2214, 2213*f*
and amino acid formulations, 2208–2209
azotemia in, 2207
and BPD, 2208–2209
care for
common cold and cough, 2215–2216
constipation, 2216, 2217*t*
dehydration, 2218
diaper rash, 2214
febrile seizures, 2215
fever, 2214–2215
gastroenteritis, 2216–2219, 2220*t*
vomiting and diarrhea, 2216
and carnitine deficiency, 2209
and chemotherapy dosage, 2067
and chronic hepatic disease, 2206–2207
complications associated with breast-feeding, 2202
and diarrhea, 2216
enteral nutrition, 2201–2211
breast feeding, 2202–2203
and carbohydrate absorption, 2205
and formula intolerance, 2205
hypertonic formulas, 2205
lactose-free formula, 2205
management of metabolic errors, 2203
nutritional assessment, 2205–2206
phenylalanine-free therapeutic formulas, 2204
pure cow’s milk, 2203
ready-to-feed form feeds, 2203
route of administration, 2204, 2204*t*
solid foods, 2203
soy-based formulas, 2202–2203
therapeutic formulas, 2203–2204
essential amino acids for, 2208

and fat emulsion complications, 2207–2208
and formula intolerance, 2205
gastroesophageal reflux (GER) disease, 2219–2221
and gastrointestinal (GI) anomalies, 2206
and glucose intolerance, 2208
introduction of solid foods, 2203
and milk-based diet, 2202–2203
nutritional status, 2205–2206
and oral replacement therapy, 2218–2219, 2220*t*
parenteral nutrient regimen for, 2206
calcium content, 2206
with chronic renal, 2206–2207
fat emulsion complications, 2207–2208
with GI anomalies, 2206
goals of, 2207
with hepatic disease, 2206–2207
and liver diseases, 2210–2211
with respiratory distress, 2206
for very low-birth-weight (VLBW), 2206
pediatric amino acid formulations (PAAFs), 2208–2209
and pure cow's milk, 2203
and respiratory distress, 2206
and rickets, 2209
sepsis and septic shock in, 2261–2265, 2263*t*, 2264*t*
cardiovascular drug therapy, 2266–2269, 2267*t*
corticosteroid therapy, 2269
management, 2265–2266
and soy-based formulas, 2202–2203
therapeutic formulas for, 2203–2204
very low-birth-weight (VLBW), 2206
Infection
antimicrobial dose, 1382, 1386–1387
antimicrobial failure, 1388–1389
causative organisms, 1369–1371, 1369*t*
confabulating variables and, 1368
definition of, 2263*t*
diagnosis of, problems in, 1368–1369
drug effects and, 1368
endocarditis, 1370*t*
fever and, 1368–1369
intra-abdominal, 1370*t*, 1525–1537
isolate pathogenicity, determination of, 1378
and microbiologic tests, 1371–1378
pharmacokinetics, 1387–1388
pharmadynamics, 1387–1388

presence of, 1366
principles related to, 1365–1389
prophylaxis, 582
of respiratory system, 1370*t*
routes of antibiotic administration, 1382
severity of, 1366–1368
sites of, 1369, 1370*t*
of skin, 1370*t*
of soft tissue, 1370*t*
of urinary tract, 1370*t*
Infectious diarrhea, 1453, 1501–1523
AIDS and, 1508
Bacillus cereus and, 1507
Campylobacter jejuni and, 1513–1514
chemotherapy and, 1504
clinical presentation of, 1505
Clostridium difficile and, 1502*t*, 1518–1523
Clostridium perfringens and, 1507
Cryptosporidium parvum and, 1507–1508
drug therapy for, 1503–1504
Escherichia coli O157:H7 and, 1518
introduction of, 1501–1502
laboratory tests for, 1503
norovirus and, 1505
pathogenesis of, 1503
pharmacologic agents and, 1503
and PI-IBS, 1516
predisposing factors for, 1503
prevention of, 1504
rehydration therapy for, 1503
Salmonella spp. and, 1502*t*, 1508–1509
Shigella spp. and, 1502*t*, 1511–1513
Staphylococcus aureus and, 1507
symptoms of, 1502*t*
travelers, 1502*t*, 1514–1516
treatment for, 1502*t*, 1504–1505
viral gastroenteritis, 1502*t*, 1505
Infectious Diseases Society of America (IDSA), 1542
Infective endocarditis (IE), 1439
causative organism, 1439
CHF and, 1441
diagnostic criteria for, 1442*t*
epidemiology of, 1439
modified Duke Criteria on, 1442*t*
pathogenesis of, 1439

peripheral manifestations of, 1441
predisposing factors for, 1439
site of involvement in, 1439–1440
Infertility, 987–998
female, 988–990, 988*t*, 989*f*
general risk factors, 988
IVF protocol, 994–995*t*, 994–998, 995*f*
male, 990, 990*t*
pathophysiology and diagnosis, 988–990, 988*t*, 989*f*, 990*t*
treatment approaches, 991–998, 991*t*, 993*f*, 993*t*, 994*t*, 995*f*, 995*t*, 997–998*t*
in vitro fertilization (IVF) protocol, 993*f*
Inflammatory bowel disease (IBD)
clinical presentation of, 541–542, 542–543*t*
Crohn disease diagnosis, 542–543*t*
ulcerative colitis diagnosis, 541–542, 542*t*
definition of, 541
epidemiology of, 541
pathophysiology of, 541
treatment of, 542–557, 544–556*t*
nutrition, 543, 556
supportive care, 556
surgery, 556
Inflammatory pain, 1210
Inflammatory response, 480–481
Influenza
clinical presentation of, 1709
epidemics of, 1708
individuals at high risk for transmission, 1708
prevention, 1710–1711
systemic symptoms of, 1709
treatment, 1709–1710
types of viruses, 1708
vaccines, 1411–1412, 1708
Influenza virus infection, 1656
Inhalation of hypertonic saline (IHS), 478–479
Inhaled corticosteroids (ICS), 413
INR (*See* International normalized ratio (INR))
Insomnia, 1859
algorithm for treatment of, 1836*f*
CBT for, 1834, 1834*t*
in elderly, 1844–1845
in a healthy patient, 1834–1836
in a medically ill patient, 1840–1842
melatonin, 1837
nonbenzodiazepine receptor agonists for, 1836–1837

nonpharmacologic treatment, 1834, 1834*t*
nonprescription sleep aids, 1836
patient assessment, 1833–1834
pediatric, 1846
pharmacologic treatment, 1834–1840
and psychiatric disorders, 1842–1844
rebound, 1837
and time-zone shift, 1836–1837
triazolam therapy, 1836–1837
Institute of Medicine (IOM), 97
Insulin, 26, 1116*t*, 1132*t*
β-cells and, 1115
exogenous, 1115
hospitalized patient, management of, 1136–1138, 1137*t*
renal failure and, 1136
role of, 1115
stacking, 1139
Intellectual disability (ID)
anatomy, 1922
characteristics, 1922
clinical presentation, 1923–1924
diagnosis, 1924–1925
epidemiology, 1923
etiology, 1923
natural course of, 1923
pathophysiology, 1923
physiology, 1923
prognosis, 1923
treatment, 1925–1929
hyperactivity, 1926
pharmacologic interventions, 1926
psychosocial interventions, 1925–1926
Intensive care unit (ICU)
characteristics of opioids used in, 1244*t*
clinician roles in, 1250*t*
dynamic nature of, 1239
glycemic control in, 1248–1249
home medications in, 1238
interprofessional care in, 1250
nonsurgical patients in, 1238–1239
pain, agitation, and delirium in, 1243–1247, 1243*t*
pharmacokinetics in, 1241–1243
stress ulcer prophylaxis in, 1247–1248, 1249*t*
surgical patients in, 1239–1240
Intensive glucose control, 641–642

Interferon-γrelease assay (IGRA), 1482
INTERHEART study, 219, 220*t*
Interleukin-1 (IL-1), 389
Interleukin (IL)-1 β, 512
Intermediate-density lipoproteins (IDL), 107, 107*t*
Intermittent CF arthritis, 474
Intermittent claudication (IC), 169
annual incidence of, 170*t*
aspirin in, 174–175
cilostazol in, 175
diabetes mellitus effect on, 174*t*
erythrocyte inflexibility in, 171*f*
exercise therapy in, 173, 173*t*
outcomes in patients with, 170*t*
pentoxifylline in, 175–176
smoking cessation and, 172–173, 172*t*
Intermittent hemodialysis, 677
Intermittent pneumatic compression (IPC), 196
Internal mammary artery (IMA), 236, 236*f*
International ascites club (IAC), 588
International Classification of Headache Disorders, 1269
International Conference on Harmonization (ICH), 346
International Index of Erectile Function (IIEF), 2324
International normalized ratio (INR), 36, 71, 80–82, 188–189, 495, 573
International sensitivity index (ISI), 188
International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN), 584
International Society for Premenstrual Disorders (ISPMD), 1055
International Society of Peritoneal Dialysis (ISPD), 681
International System of Units (SI), 18
Interprofessional care in
in ICU, 1250
Interprofessional Education Collaboration (IPEC), 98
Interprofessional education (IPE)
core competencies, 98–99
future of, 104
guidance document, 102–103
incorporating in curriculum, 101–102
models, 100–101
terminology, 100
Interstitial nephritis, 725
Intestinal failure-associated liver disease (IFALD), 850
Intra-abdominal abscess, 1536
Intra-abdominal infections, 1525–1537
abscesses, 1536

after abdominal trauma, 1536–1537
bacteriology of, 1534*t*
biliary tract infections, 1528
duration of antimicrobial therapy, 1537
GI flora and, 1530
pathogens in, 1526*t*
as postoperative complications, 1536–1537
primary peritonitis, 1528–1532
secondary peritonitis, 1532–1536
Intra-aortic balloon pump (IABP), 371
complications of, 387
Intra-articular therapy, for OA of knee, 907
Intracellular fluid (ICF), 18
Intractable migraine, 1274
Intradialytic hypotension, 689–690
Intramuscular drug absorption, 2187
Intraocular pressure (IOP), 1185
Intrauterine insemination (IUI), 991
Intravenous fat emulsion (IVFE), 834
Intravenous immunoglobulins (IVIG), 750
Intravenous lipid emulsion (IVFE), 836*t*
Intravenously (IV), 182
Introductory Pharmacy Practice Experience (IPPE), 102
Intussusception, 473
Invasive fungal infections (IFIs), 1612
In Vitro fertilization (IVF), 993*f*, 994–995*t*, 994–998, 995*f*
IOM (*See* Institute of Medicine (IOM))
Ionic binding, 50
IOP (*See* Intraocular pressure (IOP))
IPC (*See* Intermittent pneumatic compression (IPC))
IPE (*See* Interprofessional education (IPE))
IPEC (*See* Interprofessional Education Collaboration (IPEC))
Ipecac-induced emesis, 68
IPPE (*See* Introductory Pharmacy Practice Experience (IPPE))
IRIS (*See* Immune reconstitution inflammatory syndrome (IRIS))
Iron
for anemia, 2203
in breast milk, 2202
chelator, 2044
in cow's milk, 2203
fortified infant formula, 2203
and hepatic dysfunction, 2183
in human milk, 2202
therapy, 644–645, 644–645*t*
toxicity, stages of, 75

Iron deficiency anemia
causes of, 1998*t*
dietary reference intakes, 1998, 1998*t*
laboratory tests, 1999
predisposing factors, 1998–1999
signs, 1999
symptoms, 1999
therapy, 1999–2002
goals of, 2000
oral dosing, 1999
parenteral, 2001–2002
patient information, 2000
product selection, 1999–2000
Irreversible enzyme inhibition, 43–44
Irritable bowel syndrome (IBS), 1051
clinical presentation of, 564
with constipation, 567–568
diagnosis of, 564–565, 564–565*t*, 565*f*
with diarrhea, 569–570
management algorithm for, 566*f*
overview of treatment of, 565–567
lifestyle modifications, 566–567
psychological therapies, 567
pain and bloating, 568–569
pathophysiology of, 564
Irritant contact dermatitis, 862
IRT (*See* Immunoreactive trypsin (IRT) levels)
IRT testing, 476
Ischemia, 217
Ischemic bowel, 1241
Ischemic stroke
acute
alteplase use in treatment of, 1352*t*
blood pressure treatment in, 1352*t*
complications of, 1357
early management of, 1348–1351
prognosis of, 1357
stroke education, 1356–1357
treatment algorithm for, 1349*f*
treatment of, 1348–1356
definition of, 1346
drugs for preventing, 1358*t*
epidemiology of, 1346
pathophysiology, 1346–1348
and postmenopausal hormone therapy, 1064*t*

risk factors for, 1347*t*
secondary prevention after, 1357–1360
antiplatelet therapy for, 1357–1360
surgical interventions for, 1360
treatment principles, 1348
ISH (*See* Isolated systolic hypertension (ISH))
ISHEN (*See* International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN))
ISI (*See* International sensitivity index (ISI))
Islet cell autoantibodies (ICA), 1105
Isolated systolic hypertension (ISH), 152
Isoniazid hepatitis, 1490–1491
Isotope dilution, 785
ISPMD (*See* International Society for Premenstrual Disorders (ISPMD))
IUI (*See* Intrauterine insemination (IUI))
IV (*See* Intravenously (IV))
IVF (*See* In Vitro fertilization (IVF))
IVFE (*See* Intravenous fat emulsion (IVFE))
IVIG (*See* Intravenous immunoglobulins (IVIG))

J

Janeway lesions, 1440*f*, 1441
Jarisch-Herxheimer reaction (JHR), 1576–1577, 1793
JC DNA polyomavirus (JCV), 1262
JCV (*See* JC DNA polyomavirus (JCV))
Jelliffe formula, for CrCl estimation, 24
JHR (*See* Jarisch-Herxheimer reaction (JHR))
JIA (*See* Juvenile idiopathic arthritis (JIA))
Joint and bone involvement, in cystic fibrosis, 473–474
Joint Commission, The, 2, 783
Juvenile idiopathic arthritis (JIA), 929–934, 934–937*t*
clinical presentation and classification, 929–930
enthesitis-related, 931
prognosis, 930
psoriatic, 929–930
symptoms, 929
systemic, 931
treatment, 930–934, 934–937*t*
biologic agents, 932–933
conventional synthetic DMARD, 933–934
corticosteroids, 934
DMARD therapy, 932–934
nonpharmacologic efforts, 930
Juvenile myoclonic epilepsy, 1314*t*

K

Kansas City Cardiomyopathy Questionnaire (KCCQ), 284
Katal (kat), 28
KCCQ (*See* Kansas City Cardiomyopathy Questionnaire (KCCQ))
KDIGO (*See* Kidney Disease: Improving Global Outcomes (KDIGO))
Ketone testing, for type 1 diabetes, 1113
Kidney clearance, 705
Kidney Disease Clinical Practice Guidelines, 633*t*
Kidney Disease: Improving Global Outcomes (KDIGO), 633, 633*t*, 635*t*, 639, 662, 662*t*, 681
clinical practice guideline for lipid management, 119, 119*t*
Kidney Disease Outcomes Quality Initiative (K/DOQI), 633
Kidney, drug hypersensitivity reactions in, 725
Kidney dysfunction, 940, 1242
on metabolism, effect, 705
Kidney failure, dosing of drugs in
advantages and disadvantages of, 701*t*
drug disposition, effect on
bioavailability, 697–698
elimination, 698–699
protein binding and volume of distribution, 698, 698*t*
drug removal by dialysis
continuous ambulatory peritoneal dialysis, 699
continuous renal replacement therapy, 699–700
drug-specific properties, 699
hemoperfusion, 700
high-flux hemodialysis, 699
drugs with active or toxic metabolites, 709*t*
enteral formulas for, 818–820
kidney function in elderly, assessing, 709
metabolized drugs, effect on
enoxaparin, 709
meperidine, 708
narcotic analgesics, 708–709
pharmacodynamics and kidney disease, 700
pharmacokinetics and pharmacodynamics of specific drugs in
acyclovir, 705
aminoglycosides, 701–702, 701*f*, 701*t*
antipseudomonal penicillins, 706
cefazolin, 707
ceftazidime, 700–701
effect of hemodialysis, 703–705
fluconazole, 707
penicillin, 706
phenytoin, 708

tenofovir, 705
vancomycin, 706–707
plasma protein binding of acidic drugs, 698*t*
Kidney function
in elderly, assessing, 709
Kidney function, and ACEI, 302
Kidney Injury Molecule-1 (KIM-1), 665
Kidney replacement therapy (KRT), 677–679, 678*f*, 678*t*, 681
Kidney transplantation
acute rejection treatment, 762
calcineurin inhibitor avoidance, withdrawal, or minimization, 763–764
calcineurin inhibitor-induced nephrotoxicity, 763
cyclosporine, 755
donor and recipient matching, 757–758
immunosuppressive therapy, 758–760
indications and evaluation, 757
postoperative course and delayed graft function, 760
rejection, 760–762
Koebner phenomenon, 872
KOH (*See* Potassium hydroxide (KOH) stain)
Korotkoff sounds, 142, 142*f*, 142*t*
Kwashiorkor malnutrition, 786

L

Labor (*See also* Pregnancy)
cervical ripening, 1021–1022
false, 1020
human immunodeficiency virus in, 1029
indications, contraindications, and requirements of, 1021
induction of, 1020–1023
infectious complications during
bacterial vaginosis, 1027
chorioamnionitis, 1028–1029
group B streptococcus intrapartum prophylaxis, 1027–1028
preterm premature rupture of membranes, 1027
mechanisms of term, 1020–1021
oxytocin, 1022–1023
preterm
antenatal glucocorticoid administration, 1026–1027
clinical presentation and evaluation of, 1023–1024
etiology of, 1023
risk factors of, 1024
tocolysis, 1024
tocolytic agents, 1024–1026

uterine activity, 1020
Laboratory tests, 16–38
acid-base status and, 592–593, 593*t*
and blood chemistry reference values, 18–21*t*
cardiac biomarkers and, 28–30
for drug poisoning, 78
for electrolytes, 18, 22–25
general principles related to, 16–18
hematologic, 21*t*, 32–36
for infectious diarrhea, 1503
liver function tests, 30–31
miscellaneous tests, 20*t*, 31–32
multichemistry panels, 26–28, 27*t*
in osteomyelitis, 1592
patient-directed monitoring/testing, 38
preanalytical variation and, 15*t*
proteins and, 28
and reference range, 16–17
reliability indicators of, 17–18
for syphilis, 1574
therapeutic drug monitoring, 38
units of measure for, 18
urinalysis, 36–38
Lactate dehydrogenase (LDH), 30
blood chemistry reference values for, 20*t*
Lactation
stimulation
milk production, enhancement of, 1032–1033
nonpharmacologic measures, 1032
suppression, 1033
***Lactobacillus*, 515, 2219**
LAR (*See* Late asthmatic response (LAR))
LAST (*See* Local anesthetic systemic toxicity (LAST))
Late asthmatic response (LAR), 400
LBBB (*See* Left bundle branch block (LBBB))
LBW (*See* Lean body weight (LBW))
LCDs (*See* Local coverage determinations (LCDs))
LDH (*See* Lactate dehydrogenase (LDH))
LDL (*See* Low-density lipoprotein (LDL))
LDUFH (*See* Low-dose unfractionated heparin (LDUFH))
Lead intoxication, 940
Lean body weight (LBW), 603
Left bundle branch block (LBBB), 340
Left ventricular assist devices, 287–288
Left ventricular dysfunction, 275–276, 289

classification and etiology of, 276*t*
Left ventricular ejection fraction (LVEF), 245, 275, 343
and HF, 321–324
Left ventricular end-diastolic pressure (LVEDP), 372
Left ventricular end-diastolic volume (LVEDV), 372
Left ventricular hypertrophy (LVH), 290
hypertension and, 148–149
Left ventricular (LV), 372
Left ventricular systolic dysfunction (LVSD), 275
Lennox-Gastaut syndrome, 1314*t*
Leptin dysregulation and obesity, 795–796
LES (*See* Lower esophageal sphincter (LES))
Leukocytes (*See* White blood cells (WBCs))
Leukotriene modifiers and chronic asthma, 417
Lewy body dementia, 2300–2301
LFTs (*See* Liver function tests (LFTs))
LGV (*See* Lymphogranuloma venereum (LGV))
Lice infections (*See* Pediculosis (lice infections))
Lifestyle modifications
for chronic stable angina, 222, 228
for GERD, 528*t*
for hypertension, 145–146, 146*t*, 151
for menopause, 1063
for PCOS, 1041
Life-threatening hypersensitivity syndrome, 714
Limb rigidity, 1284
Lipase, 31–32
blood chemistry reference values for, 20*t*
Lipid metabolism, 106–110
abnormalities in
atherogenic dyslipidemia, 110–111, 110*t*
familial combined hyperlipidemia, 110*t*, 111
familial defective apo B-100, 110*t*, 111
familial disorders of triglyceride metabolism, 112
familial dysbetalipoproteinemia, 110*t*, 112
familial hypercholesterolemia, 110*t*, 111
hypoalphalipoproteinemia, 110*t*, 112
polygenic hypercholesterolemia, 110, 110*t*
proprotein convertase subtilisin/kexin type 9 gain-of-function gene mutation, 111
apolipoproteins, 109
in transport of cholesterol and triglycerides, 108*f*
lipoproteins, 106–109
chylomicrons, 109
high-density lipoproteins, 108–109

low-density lipoproteins, 108
non-high-density lipoprotein cholesterol, 109
plasma, classification and properties of, 107*t*
relative sizes and densities, 107*f*
structure of, 102*f*
in transport of cholesterol and triglycerides, 108*f*
very low density lipoprotein remnants, 108
very low density lipoproteins, 107–108
low-density lipoprotein receptor, 109–110
Lipids, 780–781
chemical structure of, 106*f*
in parenteral nutrient formulation, 834–835
Lipoproteins
atherosclerosis, pathogenesis of, 112–113, 113*f*
chylomicrons, 109
high-density lipoproteins, 108–109
low-density lipoproteins, 108
non-high-density lipoprotein cholesterol, 109
plasma, classification and properties of, 107*t*
relative sizes and densities, 107*f*
structure of, 107*f*
in transport of cholesterol and triglycerides, 108*f*
very low density lipoprotein remnants, 108
very low density lipoproteins, 107–108
Lithium-induced nephropathy, 659–660
Lithium-induced thyroid abnormalities, 1100
Liver
drug hypersensitivity reactions in, 725
laboratory tests for, 20*t*
Liver biopsy, 921
Liver disease, end-stage
ascites
alternative therapy, 578–579
diuretic therapy, 575–577
fluid and electrolyte balance, 575
goals of therapy, 575
pathogenesis of, 574–575
refractory, 577–578
cirrhosis
complications of, 573–574, 573*f*, 574*t*
pathogenesis of, 572
esophageal varices
treatment, 579–584, 581*t*
hepatic encephalopathy, 584–587
hepatorenal syndrome, 587–589

pathogenesis, 585
treatment and general management, 585–587
Liver function tests (LFTs), 30–31, 1157
Liver metabolism, 1242
Liver transplantation, 588–589
of ALF patients, 1732
cyclosporine, 766–767
drug interactions with immunosuppressives, 769–770
for HBV-related cirrhosis, 1743
for HCV, 1743
and HDV patients, 1758
indications and evaluation of, 765
and mannitol therapy, 1731
mycophenolic acid derivatives, 768–769
patient monitoring, 766
rejection, 767–768
tacrolimus, 755
treatment for rejection, 767–768
LN (*See* Lupus nephritis (LN))
Local anesthetic systemic toxicity (LAST), 1214
Local coverage determinations (LCDs), 89
Long-acting inhaled b_2-agonist (LABA), 413
adverse effects of, 417
Long QT syndrome (LQTS), 346
Low back pain
assessment of, 1224
definition of, 1221
myofascial pain, 1221–1223
recommendations for treatment of, 1223*t*
red flags for potentially serious conditions causing, 1222*t*
spine anatomy and disc herniation, 1222*f*
Low-density lipoprotein cholesterol (LDL-C), 173
Low-density lipoprotein (LDL), 107*t*, 108, 250, 636
for, 21*t*
Low-density lipoprotein receptor, 109–110
Low-dose unfractionated heparin (LDUFH), 196
Lower esophageal sphincter (LES), 504
transient relaxations of, 525–526
Lower gastrointestinal disorders, 540–570
Crohn disease
diagnosis of, 542, 543*t*
severity classification of, 543*t*
treatment algorithm, 557*f*
and ulcerative colitis, pathophysiologic differences between, 542*t*
inflammatory bowel disease

clinical presentation of, 541–542, 542–543*t*
definition of, 541
epidemiology of, 541
pathophysiology of, 541
treatment of, 542–557, 544–556*t*
irritable bowel syndrome
clinical presentation of, 564
with constipation, 567–568
diagnosis of, 564–565, 564–565*t*, 565*f*
with diarrhea, 569–570
management algorithm for, 566*f*
overview of treatment of, 565–567
pain and bloating, 568–569
pathophysiology of, 564
ulcerative colitis
and Crohn disease, pathophysiologic differences between, 542*t*
diagnosis of, 541–542
diarrhea associated with, 558
pathophysiology and clinical presentation of, 558–564
severity classification of, 542*t*
treatment algorithm, 557*f*
LQTS (*See* Long QT syndrome (LQTS))
Lung Allocation Score, 485
Lung cancer
and cigarette smoking, 1977, 1987
cumulative risk of death from, 2113*t*
neoadjuvant therapy, 2024
non-small-cell (NSCLC), 2024, 2111–2113
signs and symptoms for, 2112*t*
sites of metastases, 2019*t*
small cell (SCLC), 2118–2121
Lung, drug hypersensitivity reactions in, 725
Lung transplantation, 485
Lung volume reduction surgery, 443, 444*t*
Lupus nephritis (LN), 655–656
Luteal phase support, in IVF, 997
LV (*See* Left ventricular (LV))
LVEDP (*See* Left ventricular end-diastolic pressure (LVEDP))
LVEDV (*See* Left ventricular end-diastolic volume (LVEDV))
LVEF (*See* Left ventricular ejection fraction (LVEF))
LVH (*See* Left ventricular hypertrophy (LVH))
LVSD (*See* Left ventricular systolic dysfunction (LVSD))
Lyme disease, 1798
Lymphocytes, 35
Lymphogranuloma venereum (LGV), 1572

Lymphokines, 750
Lymphomas
classification of, 2091*t*
clinical presentation of, 2090–2091
diagnosis of, 2090–2091
epidemiology, 2090
etiology of, 2090
pathophysiology of, 2090
staging of, 2091*t*
treatment of, 2091, 2092*t*
Lynch syndrome, 2141

M

***MAC* (*See Mycobacterium avium complex (MAC)*)**
Macronutrients, 780
carbohydrates, 780
lipids, 780–781
protein, 780
Macrosomia, 1011
Macrovascular disease
and glycemic control, 1109–1111, 1110*t*
Macular degeneration, age-related, 1205
Maculopapular acne, 866*t*, 868–869
MADRS (*See* Montgomery Asberg Depression Rating Scale (MADRS))
Magnesium, 27
blood chemistry reference values for, 19*t*
disorders of, 628–630
homeostasis, 628
hypermagnesemia, 630–63
hypomagnesemia, 628–630
Magnetic resonance imaging (MRI), 198
Maintenance fluids, 790–791
Major depressive disorder
diagnosis of, 1890
suicide assessment, 1895
Major histocompatibility complex (MHC), 751–752
Malaria
acute
signs of, 1763
symptoms of, 1763
treatment, 1763–1764
antimalarial drugs, 1765–1767*t*
characteristic paroxysms of, 1762
distribution, 1762

drug-resistant, 1763
epidemiology of, 1762
and G6PD deficiency, 1764
hemoprophylaxis against, 1769
life cycle of parasites, 1762–1763
mosquito protection measures, 1768*t*
non-falciparum prophylaxis, 1769
Plasmodium falciparum infections, 1763
prevention, 1764, 1767
prophylaxis for Plasmodium falciparum, 1769–1770
sporozoites, 1763
standby emergency treatment, 1767–1770
transmission, 1762–1763
vaccination, 1770
Male libido, 2322
Malignancy, 772, 1076
Malignancy-related anemia, 2011–2012
Malignant melanoma, UVR exposure and, 884
Malnutrition, 782, 833
classification of, 786
defining, 782–783
Mania, in BD, 1909–1917
Manic-depression (*See* Bipolar disorder (BD))
Mantoux method (*See* Tuberculin skin test (Mantoux method))
MAO (*See* Maximal acid output (MAO))
MAP (*See* Mean arterial pressure (MAP); Medication action plan (MAP))
Maple syrup urine disease, 2204
MAR (*See* Medication administration record (MAR))
MARISA (*See* Monotherapy Assessment of Ranolazine in Stable Angina (MARISA))
MASCC (*See* Multinational Association of Supportive Care in Cancer (MASCC))
Matrix metalloproteinases (MMP), 902
Matthew-Rumack nomogram, 82
Maturity-onset diabetes of the young (MODY), 1106
Maximal acid output (MAO), 515
MBSR (*See* Mindfulness-based stress reduction (MBSR))
McGill Pain Questionnaire, 1210, 1212*t*, 1224
MCH (*See* Mean cell hemoglobin (MCH))
MCHC (*See* Mean cell Hgb concentration (MCHC))
MCTs (*See* Medium-chain triglycerides (MCTs))
MCV (*See* Mean cell volume (MCV))
MDCT (*See* Multi-detector CT (MDCT))
MDI (*See* Metered-dose inhaler (MDI))
MDRD (*See* Modification of Diet in Renal Disease (MDRD))

Mean arterial pressure (MAP), 141, 367
normal values of, 369*t*
Mean cell hemoglobin (MCH), 33
Mean cell Hgb concentration (MCHC), 32
Mean cell volume (MCV), 33
Measles, mumps, rubella (MMR), 1404
Mechanical ventilation, 48
Meconium ileus equivalent, 473 (*See also* Distal intestinal obstruction syndrome (DIOS))
MED (*See* Minimal erythemal dose (MED), of UV radiation)
Medical history, 4–5
Medical nutrition therapy (MNT), 1107, 1111–1112
physical activity, 1112–1113
principles of, 1111
specific components, 1112
for type 1 diabetes, 1111
for type 2 diabetes, 1112
Medical Therapy of Prostate Symptoms (MTOPS), 2321
Medicare, EN and, 829, 830*t*
Medicare Hospice Benefit, 87–88
Medicare Prescription Drug Improvement and Modernization Act of 2003, 2279
Medication action plan (MAP), 10, 11*f*
Medication administration record (MAR), 3
Medication history, 5–6
Medication overuse, definition of, 1278
Medication reconciliation, 2
Medication therapy management (MTM), 1
Medication therapy management services (MTMS), 1–14
in acute care setting, 13–14
community pharmacy or ambulatory setting
documentation and follow-up, 10–13
intervention and referral, 10
medication action plan, 10, 11*f*
medication therapy review, 9, 9*t*
personalized medication record, 9–10, 10*f*
effective communication, 4
general approach to, 3*f*
patient history
medical history, 4–5
medication history, 5–6
social history, 6
patient information, sources of, 2–4, 3*t*
data-rich and data-poor environments, 3–4
patient interview, 4

patient therapy, approach to and assessment of, 6–7
assessment, 8–9
patient education, 9
plan, 9
problem list, 7, 8*t*
subjective and objective data, 7–8
and pharmacogenomics, 14
Medication therapy review (MTR), 5, 9, 9*t*
Meditation, 1236*t*
Mediterranean diet, 1176
Medium-chain triglycerides (MCTs), 835
Megaloblastic anemia, 2002–2006
Melancholia, 1886
Melanoma, UVR exposure and, 882–883
MELD (*See* Model for End-Stage Liver Disease (MELD))
Meninges, 1419–1420
Meningitis, 1370*t*, 1420–1434
aseptic, 1420
cerebrospinal fluid findings in, 1423, 1423*t*
clinical features of, 1422–1423, 1422*t*
Enterobacter, 1432
gram-negative bacillary, 1431–1432
Haemophilus influenzae-induced, 1421
microbiology of, 1420–1421, 1421*t*, 1423
Neisseria meningitidis, 1427–1429
in neonates, 1371, 1421
pathogenesis and pathophysiology of, 1421–1422
penicillin-susceptible pneumococcal, 1431
Streptococcus pneumoniae, 1429–1431
treatment of, 1423–1427
Meningococcal disease, 1410
Menopause
average age of women at, 1061
clinical presentation of, 1062
definition of, 1061
and hot flushes, 1062–1063
pathophysiology of, 1061–1062, 1062*f*
symptoms of, 1062–1063
treatment, 1063–1066
estrogen/progestogen (EPT) therapy, 1063
lifestyle modification, 1063
postmenopausal hormone therapy, 1064–1065*t*
Menorrhagia, 1074*t*
Menstrual cycle, 1039*f*
daily diary chart, 1058–1059*t*

disorders related to, 1038–1060
Menstrual dysfunction
in polycystic ovary syndrome, 1041
MERS (*See* Middle East Respiratory Syndrome (MERS))
MERS-CoV (*See* Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV))
Mesenchymal cells, 878
Metabolic acidosis, 594–597, 597*tt*, 643, 675, 1731, 2191, 2200, 2206
causes of, 594*t*
with elevated anion gap, 596–597, 597*t*
hyperkalemia and, 23
in infants, 2208
in NEC, 2239
with normal-anion gap, 595–596
and pediatric shock, 2260–2261
in RDS, 2227
in VLBW infants, 2240
Metabolic alkalosis, 577, 597–598, 597*t*, 2200
classification of, 597*t*
evaluation of, 597
PN and, 846–847
treatment of, 598
Metabolic bone disease
in long-term PN, 850
Metabolic syndrome, 171, 1106, 1107*f*
Metabolism of drug interactions, 43–45, 44*f*
Metastatic breast cancer, 2106–2110
Metered-dose inhaler (MDI), 431
Methicillin-resistant strain of S. aureus (MRSA), 475, 1389, 1399, 1433, 1443, 1525, 1591
CAP and, 1465
Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF), 303
MHC (*See* Major histocompatibility complex (MHC))
MI (*See* Motivational Interviewing (MI); Myocardial infarction (MI))
MIC (*See* Minimum inhibitory concentration (MIC) test)
Michaelis-Menton kinetics, 58
Micronutrients, 788, 790
electrolytes, 781
trace elements, 782
vitamins, 781–782
Microsomal triglyceride protein inhibitors, 132–133
Microsporidiosis, 1656
Microvascular angina, 239
Microvascular disease

and glycemic control, 1109–1111, 1110*t*
MIDAS (*See* Migraine Disability Assessment (MIDAS))
Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV), 1718–1719
Middle East Respiratory Syndrome (MERS), 1713
Migraine
and EPT, 2341
headache, 1269
assessment tools, 1271
intractable, 1274
medication overuse, 1278
pathophysiology of, 1270–1271
prophylactic therapy for, 1275
without aura, 1271–1273
and postmenopausal hormone therapy, 1065*t*
Migraine Disability Assessment (MIDAS), 1271
Migraine-Specific Quality of Life Questionnaire (MSQ), 1271
Mindfulness-based stress reduction (MBSR), 1227
Mineral and bone disorders
etiology, 649–650, 649*f*
treatment, 650–654, 651*t*
Minimal erythemal dose (MED), of UV radiation, 891
Minimal hepatic encephalopathy, 584
Mini Mental State Exam (MMSE), 122
Minimum inhibitory concentration (MIC) test, 1371, 1378
Miosis, 1185
MIRACL (*See* Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL))
Misoprostol, 509
Mitral valve prolapse, panic disorder and, 1817
MMP (*See* Matrix metalloproteinases (MMP))
MMR (*See* Measles, mumps, rubella (MMR))
mMRC (*See* Modified British Medical Research Council Questionnaire (mMRC))
MMSE (*See* Mini Mental State Exam (MMSE))
MNT (*See* Medical nutrition therapy (MNT))
Model for End-Stage Liver Disease (MELD), 573
Modification of Diet in Renal Disease (MDRD), 637, 665
equation, 703
for GFR estimation, 25
Modified British Medical Research Council Questionnaire (mMRC), 433
MODY (*See* Maturity-onset diabetes of the young (MODY))
Molar absorptivity, 887
Monoclonal antibodies, 756–757
Monocytes, 35
Monosaccharides, 780

Monotherapy Assessment of Ranolazine in Stable Angina (MARISA), 233
Montgomery Asberg Depression Rating Scale (MADRS), 1888, 1917
***Moraxella catarrhalis*, 436, 2221**
Motion sickness, 488–490, 490*t*
Motivational interviewing (MI), 4, 4*t*
MRI (*See* Magnetic resonance imaging (MRI))
MRSA (*See* Methicillin-resistant strain of *S. aureus* (MRSA))
MS (*See* Multiple sclerosis (MS))
MSQ (*See* Migraine-Specific Quality of Life Questionnaire (MSQ))
MTMS (*See* Medication therapy management services (MTMS))
MTOPS (*See* Medical Therapy of Prostate Symptoms (MTOPS))
MTOR inhibitors, 756, 764–765
MTR (*See* Medication therapy review (MTR))
Mucociliary clearance, 478
Mucocutaneous candidiasis, 1671–1672
Mucosal resistance, 526
Multichemistry panels, 26–28, 27*t*
Multi-detector CT (MDCT), 198
Multidrug resistant strains, 481
Multifactorial inheritance, 1003
Multimodal pain management, 1217–1221
Multinational Association of Supportive Care in Cancer (MASCC), 1612, 2042
Multinodular goiter, 1101
Multiple endocrine neoplasia type 1 (MEN1), 524
Multiple organ dysfunction syndrome, 367
Multiple sclerosis (MS), 1735, 1837*t*, 1887*t*
acute relapses, treatment of, 1255
clinical presentation of, 1254
development of clinically definite, 1258
diagnosis of, 1254–1255
factors associated with, 1252*t*
impaired ambulation, 1256
inflammation in, 1253–1254
introduction, 1251–1253
myelin destruction in, 1253*f*
neurodegeneration, 1254
pain, 1256–1257, 1257*t*
pathophysiology of, 1253–1254
primary-progressive, 1252
treatment of, 1256
relapsing-remitting, 1252
treatment of, 1255
secondary-progressive, 1252
treatment of, 1256
symptoms in, 1254*t*

treatment of, 1255–1267
types of, 1252
Multisystem vasculitic disorders, 670
Murphy's sign, 1527
Muscle relaxants, for pain management, 1225, 1226*t*
Musculoskeletal pain, 1210
Mutations classification, 472*f*
Mycelium-to-yeast conversion, 1674
Mycobacteria, 1654
***Mycobacterium avium complex (MAC)*, 1655**
clinical presentation of, 1670
IRIS-associated fever in, 1671
prophylaxis, 1671
treatment, 1670–1671
Mycobacterium tuberculosis
clinical presentation of, 1669
definitive diagnosis of, 1669
in HIV-infected patients, 1669
drug-susceptible, 1669
treatment, 1670–1671
incidence of, 1669
mortality rate, 1669
Mycophenolic acid derivatives, 768–769
Mycotic (fungal) infections
antimycotics
antifungal spectrum and susceptibility testing, 1676–1677
CLSI-recommended tests, 1676
mechanism of action, 1675–1676, 1676*t*
novel antifungal compounds, 1678
prophylaxis regimens and approximate costs, 1678*t*
aspergillosis, 1692–1694
blastomycosis, 1687–1689
candida infection, 1680–1687
candiduria, 1687
classification of, 1674, 1675*t*
clinical, 1675*t*
coccidioidomycosis, 1691–1692
cryptococcosis, 1695
cutaneous infections, 1677–1679
cutaneous mycoses, 1674
histoplasmosis, 1689–1691, 1690*f*, 1690*t*
host defenses, 1675
morphology, 1674
organism classification, 1674*t*
pathogenesis of infection

endogenous sources, 1674
exogenous sources, 1674–1675
subcutaneous, 1679–1680, 1679*f*
mycoses, 1674
superficial infections, 1677–1679
systemic, 1680–1695
Mydriasis, 1185
Myeloma cancer
sites of metastases, 2019*t*
Myelopathy, 2047
Myocardial contractibility, levosimendan for, 280
Myocardial infarction (MI), 170, 182, 217, 380
risk factors of, 220*t*
Myocardial ischemia
calcium and, 220
sodium and, 220
with sorafenib, 2052
Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL), 120, 267
Myocardial oxygen
hematocrit and, 217
Hgb and, 217
supply and demand, 217, 218*f*
Myofascial pain, 1221
treatment of, 1223
Myoglobin, 29
for, 19*t*
Myopathy, definition of, 121
Myxedema coma, 1072
clinical presentation, 1086–1087
treatment, 1086–1087

N

NAA (*See* Nucleic acid amplification (NAA) techniques)
NAATs (*See* Nucleic acid amplification tests (NAATs))
N-acetyl-p-benzoquinone-imine (NAPQ1), 47
N-acetyltransferase-2 (NAT2), 55
genotype-based dosing recommendations for isoniazid, 56*t*
genotypes and hepatotoxicity risk with isoniazid studies, 56*t*
genotypes and phenotypes, 55*t*
NAFLD (*See* Nonalcoholic fatty liver disease (NAFLD))
NAPQ1, 47
Narcolepsy, 1847–1849
NARES (*See* Nonallergic rhinitis with eosinophilia syndrome (NARES))

Narrowband ultraviolet B (NB-UVB) phototherapy, 877
Narrow therapeutic index (NTI), 41
NASH (*See* Nonalcoholic steatohepatitis (NASH))
Nasogastric (NG) tube, 69, 808, 808*f*
Nasolacrimal occlusion, 1190
National Emphysema Treatment Trial (NETT), 443
National Health and Nutrition Examination Survey (NHANES), 794
National Institute of Neurological Disorders and Stroke (NINDS), 1352, 1353
National Institutes of Health (NIH), 398, 427
National Kidney Disease Education Program (NKDEP), 2192
National Kidney Foundation (NKF), 633
National Lung Screening Trial (NLST), 2113
National Osteoporosis Foundation (NOF), 2353
National provider identifier (NPI), 11
National Survey of Family Growth, 987
Natriuretic peptides
and HF, 279
role of, 279
Nausea and vomiting, 487–501
anticipatory, 490
causes of, 488
chemotherapy and, 490–498, 491–493*t*, 494*t*, 497*t*, 498–499*f*
clinical presentation of, 488
definition of, 488
diagnosis of, 488
epidemiology of, 488
motion sickness, 488–490, 490*t*
nonpharmacologic management of, 1007
pathophysiology of, 488, 489*f*
pharmacologic management of, 1007–1009, 1008*t*
postoperative, 499–501, 501*t*
during pregnancy, 1006–1009
radiation and, 498–499, 500*t*
reflux esophagitis, 1009
NBRA (*See* Nonbenzodiazepine receptor agonists (NBRA))
NBTE (*See* Nonbacterial thrombotic endocarditis (NBTE))
NE (*See* Norepinephrine (NE))
NEC (*See* Necrotizing enterocolitis (NEC))
Necrotizing enterocolitis (NEC)
clinical signs of, 2239
complications, 2241
incidence of, 2239
pathogenesis of, 2240
prevention, 2241–2242
prognosis, 2241

risks of, 2239
stages, 2239
treatment, 2240–2241
Neisseria gonorrhoeae
antibiotic-resistant, 1564
gonorrhea by, 1562
Neisseria meningitidis meningitis, 1427–1429
prevention of, 1429
therapy for, 1427–1428
Neonatal herpes, 1588, 1699, 1701–1702
Neonatal HSV-1 infections, 1701
Neonatal sepsis and meningitis
incidence of, 2242
pathogens, 2243
treatment, 2243–2246
Neonates
apnea in, 2246–2248
bronchopulmonary dysplasia in, 2230–2235
cardiovascular drug therapy, 2266–2269, 2267*t*
congenital heart disease, 2269–2270, 2270*t*
management of pediatric septic shock, 2265–2266
medications for intubation and mechanical ventilation, 2257–2259*t*, 2257–2260
necrotizing enterocolitis in, 2239–2242
neonatal sepsis and meningitis, 2242–2246
patent ductus arteriosus in, 2235–2239
pediatric cardiopulmonary resuscitation, 2254–2255
pediatric shock, 2260–2261
corticosteroid therapy, 2269
RDS in, 2225–2229
respiratory distress problems in, 2255–2257
seizures in, 2248–2251
sepsis and septic shock in, 2261–2265, 2263*t*, 2264*t*
TORCH titers in, 2246
traumatic brain injury, 2270–2275
Nephrogenic systemic fibrosis (NSF), 672
Nephron, tubular function of, 604–605, 605*f*
Nephropathy and diabetes, 1177
Nephrotic syndrome, 607, 654–655, 666
NERD (*See* Nonerosive reflux disease (NERD))
NETT (*See* National Emphysema Treatment Trial (NETT))
Neuroblastoma, in children, 2062–2065, 2064–2066*t*
association of MYCN oncogene, 2065
clinical presentation of, 2064
COG protocols, 2062
description, 2062–2063

diagnosis of, 2063
epidemiology, 2062–2063
and hydration, 2065
hypotensive reactions to etoposide, 2065
A123 I metaiodobenzylguanidine (MIBG) test, 2063
incidence, 2062–2063
neural tumors related to, 2063
pathophysiology of, 2063
prognostic factors, 2063
staging, 2063
treatment, 2063, 2064–2065, 2065*t*
Neurocysticercosis, 1778
Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, 1339
Neurohormones
and obesity, 795–796
Neuroleptic malignant syndrome (NMS), 1876–1879
Neuromuscular blockade, 49
Neuromuscular blocking agent, 49
Neuropathic pain, 1210, 1227–1231
analgesic drug-drug interactions, 1231
central, 1227
modifying regimen, 1231
Neuropeptide dysregulation and obesity, 795–796
Neurosurgery, prophylaxis for, 1392*t*
Neurosyphilis, 1574
Neurotoxicity, 706
Neurotransmitter dysregulation and obesity, 796
Neutralizing antibodies, and MS, 1263
Neutropenia, 35
antibacterials in patients with, 1623–1624*t*
definition of, 1610
fungal infections in, 1625–1626
infections in, 1610–1627
alterations in immune system in, 1610–1611
clinical signs and symptoms in, 1616
colonization in, 1611, 1617
confirmation of, 1617
damage to physical barriers in, 1610
empiric antibiotic therapy for, 1617–1621
functional asplenia and, 1611
pathogens in, 1611–1612
prophylaxis against, 1612–1616
radiation therapy and, 1611
risk stratification in, 1612
transplantation and, 1611

Neutrophils, 33–34
New York Heart Association (NYHA), 281
classification of HF, 281
staging of, 282*f*
NGU (*See* Nongonococcal urethritis (NGU))
NHANES (*See* National Health and Nutrition Examination Survey (NHANES))
NHL (*See* Non-Hodgkin lymphoma (NHL))
Nicotine gum, 1985
Nicotine lozenge, 1985–1986
NIH (*See* National Institutes of Health (NIH))
NINDS (*See* National Institute of Neurological Disorders and Stroke (NINDS))
Nitric oxide (NO)
arginine and, 817
and arterial BP, 141
asthma and, 399
Nitrogen balance, 787
Nitroglycerin (NTG), 217, 228–229
NKDEP (*See* National Kidney Disease Education Program (NKDEP))
NKF (*See* National Kidney Foundation (NKF))
NLST (*See* National Lung Screening Trial (NLST))
NMS (*See* Neuroleptic malignant syndrome (NMS))
NO (*See* Nitric oxide (NO))
Nociception, 1208
Nocturnal asthma, 421 (*See also* Asthma)
Nocturnal hypoglycemia, 1135, 1138
symptoms of, 1139
Nocturnal Oxygen Treatment Trial (NOTT), 443
Nodular acne, 866*t*, 869–870
Nodular goiters, 1075
NOF (*See* National Osteoporosis Foundation (NOF))
Nonalcoholic fatty liver disease (NAFLD), 572
Nonalcoholic steatohepatitis (NASH), 572
Nonallergic rhinitis with eosinophilia syndrome (NARES), 447*f*, 448
Nonbacterial thrombotic endocarditis (NBTE), 1439
Nonbenzodiazepine receptor agonists (NBRA), 1836–1837
Noncompetitive enzyme inhibition, 43
Nonerosive reflux disease (NERD), 525, 531–532
Nongonococcal arthritis, 1598–1599
Nongonococcal urethritis (NGU), 1571–1572
Non-high-density lipoprotein cholesterol (non-HDL-C), 109
Non-Hodgkin lymphoma (NHL), 1655, 2078–2081, 2093
aggressive, 2093–2094
classification of, 2078
clinical presentation of, 2078
indolent, 2094–2095

staging systems, 2078
treatment
for B cell, 2079–2080
for large cell lymphomas, 2080
for lymphoblastic lymphoma, 2080–2081
for T cell, 2078–2079, 2079*t*
Non-IgE reactions, 725–727, 726*t*
angiotensin-converting enzyme inhibitors and angiotensin II-receptor blockers, 727–728
aspirin/nonsteroidal anti-inflammatory drugs, 727
iron-dextran injection, 729
narcotic analgesics, 729
radiocontrast media, 728–729
Noninfectious AIDS-related mortality, 1654
Nonrapid eye movement (NREM) sleep, 1832
Non-small-cell lung cancer (NSCLC), 2111–2113
chemoradiation regimens for inoperable stage III, 2115*t*
chemotherapy, 2114, 2114*t*, 2115
clinical presentation of, 2112
clinical staging for, 2112*t*
diagnosis of, 2112
early-stage, 2113–2114
epidemiology of, 2111
initial regimens for advanced or metastatic, 2116*t*
late-stage, 2114–2118
palliative care, 2116–2118
pathophysiology of, 2111–2112
radiotherapy, 2114, 2115
risk factors of, 2112
surgery, 2115
treatment, 2112–2113
Nonsteroidal anti-inflammatory drugs (NSAIDs), 201, 235, 420, 577, 659, 1684, 1789, 2069, 2289
for acute gout, 944
adverse effects, 1049
common cold, 1719
contraindications, 1049
for dysmenorrhea, 1048–1049
effects on kidney, 919
for endometriosis, 1052
and GI bleeding, 918
for JIA, 931–932
for PMS, 1056–1057
for RA, 914–915
Non-ST segment myocardial infarction (NSTEMI), 241

treatment algorithm for, 253*f*
Nonsustained ventricular tachycardia (NSVT), 341, 341*f*
Nontreponemal tests, 1574
Non-ulcer dyspepsia (NUD) (*See* Functional dyspepsia)
Norepinephrine (NE), 278
and obesity, 796
Normal values, laboratory tests and, 16
Noroviruses, and diarrhea, 1505
Nose
anatomy of, 448
function of, 448
IgA in, 448
physiology of, 448
NOTT (*See* Nocturnal Oxygen Treatment Trial (NOTT))
NPI (*See* National provider identifier (NPI))
NREM sleep (*See* Nonrapid eye movement (NREM) sleep)
NRS (*See* Numerical rating scales (NRS))
NSAIDs (*See* Nonsteroidal anti-inflammatory drugs (NSAIDs))
NSCLC (*See* Non-small-cell lung cancer (NSCLC))
NSF (*See* Nephrogenic systemic fibrosis (NSF))
NSVT (*See* Nonsustained ventricular tachycardia (NSVT))
N-terminal proBNP (NT-proBNP), 30
NTG (*See* Nitroglycerin (NTG))
NTI (*See* Narrow therapeutic index (NTI))
Nucleic acid amplification (NAA) techniques, 1481
Nucleic acid amplification tests (NAATs), 1563
Nucleotide polymorphisms, 45
Numerical rating scales (NRS), 1212*t*
Nutrition, 543, 556
Nutritional deficiencies, 784
Nutritionally deficient or variant streptococci (NVS), IE and, 1444
Nutritional support effectiveness, 791
Nutrition basics, 779–782
conditions impacting nutrient requirements, 788, 789*t*
essential nutrients (water), 781
macronutrients, 780
carbohydrates, 780
lipids, 780–781
protein, 780
micronutrients
electrolytes, 781
trace elements, 782
vitamins, 781–782
patient assessment
assessing growth, 787–788

goals of therapy, 790
maintenance fluids, 790–791
male with ulcerative colitis, 789–791
micronutrients, 788, 790
nutritional support effectiveness, 791
Nutrition history, 783
components of, 783*t*
Nutrition screening, 783
biochemical assessment, 785–786
energy expenditure, 786–787, 787*t*
nutritional assessment, visceral proteins for, 786*t*
patient assessment, 783
anthropometrics, 784–785
body weight and body mass index, 784
nutrition history, 783
physical examination, 784
weight history, 783–784
protein goals, 787, 787*t*
NVS (*See* Nutritionally deficient or variant streptococci (NVS), IE and)
NYHA (*See* New York Heart Association (NYHA))

O

OA (*See* Osteoarthritis (OA))
OARSI (*See* Osteoarthritis Research Society International (OARSI))
OASIS (*See* Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS))
OATs (*See* Organic anion transporters (OATs))
Obesity, 940
assessment and treatment of, 798–804
behavior therapy for, 798–799
BMI and guidelines for classes, 794*t*
classes of, 793
course and prognosis of, 797
definitions of, 793–794
dietary supplements for, 803*t*
diets for, 798
drugs and effect on weight, 796*t*
environmental influences and behavioral factors, 797
epidemiology of, 794–795
etiology and pathophysiology of, 795–797
genetics and, 795–796
hypothalamus dysregulation, 795
initial assessment of, 797
investigational agents, 801–802

lifestyle therapy, 798–799
medical complications of, 797–798
medical conditions and medications, 796
medical devices for, 802–803
medications for the treatment of, 800*t*
neuropeptide and leptin dysregulation, 795–796
neurotransmitter dysregulation, 796
and PCOS, 1041
pharmacologic therapy for, 799–801
physical activity for, 798
PN and, 843
-related health conditions, 794*t*
surgery for, 804
OBRA (*See* Omnibus Budget Reconciliation Act (OBRA))
Obsessive-compulsive disorder (OCD), 1802
assessment of, 1827
clinical course of, 1824–1825
clinical presentation of, 1827
diagnostic criteria, 1824
epidemiology of, 1824–1825
etiology of, 1825
pathophysiology of, 1825
psychiatric comorbidity and, 1825
treatment of
augmentation therapy, 1826
benzodiazepines, 1826
CBT, 1826
clomipramine, 1826, 1829–1830
course and duration of, 1818–1819
deep brain stimulation, 1826
defining response to therapy, 1827
MAOI phenelzine, 1826
neurosurgery, 1826
nonpharmacologic, 1826–1827
SSRIs, 1825–1826, 1827–1828
strategies for managing partial response and nonresponse, 1827
Obstructive sleep apnea (OSA), 1043, 1846–1847
CPAP and, 1847
Obstructive *vs.* restrictive airway disease, 403–404
Occlusion, 856–857
OCD (*See* Obsessive-compulsive disorder (OCD))
Octreotide, 580
Ocular
anatomy and physiology of, 1184–1185, 1184*f*
disorders, 1200–1202

emergencies, 1200
herpes simplex virus infections, 1203–1204
hypertension, 1150
nonsteroidal anti-inflammatory drugs, 1203, 1204*t*
side effects, 1196–1199*t*
ODS (*See* Osmotic demyelination syndrome (ODS))
OGTT (*See* Oral glucose tolerance test (OGTT))
OHE (*See* Overt Hepatic Encephalopathy (OHE))
OHSS (*See* Ovarian hyperstimulation syndrome (OHSS))
OI (*See* Ovulation induction (OI))
OIH (*See* Opioid-induced hyperalgesia (OIH))
OIs (*See* Opportunistic infections (OIs))
Oligomenorrhea, 1043
Oligomeric formulas, 809, 810*t*, 811
Oligosaccharides, 780
Omegaven, 2210
Omnibus Budget Reconciliation Act (OBRA), 2289
On-demand pharmacotherapy, 531
ONgoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), 162, 174
ONTARGET (*See* ONgoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET))
Onychomycosis (*See* Tinea unguium (onychomycosis))
Oocyte retrieval, in IVF, 996–997
OPEP (*See* Oscillating positive-end pressure (OPEP))
Ophthalmic corticosteroids
adverse effects of, 1202, 1203*t*
preparations and clinical use, 1202, 1202*t*
Ophthalmic medication, side effects from, 1203
Ophthalmopathy, 1074
clinical presentation of, 1097
eye symptoms, 1097–1098
Opioid-induced hyperalgesia (OIH), 1209
Opioid Risk Tool (ORT), 1224, 1235
Opportunistic infections, 773, 774*t*
Opportunistic infections (OIs), 2178, 2179
AIDS-related opportunistic illnesses in US, 1655–1656
chronic suppressive therapy, 1656, 1658–1659
cytomegalovirus, 1664–1666
groups of, 1656
with HIV patients, 1654–1656
IDSA guidelines, 1656
mucocutaneous candidiasis, 1671–1672
Mycobacterium avium complex (MAC), 1670–1671
Mycobacterium tuberculosis, 1669–1670

natural history
and antiretroviral agents, 1655
CD4+ lymphocyte functions, 1654–1655
viral load and survival, 1655
Pneumocystis jiroveci pneumonia, 1659–1662
primary prophylaxis, 1662
discontinuation prophylactic therapy, 1662
in HIV-infected patients, 1657–1658*t*
secondary prophylaxis, 1656
discontinuation of, 1662
Toxoplasma gondii encephalitis, 1662–1664
OPTIMAAL (*See* Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL))
Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL), 266
Oral drug absorption, 2187
Oral electrolyte solutions, 2218*t*
Oral glucose tolerance test (OGTT), 1107, 1108, 1108*t*
Oral replacement therapy
in infants and children, 2218–2219, 2218*t*
and reinstitution of oral feedings, 2218–2219
Organic anion transporters (OATs), 698
Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS), 261
Organ transplant, 940
ORT (*See* Opioid Risk Tool (ORT))
Orthopedic surgery, prophylaxis for, 1393*t*
Orthostasis, 1873
in patients with schizophrenia, 1873
Orthostatic hypotension, 152, 2281
OSA (*See* Obstructive sleep apnea (OSA))
Oscillating positive-end pressure (OPEP), 478
Osler nodes, 1441
Osmolal gap, 604
Osmolality, 26, 603–604
Osmol gap, 26
Osmoregulation, 605–606
Osmotic demyelination syndrome (ODS), 612
Osteoarthritis (OA), 899–908, 2288–2289
clinical presentation of, 901–902
dietary supplements and, 907–908
drug therapy, 900–901
etiology of, 900, 900*f*
joint trauma and, 900
modifiable risk factors of, 900, 900*f*

nonmodifiable risk factors of, 900, 900*f*
nonpharmacologic management of, 902, 903*t*
pathogenesis of, 900
pharmacologic management of, 902–907, 903t, 905*f*
treatment of, 902–908, 903*t*, 905*f*
Osteoarthritis Research Society International (OARSI), 903
Osteomalacia, 850
Osteomyelitis, 1591–1600
acute, 1592–1594
bone anatomy and physiology and, 1591
causative organism, 1591
chronic, 1596–1597
features of, 1593*t*
hematogenous, 1592
with prosthetic material, 1597–1598
secondary to contiguous focus of infection, 1594–1595
with vascular insufficiency, 1596
Osteoporosis, 850
androgens, 2354–2355
drug therapy, 2335
and estrogen, 1063, 2354–2355
etiology, 2333–2334
glucocorticoid-induced, 2352
from heparin, 193
in men, 2353–2354
overview of, 2332–2333
pathophysiology, 2334–2335
and postmenopausal hormone therapy, 1064*t*
prevalence, 2333
prevention
pharmacologic, 2341–2347
postmenopausal women, 2338–2341
premenopausal women, 2337–2338
risk factors, 2335–2337
alcohol ingestion, 2336
cigarette smoking, 2336
dietary intake, 2336–2337
family history, 2336
genetic factors, 2336
low body mass, 2336
mobility, 2336
physical activity, 2336
treatment, 2347–2351
Osteoporosis, posttransplant, 771
Osteosarcoma, 2067–2069

age range and bones involved, 2067
and clinically detectable metastases, 2068
clinical presentation of, 2068
degree of tumor necrosis, 2068
diagnosis, 2068
epidemiology, 2067–2068
goal of chemotherapy in, 2068
neoadjuvant chemotherapy, 2068
pathophysiology, 2067–2068
prognostic factors, 2068–2069
staging system, 2068
treatment overview, 2068
OTC (*See* Over-the-counter (OTC) medicines)
Ovarian cancer
and postmenopausal hormone therapy, 1065*t*
sites of metastases, 2019*t*
Ovarian hyperstimulation syndrome (OHSS), 996–997
Ovarian stimulation, 991–992, 991*t*, 994–996
Over-the-counter (OTC) medicines, 3, 215
antacid, 505
Overt Hepatic Encephalopathy (OHE), 584
Overweight, definition of, 793
Ovulation induction (OI), 991–992, 991*t*
Ovulatory dysfunction, 988
in polycystic ovary syndrome, 1041
Oxygen
for AMI, 257
for COPD, 443
myocardial, 217, 218*f*
saturation, 405
Oxygen consumption (VO2)
definition of, 367
normal values of, 369*t*
Oxygen delivery (DO2)
definition of, 367
normal values of, 369*t*
Ozone, 882, 884

P

PA (*See* Pulmonary artery (PA) catheter)
PAC (*See* Perennial allergic conjunctivitis (PAC); Premature atrial contraction (PAC))
Pacemaker cells, 326
PAD (*See* Peripheral arterial disease (PAD))

PAE (*See* Post-antibiotic effect (PAE))
PAF (*See* Paroxysmal atrial fibrillation (PAF))
PAHs (*See* Polycyclic aromatic hydrocarbons (PAHs))
Pain (*See also specific pains*)
abdominal pain, clinical relevance of, 1233–1234, 1234*t*
assessment of, 1210–1211, 1212*f*, 1212*t*
cognitive behavioral therapies, 1236, 1236*t*
definition of, 1208
description of, 1208
diagnosis and clinical presentation of, 1210
factors affecting, 1208*f*
fibromyalgia, 1231–1233
functional pain syndromes, 1231–1236
in ICU, 1243–1247, 1243*t*
low back, 1221–1227
multimodal management, 1217–1221
neuropathic pain, 1227–1231
analgesic drug-drug interactions, 1231
central, 1227
modifying regimen, 1231
opioid therapy, 1235*t*
addiction, risk of, 1234–1235, 1234*t*
chronic, assessment of, 1235
discontinuing, 1235–1236
pathophysiology, 1208–1210
pathways of, 1209*f*
patient evaluation, 1211*t*
perioperative management, 1212–1217
postherpetic neuralgia
treatment, 1230–1231
prevalence of chronic postsurgical pain, 1213*t*
psychological comorbidity and opioid risk management, 1233
synaptic activity at dorsal horn, 1209, 1209*f*
treatment, overview of, 1211
Palliative care, 86–87
symptom management in, 91–96
Palliative Performance Scale (PPS), 89, 90*t*
Palliative sedation, 95–96
Pancreatic involvement, in cystic fibrosis, 473
Pancreatitis
and antimycotic, 1685
and candidemia, 1682
with denosumab, 2350
pentamidine isethionate and, 1660*t*
PN and, 844

and SIRS, 2263
with VPA, 1910
Panic disorder
affective disorders, 1815
alcohol/substance use disorders, 1817
anxiety disorders, 1815
assessment of, 1818
clinical course of, 1815–1816
clinical presentation of, 1817
diagnosis of, 1815
epidemiology of, 1815–1816
etiology, 1816
goals of therapy, 1818
mitral valve prolapse and, 1817
nocturnal, 1815
and OCD, 1817
pathophysiology, 1816
patient counseling, 1818
personality disorders, 1815
physical manifestations of panic attacks, 1815
and psychiatric comorbidity, 1815
symptoms of, 1815*t*
and traumatic stressor, 1817
treatment, 1816–1817
CBT and, 1816
duration of, 1818–1819
nonpharmacologic, 1817
selection of, 1818
triggers of, 1817
Pap smear, 1051
Paracentesis-induced circulatory dysfunction (PICD), 577
Paradoxical sleep, 1832–1833
Parasitic infections
amebiasis, 1770–1775
cestodiasis, 1777–1779
enterobiasis, 1777–1779
giardiasis, 1775–1776
malaria, 1762–1770
pediculosis, 1779–1781
scabies, 1781
Parathyroidectomy, 653–654
Parenteral nutrition-associated liver disease (PNALD), 2210–2211
Parenteral nutrition (PN)
for adults, 833–850
advantages and disadvantages of, 842*t*

chronic, 847–850
diabetes and, 844
EFAD and, 839
electrolytes and, 845*t*
and elevations in liver enzymes, 850
formulations for, 834
  amino acids in, 835–836, 837*t*
  caloric density of nutrients in, 837*t*
  carbohydrate in, 834
  components of, 834–837, 835–837*t*
  cycling of, 849
  lipids in, 834–835
  medications addition to, 849
  microbial growth in, 842
  micronutrients in, 837
  total nutrient admixture in, 834
hyperglycemia and, 839, 844, 845
hypokalemia and, 845–846
hypomagnesemia and, 846
hypophosphatemia and, 846
for infants, 2206–2207, 2210–2211
  calcium content, 2206
  with chronic renal, 2206–2207
  fat emulsion complications, 2207–2208
  with GI anomalies, 2206
  goals of, 2207
  with hepatic disease, 2206–2207
  and liver diseases, 2210–2211
  with respiratory distress, 2206
  for VLBW, 2206
metabolic alkalosis and, 846–847
mixed-fuel system and, 839
monitoring parameters for, 843*t*
obesity and, 843
pancreatitis and, 844
patient assessment
  moderate stress, 839–850, 842*t*, 843*t*, 845*t*
  population-based formulation, 837–839
phlebitis and, 838
short bowel syndrome and, 847
therapy, 834
trace elements and, 845, 845*t*
venous access sites for, 834
  central, 834
  peripheral, 834

vitamins and, 845, 845*t*
weight loss and, 840
Parietal cell, 502*f*, 505
Parity, 1000
Parkinsonism, 1870
Parkinson disease (PD)
and anxiety disorders, 1806*t*
classic features of, 1284
clinical presentation of, 1283–1284, 1307*t*
diagnosis of, 1284
early, treatment of, 1285–1295, 1288*f*
essential tremor and, 1309*t*
etiology of, 1283
introduction of, 1283
medications used for, 1286–1288*t*
motor complications, 1296–1297
nonmotor symptoms of, 1304–1306
autonomic dysfunction, 1306
dementia, 1305
depression/anxiety, 1305–1306
falls, 1306
psychosis, 1306
sleep disorders, 1306
pathophysiology of, 1283
progression of, 1295–1302
staging of, 1284, 1285*t*
surgical therapies for, 1302
treatment algorithm for management motor complications in, 1299*f*
treatment of, 1284–1285
Paroxysmal atrial fibrillation (PAF), 330
Paroxysmal supraventricular tachycardia (PSVT), 328, 337
arrhythmogenesis and reentry, 338
clinical presentation of, 337–338
treatment of, 338–339
PASI (*See* Psoriasis Area and Severity Index (PASI))
Patent ductus arteriosus (PDA), 2226
changes at birth, 2236
circulatory structures, 2235, 2235*f*
clinical presentation of, 2236–2237
closure
of ductus arteriosus, 2236
of foramen ovale, 2236
and pulmonary vasoconstriction, 2235
recurrence of, 2238
treatment, 2237–2238

indomethacin therapy, 2237–2238
NSAID, 2237–2238
Patient-directed monitoring/testing, 38
Patient Health Questionnaire (PHQ-9), 1889
Patient history
medical history, 4–5
medication history, 5–6
social history, 6
Patient information, sources of, 2–4, 3*t*
Patient interview, 4
Patient monitoring, 766
Patient therapy, approach to and assessment of, 6–7
assessment, 8–9
patient education, 9
plan, 9
problem list, 7, 8*t*
subjective and objective data, 7–8
***Pauci-immune*, 670**
PBPCs (*See* Peripheral blood progenitor cells (PBPCs))
PCI (*See* Percutaneous coronary intervention (PCI))
PCI-Clopidogrel as Adjunctive Reperfusion Therapy (PCI-CLARITY), 265
PCOS (*See* Polycystic ovary syndrome (PCOS))
PCP (*See Pneumocystis jiroveci*)
PCT (*See* Procalcitonin (PCT))
PCWP (*See* Pulmonary capillary wedge pressure (PCWP))
P-450 (CYP450) isoenzymes, 507
PD (*See* Parkinson disease (PD))
PE (*See* Pulmonary embolism (PE))
PEA (*See* Pulseless electrical activity (PEA))
Peak expiratory flow (PEF), 400
green zone, 422
measurement of, 403
red zone, 422
yellow zone, 422
Peak inspiratory flow (PIF), 413
Pediatric depression, 1902
Pediatric malignancies
acute lymphoblastic leukemia, 2071–2078
and age factor, 2062
children and radiation-related toxicity, 2062
Ewing sarcomas, 2067
genetics associated, 2062
late effects, 2062
neuroblastoma, 2062–2065, 2064–2066*t*
non-Hodgkin lymphoma, 2078–2081

osteosarcoma, 2067–2069
pediatric multi-institutional research groups, 2062
rhabdomyosarcoma, 2069–2071
risk of a health problems, 2062
role of carcinogens, 2062
of small round cells, 2070
Wilms tumor, 2065–2067, 2066*t*
Pediatric Rule and the Research Equity Act of 2003, 2195
Pediculosis (lice infections), 1779–1781
epidemiology, 1779
life cycle of lice, 1779, 1779*f*
prevalence, 1779
signs and symptoms, 1779–1780
treatment, 1780–1781, 1780*t*
PEF (*See* Peak expiratory flow (PEF))
PEJ (*See* Percutaneous endoscopic jejunostomy (PEJ))
Pelvic inflammatory disease (PID), 1567–1568
clinical sequelae in, 1568
diagnosis and treatment of, 1569*t*
etiology of, 1567
gonococcal infection and, 1567–1568
incidence of, 1568
risk factors for, 1567
signs and symptoms of, 1568
Penicillin
induced AIN, 674–675
induced neurotoxicity, 706
Penicillin-binding proteins (PBPs), 50
Penile vasocongestion, 2322
Pepsin, 509
Peptic ulcer bleeding
clinical assessment and diagnosis, 534
epidemiology, 533–534
pathophysiology, 534
treatment, 534–535
Peptic ulcer disease (PUD)
clinical assessment and diagnosis, 513–515, 514*t*
clinical course and prognosis, 515
clinical presentation, 513
epidemiology, 511
etiology and risk factors, 511–512
Helicobacter pylori-related, 518–521
patients with penicillin allergies, 520
secondary or rescue therapy for, 520–521
treatment of, 518–519

NSAID induced ulcers, 512, 512*t*, 513, 513*t*, 521–524
cyclooxygenase-2 inhibitors and cardiovascular toxicity, 522–523
strategies to reduce risk of, 522
stratification of future risk for, 523–524
pathophysiology, 512
patient education, 519–520
treatment, 515–518, 516*t*, 517*f*
Perception, 1210
Percussion and postural drainage (P&PD), 478
Percutaneous coronary intervention (PCI), 221, 235–238, 241, 381
advantages of, 258
disadvantages of, 258
Percutaneous endoscopic jejunostomy (PEJ), 808
Percutaneous radiologic gastrostomy (PRG), 808
Perennial allergic conjunctivitis (PAC), 459
Perimenopause
definition of, 1061
pathophysiology of, 1061–1062, 1062*f*
Periodic limb movements of sleep (PLMS), 1307
Perioperative and postoperative antibacterial therapy, 773
Perioperative pain management, 1212–1217
Periorbital edema, 1097
Peripheral arterial disease (PAD), 169–177
cause of, 169
cigarette smoking and, 169–170
clinical presentation of, 171–172
diabetes and, 169–170
epidemiology of, 169–170
hypertension and, 149, 169, 170
hypertriglyceridemia, 169
pathophysiology of, 170–171
treatment of, 172–177, 172*t*
antithrombotic therapy, 176
pharmacologic therapies, 174–176
therapeutic objectives of, 172–174
Peripheral blood progenitor cells (PBPCs)
mobilization and collection of autologous, 2162–2163
Peripherally inserted central catheter (PICC), 348, 834
Peripheral nervous system, 736
Peripheral parenteral nutrition (PPN), 834
Peripheral vascular disorders
peripheral arterial disease, 169–177
Raynaud phenomenon, 177–179
Peripheral venous access, 834
Peritoneal dialysis (PD), 681

access, 692
complications of
exit-site infection, 694–695
peritonitis, 695–696
prophylaxis, 694–695
treatment of, 695
weight gain, 696
continuous ambulatory, 693*f*
dialysate, 692–694
ultrafiltration, process of, 694
urea clearance, 694
Peritoneovenous shunt, 578–579
Peritonitis, 695–696
definition of, 1528
primary, 1528–1532
secondary, 1532–1536
Persistent pulmonary hypertension (PPHN), 2265
Personalized medicine
pharmacogenomics and (***See* Pharmacogenomics**)
Personal medication record (PMR), 9–10, 10*f*
Pertussis, 1408
PESI (*See* Pulmonary Embolism Severity Index (PESI) scoring systems)
Petechial skin lesions, 1440*f*, 1441
Petrolatum, 1780
P-glycoprotein (PGP), 185, 309
P-glycoprotein (P-gp), 43, 50
Pharmaceutical care, 2
Pharmacists Patient Care Process (PPCP), 2
Pharmacodynamic drug interactions, 40, 45–46, 46*t*
Pharmacogenetics
definition of, 53
familial implications of, 62–63
making case for, 63–64
Pharmacogenomics
acute toxicity implications of, 57–59
CYP2D6, peculiarities of, 61–62
definition of, 53
drug target implications of, 59
nonmetabolic implications of, 59–61
pediatri cenzyme developmental impact and, 62
pharmacodynamic implications of, 57
pharmacokinetic implications of, 55–56*t*, 55–57, 56*t*
Pharmacogenomics, medication therapy management services and, 14
Pharmacokinetic drug interactions, 40, 41–45, 43–44*f*, 45–46*t*
Pharmacokinetic implications, 55–57

Pharmacy information systems (PIS), 3
PharmD curriculum, 102
Phlebitis, 838
PHN (*See* Postherpetic neuralgia (PHN))
Phobic disorders
difference between SAD and, 1819
subtypes, 1819
Phosphate, 28
binders, 651*t*
blood chemistry reference values for, 19*t*
Phosphate-binding agents, 650
calcium-containing preparations, 650
iron-based phosphate binders, 652
lanthanum carbonate, 651–652
magnesium agents, 652
non-calcium-containing phosphate binders, 650–652
sevelamer, 650–651
Phospholipids (PL), 106–107
Phosphorus
disorders of, 625–628
homeostasis, 625–626
hyperphosphatemia, 628
hypophosphatemia, 626–628
Photoaging, 893
clinical application of, 893–894
epidemiology of, 893
etiology of, 893
Photoallergy, 885, 892–893
Photocarcinogenesis, mechanisms of, 884
Photoprotection, 885, 885*t*
Photosensitivity, 882–898
Photostability, 888
Phototherapy, 1889
Phototoxicity, 885, 892–893
Physical activity, for hypertension reduction, 146
PICC (*See* Peripherally inserted central catheter (PICC))
PICD (*See* Paracentesis-induced circulatory dysfunction (PICD))
PID (*See* Pelvic inflammatory disease (PID))
Pilocarpine iontophoresis test, 476
Piperacillin/tazobactam, 1242
PIS (*See* Pharmacy information systems (PIS))
***Pityrosporum orbiculare*, 1674**
PL (*See* Phospholipids (PL))
Placental-fetal compartment effect, 1002–1003, 1002*f*
Plasma expanders, 578

Plasma osmolality, 603–604
Plasmapheresis, 670
Platelet adhesion, 181
vonWillebrand factor in, 181
Platelet factor 4 (PF4), 192
Platelet function tests, 237*t*
Platelet Inhibition and Patient Outcomes (PLATO), 265
PLATO (*See* Platelet Inhibition and Patient Outcomes (PLATO))
Pleiotropic drug resistance, 2023
PLMS (*See* Periodic limb movements of sleep (PLMS))
PM (*See* Polymyositis (PM))
PMDD (*See* Premenstrual dysphoric disorder (PMDD))
PML (*See* Progressive multifocal leukoencephalopathy (PML))
PMS (*See* Premenstrual syndrome (PMS))
PNALD (*See* Parenteral nutrition-associated liver disease (PNALD))
Pneumococcal vaccines, 1411
***Pneumocystis jiroveci*, 1655**
lung infections in cancer patients by pathogens in, 1612
***Pneumocystis jiroveci* pneumonia (PCP), 773**
and allogeneic HSCT, 2182
HIV and, 1659–1662
classification, 1659
clinical presentation of, 1662
diagnose, 1663
natural course of, 1659
prophylaxis, 1662
treatment, 1660*t*, 1661–1662
Pneumonia, 2287–2288
causative organisms for, 1371
Pneumonia severity index (PSI), 1464
POAG (*See* Primary open-angle glaucoma (POAG))
POISINDEX, 67
Poison control centers, 67
Poisoning and Drug Overdose, 67
Poisoning, from drugs, 65–84
Poison ivy *(Rhus)* dermatitis, 862
Polyclonal antibodies, 756
Polycyclic aromatic hydrocarbons (PAHs), 1977
Polycystic ovary syndrome (PCOS), 988
and amenorrhea, 1041
and androgen production, 1041
and cardiovascular risk, 1043
clinical characteristics of, 1040–1041
complications of, 1043
and congenital adrenal hyperplasia, 1040

diagnosis of, 1039–1040
and dyslipidemia, 1043
and endometrial cancer, 1043
and endometrial hyperplasia, 1043
genetic basis for, 1041
and gonadotropin secretion, 1041
and hirsutism, 1040
and hyperandrogenemia, 1040
and hyperandrogenism, 1040
and hyperprolactinemia, 1040
and IGT, 1043
lifestyle modification for, 1041
menstrual dysfunction in, 1041
and metabolic syndrome, 1043
and obstructive sleep apnea, 1043
and oligomenorrhea, 1043
ovulatory dysfunction in, 1041
pathophysiology of, 1041–1043, 1042*f*
and risk of insulin resistance, 1041
and thyroid abnormalities, 1040
treatment
agents for insulin resistance, 1044–1045
for anovulation, 1046
COCs, 1044
diet modification, 1044
exercise, 1044
glycemic index foods, 1043
for hirsutism, 1045–1046
impact of weight loss, 1044
nonpharmacologic, 1044
for oligo-ovulation, 1046
for ovulation induction, 1046
pharmacologic, 1044–1046
weight reduction programs, 1044
Polygenic hypercholesterolemia, 110, 110*t*
Polymeric formulas, 809, 810*t*, 812
caloric density/macronutrient quantities in, 812, 812*t*
fiber in, 812–813
nutrient sources in, 812
protein in, 812–813
Polymorphism in drug metabolizing enzymes, 714
Polymyalgia rheumatica (PMR), 954–955, 955*t*
Polymyositis (PM), 957–958
Polypeptides, 780
Polypharmacy, defined, 40

Polysaccharides, 780
Polysomnography, 1832
Polyunsaturated fatty acids (PUFA), 835
POMR (*See* Problem-oriented medical record (POMR))
PONV (*See* Postoperative nausea and vomiting (PONV))
Pooled Cohort Equations, 114
Porcine skin, 897
Porcine xenografts, 897
Pork tapeworm (*See* Cestodiasis (tapeworm infection))
Porphyria, and EPT, 2341
Portal hypertension, 572–574, 573*f*, 574*t*
Child-Turcotte-Pugh classification of severity, 574*t*
clinical presentation, 574
laboratory findings, 573–574
portal venous system, schematic diagram of, 573*f*
Portal vein pressure (PVP), 579
Post-antibiotic effect (PAE), 1387
Postherpetic neuralgia (PHN), 1227, 1704 (*See also* Neuropathic pain)
treatment, 1230–1231
Postinfectious irritable bowel syndrome (PI-IBS), 1512
Post-Lyme disease syndrome, 1789
Postoperative course and delayed graft function, 760
Postoperative nausea and vomiting (PONV), 499–501, 501*t*
Postoperative pain
prevalence of chronic, 1213*t*
risk factors for increased, 1214*t*
Postpartum hemorrhage
prevention of, 1029–1030
treatment of, 1030–1031, 1030*t*
Postpartum prophylaxis, 1031
Postprandial distress syndrome, 509
Poststreptococcal glomerulonephritis (PSGN), 669–670
Post-transplantation diabetes mellitus (PTDM), 770–771
Posttransplant complications
antifungal, 773
BK polyomavirus infection, 777–778
cytomegalovirus, 774–777
donor-derived infections, 773
hepatitis B, 774
hepatitis C, 774
malignancy, 772
opportunistic infections, 773, 774*t*
perioperative and postoperative antibacterial therapy, 773
pneumocystis jiroveci pneumonia, 773
posttransplant diabetes mellitus, 770–771

posttransplant hyperlipidemia, 771
posttransplant hypertension, 771
posttransplant lymphoproliferative disorder, 772–773
posttransplant osteoporosis, 771
Posttransplant diabetes mellitus, 770–771
Posttransplant hyperlipidemia, 771
Posttransplant hypertension, 771
Posttransplant lymphoproliferative disorder, 772–773
Posttransplant lymphoproliferative disorder ((PTLD), 756
Posttransplant osteoporosis, 771
Posttraumatic hyperthermia, 2274
Posttraumatic seizures (PTS), 2274
Post-traumatic stress disorder (PTSD)
clinical assessment and goals of therapy, 1824
clinical course, 1821–1822
clinical presentation of, 1823
diagnostic criteria, 1821
epidemiology, 1821–1822
etiology, 1822
panic disorder associated with, 1817
pathophysiology, 1822
rating scales, 1824
symptoms, 1822
symptoms of, 1822*t*
treatment
antidepressants, 1822–1823
course and duration of, 1824
nonpharmacologic, 1823
SSRIs, 1822
Potassium, 22–23
blood chemistry reference values for, 18*t*
and children, 2198*t*
disorders of
hyperkalemia, 617–619
hypokalemia, 615–617
and diuretics, 2281
homeostasis, 614–615
loss due to diarrhea, 2201
maintenance doses of, 2200
normal daily intake of, 614
in oral electrolyte solutions, 2218*t*
and renal dysfunction, 2054
supplementation in hypertension, 146
and tumor lysis syndrome, 2086
in WHO formula, 2218*t*

Potassium hydroxide (KOH) stain, 1371
Powassan disease, 1798
PPHN (*See* Persistent pulmonary hypertension (PPHN))
PPIs (*See* Proton-pump inhibitors (PPIs))
PPN (*See* Peripheral parenteral nutrition (PPN))
P7056 protein kinase, 756
PPS (*See* Palliative Performance Scale (PPS))
Prealbumin, 28 (*See also* Transthyretin (prealbumin))
blood chemistry reference values for, 19*t*
Preeclampsia
antihypertensive drug therapy, 1016
mild, 1016–1018
etiology and pathogenesis of, 1016–1018
monitoring of, 1015–1016
risk factors for, 1015
severe
clinical presentation of, 1018
complications of, 1018
treatment of, 1018
Pregestational diabetes, 1010
Pregnancy
acetaminophen overdoses during, 81
anticoagulation during, 207*t*
calcium requirements, 1001
chronic hypertension, 1015, 1018–1019
and clozapine, 1883
delivery, 1000
diabetes mellitus, 1010–1015
blood glucose and glycated hemoglobin monitoring, 1012
dietary management for, 1011–1012
gestational, 1013–1015, 1014*f*
insulin therapy, 1012–1013
modified White classification of, 1010, 1010*t*
oral hypoglycemic use, 1013
preconception management, 1011
preexisting, 1010–1013
type 1 diabetes treatment, 1011–1012
type 2 diabetes treatment, 1012–1013
DKA and, 1142
eclampsia
magnesium sulfate prophylaxis, 1019–1020
treatment of, 1020
folate requirements, 1001
GDM and, 1108
and genital herpes, 1587–1588

HIV and, 1649–1650
home pregnancy tests, 1001
human immunodeficiency virus in, 1029
hyperthyroidism in, 1095–1096
intestinal amebiasis, treatment for, 1772, 1775
and iodide use, 1095
iron requirements, 1000–1001
labor
  bacterial vaginosis, 1027
  cervical ripening, 1021–1022
  chorioamnionitis, 1028–1029
  false, 1020
  group B streptococcus intrapartum prophylaxis, 1027–1028
  indications, contraindications, and requirements of, 1021
  induction of, 1020–1023
  mechanisms of term, 1020–1021
  oxytocin, 1022–1023
  preterm, 1023–1027
  preterm premature rupture of membranes, 1027
  uterine activity, 1020
medication use in, 1004–1005, 1004*t*
  critical stage of exposure, 1005, 1005*f*
  dose-response curve, 1005
  extrapolation from animal studies, 1005–1006
  genetic variability, 1006
  placental transfer of drugs, 1006
NAC therapy in, 82
nausea and vomiting in, 1006–1009
pharmacokinetic changes, 1001–1002
  absorption, 1002
  distribution, 1002
  elimination, 1002
  metabolism, 1002
  placental-fetal compartment effect, 1002–1003, 1002*f*
postpartum hemorrhage
  prevention of, 1029–1030
  treatment of, 1030–1031, 1030*t*
preconceptional care, 1000
preeclampsia
  antihypertensive drug therapy, 1016
  mild, 1016–1018
  monitoring of, 1015–1016
  risk factors for, 1015
  severe, 1018
  treatment of, 1018

Rh D alloimmunization
immunoprophylaxis, failure of, 1032
maternal-fetal Rh incompatibility, 1031
prophylaxis for first- and second-trimester events and procedures, 1032
Rho(D) immunoglobulin, 1031
rhinitis and, 456
syphilis and, 1576
TB in, 1498
trichomoniasis in, 1582
trimesters of, 1000
urinary tract infections, 1540
acute cystitis, 1009–1010
asymptomatic bacteriuria, 1009–1010
pathogenesis of, 1009
vitamins and mineral supplementation, 1000–1001
VVC in, 1579
warfarin interactions, 203*t*
Preload, defined, 372 (*See also* Shock)
Premature atrial contraction (PAC), 328
Premature ejaculation, 2322
Premature ventricular contraction (PVC), 311, 328, 341*f*, 342–343
Premenstrual dysphoric disorder (PMDD), 977
COC formulation for, 1057
diagnosis of, 1055–1056
pathophysiology, 1056
selective serotonin reuptake inhibitors for, 1057, 1060*t*
symptoms of, 1055–1056
treatment, 1057–1060
Premenstrual syndrome (PMS), 977
chasteberry, 1056
diagnosis of, 1055–1056
mind-body approaches for, 1056
pathophysiology, 1056
symptoms of, 1055–1056
treatment, 1056–1057
Prerenal azotemia, 577, 663*t*, 664
PRESERVE (*See* Prevention of Serious Adverse Events following Angiography (PRESERVE))
Prevention of Serious Adverse Events following Angiography (PRESERVE), 673
PRG (*See* Percutaneous radiologic gastrostomy (PRG))
Primary headache disorders, 1269
cluster headache, 1269
abortive therapy for, 1279
pathophysiology of, 1278

prophylactic therapy for, 1280
signs and symptoms of, 1278–1279
migraine, 1269
assessment tools, 1271
intractable, 1274
medication overuse, 1278
pathophysiology of, 1270–1271
prophylactic therapy for, 1275
without aura, 1271–1273
tension-type headache, 1269
general management and abortive therapy for, 1280
interprofessional management of, 1280
pathophysiology of, 1280
prophylactic therapy for, 1280
Primary open-angle glaucoma (POAG), 1186–1195
Primary peritonitis, 1528–1532
CAPD-associated, 1531–1532
in cirrhotic patients, 1529–1531
fungal CAPD-associated, 1532
Primary prophylaxis, 582–583
Prinzmetal variant angina, 238
Probiotics, 515
Problem-oriented medical record (POMR), 6–7, 7*t*
Procalcitonin (PCT), 32, 1367, 1464
blood chemistry reference values for, 20*t*
Progesterone, 997, 997*t*
Progressive multifocal leukoencephalopathy (PML), 1262
Proinsulin, 1115
Prophylactic co-therapy, 515
Prophylaxis, 694–695
for cluster headache, 1280
for migraine headache, 1275
for tension-type headache, 1280
***Propionibacterium acnes*, 865**
Proprotein convertase subtilisin/kexin type 9 (PCSK9), 111
Prostate cancer
androgen deprivation therapy, 2147*t*, 2146–2148
castration-resistant, 2149–2150
adverse effects of, 2151
androgen deprivation therapy, 2154–2155
metastatic disease, 2149–2150
radiation effects, 2155–2156
clinical presentation, 2140
diagnosis, 2140
Gleason score, 2144*f*, 2144

incidence, 2139
life expectancy, 2143
overview of, 2139
pathophysiology, 2139–2140
prevention, 2157
radiation therapy, 2146–2148
risk factors
age, 2141
ethnicity, 2141, 2142*f*
family history, 2141
genetic syndromes, 2141
screening, 2142
sites of metastases, 2019*t*
specific antigen, 2143–2144
staging, 2144
survivorship, 2157
treatment, 2140–2141
definitive local therapy, 2145–2148
locally advanced disease, 2140
observation *versus* active surveillance, 2145
progression, 2148–2149
recurrence, 2148–2149
surgery, 2145–2146
Prostate-specific antigen (PSA), 20*t*, 32, 2319
Prosthetic valve endocarditis (PVE), 1445–1447
antimicrobial therapy for, 1445–1447
etiology of, 1445
prophylaxis for, 1445
Proteases, 475
Protein-binding alterations, 1242
Proteins, 780
diabetes and, 1112
in enteral formulas, 812–813
laboratory tests for, 19*t*
Proteinuria, 37, 637, 655, 659
Prothrombin ratio (PTR), 36
Prothrombin time (PT), 36, 188–189, 573
Proton pump, 505
Proton-pump inhibitor, 531
Proton-pump inhibitors (PPIs), 238, 507–509
Pruritus, 861
PSA (*See* Prostate-specific antigen (PSA))
PsA (*See* Psoriatic arthritis (PsA))
Pseudoaddiction, 1947
Pseudomenopause, 1051

***Pseudomonas aeruginosa*, 436, 475**
endocarditis by, 1454–1455
eradication of, 481
PSGN (*See* Poststreptococcal glomerulonephritis (PSGN))
PSI (*See* Pneumonia severity index (PSI))
Psoralen plus ultraviolet A (PUVA) light therapy, 877
Psoriasis, 871
biologic systemic therapy for, 879–881
categorization of, 873
classification of, 873
clinical presentation of, 871–872
definition of, 871
drug-induced, 872–873, 872*t*
epidemiology of, 871
erythrodermic, 872
flexural/inverse, 872
Guttate, 872
mild-to-moderate, 873–874*t*, 873–876
moderate-to severe, 876–881, 880*t*
nonbiologic systemic therapy for, 877–878
nonpharmacologic therapy for, 874
pathogenesis of, 871
phototherapy for, 876–878
prevalence of, 871
primary and secondary treatment failure, 880–881
prognosis for, 871
pustular, 872
topical corticosteroids for, 874–875
treatment of, 873–874*t*, 873–881, 880*t*
ultraviolet B treatment for, 876–877
Psoriasis Area and Severity Index (PASI), 873
Psoriatic arthritis (PsA), 872, 876, 879
PSVT (*See* Paroxysmal supraventricular tachycardia (PSVT))
Psychiatric dysfunction and MS, 1257–1258
Psychological addiction, 1946
Psychosis, 1883, 1942–1943
Parkinson disease and, 1306
Psychosocial issues of infertility, 998, 998*t*
Psychotherapy, 1888
Psychotic depression, 1889
PT (*See* Prothrombin time (PT))
PTDM (*See* Post-transplantation diabetes mellitus (PTDM))
PTSD (*See* Post-traumatic stress disorder (PTSD))
PTU-induced hepatitis, 1094
PUD (*See* Peptic ulcer disease (PUD))

PUFA (*See* Polyunsaturated fatty acids (PUFA))
Pulmonary arterial hypertension, 276
Pulmonary artery (PA) catheter, 372
Pulmonary capillary wedge pressure (PCWP), 372
normal values of, 369*t*
Pulmonary disorders, methotrexate-related, 921–922
Pulmonary edema, from salicylate toxicity, 72
Pulmonary embolism (PE), 180, 197–206
cancer and, 198*t*
clinical presentation of, 197–198
diagnosis of, 198
hemoptysis and, 197
symptoms of, 197–198
treatment of, 198–206
V/Q scans, 198
Pulmonary Embolism Severity Index (PESI) scoring systems, 198*t*
Pulmonary exacerbations, 474
Pulmonary function
drug poisoning and, 77
tests, for asthma, 402–403
Pulmonary interventions, 478
Pulmonary involvement
airway obstruction, infection, and inflammation, 474–475
cystic fibrosis, 474–475
microbiology
Aspergillus fumigatus, 475
Burkholderia cepacia, 475
methicillin-resistant Staphylococcus aureus, 475
Pseudomonas aeruginosa, 475
Pulmonary vein, reentrant circuit in, 328*f*
Pulmozyme Early Intervention Trial, 480
Pulseless electrical activity (PEA), 348, 349–350
Pulsus paradoxus, defined, 406
Purple toe syndrome, from warfarin, 201–202
Pustular psoriasis, 872 (*See also* Psoriasis)
PVC (*See* Premature ventricular contraction (PVC))
PVE (*See* Prosthetic valve endocarditis (PVE))
PVP (*See* Portal vein pressure (PVP))
Pyelonephritis, 666, 1453, 1546*t*

Q

QIDS (*See* Quick Inventory of Depressive Symptoms (QIDS))
QPCR (*See* Quantitative polymerase chain reaction (QPCR))
QRS complex, 318

QTc interval, 328
Qualitative screening, drug poisoning and, 78–79
QuantiFERON-TB Gold test, 1482
Quantitative polymerase chain reaction (QPCR), 2088
Quantitative testing, drug poisoning and, 79
Quick Inventory of Depressive Symptoms (QIDS), 1889

R

RA (*See* Rheumatoid arthritis (RA))
RAAS (*See* Renin-angiotensin-aldosterone system (RAAS))
Radiation-induced nausea and vomiting (RINV), 498–499, 500*t*
Radiation therapy, prostate cancer, 2146
Radical prostatectomy, 2145–2146
Radiologic-isolated syndrome, 1254
Radiologic testing, 529
Radionuclide left ventriculography, usage of, 290
RAFT (*See* Resynchronization/Defi brillation for Ambulatory Heart Failure Trial (RAFT))
RALES (*See* Randomized Aldactone Evaluation Study (RALES))
Randomized Aldactone Evaluation Study (RALES), 267
Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (*See* REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial)
Ranolazine Open Label Experience (ROLE), 233
Rapid Early Action for Coronary Treatment (REACT), 262
Rapid eye movement (REM) sleep, 1832–1833
Rapidly progressive glomerulonephritis (RPGN), 655, 670
Rapid urease test, for *Helicobacter pylori*, 514*t*, 515
RASS (*See* Richmond Agitation-Sedation Scale (RASS))
Raynaud phenomenon, 177–179, 953
cause of, 177
clinical presentation of, 178
diagnosis of, 177
epidemiology of, 177
pathophysiology of, 177
primary, 177–179
secondary, 177–179
serotonin and, 177
treatment of, 178–179
calcium-channel blockers, 178
nonpharmacologic management, 178
RBBB (*See* Right bundle branch block (RBBB))
RBCs (*See* Red blood cells (RBCs))
RBF (*See* Renal blood flow (RBF))

RCA (*See* Right coronary artery (RCA))
RDS (*See* Respiratory distress syndrome (RDS))
REACT (*See* Rapid Early Action for Coronary Treatment (REACT))
Reactive arthritis, 955–957
bacterial pathogens associated with development of, 956*t*
clinical signs of, 956*t*
definition of, 955
Readiness for Interprofessional Learning Scale (RIPLS), 103
Rebleeding, 580
Rectal drug absorption, 2188
Rectal prolapse, 473
Red blood cells (RBCs), 32–33, 171
indices, 33
Red man syndrome, 726
Red neck syndrome, 726
Red zone, of PEF, 422
Reentry
conduction and, 328
with PSVT, 338
Refeeding syndrome, 840
Refractory CMV retinitis, 1666
Rehabilitation, 1362–1363
Relapsing CMV retinitis, 1666
Relapsing fever, 1790–1792
characteristics, 1791
disease characterization, 1791–1792
geographic distribution of, 1791
spirochetal behavior, 1791
spirochete, role of, 1791
tick species responsible, 1791
treatment, 1791
REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial, 287
REMS (*See* Risk Evaluation and Management Strategy (REMS); Risk Evaluation Mitigation Strategy (REMS))
REM sleep (*See* Rapid eye movement (REM) sleep)
Renagel in New Dialysis (RIND) trial, 651
Renal blood flow (RBF), 284
factors affecting, 302*f*
Renal Fanconi syndrome, 2071
Renal function
assessment, 1242
in ICU, 1239
and renin-angiotensin aldosterone system, 279
Renal hemodynamics, 639*f*

Renal insufficiency-related anemia, 2011
Renal tubular acidosis (RTA), 594, 1685
Renin-angiotensin-aldosterone system (RAAS), 279, 575, 666
Reperfusion
determination of, 262
of occluded artery, 381
Repetitive transcranial magnetic stimulation (rTMS), 1889
Repolarization, TdP and, 328
Residual volume (RV), 402
Respiratory acidosis, 598–600, 599*t*
evaluation of, 599–600
treatment of, 599
Respiratory alkalosis, 600–601
evaluation of, 600
treatment of, 601
Respiratory distress syndrome (RDS)
cause of, 2225
characteristics, 2225
clinical presentation of, 2226–2227
incidence of, 2225
treatment, 2227–2229
Respiratory reaction, aspirin-induced, 727
Respiratory tract infections, 1459–1475
acute bronchitis, 1459–1460
AECOPD, 1460–1462
community-acquired pneumonia, 1463–1469
hospital-acquired pneumonia, 1469–1475
vaccination and, 1462
ventilator-associated pneumonia, 1469–1475
Restless legs syndrome (RLS), 1832
clinical features of, 1307*t*
clinical presentation of, 1306–1307
treatment of, 1307–1308
Restorative sleep, 1832
Restrictive *vs.* obstructive airway disease, 403–404
Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT), 321
Retarded ejaculation, 2322
Retching, definition of, 488
Reticulocytes, 33
Retinol-binding protein, 786
Retinopathy
hypertension and, 149
of prematurity (ROP), 2226
risk of, 920–921

Retrograde ejaculation, 2322
Reversible inhibition mechanisms, 43
Rhabdomyolysis, 121
Rhabdomyosarcoma, 2069–2071
clinical presentation, 2070
description, 2069
diagnosis, 2070
epidemiology, 2069
pathophysiology, 2069
prognostic factors, 2070–2071
treatment, 2070–2071
Rh D alloimmunization
immunoprophylaxis, failure of, 1032
maternal-fetal Rh incompatibility, 1031
prophylaxis for first- and second-trimester events and procedures, 1032
Rho(D) immunoglobulin, 1031
Rheumatoid arthritis (RA), 909–937
characteristic finger deformities in, 913*f*
clinical presentation, diagnosis, and disease course, 912–913
etiology, 910
extra-articular manifestations and complications, 913–914
frequency of involvement of different joint sites in, 912*f*
juvenile idiopathic arthritis (JIA), 930–934, 934–937*t*
overview of joint changes in, 910*f*
pathogenesis of, 911*f*
pathophysiology, 910
treatment, 914–917
biologic DMARDs, 915–916, 923
clinical use of DMARDs, 916–917
conventional synthetic DMARDs, 915
corticosteroids, 916, 929
NSAIDs, 914–915, 917–920
quantifying response to drug therapy, 917
targeted synthetic DMARDs, 915
traditional DMARDs, 920–929, 926*t*
ulnar deviation and metacarpophalangeal synovitis, 912*f*
Rhinitis, 446–470
acute, 446
allergen and irritant avoidance, 451, 457–458
allergic, 447, 448
alternative therapies for, 465
anatomy of, 448
assessment of, 449–451, 450*f*
asthma and, 448
cause of, 446–448, 447*f*

chronic, 447
classification of, 446–448, 447*f*
clinical presentation of, 449–451, 450*f*
defined, 446
diagnosis of, 451, 456–457
early response, 449
epidemiology and impact of, 448
hypothyroidism and, 447*f*
idiopathic, 468–470
laboratory tests for, 451
late response, 449
medicamentosa, 467–468, 469*t*
mixed allergic-nonallergic, 470
nondrug therapies for, 456
oral and intranasal agents for, 461*t*
pathophysiology of, 448–449, 449*f*
patient education for, 451
pharmacotherapy for, 451
physical examination of, 451
physiology of, 448
pregnancy and, 456
risk factors, 449
sensitization, 448
signs, and symptoms of, 449–450
treatment, overview of, 451–456, 452*f*, 453*f*, 454–456*f*
Rhus (*See* Poison ivy (Rhus) dermatitis)
Richmond Agitation-Sedation Scale (RASS), 1245
Right bundle branch block (RBBB), 340
Right coronary artery (RCA), 218*f*
Right ventricular dysfunction, 289–290
RIND (*See* Renagel in New Dialysis (RIND) trial)
RINV (*See* Radiation-induced nausea and vomiting (RINV))
RIPLS (*See* Readiness for Interprofessional Learning Scale (RIPLS))
Risk Evaluation and Management Strategy (REMS), 1156
Risk Evaluation Mitigation Strategy (REMS), 870
RLS (*See* Restless legs syndrome (RLS))
RMSF (*See* Rocky Mountain spotted fever (RMSF))
Robust inflammatory response, 475
Rocky Mountain spotted fever (RMSF), 1793–1795
ROLE (*See* Ranolazine Open Label Experience (ROLE))
Rotavirus, 1413
and diarrhea, 1505
RPGN (*See* Rapidly progressive glomerulonephritis (RPGN))
RTA (*See* Renal tubular acidosis (RTA))
rTMS (*See* Repetitive transcranial magnetic stimulation (rTMS))

Rule of nines, burn injuries, 895
RV (*See* Residual volume (RV))

S

SAC (*See* Seasonal allergic conjunctivitis (SAC))
Saccharides (*See* Carbohydrates)
***Saccharomyces*, 2219**
Sacroiliitis, 931
Safe Practices for Parenteral Nutrition Formulations, 834
Salicylism, 70–73
***Salmonella* infection, 1508–1509**
extraintestinal, 1509
nontyphoidal, 1508–1509
***Sarcoptes scabiei var. hominis*, 1781**
SARS (*See* Severe acute respiratory distress syndrome (SARS))
SARS coronavirus (SARS-CoV), 1713–1718
SAS (*See* Sedation-Agitation Scale (SAS))
SBP (*See* Spontaneous bacterial peritonitis (SBP); Systolic blood pressure (SBP))
SBS (*See* Short bowel syndrome (SBS))
Scabies, 1781
SCC (*See* Squamous cell carcinoma (SCC))
SCCM (*See* Society of Critical Care Medicine (SCCM))
SCD (*See* Sudden cardiac death (SCD))
Schizophrenia, 1859
antidepressants, 1881
antipsychotic selection, 1859–1878
anxiety in, 1854
assessment, 1856
clinical presentation of, 1852–1854
course of, 1854
depression in, 1854
diagnosis and differential diagnosis, 1852, 1852*t*
DSM-5 criteria for, 1852*t*
early-onset, 1883
economic burden, 1851
epidemiology, 1850
genetic and environmental risk factors, 1851
historical concept, 1852
inadequate response, 1878–1880
nonantipsychotic agents, 1881
pathophysiology, 1851–1852
pharmacotherapy interventions, 1856–1859
prognosis, 1854

psychosis, 1852, 1883
serum concentration monitor, 1880–1881
symptoms, 1853–1854
treatment, 1881
CBT for, 1855
goals of, 1855
group therapy, 1856
nonpharmacologic interventions, 1855–1856
pharmacologic interventions, 1856
psychosocial, 1855
SCIP (*See* Surgical Care Improvement Project (SCIP))
SCIT (*See* Subcutaneous immunotherapy (SCIT))
SCr (*See* Serum creatinine (SCr))
Screener and Opioid Assessment of Patients with Pain-Revised (SOAPP-R), 1224, 1235
SDAI (*See* Simplified Disease Activity Index (SDAI))
Seasonal allergic conjunctivitis (SAC), 459
Secondary headache, 1269–1270
acute, 1269–1270
subacute, 1270
Secondary hypertension, 143–144*t*
Secondary peritonitis, 1532–1536
diagnosis of, 1532–1534
epidemiology of, 1532
pathogenesis of, 1532
Secondary prophylaxis, 583–584
Second Assessment of Safety and Efficacy of a New Thrombolytic (ASSENT-2), 260
Second-degree atrioventricular block, 340*f*
Secondhand smoke exposure, 1977
Second International Study of Infarct Survival (ISIS-2), 262
Sedation-Agitation Scale (SAS), 1245
Sedative-hypnotics, 1952–1953
Seizures, 80–81, 1312–1343, 2248–2251
classification of, 1313, 1314*t*
definition of, 1313
diagnosis of, 1313–1314
in elderly, 1332
neonatal, 2248–2251
from salicylate toxicity, 72
treatment of, 1314–1319
Self-monitored blood glucose (SMBG), 1114, 1124*t*
concentrations, interpreting, 1124*t*
factors affecting, 1128*t*
testing, 1124*t*

for type 1 diabetes, 1127–1128
for type 2 diabetes, 1145
Semisynthetic dressings, 897
Sepsis, 1366
ARDS and, 1368
cellular changes in, 1367
CNS changes in, 1368
coagulation changes in, 1368
definition of, 2263*t*
DIC and, 1368
hemodynamic changes in, 1366–1367
neurologic changes in, 1368
pathogenesis of, 1367*f*
respiratory changes in, 1367–1368
syndrome, 388
clinical features, 389
Septic arthritis, 1598–1600
Septic shock
characteristics of, 389
clinical and hemodynamic features, 390
definition of, 263*t*
distributive shock, 388–395
therapeutic approach, 390–395
Sequential organ failure assessment (SOFA), 388
Sequential Organ Failure Assessment (SOFA) score, 388, 389*t*
Serologic tests, for syphilis, 1574
Serotonin
and obesity, 796
and Raynaud phenomenon, 177
syndrome, 1897
Serotonin-norepinephrine reuptake inhibitor (SNRI), 2048
Serotonin reuptake inhibitors
for PMDD, 1057, 1060*t*
for PMS, 1060*t*
Serum and urinary tests, 665
Serum creatinine (SCr), 666
Serum ferritin, 644
Serum iron concentration, iron toxicity and, 74
Serum sickness, 721–722
Severe acute respiratory distress syndrome (SARS), 1713–1718
Severe sepsis, definition of, 2263*t*
Sexual dysfunction
erectile dysfunction, 2323–2330
male, 2322–2323
and MS, 1256

Sexual intercourse, and UTI, 1540, 1555–1556
Sexually transmitted diseases (STDs), 1562–1589
chancroid, 1577
genital herpes, 1583–1588
genital warts, 1588–1589
gonorrhea, 1562–1567
lymphogranuloma venereum, 1572
nongonococcal urethritis, 1571–1572
pelvic inflammatory disease, 1567–1568
prevention of, 1567
syphilis, 1572–1577
vaccines for, 1589
vaginitis, 1577–1583
SHARP (*See* Study of Heart and Renal Protection (SHARP))
Shiga toxin-producing E. coli (STEC), 1517
***Shigella*, 2219**
Shigella dysenteriae, dysentery by, 1511–1513
Shock, 366–395 (*See also* Cardiogenic shock; Hypovolemic shock)
ABG and, 371
ATP and, 367
causes of, 366–367
classification of, 368*t*
clinical presentation of, 367–370
defined, 366
diagnosis of, 367–370
distributive, 388–395
etiologic classification of, 372, 373*t*
hemodynamic monitoring for, 369–370*t*, 370–372
pathophysiology of, 367
septic, 388–390
treatment of, 370
Short-acting inhaled b_2-agonists (SABAs), 407
Short bowel syndrome (SBS), 847
Shortness of breath (SOB), 220
Shrinking lung syndrome, 737
SHyper (*See* Subclinical hyperthyroidism (SHyper))
SI (*See* International System of Units (SI))
SIA (*See* Sunscreen Innovation Act (SIA))
SIADH (*See* Syndrome of inappropriate antidiuretic hormone secretion (SIADH))
Sickle cell anemia
clinical course, 2007
infections, 2007
laboratory evaluation, 2007
management, 2007

pathogenesis, 2006–2007
treatment
for frequent vaso-occlusive crises, 2008–2009
iron chelation therapy, 2009–2010
vaso-occlusive complications, 2007–2010
Sieving coefficient (SC) of drug, 677
Simple partial seizures, 1313
Simplified Disease Activity Index (SDAI), 917
Single-nucleotide polymorphism (SNP), 54, 54*f*
Sinus involvement, in cystic fibrosis, 474
Sinus rhythm
maintenance of, 334
with second-degree AV block, 340*f*
SIRS (*See* Systemic inflammatory response syndrome (SIRS))
SJS (*See* Stevens-Johnson syndrome (SJS))
Skeletal events, prevention of, 2108
Skeletal muscle cramps, 690
Skin, 851–864
aerosols for, 853
allergic contact dermatitis, 862, 863
anatomy of, 851–852, 852*f*
assessment of, factors for, 853–855
age, 853, 855
history, 853
location, 853, 855*t*
morphology, 853, 854*t*
sex, 855
symptoms, 853
baths for, 860–861
corticosteroids for, 526*t*, 528–859*t*, 855–862, 861*t*
adverse drug effects, 857–858
contraindications, 855–856
occlusion, 856–857
topical antibiotics with, 860–861
creams for, 853
delivery system, selection of, 852
drug eruptions on, 862–864
drug hypersensitivity reactions in, 725
drug poisoning and, 78
emulsions for, 852
gels for, 852–853
indications of, 855
lesions of, 854*t*
acute, 852
chronic, 852

subacute, 852
liquid emulsions for, 852
lotions for, 852
necrosis, from warfarin, 201
ointments for, 853
physiology of, 851–852, 852*f*
powders for, 852
rash, ASD and, 1337–1338
reaction to sunlight, 886*t*, 889
solutions for, 852
testing, 716–717, 717*t*
before desensitization, 731
xerosis (dry skin), 859
Skin and soft tissue infections, 1602–1605
animal bite wounds, 1607–1608
in diabetic patients, 1605–1607
necrotizing soft tissue infections, 1607
erysipelas, 1605
human bite wounds, 1608
Skin-prick testing, for allergic rhinitis, 466
SLCO1B1,* genotype-based dosing recommendations for HMG-CoA reductase inhibitors, 59*t
SLE (*See* Systemic lupus erythematosus (SLE))
Sleep, 1932–1933
drug-induced effects on neurochemicals, 1833
and melatonin, 1837
ramelteon agonist for, 1837
nonrapid eye movement, 1832
normal, 1832*f*
rapid eye movement, 1832–1833
and time-zone shift, 1836–1837
wakefulness- and sleep-promoting neurochemicals, 1833
Sleep apnea, 1846–1847
Sleep disorders
benzodiazepines for, 1839–1840
circadian rhythm, 1832–1833
classification of, 1834*t*
hypnotics for, 1841
use during pregnancy, 1846
insomnia, 1833–1846
narcolepsy, 1847–1849
neurochemistry of sleep-wake cycle, 1833
overview of, 1832
Parkinson disease and, 1306
pharmacologic treatment, 1834

potential causes and contributing factors for, 1837*t*, 1841*t*
pregnancy and lactation, 1846
sleep apnea, 1846–1847
sleep cycles, 1832–1833, 1832*f*
Sleep-wake cycle, neurochemistry of, 1833
SLIT (*See* Sublingual immunotherapy (SLIT))
Slow continuous ultrafiltration, 677
Small cell lung cancer (SCLC), 2118–2121
clinical presentation of, 2119
diagnosis of, 2119
epidemiology of, 2118–2119
pathophysiology of, 2119
treatment, 2120–2121
chemotherapy, 2121
radiotherapy, 2120
Small dense LDL, 111
SMBG (*See* Self-monitored blood glucose (SMBG))
Smoking (*See also* Tobacco use and dependence)
and COPD, 427, 433, 437
CV disease and, 151
diabetes and, 1166
and IC pain, 169–170, 172–173, 172*t*
and lung cancer, 1977, 1987
multiple sclerosis, 1252*t*
and peripheral arterial disease, 169–170
and weight gain, 1980*t*, 1986
SNIIRAM (*See* Systeme National d'Information Inter-Regimes Assurance Maladie (SNIIRAM))
SNP (*See* Single-nucleotide polymorphism (SNP))
SO (*See* Superovulation (SO))
SOB (*See* Shortness of breath (SOB))
Social anxiety disorder (SAD)
and CBT, 1819–1821
classification of, 1819
clinical presentation of, 1821–1822
clinical significance, 1819
comorbidity in, 1819
course of, 1819
diagnosis of, 1819
difference between specific phobias and, 1819
epidemiology of, 1819
etiology of, 1819–1820
pathophysiology of, 1819–1820
treatment, 1820
Social history, 6

Socialization, 101
Society of Critical Care Medicine (SCCM), 786, 843, 2263
Sodium bicarbonate (*See* Bicarbonate (Sodium bicarbonate))
Sodium disorders, 608–614
Sodium (Na), 18, 22
for, 18*t*
and BP, 141
and children, 2198*t*
depletion of, 603–604
diabetes and, 1112
loss due to diarrhea, 2201
in oral electrolyte solutions, 2219*t*
restriction in hypertension, 145–146
and water retention, 642
in WHO formula, 2218*t*
Sodium-restricted diet, for HF patients, 284
Sodium restriction, 575
SOFA (*See* Sequential Organ Failure Assessment (SOFA) score)
Soft tissue infections, 1607
Somatization, 567
Southern tick-associated rash illness (STARI), 1792
Soybean/safflower oil emulsion, 835
SPAF (*See* Stroke Prevention in Atrial Fibrillation (SPAF))
Spasticity, defined, 1257 (*See also* Multiple sclerosis (MS))
Specific allergen immunotherapy (SIT)
for allergic rhinitis, 454
SPF (*See* Sun protection factor (SPF))
Spirometry
for asthma, 402–403, 405*f*
for COPD, 431–432, 431*f*
interpretation of outcomes of, 406*f*
Splinter hemorrhages, in nailbed, 1440*f*, 1441
Spontaneous bacterial peritonitis (SBP), 572, 575 (*See also* Primary peritonitis)
Spontaneous intracerebral hemorrhage, 1360–1362
***Sporothrix schenckii*, 1677**
Sporotrichosis, 1679
SPRINT (*See* The Systolic Blood Pressure Intervention Trial (SPRINT))
Squamous cell carcinoma (SCC)
UVR exposure and, 882, 884
SSc (*See* Systemic sclerosis (SSc))
Staphylococcal food poisoning, 1502*t*
***Staphylococcus aureus*, 390, 475, 850, 860**
endocarditis, 1447–1450
foodborne illnesses and, 1507

IE and, 1439
Staphylococcus epidermidis
meningitis, 1432–1434
prosthetic valve endocarditis, 1445–1447, 1446*t*
***Staphylococcus epidermis*, 850**
STARI (*See* Southern tick-associated rash illness (STARI))
***Status epilepticus*, 1340–1343**
definition of, 1340
pathophysiology of, 1340
refractory, 1343
treatment of, 1340–1343
STDs (*See* Sexually transmitted diseases (STDs))
Steal phenomenon, 176 (*See also* Peripheral arterial disease (PAD))
Steatorrhea, 561
Steatosis, 572
STEC (*See* Shiga toxin-producing E. coli (STEC))
STEMI (*See* ST segment elevation myocardial infarction (STEMI))
Stents, 235
Stereotactic needle aspiration, 1435
Steroid
avoidance or withdrawal, 764
Stevens-Johnson syndrome (SJS), 863, 1661
St. John's-wort, 47, 51
"Stocking-glove" neuropathy, 2048
STOP-BANG questionnaire, 1213, 1213*t*
Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial, 262
Stratum corneum, 852
STREAM (*See* Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial)
***Streptococcus*, 2219**
***Streptococcus pneumoniae*, 436**
meningitis, 1429–1431
***Streptococcus viridans* endocarditis, 1440–1445**
clinical presentation of, 1440–1441, 1440*f*
Stress-related mucosal bleeding, 535–539
epidemiology, 536
monitoring, 539
pathophysiology, 536
prevention, 537*t*
risk factors, 536, 536*t*
treatment, 537–539, 538*t*
Stress ulcer prophylaxis (SUP)
in ICU, 1247–1248, 1249*t*
Stroke
AF and, 208

dabigatran for, 336
diabetes and, 1157
HVAD and, 287
hypertensive emergencies and, 352*t*
IE and, 1441
prevention
antithrombotic therapy for, 336–337
dabigatran for, 336
warfarin for, 209
Stroke Prevention in Atrial Fibrillation (SPAF), 336
Stroke volume (SV), 276
definition of, 276
normal values of, 369*t*
Stromal cell-derived factor-1 (SDF-1), 2162
ST segment elevation myocardial infarction (STEMI), 241
algorithm for, 252*f*
drug and nondrug therapy of, 245–258
antiplatelet and anticoagulant drugs, 254–257
fibrinolytic drugs, 245, 252, 254
ECG changes to, 243*f*
morphine sulfate for, 258
treatment for
fibrinolytic therapy, 260–262
Study of Heart and Renal Protection (SHARP), 648
Stye (Hordeolum), 1200
Subacute headaches, 1270
Subclinical hyperthyroidism (SHyper), 1099–1100
subcutaneous ICDs (s-ICDs), 343
Subcutaneous immunotherapy (SCIT)
for allergic rhinitis, 446, 467
Subcutaneous injection immunotherapy (SCIT)
for allergic rhinitis, 454
Subcutaneous layer, 852
Sublingual immunotherapy (SLIT)
for allergic rhinitis, 454, 466, 467
Substance use disorders
adjunctive treatments, 1968
alcohol toxicity, 1964–1965
alcohol use disorders, 1962–1964
alcohol withdrawal, 1965–1968
American Psychiatric Association, 1946*t*
central nervous system stimulants, 1953–1956
Diagnostic and Statistical Manual of Mental Disorders, criteria, 1946, 1946*t*
hallucinogens, 1957–1959
inhalants, 1961–1962

pharmacologic treatment, 1946
pharmacotherapy, 1972–1974
pharmacotherapy of, alcohol dependence, 1968–1969
sedative-hypnotics, 1952–1953
Substantivity, 887
Sudden cardiac death (SCD), 287
Suicidal ideation, 1895
Sulfonylurea antidiabetic agents, 709
Sunburn, treatment of, 891
Sunless tanner, 891
Sun protection factor (SPF), 886–887
for various skin types, 886*t*
Sunscreen
application of, 890
chemical organic, 887–888
for children, 889–890, 890*t*
cross-sensitivity reaction and, 889
definition of, 887
evaluation of, 887
inorganic, 888–889
product selection of, 890
and UVR absorption, 885*t*
Sunscreen Innovation Act (SIA), 887
SUP (*See* Stress ulcer prophylaxis (SUP))
Superior vena cava (SVC), 834
Superovulation (SO), 991–992, 991*t*
Supportive care, 556
Supraventricular arrhythmias, 328
atrial fibrillation
and atrial flutter, 328–331
consequences of, 331–337
treatment of, 309–310
Supraventricular tachycardias, 337*f*
ventricular rate in, 332*t*
Surface reflection, 884
Surgery, 556
antibiotics for, 1391–1400
for breast cancer, 2102
for hyperthyroidism, 1074, 1091–1092
preoperative preparation, 1095
for NSCLC, 2115
for osteosarcoma, 2068
for SCLC, 2120
Surgical antimicrobial prophylaxis
decision to use, 1396

duration of administration, 1398–1399
indiscriminate antimicrobial use, risks of, 1399
optimizing, 1400
route of administration, 1398
selection of antimicrobial agent, 1395
timing of antimicrobial administration, 1397–1398
Surgical Care Improvement Project (SCIP), 1395
Surgical site infections, 1391
classification of, 1392*t*, 1395–1400
signs of, 1399–1400
Sustained Monomorphic Ventricular Tachycardia
treatment of, 343
Sustained ventricular tachycardia (SuVT), 341*f*
Sustained VT (SuVT), 341
SuVT (*See* Sustained ventricular tachycardia (SuVT))
SV (*See* Stroke volume (SV))
SVC (*See* Superior vena cava (SVC))
SVR (*See* Systemic vascular resistance (SVR))
Sweat chloride test, 476
Sweat glands
chloride transport, 474*f*
cystic fibrosis, 472–473
Syndrome of inappropriate antidiuretic hormone secretion (SIADH), 22, 613
Syphilis, 1572–1577
congenital, 1572
epidemiology of, 1572
laboratory tests for, 1574
latent, 1573
neonatal, 1577
pregnancy and, 1576
primary, 1573
secondary, 1573
tertiary, 1574
treatment of, 1574–1577, 1575*t*
by Treponema pallidum, 1572
Systeme National d'Information Inter-Regimes Assurance Maladie (SNIIRAM), 51
Systemic inflammatory response syndrome (SIRS), 367, 2262–2263, 2263*t*
Systemic JIA (sJIA), 931
Systemic lupus erythematosus (SLE), 655, 724
antimalarials for, 739–740
atherosclerosis and, 737
cardiovascular system and, 737
classification criteria of, 733
clinical presentation of, 733, 736

diagnosis of, 738–739
drug-induced lupus erythematosus, 746
drug interactions with medications for, 746*t*
epidemiology of, 732–733
and EPT, 2341
female hormones and, 733
gastrointestinal symptoms and, 737
hematologic disorders and, 738
immunologic abnormalities and, 733
investigational agents, 747
medications causing, 747*t*
medications used for treatment of, 744–745*t*
nervous system and, 736–737
nonsteroidal anti-inflammatory drugs for, 739
pathophysiology of, 733
pharmacists, role for, 747–748
pharmacologic and nonpharmacologic treatments, 739–746
pulmonary involvement in, 737
renal complication and, 738
selective cyclooxygenase-2 inhibitor for, 739
symptoms of, 736*f*
treatment approaches for, 747
UV radiation and, 733
viral infection and, 733
Systemic Lupus International Collaborating Clinics (SLICC), 738
Systemic mycoses, 1680–1695
Systemic sclerosis (SSc), 179, 952–954
risk factors for development of, 953*t*
Systemic vascular resistance (SVR), 277, 372
normal values of, 370*t*
Systolic blood pressure (SBP), 141, 356, 367
normal values of, 369*t*
Systolic dysfunction, 276

T

Tachyarrhythmia, 328
Tachycardia, in schizophrenia, 1873
Tachyphylaxis, 676, 861–862, 875
Tacrolimus, 755
Tai Chi, knee OA and, 900–902
Tamponade, 380
TandemHeart, complications of, 387
Tanning, 884
Tanning booths, 891

Tapeworm infection (*See* Cestodiasis (tapeworm infection))
Tardive dyskinesia, in schizophrenia, 1871–1872
Target hemoglobin, 645
TAVR (*See* Transcatheter aortic valve replacement (TAVR))
TB (*See* Tuberculosis (TB))
TBE (*See* Tick-borne encephalitis (TBE))
TBW (*See* Total body water (TBW))
TC (*See* Total cholesterol (TC))
T-cell activation, 750
TD (*See* Travelers' diarrhea (TD))
TDM (*See* Therapeutic drug monitoring (TDM))
TdP (*See* Torsades de pointes (TdP))
TEE (*See* Transesophageal echocardiography (TEE))
Telangiectasia, 857
Temporal arteritis, 954–955
Temporomandibular joint arthritis (TMJ), 931
Tension-type headache, 1269
general management and abortive therapy for, 1280
interprofessional management of, 1280
pathophysiology of, 1280
prophylactic therapy for, 1280
Teratogenicity
congenital malformations, prevalence of, 1003
Food and Drug Administration risk factors, 1006
malformations, causes of, 1003–1004
medication use in, 1004–1005, 1004*t*
critical stage of exposure, 1005, 1005*f*
dose-response curve, 1005
extrapolation from animal studies, 1005–1006
genetic variability, 1006
placental transfer of drugs, 1006
TERISA (*See* Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA))
Terlipressin, 581
Testosterone deficiency, 2329–2330
TGN (*See* Thioguanine nucleotides (TGN))
TGs (*See* Triglycerides (TGs))
Thallium-201 myocardial perfusion imaging, of chronic stable angina, 221
The Health Care and Education Reconciliation Act of 2010, 11
The National Consensus Project for Quality Palliative Care, 91
The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), 210
The Patient Protection and Affordable Care Act of 2010, 11
Therapeutic drug monitoring (TDM), 38, 768
Therapeutic hypothermia, 1242

The Systolic Blood Pressure Intervention Trial (SPRINT), 145
Thiamine, 394–395
Thiazide-induced hyperuricemia, 158
Thioguanine nucleotides (TGN), 752
Thiopurine methyltransferase (TPMT), 59
Thoracic surgery, prophylaxis for, 1393*t*
Thrombocytes, 36
Thrombocytopenia, 36, 192–193, 507
Thromboembolic disease (TED), and postmenopausal hormone therapy, 1064*t*, 1066
Thromboembolism
etiology of, 181
risk factors for, 181*f*
Thrombolysis in Myocardial Infarction (TIMI), 244
Thrombosis, 180–215
AF and, 206–208
antithrombotic therapy, tests for, 187–189
bridge therapy, 210–212, 211–212*t*, 211*t*
cardiac valve replacement and, 209
cardiogenic thromboembolism, 206–209
chemotherapy and, 181*f*
clot formation, 181–182, 181*f*
deep venous thrombosis, 189–197, 190*t*, 191*t*
drug interactions, 212–215
principles of, 180–181
pulmonary embolism, 197–206, 198*t*
risk factors, 189–190
Thrombus, formation and ACS, 242*f*
Thyroid disease
cold nodule, 1075
drug-induced
amiodarone, 1100–1101
iodides, 1100–1101
lithium, 1100
Hashimoto thyroiditis, 1072
hot nodule, 1075
hyperthyroidism, 1074
causes of, 1074, 1074*t*
prevalence of, 1072
treatment, 1074
hypothyroidism, 1072
causes of, 1073*t*
and goiter, 1072
laboratory findings, 1071*t*
multinodular goiter, 1101

thyroid function tests, 1077*t*
application and interpretation, 1079–1080
for autoimmunity, 1079
and drug interference, 1080–1081
evaluation of, 1078*f*
for free and total hormone level, 1078
for gland function, 1078
for hypothalamic-pituitary-thyroid axis, 1078
for total thyroxine, 1078
for total triiodothyronine, 1078
thyroid storm, 1098–1099
Thyroidectomy, 1091–1092
Thyroid function tests
in euthyroid patients, 1073*t*
Thyroid hormone secretion, regulation of, 1072*f*
Thyroid receptor-stimulating antibodies (TRAb), 1079
Thyroid scan, 1078
Thyroid-stimulating hormone (TSH), 32
blood chemistry reference values for, 20*t*
Thyroid-stimulating immunoglobulin (TSI), 1079
Thyroid storm, 1098–1099
β-blocker, 1098–1099
clinical presentation, 1098
elimination of precipitating causes, 1099
role of catecholamines, 1098
treatment, 1098–1099
Thyroid ultrasound, 1079
Thyrotoxicosis, 1074, 1099
Thyrotropin, 32
Thyroxine-binding prealbumin (TBPA) (*See* Prealbumin)
Thyroxine (T4), 1072
TIA (*See* Transient ischemic attacks (TIA))
TIC disorder, 1942
Tick-borne diseases, 1785–1786*t*
babesiosis, 1795–1796
Colorado tick fever, 1797–1798
genera of, 1784
Lyme disease, 1784–1788
Mixed infections, 1798
relapsing fever, 1790–1792
tick-borne encephalitis, 1797
tick paralysis (tick toxicosis), 1798
tick vectors, 1793
Tick-borne encephalitis (TBE), 1797
CNS manifestations, 1797

and infected unpasteurized milk or cheese, 1797
subtypes, 1797
tick vector, 1797
Tick paralysis (tick toxicosis), 1798
Ticlopidine, role of, 175
Time of day, 884
TIMI (*See* Thrombolysis in Myocardial Infarction (TIMI))
Tinea pedis, 1677–1679
Tinea unguium (onychomycosis), 1678–1679
TIPS (*See* Transjugular intrahepatic portosystemic shunt (TIPS))
Tissue-engineered biological dressings, 897
Tissue-selective estrogen complex (TSEC), 1068
TKIs (*See* Tyrosine kinase inhibitors (TKIs))
TLC (*See* Total lung capacity (TLC))
TLS (*See* Tumor lysis syndrome (TLS))
TNA (*See* Total nutrient admixture (TNA))
Tobacco use and dependence
benefits of quitting, 1977–1978
tobacco cessation counseling (“5 R’s”), 1979, 1979*t*
and cardiovascular disease, 1986–1987
cigar smoking, 1987
cognitive and behavioral strategies for, 1980*t*
counseling interactions, 1979–1981, 1979*t*
drug interactions with smoking, 1977, 1978–1979*t*
factors contributing to, 1976
health consequences, 1977
nicotine gum, 1985
nicotine inhaler, 1988
nicotine lozenge, 1985–1986
nicotine nasal spray, 1987–1988
nicotine pharmacology, 1976–1977, 1977*f*
pharmacotherapy for, 1981–1994
relapse chances, 1986
transdermal nicotine patch, 1981–1985
treatment, 1978–1979
behavioral counseling services, 1979–1981
extended-duration medication therapy, 1994
telephone counseling services, 1978
weight-suppressing effects of tobacco, 1986
TOPCAT (*See* Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial)
Torsades de pointes (TdP), 327, 345*f*
antiarrhythmic drugs and clinical presentation of, 345–346
and nonantiarrhythmic agents, 346–347, 347*t*
treatment of, 347–348

Total body surface area (TBSA), burns of skin, 895
Total body water (TBW), 603
Total cholesterol (TC), 32, 964
blood chemistry reference values for, 21*t*
Total iron binding capacity, in iron toxicity, 74–75
Total lung capacity (TLC), 402, 432
Total nutrient admixture (TNA), 834
Tourette syndrome, 1942
Toxic epidermal necrolysis(TEN), 863
Toxic exposure, history of, 67
Toxicities, associated with anticancer therapies, 2035
angina and myocardial infarction, 2052
arrhythmias, 2052
autonomic neuropathy, 2049
cardiomyopathy, 2049–2052
cardiotoxicity, 2049–2052
cranial nerve toxicity, 2049
dermatologic, 2041–2045
GI tract, 2038–2041
hematologic, 2035–2038
hemorrhagic cystitis, 2054–2055
hepatotoxicity, 2056–2057
hypersensitivity reactions, 2044–2045, 2045*t*
hypertension, 2052
irritant and vesicant reactions, 2043–2044, 2043*t*
nephrotoxicity, 2052–2054, 2054*t*
neurotoxicity, 2046, 2048*t*
peripheral nerve toxicity, 2048
proteinuria, 2054
pulmonary, 2055–2056
specific organ, 2047–2057
synergistic interaction between a cytotoxic agents and radiation therapy, 2042
Toxidromes, 67–68
Toxins, 585
Toxoplasma gondii encephalitis, HIV and
brain lesions by, 1434
clinical presentation of, 1662
diagnosis of, 1663
prophylaxis, 1663
treatment
acute, 1663–1664
alternative, 1664
suppressive therapy (secondary prophylaxis), 1664
Toxoplasmosis, 1655
TPMT (*See* Thiopurine methyltransferase (TPMT))

Trace elements, 782
Trade-off hypothesis, 649
Transcatheter aortic valve replacement (TAVR), 209
Transdermal drug absorption, 2188
Transdermal nicotine patch, 1981–1985
Transduction, 1208
Transesophageal echocardiography (TEE), 207, 1441–1442
Transferrin, 786
Transient ischemic attacks (TIA)
definition of, 1346
drugs for preventing, 1358*t*
epidemiology of, 1346
pathophysiology, 1346–1348
risk factors for, 1347*t*
secondary prevention after, 1357–1360
antiplatelet therapy for, 1357–1360
surgical interventions for, 1360
treatment of, 1348–1356
complications of, 1357
principles, 1348
prognosis of, 1357
stroke education, 1356–1357
Transjugular intrahepatic portosystemic shunt (TIPS), 578, 578*f*, 582
Transmission of signals, 1208
Transplantation, 750
immunology
HLA typing, 752
MHC and HLA, 751–752
immunosuppressive agents, 752, 753–754*t*
antithymocyte globulins, 759–760
azathioprine, 752, 755–756
calcineurin inhibitors, 755
corticosteroids, 755
monoclonal antibodies, 756–757
mTOR inhibitors, 756, 764–765
mycophenolate mofetil and mycophenolate sodium, 755
polyclonal antibodies, 756
kidney
acute rejection treatment, 762
calcineurin inhibitor avoidance, withdrawal, or minimization, 763–764
calcineurin inhibitor-induced nephrotoxicity, 763
cyclosporine, 755
donor and recipient matching, 758–759
immunosuppressive therapy, 758–760
indications and evaluation, 757

postoperative course and delayed graft function, 760
rejection, 760–762
liver, 588–589
of ALF patients, 1732
cyclosporine, 766–767
drug interactions with immunosuppressive, 769–770
for HBV-related cirrhosis, 1743
for HCV, 1743
and HDV patients, 1758
indications and evaluation of, 765
and mannitol therapy, 1731
mycophenolic acid derivatives, 768–769
patient monitoring, 766
rejection, 767–768
tacrolimus, 755
treatment for rejection, 767–768
posttransplant complications
antifungal, 773
BK polyomavirus infection, 777–778
cytomegalovirus, 774–777
donor-derived infections, 773
hepatitis B, 774
hepatitis C, 774
malignancy, 772
opportunistic infections, 773, 774*t*
perioperative and postoperative antibacterial therapy, 773
pneumocystis jiroveci pneumonia, 773
posttransplant diabetes mellitus, 770–771
posttransplant hyperlipidemia, 771
posttransplant hypertension, 771
posttransplant lymphoproliferative disorder, 772–773
posttransplant osteoporosis, 771
Transport proteins, 43
Transthoracic echocardiogram (TTE), 1441–1442
Transthyretin (prealbumin), 785–786
Travelers' diarrhea (TD), 1514–1516
TRD (*See* Treatment refractory depression (TRD))
Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, 322
Treatment refractory depression (TRD), 1901–1902
Tremor, 1284
Treponemal test, 1574
Trichomoniasis, 1582
Trigeminal neuralgia, 1270
Triglycerides, 32

Triglycerides (TGs), 106
blood chemistry reference values for, 21*t*
role in pathogenesis of ASCVD, 112
Triiodothyronine (T3), 1072
Troponin, 29
4-T score, role of, 192
TSEC (*See* Tissue-selective estrogen complex (TSEC))
TSH (*See* Thyroid-stimulating hormone (TSH))
TSI (*See* Thyroid-stimulating immunoglobulin (TSI))
T-SPOT TB test, 1482
TTE (*See* Transthoracic echocardiogram (TTE))
T2 thyrotoxicosis, 1099
Tuberculin skin test (Mantoux method), 1478
Tuberculosis (TB), 1477–1500 (*See also Mycobacterium tuberculosis*)
active TB disease, 1478–1479
clinical presentation of, 1479–1480
diagnosis of, 1480–1482
multiple-drug therapy for, 1488
and susceptibility testing, 1486
treatment of, 1482–1489, 1483*t*
in children, 1498–1499
drug treatment of, 1479
elderly and, 1493–1494
epidemiology of, 1477–1478
etiology of, 1478
extensively drug-resistant TB (XDR-TB), 1477–1478
extrapulmonary, 1499–1500
history of, 1477
HIV and, 1495–1498
incidence of, 1477–1478
lactation and, 1498
latent infection and, 1478–1479
treatment of, 1489–1490
multidrug-resistant TB (MDR-TB), 1477–1478, 1494–1495
pathogenesis of, 1478–1479
PPD skin test for, 1480–1481
pregnancy and, 1498
therapeutic drug monitoring, 1500
totally drug-resistant (TDR), 1477
transmission of, 1478
Tuberculous meningitis, 1499–1500
Tubulointerstitial diseases
acute tubular necrosis, 670, 671*f*
aminoglycoside-induced ATN, 673–674, 673*t*
Tularemia

clinical manifestations, 1792
epidemiology, 1792
etiology, 1792
laboratory diagnosis, 1793
transmission of, 1792
treatment, 1794
type A, 1792
type B, 1792
Tumor lysis syndrome (TLS), 665, 2085–2086
Tumor necrosis factor α (TNF-α), 512
Type 1 diabetes, 1104*t*, 1105–1106, 1105*f*
basal-bolus insulin therapy, 1119–1123, 1121–1122*t*, 1121*f*
β-cells and, 1105
in children, 1133–1138
clinical presentation of, 1105
diet for, 1111
DKA with, 1134
honeymoon period with, 1106
human leukocyte antigen (HLA) and, 1105
ketone testing for, 1113
nutrition therapy and, 1111
pathogenesis of, 1105, 1105*f*
prevention of, 1111
treatment of, 1119
weight and, 1105
Type 2 diabetes, 1104*t*
CHD and, 1177–1178
clinical presentation of, 1107
diet for, 1112
in elderly, 1175–1180
diet for, 1176
exercise for, 1176
nutrition therapy and, 1112
obesity and, 1106
pathogenesis of, 1106–1107, 1107*f*
prevention of, 1111
risk factors for, 1108*t*
screening, 1107–1108, 1108*t*
SMBG for, 1145
sulfonylureas for, 1155
treatment of, 1145–1165
weight and, 1106
Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA), 233
Type II idiopathic RPGN, 670

Typhoid fever (enteric fever), 1510–1511
Tyrosine kinase inhibitors (TKIs), 50, 51

U

UACR (*See* Urine albumin to urine creatinine ratio (UACR))
UBT (*See* Urea breath test (UBT))
UFH (*See* Unfractionated heparin (UFH))
UFR (*See* Ultrafiltration (UFR))
UKPDS (*See* United Kingdom Prospective Diabetes Study (UKPDS))
Ulcerative colitis (UC)
and Crohn disease, pathophysiologic differences between, 542*t*
diagnosis of, 541–542
diarrhea associated with, 558
male with, 789–791
goals of therapy, 790
maintenance fluids, 790–791
micronutrients, 790
nutritional support effectiveness, 791
pathophysiology and clinical presentation of, 558–564
severity classification of, 542*t*
treatment algorithm, 557*f*
ULT (*See* Urate-lowering therapy (ULT))
Ultrafiltration, 682
Ultrafiltration, process of, 694
Ultrafiltration rate (UFR), 677
Ultrafiltration (UFR)
for HF, 314
Ultrarapid opiate detoxification (UROD), 1950
Ultrasonography, for biliary obstruction, 1527
Ultraviolet A (UVA), psoriasis and, 877
Ultraviolet B (UVB), psoriasis and, 876–877, 877
Ultraviolet index, 884
Ultraviolet protection factor (UPF), 890, 890*t*
Ultraviolet radiation (UVR)
BCC and, 884
CMM and, 884
environmental effects on, 884
erythema and, 884
exposure to, 882–893
eye and, 884–885
long-term effects of, 886
oxygen free radicals and, 884
photocarcinogenesis, 884
and photocarcinogenesis, 884

protective eyewear for, 890–891
SCC and, 884
skin diseases and, 882
skin tanning and, 884
spectrum of, 883–884, 883*f*, 883*t*
sunburn and, 884
sunscreens and, 885*t*
Uncompetitive enzyme inhibition, 43
Unfractionated heparin (UFH), 182
limitations of, 254
LMWH and, 183*t*
United Kingdom Prospective Diabetes Study (UKPDS), 641, 1109
United Network for Organ Sharing (UNOS), 573–574
United States Renal Data System (USRDS), 634, 681
UNOS (*See* United Network for Organ Sharing (UNOS))
Unstable angina (UA), 241
treatment for
anticoagulant therapy, 264
antithrombotic therapy, 264–266
invasive vs. ischemia-guided strategy, 263–264
ischemia-guided strategy, 266
UPF (*See* Ultraviolet protection factor (UPF))
Upper endoscopy and biopsy, 529
Upper gastrointestinal (GI) disorders
acid-related disorders, pharmacotherapy of drugs
antacids, 505, 507
bismuth salts, 509
histamine-2 receptor antagonists (H2RA), 507
misoprostol, 509
proton-pump inhibitors (PPI), 507–509
sucralfate, 509
dyspepsia, 510*f*
clinical assessment and diagnosis, 510
pathophysiology, 509–510
treatment, 510–511, 511*t*
gastroesophageal reflux disease (GERD)
antireflux surgery, 533
classification systems for endoscopically determined, 530*t*
clinical assessment and diagnosis, 529–530
clinical presentation, 527
dietary and lifestyle modifications to manage, 528*t*
epidemiology, 525
etiology and risk factors, 525
extraesophageal manifestations, 532–533
maintenance therapy, 531

nonerosive reflux disease, 531–532
on-demand pharmacotherapy, 531
pathophysiology, 525–527
pharmacotherapy, 530–531
proton-pump inhibitor and histamine-2 receptor antagonists, 531
risk factors, 526*t*
treatment, 527–529, 528*f*, 528*t*
oral medications used to treat, 506*t*
overview of, 504
peptic ulcer disease (PUD)
clinical assessment and diagnosis, 513–515, 514*t*
clinical course and prognosis, 515
clinical presentation, 513
epidemiology, 511
etiology and risk factors, 511–512
Helicobacter pylori-related, 518–521
NSAID induced ulcers, 512, 512*t*, 513, 513*t*, 521–524
pathophysiology, 512
patient education, 519–520
treatment, 515–518, 516*t*, 517*f*
upper GI bleeding
peptic ulcer bleeding, 533–535
stress-related mucosal bleeding, 535–539
upper GI tract, physiology of, 504–505, 504–505*f*
anatomic regions, 504*f*
Zollinger-Ellison syndrome (ZES)
clinical assessment and diagnosis, 524
epidemiology, 524
pathophysiology, 524
treatment, 524–525
Upper GI bleeding
peptic ulcer bleeding, 533–535
stress-related mucosal bleeding, 535–539
Upper reference limit (URL), 243
Urate-elevating medications, 940, 940*t*
Urate-lowering therapy (ULT), 947
choice of agent, 949–950
drug therapy of, 947–948, 948–949*t*
flare prophylaxis, 950
goal of, 947
monitoring and follow-up, 950
starting, 947
Urea breath test (UBT), 514*t*, 515
Urea clearance, 694
Uremia, 676

Uremic bleeding, 654
Uric acid, 28
blood chemistry reference values for, 19*t*
overproduction of, 939
underexcretion, 939
Urinalysis (UA), 36–38, 665–666, 666*t*, 1541
Urinary alkalinization, 45, 72, 505
in salicylate toxicity, 72
Urinary chemistries, 666–667
Urinary incontinence
age-related changes, 2309, 2309*t*
anatomy and physiology, 2309*f*
causes of, 2309*t*
Classification, 2309
clinical presentation of, 2310–2311, 2311*t*
drug therapy, 2312–2316
evaluation of, 2310–2311
nonpharmacologic options, 2311–2312
pharmacologic options, 2311–2312
and postmenopausal hormone therapy, 1065*t*
Urinary NA:K ratio, 575
Urinary tract infections (UTI), 1539–1560
acute cystitis, 1009–1010
asymptomatic abacteriuria and, 1557
asymptomatic bacteriuria, 1009–1010
asymptomatic bacteriuria and, 1557
catheter-associated, 1540–1541
in children, 1557
clinical presentation of, 1541
community-acquired, 1539
complicated, 1539
contraception and, 1540
diabetes and, 1540
diagnosis of, 1541–1542
drug therapy for, 1542, 1544–1545*t*
epidemiology of, 1539
etiology of, 1539–1540
females and, 1539
hospital-acquired, 1540, 1557–1558
incidence of, 1539
lower, 1542–1550
pathogenesis of, 1009, 1540–1541
and postmenopausal hormone therapy, 1064*t*
predisposing factors for, 1540–1541
during pregnancy, 1540, 1556–1557

prevalence of, 1539
prostatitis, 1559–1560
recurrence of, 1553–1557
renal failure and, 1548
sexual intercourse and, 1540, 1555–1556
uncomplicated, 1539
Urine albumin to urine creatinine ratio (UACR), 37
Urine drug screen, 68
URL (*See* Upper reference limit (URL))
UROD (*See* Ultrarapid opiate detoxification (UROD))
Urticaria, 863–864
US Food and Drug Administration (FDA), 507
US Medical Eligibility Criteria, 975
US Preventive Services Task Force (USPSTF), 151
USPSTF (*See* US Preventive Services Task Force (USPSTF))
USRDS (*See* United States Renal Data System (USRDS))
UTI (*See* Urinary tract infections (UTI))
UVA (*See* Ultraviolet A (UVA), psoriasis and)
UVB (*See* Ultraviolet B (UVB), psoriasis and)
Uveitis, JIA-associated, 931
UV Index, 884
UVR (*See* Ultraviolet radiation (UVR))

V

Vaccination, 1402–1418 (*See also* Immunization)
cancer vaccines, 2018
hepatitis A vaccine, 1725
dosage, 1725, 1725*t*
with HBV vaccine, 1726
indications for, 1726
hepatitis B vaccines
adverse effects, 1735
dosage, 1733
duration of vaccine-induced immunity, 1734
immune response to, 1733
indications for, 1734
and infants, 1736
with Recombivax HB, 1733
universal, 1735
herpes zoster vaccine (Zostavax), 1704
HPV vaccines, 2018
influenza, 1710, 2288
for Lyme disease, 1790
for malaria, 1770

for OIs, 1656
pneumococcal vaccine, 2288
for protection against S. typhi, 1511
Vaccine-associated paralytic polio (VAPP), 1409
VAD (*See* Vascular dementia (VAD))
VADT (*See* Veterans Affairs Diabetes Trial (VADT))
Vaginal atrophy, and postmenopausal hormone therapy, 1064*t*
Vaginal discharge, characteristics of, 1579*t*
Vaginitis, 1577–1583
VALIANT (*See* Valsartan in Acute Myocardial Infarction Trial (VALIANT))
Valsalva maneuver, for PSVT, 338
Valsartan Heart Failure Trial (Val-HeFT), 299
Valsartan in Acute Myocardial Infarction Trial (VALIANT), 266, 299
Vancomycin, 1242
VAP (*See* Ventilator-associated pneumonia (VAP))
VAPP (*See* Vaccine-associated paralytic polio (VAPP))
Variant angina
clinical presentation of, 238
therapy for, 238–239
Variceal hemorrhage, 583
Varicella-zoster virus (VZV), 1656
VAS (*See* Visual analog scale (VAS))
Vascular access, 682, 684
arteriovenous (AV) graft, 684*f*, 685
arteriovenous fistula, 684–685, 684*f*
central venous catheter, 685–686, 685*f*
flow dysfunction, preventing and treating, 690–691
Vascular dementia (VAD)
clinical presentation, 2301–2302
diagnosis, 2302
etiology, 2301
neuropathology, 2301
treatment, 2302–2303
Vascular stent, 235*f*
Vascular surgery, prophylaxis for, 1392*t*
Vasculoprotective therapy, for chronic stable angina
antiplatelet therapy, 223
lifestyle modifications, 222
risk factor modification, 222–223
Vasomotor rhinitis, 469
Vasomotor symptom (VMS), 1063
and postmenopausal hormone therapy, 1064*t*
Vasopressin, 580–581
Vasopressin receptor antagonists (VRAs), 280, 575
Vasopressors, inotropic agents and, 384*t*

Vaughn-Williams classification, of antiarrhythmic agents, 329*t*
VDS (*See* Verbal description scales (VDS))
Venography, for DVT, 190
Venous thrombi, 182
occurrence of, 182
Venous thromboembolism (VTE), 966, 966*t*
prevention of, 196
treatment of, 195*t*
Ventilation
for apnea, 2246
for BPD, 2208, 2232–2233
for hantavirus infections, 1712
medications for intubation, 2257–2259*t*, 2257–2260
ribavirin, 1712
for RDS, 229, 2226, 2227
for SS, 2266
Ventilator-associated pneumonia prophylaxis, 1474–1475
Ventilator-associated pneumonia (VAP), 1469–1475
Ventricle, remodeling of, 266
Ventricular arrhythmias, 258, 341, 1691, 1889, 1900
ambulatory monitoring of, 342
amiodarone, 344–345
electrophysiologic studies, 342
etiology of, 341
evaluation of life-threatening, 341–342
implantable cardiac defibrillators, 343–345
premature ventricular contractions, 342–343
sustained monomorphic ventricular tachycardia, 343
TdP, 345–346
Ventricular fibrillation (VF), 341*f*
Ventricular flutter (VF), 341
Ventricular function curve, 383*f*
Ventricular remodeling, 245
Ventricular tachycardia (VT), 327, 341
nonsustained, 341*f*
Verbal description scales (VDS), 1212*t*
Very low density lipoproteins (VLDL), 107–108, 107*t*, 1105
Veterans Affairs Diabetes Trial (VADT), 1110
VF (*See* Ventricular fibrillation (VF); Ventricular flutter (VF))
***Vibrio cholerae,* infection from, 1505–1506**
***Vibrio parahaemolyticus,* infection from, 1506–1507**
Viral gastroenteritis, 1502*t*, 1505
Viral hepatitis
immunization for, 1759
Viral infections, 733

common cold, 1719
of Hantavirus, 1712
herpes simplex, 1698–1703
influenza, 1708–1711
middle east respiratory syndrome, 1718–1719
respiratory syncytial virus (RSV), 1711–1712
severe acute respiratory distress syndrome (SARS), 1713–1718
and systemic lupus erythematosus, 733
varicella-zoster (VZV), 1703–1708
West Nile virus (WNV), 1712–1713
Virchow's Triad, 181
Visceral pain, 1210
treatment of, 1211
Visual analog scale (VAS), 1212*t*
Vital capacity (VC), 402
Vitamin D, 652
biotransformation, 649*f*
Vitamin K Epoxide Reductase Complex subunit 1 (VKORC1), 57
Vitamin K epoxide reductase (VKOR), 187
Vitamin K-hydroquinone (KH2), 47
Vitamins, 781–782
and mineral supplementation, 476–477, 477*t*
PN and, 845, 845*t*
VKOR (*See* Vitamin K epoxide reductase (VKOR))
VLDL (*See* Very low density lipoproteins (VLDL))
VMS (*See* Vasomotor symptom (VMS))
Volume depletion, 606
Volume excess, 607–608
Volume regulation, 606
disorders in, 606–608
volume depletion, 606
volume excess, 607–608
Vomiting (*See also* Nausea and vomiting)
clinical presentation of, 2216
definition of, 488
pathogenesis, 2216
and pazopanib, 2027*t*
VRAs (*See* Vasopressin receptor antagonists (VRAs))
VTE (*See* Venous thromboembolism (VTE))
Vulvovaginal candidiasis (VVC), 1578–1581
causative agents of, 1578
complicated, 1581
differential diagnosis of, 1579
patient counseling in, 1581
in pregnancy, 1579

recurrent, 1581–1582, 1582*t*
risk factors for, 1579–1580
signs and symptoms, 1578
treatment of, 1580–1581
vaginal discharge in, 1579
VVC (*See* Vulvovaginal candidiasis (VVC))
VZV (*See* Varicella-zoster virus (VZV))

W

Waist-to-hip ratio (WHR), 794
Water, 781
in body, 603
homeostasis, 605
Water restriction, 575
WBC (*See* White blood cells (WBCs); White blood count (WBC))
Wegener granulomatosis, 656–658, 657*t*
Weight, 2188–2189
and AmB formulations, 1684–1687
and dehydration, 2197–2200, 2200*t*, 2218
and giardiasis, 1776
loss, 798
with alcohol, 2285
behavior therapy for, 798–799
with bupropion, 1898
in CML, 2088
and CPAP, 1847
dietary supplements for, 803*t*
diets for, 798
for hypertension prevention, 145, 151
in leukemias, 2088
physical activity for, 798
and PN, 840
and parenteral nutrient requirements, 2198*t*
and PCP therapy, 1661
for SGAs, 1875
and tapeworm infections, 1778
and terbinafine, 1679
type 1 diabetes and, 1105
type 2 diabetes and, 1106
Weight gain, 696
Western blot tests, 1634
West Haven Criteria (WHC), 584
West Nile virus (WNV), 1712–1713

WFSBP (*See* World Federation of Societies of Biological Psychiatry (WFSBP))
WHC (*See* West Haven Criteria (WHC))
White blood cells (WBCs), 33, 377
White blood count (WBC), 2088
in iron toxicity, 74–75
White-coat hypertension, 143–144
WHO (*See* World Health Organization (WHO))
Whole bowel irrigation (WBI), 69
in iron ingestion, 74
Willis-Ekbom disease (*See* Restless legs syndrome (RLS))
Wilms tumor, 2065–2067, 2066*t*
chemotherapy, 2067
clinical presentation of, 2066–2067
diagnosis, 2066
epidemiology, 2065–2066
pathophysiology, 2065
staging, 2066, 2066*t*
treatment of, 2066–2067
Windup, pain and, 1209
WNV (*See* West Nile virus (WNV))
Wolff-Chaikoff effect, 1089
Wolff-Parkinson-White (WPW) syndrome, 338*f*, 339–340
World Federation of Societies of Biological Psychiatry (WFSBP), 1917
World Health Organization (WHO), 427, 990
obesity and, 794
Wounds, classification of, 895, 1392*t*
WPW (*See* Wolff-Parkinson-White (WPW) syndrome)

X

Xerosis (dry skin), 859
Xerostomia, 2039

Y

Yale-Brown Obsessive-Compulsive Symptom Checklist (Y-BOCS), 1827
Yellow zone, of PEF, 422

Z

ZES (*See* Zollinger-Ellison syndrome (ZES))
Zollinger-Ellison syndrome (ZES)
clinical assessment and diagnosis, 524
epidemiology, 524

pathophysiology, 524
treatment, 524–525